Effective Health Care Program

Comparative Effectiveness Review
Number 129

Antiplatelet and Anticoagulant Treatments for Unstable Angina/ Non-ST Elevation Myocardial Infarction

Agency for Healthcare Research and Quality
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Addendum

This report has been updated to include an additional article identified in the literature related to dual antiplatelet versus triple therapy, with revisions to the key points, results, strength of evidence tables, and appendixes.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Antiplatelet and Anticoagulant Treatments for Unstable Angina/Non–ST Elevation Myocardial Infarction

Structured Abstract

Objectives. For patients with unstable angina or non–ST elevation myocardial infarction (UA/NSTEMI), antiplatelet and anticoagulant medications are prescribed to reduce and prevent ischemic events and mortality. There is uncertainty about the optimal dosing and timing of these medications to balance ischemic risk and bleeding risk across different treatment strategies (early invasive, initial conservative, and postdischarge).

Data sources. We searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews for relevant English-language comparative studies.

Review methods. Two investigators screened each abstract and full-text article for inclusion, abstracted data, rated quality and applicability, and graded evidence. When possible, random-effects meta-analysis was used to compute summary estimates of effects.

Results. Our review included 175 studies (302 articles); 87 studies were relevant to early invasive management, 33 were relevant to initial conservative management, and 71 were relevant to the postdischarge setting.

Patients undergoing an early invasive approach. Upstream (precatheterization) treatment using glycoprotein IIb/IIIa inhibitors (GPIs) was associated with lower rates of revascularization (odds ratio [OR] 0.77; 95% confidence interval [CI], 0.65 to 0.92) but higher risk of major bleeding events (OR 1.24; 95% CI, 1.08 to 1.43) at 30 days compared with deferred (periprocedural) GPI treatment (high strength of evidence [SOE]). This higher risk of bleeding from upstream GPI administration also occurred with either pretreatment (OR 1.49; 95% CI, 1.10 to 2.01; moderate SOE) or deferred clopidogrel administration (OR 1.27; 95% CI, 1.08 to 1.50; high SOE). Compared with clopidogrel, prasugrel reduced rates of cardiovascular death, myocardial infarction, or stroke at 30 days (5.7% prasugrel vs. 7.4% clopidogrel; moderate SOE). After 1 year, in a subgroup of patients who all had UA/NSTEMI, prasugrel reduced rates of the same composite endpoint compared with clopidogrel (9.9% prasugrel vs. 12.1% clopidogrel), as did ticagrelor (10.6% ticagrelor vs. 12.6% clopidogrel) (moderate SOE). Bivalirudin reduced major bleeding events at 30 days compared with heparin in several clinical scenarios: with planned GPI use (OR 0.52; 95% CI, 0.43 to 0.63); without planned GPI use (OR 0.63; 95% CI, 0.47 to 0.85; both high SOE); and in patients treated with clopidogrel before undergoing percutaneous coronary intervention (OR 0.64; 95% CI, 0.49 to 0.85; moderate SOE). Bivalirudin also reduced minor bleeding events at 30 days compared with heparin plus GPI (OR 0.49; 95% CI, 0.42 to 0.59; high SOE).

Patients undergoing an initial conservative approach. In randomized trials, enoxaparin reduced composite ischemic events (OR 0.84; 95% CI, 0.76 to 0.93; high SOE) and myocardial infarction (OR 0.85; 95% CI, 0.76 to 0.95; moderate SOE) at around 30 days compared with unfractionated heparin. The addition of GPIs to unfractionated heparin reduced the rate of mortality up to 30 days (OR 0.80; 95% CI, 0.67 to 0.96), but minor bleeding rates were increased (OR 1.62; 95% CI, 1.20 to 2.19; both high SOE).

Postdischarge treatment. Dual antiplatelet therapy (DAPT) reduced the rates of composite ischemic outcomes (ORs/relative risks ranging from 0.69 to 0.80; in-hospital, 9 months, and 1 year) and nonfatal myocardial infarction (DAPT 2.3% to 5.8% vs. aspirin 3.0% to 8.5%; 9 months and 1 year) compared with single antiplatelet therapy (high SOE). Meta-analyses using adjusted or propensity-scored hazard ratios from observational studies showed an association between proton pump inhibitor (PPI) use (any type with dual antiplatelet use) and increased rates of composite ischemic endpoints, death, nonfatal myocardial infarction, stroke, revascularization, stent thrombosis, and major bleeding. (Most outcomes were measured around 1 year and rated low SOE, and ratings were downgraded since the findings conflicted with the few randomized trials of omeprazole.) However PPIs with DAPT use reduced rates of upper gastrointestinal bleeding (moderate SOE).

Limitations. This review was limited to comparative studies of antiplatelet and anticoagulant treatments, many of which did not separate findings by treatment approach (invasive, conservative, postdischarge) and included a mix of UA/NSTEMI and acute coronary syndrome populations. Also, different definitions of composite endpoints made quantitative analysis less feasible. Few trials of percutaneous coronary intervention reported long-term outcomes, and very few studies reported findings in the subpopulations of interest.

Conclusions. The number of studies available for each comparison was relatively small, and the preponderance of observational studies made the findings for some comparisons inconclusive. Further study is needed to determine the effectiveness and safety of newer agents in combination with other antiplatelet and anticoagulant strategies. Uncertainty remains about the optimal dosing, timing, duration, and combinations of these options, especially in subpopulations of interest (e.g., the elderly, patients with diabetes, women, obese patients, and people with comorbid illness).

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Executive Summary

Background

Acute coronary syndrome (ACS) encompasses three similar yet distinct disorders: (1) ST–elevation myocardial infarction (STEMI), (2) non–ST elevation myocardial infarction (NSTEMI), and (3) unstable angina (UA). These disorders are often collapsed into just two categories—STEMI and UA/NSTEMI—because UA and NSTEMI have a similar pathophysiology, mortality rate, and management strategy when compared with STEMI. In the United States, approximately 1.4 million people are diagnosed with ACS each year, and 70 percent of them have UA/NSTEMI.[1-4]

UA/NSTEMI is defined by the presence of ischemic chest pain (or an equivalent), the notable absence of ST segment elevation on electrocardiography, and the presence of either ST segment depression or T-wave inversion on electrocardiography and/or abnormal cardiac biomarkers.[1] The pathophysiology of UA/NSTEMI involves six possible etiologies: (1) thrombus arising from a disrupted or eroded plaque, (2) thromboembolism from an erosive plaque, (3) dynamic obstruction (such as coronary spasm), (4) progressive mechanical obstruction, (5) inflammation, or (6) coronary artery dissection.[5] Most patients with UA/NSTEMI have thrombus formation or progressive arterial narrowing that leads to subtotal occlusion of an epicardial coronary artery.[6] The difference between UA and NSTEMI is based on the presence of myocardial necrosis or infarction as suggested by serum tests such as creatine kinase-myocardial band, troponin I, or troponin T in NSTEMI.

Treatment Strategies for UA/NSTEMI

The standard treatment goals for patients with UA/NSTEMI involve the elimination of ischemic pain and the prevention of adverse events—death, recurrent ischemia, or myocardial infarction (MI). The cornerstone of short- and long-term treatment in all cases is medical therapy with antiplatelet and anticoagulant medications. Antiplatelet medications work by decreasing platelet aggregation and inhibiting thrombus formation. The timing of initiation of antiplatelet therapy in patients presenting with UA/NSTEMI is broadly classified as *upstream* if the therapy is initiated after admission but prior to cardiac catheterization or *periprocedural* if the agent is initiated at the time of or during the procedure. Antiplatelet therapy initiated during a hospitalization for UA/NSTEMI and continued for long-term management has been shown to reduce future cardiovascular events. Anticoagulant medications work by inhibiting blood clotting, either by antagonizing the effects of vitamin K or by blocking/inhibiting thrombin. The use of a parenteral anticoagulant, traditionally heparin, is standard treatment for patients hospitalized with ACS, and newer anticoagulants have been developed that improve outcomes, with similar or reduced bleeding risk compared with heparin.

By virtue of its ability to inhibit factors associated with thrombosis and to reduce ischemic outcomes, each antiplatelet or anticoagulant agent has the potential to increase the risk of bleeding. The tradeoff between reduced ischemic risk and increased bleeding risk has been highlighted in a number of recent large clinical trials that evaluated antiplatelet and anticoagulant therapies, as discussed below. Despite these recent data, a number of questions remain about the use of antiplatelet and anticoagulant agents, including the optimal dosing of certain agents and the timing of their use, and whether certain agents might be preferred for specific subgroups of patients.[7]

There are a number of challenges in determining optimal medical management in patients with UA/NSTEMI. First, there are a large number of agents in each category, increasing the complexity of assessing which combinations have the best outcomes. Second, optimal medical management may be affected by the choice of revascularization strategy. For the majority of patients who are at high risk of recurrent ischemia, MI, or death, an *early invasive treatment strategy*—defined as diagnostic angiography and coronary revascularization without prior noninvasive stress testing—has been proven to reduce death or MI.[8-11] For the minority of patients at low or intermediate risk of recurrent ischemia, MI, or death, an *initial conservative treatment strategy* is often chosen: noninvasive stress testing followed by angiography and revascularization only in patients who develop recurrent infarction, angina at rest, or inducible ischemia during stress testing.[1] Therefore, the comparative effectiveness of concurrent medical therapy needs to be considered separately for early invasive and initial conservative strategies. Finally, it is also important to consider the *postdischarge treatment strategy* (after hospitalization), using antiplatelet and/or anticoagulant treatments to reduce recurrent ischemic events.

Antiplatelet and Anticoagulant Medications for UA/NSTEMI

Table A outlines the antiplatelet and anticoagulant therapies available for each clinical scenario: early invasive, initial conservative, and postdischarge. These therapies are discussed below.

Table A. Antiplatelet and anticoagulant therapies for each clinical scenario

Drug Category	Early Invasive	Initial Conservative	Postdischarge
Aspirin	Aspirin[a] (low or high dose)	Aspirin[a] (low or high dose)	Aspirin[a] (low or high dose)
Intravenous antiplatelet (glycoprotein IIb/IIIa inhibitor)	*Upstream:* Eptifibatide Tirofiban *Periprocedure:* Eptifibatide Tirofiban Abciximab	Eptifibatide Tirofiban Abciximab	None
Oral antiplatelet ($P2Y_{12}$ Inhibitor)	*Upstream*: Clopidogrel Ticagrelor *Periprocedure*: Clopidogrel Prasugrel Ticagrelor	Clopidogrel Ticagrelor Prasugrel	Clopidogrel Prasugrel Ticagrelor

Table A. Antiplatelet and anticoagulant therapies for each clinical scenario (continued)

Drug Category	Early Invasive	Initial Conservative	Postdischarge
Anticoagulant	Bivalirudin Fondaparinux Enoxaparin Unfractionated heparin	Fondaparinux Enoxaparin Unfractionated heparin	Warfarin Dabigatran Rivaroxaban Apixaban
Other considerations	Dose and timing	Dose and timing	Duration related to PCI vs. no PCI Proton pump inhibitors Patients requiring triple therapy

PCI = percutaneous coronary intervention; triple therapy = aspirin plus antiplatelet plus anticoagulant
[a]In studies, low-dose aspirin ranged from 81 mg to less than 300 mg; high-dose aspirin ranged from 150 mg to 325 mg.

Aspirin and Antiplatelet Agents

In the absence of contraindications, aspirin is currently recommended for all patients presenting with ACS.[1] Clopidogrel, the most widely used oral $P2Y_{12}$ inhibitor, is currently recommended for patients with UA/NSTEMI. Other oral $P2Y_{12}$ inhibitors include prasugrel and ticagrelor. While robust clinical data support the use of clopidogrel in patients with ACS,[12-14] several factors have been observed that make clopidogrel less than ideal. Clopidogrel belongs to the thienopyridine class of antiplatelet medications and is a prodrug that requires biotransformation to the active metabolite. This metabolic conversion takes place via the hepatic cytochrome P-450 isoenzymes and is susceptible to drug interactions and genetic polymorphisms that can potentially reduce the antiplatelet activity of the drug. Prasugrel is also a thienopyridine, but it provides a more potent and faster acting antiplatelet effect than clopidogrel and does not appear to be susceptible to genetic polymorphisms of the hepatic isoenzymes. Ticagrelor is a reversibly binding $P2Y_{12}$ receptor antagonist that also provides a more rapid and more potent inhibition of platelets than clopidogrel does.[15]

The antiplatelet agents belonging to the glycoprotein IIb/IIIa inhibitor (GPI) class are administered intravenously. They include abciximab, eptifibatide, and tirofiban. Eptifibatide and tirofiban are reversible platelet inhibitors, whereas abciximab, a selective antibody, is an irreversible platelet inhibitor.

Anticoagulant Agents

Anticoagulants used to manage patients with UA/NSTEMI include unfractionated heparin (UFH), low molecular weight heparin (enoxaparin), bivalirudin, and fondaparinux. Intravenous UFH is the traditional anticoagulant used to manage UA/NSTEMI. Because of its short biologic half-life of approximately 1 hour, heparin must be given frequently or as a continuous infusion. Enoxaparin is a low molecular weight heparin that has the advantage of being administered subcutaneously once or twice daily and does not require frequent blood monitoring. Bivalirudin is a bivalent direct thrombin inhibitor that binds reversibly to thrombin. Bivalirudin possesses a favorable pharmacokinetic profile in that it is eliminated primarily by proteolytic cleavage, with approximately 20 percent being cleared by the kidneys, and has a plasma half-life of 25 minutes in patients with normal renal function. Fondaparinux is an indirect factor Xa inhibitor that is injected subcutaneously on a daily basis. Fondaparinux has been associated with a favorable bleeding profile when compared with other anticoagulants used in patients with ACS.

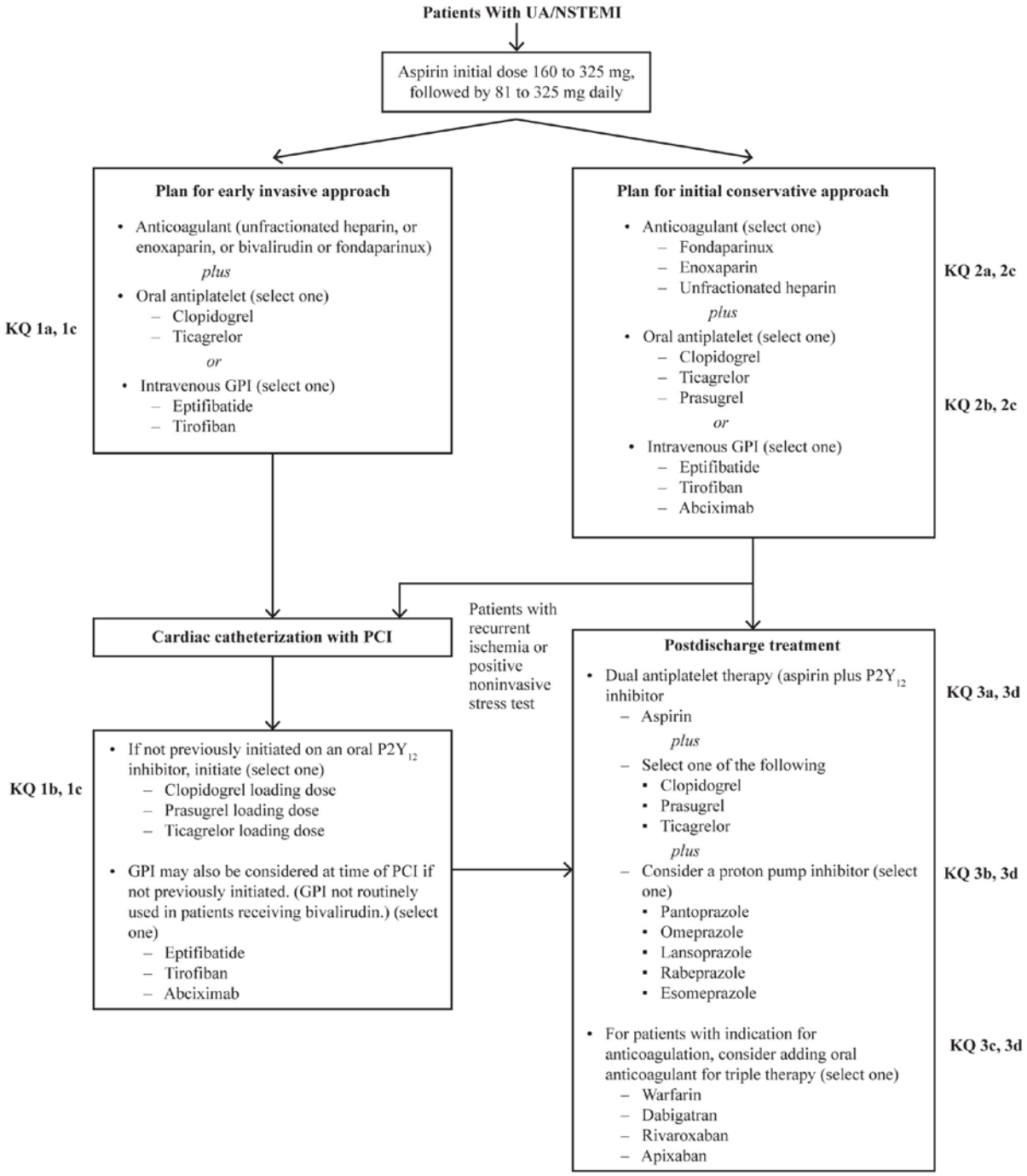
Treatment Strategy Algorithm

Figure A illustrates the treatment strategy algorithm for patients with UA/NSTEMI. First, all patients presenting with UA/NSTEMI are treated with an initial dose of aspirin, followed by either an early invasive or an initial conservative approach. An early invasive approach consists of an oral antiplatelet agent or intravenous (IV) GPI as initial therapy prior to going to the cardiac catheterization laboratory. After catheterization with percutaneous coronary intervention (PCI), the next stage involves consideration of the use of antiplatelet agents to improve cardiovascular outcomes. An initial conservative approach consists of using different anticoagulants and oral antiplatelets to improve cardiovascular outcomes in patients with UA/NSTEMI.

For all patients with UA/NSTEMI, the postdischarge phase of treatment considers oral antiplatelet agents, aspirin for patients who are also receiving another oral antiplatelet agent, and the addition of proton pump inhibitors for reducing bleeding events in patients receiving dual antiplatelet therapy (DAPT). Last, the postdischarge strategy may include triple therapy (aspirin plus antiplatelet plus anticoagulant) for UA/NSTEMI patients with an indication (e.g., atrial fibrillation) for long-term anticoagulant therapy.

Although the treatment algorithm provides guidance to clinicians, there is still considerable uncertainty about the specifics of which medications to use in combination with other agents, the optimal dosing and timing of their use, and whether certain agents are more effective and safer in specific subgroups of patients. The treatment strategy usually consists of an anticoagulant with either an oral antiplatelet or IV GPI medication. Some trials assessed the combination and timing of using all three treatments (i.e., an anticoagulant, IV GPI, and an oral antiplatelet medication).

Figure A. Treatment strategy algorithm for patients with UA/NSTEMI



GPI = glycoprotein IIb/IIIa inhibitor; KQ = Key Question; PCI = percutaneous coronary intervention; triple therapy = aspirin plus antiplatelet plus anticoagulant; UA/NSTEMI = unstable angina/non–ST elevation myocardial infarction

Scope and Key Questions

Scope of Review

This Comparative Effectiveness Review was funded by the Agency for Healthcare Research and Quality (AHRQ). The review was designed to evaluate the effectiveness and safety of antiplatelet and anticoagulant medications used to treat patients with UA/NSTEMI in an early invasive approach, an initial conservative approach, and after hospitalization (postdischarge).

Key Questions

With input from our Technical Expert Panel, we constructed Key Questions (KQs) using the general approach of specifying the population of interest, interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS). The KQs considered in this Comparative Effectiveness Review were:

KQ 1. In patients undergoing an early invasive approach for treating unstable angina/non–ST elevation myocardial infarction (UA/NSTEMI):

a. What are the comparative effectiveness (dose and timing) and comparative safety of an intravenous (IV) glycoprotein IIb/IIIa inhibitor versus oral antiplatelet agent as initial therapy before going to the catheterization laboratory?
b. What are the comparative effectiveness (dose and timing) and comparative safety of coadministration of IV or oral antiplatelet agents in patients undergoing percutaneous coronary intervention for improving cardiovascular outcomes? Do the effectiveness and safety vary based on which initial anticoagulant is used or the combination of anticoagulant and antiplatelet agents?
c. Based on demographic and other clinical characteristics, are there subgroups of patients for whom the effectiveness and safety differ?

KQ 2. In patients undergoing an initial conservative approach for treating UA/NSTEMI:

a. What are the comparative effectiveness (dose and timing) and comparative safety of different anticoagulants for improving cardiovascular outcomes?
b. What are the comparative effectiveness (dose and timing) and comparative safety of different antiplatelet agents for improving cardiovascular outcomes?
c. Based on demographic and other characteristics, are there subgroups of patients for whom the effectiveness and safety differ?

KQ 3. In patients treated for UA/NSTEMI after hospitalization (postdischarge):

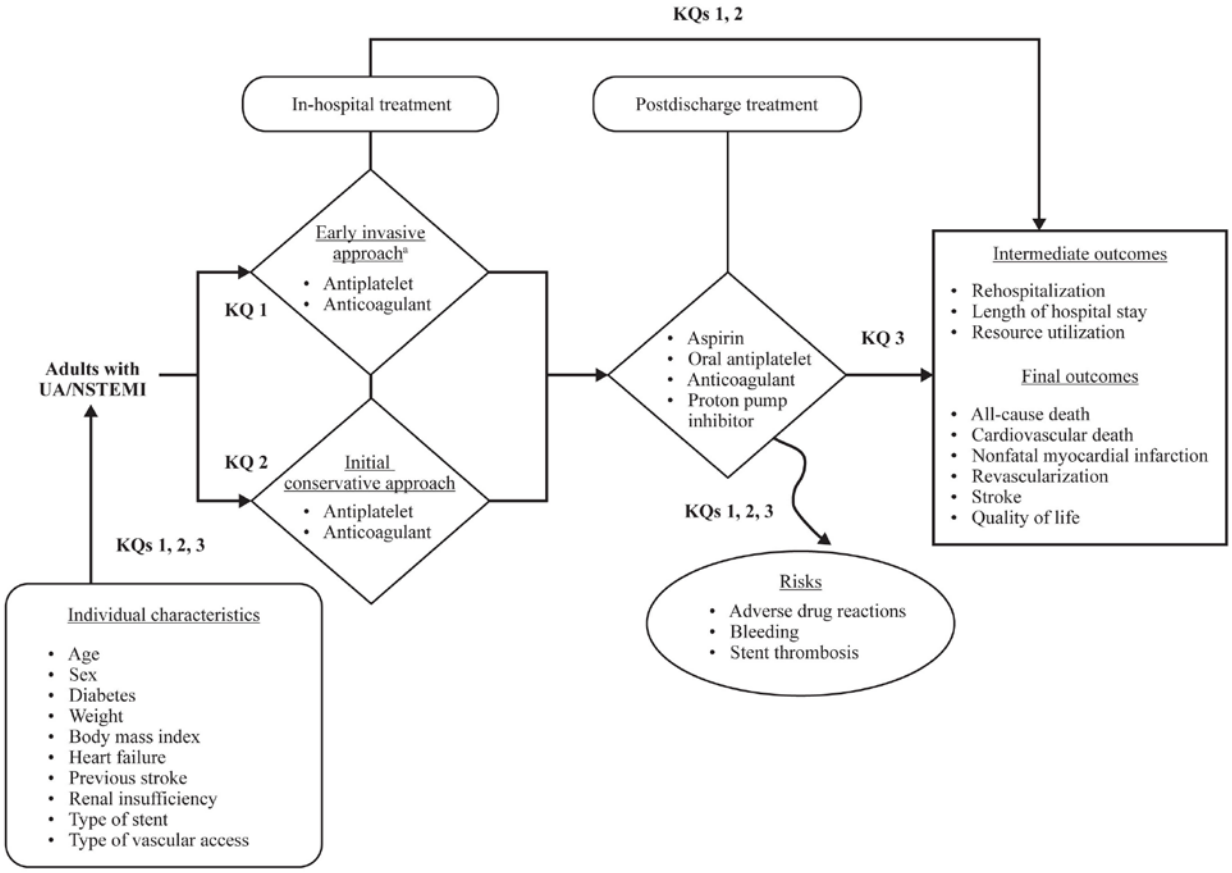
a. What are the comparative effectiveness (dose and duration) and comparative safety of the available oral antiplatelet agents given in combination with aspirin? Do the effectiveness and safety vary based on the dose of aspirin used?
b. What are the comparative effectiveness and comparative safety of proton pump inhibitors (PPIs) for reducing bleeding events in patients receiving dual antiplatelet therapy after UA/NSTEMI? Do the effectiveness and safety vary by oral antiplatelet therapy and PPI?
c. In patients with an indication for long-term anticoagulant therapy, what are the comparative effectiveness and comparative safety of adding an oral anticoagulant to aspirin and another antiplatelet agent for improving cardiovascular outcomes?

d. Based on demographic and other characteristics, are there subgroups of patients for whom the effectiveness and safety differ?

Analytic Framework

Figure B shows the analytic framework for this Comparative Effectiveness Review.

Figure B. Analytic framework



KQ = Key Question; UA/NSTEMI = unstable angina/non–ST elevation myocardial infarction
[a]Prior to catheterization or during percutaneous coronary intervention.

The analytic framework depicts the treatment strategies and outcomes for adult patients with UA/NSTEMI. In-hospital treatment interventions include an early invasive approach prior to catheterization or during percutaneous coronary intervention (KQ 1) or an initial conservative approach (KQ 2) involving the use of combinations of antiplatelets and/or anticoagulants to improve cardiovascular outcomes. Postdischarge treatment interventions (KQ 3) involve the use of aspirin, oral antiplatelets, anticoagulants, and proton pump inhibitors to prevent recurrent ischemic events and other outcomes.

Intermediate outcomes considered include rehospitalization, length of hospital stay, and resource utilization (e.g., emergency department visits). Final outcomes considered include all-cause death, cardiovascular-related death, nonfatal myocardial infarction, revascularization, stroke, and quality of life. The figure also includes consideration of whether there are subgroups of patients, based on demographic and other characteristics, for whom the effectiveness and safety differ. All three KQs consider subgroups by age, sex, weight, body mass index, diabetes,

heart failure, previous stroke, renal insufficiency, type of stent, and type of vascular access. Finally, all three KQs consider safety risks, including adverse drug reactions, bleeding, and stent thrombosis.

Methods

The methods for this Comparative Effectiveness Review follow those suggested in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[16]

Input From Stakeholders

During the topic refinement stage, we solicited input from Key Informants representing clinicians (cardiology, internal medicine, pharmacology, emergency medicine), patients, scientific experts, and Federal agencies to help define the KQs. The KQs were then posted for public comment in October 2011 for 4 weeks, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP), comprising clinical, content, and methodological experts, to provide input in defining populations, interventions, comparisons, or outcomes, as well as identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP did analysis of any kind or contributed to the writing of the report.

Literature Search Strategy

Our search strategy used the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. In consultation with our research librarians, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (last search data for all three sources, July 19, 2012). Our search strategy for PubMed is included in Appendix A of the full report; this strategy was adapted as necessary for use in the other databases. We date-limited our search to articles published since January 1995, corresponding to the period when contemporary studies on antiplatelet therapy, anticoagulant therapy, and combined therapies were published. The reference lists for identified pivotal articles were hand-searched and cross-referenced against our library, and additional manuscripts were retrieved. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We also searched the gray literature of study registries and conference abstracts for relevant articles from completed studies. Gray literature databases included ClinicalTrials.gov (August 20, 2012); the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (March 7, 2012); and ProQuest COS Conference Papers Index (February 15, 2012). Scientific information packets were requested from the manufacturers of medications and devices and reviewed for relevant articles from completed studies not previously identified in the literature searches. Based on our search of ClinicalTrials.gov and the four trial records without publications in peer-reviewed literature, we do not believe that there is significant publication bias in the evidence base that would impact our overall findings.

Inclusion and Exclusion Criteria

Criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed the full report. The search focused on English-language studies (randomized controlled trials [RCTs] or observational) published since 1995 that were comparative assessments of strategies for treating patients with UA/NSTEMI using oral antiplatelets, anticoagulants, and proton pump inhibitors across three approaches: early invasive (KQ 1), initial conservative (KQ 2), and after hospitalization (KQ 3) with the outcomes listed in the analytic framework.

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were examined independently by two reviewers for potential relevance to the KQs. Articles included by any reviewer underwent full-text screening. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to include or exclude the article for data abstraction. When the paired reviewers arrived at different decisions about whether to include or exclude an article, we reconciled the difference through a third-party arbitrator. Articles meeting our eligibility criteria were included for data abstraction. Relevant systematic review articles, meta-analyses, and methods articles were flagged for hand-searching and cross-referencing against the library of citations identified through electronic database searching.

Data Extraction

The investigative team created data abstraction forms and evidence table templates for abstracting data for the KQs. Based on clinical and methodological expertise, two investigators were assigned to the research questions to abstract data from the eligible articles. One investigator abstracted the data, and the second overread the article and the accompanying abstraction to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus was not reached between the first two investigators. To aid in both reproducibility and standardization of data collection, investigators received data abstraction instructions directly on each form created specifically for this project with the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, Ontario, Canada).

We designed the data abstraction forms for this project to collect data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate outcomes, health outcomes, and safety outcomes). The safety outcomes were framed to help identify adverse events, including adverse drug reactions and bleeding. Data necessary for assessing quality and applicability, as described in the Methods Guide,[16] were also abstracted. Before they were used, abstraction form templates were pilot tested with a sample of included articles to ensure that all relevant data elements were captured and that there were consistency and reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies by using the approach described in the Methods Guide.[16] To assess quality, we used the strategy of (1) classifying the study design, (2) applying predefined criteria for quality and critical appraisal, and (3) arriving at a summary

judgment of the study's quality. To evaluate methodological quality, we applied criteria for each study type derived from the core elements described in the Methods Guide. For RCTs, criteria included adequacy of randomization and allocation concealment, the comparability of groups at baseline, blinding, the completeness of followup and differential loss to followup, whether incomplete data were addressed appropriately, the validity of outcome measures, and conflict of interest. We used the summary ratings of good, fair, or poor based on the study's adherence to well-accepted standard methodologies and adequate reporting.

For nonrandomized clinical trials, such as those with an observational control group that was not randomized, we assessed the following study-specific issues that may affect the internal validity of our systematic review: potential for selection bias (i.e., degree of similarity between intervention and control patients); performance bias (i.e., differences in care provided to intervention and control patients not related to the study intervention); attribution and detection bias (i.e., whether outcomes were differentially detected between intervention and control groups); and magnitude of reported intervention effects.[17] Quality ratings for individual studies are in Appendix E of the full report.

Data Synthesis

We summarized the primary literature by abstracting relevant continuous data (e.g., age) and categorical data (e.g., race, presence of coronary disease risk factors). Continuous variable outcomes reported by study authors included means, medians, standard deviations, interquartile ranges, ranges, and associated p-values. Dichotomous variable outcomes were summarized by proportions and associated p-values. We then determined the feasibility of completing a quantitative analysis (i.e., meta-analysis). Feasibility depended on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the reporting of results. For our main analyses, we considered meta-analysis for comparisons in which at least three studies reported the same outcome. For the KQ 2 sensitivity analyses, we grouped studies by trial size (small, <1,000 patients; large, ≥1,000 patients) and by use (aspirin monotherapy vs. dual antiplatelet therapy) to help explain any heterogeneity, if present. Any subgroup summary estimate based on fewer than three studies is noted as such and should be interpreted with caution.

Meta-analyses were based on the nature of the outcome variable, but random-effects models were used for all outcomes because of the heterogeneity of the studies. Dichotomous outcome measures comparing two treatments were combined using odds ratios and a random-effects model as implemented in Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ). We tested for statistical heterogeneity between studies (Q and I^2 statistics), while recognizing that the power to detect such heterogeneity may be limited. Potential heterogeneity between studies was reflected through the confidence intervals (CIs) of the summary statistics obtained from a random-effects approach. When substantial heterogeneity was present, we conducted sensitivity analyses to assess whether omitting the poor-quality studies would reduce the heterogeneity.

We present summary estimates, standard errors, and CIs in our data synthesis. When the summary estimate and CI were precise and crossed 1, we looked at the particular studies to determine the minimally important difference for noninferiority, or at the total number of events in both arms from the set of studies to see if it met criteria for optimal information size for the level of risk reduction.[18] If the CI was within the minimally important difference or the number

of events met the optimal information size, then we concluded equivalence; otherwise we concluded insufficient evidence.

Strength of the Body of Evidence

We graded the SOE (SOE) for each outcome assessed because a given study may be of different quality for two individual outcomes reported within that study. The SOE for each KQ and outcome was assessed using the approach described in the Methods Guide.[16,19] In brief, the approach required assessment of four domains: risk of bias, consistency, directness, and precision. Risk-of-bias ratings were based on the studies that were used in the meta-analysis (when performed) or on the findings from RCTs, which carry the lowest risk of bias (when meta-analysis was not performed). For some comparisons, especially those for KQ 3, the only available literature was from observational studies. Additionally, when appropriate, the studies were evaluated for the presence of confounders that would diminish an observed effect, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, or low SOE was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make (e.g., when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn), and therefore the evidence was rated insufficient.

Applicability

We assessed applicability across our KQs using the method described in the Methods Guide.[16,20] In brief, the PICOTS format was used as a way to organize information relevant to applicability. We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population (e.g., age, ethnicity, and sex) in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use (such as specific components of treatments considered to be supportive therapy), and clinical relevance and timing of the outcome measures.

Results

In the initial phases of title-and-abstract screening, we focused on identifying articles on the UA/NSTEMI population; therefore, citations that included the ACS population were moved forward to the full-text screening phase. In examining these citations, we found 59 articles that addressed an exclusively UA/NSTEMI population and 110 articles that addressed an ACS population that included the UA/NSTEMI population but did not report separate results for that population. The investigative team felt that limiting our review to the pure UA/NSTEMI population would result in a narrow focus on the antiplatelet and anticoagulant therapies that are used in clinical practice. Therefore, we have chosen to exclude studies that did not include a UA/NSTEMI population. Note that any studies that were exclusively in the STEMI or stable angina population were also excluded.

Also, we found studies that were not easily grouped into the early invasive, initial conservative, or postdischarge strategies. There was substantial overlap in the treatment strategies within these studies. For example, in a study comparing antithrombotic therapies, a proportion of patients in each treatment arm could have undergone PCI or conservative

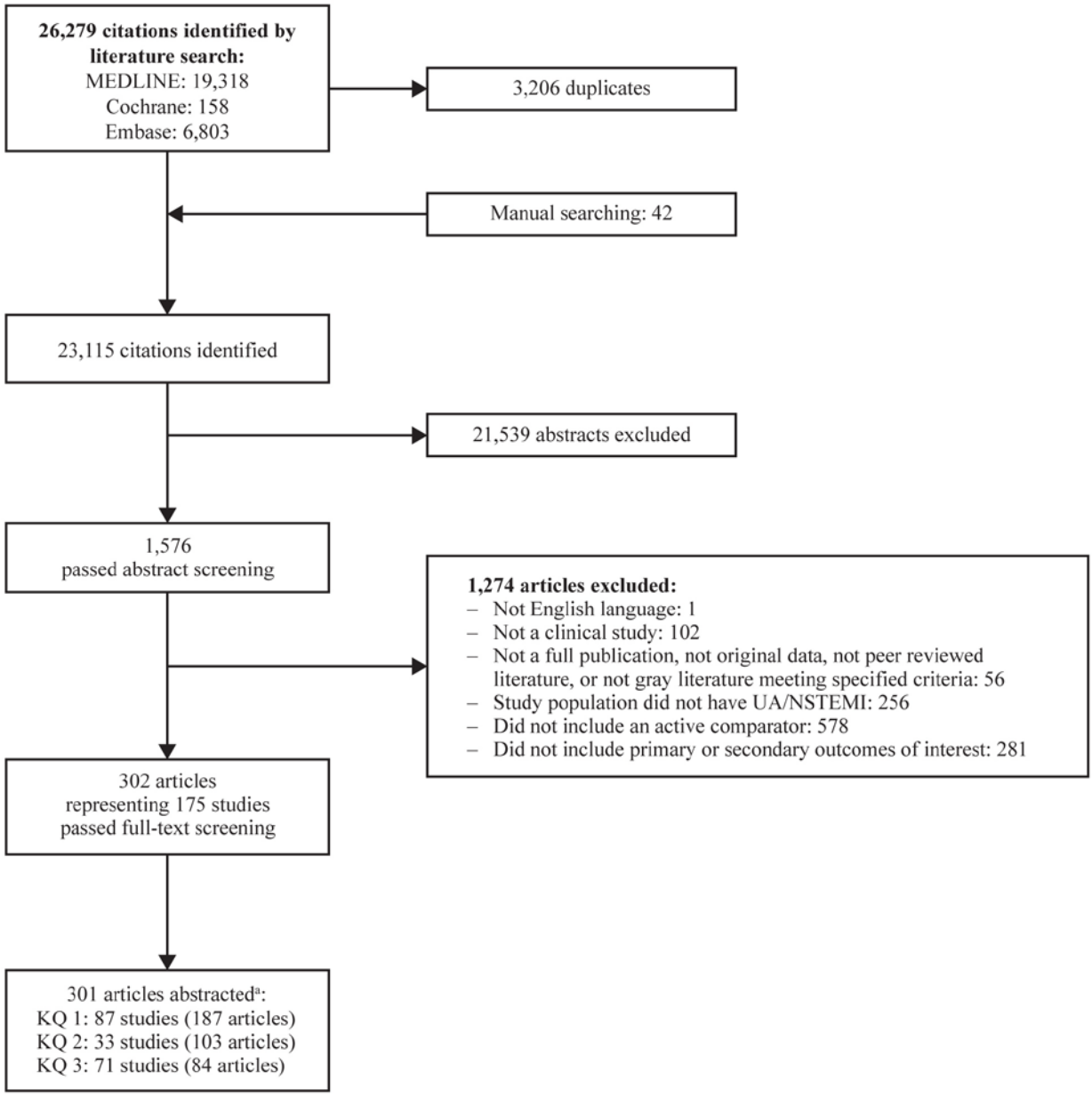
treatment. The results were reported by each treatment arm but not by the subgroups that received PCI or conservative treatment. For these reasons, this review is structured in the following manner:

- In KQ 1 (*early invasive*), we focus on studies that assessed dosage, timing, and combinations of antiplatelet and anticoagulant therapies delivered at the time of PCI. We present the findings of studies comparing (1) upstream versus deferred GPI, (2) different loading doses of clopidogrel, (3) clopidogrel versus ticagrelor or prasugrel, (4) bivalirudin versus a heparin-based strategy, (5) enoxaparin versus UFH versus fondaparinux, and (6) upstream or deferred clopidogrel administration.
- In KQ 2 (*initial conservative*), we present the findings of studies that either focused on conservatively managed patients or presented information about antiplatelet and anticoagulant therapies in UA/NSTEMI or ACS populations who were not included in KQ 1. Thus we present the findings of studies comparing (1) UFH versus enoxaparin or fondaparinux (full UA/NSTEMI cohort), (2) GPI plus UFH versus UFH alone in a patient population for whom coronary angiography was discouraged in the first 24 to 60 hours after study drug administration or in populations who did not receive PCI, and (3) clopidogrel versus ticagrelor or prasugrel.
- In KQ 3 (*postdischarge*), we present the findings of studies comparing (1) low-dose versus high-dose aspirin, (2) single antiplatelet versus DAPT, (3) short-term versus long-term clopidogrel, (4) antiplatelet therapy with or without the addition of a PPI, and (5) DAPT versus triple antiplatelet therapy in patients with an indication for long-term anticoagulation (e.g., atrial fibrillation, prosthetic valve).

Results of Literature Searches

Figure C depicts the flow of articles through the literature search and screening process for the review. Searches of PubMed®, Embase®, and the Cochrane Database of Systematic Reviews from January 1995 to July 2012 yielded 26,279 citations, 3,206 of which were duplicates. Manual searching and contacts with drug manufacturers identified 42 additional citations, for a total of 23,115. After applying inclusion/exclusion criteria at the title-and-abstract level, 1,576 full-text articles were retrieved and screened. Of these, 1,274 were excluded at the full-text screening stage, leaving 302 articles (representing 175 unique studies) for data abstraction. Note that several articles/studies were relevant to more than one KQ.

Figure C. Literature flow diagram



KQ = Key Question; UA/NSTEMI=unstable angina/non–ST elevation myocardial infarction
[a]Studies/articles could be relevant to more than 1 KQ.

Key Question 1. Early Invasive Approach for UA/NSTEMI

We identified 87 unique studies that evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 354,511 patients with UA/NSTEMI treated with an *early invasive approach* (PCI-based strategy). Six comparisons assessed dosage, timing, and combinations of antiplatelet and anticoagulant therapies in the included studies and are detailed in this analysis. (Note that "upstream" and "pretreatment" refer to the time before the PCI is begun; "deferred treatment" refers to medications given at the same time as the PCI.)

The following six comparisons were assessed in the included studies for KQ 1:

1. Upstream versus deferred administration of GPI (KQ 1a)
   - 16 studies (12 RCTs, 4 observational; 149,847 total patients)
2. Clopidogrel loading dose (KQ 1b)
   - 11 studies (8 RCTs, 3 observational; 36,347 total patients)
3. Clopidogrel versus ticagrelor or prasugrel (PCI cohort; KQ 1b)
   - 3 studies (3 RCTs; 33,216 total patients)
4. Bivalirudin versus a heparin-based strategy, without or with planned GPI (KQ 1b)
   - 13 studies (8 RCTs, 5 observational; 30,486 total patients)
5. Enoxaparin versus UFH versus fondaparinux (KQ 1b)
   - 13 studies (10 RCTs, 3 observational; 41,201 total patients)
6. Upstream or deferred clopidogrel administration (before or after PCI) in studies with a defined anticoagulant strategy (comparing bivalirudin vs. a heparin-based therapy; KQ 1b) or a defined intravenous antiplatelet strategy (comparing upstream vs. deferred GPI use; KQ 1a)
   - 18 studies (16 RCTs, 2 observational; 40,218 patients)

For each comparison in KQ 1, we present the key points, followed by a table summarizing the SOE and estimates of the magnitude of effect (Tables B-G).

Key Points: Upstream (Precatheterization) Versus Deferred (Periprocedural) GPI

- Upstream (precatheterization) treatment with GPIs was associated with lower rates of revascularization (high SOE) but with a higher risk of major bleeding events at 30 days compared with deferred (periprocedural) GPI administration (high SOE). However, we found no statistically significant difference between upstream and deferred GPI therapy for the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 30 days (low SOE).
- Evidence for the comparative effect of upstream versus deferred GPI therapy on all-cause mortality and nonfatal MI at 30 days was rated insufficient due to inconsistency and imprecision, despite the large number of studies and total number of enrolled patients.

Table B. Summary strength of evidence and effect estimates: upstream versus deferred glycoprotein inhibitor

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Low (6 RCTs; 19,662 patients) OR 0.88 (0.77 to 1.01); no difference
Composite of all-cause mortality, nonfatal MI, or revascularization after 6 months	SOE = Insufficient (4 RCTs; 773 patients) Insufficient evidence due to imprecision: OR 0.77 (0.46 to 1.28)
All-cause mortality at 30 days	SOE=Insufficient (10 RCTs, 20,521 patients) Insufficient evidence due to inconsistency and imprecision, with a CI that crosses 1: OR 0.80 (0.57 to 1.11)
All-cause mortality at 6 months	SOE = Insufficient (3 RCTs; 673 patients) Insufficient evidence due to inconsistency and imprecision: 1 study reported no deaths in either arm; 1 study reported 1 death in the upstream GPI arm; 1 study reported similar rates (2.0% upstream GPI, 3.6% deferred GPI)
Nonfatal MI at 30 days	SOE = Insufficient (9 RCTs; 20,263 patients) Insufficient evidence due to inconsistency and imprecision: OR 0.84 (0.65 to 1.10)

Table B. Summary strength of evidence and effect estimates: upstream versus deferred glycoprotein inhibitor (continued)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Nonfatal MI at 6 months	SOE = Insufficient (3 RCTs; 673 patients) Insufficient evidence due to inconsistency and imprecision: 1 study reported 1 MI in the deferred GPI arm only; 2 other studies reported MI rates of 12% upstream vs. 15% deferred, and 10% upstream vs. 9% deferred
Revascularization at 30 days	SOE = High (6 RCTs; 19,454 patients) OR 0.77 (0.65 to 0.92); favors upstream GPI
Revascularization at 6 months	SOE = Insufficient (3 RCTs; 673 patients) Insufficient evidence due to inconsistency and imprecision: OR 0.69 (0.34 to 1.39)
Major bleeding at 30 days	SOE = High (9 RCTs; 20,242 patients) OR 1.24 (1.08 to 1.43); favors deferred GPI
Minor bleeding at 30 days	SOE = Insufficient (5 RCTs; 969 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.58 (0.95 to 2.64)
Stent thrombosis at 30 days	SOE = Insufficient (0 studies; 0 patients)

CI = confidence interval; GPI = glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor upstream GPI; ORs greater than 1 favor deferred GPI.

Key Points: 300 mg Versus 600 mg Clopidogrel Loading Dose

- A 600 mg loading dose of clopidogrel was associated with lower rates of nonfatal MI and lower incidences of stent thrombosis at 30 days than a 300 mg loading dose (low SOE).

Table C. Summary strength of evidence and effect estimates: 300 mg versus 600 mg clopidogrel loading dose

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days	SOE = Low (1 RCT; 25,086 patients) HR 0.94 (0.83 to 1.06) in this large good-quality RCT sufficiently powered to assess this composite endpoint; no difference
Composite of cardiovascular mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (1 RCT; 119 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (10.4% vs. 23.8%)
Composite of cardiovascular mortality, nonfatal MI, or recurrent ACS at 30 days	SOE = Insufficient (1 RCT; 387 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (4.8% vs. 12.3%)
Composite of all-cause mortality, nonfatal MI, revascularization, or rehospitalization at 30 days	SOE = Insufficient (1 RCT; 103 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (5.9% vs. 11.4%)
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (1 RCT; 255 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (4.0% vs. 11.6%)
Composite of all-cause mortality, nonfatal MI, nonfatal stroke, or rehospitalization at 6 months	SOE = Insufficient (1 RCT; 256 patients) Insufficient evidence due to imprecision: no difference in event rates between groups (13.3% vs. 13.2%)
All-cause mortality at 30 days	SOE = Low (3 RCTs; 25,802 patients) 2 small studies reported no deaths in either group; largest study reported HR 0.93 (0.83 to 1.05); no difference

Table C. Summary strength of evidence and effect estimates: 300 mg versus 600 mg clopidogrel loading dose (continued)

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
All-cause mortality at 6 months	SOE = Insufficient (1 RCT; 256 patients) Insufficient evidence due to sparse data: 3 deaths in 300 mg group; 1 death in 600 mg group
Cardiovascular mortality at 30 days	SOE = Low (3 RCTs; 25,497 patients) HR 0.95 (0.81 to 1.13) in the large good-quality RCT; no difference
Nonfatal MI at 30 days	SOE = Low (5 RCTs; 25,855 patients) OR 1.74 (0.99 to 3.05); favors 600 mg dose
Nonfatal MI at 6 months	SOE = Insufficient (1 RCT; 256 patients) Insufficient evidence due to imprecision: higher MI rate in 600 mg group (8.6% vs. 5.0%; p = 0.26)
Nonfatal stroke at 30 days	SOE = Insufficient (2 RCTs; 25,378 patients) Insufficient evidence due to imprecision: largest study reported HR 1.19 (0.84 to 1.68); smaller study reported 2 strokes in 300 mg group, 1 stroke in 600 mg group
Nonfatal stroke at 6 months	SOE = Insufficient (1 RCT; 256 patients) Insufficient evidence due to sparse data: only 1 stroke in overall cohort (600 mg group)
Revascularization at 30 days	SOE = Insufficient (3 RCTs; 477 patients) Insufficient evidence due to inconsistency and low overall event rate, ranging from 0 to 1.3% in 600 mg group and from 0 to 4.8% in 300 mg group
Revascularization at 6 months	SOE = Insufficient (1 RCT; 256 patients) Insufficient evidence due to imprecision: lower incidence in 600 mg group (2.3% vs. 3.3%; p = 0.64)
Major bleeding at 30 days	SOE = Insufficient (6 RCTs; 26,111 patients) Insufficient evidence due to inconsistency and imprecision: 3 studies reported no bleeding events; inconsistent findings from 3 other studies, with largest study reporting HR 1.09 (0.89 to 1.34)
Minor bleeding at 30 days	SOE = Insufficient (5 RCTs; 25,819 patients) Insufficient evidence due to inconsistency and imprecision: incidence ranged from 0.8% to 9.5% in 300 mg group and from 0.8% to 3.9% in 600 mg group
Stent thrombosis at 30 days	SOE = Low (1 RCT; 17,263 patients) HR 0.68 (0.55 to 0.85); favors 600 mg dose

ACS = acute coronary syndrome; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

Key Points: Clopidogrel Versus Ticagrelor or Prasugrel (PCI Cohort)

- Ticagrelor was associated with mixed results for the composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke compared with clopidogrel at 30 days (insufficient SOE for a reduction in the composite outcome for ticagrelor) and had similar rates of major bleeding events (low SOE) at 1 year.
- Prasugrel showed a reduction in the event rate of the above composite outcome at 30 days (moderate SOE) and the individual outcome of revascularization at 6 months (moderate SOE), but an increase in major bleeding events at 1 year (moderate SOE) when compared with clopidogrel.
- After 1 year, ticagrelor was associated with lower composite ischemic endpoints (moderate SOE) and individual endpoints (all-cause mortality, cardiovascular mortality, nonfatal MI, stent thrombosis; all moderate SOE) when compared with clopidogrel.

- After 1 year, prasugrel was associated with lower composite ischemic endpoints (moderate SOE), individual endpoints (all-cause mortality, cardiovascular mortality; both low SOE), and nonfatal MI and stent thrombosis (moderate SOE) when compared with clopidogrel.

Table D. Summary strength of evidence and effect estimates: clopidogrel versus ticagrelor or prasugrel (percutaneous coronary intervention cohort)

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (2 RCTs; 19,608 patients) Insufficient evidence due to inconsistency and imprecision: compared with clopidogrel (3.8% and 5.4%), ticagrelor had mixed results (4.3% and 4.8%)
	Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) Compared with clopidogrel (7.4%), prasugrel (5.7%) was associated with lower composite endpoint; favors prasugrel
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (12.6%), ticagrelor (10.6%) was associated with lower composite endpoint; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) HR 0.81 (0.73 to 0.90) Compared with clopidogrel (12.1%), prasugrel (9.9%) was associated with lower composite endpoint at 15 months; favors prasugrel
Composite of cardiovascular mortality, nonfatal MI, or revascularization at 15 months	Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) HR 0.81 (0.73 to 0.87); favors prasugrel
All-cause mortality at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 0.6%, ticagrelor 1.9%; p = 0.18
All-cause mortality after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (5.9%), ticagrelor (4.5%) was associated with fewer deaths; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Low (1 RCT; 13,608 patients) Compared with clopidogrel (3.2%), prasugrel (3.0%) was associated with fewer deaths; favors prasugrel
Cardiovascular mortality at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 0.6%, ticagrelor 1.9%; p = 0.18
Cardiovascular mortality after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (5.1%), ticagrelor (4.0%) was associated with fewer cardiovascular deaths; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Low (1 RCT; 13,608 patients) Compared with clopidogrel (2.4%), prasugrel (2.1%) was associated with fewer cardiovascular deaths; favors prasugrel

Table D. Summary strength of evidence and effect estimates: clopidogrel versus ticagrelor or prasugrel (percutaneous coronary intervention cohort) (continued)

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Nonfatal MI at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 3.5%, ticagrelor 2.2%; p = 0.34
Nonfatal MI after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (6.9%), ticagrelor (5.8%) was associated with fewer MIs; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) Compared with clopidogrel (9.5%), prasugrel (7.3%) was associated with fewer MIs; favors prasugrel
Nonfatal stroke at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 0.3%, ticagrelor 0.6%; p = 0.57
Nonfatal stroke after 1 year	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 18,624 patients) Insufficient evidence due to imprecision: clopidogrel 1.3%, ticagrelor 1.5% Clopidogrel vs. prasugrel: SOE = Insufficient (1 RCT; 13,608 patients) Insufficient evidence due to imprecision: clopidogrel 1.0%, prasugrel 1.0%
Revascularization at 30 days	Both comparisons: SOE = Insufficient (0 studies; 0 patients)
Revascularization after 6 months	Clopidogrel vs. prasugrel (1 RCT, 13,608 patients) SOE = Moderate HR 0.66 (0.54 to 0.81); favors prasugrel
Major bleeding at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 6.9%, ticagrelor 7.1%
Major bleeding after 1 year	Clopidogrel vs. ticagrelor: SOE = Low (1 RCT; 18,624 patients) Compared with clopidogrel (7.7%), ticagrelor (7.9%) had similar event rates; no difference Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) Compared with clopidogrel (1.8%), prasugrel (2.4%) was associated with higher event rates; favors clopidogrel
Minor bleeding at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 1.3%, ticagrelor 2.7%; p = 0.18
Stent thrombosis after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (2.9%), ticagrelor (2.2%) was associated with lower event rates; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) Compared with clopidogrel (2.4%), prasugrel (1.1%) was associated with lower event rates; favors prasugrel

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

Key Points: Bivalirudin Versus Heparin-Based Strategy Without and With Planned GPI Use

- Without planned GPI use, there was a statistically significantly lower incidence in major and minor bleeding at 30 days favoring bivalirudin when compared with heparin (high SOE for major bleeding; low SOE for minor bleeding).
- With planned GPI use, bivalirudin reduced the rate of the composite outcome of all-cause mortality, nonfatal MI, revascularization, or major bleeding, and the individual endpoint of minor bleeding compared with heparin at 30 days (high SOE).

Table E. Summary strength of evidence and effect estimates: bivalirudin versus heparin-based strategy without and with planned glycoprotein inhibitor use

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Bivalirudin vs. Heparin-Based Strategy Without Planned GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or major bleeding at 30 days	SOE = Insufficient (1 RCT; 4,571 patients) Insufficient evidence due to imprecision: bivalirudin 8.4% vs. heparin 8.7%
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: 1 study found no difference, OR 1.19 (0.92 to 1.54); 1 study found statistically significant lowering in the bivalirudin group, OR 0.42 (0.21 to 0.84)
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: 1 study found no difference, OR 0.97 (0.83 to 1.13); 1 study found statistically significant lowering in the bivalirudin group, OR 0.58 (0.37 to 0.92)
All-cause mortality at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to inconsistency and imprecision: OR 0.46 (0.12 to 1.81)
All-cause mortality after 6 months	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: disparate results in 2 RCTs: bivalirudin 1.2% vs. heparin 2.4%; bivalirudin 1.9% vs. heparin 1.7%
Nonfatal MI at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.00 (0.64 to 1.55)
Nonfatal MI after 6 months	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: disparate results in 2 RCTs: bivalirudin 3.3% vs. heparin 5.7%; bivalirudin 6.0% vs. heparin 5.3%
Revascularization at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.10 (0.60 to 2.04)
Revascularization after 6 months	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to imprecision: lower rate of revascularization in bivalirudin-treated patients (4.1% and 11.2%) vs. heparin-treated (5.7% and 12.5%)
Major bleeding at 30 days	SOE = High (3 RCTs; 5,822 patients) OR 0.63 (0.47 to 0.85); favors bivalirudin
Minor bleeding at 30 days	SOE = Low (3 RCTs; 5,822 patients) OR 0.64 (0.43 to 0.95); favors bivalirudin
Stent thrombosis at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to imprecision: OR 1.42 (0.64 to 3.15)

Table E. Summary strength of evidence and effect estimates: bivalirudin versus heparin-based strategy without and with planned glycoprotein inhibitor use (continued)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Bivalirudin vs. Heparin-Based Strategy With Planned GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or major bleeding at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 0.87 (0.78 to 0.97); favors bivalirudin
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 1.07 (0.95 to 1.22); no difference
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Low (2 RCTs; 10,566 patients) Both RCTs found no difference between treatments: OR 1.11 (0.74 to 1.63) and OR 1.08 (0.92 to 1.25); no difference
All-cause mortality at 30 days	SOE = Insufficient (3 RCTs; 12,287 patients) Insufficient evidence due to imprecision: OR 1.21 (0.89 to 1.65)
All-cause mortality after 6 months	SOE = Insufficient (2 RCTs; 10,566 patients) Insufficient evidence due to imprecision: similar event rate in 1 RCT (3.8% bivalirudin, 3.8% GPI); slightly lower event rate in other RCT (0.9% bivalirudin,1.3% GPI; p = 0.46)
Nonfatal MI at 30 days	SOE = Moderate (3 RCTs; 12,287 patients) OR 1.06 (0.92 to 1.23); no difference
Nonfatal MI after 6 months	SOE = Moderate (2 RCTs; 10,566 patients) Higher event rate with bivalirudin (7.8% and 8.1%) vs. heparin (6.9% and 7.6%); favors heparin
Revascularization at 30 days	SOE = Low (3 RCTs; 12,287 patients) OR 1.11 (0.86 to 1.42); favors bivalirudin
Revascularization after 6 months	SOE = Low (2 RCTs; 10,566 patients) Higher event rate with bivalirudin (8.7% and 11.7%) vs. heparin (8.4% in both studies); favors heparin
Major bleeding at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 0.52 (0.43 to 0.63); favors bivalirudin
Minor bleeding at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 0.49 (0.42 to 0.59); favors bivalirudin
Stent thrombosis at 30 days	SOE = Insufficient (2 RCTs; 10,936 patients) Insufficient evidence due to imprecision: similar event rates between treatment arms in both studies (bivalirudin 0.7% to 1.0%; heparin 0.6% to 0.8%)

CI = confidence interval; GPI = glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor bivalirudin; ORs greater than 1 favor heparin-based strategy.

Key Points: Enoxaparin Versus UFH Versus Fondaparinux (PCI Cohort)

- At 30 days, there were no significant differences in the incidence of the composite ischemic endpoints in PCI patients treated with enoxaparin versus UFH or enoxaparin versus fondaparinux (low SOE).
- There was a statistically significantly lower incidence of major bleeding at 30 days favoring fondaparinux over enoxaparin in the PCI cohort (moderate SOE).

Table F. Summary strength of evidence and effect estimates: enoxaparin versus unfractionated heparin versus fondaparinux (percutaneous coronary intervention cohort)

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Composite ischemic endpoints prior to 7 days	Enoxaparin vs. UFH: SOE = Low (1 RCT; 3,987 patients) HR 0.89 (0.75 to 1.05); no difference (adequately powered for noninferiority hypothesis)
	Fondaparinux vs. UFH: SOE = Insufficient (1 RCT; 350 patients) Insufficient evidence due to imprecision: 4.2% vs. 6%
Composite ischemic endpoints at 30 days	Enoxaparin vs. UFH: SOE = Low (2 RCTs; 10,773 patients) 14% vs. 14.5% and 14% vs. 16.1%; no difference Enoxaparin vs. fondaparinux: SOE = Low (1 RCT; 20,078 patients) 7.4% vs. 7.4%; no difference
Composite of all-cause mortality, nonfatal MI, or revascularization at 6 months	Enoxaparin vs. fondaparinux: SOE = Low (1 RCT; 20,078 patients) Enoxaparin 10.2% and fondaparinux 10.1%; no difference (adequately powered for noninferiority hypothesis)
Major bleeding at 30 days	Enoxaparin vs. UFH: SOE = Moderate (1 RCT; 10,027 patients) Lower event rates with UFH (7.6%) vs. enoxaparin (9.1%); favors UFH Enoxaparin vs. UFH: SOE = Low (2 observational studies; 29,017 patients) Lower event rates with enoxaparin (2.7% UFH vs. 1.8% enoxaparin; 7% UFH vs. 6.7% enoxaparin); favors enoxaparin Enoxaparin vs. fondaparinux: SOE = Moderate (1 RCT; 20,078 patients) Lower event rates with fondaparinux (3.1%) vs. enoxaparin (5.0%); p <0.001; favors fondaparinux

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence; UFH = unfractionated heparin

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

Key Points: Upstream or Deferred Clopidogrel for Patients Undergoing PCI for UA/NSTEMI in Studies With a Defined Anticoagulant or Intravenous Antiplatelet Strategy

- In patients pretreated with clopidogrel, there was no statistically significant difference in composite ischemic endpoints at 30 days between bivalirudin-treated patients and heparin-treated patients (low SOE).
- In both clopidogrel-pretreated and clopidogrel-deferred patients, bivalirudin resulted in fewer major bleeding events at 30 days than heparin-based treatment (moderate SOE for clopidogrel-pretreated patients and low SOE for clopidogrel-deferred patients).
- In both clopidogrel-pretreated and clopidogrel-deferred patients, deferred GPI use resulted in fewer major bleeding events at 30 days than upstream GPI use (moderate SOE for clopidogrel-pretreated patients and high SOE for clopidogrel-deferred patients).

Table G. Summary strength of evidence and effect estimates: clopidogrel upstream (pretreatment) and deferred treatment strategies

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Upstream Clopidogrel: Bivalirudin vs. Heparin-Based Strategy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Low (2 RCTs; 7,104 patients) Both studies showed no statistically significant difference in composite event rates ranging from OR 1.11 to 1.25; no difference
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Insufficient (1 RCT; 4,570 patients) Insufficient evidence due to imprecision: bivalirudin 21.5%, heparin 20.1%
All-cause mortality at 1 year	SOE = Insufficient (1 RCT; 5,126 patients) Insufficient evidence due to imprecision: bivalirudin 16.0%, heparin 16.3%
Major bleeding at 30 days	SOE = Moderate (3 RCTs; 6,322 patients) OR 0.65 (0.49 to 0.85); favors bivalirudin
Upstream Clopidogrel: Upstream vs. Deferred GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or thrombotic bailout with GPI at 96 hours	SOE = Insufficient (1 RCT; 6,895 patients) Insufficient evidence due to imprecision: upstream GPI 8.7%, deferred GPI 9.4%
Composite of all-cause mortality, nonfatal MI, or rehospitalization at 30 days	SOE = Insufficient (1 RCT; 300 patients) Insufficient evidence due to imprecision: upstream GPI 9%, deferred GPI 10%
Composite of all-cause mortality, nonfatal MI, or ischemia/ revascularization at 30 days	SOE = Low (2 RCTs; 638 patients) Upstream GPI 15.7%, deferred GPI 20.3%; favors upstream GPI
All-cause mortality at 30 days	SOE = Low (5 RCTs; 8,168 patients) OR 0.56 (0.30 to 1.05); favors upstream GPI
Major bleeding at 30 days	SOE = Moderate (5 RCTs; 7,416 patients) OR 1.49 (1.10 to 2.01); favors deferred GPI
Deferred Clopidogrel: Bivalirudin vs. Heparin-Based Strategy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (2 RCTs; 2,571 patients) Insufficient evidence due to inconsistency and imprecision: 1 RCT (fair) showed a significant reduction favoring bivalirudin, OR 0.42 (0.21 to 0.84; p = 0.02); the other RCT (good) showed no difference, OR 1.05 (0.80 to 1.40)
Major bleeding at 30 days	SOE = Low (2 RCTs; 2,571 patients) 1 RCT (fair) showed no statistical difference between the groups, OR 0.32 (0.10 to 1.01); the other RCT (good) showed a statistically significant reduction favoring bivalirudin, OR 0.53 (0.31 to 0.91, p = 0.02); favors bivalirudin
Deferred Clopidogrel: Upstream vs. Deferred GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or thrombotic bailout with GPI at 96 hours	SOE = Insufficient (1 RCT; 2,271 patients) Insufficient evidence due to imprecision: upstream GPI 10.3%, deferred GPI 11.2%
All-cause mortality at 30 days	SOE = Low (4 RCTs; 11,858 patients) OR 0.97 (0.80 to 1.18); no difference
Major bleeding at 30 days	SOE = High (3 RCTs; 11,698 patients) OR 1.27 (1.08 to 1.50); favors deferred GPI

CI = confidence interval; GPI = glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence; UFH = unfractionated heparin

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor bivalirudin or upstream GPI; ORs greater than 1 favor UFH or deferred GPI.

Key Question 2. Initial Conservative Approach for UA/NSTEMI

Thirty-three studies evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 225,891 patients with UA/NSTEMI treated with an initial conservative approach or a mixed population for whom the approach (conservative or invasive) was not presented separately. The following three comparisons were assessed in the included studies in KQ 2:

1. UFH versus enoxaparin or fondaparinux (full UA/NSTEMI cohort; KQ 2a)
    - 21 studies (12 RCTs, 9 observational; 161,506 total patients)
        - Enoxaparin versus UFH (10 RCTs, 4 observational; 24,567 patients)
        - Enoxaparin versus fondaparinux (1 RCT; 20,078 patients)
        - Fondaparinux versus UFH (1 RCT; 350 patients)
        - UFH versus low molecular weight heparin (either enoxaparin or fondaparinux; 4 observational; 56,152 patients)
        - Enoxaparin (normal dose) versus low- or high-dose enoxaparin (1 observational; 10,687 patients)
2. GPI plus UFH versus UFH alone (KQ 2b)
    - 10 studies (10 RCTs; 38,518 total patients)
3. Clopidogrel versus ticagrelor or prasugrel (initial conservative cohort; KQ 2b)
    - 2 studies (2 RCTs; 12,459 total patients)

For each comparison in KQ 2, we present the key points, followed by a table summarizing the SOE and estimates of the magnitude of effect (Tables H-J).

Key Points: UFH Versus Enoxaparin or Fondaparinux (Full UA/NSTEMI Cohort)

- Compared with UFH, enoxaparin treatment showed a significant reduction in composite ischemic events (high SOE) and nonfatal MI (moderate SOE) at around 30 days. There was no difference in all-cause mortality at 30 days (low SOE), but there was insufficient evidence to reach a conclusion on the comparative treatment effect on all-cause mortality and major bleeding at 30 days.
- Based on an indirect comparison of fondaparinux and UFH, there was a significant reduction in composite ischemic events (low SOE) and major bleeding (low SOE) at around 30 days favoring fondaparinux, but there was insufficient evidence to reach a conclusion on the comparative treatment effect on nonfatal MI or all-cause mortality.
- Observational studies within subgroups showed that the use of enoxaparin was associated with lower rates of ischemic events in obese patients, those with renal impairment, and those with ST depression on electrocardiography.

Table H. Summary strength of evidence and effect estimates: unfractionated heparin versus enoxaparin or fondaparinux (full UA/NSTEMI cohort)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Composite endpoint of all-cause mortality, nonfatal MI, revascularization, or recurrent ischemia at around 30 days	Enoxaparin vs. UFH: SOE = High (6 RCTs; 12,124 patients) OR 0.84 (0.76 to 0.93); favors enoxaparin Fondaparinux vs. UFH: SOE = Low (1 RCT; 20,078 patients) OR 0.78 (0.67 to 0.90); favors fondaparinux
Composite ischemic outcome at 6 months	Enoxaparin vs. fondaparinux: SOE = Low (1 RCT, 20,078 patients) 10.2% vs. 10.1% in large good-quality RCT adequately powered for a noninferiority hypothesis; no difference
All-cause mortality at around 30 days	Enoxaparin vs. UFH: SOE = Low (8 RCTs; 23,015 patients) OR 0.98 (0.84 to 1.14); no difference
	Fondaparinux vs. UFH: SOE = Insufficient (1 RCT; 20,078 patients) Insufficient evidence due to imprecision and indirect comparison: OR 0.93 (0.71 to 1.20)
Nonfatal MI at around 30 days	Enoxaparin vs. UFH: SOE = Moderate (9 RCTs; 22,970 patients) OR 0.85 (0.76 to 0.95); favors enoxaparin
	Fondaparinux vs. UFH: SOE = Insufficient (1 RCT; 20,078 patients) Insufficient evidence due to imprecision and indirect comparison: OR 0.85 (0.69 to 1.04)
Major bleeding at around 30 days	Enoxaparin vs. UFH: SOE = Insufficient (8 RCTs; 22,901 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.11 (0.81 to 1.51)
	Fondaparinux vs. UFH: SOE = Low (1 RCT; 20,078 patients) OR 0.69 (0.49 to 0.97); favors fondaparinux

CI = confidence interval; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non–ST elevation myocardial infarction; UFH = unfractionated heparin

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor enoxaparin or fondaparinux; ORs greater than 1 favor UFH.

Key Points: GPI Plus UFH Versus UFH Alone

- Adding a GPI to UFH reduced the rate of mortality at 30 days (high SOE) and reduced composite ischemic events and nonfatal MI (moderate SOE).
- There was insufficient evidence for the effect of GPIs on revascularization, although fewer events were seen in patients receiving GPIs in two small trials.
- While the use of GPIs reduces the rates of the adverse events mentioned above, the tradeoff is an increase in minor bleeding rates (high SOE). There was insufficient evidence on the effect of GPIs on major bleeding.

Table I. Summary strength of evidence and effect estimates: glycoprotein inhibitor plus unfractionated heparin versus unfractionated heparin alone

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Composite ischemic endpoints up to 30 days	SOE = Moderate (10 RCTs; 38,518 patients) Studies of eptifibatide and tirofiban showed a consistent reduction in composite events compared with UFH alone (RRs 0.58 to 0.84; favors eptifibatide or tirofiban); 1 large trial of abciximab showed no difference in events—24 hr OR 1.00 (CI 0.83 to 1.24); 48 hr OR 1.10 (CI 0.94 to 1.39); a small trial showed a reduction in major events with abciximab (1 out of 30) versus UFH alone (7 out of 30); favors GPI plus UFH
Mortality up to 30 days	SOE = High (9 RCTs; 24,699 patients) OR 0.80 (0.67 to 0.96); favors GPI plus UFH
Nonfatal MI up to 30 days	SOE = Moderate (9 RCTs; 24,699 patients) OR 0.79 (0.61 to 1.02); favors GPI plus UFH
Recurrent ischemia up to 30 days	SOE = Insufficient (6 RCTs; 5,755 patients) Insufficient evidence due to inconsistency and imprecision: OR 0.81 (0.56 to 1.18)
Revascularization up to 30 days	SOE = Insufficient (2 RCTs; 279 patients) Insufficient evidence due to imprecision; low number of events reported in both RCTs, with fewer in GPI plus UFH group
Major bleeding up to 30 days	SOE = Insufficient (4 RCTs; 18,855 patients) Insufficient evidence due to imprecision: OR 1.13 (0.80 to 1.59)
Minor bleeding up to 30 days	SOE = High (5 RCTs; 22,259 patients) OR 1.62 (1.20 to 2.19); favors heparin alone

CI = confidence interval; GPI = glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence; UFH = unfractionated heparin

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor GPI plus UFH; ORs greater than 1 favor UFH alone.

Key Points: Clopidogrel Versus Ticagrelor or Prasugrel (Initial Conservative Cohort)

- Ticagrelor reduced the rates of composite ischemic and all-cause mortality events; however, it also increased rates of major bleeding and the combination of major or minor bleeding events (moderate SOE) compared with clopidogrel at up to 30 months. There was no difference in revascularization at 12 months for this comparison (moderate SOE).
- Prasugrel showed similar rates of composite ischemic events, all-cause mortality, and nonfatal MI compared with clopidogrel (moderate SOE) at up to 30 months. There was insufficient evidence to support findings concerning stroke or major bleeding events for this comparison; however, there was low SOE that the combination of major or minor bleeding events up to 30 months was lower in the clopidogrel group.

Table J. Summary strength of evidence and effect estimates for UA/NSTEMI patients treated with clopidogrel versus ticagrelor or prasugrel (initial conservative cohort)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Composite ischemic endpoints up to 30 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) HR 0.85 (0.73 to 1.00); favors ticagrelor Prasugrel vs. clopidogrel: SOE = Moderate (1 RCT; 7,243 patients) HR 0.91 (0.79 to 1.05); no difference
Mortality up to 30 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) HR 0.75 (0.61 to 0.93); favors ticagrelor Prasugrel vs. clopidogrel: SOE = Moderate (1 RCT; 7,243 patients) HR 0.96 (0.79 to 1.16); no difference
Nonfatal MI up to 30 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) HR 0.94 (0.77 to 1.15); no difference Prasugrel vs. clopidogrel: SOE = Moderate (1 RCT; 7,243 patients) HR 0.89 (0.74 to 1.07); no difference
Stroke up to 30 months	Ticagrelor vs. clopidogrel: SOE = Insufficient (1 RCT; 5,216 patients) Insufficient evidence due to imprecision: HR 1.35 (0.89 to 2.07) Prasugrel vs. clopidogrel: SOE = Insufficient (1 RCT; 7,243 patients) Insufficient evidence due to imprecision: HR 0.67 (0.42 to 1.06)
Revascularization up to 12 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) No difference
Major bleeding up to 30 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) HR 1.17 (0.98 to 1.39); favors clopidogrel
	Prasugrel vs. clopidogrel: SOE = Insufficient (1 RCT; 7,243 patients) Insufficient evidence due to imprecision: HR 1.31 (0.81 to 2.11)
Major or minor bleeding up to 30 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) HR 1.17 (1.01 to 1.36); favors clopidogrel Prasugrel vs. clopidogrel: SOE = Low (1 RCT; 7,243 patients) HR 1.54 (1.06 to 2.23); favors clopidogrel

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non–ST elevation myocardial infarction

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]HRs less than 1 favor ticagrelor or prasugrel; HRs greater than 1 favor clopidogrel.

Key Question 3. Postdischarge Treatment for UA/NSTEMI

Seventy-one studies evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 693,025 patients with UA/NSTEMI continued on treatment after hospitalization (postdischarge). The following five comparisons were assessed in the included studies for KQ 3:

1. Low-dose versus high-dose aspirin (KQ 3a)
    - 6 studies (all observational; 60,904 total patients)
2. Single antiplatelet versus dual antiplatelet therapy (KQ 3a)

- 7 studies (1 RCT, 6 observational; 173,035 total patients)

3. Short-term versus long-term dual antiplatelet therapy (clopidogrel) (KQ 3a)
   - 11 studies (5 RCTs, 6 observational; 52,121 total patients)
4. Antiplatelet therapy with a PPI versus antiplatelet alone (KQ 3b)
   - 35 studies (4 RCTs, 30 observational; 340,559 total patients)
     - Dual antiplatelet with and without a PPI
     - Aspirin monotherapy with and without a PPI
5. Dual antiplatelet therapy alone versus dual antiplatelet plus oral anticoagulant (i.e., triple therapy) (KQ 3c)
   - 14 studies (all observational; 97,067 total patients)

For each comparison in KQ 3, we present the key points, followed by a table summarizing the SOE and estimates of the magnitude of effect (Tables K-O).

Key Points: Low-Dose Versus High-Dose Aspirin

- In the postdischarge setting, high-dose aspirin was associated with fewer nonfatal MIs and more major bleeding events than low-dose aspirin at 6 months (low SOE for both outcomes). Evidence for all other outcomes was insufficient.

Table K. Summary strength of evidence and effect estimates: low-dose versus high-dose aspirin

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Composite of all-cause mortality, nonfatal MI, or stroke at 6 months	SOE = Insufficient (1 observational study; 20,469 patients) Insufficient evidence due to CI that crosses 1: HR 0.92 (0.79 to 1.07)
Composite of all-cause mortality, nonfatal MI, or stroke at 1 year	SOE = Insufficient (2 observational studies; 31,186 patients) Insufficient evidence due to inconsistency and imprecision: 1 study showed similar rates of composite events across 3 dosage categories for aspirin monotherapy and DAPT; the other study showed lower event rates when combining low-dose aspirin with ticagrelor and high-dose aspirin with clopidogrel
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Insufficient (3 observational studies; 9,249 patients) Insufficient evidence due to imprecision: low-dose aspirin and high-dose aspirin had similar rates of ischemic events in all 3 studies
All-cause mortality at 6 months	SOE = Insufficient (1 observational study; 20,469 patients) Insufficient evidence due to imprecision: HR 0.89 (0.72 to 1.10)
All-cause mortality at 1 year	SOE = Insufficient (2 observational studies; 6,429 patients) Insufficient evidence due to inconsistency and imprecision: 1 study (aspirin/clopidogrel) showed no difference between doses; the other found that high-dose aspirin (monotherapy) reduced mortality
Nonfatal MI at 6 months	SOE = Low (1 observational study; 20,469 patients) HR 0.79 (0.64 to 0.98); favors high-dose aspirin
Nonfatal MI at 1 year	SOE = Insufficient (1 observational study; 4,589 patients) Insufficient evidence due to imprecision: HR 0.98 (0.66 to 1.48)
Stroke at 6 months	SOE = Insufficient (1 observational study; 20,469 patients) Insufficient evidence due to imprecision: HR 1.59 (0.95 to 2.65)

Table K. Summary strength of evidence and effect estimates: low-dose versus high-dose aspirin (continued)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Stroke at 1 year	SOE = Insufficient (1 observational study; 4,589 patients) Insufficient evidence due to imprecision: HR 1.37 (0.94 to 2.00)
Revascularization at 1 year	SOE = Insufficient (2 observational studies; 6,429 patients) Insufficient evidence due to inconsistency and imprecision: 1 study (aspirin/clopidogrel) showed no difference between doses; the other study (aspirin monotherapy) showed more events with high dose
Major bleeding at 1 year	SOE = Low (3 observational studies; 19,971 patients) 1 study had high bleeding rates in low-dose group; 2 studies had high bleeding rates in high-dose group; favors low-dose aspirin

CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; MI = myocardial infarction; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]HRs less than 1 favor high-dose aspirin; HRs greater than 1 favor low-dose aspirin.

Key Points: Single Antiplatelet Versus Dual Antiplatelet Therapy

- DAPT reduced the rates of composite ischemic outcomes and nonfatal MI compared with single antiplatelet therapy from in-hospital up to 1 year (high SOE).
- DAPT reduced all-cause mortality compared with single antiplatelet therapy from in-hospital up to 1 year (moderate SOE).

Table L. Summary strength of evidence and effect estimates: single antiplatelet versus dual antiplatelet therapy

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Composite ischemic endpoints, in-hospital to 1 year	SOE = High (1 RCT, 2 observational studies; 106,749 patients) All studies showed statistically significant lowering of composite events in DAPT arm, ranging from RR 0.69 to OR 0.80; favors DAPT
Stroke, in-hospital to 1 year	SOE = Insufficient (1 RCT, 3 observational studies; 116,136 patients) Insufficient evidence due to inconsistency and imprecision: 3 out of 4 studies showed no statistically significant difference in stroke rates
Nonfatal MI, in-hospital to 1 year	SOE = High (1 RCT, 2 observational studies; 106,749 patients) All studies showed fewer recurrent MIs in DAPT group (2.3% to 5.8%) vs. aspirin alone (3.0% to 8.5%); favors DAPT
All-cause mortality, in-hospital to 1 year	SOE = Moderate (1 RCT, 4 observational studies; 117,467 patients) All studies showed fewer deaths in DAPT group, ranging from OR/RR 0.66 to OR/RR 0.93; favors DAPT
Major bleeding, in-hospital to 9 months	SOE = Low (1 RCT, 1 observational study; 105,607 patients) 2 studies showed a reduction in major bleeding in DAPT group (1 statistically significant [16% vs. 21%]; 1 not statistically significant); favors DAPT

CI = confidence interval; DAPT = dual antiplatelet therapy; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

Key Points: Short-Term Versus Long-Term Dual Antiplatelet Therapy

- There was insufficient evidence for comparing short-term with long-term DAPT for composite ischemic events, all-cause mortality, cardiovascular mortality, nonfatal MI, stroke, revascularization, stent thrombosis, major bleeding, or minor bleeding. The findings were inconclusive because of heterogeneity of DAPT duration, timing of the endpoint measurement, and imprecision.

Table M. Summary strength of evidence and effect estimates: short-term versus long-term dual antiplatelet therapy

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Composite of all-cause mortality or nonfatal MI within 2 years	SOE = Insufficient (2 RCTs, 2 observational studies; 34,179 patients) Insufficient evidence due to heterogeneity of DAPT duration, inconsistency, and imprecision: 2 RCTs showed no difference between 6- and 12-month therapy and 6- and 24-month therapy; 1 observational study showed that discontinuation before 6 months increased events; 1 observational study showed increased events within first 3 months of stopping clopidogrel after 1 year of therapy
Composite of all-cause mortality or stroke at 2 years	SOE = Insufficient (1 RCT; 2,013 patients) Insufficient evidence due to imprecision: no difference between 6- and 24-month therapy
Composite of all-cause mortality, nonfatal MI, or revascularization at 6 months and 1 year	SOE = Insufficient (2 RCTs, 1 observational study; 4,701 patients) Insufficient evidence due to heterogeneity of DAPT duration and imprecision: both RCTs (1 month vs. 6 months and 6 months vs. 12 months) found similar rates between short- and long-term therapy; the observational study (<3 months vs. 6 months vs. >12 months) showed similar rates across treatment groups in both DES-treated and BMS-treated populations
Composite of all-cause mortality, nonfatal MI, stroke, or revascularization at 1 year	SOE = Insufficient (1 RCT; 1,443 patients) Insufficient evidence due to imprecision: no difference between 6- and 12-month therapy
Composite of all-cause mortality, nonfatal MI, or stroke at 6 months, 1 year, and 2 years	SOE = Insufficient (3 RCTs; 5,133 patients) Insufficient evidence due to heterogeneity of DAPT duration, inconsistency, and imprecision: 2 studies found significant reductions in events from long-term DAPT at 6 months and 1 year; 1 study found no difference between 6- and 24-month therapy
All-cause mortality at 6 months, 1 year, and 2 years	SOE = Insufficient (4 RCTs, 3 observational studies; 38,441 patients) Insufficient evidence due to heterogeneity of DAPT duration, inconsistency, and imprecision: 2 RCTs showed a reduction with longer therapy (1 month vs. 6 months) but 1 was statistically significant and the other was not; 1 RCT (6 months vs. 12 months) showed no difference; 1 observational study (<3 months vs. 6 months vs. >12 months) showed lower mortality in DES-treated patients receiving >12 months of therapy but no difference in the BMS-treated patients; 1 observational study found a higher rate of mortality in those who discontinued clopidogrel within the first 6 months; 1 observational study found a higher risk of death within the first 90 days of discontinuation after a 12-month treatment
Cardiovascular mortality at 6 months, 1 year, and 2 years	SOE = Insufficient (3 RCTs, 1 observational study; 33,728 patients) Insufficient evidence due to heterogeneity of DAPT duration, timing of endpoint measurement, and imprecision: all RCTs found similar rates between short- and long-term therapy (1 month vs. 6 months, 6 months vs. 12 months, and 6 months vs. 24 months); 1 observational study found no difference in CV mortality within the first 90 days of discontinuation after a 12-month treatment
Nonfatal MI at 6 months, 1 year, and 2 years	SOE = Insufficient (4 RCTs, 2 observational studies; 9,173 patients) Insufficient evidence due to imprecision: 5 studies (4 RCTs and 1 observational) showed similar rates of MI in short- and long-term therapy groups; 1 observational study showed statistically significant higher risk in DES patients who discontinued clopidogrel within first 6 months
Stroke at 6 months, 1 year, and 2 years	SOE = Insufficient (3 RCTs; 4,460 patients) Insufficient evidence due to imprecision: all RCTs (1 month vs. 6 months, 6 months vs. 12 months, and 6 months vs. 24 months) found similar rates between short- and long-term therapy, but heterogeneity of DAPT duration makes this inconclusive

Table M. Summary strength of evidence and effect estimates: short-term versus long-term dual antiplatelet therapy (continued)

Outcome and Timing	1. SOE[a] and Effect Estimate (95% CI)
Revascularization at 6 months and 1 year	SOE = Insufficient (3 RCTs, 1 observational study; 5,705 patients) Insufficient evidence due to imprecision: rates of revascularization were similar between short- and long-term therapy (1 month vs. 6 months and 6 months vs. 24 months)
Stent thrombosis at 6 months, 1 year, and 2 years	SOE = Insufficient (3 RCTs, 3 observational studies; 15,298 patients) Insufficient evidence due to heterogeneity of DAPT duration and imprecision: rates of stent thrombosis were higher when clopidogrel was stopped within 30 days or 6 months in 2 observational studies; 4 studies (3 RCTs and 1 observational) showed no statistically significant difference in event rates at 1 or 2 years
Major bleeding at 1 year and 2 years	SOE = Insufficient (3 RCTs; 5,572 patients) Insufficient evidence due to inconsistency and imprecision: 1 RCT (6 months vs. 24 months) showed a statistically significant lower rate of major bleeding with clopidogrel with 6-month treatment; the other 2 RCTs (1 month vs. 12 months and 6 months vs. 12 months) showed no statistically significant difference in rates with 1-year treatment
Minor bleeding at 1 year and 2 years	SOE = Insufficient (2 RCTs; 4,129 patients) Insufficient evidence due to imprecision: both RCTs (1 month vs. 12 months and 6 months vs. 24 months) found no difference at 1 and 2 years

BMS = bare metal stent; CI = confidence interval; CV = cardiovascular; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

Key Points: Antiplatelet Treatments With and Without Use of PPI

- In RCTs that evaluated the specific PPI omeprazole versus placebo and in observational studies assessing the use of diverse PPIs given in combination *with DAPT*, use of PPIs reduced rates of upper gastrointestinal bleeding (moderate SOE). However, use of PPIs was associated with higher rates of composite ischemic outcomes (death or MI) at 1 year (moderate SOE). There was low SOE that use of PPIs was associated with higher event rates for the following outcomes: composite ischemic events at 1 year, all-cause mortality at 6 years, nonfatal MI at 1 year, stroke at 1 year, revascularization at 1 year, stent thrombosis at 1 year, major bleeding at 1 year, and rehospitalization at 3 months. No difference between groups was seen for all-cause mortality at 1 year (moderate SOE) or revascularization at 6 months (low SOE)
- In observational studies assessing use of PPIs *with aspirin monotherapy*, there was a higher rate of nonfatal MI events and no difference in stroke events at 1 year in the group receiving any type of PPI (low SOE). These results are based on adjusted hazard ratios to reduce confounding due to patient and clinical characteristics; however, residual confounding cannot be excluded.
- There was insufficient evidence that the type of PPI affected any of the clinical outcomes (composite or individual) from subgroup analyses of observational studies.

Table N. Summary strength of evidence and effect estimates: antiplatelet therapies with and without proton pump inhibitor

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Dual Antiplatelet Therapy With and Without PPI[b]	
Composite ischemic endpoints at about 1 year	SOE = Low (2 RCTs, 21 observational studies; 272,311 patients) RCTs of omeprazole showed no difference; however, meta-analysis of observational studies of any PPI showed adj HR 1.35 (1.18 to 1.54), which favors no PPI. The discrepancy between the RCTs and the observational studies makes it difficult to draw a firm conclusion about the effect.
Composite of all-cause mortality or MI at about 1 year	SOE = Moderate (3 observational studies; 60,389 patients) Adj HR 1.27 (1.12 to 1.43); favors no PPI
All-cause mortality within first 3 months	SOE = Insufficient (3 observational studies; 8,943 patients) Insufficient evidence due to inconsistency and imprecision: 2 studies showed no differences in mortality rates; 1 study showed a statistically significant increase in mortality in PPI group, adj HR 2.2 (1.1 to 4.3)
All-cause mortality at about 1 year	SOE = Moderate (2 RCTs, 18 observational studies; 264,172 patients) RCTs of omeprazole showed no difference or favored omeprazole, and the meta-analysis of observational studies of any PPI showed adj HR 1.17 (0.92 to 1.48); no difference
All-cause mortality at 6 years	SOE = Low (1 observational study; 23,200 patients) Adj HR 1.32 (1.00 to 1.73); favors no PPI
Cardiovascular mortality at 1 year	SOE = Insufficient (3 observational studies; 76,184 patients) Insufficient evidence due to inconsistency and imprecision: 2 out of 3 studies showed statistically significant increase in CV mortality in PPI group
Nonfatal MI within first 3 months	SOE = Insufficient (3 observational studies; 8,943 patients) Insufficient evidence due to inconsistency and imprecision: 2 studies showed no statistically significant difference in MI rates; 1 study showed statistically significant increase in MI events in PPI group
Nonfatal MI at about 1 year	SOE = Low (1 RCT, 11 observational studies; 225,687 patients) The RCT and observational study of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.33 (1.15 to 1.55), which favors no PPI. The discrepancy between the omeprazole studies and the observational studies of any PPI makes it difficult to draw a firm conclusion about the effect.
Stroke at about 1 year	SOE = Low (2 RCTs, 5 observational studies; 165,212 patients) RCTs of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.49 (1.20 to 1.84), which favors no PPI. The discrepancy between the RCTs and the observational studies makes it difficult to draw a firm conclusion about the effect.
Revascularization at 6 months	SOE = Low (1 RCT, 1 observational study; 22,326 patients) Both studies showed no difference in revascularization rates; no difference
Revascularization at 1 year	SOE = Low (5 observational studies; 53,164 patients) Observational study of omeprazole showed no difference; meta-analysis of observational studies of any PPI showed adj OR 1.48 (1.21 to 1.82); favors no PPI
Revascularization at 4 years	SOE = Insufficient (1 observational study; 315 patients) Insufficient evidence due to imprecision; no statistically significant difference in revascularization rate between groups
Stent thrombosis at 30 days	SOE = Insufficient (1 observational study; 3,408 patients) Insufficient evidence due to imprecision: no statistically significant difference in stent thrombosis rate between groups
Stent thrombosis at about 1 year	SOE = Low (1 RCT, 7 observational studies; 45,198 patients) The RCT and observational study of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.34 (1.17 to 1.55), which favors no PPI. The discrepancy between the RCT and the observational studies makes it difficult to draw a firm conclusion about the effect.

Table N. Summary strength of evidence and effect estimates: antiplatelet therapies with and without proton pump inhibitor (continued)

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Dual Antiplatelet Therapy With and Without PPI[b] *(continued)*	
Major bleeding at 30 days	SOE = Insufficient (3 observational studies; 7,498 patients) Insufficient evidence due to inconsistency and imprecision: adj HR 1.73 (0.61 to 4.88)
Major bleeding at about 1 year	SOE = Low (4 observational studies; 36,231 patients) Adj HR 1.26 (1.12 to 1.41); favors no PPI
GI bleeding	SOE = Moderate (4 RCTS, 4 observational studies; 28,032 patients) 3 out of 4 RCTs of omeprazole and 2 out of 4 observational studies of any PPI showed statistically significant lower rates of GI bleed in the PPI group; favors PPI
Minor bleeding	SOE = Insufficient (1 observational study; 1,346 patients) Insufficient evidence due to imprecision: no difference in minor bleed in-hospital or at 1 year
Rehospitalization at 3 months	SOE = Low (1 observational study; 5,862 patients) Significant increase in rehospitalization in PPI group at 3 months; adj HR 1.32 (1.00 to 1.73); favors no PPI
Rehospitalization at about 1 year	SOE = Insufficient (4 observational studies; 16,925 patients) Insufficient due to inconsistency and imprecision: adj HR 1.70 (0.86 to 3.34)
Aspirin Monotherapy With and Without PPI[b]	
Composite of CV death, nonfatal MI, or stroke at 1 year	SOE = Insufficient (2 observational studies; 52,196 patients) Insufficient evidence due to inconsistency: 1 study reported increased risk among PPI group (adj HR 1.61 [1.45 to 1.79]), while the other study showed no difference (adj HR 1.00 [0.88 to 1.15])
All-cause mortality (in-hospital)	SOE = Insufficient (1 observational study; 2,744 patients) Insufficient evidence due to imprecision: adj OR 0.96 (0.49 to 1.88)
All-cause mortality at 1 year	SOE = Insufficient (2 observational studies; 52,196 patients) Insufficient evidence due to imprecision: 1 study reported increased risk among PPI group (adj HR 2.38 [2.12 to 2.67]), while the other study showed no difference (adj HR 0.99 [0.86 to 1.14])
Nonfatal MI (in-hospital)	SOE = Insufficient (1 observational study; 2,744 patients) Insufficient evidence due to imprecision: adj HR 1.50 (0.41 to 5.43)
Nonfatal MI at 1 year	SOE = Low (1 observational study; 49,452 patients) Adj HR 1.33 (1.13 to 1.56); favors no PPI
Stroke (in-hospital)	SOE = Insufficient (1 observational study; 2,744 patients) Insufficient evidence due to imprecision: adj HR 0.75 (0.11 to 4.85)
Stroke at 1 year	SOE = Low (2 observational studies; 52,196 patients) Both studies showed no difference, adj HR 1.20 (0.99 to 1.46) and adj HR 0.75 (0.11 to 4.85); no difference
Major bleeding (in-hospital)	SOE = Insufficient (1 observational study; 2,744 patients) Insufficient evidence due to imprecision: adj OR 1.30 (0.38 to 4.39)

adj = adjusted; CI = confidence interval; CV = cardiovascular; GI = gastrointestinal; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; PPI = proton pump inhibitor; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor PPI use; ORs greater than 1 favor no PPI use.

Key Points: Dual Antiplatelet Versus Triple Therapy

- DAPT reduced rates of nonfatal MI and major bleeding at 1 to 5 years, and triple therapy (dual antiplatelet plus anticoagulant) reduced rates of stroke at 6 months (low SOE). The findings for all other clinical endpoints were rated insufficient SOE due to inconsistency, imprecision of results, or both.

Table O. Summary strength of evidence and effect estimates: dual antiplatelet versus triple therapy[a]

Outcome and Timing	SOE[b] and Effect Estimate[c] (95% CI)
Composite of all-cause mortality, nonfatal MI, revascularization, or stroke at 1 year or more	SOE = Insufficient (4 observational studies; 8,509 patients) Insufficient evidence due to inconsistency and imprecision: 2 studies showed statistically nonsignificant differences; 2 studies showed statistically significant increases in events in DAPT group
Composite of all-cause mortality or nonfatal MI within first year	SOE = Insufficient (4 observational studies; 57,144 patients) Insufficient evidence due to inconsistency and imprecision: 1 study showed a statistically significant increase, 1 statistically significant decrease in the triple therapy group, and 2 studies showed statistically nonsignificant difference in events between the DAPT and triple therapy
All-cause mortality at 30 days to 6 months	SOE = Insufficient (2 observational studies; 7,075 patients) Insufficient evidence due to inconsistency and imprecision: 1 study found no difference, another found statistically significantly lower deaths in triple therapy group
All-cause mortality at 1 to 5 years	SOE = Insufficient (8 observational studies; 41,192 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.03 (0.59 to 1.83)
Nonfatal MI at 6 months	SOE = Insufficient (1 observational study; 800 patients) Insufficient evidence due to unknown precision: triple therapy 3.3%; warfarin/aspirin 4.5% (p = 0.49)
Nonfatal MI at 1 to 5 years	SOE = Low (4 observational studies; 1,425 patients) OR 1.85 (1.13 to 3.02); favors DAPT
Stroke at 6 months	SOE = Low (1 observational study; 800 patients) Triple therapy 0.7%; warfarin/aspirin 3.4% (p = 0.02); favors triple therapy
Stroke at 1 to 5 years	SOE = Insufficient (4 observational studies; 6,485 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.01 (0.59 to 2.67)
Revascularization up to 5 years	SOE = Insufficient (4 observational studies; 2,066 patients) Insufficient evidence due to imprecision: no statistical difference between DAPT and triple therapy groups
Major bleeding at 30 days	SOE = Insufficient (5 observational studies; 11,095 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.70 (0.88 to 3.30)
Major bleeding at 1 to 5 years	SOE = Low (7 observational studies; 38,398 patients) OR 1.46 (1.07 to 2.00); favors DAPT
Minor bleeding at 1 to 5 years	SOE = Insufficient (3 observational studies; 890 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.33 (0.48 to 3.69)
Major and minor bleeding	SOE = Insufficient (2 observational studies; 21,545 patients) Insufficient evidence due to imprecision: both studies failed to show a difference between DAPT and triple therapy in the combined endpoint of major and minor bleeding
Stent thrombosis	SOE = Insufficient (2 observational studies; 840 patients) Insufficient evidence due to inconsistency and imprecision: no significant difference in rates (triple therapy 1.4% to 4.1%; dual antiplatelet 1.3% to 3.6%)

CI = confidence interval; DAPT = dual antiplatelet therapy; MI = myocardial infarction; OR = odds ratio; SOE = strength of evidence

[a]Triple therapy refers to aspirin plus antiplatelet plus anticoagulant.

[b]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[c]ORs less than 1 favor triple therapy; ORs greater than 1 favor DAPT.

Discussion

Key Findings

In this Comparative Effectiveness Review, we reviewed 175 studies represented by 302 articles that directly compared antiplatelet and anticoagulant medications prescribed for the treatment of UA/NSTEMI. We included 87 unique studies with 354,511 patients treated with an early invasive approach or PCI-based strategy, 33 unique studies with 209,231 patients treated with an initial conservative strategy, and 71 unique studies with 693,025 patients continued on treatment after hospitalization (postdischarge). One of the main challenges in this report was that studies were not easily grouped into the early invasive, initial conservative, or postdischarge strategies. The current evidence base was greatest for the comparative safety and effectiveness of GPIs, UFH, enoxaparin, and DAPT with clopidogrel. Numerous uncertainties remain about the use of newer antiplatelets (e.g., ticagrelor, prasugrel) and newer anticoagulants (e.g., fondaparinux, bivalirudin), as well as the related use of older and newer therapies on specific patient populations of interest.

For KQ 1, which addresses the use of antiplatelet and anticoagulant therapy in UA/NSTEMI patients treated with an early invasive or PCI-based strategy, our findings are consistent with those of previously published guidelines and meta-analyses in many respects. Many large RCTs (including EARLY-ACS, CURRENT-OASIS 7, PLATO, and TRITON-TIMI 38) have impacted our comparisons, and these studies were incorporated into the recent American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines update. Our major findings mirror those of other meta-analyses in that upstream GPI use was not associated with a significant reduction in ischemic endpoints, the optimal loading dose of clopidogrel remains unclear, and prasugrel was associated with a significant reduction in ischemic endpoints compared with clopidogrel. One new finding from this report is that upstream GPI use was associated with lower rates of revascularization, but the tradeoff was a higher risk of major bleeding at 30 days.

Our review expands on what is known about one of the newer antiplatelets: ticagrelor. Based on two new RCTs, ticagrelor was associated with a significant reduction in ischemic endpoints compared with clopidogrel at 1 year, but unlike the case with prasugrel, the incidence of major bleeding was not significantly higher in ticagrelor-treated patients.

There was a paucity of data on the optimal timing of oral antiplatelet agents as initial treatment for UA/NSTEMI, since the four previous studies (two RCTs, two observational studies) contained a mixture of non-ACS and ACS patients, and the use of anticoagulants (bivalirudin or UFH) and IV antiplatelets (upstream or deferred GPI) was not well defined. Thus, we analyzed the subgroup results of patients receiving either clopidogrel pretreatment or clopidogrel treatment at the time of PCI from randomized trials of (1) bivalirudin versus heparin-based strategy and (2) upstream GPI use versus deferred GPI use. These studies confirmed that in patients pretreated with clopidogrel, the use of bivalirudin at the time of PCI was associated with less major bleeding than a heparin-based strategy. In patients pretreated with clopidogrel, the use of deferred GPI was associated with higher rates of ischemic endpoints (all-cause mortality, nonfatal MI, ischemia, revascularization) and lower rates of major bleeding at 30 days than the use of upstream GPI was. In patients treated with clopidogrel at the time of PCI there was less major bleeding at 30 days with the use of deferred GPI.

For KQ 2, which addresses antiplatelet and anticoagulant treatment in patients undergoing an initial conservative approach for treating UA/NSTEMI, our findings were concordant with the

recently published ACCF/AHA guideline recommendations. A direct comparison of enoxaparin and UFH showed a significantly lower incidence of composite ischemic endpoints, mostly driven by nonfatal MI reduction, among patients receiving enoxaparin, with no difference in the rate of major bleeding. An indirect comparison of fondaparinux and UFH showed significant reductions in composite ischemic events and major bleeding favoring fondaparinux. These results, based mostly on RCTs and supported by observational studies, are consistent with guideline recommendations of initial anticoagulant treatment among UA/NSTEMI patients undergoing an initial conservative approach, in which all three anticoagulants are recommended but with indication of a preferable option for enoxaparin and fondaparinux.

Our findings on the effectiveness and safety of GPIs when administered with UFH compared with UFH alone have shown that the use of tirofiban or eptifibatide reduced the rate of composite ischemic events, mortality, nonfatal MI, and recurrent ischemia. The administration of abciximab with UFH did not significantly reduce ischemic events compared with UFH alone. Use of GPIs increased the rates of major and minor bleeding. Data gained from these studies are more challenging to extrapolate and implement in the context of actual clinical practice because the majority were performed before an early invasive strategy was widely implemented, and they employed an initial conservative strategy followed by percutaneous revascularization after 18 to 72 hours. Further, several GPI studies reported results from a combination of treatment approaches (both invasive and medically managed), and the proportion of patients receiving percutaneous revascularization ranged widely. Lastly, the treatment approach seems to vary by country, with greater use of conservative, medically managed approaches in countries with less access to cardiac catheterization laboratories than in more developed countries.

Current ACCF/AHA UA/NSTEMI guidelines recommend adding a GPI (tirofiban or eptifibatide) to patients who were initially treated conservatively but then required diagnostic angiography due to an increase or new onset of symptoms (class I recommendation, level of evidence A). These guidelines, including the recently published update,[21] show no change in the recommendation of administering a GPI (tirofiban or eptifibatide) in addition to an anticoagulant or oral antiplatelet for patients for whom an initial conservative strategy is selected (class IIb, level of evidence B). At the same time, they recommend withholding a GPI if patients are clinically stable; if, after angiography, a percutaneous revascularization is deemed not necessary; or if they do not undergo diagnostic angiography (class IIa, level of evidence C). These recommendations may require modification, since our analysis shows that newer, smaller studies and the use of DAPT in the conservatively managed population resulted in summary estimates that were more favorable for GPI plus UFH.

For KQ 3, which addresses antiplatelet and anticoagulant treatment after hospital discharge in patients with UA/NSTEMI, our findings are mostly consistent with recently published guidelines. We found conflicting results on aspirin dosing due to different dosing comparisons and a paucity of studies. Comparison of single antiplatelet therapy versus DAPT supported current recommendations, with evidence of better outcomes among patients treated with DAPT.

Effect of clopidogrel duration was assessed in nine studies; however, because of differences in the comparison of duration of treatment and outcomes that were assessed, a meta-analysis was not performed and only a qualitative assessment was possible. Significant differences in outcomes were observed when clopidogrel was discontinued early after discharge, and no differences in outcomes were observed when treatment comparisons were greater than 6 months. Only two studies looked at treatment effect based on stent type, and again the worst outcomes were observed among patients with either bare metal or drug-eluting stents who discontinued

clopidogrel (either stopped taking it or were taken off it by their doctor) within the first 6 months. Guidelines recommend a treatment duration of 1 year if there is no increased risk of bleeding. Our findings support the recommendation not to treat beyond 1 year; however, there is uncertainty about whether discontinuation at an earlier time point (between 6 and 12 months) could be safely done, since the data are not clear about when exactly the benefit fades.

In our analysis of the use of PPIs with dual antiplatelet therapies, meta-analyses using adjusted or propensity-scored hazard ratios from observational studies showed an association between PPI use (any type) and increased rates of composite ischemic endpoints, death, nonfatal MI, stroke, revascularization, stent thrombosis, and major bleeding. We downgraded the SOE ratings, since the findings from observational studies conflicted with the few randomized trials of omeprazole. We cannot exclude the possibility of residual confounding in the observational studies, despite the adjustment for comorbid illness and other clinical factors. A recent update of the ACCF/AHA guidelines has removed the recommendation to administer PPIs among patients with a history of gastrointestinal bleeding and instead suggests that health care providers reevaluate the need for starting or continuing PPI treatment in patients taking clopidogrel. Their statement does not prohibit the use of PPI agents in appropriate clinical settings; however, they describe the potential risks and benefits from use of PPI agents in combination with clopidogrel. Our findings support a cautious approach to PPI use with DAPT therapy in UA/NSTEMI patients.

Finally, we assessed the use of triple therapy (dual antiplatelet plus anticoagulation) and found low SOE that nonfatal MI and major bleeding rates were higher and stroke rates were lower with triple therapy than with DAPT. However, the findings for all other endpoints were rated insufficient due to either inconsistency or imprecision of results, or both, making it impossible to reach a firm conclusion. The current ACCF/AHA guidelines give a class I recommendation that warfarin in combination with aspirin or DAPT is associated with an increased risk of bleeding and a class IIb recommendation that targeting oral anticoagulant therapy to a lower international normalized ratio (INR) (e.g., 2.0 to 2.5) is reasonable in patients managed with DAPT due to inconsistency and imprecision of existing data for this comparison.

Applicability

Studies included in this review were primarily multicenter international studies that included the United States and Canada, so the applicability of our findings spans multiple geographic locations. While many studies were conducted outside the United States, there are similarities in UA/NSTEMI treatments internationally and this should therefore not be seen as a limitation in treatment setting. However, two main factors limit our findings: population and intervention.

First, in order to have adequate numbers of citations to address the safety and effectiveness of antiplatelet and anticoagulant therapies in UA/NSTEMI patients, we had to broaden our eligible patient population to include studies of either UA/NSTEMI or ACS (STEMI, NSTEMI, and UA). In addition, some antiplatelet and anticoagulant studies included ACS and stable angina populations. To improve the applicability of our findings to the UA/NSTEMI population, we excluded studies that focused exclusively on the STEMI or stable angina population.

Second, due to a change in terminology regarding treatment approach (i.e., early invasive strategy and initial conservative strategy), we had to make an assumption that trials that discouraged coronary angiography or PCI in the early phase of MI treatment could be labeled as a conservatively managed approach. Many of those types of studies are older (mid-1990s) or

were conducted in non-U.S. settings. We did not find any limits to applicability regarding the comparisons or outcomes reported.

Implications for Clinical and Policy Decisionmaking

More than one million patients in the United States are treated for UA/NSTEMI each year. Ischemic heart disease has remained a leading cause of death in the United States despite major advances in cardiovascular care over the past decade. Due to the prevalence, associated morbidity and mortality, cost, and multiple effective treatment options for UA/NSTEMI patients, this Comparative Effectiveness Review provides important information to guide both future research and clinical and policy decisionmaking.

Regarding the invasive treatment strategy in UA/NSTEMI patients, this review found that several therapies were effective at improving ischemic endpoints while minimizing bleeding endpoints. Two new antiplatelet medications (prasugrel and ticagrelor) were superior to clopidogrel in terms of reduction of ischemic endpoints, but the cost-effectiveness of these novel agents is not currently known because generic formulations of clopidogrel have recently become available in the United States. Additionally, due to the different pharmacokinetic and pharmacodynamic properties of these novel agents, their effectiveness may differ when studying the combination of strategies that were compared in this review (i.e., upstream GPI vs. deferred GPI, bivalirudin vs. heparin, timing of $P2Y_{12}$ administration). Further study is needed to determine the effectiveness and safety of these newer agents in these specific contexts.

Regarding the conservative management approach, in our review of observational studies we found a growing use of low molecular weight heparin (i.e., enoxaparin) based on evidence of better effectiveness and similar bleeding rates compared with UFH. The effectiveness of fondaparinux in comparison with enoxaparin requires further study; however, our indirect analysis provides preliminary evidence that fondaparinux also reduces composite ischemic events and does not increase the risk of bleeding compared with UFH. Our review shows that the administration of GPI in the conservatively managed population is beneficial; however, newer ACCF/AHA guideline recommendations suggest that GPIs should be administered only prior to PCI or for recurrent symptoms. The guideline recommendation is primarily based on findings in the invasively managed population (presented for KQ 1) and not specifically on the findings from the conservatively managed population.

For the postdischarge setting, the optimal aspirin dose to use with clopidogrel for DAPT is uncertain; however, it is clear that DAPT is beneficial in reducing future ischemic events compared with single antiplatelet therapy and that treatment durations of 6 months to 1 year are better than shorter durations of therapy. Our findings support a cautious approach to PPI use with DAPT therapy in UA/NSTEMI patients, given the higher number of ischemic events in patients who receive a PPI. Finally, our analysis of observational studies of DAPT and triple therapy in patients with a long-term indication for warfarin shows inconsistent and insufficient evidence for the impact on ischemic events; however, bleeding events are increased with triple therapy. Further study on aspirin dosing with DAPT, the role of newer antiplatelet agents (prasugrel, ticagrelor), and newer anticoagulants (dabigatran, rivaroxaban, and apixaban) for triple therapy are needed.

Limitations of the Review Process

The current review was limited to English-language studies and focused on those that directly compared various antiplatelet and anticoagulation agents, either individually or in

combination. Any studies that reported noncomparative findings, such as a study assessing the outcomes of patients treated with one antiplatelet or anticoagulant agent over time without a control or comparator group, were excluded. However, it is unlikely that these studies would have provided substantial additional information, given the quality and SOE of the studies reviewed.

For most of the comparisons, a quantitative analysis of composite ischemic endpoints was challenging to conduct, given the different composite endpoint definitions. In some comparisons, we pooled the studies for the most frequently reported composite, but this resulted in excluding relevant studies with a different composite endpoint definition. In some comparisons, the number of studies for each composite endpoint definition was too small to put into a meta-analysis model. Another option is to pool studies with composite endpoints that are essentially similar (e.g., 2 out of 3 of the components are the same, with the event rates of the third component reasonably similar to each other). For some studies, we treated total mortality and cardiovascular mortality as essentially similar, since the event rates of cardiovascular mortality usually dominate the event rates for total mortality.

Related to the variations in the composite ischemic endpoint definition outlined above, there was also heterogeneity in the individual endpoint definitions (e.g., MI, stroke, bleeding) and how these endpoints were reported within the published literature. We were not able to focus on the nuances in the endpoint definitions but instead relied on the study authors' definitions. This is another limitation of the review process, which can be resolved with further standardization of outcome definitions and reporting.

A final limitation of this review is the separation of the effectiveness and safety outcomes in our analyses. We did not conduct an analysis of the net benefit (i.e., assessing the effectiveness while accounting for the risk of these therapies). Very few studies reported the net benefit of their interventions. Further, a calculation of net benefit across studies may not be robust since often there was heterogeneity in the composite endpoint definition, and pooling in order to combine individual outcomes into a standard composite benefit may have overestimated the number of events if patients experienced more than one individual outcome. We also did not assess for consistency in endpoint definitions across studies, assuming that the differences between studies and any definition changes over time were minimal. Bleeding definitions were also variable across studies. In our analyses of bleeding definitions we used TIMI (thrombolysis in myocardial infarction) criteria when they were reported; otherwise, we accepted the study definition of a major and minor bleed.

Limitations of the Evidence Base

The main limitation was the change in terminology regarding treatment approach (i.e., early invasive strategy and initial conservative strategy) in the early 2000s. There is no MeSH search term for these types of treatment approaches; thus, it was difficult to group studies and patient populations into an early invasive treatment or initial conservative strategy. Some studies included both early invasive and early conservative treatment approaches, and some studies did not report which treatment approach was used. Fortunately, newer publications are starting to report findings by treatment approach, so future evidence reviews will benefit from further specification. However, in clinical practice the treatment approach for a UA/NSTEMI patient may not always be determined before the pharmacologic therapy is selected. For this review, we tried to separate the early invasive and initial conservative studies into a PCI-based strategy and a medically managed strategy. This led to some overlap in the comparisons of enoxaparin, UFH,

and fondaparinux in both the KQ 1 and KQ 2 sections of this report. Another limitation was the patient population enrolled in these antiplatelet and anticoagulant studies. While the focus of this review was the UA/NSTEMI population, we found a lower proportion of studies (about 35%) that solely enrolled UA/NSTEMI patients. Instead, the majority of studies (65%) contained a mixed population of ACS patients, including UA/NSTEMI and STEMI patients. Also, improvements in diagnostic testing have altered the definition and classification of MI and UA over time, thus leading to variations in these definitions across studies.

Important limitations of the literature across the KQs include: (1) few studies that assess long-term clinical outcomes for both ischemic and bleeding events, (2) few studies in specific patient subgroups of interest, and (3) few studies that looked at combinations of antiplatelet and anticoagulant treatments, specifically dosage, timing, and duration of these combinations.

Research Gaps

Acute coronary syndromes, including UA/NSTEMI, are widely studied, as evidenced by our screening of over 20,000 abstracts to identify 290 articles (166 studies) of antiplatelet and anticoagulant agents. In our review, we found research gaps involving both established and newer therapies, particularly related to the comparative effectiveness of these treatments; issues related to dosage, timing, and type of administration (IV or oral), and combinations of therapy. We used the framework recommended by Robinson et al.[22] to identify gaps in evidence and describe the reasons why these gaps exist. This approach considers PICOTS criteria to classify gaps as due to (1) insufficient or imprecise information, (2) biased information, (3) inconsistency or unknown consistency, and (4) not the right information. Results are presented for each KQ.

Across all KQs, we found a gap in reporting of racial and ethnic demographics of study participants. Future studies should take care to report the comparative effectiveness and safety of antiplatelet and anticoagulant treatment regimens in racial and ethnic subpopulations as well as summary population effects.

Key Question 1

In KQ 1, the primary research gap was the lack of direct comparisons of IV and oral combination treatment strategies. While many studies investigated the use of one oral antiplatelet versus another oral antiplatelet, there were scant data on combinations of antiplatelet and anticoagulant medications used for UA/NSTEMI patients. In addition, there is a paucity of evidence surrounding the optimal timing and administration of these antiplatelet and anticoagulant medications when used in combination for patients with UA/NSTEMI. Our review highlights the need for future studies to compare novel antiplatelet agents (ticagrelor, prasugrel) in a head-to-head manner. In clinical practice, the use of bleeding-avoidance strategies has prompted many clinicians to avoid the use of GPI while using clopidogrel pretreatment and bivalirudin at the time of PCI. Validation of the use of these medications in combination when compared with the use of GPI is needed. Further, given the importance of reducing ischemic events and bleeding events, a gap was present, as no included studies measured the effect of specific strategies to reduce bleeding (i.e., radial artery access, vascular closure devices).

Key Question 2

In KQ 2, the primary research gap is reporting safety and effectiveness among the subgroup of conservatively managed patients within trials or observational studies of mixed treatment

approaches. We found only a couple of studies presenting subgroup analysis by medically managed patients for both the low molecular weight heparin and GPI analyses—and often the data were not concordant. Future studies can address this either by stratification of the antiplatelet or anticoagulant therapy by treatment approach (invasive or conservative) or by reporting the subgroup findings for the conservatively managed population within a larger trial or observational study.

Key Question 3

In KQ 3, there were many research gaps. First, more studies assessing the optimal loading and maintenance dose of aspirin are needed, since our review found heterogeneity in the definitions of low- and high-dose aspirin. In addition, the optimal dose of aspirin within a DAPT strategy requires further study, especially within subgroups of patients at risk for bleeding complications.

Second, more randomized trials are needed on clopidogrel duration up to and beyond 1 year of ongoing treatment. There were few RCTs on this subject, and the small number of observational studies showed no difference in clinical outcomes when assessing 6-month versus longer treatment durations. While published literature has shown that early discontinuation of DAPT (within 3 months, 6 months, or 1 year) is associated with a poorer clinical outcome, the need for treatment beyond 1 year is still uncertain. Also, as stated above in the KQ 1 research gaps, the duration of new antiplatelet agents (prasugrel and ticagrelor) in combination with aspirin requires further study, as does the comparative effectiveness of use of these agents based on the type of stent used during PCI.

Third, observational studies have concluded that concomitant PPI treatment is related to worse clinical outcomes, while RCTs of one specific PPI (omeprazole) showed no effect. This suggests that the observational studies are confounded by comorbid conditions (i.e., selection bias). It is unclear whether genetic resistance to clopidogrel is a causal factor or whether the negative interaction is drug or class specific, since those variables were not included in the studies we reviewed. Further research, preferably additional RCTs of specific PPIs compared with each other or prospective propensity-score–matched cohort studies, is warranted on whether the detrimental effect of PPIs is due to comorbid conditions of the patient population, type of PPI, or genetic predisposition for reduced clopidogrel sensitivity.

The final research gap for KQ 3 is the limited and inconsistent data on long-term anticoagulant therapy. Further study on aspirin dosing with DAPT, the role of newer antiplatelet agents (prasugrel, ticagrelor), and newer anticoagulants (dabigatran, rivaroxaban, and apixaban) for triple therapy are needed.

Conclusions

- Overall, the administration of GPIs prior to PCI is associated with a reduction in revascularization rates but an increase in major bleeding events, regardless of whether clopidogrel is administered prior to or during the PCI.
- Prasugrel reduces rates of composite ischemic events (death, MI, or stroke) at 30 days and 1 year, but also results in an increase in major bleeding events at 1 year in comparison with clopidogrel. Ticagrelor reduces rates of composite ischemic events but has similar rates of major bleeding at 1 year compared with clopidogrel.

- Bivalirudin is associated with a lower incidence of major bleeding events compared with heparin-based treatment, regardless of whether a GPI administration is planned. Bivalirudin also reduces rates of minor bleeding events compared with heparin with GPI use.
- Enoxaparin and fondaparinux are associated with a significant reduction in composite ischemic events when compared with UFH in a conservatively managed population.
- Dual antiplatelet therapy of 6 months to 1 year reduces the rates of composite ischemic outcomes and nonfatal MI; however, the optimal dose of aspirin in combination with clopidogrel is less certain.
- While PPIs have been associated with worse clinical outcomes compared with no PPI use in observational studies, the results from a small number of RCTs of omeprazole show no significant difference in clinical events compared with placebo. Therefore PPIs should be used with caution in patients receiving clopidogrel with aspirin (DAPT).

Although we identified many citations, the number of studies for each comparison was relatively small, and the preponderance of observational studies in some of the comparisons made the findings less conclusive. To improve the findings of this report, more good-quality studies (both RCTs and observational) of antiplatelet and anticoagulant treatments are required. Uncertainty remains about the optimal dosing, timing, duration, and combinations of many of the options. This uncertainty is seen especially in subpopulations of interest (e.g., the elderly, patients with diabetes, women, obese patients, and those with comorbid illness).

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Glossary

ACCF/AHA	American College of Cardiology Foundation/American Heart Association
ACS	acute coronary syndrome
AHRQ	Agency for Healthcare Research and Quality
CI	confidence interval
DAPT	dual antiplatelet therapy
GPI	glycoprotein IIb/IIIa inhibitor
INR	international normalized ratio
IV	intravenous
KQ	Key Question
MI	myocardial infarction
NSTEMI	non–ST elevation myocardial infarction
PCI	percutaneous coronary intervention
PICOTS	population, interventions, comparisons, outcomes, timing of outcomes, setting
PPI	proton pump inhibitor
RCT	randomized controlled trial
RR	relative risk
SOE	strength of evidence
STEMI	ST elevation myocardial infarction
TEP	Technical Expert Panel
TIMI	thrombolysis in myocardial infarction
UA	unstable angina
UFH	unfractionated heparin

Introduction

Background

Acute coronary syndrome (ACS) encompasses three similar yet distinct disorders: (1) ST-elevation myocardial infarction (STEMI), (2) non-ST elevation myocardial infarction (NSTEMI), and (3) unstable angina (UA). These disorders are often collapsed into just two categories—STEMI and UA/NSTEMI—because UA and NSTEMI have a similar pathophysiology, mortality rate, and management strategy when compared with STEMI. In the United States, approximately 1.4 million people are diagnosed with ACS each year, and 70 percent of them have UA/NSTEMI.[1-4]

UA/NSTEMI is defined by the presence of ischemic chest pain (or an equivalent), the notable absence of ST segment elevation on electrocardiography, and the presence of either ST segment depression or T-wave inversion on electrocardiography and/or abnormal cardiac biomarkers.[1] The pathophysiology of UA/NSTEMI involves six possible etiologies: (1) thrombus arising from a disrupted or eroded plaque, (2) thromboembolism from an erosive plaque, (3) dynamic obstruction (such as coronary spasm), (4) progressive mechanical obstruction, (5) inflammation, or (6) coronary artery dissection.[5] Most patients with UA/NSTEMI have thrombus formation or progressive arterial narrowing that leads to subtotal occlusion of an epicardial coronary artery.[6] The difference between UA and NSTEMI is based on the presence of myocardial necrosis or infarction as suggested by serum tests such as creatine kinase-myocardial band, troponin I, or troponin T in NSTEMI.

Treatment Strategies for UA/NSTEMI

The standard treatment goals for patients with UA/NSTEMI involve the elimination of ischemic pain and the prevention of adverse events—death, recurrent ischemia, or myocardial infarction (MI). The cornerstone of short- and long-term treatment in all cases is medical therapy with antiplatelet and anticoagulant medications. Antiplatelet medications work by decreasing platelet aggregation and inhibiting thrombus formation. The timing of initiation of antiplatelet therapy in patients presenting with UA/NSTEMI is broadly classified as *upstream* if the therapy is initiated after admission but prior to cardiac catheterization or *periprocedural* if the agent is initiated at the time of or during the procedure. Antiplatelet therapy initiated during a hospitalization for UA/NSTEMI and continued for long-term management has been shown to reduce future cardiovascular events. Anticoagulant medications work by inhibiting blood clotting, either by antagonizing the effects of vitamin K or by blocking/inhibiting thrombin. The use of a parenteral anticoagulant, traditionally heparin, is standard treatment for patients hospitalized with ACS, and newer anticoagulants have been developed that improve outcomes, with similar or reduced bleeding risk compared with heparin.

By virtue of its ability to inhibit factors associated with thrombosis and to reduce ischemic outcomes, each antiplatelet or anticoagulant agent has the potential to increase the risk of bleeding. The tradeoff between reduced ischemic risk and increased bleeding risk has been highlighted in a number of recent large clinical trials that evaluated antiplatelet and anticoagulant therapies, as discussed below. Despite these recent data, a number of questions remain about the use of antiplatelet and anticoagulant agents, including the optimal dosing of certain agents and the timing of their use, and whether certain agents might be preferred for specific subgroups of patients.[7]

There are a number of challenges in determining optimal medical management in patients with UA/NSTEMI. First, there are a large number of agents in each category, increasing the complexity of assessing which combinations have the best outcomes. Second, optimal medical management may be affected by the choice of revascularization strategy. For the majority of patients who are at high risk of recurrent ischemia, MI, or death, an *early invasive treatment strategy*—defined as diagnostic angiography and coronary revascularization without prior noninvasive stress testing—has been proven to reduce death or MI.[8-11] For the minority of patients at low or intermediate risk of recurrent ischemia, MI, or death, an *initial conservative treatment strategy* is often chosen: noninvasive stress testing followed by angiography and revascularization only in patients who develop recurrent infarction, angina at rest, or inducible ischemia during stress testing.[1] Therefore, the comparative effectiveness of concurrent medical therapy needs to be considered separately for early invasive and initial conservative strategies. Finally, it is also important to consider the *postdischarge treatment strategy* (after hospitalization) using antiplatelet and/or anticoagulant treatments to reduce recurrent ischemic events.

Antiplatelet and Anticoagulant Medications for UA/NSTEMI

Table 1 outlines the antiplatelet and anticoagulant therapies available for each clinical scenario: early invasive, initial conservative, and postdischarge. These therapies are discussed below.

Table 1. Antiplatelet and anticoagulant therapies for each clinical scenario

Drug Category	Early Invasive	Initial Conservative	Postdischarge
Aspirin	Aspirin[a] (low or high dose)	Aspirin[a] (low or high dose)	Aspirin[a] (low or high dose)
Intravenous antiplatelet (glycoprotein IIb/IIIa inhibitor)	*Upstream:* Eptifibatide Tirofiban *Periprocedure:* Eptifibatide Tirofiban Abciximab	Eptifibatide Tirofiban Abciximab	None
Oral antiplatelet ($P2Y_{12}$ Inhibitor)	*Upstream*: Clopidogrel, Ticagrelor *Periprocedure*: Clopidogrel Prasugrel Ticagrelor	Clopidogrel Ticagrelor Prasugrel	Clopidogrel Prasugrel Ticagrelor
Anticoagulant	Bivalirudin Fondaparinux Enoxaparin Unfractionated heparin	Fondaparinux Enoxaparin Unfractionated heparin	Warfarin Dabigatran Rivaroxaban Apixaban
Other considerations	Dose and timing	Dose and timing	Duration related to PCI vs. no PCI Proton pump inhibitors Patients requiring triple therapy

PCI = percutaneous coronary intervention; triple therapy = aspirin plus antiplatelet plus anticoagulant

[a]In studies, low-dose aspirin ranged from 81 mg to less than 300 mg; high-dose aspirin ranged from 150 mg to 325 mg.

Aspirin and Antiplatelet Agents

In the absence of contraindications, aspirin is currently recommended for all patients presenting with ACS.[1] Clopidogrel, the most widely used oral $P2Y_{12}$ inhibitor, is currently recommended for patients with UA/NSTEMI. Other oral $P2Y_{12}$ inhibitors include prasugrel and ticagrelor. While robust clinical data to support the use of clopidogrel in patients with ACS,[12-14] several factors have been observed that make clopidogrel less than ideal. Clopidogrel belongs to the thienopyridine class of antiplatelet medications and is a prodrug that requires biotransformation to the active metabolite. This metabolic conversion takes place via the hepatic cytochrome P-450 isoenzymes and is susceptible to drug interactions and genetic polymorphisms that can potentially reduce the antiplatelet activity of the drug. Prasugrel is also a thienopyridine, but it provides a more potent and faster acting antiplatelet effect than clopidogrel and does not appear to be susceptible to genetic polymorphisms of the hepatic isoenzymes. Ticagrelor is a reversibly binding $P2Y_{12}$ receptor antagonist that, when compared with clopidogrel, also provides a more rapid and more potent inhibition of platelets than clopidogrel does.[15]

The antiplatelet agents belonging to the glycoprotein IIb/IIIa inhibitor (GPI) class are administered intravenously. They include abciximab, eptifibatide, and tirofiban. Eptifibatide and tirofiban are reversible platelet inhibitors, whereas abciximab, a selective antibody, is an irreversible platelet inhibitor.

Anticoagulant Agents

Anticoagulants used to manage patients with UA/NSTEMI include unfractionated heparin (UFH), low molecular weight heparin (enoxaparin), bivalirudin, and fondaparinux. Intravenous UFH is the traditional anticoagulant used to manage UA/NSTEMI. Because of its short biologic half-life of approximately 1 hour, heparin must be given frequently or as a continuous infusion. Enoxaparin is a low molecular weight heparin that has the advantage of being administered subcutaneously once or twice daily and does not require frequent blood monitoring. Bivalirudin is a bivalent direct thrombin inhibitor that binds reversibly to thrombin. Bivalirudin possesses a favorable pharmacokinetic profile in that it is eliminated primarily by proteolytic cleavage, with approximately 20 percent being cleared by the kidneys, and has a plasma half-life of 25 minutes in patients with normal renal function. Fondaparinux is an indirect factor Xa inhibitor that is injected subcutaneously on a daily basis. Fondaparinux has been associated with a favorable bleeding profile when compared with other anticoagulants used in patients with ACS.

Treatment Strategy Algorithm

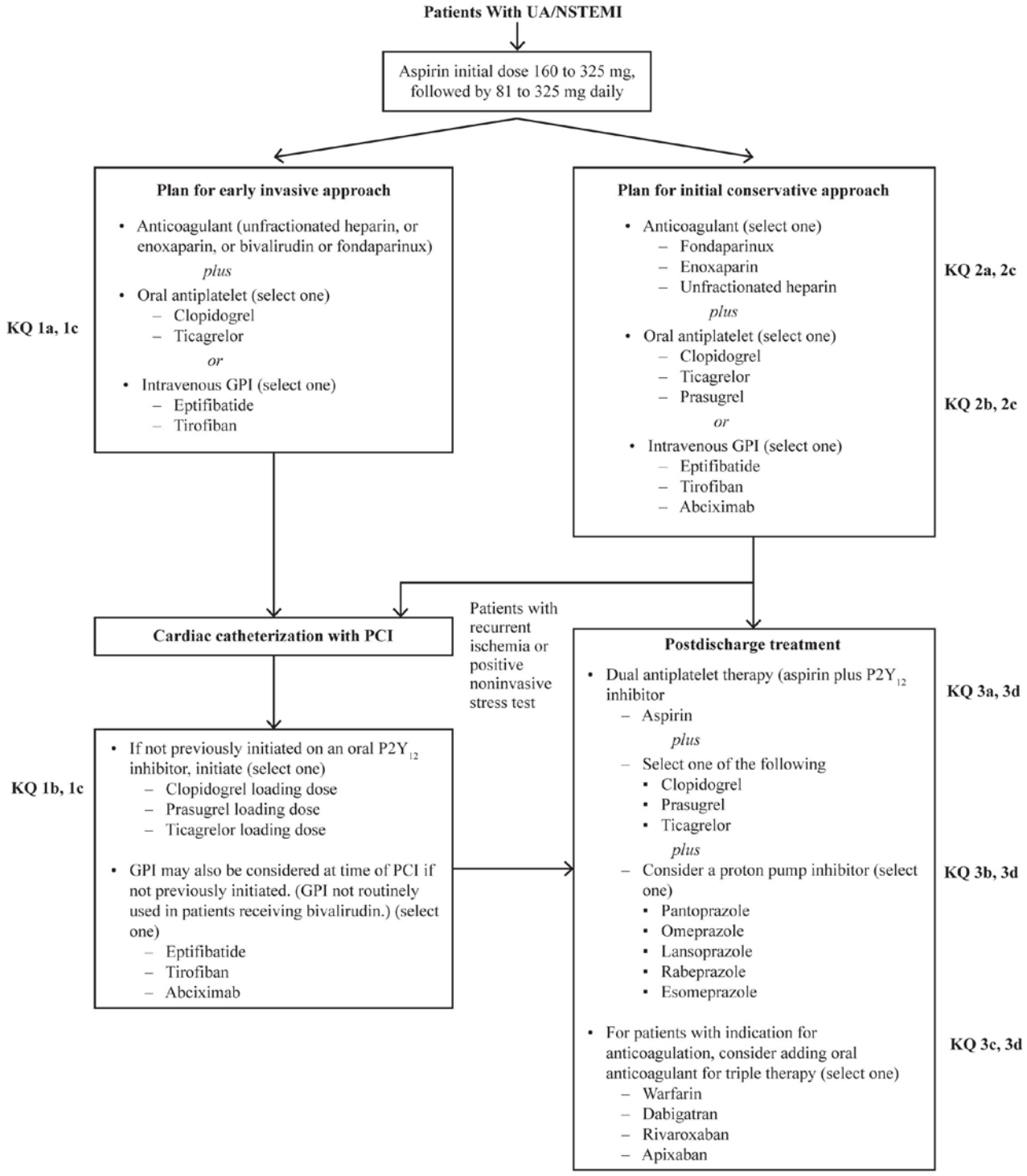
Figure 1 illustrates the treatment strategy algorithm for patients with UA/NSTEMI. First, all patients presenting with UA/NSTEMI are treated with an initial dose of aspirin, followed by either an early invasive or an initial conservative approach. An early invasive approach consists of an oral antiplatelet agent or intravenous (IV) GPI as initial therapy prior to going to the cardiac catheterization laboratory. After catheterization with percutaneous coronary intervention (PCI), the next stage involves consideration of the use of antiplatelet agents to improve cardiovascular outcomes. An initial conservative approach consists of using different anticoagulants and oral antiplatelets to improve cardiovascular outcomes in patients with UA/NSTEMI.

For all patients with UA/NSTEMI, the postdischarge phase of treatment considers oral antiplatelet agents, aspirin for patients who are also receiving another oral antiplatelet agent, and the addition of proton pump inhibitors for reducing bleeding events in patients receiving dual

antiplatelet therapy. Last, the postdischarge strategy may include triple therapy (aspirin plus antiplatelet plus anticoagulant) for UA/NSTEMI patients with an indication (e.g., atrial fibrillation) for long-term anticoagulant therapy.

Although the treatment algorithm provides guidance to clinicians, there is still considerable uncertainty about the specifics of which medications to use in combination with other agents, the optimal dosing and timing of their use, and whether certain agents are more effective and safe in specific subgroups of patients. The treatment strategy usually consists of an anticoagulant with either an oral antiplatelet or IV GPI medication. Some trials assessed the combination and timing of using all three treatments (i.e., an anticoagulant, IV GPI, and an oral antiplatelet medication).

Figure 1. Treatment strategy algorithm for patients with UA/NSTEMI



GPI = glycoprotein IIb/IIIa inhibitor; KQ = Key Question; PCI = percutaneous coronary intervention; triple therapy = aspirin plus antiplatelet plus anticoagulant; UA/NSTEMI=unstable angina/non–ST elevation myocardial infarction

Scope and Key Questions

Scope of Review

This Comparative Effectiveness Review was funded by the Agency for Healthcare Research and Quality (AHRQ). The review was designed to evaluate the effectiveness and safety of antiplatelet and anticoagulant medications used to treat patients with UA/NSTEMI in an early invasive approach, an initial conservative approach, and after hospitalization (postdischarge).

Key Questions

With input from our Technical Expert Panel, we constructed Key Questions (KQs) using the general approach of specifying the population of interest, interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS; see the section on "Inclusion and Exclusion Criteria" in the Methods section for details). The KQs considered in this Comparative Effectiveness Review were:

KQ 1. In patients undergoing an early invasive approach for treating unstable angina/non–ST elevation myocardial infarction (UA/NSTEMI):

a. What are the comparative effectiveness (dose and timing) and comparative safety of an intravenous (IV) glycoprotein IIb/IIIa inhibitor versus oral antiplatelet agent as initial therapy before going to the catheterization laboratory?
b. What are the comparative effectiveness (dose and timing) and comparative safety of coadministration of IV or oral antiplatelet agents in patients undergoing percutaneous coronary intervention for improving cardiovascular outcomes? Do the effectiveness and safety vary based on which initial anticoagulant is used or the combination of anticoagulant and antiplatelet agents?
c. Based on demographic and other clinical characteristics, are there subgroups of patients for whom the effectiveness and safety differ?

KQ 2. In patients undergoing an initial conservative approach for treating UA/NSTEMI:

a. What are the comparative effectiveness (dose and timing) and comparative safety of different anticoagulants for improving cardiovascular outcomes?
b. What are the comparative effectiveness (dose and timing) and comparative safety of different antiplatelet agents for improving cardiovascular outcomes?
c. Based on demographic and other characteristics, are there subgroups of patients for whom the effectiveness and safety differ?

KQ 3. In patients treated for UA/NSTEMI after hospitalization (postdischarge):

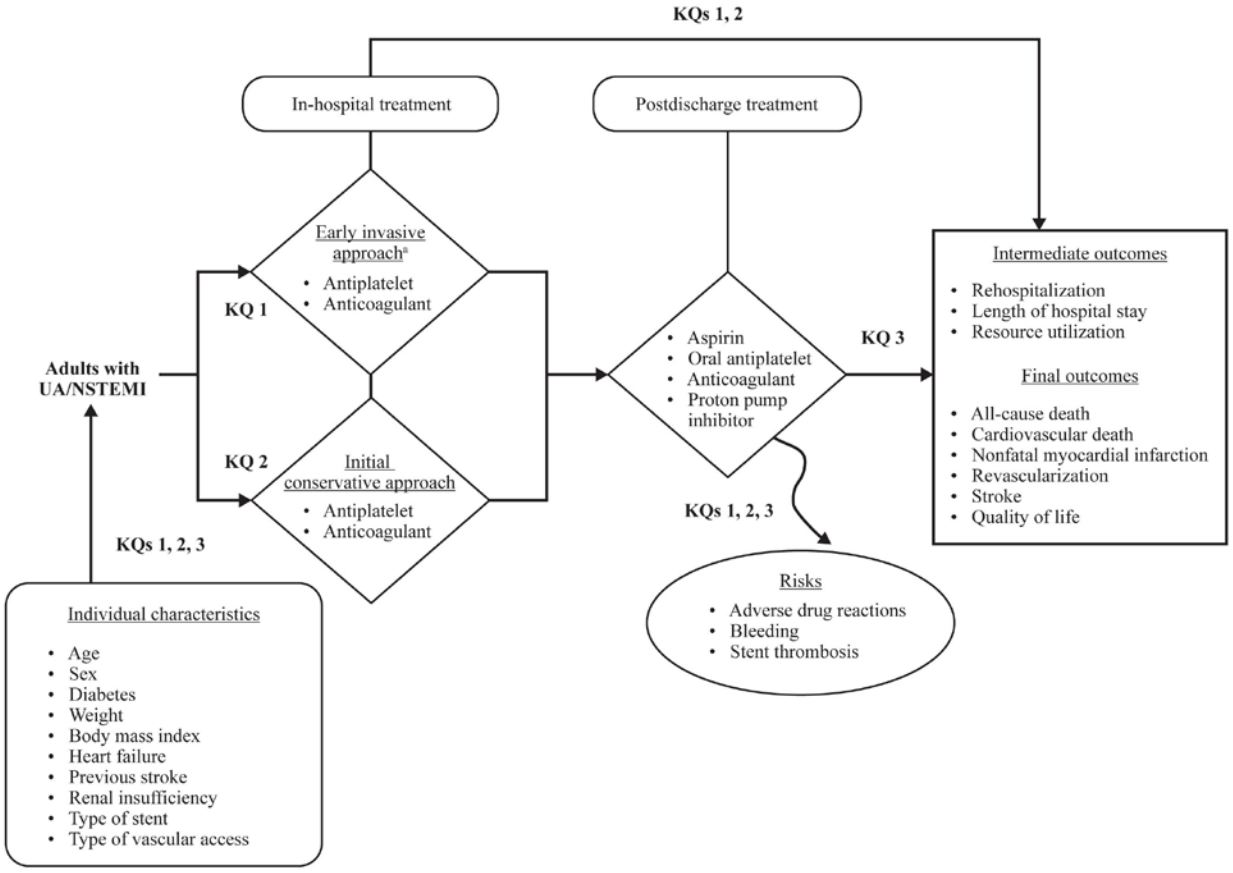
a. What are the comparative effectiveness (dose and duration) and comparative safety of the available oral antiplatelet agents given in combination with aspirin? Do the effectiveness and safety vary based on the dose of aspirin used?
b. What are the comparative effectiveness and comparative safety of proton pump inhibitors (PPIs) for reducing bleeding events in patients receiving dual antiplatelet therapy after UA/NSTEMI? Do the effectiveness and safety vary by oral antiplatelet therapy and PPI?
c. In patients with an indication for long-term anticoagulant therapy, what are the comparative effectiveness and comparative safety of adding an oral anticoagulant to aspirin and another antiplatelet agent for improving cardiovascular outcomes?

d. Based on demographic and other characteristics, are there subgroups of patients for whom the effectiveness and safety differ?

Analytic Framework

Figure 2 shows the analytic framework for this Comparative Effectiveness Review.

Figure 2. Analytic framework



KQ = Key Question; UA/NSTEMI = unstable angina/non–ST elevation myocardial infarction
[a]Prior to catheterization or during percutaneous coronary intervention.

The analytic framework depicts the treatment strategies and outcomes for adult patients with UA/NSTEMI. In-hospital treatment interventions include an early invasive approach prior to catheterization or during percutaneous coronary intervention (KQ 1) or an initial conservative approach (KQ 2) involving the use of combinations of antiplatelets and/or anticoagulants to improve cardiovascular outcomes. Postdischarge treatment interventions (KQ 3) involve the use of aspirin, oral antiplatelets, anticoagulants, and proton pump inhibitors to prevent recurrent ischemic events and other outcomes.

Intermediate outcomes considered include rehospitalization, length of hospital stay, and resource utilization (e.g., emergency department visits). Final outcomes considered include all-cause death, cardiovascular-related death, nonfatal myocardial infarction, revascularization, stroke, and quality of life. The figure also includes consideration of whether there are subgroups of patients, based on demographic and other characteristics, for whom the effectiveness and

safety differ. All three KQs consider subgroups by age, sex, weight, body mass index, diabetes, heart failure, previous stroke, renal insufficiency, type of stent, and type of vascular access. Finally, all three KQs consider safety risks including adverse drug reactions, bleeding, and stent thrombosis.

Methods

The methods for this Comparative Effectiveness Review follow those suggested in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter referred to as the Methods Guide).[16] The main sections in this chapter reflect the elements of the protocol established for the systematic review; certain methods map to the PRISMA checklist.[17] All methods and analyses were determined a priori.

Topic Refinement and Review Protocol

During the topic refinement stage, we solicited input from Key Informants representing clinicians (cardiology, internal medicine, pharmacology, emergency medicine), patients, scientific experts, and Federal agencies to help define the KQs. The KQs were then posted for public comment in October 2011 for 4 weeks, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP), comprising clinical, content, and methodological experts, to provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP did analysis of any kind or contributed to the writing of the report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol, which was then refined based on their input, reviewed by AHRQ, and posted for public access at the AHRQ Effective Health Care Web site.[18]

Literature Search Strategy

Sources Searched

Our search strategy used the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. In consultation with our research librarians, we searched PubMed®, Embase®, and the Cochrane Database of Systematic Reviews (last search data for all three sources July 19, 2012). Our search strategy for PubMed is included in Appendix A; this strategy was adapted as necessary for use in the other databases. We date-limited our search to articles published since January 1995, corresponding to the period when contemporary studies on antiplatelet therapy, anticoagulant therapy, and combined therapies were published. The reference lists for identified pivotal articles were hand-searched and cross-referenced against our library, and additional manuscripts were retrieved. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We also searched the gray literature of study registries and conference abstracts for relevant articles from completed studies. Gray literature databases included ClinicalTrials.gov (August 20, 2012); the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (March 7, 2012); and ProQuest COS Conference Papers Index (February 15, 2012). Scientific information packets were requested from the manufacturers of medications and devices and reviewed for relevant articles from completed studies not previously identified in the literature searches.

Although this was not an exhaustive strategy, the search of ClinicalTrials.gov was also used as a mechanism to ascertain publication bias by identifying completed but unpublished studies. During peer and public review of the draft report, we updated all database searches and included any eligible studies identified either through that search or through suggestions from peer and public reviewers.

Inclusion and Exclusion Criteria

The PICOTS criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 2.

Table 2. Inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	Adult patients with UA or NSTEMI	• Studies with only a STEMI or stable angina population • All patients are <18 years of age, or some patients are ≥18 years of age, but results are not reported for the adult population separately from the pediatric population
Interventions	• KQ 1: *Early invasive strategy* (before cardiac catheterization or during PCI) o Aspirin o Intravenous glycoprotein IIb/IIIa inhibitors ▪ Abciximab ▪ Eptifibatide ▪ Tirofiban o Oral antiplatelets ▪ Clopidogrel ▪ Prasugrel ▪ Ticagrelor o Anticoagulants ▪ Bivalirudin ▪ Fondaparinux ▪ Enoxaparin ▪ Unfractionated heparin	• Study does not include any of the medications listed • Medications are not administered as part of an early invasive strategy
	• KQ 2: *Initial conservative strategy* o Aspirin o Oral antiplatelets ▪ Clopidogrel ▪ Prasugrel ▪ Ticagrelor o Anticoagulants ▪ Fondaparinux ▪ Enoxaparin ▪ Unfractionated heparin o Intravenous glycoprotein IIb/IIIa inhibitors ▪ Abciximab ▪ Eptifibatide ▪ Tirofiban	• Study does not include any of the medications listed • Medications are not administered as part of an initial conservative strategy

Table 2. Inclusion and exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Interventions (continued)	• KQ 3: *Postdischarge treatment* o Aspirin o Oral antiplatelets ▪ Clopidogrel ▪ Prasugrel ▪ Ticagrelor o Anticoagulants ▪ Warfarin ▪ Dabigatran ▪ Rivaroxaban ▪ Apixaban o PPIs ▪ Pantoprazole ▪ Omeprazole ▪ Lansoprazole ▪ Rabeprazole ▪ Esomeprazole	Study does not include any of the medications listed • Medications are not administered as part of postdischarge treatment
Comparators	• KQ 1a: Before catheterization, dose and timing of intravenous or oral antiplatelets with anticoagulants plus aspirin • KQ 1b: During PCI, dose and timing of intravenous or oral antiplatelet with anticoagulants plus aspirin • KQ 2a: Dose and timing of anticoagulants plus aspirin • KQ 2b: Dose and timing of oral antiplatelets plus aspirin • KQ 3a: Dose and duration of oral antiplatelets in combination with aspirin at different doses • KQ 3b: PPIs versus no PPIs • KQ 3c: Dual antiplatelet therapy (aspirin with oral antiplatelet) versus triple therapy (oral anticoagulant, aspirin, and oral antiplatelet)	Studies without an active comparator
Outcomes	• Intermediate outcomes o Rehospitalization o Length of hospital stay o Resource utilization (e.g., emergency department visits) • Final outcomes o All-cause death o Cardiovascular-related death o Nonfatal myocardial infarction o Revascularization o Stroke e. Quality of life	No intermediate or final outcomes of interest are reported
Outcomes (subgroups)	KQs 1–3: Individual characteristics including age, sex, weight, body mass index, diabetes, heart failure, previous stroke, renal insufficiency, type of stent, type of vascular access	None
Outcomes (safety)	KQs 1–3: Adverse effects of treatments such as adverse drug reactions (thrombocytopenia, allergic drug reaction), bleeding[a], and stent thrombosis	None

Table 2. Inclusion and exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Timing	Short-term (≤ 30 days), intermediate-term (31 days to 1 year), and long-term (> 1 year)	None
Setting	• Inpatient for early invasive and initial conservative therapies • Outpatient for after hospitalization (postdischarge) therapies	None
Study design	• Randomized controlled trial, prospective or retrospective observational cohort study • Original data (or related methodology paper of an included article) for interventions listed in KQs 1–3 • Relevant systematic review or meta-analysis (used for background only) All sample sizes	Not a clinical study (e.g., editorial, non–systematic review, letter to the editor, case series)
Publications	• English-language only • Peer-reviewed article Published from January 1, 1995, to present	Given the high volume of literature available in English-language publications (including the majority of known important studies), non-English articles were excluded

KQ = Key Question; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; STEMI = ST elevation myocardial infarction; UA = unstable angina
[a]Major and minor bleeding were defined by multiple validated criteria or by study protocol.

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were examined independently by two reviewers for potential relevance to the KQs. Articles included by any reviewer underwent full-text screening. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to include or exclude the article for data abstraction. When the paired reviewers arrived at different decisions about whether to include or exclude an article, we reconciled the difference through a third-party arbitrator. Articles meeting our eligibility criteria were included for data abstraction. Relevant systematic review articles, meta-analyses, and methods articles were flagged for hand-searching and cross-referencing against the library of citations identified through electronic database searching.

Data Extraction

The investigative team created data abstraction forms and evidence table templates for abstracting data for the KQs. Based on clinical and methodological expertise, two investigators were assigned to the research questions to abstract data from the eligible articles. One investigator abstracted the data, and the second overread the article and the accompanying abstraction to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus was not reached between the first two investigators. To aid in both reproducibility and standardization of data collection, investigators received data abstraction instructions directly on each form created specifically for this project with the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, Ontario, Canada). Data reported only in graphs were estimated quantitatively using Engauge Digitizer version 4.1 software (www.digitizer.sourceforge.net).

We designed the data abstraction forms for this project to collect data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate outcomes, health outcomes, and safety outcomes). The safety outcomes were framed to help identify adverse events, including adverse drug reactions and bleeding.

Data necessary for assessing quality and applicability, as described in the Methods Guide,[16] were also abstracted. Before they were used, abstraction form templates were pilot tested with a sample of included articles to ensure that all relevant data elements were captured and that there were consistency and reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles.

Appendix B lists the elements used in the data abstraction forms. Appendix C contains a bibliography of all articles/studies included in this review, organized alphabetically by author. Appendix D provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies by using the approach described in the Methods Guide.[16] To assess quality, we used the strategy of (1) classifying the study design, (2) applying predefined criteria for quality and critical appraisal, and (3) arriving at a summary judgment of the study's quality. To evaluate methodological quality, we applied criteria for each study type derived from the core elements described in the Methods Guide. For RCTs, criteria included adequacy of randomization and allocation concealment, the comparability of groups at baseline, blinding, the completeness of followup and differential loss to followup, whether incomplete data were addressed appropriately, the validity of outcome measures, and conflict of interest.

For nonrandomized clinical trials, such as those with an observational control group that was not randomized, we assessed the following study-specific issues that may affect the internal validity of our systematic review: potential for selection bias (i.e., degree of similarity between intervention and control patients); performance bias (i.e., differences in care provided to intervention and control patients not related to the study intervention); attribution and detection bias (i.e., whether outcomes were differentially detected between intervention and control groups); and magnitude of reported intervention effects.[19]

To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, or poor based on their adherence to well-accepted standard methodologies and adequate reporting (Table 3).

Table 3. Definitions of overall quality ratings

Quality Rating	Description
Good	A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
Fair	A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
Poor	A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Included meta-analyses were appraised according to criteria adapted from the PRISMA Statement.[17] Rating was outcome-specific; thus, a given study may have been of different quality for two individual outcomes reported within that study. Study design also was considered when rating quality. RCTs were rated as good, fair, or poor. Observational studies were rated separately, also as good, fair, or poor.

Data Synthesis

We summarized the primary literature by abstracting relevant continuous data (e.g., age) and categorical data (e.g., race, presence of coronary disease risk factors). Continuous variable outcomes reported by study authors included means, medians, standard deviations, interquartile ranges, ranges, and associated p-values. Dichotomous variable outcomes were summarized by proportions and associated p-values. We then determined the feasibility of completing a quantitative analysis (i.e., meta-analysis). Feasibility depended on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the reporting of results. We considered meta-analysis for comparisons in which at least three studies reported the same outcome. For the KQ 2 sensitivity analyses, we grouped studies by trial size (small, <1,000 patients; large, ≥1,000 patients) and by use (aspirin monotherapy vs. dual antiplatelet therapy) to help explain any heterogeneity, if present. Any subgroup summary estimate based on fewer than three studies is noted as such and should be interpreted with caution.

Meta-analyses were based on the nature of the outcome variable, but random-effects models were used for all outcomes because of the heterogeneity of the studies. Dichotomous outcome measures comparing two treatments were combined using odds ratios and a random-effects model as implemented in Comprehensive Meta-Analysis Version 2 (Biostat; Englewood, NJ). We tested for statistical heterogeneity between studies (Q and I^2 statistics) while recognizing that the power to detect such heterogeneity may be limited. Potential heterogeneity between studies was reflected through the confidence intervals (CIs) of the summary statistics obtained from a random-effects approach. When substantial heterogeneity was present, we conducted sensitivity analyses to assess whether omitting the poor-quality studies would reduce the heterogeneity.

We present summary estimates, standard errors, and CIs in our data synthesis. When the summary estimate and CI were precise and crossed 1, we looked at the particular studies to determine the minimally important difference for noninferiority, or at the total number of events in both arms from the set of studies to see if it met criteria for optimal information size for the

level of risk reduction.[20] If the CI was within the minimally important difference or the number of events met the optimal information size, then we concluded equivalence; otherwise we concluded insufficient evidence.

Strength of the Body of Evidence

We graded the strength of evidence (SOE) for each outcome assessed because a given study may be of different quality for two individual outcomes reported within that study. The SOE for each KQ and outcome was assessed using the approach described in the Methods Guide.[16,21] In brief, the approach required assessment of four domains: risk of bias, consistency, directness, and precision (Table 4). Risk of bias ratings were based on the studies that were used in the meta-analysis (when performed) or on the findings from RCTs, which carry the lowest risk of bias, when meta-analysis was not performed. For some comparisons, especially those for KQ 3, the only available literature was from observational studies.

Table 4. Strength of evidence required domains

Domain	Rating	How Assessed
Risk of bias	Low Medium High	Assessed primarily through study design (RCT versus observational study) and aggregate study quality
Consistency	Consistent Inconsistent Unknown/not applicable	Assessed primarily through whether effect sizes are generally on the same side of "no effect" and the overall range of effect sizes
Directness	Direct Indirect	Assessed by whether the evidence involves direct comparisons or indirect comparisons through use of surrogate outcomes or use of separate bodies of evidence
Precision	Precise Imprecise Unknown	Based primarily on the size of the confidence intervals of effect estimates

RCT = randomized controlled trial

Additionally, when appropriate, the studies were evaluated for the presence of confounders that would diminish an observed effect, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, or low SOE was assigned after discussion by two reviewers. In some cases, high, moderate or low ratings were impossible or imprudent to make (e.g., when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn), and therefore the evidence was rated insufficient. In these situations, a grade of insufficient was assigned. This four-level rating scale consists of the following definitions:

- **High**—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate**—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low**—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- **Insufficient**—Evidence either is unavailable or does not permit estimation of an effect.

Applicability

We assessed applicability across our KQs using the method described in the Methods Guide.[16,22] In brief, the PICOTS format was used as a way to organize information relevant to applicability. We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population (e.g., age, ethnicity, and sex) in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use (such as specific components of treatments considered to be supportive therapy), and clinical relevance and timing of the outcome measures. We used a checklist to guide our assessment and summarized issues of applicability qualitatively (Appendix E).

Peer Review and Public Commentary

The peer review process is our principal external quality-monitoring device. Nominations for peer reviewers were solicited from several sources, including the TEP and interested Federal agencies. Experts in cardiology, radiology, vascular surgery, general medicine, and nursing along with individuals representing stakeholder and user communities, were invited to provide external peer review of this draft report; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Web site from November 1 through November 29, 2012. We have addressed reviewer comments, revising the report as appropriate, and have documented our responses in a disposition of comments report available on the AHRQ Web site. A list of peer reviewers is given in the preface of this report.

Results

Introduction

In what follows, we begin by describing the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by KQ. For each KQ, we begin by listing the key points of the findings, followed by a brief description of included studies and a more detailed synthesis of the evidence.

In the initial phases of title-and-abstract screening, we focused on identifying articles on the UA/NSTEMI population; therefore, citations that included the ACS population were moved forward to the full-text screening phase. In examining these citations, we found 59 articles that addressed an exclusively UA/NSTEMI population and 110 articles that addressed an ACS population that included the UA/NSTEMI population but did not report separate results for that population. The investigative team felt that limiting our review to the pure UA/NSTEMI population would result in a narrow focus on the antiplatelet and anticoagulant therapies that are used in clinical practice. Therefore, we have chosen to include studies of either the UA/NSTEMI population or the ACS population that included UA/NSTEMI patients. Note that any studies that were exclusively in the STEMI or stable angina population are excluded.

Also, we found studies that were not easily grouped into the early invasive, initial conservative, or postdischarge strategies. There was substantial overlap in the treatment strategies within these studies. For example, in a study comparing antithrombotic therapies, a proportion of patients in each treatment arm could have undergone PCI or conservative treatment. The results were reported by each treatment arm but not by the subgroups that received PCI or conservative treatment. For these reasons, this review is structured in the following manner:

- In KQ 1 (*early invasive*), we focus on studies that assessed dosage, timing, and combinations of antiplatelet and anticoagulant therapies delivered at the time of PCI. We present the findings of studies comparing (1) upstream versus deferred GPI, (2) different loading doses of clopidogrel, (3) clopidogrel versus ticagrelor or prasugrel, (4) bivalirudin versus a heparin-based strategy, (5) enoxaparin versus UFH versus fondaparinux, and (6) upstream or deferred clopidogrel administration.
- In KQ 2 (*initial conservative*), we present the findings of studies that either focused on the conservatively managed patient or presented information about antiplatelet and anticoagulant therapies in UA/NSTEMI or ACS populations who were not included in KQ 1. Thus we present the findings of studies comparing (1) UFH versus enoxaparin or fondaparinux (full UA/NSTEMI cohort), (2) GPI plus UFH versus UFH alone in a patient population for whom coronary angiography was discouraged in the first 24 to 60 hours after study drug administration or in populations who did not receive PCI, and (3) clopidogrel versus ticagrelor or prasugrel.

- In KQ 3 (*postdischarge*), we present the findings of studies comparing (1) low-dose versus high-dose aspirin, (2) single antiplatelet versus dual antiplatelet therapy, (3) short-term versus long-term clopidogrel, (4) antiplatelet therapy with or without the addition of a PPI, and (5) dual antiplatelet versus triple antiplatelet therapy in patients with an indication for long-term anticoagulation (e.g., atrial fibrillation, prosthetic valve).

Across all KQs we present any relevant subgroup or harms data. We conducted quantitative syntheses where possible, as described in the Methods section. A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

Results of Literature Searches

In Figure 3, we depict the flow of articles through the literature search and screening process for the review. Searches of PubMed®, Embase®, and the Cochrane Database of Systematic Reviews from January 1995 to July 2012 yielded 26,279 citations, 3,206 of which were duplicates. Manual searching and contacts with drug manufacturers identified 42 additional citations, for a total of 23,115. After applying inclusion/exclusion criteria at the title-and-abstract level, 1,576 full-text articles were retrieved and screened. Of these, 1,274 were excluded at the full-text screening stage, leaving 302 articles (representing 175 unique studies) for data abstraction. Note that several articles/studies were relevant to more than one KQ.

Description of Included Studies

Of the included 175 studies, 87 were relevant to KQ 1, 33 to KQ 2, and 71 to KQ 3. Studies were conducted wholly or in part in Europe (41%); Asia (13%); the United States or Canada (34%); Australia or New Zealand (6%); other international settings (18%); and 3% did not report the setting. Further details are provided in the relevant KQ results sections that follow.

As described in the Methods chapter, we searched ClinicalTrials.gov to identify completed but unpublished studies as a mechanism for ascertaining publication bias. Our search yielded 503 trial records, 270 of which were completed at least 1 year prior to our search of the database and review of the published literature. A single reviewer identified 29 of these records as potentially relevant. We identified and screened publications for 23 of the 29 trial records. We also identified publications for two additional trial records that were not captured by our search. After reviewing these publications, neither would have been included in this report: one did not report any outcomes of interest, and the other had no comparisons of interest. Of the four trial records for which we did not identify publications, two were considered potentially relevant to KQ 1, one was considered potentially relevant to both KQs 1 and 2, and one was of indeterminate relevance.

Of the two trial records with potential relevance to KQ 1, one has been completed while the other has been suspended. The completed trial is a platelet inhibition study using two doses of prasugrel. The only potentially applicable data would be if the study is collecting adverse events of interest to this report, as the main study outcomes are not clinical outcomes of interest. As there is only one study reporting outcomes of interest associated with prasugrel, relevant adverse event data would bolster the SOE in this report. The suspended trial has greater potential applicability, given that it is a study of the efficacy and safety of tirofiban versus placebo in patients undergoing PCI. If data were to be published, it would add to and possibly help clarify the data from the upstream versus deferred GPI section of KQ 1, as the SOE was rated insufficient or low for nine of 11 outcomes analyzed.

The trial record of potential relevance to either or both KQs 1 and 2 was a study comparing the efficacy and safety of enoxaparin to unfractionated heparin for patients diagnosed with ACS in the emergency department. There was no information in the record regarding early invasive or conservative management, so the trial may relate more to one KQ than the other. The trial has been completed, with a primary completion date of February 2005, and was last updated in October 2009. A summary of this trial, published by Sanofi-Aventis on November 9, 2009, indicates that it was terminated early due to low event rates and slow recruitment. This summary also contained some of the collected safety data, which cannot be used in this report since they are not peer-reviewed data.

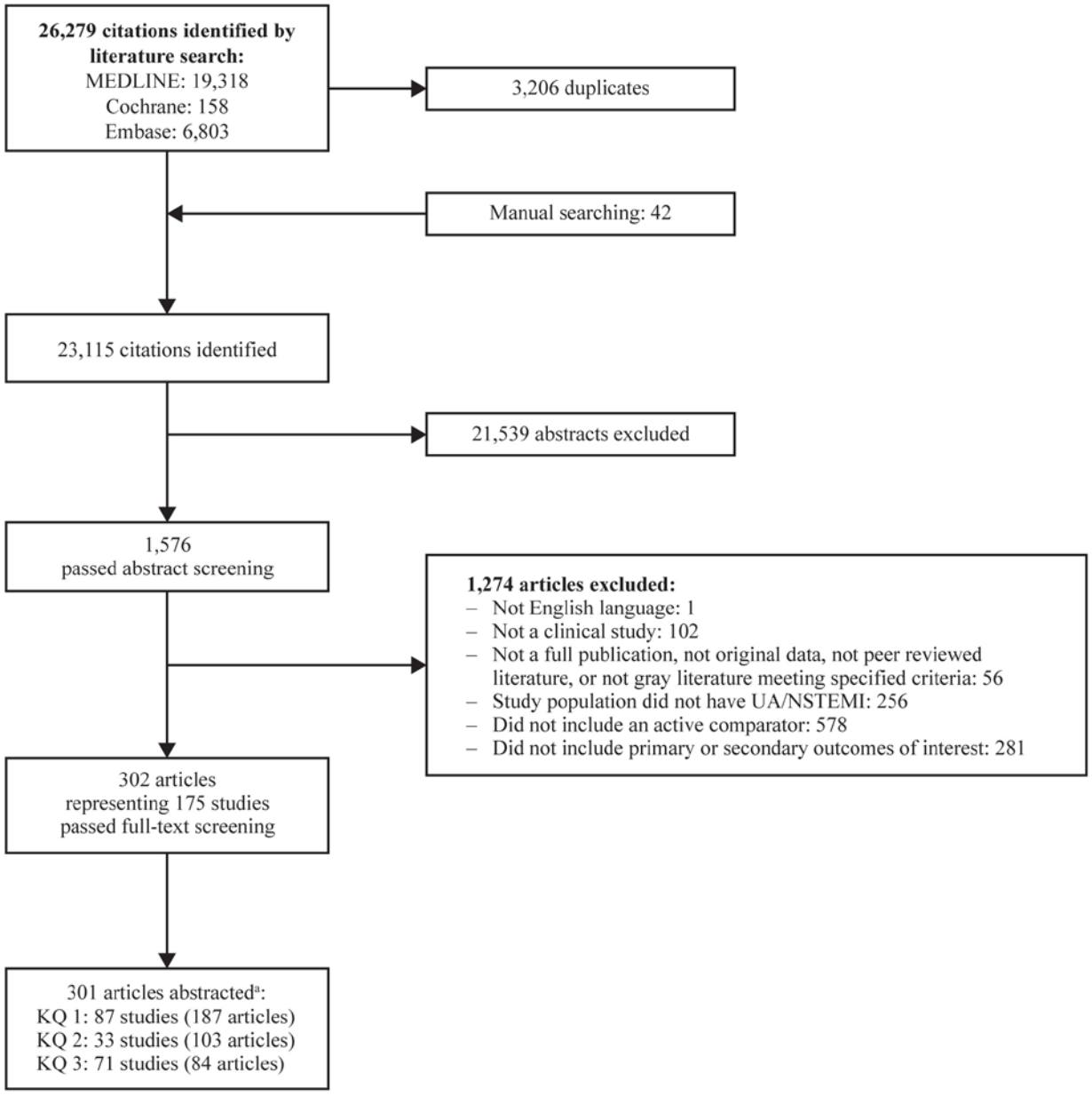
The trial record of indeterminate relevance contained an insufficient amount of information for us to give a KQ designation. This trial is a retrospective observational study on anti-thrombotic treatment patterns in India. Since the patterns of medication use between India and the United States vary greatly, it is unlikely that data published from this trial will be applicable to the target audience of this report.

Based on our search of ClinicalTrials.gov and the four trial records without publications in peer-reviewed literature, we do not believe that there is significant publication bias in the evidence base that would impact our overall findings.

Study Characteristics Tables

Tables F-1, F-2, and F-3 in Appendix F provide details and quality ratings for the included studies by population and comparison for each KQ.

Figure 3. Literature flow diagram



KQ = Key Question; STEMI = ST elevation myocardial infarction; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

[a]Studies/articles could be relevant to more than 1 KQ.

Key Question 1. Early Invasive Approach for UA/NSTEMI

KQ 1: In patients undergoing an early invasive approach for treating unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI):

a. What are the comparative effectiveness (dose and timing) and comparative safety of an intravenous (IV) glycoprotein IIb/IIIa inhibitor versus oral antiplatelet agent as initial therapy before going to the catheterization laboratory?
b. What are the comparative effectiveness (dose and timing) and comparative safety of coadministration of IV or oral antiplatelet agents in patients undergoing percutaneous coronary intervention for improving cardiovascular outcomes? Do the effectiveness and safety vary based on which initial anticoagulant is used or the combination of anticoagulant and antiplatelet agents?
c. Based on demographic and other clinical characteristics, are there subgroups of patients for whom the effectiveness and safety differ?

Key Points

- Upstream (precatheterization) treatment with GPIs was associated with lower rates of revascularization (high SOE) but with a higher risk of major bleeding events at 30 days compared with deferred (periprocedural) GPI administration (high SOE). However, we found no statistically significant difference between upstream and deferred GPI therapy for the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 30 days (low SOE).
- Evidence for the comparative effect of upstream versus deferred GPI therapy on all-cause mortality and nonfatal MI at 30 days was rated insufficient due to inconsistency and imprecision, despite the large number of studies and total number of enrolled patients.
- A 600 mg loading dose of clopidogrel was associated with lower rates of nonfatal MI and lower incidences of stent thrombosis at 30 days than a 300 mg loading dose (low SOE).
- Ticagrelor was associated with mixed results for the composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke compared with clopidogrel at 30 days (insufficient SOE for a reduction in the composite outcome for ticagrelor) and had similar rates of major bleeding events (low SOE) at 1 year.
- Prasugrel showed a reduction in the event rate of the above composite outcome at 30 days (moderate SOE) and the individual outcome of revascularization at 6 months (moderate SOE), but an increase in major bleeding events at 1 year (moderate SOE) when compared with clopidogrel.
- After 1 year, ticagrelor was associated with lower composite ischemic endpoints (moderate SOE) and individual endpoints (all-cause mortality, cardiovascular mortality, nonfatal MI, stent thrombosis; all moderate SOE) when compared with clopidogrel.
- After 1 year, prasugrel was associated with lower composite ischemic endpoints (moderate SOE), individual endpoints (all-cause mortality, cardiovascular mortality; both low SOE), and nonfatal MI and stent thrombosis (moderate SOE) when compared with clopidogrel.
- Without planned GPI use, there was a statistically significantly lower incidence in major and minor bleeding at 30 days favoring bivalirudin when compared with heparin (high SOE for major bleeding; low SOE for minor bleeding).

- With planned GPI use, bivalirudin reduced the rate of the composite outcome of all-cause mortality, nonfatal MI, revascularization, or major bleeding, and the individual endpoint of minor bleeding compared with heparin at 30 days (high SOE).
- At 30 days, there were no significant differences in the incidence of the composite ischemic endpoints in PCI patients treated with enoxaparin versus UFH and enoxaparin versus fondaparinux (low SOE).
- There was a statistically significantly lower incidence of major bleeding at 30 days favoring fondaparinux over enoxaparin in the PCI cohort (moderate SOE).
- In patients pretreated with clopidogrel, there was no statistically significant difference in composite ischemic endpoints at 30 days between bivalirudin-treated patients and heparin-treated patients (low SOE).
- In both clopidogrel pretreated and clopidogrel deferred patients, bivalirudin resulted in fewer major bleeding events at 30 days than heparin-based treatment (moderate SOE for clopidogrel pretreated patients and low SOE for clopidogrel deferred patients).
- In both clopidogrel pretreated and clopidogrel deferred patients, deferred GPI use resulted in fewer major bleeding events at 30 days when compared with upstream GPI use (moderate SOE for clopidogrel pretreated and high SOE for clopidogrel deferred).

Description of Included Studies

We identified 87 unique studies that evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 354,511 patients with UA/NSTEMI treated with an *early invasive approach* or PCI-based strategy.[23-109] Of these studies, 54 were RCTs (25 good quality, 23 fair, 6 poor) and 33 were observational (2 good quality, 24 fair, 7 poor) (see Table E-1 in Appendix E for quality and applicability of each included study). The majority of studies were published from 2000 through 2012, with two studies[28,73] published in 1999. Thirty-eight studies were single-center,[23,28,31,32,34,35,38,39,41,42,44,45,48,49,70,71,76,83,84,86-96,98,100-102,105,107-109] and 40 were multicenter;[24,25,29,30,33,36,43,46,47,50-56,59-63,65-69,72-75,77,80-82,85,97,99,103,104,106] in 9 studies,[26,27,37,40,57,58,64,78,79] the number of sites was unclear or not stated. Forty-four studies included sites in the United States or Canada,[24,25,29,30,33,43,46,48,53-55,58-63,65-69,72-74,78-80,83-85,88,90-92,96,98-100,103,104,107-109] 46 included sites in Europe,[23,26,28,30-32,34,36,39,42-44,46,49-52,54,55,57,58,61-63,65,66,68-70,73-77,80-82,86,93-95,97,101,102,104,106] 9 included sites in Asia,[27,35,38,40,41,45,66,71,74] 8 included sites in Australia or New Zealand,[30,47,55,62,65,80,87,104] 1 was in Israel,[89] and 4 included locations that were either unreported or unclear.[37,56,64,105] A total of 37 studies used industry funding,[23-25,29,30,32,36,37,43,46,47,50,53-56,58-68,73,74,77-80,96,97,103,104] 1 was government-only funded,[26] 6 were funded by nongovernment/nonindustry sources,[33,52,57,75,81,93] and funding was unclear or not reported in 43 studies.[27,28,31,34,35,38-42,44,45,48,49,51,69-72,76,82-92,94,95,98-102,105-109]

As stated in the Introduction, a large number of studies reported findings in patients treated with antiplatelets and/or anticoagulants as part of a PCI-based strategy and therefore did not delineate the findings into early invasive and initial conservative populations. In addition, results for the UA/NSTEMI population were often not presented separately from the acute coronary syndrome (ACS) population (including STEMI). The study characteristics table for KQ 1 (Table F-1 in Appendix F) contains details about the proportion of UA/NSTEMI patients, the proportion of patients undergoing PCI, and the proportion of patients undergoing an early invasive approach.

The majority of UA/NSTEMI studies assessed the comparative effectiveness of GPIs. We identified and abstracted 44 studies (25 RCTs, 19 observational) that evaluated the use of GPIs in 184,946 patients with UA/NSTEMI.[23-45,77-96,110]

- Five RCTs and five observational studies assessed the effectiveness of GPI versus placebo at the time of PCI.[24-28,83,93-96] In general, the studies assessing GPI at the time of PCI versus placebo reported a statistically significant reduction in the incidence of composite ischemic endpoints, in favor of GPI use, at 30 days (4% to 6%) versus placebo (8% to 10%).
- Three RCTs and seven observational studies assessed the effectiveness of upstream GPI versus GPI at the time of PCI.[29-31,86-92] In these studies, the incidence of composite ischemic endpoints varied dramatically across studies due to inclusion of stable angina, unstable angina, and MI patients. Additionally, there were multiple comparisons of GPI (abciximab versus abciximab, tirofiban versus tirofiban, abciximab versus tirofiban, abciximab versus eptifibatide, eptifibatide versus eptifibatide, eptifibatide versus tirofiban) that precluded direct comparison of a treatment effect of a specific GPI. No conclusions were made based on these observations.
- Two RCTs assessed the effectiveness of differential GPI treatment duration after PCI.[32,33] One study[32] involved the use of abciximab bolus versus abciximab bolus plus 12-hour infusion in 73 patients. There was no statistically significant difference in the incidence of outcomes in these patients at 30 days. In the other study,[33] 624 patients with stable angina and ACS were randomly assigned to eptifibatide double bolus and 2-hour infusion versus eptifibatide double bolus and 18-hour infusion. There was no statistically significant difference in the occurrence of the composite or individual ischemic endpoints; however, there was significantly lower major bleeding in the 2-hour infusion group.
- Two RCTs assessed the effectiveness with unique comparisons. One RCT evaluated high versus low tirofiban dose,[35] and one RCT evaluated GPI only in patients who had saphenous vein graft stenoses.[34] The study by Lin et al.[35] showed significantly higher platelet inhibition in the high-dose group, but similar rates of angiographic success between the two groups. Major bleeding events were higher in the high-dose group (10.4% versus 0%), but major adverse cardiac events were similar between groups. The study by Ozkan et al.[34] showed a significantly lower rate of no-flow or slow-flow through the vein graft in the treated group compared with the non-treated group (1 patient vs. 9 patients), but no significant differences in major adverse cardiac events or major bleeding.
- Five observational studies (including one study discussed above)[83] assessed the effectiveness of GPI treatment within specific subgroups of patients: patients with diabetes mellitus,[82,83] patients undergoing saphenous vein graft PCI,[84] patients undergoing rotational atherectomy,[85] and patients on chronic warfarin treatment.[81] Despite current guidelines, Bauer et al.[82] found that only 22.2 percent of diabetic patients received GPI, but found no difference in hospital mortality between those who received treatment and those who did not. They did find higher rates of postprocedural MI in patients receiving treatment prior to intervention. Velianou et al.[83] found significantly lower rates of 30-day mortality (0.6% vs. 3.0%) and repeat PCI (0% vs. 1.1%) in diabetic patients receiving GPI versus those who did not, but no significant differences in 30-day or 1-year rates of bypass surgery, MI, or a composite cardiac endpoint. Karha et al.[84]

showed that in patients undergoing saphenous vein graft PCI there was no significant difference in survival, myonecrosis, in-hospital morality, Q wave MI, or bleeding between those receiving GPI and those not. Berger et al.[85] found no significant differences in PCI success rates, major adverse cardiac events, or mortality in patients undergoing rotational atherectomy treated with GPI versus those who were not. In patients on chronic warfarin undergoing PCI, Lahtela et al.[81] showed higher rates of major bleeding (9.0% vs 1.5) in patients treated with GPI compared with those not treated, but no significant differences in rates of MACE.

- Twelve RCTs and four observational studies assessed the effectiveness of upstream versus deferred administration of GPI and are further described in comparison 1, below.

In the next section, we present the following six comparisons that were assessed in the included studies for KQ 1:

1. Upstream versus deferred administration of GPI (KQ 1a)
   - 16 studies (12 RCTs, 4 observational; 149,847 total patients)
2. Clopidogrel loading dose (KQ 1b)
   - 11 studies (8 RCTs, 3 observational; 36,347 total patients)
3. Clopidogrel versus ticagrelor or prasugrel (PCI cohort; KQ 1b)
   - 3 studies (3 RCTs; 33,216 total patients)
4. Bivalirudin versus a heparin-based strategy, without or with planned GPI (KQ 1b)
   - 13 studies (8 RCTs, 5 observational; 30,486 total patients)
5. Enoxaparin versus UFH versus fondaparinux (KQ 1b)
   - 13 studies (10 RCTs, 3 observational; 41,201 total patients)
6. Upstream or deferred clopidogrel administration (before or after PCI) in studies with a defined anticoagulant strategy (comparing bivalirudin versus a heparin-based therapy; KQ 1b) or a defined intravenous antiplatelet strategy (comparing upstream versus deferred GPI use; KQ 1a)
   - 18 studies (16 RCTs, 2 observational; 40,218 patients)

The subgroup findings (KQ 1c) are presented after each comparison.

Detailed Synthesis

1. Upstream Versus Deferred Glycoprotein Inhibitor Administration (KQ 1a)

Sixteen studies (12 RCTs and 4 observational) compared upstream versus deferred GPI administration in 149,847 patients.[23,36-45,77-80,110] The terms *upstream* and *pretreatment* both refer to the time before the PCI is begun, whereas *deferred* treatment means that GPI medications are delayed or given at the same time as the PCI.

Of the 16 studies, we were able to pool 11 RCTs[23,36,38-45,110] for meta-analysis (detailed in the next section). One RCT[37] was not analyzed since it was a *pilot study* of early versus late administration of eptifibatide with a primary outcome of serial cardiac marker release and infarct size in NSTEMI patients. The clinical and bleeding events (death, reinfarction, recurrent ischemia, composite endpoint, major bleeding) were *measured at 72 hours*, and no statistically significant differences were found between early and late GPI administration. The four observational studies (all rated fair quality) were not included in the meta-analysis due to the lack of clarity regarding the timing of PCI and early invasive management strategy.[77-80] In each of these studies, eptifibatide, tirofiban, and abciximab were used. The rate of composite ischemic

endpoints was inconsistent between groups and ranged from 4 to 9 percent in the upstream GPI group and 3 to 10 percent in the deferred GPI group.

Upstream (Precatheterization) Versus Deferred (Periprocedural) GPI Administration

Eleven RCTs (20,743 patients) compared an upstream versus deferred use of GPI and were included in our meta-analyses for one or more outcomes.[23,36,38-45,110] Of these 11 RCTs, 3 (27%) were rated good quality, 6 (55%) fair, and 2 (18%) poor. Sample sizes ranged from 100 to 9378 patients. Study duration ranged from 3 days to 319 days, and all reported 30 day outcomes. The GPIs administered included eptifibatide in 4 studies, tirofiban in 8 studies, and abciximab in 2 studies.

The mean age of study participants ranged from 53 to 68 years. The proportion of female patients ranged from 27 to 54 percent. None of the studies reported the racial and ethnic demographics of study participants. No studies (0%) were conducted within the United States or Canada; they were all international with the exception of one study where the location was not reported. Funding source was reported in four studies (36%), all of which were funded by an industry source.

The following outcomes were quantitatively assessed: composite ischemic endpoints at 30 days and 6 months, all-cause mortality at 30 days, nonfatal MI at 30 days, revascularization at 30 days and 6 months, major bleeding at 30 days, and minor bleeding at 30 days. Outcomes including all-cause mortality at 6 months, nonfatal MI at 6 months, and revascularization at 6 months did not have sufficient data to be meta-analyzed and have been qualitatively described below. Results for all studies in this comparison are included in Table G-1 in Appendix G.

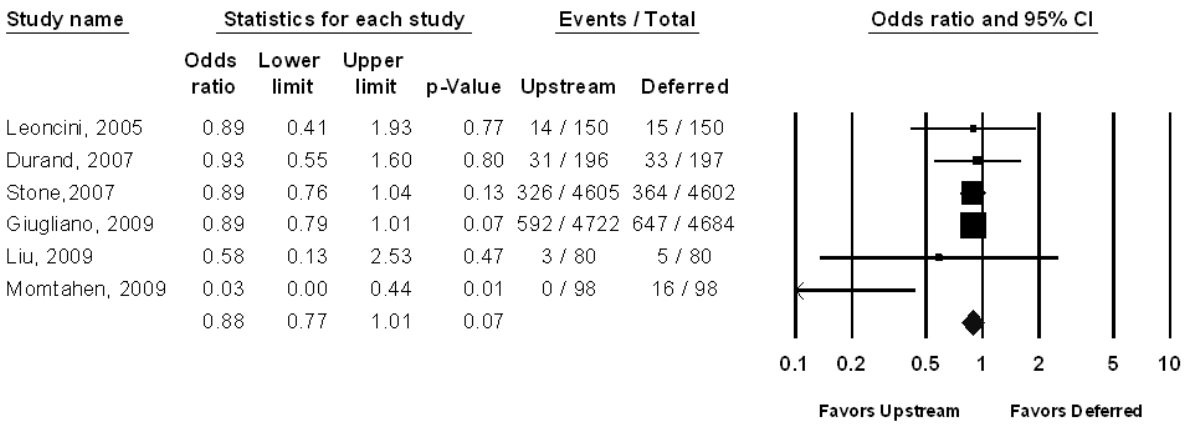
Effect on Composite Endpoint of All-Cause Mortality, Nonfatal Myocardial Infarction, or Revascularization at 30 Days

A random-effects meta-analysis of six RCTs[36,39-41,43,110] (2 good quality, 3 fair, 1 poor) including 19,662 UA/NSTEMI patients reporting the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 30 days found that the odds ratio was 0.88 (95% CI, 0.77 to 1.01), demonstrating no statistically significant difference between upstream GPI and deferred GPI (Figure 4). There was no evidence of heterogeneity, with a Q-value of 6.35 for 5 degrees of freedom, p=0.27.

The result from one fair-quality study by Momtahen[40] was different from the other studies. Potential reasons for this difference include that the study was conducted at a single center in Iran, did not clearly enroll consecutive patients, and had a small sample size (n=196). We performed sensitivity analyses to understand the impact of the Momtahen study by running a fixed-effects model and another with that study removed. A fixed-effects model resulted in a summary odds ratio of 0.89 (95% CI, 0.81 to 0.97, p=0.01) favoring upstream GPI administration, which suggests that the summary estimate is sensitive to a random-effects versus a fixed-effects model. Removal of the Momtahen study resulted in an odds ratio of 0.89 (95% CI, 0.81 to 0.98, p=0.02) favoring upstream GPI administration in both the fixed- and random-effects models. There was no evidence of heterogeneity by Q-value or I^2 statistic with the fixed- or random-effects models, with or without the Momtahen study. Study quality affected the individual study precision, with the poor study[39] and fair studies[36,40,41] having wider CIs. The studies were consistent with fewer composite events occurring in the upstream GPI group.

The SOE was rated low for the composite endpoint at 30 days based on imprecise results across the six RCTs (although the two large, good-quality RCTs were consistent) that upstream GPI is not superior to deferred GPI.

Figure 4. Meta-analysis of upstream versus deferred glycoprotein inhibitor use on composite endpoint of all-cause mortality, nonfatal myocardial infarction, or revascularization at 30 days

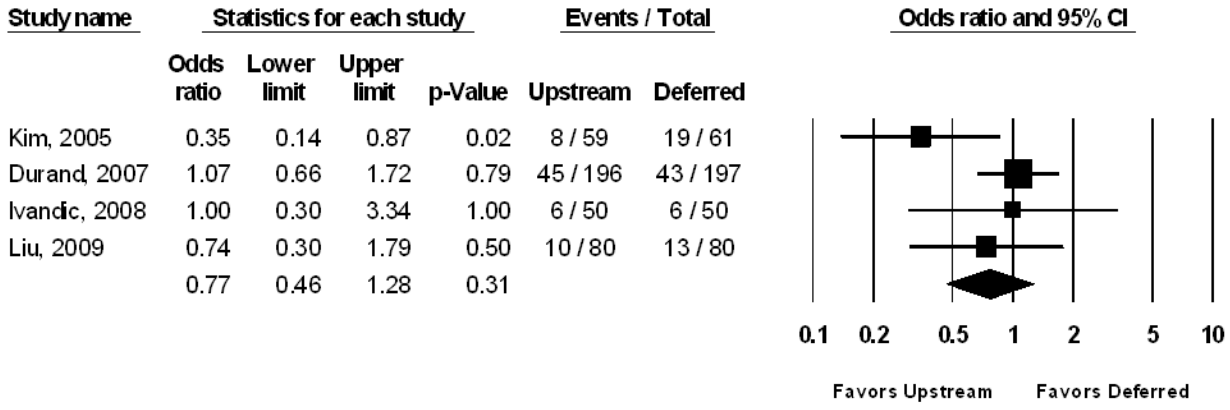


CI = confidence interval

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal Myocardial Infarction, or Revascularization After 6 Months

A random-effects meta-analysis of four RCTs[23,36,41,45] (all fair quality) including 773 UA/NSTEMI patients reporting the composite outcome of all-cause mortality, nonfatal MI, or revascularization after 6 months found that the odds ratio was 0.77 (95% CI, 0.46 to 1.28) demonstrating no significant difference between upstream or deferred GPI use (Figure 5). There was no evidence of heterogeneity, with a Q-value of 4.68 for 3 degrees of freedom, p=0.20. The results from one fair-quality study by Kim[45] were different from the other studies. Potential reasons for this difference include that the study was conducted at a single center in Asia, did not clearly enroll consecutive patients, and had a small sample size (n=120). The SOE was rated insufficient for the composite outcome after 6 months based on four fair-quality RCTs with mostly consistent results of a direct outcome and a wide confidence interval that crossed 1.

Figure 5. Meta-analysis of upstream versus deferred glycoprotein inhibitor use on composite endpoint of all-cause mortality, nonfatal myocardial infarction, or revascularization after 6 months



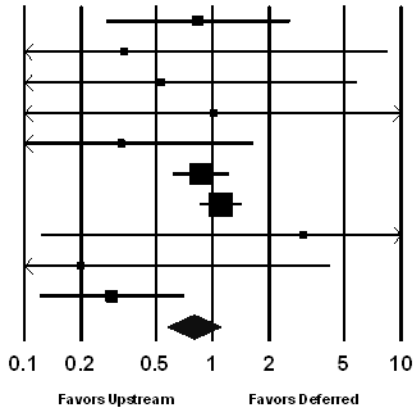
CI = confidence interval

Effect on All-Cause Mortality at 30 Days

A random-effects meta-analysis of 10 RCTs[36,38-45,110] (3 good quality, 5 fair, 2 poor) including 20,521 UA/NSTEMI patients reporting all-cause mortality at 30 days found that the odds ratio was 0.80 (95% CI, 0.57 to 1.11), demonstrating no statistically significant difference between upstream GPI and deferred GPI (Figure 6). There was no evidence of heterogeneity, with a Q-value of 12.31 for 9 degrees of freedom, p=0.20. The inclusion of one good, four fair, and two poor quality single-center studies likely contributed to the inconsistent results.[38-42,44,45] Removal of the two poor-quality studies[39,42] resulted in a similar summary estimate (OR 0.76; 95% CI, 0.50 to 1.14) when compared with the full model, and there was no evidence of heterogeneity. The overall SOE was rated insufficient for all-cause mortality at 30 days based on three good-, five fair-, and two poor-quality RCTs with inconsistent results of a direct outcome and a wide confidence interval.

Figure 6. Meta-analysis of upstream versus deferred glycoprotein inhibitor use on all-cause mortality at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Upstream	Deferred
van't Hof, 2003	0.83	0.27	2.57	0.75	6 / 111	7 / 109
Kim, 2005	0.34	0.01	8.48	0.51	0 / 59	1 / 61
Leoncini, 2005	0.54	0.05	5.80	0.61	1 / 150	2 / 150
Rasoul, 2006	1.02	0.06	16.41	0.99	1 / 162	1 / 163
Durand, 2007	0.33	0.07	1.64	0.17	2 / 196	6 / 197
Stone, 2007	0.86	0.61	1.23	0.41	60 / 4605	69 / 4602
Giugliano, 2009	1.10	0.86	1.42	0.44	134 / 4722	121 / 4684
Liu, 2009	3.04	0.12	75.69	0.50	1 / 80	0 / 80
Momtahen, 2009	0.20	0.01	4.22	0.30	0 / 98	2 / 98
Bhattacharya, 2010	0.29	0.12	0.71	0.01	7 / 122	23 / 133
	0.80	0.57	1.11	0.17		



CI = confidence interval

Effect on All-Cause Mortality at 6 Months

Of the three RCTs (all fair quality) that reported the incidence of all-cause mortality at 6 months, one study involving 120 patients reported no deaths in either treatment arm,[45] and one study involving 160 patients reported a single death in the upstream GPI arm.[41] The remaining study[36] included 393 UA/NSTEMI patients and reported similar all-cause mortality rates at 6 months of 2.0 percent and 3.6 percent (p=0.36) for upstream and deferred GPI use, respectively. The SOE was rated insufficient for all-cause mortality at 6 months based on a low event rate in three RCTs, which rendered the trials underpowered to answer the question.

Effect on Nonfatal MI at 30 Days

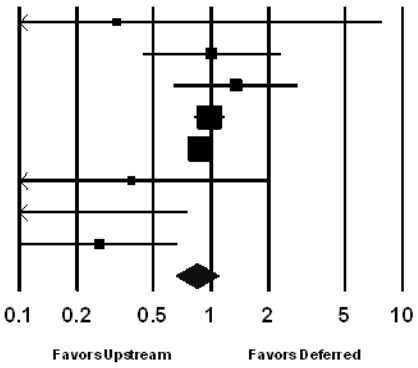
Nine RCTs[36,38-41,43-45,110] (three good quality, five fair, and one poor) involving 20,263 UA/NSTEMI patients reported the incidence of nonfatal MI at 30 days. The study by Kim et al.[45] had no events in either treatment arm and was not included in the random-effects meta-analysis. Figure 7 shows the odds ratio was 0.84 (95% CI, 0.65 to 1.10), demonstrating no statistically significant difference between upstream GPI and deferred GPI. There was evidence of some heterogeneity, with a Q-value of 14.37 for 7 degrees of freedom, p=0.05. The I^2 value was 51.29.

The inclusion of one good-quality, three fair-quality, and one poor-quality single-center studies[38-41,44] likely contributed to the inconsistent results and heterogeneity. In the two largest studies (good quality)[43,110] by Giugliano and Stone of 18,585 patients, the results were consistent but still not statistically significant. We performed sensitivity analyses to understand the impact of the Momtahen study by running a fixed-effects model and another with that study removed.

A fixed-effects model resulted in a summary odds ratio of 0.90 (95% CI, 0.81 to 1.00, p=0.06) favoring upstream GPI administration, while removal of the Momtahen study resulted in a fixed-effects odds ratio of 0.91 (95% CI, 0.81 to 1.01, p=0.26) and a random-effects odds ratio of 0.88 (95% CI, 0.71 to 1.10, p=0.26). Heterogeneity was reduced to an I^2 of 40.25. The SOE was rated insufficient for nonfatal MI at 30 days based on three good-, five fair-, and one poor-quality RCTs with inconsistent results of a direct outcome and a statistically nonsignificant confidence interval.

Figure 7. Meta-analysis of upstream versus deferred glycoprotein inhibitor use on nonfatal myocardial infarction at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Events / Total Upstream	Events / Total Deferred
Leoncini, 2005	0.32	0.01	7.82	0.49	0 / 150	1 / 150
Rasoul, 2006	1.01	0.44	2.31	0.99	12 / 162	12 / 163
Durand, 2007	1.34	0.63	2.85	0.44	17 / 196	13 / 197
Stone, 2007	0.98	0.81	1.18	0.82	226 / 4605	230 / 4602
Giugliano, 2009	0.89	0.77	1.01	0.08	447 / 4722	495 / 4684
Liu, 2009	0.38	0.07	2.04	0.26	2 / 80	5 / 80
Momtahen, 2009	0.04	0.00	0.76	0.03	0 / 98	10 / 98
Bhattacharya, 2010	0.26	0.10	0.67	0.01	6 / 122	22 / 133
	0.84	0.65	1.10	0.21		



CI = confidence interval

Effect on Nonfatal MI at 6 Months

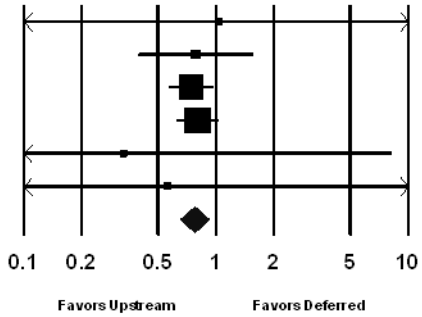
Of the three RCTs (all fair quality) that reported the incidence of nonfatal MI, one study involving 120 patients reported a single MI in the deferred GPI treatment arm.[45] The remaining two studies[36,41] included 553 UA/NSTEMI patients and reported similar nonfatal MI rates (12% vs. 15%, p=0.65;[41] 10% vs. 9%, p=0.59[36]) at 6 months for upstream versus deferred GPI use, respectively. The SOE was rated insufficient for nonfatal MI at 6 months based on three RCTs with inconsistent results.

Effect on Revascularization at 30 Days

A random-effects meta-analysis of six RCTs[36,40,41,43,45,110] (2 good quality, 4 fair) including 19,454 UA/NSTEMI patients reporting the need for revascularization at 30 days found that the odds ratio was 0.77 (95% CI, 0.65 to 0.92), demonstrating a statistically significant reduction in revascularization favoring upstream GPI compared with deferred GPI (Figure 8). There was no evidence of heterogeneity, with a Q-value of 0.49 for 5 degrees of freedom, p=0.99. The SOE was rated high for revascularization at 30 days based on three good- and three fair-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

Figure 8. Meta-analysis of upstream versus deferred glycoprotein inhibitor use on revascularization at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Upstream	Deferred
Kim, 2005	1.031	0.063	16.903	0.983	1 / 59	1 / 61
Durand, 2007	0.787	0.395	1.567	0.495	16 / 196	20 / 197
Stone, 2007	0.745	0.570	0.972	0.030	97 / 4605	129 / 4602
Giugliano, 2009	0.799	0.620	1.028	0.081	112 / 4722	138 / 4684
Liu, 2009	0.329	0.013	8.203	0.498	0 / 80	1 / 80
Momtahen, 2009	0.558	0.017	18.011	0.742	0 / 98	0 / 98
	0.772	0.647	0.921	0.004		



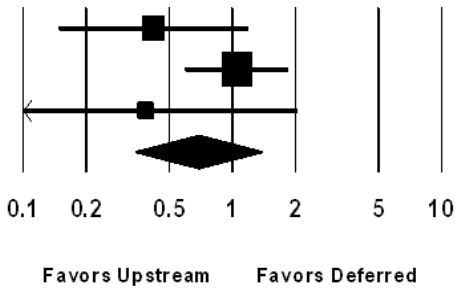
CI = confidence interval

Effect on Revascularization at 6 Months

Of the three RCTs (all fair quality) that included 673 UA/NSTEMI patients reporting the incidence of revascularization at 6 months, there were similar pooled rates of revascularization at 6 months in the upstream GPI (10.7%) versus deferred GPI (13.3%) treatment arms.[36,41,45] A random-effects model of three studies comparing upstream with deferred GPI use resulted in a summary odds ratio of 0.69 (95% CI, 0.34 to 1.39, p=0.30) (Figure 9). There was no evidence of heterogeneity with a Q-value of 3.09 for 2 degrees of freedom, p=0.21. The SOE was rated insufficient for revascularization at 6 months based on three RCTs with an imprecise estimate and inconsistent results.

Figure 9. Meta-analysis of upstream versus deferred glycoprotein inhibitor use on revascularization at 6 months

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Upstream	Deferred
Kim, 2005	0.42	0.15	1.19	0.10	6 / 59	13 / 61
Durand, 2007	1.05	0.59	1.86	0.86	28 / 196	27 / 197
Liu, 2009	0.38	0.07	2.04	0.26	2 / 80	5 / 80
	0.69	0.34	1.39	0.30		



CI = confidence interval

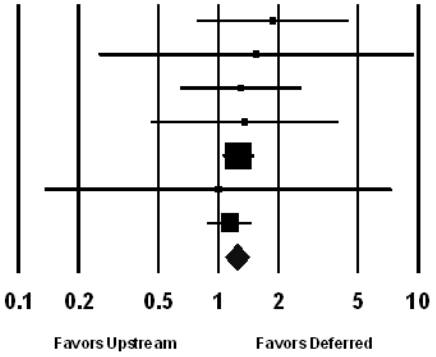
Effect on Major Bleeding at 30 Days

Nine RCTs[23,36,39,40,42-45,110] (2 good quality, 5 fair, 2 poor) including 20,242 UA/NSTEMI patients reported the incidence of major bleeding at 30 days. Two studies were excluded from the meta-analysis because no endpoints occurred in either treatment group.[40,45] Figure 10 shows that the odds ratio was 1.24 (95% CI, 1.08 to 1.43), demonstrating a statistically significant reduction in major bleeding favoring deferred GPI. There was no evidence of heterogeneity, with a Q-

value of 1.43 for 6 degrees of freedom, p=0.96. The SOE was rated high for major bleeding at 30 days based on two good-, five fair-, and two poor-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

Figure 10. Meta-analysis of upstream versus deferred glycoprotein inhibitor use on major bleeding at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Upstream	Deferred
van't Hof, 2003	1.872	0.780	4.493	0.160	16 / 111	9 / 109
Leoncini, 2005	1.549	0.252	9.537	0.637	3 / 150	2 / 150
Rasoul, 2006	1.294	0.645	2.597	0.468	20 / 162	16 / 163
Durand, 2007	1.352	0.460	3.970	0.583	8 / 196	6 / 197
Stone, 2007	1.261	1.053	1.510	0.012	281 / 4605	225 / 4602
Ivandic, 2008	1.000	0.135	7.392	1.000	2 / 50	2 / 50
Giugliano, 2009	1.141	0.881	1.477	0.317	127 / 4627	111 / 4597
	1.239	1.077	1.427	0.003		



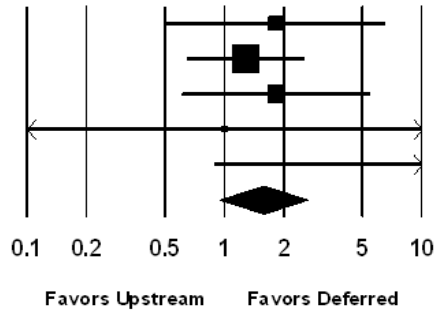
CI = confidence interval

Effect on Minor Bleeding at 30 Days

A random-effects meta-analysis of five RCTs[23,36,40,41,45] (all fair quality) including 969 UA/NSTEMI patients reporting minor bleeding at 30 days found that the odds ratio was 1.58 (95% CI, 0.95 to 2.64), showing a reduction in minor bleeding with deferred GPI which did not reach statistical significance (Figure 11). There was no evidence of heterogeneity, with a Q-value of 3.028 for 4 degrees of freedom, p=0.553. One study by Momtahen[40] reported no minor bleeding events in the deferred GPI treatment arm and seven minor bleeding events in the upstream GPI arm, thus contributing to inconsistency and imprecision of results. The SOE was rated insufficient for minor bleeding at 30 days based on five fair-quality RCTs with inconsistent results of a direct outcome and a wide confidence interval.

Figure 11. Meta-analysis of upstream versus deferred glycoprotein inhibitor use on minor bleeding at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Upstream	Deferred
Kim, 2005	1.82	0.51	6.49	0.35	7 / 80	4 / 80
Durand, 2007	1.29	0.65	2.56	0.48	20 / 196	16 / 197
Ivandic, 2008	1.83	0.61	5.50	0.28	10 / 50	6 / 50
Liu, 2009	1.00	0.06	16.27	1.00	1 / 80	1 / 80
Momtahen, 2009	15.82	0.89	281.43	0.06	7 / 98	0 / 98
	1.58	0.95	2.64	0.08		



CI = confidence interval

Findings by Subgroup (KQ 1c)

Two studies[43,110] (both good quality) reported variations in treatment effectiveness by subgroup. Subgroups analyzed were age, sex, diabetes, chronic renal disease, troponin positivity, and TIMI risk score. Prespecified subgroup analyses of intended clopidogrel pretreatment are covered in a separate section of this report. Race, type of coronary stent, presence of smoking, geographic location, and other patient and demographic characteristics were not clearly described. The SOE for subgroup findings was rated insufficient since there are only two studies that looked at subgroups, and some of the subgroup definitions were heterogeneous (e.g., age grouping, or definition of renal insufficiency) which did not allow for direct comparison. Table H-1 in Appendix H presents the results data for these subgroups.

Age

There were two studies comparing the efficacy of upstream GPI use versus deferred GPI use in different age subgroups. In the first study, in a subgroup of 7026 patients under age 75, composite ischemic endpoints in patients treated with upstream GPI use (8.6%) was lower when compared with deferred GPI use (9.5%) but was statistically nonsignificant. In the other subgroup of 2377 patients over age 75, there was no difference in ischemic event rates in those who were treated with upstream GPI use (11.4%) or deferred GPI use (11.4%).[43]

Similar composite ischemic event rates occurred in the subgroup of 5054 patients under age 65 in the ACUITY TIMING study treated with upstream GPI use (6.4%) versus deferred GPI use (6.6%). There was no difference in major bleeding events in this subgroup (upstream GPI=3.7%; deferred GPI=4.1%). In the subgroup of 4153 patients over age 65, there was a reduction in ischemic events with upstream GPI use (7.7%) when compared with deferred GPI use (9.8%). In patients over age 65, there was a statistically significant reduction in major bleeding favoring treatment with deferred GPI use (6.3%) versus upstream GPI use (8.5%).[110]

Sex

There were two studies of upstream versus deferred GPI use reporting subgroup results for men versus women. In the first study, in a subgroup of 6431 male patients, there was a statistically nonsignificant reduction in the incidence of composite ischemic endpoints for men treated with upstream GPI use (9.1%) when compared with deferred GPI use (9.8%). A similar statistically nonsignificant reduction in ischemic events was observed in the 2975 female patients in this study who were treated with upstream GPI use (9.7%) versus deferred GPI use (10.4%).[43]

In the other study, there was a similar statistically nonsignificant trend toward a reduction in ischemic events in the 6467 male patients who were treated with upstream GPI use (7.0%) when compared with deferred GPI use (8.5%). The lower rate of major bleeding was statistically significant in men treated with deferred GPI use (3.4%) when compared with upstream GPI use (4.6%). However, there was a slightly higher rate of ischemic events in the 2740 female patients treated with upstream GPI use (7.2%) when compared with deferred GPI use (6.5%), p=NS. There was no difference in major bleeding in women (upstream GPI=9.7%; deferred GPI=8.3%).[110]

Diabetes Mellitus

Two studies compared the efficacy of upstream versus deferred GPI use among patients with and without diabetes mellitus. In one study of 2860 patients with diabetes, there was a statistically nonsignificant reduction in the incidence of composite ischemic events when diabetic patients were treated with upstream GPI use (8.9%) versus deferred GPI use (10.6%).[43]

In the other study of 2565 patients with diabetes, a similar nonsignificant reduction in ischemic events was observed in patients treated with upstream GPI use (8.4%) when compared with deferred GPI use (9.7%). There was a nonsignificant reduction in major bleeding in patients treated with deferred GPI use (4.4%) versus upstream GPI use (5.6%).[110]

Chronic Kidney Disease

There were two studies reporting subgroup results for patients with chronic kidney disease (CKD) treated with upstream versus deferred GPI use. In the EARLY ACS study, there was no statistically significant difference in composite ischemic endpoints or bleeding events in patients with CrCl<50 ml/min.[43] In ACUITY TIMING, there was a statistically nonsignificant trend toward higher ischemic event rates in patients with CrCl less than 60 ml/min treated with upstream GPI use (11.8%) when compared with deferred GPI use (9.2%). A statistically significant reduction in major bleeding events was observed in patients with CrCl less than 60 ml/min favoring patients treated with deferred GPI use (8.5%) versus upstream GPI use (12.8%).[110]

Serum Biomarker Level

Two studies of upstream versus deferred GPI use reported results for patients with elevated serum biomarkers (CK-MB or troponin) on presentation. In 7650 patients with an abnormal troponin level in EARLY ACS, there was a statistically nonsignificant trend toward a reduction in composite ischemic events with upstream GPI use (9.5%) when compared with deferred GPI use (10.6%).[43] In 4962 patients with an abnormal CK-MB or troponin level in ACUITY TIMING, there was no difference in composite ischemic events with upstream GPI use (9.1%) versus deferred GPI use (8.3%). There was a statistically significant difference in major bleeding events favoring patients treated with deferred GPI use (5.6%) when compared with upstream GPI use (7.2%).[110]

TIMI Risk Score

Two studies of upstream versus deferred GPI use reported results for patients' TIMI risk score on presentation. In both EARLY ACS and ACUITY TIMING, there was no difference in the incidence of composite ischemic endpoints between any level of TIMI risk score (low, intermediate, high).[43,110] There were statistically nonsignificant reductions in major bleeding favoring deferred GPI use in patients with intermediate (upstream GPI 5.6%; deferred GPI 4.4%) and high (upstream GPI 8.2%; deferred GPI 6.3%) TIMI risk score.[110]

Summary of Results for Upstream Versus Deferred GPI Administration

In our analysis of upstream versus deferred GPI administration, we found no statistically significant difference between upstream and deferred GPI therapy for the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 30 days and 6 months. For the individual outcomes of all-cause mortality and nonfatal MI, there was no statistically significant difference between upstream and deferred GPI therapy at 30 days, but the results are less certain at 6 months since fewer trials reported results at this time point, although the ones that did report outcomes also showed no difference. For revascularization, there was a statistically significant difference favoring upstream GPI therapy at 30 days, but the results are less certain at 6 months due to a small number of trials that showed no difference in outcomes. For bleeding outcomes, there was a statistically significant difference favoring deferred GPI therapy in major bleeding events at 30 days but no statistically significant differences between therapies in minor bleeding

events at 30 days. No studies reported the occurrence of stent thrombosis during study followup. In summary, upstream GPI reduced short-term revascularization at the cost of increased short-term major bleeding, and the final impact on clinical outcomes is likely somewhere in the middle, although the studies are too inconsistent or imprecise to determine whether the net benefit is truly zero or whether there is a small benefit from either therapy.

Subgroups analyzed in two studies included age, sex, diabetes, chronic renal disease, troponin positivity, and TIMI risk score and most findings showed statistically nonsignificant reductions in ischemic outcomes from upstream GPI; the only statistically significant findings were a lower risk of major bleeding favoring treatment with deferred GPI use in patients over age 65, CrCl less than 60 ml/min, and elevated serum biomarkers (all findings from one RCT). Detailed SOE ratings are shown in Table 5. Odds ratios less than 1 favor upstream GPI; odds ratios greater than 1 favor deferred GPI.

Table 5. Detailed strength of evidence for UA/NSTEMI patients treated with upstream versus deferred glycoprotein inhibitor

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 30 Days					Low SOE
6 (19,662)	6 RCTs/2 good quality, 3 fair, 1 poor	Consistent	Direct	Imprecise	OR 0.88 (0.77 to 1.01) No difference
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization After 6 Months					Insufficient SOE
4 (773)	4 RCTs/All fair quality	Consistent	Direct	Imprecise	OR 0.77 (0.46 to 1.28)
All-cause Mortality at 30 Days					Insufficient SOE
10 (20,521)	10 RCTs/3 good quality, 5 fair, 2 poor	Inconsistent	Direct	Imprecise	OR 0.80 (0.57 to 1.11)
All-Cause Mortality at 6 Months					Insufficient SOE
3 (673)	3 RCTs/All fair quality	Inconsistent	Direct	Imprecise	1 study reported no deaths in both arms; 1 study reported 1 death in the upstream GPI arm; 1 study reported similar rates (2.0% upstream GPI, 3.6% deferred GPI)
Nonfatal MI at 30 Days					Insufficient SOE
9 (20,263)	9 RCTs/3 good quality, 5 fair, 1 poor	Inconsistent	Direct	Imprecise	OR 0.84 (0.65 to 1.10)
Nonfatal MI at 6 Months					Insufficient SOE
3 (673)	3 RCTs/All fair quality	Inconsistent	Direct	Imprecise	1 study reported 1 MI in the deferred GPI arm only; 2 other studies reported MI rates of 12% upstream vs. 15% deferred, and 10% upstream and 9% deferred
Revascularization at 30 Days					High SOE
6 (19,454)	6 RCTs/3 good quality, 3 fair	Consistent	Direct	Precise	OR 0.77 (0.65 to 0.92) Favors upstream GPI

Table 5. Detailed strength of evidence for UA/NSTEMI patients treated with upstream versus deferred glycoprotein inhibitor (continued)

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	2. Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Revascularization at 6 Months					Insufficient SOE
3 (673)	3 RCTs/3 fair quality	Inconsistent	Direct	Imprecise	OR 0.69 (0.34 to 1.39)
Major Bleeding at 30 Days					High SOE
9 (20,242)	9 RCTs/2 good quality, 5 fair, 2 poor	Consistent	Direct	Precise	OR 1.24 (1.08 to 1.43) Favors deferred GPI
Minor Bleeding at 30 Days					Insufficient SOE
5 (969)	5 RCTs/All fair quality	Inconsistent	Direct	Imprecise	OR 1.58 (0.95 to 2.64)
Stent thrombosis at 30 Days					Insufficient SOE
0	NA	NA	NA	NA	NA

CI = confidence interval; GPI = glycoprotein inhibitor; MI = myocardial infarction; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

2. Clopidogrel Loading Dose (KQ 1b)

Eleven studies (8 RCTs, 3 observational) compared loading doses of clopidogrel in 36,347 UA/NSTEMI patients undergoing an invasive strategy.[46-53,97-99] Outcomes assessed in this comparison included composite ischemic endpoints, all-cause mortality, cardiovascular mortality, nonfatal MI, nonfatal stroke, revascularization, stent thrombosis, major bleeding, and minor bleeding. Results for all studies in this comparison are included in Table G-2 in Appendix G. We outline below the types of comparisons in these clopidogrel loading studies and describe qualitatively those studies which were too heterogeneous in terms of dose or population to synthesize quantitatively:

- Two studies of clopidogrel versus placebo.[52,53] One RCT of clopidogrel loading dose (600 mg) versus placebo (0 mg) in 647 ACS and stable patients previously treated with clopidogrel.[52] In this study, those treated with an additional dose of clopidogrel had an incidence of 30-day composite ischemic endpoints of 5 percent compared with 7 percent in those receiving a placebo loading dose. Another RCT, of an additional clopidogrel loading dose (600 mg) in patients with poor clopidogrel responsiveness to an initial clopidogrel loading dose versus placebo in patients with standard clopidogrel responsiveness.[53] In this study of 2214 ACS and stable patients, there was no difference in the incidence of 30-day composite ischemic endpoints between the groups at 2.3 percent.
- Three observational studies (one good quality, two fair).[97-99] lacked a standard loading dose (300 mg or 600 mg) in one treatment arm or had heterogeneity in the patient populations (an unselected PCI population), and we therefore describe these qualitatively. One study[97] reported fewer all-cause deaths (7.9% vs. 10.2%) and similar major bleeding (3.2% vs. 3.7%) in patients who received a loading dose of clopidogrel (300 mg or 600 mg) versus patients who did not receive a loading dose, respectively. In another study,[98] the incidence of composite ischemic endpoints was statistically significantly lower (2.9% vs. 5.2%), and the incidence of major bleeding was not different (0.2% vs. 0.5%) in unselected PCI patients receiving 600 mg clopidogrel loading dose versus 300 mg

clopidogrel loading dose, respectively. The last observational study[99] reported statistically significantly higher rates of composite ischemic endpoints (37.1% vs. 20.5%) in ACS patients treated with greater than 300 mg clopidogrel loading dose versus a 300 mg clopidogrel loading dose, respectively.

- Six RCTs compared clopidogrel 300 mg loading dose with clopidogrel 600 mg loading dose and included a total of 26,211 patients.[46-51] One RCT[50] was the only study to also randomly assign patients to clopidogrel 900 mg loading dose. These six RCTs are synthesized below

Of the six RCTs included in the endpoint findings described below, two (33%) were rated good quality and four (66%) fair. Sample sizes for included individual studies ranged from 103 to 25,806 patients. All included RCTs reported 30 day outcomes, while two observational studies reported 30 day outcomes and one study reported 6 month outcomes.

The mean age of study participants ranged from 57 to 65 years of age. The proportion of female patients ranged from 23 to 35 percent. Two studies (33%) reported the racial and ethnic demographics of study participants. Two studies (33%) were conducted within the United States or Canada, with the rest international. Funding source was reported in three studies (50%), with all three studies funded by industry source.

Effect on Composite Ischemic Endpoints at 30 Days and 6 Months

Five RCTs reported composite ischemic endpoints at 30 days in patients treated with a clopidogrel loading dose of 600 mg versus 300 mg; however, each of the five studies reported different composite endpoints.[46,48-51] Because of this, a meta-analysis was not performed and the results are described qualitatively below. In the largest study of 25,086 UA/NSTEMI patients (good quality), the incidence of cardiovascular mortality, nonfatal MI, or nonfatal stroke was not different in the clopidogrel 600 mg loading dose group (4.2%) versus 300 mg loading dose group (4.4%) (HR 0.94; 95% CI, 0.83 to 1.06; p=0.30).[46] The SOE was rated low for this composite outcome at 30 days based on a large, good-quality RCT that was sufficiently powered to assess this endpoint.

Four single-center RCTs reported a lower incidence of a composite ischemic outcome with clopidogrel 600 mg loading dose. One fair-quality study of 119 patients reported a lower incidence of cardiovascular mortality, nonfatal MI, or revascularization in the clopidogrel 600 mg loading dose group (10.4%) versus 300 mg loading dose group (23.8%).[48] One fair-quality study of 387 patients reported a lower incidence of cardiovascular mortality, nonfatal stroke, or recurrent ACS in the clopidogrel 600 mg loading dose group (4.8%) versus 300 mg loading dose group (12.3%).[49] Similarly, another fair-quality study of 103 patients reported a lower incidence of all-cause mortality, nonfatal MI, revascularization, or rehospitalization in the clopidogrel 600 mg loading dose group (5.9%) versus 300 mg loading dose group (11.4%).[50] Of note, there were no occurrences of the same composite endpoint in 34 patients receiving clopidogrel 900 mg loading dose (third treatment arm). In the final good-quality study of 255 patients reporting a 30-day composite ischemic endpoint, there was a lower incidence of all-cause mortality, nonfatal MI, or revascularization in the clopidogrel 600 mg loading dose group (4.0%) versus 300 mg loading dose group (11.6%).[51] The SOE was rated insufficient for the four other single-center studies at 30 days due to smaller sample sizes and imprecise estimates of effect, which may be due to the composite endpoint definition; i.e., inclusion of revascularization, recurrent ACS, or rehospitalization.

Only one good-quality study of 256 UA/NSTEMI patients reported a composite ischemic endpoint at 6 months in different clopidogrel loading doses. There was a similar incidence of all-cause mortality, nonfatal MI, nonfatal stroke, or rehospitalization for recurrent ischemia at 6 months in the clopidogrel 600 mg loading dose group (13.3%) versus 300 mg loading dose group (13.2%).[47] The SOE was rated insufficient for composite ischemic endpoints at 6 months based on findings from one small trial and an imprecise estimate.

Effect on All-Cause Mortality at 30 Days and 6 Months

Of the three RCTs (two good quality, one fair) that reported the incidence of all-cause mortality at 30 days, two studies involving 358 patients reported no deaths in either treatment arm.[50,51] The remaining study (good quality)[46] included 25,086 UA/NSTEMI patients and reported similar all-cause mortality rates at 30 days for clopidogrel 300 mg loading dose versus 600 mg loading dose (2.3% vs. 2.4%) (HR 0.93; 95 % CI, 0.83 to 1.05, p=0.25). The SOE was rated low for no difference in all-cause mortality at 30 days based on a single large, good-quality RCT.

Only one study (fair quality) in 256 patients reported the incidence of all-cause mortality at 6 months.[47] There were only four deaths in the overall cohort (three in 300 mg loading dose group, one in 600 mg loading dose group). The SOE was rated insufficient for all-cause mortality at 6 months based on a single small, fair-quality RCT.

Effect on Cardiovascular Mortality at 30 Days

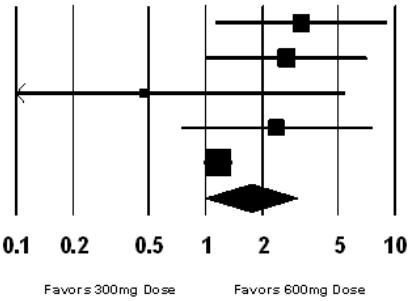
Of these three RCTs (one good quality, two fair) with 25,497 patients that reported the incidence of cardiovascular mortality at 30 days, there was one good-quality study[46] that included 25,086 patients and reported similar outcomes in the 300 mg loading dose group (2.2%) versus 600 mg loading dose (2.1%), HR 0.95 (95% CI, 0.81 to 1.13). The results of one fair-quality study reported one cardiovascular death in the clopidogrel 300 mg loading dose group and no deaths in the 600 mg loading dose group.[49] The other fair-quality study reported a higher rate of cardiovascular mortality at 30 days in patients treated with clopidogrel 300 mg loading dose (2.4%) when compared with 600 mg loading dose (1.3%).[48] The SOE was rated low for no difference in cardiovascular mortality at 30 days based on one good- and two fair-quality RCTs with inconsistent results of a direct outcome.

Effect on Nonfatal MI at 30 Days

A random-effects meta-analysis of five RCTs[46,48-51] (two good quality, three fair) including 25,855 UA/NSTEMI patients reporting nonfatal MI at 30 days found that the odds ratio was 1.74 (95% CI, 0.99 to 3.05) showing a reduction in nonfatal MI favoring clopidogrel 600 mg, which did not reach statistical significance (Figure 12). There was some evidence of heterogeneity, with a Q-value of 7.832 for 4 degrees of freedom, p=0.098. The I^2 value was 48.927. The largest RCT by Mehta resulted in an odds ratio of 1.16 (95% CI, 0.98 to 1.38). The inclusion of four single-center studies of fair-quality with a diverse patient population (not entirely UA/NSTEMI patients) likely contributed to the inconsistent and imprecise results. The SOE was rated low for nonfatal MI at 30 days based on two good- and three fair-quality RCTs with inconsistent and imprecise results of a direct outcome.

Figure 12. Meta-analysis of 300 mg versus 600 mg clopidogrel loading dose on nonfatal myocardial infarction at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Clop 300 mg	Clop 600 mg
Patti, 2005	3.18	1.12	9.04	0.03	15 / 129	5 / 126
Cuisset, 2006	2.67	1.01	7.09	0.05	15 / 146	6 / 146
Montalescot, 2006	0.47	0.04	5.45	0.55	1 / 35	2 / 34
Abuzahra, 2008	2.37	0.74	7.57	0.15	7 / 42	6 / 77
Mehta, 2010	1.16	0.97	1.38	0.09	276 / 12566	238 / 12520
	1.74	0.99	3.05	0.05		



CI = confidence interval; Clop = clopidogrel; mg = milligram

Effect on Nonfatal MI at 6 Months

Only one RCT (fair quality) with 256 patients reported the incidence of nonfatal MI at 6 months.[47] The lower incidence of nonfatal MI was statistically not significant in the 300 mg loading dose group (5.0% in 300 mg loading dose group, 8.6% in 600 mg loading dose group), p=0.26. The SOE was rated insufficient for nonfatal MI at 6 months based on one small, fair-quality RCT that was underpowered to answer the question.

Effect on Nonfatal Stroke at 30 Days and 6 Months

Two RCTs (one good quality, one fair) with 25,378 patients reported the incidence of nonfatal stroke at 30 days in patients treated with clopidogrel 600 mg loading dose versus 300 mg loading dose.[46,49] In the largest study,[46] the event rate was 0.5% in both loading dose groups (HR 1.19; 95% CI, 0.84 to 1.68). In the other study of 292 patients,[49] there were two strokes in 300 mg loading dose group and one stroke in the 600 mg loading dose group. The SOE was rated insufficient for nonfatal stroke at 30 days since the total number of stroke events was insufficient to make a definitive conclusion.

Only one RCT (fair quality) in 256 patients reported the incidence of nonfatal stroke at 6 months.[47] There was only one stroke in the entire cohort (600 mg loading dose group). The SOE was rated insufficient for nonfatal stroke at 6 months based on a single fair-quality RCT.

Effect on Revascularization at 30 Days and 6 Months

Three RCTs (one good quality, two fair) with 477 patients reported the incidence of revascularization at 30 days in patients treated with clopidogrel 600 mg loading dose versus 300 mg loading dose.[48,50,51] Overall, there was a low event rate that was different among the studies. In one study,[48] the higher rate of revascularization in patients treated with a 300 mg loading dose (4.8%) was not statistically significant when compared with those receiving a 600 mg loading dose (1.3%), p=0.61. In another study,[50] there were no revascularization events in one treatment arm (600 mg loading dose group) and one revascularization in the other arm (300 mg loading dose group). In the third study,[51] there was only one revascularization event (600 mg loading dose group) in the entire cohort. The SOE was rated insufficient for revascularization at 30 days based on one good- and two fair-quality RCTs with inconsistent results of a direct outcome.

Only one RCT (fair quality) in 256 patients reported the incidence of revascularization at 6 months.[47] The lower incidence of revascularization was statistically nonsignificant in the 600 mg loading dose group (3.3% in 300 mg loading dose group, 2.3% in 600 mg loading dose group, p=0.64). The SOE was rated insufficient for revascularization at 6 months based on only one fair-quality RCT.

Effect on Major Bleeding at 30 Days

Of the six RCTs (two good quality, four fair) that reported the incidence of major bleeding at 30 days in 26,111 UA/NSTEMI patients, three studies reported no major bleeding in either treatment arm.[49-51] In two of the remaining studies,[47,48] there were more major bleeding events in the group treated with clopidogrel 300 mg loading dose (2.4% in both studies) compared with 600 mg loading dose (1.5%[47] and 1.3%[48]) which were not statistically significant. In the largest study[46] involving 25,086 UA/NSTEMI patients, there was a statistically nonsignificant difference in TIMI major bleeding favoring clopidogrel 300 mg loading dose (1.4%) compared with clopidogrel 600 mg loading dose (1.6%), p=0.39 (HR 1.09; 95% CI, 0.89 to 1.34). The SOE was rated insufficient for major bleeding at 30 days based on low event rates in two RCTs and inconsistent findings.

Effect on Minor Bleeding at 30 Days

Five RCTs (two good quality, three fair) including 25,819 UA/NSTEMI patients reported minor bleeding at 30 days.[46-48,50,51] Of the five studies, three studies reported minor bleeding according to TIMI criteria[47,48,51] and two studies reported minor bleeding according to non-TIMI criteria.[46,50] Based on this, we did not perform meta-analysis of minor bleeding.

Of the three studies that reported TIMI minor bleeding, one study of 119 patients reported statistically significant higher bleeding rates in the 300 mg loading dose group (9.5%) when compared with 600 mg loading dose group (3.9%).[48] In the other two studies reporting TIMI minor bleeding, there was no statistically significant difference in the incidence of minor bleeding (range 0.8% to 2.3% vs. 0.8% to 2.4%).[47,51]

In the studies that used non-TIMI criteria, the largest study of 25,086 patients found a lower incidence of minor bleeding that was statistically significant lower in the 300 mg loading dose group (4.3%) when compared with the 600 mg loading dose group (5.1%) (HR 1.13; 95% CI, 1.00 to 1.27, p=0.04).[46] Conversely, in the other study, there was a lower incidence of minor bleeding in the clopidogrel 600 mg loading dose group (29.4%) when compared with the 300 mg loading dose group (31.4%).[50] The SOE was rated insufficient for minor bleeding at 30 days based on two good- and three fair-quality RCTs with inconsistent results of a direct outcome and a wide confidence interval.

Effect on Stent Thrombosis at 30 Days

In the subgroup of 17,263 patients receiving PCI in a single, good-quality RCT (a prespecified subgroup),[46] there was a lower incidence of stent thrombosis at 30 days in patients treated with clopidogrel 600 mg loading dose (1.6%) when compared with clopidogrel 300 mg loading dose (2.6%) (HR 0.68; 95% CI, 0.55 to 0.85, p<0.0001). The SOE was rated low for stent thrombosis at 30 days based on one large good-quality RCT.

Findings by Subgroup (KQ 1c)

Only one study (good quality) of 25,086 patients reported variations in treatment effectiveness by subgroup.[46] Subgroups analyzed were age, sex, diabetes mellitus, GRACE risk score, the performance of PCI after randomization, and the presence of smoking. Prespecified subgroup analyses of intended clopidogrel pretreatment and the use of proton pump inhibitors after randomization are covered in separate sections of this report. Race, chronic kidney disease, troponin positivity, the type of coronary stent, geographic location, and other patient and demographic characteristics were not clearly described. The SOE for subgroup findings was rated insufficient since there was only one study reporting these results for this comparison. Table H-1 in Appendix H presents the results data for these subgroups.

Age

In 9321 patients over age 65, there was a statistically nonsignificant reduction in the incidence of composite ischemic events favoring clopidogrel 600 mg loading dose (6.3%) when compared with clopidogrel 300 mg loading dose (7.1%), p=0.15.

Sex

In 18,213 male patients, there was no difference in the incidence of composite ischemic events between those treated with clopidogrel 600 mg loading dose (4.1%) when compared with clopidogrel 300 mg loading dose (4.1%). In 6871 female patients, there was a statistically nonsignificant reduction in the incidence of composite ischemic events favoring clopidogrel 600 mg loading dose (4.5%) when compared with clopidogrel 300 mg loading dose (5.4%), p=0.09.

Diabetes Mellitus

In 5880 patients with diabetes mellitus, there was a statistically nonsignificant reduction in the incidence of composite ischemic events favoring clopidogrel 600 mg loading dose (5.2%) when compared with clopidogrel 300 mg loading dose (6.1%), p=0.16.

GRACE Risk Score

In 17,410 patients with a GRACE risk score less than 140, there was a statistically nonsignificant reduction in the incidence of composite ischemic events favoring treatment with clopidogrel 600 mg loading dose (2.5%) when compared with clopidogrel 300 mg loading dose (3.0%), p=0.06. In 6317 patients with a GRACE risk score more than 140, there was no difference in the incidence of composite ischemic events in those treated with clopidogrel 600 mg loading dose (7.7%) when compared with clopidogrel 300 mg loading dose (7.4%).

PCI After Randomization

In 17,263 patients who underwent PCI after randomization, there was a statistically significant reduction in the incidence of composite ischemic events favoring clopidogrel 600 mg loading dose (3.9%) when compared with clopidogrel 300 mg loading dose (4.5%), p=0.04.

Presence of Smoking

In 8373 patients who were smokers at the time of randomization, there was a statistically nonsignificant reduction in the incidence of composite ischemic events favoring clopidogrel 600 mg loading dose (2.9%) when compared with clopidogrel 300 mg loading dose (3.6%), p=0.07.

Summary of Results for Clopidogrel Loading Dose of 300 mg Versus 600 mg

In our analysis of clopidogrel loading doses (300 mg vs. 600 mg), each of the six studies reported different composite ischemic outcomes, thus prohibiting a meta-analysis. One large RCT reported no differences by loading dose for the composite endpoint of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days. For the individual outcomes of all-cause mortality and cardiovascular mortality, there were no statistically significant differences between clopidogrel loading doses. For nonfatal MI, there was a statistically nonsignificant difference in event rate but a trend favoring clopidogrel 600 mg loading dose at 30 days. There was a statistically significant lower rate of stent thrombosis favoring a clopidogrel loading dose of 600 mg versus 300 mg. Insufficient SOE exists for the comparative effectiveness of clopidogrel loading doses on composite ischemic endpoints, cardiovascular mortality at 30 days, nonfatal MI at 6 months, nonfatal stroke, revascularization, major bleeding, and minor bleeding, with most of these outcomes reported in smaller trials with imprecise estimates,

Subgroups analyzed in one study included age, sex, diabetes mellitus, GRACE risk score, the performance of PCI after randomization, and the presence of smoking. The analyses showed nonsignificant reductions in composite ischemic events favoring clopidogrel 600 mg for five subgroup categories, with statistically significant findings in patients who underwent PCI after randomization. Detailed SOE ratings are shown in Table 6.

Table 6. Detailed SOE for UA/NSTEMI patients treated with 300 mg versus 600 mg clopidogrel loading dose

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of Cardiovascular Mortality, Nonfatal MI, or Nonfatal Stroke at 30 Days					Low SOE
1 (25,086)	RCT/Good quality	NA	Direct	Precise	HR 0.94 (0.83 to 1.06) No difference
Composite of Cardiovascular Mortality, Nonfatal MI, or Revascularization at 30 Days					Insufficient SOE
1 (119)	RCT/Fair quality	NA	Direct	Imprecise	Lower rate in 600 mg group (10.4% vs. 23.8%)
Composite of Cardiovascular Mortality, Nonfatal MI, or Recurrent ACS at 30 Days					Insufficient SOE
1 (387)	RCT/Fair quality	NA	Direct	Imprecise	Lower rate in 600 mg group (4.8% vs. 12.3%)
Composite of All-Cause Mortality, Nonfatal MI, Revascularization, or Rehospitalization at 30 Days					Insufficient SOE
1 (103)	RCT/Fair quality	NA	Direct	Imprecise	Lower rate in 600 mg group (5.9% vs. 11.4%)
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 30 Days					Insufficient SOE
1 (255)	RCT/Good quality	NA	Direct	Imprecise	Lower rate in 600 mg group (4.0% vs. 11.6%)
Composite of All-Cause Mortality, Nonfatal MI, Nonfatal Stroke, or Rehospitalization at 6 Months					Insufficient SOE
1 (256)	RCT/Good quality	NA	Direct	Imprecise	No difference in event rates between groups (13.3% vs. 13.2 %)
All-Cause Mortality at 30 Days					Low SOE
3 (25,444)	3 RCTs/2 good quality, 1 fair	Consistent	Direct	Precise	2 small studies reported no deaths in both groups; largest study reported HR 0.93 (0.83 to 1.05) No difference

Table 6. Detailed SOE for UA/NSTEMI patients treated with 300 mg versus 600 mg clopidogrel loading dose (continued)

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	3. Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
All-Cause Mortality at 6 Months					Insufficient SOE
1 (256)	RCT/Fair quality	NA	Direct	Imprecise	3 deaths in 300 mg group; 1 death in 600 mg group
Cardiovascular Mortality at 30 Days					Low SOE
3 (25,497)	3 RCTs/1 good quality, 2 fair	Inconsistent	Direct	Precise	Largest study reported HR 0.95 (0.81 to 1.13) No difference
Nonfatal MI at 30 Days					Low SOE
5 (25,855)	5 RCTs/2 good quality, 3 fair	Inconsistent	Direct	Imprecise	OR 1.74 (0.99 to 3.05) Favors 600 mg dose
Nonfatal MI at 6 Months					Insufficient SOE
1 (256)	RCT/Fair quality	NA	Direct	Imprecise	Higher MI rate in 600 mg dose group (8.6% vs. 5.0%, p=0.26)
Nonfatal Stroke at 30 Days					Insufficient SOE
2 (25,378)	2 RCTs/1 good quality, 1 fair	Consistent	Direct	Imprecise	Largest study reported HR 1.19 (0.84 to 1.68); smaller study reported 2 strokes in 300 mg group and 1 stroke in 600 mg group
Nonfatal Stroke at 6 Months					Insufficient SOE
1 (256)	RCT/Fair quality	NA	Direct	Imprecise	Only 1 stroke in overall cohort (600 mg group)
Revascularization at 30 days					Insufficient SOE
3 (477)	3 RCTs/1 good quality, 2 fair	Inconsistent	Direct	Imprecise	Low overall event rate, ranging from 0 to 1.3% in 600 mg group and from 0 to 4.8% in 300 mg group
Revascularization at 6 months					Insufficient SOE
1 (256)	RCT/Fair quality	NA	Direct	Imprecise	Lower incidence in 600 mg dose group (2.3% vs. 3.3%, p=0.64)
Major bleeding at 30 days					Insufficient SOE
6 (26,111)	6 RCTs/2 good quality, 4 fair	Inconsistent	Direct	Imprecise	3 studies reported no bleeding events; inconsistent findings from 3 other studies, with largest study reporting HR 1.09 (0.89 to 1.34)
Minor bleeding at 30 days					Insufficient SOE
5 (25,819)	5 RCTs/2 good quality, 3 fair	Inconsistent	Direct	Imprecise	Incidence ranged from 0.8% to 9.5% in 300 mg group, and from 0.8% to 3.9% in 600 mg group
Stent thrombosis at 30 days					Low SOE
1 (17,263)	RCT/Good quality	NA	Direct	Precise	HR 0.68 (0.55 to 0.85) Favors 600 mg dose

CI = confidence interval; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

3. Clopidogrel Versus Ticagrelor or Prasugrel (KQ 1b)

Two RCTs compared ticagrelor with clopidogrel in 19,608 patients with ACS undergoing an early invasive strategy: one fair-quality study of 984 patients for 3 months' duration[56] and a good-quality study of 18,624 patients for 277 days' median duration.[54] One good-quality RCT of 13,608 patients compared prasugrel with clopidogrel for a median duration of 15 months.[55]

All three RCTs reported 30-day outcomes. The mean age of study participants ranged from 61 to 63 years of age. The proportion of female patients ranged from 26 to 36 percent. All three studies reported the percentage of White study participants (range 92 to 95%) while only one study additionally reported the percentage of African-American (1%) and Asian (6%) study participants.[54] All three studies were conducted internationally and included sites in the United States or Canada. All three studies were funded by industry.

In two of the three studies investigating clopidogrel, ticagrelor, and prasugrel, a mixed population of patients (unstable angina, NSTEMI, and STEMI) was evaluated.[54,55] Combined UA/NSTEMI subgroup data for the primary composite endpoint were available for the TRITON-TIMI 38 study;[55] these percentages were manually calculated for the PLATO study[54] from the individually reported UA and NSTEMI subgroup data. Given the heterogeneity of treatment comparisons, the small number of studies, and differences in treatment duration, no meta-analysis was performed to summarize the effect of these treatments. The full results across all outcomes are reported in Table G-3 in Appendix G.

Effect on Composite Ischemic Endpoints at 30 Days and After 1 Year

All three RCTs[54-56] reported a composite outcome of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke at 30 days. There were mixed results in the two studies (one good quality, one fair) of 19,608 patients comparing ticagrelor (4.3%;[56] 4.8%[54]) and clopidogrel (3.8%;[56] 5.4%[54]) at 30 days. When subgroups of only UA/NSTEMI patients in one study were evaluated for the occurrence of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke after 1 year, the lower rates of major adverse cardiovascular events (MACE) were statistically significant in patients treated with ticagrelor (10.6%) when compared with clopidogrel (12.6%),[54] The SOE for the composite endpoint was rated insufficient at 30 days due to inconsistent and imprecise results and moderate at 1 year due to precise and statistically significant results.

One good-quality study of 13,608 patients[55] showed statistically significantly lower rates of MACE in patients randomized to prasugrel (5.7%) when compared with clopidogrel (7.4%) at 30 days. In the UA/NSTEMI subgroup, the occurrence of this composite outcome at 15 months was statistically significant with prasugrel (9.9%) when compared with clopidogrel (12.1%) (HR 0.81; 95% CI, 0.73 to 0.90; $p<0.001$).[55] At 15 months, they found a statistically significant reduction in the group receiving prasugrel (HR 0.81; 95% CI, 0.73 to 0.89) for the composite outcome of cardiovascular mortality, nonfatal MI, or revascularization. The SOE was rated moderate for the composite endpoints at 30 days, 12 months, and 15 months based on one large, good-quality RCT with a significant finding.

Effect on All-Cause Mortality at 30 Days and After 1 Year

One fair-quality RCT of 984 patients comparing ticagrelor with clopidogrel[56] reported all-cause mortality results at 30 days and found no difference between clopidogrel (0.6%) and ticagrelor (1.9%), $p=0.18$. The SOE was rated insufficient for all-cause mortality at 30 days based on one small, fair-quality RCT.

One good-quality RCT of 18,624 patients, the lower incidence of all-cause death after 1 year was statistically significant in patients treated with ticagrelor (4.5%) when compared with clopidogrel (5.9%) (HR 0.78; 95% CI, 0.69 to 0.89, p<0.001).[54] The SOE was rated moderate for a benefit of ticagrelor compared with clopidogrel for all-cause mortality after 1 year.

One good-quality RCT of 13,608 patients showed a statistically nonsignificant reduction in all-cause deaths in patients treated with prasugrel (3.0%) when compared with clopidogrel (3.2%) (HR 0.95; 95% CI, 0.78 to 1.16, p=0.64).[55] The SOE was rated low for a reduction in all-cause mortality after 1 year for prasugrel compared with clopidogrel.

Effect on Cardiovascular Mortality at 30 Days and After 1 Year

One fair-quality RCT of 984 patients comparing ticagrelor with clopidogrel[56] reported cardiovascular mortality results at 30 days and found no difference between clopidogrel (0.6%) and ticagrelor (1.9%), p=0.18. In one good-quality RCT, there was a lower incidence of cardiovascular deaths after 1 year that was statistically significant in 18,624 patients treated with ticagrelor (4.0%) when compared with clopidogrel (5.1%) (HR 0.79; 95% CI, 0.69 to 0.91, p=0.001).[54] The SOE was rated insufficient for any difference in cardiovascular mortality at 30 days and was rated moderate for a reduction in cardiovascular mortality at 1 year for patients on ticagrelor compared with clopidogrel.

One good-quality RCT of 13,608 patients showed a statistically nonsignificant reduction in cardiovascular mortality in patients treated with prasugrel (2.1%) when compared with clopidogrel (2.4%) (HR 0.89; 95% CI, 0.70 to 1.12, p=0.31.[55] The overall SOE was rated low for cardiovascular mortality after 1 year based on one good-quality RCT with imprecise results.

Effect on Nonfatal MI at 30 Days and After 1 Year

One fair-quality RCT of 984 patients comparing ticagrelor with clopidogrel[56] reported nonfatal MI results at 30 days and found no difference between clopidogrel (3.5%) and ticagrelor (2.2%), p=0.34. The lower incidence of nonfatal MI after 1 year was statistically significant in 18,624 patients treated with ticagrelor (5.8%) when compared with clopidogrel (6.9%) (HR 0.84; 95% CI, 0.75 to 0.95), p=0.005.[54] The SOE was rated insufficient for any difference in nonfatal MI at 30 days and moderate SOE for a benefit of clopidogrel in reducing nonfatal MI at 1 year based on a large, good-quality RCT.

One good-quality RCT of 13,608 patients showed a lower incidence of nonfatal MI at 1 year prasugrel (7.3%) when compared with clopidogrel (9.5%) (HR 0.76; 95% CI, 0.67 to 0.85, p<0.001).[55] The SOE was rated moderate for nonfatal MI after 1 year based on one large, good-quality RCT.

Effect on Nonfatal Stroke at 30 Days and After 1 Year

One fair-quality RCT of 984 patients comparing ticagrelor with clopidogrel[56] reported nonfatal stroke results at 30 days and found no difference between clopidogrel (0.3%) and ticagrelor (0.6%), p=0.57. At 1 year, the incidence of nonfatal stroke was similar in 18,624 patients treated with ticagrelor (1.5%) when compared with patients treated with clopidogrel (1.3%) (HR 1.17; 95% CI, 0.91 to 1.52, p=0.22).[54] The SOE was rated insufficient for nonfatal stroke at 30 days and 1 year based on imprecise estimates due to sparse numbers of stroke events.

The incidence of nonfatal stroke after 1 year was similar in all patients (13,608 patients, not limited to UA/NSTEMI patients) treated with prasugrel (1.0%) and clopidogrel (1.0%) (HR 1.02;

95% CI, 0.71 to 1.45, p=0.93).[55] The SOE was rated insufficient for nonfatal stroke at 1 year based on imprecise estimates likely due to inadequate total number of stroke events to detect a difference between the treatments.

Effect on Revascularization at 30 days and After 6 Months

None of the studies reported revascularization event rates at 30 days. One study comparing prasugrel to clopidogrel in 13,608 patients[55] reported revascularization events after 6 months and found a statistically significant reduction in the group receiving prasugrel (HR 0.66; 95% CI, 0.54 to 0.81). The SOE was rated insufficient for revascularization at 30 days for no available data and rated moderate for revascularization after 6 months based on one good-quality RCT with a direct and precise estimate.

Effect on Major and Minor Bleeding at 30 Days and After 1 Year

One fair-quality RCT of 984 patients comparing ticagrelor with clopidogrel[56] reported major bleeding results at 30 days and found no difference between clopidogrel (6.9%) and ticagrelor (7.1%), p=0.91. The same study found no difference in minor bleeding: clopidogrel (1.3%) and ticagrelor (2.7%), p=0.18. After 1 year, the incidence of TIMI major bleeding was similar in all patients (not limited to UA/NSTEMI patients) treated with ticagrelor (7.9%) and clopidogrel (7.7%) (HR 1.03; 95% CI, 0.93 to 1.15, p=0.57).[54] The SOE was rated insufficient for major and minor bleeding at 30 days and low at 1 year.

In the RCT of 13,608 patients treated with prasugrel (2.4%) had a higher rate of TIMI major bleeding when compared with clopidogrel (1.8%) (HR 1.32; 95% CI, 1.03 to1.68, p=0.03).[55] The SOE was rated moderate for major bleeding after 1 year based on one good-quality RCT.

Effect on Stent Thrombosis After 1 Year

One RCT of 18,624 patients showed a lower incidence of definite or probable stent thrombosis after 1 year in patients treated with ticagrelor (2.2%) when compared with clopidogrel (2.9%) (HR 0.75; 95% CI, 0.59 to 0.95, p=0.02).[54] The SOE was rated moderate for stent thrombosis after 1 year based on one large, good-quality RCT.

One RCT of 13,608 patients showed a lower incidence of definite or probable stent thrombosis after 1 year in patients treated with prasugrel (1.1%) when compared with clopidogrel (2.4%) (HR 0.48; 95% CI, 0.36 to 0.64, p<0.001).[55] The SOE was rated moderate for stent thrombosis after 1 year based on one large, good-quality RCT.

Findings by Subgroup (KQ 1c)

Two RCTs (good quality) of 32,232 patients reported variations in treatment effectiveness by subgroup.[54,55] Subgroups analyzed were age, sex, race, diabetes mellitus, chronic kidney disease, troponin positivity, TIMI risk score, weight, prior TIA or stroke, prior coronary revascularization, the performance of PCI after randomization, type of coronary stent, geographic location, and high risk of bleeding. Other patient and demographic characteristics were not clearly described. Table H-1 in Appendix H presents the results data for these subgroups.

Age

In 8322 patients under age 65 enrolled in the TRITON-TIMI 38 study, there was a statistically significant reduction in the incidence of composite ischemic events favoring

prasugrel (8.1%) when compared with clopidogrel (10.6%). In 3477 patients between ages 65 and 74, there was a statistically nonsignificant reduction in the incidence of composite ischemic events favoring prasugrel (10.7%) when compared with clopidogrel (12.3%). In 1809 patients over age 75, there was no difference in the incidence of composite ischemic events between prasugrel (17.2%) and clopidogrel (18.3%).[55]

In 10,643 patients under age 65 enrolled in the PLATO study, there was a statistically significant reduction in the incidence of composite ischemic events favoring ticagrelor (7.2%) when compared with clopidogrel (8.5%). A similar benefit was observed in 7979 patients over age 65 in PLATO (ticagrelor 13.2%; clopidogrel 16.0%). When the results were analyzed using an older age cohort, a similar benefit was observed in 15744 patients under age 75 (ticagrelor 8.6%; clopidogrel 10.4%). In 2878 patients over age 75, there was no significant difference in the incidence of composite ischemic events between ticagrelor (16.8%) and clopidogrel (18.3%). There were no significant differences in major bleeding events based on age.[54]

Sex

In 10,085 male patients in TRITON-TIMI 38, there was a statistically significant reduction in the incidence of composite ischemic events favoring prasugrel (9.5%) when compared with clopidogrel (11.9%). In 3523 female patients, a trend toward reduction in the incidence of composite ischemic events did not reach statistical significance favoring prasugrel (11.0%) when compared with clopidogrel (12.6%).[55]

In 13,336 male patients in PLATO, there was a statistically significant reduction in the incidence of composite ischemic events favoring ticagrelor (9.2%) when compared with clopidogrel (11.1%). In 5288 female patients, a similar, statistically significant reduction in the incidence of composite ischemic events was observed favoring ticagrelor (11.2%) when compared with clopidogrel (13.2%). There were no statistically significant differences in major bleeding events based on sex.[54]

Race

There was no subgroup analysis of race in TRITON-TIMI 38. In 17,077 Caucasian patients in PLATO, there was a statistically significant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor (9.5%) when compared with clopidogrel (11.2%). There were statistically nonsignificant differences in favor of ticagrelor in 229 Black patients (ticagrelor 13.0%; clopidogrel 19.6%), 1096 Asian patients (ticagrelor 12.5%; clopidogrel 14.8%), and 221 “other” patients (ticagrelor 14.4%; clopidogrel 21.4%). There were no statistically significant differences in major bleeding events based on race.[54]

Diabetes Mellitus

In 3146 patients with diabetes in TRITON-TIMI 38, there was a statistically significant reduction in the composite incidence of cardiovascular death/nonfatal MI, or nonfatal stroke favoring prasugrel (12.2%) when compared with clopidogrel (17.0%), $p<0.001$. This effect was mostly driven by a significant reduction in nonfatal MI in diabetic patients (prasugrel 8.2%; clopidogrel 13.2%). There was also a statistically significant reduction in probable or definite stent thrombosis favoring prasugrel (2.0%) over clopidogrel (3.6%) in diabetic patients. There was no significant difference in major bleeding (not related to CABG) in diabetics treated with prasugrel (2.5%) or clopidogrel (2.6%).[55]

In 4662 patients with diabetes mellitus in PLATO, there was a statistically nonsignificant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor

(14.1%) when compared with clopidogrel (16.2%). There were no statistically significant differences in major bleeding events based on the presence of diabetes mellitus.[54]

Chronic Kidney Disease

In 1490 patients with chronic kidney disease (defined as CrCl<60 ml/min) in TRITON-TIMI 38, there was a statistically nonsignificant reduction in the composite incidence of cardiovascular death, nonfatal MI, or nonfatal stroke favoring prasugrel (15.1%) when compared with clopidogrel (17.5%).[55]

In 3237 patients with chronic kidney disease (defined as CrCl60 ml/min) in PLATO, there was a statistically significant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor (17.3%) when compared with clopidogrel (22.0%).[54]

Troponin Positivity

There was no subgroup analysis of troponin positivity or negativity in TRITON-TIMI 38.[55] In 15,089 patients who presented with a positive first troponin I in PLATO, there was a statistically significant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor (10.3%) when compared with clopidogrel (12.3%). In those patients who presented with a negative first troponin I, there was no difference in the incidence of the primary composite ischemic endpoint in patients treated with ticagrelor (7.0%) or clopidogrel (7.0%). There was no difference in major bleeding based on troponin positivity or negativity.[54]

TIMI Risk Score

There was no subgroup analysis of TIMI risk score in TRITON-TIMI 38.[55] In 730 patients who had a low TIMI risk score in PLATO, there was no difference in the incidence of the primary composite ischemic endpoint between ticagrelor (4.2%) when compared with clopidogrel (4.1%). In 5488 patients who had an intermediate TIMI risk score, there was a statistically significant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor (8.2%) when compared with clopidogrel (10.9%). In 4849 patients who had a high TIMI risk score, there was a statistically nonsignificant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor (14.4%) when compared with clopidogrel (15.6%). There was no difference in major bleeding based on TIMI risk score.[54]

Weight

In 664 patients with low body weight (defined as weight <60 kg) in TRITON-TIMI 38, there was a statistically nonsignificant reduction in the composite incidence of cardiovascular death, nonfatal MI, or nonfatal stroke favoring clopidogrel (6.5%) when compared with prasugrel (10.1%).[55]

In 1312 patients with low body weight (defined as weight <60 kg) in PLATO, there was a statistically significant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor (13.1%) when compared with clopidogrel (17.3%). However there was a lower incidence of major bleeding in patients treated with ticagrelor (12.6%) versus clopidogrel (15.2%) in patients with body weight less than 60 kg was not statistically significant.[54]

Prior Transient Ischemic Attack or Stroke

In 518 patients with a prior history of TIA or stroke in TRITON-TIMI 38, there was a statistically nonsignificant reduction in the composite incidence of cardiovascular death, nonfatal MI, or nonfatal stroke favoring clopidogrel (14.4%) when compared with prasugrel (19.1%).

There was a statistically nonsignificant reduction in major bleeding not related to CABG favoring clopidogrel (2.9%) when compared with prasugrel (5.0%).[55]

In 1152 patients with a prior history of TIA or stroke in PLATO, there was a statistically nonsignificant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor (19.0%) when compared with clopidogrel (20.8%). There was no difference in major bleeding based on a prior history of TIA or stroke.[54]

Prior Coronary Revascularization

There was no subgroup analysis of prior coronary revascularization in TRITON-TIMI 38.[55] In 2492 patients with a prior history of PCI in PLATO, there was no difference in the incidence of the primary composite ischemic endpoint between ticagrelor (14.1%) and clopidogrel (14.6%). In 16,312 patients without a prior history of PCI in PLATO, there was a statistically significant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor (9.1%) when compared with clopidogrel (11.2%). In 1106 patients with a prior history of CABG in PLATO, there was a statistically nonsignificant difference in the incidence of the primary composite ischemic endpoint between ticagrelor (19.5%) and clopidogrel (21.7%). In 17,518 patients without a prior history of CABG in PLATO, there was a statistically significant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor (9.2%) when compared with clopidogrel (11.1%). There was no difference in major bleeding based on prior history of coronary revascularization with either PCI or CABG.[54]

PCI After Randomization

All patients in TRITON-TIMI 38 underwent PCI, thus no subgroup analysis was performed.[55] There was no subgroup analysis of patients who underwent PCI after randomization in PLATO.[54]

Type of Coronary Stent

In 6461 patients who underwent bare metal stent implantation in TRITON-TIMI 38, there was a statistically significant reduction in the composite incidence of cardiovascular death, nonfatal MI, or nonfatal stroke favoring prasugrel (10.0%) when compared with clopidogrel (12.2%). A similar, statistically significant difference in composite ischemic events was observed in 6383 patients who underwent drug-eluting stent implantation (prasugrel=9.4%; clopidogrel=11.6%).[55] There was no subgroup analysis of coronary stenting in PLATO.[54]

Geographic Region

There was no subgroup analysis of geographic region in TRITON-TIMI 38.[55] In 13,859 patients enrolled in Europe/Middle East/Africa in PLATO, there was a statistically significant reduction in the incidence of the primary composite ischemic endpoint between ticagrelor (8.8%) when compared with clopidogrel (11.0%). In 1237 patients enrolled from Central/South America, there was a statistically nonsignificant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor (15.2%) when compared with clopidogrel (17.9%). In 1714 patients enrolled from Asia/Australia, there was a statistically nonsignificant reduction in the incidence of the primary composite ischemic endpoint favoring ticagrelor (11.4%) when compared with clopidogrel (14.8%). In 1814 patients enrolled from North America, there was a statistically nonsignificant reduction in the incidence of the primary composite ischemic endpoint favoring clopidogrel (9.6%) when compared with ticagrelor (11.9%). There was no difference in major bleeding based on geographic region.[54]

High Risk of Bleeding

In a subgroup analysis of patients with a high risk of bleeding (i.e., age >75 years, body weight <60 kg, or history of stroke or TIA), there was a statistically nonsignificant increase in non-CABG-related TIMI major bleeding favoring clopidogrel (3.3%) when compared with prasugrel (4.3%).[55] This subgroup was not reported in studies of ticagrelor versus clopidogrel.

Summary of Results for Clopidogrel Versus Ticagrelor or Prasugrel

The studies comparing clopidogrel with ticagrelor or prasugrel (one study of prasugrel and one of ticagrelor) reported a lower incidence of the composite outcome of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days. When this same composite endpoint was measured after 1 year, both ticagrelor and prasugrel had lower event rates than clopidogrel. Prasugrel reduced the composite endpoint of cardiovascular mortality, nonfatal MI, or revascularization at 15 months compared with clopidogrel. There was insufficient evidence for the following individual outcomes at 30 days: all-cause mortality, cardiovascular mortality, nonfatal MI, nonfatal stroke, major bleeding, and minor bleeding. There was also insufficient evidence for nonfatal stroke after 1 year. However, after 1 year, all-cause mortality and cardiovascular mortality had statistically significant decreases in event rates in patients treated with ticagrelor, but the difference in event rates between prasugrel and clopidogrel was not statistically significant. For nonfatal MI after 1 year, there was a statistically significant difference in event rates favoring both ticagrelor and prasugrel when compared with clopidogrel. None of the studies reported revascularization event rates at 30 days; after 6 months, one study found a statistically significant reduction favoring prasugrel. After 1 year, there was no statistically significant difference in major bleeding event rates between ticagrelor and clopidogrel; however, prasugrel was associated with higher major bleeding event rates than clopidogrel. For stent thrombosis, there was a statistically significant difference in event rates favoring ticagrelor and prasugrel when compared with clopidogrel.

Subgroup findings from two studies included age, sex, race, diabetes mellitus, chronic kidney disease, troponin positivity, TIMI risk score, weight, prior TIA or stroke, prior coronary revascularization, the performance of PCI after randomization, type of coronary stent, geographic location, and high risk of bleeding. Both studies showed similar reductions in ischemic outcomes on patients receiving the newer agent (prasugrel or ticagrelor) compared with clopidogrel across all subgroups; most subgroups' differences were not statistically significant, except among subgroups where the sample size was sufficiently large to detect a difference. Detailed SOE ratings are shown in Table 7.

Table 7. Detailed strength of evidence for UA/NSTEMI patients treated with clopidogrel versus ticagrelor or prasugrel

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of Cardiovascular Mortality, Nonfatal MI, or Nonfatal Stroke at 30 Days					
Clopidogrel vs. Ticagrelor 2 (19,608)	2 RCTs/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	**Insufficient SOE** Compared with clopidogrel (3.8% and 5.4%), ticagrelor had mixed results (4.3% and 4.8%)
Clopidogrel vs. Prasugrel 1 (13,608)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** Compared with clopidogrel (7.4%), prasugrel (5.7%) was associated with lower composite endpoint Favors prasugrel
Composite of Cardiovascular Mortality, Nonfatal MI, or Nonfatal Stroke After 1 Year					
Clopidogrel vs. Ticagrelor 1 (18,624)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** Compared with clopidogrel (12.6%), ticagrelor (10.6%) was associated with lower composite endpoint Favors ticagrelor
Clopidogrel vs. Prasugrel 1 (13,608)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** HR 0.81 (0.73 to 0.90) Compared with clopidogrel (12.1%), prasugrel (9.9%) was associated with lower composite endpoint at 15 months Favors prasugrel
Composite of Cardiovascular Mortality, Nonfatal MI, or Revascularization at 15 Months					
Clopidogrel vs. Prasugrel 1 (13,608)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** HR 0.81 (0.73 to 0.89) Favors prasugrel
All-Cause Mortality at 30 Days					
Clopidogrel vs. Ticagrelor 1 (984)	RCT/Fair quality	NA	Direct	Imprecise	**Insufficient SOE** Clopidogrel: 0.6% Ticagrelor 1.9% p=0.18
All-Cause Mortality After 1 Year					
Clopidogrel vs. Ticagrelor 1 (18,624)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** Compared with clopidogrel (5.9%), ticagrelor (4.5%) was associated with fewer deaths Favors ticagrelor
Clopidogrel vs. Prasugrel 1 (13,608)	RCT/Good quality	NA	Direct	Imprecise	**Low SOE** Compared with clopidogrel (3.2%), prasugrel (3.0%) was associated with fewer deaths Favors prasugrel
Cardiovascular Mortality at 30 Days					
Clopidogrel vs. Ticagrelor 1 (984)	RCT/Fair quality	NA	Direct	Imprecise	**Insufficient SOE** Clopidogrel: 0.6% Ticagrelor: 1.9% p=0.18

Table 7. Detailed strength of evidence for UA/NSTEMI patients treated with clopidogrel versus ticagrelor or prasugrel (continued)

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Cardiovascular Mortality After 1 Year					
Clopidogrel vs. Ticagrelor 1 (18,624)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** Compared with clopidogrel (5.1%), ticagrelor (4.0%) was associated with fewer cardiovascular deaths Favors ticagrelor
Clopidogrel vs. Prasugrel 1 (13,608)	RCT/Good quality	NA	Direct	Imprecise	**Low SOE** Compared with clopidogrel (2.4%), prasugrel (2.1%) was associated with fewer cardiovascular deaths Favors prasugrel
Nonfatal MI at 30 Days					
Clopidogrel vs. Ticagrelor 1 (984)	RCT/Fair quality	NA	Direct	Imprecise	**Insufficient SOE** Clopidogrel: 3.5% Ticagrelor: 2.2% p=0.34
Nonfatal MI After 1 Year					
Clopidogrel vs. Ticagrelor 1 (18,624)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** Compared with clopidogrel (6.9%), ticagrelor (5.8%) was associated with fewer MIs Favors ticagrelor
Clopidogrel vs. Prasugrel 1 (13,608)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** Compared with clopidogrel (9.5%), prasugrel (7.3%) was associated with fewer MIs Favors prasugrel
Nonfatal Stroke at 30 days					
Clopidogrel vs. Ticagrelor 1 (984)	RCT/Fair quality	NA	Direct	Imprecise	**Insufficient SOE** Clopidogrel: 0.3% Ticagrelor: 0.6% p=0.57
Nonfatal Stroke After 1 Year					
Clopidogrel vs. Ticagrelor 1 (18,624)	RCT/Good quality	NA	Direct	Imprecise	**Insufficient SOE** Clopidogrel: 1.3% Ticagrelor: 1.5%
Clopidogrel vs. Prasugrel 1 (13,608)	RCT/Good quality	NA	Direct	Imprecise	**Insufficient SOE** Clopidogrel: 1.0% Prasugrel: 1.0%
Revascularization at 30 Days					
Both comparisons 0	NA	NA	NA	NA	**Insufficient SOE** NA
Revascularization After 6 Months					
Clopidogrel vs. Prasugrel 1 (13,608)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** HR 0.66 (0.54 to 0.81) Favors prasugrel
Major Bleeding at 30 Days					
Clopidogrel vs. Ticagrelor 1 (984)	RCT/fair quality	NA	Direct	Imprecise	**Insufficient SOE** Clopidogrel: 6.9% Ticagrelor: 7.1%

Table 7. Detailed strength of evidence for UA/NSTEMI patients treated with clopidogrel versus ticagrelor or prasugrel (continued)

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Major Bleeding After 1 Year					
Clopidogrel vs. Ticagrelor 1 (18,624)	RCT/Good quality	NA	Direct	Imprecise	**Low SOE** Compared with clopidogrel (7.7%), ticagrelor (7.9%) had similar event rates No difference
Clopidogrel vs. Prasugrel 1 (13,608)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** Compared with clopidogrel (1.8%), prasugrel (2.4%) was associated with higher event rates Favors clopidogrel
Minor Bleeding at 30 Days					
Clopidogrel vs. Ticagrelor 1 (984)	RCT/Fair quality	NA	Direct	Imprecise	**Insufficient SOE** Clopidogrel: 1.3% Ticagrelor: 2.7% p=0.18
Stent Thrombosis After 1 Year					
Clopidogrel vs. Ticagrelor 1 (18,624)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** Compared with clopidogrel (2.9%), ticagrelor (2.2%) was associated with lower event rates Favors ticagrelor
Clopidogrel vs. Prasugrel 1 (13,608)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** Compared with clopidogrel (2.4%), prasugrel (1.1%) was associated with lower event rates Favors prasugrel

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; NA = not applicable; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

4. Bivalirudin Versus Heparin-Based Strategy Without and With Planned GPI (KQ 1b)

Thirteen studies (eight RCTs, five observational) compared bivalirudin with a heparin-based strategy in 30,486 UA/NSTEMI patients undergoing an invasive approach.[57-64,100,101,107-109] Outcomes that were assessed in this comparison included composite ischemic endpoints, all-cause mortality, nonfatal MI, revascularization, stent thrombosis, major bleeding, and minor bleeding. These results are reported in Table G-4 in Appendix G.

- Three RCTs compared bivalirudin with unfractionated heparin (UFH) or enoxaparin without planned GPI and included a total of 5822 patients.[57-59] One additional RCT compared bivalirudin with UFH or enoxaparin without planned GPI[60] and met inclusion criteria but was not included in our synthesis due to a low use of invasive strategy and because the sponsor terminated the study with 3 percent of patients enrolled. However because the study was designed to answer the question of interest we included it in our listing of studies.[60]
- Four RCTs compared bivalirudin with UFH or enoxaparin with planned GPI and included a total of 17,748 patients.[61-64] One RCT[64] reported outcomes in patients randomized to bivalirudin versus UFH plus GPI, but because *followup was limited to 48*

hours, these results were not included in the meta-analysis. The results, however, were similar to other studies in this comparison; total mortality and nonfatal MI were slightly higher in bivalirudin-treated patients when compared with UFH plus GPI, but major bleeding and minor bleeding were lower.

- Five observational studies (all fair quality) evaluated the use of bivalirudin in patients undergoing PCI for varying indications. Two studies evaluated patients with ACS only, but there was not clarity on the use of an early invasive strategy, and both studies had differential utilization of GPI.[100,101] In both studies, the rate of ischemic complications was similar in the bivalirudin and heparin-treated groups. The other three studies included an unselected patient population undergoing PCI and there was differential use of GPI, thus limiting the estimation of effect of the treatment comparisons in UA/NSTEMI patients.[107-109] In each of these studies, the rate of bleeding and ischemic complications was lower in bivalirudin-treated patients when compared with heparin or heparin + GPI treated patients. Because of patient population heterogeneity and differential use of GPI, none of these observational studies were included in the meta-analysis.

Of the six RCTs included in the meta-analyses,[57-59,61-63] five (83%) were rated good quality and one (17%) fair. Sample sizes for individual studies ranged from 401 to 13,819 patients. Study duration ranged from 48 hours to 1 year, with each RCT reporting 30 day outcomes.

The mean age of study participants ranged from 61 to 70 years of age. The proportion of female patients ranged from 23 to 30 percent. One study (17%) reported the racial and ethnic demographics of study participants. One study (17%) was conducted entirely within the United States or Canada, with the other conducted internationally. Funding source was reported in all six studies, with five studies (83%) funded by an industry source.

Across all outcomes, we present the results of the bivalirudin versus heparin-based strategy for the "without planned GPI" studies separately from the "with planned GPI" studies since the event rates for ischemic and bleeding outcomes may differ across combinations of anticoagulant and antiplatelets administered.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal Myocardial Infarction, Revascularization, or Major Bleeding at 30 Days

Bivalirudin Versus UFH Without Planned GPI

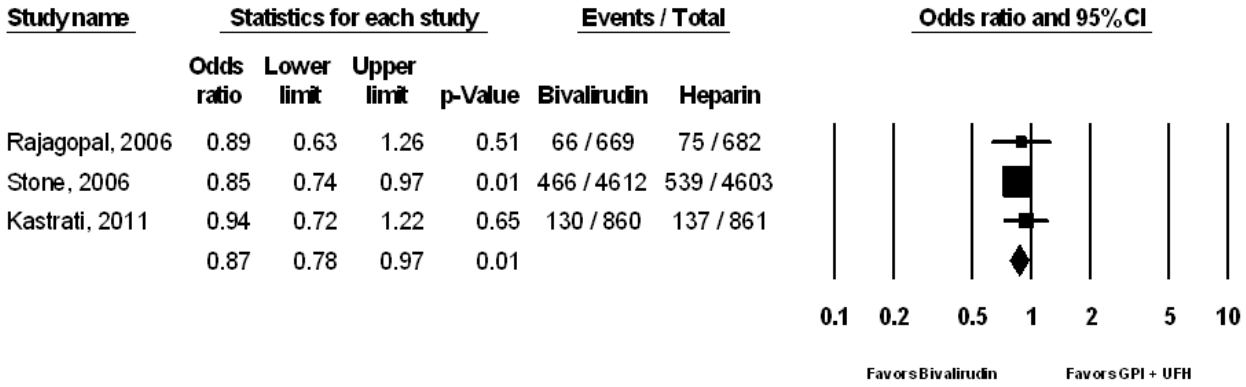
Only one RCT (good quality) reported the composite endpoint of all-cause mortality, nonfatal MI, revascularization, or major bleeding at 30 days in 4571 patients randomized to a bivalirudin versus heparin-based strategy without planned GPI.[58] In this study, there was a similar incidence of the composite endpoint for patients treated with bivalirudin (8.4%) and heparin without planned GPI (8.7%), relative risk (RR) 0.94 (95% CI, 0.77 to 1.15). The SOE was rated insufficient for this composite outcome based on one good-quality RCT that was underpowered to answer the question (i.e., study was powered to detect 27.5% risk reduction with bivalirudin for this primary endpoint; a larger sample size would be required to detect smaller differences).

Bivalirudin Versus UFH With Planned GPI

A random-effects meta-analysis of three RCTs[61-63] (all good quality) including 12,287 UA/NSTEMI patients reporting the composite outcome of all-cause mortality, nonfatal MI,

revascularization, or major bleeding at 30 days found that the odds ratio was 0.87 (95% CI, 0.78 to 0.97) favoring bivalirudin compared with a heparin-based strategy and planned GPI (Figure 13). There was no evidence of heterogeneity, with a Q-value of 0.51 for 2 degrees of freedom, p=0.78. The SOE was rated high for this composite outcome based on consistent results of a direct outcome and a narrow confidence interval.

Figure 13. Meta-analysis of bivalirudin versus heparin-based strategy with planned glycoprotein inhibitor on all-cause mortality, nonfatal myocardial infarction, revascularization, or major bleeding at 30 days



CI = confidence interval

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal Myocardial Infarction, or Revascularization at 30 Days

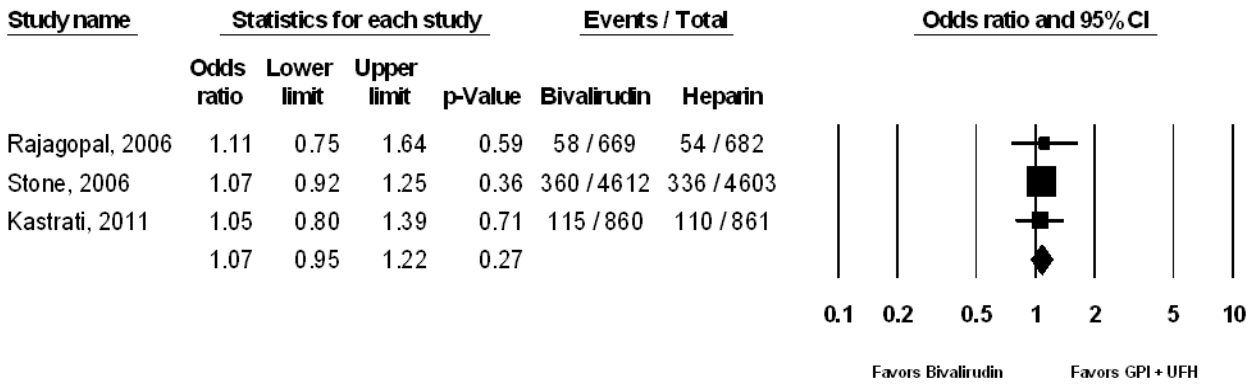
Bivalirudin Versus UFH Without Planned GPI

Two RCTs[57,58] (one good quality, one fair) including 5420 UA/NSTEMI patients reported the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 30 days. The study by Kastrati reported an odds ratio of 1.19 (95% CI, 0.92 to 1.54) with no statistically significant difference between treatment groups. The study by Parodi reported an odds ratio of 0.42 (95% CI, 0.21 to 0.84) with statistically significant reduction of composite events in the bivalirudin group, p=0.02. The differential use of clopidogrel loading, the discretionary use of bailout GPI at the time of PCI, and the inclusion of a different proportion of ACS and stable angina patients likely contributed to the inconsistent results. The SOE was rated insufficient for this composite outcome based on one good- and one fair-quality RCT with inconsistent results of a direct outcome and imprecise results.

Bivalirudin Versus UFH With Planned GPI

A random-effects meta-analysis of three RCTs[61-63] (all good quality) including 12,287 UA/NSTEMI patients reporting the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 30 days found that the odds ratio was 1.07 (95% CI, 0.95 to 1.22) showing noninferiority of a heparin-based strategy with planned GPI compared with bivalirudin (Figure 14). There was no evidence of heterogeneity, with a Q-value of 0.05 for 2 degrees of freedom, p=0.98. The SOE was rated high for this composite outcome based on three good-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

Figure 14. Meta-analysis of bivalirudin versus heparin-based strategy with planned glycoprotein inhibitor on all-cause mortality, nonfatal myocardial infarction, or revascularization at 30 days



CI = confidence interval

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal Myocardial Infarction, or Revascularization at 1 Year

Bivalirudin Versus UFH Without Planned GPI

Two RCTs[57,58] (one good quality, one fair) including 5420 UA/NSTEMI patients reported the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 1 year. The good-quality study by Kastrati reported an odds ratio of 0.97 (95% CI, 0.83 to 1.13) with no statistically significant difference between treatment groups. The fair-quality study by Parodi reported an odds ratio of 0.58 (95% CI, 0.37 to 0.92) with a statistically significant reduction in composite events in the bivalirudin group, p=0.02. The differential use of clopidogrel loading, the discretionary use of bailout GPI at the time of PCI, and the inclusion of a different proportion of ACS and stable angina patients likely contributed to the inconsistent findings. The SOE was rated insufficient for this composite outcome based on one good- and one fair-quality RCT with inconsistent and imprecise results of a direct outcome.

Bivalirudin Versus UFH With Planned GPI

Two RCTs[62,63] (both good quality) including 10,566 UA/NSTEMI patients reported the composite outcome of all-cause mortality, nonfatal MI, or revascularization between 6 months and 1 year. The Rajagopal study found an OR of 1.11 (95% CI, 0.74 to 1.63), and the Stone study found an odds ratio of 1.08 (95% CI, 0.92 to 1.25). While both ORs favored GPI with UFH, the findings were not statistically significant and did not support a difference. The SOE of no difference was rated low for this composite outcome based on two good-quality RCTs with consistent results of a direct outcome and imprecise estimates with confidence intervals that cross 1.

Effect on All-Cause Mortality at 30 Days

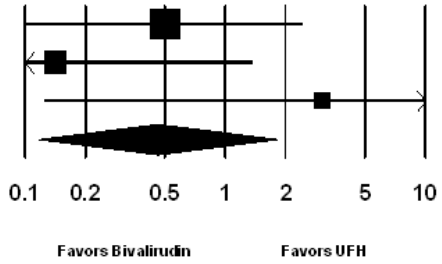
Bivalirudin Versus UFH Without Planned GPI

A random-effects meta-analysis of three RCTs[57-59] (two good quality, one fair) including 5822 UA/NSTEMI patients reporting all-cause mortality at 30 days found that the odds ratio was 0.46 (95% CI, 0.12 to 1.81) favoring bivalirudin compared with a heparin-based strategy without planned GPI (Figure 15). There was no evidence of heterogeneity, with a Q-value of 2.39 for 2

degrees of freedom, p=0.30. The SOE was rated insufficient based on two good- and one fair-quality RCTs with inconsistent results of a direct outcome and a wide confidence interval.

Figure 15. Meta-analysis of bivalirudin versus heparin-based strategy without planned glycoprotein inhibitor on all-cause mortality at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Bivalirudin	Heparin
Kastrati, 2008	0.50	0.10	2.45	0.39	2 / 2289	5 / 2281
Parodi, 2010	0.14	0.01	1.38	0.09	1 / 425	6 / 425
Patti, 2012	3.07	0.12	76.03	0.49	1 / 198	0 / 203
	0.46	0.12	1.81	0.27		



CI = confidence interval

Bivalirudin Versus UFH With Planned GPI

A random-effects meta-analysis of three RCTs[61-63] (all good quality) including 12,287 UA/NSTEMI patients reporting all-cause mortality at 30 days found that the odds ratio was 1.21 (95% CI, 0.89 to 1.65) for bivalirudin compared with a heparin-based strategy and planned GPI (Figure 16). There was evidence of no heterogeneity, with a Q-value of 0.08 for 2 degrees of freedom, p=0.96. The SOE was rated insufficient based on three good-quality RCTs with consistent results of a direct outcome and a wide confidence interval.

Figure 16. Meta-analysis of bivalirudin versus heparin-based strategy with planned glycoprotein inhibitor on all-cause mortality at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Bivalirudin	Heparin
Rajagopal, 2006	1.00	0.18	5.42	1.00	3 / 669	3 / 682
Stone, 2006	1.23	0.88	1.74	0.23	74 / 4612	60 / 4603
Kastrati, 2011	1.15	0.53	2.50	0.73	14 / 860	12 / 861
	1.21	0.89	1.65	0.22		

CI = confidence interval

Effect on All-Cause Mortality After 6 Months

Bivalirudin Versus UFH Without Planned GPI

Only two studies[57,58] (one good quality, one fair) reported the incidence of all-cause mortality after 6 months in 5420 patients treated with bivalirudin versus heparin-based strategy. In one study of 850 patients, fewer patients treated with bivalirudin (1.2%) died compared with patients treated with a heparin-based strategy (2.4%) at 1 year, p=0.193.[57] In the other study of 4570

patients, there was a slightly higher rate of death in patients treated with bivalirudin (1.9%) versus heparin-based strategy (1.7%) at 6 months, p=0.667.[58] The SOE was rated insufficient based on one good- and one fair-quality RCTs with inconsistent results of a direct outcome.

Bivalirudin Versus UFH With Planned GPI

Only two studies[62,63] (both good quality) reported the incidence of all-cause mortality after 6 months in 10,566 patients treated with bivalirudin versus heparin plus GPI. In one study of 1351 patients, death rates were similar between patients treated with bivalirudin (0.9%) and those treated with heparin plus GPI (1.3%) at 6 months, p=0.46.[63] In the other study of 9215 patients, there was a similar rate of death in patients treated with bivalirudin (3.8%) versus heparin plus GPI (3.8%) at 1 year.[62] The SOE was rated insufficient based on two good-quality RCTs with consistent results of a direct outcome.

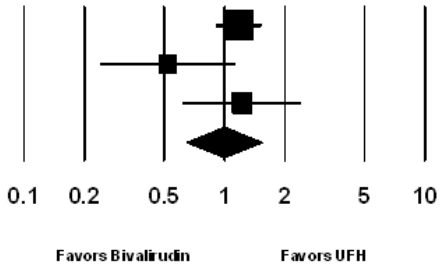
Effect on Nonfatal MI at 30 Days

Bivalirudin Versus UFH Without Planned GPI

A random-effects meta-analysis of three RCTs[57-59] (two good quality, one fair) including 5822 UA/NSTEMI patients reporting nonfatal MI at 30 days found that the odds ratio was 1.00 (95% CI, 0.64 to 1.55) for bivalirudin compared with a heparin-based strategy without planned GPI (Figure 17). There was some evidence of heterogeneity, with a Q-value of 3.93 for 2 degrees of freedom, p=0.14. The I^2 value was 49.15. The differential use of clopidogrel loading, the discretionary use of bailout GPI at the time of PCI, and the inclusion of a different proportion of ACS and stable angina patients likely contributed to the statistical heterogeneity. The SOE was rated insufficient based on two good- and one fair-quality RCTs with inconsistent results of a direct outcome and a wide confidence interval.

Figure 17. Meta-analysis of bivalirudin versus heparin-based strategy without planned glycoprotein inhibitor on nonfatal myocardial infarction at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Bivalirudin	Heparin
Kastrati, 2008	1.18	0.91	1.53	0.22	128 / 2289	109 / 2281
Parodi, 2010	0.52	0.24	1.13	0.10	10 / 425	19 / 425
Patti, 2012	1.23	0.62	2.41	0.56	20 / 198	17 / 203
	1.00	0.64	1.55	0.99		



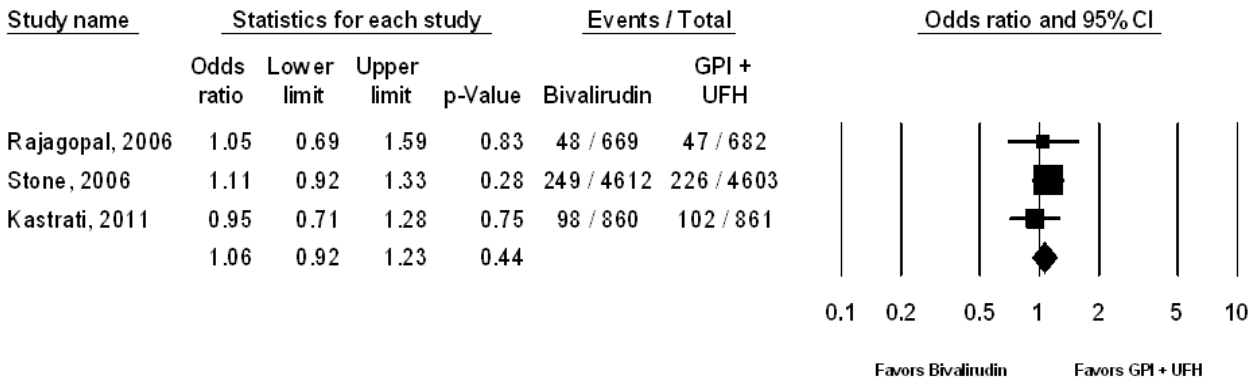
CI = confidence interval

Bivalirudin Versus UFH With Planned GPI

A random-effects meta-analysis of three RCTs[61-63] (all good quality) including 12,287 UA/NSTEMI patients reporting nonfatal MI at 30 days found that the odds ratio was 1.06 (95% CI, 0.92 to 1.23) for bivalirudin compared with a heparin-based strategy and planned GPI (Figure 18). There was no evidence of heterogeneity, with a Q-value of 0.78 for 2 degrees of

freedom, p=0.70. The SOE was rated moderate for no difference based on three good-quality RCTs with consistent results of a direct outcome and confidence interval that crosses 1.

Figure 18. Meta-analysis of bivalirudin versus heparin-based strategy with planned glycoprotein inhibitor on nonfatal myocardial infarction at 30 days



CI = confidence interval; GPI = glycoprotein inhibitor; UFH = unfractionated heparin

Effect on Nonfatal MI After 6 Months

Bivalirudin Versus UFH Without Planned GPI

Only two studies[57,58] (one good quality, one fair) reported the incidence of nonfatal MI after 6 months in 5420 patients treated with bivalirudin versus a heparin-based strategy. In one study of 850 patients, although there were fewer MI events in patients treated with bivalirudin (3.3%) compared with patients treated with a heparin-based strategy (5.7%) at 6 months, the finding was not statistically significant, p=0.095.[57] In the other study of 4570 patients, there was a higher rate of MI in patients treated with bivalirudin (6.0%) versus a heparin-based strategy (5.3%) at 6 months which was also not statistically significant, p=0.320.[58] The SOE was rated insufficient based on one good- and one fair-quality RCTs with inconsistent results of a direct outcome.

Bivalirudin Versus UFH With Planned GPI

Two studies[62,63] (both good quality) reported the incidence of nonfatal MI after 6 months in 10,566 patients treated with bivalirudin versus a heparin-based strategy plus GPI strategy. In both studies, there was a higher rate of nonfatal MI in patients treated with bivalirudin (7.8%;[62] 8.1%[63]) versus heparin plus GPI (6.9%;[62] 7.6%[63]) at 6 months and 1 year (p=NS for both studies). The SOE was rated moderate for a benefit of heparin based on two good-quality RCTs with consistent results of a direct outcome.

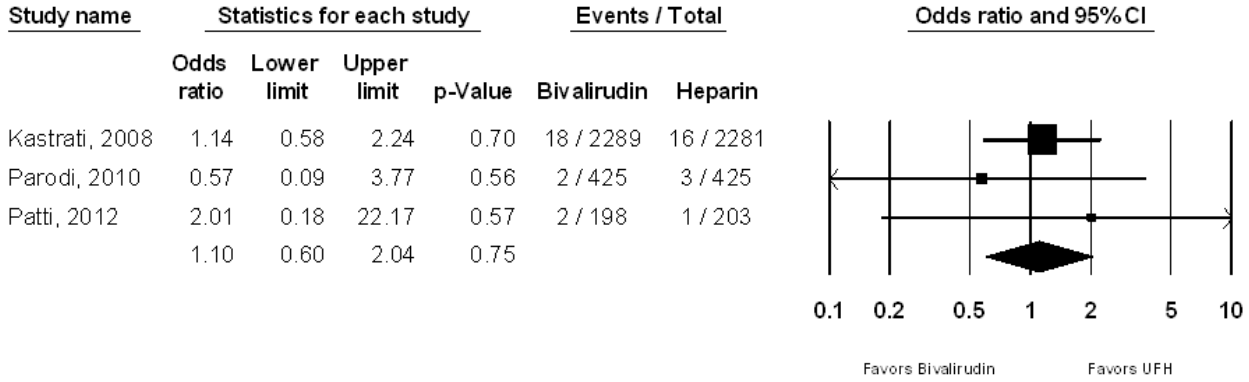
Effect on Revascularization at 30 Days

Bivalirudin Versus UFH Without Planned GPI

A random-effects meta-analysis of three RCTs[57-59] (two good quality, one fair) including 5822 UA/NSTEMI patients reporting revascularization at 30 days found that the odds ratio was 1.10 (95% CI, 0.60 to 2.04) for bivalirudin compared with a heparin-based strategy without planned GPI (Figure 19). There was no evidence of heterogeneity, with a Q-value of 0.721 for 2 degrees of freedom, p=0.697. The differential use of clopidogrel loading, the discretionary use of bailout GPI at the time of PCI, and the inclusion of a different proportion of ACS and stable angina patients likely contributed to the inconsistent results. The SOE was rated insufficient

based on two good- and one fair-quality RCTs with inconsistent results of a direct outcome and a wide confidence interval.

Figure 19. Meta-analysis of bivalirudin versus heparin-based strategy without planned glycoprotein inhibitor on revascularization at 30 days

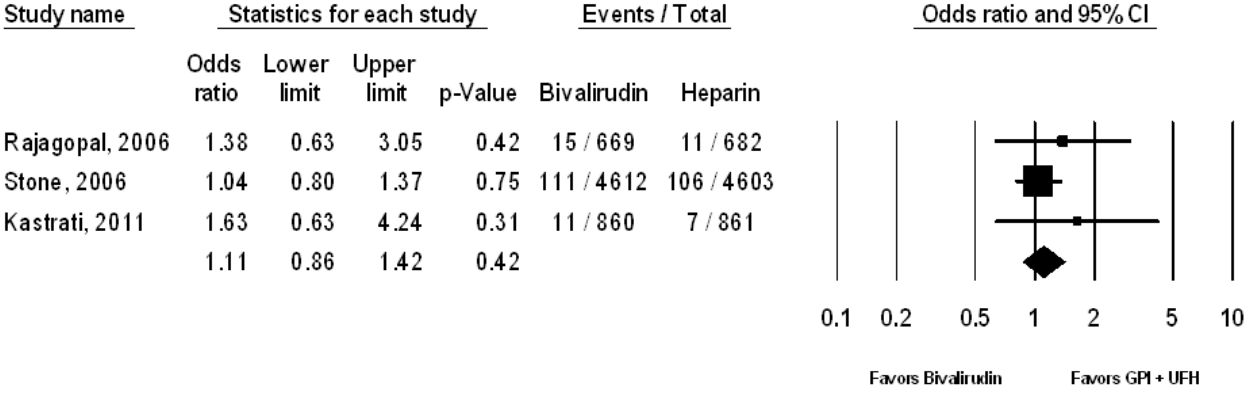


CI = confidence interval

Bivalirudin Versus UFH With Planned GPI

A random-effects meta-analysis of three RCTs[61-63] (all good quality) including 12,287 UA/NSTEMI patients reporting revascularization at 30 days found that the odds ratio was 1.11 (95% CI, 0.86 to 1.42) demonstrating a trend favoring bivalirudin compared with a heparin-based strategy and planned GPI (Figure 20). There was no evidence of heterogeneity, with a Q-value of 1.12 for 2 degrees of freedom, p=0.57. The SOE was rated low for a benefit of bivalirudin based on three good-quality RCTs with consistent results of a direct outcome and a wide confidence interval that crosses 1.

Figure 20. Meta-analysis of bivalirudin versus heparin-based strategy with planned glycoprotein inhibitor on revascularization at 30 days



CI = confidence interval

Effect on Revascularization After 6 Months

Bivalirudin Versus UFH Without Planned GPI

Only two studies[57,58] (one good quality, one fair) reported the incidence of revascularization after 6 months in 5420 patients treated with bivalirudin versus heparin-based strategy without planned GPI. In both studies, there was a lower rate of revascularization in patients treated with bivalirudin (4.1%[57] 11.2%[58]) versus heparin-based strategy (5.7%;[57] 12.5%[58]) at 6 months and 1

year (p=NS for both studies). The SOE was rated insufficient based on inconclusive and imprecise findings.

Bivalirudin Versus UFH With Planned GPI

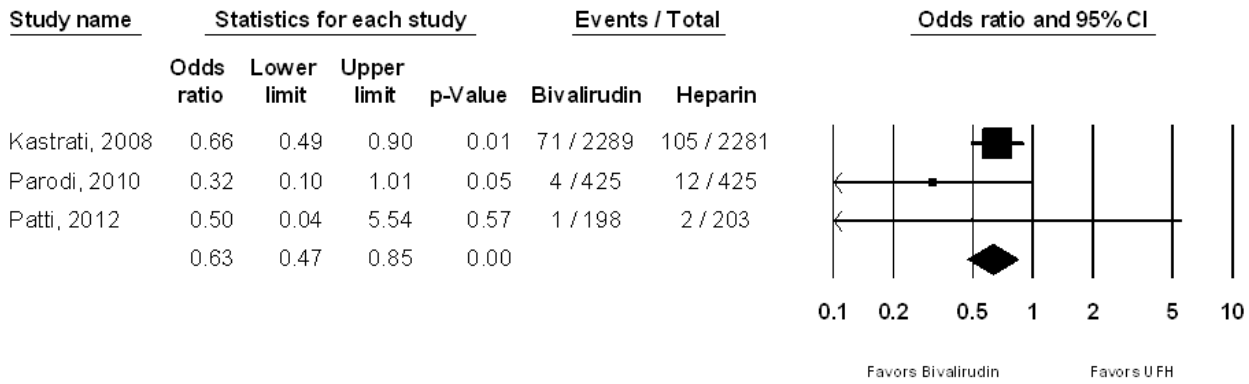
Only two studies[62,63] (both good quality) reported the incidence of revascularization after 6 months in 10,566 patients treated with bivalirudin versus heparin plus GPI. In both studies, there was a higher rate of revascularization in patients treated with bivalirudin (8.7%;[62] 11.7%[63]) versus heparin plus GPI (8.4% in both studies) at 6 months and 1 year (p=0.49 and 0.04, respectively). The SOE was rated low that favors heparin after 6 months with planned GPI based on two good-quality RCTs with consistent results of a direct outcome.

Effect on Major Bleeding at 30 Days

Bivalirudin Versus UFH Without Planned GPI

A random-effects meta-analysis of three RCTs[57-59] (two good quality, one fair) including 5822 UA/NSTEMI patients reporting major bleeding at 30 days found that the odds ratio was 0.63 (95% CI, 0.47 to 0.85) favoring bivalirudin compared with a heparin-based strategy without planned GPI (Figure 21). There was no evidence of heterogeneity, with a Q-value of 1.51 for 2 degrees of freedom, p=0.47. The SOE was rated high based on two good- and one fair-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

Figure 21. Meta-analysis of bivalirudin versus heparin-based strategy without planned glycoprotein inhibitor on major bleeding at 30 days

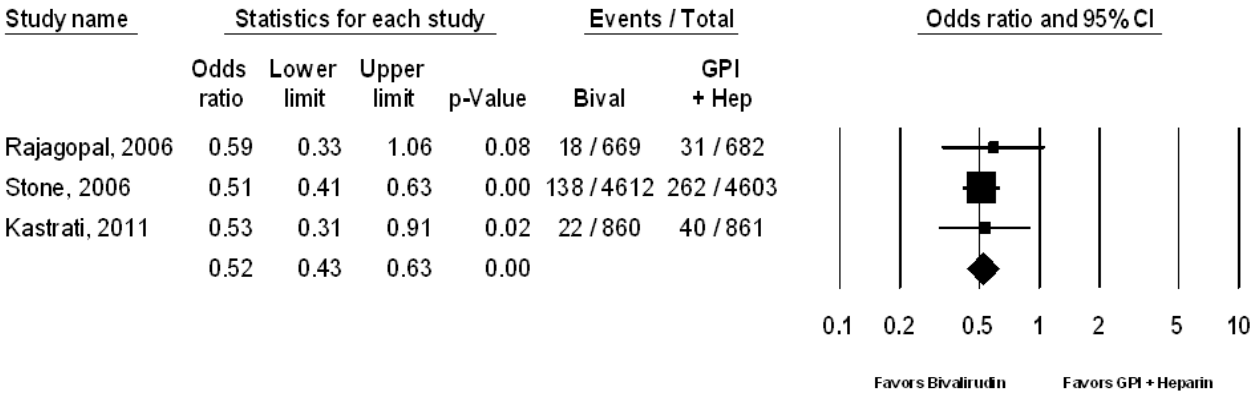


CI = confidence interval

Bivalirudin Versus UFH With Planned GPI

A random-effects meta-analysis of three RCTs[61-63] (all good quality) including 12,287 UA/NSTEMI patients reporting major bleeding at 30 days found that the odds ratio was 0.52 (95% CI, 0.43 to 0.63) favoring bivalirudin compared with a heparin-based strategy without planned GPI (Figure 22). There was no evidence of heterogeneity, with a Q-value of 0.20 for 2 degrees of freedom, p=0.91. The SOE was rated high based on three good-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

Figure 22. Meta-analysis of bivalirudin versus heparin-based strategy with planned glycoprotein inhibitor use on major bleeding at 30 days



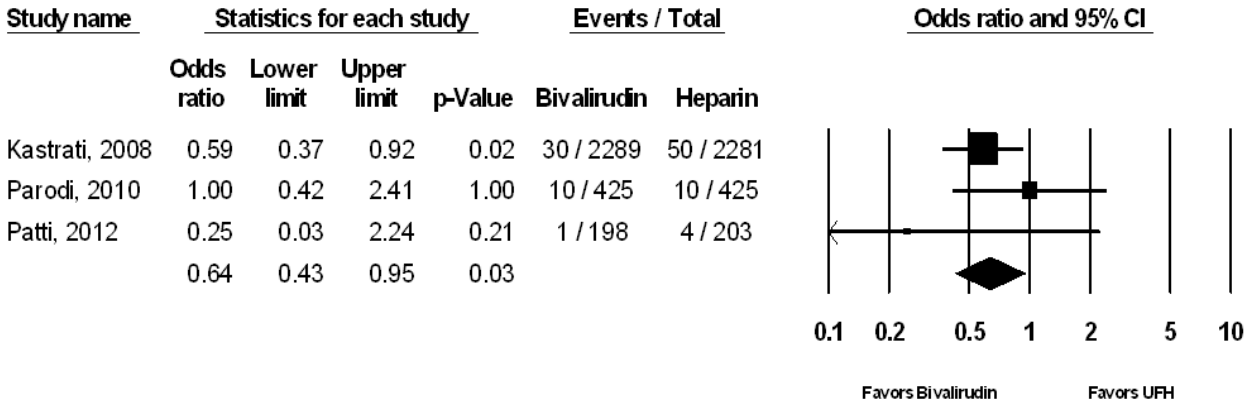
Bival = bivalirudin; CI = confidence interval; GPI = glycoprotein inhibitor; Hep = heparin

Effect on Minor Bleeding at 30 Days

Bivalirudin Versus UFH Without Planned GPI

A random-effects meta-analysis of three RCTs57-59 (two good quality, one fair) including 5822 UA/NSTEMI patients reporting minor bleeding at 30 days found that the odds ratio was 0.64 (95% CI, 0.43 to 0.95) favoring bivalirudin compared with a heparin-based strategy without planned GPI (Figure 23). There was no evidence of heterogeneity, with a Q-value of 1.86 for 2 degrees of freedom, p=0.395. The differential use of clopidogrel loading, the discretionary use of bailout GPI at the time of PCI, and the inclusion of a different proportion of ACS and stable angina patients likely contributed to the inconsistent results. The SOE was rated low based on two good- and one fair-quality RCTs with inconsistent results of a direct outcome and a wide confidence interval.

Figure 23. Meta-analysis of bivalirudin versus heparin-based strategy without planned glycoprotein inhibitor on minor bleeding at 30 days



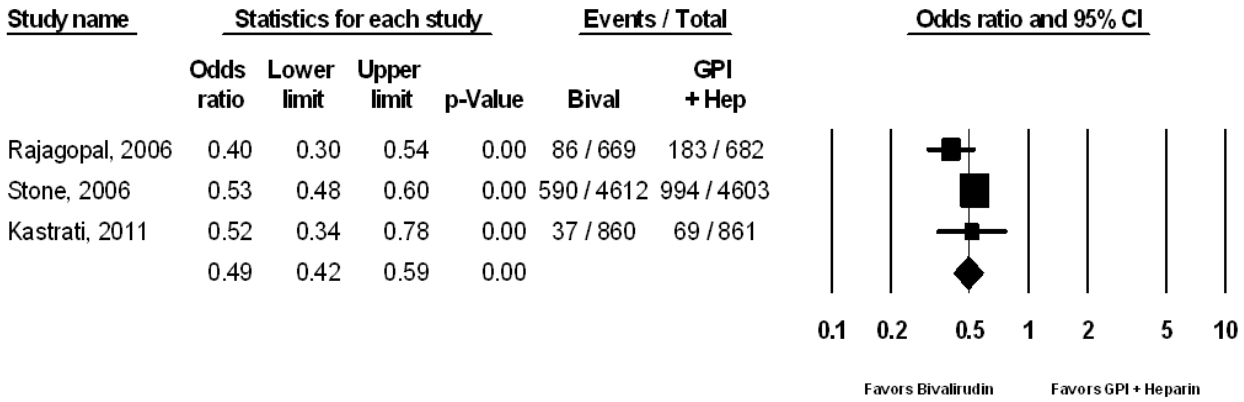
CI = confidence interval

Bivalirudin Versus UFH With Planned GPI

A random-effects meta-analysis of three RCTs[61-63] (all good quality) including 12,287 UA/NSTEMI patients reporting minor bleeding at 30 days found that the odds ratio was 0.49 (95% CI, 0.42 to 0.59) favoring bivalirudin compared with heparin-based strategy with planned

GPI (Figure 24). There was no evidence of heterogeneity, with a Q-value of 3.16 for 2 degrees of freedom, p=0.21. The SOE was rated high based on three good-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

Figure 24. Meta-analysis of bivalirudin versus heparin-based strategy with planned glycoprotein inhibitor on minor bleeding at 30 days



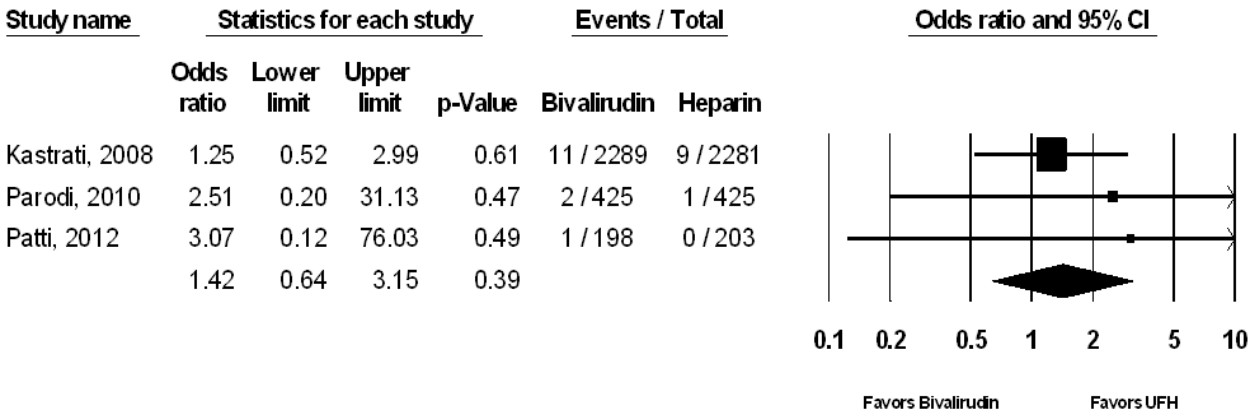
Bival = bivalirudin; CI = confidence interval; GPI = glycoprotein inhibitor; Hep = heparin

Effect on Stent Thrombosis at 30 Days

Bivalirudin Versus UFH Without Planned GPI

Of the three RCTs[57-59] (two good quality, one fair) including 5822 UA/NSTEMI patients that reported stent thrombosis at 30 days, there was a higher incidence of stent thrombosis in patients treated with bivalirudin (event rate was 0.5% in all three studies) when compared with patients treated with a heparin-based strategy without planned GPI (range 0 to 0.4%) which was not statistically significant. A random effects meta-analysis of three RCTs (two good quality, one fair) including 5822 UA/NSTEMI patients reporting stent thrombosis at 30 days found that the odds ratio was 1.42 (95% CI, 0.64 to 3.15) comparing bivalirudin with a heparin-based strategy without planned GPI (Figure 25). There was no evidence of heterogeneity with a Q-value of 0.50 for 2 degrees of freedom, p=0.78. The SOE was rated insufficient based on an imprecise estimate and a low total number of events.

Figure 25. Meta-analysis of bivalirudin versus heparin-based strategy without planned glycoprotein inhibitor on stent thrombosis at 30 days



CI = confidence interval

Bivalirudin Versus UFH With Planned GPI

Of the two RCTs[62,63] (both good quality) including 10,936 UA/NSTEMI patients that reported stent thrombosis at 30 days, there was a higher incidence in event rates between those treated with bivalirudin (0.7%;[62] 1.0%[63]) when compared with those treated with a heparin-based strategy plus GPI (0.6 %;[62] 0.8%[63]) which was not statistically significant. The SOE was rated insufficient based on studies not sufficiently powered to detect a difference.

Findings by Subgroup (KQ 1c)

Three studies (good quality) of 15,494 patients reported variations in treatment effectiveness by subgroup.[58,61,62] The main report from an additional study reported subgroups, but because data were abstracted from the subgroup report of UA/NSTEMI patients, this was not included in the findings by subgroup.[63] Subgroups analyzed were age, sex, diabetes mellitus, chronic kidney disease, serum biomarker positivity, TIMI risk score, weight, and the performance of PCI or CABG after randomization. Prespecified subgroup analysis of intended clopidogrel pretreatment is covered in a separate section of this report. Other patient and demographic characteristics were not clearly described. Table H-1- in Appendix H presents the results data for these subgroups.

Age

In 4570 patients in the ISAR-REACT 3 study, there was no significant difference in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding in patients less than or greater than 67.6 years of age (prespecified subgroup).[58]

In 5051 patients under 65 years of age and in 4164 patients over 65 years of age in ACUITY, there was no statistically significant difference in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 1 year between bivalirudin and heparin-based strategy with planned GPI use.[62]

In 1721 patients in ISAR-REACT 4, there was no statistically significant difference in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding in patients less than or greater than 68.3 years of age (prespecified subgroup).[61]

Sex

In 3495 male patients in ISAR-REACT 3, there was no difference in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 1 year between bivalirudin (7.3%) and heparin-based strategy without planned GPI use (7.4%). In 1075 female patients, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 1 year favoring bivalirudin (11.4%) when compared with heparin-based strategy without planned GPI use (13.2%).[58]

In 6444 male patients in ACUITY, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 1 year favoring heparin-based strategy with planned GPI use (16.2%) when compared with bivalirudin (17.1%). In 2771 female patients, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 1 year favoring bivalirudin (13.7%) when compared with heparin-based strategy with planned GPI use (14.3%).[62]

In 399 male patients in ISAR-REACT 4, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding favoring treatment with bivalirudin (12.6%) when compared with heparin-based strategy plus planned GPI use (15.5%). In 1332 female patients, there was a statistically nonsignificant

reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding favoring treatment with heparin-based strategy plus planned GPI use (9.5%) when compared with bivalirudin (10.6%).[61] Even though the findings in men and women favor opposite treatments, the test for an interaction was not significant (p=0.27).

Diabetes Mellitus

In 1254 patients with diabetes mellitus in ISAR-REACT 3, there was no difference in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days between bivalirudin (10.0%) and heparin-based strategy without planned GPI use (9.7%).[58]

In 2585 patients with diabetes mellitus in ACUITY, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 1 year favoring heparin-based strategy with planned GPI use (17.9%) when compared with bivalirudin (19.5%).[62]

In 500 patients with diabetes mellitus in ISAR-REACT 4, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days favoring treatment with bivalirudin (9.9%) when compared with heparin-based strategy plus planned GPI use (10.5%).[61]

Chronic Kidney Disease

In 2598 patients with chronic kidney disease (defined as serum creatinine > 0.9) in ISAR-REACT 3, there was no difference in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days between bivalirudin (8.4%) and heparin-based strategy without planned GPI use (8.3%).[58]

In 1643 patients with chronic kidney disease (defined as CrCl<60 ml/min) in ACUITY, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days favoring bivalirudin (16.1%) when compared with heparin-based strategy with planned GPI use (16.9%). There was a statistically significant reduction in the incidence of major bleeding at 30 days favoring bivalirudin (6.2%) when compared with heparin-based strategy with planned GPI use (9.8%).[62]

In 860 patients with glomerular filtration rate less than 83 ml/min (prespecified subgroup) in ISAR-REACT 4, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days favoring treatment with heparin-based strategy plus planned GPI use (10.7%) when compared with bivalirudin (12.1%).[61]

Serum Biomarker Positivity

There was no subgroup analysis of serum biomarkers in ISAR-REACT 3.[58] In 5073 patients with abnormal CK MB or troponin in ACUITY, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days favoring bivalirudin (16.1%) when compared with heparin-based strategy with planned GPI use (16.9%). There was a statistically significant reduction in the incidence of major bleeding at 30 days favoring bivalirudin (3.8%) when compared with heparin-based strategy with planned GPI use (6.4%) in patients with abnormal CK MB or troponin. The same finding was observed in patients without abnormal CK MB or troponin.[62]

In 849 patients with troponin T level greater than 0.12 mcg/l (prespecified subgroup) in ISAR-REACT 4, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days favoring

treatment with heparin-based strategy plus planned GPI use (13.2%) when compared with bivalirudin (15.5%).[61]

TIMI Risk Score

There was no subgroup analysis of TIMI risk score in ISAR-REACT 3[58] or ISAR-REACT 4.[61] In 1291 patients with a low TIMI risk score in ACUITY, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days favoring bivalirudin (4.2%) when compared with heparin-based strategy with planned GPI use (5.8%). In 4407 patients with an intermediate TIMI risk score, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days favoring heparin-based strategy with planned GPI use (6.1%) when compared with bivalirudin (7.4%). In 2449 patients with a high TIMI risk score, there was no difference in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days between bivalirudin (11.0%) and heparin-based strategy with planned GPI use (10.6%).[62]

Weight

There was no subgroup analysis of weight or body-mass index in ISAR-REACT 3,[58] or ACUITY.[62] In ISAR-REACT 4, there was no significant difference in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days in patients with a body-mass index greater than or less than 27.3 (prespecified subgroup).[61]

PCI or CABG After Randomization

There was no subgroup analysis of PCI or CABG in ISAR-REACT 3[58] or ISAR-REACT 4.[61] In 5180 patients treated with PCI as initial treatment strategy in ACUITY, there was no difference in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days between bivalirudin (8.8%) and heparin-based strategy with planned GPI use (8.2%). In 1040 patients treated with CABG as initial treatment strategy in ACUITY, there was a statistically nonsignificant difference in the incidence of death, nonfatal MI, urgent target vessel revascularization or major bleeding at 30 days between bivalirudin (16.1%) and heparin-based strategy with planned GPI use (15.1%).[62]

Summary of Results for Bivalirudin Versus Heparin-Based Strategy

In our analysis of studies comparing bivalirudin versus heparin-based strategy with or without planned GPI use, there were no statistically significant differences in the incidence of the composite endpoints of mortality, nonfatal MI, or revascularization at 30 days, and the data were rated insufficient after 1 year without GPI use, and rated low after 1 year with GPI use. When major bleeding was added to this composite outcome (all-cause mortality, nonfatal MI, revascularization, or major bleeding), a statistically significant net clinical difference favoring bivalirudin was observed in the comparison of bivalirudin versus heparin-based strategy plus planned GPI, but there was insufficient SOE for the group without planned GPI. For the individual outcomes of all-cause mortality at 30 days and after 6 months, there was insufficient evidence with or without planned GPI use. For nonfatal MI and revascularization, there was insufficient SOE for the group without planned GPI use. There was no difference in nonfatal MI in patients treated with bivalirudin versus heparin-based strategy at 30 days in the planned GPI group; however, the incidence of nonfatal MI at 6 months in this group was significantly higher in bivalirudin-treated patients when compared with patients treated with heparin-based strategy

with planned GPI. For revascularization in the planned GPI group, at 30 days there were higher rates of revascularization in heparin-treated patients (favoring bivalirudin), but revascularization after 6 months was statistically significantly higher in bivalirudin-treated patients when compared with patients treated with heparin-based strategy. For bleeding outcomes, the lower incidence in major and minor bleeding at 30 days was statistically significant favoring bivalirudin when compared with heparin-based strategy with or without GPI use. There was insufficient evidence for stent thrombosis at 30 days with or without GPI use.

Subgroups analyzed included age, sex, diabetes mellitus, chronic kidney disease, serum biomarker positivity, TIMI risk score, weight, and the performance of PCI or CABG after randomization. A majority of the subgroup analyses of the primary composite outcome showed no difference between bivalirudin and a heparin-based strategy, or a statistically nonsignificant reduction that favored bivalirudin. Detailed SOE ratings are shown in Tables 8 and 9. Odds ratios less than 1 favor bivalirudin-treated patients; odds ratios greater than 1 favor a heparin-based strategy.

Table 8. Detailed strength of evidence for UA/NSTEMI patients treated with bivalirudin versus heparin-based strategy without planned glycoprotein inhibitor use

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of All-Cause Mortality, Nonfatal MI, Revascularization, or Major Bleeding at 30 Days					**Insufficient SOE**
1 (4571)	RCT/Good quality	NA	Direct	Imprecise	Bivalirudin 8.4% vs. heparin 8.7%
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 30 Days					**Insufficient SOE**
2 (5420)	2 RCTs/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	1 study found no difference, OR 1.19 (0.92 to 1.54); 1 study found statistically significant lowering in the bivalirudin group, OR 0.42 (0.21 to 0.84)
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 1 Year					**Insufficient SOE**
2 (5420)	2 RCTs/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	1 study found no difference, OR 0.97 (0.83 to 1.13); 1 study found statistically significant lowering in the bivalirudin group, OR 0.58 (0.37 to 0.92)
All-Cause Mortality at 30 Days					**Insufficient SOE**
3 (5822)	3 RCTs/2 good quality, 1 fair	Inconsistent	Direct	Imprecise	OR 0.46 (0.12 to 1.81)
All-cause Mortality After 6 Months					**Insufficient SOE**
2 (5420)	2 RCTs/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	Disparate results in 2 RCTs: bivalirudin 1.2% vs. heparin 2.4%; bivalirudin 1.9% vs. heparin 1.7%
Nonfatal MI at 30 days					**Insufficient SOE**
3 (5822)	3 RCTs/2 good quality, 1 fair	Inconsistent	Direct	Imprecise	OR 1.00 (0.64 to 1.55)

Table 8. Detailed strength of evidence for UA/NSTEMI patients treated with bivalirudin vs. heparin-based strategy without planned glycoprotein inhibitor use (continued)

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Nonfatal MI After 6 Months					**Insufficient SOE**
2 (5420)	2 RCTs/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	Disparate results in 2 RCTs; bivalirudin 3.3% vs. heparin 5.7%; bivalirudin 6.0% vs. heparin 5.3%
Revascularization at 30 Days					**Insufficient SOE**
3 (5822)	3 RCTs/2 good quality, 1 fair	Inconsistent	Direct	Imprecise	OR 1.10 (0.60 to 2.04)
Revascularization After 6 Months					**Insufficient SOE**
2 (5420)	2 RCTs/1 good quality, 1 fair	Consistent	Direct	Imprecise	Lower rate of revascularization in bivalirudin-treated patients (4.1% and 11.2%) vs. heparin-treated (5.7% and 12.5%)
Major Bleeding at 30 Days					**High SOE**
3 (5822)	3 RCTs/2 good quality, 1 fair	Consistent	Direct	Precise	OR 0.63 (0.47 to 0.85) Favors bivalirudin
Minor Bleeding at 30 Days					**Low SOE**
3 (5822)	3 RCTs/2 good quality, 1 fair	Inconsistent	Direct	Imprecise	OR 0.64 (0.43 to 0.95) Favors bivalirudin
Stent Thrombosis at 30 Days					**Insufficient SOE**
3 (5822)	3 RCTs/2 good quality, 1 fair	Consistent	Direct	Imprecise	OR 1.42 (0.64 to 3.15)

CI = confidence interval; GPI = glycoprotein inhibitor; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

Table 9. Detailed strength of evidence for UA/NSTEMI patients treated with bivalirudin versus heparin-based strategy with planned glycoprotein inhibitor use

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of All-Cause Mortality, Nonfatal MI, Revascularization, or Major Bleeding at 30 Days					**High SOE**
3 (12,287)	3 RCTs/All good quality	Consistent	Direct	Precise	OR 0.87 (0.78 to 0.97) Favors bivalirudin
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 30 Days					**High SOE**
3 (12,287)	3 RCTs/All good quality	Consistent	Direct	Precise	OR 1.07 (0.95 to 1.22) No difference
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 1 Year					**Low SOE**
2 (10,566)	2 RCTs/Both good quality	Consistent	Direct	Imprecise	Both RCTs found no difference between treatments, OR 1.11 (0.74 to 1.63); and OR 1.08 (0.92 to 1.25) No difference
All-Cause Mortality at 30 Days					**Insufficient SOE**
3 (12,287)	3 RCTs/All good quality	Consistent	Direct	Imprecise	OR 1.21 (0.89 to 1.65)

Table 9. Detailed strength of evidence for UA/NSTEMI patients treated with bivalirudin vs. heparin-based strategy with planned glycoprotein inhibitor use (continued)

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
All-Cause Mortality After 6 Months					**Insufficient SOE**
2 (10,566)	2 RCTs/Both good quality	Consistent	Direct	Imprecise	Similar event rate in 1 RCT (3.8% bivalirudin, 3.8% GPI), slightly lower event rate in other RCT (0.9% bivalirudin,1.3% GPI, p=0.46)
Nonfatal MI at 30 Days					**Moderate SOE**
3 (12,287)	3 RCTs/All good quality	Consistent	Direct	Precise	OR 1.06 (0.92 to 1.23) No difference
Nonfatal MI After 6 Months					**Moderate SOE**
2 (10,566)	2 RCTs/Both good quality	Consistent	Direct	Precise	Higher event rate in bivalirudin (7.8% and 8.1%) vs. heparin (6.9% and 7.6%) Favors heparin
Revascularization at 30 Days					**Low SOE**
3 (12,287)	3 RCTs/All good quality	Consistent	Direct	Imprecise	OR 1.11 (0.86 to 1.42) Favors bivalirudin
Revascularization After 6 Months					**Low SOE**
2 (10,566)	2 RCTs/Both good quality	Consistent	Direct	Imprecise	Higher event rate with bivalirudin (8.7% and 11.7%) vs. heparin (8.4% in both studies) Favors heparin
Major Bleeding at 30 Days					**High SOE**
3 (12,287)	3 RCTs/All good quality	Consistent	Direct	Precise	OR 0.52 (0.43 to 0.63) Favors bivalirudin
Minor Bleeding at 30 Days					**High SOE**
3 (12,287)	3 RCTs/All good quality	Consistent	Direct	Precise	OR 0.49 (0.42 to 0.59) Favors bivalirudin
Stent thrombosis at 30 Days					**Insufficient SOE**
2 (10,936)	2 RCTs/Both good quality	Consistent	Direct	Imprecise	Similar event rates between treatment arms in both studies (bivalirudin 0.7% to 1.0%; heparin 0.6% to 0.8%)

CI = confidence interval; GPI = glycoprotein inhibitor; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

5. Enoxaparin Versus Unfractionated Heparin Versus Fondaparinux (Percutaneous Coronary Intervention Cohort) (KQ 1b)

Thirteen studies (10 RCTs, 3 observational) compared the use of enoxaparin, UFH, and fondaparinux in 41,201 UA/NSTEMI patients undergoing an invasive strategy.[65-74,102-104] Three RCTs compared enoxaparin with UFH prior to PCI and included a total of 14,760 patients.[65-67] One RCT (20,078 patients) compared enoxaparin with fondaparinux,[68] and one RCT (350 patients) compared fondaparinux with UFH.[69]

Eight studies contained important comparative effectiveness results of anticoagulant treatment in UA/NSTEMI patients even though they were not included in the meta-analysis for this comparison as their populations, comparisons, or outcomes of interest were too

heterogeneous. However, because these studies were designed to answer the question of interest, they met our inclusion criteria, and we included them in our listing of studies and explored their findings qualitatively. Findings were as follows:

- Three RCTs compared enoxaparin with UFH at the time of PCI;[70-72] however, the study populations had a low percentage of UA/NSTEMI patients, and it was unclear whether these patients underwent an early invasive approach. These three studies were therefore not included in the quantitative analysis. The Bertel study[70] showed lower major cardiovascular events and bleeding events in ACS patients who received enoxaparin, but was stopped prematurely due to slow patient enrollment and a lower than expected event rate. The Chen study[71] showed no differences in bleeding or ischemic event rates between enoxaparin and UFH, but 29 percent of the study population underwent PCI for UA/NSTEMI. The Bhatt study[72] showed no difference in major cardiovascular events at 48 hours and 30 days, plus similar rates of bleeding and vascular site complications in both treatment groups.
- One RCT compared the use of enoxaparin with UFH in UA/NSTEMI patients; however, in those patients that underwent coronary angiography and PCI, open-label UFH was used instead of the study drug, and so this study was not included in our quantitative analysis.[73] This study demonstrated that enoxaparin reduced the composite of death and serious cardiac ischemic events at 43 days compared with UFH (OR 0.85; 95% CI 0.72 to 1.00; p=0.048).
- One additional RCT compared the use of different doses of UFH at the time of PCI in patients who underwent an early invasive strategy and were initially treated with fondaparinux; as a result, we could not include it in our quantitative analysis.[74] This study demonstrated that low-dose UFH did not reduce major peri-PCI bleeding or vascular site complications compared with standard-dose UFH.
- Multiple observational studies were screened and abstracted. With the exception of three studies, most were excluded due to lack of clarity about an early invasive management strategy or heterogeneity in the study population. Of the three included studies, one[102] evaluated the use of enoxaparin and UFH in an unselected PCI population at the time of PCI, where the use of GPI varied from 44 to 96 percent. In this study, there was no difference in outcomes between patients treated with UFH and enoxaparin. The remaining two observational studies[103,104] evaluated outcomes and comparisons of interest with greater detail and clarity and are discussed below.

Of the five analyzed RCTs, four were rated good quality,[65-68] and one was rated fair.[69] The two observational studies[103,104] were both rated fair quality. Sample sizes for included individual studies ranged from 350 to 20,078 patients. Study duration ranged from 48 hours to 30 days, with three RCTs reporting 30 day outcomes and both observational studies reporting in hospital outcomes only.

The mean age of study participants ranged from 61 to 68 years of age. The proportion of female patients ranged from 23 to 38 percent. Two studies (29%) reported the racial and ethnic demographics of study participants. All five RCTs and both observational studies were international, multi-center studies, including sites in the United States and Canada. All five RCTs and the two observational studies were industry-sponsored.

The majority of these studies were performed prior to the time when an early invasive strategy was widely implemented. Most of the RCTs in this comparison allowed treatment by early invasive or initial conservative strategies, and subgroup analyses were reported in these

studies. In the RCTs that reported subgroup analyses of patients treated with an early invasive strategy, only the patients in the subgroup undergoing early invasive treatment were used for analytic purposes,[66,68] and this limited the number of outcome measures that were reported (specifically composite ischemic endpoints and bleeding endpoints). No individual ischemic endpoints were reported for the subgroup of invasively treated patients; therefore, only descriptions of composite outcome measures and major bleeding were included in this report. These results are also reported in Table G-5 in Appendix G.

Effect on Composite Ischemic Endpoints Prior to 7 Days and at 30 Days

Three good-quality RCTs[65,67,68] (two studies evaluating enoxaparin versus UFH, one study evaluating enoxaparin versus fondaparinux) reported a composite ischemic endpoint at 30 days. One good-quality RCT[66] comparing enoxaparin with UFH reported a composite endpoint at 7 days, and one fair-quality RCT[69] comparing fondaparinux with UFH reported a composite endpoint at 48 hours. Of the three studies reporting a 30-day outcome, each reported separate composite outcome measures that prohibited incorporation of these studies into a meta-analysis.

In three good-quality RCTs, the use of enoxaparin was associated with a similar incidence of composite ischemic endpoints prior to 30 days when compared with UFH: all-cause mortality, nonfatal MI, or recurrent ischemia at 7 days (enoxaparin 8.8% vs. UFH 8.5% (HR 0.89; 95% CI, 0.75 to 1.05);[66] all-cause mortality or nonfatal MI at 30 days (enoxaparin 14.0% vs. UFH 14.5%);[65] and all-cause mortality, nonfatal MI, or revascularization at 30 days (enoxaparin 14.0% vs. UFH 16.1%).[67] In the two observational studies (both fair quality) of enoxaparin versus unfractionated heparin, Brieger et al.[104] reported a lower incidence of death during hospitalization in patients treated with enoxaparin when compared with unfractionated heparin. Singh et al.[103] reported similar composite ischemic endpoints in enoxaparin-treated and unfractionated heparin-treated patients (7.4% in each group).

There were also similar rates of the composite outcome (all-cause mortality, nonfatal MI, or revascularization) at 30 days in patients treated with enoxaparin (7.4%) when compared with fondaparinux (7.4%).[68] In the single, small RCT (fair quality) of fondaparinux versus UFH, there was a statistically nonsignificant reduction in the composite outcome of all-cause mortality, nonfatal MI, revascularization, or thrombotic GPI bailout in patients treated with fondaparinux (4.2%) when compared with UFH (6.0%) at 48 hours.[69]

Overall, the SOE was rated low for similar incidence in the composite ischemic endpoint at 7 days between enoxaparin and UFH based on one RCT (A to Z study),[66] which was adequately powered for a noninferiority hypothesis. In the A to Z study, enoxaparin was to be considered noninferior to UFH if the upper one-sided 95% confidence boundary for the enoxaparin effect relative to UFH was less than 1.14. The SOE was rated insufficient between fondaparinux and UFH based on a fair-quality study assessing the composite outcome at 48 hours. The SOE was rated low for similar incidence of the composite ischemic endpoint at 30 days for enoxaparin versus UFH (based on two good-quality RCTs) and for enoxaparin versus fondaparinux (based on one good-quality RCT), all with consistent results of a direct outcome.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal MI, or Revascularization at 6 Months

One RCT[68] (good quality) of 20,078 patients in this comparison group evaluated the effect of treatment on the composite endpoint of all-cause mortality, nonfatal MI, or revascularization at 6 months. In this study, there was a similar incidence of composite ischemic outcomes in patients

treated with enoxaparin (10.2%) and fondaparinux (10.1%). The SOE was rated low for similar composite ischemic outcomes at 6 months between treatments based on a single, very large RCT that was adequately powered for a noninferiority hypothesis (i.e., noninferiority margin or delta of 1.185).

Effect on Major Bleeding at 30 Days

Two RCTs (both good quality, 30,105 patients)[65,68] and two observational studies (both fair quality, 29,017 patients)[103,104] evaluated the effect of treatment with enoxaparin, UFH, or fondaparinux on major bleeding. In one RCT, there was a significantly higher incidence of major bleeding in patients treated with enoxaparin when compared with fondaparinux at 30 days and at 6 months (5.0% vs. 3.1% at 30 days, 5.8% vs. 4.3% at 6 months, both $p<0.001$).[68] In the other RCT, there was a significantly higher incidence of in-hospital major bleeding in patients treated with enoxaparin (9.1%) when compared with UFH (7.6%), $p=0.008$.[65]

In the observational studies, there was a statistically significant difference in major bleeding favoring enoxaparin (1.8%) versus UFH (2.7%), $p<0.001$,[104] but no statistically significant difference in non–CABG-related transfusions (enoxaparin 6.7%; UFH 7.0%) between treatments.[103] The SOE for major bleeding at 30 days was rated moderate for the RCT of enoxaparin versus UFH and for the RCT of enoxaparin versus fondaparinux. The SOE from the two fair-quality observational studies of enoxaparin versus UFH was rated low due to imprecise results and high risk of bias.

Findings by Subgroup (KQ 1c)

Three good-quality RCTs[65,66,68] (two studies evaluating enoxaparin vs. UFH, one study evaluating enoxaparin vs. fondaparinux) reported variations in treatment effectiveness by subgroup. Subgroups analyzed included age, sex, diabetes mellitus, chronic kidney disease, presence of smoking, prior coronary revascularization, serum biomarker positivity, TIMI risk score, and geographic location. Prespecified subgroup analysis of clopidogrel pretreatment is covered in a separate section of this report. Other patient and demographic characteristics were not clearly described. Table H-1 in Appendix H presents the results data for these subgroups.

Age

In 2540 patients over 75 years of age in SYNERGY, there was no significant difference in the incidence of death or MI at 30 days between unfractionated heparin and enoxaparin. There was a higher and statistically significant incidence in TIMI major bleeding in elderly patients treated with enoxaparin when compared with unfractionated heparin.[65]

In 1599 patients over 65 years of age in A to Z, there was no significant difference in the incidence of death, nonfatal MI, or refractory ischemia at 7 days between enoxaparin (11.3%) and unfractionated heparin (12.4%).[66]

In 12261 patients over 65 years of age in OASIS-5, there was no significant difference in the incidence of death, nonfatal MI, or refractory ischemia between fondaparinux (6.6%) and enoxaparin (6.8%). There was a lower incidence of major bleeding in patients over 65 years of age treated with fondaparinux (2.7%) versus enoxaparin (5.5%) which was statistically significant.[68]

Sex

In 6595 male patients in SYNERGY, there was a statistically nonsignificant reduction in the incidence of death or MI at 30 days favoring enoxaparin (14.2%) when compared with

unfractionated heparin (15.4%). In 3379 female patients, there was a statistically nonsignificant reduction in the incidence of death or MI at 30 days favoring unfractionated heparin (12.9%) when compared with enoxaparin (13.5%).[65]

In 2826 male patients in A to Z, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, or refractory ischemia at 7 days favoring enoxaparin (8.3%) and unfractionated heparin (9.5%). In 1141 female patients in A to Z, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, or refractory ischemia at 7 days favoring enoxaparin (8.6%) and unfractionated heparin (9.3%).[66]

In 12379 male patients in OASIS-5, there was no significant difference in the incidence of death, nonfatal MI, or refractory ischemia between fondaparinux (6.0%) and enoxaparin (5.8%). In 7699 female patients, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, or refractory ischemia favoring enoxaparin (5.3%) when compared with fondaparinux (5.7%). There was a lower incidence of major bleeding in men (fondaparinux 2.0%; enoxaparin 3.3%) and women (fondaparinux 2.5%; enoxaparin 5.5%) which was statistically significant.[68]

Diabetes Mellitus

In 2924 patients with diabetes mellitus in SYNERGY, there was no significant difference in the incidence of death or MI at 30 days between unfractionated heparin (15.7%) and enoxaparin (15.6%).[65] In 751 patients with diabetes mellitus in A to Z, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, or refractory ischemia at 7 days favoring enoxaparin (8.4%) when compared with unfractionated heparin (10.7%).[66] There was no subgroup analysis presented in patients with diabetes mellitus from OASIS-5.[68]

Chronic Kidney Disease

No subgroup analysis data on kidney function or chronic kidney disease was presented in SYNERGY or A to Z.[65,66] In the OASIS-5 trial, an exclusion criterion for the trial was a serum creatinine greater than 3 mg/dL and the authors reported a subgroup analysis of serum creatinine less than or above the median for the population. In 11,124 patients with a serum creatinine at or above the median in this trial, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, or refractory ischemia at 9 days favoring fondaparinux (5.9%) versus enoxaparin (6.4%) and a statistically significant reduction in the incidence of major bleed at 9 days favoring fondaparinux (2.4%) versus enoxaparin (4.7%).[68]

Presence of Smoking

In 1403 patients from the SYNERGY trial who were current smokers at the time of randomization, there was a statistically significant reduction in the incidence of composite ischemic events (death or MI) at 30 days favoring enoxaparin (12.3%) when compared with unfractionated heparin (15.9%), p=0.009. Composite ischemic event rates were similar and nonsignificant in the nonsmokers and prior smokers.[65]

Prior Coronary Revascularization

In 2008 patients with prior PCI in SYNERGY, there was no significant difference in the incidence of death or MI at 30 days between unfractionated heparin (14.1%) and enoxaparin (13.9%). In 1658 patients with prior CABG, there was a lower incidence of death or MI at 30 days favoring enoxaparin (13.2%) when compared with unfractionated heparin (15.8%) which

was not statistically significant.[65] There was no subgroup analysis of prior coronary revascularization (including PCI or CABG) in A to Z or OASIS-5.[66,68]

Serum Biomarker Positivity

In 8174 patients with elevated cardiac biomarkers in SYNERGY, there was a statistically nonsignificant reduction in the incidence of death or MI at 30 days favoring enoxaparin (14.2%) when compared with unfractionated heparin (14.9%).[65] In 2127 patients with an elevated troponin in A to Z, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, or refractory ischemia at 7 days favoring enoxaparin (8.3%) when compared with unfractionated heparin (9.5%).[66] There was no subgroup analysis presented in patients with abnormal serum cardiac biomarkers from OASIS-5.[68]

TIMI Risk Score

No subgroup analysis data on TIMI risk score was presented in SYNERGY.[65] In 1598 patients with a low TIMI risk score in A to Z, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, or refractory ischemia at 7 days favoring unfractionated heparin (5.7%) when compared with enoxaparin (6.4%). In 1833 patients with an intermediate TIMI risk score, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, or refractory ischemia at 7 days favoring enoxaparin (8.1%) when compared with unfractionated heparin (10.2%). In 536 patients with a high TIMI risk score, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, or refractory ischemia at 7 days favoring enoxaparin (15.1%) when compared with unfractionated heparin (17.9%).[66] There was no subgroup analysis of TIMI risk score from OASIS-5.[68]

Geographic Region

In 481 patients enrolled from North America in SYNERGY, there was a statistically nonsignificant reduction in the incidence of death or MI at 30 days favoring enoxaparin (27.3%) when compared with unfractionated heparin (29.7%).[65] In 798 patients enrolled from the United States in A to Z, there was a statistically nonsignificant reduction in the incidence of death, nonfatal MI, or refractory ischemia at 7 days favoring enoxaparin (6.7%) when compared with unfractionated heparin (7.7%).[66] There was no subgroup analysis of geographic region presented in OASIS-5.[68]

Summary of Results for Enoxaparin Versus Unfractionated Heparin Versus Fondaparinux (PCI Cohort)

In our analysis of studies comparing enoxaparin, UFH, or fondaparinux, we used subgroups of UA/NSTEMI patients who underwent early invasive treatment. This limited the available outcomes to a composite ischemic outcome prior to 7 days, at 30 days, and after 6 months, and the incidence of major bleeding at 30 days. There were no significant differences in the incidence of the composite ischemic endpoints prior to 7 days between enoxaparin and heparin, or at 30 days between enoxaparin, UFH, or fondaparinux. At 6 months, there was no difference in the composite ischemic endpoint between enoxaparin and fondaparinux. For bleeding outcomes, there was a lower and statistically significant incidence in major bleeding at 30 days favoring fondaparinux when compared with enoxaparin; the rates of major bleeding in the enoxaparin versus UFH studies were inconsistent.

Subgroup analyses from three studies included age, sex, diabetes mellitus, chronic kidney disease, presence of smoking, prior coronary revascularization, serum biomarker positivity, TIMI

risk score, and geographic location. Most showed nonsignificant reductions in composite outcomes in the enoxaparin and fondaparinux groups; there was a significant reduction in major bleeding in older persons treated with either enoxaparin or fondaparinux compared with UFH which are consistent with the total population findings. Detailed SOE ratings are shown in Table 10.

Table 10. Detailed strength of evidence for UA/NSTEMI patients treated with enoxaparin versus unfractionated heparin versus fondaparinux (percutaneous coronary intervention cohort)

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite Ischemic Endpoints Prior to 7 Days					
Enoxaparin vs. UFH 1 (3987)	RCT/Good quality	NA	Direct	Precise	**Low SOE** HR 0.89 (0.75 to 1.05) No difference (adequately powered for noninferiority hypothesis)
Fondaparinux vs. UFH 1 (350)	RCT/Fair quality	NA	Direct	Imprecise	**Insufficient SOE** 4.2% vs. 6.0%
Composite Ischemic Endpoints at 30 Days					
Enoxaparin vs. UFH 2 (10,773)	2 RCTs/Both good quality	Consistent	Direct	Precise	**Low SOE** 14% vs. 14.5% and 14% vs. 16.1% No difference
Enoxaparin vs. fondaparinux 1 (20,078)	RCT/Good quality	NA	Direct	Precise	**Low SOE** 7.4% vs. 7.4% No difference
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 6 Months					
Enoxaparin vs. fondaparinux 1 (20,078)	RCT/Good quality	NA	Direct	Precise	**Low SOE** Enoxaparin: 10.2% Fondaparinux: 10.1% No difference (adequately powered for a noninferiority hypothesis)
Major Bleeding at 30 Days					
Enoxaparin vs. UFH 1 (10,027)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** Lower events with UFH (7.6%) vs. enoxaparin (9.1%) Favors UFH
Enoxaparin vs. UFH 2 (29,017)	2 observational/Both fair quality	Consistent	Direct	Imprecise	**Low SOE** Lower events with enoxaparin (2.7% UFH vs. 1.8% enoxaparin; 7% UFH vs. 6.7% enoxaparin) Favors enoxaparin
Enoxaparin vs. fondaparinux 1 (20,078)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** Lower events with fondaparinux (3.1%) vs. enoxaparin (5.0%); p<0.001 Favors fondaparinux

CI = confidence interval; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction; UFH = unfractionated heparin

6. Upstream or Deferred Clopidogrel for Patients Undergoing Percutaneous Coronary Intervention for UA/NSTEMI in Studies With a Defined Anticoagulant or Intravenous Antiplatelet Strategy

A total of four studies—two RCTs[75,76] (both fair quality; 735 patients) and two observational studies[105,106] (both fair quality; 5590 patients)—directly compared a pretreatment (upstream) clopidogrel strategy with a deferred clopidogrel treatment strategy in a patient population receiving PCI (Tables G-6, G-7, and G-8 in Appendix G). However, the study populations were a mixture of non-ACS and ACS patients, and the use of anticoagulant (bivalirudin or UFH) and intravenous antiplatelet (upstream or deferred GPI) was not defined. In one RCT,[75] the incidence of composite ischemic endpoints at 30 days was similar between strategies in all patients undergoing PCI (pretreatment 10.3% vs. in-laboratory treatment 8.8%, p=0.72) and in the subgroup of ACS patients undergoing PCI (pretreatment 10% vs. in-lab treatment 16%, p=0.36). In the other RCT,[76] the incidence of composite ischemic endpoints was similar between the group of patients who were treated with clopidogrel at the time of PCI (12.6%) and those who underwent clopidogrel pretreatment followed by a delay in PCI (15.6%). In one observational study,[105] patients with stable angina or UA/NSTEMI who were pretreated with clopidogrel had fewer composite ischemic endpoints when compared with patients who were not pretreated with clopidogrel (deferred strategy). In the other observational study[106] of an unselected PCI cohort, patients who were pretreated with clopidogrel 6 to 24 hours prior to PCI had a 42 percent reduction in the occurrence of all-cause mortality, nonfatal MI, or revascularization at 30 days compared with patients who were not pretreated with clopidogrel.

While these data suggest that clopidogrel pretreatment is associated with improved outcomes, there are limited studies in general and in UA/NSTEMI patients. We therefore designed two types of analyses of available RCTs to determine the effect of two randomized treatment comparisons; namely, bivalirudin versus heparin-based strategy and upstream versus deferred GPI use, both in patients pretreated with clopidogrel (upstream) and patients treated with clopidogrel at the time of PCI (deferred). Therefore, the remainder of this analysis presents results for the following approaches:

- Clopidogrel upstream strategy (10 RCTs):
    a. Studies of patients pretreated with clopidogrel prior to PCI with random assignment to bivalirudin versus a heparin-based strategy (KQ 1b)
    b. Studies of patients pretreated with clopidogrel prior to PCI with random assignment to upstream versus deferred GPI use (KQ 1a)
- Clopidogrel deferred strategy (6 RCTs):
    a. Studies of patients treated with clopidogrel at the time of PCI with random assignment to bivalirudin versus heparin-based strategy (KQ 1b)
    b. Studies of patients treated with clopidogrel at the time of PCI with random assignment to upstream versus deferred GPI use (KQ 1a)

Clopidogrel Upstream Strategy

Ten RCTs compared different antithrombotic strategies in UA/NSTEMI patients pretreated with clopidogrel while undergoing an invasive strategy.[23,36,38,39,43,44,58,59,62,63] Four of these studies involved patients who were pretreated with clopidogrel and underwent random assignment to bivalirudin versus a heparin-based strategy.[58,59,62,63] Six of these studies involved patients who were pretreated with clopidogrel and underwent random assignment to upstream versus deferred use of GPI.[23,36,38,39,43,44] While the decision to treat the patient with clopidogrel

was not randomly assigned, the included studies may offer insight into the effect of these medications when used in combination for the treatment of UA/NSTEMI. To reduce potential treatment interactions, we excluded multiple studies of provisional (i.e., without planned) GPI use and other treatment options (i.e., enoxaparin, UFH).

Of the ten RCTs included in the meta-analysis, six studies (60%) were rated good quality, three (30%) fair, and one (10%) poor. Sample sizes for individual studies ranged from 100 to 13,819 patients. All studies reported 30 day outcomes.

The mean age of study participants ranged from 61 to 70 years of age. The proportion of female patients ranged from 23 to 54 percent. One study (10%) reported the racial and ethnic demographics of study participants. Five studies (50%) were conducted within the United States or Canada, with the rest international. Funding source was reported in seven studies (70%) as an industry source.

Bivalirudin Versus Heparin-Based Strategy in Patients Pretreated With Clopidogrel (KQ 1b)

Effect on Composite Ischemic Endpoints at 30 Days

Two good-quality RCTs[62,63] including 7104 UA/NSTEMI patients treated with clopidogrel prior to PCI reported the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 30 days. The study by Rajagopal had fewer composite ischemic events in the heparin-treated group (OR 1.11; 95% CI, 0.75 to 1.64), as did the study by Stone (OR 1.25; 95% CI, 0.99 to 1.56), but neither were statistically significant. The SOE was rated low for no difference based on two good-quality RCTs with consistent results of direct outcome and a wide confidence interval that crossed 1.

Effect on Composite Ischemic Endpoints at 1 Year

We identified one good-quality RCT[58] of 4570 patients that reported the effect of treatment on all-cause mortality, nonfatal MI, or revascularization at 1 year. This study showed that in patients who were pretreated with clopidogrel, those patients randomly assigned to bivalirudin (21.5%) had a statistically nonsignificant difference in the incidence of composite ischemic endpoints when compared with a heparin-based strategy (20.1%). The SOE was rated insufficient based on subgroup findings from only one moderate-sized good-quality RCT that was underpowered to detect a difference for this subgroup.

Effect on All-Cause Mortality at 1 Year

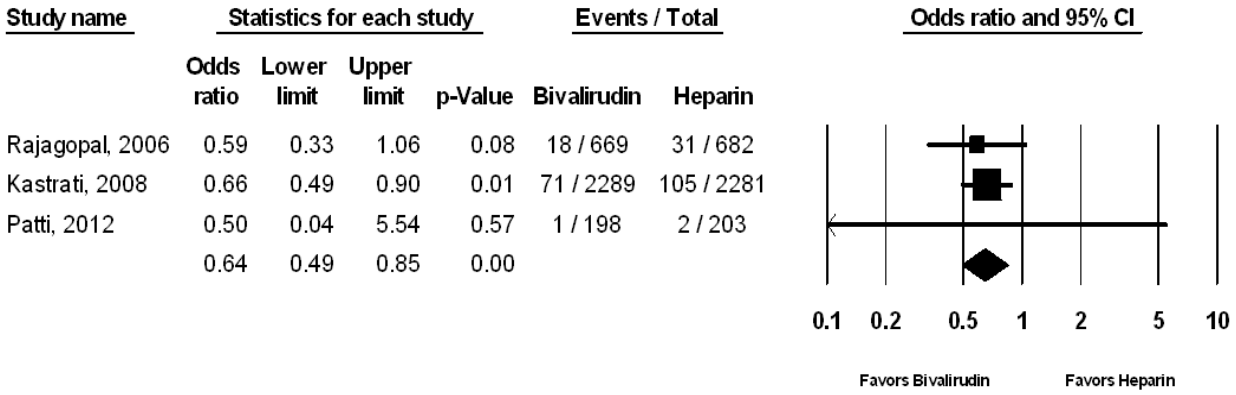
One good-quality RCT[62] of 5126 patients reported the effect of bivalirudin versus heparin on all-cause mortality at 1 year in patients pretreated with clopidogrel. Patients treated with bivalirudin had a similar incidence of all-cause mortality compared with those treated with a heparin-based strategy (16.0% vs. 16.3%, p=NS). The SOE was rated insufficient based on subgroup findings from only one moderate-sized good-quality RCT that was underpowered to detect a difference for this subgroup.

Effect on Major Bleeding at 30 Days

A random-effects meta-analysis of three RCTs[58,59,63] (two good quality, one fair) including 6322 UA/NSTEMI patients pretreated with clopidogrel prior to PCI reporting major bleeding at 30 days found that the odds ratio was 0.64 (95% CI, 0.49 to 0.85) favoring bivalirudin compared with a heparin-based strategy (Figure 26). There was no evidence of heterogeneity, with a Q-

value of 0.17 for 2 degrees of freedom, p=0.92. The SOE was rated moderate based on two good- and one fair-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

Figure 26. Meta-analysis of patients pretreated with clopidogrel randomly assigned to bivalirudin versus heparin-based strategy on major bleeding at 30 days



CI = confidence interval

Upstream Versus Deferred GPI Use in Patients Pretreated With Clopidogrel (KQ 1a)

Effect on Composite Ischemic Endpoints Prior to 30 Days

Only one good-quality RCT[43] including 6895 UA/NSTEMI patients reported a composite endpoint of all-cause mortality, nonfatal MI, revascularization, or thrombotic GPI bailout at 96 hours in patients pretreated with clopidogrel prior to PCI who were randomly assigned to upstream versus deferred GPI use. This study showed that there was a small, statistically nonsignificant difference in composite endpoint in those patients treated with upstream GPI (8.7%) versus deferred GPI (9.4%). The SOE for this composite endpoint was rated insufficient based on only one good-quality RCT.

One poor-quality RCT[39] that included 300 UA/NSTEMI patients reported a composite endpoint of all-cause mortality, nonfatal MI, or rehospitalization at 30 days in patients pretreated with clopidogrel prior to PCI who were randomly assigned to upstream versus deferred GPI use. In this study, patients treated with upstream GPI (9.0%) had a statistically nonsignificant lower incidence of the composite endpoint when compared with patients treated with deferred GPI (10.0%). The SOE for this composite endpoint was rated insufficient based on only one small, poor-quality RCT.

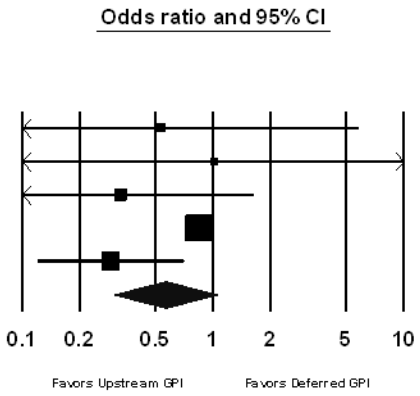
Two randomized studies (one good quality, one fair)[36,38] that included 638 UA/NSTEMI patients reported a composite endpoint of all-cause mortality, nonfatal MI, or ischemia/revascularization at 30 days in patients pretreated with clopidogrel prior to PCI who were randomly assigned to upstream versus deferred GPI use. Patients treated with upstream GPI had a reduction in the incidence of the composite outcome when compared with deferred GPI (Durand, fair quality, 16% vs. 17%; Bhattacharya, good quality, 16% vs. 26%; combined average 15.7% vs. 20.3%). This effect was mainly driven by refractory ischemia in the good-quality study.[38] The SOE was rated low based on one good-and one fair-quality RCT with consistent and imprecise results of a direct outcome.

Effect on All-Cause Mortality at 30 Days

A random-effects meta-analysis of five RCTs[36,38,39,43,44] (two good quality, two fair, one poor) including 8168 UA/NSTEMI patients reporting all-cause mortality at 30 days in patients pretreated with clopidogrel prior to PCI randomly assigned to upstream versus deferred GPI found that the odds ratio was 0.56 (95% CI, 0.30 to 1.05) demonstrating a benefit of upstream GPI (Figure 27). There was no evidence of heterogeneity, with a Q-value of 6.76 for 4 degrees of freedom, p=0.15. The SOE was rated low based on two good-, two fair-, and one poor-quality RCTs with consistent results of a direct outcome and a wide confidence interval that crosses 1.

Figure 27. Meta-analysis of patients pretreated with clopidogrel randomly assigned to upstream versus deferred glycoprotein inhibitor use on all-cause mortality at 30 days

Study name	Statistics for each study				Events / Total	
	Odds ratio	Lower limit	Upper limit	p-Value	Upstream GPI	Deferred GPI
Leoncini, 2005	0.54	0.05	5.80	0.61	1 / 150	2 / 150
Rasoul, 2006	1.02	0.06	16.41	0.99	1 / 162	1 / 163
Durand, 2007	0.33	0.07	1.64	0.17	2 / 196	6 / 197
Giugliano, 2009	0.84	0.73	0.98	0.03	348 / 3443	406 / 3452
Bhattacharya, 2010	0.29	0.12	0.71	0.01	7 / 122	23 / 133
	0.56	0.30	1.05	0.07		



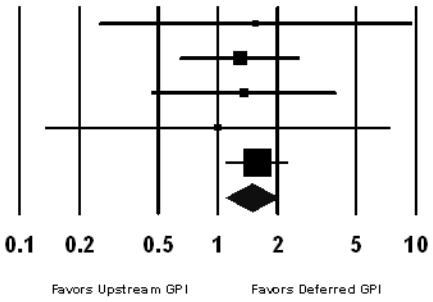
CI = confidence interval; GPI = glycoprotein inhibitor

Effect on Major Bleeding at 30 Days

A random-effects meta-analysis of five RCTs[23,36,39,43,44] (two good quality, two fair, one poor) including 7416 UA/NSTEMI patients reporting major bleeding at 30 days in patients pretreated with clopidogrel prior to PCI randomly assigned to upstream versus deferred GPI found that the odds ratio was 1.49 (95% CI, 1.10 to 2.01), favoring deferred GPI, p=0.01 (Figure 28). There was no evidence of heterogeneity, with a Q-value of 0.44 for 4 degrees of freedom, p=0.98. The SOE was rated moderate based on consistent results of a direct outcome and a wide confidence interval.

Figure 28. Meta-analysis of patients pretreated with clopidogrel randomly assigned to upstream versus deferred glycoprotein inhibitor use on major bleeding at 30 days

Study name	Statistics for each study				Events / Total	
	Odds ratio	Lower limit	Upper limit	p-Value	Upstream GPI	Deferred GPI
Leoncini, 2005	1.55	0.25	9.54	0.64	3 / 150	2 / 150
Rasoul, 2006	1.29	0.64	2.60	0.47	20 / 162	16 / 163
Durand, 2007	1.35	0.46	3.97	0.58	8 / 196	6 / 197
Ivandic, 2008	1.00	0.14	7.39	1.00	2 / 50	2 / 50
Giugliano, 2009	1.58	1.10	2.28	0.01	75 / 3443	48 / 3452
	1.49	1.10	2.01	0.01		



CI = confidence interval; GPI = glycoprotein inhibitor

Clopidogrel Deferred Strategy

Six RCTs (three good quality, two fair, one poor) compared different antithrombotic strategies in 14,429 UA/NSTEMI patients treated with clopidogrel at the time of PCI while undergoing an invasive strategy.[41-43,57,61,110] Two of these studies (one good quality, one fair) involved patients who were treated with clopidogrel at the time of PCI (not pretreated with clopidogrel) and underwent random assignment to bivalirudin versus a heparin-based strategy.[57,61] Four of these studies (two good quality, one fair, one poor) involved patients who were treated with clopidogrel at the time of PCI (not pretreated with clopidogrel) and underwent random assignment to upstream versus deferred use of GPI.[41-43,110].

Of the six RCTs, three studies (50%) were rated good quality, two (33%) fair, and one (16%) poor. Sample sizes for individual studies ranged from 160 to 9378 patients. All studies reported 30 day outcomes.

The mean age of study participants ranged from 60 to 69 years of age. The proportion of female patients ranged from 23 to 32 percent. None of the studies reported the racial and ethnic demographics of study participants. Three studies (50%) were conducted within the United States or Canada, with the rest international. Funding source was reported in four studies (66%), with all four of the studies being funded by industry source.

Bivalirudin Versus Heparin-Based Strategy in Patients Treated With Clopidogrel at the Time of PCI (KQ 1b)

Effect on All-Cause Mortality, Nonfatal Myocardial Infarction, or Revascularization at 30 Days

Two RCTs[57,61] (one good quality, one fair) including 2571 UA/NSTEMI patients treated with clopidogrel at the time of PCI reported the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 30 days. The Parodi study (fair) showed a significant reduction in composite events in the group that received bivalirudin (OR 0.42; 95% CI, 0.21 to 0.84, p=0.02). The Kastrati study (good) showed no statistical difference between the groups (OR 1.05; 95% CI, 0.80 to 1.40). The SOE was rated insufficient based on one good- and one fair-quality RCT with inconsistent results of a direct outcome and a wide confidence interval.

Effect on Major Bleeding at 30 Days

Two RCTs[57,61] (one good quality, one fair) including 2571 UA/NSTEMI patients treated with clopidogrel at the time of PCI reported major bleeding at 30 days. The Parodi study (fair) showed no statistical difference between the groups (OR 0.32; 95% CI, 0.10 to 1.01) and the Kastrati study (good) showed a statistically significant reduction favoring bivalirudin (OR 0.53; 95% CI, 0.31 to 0.91, p=0.02). The SOE was rated low based on one good- and one fair-quality RCT with consistent results of a direct outcome and a wide confidence interval.

Upstream Versus Deferred GPI Use in Patients Treated With Clopidogrel at the Time of PCI (KQ 1a)

Effect on All-Cause Mortality, Nonfatal Myocardial Infarction, Revascularization, or Thrombotic GPI Bailout at 96 Hours

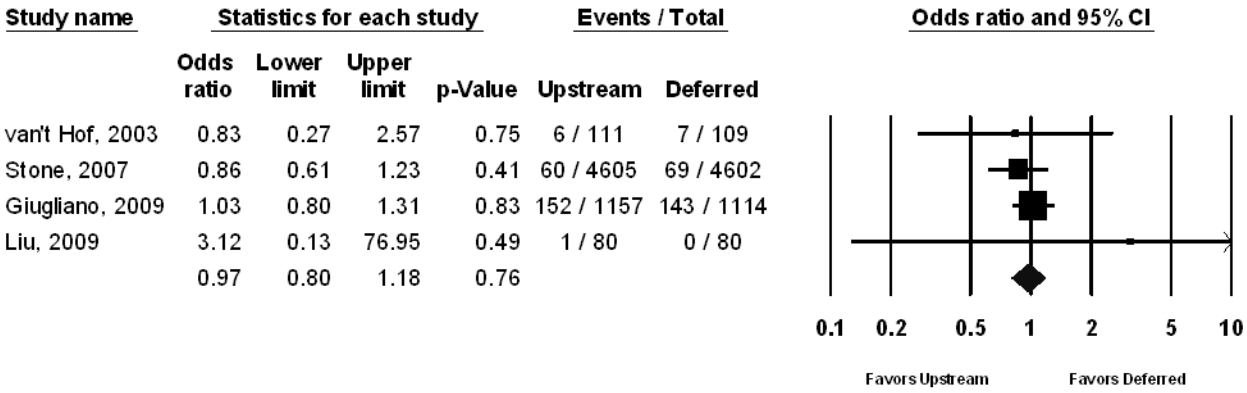
Only one RCT (good quality)[43] including 2271 UA/NSTEMI patients reported a composite endpoint of all-cause mortality, nonfatal MI, revascularization, thrombotic GPI bailout at 96 hours in patients treated with clopidogrel at the time of PCI randomly assigned to upstream

versus deferred GPI use. This study showed that there was a small but not statistically significant difference in composite endpoint in those patients treated with upstream GPI (10.3%) versus deferred GPI (11.2%). The SOE was rated insufficient based on a subgroup analysis from one good-quality RCT.

Effect on All-Cause Mortality at 30 Days

A random-effects meta-analysis of four RCTs[41-43,110] (two good quality, one fair, one poor) including 11,858 UA/NSTEMI patients reported all-cause mortality at 30 days in patients treated with clopidogrel at the time of PCI randomly assigned to upstream versus deferred GPI found that the odds ratio was 0.97 (95% CI, 0.80 to 1.18) demonstrating no difference (Figure 29). There was no evidence of heterogeneity, with a Q-value of 1.20 for 3 degrees of freedom, p=0.75. The low event rate (one death in upstream GPI group; no deaths in deferred GPI group) in one fair-quality study[41] contributed to the inconsistent results. The exclusion of the poor-quality study[42] did not impact our findings. The SOE of no difference was rated as low based on two good-, one fair-, and one poor-quality RCTs with inconsistent results of a direct outcome.

Figure 29. Meta-analysis of patients treated with clopidogrel at time of percutaneous coronary intervention randomly assigned to upstream versus deferred glycoprotein inhibitor use on all-cause mortality at 30 days

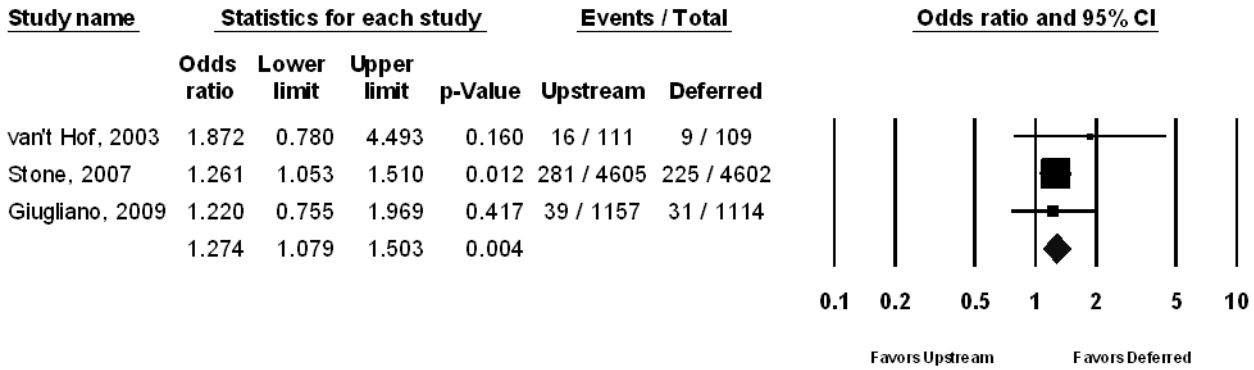


CI = confidence interval

Effect on Major Bleeding at 30 Days

A random-effects meta-analysis of three RCTs[42,43,110] (two good quality, one fair) including 11,698 UA/NSTEMI patients reported major bleeding at 30 days in patients treated with clopidogrel at the time of PCI randomly assigned to upstream versus deferred GPI found that the odds ratio was 1.27 (95% CI, 1.08 to 1.50), favoring deferred GPI (Figure 30). There was no evidence of heterogeneity, with a Q-value of 0.79 for 2 degrees of freedom, p=0.68. The SOE was rated high based on two good- and one fair-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

Figure 30. Meta-analysis of patients treated with clopidogrel at the time of percutaneous coronary intervention randomly assigned to upstream versus deferred glycoprotein inhibitor use on major bleeding at 30 days



CI = confidence interval

Findings by Subgroup (KQ 1c)

Since the findings from this comparison were derived from a subgroup of patients who were pretreated with clopidogrel or treated with clopidogrel prior to PCI, further attempts at subgroup analysis could not be performed.

Summary of Results for Upstream or Deferred Clopidogrel Strategy

In randomized comparisons of patients treated with (1) bivalirudin versus heparin-based strategy and (2) upstream versus deferred GPI use, the nonrandomized effectiveness and safety of clopidogrel pretreatment and deferred clopidogrel treatment was assessed. In these analyses, patients pretreated with clopidogrel and randomized to a heparin-based strategy had no differences in composite ischemic outcomes compared with patients randomized to bivalirudin, but the evidence was insufficient. However, the occurrence of major bleeding was significantly lower in bivalirudin-treated patients when compared with heparin-treated patients. There were no significant differences in the occurrence of composite ischemic endpoints at 1 year or all-cause mortality at 1 year between bivalirudin and heparin groups, based on insufficient SOE. Patients pretreated with clopidogrel and randomized to upstream GPI use had a trend toward fewer composite ischemic outcomes at 30 days and fewer deaths at 30 days when compared with patients randomized to deferred GPI use. There was insufficient SOE for the composite outcome at 96 hours, and for the composite of all-cause mortality, nonfatal MI, or rehospitalization at 30 days. The occurrence of major bleeding at 30 days was significantly higher in patients pretreated with clopidogrel who were randomized to upstream GPI when compared with deferred GPI use.

In patients treated with deferred clopidogrel strategy, there were conflicting results for composite ischemic events at 30 days in patients randomized to bivalirudin when compared with heparin-based strategy, therefore the SOE was insufficient. There was low SOE for the effect on major bleeding at 30 days in those patients treated with deferred clopidogrel and randomized to bivalirudin, with one good-quality study showing a reduction in major bleeding favoring bivalirudin. In studies of patients treated with deferred clopidogrel and randomized to upstream GPI, there was insufficient SOE for composite ischemic outcomes at 30 days, and low SOE for no difference in all-cause mortality at 30 days. The occurrence of major bleeding at 30 days was significantly higher in patients treated with deferred clopidogrel who were randomized to upstream GPI when compared with deferred GPI use. Detailed SOE ratings are shown in Tables

11–14. Odds ratios less than 1 favor bivalirudin or upstream GPI; odds ratios greater than 1 favor a heparin-based strategy or deferred GPI use.

Table 11. Detailed strength of evidence for bivalirudin versus heparin-based strategy in patients pretreated with clopidogrel

Number of Studies (Patients)	Domains				Strength of Evidence and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 30 Days					**Low SOE**
2 (7104)	2 RCTs/Both good quality	Consistent	Direct	Imprecise	Both studies showed no statistically significant difference in composite event rates ranging from OR 1.11 to 1.25 No difference
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 1 Year					**Insufficient SOE**
1 (4570)	RCT/Good quality	NA	Direct	Imprecise	Bivalirudin: 21.5% Heparin: 20.1%
All-Cause Mortality at 1 Year					**Insufficient SOE**
1 (5126)	RCT/Good quality	NA	Direct	Imprecise	Bivalirudin: 16.0% Heparin: 16.3%
Major Bleeding at 30 Days					**Moderate SOE**
3 (6322)	3 RCTs/2 good quality, 1 fair	Consistent	Direct	Precise	OR 0.64 (0.49 to 0.85) Favors bivalirudin

CI = confidence interval; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

Table 12. Detailed strength of evidence for upstream versus deferred GPI use in patients pretreated with clopidogrel

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of All-Cause Mortality, Nonfatal MI, Revascularization, or Thrombotic GPI Bailout at 96 Hours					**Insufficient SOE**
1 (6895)	RCT/Good quality	NA	Direct	Imprecise	Upstream GPI: 8.7% Deferred GPI: 9.4%
Composite of All-Cause Mortality, Nonfatal MI, or Rehospitalization at 30 Days					**Insufficient SOE**
1 (300)	RCT/Poor quality	NA	Direct	Imprecise	Upstream GPI: 9% Deferred GPI: 10%
Composite of All-Cause Mortality, Nonfatal MI, or Ischemia/Revascularization at 30 Days					**Low SOE**
2 (638)	2 RCTs/1 good quality, 1 fair	Consistent	Direct	Imprecise	Upstream GPI: 15.7% Deferred GPI: 20.3% Favors upstream GPI
All-Cause Mortality at 30 Days					**Low SOE**
5 (8168)	5 RCTs/2 good quality, 2 fair, 1 poor	Consistent	Direct	Imprecise	OR 0.56 (0.30 to 1.05) favors upstream GPI
Major Bleeding at 30 Days					**Moderate SOE**
5 (7416)	5 RCTs/2 good quality, 2 fair, 1 poor	Consistent	Direct	Imprecise	OR 1.49 (1.10 to 2.01) Favors deferred GPI

CI = confidence interval; GPI = glycoprotein inhibitor; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

Table 13. Detailed strength of evidence for bivalirudin versus heparin-based strategy in patients treated with clopidogrel at the time of PCI

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 30 Days					**Insufficient SOE**
2 (2571)	2 RCTs/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	1 RCT (fair) showed a significant reduction favoring bivalirudin, OR 0.42 (0.21 to 0.84, p=0.02), the other RCT (good) showed no difference, OR 1.05 (0.80 to 1.40)
Major Bleeding at 30 Days					**Low SOE**
2 (2571)	2 RCTs/1 good quality, 1 fair	Consistent	Direct	Imprecise	One RCT (fair) showed no statistical difference between the groups, OR 0.32 (0.10 to 1.01); the other RCT (good) showed a statistically significant reduction favoring bivalirudin, OR 0.53 (0.31 to 0.91, p=0.02); Favors bivalirudin

CI = confidence interval; MI = myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

Table 14. Detailed strength of evidence for upstream versus deferred GPI use in patients treated with clopidogrel at the time of PCI

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of All-Cause Mortality, Nonfatal MI, Revascularization, or Thrombotic Bailout With GPI at 96 Hours					**Insufficient SOE**
1 (2271)	RCT/Good quality	NA	Direct	Imprecise	Upstream GPI: 10.3% Deferred GPI: 11.2%
All-Cause Mortality at 30 Days					**Low SOE**
4 (11,858)	4 RCTs/2 good quality, 1 fair, 1 poor	Inconsistent	Direct	Imprecise	OR 0.97 (0.80 to 1.18) No difference
Major Bleeding at 30 Days					**High SOE**
3 (11,698)	3 RCTs/2 good quality, 1 fair	Consistent	Direct	Precise	OR 1.27 (1.08 to 1.50) Favors deferred GPI

CI = confidence interval; GPI = glycoprotein inhibitor; MI = myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

Key Question 2. Initial Conservative Approach for UA/NSTEMI

KQ 2: In patients undergoing an initial conservative approach for treating UA/NSTEMI:

a. What are the comparative effectiveness (dose and timing) and comparative safety of different anticoagulants for improving cardiovascular outcomes?

b. What are the comparative effectiveness (dose and timing) and comparative safety of different antiplatelet agents for improving cardiovascular outcomes?

c. Based on demographic and other characteristics, are there subgroups of patients for whom the effectiveness and safety differ?

Key Points

- Compared with UFH, enoxaparin treatment showed a significant reduction in composite ischemic events (high SOE) and nonfatal MI (moderate SOE) at around 30 days. There was no difference in all-cause mortality at 30 days (low SOE), but there was insufficient evidence to reach a conclusion on the comparative treatment effect on major bleeding at 30 days.
- Based on an indirect comparison of fondaparinux and UFH, there was a significant reduction in composite ischemic events (low SOE) and major bleeding (low SOE) at around 30 days favoring fondaparinux, but there was insufficient evidence to reach a conclusion on the comparative treatment effect on nonfatal MI or all-cause mortality.
- Observational studies within subgroups showed that the use of enoxaparin was associated with lower rates of ischemic events in obese patients, those with renal impairment, and those with ST depression on electrocardiography.
- Adding a GPI to UFH reduced the rate of mortality at 30 days (high SOE) and reduced composite ischemic events and nonfatal MI (moderate SOE).
- There was insufficient evidence for the effect of GPIs on revascularization although fewer events were seen in patients receiving GPIs in two small trials.
- While the use of GPIs reduces the rates of the adverse events mentioned above, the tradeoff is an increase in minor bleeding rates (high SOE). There was insufficient evidence on the effect of GPIs on major bleeding.
- Ticagrelor reduced the rates of composite ischemic and all-cause mortality events; however, it also increased rates of major bleeding and the combination of major or minor bleeding events (moderate SOE) compared with clopidogrel at up to 30 months. There was no difference in revascularization at 12 months for this comparison (moderate SOE).
- Prasugrel showed similar rates of composite ischemic events, all-cause mortality, and nonfatal MI compared with clopidogrel (moderate SOE) at up to 30 months. There was insufficient evidence to support findings concerning stroke or major bleeding events for this comparison; however, there was low SOE that the combination of major or minor bleeding events up to 30 months was lower in the clopidogrel group.

Description of Included Studies

We identified 33 unique studies that evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 225,891 patients with UA/NSTEMI treated with an *initial conservative* approach or a mixed population for whom the approach (conservative or invasive) was not presented separately.[38,40,62,65-73,103,104,111-129] Of these studies, 24 were RCTs (14 good quality, 9 fair, 1 poor) and 9 were observational (4 good quality, 4 fair, 1 poor) (Table E-2 in Appendix E). 28 studies were multicenter,[62,65-69,71-73,103,104,111-116,118-120,122-129] four studies were single-center,[38,70,117,121] and in one study the number of sites was unclear or not reported.[40] Twenty-one studies included sites in the U.S. or Canada,[62,65-69,72,73,103,104,114,116,118-120,122-125,128,129]18 included sites in Europe,[62,65,66,68-70,73,104,112,116,117,119,122,123,125,126,128,129] 11 included sites in Asia,[38,40,66,68,71,111,113,115,121,128,129] and in 1 study the site location was unclear or not reported.[127] A total of 18 studies used industry funding,[62,65-69,71,73,103,104,114,118,122-125,128,129] and in 15 studies the funding source was either not reported or unclear.[38,40,70,72,111-113,115-117,119-121,126,127] The study characteristics table for KQ 2 (Table F-2 in Appendix F) contains details about the study design, proportion of UA/NSTEMI patients, antiplatelet/anticoagulant comparisons, outcomes measured, and study quality for studies included in the analysis of an initial conservative approach.

In the next section, we present the following three comparisons that were assessed in the included studies in KQ 2:

1. UFH versus enoxaparin or fondaparinux (full UA/NSTEMI cohort; KQ 2a)
    - 21 studies (12 RCTs, 9 observational; 161,506 total patients)
        a. Enoxaparin versus UFH (10 RCTs, 4 observational; 24,567 patients)
        b. Enoxaparin versus fondaparinux (1 RCT; 20,078 patients)
        c. Fondaparinux versus UFH (1 RCT; 350 patients)
        d. UFH versus low molecular weight heparin (either enoxaparin or fondaparinux; 4 observational; 56,152 patients)
        e. Enoxaparin (normal dose) versus low- or high-dose enoxaparin (1 observational; 10,687 patients)
2. GPI plus UFH versus UFH alone (KQ 2b)
    - 10 studies (10 RCTs; 38,518 total patients)
3. Clopidogrel versus ticagrelor or prasugrel (initial conservative cohort; KQ 2b)
    - 2 studies (2 RCTs; 12,459 total patients)

The subgroup findings (KQ 2c) are presented after each comparison.

Detailed Synthesis

1. Unfractionated Heparin Versus Enoxaparin or Fondaparinux (Full UA/NSTEMI Cohort; KQ 2a)

Twenty-one studies (12 RCTs, 9 observational) evaluated the use of UFH versus enoxaparin or fondaparinux in 161,506 patients with UA/NSTEMI.[65-73,103,104,111-114,116,118,119,121,125,127] The majority of these studies were performed prior to the time (pre-2005) when an early invasive strategy was widely implemented, and employed an initial conservative strategy followed by percutaneous revascularization. An initial conservative strategy was particularly common during the study period for centers outside the United States. Proportions of patients proceeding to revascularization ranged from 29 percent[67] to 63 percent.[68]

Six RCTs compared enoxaparin with UFH as an initial management strategy prior to PCI and included a total of 18,554 patients.[65-67,119,121,125] One RCT (20,078 patients) compared enoxaparin with fondaparinux[68] and one RCT (350 patients) compared fondaparinux with UFH.[69] Three studies compared enoxaparin with UFH at the time of PCI.[70-72] The study populations reflected a mixture of UA/NSTEMI and elective PCI patients, and the timing of PCI relative to presentation with ACS was not specified. One study compared the use of enoxaparin with UFH in UA/NSTEMI patients.[73] Patients who underwent PCI uniformly received open-label UFH by protocol for the intervention, but all patients received double-blind, subcutaneous injections until hospital discharge or Day 8, whichever came first.

Sample sizes for the RCTs ranged from 93 to 20,078 patients. Study duration ranged from 48 hours to 6 months. The mean age of study participants ranged from 56 to 68 years of age. The proportion of female patients ranged from 23 to 38 percent. Two studies[65,66] reported the racial and ethnic demographics of study participants and also contained a predominately Caucasian population (85% and 86%). The RCTs included 9 multicenter and 3 single-center studies, representing an international patient population including North America, Europe, and Asia. Eight of the 12 RCTs were industry-sponsored. The full results across all outcomes are reported in Table G-9 in Appendix G.

Nine observational studies met our inclusion criteria but were excluded from meta-analysis due to heterogeneity in the study population or risk for selection bias in the setting of nonrandomized treatment selection.[103,104,111-114,116,118,127] A description of the observational studies follows our analysis of the RCTs; these are included in this section to compare their findings with the RCTs and to report subgroup findings that were not addressed in the RCTs. The Goodman 2006 article[130] considered in this group is a prospective observational study on subgroups from the ESSENCE trial,[125] which has been analyzed with the rest of the RCTs in this section. Sample sizes for these observational studies ranged from 2397 to 37,320 patients. The mean age of study participants ranged from 62 to 70 years. The proportion of female patients ranged from 30 to 48 percent. Three studies[114,116,118] reported the racial and ethnic demographics of study participants and had a predominately Caucasian population (ranging from 82% to 85%). The observational studies were all multicenter trials representing an international population including North America, South America, Europe, and Asia, with the exception of one study where this was unreported.[127] Four of the nine studies were industry sponsored and will be discussed qualitatively below.

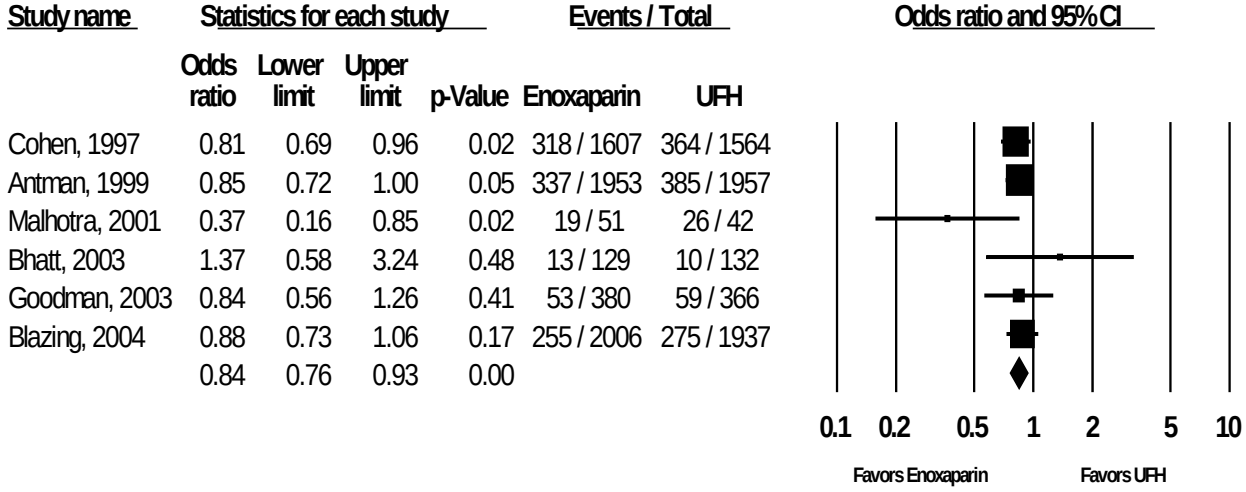
Effect on Composite Endpoint of All-Cause Mortality, Nonfatal Myocardial Infarction, Revascularization, or Recurrent Ischemia at Around 30 Days

Six studies[66,67,72,73,121,125] (all RCTs; 4 good quality, 2 fair) evaluated the effect of low molecular weight heparin and UFH on a composite endpoint of total mortality, nonfatal MI, or recurrent ischemia/revascularization in a total of 12,124 UA/NSTEMI patients. These endpoints were reported for short-term outcomes ranging from 7 days (Blazing et al.[66]) to 43 days (Antman et al.[73]), with the majority of studies reporting the composite outcome at 30 days (4 studies). Because the bulk of recurrent ischemic events in ACS occur soon after PCI, we assumed that relative estimates of effect would be comparable within this range of time points. This assumption holds for all analyses in this section.

A random-effects meta-analysis of the 6 studies comparing the effect of treatment strategies incorporating enoxaparin versus UFH found an estimated odds ratio of 0.84 (95% CI, 0.76 to 0.93) (Figure 31). There was no evidence of heterogeneity, with a Q-value of 5.38 for 5 degrees

of freedom, p=0.37. The study by Malhotra et al. was a small, single-center, fair-quality study.[121] The I^2 value was 7.08. Accommodating for between-study variance, the relative estimates of effect on the composite endpoint were generally consistent among studies, suggesting a significant overall reduction in the ischemic composite endpoint in the setting of an enoxaparin-based treatment strategy. The SOE was rated high for this composite endpoint based on multiple head-to-head RCTs with a consistent evidence base, precise estimates of the overall effect, and moderate scores for risk of bias due to the clinical heterogeneity among studies.

Figure 31. Meta-analysis of enoxaparin versus unfractionated heparin on composite outcome of all-cause mortality, nonfatal myocardial infarction, revascularization, or recurrent ischemia at around 30 days



CI = confidence interval; UFH = unfractionated heparin

The effect of fondaparinux versus UFH on the composite short-term endpoint was estimated using methods described by Hasselblad and Kong.[131] We created an indirect comparison of fondaparinux versus UFH by combining the above estimate of enoxaparin versus UFH with the results for fondaparinux versus enoxaparin in the study by Yusuf et al.[68] (20,078 patients). The uncertainty around the estimate is the sum of the variances of the meta-analysis and the results from Yusuf et al.[68] The result is an estimated odds ratio of 0.78 (95% CI, 0.67 to 0.90), favoring fondaparinux. The SOE was rated low for this composite endpoint based on an indirect comparison with only a single trial contributing information on fondaparinux versus enoxaparin.

Effect on Composite Ischemic Endpoint at 6 Months

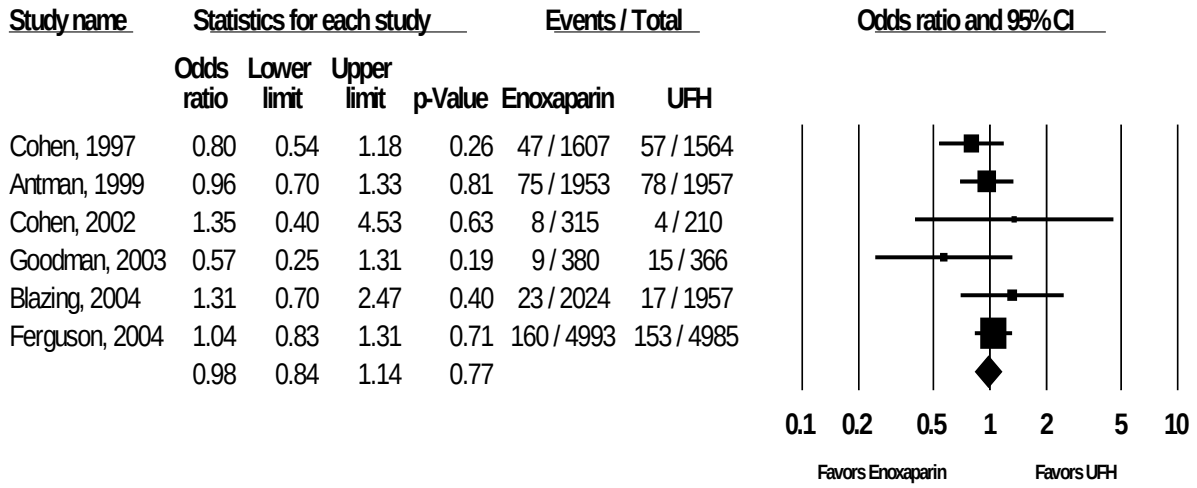
Only one good-quality RCT of 20,078 patients in this comparison group evaluated the effect of treatment on the composite ischemic outcome at 6 months.[68] In this study, which was adequately powered for a noninferiority hypothesis (difference of 1.185 between groups), there was a similar incidence of composite ischemic outcomes in patients treated with enoxaparin (10.2%) and fondaparinux (10.1%). The SOE was rated low for the composite ischemic outcome at 6 months based on a single large RCT.

Effect on All-Cause Mortality at Around 30 Days

Eight studies[65-67,72,73,119,121,125] (all RCTs, 5 good quality, 3 fair) reported the effect of low molecular weight heparin and UFH on total mortality in a total of 23,015 UA/NSTEMI patients. Two studies[72,121] had no deaths and so were not included in the analysis.

A random-effects meta-analysis of the 6 studies comparing the effect of treatment strategies incorporating enoxaparin versus UFH on total mortality found an estimated odds ratio of 0.98 (95% CI, 0.84 to 1.14) (Figure 32). There was no evidence of heterogeneity, with a Q-value of 4.11 for 5 degrees of freedom, p=0.53. The I^2 value was 0.00. Accommodating for between-study variance, the relative estimates of effect on the composite endpoint were generally consistent among studies, and the overall estimate does not detect a mortality difference in the setting of an enoxaparin-based treatment strategy. The SOE was rated low for no difference in all-cause mortality based on multiple head-to-head RCTs with a consistent evidence base, imprecise estimates of the overall effect, and moderate scores for risk of bias due to the clinical heterogeneity among studies. Note that failure to detect a difference does not imply that a difference does not exist. This analysis was not designed to test for equivalence between enoxaparin and UFH.

Figure 32. Meta-analysis of enoxaparin versus unfractionated heparin on all-cause mortality at around 30 days



CI = confidence interval; UFH = unfractionated heparin

We created an indirect comparison of fondaparinux versus UFH by combining the above estimate of enoxaparin versus UFH with the results for fondaparinux versus enoxaparin in Yusuf et al.[68] (20,078 patients). The result is an estimated odds ratio of 0.93 (95% CI, 0.71 to 1.20), showing no difference between treatments. The SOE was rated insufficient for all-cause mortality based on an indirect comparison with only one trial contributing information on fondaparinux versus enoxaparin and imprecise results.

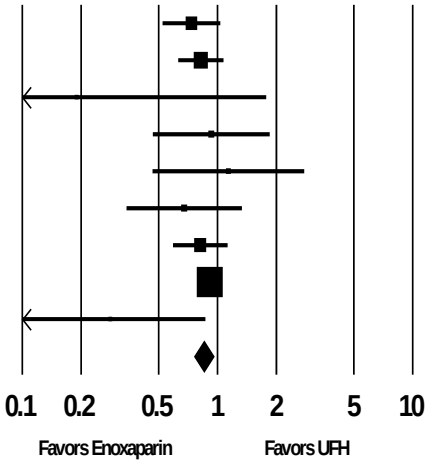
Effect on Nonfatal Myocardial Infarction at Around 30 Days

Nine studies[65-67,70,72,73,119,121,125] (all RCTs; 5 good quality, 4 fair) reported the effect of low molecular weight heparin and UFH on nonfatal (re)infarction in a total of 22,970 UA/NSTEMI patients. A random-effects meta-analysis of the 9 studies comparing the effect of treatment strategies incorporating enoxaparin versus UFH on nonfatal (re)infarction found an odds ratio of 0.85 (95% CI, 0.76 to 0.95) (Figure 33).There was no evidence of heterogeneity, with a Q-value of 8.49 for 8 degrees of freedom, p=0.39. The I^2 value was 5.75. Accommodating for between-study variance, the relative estimates of effect on the composite endpoint were generally

consistent among studies, suggesting a significant overall reduction in myocardial (re)infarction in the setting of an enoxaparin-based treatment strategy. The SOE was rated moderate for nonfatal MI based on multiple head-to-head RCTs with a consistent evidence base, imprecise estimates of the overall effect, and moderate scores for risk of bias due to the clinical heterogeneity among studies.

Figure 33. Meta-analysis of enoxaparin versus unfractionated heparin on nonfatal myocardial infarction at around 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Enoxaparin	UFH
Cohen, 1997	0.73	0.52	1.03	0.07	62 / 1607	81 / 1564
Antman, 1999	0.82	0.63	1.07	0.15	107 / 1953	129 / 1957
Malhotra, 2001	0.19	0.02	1.77	0.14	1 / 51	4 / 42
Cohen, 2002	0.93	0.47	1.85	0.83	21 / 315	15 / 210
Bhatt, 2003	1.14	0.47	2.78	0.78	11 / 129	10 / 132
Goodman, 2003	0.68	0.34	1.33	0.26	15 / 380	21 / 366
Blazing, 2004	0.82	0.59	1.12	0.21	73 / 1998	86 / 1938
Ferguson, 2004	0.91	0.81	1.03	0.14	580 / 4993	627 / 4985
Bertel, 2010	0.28	0.09	0.86	0.03	4 / 436	14 / 440
	0.85	0.76	0.95	0.00		



CI = confidence interval; UFH = unfractionated heparin

We created an indirect comparison of fondaparinux versus UFH by combining the above estimate of enoxaparin versus UFH with the results for fondaparinux versus enoxaparin in Yusuf et al.[68] (20,078 patients). The result is an estimated odds ratio of 0.85 (95% CI, 0.69 to 1.04) suggesting a benefit of fondaparinux, but the CI crosses 1, making the finding imprecise. The SOE was rated insufficient for nonfatal MI based on an indirect comparison with only one trial contributing information on fondaparinux versus enoxaparin.

Effect on Major Bleeding at Around 30 Days

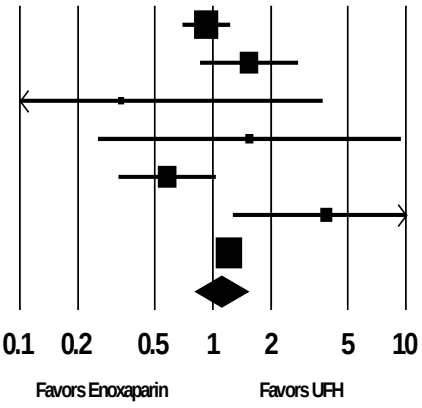
Eight studies[65-67,72,73,119,121,125] (all RCTs; 5 good quality, 3 fair) reported the effect of low molecular weight heparin and UFH on major bleeding in a total of 22,901 UA/NSTEMI patients. The study by Malhotra et al.[121] had no events and so was not included in the analysis.

A random-effects meta-analysis of the seven studies comparing the effect of treatment strategies incorporating enoxaparin versus UFH found an odds ratio of 1.11 (95% CI, 0.81 to 1.51) (Figure 34). There was evidence of heterogeneity, with a Q-value of 14.87 for 6 degrees of freedom, p=0.02. The I^2 value was 59.66. The heterogeneity likely represents the between-study differences in PCI utilization and dosing. For instance, the Cohen 2002 study[119] was a double-blind, small-sized RCT with 30 percent of patients undergoing PCI. In contrast, the study by Blazing et al.[66] was an open-label, large-sized RCT with 60 percent of patients undergoing PCI. Removal of that study reduced the heterogeneity to a Q-value of 10.18 (p=-0.07), but the summary estimate was essentially unchanged, 1.03 (95% CI, 0.78 to 1.35). Accommodating between-study variance, the overall estimate does not detect a difference in major bleeding rates

in the setting of an enoxaparin-based treatment strategy. The SOE was rated insufficient for major bleeding based on multiple head-to-head RCTs with an inconsistent evidence base, imprecise estimates of the overall effect, and moderate scores for risk of bias due to the clinical heterogeneity among studies.

Figure 34. Meta-analysis of enoxaparin versus unfractionated heparin on major bleeding at around 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Enoxaparin	UFH
Cohen, 1997	0.92	0.70	1.22	0.58	102 / 1607	107 / 1564
Antman, 1999	1.54	0.86	2.75	0.15	29 / 1938	19 / 1936
Cohen, 2002	0.33	0.03	3.70	0.37	1 / 315	2 / 210
Bhatt, 2003	1.55	0.25	9.38	0.64	3 / 129	2 / 132
Goodman, 2003	0.58	0.33	1.03	0.06	20 / 380	32 / 366
Blazing, 2004	3.87	1.27	11.78	0.02	15 / 1940	4 / 1965
Ferguson, 2004	1.21	1.05	1.40	0.01	453 / 4993	379 / 4983
	1.11	0.81	1.51	0.52		



CI = confidence interval; UFH = unfractionated heparin

We created an indirect comparison of fondaparinux versus UFH by combining the above estimate of enoxaparin versus UFH with the Yusuf et al.[68] (20,078 patients). The result is an estimated odds ratio of 0.69 (95% CI, 0.49 to 0.97), favoring fondaparinux. The SOE was rated low for major bleeding based on an indirect comparison with only one trial contributing information on fondaparinux versus enoxaparin.

Findings in Observational Studies

As stated earlier, we identified nine observational studies (in addition to the Goodman 2006 prospective observational subgroup cohort of the ESSENCE trial), but none were meta-analyzed due to heterogeneity in the study population or risk for selection bias in the setting of nonrandomized treatment selection.[103,104,111-114,116,118,127,130] Of these observational studies, only one[112] included information on fondaparinux. We describe below the findings of these observational studies and how the findings relate to the RCT evidence base.

Prescribed Use Over Time

Six studies described use and overall trends from 1999 through 2007.[103,104,112,113,116,118] The Thai registry[113] described use in 17 centers in Thailand from 2002-2005 among 3,963 patients with NSTEMI or UA. Many more patients were treated with enoxaparin (84%) than with UFH (16%) overall. The U.S.-based CRUSADE Registry of 11,358 patients[103] demonstrated a greater use of UFH (60.6%) than enoxaparin (39.4%) among invasively managed patients also treated with GPI. The GRACE Registry of 17,659 patients[116] noted that 37.9 percent of patients received enoxaparin in first 24 hours with continued use; 17.0 percent received UFH in the first 24 hours with continued use; 12.7 percent received neither, and 31.7 percent had cross-over from

enoxaparin to UFH or vice versa. Over time intervals from 1999 to 2005 there was an increased use of enoxaparin alone, and more crossovers, with less UFH alone. There was a greater use of enoxaparin outside of the United States. Patients treated with enoxaparin were less likely to undergo PCI in the first 24 hours, and those undergoing PCI were more likely to be treated with UFH or to be in the crossover group.

Another GRACE article[104] evaluated heparin use in relation to GPI and invasive care. Enoxaparin was used in 51 percent, UFH in 32 percent, and 17 percent received both UFH and enoxaparin at some time. Patients given UFH had more comorbidity than those given enoxaparin or both. A multicenter registry of 2874 patients in France[112] found that between 2006 and 2007, the use of fondaparinux increased considerably (5% to 25%) Patients given UFH were older, with more comorbidities and fewer guideline-associated treatments. Finally, the NRMI (National Registry of Myocardial Infarctions) study[118] described use of heparins among 37,320 patients treated with GPI from 1998 to 2000. Only seven percent were treated with enoxaparin, and 93 percent were treated with UFH. Thus the older study (NRMI registry) showed low use of enoxaparin in the late 1990s, with more recent studies published in 2007 and 2010 showing increasing use of enoxaparin and fondaparinux.

Effect on Cardiovascular Events

Seven observational studies reported the effect on mortality, myocardial infarction, and/or recurrent ischemia. In the Thai registry[113] the UFH group had more cardiac deaths than the enoxaparin group (9.3% vs. 5.2%, $p<0.0001$). Within the U.S.-based CRUSADE Registry[103] the point estimate of risk of in-hospital death or reinfarction was lower in patients treated with enoxaparin (OR 0.81, 95% CI, 0.67 to 0.99) than with UFH. There were particular benefits in this study to enoxaparin among those who did not undergo revascularization. The GRACE Registry[116] found that the adjusted ORs for death were not significant but favored enoxaparin over either UFH or crossover compared with no heparin. Also, the composite of death, MI, and recurrent ischemia were all higher in the treated groups compared with those not treated with any heparin, suggesting selection biases despite adjustment. Another GRACE article[104] evaluated heparin use in relation to GPI and invasive care. Overall adjusted comparison demonstrated that enoxaparin was associated with lower mortality (OR 0.76; 95% CI, 0.63 to 0.91). Among subgroups by treatment, this was particularly true for those who did not receive GPI or PCI or who had PCI without GPI. There were no differences in enoxaparin or UFH in the subgroup receiving both GPI and PCI. The multicenter registry in France[112] found that fondaparinux was associated with lower adjusted mortality than UFH and similar adjusted mortality to enoxaparin. Again, patients given UFH in the French registry were older, with more comorbidities and fewer guideline-associated treatments. The KAMIR (Korean Acute MI registry) study[111] assessed the use of enoxaparin with low-dose UFH compared with usual-dose UFH alone in 2397 patients undergoing PCI with a drug-eluting stent. This study found that the enoxaparin group had similar incidences of cardiac death, total death, and total MACE at 8 months compared with the UFH group. However, there were significantly lower rates of recurrent myocardial infarction in the enoxaparin group (0.3%) compared with the UFH group (1.0, $p=0.024$). Finally, the NRMI study[118] found no differences recurrent MI or death in those treated with enoxaparin compared with UFH. Similar to the RCT meta-analyses, most studies show a benefit of enoxaparin in reducing composite ischemic events, while the effect of enoxaparin on individual endpoints was inconsistent across studies.

Effect on Major Bleeding

Seven observational studies reported the findings on major bleeding. In the Thai registry,[113] major bleeding was 6.3 percent in the enoxaparin group and 3.7 percent in the UFH group (p-value not reported). The U.S.-based CRUSADE Registry[103] showed similar bleeding risks between the enoxaparin and UFH groups. In the GRACE Registry,[116] the adjusted ORs for bleeding were not different in enoxaparin, UFH, or crossover groups compared with no heparin. Another GRACE article[104] evaluated heparin use in relation to GPI, invasive care, and major bleeding (OR 0.78; 95% CI, 0.64 to 0.95). There was a slight trend to increase major bleeding with enoxaparin after adjustment. In patients who had crossover, UFH was superior in those with GPI and no PCI. A multicenter registry in France[112] reported rates of in-hospital bleeding of 2.1 percent in the enoxaparin group, 5.0 percent in the UFH group, and 3.3 percent in the fondaparinux group; thus bleeding rates were similar in the enoxaparin and fondaparinux groups but significantly higher in the UFH group. The KAMIR study[111] did not find any significant differences in in-hospital major or minor bleeding rates. Finally, the NRMI study[118] noted no differences in major bleeding rates in those treated with enoxaparin compared with UFH. Overall, the major bleeding rates varied across observational studies with some showing no differences between enoxaparin and UFH, while other showed higher rates with either agent. Regional differences in the selection of anticoagulants to use based on clinical presentation and comorbidities may be responsible for the heterogeneity. The meta-analysis of randomized trials above failed to show a significant difference in major bleeding rates.

Effect on Other Outcomes

One observational study, the Thai registry,[113] reported a longer length of hospital stay in the UFH group (56.9%, $p<0.0001$) compared with the enoxaparin group (44.7%). Two RCTs reported length of hospital stay. The ACUTE II study found similar duration of hospitalization in the UFH (208 ± 180 hours) and enoxaparin groups (209 ± 149 hours, $p=0.20$).[119] The ESCAPEU study found a significantly lower duration of hospitalization in the enoxaparin group (156 ± 14 hours) compared with the UFH group (166 ± 19 hours, $p=0.01$).[121]

Findings by Subgroup (KQ 2c)

The subgroup findings for the RCTs of low molecular weight heparin and UFH are described in the KQ 1 section, so to avoid redundancy the following section focuses on the observational studies. Three other observational studies evaluated enoxaparin in relation to key subgroups; namely, patient factors related to excess dosage, obesity, renal impairment, and ECG changes.[114,127,130] Among a CRUSADE Registry population who received enoxaparin,[114] 18.7 percent received an excess dose, and 29.2 percent received lower than recommended dose. Those receiving excess doses were more likely to be older, smaller, and female based upon the need to adjust for both weight and renal function. Lower than recommended dose was associated with a trend to higher mortality, and an excess dose was associated with more major bleeding and death compared with recommended doses. In an analysis from the clinical trial data in ESSENCE and TIMI 11B,[127] enoxaparin was associated with lower rates of death, nonfatal MI, or unplanned revascularization among obese patients and those with renal impairment. There was a slight increased risk of bleeding with enoxaparin in those with renal impairment. Finally, a subgroup from the ESSENCE trial[130] found that enoxaparin was particularly beneficial over UFH among patients with ECG changes, specifically ST-depression. This identified a higher risk subgroup, more likely to benefit from the use of enoxaparin. Table H-2 in Appendix H presents the results data for these subgroups.

Summary of Results for Enoxaparin Versus Unfractionated Heparin Versus Fondaparinux (Full UA/NSTEMI Cohort)

In our analysis of studies comparing enoxaparin, UFH, and fondaparinux, we present the findings of UA/NSTEMI patients who received primarily initial conservative treatment. There was a significant reduction in composite ischemic events and nonfatal MI at around 30 days with enoxaparin compared with UFH, but insufficient SOE for the outcomes of all-cause mortality and major bleeding for that time period. An indirect comparison of fondaparinux and UFH found a significant reduction in composite ischemic events and a nonsignificant reduction in major bleeding events favoring fondaparinux. Evidence was insufficient for the outcomes of nonfatal MI and all-cause mortality at around 30 days in this comparison. Results from observational studies show that use of low molecular weight heparin is increasing over time in the conservatively managed population and confirmed RCT findings that enoxaparin is associated with fewer ischemic events, although the results for bleeding events were mixed. Fondaparinux was associated with lower adjusted mortality than UFH and similar adjusted mortality to enoxaparin. In an RCT, fondaparinux significantly lowered mortality at 30 days and 180 days and major bleeding at 9 days compared with enoxaparin. Subgroups analyzed were dosage, obesity, renal impairment, and ECG changes. Excess dosage was associated with more major bleeding and death and was more likely to be received by older, smaller, and female patients. Use of enoxaparin was associated with lower rates of ischemic events in obese patients, those with renal impairment, and those with ST depression on ECG. Detailed SOE ratings are shown in Table 15. Odds ratios less than 1 favor enoxaparin or fondaparinux; odds ratios greater than 1 favor UFH.

Table 15. Detailed strength of evidence for UA/NSTEMI patients treated with unfractionated heparin versus enoxaparin or fondaparinux (full UA/NSTEMI cohort)

Number of Studies (Patients)[a]	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of All-Cause Mortality, Nonfatal MI, Revascularization, or Recurrent Ischemia at around 30 days					
Enoxaparin vs. UFH 6 (12,124)	6 RCTs/4 good quality, 2 fair	Consistent	Direct	Precise	**High SOE** OR 0.84 (0.76 to 0.93) Favors enoxaparin
Fondaparinux vs. UFH 1 (20,078)	RCT/Good quality	NA	Indirect	Precise	**Low SOE** OR 0.78 (0.67 to 0.90) Favors fondaparinux
Composite Ischemic Endpoint at 6 Months					
Enoxaparin vs. fondaparinux 1 (20,078)	RCT/Good quality	NA	Direct	Precise	**Low SOE** No significant difference between fondaparinux and enoxaparin (10.1% vs. 10.2%)

Table 15. Detailed strength of evidence for UA/NSTEMI patients treated with unfractionated heparin versus enoxaparin or fondaparinux (full UA/NSTEMI cohort) (continued)

Number of Studies (Patients)[a]	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
All-Cause Mortality at Around 30 Days					
Enoxaparin vs. UFH 8 (23,015)	8 RCTs/5 good quality, 3 fair	Consistent	Direct	Imprecise	**Low SOE** OR 0.98 (0.84 to 1.14) No difference
Fondaparinux vs. UFH 1 (20,078)	RCT/Good quality	NA	Indirect	Imprecise	**Insufficient SOE** OR 0.93 (0.71 to 1.20)
Nonfatal MI at Around 30 Days					
Enoxaparin vs. UFH 9 (22,970)	9 RCTs/5 good quality, 4 fair	Consistent	Direct	Imprecise	**Moderate SOE** OR 0.85 (0.76 to 0.95) Favors enoxaparin
Fondaparinux vs. UFH 1 (20,078)	RCT/Good quality	NA	Indirect	Imprecise	**Insufficient SOE** OR 0.85 (0.69 to 1.04)
Major bleeding at Around 30 Days					
Enoxaparin vs. UFH 8 (22,901)	8 RCTs/5 good quality, 3 fair	Inconsistent	Direct	Imprecise	**Insufficient SOE** OR 1.11 (0.81 to 1.51)
Fondaparinux vs. UFH 1 (20,078)	RCT/Good quality	NA	Indirect	Precise	**Low SOE** OR 0.69 (0.49 to 0.97) Favors fondaparinux

CI = confidence interval; ECG = electrocardiogram; MI = myocardial infarction; NA = not applicable; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction; UFH = unfractionated heparin

[a]Populations for the indirect fondaparinux comparisons included the 20,078 patients from the Yusuf study.

2. GPI Plus Unfractionated Heparin Versus Unfractionated Heparin Alone (KQ 2b)

Ten RCTs (7 good quality, 3 fair) evaluated GPIs versus UFH in 38,518 patients with UA/NSTEMI.[38,40,62,115,117,120,122-124,126] The majority of these studies were performed prior to the time when an early invasive strategy was widely implemented, and employed an initial conservative strategy followed by percutaneous revascularization after 18 to 72 hours. Some of the studies had a mixture of treatment approaches and reported subgroup findings for the medically managed population. Subjects in older studies (pre-2000) were enrolled on the basis of high-risk MI features, while newer studies followed the standard definition for conservative strategy and are likely lower risk patients.

Proportions of patients proceeding to revascularization ranged from 0 percent[38,115,117] to 100 percent.[126] Sample sizes for the RCTs ranged from 60 to 13,819 patients. Study duration ranged from 30 days to 1 year. The mean age of study participants ranged from 53 to 65 years of age. The proportion of female patients ranged from 25 to 54 percent. Three studies[122-124] reported the racial and ethnic demographics of study participants. The RCTs included eight multicenter and two single-center studies, representing an international patient population including North America, Europe, and Asia. Six of the studies were industry-sponsored. GPIs assessed included: abciximab (two studies[120,126]), eptifibatide (two studies[40,122]), tirofiban (five studies[38,115,117,123,124]), and any of the three GPIs with either UFH or enoxaparin (1 study[62]). The full results across all outcomes are reported in Table G-10 in Appendix G.

Effect on Composite Ischemic Endpoints up to 30 Days

All 10 RCTs (7 good quality, 3 fair; 38,518 patients) reported composite endpoints at 30 days.[38,40,62,115,117,120,122-124,126] The results are described qualitatively since the specific components of the composite endpoints differed among the studies; pooling all the studies into an quantitative analysis was not possible due to the heterogeneity of the composite endpoint definition, and pooling only the studies that had similar composite endpoints would have reduced the number of studies available for analysis.

In the PURSUIT study,[122] rates of the composite outcome (death or nonfatal MI) were significantly lower in the eptifibatide group compared with heparin (14.2% vs. 15.7%, p=0.04). Likewise, Momtahen et al.[40] found that the composite of total mortality, nonfatal MI, or revascularization was significantly lower in the eptifibatide group (0%) compared with heparin (16%, p<0.01).

In the PRISM study,[123] the primary composite endpoint (death, MI, refractory ischemia, or UA readmission) was lower in the tirofiban group compared with heparin (RR 0.67; 95% CI, 0.48 to 0.92, p=0.01). The secondary composite endpoint of death or MI showed a nonsignificant reduction in event rates in the tirofiban group (RR 0.80; 95% CI, 0.61 to 1.05). In an analysis of the medically managed (no PCI) subgroup (tirofiban, n=992 and UFH n=1007), the primary composite outcome also showed a lower risk of events in the tirofiban group, for both the primary composite endpoint (RR 0.84; 95% CI, 0.65 to 1.10) and the secondary composite endpoint (RR 0.58; 95% CI, 0.38 to 0.87).

In the PRISM-PLUS study,[124] the primary composite endpoint (death, MI, or refractory ischemia) was lower in the tirofiban group compared with tirofiban plus heparin (RR 0.78 (95% CI, 0.63 to 0.98, p=0.03). The secondary composite endpoint of death or MI was also significant and favored the tirofiban group (RR 0.70 CI, 0.51 to 0.96, p=0.03). An analysis of the medically managed (no PCI) subgroup showed a nonsignificant reduction in the primary composite endpoint (RR 0.87; 95% CI, 0.60 to 1.25) and secondary composite endpoint (RR 0.75; 95% CI, 0.46 to 1.23).

The Bhattacharya study[38] reported significant reduction in the composite endpoint of fatal/nonfatal MI, refractory ischemia or death with tirofiban with enoxaparin (19%) compared with enoxaparin (34%, p=0.01) at 30 days.

In the Okmen study,[117] the in-hospital rate of composite events (total mortality, nonfatal MI, revascularization, or refractory angina) was significantly lower in the tirofiban group (26% vs. 54%, p=0.01) In the ACUITY TIMING study,[110] the medical therapy subgroup also had fewer composite events (death, MI, or revascularization) in patients who received *upstream* GPI (2.4%) compared with *deferred* GPI (3.3%) (HR 1.39; 95% CI, 0.91 to 2.12). The medical therapy subgroup of the ACUITY trial showed a nonsignificant reduction in the same composite event at 30 days favoring UFH plus GPI over bivalirudin (RR 1.24; 95% CI, 0.83 to 1.85).

In the RCT by Song et al.,[115] the frequency of the composite endpoint (total mortality, nonfatal MI, or refractory ischemia) in the tirofiban plus UFH arm was lower than UFH alone (13,9% vs. 29.3%, p=0.01).

The GUSTO-IV study reported no significant differences between abciximab and heparin in acute coronary syndrome patients who do not undergo early coronary revascularization (angiography was discouraged within 60 hours of randomization).[120] The odds ratio of the primary composite endpoint of total mortality or nonfatal MI was 1.00 in the 24-hour infusion group (95% CI, 0.83 to 1.24) and 1.10 in the 48-hour infusion group (95% CI, 0.94 to 1.39) compared with heparin.

Finally, the study by van den Brand et al.[126] showed lower rates of major events (total mortality, nonfatal MI, or recurrent ischemia) in the group receiving abciximab (1 out of 30) compared with heparin (7 out of 30), p=0.03.

Overall, the studies of eptifibatide and tirofiban showed a risk reduction in composite events compared with UFH alone, ranging from 0.58 to 0.84; one large trial of abciximab (GUSTO-IV ACS study)[120] showed no difference in events, but a small trial[126] showed lower rates of major events with abciximab versus heparin. The SOE was rated moderate for composite ischemic events up to 30 days based on multiple RCTs with consistent results of a direct outcome and imprecise estimates of the overall effect.

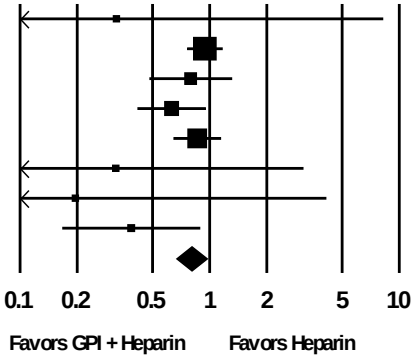
Effect on Mortality up to 30 Days

Nine RCTs (6 good quality, 3 fair) reported mortality rates in 24,699 UA/NSTEMI patients at 30 days.[38,40,115,117,120,122-124,126] In the PURSUIT study[122] the mortality rate was similar in the eptifibatide and heparin groups (3.5% vs. 3.7%). In the PRISM study[123] the mortality rate was significantly lower in the tirofiban group (RR 0.62; 95% CI, 0.41 to 0.93, p=0.02). In the PRISM-PLUS study,[124] the mortality rate was nonsignificantly lower in the tirofiban plus heparin group (RR 0.79; 95% CI, 0.48 to 1.30). The GUSTO-IV trial[120] showed no differences in mortality at 30 days for both the abciximab 24-hour infusion group (OR 0.90; 95% CI, 0.64 to 1.50) and the 48-hour infusion group (OR 1.1; 95% CI, 0.83 to 1.43) compared with heparin.

Fewer deaths were also seen in the smaller trials of GPIs compared with UFH. The Bhattacharya study[38] reported number of combined deaths due to unknown causes and fatal MI events (tirofiban 6%, heparin 14%) at 30 days. Momtahen et al.[40] reported no deaths in the eptifibatide group (n=98) and two deaths in the heparin group (n=98). Note that no in-hospital deaths occurred in the Okmen study[117] for both the tirofiban group (n=41) and the no tirofiban group (n=42); therefore, that study does not appear in the meta-analysis. Song et al.[115] reported one death in the tirofiban group (n=101) and three deaths in the heparin group (n=99). Similarly, van den Brand[126] reported no deaths in the abciximab group (n=30) and one death in the heparin group (n=30).

A random-effects meta-analysis of 8 studies[38,40,115,120,122-124,126] in 24,616 patients reporting mortality rates at 30 days found that the odds ratio was 0.80 (95% CI, 0.67 to 0.96), favoring GPI use (Figure 35). There was no evidence of heterogeneity, with a Q-value of 8.18 and 7 degrees of freedom, p=0.32. The I^2 value was 14.41.

Figure 35. Meta-analysis of glycoprotein inhibitor versus unfractionated heparin on mortality up to 30 days



Study name	Statistics for each study				Events / Total	
	Odds ratio	Lower limit	Upper limit	p-Value	GPI + heparin	Heparin
Van den Brand, 1995	0.32	0.01	8.24	0.49	0 / 30	1 / 30
Anon. (PURSUIT), 1998	0.94	0.76	1.17	0.60	165 / 4722	175 / 4739
Anon. (PRISM-PLUS), 1998	0.79	0.48	1.32	0.37	28 / 773	36 / 797
Anon. (PRISM), 1998	0.63	0.42	0.96	0.03	37 / 1616	58 / 1616
Simoons, 2001	0.86	0.64	1.15	0.31	88 / 2590	102 / 2598
Song, 2007	0.32	0.03	3.13	0.33	1 / 101	3 / 99
Momtahen, 2009	0.20	0.01	4.13	0.29	0 / 98	2 / 98
Bhattacharya, 2010	0.39	0.17	0.89	0.03	8 / 136	23 / 165
	0.80	0.67	0.96	0.02		

CI = confidence interval; GPI = glycoprotein inhibitor

A fixed-effects model had minimal changes to the summary estimate, with an odds ratio of 0.83 (95% CI, 0.71 to 0.96). In an effort to explain the between-study variation, we performed a sensitivity analysis based on features we suspected might account for the variation and that had suitable distributions among the studies. The results of the subgroup sensitivity analyses are shown in Table 16 (forest plot appears in Appendix I).

Table 16. Sensitivity analysis of glycoprotein inhibitor versus unfractionated heparin on mortality up to 30 days

Study Characteristic	Number of Studies (Patients)[a]	Summary Estimate (95% CI)
Trial Size		
Small (<1000 patients)	4 (761)	OR 0.36 (0.17 to 0.76)
Large (≥1000 patients)	4 (23,855)	OR 0.86 (0.74 to 1.00)
Antiplatelet Use		
Aspirin monotherapy	6 (24,119)	OR 0.85 (0.73 to 0.99)
Dual antiplatelet therapy	2 (497)	OR 0.37 (0.16 to 0.83)

CI = confidence interval

[a]Subgroup summary estimates with fewer than three studies should be interpreted with caution.

Studies with larger or smaller sample sizes favored GPI plus UFH, although the summary estimate for the smaller trials was more favorable toward GPI use than the larger trials. Also, the use of aspirin monotherapy and dual antiplatelet therapy favored GPI plus UFH with studies including dual antiplatelet therapy more favorable toward GPI use than the trials using aspirin monotherapy. The similarities between the fixed-effects and random-effects models support the conclusion that there is no statistical heterogeneity. Overall, the rates of mortality at 30 days were higher in the heparin group from these eight RCTs with consistent results of a direct outcome with precise results, thus leading us to conclude that the SOE was high.

Effect on Nonfatal MI up to 30 Days

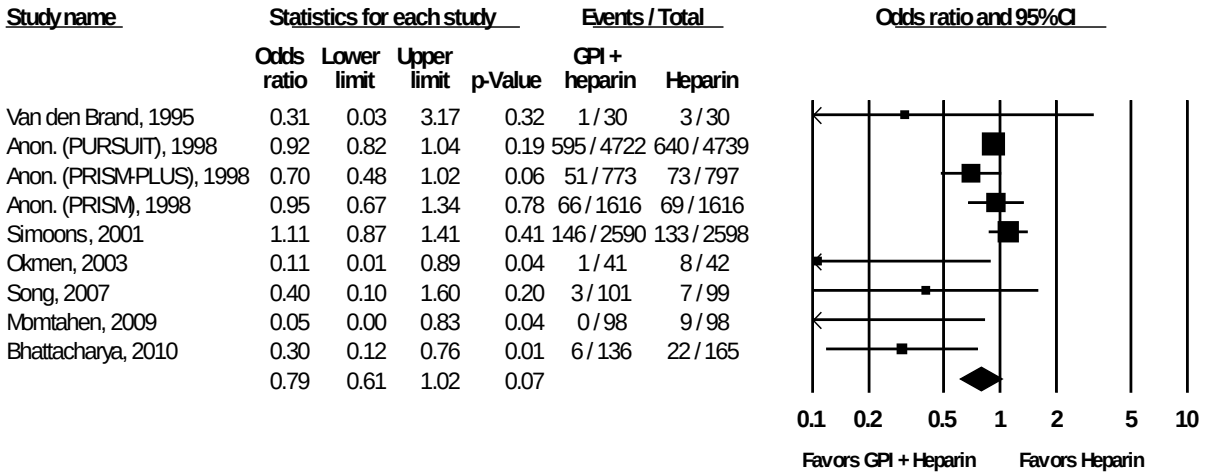
Nine RCTs (6 good quality, 3 fair) with a total of 24,699 patients reported nonfatal MI event rates either in-hospital or at 30 days.[38,40,115,117,120,122-124,126] In the PURSUIT study[122] the rates nonfatal MI were nonsignificantly lower in the eptifibatide group compared with heparin (12.6% vs. 13.5%). In the PRISM study[123] tirofiban had similar rates of nonfatal MI compared with heparin (RR 0.95; 95% CI, 0.58 to 1.34). In the PRISM-PLUS study,[124] the rate of MI events

was lower in the tirofiban plus heparin group (RR 0.70; 95% CI, 0.40 to 1.00). The GUSTO-IV trial[120] showed no differences in mortality at 30 days for both the abciximab 24-hour infusion group (OR 1.1; 95% CI, 0.87 to 1.41) and the 48-hour infusion group (OR 1.2; 95% CI, 0.91 to 1.46) compared with heparin.

The smaller RCTs also reported lower nonfatal MI events in the GPI group compared with heparin. The Bhattacharya study[38] reported six nonfatal MI events in the tirofiban group and 22 MIs in the heparin group up to 30 days. Momtahen et al.[40] reported no MIs in the eptifibatide group (n=98) and five MIs in the heparin group (n=98). In the Okmen study[117] one MI occurred in the tirofiban and eight MIs occurred in the no tirofiban group. Song et al.[115] reported three MIs in the tirofiban group and seven deaths in the heparin group. Similarly, van den brand[126] reported one MI in the abciximab group (n=30) and three MIs in the heparin group (n=30).

A random-effects meta-analysis of the 9 studies in 24,699 patients reporting nonfatal MI rates at 30 days found that the odds ratio was 0.79 (95% CI, 0.61 to 1.02), favoring GPI use (Figure 36). There was evidence of moderate heterogeneity, with a Q-value of 20.14 for 8 degrees of freedom, p=0.01. The I^2 value was 60.27.

Figure 36. Meta-analysis of glycoprotein inhibitor versus unfractionated heparin on nonfatal myocardial infarction up to 30 days



CI = confidence interval; GPI = glycoprotein inhibitor

A fixed-effects model had minimal changes to the summary estimate, with an odds ratio of 0.91 (95% CI, 0.83 to 1.00). Again, we performed a sensitivity analysis based on subgroups, and the results are shown in Table 17 (forest plot appears in Appendix I).

Table 17. Sensitivity analysis of glycoprotein inhibitor versus unfractionated heparin on nonfatal myocardial infarction up to 30 days

Study Characteristic	Number of Studies (Patients)[a]	Summary Estimate (95% CI)
Trial size		
Small (<1000 patients)	5 (844)	OR 0.26 (0.13 to 0.52)
Large (≥1000 patients)	4 (23,855)	OR 0.94 (0.81 to 1.08)
Antiplatelet use		
Aspirin monotherapy	7 (24,202)	OR 0.89 (0.74 to 1.08)
Dual antiplatelet therapy	2 (497)	OR 0.20 (0.05 to 0.89)

CI = confidence interval

[a]Subgroup summary estimates with fewer than three studies should be interpreted with caution.

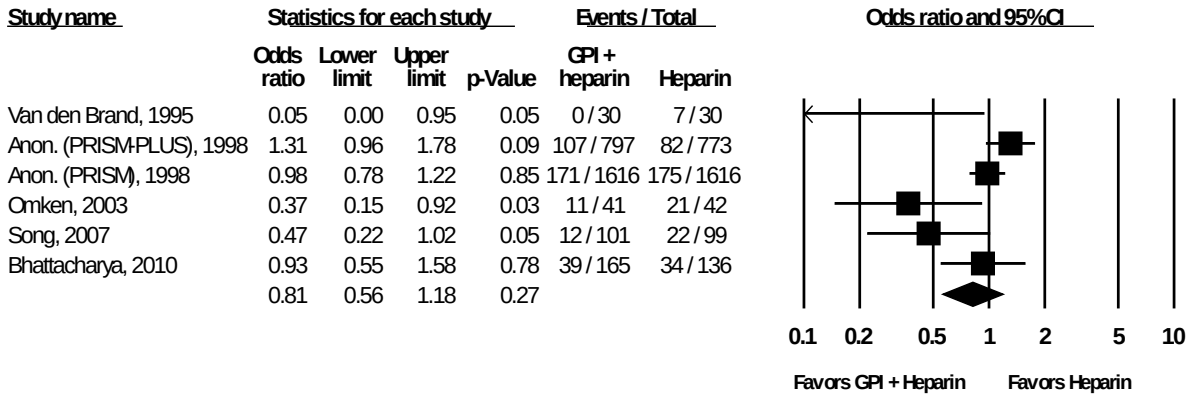
Studies with smaller sample sizes favored GPI plus UFH, but the larger studies showed no significant difference. The summary estimate for the smaller studies was less precise than for the larger studies. Note that study quality was also highly correlated with study size, with three fair studies also being smaller in size. The use of dual antiplatelet therapy also favored GPI plus UFH, but the use of aspirin monotherapy showed no statistical difference, especially in the larger studies. Thus, the moderate heterogeneity seen in the full meta-analysis can be due to trial size and antiplatelet use. The similarities between the fixed and random effects model support the conclusion that there is no statistical heterogeneity. Overall, the rates of nonfatal MI at 30 days were higher in the heparin group from these nine RCTs with inconsistent results between smaller and larger trials of a direct outcome with precise results, thus leading us to conclude that the evidence is moderate.

Effect on Recurrent Ischemia up to 30 Days

Six RCTs (4 good quality, 2 fair) with a total of 5755 UA/NSTEMI patients reported recurrent or refractory ischemia either in-hospital or at 30 days.[38,115,117,123,124,126] In the PRISM study,[123] the rates of refractory ischemia were similar in the tirofiban and heparin groups, RR 0.98 (95% CI, 0.79 to 1.09). The PRISM-PLUS study[124] found a slight increase in refractory ischemia events in the heparin group compared with tirofiban plus heparin, (95% CI, 0.57 to 1.01; p=0.05).The Okmen study[117] reported an in-hospital recurrent angina rate of 27% in the tirofiban group and 50% in the heparin group. The Bhattacharya study[38] reported a refractory ischemia rate at 30 days of 25 percent in the tirofiban group and 24 percent in the heparin group. The Song study[115] saw a refractory ischemia rate at 30 days of 12 percent in the tirofiban group and 22 percent in the heparin group. In the Van den Brand study[126] there was no recurrent ischemia at 30 days in the abciximab group and 23 percent rate in the heparin group.

A random-effects meta-analysis of these 6 studies in 5755 patients reporting recurrent ischemia rates at 30 days found that the odds ratio for GPI use was 0.81 (95% CI, 0.56 to 1.18) (Figure 37). There was evidence of extreme heterogeneity, with a Q-value of 15.26 for 5 degrees of freedom, p=0.009. The I^2 value was 67.23.

Figure 37. Meta-analysis of glycoprotein inhibitor versus unfractionated heparin on recurrent ischemia at 30 days



CI = confidence interval; GPI = glycoprotein inhibitor

A fixed-effects model had minimal changes to the summary estimate, with an odds ratio of 0.98 (95% CI, 0.83 to 1.16). Similar to the other outcomes, we performed the subgroup sensitivity analyses and the results are shown in Table 18 (forest plot appears in Appendix I).

Table 18. Sensitivity analysis of glycoprotein inhibitor versus unfractionated heparin on recurrent ischemia up to 30 days

Study Characteristic	Number of Studies (Patients)[a]	Summary Estimate (95% CI)
Trial Size		
Small (<1000 patients)	4 (648)	OR 0.51 (0.26 to 1.02)
Large (≥1000 patients)	2 (5107)	OR 1.11 (0.84 to 1.47)
Antiplatelet Use		
Aspirin monotherapy	5 (5454)	OR 0.97 (0.83 to 1.17)
Dual antiplatelet therapy	1 (301)	OR 0.93 (0.55 to 1.58)

CI = confidence interval

[a]Subgroup summary estimates with fewer than three studies should be interpreted with caution.

Studies with smaller sample sizes favored GPI plus UFH, while larger studies did not. Note that the quality of the studies was highly correlated with study size, and that the use of dual antiplatelet therapy was highly correlated with publication year. We did not, however, find evidence of publication bias. The use of aspirin monotherapy showed no statistical difference between the two treatment strategies. Thus the heterogeneity is due to the size of the trial but not to the type of antiplatelet used. Again, the similarity between the fixed and random effects summary estimates shows that there is no statistical heterogeneity. Overall, the rates of recurrent ischemia/angina were lower in the GPI group from these six RCTs with inconsistent results of a direct outcome with wide confidence interval, thus leading us to conclude that the SOE was insufficient.

Effect on Revascularization up to 30 Days

Two fair-quality RCTs[40,117] with a total of 279 UA/NSTEMI patients reported the revascularization rates at up to 30 days. The Okmen study[117] found low numbers of in-hospital revascularization events (1 event in the tirofiban group and none in the heparin group). The Momtahen study[40] found a revascularization rate of zero in the epitfibatide group and 4 percent (4 out of 98) in the heparin group at 30 days. Given the low number of events in both studies, the evidence for the effectiveness on revascularization is inconclusive and insufficient.

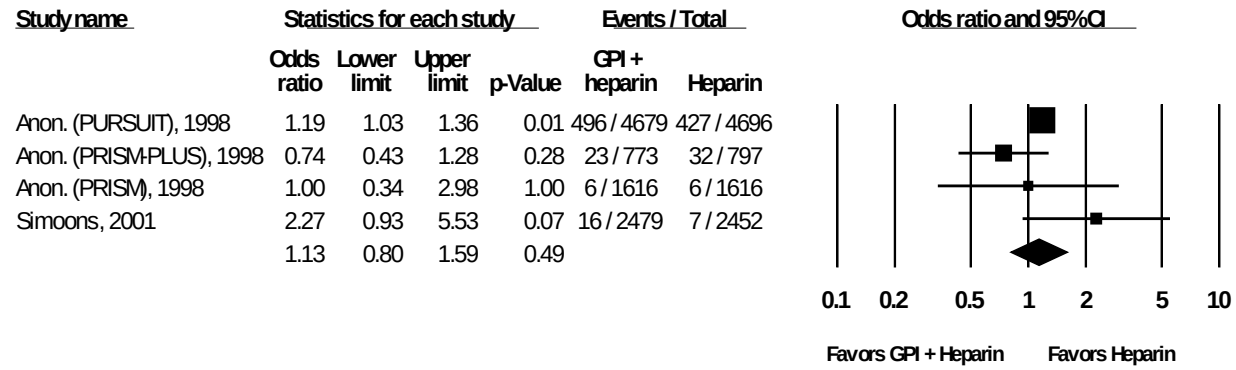
Effect on Major Bleeding up to 30 Days

Seven RCTs (5 good quality, 2 fair) with a total of 37,593 UA/NSTEMI patients reported major bleeding events either in-hospital or at 30 days.[40,62,117,120,122-124] In the PURSUIT study[122] the rate of TIMI-criteria major bleeding was higher in the eptifibatide group (10.6%) compared with heparin (9.1%). In the PRISM study,[123] the rates of major bleeding were similar in the tirofiban and heparin groups (both 0.4%). In the PRISM-PLUS study,[124] the rates of major bleeding were similar in the heparin and tirofiban plus heparin group, both by study definition (3.0% vs. 4.0%) and TIMI criteria (0.8% and 1.4%). The Okmen study[117] reported zero in-hospital major bleeding events in both the tirofiban and heparin groups. The GUSTO-IV study[120] reported in-hospital major bleeds of 0.6 percent with abciximab 24-hour infusion, 1.0 percent with abciximab 48-hour infusion, and 0.3 percent in the heparin group. The Momtahen study[40] found no major bleeding events at 30 days in either the eptifibatide or heparin groups. In the ACUITY study[62] subgroup that received medical therapy the rates of major bleeding at 30 days were 2.5 percent in the group receiving bivalirudin alone and 4.4 percent in the group receiving

GPI with UFH (RR 0.57; 95% CI, 0.38 to 0.84) favoring bivalirudin. In the ACUITY TIMING[110] subgroup that received medical therapy, the rates of major bleeding at 30 days were 2.6 percent in the deferred GPI group and 3.7 percent in the upstream GPI group (HR 0.70; 95% CI, 0.47 to 1.05), favoring deferred GPI. Thus major bleeding rates appear higher from longer infusion of GPI, lower in patients receiving bivalirudin alone and higher in patients who received upstream GPI.

A random-effects meta-analysis of 4 good-quality studies in 23,855 patients reporting major bleeding rates at 30 days found that the odds ratio was 1.13 (95% CI, 0.80 to 1.59), favoring heparin alone (Figure 38). There was no evidence of heterogeneity, with a Q-value of 4.927 for 3 degrees of freedom, p=0.18. The I^2 value was 39.11. A fixed-effects model gave a summary odds ratio of 1.17 (95% CI, 1.02 to 1.33), which is similar to the random-effects model (therefore, no statistical heterogeneity). All studies were large RCTs that used aspirin monotherapy, and so a sensitivity analysis by these factors was not performed. The evidence for the effect of GPIs on major bleeding in the conservatively managed group is insufficient, with most trials reporting similar rates of major bleeding between the GPI and heparin groups. Since the studies by Okmen and Momtahen had no events in either group, they were not included in this meta-analysis. Also, the ACUITY study compared bivalirudin to GPI, and the ACUITY TIMING subgroup study compared deferred and upstream GPI use, so those studies were not included in this meta-analysis.

Figure 38. Meta-analysis of glycoprotein inhibitor versus unfractionated heparin on major bleeding up to 30 days



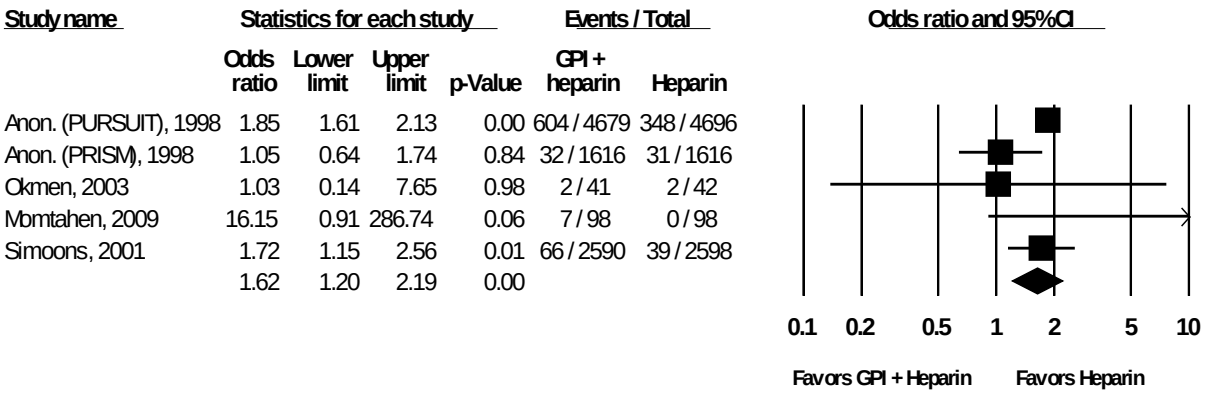
CI = confidence interval; GPI = glycoprotein inhibitor

Effect on Minor Bleeding up to 30 Days

Five RCTs[40,117,120,122,123] (three good quality, two fair) with a total of 22,259 UA/NSTEMI patients reported minor bleeding events up to 30 days. In the PURSUIT study[122] the minor bleeding rate was higher in the eptifibatide group compared with heparin (12.9% vs. 7.4%). In the PRISM study[123] the rates of minor bleeding were similar in the tirofiban and heparin groups (2.0% and 1.9% respectively). The GUSTO-IV study[120] reported in-hospital minor bleeds of 3percent with abciximab 24-hour infusion, 4 percent with abciximab 48-hour infusion, and 2 percent in the heparin group. The Okmen study[117] reported an in-hospital minor bleeding rate of 5% in both the tirofiban and heparin groups. The Momtahen study[40] found a minor bleeding rate of 7% in the epitfibatide group and 0% in the heparin group at 30 days. Thus, minor bleeding is common with administration of GPI.

A random-effects meta-analysis of 5 studies in 22,259 patients reporting minor bleeding rates at 30 days found that the odds ratio was 1.62 (95% CI, 1.20 to 2.19), favoring heparin alone (Figure 39). There was no evidence of heterogeneity, with a Q-value of 7.14 for 4 degrees of freedom, p=0.13. The I^2 value was 43.94.

Figure 39. Meta-analysis of glycoprotein inhibitor versus unfractionated heparin on minor bleeding up to 30 days



CI = confidence interval; GPI = glycoprotein inhibitor

A fixed-effects model had minimal changes to the summary estimate, with an odds ratio of 1.78 (95% CI, 1.56 to 2.02). Similar to the other outcomes, we performed a subgroup sensitivity analysis and the results are shown in Table 19 (forest plot appears in Appendix I).

Table 19. Sensitivity analysis of glycoprotein inhibitor versus unfractionated heparin on minor bleeding up to 30 days

Study Characteristic	Number of Studies (Patients)[a]	Summary Estimate (95% CI)
Trial Size		
Small (<1000 patients)	2 (279)	OR 3.33 (0.23 to 48.23)
Large (≥ 1000 patients)	3 (21,980)	OR 1.61 (1.20 to 2.15)
Antiplatelet Use		
Aspirin monotherapy	4 (22,063)	OR 1.62 (1.25 to 2.09)
Dual antiplatelet therapy	1 (196)	OR 16.15 (0.91 to 286.74)

CI = confidence interval

[a]Subgroup summary estimates with fewer than three studies should be interpreted with caution.

Studies with larger or smaller sample sizes both favored heparin. The use of aspirin monotherapy also favored heparin. Thus, there was no clinical heterogeneity. Again, the similarity between the fixed and random effects summary estimates shows that there is no statistical heterogeneity. Given the consistent results in five RCTs with a narrow CI, the SOE was rated high for the effect of GPIs on minor bleeding, with fewer minor bleeds in the heparin group.

Findings by Subgroup (KQ 2c)

Four good-quality RCTs (PURSUIT, PRISM, PRISM PLUS, and GUSTO)[120,122-124] with 23,855 UA/NSTEMI patients evaluated the effectiveness of GPIs in relation to key subgroups, namely patient factors related to diabetes (4 studies), sex (4 studies), age (4 studies), geographic location (2 studies), smoking status (2 studies) and weight (1 study). Table H-2 in Appendix H presents the results data for these subgroups. Of note, the ACUITY and ACUITY-TIMING study

results reported above were from the subgroup of patients who received medical management; therefore, further subgroup analyses on the medically-managed population were not reported.

Diabetes

Four studies assessed the study primary composite endpoint in patients with or without diabetes. The PURSUIT study[122] found a higher reduction in composite ischemic events in patients without diabetes receiving eptifibatide; there was also a reduction in events in diabetic patients and favoring eptifibatide but the results were nonsignificant. The PRISM study[123] reported that patients with diabetes benefitted more than patients without diabetes from tirofiban treatment from the reduction in composite ischemic events. The PRISM-PLUS study[124] reported a statistically significant benefit of tirofiban plus heparin compared with heparin alone in patients without diabetes. There was also a reduction in composite events in diabetic patients receiving tirofiban and heparin but the finding was not statistically significant. The GUSTO-IV study[120] found no statistically significant difference between abciximab and heparin in patients with and without diabetes, although the event rates were lower in patients receiving abciximab.

Sex

Four studies assessed the study primary composite endpoint in men and women. The PURSUIT study[122] found a reduction in composite ischemic events in men who received eptifibatide; however women in the heparin group had fewer events, OR 1.10 (95% CI, 0.91 to 1.34). The PRISM study[123] reported a reduction in composite ischemic events in both men and women treated with tirofiban. The PRISM-PLUS study[124] reported a statistically significant benefit of tirofiban plus heparin compared with heparin alone in male and female patients. The GUSTO-IV study[120] found no significant difference between abciximab and heparin in men and women who received a 24-hour infusion of the drug; however, women receiving a 48-hour infusion fared worse with abciximab (10.1% vs. heparin 7.2%).

Age

Four studies assessed the study primary composite endpoint in different age subgroups. The PURSUIT study[122] found statistically fewer events in patients <65 years of age favoring eptifibatide. Patients age 65 or older also benefitted from eptifibatide but the findings were nonsignificant. The PRISM study[123] reported a reduction in composite ischemic events across all age groups (<65, 65-74, >75 and >65 years of age) in those treated with tirofiban, with the results being statistically significant in patients older than 65 years of age. The PRISM-PLUS study[124] reported a statistically significant benefit of tirofiban plus heparin compared with heparin alone in patients under age 65 and 65 years of age or over. The GUSTO-IV study[120] found no significant difference between abciximab and heparin in patients under age 65 or 65 years of age or over.

Geographic Location

Two studies assessed the study primary composite endpoint in different geographic regions. The PURSUIT study[122] found a greater reduction in composite event rates from patients treated in North America with eptifibatide; there were also fewer composite events in patients from Western Europe, Eastern Europe, and Latin America, but the smaller sample sizes made the finding nonsignificant. The PRISM study[123] reported a reduction in composite events in patients from the US and other countries treated with tirofiban.

Smoking Status

Two studies assessed the study primary composite endpoint based on smoking status. The PRISM study[123] reported a statistically significant reduction in composite ischemic events in patients who received tirofiban and who never smoked; there was also a reduction in events in former and current smokers, but the findings were nonsignificant in both groups. The PRISM-PLUS study[124] reported a benefit of tirofiban plus heparin compared with heparin alone in smokers and nonsmokers; however the finding in smokers was statistically nonsignificant.

Weight

The GUSTO-IV study[120] analyzed the effect of abciximab on the composite endpoint of death or MI based on weight subgroups and found no significant difference between abciximab and heparin in patients under 75 kg, between 75 and 90 kg, or over 90 kg.

Summary of Results for Glycoprotein Inhibitor Plus Unfractionated Heparin Versus Unfractionated Heparin Alone

In our analysis of studies comparing GPIs with UFH, we present the findings of UA/NSTEMI patients who received primarily initial conservative treatment. Adding GPIs to UFH reduced the rate of mortality, composite ischemic events, and nonfatal MI, especially in trials of eptifibatide and tirofiban, and increased the rate of minor bleeding at 30 days. The addition of abciximab to UFH did not significantly reduce ischemic events compared with UFH alone. There was insufficient evidence for the effect of GPIs on recurrent ischemia, major bleeding, and revascularization, although fewer revascularization events were seen in patients receiving GPIs in two small trials. A sensitivity analysis subgrouping the studies by trial size (small, <1,000 patients; large, ≥1,000 patients) and antiplatelet use (aspirin monotherapy vs. dual antiplatelet therapy) showed that these two factors helped to explain the heterogeneity, if present, in the meta-analyses performed. For the mortality, nonfatal MI, and recurrent ischemia endpoints at 30 days, the smaller sized studies had summary estimates that were more favorable for GPI plus UFH. For the mortality and nonfatal MI endpoints at 30 days, the use of DAPT had summary estimates that were more favorable for GPI plus UFH.

Subgroups analyzed were diabetes, sex, age, geographic location, smoking status, and weight. Almost all subgroups experienced a reduction in composite ischemic events from adding GPI therapy to heparin (UFH or low molecular weight heparin). While some subgroups may have had a greater magnitude of benefit, there did not appear to be a significant interaction between the assigned treatment and demographic or clinical variables. Notable exceptions included the PURSUIT trial, where women in the heparin group had fewer ischemic events than the eptifibatide group (statistically nonsignificant), and the GUSTO IV study where women treated with a 48-hour infusion of abciximab had higher event rates. Detailed SOE ratings are shown in Table 20. Odds ratios less than 1 favor GPI plus UFH; odds ratios greater than 1 favor UFH alone.

Table 20. Detailed strength of evidence for UA/NSTEMI patients treated with glycoprotein inhibitor plus unfractionated heparin versus unfractionated heparin alone

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI) Odds ratios less than 1 favor GPI plus UFH; odds ratios greater than 1 favor UFH alone
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite Ischemic Endpoints up to 30 Days					**Moderate SOE**
10 (38,518)	10 RCTs/7 good quality, 3 fair	Consistent	Direct	Imprecise	Studies of eptifibatide and tirofiban showed a consistent reduction in composite events compared with UFH alone (RRs 0.58 to 0.84, favoring eptifibatide or tirofiban); one large trial of abciximab showed no difference in events (24 hr, OR 1.00, CI 0.83 to 1.24; 48 hr, OR 1.10, CI 0.94 to 1.39), while a small trial showed a reduction in major events with abciximab (1 out of 30) versus UFH alone (7 out of 30). Favors GPI plus UFH
Mortality up to 30 Days					**High SOE**
9 (24,699)	9 RCTs/6 good quality, 3 fair	Consistent	Direct	Precise	OR 0.80 (0.67 to 0.96) Favors GPI plus UFH
Nonfatal MI up to 30 Days					**Moderate SOE**
9 (24,699)	9 RCTs/6 good quality,3 fair	Inconsistent	Direct	Precise	OR 0.79 (0.61 to 1.02) Favors GPI plus UFH
Recurrent Ischemia up to 30 Days					**Insufficient SOE**
6 (5755)	6 RCTs/4 good quality, 2 fair	Inconsistent	Direct	Imprecise	OR 0.81 (0.56 to 1.18)
Revascularization up to 30 Days					**Insufficient SOE**
2 (279)	2 RCTs/Both fair quality	Consistent	Direct	Imprecise	Low number of events reported in both RCTs, with fewer in GPI plus UFH group
Major Bleeding up to 30 Days					**Insufficient SOE**
7 (37,953)	7 RCTs/5 good quality. 2 fair	Consistent	Direct	Imprecise	OR 1.13 (0.80 to 1.59)
Minor Bleeding up to 30 Days					**High SOE**
5 (22,259)	5 RCTs/3 good quality, 2 fair	Consistent	Direct	Precise	OR 1.62 (1.20 to 2.19) Favors heparin alone

CI = confidence interval; GPI = glycoprotein inhibitor; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction; UFH = unfractionated heparin

3. Clopidogrel Versus Ticagrelor or Prasugrel (KQ 2b)

Two good-quality RCTs evaluated the use of clopidogrel versus ticagrelor or prasugrel in 12,459 patients with UA/NSTEMI.[128,129] These trials were in patients undergoing an initial conservative strategy. Proportions of patients proceeding to revascularization ranged from 7.9 percent[128] to 24 percent.[129]

One RCT (PLATO trial) compared ticagrelor with clopidogrel and included a total of 5216 conservatively managed patients.[129] The other RCT (7243 patients; TRILOGY ACS trial) compared prasugrel with clopidogrel.[128] The PLATO study included 8.7% STEMI patients, with the majority comprised of either NSTEMI (56%) or UA patients (35%). The TRILOGY study population consisted of only UA/NSTEMI patients and the primary analysis was based on the 7243 patients under the age of 75 therefore the results of this primary analysis population are reported in this section.

Study duration ranged from 12 to 30 months. The median age of study participants ranged from 65 to 66 years of age. The proportion of female patients ranged from 36 to 39 percent. Neither study reported the racial and ethnic demographics of study. The RCTs were both multi-center, representing an international patient population including North America, Europe, and Asia. Both RCTs were industry-sponsored. The full results across all outcomes are reported in Table G-11 in Appendix G.

Effect on Composite Ischemic Endpoints up to 30 Months

The PLATO RCT (good quality, 5216 patients)[129] found lower rates of cardiovascular death, MI, or cerebrovascular accident (primary endpoint) in the ticagrelor group (12.0%) compared with the clopidogrel group (14.3%) at 12 months, HR 0.85 (95% CI, 0.73 to 1.00), p=0.04. The TRILOGY ACS RCT (good quality, 7243 patients)[128] found similar rates of cardiovascular death, MI, or stroke (primary endpoint) in the prasugrel group (13.9%) and clopidogrel groups (16.0%) at a median followup of 17 months (or 30 months total followup), HR (95% CI, 0.79 to 1.05), p=0.21. Compared with clopidogrel, the evidence for a benefit of ticagrelor but similar effectiveness of prasugrel on composite outcomes is moderate (both studies meet OIS, optimum information size, criteria).

Effect on Mortality up to 30 Months

The PLATO RCT (good quality, 5216 patients)[129] found lower rates of mortality in the ticagrelor group (6.1%) compared with the clopidogrel group (8.2%) at 12 months, HR 0.75 (95% CI, 0.61 to 0.93), p=0.01. The TRILOGY ACS RCT (good quality, 7243 patients)[128] found similar mortality rates in the prasugrel (7.8%) and clopidogrel (8.1%) at 30 months, HR 0.96 (95% CI, 0.79 to 1.16), p=0.63. Compared with clopidogrel, the evidence for a benefit of ticagrelor but similar effectiveness of prasugrel on mortality is moderate (both studies meet OIS criteria).

Effect on Nonfatal MI up to 30 Months

The PLATO RCT (good quality, 5216 patients)[129] found similar rates of nonfatal MI in the ticagrelor group (7.2%) compared with the clopidogrel group (7.8%) at 12 months, HR 0.94 (95% CI, 0.77 to 1.15), p=0.56. The TRILOGY ACS RCT (good quality, 7243 patients)[128] found similar nonfatal MI rates in the prasugrel (8.3%) and clopidogrel (10.5%) at 30 months, HR 0.89 (95% CI, 0.74 to 1.07), p=0.21. The evidence for the effectiveness on nonfatal MI is moderate for ticagrelor and for prasugrel (both studies meet OIS criteria).

Effect on Stroke up to 30 Months

The PLATO RCT (good quality, 5216 patients)[129] found similar rates of stroke in the ticagrelor group (2.1%) compared with the clopidogrel group (1.7%) at 12 months, HR 1.35 (95% CI, 0.89 to 2.07), p=0.16. The TRILOGY ACS RCT (good quality, 7243 patients)[128] found similar stroke rates in the prasugrel (2.2%) and clopidogrel (1.5%) at 30 months, HR 0.67 (95% CI, 0.42 to 1.06), p=0.08. The evidence for the effectiveness on nonfatal MI is insufficient for ticagrelor and for prasugrel (neither study meets OIS criteria).

Effect on Revascularization up to 12 Months

The PLATO RCT (good quality, 5216 patients)[129] found similar rates of PCI (28.4% ticagrelor, 29.7% clopidogrel) and CABG (11.0% ticagrelor, 10.4% clopidogrel) between the groups at 12 months. The evidence for the effectiveness on revascularization is moderate for ticagrelor (meets OIS criteria).

Effect on Major Bleeding up to 30 Months

The PLATO RCT (good quality, 5216 patients [129] found numerically higher rates of major bleeding with ticagrelor (11.9%) compared with clopidogrel (10.3%) at 12 months, HR 1.17 (95% CI, 0.98 to 1.39, p=0.08. The TRILOGY ACS RCT (good quality, 7243 patients)[128] found similar TIMI criteria major bleeding rates in the prasugrel (2.1%) and clopidogrel (1.5%) groups at 30 months, HR 1.31 (95% CI, 0.81 to 2.11), p=0.27. The evidence for the effectiveness on major bleeding is moderate for ticagrelor (meets OIS) and insufficient for prasugrel (does not meet OIS).

Effect on Major or Minor Bleeding up to 30 Months

The PLATO RCT (good quality, 5216 patients)[129] found higher major or minor bleeding rates in the ticagrelor group (16.4%) compared with clopidogrel (14.4%) at 12 months, HR 1.17 (95% CI, 1.01 to 1.36), p=0.04. The TRILOGY ACS RCT (good quality, 7243 patients)[128] found higher TIMI criteria major or minor bleeding rates in the prasugrel (3.3%) and clopidogrel (2.1%) groups at 30 months, HR 1.54 (95% CI, 1.06 to 2.23), p=0.02. The evidence for the effectiveness on major or minor bleeding is moderate for ticagrelor (meets OIS) and low for prasugrel.

Findings by Subgroup (KQ 2c)

One good-quality RCT[128] with a total of 7243 UA/NSTEMI patients under the age of 75 years evaluated the effectiveness of antiplatelet therapy on the primary composite endpoint (CV death, MI, or stroke) and TIMI criteria major bleeding events in relation to key subgroups, namely patient factors related to diabetes (yes or no), sex (female or male), age (<65 yr or≥ 65 yr) , geographic location (multiple international regions), smoking status (current or not current), aspirin dose at randomization (<100 mg/d or ≥100 mg/d), PPI at randomization, previous history of MI, PCI, CABG, or PAD, creatinine clearance, GRACE risk score, clopidogrel use, and weight(<60 kg or ≥ 60 yr). Table H-2 in Appendix H presents the results data for these subgroups. The rates of the primary composite endpoint did not differ significantly among most of the prespecified subgroups, however there was a treatment interaction favoring prasugrel among 3 subgroups: current/recent smokers (HR 0.54; 95% CI, 0.39 to 0.74, p<0.001), those undergoing angiography prior to randomization (HR 0.77; 95% CI, 0.61 to 0.98, p=0.08), and those taking PPIs at randomization (HR 0.70; 95% CI, 0.53 to 0.92, p=0.02). For the TIMI

criteria major bleeding endpoint, the only subgroup with a significant treatment interaction favoring those receiving clopidogrel with a reduced dose of aspirin (HR 4.56; 95% CI, 1.31 to 15.89, p=0.02). Note that the subgroup findings for the PLATO population[54,129] were reported for the overall (invasive and noninvasive) population, and are described in KQ 1 (comparison 3) of this report.

Summary of Results for Clopidogrel Versus Ticagrelor or Prasugrel

In our analysis of studies comparing clopidogrel versus ticagrelor or prasugrel, we present the findings of UA/NSTEMI patients who received initial conservative treatment. Ticagrelor reduced the rates of composite ischemic and all-cause mortality events; however, ticagrelor also increased rates of major bleeding, and the combination of major or minor bleeding events. In contrast, prasugrel and clopidogrel had similar rates of composite ischemic and most individual clinical outcomes, except that there was a higher rate of TIMI criteria combined major or minor bleeding event rate in the prasugrel group at 30 months. Multiple subgroups were analyzed in the TRILOGY ACS study and found a treatment interaction favoring prasugrel among current/recent, those undergoing angiography prior to randomization, and those taking PPIs at randomization on the primary composite endpoint. For the TIMI criteria major bleeding endpoint, the only subgroup with a significant treatment interaction favored those receiving clopidogrel with a reduced dose of aspirin. Detailed SOE ratings are shown in Table 21.

Table 21. Detailed strength of evidence for UA/NSTEMI patients treated with clopidogrel versus ticagrelor or prasugrel

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite ischemic Endpoints up to 30 Months					
Ticagrelor vs. clopidogrel 1 (5216)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** HR 0.85 (0.73 to 1.00) Favors ticagrelor
Prasugrel vs. clopidogrel 1 (7243)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** HR 0.91 (0.79 to 1.05) No difference
Mortality up to 30 Months					
Ticagrelor vs. clopidogrel 1 (5216)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** HR 0.75 (0.61 to 0.93) Favors ticagrelor
Prasugrel vs. clopidogrel 1 (7243)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** HR 0.96 (0.79 to 1.16) No difference
Nonfatal MI up to 30 Months					
Ticagrelor vs. clopidogrel 1 (5216)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** HR 0.94 (0.77 to 1.15) No difference
Prasugrel vs. clopidogrel 1 (7243)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** HR 0.89 (0.74 to 1.07) No difference

Table 21. Detailed strength of evidence for UA/NSTEMI patients treated with clopidogrel versus ticagrelor or prasugrel (continued)

Number of Studies (Patients)	Domains				Strength of Evidence Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Stroke up to 30 Months					
Ticagrelor vs. clopidogrel 1 (5216)	RCT/Good quality	NA	Direct	Imprecise	**Insufficient SOE** HR 1.35 (0.89 to 2.07) Insufficient evidence due to imprecision
Prasugrel vs. clopidogrel 1 (7243)	RCT/Good quality	NA	Direct	Imprecise	**Insufficient SOE** HR 0.67 (0.42 to 1.06) Insufficient evidence due to imprecision
Revascularization up to 12 Months					
Ticagrelor vs. clopidogrel 1 (5216)	RCT/Good quality	NA	Direct	Unknown	**Moderate SOE** No difference
Major Bleeding up to 30 Months					
Ticagrelor vs. clopidogrel 1 (5216)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** HR 1.17 (0.98 to 1.39) Favors clopidogrel
Prasugrel vs. clopidogrel 1 (7243)	RCT/Good quality	NA	Direct	Imprecise	**Insufficient SOE** HR 1.31 (0.81 to 2.11) Insufficient evidence due to imprecision
Major or Minor Bleeding up to 30 Months					
Ticagrelor vs. clopidogrel 1 (5216)	RCT/Good quality	NA	Direct	Precise	**Moderate SOE** HR 1.17 (1.01 to 1.36) Favors clopidogrel
Prasugrel vs. clopidogrel 1 (7243)	RCT/Good quality	NA	Direct	Imprecise	**Low SOE** HR 1.54 (1.06 to 2.23) Favors clopidogrel

CI = confidence interval; GPI = glycoprotein inhibitor; HR = hazard ratio; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction; UFH = unfractionated heparin

Key Question 3. Postdischarge Treatment for UA/NSTEMI

KQ 3: In patients treated for UA/NSTEMI after hospitalization (postdischarge):

a. What are the comparative effectiveness (dose and duration) and comparative safety of the available oral antiplatelet agents given in combination with aspirin? Do the effectiveness and safety vary based on the dose of aspirin used?

b. What are the comparative effectiveness and comparative safety of proton pump inhibitors (PPIs) for reducing bleeding events in patients receiving dual antiplatelet therapy after UA/NSTEMI? Do the effectiveness and safety vary by oral antiplatelet therapy and PPI?

c. In patients with an indication for long-term anticoagulant therapy, what are the comparative effectiveness and comparative safety of adding an oral anticoagulant to aspirin and another antiplatelet agent for improving cardiovascular outcomes?

d. Based on demographic and other characteristics, are there subgroups of patients for whom the effectiveness and safety differ?

Key Points

Low-Dose Versus High-Dose Aspirin (KQ 3a)

- In the postdischarge setting, high-dose aspirin was associated with fewer nonfatal MIs and more major bleeding events than low-dose aspirin at 6 months (low SOE for both outcomes). Evidence for all other outcomes was insufficient.

Single Antiplatelet Versus Dual Antiplatelet Therapy (KQ 3a)

- DAPT reduced the rates of composite ischemic outcomes and nonfatal MI compared with single antiplatelet therapy from in-hospital up to 1 year (high SOE).
- DAPT reduced all-cause mortality to 1 year compared with single antiplatelet therapy from in-hospital up to 1 year (moderate SOE).

Short-Term Versus Long-Term Dual Antiplatelet Therapy (KQ 3a)

- There was insufficient evidence for comparing short-term with long-term DAPT for composite ischemic events, all-cause mortality, cardiovascular mortality, nonfatal MI, stroke, revascularization, stent thrombosis, major bleeding, and minor bleeding. The findings were inconclusive because of heterogeneity of DAPT duration, timing of the endpoint measurement, and imprecision.

Antiplatelet Therapy With a PPI Versus Antiplatelet Alone (KQ 3b)

- In RCTs that evaluated the specific PPI omeprazole versus placebo and in observational studies assessing the use of diverse PPIs given in combination *with DAPT*, use of PPIs reduced rates of upper gastrointestinal bleeding (moderate SOE). However, use of PPIs was associated with higher rates of composite ischemic outcomes (death or MI) at 1 year (moderate SOE). There was low SOE that use of PPIs was associated with higher event rates for the following outcomes: composite ischemic events at 1 year, all-cause mortality at 6 years, nonfatal MI at 1 year, stroke at 1 year, revascularization at 1 year, stent thrombosis at 1 year, major bleeding at 1 year, or rehospitalization at 3 months. No difference between groups was seen for all-cause mortality at 1 year (moderate SOE) or revascularization at 6 months (low SOE)
- In observational studies assessing use of PPIs *with aspirin monotherapy*, there was a higher rate of nonfatal MI events and no difference in stroke events at 1 year in the group receiving any type of PPI (low SOE). These results are based on adjusted hazard ratios to reduce confounding due to patient and clinical characteristics; however, residual confounding cannot be excluded.
- There was insufficient evidence that the type of PPI affected any of the clinical outcomes (composite or individual) from subgroup analyses of observational studies.

Dual Antiplatelet Versus Triple Therapy (KQ 3c)

- DAPT reduced rates of nonfatal MI and major bleeding at 1 to 5 years, and triple therapy (dual antiplatelet plus anticoagulant) reduced rates of stroke at 6 months (low SOE). The findings for all other clinical endpoints were rated insufficient SOE due to inconsistency, imprecision of results, or both.

Description of Included Studies

We identified 71 unique studies that evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 693,025 patients with UA/NSTEMI continuing treatment *after hospitalization*.[14,132-200] Of these studies, 12 were RCTs (8 good quality, 2 fair, 2 poor) and 58 were observational (36 good quality, 16 fair, 6 poor). (Table E-3 in Appendix E details the quality ratings.)

Fifty-three studies were multicenter,[14,133-139,143,145,146,148-151,154-161,163,165,166,168,170,173-177,179,180,182-189,191,192,194-200] 15 were single-center,[140,142,147,152,153,162,164,167,169,171,172,178,181,190,193] and in three studies the number of sites was unclear or not reported.[132,141,144] Twenty-five studies included sites in the United States or Canada,[133,135,142,145,150,161-163,166,167,169,171-174,176,179,183,185,190-192,194,197,199] 31 in Europe,[132,134,137,138,143,146-149,152-154,156-158,164,168,175,176,178,180,184-186,188,191,192,194,196-198] 13 in Asia,[136,139-141,144,155,159,160,176,177,182,195,197] 6 in other locations,[170,181,187,189,193,201] and in 3 studies the site location was unclear or not reported.[14,151,165]

A total of 11 studies were funded by industry,[14,135,151,156,176,179,185,191,194,197,199] 7 were funded by government-only sources,[133,159,163,166,173,183,190] 15 were funded by nongovernment/nonindustry sources,[134,135,137,139-141,143,148,149,152-154,169,186,198] 3 had a mix of government and private foundation funding,[174,188,196] 1 had a mix of government and industry funding,[136] and in 33 studies the funding source was either not reported or unclear.[132,138,142,144-147,150,155,157,158,160-162,164,165,167,168,170-172,175,177,178,180-182,184,187,189,192,193,195] Table F-3 in Appendix F details the study characteristics, including study design, proportion of UA/NSTEMI patients, antiplatelet/anticoagulant comparison, concomitant therapy, outcomes measured, and study quality.

In the next section, we present the following five comparisons that were assessed in the included studies for KQ 3:

1. Low-dose versus high-dose aspirin (KQ 3a)
   - 6 studies (all observational; 60,904 total patients)
2. Single antiplatelet versus dual antiplatelet therapy (KQ 3a)
   - 7 studies (1 RCT, 6 observational; 173,035 total patients)
3. Short-term versus long-term dual antiplatelet therapy (clopidogrel) (KQ 3a)
   - 11 studies (5 RCTs, 6 observational; 52,121 total patients)
4. Antiplatelet therapy with a PPI versus antiplatelet alone (KQ 3b)
   - 35 studies (4 RCTs, 30 observational; 340,559 total patients)
     a. Dual antiplatelet with and without a PPI
     b. Aspirin monotherapy with and without a PPI
5. Dual antiplatelet therapy alone versus dual antiplatelet plus oral anticoagulant (i.e., triple therapy) (KQ 3c)
   - 14 studies (all observational; 97,067 total patients)

The subgroup findings (KQ 3d) are presented after each comparison.

Detailed Synthesis

1. Low-Dose Versus High-Dose Aspirin (KQ 3a)

Six observational studies compared low-dose with high-dose aspirin in the postdischarge treatment of UA/NSTEMI patients.[142,172,176,192,201,202] One study each compared:

- 81 mg versus 161 to 325 mg aspirin (Harjai et al. study; clopidogrel use was 53% in each group; fair quality; 2,820 patients)[142]
- 81 mg versus 325 mg aspirin (So et al. study; clopidogrel use 99% in each group; fair quality; 1,840 patients)[172]
- <162 mg versus ≥162 mg aspirin (Aronow et al. study; ticlopidine/clopidogrel use not permitted except for after revascularization for 30 days or less; good quality; 4,589 patients)[176]
- <150 mg versus ≥150 mg aspirin (Quinn et al. study; clopidogrel use not reported; good quality; 20,469 patients)[192]
- ≤100 mg versus 101–199 mg versus ≥200 mg (Peters et al. observational substudy of CURE; aspirin monotherapy or aspirin plus clopidogrel; good quality; 12,562 patients)[202]
- <300 mg versus ≥300 mg (Mahaffey et al. observational substudy of PLATO, aspirin plus clopidogrel and aspirin plus ticagrelor; good quality; 18,624 patients)[201]

Of the six observational studies, two (33%) were rated fair quality and four (67%) were good quality. Sample sizes for individual studies ranged from 1840 to 20,469 patients. Study duration ranged from 30 days to 12 months. The mean age of study participants ranged from 62 to 64 years. The proportion of female patients ranged from 27 to 38 percent. Three studies (50%) reported the racial and ethnic demographics of study participants. Two studies (33%) were conducted within the United States or Canada, with the rest international. Funding source was reported in four studies, and all were funded by industry.

These six studies assessed a composite endpoint of all-cause or cardiovascular mortality, nonfatal MI, or stroke in addition to individual endpoints of all-cause or cardiovascular mortality, nonfatal MI, stroke, and major bleeding. All studies, with the exception of the Mahaffey substudy, reported a revascularization endpoint. Table G-12 in Appendix G summarizes the results reported by each study. Because of the heterogeneity of aspirin dosage comparisons, dual antiplatelet use, patient populations, and measured composite outcomes, a quantitative analysis could not be performed. Therefore we discuss the results qualitatively by outcome.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal Myocardial Infarction, or Stroke at 6 Months and 1 Year

Only the Quinn study[192] (good quality; 20,469 patients) reported the composite outcome of all-cause mortality, nonfatal MI, or stroke at 6 months and found that low-dose aspirin (<150 mg) had similar composite ischemic events compared with high-dose aspirin (≥150 mg) (HR 0.92; 95% CI, 0.79 to 1.07, p=0.28). Given the findings from one observational study with a confidence interval that crosses 1, the SOE was rated insufficient for this composite outcome at 6 months.

The CURE substudy[202] (good quality; 12,562 patients) found that at 1 year, patients on aspirin monotherapy receiving a medium-dose aspirin (101–199 mg) had similar composite ischemic events compared with patients receiving a low-dose aspirin (≤100 mg) (9.8% vs. 10.5%; HR 1.0; 95% CI, 0.82 to 1.23). Patients receiving the highest dose (≥200 mg)

experienced a higher rate of composite ischemic events compared with those receiving a low dose (13.6% vs. 10.5%; HR 1.3; 95% CI, 1.08 to 1.52). The rate of composite ischemic events was similar across aspirin doses among patients on DAPT (aspirin plus clopidogrel) (medium dose 9.5% vs. low dose 8.6%; HR 1.2; 95% CI, 0.98 to 1.48; high dose 9.8% vs. low dose 8.6%; HR 1.2; 95% CI, 0.95 to 1.40).

The PLATO substudy[201] (good quality; 18,624 patients) found that at 1 year, patients on low-dose aspirin (<300mg) had a lower rate of composite ischemic events when treated with ticagrelor compared with patients treated with clopidogrel (HR 0.79; 95% CI, 0.71 to 0.88), while patients on high-dose aspirin (≥300 mg) had fewer events when treated with clopidogrel compared with those treated with ticagrelor (HR1.45; 95% CI, 1.01 to 2.09). The heterogeneity of the aspirin dosage comparisons between the CURE and PLATO substudies, plus the differences in the dual antiplatelet analysis (clopidogrel in CURE and ticagrelor vs. clopidogrel in PLATO), makes it difficult to combine these studies; thus the SOE was rated insufficient for this composite outcome at 1 year.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal Myocardial Infarction, or Revascularization at 1 Year

Three studies[142,172,176] (1 good quality, 2 fair; 9249 patients) reported the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 12 months. In general, low-dose aspirin had similar composite event rates as high-dose aspirin. The study by Harjai et al.[142] comparing 81 mg of aspirin with 162–325 mg found no significant difference in the composite of death or MI at 1 year (6.7% vs. 6.1%, respectively) or in the composite of death, MI, or stent thrombosis or target vessel revascularization (8.6% vs. 9.2%). Similarly, in the study by So et al.[172] comparing 81 mg of aspirin with 325 mg, the risk of death or MI, and death, MI, or revascularization was not significantly different between the two treatment arms (adjusted OR 1.16; 95% CI, 0.73 to 1.85; and adjusted OR 1.08; 95% CI, 0.80 to 1.47). The third study, by Aronow et al.,[176] included a mixed population of UA/NSTEMI, STEMI, and stable angina and showed no significant difference in the incidence of the composite endpoint of death, MI, or stroke (HR 0.96; 95% CI, 0.76 to 1.21) and death, MI, stroke, revascularization, or rehospitalization (HR 1.11; 95% CI, 0.97 to 1.28) between aspirin doses of <162 mg compared with ≥162 mg. Thus, composite outcomes at 6 months and 1 year were similar between low-dose and high-dose aspirin in studies that used aspirin monotherapy or dual antiplatelet therapy. While the findings are consistent between these three observational studies the imprecise estimates make the evidence insufficient to detect a difference in this composite outcome at 1 year.

Effect on All-Cause Mortality at 6 Months and 1 Year

The Quinn study[192] (good quality; 20,469 patients) reported total mortality at 6 months and showed no effect of high-dose aspirin (≥150 mg) on mortality risk compared with lower dose (<150 mg) (HR 0.89; 95% CI, 0.72 to 1.10, p=0.30). Two studies[172,176] (1 good quality, 1 fair; 6429 patients) reported 1-year mortality risk. In the So study,[172] mortality risk was similar among patients discharged on low-dose aspirin (81 mg) compared with those discharged on a higher dose (325 mg) (adjusted OR 0.88; 95% CI, 0.51 to 1.55, p=0.664) in patients who also received clopidogrel. The Aronow study[176] found that high-dose aspirin (≥162 mg) was associated with a significant reduction of all-cause mortality (HR 0.55; 95% CI, 0.37 to 0.83) compared with low-dose aspirin (<162 mg) in a population that received aspirin monotherapy. The SOE for assessing the comparative effectiveness between low- and high-dose aspirin was rated

insufficient for all-cause mortality at 6 months and 1 year given the inconsistent and imprecise results.

Effect on Nonfatal MI at 6 Months and 1 Year

Two studies[176,192] reported nonfatal MI, one at 6 months and the other at 1 year. While the study by Quinn et al.[192] found a significant reduction of nonfatal MI events (HR 0.79; 95% CI, 0.64 to 0.98, p=0.03) among patients treated with high-dose of aspirin (≥150 mg vs. <150 mg) at 6 months, the study by Aronow et al.[176] comparing similar doses of aspirin found no effect of high-dose versus low-dose (≥162 mg vs. <162 mg) in 1-year mortality (HR 0.98; 95% CI, 0.66 to 1.48). The Quinn study did not report clopidogrel use in the treatment groups, therefore we assume that their findings are based on aspirin monotherapy, while the Aronow study would only permit use of ticlopidine or clopidogrel for 30 days after PCI. The SOE for nonfatal MI at 6 months was rated low based on one large observational study that reported a statistically significant reduction; however, the evidence for nonfatal MI at 1 year was rated insufficient based on a moderate sized observational study with imprecise results.

Effect on Stroke at 6 Months and 1 Year

Two studies reported stroke events,[176,192] one at 6 months and the other at 1 year. High-dose aspirin was associated with a trend toward higher risk of stroke both at 6 months in the Quinn study[192] (≥150 mg vs. <150 mg; HR 1.59; 95% CI, 0.95 to 2.65) and at 1 year in the Aronow study[176] (≥162 mg vs. <162 mg; HR 1.37; 95% CI, 0.94 to 2.00).The SOE for the comparative effectiveness of low- versus high-dose aspirin on stroke outcomes at 6 months and 1 year was rated insufficient based on imprecise results from observational studies.

Effect on Revascularization at 1 Year

Two studies reported revascularization at 1 year[172,176] (1 good quality, 1 fair; 6429 patients). In the So study[172] repeat revascularization was similar among patients discharged on low-dose aspirin (81 mg) compared with higher dose (325 mg) when both groups were also treated with clopidogrel (adjusted OR 1.05; 95% CI, 0.74 to 1.51, p=0.772). In the Aronow study[176] patients treated with high-dose aspirin (≥162 mg) were more likely to undergo urgent revascularization (HR 1.34; 95% CI, 1.10 to 1.64). The inconsistent and imprecise findings for revascularization outcomes at 1 year resulted in a SOE rating of insufficient.

Effect on Major Bleeding at 1 Year

Three studies[142,176,202] (2 good quality, 1 fair; 19,971 patients) reported major bleeding at 1 year. The fair-quality study by Harjai[142] found a higher TIMI bleeding rate in the group taking low-dose aspirin (81 mg) compared with higher dose (162–325 mg) (3.8% vs. 1.6%); this was due to the higher baseline risk of the patients who received low-dose aspirin, and about half (53%) of the patients in each group had received clopidogrel. The Aronow study[176] found a higher incidence of any bleeding among patients treated with high-dose aspirin monotherapy (≥162 mg vs. <162 mg; adjusted HR 1.32; 95% CI, 1.12 to 1.55).

Similarly, the CURE substudy found a higher risk of bleeding among patients receiving a medium-dose aspirin (101–199 mg) or a high-dose aspirin (≥200 mg) when compared with patients receiving a low-dose aspirin (≤ 100 mg), when patients received aspirin monotherapy (2.82% vs. 1.86%; OR 1.52; 95% CI, 1.00 to 2.31, and 3.67% vs. 1.86%; OR 1.7; 95% CI, 1.22 to 2.59, respectively). The CURE substudy also found a higher risk of bleeding on high-dose

aspirin compared with low-dose aspirin among patients receiving dual antiplatelet therapy (4.89% vs. 2.97%; OR 1.63; 95% CI, 1.19 to 2.23). For patients receiving dual antiplatelet therapy, no differences in bleeding were found between the medium dose and the low dose (3.41% vs. 2.97%; OR 1.20; 95% CI, 0.84 to 1.73). Although the two good-quality studies both demonstrated a benefit of lower-dose aspirin in terms of major bleeding, the heterogeneity in aspirin dosage and the variable use of dual antiplatelet therapy across studies resulted in a SOE rating of low for an increase in major bleeding with high-dose aspirin outcomes at 1 year.

Findings by Subgroup (KQ 3d)

Three studies reported the treatment effectiveness of aspirin dosage by subgroup[142,172,201] (Table H-3 in Appendix H). One fair-quality study by So et al.[172] comparing aspirin doses in patients also receiving clopidogrel, reported variations in treatment effectiveness by subgroup This study compared the efficacy of low-dose aspirin (81 mg) with high-dose (325 mg) among diabetic patients, patients with multivessel disease, and by type of stent (drug-eluting stent [DES] vs. bare metal stent [BMS]). Patients with diabetes receiving low-dose aspirin had no advantage in terms of death or MI at 1 year (log OR=0) compared with high-dose aspirin. Patients with multivessel disease receiving low-dose aspirin were at higher risk of death or MI when compared with the high-dose aspirin group (p=0.07). Patients in the DES group receiving low-dose aspirin had a similar risk of death or MI (OR 1.12; 95% CI, 0.53 to 2.34) and of death, MI, or revascularization (OR 0.75; 95% CI, 0.46 to 1.25) compared with the high-dose aspirin group. Patients in the BMS group receiving low-dose aspirin were at similar risk of death or MI (OR 1.25; 95% CI, 0.67 to 2.33) and of death, MI, or revascularization (OR 1.38; 95% CI, 0.92 to 2.06) compared with the high-dose aspirin group.

The PLATO substudy reported variations in treatment effectiveness of aspirin dosage when combined with either ticagrelor or clopidogrel for patients located inside and outside the United States.[201] When effect by location was evaluated, high-dose aspirin (>300 mg) was not associated with a significant effect on the primary composite endpoint in either U.S. patients (HR 1.62; 95% CI, 0.99 to 2.64) or non-U.S. patients (HR 1.23; 95% CI, 0.71 to 2.14). However, among patients receiving low-dose aspirin (≤300 mg), ticagrelor was associated with statistically significantly lower rates of the primary composite outcome when compared with clopidogrel (HR 0.78, 95% CI, 0.69 to 0.87) in non-U.S. patients versus U.S. patients (HR 0.73; 95% CI, 0.40 to 1.33).

The study by Harjai et al. reported variations in treatment effectiveness of aspirin dosage (81 mg vs. 162–325 mg) for patients with diabetes and those with a DES.[142] Results between the low-dose and high-dose aspirin groups were similar, both for patients with diabetes and those with a DES for the outcomes of death, MI, stent thrombosis, revascularization (diabetes: 12.1% low-dose vs. 12.6% high-dose; DES: 6.3% low-dose vs. 6.7% high-dose), or stent thrombosis (diabetes: 2.2% low-dose vs. 2.6% high-dose; DES: 1.7% low-dose vs. 1.8% high-dose). However, the low-dose aspirin groups had a higher incidence of bleeding (diabetes: 6.6% low-dose vs. 2.1% high-dose; DES: 3.5% low-dose vs. 1.3% high-dose). In patients with diabetes, the low-dose aspirin group also had higher rates of death or MI (11.0% low-dose vs. 8.3% high-dose), but there was little difference in death or MI between groups in patients receiving a DES (4.6% low-dose vs. 5.3% high dose).

Summary of Results for Low-Dose Versus High-Dose Aspirin

In our analysis of low-dose versus high-dose aspirin, we found insufficient evidence for composite ischemic event rates and all-cause mortality at 6 months and 1 year. Nonfatal MI was lower from high-dose aspirin (≥150 mg vs. <150 mg) at 6 months in one study, but the evidence was insufficient from a second, smaller study at 1 year. Insufficient evidence was also found for stroke rates in these two studies at 6 months and 1 year. There were conflicting results on revascularization rates at 1 year, with one study showing no difference (81 mg vs. 325 mg) and another study showing higher rates of urgent revascularization in the high-dose (≥162 mg) group. The effect on major bleeding at 1 year was also inconsistent, with one fair-quality study reporting higher bleeding rates in the low-dose (81 mg) group and two good-quality studies reporting higher rates in the high-dose group (162 mg or ≥200 mg). Differences in consistency of the results may be that the Harjai[142] and So[172] studies were smaller, single-center studies that had higher rates of clopidogrel use (53% and 99% respectively) while the Aronow,[176] Quinn,[192] Peters,[202] and Mahaffey[201] studies were secondary analyses of larger RCTs (i.e., BRAVO, Gusto IIb, and PURSUIT, CURE, and PLATO)—one of which did not allow use of thienopyridines, one study did not report its use, one study reported results for aspirin monotherapy and dual antiplatelet therapy, and one study had only dual antiplatelet with two different thienopyridine medications In addition, the doses of aspirin compared differed among the six studies. Subgroup analyses included diabetes, multivessel disease, and type of stent from one study comparing low-dose aspirin (81 mg) with high-dose (325 mg) in addition to clopidogrel; geographic location from one study comparing low-dose aspirin (<300 mg) with high-dose (≥300 mg) in patients receiving either ticagrelor or clopidogrel; and diabetes and type of stent from one study comparing low-dose aspirin (81 mg) with high-dose aspirin (161–325 mg). Patients with multivessel disease had higher events rates on low-dose aspirin; however, patients with diabetes, drug-eluting stents, and bare metal stents had similar event rates on low-dose and high-dose aspirin as part of a dual antiplatelet treatment strategy. Patients on low-dose aspirin (<300 mg) and ticagrelor had lower events rates than those on low-dose aspirin and clopidogrel. Patients with diabetes and those with a DES receiving low-dose aspirin both had an increased incidence of bleeding, while patients with diabetes on low-dose aspirin also had an increased rate of death or MI. Detailed SOE ratings are shown in Table 22.

Table 22. Detailed strength of evidence for UA/NSTEMI patients treated with low-dose versus high-dose aspirin

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of All-Cause Mortality, Nonfatal MI, or Stroke at 6 Months					**Insufficient SOE**
1 (20,469)	Observational/Good quality	NA	Direct	Precise	HR 0.92 (0.79 to 1.07) Insufficient evidence due to confidence interval that crosses 1
Composite of All-Cause Mortality, Nonfatal MI, or Stroke at 1 Year					**Insufficient SOE**
2 (31,186)	2 observational/Both good quality	Inconsistent	Direct	Imprecise	Insufficient evidence due to inconsistency and imprecision. One study showed similar rates of composite events across 3 dosage categories for aspirin monotherapy and dual antiplatelet therapy; the other study showed lower event rates when combining low-dose aspirin with ticagrelor and high-dose aspirin with clopidogrel.
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 1 Year					**Insufficient SOE**
3 (9249)	3 observational/1 good quality, 2 fair	Consistent	Direct	Imprecise	Insufficient evidence due to imprecision. Low-dose aspirin and high-dose aspirin had similar rates of ischemic events in all 3 studies.
All-Cause Mortality at 6 Months					**Insufficient SOE**
1 (20,469)	Observational/Good quality	NA	Direct	Imprecise	HR 0.89 (0.72 to 1.10) Insufficient evidence due to imprecision
All-Cause Mortality at 1 Year					**Insufficient SOE**
2 (6429)	2 observational/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	Insufficient evidence due to inconsistency and imprecision. One study (aspirin/clopidogrel) showed no difference between doses, the other found that high-dose aspirin (monotherapy) reduced mortality.
Nonfatal MI at 6 Months					**Low SOE**
1 (20,469)	Observational/Good quality	NA	Direct	Precise	HR 0.79 (0.64 to 0.98) Favors high-dose aspirin
Nonfatal MI at 1 Year					**Insufficient SOE**
1 (4589)	Observational/Good quality	NA	Direct	Imprecise	HR 0.98 (0.66 to 1.48) Insufficient evidence due to imprecision.
Stroke at 6 Months					**Insufficient SOE**
1 (20,469)	Observational/Good quality	NA	Direct	Imprecise	HR 1.59 (0.95 to 2.65) Insufficient evidence due to imprecision.

Table 22. Detailed strength of evidence for UA/NSTEMI patients treated with low-dose versus high-dose aspirin (continued)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Stroke at 1 Year					**Insufficient SOE**
1 (4589)	Observational/Good quality	NA	Direct	Imprecise	HR 1.37 (0.94 to 2.00) Insufficient evidence due to imprecision.
Revascularization at 1 Year					**Insufficient SOE**
2 (6429)	2 observational/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	Insufficient evidence due to inconsistency and imprecision. One study (aspirin/clopidogrel) showed no difference between doses, the other study (aspirin monotherapy) showed more events with high dose.
Major Bleeding at 1 Year					**Low SOE**
3 (19,971)	3 observational/2 good quality, 1 fair	Inconsistent	Direct	Imprecise	1 study had high bleeding rates in low-dose group; 2 studies had high bleeding rates in high-dose group. Favors low-dose aspirin

BMS = bare metal stent; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MI = myocardial infarction; NA = not applicable; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

2. Single Antiplatelet Versus Dual Antiplatelet Therapy (KQ 3a)

Seven studies (one RCT, six observational) compared single antiplatelet with dual antiplatelet therapy in the postdischarge treatment of UA/NSTEMI patients.[138,151,160,179,184,191,194] Of these studies, six compared aspirin monotherapy (single antiplatelet) with aspirin plus clopidogrel (dual antiplatelet), and one study contained three arms comparing aspirin monotherapy, clopidogrel monotherapy, and aspirin plus clopidogrel.[160] The RCT was rated good quality, and of the six observational studies, two were rated good quality, three fair, and one poor. The RCT (CURE study[194]) allowed a dose of 75 mg to 325 mg daily. None of the observational studies reported the dose of aspirin used in the patient cohorts. Sample sizes for individual studies ranged from 1,331 to 44,426 patients. Study duration ranged from in-hospital to 12 months.

The mean age of study participants ranged from 64 to 70 years. The proportion of female patients ranged from 27 to 42 percent. None of the studies reported the racial or ethnic demographics of study participants. One study (14%)was conducted solely in the United States, two were conducted in Asia (29%), one was conducted in Europe (14%), and the other three were international (43%). Funding source was reported in five studies, with all five studies funded by industry. Table G-13 in Appendix G contains the results reported by each study.

Effect on Composite Ischemic Endpoints In-Hospital to 1 Year

One good-quality RCT and two observational studies (1 fair quality, 1 poor) including 106,749 patients comparing aspirin alone with aspirin plus clopidogrel reported composite outcomes. In the CURE RCT,[194] the rate of cardiovascular mortality, nonfatal MI, or stroke and cardiovascular mortality, nonfatal MI, stroke, or refractory ischemia were both significantly lower among patients who were discharged on aspirin plus clopidogrel compared with those on

aspirin alone (9.3% vs. 11.4%; RR 0.80; 95% CI, 0.72 to 0.90 and 16.5% vs. 18.8%; RR 0.86; 95% CI, 0.79 to 0.94) at the 9-month followup assessment. In one observational study (CRUSADE registry[179]), the rate of in-hospital total mortality and nonfatal MI was 5.4 percent for patients receiving aspirin plus clopidogrel and 7.6 percent for patients on aspirin alone (p <0.01). The other observational study (ACOS registry[184]) showed significantly lower rates of total mortality, nonfatal MI, or nonfatal stroke for patients receiving aspirin plus clopidogrel compared with aspirin alone (OR 0.69; 95% CI, 0.60 to 0.80) at 1-year followup. The consistent, precise, and statistically significant findings across studies favoring DAPT result in a high SOE rating.

Effect on Stroke In-Hospital to 1 Year

Four studies (1 good quality RCT and 3 observational, 2 fair quality, 1 poor) including 116,136 total patients reported stroke events within the first 9 months postdischarge. An observational study[191] found a similar stroke rate at 6 months after discharge among patients discharged on aspirin alone and those on dual antiplatelet therapy (1.3% vs. 1.0%). In the CRUSADE registry,[179] there was a significant reduction in in-hospital stroke in patients treated with aspirin plus clopidogrel compared with those treated with aspirin alone (0.7% vs. 1.0% , p<0.01). The ACOS registry[184] showed similar rates of stroke for patients receiving aspirin plus clopidogrel compared with aspirin alone (1.88% and 1.98%, respectively) at 1-year followup.

The CURE RCT[194] showed a nonsignificant reduction in stroke events at 9 months among patients treated with aspirin plus clopidogrel compared with those treated with aspirin alone (1.2% vs. 1.4%; RR 0.86; 95% CI, 0.63 to 1.18). The SOE was rated insufficient for stroke outcomes based on inconsistent and imprecise findings from these four studies.

Effect on Nonfatal MI In-Hospital to 1 Year

One good-quality RCT and two observational studies (1 fair quality, 1 poor) including 106,749 patients reported the effect of single versus DAPT on nonfatal MI. The CURE RCT[194] showed a significant reduction in nonfatal MI events at 9 months among patients treated with aspirin plus clopidogrel compared with those treated with aspirin alone (5.2% vs.6.7%, RR 0.77; 95% CI, 0.67 to 0.89). In the CRUSADE registry,[179] there was a significant reduction in postadmission (in-hospital) MI in patients treated with aspirin plus clopidogrel compared with those treated with aspirin alone (2.3% vs. 3.0%, p<0.01). The ACOS registry[184] showed lower rates of nonfatal MI for patients receiving aspirin plus clopidogrel compared with aspirin alone (5.8% and 8.5%, respectively) at 1-year followup. The SOE was rated high for nonfatal MI outcomes based on consistent, statistically significant results favoring DAPT.

Effect on All-Cause Mortality In-Hospital to 1 Year

Five studies (1 good-quality RCT and 4 observational, 1 good quality, 2 fair, 1 poor) including 117,467 patients reported the effect of single versus dual antiplatelet therapy on mortality. One observational study[191] reported higher mortality at 6 months among patients discharged on aspirin compared with those discharged on aspirin plus clopidogrel (5.8% vs. 4.45%). Another observational registry[160] comparing single antiplatelet treatment (aspirin or clopidogrel) with dual antiplatelet treatment (aspirin plus clopidogrel) showed a significantly lower survival rate at 1 year among patients on single antiplatelet treatment (aspirin 53.9%, clopidogrel 51.9%, and aspirin plus clopidogrel 93.2%). No differences in survival rate were observed when duration of dual antiplatelet treatment was considered (0 to 3 months or 3 to 6

months or 6 to 9 months vs. 9 to 12 months). In the CRUSADE registry,[179] there was a significant reduction in in-hospital mortality in patients treated with aspirin plus clopidogrel compared with those treated with aspirin alone (3.5% vs. 5.3%, p<0.01). The ACOS registry[184] showed a significant reduction in mortality for patients receiving aspirin plus clopidogrel compared with aspirin alone (OR 0.66; 95% CI, 0.55 to 0.80) at 1-year followup. The CURE RCT[194] showed a nonsignificant reduction in cardiovascular mortality at 9 months among patients treated with aspirin plus clopidogrel compared with those treated with aspirin alone (5.1% vs. 5.5%; RR 0.93; 95% CI, 0.79 to 1.08). The SOE was rated moderate based on consistent but imprecise findings that DAPT reduces all-cause mortality.

Effect on Major Bleeding In-Hospital to 9 Months

Two studies (1 good quality RCT, 1 fair observational) including 105,607 patients reported the effect of single versus dual antiplatelet therapy on major bleeding. In the CRUSADE registry,[179] there was a significant reduction in in-hospital major bleeding in patients treated with aspirin plus clopidogrel compared with those treated with aspirin alone (16.0% vs. 20.6%, p<0.01). The CURE RCT[194] showed a nonsignificant reduction in major bleeding at 9 months among patients treated with aspirin plus clopidogrel compared with those treated with aspirin alone (RR 0.93; 95% CI, 0.79 to 1.08). The SOE was rated low for major bleeding outcomes based on consistent and imprecise findings.

Findings by Subgroup (KQ 3d)

Four studies[138,151,160,194] (one good-quality RCT; 1 good-, 1 fair-, and 1 poor-quality observational studies) reported variations in treatment effectiveness by subgroup. Subgroups analyzed were diabetes (1 study), sex (1), age (1), clinical presentation (1), heart failure (1), revascularization (1), chronic kidney disease (1), aspirin dosing (1), PCI (2), duration of treatment (1), and presence of smoking (1). Table H-3 in Appendix H presents the results data for these subgroups.

Diabetes

One RCT[194] comparing aspirin alone with aspirin plus clopidogrel in postdischarge UA/NSTEMI patients reported a composite outcome (cardiovascular death, nonfatal MI, or stroke) at 9 months in the diabetic patients subgroup (n=2,840). Among this subgroup, the rate of the composite outcome was 14.2 percent in the aspirin plus clopidogrel arm and 16.7 percent in the aspirin-only arm.

Sex

One study assessed composite ischemic outcomes by sex. The CURE RCT[194] comparing aspirin alone with aspirin plus clopidogrel in postdischarge UA/NSTEMI patients reported a composite outcome (cardiovascular death, nonfatal MI, or stroke) at 9 months by sex. Among men (n=7726), the rate of the composite outcome was 9.1 percent in the aspirin plus clopidogrel arm and 11.9 percent in the aspirin-only arm. Among women (n=4836), the rate of composite outcome was 9.5 percent in the aspirin plus clopidogrel arm and 10.7 percent in the aspirin-only arm.

Age

One RCT assessed composite ischemic outcomes by age. The CURE RCT[194] comparing aspirin alone with aspirin plus clopidogrel in postdischarge UA/NSTEMI patients reported a

composite outcome (cardiovascular death, nonfatal MI, or stroke) at 9 months by age subgroups (≤65 years vs. >65 years). Among those aged 65 years or less (n=6354), the rate of composite outcome was 5.4 percent in the aspirin plus clopidogrel arm and 7.6 percent in the aspirin-only arm. Among those aged over 65 years (n=6,208), the rate of the composite outcome was 13.3 percent in the aspirin plus clopidogrel arm and 15.3 percent in the aspirin-only arm.

Clinical Presentation

One RCT[194] comparing aspirin alone with aspirin plus clopidogrel in postdischarge UA/NSTEMI patients reported a composite outcome (cardiovascular death, nonfatal MI, or stroke) at 9 months by clinical presentation (NSTEMI or UA). Among those with NSTEMI (n=3283), the rate of composite outcome was 11.3 percent in the aspirin plus clopidogrel arm and 13.7 percent in the aspirin-only arm. Among those with UA (n=9279), the rate of composite outcome was 8.6 percent in the aspirin plus clopidogrel arm and 10.6 percent in the aspirin-only arm.

Heart Failure

One observational study[138] comparing aspirin alone with aspirin plus clopidogrel among patients with acute MI and concomitant heart failure not receiving PCI, found a nonsignificant decreased risk of death among heart failure patients treated with dual therapy compared with those receiving aspirin alone (28.1% vs. 32.2%; HR 0.86; 95% CI, 0.83 to 1.16). The effect of clopidogrel was not significant among the cohort without heart failure (9.4% vs. 9.7%; HR 0.98; 95% CI, 0.83 to 1.16).

Revascularization

One RCT[194] comparing aspirin alone with aspirin plus clopidogrel in postdischarge UA/NSTEMI patients reported a composite outcome (cardiovascular death, nonfatal MI, or stroke) at 9 months by revascularization (PCI or CABG) after randomization. Among those receiving revascularization (n=4577), the rate of composite outcome was 11.5 percent in the aspirin plus clopidogrel arm and 13.9 percent in the aspirin-only arm. Among those not receiving revascularization (n=7985), the rate of composite outcome was 8.1 percent in the aspirin plus clopidogrel arm and 10 percent in the aspirin-only arm.

Chronic Kidney Disease

One RCT[194] comparing aspirin alone with aspirin plus clopidogrel in postdischarge UA/NSTEMI patients reported a composite outcome (cardiovascular death, nonfatal MI, or stroke) at 9 months among patients with chronic kidney disease (CKD) (defined as creatinine clearance <64 mL/min). Among patients with CKD (n=4087), the rate of the composite outcome was 13.4 percent in the aspirin plus clopidogrel arm and 14.9 percent in the aspirin-only arm (RR 0.89; 95% CI, 0.76 to 1.05). The rate of cardiovascular mortality was 8.3 percent in the aspirin plus clopidogrel arm and 8.7 percent in the aspirin-only arm (RR 0.95; 95% CI, 0.77 to 1.17). The rate of all-cause mortality was 9.6 percent in the aspirin plus clopidogrel arm and 10.0 percent in the aspirin-only arm (RR 0.95; 95% CI, 0.78 to 1.16). The rate of major bleeding was 2.3 percent in the aspirin plus clopidogrel arm and 1.7 percent in the aspirin-only arm (RR 1.37; 95% CI, 0.89 to 2.12), and the rate of minor bleeding was 5.2 percent in the aspirin plus clopidogrel arm and 2.4 percent in the aspirin-only arm (RR 1.5; 95% CI, 1.21 to 1.86).

Aspirin Dosing

One RCT[194] comparing aspirin alone with aspirin plus clopidogrel in postdischarge UA/NSTEMI patients reported a composite outcome (cardiovascular death, nonfatal MI, or stroke) at 9 months by aspirin dosing (≤100 mg/day vs. 101 to 199 mg/day). Among those receiving ≤100 mg/day (n=5,320), the rate of the composite outcome was lower in the aspirin plus clopidogrel arm than in the aspirin-only arm (RR 0.81; 95% CI, 0.68 to 0.97), although the rate of major bleed was nonsignificantly higher in the clopidogrel arm (3% vs. 1.9%). Among those receiving 100 to 199 mg/day of aspirin (n=3109), the rate of the composite outcome was not significantly lower in the aspirin plus clopidogrel arm compared with the aspirin arm (RR 0.97; 95% CI, 0.77 to 1.22), and again the rate of major bleed was slightly higher in the clopidogrel arm (3.4% vs. 2.8%).

PCI

Two studies (one RCT and one observational study) comparing aspirin alone with aspirin plus clopidogrel in postdischarge UA/NSTEMI patients reported findings by receipt of PCI. In the CURE RCT,[194] those receiving PCI had a lower rate of the composite outcome of cardiovascular death, nonfatal MI, or stroke (RR 0.75; 95% CI, 0.56 to 1.00, p=0.047), but higher rates of minor bleeding (RR 1.68; 95% CI, 1.06 to 2.68, p=0.03), and similar rates of major bleeding (RR 1.12; 95% CI, 0.7 to 1.78, p=0.64). The observational study[184] reported significantly lower mortality rates in patients who received PCI and were treated with aspirin plus clopidogrel compared with aspirin alone (OR 0.51; 95% CI, 0.33 to 0.77), whereas the group without PCI receiving aspirin plus clopidogrel had a nonsignificant reduction in total mortality compared with aspirin alone (OR 0.90; 95% CI, 0.73 to 1.11).

Duration of Treatment

One observational study[160] comparing single antiplatelet treatment (aspirin or clopidogrel) with dual antiplatelet treatment (aspirin plus clopidogrel) showed a significantly lower survival rate at 1 year among patients on single antiplatelet treatment (aspirin 53.9%, clopidogrel 51.9%, and aspirin plus clopidogrel 93.2%). No significant differences in survival rate were observed when duration of dual antiplatelet treatment was considered: 0 to 3 months (96.5%), or 3 to 6 months (94.6%), or 6 to 9 months (100%) versus 9 to 12 months (100%).

Presence of Smoking

One observational study[151] comparing early clopidogrel use to aspirin in an acute coronary syndrome population (30% UA, 34% NSTEMI, and 36% STEMI) evaluated the composite event rate in nonsmokers and current smokers. In both groups, early clopidogrel use was associated with a reduction in the composite endpoint of mortality and MI in-hospital and at 6 months (OR 0.77; 95% CI, 0.6 to 0.95); no interaction between smoking status and ischemic endpoints was found. In addition, current smokers with early clopidogrel use had lower rates of major bleeding (2%) compared with nonsmokers (3.1%).

Summary of Results for Single Antiplatelet Versus Dual Antiplatelet Therapy

Our analysis of single antiplatelet versus dual antiplatelet therapy addresses the question about the effectiveness of combinations of antiplatelet agents. The identified literature predominately reports the comparison of aspirin monotherapy (single antiplatelet) with aspirin plus clopidogrel therapy (dual antiplatelet). Use of newer antiplatelet agents (prasugrel, ticagrelor) with aspirin in comparison to clopidogrel plus aspirin was previously summarized

under KQ 1; there we presented the findings from direct comparisons of different dual antiplatelet treatment strategies. In the analysis of single versus dual antiplatelet therapy, dual antiplatelet therapy reduces the rates of composite ischemic outcomes and nonfatal MI in UA/NSTEMI patients based on 3 studies (1 RCT and 2 observational registries). While five studies (1 RCT and 4 observational) showed a reduction in all-cause mortality in the dual antiplatelet therapy group, the wide CIs around the reported RRs in many of the studies made this finding less precise than the results on composite ischemic outcomes and nonfatal MI. Four out of five studies (2 RCTs and 3 observational studies) showed no significant difference in stroke rates between dual antiplatelet and single antiplatelet therapy; the evidence for this outcome was rated insufficient. The effect of dual antiplatelet therapy on major bleeding varied in three studies (two RCTs and one observational registry), and was also rated insufficient. Subgroup findings from four studies (two RCTs, two observational registries) assessed the effectiveness based on age, sex, clinical presentation, duration of treatment, receipt of PCI, receipt of any type of revascularization, or presence of diabetes, chronic kidney disease, heart failure, or smoking (one or two studies reported findings for each subgroup listed). Almost all of the studies showed similar rates of composite ischemic outcomes in the various subgroups, except for subgroup analyses of PCI and treatment duration. One study showed a significantly lower rate of composite ischemic outcomes, and another study showed a significantly lower rate of death in patients who received dual antiplatelet therapy and underwent PCI. One study showed a significantly lower survival rate at 1 year in the groups that received single antiplatelet therapy. The SOE for subgroup findings was rated insufficient given the small number of studies reporting results for each subgroup. Detailed SOE ratings are shown in Table 23.

Table 23. Detailed strength of evidence for UA/NSTEMI patients treated with single versus dual antiplatelet therapy

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite Ischemic Endpoints In-Hospital to 1 Year					**High SOE**
3 (106,749)	1 RCT/Good quality 2 observational/1 fair quality, 1 poor	Consistent	Direct	Precise	All studies showed significant lowering of composite events in dual antiplatelet arm, ranging from OR 0.69 to RR 0.86 Favors DAPT
Stroke In-Hospital to 1 Year					**Insufficient SOE**
4 (116,136)	1 RCT/Good quality 3 observational/2 fair quality, 1 poor	Inconsistent	Direct	Imprecise	Insufficient evidence due to inconsistency and imprecision with 3 out of 4 studies showing no statistically significant difference in stroke rates
Nonfatal MI In-Hospital to 1 Year					**High SOE**
3 (106,749)	1 RCT/Good quality 2 observational/1 fair quality, 1 poor	Consistent	Direct	Precise	2.3% to 5.8% vs. 3.0% to 8.5% Favors DAPT

Table 23. Detailed strength of evidence for UA/NSTEMI patients treated with single versus dual antiplatelet therapy (continued)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
All-Cause Mortality In-Hospital to 1 Year					**Moderate SOE**
5 (117,467)	1 RCTs/Good quality 4 observational/1 good quality, 2 fair, 1 poor	Consistent	Direct	Imprecise	OR/RR 0.66 to OR/RR 0.93 Favors DAPT
Major Bleeding In-Hospital to 9 Months					**Low SOE**
2 (105,607)	1 RCT/Good quality 1 observational/Fair quality	Consistent	Direct	Imprecise	2 studies showed a reduction in major bleed in DAPT group (1 statistically significant [16% vs. 21%], 1 not statistically significant) Favors DAPT

CI = confidence interval; DAPT = dual antiplatelet therapy; MI = myocardial infarction; NA = not applicable; RR = risk ratio; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

3. Short-Term Versus Long-Term Dual Antiplatelet Therapy (KQ 3a)

Eleven studies (5 RCTs, 6 observational) compared short-term with long-term dual antiplatelet therapy (clopidogrel plus aspirin) in the postdischarge treatment of UA/NSTEMI patients.[134,136,168-171,183,187,193,198,199] Of the RCTs, two studies compared 1 month versus 6 months of dual antiplatelet therapy (DAPT);[187,193] one compared 1 month versus 12 months of DAPT;[199] one compared 6 months versus 12 months of DAPT;[136] and another compared 6 months versus 24 months.[198]

In the observational studies, one evaluated planned duration of DAPT use for less than 3 months versus 6 months versus 12 months;[170] a second evaluated clopidogrel discontinuation by multivariable analysis at 6-month intervals;[183] one assessed patients with stent thrombosis for independent predictors;[171] one evaluated clopidogrel cessation by a competing risk approach;[168] one compared dual antiplatelet therapy for more than 12 months with less than 12 months[169] and one assessed the effect of clopidogrel discontinuation after 12 months of clopidogrel treatment.[134]

Of the RCTs, three (60%) were rated good quality and two (40%) fair. Of the observational studies, one (17%) was rated good quality, four (66%) fair, and one (17%) poor quality. Sample sizes for individual studies ranged from 278 to 29,268 patients. Study duration ranged from 30 days to 4 years.

The mean age of study participants ranged from 57 to 67 years. The proportion of female patients ranged from 2 to 43 percent. Two studies (18%) reported the racial and ethnic demographics of study participants. Three studies (27%) were conducted within the United States or Canada, one was conducted in Europe (9%), one was conducted in Asia (9%), and the rest were international. Funding source was reported in 6 studies (55%), with 1 study (9%) funded by an industry source, one by a private foundation (9%), and one by government (9%). Table G-14 in Appendix G summarizes the results reported by each study.

Effect on Composite Endpoint of All-Cause Mortality or Nonfatal MI Within 2 Years

Four studies (two RCTs,[136,198] both good quality; two observational,[134,183] both fair quality) including 34,179 patients reported the composite outcome of all-cause mortality or nonfatal MI. Both RCTs, one assessing DAPT for 6 months versus 24 months and the other evaluating DAPT for 6 months versus 12 months, showed no differences in the rate of the composite outcome at 2 years and 12 months respectively between the two treatment arms (9.6% vs. 8.9%; OR 1.07; 95% CI, 0.80 to 1.43, p=0.62; 2.4% vs.1.9%; HR 1.21; 95% CI, 0.60 to 2.47, p=0.58).

One retrospective observational study[183], assessing the effect of clopidogrel discontinuation on the composite outcome at a median of 538 days, found that among patients who discontinue clopidogrel within the first 6 months after discharge, the rate of all-cause mortality and nonfatal MI was higher compared with those who continue clopidogrel treatment (HR 1.90; 95% CI, 1.39 to 2.59). The other observational study[134] assessing the effect of clopidogrel discontinuation after 12 months of treatment subsequent to an MI, found a higher risk in the composite of cardiovascular death or MI during the first 90 days of discontinuation of clopidogrel compared with the next 90 days of discontinuation among those who were treated with PCI (IRR1.59; 95% CI, 1.11 to 2.30) but not among patients who were medically managed (IRR 1.07; 95% CI, 0.65 to 1.76). The SOE was rated insufficient for the composite outcome of all-cause mortality or nonfatal MI due to heterogeneity of DAPT duration, plus inconsistent and imprecise findings between the observational studies and randomized trials.

Effect on Composite Endpoint of All-Cause Mortality or Stroke at 2 Years

One good-quality RCT[198] with 2013 patients evaluating DAPT for 6 months versus 24 months showed no differences in the rate of the composite outcome of all-cause mortality or stroke at 2 years between the two treatments arms (7.1% vs. 7.8%; OR 0.91; 95% CI, 0.66 to 1.26, p=0.57). The SOE was rated insufficient for the composite outcome of all-cause mortality or stroke based on one study with an imprecise estimate.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal MI, or Revascularization at 6 Months and 1 Year

Three studies (two RCTs,[136,193] one good quality, one fair; and one fair-quality observational[170]) including 4701 patients reported the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 6 months and 1 year.

One RCT,[193] comparing 1-month with 6-month treatment with DAPT, found that the rate of composite outcomes at 6 months was similar between the two treatment groups (12.9% vs. 13.8%). Likewise, the other RCT[136] assessing 6-month versus 12-month DAPT treatment, found no difference in the composite outcome at 12 months (4.8% vs. 4.3%; HR 1.14; 95% CI, 0.70 to 1.86). In the observational study[170] assessing DAPT use for <3 months versus 6 months versus >12 months, the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 1 year was reported based on type of stent (DES and BMS) used during PCI. The rate of composite outcome in both the DES-treated and BMS-treated patients at 1 year was similar across clopidogrel treatment groups (DES 11.2% vs. 16.0% vs. 14.3%, p=0.33; BMS 15.8% vs. 12.9% vs. 17.6%, p=0.26). The SOE was rated insufficient for this composite outcome based on the heterogeneity of the study durations assessed and imprecise estimates.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal MI, Stroke, or Revascularization at 1 Year

One good-quality RCT[136] with 1443 patients assessing 6-month versus 12-month DAPT treatment found no difference in the composite endpoint at 1 year (8.0% vs. 8.5%, HR 0.94, 95% CI, 0.65 to 1.35). The SOE was rated insufficient for the composite outcome of all-cause mortality, nonfatal MI, stroke, or revascularization based on one study with an imprecise estimate.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal MI, or Stroke at 6 Months, 1 Year, and 2 Years

Three RCTs[187,198,199] (two good quality, 1 fair) including 5133 patients reported the composite outcome of all-cause mortality, nonfatal MI, or stroke at 6 months, 1 year, and 2 years. One RCT[187] comparing 1-month with 6-month treatment with DAPT found that the rate of the composite outcome at 6 months was significantly lower among patients treated with DAPT for 6 months compared with those treated for 30 days (1.7% vs. 5.0%; RR decrease 65%, p=0.010).

One RCT[199] assessing DAPT treatment for 1 month versus 12 months found a significant reduction in the risk of the composite outcome at 12 months among patients treated with DAPT for 12 months (8.5% vs. 11.5%; RR 26.9; 95% CI, 3.9 to 44.4). The other RCT[198] evaluating DAPT for 6 months versus 24 months showed no differences in the rate of the composite outcome at 2 years between the two treatments arms (10.0% vs. 10.1%; OR 0.98; 95% CI, 0.74 to 1.29, p=0.91). The SOE was rated insufficient for this composite outcome at each time point due to the heterogeneity of the study durations, timing of the outcome measurement (only one study available at each time point), and imprecise estimates.

Effect on All-Cause Mortality at 6 Months, 1 Year, and 2 Years

Seven studies[134,136,170,183,187,193,198] (4 RCTs, 2 good quality, 2 fair; 3 observational, all fair quality) including 38,441 patients reported total mortality results. Two RCTs[187,193] comparing 1-month with 6-month treatment with DAPT found that the rate of all-cause mortality at 6 months was lower among patients treated with DAPT for 6 months compared with those treated for 1-month. The difference in event rate was statistically different in only one study (0.87% vs. 2.6%, p=0.05[187] and 0.7% vs. 1.4%[193]).

An RCT[136] assessing DAPT for 6 months versus 12 months showed no difference in 1-year mortality between the two treatment arms (6.6% vs. 6.6%; HR 1.0; 95% CI, 0.72 to 1.40, p=0.98). Another RCT[198] assessing DAPT for 6 months versus 24 months showed no difference in 2-year mortality between the two treatment arms (6.6% vs. 6.6%; OR 1.0; 95% CI, 0.72 to 1.40, p=0.98).

In one observational study[170] evaluating DAPT use for less than 3 months versus 6 months versus more than 12 months, all-cause mortality at 1 year was reported based on type of stent used during PCI. In DES-treated patients, 1 year mortality was significantly lower in patients receiving DAPT for more than 12 months when compared with shorter duration of DAPT (2.8% vs. 5.3% vs. 5.3%, p=0.01), while in BMS-treated patients, 1 year mortality was similar among the three DAPT duration strategies (5.9% vs. 4.5% vs. 6.0%, 12 vs. 6 vs. 3 months, respectively). Although an observational study, this study highlights the different impact of DAPT among DES versus BMS patient populations.

A retrospective study[183] assessing the effect of clopidogrel discontinuation on all-cause mortality at a median of 538 days found that among patients who discontinue clopidogrel within the first 6 months after discharge, the rate of all-cause mortality was higher compared with those who continue clopidogrel treatment (19.9% vs. 6.9%; adjusted HR 2.4; 95% CI, 1.61to 3.58). The other observational study,[134] assessing the effect of clopidogrel discontinuation after 12 months of treatment subsequent to an MI, found a higher risk of cardiovascular death during the first 90 days of discontinuation of clopidogrel compared with the next 90 days of discontinuation among those who were treated with PCI (adjusted IRR 1.87; 95% CI, 1.11 to 3.15) but not among patients who were medically managed (adjusted IRR 0.77; 95% CI, 0.36 to 1.67). The SOE was rated insufficient for all-cause mortality based on the heterogeneity of DAPT duration, timing of endpoint measurement, and imprecision.

Effect on Cardiovascular Mortality at 6 Months, 1 Year, and 2 Years

Three RCTs[136,187,198] (2 good quality, 1 fair) including 4460 patients reported cardiovascular mortality results, and one observational study[134] (29,268 patients) reported all-cause mortality. One RCT[187] comparing 1-month with 6-month treatment with DAPT found that the rate of cardiovascular mortality at 6 months was similar between the two treatment groups (1.7 vs. 0.87%, p=0.25). Another RCT[136] assessing DAPT for 6 months versus 12 months found no difference in the rate of cardiovascular mortality between the two treatment arms (0.3% vs. 0.4%; HR 0.67; 95% CI, 0.11 to 3.99, p=0.66) at 1 year. Similarly, the third RCT[198] comparing DAPT for 6 months and 24 months showed no difference in 2-year cardiovascular mortality between the two treatment arms (3.8% vs. 3.70%; OR 1.03; 95% CI, 0.66 to 1.61, p=0.89).

The fair-quality observational study with 29,268 patients[134] that assessed the effect of clopidogrel discontinuation after 12 months of treatment subsequent to an MI found no significant difference in the risk of death between the first 90 days of discontinuation of clopidogrel compared with the next 90 days of discontinuation among both those who were treated with PCI (IRR 1.18; 95% CI, 0.73 to 1.91) and patients who were medically managed (IRR 1.56, 95% CI, 0.85 to 2.87). The SOE was rated insufficient for cardiovascular mortality based on imprecise and inconclusive findings from the three RCTs.

Effect on Nonfatal MI at 6 Months, 1 Year, and 2 Years

Six studies (four RCTs,[136,187,193,198] two good quality, two fair; two fair-quality observational[170,183]) including 9173 patients reported nonfatal MI results. Two RCTs[187,193] comparing 1-month and 6-month treatment with DAPT found that the rate of nonfatal MI at 6 months was similar between the two treatment groups (2.1% vs. 2.2%[193] and 2.8% vs. 1.5%, p=0.18[187]).

An RCT[136] evaluating DAPT for 6 months versus 12 months duration, found no difference in the rate of cardiovascular mortality between the two treatment arms (1.8% vs. 1.0%; HR 1.86; 95% CI, 0.74 to 4.67, p=0.19) at 1 year. In the fourth RCT[198] comparing DAPT for 6 months with 24 months showed no difference in 2-year nonfatal MI rate between the two treatment arms (4.2% vs. 4.0%; OR 1.06; 95% CI, 0.69 to 1.63, p=0.80).

In one observational study[170] assessing DAPT use for less than 3 months versus 6 months versus more than 12 months, nonfatal MI at 1 year was reported based on the type of stent used during PCI. The rate of composite outcome in both the DES-treated and BMS-treated patients at 1 year was similar across treatment groups (DES 3.3% vs. 7.7% vs. 6.4%, p=0.15; BMS 5.3% vs. 4.5% vs. 7.4%).

A retrospective observational study[183] assessing the effect of clopidogrel discontinuation on all-cause mortality at a median of 538 days found that patients who discontinued clopidogrel within the first 6 months after discharge were at higher risk for subsequent acute MI if they received DES (HR 3.57; 95% CI, 1.13 to 11.3) than if they received BMS (HR 1.26; 95% CI, 0.58 to 2.74). The SOE was rated insufficient for nonfatal MI based on imprecise and inconclusive findings across studies.

Effect on Stroke at 6 Months, 1 Year, and 2 Years

Three RCTs[136,187,198] (two good quality, 1 fair) including 4460 patients reported stroke results. One[187] comparing 1-month with 6-month treatment with DAPT, found that the rate of stroke at 6 months was similar between the two treatment groups (0.21% vs. 0%, p=0.32). The study[136] assessing DAPT for 6 months versus 12 months found a trend favoring 6 months but no statistically significant difference in the rate of cardiovascular mortality between the two treatment arms (0.4% vs. 0.7%; HR 0.60; 95% CI, 0.14 to 2.51, p=0.48) at 1 year. The third RCT[198] assessing DAPT for 6 months versus 24 months again showed a trend towards a benefit of the 6 month duration but this was not statistically significant between the two treatment arms and had a wide confidence interval that crossed 1 (1.4% vs. 2.1%; OR 0.60; 95% CI, 0.29 to 1.23, p=0.17). The SOE was rated insufficient for stroke based on the differences in the treatment durations that were compared and imprecise findings from three RCTs.

Effect on Revascularization at 6 Months and 1 Year

Four studies (three RCTs,[136,187,193] one good quality, two fair; and one fair-quality observational[170]) including 5705 patients reported target vessel revascularization results. Two studies[187,193] comparing 1-month with 6-month treatment with DAPT found that the rate of target vessel revascularization (TVR) at 6 months was similar between the two treatment groups (5.6% vs. 3.98%, p=0.22 in one study[187] and 11.4% vs.12.3% in the other[193]). The third RCT[136] assessing DAPT for 6 months versus 12 months found no difference in the rate of TVR between the two treatment arms (3.1% vs. 3.2%; HR 1.00; 95% CI, 0.56 to 1.81, p=0.99) at 1 year.

In one observational study[170] evaluating DAPT use for less than 3 months versus 6 months versus more than 1 year, TVR at 1 year was reported based on type of stent used during PCI. Both in DES-treated and BMS-treated patients, the rate of TVR at 1 year was similar across DAPT groups (DES 4.6% vs. 7.1% vs. 7.1%, p=0.51; BMS 7.2% vs. 7.0% vs. 7.9%). The SOE was rated insufficient for revascularization outcomes based on imprecise and inconclusive findings across the three RCTs.

Effect on Stent Thrombosis at 6 Months, 1 Year, and 2 Years

Six studies (three RCTs,[136,193,198] two good quality, 1 fair; three observational,[168,169,171] 1 good quality, 1 fair, 1 poor) including 15,298 patients reported stent thrombosis results. One RCT[193] comparing 1-month with 6-month treatment with DAPT found that the rate of subacute and late stent occlusion at 6 months was similar between the two treatment groups (3.6% vs. 2.2% and 2.2% vs. 1.6%). Another RCT[136] assessing DAPT for 6 months versus 12 months found no difference in the rate of stent thrombosis between the two treatment arms (0.9% vs. 0.1%; HR 6.02; 95% CI, 0.72 to 49.96, p=0.10) at 1 year. The third RCT[198] assessing DAPT for 6 months versus 24 months showed no difference in 2-year stent thrombosis between the two treatment arms (0.8% vs. 0.70%; OR 0.88; 95% CI, 0.32 to 2.42, p=0.80).

One observational study[171] evaluated the temporal relation between clopidogrel cessation and stent thrombosis and found that clopidogrel cessation was an independent predictor of cumulative stent thrombosis at 1 month (OR 4.5; 95% CI, 2.0 to 10.4) and at 6 months (OR 2.4; 95% CI, 1.2 to 4.9) but not at 1 year (OR 1.7; 95% CI, 0.9 to 3.1). Another observational study[168] assessing the change in risk of stent thrombosis over time based on DAPT found that the cumulative incidence of stent thrombosis was 12.36 percent among those who discontinued clopidogrel at 6 months and 0.58 percent among those still on clopidogrel treatment. One observational study[169] evaluating DAPT for more than 12 months versus less than or equal to 12 months found no difference in the number of stent thromboses that occurred at 3 years between the two groups (14 vs. 7, log rank p=0.097).

The SOE was rated insufficient due to heterogeneity of DAPT duration and imprecision. The findings in observational studies were consistent that discontinuation of clopidogrel within 30 days or 6 months was associated with higher rates of stent thrombosis, and the findings from RCTs consistently showed that discontinuation of clopidogrel at 1 or more years showed no statistically significant differences in rates of stent thrombosis.

Effect on Major Bleeding at 1 and 2 Years

Three good-quality RCTs[136,198,199] with 5572 patients reported major bleeding results. One[199] assessing DAPT for 1 month versus 12 months found no significant increase in the risk of major bleeding among patients treated with DAPT at 1 year (6.7% vs. 8.8%, p= 0.7). The other[198] evaluating DAPT for 6 months versus 24 months, showed a significantly lower rate of TIMI major bleeding at 2 years among patients treated with DAPT for 6 months (0.6% vs. 1.6%; OR 0.38; 95% CI, 0.15 to 0.97, p=0.041). The third RCT[136], assessing DAPT for 6 months versus 12 months found no difference in the rate of major bleeding between the two treatment arms (0.3% vs. 0.6%; HR 0.50; 95% CI, 0.09 to 2.73, p=0.42) at 1 year. The SOE was rated insufficient for major bleeding outcomes based on the differences in the treatment durations that were compared and on inconsistent and imprecise results.

Effect on Minor Bleeding at 1 and 2 Years

Two good-quality RCTs[198,199] with 4129 patients reported minor bleeding results. One[199] assessing DAPT for 1 month versus 12 months found no difference in the rate of minor bleeding between the two treatment arms (5.6% vs. 5.3%, p= 0.84). Similarly, the other[198] comparing DAPT for 6 months with 24 months found no difference in the rate of TIMI minor bleeding at 2 years between the two treatment arms (0.9% vs. 1.1%; OR 0.82; 95% CI, 0.34 to 1.94, p=0.66). The SOE was rated insufficient based on imprecise results.

Findings by Subgroup (KQ 3d)

Four studies[136,169,183,198] (two good-quality RCTs; one good-quality, one fair observational) reported variations in treatment effectiveness by subgroup. Subgroups analyzed were diabetes (3 studies), age (2), sex (1), chronic kidney disease (1), and stent type (2). Table H-3 in Appendix H presents the results data for these subgroups.

Diabetes

Three studies[136,169,198] reported a composite outcome in the diabetic subgroup. One RCT[198] evaluating DAPT for 6 months versus 24 months showed no differences in the rate of composite outcomes (all-cause mortality, nonfatal MI, or stroke) at 2 years, both in the group of patients

with diabetes (HR 0.85; 95% CI, 0.53 to 1.38) and without diabetes (OR 1.06; 95% CI, 0.76 to 1.50). The other RCT[136] found a significantly higher rate of composite outcome (cardiovascular death, nonfatal MI, or target vessel revascularization) at 12 months in patients with diabetes receiving 6-month DAPT versus 12-month DAPT (9.1% vs. 3.0%; HR 3.16; 95% CI, 1.42 to 7.03, p=0.005). The rate of composite outcome (cardiovascular death, nonfatal MI, or target vessel revascularization) at 1 year in patients without diabetes was significantly lower among those receiving 6-month DAPT versus 12-month DAPT (2.3% vs. 5.1%; HR 0.44; 95% CI, 0.21 to 0.94, p=0.03). In the other study[169] assessing DAPT for more than 12 months versus less than or equal 12 months, found no difference in the rate of the composite outcome (all-cause mortality or nonfatal MI) at 3 years between the two treatment groups among patients with diabetes (12% vs. 16%; HR 0.85; 95% CI, 0.51 to 1.43, p=0.55).

Age

Two RCTs reported a composite outcome by age subgroups (<65 vs. ≥65 years). One study[198] assessing DAPT for 6 months versus 24 months reported no significant differences in the rate of composite outcomes (cardiovascular death, nonfatal MI, or stroke) at 2 years in either age group (<65 years, HR 0.57; 95% CI, 0.28 to 1.16; and ≥ 65 years, OR 1.12; 95% CI, 0.82 to 1.51). The other RCT[136] evaluating DAPT for 6 months versus 12 months similarly found no difference in the rate of composite outcome (cardiovascular death, nonfatal MI, target vessel revascularization) at 1 year in either age group (<65 years, HR 1.61; 95% CI, 0.78 to 3.31; and ≥ 65 years, HR 0.83; 95% CI, 0.42 to 1.65).

Sex

One RCT[198] assessing DAPT for 6 months versus 24 months, reported a composite outcome (cardiovascular death, nonfatal MI, or stroke) at 2 years by sex. No significant differences in the rate of composite outcomes were observed in either group (women, HR 1.00; 95% CI, 0.60 to 1.68; and men, OR 1.09; 95% CI, 0.77 to 1.29).

Chronic Kidney Disease

One RCT[198] assessing DAPT for 6 months versus 24 months, reported a composite outcome (cardiovascular death, nonfatal MI, or stroke) at 2 years by renal function (creatinine clearance >60 mL/min vs. creatinine clearance ≤60 mL/min). No significant differences in the rate of composite outcomes were observed in either renal function group (creatinine clearance >60 mL/min, HR 0.90; 95% CI, 0.58 to 1.38; and creatinine clearance ≤60 mL/min, OR 1.14; 95% CI, 0.78 to 1.65).

Stent Type

One RCT[198] evaluating DAPT for 6 months versus 24 months, reported a composite outcome (cardiovascular death, nonfatal MI, or stroke) at 2 years by stent type (BMS and DES). No significant differences in the rate of composite outcomes were observed in either stent type groups (BMS, HR 1.13; 95% CI, 0.68 to 1.86; and DES, 0.93; 95% CI, 0.67 to 1.30).

Two studies[183,198] reported outcomes by stent type. One study[183] assessing the effect of clopidogrel discontinuation on all-cause mortality at a median of 538 days, reported data by stent type (DES and BMS). The study found that among patients who discontinue clopidogrel within the first 6 months after discharge, the rate of all-cause mortality was higher compared with those who continue clopidogrel treatment, both in the BMS group (HR 2.65; 95% CI, 1.59 to 4.42) and DES group (HR 2.0; 95% CI, 1.06 to 3.75). Similarly, among patients who discontinue

clopidogrel within the first 6 months after discharge, the rate of nonfatal MI was higher compared with those who continued clopidogrel treatment both in the BMS group (HR 1.26; 95% CI, 0.58 to 2.74) and the DES group (HR 3.57; 95% CI, 1.13 to 11.3).

Summary of Results for Short-Term Versus Long-Term Dual Antiplatelet Therapy

In our analysis of short-term versus long-term DAPT use, we aimed to address the question about the optimal duration of therapy by comparing short-term to long-term use of clopidogrel. The variations in the duration of therapy and the definitions of short-term and long-term treatment made meta-analysis impossible. Evidence was insufficient for the outcomes of composite ischemic events, all-cause mortality (7 studies), cardiovascular mortality (4 studies), nonfatal MI (6 studies), stroke (3 studies), and revascularization (4 studies). Rates of stent thrombosis (6 studies) were higher when DAPT was stopped within 30 days or 6 months, but the differences between therapies beyond 6 months were nonsignificant, thus the evidence was rated insufficient. Stent thrombosis rates may vary based on use of bare metal or drug-eluting stents. There was insufficient evidence that clopidogrel duration had an effect on major bleeding outcomes, with one RCT showing a significantly lower rate of major bleed with 6-month treatment compared with 24-month therapy, another RCT showing no significant increase in major bleed among patients treated for 28 days compared with 12 months, and a third RCT showing no difference in major bleeding among patients treated for 6 months compared with 12 months. There was also insufficient evidence that clopidogrel duration had an effect on minor bleeding rates, which were similar in the short- and long-term duration groups from the same RCTs. Four studies (two good-quality RCTs and two observational of good and fair quality) reported variations in treatment effectiveness by subgroup. Subgroups analyzed were diabetes (3 studies), age (2), sex (1), chronic kidney disease (1), and stent type (2). No differences in composite ischemic events were found among the different subgroup comparisons. The SOE was low based on the small number of studies that reported subgroup findings and the imprecise estimates of effect. Detailed SOE ratings are shown in Table 24.

Table 24. Detailed strength of evidence for UA/NSTEMI patients treated with short-term versus long-term dual antiplatelet therapy

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of All-Cause Mortality or Nonfatal MI Within 2 Years					**Insufficient SOE**
4 (34,179)	2 RCTs/Both good quality 2 observational/Both fair quality	Inconsistent	Direct	Imprecise	2 RCTs showed no difference between 6- and 12-month therapy and 6- and 24-month therapy; 1 observational study showed that discontinuation before 6 months increased events; 1 observational study showed increased events within first 3 months of stopping clopidogrel after 1 year of therapy

Table 24. Detailed strength of evidence for UA/NSTEMI patients treated with short-term versus long-term dual antiplatelet therapy (continued)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of All-Cause Mortality or Stroke at 2 Years					**Insufficient SOE**
1 (2013)	RCT/Good quality	NA	Direct	Imprecise	No difference between 6- and 24-month therapy: OR 0.91; 95% CI, 0.66 to 1.26, p=0.57
Composite of All-Cause Mortality, Nonfatal MI, or Revascularization at 6 Months and 1 Year					**Insufficient SOE**
3 (4701)	2 RCTs/1 good quality, 1 fair 1 observational/Fair quality	Consistent	Direct	Imprecise	Both RCTs (1 month vs. 6 months and 6 months vs. 12 months) found similar rates between short- and long-term therapy; the observational study (<3 months vs. 6 months vs. >12 months) showed similar rates across treatment groups in both DES-treated and BMS-treated populations
Composite of All-Cause Mortality, Nonfatal MI, Stroke, or Revascularization at 1 Year					**Insufficient SOE**
1 (1443)	RCT/Good quality	NA	Direct	Imprecise	No difference between 6- and 12-month therapy: HR 0.94, 95% CI, 0.65 to 1.35
Composite of All-Cause Mortality, Nonfatal MI, or Stroke at 6 Months, 1 Year, and 2 Years					**Insufficient SOE**
3 (5133)	3 RCTs/2 good quality, 1 fair	Inconsistent	Direct	Imprecise	2 studies found significant reductions in events from long-term DAPT at 6 months and 1 year; 1 study found no difference between 6- and 24-month therapy

Table 24. Detailed strength of evidence for UA/NSTEMI patients treated with short-term versus long-term dual antiplatelet therapy (continued)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
All-Cause Mortality at 6 Months, 1 Year, and 2 Years					**Insufficient SOE**
7 (38,441)	4 RCTs/2 good quality, 2 fair 3 observational/All fair quality	Inconsistent	Direct	Imprecise	2 RCTs showed a reduction with longer therapy (1 month vs. 6 months) but 1 was statistically significant and the other was not; 1 RCT (6 months vs. 12 months) showed no difference; 1 observational study (<3 months vs. 6 months vs. <12 months) showed lower mortality in DES-treated patients receiving >12 months of therapy, but no difference in the BMS-treated patients; 1 observational study found a higher rate of mortality in those who discontinued clopidogrel within the first 6 months; 1 observational study fund a higher risk of death within the first 90 days of discontinuation after a 12-month treatment
Cardiovascular Mortality at 6 Months, 1 Year, and 2 Years					**Insufficient SOE**
4 (33,728)	3 RCTs/2 good quality, 1 fair 1 observational/Fair quality	Consistent	Direct	Imprecise	All RCTs found similar rates between short-and long-term therapy (1 month vs. 6 months, 6 months vs. 12 months, and 6 months vs. 24 months); 1 observational study found no difference in CV mortality within the first 90 days of discontinuation after a 12-month treatment
Nonfatal MI at 6 Months, 1 Year, and 2 Years					**Insufficient SOE**
6 (9173)	4 RCTs/2 good quality, 2 fair 2 observational/2 fair quality	Consistent	Direct	Imprecise	5 studies (4 RCTs and 1 observational) showed similar rates of MI in short- and long-term therapy groups; 1 observational study showed statistically significant higher risk in DES patients who discontinue clopidogrel within first 6 months

Table 24. Detailed strength of evidence for UA/NSTEMI patients treated with short-term versus long-term dual antiplatelet therapy (continued)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Stroke at 6 Months, 1 Year, and 2 Years					**Insufficient SOE**
3 (4460)	3 RCTs/2 good quality, 1 fair	Consistent	Direct	Imprecise	All RCTs (1 month vs. 6 months, 6 months vs. 12 months, and 6 months vs. 24 months) found similar rates between short-and long-term therapy, but heterogeneity of DAPT duration makes this inconclusive
Revascularization at 6 Months and 1 Year					**Insufficient SOE**
4 (5705)	3 RCTs/1 good quality, 2 fair 1 observational/Fair quality	Consistent	Direct	Imprecise	Rates of revascularization were similar between short- and long-term therapy (1 month vs. 6 months and 6 months vs. 24 months)
Stent thrombosis at 6 Months, 1 Year, and 2 Years					**Insufficient SOE**
6 (15,298)	3 RCTs/2 good quality, 1 fair 3 observational/1 good quality, 1 fair, 1 poor	Consistent	Direct	Imprecise	Rates of stent thrombosis were higher when clopidogrel was stopped within 30 days or 6 months in 2 observational studies; 4 studies (3 RCTs and 1 observational) showed no statistically significant difference in event rates at 1 or 2 years
Major Bleeding at 1 and 2 Years					**Insufficient SOE**
3 (5572)	3 RCTs/All good quality	Inconsistent	Direct	Imprecise	1 RCT (6 months vs. 24 months) showed a statistically significant lower rate of major bleeding with clopidogrel with 6-month treatment; the other 2 RCTs (1 months vs. 12 months and 6 months vs. 12 months) showed no statistically significant difference in rates with 1-year treatment
Minor Bleeding at 1 and 2 Years					**Insufficient SOE**
2 (4129)	2 RCTs/Both good quality	Consistent	Direct	Imprecise	Both RCTs (1 month vs. 12 months and 6 months vs. 24 months) found no difference at 1 and 2 years

BMS = bare metal stent; CI = confidence interval; CV = cardiovascular; DES = drug-eluting stent; MI = myocardial infarction; NA = not applicable; NR = not reported; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/ non-ST elevation myocardial infarction

[a]Consistency cannot be determined because treatment durations were heterogeneous.

4. Antiplatelet Treatments With and Without Use of PPI (KQ 3b)

Thirty-five studies (4 RCTs, 31 observational) evaluated antiplatelet treatments with PPI versus antiplatelets alone in the postdischarge treatment of 340,559 UA/NSTEMI

patients.[14,133,137,139-141,143-150,152-159,161-164,166,167,173,174,177,181,182,197,200] Three of these studies compared esomeprazole with placebo and were included in the analysis; one study compared esomeprazole with famotidine. All other studies evaluated treatment with a PPI (not otherwise specified) versus no PPI when given at hospital discharge in UA/NSTEMI patients.

Of the four RCTs, two (50%) were rated good quality and two (50%) poor. Of the 31 observational studies, 25 (80%) were rated good quality, 3 (10%) fair, and 3 (10%) poor. Sample sizes for individual studies ranged from 72 to 56,406 patients. Study duration ranged from 14 days to 6 years.

The mean age of study participants ranged from 58 to 77 years of age. The proportion of female patients ranged from 1 percent to 76 percent. Four studies (13%) reported the racial and ethnic demographics of study participants. Eleven studies (37%) were conducted within the United States or Canada, with the rest international. Funding source was reported in 19 studies (63%), with 4 studies (13%) funded by an industry source. Table G-15 in Appendix G contains the results reported by each study.

The PPI studies were grouped into the following two comparisons:

4a. Dual antiplatelet therapy with and without PPI (4 RCTs of omeprazole; 1 observational study of omeprazole; 29 observational studies of any PPI)

4b. Aspirin monotherapy (i.e., no clopidogrel) with and without PPI (two observational studies of any PPI)

4a. Dual Antiplatelet Therapy With and Without PPI

All 35 studies (4 RCTs, 31 observational) assessed the effect of antiplatelet treatments with PPI versus antiplatelets alone (no PPI) in the postdischarge treatment of UA/NSTEMI patients. Five of these, consisting of 4 RCTs[14,140,144,177] (2 good quality, 2 poor) and one good-quality observational study[164] in 5183 UA/NSTEMI patients, assessed the effect of omeprazole when added to dual antiplatelet treatment. One study was an RCT comparing omeprazole with famotidine for the prevention of gastrointestinal (GI) bleeding in patients with UA/NSTEMI.[140] The other 30 observational studies assessed the effect of any type of PPI versus no PPI in the postdischarge treatment of UA/NSTEMI patients.

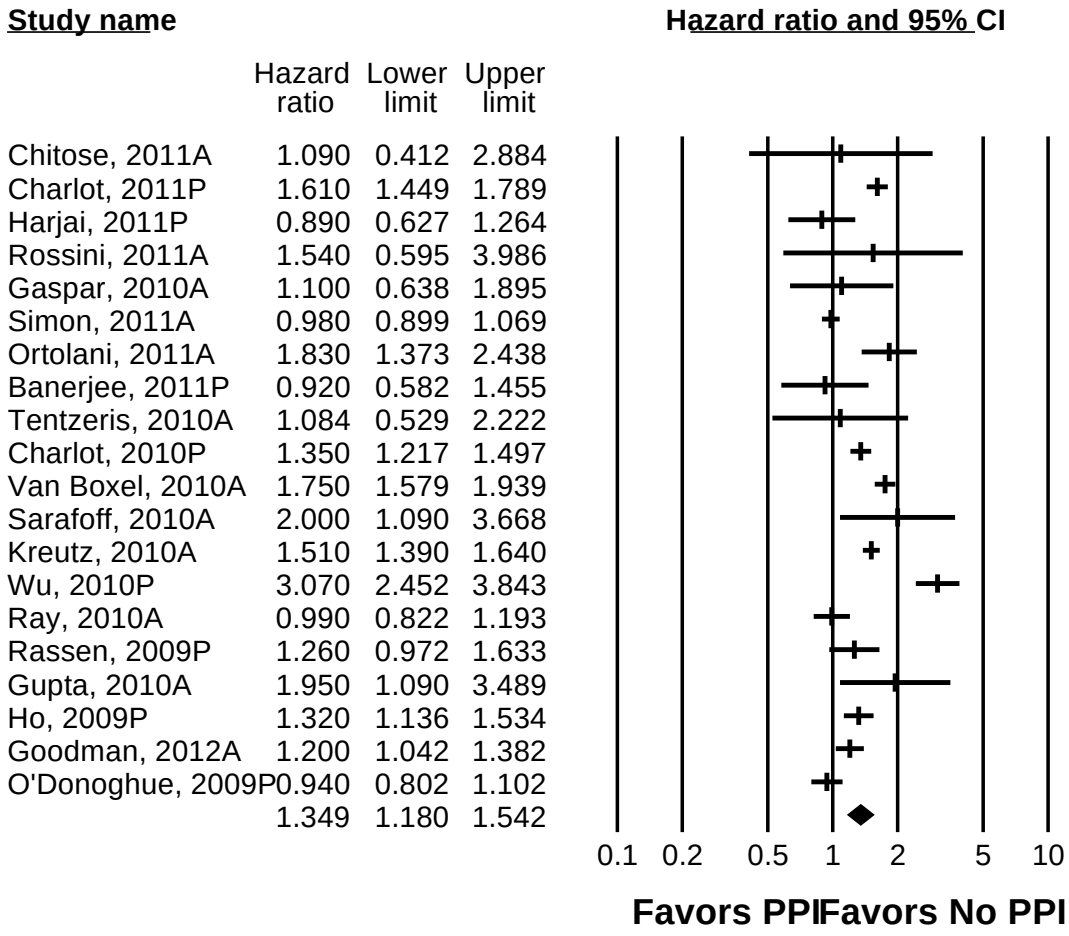
Effect on Composite Ischemic Endpoints at About 1 Year

Two good-quality RCTs and one good-quality observational study of omeprazole reported a composite outcome within about 1 year of enrollment (6 to 18 months). One RCT[140] comparing omeprazole with famotidine reported a nonsignificant difference in the rate of composite outcomes (cardiovascular mortality, nonfatal MI, or stroke) at 4 months between the two treatment groups (4.3% vs. 3.4%, p=0.7788). One RCT[14] comparing omeprazole with placebo reported a nonsignificant difference in the rate of composite outcomes (cardiovascular mortality, nonfatal MI, stroke, or revascularization) at 6 months between the two treatment arms (4.9% vs. 5.7%; HR 0.99; 95% CI, 0.68 to 1.44, p=0.96). Similarly, an observational study[164] comparing omeprazole with placebo reported a nonsignificant difference in the rate of composite outcomes (cardiovascular mortality or nonfatal MI) at 12 months between the two treatment arms (10% vs. 9.7%; unadjusted HR 1.1; 95% CI, 0.6 to 1.8, p=0.89).

Twenty observational studies (18 good quality, 2 fair) reported the effect of any PPI on the composite endpoint of all-cause mortality, stroke, or MI at 6 to 18 months.[139,143,145-150,153,154,156-159,163,166,167,173,197,200] Of these studies, 10 reported only standard adjusted results, 3 reported only propensity-adjusted results, and 7 reported both. We first did a meta-analysis that compared the two types of estimates. The overall estimate for the standard adjusted hazard ratios was 1.40

whereas the overall estimate for the propensity-adjusted hazard ratios was 1.34. The chi-square test for the difference was 0.111 for 1 degree of freedom, p=0.739. Next we did a meta-analysis using the propensity-adjusted hazard ratio (P) when it was available and the standard adjusted hazard ratio (A) when the propensity-adjusted was not available. The result of this analysis is shown in Figure 40.

Figure 40. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on composite endpoint at about 1 year



A = standard adjusted hazard ratio; CI = confidence interval; P = propensity-adjusted hazard ratio; PPI = proton pump inhibitor

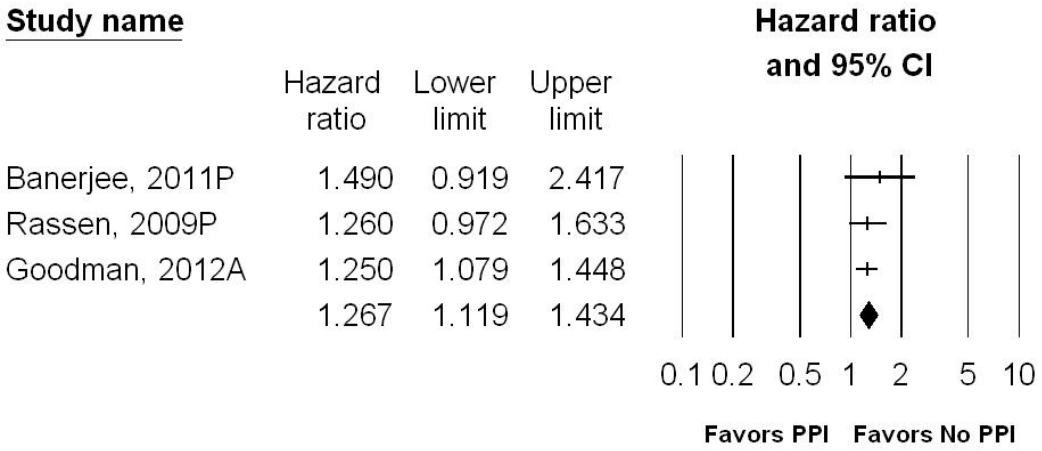
The random-effects combined estimate was 1.35 (95% CI, 1.18 to 1.54). The result was highly significant (p<0.001). The Q-value for the analysis was 196.64 for 19 degrees of freedom (p<0.001). The I^2 was 90.34. Thus there was very significant heterogeneity. The SOE was rated low that favors no PPI for composite ischemic outcomes based on two RCTs and one observational study of omeprazole that failed to show a difference in events and the meta-analysis of 20 observational studies of nonspecific PPI that demonstrated significant heterogeneity, despite inconsistent and precise results.

Effect on Composite Endpoint of All-Cause Mortality or Myocardial Infarction at About 1 Year

Three good-quality observational studies with 60,389 patients reported the effect of any PPI on all-cause mortality or MI at about 1 year (6 to 18 months).[150,166,197] Of these studies, one

reported only standard adjusted results, and two reported both standard adjusted results and propensity-adjusted results. We first did a meta-analysis that compared the two types of estimates. The overall estimate for the standard adjusted hazard ratios was 1.23 whereas the overall estimate for the propensity-adjusted hazard ratios was 1.31. The chi-square test for the difference was 0.265 for 1 degree of freedom, p=0.607. Next we did a meta-analysis using the propensity-adjusted hazard ratio (P) when it was available and the standard adjusted hazard ratio (A) when the propensity-adjusted was not available. The result of this analysis is shown in Figure 41.

Figure 41. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on all-cause mortality or myocardial infarction at about 1 year



CI = confidence interval; PPI = proton pump inhibitor

The random-effects combined estimate was 1.27 (95% CI, 1.12 to 1.43). The result was highly significant (p<0.001). The Q-value for the analysis was 0.466 for 2 degrees of freedom (p=0.792). The I^2 was 0.00. Thus there was no evidence of heterogeneity. The SOE was rated moderate that favors no PPI for composite ischemic outcomes based on consistent and precise results from three observational studies.

Effect on All-Cause Mortality Within First 3 Months

Three observational studies (all good quality; 8943 patients) reported the effect of any PPI versus no PPI on all-cause mortality within the first 3 months after hospital discharge for a UA/NSTEMI event. One study[148] reported no difference in the rate of in-hospital all-cause mortality (3.0% vs. 4.0%, adjusted OR 1.04; 95% CI, 0.61 to 1.77). Another study[157] reported significant increase in the risk of all-cause mortality at 30 days among patients treated with PPI (2.6% vs. 0.9%, adjusted HR 2.2; 95% CI, 1.1 to 4.3). A case-control study[174] found no difference in the risk of all-cause mortality at 3 months among UA/NSTEMI patients treated with PPI versus those not treated with PPI (adjusted OR 0.82; 95% CI, 0.57 to 1.18). The SOE was rated insufficient for all-cause mortality within the first 3 months based on inconsistent and imprecise results.

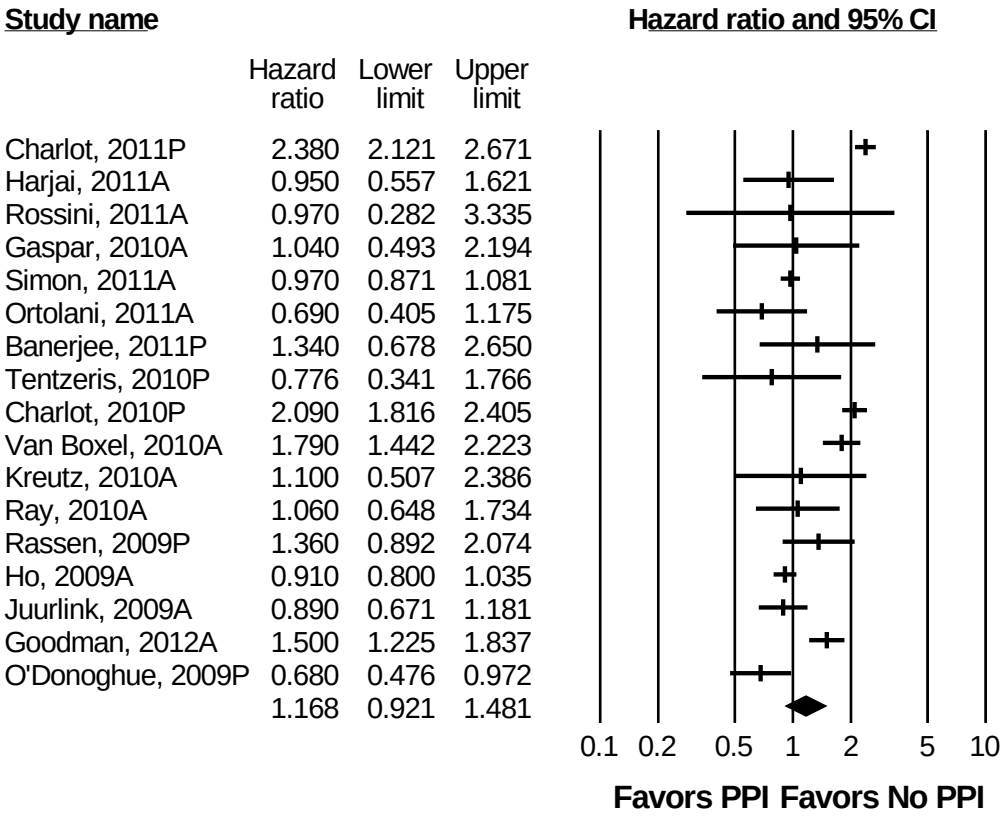
Effect on All-Cause Mortality at About 1 Year

Three studies of omeprazole (2 RCT, 1 observational) reported all-cause or cardiovascular mortality within about 1 year of enrollment (6 to 18 months). One poor-quality RCT[177]

comparing omeprazole with placebo in 237 acute MI patients reported a significant difference in the rate of all-cause mortality at 14 days favoring omeprazole (3.5% versus placebo 10.6%, p=0.035). One good-quality RCT[14] comparing omeprazole with placebo in a mixed population of 3,873 ACS and PCI patients reported a nonsignificant difference in the rate of all-cause mortality at 6 months between the two treatment arms (omeprazole 4%, placebo 5%). Similarly, a good-quality observational study[164] comparing omeprazole with placebo in a mixed population of 558 stable angina and ACS patients reported a nonsignificant difference in the rate of cardiovascular mortality at 12 months between the two treatment arms (omeprazole 3.5% vs. placebo 3.2%; unadjusted HR 1.10; 95% CI, 0.44 to 2.84, p=0.84).

Seventeen observational studies (16 good quality, 1 fair) reported the effect of any PPI on all-cause mortality at 6 to 18 months.[143,145-150,153,154,156,158,163,166,173,174,197,200] Of these studies, 11 reported only standard adjusted results, 2 reported only propensity-adjusted results, and 4 reported both. We first did a meta-analysis that compared the two types of estimates. The overall estimate for the standard adjusted hazard ratios was 1.18 whereas the overall estimate for the propensity-adjusted hazard ratios was 1.44. The chi-square test for the difference was 1.271 for 1 degree of freedom, p=0.258. Next we did a meta-analysis using the propensity-adjusted hazard ratio (P) when it was available and the standard adjusted hazard ratio (A) when the propensity-adjusted was not available. The result of this analysis is shown in Figure 42.

Figure 42. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on all-cause mortality at about 1 year



A = standard adjusted hazard ratio; CI = confidence interval; P = propensity-adjusted hazard ratio; PPI = proton pump inhibitor

The random-effects combined estimate was 1.17 (95% CI, 0.92 to 1.48). The result was not significant (p=0.20). The Q-value for the analysis was 243.34 for 16 degrees of freedom (p<0.000). The I^2 was 93.425. There was evidence of extreme heterogeneity. The SOE was rated moderate for no difference for all-cause mortality based on two RCTs and one observational study of omeprazole that showed no difference in events or favored omeprazole and the meta-analysis of observational studies of nonspecific PPI that demonstrated significant heterogeneity and nonsignificant findings.

Effect on All-Cause Mortality at 6 Years

Only one good-quality observational study of 23,200 patients[150] reporting the effect of any PPI on all-cause mortality 6 years after hospital discharge for a UA/NSTEMI event, found an increase of all-cause mortality among patients treated with PPI (26.8% vs. 21.4%, adjusted HR 1.32; 95% CI, 1.00 to 1.73). The SOE was rated low that favors no PPI for all-cause mortality at 6 years based on one large observational study.

Effect on Cardiovascular Mortality at 1 Year

Three good-quality observational studies[153,154,197] with 76,184 patients reported the effect of any PPI use on cardiovascular mortality at 1 year. Two studies assessing PPI versus no PPI in patients with UA/NSTEMI found a statistically significant increase in the risk of cardiovascular mortality at 1 year among patients treated with PPI (6.0% vs. 4.6%, adjusted HR 1.42; 95% CI, 1.14 to 1.76[197] and adjusted HR 1.57; 95% CI, 1.36 to 1.82[154]). Another study[153] assessing PPI versus no PPI in patients with UA/NSTEMI found no difference in the rate of cardiovascular mortality between the two treatment arms (1.2% vs. 1.9%, adjusted HR 0.56; 95% CI, 0.21 to 1.55). The SOE was rated insufficient for cardiovascular mortality at 1 year based on inconsistent and imprecise findings.

Effect on Nonfatal Myocardial Infarction Within First 3 Months

Three good-quality observational studies with 8943 patients reported the effect of PPIs on nonfatal MI within the first 3 months after hospital discharge for a UA/NSTEMI event. Two studies[148,157] comparing PPI versus no PPI in patients with UA/NSTEMI, reported a nonsignificant difference in the rate of nonfatal MI in-hospital[148] (2.0% vs. 1.4%, adjusted OR 1.15; 95% CI, 0.57 to 2.32) and at 30 days[157] (3.0% vs. 2.0%, adjusted HR 1.3; 95% CI, 0.8 to 2.3). A case-control study[174] found an increased risk of nonfatal MI events at 3 months among UA/NSTEMI patients treated with PPI versus those not treated with PPI (adjusted OR 1.27; 95% CI, 1.03 to 1.57). The SOE was rated insufficient for nonfatal MI within the first 3 months based on inconsistent and imprecise findings.

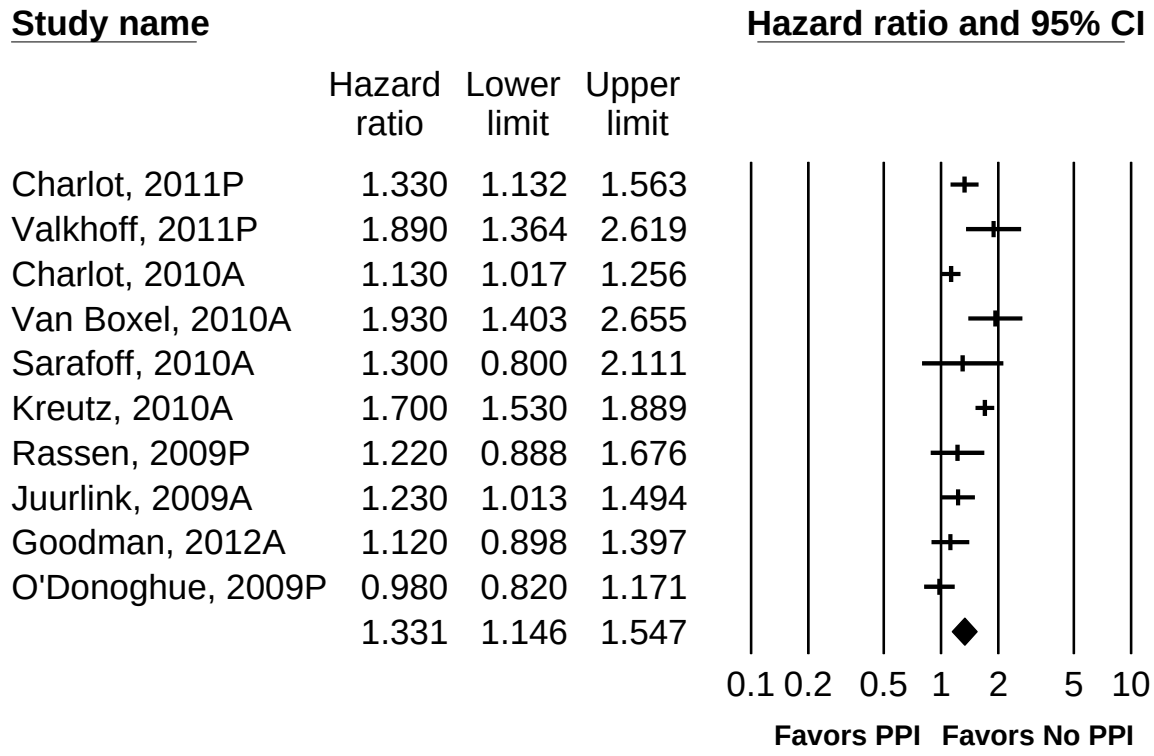
Effect on Nonfatal Myocardial Infarction at About 1 Year

Two studies (1 good-quality RCT, 1 good-quality observational) of omeprazole[14,164] reported nonfatal MI, one at 6 months and one at 1 year. The RCT[14] reporting the event at 6 months found a nonsignificant reduction of nonfatal MI events (1.2% vs. 1.5%; HR 0.92; 95% CI, 0.44 to 1.90, p=0.81) among patients treated with omeprazole. Similarly, the observational study[164] found no effect of omeprazole versus placebo on nonfatal MI (6.5% vs. 6.5%; HR 1.0; 95% CI, 0.5 to 1.9).

Ten observational studies (8 good quality, 1 fair, 1 poor) reported the effect of any PPI on nonfatal MI at about 1 year (6 to 18 months).[143,152,154,156-158,166,174,197,200] Of these studies, six reported only standard adjusted results, three reported both standard adjusted results and propensity adjusted-results, and one reported only propensity-adjusted results. We first did a

meta-analysis that compared the two types of estimates. The overall estimate for the standard adjusted hazard ratios was 1.352 whereas the overall estimate for the propensity adjusted hazard ratios was 1.33. The chi-square test for the difference was 0.005 for 1 degree of freedom, p=0.941. Next we did a meta-analysis using the propensity-adjusted hazard ratio (P) when it was available and the standard adjusted hazard ratio (A) when the propensity-adjusted was not available. The result of this analysis is shown in Figure 43.

Figure 43. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on nonfatal myocardial infarction at about 1 year



A = standard adjusted hazard ratio; CI = confidence interval; P = propensity-adjusted hazard ratio; PPI = proton pump inhibitor

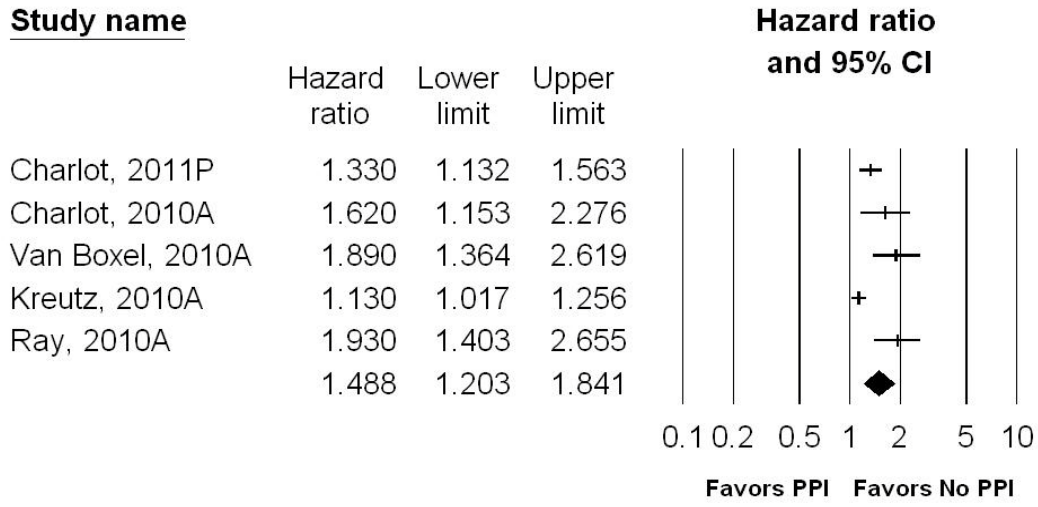
The random-effects combined estimate was 1.33 (95% CI, 1.15 to 1.55). The result was highly significant (p<0.001).The Q-value for the analysis was 54.103 for 9 degrees of freedom (p<0.001). The I^2 was 83.365. There was evidence of extreme heterogeneity. The SOE was rated low that favors no PPI for nonfatal MI at 1 year based on one RCT and one observational study of omeprazole that showed no difference in events or favored omeprazole and the meta-analysis of observational studies of nonspecific PPI that demonstrated significant heterogeneity, despite inconsistent and precise results.

Effect on Stroke at 30 Days and About 1 Year

Two RCTs (1 good quality, 1 poor) of omeprazole reported cerebrovascular events; one reported a transient ischemic attack (TIA) at 30 days,[144] and the other reported stroke events at 6 months.[14] Nonsignificant differences were found in the rate of TIA events in the poor-quality study[144] and in the rate of stroke events in the good-quality RCT[14] between patients treated with omeprazole versus those receiving placebo (TIA 2.3% vs. 1.0%; stroke 0.2% vs. 0.3%).

Five observational studies (4 good quality, 1 fair) reported the effect of any PPI on stroke at about 1 year (6 to 18 months).[143,154,156,158,163] Of the five studies, four reported only standard adjusted results, and one reported both standard adjusted results and propensity-adjusted results. We did a meta-analysis using the propensity-adjusted hazard ratio (P) when it was available and the standard adjusted hazard ratio (A) when the propensity-adjusted was not available. The result of this analysis is shown in Figure 44.

Figure 44. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on stroke at about 1 year



A = standard adjusted hazard ratio; CI = confidence interval; P = propensity-adjusted hazard ratio; PPI = proton pump inhibitor

The random-effects combined estimate was 1.49 (95% CI, 1.20 to 1.84). The result was highly significant (p<0.001). The Q-value for the analysis was 16.258 for 4 degrees of freedom (p=0.001). The I^2 was 70.230. There was evidence of extreme heterogeneity. The SOE was rated low favoring no PPI for stroke at about 1 year based on two RCTs of omeprazole that showed no difference in events and the meta-analysis of observational studies of nonspecific PPI that demonstrated a benefit of no PPI but had significant heterogeneity, despite consistent and precise results.

Effect on Revascularization at 6 Months, 1 Year, and 4 Years

One good-quality RCT of omeprazole[14] and one good-quality observational study of PPI versus no PPI[166] with 22,326 patients reported revascularization results at 6 months. The RCT[14] found a similar rate of revascularization among patients discharged on omeprazole compared with those discharged without omeprazole (4.0% vs. 4.6%). The observational study[166] reporting the effect of PPIs on revascularization after hospital discharge for a UA/NSTEMI event, found no difference in the risk of revascularization at 6 months among patients treated with PPI compared with those not treated with PPI (adjusted HR 0.97; 95% CI, 0.79 to 1.21). The SOE was rated low for revascularization at 6 months based on imprecise findings.

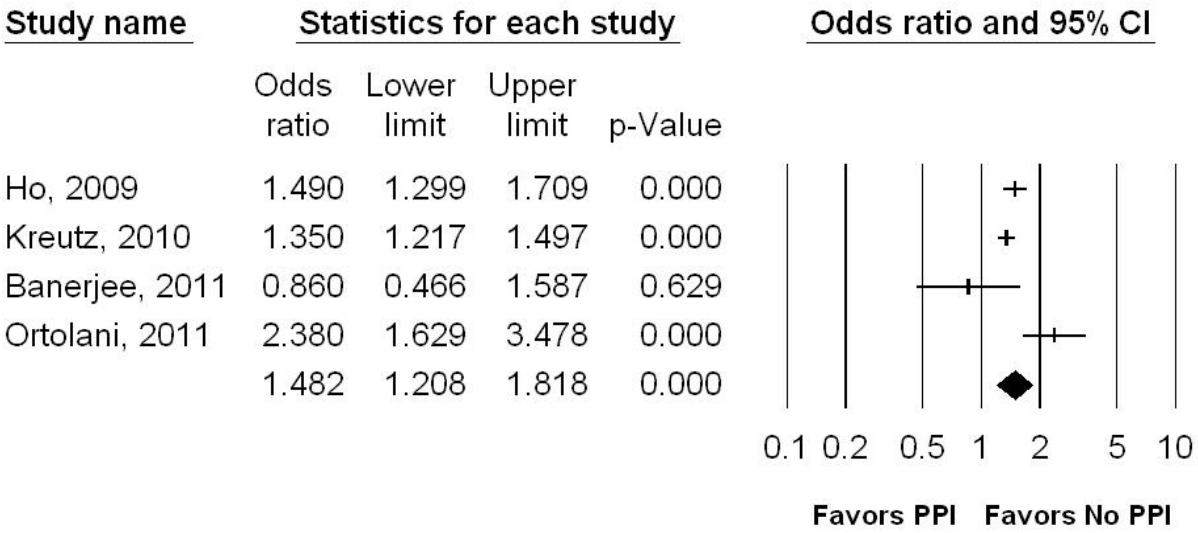
One good-quality observational study of omeprazole reported repeat revascularization at 1 year[164] in 588 UA/NSTEMI patients and found a similar rate of revascularization among patients discharged on omeprazole compared with those discharged without omeprazole (9.4% vs. 8.9%).

A random-effects meta-analysis of four observational studies of any PPI[149,150,158,173] (all good quality), including 52,576 UA/NSTEMI patients reporting revascularization at 1 year reported

standard adjusted results, and 1 study additionally reported propensity adjusted results.[150] We first performed a meta-analysis where we preferentially used the propensity adjusted hazard ratio when available but used the standard adjusted hazard ratio when it was the only one available. The result of the analysis is shown in Figure 45.

The fair-quality observational study[167] of 315 UA/NSTEMI patients reporting the effect of PPI on revascularization (TVR) after hospital discharge for a UA/NSTEMI event found no difference in the risk of revascularization at 4 years among patients treated with PPI compared with those not treated with PPI (29.0% vs. 22%, adjusted HR 1.57; 95% CI, 0.80 to 3.03). The SOE was rated insufficient for revascularization at 4 years based on imprecise findings.

Figure 45. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on revascularization at 1 year



CI = confidence interval; PPI = proton pump inhibitor

The random-effects combined estimate was 1.48 (95% CI, 1.21 to 1.82). The Q-value for the analysis was 11.092 for 3 degrees of freedom (p=0.011). The I^2 was 72.955. There was evidence of heterogeneity which appeared to be due to the Banerjee study. As a sensitivity analysis, we performed a meta-analysis where we used only the adjusted hazard ratio from the Banerjee study. The random-effects combined estimate was 1.438 (95% CI, 1.215 to 1.703).The Q-value for the analysis was 13.347 for 3 degrees of freedom (p=0.004). The I^2 was 77.523. There was evidence of heterogeneity that was due to the Ortolani study estimate.

The SOE was rated low that favors no PPI for revascularization at 1 year based on one observational study of omeprazole that showed no difference in events and the meta-analysis of four observational studies of nonspecific PPI that demonstrated significant heterogeneity.

Effect on Stent Thrombosis at 30 Days

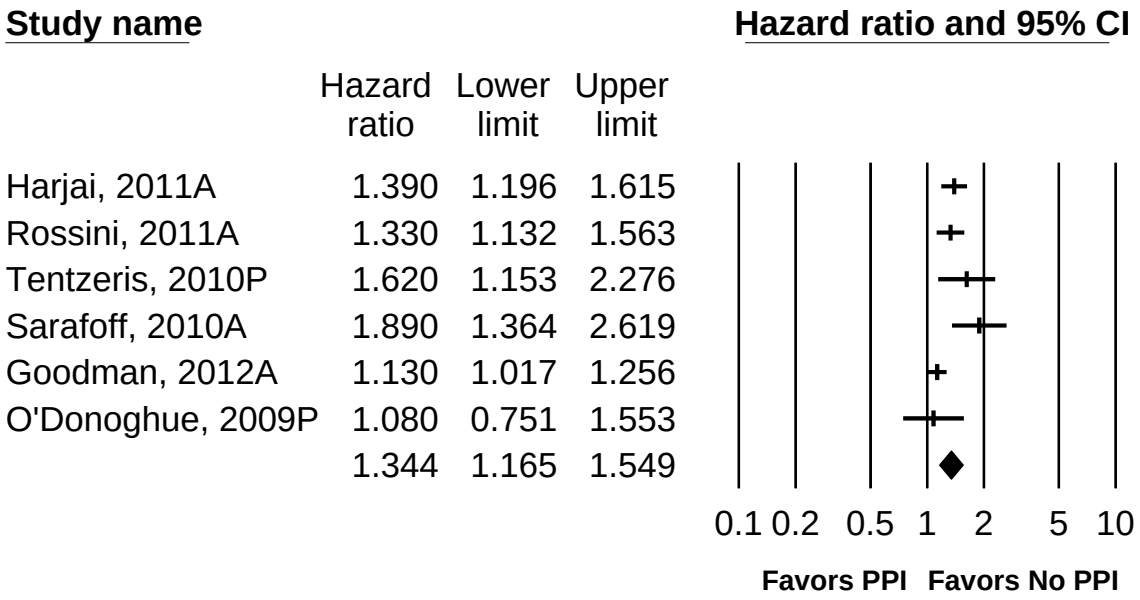
Only one good-quality observational study[157] of 3408 patients reporting the effect of PPI on stent thrombosis at 30 days after hospital discharge for a UA/NSTEMI event, found no significant difference in the rate of stent thrombosis between the two treatment arms (PPI 1.1% vs. 0.5%, adjusted HR 1.8; 95% CI, 0.7 to 4.7). The SOE was rated insufficient for stent thrombosis at 30 days based on imprecise findings.

Effect on Stent Thrombosis at About 1 Year

Two studies (1 good-quality RCT, 1 good-quality observational) of omeprazole reported stent thrombosis (definite, possible, probable) at 6 months[14] and 1 year[164] after hospital discharge for UA/NSTEMI. In the RCT, two cases of definite or probable stent thrombosis occurred in the placebo group and no cases occurred in the omeprazole group.[14] A nonsignificant difference in the rate of stent thrombosis was found among patients discharged on omeprazole compared with those discharged without omeprazole (8.8% vs. 5.8%; HR 1.1; 95% CI, 0.7 to 1.8) at 1 year in the observational study.[164]

Six good-quality observational studies reported the effect of any PPI on stent thrombosis at about 1 year (6 to 18 months).[145,146,153,157,197,200] Of these studies, four reported only standard adjusted results, and two reported only propensity-adjusted results. We first did a meta-analysis that compared the two types of estimates. The overall estimate for the standard adjusted hazard ratios was 1.35 whereas the overall estimate for the propensity-adjusted hazard ratios was 1.33. The chi-square test for the difference was 0.005 for 1 degree of freedom, p=0.941.Next we did a meta-analysis using the propensity-adjusted hazard ratio (P) when it was available and the standard adjusted hazard ratio (A) when the propensity-adjusted was not available. The result of the analysis is shown in Figure 46.

Figure 46. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on stent thrombosis at about 1 year



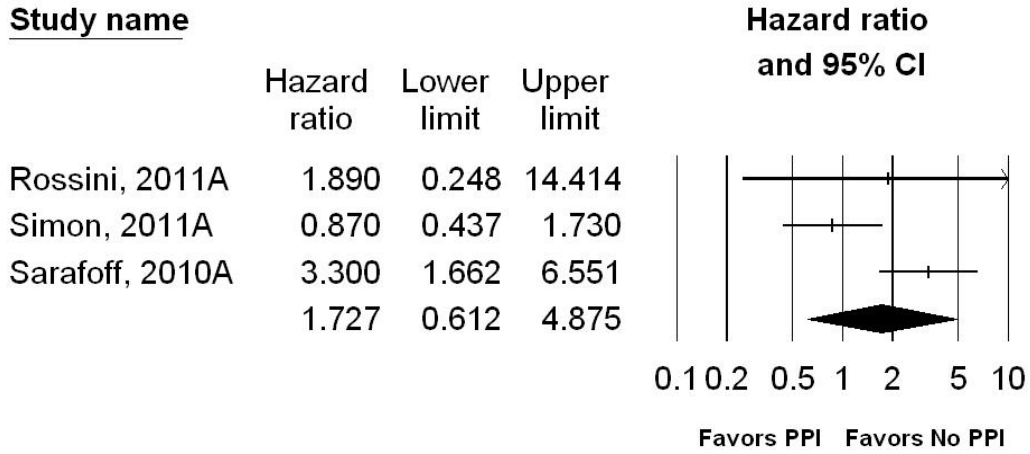
A = standard adjusted hazard ratio; CI = confidence interval; P = propensity-adjusted hazard ratio; PPI = proton pump inhibitor

The random-effects combined estimate was 1.34 (95% CI, 1.17 to 1.55). The result was highly significant (p<0.001). The Q-value for the analysis was 14.845 for 5 degrees of freedom (p=0.011). The I^2 was 66.318. There was evidence of heterogeneity. The SOE was rated low that favors no PPI for stent thrombosis at 1 year based on one RCT and one observational study of omeprazole that showed no difference in events and the meta-analysis of observational studies of nonspecific PPI that demonstrated heterogeneity, despite inconsistent and precise results.

Effect on Major Bleeding at 30 Days

Three good-quality observational studies with 7498 patients reported the effect of any PPI on major bleeding at 30 days.[146,148,157] All three studies reported only standard adjusted (A) results. We did a meta-analysis of these studies as shown in Figure 47.

Figure 47. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on major bleeding at 30 days



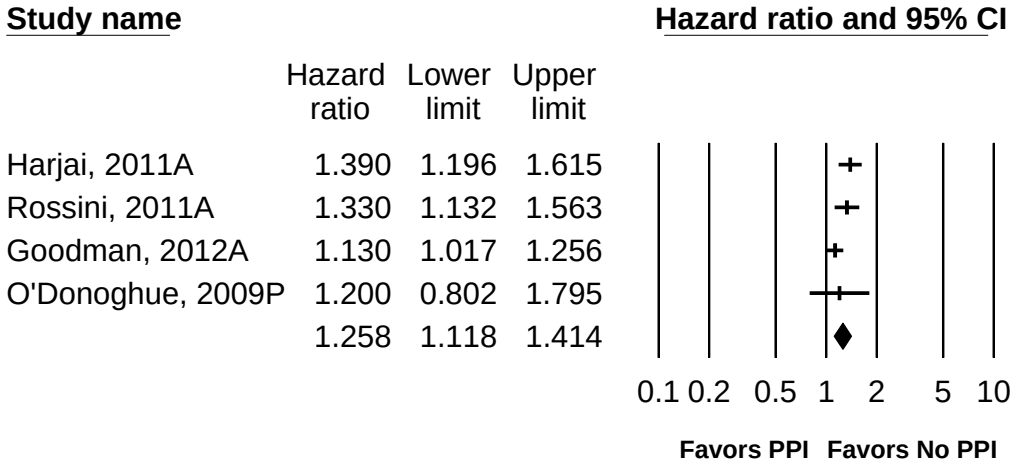
A = standard adjusted hazard ratio; CI = confidence interval; P = propensity-adjusted hazard ratio; PPI = proton pump inhibitor

The random-effects combined estimate was 1.73 (95% CI, 0.61 to 4.88). The result was not significant (p=0.302). The Q-value for the analysis was 7.252 for 2 degrees of freedom (p=0.027). The I^2 was 72.422. There was evidence of heterogeneity. The SOE was rated insufficient for major bleeding at 30 days given the inconsistent and imprecise results.

Effect on Major Bleeding at About 1 Year

Four good-quality observational studies with 36,231 patients reported the effect of any PPI on major bleeding at about 1 year (6 to 18 months).[145,146,197,200] Of these studies, three reported only standard adjusted results, and one reported only propensity-adjusted results. We first did a meta-analysis that compared the two types of estimates. The overall estimate for the standard adjusted hazard ratios was 1.27 whereas the overall estimate for the propensity-adjusted hazard ratios was 1.20. The chi-square test for the difference was 0.050 for 1 degree of freedom, p=0.823. Next we did a meta-analysis using the propensity-adjusted hazard ratio (P) when available and the standard adjusted hazard ratio (A) when the propensity-adjusted was not available. The result of the analysis is shown in Figure 48.

Figure 48. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on major bleeding at about 1 year



A = standard adjusted hazard ratio; CI = confidence interval; P = propensity-adjusted hazard ratio; PPI = proton pump inhibitor

The random-effects combined estimate was 1.26 (95% CI, 1.12 to 1.41). The result was highly significant (p <0.0001). The Q-value for the analysis was 5.933 for 3 degrees of freedom (p=0.115). The I^2 was 49.435. There was some evidence of heterogeneity. The SOE was rated low that favors no PPI for major bleeding at about 1 year based on some heterogeneity with consistent results of a direct outcome and a narrow confidence interval.

Effect on Gastrointestinal Bleeding

Four RCTs (two good quality, 2 poor) of omeprazole reported gastrointestinal bleeding during the first year after hospital discharge.[14,140,144,177] One RCT[140] comparing omeprazole with famotidine reported a significantly lower incidence of overt upper GI bleeding at 4 months in the omeprazole group compared with the famotidine group (0.6% vs. 6.1%; HR 0.095; 95% CI, 0.005 to 0.504, p=0.0052). An RCT[177] reported a significantly lower rate of upper GI bleeding at 14 days among patients treated with omeprazole compared with those not receiving omeprazole (5.3% vs. 14.6%, p=0.017). One RCT[144] reported a nonsignificant difference in the rate of overt GI bleeding at 30 days between patients discharged on omeprazole compared with those discharged on placebo (0% vs. 2.0%). Another RCT[14] reported a significantly lower rate of upper GI bleeding at 6 months among patients treated with omeprazole compared with those not receiving omeprazole (1.1% vs. 2.9%; HR 0.34; 95% CI, 0.18 to 0.63, p<0.001).

Four observational studies (three good quality, 1 poor) of any PPI reported GI bleeding with any PPI: two[181,182] in-hospital, and two[139,163] at long term in 23,555 patients. One study[181] assessing the use of PPI versus no PPI, found no difference in the rate of in-hospital GI bleeding between the two treatment groups (0.7% vs. 0.6%, p=0.88). The other study[182] found a significant increase in the rate of in-hospital GI bleeding among patients not receiving PPI compared with those treated with PPI (4.8% vs. 0.6%, p=0.001).

The two studies reporting GI events at longer followup found dissimilar results. One study[139] found no differences in the risk of GI bleeding at 18 months between UA/NSTEMI patients treated with or without PPI (3.5% vs. 3.8%, HR 0.39; 95% CI, 0.04 to 3.26, p=0.38). The other study[163] found a significant reduction in the risk of GI bleeding at 1 year among patients treated with PPI compared with those not treated with PPI (HR 0.50; 95% CI, 0.39 to 0.65).

Given the differences in the timing of followup in the RCTs (14 days, 30 days, 4 months, and 6 months) and the observational studies (in-hospital, 1 year, and 18 months), a meta-analysis was not performed, however the SOE was rated moderate that favors PPI for GI bleeding based on mostly consistent and precise findings from three of four randomized trials.

Effect on Minor Bleeding

One good-quality observational study[146] of 1346 UA/NSTEMI patients evaluating the use of PPI versus no PPI found no differences in the rate of minor bleeding between the two treatments groups both in-hospital (3.5% vs. 3.1%) and at 1 year followup (5.3% vs. 5.4%). The SOE was rated insufficient for minor bleeding outcomes based on imprecise results.

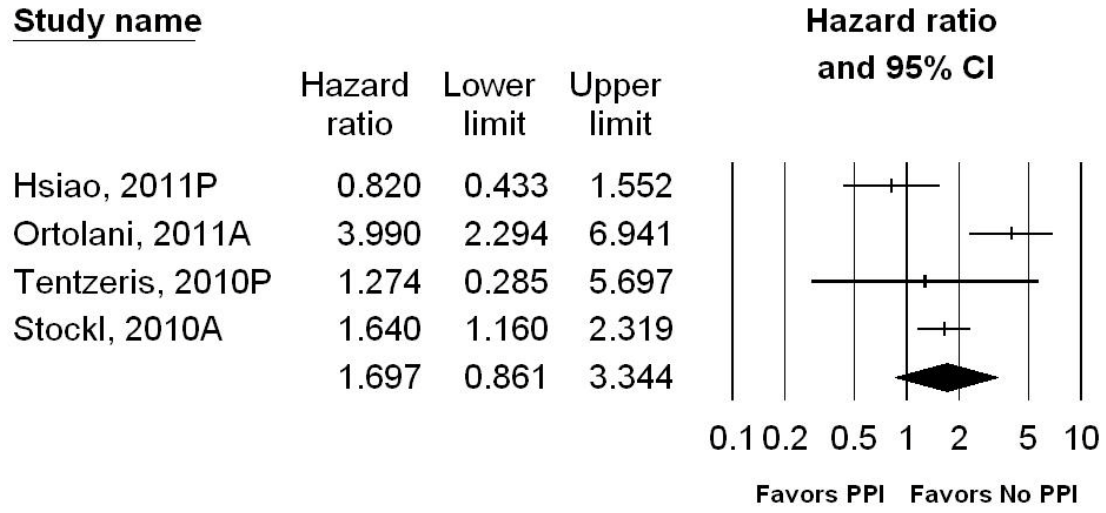
Effect on Rehospitalization at 3 Months

One good-quality observational study[159] of 5862 patients reporting the effect of PPI on rehospitalization after hospital discharge for a UA/NSTEMI event found a significant increase in the rate of rehospitalization at 3 months among patients treated with PPI compared with those not treated with PPI (24.6% vs. 10.1%, adjusted HR 1.32; 95% CI, 1.00 to 1.73). The SOE was rated low that favors no PPI for rehospitalization at 3 months based on significant results of an indirect outcome.

Effect on Rehospitalization at About 1 Year

Four good-quality observational studies with 16,925 patients reported the effect of a PPI on rehospitalization at about 1 year (6 to 18 months).[141,149,153,161] Of these studies, two reported only standard adjusted results, one reported propensity-adjusted result, and one reported both. We first did a meta-analysis that compared the two types of estimates. The overall estimate for the standard adjusted hazard ratios was 1.89 whereas the overall estimate for the propensity-adjusted hazard ratios was 0.93. The chi-square test for the difference was 1.500 for 1 degree of freedom, p=0.221. Next we did a meta-analysis using the propensity-adjusted hazard ratio (P) when it was available and the standard adjusted hazard ratio (A) when the propensity-adjusted was not available. The result of this analysis is shown in Figure 49.

Figure 49. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on rehospitalization at about 1 year



A = standard adjusted hazard ratio; CI = confidence interval; P = propensity-adjusted hazard ratio; PPI = proton pump inhibitor

The random-effects combined estimate was 1.70 (95% CI, 0.86 to 3.34). The result was not significant (p=0.126). The Q-value for the analysis was 14.240 for 3 degrees of freedom (p=0.003). The I^2 was 78.932. There was evidence of heterogeneity. The SOE was rated insufficient for rehospitalization at about 1 year based on observational studies with inconsistent results of an indirect outcome and a wide confidence interval.

Summary of Results for Dual Antiplatelet Therapy With and Without PPI

In our analysis of DAPT with and without concomitant PPI therapy, we found that omeprazole was the most commonly studied PPI in both randomized trials and observational registries. These patient populations were treated with aspirin plus clopidogrel. Event rates were lower in patients who did not receive PPI medication for the various clinical outcomes: composite ischemic endpoints at 1 year, all-cause mortality at 6 years, nonfatal MI at 1 year, stroke at 1 year, revascularization at 1 year, or rehospitalization at 3 months, stent thrombosis at 1 year, and major bleeding at 1 year. There was no difference between groups for all-cause mortality at 1 year and revascularization at 6 months. As expected, GI bleeding was lower in patients treated with PPI medication. The findings were inconsistent (i.e., showing no differences between groups or showing increased event rates in the PPI group), and the evidence base was insufficient for all-cause mortality within the first 3 months, cardiovascular mortality at 1 year, nonfatal MI within the first 3 months, revascularization at 4 years, stent thrombosis at 30 days, major bleeding at 30 days, minor bleeding, and rehospitalization at 1 year.

The detailed SOE ratings are shown in Table 25. Odds ratios less than 1 favor PPI use; odds ratios greater than 1 favor no PPI use.

Table 25. Detailed strength of evidence for UA/NSTEMI patients treated with dual antiplatelet therapy with and without proton pump inhibitor

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite Ischemic Endpoints at About 1 Year					**Low SOE**
23 (272,311)	2 RCTs/Both good quality 21 observational/19 good quality, 2 fair	Inconsistent	Direct	Precise	RCTs of omeprazole showed no difference; however, meta-analysis of observational studies of any PPI showed adj HR 1.35 (1.18 to 1.54), which favors no PPI. The discrepancy between the RCTs and the observational studies makes it difficult to draw a firm conclusion about the effect.
Composite of All-Cause Mortality or MI at About 1 Year					**Moderate SOE**
3 (60,389)	3 observational/All good quality	Consistent	Direct	Precise	Adj HR 1.27 (1.12 to 1.43) Favors no PPI

Table 25. Detailed strength of evidence for UA/NSTEMI patients treated with dual antiplatelet therapy with and without proton pump inhibitor (continued)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
All-Cause Mortality Within First 3 Months					**Insufficient SOE**
3 (8943)	3 observational/All good quality	Inconsistent	Direct	Imprecise	Two studies showed no differences in mortality rates; one study showed a statistically significant increase in mortality in PPI group Adj HR 2.2 (1.1 to 4.3)
All-Cause Mortality at About 1 Year					**Moderate SOE**
20 (264,172)	2 RCTs/1 good quality, 1 poor 18 observational/17 good quality, 1 fair	Consistent	Direct	Precise	RCTs of omeprazole showed no difference or favored omeprazole, and the meta-analysis of observational studies of any PPI showed adj HR 1.17 (0.92 to 1.48) No difference
All-Cause Mortality at 6 Years					**Low SOE**
1 (23,200)	Observational/Good quality	NA	Direct	Precise	Adj HR 1.32 (1.00 to 1.73) Favors no PPI
Cardiovascular Mortality at 1 Year					**Insufficient SOE**
3 (76,184)	3 observational/All good quality	Inconsistent	Direct	Imprecise	Two out of 3 studies showed statistically significant increase in CV mortality in PPI group
Nonfatal MI Within First 3 Months					**Insufficient SOE**
3 (8943)	3 observational/All good quality	Inconsistent	Direct	Imprecise	Two studies showed no statistically significant difference in MI rates; one study showed statistically significant increase in MI events in PPI group
Nonfatal MI at About 1 Year					**Low SOE**
12 (225,687)	1 RCT/Good quality 11 observational/9 good quality, 1 fair, 1 poor	Inconsistent	Direct	Precise	The RCT and observational study of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.33 (1.15 to 1.55), which favors no PPI. The discrepancy between the omeprazole studies and the observational studies of any PPI makes it difficult to draw a firm conclusion about the effect.

Table 25. Detailed strength of evidence for UA/NSTEMI patients treated with dual antiplatelet therapy with and without proton pump inhibitor (continued)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Stroke at About 1 Year					**Low SOE**
7 (165,212)	2 RCTs/1 good quality, 1 poor 5 observational/ 4 good quality, 1 fair	Consistent	Direct	Precise	RCTs of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.49 (1.20 to 1.84), which favors no PPI. The discrepancy between the RCTs and the observational studies makes it difficult to draw a firm conclusion about the effect.
Revascularization at 6 Months					**Low SOE**
2 (22,326)	1 RCT, 1 observational/Both good quality	Consistent	Direct	Imprecise	Both studies showed no difference in revascularization rates
Revascularization at 1 Year					**Low SOE**
5 (53,164)	5 observational/All good quality	Inconsistent	Direct	Precise	Observational study of omeprazole showed no difference. Meta-analysis of observational studies of any PPI showed adj OR 1.48 (1.21 to 1.82), which favors no PPI
Revascularization at 4 Years					**Insufficient SOE**
1 (315)	Observational/Fair quality	NA	Direct	Imprecise	Insufficient evidence due to imprecision: no statistically significant difference in revascularization rate between groups
Stent Thrombosis at 30 Days					**Insufficient SOE**
1 (3408)	Observational/Good quality	NA	Direct	Imprecise	No statistically significant difference in stent thrombosis rate between groups
Stent Thrombosis at About 1 Year					**Low SOE**
8 (45,198)	1 RCT/1 good quality 7 observational/All good quality	Inconsistent	Direct	Precise	The RCT and observational study of omeprazole showed no difference, however the meta-analysis of observational studies of any PPI showed adj HR 1.34 (1.17 to 1.55), which favors no PPI. The discrepancy between the RCT and the observational studies makes it difficult to draw a firm conclusion about the effect.
Major Bleeding at 30 Days					**Insufficient SOE**
3 (7498)	3 observational/All good quality	Inconsistent	Direct	Imprecise	Adj HR 1.73 (0.61 to 4.88)
Major Bleeding at About 1 Year					**Low SOE**
4 (36,231)	4 observational/All good quality	Consistent	Direct	Precise	Adj HR 1.26 (1.12 to 1.41) Favors no PPI

Table 25. Detailed strength of evidence for UA/NSTEMI patients treated with dual antiplatelet therapy with and without proton pump inhibitor (continued)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
GI Bleeding					**Moderate SOE**
8 (28,032)	4 RCTs/2 good quality, 2 poor 4 observational/3 good quality, 1 poor	Consistent	Direct	Precise	3 out of 4 RCTs of omeprazole and 2 out of 4 observational studies of any PPI showed statistically significant lower rates of GI bleed in the PPI group Favors PPI
Minor Bleeding					**Insufficient SOE**
1 (1346)	Observational/Good quality	NA	Direct	Imprecise	No difference in minor bleed in-hospital or at 1 year
Rehospitalization at 3 Months					**Low SOE**
1 (5862)	Observational/Good quality	NA	Indirect	Precise	Significant increase in rehospitalization in PPI group at 3 months Adj HR 1.32 (1.00 to 1.73) Favors no PPI
Rehospitalization at About 1 Year					**Insufficient SOE**
4 (16,925)	4 observational/All good quality	Inconsistent	Indirect	Imprecise	Adj HR 1.70 (0.86 to 3.34)

CI = confidence interval; CV = cardiovascular; GI = gastrointestinal; HR = hazard ratio; MI = myocardial infarction; NA = not applicable; OR = odds ratio; PPI = proton pump inhibitor; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

4b. Aspirin Monotherapy With and Without PPI

Two observational studies (both good quality)[143,148] reported the results of 52,196 UA/NSTEMI patients who were given aspirin monotherapy (i.e., not prescribed clopidogrel) and then either treated or not treated with PPIs.

Effect on Composite Endpoint of Cardiovascular Death, Nonfatal MI, or Stroke at 1 Year

Both observational studies[143,148] compared the effect of PPI versus no PPI on the composite of cardiovascular death, nonfatal MI, or stroke at 1 year. One study[143] showed an increased risk among patients receiving PPI at hospital discharge (PPI 22.9% vs. no PPI 15.2%, propensity-score adj HR 1.61; 95% CI, 1.45 to 1.79). The other study[148] showed no difference in the risk of the composite outcome at 1 year among patients receiving PPI at hospital discharge (PPI 42% vs. no PPI 38%; adj HR 1.00; 95% CI, 0.88 to 1.15). The SOE was rated insufficient for this composite endpoint at 1 year based on two observational studies reporting adjusted findings with inconsistent results of a direct outcome and precise results.

Effect on In-Hospital Outcomes

One good-quality observational study[148] comparing PPI with no PPI among 2744 UA/NSTEMI patients receiving aspirin monotherapy reported the in-hospital rate of individual components of the composite outcomes and major bleeding. The study found no differences in the rate of in-hospital all-cause mortality (PPI 12.8% vs. no PPI.15.9%, adj OR 0.96; 95% CI, 0.49 to 1.88), nonfatal MI (3.4% vs. 2.9%, adj HR 1.50; 95% CI, 0.41 to 5.43), stroke (1.5% vs.1.8%, adj HR 0.75; 95% CI, 0.11 to 4.85), or major bleeding (3.8% vs. 2.5%, adj OR 1.30;

95% CI, 0.38 to 4.39). The SOE was rated insufficient for all four in-hospital outcomes (all-cause mortality, nonfatal MI, stroke, and major bleeding) based on one study with imprecise results.

Effect on All-Cause Mortality at 1 Year

Both observational studies[143,148] compared the effect of PPI versus no PPI on all-cause mortality at 1 year. One study[143] showed an increased risk among patients receiving PPI at hospital discharge (PPI 15.9% vs. no PPI 10.3%, adj HR 2.38; 95% CI, 2.12 to 2.67). The other study[148] showed no difference in all-cause mortality at 1 year among patients receiving PPI at hospital discharge (PPI 38% vs. no PPI 34%; adj HR 0.99; 95% CI, 0.86 to 1.14). The SOE was rated insufficient for all-cause mortality at 1 year based on two observational studies reporting adjusted findings with inconsistent results of a direct outcome and precise results.

Effect on Nonfatal MI at 1 Year

One good-quality observational study[143] with 49,452 patients comparing the effect of PPI versus no PPI on nonfatal MI at 1 year showed an increased risk among patients receiving PPI at hospital discharge (11.5% vs.7.1%, adj HR 1.33; 95% CI, 1.13 to 1.56). The SOE was rated low for nonfatal MI at 1 year based on one good-quality observational study reporting adjusted results.

Effect on Stroke at 1 Year

Both observational studies[143,148] compared the effect of PPI versus no PPI on stroke at 1 year. One study[143] showed no difference in the rate of stroke at 1 year (7.9% vs.7.7%, adj HR 1.20; 95% CI, 0.99 to 1.46). The other study[148] showed no difference in stroke at 1 year among patients receiving PPI at hospital discharge (PPI 1.5 % vs. no PPI 1.8%; adj HR 0.75; 95% CI, 0.11 to 4.85). The SOE was rated low for stroke at 1 year based on two good-quality observational studies reporting adjusted findings with consistent but imprecise results of a direct outcome.

Summary of Results for Aspirin Monotherapy With and Without PPI

In our analysis of aspirin monotherapy with and without concomitant PPI therapy, we presented the findings from two good-quality observational studies that compared clinical outcomes between patients receiving different PPI medications with patients who did not receive a PPI. In contrast to the previous section, these patient populations were not prescribed dual antiplatelet therapy; therefore, this evaluation focuses on the addition of PPIs to aspirin monotherapy. There was insufficient evidence for the effect of PPIs on aspirin monotherapy for in-hospital outcomes; only one study of 2744 patients reported the rates of all-cause mortality, nonfatal MI, stroke, and major bleeding. That study found no significant differences between the PPI and no PPI groups. There were inconsistent results for composite ischemic events (cardiovascular mortality, nonfatal MI, or stroke) and lower all-cause mortality at 1 year of followup, with one study showing an increased risk of events in the PPI group and the other study showing no difference. One study reported rates of nonfatal MI at 1 year and showed an increased risk of MI events in the PPI group. Both studies showed no difference in stroke events at 1 year. Detailed SOE ratings are shown in Table 26. Odds ratios less than 1 favor PPI use; odds ratios greater than 1 favor no PPI use.

Table 26. Detailed strength of evidence for UA/NSTEMI patients treated with aspirin monotherapy with and without proton pump inhibitor

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of CV Death, Nonfatal MI, or Stroke at 1 Year					**Insufficient SOE**
2 (52,196)	2 observational/Both good quality	Inconsistent	Direct	Precise	One study reported increased risk among PPI group Adj HR 1.61 (1.45 to 1.79), while the other study showed no difference Adj HR 1.00 (0.88 to 1.15)
All-cause Mortality (In-Hospital)					**Insufficient SOE**
1 (2744)	Observational/Good quality	NA	Direct	Imprecise	Adj OR 0.96 (0.49 to 1.88)
All-cause Mortality at 1 Year					**Insufficient SOE**
2 (52,196)	2 observational/Both good quality	Inconsistent	Direct	Precise	One study reported increased risk among PPI group Adj HR 2.38 (2.12 to 2.67), while the other study showed no difference Adj HR 0.99 (0.86 to 1.14)
Nonfatal MI (In-Hospital)					**Insufficient SOE**
1 (2744)	Observational/Good quality	NA	Direct	Imprecise	Adj HR 1.50 (0.41 to 5.43)
Nonfatal MI at 1 Year					**Low SOE**
1 (49,452)	Observational/Good quality	NA	Direct	Precise	Adj HR 1.33 (1.13 to 1.56) Increased risk for PPI group
Stroke (In-Hospital)					**Insufficient SOE**
1 (2744)	Observational/Good quality	NA	Direct	Imprecise	Adj HR 0.75 (0.11 to 4.85)
Stroke at 1 Year					**Low SOE**
2 (52,196)	2 observational/Both good quality	Consistent	Direct	Imprecise	Both studies showed no difference Adj HR 1.20 (0.99 to 1.46) and Adj HR 0.75 (0.11 to 4.85)
Major Bleeding (In-Hospital)					**Insufficient SOE**
1 (2744)	Observational/Good quality	NA	Direct	Imprecise	Adj OR 1.30 (0.38 to 4.39)

CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; NA = not applicable; OR = odds ratio; PPI = proton pump inhibitor; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

Findings by Subgroup Across All PPI/No PPI Comparisons (Omeprazole, Dual Antiplatelet Therapy, and Aspirin Monotherapy) (KQ 3d)

Thirteen studies (11 good quality, 1 fair, 1 poor) reported variations in treatment effectiveness by subgroup. Subgroups analyzed were diabetes (2 studies), sex (1), age (2), the use or timing of PCI (1), chronic renal disease (1), type of PPI (9), timing of PPI (3), dose of PPI (1), and clopidogrel use (2).Table H-3 in Appendix H presents the results data for these subgroups.

Diabetes

Two good-quality observational studies[146,154] assessing PPI versus no PPI in 57,752 UA/NSTEMI patients, reported outcomes among patients with diabetes. One study[154] reported the rate of the composite outcome (cardiovascular death, nonfatal MI, or stroke) by clopidogrel

use among patients with and without diabetes. The study found a significant increase in the risk of composite outcome at 1 year among patients treated with PPI and concomitant clopidogrel, both in patients with diabetes (HR 1.36; 95% CI, 1.10 to 1.70) and without diabetes (HR 1.28; 95% CI, 1.16 to 1.43). A significant increase in the risk of composite outcome at 1 year was also found among patients treated with PPI but no concomitant clopidogrel, both in patients with diabetes (HR 1.25; 95% CI, 1.06 to 1.45) and those without diabetes (HR 1.35; 95% CI, 1.26 to 1.44).

The other study[146] assessing PPI versus no PPI in UA/NSTEMI patients, reported the rate of composite outcome (all-cause mortality, nonfatal MI, stroke, or rehospitalization) among patients with and without diabetes and found a nonsignificant increase in the risk of composite outcomes in both groups (diabetes OR 1.31; 95% CI, 0.38 to 4.53; without diabetes OR 1.72; 95% CI, 0.61 to 4.88).

Sex

Only one good-quality observational study[154] assessing PPI versus no PPI in 56,406 UA/NSTEMI patients reported the rate of the composite outcome (cardiovascular death, nonfatal MI, or stroke) by clopidogrel use among male and female patients. The study found a significant increase in the risk of composite outcome at 1 year among patients treated with PPI and concomitant clopidogrel, both in women (HR 1.18; 95% CI, 1.00 to 1.37) and men (HR 1.38; 95% CI, 1.23 to 1.58). A significant increase in the risk of the composite outcome at 1 year was found also among patients treated with PPI but no concomitant clopidogrel, both women (HR 1.32; 95% CI, 1.21 to 1.44) and men (HR 1.34; 95% CI, 1.23 to 1.46).

Age

Two good-quality observational studies[146,154] assessing PPI versus no PPI in 57,752 UA/NSTEMI patients reported outcomes by age group. One study[154] reported the rate of the composite outcome (cardiovascular death, nonfatal MI, or stroke) by clopidogrel use among patients of under age 70 and over age 70. This study found a significant increase in the risk of the composite outcome at 1 year among patients treated with PPI and concomitant clopidogrel both age groups (≤70 years HR 1.37; 95% CI, 1.19 to 1.62 and >70 years HR 1.30; 95% CI, 1.18 to 1.43). A significant increase in the risk of composite outcome at 1 year was found among patients treated with PPI but no concomitant clopidogrel in the older patients group (> 70 years HR 1.33; 95% CI, 1.24 to 1.43) but not the younger group (≤70 years HR 1.19; 95% CI, 0.99 to 1.39).

The other study[146] reporting the rate of a composite outcome (all-cause mortality, nonfatal MI, stroke, or rehospitalization) among patients by age group (≤75 vs. >75 years), found a nonsignificant increase in the risk of composite outcomes in both groups (≤75 years OR 1.46; 95% CI, 0.62 to 3.46 and >75 years OR 1.61; 95% CI, 0.35 to 7.37).

Chronic Kidney Disease

Only one good-quality observational study[146] comparing PPI versus no PPI in 1346 UA/NSTEMI patients reported rate of composite outcome (all-cause mortality, nonfatal MI, stroke, or rehospitalization) among patients by renal function (CKD vs. no CKD). This study found a nonsignificant increase in the risk of composite outcomes in both groups (CKD OR 0.65; 95% CI, 0.18 to 2.36 and no CKD OR 2.48; 95% CI, 0.76 to 8.06).

Type of PPI

Nine observational studies[137,146,148,154,156,163,166,173,200] (7 good quality, 1 fair, 1 poor) assessing PPI versus no PPI in 153,195 UA/NSTEMI patients reported outcomes by type of PPI. Table 27 summarizes the results reported by each study for each PPI. The studies by Charlot et al.[154] and Schmidt et al.[137] reported the rate of a composite outcome (Charlot: cardiovascular death, nonfatal MI, or stroke; Schmidt: cardiovascular death, nonfatal MI, stroke, stent thrombosis, or target lesion revascularization) by concomitant clopidogrel use and by type of PPI (pantoprazole, omeprazole, lansoprazole, esomeprazole). Both studies found significant increases in the risk of the composite outcome at 1 year among patients treated with PPI *and* concomitant clopidogrel for all types of PPI. Similarly both studies also found increases in the risk of the composite outcome at 1 year among patients treated with PPI but *no* concomitant clopidogrel for all types of PPI, with the results from the Charlot study being statistically significant. A Cox proportional hazards regression analysis in the Charlot study demonstrated no difference in risk associated with the type of PPI independent of clopidogrel treatment, and interaction effect calculations in the Schmidt study resulted in similar findings.

The study by Ho[173] found a significant increase in the composite of all-cause mortality or rehospitalization both with omeprazole and with rabeprazole. A third study by Rassen[166] found a nonsignificant increase in the composite of all-cause mortality or nonfatal MI with omeprazole as well as with pantoprazole.

The study by Ray[163] found a nonsignificant difference in the composite of cardiovascular mortality, nonfatal MI, or stroke with omeprazole, pantoprazole, esomeprazole, and lansoprazole. Only the treatment with rabeprazole showed a significant reduction in the composite outcome (HR 0.54; 95% CI, 0.30 to 0.97). The same study evaluated the effect of different PPIs on the incidence of GI bleeding and found a nonsignificant reduction in GI bleeding with omeprazole, or esomeprazole, or lansoprazole, or rabeprazole. However, treatment with pantoprazole showed a significant reduction in the incidence of GI bleeding (HR 0.46; 95% CI, 0.33 to 0.63).

The study by Rossini[146] found no differences in event rate for different outcomes by PPI type: in-hospital MACE and major bleeding. Only in-hospital minor bleeding was lower in the pantoprazole (1.1%) and lansoprazole group (2.9%, p=0.009) compared with omeprazole (7.1%). No differences in event rates by PPI were found for all outcomes at 1 year, all-cause mortality, stent thrombosis, major bleeding, and minor bleeding.

The study by Simon[148] found no significant differences in the risk of different outcomes with each PPI studied. Patients treated with esomeprazole, lansoprazole, omeprazole, and pantoprazole were at similar risk of the composite outcome of death, MI, or stroke (in-hospital and at 1 year), and individual outcomes of total mortality nonfatal MI, stroke, or bleeding compared with those not receiving those PPIs.

The study by van Boxel[156] found a significant increase in the composite outcome (all-cause mortality, nonfatal MI, or stroke) with omeprazole, pantoprazole, esomeprazole and rabeprazole.

The study by O'Donoghue[200] found no significant differences in event rates by type of PPI (omeprazole, esomeprazole, pantoprazole, or lansoprazole) at 6 months for myocardial infarction, or the composite of cardiovascular death, myocardial infarction, or stroke for patients randomized to clopidogrel or prasugrel in the TRITON-TIMI 38 trial. Rabeprazole was not analyzed given the small number of patients (n=66) receiving it at baseline. In addition, they reported that use of an H2 receptor antagonist or PPI at baseline was not associated with risk of

cardiovascular death, myocardial infarction, or stroke for patients randomly assigned to clopidogrel (adj HR 0.80; 95% CI 0.51 to 1.26) or prasugrel (adj HR 0.91; 95% CI 0.55 to 1.51).

Table 27. Summary of findings by type of proton pump inhibitor prescribed

Study Details	Outcome(s) Effect Estimate (95% CI)				
	Esomeprazole	**Lansoprazole**	**Omeprazole**	**Pantoprazole**	**Rabeprazole**
Charlot, 2010[154] Total N: 56,406 Quality: Good	CV death/MI/CVA 1 yr With clopidogrel HR 1.29 (1.09 to 1.48) Without clopidogrel HR 1.53 (1.39 to 1.71)	CV death/MI/CVA 1 yr With clopidogrel HR 1.47 (1.21 to 1.81) Without clopidogrel HR 1.45 (1.27 to 1.68)	CV death/MI/CVA 1 yr With clopidogrel HR 1.40 (1.10 to 1.78) Without clopidogrel HR 1.25 (1.09 to 1.41)	CV death/MI/CVA 1 yr With clopidogrel HR 1.42 (1.22 to 1.67) Without clopidogrel HR 1.5 (1.36 to 1.69)	NR
Ho, 2009[173] Total N: 8790 Quality: Good	NR	NR	Death/rehospitalization Adj OR 1.24 (1.08 to 1.41)	NR	Death/rehospitalization Adj OR 2.83 (1.96 to 4.0)
O'Donoghue, 2009[200] Total N: 4529 Quality: Good	CV death/MI/CVA Clopidogrel Adj HR 1.07 (0.75 to 1.52) Prasugrel Adj HR 0.86 (0.55 to 1.33) MI Clopidogrel Adj HR 1.18 (0.81 to 1.73) Prasugrel Adj HR 0.92 (0.57 to 1.48)	CV death/MI/CVA Clopidogrel Adj HR 1.00 (0.63 to 1.59) Prasugrel Adj HR 0.98 (0.61 to 1.57) MI Clopidogrel Adj HR 0.86 (0.51 to 1.46) Prasugrel Adj HR 1.08 (0.66 to 1.79)	CV death/MI/CVA Clopidogrel Adj HR 0.91 (0.72 to 1.15) Prasugrel Adj HR 1.04 (0.81 to 1.34) MI Clopidogrel Adj HR 0.95 (0.73 to 1.23) Prasugrel Adj HR 1.02 (0.76 to 1.36)	CV death/MI/CVA Clopidogrel Adj HR 0.94 (0.74 to 1.18) Prasugrel Adj HR 1.09 (0.86 to 1.39) MI Clopidogrel Adj HR 0.97 (0.75 to 1.24) Prasugrel Adj HR 1.09 (0.83 to 1.43)	Not analyzed since only 66 patients were given this at baseline
Rassen, 2009[166] Total N: 18,565 Quality: Good	NR	NR	Death/MI HR 1.17 (0.68 to 2.01)	Death/MI HR 1.26 (0.93 to 1.71)	NR
Ray, 2010[163] Total N: 20,596 Quality: Good	CV death/MI/CVA HR 0.71 (0.48 to 1.06) GI bleeding HR 0.43 (0.18 to 1.07)	CV death/MI/CVA HR 1.06 (0.77 to 1.45) GI bleeding HR 0.71 (0.43 to 1.18)	CV death/MI/CVA HR 0.79 (0.54 to 1.15) GI bleeding HR 0.43 (0.16 to 1.13)	CV death/MI/CVA HR 1.08 (0.88 to 1.32) GI bleeding HR 0.46 (0.33 to 0.63)	CV death/MI/CVA HR 0.54 (0.30 to 0.97) GI bleeding HR 0.25 (0.03 to 2.01)

Table 27. Summary of findings by type of proton pump inhibitor prescribed (continued)

Study Details	Outcome(s) Effect Estimate (95% CI)				
	Esomeprazole	**Lansoprazole**	**Omeprazole**	**Pantoprazole**	**Rabeprazole**
Rossini, 2011[146] Total N: 1346 Quality: Good	NR	MACE in-hospital: 2.2% MACE at 1 yr: 7.8% Major bleeding in-hospital: 1.3% Major bleeding at 1 yr: 3.3% Minor bleeding in-hospital: 2.9% Minor bleeding at 1 yr: 5.1% Total mortality at 1 yr: 2.1% Stent thrombosis at 1 yr: 2.1%	MACE in-hospital: 2.5% MACE at 1 yr: 4.2% Major bleeding in-hospital: 1.6% Major bleeding at 1 yr: 3.2% Minor bleeding in-hospital: 7.1% Minor bleeding at 1 yr: 9.6% Total mortality: 0.8% Stent thrombosis at 1 yr: 1.7%	MACE in-hospital: 4.1%; p=0.346 MACE at 1 yr: 8.1%; p=0.465 Major bleeding in-hospital: 1.1%; p=0.936 Major bleeding at 1 yr: 3.4%; p=0.996 Minor bleeding in-hospital: 1.1% p=0.009 Minor bleeding at 1 yr: 3.4% p=0.052 Total mortality: 3.1%; p=0.424 Stent thrombosis at 1 yr: 3.1%; p=0.671	NR
Schmidt, 2012[137] Total N: 13,001 Quality: Poor	<u>CV death/MI/stroke/stent thrombosis/ revascularization</u> With clopidogrel HR 1.37 (1.04 to 1.79) Without clopidogrel HR 1.03 (0.74 to 1.44)	<u>CV death/MI/stroke/ stent thrombosis/ revascularization</u> With clopidogrel HR 1.28 (0.88 to 1.87) Without clopidogrel HR 1.17 (0.79 to 1.75)	<u>CV death/MI/stroke/ stent thrombosis/ revascularization</u> With clopidogrel HR 1.09 (0.69 to 1.72) Without clopidogrel HR 1.08 (0.71 to 1.66)	<u>CV death/MI/stroke/ stent thrombosis/ revascularization</u> With clopidogrel HR 1.55 (1.09 to 2.19) Without clopidogrel HR 1.05 (0.67 to 1.66)	NR

Table 27. Summary of findings by type of proton pump inhibitor prescribed (continued)

Study Details	Outcome(s) Effect Estimate (95% CI)				
	Esomeprazole	**Lansoprazole**	**Omeprazole**	**Pantoprazole**	**Rabeprazole**
Simon, 2011[148] FAST-MI Study Total N: 2744 Quality: Good	Death/ MI/CVA in-hospital: Adj OR 0.77 (0.41 to 1.46) Death/ MI/CVA at 1 yr: Adj OR 1.05 (0.62 to 1.77) Total mortality: Adj OR 0.72 (0.30 to 1.7) Nonfatal MI: Adj OR 1.20 (0.44 to 3.30) Stroke: Adj OR 0.54 (0.14 to 2.16) Bleeding: Adj OR 0.97 (0.33 to 2.86)	Death/ MI/CVA in-hospital: Adj OR 0.59 (0.07 to 4.72) Death/ MI/CVA at 1 yr: Adj OR 0.40 (0.05 to 2.95) Total mortality: Adj OR 1.30 (0.15 to 11.5) Nonfatal MI: 0 Stroke: 0 Bleeding: Adj OR 1.82 (0.22 to 15.3)	Death/ MI/CVA in-hospital: Adj OR 0.92 (0.59 to 1.43) Death/ MI/CVA at 1 yr: Adj OR 0.82 (0.54 to 1.24) Total mortality: Adj OR 1.16 (0.66 to 2.05) Nonfatal MI: Adj OR 1.18 (0.55 to 2.52) Stroke: Adj OR 0.14 (0.03 to 0.67) Bleeding: Adj OR 0.94 (0.44 to 1.98)	Death/ MI/CVA in-hospital: Adj OR 1.31 (0.54 to 3.17) Death/ MI/CVA at 1 yr: Adj OR 1.79 (0.95 to 3.37) Total mortality: Adj OR 1.00 (0.27 to 3.68) Nonfatal MI: Adj OR 1.22 (0.26 to 5.77) Stroke: Adj OR 1.78 (0.36 to 8.83) Bleeding: 0	NR
Van Boxel, 2010[156] Total N: 18,139 Quality: Fair	Death/MI/CVA: HR 1.83 (1.52 to 2.21)	NR	Death/MI/CVA: HR 1.62 (1.38 to 1.91)	Death/MI/CVA: HR 1.83 (1.61 to 2.08)	Death/MI/CVA: HR 1.76 (1.07 to 2.88)

Adj = adjusted; CI = confidence interval; CV = cardiovascular; CVA = cardiovascular accident; GI = gastrointestinal; HR = hazard ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; N = number of patients; NR = not reported; OR = odds ratio; PPI = proton pump inhibitor

Timing of PPI

Three observational studies[152,158,174] (2 good quality, 1 poor quality) comparing PPI versus no PPI in 43,136 UA/NSTEMI patients reported outcomes by timing of PPI use. One study[158] found a significant increase in the rate of major cardiovascular events at 1 year among patients with no prior PPI use (PPI vs. no PPI 27.8% vs. 17.9%, HR 1.57; 95% CI, 1.44 to 1.71) but not among patients who were on PPI already at hospital admission (PPI vs. no PPI 23.2% vs. 19.2%, HR 1.24; 95% CI, 0.98 to 1.71). Another study[174] found no difference in the rate of nonfatal MI among patients with both prior use (HR 0.86; 95% CI, 0.63 to 1.19) and remote use (HR 0.81; 95% CI, 0.46 to 1.41). Another study[152] comparing current PPI use with past PPI use found no difference in the rate of nonfatal MI among patients (OR 0.95; 95% CI, 0.38 to 2.41).

Dose of PPI

One good-quality observational study[163] comparing PPI versus no PPI in 20,596 UA/NSTEMI patients, assessed the effect of a low-dose or high-dose PPIs on gastroduodenal bleeding and composite cardiovascular events. The study found that both low doses and high doses had similar rates of composite cardiovascular events (cardiovascular death, nonfatal MI, stroke) (low dose HR 1.0; 95% CI, 0.81 to 1.22 and high dose HR 0.94; 95% CI, 0.75 to 1.17). Low doses and high doses of PPI were both associated with a lower risk of gastroduodenal bleeding (low dose HR 0.48; 95% CI, 0.36 to 0.64 and high dose HR 0.53; 95% CI, 0.32 to 0.89).

5. Dual Antiplatelet Versus Triple Therapy (KQ 3c)

Fourteen studies (all observational) compared dual antiplatelet therapy (DAPT), defined as aspirin with oral antiplatelet, with triple therapy, defined as dual antiplatelet therapy with an oral anticoagulant, in the postdischarge treatment of 97,067 total patients with UA/NSTEMI and a long-term indication for anticoagulation. The dual versus triple therapy comparisons studied included:

- Seven studies comparing DAPT (with aspirin and clopidogrel) with triple therapy (with oral anticoagulant, aspirin, and clopidogrel)[135,175,180,186,189,195,196]
- One study comparing warfarin with no warfarin among patients with atrial fibrillation complicating a UA/NSTEMI event[165]
- One study comparing DAPT (aspirin plus clopidogrel) with two triple therapy arms—one consisting of oral anticoagulant, aspirin, and clopidogrel, and one consisting of LMWH, aspirin, and clopidogrel[178]
- One study comparing triple therapy (oral anticoagulant, aspirin, and clopidogrel) with warfarin plus aspirin or thienopyridine[185]
- Two studies comparing aspirin and/or thienopyridine versus oral anticoagulant with or without an antiplatelet agent[132,188]
- One study with five treatment arms comparing aspirin, warfarin, aspirin plus warfarin, aspirin plus a thienopyridine (DAPT), and aspirin plus warfarin plus a thienopyridine (triple therapy)[190]
- One study comparing monotherapy with aspirin, oral anticoagulant, or clopidogrel; aspirin plus oral anticoagulant; aspirin plus clopidogrel (DAPT); oral anticoagulant plus clopidogrel; and aspirin plus oral anticoagulant plus thienopyridine (triple therapy)[203]

Of the 14 observational studies, 10 (71%) were rated good quality, 3 (21%) were fair quality, and 1 (7%) was poor quality. Sample sizes for individual studies ranged from 102 to 27,972 patients. Study duration ranged from 30 days to 5 years. The mean age of study participants ranged from 61 to 80 years of age. The proportion of female patients ranged from 28 to 51 percent. Four studies (33%) reported the racial and/or ethnic demographics of study participants. Two studies (14%) were conducted within the United States or Canada, 7 studies (50%) were conducted in Europe, one was conducted in Asia (7%), one was conducted in Israel (7%), one was international (7%), and one study did not report the location (7%). Funding source was reported in seven studies (50%), with two studies (14%) funded by an industry source. Table G-16 in Appendix G contains the results reported by each study.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal MI, Revascularization, or Stroke at 1 Year or More

Four observational studies (2 good quality, 1 fair, 1 poor) with 8,509 patients reported four different combinations of composite endpoints. Given the low number of studies for each combination, a quantitative analysis was not conducted.

Two studies comparing DAPT with triple therapy reported a composite of all-cause mortality, nonfatal MI, or revascularization at long-term followup. One study[180] showed a significant increase in the composite outcomes at 5 years among patients treated with DAPT compared with triple therapy (38.7% vs.26.5%, HR 4.9; 95% CI, 2.17 to 11.1). The other study[195] showed a nonsignificant difference in the rate of composite outcomes at 3 years between patients treated with DAPT and triple therapy (15.5% vs.11.9%, HR 0.94; 95% CI, 0.56 to 1.59).

One study comparing DAPT with triple therapy showed that patients discharged on DAPT were at higher risk for the composite outcome of all-cause mortality, nonfatal MI, or stroke at 1 year (32.5% vs. 25.6%).[135] One study evaluating aspirin and/or thienopyridine versus oral anticoagulant with or without an antiplatelet agent among patients at risk for high bleeding (HAS-BLED $\geq$3) showed that patients on an oral anticoagulant had a lower rate of composite outcome (death, MI, or target vessel failure) (13.0% vs.26.4%, HR 0.48; 95%CI 0.29-0.77, p<0.01).[132]

One study reported a composite of all-cause mortality, nonfatal MI, or stroke at long-term followup.[175] This study, comparing DAPT with triple therapy showed a nonsignificant difference in the rate of composite outcomes at 18 months between the two treatment arms (4.9% versus 5.8%, respectively, p=0.7).

One study[180] comparing DAPT with triple therapy showed that patients discharged on DAPT were at higher risk of the composite outcome of stroke, major bleeding, death, nonfatal MI, or revascularization at 5 years (HR 4.33; 95% CI, 1.96 to 9.59). The SOE was rated insufficient for the various combinations of composite outcomes based on inconsistent and imprecise results.

Effect on Composite Endpoint of All-Cause Mortality or Nonfatal MI Within First Year

Four good-quality observational studies with 57,144 patients reported a composite endpoint of all-cause mortality or nonfatal MI during the first year of followup. One study,[165] comparing the use of warfarin with no warfarin among patients with atrial fibrillation complicating a UA/NSTEMI event, showed a significant reduction of the composite of all-cause mortality or nonfatal MI at 6 months among patients treated with warfarin (adjusted OR 0.39; 95% CI, 0.15 to 0.98, p=0.04). Another study[196] showed a higher incidence of the composite of all-cause

mortality or nonfatal MI at 1 year among patients treated with warfarin (adjusted RR 1.20; 95% CI, 1.00 to 1.45).

A study[186] comparing triple therapy with DAPT found a nonsignificant difference in the rate of composite outcomes (all-cause mortality, nonfatal MI, revascularization, or stent thrombosis) at 12 months between the two treatment arms (2.7% vs.1.3%, OR 2.1; 95% CI, 0.5 to 8.6, p=0.30). Another study[203] comparing DAPT with triple therapy found no significant difference in the rate of all-cause mortality or nonfatal MI at 1 year (HR 1.17; 95% CI, 0.96 to 1.42). The SOE was rated insufficient for the composite outcome of all-cause mortality or nonfatal MI within the first year due to inconsistent and imprecise results.

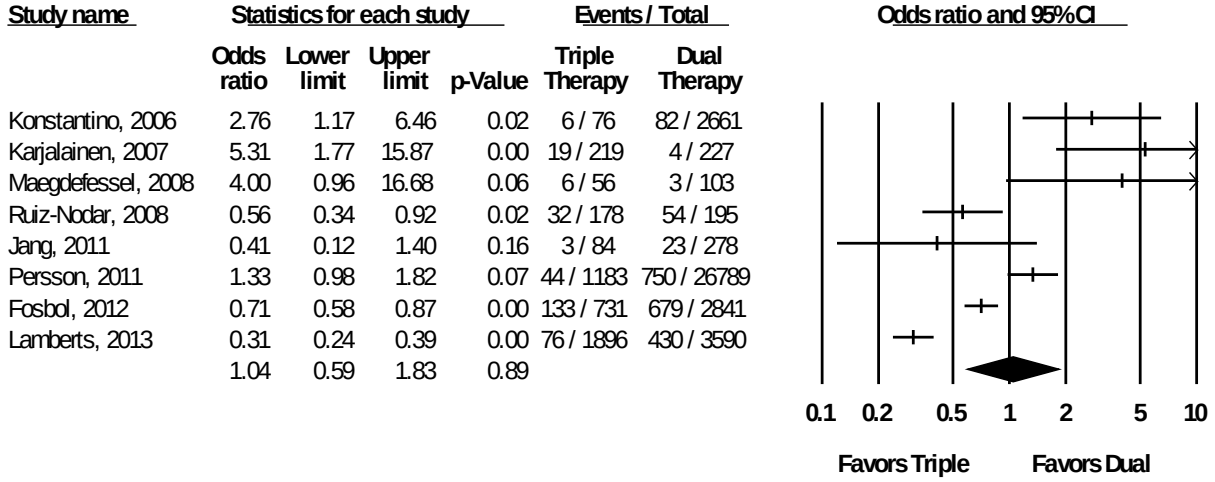
Effect on All-Cause Mortality at 30 Days to 6 Months

Two good-quality observational studies with 7,075 patients reported mortality at 30 days and 6 months. One study[185] comparing triple therapy versus warfarin plus single antiplatelet found no difference in the rate of all-cause mortality at 6 months between the two groups (5.1% vs.6.5%, p=0.47). The other study[188] comparing DAPT versus triple therapy found a significantly lower rate of all-cause mortality at 30 days among patients in the triple therapy group (4.1% vs.6.1%, p=0.002). The SOE was rated insufficient for all-cause mortality at 30 days to 6 months due to inconsistent results and unknown precision.

Effect on All-Cause Mortality at 1 to 5 Years

A random-effects meta-analysis of eight observational studies[135,178,180,186,189,195,196,203] (4 good quality, 3 fair, 1 poor) including 41,192 UA/NSTEMI patients reporting all-cause mortality at 1 to 5 years found that the odds ratio for triple therapy compared with DAPT was 1.04 (95% CI, 0.59 to 1.83) (Figure 1). There was evidence of extreme heterogeneity, with a Q-value of 87.83 for 7 degrees of freedom, p<0.001, I^2= 92.03.

Figure 50. Meta-analysis of triple versus dual therapy on all-cause mortality at 1 to 5 years



CI = confidence interval

Two studies[132,188] reported all-cause mortality but were not included in the analysis because they had different treatment comparison groups: aspirin and/or thienopyridine versus oral anticoagulant with or without an antiplatelet agent. The Stenestrand study[188] found that the

mortality rate at 1 year was significantly lower in patients in the oral anticoagulant arm (22.4% vs. 31.4%, RR 0.73; 95% CI, 0.62 to 0.86, p≤0.001). The other study[132] showed that among patients at high bleeding risk (HAS-BLED ≥3) those on an oral anticoagulant had a lower rate of death (9.3% vs. 20.1%, HR 0.45; 95% CI, 0.26 to 0.78, p<0.01). The SOE was rated insufficient based on eight observational studies with inconsistent results of a direct outcome and a wide confidence interval.

Effect on Nonfatal MI at 6 Months

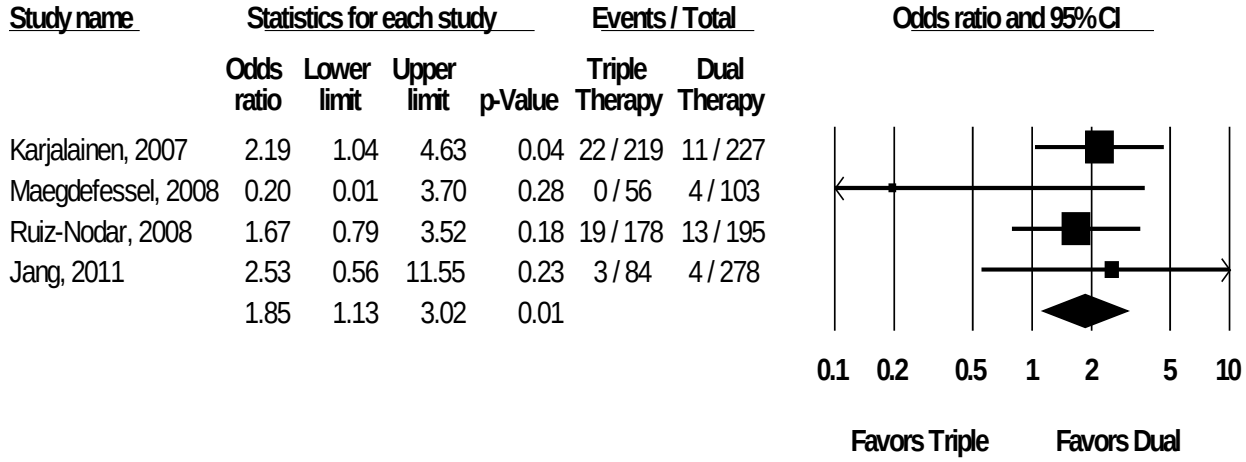
Only one good-quality observational study[185] with 800 patients reported nonfatal MI at 6 months. This study comparing triple therapy versus warfarin plus single antiplatelet found no difference in the rate of nonfatal MI at 6 months between the two groups (3.3% vs.4.5%, p=0.49). The SOE was rated insufficient for nonfatal MI at 6 months based on findings from one small observational study.

Effect on Nonfatal MI at 1 to 5 Years

A random-effects meta-analysis of four observational studies[178,180,186,195] (2 good quality, 1 fair, 1 poor) including 1425 UA/NSTEMI patients reporting nonfatal MI at 1 to 5 years found that the odds ratio for triple therapy compared with DAPT was 1.85 (95% CI, 1.13 to 3.02), favoring DAPT (Figure 51). There was no evidence of heterogeneity, with a Q-value of 2.68 for 3 degrees of freedom, p=0.44.

The study comparing aspirin versus warfarin versus aspirin plus warfarin found that patients treated with warfarin plus aspirin were at a significantly lower risk of nonfatal MI at 4 years compared with those treated with aspirin alone (RR 0.56; 95% CI, 0.41 to 0.78, p<0.001) as well as those treated with warfarin compared with aspirin alone (RR 0.74; 95% CI, 0.55 to 0.98), p=0.03). The SOE was rated low based on four observational studies with consistent results of a direct outcome and a wide confidence interval.

Figure 51. Meta-analysis of triple versus dual therapy on nonfatal myocardial infarction at 1 to 5 years



CI = confidence interval

Effect on Stroke at 6 Months

Only one good-quality observational study[185] with 800 patients reported stroke at 6 months. This study comparing triple therapy versus warfarin plus single antiplatelet found a significantly

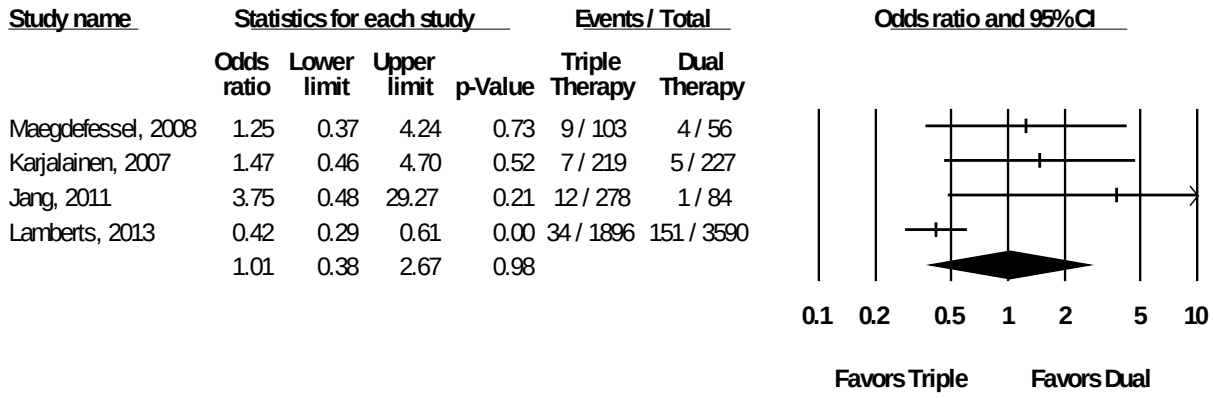
lower rate of stroke at 6 months among patients treated with triple therapy (0.7% vs.3.4%, p=0.02). The SOE was rated low for stroke at 6 months based on significant findings from one small study.

Effect on Stroke at 1 to 5 Years

A random-effects meta-analysis of four observational studies[178,186,195,203] (2 good quality, 1 fair, 1 poor) including 6,485 UA/NSTEMI patients reporting stroke at 1 to 5 years found that the odds ratio for triple therapy compared with DAPT was 1.01 (95% CI, 0.38 to 2.67) (Figure 2). There was evidence of heterogeneity, with a Q-value of 9.90 for 3 degrees of freedom, p=0.018.

The study comparing aspirin versus warfarin versus aspirin plus warfarin found that patients treated with warfarin plus aspirin were at significantly lower risk of stroke at 4 years compared with those treated with aspirin alone (RR 0.52; 95% CI, 0.28 to 0.98, p<0.03) as were those treated with warfarin compared with aspirin alone (RR 0.52; 95% CI, 0.28 to 0.97, p=0.03). The SOE was rated insufficient on the basis of four observational studies with inconsistent results of a direct outcome and a wide confidence interval that crosses 1.

Figure 52. Meta-analysis of triple versus dual therapy on stroke at 1 to 5 years



CI = confidence interval

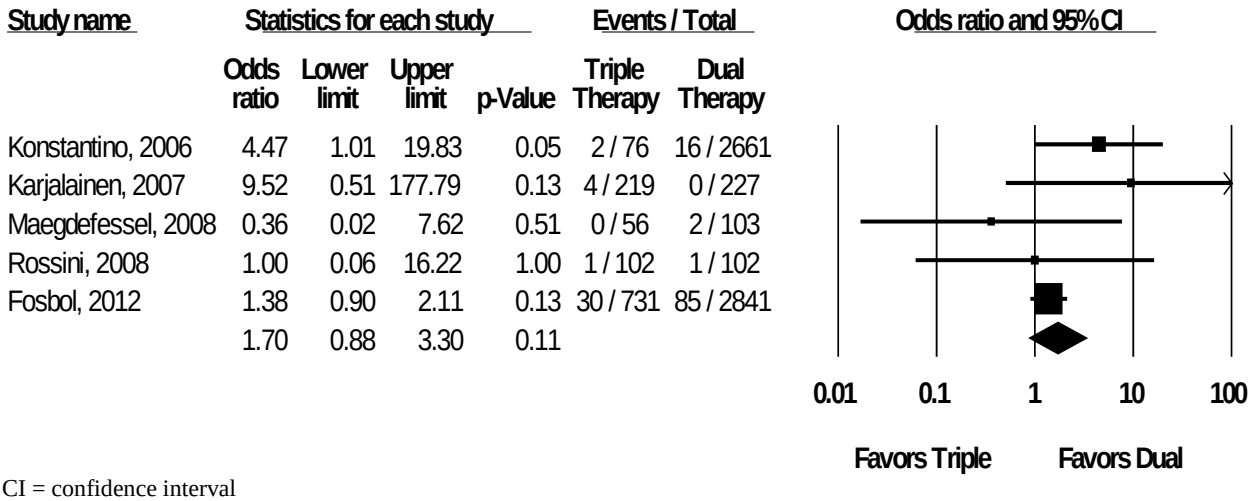
Effect on Revascularization up to 5 Years

Four observational studies[180,185,186,195] (3 good quality, 1 poor) with 2066 patients reported revascularization between 6 months and 5 years of followup. One study[185] comparing triple therapy versus warfarin plus single antiplatelet found no difference in the rate of repeat revascularization (unscheduled PCI) at 6 months between the two groups (10.6% vs.12.5%, p=0.50). Another study[186] comparing triple therapy with DAPT found no difference in the rate of revascularization (TVR) at 1 year between the two treatment groups (11.0% vs.7.5%, OR 1.5; 95% CI, 0.8 to 2.9, p=0.21). A third study[195] comparing triple therapy with DAPT found no significant difference in the rate of revascularization (TLR) at 3 years between the two treatment groups (4.3% vs.1.2%, p=0.13). The fourth study,[180] again comparing DAPT with triple therapy found no difference in the rate of revascularization (TVR) between the two treatment groups (8.4% vs.7.1%, p=0.3). The SOE was rated insufficient for revascularization outcomes due to nonsignificant results from four observational studies.

Effect on Major Bleeding at 30 Days

A random-effects meta-analysis of five observational studies[135,146,178,186,189] (2 good quality, 3 fair) including 12,339 UA/NSTEMI patients reporting major bleeding at 30 days found that the odds ratio for triple therapy compared with DAPT was 1.70 (95% CI, 0.88 to 3.30) (Figure 53). There was no evidence of heterogeneity, with a Q-value of 4.66 for 4 degrees of freedom, p=0.33. The SOE was rated insufficient for major bleeding at 30 days based on five observational studies with inconsistent results of a direct outcome and a wide confidence interval.

Figure 53. Meta-analysis of triple versus dual therapy on major bleeding at 30 days



CI = confidence interval

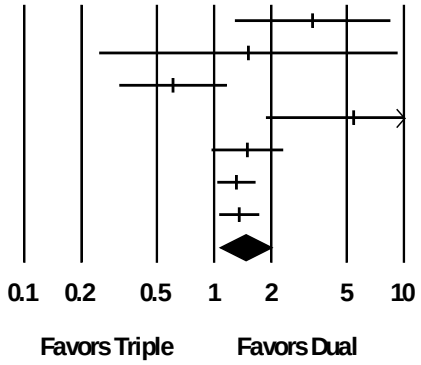
Effect on Major Bleeding at 1 to 5 Years

A random-effects meta-analysis of seven observational studies[135,175,180,186,195,196,203] (6 good quality, 1 fair) including 38,398 UA/NSTEMI patients reporting major bleeding at 1 to 5 years found that the odds ratio for triple therapy was 1.46 (95% CI, 1.07 to 2.00) (Figure 3). There was evidence of heterogeneity, with a Q-value of 16.04 for 6 degrees of freedom, p= 0.014. The I^2 value was 62.59.

Three observational studies[178,132,190] reported major bleeding at long-term followup but were not included in the analysis because of different treatment comparison groups and/or very low event rates. In one study[178] comparing three treatment arms (clopidogrel plus aspirin; clopidogrel plus aspirin plus LMWH; and clopidogrel plus aspirin plus oral anticoagulant), only two severe bleeding events occurred—both in the clopidogrel plus aspirin arm. The other study[190] comparing aspirin versus warfarin versus aspirin plus warfarin found a significantly increased risk of bleeding at 2 years among patients treated with warfarin compared with those treated with aspirin (OR 1.85; 95% CI, 1.54 to 2.22) and among those treated with warfarin plus aspirin compared with aspirin alone (OR 1.84; 95% CI, 1.23 to 2.76). In the third study,[132] which evaluated aspirin and/or thienopyridine versus oral anticoagulant with or without an antiplatelet agent among patients at high bleeding risk (HAS-BLED $\geq$ 3), major bleeding at 1 year was significantly increased in patients on an oral anticoagulant (11.8% versus 4.0%; HR 3.03, 95%CI 1.24 to 7.38; p=0.01). The SOE was rated low favoring DAPT for major bleeding outcomes at 1 to 5 years based on six observational studies with inconsistent results of a direct outcome and a precise estimate.

Figure 54. Meta-analysis of triple versus dual therapy on major bleeding at 1 to 5 years

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Triple Therapy	Dual Therapy
Karjalainen, 2007	3.30	1.29	8.49	0.01	18 / 219	6 / 227
Rossini, 2008	1.52	0.25	9.27	0.65	3 / 102	2 / 102
Ruiz-Nodar, 2008	0.61	0.32	1.17	0.14	16 / 178	27 / 195
Jang, 2011	5.43	1.87	15.74	0.00	9 / 84	6 / 278
Persson, 2011	1.50	0.97	2.31	0.07	22 / 1183	335 / 26789
Fosbol, 2012	1.31	1.04	1.66	0.02	109 / 731	335 / 2841
Lamberts, 2013	1.36	1.06	1.73	0.01	117 / 1896	166 / 3590
	1.46	1.07	1.99	0.02		



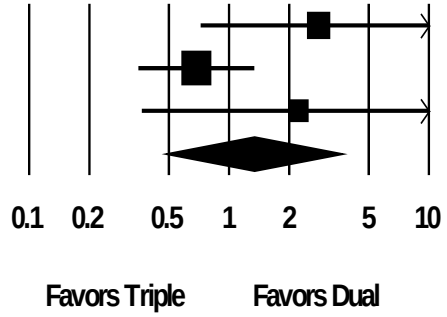
CI = confidence interval

Effect on Minor Bleeding at 1 to 5 Years

A random-effects meta-analysis of three observational studies[146,180,195] (2 good quality, 1 poor) including 890 UA/NSTEMI patients reporting minor bleeding at 1 to 5 years found that the odds ratio for triple therapy compared with DAPT was 1.33 (95% CI, 0.48 to 3.69) (Figure 55). There was some evidence of heterogeneity, with a Q-value of 4.22 for 2 degrees of freedom, p=0.12. The SOE was rated insufficient based on three observational studies with inconsistent results of a direct outcome and a wide confidence interval.

Figure 55. Meta-analysis of triple versus dual therapy on minor bleeding at 1 to 5 years

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Triple Therapy	Dual Therapy
Rossini, 2008	2.81	0.72	10.91	0.14	8 / 102	3 / 102
Ruiz-Nodar, 2008	0.69	0.35	1.33	0.27	16 / 178	25 / 195
Jang, 2011	2.23	0.37	13.59	0.38	2 / 84	3 / 278
	1.33	0.48	3.69	0.58		



CI = confidence interval

Effect on Major and Minor Bleeding

One good-quality observational study[175] comparing DAPT with triple therapy found a nonsignificant increase in major and minor bleeding at 18 months followup among UA/NSTEMI patients treated with triple therapy after discharge (10.8% vs.4.9%, p=0.1). Another good-quality observational study[190] compared aspirin, warfarin, aspirin plus warfarin, aspirin plus a thienopyridine (DAPT), and aspirin plus warfarin plus a thienopyridine (triple therapy). In the triple therapy group, only 1 of 141 had a bleeding event (or 1 bleeding event per 11.8 patient-years), and the authors were unable to calculate an odds ratio. In the DAPT group, there was an incidence rate per patient-year of 0.07 (95% CI, 0.04 to 0.10). Both studies failed to show a difference between DAPT and triple therapy in the combined endpoint of major and minor bleeding. The overall SOE was rated insufficient based on two observational studies with consistent results of a direct outcome and imprecise estimates.

Effect on Stent Thrombosis

Two observational studies reported stent thrombosis at 1 and 3 years. One good-quality study[186] comparing triple therapy with DAPT found no difference in the rate of stent thrombosis at 1 year between the two treatment groups (4.1% vs.1.3%, OR 3.2; 95% CI, 0.8 to 12.1, p=0.09). One poor-quality observational study[195] comparing triple therapy with DAPT found no significant difference in the rate of stent thrombosis at 3 years between the two treatment groups (1.4% vs.3.6%, p=0.206). The SOE was rated insufficient for stent thrombosis outcomes due to inconsistent and imprecise results.

Findings by Subgroup (KQ 3d)

One good-quality observational study[188] reported variations in treatment effectiveness by subgroup. Subgroups analyzed were diabetes, sex, and age. Table H-3 in Appendix H presents the results data for these subgroups.

Diabetes

One study comparing dual antiplatelet therapy versus triple therapy reported all-cause mortality at 1 year[188] and found no difference in the rate of all-cause mortality at 30 days between the two treatment groups among patients with diabetes (RR 0.85; 95% CI, 0.56 to 1.30). However a significantly lower rate of all-cause mortality at 30 days was found among nondiabetic patients in the triple therapy group compared with those treated with dual antiplatelet therapy (RR 0.64; 95% CI, 0.47 to 0.86).

Age

The same study reported all-cause mortality by age group (≤75 years vs. >75 years)[188] and found a significantly lower rate of all-cause mortality at 30 days among patients receiving triple therapy in both age groups (≤75 RR 0.61; 95% CI, 0.40 to 0.93; >75 RR 0.71; 95% CI, 0.53 to 0.96).

Sex

This study also reported all-cause mortality by sex[188] and found a significantly lower rate of all-cause mortality at 30 days among patients receiving triple therapy in men (RR 0.60; 95% CI, 0.43 to 0.82) but not in women (RR 0.93; 95% CI, 0.64 to 1.36).

Summary of Results for Dual Antiplatelet Versus Triple Therapy

In our analysis of DAPT versus triple therapy, we present the findings from studies comparing treatment groups that received two antiplatelet agents with groups that received long-term anticoagulation in addition to the two antiplatelet agents. Indications for long-term anticoagulation include atrial fibrillation, presence of a prosthetic valve, chronic deep venous thrombosis, or hypercoagulable states (e.g., protein C or S deficiency). We found 14 observational studies that examined the differences between adding anticoagulant therapy (i.e., warfarin) to various combinations of antiplatelet therapy. These studies had inconsistent and imprecise findings on the differences between dual and triple therapy on composite ischemic endpoints (all-cause mortality, nonfatal MI, or revascularization and all-cause mortality or nonfatal MI) at all time points—with some studies showing no difference and others showing increases or decreases in events in the triple therapy group. Dual therapy is better than triple therapy in reducing nonfatal MI and major bleeding at 1 year or longer. One observational study of 800 patients that evaluated the effect of dual versus triple therapy showed a significantly lower rate of stroke at 6 months in the triple therapy group, but the evidence from this study was insufficient for nonfatal MI at 6 months. Evidence for an effect of dual therapy versus triple therapy was also insufficient for the outcomes of all-cause mortality at 30 days to 6 months and 1 to 5 years, stroke at 1 to 5 years, revascularization up to 5 years, major bleeding at 30 days, minor bleeding at 1 to 5 years, major and minor bleeding at 1 to 5 years, and stent thrombosis. One observational study of 6,275 patients reported findings in subgroups of sex, age, and patients with diabetes. That study found lower rates of all-cause mortality in men, across all age groups, and in nondiabetic patients receiving triple therapy; SOE was low for the findings by subgroup since only one study was identified. Detailed SOE ratings are shown in Table 28.

Table 28. Detailed strength of evidence for UA/NSTEMI patients treated with dual antiplatelet versus triple therapy

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite of all-cause mortality, nonfatal MI, revascularization, or stroke at 1 year or more					**Insufficient SOE**
4 (8509)	4 observational/2 good quality, 1 fair, 1 poor	Inconsistent	Direct	Imprecise	2 studies showed statistically nonsignificant differences; 2 studies showed statistically significant increases in events in DAPT group
Composite of all-cause mortality or nonfatal MI within first year					**Insufficient SOE**
4 (57,144)	4 observational/All good quality	Inconsistent	Direct	Imprecise	1 study showed a statistically significant increase, 1 a statistically significant decrease in the triple therapy group, and 2 studies showed statistically nonsignificant difference in events between DAPT and triple therapy.
All-cause mortality at 30 days to 6 months					**Insufficient SOE**
2 (7075)	2 observational/Both good quality	Inconsistent	Direct	Unknown	One study found no difference, another found statistically significant lower deaths in in triple therapy group

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
All-cause mortality at 1 to 5 years					**Insufficient SOE**
8 (41,192)	8 observational/4 good quality, 3 fair, 1 poor	Inconsistent	Direct	Imprecise	OR 1.03(0.59 to 1.83)
Nonfatal MI at 6 months					**Insufficient SOE**
1 (800)	Observational/Good quality	NA	Direct	Unknown	Triple therapy 3.3% Warfarin/aspirin 4.5% (p=0.49)
Nonfatal MI at 1 to 5 years					**Low SOE**
4 (1425)	4 observational/2 good quality, 1 fair, 1 poor	Consistent	Direct	Imprecise	OR 1.85 (1.13 to 3.02) Favors DAPT
Stroke at 6 months					**Low SOE**
1 (800)	Observational/Good quality	NA	Direct	Unknown	Triple therapy 0.7% Warfarin/aspirin 3.4% (p=0.02) Favors triple therapy
Stroke at 1 to 5 years					**Insufficient SOE**
4 (6,485)	4 observational/2 good quality, 1 fair, 1 poor	Inconsistent	Direct	Imprecise	OR 1.01 (0.38 to 2.67)
Revascularization up to 5 years					**Insufficient SOE**
4 (2066)	4 observational/3 good quality, 1 poor	Consistent	Direct	Imprecise	No statistical difference between DAPT and triple therapy groups
Major bleeding at 30 days					**Insufficient SOE**
5 (12,339)	5 observational/2 good quality, 3 fair	Inconsistent	Direct	Imprecise	OR 1.70 (0.88 to 3.30)
Major bleeding at 1 to 5 years					**Low SOE**
7 (38,398)	7 observational/6 good quality, 1 fair	Inconsistent	Direct	Precise	OR 1.46 (1.07 to 2.00) Favors DAPT
Minor bleeding at 1 to 5 years					**Insufficient SOE**
3 (890)	3 observational /2 good quality, 1 poor	Inconsistent	Direct	Imprecise	OR 1.33 (0.48 to 3.69)
Major and minor bleeding					**Insufficient SOE**
2 (21,545)	2 observational/Both good quality	Consistent	Direct	Imprecise	Both studies failed to show a difference between DAPT and triple therapy in the combined endpoint of minor and major bleeding.
Stent thrombosis					**Insufficient SOE**
2 (840)	2 observational/1 good quality, 1 poor	Inconsistent	Direct	Imprecise	No significant difference in rates (triple therapy 1.4% to 4.1%; dual antiplatelet 1.3%to 3.6%)

CI = confidence interval; CV = cardiovascular; DAPT = dual antiplatelet therapy; MI = myocardial infarction; NA = not applicable; OR = odds ratio; PPI = proton pump inhibitor; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction

Discussion

Key Findings and Strength of Evidence

In this Comparative Effectiveness Review, we reviewed 175 studies represented by 302 articles that directly compared antiplatelet and anticoagulant medications prescribed for the treatment of UA/NSTEMI. We included 87 unique studies with 354,511 patients treated with an early invasive approach or PCI-based strategy, 33 unique studies with 225,891 patients treated with an initial conservative strategy, and 71 unique studies with 693,539 patients continued on treatment after hospitalization (postdischarge). One of the main challenges in this report was that studies were not easily grouped into the early invasive, initial conservative, or postdischarge strategies.

Another challenge was grouping the studies to come up with valid comparisons of treatments. For some sections we describe the full number of studies that included a comparative study of the treatment of interest, but then describe the ones that were not included in the quantitative analysis due to study design, patient population, or variations in the concomitant antiplatelet or anticoagulation therapy that did not match the other studies. The findings from the studies that were not included in those sections were described qualitatively, and the results are available in the Appendix.

The current evidence base was greatest for the comparative safety and effectiveness of glycoprotein IIb/IIIa inhibitors (GPIs), UFH, enoxaparin, and dual antiplatelet therapy with clopidogrel. Numerous uncertainties remain about the use of newer antiplatelets (e.g., ticagrelor, prasugrel) and newer anticoagulants (e.g., fondaparinux, bivalirudin), as well as the related use of older and newer therapies on specific patient populations of interest.

We provide important information on the SOE that supports, or requires more evidence to support, current antiplatelet- and anticoagulant-prescribing practices as detailed below. This information will help to inform clinical decisionmaking by health care providers and patients and help to inform policymakers about which prescribing patterns have an adequate evidence-base and which findings are less robust. We also define important gaps in knowledge and identify areas in need of future research, which will help guide funding agencies in prioritizing these research areas.

Key Question 1. Early Invasive Approach to UA/NSTEMI

Eighty-seven unique studies evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 354,511 patients with UA/NSTEMI treated with an early invasive approach or PCI-based strategy. Studies that assessed dosage, timing, and combinations of antiplatelet and anticoagulant therapies delivered at the time of PCI were analyzed, including (1) upstream versus deferred GPIs, (2) different loading doses of clopidogrel, (3) clopidogrel versus ticagrelor or prasugrel, (4) bivalirudin versus a heparin-based strategy (without and with planned GPI use), (5) enoxaparin versus UFH versus fondaparinux, and (6) upstream or deferred clopidogrel administration. A narrative of our findings for each comparison is included below, followed by a summary SOE table. The detailed SOE tables are located in the Results section after each comparison.

Upstream Versus Deferred GPI Administration

In our analysis of upstream versus deferred GPI administration, we found no statistically significant difference between upstream and deferred GPI therapy for the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 30 days and 6 months. For the individual outcomes of all-cause mortality and nonfatal MI, there was no statistically significant difference between upstream and deferred GPI therapy at 30 days, but the results are less certain at 6 months since fewer trials reported results at this time point, although the ones that did report outcomes also showed no difference. For revascularization, there was a statistically significant difference favoring upstream GPI therapy at 30 days, but the results are less certain at 6 months due to a small number of trials that showed no difference in outcomes. For bleeding outcomes, there was a statistically significant difference favoring deferred GPI therapy in major bleeding events at 30 days but no statistically significant differences between therapies in minor bleeding events at 30 days. No studies reported the occurrence of stent thrombosis during study followup. In summary, upstream GPI reduced short-term revascularization at the cost of increased short-term major bleeding, and the final impact on clinical outcomes is likely somewhere in the middle, although the studies are too inconsistent or imprecise to determine whether the net benefit is truly zero or whether there is a small benefit from either therapy. Table 29 shows the summary SOE and effect estimates for these outcomes.

Subgroups analyzed in two studies included age, sex, diabetes, chronic renal disease, troponin positivity, and TIMI risk score and most findings showed statistically nonsignificant reductions in ischemic outcomes from upstream GPI; the only statistically significant findings were a lower risk of major bleeding favoring treatment with deferred GPI use in patients over age 65, CrCl less than 60 ml/min, and elevated serum biomarkers (all findings from one RCT).

Table 29. Summary strength of evidence and effect estimates: upstream versus deferred glycoprotein inhibitors

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Low (6 RCTs; 19,662 patients) OR 0.88 (0.77 to 1.01); no difference
Composite of all-cause mortality, nonfatal MI, or revascularization after 6 months	SOE = Insufficient (4 RCTs; 773 patients) Insufficient evidence due to imprecision: OR 0.77 (0.46 to 1.28)
All-cause mortality at 30 days	SOE=Insufficient (10 RCTs, 20,521 patients) Insufficient evidence due to inconsistency and imprecision, with a CI that crosses 1: OR 0.80 (0.57 to 1.11)
All-cause mortality at 6 months	SOE = Insufficient (3 RCTs; 673 patients) Insufficient evidence due to inconsistency and imprecision: 1 study reported no deaths in either arm; 1 study reported 1 death in the upstream GPI arm; 1 study reported similar rates (2.0% upstream GPI, 3.6% deferred GPI)
Nonfatal MI at 30 days	SOE = Insufficient (9 RCTs; 20,263 patients) Insufficient evidence due to inconsistency and imprecision: OR 0.84 (0.65 to 1.10)
Nonfatal MI at 6 months	SOE = Insufficient (3 RCTs; 673 patients) Insufficient evidence due to inconsistency and imprecision: 1 study reported 1 MI in the deferred GPI arm only; 2 other studies reported MI rates of 12% upstream vs. 15% deferred, and 10% upstream vs. 9% deferred

Table 29. Summary strength of evidence and effect estimates: upstream versus deferred glycoprotein inhibitors (continued)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Revascularization at 30 days	SOE = High (6 RCTs; 19,454 patients) OR 0.77 (0.65 to 0.92); favors upstream GPI
Revascularization at 6 months	SOE = Insufficient (3 RCTs; 673 patients) Insufficient evidence due to inconsistency and imprecision: OR 0.69 (0.34 to 1.39)
Major bleeding at 30 days	SOE = High (9 RCTs; 20,242 patients) OR 1.24 (1.08 to 1.43); favors deferred GPI
Minor bleeding at 30 days	SOE = Insufficient (5 RCTs; 969 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.58 (0.95 to 2.64)
Stent thrombosis at 30 days	SOE = Insufficient (0 studies; 0 patients)

CI = confidence interval; GPI = glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor upstream GPI; ORs greater than 1 favor deferred GPI.

Clopidogrel Loading Dose of 300 mg Versus 600 mg

In our analysis of clopidogrel loading doses (300 mg vs. 600 mg), each of the six studies reported different composite ischemic outcomes, thus prohibiting a meta-analysis. One large RCT reported no differences by loading dose for the composite endpoint of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days. For the individual outcomes of all-cause mortality and cardiovascular mortality, there were no statistically significant differences between clopidogrel loading doses. For nonfatal MI, there was a statistically nonsignificant difference in event rate but a trend favoring clopidogrel 600 mg loading dose at 30 days. There was a statistically significant lower rate of stent thrombosis favoring a clopidogrel loading dose of 600 mg versus 300 mg. Insufficient evidence exists for the comparative effectiveness of clopidogrel loading doses on composite ischemic endpoints, cardiovascular mortality at 30 days, nonfatal MI at 6 months, nonfatal stroke, revascularization, major bleeding, and minor bleeding, with most of these outcomes reported in smaller trials with imprecise estimates. Table 30 shows the summary SOE and effect estimates for these outcomes.

Subgroups analyzed in one study included age, sex, diabetes mellitus, GRACE risk score, the performance of PCI after randomization, and the presence of smoking. The analyses showed nonsignificant reductions in composite ischemic events favoring clopidogrel 600 mg for five subgroup categories, with statistically significant findings in patients who underwent PCI after randomization.

Table 30. Summary strength of evidence and effect estimates: 300 mg versus 600 mg clopidogrel loading dose

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days	SOE = Low (1 RCT; 25,086 patients) HR 0.94 (0.83 to 1.06) in this large good-quality RCT sufficiently powered to assess this composite endpoint; no difference
Composite of cardiovascular mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (1 RCT; 119 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (10.4% vs. 23.8%)
Composite of cardiovascular mortality, nonfatal MI, or recurrent ACS at 30 days	SOE = Insufficient (1 RCT; 387 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (4.8% vs. 12.3%)
Composite of all-cause mortality, nonfatal MI, revascularization, or rehospitalization at 30 days	SOE = Insufficient (1 RCT; 103 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (5.9% vs. 11.4%)
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (1 RCT; 255 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (4.0% vs. 11.6%)
Composite of all-cause mortality, nonfatal MI, nonfatal stroke, or rehospitalization at 6 months	SOE = Insufficient (1 RCT; 256 patients) Insufficient evidence due to imprecision: no difference in event rates between groups (13.3% vs. 13.2%)
All-cause mortality at 30 days	SOE = Low (3 RCTs; 25,802 patients) 2 small studies reported no deaths in either group; largest study reported HR 0.93 (0.83 to 1.05); no difference
All-cause mortality at 6 months	SOE = Insufficient (1 RCT; 256 patients) Insufficient evidence due to sparse data: 3 deaths in 300 mg group; 1 death in 600 mg group
Cardiovascular mortality at 30 days	SOE = Low (3 RCTs; 25,497 patients) HR 0.95 (0.81 to 1.13) in the large good-quality RCT; no difference
Nonfatal MI at 30 days	SOE = Low (5 RCTs; 25,855 patients) OR 1.74 (0.99 to 3.05); favors 600 mg dose
Nonfatal MI at 6 months	SOE = Insufficient (1 RCT; 256 patients) Insufficient evidence due to imprecision: higher MI rate in 600 mg group (8.6% vs. 5.0%; p = 0.26)
Nonfatal stroke at 30 days	SOE = Insufficient (2 RCTs; 25,378 patients) Insufficient evidence due to imprecision: largest study reported HR 1.19 (0.84 to 1.68); smaller study reported 2 strokes in 300 mg group, 1 stroke in 600 mg group
Nonfatal stroke at 6 months	SOE = Insufficient (1 RCT; 256 patients) Insufficient evidence due to sparse data: only 1 stroke in overall cohort (600 mg group)
Revascularization at 30 days	SOE = Insufficient (3 RCTs; 477 patients) Insufficient evidence due to inconsistency and low overall event rate, ranging from 0 to 1.3% in 600 mg group and from 0 to 4.8% in 300 mg group
Revascularization at 6 months	SOE = Insufficient (1 RCT; 256 patients) Insufficient evidence due to imprecision: lower incidence in 600 mg group (2.3% vs. 3.3%; p = 0.64)
Major bleeding at 30 days	SOE = Insufficient (6 RCTs; 26,111 patients) Insufficient evidence due to inconsistency and imprecision: 3 studies reported no bleeding events; inconsistent findings from 3 other studies, with largest study reporting HR 1.09 (0.89 to 1.34)
Minor bleeding at 30 days	SOE = Insufficient (5 RCTs; 25,819 patients) Insufficient evidence due to inconsistency and imprecision: incidence ranged from 0.8% to 9.5% in 300 mg group and from 0.8% to 3.9% in 600 mg group
Stent thrombosis at 30 days	SOE = Low (1 RCT; 17,263 patients) HR 0.68 (0.55 to 0.85); favors 600 mg dose

ACS = acute coronary syndrome; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

Clopidogrel Versus Ticagrelor or Prasugrel (PCI Cohort)

In our analysis of studies comparing clopidogrel, ticagrelor, or prasugrel, two studies reported a lower incidence of the composite outcome of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days in patients treated with prasugrel or ticagrelor. When this same composite endpoint was measured after 1 year, both ticagrelor and prasugrel had lower event rates than clopidogrel. Prasugrel reduced the composite endpoint of cardiovascular mortality, nonfatal MI, or revascularization at 15 months compared with clopidogrel. There was insufficient evidence for the following individual outcomes at 30 days: all-cause mortality, cardiovascular mortality, nonfatal MI, nonfatal stroke, major bleeding, and minor bleeding. There was also insufficient evidence for nonfatal stroke after 1 year. However after 1 year, all-cause mortality and cardiovascular mortality had statistically significant decreases in event rates in patients treated with ticagrelor; but, the difference in event rates between prasugrel and clopidogrel was not statistically significant. For nonfatal MI after 1 year, there was a statistically significant difference in event rates favoring both ticagrelor and prasugrel when compared with clopidogrel. None of the studies reported revascularization event rates at 30 days; after 6 months, one study found a statistically significant reduction favoring prasugrel. After 1 year, there was no statistically significant difference in major bleeding event rates between ticagrelor and clopidogrel; however, prasugrel was associated with higher major bleeding event rates than clopidogrel. For stent thrombosis, there was a statistically significant difference in event rates favoring ticagrelor and prasugrel when compared with clopidogrel. Table 31 shows the summary SOE and effect estimates for these outcomes.

Subgroup findings from two studies included age, sex, race, diabetes mellitus, chronic kidney disease, troponin positivity, TIMI risk score, weight, prior TIA or stroke, prior coronary revascularization, the performance of PCI after randomization, type of coronary stent, geographic location, and high risk of bleeding. Both studies showed similar reductions in ischemic outcomes on patients receiving the newer agent (prasugrel or ticagrelor) compared with clopidogrel across all subgroups; most subgroups' differences were not statistically significant, except among subgroups where the sample size was sufficiently large to detect a difference.

Table 31. Summary strength of evidence and effect estimates: clopidogrel versus ticagrelor or prasugrel

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (2 RCTs; 19,608 patients) Insufficient evidence due to inconsistency and imprecision: compared with clopidogrel (3.8% and 5.4%), ticagrelor had mixed results (4.3% and 4.8%)
	Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) Compared with clopidogrel (7.4%), prasugrel (5.7%) was associated with lower composite endpoint; favors prasugrel
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (12.6%), ticagrelor (10.6%) was associated with lower composite endpoint; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) HR 0.81 (0.73 to 0.90) Compared with clopidogrel (12.1%), prasugrel (9.9%) was associated with lower composite endpoint at 15 months; favors prasugrel

Table 31. Summary strength of evidence and effect estimates: clopidogrel versus ticagrelor or prasugrel (continued)

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Composite of cardiovascular mortality, nonfatal MI, or revascularization at 15 months	Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) HR 0.81 (0.73 to 0.87); favors prasugrel
All-cause mortality at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 0.6%, ticagrelor 1.9%; p = 0.18
All-cause mortality after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (5.9%), ticagrelor (4.5%) was associated with fewer deaths; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Low (1 RCT; 13,608 patients) Compared with clopidogrel (3.2%), prasugrel (3.0%) was associated with fewer deaths; favors prasugrel
Cardiovascular mortality at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 0.6%, ticagrelor 1.9%; p = 0.18
Cardiovascular mortality after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (5.1%), ticagrelor (4.0%) was associated with fewer cardiovascular deaths; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Low (1 RCT; 13,608 patients) Compared with clopidogrel (2.4%), prasugrel (2.1%) was associated with fewer cardiovascular deaths; favors prasugrel
Nonfatal MI at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 3.5%, ticagrelor 2.2%; p = 0.34
Nonfatal MI after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (6.9%), ticagrelor (5.8%) was associated with fewer MIs; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) Compared with clopidogrel (9.5%), prasugrel (7.3%) was associated with fewer MIs; favors prasugrel
Nonfatal stroke at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 0.3%, ticagrelor 0.6%; p = 0.57
Nonfatal stroke after 1 year	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 18,624 patients) Insufficient evidence due to imprecision: clopidogrel 1.3%, ticagrelor 1.5% Clopidogrel vs. prasugrel: SOE = Insufficient (1 RCT; 13,608 patients) Insufficient evidence due to imprecision: clopidogrel 1.0%, prasugrel 1.0%
Revascularization at 30 days	Both comparisons: SOE = Insufficient (0 studies; 0 patients)
Revascularization after 6 months	Clopidogrel vs. prasugrel (1 RCT, 13,608 patients) SOE = Moderate HR 0.66 (0.54 to 0.81); favors prasugrel

Table 31. Summary strength of evidence and effect estimates: clopidogrel versus ticagrelor or prasugrel (continued)

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Major bleeding at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 6.9%, ticagrelor 7.1%
Major bleeding after 1 year	Clopidogrel vs. ticagrelor: SOE = Low (1 RCT; 18,624 patients) Compared with clopidogrel (7.7%), ticagrelor (7.9%) had similar event rates; no difference Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) Compared with clopidogrel (1.8%), prasugrel (2.4%) was associated with higher event rates; favors clopidogrel
Minor bleeding at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 1.3%, ticagrelor 2.7%; p = 0.18
Stent thrombosis after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (2.9%), ticagrelor (2.2%) was associated with lower event rates; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) Compared with clopidogrel (2.4%), prasugrel (1.1%) was associated with lower event rates; favors prasugrel

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

Bivalirudin Versus Heparin-Based Strategy

In our analysis of studies comparing bivalirudin versus heparin-based strategy with or without planned GPI use, there were no statistically significant differences in the incidence of the composite endpoints of mortality, nonfatal MI, or revascularization at 30 days, and the data were rated insufficient after 1 year without GPI use and rated low after 1 year with GPI use. When major bleeding was added to this composite outcome (all-cause mortality, nonfatal MI, revascularization, or major bleeding), a statistically significant net clinical difference favoring bivalirudin was observed in the comparison of bivalirudin versus heparin-based strategy plus planned GPI, but there was insufficient evidence for the group without planned GPI. For the individual outcomes of all-cause mortality at 30 days and after 6 months, there was insufficient evidence with or without planned GPI use. For nonfatal MI and revascularization, there was insufficient evidence for the group without planned GPI use. There was no difference in nonfatal MI in patients treated with bivalirudin versus heparin-based strategy at 30 days in the planned GPI group; however, the incidence of nonfatal MI at 6 months in this group was significantly higher in bivalirudin-treated patients when compared with patients treated with heparin-based strategy with planned GPI use although the SOE was rated insufficient for this outcome. For revascularization in the planned GPI group, at 30 days there were higher rates of revascularization in heparin-treated patients (favoring bivalirudin), but revascularization after 6 months was statistically significantly higher in bivalirudin-treated patients when compared with patients treated with heparin-based strategy. For bleeding outcomes, the lower incidence in major and minor bleeding at 30 days was statistically significant favoring bivalirudin when compared

with heparin-based strategy with or without GPI use. There was insufficient evidence for stent thrombosis at 30 days with or without GPI use. Table 32 shows the summary SOE and effect estimates for these outcomes.

Subgroups analyzed included age, sex, diabetes mellitus, chronic kidney disease, serum biomarker positivity, TIMI risk score, weight, and the performance of PCI or CABG after randomization. A majority of the subgroup analyses of the primary composite outcome showed no difference between bivalirudin and a heparin-based strategy, or a statistically nonsignificant reduction that favored bivalirudin.

Table 32. Summary strength of evidence and effect estimates: bivalirudin versus heparin-based strategy without and with planned glycoprotein inhibitor use

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Bivalirudin vs. Heparin-Based Strategy Without Planned GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or major bleeding at 30 days	SOE = Insufficient (1 RCT; 4,571 patients) Insufficient evidence due to imprecision: bivalirudin 8.4% vs. heparin 8.7%
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: 1 study found no difference, OR 1.19 (0.92 to 1.54); 1 study found statistically significant lowering in the bivalirudin group, OR 0.42 (0.21 to 0.84)
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: 1 study found no difference, OR 0.97 (0.83 to 1.13); 1 study found statistically significant lowering in the bivalirudin group, OR 0.58 (0.37 to 0.92)
All-cause mortality at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to inconsistency and imprecision: OR 0.46 (0.12 to 1.81)
All-cause mortality after 6 months	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: disparate results in 2 RCTs: bivalirudin 1.2% vs. heparin 2.4%; bivalirudin 1.9% vs. heparin 1.7%
Nonfatal MI at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.00 (0.64 to 1.55)
Nonfatal MI after 6 months	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: disparate results in 2 RCTs: bivalirudin 3.3% vs. heparin 5.7%; bivalirudin 6.0% vs. heparin 5.3%
Revascularization at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.10 (0.60 to 2.04)
Revascularization after 6 months	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to imprecision: lower rate of revascularization in bivalirudin-treated patients (4.1% and 11.2%) vs. heparin-treated (5.7% and 12.5%)
Major bleeding at 30 days	SOE = High (3 RCTs; 5,822 patients) OR 0.63 (0.47 to 0.85); favors bivalirudin
Minor bleeding at 30 days	SOE = Low (3 RCTs; 5,822 patients) OR 0.64 (0.43 to 0.95); favors bivalirudin
Stent thrombosis at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to imprecision: OR 1.42 (0.64 to 3.15)

Table 32. Summary strength of evidence and effect estimates: bivalirudin versus heparin-based strategy without and with planned glycoprotein inhibitor use (continued)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Bivalirudin vs. Heparin-Based Strategy With Planned GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or major bleeding at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 0.87 (0.78 to 0.97); favors bivalirudin
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 1.07 (0.95 to 1.22); no difference
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Low (2 RCTs; 10,566 patients) Both RCTs found no difference between treatments: OR 1.11 (0.74 to 1.63) and OR 1.08 (0.92 to 1.25); no difference
All-cause mortality at 30 days	SOE = Insufficient (3 RCTs; 12,287 patients) Insufficient evidence due to imprecision: OR 1.21 (0.89 to 1.65)
All-cause mortality after 6 months	SOE = Insufficient (2 RCTs; 10,566 patients) Insufficient evidence due to imprecision: similar event rate in 1 RCT (3.8% bivalirudin, 3.8% GPI); slightly lower event rate in other RCT (0.9% bivalirudin,1.3% GPI; p = 0.46)
Nonfatal MI at 30 days	SOE = Moderate (3 RCTs; 12,287 patients) OR 1.06 (0.92 to 1.23); no difference
Nonfatal MI after 6 months	SOE = Moderate (2 RCTs; 10,566 patients) Higher event rate with bivalirudin (7.8% and 8.1%) vs. heparin (6.9% and 7.6%); favors heparin
Revascularization at 30 days	SOE = Low (3 RCTs; 12,287 patients) OR 1.11 (0.86 to 1.42); favors bivalirudin
Revascularization after 6 months	SOE = Low (2 RCTs; 10,566 patients) Higher event rate with bivalirudin (8.7% and 11.7%) vs. heparin (8.4% in both studies); favors heparin
Major bleeding at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 0.52 (0.43 to 0.63); favors bivalirudin
Minor bleeding at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 0.49 (0.42 to 0.59); favors bivalirudin
Stent thrombosis at 30 days	SOE = Insufficient (2 RCTs; 10,936 patients) Insufficient evidence due to imprecision: similar event rates between treatment arms in both studies (bivalirudin 0.7% to 1.0%; heparin 0.6% to 0.8%)

CI = confidence interval; GPI = glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor bivalirudin; ORs greater than 1 favor heparin-based strategy.

Enoxaparin Versus Unfractionated Heparin Versus Fondaparinux (PCI Cohort)

In our analysis of studies comparing enoxaparin, UFH, and fondaparinux, we used subgroups of UA/NSTEMI patients who underwent early invasive treatment. This limited the available outcomes to a composite ischemic outcome prior to 7 days, at 30 days, and after 6 months, and the incidence of major bleeding at 30 days. There were no significant differences in the incidence of the composite ischemic endpoints prior to 7 days between enoxaparin and heparin, or at 30 days between enoxaparin, UFH, and fondaparinux. At 6 months, there was no difference in the composite ischemic endpoint between enoxaparin and fondaparinux. For bleeding outcomes, there was a lower and statistically significant incidence in major bleeding at 30 days favoring fondaparinux when compared with enoxaparin; the rates of major bleeding in the enoxaparin

versus UFH studies were inconsistent. Table 33 shows the summary SOE and effect estimates for these outcomes.

Subgroup analyses from three studies included age, sex, diabetes mellitus, chronic kidney disease, presence of smoking, prior coronary revascularization, serum biomarker positivity, TIMI risk score, and geographic location. Most showed nonsignificant reductions in composite outcomes in the enoxaparin and fondaparinux groups; there was a significant reduction in major bleeding in older persons treated with either enoxaparin or fondaparinux compared with UFH which are consistent with the total population findings.

Table 33. Summary strength of evidence and effect estimates: enoxaparin versus unfractionated heparin versus fondaparinux (percutaneous coronary intervention cohort)

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Composite ischemic endpoints prior to 7 days	Enoxaparin vs. UFH: SOE = Low (1 RCT; 3,987 patients) HR 0.89 (0.75 to 1.05); no difference (adequately powered for noninferiority hypothesis)
	Fondaparinux vs. UFH: SOE = Insufficient (1 RCT; 350 patients) Insufficient evidence due to imprecision: 4.2% vs. 6%
Composite ischemic endpoints at 30 days	Enoxaparin vs. UFH: SOE = Low (2 RCTs; 10,773 patients) 14% vs. 14.5% and 14% vs. 16.1%; no difference Enoxaparin vs. fondaparinux: SOE = Low (1 RCT; 20,078 patients) 7.4% vs. 7.4%; no difference
Composite of all-cause mortality, nonfatal MI, or revascularization at 6 months	Enoxaparin vs. fondaparinux: SOE = Low (1 RCT; 20,078 patients) Enoxaparin 10.2% and fondaparinux 10.1%; no difference (adequately powered for noninferiority hypothesis)
Major bleeding at 30 days	Enoxaparin vs. UFH: SOE = Moderate (1 RCT; 10,027 patients) Lower event rates with UFH (7.6%) vs. enoxaparin (9.1%); favors UFH Enoxaparin vs. UFH: SOE = Low (2 observational studies; 29,017 patients) Lower event rates with enoxaparin (2.7% UFH vs. 1.8% enoxaparin; 7% UFH vs. 6.7% enoxaparin); favors enoxaparin Enoxaparin vs. fondaparinux: SOE = Moderate (1 RCT; 20,078 patients) Lower event rates with fondaparinux (3.1%) vs. enoxaparin (5.0%); p <0.001; favors fondaparinux

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence; UFH = unfractionated heparin

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

Upstream or Deferred Clopidogrel for Patients Undergoing PCI for UA/NSTEMI in Studies With a Defined Anticoagulant or Intravenous Antiplatelet Strategy

In randomized comparisons of patients treated with (1) bivalirudin versus heparin-based strategy and (2) upstream versus deferred GPI use, the nonrandomized effectiveness and safety of clopidogrel pretreatment and deferred clopidogrel treatment was assessed. In these analyses, patients pretreated with clopidogrel and randomized to a heparin-based strategy had no differences in composite ischemic outcomes compared with patients randomized to bivalirudin,

but the evidence was insufficient. However, the occurrence of major bleeding was significantly lower in bivalirudin-treated patients when compared with heparin-treated patients. There were no significant differences in the occurrence of composite ischemic endpoints at 1 year or all-cause mortality at 1 year between bivalirudin and heparin groups, based on insufficient SOE. Patients pretreated with clopidogrel and randomized to upstream GPI use had a trend toward fewer composite ischemic outcomes at 30 days and fewer deaths at 30 days when compared with patients randomized to deferred GPI use. There was insufficient SOE for the composite outcome at 96 hours, and the composite of all-cause mortality, nonfatal MI, or rehospitalization at 30 days. The occurrence of major bleeding at 30 days was significantly higher in patients pretreated with clopidogrel who were randomized to upstream GPI when compared with deferred GPI use.

In patients treated with deferred clopidogrel strategy, there were conflicting results for composite ischemic events at 30 days in patients randomized to bivalirudin when compared with heparin-based strategy, therefore the SOE was insufficient. There was low SOE for the effect on major bleeding at 30 days in those patients treated with deferred clopidogrel and randomized to bivalirudin, with one good-quality study showing a reduction in major bleeding favoring bivalirudin. In studies of patients treated with deferred clopidogrel and randomized to upstream GPI, there was insufficient SOE for composite ischemic outcomes at 30 days and low SOE for no difference in all-cause mortality at 30 days. The occurrence of major bleeding at 30 days was significantly higher in patients treated with deferred clopidogrel who were randomized to upstream GPI when compared with deferred GPI use. Detailed SOE ratings are shown in Tables 11–14. Odds ratios less than 1 favor bivalirudin or upstream GPI; odds ratios greater than 1 favor a heparin-based strategy or deferred GPI use. Table 34 shows the summary SOE and effect estimates for these outcomes.

Table 34. Summary strength of evidence and effect estimates: clopidogrel upstream (pretreatment) and deferred treatment strategies

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Upstream Clopidogrel: Bivalirudin vs. Heparin-Based Strategy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Low (2 RCTs; 7,104 patients) Both studies showed no statistically significant difference in composite event rates ranging from OR 1.11 to 1.25; no difference
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Insufficient (1 RCT; 4,570 patients) Insufficient evidence due to imprecision: bivalirudin 21.5%, heparin 20.1%
All-cause mortality at 1 year	SOE = Insufficient (1 RCT; 5,126 patients) Insufficient evidence due to imprecision: bivalirudin 16.0%, heparin 16.3%
Major bleeding at 30 days	SOE = Moderate (3 RCTs; 6,322 patients) OR 0.65 (0.49 to 0.85); favors bivalirudin
Upstream Clopidogrel: Upstream vs. Deferred GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or thrombotic bailout with GPI at 96 hours	SOE = Insufficient (1 RCT; 6,895 patients) Insufficient evidence due to imprecision: upstream GPI 8.7%, deferred GPI 9.4%
Composite of all-cause mortality, nonfatal MI, or rehospitalization at 30 days	SOE = Insufficient (1 RCT; 300 patients) Insufficient evidence due to imprecision: upstream GPI 9%, deferred GPI 10%
Composite of all-cause mortality, nonfatal MI, or ischemia/ revascularization at 30 days	SOE = Low (2 RCTs; 638 patients) Upstream GPI 15.7%, deferred GPI 20.3%; favors upstream GPI
All-cause mortality at 30 days	SOE = Low (5 RCTs; 8,168 patients) OR 0.56 (0.30 to 1.05); favors upstream GPI

Table 34. Summary strength of evidence and effect estimates: clopidogrel upstream (pretreatment) and deferred treatment strategies (continued)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Upstream Clopidogrel: Upstream vs. Deferred GPI Use (continued)	
Major bleeding at 30 days	SOE = Moderate (5 RCTs; 7,416 patients) OR 1.49 (1.10 to 2.01); favors deferred GPI
Deferred Clopidogrel: Bivalirudin vs. Heparin-Based Strategy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (2 RCTs; 2,571 patients) Insufficient evidence due to inconsistency and imprecision: 1 RCT (fair) showed a significant reduction favoring bivalirudin, OR 0.42 (0.21 to 0.84; p = 0.02); the other RCT (good) showed no difference, OR 1.05 (0.80 to 1.40)
Major bleeding at 30 days	SOE = Low (2 RCTs; 2,571 patients) 1 RCT (fair) showed no statistical difference between the groups, OR 0.32 (0.10 to 1.01); the other RCT (good) showed a statistically significant reduction favoring bivalirudin, OR 0.53 (0.31 to 0.91, p = 0.02); favors bivalirudin
Deferred Clopidogrel: Upstream vs. Deferred GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or thrombotic bailout with GPI at 96 hours	SOE = Insufficient (1 RCT; 2,271 patients) Insufficient evidence due to imprecision: upstream GPI 10.3%, deferred GPI 11.2%
All-cause mortality at 30 days	SOE = Low (4 RCTs; 11,858 patients) OR 0.97 (0.80 to 1.18); no difference
Major bleeding at 30 days	SOE = High (3 RCTs; 11,698 patients) OR 1.27 (1.08 to 1.50); favors deferred GPI

CI = confidence interval; GPI = glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence; UFH = unfractionated heparin

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor bivalirudin or upstream GPI; ORs greater than 1 favor UFH or deferred GPI.

Key Question 2. Initial Conservative Approach to UA/NSTEMI

Thirty-three studies evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 225,891 patients with UA/NSTEMI treated with an initial conservative approach or a mixed population for whom the approach (conservative or invasive) was not presented separately. Thus we present the findings of studies comparing (1) UFH versus enoxaparin or fondaparinux in the conservatively managed or total population (if results by treatment strategy are not presented) and (2) GPI plus UFH versus UFH alone in a patient population where coronary angiography was discouraged in the first 24 to 60 hours after study drug administration or in populations who did not receive PCI, and (3) clopidogrel versus ticagrelor or prasugrel. A narrative of our findings for each comparison is included below, followed by a summary SOE table. The detailed SOE tables are located in the Results section after each comparison.

Unfractionated Heparin Versus Enoxaparin or Fondaparinux

In our analysis of studies that evaluated the use of UFH versus enoxaparin or fondaparinux, we present the findings of UA/NSTEMI patients who received primarily initial conservative treatment. From the comparison of enoxaparin and UFH, there was a significant reduction in composite ischemic events and nonfatal MI at around 30 days with enoxaparin. There was insufficient evidence for the outcomes of all-cause mortality and major bleeding at around 30 days. From an indirect comparison of fondaparinux and UFH, there was a significant reduction in composite ischemic events and a nonsignificant reduction in major bleeding events favoring

fondaparinux. Evidence was insufficient for the outcomes of nonfatal MI and all-cause mortality at around 30 days in this comparison. Results from observational studies show that use of low molecular weight heparin is increasing over time in the conservatively managed population. Use of low molecular weight heparin was associated with fewer ischemic events and similar or lower bleeding events compared with UFH. Fondaparinux was associated with lower adjusted mortality than UFH and similar adjusted mortality enoxaparin. In an RCT, fondaparinux significantly lowered mortality at 30 days and 180 days and major bleeding at 9 days compared with enoxaparin. Table 35 shows the summary SOE and effect estimates for these outcomes.

Subgroups analyzed were dosage, obesity, renal impairment, and ECG changes. Excess dosage was associated with more major bleeding and death and was more likely to be received by older, smaller, and female patients. Use of enoxaparin was associated with lower rates of ischemic events in obese patients, those with renal impairment, and those with ST depression on ECG.

Table 35. Summary strength of evidence and effect estimates: unfractionated heparin versus enoxaparin or fondaparinux (full UA/NSTEMI cohort)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Composite endpoint of all-cause mortality, nonfatal MI, revascularization, or recurrent ischemia at around 30 days	Enoxaparin vs. UFH: SOE = High (6 RCTs; 12,124 patients) OR 0.84 (0.76 to 0.93); favors enoxaparin Fondaparinux vs. UFH: SOE = Low (1 RCT; 20,078 patients) OR 0.78 (0.67 to 0.90); favors fondaparinux
Composite ischemic outcome at 6 months	Enoxaparin vs. fondaparinux: SOE = Low (1 RCT, 20,078 patients) 10.2% vs. 10.1% in large good-quality RCT adequately powered for a noninferiority hypothesis; no difference
All-cause mortality at around 30 days	Enoxaparin vs. UFH: SOE = Low (8 RCTs; 23,015 patients) OR 0.98 (0.84 to 1.14); no difference
	Fondaparinux vs. UFH: SOE = Insufficient (1 RCT; 20,078 patients) Insufficient evidence due to imprecision and indirect comparison: OR 0.93 (0.71 to 1.20)
Nonfatal MI at around 30 days	Enoxaparin vs. UFH: SOE = Moderate (9 RCTs; 22,970 patients) OR 0.85 (0.76 to 0.95); favors enoxaparin
	Fondaparinux vs. UFH: SOE = Insufficient (1 RCT; 20,078 patients) Insufficient evidence due to imprecision and indirect comparison: OR 0.85 (0.69 to 1.04)
Major bleeding at around 30 days	Enoxaparin vs. UFH: SOE = Insufficient (8 RCTs; 22,901 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.11 (0.81 to 1.51)
	Fondaparinux vs. UFH: SOE = Low (1 RCT; 20,078 patients) OR 0.69 (0.49 to 0.97); favors fondaparinux

CI = confidence interval; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non–ST elevation myocardial infarction; UFH = unfractionated heparin

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor enoxaparin or fondaparinux; ORs greater than 1 favor UFH.

GPI Plus Unfractionated Heparin Versus Unfractionated Heparin Alone

In our analysis of studies comparing GPIs with UFH, we present the findings of UA/NSTEMI patients who received primarily initial conservative treatment. Adding GPIs to UFH reduced the rate of mortality, composite ischemic events, and nonfatal MI, especially in trials of eptifibatide and tirofiban, and increased the rate of minor bleeding at 30 days. The addition of abciximab to UFH did not significantly reduce ischemic events compared with UFH alone. There was insufficient evidence for the effect of GPIs on recurrent ischemia, major bleeding, and revascularization, although fewer revascularization events were seen in patients receiving GPIs in two small trials. A sensitivity analysis subgrouping the studies by trial size (small, <1,000 patients; large, ≥1,000 patients) and antiplatelet use (aspirin monotherapy vs. dual antiplatelet therapy) showed that these two factors helped to explain the heterogeneity, if present, in the meta-analyses performed. For the mortality, nonfatal MI, and recurrent ischemia endpoints at 30 days, the smaller sized studies had summary estimates that were more favorable for GPI plus UFH. For the mortality and nonfatal MI endpoints at 30 days, the use of DAPT had summary estimates that were more favorable for GPI plus UFH. Table 36 shows the summary SOE and effect estimates for these outcomes.

Subgroups analyzed were diabetes, sex, age, geographic location, smoking status, and weight. Almost all subgroups experienced a reduction in composite ischemic events from adding GPI therapy to heparin (UFH or low molecular weight heparin). While some subgroups may have had a greater magnitude of benefit, there did not appear to be a significant interaction between the assigned treatment and demographic or clinical variables. Notable exceptions included the PURSUIT trial, where women in the heparin group had fewer ischemic events than the eptifibatide group (statistically nonsignificant), and the GUSTO IV study where women treated with a 48-hour infusion of abciximab had higher event rates.

Table 36. Summary strength of evidence and effect estimates: glycoprotein inhibitor plus unfractionated heparin versus unfractionated heparin alone

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Composite ischemic endpoints up to 30 days	SOE = Moderate (10 RCTs; 38,518 patients) Studies of eptifibatide and tirofiban showed a consistent reduction in composite events compared with UFH alone (RRs 0.58 to 0.84; favors eptifibatide or tirofiban); 1 large trial of abciximab showed no difference in events—24 hr OR 1.00 (CI 0.83 to 1.24); 48 hr OR 1.10 (CI 0.94 to 1.39); a small trial showed a reduction in major events with abciximab (1 out of 30) versus UFH alone (7 out of 30); favors GPI plus UFH
Mortality up to 30 days	SOE = High (9 RCTs; 24,699 patients) OR 0.80 (0.67 to 0.96); favors GPI plus UFH
Nonfatal MI up to 30 days	SOE = Moderate (9 RCTs; 24,699 patients) OR 0.79 (0.61 to 1.02); favors GPI plus UFH
Recurrent ischemia up to 30 days	SOE = Insufficient (6 RCTs; 5,755 patients) Insufficient evidence due to inconsistency and imprecision: OR 0.81 (0.56 to 1.18)

Table 36. Summary strength of evidence and effect estimates: glycoprotein inhibitor plus unfractionated heparin versus unfractionated heparin alone (continued)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Revascularization up to 30 days	SOE = Insufficient (2 RCTs; 279 patients) Insufficient evidence due to imprecision; low number of events reported in both RCTs, with fewer in GPI plus UFH group
Major bleeding up to 30 days	SOE = Insufficient (4 RCTs; 18,855 patients) Insufficient evidence due to imprecision: OR 1.13 (0.80 to 1.59)
Minor bleeding up to 30 days	SOE = High (5 RCTs; 22,259 patients) OR 1.62 (1.20 to 2.19); favors heparin alone

CI = confidence interval; GPI = glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence; UFH = unfractionated heparin

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor GPI plus UFH; ORs greater than 1 favor UFH alone.

Clopidogrel Versus Ticagrelor or Prasugrel (Initial Conservative Cohort)

In our analysis of studies comparing clopidogrel versus ticagrelor or prasugrel, we present the findings of UA/NSTEMI patients who received initial conservative treatment. Ticagrelor reduced the rates of composite ischemic and all-cause mortality events; however, ticagrelor also increased rates of major bleeding, and the combination of major or minor bleeding events. In contrast, prasugrel and clopidogrel had similar rates of composite ischemic and most individual clinical outcomes, except that there was a higher rate of TIMI criteria combined major or minor bleeding events in the prasugrel group at 30 months. Table 37 shows the summary SOE and effect estimates for these outcomes.

Multiple subgroups were analyzed in the TRILOGY ACS study, which found a treatment interaction favoring prasugrel among current/recent users, patients undergoing angiography prior to randomization, and those taking PPIs at randomization on the primary composite endpoint. For the TIMI criteria major bleeding endpoint, the only subgroup with a significant treatment interaction favored patients receiving clopidogrel with a reduced dose of aspirin.

Table 37. Summary strength of evidence for UA/NSTEMI patients treated with clopidogrel versus ticagrelor or prasugrel

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Composite ischemic endpoints up to 30 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) HR 0.85 (0.73 to 1.00); favors ticagrelor Prasugrel vs. clopidogrel: SOE = Moderate (1 RCT; 7,243 patients) HR 0.91 (0.79 to 1.05); no difference
Mortality up to 30 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) HR 0.75 (0.61 to 0.93); favors ticagrelor Prasugrel vs. clopidogrel: SOE = Moderate (1 RCT; 7,243 patients) HR 0.96 (0.79 to 1.16); no difference

Table 37. Summary strength of evidence for UA/NSTEMI patients treated with clopidogrel versus ticagrelor or prasugrel (continued)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Nonfatal MI up to 30 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) HR 0.94 (0.77 to 1.15); no difference Prasugrel vs. clopidogrel: SOE = Moderate (1 RCT; 7,243 patients) HR 0.89 (0.74 to 1.07); no difference
Stroke up to 30 months	Ticagrelor vs. clopidogrel: SOE = Insufficient (1 RCT; 5,216 patients) Insufficient evidence due to imprecision: HR 1.35 (0.89 to 2.07) Prasugrel vs. clopidogrel: SOE = Insufficient (1 RCT; 7,243 patients) Insufficient evidence due to imprecision: HR 0.67 (0.42 to 1.06)
Revascularization up to 12 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) No difference
Major bleeding up to 30 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) HR 1.17 (0.98 to 1.39); favors clopidogrel
	Prasugrel vs. clopidogrel: SOE = Insufficient (1 RCT; 7,243 patients) Insufficient evidence due to imprecision: HR 1.31 (0.81 to 2.11)
Major or minor bleeding up to 30 months	Ticagrelor vs. clopidogrel: SOE = Moderate (1 RCT; 5,216 patients) HR 1.17 (1.01 to 1.36); favors clopidogrel Prasugrel vs. clopidogrel: SOE = Low (1 RCT; 7,243 patients) HR 1.54 (1.06 to 2.23); favors clopidogrel

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence; UA/NSTEMI = unstable angina/non–ST elevation myocardial infarction

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]HRs less than 1 favor ticagrelor or prasugrel; HRs greater than 1 favor clopidogrel.

Key Question 3. Postdischarge Treatment for UA/NSTEMI

Seventy-one studies evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 693,025 patients with UA/NSTEMI continued on treatment after hospitalization (postdischarge). We present the findings of studies comparing (1) low-dose versus high-dose aspirin, (2) single antiplatelet versus dual antiplatelet therapy, (3) short-term versus long-term clopidogrel, (4) antiplatelet therapy with or without the addition of proton pump inhibitors (PPIs), (5) dual antiplatelet versus triple therapy in patients with an indication for long-term anticoagulation (e.g., atrial fibrillation, prosthetic valve). A narrative of our findings for each comparison is included below, followed by a summary SOE table. The detailed SOE tables are located in the Results section after each comparison.

Low-Dose Versus High-Dose Aspirin

In our analysis of low-dose versus high-dose aspirin, we found insufficient evidence for composite ischemic event rates and all-cause mortality at 6 months and 1 year. Nonfatal MI was lower from high-dose aspirin (≥150 mg vs. <150 mg) at 6 months in one study, but the evidence was insufficient from a second, smaller study at 1 year. Insufficient evidence was also found for stroke rates in these two studies at 6 months and 1 year. There were conflicting results on

revascularization rates at 1 year, with one study showing no difference (81 mg vs. 325 mg) and another study showing higher rates of urgent revascularization in the high-dose (≥162 mg) group. The effect on major bleeding at 1 year was also inconsistent, with one fair-quality study reporting higher bleeding rates in the low-dose (81 mg) group and two good-quality studies reporting higher rates in the high-dose group (162 mg or ≥200 mg). Differences in consistency of the results may be that the Harjai[142] and So[172] studies were smaller, single-center studies that had higher rates of clopidogrel use (53% and 99% respectively) while the Aronow,[176] Quinn,[192] Peters,[202] and Mahaffey[201] studies were secondary analyses of larger RCTs (i.e., BRAVO, Gusto IIb, and PURSUIT, CURE, and PLATO)—one of which did not allow use of thienopyridines, one study did not report its use, one study reported results for aspirin monotherapy and dual antiplatelet therapy, and one study had only dual antiplatelet with two different thienopyridine medications In addition, the doses of aspirin compared differed among the six studies. Table 38 shows the summary SOE and effect estimates for these outcomes.

Subgroup analyses included diabetes, multivessel disease, and type of stent from one study comparing low-dose aspirin (81 mg) with high-dose (325 mg) in addition to clopidogrel; geographic location from one study comparing low-dose aspirin (<300 mg) with high-dose (≥300 mg) in patients receiving either ticagrelor or clopidogrel; and diabetes and type of stent from one study comparing low-dose aspirin (81 mg) with high-dose aspirin (161–325 mg). Patients with multivessel disease had higher events rates on low-dose aspirin; however, patients with diabetes, drug-eluting stents, and bare metal stents had similar event rates on low-dose and high-dose aspirin as part of a dual antiplatelet treatment strategy. Patients on low-dose aspirin (<300 mg) and ticagrelor had lower events rates than those on low-dose aspirin and clopidogrel. Patients with diabetes and those with a DES receiving low-dose aspirin both had an increased incidence of bleeding, while patients with diabetes on low-dose aspirin also had an increased rate of death or MI.

Table 38. Summary strength of evidence and effect estimates: low-dose versus high-dose aspirin

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Composite of all-cause mortality, nonfatal MI, or stroke at 6 months	SOE = Insufficient (1 observational study; 20,469 patients) Insufficient evidence due to CI that crosses 1: HR 0.92 (0.79 to 1.07)
Composite of all-cause mortality, nonfatal MI, or stroke at 1 year	SOE = Insufficient (2 observational studies; 31,186 patients) Insufficient evidence due to inconsistency and imprecision: 1 study showed similar rates of composite events across 3 dosage categories for aspirin monotherapy and DAPT; the other study showed lower event rates when combining low-dose aspirin with ticagrelor and high-dose aspirin with clopidogrel
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Insufficient (3 observational studies; 9,249 patients) Insufficient evidence due to imprecision: low-dose aspirin and high-dose aspirin had similar rates of ischemic events in all 3 studies
All-cause mortality at 6 months	SOE = Insufficient (1 observational study; 20,469 patients) Insufficient evidence due to imprecision: HR 0.89 (0.72 to 1.10)
All-cause mortality at 1 year	SOE = Insufficient (2 observational studies; 6,429 patients) Insufficient evidence due to inconsistency and imprecision: 1 study (aspirin/clopidogrel) showed no difference between doses; the other found that high-dose aspirin (monotherapy) reduced mortality
Nonfatal MI at 6 months	SOE = Low (1 observational study; 20,469 patients) HR 0.79 (0.64 to 0.98); favors high-dose aspirin
Nonfatal MI at 1 year	SOE = Insufficient (1 observational study; 4,589 patients) Insufficient evidence due to imprecision: HR 0.98 (0.66 to 1.48)
Stroke at 6 months	SOE = Insufficient (1 observational study; 20,469 patients) Insufficient evidence due to imprecision: HR 1.59 (0.95 to 2.65)

Table 38. Summary strength of evidence and effect estimates: low-dose vs. high-dose aspirin (continued)

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Stroke at 1 year	SOE = Insufficient (1 observational study; 4,589 patients) Insufficient evidence due to imprecision: HR 1.37 (0.94 to 2.00)
Revascularization at 1 year	SOE = Insufficient (2 observational studies; 6,429 patients) Insufficient evidence due to inconsistency and imprecision: 1 study (aspirin/clopidogrel) showed no difference between doses; the other study (aspirin monotherapy) showed more events with high dose
Major bleeding at 1 year	SOE = Low (3 observational studies; 19,971 patients) 1 study had high bleeding rates in low-dose group; 2 studies had high bleeding rates in high-dose group; favors low-dose aspirin

CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; MI = myocardial infarction; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]HRs less than 1 favor high-dose aspirin; HRs greater than 1 favor low-dose aspirin.

Single Antiplatelet Versus Dual Antiplatelet Therapy

Our analysis of single antiplatelet versus dual antiplatelet therapy addresses the question about the effectiveness of combinations of antiplatelet agents. The identified literature predominately reports the comparison of aspirin monotherapy (single antiplatelet) with aspirin plus clopidogrel therapy (dual antiplatelet). Use of newer antiplatelet agents (prasugrel, ticagrelor) with aspirin in comparison to clopidogrel plus aspirin was previously summarized under KQ 1; there we presented the findings from direct comparisons of different dual antiplatelet treatment strategies. In the analysis of single versus dual antiplatelet therapy, dual antiplatelet therapy reduced the rates of composite ischemic outcomes and nonfatal MI in UA/NSTEMI patients based on 3 studies (1 RCT and 2 observational registries). While 5 studies (1 RCT and 4 observational) showed a reduction in all-cause mortality in the dual antiplatelet therapy group, the wide confidence intervals around the reported risk ratios in many of the studies made this finding less precise than the results on composite ischemic outcomes and nonfatal MI. Four out of five studies (2 RCTs and 3 observational studies) showed no significant difference in stroke rates between dual antiplatelet and single antiplatelet therapy; the evidence for this outcome was rated insufficient. The effect of dual antiplatelet therapy on major bleeding varied in three studies (two RCTs and one observational registry), and was also rated insufficient. Table 39 shows the SOE and effect estimates for these outcomes.

Subgroup findings from four studies (two RCTs, two observational registries) assessed the effectiveness based on age, sex, clinical presentation, duration of treatment, receipt of PCI, receipt of any type of revascularization, or presence of diabetes, chronic kidney disease, or smoking (one or two studies reported findings for each subgroup listed). Almost all of the studies showed similar rates of composite ischemic outcomes in the various subgroups, except for subgroup analyses of PCI and treatment duration. One study showed a significantly lower rate of composite ischemic outcomes, and another study showed a significantly lower rate of death in patients who received dual antiplatelet therapy and underwent PCI. One study showed a significantly lower survival rate at 1 year in the groups that received single antiplatelet therapy. Strength of evidence for subgroup findings was rated insufficient given the small number of studies reporting results for each subgroup.

Table 39. Summary strength of evidence and effect estimates: single antiplatelet versus dual antiplatelet therapy

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Composite ischemic endpoints, in-hospital to 1 year	SOE = High (1 RCT, 2 observational studies; 106,749 patients) All studies showed statistically significant lowering of composite events in DAPT arm, ranging from RR 0.69 to OR 0.80; favors DAPT
Stroke, in-hospital to 1 year	SOE = Insufficient (1 RCT, 3 observational studies; 116,136 patients) Insufficient evidence due to inconsistency and imprecision: 3 out of 4 studies showed no statistically significant difference in stroke rates
Nonfatal MI, in-hospital to 1 year	SOE = High (1 RCT, 2 observational studies; 106,749 patients) All studies showed fewer recurrent MIs in DAPT group (2.3% to 5.8%) vs. aspirin alone (3.0% to 8.5%); favors DAPT
All-cause mortality, in-hospital to 1 year	SOE = Moderate (1 RCT, 4 observational studies; 117,467 patients) All studies showed fewer deaths in DAPT group, ranging from OR/RR 0.66 to OR/RR 0.93; favors DAPT
Major bleeding, in-hospital to 9 months	SOE = Low (1 RCT, 1 observational study; 105,607 patients) 2 studies showed a reduction in major bleeding in DAPT group (1 statistically significant [16% vs. 21%]; 1 not statistically significant); favors DAPT

CI = confidence interval; DAPT = dual antiplatelet therapy; MI = myocardial infarction; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

Short-Term Versus Long-Term Dual Antiplatelet Therapy

In our analysis of short-term versus long-term DAPT use, we aimed to address the question about the optimal duration of therapy by comparing short-term to long-term use of clopidogrel. The variations in the duration of therapy and the definitions of short-term and long-term treatment made meta-analysis impossible. Our qualitative analysis showed that DAPT duration of either 6 months or 1 year reduced the rate of composite ischemic events (all-cause mortality, nonfatal MI, or stroke) compared with therapy less than 6 months in duration based on two RCTs; however, the findings from an RCT comparing 6-month and 24-month duration showed no differences in the rate of the same composite outcomes at 2 years. Similar results were found when assessing the effect of DAPT duration on all-cause mortality from the same set of RCTs. In addition, one observational study showed that patients receiving a drug-eluting stent benefited from longer dual antiplatelet therapy more than patients receiving a bare metal stent. Evidence was insufficient for the outcomes of composite ischemic events, all-cause mortality (7 studies), cardiovascular mortality (4 studies), nonfatal MI (6 studies), stroke (3 studies), and revascularization (4 studies). Rates of stent thrombosis (6 studies) were higher when DAPT was stopped within 30 days or 6 months, but the differences between therapies beyond 6 months were nonsignificant, thus the evidence was rated insufficient. Stent thrombosis rates may vary based on use of bare metal or drug-eluting stents. There was insufficient evidence that clopidogrel duration had an effect on major bleeding outcomes, with one RCT showing a significantly lower rate of major bleed with 6-month treatment compared with 24-month therapy, another RCT showing no significant increase in major bleed among patients treated for 28 days compared with 12 months, and a third RCT showing no difference in major bleeding among patients treated for 6 months compared with 12 months. There was also insufficient evidence that clopidogrel duration had an effect on minor bleeding rates, which were similar in the short- and long-term duration groups from the same RCTs. Table 40 shows summary SOE and effect estimates for these outcomes.

Four studies (two good-quality RCTs and two observational of good and fair quality) reported variations in treatment effectiveness by subgroup. Subgroups analyzed were diabetes (3

studies), age (2), sex (1), chronic kidney disease (1), and stent type (2). No differences in composite ischemic events were found among the different subgroup comparisons. The SOE was low based on the small number of studies that reported subgroup findings and the imprecise estimates of effect.

Table 40. Summary strength of evidence and effect estimates: short-term versus long-term dual antiplatelet therapy

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Composite of all-cause mortality or nonfatal MI within 2 years	SOE = Insufficient (2 RCTs, 2 observational studies; 34,179 patients) Insufficient evidence due to heterogeneity of DAPT duration, inconsistency, and imprecision: 2 RCTs showed no difference between 6- and 12-month therapy and 6- and 24-month therapy; 1 observational study showed that discontinuation before 6 months increased events; 1 observational study showed increased events within first 3 months of stopping clopidogrel after 1 year of therapy
Composite of all-cause mortality or stroke at 2 years	SOE = Insufficient (1 RCT; 2,013 patients) Insufficient evidence due to imprecision: no difference between 6- and 24-month therapy
Composite of all-cause mortality, nonfatal MI, or revascularization at 6 months and 1 year	SOE = Insufficient (2 RCTs, 1 observational study; 4,701 patients) Insufficient evidence due to heterogeneity of DAPT duration and imprecision: both RCTs (1 month vs. 6 months and 6 months vs. 12 months) found similar rates between short- and long-term therapy; the observational study (<3 months vs. 6 months vs. >12 months) showed similar rates across treatment groups in both DES-treated and BMS-treated populations
Composite of all-cause mortality, nonfatal MI, stroke, or revascularization at 1 year	SOE = Insufficient (1 RCT; 1,443 patients) Insufficient evidence due to imprecision: no difference between 6- and 12-month therapy
Composite of all-cause mortality, nonfatal MI, or stroke at 6 months, 1 year, and 2 years	SOE = Insufficient (3 RCTs; 5,133 patients) Insufficient evidence due to heterogeneity of DAPT duration, inconsistency, and imprecision: 2 studies found significant reductions in events from long-term DAPT at 6 months and 1 year; 1 study found no difference between 6- and 24-month therapy
All-cause mortality at 6 months, 1 year, and 2 years	SOE = Insufficient (4 RCTs, 3 observational studies; 38,441 patients) Insufficient evidence due to heterogeneity of DAPT duration, inconsistency, and imprecision: 2 RCTs showed a reduction with longer therapy (1 month vs. 6 months) but 1 was statistically significant and the other was not; 1 RCT (6 months vs. 12 months) showed no difference; 1 observational study (<3 months vs. 6 months vs. >12 months) showed lower mortality in DES-treated patients receiving >12 months of therapy but no difference in the BMS-treated patients; 1 observational study found a higher rate of mortality in those who discontinued clopidogrel within the first 6 months; 1 observational study found a higher risk of death within the first 90 days of discontinuation after a 12-month treatment
Cardiovascular mortality at 6 months, 1 year, and 2 years	SOE = Insufficient (3 RCTs, 1 observational study; 33,728 patients) Insufficient evidence due to heterogeneity of DAPT duration, timing of endpoint measurement, and imprecision: all RCTs found similar rates between short- and long-term therapy (1 month vs. 6 months, 6 months vs. 12 months, and 6 months vs. 24 months); 1 observational study found no difference in CV mortality within the first 90 days of discontinuation after a 12-month treatment

Table 40. Summary strength of evidence and effect estimates: short-term versus long-term dual antiplatelet therapy (continued)

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Nonfatal MI at 6 months, 1 year, and 2 years	SOE = Insufficient (4 RCTs, 2 observational studies; 9,173 patients) Insufficient evidence due to imprecision: 5 studies (4 RCTs and 1 observational) showed similar rates of MI in short- and long-term therapy groups; 1 observational study showed statistically significant higher risk in DES patients who discontinued clopidogrel within first 6 months
Stroke at 6 months, 1 year, and 2 years	SOE = Insufficient (3 RCTs; 4,460 patients) Insufficient evidence due to imprecision: all RCTs (1 month vs. 6 months, 6 months vs. 12 months, and 6 months vs. 24 months) found similar rates between short- and long-term therapy, but heterogeneity of DAPT duration makes this inconclusive
Revascularization at 6 months and 1 year	SOE = Insufficient (3 RCTs, 1 observational study; 5,705 patients) Insufficient evidence due to imprecision: rates of revascularization were similar between short- and long-term therapy (1 month vs. 6 months and 6 months vs. 24 months)
Stent thrombosis at 6 months, 1 year, and 2 years	SOE = Insufficient (3 RCTs, 3 observational studies; 15,298 patients) Insufficient evidence due to heterogeneity of DAPT duration and imprecision: rates of stent thrombosis were higher when clopidogrel was stopped within 30 days or 6 months in 2 observational studies; 4 studies (3 RCTs and 1 observational) showed no statistically significant difference in event rates at 1 or 2 years
Major bleeding at 1 year and 2 years	SOE = Insufficient (3 RCTs; 5,572 patients) Insufficient evidence due to inconsistency and imprecision: 1 RCT (6 months vs. 24 months) showed a statistically significant lower rate of major bleeding with clopidogrel with 6-month treatment; the other 2 RCTs (1 month vs. 12 months and 6 months vs. 12 months) showed no statistically significant difference in rates with 1-year treatment
Minor bleeding at 1 year and 2 years	SOE = Insufficient (2 RCTs; 4,129 patients) Insufficient evidence due to imprecision: both RCTs (1 month vs. 12 months and 6 months vs. 24 months) found no difference at 1 and 2 years

BMS = bare metal stent; CI = confidence interval; CV = cardiovascular; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; MI = myocardial infarction; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

Dual Antiplatelet Therapy With and Without PPI

In our analysis of antiplatelet treatment with and without concomitant PPI therapy, we found that omeprazole was the most commonly studied PPI in both randomized trials and observational registries. In our analysis of DAPT with and without concomitant PPI therapy, we found that omeprazole was the most commonly studied PPI in both randomized trials and observational registries. These patient populations were treated with aspirin plus clopidogrel. Event rates were lower in patients who did not receive PPI medication for the various clinical outcomes: composite ischemic endpoints at 1 year, all-cause mortality at 6 years, nonfatal MI at 1 year, stroke at 1 year, revascularization at 1 year, or rehospitalization at 3 months, stent thrombosis at 1 year, and major bleeding at 1 year. There was no difference between groups for all-cause mortality at1 year and revascularization at 6 months. As expected, GI bleeding was lower in patients treated with PPI medication. The findings were inconsistent (i.e., showing no differences between groups or showing increased event rates in the PPI group), and the evidence base was insufficient for all-cause mortality within the first 3 months, cardiovascular mortality at 1 year, nonfatal MI within the first 3 months, revascularization at 4 years, stent thrombosis at 30 days,

major bleeding at 30 days, minor bleeding, and rehospitalization at 1 year. Table 41 shows summary SOE and effect estimates for these outcomes.

Table 41. Summary strength of evidence and effect estimates: dual antiplatelet therapy with and without proton pump inhibitor

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Dual Antiplatelet Therapy With and Without PPI[b]	
Composite ischemic endpoints at about 1 year	SOE = Low (2 RCTs, 21 observational studies; 272,311 patients) RCTs of omeprazole showed no difference; however, meta-analysis of observational studies of any PPI showed adj HR 1.35 (1.18 to 1.54), which favors no PPI. The discrepancy between the RCTs and the observational studies makes it difficult to draw a firm conclusion about the effect.
Composite of all-cause mortality or MI at about 1 year	SOE = Moderate (3 observational studies; 60,389 patients) Adj HR 1.27 (1.12 to 1.43); favors no PPI
All-cause mortality within first 3 months	SOE = Insufficient (3 observational studies; 8,943 patients) Insufficient evidence due to inconsistency and imprecision: 2 studies showed no differences in mortality rates; 1 study showed a statistically significant increase in mortality in PPI group, adj HR 2.2 (1.1 to 4.3)
All-cause mortality at about 1 year	SOE = Moderate (2 RCTs, 18 observational studies; 264,172 patients) RCTs of omeprazole showed no difference or favored omeprazole, and the meta-analysis of observational studies of any PPI showed adj HR 1.17 (0.92 to 1.48); no difference
All-cause mortality at 6 years	SOE = Low (1 observational study; 23,200 patients) Adj HR 1.32 (1.00 to 1.73); favors no PPI
Cardiovascular mortality at 1 year	SOE = Insufficient (3 observational studies; 76,184 patients) Insufficient evidence due to inconsistency and imprecision: 2 out of 3 studies showed statistically significant increase in CV mortality in PPI group
Nonfatal MI within first 3 months	SOE = Insufficient (3 observational studies; 8,943 patients) Insufficient evidence due to inconsistency and imprecision: 2 studies showed no statistically significant difference in MI rates; 1 study showed statistically significant increase in MI events in PPI group
Nonfatal MI at about 1 year	SOE = Low (1 RCT, 11 observational studies; 225,687 patients) The RCT and observational study of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.33 (1.15 to 1.55), which favors no PPI. The discrepancy between the omeprazole studies and the observational studies of any PPI makes it difficult to draw a firm conclusion about the effect.
Stroke at about 1 year	SOE = Low (2 RCTs, 5 observational studies; 165,212 patients) RCTs of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.49 (1.20 to 1.84), which favors no PPI. The discrepancy between the RCTs and the observational studies makes it difficult to draw a firm conclusion about the effect.
Revascularization at 6 months	SOE = Low (1 RCT, 1 observational study; 22,326 patients) Both studies showed no difference in revascularization rates; no difference
Revascularization at 1 year	SOE = Low (5 observational studies; 53,164 patients) Observational study of omeprazole showed no difference; meta-analysis of observational studies of any PPI showed adj OR 1.48 (1.21 to 1.82); favors no PPI
Revascularization at 4 years	SOE = Insufficient (1 observational study; 315 patients) Insufficient evidence due to imprecision; no statistically significant difference in revascularization rate between groups
Stent thrombosis at 30 days	SOE = Insufficient (1 observational study; 3,408 patients) Insufficient evidence due to imprecision: no statistically significant difference in stent thrombosis rate between groups

Table 41. Summary strength of evidence and effect estimates: dual antiplatelet therapy with and without proton pump inhibitor (continued)

Outcome and Timing	SOE[a] and Effect Estimate (95% CI)
Dual Antiplatelet Therapy With and Without PPI[b] *(continued)*	
Stent thrombosis at about 1 year	SOE = Low (1 RCT, 7 observational studies; 45,198 patients) The RCT and observational study of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.34 (1.17 to 1.55), which favors no PPI. The discrepancy between the RCT and the observational studies makes it difficult to draw a firm conclusion about the effect.
Major bleeding at 30 days	SOE = Insufficient (3 observational studies; 7,498 patients) Insufficient evidence due to inconsistency and imprecision: adj HR 1.73 (0.61 to 4.88)
Major bleeding at about 1 year	SOE = Low (4 observational studies; 36,231 patients) Adj HR 1.26 (1.12 to 1.41); favors no PPI
GI bleeding	SOE = Moderate (4 RCTS, 4 observational studies; 28,032 patients) 3 out of 4 RCTs of omeprazole and 2 out of 4 observational studies of any PPI showed statistically significant lower rates of GI bleed in the PPI group; favors PPI
Minor bleeding	SOE = Insufficient (1 observational study; 1,346 patients) Insufficient evidence due to imprecision: no difference in minor bleed in-hospital or at 1 year
Rehospitalization at 3 months	SOE = Low (1 observational study; 5,862 patients) Significant increase in rehospitalization in PPI group at 3 months; adj HR 1.32 (1.00 to 1.73); favors no PPI
Rehospitalization at about 1 year	SOE = Insufficient (4 observational studies; 16,925 patients) Insufficient due to inconsistency and imprecision: adj HR 1.70 (0.86 to 3.34)

adj = adjusted; CI = confidence interval; CV = cardiovascular; GI = gastrointestinal; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; PPI = proton pump inhibitor; RCT = randomized controlled trial; SOE = strength of evidence

[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[b]ORs less than 1 favor PPI use; ORs greater than 1 favor no PPI use.

Aspirin Monotherapy With and Without PPI

In our analysis of aspirin monotherapy with and without concomitant PPI therapy, we presented the findings from two good-quality observational studies that compared clinical outcomes between patients receiving different PPI medications with patients who did not receive a PPI (Table 42). In contrast to the previous section, these patient populations were not prescribed dual antiplatelet therapy; therefore, this evaluation focuses on the addition of PPIs to aspirin monotherapy. There was insufficient evidence for the effect of PPIs on aspirin monotherapy for in-hospital outcomes; only one study of 2744 patients reported the rates of all-cause mortality, nonfatal MI, stroke, and major bleeding. That study found no significant differences between the PPI and no PPI groups. There were inconsistent results for composite ischemic events (cardiovascular mortality, nonfatal MI, or stroke) and lower all-cause mortality at 1 year of followup, with one study showing an increased risk of events in the PPI group and the other study showing no difference. One study reported rates of nonfatal MI at 1 year and showed an increased risk of MI events in the PPI group. Both studies showed no difference in stroke events at 1 year.

Table 42. Summary strength of evidence and effect estimates: aspirin monotherapy with and without proton pump inhibitor

Aspirin Monotherapy With and Without PPI[b]	
Composite of CV death, nonfatal MI, or stroke at 1 year	SOE = Insufficient (2 observational studies; 52,196 patients) Insufficient evidence due to inconsistency: 1 study reported increased risk among PPI group (adj HR 1.61 [1.45 to 1.79]), while the other study showed no difference (adj HR 1.00 [0.88 to 1.15])
All-cause mortality (in-hospital)	SOE = Insufficient (1 observational study; 2,744 patients) Insufficient evidence due to imprecision: adj OR 0.96 (0.49 to 1.88)
All-cause mortality at 1 year	SOE = Insufficient (2 observational studies; 52,196 patients) Insufficient evidence due to imprecision: 1 study reported increased risk among PPI group (adj HR 2.38 [2.12 to 2.67]), while the other study showed no difference (adj HR 0.99 [0.86 to 1.14])
Nonfatal MI (in-hospital)	SOE = Insufficient (1 observational study; 2,744 patients) Insufficient evidence due to imprecision: adj HR 1.50 (0.41 to 5.43)
Nonfatal MI at 1 year	SOE = Low (1 observational study; 49,452 patients) Adj HR 1.33 (1.13 to 1.56); favors no PPI
Stroke (in-hospital)	SOE = Insufficient (1 observational study; 2,744 patients) Insufficient evidence due to imprecision: adj HR 0.75 (0.11 to 4.85)
Stroke at 1 year	SOE = Low (2 observational studies; 52,196 patients) Both studies showed no difference, adj HR 1.20 (0.99 to 1.46) and adj HR 0.75 (0.11 to 4.85); no difference
Major bleeding (in-hospital)	SOE = Insufficient (1 observational study; 2,744 patients) Insufficient evidence due to imprecision: adj OR 1.30 (0.38 to 4.39)

adj = adjusted; CI = confidence interval; CV = cardiovascular; GI = gastrointestinal; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; PPI = proton pump inhibitor; RCT = randomized controlled trial; SOE = strength of evidence
[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.
[b]ORs less than 1 favor PPI use; ORs greater than 1 favor no PPI use.

Dual Antiplatelet Versus Triple Therapy

In our analysis of dual antiplatelet therapy versus triple therapy, we present the findings from studies that compared two antiplatelet agents to a treatment group that received long-term anticoagulation in addition to the two antiplatelet agents. Indications for long-term anticoagulation include atrial fibrillation, presence of a prosthetic valve, chronic deep venous thrombosis, or hypercoagulable states (e.g., protein C or S deficiency). We found 14 observational studies that examined the differences between adding anticoagulant therapy (i.e., warfarin) to various combinations of antiplatelet therapy. In these observational studies there were inconsistent and imprecise findings on the differences between dual and triple therapy on composite ischemic endpoints (all-cause mortality, nonfatal MI, or revascularization, and all-cause mortality or nonfatal MI) at all time points, with some studies showing no difference and others showing increases or decreases in events in the triple therapy group. Dual therapy is better than triple therapy in reducing nonfatal MI and major bleeding at 1 year or longer. One observational study of 800 patients on the effect of dual versus triple therapy showed a significantly lower rate of stroke at 6 months in the triple therapy group, but the evidence from this study was insufficient for nonfatal MI at 6 months. Evidence for an effect of dual therapy versus triple therapy was also insufficient for the outcomes of all-cause mortality at 30 days to 6 months and 1 to 5 years, stroke at 1 to 5 years, revascularization up to 5 years, major bleeding at 30 days, minor bleeding at 1 to 5 years, major and minor bleeding at 1 to 5 years, and stent thrombosis. Table 43 shows the summary SOE and effect estimates for these outcomes.

One observational study of 6275 patients reported findings in subgroups of sex, age, and patients with diabetes. That study found lower rates of all-cause mortality in men, across all age

groups, and in nondiabetic patients receiving triple therapy; SOE was low for the findings by subgroup since only one study was identified.

Table 43. Summary strength of evidence and effect estimates: dual antiplatelet versus triple therapy[a]

Outcome and Timing	SOE[b] and Effect Estimate[c] (95% CI)
Composite of all-cause mortality, nonfatal MI, revascularization, or stroke at 1 year or more	SOE = Insufficient (4 observational studies; 8,509 patients) Insufficient evidence due to inconsistency and imprecision: 2 studies showed statistically nonsignificant differences; 2 studies showed statistically significant increases in events in DAPT group
Composite of all-cause mortality or nonfatal MI within first year	SOE = Insufficient (4 observational studies; 57,144 patients) Insufficient evidence due to inconsistency and imprecision: 1 study showed a statistically significant increase, 1 statistically significant decrease in the triple therapy group, and 2 studies showed statistically nonsignificant difference in events between the DAPT and triple therapy.
All-cause mortality at 30 days to 6 months	SOE = Insufficient (2 observational studies; 7,075 patients) Insufficient evidence due to inconsistency and imprecision: 1 study found no difference, another found statistically significantly lower deaths in triple therapy group
All-cause mortality at 1 to 5 years	SOE = Insufficient (8 observational studies; 41,192 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.03 (0.59 to 1.83)
Nonfatal MI at 6 months	SOE = Insufficient (1 observational study; 800 patients) Insufficient evidence due to unknown precision: triple therapy 3.3%; warfarin/aspirin 4.5% (p = 0.49)
Nonfatal MI at 1 to 5 years	SOE = Low (4 observational studies; 1,425 patients) OR 1.85 (1.13 to 3.02); favors DAPT
Stroke at 6 months	SOE = Low (1 observational study; 800 patients) Triple therapy 0.7%; warfarin/aspirin 3.4% (p = 0.02); favors triple therapy
Stroke at 1 to 5 years	SOE = Insufficient (4 observational studies; 6,485 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.01 (0.59 to 2.67)
Revascularization up to 5 years	SOE = Insufficient (4 observational studies; 2,066 patients) Insufficient evidence due to imprecision: no statistical difference between DAPT and triple therapy groups
Major bleeding at 30 days	SOE = Insufficient (5 observational studies; 11,095 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.70 (0.88 to 3.30)
Major bleeding at 1 to 5 years	SOE = Low (7 observational studies; 38,398 patients) OR 1.46 (1.07 to 2.00); favors DAPT
Minor bleeding at 1 to 5 years	SOE = Insufficient (3 observational studies; 890 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.33 (0.48 to 3.69)
Major and minor bleeding	SOE = Insufficient (2 observational studies; 21,545 patients) Insufficient evidence due to imprecision: both studies failed to show a difference between DAPT and triple therapy in the combined endpoint of major and minor bleeding
Stent thrombosis	SOE = Insufficient (2 observational studies; 840 patients) Insufficient evidence due to inconsistency and imprecision: no significant difference in rates (triple therapy 1.4% to 4.1%; dual antiplatelet 1.3% to 3.6%)

CI = confidence interval; DAPT = dual antiplatelet therapy; MI = myocardial infarction; OR = odds ratio; SOE = strength of evidence

[a]Triple therapy refers to aspirin plus antiplatelet plus anticoagulant.

[b]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.

[c]ORs less than 1 favor triple therapy; ORs greater than 1 favor DAPT.

Findings in Relation to What Is Already Known

The American College of Cardiology/American Heart Association guidelines have been published and recently updated to guide clinicians in the treatment of patients with UA/NSTEMI.[204] For each KQ, we discuss the findings of this report in relationship to current guidelines and previous systematic reviews or meta-analyses.

KQ 1

For KQ 1, which addresses the use of antiplatelet and anticoagulant therapy in UA/NSTEMI patients treated with an early invasive or PCI-based strategy, our findings are consistent with those of previously published guidelines and meta-analyses in many respects. Many large RCTs (including EARLY-ACS, CURRENT-OASIS 7, PLATO, and TRITON-TIMI 38) have impacted our comparisons, and these studies were incorporated into the recent American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines update. Our major findings mirror those of other meta-analyses in that upstream GPI use was not associated with a significant reduction in ischemic endpoints, the optimal loading dose of clopidogrel remains unclear, and prasugrel was associated with a significant reduction in ischemic endpoints compared with clopidogrel. One new finding from this report is that upstream GPI use was associated with lower rates of revascularization, but the tradeoff was a higher risk of major bleeding at 30 days.

Our review expands on what is known about one of the newer antiplatelets: ticagrelor. Based on two new RCTs, ticagrelor was associated with a significant reduction in ischemic endpoints when compared with clopidogrel at 1 year, but unlike the case with prasugrel, the incidence of major bleeding was not significantly higher in ticagrelor-treated patients.

There was a paucity of data on the optimal timing of oral antiplatelet agents as initial treatment for UA/NSTEMI, since the four previous studies (two RCTs, two observational studies) contained a mixture of non-ACS and ACS patients, and the use of anticoagulant (bivalirudin or UFH) and IV antiplatelet (upstream or deferred GPI) was not well defined. Thus, we analyzed the subgroup results of patients receiving either clopidogrel pretreatment or clopidogrel treatment at the time of PCI from randomized trials of (1) bivalirudin versus heparin-based strategy and (2) upstream GPI use versus deferred GPI use. These studies confirmed that in patients pretreated with clopidogrel, the use of bivalirudin at the time of PCI was associated with less major bleeding than a heparin-based strategy. In patients pretreated with clopidogrel, the use of deferred GPI was associated with higher rates of ischemic endpoints (all-cause mortality, nonfatal MI, ischemia, revascularization) and lower rates of major bleeding at 30 days than with the use of upstream GPI was. In patients treated with clopidogrel at the time of PCI there was less major bleeding at 30 days with the use of deferred GPI.

KQ 2

For KQ 2, which addresses antiplatelet and anticoagulant treatment in patients undergoing an initial conservative approach for treating UA/NSTEMI, our findings were concordant with the recently published ACCF/AHA guideline recommendations. A direct comparison of enoxaparin and UFH showed a significantly lower incidence of composite ischemic endpoint mostly driven by nonfatal MI reduction among patients receiving enoxaparin, with no difference in the rate of major bleeding. An indirect comparison of fondaparinux and UFH showed significant reductions in composite ischemic events and major bleeding favoring fondaparinux. These results, based mostly on RCTs and supported by observational studies, are consistent with guideline

recommendations of initial anticoagulant treatment among UA/NSTEMI patients undergoing an initial conservative approach, in which all three anticoagulants are recommended but with indication of a preferable option for enoxaparin and fondaparinux.

Our findings on the effectiveness and safety of GPIs when administered with UFH compared with UFH alone have shown that the use of tirofiban or eptifibatide reduced the rate of composite ischemic events, mortality, nonfatal MI, and recurrent ischemia. The administration of abciximab with UFH did not significantly reduce ischemic events compared with UFH alone. Use of GPIs increased the rates of major and minor bleeding. Data gained from these studies are more challenging to extrapolate and implement in the context of actual clinical practice because the majority were performed before an early invasive strategy was widely implemented, and they employed an initial conservative strategy followed by percutaneous revascularization after 18 to 72 hours. Further, several GPI studies reported results from a combination of treatment approaches (both invasive and medically managed), and the proportion of patients receiving percutaneous revascularization ranged widely. Lastly, the treatment approach seems to vary by country, with greater use of conservative, medically managed approaches in countries with less access to cardiac catheterization laboratories than in more developed countries.

Current ACCF/AHA UA/NSTEMI guidelines recommend adding a GPI (tirofiban or eptifibatide) to patients who were initially treated conservatively but then require diagnostic angiography due to an increase or new onset of symptoms (class I recommendation, level of evidence A). These guidelines, including the recently published update,[204] show no change in the recommendation of administering a GPI (tirofiban or eptifibatide) in addition to an anticoagulant or oral antiplatelet for patients for whom an initial conservative strategy is selected (class IIb, level of evidence B). At the same time, they recommend withholding a GPI if patients are clinically stable; if, after angiography, a percutaneous revascularization is deemed not necessary or if they do not undergo diagnostic angiography (class IIa, level of evidence C). Our analysis shows that newer, smaller studies and the use of DAPT in the conservatively managed population resulted in summary estimates that were more favorable for GPI plus UFH, which supports the class IIb ACCF/AHA recommendation for use of GPI with an anticoagulant or oral antiplatelet for patients treated with an initial conservative strategy.

KQ 3

For KQ 3, which addresses antiplatelet and anticoagulant treatment after hospital discharge in patients with UA/NSTEMI, our findings are mostly consistent with recently published guidelines. We found conflicting results on aspirin dosing due to different dosing comparisons and a paucity of studies. Comparison of single antiplatelet therapy versus DAPT supported current recommendations, with evidence of better outcomes among patients treated with dual antiplatelet therapy.

Effect of clopidogrel duration was assessed in nine studies; however, because of differences in the comparison of duration of treatment and outcomes that were assessed, a meta-analysis was not performed and only a qualitative assessment was possible. Significant differences in outcomes were observed when clopidogrel was discontinued early after discharge, and no differences in outcomes were observed when treatment comparisons were greater than 6 months. Only two studies looked at treatment effect based on stent type, and again the worst outcomes were observed among patients with either bare metal or drug-eluting stents who discontinued clopidogrel (either stopped taking it or were taken off it by their doctor) within the first 6 months. Guidelines recommend a treatment duration of 1 year if there is no increased risk of

bleeding. Our findings support the recommendation not to treat beyond 1 year; however, there is uncertainty about whether discontinuation at an earlier time point (between 6 and 12 months) could be safely done since the data are not clear about when exactly the benefit fades.

In our analysis of the use of PPIs with dual antiplatelet therapies meta-analyses using adjusted or propensity-scored hazard ratios from observational studies, showed an association between PPI use (any type) and increased rates of composite ischemic endpoints, death, nonfatal MI, stroke, revascularization, stent thrombosis and major bleeding. We downgraded the SOE ratings since the findings from observational studies conflicted with the few randomized trials of omeprazole. We cannot exclude the possibility of residual confounding in the observational studies, despite the adjustment for comorbid illness and other clinical factors. A recent update of the ACCF/AHA guidelines has removed the recommendation to administer PPIs among patients with a history of gastrointestinal bleeding and instead suggests that health care providers reevaluate the need for starting or continuing PPI treatment in patients taking clopidogrel. Their statement does not prohibit the use of PPI agents in appropriate clinical settings; however, they describe the potential risks and benefits from use of PPI agents in combination with clopidogrel. Our findings support a cautious approach to PPI use with DAPT therapy in UA/NSTEMI patients.

Finally, we assessed the use of triple therapy (dual antiplatelet plus anticoagulation) and found low SOE that nonfatal MI and major bleeding rates were higher and stroke rates were lower with triple therapy than with DAPT. However, the findings for all other endpoints were rated insufficient due to either inconsistency or imprecision of results, or both—making it impossible to reach a firm conclusion. The current ACCF/AHA guidelines give a class I recommendation that warfarin in combination with aspirin or dual antiplatelet therapy is associated with an increased risk of bleeding and a class IIb recommendation that targeting oral anticoagulant therapy to a lower international normalized ratio (INR) (e.g., 2.0 to 2.5) is reasonable in patients managed with DAPT due to inconsistency and imprecision of existing data for this comparison.

Applicability

Studies included in this review were primarily multicenter international studies that included the United States and Canada, so the applicability of our findings spans multiple geographic locations. While many studies were also conducted outside the United States, there are similarities in UA/NSTEMI treatments internationally and this should therefore not be seen as a limitation in treatment setting. However, two main factors limit our findings: population and intervention. First, in order to have adequate numbers of citations to address the safety and effectiveness of antiplatelet and anticoagulant therapies in UA/NSTEMI patients, we had to broaden our eligible patient population to include studies of either UA/NSTEMI or ACS (STEMI, NSTEMI, and UA). In addition, some antiplatelet and anticoagulant studies included ACS and stable angina populations. To improve the applicability of our findings to the UA/NSTEMI population, we excluded studies that focused exclusively on the STEMI or stable angina population.

Second, due to a change in terminology regarding treatment approach (i.e., early invasive strategy and initial conservative strategy), we had to make an assumption that trials that discouraged coronary angiography or PCI in the early phase of MI treatment could be labeled as a conservatively managed approach. Many of those types of studies are older (mid-1990s), or

were conducted in non-U.S. settings. We did not find any limits to applicability regarding the comparisons or outcomes reported.

Implications for Clinical and Policy Decisionmaking

More than one million patients in the United States are treated for UA/NSTEMI each year. Ischemic heart disease has remained a leading cause of death in the United States despite major advances in cardiovascular care over the past decade. Due to the prevalence, associated morbidity and mortality, cost, and multiple effective treatment options for UA/NSTEMI patients, this Comparative Effectiveness Review provides important information to guide both future research and clinical and policy decisionmaking.

Regarding the invasive treatment strategy in UA/NSTEMI patients, this review found that several therapies were effective at improving ischemic endpoints while minimizing bleeding endpoints. Two new antiplatelet medications (prasugrel and ticagrelor) were superior to clopidogrel in terms of reduction of ischemic endpoints, but the cost-effectiveness of these novel agents is not currently known because generic formulations of clopidogrel have recently become available in the United States. Additionally, due to the different pharmacokinetic and pharmacodynamic properties of these novel agents, their effectiveness may differ when studying the combination of strategies that were compared in this review (i.e., upstream GPI vs. deferred GPI, bivalirudin vs. heparin, timing of $P2Y_{12}$ administration). Further study is needed to determine the effectiveness and safety of these newer agents in these specific contexts.

Regarding the conservative management approach, in our review of observational studies we found a growing use of low molecular weight heparin (i.e., enoxaparin) based on evidence of better effectiveness and similar bleeding rates compared with UFH. The effectiveness of fondaparinux in comparison with enoxaparin requires further study; however, our indirect analysis comparing fondaparinux with UFH provides preliminary evidence that fondaparinux also reduces composite ischemic events and does not increase the risk of bleeding. Our review shows that the administration of GPI in the conservatively managed population is beneficial; however, newer ACCF/AHA guideline recommendations suggest that GPIs should be administered only prior to PCI or for recurrent symptoms. The guideline recommendation is primarily based on findings in the invasively managed population (presented for KQ 1) and not specifically on the findings from the conservatively managed population.

For the postdischarge setting, the optimal aspirin dose to use with clopidogrel for dual antiplatelet therapy is uncertain; however, it is clear that DAPT is beneficial in reducing future ischemic events compared with single antiplatelet therapy and that treatment durations of 6 months to 1 year are better than shorter duration of therapy. Our findings support a cautious approach to PPI use with DAPT therapy in UA/NSTEMI patients given the higher number of ischemic events in patients who receive a PPI. Finally, our analysis of observational studies of DAPT and triple therapy in patients with a long-term indication for warfarin shows inconsistent and insufficient evidence for the impact on ischemic events; however, bleeding events are increased with triple therapy. Further study on aspirin dosing with DAPT, the role of newer antiplatelet agents (prasugrel, ticagrelor), and newer anticoagulants (dabigatran, rivaroxaban, and apixaban) for triple therapy are needed.

Limitations of the Review Process

The current review was limited to English-language studies and focused on those that directly compared various antiplatelet and anticoagulation agents, either individually or in

combination. Any studies that reported noncomparative findings, such as a study assessing the outcomes of patients treated with one antiplatelet or anticoagulant agent over time without a control or comparator group, were excluded. However, it is unlikely that these studies would have provided substantial additional information given the quality and SOE of the studies reviewed.

For most of the comparisons, a quantitative analysis of composite ischemic endpoints was challenging to conduct given the different composite endpoint definitions. In some comparisons, we pooled the studies for the most frequently reported composite, but this resulted in excluding relevant studies with a different composite endpoint definition. In some comparisons, the number of studies for each composite endpoint definition was too small to put into a meta-analysis model. Another option is to pool studies with composite endpoints that are essentially similar (e.g., 2 out of 3 of the components are the same, with the event rates of the third component reasonably similar to each other). For some studies, we treated total mortality and cardiovascular mortality as essentially similar, since the event rates of cardiovascular mortality usually dominate the event rates for total mortality.

Related to the variations in the composite ischemic endpoint definition outlined above, there was also heterogeneity in the individual endpoint definitions (e.g., MI, stroke, bleeding) and how these endpoints were reported within the published literature. We were not able to focus on the nuances in the endpoint definitions but instead relied on the study authors' definitions. This is another limitation of the review process, which can be resolved with further standardization of outcome definitions and reporting.

A final limitation of this review is the separation of the effectiveness and safety outcomes in our analyses. We did not conduct an analysis of the net benefit (i.e., assessing the effectiveness while accounting for the risk of these therapies). Very few studies reported the net benefit of their interventions. Further, a calculation of net benefit across studies may not be robust since often there was heterogeneity in the composite endpoint definition, and pooling in order to combine individual outcomes into a standard composite benefit may have overestimated the number of events if patients experienced more than one individual outcome. We also did not assess for consistency in endpoint definitions across studies, assuming that the differences between studies and any definition changes over time were minimal. Bleeding definitions were also variable across studies. In our analyses of bleeding definitions we used TIMI (thrombolysis in myocardial infarction) criteria when they were reported; otherwise we accepted the study definition of a major and minor bleed.

Limitations of the Evidence Base

The main limitation was the change in terminology regarding treatment approach (i.e., early invasive strategy and initial conservative strategy) in the early 2000s. There is no MeSH search term for these types of treatment approaches; thus, it was difficult to group studies and patient populations into an early invasive treatment or initial conservative strategy. Some studies included both early invasive and early conservative treatment approaches and some studies did not report which treatment approach was used. Fortunately, newer publications are starting to report findings by treatment approach, so future evidence reviews will benefit from further specification. However, in clinical practice the treatment approach for a UA/NSTEMI patient may not always be determined before the pharmacologic therapy is selected. For this review, we tried to separate the early invasive and initial conservative studies into a PCI-based strategy and a medically managed strategy. This led to some overlap in the comparisons of enoxaparin, UFH,

and fondaparinux in both the KQ 1 and KQ 2 sections of this report. Another limitation was the patient population enrolled in these antiplatelet and anticoagulant studies. While the focus of this review was the UA/NSTEMI population, we found a lower proportion of studies (about 35%) that solely enrolled UA/NSTEMI patients. Instead, the majority of studies (65%) contained a mixed population of ACS patients, including UA/NSTEMI and STEMI patients. Also, improvements in diagnostic testing have altered the definition and classification of MI and UA over time, thus leading to variations in these definitions across studies.

Important limitations of the literature across the KQs include: (1) few studies that assess long-term clinical outcomes for both ischemic and bleeding events, (2) few studies in specific patient subgroups of interest, and (3) few studies that looked at combinations of antiplatelet and anticoagulant treatments, specifically dosage, timing, and duration of these combinations.

Research Gaps

Acute coronary syndromes, including UA/NSTEMI, are widely studied, as evidenced by our screening of over 20,000 abstracts to identify 290 articles (166 studies) of antiplatelet and anticoagulant agents. In our review, we found research gaps involving both established and newer therapies, particularly related to the comparative effectiveness of these treatments; issues related to dosage, timing, and type of administration (IV or oral), and combinations of therapy. We used the framework recommended by Robinson et al.[205] to identify gaps in evidence and describe the reasons why these gaps exist. This approach considers PICOTS criteria to classify gaps as due to (1) insufficient or imprecise information, (2) biased information, (3) inconsistency or unknown consistency, and (4) not the right information. Results are presented for each KQ.

Across all KQs, we found a gap in reporting of racial and ethnic demographics of study participants. Future studies should take care to report the comparative effectiveness and safety of antiplatelet and anticoagulant treatment regimens in racial and ethnic subpopulations as well as summary population effects.

KQ 1

In KQ 1, the primary research gap was the lack of direct comparisons of IV and oral combination treatment strategies. While many studies investigated the use of one oral antiplatelet versus another oral antiplatelet, there were scant data on combinations of antiplatelet and anticoagulant medications used for UA/NSTEMI patients. In addition, there is a paucity of evidence surrounding the optimal timing and administration of these antiplatelet and anticoagulant medications when used in combination for patients with UA/NSTEMI. Our review highlights the need for future studies to compare novel antiplatelet agents (ticagrelor, prasugrel) in a head-to-head manner. In clinical practice, the use of bleeding-avoidance strategies has prompted many clinicians to avoid the use of GPI while using clopidogrel pretreatment and bivalirudin at the time of PCI. Validation of the use of these medications in combination when compared with the use of GPI is needed. Further, given the importance of reducing ischemic events and bleeding events, a gap was present, as no included studies measured the effect of specific strategies to reduce bleeding (i.e., radial artery access, vascular closure devices).

KQ 2

In KQ 2, the primary research gap is reporting safety and effectiveness among the subgroup of conservatively managed patients within trials or observational studies of mixed treatment

approaches. We found only a couple of studies presenting subgroup analysis by medically managed patients for both the low molecular weight heparin and GPI analyses—and often the data were not concordant. Future studies can address this either by stratification of the antiplatelet or anticoagulant therapy by treatment approach (invasive or conservative) or by reporting the subgroup findings for the conservatively managed population within a larger trial or observational study.

KQ 3

In KQ 3, there were many research gaps. First, more studies assessing the optimal loading and maintenance dose of aspirin are needed since our review found heterogeneity in the definitions of low- and high-dose aspirin. In addition, the optimal dose of aspirin within a DAPT strategy requires further study, especially within subgroups of patients at risk for bleeding complications.

Second, more randomized trials are needed on clopidogrel duration up to and beyond 1 year of ongoing treatment. There were few RCTs on this subject, and the small number of observational studies showed no difference in clinical outcomes when assessing 6-month versus longer treatment durations. While published literature has shown that early discontinuation of dual antiplatelet therapy (within 3 months, 6 months, or 1 year) is associated with a poorer clinical outcome, the need for treatment beyond 1 year is still uncertain. Also, as stated above in the KQ 1 research gaps, the duration of new antiplatelet agents (prasugrel and ticagrelor) in combination with aspirin requires further study, as does the comparative effectiveness of use of these agents based on the type of stent used during PCI.

Third, observational studies have concluded that concomitant PPI treatment is related to worse clinical outcomes, while RCTs of one specific PPI (omeprazole) showed no effect. This suggests that the observational studies are confounded by comorbid conditions (i.e., selection bias). It is unclear whether genetic resistance to clopidogrel is a causal factor, or whether the negative interaction is drug or class specific, since those variables were not included in the studies we reviewed. Further research, preferably additional RCTs of specific PPIs compared with each other or prospective propensity score-matched cohort studies, is warranted on whether the detrimental effect of PPIs is due to comorbid conditions of the patient population, type of PPI, or genetic predisposition for reduced clopidogrel sensitivity.

The final research gap for KQ 3 is the limited and inconsistent data on long-term anticoagulant therapy. Further study on aspirin dosing with dual antiplatelet therapy, the role of newer antiplatelet agents (prasugrel, ticagrelor), and newer anticoagulants (dabigatran, rivaroxaban, and apixaban) for triple therapy are needed.

Across all KQs, we found a gap in reporting of racial and ethnic demographics of study participants. Thus, we had few studies that looked at the comparative effectiveness and safety of antiplatelet and anticoagulant treatment regimens in racial and ethnic subpopulations.

Conclusions

- Overall, the administration of GPIs prior to PCI is associated with a reduction in revascularization rates but an increase in major bleeding events, regardless of whether clopidogrel is administered prior to or during the PCI.
- Prasugrel reduces rates of composite ischemic events (death, MI, or stroke) at 30 days and 1 year, but also results in an increase in major bleeding events at 1 year in

comparison with clopidogrel. Ticagrelor reduces rates of composite ischemic events, but has similar rates of major bleeding at 1 year compared with clopidogrel.

- Bivalirudin is associated with a lower incidence of major bleeding events compared with heparin-based treatment, regardless of whether GPI administration was planned; bivalirudin also reduces rates of minor bleeding events compared with heparin with GPI use.
- Enoxaparin and fondaparinux are associated with a significant reduction in composite ischemic events when compared with UFH in a conservatively managed population.
- Dual antiplatelet therapy of 6 months to 1 year reduces the rates of composite ischemic outcomes and nonfatal MI; however, the optimal dose of aspirin in combination with clopidogrel is less certain.
- While PPIs have been associated with worse clinical outcomes compared with no PPI use in observational studies, the results from a small number of RCTs of omeprazole show no significant difference in clinical events compared with placebo. Therefore, PPIs should be used with caution in patients receiving clopidogrel with aspirin (DAPT).

Although we identified many citations, the number of studies for each comparison was relatively small, and the preponderance of observational studies in some of the comparisons made the findings less conclusive. To improve the findings of this report, more good-quality studies (both RCTs and observational) of antiplatelet and anticoagulant treatments are required. Uncertainty remains about the optimal dosing, timing, duration, and combinations of many of the options. This uncertainty is seen especially in subpopulations of interest (e.g., the elderly, patients with diabetes, women, obese patients, and those with comorbid illness).

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Abbreviations

ACS	acute coronary syndrome
AHRQ	Agency for Healthcare Research and Quality
ASA	aspirin
BMS	bare metal stent
CI	confidence interval
CV	cardiovascular
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
GI	gastrointestinal
GPI	glycoprotein IIb/IIIa inhibitor
HR	hazard ratio
IV	intravenous
KQ	Key Question
MI	myocardial infarction
mo	month/months
NSTEMI	non-ST elevation myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
PPI	proton pump inhibitor
RCT	randomized controlled trial
RR	risk ratio
SOE	strength of evidence
STEMI	ST elevation myocardial infarction
TEP	Technical Expert Panel
UA	unstable angina
UFH	unfractionated heparin
wk	week/weeks
yr	year/years

Appendix A. Exact Search Strings

PubMed® Search Strategy (July 19, 2012)

Table A-1. PubMed search strategy

Set #	Terms
1	ACS[tw] OR acute coronary syndrome[MeSH Terms] OR (acute[tw] AND coronary[tw] AND syndrome[tw]) OR "acute coronary syndrome"[tw] OR non-st[tw] OR nstemi[tw] OR n-stemi[tw] OR non-stemi[tw] OR nonstemi[tw] OR nsteacs[tw] OR angina, unstable[MeSH Terms] OR (angina[tw] AND unstable[tw]) OR "unstable angina"[tw] OR (preinfarction[tw] AND angina[tw]) OR "preinfarction angina"[tw] OR myocardial infarction[mesh] OR "myocardial infarction"[tw] OR "heart attack"[tw]
2	platelet aggregation inhibitors[MeSH Terms] OR (platelet[tw] AND aggregation[tw] AND inhibitors[tw]) OR (antiplatelet[tw] AND agent*[tw]) OR "platelet aggregation inhibitors"[Pharmacological Action] OR Purinergic P2Y Receptor Antagonists[Pharmacological Action] OR purinergic p2y receptor antagonists[MeSH Terms] OR (purinergic[tw] AND p2y[tw] AND receptor[tw] AND antagonists[tw]) OR "ADP receptor antagonist"[tw] OR "ADP receptor antagonists"[tw] OR aspirin[mesh] OR aspirin[tw] OR clopidogrel[supplementary concept] OR clopidogrel[tw] OR plavix[tw] OR prasugrel[supplementary concept] OR prasugrel[tw] OR effient[tw] OR ticagrelor[supplementary concept] OR ticagrelor[tw] OR brilinta[tw]
3	factor xa[mesh] OR "factor xa inhibitor"[tw] OR "factor xa inhibitors"[tw] OR rivaroxaban[Supplementary Concept] OR rivaroxaban[tw] OR xarelto[tw] OR bivalirudin[Supplementary Concept] OR bivalirudin[tw] OR angiomax[tw] OR apixaban[Supplementary Concept] OR eliquis[tw] OR apixaban[tw] OR "2-(3-carbamimidoylbenzyl)-3-(4-(1-oxypyridin-4-yl)benzoylamino)butyric acid methyl ester"[Supplementary Concept] OR "2-(3-carbamimidoylbenzyl)-3-(4-(1-oxypyridin-4-yl)benzoylamino)butyric acid methyl ester"[tw] OR otamixaban[tw] OR "YM 60828"[Supplementary Concept] OR "YM 60828"[tw] OR "ym466"[tw]
4	heparin[MeSH] OR heparin[tw] OR (low[tw] AND molecular[tw] AND weight[tw] AND heparin[tw]) OR (unfractionated[tw] AND heparin[tw]) OR fondaparinux[Supplementary Concept] OR fondaparinux[tw] OR arixtra[tw] OR Dalteparin[tw] OR fragmin[tw] OR Enoxaparin[tw] OR lovenox[tw] OR Nadroparin[tw] OR fraxiparine[tw]
5	Vitamin K/antagonists and inhibitors[mesh] OR "vitamin k antagonist"[tw] OR "vitamin k antagonists"[tw] OR warfarin[mesh] OR warfarin[tw] OR Coumadin[tw] OR VKA[tw] OR coumarol[tw] OR dicoumarol[tw] OR coumarin[tw] OR dicoumarin[tw]
6	antithrombins[mesh] OR antithrombins[pharmacological action] OR "direct thrombin inhibitor"[tw] OR "direct thrombin inhibitors"[tw] OR "N-((2-(((4-(aminoiminomethyl)phenyl)amino)methyl)-1-methyl-1H-benzimidazol-5-yl)carbonyl)-N-2-pyridinyl-beta-alanine"[Supplementary Concept] OR "N-((2-(((4-(aminoiminomethyl)phenyl)amino)methyl)-1-methyl-1H-benzimidazol-5-yl)carbonyl)-N-2-pyridinyl-beta-alanine"[tw] OR dabigatran[tw] OR pradaxa[tw]
7	"Glycoprotein IIb/IIIa inhibitor"[tw] OR "GP IIb/IIIa inhibitor"[tw] OR "Glycoprotein IIb/IIIa inhibitors"[tw] OR "GP IIb/IIIa inhibitors"[tw] OR abciximab[Supplementary Concept] OR abciximab[tw] OR reopro[tw] OR eptifibatide[Supplementary Concept] OR eptifibatide[tw] OR integrilin[tw] OR tirofiban[Supplementary Concept] OR tirofiban[tw] OR aggrastat[tw]
8	Proton Pump Inhibitors[Mesh] OR Proton Pump Inhibitors[Pharmacological Action] OR Proton Pumps/antagonists and inhibitors[Mesh] OR omeprazole[MeSH] OR omeprazole[tw] OR esomeprazole[tw] OR lansoprazole[Supplementary Concept] OR lansoprazole[tw] OR pantoprazole[Supplementary Concept] OR pantoprazole[tw] OR rabeprazole[Supplementary Concept] OR rabeprazole[tw] OR dexlansoprazole[tw] OR "omeprazole, sodium bicarbonate drug combination"[Supplementary Concept] OR zegerid[tw] OR nexium[tw] OR aciphex[tw] OR protonix[tw] OR prevacid[tw] OR kapidex[tw] OR prilosec[tw]
9	"Angioplasty, Balloon, Coronary"[Mesh] OR (Percutaneous[tw] AND Transluminal[tw] AND Coronary[tw] AND Angioplasty[tw]) OR "percutaneous transluminal coronary angioplasty"[tw] OR angioplasty[mesh] OR angioplasty[tw] OR PTCA[tw] OR PCI[tw] OR (percutaneous[tw] AND coronary[tw] AND intervention[tw]) OR ((coronary[tw] OR heart[mesh] OR heart[tw]) AND (stents[mesh] OR stent[tw] OR stents[tw] OR stenting[tw] OR stented[tw]))
10	1 AND (2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9)

Set #	Terms
12	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw]
13	10 AND 12
14	13 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[MeSH] NOT humans[MeSH]) Limits: English, 1995 - Present

Embase® Search Strategy (July 19, 2012)

Platform: Embase.com

Table A-2. Embase search strategy

Set #	Terms
1	ACS:ab,ti OR (acute:ab,ti AND coronary:ab,ti AND syndrome:ab,ti) OR non-st:ab,ti OR nstemi:ab,ti OR n-stemi:ab,ti OR non-stemi:ab,ti OR nonstemi:ab,ti OR nsteacs:ab,ti OR 'unstable angina pectoris'/exp OR (unstable:ab,ti AND angina:ab,ti) OR (preinfarction:ab,ti AND angina:ab,ti) OR 'heart infarction'/exp OR "myocardial infarction":ab,ti OR "heart attack":ab,ti
2	'antithrombocytic agent'/exp OR 'purinergic receptor blocking agent'/exp OR 'acetylsalicylic acid'/exp OR 'adenosine receptor blocking agent'/exp OR 'clopidogrel'/exp OR 'prasugrel'/exp OR 'ticagrelor'/exp OR (platelet:ab,ti AND aggregation:ab,ti AND inhibitors:ab,ti) OR (antiplatelet:ab,ti OR antiplatelets:ab,ti) OR (purinergic:ab,ti AND p2y:ab,ti AND receptor:ab,ti AND antagonists:ab,ti) OR "ADP receptor antagonist":ab,ti OR "ADP receptor antagonists":ab,ti OR aspirin:ab,ti OR clopidogrel:ab,ti OR plavix:ab,ti OR prasugrel:ab,ti OR effient:ab,ti OR ticagrelor:ab,ti OR brilinta:ab,ti
3	'blood clotting factor 10a'/exp OR 'rivaroxaban'/exp OR 'hirulog'/exp OR 'apixaban'/exp OR '(n (4 ((1 acetimidoyl 4 piperidyl)oxy)phenyl) n ((7 amidino 2 naphthyl)methyl)sulfamoyl)acetic acid'/exp OR 'otamixaban'/exp OR "factor xa inhibitor":ab,ti OR "factor xa inhibitors":ab,ti OR rivaroxaban:ab,ti OR xarelto:ab,ti OR bivalirudin:ab,ti OR angiomax:ab,ti OR eliquis:ab,ti OR apixaban:ab,ti OR "2-(3-carbamimidoylbenzyl)-3-(4-(1-oxypyridin-4-yl)benzoylamino)butyric acid methyl ester":ab,ti OR otamixaban:ab,ti OR "YM 60828":ab,ti OR "ym466":ab,ti
4	'heparin'/exp OR 'fondaparinux'/exp OR 'dalteparin'/exp OR 'enoxaparin'/exp OR 'nadroparin'/exp OR 'low molecular weight heparin'/exp OR heparin:ab,ti OR (low:ab,ti AND molecular:ab,ti AND weight:ab,ti AND heparin:ab,ti) OR (unfractionated:ab,ti AND heparin:ab,ti) OR fondaparinux:ab,ti OR arixtra:ab,ti OR Dalteparin:ab,ti OR fragmin:ab,ti OR Enoxaparin:ab,ti OR lovenox:ab,ti OR Nadroparin:ab,ti OR fraxiparine:ab,ti
5	'antivitamin K'/exp OR 'warfarin'/exp OR 'coumarin'/exp OR "vitamin k antagonist":ab,ti OR "vitamin k antagonists":ab,ti OR warfarin:ab,ti OR Coumadin:ab,ti OR VKA:ab,ti OR coumarol:ab,ti OR dicoumarol:ab,ti OR coumarin:ab,ti OR dicoumarin:ab,ti
6	'antithrombin'/exp OR 'dabigatran'/exp OR "direct thrombin inhibitor":ab,ti OR "direct thrombin inhibitors":ab,ti OR "N-((2-(((4-(aminoiminomethyl)phenyl)amino)methyl)-1-methyl-1H-benzimidazol-5-yl)carbonyl)-N-2-pyridinyl-beta-alanine":ab,ti OR dabigatran:ab,ti OR pradaxa:ab,ti
7	'abciximab'/exp OR 'eptifibatide'/exp OR 'tirofiban'/exp OR "Glycoprotein IIb/IIIa inhibitor":ab,ti OR "GP IIb/IIIa inhibitor":ab,ti OR "Glycoprotein IIb/IIIa inhibitors":ab,ti OR "GP IIb/IIIa inhibitors":ab,ti OR abciximab:ab,ti OR reopro:ab,ti OR eptifibatide:ab,ti OR integrilin:ab,ti OR tirofiban:ab,ti OR aggrastat:ab,ti

Set #	Terms
8	'proton pump inhibitor'/exp OR omeprazole:ab,ti OR esomeprazole:ab,ti OR lansoprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR dexlansoprazole:ab,ti OR zegerid:ab,ti OR nexium:ab,ti OR aciphex:ab,ti OR protonix:ab,ti OR prevacid:ab,ti OR kapidex:ab,ti OR prilosec:ab,ti
9	'transluminal coronary angioplasty'/exp OR 'percutaneous coronary intervention'/exp OR (Percutaneous:ab,ti AND Transluminal:ab,ti AND Coronary:ab,ti AND Angioplasty:ab,ti) OR "percutaneous transluminal coronary angioplasty":ab,ti OR 'angioplasty'/exp OR angioplasty:ab,ti OR PTCA:ab,ti OR PCI:ab,ti OR (percutaneous:ab,ti AND coronary:ab,ti AND intervention:ab,ti) OR ((coronary:ab,ti OR 'heart'/exp OR heart:ab,ti) AND ('stent'/exp OR stent:ab,ti OR stents:ab,ti OR stenting:ab,ti OR stented:ab,ti))
10	1 AND (2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9)
12	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR “clinical trial”:ti,ab OR “clinical trials”:ti,ab OR 'evaluation'/exp OR “evaluation study”:ab,ti OR “evaluation studies”:ab,ti OR “intervention study”:ab,ti OR “intervention studies”:ab,ti OR “case control”:ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR “follow up”:ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR “comparative study”:ab,ti OR “comparative studies”:ab,ti OR 'evidence based medicine'/exp OR “systematic review”:ab,ti OR “meta-analysis”:ab,ti OR “meta-analyses”:ab,ti
13	10 AND 12
14	13 AND [embase]/lim NOT [medline]/lim
14	13 NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp) Limits: English, Human, 1995 - Present

Cochrane Search Strategy (July 19, 2012)

Platform: Wiley

Databases searched: Cochrane Central Registry of Controlled Trials and Cochrane Database of Systematic Reviews

Table A-3. Cochrane search strategy

Set #	Terms
1	"heart diseases"[MeSH Terms] OR "myocardium"[MeSH Terms] OR "cardiovascular diseases"[MeSH Terms] OR angina, unstable[MeSH Terms] OR "heart"[MeSH Terms] OR myocardial infarction[mesh] OR acute coronary syndrome[MeSH Terms] OR (acute:ti,ab AND coronary:ti,ab AND syndrome:ti,ab) OR "acute coronary syndrome":ti,ab OR non-st:ti,ab OR nstemi:ti,ab OR n-stemi:ti,ab OR non-stemi:ti,ab OR nonstemi:ti,ab OR nsteacs:ti,ab OR (angina:ti,ab AND unstable:ti,ab) OR "unstable angina":ti,ab OR (preinfarction:ti,ab AND angina:ti,ab) OR "preinfarction angina":ti,ab OR ("cardiovascular":ti,ab AND "diseases":ti,ab) OR OR ("heart":ti,ab AND "diseases":ti,ab) OR "heart":ti,ab OR "coronary":ti,ab OR cardiovas*:ti,ab OR cardiac*:ti,ab OR "myocardium":ti,ab OR "myocardial":ti,ab OR ACS:ti,ab
2	(platelet:ti,ab AND aggregation:ti,ab AND inhibitors:ti,ab) OR (antiplatelet:ti,ab AND agent*:ti,ab) OR (purinergic:ti,ab AND p2y:ti,ab AND receptor:ti,ab AND antagonists:ti,ab) OR "ADP receptor antagonist":ti,ab OR "ADP receptor antagonists":ti,ab OR aspirin:ti,ab OR clopidogrel:ti,ab OR plavix:ti,ab OR prasugrel:ti,ab OR effient:ti,ab OR ticagrelor:ti,ab OR brilinta:ti,ab OR "factor xa inhibitor":ti,ab OR "factor xa inhibitors":ti,ab OR rivaroxaban:ti,ab OR xarelto:ti,ab OR bivalirudin:ti,ab OR angiomax:ti,ab OR eliquis:ti,ab OR apixaban:ti,ab OR "2-(3-carbamimidoylbenzyl)-3-(4-(1-oxypyridin-4-yl)benzoylamino)butyric acid methyl ester":ti,ab OR otamixaban:ti,ab OR "YM 60828":ti,ab OR "ym466":ti,ab OR heparin:ti,ab OR (low:ti,ab AND molecular:ti,ab AND weight:ti,ab AND heparin:ti,ab) OR (unfractionated:ti,ab AND heparin:ti,ab) OR fondaparinux:ti,ab OR arixtra:ti,ab OR Dalteparin:ti,ab OR fragmin:ti,ab OR Enoxaparin:ti,ab OR lovenox:ti,ab OR Nadroparin:ti,ab OR fraxiparine:ti,ab OR "vitamin k antagonist":ti,ab OR "vitamin k antagonists":ti,ab OR warfarin:ti,ab OR Coumadin:ti,ab OR VKA:ti,ab OR coumarol:ti,ab OR dicoumarol:ti,ab OR coumarin:ti,ab OR dicoumarin:ti,ab OR "direct thrombin inhibitor":ti,ab OR "direct thrombin inhibitors":ti,ab OR "N-((2-(((4-(aminoiminomethyl)phenyl)amino)methyl)-1-methyl-1H-benzimidazol-5-yl)carbonyl)-N-2-pyridinyl-beta-alanine":ti,ab OR dabigatran:ti,ab OR pradaxa:ti,ab OR "Glycoprotein IIb/IIIa inhibitor":ti,ab OR "GP IIb/IIIa inhibitor":ti,ab OR "Glycoprotein IIb/IIIa inhibitors":ti,ab OR "GP IIb/IIIa inhibitors":ti,ab OR abciximab:ti,ab OR reopro:ti,ab OR eptifibatide:ti,ab OR integrilin:ti,ab OR tirofiban:ti,ab OR aggrastat:ti,ab OR omeprazole:ti,ab OR esomeprazole:ti,ab OR lansoprazole:ti,ab OR pantoprazole:ti,ab OR rabeprazole:ti,ab OR dexlansoprazole:ti,ab OR zegerid:ti,ab OR nexium:ti,ab OR aciphex:ti,ab OR protonix:ti,ab OR prevacid:ti,ab OR kapidex:ti,ab OR prilosec:ti,ab OR (Percutaneous:ti,ab AND Transluminal:ti,ab AND Coronary:ti,ab AND Angioplasty:ti,ab) OR "percutaneous transluminal coronary angioplasty":ti,ab OR angioplasty:ti,ab OR PTCA:ti,ab OR PCI:ti,ab OR (percutaneous:ti,ab AND coronary:ti,ab AND intervention:ti,ab) OR ((coronary:ti,ab OR heart:ti,ab) AND (stent:ti,ab OR stents:ti,ab OR stenting:ti,ab OR stented:ti,ab)) OR MeSH descriptor Myocardial Infarction OR MeSH descriptor Angina, Unstable OR MeSH descriptor Acute Coronary Syndrome OR MeSH descriptor Aspirin OR MeSH descriptor Purinergic P2Y Receptor Antagonists OR MeSH descriptor Platelet Aggregation Inhibitors OR MeSH descriptor Factor Xa OR MeSH descriptor Heparin OR MeSH descriptor Vitamin K with qualifier: AI OR MeSH descriptor Warfarin OR MeSH descriptor Antithrombins OR MeSH descriptor Proton Pump Inhibitors OR MeSH descriptor Proton Pumps with qualifier: AI OR MeSH descriptor Omeprazole OR MeSH descriptor Heart OR MeSH descriptor Angioplasty OR MeSH descriptor Stents OR MeSH descriptor Angioplasty, Balloon, Coronary
3	1 AND 2 *Each MeSH descriptor was searched separately and then combined with OR*
4	3, Limits: English, 2005-, Systematic Reviews

Gray Literature Searches

ClinicalTrials.gov (Final Search Date August 20, 2012)

	Terms
Condition	acute coronary syndrome OR non-st OR nstemi OR n-stemi OR non-stemi OR nonstemi OR nsteacs OR unstable angina OR preinfarction angina
First received	From 01/01/1995

Total number of results: 630

WHO International Clinical Trials Registry Platform Search Portal (Final Search Date March 7, 2012)

Terms: acute coronary syndrome OR non-st OR nstemi OR n-stemi OR non-stemi OR nonstemi OR nsteacs OR unstable angina OR preinfarction angina

Total number of results: 623

ProQuest COS Conference Papers Index (Final Search Date February 15, 2012)

Set #	Terms
1	all(acs OR "acute coronary syndrome" OR non-st OR nstemi OR n-stemi OR non-stemi OR nonstemi OR nsteacs OR (unstable AND angina) OR (preinfarction AND angina) OR “myocardial infarction” OR “heart attack”)
2	all ((platelet AND aggregation AND inhibitor*) OR (antiplatelet AND agent*) OR (purinergic AND p2y AND receptor AND antagonists) OR "ADP receptor antagonist" OR "ADP receptor antagonists" OR aspirin OR clopidogrel OR plavix OR prasugrel OR effient OR ticagrelor OR brilinta OR “factor xa” OR rivaroxaban OR xarelto OR bivalirudin OR angiomax OR apixaban OR eliquis OR otamixaban OR “YM 60828” OR ym466 OR heparin OR fondaparinux OR arixtra OR Dalteparin OR fragmin OR Enoxaparin OR lovenox OR Nadroparin OR fraxiparine OR (“Vitamin K” AND antagonist*) OR warfarin OR Coumadin OR VKA OR coumarol OR dicoumarol OR coumarin OR dicoumarin OR antithrombins OR "direct thrombin inhibitor" OR "direct thrombin inhibitors" OR dabigatran OR pradaxa OR (Glycoprotein AND inhibitor*) OR (GP AND inhibitor*) OR abciximab OR reopro OR eptifibatide OR integrilin OR tirofiban OR aggrastat OR “Proton Pump Inhibitors” OR “Proton Pump Inhibitor” OR omeprazole OR esomeprazole OR lansoprazole OR pantoprazole OR rabeprazole OR dexlansoprazole OR zegerid OR nexium OR aciphex OR protonix OR prevacid OR kapidex OR prilosec OR Angioplasty OR PTCA OR PCI OR (percutaneous AND coronary AND intervention) OR ((coronary OR heart) AND (stent OR stents OR stenting OR stented)))
3	1 and 2

Total number of results: 1467

Appendix B. Data Abstraction Elements

I. Study Characteristics

- Author Last Name and Year
- Study Name and Acronym
- Additional Articles Used in This Abstraction
- Key Question (s) (check all that apply)
    - KQ 1a, KQ 1b, KQ 1c, KQ 2a, KQ 2b, KQ 2c, KQ 3a, KQ 3b, KQ 3c, KQ 3d
- Study Dates
    - Date enrollment started (MM/YYYY)
    - Date enrollment ended (MM/YYYY)
    - Length of Followup (months or years)
- Study Type
    - RCT
    - Observational (prospective or retrospective)
- Enrollment Approach
    - Check all that apply
        - Consecutive patients
        - Convenience sample (not explicitly consecutive)
        - Other (specify)
        - Not reported/unclear
    - Number eligible for study
    - Number randomized/enrolled
    - Number completing follow-up
    - Number included in primary outcome analysis
- Study Sites
    - Single Center
    - Multicenter
    - Not reported/Unclear
- Number of Sites
- Geographical Location (select all applicable geographic regions
    - US, Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ, Not reported/Unclear, Other (specify)
- Funding Source (check all that apply)
    - Government, Private Foundation, Non-profit, Industry, Not reported, Other (specify)
- Setting (check all that apply)
    - Academic centers, Community hospitals, Outpatient, VA, Not reported/Unclear, Other (specify)
- Study Inclusion and Exclusion Criteria
    - Copy and paste inclusion/exclusion criteria as reported in the article
- Clinical Presentation of Population Studied
    - UA/NSTEMI only
    - Mixed Population

- Comments

II. Baseline Characteristics

- Number of Subjects
  - Total, Tx 1, Tx 2, Tx 3, Tx 4
    - N
      - Total
      - Female
      - Male
    - %
      - Female
      - Male
- Total Population – Age in Years
  - Total, Tx 1, Tx 2, Tx 3, Tx 4
    - Mean
    - SD
    - Median
    - IQR
- Ethnicity
  - Total, Tx 1, Tx 2, Tx 3, Tx 4
    - Hispanic or Latino (N, %)
    - Not Hispanic or Latino (N, %)
- Race
  - Total, Tx 1, Tx 2, Tx 3, Tx 4
    - Black/African American (N, %)
    - American Indian or Alaska Native (N, %)
    - Asian (N, %)
    - Native Hawaiian or other Pacific Islander (N, %)
    - White (N, %)
    - Multiracial (N, %)
    - Other (specify) (N, %)
- Baseline Characteristics
  - Total, Tx 1, Tx 2, Tx 3, Tx 4
    - Diabetes (N, %)
    - Hypertension (N, %)
    - Hyperlipidemia (N, %)
    - Prior MI (N, %)
    - Prior PCI (N, %)
    - Prior CABG (N, %)
    - Heart Failure (N, %)
    - CKD/Renal Insufficiency (N, %)
    - Smoking/Tobacco Use (N, %)
    - Known PAD (N, %)
    - Prior Stroke (N, %)
    - Obesity (N, %)
    - Other (Specify) (N, %)

        - Weight
            - Result (Mean, Median)
            - Variability (Standard deviation, Standard error, 95% CI, IQR)
        - BMI
            - Result (Mean, Median)
            - Variability (Standard deviation, Standard error, 95% CI, IQR)
- Presentation
    - Total, Tx 1, Tx 2, Tx 3, Tx 4
        - UA only (N, %)
        - NSTEMI only (N, %)
        - UA/NSTEMI (N, %)
        - STEMI only (N, %)
        - ACS (N, %)
        - Stable CAD (N, %)
- Comments

III. Intervention Characteristics

- Treatment Strategy (check all that apply
    - Early Invasive, Initial Conservative, Post-Discharge, Unclear/Not Specified
- Intervention Characteristics
    - Tx 1, Tx 2, Tx 3, Tx 4
        - Specify Treatment – Clopidogrel, Prasugrel, Ticagrelor, Bivalirudin, Fondaparinux, Aspirin, Abciximab, Eptifibatide, Tirofiban, Enoxaparin, Unfractionated Heparin, Warfarin, Dabigatran, Rivaroxaban, Apixaban, Pantoprazole, Omeprazole, Lansoprazole, Rabeprazole, Esomeprazole, Dual Therapy (specify), Triple Therapy (specify), Placebo, Other (specify)
        - Intervention
            - Admission, In-Lab, In-Hospital, Discharge, Unknown
            - Loading Dose
            - Maintenance Dose
            - Timing
            - Duration of Treatment
        - Co-Interventions (check all that apply)
            - Clopidogrel, Prasugrel, Ticagrelor, Bivalirudin, Fondaparinux, Aspirin, Abciximab, Eptifibatide, Tirofiban, Enoxaparin, Unfractionated Heparin, Warfarin, Dabigatran, Rivaroxaban, Apixaban, Pantoprazole, Omeprazole, Lansoprazole, Rabeprazole, Esomeprazole, Placebo/Control, Other (specify), Glycoprotein IIB/IIA inhibitors, Low molecular weight heparins, Proton pump inhibitors
        - Description of Co-Intervention (dose, frequency, duration, administration)
        - Hours from Admission to Angiography
            - Result (Mean, Median)
            - Variability (IQR, 95% CI, Standard deviation, Standard error)
        - Hours from Antithrombotic Study Drug to Angiography

        - Result (Mean, Median)
        - Variability (IQR, 95% CI, Standard deviation, Standard error)
    - Hours from Antithrombotic Study Drug to PCI
        - Result (Mean, Median)
        - Variability (IQR, 95% CI, Standard deviation, Standard error)
    - Treatment Given
        - Medical Therapy
        - PCI
        - CABG
- Intervention Description
- Describe the Concomitant Medical Therapy/Optimal Medical Therapy from this study
- PCI Characteristics
    - Tx 1, Tx 2, Tx 3, Tx 4
        - Lesions Treated (mean per patient)
            - Mean
            - Standard Deviation
            - Standard Error
        - Access Site – Radial (list %)
        - Access Site – Femoral (list %)
        - Interventional Approach – Balloon (N, %)
        - Interventional Approach – Atherectomy (N, %)
        - Stents – patient receiving stents
            - N and/or %
            - Type of Stent
                - Bare Metal
                - Drug-Eluting
                - Closed-Cell
                - Open-Cell
        - Stents Used (mean per patient)
            - Mean
            - Standard Deviation
            - Standard Error
- PCI Intervention Description

IV. Individual Outcomes

- Primary or Secondary Outcome
    - Primary/Secondary/ Unclear
- Select Outcome
    - Total Mortality, Cardiovascular mortality, Nonfatal myocardial infarction, Stroke (any kind), Revascularization, Rehospitalization, Length of hospital stay, Stent thrombosis, Resource utilization (e.g. emergency dept. visits), Major bleeding, Minor bleeding, Quality of life, Adverse drug reactions, Contrast nephropathy, Radiation, Other 1, 2, 3, 4 (specify)
- Describe Outcome
- Table 1, Table 2, Table 3, Table 4, Table 5

- Specify the Treatment Strategy
  - Early Invasive, Initial Conservative, Post-Discharge, Not Specified
- Timing of Outcome
  - Baseline
  - Short term ≤ 30 days
    - In-hospital – before cath
    - In-hospital – during PCI
    - 30 days
    - Other (specify)
  - Intermediate term >30 days and ≤ 1 year
    - 6 weeks
    - 6 months
    - 1 year
    - Other (specify)
  - Long term > 1 year
    - 2 years
    - 3 years
    - 4 years
    - 5 years
    - Other (specify)
- Adjustment(s) of outcome data (check all that apply)
  - Results are not adjusted, Age, Sex, Race/ethnicity, Comorbidity(ies) (specify), Body Weight/BMI, Risk factors (smoking), Other (specify all)
- Group (Tx 1, Tx 2, Tx 3, Tx 4)
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
  - Bivalirudin
  - Fondaparinux
  - Aspirin
  - Abciximab
  - Eptifibatide
  - Tirofiban
  - Enoxaparin
  - Unfractionated Heparin
  - Warfarin
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Pantoprazole
  - Omeprazole
  - Lansoprazole
  - Rabeprazole
  - Esomeprazole
  - Dual Therapy (specify)
  - Triple Therapy (specify)

        - Placebo, Other (specify)
    - N for Analysis
    - Result
        - Mean
        - Median
        - Number Patients w/Outcome
        - % Patients w/Outcome
        - Relative Risk (RR)
        - Relative Hazard (HR)
        - Odds Ratio (OR)
        - Risk difference
        - Other (specify)
    - Variability
        - Standard Error (SE)
        - Standard Deviation (SD)
        - Other (specify)
    - Confidence Interval (CI) or Interquartile Range (IQR)
        - LL (25% if IQR)
        - UL (75% if IQR)
    - P-value between tx groups
    - Reference group (for comparison between tx groups)
- Comments

V. Composite Outcomes

- Label the composite outcome reported on this form
    - Composite #1/ Composite #2/ Composite #3/ Composite #4
- Primary or Secondary Outcome
    - Primary/Secondary/ Unclear
- Indicate components that make up this composite outcome (Check all that apply)
    - Total Mortality, Cardiovascular mortality, Nonfatal myocardial infarction, Stroke (any kind), Revascularization, Rehospitalization, Length of hospital stay, Stent thrombosis, Resource utilization (e.g. Emergency Dept. visits), Major bleeding, Minor bleeding, Quality of life, Adverse drug reactions, Contrast nephropathy, Radiation, Other 1, 2, 3, 4 (specify)
- Table 1, Table 2, Table 3, Table 4, Table 5
    - Specify the Treatment Strategy
        - Early Invasive, Initial Conservative, Post-Discharge, Not Specified
    - Timing of Outcome
        - Baseline
        - Short term ≤ 30 days
            - In-hospital – before cath
            - In-hospital – during PCI
            - 30 days
            - Other (specify)
        - Intermediate term >30 days and ≤ 1 year
            - 6 weeks

            - 6 months
            - 1 year
            - Other (specify)
        - Long term > 1 year
            - 2 years
            - 3 years
            - 4 years
            - 5 years
            - Other (specify)
- Adjustment(s) of outcome data (check all that apply)
    - Results are not adjusted, Age, Sex, Race/ethnicity, Comorbidity(ies) (specify), Body Weight/BMI, Risk factors (smoking), Other (specify all)
- Group (Tx 1, Tx 2, Tx 3, Tx 4)
    - Clopidogrel
    - Prasugrel
    - Ticagrelor
    - Bivalirudin
    - Fondaparinux
    - Aspirin
    - Abciximab
    - Eptifibatide
    - Tirofiban
    - Enoxaparin
    - Unfractionated Heparin
    - Warfarin
    - Dabigatran
    - Rivaroxaban
    - Apixaban
    - Pantoprazole
    - Omeprazole
    - Lansoprazole
    - Rabeprazole
    - Esomeprazole
    - Dual Therapy (specify)
    - Triple Therapy (specify)
    - Placebo, Other (specify)
- N for Analysis
- Result
    - Mean
    - Median
    - Number Patients w/Outcome
    - % Patients w/Outcome
    - Relative Risk (RR)
    - Relative Hazard (HR)
    - Odds Ratio (OR)
    - Risk difference

        - Other (specify)
    - Variability
        - Standard Error (SE)
        - Standard Deviation (SD)
        - Other (specify)
    - Confidence Interval (CI) or Interquartile Range (IQR)
        - LL (25% if IQR)
        - UL (75% if IQR)
    - P-value between tx groups
    - Reference group (for comparison between tx groups)
- Comments

VI. Quality

- Was this study randomized? (Yes/No)
    - If yes:
        - Were study subjects randomized? (Yes/No/Unclear)
        - Was the randomization process described? (Yes/No/Unclear)
        - Was the outcome assessor blinded to study assignment? (Yes/No/Unclear)
        - Were patients blinded to study intervention? (Yes/No/Unclear)
        - Were results adjusted for clustering? (Yes/No/Unclear)
        - Were measures of outcomes based on validated procedures or instruments? (Yes/No/Unclear)
        - Conducted an intent to treat analysis? (Yes/No/Unclear)
        - Were all outcomes reported (i.e. was there evidence of selective outcome reporting)? (Yes/No/Unclear)
        - Were incomplete data adequately addressed (i.e. no systematic differences between groups in withdrawals/loss to follow-up AND no high drop-out or loss to follow-up rate [>30%])? (Yes/No/Unclear)
        - Was there adequate power (either based on pre-study or post-hoc power calculations [80% power for primary outcome])? (Yes/No/Unclear)
        - Were systematic differences observed in baseline characteristics and prognostic factors across the groups compared? (Yes/No/Unclear)
        - Were comparable groups maintained? (Includes crossovers, adherence, and contamination. Consider issues of crossover [e.g. from one intervention to another], adherence [major differences in adherence to the interventions being compared], contamination [e.g. some members of control group get intervention], or other systematic difference in care that was provided.) (Yes/No/Unclear)
        - Was there absence of potential important conflict-of-interest? (Focus on financial conflicts with for-profit capacities; government or non-profit funding = 'yes') (Yes/No/Unclear)
        - Overall Study Rating (Good/Fair/Poor) – Please give reasons for a rating of Fair or Poor
            - A "**Good**" study has the least bias, and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid

approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.

- A "**Fair**" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.
- A "**Poor**" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

- If no:
  - Basic Design
    - Is the study design prospective, retrospective, or mixed? (Prospective/Mixed/Retrospective/Cannot determine)
  - Selection Bias
    - Inclusion/Exclusion Criteria
      - Are the inclusion/exclusion criteria clearly stated (does not require the reader to infer)? (Yes/Partially/No)
      - Did the study apply inclusion/exclusion criteria uniformly to all comparison groups? (Yes/Partially/No/NA
    - Recruitment
      - Did the strategy for recruiting participants into the study differ across study groups? (Yes/No/Cannot determine/NA)
    - Baseline characteristics similar or appropriate adjusted analysis
      - Are key characteristics of study participants similar between intervention and control group? If not similar, did the analysis appropriately adjust for important differences? (Yes – similar or appropriate adjusted analysis/Partially – only some characteristics described or some characteristics not clearly described; analysis adjust for some/No – important baseline differences; unadjusted analysis/Insufficient reporting to be able to determine)
    - Comparison Group
      - Is the selection of the comparison group appropriate? (Yes/No/Cannot determine/NA)
  - Performance Bias
    - Intervention implementation
      - What is the level of detail in describing the intervention or exposure? (High – very clear, all PI-required details provided/Medium – somewhat clear, majority of PI-

required details provided/Low – unclear, many PI-required details missing)

- Concurrent/concomitant interventions
  - Did researches isolate the impact from a concurrent intervention or unintended exposure that might bias the results, e.g., through multivariate analysis, stratification, or subgroup analysis? (Yes/Partially/Not described)

- Attrition Bias
  - Equality of length of follow-up for participants
    - In cohort studies, is the length of follow-up different between groups? (Yes/No or cannot determine/Not applicable)
  - Completeness of follow-up
    - Was there a high rate of differential or overall attrition? (Yes/No/Cannot determine)
  - Attrition affecting participant composition
    - Did attrition result in a difference in group characteristics between baseline and follow-up? (Yes/No/Cannot determine)
  - Any attempt to balance
    - Any attempt to balance the allocation between groups (e.g. through stratification, matching, propensity scores)? (Yes/No/Cannot determine)
  - Intention-to-treat analysis
    - Is the analysis conducted on an intention-to-treat (ITT) basis, that is, the intervention allocation status rather than the actual intervention received? (Yes/No/Cannot determine/NA)
- Detection Bias
  - Source of information re: outcomes
    - Are procedural outcomes (e.g. stent thrombosis) assessed using valid and reliable measures and implemented consistently across all study participants? (Yes/No/Cannot determine)
    - Are event outcomes (e.g. mortality, MI, CVA, revascularization) assessed using valid and reliable measures and implemented consistently across all study participants? (Yes/No/Cannot determine)
    - Are patient-reported outcomes (e.g. quality of life) assessed using valid and reliable measure and implemented consistently across all study participants? (Yes/No/Cannot determine)
- Reporting Bias
  - Are any important primary outcomes missing from the results? (Yes/No/Cannot determine/Primary outcomes no pre-specified)
- Other risk of bias issues

- Are the statistical methods used to assess the primary outcomes appropriate to the data? (Yes/Partially/No/Cannot determine)
- Power and sample size
    - Did the authors report conducting a power analysis or some other basis for determining the adequacy of study group sizes for the primary outcome(s) being abstracted? (Yes/No/NA)

- Overall rating of the study
    - Good/Low risk of Bias (good quality study with clear description)
    - Fair/Moderate risk of Bias (fair quality study; some bias but not enough to invalidate results)
    - Poor/High risk of Bias (low quality study; significant bias that may invalidate results)
- A "Good/Low Risk of Bias" study has the least bias, and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses recruitment and eligibility criteria that minimizes selection bias; has a low attrition rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. These studies will meet the majority of items in each domain.
- A "Fair/Moderate Risk of Bias" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid. These studies will meet the majority of items in most but not all domains.
- A "Poor/High Risk of Bias" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

VII. Applicability

- Did this study have any limitations that would affect its applicability? (Yes/No)
    - If Yes:
        - Population (P)
            - Study did not report participants' baseline characteristics.
            - Study did not report participant' comorbid conditions.
            - Participant diagnosis and identification for eligibility screening before random allocation was not appropriate/Cohort selection was not appropriate.
            - Study eligibility criteria were poorly described or not appropriate.
            - Study exclusion criteria were poorly described or not appropriate.

        - Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition.
    - Intervention (I)
        - Study interventions (active arm) were not similar to interventions used in routine clinical practice.
        - Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control).
        - Study prohibited interventions that are routinely used in clinical practice.
        - Diagnostic or therapeutic advances have been made in routine practice since the study was conducted.
    - Comparator (C)
        - Comparator(s) not well described.
        - Use of substandard alternative therapy (e.g., standard of treatment not from current practice).
    - Outcomes (O)
        - Study did not use a clinically relevant surrogate outcome where applicable.
        - Study centers and/or clinicians were not selected on the basis of their skill or experience.
        - Study excluded participants at elevated risk of intervention complications.
        - Composite outcomes that mix outcomes of different significance.
    - Timing (T)
        - Duration of participant followup was inadequate.
    - Setting (S)
        - Study conducted solely outside the US.
        - Study was conducted only at a single site.
    - Comments
- If No:
    - Comments

Appendix C. List of Included Studies

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Study Groupings Table

Table C-1 presents a key to the 302 primary and companion articles included in this report, organized alphabetically by study designation (if applicable). A full reference list follows the table.

Table C-1. Primary articles and companion articles

Study Designation	Primary Article(s)	Companion Article(s)
A to Z Trial	Blazing, 2004[1]	Blazing, 2001[2] de Lemos, 2004[3]
ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy Trial) ACUITY TIMING	Stone, 2006[4] Stone, 2007[5]	Ambrosio, 2011[6] Aoki, 2009[7] Caixeta, 2011[8] Feit, 2008[9] Goto, 2010[10] Kumar, 2010[11] Kirtane, 2010[12] Lansky, 2009[13] Lincoff, 2008[14] Lopes, 2009[15] Manoukian, 2007[16] Mehran, 2009[17] Miller, 2009[18] Pinto, 2008[19] Stone, 2004[20] Stone, 2007[21] Stone, 2007[22] White, 2008[23] White, 2008[24]
ACUTE II	Cohen, 2002[25]	None
ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis Trial)	Montalescot, 2006[26]	None
ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty)	Patti, 2005[27]	None
ARMYDA-4 RELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty)	Di Sciascio, 2010[28]	None
ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty)	Di Sciascio, 2010[29]	None
ARMYDA-7 BIVALVE (Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty – Bivalirudin vs Heparin)	Patti, 2012[30]	None
ARNO (Antithrombotic Regimens aNd Outcome trial)	Parodi, 2010[31]	None
ASPIRE pilot trial (Arixtra Study in Percutaneous Coronary Intervention: a Randomized Evaluation)	Mehta, 2005[32]	None
BRAVO (Blockage of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion)	Aronow, 2008[33]	None
BRIEF-PCI (Brief Infusion of Eptifibatide Following Percutaneous Coronary Intervention)	Fung, 2009[34]	None
Clopidogrel Medco Outcomes Study	Kreutz, 2010[35]	None
CLOTILDA (CLOpidogrel, upstream TIrofiban, in cath Lab Downstream Abciximab study)	Leoncini, 2005[36]	None
COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial)	Bhatt, 2010[37]	None
CREDO (Clopidogrel for the Reduction of Events During Observation Trial)	Steinhubl, 2002[38]	Aronow, 2009[39] Best, 2008[40] Brener, 2007[41]

Study Designation	Primary Article(s)	Companion Article(s)
CRUISE (Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin Study)	Bhatt, 2003[42]	None
CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines)	Alexander, 2008[43] Fosbol, 2012[44] LaPointe, 2007[45] Singh, 2006[46] Tricoci, 2007[47]	None
CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial)	Yusuf, 2001[48]	Budaj, 2002[49] Fox, 2004[50] Jolly, 2009[51] Keltai, 2007[52] Lewis, 2005[53] Peters, 2003[54] Mehta, 2001[55] Moliterno, 2002[56] Yusuf, 2003[57]
CURRENT-OASIS 7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events – Seventh Organization to Assess Strategies in Ischemic Syndromes)	Mehta, 2010[58]	Mehta, 2008[59] Mehta, 2010[60]
DISPERSE-2	Cannon, 2007[61]	None
EARLY ACS	Giugliano, 2009[62]	Giugliano, 2005[63] Melloni, 2011[64] Wang, 2011[65]
EARLY Pilot Trial (Eptifibatide for Acute Coronary Syndromes – Rapid Versus Late Administration for Therapeutic Yield)	Roe, 2003[66]	None
ELISA Pilot Study (Early or Late Intervention in unstable Angina)	van't Hof, 2003[67]	None
ELISA-2 (Early or Late Intervention in unstable Angina 2)	Rasoul, 2006[68]	None
EPISTENT (Evaluation of Platelet IIb/IIIa Inhibition in Stenting Trial)	Islam, 2002[69]	Anonymous, 1998[70] Price, 2001[71]
ESCAPEU (Efficacy, Safety, Cost, and Platelet Aggregation Effects of Enoxaparin and Unfractionated Heparin)	Malhotra, 2001[72]	None
ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy)	Anonymous, 2000[73]	Labinaz, 2002[74] O'Shea, 2001[75] Puma, 2006[76]
ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Trial)	Cohen, 1997[77]	Brosa, 2002[78] Cohen, 1997[79] Cohen, 1998[80] Fox, 2002[81] Goodman, 2000[82] Goodman, 2006[83] Mark, 1998[84] Spinler, 2003[85a]
EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting)	Gwon, 2012[86]	None
FABOLUS SYNCHRO (Facilitation through Abciximab By drOpping Infusion Line in patients Undergoing coronary Stenting. SYNergy with Clopidogrel at High loading dOse Regimen)	Valgimigli, 2010[87]	None
FAST-MI Registry (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction)	Puymirat, 2011[88] Simon, 2011[89]	None
FUTURA/OASIS 8 Randomized Trial (Fondaparinux Trial With Unfractionated Heprin During Revascularization in Acute Coronary Syndromes)	Steg, 2010[90]	Steg, 2010[91]
GHOST Guthrie Health Off-Label Stent)	Harjai, 2011[92] Harjai, 2011[93]	None

Study Designation	Primary Article(s)	Companion Article(s)
GRACE (Global Registry of Acute Coronary Events)	Brieger, 2007[94] Dabbous, 2008[95] Gore, 2007[96] Lim, 2005[97] Nguyen, 2007[98] Sibbald, 2010[99]	None
GRAVITAS (Gauging Responsiveness with A Verify Now assay – Impact on Thrombosis And Safety)	Price, 2011[100]	None
GUSTO IIb (Global Use of Strategies to open Occluded coronary Arteries	Quinn, 2004[101a]	None
GUSTO IV-ACS (Global Use of Strategies To Open Occluded Coronary Arteries IV – Acute Coronary Syndrome Trial)	Simoons, 2001[102]	Lenderink, 2004[103] Ottervanger, 2003[104]
INTERACT (Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment)	Goodman, 2003[105]	Fitchett, 2006[106] Goodman, 2005[107]
ISAR-REACT 2 Randomized Trial (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2)	Kastrati, 2006[108]	Iijima, 2008[109] Iijima, 2008[110] Mehilli, 2007[111] Ndrepepa, 2008[112] Ndrepepa, 2006[113]
ISAR-REACT 3 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 3 Trial)	Kastrati, 2008[114]	Iijima, 2009[115] Schulz, 2010[116] Schulz, 2010[117]
ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 4 Trial)	Kastrati, 2011[118]	None
KAMIR (Korea Acute Myocardial Infarction Registry)	Li, 2012[119]	None
KICS (Kumamoto Intervention Conference Study)	Chitose, 2011[120]	None
NRMI3 (National Registry of Myocardial Infarction 3)	Kovar, 2002[121]	None
NRMI4 (National Registry of Myocardial Infarction 4)	Peterson, 2003[122]	None
OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes)	Yusuf, 2006[123]	Budaj, 2009[124] Fox, 2007[125] Jolly, 2009[126] Joyner, 2009[127] Mehta, 2005[128] Mehta, 2008[129] Mehta, 2007[130] Sculpher, 2009[131]
Ottawa Heart Institute PCI Registry	So, 2009[132]	None
PARAGON-A (Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network A)	Lopes, 2010[133a]	None
PLATO (Platelet Inhibition and Patient Outcomes)	Wallentin, 2009[134] James, 2011[135]	Cannon, 2010[136] Becker, 2011[137] Goodman, 2012[138] Held, 2011[139] Husted, 2012[140] James, 2010[141] James, 2010[142] James, 2009[143] Mahaffey, 2011[144] Storey, 2011[145]
PRACTICAL Platelet Responsiveness to Aspirin and Clopidogrel and Troponin Increment after Coronary intervention in Acute coronary Lesions)	Yong, 2009[146]	None
PRACTICE (Prospective RAndomised placebo Controlled trial to assess the role of BP IIb/IIIa blockade by integrilin in patients with troponin Increase and nonpersistent ST segment elevation acute Coronary syndrome study)	Durand, 2007[147]	None

Study Designation	Primary Article(s)	Companion Article(s)
PRISM (Platelet Receptor Inhibition in Ischemic Syndrome Management)	Anonymous, 1998[148]	None
PRISM-PLUS (Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms)	Anonymous, 1998[149]	Huynh, 2003[150] Huynh, 2005[151] Januzzi, 2000[152] Januzzi, 2001[153] Januzzi, 2002[154] Morrow, 2004[155] Mozes, 2004[156] Theroux, 2000[157]
PRODIGY (PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY)	Valgimigli, 2012[158]	None
PROTECT-TIMI-30 (Randomized Trial to Evaluate the Relative PROTECTion against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Anti-Platelet and Anti-Thrombotic Agents-Thrombolysus In Myocardial Infarction-30)	Gibson, 2006[159]	None
PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy Trial)	Anonymous, 1998[160]	Brown, 2003[161] Chang, 2002[162] Harrington, 1997[163] Hasdai, 2000[164] Kleiman, 2000[165] Labinaz, 2004[166] Lincoff, 2000[167] Lopes, 2010[133a] Quinn, 2004[101a] Ronner, 2002[168] Srichai, 2004[169]
RACS (Randomized Argentine Clopidogrel Stent Trial)	Bernardi, 2007[170]	None
REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events Trial)	Rajagopal, 2006[171]	None
RIKS-HIA (Register of Information and Knowledge About Swedish Heart Intensive Care Admissions)	Stenestrand, 2005[172]	None
ROSAI-2 (Registro Osservazionale Angina Instabile)	De Servi, 2006[173]	None
SANTISS (Sant'ANna TIrofiban Safety Study)	Schiariti, 2011[174]	Schiariti, 2010[175]
SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors Trial)	Ferguson, 2004[176]	Anonymous, 2002[177] Chew, 2008[178] Cohen, 2006[179] Cohen, 2010[180] Ferguson, 2002[181] Lopes, 2008[182] Lopes, 2010[133a] Petersen, 2004[183] White, 2006[184]
T-ACCORD Registry (Taiwan Acute CORonary Syndrome Descriptive Registry)	Cheng, 2010[185]	None
TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial)	Topol, 2001[186]	Berger, 2005[187] Chan, 2003[188] Merlini, 2004[189] Moliterno, 2000[190] Mukherjee, 2005[191] Roffi, 2002[192] Stone, 2002[193]
TENACITY (Tirofiban Evaluation of Novel Dosing versus Abciximab with Clopidogrel and Inhibition of Thrombin Study Trial)	Moliterno, 2011[194]	None
TIMI 8 (Thrombolysis in Myocardial Infarction)	Antman, 2002[195]	None
TIMI 11B (Thrombolysis In Myocardial Infarction)	Antman, 1999[196]	Antman, 1998[197] Spinler, 2003[85a]

Study Designation	Primary Article(s)	Companion Article(s)
TRILOGY-ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes)	Roe, 2012[198]	Chin, 2010[199]
TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction)	Wiviott, 2007[200]	Antman, 2008[201] Morrow, 2009[202] Murphy, 2008[203] O'Donoghue, 2009[204] O'Donoghue, 2009[205] Pride, 2009[206] Wiviott, 2006[207] Wiviott, 2008[208] Wiviott, 2008[209] Wiviott, 2011[210]
ZEUS (Zurich Enoxaparin versus Unfractionated heparin in PCI Study)	Bertel, 2010[211]	None
None indicated	Abuzahra, 2008[212]	None
None indicated	Ajani, 2003[213]	None
None indicated	Angkasuwapala, 2007[214]	None
None indicated	Banerjee, 2011[215]	None
None indicated	Barada, 2008[216]	None
None indicated	Bauer, 2010[217]	None
None indicated	Berger, 2005[218]	None
None indicated	Berglund, 2002[219]	None
None indicated	Bhattacharya, 2010[220]	None
None indicated	Bhurke, 2012[221]	None
None indicated	Bonde, 2010[222]	None
None indicated	Bonello, 2008[223]	None
None indicated	Brener, 2003[224]	None
None indicated	Buresly, 2005[225]	None
None indicated	Burgess, 2002[226]	None
None indicated	Butler, 2009[227]	None
None indicated	Charlot, 2010[228]	None
None indicated	Charlot, 2011[229]	None
None indicated	Charlot, 2012[230]	None
None indicated	Chen, 2006[231]	None
None indicated	Chu, 2006[232]	None
None indicated	Cortese, 2009[233]	None
None indicated	Cuisset, 2006[234]	None
None indicated	Danzi, 2006[235]	None
None indicated	Daviouros, 2009[236]	None
None indicated	Evanchan, 2010[237]	None
None indicated	Galassi, 1999[238]	None
None indicated	Galasso, 2008[239]	None
None indicated	Gao, 2009[240]	None
None indicated	Gaspar, 2010[241]	None
None indicated	Gowda, 2003[242]	None
None indicated	Gunasekara, 2006[243]	None
None indicated	Gupta, 2010[244]	None
None indicated	Harjai, 2009[245]	None
None indicated	Ho, 2007[246]	None
None indicated	Ho, 2009[247]	None
None indicated	Hsaio, 2011[248]	None
None indicated	Ivandic, 2008[249]	None
None indicated	Iversen, 2011[250]	None
None indicated	Iversen, 2011[251]	None
None indicated	Jang, 2011[252]	None
None indicated	Juurlink, 2009[253]	None

Study Designation	Primary Article(s)	Companion Article(s)
None indicated	Karha, 2006[254]	None
None indicated	Karjalainen, 2007[255]	None
None indicated	Kim, 2005[256]	None
None indicated	Konstantino, 2006[257]	None
None indicated	Korovesis, 2005[258]	None
None indicated	Lahtela, 2009[259]	None
None indicated	Lamberts, 2013[260]	None
None indicated	Lemesle, 2009[261]	None
None indicated	Lemesle, 2009[262]	None
None indicated	Lin, 2009[263]	None
None indicated	Liu, 2009[264]	None
None indicated	Maegdefessel, 2008[265]	None
None indicated	Momtahen, 2009[266]	None
None indicated	Ng, 2011[267]	None
None indicated	Ng, 2008[268]	None
None indicated	Okmen, 2003[269]	None
None indicated	Ortolani, 2011[270]	None
None indicated	Ozkan, 2005[271]	None
None indicated	Pekdemir, 2003[272]	None
None indicated	Persson, 2011[273]	None
None indicated	Rassen, 2009[274]	None
None indicated	Ray, 2010[275]	None
None indicated	Ren, 2011[276]	None
None indicated	Rossini, 2011[277]	None
None indicated	Rossini, 2008[278]	None
None indicated	Roy, 2009[279]	None
None indicated	Ruiz-Nodar, 2008[280]	None
None indicated	Ruiz-Nodar, 2012[281]	None
None indicated	Sarafoff, 2010[282]	None
None indicated	Schiele, 2010[283]	None
None indicated	Schmidt, 2012[284]	None
None indicated	Schulz, 2009[285]	None
None indicated	Schweiger, 2003[286]	None
None indicated	Song, 2007[287]	None
None indicated	Stockl, 2010[288]	None
None indicated	Suleiman, 2003[289]	None
None indicated	Szuk, 2007[290]	None
None indicated	Tentzeris, 2010[291]	None
None indicated	Tsai, 2011[292]	None
None indicated	Valkhoff, 2011[293]	None
None indicated	van Boxel, 2010[294]	None
None indicated	van den Brand, 1995[295]	None
None indicated	Velianou, 2000[296]	None
None indicated	Wang, 2007[297]	None
None indicated	Wolfram, 2003[298]	None
None indicated	Wu, 2010[299]	None
None indicated	Yan, 2009[300]	None
None indicated	Zairis, 2010[301]	None
None indicated	Zeymer, 2008[302]	None

[a] Article reported data from multiple separate trials.

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2. Blazing MA, De Lemos JA, Dyke CK, et al. The A-to-Z Trial: Methods and rationale for a single trial investigating combined use of low-molecular-weight heparin with the glycoprotein IIb/IIIa inhibitor tirofiban and defining the efficacy of early aggressive simvastatin therapy. Am Heart J. 2001;142(2):211-7. PMID: 11479456.
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5. Stone GW, Bertrand ME, Moses JW, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. JAMA. 2007;297(6):591-602. PMID: 17299194.
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Appendix D. List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reason shown in italics. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Aalbers J. Prasugrel study addresses timing of thienopyridine loading dose in NSTEMI patients pre-PCI (the ACCOAST study). Cardiovasc J Afr. 2011;22(3):168. PMID: 21713311. *Exclude - not a Clinical Study.*

Abdallah M, Karrowni W, Shamseddeen W, et al. Acute coronary syndromes: clinical characteristics, management, and outcomes at the American University of Beirut Medical Center, 2002-2005. Clin Cardiol. 2010;33(1):E6-E13. PMID: 20014175. *Exclude - no active comparator*.

Abdel-Latif A, Moliterno DJ. Prasugrel versus clopidogrel in primary PCI: Considerations of the TRITON-TIMI 38 substudy. Curr Cardiol Rep. 2009;11(5):323-324. *Exclude - not a Clinical Study.*

Abu-Assi E, Raposeiras Roubin S, Agra-Bermejo RM, et al. Utility and reliability of the REACH risk score in evaluating the risk of post-discharge bleeding in a contemporary cohort of patients with ACS patients. Eur Heart J. 2011;32:735. *Exclude - no outcomes of interest.*

Acharji S, Baber U, Mehran R, et al. Prognostic significance of elevated baseline troponin in patients with acute coronary syndromes and chronic kidney disease treated with different antithrombotic regimens: a substudy from the ACUITY trial. Circ Cardiovasc Interv. 2012;5(2):157-65. PMID: 22354934. *Exclude - population not UA/NSTEMI (only STEMI, or cannot separate data).*

Acikel S, Yildirir A, Aydinalp A, et al. The clinical importance of laboratory-defined aspirin resistance in patients presenting with non-ST elevation acute coronary syndromes. Blood Coagul Fibrinolysis. 2009;20(6):427-32. PMID: 19542882. *Exclude - no active comparator*.

Agahtehrani A, Dangas GD. Bolus-only glycoprotein IIb/IIIa inhibitor revisited. J Invasive Cardiol. 2006;18(11):527. PMID: 17090814. *Exclude - not a Clinical Study.*

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Aguiar AA, Mourilhe-Rocha R, Esporcatte R, et al. Long-term analysis in acute coronary syndrome: are there any differences in morbidity and mortality? Arq Bras Cardiol. 2010;95(6):705-12. PMID: 21152701. *Exclude - no active comparator*.

Ahmad WA, Ramesh SV, Zambahari R. Malaysia-ACute CORonary syndromes Descriptive study (ACCORD): evaluation of compliance with existing guidelines in patients with acute coronary syndrome. Singapore Med J. 2011;52(7):508-11. PMID: 21808962. *Exclude - no active comparator*.

Ahmad WAW, Ali RM, Zambahari R, et al. Highlights of the first Malaysian National Cardiovascular Disease Database (NCVD): Percutaneous Coronary Intervention (PCI) registry. CVD Prev Contr. 2011;6(2):57-61. *Exclude - no active comparator*.

Aihara H, Sato A, Takeyasu N, et al. Effect of individual proton pump inhibitors on cardiovascular events in patients treated with clopidogrel following coronary stenting:: Results From the Ibaraki Cardiac Assessment Study Registry. Catheter Cardiovasc Interv. 2012. PMID: 22234956. *Exclude - population not UA/NSTEMI (only STEMI, or cannot separate data).*

Aiqing Z, Dongming X, Yihong Y. Clinical study of intracoronary injection of tirofiban during primary pci in treatment of acute coronary syndrome. Heart. 2011;97:A133-A134. *Exclude - Grey Literature (meeting abstract, poster, other non-peer-reviewed item).*

Ait Mokhtar O, Bonello L, Armero S, et al. Early and late outcomes of clopidogrel and coumadin combination for patients on oral anticoagulants undergoing coronary stenting. Cardiovasc Revasc Med. 2010;11(3):159-62. PMID: 20599166. *Exclude - no outcomes of interest*.

Akhter N, Milford-Beland S, Roe MT, et al. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). Am Heart J. 2009;157(1):141-8. PMID: 19081410. *Exclude - no outcomes of interest.*

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Akkerhuis KM, Maas AC, Klootwijk PA, et al. Recurrent ischemia during continuous 12-lead ECG-ischemia monitoring in patients with acute coronary syndromes treated with eptifibatide: relation with death and myocardial infarction. PURSUIT ECG-Ischemia Monitoring Substudy Investigators. Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy. J Electrocardiol. 2000;33(2):127-36. PMID: 10819406. *Exclude - no outcomes of interest.*

Akkerhuis KM, Neuhaus KL, Wilcox RG, et al. Safety and preliminary efficacy of one month glycoprotein IIb/IIIa inhibition with lefradafiban in patients with acute coronary syndromes without ST-elevation; a phase II study. Eur Heart J. 2000;21(24):2042-55. PMID: 11102255. *Exclude - no outcomes of interest.*

Akowuah E, Shrivastava V, Jamnadas B, et al. Comparison of two strategies for the management of antiplatelet therapy during urgent surgery. Ann Thorac Surg. 2005;80(1):149-52. PMID: 15975358. *Exclude - no active comparator.*

Al Suwaidi J, Reddan DN, Williams K, et al. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. Circulation. 2002;106(8):974-80. PMID: 12186803. *Exclude - not a Clinical Study.*

Alexander JH, Becker RC, Bhatt DL, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation. 2009;119(22):2877-85. PMID: 19470889. *Exclude - population not UA/NSTEMI (only STEMI, or cannot separate data).*

Alexander JH, Harrington RA, Tuttle RH, et al. Prior aspirin use predicts worse outcomes in patients with non-ST-elevation acute coronary syndromes. PURSUIT Investigators. Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy. Am J Cardiol. 1999;83(8):1147-51. PMID: 10215274. *Exclude - population not UA/NSTEMI (only STEMI, or cannot separate data).*

Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med. 2011;365(8):699-708. PMID: 21780946. *Exclude - population not UA/NSTEMI (only STEMI, or cannot separate data).*

Alexander JH, Yang H, Becker RC, et al. First experience with direct, selective factor Xa inhibition in patients with non-ST-elevation acute coronary syndromes: results of the XaNADU-ACS Trial. J Thromb Haemost. 2005;3(3):439-47. PMID: 15748230. *Exclude - no active comparator.*

Alexander KP, Chen AY, Newby LK, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative. Circulation. 2006;114(13):1380-7. PMID: 16982940. *Exclude - no outcomes of interest.*

Alexopoulos D, Galati A, Xanthopoulou I, et al. Ticagrelor versus prasugrel in acute coronary syndrome patients with high on-clopidogrel platelet reactivity following percutaneous coronary intervention: a pharmacodynamic study. J Am Coll Cardiol. 2012;60(3):193-9. PMID: 22789884. *Exclude - no outcomes of interest.*

Alhabib KF, Hersi A, Alsheikh-Ali AA, et al. Prevalence, Predictors, and Outcomes of Conservative Medical Management in Non-ST-Segment Elevation Acute Coronary Syndromes in Gulf RACE-2. Angiology. 2011. PMID: 21561993. *Exclude - no active comparator.*

Ali A, Hashem M, Rosman HS, et al. Glycoprotein IIb/IIIa receptor antagonists and risk of bleeding: a single-center experience in 1020 patients. J Clin Pharmacol. 2004;44(11):1328-32. PMID: 15496651. *Exclude - no active comparator.*

Ali A, Rehan A, Ganji J, et al. Eptifibatide and risk of bleeding after failed thrombolysis. J Invasive Cardiol. 2004;16(1):20-2. PMID: 14699218. *Exclude - population not UA/NSTEMI (only STEMI, or cannot separate data).*

Alidoosti M, Salarifar M, Kassaian SE, et al. In-hospital and late clinical outcomes of direct stenting strategy versus stenting after predilatation for the treatment of coronary artery lesions. Indian Heart J. 2008;60(4):318-24. PMID: 19242009. *Exclude - population not UA/NSTEMI (only STEMI, or cannot separate data).*

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Ammer M, Paget MA, Hronkova M, et al. Practice patterns and quality of life in acute coronary syndrome patients in 2008-2009: Baseline results for austria from the antiplatelet treatment observational registry ii (Aptor II). Value Health. 2010;13(7):A365. *Exclude - Grey Literature (meeting abstract, poster, other non-peer-reviewed item).*

Amsterdam EA, Peterson ED, Ou FS, et al. Comparative trends in guidelines adherence among patients with non-ST-segment elevation acute coronary syndromes treated with invasive versus conservative management strategies: Results from the CRUSADE quality improvement initiative. Am Heart J. 2009;158(5):748-754 e1. PMID: 19853692. *Exclude - no active comparator*.

Anand SS. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) Pilot Study: evaluation of acute and long-term therapies for patients with acute coronary syndromes without ST elevation. Am J Cardiol. 1999;84(5A):13M-19M. PMID: 10505538. *Exclude - no active comparator*.

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Anand SS, Yusuf S, Pogue J, et al. Long-term oral anticoagulant therapy in patients with unstable angina or suspected non-Q-wave myocardial infarction: organization to assess strategies for ischemic syndromes (OASIS) pilot study results. Circulation. 1998;98(11):1064-70. PMID: 9736592. *Exclude - no active comparator*.

Anderson KM, Califf RM, Stone GW, et al. Long-term mortality benefit with abciximab in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol. 2001;37(8):2059-65. PMID: 11419888. *Exclude - population not UA/NSTEMI (only STEMI, or cannot separate data).*

Anonymous. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. N Engl J Med. 1994;330(14):956-61. PMID: 8121459. *Exclude - population not UA/NSTEMI (only STEMI, or cannot separate data).*

Anonymous. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb investigators. N Engl J Med. 1996;335(11):775-82. PMID: 8778585. *Exclude - no active comparator*.

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Appendix E. Quality and Applicability of Included Studies

Table E-1. Quality and applicability table for KQ 1 studies—early invasive approach for UA/NSTEMI

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Abuzahra, 2008[1]	• Clopidogrel 300 mg loading dose at time of PCI, 75 mg daily • Clopidogrel 600 mg loading dose at time of PCI, 150 mg daily	Fair	• None
Ajani, 2003[2]	• Eptifibatide 180 mcg/kg bolus, 2 mcg/kg/min maintenance • Abciximab 0.25 mg/kg bolus, 10 mcg/min maintenance	Fair	• Study was conducted only at a single site
Anonymous, 2000[3] ESPRIT	• Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at time of PCI • Placebo	Good	• None
Antman, 1999[4] TIMI 11B	• Enoxaparin 30 mg IV loading dose, 1 mg/kg every 12 hr during hospitalization • UFH 70 units/kg bolus, 15 units/kg/hr infusion with goal aPTT 50–70 sec during hospitalization	Good	• Study interventions (active arm) were not similar to interventions used in routine clinical practice • Diagnostic or therapeutic advances have been made in routine practice since the study was conducted • Use of substandard alternative therapy (e.g., standard of treatment not from current practice)
Antman, 2002[5] TIMI 8	• Bivalirudin 0.1 mg/kg bolus, 0.25 mg/kg/hr infusion at hospital admission • UFH 70 units/kg bolus, 15 units/kg/hr at hospital admission	Poor	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)
Bauer, 2010[6]	• Upstream GPI • Downstream GPI • No GPI	Fair	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Comparator(s) not well described
Berger, 2005[7]	• GPI • No GPI	Poor	• Study interventions (active arm) were not similar to interventions used in routine clinical practice
Berglund, 2002[8]	• Early clopidogrel 375 mg • No early clopidogrel	Fair	• None

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Bertel, 2010[9] ZEUS	• Enoxaparin 0.75 mg/kg IV bolus at time of PCI • UFH 60 units/kg bolus at time of PCI	Fair	• Study did not report participants' baseline characteristics • Study did not report participants' comorbid conditions. • Study prohibited interventions that are routinely used in clinical practice • Study conducted solely outside the US • Study was conducted only at a single site
Bhatt, 2003[10] CRUISE	• Enoxaparin 0.75 mg/kg IV bolus at time of PCI • UFH 60 units/kg bolus	Fair	• Study conducted solely outside the US • Study was conducted only at a single site
Bhattacharya, 2010[11]	• Tirofiban 0.1 mcg/kg bolus, 0.1 mcg/kg/min infusion • Placebo	Good	• None
Blazing, 2004[12] A to Z Trial	• Enoxaparin 1 mg/kg every 12 hr during hospitalization • UFH 60 units/kg bolus (max 4000 units), 12 units/kg/hr infusion (max 900 units/hr) with goal aPTT 50–70 sec during hospitalization	Good	• None
Bonello, 2008[13]	• Clopidogrel loading dose 600 mg, 75 mg maintenance • Clopidogrel loading dose 300 mg, 75 mg maintenance	Good	• None
Brener, 2003[14]	• Abciximab • No Abciximab	Poor	• Study was conducted only at a single site
Brieger, 2007[15]	• LMWH 89% enoxaparin • UFH	Fair	• Duration of participant followup was inadequate.
Burgess, 2002[16]	• Eptifibatide 180 mcg/kg bolus, 2 mcg/kg/min maintenance • Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min maintenance	Poor	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Study was conducted only at a single site
Cannon, 2007[17] DISPERSE-2	• Ticagrelor 90 mg twice daily • Clopidogrel 300 mg loading dose, 75 mg daily • Ticagrelor 180 mg twice daily	Fair	• None

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Chen, 2006[18]	• Enoxaparin 1 mg/kg injection every 12 hr, at least twice before catheterization • UFH 25 mg IV before angiography, additional 65 mg if PCI performed	Poor	• Study did not report participants' comorbid conditions. • Study exclusion criteria were poorly described or not appropriate • Study interventions (active arm) were not similar to interventions used in routine clinical practice • Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Study conducted solely outside the US • Study was conducted only at a single site
Chu, 2006[19]	• Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr maintenance • UFH 40 units/kg with goal ACT 250-300 sec	Fair	• None
Cortese, 2009[20]	• Prolonged Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr during procedure, 0.25 mg/kg/hr post procedure • UFH + GPI • UFH to ACT 200-250 sec, 180 mcg/kg (eptifibatide) or 0.25 mg/kg (abciximab) bolus, 2 mcg/kg/min (eptifibatide) or 0.125 mg/kg/min (abciximab) maintenance	Fair	• None
Cuisset, 2006[21]	• Bivalirudin 0.75 mg/kg loading dose, 1.75 mg/kg/hr maintenance dose for duration of procedure • UFH 100 units/kg loading dose	Fair	• None
Dabbous, 2008[22]	• Eligible patients receiving GPI • Ineligible patients receiving GPI	Fair	• Study did not report participants' baseline characteristics
Danzi, 2006[23]	• Tirofiban 25 mcg/kg bolus, 0.15 mcg/kg/min infusion at time of PCI • Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion at time of PCI	Good	• None
Davlouros, 2009[24]	• Clopidogrel 900 mg loading dose at time of PCI, 75 mg daily • Clopidogrel 900 mg loading dose 2–4 hr prior to PCI, 75 mg daily	Fair	• None
De Servi, 2006[25] ROSAI-2	• GPI upstream • GPI periprocedural	Fair	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Di Sciascio, 2010[26] ARMYDA-5 PRELOAD	• Clopidogrel 600 mg loading dose at time of PCI, 75 mg • Clopidogrel 600 mg loading dose 4–6 hr prior to angiography, 75 mg daily	Fair	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Study conducted solely outside the US
Di Sciascio, 2010[27] ARMYDA-4 RELOAD	• Clopidogrel 600 mg loading dose 4–8 hr prior to angiogram • Placebo 600 mg loading dose	Good	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Study conducted solely outside the US
Durand, 2007[28] PRACTICE	• Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion initiated at hospital admission • Placebo	Fair	• Study conducted solely outside the US
Ferguson 2004, 2004[29] SYNERGY	• Enoxaparin 1 mg/kg every 12 hr during hospitalization, 0.3 mg/kg IV prior to PCI if last dose was >8 hr before • UFH 60 units/kg bolus (max 5000 units), 12 units/kg/hr infusion (max 1000 units/hr) with goal aPTT 50–70 sec during hospitalization	Good	• None
Fung, 2009[30] BRIEF-PCI	• Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at the time of PCI • Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at the time of PCI	Fair	• None
Galassi, 1999[31]	• Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion 10-60 min prior to PCI • Placebo	Poor	• Study did not report participants' baseline characteristics • Study did not report participants' comorbid conditions. • Diagnostic or therapeutic advances have been made in routine practice since the study was conducted • Study conducted solely outside the US • Study was conducted only at a single site
Galasso, 2008[32]	• Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg maintenance • No abciximab	Fair	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)
Gibson, 2006[33] PROTECT-TIMI-30	• Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion at the time of PCI • UFH (50 units/kg bolus, goal ACT 200–250 sec) or enoxaparin (0.5 mg/kg IV) at the time of PCI • Eptifibatide 180 mcg/kg double bolus, 2 mcg kg/min infusion	Fair	• Duration of participant followup was inadequate.

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Giugliano, 2009[34] EARLY ACS	• Eptifibatide180 mcg/kg double bolus + 2 mcg/kg/min infusion • Placebo	Good	• None
Goodman, 2003[35] INTERACT	• Enoxaparin 1 mg/kg every 12 hr during hospitalization • UFH 70 units/kg bolus, 15 units/kg/hr infusion with goal aPTT 50–70 sec during hospitalization	Good	• Diagnostic or therapeutic advances have been made in routine practice since the study was conducted • Study conducted solely outside the US
Gowda, 2003[36]	• Tirofiban • Abciximab	Fair	• None
Gunasekara, 2006[37]	• Tirofiban 25 mcg/kg bolus, 0.15 mcg/kg/min infusion at time of PCI • Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion at time of PCI	Fair	• None
Islam, 2002[38] EPISTENT	• Abciximab 0.25 mg/kg bolus, 0.125 mg/kg/min infusion at start of PCI, UFH 70 units/kg IV bolus at start of PCI, goal ACT • Placebo, UFH 100 units/kg IV bolus at start of PCI, goal ACT >300 sec	Good	• Study did not report participants' comorbid conditions. • Study interventions (active arm) were not similar to interventions used in routine clinical practice • Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)
Ivandic, 2008[39]	• Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion at time of ACS diagnosis • Placebo	Fair	• Study did not use a clinically relevant surrogate outcome where applicable. • Study conducted solely outside the US • Study was conducted only at a single site
Iversen, 2011[40]	• Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg maintenance • No abciximab	Fair	• None
Iversen, 2011[41]	• Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg maintenance • No abciximab	Fair	• None
Karha, 2006[42]	• GPI • No GPI	Poor	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)
Kastrati, 2006[43] ISAR-REACT 2	• Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion started at time of PCI • Placebo	Good	• None
Kastrati, 2008[44] ISAR-REACT 3	• Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion at the time of PCI • UFH 100–140 units/kg bolus, placebo infusion at time of PCI	Good	• None

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Kastrati, 2011[45] ISAR-REACT 4	• Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion at the time of PCI • UFH 70 units/kg bolus • Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/hr infusion at the time of PCI	Good	• Lower event rate in the bivalirudin arm reduced the power of this trial to 73% to detect a difference between the treatment groups.
Kim, 2005[46]	• UFH 5000 unit bolus, 12 unit/kg/hr with goal aPTT of 1.5-2 times control + tirofiban 0.4 mcg/kg/min for 30 min bolus, 0.1 mcg/kg/min maintenance • UFH 5000 unit bolus, 12 unit/kg/hr with goal aPTT of 1.5-2 times control	Fair	• Conducted at single center outside the US • Stenting only performed if >35% stenosis after balloon angioplasty. • Concomitant therapy with clopidogrel (use, dose) not described
Korovesis, 2005[47]	• Enoxaparin alone – 1 mg/kg • Enoxaparin with GPI – 0.75 mg/kg • UFH alone - 100 unit/kg bolus, 10-20 unit/kg maintenance with goal ACT of >250 sec • UFH with GPI – 60 unit/kg bolus with goal ACT 200-250 sec	Poor	• All patients were taking ASA and clopidogrel (or ticlopidine) which had been started prior to the cath lab. • Single center study done outside the US
Lahtela, 2009[48]	• GPI • No GPI	Fair	• None
Lemesle, 2009[49]	• Bivalirudin ACT >250 sec • Unfractionated Heparin maintain ACT >250 sec	Fair	• None
Lemesle, 2009[50]	• Bivalirudin • Unfractionated Heparin	Fair	• None
Leoncini, 2005[51] CLOTILDA	• Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion • Placebo	Poor	• Study conducted solely outside the US • Study was conducted only at a single site
Lin, 2009[52]	• Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion prior to angiography • Tirofiban 0.1 mg/kg bolus, 0.075 mcg/kg/min infusion prior to angiography	Good	• None
Liu, 2009[53]	• Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion 4–6 hr prior to angiography • Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion at the time of PCI	Fair	• None
Mehta, 2005[54] ASPIRE	• UFH 100 units/kg IV bolus (65 units/kg if GPI intended) at time of PCI • Fondaparinux 2.5 mg (low dose) or • Fondaparinux 5.0 mg (high dose) • IV at time of PCI	Fair	• None

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Mehta, 2010[55] CURRENT-OASIS 7	• Clopidogrel 300 mg loading dose, 75 mg daily • Clopidogrel 600 mg loading dose, 150 mg daily for 7 days, then 75 mg daily	Good	• Study conducted solely outside the US
Moliterno, 2011[56] TENACITY	• Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion at the time of PCI • Tirofiban 0.25 mg/kg bolus, 0.15 mcg/kg/min infusion at the time of PCI	Fair	• Study interventions (active arm) were not similar to interventions used in routine clinical practice • Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)
Momtahen, 2009[57]	• Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at hospital admission • Placebo	Fair	• None
Montalescot, 2006[58] ALBION	• Clopidogrel 300 mg loading dose prior to PCI (>12 hr prior to PCI), 75 mg daily • Clopidogrel 600 mg loading dose prior to PCI (>12 hr prior to PCI), 75 mg daily	Fair	• None
Ozkan, 2005[59]	• Tirofiban 0.12 mg/kg bolus, 0.1 mcg/kg/min infusion after initial angiography • No tirofiban	Fair	• None
Parodi, 2010[60] ARNO	• Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion at the time of PCI • UFH 100 units/kg bolus, additional doses to maintain ACT >250 sec at time of PCI	Fair	• Study conducted solely outside the US • Study was conducted only at a single site
Patti, 2005[61] ARMYDA-2	• Clopidogrel 300 mg loading dose 4–8 hr prior to angiography, 75 mg daily • Clopidogrel 600 mg loading dose 4–8 hr prior to angiography, 75 mg daily	Good	• None
Patti, 2012[62] ARMYDA-7 BIVALVE	• Bivalirudin 0.75 mg/kg bolus, infusion, 1.75 mg/kg/h at time of PCI + provisional GPI • UFH 75 units/kg bolus + provisional GPI	Good	• None
Peterson, 2003[63]	• Upstream GPI • No upstream GPI	Fair	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)
Price, 2011[64] GRAVITAS	• Clopidogrel 600 mg loading dose, 150 mg daily • Placebo loading dose, Clopidogrel 75 mg daily	Good	• None

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Puymirat, 2011[65] FAST-MI	• Clopidogrel loading dose ≥300 mg • Clopidogrel no loading dose	Fair	• Study interventions (active arm) were not similar to interventions used in routine clinical practice • Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Comparator(s) not well described
Rajagopal, 2006[66] REPLACE-2 ACS Substudy	• Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion at the time of PCI • UFH 65 units/kg bolus • Abciximab 0.25 mg/kg bolus, 0.125 mg/kg/hr infusion • Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion	Good	• None
Rasoul, 2006[67] ELISA-2	• Dual therapy: ASA + clopidogrel 600 mg • Triple therapy: ASA + clopidogrel 300 mg + tirofiban 10 mcg/kg bolus, 0.15 mcg/kg/min maintenance dose	Fair	• None
Roe, 2003[68] EARLY	• Eptifibatide 180 mcg/kg single bolus, 2 mcg/kg/min infusion at hospital admission for 12-24 hr, crossover occurred with investigator directed 2nd bolus of study drug • Placebo	Good	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)
Schiariti, 2011[69] SANTISS	• Tirofiban 0.25 mg/kg bolus, 0.15 mcg/kg/min infusion at the time of PCI • Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at the time of PCI	Fair	• None
Schweiger, 2003[70]	• Eptifibatide 180 mcg/kg bolus, 2 mcg/kg/min maintenance • Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min maintenance	Poor	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Study was conducted only at a single site
Singh, 2006[71]	• LMWH • UFH	Fair	• None
Steg, 2010[72] FUTURA/OASIS-8	• High-dose UFH • Low-dose UFH	Good	• None

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Stone, 2006[73] Stone, 2007[74] ACUITY/ACUITY TIMING	• Bivalirudin 0.1 mg/kg bolus, 0.25 mg/kg/hr infusion • UFH 60 units/kg bolus, 12 units/kg/hr infusion at hospital admission, goal ACT 200–250 sec during PCI • Enoxaparin 1 mg/kg SC twice daily at hospital admission, 0.3 mg/kg IV bolus if needed at time of PCI+ GPI use was randomly assigned to upstream or deferred use at time of PCI • Bivalirudin + GPI	Good	• None
Suleiman, 2003[75]	• Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min maintenance • Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min	Poor	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Study conducted solely outside the US • Study was conducted only at a single site
Szuk, 2007[76] Clopidogrel Registry (Hungary)	• Clopidogrel at PCI • Clopidogrel 6-24 hr prior to PCI	Fair	• Study conducted solely outside the US
Topol, 2001[77] TARGET	• Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion at time of PCI • Abciximab 0.25 mcg/kg bolus, 0.125 mcg/kg/min infusion at time of PCI	Good	• None
Tricoci, 2007[78]	• GPI upstream • No GPI	Fair	• None
Valgimigli, 2010[79] FABOLUS SYNCHRO	• Abciximab 0.25 mg/kg bolus, placebo infusion at the time of PCI • Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion at the time of PCI	Fair	• Study exclusion criteria were poorly described or not appropriate • Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Study conducted solely outside the US
van't Hof, 2003[80] ELISA	• Early angiography, Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion at time of PCI • Late angiography, Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion at hospital admission	Poor	• Study conducted solely outside the US • Study was conducted only at a single site
Velianou, 2000[81]	• Abciximab 0.25 mg/kg bolus, 12 mcg/min maintenance • No abciximab	Fair	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Wallentin, 2009[82] PLATO	• Ticagrelor 180 mg loading dose, 90 mg twice daily • Clopidogrel 300 mg or 600 mg loading dose, 75 mg daily	Good	• None
Wang, 2007[83]	• Clopidogrel 300 mg • Clopidogrel >300 mg	Fair	• Study exclusion criteria were poorly described or not appropriate
Wiviott, 2007[84] TRITON-TIMI 38	• Prasugrel 60 mg loading dose, 10 mg daily • Clopidogrel 300 mg loading dose, 75 mg daily	Good	• None
Wolfram, 2003[85]	• Bivalirudin 0.75 mg/kg loading dose, 1.75 mg/kg/hr • UFH + eptifibatide • UFH 40 units/kg loading dose	Fair	• Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate • Duration of participant followup was inadequate. • Study was conducted only at a single site
Yan, 2009[86]	• Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion after PCI • Placebo	Fair	• None
Yong, 2009[87] PRACTICAL	• Clopidogrel 300 mg loading dose and 2nd placebo dose • Clopidogrel 300 mg loading dose and 2nd 300 mg loading dose at time of PCI	Fair	• Study conducted solely outside the US
Yusuf, 2006[88] OASIS-5	• Enoxaparin 1 mg/kg SC every 12 hr at hospital admission, additional dose of UFH if >6 hr since last dose during PCI • Fondaparinux 2.5 mg SC daily at hospital admission, additional dose of IV fondaparinux based on timing of last dose and intended use of GPI at time of PCI	Good	• None

Abbreviations: ACT=activated clotting time; aPTT=activated partial thromboplastin time; ASA=aspirin; DM=diabetes mellitus; GPI=glycoprotein IIb/IIIa inhibitor; hr=hour/hours; HTN=hypertension; IV=intravenous; kg=kilogram/kilograms; LMWH=low molecular weight heparin; mcg=microgram/micrograms; mg=milligram/milligrams; min=minute/minutes; PCI=percutaneous coronary intervention; sec=second/seconds; SC=subcutaneous; UFH=unfractionated heparin

Table E-2. Quality and applicability table for KQ 2 studies—initial conservative approach for UA/NSTEMI

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Angkasuwapala, 2007[89] Thai ACS Registry	• LMWH • UFH	Poor	• Study did not report participants' baseline characteristics • Study interventions (active arm) were not similar to interventions used in routine clinical practice • Study conducted solely outside the US
Anonymous, 1998[90] PURSUIT	• Eptifibatide 180 mcg/kg bolus, 2.0 mcg/kg/min infusion • Placebo	Good	• None
Anonymous, 1998[91] PRISM	• Tirofiban 0.6 mcg/kg/min x 30 min bolus, 0.15 mcg/kg/min infusion • UFH 5000 unit bolus, 1000 unit infusion	Good	• None
Anonymous, 1998[92] PRISM-PLUS	• Tirofiban 0.4 mcg/kg bolus, 0.1 mg/kg/min infusion + UFH • Placebo + UFH	Good	• Diagnostic or therapeutic advances have been made in routine practice since the study was conducted
Antman, 1999[4] TIMI 11B	• Enoxaparin 30 mg IV loading dose, 1 mg/kg every 12 hr during hospitalization • UFH 70 units/kg bolus, 15 units/kg/hr infusion with goal aPTT 50–70 sec during hospitalization	Good	• Study interventions (active arm) were not similar to interventions used in routine clinical practice • Diagnostic or therapeutic advances have been made in routine practice since the study was conducted • Use of substandard alternative therapy (e.g., standard of treatment not from current practice)
Bertel, 2010[9] ZEUS	• Enoxaparin loading dose 0.75 mg/kg • Unfractionated heparin loading dose 60 units/kg	Fair	• Study did not report participants' baseline characteristics • Study did not report participants' comorbid conditions. • Study prohibited interventions that are routinely used in clinical practice • Study conducted solely outside the US • Study was conducted only at a single center.
Bhatt, 2003[10] CRUISE	• Enoxaparin loading dose 0.75 mg/kg IV • Unfractionated heparin loading dose 60 units/kg IV	Fair	• None
Bhattacharya, 2010[11]	• Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion at hospital admission • Placebo	Good	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Duration of participant followup was inadequate. • Study conducted solely outside the US • Study was conducted only at a single site

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Blazing, 2004[12] A to Z Trial	• Enoxaparin 1 mg/kg every 12 hr during hospitalization • UFH 60 units/kg bolus (max 4000 units), 12 units/kg/hr infusion (max 900 units/hr) with goal aPTT 50–70 sec during hospitalization	Good	• None
Brieger, 2007[15]	• LMWH 89% enoxaparin • UFH	Fair	• Duration of participant followup was inadequate.
Chen, 2006[18]	• Enoxaparin 1 mg/kg injection every 12 hr, at least twice before catheterization • UFH 25 mg IV before angiography, additional 65 mg if PCI performed	Poor	• Study did not report participants' comorbid conditions. • Study exclusion criteria were poorly described or not appropriate • Study interventions (active arm) were not similar to interventions used in routine clinical practice • Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Study conducted solely outside the US • Study was conducted only at a single site
Cohen, 1997[93] ESSENCE	• Enoxaparin 1 mg/kg every 12 hr during hospitalization • UFH 5000 unit bolus, infusion with goal aPTT 55–85 sec during hospitalization	Good	• Diagnostic or therapeutic advances have been made in routine practice since the study was conducted
Cohen, 2002[94] ACUTE II	• UFH 5000 unit bolus, 1000 units/hr infusion during hospitalization • Enoxaparin 1 mg/kg every 12 hr during hospitalization	Fair	• None
Ferguson, 2004[29] SYNERGY	• Enoxaparin 1 mg/kg every 12 hr during hospitalization, 0.3 mg/kg IV prior to PCI if last dose was >8 hr before • UFH 60 units/kg bolus (max 5000 units), 12 units/kg/hr infusion (max 1000 units/hr) with goal aPTT 50–70 sec during hospitalization	Good	• None
Goodman, 2003[35] INTERACT	• Enoxaparin 1 mg/kg every 12 hr during hospitalization • UFH 70 units/kg bolus, 15 units/kg/hr infusion with goal aPTT 50–70 sec during hospitalization	Good	• Diagnostic or therapeutic advances have been made in routine practice since the study was conducted • Study conducted solely outside the US
Gore, 2007[95]	• LMWH in first 24 hours • UFH in first 24 hours • No heparin in first 24 hours	Fair	• Comparator(s) not well described

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
James, 2011[96] PLATO Substudy	• Ticagrelor loading dose 180 mg, maintenance dose 90 mg twice daily • Clopidogrel loading dose 300-600 mg, maintenance dose 75 mg daily	Good	• None
Kovar, 2002[97]	• Enoxaparin • UFH	Fair	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Comparator(s) not well described
LaPointe, 2007[98]	• Enoxaparin >10 mg above recommended dose • Enoxaparin >10 mg below recommended dose • Enoxaparin recommended dose (2 mg/kg for creatinine clearance >30 mL/min, 1 mg/kg for <30 mL/min)	Good	• Study exclusion criteria were poorly described or not appropriate • Study centers and/or clinicians were not selected on the basis of their skill or experience. • Duration of participant followup was inadequate.
Li, 2012[99] KAMIR	• Enoxaparin 1mg/kg twice daily • UFH 24,000 units/day	Good	• None
Malhotra, 2001[100] ESCAPEU	• UFH 70 units/kg bolus, infusion during hospitalization, adjusted for therapeutic aPTT • Enoxaparin 1 mg/kg every 12 hr during hospitalization	Fair	• None
Mehta, 2005[54] ASPIRE	• Unfractionated heparin loading dose 100 units/kg (without GPI) and 65 u/kg (with GPI) • Fondaparinux loading dose 2.5 mg IV • Fondaparinux loading dose 5.0 mg IV	Fair	• None
Momtahen, 2009[57]	• Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at hospital admission • Placebo	Fair	• None
Okmen, 2003[101]	• Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion at hospital admission • No tirofiban	Fair	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control) • Study was conducted only at a single site
Roe, 2012[102]	• Prasugrel 30 mg loading dose, 10 mg daily • Clopidogrel 300 mg loading dose, 75 mg daily	Good	• None
Schiele, 2010[103]	• Enoxaparin 1mg/kg every 12 hr • UFH 60 units/kg bolus (max 5000 units), 12–15 units/kg/hr maintenance (max 1000 units/hr) to aPTT 50-75 sec • Fondaparinux 2.5 mg/day	Good	• Comparator(s) not well described • Study conducted solely outside the US

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Simoons, 2001[104] GUSTO-IV	• Abciximab 0.25 mg/kg bolus, 0.125 mg/kg/min maintenance • Placebo	Good	• None
Singh, 2006[71]	• LMWH • UFH	Fair	• None
Song, 2007[105]	• Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion at hospital admission • Placebo	Good	• None
Spinler, 2003[106]	• Enoxaparin 1 mg/kg SC • UFH • Goal aPTT of 55–85 sec	Fair	• Study did not report participants' baseline characteristics • Study did not report participants' comorbid conditions. • Diagnostic or therapeutic advances have been made in routine practice since the study was conducted • Use of substandard alternative therapy (e.g., standard of treatment not from current practice)
Stone, 2006[73] ACUITY	• Bivalirudin 0.1 mg/kg bolus, 0.25 mg/kg/hr infusion • UFH 60 units/kg bolus, 12 units/kg/hr infusion at hospital admission, goal ACT 200–250 sec during PCI • Enoxaparin 1 mg/kg SC twice daily at hospital admission, 0.3 mg/kg IV bolus if needed at time of PCI+ GPI use was randomly assigned to upstream or deferred use at time of PCI • Bivalirudin + GPI	Good	• None
Stone, 2007[74] ACUITY TIMING	• Upstream GPI • In-lab GPI	Good	• None
van den Brand, 1995[107]	• Abciximab 0.25 mg/kg bolus, 10 mcg/kg/min infusion • Placebo	Fair	• Study interventions (active arm) were not similar to interventions used in routine clinical practice • Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)
Yusuf, 2006[88] OASIS-5	• Enoxaparin 1 mg/kg SC every 12 hr at hospital admission, additional dose of UFH if >6 hr since last dose during PCI • Fondaparinux 2.5 mg SC daily at hospital admission, additional dose of IV fondaparinux based on timing of last dose and intended use of GPI at time of PCI	Good	• None

Abbreviations: ACT=activated clotting time; aPTT=activated partial thromboplastin time; DM=diabetes mellitus; GPI=glycoprotein IIb/IIIa inhibitor; hr=hour/hours; HTN=hypertension; IV=intravenous; kg=kilogram/kilograms; LMWH=low molecular weight heparin; mcg=microgram/micrograms; mg=milligram/milligrams; min=minute/minutes; mL=milliliter/milliliters; PCI=percutaneous coronary intervention; sec=second/seconds; SC=subcutaneous; UFH=unfractionated heparin

Table E-3. Quality and applicability table for KQ 3 studies—postdischarge treatment for UA/NSTEMI

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Alexander, 2008[108] CRUSADE	• Clopidogrel • No clopidogrel	Fair	• None
Aronow, 2008[109] BRAVO	• ASA <162mg/day, maintenance dose: 100 mg • ASA >162 mg/day, maintenance dose: 325 mg	Good	• Study's cointerventions did not adequately reflect routine clinical practice (e.g., use of medical therapy for secondary prevention – antiplatelet agents, HTN/DM/lipid control)
Banerjee, 2011[110]	• No PPI • PPI	Good	• None
Barada, 2008[111]	• PPI • Placebo	Poor	• Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate • Study conducted solely outside the US • Study was conducted only at a single site
Bernardi, 2007[112] RACS	• Dual therapy: clopidogrel 30 day + ASA • Dual therapy: clopidogrel 180 day + ASA	Fair	• Study conducted solely outside the US
Bhatt, 2010[113] COGENT	• Omeprazole 20 mg • Placebo	Good	• None
Bhurke, 2012[114]	• Clopidogrel + PPI • Clopidogrel	Fair	• Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate
Bonde, 2010[115]	• Placebo • Clopidogrel	Fair	• Study conducted solely outside the US
Buresly, 2005[116]	• ASA • Warfarin	Good	• Study conducted solely outside the US
Butler, 2009[117]	• DES with clopidogrel intended duration ≤3 mo • DES with clopidogrel intended duration • 6 mo • BMS with clopidogrel intended duration ≤3 mo • BMS with clopidogrel intended duration 6 mo • DES with clopidogrel intended duration ≥12 mo • BMS with clopidogrel intended duration ≥12 mo	Fair	• Study conducted solely outside the US

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Charlot, 2010[118]	• No PPI • PPI • Placebo • Clopidogrel	Good	• None
Charlot, 2011[119]	• PPI • No PPI	Good	• None
Charlot, 2012[120]	• Clopidogrel up to 90 days • Clopidogrel >90 days	Fair	• Study did not report participants' baseline characteristics
Cheng, 2010[121] T-ACCORD Registry	• ASA • Clopidogrel • Dual therapy (ASA + clopidogrel)	Good	• Study conducted solely outside the US
Chitose, 2011[122] KICS	• PPI • No PPI	Good	• None
Evanchan, 2010[123]	• PPI • Placebo	Good	• Study exclusion criteria were poorly described or not appropriate • Study was conducted only at a single site
Fosbol, 2012[124]	• ASA • Warfarin • ASA + clopidogrel • ASA + clopidogrel + warfarin	Fair	• None
Gao, 2009[125]	• Omeprazole 40 mg loading, 20 mg maintenance	Poor	• Study did not report participants' baseline characteristics • Study did not report participants' comorbid conditions. • Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate • Study conducted solely outside the US
Gaspar, 2010[126]	• PPI • No PPI	Good	• None
Goodman, 2012[127] Mahaffey, 2011[128] Wallentin, 2009[82] PLATO	• PPI • Placebo	Good	• None
Gupta, 2010[129]	• PPI • Placebo	Fair	• Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate • Study was conducted only at a single site

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Gwon, 2012[130]	• ASA + clopidogrel 6 mo • ASA + clopidogrel 12 mo	Good	• Study conducted solely outside the US
Harjai, 2009[131]	• ASA 81–325 mg/day + clopidogrel >12 mo (whole cohort any stent), Maintenance dose: ASA 81–325 mg/day + clopidogrel 75 mg/day or ticlopidine (dose not specified). • ASA 81–325 mg/day + clopidogrel ≤ 12 mo (whole cohort any stent), Maintenance dose: ASA 81–325 mg/day + clopidogrel 75 mg/day or ticlopidine (dose not specified).	Good	• None
Harjai, 2011[132] GHOST	• ASA, maintenance dose: 81 mg/day • ASA, maintenance dose: 162-325 mg/day	Fair	• Study selectively recruited participants who demonstrated a history of favorable or unfavorable response to drug or other interventions for the condition.
Harjai, 2011[133]	• PPI • No PPI	Good	• None
Ho, 2007[134]	• Continued clopidogrel • Discontinued clopidogrel	Fair	• Population was almost entirely male.
Ho, 2009[135]	• PPI • Placebo	Good	• None
Hsiao, 2011[136]	• PPI • No PPI	Good	• None
Jang, 2011[137]	• Warfarin • Placebo	Poor	• Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate • Study conducted solely outside the US
Juurlink, 2009[138]	• Clopidogrel + nonfatal MI in 90 days • Clopidogrel	Good	• Study conducted solely outside the US
Karjalainen, 2007[139]	• Warfarin • Placebo	Good	• Study conducted solely outside the US
Konstantino, 2006[140]	• ASA + ticlopidine/ clopidogrel • ASA + ticlopidine/clopidogrel +warfarin	Fair	• Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate • Study conducted solely outside the US
Kreutz, 2010[141]	• PPI • Placebo	Good	• Study eligibility criteria were poorly described or not appropriate • Study conducted solely outside the US
Lamberts, 2013[142]	• Clopidogrel + ASA • Clopidogrel + ASA + oral anticoagulant	Good	• Study conducted solely outside the US

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Lim, 2005[143]	• ASA • ASA + clopidogrel	Fair	• Groups were significantly different with respect to in hospital revascularization procedures. • Statistical comparison of the results not reported. • In hospital antithrombotic management and bleeding events not reported.
Lopes, 2010[144]	• Warfarin • Placebo	Good	• None
Maegdefessel, 2008[145]	• Clopidogrel	Fair	• Study exclusion criteria were poorly described or not appropriate • Study conducted solely outside the US • Study was conducted only at a single site
Ng, 2008[146]	• PPI • Placebo	Good	• Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate • Study conducted solely outside the US
Ng, 2011[147]	• Esomeprazole 20 mg • Famotidine 40 mg	Good	• Study conducted solely outside the US • Study was conducted only at a single site
Nguyen, 2007[148] GRACE	• ASA + thienopyridine • ASA or thienopyridine	Good	• None
O'Donoghue, 2009[149] TRITON-TIMI 38	• PPI • No PPI	Good	• None
Ortolani, 2011[150]	• PPI • No PPI	Good	• None
Pekdemir, 2003[151]	• 1 mo ASA 100 mg/day + clopidogrel 75 mg/day Loading dose: 300 mg clopidogrel + 300 mg ASA + 10,000 IU heparin IV intraoperative Maintenance dose: 75 mg/day clopidogrel + 100 mg/day ASA • 6 mo ASA 100 mg/day + clopidogrel 75 mg/day Loading dose: 300 mg clopidogrel + 300 mg ASA + 10,000 IU heparin IV intraoperative Maintenance dose: 75 mg/day clopidogrel + 100 mg/day ASA	Fair	• Study conducted solely outside the US • Study was conducted only at a single site
Persson, 2011[152] RIKS-HIA and SCAAR	• Warfarin • Placebo	Good	• Study conducted solely outside the US
Quinn, 2004[153] Gusto IIb and PURSUIT	• ASA maintenance dose <150mg • ASA maintenance dose ≥150mg	Good	• None

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Rassen, 2009[154]	• PPI • Placebo	Good	• None
Ray, 2010[155]	• PPI • Placebo	Good	• None
Ren, 2011[156]	• Omeprazole 20 mg • Placebo	Poor	• Study did not report participants' comorbid conditions. • Study conducted solely outside the US
Rossini, 2008[157]	• Clopidogrel + ASA + Warfarin • Clopidogrel + ASA	Good	• Study conducted solely outside the US
Rossini, 2011[158]	• PPI • No PPI	Good	• None
Roy, 2009[159]	• Clopidogrel loading dose 300mg • Clopidogrel loading dose 600mg	Poor	• Study was conducted only at a single site
Ruiz-Nodar, 2008[160]	• Warfarin • ASA	Good	• Study exclusion criteria were poorly described or not appropriate • Study conducted solely outside the US
Ruiz-Nodar, 2012[161]	• Warfarin • No oral anticoagulant	Fair	• Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate • Study conducted solely outside the US
Sarafoff, 2010[162]	• PPI • Placebo	Good	• None
Schmidt, 2012[163]	• Clopidogrel 75 mg maintenance dose • PPI	Poor	• Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate • Study conducted solely outside the US
Schulz, 2009[164]	• Clopidogrel + ASA Loading dose: 600 mg clopidogrel + 500 mg ASA Maintenance dose: 75mg clopidogrel daily + ASA 100 mg twice daily	Fair	• Study conducted solely outside the US
Sibbald, 2010[165]	• Early clopidogrel in-hospital • No early clopidogrel in-hospital	Good	• None
Simon, 2011[166] FAST-MI	• PPI • Placebo	Good	• None
So, 2009[167]	• Clopidogrel • Placebo	Fair	• Study conducted solely outside the US • Study was conducted only at a single site
Steinhubl, 2002[168] CREDO	• Clopidogrel 1 mo • Clopidogrel 12 mo	Good	• None

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Stenestrand, 2005[169] RIKS-HIA	• ASA • Oral anticoagulant	Good	• Study conducted solely outside the US
Stockl, 2010[170]	• PPI • Placebo	Good	• None
Tentzeris, 2010[171]	• PPI • No PPI	Good	• None
Tsai, 2011[172]	• Clopidogrel + PPI • Clopidogrel	Good	• None
Valgimigli, 2012[173] PRODIGY	• Clopidogrel Loading dose: 300 or 600 mg Maintenance dose: 75 mg Duration 6 mo • Clopidogrel Loading dose: 300 or 600 mg Maintenance dose: 75 mg Duration 24 mo	Good	• Study conducted solely outside the US
Valkhoff, 2011[174]	• PPI • Placebo	Poor	• Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate • Comparator(s) not well described • Study conducted solely outside the US • Study was conducted only at a single site
van Boxel, 2010[175]	• Clopidogrel + PPI • Clopidogrel	Fair	• Study eligibility criteria were poorly described or not appropriate • Study exclusion criteria were poorly described or not appropriate • Study conducted solely outside the US
Wu, 2010[176]	• PPI • Placebo	Good	• Study exclusion criteria were poorly described or not appropriate • Study conducted solely outside the US
Yusuf, 2001[177] Peters, 2003[178] CURE	• Clopidogrel 300 mg loading dose, 75 mg daily • Placebo	Good	• None
Zairis, 2010[179]	• Omeprazole • Placebo	Good	• Study conducted solely outside the US • Study was conducted only at a single site

Study	Intervention/Comparator	Study Quality	Limitations to Applicability
Zeymer, 2008[180] ACOS Registry	• ASA + clopidogrel • ASA	Poor	• Study exclusion criteria were poorly described or not appropriate • Diagnostic or therapeutic advances have been made in routine practice since the study was conducted • Revascularization as well as postdischarge medications are poorly described • Use of substandard alternative therapy (e.g., standard of treatment not from current practice)

Abbreviations: ACT=activated clotting time; ASA=aspirin; BMS=bare metal stent; DES=drug-eluting stent; DM=diabetes mellitus; HTN=hypertension; IU=international units; IV=intravenous; mg=milligram/milligrams; MI=myocardial infarction; mo=month/months; PPI=proton pump inhibitor; sec=second/seconds

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Appendix F. Study Characteristics Tables

Table F-1. Study characteristics table for Key Question 1 comparisons—early invasive approach for UA/NSTEMI

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Abuzahra, 2008[1]	RCT Single site in U.S. Funding: NR Timeframe: NR <u>Population</u> 20% UA 18% NSTEMI 5% STEMI 56% Stable angina Total N: 119 Mean Age: 57 Female: 35% Race: 30% Hispanic, 39% African American, 20% White	Clopidogrel 300 mg loading dose at time of PCI, 75 mg daily (N=42) Duration: 1 mo	Clopidogrel 600 mg loading dose at time of PCI, 150 mg daily (N=77) Duration: 1 mo	ASA 325 mg loading dose, 81 mg daily after PCI Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion during PCI	Timing: 30 days <u>Composite</u> (primary) CV mortality Nonfatal MI Revascularization <u>Individual</u> CV mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair
Ajani, 2003[2]	Observational Single site in U.S. Funding: NR Timeframe: 06/1998-08/2000 <u>Population</u> 72% UA Total N: 359 Mean Age: 62 to 65 Female: 23% Race: NR	Eptifibatide 180 mcg/kg bolus, 2 mcg/kg/min maintenance (N=152) Duration: 12-48 hr	Abciximab 0.25 mg/kg bolus, 10 mcg/min maintenance (N=207) Duration: 12 hr	ASA dose unspecified UFH to ACT 200 sec Clopidogrel 300 mg bolus + 75 mg daily for 14 days Or Ticlopidine 500 mg bolus + 250 mg twice daily for 14 days	Timing: In-hospital <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Anonymous, 2000[3] ESPRIT	RCT 92 sites in U.S., Canada Funding: Industry Timeframe: 06/1999–02/2000 <u>Population</u> 14% UA 5% STEMI 39% Stable angina 33% had UA/NSTEMI within prior 6 mo 100% PCI 3% PTCA only 96% PTCA + stent Total N: 2,064 Median Age: 62 Female: 27% Race: NR	Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at time of PCI (N=1040) Duration: 18-24 hr or hospital discharge	Placebo (N=1024) Thrombotic bailout with GPI occurred in 2% of patients (a clinical endpoint)	ASA + thienopyridine (clopidogrel or ticlopidine) were loaded on the days of randomization UFH 60 units/kg bolus at time of PCI, goal ACT >250 sec	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Urgent TVR Thrombotic bailout with GPI (secondary) Total mortality Nonfatal MI Urgent TVR <u>Individual</u> Total mortality Nonfatal MI Stroke TVR Major bleeding Minor bleeding	Good
Antman, 1999[4] TIMI 11B	RCT 200 international sites Funding: Industry Timeframe: 08/1996–03/1998 <u>Population</u> 59% UA 38% NSTEMI Total N: 3,910 Median Age: 65 to 66 Female: NR Race: NR	Enoxaparin 30 mg IV loading dose, 1 mg/kg every 12 hr during hospitalization (N=1953) Duration: until discharge or days 8	UFH 70 units/kg bolus, 15 units/kg/hr infusion with goal aPTT 50–70 sec during hospitalization (N=1957) Duration: 3–8 days	ASA 100–325 mg daily	Timing: 48 hr,72 hr, 8 days, 14 days, 43 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Major bleeding Minor bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Antman, 2002[5] TIMI 8	RCT 14 sites in U.S. Funding: Industry Timeframe: 6/1994-11/1994 <u>Population</u> 100% UA/NSTEMI Total N: 133 Median Age: 66 to 68 Female: 37% Race: NR	Unfractionated Heparin 70 units/kg loading dose, 15 units/kg/hr (N=65) Duration: Minimum of 72 hr	Bivalirudin 0.1 mg/kg loading dose, 0.25 mg/kg/hr (N=68) Duration: Minimum of 72 hr	patients received 100-325mg aspirin daily. UFH infusion of < 12 hr was allowed prior to randomization	Timing: in-hospital, 14 days, 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI (secondary) Total mortality Nonfatal MI Major bleeding (unclear) Total mortality Nonfatal MI <u>Individual</u> Major bleeding	Poor
Bauer, 2010[6]	Observational 176 sites in Europe Funding: NR Timeframe: 05/2005-04/2008 <u>Population</u> 100% UA/NSTEMI Total N: 2,922 Median/Mean Age: 67 to 69 Female: 35% Race: NR	Upstream GPI (N=259) 3rd treatment arm: Downstream GPI (N=391)	No GPI (N=2,272)	ASA dose unspecified Clopidogrel dose unspecified UFH dose unspecified LMWH dose unspecified	Timing: In-hospital <u>Individual</u> Total mortality Nonfatal MI Stroke Major bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Berger, 2005[7]	Observational 5 sites in U.S. Funding: NR Timeframe: 01/1998-10/1999 <u>Population</u> 40% UA Total N: 1,138 Mean Age: 65 Female: 33% Race: 85% white	GPI (N=315)	No GPI (N=823)	22% UFH, dose unspecified	Timing: In-hospital, 3 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Stroke Revascularization Stent thrombosis <u>Individual</u> Total mortality Nonfatal MI Stroke Revascularization Stent thrombosis	Poor
Berglund, 2002[8]	Observational Single site location NR Funding: NR Timeframe: 01/1999-12/2000 <u>Population</u> NR 100% PCI Total N: 1,430 Mean Age: 63 Female: 26% Race: NR	Early clopidogrel 375 mg (N=706)	No early clopidogrel (N=724)	ASA 75 mg UFH with goal ACT of 300 sec (200-250 sec if abciximab used)	Timing: in-hospital <u>Composite</u> Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Transfusion Revascularization	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Bertel, 2010[9] ZEUS	RCT Single site in Europe Funding: NR Timeframe: NR <u>Population</u> 14% UA/NSTEMI 12% STEMI 74% Stable angina 100% PCI Total N: 876 Mean Age: 64 Female: 24% Race: NR	Enoxaparin 0.75 mg/kg IV bolus at time of PCI (N=436)	UFH 60 units/kg bolus at time of PCI (N=440)	ASA 500 mg IV bolus Clopidogrel 300–600 mg loading dose, 75 mg daily after PCI 20% of patients received GPI	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization Major bleeding (secondary) Major bleeding Minor bleeding Thrombocytopenia <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding Stent thrombosis	Fair
Bhatt, 2003[10] CRUISE	RCT 12 sites in U.S. Funding: NR Timeframe: NR <u>Population</u> 45% ACS Total N: 261 Mean Age: 63 to 64 Female: 24% Race: NR	Enoxaparin 0.75 mg/kg IV bolus at time of PCI (N=129)	UFH 60 units/kg bolus (N=132)	ASA 325 mg daily Clopidogrel loading dose at discretion of operator, then 75 mg daily Eptifibatide 180 ug/kg IV double bolus, 2 ug/kg/min infusion (in all patients)	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Bhattacharya, 2010[11]	RCT Single site in Asia Funding: NR Timeframe: 06/2007–05/2009 <u>Population</u> 100% UA/NSTEMI Total N: 301 Mean Age: 63 Female: 54% Race: NR	Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion at hospital admission (N=136) Duration: 48 hr	Placebo (N=165)	NR	Timing: 7 days, 14 days, 30 days, 3 mo <u>Individual</u> Death due to unknown causes Nonfatal MI Fatal MI Refractory ischemia Major bleeding	Good
Blazing, 2004[12] A to Z Trial	RCT 240 international sites Funding: Industry Timeframe: 12/1999–05/2002 <u>Population</u> 100% UA/NSTEMI 80% positive biomarkers 43% of patients underwent angiography within 48 hr; 40% did not undergo angiography Total N: 3,987 Median Age: 61 Female: 29% Race: 3% African American, 4% Asian, 85% White	Enoxaparin 1 mg/kg every 12 hr during hospitalization (N=2026) Duration: 48–120 hr, until PCI	UFH 60 units/kg bolus (max 4000 units), 12 units/kg/hr infusion (max 900 units/hr) with goal aPTT 50–70 sec during hospitalization (N=1961) Duration: 48–120 hr, until PCI	ASA 150–325 mg initially, 75–325 mg daily Tirofiban 10 mcg/kg over 30 min, infusion 0.1 mcg/kg/min for 12 hr post PCI (in all patients)	Timing: 7 days <u>Composite</u> (primary) Total mortality Nonfatal MI Refractory ischemia (secondary) Total mortality Nonfatal MI Revascularization Refractory ischemia Clinical ischemia <u>Individual</u> Total mortality Nonfatal MI Revascularization Refractory ischemia Major bleeding Major or minor bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Bonello, 2008[13]	Observational Single site in U.S. Funding: NR Timeframe: 4/2003-12/2007 <u>Population</u> 42% UA Total N: 4105 Mean Age: 64 to 65 Female: 34% Race: NR	Clopidogrel 600 mg loading dose, 75 mg daily (N=3146) Duration: at least 1 yr	Clopidogrel 300 mg loading dose, 75 mg daily (N=959) Duration: at least 1 yr	ASA 325 mg Patients undergoing PCI routinely receive either UFH or bivalirudin. Glycoprotein IIb/IIIa inhibitor use was at the operator's discretion (~12% of population). Other medical therapy at time of discharge includes ASA (99%), ACE inhibitors (47%), statins (98%), clopidogrel (99%), beta blockers (78%)	Timing: in-hospital, 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Stroke (any kind) Revascularization <u>Individual</u> Total mortality Cardiovascular mortality Revascularization Stroke (any kind) Nonfatal MI Major bleeding	Good
Brener, 2003[14]	Observational Single site in U.S. Funding: Industry Timeframe: 02/1995-12/2001 <u>Population</u> 72% ACS 60% UA 100%PCI Total N: 10,471 Mean Age: 64 Female: 30% Race: NR	Abciximab (N=5,655)	No abciximab (N=4,816)	NR	Timing: In-hospital, 7 days, 4 yr <u>Individual</u> Total mortality Major bleeding Transfusion	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Brieger, 2007[15]	Observational 113 international sites Funding: Industry Timeframe: 04/1999-03/2005 <u>Population</u> 52% UA 48% NSTEMI 25% PCI Total N: 17,659 Median Age: 67 to 68 Female: 35% Race: NR	LMWH 89% enoxaparin (N=10,839)	UFH (N=6,820)	93% ASA 6% warfarin 21% GPI 40% thienopyridine	Timing: in-hospital <u>Individual</u> Total mortality Major bleeding	Fair
Burgess, 2002[16]	Observational Single site in U.S. Funding: NR Timeframe: 01/1998-06/1999 <u>Population</u> 73% ACS 39% UA Total N: 188 Mean Age: 63 to 65 Female: 29% Race: NR	Eptifibatide 180 mcg/kg bolus, 2 mcg/kg/min maintenance (N=103) Duration: 18-24 hr	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min maintenance (N=85) Duration: 12 hr	ASA dose unspecified Thienopyridine dose unspecified	Timing: In-hospital, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI UA <u>Individual</u> Total mortality Nonfatal MI UA Revascularization Rehospitalization Major bleeding Minor bleeding	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Cannon, 2007[17] DISPERSE-2	RCT 152 international sites Funding: Industry <u>Population</u> 100% UA/NSTEMI 67% early angiography 42% PCI Total N: 984 Mean Age: 62 to 64 Female: 36% Race: 95% White	Ticagrelor 90 mg twice daily (N=334) 3rd treatment arm: Ticagrelor 180 mg twice daily (N=323) Duration: 3 mo	Clopidogrel 300 mg loading dose, 75 mg daily (N=327) Additional 300 mg loading dose permitted at time of PCI Duration: 3 mo	ASA 325 mg loading dose, 75–100 mg daily 51% UFH, 40% LMWH 31% GPI use	Timing: 30 days, 3 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Nonfatal stroke Recurrent ischemia (primary safety) Major bleeding Minor bleeding <u>Individual</u> Total mortality Nonfatal MI Nonfatal stroke Recurrent ischemia Major bleeding Minor bleeding	Fair
Chen, 2006[18]	RCT Single site in Asia Funding: NR Timeframe: 10/2003–02/2005 <u>Population</u> 29% UA/NSTEMI 18% Stable angina 47% PCI Total N: 966 Mean Age: 55 to 57 Female: 29% Race: NR	Enoxaparin 1 mg/kg injection every 12 hr, at least twice before catheterization (N=484)	UFH 25 mg IV before angiography, additional 65 mg if PCI performed (N=482)	None reported	Timing: In-hospital, 30 days <u>Composite</u> Total mortality Nonfatal MI Revascularization <u>Individual</u> Stent thrombosis Nonfatal MI	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Chu, 2006[19]	Observational Single site in U.S. Funding: NR Timeframe: NR <u>Population</u> NSTEMI % unknown STEMI % unknown Total N: 672 Mean Age: 65 to 66 Female: 39% Race: NR	Bivalirudin 0.75 mg/kg loading dose, 1.75 mg/kg/hr (N=216)	Unfractionated Heparin 40 U/kg loading dose, titrated for ACT 250-300s (N=456)	All patients were pretreated with aspirin (325 mg po) before PCI. Clopidogrel (300–600 mg) was preloaded before the intervention, followed by daily administration of 75 mg. The patients were instructed to continue this regimen for >6 months. Platelet glycoprotein IIb/IIIa inhibitors were administered at the operator's discretion (14.8%).	Timing: in-hospital, 30 days, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Transfusion Nonfatal MI Revascularization Stent thrombosis	Fair
Cortese, 2009[20]	Observational Single site in Europe Funding: NR Timeframe: 2007-2007 <u>Population</u> 51% UA 100% ACS Total N: 159 Mean Age: 69 to 70 Female: 30% Race: NR	UFH+GPI Loading dose: 180 mcg/kg (eptifibatide) or 0.25 mg/kg (abciximab) Maintenance dose: 2 mcg/kg/min (eptifibatide) or 0.125 mg/kg/min (abciximab) (N=59) Duration: 12h (abciximab) or 18h (eptifibatide) post procedure	Prolonged bivalirudin 0.75 mg/kg loading dose, 1.75 mg/kg/h (during) and 0.25 mg/kg/h (post) (N=50) Duration: 4 hr post procedure Bivalirudin 0.75 mg/kg loading dose, 1.75 mg/kg/hr (N=50) Duration: during procedure	All patients were treated with 250mg aspirin, a clopidogrel loading dose, and UFH (60-80 IU/kg bolus and 12 IU/kg/h infusion). UFH infusion discontinued before coronary angiography. Patients were considered to be adequately treated with clopidogrel if they were on chronic therapy or had been treated with a loading dose of 600mg for more than 2h or 300mg for more than 6h before PCI.	Timing: in-hospital, 30 days <u>Composite</u> (secondary) Total mortality Revascularization <u>Individual</u> Nonfatal MI Total mortality Revascularization Stent thrombosis Major bleeding Minor bleeding	Fair
Cuisset, 2006[21]	RCT Single site in Europe Funding: NR Timeframe: 06/2004–10/2005 <u>Population</u> 75% UA/NSTEMI Total N: 387 Mean Age: 64 to 65 Female: 24% Race: NR	Clopidogrel 300 mg loading dose prior to PCI (>12 hr prior to PCI), 75 mg daily (N=146) Duration: 30 days	Clopidogrel 600 mg loading dose prior to PCI (>12 hr prior to PCI), 75 mg daily (N=146) Duration: 30 days	ASA 250 mg loading dose, 160 mg daily LMWH administered in 66% of patients UFH administered in 34% of patients (age>75 yrs, renal insufficiency) GPI administered in 35% (Group 1) and 33% (Group 2) of patients	Timing: 30 days <u>Composite</u> (primary) CV mortality Nonfatal stroke Recurrent ACS <u>Individual</u> CV mortality Nonfatal stroke Recurrent ACS Major bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Dabbous, 2008[22]	Observational 106 international sites Funding: Industry Timeframe: 04/1999-12/2004 <u>Population</u> 100% UA/NSTEMI Total N: 29,039 Mean Age: NR Female: NR Race: NR	Patients eligible for inclusion in RCTs receiving GPI (N=4374)	Patients ineligible for inclusion in RCTs receiving GPI (N=1105)	ASA LMWH UFH Warfarin/Vitamin K agonist Thienopyridines	Timing: in-hospital, 6 mo <u>Individual</u> Total mortality Major bleeding Stroke	Fair
Danzi, 2006[23]	Observational Single site in Europe Funding: NR Timeframe: 07/2002-09/2003 <u>Population</u> 100% UA/NSTEMI Total N: 302 Mean Age: 65 to 66 Female: 31% Race: NR	Tirofiban 25 mcg/kg bolus, 0.15 mcg/kg/min infusion at time of PCI (N=140) Duration: 18 hr	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion at time of PCI (N=162) Duration: 12 hr	ASA 250-500 mg daily UFH 70 units/kg during PCI with goal ACT 200-250 sec Ticlopidine 250 mg twice daily for 30 days Or Clopidogrel 75 mg for 30 days	Timing: In-hospital, 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Good
Davlouros, 2009[24]	RCT Single site in Europe Funding: NR Timeframe: 10/2005–04/2008 <u>Population</u> 44% UA 0% NSTEMI 56% Stable angina Total N: 199 Mean Age: 65 to 67 Female: 23% Race: NR	Clopidogrel 900 mg loading dose at time of PCI, 75 mg daily (N=103) Duration: Clopidogrel continued for 1 month except for DES or ACS patients (12 mo)	Clopidogrel 900 mg loading dose 2–4 hr prior to PCI, 75 mg daily (N=96) Duration: Clopidogrel continued for 1 month except for DES or ACS patients (12 mo)	ASA 100 mg daily UFH used during PCI (250–300 sec, or 200 sec with use of GPI) GPI use 31% in Group 1 and 255 in Group 2	Timing: 30 days <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke Revascularization <u>Individual</u> CV mortality Nonfatal MI Stroke Revascularization Major bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
De Servi, 2006[25] ROSAI-2	Observational 76 sites in Europe Funding: Industry Timeframe: 05/2002-06/2002 <u>Population</u> 100% UA/NSTEMI Total N: 789 Mean Age: 67 to 68 Female: 29% Race: NR	Upstream GPI (N=241)	In-lab GPI (N=548)	LMWH UFH ASA Beta blockers Calcium channel blockers Statins ACE inhibitors Clopidogrel Ticlopidine	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Stroke <u>Individual</u> Total mortality Nonfatal MI Stroke	Fair
Di Sciascio, 2010[26] ARMYDA-5 PRELOAD	RCT 3 sites in Europe Funding: NR <u>Population</u> 40% UA/NSTEMI 60% Stable angina 76% received PCI Total N: 536 Mean Age:65 to 66 Female:19% Race: NR	Clopidogrel 600 mg loading dose at time of PCI, 75 mg daily (N=205) Duration of treatment: at least 30 days	Clopidogrel 600 mg loading dose 4–6 hr prior to angiography, 75 mg daily (N=204) Duration of treatment: at least 30 days	ASA 100 mg/day Clopidogrel 75 mg/day after PCI GPIs used in 41% of in-lab load group, 38% of preload group	Timing: 30 days <u>Composite</u> (primary) CV mortality Nonfatal MI Revascularization <u>Individual</u> CV mortality Nonfatal MI Revascularization Major Bleeding Minor Bleeding Entry-site complications	Fair
Di Sciascio, 2010[27] ARMYDA-4 RELOAD	RCT 4 sites in Europe Funding: None Timeframe: NR <u>Population</u> 41% NSTEMI Total N: 503 Mean Age: 65 to 66 Female: 23% Race: NR	Clopidogrel 600 mg loading dose (N=252)	Placebo (N=251)	Aspirin use 100% in each group at baseline. 97% of patients in each group received UFH during PCI and 3% received bivalirudin during PCI. 12% in reload group and 11% in placebo group received IIb/IIIa inhibitor during PCI	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI TVR <u>Individual</u> Minor bleeding Nonfatal MI	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Durand, 2007[28] PRACTICE	RCT 46 sites in Europe, Israel Funding: Industry Timeframe: 09/2001–07/2004 <u>Population</u> 100% NSTEMI All patients planned for early invasive strategy 61% PCI Total N: 393 Mean Age: 63 to 64 Female: 27% Race: NR	Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion initiated at hospital admission (N=196) Duration: 72 hr total or 24 hr after PCI	Placebo (N=197) 12% received bailout Eptifibatide	ASA given to all patients at randomization Clopidogrel 300 mg loading dose at time of randomization then 75 mg daily UFH or LMWH used	Timing: 30 days, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Urgent revascularization (secondary) Total mortality Nonfatal MI Urgent revascularization <u>Individual</u> Total mortality Nonfatal MI Urgent revascularization Major bleeding Minor bleeding	Fair
Ferguson, 2004[29] SYNERGY	RCT 467 international sites Funding: Industry Timeframe: 08/2001–12/2003 <u>Population</u> 100% UA/NSTEMI 100% early invasive strategy; Median time from admission to angiography = 21 hr Total N: 10,027 Median Age: 68 Female: 34% Race: 5% Hispanic, 6% African American, 1% Asian, 86% White	Enoxaparin 1 mg/kg every 12 hr during hospitalization 0.3 mg/kg IV prior to PCI if last dose was >8 hr before (N=4993) Duration: until PCI	UFH 60 units/kg bolus (max 5000 units), 12 units/kg/hr infusion (max 1000 units/hr) with goal aPTT 50–70 sec during hospitalization (N=4985) Duration: 48–120 hr, until PCI	95% of patients were administered ASA 63% of patients were administered clopidogrel Use of GPI was 56.5% in group 1, 58.2% in group 2	Timing: In-hospital, 48 hr, 14 days, 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Major bleeding Stroke Recurrent ischemia	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Fung, 2009[30] BRIEF-PCI	RCT 2 sites in Canada Funding: Hospital sponsored Timeframe: 12/2004–07/2007 <u>Population</u> 37% ACS 14% STEMI 49% Stable angina Total N: 624 Mean Age: 62 to 63 Female: 18% Race: 90% White	Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at the time of PCI (N=312) Duration: 2 hr	Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at the time of PCI (N=312) Duration: 18 hr	ASA Clopidogrel pretreatment occurred in some; in those who did not undergo pretreatment, 600 mg clopidogrel was given at start of PCI UFH or LMWH acceptable	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI Revascularization Major bleeding <u>Individual</u> Total mortality Nonfatal MI Nonfatal stroke Revascularization Major bleeding Minor bleeding	Fair
Galassi, 1999[31]	RCT Single site in Europe Funding: NR Timeframe: 10/1996–02/1998 <u>Population</u> 49% UA 100% PCI Total N: 106 Mean Age: 61 to 63 Female: 6% Race: NR	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion 10-60 min prior to PCI (N=52) Duration: 12 hr	Placebo (N=54)	ASA 325 mg daily Ticlopidine 250 mg twice daily on days prior to PCI and for 1 mo post PCI UFH 70 units/kg bolus, goal ACT>200 sec for abciximab group; 100 units/kg bolus, goal ACT>300 sec for placebo group	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Stent thrombosis Urgent TVR <u>Individual</u> Total mortality Nonfatal MI Stent thrombosis Urgent TVR Major bleeding Minor bleeding Adverse drug reaction Vascular complications	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Galasso, 2008[32]	Observational Single site in Europe Funding: NR Timeframe: 01/2001-12/2003 <u>Population</u> 100% UA/NSTEMI 100%PCI Total N: 500 Mean Age: 77 Female: 26% Race: NR	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg maintenance (N=247) Duration: 12 hr	No abciximab (N=253)	ASA 325 mg daily Clopidogrel 250 mg daily for 3 mo UFH 50 units/kg IV with goal ACT 250 - 300 sec	Timing: In-hospital, 2 yr <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair
Gibson, 2006[33] PROTECT-TIMI-30	RCT Multiple international sites Funding: Industry Timeframe: 08/2003–09/2004 <u>Population</u> 51% UA 50% NSTEMI 79% DES, 24% BMS Total N: 857 Mean Age: 60 Female: 33% Race: NR	Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion at the time of PCI (N=284) Duration: terminated at end of procedure	UFH (50 units/kg bolus, goal ACT 200–250 sec) or Enoxaparin (0.5 mg/kg IV) at the time of PCI Eptifibatide 180 mcg/kg double bolus, 2 mcg kg/min infusion (N=573) Duration: Eptifibatide continued for 18–24 hr post PCI	ASA 160–325 mg orally before PCI Clopidogrel 300 mg orally at time of PCI	Timing: 48 hr <u>Composite</u> (primary) Total mortality Nonfatal MI Ischemia (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Ischemia Major Bleeding Minor Bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Giugliano, 2009[34] EARLY ACS	RCT 440 international sites Funding: Industry Timeframe: 05/2004–08/2008 <u>Population</u> 100% UA/NSTEMI 5 hr (median) from admission to angiography 59% PCI Total N: 9,378 Median Age: 67 to 68 Female: 32% Race: NR	Eptifibatide 180 mcg/kg double bolus + 2 mcg/kg/min infusion (N=4722) Duration: 18–96 hr	Placebo (N=4684) Duration: 18–96 hr	ASA 162–325 mg orally or 150–500 mg IV loading dose, >75 mg daily indefinitely Clopidogrel 300 mg loading dose, 75 mg daily maintenance dose UFH or LMWH acceptable	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization Thrombotic bailout with GPI (secondary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Nonfatal stroke Revascularization Major bleeding Adverse drug reactions Thrombotic bailout	Good
Goodman, 2003[35] INTERACT	RCT 50 sites in Canada Funding: Industry Timeframe: 09/2000–12/2001 <u>Population</u> 83% NSTEMI Angiography and PCI left to discretion of investigator 63% underwent angiography; 29% PCI Total N: 746 Median Age: 64 Female: 31% Race: NR	Enoxaparin 1 mg/kg every 12 hr during hospitalization (N=380) Duration: 48 hr	UFH 70 units/kg bolus, 15 units/kg/hr infusion with goal aPTT 50–70 sec during hospitalization (N=366) Duration: 48 hr	ASA >160 mg loading dose, 80–325 mg daily 15% received clopidogrel Eptifibatide 180 ug/kg IV double bolus, 2 ug/kg/min infusion for 48 hr	Timing: 48 hr, 30 days, 300 days, 600 days, 900 days <u>Composite</u> (secondary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Recurrent ischemia	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Gowda, 2003[36]	Observational Single site in U.S. Funding: NR Timeframe: 01/1998-12/1999 <u>Population</u> 100% ACS 62% UA Total N: 228 Mean Age: 65 Female: 25% Race: NR	Tirofiban (N=114) Duration: mean 24 hr	Abciximab (N=114) Duration: mean 13 hr	ASA UFH Ticlopidine or clopidogrel	Timing: In-hospital, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Rehospitalization <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Length of hospital stay Ischemia	Fair
Gunasekara, 2006[37]	Observational Single site in Australia/NZ Funding: NR Timeframe: 01/2002-06/2003 <u>Population</u> 12% UA 18% Stable angina 32% NSTEMI 39% STEMI Total N: 219 Mean Age: 59 Female: 23% Race: NR	Tirofiban 25 mcg/kg bolus, 0.15 mcg/kg/min infusion at time of PCI (N=109) Duration: 18 hr	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion at time of PCI (N=110) Duration: 12 hr	ASA 100-150 mg daily Clopidogrel 75 mg daily for 6 mo UFH 5000 unit bolus with goal ACT 250 sec	Timing: 30 days, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization Stroke <u>Individual</u> Total mortality Nonfatal MI Revascularization Stroke Minor bleeding Transfusion	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Islam, 2002[38] EPISTENT	RCT 63 sites in U.S., Canada Funding: Industry Timeframe: 07/1996–09/1997 <u>Population</u> 52% ACS 36% UA 43% Stable angina 100% PCI Total N: 2,399 Mean Age: 59 to 60 Female: 25% Race: NR	Abciximab 0.25 mg/kg bolus, 0.125 mg/kg/min infusion at start of PCI (N=794) UFH 70 units/kg IV bolus at start of PCI, goal ACT >250 sec Duration: Abciximab continued for 12 hr after PCI 3rd arm of study excluded (abciximab-treated patients who underwent PTCA) (N=796)	Placebo (N=809) UFH 100 units/kg IV bolus at start of PCI, goal ACT >300 sec	ASA 325 mg given prior to PCI Ticlopidine 250 mg twice daily at discretion of investigator (not pretreated)	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Urgent TVR (secondary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Urgent TVR Major bleeding Minor bleeding	Good
Ivandic, 2008[39]	RCT Single sites in Europe Funding: Industry Timeframe: 06/2004–11/2006 <u>Population</u> 100% NSTEMI 78% successful PCI Clopidogrel naïve patients Total N: 100 Mean Age: 64 to 65 Female: 32% Race: NR	Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion at time of ACS diagnosis (N=50)	Placebo (N=50) Bailout tirofiban allowed at discretion of operator	ASA 500 mg IV loading dose, 100 mg daily Clopidogrel 600 mg loading dose at time of randomization, 75 mg daily UFH 5000 unit bolus, 1000 unit/hr at time of randomization	Timing: 30 days, 319 days <u>Composite</u> (secondary) CV mortality Nonfatal MI Revascularization <u>Individual</u> CV mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Iversen, 2011[40]	Observational Single site in Europe Funding: NR Timeframe: 01/2003-11/2008 <u>Population</u> 32% UA/NSTEMI 100%PCI Total N: 870 Median Age: 76 to 78 Female: 40% Race: NR	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg maintenance (N=201) Duration: 12 hr	No abciximab (N=669)	ASA 300-500 mg Clopidogrel 300-600 mg Enoxaparin SC 1 mg/kg twice daily Or Fondaparinux 2.5 mg daily	Timing: 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization	Fair
Iversen, 2011[41]	Observational Single site in Europe Funding: NR Timeframe: 01/2003-11/2008 <u>Population</u> 100% ACS 100%PCI Total N: 629 Mean Age: 68 Female: 35% Race: NR	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg maintenance (N=169) Duration: 12 hr	No abciximab (N=460)	ASA 300-500 mg Clopidogrel 300-600 mg Enoxaparin SC 1 mg/kg twice daily Or Fondaparinux 2.5 mg daily	Timing: 30 days, 1 yr, 3 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization	Fair
Karha, 2006[42]	Observational Single site in U.S. Funding: NR Timeframe: 08/1998-08/2004 <u>Population</u> 69% UA Total N: 1,537 Mean Age: 68 Female: 19% Race: NR	GPI (N=941)	No GPI (N=596)	NR	Timing: In-hospital, 5 yr <u>Individual</u> Total mortality Nonfatal MI Major bleeding	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Kastrati, 2006[43] ISAR-REACT 2	RCT 7 sites in Europe, S. America Funding: Government Timeframe: 03/2003–12/2005 <u>Population</u> 48% UA 52% NSTEMI All patients planned for PCI within 6 hr of diagnosis of ACS 97% stent (48% BMS, 49% DES) Total N: 2,022 Mean Age: 66 to 67 Female: 26% Race: NR	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion started at time of PCI (N=1012) Duration: 12 hr after PCI	Placebo (N=1010)	Pre-PCI: 600 mg clopidogrel at least 2 hr prior to PCI 500 mg of oral or IV ASA In-lab: 70 U/kg UFH bolus Post PCI: 200 mg ASA 75 mg clopidogrel twice daily (for 3 days) then 75 mg daily for 6 mo	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Urgent TVR (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Urgent TVR Major bleeding Minor bleeding	Good
Kastrati, 2008[44] ISAR-REACT 3	RCT Multiple sites in U.S., Europe Funding: Industry Timeframe: 09/2005–01/2008 <u>Population</u> 18% UA 82% Stable angina 88% DES, 5% BMS Total N: 4571 Mean Age: 67 Female: 23% Race: NR	Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion at the time of PCI (N=2289) Duration: terminated at end of procedure	UFH 100–140 units/kg bolus, placebo infusion at time of PCI (N=2281)	ASA 325–500 mg orally at time of PCI, 80–325 mg daily indefinitely Clopidogrel 600 mg at least 2 hr prior to PCI, 75 mg daily for 1 month (BMS), 6 mo (DES) GPI use was 0.2% in each group	Timing: 30 days, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization Major Bleeding (secondary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Revascularization Stent Thrombosis Major Bleeding Minor Bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Kastrati, 2011[45] ISAR-REACT 4	RCT 8 sites in U.S., Europe Funding: Industry Timeframe: NR <u>Population</u> 100% NSTEMI Randomized after initial angiography 89% DES, 7% BMS Total N: 1721 Mean Age: 68 Female: 23% Race: NR	Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion at the time of PCI (N=860) Duration: terminated at end of procedure	UFH 70 units/kg bolus Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/hr infusion at the time of PCI (N=861) Duration: Abciximab continued for 12 hr post PCI	ASA 325–500 mg orally Clopidogrel 600 mg orally given at time of PCI	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization Major Bleeding (secondary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Stroke Revascularization Stent Thrombosis Major Bleeding Minor Bleeding Thrombocytopenia	Good
Kim, 2005[46]	RCT Single site in Asia Funding: NR Timeframe: 03/2001-12/2002 <u>Population</u> 50% UA 50%NSTEMI 75% early invasive treatment 71% PCI Total N: 160 N for analysis: 80 Mean Age: 61 Female: 35% Race: NR	UFH 5000 unit bolus, 12 unit/kg/hr with goal aPTT of 1.5-2 times control + tirofiban 0.4 mcg/kg/min for 30 min bolus, 0.1 mcg/kg/min maintenance (N=40) Duration: 48-96 hr	UFH 5000 unit bolus, 12 unit/kg/hr with goal aPTT of 1.5-2 times control (N=40) Duration: 48-96 hr	ASA 300 mg bolus, 100 mg daily for 6 mo Clopidogrel 75 mg for 1 mo	Timing: 30 days, 6 mo <u>Individual</u> CV mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Korovesis, 2005[47]	Observational Single site in Europe Funding: NR Timeframe: NR Population 57% UA 28% Stable angina 100% early invasive strategy Total N: 333 Mean Age: 55 to 57 Female: 7% Race: NR	Enoxaparin alone – 1 mg/kg Enoxaparin with GPI – 0.75 mg/kg (N=116)	UFH alone - 100 unit/kg bolus, 10-20 unit/kg maintenance with goal ACT of >250 sec UFH with GPI – 60 unit/kg bolus with goal ACT 200-250 sec (N=217)	ASA dose unspecified Clopidogrel dose unspecified Or Ticlopidine dose unspecified	Timing: 30 days Individual Total mortality Nonfatal MI Revascularization	Poor
Lahtela, 2009[48]	Observational 7 sites in Europe Funding: Private Foundation Timeframe: 2002-2006 Population 17% UA 25% NSTEMI 9% STEMI Total N: 377 Mean Age: 70 to 71 Female: 28% Race: NR	GPI (N=111)	No GPI (N=266)	NR	Timing: In-hospital Composite Total mortality Nonfatal MI Revascularization Stent thrombosis Stroke Individual Total mortality Nonfatal MI Revascularization Stent thrombosis Stroke Major bleeding	Fair
Lemesle, 2009[49]	Observational Single site in U.S. Funding: NR Timeframe: 1/2000-12/2007 Population 50% UA 61% ACS Total N: 2766 Mean Age: 84 Female: 51% Race: NR	Bivalirudin (N=1207)	Unfractionated Heparin (N=1559)	Glycoprotein (GP) IIb/IIIa inhibitors were used at the operator's discretion (2%). All patients received an aspirin loading dose of 325 mg, with indefinite continuation encouraged. A clopidogrel loading dose of 300 mg and a 75-mg clopidogrel maintenance dose were instituted in all patients.	Timing: in-hospital, 6 mo Composite (primary) Total mortality Nonfatal MI Revascularization Individual Total mortality Nonfatal MI Revascularization Major bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Lemesle, 2009[50]	Observational Single site in U.S. Funding: NR Timeframe: 1/2002-12/2007 <u>Population</u> 22% UA 81% ACS Total N: 171 Megan Age: 92 to 93 Female: 51% Race: NR	Bivalirudin (N=79)	Unfractionated Heparin (N=92)	All patients received an aspirin-loading dose of 325 mg and were encouraged to continue this regimen indefinitely. After a clopidogrel-loading dose of 300 mg, additional antiplatelet therapy with a 75-mg clopidogrel maintenance dose was instituted in all patients who were advised to continue this regimen for ≥1 yr. Glycoprotein IIb/IIIa inhibitors were used at the operator's discretion (1.3% bivalirudin group and 16.7% heparin group)	Timing: in-hospital <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization Major bleeding <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding	Fair
Leoncini, 2005[51] CLOTILDA	RCT Single site in Europe Funding: NR Timeframe: 11/2002–10/2004 <u>Population</u> 100% ACS 66% PCI Total N: 300 Median Age: 65 to 67 Female: 29% Race: NR	Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion (N=150) Duration: 18 hr after PCI	Placebo (N=150) Bailout abciximab allowed at discretion of operator	ASA 500 mg IV loading dose, 100 mg daily indefinitely Clopidogrel 300 mg loading dose, 75 mg daily for at least 1 mo UFH 60 unit/kg bolus, 7 units/kg/hr infusion, terminated at end of PCI	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Rehospitalization <u>Individual</u> Total mortality Nonfatal MI Rehospitalization Major bleeding	Poor
Lin, 2009[52]	RCT Single site in Asia Funding: NR Timeframe: 01/2005–01/2008 <u>Population</u> 100% UA/NSTEMI 10 hr (mean) from admission to angiography Total N: 94 Mean Age: 82 to 83 Female: 18% Race: NR	Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion prior to angiography (N=48) Duration: 36-48 hr after PCI	Tirofiban 0.1 mg/kg bolus, 0.075 mcg/kg/min infusion prior to angiography (N=46) Duration: 36-48 hr after PCI	ASA 300 mg loading dose, 100 mg daily Clopidogrel 75 mg daily UFH 40-70 units/kg bolus, goal ACT >200 sec OR Enoxaparin 1 mg/kg every 12 hr before PCI and for 5 days post PCI	Timing: 7 days <u>Individual</u> Total mortality Nonfatal MI Major bleeding Minor bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Liu, 2009[53]	RCT Single site in Asia Funding: NR Timeframe: 07/2006–07/2007 Population 100% UA/NSTEMI Total N: 160 Mean Age: 60 Female: 31% Race: NR	Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion 4–6 hr prior to angiography (N=80) Duration: 24–36 hr after PCI	Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion at the time of PCI (N=80) Duration: 24–36 hr after PCI	ASA 300 mg daily for 30 days, 100 mg daily indefinitely Clopidogrel 300 mg loading dose, 75 mg daily for 1 yr Enoxaparin 1 mg/kg every 12 hr before PCI and for 5 days post PCI	Timing: In-hospital, 30 days, 6 mo Composite (primary) Total mortality Nonfatal MI Revascularization Individual Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair
Mehta, 2005[54] ASPIRE	RCT 22 sites in U.S., Canada, Europe Funding: Industry Timeframe: 06/2003–11/2003 Population 79% UA/NSTEMI 1% STEMI 20% Stable angina Total N: 350 Mean Age: 62 to 64 Female: 23% Race: NR	UFH 100 units/kg IV bolus (65 units/kg if GPI intended) at time of PCI (N=117) Duration: terminated at end of PCI	Fondaparinux 2.5 mg (low dose) (N=118) or 5.0 mg (high dose) (N=115) IV at time of PCI Duration: terminated at end of PCI	ASA Clopidogrel (pre-PCI) = 88%. Clopidogrel (>3 hr pre-PCI)=35% Use of GPI was 56% in UFH group, and 59% in both fondaparinux groups	Timing: 48 hr Composite (primary) Total mortality Nonfatal MI Revascularization Bailout GPI Use Individual Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Mehta, 2010[55] CURRENT-OASIS 7	RCT 597 international sites Funding: Industry Timeframe: <u>Population</u> 73% UA/NSTEMI 27% STEMI 100% underwent early invasive strategy 99% received PCI Total N: 25,086 Mean Age:61 to 62 Female:27 Race: 50% White, 1% Black, 11% south Asian, 12% east Asian	Clopidogrel 300 mg loading dose, 75 mg daily (N=12,520) Duration: 30 days	Clopidogrel 600 mg loading dose, 150 mg daily for 7 days, then 75 mg daily (N=12,566) Duration: 30 days	2x2 factorial design: ASA >300 mg loading dose, 300–325 mg daily x 30 days ASA >300 mg loading dose, 75–100 mg daily x 30 days	Timing: 30 days <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke (secondary) CV mortality Nonfatal MI Nonfatal stroke Recurrent ischemia <u>Individual</u> Total mortality CV mortality Nonfatal MI Nonfatal stroke Major Bleeding Minor Bleeding, Recurrent ischemia	Good
Moliterno, 2011[56] TENACITY	RCT 28 sites in U.S. Funding: Industry Timeframe: 11/2004–07/2005 <u>Population</u> 60% UA 12% NSTEMI 4% STEMI Total N: 383 Mean Age: 63 Female: 27% Race: 92% White	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion at the time of PCI (N=194) Duration: 12 hr	Tirofiban 0.25 mg/kg bolus, 0.15 mcg/kg/min infusion at the time of PCI (N=189) Duration: 12 hr	ASA 325 mg loading dose, 81-325 mg daily Clopidogrel 600 mg loading dose 2-6 hr prior to PCI (if naïve); 75-375 mg loading dose 2-6 hr prior to PCI (if previously on clopidogrel) Patients were randomized to bivalirudin vs. UFH but due to early study discontinuation, only GPI results are reported	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Urgent TVR (secondary) Total mortality Nonfatal MI Urgent TVR Major bleeding <u>Individual</u> Total mortality Nonfatal MI Urgent TVR Major bleeding Minor bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Momtahen, 2009[57]	RCT Setting: NR Funding: NR Timeframe: 02/2006–NR Population 100% UA/NSTEMI Total N: 196 Mean Age: 51 to 55 Female: 43% Race: NR	Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at hospital admission (N=98) Duration: 72 hr	Placebo (N=98)	ASA 160 mg daily Clopidogrel – dose NR UFH 5000 unit bolus, infusion to achieve therapeutic aPTT	Timing: 30 days Composite (primary) Total mortality Nonfatal MI Revascularization Individual Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair
Montalescot, 2006[58] ALBION	RCT 7 sites in Europe Funding: Industry Timeframe: NR Population 100% UA/NSTEMI Total N: 103 Mean Age: 60 to 64 Female: 23% Race: NR	Clopidogrel 300 mg loading dose prior to PCI (>12 hr prior to PCI), 75 mg daily (N=35)	Clopidogrel 600 mg loading dose prior to PCI (>12 hr prior to PCI), 75 mg daily (N=34) 3rd treatment arm: 900 mg loading dose prior to PCI, 75 mg daily (N=34)	ASA 250–500 mg orally or IV loading dose, <100 mg daily LMWH twice daily	Timing: 30 days Composite (primary) Total mortality Nonfatal MI Revascularization Rehospitalization Individual Total mortality Nonfatal MI Revascularization Rehospitalization Major bleeding Minor bleeding	Fair
Ozkan, 2005[59]	RCT Single site in Europe Funding: NR Timeframe: 03/1999–06/2004 Population 100% ACS Total N: 47 Mean Age: 62 to 64 Female: 23% Race: NR	Tirofiban 0.12 mg/kg bolus, 0.1 mcg/kg/min infusion after initial angiography (N=24) Duration: 48 hr	No tirofiban (N=23)	ASA 300 mg daily Clopidogrel 300 mg loading dose, 75 mg daily Enoxaparin (Group 1) 0.4 mg/kg twice daily x 48 hr UFH 10,000 unit bolus, infusion	30 days Individual Total mortality Nonfatal MI Major bleeding Minor bleeding No reflow phenomenon	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Parodi, 2010[60] ARNO	RCT NR sites in Europe Funding: Investigator-supported Timeframe: 10/2006–07/2008 <u>Population</u> 27% UA 43% Stable angina 76% DES, 9% BMS Total N: 850 Mean Age: 69 Female: 24% Race: NR	Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion at the time of PCI (N=425) Duration: terminated at end of procedure	UFH 100 units/kg bolus, additional doses to maintain ACT >250 sec at time of PCI (N=425) Duration: terminated at end of procedure	ASA 325 mg orally Clopidogrel 75 mg daily after PCI Abciximab allowed at discretion of investigator (15% in group 1, 28% in group 2)	Timing: 30 days, 6 mo, 1 yr <u>Composite</u> Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization Stent Thrombosis Major Bleeding Minor Bleeding Net Clinical Benefit	Fair
Patti, 2005[61] ARMYDA-2	RCT 2 sites in Europe Funding: NR Timeframe: 03/2004–NR <u>Population</u> 25% UA/NSTEMI 75% Stable angina Total N: 255 Mean Age: 63 to 65 Female: 23% Race: NR	Clopidogrel 300 mg loading dose 4–8 hr prior to angiography, 75 mg daily (N=126) Duration: 30 days for BMS, 6 mo for DES, 9 mo for ACS	Clopidogrel 600 mg loading dose 4–8 hr prior to angiography, 75 mg daily (N=129) Duration: 30 days for BMS, 6 mo for DES, 9 mo for ACS	ASA 100 mg daily UFH given at time of PCI, goal ACT 300 sec without GPI, goal ACT 200–300 sec with GPI GPI use at discretion of operator	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Patti, 2012[62] ARMYDA-7 BIVALVE	RCT 14 sites in U.S. Funding: Industry Timeframe: 06/2009–06/2011 <u>Population</u> 17% UA 13% NSTEMI 70% Stable angina Total N: 401 Mean Age: 70 Female: 29% Race: NR	Bivalirudin 0.75 mg/kg bolus, infusion 1.75 mg/kg/h at time of PCI + Provisional GPI (N=198)	UFH 75 units/kg bolus + Provisional GPI (N=203)	ASA >100 mg loading dose, 100 mg daily Clopidogrel 600 mg loading dose >6 hr prior to procedure, 75 mg daily for 1 month (12 mo for patients with ACS or DES) GPI use in 12% (Group 1) and 14% (Group 2)	Timing: 30 days <u>Composite</u> (primary) CV mortality Nonfatal MI Revascularization Stent thrombosis <u>Individual</u> CV mortality Nonfatal MI Revascularization Stent thrombosis Major bleeding Minor bleeding Entry-site complications	Good
Peterson, 2003[63]	Observational Multiple sites in U.S. Funding: Industry Timeframe: 07/2000-07/2001 <u>Population</u> 100% UA/NSTEMI Total N: 60,770 Mean Age: 70 Female: 44% Race: NR	Early GPI (N=15379)	No Early GPI (N=45391)	NR	Timing: in-hospital <u>Composite</u> Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Stroke (any kind) Major bleeding	Fair
Price, 2011[64] GRAVITAS	RCT 83 sites in U.S., Canada Funding: Industry Timeframe: 7/2008-7/2010 <u>Population</u> 25% UA 16% UA/NSTEMI Total N: 2214 Mean Age: 64 Female: 32% Race: NR	Clopidogrel 600 mg loading dose, 150 mg maintenance dose (N=1109)	Placebo loading dose, clopidogrel 75 mg maintenance dose (N=1105)	Aspirin treatment was required at a dose of 75 to 162 mg daily.	Timing: 6 mo <u>Composite</u> (primary) Cardiovascular mortality Nonfatal MI Stent thrombosis (secondary) Cardiovascular mortality Nonfatal MI <u>Individual</u> Cardiovascular mortality Stent thrombosis	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Puymirat, 2011[65] FAST-MI	Observational 223 sites in Europe Funding: Industry Timeframe: 10/2005-10/2005 <u>Population</u> 35% STEMI Total N: 791 Mean Age: 81 to 82 Female: 48% Race: NR	Clopidogrel < 300 mg (N=325)	Clopidogrel ≥ 300 mg (N=466)	For therapies appropriate for NSTEMI patients, only the rates of GP IIb/IIIa inhibitor use provided. 139 patients in the loading dose group and 80 in the no loading dose group were treated with GP IIb/IIIa inhibitors during the index hospitalization. More patients in the no loading dose group (117 patients) had a history of previous clopidogrel use at baseline than in the loading dose group (39 patients)	Timing: in-hospital, 30 days, 1 yr <u>Composite</u> Major bleeding need for transfusion <u>Individual</u> Total mortality Major bleeding MI Stroke (any kind)	Fair
Rajagopal, 2006[66] REPLACE-2 ACS Substudy	RCT 233 sites in U.S., Canada, Europe Funding: Industry Timeframe: 10/2001–08/2002 <u>Population</u> 63% UA 89% BMS Total N: 1351 Mean Age: 61 Female: 26% Race: 91% White	Bivalirudin 0.75 mg/kg bolus, 1.75 mg/kg/hr infusion at the time of PCI (N=669) Duration: terminated at end of procedure	UFH 65 units/kg bolus GPI: Abciximab 0.25 mg/kg bolus, 0.125 mg/kg/hr infusion Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion (N=682) Duration: UFH terminated at end of procedure GPI for 12 hr (abciximab) or 18 hr (eptifibatide)	ASA given to all patients Clopidogrel 300 mg loading dose (2–12 hr pre procedure) was given in 85% of patients, 75 mg daily for at least 1 month Provisional GPI could be administered for procedural complications during PCI in the bivalirudin group (6% received GPI)	Timing: 30 days, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI Revascularization Major Bleeding (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Revascularization Major Bleeding Minor Bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Rasoul, 2006[67] ELISA 2	RCT Single site in Europe Funding: NR Timeframe: 09/2002–01/2005 <u>Population</u> 100% UA/NSTEMI 23 hr (median) from admission to angiography 59% PCI Total N: 328 Median Age: 62 to 65 Female: 29% Race: NR	Dual therapy ASA + clopidogrel 600 mg (N=166) Downstream tirofiban bailout left to operator discretion Open label	Triple therapy ASA + clopidogrel 300 mg + tirofiban 10 mcg/kg bolus, 0.15 mcg/kg/min maintenance dose (N=162) Duration: tirofiban 12 hr in case of PCI Open label	LMWH	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Stroke Major bleeding	Fair
Roe, 2003[68] EARLY	RCT 20 sites in U.S. Funding: Industry Timeframe: NR <u>Population</u> 100% UA/NSTEMI Total N: 311 Median Age: 60 to 64 Female: 40% Race: NR	Eptifibatide 180 mcg/kg single bolus, 2 mcg/kg/min infusion at hospital admission for 12-24 hr, crossover occurred with investigator directed 2nd bolus of study drug (N=153) Open label after 18-24 hr	Placebo (N=158)	ASA 162-325 mg daily Clopidogrel UFH 60 units/kg bolus, 12 units/kg/hr infusion (max 1000 units/hr)	Timing: 3 days <u>Composite:</u> (secondary) Total mortality Nonfatal MI Recurrent ischemia <u>Individual</u> Total mortality Nonfatal MI Recurrent ischemia Major bleeding	Good
Schiariti, 2011[69] SANTISS	RCT Single site in Europe Funding: NR Timeframe: 02/2005–03/2007 <u>Population</u> 35% UA 14% Stable angina Total N: 666 Mean Age: 62 Female: 20% Race: NR	Tirofiban 0.25 mg/kg bolus, 0.15 mcg/kg/min infusion at the time of PCI (N=519) Duration: 12 hr	Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at the time of PCI (N=147) Duration: 18 hr	ASA 160-325 mg loading dose, 80-125 mg daily Clopidogrel 300 mg loading dose at time of PCI, 75 mg daily for 3 mo UFH with goal ACT >250 sec	Timing: 1 yr <u>Composite</u> (primary) CV mortality Nonfatal MI Revascularization Stent thrombosis Recurrent angina <u>Individual</u> CV mortality Nonfatal MI Revascularization Stent thrombosis Major bleeding Recurrent angina	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Schweiger, 2003[70]	Observational Single site in U.S. Funding: NR Timeframe: 09/1998-04/1999 <u>Population</u> 56% UA 6% Stable angina Total N: 620 Mean Age: 62 Female: 31% Race: NR	Eptifibatide 180 mcg/kg bolus, 2 mcg/kg/min maintenance (N=301) Duration: 18-24 hr	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min maintenance (N=319) Duration: 12 hr	UFH 70 unit/kg bolus with goal ACT of >200 sec Clopidogrel 75 mg daily for 30 days	Timing: In-hospital, 30 days <u>Individual</u> Total mortality Nonfatal MI Revascularization	Poor
Singh, 2006[71]	Observational 407 sites in U.S. Funding: Industry Timeframe: 01/2002-06/2003 <u>Population</u> 100% UA/NSTEMI 65% PCI Total N: 11,358 Median Age: 62 to 63 Female: 33% Race: NR	LMWH (N=4,477)	UFH (N=6,881)	58% clopidogrel 95% ASA	Timing: In-hospital <u>Composite</u> Total mortality Nonfatal MI <u>Individual</u> Total mortality Transfusion	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Steg, 2010[72] FUTURA/OASIS-8	RCT 179 international sites Funding: Industry Timeframe: 02/2009–03/2010 <u>Population</u> 20% UA 80% NSTEMI 100% early invasive strategy Total N: 2,026 Mean Age: 65 to 66 Female: 32% Race: NR	High-dose UFH UFH 85 units/kg IV bolus (max 10,000 units; 60 units/kg if GPI use intended) at time of PCI, goal ACT of 300–350 sec/250–300 sec depending on instrument (N=1024) Duration: only during PCI All patients initially treated with fondaparinux	Low-dose UFH UFH 50 units/kg IV bolus (additional 40 units/kg bolus allowed if procedure lasts >1 hr) at time of PCI, no ACT adjustment (N=1002) Duration: only during PCI All patients initially treated with fondaparinux	89% of patients taking ASA prior to enrollment 80% of patients taking clopidogrel prior to enrollment Use of GPI not specified	Timing: 30 days <u>Composite</u> (primary) Major bleeding Minor bleeding Major vascular complication (secondary) Total mortality Nonfatal MI TVR Major bleeding (secondary) Total mortality Nonfatal MI TVR <u>Individual</u> Total mortality Nonfatal MI Urgent TVR Stent thrombosis Major bleeding Minor bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Stone, 2006[73] ACUITY	RCT 450 international sites Funding: Industry Timeframe: 08/2003–12/2005 <u>Population</u> 41% UA 59% NSTEMI Median time from admission to angiography = 20 hr 56% PCI 65% DES Total N: 13,819 Median Age: 63 Female: 30% Race: NR	Bivalirudin 0.1 mg/kg bolus, 0.25 mg/kg/hr infusion at hospital admission (N=4612) Duration: terminated at end of procedure	UFH 60 units/kg bolus, 12 units/kg/hr infusion at hospital admission, goal ACT 200–250 sec during PCI (48% of nonbivalirudin-treated patients received UFH) Or Enoxaparin 1 mg/kg SC twice daily at hospital admission, 0.3 mg/kg IV bolus if needed at time of PCI (47% of nonbivalirudin-treated patients received LMWH) (N=4603) GPI use was randomly assigned to “upstream” or deferred use at time of PCI Duration: terminated at the end of procedure 3rd treatment arm: Bivalirudin + GPI (N=4604)	ASA 300–325 mg orally or 250–500 mg IV during hospitalization, 75–325 mg orally daily after hospitalization Clopidogrel 300 mg loading dose was recommended (no later than 2 hr after PCI) but clopidogrel dose and timing left to discretion of operator (64% of patients received pretreatment) 75 mg daily x 1 yr	Timing: 30 days, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI Revascularization Major bleeding <u>Individual</u> Total mortality Nonfatal MI Revascularization Major Bleeding Minor Bleeding Thrombocytopenia Stent thrombosis Length of hospital stay	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Stone, 2007[74] ACUITY TIMING* *This population is a subset of the ACUITY study[73]	RCT 450 international sites Funding: Industry Timeframe: 08/2003–12/2005 <u>Population</u> 59% NSTEMI All patients underwent early invasive treatment 56% PCI Total N: 9207 Median Age: 63 Female: 30% Race: NR	Upstream GPI (N=4605) Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion OR Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion Duration: 12–18 hr after PCI	In-lab GPI (N=4602) Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion OR Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion Duration: 12 hr for abciximab, 12–18 hr for eptifibatide after PCI	ASA 300–325 mg orally or 250–500 mg IV loading dose, 75–325 mg daily indefinitely Clopidogrel >300 mg recommended but left to discretion of investigator, occurred within 2 hr after PCI (64% had upstream use); 75 mg daily Anticoagulant not specified	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI Revascularization Major bleeding (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding	Good
Suleiman, 2003[75]	Observational Single site in Israel Funding: NR Timeframe: 01/2000-12/2001 <u>Population</u> 65% ACS 44% UA 19% STEMI Total N: 642 Mean Age: 60 Female: 24% Race: NR	Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min maintenance (N=342) Duration: 18-24 hr	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min (N=300) Duration: 12 hr	ASA 75-325 mg daily Clopidogrel 75 mg daily for 4 wk UFH with goal ACT of 200-250 sec	Timing: In-hospital <u>Composite</u> (primary) Total mortality Revascularization <u>Individual</u> Total mortality Revascularization Major bleeding Minor bleeding	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Szuk, 2007[76] Clopidogrel Registry (Hungary)	Observational 3 sites in Europe Funding: NR Timeframe: 03/2002-02/2004 <u>Population</u> 38% UA/NSTEMI 100% PCI Total N: 4,160 Mean Age: 61 to 62 Female: 27% Race: NR	Clopidogrel at PCI (N=2,679)	Clopidogrel 6-24 hr prior to PCI (N=1,481)	ASA 100 mg daily UFH with goal ACT 250-300 sec GPI at discretion of operator	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization Stent thrombosis Major bleeding GPI	Fair
Topol, 2001[77] TARGET	RCT 149 international sites Funding: Industry Timeframe: 12/1999–08/2000 <u>Population</u> 63% ACS Total N: 4809 Mean Age: 62 to 63 Female: 27% Race: NR	Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion at time of PCI (N=2398) Duration: 18-24 hr	Abciximab 0.25 mcg/kg bolus, 0.125 mcg/kg/min infusion at time of PCI (N=2411) Duration: 12 hr	ASA 250-500 mg loading dose, 75-325 mg daily Clopidogrel 300 mg loading dose 2-6 hr prior to PCI, 75 mg daily for 30 days UFH with goal ACT >250 sec	Timing: 30 days, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Good
Tricoci, 2007[78]	Observational Multiple sites in U.S. Funding: Industry Timeframe: 01/2001-12/2004 <u>Population</u>: 100% UA/NSTEMI Total N: 38,195 Median Age: 61 to 68 Female: 33% Race: NR	Upstream GPI (started > 1 hr prior to PCI) (N=13,279)	periprocedural GPI (started < 1 hr prior to PCI or during PCI procedure) (N=17,551) no GPI (N=7,365)	ASA within 24 hrs Clopidogrel within 24 hrs UFH or LMWH	Timing: in-hospital <u>Composite</u> Total mortality Nonfatal MI <u>Individual</u> Nonfatal MI Stroke (any kind) Any red cell transfusion Total mortality Heart failure Cardiogenic shock	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Valgimigli, 2010[79] FABOLUS SYNCHRO	RCT Single site in Europe Funding: Industry Timeframe: 09/2008–04/2009 <u>Population</u> 43% UA 57% NSTEMI 100% PCI Total N: 73 Mean Age: 73 Female: 29% Race: NR	Abciximab 0.25 mg/kg bolus, placebo infusion at the time of PCI (N=37) Duration: 12 hr	Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion at the time of PCI (N=36) Duration: 12 hr	ASA 160-325 mg orally or 250 mg IV, 100 mg daily indefinitely Clopidogrel 600 mg loading dose (in group 1), 300 mg loading dose (in group 2); 75 mg daily for at least 30 days at time of study drug Data on use of anticoagulant not provided	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Revascularization Stent thrombosis Major bleeding Minor bleeding Net clinical outcome	Fair
van't Hof, 2003[80] ELISA	RCT Single site in Europe Funding: NR Timeframe: 04/2000–12/2001 <u>Population</u> 100% UA/NSTEMI 6 hr (mean) from admission to angiography Total N: 220 Mean Age: 63 to 65 Female: 30% Race: NR	Early group Early angiography Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion at time of PCI (N=109) Duration 12 hr after PCI	Late group Delayed angiography Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion at hospital admission (N=111) Duration 12 hr after PCI	ASA 500 mg IV loading dose Clopidogrel 300 mg loading dose, 75 mg daily LMWH pre-PCI and for 48 hr post-PCI	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Major bleeding	Poor
Velianou, 2000[81]	Observational Single site in U.S. Funding: NR Timeframe: 01/1995-12/1997 <u>Population</u> 65% UA 100%PCI Total N: 570 Mean Age: 66 Female: 39% Race: NR	Abciximab 0.25 mg/kg bolus, 12 mcg/min maintenance (N=157) Duration: 12 hr	No abciximab (N=413)	ASA 325 mg UFH to ACT of 300 sec Ticlopidine 500 mg bolus, 250 mg twice a days for 2-4 wk	Timing: 30 days, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Wallentin, 2009[82] PLATO	RCT 862 international sites Funding: Industry <u>Population</u> 16.7% UA 42.7% NSTEMI 37.6% STEMI 72% underwent early invasive strategy 64% received PCI Total N: 18,624 Median Age: 62 Female:28% Race: 92% White, 6% Asian, 1% Black	Ticagrelor 180 mg loading dose, 90 mg twice daily (N=9,333) Duration: 277 days (median)	Clopidogrel 300 mg or 600 mg loading dose, 75 mg daily (N=9,291) Duration: 277 days (median)	ASA use (97%) during hospitalization was similar between groups UFH (56%) and LMWH (51%) used during hospitalization was similar between groups GPI use was similar between groups (26%)	Timing: 30 days, 1 yr <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke (secondary) Total mortality Nonfatal MI Stroke (secondary) CV mortality Nonfatal MI Stroke Recurrent ischemia Other arterial thrombotic event <u>Individual</u> Total mortality CV mortality Nonfatal MI Stroke Stent Thrombosis Major Bleeding Minor Bleeding Adverse drug reactions	Good
Wang, 2007[83]	Observational 27 sites in U.S. Funding: NR Timeframe: 1/2003-9/2004 <u>Population</u> 100% ACS Total N: 2484 Mean Age: NR Female: 33% Race: NR	Clopidogrel 300 mg (N=1199)	Clopidogrel > 300 mg (N=1285)	84.8% of patients in 300mg group and 86.8% in > 300mg group were receiving aspirin (dose not specified). 15.1% of patients in 300mg group received thrombolytic therapy, 13.9% of patients in the > 300mg group received thrombolytic therapy. However, the timing of the lytic relative to the loading dose of clopidogrel not specified. Groups were significantly different at baseline with respect to those that had an urgent/emergency admission (47.7% in 300mg vs. 56.1% in > 300mg group). Anticoagulant use was also significantly higher in >300mg group (73.5%) compared to 63.9% in 300mg group. Discharge medication records were not available for this registry.	Timing: 60 days, 6 mo <u>Composite</u> Nonfatal MI Total mortality Stroke (any kind) Revascularization <u>Individual</u> Nonfatal MI Total mortality Stroke (any kind) Revascularization Bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Wiviott, 2007[84] TRITON-TIMI 38	RCT 707 international sites Funding: Industry <u>Population</u> 74% UA/NSTEMI 26% STEMI 100% early invasive strategy 99% received PCI Total N: 13,608 Median Age: 61 Female: 26% Race: 93% White	Prasugrel 60 mg loading dose, 10 mg daily (N=6813) Duration: 14.5 mo (median) Randomization occurred in the cath lab at time of PCI, study drug initiated within 1 hr of randomization	Clopidogrel 300 mg loading dose, 75 mg daily (N=6975) Duration: 14.5 mo (median) Randomization occurred in the cath lab at time of PCI, study drug initiated within 1 hr of randomization	ASA daily dose 75–162 mg daily 3% of patients received bivalirudin 55% of patients received GPIs	Timing: 30 days, 15 mo <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke (secondary) CV mortality Nonfatal MI Revascularization (secondary) CV mortality Nonfatal MI Stroke Rehospitalization (secondary) Major bleeding Minor bleeding <u>Individual</u> Total mortality CV mortality Nonfatal MI Nonfatal stroke Revascularization Stent Thrombosis Major Bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Wolfram, 2003[85]	Observational Single site in U.S. Funding: NR Timeframe: 1/2000-9/2002 <u>Population</u> 87% ACS Total N: 3015 Mean Age: 74 to 76 Female: 71% Race: NR	Bivalirudin 0.75 loading dose, 1.75 mg/kg/hr (N=335)	UFH + eptifibatide 180 mcg/kg repeated times 1 10 min following the first bolus; UFH 40 units/kg bolus 2 mcg/kg/min; UFH repeated to maintain ACT< 250 seconds (N=1340) Duration: ≥ 12 hr Unfractionated Heparin 40 units/kg loading dose, additional UFH bolus to maintain goal ACT of 250 to 300 sec. (N=1340)	Most patients received aspirin 325 mg orally 24 hr before and continued indefinitely after the procedure and clopidogrel at the time of procedure. Patients were discharged with clopidogrel (75 mg/ day) for 4 wk after PCI. Baseline Rates of Use of aspirin in the 3 groups was 98.5% in the bivalirudin group, 98.2% in the UFH + eptifibatide and 97.1% in the UFH alone. Baseline Rates of clopidogrel use were 95.4%, 95.3% and 93% in the 3 groups, respectively	Timing: in-hospital <u>Individual</u> Total mortality Nonfatal MI Neurologic event Abrupt vessel closure Revascularization Non-Q wave MI Length of hospital stay Major bleeding	Fair
Yan, 2009[86]	RCT NR sites in Asia Funding: NR Timeframe: 06/2005–06/2006 <u>Population</u> 77% UA 23% NSTEMI Total N: 240 Mean Age: 63 to 64 Female: 28% Race: NR	Tirofiban 0.1 mg/kg bolus, 0.15 mcg/kg/min infusion after PCI (N=120) Duration: 24 hr	Placebo (N=120)	ASA 300 mg loading dose, 100 mg daily Clopidogrel 300 mg loading dose at time of PCI, 75 mg daily UFH 5000 unit bolus, 1000 unit/hr infusion, goal ACT >300 sec	Timing: 30 days, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Yong, 2009[87] PRACTICAL	RCT 10 sites in Australia/NZ Funding: Industry Timeframe: 01/2004–11/2005 <u>Population</u> 18% UA 82% NSTEMI 55% PCI Total N: 256 Mean Age: 61 to 64 Female: 30% Race: NR	Clopidogrel 300 mg loading dose and 2nd placebo dose (N=124) Open label	Clopidogrel 300 mg loading dose and 2nd 300 mg loading dose at time of PCI (N=132)	All patients treated with ASA 69% of patients underwent GPI use	Timing: 30 days, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Nonfatal stroke Rehospitalization <u>Individual</u> Total mortality Nonfatal MI Nonfatal stroke Revascularization Rehospitalization Major bleeding Minor bleeding	Fair
Yusuf, 2006[88] OASIS-5	RCT 576 international sites Funding: Industry Timeframe: NR <u>Population</u> 45% UA 55% NSTEMI 63% of patients underwent angiography during hospitalization 31% PCI Total N: 20,078 Mean Age: 67 Female: 38% Race: NR	Enoxaparin 1 mg/kg SC every 12 hr at hospital admission, additional dose of UFH if >6 hr since last dose during PCI (N=10,021) Duration: 2–8 days	Fondaparinux 2.5 mg SC daily at hospital admission, additional dose of IV Fondaparinux based on timing of last dose and intended use of GPI at time of PCI (N=10,057) Duration: hospital discharge or 8 days	ASA and Clopidogrel recommended 6 hr pre PCI Use of GPI was 41% in enoxaparin group, 41.7% in fondaparinux group	Timing: 9 days, 30 days, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Refractory ischemia (secondary) Total mortality Nonfatal MI (secondary) Total mortality Nonfatal MI Refractory ischemia Major bleeding <u>Individual</u> Total mortality Nonfatal MI Stroke Refractory ischemia Major bleeding	Good

Abbreviations: ACE=angiotensin converting enzyme; ACS=acute coronary syndrome; ACT=activated clotting time; aPTT=activated partial thromboplastin time; ASA=aspirin; BMS=bare metal stent; Cath=catheterization; CV=cardiovascular; DES=drug-eluting stent; GP=glycoprotein; GPI=glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; hr/h=hour/hours; IV=intravenous; kg=kilogram/kilograms; LMWH=low molecular weight heparin; max=maximum; mcg=microgram/micrograms; mg=milligram/milligrams; MI=myocardial infarction; min=minute/minutes; mo=month/months; N=number of patients; NR=not reported; NSTEMI=non-ST elevation myocardial infarction; NZ=New

Zealand; PCI=percutaneous coronary intervention; PTCA=percutaneous transluminal coronary angioplasty; RCT=randomized controlled trial; SC=subcutaneous; sec=second/seconds; STEMI=ST elevation myocardial infarction; TVR=target vessel revascularization; U=unit/units; UA=unstable angina; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin; ug=microgram; U.S./US=United States; wk=week/weeks; yr=year/years

Table F-2. Study characteristics table for KQ 2 comparisons—initial conservative approach for UA/NSTEMI

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Angkasuwapala, 2007[89] Thai ACS Registry	Observational 17 sites in Asia Funding: NR Timeframe: 08/2002–10/2005 <u>Population</u> 33% UA 67% NSTEMI PCI NR Total N: 3,963 Mean Age: NR Female: 48% Race: NR	LMWH Dosage not specified (N=3,341)	UFH Dosage not specified (N=622)	ASA 96% GPI 6% LMWH, 4% UFH Dosage not specified	Timing: Not specified <u>Individual</u> Total mortality	Poor
Anonymous, 1998[90] PURSUIT	RCT 726 international sites Funding: Industry Timeframe: 11/1995–01/1997 <u>Population</u> 54% UA 46% NSTEMI Angiography timing at discretion of investigator 24% PCI Total N: 10,948 Median Age: 64 Female: 35% Race: 89% White	Eptifibatide 180 mcg/kg bolus, 2.0 mcg/kg/min infusion (N=4722) Third treatment arm: Eptifibatide 180 mcg/kg bolus, 1.3 mcg/kg/min infusion (N=1487) Duration: 72–96 hr	Placebo (N=4739) Duration: 72–96 hr	ASA 80–325 mg daily Thienopyridine use NR UFH 5000 unit bolus, 1000 units/hr infusion	Timing: 96 hr, 7 days, 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Major bleeding Minor bleeding Length of hospital stay	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Anonymous, 1998[91] PRISM	RCT 128 international sites Funding: Industry Timeframe: 03/1994–10/1996 <u>Population</u> 100% UA/NSTEMI 21% PCI Total N: 3232 Mean Age: 62 to 63 Female: 32% Race: 5% Hispanic, 5% Black, 2% Asian, 84% White	Tirofiban 0.6 mcg/kg/min x 30 min bolus, 0.15 mcg/kg/min infusion (N=1616) Duration: 48 hr	UFH 5000 unit bolus, 1000 unit infusion (N=1616) Duration: 48 hr	ASA 300–325 mg daily	Timing: 48 hr, 7 days, 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Refractory angina (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Refractory ischemia	Good
Anonymous, 1998[92] PRISM-PLUS	RCT 72 international sites Funding: Industry Timeframe: 11/1994–09/1996 <u>Population</u> 55% UA 45% NSTEMI Angiography performed after 48 hr 31% PCI Total N:1875 Mean Age: 63 Female: 33% Race: 86% White, 4% Black	Tirofiban 0.4 mcg/kg bolus, 0.1 mg/kg/min infusion + UFH (N=773) Duration 48–96 hr	Placebo + UFH (N=797)	ASA 325 mg daily	Timing: in-hospital, 48 hr, 7 days, 30 days, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Rehospitalization Refractory ischemia (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Major bleeding Transfusion	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Antman, 1999[4] TIMI 11B	RCT 200 international sites Funding: Industry Timeframe: 08/1996–03/1998 <u>Population</u> 59% UA 38% NSTEMI Total N: 3,910 Median Age: 65 to 66 Female: NR Race: NR	Enoxaparin 30 mg IV loading dose, 1 mg/kg every 12 hr during hospitalization (N=1953) Duration: until discharge or days 8	UFH 70 units/kg bolus, 15 units/kg/hr infusion with goal aPTT 50–70 sec during hospitalization (N=1957) Duration: 3–8 days	ASA 100–325 mg daily	Timing: 48 hr,72 hr, 8 days, 14 days, 43 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Major bleeding Minor bleeding	Good
Bertel, 2010[9] ZEUS	RCT Single site in Europe Funding: NR Timeframe: NR <u>Population</u> 14% UA/NSTEMI 12% STEMI 74% Stable angina 100% PCI Total N: 876 Mean Age: 64 Female: 24% Race: NR	Enoxaparin 0.75 mg/kg IV bolus at time of PCI (N=436)	UFH 60 units/kg bolus at time of PCI (N=440)	ASA 500 mg IV bolus Clopidogrel 300–600 mg loading dose, 75 mg daily after PCI 20% of patients received GPI	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization Major bleeding (secondary) Major bleeding Minor bleeding Thrombocytopenia <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding Stent thrombosis	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Bhatt, 2003[10] CRUISE	RCT 12 sites in U.S. Funding: NR Timeframe: NR <u>Population</u> 45% ACS Total N: 261 Mean Age: 63 to 64 Female: 24% Race: NR	Enoxaparin 0.75 mg/kg IV bolus at time of PCI (N=129)	UFH 60 units/kg bolus (N=132)	ASA 325 mg daily Clopidogrel loading dose at discretion of operator, then 75 mg daily Eptifibatide 180 ug/kg IV double bolus, 2 ug/kg/min infusion (in all patients)	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair
Bhattacharya, 2010[11]	RCT Single site in Asia Funding: NR Timeframe: 06/2007–05/2009 <u>Population</u> 100% UA/NSTEMI No PCI Total N: 301 Mean Age: 63 Female: 54% Race: NR	Tirofiban 0.1 mcg/kg bolus, 0.1 mcg/kg/min infusion (N=136) Duration: 48 hr	Placebo (N=165)	None reported	Timing: 7 days, 14 days, 30 days, 3 mo <u>Individual</u> Death due to unknown causes Nonfatal MI Fatal MI Refractory ischemia Major bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Blazing, 2004[12] A to Z Trial	RCT 240 international sites Funding: Industry Timeframe: 12/1999–05/2002 <u>Population</u> 100% UA/NSTEMI 80% positive biomarkers 60% PCI Total N: 3,987 Median Age: 61 Female: 29% Race: 3% Black, 4% Asian, 85% White	Enoxaparin 1 mg/kg every 12 hr during hospitalization (N=2026) Duration: 48–120 hr, until PCI	UFH 60 units/kg bolus (max 4000 units), 12 units/kg/hr infusion (max 900 units/hr) with goal aPTT 50–70 sec during hospitalization (N=1961) Duration: 48–120 hr, until PCI	ASA 150–325 mg initially, 75–325 mg daily Tirofiban 10 mcg/kg over 30 min, infusion 0.1 mcg/kg/min for 12 hr post-PCI	Timing: 7 days <u>Composite</u> (primary) Total mortality Nonfatal MI Refractory ischemia (secondary) Total mortality Nonfatal MI Revascularization Refractory ischemia Clinical ischemia <u>Individual</u> Total mortality Nonfatal MI Revascularization Refractory ischemia Major bleeding Major or minor bleeding	Good
Brieger, 2007[15]	Observational 113 international sites Funding: Industry Timeframe: 04/1999–03/2005 <u>Population</u> 52% UA 48% NSTEMI 25% PCI Total N: 17,659 Median Age: 67 to 68 Female: 35% Race: NR	LMWH 89% enoxaparin (N=10,839)	UFH (N=6820)	93%ASA 6% warfarin 21% GPI 40% thienopyridine	Timing: In-hospital <u>Individual</u> Total mortality Major bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Chen, 2006[18]	RCT Single site in Asia Funding: NR Timeframe: 10/2003–02/2005 <u>Population</u> 29% UA/NSTEMI 18% Stable angina 47% PCI Total N: 966 Mean Age: 55 to 57 Female: 29% Race: NR	Enoxaparin 1 mg/kg injection every 12 hr, at least twice before catheterization (N=484)	UFH 25 mg IV before angiography, additional 65 mg if PCI performed (N=482)	None reported	Timing: In-hospital, 30 days <u>Composite</u> Total mortality Nonfatal MI Revascularization <u>Individual</u> Stent thrombosis Nonfatal MI	Poor
Cohen, 1997[93] ESSENCE	RCT 176 international sites Funding: Industry Timeframe: 10/1994–05/1996 <u>Population</u> 100% UA/NSTEMI Total N: 3,171 Mean Age: 63 to 64 Female: 34% Race: NR	Enoxaparin 1 mg/kg every 12 hr during hospitalization (N=1607) Duration: 2.6 days (median), 8 days (max)	UFH 5000 unit bolus, infusion with goal aPTT 55–85 sec during hospitalization (N=1564) Duration: 2.6 days (median), 8 days (max)	ASA 100–325 mg daily	Timing: 48 hr, 14 days, 30 days, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Recurrent angina (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Recurrent angina Length of hospital stay Revascularization Stroke Major bleeding Minor bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Cohen, 2002[94] ACUTE II	RCT 54 international sites Funding: Industry Timeframe: NR <u>Population</u> 38% UA 46% NSTEMI 30% PCI 21% stent Total N: 525 Mean Age: 64 to 65 Female: 34% Race: NR	UFH 5000 unit bolus, 1000 units/hr infusion during hospitalization (N=210) Duration: 24–96 hr	Enoxaparin 1 mg/kg every 12 hr during hospitalization (N=315) Duration: 24–96 hr	ASA 160–325 mg daily Tirofiban 0.4 mcg/kg/min x 30 min, 0.1 mcg/kg/min infusion for 12 hr post PCI	Timing: 30 days <u>Individual</u> Total mortality Nonfatal MI Rehospitalization Length of hospital stay Major bleeding Minor bleeding	Fair
Ferguson, 2004[29] SYNERGY	RCT 467 international sites Funding: Industry Timeframe: 08/2001–12/2003 <u>Population</u> 100% UA/NSTEMI 100% early invasive strategy; Median time from admission to angiography = 21 hr Total N: 10,027 Median Age: 68 Female: 34% Race: 5% Hispanic, 6% African American, 1% Asian, 86% White	Enoxaparin 1 mg/kg every 12 hr during hospitalization 0.3 mg/kg IV prior to PCI if last dose was >8 hr before (N=4993) Duration: until PCI	UFH 60 units/kg bolus (max 5000 units), 12 units/kg/hr infusion (max 1000 units/hr) with goal aPTT 50–70 sec during hospitalization (N=4985) Duration: 48–120 hr, until PCI	95% of patients were administered ASA 63% of patients were administered clopidogrel Use of GPI was 56.5% in group 1, 58.2% in group 2	Timing: In-hospital, 48 hr, 14 days, 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Major bleeding Stroke Recurrent ischemia	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Goodman, 2003[35] INTERACT	RCT 50 sites in Canada Funding: Industry Timeframe: 09/2000–12/2001 <u>Population</u> 83% NSTEMI Angiography and PCI left to discretion of investigator 63% underwent angiography; 29% PCI Total N: 746 Median Age: 64 Female: 31% Race: NR	Enoxaparin 1 mg/kg every 12 hr during hospitalization (N=380) Duration: 48 hr	UFH 70 units/kg bolus, 15 units/kg/hr infusion with goal aPTT 50–70 sec during hospitalization (N=366) Duration: 48 hr	ASA >160 mg loading dose, 80–325 mg daily 15% received clopidogrel Eptifibatide 180 ug/kg IV double bolus, 2 ug/kg/min infusion for 48 hr	Timing: 48 hr, 30 days, 300 days, 600 days, 900 days <u>Composite</u> (secondary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Recurrent ischemia	Good
Gore, 2007[95]	Observational 111 sites in U.S., Canada, Europe, S. America, Australia/NZ Funding: NR Timeframe: 04/1999-12/2005 <u>Population</u> 100% UA/NSTEMI 19.1% of LMWH group received PCI; 23.2% of UFH group received PCI; 34.8% of crossover group received PCI; 20% of no heparins group received PCI Total N: 23172 Median Age: 66 to 67 Female: 35% Race: NR	LMWH (N=8791) UFH (N=4076) Crossover (N=7352)	No heparin (N=2953)	94% received ASA, 19% GPI, 46% Ticlopidine/clopidogrel, 3% Fibrinolytic	Timing: In-hospital <u>Composite</u> Total mortality Nonfatal MI Recurrent ischemia <u>Individual</u> Total mortality Major bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
James, 2011[96] Wallentin, 2009[82] PLATO Substudy	RCT 862 international sites Funding: Industry <u>Population</u> 16.7% UA 42.7% NSTEMI 37.6% STEMI 72% underwent early invasive strategy 64% received PCI Total N: 18,624 Median Age: 62 Female:28% Race: 92% White, 6% Asian, 1% Black	Ticagrelor 180 mg loading dose, 90 mg twice daily (N=9,333) Duration: 277 days (median)	Clopidogrel 300 mg or 600 mg loading dose, 75 mg daily (N=9,291) Duration: 277 days (median)	ASA use (97%) during hospitalization was similar between groups UFH (56%) and LMWH (51%) used during hospitalization was similar between groups GPI use was similar between groups (26%)	Timing: 30 days, 1 yr <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke (secondary) Total mortality Nonfatal MI Stroke (secondary) CV mortality Nonfatal MI Stroke Recurrent ischemia Other arterial thrombotic event <u>Individual</u> Total mortality CV mortality Nonfatal MI Stroke Stent Thrombosis Major Bleeding Minor Bleeding Adverse drug reactions	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Kovar, 2002[97]	Observational 1508 sites in U.S. Funding: Industry Timeframe: 04/1998–09/2000 <u>Population</u> % UA NR 5% NSTEMI (of 16,459) 4% PCI (of 18,901) Total N: 37,320 Mean Age: 62 to 66 Female: 30% Race: 3% Hispanic, 0.5% Black, 5.4% Asian, 85% White	Enoxaparin (N=2482)	UFH (N=34,838)	100% GPI	Timing: In-hospital <u>Composite</u> (primary) Total mortality Nonfatal MI Major bleeding Recurrent ischemia <u>Individual</u> Total mortality Nonfatal MI Major bleeding Recurrent ischemia	Fair
LaPointe, 2007[98]	Observational 332 sites in U.S. Funding: Industry Timeframe: 01/2001–12/2005 <u>Population</u> 100% UA/NSTEMI 36% PCI within 48 hr Total N: 10,687 Median Age: 66 to 78 Female: 41% Race: 82% White	Enoxaparin >10 mg above recommended dose (N=2002) Third arm: Enoxaparin >10 mg below recommended dose (N=3116)	Enoxaparin recommended dose (2 mg/kg for creatinine clearance >30 mL/min, 1 mg/kg for <30 mL/min) (N=5569)	97% ASA 55% clopidogrel 46% GPI	Timing: In-hospital <u>Individual</u> Total mortality Major bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Li, 2012[99] KAMIR	Observational 41 sites in Asia Funding: Other Timeframe: 11/2005-12/2007 <u>Population</u> 100% NSTEMI Total N: 2,397 Mean Age: 64 to 68 Female: 32% Race: NR	Enoxaparin 1mg/kg twice daily (N=1,178) Duration: 3-5 days	UFH 24,000 units/day (N=1,219) Duration: 48 hr	ASA 100 mg daily Clopidogrel 75 mg daily	Timing: In-hospital, 8 mo <u>Composite</u> (secondary) Total mortality CV mortality Repeat revascularization <u>Individual</u> Total mortality Nonfatal MI CV mortality Major bleeding Minor bleeding	Good
Malhotra, 2001[100] ESCAPEU	RCT Single site in Asia Funding: NR Timeframe: 08/1998–09/1999 <u>Population</u> 95% ACS Total N: 98 Mean Age: 59 to 61 Female: 34% Race: NR	UFH 70 units/kg bolus, infusion during hospitalization, adjusted for therapeutic aPTT (N=42) Duration: 72 hr	Enoxaparin 1 mg/kg every 12 hr during hospitalization (N=51) Duration: 72 hr	ASA 162.5 mg daily	Timing: In-hospital <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization Recurrent angina <u>Individual</u> Total mortality Recurrent angina Length of hospital stay	Fair
Mehta, 2005[54] ASPIRE	RCT 22 sites in U.S., Canada, Europe Funding: Industry Timeframe: 06/2003–11/2003 <u>Population</u> 79% UA/NSTEMI 1% STEMI 20% Stable angina Total N: 350 Mean Age: 62 to 64 Female: 23% Race: NR	UFH 100 units/kg IV bolus (65 units/kg if GPI intended) at time of PCI (N=117) Duration: terminated at end of PCI	Fondaparinux 2.5 mg (low dose) (N=118) or 5.0 mg (high dose) (N=115) IV at time of PCI Duration: terminated at end of PCI	ASA Clopidogrel (pre-PCI) = 88%. Clopidogrel (>3 hr pre-PCI)=35% Use of GPI was 56% in UFH group, and 59% in both fondaparinux groups	Timing: 48 hr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization Bailout GPI Use <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Momtahen, 2009[57]	RCT Setting: NR Funding: NR Timeframe: 02/2006–NR <u>Population</u> 100% UA/NSTEMI 76% vs. 66% PCI in Eptifibatide and Placebo groups Total N: 196 Mean Age: 51 to 55 Female: 43% Race: NR	Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion at hospital admission (N=98) Duration: 72 hr	Placebo (N=98)	ASA 160 mg daily All patients received clopidogrel (dose and timing NR) UFH 5000 unit bolus, infusion to achieve therapeutic aPTT	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Fair
Okmen, 2003[101]	RCT Single site in Europe Funding: NR Timeframe: NR <u>Population</u> 61% UA 39% NSTEMI No PCI Total N: 83 Mean Age: 55 to 57 Female: 25% Race: NR	Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion at hospital admission (N=41) Duration: at least 48 hr	No tirofiban (N=42)	ASA 325 mg loading dose, 100–300 mg daily UFH 5000 unit bolus, infusion to maintain therapeutic aPTT for >48 hr	Timing: In-hospital <u>Composite</u> (secondary) Total mortality Nonfatal MI Revascularization Refractory angina <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding Recurrent angina	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Roe, 2012[102]	RCT 966 international sites Funding: Industry Timeframe: 6/2008-9/2011 <u>Population</u> 100% UA/NSTEMI Total N: 7243 Median Age: 62 Female: 36% Race: NR	Prasugrel 30 mg loading dose, 10 mg daily (N=3620) Duration: up to 30 months	Clopidogrel 300 mg loading dose, 75 mg daily (N=3623) Duration: up to 30 months	aspirin recommended at a daily dose of 100mg or less	Timing: 17 mo <u>Composite</u> (primary) Cardiovascular mortality Nonfatal MI Stroke (any kind) (secondary) Cardiovascular mortality Nonfatal MI (secondary) Total mortality Nonfatal MI Stroke (any kind) <u>Individual</u> Rehospitalization Cardiovascular mortality Nonfatal MI Stroke (any kind) Total mortality Major bleeding Major or minor bleed	Good
Schiele, 2010[103]	Observational 10 sites in Europe Funding: NR Timeframe: 01/2006–12/2007 <u>Population</u> 8% UA 55% NSTEMI 75% PCI Total N: 2,874 Mean Age: 65 to 76 Female: 33% Race: NR	Enoxaparin 1mg/kg every 12 hr (N=1694) Third treatment arm: Fondaparinux 2.5 mg/day (N=426) Duration: at least 2 days	UFH 60 units/kg bolus (max 5000 units), 12–15 units/kg/hr maintenance (max 1000 units/hr) to aPTT 50-75 sec (N=754) Duration: at least 2 days	99% ASA 97% clopidogrel 54% GPI for NSTEMI patients	Timing: In-hospital, 30 days <u>Individual</u> Total mortality Major bleeding Transfusion	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Simoons, 2001[104] GUSTO-IV	RCT 458 sites in 24 countries Funding: Industry Timeframe: 07/1998–04/2000 <u>Population</u> 72% UA 28% NSTEMI 19% underwent PCI (Angiography was not permitted within ~60 hr of study drug) Total N: 7800 Mean Age: 65 Female: 38% Race: NR	Abciximab 0.25 mg/kg bolus, 0.125 mg/kg/min maintenance (Group 2 N=2590, Group 3 N=2612) Duration: 24 hr (Group 2) and 48 hr (Group 3)	Placebo (N=2598)	UFH 70 units/kg bolus, 10 units/kg/hr to goal aPTT 50–70 sec Duration: 48 hr after starting study drug	Timing: in-hospital, 48 hr, 7 days, 30 days, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Major bleeding Transfusion	Good
Singh, 2006[71]	Observational 407 sites in U.S. Funding: Industry Timeframe: 01/2002–06/2003 <u>Population</u> 100% UA/NSTEMI 65% PCI Total N: 11,358 Median Age: 62 to 63 Female: 33% Race: NR	LMWH (N=4477)	UFH (N=6881)	58% clopidogrel 95% ASA	Timing: In-hospital <u>Composite</u> Total mortality Nonfatal MI <u>Individual</u> Total mortality Transfusion	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Song, 2007[105]	RCT 3 sites in Asia Funding: NR Timeframe: NR <u>Population</u> 100% UA/NSTEMI No PCI Total N: 204 Mean Age: NR Female: NR Race: NR	Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion at hospital admission (N=101) Duration: 2–5 days	Placebo (N=99)	ASA 50 mg daily UFH (1) Placebo group: 5000 unit bolus with 1000 units/hr infusion (2)Tirofiban group: 0.4 mcg/kg/min for 30 min, 0.1 mcg/kg/min infusion	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Refractory ischemia <u>Individual</u> Total mortality Nonfatal MI Refractory ischemia	Good
Spinler, 2003[106]	Observational Setting: NR Funding: NR Timeframe: 10/1994–03/1998 <u>Population</u> 100% UA/NSTEMI PCI NR Total N: 7,081 Mean Age: NR Female: NR Race: NR	Enoxaparin 1 mg/kg (N=NR)	UFH Goal aPTT of 55–85 sec (N=NR)	ASA, IV anticoagulants, oral anticoagulants, SC anticoagulants NR	Timing: 43 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Any bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Stone, 2006[73] ACUITY	RCT 450 international sites Funding: Industry Timeframe: 08/2003–12/2005 <u>Population</u> 41% UA 59% NSTEMI Median time from admission to angiography = 20 hr 56% PCI 65% DES Total N: 13,819 Median Age: 63 Female: 30% Race: NR	Bivalirudin 0.1 mg/kg bolus, 0.25 mg/kg/hr infusion (N=4612) Duration: terminated at end of procedure	UFH 60 units/kg bolus, 12 units/kg/hr infusion at hospital admission, goal ACT 200–250 sec during PCI (48% of nonbivalirudin-treated patients received UFH) Or Enoxaparin 1 mg/kg SC twice daily at hospital admission, 0.3 mg/kg IV bolus if needed at time of PCI (47% of nonbivalirudin-treated patients received LMWH) + GPI use was randomly assigned to “upstream” or deferred use at time of PCI (N=4603) Third treatment arm: Bivalirudin + GPI (N=4604) Duration: terminated at the end of procedure	ASA 300–325 mg orally or 250–500 mg IV during hospitalization, 75–325 mg orally daily after hospitalization Clopidogrel 300 mg loading dose was recommended (no later than 2 hr after PCI) but clopidogrel dose and timing left to discretion of operator (64% of patients received pretreatment) 75 mg daily x 1 yr	Timing: 30 days, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI Revascularization Major bleeding <u>Individual</u> Total mortality Nonfatal MI Revascularization Major Bleeding Minor Bleeding Thrombocytopenia Stent thrombosis Length of hospital stay	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Stone, 2007[74] ACUITY TIMING* *This population is a subset of ACUITY[73]	RCT 450 international sites Funding: Industry Timeframe: 08/2003–12/2005 <u>Population</u> 59% NSTEMI 56% PCI All patients underwent early invasive treatment 56% PCI Total N: 9207 Median Age: 63 Female: 30% Race: NR	Upstream GPI (N=4605) Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion OR Tirofiban 0.1 mg/kg bolus, 0.1 mcg/kg/min infusion Duration: 12–18 hr after PCI	In-lab GPI (N=4602) Eptifibatide 180 mcg/kg double bolus, 2 mcg/kg/min infusion OR Abciximab 0.25 mg/kg bolus, 0.125 mcg/kg/min infusion Duration: 12 hr for abciximab, 12–18 hr for eptifibatide after PCI	ASA 300–325 mg orally or 250–500 mg IV loading dose, 75–325 mg daily indefinitely Clopidogrel >300 mg recommended but left to discretion of investigator, occurred within 2 hr after PCI (64% had upstream use); 75 mg daily UFH goal ACT of 200–250 sec during PCI	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI Revascularization Major bleeding (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding	Good
Van den Brand, 1995[107]	RCT 6 sites in Europe Funding: NR Timeframe: 09/1991–07/1992 <u>Population</u> 100% UA 100% PCI PCI delayed for 18–24 hr after angiography Total N: 60 Median Age: 60 to 61 Female: 27% Race: NR	Abciximab 0.25 mg/kg bolus, 10 mcg/min infusion after initial angiogram (N=30) Duration: 1 hr after PCI	Placebo (N=30)	ASA 250 mg loading dose, minimum of 80 mg daily UFH infusion with therapeutic aPTT 2–2.5x control value	Timing: 30 days <u>Composite</u> (primary) Total mortality Nonfatal MI Recurrent ischemia <u>Individual</u> Total mortality Nonfatal MI Recurrent ischemia	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Yusuf, 2006[88] OASIS-5	RCT 576 international sites Funding: Industry Timeframe: NR <u>Population</u> 45% UA 55% NSTEMI 63% of patients underwent angiography during hospitalization 31% PCI Total N: 20,078 Mean Age: 67 Female: 38% Race: NR	Enoxaparin 1 mg/kg SC every 12 hr at hospital admission, additional dose of UFH if >6 hr since last dose during PCI (N=10,021) Duration: 2–8 days	Fondaparinux 2.5 mg SC daily at hospital admission, additional dose of IV fondaparinux based on timing of last dose and intended use of GPI at time of PCI (N=10,057) Duration: hospital discharge or 8 days	ASA and clopidogrel recommended 6 hr pre PCI Use of GPI not specified	Timing: 9 days, 30 days, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Refractory ischemia (secondary) Total mortality Nonfatal MI (secondary) Total mortality Nonfatal MI Refractory ischemia Major bleeding <u>Individual</u> Total mortality Nonfatal MI Stroke Refractory ischemia Major bleeding	Good

Abbreviations: ACS=acute coronary syndrome; ACT=activated clotting time; aPTT=activated partial thromboplastin time; ASA=aspirin; CV=cardiovascular; GPI=glycoprotein IIb/IIIa inhibitor; hr/h=hour/hours; IV=intravenous; kg=kilogram/kilograms; LMWH=low molecular weight heparin; max=maximum; mcg=microgram/micrograms; mg=milligram/milligrams; MI=myocardial infarction; min=minute/minutes; mL=milliliter/milliliters; mo=month/months; N=number of patients; NR=not reported; NSTEMI=non-ST elevation myocardial infarction; NZ=New Zealand; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SC=subcutaneous; sec=second/seconds; STEMI=ST elevation myocardial infarction; UA=unstable angina; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin; ug=microgram; U.S./US=United States; yr=year/years

Table F-3. Study characteristics table for KQ 3 comparisons—postdischarge treatment for UA/NSTEMI

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Alexander, 2008[108] CRUSADE	Observational 550 sites in U.S. Funding: Industry Timeframe: 01/2001–12/2005 <u>Population</u> 100% NSTEMI 27% PCI Total N: 93,045 Median Age: 70 to 71 Female: 42% Race: 79% White	Clopidogrel (N=35,880)	No clopidogrel (N=57,165)	93% ASA 39% UFH 29% GPI	Timing: In-hospital <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Nonfatal MI Stroke Major bleeding Transfusion	Fair
Aronow, 2008[109] BRAVO	Observational 690 sites in U.S., Canada, Europe, Asia, Australia/NZ Other: 23 countries Funding: Industry Timeframe: 05/1999–06/2000 <u>Population</u> N= 954 UA/NSTEMI N=465 STEMI N=347 Stable CAD Total N: 4,589 Median Age: 62 to 63 Female: 29% Race: White 93%	ASA <162mg/day Maintenance dose: 100 mg (N=2,368)	ASA >162 mg/day Maintenance dose: 325 mg (N=2,221)	Placebo/control	Timing: 1 yr (366 days) <u>Composite</u> (secondary) Total mortality Nonfatal MI Stroke (secondary) Total mortality Nonfatal MI Stroke Revascularization Rehospitalization <u>Individual</u> Total mortality Nonfatal MI Anemia Stroke Rehospitalization Revascularization Major bleeding Any bleeding Transfusion Intracranial hemorrhage	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Banerjee, 2011[110]	Observational NR sites in U.S. Funding: NR Timeframe: 01/2003–12/2008 <u>Population</u> 89% ACS Total N: 23,200 Mean Age: 64 to 65 Female: 1.7% Race: Hispanic 4%, Black 6%, White 54%, Other 37%	No PPI (N=3,678)	PPI (N=867)	Clopidogrel All patients received clopidogrel	Timing: 1 yr, 6 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Revascularization	Good
Barada, 2008[111]	Observational Single site in Africa Funding: None Timeframe: 09/2001–11/2005 <u>Population:</u> NR Total N: 1,023 Mean Age: 63 to 64 Female: 26% Race: NR	No PPI (N=705)	PPI (N=318)	Clopidogrel, ASA	Timing: In-hospital <u>Individual</u> UGI bleeding	Poor
Bernardi, 2007[112] RACS	RCT 18 sites in S. America Funding: NR Timeframe: 04/2002–08/2003 <u>Population</u> 15% STEMI 72% ACS Total N: 1,004 Mean Age:60 to 61 Female: 20% Race: NR	Dual therapy clopidogrel 30 days + ASA 300 mg loading, 75 mg maintenance (N=502)	Dual Therapy clopidogrel 180 days + ASA 300 mg loading, 75 mg maintenance (N=502)	GPIs ASA dose varied by physician, 75–325mg/d GPI was administered to 17% of patients by physician preference (tirofiban 32%, eptifibatide 17%, abciximab 50%) homogeneous distribution between groups	Timing: 30 days, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Stroke (secondary) Total mortality Nonfatal MI Stroke Revascularization <u>Individual</u> Total mortality	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Bhatt, 2010[113] COGENT	RCT 393 sites location NR Funding: Industry Timeframe: Jan2008-Dec2008 <u>Population</u> NR Total N: 3,761 Median Age: 69 Female: 32% Race: NR	Omeprazole 20 mg (N=1,876) Duration: 12 mo	Placebo (N=1,885)	ASA 75-325 mg Clopidogrel 75 mg	Timing: 6 mo <u>Composite:</u> (primary) CV mortality Nonfatal MI Stroke Revascularization <u>Individual</u> Upper GI events Overt gastroduodenal or upper GI bleeding Nonfatal MI Revascularization Stroke Total mortality CV mortality	Good
Bhurke, 2012[114]	Observational Multiple sites in U.S. Funding: Government Timeframe: 1/2001-12/2008 <u>Population</u> 100% ACS Total N: 5348 Mean Age: 61 Female: 30 % Race: NR	Clopidogrel + PPI (N=2674)	Clopidogrel (N=2674)	NR	Timing: 1 yr <u>Composite</u> (primary) Nonfatal MI Stents Non-stenting revasc Intermediate coronary syndrome <u>Individual</u> Nonfatal MI Stents	Fair
Bonde, 2010[115]	Observational Multiple sites in Europe Timeframe: 1/2000-12/2005 <u>Population</u> 100% ACS Total N: 11,142 Mean Age: 70 Female: 40% Race: NR	Placebo	Clopidogrel	Concomitant pharmacotherapy (range in 4 groups Clopidogrel Y, N and HF Y, N) Beta-blockers (75.7-83.7%) p=0.89 ACE inhibitors (59.3-38.9%) p=0.58 Statins (62.7-82.3%) p=0.55 Glucose lowering drugs (9.0-21.3%) p= 0.18 Vitamin K antagonist (4.3-8.8%) p=0.40	Timing: 2 yr <u>Individual</u> Total mortality	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Buresly, 2005[116]	Observational Single site in Canada Funding: Government Timeframe: 01/1996–03/1996 <u>Population:</u> NR Total N: 21,443 Median Age 74 Female: 43% Race: NR	ASA (N=656) Warfarin (N=195)	ASA (N=34) ASA (N=20)	Warfarin, Thienopyridine	Timing: 2 yr <u>Composite</u> (primary) Major bleeding Minor bleeding	Good
Butler, 2009[117]	Observational 12 sites in Australia/NZ Funding: NR Timeframe: 04/2004–03/2007 <u>Population</u> N= 418 STEMI N=1,393 ACS Total N: 2,980 Mean Age: 64 to 69 Female: 27% Race: NR	(1) DES with clopidogrel intended duration ≤3 mo (N=152) DES with clopidogrel intended duration 6 mo (N=495) (2) BMS with clopidogrel intended duration ≤3 mo (N=287) BMS with clopidogrel intended duration 6 mo (N=340)	DES with clopidogrel intended duration ≥12 mo (N=1,022) BMS with clopidogrel intended duration ≥12 mo (N=684)	ASA, GPIs	Timing; 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Major bleeding Nonfatal MI Revascularization Propensity score Equality of survival Discharged alive Cumulative hazard of MACE for DES patients	Fair
Charlot, 2010[118]	Observational NR sites in Europe Funding: Private foundation Timeframe: 2000–2006 <u>Population:</u> NR Total N: 56,406 Mean Age: 68.5 Female: 41% Race: NR	No PPI (N=22,815) PPI (N=8,889)	No PPI (N=17,949) PPI (N=6,753)	No clopidogrel Clopidogrel	Timing: 1 yr <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke <u>Individual</u> Total mortality CV mortality Nonfatal MI Stroke	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Charlot, 2011[119]	Observational NR sites in Europe Funding: Private Foundation Timeframe: 1997–2006 <u>Population</u> N= 19,925 ACS Total N: 49,452 Mean Age: 64 to 73 Female: 76% Race: NR	No PPI (N=15,619)	PPI (N=4,306)	ASA 75 mg once a days	Timing: 1 yr <u>Composite</u> (primary) CV mortality Stroke Rehospitalization <u>Individual</u> Total mortality CV mortality Nonfatal MI Stroke	Good
Charlot, 2012[120]	Observational Multiple sites in Europe Funding: Private Foundation Timeframe: 2004-2009 <u>Population</u> 67% NSTEMI 19% STEMI Total N: 29,268 Mean Age: 67 Female: 33% Race: NR	Clopidogrel up to 90 days	Clopidogrel > 90 days	Intervention: 78.3% of patients were on ASA Comparator: 88.3% of patients on ASA	Timing: 3 mo, 6 mo, 9 mo, 1 yr, 15 mo <u>Composite</u> (primary) Total mortality Nonfatal MI	Fair
Cheng, 2010[121] T-ACCORD Registry	Observational 27 sites in Asia Funding: NR Timeframe: 04/2004–12/2006 <u>Population</u> N=905 UA N=426 NSTEMI Total N: 1,331 Mean Age: 63 to 69 Female: 30% Race: NR	ASA (N=225) 3rd treatment arm: Clopidogrel (N=250)	Dual therapy (N=856)	GPIs	Timing: 1 yr <u>Individual</u> Survival rate	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Chitose, 2011[122] KICS	Observational 16 sites in Asia Funding: Private foundation Timeframe: 06/2008–03/2009 <u>Population</u> N=621 ACS Total N: 1,270 Mean Age: 69 to 72 Female:30 % Race: Asian 100%	PPI (N=171)	No PPI (N=450)	Clopidogrel, ASA ASA 100 mg/day thienopyridine agent (75 mg/day clopidogrel or 200 mg/day ticlopidine)	Timing: 18 mo <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke <u>Individual</u> CV mortality Nonfatal MI Stroke GI event	Good
Evanchan, 2010[123]	Observational Single site in U.S. Funding: NR Timeframe: 01/2003–01/2008 <u>Population:</u> NR Total N: 5,794 Mean Age: 63 to 64 Female: NR Race: NR	PPI (N=1,369)	No PPI (N=4,425)	Clopidogrel at discharge	Timing: 1 yr <u>Individual</u> Nonfatal MI	Good
Fosbol, 2012[124]	Observational 514 sites in U.S. Funding: Private foundation, Industry Timeframe: 1/2003-12/2006 <u>Population</u> 100% UA/NSTEMI Total N: 7619 Median Age: 80 Female: 48% Race: NR	Aspirin (N=2213) ASA + clopidogrel (N=2841)	Warfarin (N=563) ASA + warfarin (N=1271) ASA + clopidogrel + warfarin (N=731)	NR	Timing: 30 days, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Stroke (any kind) <u>Individual</u> Major bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Gao, 2009[125]	RCT 2 sites in Asia Funding: NR Timeframe: Jan/2003-Dec/2007 <u>Population:</u> NR Total N: 237 Mean Age: 58 Female: 47% Race: NR	Omeprazole 40 mg loading, 20 mg maintenance (N=114)	Placebo (N=123)	NR	Timing: 14 days <u>Individual</u> Total mortality Upper GI bleeding	Poor
Gaspar, 2010[126]	Observational Single site in Europe Funding: NR Timeframe: 12/2004–03/2008 <u>Population</u> 65% UA/NSTEMI 35% STEMI Total N: 876 Mean Age: 61 to 65 Female: 24% Race: NR	PPI (N=274)	No PPI (N=528)	Clopidogrel, ASA, GPIs	Timing: 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI UA <u>Individual</u> Total mortality	Good
Goodman, 2012[127] PLATO	Observational 43 sites in U.S., Canada, UK, Europe, S. America, C. America, Asia, Africa, Australia/NZ Funding: Industry Timeframe: 10/2006–07/2008 <u>Population</u> N= 3111 UA N=7950 NSTEMI N=7023 STEMI Total N: 18,624 Median Age: 62 to 63 Female: 28% Race: Black 1%, Asian 6%, White 92%	PPI (N=6,538)	No PPI (N=12,062)	Clopidogrel (N=9291; 300-mg loading dose, 75-mg daily maintenance dose) Clopidogrel (N=9291; 300-mg loading dose, 75-mg daily maintenance dose) Ticagrelor (N=9333; 180-mg loading dose, 90-mg twice daily maintenance dose) Ticagrelor (N=9333; 180-mg loading dose, 90-mg twice daily maintenance dose)	Timing; 1 yr <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke (secondary) CV mortality Nonfatal MI <u>Individual</u> Total mortality CV mortality Nonfatal MI Major bleeding Stent thrombosis	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Gupta, 2010[128]	Observational Single site in U.S. Funding: NR Timeframe: 01/2003–08/2004 <u>Population:</u> NR Total N: 315 Mean Age: 62 Female: NR Race: NR	PPI (N=72)	No PPI (N=243)	Clopidogrel 75 mg/day	Timing: 4 yr <u>Composite</u> (primary) Total mortality Nonfatal MI TVF <u>Individual</u> Total mortality TLR TVF	Fair
Gwon, 2012[129]	RCT 19 sites in Asia Funding: Government, Industry Timeframe: 6/2008-7/2009 <u>Population</u> 48% UA/NSTEMI 3% STEMI Total N: 1443 Mean Age: 62 to 63 Female: 35% Race: NR	ASA + Clopidogrel (N=722) Duration: 6 mo	ASA + Clopidogrel (N=721) Duration: 12 mo	Unfractionated heparin was administered throughout the procedure to maintain an activated clotting time of □250 seconds. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. After the procedure, all patients were recommended to receive optimal pharmacological therapy, including statins, □-blockers, or angiotensin-converting enzyme inhibitors at the discretion of the responsible clinicians. Any P2Y12 receptor antagonist other than clopidogrel was not used.	Timing: 1 yr <u>Composite</u> (primary) Cardiovascular mortality Nonfatal MI TVR (secondary) Total mortality Nonfatal MI (secondary) Total mortality Nonfatal MI Stroke (any kind) Revascularization (secondary) Total mortality Nonfatal MI Stroke (any kind) Stent thrombosis Major bleeding <u>Individual</u> Total mortality Cardiovascular mortality Nonfatal MI Revascularization Stent thrombosis Major bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Harjai, 2009[130]	Observational Single site in U.S. Funding: Entirely funded by the Guthrie Health Foundation Timeframe: 04/2001–12/2006 <u>Population</u> 16% NSTEMI 15% STEMI 35% ACS Total N: 1,859 Mean Age: 64 Female: 31% Race: NR	ASA 81–325 mg/day + clopidogrel 75 mg/day>12 mo (whole cohort any stent) (N=918) ASA 81–325 mg/day + clopidogrel 75 mg/day ≤ 12 mo (whole cohort any stent) (N=941)	DES subset of ASA 81–325 mg/day + clopidogrel 75 mg/day>12 mo (whole cohort any stent) (N=1,024) DES subset of ASA 81–325 mg/day + clopidogrel 75 mg/day ≤ 12 mo (whole cohort any stent) (N=588)	Clopidogrel, ASA, GPIs	Timing: 1775 days, 1080 days, 1287 days, 1226 days, 1 yr, 2 yr, 3 yr, 4 yr, 5 yr <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Stent thrombosis	Good
Harjai, 2011[131] GHOST	Observational Single site in U.S. Funding: NR Timeframe: 07/2001–12/2007 <u>Population</u> 40% NSTEMI Total N: 2820 Mean Age: 64 to 67 Female: 31% Race: NR	ASA Maintenance dose: 81 mg/day (N=313)	ASA Maintenance dose: 162-325 mg/day (N=2,507)	Clopidogrel Discharge ASA dose	Timing: 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Major bleeding	Fair
Harjai, 2011[132]	Observational NR sites in U.S. Funding: NR Timeframe: 07/2001–12/2007 <u>Population</u> 39% NSTEMI Total N: 2,653 Mean Age: 64 to 66 Female: 31% Race: NR	PPI (N=1,902)	No PPI (N=751)	ASA.	Timing: 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization Stent thrombosis <u>Individual</u> Total mortality Nonfatal MI Revascularization Stent thrombosis Major bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Ho, 2007[133]	Observational 127 sites in U.S. Funding: Government Timeframe: 10/2003–09/2004 <u>Population</u> N= 68 UA N=1387 ACS Total N: 1,455 Mean Age: 64 Female: 2% Race: White 54%	Patients discontinued clopidogrel (N=variable) Duration: ongoing	Patients continued clopidogrel (N=variable) Duration: patients discontinued	GPIs	Timing: 6 mo, 299 days, 1 yr, 18 mo, 538 days <u>Composite</u> (secondary) Total mortality Rehospitalization for acute MI <u>Individual</u> Total mortality Rehospitalization for acute MI Nonfatal MI	Fair
Ho, 2009[134]	Observational 127 sites in U.S. Funding: Government Timeframe: 10/2003–12/2006 <u>Population</u> Total N: 8,790 Mean Age: 66 to 68 Female: 1% Race: NR	PPI (N=5,244)	No PPI (N=2,961)	Clopidogrel, ASA	Timing: 18 mo <u>Composite</u> (primary) Total mortality Rehospitalization <u>Individual</u> Rehospitalization Revascularization Total mortality	Good
Hsiao, 2011[135]	Observational NR sites in Asia Funding: Private Foundation Timeframe: 01/2001–12/2006 <u>Population</u> N= 9753 ACS Total N: 9,753 Mean Age: 62 to 66 Female: 23% Race: NR	PPI (N=622)	No PPI (N=9,131)	Clopidogrel, ASA	Timing: 6 mo <u>Individual</u> Rehospitalization	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Jang, 2011[136]	Observational 5 sites in Asia Funding: NR Timeframe: 01/2005–12/2005 <u>Population</u> 21% UA 17% NSTEMI 19% STEMI 43% Stable CAD Total N: 362 Mean Age: 68 Female: 32% Race: NR	Warfarin (N=84)	Placebo (N=278)	Clopidogrel, ASA	Timing: 3 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Total mortality Nonfatal MI Stroke Revascularization Major bleeding Minor bleeding <u>Individual</u> Total mortality Nonfatal MI Revascularization Stent thrombosis Major bleeding Minor bleeding Stroke	Poor
Juurlink, 2009[137]	Observational NR sites in Canada Funding: Government, Private Foundation Timeframe: Apr 2002-Dec 2007 <u>Population:</u> NR Total N: 2791 Median Age: 77 Female: 46% Race: NR	Clopidogrel + nonfatal MI in 90 days (N=734)	Clopidogrel (N=2,057)	PPI (intervention 39%, comparator 36%)	Timing: 3 mo, 1 yr <u>Individual</u> Total mortality Nonfatal MI	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Karjalainen, 2007[138]	Observational 3 sites in Europe Funding: Private foundation Timeframe: 2003–2004 <u>Population</u> 18% UA 24% NSTEMI 12% STEMI Total N: 478 Mean Age: 70 Female: 26% Race: NR	Warfarin (N=239)	Placebo (N=239)	Clopidogrel, ASA	Timing: Discharge, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization Stent thrombosis (secondary) Stroke Major bleeding <u>Individual</u> Stroke Major bleeding Total mortality Nonfatal MI Revascularization Stent thrombosis	Good
Konstantino, 2006[139]	Observational NR sites in Israel Funding: NR Timeframe: 2000–2004 <u>Population</u> 100% ACS 42% NSTEMI 56% STEMI Total N: 2737 Mean Age: 61 to 64 Female: 21% Race: NR	Dual therapy ASA + ticlopidine/ clopidogrel (N=2,661)	Triple therapy ASA, ticlopidine/clopidogrel +warfarin (N=76)	Clopidogrel, ASA	Timing: In-hospital, 30 days, 6 mo <u>Individual</u> Nonfatal MI Stroke Major bleeding Rehospitalization Total mortality	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Kreutz, 2010[140]	Observational NR sites in Europe Funding: NR Timeframe: 10/2005–09/2006 Population: NR Total N: 16,690 Mean Age: 65 to 68 Female: 31% Race: NR	PPI (N=6,828)	No PPI (N=9,862)	Clopidogrel 75 mg/day	Timing: 1 yr Composite (primary) CV mortality Nonfatal MI Stroke Rehospitalization Individual Stroke Nonfatal MI Revascularization CV mortality	Good
Lamberts, 2013[141]	Observational Denmark Funding: private foundation Timeframe: 1/2001–12/2009 Population: MI 90% PCI 10% Total N: 12,165 Mean Age: 75.6 ±10.3 Female: 29% Race: NR	DAPT (ASA + clopidogrel) (N=3,590)	TT (ASA + clopidogrel + oral anticoagulant) (N=1,896)	NR	Timing: 1 yr Composite Nonfatal MI Total mortality Individual Total mortality Stroke Major bleeding	Good
Lim, 2005[142]	Observational 94 sites in U.S., Canada, UK, Europe, S. America, Australia/NZ Funding: Industry Timeframe: NR Population: 55% UA 45% NSTEMI Total N: 6,239 Mean Age: 67 to 68 Female: 38% Race: NR	ASA (N=4,625)	ASA + clopidogrel (N=1,614)	NR	Timing: 6 mo Individual Total mortality Rehospitalization Revascularization Stroke	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Lopes, 2010[143]	Observational Setting: NR Funding: NR Timeframe: 1995–2003 <u>Population</u> N= 917 NSTEMI Total N: 23,208 Median Age: 69 Female: 32% Race: Black 4%, White 91%, Other 5%	Warfarin (N=124)	Placebo (N=793)	Clopidogrel, ASA ASA 62.9%, clopidogrel 10.5% Clopidogrel, ASA ASA 89.0%, clopidogrel 26.4%	Timing: In-hospital, 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Major bleeding Stroke	Good
Maegdefessel, 2008[144]	Observational Single site in Europe Funding: NR Timeframe: 1999–2004 <u>Population</u> 40% UA 32% NSTEMI 14% STEMI 14% Stable CAD Total N: 159 Mean Age: 70.3 Female: 28% Race: White 100%	Clopidogrel (N=103)	Clopidogrel (N=42)	ASA, Enoxaparin, Warfarin	Timing: 1.4 yr <u>Individual</u> Major bleeding Nonfatal MI Stroke CV mortality	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Mahaffey, 2011[145] Wallentin, 2009[82] PLATO	RCT 862 international sites Funding: Industry <u>Population</u> 16.7% UA 42.7% NSTEMI 37.6% STEMI 72% underwent early invasive strategy 64% received PCI Total N: 18,624 Median Age: 62 Female:28% Race: 92% White, 6% Asian, 1% Black	Ticagrelor 180 mg loading dose, 90 mg twice daily (N=9,333) Duration: 277 days (median)	Clopidogrel 300 mg or 600 mg loading dose, 75 mg daily (N=9,291) Duration: 277 days (median)	ASA use (97%) during hospitalization was similar between groups UFH (56%) and LMWH (51%) used during hospitalization was similar between groups GPI use was similar between groups (26%)	Timing: 30 days, 1 yr <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke (secondary) Total mortality Nonfatal MI Stroke (secondary) CV mortality Nonfatal MI Stroke Recurrent ischemia Other arterial thrombotic event <u>Individual</u> Total mortality CV mortality Nonfatal MI Stroke Stent Thrombosis Major Bleeding Minor Bleeding Adverse drug reactions	Good
Ng, 2008[146]	Observational 38 sites in Asia Funding: None Timeframe: 01/2002–12/2006 <u>Population</u> N= 375 UA Total N: 666 Mean Age: 72 Female: NR Race: NR	PPI (N=336)	No PPI (N=290)	Clopidogrel, ASA, enoxaparin	Timing: 7 days <u>Individual</u> GI bleeding GI bleeding/occult bleed	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Ng, 2011[147]	RCT Single site in Asia Funding: Private Foundation Timeframe: Jul 2008-Sep 2010 <u>Population</u> NR Total N: 311 Mean Age: 63 to 64 Female: 25% Race: NR	Esomeprazole 20 mg (N=163) Duration: 16 wk	Famotidine 40 mg (N=148) Duration: 16 wk	ASA 80-160 mg Clopidogrel 75 mg	Timing: 4 mo <u>Composite</u> (secondary) CV mortality Nonfatal MI Stroke (secondary) GI events Occult bleeding of unknown origin <u>Individual</u> GI events	Good
Nguyen, 2007[148] GRACE	Observational 113 sites in U.S., Europe, S. America, Australia/NZ Funding: Industry Timeframe: 04/1999–09/2006 <u>Population</u> 16% UA 23% NSTEMI 61% STEMI Total N: 800 Median Age: 64 to 66 Female: 30% Race: NR	Triple therapy ASA + thienopyridine (N=580)	Dual therapy ASA or thienopyridine (N=220)	Warfarin	Timing: In-hospital, 6 mo <u>Individual</u> Nonfatal MI Stroke CHF Major bleeding Total mortality Revascularization	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
O'Donoghue, 2009[149] TRITON-TIMI 38 * Substudy of Wiviott, 2007[84]	Observational 707 international sites Funding: Industry <u>Population</u> 74% UA/NSTEMI 26% STEMI Total N: 13,608 Median Age: 61 Female: 26% Race: 93% White	Treated with a PPI Prasugrel 60 mg loading dose, 10 mg daily (N=2272) Clopidogrel 300 mg loading dose, 75 mg daily (N=2257) Duration: 14.5 mo (median)	Not treated with a PPI Prasugrel 60 mg loading dose, 10 mg daily (N=4541) Clopidogrel 300 mg loading dose, 75 mg daily (N=4538) Duration: 14.5 mo (median)	ASA daily dose 75–162 mg daily 3% of patients received bivalirudin 55% of patients received GPIs	Timing: 3 mo, 6 mo <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke (secondary) Major bleeding Minor bleeding (secondary) Mortality MI Stroke Major bleeding <u>Individual</u> Total mortality CV mortality Nonfatal MI Stent thrombosis Major bleeding	Good
Ortolani, 2011[150]	Observational NR sites in Europe Funding: Private foundation Timeframe: 01/2008–08/2008 <u>Population</u> N= 1141 UA N=1377 NSTEMI N=1378 STEMI Total N: 3,896 Mean Age: 63 to 69 Female: 30% Race: NR	PPI (N=3,519)	No PPI (N=377)	Clopidogrel, ASA	Timing: 1 yr <u>Composite</u> (secondary) Total mortality Revascularization Rehospitalization <u>Individual</u> Rehospitalization Revascularization Total mortality	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Pekdemir, 2003[151]	RCT Single site in Turkey Funding: NR Timeframe: 06/2000–12/2001 <u>Population</u> N= 84 UA N=36 ACS N=110 Stable CAD Total N: 278 Mean Age: 55 to 58 Female: 43% Race: NR	Dual therapy 1 mo ASA 100 mg/d + clopidogrel 75 mg/d (N=140) Duration: 1 mo	Dual therapy 6 mo ASA 100 mg/d + clopidogrel 75 mg/d (N=138) Duration: 6 mo	Clopidogrel, ASA, tirofiban	Timing: 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Major bleeding Total mortality Nonfatal MI Revascularization CABG Re-PTCA Subacute stent occlusion Late stent occlusion	Fair
Persson, 2011[152] RIKS-HIA and SCAAR	Observational 20 sites in Europe Funding: Government, Private foundation Timeframe: 1997–2005 <u>Population</u> 79% UA/NSTEMI 12% STEMI 8% Stable CAD Total N: 27,972 Median Age: 56 to 59 Female: 28% Race: NR	Warfarin (N=1,183)	Placebo (N=26,789)	Clopidogrel, ASA, unfractionated heparin, low molecular weight heparins	Timing: 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Total mortality Stroke Major bleeding Any bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Peters, 2003[153] Yusuf, 2001[154] CURE	RCT 482 sites in U.S., Canada, UK, Europe, S. America, C. America, Africa, Australia/NZ Funding: Industry Timeframe: D12/1998–09/2000 <u>Population</u> N= 9414 UA N=3148 NSTEMI Total N: 12,562 Mean Age: 64 Female: 38% Race: NR	Clopidogrel Loading dose: 300 mg Maintenance dose: 75 mg daily (N=6,259)	Placebo Loading dose: 300 mg Maintenance dose: 75 mg daily (N=6,303)	ASA, unfractionated heparin, GPIs, low molecular weight heparins ASA (75 to 325mg) daily. Patients in each group were to receive open label thienopyridine following PCI	Timing: 9 mo <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke (primary) CV mortality Nonfatal MI Stroke Refractory ischemia <u>Individual</u> CV mortality Nonfatal MI Stroke Refractory ischemia Heart failure Severe ischemia Revascularization Major bleeding Minor bleeding	Good
Quinn, 2004[155] Gusto IIb and PURSUIT	Observational 373 + 726 sites in U.S., Canada, UK, Europe, Australia/NZ Funding: NR, Other: Original studies, both supported by industry Timeframe: 11/1995–01/1997 (PURSUIT) and 05/1994-10/1995 (GUSTO IIb) <u>Population:</u> NR Total N: 20,469 Median Age: 63 to 65 Female: 32% Race: White 91%	ASA Maintenance dose: <150mg (N=6,128)	ASA Maintenance dose: =>150mg (N=14,341)	Eptifibatide, Unfractionated heparin, hirudin	Timing: 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI Stroke <u>Individual</u> Total mortality Nonfatal MI Stroke	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Rassen, 2009[156]	Observational NR sites in U.S., Canada Funding: Government Timeframe: 01/2001–12/2005 <u>Population:</u> NR Total N: 18,565 Mean Age: NR Female: 20% Race: NR	PPI (N=3,996)	No PPI (N=14,569)	Clopidogrel	Timing: 6 mo <u>Composite</u> (primary) Total mortality Nonfatal MI <u>Individual</u> Nonfatal MI Total mortality Revascularization	Good
Ray, 2010[157]	Observational NR sites in U.S. Funding: Government Timeframe: 01/1999–12/2005 <u>Population:</u> NR Total N: 20,596 Mean Age: 60 to 61 Female: 50% Race: White 78%	No PPI (N=13,003)	PPI (N=7,593)	Clopidogrel	Timing: 1 yr <u>Composite</u> (primary) Total mortality CV mortality Nonfatal MI Stroke (secondary) Nonfatal MI CV mortality <u>Individual</u> CV mortality Stroke Gastroduodenal bleeding Other bleeding	Good
Ren, 2011[158]	RCT Single site in Asia Funding: NR Timeframe: NR <u>Population:</u> 100% ACS Total N: 168 Mean Age: 62 Female: 28% Race: White NR	Omeprazole 20 mg (N=86) Duration: 30 days	Placebo (N=82)	ASA 100 mg Clopidogrel 75 mg	Timing: 30 days <u>Individual</u> Slight chest pressure Occasional angina TIA Major bleeding	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Rossini, 2008[159]	Observational 3 sites in Europe Funding: NR Timeframe: 10/2005–08/2006 Population 45% UA/NSTEMI 34% STEMI 21% Stable CAD Total N: 204 Mean Age: 68 Female: 20% Race: NR	Triple therapy (N=102)	Dual therapy (N=102)	Clopidogrel 300 mg loading dose/75 mg/day, ASA 100 mg/day, warfarin	Timing: 30 days,18 mo Composite (primary) Major bleeding Minor bleeding (secondary) Total mortality Nonfatal MI Stroke Individual Major bleeding Minor bleeding	Good
Rossini, 2011[160]	Observational 2 sites in Europe Funding: NR Timeframe: NR Population 18% UA 22% NSTEMI 29% STEMI 31% Stable CAD Total N: 1346 Mean Age: 63 to 64 Female: 24% Race: NR	PPI (N=1,158)	No PPI (N=170)	ASA 100 mg/day, clopidogrel 75 mg/day, GPIs	Timing: 1 yr Composite Total mortality Nonfatal MI Stroke Rehospitalization Individual Major bleeding Minor bleeding Total mortality Stent thrombosis	Good
Roy, 2009[161]	Observational Single site in U.S. Funding: NR Timeframe: 04/2003–01/2007 Population N=1,331 UA Total N: 2889 Mean Age: 63 to 65 Female: 34% Race: NR	Patients discontinued clopidogrel (N=61)	Patients continued clopidogrel (N=2,828)	ASA 325 mg, bivalirudin (bolus of 0.75 mg/kg, followed by an intravenous infusion of 1.75 mg/kg/hr) or unfractionated heparin (bolus of 40 U/kg and additional heparin to achieve an activated clotting time of 250 to 300 seconds), platelet GPIs	Timing: 30 days, 6 mo, 1 yr Individual Stent thrombosis	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Ruiz-Nodar, 2008[162]	Observational 2 sites in Europe Funding: NR Timeframe: 01/2001–12/2006 <u>Population</u> 64% NSTEMI 20% STEMI 16% Stable CAD Total N: 426 Mean Age: 71 Female: 30% Race: NR	Warfarin (N=242)	ASA (N=184)	Clopidogrel, ASA warfarin + ASA+ clopidogrel (N= 213), coumarin +ASA (N=8), coumarin + clopidogrel (N=16), coumarin N=5	Timing: 5 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Revascularization (secondary) Stroke Major bleeding MACE <u>Individual</u> Total mortality Nonfatal MI Revascularization Major bleeding Minor bleeding	Good
Ruiz-Nodar, 2012[163]	Observational NR sites in Europe Funding: NR Timeframe: 1/2001-3/2008 <u>Population</u> 63% NSTEMI 23% STEMI Total N: 590 Mean age: 72 Female: 28.8% Race: NR	Warfarin	Non-OAC	clopidogrel 94% of the total population ASA 89.6% of total population warfarin 56.3% of total population warfarin +ASA+clop 44.6%	Timing: 1 yr <u>Composite</u> (secondary) Total mortality Nonfatal MI target vessel failure <u>Individual</u> Total mortality Major bleeding	Fair

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Sarafoff, 2010[164]	Observational 2 sites in Europe Funding: NR Timeframe: 07/2002–12/2006 <u>Population</u> N= 781 UA N=2208 Stable CAD Total N: 3408 Mean Age: 66 to 69 Female: 24% Race: NR	PPI (N=698)	No PPI (N=2,640)	Clopidogrel, ASA Clopidogrel 75 mg twice daily together with ASA 100 mg twice daily	Timing: 30 days <u>Composite</u> (secondary) Nonfatal MI Stent thrombosis <u>Individual</u> Stent thrombosis Total mortality Nonfatal MI Major bleeding	Good
Schmidt, 2012[165]	Observational NR sites in Europe Funding: Private Foundation Timeframe: 01/2002-06/2005 <u>Population</u> 30.7% UA Total N: 13,001 Mean Age: NR Female: 28% Race: NR	PPI (N=2742)	No PPI (N=10,259)	Clopidogrel 75 mg maintenance dose	Timing: In-hospital <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke Stent Thrombosis Target lesion revascularization <u>Individual</u> CV mortality Nonfatal MI Target lesion revascularization	Poor

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Schulz, 2009[166]	Observational 2 sites in Europe Funding: "No industry involvement" but does not specify source of funds Timeframe: 07/2002–12/2006 <u>Population</u> N= 1197 UA N=561 NSTEMI N=627 STEMI N=1188 ACS N=4431 Stable CAD Total N: 6,816 Mean Age: 67 Female: 24% Race: NR	Clopidogrel + ASA Loading dose: 600 mg clopidogrel + 500 mg ASA Maintenance dose: 75mg clopidogrel daily + ASA 100 mg twice daily (N=6,816)	None	Bivalirudin, abciximab, unfractionated heparin	Timing: 29 days, 181 days, 30 days, 6 mo, 1 yr, 2 yr, 3 yr, 4 yr <u>Individual</u> Stent thrombosis Hazard reduction per 1 days treatment continuation Risk of stent thrombosis within 4 yr	Fair
Sibbald, 2010[167]	Observational 247 sites location NR Funding: Industry Timeframe: 04/1999–2007 <u>Population</u> 30% UA 34% NSTEMI 36% STEMI Total N: 44,426 Median Age: 69 to 72 Female: 33% Race: NR	Nonsmoker + no early clopidogrel In-hospital (N=15,110) Nonsmoker + early clopidogrel In-hospital (N=17,167)	Smoker + no early clopidogrel In-hospital (N=4,791) Smoker + early clopidogrel In-hospital (N=7,358)	ASA, unfractionated heparin, fibrinolytics, GPIs ASA, enoxaparin, unfractionated heparin, fibrinolytics, GPIs	Timing: In-hospital <u>Composite</u> (primary) Total mortality Nonfatal MI	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Simon, 2011[168] FAST-MI	Observational 223 sites in Europe Funding: Private Foundation, Industry Timeframe: 10/2005–11/2005 <u>Population</u> NSTEMI: % unreported STEMI: % unreported UA: 0% Total N: 2744 Mean Age: 64 to 74 Female: 29.8% Race: NR	<u>Clopidogrel at 48 hrs</u> No PPI (N=900) PPI (N=1,453)	<u>No clopidogrel</u> No PPI (N=233) PPI (N=158)	Clopidogrel	Timing: In-hospital, 1 yr <u>Composite</u> Total mortality Nonfatal MI Stroke <u>Individual</u> Total mortality Nonfatal MI Stroke Major bleeding	Good
So, 2009[169]	Observational Single site in Canada Funding: NR Timeframe: 12/2003–11/2004 <u>Population</u> 52% UA/NSTEMI\ 25% STEMI 19% Stable CAD Total N: 1,840 Mean Age: 61 to 64 Female: 27% Race: NR	ASA 81 mg/d Maintenance dose: 81mg/d (N=910)	ASA 325mg/d Maintenance dose: 325mg/d (N=930)	On clopidogrel n=906 (99.56%), on coumadin n= 84 (9.23%) On clopidogrel n=922 (99.14%), on coumadin n= 28 (3.01%)	Timing: 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI (secondary) Total mortality Nonfatal MI Revascularization <u>Individual</u> Total mortality Revascularization	Fair
Steinhubl, 2002[170] CREDO	RCT 99 sites in U.S., Canada Funding: Industry Timeframe: 06/1999–04/2001 <u>Population</u> 53% UA 14% NSTEMI 33% Stable CAD Total N: 2,116 Mean Age: 62 Female: 29% Race: White 89%	Clopidogrel 300 or 600 mg loading dose, 75 mg maintenance dose (N=1,053)	Placebo loading dose, clopidogrel 75 mg maintenance dose (N=1,063)	ASA 325 mg loading dose/325 mg/d, clopidogrel 300 mg loading dose/75 mg/d	Timing: 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Stroke <u>Individual</u> Major bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Stenestrand, 2005[171] RIKS-HIA	Observational 38 sites in Europe Funding: Government, Private foundation Timeframe: 1995–2002 <u>Population</u> 29% STEMI Total N: 6275 Mean Age: 75 to 79 Female: 38% Race: NR	ASA (N=3,768)	OAC (N=1,848)	Thienopyridine ASA and/or thienopyridine	Timing: 30 days, 1 yr <u>Individual</u> Total mortality	Good
Stockl, 2010[172]	Observational NR sites in U.S. Funding: NR Timeframe: 01/2004–12/2006 <u>Population:</u> NR Total N: 2,066 Mean Age: 69 Female: 44% Race: NR	PPI (N=1,033)	No PPI (N=1,033)	Clopidogrel	Timing: 1 yr <u>Individual</u> Rehospitalization	Good
Tentzeris, 2010[173]	Observational Single site in Europe Funding: Private foundation Timeframe: 01/2003–12/2006 <u>Population</u> 45% ACS Total N: 1,210 Mean Age: 64 Female: 31% Race: NR	PPI (N=691)	No PPI (N=519)	Clopidogrel, ASA ASA (100 mg/day after a loading dose of 250 mg IV), clopidogrel (75 mg/day after a loading dose of 300 mg or 600 mg)	Timing: 1 yr <u>Composite</u> Total mortality Rehospitalization Stent thrombosis <u>Individual</u> Total mortality CV mortality Rehospitalization Stent thrombosis	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Tsai, 2011[174]	Observational NR sites in Asia Funding: NR Timeframe: Jan 2001-Dec 2006 <u>Population:</u> NR Total N: 3,580 Mean Age: 71 Female: 38% Race: NR	Clopidogrel + PPI (N=1,052) 3rd treatment arm: ASA + PPI (N=1,203)	Clopidogrel (N=1,325)	NR	Timing: 1 yr <u>Composite</u> (primary) Nonfatal MI Stroke Rehospitalization <u>Individual</u> GI events	Good
Valgimigli, 2012[175] PRODIGY	RCT 3 sites in Europe Funding: Private Foundation Timeframe: 12/2006–12/2008 <u>Population</u> N= 365 UA N=450 NSTEMI N=648 STEMI N=507 Stable CAD Total N: 2013 Mean Age: 68 Female: 23% Race: NR	Clopidogrel 300 or 600 mg loading dose, 75 mg maintenance dose (N=987) Duration: 24 mo	Clopidogrel 300 or 600 mg loading dose, clopidogrel 75 mg maintenance dose (N=983) Duration: 6 mo	ASA 160–325 mg orally or 500 mg IV as a loading dose and then 80–160 mg orally indefinitely	Timing: 2 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Stroke (secondary) Total mortality Nonfatal MI (secondary) Total mortality Stroke <u>Individual</u> Total mortality CV mortality Stroke Stent thrombosis Minor bleeding	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Valkhoff, 2011[176]	Observational Single site in Europe Funding: Private foundation Timeframe: 01/1999–12/2008 <u>Population:</u> NR Total N: 23,655 Mean Age: 65 Female: 33% Race: NR	PPI (N=NR)	No PPI (N=NR)	Clopidogrel	Timing: 1 yr <u>Individual</u> Nonfatal MI	Poor
Van Boxel, 2010[177]	Observational Multiple sites in Europe Funding: Industry Timeframe: Jan 2006-Dec 2007 <u>Population:</u> NSTEMI % unknown STEMI % unknown Total N: 18,139 Mean Age: 66 to 69 Female: 36% Race: NR	Clopidogrel + PPI (N=5,734)	Clopidogrel (N=12,405)	NR	Timing: 30 days, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Stroke UA <u>Individual</u> Nonfatal MI UA Stroke Total mortality Peptic ulcer disease	Fair
Wu, 2010[178]	Observational NR sites in Asia Funding: Government Timeframe: 07/2002–06/2005 <u>Population</u> N= 5862 ACS Total N: 6,300 Mean Age: 66 Female: NR Race: NR	PPI (N=311)	No PPI (N=5,551)	Clopidogrel	Timing: 3 mo <u>Composite</u> (primary) Total mortality Rehospitalization <u>Individual</u> Rehospitalization Revascularization Total mortality	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Yusuf, 2001[154] CURE	RCT 482 sites in U.S., Canada, UK, Europe, S. America, C. America, Africa, Australia/NZ Funding: Industry Timeframe: 12/1998–09/2000 <u>Population</u> N= 9414 UA N=3148 NSTEMI Total N: 12,562 Mean Age: 64 Female: 38% Race: NR	Clopidogrel Loading dose: 300 mg Maintenance dose: 75 mg daily (N=6,259)	Placebo Loading dose: 300 mg Maintenance dose: 75 mg daily (N=6,303)	ASA, unfractionated heparin, GPIs, low molecular weight heparins ASA (75 to 325mg) daily. Patients in each group were to receive open label thienopyridine following PCI	Timing: 9 mo <u>Composite</u> (primary) CV mortality Nonfatal MI Stroke (primary) CV mortality Nonfatal MI Stroke Refractory ischemia <u>Individual</u> CV mortality Nonfatal MI Stroke Refractory ischemia Heart failure Severe ischemia Revascularization Major bleeding Minor bleeding	Good
Zairis, 2010[179]	Observational Single site in Europe Funding: NR Timeframe: Apr 2003-Jan 2005 <u>Population</u> 37% STEMI 23% Stable angina 40% UA/NSTEMI Total N: 588 Mean Age: 62 Female: 18% Race: NR	Omeprazole (N=340)	No PPI (N=248)	ASA 100-325 mg Clopidogrel 75 mg	Timing: 1 yr <u>Composite</u> (primary) CV mortality Rehospitalization <u>Individual</u> Rehospitalization CV mortality Stent thrombosis Revascularization	Good

Study	Study Details	Intervention (N)	Comparator (N)	Cointerventions	Timing Outcomes Reported	Quality
Zeymer, 2008[180] ACOS Registry	Observational 155 sites in Europe Funding: NR Timeframe: 06/2000–12/2002 <u>Population</u> 100% NSTEMI 42% PCI Total N: 4,290 Median Age: 67 to 72 Female: 27% Race: NR	ASA + clopidogrel (N=2119)	ASA (N=2171)	NR	Timing: In-hospital, 1 yr <u>Composite</u> (primary) Total mortality Nonfatal MI Nonfatal stroke <u>Individual</u> Total mortality Nonfatal MI Stroke	Poor

Abbreviations: ACE=angiotensin converting enzyme; ACS=acute coronary syndrome; ASA=aspirin; BMS=bare metal stent; CABG=coronary artery bypass graft; CAD=coronary artery disease; CHF=congestive heart failure; CV=cardiovascular; d=day/days; DES=drug-eluting stent; GI=gastrointestinal; GPI=glycoprotein IIb/IIIa inhibitor; IV=intravenous; LMWH=low molecular weight heparin; MACE=major adverse cardiac event; mg=milligram/milligrams; MI=myocardial infarction; mo=month/months; N=number of patients; NR=not reported; NSTEMI=non-ST elevation myocardial infarction; NZ=New Zealand; OAC=oral anticoagulation; PCI=percutaneous coronary intervention; PPI=proton pump inhibitor; PTCA=percutaneous transluminal coronary angioplasty; RCT=randomized controlled trial; STEMI=ST elevation myocardial infarction; TIA=transient ischemic attack; TLR=target lesion revascularization; TVF=target vessel failure; U=unit/units; UA=unstable angina; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin; UGI=upper gastrointestinal; UK=United Kingdom; U.S./US=United States; wk=week/weeks; yr=year/years

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Appendix G. Results Tables

Key Question 1: Comparisons for Early Invasive Approach

Table G-1. Results data for upstream vs. deferred GPI: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Bhattacharya, 2010[1]	RCT Total N: 301 Good quality	Fatal MI at 7 days	GPI upstream	1/136
			GPI deferred	8/165
		Fatal MI at 14 days	GPI upstream	1/122
			GPI deferred	6/133
		Fatal MI at 30 days	GPI upstream	2/105
			GPI deferred	5/99
		Fatal MI at 3 mo	GPI upstream	2/85
			GPI deferred	2/64
		Nonfatal MI at 7 days	GPI upstream	1/136
			GPI deferred	8/165
		Nonfatal MI at 14 days	GPI upstream	2/122
			GPI deferred	9/133
		Nonfatal MI at 30 days	GPI upstream	3/105
			GPI deferred	5/99
		Nonfatal MI at 3 mo	GPI upstream	2/85
			GPI deferred	5/64
		Refractory ischemia at 7 days	GPI upstream	10/136
			GPI deferred	13/165
		Refractory ischemia at 14 days	GPI upstream	10/122
			GPI deferred	12/133
		Refractory ischemia at 30 days	GPI upstream	14/105
			GPI deferred	24/99
		Refractory ischemia at 3 mo	GPI upstream	25/85
			GPI deferred	36/64
		Death due to unknown causes at 7 days	GPI upstream	2/136
			GPI deferred	3/165
		Death due to unknown causes at 14 days	GPI upstream	1/122
			GPI deferred	1/133
		Death due to unknown causes at 30 days	GPI upstream	0/105
			GPI deferred	0/99
		Death due to unknown causes at 3 mo	GPI upstream	1/85
			GPI deferred	1/64
		Major bleeding at 7 days, 14 days, 30 days, or 3 mo	GPI upstream	0/136
			GPI deferred	0/165
Dabbous, 2008[2]	Observational Total N: 29,039 Fair quality	Total mortality	GPI upstream	153/5479
			No GPI upstream	895/23560
		Major bleeding	GPI upstream	236/5479
			No GPI upstream	495/23560
		Stroke (any kind)	GPI upstream	25/5479
			No GPI upstream	148/23560
De Servi, 2006[3]	Observational Total N: 789 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Stroke (any kind)	GPI upstream	23/241
			GPI deferred	30/548
		Total mortality at 30 days	GPI upstream	6/241
			GPI deferred	9/548
		Nonfatal MI at 30 days	GPI upstream	15/241
			GPI deferred	20/548

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Stroke (any kind) at 30 days	GPI upstream	2/241
			GPI deferred	1/548
Durand, 2007[4] PRACTICE	RCT Total N: 393 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Urgent revascularization	GPI upstream	31/196
			GPI deferred	33/197
		Secondary Composite at 6 mo: Total mortality Nonfatal MI Urgent revascularization	GPI upstream	45/196
			GPI deferred	43/197
		Total mortality at 30 days	GPI upstream	2/196
			GPI deferred	6/197
		Nonfatal MI at 30 days	GPI upstream	17/196
			GPI deferred	13/197
		Urgent revascularization at 30 days	GPI upstream	16/196
			GPI deferred	20/197
		Major bleeding at 30 days	GPI upstream	8/196
			GPI deferred	6/197
		Minor bleeding at 30 days	GPI upstream	20/196
			GPI deferred	16/197
		Total mortality at 6 mo	GPI upstream	4/196
			GPI deferred	7/197
		Nonfatal MI at 6 mo	GPI upstream	20/196
			GPI deferred	17/197
		Urgent revascularization at 6 mo	GPI upstream	28/196
			GPI deferred	27/197
Giugliano, 2009[5] EARLY ACS	RCT Total N: 9,378 Good quality	Primary Composite at 96 hr: Total mortality Nonfatal MI Revascularization Thrombotic bailout with GPI	GPI upstream	302/3443
			GPI deferred	324/3452
		Secondary Composite at 96 hr: Total mortality Nonfatal MI	GPI upstream	354/4722
			GPI deferred	390/4684
		Secondary Composite at 96 hr: Total mortality Nonfatal MI Revascularization	GPI upstream	398/4722
			GPI deferred	438/4684
		Secondary Composite at 30 days: Total mortality Nonfatal MI	GPI upstream	348/3443
			GPI deferred	406/3452
		Secondary Composite at 30 days: Total mortality Nonfatal MI Revascularization	GPI upstream	592/4722
			GPI deferred	647/4684
		Total mortality at 96 hr	GPI upstream	39/4722
			GPI deferred	40/4684
		Nonfatal MI at 96 hr	GPI upstream	332/4722
			GPI deferred	358/4684
		Revascularization at 96 hr	GPI upstream	69/4722
			GPI deferred	79/4684
		Thrombotic bailout at 96 hr	GPI upstream	58/4722
			GPI deferred	59/4684
		Major bleeding at 120 hr	GPI upstream	118/4627
			GPI deferred	83/4597
		Total mortality at 30 days	GPI upstream	134/4722

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
			GPI deferred	121/4684
		Nonfatal MI at 30 days	GPI upstream	447/4722
			GPI deferred	495/4684
		Revascularization at 30 days	GPI upstream	112/4722
			GPI deferred	138/4684
		Major bleeding at 30 days	GPI upstream	127/4627
			GPI deferred	111/4597
		Nonfatal stroke at 30 days	GPI upstream	28/4686
			GPI deferred	35/4643
		Adverse drug reactions at 30 days	GPI upstream	68/4686
			GPI deferred	60/4643
		Thrombocytopenia at 30 days	GPI upstream	16/4356
			GPI deferred	10/4348
Ivandic, 2008[6]	RCT Total N: 100 Fair quality	Secondary Composite at 319 days: CV mortality Nonfatal MI Revascularization	GPI upstream	6/50
			GPI deferred	6/50
		Major bleeding at 30 days	GPI upstream	2/50
			GPI deferred	2/50
		Minor bleeding at 30 days	GPI upstream	10/50
			GPI deferred	6/50
		CV mortality at 319 days	GPI upstream	2/50
			GPI deferred	2/50
		Nonfatal MI at 319 days	GPI upstream	2/50
			GPI deferred	1/50
		Revascularization at 319 days	GPI upstream	2/50
			GPI deferred	3/50
Kim, 2005[7]	RCT Total N: 160 Poor quality	CV mortality at 30 days	GPI upstream	0/59
			GPI deferred	1/61
		Nonfatal MI at 30 days	GPI upstream	0/59
			GPI deferred	0/61
		Revascularization at 30 days	GPI upstream	1/59
			GPI deferred	1/61
		Major bleeding at 30 days	GPI upstream	0/80
			GPI deferred	0/80
		Minor bleeding at 30 days	GPI upstream	7/80
			GPI deferred	4/80
		CV mortality at 6 mo	GPI upstream	0/59
			GPI deferred	0/61
		Nonfatal MI at 6 mo	GPI upstream	0/59
			GPI deferred	1/61
		Revascularization at 6 mo	GPI upstream	6/59
			GPI deferred	13/61
Leoncini, 2005[8] CLOTILDA	RCT Total N: 300 Poor quality	Composite at 30 days: Total mortality Nonfatal MI Rehospitalization	GPI upstream	14/150
			GPI deferred	15/150
		Total mortality at 30 days	GPI upstream	1/150
			GPI deferred	2/150
		Nonfatal MI at 30 days	GPI upstream	0/150
			GPI deferred	1/150
		Major bleeding at 30 days	GPI upstream	3/150
			GPI deferred	2/150
		Rehospitalization at 30 days	GPI upstream	1/150
			GPI deferred	1/150

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Liu, 2009[9]	RCT Total N: 160 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization	GPI upstream	3/80
			GPI deferred	5/80
		Primary Composite at 6 mo: Total mortality Nonfatal MI Revascularization	GPI upstream	10/80
			GPI deferred	13/80
		Minor bleeding in-hospital	GPI upstream	1/80
			GPI deferred	1/80
		Total mortality at 30 days	GPI upstream	1/80
			GPI deferred	0/80
		Nonfatal MI at 30 days	GPI upstream	2/80
			GPI deferred	5/80
		Revascularization at 30 days	GPI upstream	0/80
			GPI deferred	1/80
		Total mortality at 6 mo	GPI upstream	1/80
			GPI deferred	0/80
		Nonfatal MI at 6 mo	GPI upstream	9/80
			GPI deferred	11/80
		Revascularization at 6 mo	GPI upstream	2/80
			GPI deferred	5/80
		Major bleeding at 30 days	GPI upstream	2/80
			GPI deferred	1/80
Momtahen, 2009[10]	RCT Total N: 196 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization	GPI upstream	0/98
			GPI deferred	16/98
		Total mortality at 30 days	GPI upstream	0/98
			GPI deferred	2/98
		Nonfatal MI at 30 days	GPI upstream	0/98
			GPI deferred	10/98
		Revascularization at 30 days	GPI upstream	0/98
			GPI deferred	4/98
		Major bleeding at 30 days	GPI upstream	0/98
			GPI deferred	0/98
		Minor bleeding at 30 days	GPI upstream	7/98
			GPI deferred	0/98
Peterson, 2003[11]	Observational Total N: 60,770 Fair quality	Composite in hospital: Total mortality Nonfatal MI	GPI upstream	692/15379
			GPI deferred	4675/45391
		Total mortality in hospital	GPI upstream	508/15379
			GPI deferred	4358/45391
		Nonfatal MI in hospital	GPI upstream	231/15379
			GPI deferred	499/45391
		Stroke in hospital	GPI upstream	108/15379
			GPI deferred	545/45391
		Major bleeding in hospital	GPI upstream	154/15379
			GPI deferred	4312/45391

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Rasoul, 2006[12] ELISA-2	RCT Total N: 328 Fair quality	Primary composite at 30 days: Total mortality Nonfatal MI	GPI upstream	74/162
			GPI deferred	92/163
		Total mortality at 30 days	GPI upstream	1/162
			GPI deferred	1/163
		Major bleeding at 30 days	GPI upstream	20/162
			GPI deferred	16/163
		Nonfatal MI at 30 days	GPI upstream	74/162
			GPI deferred	92/163
		Stroke at 30 days	GPI upstream	0/162
			GPI deferred	0/163
Roe, 2003[13] EARLY	RCT Total N: 311 Good quality	Secondary Composite at 72 hr: Total mortality Nonfatal MI Recurrent ischemia	GPI upstream	8/153
			GPI deferred	7/158
		Total mortality at 72 hr	GPI upstream	2/153
			GPI deferred	0/158
		Nonfatal MI at 72 hr	GPI upstream	3/153
			GPI deferred	2/158
		Recurrent ischemia at 72 hr	GPI upstream	4/153
			GPI deferred	5/158
		Major bleeding at 72 hr	GPI upstream	12/153
			GPI deferred	8/158
Stone, 2007[14] ACUITY TIMING Study	RCT Total N: 9207 Good quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization	GPI upstream	326/4605
			GPI deferred	364/4602
		Secondary Composite at 30 days: Total mortality Nonfatal MI	GPI upstream	272/4605
			GPI deferred	285/4602
		Secondary Composite at 30 days: Total mortality Nonfatal MI Revascularization Major bleeding	GPI upstream	539/4605
			GPI deferred	538/4602
		Total mortality at 30 days	GPI upstream	60/4605
			GPI deferred	70/4602
		Nonfatal MI at 30 days	GPI upstream	226/4605
			GPI deferred	230/4602
		Revascularization at 30 days	GPI upstream	97/4605
			GPI deferred	129/4602
		Major bleeding at 30 days	GPI upstream	281/4605
			GPI deferred	225/4602
Tricoci, 2007[15]	Observational Total N: 30,830 Fair quality	Composite in hospital: Total mortality Nonfatal MI	GPI upstream	505/13279
			GPI deferred	755/17551
		Nonfatal MI in hospital	GPI upstream	372/13279
			GPI deferred	544/17551
		Stroke in hospital	GPI upstream	40/13279
			GPI deferred	70/17551
		Any red cell transfusion in hospital	GPI upstream	969/13279
			GPI deferred	1229/17551
		Total mortality in hospital	GPI upstream	173/13279
			GPI deferred	246/17551
		Heart failure in hospital	GPI upstream	651/13279
			GPI deferred	790/17551
		Cardiogenic shock in hospital	GPI upstream	279/13279
			GPI deferred	439/17551

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
van 't Hof, 2003[16] ELISA	RCT Total N: 220 Poor quality	Composite at 30 days: Total mortality Nonfatal MI	GPI upstream	10/109
			GPI deferred	10/111
		Nonfatal MI – PCI at 30 days	GPI upstream	4/109
			GPI deferred	3/111
		Nonfatal MI – CABG at 30 days	GPI upstream	3/109
			GPI deferred	1/111
		Total mortality at 30 days	GPI upstream	6/111
			GPI deferred	7/109
		Major bleeding at 30 days	GPI upstream	16/111
			GPI deferred	9/109

Abbreviations: CABG=coronary artery bypass grafting; CV=cardiovascular; GPI=glycoprotein IIb/IIIa inhibitor; hr/h=hour/hours; MI=myocardial infarction; mo=month/months; N=number of patients; PCI=percutaneous coronary intervention; RCT=randomized controlled trial;

Table G-2. Results data for clopidogrel loading dose 300 mg vs. 600 mg: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Abuzahra, 2008[17]	RCT Total N: 119 Fair quality	Primary Composite at 30 days: CV mortality Nonfatal MI Revascularization	Clopidogrel 300 mg LD	10/42
			Clopidogrel 600 mg LD	8/77
		CV mortality at 30 days	Clopidogrel 300 mg LD	1/42
			Clopidogrel 600 mg LD	1/77
		Nonfatal MI at 30 days	Clopidogrel 300 mg LD	7/42
			Clopidogrel 600 mg LD	6/77
		Revascularization at 30 days	Clopidogrel 300 mg LD	2/42
			Clopidogrel 600 mg LD	1/77
		Major bleeding at 30 days	Clopidogrel 300 mg LD	1/42
			Clopidogrel 600 mg LD	1/77
		Minor bleeding at 30 days	Clopidogrel 300 mg LD	4/42
			Clopidogrel 600 mg LD	3/77
Bonello, 2008[18]	Observational Total N: 4,105 Good quality	Primary composite at 30 days: Total mortality Nonfatal MI Stroke Revascularization	Clopidogrel 300 mg LD	50/959
			Clopidogrel 600 mg LD	91/3146
		Total mortality	Clopidogrel 300 mg LD	21/959
			Clopidogrel 600 mg LD	35/3146
		CV mortality	Clopidogrel 300 mg LD	12/959
			Clopidogrel 600 mg LD	22/3146
		Revascularization	Clopidogrel 300 mg LD	12/959
			Clopidogrel 600 mg LD	31/3146
		Stroke	Clopidogrel 300 mg LD	4/959
			Clopidogrel 600 mg LD	9/3146
		Nonfatal MI	Clopidogrel 300 mg LD	6/959
			Clopidogrel 600 mg LD	13/3146
		Major bleeding	Clopidogrel 300 mg LD	5/959
			Clopidogrel 600 mg LD	7/3146
Cuisset, 2006[19]	RCT Total N: 387 Fair quality	Primary Composite at 30 days: CV mortality Nonfatal stroke Recurrent ACS	Clopidogrel 300 mg LD	18/146
			Clopidogrel 600 mg LD	7/146
		CV mortality at 30 days	Clopidogrel 300 mg LD	1/146
			Clopidogrel 600 mg LD	0/146
		Nonfatal stroke at 30 days	Clopidogrel 300 mg LD	2/146
			Clopidogrel 600 mg LD	1/146
		Recurrent ACS at 30 days	Clopidogrel 300 mg LD	15/146
			Clopidogrel 600 mg LD	6/146
		Major bleeding at 30 days	Clopidogrel 300 mg LD	0/146
			Clopidogrel 600 mg LD	0/146
Di Sciascio, 2010[20] ARMYDA-4 RELOAD	RCT Total N: 647 Good quality	Primary Composite at 30 days: Total mortality Nonfatal MI TVR	Clopidogrel 600 mg LD	22/324
			Placebo	28/323
		Minor bleeding at 30 days	Clopidogrel 600 mg LD	15/252
			Placebo	15/251
		Nonfatal MI at 30 days	Clopidogrel 600 mg LD	16/252
			Placebo	22/251

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Mehta, 2010[21] CURRENT-OASIS 7	RCT Total N: 25,086 Good quality	Primary Composite at 30 days: CV mortality Nonfatal MI Stroke	Clopidogrel 300 mg LD	553/12566
			Clopidogrel 600 mg LD	526/12520
		Secondary Composite at 30 days: CV mortality Nonfatal MI Nonfatal stroke Recurrent ischemia	Clopidogrel 300 mg LD	603/12566
			Clopidogrel 600 mg LD	563/12520
		Total mortality at 30 days	Clopidogrel 300 mg LD	302/12566
			Clopidogrel 600 mg LD	288/12520
		CV mortality at 30 days	Clopidogrel 300 mg LD	276/12566
			Clopidogrel 600 mg LD	263/12520
		Nonfatal MI at 30 days	Clopidogrel 300 mg LD	276/12566
			Clopidogrel 600 mg LD	238/12520
		Nonfatal stroke at 30 days	Clopidogrel 300 mg LD	63/12566
			Clopidogrel 600 mg LD	63/12520
		Major Bleeding at 30 days	Clopidogrel 300 mg LD	163/12566
			Clopidogrel 600 mg LD	213/12520
		Minor Bleeding at 30 days	Clopidogrel 300 mg LD	540/12566
			Clopidogrel 600 mg LD	639/12520
		Recurrent ischemia at 30 days	Clopidogrel 300 mg LD	50/12566
			Clopidogrel 600 mg LD	50/12520
Montalescot, 2006[22] ALBION	RCT Total N: 103 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization Rehospitalization	Clopidogrel 300 mg LD	4/35
			Clopidogrel 600 mg LD	2/34
			Clopidogrel 900 mg LD	0/34
		Total mortality at 30 days	Clopidogrel 300 mg LD	0/35
			Clopidogrel 600 mg LD	0/34
			Clopidogrel 900 mg LD	0/34
		Nonfatal MI at 30 days	Clopidogrel 300 mg LD	1/35
			Clopidogrel 600 mg LD	2/34
			Clopidogrel 900 mg LD	0/34
		Revascularization at 30 days	Clopidogrel 300 mg LD	1/35
			Clopidogrel 600 mg LD	0/34
			Clopidogrel 900 mg LD	0/34
		Rehospitalization at 30 days	Clopidogrel 300 mg LD	2/35
			Clopidogrel 600 mg LD	0/34
			Clopidogrel 900 mg LD	0/34
		Major bleeding at 30 days	Clopidogrel 300 mg LD	0/35
			Clopidogrel 600 mg LD	0/34
			Clopidogrel 900 mg LD	0/34
		Minor bleeding at 30 days	Clopidogrel 300 mg LD	11/35
			Clopidogrel 600 mg LD	10/34
			Clopidogrel 900 mg LD	14/34
Patti, 2005[23] ARMYDA-2	RCT Total N: 255 Good quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization	Clopidogrel 300 mg LD	15/129
			Clopidogrel 600 mg LD	5/126
		Total mortality at 30 days	Clopidogrel 300 mg LD	0/129
			Clopidogrel 600 mg LD	0/126
		Nonfatal MI at 30 days	Clopidogrel 300 mg LD	15/129
			Clopidogrel 600 mg LD	5/126

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Revascularization at 30 days	Clopidogrel 300 mg LD	1/126
			Clopidogrel 600 mg LD	0/129
		Major bleeding at 30 days	Clopidogrel 300 mg LD	0/129
			Clopidogrel 600 mg LD	0/126
		Minor bleeding at 30 days	Clopidogrel 300 mg LD	1/129
			Clopidogrel 600 mg LD	1/126
Price, 2011[24]	RCT Total N: 2,214 Good quality	Primary Composite at 6 mo: CV mortality Nonfatal MI Stent thrombosis	Clopidogrel 75 mg LD	25/1105
			Clopidogrel 150 mg LD	25/1109
		Secondary Composite at 6 mo: CV mortality Nonfatal MI	Clopidogrel 75 mg LD	25/1105
			Clopidogrel 150 mg LD	23/1109
		CV mortality	Clopidogrel 75 mg LD	8/1105
			Clopidogrel 150 mg LD	3/1109
		Stent thrombosis	Clopidogrel 75 mg LD	8/1105
			Clopidogrel 150 mg LD	5/1109
Puymirat, 2011[25] FAST-MI	Observational Total N: 791 Fair quality	Composite at 30 days: Major bleeding Need for transfusion	Clopidogrel ≥300 mg	25/466
			Clopidogrel <300 mg	20/325
		Total mortality in hospital	Clopidogrel ≥300 mg	37/466
			Clopidogrel <300 mg	33/325
		Total mortality 30 days	Clopidogrel ≥300 mg	47/466
			Clopidogrel <300 mg	35/325
		Major bleeding 30 days	Clopidogrel ≥300 mg	15/466
			Clopidogrel <300 mg	12/325
		Myocardial infarction 1 yr	Clopidogrel ≥300 mg	17/466
			Clopidogrel <300 mg	15/325
		Stroke 1 yr	Clopidogrel ≥300 mg	7/466
			Clopidogrel <300 mg	11/325
Wang, 2007[26]	Observational Total N: 2,484 Fair quality	Primary composite at 60 days: Total mortality Nonfatal MI Stroke Revascularization	Clopidogrel 300 mg	246/1199
			Clopidogrel >300 mg	477/1285
		Nonfatal MI at 60 days	Clopidogrel 300 mg	207/1199
			Clopidogrel >300 mg	446/1285
		Total mortality at 60 days	Clopidogrel 300 mg	13/1199
			Clopidogrel >300 mg	12/1285
		Stroke at 60 days	Clopidogrel 300 mg	16/1199
			Clopidogrel >300 mg	19/1285
		Revascularization at 6 mo	Clopidogrel 300 mg	31/1199
			Clopidogrel >300 mg	43/1285
		Bleeding at 60 days	Clopidogrel 300 mg	19/1199
			Clopidogrel >300 mg	18/1285
Yong, 2009[27] PRACTICAL	RCT Total N: 256 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Nonfatal stroke Rehospitalization	Clopidogrel 300 mg LD	RR (95% CI): 1.00 (0.53-1.98), reference group clopidogrel 600 mg LD
		Total mortality at 6 mo	Clopidogrel 300 mg LD	RR (95% CI): 2.13 (0.2-23.19), reference group clopidogrel 600 mg LD

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Nonfatal MI at 6 mo	Clopidogrel 300 mg LD	RR (95% CI): 0.58 (0.22-1.52), reference group clopidogrel 600 mg LD
		Nonfatal stroke at 6 mo	Clopidogrel 300 mg LD	RR (95% CI): 0.35 (0.01-8.63), reference group clopidogrel 600 mg LD
		Revascularization at 6 mo	Clopidogrel 300 mg LD	RR (95% CI): 1.42 (0.32-6.21), reference group clopidogrel 600 mg LD
		Rehospitalization at 6 mo	Clopidogrel 300 mg LD	RR (95% CI): 1.16 (0.53-2.53), reference group clopidogrel 600 mg LD
		Major bleeding at 30 days	Clopidogrel 300 mg LD	3/124
			Clopidogrel 600 mg LD	2/132
		Minor bleeding at 30 days	Clopidogrel 300 mg LD	3/124
			Clopidogrel 600 mg LD	3/132

Abbreviations: ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; LD=loading dose; mg=milligram/milligrams; MI=myocardial infarction; mo=month/months; N=number of patients; RCT=randomized controlled trial; RR=relative risk; TVR=target vessel revascularization; yr=year/years

Table G-3. Results data for clopidogrel vs. ticagrelor vs. prasugrel: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Cannon, 2007[28] DISPERSE-2	RCT Total N: 984 Fair quality	Secondary Efficacy Composite at 30 days: CV mortality Nonfatal MI Nonfatal stroke	Ticagrelor	14/334
			Clopidogrel	12/327
		Secondary Efficacy Composite at 3 mo: CV mortality Nonfatal MI Nonfatal stroke	Ticagrelor	19/334
			Clopidogrel	17/327
		Primary Safety Composite at 30 days: Major bleeding Minor bleeding	Ticagrelor	32/334
			Clopidogrel	26/327
		Secondary Safety Composite at 3 mo: Major bleeding Minor bleeding	Ticagrelor	34/334
			Clopidogrel	30/327
		Total mortality at 30 days	Ticagrelor	6/334
			Clopidogrel	2/327
		Total mortality at 3 mo	Ticagrelor	7/334
			Clopidogrel	4/327
		Nonfatal MI at 30 days	Ticagrelor	7/334
			Clopidogrel	11/327
		Nonfatal MI at 3 mo	Ticagrelor	12/334
			Clopidogrel	15/327
		Nonfatal stroke at 30 days	Ticagrelor	2/334
			Clopidogrel	1/327
		Nonfatal stroke at 3 mo	Ticagrelor	2/334
			Clopidogrel	1/327
		Recurrent ischemia at 30 days	Ticagrelor	10/334
			Clopidogrel	5/327
		Recurrent ischemia at 3 mo	Ticagrelor	13/334
			Clopidogrel	9/327
		Major bleeding at 30 days	Ticagrelor	23/334
			Clopidogrel	22/327
		Major bleeding at 3 mo	Ticagrelor	26/334
			Clopidogrel	26/327
		Minor bleeding at 30 days	Ticagrelor	9/334
			Clopidogrel	4/327
		Minor bleeding at 3 mo	Ticagrelor	9/334
			Clopidogrel	4/327

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Wallentin, 2009[29] PLATO	RCT Total N: 18,624 Good quality	Primary Composite at 30 days: CV mortality Nonfatal MI Stroke	Ticagrelor	443/9333
			Clopidogrel	502/9291
		Primary Composite at 12 months: CV mortality Nonfatal MI Stroke	Ticagrelor	864/9333
			Clopidogrel	1014/9291
		Secondary Composite at 12 months: Total mortality Nonfatal MI Stroke	Ticagrelor	901/9333
			Clopidogrel	1065/9291
		Secondary Composite at 12 months: CV mortality Nonfatal MI Stroke Recurrent ischemia Other arterial thrombotic event	Ticagrelor	1290/9333
			Clopidogrel	1456/9291
		Total mortality at 12 months	Ticagrelor	399/9333
			Clopidogrel	506/9291
		CV mortality at 12 months	Ticagrelor	353/9333
			Clopidogrel	442/9291
		Nonfatal MI at 12 months	Ticagrelor	504/9333
			Clopidogrel	593/9291
		Stroke at 12 months	Ticagrelor	125/9333
			Clopidogrel	106/9291
		Stent Thrombosis at 12 months	Ticagrelor	71/5640
			Clopidogrel	106/5649
		TIMI Major Bleeding at 12 months	Ticagrelor	657/9235
			Clopidogrel	638/9186
		TIMI Minor Bleeding at 12 months	Ticagrelor	314/9235
			Clopidogrel	288/9186
		Adverse drug reactions at 12 months - dyspnea	Ticagrelor	1270/9235
			Clopidogrel	721/9186
		Adverse drug reactions at 12 months - bradycardia	Ticagrelor	409/9235
			Clopidogrel	372/9186

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Wiviott, 2007[30] TRITON-TIMI38	RCT Total N: 13,608 Good quality	Primary Composite at 30 days: CV mortality Nonfatal MI Stroke	Prasugrel	388/6813
			Clopidogrel	503/6795
		Secondary Composite at 15 months: CV mortality Nonfatal MI Revascularization	Prasugrel	HR (95% CI): 0.81 (0.73-0.87), reference group clopidogrel
		Secondary Composite at 15 months: CV mortality Nonfatal MI Stroke Rehospitalization	Prasugrel	HR (95% CI): 0.84 (0.76-0.92), reference group clopidogrel
		Secondary Composite at 15 months: Major bleeding Minor bleeding	Prasugrel	HR (95% CI): 1.31 (1.11-1.56), reference group clopidogrel
		Total mortality at 15 months	Prasugrel	204/6813
			Clopidogrel	217/6795
		CV mortality at 15 months	Prasugrel	143/6813
			Clopidogrel	163/6795
		Nonfatal MI at 15 months	Prasugrel	497/6813
			Clopidogrel	646/6795
		Nonfatal stroke at 15 months	Prasugrel	68/6813
			Clopidogrel	68/6795
		Revascularization at 15 months	Prasugrel	HR (95% CI): 0.66 (0.54-0.81), reference group clopidogrel
		Stent Thrombosis at 15 months	Prasugrel	75/6813
			Clopidogrel	161/6716
		Major Bleeding at 15 months	Prasugrel	162/6741
			Clopidogrel	121/6716

Abbreviations: CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MI=myocardial infarction; mo=month/months; N=number of patients; RCT=randomized controlled trial; TIMI=thrombolysis in myocardial infarction; vs=versus

Table G-4. Results data for bivalirudin vs. heparin-based strategy with or without GPI: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Antman, 2002[31] TIMI 8	RCT Total N: 133 Poor quality	Primary Composite at 14 days: Total mortality Nonfatal MI	UFH	6/65
			Bivalirudin	2/68
		Secondary Composite at 14 days: Total mortality Nonfatal MI Major bleeding	Bivalirudin	OR (95% CI): 0.19 (0.04 to 0.94), reference group UFH
		Secondary Composite at 30 days: Total mortality Nonfatal MI Major bleeding	Bivalirudin	OR (95% CI): 0.23 (0.06 to 0.85) reference group UFH
		Primary Composite at 30 days: Total mortality Nonfatal MI	UFH	8/65
			Bivalirudin	3/68
		Major bleeding at 14 days	UFH	3/65
			Bivalirudin	0/68
Chu, 2006[32]	Observational Total N: 672 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization	Bivalirudin	9/216
			UFH	19/456
		Primary Composite at 6 mo: Total mortality Nonfatal MI Revascularization	Bivalirudin	29/216
			UFH	50/456
		Transfusion in hospital	Bivalirudin	19/216
			UFH	45/456
		Stent thrombosis in hospital	Bivalirudin	1/216
			UFH	6/456
		Total mortality at 30 days	Bivalirudin	7/216
			UFH	9/456
		Nonfatal MI at 30 days	Bivalirudin	1/216
			UFH	5/456
		Revascularization at 30 days	Bivalirudin	2/216
			UFH	6/456
		Stent thrombosis at 30 days	Bivalirudin	0/216
			UFH	1/456
		Total mortality at 6 mo	Bivalirudin	17/216
			UFH	21/456
		Nonfatal MI at 6 mo	Bivalirudin	5/216
			UFH	12/456
		Revascularization at 6 mo	Bivalirudin	10/216
			UFH	20/456

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Cortese, 2009[33]	Observational Total N: 159 Fair quality	Secondary Composite at 30 days: Total mortality Revascularization	UFH + GPI	5/59
			Bivalirudin prolonged	3/50
			Bivalirudin	5/50
		Major bleeding in hospital	UFH + GPI	5/59
			Bivalirudin prolonged	2/50
			Bivalirudin	0/50
		Minor bleeding in hospital	UFH + GPI	12/59
			Bivalirudin prolonged	2/50
			Bivalirudin	2/50
		Nonfatal MI periprocedure	UFH + GPI	7/59
			Bivalirudin prolonged	4/50
			Bivalirudin	13/50
		Nonfatal MI at 30 days	UFH + GPI	1/59
			Bivalirudin prolonged	1/50
			Bivalirudin	2/50
		Total mortality at 30 days	UFH + GPI	2/59
			Bivalirudin prolonged	1/50
			Bivalirudin	2/50
		Revascularization at 30 days	UFH + GPI	2/59
			Bivalirudin prolonged	1/50
			Bivalirudin	2/50
		Stent thrombosis at 30 days	UFH + GPI	0/59
			Bivalirudin prolonged	0/50
			Bivalirudin	1/50
Gibson, 2006[34] PROTECT-TIMI-30	RCT Total N: 857 Fair quality	Primary Composite at 48 hrs: Total mortality Nonfatal MI Ischemia	Bivalirudin	OR (95% CI): 1.35 (0.91-2.01), reference group eptifibatide
		Secondary Composite at 48 hrs: Total mortality Nonfatal MI	Bivalirudin	OR (95% CI): 1.37 (0.81-2.31), reference group eptifibatide
		Total mortality at 48 hrs	Bivalirudin	1/267
			Eptifibatide	0/530
		Nonfatal MI at 48 hrs	Bivalirudin	23/267
			Eptifibatide	35/530
		Ischemia on Holt monitoring at 48 hrs	Bivalirudin	169 min
			Eptifibatide	36 min
		Major Bleeding at 48 hrs	Bivalirudin	0/282
			Eptifibatide	4/567
		Minor Bleeding at 48 hrs	Bivalirudin	1/282
			Eptifibatide	14/567

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Kastrati, 2008[35] ISAR-REACT 3	RCT Total N: 4,571 Good quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization Major Bleeding	Bivalirudin	190/2289
			UFH	198/2281
		Secondary Composite at 30 days: Total mortality Nonfatal MI Revascularization	Bivalirudin	135/2289
			UFH	114/2281
		Secondary Composite at 1 yr: Total mortality Nonfatal MI Revascularization	Bivalirudin	391/2289
			UFH	399/2281
		Secondary Composite at 1 yr: Total mortality Nonfatal MI	Bivalirudin	176/2289
			UFH	153/2281
		Total mortality at 30 days	Bivalirudin	2/2289
			UFH	5/2281
		Nonfatal MI at 30 days	Bivalirudin	128/2289
			UFH	109/2281
		Revascularization at 30 days	Bivalirudin	18/2289
			UFH	16/2289
		Stent Thrombosis at 30 days	Bivalirudin	11/2289
			UFH	9/2281
		Major Bleeding at 30 days	Bivalirudin	71/2289
			UFH	105/2281
		Minor Bleeding at 30 days	Bivalirudin	30/2289
			UFH	50/2281
		Total mortality at 1 yr	Bivalirudin	43/2289
			UFH	39/2281
		Nonfatal MI at 1 yr	Bivalirudin	137/2289
			UFH	121/2281
		Revascularization at 1 yr	Bivalirudin	256/2289
			UFH	285/2281

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Kastrati, 2011[36] ISAR-REACT 4	RCT Total N: 1,721 Good quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization Major Bleeding	Bivalirudin	130/860
			UFH+GPI	137/861
		Secondary Composite at 30 days: Total mortality Nonfatal MI Revascularization	Bivalirudin	115/860
			UFH+GPI	110/861
		Total mortality at 30 days	Bivalirudin	14/860
			UFH+GPI	12/861
		Nonfatal MI at 30 days	Bivalirudin	98/860
			UFH+GPI	102/861
		Stroke at 30 days	Bivalirudin	6/860
			UFH+GPI	4/861
		Revascularization at 30 days	Bivalirudin	11/860
			UFH+GPI	7/861
		Stent Thrombosis at 30 days	Bivalirudin	6/860
			UFH+GPI	5/861
		Major Bleeding at 30 days	Bivalirudin	22/860
			UFH+GPI	40/861
		Minor Bleeding at 30 days	Bivalirudin	37/860
			UFH+GPI	69/861
		Adverse drug reactions at 30 days	Bivalirudin	0/860
			UFH+GPI	10/861
Lemesle, 2009[37]	Observational Total N: 2,766 Fair quality	Primary Composite at 6 mo: Total mortality Nonfatal MI Revascularization	Bivalirudin	122/1207
			UFH	315/1559
		Major bleeding in hospital	Bivalirudin	27/1207
			UFH	101/1559
		Total mortality at 6 mo	Bivalirudin	106/1207
			UFH	209/1559
		Nonfatal MI at 6 mo	Bivalirudin	29/1207
			UFH	51/1559
		Revascularization at 6 mo	Bivalirudin	29/1207
			UFH	107/1559
Lemesle, 2009[38]	Observational Total N: 171 Fair quality	Primary Composite in hospital: Total mortality Nonfatal MI Revascularization Major bleeding	Bivalirudin	11/79
			UFH	26/92
		Total mortality in hospital	Bivalirudin	3/79
			UFH	4/92
		Nonfatal MI in hospital	Bivalirudin	1/79
			UFH	2/92
		Revascularization in hospital	Bivalirudin	7/79
			UFH	1/92
		Major bleeding in hospital	Bivalirudin	10/79
			UFH	20/92

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Parodi, 2010[39] ARNO	RCT Total N: 850 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization	Bivalirudin	12/425
			UFH	27/425
		Primary Composite at 1 year: Total mortality Nonfatal MI Revascularization	Bivalirudin	32/425
			UFH	53/425
		Total mortality at 30 days	Bivalirudin	1/425
			UFH	6/425
		Nonfatal MI at 30 days	Bivalirudin	10/425
			UFH	19/425
		Revascularization at 30 days	Bivalirudin	2/425
			UFH	3/425
		Stent Thrombosis at 30 days	Bivalirudin	2/425
			UFH	1/425
		Major Bleeding at 30 days	Bivalirudin	4/425
			UFH	12/425
		Minor Bleeding at 30 days	Bivalirudin	10/425
			UFH	10/425
		Net Clinical Benefit at 30 days	Bivalirudin	14/425
			UFH	33/425
		Total mortality at 6 months	Bivalirudin	5/425
			UFH	10/425
		Nonfatal MI at 6 months	Bivalirudin	14/425
			UFH	24/425
		Revascularization at 6 months	Bivalirudin	17/425
			UFH	24/425
		Net Clinical Benefit at 6 months	Bivalirudin	36/425
			UFH	63/425
Patti, 2012[40] ARMYDA-7 BIVALVE	RCT Total N: 401 Good quality	Primary Composite at 30 days: CV mortality Nonfatal MI Revascularization Stent thrombosis	Bivalirudin	22/198
			UFH	18/203
		CV mortality at 30 days	Bivalirudin	1/198
			UFH	0/203
		Nonfatal MI at 30 days	Bivalirudin	20/198
			UFH	17/203
		Revascularization at 30 days	Bivalirudin	2/198
			UFH	1/203
		Stent thrombosis at 30 days	Bivalirudin	1/198
			UFH	0/203
		Major bleeding at 30 days	Bivalirudin	1/198
			UFH	2/203
		Minor bleeding at 30 days	Bivalirudin	1/198
			UFH	4/203
		Entry-site complications at 30 days	Bivalirudin	1/198
			UFH	14/203

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Rajagopal, 2006[41] REPLACE-2 ACS Substudy	RCT Total N: 1,351 Good quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization	Bivalirudin	58/669
			UFH+GPI	54/682
		Secondary Composite at 30 days: Total mortality Nonfatal MI Revascularization Major Bleeding	Bivalirudin	66/669
			UFH+GPI	75/682
		Secondary Composite at 30 days: Total mortality Nonfatal MI	Bivalirudin	48/682
			UFH+GPI	49/669
		Secondary Composite at 6 mo: Total mortality Nonfatal MI	Bivalirudin	58/669
			UFH+GPI	56/862
		Total mortality at 30 days	Bivalirudin	3/669
			UFH+GPI	3/682
		Nonfatal MI at 30 days	Bivalirudin	48/669
			UFH+GPI	47/682
		Revascularization at 30 days	Bivalirudin	15/669
			UFH+GPI	11/682
		Major Bleeding at 30 days	Bivalirudin	18/669
			UFH+GPI	31/682
		Minor Bleeding at 30 days	Bivalirudin	86/669
			UFH+GPI	183/682
		Total mortality at 6 months	Bivalirudin	6/669
			UFH+GPI	9/682
		Nonfatal MI at 6 months	Bivalirudin	54/669
			UFH+GPI	52/682
		Revascularization at 6 months	Bivalirudin	78/669
			UFH+GPI	57/682
Stone, 2006[42] ACUITY Study	RCT Total N: 13,819 Good quality	Primary Composite#1 at 30 days: Total mortality Nonfatal MI Revascularization	Bivalirudin	360/4612
			UFH+GPI	336/4603
		Primary Composite#1 at 1 yr: Total mortality Nonfatal MI Revascularization	Bivalirudin	747/4612
			UFH+GPI	709/4603
		Primary Composite #2 at 30 days: Total mortality Nonfatal MI Revascularization Major bleeding	Bivalirudin	466/4612
			UFH+GPI	709/4603
		Total mortality at 30 days	Bivalirudin	74/4612
			UFH+GPI	60/4603
		Nonfatal MI at 30 days	Bivalirudin	249/4612
			UFH+GPI	226/4603
		Revascularization at 30 days	Bivalirudin	111/4612
			UFH+GPI	106/4603
		Major Bleeding at 30 days	Bivalirudin	138/4612
			UFH+GPI	262/4603
		Minor Bleeding at 30 days	Bivalirudin	590/4612
			UFH+GPI	994/4603
		Thrombocytopenia at 30 days	Bivalirudin	457/4612

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
			UFH+GPI	511/4603
		Stent thrombosis at 30 days	Bivalirudin	11/1128
			UFH+GPI	9/1112
		Total mortality at 1 yr	Bivalirudin	175/4612
			UFH+GPI	180/4603
		Revascularization at 1 yr	Bivalirudin	401/4612
			UFH+GPI	387/4603
		Nonfatal MI at 1 yr	Bivalirudin	360/4612, 401/4612
			UFH+GPI	318/4603, 262/4603
Wolfram, 2003[43]	Observational Total N: 3,015 Fair quality	Total mortality in hospital	Bivalirudin	0/335
			UFH+eptifibatide	0/1340
			UFH	1/1340
		Nonfatal MI in hospital	Bivalirudin	0/335
			UFH+eptifibatide	7/1340
			UFH	4/1340
		Neurologic event in hospital	Bivalirudin	4/335
			UFH+eptifibatide	12/1340
			UFH	17/1340
		Abrupt vessel closure in hospital	Bivalirudin	0/335
			UFH+eptifibatide	4/1340
			UFH	5/1340
		Revascularization in hospital	Bivalirudin	5/335
			UFH+eptifibatide	38/1340
			UFH	32/1340
		Non Q wave MI in hospital	Bivalirudin	55/335
			UFH+eptifibatide	354/1340
			UFH	369/1340
		Length of hospital stay	Bivalirudin	Mean (SD) 4.7 (17.3)
			UFH+eptifibatide	Mean (SD) 12.1 (223.8)
			UFH	Mean (SD) 3.6 (19.1)
		Major bleeding in hospital	Bivalirudin	4/335
			UFH+eptifibatide	42/1340
			UFH	35/1340

Abbreviations: CI=confidence interval; CV=cardiovascular; GPI=glycoprotein IIb/IIIa inhibitor; hr=hour/hours; MI=myocardial infarction; mo=month/months; N=number of patients; OR=odds ratio; RCT=randomized controlled trial; UFH=unfractionated heparin; vs=versus; yr=year/years

Table G-5. Results data for enoxaparin vs. unfractionated heparin vs. fondaparinux: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Antman, 1999[44] TIMI 11B	RCT Total N: 3,910 Good quality	Primary Composite at 48 hr: Total mortality Nonfatal MI Revascularization	Enoxaparin	OR (95% CI): 0.75 (0.58 to 0.97), reference group UFH
		Primary Composite at 8 days: Total mortality Nonfatal MI Revascularization	Enoxaparin	OR (95% CI): 0.83 (0.69 to 1.00), reference group UFH
		Primary Composite at 14 days: Total mortality Nonfatal MI Revascularization	Enoxaparin	OR (95% CI): 0.82 (0.69 to 0.98), reference group UFH
		Primary Composite at 43 days: Total mortality Nonfatal MI Revascularization	Enoxaparin	OR (95% CI): 0.85 (0.72 to 1.00), reference group UFH
		Secondary Composite at 48 hr: Total mortality Nonfatal MI	Enoxaparin	OR (95% CI): 0.78 (0.49 to 1.24), reference group UFH
		Secondary Composite at 8 days: Total mortality Nonfatal MI	Enoxaparin	OR (95% CI): 0.77 (0.58 to 1.02), reference group UFH
		Secondary Composite at 14 days: Total mortality Nonfatal MI	Enoxaparin	OR (95% CI): 0.81 (0.62 to 1.05), reference group UFH
		Secondary Composite at 43 days: Total mortality Nonfatal MI	Enoxaparin	OR (95% CI): 0.88 (0.70 to 1.11), reference group UFH
		Total mortality at 48 hr	Enoxaparin	OR (95% CI): 1.84 (0.68 to 4.99), reference group UFH
		Total mortality at 8 days	Enoxaparin	OR (95% CI): 0.83 (0.52 to 1.31), reference group UFH
		Total mortality at 14 days	Enoxaparin	OR (95% CI): 0.78 (0.52 to 1.17), reference group UFH
		Total mortality at 43 days	Enoxaparin	OR (95% CI): 0.85 (0.72 to 1.00), reference group UFH
		Nonfatal MI at 48 hr	Enoxaparin	OR (95% CI): 0.68 (0.41 to 1.13), reference group UFH
		Nonfatal MI at 8 days	Enoxaparin	OR (95% CI): 0.70 (0.51 to 0.97), reference group UFH

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Nonfatal MI at 14 days	Enoxaparin	OR (95% CI): 0.78 (0.58 to 1.05), reference group UFH
		Nonfatal MI at 43 days	Enoxaparin	OR (95% CI): 0.82 (0.63 to 1.07), reference group UFH
		Major bleeding at 72 hr	Enoxaparin	16/1938
			UFH	14/1936
		Major bleeding in hospital	Enoxaparin	29/1938
			UFH	19/1936
		Major bleeding 8-43 days	Enoxaparin	34/1938
			UFH	18/1936
		Minor bleeding 72 hr	Enoxaparin	99/1938
			UFH	45/1936
		Minor bleeding in hospital	Enoxaparin	176/1938
			UFH	48/1936
		Minor bleeding 8-43 days	Enoxaparin	227/1938
			UFH	62/1936
Bertel, 2010[45] ZEUS	RCT Total N: 876 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Major bleeding Target Vessel Revascularization (unplanned)	Enoxaparin	24/436
			UFH	31/440
		Secondary Composite at 30 days: Major bleeding Minor bleeding Thrombocytopenia	Enoxaparin	43/436
			UFH	88/440
		Total mortality at 30 days	Enoxaparin	0/436
			UFH	0/440
		Nonfatal MI at 30 days	Enoxaparin	4/436
			UFH	14/440
		Revascularization at 30 days	Enoxaparin	7/436
			UFH	6/440
		Major bleeding at 30 days	Enoxaparin	16/436
			UFH	27/440
		Minor bleeding at 30 days	Enoxaparin	37/436
			UFH	76/440
		Stent thrombosis at 30 days	Enoxaparin	0/436
			UFH	4/440
Bhatt, 2003[46] CRUISE	RCT Total N: 261 Fair quality	Composite at 30 days: Total mortality Nonfatal MI Revascularization	Enoxaparin	13/129
			UFH	10/132
		Total mortality at 30 days	Enoxaparin	0/129
			UFH	0/132
		Nonfatal MI at 30 days	Enoxaparin	11/129
			UFH	10/132
		Revascularization at 30 days	Enoxaparin	2/129
			UFH	1/132
		Major bleeding at 30 days	Enoxaparin	3/129
			UFH	2/132
		Minor bleeding at 30 days	Enoxaparin	18/129
			UFH	19/132

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Blazing, 2004[47] A to Z Study	RCT Total N: 3,987 Good quality	Primary Composite at 7 days: Total mortality Nonfatal MI Refractory ischemia	Enoxaparin	98/1111
			UFH	92/1080
		Secondary Composite at 7 days: Total mortality Nonfatal MI Revascularization Refractory ischemia Clinical ischemia	Enoxaparin	HR (95% CI): 0.89 (0.75-1.05), reference group UFH
		Total mortality at 7 days	Enoxaparin	HR (95% CI): 1.26 (0.67-2.38), reference group UFH
		Nonfatal MI at 7 days	Enoxaparin	HR (95% CI): 0.82 (0.60-1.13), reference group UFH
		Revascularization at 7 days	Enoxaparin	HR (95% CI): 0.98 (0.74-1.29), reference group UFH
		Refractory ischemia at 7 days	Enoxaparin	HR (95% CI): 0.82 (0.61-1.10), reference group UFH
		Major bleeding at 7 days	Enoxaparin	0.9%
			UFH	0.4%
		Major or minor bleeding at 7 days	Enoxaparin	3%
			UFH	2.2%
Brieger, 2007[48]	Observational Total N: 17,659 Fair quality	Total mortality in hospital	LMWH	293/10839
			UFH	326/7959
		Major bleeding in hospital	LMWH	195/10839
			UFH	215/7959
Chen, 2006[49]	RCT Total N: 455 Poor quality	Composite outcome in hospital: Total mortality Nonfatal MI Revascularization	Enoxaparin	1/227
			UFH	0/228
		Composite outcome from hospital discharge: Total mortality Nonfatal MI Revascularization	Enoxaparin	0/227
			UFH	1/228
		Total mortality in hospital	Enoxaparin	0/227
			UFH	0/228
		Total mortality from hospital discharge	Enoxaparin	0/227
			UFH	0/228
Ferguson, 2004[50] SYNERGY	RCT Total N: 10,027 Good quality	Primary Composite at 30 days: Total mortality Nonfatal MI	Enoxaparin	699/4993
			UFH	773/4985
		Primary Composite at 14 days: Total mortality Nonfatal MI	Enoxaparin	639/4993
			UFH	668/4985
		Primary Composite at 48 hrs: Total mortality Nonfatal MI	Enoxaparin	285/4993
			UFH	324/4985

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Total mortality at 30 days	Enoxaparin	160/4993
			UFH	155/4985
		Total mortality at 14 days	Enoxaparin	559/4993
			UFH	588/4985
		Total mortality at 48 hrs	Enoxaparin	270/4993
			UFH	299/4985
		Nonfatal MI at 30 days	Enoxaparin	584/4993
			UFH	633/4985
		Nonfatal MI at 14 days	Enoxaparin	120/4993
			UFH	120/4985
		Nonfatal MI at 48 hrs	Enoxaparin	20/4993
			UFH	26/4985
		GUSTO severe bleeding pre-catheterization	Enoxaparin	135/4993
			UFH	110/4983
		TIMI major bleeding pre-catheterization	Enoxaparin	454/4993
			UFH	379/4983
		Recurrent ischemia pre-catheterization	Enoxaparin	200/4993
			UFH	214/4985
		Stroke pre-catheterization	Enoxaparin	50/4993
			UFH	45/4985
Goodman, 2003[51] INTERACT	RCT Total N: 746 Good quality	Secondary Composite at 30 days: Total mortality Nonfatal MI Revascularization	Enoxaparin	53/380
			UFH	59/366
		Secondary Composite at 30 days: Total mortality Nonfatal MI	Enoxaparin	19/380
			UFH	33/366
		Secondary Composite at 300 days: Total mortality Nonfatal MI	Enoxaparin	19/380
			UFH	26/366
		Secondary Composite at 600 days: Total mortality Nonfatal MI	Enoxaparin	23/380
			UFH	36/366
		Secondary Composite at 900 days: Total mortality Nonfatal MI	Enoxaparin	31/380
			UFH	51/366
		Total mortality at 30 days	Enoxaparin	9/380
			UFH	15/366
		Nonfatal MI at 30 days	Enoxaparin	15/380
			UFH	21/366
		Revascularization at 30 days	Enoxaparin	28/380
			UFH	20/366
		Major bleeding at 48 hr	Enoxaparin	4/380
			UFH	14/366
		Recurrent ischemia at 48 hr	Enoxaparin	3/379
			UFH	1/365

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Korovesis, 2005[52]	Observational Total N: 333 Fair quality	Composite outcome at 30 days: Total mortality Nonfatal MI Revascularization	UFH	0/217
			Enoxaparin	0/116
		Total mortality at 30 days	UFH	0/217
			Enoxaparin	0/116
		Nonfatal MI at 30 days	UFH	0/217
			Enoxaparin	0/116
		Stroke at 30 days	UFH	0/217
			Enoxaparin	1/116
		Major hematoma at 30 days	UFH	0/217
			Enoxaparin	1/116
		Stable, non-deteriorating hematoma at 30 days	UFH	108/217
			Enoxaparin	96/116
Mehta, 2005[53] ASPIRE	RCT Total N: 350 Fair quality	Primary Composite at 48 hr: Total mortality Nonfatal MI Revascularization Bailout GPI use	UFH	7/117
			Fondaparinux 2.5mg	5/118
			Fondaparinux 5 mg	9/115
		Total mortality at 48 hr	UFH	0/117
			Fondaparinux 2.5mg	0/118
			Fondaparinux 5 mg	1/115
		Nonfatal MI at 48 hr	UFH	7/117
			Fondaparinux 2.5mg	4/118
			Fondaparinux 5 mg	9/115
		Revascularization at 48 hr	UFH	1/117
			Fondaparinux 2.5mg	0/118
			Fondaparinux 5 mg	2/115
		Major bleeding at 48 hr	UFH	0/117
			Fondaparinux 2.5mg	1/118
			Fondaparinux 5 mg	3/115
		Minor bleeding at 48 hr	UFH	9/117
			Fondaparinux 2.5mg	3/118
			Fondaparinux 5 mg	8/115
Singh, 2006[54]	Observational Total N: 11,358 Fair quality	Composite outcome in hospital: Total mortality Nonfatal MI	LMWH	210/4477
			UFH	396/6881
		Total mortality in hospital	LMWH	126/4477
			UFH	196/6881
		RBC transfusion (all) in hospital	LMWH	595/4477
			UFH	846/6881
		RBC transfusion (non-CABG) in hospital	LMWH	300/4477
			UFH	482/6881

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Steg, 2010[55] FUTURA/OASIS-8	RCT Total N: 2,026 Good quality	Primary Composite at 48 hr: Peri-PCI major and minor bleeds Major vascular access site complications	UFH	58/1002
			UFH (low dose)	48/1024
		Secondary Composite at 30 days: Total mortality Nonfatal MI Target vessel revascularization	UFH	29/1002
			UFH (low dose)	46/1024
		Secondary Composite at 30 days: Total mortality Nonfatal MI Peri-PCI major bleed Target vessel revascularization	UFH	39/1002
			UFH (low dose)	59/1024
		Stent thrombosis at 30 days	UFH	5/1002
			UFH (low dose)	11/1024
		Target vessel revascularization at 30 days	UFH	3/1002
			UFH (low dose)	9/1024
		Minor bleeding at 30 days	UFH	21/1002
			UFH (low dose)	9/1024
		Major bleeding at 30 days	UFH	18/1002
			UFH (low dose)	22/1024
		Nonfatal MI at 30 days	UFH	25/1002
			UFH (low dose)	31/1024
		Total mortality at 30 days	UFH	6/1002
			UFH (low dose)	8/1024
		Stroke at 30 days	UFH	5/1002
			UFH (low dose)	5/1024
		Major PCI related procedural complications at 30 days	UFH	44/1002
			UFH (low dose)	44/1024
Yusuf, 2006[56] OASIS-5	RCT Total N: 20,078 Good quality	Primary Composite at 9 days: Total mortality Nonfatal MI Refractory ischemia	Fondaparinux	HR (95% CI): 1.01 (0.9-1.13), reference group enoxaparin
		Primary Composite at 30 days: Total mortality Nonfatal MI Refractory ischemia	Fondaparinux	HR (95% CI): 0.93 (0.84-1.02), reference group enoxaparin
		Primary Composite at 6 mo: Total mortality Nonfatal MI Refractory ischemia	Fondaparinux	HR (95% CI): 0.93 (0.86-1.00), reference group enoxaparin
		Secondary Composite at 9 days: Total mortality Nonfatal MI	Fondaparinux	HR (95% CI): 0.99 (0.86-1.13), reference group enoxaparin
		Secondary Composite at 30 days: Total mortality Nonfatal MI	Fondaparinux	HR (95% CI): 0.9 (0.81-1.01), reference group enoxaparin
		Secondary Composite at 6 mo: Total mortality Nonfatal MI	Fondaparinux	HR (95% CI): 0.92 (0.84-1.00), reference group enoxaparin

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Secondary Composite at 9 days: Total mortality Nonfatal MI Refractory ischemia Major bleeding	Fondaparinux	HR (95% CI): 0.81 (0.73-0.89), reference group enoxaparin
		Secondary Composite at 30 days: Total mortality Nonfatal MI Refractory ischemia Major bleeding	Fondaparinux	HR (95% CI): 0.92 (0.84-1.00), reference group enoxaparin
		Secondary Composite at 6 mo: Total mortality Nonfatal MI Refractory ischemia Major bleeding	Fondaparinux	HR (95% CI): 0.82 (0.75-0.89), reference group enoxaparin
		Total mortality at 9 days	Fondaparinux	HR (95% CI): 0.95 (0.77-1.17), reference group enoxaparin
		Total mortality at 30 days	Fondaparinux	HR (95% CI): 0.83 (0.71-0.97), reference group enoxaparin
		Total mortality at 6 mo	Fondaparinux	HR (95% CI): 0.89 (0.8-1.00), reference group enoxaparin
		Nonfatal MI at 9 days	Fondaparinux	HR (95% CI): 0.99 (0.84-1.18), reference group enoxaparin
		Nonfatal MI at 30 days	Fondaparinux	HR (95% CI): 0.94 (0.82-1.08), reference group enoxaparin
		Nonfatal MI at 6 mo	Fondaparinux	HR (95% CI): 0.95 (0.85-1.06), reference group enoxaparin
		Stroke at 9 days	Fondaparinux	HR (95% CI): 0.82 (0.53-1.27) , reference group enoxaparin
		Stroke at 30 days	Fondaparinux	HR (95% CI): 0.77 (0.57-1.05) , reference group enoxaparin
		Stroke at 180 days	Fondaparinux	HR (95% CI): 0.78 (0.62-0.99) , reference group enoxaparin
		Refractory ischemia at 9 days	Fondaparinux	HR (95% CI): 1.03 (0.84-1.26), reference group enoxaparin

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Refractory ischemia at 30 days	Fondaparinux	HR (95% CI): 0.99 (0.82-1.19), reference group enoxaparin
		Refractory ischemia at 6 mo	Fondaparinux	HR (95% CI): 0.97 (0.81-1.16), reference group enoxaparin
		Major bleeding at 9 days	Fondaparinux	HR (95% CI): 0.52 (0.44-0.61) , reference group enoxaparin
		Major bleeding at 30 days	Fondaparinux	HR (95% CI): 0.62 (0.54-0.72) , reference group enoxaparin
		Major bleeding at 180 days	Fondaparinux	HR (95% CI): 0.72 (0.64 -0.82) , reference group enoxaparin

Abbreviations: CABG=coronary artery bypass grafting; CI=confidence interval; GPI=glycoprotein IIb/IIIa inhibitor; GUSTO=global utilization of streptokinase and t-PA for occluded arteries; HR=hazard ratio; hr=hour/hours; LMWH=low molecular weight heparin; mg=milligram/milligrams; MI=myocardial infarction; mo=month/months; N=number of patients; OR=odds ratio; PCI=percutaneous coronary intervention; RBC=red blood cell; RCT=randomized controlled trial; SD=standard deviation; TIMI= thrombolysis in myocardial infarction; UFH=unfractionated heparin; vs=versus

Table G-6. Results data for clopidogrel timing: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Davlouros, 2009[57]	RCT Total N: 199 Fair quality	Primary composite at 30 days: CV mortality Nonfatal MI Stroke Revascularization	Clopidogrel pretreatment	13/103
			Clopidogrel at time of PCI	15/96
		CV mortality at 30 days	Clopidogrel pretreatment	2/103
			Clopidogrel at time of PCI	0/96
		Nonfatal MI at 30 days	Clopidogrel pretreatment	13/103
			Clopidogrel at time of PCI	14/96
		Stroke at 30 days	Clopidogrel pretreatment	0/103
			Clopidogrel at time of PCI	1/96
		Revascularization at 30 days	Clopidogrel pretreatment	0/103
			Clopidogrel at time of PCI	1/96
		Major bleeding at 30 days	Clopidogrel pretreatment	3/103
			Clopidogrel at time of PCI	3/96
Di Sciascio, 2010[58] ARMYDA-5 PRELOAD Study	RCT Total N: 536 Fair quality	Primary composite at 30 days: CV mortality Nonfatal MI Revascularization	Clopidogrel pretreatment	21/204
			Clopidogrel at time of PCI	18/205
		CV mortality at 30 days	Clopidogrel pretreatment	1/204
			Clopidogrel at time of PCI	0/205
		Nonfatal MI at 30 days	Clopidogrel pretreatment	19/204
			Clopidogrel at time of PCI	18/205
		Revascularization at 30 days	Clopidogrel pretreatment	1/204
			Clopidogrel at time of PCI	0/205
		Major bleeding at 30 days	Clopidogrel pretreatment	0/204
			Clopidogrel at time of PCI	0/205
		Minor bleeding at 30 days	Clopidogrel pretreatment	16/204
			Clopidogrel at time of PCI	11/205

Abbreviations: CV=cardiovascular; MI=myocardial infarction; N=number of patients; PCI=percutaneous coronary intervention; RCT=randomized controlled trial;

Table G-7. Results data for clopidogrel pretreatment: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Kastrati, 2008[35] ISAR-REACT 3 Study	RCT Total N: 4,571 Good quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization Major Bleeding	Bivalirudin	190/2289
			UFH	198/2281
		Secondary Composite at 30 days: Total mortality Nonfatal MI Revascularization	Bivalirudin	135/2289
			UFH	114/2281
		Secondary Composite at 1 yr: Total mortality Nonfatal MI Revascularization	Bivalirudin	391/2289
			UFH	399/2281
		Secondary Composite at 1 yr: Total mortality Nonfatal MI	Bivalirudin	176/2289
			UFH	153/2281
		Total mortality at 30 days	Bivalirudin	2/2289
			UFH	5/2281
		Nonfatal MI at 30 days	Bivalirudin	128/2289
			UFH	109/2281
		Revascularization at 30 days	Bivalirudin	18/2289
			UFH	16/289
		Stent Thrombosis at 30 days	Bivalirudin	11/2289
			UFH	9/2281
		Major Bleeding at 30 days	Bivalirudin	71/2289
			UFH	105/2281
		Minor Bleeding at 30 days	Bivalirudin	30/2289
			UFH	50/2281
		Total mortality at 1 yr	Bivalirudin	44/289
			UFH	39/2281
		Nonfatal MI at 1 yr	Bivalirudin	137/2289
			UFH	121/2281
		Revascularization at 1 yr	Bivalirudin	256/2289
			UFH	285/2281
Stone, 2006[42] ACUITY Study	RCT Total N: 13,819 Good quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization	Bivalirudin	360/4612
			UFH+GPI	336/4603
		Primary Composite at 1 year: Total mortality Nonfatal MI Revascularization	Bivalirudin	747/4612
			UFH+GPI	709/4603
		Secondary Composite at 30 days: Total mortality Nonfatal MI Revascularization Major bleeding	Bivalirudin	466/4612
			UFH+GPI	709/4603
		Total mortality at 30 days	Bivalirudin	74/4612
			UFH+GPI	60/4603
		Nonfatal MI at 30 days	Bivalirudin	249/4612
			UFH+GPI	226/4603
		Revascularization at 30 days	Bivalirudin	111/4612
			UFH+GPI	106/4603
		Major Bleeding at 30 days	Bivalirudin	138/4612
			UFH+GPI	262/4603
		Minor Bleeding at 30 days	Bivalirudin	590/4612

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
			UFH+GPI	994/4603
		Thrombocytopenia at 30 days	Bivalirudin	457/4612
			UFH+GPI	511/4603
		Stent thrombosis at 30 days	Bivalirudin	11/1128
			UFH+GPI	9/1112
		Total mortality at 1 year	Bivalirudin	175/4612
			UFH+GPI	180/4603
		Revascularization at 1 yr	Bivalirudin	401/4612
			UFH+GPI	387/4603
		Nonfatal MI at 1 year	Bivalirudin	360/4612, 401/4612
			UFH+GPI	318/4603, 262/4603
Rajagopal, 2006[41] REPLACE-2 ACS Substudy	RCT Total N: 1,351 Good quality	Primary Composite at 30 days: Total mortality Nonfatal MI Revascularization	Bivalirudin	58/669
			UFH+GPI	54/682
		Secondary Composite at 30 days: Total mortality Nonfatal MI Revascularization Major Bleeding	Bivalirudin	66/669
			UFH+GPI	75/682
		Secondary Composite at 30 days: Total mortality Nonfatal MI	Bivalirudin	48/682
			UFH+GPI	49/669
		Secondary Composite at 6 months: Total mortality Nonfatal MI	Bivalirudin	58/669
			UFH+GPI	56/862
		Total mortality at 30 days	Bivalirudin	3/669
			UFH+GPI	3/682
		Nonfatal MI at 30 days	Bivalirudin	48/669
			UFH+GPI	47/682
		Revascularization at 30 days	Bivalirudin	15/669
			UFH+GPI	11/682
		Major Bleeding at 30 days	Bivalirudin	18/669
			UFH+GPI	31/682
		Minor Bleeding at 30 days	Bivalirudin	86/669
			UFH+GPI	183/682
		Total mortality at 6 months	Bivalirudin	6/669
			UFH+GPI	9682
		Nonfatal MI at 6 months	Bivalirudin	54/669
			UFH+GPI	52/682
		Revascularization at 6 months	Bivalirudin	78/669
			UFH+GPI	57/682

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Patti, 2012[40] ARMYDA-7 BIVALVE	RCT Total N: 401 Good quality	Primary Composite at 30 days: CV death Nonfatal MI TVR Stent thrombosis	Bivalirudin	22/198
			UFH	18/203
		Total mortality at 30 days	Bivalirudin	1/198
			UFH	0/203
		Nonfatal MI at 30 days	Bivalirudin	20/198
			UFH	17/203
		Revascularization at 30 days	Bivalirudin	2/198
			UFH	1/203
		Stent thrombosis at 30 days	Bivalirudin	1/198
			UFH	0/203
		Major bleeding at 30 days	Bivalirudin	1/198
			UFH	2/203
		Minor bleeding at 30 days	Bivalirudin	1/198
			UFH	4/203
		Entry-site complications at 30 days	Bivalirudin	14/203
			UFH	130/860
Giugliano, 2009[5] EARLY ACS Study	RCT Total N: 9,378 Good quality	Primary Composite at 96 hr: Total mortality Nonfatal MI Revascularization Thrombotic bailout with GPI	GPI upstream	439/4722
			GPI deferred	469/4684
		Secondary Composite at 96 hr: Total mortality Nonfatal MI	GPI upstream	354/4722
			GPI deferred	390/4684
		Secondary Composite at 96 hr Total mortality Nonfatal MI Revascularization	GPI upstream	398/4722
			GPI deferred	438/4684
		Secondary Composite at 30 days: Total mortality Nonfatal MI	GPI upstream	528/4722
			GPI deferred	578/4684
		Secondary Composite at 30 days: Total mortality Nonfatal MI Revascularization	GPI upstream	592/4722
			GPI deferred	647/4684
		Total mortality at 96 hr	GPI upstream	39/4722
			GPI deferred	40/4684
		Nonfatal MI at 96 hr	GPI upstream	332/4722
			GPI deferred	358/4684
		Revascularization at 96 hr	GPI upstream	69/4722
			GPI deferred	79/4684
		Thrombotic bailout at 96 hr	GPI upstream	58/4722
			GPI deferred	59/4684
		Major bleeding at 120 hr	GPI upstream	118/4627
			GPI deferred	83/4597
		Total mortality at 30 days	GPI upstream	134/4722
			GPI deferred	121/4684
		Nonfatal MI at 30 days	GPI upstream	147/4722
			GPI deferred	495/4684
		Nonfatal stroke at 30 days	GPI upstream	28/4686
			GPI deferred	35/4643
		Revascularization at 30 days	GPI upstream	112/4722
			GPI deferred	138/4684
		Major bleeding at 30 days	GPI upstream	127/4627
			GPI deferred	111/4597

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Adverse drug reactions at 30 days	GPI upstream	68/4686
			GPI deferred	60/4643
		Thrombocytopenia at 30 days	GPI upstream	16/4356
			GPI deferred	10/4348
Bhattacharya, 2010[1]	RCT Total N: 301 Good quality	Fatal MI at 7 days	GPI upstream	1/136
			GPI deferred	8/165
		Fatal MI at 14 days	GPI upstream	1/122
			GPI deferred	6/133
		Fatal MI at 30 days	GPI upstream	2/105
			GPI deferred	5/99
		Fatal MI at 3 mo	GPI upstream	2/85
			GPI deferred	2/64
		Nonfatal MI at 7 days	GPI upstream	1/136
			GPI deferred	8/165
		Nonfatal MI at 14 days	GPI upstream	2/122
			GPI deferred	9/133
		Nonfatal MI at 30 days	GPI upstream	3/105
			GPI deferred	5/99
		Nonfatal MI at 3 mo	GPI upstream	2/85
			GPI deferred	5/64
		Refractory ischemia at 7 days	GPI upstream	10/136
			GPI deferred	13/165
		Refractory ischemia at 14 days	GPI upstream	10/122
			GPI deferred	12/133
		Refractory ischemia at 30 days	GPI upstream	14/105
			GPI deferred	24/99
		Refractory ischemia at 3 mo	GPI upstream	25/85
			GPI deferred	36/64
		Death due to unknown causes at 7 days	GPI upstream	2/136
			GPI deferred	3/165
		Death due to unknown causes at 14 days	GPI upstream	1/122
			GPI deferred	1/133
		Death due to unknown causes at 30 days	GPI upstream	0/105
			GPI deferred	0/99
		Death due to unknown causes at 3 mo	GPI upstream	1/85
			GPI deferred	1/64
		Major bleeding at 7 days, 14 days, 30 days, and 3 mo	GPI upstream	0/136
			GPI deferred	0/165
Ivandic, 2008[6]	RCT Total N: 100 Fair quality	Secondary Composite at 319 days: CV mortality Nonfatal MI Revascularization	GPI upstream	6/50
			GPI deferred	6/50
		CV mortality at 319 days	GPI upstream	2/50
			GPI deferred	2/50
		Nonfatal MI at 319 days	GPI upstream	2/50
			GPI deferred	1/50
		Revascularization at 319 days	GPI upstream	2/50
			GPI deferred	3/50
		Major bleeding at 30 days	GPI upstream	2/50
			GPI deferred	2/50
		Minor bleeding at 30 days	GPI upstream	10/50
			GPI deferred	6/50

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Leoncini, 2005[8] CLOTILDA Study	RCT Total N: 300 Poor quality	Composite at 30 days: Total mortality Nonfatal MI Rehospitalization	GPI upstream	14/150
			GPI deferred	15/150
		Total mortality at 30 days	GPI upstream	1/150
			GPI deferred	2/150
		Nonfatal MI at 30 days	GPI upstream	0/150
			GPI deferred	1/150
		Rehospitalization at 30 days	GPI upstream	1/150
			GPI deferred	1/150
		Major bleeding at 30 days	GPI upstream	3/150
			GPI deferred	2/150
Durand, 2007[4] PRACTICE	RCT Total N: 393 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Urgent revascularization	GPI upstream	31/196
			GPI deferred	33/197
		Secondary Composite: Total mortality Nonfatal MI Urgent revascularization	GPI upstream	45/196
			GPI deferred	43/197
		Total mortality at 30 days	GPI upstream	2/196
			GPI deferred	6/197
		Nonfatal MI at 30 days	GPI upstream	17/196
			GPI deferred	13/197
		Urgent revascularization at 30 days	GPI upstream	16/196
			GPI deferred	20/197
		Major bleeding at 30 days	GPI upstream	8/196
			GPI deferred	6/197
		Minor bleeding at 30 days	GPI upstream	20/196
			GPI deferred	16/197
		Total mortality at 6 months	GPI upstream	4/196
			GPI deferred	7/197
		Nonfatal MI at 6 months	GPI upstream	20/196
			GPI deferred	17/197
		Urgent revascularization at 6 months	GPI upstream	28/196
			GPI deferred	27/197

Abbreviations: GPI=glycoprotein IIb/IIIa inhibitor; hr=hour/hours; MI=myocardial infarction; mo=month/months; N=number of patients; RCT=randomized controlled trial; TVR=target vessel revascularization; UFH=unfractionated heparin; yr=year/years

Table G-8. Results data for clopidogrel deferred treatment: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Parodi, 2010[39] ARNO	RCT Total N: 850 Fair quality	Composite Endpoint at 30 days: All-cause mortality Nonfatal MI Revascularization	Bivalirudin	**12/425**
			Heparin-based strategy	27/425
		Major Bleeding at 30 days	Bivalirudin	4/425
			Heparin-based strategy	12/425
Kastrati, 2011[36] ISAR-REACT 4	RCT Total N: 1,721 Good quality	Composite Endpoint at 30 days: All-cause mortality Nonfatal MI Revascularization	Bivalirudin	**115/860**
			Heparin-based strategy	110/861
		Major Bleeding at 30 days	Bivalirudin	22/860
			Heparin-based strategy	40/861
Giugliano, 2009[5] EARLY ACS	RCT Total N: 9,378 Good quality	Composite Endpoint at 30 days: All-cause mortality Nonfatal MI Revascularization	Upstream GPI	**592/4722**
			Deferred GPI	647/4684
		Major Bleeding at 30 days	Upstream GPI	127/4627
			Deferred GPI	111/4597
Stone, 2007[14] ACUITY TIMING Study	RCT Total N: 9,207 Good quality	Composite Endpoint at 30 days: All-cause mortality Nonfatal MI Revascularization	Upstream GPI	**326/4605**
			Deferred GPI	364/4602
		Major Bleeding at 30 days	Upstream GPI	281/4605
			Deferred GPI	225/4602
Liu, 2009[9]	RCT Total N: 160 Fair quality	Composite Endpoint at 30 days: Total mortality Nonfatal MI Revascularization	Upstream GPI	**3/80**
			Deferred GPI	5/80
		Major bleeding at 30 days	Upstream GPI	2/80
			Deferred GPI	1/80
van 't Hof, 2003[16] ELISA	RCT Total N: 220 Poor quality	Composite Endpoint at 30 days: Total mortality Nonfatal MI	Upstream GPI	10/109
			Deferred GPI	10/111
		Major bleeding at 30 days	Upstream GPI	16/111
			Deferred GPI	9/109
Berglund, 2002[59]	Observational Total N: 1,430 Fair quality	Composite in hospital: Total mortality Nonfatal MI Revascularization	Clopidogrel	34/706
			No early clopidogrel	59/724
		Total mortality in hospital	Clopidogrel	2/706
			No early clopidogrel	1/724
		Nonfatal MI in hospital	Clopidogrel	31/706
			No early clopidogrel	52/724
		Revascularization in hospital	Clopidogrel	4/706
			No early clopidogrel	11/724

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Rasoul, 2006[12] ELISA-2	RCT Total N: 328 Fair quality	Primary composite at 30 days: Total mortality Nonfatal MI	GPI upstream	74/162
			GPI deferred	92/163
		Total mortality at 30 days	GPI upstream	1/162
			GPI deferred	1/163
		Major bleeding at 30 days	GPI upstream	20/162
			GPI deferred	16/163
		Nonfatal MI at 30 days	GPI upstream	74/162
			GPI deferred	92/163
		Stroke at 30 days	GPI upstream	0/162
			GPI deferred	0/163
Szuk, 2007[60]	Observational Total N: 4,160 Fair quality	Primary composite at 30 days: Total mortality Nonfatal MI Revascularization	Clopidogrel after PCI	127/2679
			Clopidogrel before PCI	41/1481
		Total mortality at 30 days	Clopidogrel after PCI	19/2679
			Clopidogrel before PCI	6/1481
		Nonfatal MI at 30 days	Clopidogrel after PCI	80/2679
			Clopidogrel before PCI	27/1481
		Revascularization at 30 days	Clopidogrel after PCI	29/2679
			Clopidogrel before PCI	9/1481
		Stent thrombosis at 30 days	Clopidogrel after PCI	56/2679
			Clopidogrel before PCI	16/1481
		Major bleeding at 30 days	Clopidogrel after PCI	11/2679
			Clopidogrel before PCI	21/1481
		Need for procedural GPI IIb/IIIa at 30 days	Clopidogrel after PCI	276/2679
			Clopidogrel before PCI	132/1481

Abbreviations: GP=glycoprotein; GPI=glycoprotein IIb/IIIa inhibitor; MI=myocardial infarction; N=number of patients; PCI=percutaneous coronary intervention; RCT=randomized controlled trial

Key Question 2: Comparisons for Initial Conservative Approach

Table G-9. Results data for enoxaparin vs. unfractionated heparin vs. fondaparinux: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
RCTs				
Antman, 1999[44] TIMI 11B Study	RCT Total N: 3,910 Good quality	Primary composite at 48 hrs: Total mortality Nonfatal MI Revascularization	Enoxaparin	OR (95% CI): 0.75 (0.58-0.97), reference group UFH
		Primary composite at 8 days: Total mortality Nonfatal MI Revascularization	Enoxaparin	OR (95% CI): 0.83 (0.69-1.00), reference group UFH
		Primary composite at 14 days: Total mortality Nonfatal MI Revascularization	Enoxaparin	OR (95% CI): 0.82 (0.69-0.98), reference group UFH
		Primary composite at 43 days: Total mortality Nonfatal MI Revascularization	Enoxaparin	OR (95% CI): 0.85 (0.72-1.00), reference group UFH
		Secondary composite at 48 hrs: Total mortality Nonfatal MI	Enoxaparin	OR (95% CI): 0.78 (0.49-1.24), reference group UFH
		Secondary composite at 8 days: Total mortality Nonfatal MI	Enoxaparin	OR (95% CI): 0.77 (0.58-1.02), reference group UFH
		Secondary composite at 14 days: Total mortality Nonfatal MI	Enoxaparin	OR (95% CI): 0.81 (0.62-1.05), reference group UFH
		Secondary composite at 43 days: Total mortality Nonfatal MI	Enoxaparin	OR (95% CI): 0.88 (0.70-1.11), reference group UFH
		Total mortality at 48 hrs	Enoxaparin	OR (95% CI): 1.84 (0.68-4.99), reference group UFH
		Total mortality at 8 days	Enoxaparin	OR (95% CI): 0.83 (0.52-1.31), reference group UFH
		Total mortality at 14 days	Enoxaparin	OR (95% CI): 0.78 (0.52-1.17), reference group UFH
		Total mortality at 43 days	Enoxaparin	OR (95% CI): 0.85 (0.72-1.00), reference group UFH

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Nonfatal MI at 48 hrs	Enoxaparin	OR (95% CI): 0.68 (0.41-1.13), reference group UFH
		Nonfatal MI at 8 days	Enoxaparin	OR (95% CI): 0.70 (0.51-0.97), reference group UFH
		Nonfatal MI at 14 days	Enoxaparin	OR (95% CI): 0.78 (0.58-1.05), reference group UFH
		Nonfatal MI at 43 days	Enoxaparin	OR (95% CI): 0.82 (0.63-1.07), reference group UFH
		Major bleeding at 72 hrs	Enoxaparin	15/1936
			UFH	14/1936
		Major bleeding during PCI	Enoxaparin	29/1936
			UFH	19/1936
		Major bleeding day at 8-43 hrs	Enoxaparin	34/1179
			Placebo	18/1185
		Minor bleeding at 72 hrs	Enoxaparin	99/1936
			UFH	45/1936
		Minor bleeding pre-catheterization	Enoxaparin	176/1936
			Placebo	228/1179
		Minor bleeding day 8-43	Enoxaparin	62/1185
			UFH	48/1936
Bertel, 2010[45] ZEUS Study	RCT Total N: 876 Fair quality	Primary composite at 30 days: Total mortality Nonfatal MI Revascularization Major bleeding	Enoxaparin	HR (95% CI): 0.78 (0.35-1.65), reference group UFH
		Secondary composite at 30 days: Major bleeding Minor bleeding Thrombocytopenia	Enoxaparin	HR (95% CI): 0.49 (0.30-0.78), reference group UFH
		Total mortality at 30 days	Enoxaparin	0/436
			UFH	0/440
		Nonfatal MI at 30 days	Enoxaparin	HR (95% CI): 0.28 (0.07-1.06), reference group UFH
		Revascularization at 30 days	Enoxaparin	HR (95% CI): 1.23 (0.17-11.49), reference group UFH
		Major bleeding at 30 days	Enoxaparin	16/436
			UFH	27/440
		Minor bleeding at 30 days	Enoxaparin	HR (95% CI): 0.49 (0.28-0.81), reference group UFH
		Stent thrombosis at 30 days	Enoxaparin	0/440
			UFH	4/440

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Bhatt, 2003[46] CRUISE Study	RCT Total N: 261 Fair quality	Primary composite at 30 days: Total mortality Nonfatal MI Revascularization	Enoxaparin	13/129
			UFH	10/132
		Total mortality at 30 days	Enoxaparin	0/129
			UFH	0/132
		Nonfatal MI at 30 days	Enoxaparin	11/129
			UFH	10/132
		Revascularization at 30 days	Enoxaparin	2/129
			UFH	1/132
		Major bleeding at 30 days	Enoxaparin	3/129
			UFH	2/132
		Minor bleeding at 30 days	Enoxaparin	18/129
			UFH	2/132
Blazing, 2004 [47] A to Z Study	RCT Total N: 3,987 Good quality	Primary composite at 7 days: Total mortality Nonfatal MI Refractory ischemia	Enoxaparin	HR (95% CI): 0.89 (0.72-1.11), reference group UFH
		Secondary composite at 7 days: Total mortality Nonfatal MI Revascularization Refractory ischemia Clinical ischemia	Enoxaparin	HR (95% CI): 0.89 (0.75-1.05), reference group UFH
		Total mortality at 7 days	Enoxaparin	HR (95% CI): 1.26 (0.67-2.38), reference group UFH
		Nonfatal MI at 7 days	Enoxaparin	HR (95% CI): 0.82 (0.60-1.13), reference group UFH
		Refractory ischemia at 7 days	Enoxaparin	HR (95% CI): 0.82 (0.61-1.10), reference group UFH
		Revascularization at 7 days	Enoxaparin	HR (95% CI): 0.98 (0.74 -1.29), reference group UFH
		Major bleeding at 7 days	Enoxaparin	0.9%
			UFH	0.4%
		Major or minor bleeding at 7 days	Enoxaparin	3%
			UFH	2.2%
Chen, 2006[49]	RCT Total N: 966 Poor quality	Composite in-hospital: Total mortality Nonfatal MI Revascularization	Enoxaparin	1/227
			UFH	0/228
		Composite 30 days: Total mortality Nonfatal MI Revascularization	Enoxaparin	0/227
			UFH	1/228
		Stent thrombosis in-hospital	Enoxaparin	1/227
			UFH	0/228
		Nonfatal MI in-hospital	Enoxaparin	1/227
			UFH	0/228

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Cohen, 1997[61] ESSENCE Study	RCT Total N: 3,171 Good quality	Primary Composite at 48 hrs: Total mortality Nonfatal MI Recurrent angina	Enoxaparin	OR (95% CI): 0.83 (0.62-1.09), reference group UFH
		Primary Composite at 14 days: Total mortality Nonfatal MI Recurrent angina	Enoxaparin	OR (95% CI): 0.80 (0.67-0.96), reference group UFH
		Primary Composite at 30 days: Total mortality Nonfatal MI Recurrent angina	Enoxaparin	OR (95% CI): 0.81 (0.68-0.96), reference group UFH
		Primary Composite at 1 yr: Total mortality Nonfatal MI Recurrent angina	Enoxaparin	HR (95% CI): 0.87 (0.77-0.98), reference group UFH
		Secondary Composite at 14 days: Total mortality Nonfatal MI	Enoxaparin UFH	79/1607 95/1564
		Secondary Composite at 30 days: Total mortality Nonfatal MI	Enoxaparin UFH	120/1564 99/1607
		Secondary Composite at 1 yr: Total mortality Nonfatal MI	Enoxaparin	HR (95% CI): 0.84 (0.69-1.02), reference group UFH
		Total mortality at 48 hrs	Enoxaparin	OR (95% CI): 1.12 (0.40-3.23)
		Total mortality at 14 days	Enoxaparin	OR (95% CI): 0.98 (0.61-1.56), reference group UFH
		Total mortality at 30 days	Enoxaparin	OR (95% CI): 0.79 (0.53-1.18), reference group UFH
		Nonfatal MI at 48 hrs	Enoxaparin	OR (95% CI): 0.76 (0.34-1.69)
		Nonfatal MI at 14 days	Enoxaparin	OR (95% CI): 0.70 (0.48-1.01), reference group UFH
		Nonfatal MI at 30 days	Enoxaparin	OR (95% CI): 0.74 (0.52-1.03), reference group UFH
		Recurrent angina at 48 hrs	Enoxaparin	OR (95% CI): 0.80 (0.60-1.09)
		Recurrent angina at 14 days	Enoxaparin	OR (95% CI): 0.80 (0.65-0.98), reference group UFH

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Recurrent angina at 30 days	Enoxaparin	OR (95% CI): 0.85 (0.70-1.02), reference group UFH
		Length of hospital stay at 30 days	Enoxaparin	Mean (SD): 8.9 +/- 6.7
			UFH	Mean (SD): 9.2 +/- 6.9
		Revascularization at 30 days	Enoxaparin	434/1607
			UFH	504/1564
		Major bleeding at 30 days	Enoxaparin	104/1607
			UFH	109/1564
		Stroke at 30 days	Enoxaparin	6/1607
			UFH	8/1564
		Minor bleeding at 30 days	Enoxaparin	191/1607
			UFH	113/1564
Cohen, 2002[62] ACUTE II Study	RCT Total N: 525 Fair quality	Total mortality at 30 days	Enoxaparin	8/315
			UFH	4/210
		Nonfatal MI at 30 days	Enoxaparin	21/315
			UFH	15/210
		Rehospitalization at 30 days	Enoxaparin	5/315
			UFH	15/210
		Length of hospital stay at 30 days	Enoxaparin	Mean (SD): 209 +/- 149 hrs
			UFH	Mean (SD): 208 +/- 189 hrs
		Major bleeding at 30 days	Enoxaparin	1/315
			UFH	2/210
		Minor bleeding at 30 days	Enoxaparin	7/315
			UFH	7/210
Ferguson, 2004[50] SYNERGY Study	RCT Total N: 10,027 Good quality	Primary Composite at 30 days: Total mortality Nonfatal MI	Enoxaparin	699/4993
			UFH	773/4985
		Primary Composite at 14 days: Total mortality Nonfatal MI	Enoxaparin	639/4993
			UFH	668/4985
		Primary Composite at 48 hrs: Total mortality Nonfatal MI	Enoxaparin	285/4993
			UFH	324/4985
		Total mortality at 30 days	Enoxaparin	160/4993
			UFH	155/4985
		Total mortality at 14 days	Enoxaparin	559/4993
			UFH	588/4985
		Total mortality at 48 hrs	Enoxaparin	270/4993
			UFH	299/4985
		Nonfatal MI at 30 days	Enoxaparin	584/4993
			UFH	633/4985
		Nonfatal MI at 14 days	Enoxaparin	120/4993
			UFH	120/4985
		Nonfatal MI at 48 hrs	Enoxaparin	20/4993
			UFH	26/4985
		GUSTO severe bleeding pre-catheterization	Enoxaparin	135/4993
			UFH	110/4983
		TIMI major bleeding pre-catheterization	Enoxaparin	454/4993
			UFH	379/4983
		Recurrent ischemia pre-	Enoxaparin	200/4993

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		catheterization	UFH	214/4985
		Stroke pre-catheterization	Enoxaparin	50/4993
			UFH	45/4985
Goodman, 2003[51] INTERACT Study	RCT Total N: 746 Good quality	Secondary Composite at 30 days: Total mortality Nonfatal MI Revascularization	Enoxaparin	53/380
			UFH	59/366
		Secondary Composite at 30 days: Total mortality Nonfatal MI	Enoxaparin	19/380
			UFH	33/366
		Secondary Composite at 300 days: Total mortality Nonfatal MI	Enoxaparin	19/380
			UFH	26/366
		Secondary Composite at 600 days: Total mortality Nonfatal MI	Enoxaparin	23/380
			UFH	36/366
		Secondary Composite at 900 days: Total mortality Nonfatal MI	Enoxaparin	31/380
			UFH	51/366
		Total mortality at 30 days	Enoxaparin	9/380
			UFH	15/366
		Nonfatal MI at 30 days	Enoxaparin	15/380
			UFH	21/366
		Revascularization at 30 days	Enoxaparin	28/380
			UFH	20/366
		Major bleeding at 48 hr	Enoxaparin	4/380
			UFH	14/366
		Recurrent ischemia at 48 hr	Enoxaparin	3/379
			UFH	1/365
Malhotra, 2001[63] ESCAPEU Study	RCT Total N: 98 Fair quality	Primary composite in-hospital pre-catheterization: Total mortality Nonfatal MI Revascularization Recurrent angina	Enoxaparin	19/51
			UFH	26/42
		Total mortality in-hospital pre-catheterization	Enoxaparin	0/51
			UFH	0/42
		Recurrent angina in-hospital pre-catheterization	Enoxaparin	17/51
			UFH	20/42
		Length of hospital stay	Enoxaparin	Mean (SD): 50 +/- 5
			UFH	Mean (SD): 56 +/- 6

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Mehta, 2005[53] ASPIRE	RCT Total N: 350 Fair quality	Primary Composite at 48 hr: Total mortality Nonfatal MI Revascularization Bailout GPI Use	UFH	7/117
			Fondaparinux 2.5mg	5/118
			Fondaparinux 5 mg	9/115
		Total mortality at 48 hr	UFH	0/117
			Fondaparinux 2.5mg	0/118
			Fondaparinux 5 mg	1/115
		Nonfatal MI at 48 hr	UFH	7/117
			Fondaparinux 2.5mg	4/118
			Fondaparinux 5 mg	9/115
		Revascularization at 48 hr	UFH	1/117
			Fondaparinux 2.5mg	0/118
			Fondaparinux 5 mg	2/115
		Major bleeding at 48 hr	UFH	0/117
			Fondaparinux 2.5mg	1/118
			Fondaparinux 5 mg	3/115
		Minor bleeding at 48 hr	UFH	9/117
			Fondaparinux 2.5mg	3/118
			Fondaparinux 5 mg	8/115
Yusuf, 2006[56] OASIS-5	RCT Total N: 20,078 Good quality	Primary Composite 9 days: Total mortality Nonfatal MI Refractory ischemia	Fondaparinux	HR (95% CI): 1.01 (0.90-1.13), reference group enoxaparin
		Primary Composite 30 days: Total mortality Nonfatal MI Refractory ischemia	Fondaparinux	HR (95% CI): 0.93 (0.84-1.02), reference group enoxaparin
		Primary Composite at 6 mo: Total mortality Nonfatal MI Refractory ischemia	Fondaparinux	HR (95% CI): 0.93 (0.86-1.00), reference group enoxaparin
		Secondary Composite at 9 days: Total mortality Nonfatal MI	Fondaparinux	HR (95% CI): 0.99 (0.86-1.13), reference group enoxaparin
		Secondary Composite at 30 days: Total mortality Nonfatal MI	Fondaparinux	HR (95% CI): 0.90 (0.81-1.01), reference group enoxaparin
		Secondary Composite at 6 mo: Total mortality Nonfatal MI	Fondaparinux	HR (95% CI): 0.92 (0.84-1.00), reference group enoxaparin

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Secondary Composite at 9 days: Total mortality Nonfatal MI Refractory ischemia Major bleeding	Fondaparinux	HR (95% CI): 0.81 (0.73-0.89), reference group enoxaparin
		Secondary Composite at 30 days: Total mortality Nonfatal MI Refractory ischemia Major bleeding	Fondaparinux	HR (95% CI): 0.82 (0.75-0.89), reference group enoxaparin
		Secondary Composite at 6 mo: Total mortality Nonfatal MI Refractory ischemia Major bleeding	Fondaparinux	HR (95% CI): 0.86 (0.81-0.93), reference group enoxaparin
		Total mortality at 9 days	Fondaparinux	HR (95% CI): 0.95 (0.77-1.17), reference group enoxaparin
		Total mortality at 30 days	Fondaparinux	HR (95% CI): 0.83 (0.71-0.97) , reference group enoxaparin
		Total mortality at 6 mo	Fondaparinux	HR (95% CI): 0.89 (0.80-1.00) , reference group enoxaparin
		Nonfatal MI at 9 days	Fondaparinux	HR (95% CI): 0.99 (0.84-1.18) , reference group enoxaparin
		Nonfatal MI at 30 days	Fondaparinux	HR (95% CI): 0.94 (0.82-1.08) , reference group enoxaparin
		Nonfatal MI at 6 mo	Fondaparinux	HR (95% CI): 0.95 (0.85-1.06) , reference group enoxaparin
		Stroke at 9 days	Fondaparinux	HR (95% CI): 0.82 (0.53-1.27) , reference group enoxaparin
		Stroke at 30 days	Fondaparinux	HR (95% CI): 0.77 (0.57-1.05) , reference group enoxaparin
		Stroke at 180 days	Fondaparinux	HR (95% CI): 0.78 (0.62-0.99) , reference group enoxaparin
		Refractory ischemia at 9 days	Fondaparinux	HR (95% CI): 1.03 (0.84-1.18) , reference group enoxaparin

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Refractory ischemia at 30 days	Fondaparinux	HR (95% CI): 0.99 (0.82-1.19) , reference group enoxaparin
		Refractory ischemia at 180 days	Fondaparinux	HR (95% CI): 0.97 (0.81-1.16) , reference group enoxaparin
		Major bleeding at 9 days	Fondaparinux	HR (95% CI): 0.52 (0.44-0.61) , reference group enoxaparin
		Major bleeding at 30 days	Fondaparinux	HR (95% CI): 0.62 (0.54-0.72) , reference group enoxaparin
		Major bleeding at 180 days	Fondaparinux	HR (95% CI): 0.72 (0.64 -0.82) , reference group enoxaparin
Observational Studies				
Angkasuwapala, 2007[64] Thai ACS Registry	Observational Total N: 3,963 Poor quality	Total mortality in-hospital	LMWH	174/3341
			UFH	58/622
Brieger, 2007[48]	Observational Total N: 17,659 Fair quality	Total mortality in-hospital	LMWH	OR (95% CI): 0.76 (0.63-0.91), reference group UFH
		Major bleeding in-hospital	LMWH	OR (95% CI): 0.78 (0.64-0.95), reference group UFH
Gore, 2007[65]	Observational Total N: 23,172 Fair quality	Composite in-hospital: Total mortality Nonfatal MI Recurrent ischemia	LMWH	OR (95% CI): 1.44 (1.29-1.62), reference group no heparin
			UFH	OR (95% CI): 1.63 (1.43-1.85), reference group no heparin
			Crossover	OR (95% CI): 1.93 (1.71-2.17), reference group no heparin
		Total mortality in-hospital	LMWH	OR (95% CI): 0.79 (0.56-1.11), reference group no heparin
			UFH	OR (95% CI): 1.18 (0.81-1.70), reference group no heparin
			Crossover	OR (95% CI): 1.15 (0.81-1.62)

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Major bleeding in-hospital	LMWH	OR (95% CI): 0.97 (0.66-1.43) , reference group no heparin
			UFH	OR (95% CI): 0.91 (0.60-1.39) , reference group no heparin
			Crossover	OR (95% CI): 1.00 (0.68-1.47) , reference group no heparin
Kovar, 2002[66]	Observational Total N: 37,320 Fair quality	Primary composite in-hospital: Total mortality Nonfatal MI Major bleeding Recurrent ischemia	Enoxaparin	OR (95% CI): 0.92 (0.83-1.02), reference group UFH
		Major bleeding in-hospital	Enoxaparin	OR (95% CI): 1.01 (0.78-1.31), reference group UFH
		Total mortality in-hospital	Enoxaparin	OR (95% CI): 0.88 (0.70-1.11), reference group UFH
		Nonfatal MI in-hospital	Enoxaparin	OR (95% CI): 0.74 (0.52-1.05), reference group UFH
		Recurrent ischemia in-hospital	Enoxaparin	OR (95% CI): 0.93 (0.82-1.06)
LaPointe, 2007[67]	Observational Total N: 10,687 Good quality	Major bleeding in-hospital	Enoxaparin above recommended	OR (95% CI): 1.47 (1.21-1.80), reference group enoxaparin recommended dose
			Enoxaparin below recommended	OR (95% CI): 1.01 (0.84-1.22), reference group enoxaparin recommended dose
		Total mortality in-hospital	Enoxaparin above recommended	OR (95% CI): 1.31 (0.99-1.73), reference group enoxaparin recommended dose
			Enoxaparin below recommended	OR (95% CI): 1.19 (0.89-1.59), reference group enoxaparin recommended dose

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Li, 2012[68] KAMIR Study	Observational Total N: 2,397 Good quality	Secondary composite at 8 mo: Total mortality CV mortality Repeat revascularization	Enoxaparin	89/1178
			UFH	92/1219
		Total mortality in-hospital	Enoxaparin	20/1178
			UFH	16/1219
		Total mortality at 8 mo	Enoxaparin	41/1178
			UFH	33/1219
		Nonfatal MI at 8 mo	Enoxaparin	3/1178
			UFH	12/1219
		CV mortality in-hospital	Enoxaparin	15/1178
			UFH	12/1219
		CV mortality at 8 mo	Enoxaparin	29/1178
			UFH	22/1219
		Major bleeding in-hospital	Enoxaparin	4/1178
			UFH	3/1219
		Minor bleeding in-hospital	Enoxaparin	13/1178
			UFH	11/1219
Schiele, 2010[69]	Observational Total N: 2,874 Good quality	Total mortality at 30 days	Enoxaparin	51/1418
			UFH	105/604
			Fondaparinux	10/301
		Major bleeding in-hospital pre-catheterization	Enoxaparin	30/1418
			UFH	30/604
			Fondaparinux	10/301
Singh, 2006[54]	Observational Total N: 11,358 Fair quality	Composite in-hospital: Total mortality Nonfatal MI	LMWH	OR (95% CI): 0.81 (0.67-0.99), reference group UFH
		Total mortality in-hospital	LMWH	OR (95% CI): 0.89 (0.68-1.18), reference group UFH
		Transfusion in-hospital	LMWH	OR (95% CI): 1.01 (0.89-1.15), reference group UFH

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Spinler, 2003[70]	Observational Total N: 7,081 Fair quality	Primary composite at 43 days in non-obese group: Total mortality Nonfatal MI Revascularization	UFH	492/2563
			Enoxaparin	418/2595
		Primary composite at 43 days in non-CKD group: Total mortality Nonfatal MI Revascularization	UFH	625/3394
			Enoxaparin	539/3432
		Total mortality at 43 days in non-obese group	UFH	113/2563
			Enoxaparin	91/2595
		Total mortality at 43 days in non-CKD group	UFH	115/3394
			Enoxaparin	106/3432
		Nonfatal MI at 43 days in non-obese group	UFH	154/2563
			Enoxaparin	125/2595
		Nonfatal MI at 43 days in non-CKD group	UFH	204/3394
			Enoxaparin	165/3432
		Revascularization at 43 days in non-obese group	UFH	308/2563
			Enoxaparin	257/2595
		Revascularization at 43 days in non-CKD group	UFH	404/3394
			Enoxaparin	340/3432
		Major bleeding at 43 days in non-obese group	UFH	25/2563
			Enoxaparin	41/2595
		Major bleeding at 43 days in non-CKD group	UFH	34/3394
			Enoxaparin	41/3432
		All bleeding at 43 days in non-obese group	UFH	101/2563
			Enoxaparin	243/2595
		All bleeding at 43 days in non-CKD group	UFH	132/3394
			Enoxaparin	336/3432

Abbreviations: CI=confidence interval; CKD=chronic kidney disease; CV=cardiovascular; GPI=glycoprotein IIb/IIIa inhibitor; GUSTO=global utilization of streptokinase and t-PA for occluded arteries; HR=hazard ratio; hr=hour/hours; LMWH=low molecular weight heparin; mg=milligram/milligrams; MI=myocardial infarction; mo=month/months; N=number of patients; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SD=standard deviation; TIMI=thrombolysis in myocardial infarction; UFH=unfractionated heparin; vs=versus

Table G-10. Results data for glycoprotein IIb/IIIa inhibitors: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Anonymous, 1998[71] PURSUIT Study	RCT Total N: 10,948 Good quality	Primary composite at 96 hrs: Total mortality Nonfatal MI	Eptifibatide 2.0 mcg/kg/min	359/4722
			Placebo	431/4739
		Primary composite at 7 days: Total mortality Nonfatal MI	Eptifibatide 2.0 mcg/kg/min	477/4722
			Placebo	550/4739
		Primary composite at 30 days: Total mortality Nonfatal MI	Eptifibatide 2.0 mcg/kg/min	671/4722
			Placebo	744/4739
		Total mortality at 96 hrs	Eptifibatide 2.0 mcg/kg/min	42/4722
			Placebo	33/4739
		Total mortality at 7 days	Eptifibatide 2.0 mcg/kg/min	71/4722
			Placebo	95/4739
		Total mortality at 30 days	Eptifibatide 2.0 mcg/kg/min	165/4722
			Placebo	175/4739
		Nonfatal MI at 96 hrs	Eptifibatide 2.0 mcg/kg/min	335/4722
			Placebo	393/4739
		Nonfatal MI at 7 days	Eptifibatide 2.0 mcg/kg/min	439/4722
			Placebo	493/4739
		Nonfatal MI at 30 days	Eptifibatide 2.0 mcg/kg/min	595/4722
			Placebo	640/4739
		TIMI major bleeding pre-catheterization	Eptifibatide 2.0 mcg/kg/min	496/4679
			Placebo	427/4696
		GUSTO severe bleeding pre-catheterization	Eptifibatide 2.0 mcg/kg/min	70/4679
			Placebo	42/4696
		Minor bleeding pre-catheterization	Eptifibatide 2.0 mcg/kg/min	604/4679
			Placebo	348/4696
		Length of hospital stay	Eptifibatide 2.0 mcg/kg/min	9.4 days
			Placebo	10.4 days
Anonymous, 1998[72] PRISM Study	RCT Total N: 3232 Good quality	Primary composite at 48 hrs: Total mortality Nonfatal MI Refractory ischemia	Tirofiban	RR (95% CI): 0.67 (0.48-0.92), reference group UFH
		Primary composite at 7 days: Total mortality Nonfatal MI Refractory ischemia	Tirofiban	RR (95% CI): 0.90 (0.73-1.11), reference group UFH
		Primary composite at 30 days: Total mortality Nonfatal MI Refractory ischemia	Tirofiban	RR (95% CI): 0.92 (0.78-1.09), reference group UFH

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Secondary composite at 48 hrs: Total mortality Nonfatal MI	Tirofiban	RR (95% CI): 0.76 (0.42-1.39), reference group UFH
		Secondary composite at 7 days: Total mortality Nonfatal MI	Tirofiban	RR (95% CI): 0.77 (0.54-1.11), reference group UFH
		Secondary composite at 30 days: Total mortality Nonfatal MI	Tirofiban	RR (95% CI): 0.80 (0.61-1.05), reference group UFH
		Refractory ischemia at 48 hrs	Tirofiban	RR (95% CI): 0.65 (0.46-0.91), reference group UFH
		Refractory ischemia at 7 days	Tirofiban	RR (95% CI): 0.91 (0.73-1.14), reference group UFH
		Refractory ischemia at 30 days	Tirofiban	RR (95% CI): 0.98 (0.79-1.21), reference group UFH
		Nonfatal MI at 48 hrs	Tirofiban	RR (95% CI): 0.64 (0.33-1.25), reference group UFH
		Nonfatal MI at 7 days	Tirofiban	RR (95% CI): 0.84 (0.56-1.26), reference group UFH
		Nonfatal MI at 30 days	Tirofiban	RR (95% CI): 0.95 (0.68-1.34), reference group UFH
		Total mortality at 48 hrs	Tirofiban	RR (95% CI): 1.48 (0.42-5.27), reference group UFH
		Total mortality at 7 days	Tirofiban	RR (95% CI): 0.63 (0.34-1.18), reference group UFH
		Total mortality at 30 days	Tirofiban	RR (95% CI): 0.62 (0.41-0.93), reference group UFH
		Major bleeding at 48 hrs	Tirofiban	6/1616
			UFH	6/1616
		Minor bleeding at 48 hrs	Tirofiban	32/1616
			UFH	32/1616

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Anonymous, 1998[73] PRISM-PLUS Study	RCT Total N:1875 Good quality	Primary composite at 48 hrs: Total mortality Nonfatal MI Rehospitalization Refractory ischemia	Tirofiban + UFH	RR (95% CI): 0.71 (0.48-1.04), reference group UFH
		Primary composite at 7 days: Total mortality Nonfatal MI Rehospitalization Refractory ischemia	Tirofiban + UFH	RR (95% CI): 0.68 (0.53-0.88) , reference group UFH
		Primary composite at 30 days: Total mortality Nonfatal MI Rehospitalization Refractory ischemia	Tirofiban + UFH	RR (95% CI): 0.78 (0.63-0.98) , reference group UFH
		Primary composite at 6 mo: Total mortality Nonfatal MI Rehospitalization Refractory ischemia	Tirofiban + UFH	RR (95% CI): 0.81 (0.68-0.97) , reference group UFH
		Secondary composite at 48 hrs: Total mortality Nonfatal MI	Tirofiban + UFH	RR (95% CI): 0.34 (0.14-0.79) , reference group UFH
		Secondary composite at 7 days: Total mortality Nonfatal MI	Tirofiban + UFH	RR (95% CI): 0.57 (0.38-0.85) , reference group UFH
		Secondary composite at 30 days: Total mortality Nonfatal MI	Tirofiban + UFH	RR (95% CI): 0.70 (0.51-0.96) , reference group UFH
		Secondary composite at 6 mo: Total mortality Nonfatal MI	Tirofiban + UFH	RR (95% CI): 0.78 (0.59-1.01) , reference group UFH
		Nonfatal MI at 48 hrs	Tirofiban + UFH	RR (95% CI): 0.32 (0.13-0.80)
		Nonfatal MI at 7 days	Tirofiban + UFH	RR (95% CI): 0.53 (0.34-0.83)
		Nonfatal MI at 30 days	Tirofiban + UFH	RR (95% CI): 0.70 (0.49-1.00)
		Nonfatal MI at 6 mo	Tirofiban + UFH	RR (95% CI): 0.76 (0.59-1.01)
		Total mortality at 48 hrs	Tirofiban + UFH	RR (95% CI): 0.51 (0.05-5.63)
		Total mortality at 7 days	Tirofiban + UFH	RR (95% CI): 1.01 (0.49-2.06)
		Total mortality at 30 days	Tirofiban + UFH	RR (95% CI): 0.79 (0.48-1.30)
		Total mortality at 6 mo	Tirofiban + UFH	RR (95% CI): 0.97 (0.66-1.41)
		Major bleeding in-hospital	Tirofiban + UFH	31/773
			UFH	24/797
		TIMI major bleeding at undefined time point	Tirofiban + UFH	11/773
			UFH	6/797

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Transfusion in-hospital	Tirofiban + UFH	31/773
			UFH	22/797
Bhattacharya, 2010[1]	RCT Total N: 301 Good quality	Fatal MI at 7 days	Tirofiban	1/136
			Placebo	8/165
		Fatal MI at 14 days	Tirofiban	1/122
			Placebo	6/133
		Fatal MI at 30 days	Tirofiban	2/105
			Placebo	5/99
		Fatal MI at 3 mo	Tirofiban	2/85
			Placebo	2/64
		Nonfatal MI at 7 days	Tirofiban	1/136
			Placebo	8/165
		Nonfatal MI at 14 days	Tirofiban	2/122
			Placebo	9/133
		Nonfatal MI at 30 days	Tirofiban	3/105
			Placebo	5/99
		Nonfatal MI at 3 mo	Tirofiban	2/85
			Placebo	5/64
		Refractory ischemia at 7 days	Tirofiban	10/136
			Placebo	13/165
		Refractory ischemia at 14 days	Tirofiban	10/122
			Placebo	12/133
		Refractory ischemia at 30 days	Tirofiban	14/105
			Placebo	24/99
		Refractory ischemia at 3 mo	Tirofiban	25/85
			Placebo	36/64
		Death due to unknown causes at 7 days	Tirofiban	2/136
			Placebo	3/165
		Death due to unknown causes at 14 days	Tirofiban	1/122
			Placebo	1/133
		Death due to unknown causes at 30 days	Tirofiban	0/105
			Placebo	0/99
		Death due to unknown causes at 3 mo	Tirofiban	1/85
			Placebo	1/64
		Major bleeding at 7 days, 14 days, 30 days, and 3 mo	Tirofiban	0/136
			Placebo	0/165
Momtahen, 2009[10]	RCT Total N: 196 Fair quality	Primary composite at 30 days: Total mortality Nonfatal MI Revascularization	Eptifibatide	0/98
			Placebo	16/98
		Nonfatal MI at 30 days	Eptifibatide	0/98
			Placebo	9/98
		Minor bleeding at 30 days	Eptifibatide	7/98
			Placebo	0/98
		Total mortality at 30 days	Eptifibatide	0/98
			Placebo	2/98
		Major bleeding at 30 days	Eptifibatide	0/98
			Placebo	0/98
		Revascularization at 30 days	Eptifibatide	0/98
			Placebo	4/98

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Okmen, 2003[74]	RCT Total N: 83 Fair quality	Secondary composite in-hospital: Total mortality Nonfatal MI Revascularization Refractory angina	Tirofiban	11/41
			No Tirofiban	23/42
		Total mortality in-hospital	Tirofiban	0/41
			No Tirofiban	0/42
		Nonfatal MI in-hospital	Tirofiban	1/41
			No Tirofiban	8/42
		Revascularization in-hospital	Tirofiban	1/41
			No Tirofiban	0/42
		Major bleeding in-hospital	Tirofiban	0/41
			No Tirofiban	0/42
		Minor bleeding in-hospital	Tirofiban	2/41
			No Tirofiban	2/42
		Recurrent angina in-hospital	Tirofiban	11/41
			No Tirofiban	21/42
Simoons, 2001[75] GUSTO-IV Study	RCT Total N: 7800 Good quality	Primary composite at 48 hrs: Total mortality Nonfatal MI	Abciximab 24 hr	OR (95% CI): 1.3 (0.83-1.91), reference group placebo
			Abciximab 48 hr	OR (95% CI): 1.5 (0.97-2.18) , reference group placebo
		Primary composite at 7 days: Total mortality Nonfatal MI	Abciximab 24 hr	OR (95% CI): 0.9 (0.68-1.16) , reference group placebo
			Abciximab 48 hr	OR (95% CI): 0.9 (0.69-1.18) , reference group placebo
		Primary composite at 30 days: Total mortality Nonfatal MI	Abciximab 24 hr	OR (95% CI): 1.0 (0.83-1.24) , reference group placebo
			Abciximab 48 hr	OR (95% CI): 1.1 (0.94-1.39) , reference group placebo
		Total mortality at 48 hrs	Abciximab 24 hr	OR (95% CI): 2.3 (0.98-5.22) , reference group placebo
			Abciximab 48 hr	OR (95% CI): 2.9 (1.28-6.44) , reference group placebo
		Total mortality at 7 days	Abciximab 24 hr	OR (95% CI): 0.90 (0.55-1.30) , reference group placebo
			Abciximab 48 hr	OR (95% CI): 1.1 (0.77-1.71) , reference group placebo
		Total mortality at 30 days	Abciximab 24 hr	OR (95% CI): 0.90

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
				(0.64-1.50) , reference group placebo
			Abciximab 48 hr	OR (95% CI): 1.1 (0.83-1.43) , reference group placebo
		Total mortality at 1 yr	Abciximab 24 hr	212/2590
			Abciximab 48 hr	235/2612
			Placebo	203/2598
		Nonfatal MI at 48 hrs	Abciximab 24 hr	OR (95% CI): 1.0 (0.62-1.62) , reference group placebo
			Abciximab 48 hr	OR (95% CI): 1.1 (0.68-1.73) , reference group placebo
		Nonfatal MI at 7 days	Abciximab 24 hr	OR (95% CI): 0.90 (0.62-1.19) , reference group placebo
			Abciximab 48 hr	OR (95% CI): 0.80 (0.60-1.15) , reference group placebo
		Nonfatal MI at 30 days	Abciximab 24 hr	OR (95% CI): 1.1 (0.87-1.41) , reference group placebo
			Abciximab 48 hr	OR (95% CI): 1.2 (0.91-1.46) , reference group placebo
		Major bleeding in-hospital	Abciximab 24 hr	16/2590
			Abciximab 48 hr	26/2612
			Placebo	8/2598
		Transfusion in-hospital	Abciximab 24 hr	52/2590
			Abciximab 48 hr	78/2612
			Placebo	52/2598
Song, 2007[76]	RCT Total N: 204 Good quality	Primary composite at 30 days: Total mortality Nonfatal MI Refractory ischemia	Tirofiban	14/101
			Placebo	29/99
		Total mortality at 30 days	Tirofiban	1/101
			Placebo	3/99
		Nonfatal MI at 30 days	Tirofiban	3/101
			Placebo	7/99
		Refractory ischemia at 30 days	Tirofiban	12/101
			Placebo	22/99

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Stone, 2006[42] ACUITY Study	RCT Total N: 13,819 Good quality	Primary composite #1 at 30 days: Total mortality Nonfatal MI Revascularization	Bivalirudin	360/4612
			Bivalirudin + GPI	355/4604
			UFH/enoxaparin +GPI	336/4603
		Primary composite #1 at 1 yr: Total mortality Nonfatal MI Revascularization	Bivalirudin	585/3612
			Bivalirudin + GPI	737/4604
			UFH/enoxaparin +GPI	709/4603
		Primary composite #2 at 30 days: Total mortality Nonfatal MI Revascularization Major bleeding	Bivalirudin	466/4612
			Bivalirudin + GPI	543/4603
			UFH/enoxaparin +GPI	539/4603
		Major bleeding at 30 days	Bivalirudin	138/4612
			Bivalirudin + GPI	244/4604
			UFH/enoxaparin +GPI	262/4603
		Thrombocytopenia at 30 days	Bivalirudin	457/4612
			Bivalirudin + GPI	497/4604
			UFH/enoxaparin +GPI	511/4603
		Minor bleeding at 30 days	Bivalirudin	590/4612
			Bivalirudin + GPI	999/4604
			UFH/enoxaparin +GPI	994/4603
		Total mortality at 30 days	Bivalirudin	74/4612
			Bivalirudin + GPI	69/4604
			UFH/enoxaparin +GPI	60/4603
		Total mortality at 1 yr	Bivalirudin	175/4612
			Bivalirudin + GPI	180/4604
			UFH/enoxaparin +GPI	180/4603
		Nonfatal MI at 30 days	Bivalirudin	249/4612
			Bivalirudin + GPI	230/4604
			UFH/enoxaparin +GPI	225/4603
		Nonfatal MI at 1 yr	Bivalirudin	360/4612
			Bivalirudin + GPI	327/4604
			UFH/enoxaparin +GPI	318/4603
		Revascularization at 30 days	Bivalirudin	111/4612
			Bivalirudin + GPI	124/4604
			UFH/enoxaparin +GPI	106/4603
		Revascularization at 1 yr	Bivalirudin	401/4612
			Bivalirudin +	419/4604

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
			GPI	
			UFH/enoxaparin +GPI	387/4603
		Stent thrombosis at 30 days	Bivalirudin	11/1128
			Bivalirudin + GPI	12/1165
			UFH/enoxaparin +GPI	9/1112
		Length of hospital stay	Bivalirudin	Mean (SD): 3.4 +/- 3.3 days
			Bivalirudin + GPI	Mean (SD): 3.5 +/- 3.5 days
			UFH/enoxaparin +GPI	Mean (SD): 3.7 +/- 3.5 days
Stone, 2007[14] ACUITY TIMING Study	RCT Total N: 9,207 Good quality	Primary composite at 30 days: Total mortality Nonfatal MI Revascularization	GPI upstream	326/4605
			GPI deferred	364/4602
		Secondary composite at 30 days: Total mortality Nonfatal MI	GPI upstream	272/4605
			GPI deferred	285/4602
		Secondary composite at 30 days: Total mortality Nonfatal MI Revascularization Major bleeding	GPI upstream	539/4605
			GPI deferred	538/4602
		Total mortality at 30 days	GPI upstream	60/4605
			GPI deferred	69/4602
		Nonfatal MI at 30 days	GPI upstream	211/4605
			GPI deferred	230/4602
		Revascularization at 30 days	GPI upstream	97/4605
			GPI deferred	129/4602
		Major bleeding at 30 days	GPI upstream	281/4605
			GPI deferred	225/4602
Van den Brand, 1995[77]	RCT Total N: 60 Fair quality	Primary composite at 30 days: Total mortality Nonfatal MI Recurrent ischemia	Abciximab	1/30
			Placebo	12/30
		Total mortality at 30 days	Abciximab	0/30
			Placebo	1/30
		Nonfatal MI at 30 days	Abciximab	1/30
			Placebo	3/30
		Recurrent ischemia at 30 days	Abciximab	0/30
			Placebo	7/30

Abbreviations: CI=confidence interval; GPI=glycoprotein IIb/IIIa inhibitor; GUSTO=global utilization of streptokinase and t-PA for occluded arteries; hr=hour/hours; kg=kilogram/kilograms; mcg=microgram/micrograms; MI=myocardial infarction; min=minute/minutes; mo=month/months; N=number of patients; OR=odds ratio; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation; TIMI=thrombolysis in myocardial infarction; UFH=unfractionated heparin

Table G-11. Results data for clopidogrel versus ticagrelor or prasugrel: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
Roe, 2012[78] TRILOGY ACS	RCT Total N: 7243 Good quality	Primary Composite at 17 mo: CV mortality Nonfatal MI Stroke	Prasugrel	364/3620
			Clopidogrel	397/3623
		Secondary Composite at 17 mo: CV mortality Nonfatal MI	Prasugrel	348/3620
			Clopidogrel	370/3623
		Secondary Composite at 17 mo: Total mortality Nonfatal MI Stroke	Prasugrel	399/3620
			Clopidogrel	429/3623
		Rehospitalization at 17 mo	Prasugrel	95/3620
			Clopidogrel	92/3623
		CV mortality at 17 mo	Prasugrel	167/3620
			Clopidogrel	179/3623
		Nonfatal MI at 17 mo	Prasugrel	217/3620
			Clopidogrel	244/3623
		Stroke at 17 mo	Prasugrel	31/3620
			Clopidogrel	46/3623
		Total mortality at 17 mo	Prasugrel	208/3620
			Clopidogrel	218/3623
		Major bleeding at 17 mo	Prasugrel	39/3590
			Clopidogrel	30/3590
		Major or minor bleeding at 17 mo	Prasugrel	70/3590
			Clopidogrel	46/3590
Wallentin, 2009[29] James, 2011[79] PLATO	RCT Total N: 18,624 Good quality	Primary Composite at 30 days: CV mortality Nonfatal MI Stroke	Ticagrelor	505/9333
			Clopidogrel	447/9291
		Primary Composite at 277 days: CV mortality Nonfatal MI Stroke	Ticagrelor	915/9333
			Clopidogrel	1087/9291
		Secondary Composite at 277 days: CV mortality Nonfatal MI Stroke Recurrent ischemia Other arterial thrombotic event	Ticagrelor	1290/9333
			Clopidogrel	1456/9291
		Secondary Composite at 277 days: Total mortality Nonfatal MI Stroke	Ticagrelor	901/9333
			Clopidogrel	1065/9291
		Secondary Composite (invasive treatment planned) at 277 days: CV mortality Nonfatal MI	Ticagrelor	569/6732
			Clopidogrel	688/6676

Study	Study Details	Outcome(s) Length of Followup	Results Reported by Authors	
		Stroke		
		Minor bleeding at 277 days	Ticagrelor	360/9235
			Clopidogrel	322/9186
		Major or minor bleeding at 277 days	Ticagrelor	1339/9235
			Clopidogrel	1215/9186
		Total mortality at 277 days	Ticagrelor	420/9333
			Clopidogrel	548/9291
		Adverse drug reactions (bradycardia) at 277 days	Ticagrelor	409/9235
			Clopidogrel	372/9186
		Stroke at 277 days	Ticagrelor	140/9333
			Clopidogrel	121/9291
		Major bleeding at 277 days	Ticagrelor	961/9235
			Clopidogrel	929/9186
		Adverse drug reactions (dyspnea) at 277 days	Ticagrelor	1270/9235
			Clopidogrel	721/9186
		CV mortality at 277 days	Ticagrelor	373/9333
			Clopidogrel	474/9291
		Nonfatal MI at 277 days	Ticagrelor	541/9333
			Clopidogrel	641/9291
		TIMI major or minor bleeding at 277 days	Ticagrelor	946/9235
			Clopidogrel	906/9186
		TIMI major bleeding at 277 days	Ticagrelor	657/9235
			Clopidogrel	638/9186
		Stent thrombosis at 277 days	Ticagrelor	73/5640
			Clopidogrel	107/5649

Abbreviations: CV=cardiovascular; MI=myocardial infarction; mo=month/months; N=number of patients; RCT=randomized controlled trial; TIMI=thrombolysis in myocardial infarction

Key Question 3: Comparisons for Postdischarge Treatment

Table G-12. Results data for low-dose vs. high-dose aspirin: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Aronow, 2008[80] BRAVO Study	Observational Total N: 4,589 Good quality	Secondary Composite at 1 yr: Total mortality Nonfatal MI Stroke	ASA <162mg/d	147/2368
			ASA >162mg/d	135/2221
		Secondary Composite at 1 yr: Total mortality Nonfatal MI Stroke Revascularization Rehospitalization	ASA <162mg/d	391/2368
			ASA >162mg/d	410/2221
		Total mortality at 1 yr	ASA <162mg/d	68/2368
			ASA >162mg/d	36/2221
		Nonfatal MI at 1 yr	ASA <162mg/d	48/2368
			ASA >162mg/d	45/2221
		Anemia at 1 yr	ASA <162mg/d	70/2368
			ASA >162mg/d	97/2221
		Stroke at 1 yr	ASA <162mg/d	48/2368
			ASA >162mg/d	63/2221
		Rehospitalization at 1 yr	ASA <162mg/d	228/2368
			ASA >162mg/d	230/2221
		Revascularization at 1 yr	ASA <162mg/d	175/2368
			ASA >162mg/d	220/2221
		Major bleeding at 1 yr	ASA <162mg/d	56/2368
			ASA >162mg/d	74/2221
		Any bleeding at 1 yr	ASA <162mg/d	264/2368
			ASA >162mg/d	339/2221
		Transfusion at 1 yr	ASA <162mg/d	25/2368
			ASA >162mg/d	43/2221
		Intracranial Hemorrhage at 1 yr	ASA <162mg/d	4/2368
			ASA >162mg/d	5/2221
Harjai, 2011[81] GHOST Registry	Observational Total N: 2,820 Fair quality	Primary Composite at 1 yr: Total mortality Nonfatal MI	ASA 81 mg/d	15/136
			ASA 161-325 mg/d	65/996
		Major bleeding at 1 yr	ASA 81 mg/d	6/136
			ASA 161-325 mg/d	17/996
Quinn, 2004[82] Gusto IIb and PURSUIT trials	Observational Total N: 20,469 Good quality	Primary Composite at 6 mo: Total mortality Nonfatal MI Stroke	ASA < 150 mg	374/6128
			ASA >150 mg	936/14393
		Total mortality at 6 mo	ASA < 150 mg	194/6107
			ASA >150 mg	433/14360
		Nonfatal MI at 6 mo	ASA < 150 mg	209/6084
			ASA >150 mg	515/14262
		Stroke at 6 mo	ASA < 150 mg	28/6019
			ASA >150 mg	102/14169

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
So, 2009[83]	Observational Total N: 1,840 Fair quality	Primary Composite at 1 yr: Total mortality Nonfatal MI	ASA 81 mg/d	50/910
			ASA 325 mg/d	39/930
		Secondary Composite at 1 yr: Total mortality Nonfatal MI Revascularization	ASA 81 mg/d	105/910
			ASA 325 mg/d	100/930
		Total mortality at 1 yr	ASA 81 mg/d	33/910
			ASA 325 mg/d	29/930
		Revascularization at 1 yr	ASA 81 mg/d	69/910
			ASA 325 mg/d	73/930
Wallentin, 2009[29] Mahaffey, 2012[84] PLATO	RCT Total N: 18,624 Good quality	Primary composite outcome at 1 yr: CV mortality Nonfatal MI Stroke	ASA <300 mg + ticagrelor	629/8258
			ASA <300 mg + clopidogrel	788/8233
			ASA ≥300 mg + ticagrelor	68/464
			ASA ≥300 mg + clopidogrel	50/492
Yusuf, 2001[85] Peters, 2003[86] CURE study	RCT Total N: 12,562 Good quality	Primary composite outcome at 1 yr: CV mortality Nonfatal MI Stroke	ASA ≤100 mg	559/5320
			ASA 101-199 mg	305/3109
			ASA ≥ 200 mg	559/4110
			DAPT, ASA ≤100 mg	457/5320
			DAPT, ASA 101-199 mg	295/3109
			DAPT, ASA ≥ 200 mg	403/4110
		Major bleeding at 1 yr	ASA ≤100 mg	101/5320
			ASA 101-199 mg	87/3109
			ASA ≥ 200 mg	152/4110
			DAPT, ASA ≤100 mg	160/5320
			DAPT, ASA 101-199 mg	106/3109
			DAPT, ASA ≥ 200 mg	201/4110

Abbreviations: ASA=aspirin; CV=cardiovascular; d=day/days; mg=milligram/milligrams; MI=myocardial infarction; mo=month/months; N=number of patients; yr=year/years

Table G-13. Results data for single antiplatelet vs. dual antiplatelet therapy: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Alexander, 2008[87] CRUSADE Registry	Observational Total N: 93,045 Fair quality	Primary composite in-hospital: Total mortality Nonfatal MI	Clopidogrel	1938/35880
			No clopidogrel	4345/57165
		Total mortality in-hospital	Clopidogrel	1256/35880
			No clopidogrel	3030/57165
		Major bleeding in-hospital	Clopidogrel	5741/35880
			No clopidogrel	11776/57165
		Nonfatal MI in-hospital	Clopidogrel	852/33880
			No clopidogrel	1715/57165
		Stroke in-hospital	Clopidogrel	251/33880
			No clopidogrel	572/57165
		Transfusion in-hospital	Clopidogrel	4811/33880
			No clopidogrel	10118/57165
Bonde, 2010[88]	Observational Total N: 11,142 Fair quality	Total mortality at 2 yr	Clopidogrel	325/3453
			No Clopidogrel	1199/12360
Cheng, 2010[89] T-ACCORD Registry	Observational Total N: 1,331 Good quality	Survival rate at 1 yr	ASA	121/225
			Clopidogrel	130/250
Lim, 2005[90]	Observational Total N: 6,239 Fair quality	Total mortality at 6 mo	ASA	194/3342
			ASA + Clopidogrel	38/886
		Rehospitalization at 6 mo	ASA	568/3342
			ASA + Clopidogrel	182/886
		Revascularization at 6 mo	ASA	317/3342
			ASA + Clopidogrel	113/886
		Stroke at 6 mo	ASA	43/3342
			ASA + Clopidogrel	9/886
Sibbald, 2010[91]	Observational Total N: 44,426 Good quality	Primary Composite in-hospital: Total mortality Nonfatal MI	Nonsmoker + early clopidogrel	OR (95% CI): 0.71 (0.64-0.79), reference group nonsmoker + no early clopidogrel
			Smoker + early clopidogrel	OR (95% CI): 0.77 (0.62-0.95), reference group smoker + no early clopidogrel

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Yusuf, 2001[85] CURE Study	RCT Total N: 12,562 Good quality	Primary Composite #1 at 9 mo: CV mortality Nonfatal MI Stroke	Clopidogrel	RR (95% CI): 0.93 (0.79-1.08), reference group placebo
		Primary Composite #2 at 9 mo: CV mortality Nonfatal MI Stroke Refractory ischemia	Clopidogrel	RR (95% CI): 0.77 (0.67-0.89), reference group placebo
		CV mortality at 9 mo	Clopidogrel	RR (95% CI): 0.86 (0.63-1.18), reference group placebo
		Nonfatal MI at 9 mo	Clopidogrel	RR (95% CI): 0.93 (0.82-1.04), reference group placebo
		Stroke at 9 mo	Clopidogrel	RR (95% CI): 0.82 (0.69-0.98), reference group placebo p=0.026
		Refractory ischemia at 9 mo	Clopidogrel	RR (95% CI): 0.74 (0.61-0.9), reference group placebo p=0.003
		Heart failure during index hospitalization	Clopidogrel	RR (95% CI): 1302 (- reference group placebo p=0.03
		Severe ischemia during index hospitalization	Clopidogrel	1302/6259
			Placebo	1431/6303
		Revascularization during index hospitalization	Clopidogrel	RR (95% CI): 2.12 (1.75-2.56), reference group placebo p=0.001
		Major bleeding at 9 mo	Clopidogrel	RR (95% CI): 0.93 (0.79-1.08), reference group placebo
		Minor bleeding at 9 mo	Clopidogrel	RR (95% CI): 0.77 (0.67-0.89), reference group placebo

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Zeymer, 2008[92] ACOS Registry	Observational Total N: 4,290 Poor quality	Primary composite at 1 yr: Total mortality Nonfatal MI Nonfatal stroke	Clopidogrel + ASA	OR (95% CI): 0.69 (0.60-0.80), reference group ASA
		Primary composite in-hospital: Total mortality Nonfatal MI Nonfatal stroke	ASA	298/2119
			Clopidogrel + ASA	134/2171
		Total mortality in-hospital	ASA	167/2119
			Clopidogrel + ASA	70/2171
		Total mortality at 1 yr	Clopidogrel + ASA	OR (95% CI): 0.66 (0.55-0.80), reference group ASA
		Nonfatal MI in-hospital	ASA	109/2119
			Clopidogrel + ASA	53/2171
		Nonfatal MI at 1 yr	ASA	180/2119
			Clopidogrel + ASA	126/2171
		Stroke in-hospital	ASA	23/2119
			Clopidogrel + ASA	13/2171
		Stroke at 1 yr	ASA	42/2119
			Clopidogrel + ASA	41/2171

Abbreviations: ASA=aspirin; CI=confidence interval; CV=cardiovascular; MI=myocardial infarction; mo=month/months; N=number of patients; OR=odds ratio; RCT=randomized controlled trial; RR=relative risk; vs=versus; yr=year/years

Table G-14. Results data for short-term vs. long-term dual antiplatelet therapy (clopidogrel): composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Bernardi, 2007[93] RACS Study	RCT Total N: 1,004 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Stroke	Clopidogrel at 30 days + ASA	41/502
			Clopidogrel at 180 days + ASA	39/502
		Primary Composite at 6 mo: Total mortality Nonfatal MI Stroke	Clopidogrel at 30 days + ASA	23/461
			Clopidogrel at 180 days + ASA	8/460
		Secondary Composite at 30 days: Total mortality Nonfatal MI Stroke Target vessel revascularization	Clopidogrel at 30 days + ASA	58/502
			Clopidogrel at 180 days + ASA	51/502
		Secondary Composite at 30 days: Total mortality Nonfatal MI Stroke Revascularization	Clopidogrel at 30 days + ASA	40/461
			Clopidogrel at 180 days + ASA	25/460
		Total mortality at 30 days	Clopidogrel at 30 days + ASA	10/502
			Clopidogrel at 180 days + ASA	12/502
		Total mortality at 6 mo	Clopidogrel at 30 days + ASA	12/461
			Clopidogrel at 180 days + ASA	4/460
Butler, 2009[94]	Observational Total N: 2,980 Fair quality	Primary Composite at 1 yr: Total mortality Nonfatal MI Revascularization	Clopidogrel ≤ 3 mo after DES	17/152
			Clopidogrel 6 mo after DES	79/495
			Clopidogrel ≤ 3 mo after BMS	108/684
			Clopidogrel 6 mo after BMS	37/287
		Total mortality at 1 yr	Clopidogrel ≤ 3 mo after DES	8/152
			Clopidogrel 6 mo after DES	26/495
			Clopidogrel ≥12 mo after DES	29/1022
			Clopidogrel ≤3 mo after BMS	41/684
			Clopidogrel 6 mo after BMS	13/287
			Clopidogrel ≥ 12 mo after BMS	20/340
		Nonfatal MI at 1 yr	Clopidogrel ≤ 3 mo after DES	5/152
			Clopidogrel 6 mo after DES	38/495
			Clopidogrel ≥12 mo after DES	65/1022

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
			Clopidogrel ≤3 mo after BMS	36/684
			Clopidogrel 6 mo after BMS	13/287
			Clopidogrel ≥ 12 mo after BMS	25/340
		Revascularization at 1 yr	Clopidogrel ≤ 3 mo after DES	7/152
			Clopidogrel 6 mo after DES	35/495
			Clopidogrel ≥12 mo after DES	73/1022
			Clopidogrel ≤3 mo after BMS	49/684
			Clopidogrel 6 mo after BMS	20/287
			Clopidogrel ≥ 12 mo after BMS	27/340
		Propensity score at 1 yr	Clopidogrel ≥12 mo after DES	Median (IQR): 0.73 (0.58-0.86)
			Clopidogrel 6 mo after DES	Median (IQR): 0.65 (0.47-0.80)
		Equality of survival at 1 yr	Clopidogrel ≥12 mo after DES	chi squared statistic: 5.67, reference group intended duration of Clopidogrel therapy ≤6 mo after DES
		Discharged alive	Clopidogrel ≤ 3 mo after DES	151/152
			Clopidogrel 6 mo after DES	484/495
			Clopidogrel ≥12 mo after DES	1011/1022
			Clopidogrel ≤3 mo after BMS	659/684
			Clopidogrel 6 mo after BMS	283/287
			Clopidogrel ≥ 12 mo after BMS	329/340
		Cumulative hazard of MACE for DES patients at 1 yr	Clopidogrel ≥12 mo after DES	chi squared statistic: 6.40, reference group intended duration of clopidogrel therapy ≤6 mo after DES
		Major bleeding at 1 yr	Clopidogrel ≤ 3mo after DES	1/152
			Clopidogrel 6 mo after DES	8/495
			Clopidogrel ≥12 mo after DES	19/1022
			Clopidogrel ≤3 mo after BMS	9/684
			Clopidogrel 6 mo after BMS	3/287

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
			Clopidogrel ≥ 12 mo after BMS	8/340
Charlot, 2012[95]	Observational Total N: 29,268 Fair quality	Primary Composite (medically treated) at 3 mo: Total mortality Nonfatal MI	Clopidogrel up to 90 days	115/9819
			Clopidogrel > 90 days	688/9819
		Primary Composite (medically treated) at 6 mo: Total mortality Nonfatal MI	Clopidogrel up to 90 days	123/9819
			Clopidogrel > 90 days	362/9819
		Primary Composite (medically treated) at 9 mo: Total mortality Nonfatal MI	Clopidogrel up to 90 days	55/9819
			Clopidogrel > 90 days	205/9819
		Primary Composite (medically treated) at 1 yr: Total mortality Nonfatal MI	Clopidogrel up to 90 days	31/9819
			Clopidogrel > 90 days	179/9819
		Primary Composite (medically treated) at 15 mo: Total mortality Nonfatal MI	Clopidogrel up to 90 days	34/9819
			Clopidogrel > 90 days	96/9819
		Primary Composite (PCI treated) at 3 mo: Total mortality Nonfatal MI	Clopidogrel up to 90 days	27/19449
			Clopidogrel > 90 days	386/19449
		Primary Composite (PCI treated) at 6 mo: Total mortality Nonfatal MI	Clopidogrel up to 90 days	46/19449
			Clopidogrel > 90 days	226/19449
		Primary Composite (PCI treated) at 9 mo: Total mortality Nonfatal MI	Clopidogrel up to 90 days	20/19449
			Clopidogrel > 90 days	178/19449
		Primary Composite (PCI treated) at 1 yr: Total mortality Nonfatal MI	Clopidogrel up to 90 days	20/19449
			Clopidogrel > 90 days	112/19449
		Primary Composite (PCI treated) at 15 mo: Total mortality Nonfatal MI	Clopidogrel up to 90 days	79/19449
			Clopidogrel > 90 days	66/19449

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Gwon, 2012[96] EXCELLENT	RCT Total N: 1,443 Good quality	Primary Composite at 1 yr: CV mortality Nonfatal MI TVR	6-mo DAPT	34/722
			12-mo DAPT	30/721
		Secondary Composite at 1 yr: Total mortality Nonfatal MI	6-mo DAPT	17/722
			12-mo DAPT	14/721
		Secondary Composite at 1 yr: Total mortality Nonfatal MI Stroke Revascularization	6-mo DAPT	56/722
			12-mo DAPT	60/721
		Secondary Composite at 1 yr: Total mortality Nonfatal MI Stroke Stent thrombosis Major bleeding	6-mo DAPT	24/722
			12-mo DAPT	21/721
		Total mortality at 1 yr	6-mo DAPT	4/722
			12-mo DAPT	7/721
		CV mortality at 1 yr	6-mo DAPT	2/722
			12-mo DAPT	3/721
		Nonfatal MI at 1 yr	6-mo DAPT	13/722
			12-mo DAPT	7/721
		Revascularization at 1 yr	6-mo DAPT	43/722
			12-mo DAPT	43/721
		Stent thrombosis at 1 yr	6-mo DAPT	6/722
			12-mo DAPT	1/721
		Major bleeding at 1 yr	6-mo DAPT	2/722
			12-mo DAPT	4/721
Harjai, 2009[97]	Observational Total N: 1,859 Good quality	Primary Composite at 1,287 days: Total mortality Nonfatal MI	DAP > 12 mo	13%
			DAP ≤ 12 mo	14%
		Primary Composite at 1 yr: Total mortality Nonfatal MI	DAP > 12 mo	0%
			DAP ≤ 12 mo	0%
		Primary Composite at 2 yr: Total mortality Nonfatal MI	DAP > 12 mo	4.90%
			DAP ≤ 12 mo	5.70%
		Primary Composite at 3 yr: Total mortality Nonfatal MI	DAP > 12 mo	10.80%
			DAP ≤ 12 mo	11.80%
		Primary Composite at 4 yr: Total mortality Nonfatal MI	DAP > 12 mo	16.40%
			DAP ≤ 12 mo	16.90%
		Primary Composite at 5 yr: Total mortality Nonfatal MI	DAP > 12 mo	25.60%
			DAP ≤ 12 mo	19.90%
		Stent thrombosis at 3 yr	DAP > 12 mo	14/918
			DAP ≤ 12 mo	7/941

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Ho, 2007[98]	Observational Total N: 1,455 Fair quality	Secondary Composite at 299 days: Total mortality Rehospitalization for AMI	patients discontinuing clopidogrel therapy	HR (95% CI): 1.90 (1.39-2.59), reference group patients continuing clopidogrel therapy
		Total mortality at 6 mo	patients discontinuing clopidogrel therapy	HR (95% CI): 2.67 (1.54-6.64), reference group patients continuing clopidogrel therapy
		Total mortality at 1 yr	patients discontinuing clopidogrel therapy	HR (95% CI): 2.26 (1.18-4.33), reference group patients continuing clopidogrel therapy
		Total mortality at 18 mo	patients discontinuing clopidogrel therapy	HR (95% CI): 2.85 (0.96-8.50), reference group patients continuing clopidogrel therapy
		Rehospitalization for AMI median follow-up 538 days	patients discontinuing clopidogrel therapy	HR (95% CI): 1.78 (1.15-2.75), reference group patients continuing clopidogrel therapy
		Nonfatal MI median 538 days	patients after BMS discontinuing clopidogrel	HR (95% CI): 3.57 (1.13-11.3), reference group patients after DES continuing clopidogrel
			patients after BMS discontinuing clopidogrel	HR (95% CI): 1.26 (0.58-2.74), reference group patients after BMS continuing clopidogrel
Pekdemir, 2003[99]	RCT Total N: 278 Fair quality	Primary Composite at 6 mo: Total mortality Nonfatal MI Revascularization	ASA+clopidogrel at 1 month	18/140
			ASA+clopidogrel at 6 mo	19/138
		Major bleeding at 6 mo	ASA+clopidogrel at 1 month	8/140
			ASA+clopidogrel at 6 mo	4/138
		Total mortality at 6 mo	ASA+clopidogrel at 1 month	2/140
			ASA+clopidogrel at 6 mo	1/138
		Nonfatal MI at 6 mo	ASA+clopidogrel at 1 month	3/140
			ASA+clopidogrel at 6 mo	3/138
		Revascularization at 6 mo	ASA+clopidogrel at 1 month	16/140
			ASA+clopidogrel at 6 mo	17/138
		CABG at 6 mo	ASA+clopidogrel at 1 month	3/140

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
			ASA+clopidogrel at 6 mo	2/138
		Re-PTCA at 6 mo	ASA+clopidogrel at 1 month	13/140
			ASA+clopidogrel at 6 mo	15/138
		Subacute stent occlusion at 6 mo	ASA+clopidogrel at 1 month	5/140
			ASA+clopidogrel at 6 mo	3/138
		Late stent occlusion at 6 mo	ASA+clopidogrel at 1 month	3/140
			ASA+clopidogrel at 6 mo	2/138
Roy, 2009[100]	Observational Total N: 2,889 Poor quality	Stent thrombosis at 1 month	Clopidogrel cessation at 1 month	OR (95% CI): 4.5 (2.0-10.4)
		Stent thrombosis at 6 mo	Clopidogrel cessation at 6 month	OR (95% CI): 2.4 (1.2-4.9)
		Stent thrombosis at 1 yr	Clopidogrel cessation 12 mo	OR (95% CI): 1.7 (0.9-3.1)
Schulz, 2009[101]	Observational Total N: 6,816 Fair quality	Stent thrombosis at 30 days	clopidogrel 75mg 1xD+ ASA 100mg 2xD at 30 days	34/6816
		Stent thrombosis at 1 yr	clopidogrel 75mg 1xD+ ASA 100mg 2xD at 1 year	54/6816
		Stent thrombosis at 4 yr	clopidogrel 75mg 1xD + ASA 100mg 2xD	73/6816
		Hazard reduction per 1 day treatment continuation at 29 days	clopidogrel 75mg 1xD + ASA 100mg 2xD	Hazard reduction (95% CI): 0.95 (0.91-0.99)
		Risk of stent thrombosis within 4 yr	clopidogrel 75mg 1xD + ASA 100mg 2xD at 29 days	Risk of stent thrombosis: 0.0918
			clopidogrel 75mg 1xD + ASA 100mg 2xD at 181 days	Risk of stent thrombosis: 0.0109
Steinhubl, 2002[102] CREDO Study	RCT Total N: 2,116 Good quality	Primary Composite at 1 yr: Total mortality Nonfatal MI Stroke	Clopidogrel	8.5%
			Placebo	11.5%
		Major bleeding at 1 yr	Clopidogrel	8.8%
			Placebo	6.7%

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Valgimigli, 2012[103] PRODIGY Study	RCT Total N: 2013 Good quality	Primary Composite at 2 yr: Total mortality Nonfatal MI Stroke	Clopidogrel at 24 mo	HR (95% CI): 0.98 (0.74-1.29), reference group clopidogrel at 6 mo p= 0.91
		Secondary Composite at 2 yr: Total mortality Nonfatal MI	Clopidogrel at 6 mo	HR (95% CI): 1.07 (0.80-1.43), reference group clopidogrel at 24 mo p= 0.62
		Secondary Composite at 2 yr: Total mortality Stroke	Clopidogrel at 6 mo	HR (95% CI): 0.91 (0.66-1.26), reference group clopidogrel at 24 mo p= 0.57
		Total mortality at 2 yr	Clopidogrel at 6 mo	HR (95% CI): 1.00 (0.72-1.40), reference group clopidogrel at 24 mo p= 0.98
		CV mortality	Clopidogrel at 6 mo	HR (95% CI): 1.03 (0.66-1.61), reference group clopidogrel at 24 mo p= 0.89
		Stroke	Clopidogrel at 6 mo	HR (95% CI): 0.60 (0.29-1.23), reference group clopidogrel at 24 mo p= 0.17
		Stent thrombosis	Clopidogrel at 6 mo	HR (95% CI): 0.67 (0.19-2.37), reference group clopidogrel at 24 mo p= 0.53
		Minor bleeding	Clopidogrel at 6 mo	HR (95% CI): 0.82 (0.34-1.94), reference group clopidogrel at 24 mo p= 0.66

Abbreviations: AMI=acute myocardial infarction; ASA=aspirin; BMS=bare metal stent; CABG=coronary artery bypass grafting; CI=confidence interval; CV=cardiovascular; DAP=dual antiplatelet; DAPT=dual antiplatelet therapy; DES=drug-eluting stent; HR=hazard ratio; IQR=interquartile range; mg=milligram/milligrams; MI=myocardial infarction; mo=month/months; N=number of patients; OR=odds ratio; PCI=percutaneous coronary intervention; PTCA=percutaneous transluminal coronary angioplasty; RCT=randomized controlled trial; TVR=target vessel revascularization; vs=versus; yr=year/years

Table G-15. Results data for antiplatelet treatment with and without PPI: composite and individual outcomes

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Banerjee, 2011[104]	Observational Total N: 23,200 Good quality	Primary Composite at 1 yr: Total mortality Nonfatal MI Revascularization	Clopidogrel + PPI	HR (95% CI): 1.19 (1.06-1.33), reference group clopidogrel no PPI
		Primary Composite at 6 yr: Total mortality Nonfatal MI Revascularization	Clopidogrel + PPI	HR (95% CI): 1.24 (1.11-1.38), reference group clopidogrel no PPI
		Secondary Composite: Total mortality Nonfatal MI	Clopidogrel + PPI	HR (95% CI): 1.20 (1.02-1.41), reference group clopidogrel no PPI
		Secondary Composite: Total mortality Nonfatal MI	Clopidogrel + PPI	HR (95% CI): 1.26 (1.08-1.48), reference group clopidogrel no PPI
		Total mortality at 1 yr	Clopidogrel + PPI	HR (95% CI): 1.16 (0.87-1.55), reference group clopidogrel no PPI
		Revascularization at 1 yr	Clopidogrel + PPI	HR (95% CI): 1.18 (1.01-1.30), reference group clopidogrel no PPI
		Total mortality at 6 yr	Clopidogrel + PPI	HR (95% CI): 1.32 (1.00-1.73), reference group clopidogrel no PPI
		Revascularization at 6 yr	Clopidogrel + PPI	HR (95% CI): 1.22 (1.05-1.42), reference group clopidogrel no PPI
Barada, 2008[105]	Observational Total N: 1,023 Poor quality	UGI bleeding in-hospital	PPI	0.7%
			No PPI	0.6%
Bhatt, 2010[106] COGENT Study	RCT Total N: 3,761 Good quality	Primary Composite at 6 mo: CV mortality Nonfatal MI Stroke Revascularization	Omeprazole	92/1876
			Placebo	107/1885
		Upper GI events at 6 mo	Omeprazole	21/1876
			Placebo	55/1885
		Overt gastroduodenal or upper GI bleeding at 6 mo	Omeprazole	HR (95% CI): 0.13 (0.03-0.56), reference group placebo
		Nonfatal MI at 6 mo	Omeprazole	22/1876
			Placebo	28/1885
		Revascularization at 6 mo	Omeprazole	75/1876
			Placebo	87/1885
		Stroke at 6 mo	Omeprazole	4/1876
			Placebo	6/1885
		Total mortality at 6 mo	Omeprazole	8/1876
			Placebo	9/1885

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
		CV mortality at 6 mo	Omeprazole	8/1876
			Placebo	6/1885
Bhurke, 2012[107]	Observational Total N: 5,348 Fair quality	Primary Composite at 1 yr: Nonfatal MI Stents Non-stenting revasc Intermediate coronary syndrome	Clopidogrel + PPI	366/2674
			Clopidogrel	337/2674
		Nonfatal MI at 1 yr	Clopidogrel + PPI	172/2674
			Clopidogrel	163/2674
		Stents at 1 yr	Clopidogrel + PPI	97/2674
			Clopidogrel	91/2674
Charlot, 2010[108]	Observational Total N: 56,406 Good quality	Primary Composite at 1 yr: CV mortality Nonfatal MI Stroke	No clopidogrel no PPI	4244/22815
			PPI no clopidogrel	228/8889
			Clopidogrel no PPI	1508/17949
			Clopidogrel + PPI	1060/6753
		Total mortality at 1 yr	No clopidogrel no PPI	2923/20437
			PPI no clopidogrel	1607/7618
			Clopidogrel no PPI	551/16216
			Clopidogrel + PPI	419/5986
		CV mortality at 1 yr	No clopidogrel no PPI	2391/20437
			PPI no clopidogrel	1234/7618
			Clopidogrel no PPI	470/16216
			Clopidogrel + PPI	329/5986
		Nonfatal MI at 1 yr	No clopidogrel no PPI	1553/19662
			PPI no clopidogrel	832/7170
			Clopidogrel no PPI	861/15663
			Clopidogrel + PPI	582/5596
		Stroke at 1 yr	No clopidogrel no PPI	1506/22815
			PPI no clopidogrel	720/8889
			Clopidogrel no PPI	538/17949
			Clopidogrel + PPI	297/6753

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Charlot, 2011[109]	Observational Total N: 49,452 Good quality	Primary Composite at 1 yr: CV mortality Stroke Rehospitalization	No PPI	2374/15619
			PPI	986/4306
		Total mortality at 1 yr	PPI	1607/15619
			No PPI	686/4306
		CV mortality at 1 yr	PPI	1328/15619
			No PPI	540/4306
		Nonfatal MI at 1 yr	PPI	1110/15619
			No PPI	497/4306
		Stroke at 1 yr	PPI	1207/15619
			No PPI	338/4306
Chitose, 2011[110] KICS	Observational Total N: 1,270 Good quality	Primary Composite at 18 mo: CV mortality Nonfatal MI Stroke	PPI	6/171
			No PPI	17/450
		CV mortality at 18 mo	PPI	2/171
			No PPI	7/450
		Nonfatal MI at 18 mo	PPI	2/171
			No PPI	1/450
		Stroke at 18 mo	PPI	2/171
			No PPI	9/450
		GI event at 18 mo	PPI	1/171
			No PPI	7/450
Evanchan, 2010[111]	Observational Total N: 5,794 Good quality	Nonfatal MI at 1 yr	PPI	HR (95% CI): 1.78 (1.55-2.07), reference group no PPI
Gao, 2009[112]	RCT Total N: 237 Poor quality	Total mortality at 14 days	Omeprazole	4/114
			Placebo	13/123
		Upper GI bleeding at 14 days	Omeprazole	6/114
			Placebo	18/123
Gaspar, 2010[113]	Observational Total N: 876 Good quality	Primary Composite at 6 mo: Total mortality Nonfatal MI UA	PPI	35/274
			No PPI	49/528
		Total mortality at 6 mo	PPI	17/274
			No PPI	21/528
Goodman, 2012[114] PLATO	Observational Total N: 18,624 Good quality	Primary Composite at 1 yr: CV mortality Nonfatal MI Stroke	Clopidogrel no PPI	611/6021
			PPI + clopidogrel	398/3255
		Secondary Composite at 1 yr: CV mortality Nonfatal MI	Clopidogrel no PPI	560/6021
			PPI + clopidogrel	378/3255
		Total mortality at 1 yr	Clopidogrel no PPI	286/6021
			PPI + clopidogrel	213/3255
		CV mortality at 1 yr	Clopidogrel no PPI	256/6021
			PPI + clopidogrel	180/3255
		Nonfatal MI at 1 yr	Clopidogrel no PPI	354/6021

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
			PPI + clopidogrel	245/3255
		Major bleeding at 1 yr	Clopidogrel no PPI	175/5953
			PPI + clopidogrel	127/3231
		Stent thrombosis at 1 yr	Clopidogrel no PPI	59/3495
			PPI + clopidogrel	46/2154
Gupta, 2010[115]	Observational Total N: 315 Fair quality	Primary Composite at 4 yr: Total mortality Nonfatal MI TVF	Clopidogrel no PPI	92/243
			Clopidogrel + PPI	40/72
		Total mortality at 4 yr	Clopidogrel no PPI	35/243
			Clopidogrel + PPI	14/72
		TLR at 4 yr	Clopidogrel no PPI	53/243
			Clopidogrel + PPI	21/72
		TVF at 4 yr	Clopidogrel no PPI	70/243
			Clopidogrel + PPI	30/72
Harjai, 2011[116]	Observational Total N: 2,653 Good quality	Primary Composite at 6 mo: Total mortality Nonfatal MI Revascularization Stent thrombosis	PPI	48/751
			No PPI	122/1902
		Total mortality at 6 mo	PPI	21/751
			No PPI	48/1902
		Nonfatal MI at 6 mo	PPI	24/751
			No PPI	57/1902
		Revascularization at 6 mo	PPI	16/751
			No PPI	55/1902
		Stent thrombosis at 6 mo	PPI	13/751
			No PPI	29/1902
		Major bleeding at 6 mo	PPI	8/751
			No PPI	29/1902
Ho, 2009[117]	Observational Total N: 8,790 Good quality	Primary Composite at 18 mo: Total mortality Rehospitalization	Clopidogrel no PPI	615/2961
			Clopidogrel + PPI	1561/5244
		Rehospitalization at 18 mo	Clopidogrel no PPI	205/2961
			Clopidogrel + PPI	764/5244
		Revascularization at 18 mo	Clopidogrel no PPI	353/2961
			Clopidogrel + PPI	815/5244
		Total mortality at 18 mo	Clopidogrel no PPI	493/2961
			Clopidogrel + PPI	1042/5244

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Hsiao, 2011[118]	Observational Total N: 9,753 Good	Rehospitalization at 6 mo	PPI	24/622
			No PPI	177/9131
Juurlink, 2009[119]	Observational Total N: 2791 Good quality	Nonfatal MI at 3 mo	Clopidogrel + nonfatal MI 90 days	194/734
			Clopidogrel	424/2057
		Total mortality at 3 mo	Clopidogrel + nonfatal MI 90 days	71/323
			Clopidogrel	188/916
		Nonfatal MI at 1 yr	Clopidogrel + nonfatal MI 90 days	240/982
			Clopidogrel	497/2626
		Total mortality at 1 yr	Clopidogrel + nonfatal MI 90 days	116/531
			Clopidogrel	269/1407
Kreutz, 2010[120]	Observational Total N: 16,690 Good quality	Primary Composite at 1 yr: CV mortality Nonfatal MI Stroke Rehospitalization	Clopidogrel no PPI	1766/9862
			Clopidogrel + PPI	1710/6828
		Stroke at 1 yr	No PPI	109/9862
			PPI	140/6828
		Nonfatal MI at 1 yr	No PPI	982/9862
			PPI	1121/6828
		Revascularization at 1 yr	No PPI	1312/9862
			PPI	1109/6828
		CV mortality at 1 yr	No PPI	21/9862
			PPI	19/6828
Ng, 2008[121]	Observational Total N: 666 Good quality	GI bleeding at 7 days	No PPI	14/290
			PPI	2/336
		GI bleeding/occult bleed at 7 days	No PPI	24/290
			PPI	9/336
Ng, 2011[122]	RCT Total N: 313 Good quality	Secondary Composite at 4 mo: CV mortality Nonfatal MI Stroke	Esomeprazole	7/163
			Famotidine	5/148
		Secondary Composite at 4 mo: GI events Occult bleeding of unknown origin	Esomeprazole	1/163
			Famotidine	11/148
		GI events at 4 mo	Esomeprazole	1/163
			Famotidine	9/148

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
O'Donoghue, 2009[123] TRITON-TIMI 38	Observational Total N: 13,608 Good quality	Primary Composite: CV mortality MI Stroke	Clopidogrel + PPI	255/2257
			Clopidogrel no PPI	526/4538
			Prasugrel + PPI	220/2272
			Prasugrel no PPI	423/4541
		Secondary Composite: Major bleeding Minor bleeding	Clopidogrel + PPI	92/2234
			Clopidogrel no PPI	139/4482
			Prasugrel + PPI	98/2253
			Prasugrel no PPI	205/4488
		Secondary Composite: Mortality MI Stroke Major bleeding	Clopidogrel + PPI	299/2257
			Clopidogrel no PPI	594/4538
			Prasugrel + PPI	268/2272
			Prasugrel no PPI	516/4541
		Total mortality	Clopidogrel + PPI	58/2257
			Clopidogrel no PPI	139/4538
			Prasugrel + PPI	65/2272
			Prasugrel no PPI	123/4541
		CV mortality	Clopidogrel + PPI	44/2257
			Clopidogrel no PPI	106/4538
			Prasugrel + PPI	46/2272
			Prasugrel no PPI	87/4541
		MI	Clopidogrel + PPI	209/2257
			Clopidogrel no PPI	424/4538
			Prasugrel + PPI	166/2272
			Prasugrel no PPI	319/4541
		Stent thrombosis	Clopidogrel + PPI	50/2150
			Clopidogrel no PPI	92/4272
			Prasugrel + PPI	22/2159
			Prasugrel no PPI	46/4263
		Major bleeding	Clopidogrel + PPI	46/2234

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
			Clopidogrel no PPI	65/4482
			Prasugrel + PPI	51/2253
			Prasugrel no PPI	95/4488
Ortolani, 2011[124]	Observational Total N: 3,896 Good quality	Secondary Composite at 1 yr: Total mortality Revascularization Rehospitalization	Clopidogrel + PPI	892/3519
			Clopidogrel no PPI	50/377
		Rehospitalization at 1 yr	Clopidogrel + PPI	527/3519
			Clopidogrel no PPI	13/377
		Revascularization at 1 yr	Clopidogrel + PPI	573/3519
			Clopidogrel no PPI	28/377
		Total mortality at 1 yr	Clopidogrel + PPI	190/3519
			Clopidogrel no PPI	16/377
Rassen, 2009[125]	Observational Total N: 18,565 Good quality	Primary Composite at 6 mo: Total mortality Nonfatal MI	PPI	HR (95% CI): 1.22 (0.99-1.51), reference group no PPI
		Nonfatal MI at 6 mo	PPI	HR (95% CI): 1.22 (0.95-1.57), reference group no PPI
		Total mortality at 6 mo	PPI	HR (95% CI): 1.20 (0.84-1.70), reference group no PPI
		Revascularization at 6 mo	PPI	HR (95% CI): 0.97 (0.79-1.21), reference group no PPI
Ray, 2010[126]	Observational Total N: 20,596 Good quality	Primary Composite at 1 yr: Total mortality CV mortality Nonfatal MI Stroke	PPI	HR (95% CI): 0.99 (0.82-1.19), reference group no PPI
		Secondary Composite at 1 yr: Nonfatal MI CV mortality	PPI	HR (95% CI): 0.91 (0.75-1.09), reference group no PPI
		CV mortality at 1 yr	No PPI	80/13003
			PPI	64/7593
		Stroke at 1 yr	No PPI	97/13003
			PPI	105/7593
		Gastroduodenal bleeding at 1 yr	No PPI	117/13003
			PPI	63/7593
		Other bleeding at 1 yr	No PPI	108/13003
			PPI	117/7593

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Ren, 2011[127]	RCT Total N: 168 Poor quality	Slight chest pressure at 30 days	Omeprazole	3/86
			Placebo	2/86
		Occasional angina at 30 days	Omeprazole	17/86
			Placebo	19/86
		TIA at 30 days	Omeprazole	2/86
			Placebo	1/86
		Major bleeding at 30 days	Omeprazole	0/86
			Placebo	2/86
Rossini, 2011[128]	Observational Total N: 1346 Good quality	Primary Composite at 1 yr: Total mortality Nonfatal MI Stroke Rehospitalization	No PPI	1/170
			PPI	29/1158
		Secondary Composite in-hospital: Total mortality Nonfatal MI Stroke Rehospitalization	No PPI	9/170
			PPI	87/1158
		Major bleeding in-hospital	No PPI	1/170
			PPI	15/1158
		Minor bleeding in-hospital	No PPI	6/170
			PPI	36/1158
		Major bleeding at 1 yr	No PPI	4/170
			PPI	38/1158
		Minor bleeding at 1 yr	No PPI	9/170
			PPI	63/1158
		Total mortality at 1 yr	No PPI	5/170
			PPI	24/1158
		Stent thrombosis at 1 yr	No PPI	2/170
			PPI	25/1158
Sarafoff, 2010[129]	Observational Total N: 3408 Good quality	Secondary Composite at 30 days: Nonfatal MI Stent thrombosis	PPI	23/698
			No PPI	32/2640
		Stent thrombosis at 30 days	PPI	8/698
			Placebo	13/2640
		Total mortality at 30 days	PPI	18/698
			Placebo	23/2640
		Nonfatal MI at 30 days	PPI	21/698
			Placebo	53/2640
		Major bleeding at 30 days	PPI	19/698
			Placebo	18/2640

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
Schmidt, 2012[130]	Observational Total N: 13,001 Poor quality	Primary Composite at 1 yr CV mortality Nonfatal MI Stroke Stent thrombosis Target lesion revasc	PPI + Clopidogrel	HR (95% CI): 1.51 (1.26-1.81)
			PPI no Clopidogrel	HR (95% CI): 1.18 (0.96-1.44)
		Nonfatal MI at 1 yr	PPI + Clopidogrel	HR (95% CI): 0.46 (0.30-0.72)
			PPI no Clopidogrel	HR (95% CI): 0.33 (0.28-0.41)
		Target lesion revasc	PPI + Clopidogrel	HR (95% CI): 0.68 (0.44-1.06)
			PPI no Clopidogrel	HR (95% CI): 0.62 (0.52-0.73)
		CV mortality	PPI + Clopidogrel	HR (95% CI): 0.35 (0.19-0.64)
			PPI no Clopidogrel	HR (95% CI): 0.21 (0.15-0.29)
Simon, 2011[131] FAST-MI	Observational Total N: 2744 Good quality	Composite at 1 yr: Total mortality Nonfatal MI Stroke	Clopidogrel no PPI	100/711
			PPI + clopidogrel	125/1052
			No PPI no clopidogrel	64/180
			PPI no clopidogrel	41/111
		Total mortality in-hospital	Clopidogrel no PPI	32/900
			PPI + clopidogrel	49/1453
			No PPI no clopidogrel	32/233
			PPI no clopidogrel	20/158
		Nonfatal MI in-hospital	Clopidogrel no PPI	13/900
			PPI + clopidogrel	24/1453
			No PPI no clopidogrel	8/233
			PPI no clopidogrel	4/158
		Stroke in-hospital	Clopidogrel no PPI	11/900
			PPI + clopidogrel	7/1453
			No PPI no clopidogrel	3/233
			PPI no clopidogrel	2/158
		Major bleeding in-hospital	Clopidogrel no PPI	16/900
			PPI + clopidogrel	23/1453
			No PPI no clopidogrel	3/233
			PPI no clopidogrel	5/158

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
		Total mortality at 1 yr	Clopidogrel no PPI	77/900
			PPI + clopidogrel	94/1453
			No PPI no clopidogrel	57/233
			PPI no clopidogrel	38/158
Stockl, 2010[132]	Observational Total N: 2066 Good quality	Rehospitalization for MI at 1 yr	Clopidogrel + PPI	36/1041
			Clopidogrel no PPI	22/6008
		Rehospitalization for MI or coronary stent implantation at 1 yr	Clopidogrel + PPI	97/1041
			Clopidogrel no PPI	72/6008
Tentzeris, 2010[133]	Observational Total N: 1210 Good quality	Composite at 1 yr: Total mortality Rehospitalization Stent thrombosis	Clopidogrel + PPI	HR (95% CI): 1.084 (0.529-2.222), reference group clopidogrel no PPI
		Total mortality at 1 yr	PPI	15/691
			No PPI	11/519
		CV mortality at 1 yr	PPI	8/691
			No PPI	10/519
		Rehospitalization at 1 yr	PPI	6/691
			No PPI	3/519
		Stent thrombosis at 1 yr	PPI	6/691
			No PPI	2/519
Tsai, 2011[134]	Observational Total N: 3580 Good quality	Primary Composite at 1 yr: Nonfatal MI Stroke Rehospitalization	Clopidogrel + PPI	121/1052
			Clopidogrel no PPI	62/1325
		GI events at 1 yr	Clopidogrel + PPI	91/1052
			Clopidogrel no PPI	34/1352
Valkhoff, 2011[135]	Observational Total N: 23,655 Poor quality	Nonfatal MI at 1 yr	PPI	OR (95% CI): 1.62 (1.15-2.27), reference group no PPI
Van Boxel, 2010[136]	Observational Total N: 18,139 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Stroke Unstable angina	Clopidogrel + PPI	754/5734
			Clopidogrel no PPI	830/12405
		Nonfatal MI at 1 yr	Clopidogrel + PPI	84/5734
			Clopidogrel no PPI	78/12405
		UA at 1 yr	Clopidogrel + PPI	458/5734
			Clopidogrel no PPI	538/12405
		Stroke at 1 yr	Clopidogrel + PPI	46/5734
			Clopidogrel no PPI	78/12405

Study	Study Details	Outcome(s) Length of Followup	Results reported by authors	
		Total mortality at 1 yr	Clopidogrel + PPI	189/5734
			Clopidogrel no PPI	164/12405
		Peptic ulcer disease at 1 yr	Clopidogrel + PPI	38/5734
			Clopidogrel no PPI	27/12405
Wu, 2010[137]	Observational Total N: 6,300 Good quality	Primary Composite at 3 mo: Total mortality Rehospitalization	Clopidogrel + PPI	103/311
			Clopidogrel no PPI	644/5551
		Rehospitalization at 3 mo	Clopidogrel + PPI	77/311
			Clopidogrel no PPI	561/5551
		Revascularization at 3 mo	Clopidogrel + PPI	35/311
			Clopidogrel no PPI	222/5551
		Total mortality at 3 mo	Clopidogrel + PPI	35/311
			Clopidogrel no PPI	94/5551
Zairis, 2010[138]	Observational Total N: 588 Good quality	Primary Composite at 1 yr: CV mortality Rehospitalization	Omeprazole	34/340
			No PPI	24/248
		CV mortality at 1 yr	Omeprazole	12/340
			No PPI	8/248
		Rehospitalization at 1 yr	Omeprazole	22/340
			No PPI	16/248
		Stent thrombosis at 1 yr	Omeprazole	30/340
			No PPI	21/248
		Revascularization at 1 yr	Omeprazole	32/340
			No PPI	22/248

Abbreviations: CI=confidence interval; CV=cardiovascular; GI=gastrointestinal; HR=hazard ratio; MI=myocardial infarction; mo=month/months; N=number of patients; OR=odds ratio; PPI=proton pump inhibitor; RCT=randomized controlled trial; TIA=transient ischemic attack; UA=unstable angina; UGI=upper gastrointestinal; yr=year/years

Table G-16. Results data for dual antiplatelet therapy (aspirin with oral antiplatelet) vs. triple therapy (aspirin with oral anticoagulant and oral antiplatelet): composite and individual outcomes

Study	Study Details	Outcome(s) (Length of Followup)	Results reported by authors	
Buresly, 2005[139]	Observational Total N: 21,443 Good quality	Primary Composite at 2 yr: Major bleeding Minor bleeding	Warfarin	OR (95% CI): 1.85 (1.54-2.22), reference group ASA
			ASA + warfarin	OR (95% CI): 1.84 (1.23-2.76), reference group ASA
			ASA + thienopyridine	OR (95% CI): 1.68 (1.02-2.77), reference group ASA
Fosbol, 2012[140]	Observational Total N: 7619 Fair quality	Primary Composite at 30 days: Total mortality Nonfatal MI Stroke	Aspirin	239/2213
			ASA+clopidogrel	247/2841
			Warfarin	47/563
			ASA+warfarin	90/1271
			Triple therapy	48/731
		Primary Composite at 1 yr: Total mortality Nonfatal MI Stroke	Aspirin	808/2213
			ASA+clopidogrel	922/2841
			Warfarin	201/563
			ASA+warfarin	404/1271
			Triple therapy	187/731
		Major bleeding at 30 days	Aspirin	53/2213
			ASA+clopidogrel	85/2841
			Warfarin	15/563
			ASA+warfarin	50/1271
			Triple therapy	30/731
		Major bleeding at 1 yr	Aspirin	223/2213
			ASA+clopidogrel	336/2841
			Warfarin	78/563
			ASA+warfarin	182/1271
			Triple therapy	109/731
Jang, 2011[141]	Observational Total N: 362 Poor quality	Primary Composite at 3 yr: Total mortality Nonfatal MI Revascularization	Dual therapy	43/278
			Triple therapy	10/84
		Secondary Composite at 3 yr: Total mortality Nonfatal MI Stroke Revascularization Major bleeding Minor bleeding	Dual therapy	64/278
			Triple therapy	22/84
		Total mortality at 3 yr	Dual therapy	23/278
			Triple therapy	3/84
		Nonfatal MI at 3 yr	Dual therapy	4/278
			Triple therapy	3/84
		Revascularization at 3 yr	Dual therapy	12/278
			Triple therapy	1/84
		Stent thrombosis at 3 yr	Dual therapy	4/278
			Triple therapy	3/84
		Major bleeding at 3 yr	Dual therapy	6/278
			Triple therapy	9/84
		Minor bleeding at 3 yr	Dual therapy	3/278
			Triple therapy	2/84

Study	Study Details	Outcome(s) (Length of Followup)	Results reported by authors	
		Stroke at 3 yr	Dual therapy	12/278
			Triple therapy	1/84
Karjalainen, 2007[142]	Observational Total N: 478 Good quality	Primary Composite at 1 yr: Total mortality Nonfatal MI Revascularization Stent thrombosis	Triple therapy	6/219
			Dual therapy	3/227
		Secondary Composite at 1 yr: Stroke Major bleeding	Triple therapy	OR (95% CI): 2.5 (1.2-5.3), reference group dual therapy
		Stroke at discharge	Triple therapy	1/219
			Dual therapy	0/227
		Major bleeding at discharge	Triple therapy	4/219
			Dual therapy	0/227
		Total mortality at discharge	Triple therapy	3/219
			Dual therapy	1/227
		Nonfatal MI at discharge	Triple therapy	4/219
			Dual therapy	3/227
		Revascularization at discharge	Triple therapy	3/219
			Dual therapy	1/227
		Stent thrombosis at discharge	Triple therapy	4/219
			Dual therapy	1/227
		Stroke at 1 yr	Triple therapy	7/219
			Dual therapy	5/227
		Major bleeding at 1 yr	Triple therapy	18/219
			Dual therapy	6/227
		Total mortality at 1 yr	Triple therapy	19/219
			Dual therapy	4/227
		Nonfatal MI at 1 yr	Triple therapy	22/219
			Dual therapy	11/227
		Revascularization at 1 yr	Triple therapy	24/219
			Dual therapy	17/227
		Stent thrombosis at 1 yr	Triple therapy	9/219
			Dual therapy	3/227
Konstantino, 2006[143]	Observational Total N: 2737 Fair quality	Nonfatal MI in-hospital	Dual therapy	45/2661
			Triple therapy	5/76
		Stroke in-hospital	Dual therapy	15/2661
			Triple therapy	1/76
		Major bleeding in-hospital	Dual therapy	16/2661
			Triple therapy	2/76
		Rehospitalization at 30 days	Dual therapy	445/2661
			Triple therapy	17/76
		Total mortality at 30 days	Dual therapy	29/2661
			Triple therapy	3/76
		Total mortality at 6 mo	Dual therapy	82/2661
			Triple therapy	6/76
Lamberts, 2013[144]	Observational Total N: 12,165 Good quality	Primary composite at 1 year Total mortality Non fatal MI	Dual therapy Triple therapy	OR (95%CI) 1.17 (0.96-1.42), reference group TT
		Total mortality	Dual therapy Triple therapy	OR 0.31 (0.24-0.39) Reference group DAPT
		Stroke	Dual therapy Triple therapy	OR (95%CI) 0.42 (0.28-0.61) Reference group DAPT

Study	Study Details	Outcome(s) (Length of Followup)	Results reported by authors	
		Bleeding	Dual therapy Triple therapy	OR (95%CI) 1.36 (1.06-1.73) Reference group DAPT
Lopes, 2010[145]	Observational Total N: 23,208 Good quality	Primary Composite at 6 mo: Total mortality Nonfatal MI	Warfarin	OR (95% CI): 0.39 (0.15-0.98), reference group no warfarin (ASA only)
		Major bleeding in-hospital	Warfarin	3/124
			No warfarin (ASA only)	6/793
		Stroke in-hospital	Warfarin	2/124
			No warfarin (ASA only)	25/793
Maegdefessel, 2008[146]	Observational Total N: 159 Fair quality	Major bleeding 1.4 yr	ASA + clopidogrel	2/103
			ASA + Clopidogrel + LMWH	0/42
			ASA + Clopidogrel + OAC	0/14
		Nonfatal MI 1.4 yr	ASA + clopidogrel	4/103
			ASA + Clopidogrel + LMWH	0/42
			ASA + Clopidogrel + OAC	0/14
		Stroke 1.4 yr	ASA + clopidogrel	9/103
			ASA + Clopidogrel + LMWH	4/42
			ASA + Clopidogrel + OAC	0/14
		CV mortality1.4 yr	ASA + clopidogrel	3/103
			ASA + Clopidogrel + LMWH	5/42
			ASA + Clopidogrel + OAC	1/14
Nguyen, 2007[147] GRACE Registry	Observational Total N: 800 Good quality	Nonfatal MI in-hospital	Triple therapy (ASA + Thienopyridine)	48/508
			Dual therapy (ASA or Thienopyridine)	26/220
		Stroke in-hospital	Triple therapy (Warfarin + ASA + Thienopyridine)	6/508
			Dual therapy (Warfarin + ASA or Thienopyridine)	7/220
		CHF in-hospital	Triple therapy (Warfarin + ASA + Thienopyridine)	128/508
			Dual therapy (ASA or Thienopyridine)	65/220
		Major bleeding in-hospital	Triple therapy (Warfarin + ASA + Thienopyridine)	34/508
			Dual therapy (Warfarin + ASA or Thienopyridine)	10/220

Study	Study Details	Outcome(s) (Length of Followup)	Results reported by authors	
		Total mortality at 6 mo	Triple therapy (Warfarin + ASA + Thienopyridine)	23/453
			Dual therapy (Warfarin + ASA or Thienopyridine)	12/184
		Revascularization at 6 mo	Triple therapy (Warfarin + ASA + Thienopyridine)	45/424
			Dual therapy (Warfarin + ASA or Thienopyridine)	22/176
		Stroke at 6 mo	Triple therapy (Warfarin + ASA + Thienopyridine)	3/426
			Dual therapy (ASA or Thienopyridine)	6/179
		Nonfatal MI at 6 mo	Triple therapy (Warfarin + ASA + Thienopyridine)	13/391
			Dual therapy (Warfarin + ASA or Thienopyridine)	7/154
Persson, 2011[148] RIKS-HIA and SCAAR	Observational Total N: 27,972 Good quality	Primary Composite at 1 yr: Total mortality Nonfatal MI	Triple therapy	RR (95% CI): 1.20 (1.0-1.45), reference group dual therapy
		Total mortality at 1 yr	Triple therapy	RR (95% CI): 0.82 (0.58-1.16), reference group dual therapy
		Stroke at 1 yr	Triple therapy	RR (95% CI): 1.60 (1.09-2.34), reference group dual therapy
		Major bleeding at 1 yr	Triple therapy	RR (95% CI): 1.53 (0.95-2.48), reference group dual therapy
		Any bleeding at 1 yr	Triple therapy	RR (95% CI): 1.55 (1.08-2.22), reference group dual therapy
Rossini, 2008[149]	Observational Total N: 102 Good quality	Primary Composite at 18 mo: Major bleeding Minor bleeding	Triple therapy	11/102
			Dual therapy	5/102
		Secondary Composite at 18 mo: Total mortality Nonfatal MI Stroke	Triple therapy	6/102
			Dual therapy	5/102
		Major bleeding at 18 mo	Triple therapy	3/102
			Dual therapy	2/102
		Minor bleeding at 18 mo	Triple therapy	8/102
			Dual therapy	3/102
		Major bleeding 30 days	Triple therapy	1/102
			Dual therapy	1/102
		Minor bleeding 30 days	Triple therapy	1/102
			Dual therapy	3/102

Study	Study Details	Outcome(s) (Length of Followup)	Results reported by authors	
Ruiz-Nodar, 2008[150]	Observational Total N: 426 Good quality	Primary Composite at 5 yr: Total mortality Nonfatal MI Revascularization	Triple therapy	52/195
			Dual therapy	39/178
		Secondary Composite at 5 yr: Stroke Major bleeding MACE	Triple therapy	32/195
			Dual therapy	42/178
		Total mortality at 5 yr	Triple therapy	35/195
			Dual therapy	28/178
		Nonfatal MI at 5 yr	Triple therapy	13/195
			Dual therapy	10178
		Revascularization at 5 yr	Triple therapy	14/195
			Dual therapy	8178
		Major bleeding at 5 yr	Triple therapy	29/195
			Dual therapy	9178
		Minor bleeding at 5 yr	Triple therapy	25/195
			Dual therapy	9178
Ruiz-Nodar, 2012[151]	Observational Total N: 590 Fair quality	Secondary Composite at 1 yr: Total mortality Nonfatal MI Target vessel failure	Coumarin at discharge	HR (95% CI) 0.21 (0.08 to 0.57) Reference group no coumarin
		Total mortality at 1 yr	Coumarin at discharge	HR (95% CI) 0.20 (0.06 to 0.64) Reference group no coumarin
		Major bleeding at 1 yr	Coumarin at discharge	HR (95% CI) 2.31 (0.55 to 9.71) Reference group no coumarin
Stenestrand, 2005[152] RIKS-HIA	Observational Total N: 6,275 Good quality	Total mortality at 30 days	ASA and/or thienopyridine	230/3768
			OAC +/-platelet inhibitor	76/1848
		Total mortality at 1 yr	ASA and/or thienopyridine	1183/3768
			OAC +/-platelet inhibitor	414/1848

Abbreviations: ASA=aspirin; CHF=congestive heart failure; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; LMWH=low molecular weight heparin; MACE=major adverse cardiac event; MI=myocardial infarction; mo=month/months; N=number of patients; OAC=oral anticoagulation; OR=odds ratio; RR=relative risk; vs=versus; yr=year/years

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Appendix H. Subgroup Tables

Table H-1. Subgroup results for KQ 1: antiplatelet and anticoagulant medications in the early invasive treatment of patients with UA/NSTEMI

Study	Study Details	Subgroup	Results Reported by Authors
Anonymous, 2000[1] ESPRIT Study	RCT Total N: 2,064 GPI vs. placebo at time of PCI Good	UA/NSTEMI	UA/NSTEMI group (N=279) Composite outcome (death, MI , urgent TVR or thrombotic GPI bailout at 48 hrs): Eptifibatide: 7.9% Placebo: 15% RR (95% CI) 0.53 (0.26-1.05), P=0.063 Composite outcome (death or MI at 6 mo) Eptifibatide: 9.5% Placebo: 18.6%
		Sex	Men (N=1502) Composite outcome (death, MI , urgent TVR or thrombotic GPI bailout at 48 hrs): Eptifibatide: 6.8% Placebo: 9.0% RR (95%CI) 0.76% (0.54-1.07). P=0.12 Composite outcome (death or MI at 6 mo) Eptifibatide: 7.4% Placebo: 10.3%
			Women (N=562) Composite outcome (death, MI , urgent TVR or thrombotic GPI bailout at 48 hrs): Eptifibatide: 6.1% Placebo: 14.5% RR (95%CI) 0.42 (0.24-0.72). P=0.001 Composite outcome (death or MI at 6 mo) Eptifibatide: 7.5% Placebo: 14.6%
		Age (>65 yrs)	>65 yrs (N=892) Composite outcome (death, MI , urgent TVR or thrombotic GPI bailout at 48 hrs): Eptifibatide: 6.5% Placebo: 13.7% RR (95%CI) 0.47 (0.31-0.72) Composite outcome (death or MI at 6 mo) Eptifibatide: 7.5% Placebo: 15.2%
		Diabetes	Diabetic patients (N=419) Composite outcome (death, MI , urgent TVR or thrombotic GPI bailout at 48 hrs): Eptifibatide: 3.9% Placebo: 6.6% 0.58% (0.25-1.35), P=0.20 Composite outcome (death or MI at 6 mo) Eptifibatide: 6.3% Placebo: 10.2%

Study	Study Details	Subgroup	Results Reported by Authors
		Weight/BMI	Lowest weight tertile (female <68 kg and males < 81 kg) Composite outcome (death, MI , urgent TVR or thrombotic GPI bailout at 48 hrs): Eptifibatide: 7.9% Placebo: 14.1% RR (95%CI) 0.56 (0.36-0.87), P=0.009
			Middle weight tertile (female 68 to 82 kg and males 81 to 95 kg Composite outcome (death, MI , urgent TVR or thrombotic GPI bailout at 48 hrs): Eptifibatide: 5.3% Placebo: 9.9% RR (95%CI) 0.54 (0.31-0.93), P=0.024
			Highest weight tertile (female >82 kg and makes > 95kg) Composite outcome (death, MI , urgent TVR or thrombotic GPI bailout at 48 hrs): Eptifibatide: 6.6% Placebo: 8.0% RR (95%CI) 0.82 (0.48-1.40), P=0.47
Antman, 1999[2] TIMI 11B Study	RCT Total N: 3,910 Other enoxaparin vs. unfractionated heparin vs. fondaparinux Good	UA or MI	UA (N=2289) Composite outcome (death, MI, urgent revasc at 14 days) UFH: 15.3% Enoxaparin: 12.8%
			Non-Q Wave MI (N=1334) Composite outcome (death, MI, urgent revasc at 14 days) UFH: 18.6% Enoxaparin: 17.2%
			Q Wave MI (N=143) Composite outcome (death, MI, urgent revasc at 14 days) UFH: 23.4% Enoxaparin: 20.3%
Berglund, 2002[3]	Observational Total N: 1430 Early clopidogrel vs. no early clopidogrel Fair	Diabetes	Clopidogrel vs. no early clopidogrel Composite outcome (death, MI, TVR): OR 0.42 (0.12-1.40)
		Smoking	Clopidogrel vs. no early clopidogrel Composite outcome (death, MI, TVR): OR 0.4 (0.18-1.17)
		Unstable coronary disease	Clopidogrel vs. no early clopidogrel Composite outcome (death, MI, TVR): OR 0.59 (0.36-0.98)
		Sex	Clopidogrel (male) vs. no early clopidogrel (male) Composite outcome (death, MI, TVR): OR 0.45 (0.26-0.76)
Bertel, 2010[4] ZEUS Study	RCT Total N: 876 Other enoxaparin vs. unfractionated heparin vs. fondaparinux Fair	ACS presentation	ACEs presentation Composite outcome (death, MI, urgent TVR, or major bleed at 30 days) Enoxaparin (N=113): 1.8% UFH (N=116): 12.9% p<0.01
Bhatt, 2003[5] CRUISE Study	RCT Total N: 261 Other enoxaparin vs. unfractionated heparin vs. fondaparinux Fair	Vascular closure device	Vascular closure device Bleeding Enoxaparin (N=48): 0% UFH (N=38): 2.6% Vascular complications Enoxaparin (N=53): 13.2% UFH (N=88)

Study	Study Details	Subgroup	Results Reported by Authors
Blazing, 2004[6] A to Z Study	RCT Total N: 3,987 Enoxaparin vs. unfractionated heparin vs. fondaparinux Good	Early invasive vs. conservative management	Early invasive Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1111): 8.8% UFH (N=1080): 8.5%
			Initial conservative Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=904): 7.7% UFH (N=869): 10.6%
		Age	<65 yrs Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1213): 6.4% UFH (N=1155): 7.4%
			≥65 yrs Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=805): 11.3% UFH (N=794): 12.5%
		Sex	Male Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1438): 8.3% UFH (N=1388): 9.4%
			Female Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=580): 8.6% UFH (N=52): 9.3%
		Diabetes	Diabetes Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1395): 8.4% UFH (N=356): 10.7%
			No diabetes Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1620): 8.3% UFH (N=1593): 9.2%
		Geography	US Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=420): 6.7% UFH (N=378): 7.7%
			Non-US Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1598): 8.8% UFH (N=155): 9.8%
		Troponin level	Normal troponin level Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=334): 8.1% UFH (N=323): 8.0%
			Elevated troponin level Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1072): 8.3% UFH (N=100): 9.5%
		TIMI risk score	TIMI 0-2 Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=846): 6.4% UFH (N=752): 5.7%

Study	Study Details	Subgroup	Results Reported by Authors
			TIMI 3-4 Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=888): 8.1% UFH (N=945): 10.2%
			TIMI 5-7 Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=284): 15.1% UFH (N=45): 17.9%
		Conservative strategy	Conservative strategy UFH (N=872) Enoxaparin (N=906) Total mortality at 7 days HR 1.32 (0.61-2.82), p=0.49 Total mortality at 30 days HR 1.51 (0.81-2.83), p=0.20 Nonfatal MI at 7 days HR 0.50 (0.26-0.98) Nonfatal MI at 30 days HR 0.67 (0.41-1.08), p=0.10 Refractory ischemia at 7 days HR 0.69 (0.47-1.00), p=0.05 Refractory ischemia at 30 days HR 0.77 (0.54-1.08), p=0.13 Urgent revascularization at 7 days HR 0.66 (0.39-1.14), p=0.14 Urgent revascularization at 30 days HR 0.90 (0.59-1.37) Composite outcome (death, MI, and refractory ischemia at 7 days) HR 0.72 (0.53-0.99), p=0.04 Composite outcome (death, MI, and refractory ischemia at 30 days) HR 0.80 (0.61-1.05), p=0.10 Composite outcome (death, MI, refractory ischemia, urgent revascularization, and documented myocardial ischemia at 7 days) HR 0.73 (0.56-0.96), p=0.03 Composite outcome (death, MI, refractory ischemia, urgent revascularization, and documented myocardial ischemia at 30 days) HR 0.78 (0.62-0.99), p=0.04 TIMI major or minor bleeding within 24 hours of tirofiban infusion UFH: 0.8% Enoxaparin: 1.5%
Brener, 2003[7]	Observational Total N: 10,471 Abciximab vs. no abciximab Poor	ACS patients	Total mortality N=7533; 4 year survival was 86% in abciximab group vs. 83.6% in no abciximab group; p=0.03

Study	Study Details	Subgroup	Results Reported by Authors
Brieger, 2007[8]	Observational Total N: 17,659 LMWH vs. UFH Fair	Use of PCI and IIb/IIIa inhibitors	Patients who did not get PCI and did not receive GPIs Mortality in-hospital LMWH (N=7957) UFH (N=4271) OR (95%CI) 0.74 (0.62-0.88), Adjusted OR (95%CI) 0.77 (0.63-0.94) favoring LMWH Major bleed in-hospital LMWH (N=7957) UFH (N=4271) OR (95%CI) 0.62(0.48-0.80), Adjusted OR (95%CI) 0.80 (0.60-1.10) favoring LMWH
			Patients who did get PCI and did not receive GPIs Mortality in-hospital LMWH (N=1468) UFH (N=728) OR (95%CI) 0.41 (0.22-0.78), Adjusted OR (95%CI) 0.45 (0.21-0.98), favoring LMWH Major bleed in-hospital LMWH (N=1468) UFH (N=728) OR (95% CI) 1.04 (0.62-1.73), Adjusted OR (95%CI) 1.48 (0.84-2.60). favoring increased bleeding with LMWH
			Patients who did get PCI and did receive GPIs Mortality in-hospital LMWH (N=928) UFH (N=1091) OR (95% CI) 0.80 (0.40-1.42), Adjusted OR (95%CI) 0.83 (0.40-1.76), favoring LMWH Major bleed in-hospital LMWH (N=928) UFH (N=1091) OR (95% CI) 0.64 (0.39-1.02), Adjusted OR (95%CI) 0.64 (0.38-1.08), favoring LMWH
			Patients who did not get PCI but did receive GPIs Mortality in-hospital LMWH (N=390) UFH (N=617) OR (95% CI) 0.73 (0.40-1.35), Adjusted OR (95%CI) 0.83 (0.42-1.63) favoring LMWH Major bleed in-hospital LMWH (N=390) UFH (N=617) OR (95% CI) 1.45 (0.87-2.41), Adjusted OR (95%CI) 1.90 (1.09-3.29) favoring increased bleeding with LMWH
Cohen, 1997[9] ESSENCE Study	RCT Total N: 3,171 Enoxaparin vs. unfractionated heparin vs. fondaparinux Good	Age	<65 yrs Composite outcome (death, MI, recurrent angina at 30 days) UFH (N=798): 23.2% Enoxaparin (N=785): 17.6% OR 1.05
			≥65 yrs Composite outcome (death, MI, recurrent angina at 30 days) UFH (N=776): 124 Enoxaparin (N=128): 128 OR 1.4

Study	Study Details	Subgroup	Results Reported by Authors
		Diabetes	Diabetes Composite outcome (death, MI, recurrent angina at 30 days) UFH (N=399): 79 Enoxaparin (N=360): 66 OR 1.35
			No diabetes Composite outcome (death, MI, recurrent angina at 30 days) UFH (N=1225): 230 Enoxaparin (N=1247): 200 OR 1.21
		Prior MI	Prior MI Composite outcome (death, MI, recurrent angina at 30 days) Heparin (N=745): 149 Enoxaparin (N=723): 118 OR 1.28
			No prior MI Composite outcome (death, MI, recurrent angina at 30 days) UFH (N=791): 154 Enoxaparin (N=850): 144 OR 1.19
		In-hospital PCI	In-hospital PCI Composite outcome (death, MI at 43 days) UFH (N=3028): 244 Enoxaparin (N=3129): 210 OR 0.82 (0.68-0.99), p=0.044 Composite outcome (death, MI at 1 yr) UFH (N=3028): 387 Enoxaparin (N=3129): 384 OR 0.95 (0.82-1.11, p=0.547) Major hemorrhage at 43 days UFH (N=2982): 148 Enoxaparin (3091): 185 OR 1.22 (0.8-1.52) Major hemorrhage at 1 yr UFH (N=2982): 30 Enoxaparin (N=3091): 55 55/3091, OR 1.78 (1.14-2.79), p=0.011
			No in-hospital PCI Composite outcome (death, MI at 43 days) UFH (N=493): 29 Enoxaparin (N=431): 14 OR 0.54 (0.28-1.03), p=0.062 Composite outcome (death, MI at 1 yr) UFH (N=493): 59 Enoxaparin (N=431): 27 OR 0.49 (0.31-0.79), p=0.003 Major hemorrhage at 43 days UFH (N=483): 30 Enoxaparin (N=425): 23 OR 0.86, p=0.49-1.51, p=0.608 Major hemorrhage at 1 yr UFH (N=483): 11 Enoxaparin (N=425): 2 OR 0.20 (0.04-0.92), p=0.039

Study	Study Details	Subgroup	Results Reported by Authors
Di Sciascio, 2010[10] ARMYDA-5 PRELOAD Study	RCT Total N: 536 Timing of clopidogrel administration Fair	ACS patients	ACS patients Composite outcome (CV mortality, MI, or TVR at 30 days) Preload patients (N=87): 10% In-lab patients (N=73): 16% OR (95% CI) 1.70 (0.68-4.31), p=0.36
Di Sciascio, 2010[11] ARMYDA-4 RELOAD Study	RCT Total N: 647 Other Clopidogrel loading dose Good	ACS presentation	Patients diagnosed with ACS at randomization Composite outcome (death, MI, or TVR at 30 days) Clopidogrel reload (N=109) Placebo (N=98) OR (95%CI) 0.35 (0.12-0.96), Adjusted OR (95%CI): 0.34 (0.32-0.90)
			Patients diagnosed with ACS (intent-to treat analysis) Composite outcome (death, MI, or TVR at 30 days) Clopidogrel reload (N=139): 5% Placebo (N=127): 13% P=0.048
Durand, 2007[12] PRACTICE Study	RCT Total N: 393 Upstream GPI vs. deferred GPI Fair	Patients who underwent PCI	Patients who underwent PCI Composite outcome (death, nonfatal MI and recurrent ischemia requiring urgent revascularization at 30 days) Eptifibatide: 15.2% Placebo: 14.8% OR (95%CI) 0.96 (0.47-1.99), p=0.84
Ferguson, 2004[13] SYNERGY Study	RCT Total N: 10,027 Enoxaparin vs. UFH vs. Fondaparinux Good	Sex	Male Composite outcome (death or MI at 30 days) Enoxaparin (N=3296): 14.2% UFH (N=3299): 15.4% p=0.16
			Female Composite outcome (death or MI at 30 days) Enoxaparin: 13.5% UFH: 12.9% p=0.59
		Diabetes	Diabetes Composite outcome (death or MI at 30 days) Enoxaparin (N=1422): 15.6% UFH (N=1500): 15.7% p=0.94
			No diabetes Composite outcome (death or MI at 30 days) Enoxaparin (N=3568): 13.3% UFH (N=3482): 14.0% p=0.36
		Geography	Australia/New Zealand Composite outcome (death or MI at 30 days) Enoxaparin (N=206): 11.2% UFH (N=208): 10.6% p=0.91
			Europe Composite outcome (death or MI at 30 days) Enoxaparin (N=908): 13.0% UFH (N=904): 13.2% p=0.91

Study	Study Details	Subgroup	Results Reported by Authors
			North America Composite outcome (death or MI at 30 days) Enoxaparin (N=242): 27.3% UFH (N=239): 29.7% p=0.45
			South America Composite outcome (death or MI at 30 days) Enoxaparin (N=3636): 13.5% UFH (N=3632): 14.1% p=0.47
		History of smoking	Smoking current Composite outcome (death or MI at 30 days) Enoxaparin (N=1178): 12.3% UFH (N=1225): 15.9% p=0.009
			Smoking prior Composite outcome (death or MI at 30 days) Enoxaparin (N=1756): 15.2% UFH (N=1735): 14.9% p=0.82
			Smoking never Composite outcome (death or MI at 30 days) Enoxaparin (N=2056): 13.9% UFH (N=2018): 13.4% p=0.065
		Prior revascularization	Prior PCI Composite outcome (death or MI at 30 days) Enoxaparin (N=1044): 13.9% UFH (N=964): 14.1% p=0.92
			No prior PCI Composite outcome (death or MI at 30 days) Enoxaparin (N=3947): 14.0% UFH (N=4017): 14.6% p=0.37
			Prior CABG Composite outcome (death or MI at 30 days) Enoxaparin (N=805): 13.2% UFH (N=853): 15.8% p=0.15
			No prior CABG Composite outcome (death or MI at 30 days) Enoxaparin (N=4186): 14.1% UFH (N=4124): 14.3% p=0.77
		Prerandomization antithrombin therapy	No prerandomization antithrombin therapy Composite outcome (death or MI at 30 days) Enoxaparin (N=1212): 12.6% UFH(N=1228): 14.8% HR 0.84 (0.68-1.05)
			Prerandomization enoxaparin only Composite outcome (death or MI at 30 days) Enoxaparin (N=2186): 13.6% UFH (N=2108): 13.1% HR 1.04 (0.88-1.23)

Study	Study Details	Subgroup	Results Reported by Authors
			Prerandomization UFH only Composite outcome (death or MI at 30 days) Enoxaparin (N=1428): 15.2% UFH (N=1512): 16.7% HR 0.89 (0.74-1.08)
			Prerandomization both agents Composite outcome (death or MI at 30 days) Enoxaparin (N=167): 18.1% UFH (N=137): 9.5% HR 2.0 (1.03-3.90)
		Postrandomization crossovers	No crossover Composite outcome (death or MI at 30 days) Enoxaparin (N=4400): 13.5% UFH (N=4780): 14.2%
			Crossover Composite outcome (death or MI at 30 days) Enoxaparin(N=593): 17.4% UFH (N=205): 22.0%
		Patients who underwent PCI	PCI patients with and without crossover to alternative antithrombotic therapy Composite outcome (death or MI at 30 days) Enoxaparin (N=2323): 13.1% UFH (N=2363): 14.2% HR 0.92 (0.79-1.07), p=0.289 Total mortality at 30 days Enoxaparin: 1.7% UFH: 1.8% HR 0.95 (0.62-1.46), p=0.804 Nonfatal MI at 30 days Enoxaparin: 11.8% UFH: 13.2% HR 0.89 (0.76-1.05), p=0.172 GUSTO severe bleeding at 30 days Enoxaparin: 1.5% UFH: 1.6% HR 0.92 (0.57-1.45), p=0.688
			PCI patients without crossover antithrombotic strategy TIMI Major bleeding at 30 days Enoxaparin: 3.7% UFH: 2.5% HR 1.46 (1.04-2.04), p=0.028 TIMI minor bleeding at 30 days Enoxaparin: 11.2% UFH: 11.6% HR 0.97 (0.80-1.16), p=0.699 Any transfusion at 30 days Enox: 5.8% UFH: 5.4% HR 1.28 (1.00-1.63), p=0.047

Study	Study Details	Subgroup	Results Reported by Authors
			Composite outcome (death or MI at 30 days) Enoxaparin (N=2028): 12.5% UFH (N=2293): 13.7%, HR 0.91 (0.77-1.07), p=0.265 Total mortality at 30 days Enoxaparin: 1.3% UFH: 1.7% HR 0.76 (0.47-1.24), p=0.276 Nonfatal MI at 30 days Enoxaparin: 11.5% UFH: 12.8% HR 0.90 (0.76-1.07), p=0.222 GUSTO severe bleeding at 30 days Enoxaparin: 1.1% UFH: 1.6 % HR 0.70 (0.41-1.18), p=0.181 TIMI Major bleeding at 30 days Enoxaparin: 3.1% UFH: 2.4% HR 1.31 (0.90-1.90), p=0.154 TIMI minor bleeding at 30 days Enoxaparin 10.4% UFH: 11.4% HR 0.90 (0.75-1.10), p=0.309 Any transfusion at 30 days Enoxaparin: 5.8% UFH 5.0% HR 1.17 (0.90-1.53), p=0.243
			Patients receiving no antithrombotic before randomization Composite outcome (death or MI at 30 days) Enoxaparin (N=499): 12.0% UFH (N=524): 16.3%, HR 0.727 (0.523-1.012), p=0.053
		Patients undergoing CABG surgery	Patients undergoing CABG surgery Death or MI at 30 days Enoxaparin (N=855): 27.3% UFH (N=921): 30.9% adjusted HR 0.90 (0.75-1.07), p=0.239 Adjusted stroke rate at 6 months Enoxaparin: 2.58% (95% CI 1.54-3.63) UFH: 3.16% (95% CI 1.96-4.35), p=0.476 TIMI major bleeding at 30 days Enoxaparin: 36.1% UFH: 34.2%, adjusted HR 1.10 (0.94-1.38), p=0.229
		Timing of clopidogrel among CABG patients	Clopidogrel administration among CABG patients at baseline vs. no clopidogrel administration TIMI major bleeding at 30 days Adjusted HR 1.19 (0.99-1.43), p=0.053 Stroke at 30 days Adjusted HR 0.87 (0.66-1.12, p=0.322) Death or MI at 30 days Clopidogrel: 24.1% No clopidogrel: 29.0% Adjusted HR 0.94, CI 0.83-1.06) p=0.332

Study	Study Details	Subgroup	Results Reported by Authors
		Prerandomization antithrombin therapy	No pre-treatment with antithrombin Total mortality at 48 hrs: 15/2438 Total mortality at 30 days: 81/2438 Nonfatal MI at 48 hrs: 133/2440 Nonfatal MI at 30 days: 274/2440 Death or MI at 48 hrs: 146/2438 Death or MI at 30 days: 333/2438 Stroke at 30 days: 18/2440 GUSTO severe bleeding at 30 days: 58/2439 TIMI major bleeding (including CABG related) at 30 days: 203/2440
			Pre-randomization treatment with UFH only Total mortality at 48 hrs: 12/2939 Total mortality at 30 days: 95/2939 Nonfatal MI at 48 hrs: 189/2940 Nonfatal MI at 30 days: 411/2940 Death or MI at 48 hrs: 198/2939 Death or MI at 30 days: 468/2939 Stroke at 30 days: 23/2940 GUSTO severe bleeding at 30 days: 72/2939 TIMI major bleeding (including CABG related) at 30 days: 255/2939
			Pre-randomization treatment with enoxaparin only Total mortality at 48 hrs: 17/4294 Total mortality at 30 days: 125/4294 Nonfatal MI at 48 hrs: 234/4294 Nonfatal MI at 30 days: 488/4294 Death or MI at 48 hrs: 248/4294 Death or MI at 30 days: 574/4293 Stroke at 30 days: 47/4294 GUSTO severe bleeding at 30 days: 109/4294 TIMI major bleeding (including CABG related) at 30 days: 354/4294
			Pre-randomization treatment with both UFH and enoxaparin Total mortality at 48 hrs: 3/304, unadjusted p-value 0.312 Total mortality at 30 days: 12/304, unadjusted p-value 0.628 Nonfatal MI at 48 hrs: 13/304, unadjusted p value 0.185 Nonfatal MI at 30 days: 34/304, unadjusted p-value 0.003 Death or MI at 48 hrs: 15/304, unadjusted p-value 0.302 Death or MI at 30 days: 43/304, unadjusted p-value 0.017 Stroke at 30 days: 4/304 , unadjusted p-value 0.327 GUSTO severe bleeding at 30 days: 6/304 TIMI major bleeding (including CABG related) at 30 days: 20/304
		Consistent therapy vs. no consistent therapy	Consistent therapy Composite outcome (death or MI at 48 hrs): 374/6135 Composite outcome (death or MI at 30 days): 883/6135 Composite outcome (death, MI, or ischemia requiring revascularization at 30 days): 1024/6135
			No consistent therapy Composite outcome (death or MI at 30 days): 221/3840, unadjusted p-value=0.858 Composite outcome (death, MI, or ischemia requiring revascularization at 30 days): 641/3838, unadjusted p-value=0.989
		Prerandomization antithrombotic therapy	Prerandomization UFH only Composite outcome (adjusted death or MI at 30 days): Adjusted OR: 0.93 (0.75-1.14) GUSTO severe bleeding at 30 days: Adjusted OR 1.04 (0.64-1.70) TIMI bleeding at 30 days: Adjusted OR 1.00 (0.77-1.31)
			Prerandomization enoxaparin only Composite outcome (adjusted death or MI at 30 days): Adjusted OR 1.04 (0.87 (1.26) GUSTO severe bleeding at 30 days: Adjusted OR 1.23 (0.84-1.81) TIMI bleeding at 30 days: Adjusted OR 1.23 (0.98-1.53)

Study	Study Details	Subgroup	Results Reported by Authors
			Prerandomization both UFH and enoxaparin Composite outcome (adjusted death or MI at 30 days): Adjusted OR (1.97 (0.96-3.98) GUSTO severe bleeding at 30 days: Adjusted OR 0.39 (0.07-2.21) TIMI bleeding at 30 days
			Neither UFH nor enoxaparin Composite outcome (adjusted death or MI at 30 days): Adjusted OR 0.78 (0.62-1.00) GUSTO severe bleeding at 30 days: Adjusted OR 1.88 (1.08-3.27) TIMI bleeding at 30 days: Adjusted OR 1.40 (1.05-1.89)
			Same pretreatment as randomization Composite outcome (adjusted death or MI at 30 days): Adjusted OR 0.88 (0.73-1.06) GUSTO severe bleeding at 30 days: Adjusted OR 1.25 (0.82-1.93) TIMI bleeding at 30 days: Adjusted OR 1.11 (0.88-1.41)
		Consistent therapy vs. no consistent therapy pre-randomization	Consistent therapy pre-randomization Composite outcome (death or MI at 30 days) Adjusted OR 0.86 (0.74-0.99), favoring Enoxaparin TIMI bleeding at 30 days Adjusted Or 1.23 (1.02-1.48), favoring Enoxaparin
			No consistent therapy pre-randomization Composite outcome (death or MI at 30 days) Adjusted OR 1.15 ((0.95-1.39), favoring Enoxaparin TIMI bleeding at 30 days Adjusted OR 1.13 (0.88-1.44), favoring Enoxaparin
Fung, 2009[14] BRIEF-PCI Study	RCT Total N: 624 GPI duration Fair	Diabetes	Diabetes Ischemic myocardial injury (primary endpoint) <2-hr group (N=38):13.2% 18-hr group (N=48):18.8% p interaction=0.40
			No diabetes Ischemic myocardial injury (primary endpoint) <2-hr group (N=268):13.2% 18-hr group (N=263):18.8%
		Presence of ACS	ACS Ischemic myocardial injury (primary endpoint) <2-hr group (N=163):25.2% 18-hr group (N=152):28.3% p interaction=0.16
			No ACS Ischemic myocardial injury (primary endpoint) <2-hr group (N=143):35.7% 18-hr group (N=159):28.3%
		Clopidogrel treatment	Clopidogrel pre-treatment Ischemic myocardial injury (primary endpoint) <2-hr group (N=217):29.0% 18-hr group (N=204):27.0% p interaction=0.95
			No clopidogrel pre-treatment Ischemic myocardial injury (primary endpoint) <2-hr group (N=89):32.6% 18-hr group (N=107):30.8%

Study	Study Details	Subgroup	Results Reported by Authors
Giugliano, 2009[15] EARLY ACS Study	RCT Total N: 9,378 Pretreatment clopidogrel (upstream vs. deferred GPI) Good	Sex	Male (N=6431) Primary Composite End Point at 96 hours Early: 9.1% Delayed: 9.8% Primary Composite End Point at 30 days Early: 11.4% Delayed: 12.0%
			Female (N=2975) Primary Composite End Point at 96 hours Early: 9.7% Delayed: 10.4% Primary Composite End Point at 30 days Early: 10.7% Delayed: 13.0%
		Creatinine clearance	Excess dose, eCrCl<50 ml/min Death/MI/RIUR/TBO within 96 hours: Early Eptifibatide: 11.6% Delayed Eptifibatide: 11.4% Unadjusted OR 1.02 (0.60-1.74) Adjusted OR 1.0 (0.58-1.72) Death/MI at 30 days: Early Eptifibatide: 13.1% Delayed Eptifibatide: 14.0% Unadjusted OR 0.93 (0.57-1.53) Adjusted OR 0.93 (0.56-1.53) TIMI Major bleeding within 120 hr after randomization: Early Eptifibatide: 3.1% Delayed Eptifibatide: 0.7% Unadjusted OR 4.29 (0.90-20.4) Adjusted OR 1.92 (0.40-13.97) GUSTO severe/moderate bleeding within 120 hr after randomization: Early Eptifibatide: 9.1% Delayed Eptifibatide: 6.0% Unadjusted OR 1.58 (0.81-3.06) Adjusted OR 1.67 (0.85-3.39)

Study	Study Details	Subgroup	Results Reported by Authors
			Adjusted dose, eCrCl<50 ml/min Death/MI/RIUR/TBO within 96 hours: Early Eptifibatide: 13.1% Delayed Eptifibatide: 11.6% Unadjusted OR 1.02 (0.80-1.65) Adjusted OR 1.14 (0.80-1.65) Death/MI at 30 days: Early Eptifibatide: 17.1% Delayed Eptifibatide: 15.1% Unadjusted OR 1.16 (0.84-1.60) Adjusted OR 1.13 (0.81-1.56 TIMI Major bleeding within 120 hr after randomization: Early Eptifibatide: 2.0% Delayed Eptifibatide: 0.7% Unadjusted OR 2.75 (0.87-8.67) Adjusted OR 1.82 (0.49-8.81) GUSTO severe/moderate bleeding within 120 hr after randomization: Early Eptifibatide: 10.0% Delayed Eptifibatide: 6.6% Unadjusted OR 1.56 (1.01-2.45) Adjusted OR 1.50 (0.95-2.40)
			Standard dose, eCrCl>50 ml/min Death/MI/RIUR/TBO within 96 hours: Early Eptifibatide: 8.6% Delayed Eptifibatide: 9.5% Unadjusted OR 0.90 (0.77-1.06) Adjusted OR 0.92 (0.78-1.077) Death/MI at 30 days: Early Eptifibatide: 10.1% Delayed Eptifibatide: 11.5% Unadjusted OR 0.87 (0.75-1.01) Adjusted OR 0.87 (0.75-1.01) TIMI Major bleeding within 120 hr after randomization: Early Eptifibatide: 1.3% Delayed Eptifibatide: 0.8% Unadjusted OR 1.68 (1.05-2.69) Adjusted OR 1.78 (1.10-2.95) GUSTO severe/moderate bleeding within 120 hr after randomization: Early Eptifibatide: 4.0% Delayed Eptifibatide: 1.8% Unadjusted OR 2.32 (1.71-3.14) Adjusted OR 2.43 (1.79-3.34)

Study	Study Details	Subgroup	Results Reported by Authors
		Upstream Clopidogrel use	Upstream Clopidogrel Use (N=6895) Death/MI/RIUR/TBO within 96 hours: Early Eptifibatide: 8.8% Delayed Eptifibatide: 9.4% Adjusted OR 0.93 (0.76, 1.10) Death/MI at 30 days: Early Eptifibatide: 10.1% Delayed Eptifibatide: 11.8% Adjusted OR 0.85 (0.73, 0.99) TIMI Major bleeding within 120 hr after randomization: Early Eptifibatide: 2.2% Delayed Eptifibatide: 1.4% Adjusted OR 1.54 (1.07, 2.24) GUSTO severe/moderate bleeding within 120 hr after randomization: Early Eptifibatide: 7.2% Delayed Eptifibatide: 6.0% Adjusted OR 1.41 (1.07, 1.87)
			No Upstream Clopidogrel Use (N=2271) Death/MI/RIUR/TBO within 96 hours: Early Eptifibatide: 10.4% Delayed Eptifibatide: 11.2% Adjusted OR 0.94 (0.72 , 1.22) Death/MI at 30 days: Early Eptifibatide: 13.1% Delayed Eptifibatide: 12.8% Adjusted OR 1.02 (0.80, 1.30) TIMI Major bleeding within 120 hr after randomization: Early Eptifibatide: 3.4% Delayed Eptifibatide: 2.8% Adjusted OR 1.13 (0.69, 1.84) GUSTO severe/moderate bleeding within 120 hr after randomization: Early Eptifibatide: 13.4% Delayed Eptifibatide: 9.3% Adjusted OR 1.26 (1.03, 1.54)
		Age	<75 yrs (N=7026) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 8.6% Delayed Eptifibatide: 9.5% Death/MI at 30 days: Early Eptifibatide: 10.2% Delayed Eptifibatide: 11.6%
			≥ 75 yrs (N=2377) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 11.4% Delayed Eptifibatide: 11.4% Death/MI at 30 days: Early Eptifibatide: 14.0% Delayed Eptifibatide: 14.6%

Study	Study Details	Subgroup	Results Reported by Authors
		Troponin level	Positive troponin (N=7650) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 9.5% Delayed Eptifibatide: 10.6% Death/MI at 30 days: Early Eptifibatide: 11.6% Delayed Eptifibatide: 13.0%
			Negative troponin (N=1468) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 7.7% Delayed Eptifibatide: 6.8% Death/MI at 30 days: Early Eptifibatide: 8.1% Delayed Eptifibatide: 8.4%
		Diabetes	Diabetes (N=2860) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 8.9% Delayed Eptifibatide: 10.6% Death/MI at 30 days: Early Eptifibatide: 11.7% Delayed Eptifibatide: 13.8%
			No diabetes (N=6546) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 9.5% Delayed Eptifibatide: 9.8% Death/MI at 30 days: Early Eptifibatide: 10.6% Delayed Eptifibatide: 11.7%
		Heparin use	Unfractionated heparin only (N=3237) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 9.1% Delayed Eptifibatide: 11.0% Death/MI at 30 days: Early Eptifibatide: 11.3% Delayed Eptifibatide: 13.0%
			Low molecular weight heparin only (N=4973) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 9.9% Delayed Eptifibatide: 9.9% Death/MI at 30 days: Early Eptifibatide: 11.3% Delayed Eptifibatide: 12.8%
		Geography	North America (N=2888) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 10.3% Delayed Eptifibatide: 10.6% Death/MI at 30 days: Early Eptifibatide: 13.2% Delayed Eptifibatide: 14.5%

Study	Study Details	Subgroup	Results Reported by Authors
			Western Europe (N=3790) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 7.3% Delayed Eptifibatide: 8.6% Death/MI at 30 days: Early Eptifibatide: 8.8% Delayed Eptifibatide: 10.2%
			Eastern Europe (N=1018) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 11.2% Delayed Eptifibatide: 11.2% Death/MI at 30 days: Early Eptifibatide: 14.5% Delayed Eptifibatide: 15.2%
			Middle East, Africa, Asia-Pacific (N=1710) Death/MI/RIUR/TBO at 96 hours: Early Eptifibatide: 10.9% Delayed Eptifibatide: 11.5% Death/MI at 30 days: Early Eptifibatide: 11.0% Delayed Eptifibatide: 11.6%
Islam, 2002[16] EPISTENT Study	RCT Total N: 2,399 GPI vs. placebo at time of PCI Good	Age	≥65 yrs (N=NR) Composite outcome (death, MI, or urgent revascularization at 30 days) Placebo + Stent: 12.0% Abciximab + stent: 8.6% (p-value: 0.210). Abciximab + balloon 7.0% (p-value: 0.050 for the comparison with the placebo + stent group)
		Diabetes	Diabetes Composite outcome (death, MI, or urgent revascularization at 30 days) Placebo + stent (N=173): 12.1% Abciximab + stent (N=162): 5.6% (p-value: 0.040) Abciximab + balloon (N=156): 5.1% (p-value: 0.032 for the comparison with the placebo + stent group)
		Sex	Male Composite outcome (death, MI, or urgent revascularization at 30 days) Placebo + stent (N=603): 10.5% Abciximab + stent (N=599): 4.2% (p-value: 0.001) Abciximab + balloon (N=598): 7.6% (p-value:0.079 for the comparison with the placebo + stent group)
			Female Composite outcome (death, MI, or urgent revascularization at 30 days) Placebo + stent (N=206): 11.7% Abciximab + stent (N=195): 8.7% (p-value: 0.333) Abciximab + balloon (N=198): 5.1% (p-value: 0.021 for the comparison with the placebo + stent group)

Study	Study Details	Subgroup	Results Reported by Authors
		UA<48 hrs	UA diagnosis <48 hrs Composite outcome (death, MI, or urgent revascularization at 30 days) Placebo + stent (N=179): 14.8% Abciximab + stent (N=156): 4.5% (p-value: 0.003) Abciximab + balloon (N=152): 7.3% (p-value: 0.036 for the comparison with the placebo + stent group)
Kastrati, 2006[17] ISAR-REACT 2 Study	RCT Total N: 2,022 GPI vs. placebo at time of PCI Good	Positive troponin	Elevated troponin Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 30 days) Abciximab (n=513):13.1% Placebo(N=536): 18.3% RR: 0.71 (0.54-0.95), p=0.02 p interaction=0.07 Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 1 year) Abciximab (N=513): 28.6% Placebo(N=536): 33.3% RR:0.82 (0.66-1.02), p interaction=0.91 Composite outcome (death or MI at 30 days) Abciximab (N=513): 12.9% Placebo(N=536): 17.9% p=0.02 Composite outcome (death or MI at 1 year) Abciximab (N=513):17.2% Placebo(N=536): 22.1% RR=0.76 (0.58-0.99) p interaction=0.94 Total mortality at 1 year Abciximab (N=513): 6.6% Placebo(N=536): 6.7% p=0.95 Nonfatal MI at 1 year Abciximab (N=513): 12.7% Placebo(N=536): 16.8% p=0.06 Revascularization at 1 year Abciximab (N=513): 13.8% Placebo(N=536): 15.5% p=0.45

Study	Study Details	Subgroup	Results Reported by Authors
			No elevated troponin Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 30 days) Abciximab (N=499): 4.6% Placebo(N=474): 4.6% RR: 0.99 (0.56-1.76), p=0.98 Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 1 year) Abciximab (N=499): 17.8% Placebo(N=474): 22.0% RR: 0.79 (0.59-1.05) Composite outcome (death or MI at 30 days) Abciximab (N=513): 12.9% Placebo(N=536): 17.9% p=0.02 Composite outcome (death or MI at 1 year) Abciximab (N=499): 5.8% Placebo(N=474): 7.7% RR: 0.76 (0.49-1.24) Total mortality at 1 year Abciximab (N=499): 2.2% Placebo(N=474): 2.7% p=0.58 Nonfatal MI at 1 year Abciximab (N=499): 4.6% Placebo(N=474): 5.1% p=0.74 Revascularization at 1 year Abciximab (N=499): 13.2% Placebo(N=474): 17.1% p=0.16
		Diabetes	Diabetes Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 30 days) Abciximab (N=252): 10.3% Placebo (N=284): 11.3% p=0.37 Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 1 year) Abciximab (N=252): 27.1% Placebo (N=284): 28.6% RR: 0.94 (0.68-1.29) p interaction 0.27 Composite outcome (death or MI at 1 year) Abciximab (N=252): 12.3% Placebo (N=284): 16.7% RR: 0.94 (0.46-1.14) p interaction 0.89

Study	Study Details	Subgroup	Results Reported by Authors
			No diabetes Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 30 days) Abciximab (N=760): 8.4% Placebo (N=726): 12.1% Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 1 year) Abciximab (N=760): 22.0% Placebo (N=726): 27.8% RR: 0.76 (0.62-0.93) Composite outcome (death or MI at 1 year) Abciximab (N=760): 11.4% Placebo (N=726): 14.8% RR 0.76 (0.57-1.00)
		Timing of clopidogrel pretreatment	Clopidogrel >3 hours prior to PCI Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 30 days) Abciximab (N=475): 5.7% Placebo (N=461): 7.6% p=0.34 Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 1 year) Abciximab (N=475): 19.8% Placebo (N=461): 25.1% RR: 0.75 (0.57-0.99) p interaction=0.57 Composite outcome (death or MI at 1 year) Abciximab (N=475): 8.9% Placebo (N=461): 11.1% RR: 0.75 (0.52-1.18) p interaction=0.75
			Clopidogrel ≤3 hours prior to PCI Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 30 days) Abciximab (N=537): 11.7% Placebo (N=549): 15.5% Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 1 year) Abciximab (N=537): 26.4% Placebo (N=549): 30.4% RR: 0.84 (0.67-1.05) Composite outcome (death or MI at 1 year) Abciximab (N=537): 14.0% Placebo (N=549): 18.8% RR: 0.73 (0.55-0.98)
		Age	Age >67 yrs Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 1 yr) Abciximab (N=482): 26.6% Placebo (N=527): 30.3% RR: 0.87 (0.69-1.10) p-interaction=0.36 Composite outcome (death or MI at 1 yr) Abciximab (N=482): 15.8% Placebo (N=527): 16.4% RR: 0.97 (0.71-1.32) p interaction=0.015

Study	Study Details	Subgroup	Results Reported by Authors
			Age ≤67 yrs Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 1 yr) Abciximab (N=530): 20.2% Placebo (N=483): 25.5% RR: 0.75 (0.58-0.97) Composite outcome (death or MI at 1 yr) Abciximab (N=530): 7.8% Placebo (N=483): 14.1% RR: 0.53 (0.37-0.78)
			Age >70 yrs Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 30 days) Abciximab (N=635): 7.7% Placebo (N=585): 13.3% p=0.001 Total mortality at 30 days Abciximab (N=635): 0.3% Placebo (N=585): 1.5% p=0.007 Nonfatal MI at 30 days Abciximab (N=635): 7.4% Placebo (N=585): 12.0% p=0.002 Revascularization at 30 days Abciximab (N=635): 0.8% Placebo (N=585): 1.5% p=0.22 Bleeding at 30 days Abciximab (N=635): 0.6% Placebo (N=585): 1.0% p=0.65
			Age ≤70 yrs Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 30 days) Abciximab (N=377): 10.9% Placebo (N=425): 9.9% p=0.65 Total mortality at 30 days Abciximab (N=377): 2.4% Placebo (N=425): 1.6% p=0.69 Nonfatal MI Abciximab (N=377): 9.3% Placebo (N=425): 8.5% p=0.65 Revascularization at 30 days Abciximab (N=377): 1.3% Placebo (N=425): 0.7% p=0.59 Bleeding at 30 days Abciximab (N=377): 2.7% Placebo (N=425): 1.9% p=0.46

Study	Study Details	Subgroup	Results Reported by Authors
		Sex	Female Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 30 days) Abciximab (N=236): 9.7% Placebo (N=262): 9.9% RR 0.98 (0.56-1.12) p=0.97 Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 1 yr) Abciximab (N=236): 21.7% Placebo (N=262): 27.4% RR 0.78 (0.55-1.12) p interaction=0.89 Composite outcome (death or MI at 1 yr) Abciximab (N=236): 14.4% Placebo (N=262): 13.4% RR 1.08 (0.67-1.73) p interaction=0.07 Bleeding at 30 days Abciximab (N=236): 3.4% Placebo (N=262): 3.8% p=0.80 Total mortality at 30 days Abciximab (N=236): 2.1% Placebo (N=262): 1.1% p=0.39 Nonfatal MI at 30 days Abciximab (N=236): 8.9% Placebo (N=262): 8.8% p=0.96 Stent thrombosis at 30 days Abciximab (N=236): 0.4% Placebo (N=262): 1.1% p=0.70

Study	Study Details	Subgroup	Results Reported by Authors
			Male Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 30 days) Abciximab (N=776): 8.6% Placebo (N=748): 12.6% RR 0.69 (0.50-0.94) p=0.01 Composite outcome (death, myocardial infarction, or urgent target-vessel revascularization at 1 yr) Abciximab (N=776): 23.8% Placebo (N=748): 28.2% RR 0.80 (0.66-0.98) Composite outcome (death or MI at 1 yr) Abciximab (N=776): 10.7% Placebo (N=748): 16.0% RR 0.0.66 (0.50-0.86) Bleeding at 30 days Abciximab (N=776): 0.8% Placebo (N=748): 0.5% p=0.56 Total mortality at 30 days Abciximab (N=776): 0.8% Placebo (N=748): 1.7% p=0.09 Nonfatal MI at 30 days Abciximab (N=776): 7.9% Placebo (N=748): 11.1% p=0.03 Stent thrombosis at 30 days Abciximab (N=776): 0.9% Placebo (N=748): 0.7% p=0.72
Kastrati, 2008[18] ISAR-REACT 3 Study	RCT Total N: 4571 Bivalirudin vs. unfractionated heparin Fair	Age	Age >67.6 yrs Composite outcome (death, MI, UTVR, major bleeding at 30 days) Bivalirudin (N=1135): 7.1% UFH (N=1146): 6.9% p interaction=0.46 Composite outcome (death, MI, UTVR, major bleeding at 1 yr) Bivalirudin (N=1154): 17.0% UFH (N=1135): 18.9% p interaction=0.175

Study	Study Details	Subgroup	Results Reported by Authors
			Age <67.6 yrs Composite outcome (death, MI, UTVR, major bleeding at 30 days) Bivalirudin (N=1154): 9.4% UFH (N=1135): 10.6% Composite outcome (death, MI, UTVR, major bleeding at 1 yr) Bivalirudin (N=1135): 17.2% UFH (N=1146): 16.0%
		Sex	Female Composite outcome (death, MI, UTVR, major bleeding at 30 days) Bivalirudin (N=545): 11.4% UFH (N=530): 13.2% p interaction=0.44 Composite outcome (death, MI, UTVR, major bleeding at 1 yr) Bivalirudin (N=545): 17.2% UFH (N=530): 19.9% p interaction=0.238
			Male Composite outcome (death, MI, UTVR, major bleeding at 30 days) Bivalirudin (N=1744): 7.3% UFH (N=1751): 7.4% Composite outcome (death, MI, UTVR, major bleeding at 1 yr) Bivalirudin (N=1744): 17.1% UFH (N=1751): 16.7%
		Diabetes	Diabetes Composite outcome (death, MI, UTVR, major bleeding at 30 days) Bivalirudin (N=618): 10.0% UFH (N=636): 9.7% p interaction=0.58 Composite outcome (death, MI, UTVR, major bleeding at 1 yr) Bivalirudin (N=618): 19.9% UFH (N=636): 22.0% p interaction=0.58
			No diabetes Composite outcome (death, MI, UTVR, major bleeding at 30 days) Bivalirudin (N=1671): 7.7% UFH (N=1645): 8.3% Composite outcome (death, MI, UTVR, major bleeding at 1 yr) Bivalirudin (N=1671): 16.1% UFH (N=1645): 15.7%
		Creatinine clearance	Creatinine > 0.9 mg/dL Composite outcome (death, MI, UTVR, major bleeding at 30 days) Bivalirudin (N=987): 8.1% UFH (N=985): 9.3% p interaction=0.42 Composite outcome (death, MI, UTVR, major bleeding at 1 yr) Bivalirudin (N=987): 17.2% UFH (N=985): 18.0% p interaction=0.74

Study	Study Details	Subgroup	Results Reported by Authors
			Creatinine < 0.9 mg/dL Composite outcome (death, MI, UTVR, major bleeding at 30 days) Bivalirudin (N=1302): 8.4% UFH (N=1296): 8.3% Composite outcome (death, MI, UTVR, major bleeding at 1 yr) Bivalirudin (N=1302): 17.0% UFH (N=1296): 17.1%
		Symptom class	Unstable angina Composite outcome (death, MI, UTVR, major bleeding at 30 days) Bivalirudin (N=421): 10.0% UFH (N=415): 10.8% p interaction=0.88 Composite outcome (death, MI, UTVR, major bleeding at 1 yr) Bivalirudin (N=421): 21.5% UFH (N=415): 20.1% p interaction=0.458
			Stable angina Composite outcome (death, MI, UTVR, major bleeding at 30 days) Bivalirudin (N=1868): 7.9% UFH (N=1866): 8.3% Composite outcome (death, MI, UTVR, major bleeding at 1 yr) Bivalirudin (N=1868): 16.1% UFH (N=1866): 16.9%
Kastrati, 2011[19] ISAR-REACT 4 Study	RCT Total N: 1721 Bivalirudin vs. UFH + GPI Good	Sex	Male Composite outcome (death, large recurrent MI, urgent target-vessel revascularization, major bleeding at 30 days) Abciximab:15.5% Bivalrudin:12.6 p-value for interaction 0.27
			Female Composite outcome (death, large recurrent MI, urgent target-vessel revascularization, major bleeding at 30 days) Abciximab: 9.5% Bivalirudin: 10.6% p-value for interaction 0.27
		Diabetes	Diabetes Composite outcome (death, large recurrent MI, urgent target-vessel revascularization, major bleeding at 30 days) Abciximab: 10.5% Bivalirudin: 9.9% p-value for interaction 0.71

Study	Study Details	Subgroup	Results Reported by Authors
Mehta, 2005[20] ASPIRE Study	RCT Total N: 350 Enoxaparin vs. UFH vs. Fondaparinux Fair	Planned GP IIb/IIIa use	Planned IIb/IIIa use Composite outcome (death, MI, UR, bailout at 48 hrs) UFH (N=65): 4.6% Fondaparinux 2.5 mg (N=70): 4.3% Fondaparinux 5 mg (N=68): 5.9% Total mortality at 48 hrs UFH (N=65): 0% Fondaparinux 2.5 mg (N=70): 0% Fondaparinux 5 mg (N=68): 0% Nonfatal MI at 48 hrs UFH (N=65): 4.6% Fondaparinux 2.5 mg (N=70): 4.3% Fondaparinux 5 mg (N=68): 5.9% Revascularization at 48 hrs UFH (N=65): 0% Fondaparinux 2.5 mg (N=70): 0% Fondaparinux 5 mg (N=68): 0% Bleeding at 48 hrs Major bleeding UFH (N=65): 0% Fondaparinux 2.5 mg (N=70): 1.4% Fondaparinux 5 mg (N=68): 4.4%
			No planned IIb/IIIa use Composite outcome (death, MI, UR, bailout at 48 hrs) UFH (N=52): 4.2% Fondaparinux 2.5 mg (N=48): 7.7% Fondaparinux 5 mg (N=47): 10.6% Total mortality at 48 hrs UFH (N=52): 0% Fondaparinux 2.5 mg (N=48): 0% Fondaparinux 5 mg (N=47): 2% Nonfatal MI at 48 hrs UFH (N=52): 5.9% Fondaparinux 2.5 mg (N=48): 7.7% Fondaparinux 5 mg (N=47): 2.1% Revascularization at 48 hrs UFH (N=52): 1.9% Fondaparinux 2.5 mg (N=48): 0% Fondaparinux 5 mg (N=47): 4.3% Bleeding at 48 hrs Major bleeding UFH (N=52): 0% Fondaparinux 2.5 mg (N=48): 0% Fondaparinux 5 mg (N=47): 0%
Mehta, 2010[21] CURRENT-OASIS 7 Study	RCT Total N: 25,086 Clopidogrel 300 mg loading dose vs. clopidogrel 600 mg loading dose Good	Aspirin dose	High dose aspirin Composite outcome (CV death, MI, or stroke at 30 days) Clopidogrel double dose: 3.8% Clopidogrel standard dose: 4.6% HR (95% CI): 0.82 (0.69-0.98) p=0.03
			Low dose aspirin Composite outcome (CV death, MI, or stroke at 30 days) Clopidogrel double dose: 4.5% Clopidogrel standard dose: 4.2% HR (95% CI): 1.07 (0.90-1.26), p=0.046

Study	Study Details	Subgroup	Results Reported by Authors
		Performance of PCI	PCI (N=17263) clopidogrel dose Composite outcome (CV death, MI, or stroke at 30 days) Clopidogrel double dose: 3.9% Clopidogrel standard dose: 4.5% HR: 0.85, p=0.04 Stent thrombosis at 30 days Clopidogrel double dose: 1.6% Clopidogrel standard dose: 2.3% HR: 0.68, 95% CI 0.55-0.85, p<0.001 Composite outcome (CV death, MI, stroke, or recurrent ischemia, all-cause mortality at 30 days) Clopidogrel double dose: 4.2% Clopidogrel standard dose: 5.0% HR: 0.85, p=0.025 CV mortality at 30 days Clopidogrel double dose: 1.9% Clopidogrel standard dose: 1.9% HR: 0.96, p=0.71 Nonfatal MI at 30 days Clopidogrel double dose: 2.0% Clopidogrel standard dose: 2.6% HR: 0.79, p=0.018 Recurrent ischemia at 30 days Clopidogrel double dose: 0.5% Clopidogrel standard dose: 0.6% HR: 0.85, p=0.47 Major bleeding at 30 days Clopidogrel double dose: 1.0% Clopidogrel standard dose: 0.7% HR: 1.36, p=0.074
			No PCI (N=7823) clopidogrel dose Composite outcome (CV death, MI, or stroke at 30 days) Clopidogrel double dose: 4.9% Clopidogrel standard dose: 4.3% HR: 1.14, p=0.22

Study	Study Details	Subgroup	Results Reported by Authors
			PCI (N=17263) aspirin dose Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 4.1% Aspirin low dose: 4.2% HR: 0.97, p =0.73 p interaction = 0.93 Composite outcome (CV death, MI, stroke, or recurrent ischemia, all-cause mortality at 30 days) Aspirin high dose: 4.4% Aspirin low dose: 4.8% HR: 0.92, p =0.23 CV mortality at 30 days Aspirin high dose: 1.8% Aspirin low dose: 2.0% HR: 0.90, p =0.35 Nonfatal MI at 30 days Aspirin high dose: 2.3% Aspirin low dose: 2.4% HR: 0.97, p =0.80 Recurrent ischemia at 30 days Aspirin high dose: 0.4% Aspirin low dose: 0.7% HR: 0.56, p =0.011 Major bleeding at 30 days Aspirin high dose: 0.9% Aspirin low dose: 0.7% HR: 1.27, p =0.13
			No PCI (N=7823) aspirin dose Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 4.5% Aspirin low dose: 4.7% HR: 0.96, p =0.72 p interaction = 0.93
		Age	≤65 yrs, clopidogrel (N=15765) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 2.9% Standard dose clopidogrel: 2.9% HR: 1.01, p=0.88
			>65 yrs, clopidogrel (N=9321) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 6.3% Standard dose clopidogrel: 7.1% HR: 0.89, p=0.15
			≤65 yrs, aspirin (N=15765) Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 2.7% Aspirin low dose: 3.1% HR: 0.88, p =0.17 p interaction = 0.19
			>65 yrs, aspirin (N=9321) Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 6.8% Aspirin low dose: 6.6% HR: 1.03, p =0.69 p interaction = 0.19

Study	Study Details	Subgroup	Results Reported by Authors
		Diabetes	Diabetes, clopidogrel dose (N=5880) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 5.2% Standard dose clopidogrel: 6.1% HR: 0.86, p=0.16
			No diabetes, clopidogrel dose (N=19203) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 3.9% Standard dose clopidogrel: 3.9% HR: 0.98, p=0.77
			Diabetes, aspirin dose (N=5880) Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 5.7% Aspirin low dose: 5.6% HR: 1.01, p =0.93 p interaction = 0.62
			No diabetes, aspirin dose (N=19203) Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 3.8% Aspirin low dose: 4.0% HR: 0.95, p =0.46 p interaction = 0.62
		Sex	Female, clopidogrel dose (N=6871) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 4.5% Standard dose clopidogrel: 5.4% HR: 0.83, p=0.09 p interaction = 0.17
			Male, clopidogrel dose (N=18213) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 4.1% Standard dose clopidogrel: 4.1% HR: 1.00, p=0.95 p interaction = 0.17
			Female, aspirin dose (N=6872) Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 4.9% Aspirin low dose: 45.0% HR: 0.97, p =0.75 p interaction = 0.99
			Male, aspirin dose (N=18213) Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 4.0% Aspirin low dose: 4.1% HR: 0.97, p =0.95 p interaction = 0.99
		Smoker vs. nonsmoker	Smoker, clopidogrel dose (N=8373) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 2.9% Standard dose clopidogrel: 3.6% HR: 0.80, p=0.07 p interaction = 0.14

Study	Study Details	Subgroup	Results Reported by Authors
			Non-smoker, clopidogrel dose (N=16701) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 4.8% Standard dose clopidogrel: 4.8% HR: 0.99, p=0.89 p interaction = 0.14
			Smoker, aspirin dose (N=8373) Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 3.2% Aspirin low dose: 3.3% HR: 0.97, p =0.82 p interaction = 1.00
			Non-smoker, aspirin dose (N=16701) Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 4.7% Aspirin low dose: 4.9% HR 0.97, p =0.66 p interaction = 1.00
		Use of PPI before randomization	Use of PPI before randomization, clopidogrel dose (N=3215) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 3.9% Standard dose clopidogrel: 5.0% HR: 0.78, p=0.14 p interaction = 0.31
			No use of PPI before randomization, clopidogrel dose (N=15215) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 4.1% Standard dose clopidogrel: 4.4% HR: 0.94, p=0.43 p interaction = 0.31
			Use of PPI before randomization, aspirin dose (N=3215) Composite outcome (CV death, MI, or stroke at 30 days) High dose aspirin: 4.7% Low dose aspirin: 4.2% HR: 1.14, p=0.44 p interaction = 0.42
			No use of PPI before randomization, aspirin dose (N=15215) Composite outcome (CV death, MI, or stroke at 30 days) High dose aspirin: 4.2% Low dose aspirin: 4.3% HR: 0.99, p=0.87 p interaction = 0.42
		Use of PPI after randomization	Use of GPI after randomization, clopidogrel dose (N=5873) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 5.3% Standard dose clopidogrel: 5.8% HR: 0.91, p=0.39 p interaction = 0.71
			No use of GPI after randomization, clopidogrel dose (N=19195) Composite outcome (CV death, MI, or stroke at 30 days) Double dose clopidogrel: 3.8% Standard dose clopidogrel: 4.0% HR: 0.95, p=0.51 p interaction = 0.71

Study	Study Details	Subgroup	Results Reported by Authors
			Use of GPI after randomization, aspirin dose (N=5873) Composite outcome (CV death, MI, or stroke at 30 days) High dose aspirin: 5.6% Low dose aspirin: 5.5% HR: 1.02, p=0.84 p interaction = 0.57
			No use of GPI after randomization, aspirin dose (N=19195) Composite outcome (CV death, MI, or stroke at 30 days) High dose aspirin: 3.8% Low dose aspirin: 4.0% HR: 0.95, p=0.46 p interaction = 0.57
		Symptom status	UA/NSTEMI, clopidogrel dose (N=17759) Composite outcome (CV death, MI, or stroke at 30 days) Clopidogrel double dose: 4.0% Clopidogrel standard dose: 4.1% HR: 0.96, p =0.58 p interaction = 0.61
			STEMI, clopidogrel dose (N=7327) Composite outcome (CV death, MI, or stroke at 30 days) Clopidogrel double dose: 4.7% Clopidogrel standard dose: 5.2% HR: 0.90, p =0.32 p interaction = 0.61
			UA/NSTEMI, aspirin dose (N=17759) Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 3.9% Aspirin low dose: 4.2% HR: 0.94, p =0.41 p interaction = 0.49
			STEMI, aspirin dose (N=7327) Composite outcome (CV death, MI, or stroke at 30 days) Aspirin high dose: 5.0% Aspirin low dose: 4.8% HR: 1.03, p =0.79 p interaction = 0.49
Ozkan, 2005[22]	RCT Total N: 47 Other GPI studies Fair	Diabetes	Diabetes No or slow reflow phenomenon Diabetes group: 8.3%
			No diabetes No or slow reflow phenomenon No diabetes group: 62.5% p-value 0.012

Study	Study Details	Subgroup	Results Reported by Authors
Parodi, 2010[23] ARNO Study	RCT Total N: 850 Bivalirudin vs. UFH Fair	Abciximab treatment	Abciximab-treated patients Composite outcome (death, myocardial infarction, target vessel revascularization at 30 days) Bivalirudin (N=62): 6.5% UFH (N=117): 6.0% p=0.901 Bleeding at 30 days Bivalirudin (N=62): 1.6% UFH (N=117): 3.4% p=0.66 Composite outcome (ischemic complications bleeding complications at 30 days) Bivalirudin (N=62): 8.1% UFH (N=117): 9.4% p=0.765
			Non-abciximab treated patients Composite outcome (death, myocardial infarction, target vessel revascularization at 30 days) Bivalirudin (N=363): 2.2% UFH (N=308): 6.8% p=0.003 Bleeding at 30 days Bivalirudin (N=363): 0.8% UFH (N=308): 2.6% p=0.072 Composite outcome (ischemic complications bleeding complications at 30 days) Bivalirudin (N=363): 2.5% UFH (N=308): 7.5% p=0.003
Patti, 2012[24]	RCT Total N: 401 Bivalirudin vs. unfractionated heparin Good	NSTEMI ACS patients	MACE 30 day bival: 16.4%, UFH: 13%; p=0.80
Puymirat, 2011[25] FAST-MI	Observational Total N: 791 Clopidogrel loading dose vs. clopidogrel no loading dose Fair	GPI use	Received IIb/IIIa inhibitor during index hospitalization Mortality at 30 days No loading dose (N=80): 11 Loading dose (N=139): 11 p = 0.17 Major bleeding at 30 days No loading dose (N=80): 4 Loading dose (N=139): 10 p=0.52
			Did not receive IIb/IIIa inhibitor during index hospitalization Mortality at 30 days No loading dose (N=245): 24 Loading dose (N=327): 36 p=0.64 Major bleeding at 30 days No loading dose: (N=245): 16 Loading dose (N=327): 15 p=0.31

Study	Study Details	Subgroup	Results Reported by Authors
		Patients undergoing PCI during hospitalization	PCI during hospitalization Mortality at 30 days No loading dose (N=179): 25 Loading dose (N=176): 30 p=0.42 Major bleeding at 30 days No loading dose (N=179): 10 Loading dose (N=176): 13 p=0.49
			No PCI during hospitalization Mortality at 30 days No loading dose (N=146): 10 Loading dose (N=290): 17 p=0.69 Major bleeding at 30 days No loading dose (N=146): 10 Loading dose (N=290): 12 p=0.22
Singh, 2006[26]	Observational Total N: 11,358 LMWH vs. UFH Fair	Timing of PCI	PCI within 48 hrs of admission Total mortality LMWH (N=1970): 1.57% UFH (N=4029): 1.49% Adjusted OR (95%CI): 1.14 (0.71-0.85) Composite outcome (death or reinfarction) LMWH (N=1970): 3.45% UFH (N=4029): 3.97% Adjusted OR (95%CI): 0.93 (0.67-1.31) RBC transfusion (all) LMWH (N=1970): 5.63% UFH (N=4029): 5.21% Adjusted OR (95%CI): 1.16 (0.89-1.50)
			No PCI within 48 hrs of admission Total mortality LMWH (N=1882): 3.88% UFH (N=1989): 5.23% Adjusted OR (95%CI): 0.64 (0.46-0.88) Composite outcome (death or re-infarction) LMWH (N=1882): 5.42% UFH (N=1989): 8.70% Adjusted OR (95%CI): 0.57 (0.44-0.73) RBC transfusion (all) LMWH (N=1882): 7.76% UFH (N=1989): 10.71% Adjusted OR (95%CI): 0.66 (0.52-0.84)
		Age	Age <75 yrs Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.87 (0.69-1.09) RBC Transfusions (All) Adjusted OR (95% CI): 1.04 (0.91- 1.27) RBC Transfusions (Non-CABG) Adjusted OR (95% CI): 0.91 (0.74-1.15)

Study	Study Details	Subgroup	Results Reported by Authors
			Age ≥75 yrs Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.78 (0.55- 1.01) RBC Transfusions (All) Adjusted OR (95% CI): 0.98 (0.81-1.27) RBC Transfusions (Non-CABG) Adjusted OR (95% CI): 0.72 (0.69-1.21)
		Sex	Female Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.77 (0.57- 0.98) RBC Transfusions (All) Adjusted OR (95% CI): 1.04 (0.90- 1.30) RBC Transfusions (Non-CABG) Adjusted OR (95% CI): 1.00 (0.85- 1.30)
			Male Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.87 (0.69- 1.12) RBC Transfusions (All) Adjusted OR (95% CI): 1.00 (0.87- 1.28) RBC Transfusions (Non-CABG) Adjusted OR (95% CI): 0.80 (0.59-1.03)
		Diabetes	Diabetes Composite outcome (death or re-infarction) Adjusted OR (95%CI): 0.96 (0.72-1.38) RBC transfusions (all) Adjusted OR (95%CI): 1.05 (0.87-1.38) RBC transfusions (non-CABG) Adjusted OR (95%CI): 0.89 (0.7-1.17)
		Revascularization	Revascularization Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.94 (0.75-1.25) RBC transfusions (all) Adjusted OR (95% CI): 1.31 (1.09-1.52) RBC transfusions (non-CABG) Adjusted OR (95% CI): 1.16 (0.92-1.49)
			No revascularization Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.61 (0.50-0.82) RBC transfusions (all) Adjusted OR (95% CI): 0.67 (0.50-0.87) RBC transfusions (non-CABG) Adjusted OR (95% CI): 0.67 (0.50-0.87)

Study	Study Details	Subgroup	Results Reported by Authors
Steg, 2010[27] FUTURA/OA SIS-8 Study	RCT Total N: 2,026 Other enoxaparin vs. UFH vs. Fondaparinux Good	Sex	Male Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose UFH (N=686) Low dose UFH (N=689) OR(95% CI): 0.57 (0.33-1.01) favoring low dose heparin Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N=686) Low dose UFH (N=689) OR (95%CI): 1.85 (0.99-3.43) with more events in low dose UFH group
			Female Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose UFH N=316 in std. dose UFH and 335 in low dose UFH group; OR (95%CI) 1.11 (0.63-1.96) with more events in the low dose UFH group Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N=316) Low dose UFH (N=335) OR (95%CI) 1.25 (0.60-2.62) with more events in low dose UFH group
		Age	<75 yrs Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose UFH (N=764) Low dose UFH (N=781) OR (95%CI): 0.61 (0.37-1.00) with fewer events in low dose UFH group Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N=764) Low dose UFH (N=781) OR (95%CI): 1.46 (0.81-2.63) with more events in low dose UFH group
			≥75 yrs Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose (UFH N=238) Low dose UFH (N=243) OR (95%CI): 1.30 (0.67-2.52) with more events in low dose UFH group Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N=238) Low dose UFH (N=243) OR (95%CI) 1.83 (0.83-4.05) with more events in low dose UFH group
		Type of vascular access	Femoral access Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose UFH (N=626) Low dose UFH (N=654) OR (95%CI): 0.82 (0.54-1.26) with fewer events in low dose UFH group Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N=626) Low dose UFH (N=654) OR (95%CI): 1.58 (0.88-2.83) with more events in low dose UFH group

Study	Study Details	Subgroup	Results Reported by Authors
			Nonfemoral access Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose UFH (N=375) Low dose UFH (N=365) OR (95%CI) 0.61 (0.22-1.69) with fewer events in low dose UFH group Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N=375) Low dose UFH (N=365) OR (95%CI)1.56 (0.69-3.53) with more events in low dose UFH group
		Weight/BMI	BMI <30 Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose UFH (N=772) Low dose UFH (N=785) OR (95%CI): 0.81 (0.53-1.25) with fewer events in low dose group Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N=772) Low dose UFH (N=785) OR (95%CI): 1.67 (0.96-2.89) with more events in low dose group
			BMI ≥30 Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose UFH (N=230) Low dose UFH (N=238) OR (95%CI): 0.67 (0.25-1.78) with fewer events in low dose UFH group Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N=230) Low dose UFH (N=238) OR (95%CI): 1.35 (0.53-3.41) with more events in low dose UFH group
		Planned IIb/IIIa inhibitor use	Planned IIb/IIIa inhibitor use Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose UFH (N=242) Low dose UFH (N=246) OR (95%CI): 0.98 (0.46-2.11) with fewer events in low dose group Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N=242) Low dose UFH (N=246) OR (95%CI): 0.87 (0.33-2.29) with fewer events in low dose group
			Unplanned IIb/IIIa inhibitor use Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose UFH (N=760) Low dose UFH (N=778) OR (95%CI): 0.74 (0.47-1.18) with fewer events in low dose UFH group Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N=760) Low dose UFH (N=778) OR (95%CI): 1.90 (1.10-3.30) with more events in low dose UFH group

Study	Study Details	Subgroup	Results Reported by Authors
		Creatinine clearance	Creatinine clearance < 30 mL/min Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose UFH (N= 8) Low dose UFH (N=17) OR (95%CI): 4.16 (0.40-43.40) with more events in low dose UFH group Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N= 8) Low dose UFH (N=17) OR (95%CI): 0.15 (0.01-2.33) with fewer events in low dose UFH group
			Creatinine clearance 30 to 49 mL/min Composite outcome (Peri-PCI major bleed, minor bleed and major vascular access site complications at 30 days) Standard dose UFH (N=131) Low dose UFH (N=141) OR (95%CI): 1.08 (0.49-2.37) with more events in low dose group Composite outcome (death, MI or TVR at 30 days) Standard dose UFH (N=131) Low dose UFH (N=141) OR (95%CI): 1.76 (0.63-4.91) with more events in low dose UFH group
Steinhubl, 2002[28]	RCT Total N: 2116 Clopidogrel vs. Placebo Good	Diabetes	MACE RRR 11.2 (46.2 to -46.8)
		Sex	Men MACE RRR 24.5 (45.5 to -4.6)
			Women MACE RRR 32.1 (58.9 to -12.1)
		CrCl < 60 ml/min	MACE at 28 days RRR -57% clop 11.0% vs. placebo 7.1%
			MACE at 1 year RRR -41% clop 17.8% vs. placebo 13.1%
		ACS patients	MACE RRR 27.5 (47.8 to -0.6)
Stone, 2006[29] ACUITY Study	RCT Total N: 13,819 Bivalirudin vs. unfractionated heparin + GPI Good	Thienopyridine before angiography or PCI	Thienopyridine before angiography or PCI (N=5753) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 7.0% Heparin + GPI: 7.3% RR: 0.97 (0.80-1.17), p=0.054 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.0% Heparin + GPI: 16.3 HR: 0.98 (0.86-1.11) Total mortality at 1 yr Bival alone: 3.4 Heparin + GPI: 3.7% HR: 0.90 (0.68-1.18)

Study	Study Details	Subgroup	Results Reported by Authors
			No thienopyridine before angiography or PCI (N=3304) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 9.1% Heparin + GPI: 7.1% RR: 1.29 (1.03-1.63), p=0.054
		Treatment strategy	PCI (N=5180) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 8.8% for bival alone, 8.2% for hep + GPI, RR 1.07 (0.90-1.28), p=0.82 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 19.4% Heparin + GPI: 17.9 HR: 1.09 (0.96-1.23) Total mortality at 1 yr Bival alone: 3.1% Heparin + GPI: 3.1% HR: 0.90 (0.68-1.18)
			CABG (N=1040) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 16.1% Heparin + GPI: 15.1 RR: 1.06 (0.80-1.41), p=0.82 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 21.1% Heparin + GPI: 20.7% HR: 1.04 (0.80-1.36) Total mortality at 1 yr Bival alone: 6.8% Heparin + GPI: 6.7% HR: 1.03 (0.65-1.66)
			Medical therapy (N=2995) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 3.4 Heparin + GPI: 2.7% RR: 1.24 (0.83-1.85), p=0.82 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 9.1% Heparin + GPI: 9.2% HR: 0.98 (0.77-1.25) Total mortality at 1 yr Bival alone: 4.0% Heparin + GPI: 4.1% HR: 0.95 (0.66-1.37)

Study	Study Details	Subgroup	Results Reported by Authors
		GPI use	GP IIb/IIIa upstream (N=6906) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 7.8% Heparin + GPI: 6.9% RR: 1.13 (0.95-1.36) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.2% Heparin + GPI: 15.5% HR: 1.05 (0.93-1.20) Total mortality at 1 yr Bival alone: 3.8% Heparin + GPI: 4.1 HR: 0.90 (0.70-1.16)
			GP IIb/IIIa deferred (N=6921) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 7.8% Heparin + GPI: 7.6% RR: 1.02 (0.86-1.22) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.2% Heparin + GPI: 15.4% HR: 1.06 (0.93-1.20) Total mortality at 1 yr Bival alone: 8% Heparin + GPI: 3.6% HR: 1.02 (0.78-1.32)
		CKMB/troponin levels	Elevated biomarkers (N=5073) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 9.4% Heparin + GPI: 8.4% RR: 1.12 (0.94-1.34) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 17.7% Heparin + GPI: 15.6% HR: 1.14 (0.99-1.3) Total mortality at 1 yr Bival alone: 4.7% Heparin + GPI: 4.5% HR: 1.04 (0.80-1.34)

Study	Study Details	Subgroup	Results Reported by Authors
			Normal biomarkers (N=3403) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 5.7% Heparin + GPI: 5.4% RR: 1.04 (0.79-1.38) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.2% Heparin + GPI: 14.8% HR: 0.96 (0.80-1.14) Total mortality at 1 yr Bival alone: 2.4% Heparin + GPI: 2.8% HR: 0.84 (0.55-1.28)
		Randomization to angiography or intervention	Early (<3.0 hours) (N=2918) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 6.0% Heparin + GPI: 5.8 RR: 1.04 (0.78-1.39) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.6% Heparin + GPI: 14.7% HR: 1.00 (0.83-1.21) Total mortality at 1 yr Bival alone: 2.0% Heparin + GPI: 2.7% HR: 0.72-0.44-1.15)
			Intermediate (3.0-19.7 hours) (N=2925) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 7.0% Heparin + GPI: 5.5% RR: 1.26 (0.95-1.67) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.8% Heparin + GPI: 13.9% HR: 1.06 (0.87-1.28) Total mortality at 1 yr Bival alone: 3.0% Heparin + GPI: 2.9% HR: 0.95 (0.62-1.44)

Study	Study Details	Subgroup	Results Reported by Authors
			Late (>19.7 hours) (N=2982) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 10.0% Heparin + GPI: 9.9% RR: 1.01 (0.81-1.25) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 18.5% Heparin + GPI: 17.1% HR: 1.09 (0.92-1.29) Total mortality at 1 yr Bival alone: 5.8% Heparin + GPI: 4.9% HR: 1.17 (0.86-1.60)
		Age	<65 yrs (N=5051) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.2% Heparin + GPI: 15.4% HR: 1.06 (0.95, 1.17) Total mortality at 1 yr Bival alone: 1.9% Heparin + GPI: 2.0% HR: 0.91 (0.61-1.35)
			≥ 65 yrs (N=4164) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 18.7% Heparin + GPI: 17.6% HR: 1.07 (0.93-1.23) Total mortality at 1 yr Bival alone: 6.0% Heparin + GPI: 6.0% HR: 0.98 (0.77-1.26)
		Sex	Male (N=6444) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 17.1% Heparin + GPI: 16.2% HR: 1.06 (0.94-1.20) Total mortality at 1 yr Bival alone: 4.2% Heparin + GPI: 3.9% HR: 1.06 (0.83-1.36)
			Female (N=2771) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.3% Heparin + GPI: 13.7% HR: 1.05 (0.86-1.29) Total mortality at 1 yr Bival alone: 2.8% Heparin + GPI: 3.9% HR: 0.71 (0.47-1.08)

Study	Study Details	Subgroup	Results Reported by Authors
		Diabetes	Diabetes Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 19.5% Heparin + GPI: 17.9% HR: 1.08 (0.90-1.30) Total mortality at 1 yr Bival alone: 5.5% Heparin + GPI: 5.4% HR 0.99 (0.71-1.38)
			No diabetes Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.9% Heparin + GPI: 14.3% HR: 1.05 (0.92-1.19) Total mortality at 1 yr Bival alone: 3.1% Heparin + GPI: 3.2% HR: 0.93 (0.71-1.22)
		Creatinine clearance	Creatinine clearance ≥60 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.7% Heparin + GPI: 14.7% HR: 1.00 (0.89-1.13) Total mortality at 1 yr Bival alone: 2.9% Heparin + GPI: 3.0% HR: 0.96 (0.73-1.26)
			Creatinine clearance <60 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 22.2% Heparin + GPI: 18.8% HR: 1.19 (0.96-1.48) Total mortality at 1 yr Bival alone: 7.1% Heparin + GPI: 7.2% HR: 0.99 (0.69-1.42)
		Geography	US (N=5224) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.5% Heparin + GPI: 16.6% HR: 1.00 (0.87-1.14) Total mortality at 1 yr Bival alone: 3.6% Heparin + GPI: 3.6% HR: 1.00(0.74-1.34)

Study	Study Details	Subgroup	Results Reported by Authors
			Non-US (N=3991) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 15.9% Heparin + GPI: 13.9% HR: 1.15 (0.98-1.34) Total mortality at 1 yr Bival alone: 4.1% Heparin + GPI: 4.3% HR: 0.91 (0.68-1.23)
		Antithrombin crossovers	No prior antithrombin (N=3100) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.2% Heparin + GPI: 13.8% HR: 1.16 (0.96-1.39) Total mortality at 1 yr Bival alone: 3.4% Heparin + GPI: 3.1% HR: 1.03 (0.70-1.52)
			Consistent therapy (N=5419) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.2% Heparin + GPI: 15.6% HR: 1.02 (0.88-1.19) Total mortality at 1 yr Bival alone: 3.4% Heparin + GPI: 3.7% HR: 0.91 (0.66-1.24)
			Crossover (N=3255) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.0% Heparin + GPI: 14.0% HR: 1.16 (0.89-1.50) Total mortality at 1 yr Bival alone: 3.7% Heparin + GPI: 4.7% HR: 0.74 (0.47-1.18)
		Thrombocytopenia	Acquired thrombocytopenia (N=760) Composite outcome (ischemia, total death, MI, revascularization at 30 days): 12.5% Composite outcome (ischemia, total death, MI, revascularization at 1 yr): 22.8% Total mortality at 30 days: 3.1% Total mortality at 1 yr: 6.5% Nonfatal MI at 30 days: 7.5% Nonfatal MI at 1 yr: 10.0% Revascularization at 30 days: 5.3% Revascularization at 1 yr: 13.8% Non-CABG major bleeding at 30 days: 14.0% Non-CABG minor bleeding at 30 days: 30.25% Composite outcome (ischemia or major bleeding at 30 days): 21.7%

Study	Study Details	Subgroup	Results Reported by Authors
			No thrombocytopenia (N=10096) Composite outcome (ischemia, total death, MI, revascularization at 30 days): 6.3% Composite outcome (ischemia, total death, MI, revascularization at 1 yr): 15.1% Total mortality at 30 days: 1.1% Total mortality at 1 yr: 3.4% Nonfatal MI at 30 days: 4.1% Nonfatal MI at 1 yr: 6.4% Revascularization at 30 days: 2.4% Revascularization at 1 yr: 9.1% Non-CABG major bleeding at 30 days: 4.3% Non-CABG minor bleeding: 18.7% Composite outcome (ischemia or major bleeding at 30 days): 9.7%
		Stent thrombosis	Stent thrombosis (N=32) Total mortality at 30 days: 3.1% Nonfatal MI at 30 days: 93.8% Revascularization at 30 days: 96.9% Non-CABG major bleeding at 30 days: 12.5%
			No stent thrombosis (N=3373) Total mortality at 30 days: 0.8% p=0.23 Nonfatal MI at 30 days: 6.9% p<0.0001 Revascularization at 30 days: 2.4% p<0.0001 Non-CABG major bleeding at 30 days: 6.0% p=0.13

Study	Study Details	Subgroup	Results Reported by Authors
		Patients who underwent PCI	PCI Composite outcome (ischemia, total death, MI, revascularization at 30 days) Heparin + GPI (N=2561): 8% Bival + GPI (N=2609): 9% compared with group 1, p=0.16, RR 1.14 (0.95-1.36) Bival alone (N=2619): 9% compared with group 1, p=0.45, RR 1.07 (0.89-1.28) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Heparin + GPI: 17.8% Bival + GPI: 19.4% compared with group 1, p=0.11, HR 1.11 (0.98-1.26) Bival alone: 19.2% (502/2619), (compared with group 1, p=0.19, HR 1.09 (0.96-1.23) Total mortality at 30 days Heparin + GPI: 0.9% Bival + GPI: 1% compared with group 1, p=0.37 Bival alone: 1% compared with group 1, p=0.53 Total mortality at 1 yr Heparin + GPI: 3.2% Bival + GPI: 3.3%, compared with group 1, p=0.19, HR 1.02 (0.75-1.38) Bival alone: 3.1%, compared with group 1, p=0.76, HR 0.95 (0.70-1.3) Nonfatal MI at 30 days Heparin + GPI: 6% Bival + GPI: 7% compared with group 1, p=0.16 Bival alone: 6% compared with group 1, p=0.19 Nonfatal MI at 1 yr Heparin + GPI: 7.8% Bival + GPI: 9.1%, compared with group 1, p=0.10, HR 1.17 (0.97-1.41) Bival alone: 9.3% (compared with group 1, p=0.06, HR 1.19 (0.99-1.44)

Study	Study Details	Subgroup	Results Reported by Authors
			Revascularization at 30 days Heparin + GPI: 3% Bival + GPI: 4% compared with group 1, p=0.31 Bival alone: 3% compared with group 1, p=0.87 Revascularization at 1 yr Heparin + GPI: 11.4% Bival + GPI: 12.5% compared with group 1, p=0.21, HR 1.11 (0.94-1.29) Bival alone: 11.8% compared with group 1, p=0.63, HR 1.04 (0.89-1.22) Composite outcome (death, MI, revasc, major bleed at 30 days) Heparin + GPI: 13% Bival + GPI: 15% compared with group 1, p=0.10, RR 1.12 (0.98-1.28) Bival alone: 12% compared with group 1, p=0.057, RR 0.87 (0.75-1.00) Non-CABG major bleeding at 30 days Heparin + GPI: 7% Bival + GPI: 8% compared with group 1, p=0.32, RR 1.11 (0.91-1.35) Bival alone: 4% compared with group 1, p<0.0001, RR 0.52 (0.0-0.66) Minor bleeding at 30 days Heparin + GPI: 26% Bival + GPI: 28% compared with group 1, p=0.053 Bival alone: 15% compared with group 1, p<0.0001

Study	Study Details	Subgroup	Results Reported by Authors
		Timing of Clopidogrel in Patients receiving bival alone or hep+GPI	Clopidogrel initiated before angiography or within 30 min after PCI Composite outcome (ischemia death, MI, or revascularization at 30 days) Heparin + GPI (N=2189): 8.3% Bivalirudin (N=2284): 8.2%, RR 0.98 (0.81-1.20), p=0.88 compared to group 1 Composite outcome (ischemia death, MI, or revascularization at 1 yr) Heparin + GPI: 17.9% Bivalirudin: 18.75, RR 1.05 (0.93-1.10), p=0.45 compared to group 1 Total mortality at 30 days Heparin + GPI: 0.8% Bivalirudin: 1.0%, RR 1.22 (0.66-2.26), p=0.52 compared to group 1 Total mortality at 1 yr Heparin + GPI: 3.0% Bivalirudin: 3.1%, RR 1.05 (0.75-1.46), p=0.79 compared to group 1 Nonfatal MI at 30 days Heparin + GPI: 5.8% Bivalirudin: 6.0%, RR 1.05 (0.83-1.33), p=0.69 Revascularization at 30 days Heparin + GPI: 3.3% Bivalirudin: 2.8%, RR 0.87 (0.62-1.20), p=0.39 Non-CABG major bleeding at 30 days Heparin + GPI: 6.6% Bivalirudin: 3.5% (RR 0.53 (0.41-0.69), p<0.0001

Study	Study Details	Subgroup	Results Reported by Authors
			Clopidogrel initiated >30 minutes after PCI Composite outcome (ischemia death, MI, or revascularization at 30 days) Heparin + GPI (N=317): 8.5% Bivalirudin (N=290): 14.1%, RR 1.66 (1.05-2.63), p=0.03 compared to group 1 Composite outcome (ischemia death, MI, or revascularization at 1 yr) Heparin + GPI: 18.0% Bivalirudin: 21.7%, RR 1.21 (0.88-1.67) Total mortality at 30 days Heparin + GPI: 1.0% Bivalirudin: 1.7%, RR 0.91 (0.28-2.95), p=0.88 compared to group 1 Total mortality at 1 yr Heparin + GPI: 5.0% Bivalirudin: 3.1%, RR 0.61 (0.28-1.37), p=0.23 compared to group 1 Nonfatal MI at 30 days Heparin + GPI: 5.0% Bivalirudin: 10.3%, RR 2.05 (1.14-3.68), p=0.02 compared to group 1 Revascularization at 30 days Heparin + GPI: 3.2% Bivalirudin: 6.6%, RR 2.08 (0.98-4.39), p=0.06 compared to group 1 Non-CABG major bleeding at 30 days Heparin + GPI: 7.3% Bivalirudin: 3.4%, RR 0.48 (0.23-0.98), p=0.04 compared to group 1
		Specific timing of clopidogrel exposure among those with PCI	Pre-PCI clopidogrel among those with PCI (N=5131) Composite outcome (ischemia death, MI, or revascularization at 30 days) Heparin + GPI: 8.8% Bivalirudin + GPI: 8.9% Bivalirudin: 8.1% p=0.46 between heparin +GPI and bivalirudin alone
			Peri-PCI clopidogrel among those with PCI (N=1572) Composite outcome (ischemia death, MI, or revascularization at 30 days) Heparin + GPI: 6.9% Bivalirudin + GPI: 9.5% Bivalirudin: 8.6% p=0.29 between heparin +GPI and bivalirudin alone
			Post-PCI clopidogrel among those with PCI Heparin + GPI: 8.5% Bivalirudin + GPI: 10.8% Bivalirudin: 12.6% p=0.13 between heparin +GPI and bivalirudin alone
			No clopidogrel among those with PCI (N=129) Heparin + GPI: 8.8% Bivalirudin + GPI: 19.5% Bivalirudin: 23.3% p=0.08 between heparin +GPI and bivalirudin alone

Study	Study Details	Subgroup	Results Reported by Authors
Stone, 2007[30] ACUITY TIMING study	RCT Total N: 9,207 Upstream GPI vs. deferred GPI Good	Age	Age <65 (N=5054) Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 6.4% Upstream GPI 6.6% Major bleeding at 30 days Deferred: 3.7% Upstream 4.1%
			Age ≥65 (N=4153) Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 9.8% Upstream GPI 7.7% Major bleeding at 30 days Deferred GPI 6.3% Upstream GPI 8.5%
		Sex	Male (N=6467) Composite outcome (death MI or revascularization at 30 days) Deferred GPI 8.5% Upstream 7.0% Major bleeding at 30 days Deferred GPI 3.4% Upstream GPI: 4.6%
			Female (N=2740) Composite outcome (death MI or revascularization at 30 days) Deferred GPI 6.5% Upstream 7.2% Major bleeding at 30 days Deferred GPI: 8.3% Upstream GPI: 9.7%
		Diabetes	Diabetes (N=2565) Composite outcome (death MI or revascularization at 30 days) Deferred GPI 9.7% Upstream 8.4% Major bleeding at 30 days Deferred GPI: 6.1% Upstream GPI: 7.4%
			No diabetes (N=6567) Composite outcome (death MI or revascularization at 30 days) Deferred GPI 7.2% Upstream 6.6% Major bleeding at 30 days Deferred GPI: 4.4% Upstream GPI: 5.6%
		Creatinine clearance	Creatinine clearance ≥60 Composite outcome (death MI or revascularization at 30 days) Deferred GPI 7.1% Upstream 6.6% Major bleeding at 30 days Deferred GPI: 3.9% Upstream GPI: 4.6%

Study	Study Details	Subgroup	Results Reported by Authors
			Creatinine clearance <60 Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 11.8% Upstream 9.2% Major bleeding at 30 days Deferred GPI: 8.5% Upstream GPI: 12.8%
		Treatment strategy	PCI (N=5170) Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 9.5% Upstream 8.0% Major bleeding at 30 days Deferred GPI: 6.5% Upstream GPI: 7.8%
			CABG (N=1048) Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 13.5% Upstream 15.3% Major bleeding at 30 days Deferred GPI: 3.3% Upstream GPI: 4.5%
			Medical therapy (N=2989) Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 3.3% Upstream 2.4% Major bleeding at 30 days Deferred GPI: 2.6% Upstream GPI: 3.7%
		Downstream abciximab vs. eptifibatide	Abciximab (N=835) vs. eptifibatide (N=1376) Composite outcome (death, MI, or revascularization at 30 days) Covariate adjusted stratified by propensity score: OR 0.61 (0.38-0.98), p=0.04 Major bleeding at 30 days Covariate adjusted stratified by propensity score: OR 0.58 (0.34-1.00), p=0.051 Composite outcome (death, MI, revascularization, or major bleeding at 30 days) Covariate adjusted stratified by propensity score: OR 0.61 (0.42-0.90), p=0.01

Study	Study Details	Subgroup	Results Reported by Authors
Szuk, 2007[31] Clopidogrel Registry (Hungary)	Observational Total N: 4,160 Clopidogrel at PCI vs. clopidogrel 6-24 hrs prior to PCI Fair	Symptom status	Unstable angina Composite outcome (death, MI, UTVR at 30 days) Clopidogrel post PCI (N=922): 6.1% Clopidogrel pre PCI (N=643): 3.3% p=0.012 Nonfatal MI at 30 days Clopidogrel post PCI (N=922): 3.9% Clopidogrel pre PCI (N=643): 2.0% p=0.039 Total mortality at 30 days Clopidogrel post PCI (N=922): 0.9% Clopidogrel pre PCI (N=643): 0.6% p=0.771 Revascularization at 30 days Clopidogrel post PCI (N=922): 1.3% Clopidogrel pre PCI (N=643): 0.6% p=0.213 Stent thrombosis at 30 days Clopidogrel post PCI (N=922): 3.0% Clopidogrel pre PCI (N=643): 1.6% p=0.067 Need for procedural GPI at 30 days Clopidogrel post PCI (N=922): 13.3% Clopidogrel pre PCI (N=643): 11.9% p=0.44 Bleeding at 30 days Clopidogrel post PCI (N=922): 0.3% Clopidogrel pre PCI (N=643): 1.6% p=0.01

Study	Study Details	Subgroup	Results Reported by Authors
			Stable angina Composite outcome (death, MI, UTVR at 30 days) Clopidogrel post PCI (N=1757): 4.0% Clopidogrel pre PCI (N=838): 2.4% p=0.012 Nonfatal MI at 30 days Clopidogrel post PCI (N=1757): 2.5% Clopidogrel pre PCI (N=838): 1.6% p=0.152 Total mortality at 30 days Clopidogrel post PCI (N=1757): 0.6% Clopidogrel pre PCI (N=838): 0.2% p=0.358 Revascularization at 30 days Clopidogrel post PCI (N=1757): 1.0% Clopidogrel pre PCI (N=838): 0.6% p=0.492 Stent thrombosis at 30 days Clopidogrel post PCI (N=1757): 1.5% Clopidogrel pre PCI (N=838): 0.7% p=0.092 Need for procedural GPI at 30 days Clopidogrel post PCI (N=1757): 8.7% Clopidogrel pre PCI (N=838): 6.6% p=0.064 Bleeding at 30 days Clopidogrel post PCI (N=1757): 0.5% Clopidogrel pre PCI (N=838): 1.2% p=0.043
Topol, 2001[32] TARGET Study	RCT Total N: 4809 GPI vs. GPI at time of PCI Good	Age	Age < 65 years (N=2708) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 6.6% Abciximab: 4.6% HR 1.45
			Age > 65 years (N=2101) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 8.8% Abciximab: 7.8% HR 1.13
		Sex	Male (N=3534) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 7.2% Abciximab: 6.5% HR 1.10
			Female (N=1275) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 8.7% Abciximab: 4.7% HR 1.86

Study	Study Details	Subgroup	Results Reported by Authors
		Diabetes	Diabetes (N=1117) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 6.3% Abciximab: 5.4% HR 1.16 Total mortality at 1 yr Tirofiban: 2.1% Abciximab: 2.9% HR (95% CI): 0.74 (0.35-1.57), p=0.436
			No diabetes (N=3692) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 7.9% Abciximab: 6.2% HR 1.29 Total mortality at 1 yr Tirofiban: 1.9% Abciximab: 1.4% HR (95% CI): 1.32 (0.79-2.20), p=0.288
		Clopidogrel use pre-procedure	Clopidogrel pre-treatment (N=4477) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 7.2% Abciximab: 5.8% HR (95% CI) 0.81 (0.64-1.01), p=0.065 Total mortality at 1 yr Tirofiban: 1.8% Abciximab: 1.7% HR (95% CI): 0.95 (0.61-1.49), p=0.84 Major or minor bleeding during index hospitalization: 4.3%
			No clopidogrel pre-treatment (N=332) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 12.5% Abciximab: 8.3% HR (95% CI): 0.67 (0.33-1.32), p=0.234 Total mortality at 1 yr Tirofiban: 2.8% Abciximab: 4.6% HR (95% CI): 0.61 (0.19-1.92), p=0.392 Major or minor bleeding during index hospitalization: 3.9%, p=0.718

Study	Study Details	Subgroup	Results Reported by Authors
		Indication for stent	ACS (N=3025) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 9.3% Abciximab: 6.3% HR (95% CI): 1.49 (1.2-2.0), p=0.002 Total mortality at 1 yr Tirofiban: 2.3% Abciximab: 2.2% HR (95% CI): 1.03 (0.64-1.67), p=0.897 Total mortality at 6 months: 1.4% Nonfatal MI at 6 months: 8.5% Composite outcome (death or MI at 6 months): 9.4% Nonfatal MI at 30 days Tirofiban: 8.5% Abciximab: 5.8% HR (95% CI): 1.5 (1.1-2.0), p=0.004 Major bleeding at 30 days Tirofiban: 1.0% Abciximab: 0.7% p=0.43 Minor bleeding at 30 days Tirofiban: 2.4% Abciximab: 4.0% p=0.01
			Other (1784) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 4.5% Abciximab: 5.6% HR (95% CI): 0.82 (0.5-1.2), p=0.32 Total mortality at 1 yr Tirofiban: 1.4% Abciximab: 1.0% HR (95% CI): 1.32 (0.56-3.13), p=0.53 Total mortality at 6 months: 0.6% Nonfatal MI at 6 months: 5.5% Composite outcome (death or MI at 6 months): 6.0% Nonfatal MI at 30 days Tirofiban: 4.2% Abciximab: 4.9% HR (95% CI): 0.9 (0.5-1.3), p=0.48 Major bleeding at 30 days Tirofiban: 0.8% Abciximab: 0.8% p=0.97 Minor bleeding at 30 days Tirofiban: 3.4% Abciximab: 4.7% p=0.017

Study	Study Details	Subgroup	Results Reported by Authors
		Creatinine clearance	Creatine clearance <70 (N=1186) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 8.7% Abciximab: 6.0% p=0.074 Nonfatal MI at 30 days Tirofiban: 8.4% Abciximab: 5.5% p=0.052 Major bleeding at 30 days: 1.6% Minor bleeding at 30 days: 5.3%
			Creatine clearance 70-90 (N=1114) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 8.9% Abciximab: 8.2% p=0.693 Nonfatal MI at 30 days Tirofiban: 8.3% Abciximab: 7.3% p=0.53 Major bleeding at 30 days: 1.0% Minor bleeding at 30 days: 4.3%
			Creatine clearance 90-114 (N=1140) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 5.8% Abciximab: 4.4% p=0.293 Nonfatal MI at 30 days Tirofiban: 5.1% Abciximab: 4.0% p=0.409 Major bleeding at 30 days: 0.4% Minor bleeding at 30 days: 2.4%
			Creatine clearance >114 (N=1183) Composite outcome (death, MI, urgent TVR at 30 days) Tirofiban: 6.1% Abciximab: 5.6% p=0.704 Nonfatal MI at 30 days Tirofiban: 5.4% Abciximab: 5.1% p=0.789 Major bleeding at 30 days: 0.3% Minor bleeding at 30 days: 2.0%
Tricoci, 2007[33]	Observational Total N: 38,195 GPI upstream vs. periprocedural GPI vs. no GPI	Timing of PCI	< 12 hours from hospital arrival to PCI Composite outcome (in-hospital death or nonfatal MI) N=4113 GPI upstream: 3.3% Periprocedural GPI: 4.6% P=0.04

Study	Study Details	Subgroup	Results Reported by Authors
			12-18 hours from hospital arrival to PCI Composite outcome (in-hospital death or nonfatal MI) N=3038 GPI upstream: 3.1% Periprocedural GPI: 3.7% P=0.33
			18-24 hours from hospital arrival to PCI Composite outcome (in-hospital death or nonfatal MI) N=3511 GPI upstream: 3.8% Periprocedural GPI: 2.8% P=0.12
			24-30 hours from hospital arrival to PCI Composite outcome (in-hospital death or nonfatal MI) N=2477 GPI upstream: 3.4% Periprocedural GPI: 3.4% P=0.99
			>30 hours from hospital arrival to PCI Composite outcome (in-hospital death or nonfatal MI) N=3885 GPI upstream: 3.4% Periprocedural GPI: 3.7% P=0.63
Wallentin, 2009[34] Mahaffey, 2011[35] PLATO Study	RCT Total N: 18,624 Clopidogrel vs. ticagrelor or prasugrel Good	Age	Age <65 yrs Composite outcome (vascular death, nonfatal MI and stroke) at 1 yr N=10643 Ticagrelor: 7.2% Clopidogrel: 8.5% HR (95%CI): 0.85 (0.74-0.97) Major bleeding at 1 yr N=10528 Ticagrelor: 9.5% Clopidogrel: 9.5% HR (95%CI): 1.00 (0.87-1.13)
			Age ≥ 65 yrs Composite outcome (vascular death, nonfatal MI and stroke) at 1 yr N=7979 Ticagrelor: 13.2% Clopidogrel: 16% HR (95%CI): 0.83 (0.74-0.94) Major bleeding at 1 yr N=7892 Ticagrelor: 14.4% Clopidogrel: 13.6% HR (95%CI): 1.07 (0.95-1.22)
			Age <75 yrs Composite outcome (vascular death, nonfatal MI and stroke) at 1 yr N=15744 Ticagrelor: 8.6% Clopidogrel: 10.4% HR (95%CI): 0.82 (0.74-0.91) Major bleeding at 1 yr N=15574 Ticagrelor: 11.1% Clopidogrel: 10.8% HR (95%CI): 1.04 (0.94-1.15)

Study	Study Details	Subgroup	Results Reported by Authors
			Age ≥75 yrs Composite outcome (vascular death, nonfatal MI and stroke) at 1 yr N=2878 Ticagrelor: 16.8% Clopidogrel: 18.3% HR (95%CI): 0.94 (0.78-1.12) Major bleeding at 1 yr N=2846 Ticagrelor: 14.2% Clopidogrel: 13.3% HR (95%CI): 1.04 (0.84-1.29)
		Sex	Male Composite outcome (vascular death, nonfatal MI and stroke) at 1 yr N=13336 Ticagrelor: 9.2% Clopidogrel: 11.1% HR (95%CI): 0.85 (0.76-0.95) Major bleeding at 1 yr N=13184 Ticagrelor: 11.9% Clopidogrel: 11.4% HR (95%CI): 1.05 (0.94-1.16)
			Female Composite outcome (vascular death, nonfatal MI and stroke) at 1 yr N=5288 Ticagrelor: 11.2% Clopidogrel: 13.2% HR (95%CI): 0.83 (0.71-0.97) Major bleeding at 1 yr N=5237 Ticagrelor: 10.7% Clopidogrel: 10.5% HR (95%CI): 1.01 (0.85-1.21)
		Diabetes	Diabetes (N=4662); 47.6% NSTEMI, 20.9% UA Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr Ticagrelor: 14.1% Clopidogrel: 16.2% HR (95%CI): 0.88 (0.76-1.03) Major bleeding at 1 yr Ticagrelor: 14.1% Clopidogrel: 14.8% HR (95%CI): 0.95 (0.81-1.12) Total mortality at 1 yr HR (95% CI): 0.82 (0.66-1.01) in favor of ticagrelor Nonfatal MI at 1 yr HR (95%CI): 0.92 ((0.75-1.13) in favor of ticagrelor Stent thrombosis at 1 yr N=2518 patients with DM at risk for stent thrombosis. HR (95%CI): 0.65 (0.36-1.170

Study	Study Details	Subgroup	Results Reported by Authors
		Chronic kidney disease	Chronic kidney disease (N=3237); 72.5% non-STE ACS Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr Ticagrelor: 17.3% Clopidogrel: 22% HR (95%CI): 0.77(0.65-0.9) Major bleeding at 1 yr Ticagrelor: 15.1% Clopidogrel: 14.3% HR (95%CI): 1.07 (0.88-1.30) Total mortality at 1 yr HR (95%CI) 0.72 (0.58-0.89) in favor of ticagrelor
		Weight/BMI	BMI <30 kg/m2 Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr N=13354 Ticagrelor:; 10.1% Clopidogrel: 11.9% HR (95%CI): 0.86 (0.77-0.95) Major bleeding at 1 yr N=13229 Ticagrelor: 11.6% Clopidogrel: 11.6% HR (95%CI): 0.99 (0.89-1.09)
			BMI ≥30 kg/m2 Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr N=5178 Ticagrelor: 8.9% Clopidogrel: 10.8% HR (95%CI): 0.83 (0.69-0.99) Major bleeding at 1 yr N=5121 Ticagrelor: 11.6% Clopidogrel: 10% HR (95%CI): 1.21 (1.02 -1.45)
			Weight <60kg Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr N=1312 Ticagrelor: 13.1% Clopidogrel: 17.3% HR (95%CI): 0.75 (0.6-0.99) Major bleeding at 1 yr N=1296 Ticagrelor: 12.6% Clopidogrel: 15.2% HR (95%CI): 0.82 (0.60-1.12)
			Weight ≥60kg Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr N=17256 Ticagrelor: 9.5% Clopidogrel: 11.2% HR (95%CI): 0.86 (0.78-0.94) Major bleeding at 1 yr N=17086 Ticagrelor: 11.5% Clopidogrel: 10.9% HR (95%CI): 1.06 (0.96-1.16)

Study	Study Details	Subgroup	Results Reported by Authors
		Race/ethnicity	White Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr N=17077 Ticagrelor: 9.5% Clopidogrel: 11.2% HR (95% CI): 0.85 (0.77-0.94) Major bleeding at 1 yr N=16899 Ticagrelor: 11.6% Clopidogrel: 11.2% HR (95% CI): 1.04 (0.95-1.14)
			Black/AA Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr N=229 Ticagrelor: 13% Clopidogrel: 19.6% HR (95%CI): 0.63 (0.32-1.23) Major bleeding at 1 yr N=222 Ticagrelor: 12.5% Clopidogrel: 14.6% HR (95% CI): 0.74 (0.35-1.59)
			Asian Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr N=1096 Ticagrelor: 12.5% Clopidogrel: 14.8% HR (95%CI): 0.87 (0.62-1.21) Major bleeding at 1 yr N=1081 Ticagrelor: 10.3% Clopidogrel: 11% HR (95%CI): 1.03 (0.7 - 1.51)
		UA, NSTEMI	NSTEMI Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr N=7955 Ticagrelor: 11.4% Clopidogrel: 13.9% HR (95% CI): 0.83 (0.73-0.94) Major bleeding at 1 yr N=7883 Ticagrelor: 14.7% Clopidogrel: 14.3% HR (95% CI): 1.02 (0.9 -1.15)
			Unstable angina Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr N=3112 Ticagrelor: 8.6% Clopidogrel: 9.1% HR (95%CI): 0.96 (0.75-1.22) Major bleeding at 1 yr N=3087 Ticagrelor: 10.4% Clopidogrel: 9.9% HR (95% CI): 1.09 (0.86-1.37)

Study	Study Details	Subgroup	Results Reported by Authors
		Non-invasive mgmt. patients	Initially specified for a non-invasive strategy Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr Ticagrelor (N=2601): 12% Clopidogrel (N=2615): 14.3% p=0.045 Major bleeding at 1 yr Ticagrelor: 11.9% Clopidogrel: 10.3% p=0.079 Nonfatal MI at 1 yr Ticagrelor: 7.2% Clopidogrel: 7.8% p=0.555 CV mortality at 1 yr Ticagrelor: 5.5% Clopidogrel : 7.2% p=0.019 Total mortality at 1 yr Ticagrelor: 6.1% Clopidogrel: 8.2% p=0.010 Stroke at 1 yr Ticagrelor: 2.1% Clopidogrel: 1.7% p=0.162

Study	Study Details	Subgroup	Results Reported by Authors
		Patients with planned invasive strategy	Planned invasive strategy Ticagrelor group (N=6732): 2564 (38.2%) NSTEMI, 873 (13%) UA Clopidogrel group (N=6676): 2481 (37.2%) NSTEMI, 887 (13.3%) UA Composite outcome (vascular death, nonfatal MI or stroke) at 1 yr Ticagrelor: 9% Clopidogrel: 10.7% p=0.0025 Nonfatal MI at 1 yr Ticagrelor: 5.3% Clopidogrel: 6.6% p=0.0023 CV mortality at 1 yr Ticagrelor: 3.4% Clopidogrel: 4.3% p=0.025 Total mortality at 1 yr Ticagrelor: 3.9% Clopidogrel: 5% p=0.0103 Stent thrombosis at 1 yr Ticagrelor: 1.3% Clopidogrel: 2% p=0.0054 Major bleeding at 1 yr Ticagrelor: 11.5% Clopidogrel: 11.6% p=0.8803 Stroke at 1 yr Ticagrelor: 1.2% Clopidogrel: 1.1% p=0.6460
		GPI use	Glycoprotein IIb/IIIa inhibitors (received from time of index event to end of index hospitalization) Composite outcome (vascular death, nonfatal MI, or stroke) at 1 yr N=5062 Ticagrelor: 10% Clopidogrel: 11.1% HR (95% CI): 0.9 (0.76-1.07) Major bleeding at 1 yr N=5028 Ticagrelor: 10.1% Clopidogrel: 10.1% HR (95% CI): 0.99 (0.83-1.19)
		Location	Inside the U.S. Primary composite endpoint at 1 yr: ≥300 mg ASA + ticagrelor: 40/324 ≥300 mg ASA + clopidogrel:27/352 ≤100 mg ASA + ticagrelor: 19/284 ≤100 mg ASA + clopidogrel: 24/263
			Outside the U.S. Primary composite endpoint at 1 yr: ≥300 mg ASA + ticagrelor: 28/140 ≥300 mg ASA + clopidogrel: 23/140 ≤100 mg ASA + ticagrelor: 546/7449 ≤100 mg ASA + clopidogrel: 699/7443

Study	Study Details	Subgroup	Results Reported by Authors
Wang, 2007[36]	Observational Total N: 2,484 Clopidogrel 300 mg vs. clopidogrel >300 mg Fair	Propensity scoring range	Propensity score Quintile 1 (0-0.130) Composite outcome (death, MI, stroke or revascularization at 60 days) Clopidogrel 300mg (N=129): 10.85% Clopidogrel >300mg (N=153): 20.92% p=0.024
			Propensity score Quintile 2 (0.131-0.260) Composite outcome (death, MI, stroke or revascularization at 60 days) Clopidogrel 300mg (N=420): 13.3% Clopidogrel >300mg (N=449): 17.59% p=0.092
			Propensity score Quintile 3 (0.261-0.390) Composite outcome (death, MI, stroke or revascularization at 60 days) Clopidogrel 300mg (N=445): 26.29% Clopidogrel >300mg (N=450): 41.11% p≤0.001
			Propensity score Quintile 4 (0.391-0.520) Composite outcome (death, MI, stroke or revascularization at 60 days) Clopidogrel 300mg (N=201): 27.86% Clopidogrel >300mg (N=213): 77.0% p≤0.001
			Propensity score Quintile 5 (0.521-0.650) Composite outcome (death, MI, stroke or revascularization at 60 days) Clopidogrel 300mg (N=4): 75.0% Clopidogrel >300mg (N=20): 85.0% p=0.024
Wiviott, 2007[37] TRITON-TIMI 38 Study	RCT Total N: 13,608 Clopidogrel vs. ticagrelor or prasugrel Good	Age	Age <65 yrs Composite outcome (CV death, nonfatal MI or stroke (nonfatal at 15 months) N=8322 Prasugrel: 8.1% Clopidogrel: 10.6%
			Age 65-74 yrs Composite outcome (CV death, nonfatal MI or stroke (nonfatal at 15 months) N=3477 Prasugrel: 10.7% Clopidogrel: 12.3%
			Age ≥75 yrs Composite outcome (CV death, nonfatal MI or stroke (nonfatal at 15 months) N=1809 Prasugrel: 17.2% Clopidogrel: 18.3% TIMI major or minor bleed (non-CABG related) at 15 months Prasugrel (N=891): 9% Clopidogrel (N=894): 6.9%
		Symptom status	UA/NSTEMI Composite outcome (CV death, nonfatal MI or stroke (nonfatal at 15 months) N= 10,074 Prasugrel: 9.9% Clopidogrel: 12.1% HR (95%CI): 0.82 (0.73 to 0.93)

Study	Study Details	Subgroup	Results Reported by Authors
		Sex	Male (N=10,085) Composite outcome (CV death, nonfatal MI or stroke (nonfatal at 15 months) Prasugrel: 9.5% Clopidogrel: 11.9%
			Female (N=3523) Composite outcome (CV death, nonfatal MI or stroke (nonfatal at 15 months) Prasugrel: 11% Clopidogrel: 12.6%
		Diabetes	Diabetes (N=3146) Composite outcome (CV death, nonfatal MI or stroke (nonfatal at 15 months) Prasugrel: 12.2% Clopidogrel: 17% HR (95%CI): 0.70 (0.58-0.85). P<0.001 Any MI at 15 months Prasugrel: 8.2% in prasugrel vs. 13.2% in clopidogrel group. HR (95%CI) 0.6 (0.48-0.76) CV mortality at 15 months Prasugrel: 3.4% Clopidogrel: 4.2% HR (95%CI): 0.85 (0.58-1.24) Stent thrombosis at 15 months Prasugrel: 2% Clopidogrel: 3.6% HR (95%CI): 0.52 (0.33-0.84) Non-CABG related TIMI major bleeding at 15 months Prasugrel: 2.5% Clopidogrel: 2.6% HR (95%CI): 1.06 (0.66-1.69) Non-CABG related TIMI major or minor bleeding at 15 months Prasugrel: 5.3% Clopidogrel: 4.3% HR (95%CI): 1.30 (0.92-1.82)

Study	Study Details	Subgroup	Results Reported by Authors
		GPI use	GPIs (N=7414) Composite outcome (CV death, nonfatal MI or stroke (nonfatal at 15 months) Prasugrel: 10.4% Clopidogrel: 12.9% Composite outcome (CV death, nonfatal MI or nonfatal stroke at 30 days) Prasugrel: 6.5% Clopidogrel: 8.5% HR (95%CI): 0.76 (0.64-0.90) Non-CABG related TIMI major bleeding at 30 days Prasugrel: 1.2% Clopidogrel: 1.1% HR (95%CI): 1.06 (0.69-1.64) Non-CABG related TIMI major or minor bleed at 30 days Prasugrel: 3.3% Clopidogrel: 2.9% HR (95%CI): 1.16 (0.89-1.50) Nonfatal MI at 30 days Prasugrel: 5.5% Clopidogrel: 7.2% HR (95%CI): 0.75 (0.62-0.90) Stent thrombosis at 30 days Prasugrel: 0.8% Clopidogrel: 1.8% HR (95%CI): 0.46 (0.29-0.71) CV mortality at 30 days Prasugrel: 1% Clopidogrel: 1.2% HR (95%CI): 0.88 (0.57-1.35)

Study	Study Details	Subgroup	Results Reported by Authors
			No GPIs (N=6194) Composite outcome (CV death, nonfatal MI or stroke (nonfatal at 15 months) Prasugrel: 9.3% Clopidogrel: 11% Composite outcome (CV death, nonfatal MI or nonfatal stroke at 30 days) Prasugrel: 4.8% Clopidogrel: 6.1% HR (95%CI): 0.78 (0.63-0.97) Non-CABG related TIMI major bleeding at 30 days Prasugrel: 0.9% Clopidogrel: 0.6% HR (95%CI): 1.47 (0.81-2.66) Non-CABG related TIMI major or minor bleed at 30 days Prasugrel: 1.7% Clopidogrel: 1.1% HR (95%CI): 1.63 (1.05-2.52) Nonfatal MI at 30 days Prasugrel: 4% Clopidogrel: 5.4% in clopidogrel. HR (95%CI): 0.74 (0.59-0.93) Stent thrombosis at 30 days Prasugrel: 0.4% Clopidogrel: 1.2% HR (95%CI): 0.34 (0.17-0.85) CV mortality at 30 days Prasugrel: 0.8% Clopidogrel: 1.1% HR (95%CI): 0.69 (0.41-1.16)
		Chronic kidney disease	Creatine clearance <60 ml/min (N=1490) Composite outcome (CV death, nonfatal MI or stroke (nonfatal) at 15 months) Prasugrel: 15.1% Clopidogrel: 17.5%
		Type of stent	BMS only (N=6461) Composite outcome (CV death, nonfatal MI or stroke (nonfatal) at 15 months) Prasugrel: 10% Clopidogrel: 12% HR (95%CI): 0.8 (0.69-0.93) Stent thrombosis Prasugrel: 1.27% Clopidogrel: 2.41% HR (95%CI): 0.52 (0.35-0.77) Any MI Prasugrel: 8% Clopidogrel: 10% HR (95%CI): 0.77 (0.65-0.91)

Study	Study Details	Subgroup	Results Reported by Authors
			DES only (N=5743) Composite outcome (CV death, nonfatal MI or stroke (nonfatal) at 15 months) Prasugrel: 9% Clopidogrel: 11% HR (95%CI): 0.82 (0.69-0.97) Stent thrombosis Prasugrel: 0.84% Clopidogrel: 2.31% HR (95%CI): 0.36 (0.22-0.58) Any MI Prasugrel: 7% Clopidogrel: 9% HR (95%CI): 0.77 (0.64-0.93)
		Weight/BMI	Weight <60kg Non-CABG related major or minor bleeding at 15 months Prasugrel (N=308): 10.1% Clopidogrel (N=356): 6.5%
		History of stroke or TIA	History of stroke or TIA Composite outcome (CV death, nonfatal MI or stroke (nonfatal) at 15 months) Prasugrel (N= 262): 19.1% Clopidogrel (N=256): 14.4% HR (95%CI): 1.37 (0.89-2.13) Non-CABG related TIMI major bleeding Prasugrel (N= 257): 5% Clopidogrel (N=252): 2.9% HR (95%CI): 2.46 (0.94-6.42) Composite outcome (total mortality, nonfatal MI, nonfatal stroke, or non-CABG related TIMI major bleed) Prasugrel (N= 262): 23% Clopidogrel (N=256): 16% HR (95%CI): 1.54 (1.02-2.32)
Yusuf, 2006[38] OASIS-5 Study	RCT Total N: 20,078 Enoxaparin vs. unfractionated heparin vs. fondaparinux Good	Age	Age ≥65 yrs (N=12,261) Composite outcome (death, MI or refractory ischemia) Enoxaparin: 6.8% Fondaparinux: 6.6% Major bleeding Enoxaparin: 5.5% Fondaparinux: 2.7%
		Sex	Male (N=12,379) Composite outcome (death, MI or refractory ischemia) Enoxaparin: 6% Fondaparinux: 5.8% Major bleeding Enoxaparin: 3.3% Fondaparinux: 2%
			Female (N=7699) Composite outcome (death, MI or refractory ischemia) Enoxaparin: 5.3% Fondaparinux: 5.7% Major bleeding Enoxaparin: 5.5% Fondaparinux: 2.5%

Study	Study Details	Subgroup	Results Reported by Authors
		Revascularization	Revascularization in 9 days (N=7372) Composite outcome (death, MI or refractory ischemia) Enoxaparin: 9.6% Fondaparinux: 9.9% Major bleeding Enoxaparin: 6% Fondaparinux: 4.2%
			No revascularization in 9 days (N=12,706) Composite outcome (death, MI or refractory ischemia) Enoxaparin: 3.5% Fondaparinux: 3.3% Major bleeding Enoxaparin: 3% Fondaparinux: 1%
		Diabetes	Diabetes (GFR <58 ml/min/1.73 m2) (N=5141) Composite outcome (death, MI or refractory ischemia at 9 days) Enoxaparin: 7.4% Fondaparinux: 6.7% HR (95%CI): 0.9 (0.73-1.11) Composite outcome (death, MI or refractory ischemia at 30 days) Enoxaparin: 12.2% Fondaparinux: 10% HR (95%CI): 0.81 (0.69-0.96) Composite outcome (death, MI or refractory ischemia at 180 days) Enoxaparin: 19.6% Fondaparinux: 17.96% HR (95%CI): 0.9 (0.79-1.03) Major bleeding at 9 days Enoxaparin: 6.4% Fondaparinux: 2.8% HR (95%CI): 0.42 (0.32-0.56) Major bleeding at 30 days Enoxaparin: 7.6% Fondaparinux: 4.2% HR (95%CI) 0.54(0.42-0.68) Major bleeding at 180 days Enoxaparin: 8.7% Fondaparinux: 5.8% HR (95%CI) 0.65 (0.52-0.8)

Study	Study Details	Subgroup	Results Reported by Authors
		PCI	PCI during index hospitalization Composite outcome (death, MI or refractory ischemia at 9 days) Enoxaparin (N=3072): 6.2% Fondaparinux (N=3105): 6.3% HR (95%CI): 1.03 (0.84-1.25) Composite outcome (death, MI or refractory ischemia at 30 days) Enoxaparin (N=3072): 7.4% Fondaparinux (N=3105): 7.4% HR (95%CI): 1.00 (0.83-1.20) Composite outcome (death, MI or refractory ischemia at 180 days) Enoxaparin (N=3072): 10.2% Fondaparinux (N=3105): 10.1% HR (95%CI): 0.99 (0.85-1.16) Major bleeding at 9 days Enoxaparin (N=3072): 5.1% Fondaparinux (N=3105): 2.4% HR (95%CI): 0.46 (0.35-0.61) Major bleeding at 30 days Enoxaparin (N=3072): 5.4% Fondaparinux (N=3105): 2.9% HR (95%CI): 0.52 (0.4-0.67) Major bleeding at 180 days Enoxaparin (N=3072): 6.3% Fondaparinux (N=3105): 3.4% HR (95%CI): 0.53 (0.42-0.68)
		Use of GPI and thienopyridines during index hospitalization	Thienopyridine (N=13532) Composite outcome (death, MI or refractory ischemia at 30 days) Enoxaparin: 9.1% Fondaparinux: 8.6% Adjusted HR (95%CI): 0.94 (0.84-1.06) Major bleeding Enoxaparin: 5.4% Fondaparinux: 3.4% Adjusted HR (95%CI): 0.62 (0.52-0.73)
			GPI (N=3630) Composite outcome (death, MI or refractory ischemia at 30 days) Enoxaparin: 13.2% Fondaparinux: 11.8% Adjusted HR (95%CI): 0.87 (0.72-1.06) Major bleeding Enoxaparin: 8.3% Fondaparinux: 5.2% Adjusted HR (95%CI): 0.60 (0.46-0.78)
			Thienopyridine + GPI (N=3246) Composite outcome (death, MI or refractory ischemia at 30 days) Enoxaparin: 12.8% Fondaparinux: 11.8% Major bleeding Enoxaparin: 7.6% Fondaparinux: 4.9%

Abbreviations: ACE=angiotensin converting enzyme; ACS=acute coronary syndrome; BMI=body mass index; BMS=bare metal stent; CABG=coronary artery bypass grafting; CI=confidence interval; CKMB=creatine kinase major bleeding; CV=cardiovascular; DES=drug-eluting stent; GFR=glomerular filtration rate; GPI=glycoprotein IIb/IIIa inhibitor; GUSTO=global utilization of streptokinase and t-PA for occluded arteries; HR=hazard ratio; hr=hour/hours; kg=kilogram/kilograms; LMWH=low molecular weight heparin; MACE=major adverse cardiac event; MI=myocardial

infarction; N=number of patients; NR=not reported; NSTEMI=non-ST elevation myocardial infarction; OR=odds ratio; PCI=percutaneous coronary intervention; PPI=proton pump inhibitor; RBC=red blood cell; RCT=randomized controlled trial; RIUR=recurrent ischemia requiring urgent revascularization; RR=relative risk; RRR=relative risk reduction; STEMI=ST-elevation myocardial infarction; TBO=thrombotic bailout; TIA=transient ischemic attack; TIMI=thrombolysis in myocardial infarction; TVR=target vessel revascularization; UA=unstable angina; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin; UR=urgent revascularization; US=United States; UTVR=urgent target vessel revascularization; vs=versus; yr=year/years

Table H-2. Subgroup results for KQ 2: antiplatelet and anticoagulant medications in the initial conservative treatment of patients with UA/NSTEMI

Study	Study Details	Subgroup	Results Reported by Authors
Anonymous, 1998[39] PURSUIT study	RCT Total N: 10,948 Eptifibatide vs. placebo Good	Age	Age <50 Total mortality Eptifibatide: 0.8% Placebo: 0.9% Nonfatal MI Eptifibatide: 8.2% Placebo: 9.5% Composite outcome (death or nonfatal MI) Eptifibatide: 8.7% Placebo: 9.6% GUSTO moderate or severe bleeding Eptifibatide: 4.6% Placebo: 3.9%
			Age 50-59 Total mortality Eptifibatide: 1.4% Placebo: 01.5% Nonfatal MI Eptifibatide: 9.0% Placebo: 12.8% Composite outcome (death or nonfatal MI) Eptifibatide: 9.7% Placebo: 13.8% GUSTO moderate or severe bleeding Eptifibatide: 9.2% Placebo: 6.8%
			Age 60-69 Total mortality Eptifibatide: 3.0% Placebo: 3.5% Nonfatal MI Eptifibatide: 12.6% Placebo: 13.0% Composite outcome (death or nonfatal MI) Eptifibatide: 14.3% Placebo: 15.0% GUSTO moderate or severe bleeding Eptifibatide: 13.9% Placebo: 11.7%
			Age <65 Total mortality OR (95% CI): 0.785 (0.657-0.939), favoring eptifibatide
			Age $\geq$ 65 Total mortality OR (95% CI): 0.977 (0.840-1.136), favoring eptifibatide

Study	Study Details	Subgroup	Results Reported by Authors
		Early invasive management	Early invasive management Composite outcome (death or nonfatal MI at 96 hrs) Eptifibatide (N=606): 9.4% Placebo (N=622): 15.3% OR (95% CI): 0.576 (0.406-0.817) Composite outcome (death or nonfatal MI at 7 days) Eptifibatide (N=606): 10.2% Placebo (N=622): 16.1% OR (95% CI): 0.595 (0.424-0.835) Composite outcome (death or nonfatal MI at 30 days) Eptifibatide (N=606): 11.6% Placebo (N=622): 16.7% OR (95% CI): 0.650 (0.469-0.901)
		Sex	Male Composite outcome (death or MI) OR (95% CI): 0.795 (0.691-0.917) favoring eptifibatide
		Diabetes	Diabetes vs. no diabetes Composite outcome (death or MI) Diabetes: OR=0.960 (95% CI, 0.769 to 1.193) No diabetes: OR=0.874 (95% CI, 0.763 to 0.997), favoring eptifibatide
		CHF at presentation (Killip II/III vs. Killip I)	Killip II/III Composite outcome (death or MI at 7 days) Eptifibatide:16.9% Placebo: 18.8% OR (95% CI): 1.14 (0.8-1.6) Composite outcome (death or MI at 30 days) Eptifibatide: 23.5% Placebo: 25.5% OR (95% CI): 1.11 (0.8-1.5)
			Killip I Composite outcome (death or MI at 7 days) Eptifibatide: 9.4% Placebo: 11.0% OR (95% CI): 1.2 (1.0-1.4) Composite outcome (death or MI at 30 days) Eptifibatide: 13.3% Placebo: 14.8% OR (95% CI): 1.13 (1.0-1.3)
		Geography	US (N=1766) Total mortality at 96 hrs: 1.1% Total mortality at 7 days: 2.0% Total mortality at 30 days: 3.5% Total mortality at 6 months: 5.5% Nonfatal MI at 96 hrs: 8.9% Nonfatal MI at 7 days: 10.8% Nonfatal MI at 30 days: 13.3% Nonfatal MI at 6 months: 15.5% Composite outcome (death or nonfatal MI at 96 hrs): 9.6% Composite outcome (death or nonfatal MI at 7 days): 12.1% Composite outcome (death or nonfatal MI at 30 days): 15.4% Composite outcome (death or nonfatal MI at 6 months): 18.9% TIMI major bleeding: 1.8% GUSTO severe bleeding: 0.4% Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI): 0.53 (0.25-1.05)

Study	Study Details	Subgroup	Results Reported by Authors
			Non-US (N=1756) Total mortality at 96 hrs: 0.6%, p=0.11 Total mortality at 7 days: 1.4%, p=0.16 Total mortality at 30 days: 3.0%, p=0.41 Total mortality at 6 months: 5.0%, p=0.52 Nonfatal MI at 96 hrs: 6.0%, p=0.001 Nonfatal MI at 7 days: 8.2%, p=0.008 Nonfatal MI at 30 days: 10.2%, p=0.004 Nonfatal MI at 6 months: 12.6%, p=0.012 Composite outcome (death or nonfatal MI at 96 hrs): 6.4%, p0.005 Composite outcome (death or nonfatal MI at 7 days): 9.1%, 0.003 Composite outcome (death or nonfatal MI at 30 days): 11.9%, p=0.003 Composite outcome (death or nonfatal MI at 6 months): 15.2%, p=0.004 TIMI major bleeding: 4.8%, p<0.0001 GUSTO severe bleeding: 1.5%, p<0.0001 Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI): 0.68 (0.44-1.00)
		UA vs. MI	Unstable Angina Death at 30 days Eptifibatide (n=2584): 3.0% Placebo (n=2545): 2.4% (p=0.227) Death at 90 days Eptifibatide: 4.3% Placebo: 3.9% (p=0.440) Death at 180 days Eptifibatide: 5.8% Placebo: 4.9% (p=0.192) Composite outcome (death or MI at 30 days) Eptifibatide: 11.2% Placebo: 13.0% Composite outcome (death or MI at 90 days) Eptifibatide: 12.8% Placebo: 15.0% Composite outcome (death or MI at 180 days) Eptifibatide: 14.9% Placebo: 16.3% Moderate to severe bleeding Eptifibatide: 13.2% Placebo: 10.1% (p=0.001)

Study	Study Details	Subgroup	Results Reported by Authors
			MI Death at 30 days Eptifibatide (n=2124): 4.0% Placebo (n=2184): 5.3% (p=0.043) Death at 90 days Eptifibatide: 5.7% Placebo: 6.5% (p=0.308) Death at 180 days Eptifibatide: 7.1% Placebo: 7.9% (p=0.519) Composite outcome (death or MI at 30 days) Eptifibatide:17.9% Placebo: 18.9% (p=0.387) Composite outcome (death or MI at 90 days) Eptifibatide: 19.9% Placebo: 20.3% (p=0.732) Composite outcome (death or MI at 180 days) Eptifibatide: 21.3% Placebo: 22.2% (p=0.505) Moderate to severe bleeding Eptifibatide: 12.6% Placebo: 9.6% (p=0.002)
		PTCA	Patients treated with PTCA Composite outcome (death or MI at 30 days) Eptifibatide (n=555): 12.1% Placebo (n=596): 15.3% p=0.123 Composite outcome (death or MI at 180 days) Eptifibatide: 14.0% Placebo: 18.5% p=0.045 Death at 30 days Eptifibatide: 2.5% Placebo: 2.3% p=0.851 Death 180 days Eptifibatide: 3.8% Placebo: 3.9% p=1.00 TIMI major bleeding Eptifibatide: 7.1% Placebo: 4.5% p=0.001

Study	Study Details	Subgroup	Results Reported by Authors
		Medical management	Patients medically managed (N=992) Composite outcome (death, MI, refractory ischemia, or readmission for UA at 30 days) RR (95% CI): 0.84 (0.65-1.10), favoring tirofiban vs. UFH Composite outcome (death or MI) RR (95% CI): 0.58 (0.38-0.87) Total mortality RR (95% CI): 0.53 (0.32-0.89) Nonfatal MI RR (95% CI): 0.65 (0.36-1.15)
		MI vs. no MI	MI at enrollment Composite outcome (death or MI) OR (95% CI): 0.930 (0.795-1.09)
			No MI at enrollment Composite outcome (death or MI) OR (95% CI): 0.849 (0.715-1.01)
Anonymous, 1998[40] PRISM study	RCT Total N: 3,232 Tirofiban vs. UFH Good	Medically managed	Tirofiban (N=992) vs. UFH (N=1007) Composite outcome (death, MI, refractory ischemia, or readmission for UA at 30days) RR (95% CI): 0.84 (0.65-1.10) with lower risk in Tirofiban Composite outcome (death or MI at 30 days) RR (95% CI): 0.58 (0.38-0.87) Total mortality at 30 days RR (95% CI): 0.53 (0.32-0.89) Nonfatal MI at 30 days RR (95% CI): 0.65 (0.36-1.15)
		Percutaneous coronary revascularization	Tirofiban (N=348) vs. UFH (N=352) Composite outcome (death, MI, refractory ischemia, or readmission for UA at 30days) RR (95% CI): 0.72 (0.53-0.98) Composite outcome (death or MI at 30 days) RR (95% CI): 0.76 (0.45-1.69) Total mortality at 30 days RR (95% CI): 0.28 (0.06-1.36)
		Age	Age <65 Composite outcome (death, MI, or refractory ischemia within 48 hrs) RR (95% CI): 0.72 (0.41-1.23)
			Age 65-74 Composite outcome (death, MI, or refractory ischemia within 48 hrs) RR (95% CI): 0.55 (0.28-1.01)
			Age >75 Composite outcome (death, MI, or refractory ischemia within 48 hrs) RR (95% CI): 0.57 (0.28-1.11)
			Age >65 Composite outcome (death, MI, or refractory ischemia within 48 hrs) RR (95% CI): 0.57 (0.35-0.88)
		Sex	Female Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI): 0.54 (0.30-0.96)

Study	Study Details	Subgroup	Results Reported by Authors
			Male Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI): 0.67 (0.43-1.03)
		Diabetes	Diabetes Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI) :0.43 (0.20-0.90)
			No diabetes Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI): 0.72 (0.47-1.04)
		Geography	US Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI): 0.53 (0.25-1.05)
			Non-US Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI): 0.68 (0.44-1.00)
		Prior ASA	Prior ASA Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI): 0.82 (0.52-1.26)
			No prior ASA Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI): (0.42-0.23-0.74)
		Prior heparin	Prior heparin Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI): 0.65 (0.43-0.95) No prior heparin Composite outcome (death, MI, or refractory ischemia at 48 hrs) RR (95% CI): 0.60 (0.29-1.17)
Anonymous, 1998[41] PRISM-PLUS study	RCT Total N:1,875 Tirofiban 0.4 + UFH vs. placebo + UFH Good	Age	Age <65 yrs (N=402) Composite outcome (death, MI, refractory ischemia at 7 days) Heparin: 50 Tirofiban + heparin: 34
			Age ≥65 yrs (N=395) Composite outcome (death, MI, refractory ischemia at 7 days) Heparin: 93 Tirofiban + heparin: 66

Study	Study Details	Subgroup	Results Reported by Authors
		Sex	Female Composite outcome (death, MI, refractory ischemia at 48 hrs) Heparin (N=252): 7.5% Tirofiban + heparin (N=254): 5.9% RR (95% CI): 0.78 (0.40-1.53) p=0.47 Composite outcome (death, MI, refractory ischemia at 7 days) Heparin: 48 Tirofiban + heparin: 34 RR (95% CI): 0.67 (0.43-1.04) p=0.08 Composite outcome (death, MI, refractory ischemia at 30 days) Heparin: 21.4% Tirofiban + heparin: 20.1% RR (95% CI): 0.89 (0.61-1.31) p=0.56 Composite outcome (death, MI, refractory ischemia at 180 days) Heparin: 31.3% Tirofiban + heparin: 33.5% RR (95% CI): 1.02 (0.76-1.40) p=0.86 Composite outcome (death or MI at 48 hrs) Heparin: 1.6% Tirofiban + heparin: 5.9% RR (95% CI): 0.73 (0.16-3.3) p=0.69 Composite outcome (death or MI at 7 days) Heparin: 6.3% Tirofiban + heparin: 5.5% RR (95% CI): 0.86 (0.42-1.78) p=0.69 Composite outcome (death or MI at 30 days) Heparin: 9.9% Tirofiban + heparin: 10.2% RR (95% CI): 1.02 (0.59-1.77) p=0.94 Composite outcome (death or MI at 180 days) Heparin: 12.7% Tirofiban + heparin: 14.2% RR (95% CI): 1.11 (0.69-1.78) p=0.68 TIMI major bleeding Heparin: 0.8% Tirofiban + heparin: 2.4% RR (95% CI): 2.98 (0.61-14.61) p=0.16
			Male Composite outcome (death, MI, refractory ischemia at 48 hrs) Heparin (N=545): 95 Tirofiban + heparin (N=519): 55 TIMI major bleeding Heparin: 0.7% Tirofiban + heparin: 1.0% RR (95% CI): 1.31 (0.35-4.86) p=0.68

Study	Study Details	Subgroup	Results Reported by Authors
		Diabetes	No diabetes (N=1208) Composite outcome (death, MI, refractory ischemia at 7 days) Heparin (N=604): 101 Tirofiban + heparin (N=604): 75 TIMI major bleeding Heparin (N=604): 0.8% Tirofiban + heparin (N=604): 1.7%
			Diabetes (N=362) Composite outcome (death, MI, refractory ischemia at 7 days) Heparin (N=193): 42 Tirofiban + heparin (N=169): 25 Composite outcome (death, MI, refractory ischemia, rehospitalization for ischemia at 30 days) Heparin (N=193): 39.9% Tirofiban + heparin (N=169): 32.0% P=0.11 TIMI major bleeding Heparin (N=193): 0.5% Tirofiban + heparin (N=169): 0.6% Composite outcome (death or MI at 30 days) Heparin (N=193): 19.2% Tirofiban + heparin (N=169): 11.2% p=0.03
		UA vs. MI	UA Composite outcome (death, MI, refractory ischemia at 7 days) Heparin (N=428): 78 Tirofiban + heparin (N=428): 61
			Any MI Composite outcome (death, MI, refractory ischemia at 7 days) Heparin (N=369): 65 Tirofiban + heparin (N=345): 39
		PCI	No PCI Composite outcome (death, MI, refractory ischemia at 30 days) Tirofiban: 21.3% Tirofiban + heparin : 18.7% RR (95% CI): 12% (0.63-1.15) Composite outcome (death or MI at 30 days) Tirofiban: 11.6% Tirofiban + heparin : 8.9% RR (95% CI): 23% (0.50-1.12)
			PCI Composite outcome (death, MI, refractory ischemia at 30 days) Tirofiban: 24.7% Tirofiban + heparin : 18.15% RR (95% CI): 27% (0.44-1.04) Composite outcome (death or MI at 30 days) Tirofiban: 13% Tirofiban + heparin : 8.3% RR (95% CI): 36% (0.34-1.08)

Study	Study Details	Subgroup	Results Reported by Authors
		Prior CABG	Composite outcome (death, MI, refractory ischemia at 7 days) Heparin (N=107): 29% Tirofiban + heparin (N=124): 16.9% HR (95% CI): HR 0.548 (0.314-0.957) p=0.035 Composite outcome (death, MI, refractory ischemia at 30 days) Heparin (N=107): 40.2% Tirofiban + heparin (N=124): 25% HR (95% CI): 0.563 (0.354-0.895) p=0.015 Composite outcome (death or MI at 7 days) Heparin (N=107): 12.1% Tirofiban + heparin (N=124): 6.5% HR (95% CI): 0.508 (0.210-1.230) p=0.134 Composite outcome (death or MI at 30 days) Heparin (N=107): 17.8% Tirofiban + heparin (N=124): 12.1% HR (95% CI): 0.645 (0.327-1.272) p=0.206
		Renal insufficiency	Creatinine clearance <30 mL/min (N=40) Composite outcome (death, MI, or refractory ischemia at 48 hrs) Heparin + tirofiban: 10% Heparin: 15% Composite outcome (death, MI, or refractory ischemia at 7 days) Heparin + tirofiban: 35% Heparin: 45% Composite outcome (death, MI, or refractory ischemia at 30 days) Heparin + tirofiban: 50% Heparin: 50% Composite outcome (death or MI at 7 days) Heparin + tirofiban: 5% Heparin: 20% Composite outcome (death or MI at 30 days) Heparin + tirofiban: 15% Heparin: 25% TIMI major bleeding Heparin + tirofiban: 0% Heparin: 0%

Study	Study Details	Subgroup	Results Reported by Authors
			Creatinine clearance 30-60 mL/min (N=571) Composite outcome (death, MI, or refractory ischemia at 48 hrs) Heparin + tirofiban: 6.1% Heparin: 11.9% Composite outcome (death, MI, or refractory ischemia at 7 days) Heparin + tirofiban: 17.9% Heparin: 23.8% Composite outcome (death, MI, or refractory ischemia at 30 days) Heparin + tirofiban: 24.8% Heparin: 29.7% Composite outcome (death or MI at 7 days) Heparin + tirofiban: 4.6% Heparin: 8.6% Composite outcome (death or MI at 30 days) Heparin + tirofiban: 13% Heparin: 15.2% TIMI major bleeding Heparin + tirofiban: 1.8% Heparin: 1.4%
			Creatinine clearance 60-75 mL/min (N=354) Composite outcome (death, MI, or refractory ischemia at 48 hrs) Heparin + tirofiban: 10% Heparin: 7.5% Composite outcome (death, MI, or refractory ischemia at 7 days) Heparin + tirofiban: 13.9% Heparin: 15.5% Composite outcome (death, MI, or refractory ischemia at 30 days) Heparin + tirofiban: 19% Heparin: 19% Composite outcome (death or MI at 7 days) Heparin + tirofiban: 0.6% Heparin: 8.0% Composite outcome (death or MI at 30 days) Heparin + tirofiban: 8.9% Heparin: 9.8% TIMI major bleeding Heparin + tirofiban: 0.6% Heparin: 0%

Study	Study Details	Subgroup	Results Reported by Authors
			Creatinine clearance >75 mL/min (N=572) Composite outcome (death, MI, or refractory ischemia at 48 hrs) Heparin + tirofiban: 4.7% Heparin: 4.1% Composite outcome (death, MI, or refractory ischemia at 7 days) Heparin + tirofiban: 6.8% Heparin: 12.3% Composite outcome (death, MI, or refractory ischemia at 30 days) Heparin + tirofiban: 11.1% Heparin: 16.0% Composite outcome (death or MI at 7 days) Heparin + tirofiban: 0.4% Heparin: 7.4% Composite outcome (death or MI at 30 days) Heparin + tirofiban: 4.3% Heparin: 9.7% TIMI major bleeding Heparin + tirofiban: 1.7% Heparin:0.7%
		Troponin positive	Troponin positive Composite outcome (death or MI) Heparin + tirofiban (N=28): 3.6% Heparin (N=34): 20.6% p=0.06
			Troponin negative Composite outcome (death or MI) Heparin + tirofiban (N=27): 9.5% Heparin (N=21): 11.1% p=1.00
Antman, 1999 [2] TIMI 11B study	RCT Total N: 3,910 Enoxaparin vs. UFH Good	UA or MI	UA (N=2289) Composite outcome (death, MI, urgent revasc at 14 days) UFH: 15.3% Enoxaparin: 12.8%
			Non-Q Wave MI (N=1334) Composite outcome (death, MI, urgent revasc at 14 days) UFH: 18.6% Enoxaparin: 17.2%
			Q Wave MI (N=143) Composite outcome (death, MI, urgent revasc at 14 days) UFH: 23.4% Enoxaparin: 20.3%
Blazing, 2004 [6] A to Z study	RCT Total N: 3,987 Enoxaparin vs. UFH Good	Early invasive vs. conservative management	Early invasive Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1111): 8.8% UFH (N=1080): 8.5%
			Initial conservative Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=904): 7.7% UFH (N=869): 10.6%
		Age	<65 yrs Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1213): 6.4% UFH (N=1155): 7.4%

Study	Study Details	Subgroup	Results Reported by Authors
			≥65 yrs Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=805): 11.3% UFH (N=794): 12.5%
		Sex	Male Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1438): 8.3% UFH (N=1388): 9.4%
			Female Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=580): 8.6% UFH (N=52): 9.3%
		Diabetes	Diabetes Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1395): 8.4% UFH (N=356): 10.7%
			No diabetes Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1620): 8.3% UFH (N=1593): 9.2%
		Geography	US Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=420): 6.7% UFH (N=378): 7.7%
			Non-US Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1598): 8.8% UFH (N=155): 9.8%
		Troponin level	Normal troponin level Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=334): 8.1% UFH (N=323): 8.0%
			Elevated troponin level Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=1072): 8.3% UFH (N=100): 9.5%
		TIMI risk score	TIMI 0-2 Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=846): 6.4% UFH (N=752): 5.7%
			TIMI 3-4 Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=888): 8.1% UFH (N=945): 10.2%
			TIMI 5-7 Composite outcome (death, MI, recurrent ischemia within 7 days) Enoxaparin (N=284): 15.1% UFH (N=45): 17.9%

Study	Study Details	Subgroup	Results Reported by Authors
		Conservative strategy	Conservative strategy UFH (N=872) Enoxaparin (N=906) Total mortality at 7 days HR 1.32 (0.61-2.82), p=0.49 Total mortality at 30 days HR 1.51 (0.81-2.83), p=0.20 Nonfatal MI at 7 days HR 0.50 (0.26-0.98) Nonfatal MI at 30 days HR 0.67 (0.41-1.08), p=0.10 Refractory ischemia at 7 days HR 0.69 (0.47-1.00), p=0.05 Refractory ischemia at 30 days HR 0.77 (0.54-1.08), p=0.13 Urgent revascularization at 7 days HR 0.66 (0.39-1.14), p=0.14 Urgent revascularization at 30 days HR 0.90 (0.59-1.37) Composite outcome (death, MI, and refractory ischemia at 7 days) HR 0.72 (0.53-0.99), p=0.04 Composite outcome (death, MI, and refractory ischemia at 30 days) HR 0.80 (0.61-1.05), p=0.10 Composite outcome (death, MI, refractory ischemia, urgent revascularization, and documented myocardial ischemia at 7 days) HR 0.73 (0.56-0.96), p=0.03 Composite outcome (death, MI, refractory ischemia, urgent revascularization, and documented myocardial ischemia at 30 days) HR 0.78 (0.62-0.99), p=0.04 TIMI major or minor bleeding within 24 hours of tirofiban infusion UFH: 0.8% Enoxaparin: 1.5%
Brieger, 2007[8]	Observational Total N: 2,874 LMWH vs. UFH Fair	Use of PCI and IIb/IIIa inhibitors	Patients who did not get PCI and did not receive GPIs Mortality in-hospital LMWH (N=7957) UFH (N=4271) OR (95%CI) 0.74 (0.62-0.88), Adjusted OR (95%CI) 0.77 (0.63-0.94) favoring LMWH Major bleed in-hospital LMWH (N=7957) UFH (N=4271) OR (95%CI) 0.62(0.48-0.80), Adjusted OR (95%CI) 0.80 (0.60-1.10) favoring LMWH

Study	Study Details	Subgroup	Results Reported by Authors
			Patients who did get PCI and did not receive GPIs Mortality in-hospital LMWH (N=1468) UFH (N=728) OR (95%CI) 0.41 (0.22-0.78), Adjusted OR (95%CI) 0.45 (0.21-0.98), favoring LMWH Major bleed in-hospital LMWH (N=1468) UFH (N=728) OR (95% CI) 1.04 (0.62-1.73), Adjusted OR (95%CI) 1.48 (0.84-2.60). favoring increased bleeding with LMWH
			Patients who did get PCI and did receive GPIs Mortality in-hospital LMWH (N=928) UFH (N=1091) OR (95% CI) 0.80 (0.40-1.42), Adjusted OR (95%CI) 0.83 (0.40-1.76), favoring LMWH Major bleed in-hospital LMWH (N=928) UFH (N=1091) OR (95% CI) 0.64 (0.39-1.02), Adjusted OR (95%CI) 0.64 (0.38-1.08), favoring LMWH
			Patients who did not get PCI but did receive GPIs Mortality in-hospital LMWH (N=390) UFH (N=617) OR (95% CI) 0.73 (0.40-1.35), Adjusted OR (95%CI) 0.83 (0.42-1.63) favoring LMWH Major bleed in-hospital LMWH (N=390) UFH (N=617) OR (95% CI) 1.45 (0.87-2.41), Adjusted OR (95%CI) 1.90 (1.09-3.29) favoring increased bleeding with LMWH
Cohen, 1997 [9] ESSENCE study	RCT Total N: 3,171 Enoxaparin vs. UFH Good	Age	<65 yrs Composite outcome (death, MI, recurrent angina at 30 days) UFH (N=798): 23.2% Enoxaparin (N=785): 17.6% OR 1.05
			≥65 yrs Composite outcome (death, MI, recurrent angina at 30 days) UFH (N=776): 124 Enoxaparin (N=128): 128 OR 1.4
		Diabetes	Diabetes Composite outcome (death, MI, recurrent angina at 30 days) UFH (N=399): 79 Enoxaparin (N=360): 66 OR 1.35
			No diabetes Composite outcome (death, MI, recurrent angina at 30 days) UFH (N=1225): 230 Enoxaparin (N=1247): 200 OR 1.21
		Prior MI	Prior MI Composite outcome (death, MI, recurrent angina at 30 days) Heparin (N=745): 149 Enoxaparin (N=723): 118 OR 1.28

Study	Study Details	Subgroup	Results Reported by Authors
			No prior MI Composite outcome (death, MI, recurrent angina at 30 days) UFH (N=791): 154 Enoxaparin (N=850): 144 OR 1.19
		In-hospital PCI	In-hospital PCI Composite outcome (death, MI at 43 days) UFH (N=3028): 244 Enoxaparin (N=3129): 210 OR 0.82 (0.68-0.99), p=0.044 Composite outcome (death, MI at 1 yr) UFH (N=3028): 387 Enoxaparin (N=3129): 384 OR 0.95 (0.82-1.11, p=0.547) Major hemorrhage at 43 days UFH (N=2982): 148 Enoxaparin (3091): 185 OR 1.22 (0.8-1.52) Major hemorrhage at 1 yr UFH (N=2982): 30 Enoxaparin (N=3091): 55 55/3091, OR 1.78 (1.14-2.79), p=0.011
			No in-hospital PCI Composite outcome (death, MI at 43 days) UFH (N=493): 29 Enoxaparin (N=431): 14 OR 0.54 (0.28-1.03), p=0.062 Composite outcome (death, MI at 1 yr) UFH (N=493): 59 Enoxaparin (N=431): 27 OR 0.49 (0.31-0.79), p=0.003 Major hemorrhage at 43 days UFH (N=483): 30 Enoxaparin (N=425): 23 OR 0.86, p=0.49-1.51, p=0.608 Major hemorrhage at 1 yr UFH (N=483): 11 Enoxaparin (N=425): 2 OR 0.20 (0.04-0.92), p=0.039
Ferguson, 2004[13] SYNERGY Study	RCT Total N: 10,027 Enoxaparin vs. UFH vs. Fondaparinux Good	Sex	Male Composite outcome (death or MI at 30 days) Enoxaparin (N=3296): 14.2% UFH (N=3299): 15.4% p=0.16
			Female Composite outcome (death or MI at 30 days) Enoxaparin: 13.5% UFH: 12.9% p=0.59
		Diabetes	Diabetes Composite outcome (death or MI at 30 days) Enoxaparin (N=1422): 15.6% UFH (N=1500): 15.7% p=0.94

Study	Study Details	Subgroup	Results Reported by Authors
			No diabetes Composite outcome (death or MI at 30 days) Enoxaparin (N=3568): 13.3% UFH (N=3482): 14.0% p=0.36
		Geography	Australia/New Zealand Composite outcome (death or MI at 30 days) Enoxaparin (N=206): 11.2% UFH (N=208): 10.6% p=0.91
			Europe Composite outcome (death or MI at 30 days) Enoxaparin (N=908): 13.0% UFH (N=904): 13.2% p=0.91
			North America Composite outcome (death or MI at 30 days) Enoxaparin (N=242): 27.3% UFH (N=239): 29.7% p=0.45
			South America Composite outcome (death or MI at 30 days) Enoxaparin (N=3636): 13.5% UFH (N=3632): 14.1% p=0.47
		History of smoking	Smoking current Composite outcome (death or MI at 30 days) Enoxaparin (N=1178): 12.3% UFH (N=1225): 15.9% p=0.009
			Smoking prior Composite outcome (death or MI at 30 days) Enoxaparin (N=1756): 15.2% UFH (N=1735): 14.9% p=0.82
			Smoking never Composite outcome (death or MI at 30 days) Enoxaparin (N=2056): 13.9% UFH (N=2018): 13.4% p=0.065
		Prior revascularization	Prior PCI Composite outcome (death or MI at 30 days) Enoxaparin (N=1044): 13.9% UFH (N=964): 14.1% p=0.92
			No prior PCI Composite outcome (death or MI at 30 days) Enoxaparin (N=3947): 14.0% UFH (N=4017): 14.6% p=0.37
			Prior CABG Composite outcome (death or MI at 30 days) Enoxaparin (N=805): 13.2% UFH (N=853): 15.8% p=0.15

Study	Study Details	Subgroup	Results Reported by Authors
			No prior CABG Composite outcome (death or MI at 30 days) Enoxaparin (N=4186): 14.1% UFH (N=4124): 14.3% p=0.77
		Prerandomization antithrombin therapy	No prerandomization antithrombin therapy Composite outcome (death or MI at 30 days) Enoxaparin (N=1212): 12.6% UFH(N=1228): 14.8% HR 0.84 (0.68-1.05)
			Prerandomization enoxaparin only Composite outcome (death or MI at 30 days) Enoxaparin (N=2186): 13.6% UFH (N=2108): 13.1% HR 1.04 (0.88-1.23)
			Prerandomization UFH only Composite outcome (death or MI at 30 days) Enoxaparin (N=1428): 15.2% UFH (N=1512): 16.7% HR 0.89 (0.74-1.08)
			Prerandomization both agents Composite outcome (death or MI at 30 days) Enoxaparin (N=167): 18.1% UFH (N=137): 9.5% HR 2.0 (1.03-3.90)
		Postrandomization crossovers	No crossover Composite outcome (death or MI at 30 days) Enoxaparin (N=4400): 13.5% UFH (N=4780): 14.2%
			Crossover Composite outcome (death or MI at 30 days) Enoxaparin(N=593): 17.4% UFH (N=205): 22.0%
		Patients who underwent PCI	PCI patients with and without crossover to alternative antithrombotic therapy Composite outcome (death or MI at 30 days) Enoxaparin (N=2323): 13.1% UFH (N=2363): 14.2% HR 0.92 (0.79-1.07), p=0.289 Total mortality at 30 days Enoxaparin: 1.7% UFH: 1.8% HR 0.95 (0.62-1.46), p=0.804 Nonfatal MI at 30 days Enoxaparin: 11.8% UFH: 13.2% HR 0.89 (0.76-1.05), p=0.172 GUSTO severe bleeding at 30 days Enoxaparin: 1.5% UFH: 1.6% HR 0.92 (0.57-1.45), p=0.688

Study	Study Details	Subgroup	Results Reported by Authors
			PCI patients without crossover antithrombotic strategy TIMI Major bleeding at 30 days Enoxaparin: 3.7% UFH: 2.5% HR 1.46 (1.04-2.04), p=0.028 TIMI minor bleeding at 30 days Enoxaparin: 11.2% UFH: 11.6% HR 0.97 (0.80-1.16), p=0.699 Any transfusion at 30 days Enox: 5.8% UFH: 5.4% HR 1.28 (1.00-1.63), p=0.047
			Composite outcome (death or MI at 30 days) Enoxaparin (N=2028): 12.5% UFH (N=2293): 13.7%, HR 0.91 (0.77-1.07), p=0.265 Total mortality at 30 days Enoxaparin: 1.3% UFH: 1.7% HR 0.76 (0.47-1.24), p=0.276 Nonfatal MI at 30 days Enoxaparin: 11.5% UFH: 12.8% HR 0.90 (0.76-1.07), p=0.222 GUSTO severe bleeding at 30 days Enoxaparin: 1.1% UFH: 1.6 % HR 0.70 (0.41-1.18), p=0.181 TIMI Major bleeding at 30 days Enoxaparin: 3.1% UFH: 2.4% HR 1.31 (0.90-1.90), p=0.154 TIMI minor bleeding at 30 days Enoxaparin 10.4% UFH: 11.4% HR 0.90 (0.75-1.10), p=0.309 Any transfusion at 30 days Enoxaparin: 5.8% UFH 5.0% HR 1.17 (0.90-1.53), p=0.243
			Patients receiving no antithrombotic before randomization Composite outcome (death or MI at 30 days) Enoxaparin (N=499): 12.0% UFH (N=524): 16.3%, HR 0.727 (0.523-1.012), p=0.053
		Patients undergoing CABG surgery	Patients undergoing CABG surgery Death or MI at 30 days Enoxaparin (N=855): 27.3% UFH (N=921): 30.9% adjusted HR 0.90 (0.75-1.07), p=0.239 Adjusted stroke rate at 6 months Enoxaparin: 2.58% (95% CI 1.54-3.63) UFH: 3.16% (95% CI 1.96-4.35), p=0.476 TIMI major bleeding at 30 days Enoxaparin: 36.1% UFH: 34.2%, adjusted HR 1.10 (0.94-1.38), p=0.229

Study	Study Details	Subgroup	Results Reported by Authors
		Timing of clopidogrel among CABG patients	Clopidogrel administration among CABG patients at baseline vs. no clopidogrel administration TIMI major bleeding at 30 days Adjusted HR 1.19 (0.99-1.43), p=0.053 Stroke at 30 days Adjusted HR 0.87 (0.66-1.12, p=0.322) Death or MI at 30 days Clopidogrel: 24.1% No clopidogrel: 29.0% Adjusted HR 0.94, CI 0.83-1.06) p=0.332
		Prerandomization antithrombin therapy	No pre-treatment with antithrombin Total mortality at 48 hrs: 15/2438 Total mortality at 30 days: 81/2438 Nonfatal MI at 48 hrs: 133/2440 Nonfatal MI at 30 days: 274/2440 Death or MI at 48 hrs: 146/2438 Death or MI at 30 days: 333/2438 Stroke at 30 days: 18/2440 GUSTO severe bleeding at 30 days: 58/2439 TIMI major bleeding (including CABG related) at 30 days: 203/2440
			Pre-randomization treatment with UFH only Total mortality at 48 hrs: 12/2939 Total mortality at 30 days: 95/2939 Nonfatal MI at 48 hrs: 189/2940 Nonfatal MI at 30 days: 411/2940 Death or MI at 48 hrs: 198/2939 Death or MI at 30 days: 468/2939 Stroke at 30 days: 23/2940 GUSTO severe bleeding at 30 days: 72/2939 TIMI major bleeding (including CABG related) at 30 days: 255/2939
			Pre-randomization treatment with enoxaparin only Total mortality at 48 hrs: 17/4294 Total mortality at 30 days: 125/4294 Nonfatal MI at 48 hrs: 234/4294 Nonfatal MI at 30 days: 488/4294 Death or MI at 48 hrs: 248/4294 Death or MI at 30 days: 574/4293 Stroke at 30 days: 47/4294 GUSTO severe bleeding at 30 days: 109/4294 TIMI major bleeding (including CABG related) at 30 days: 354/4294
			Pre-randomization treatment with both UFH and enoxaparin Total mortality at 48 hrs: 3/304, unadjusted p-value 0.312 Total mortality at 30 days: 12/304, unadjusted p-value 0.628 Nonfatal MI at 48 hrs: 13/304, unadjusted p value 0.185 Nonfatal MI at 30 days: 34/304, unadjusted p-value 0.003 Death or MI at 48 hrs: 15/304, unadjusted p-value 0.302 Death or MI at 30 days: 43/304, unadjusted p-value 0.017 Stroke at 30 days: 4/304 , unadjusted p-value 0.327 GUSTO severe bleeding at 30 days: 6/304 TIMI major bleeding (including CABG related) at 30 days: 20/304
		Consistent therapy vs. no consistent therapy	Consistent therapy Composite outcome (death or MI at 48 hrs): 374/6135 Composite outcome (death or MI at 30 days): 883/6135 Composite outcome (death, MI, or ischemia requiring revascularization at 30 days): 1024/6135

Study	Study Details	Subgroup	Results Reported by Authors
			No consistent therapy Composite outcome (death or MI at 30 days): 221/3840, unadjusted p-value=0.858 Composite outcome (death, MI, or ischemia requiring revascularization at 30 days): 641/3838, unadjusted p-value=0.989
		Prerandomization antithrombotic therapy	Prerandomization UFH only Composite outcome (adjusted death or MI at 30 days): Adjusted OR: 0.93 (0.75-1.14) GUSTO severe bleeding at 30 days: Adjusted OR 1.04 (0.64-1.70) TIMI bleeding at 30 days: Adjusted OR 1.00 (0.77-1.31)
			Prerandomization enoxaparin only Composite outcome (adjusted death or MI at 30 days): Adjusted OR 1.04 (0.87 (1.26) GUSTO severe bleeding at 30 days: Adjusted OR 1.23 (0.84-1.81) TIMI bleeding at 30 days: Adjusted OR 1.23 (0.98-1.53)
			Prerandomization both UFH and enoxaparin Composite outcome (adjusted death or MI at 30 days): Adjusted OR (1.97 (0.96-3.98) GUSTO severe bleeding at 30 days: Adjusted OR 0.39 (0.07-2.21) TIMI bleeding at 30 days
			Neither UFH nor enoxaparin Composite outcome (adjusted death or MI at 30 days): Adjusted OR 0.78 (0.62-1.00) GUSTO severe bleeding at 30 days: Adjusted OR 1.88 (1.08-3.27) TIMI bleeding at 30 days: Adjusted OR 1.40 (1.05-1.89)
			Same pretreatment as randomization Composite outcome (adjusted death or MI at 30 days): Adjusted OR 0.88 (0.73-1.06) GUSTO severe bleeding at 30 days: Adjusted OR 1.25 (0.82-1.93) TIMI bleeding at 30 days: Adjusted OR 1.11 (0.88-1.41)
		Consistent therapy vs. no consistent therapy pre-randomization	Consistent therapy pre-randomization Composite outcome (death or MI at 30 days) Adjusted OR 0.86 (0.74-0.99), favoring Enoxaparin TIMI bleeding at 30 days Adjusted Or 1.23 (1.02-1.48), favoring Enoxaparin
			No consistent therapy pre-randomization Composite outcome (death or MI at 30 days) Adjusted OR 1.15 ((0.95-1.39), favoring Enoxaparin TIMI bleeding at 30 days Adjusted OR 1.13 (0.88-1.44), favoring Enoxaparin

Study	Study Details	Subgroup	Results Reported by Authors
Roe, 2012[42]	RCT Total N: 7243 Prasugrel vs. Clopidogrel Good	Age	Patients < 65 years Composite of CV death, nonfatal MI, stroke N=4327; KM rates at 30 months were 11% in the prasugrel group compared to 14.7% in the clopidogrel group; HR 0.82 (0.67-1.01) Non CABG related TIMI major bleed N=4298; KM rates at 30 months were 1.9% vs. 0.9% in clopidogrel group; HR 1.84 (0.96-3.52)
			Patients 65 years to 74 years Composite of CV death, nonfatal MI, stroke N=2916; KM rates at 30 months were 18.2% in prasugrel group vs. 18% in clopidogrel group; HR 1.02 (0.84-1.24) Non CABG related TIMI major bleed N=2882; KM rate at 30 months were 2.4% in prasugrel group vs. 2.3% in clopidogrel group; HR 0.84 (0.4-1.75)
		Sex	Female Composite of CV death, nonfatal MI, stroke N=2599; KM rate at 30 months was 14.7% in prasugrel group vs. 14.8% in clopidogrel group Composite of non CABG TIMI major bleed N=2576; KM rate at 30 months was 1.8% in prasugrel group vs. 1.1% in clopidogrel group
			Male Composite of CV death, nonfatal MI, stroke N=4644; KM rate at 30 months was 13.4% in prasugrel group vs. 16.6% in clopidogrel group Composite of non CABG TIMI major bleed N=4604; KM rate at 30 months was 2.3% in prasugrel group vs. 1.6% in clopidogrel group
		Diabetes	Diabetic Composite of CV death, nonfatal MI, stroke N=2811; KM rate at 30 months was 17.8% in prasugrel group vs. 20.4% in clopidogrel group Non CABG related TIMI major bleed N=2783; KM rate at 30 months was 1.4% in prasugrel group vs. 1.0% in clopidogrel group
			Not diabetic Composite of CV death, nonfatal MI, stroke N=4414; KM rate at 30 months was 11.5% in prasugrel group vs. 13.2% in clopidogrel group Non CABG related TIMI major bleed N=4381; KM rate at 30 months was 2.5% in prasugrel group vs. 1.7% in clopidogrel group
		Unstable Angina	Unstable Angina Composite of CV death, nonfatal MI, stroke N=2356; Km rates at 30 months were 9.7% in prasugrel group vs. 11.1% in clopidogrel group Non CABG related TIMI major bleed N=2342; Km rates at 30 months were 1.7% in prasugrel group vs. 0.9% in clopidogrel group
			NSTEMI Composite of CV death, nonfatal MI, stroke N=4887; Km rates at 30 months were 15.7% in prasugrel group vs. 18.2% in clopidogrel group Non CABG related TIMI major bleed N=4838; Km rates at 30 months were 2.2% in prasugrel group vs. 1.7% in clopidogrel group

Study	Study Details	Subgroup	Results Reported by Authors
		Weight >60 kg	> 60 kg Composite of CV death, nonfatal MI, stroke N=939; KM rates at 30 months were 15.5% in prasugrel group and 22.4% in clopidogrel group Non CABG related TIMI major bleed N=934; KM rates at 30 months were 1.0% in prasugrel group and 2.0% in clopidogrel group
			60kg or greater Composite of CV death, nonfatal MI, stroke N=6300; KM rates at 30 months were 13.6% in prasugrel group and 15.1% in clopidogrel group Non CABG related TIMI major bleed N=6244; KM rates at 30 months were 2.3% in prasugrel group and 1.4% in clopidogrel group
		Smoker	Smoker Composite of CV death, nonfatal MI, stroke N=1566; KM rates at 30 months were 11.7% in prasugrel group vs. 20.8% in clopidogrel group Non CABG related TIMI major bleed N=1555; KM rates at 30 months were 3.1% in prasugrel group vs. 1.5% in clopidogrel group
			Not smoker Composite of CV death, nonfatal MI, stroke N=5614; KM rates at 30 months were 14.6% in prasugrel group vs. 14.6% in clopidogrel group Non CABG related TIMI major bleed N=5567; KM rates at 30 months were 1.9% in prasugrel group vs. 1.5% in clopidogrel group
		<100 mg/day aspirin	< 100mg/day Composite of CV death, nonfatal MI, stroke N=2365; estimated KM rates at 30 months were 13.4% in prasugrel group and 15.9% in clopidogrel group Non CABG related TIMI major bleed N=2354; estimated KM rates at 30 months were 1.6% in prasugrel group and 0.3% in clopidogrel group
			100mg/day or greater Composite of CV death, nonfatal MI, stroke N=4295; estimated KM rates at 30 months were 13.7% in prasugrel group and 15.8% in clopidogrel group Non CABG related TIMI major bleed N=4258; estimated KM rates at 30 months were 2.4% in prasugrel group and 2.2% in clopidogrel group
		PPI	On PPI at randomization Composite of CV death, nonfatal MI, stroke N=1666; estimated KM rates at 30 months were 14.6% in prasugrel group and 23.8% in clopidogrel group Non CABG related TIMI major bleed N=1651; estimated KM rates at 30 months were 1.0% in prasugrel group and 1.6% in clopidogrel group
			No PPI at randomization Composite of CV death, nonfatal MI, stroke N=5577; estimated KM rates at 30 months were 13.7% in prasugrel group and 13.6% in clopidogrel group Non CABG related TIMI major bleed N=5529; estimated KM rates at 30 months were 2.4% in prasugrel group and 1.4% in clopidogrel group

Study	Study Details	Subgroup	Results Reported by Authors
		CrCl <30 ml/min	CrCl < 30 ml/min Composite of CV death, nonfatal MI, stroke N=105; estimated KM rates at 30 months were 28.1% in prasugrel group and 47.5% in clopidogrel group Non CABG related TIMI major bleed N=102; estimated KM rates at 30 months were 5.0% in prasugrel group and 4.3% in clopidogrel group
			CrCl 30-60 ml/min Composite of CV death, nonfatal MI, stroke N=1407; estimated KM rates at 30 months were 22.7% in prasugrel group and 23.7% in clopidogrel group Non CABG related TIMI major bleed N=1397; estimated KM rates at 30 months were 1.1% in prasugrel group and 2.6% in clopidogrel group
			CrCl > 60 ml/min Composite of CV death, nonfatal MI, stroke N=5432; estimated KM rates at 30 months were 11.9% in prasugrel group and 13.6% in clopidogrel group Non CABG related TIMI major bleed N=5388; estimated KM rates at 30 months were 2.3% in prasugrel group and 1.2% in clopidogrel group
Simoons, 2001 [43] GUSTO-IV study	RCT Total N: 1,875 Abciximab vs. placebo Good	Sex	Male Composite outcome (death or MI at 30 days) Placebo: 8.6% Abciximab 24 hrs: 8.5% Abciximab 48 hrs: 8.6% Total mortality at 1 yr Placebo: 7.7% Abciximab 24 hrs: 7.4% Abciximab 48 hrs: 8.6%
			Female Composite outcome (death or MI at 30 days) Placebo: 7.2% Abciximab 24 hrs: 7.7% Abciximab 48 hrs: 10.1% Total mortality at 1 yr Placebo: 8.0% Abciximab 24 hrs: 9.4% Abciximab 48 hrs: 9.6%
		Age	Age <65 yrs Composite outcome (death or MI at 30 days) Placebo: 4.2% Abciximab 24 hrs: 5.1% Abciximab 48 hrs: 4.9%
			Age ≥65 yrs Composite outcome (death or MI at 30 days) Placebo: 11.1% Abciximab 24 hrs: 10.6% Abciximab 48 hrs: 12.4%

Study	Study Details	Subgroup	Results Reported by Authors
		Diabetes	Diabetes Composite outcome (death or MI at 30 days) Placebo: 11.4% Abciximab 24 hrs: 9.6% Abciximab 48 hrs: 11.0% Total mortality at 1 yr Placebo: 13.7% Abciximab 24 hrs: 12.2% Abciximab 48 hrs: 14.7%
			No diabetes Composite outcome (death or MI at 30 days) Placebo: 7.1% Abciximab 24 hrs: 7.8% Abciximab 48 hrs: 8.6% Total mortality at 1 yr Placebo: 6.1% Abciximab 24 hrs: 7.0% Abciximab 48 hrs: 7.4%
		Geography	North America Composite outcome (death or MI at 30 days) Placebo: 11.7% Abciximab 24 hrs: 9.6% Abciximab 48 hrs: 9.6%
			Eastern Europe Composite outcome (death or MI at 30 days) Placebo: 7.7% Abciximab 24 hrs: 6.8% Abciximab 48 hrs: 8.7%
			Other Composite outcome (death or MI at 30 days) Placebo: 7.3% Abciximab 24 hrs: 9.0% Abciximab 48 hrs: 9.2%
Singh, 2006[26]		Timing of PCI	PCI within 48 hrs of admission Total mortality LMWH (N=1970): 1.57% UFH (N=4029): 1.49% Adjusted OR (95%CI): 1.14 (0.71-0.85) Composite outcome (death or reinfarction) LMWH (N=1970): 3.45% UFH (N=4029): 3.97% Adjusted OR (95%CI): 0.93 (0.67-1.31) RBC transfusion (all) LMWH (N=1970): 5.63% UFH (N=4029): 5.21% Adjusted OR (95%CI): 1.16 (0.89-1.50)

Study	Study Details	Subgroup	Results Reported by Authors
			No PCI within 48 hrs of admission Total mortality LMWH (N=1882): 3.88% UFH (N=1989): 5.23% Adjusted OR (95%CI): 0.64 (0.46-0.88) Composite outcome (death or re-infarction) LMWH (N=1882): 5.42% UFH (N=1989): 8.70% Adjusted OR (95%CI): 0.57 (0.44-0.73) RBC transfusion (all) LMWH (N=1882): 7.76% UFH (N=1989): 10.71% Adjusted OR (95%CI): 0.66 (0.52-0.84)
		Age	Age <75 yrs Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.87 (0.69-1.09) RBC Transfusions (All) Adjusted OR (95% CI): 1.04 (0.91- 1.27) RBC Transfusions (Non-CABG) Adjusted OR (95% CI): 0.91 (0.74-1.15)
			Age ≥75 yrs Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.78 (0.55- 1.01) RBC Transfusions (All) Adjusted OR (95% CI): 0.98 (0.81-1.27) RBC Transfusions (Non-CABG) Adjusted OR (95% CI): 0.72 (0.69-1.21)
		Sex	Female Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.77 (0.57- 0.98) RBC Transfusions (All) Adjusted OR (95% CI): 1.04 (0.90- 1.30) RBC Transfusions (Non-CABG) Adjusted OR (95% CI): 1.00 (0.85- 1.30)
			Male Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.87 (0.69- 1.12) RBC Transfusions (All) Adjusted OR (95% CI): 1.00 (0.87- 1.28) RBC Transfusions (Non-CABG) Adjusted OR (95% CI): 0.80 (0.59-1.03)
		Diabetes	Diabetes Composite outcome (death or re-infarction) Adjusted OR (95%CI): 0.96 (0.72-1.38) RBC transfusions (all) Adjusted OR (95%CI): 1.05 (0.87-1.38) RBC transfusions (non-CABG) Adjusted OR (95%CI): 0.89 (0.7-1.17)

Study	Study Details	Subgroup	Results Reported by Authors
		Revascularization	Revascularization Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.94 (0.75-1.25) RBC transfusions (all) Adjusted OR (95% CI): 1.31 (1.09-1.52) RBC transfusions (non-CABG) Adjusted OR (95% CI): 1.16 (0.92-1.49)
			No revascularization Composite outcome (death or re-infarction) Adjusted OR (95% CI): 0.61 (0.50-0.82) RBC transfusions (all) Adjusted OR (95% CI): 0.67 (0.50-0.87) RBC transfusions (non-CABG) Adjusted OR (95% CI): 0.67 (0.50-0.87)
Spinler, 2003[44]	Observational Total N: 7,081 Enoxaparin vs. UFH Fair	Weight/BMI	BMI ≥30 kg/m^2 Total mortality at 43 days UFH: 2.5% Enoxaparin: 2.6% Adjusted OR (95% CI): 1.07 (0.60-1.92) p=0.81 MI at 43 days UFH: 6.1% Enoxaparin: 4.9% Adjusted OR (95% CI): 0.81 (0.55-1.23) p=0.35 Composite outcome (death, MI or revascularization at 43 days) UFH: 18.0% Enoxaparin: 14.3% Adjusted OR (95% CI): 0.78 (0.61, 1.0) p=0.05 Major bleeding at 43 days UFH: 1.2% Enoxaparin: 0.4% Adjusted OR (95% CI): 0.38 (0.11-1.14) p=0.08

Study	Study Details	Subgroup	Results Reported by Authors
		Renal impairment	Creatinine clearance ≤30 mL/min Total mortality at 43 days UFH: 24.3% Enoxaparin: 11.6% Adjusted OR (95% CI): 0.43 (0.17-1.12) p=0.09 MI at 43 days UFH: 8.1% Enoxaparin: 8.7% Adjusted OR (95% CI): 1.45 (0.39-5.40) p=0.58 Composite outcome (death, MI or revascularization at 43 days) UFH: 32.4% Enoxaparin: 18.8% Adjusted OR (95% CI): 0.52 (0.23, 1.19) p=0.12 Major bleeding at 43 days UFH: 5.8% Enoxaparin: 7.5% Adjusted OR (95% CI): 1.53 (0.37-6.32) p=0.56
Stone, 2006 [29] ACUITY study	RCT Total N: 13,819 Bivalirudin vs. UFH or enoxaparin + GPI vs. bivalirudin + GPI Good	Thienopyridine before angiography or PCI	Thienopyridine before angiography or PCI (N=5753) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 7.0% Heparin + GPI: 7.3% RR: 0.97 (0.80-1.17), p=0.054 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.0% Heparin + GPI: 16.3 HR: 0.98 (0.86-1.11) Total mortality at 1 yr Bival alone: 3.4 Heparin + GPI: 3.7% HR: 0.90 (0.68-1.18)
			No thienopyridine before angiography or PCI (N=3304) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 9.1% Heparin + GPI: 7.1% RR: 1.29 (1.03-1.63), p=0.054
		Treatment strategy	PCI (N=5180) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 8.8% for bival alone, 8.2% for hep + GPI, RR 1.07 (0.90-1.28), p=0.82 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 19.4% Heparin + GPI: 17.9 HR: 1.09 (0.96-1.23) Total mortality at 1 yr Bival alone: 3.1% Heparin + GPI: 3.1% HR: 0.90 (0.68-1.18)

Study	Study Details	Subgroup	Results Reported by Authors
			CABG (N=1040) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 16.1% Heparin + GPI: 15.1 RR: 1.06 (0.80-1.41), p=0.82 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 21.1% Heparin + GPI: 20.7% HR: 1.04 (0.80-1.36) Total mortality at 1 yr Bival alone: 6.8% Heparin + GPI: 6.7% HR: 1.03 (0.65-1.66)
			Medical therapy (N=2995) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 3.4 Heparin + GPI: 2.7% RR: 1.24 (0.83-1.85), p=0.82 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 9.1% Heparin + GPI: 9.2% HR: 0.98 (0.77-1.25) Total mortality at 1 yr Bival alone: 4.0% Heparin + GPI: 4.1% HR: 0.95 (0.66-1.37)
		GPI use	GP IIb/IIIa upstream (N=6906) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 7.8% Heparin + GPI: 6.9% RR: 1.13 (0.95-1.36) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.2% Heparin + GPI: 15.5% HR: 1.05 (0.93-1.20) Total mortality at 1 yr Bival alone: 3.8% Heparin + GPI: 4.1 HR: 0.90 (0.70-1.16)

Study	Study Details	Subgroup	Results Reported by Authors
			GP IIb/IIIa deferred (N=6921) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 7.8% Heparin + GPI: 7.6% RR: 1.02 (0.86-1.22) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.2% Heparin + GPI: 15.4% HR: 1.06 (0.93-1.20) Total mortality at 1 yr Bival alone: 8% Heparin + GPI: 3.6% HR: 1.02 (0.78-1.32)
		CKMB/troponin levels	Elevated biomarkers (N=5073) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 9.4% Heparin + GPI: 8.4% RR: 1.12 (0.94-1.34) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 17.7% Heparin + GPI: 15.6% HR: 1.14 (0.99-1.3) Total mortality at 1 yr Bival alone: 4.7% Heparin + GPI: 4.5% HR: 1.04 (0.80-1.34)
			Normal biomarkers (N=3403) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 5.7% Heparin + GPI: 5.4% RR: 1.04 (0.79-1.38) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.2% Heparin + GPI: 14.8% HR: 0.96 (0.80-1.14) Total mortality at 1 yr Bival alone: 2.4% Heparin + GPI: 2.8% HR: 0.84 (0.55-1.28)

Study	Study Details	Subgroup	Results Reported by Authors
		Randomization to angiography or intervention	Early (<3.0 hours) (N=2918) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 6.0% Heparin + GPI: 5.8 RR: 1.04 (0.78-1.39) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.6% Heparin + GPI: 14.7% HR: 1.00 (0.83-1.21) Total mortality at 1 yr Bival alone: 2.0% Heparin + GPI: 2.7% HR: 0.72-0.44-1.15)
			Intermediate (3.0-19.7 hours) (N=2925) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 7.0% Heparin + GPI: 5.5% RR: 1.26 (0.95-1.67) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.8% Heparin + GPI: 13.9% HR: 1.06 (0.87-1.28) Total mortality at 1 yr Bival alone: 3.0% Heparin + GPI: 2.9% HR: 0.95 (0.62-1.44)
			Late (>19.7 hours) (N=2982) Composite outcome (ischemia, total death, MI, revascularization at 30 days) Bival alone: 10.0% Heparin + GPI: 9.9% RR: 1.01 (0.81-1.25) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 18.5% Heparin + GPI: 17.1% HR: 1.09 (0.92-1.29) Total mortality at 1 yr Bival alone: 5.8% Heparin + GPI: 4.9% HR: 1.17 (0.86-1.60)
		Age	<65 yrs (N=5051) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.2% Heparin + GPI: 15.4% HR: 1.06 (0.95, 1.17) Total mortality at 1 yr Bival alone: 1.9% Heparin + GPI: 2.0% HR: 0.91 (0.61-1.35)

Study	Study Details	Subgroup	Results Reported by Authors
			≥ 65 yrs (B=4164) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 18.7% Heparin + GPI: 17.6% HR: 1.07 (0.93-1.23) Total mortality at 1 yr Bival alone: 6.0% Heparin + GPI: 6.0% HR: 0.98 (0.77-1.26)
		Sex	Male (N=6444) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 17.1% Heparin + GPI: 16.2% HR: 1.06 (0.94-1.20) Total mortality at 1 yr Bival alone: 4.2% Heparin + GPI: 3.9% HR: 1.06 (0.83-1.36)
			Female (N=2771) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.3% Heparin + GPI: 13.7% HR: 1.05 (0.86-1.29) Total mortality at 1 yr Bival alone: 2.8% Heparin + GPI: 3.9% HR: 0.71 (0.47-1.08)
		Diabetes	Diabetes Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 19.5% Heparin + GPI: 17.9% HR: 1.08 (0.90-1.30) Total mortality at 1 yr Bival alone: 5.5% Heparin + GPI: 5.4% HR 0.99 (0.71-1.38)
			No diabetes Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.9% Heparin + GPI: 14.3% HR: 1.05 (0.92-1.19) Total mortality at 1 yr Bival alone: 3.1% Heparin + GPI: 3.2% HR: 0.93 (0.71-1.22)

Study	Study Details	Subgroup	Results Reported by Authors
		Creatinine clearance	Creatinine clearance ≥60 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 14.7% Heparin + GPI: 14.7% HR: 1.00 (0.89-1.13) Total mortality at 1 yr Bival alone: 2.9% Heparin + GPI: 3.0% HR: 0.96 (0.73-1.26)
			Creatinine clearance <60 Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 22.2% Heparin + GPI: 18.8% HR: 1.19 (0.96-1.48) Total mortality at 1 yr Bival alone: 7.1% Heparin + GPI: 7.2% HR: 0.99 (0.69-1.42)
		Geography	US (N=5224) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.5% Heparin + GPI: 16.6% HR: 1.00 (0.87-1.14) Total mortality at 1 yr Bival alone: 3.6% Heparin + GPI: 3.6% HR: 1.00(0.74-1.34)
			Non-US (N=3991) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 15.9% Heparin + GPI: 13.9% HR: 1.15 (0.98-1.34) Total mortality at 1 yr Bival alone: 4.1% Heparin + GPI: 4.3% HR: 0.91 (0.68-1.23)
		Antithrombin crossovers	No prior antithrombin (N=3100) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.2% Heparin + GPI: 13.8% HR: 1.16 (0.96-1.39) Total mortality at 1 yr Bival alone: 3.4% Heparin + GPI: 3.1% HR: 1.03 (0.70-1.52)

Study	Study Details	Subgroup	Results Reported by Authors
			Consistent therapy (N=5419) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.2% Heparin + GPI: 15.6% HR: 1.02 (0.88-1.19) Total mortality at 1 yr Bival alone: 3.4% Heparin + GPI: 3.7% HR: 0.91 (0.66-1.24)
			Crossover (N=3255) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Bival alone: 16.0% Heparin + GPI: 14.0% HR: 1.16 (0.89-1.50) Total mortality at 1 yr Bival alone: 3.7% Heparin + GPI: 4.7% HR: 0.74 (0.47-1.18)
		Thrombocytopenia	Acquired thrombocytopenia (N=760) Composite outcome (ischemia, total death, MI, revascularization at 30 days): 12.5% Composite outcome (ischemia, total death, MI, revascularization at 1 yr): 22.8% Total mortality at 30 days: 3.1% Total mortality at 1 yr: 6.5% Nonfatal MI at 30 days: 7.5% Nonfatal MI at 1 yr: 10.0% Revascularization at 30 days: 5.3% Revascularization at 1 yr: 13.8% Non-CABG major bleeding at 30 days: 14.0% Non-CABG minor bleeding at 30 days: 30.25% Composite outcome (ischemia or major bleeding at 30 days): 21.7%
			No thrombocytopenia (N=10096) Composite outcome (ischemia, total death, MI, revascularization at 30 days): 6.3% Composite outcome (ischemia, total death, MI, revascularization at 1 yr): 15.1% Total mortality at 30 days: 1.1% Total mortality at 1 yr: 3.4% Nonfatal MI at 30 days: 4.1% Nonfatal MI at 1 yr: 6.4% Revascularization at 30 days: 2.4% Revascularization at 1 yr: 9.1% Non-CABG major bleeding at 30 days: 4.3% Non-CABG minor bleeding: 18.7% Composite outcome (ischemia or major bleeding at 30 days): 9.7%
		Stent thrombosis	Stent thrombosis (N=32) Total mortality at 30 days: 3.1% Nonfatal MI at 30 days: 93.8% Revascularization at 30 days: 96.9% Non-CABG major bleeding at 30 days: 12.5%

Study	Study Details	Subgroup	Results Reported by Authors
			No stent thrombosis (N=3373) Total mortality at 30 days: 0.8% p=0.23 Nonfatal MI at 30 days: 6.9% p<0.0001 Revascularization at 30 days: 2.4% p<0.0001 Non-CABG major bleeding at 30 days: 6.0% p=0.13
		Patients who underwent PCI	PCI Composite outcome (ischemia, total death, MI, revascularization at 30 days) Heparin + GPI (N=2561): 8% Bival + GPI (N=2609): 9% compared with group 1, p=0.16, RR 1.14 (0.95-1.36) Bival alone (N=2619): 9% compared with group 1, p=0.45, RR 1.07 (0.89-1.28) Composite outcome (ischemia, total death, MI, revascularization at 1 yr) Heparin + GPI: 17.8% Bival + GPI: 19.4% compared with group 1, p=0.11, HR 1.11 (0.98-1.26) Bival alone: 19.2% (502/2619), (compared with group 1, p=0.19, HR 1.09 (0.96-1.23) Total mortality at 30 days Heparin + GPI: 0.9% Bival + GPI: 1% compared with group 1, p=0.37 Bival alone: 1% compared with group 1, p=0.53 Total mortality at 1 yr Heparin + GPI: 3.2% Bival + GPI: 3.3%, compared with group 1, p=0.19, HR 1.02 (0.75-1.38) Bival alone: 3.1%, compared with group 1, p=0.76, HR 0.95 (0.70-1.3) Nonfatal MI at 30 days Heparin + GPI: 6% Bival + GPI: 7% compared with group 1, p=0.16 Bival alone: 6% compared with group 1, p=0.19 Nonfatal MI at 1 yr Heparin + GPI: 7.8% Bival + GPI: 9.1%, compared with group 1, p=0.10, HR 1.17 (0.97-1.41) Bival alone: 9.3% (compared with group 1, p=0.06, HR 1.19 (0.99-1.44)

Study	Study Details	Subgroup	Results Reported by Authors
			Revascularization at 30 days Heparin + GPI: 3% Bival + GPI: 4% compared with group 1, p=0.31 Bival alone: 3% compared with group 1, p=0.87 Revascularization at 1 yr Heparin + GPI: 11.4% Bival + GPI: 12.5% compared with group 1, p=0.21, HR 1.11 (0.94-1.29) Bival alone: 11.8% compared with group 1, p=0.63, HR 1.04 (0.89-1.22) Composite outcome (death, MI, revasc, major bleed at 30 days) Heparin + GPI: 13% Bival + GPI: 15% compared with group 1, p=0.10, RR 1.12 (0.98-1.28) Bival alone: 12% compared with group 1, p=0.057, RR 0.87 (0.75-1.00) Non-CABG major bleeding at 30 days Heparin + GPI: 7% Bival + GPI: 8% compared with group 1, p=0.32, RR 1.11 (0.91-1.35) Bival alone: 4% compared with group 1, p<0.0001, RR 0.52 (0.0-0.66) Minor bleeding at 30 days Heparin + GPI: 26% Bival + GPI: 28% compared with group 1, p=0.053 Bival alone: 15% compared with group 1, p<0.0001
		Timing of Clopidogrel in Patients receiving bival alone or heparin+GPI	Clopidogrel initiated before angiography or within 30 min after PCI Composite outcome (ischemia death, MI, or revascularization at 30 days) Heparin + GPI (N=2189): 8.3% Bivalirudin (N=2284): 8.2%, RR 0.98 (0.81-1.20), p=0.88 compared to group 1 Composite outcome (ischemia death, MI, or revascularization at 1 yr) Heparin + GPI: 17.9% Bivalirudin: 18.75, RR 1.05 (0.93-1.10), p=0.45 compared to group 1 Total mortality at 30 days Heparin + GPI: 0.8% Bivalirudin: 1.0%, RR 1.22 (0.66-2.26), p=0.52 compared to group 1 Total mortality at 1 yr Heparin + GPI: 3.0% Bivalirudin: 3.1%, RR 1.05 (0.75-1.46), p=0.79 compared to group 1 Nonfatal MI at 30 days Heparin + GPI: 5.8% Bivalirudin: 6.0%, RR 1.05 (0.83-1.33), p=0.69 Revascularization at 30 days Heparin + GPI: 3.3% Bivalirudin: 2.8%, RR 0.87 (0.62-1.20), p=0.39 Non-CABG major bleeding at 30 days Heparin + GPI: 6.6% Bivalirudin: 3.5% (RR 0.53 (0.41-0.69), p<0.0001

Study	Study Details	Subgroup	Results Reported by Authors
			Clopidogrel initiated >30 minutes after PCI Composite outcome (ischemia death, MI, or revascularization at 30 days) Heparin + GPI (N=317): 8.5% Bivalirudin (N=290): 14.1%, RR 1.66 (1.05-2.63), p=0.03 compared to group 1 Composite outcome (ischemia death, MI, or revascularization at 1 yr) Heparin + GPI: 18.0% Bivalirudin: 21.7%, RR 1.21 (0.88-1.67) Total mortality at 30 days Heparin + GPI: 1.0% Bivalirudin: 1.7%, RR 0.91 (0.28-2.95), p=0.88 compared to group 1 Total mortality at 1 yr Heparin + GPI: 5.0% Bivalirudin: 3.1%, RR 0.61 (0.28-1.37), p=0.23 compared to group 1 Nonfatal MI at 30 days Heparin + GPI: 5.0% Bivalirudin: 10.3%, RR 2.05 (1.14-3.68), p=0.02 compared to group 1 Revascularization at 30 days Heparin + GPI: 3.2% Bivalirudin: 6.6%, RR 2.08 (0.98-4.39), p=0.06 compared to group 1 Non-CABG major bleeding at 30 days Heparin + GPI: 7.3% Bivalirudin: 3.4%, RR 0.48 (0.23-0.98), p=0.04 compared to group 1
		Specific timing of clopidogrel exposure among those with PCI	Pre-PCI clopidogrel among those with PCI (N=5131) Composite outcome (ischemia death, MI, or revascularization at 30 days) Heparin + GPI: 8.8% Bivalirudin + GPI: 8.9% Bivalirudin: 8.1% p=0.46 between heparin +GPI and bivalirudin alone
			Peri-PCI clopidogrel among those with PCI (N=1572) Composite outcome (ischemia death, MI, or revascularization at 30 days) Heparin + GPI: 6.9% Bivalirudin + GPI: 9.5% Bivalirudin: 8.6% p=0.29 between heparin +GPI and bivalirudin alone
			Post-PCI clopidogrel among those with PCI Heparin + GPI: 8.5% Bivalirudin + GPI: 10.8% Bivalirudin: 12.6% p=0.13 between heparin +GPI and bivalirudin alone
			No clopidogrel among those with PCI (N=129) Heparin + GPI: 8.8% Bivalirudin + GPI: 19.5% Bivalirudin: 23.3% p=0.08 between heparin +GPI and bivalirudin alone
Stone, 2007 [30] ACUITY TIMING study	RCT Total N: 9,207 Upstream GPI vs. in-lab GPI Good	Age	Age <65 (N=5054) Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 6.4% Upstream GPI 6.6% Major bleeding at 30 days Deferred: 3.7% Upstream 4.1%

Study	Study Details	Subgroup	Results Reported by Authors
			Age ≥65 (N=4153) Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 9.8% Upstream GPI 7.7% Major bleeding at 30 days Deferred GPI 6.3% Upstream GPI 8.5%
		Sex	Male (N=6467) Composite outcome (death MI or revascularization at 30 days) Deferred GPI 8.5% Upstream 7.0% Major bleeding at 30 days Deferred GPI 3.4% Upstream GPI: 4.6%
			Female (N=2740) Composite outcome (death MI or revascularization at 30 days) Deferred GPI 6.5% Upstream 7.2% Major bleeding at 30 days Deferred GPI: 8.3% Upstream GPI: 9.7%
		Diabetes	Diabetes (N=2565) Composite outcome (death MI or revascularization at 30 days) Deferred GPI 9.7% Upstream 8.4% Major bleeding at 30 days Deferred GPI: 6.1% Upstream GPI: 7.4%
			No diabetes (N=6567) Composite outcome (death MI or revascularization at 30 days) Deferred GPI 7.2% Upstream 6.6% Major bleeding at 30 days Deferred GPI: 4.4% Upstream GPI: 5.6%
		Creatinine clearance	Creatinine clearance ≥60 Composite outcome (death MI or revascularization at 30 days) Deferred GPI 7.1% Upstream 6.6% Major bleeding at 30 days Deferred GPI: 3.9% Upstream GPI: 4.6%
			Creatinine clearance <60 Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 11.8% Upstream 9.2% Major bleeding at 30 days Deferred GPI: 8.5% Upstream GPI: 12.8%

Study	Study Details	Subgroup	Results Reported by Authors
		Treatment strategy	PCI (N=5170) Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 9.5% Upstream 8.0% Major bleeding at 30 days Deferred GPI: 6.5% Upstream GPI: 7.8%
			CABG (N=1048) Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 13.5% Upstream 15.3% Major bleeding at 30 days Deferred GPI: 3.3% Upstream GPI: 4.5%
			Medical therapy (N=2989) Composite outcome (death MI or revascularization at 30 days) Deferred GPI: 3.3% Upstream 2.4% Major bleeding at 30 days Deferred GPI: 2.6% Upstream GPI: 3.7%
		Downstream abciximab vs. eptifibatide	Abciximab (N=835) vs. eptifibatide (N=1376) Composite outcome (death, MI, or revascularization at 30 days) Covariate adjusted stratified by propensity score: OR 0.61 (0.38-0.98), p=0.04 Major bleeding at 30 days Covariate adjusted stratified by propensity score: OR 0.58 (0.34-1.00), p=0.051 Composite outcome (death, MI, revascularization, or major bleeding at 30 days) Covariate adjusted stratified by propensity score: OR 0.61 (0.42-0.90), p=0.01
Yusuf, 2006[38] OASIS-5 study	RCT Total N: 20,078 Enoxaparin vs. Fondaparinux + fondaparinux Good	Age	Age ≥65 yrs (N=12,261) Composite outcome (death, MI or refractory ischemia) Enoxaparin: 6.8% Fondaparinux: 6.6% Major bleeding Enoxaparin: 5.5% Fondaparinux: 2.7%
		Sex	Male (N=12,379) Composite outcome (death, MI or refractory ischemia) Enoxaparin: 6% Fondaparinux: 5.8% Major bleeding Enoxaparin: 3.3% Fondaparinux: 2%
			Female (N=7699) Composite outcome (death, MI or refractory ischemia) Enoxaparin: 5.3% Fondaparinux: 5.7% Major bleeding Enoxaparin: 5.5% Fondaparinux: 2.5%

Study	Study Details	Subgroup	Results Reported by Authors
		Revascularization	Revascularization in 9 days (N=7372) Composite outcome (death, MI or refractory ischemia) Enoxaparin: 9.6% Fondaparinux: 9.9% Major bleeding Enoxaparin: 6% Fondaparinux: 4.2%
			No revascularization in 9 days (N=12,706) Composite outcome (death, MI or refractory ischemia) Enoxaparin: 3.5% Fondaparinux: 3.3% Major bleeding Enoxaparin: 3% Fondaparinux: 1%
		Diabetes	Diabetes (GFR <58 ml/min/1.73 m2) (N=5141) Composite outcome (death, MI or refractory ischemia at 9 days) Enoxaparin: 7.4% Fondaparinux: 6.7% HR (95%CI): 0.9 (0.73-1.11) Composite outcome (death, MI or refractory ischemia at 30 days) Enoxaparin: 12.2% Fondaparinux: 10% HR (95%CI): 0.81 (0.69-0.96) Composite outcome (death, MI or refractory ischemia at 180 days) Enoxaparin: 19.6% Fondaparinux: 17.96% HR (95%CI): 0.9 (0.79-1.03) Major bleeding at 9 days Enoxaparin: 6.4% Fondaparinux: 2.8% HR (95%CI): 0.42 (0.32-0.56) Major bleeding at 30 days Enoxaparin: 7.6% Fondaparinux: 4.2% HR (95%CI) 0.54(0.42-0.68) Major bleeding at 180 days Enoxaparin: 8.7% Fondaparinux: 5.8% HR (95%CI) 0.65 (0.52-0.8)

Study	Study Details	Subgroup	Results Reported by Authors
		PCI	PCI during index hospitalization Composite outcome (death, MI or refractory ischemia at 9 days) Enoxaparin (N=3072): 6.2% Fondaparinux (N=3105): 6.3% HR (95%CI): 1.03 (0.84-1.25) Composite outcome (death, MI or refractory ischemia at 30 days) Enoxaparin (N=3072): 7.4% Fondaparinux (N=3105): 7.4% HR (95%CI): 1.00 (0.83-1.20) Composite outcome (death, MI or refractory ischemia at 180 days) Enoxaparin (N=3072): 10.2% Fondaparinux (N=3105): 10.1% HR (95%CI): 0.99 (0.85-1.16) Major bleeding at 9 days Enoxaparin (N=3072): 5.1% Fondaparinux (N=3105): 2.4% HR (95%CI): 0.46 (0.35-0.61) Major bleeding at 30 days Enoxaparin (N=3072): 5.4% Fondaparinux (N=3105): 2.9% HR (95%CI): 0.52 (0.4-0.67) Major bleeding at 180 days Enoxaparin (N=3072): 6.3% Fondaparinux (N=3105): 3.4% HR (95%CI): 0.53 (0.42-0.68)
		Use of GPI and thienopyridines during index hospitalization	Thienopyridine (N=13532) Composite outcome (death, MI or refractory ischemia at 30 days) Enoxaparin: 9.1% Fondaparinux: 8.6% Adjusted HR (95%CI): 0.94 (0.84-1.06) Major bleeding Enoxaparin: 5.4% Fondaparinux: 3.4% Adjusted HR (95%CI): 0.62 (0.52-0.73)
			GPI (N=3630) Composite outcome (death, MI or refractory ischemia at 30 days) Enoxaparin: 13.2% Fondaparinux: 11.8% Adjusted HR (95%CI): 0.87 (0.72-1.06) Major bleeding Enoxaparin: 8.3% Fondaparinux: 5.2% Adjusted HR (95%CI): 0.60 (0.46-0.78)
			Thienopyridine + GPI (N=3246) Composite outcome (death, MI or refractory ischemia at 30 days) Enoxaparin: 12.8% Fondaparinux: 11.8% Major bleeding Enoxaparin: 7.6% Fondaparinux: 4.9%

Abbreviations: ASA=aspirin; Bival=bivalirudin; CABG=coronary artery bypass grafting; CHF=congestive heart failure; CI=confidence interval; CKMB=creatine kinase major bleeding; CrCl=Creatinine Clearance; CV=cardiovascular; GFR=glomerular filtration rate; GP=glycoprotein; GPI=glycoprotein IIb/IIIa inhibitor; GUSTO=global utilization of streptokinase and t-PA for occluded arteries; HR=hazard ratio; hr=hour/hours; KM=Kaplan-Meier; LMWH=low molecular weight heparin; m=meter/meters; MI=myocardial infarction; mg=milligram/milligrams; mL=milliliter/milliliters; min=minute/minutes; N=number of patients; OR=odds ratio; PCI=percutaneous coronary intervention; PPI=proton pump

inhibitor; PTCA=percutaneous transluminal coronary angioplasty; RBC=red blood cells; RCT=randomized controlled trial; RR=relative risk; TIMI=thrombolysis in myocardial infarction; UA=unstable angina; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin; US=United States; vs=versus; yr=year/years

Table H-3. Subgroup results for KQ 3: antiplatelet and anticoagulant medications in the postdischarge treatment of patients with UA/NSTEMI

Study	Study Details	Subgroup	Results Reported by Authors
Bonde, 2010[45]	Observational Total N: 31,295 Placebo vs. clopidogrel Fair	Heart failure	Total mortality HR 0.86 (0.78-0.95) c/w HF no clopidogrel clop 28.1% vs. 32.2% no clopidogrel
Butler, 2009[46]	Observational Total N: 2980 Clopidogrel vs. aspirin Fair	Type of stent	BMS (N=1311) Total mortality in-hospital BMS (N=1311): 3.1% DES (N=1669): 1.4% p=0.002
Charlot, 2010[47]	Observational Total N: 56,406 PPI vs. no PPI Good	PPI type	PPI + clopidogrel vs. no PPI Composite outcome (CV death, nonfatal MI, stroke) Pantoprazole: HR 1.42, 95%CI 1.22-1.67 Omeprazole: HR 1.40, 95%CI 1.10-1.78 Lansoprazole: HR 1.47, 95%CI 1.21-1.81 Esomeprazole: HR 1.29, 95%CI 1.09-1.48
			PPI vs. No PPI Composite outcome (CV death, nonfatal MI, stroke) Pantoprazole: HR 1.5, 95%CI 1.36-1.69 Omeprazole: HR 1.25, 95%CI 1.09-1.41 Lansoprazole: HR 1.45, 95%CI 1.27-1.68 Esomeprazole: HR 1.53, 95%CI 1.39-1.71
		Age	Age ≤70 yrs Composite outcome (CV death, nonfatal MI, stroke) PPI + clopidogrel vs. No PPI: HR 1.37, 95%CI 1.19-1.62 PPI vs. No PPI: HR 1.19, 95%CI 0.99-1.39
			Age >70 yrs Composite outcome (CV death, nonfatal MI, stroke) PPI + clopidogrel vs. No PPI: HR 1.30, 95%CI 1.18-1.43 PPI vs. No PPI: HR 1.33, 95%CI 1.24-1.43
		Sex	Male Composite outcome (CV death, nonfatal MI, stroke) PPI + clopidogrel vs. No PPI: HR 1.38, 95%CI 1.23-1.58 PPI vs. No PPI: HR 1.18, 95%CI 1.004-1.37
			Female Composite outcome (CV death, nonfatal MI, stroke) PPI + clopidogrel vs. No PPI: HR 1.34, 95%CI 1.23-1.46 PPI vs. No PPI: HR 1.32, 95%CI 1.21-1.44
		Diabetes	With diabetes Composite outcome (CV death, nonfatal MI, stroke) PPI + clopidogrel vs. No PPI: HR 1.36, 95%CI 1.10-1.70 PPI vs. No PPI: HR 1.28, 95%CI 1.16-1.43

Study	Study Details	Subgroup	Results Reported by Authors
			Without diabetes Composite outcome (CV death, nonfatal MI, stroke) PPI + clopidogrel vs. No PPI: HR 1.25, 95%CI 1.06-1.45 PPI vs. No PPI: HR 1.35, 95%CI 1.26-1.44
Charlot, 2012[48]	Observational Total N: 29,268 Clopidogrel up to 90 days vs. clopidogrel > 90 days Fair	Type of MI	Death or MI STEMI medically treated IRR 0.79 (0.11-5.61; p=0.81) PCI treated IRR 2.65 (1.25-5.64; p=0.011) NSTEMI medically treated IRR 0.99 (0.58-1.69; p=0.97) PCI treated IRR 1.24 (0.78-1.99; p=0.37)
Cheng, 2010[49] T-ACCORD Registry	Observational Total N: 1331 Aspirin vs. clopidogrel Good	Timing of treatment	Survival rate Aspirin & clopidogrel 0-3 months: 96.5% Aspirin & clopidogrel 3-6 months: 94.6% Aspirin & clopidogrel 6-9 months: 100% Aspirin & clopidogrel 9-12 months: 100%
Gwon, 2012[50]	RCT Total N: 1443 ASA + clopidogrel 6 months vs. ASA + clopidogrel 12 months Good	Age	<65 years (n=767) Primary endpoint DAPT 6 months vs. 12 months 5.1% vs. 3.2% HR, 95%CI 1.61 (0.78-3.31)
			=>65 year (n=676) Primary Endpoint DAPT 6 months vs. 12 months 4.5% vs. 5.5% HR, 95%CI 0.83 (0.42-1.65)
		ACS	Primary endpoint DAPT 6 months vs. 12 months 3.6% vs. 4.7% HR, 95%CI 0.78 (0.38-1.60)
		Diabetes	primary endpoint DAPT 6 months vs. 12 months 9.1% vs. 3.0% HR, 95%CI 3.16 (1.42-7.03)
Harjai, 2011[51]	Observational Total N: 2604 PPI vs. no PPI Good	propensity adjusted looking at omeprazole or esomeprazole versus no PPI	omeprazole or esomeprazole vs. no PPI MACE HR 0.51, 95%CI 0.28-0.92 NACE HR 0.59, 95%CI 0.35-1.01 Total mortality HR 0.49, 95%CI 0.17-1.37 Nonfatal MI HR 0.65, 95%CI 0.29-1.43 Death/MI HR 0.52, 95%CI 0.26-1.03 Stent thrombosis HR 0.59, 95%CI 0.18-1.97 Bleeding HR 0.59, 95%CI 0.18-1.94
Harjai, 2009[52]	Observational Total N: 1859 Aspirin vs. clopidogrel Good	Diabetes	Composite outcome (all cause death or MI) DAP > 12 months (N=277): 12% DAP ≤ 12 months (N=209): 16% log rank p-value=0.22 between group 1 and 2. Adjusted HR (95% CI): 0.85 (0.51 - 1.43) p = 0.55

Study	Study Details	Subgroup	Results Reported by Authors
		MI	Composite outcome (all cause death or MI) DAP > 12 months (N=322): 13% DAP ≤ 12 months (N=391): 14% log rank p-value = 0.76 Adjusted HR (95% CI): 0.90 (0.59 - 1.39) p = 0.63
Harjai, 2011[53] GHOST	Observational Total N: 2820 Aspirin 81 mg/day vs. aspirin 162-325 mg/day Fair	Diabetes	Patients with diabetes MACE low dose vs. high dose 12.1% vs. 12.6% NACE low dose vs. high dose 17.6% vs. 13.8% Death/MI low dose vs. high dose 11.0% vs. 8.3% Bleeding low dose vs. high dose 6.6% vs. 2.1% Stent thrombosis low dose vs. high dose 2.2% vs. 2.6%
			Patients with DES MACE low dose vs. high dose 6.3% vs. 6.7% NACE low dose vs. high dose 9.2% 7.5% Death/MI low dose vs. high dose 4.66 vs. 5.3% Bleeding low dose vs. high dose 3.5% vs. 1.3% Stent thrombosis low dose vs. high dose1.7% vs. 1.8%
Ho, 2007[54]	Observational Total N: 1455 Timing of clopidogrel Fair	Type of stent	BMS Total mortality Continuing vs. discontinuing clopidogrel therapy: discontinuation associated with higher mortality risk HR (95% CI): 2.65 (1.59 - 4.42) Nonfatal MI Continuing vs. discontinuing clopidogrel therapy: discontinuation associated with higher risk for subsequent AMI HR (95% CI): 1.26 (0.58 - 2.74)
			DES Total mortality Continuing vs. discontinuing clopidogrel therapy: discontinuation associated with higher mortality risk HR (95% CI): 2.0 (1.06 - 3.75) Nonfatal MI Continuing vs. discontinuing clopidogrel therapy: discontinuation associated with higher risk for subsequent AMI HR (95% CI): 3.57 (1.13 - 11.3)
Ho, 2009[55]	Observational Total N: 8790 PPI vs. no PPI Good	PPI use	PPI vs. no PPI at discharge Composite outcome (death or rehospitalization) Adjusted HR (95% CI): 1.27 (1.1-1.46)

Study	Study Details	Subgroup	Results Reported by Authors
			PPI type Composite outcome (death or rehospitalization) Omeprazole Adjusted OR (95% CI): 1.24 (1.08-1.41) Rabeprazole Adjusted OR (95% CI): 2.83 (1.96-4.09)
Juurlink, 2009[56]	Observational Total N: 2791 Timing of clopidogrel Good	PPI use	Previous vs. remote PPI use Nonfatal MI Previous use HR (95% CI): 0.86 (0.63-1.19) Remote use HR (95% CI): 0.81 (0.46-1.41)
			Pantoprazole vs. other PPI Nonfatal MI Pantoprazole HR (95% CI): 1.02 (0.70-1.47) Other PPI HR (95% CI): 1.40 (1.10-1.77)
Kreutz, 2010[57]	Observational Total N: 16,690 PPI vs. no PPI Good	PPI use	Prior PPI use (N=12,194) Major adverse cardiovascular event No PPI: 17.9% PPI: 27.8% HR (95% CI): 1.57 (1.44–1.71) p<0.0001
			No prior PPI use (N=4,499) Major adverse cardiovascular event No PPI: 19.2% PPI: 23.2% HR (95% CI): 1.24 (0.98–1.71) p=0.0688
O'Donoghue, 2009[58] TRITON-TIMI 38	Observational Total N: 13,608 PPI vs. no PPI Good	PPI type	PPI vs. no PPI (clopidogrel arm) Composite outcome (CV death, nonfatal MI, stroke) Pantoprazole: Adj HR 0.94 (95% CI, 0.74-1.18) Omeprazole: Adj HR 0.91 (95% CI, 0.72-1.15) Lansoprazole: Adj HR 1.00 (95% CI, 0.63-1.59) Esomeprazole: Adj HR 1.07 (95% CI, 0.75-1.52) MI Pantoprazole: Adj HR 0.97 (95% CI, 0.75-1.24) Omeprazole: Adj HR 0.95 (95% CI, 0.73-1.23) Lansoprazole: Adj HR 0.86 (95% CI, 0.51-1.46) Esomeprazole: Adj HR 1.18 (95% CI, 0.81-1.73)
			PPI vs. no PPI (prasugrel arm) Composite outcome (CV death, nonfatal MI, stroke) Pantoprazole: Adj HR 1.09 (95% CI, 0.86-1.39) Omeprazole: Adj HR 1.04 (95% CI, 0.81-1.34) Lansoprazole: Adj HR 0.98 (95% CI, 0.61-1.57) Esomeprazole: Adj HR 0.86 (95% CI, 0.55-1.33) MI Pantoprazole: Adj HR 1.09 (95% CI, 0.83-1.43) Omeprazole: Adj HR 1.02 (95% CI, 0.76-1.36) Lansoprazole: Adj HR 1.08 (95% CI, 0.66-1.79) Esomeprazole: Adj HR 0.92 (95% CI, 0.57-1.48)

Study	Study Details	Subgroup	Results Reported by Authors
Persson, 2011[59] (RIKS-HIA) and (SCAAR)	Observational Total N: 27,972 Warfarin vs. placebo Good	Clopidogrel use	Oral anticoagulants vs. oral anticoagulants + clopidogrel Composite outcome (death or MI) OR (95% CI): 0.93 (0.65-1.3) Bleeding OR (95% CI): 1.53 (0.57-4.11) Total mortality OR (95% CI): 0.98 (0.50-1.9)
Rassen, 2009[60]	Observational Total N: 18,565 PPI vs. no PPI Good	PPI type	Composite outcome (MI or death) Omeprazole HR (95% CI): 1.17 (0.68-2.01) Pantoprazole HR (95% CI): 1.26 (0.93-1.71)
Ray, 2010[61]	Observational Total N: 20,596 PPI vs. no PPI Good	PPI dose	Composite CV events Low dose HR (95% CI): 1.0 (0.81-1.22) High dose HR (95% CI): 0.94 (0.75-1.17) Gastroduodenal bleeding Low dose HR (95% CI): 0.48 (0.36-0.64) High dose HR (95% CI): 0.53 (0.32-0.89)
		PPI type	Composite CV events Esomeprazole HR (95% CI): 0.71 (0.48-1.06) Omeprazole HR (95% CI): 0.79 (0.54-1.15) Pantoprazole HR (95% CI): 1.08 (0.88-1.32) Rabeprazole HR (95% CI): 0.54 (0.30-0.97) Lansoprazole HR (95% CI): 1.06 (0.77-1.45) Gastroduodenal bleeding Esomeprazole HR (95% CI): 0.43 (0.18-1.07) Omeprazole HR (95% CI): 0.43 (0.16-1.13) Pantoprazole HR (95% CI): 0.46 (0.33-0.63) Rabeprazole HR (95% CI): 0.25 (0.03-2.01) Lansoprazole HR (95% CI): 0.71 (0.43-1.18)
		New clopidogrel user	Composite CV events All PPI HR (95% CI): 0.91 (0.70-1.19) Pantoprazole HR (95% CI): 1.02 (0.71-1.46) Omeprazole HR (95% CI): 0.79 (0.46-1.36)
		PCI	Composite CV events HR (95% CI): 1.01 (0.76-1.34) Composite outcome (MI or SCD) HR (95% CI): 1.00 (0.77-1.30) Stroke HR (95% CI): 0.97 (0.50-1.90) CV mortality HR (95% CI): 1.22 (0.57-2.58)

Study	Study Details	Subgroup	Results Reported by Authors
Rossini, 2011[62]	Observational Total N: 1346 PPI vs. no PPI Good	Diabetes	PPI use Composite outcome (death, MI, rehospitalization, stroke at 1 year) Diabetes OR (95% CI): 1.31 (0.379-4.530) No diabetes OR (95% CI): 1.723(0.608-4.879) p interaction 0.368
		Age	Age >75 yrs vs. ≤ 75 yrs Composite outcome (death, MI, rehospitalization, stroke at 1 year) Age >75 OR (95% CI): 1.609 (0.352-7.369) Age ≤75 OR (95% CI): 1.46 (0.617-3.459) p=0.809
		ACS and stable CAD	ACS vs. stable CAD Composite outcome (death, MI, rehospitalization, stroke at 1 year) ACS OR (95% CI): 1.454 (0.649-3.26) Stable CAD OR (95% CI): 2.106 (0.271-16.37) p interaction 0.998
		CKD	CKD vs. no CKD Composite outcome (death, MI, rehospitalization, stroke at 1 year) CKD OR (95% CI): 0.647 (0.178-2.358) No CKD OR (95% CI): 2.48 (0.763-8.056)
		PPI type	Lansoprazole MACE in-hospital: 2.2% MACE at 1 yr: 7.8% Major bleeding: 1.3% Minor bleeding: 2.9% Total mortality at 1 yr: 2.1% Stent thrombosis: 2.1%
			Omeprazole MACE in-hospital: 2.5% MACE at 1 yr: 4.2% Major bleeding: 1.6% Minor bleeding: 7.1% Total mortality: 0.8% Stent thrombosis: 1.7%
			Pantoprazole MACE in-hospital: 4.1% MACE at 1 yr: 8.1% Major bleeding: 1.1% Minor bleeding: 1.1% Total mortality: 3.1% Stent thrombosis: 3.1%
Ruiz-Nodar, 2012[63]	Observational Total N: 604 Warfarin vs. non-OAC	Risk of bleeding	low risk of bleeding (HAS-BLED 0-2) Bleeding OAC 7.8% vs. non-OAC1.6%; P=0.13

Study	Study Details	Subgroup	Results Reported by Authors
	Fair		high risk of bleeding (HAS-BLED =>3) Bleeding OAC vs. non-OAC 11.8% vs. 4.0% HR 3.03, 95%CI 1.24-7.38) Total mortality OAC vs. non-OAC 9.3% vs. 20.1% HR 0.45, 95%CI 0.26-0.78) MACE OAC vs. non-OAC 13.0% vs. 26.4% HR 0.48, 95%CI 0.29-0.77)
Schmidt, 2012[64]	Observational Total N: 13,001 Clopidogrel Poor	PPI Type	Esomeprazole (Clop+ Eso vs. Clop alone) Primary composite endpoint Clop+ Eso vs. Clop alone 153 vs. 108 Nonfatal MI no PPI no Clop vs. no PPI +clop HR 95% CI 0.22 (0.19-0.26) PPI no Clop vs. PPI + Clop HR 95%CI 0.40 (0.19-0.82) Revascularization no PPI no Clop vs. no PPI +clop HR 95% CI 0.50 (0.43-0.58 PPI no Clop vs. PPI + Clop HR 95%CI 0.61 (0.31-1.20) Cardiovascular mortality no PPI no Clop vs. no PPI +clop HR 95% CI 0.12 (0.09-0.15) PPI no Clop vs. PPI + Clop HR 95%CI 0.27 (0.11-0.69)
			lansoprazole (Clop+lanso vs. Clop alone) Primary composite endpoint Clop+lanso vs. Clop alone 138 vs. 109 Nonfatal MI no PPI no Clop vs. no PPI +clop HR 95% CI 0.23 (0.19-0.27) PPI no Clop vs. PPI + Clop HR 95%CI 0.28 (0.12-0.67) Revascularization no PPI no Clop vs. no PPI +clop HR 95% CI 0.51 (0.44-0.59) PPI no Clop vs. PPI + Clop HR 95%CI 0.28 (0.10-0.82) Cardiovascular mortality no PPI no Clop vs. no PPI +clop HR 95% CI 0.12 (0.09-0.16) PPI no Clop vs. PPI + Clop HR 95%CI 0.22 (0.06-0.78)

Study	Study Details	Subgroup	Results Reported by Authors
			omeprazole (clop +omep vs. clop alone) Primary composite endpoint clop +omep vs. clop alone 145 vs110 Nonfatal MI no PPI no Clop vs. no PPI +clop HR 95% CI 0.23 (0.19-0.27) PPI no Clop vs. PPI + Clop HR 95%CI 0.18 (0.05-0.60) Revascularization no PPI no Clop vs. no PPI +clop HR 95% CI 0.51 (0.44-0.59) PPI no Clop vs. PPI + Clop HR 95%CI 0.49 (0.19-1.32) Cardiovascular mortality no PPI no Clop vs. no PPI +clop HR 95% CI 0.12 (0.09-0.16) PPI no Clop vs. PPI + Clop HR 95%CI 0.27 (0.06-1.20)
			pantoprazole (clop+panto vs. clop alone) Primary composite endpoint clop+panto vs. clop alone 154 vs. 109 Nonfatal MI no PPI no Clop vs. no PPI +clop HR 95% CI 0.22 (0.19-0.26) PPI no Clop vs. PPI + Clop HR 95%CI 0.80 (0.25-2.51) Revascularization no PPI no Clop vs. no PPI +clop HR 95% CI 0.50 (0.43-0.58) PPI no Clop vs. PPI + Clop HR 95%CI 1.26 (0.42-3.77) Cardiovascular mortality no PPI no Clop vs. no PPI +clop HR 95% CI 0.12 (0.09-0.16) PPI no Clop vs. PPI + Clop HR 95%CI 0.16 (0.05-0.54)
Simon, 2011[65] FAST-MI	Observational Total N: 2744 PPI vs. No PPI Good	PPI type	Omeprazole (N=993) Composite outcome (death, MI, or stroke in-hospital) Adjusted OR (95% CI): 0.92 (0.59-1.43) Composite outcome (death, MI, or stroke at 1 yr) Adjusted OR (95% CI): 0.82 (0.54-1.24) Total mortality Adjusted OR (95% CI): 1.16 (0.66-2.05) Nonfatal MI Adjusted OR (95% CI): 1.18 (0.55-2.52) Stroke Adjusted OR (95% CI): 1.18 (0.55-2.52) Bleeding Adjusted OR (95% CI): 0.94 (0.44-1.98)

Study	Study Details	Subgroup	Results Reported by Authors
			Esomeprazole (N=311) Composite outcome (death, MI, or stroke in-hospital) Adjusted OR (95% CI): 0.77 (0.41-1.46) Total mortality Adjusted OR (95% CI): 0.72 (0.30-1.7) Nonfatal MI Adjusted OR (95% CI): 1.20 (0.44-3.30) Stroke Adjusted OR (95% CI): 0.54 (0.14-2.16) Bleeding Adjusted OR (95% CI): 0.97 (0.33-2.86) Composite outcome (death, MI, or stroke at 1 yr) Adjusted OR (95% CI): 1.05 (0.62-1.77)
			Lansoprazole (N=46) Composite outcome (death, MI, or stroke in-hospital) Adjusted OR (95% CI): 0.59 (0.07-4.72) Total mortality Adjusted OR (95% CI): 1.30 (0.15-11.5) Nonfatal MI 0 Stroke 0 Bleeding Adjusted OR (95% CI): 1.82 (0.22-15.3) Composite outcome (death, MI, or stroke at 1 yr) Adjusted OR (95% CI): 0.40 (0.05-2.95)
			Pantoprazole (N=99) Composite outcome (death, MI, or stroke in-hospital) Adjusted OR (95% CI): 1.31 (0.54-3.17) Total mortality Adjusted OR (95% CI): 1.00 (0.27-3.68) Nonfatal MI Adjusted OR (95% CI): 1.22 (0.26-5.77) Stroke Adjusted OR (95% CI): 1.78 (0.36-8.83) Bleeding 0 Composite outcome (death, MI, or stroke at 1 yr) Adjusted OR (95% CI): 1.79(0.95-3.37)
So, 2009[66]	Observational Total N: 1840 ASA dose Fair	Diabetes	Composite outcome (death or MI) Low dose ASA (81mg/d): log OR = -0.0103324
		Multivessel disease	Composite outcome (death or MI) Low dose ASA (81mg/d): p-value=0.07, compared with diabetes group

Study	Study Details	Subgroup	Results Reported by Authors
		Type of stent	BMS Composite outcome (death or MI) ASA 81 mg/d (N=1120): 5.65% ASA 325mg/d (N=1120): 3.73% OR (95% CI): 1.25 (0.67 - 2.33) Composite outcome (death, MI, or revascularization) ASA 81 mg/d (N=1120): 12.67% ASA 325mg/d (N=1120): 8.96% OR (95% CI): 1.38 (0.92 - 2.06)
			DES Composite outcome (death or MI) ASA 81 mg/d (N=720): 5.21% ASA 325mg/d (N=720): 4.82% OR (95% CI): 1.12 (0.53 - 2.34) Composite outcome (death, MI, or revascularization) ASA 81 mg/d (N=720): 9.51% ASA 325mg/d (N=720): 13.20% OR (95% CI): 0.75 (0.46 - 1.25)
Steinhubl, 2002[28]	RCT Total N: 2116 Clopidogrel vs. placebo Good	Diabetes	MACE RRR 11.2 (46.2 to -46.8)
		Sex	Men vs. women MACE Men RRR 24.5 (45.5 to -4.6) Women RRR 32.1 (58.9 to -12.1)
		CrCl < 60 ml/min	MACE at 28 days RRR -57% clop 11.0% vs. placebo 7.1% MACE at 1 year RRR -41% clop 17.8% vs. placebo 13.1%
		ACS	MACE RRR 27.5 (47.8 to -0.6)
Stenestrand, 2005[67] RIKS-HIA	Observational Total N: 6275 Aspirin vs. OAC Good	Age	Age ≤75 yrs vs. age >75 yrs Total mortality Age ≤75 yrs RR (95% CI): 0.61 (0.40-0.93) Age >75 RR (95% CI): 0.71 (0.53-0.96)
		Sex	Male vs. female Total mortality Male RR (95% CI): 0.60 (0.43-0.82) Female RR (95% CI): 0.93 (0.64-1.36)
		Diabetes	Diabetes vs. no diabetes Total mortality Diabetes RR (95% CI): 0.85 (0.56-1.30) No diabetes RR (95% CI): 0.64 (0.47-0.86)
Stockl, 2010[68]	Observational Total N: 2066 PPI vs. No PPI Good	Clopidogrel use	Clopidogrel + Pantoprazole vs. clopidogrel alone Rehospitalization for MI Adjusted HR (95% CI): 21.8 (0.88-5.39) Rehospitalization for MI and coronary stent procedure Adjusted HR (95% CI): 1.91 (1.19-3.06)

Study	Study Details	Subgroup	Results Reported by Authors
Valgimigli, 2012[69] PRODIGY	RCT Total N: 2013 Clopidogrel dose Good	Age	Age ≥65 yrs vs. age <65 yrs Composite outcome (total mortality, nonfatal MI, or stroke) Age ≥65 yrs HR (95% CI): 1.12 (0.82-1.51) Age <65 yrs HR (95% CI): 0.57 (0.28-1.16)
		Sex	Male vs. female Composite outcome (total mortality, nonfatal MI, or stroke) Male HR (95% CI): 1.09 (0.77-1.29) Female HR (95% CI): 1.00 (0.60-1.68)
		Diabetes	Diabetes vs. no diabetes Composite outcome (total mortality, nonfatal MI, or stroke) Diabetes HR (95% CI): 0.85 (0.53-1.38) No diabetes HR (95% CI): 1.06 (0.76-1.50)
		Stent type	BMS vs. DES Composite outcome (total mortality, nonfatal MI, or stroke) BMS HR (95% CI): 1.13 (0.68-1.86) DES HR (95% CI): 0.93 (0.67-1.30)
		Renal function	Creatinine clearance >60 mL/min vs. Creatinine clearance ≤60 mL/min Composite outcome (total mortality, nonfatal MI, or stroke) CrCl >60 mL/min HR (95% CI): 0.90 (0.58-1.38) CrCl ≤60 mL/min HR (95% CI): 1.14 (0.78-1.65)
Valkhoff, 2011[70]	Observational Total N: 23,655 PPI vs. No PPI Poor	PPI timing	Current PPI use vs. past PPI use Nonfatal MI OR (95% CI): 0.95 (0.38-2.41)
Van Boxel, 2010[71]	Observational Total N: 18,139 Clopidogrel dose Fair	PPI type	Composite outcome (total mortality, nonfatal MI, stroke) Omeprazole HR (95% CI): 1.622 (1.379-1.907) Pantoprazole HR (95% CI): 1.827 (1.606-2.079) Esomeprazole HR (95% CI): 1.833 (1.518-2.214) Rabeprazole HR (95% CI): 1.758 (1.073-2.881)
Yusuf, 2001[72] CURE Study	RCT Total N: 12,562 Clopidogrel vs. placebo Good	Diabetes	Diabetes (N=2840) Composite outcome (CV death, nonfatal MI or stroke at 9 months) Clopidogrel: 14.2% Placebo: 16.7%
		Age	Age ≤65 yrs (N=6354) Composite outcome (CV death, nonfatal MI or stroke at 9 months) Clopidogrel: 5.4% Placebo: 7.6%
			Age >65 yrs (N=6208) Composite outcome (CV death, nonfatal MI or stroke at 9 months) Clopidogrel: 13.3% Placebo: 15.3%
		Sex	Male (N=7726) Composite outcome (CV death, nonfatal MI or stroke at 9 months) Clopidogrel: 9.1% Placebo: 11.9%

Study	Study Details	Subgroup	Results Reported by Authors
			Female (N=4836) Composite outcome (CV death, nonfatal MI or stroke at 9 months) Clopidogrel: 9.5% Placebo: 10.7%
		NSTEMI	Associated MI (NSTEMI patients) (N=3283) Composite outcome (CV death, nonfatal MI or stroke at 9 months) Clopidogrel: 11.3% Placebo: 13.7%
			No associated MI (UA patients) (N=9279) Composite outcome (CV death, nonfatal MI or stroke at 9 months) Clopidogrel: 8.6 Placebo: 10.6%
		Revascularization	Revascularization after randomization (N=4577) Composite outcome (CV death, nonfatal MI or stroke at 9 months) Clopidogrel: 11.5% Placebo: 13.9%
			No revascularization after randomization (N=7985) Composite outcome (CV death, nonfatal MI or stroke at 9 months) Clopidogrel: 8.1% Placebo: 10%
		Chronic kidney disease	Creatinine clearance <64 mL/min (N=4087) Composite outcome (CV death, nonfatal MI or stroke at 9 months) Clopidogrel: 13.4% Placebo: 14.9% RR (95%CI): 0.89 (0.76-1.05) CV mortality Clopidogrel: 8.3% Placebo: 8.7% RR (95%CI): 0.95 (0.77-1.17) Total mortality Clopidogrel: 9.6% Placebo: 10% RR (95%CI): 0.95(0.78-1.16) Major bleeding Clopidogrel: 2.3% Placebo: 1.7% RR (95%CI): 1.37 (0.89-2.12) Minor bleeding Clopidogrel: 5.2% Placebo: 2.4% RR (95%CI): 1.5(1.21-1.86)
		PCI	Patients undergoing PCI Composite outcome (CV death or nonfatal MI) Clopidogrel (N= 1313): 79 Placebo (N=1345): 108 RR (95%CI): 0.75(0.56-1.00) p=0.047 Major bleeding Clopidogrel (N= 1313): 36 Placebo (N=1345): 32 RR (95%CI): 1.12(0.7-1.78) P=0.64 Minor bleeding Clopidogrel (N= 1313): 46 Placebo (N=1345): 28 RR (95%CI): 1.68(1.06-2.68) p=0.03

Study	Study Details	Subgroup	Results Reported by Authors
			Patients undergoing PCI who received a stent (N= 2172) Composite outcome (CV death or nonfatal MI) Clopidogrel: 8.7% Placebo: 11.7% RR (95%CI): 0.73(0.56-0.95)
		Aspirin dose	Aspirin dose ≤100 mg/d (N=5320) Composite outcome (CV death, nonfatal MI or stroke) RR (95%CI): 0.81 (0.68-0.97) in favor of clopidogrel Major bleeding Clopidogrel: 3% Placebo: 1.9%
			Aspirin dose 101-199 mg/d (N=3109) Composite outcome (CV death, nonfatal MI or stroke) RR (95%CI): 0.97 (0.77-1.22) in favor of clopidogrel Major bleeding Clopidogrel: 3.4% Placebo: 2.8%
			Aspirin dose ≥200 mg/d (N=4110) Composite outcome (CV death, nonfatal MI or stroke) RR (95%CI): 0.71 (0.59-0.85) in favor of clopidogrel Major bleeding Clopidogrel: 4.9% Placebo: 3.7%
Zeymer, 2008[73] ACOS Registry	Observational Total N: 4,290 ASA + clopidogrel vs. ASA Poor	PCI use	PCI Total mortality ASA vs. ASA + clopidogrel OR (95% CI): 0.51 (0.33-0.77) Composite outcome (death, MI, stroke) ASA vs. ASA + clopidogrel OR (95% CI): 0.55 (0.40-0.75)
			No PCI Total mortality ASA vs. ASA + clopidogrel OR (95% CI): OR 0.90 (0.73-1.11)

Abbreviations: ASA=aspirin; BMS=bare metal stent; c/w=cases with; CAD=coronary artery disease; CI=confidence interval; CKD=chronic kidney disease; clop=Clopidogrel; CV=cardiovascular; d=day/days; DAP=dual antiplatelet; DAPT=dual antiplatelet therapy; DES=drug-eluting stent; Eso=esomeprazole; HR=hazard ratio; IRR=incidence rate ratio; MACE=major adverse cardiac event; mg=milligram/milligrams; MI=myocardial infarction; min=minute/minutes; mL=milliliter/milliliters; N=number of patients; NACE=net adverse clinical events; NSTEMI=non-ST elevation myocardial infarction; OAC=oral anticoagulation; omep=omeprazole; OR=odds ratio; panto=pantoprazole; PPI=proton pump inhibitor; RCT=randomized controlled trial; RR=relative risk; RRR=relative risk reduction; STEMI=ST elevation myocardial infarction; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; vs=versus; yr=year/years

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Appendix I. Sensitivity Analyses

Key Question 2: Initial Conservative Approach for UA/NSTEMI

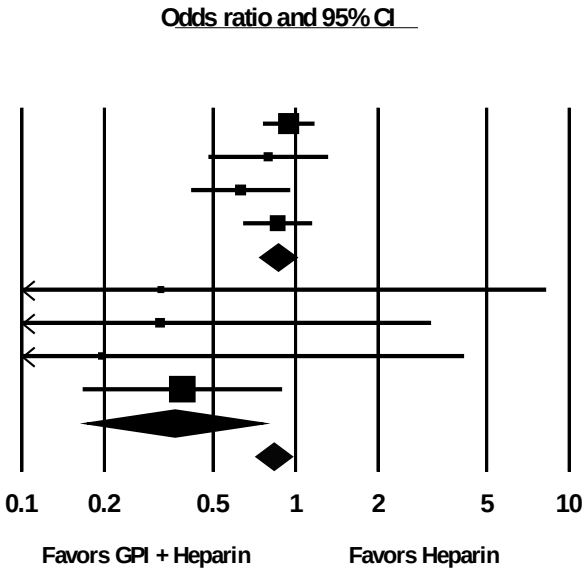
In an effort to explain between-study variations in the use of a glycoprotein IIb/IIIa inhibitor (GPI) plus unfractionated heparin versus heparin alone, we performed sensitivity analyses on features we suspected might account for the variations and that had suitable distributions among the studies. This appendix contains the forest plots of the sensitivity analyses we performed.

Sensitivity was evaluated by study size (<1000 vs. ≥1000 patients) and by aspirin-only use. Outcomes (up to 30 days) included mortality, nonfatal myocardial infarction (MI), recurrent ischemia, and minor bleeding.

Figure I-1 shows the forest plot of the sensitivity analysis by study size for mortality up to 30 days. The 4 larger studies gave an estimated odds ratio of 0.86 (95% CI, 0.74 to 1.00), favoring GPI plus heparin. The 4 smaller studies gave an estimated odds ratio of 0.36 (95% CI, 0.17 to 0.76), also favoring GPI plus heparin.

Figure I-1. Meta-analysis of glycoprotein inhibitors vs. unfractionated heparin on mortality up to 30 days by study size

Group by Size	Study name	Statistics for each study					Events / Total	
		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	GPI + heparin	Heparin
Large	Harrington, 1998	0.94	0.76	1.17	-0.52	0.60	165 / 4722	175 / 4739
Large	Theroux, 1998	0.79	0.48	1.32	-0.89	0.37	28 / 773	36 / 797
Large	White, 1998	0.63	0.42	0.96	-2.17	0.03	37 / 1616	58 / 1616
Large	Simoons, 2001	0.86	0.64	1.15	-1.01	0.31	88 / 2590	102 / 2598
Large		0.86	0.74	1.00	-1.96	0.05		
Small	Van den Brand, 1995	0.32	0.01	8.24	-0.68	0.49	0 / 30	1 / 30
Small	Song, 2007	0.32	0.03	3.13	-0.98	0.33	1 / 101	3 / 99
Small	Momtahen, 2009	0.20	0.01	4.13	-1.05	0.29	0 / 98	2 / 98
Small	Bhattacharya, 2010	0.39	0.17	0.89	-2.22	0.03	8 / 136	23 / 165
Small		0.36	0.17	0.76	-2.70	0.01		
Overall		0.83	0.71	0.96	-2.47	0.01		

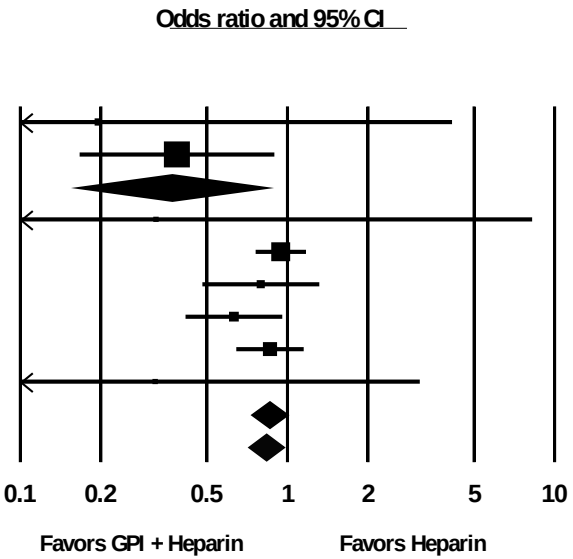


Abbreviations: CI=confidence interval; GPI=glycoprotein inhibitor

Figure I-2 shows the forest plot of the sensitivity analysis by aspirin-only use for mortality up to 30 days. The 6 aspirin-only studies gave an estimated odds ratio of 0.85 (95% CI, 0.73 to 0.99), favoring GPI plus heparin. The other 2 studies gave an estimated odds ratio of 0.37 (95% CI, 0.16 to 0.83), also favoring GPI plus heparin.

Figure I-2. Meta-analysis of glycoprotein inhibitors vs. unfractionated heparin on mortality up to 30 days by aspirin-only use

Group by ASA Only	Study name	Statistics for each study					Events / Total	
		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	GPI + heparin	Heparin
No	Momtahen, 2009	0.20	0.01	4.13	-1.05	0.29	0 / 98	2 / 98
No	Bhattacharya, 2010	0.39	0.17	0.89	-2.22	0.03	8 / 136	23 / 165
No		0.37	0.16	0.83	-2.42	0.02		
Yes	Van den Brand, 1995	0.32	0.01	8.24	-0.68	0.49	0 / 30	1 / 30
Yes	Harrington, 1998	0.94	0.76	1.17	-0.52	0.60	165 / 4722	175 / 4739
Yes	Theroux, 1998	0.79	0.48	1.32	-0.89	0.37	28 / 773	36 / 797
Yes	White, 1998	0.63	0.42	0.96	-2.17	0.03	37 / 1616	58 / 1616
Yes	Simoons, 2001	0.86	0.64	1.15	-1.01	0.31	88 / 2590	102 / 2598
Yes	Song, 2007	0.32	0.03	3.13	-0.98	0.33	1 / 101	3 / 99
Yes		0.85	0.73	0.99	-2.05	0.04		
Overall		0.83	0.71	0.96	-2.47	0.01		

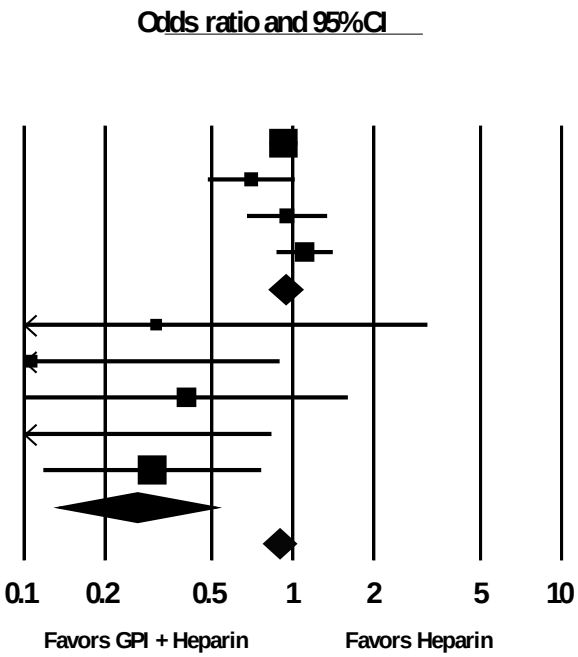


Abbreviations: CI=confidence interval; GPI=glycoprotein inhibitor

Figure I-3 shows the forest plot of the sensitivity analysis by study size for nonfatal MI up to 30 days. The summary estimate was significant from pooling the 5 smaller studies (OR 0.26; 95% CI, 0.13 to 0.52; $p<0.001$), favoring GPI plus heparin; it was nonsignificant from pooling the 4 larger studies (OR 0.94; 95% CI, 0.81 to 1.08; $p=0.36$).

Figure I-3. Meta-analysis of glycoprotein inhibitors vs. unfractionated heparin on nonfatal MI up to 30 days by study size

Group by Size	Study name	Statistics for each study				Events / Total	
		Odds ratio	Lower limit	Upper limit	p-Value	GPI + heparin	Heparin
Large	Harrington, 1998	0.92	0.82	1.04	0.19	595 / 4722	640 / 4739
Large	Theroux, 1998	0.70	0.48	1.02	0.06	51 / 773	73 / 797
Large	White, 1998	0.95	0.67	1.34	0.78	66 / 1616	69 / 1616
Large	Simoons, 2001	1.11	0.87	1.41	0.41	146 / 2590	133 / 2598
Large		0.94	0.81	1.08	0.36		
Small	Van den Brand, 1995	0.31	0.03	3.17	0.32	1 / 30	3 / 30
Small	Omken, 2003	0.11	0.01	0.89	0.04	1 / 41	8 / 42
Small	Song, 2007	0.40	0.10	1.60	0.20	3 / 101	7 / 99
Small	Momtahen, 2009	0.05	0.00	0.83	0.04	0 / 98	9 / 98
Small	Bhattacharya, 2010	0.30	0.12	0.76	0.01	6 / 136	22 / 165
Small		0.26	0.13	0.52	0.00		
Overall		0.89	0.77	1.02	0.09		

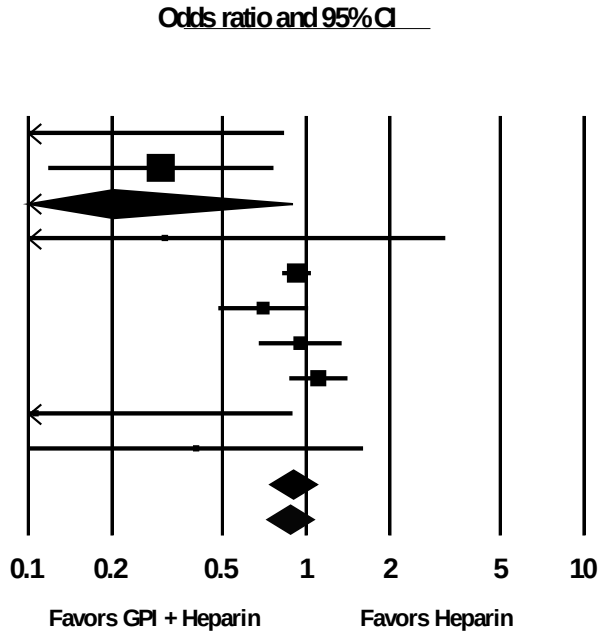


Abbreviations: CI=confidence interval; GPI=glycoprotein inhibitor

Figure I-4 shows the forest plot of the sensitivity analysis by aspirin-only use for nonfatal myocardial infarction up to 30 days. The 7 aspirin-only studies gave an estimated odds ratio of 0.89 (95% CI 0.74 to 1.08), favoring GPI plus heparin. The other 2 studies gave an estimated odds ratio of 0.20 (95% CI 0.05 to 0.89), also favoring GPI plus heparin.

Figure I-4. Meta-analysis of glycoprotein inhibitors vs. unfractionated heparin on nonfatal myocardial infarction up to 30 days by aspirin-only use

Group by ASA only	Study name	Statistics for each study				Events / Total	
		Odds ratio	Lower limit	Upper limit	p-Value	GPI + heparin	Heparin
No	Momtahen, 2009	0.05	0.00	0.83	0.04	0 / 98	9 / 98
No	Bhattacharya, 2010	0.30	0.12	0.76	0.01	6 / 136	22 / 165
No		0.20	0.05	0.89	0.03		
Yes	Van den Brand, 1995	0.31	0.03	3.17	0.32	1 / 30	3 / 30
Yes	Harrington, 1998	0.92	0.82	1.04	0.19	595 / 4722	640 / 4739
Yes	Theroux, 1998	0.70	0.48	1.02	0.06	51 / 773	73 / 797
Yes	White, 1998	0.95	0.67	1.34	0.78	66 / 1616	69 / 1616
Yes	Simoons, 2001	1.11	0.87	1.41	0.41	146 / 2590	133 / 2598
Yes	Omlen, 2003	0.11	0.01	0.89	0.04	1 / 41	8 / 42
Yes	Song, 2007	0.40	0.10	1.60	0.20	3 / 101	7 / 99
Yes		0.89	0.74	1.08	0.25		
Overall		0.87	0.72	1.05	0.16		

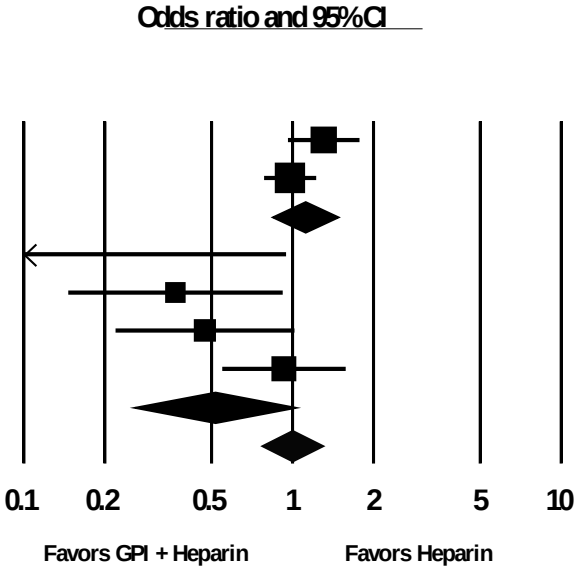


Abbreviations: CI=confidence interval; GPI=glycoprotein inhibitor

Figure I-5 shows the forest plot of the sensitivity analysis by study size for recurrent ischemia up to 30 days. The 2 larger studies gave an estimated odds ratio of 1.11 (95% CI, 0.84 to 1.47), favoring heparin alone. The 4 smaller studies gave an estimated odds ratio of 0.51 (95% CI, 0.26 to 1.02), favoring GPI plus heparin.

Figure I-5. Meta-analysis of glycoprotein inhibitors vs. unfractionated heparin on recurrent ischemia up to 30 days by study size

Group by Size	Study name	Statistics for each study				Events / Total	
		Odds ratio	Lower limit	Upper limit	p-Value	GPI + heparin	Heparin
Large	Theroux, 1998	1.31	0.96	1.78	0.09	107 / 797	82 / 773
Large	White, 1998	0.98	0.78	1.22	0.85	171 / 1616	175 / 1616
Large		1.11	0.84	1.47	0.47		
Small	Van den Brand, 1995	0.05	0.00	0.95	0.05	0 / 30	7 / 30
Small	Omken, 2003	0.37	0.15	0.92	0.03	11 / 41	21 / 42
Small	Song, 2007	0.47	0.22	1.02	0.05	12 / 101	22 / 99
Small	Bhattacharya, 2010	0.93	0.55	1.58	0.78	39 / 165	34 / 136
Small		0.51	0.26	1.02	0.06		
Overall		0.99	0.77	1.29	0.96		

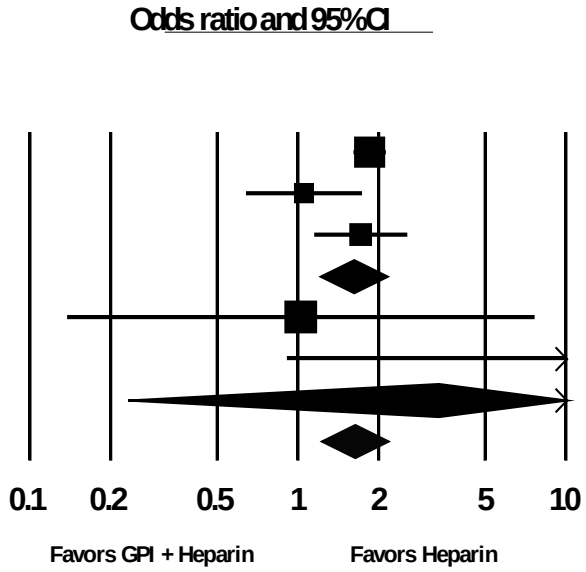


Abbreviations: CI=confidence interval; GPI=glycoprotein inhibitor

Figure I-6 shows the forest plot of the sensitivity analysis by study size for minor bleeding up to 30 days. The 3 larger studies gave an estimated odds ratio of 1.61 (95% CI, 1.20 to 2.15), favoring heparin alone. The 2 smaller studies gave an estimated odds ratio of 3.33 (95% CI, 0.23 to 48.23), also favoring heparin alone.

Figure I-6. Meta-analysis of glycoprotein inhibitors vs. unfractionated heparin on minor bleeding up to 30 days by study size

Group by Size	Study name	Statistics for each study				Events / Total	
		Odds ratio	Lower limit	Upper limit	p-Value	GPI + heparin	Heparin
Large	Harrington, 1998	1.85	1.61	2.13	0.00	604 / 4679	348 / 4696
Large	White, 1998	1.05	0.64	1.74	0.84	32 / 1616	31 / 1616
Large	Simoons, 2001	1.72	1.15	2.56	0.01	66 / 2590	39 / 2598
Large		1.61	1.20	2.15	0.00		
Small	Omken, 2003	1.03	0.14	7.65	0.98	2 / 41	2 / 42
Small	Momtahen, 2009	16.15	0.91	286.74	0.06	7 / 98	0 / 98
Small		3.33	0.23	48.23	0.38		
Overall		1.62	1.22	2.16	0.00		



Abbreviations: CI=confidence interval; GPI=glycoprotein inhibitor

Appendix J. Unadjusted, Adjusted, and Propensity-Scored Results for Studies of Proton Pump Inhibitors

Table J-1. Unadjusted, adjusted, and propensity-scored results for PPI versus no PPI from Key Question 3

Study Population (N/%) Quality	PPI Used	Primary Outcomes/Timing	PPI vs. No PPI Unadjusted Results	Adjusted HR/OR/RR (95% CI)	Propensity Score Matching HR/OR (95% CI)
Banerjee, 2011[1] Total N: 23,200 ACS: 89% Good	Esomeprazole, omeprazole, pantoprazole, rabeprazole, lansoprazole	<u>Composite1 yr</u> Total mortality, nonfatal MI, revascularization Total mortality, nonfatal MI <u>Composite 6 yr</u> Total mortality, nonfatal MI, revascularization Total mortality, nonfatal MI <u>Individual 1 yr</u> Total mortality Revascularization <u>Individual 6 yr</u> Total mortality Revascularization	 HR 1.18 (1.05 to 1.31) HR 1.26 (1.07 to 1.48) HR 1.23 (1.10 to 1.37) HR 1.31 (1.12 to 1.53) HR 1.37 (1.03-1.82) HR 1.11 (0.95 to 1.29) HR 1.48 (1.13 to 1.19) HR 1.16 (1.00 to 1.35)	 HR 1.19 (1.06 to 1.33) HR 1.20 (1.02 to 1.41) HR 1.24 (1.11 to 1.38) HR 1.26 (1.08 to 1.48) HR 1.16 (0.87 to 1.55) HR 1.18 (1.01 to 1.30) HR 1.32 (1.00 to 1.73) HR 1.22 (1.05 to 1.42)	 OR 0.92 (0.58 to 1.45) OR 1.49 (0.92 to 2.42) OR 0.97 (0.65 to 1.44) OR 1.46 (0.94 to 2.66) OR 1.34 (0.68 to 2.66) OR 0.86 (0.47 to 1.6) OR 1.18 (0.64 to 2.16) OR 0.93 (0.55 to 1.59)
Barada, 2008[2] Total N: 1023 ACS: 100% Poor	Omeprazole, rabeprazole, other	<u>Individual in-hospital</u> GI bleeding	0.7% vs. 0.6%	NR	NR

Study Population (N/%) Quality	PPI Used	Primary Outcomes/Timing	PPI vs. No PPI Unadjusted Results	Adjusted HR/OR/RR (95% CI)	Propensity Score Matching HR/OR (95% CI)
Bhatt, 2010[3] COGENT Study Total N: 3761 ACS: 42% Good	Omeprazole	<u>Composite 6 mo</u> Upper GI or gastroduodenal bleeding CV mortality, nonfatal MI, stroke, revascularization <u>Individual 6 mo</u> Nonfatal MI Revascularization Stroke Total mortality CV mortality Stent thrombosis	HR 0.13 (0.03 to 0.56) HR 0.99 (0.68 to 1.44) 1.2% vs. 1.5% 4.0% vs. 4.6% 0.2% vs. 0.3% 0.4% vs. 0.5% 0.4% vs. 0.3% N=2 vs. N=0	NR	NR
Bhurke, 2012[4] Total N: 10,101 ACS: 100% Fair	Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	<u>Composite 1 yr</u> Nonfatal MI, PCI, intermediate coronary syndrome	HR 1.30 (1.15 to 1.47)	HR 1.28 (1.12 to 1.46)	HR 1.44 (1.24 to 1.67)
Charlot, 2010[5] Total N: 56,406 Population NR Good	Pantoprazole, omeprazole, lansoprazole, esomeprazole	<u>Composite 1 yr</u> CV mortality, nonfatal MI, stroke, revascularization <u>Individual 1 yr</u> Total mortality CV mortality Nonfatal MI Stroke	15.7% vs. 18.4% 7.0% vs. 3.4% 5.5% vs. 2.9% 10.4% vs. 5.5% 4.4% vs. 3.0%	HR 1.29 (1.17 to 1.42) HR 1.75 (1.53 to 1.99) HR 1.57 (1.36 to 1.82) HR 1.19 (1.05 to 1.35) HR 1.43 (1.19 to 1.71)	HR 1.35, 1.22 to 1.50 HR 2.09 (1.82 to 2.41) HR 1.91 (1.63 to 2.24) HR 1.18 (1.04 to 1.35) HR 1.78 (1.47 to 2.16)
Charlot, 2011[6] Total N: 19,925 ACS: 100% Fair	Pantoprazole, omeprazole, lansoprazole, esomeprazole	<u>Composite 1 yr</u> CV mortality, nonfatal MI, stroke <u>Individual 1 yr</u> Total mortality CV mortality Nonfatal MI Stroke	N= 2378 vs 987 N=1607 vs. 686 N= 1328 vs. 540 N=1110 vs. 497 N=1207 vs. 338	HR 1.46 (1.33 to 1.61) HR 1.78 (1.60 to 1.98) HR 1.71 (1.51 to 1.92) HR 1.39 (1.20 to 1.62) HR 1.23 (1.03 to 1.47)	HR 1.61 (1.45 to 1.79) HR 2.38 (2.12 to 2.67) HR 2.19 (1.92 to 2.49) HR 1.33 (1.13 to 1.56) HR 1.2 (0.99 to 1.46)

Study Population (N/%) Quality	PPI Used	Primary Outcomes/Timing	PPI vs. No PPI Unadjusted Results	Adjusted HR/OR/RR (95% CI)	Propensity Score Matching HR/OR (95% CI)
Chitose, 2011[7] KICS Study Total N: 1270 ACS: 49% Good	Rabeprazole, omeprazole, lansoprazole	<u>Composite 18 mo</u> CV mortality, nonfatal MI, stroke <u>Individual 18 mo</u> CV mortality Nonfatal MI Stroke GI event	NR N=2 vs. 7 N=2 vs. 1 N=2 vs. 9 N=1 vs. 7	HR 1.09 (0.41 to 2.87) NR NR NR HR 0.39 (0.04 to 3.26)	NR
Evanchan, 2010[8] Total N: 5794 Population NR Good	Esomeprazole, lansoprazole, omeprazole, pantoprazole	<u>Individual 1 yr</u> Nonfatal MI	NR	OR 1.78 (1.55 to 2.07)	NR
Gao, 2009[9] Total N: 237 Population NR Poor	Omeprazole	<u>Individual 7 days</u> Total mortality Upper GI bleeding	3.5% vs 10.6% 5.3% vs 14.6%	NR	NR
Gaspar, 2010[10] Total N: 876 UA/NSTEMI: 65% STEMI: 35% Good	Omeprazole, lansoprazole, rabeprazole	<u>Composite 6 mo</u> Total mortality, nonfatal MI, UA <u>Individual outcome 6 mo</u> Total mortality	12.9% vs. 9.2% 6.5% vs. 3.9%	OR 1.1 (0.64 to 1.9) OR 1.04 (0.49 to 2.18)	NR

Study Population (N/%) Quality	PPI Used	Primary Outcomes/Timing	PPI vs. No PPI Unadjusted Results	Adjusted HR/OR/RR (95% CI)	Propensity Score Matching HR/OR (95% CI)
Goodman, 2012[11] PLATO Total N: 18,568 UA: 17% NSTEMI: 43% STEMI: 38% Good	Omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole.	*Clopidogrel* <u>Composite 1 yr</u> CV mortality, nonfatal MI, stroke Total mortality, nonfatal MI <u>Individual 1 yr</u> Total mortality CV mortality Nonfatal MI Major bleeding Stent thrombosis *Ticagrelor* <u>Composite 1 yr</u> CV mortality, nonfatal MI, stroke Total mortality, nonfatal MI <u>Individual 1 yr</u> Total mortality CV mortality Nonfatal MI Major bleeding Stent thrombosis	 HR 1.22 (1.08 to 1.39) HR 1.27 (1.11 to 1.45) HR 1.38 (1.16 to 1.65) HR 1.31 (1.08 to 1.58) HR 1.17 (0.96 to 1.42) HR 1.22 (1.07 to 1.39) HR 1.30 (0.89 to 1.91) HR 1.23 (1.07 to 1.41) HR 1.24 (1.08 to 1.44) HR 1.08 (0.88 to 1.33) HR 1.03 (0.83 to 1.28) HR 1.25 (1.01 to 1.55) HR 1.11 (0.97 to 1.26) HR 1.16 (0.73 to 1.86)	 HR 1.20 (1.04 to 1.38) HR 1.25 (1.08 to 1.45) HR 1.5 (1.22 to 1.83) HR 1.42 (1.14 to 1.76) HR 1.12 (0.9 to 1.4) HR 1.3 (0.99 to 1.7) HR 1.19 (0.74 to 1.90) HR 1.24 (1.07 to 1.45) HR 1.26 (1.07 to 1.48) HR 1.10 (0.88 to 1.39) HR 1.13 (0.88 to 1.44) HR 1.14 (0.89 to 1.45) HR 1.02 (0.8 to 1.29) HR 1.17 (0.69 to 1.99)	 NR
Gupta, 2010[12] Total N: 315 Population NR Fair	Rabeprazole, omeprazole, lansoprazole	<u>Composite 4 yr</u> Total mortality, nonfatal MI, target vessel failure <u>Individual 4 yr</u> Total mortality Revascularization Target vessel failure	 N=40 vs. 92 N=35 vs. 14 N=53 vs. 21 N=70 vs. 30	 OR 1.95 (1.09 to 3.49) OR 1.20 (0.53 to 2.70) OR 1.57 (0.8 to 3.03) OR 1.51 (0.82 to 2.77)	 NR

Study Population (N/%) Quality	PPI Used	Primary Outcomes/Timing	PPI vs. No PPI Unadjusted Results	Adjusted HR/OR/RR (95% CI)	Propensity Score Matching HR/OR (95% CI)
Harjai, 2011[13] Total N: 2651 NSTEMI or STEMI: 39% Good	PPI not specified	<u>Composite 6 mo</u> Total mortality, nonfatal MI, revascularization, stent thrombosis Total mortality. nonfatal MI <u>Individual 6 mo</u> Total mortality Nonfatal MI Revascularization Stent thrombosis Major bleeding	6.4% vs. 6.4% 5.6% vs. 5.1% 2.8% vs. 2.5% 3.2% vs. 3.0% 2.1% vs. 2.9% 1.7% vs. 1.5% 1.1% vs. 1.5%	NR	HR 0.89 (0.63 to 1.27) HR 0.99 (0.68 to 1.44) HR 0.95 (0.56 to 1.63) HR 1.04 (0.64 to 1.69) HR 0.74 (0.42 to 1.29) HR 1.32 (0.67 to 2.58) HR 0.67 (0.31 to 1.47)
	Omeprazole or esomeprazole only	<u>Composite 6 mo</u> Total mortality, nonfatal MI, revascularization, stent thrombosis Total mortality, nonfatal MI <u>Individual 6 mo</u> Total mortality Nonfatal MI Revascularization Stent thrombosis Major bleeding	3.9% vs. 6.4% 3.2% vs. 5.1% 1.6% vs. 2.5% 2.2% vs. 3.0% 1.0% vs. 3.0% 1.0% vs. 1.5% 1.0% vs. 1.5%		HR 0.51 (0.28 to 0.92) HR 0.52 (0.26 to 1.03) HR 0.49 (0.17 to 1.37) HR 0.65 (0.29 to 1.43) HR 0.32 (0.10 to 1.03) HR 0.59 (0.18 to 1.97) HR 0.59 (0.18 to 1.94)
Ho, 2009[14] Total N: 8205 ACS: 100% Nested case-control analysis Good	Omeprazole, rabeprazole, lansoprazole, pantoprazole	<u>Composite 1.5 yr</u> Total mortality, rehospitalization for ACS <u>Individual 1.5 yr</u> Rehospitalization for ACS Revascularization Total mortality	OR 1.62 (1.45 to 1.80) OR 2.29 (1.95 to 2.69) OR 1.36 (1.19 to 1.55) OR 1.24 (1.10 to 1.40)	OR 1.25 (1.11 to 1.41) OR 1.86 (1.57 to 2.2) OR 1.49 (1.30 to 1.71) OR 0.91 (0.80 to 1.05)	OR 1.32 (1.14 to 1.54) NR NR NR

Study Population (N/%) Quality	PPI Used	Primary Outcomes/Timing	PPI vs. No PPI Unadjusted Results	Adjusted HR/OR/RR (95% CI)	Propensity Score Matching HR/OR (95% CI)
Hsiao, 2011[15] Total N: 9753 ACS: 100% Good	Omeprazole, pantoprazole, rabeprazole, esomeprazole, lansoprazole	<u>Individual 6 mo</u> Rehospitalization	HR 1.26(0.82 to 1.94)	HR 1.12 (0.72 to 1.73)	HR 0.82 (0.43 to 1.54)
Juurlink, 2009[16] Total N: 2791 Population NR Nested case-control analysis Good	Pantoprazole, omeprazole, lansoprazole, rabeprazole	<u>Individual 3 mo</u> Nonfatal MI Total mortality <u>Individual 1 yr</u> Nonfatal MI Total mortality	 N=194 vs. 424 N=71 vs. 188 N=240 vs. 497 N=116 vs. 269	 OR 1.27 (1.03 to 1.57) OR 0.82 (0.57 to 1.18) OR 1.23 (1.01 to 1.49) OR 0.89 (0.67 to 1.18)	NR
Kreutz, 2010[17] Total N: 16,690 Population NR Good	PPI not specified	<u>Composite 1 yr</u> CV mortality, nonfatal MI, stroke, rehospitalization Nonfatal MI, UA <u>Individual 1 yr</u> Stroke Nonfatal MI UA Revascularization CV mortality	 HR 1.45 (1.36 to 1.55) HR 1.71 (1.57 to 1.86) HR 1.86 (1.456 to 2.39) HR 1.46 (1.29 to 1.66) HR 1.93 (1.74 to 2.14) HR 1.24 (1.14 to 1.34) HR 1.31 (0.70 to 2.43)	 HR 1.51 (1.39 to 1.64) HR 1.70 (1.53 to 1.89) HR 1.48 (1.08 to 2.01) HR 1.63 (1.40 to 1.90) HR 1.86 (1.64 to2.11) HR 1.35 (1.22 to 1.50) HR 1.10 (0.51 to 2.40)	NR
Ng, 2008[18] Total N: 666 UA: 56% Good	Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole	<u>Individual 7 days</u> GI bleeding GI bleeding/occult blood	 N=2 vs. 14 N= 9 vs. 24	 OR 0.07 (0.010 to 0.27) OR 0.23 (0.09 to 0.49)	NR

Study Population (N/%) Quality	PPI Used	Primary Outcomes/Timing	PPI vs. No PPI Unadjusted Results	Adjusted HR/OR/RR (95% CI)	Propensity Score Matching HR/OR (95% CI)
Ng, 2011[19] Total N: 311 UA: 36.7% NSTEMI: 44.7% STEMI: 18.6% Good	Esomeprazole	Composite 1 yr Upper GI bleeding, gastric-outlet obstruction, gastric or duodenal perforation CV mortality, nonfatal MI, stroke	HR 0.095 (0.005 to 0.504) 4.3% vs 3.4%	NR	NR
O'Donoghue, 2009[20] Total N:13,608 Only ACS population used for outcomes (PPI N=4529 vs. no PPI N=9079) Good	Omeprazole, pantoprazole, esomeprazole, lansoprazole	Composite 6 mo CV mortality, nonfatal MI, stroke Individual 6 mo All-cause mortality CV mortality MI Stent thrombosis TIMI major bleeding	11.8% vs 12.2% 2.9% vs 3.3% 2.2% vs 2.5% 9.5% vs 9.8% 2.4% vs 2.3% 2.4% vs 1.6%	NR	HR 0.94 (0.80 to 1.11) HR 0.68 (0.47 to 0.96) HR 0.71 (0.47 to 1.07) HR 0.98 (0.82 to 1.17) HR 1.08 (0.75 to 1.55) HR 1.20 (0.80 to 1.79)
Ortolani, 2011[21] Total N: 3896 UA: 29% NSTEMI: 35% STEMI: 35% Good	Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole	Composite 1 yr Total mortality, revascularization, rehospitalization Individual 1 yr Rehospitalization Revascularization Total mortality	HR 2.01 (1.51 to 2.68) HR 4.61 (2.66 to 7.99) HR 2.28 (1.56 to 3.34) HR 1.27 (0.76 to 2.11)	HR 1.83 (1.38 to 2.45) HR 3.99 (2.29 to 6.93) HR 2.38 (1.63 to 3.48) HR 0.69 (0.40 to 1.16)	NR
Rassen, 2009[22] Total N: 18,565 ACS: % unknown Good	Omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole	Composite 6 mo Total mortality, nonfatal MI Individual 6 mo Nonfatal MI Total mortality Revascularization	RR: 1.74 (1.44 to 2.10) RR 1.76 (1.4 to 2.22) RR 1.69 (1.23 to 2.31) RR 1.03 (0.85 to 1.26)	RR 1.22 (0.99 to 1.51) RR 1.22 (0.95 to 1.57) RR 1.20 (0.84 to 1.70) RR 0.97 (0.79 to 1.21)	RR 1.26 (0.97 to 1.63) RR 1.22 (0.89 to 1.68) RR 1.36 (0.89 to 2.07) RR 0.91 (0.7 to 1.16)

Study Population (N/%) Quality	PPI Used	Primary Outcomes/Timing	PPI vs. No PPI Unadjusted Results	Adjusted HR/OR/RR (95% CI)	Propensity Score Matching HR/OR (95% CI)
Ray, 2010[23] Total N: 20,596 Population NR Good	Esomeprazole, omeprazole, pantoprazole, rabeprazole, lansoprazole	<u>Composite 1 yr</u> CV mortality, nonfatal MI, stroke, sudden cardiac death Nonfatal MI, sudden cardiac death <u>Individual 1 yr</u> CV mortality Stroke Gastroduodenal bleeding Other bleeding	 N=461 vs. 580 N= 292 vs, 403 N= 64 vs. 80 N= 105 vs. 97 N= 63 vs. 117 N= 117 vs. 108	 HR 0.99, 0.82 to 1.19 HR 0.91, 0.75 to 1.09 HR 1.06 (0.65 to 1.74) HR 1.21 (0.82 to 1.78) HR 0.50 (0.39 to 0.65) HR 1.07 (0.74 to 1.53)	NR
Ren, 2011[24] Total N: 172 ACS: 100% Poor	Omeprazole	<u>Individual 30 days</u> Chest pressure Occasional angina Transient ischemic attack Upper GI bleeding	 N=3 vs. 2 N=17 vs. 19 N=2 vs. 1 N=0 vs. 2	NR	NR
Rossini, 2011[25] Total N: 1328 UA: 18% NSTEMI: 22% STEMI: 29% Stable angina: 31% Good	Lansoprazole, pantoprazole, omeprazole	<u>Composite in-hospital</u> Total mortality, nonfatal MI, stroke, rehospitalization <u>Composite 1 yr</u> Total mortality, nonfatal MI, stroke, rehospitalization <u>Individual in-hospital</u> Major bleeding Minor bleeding <u>Individual 1 yr</u> Major bleeding Minor bleeding Total mortality Stent thrombosis	 RR 4.30 (0.58 to 31.88) RR 1.52 (0.72 to 3.22) RR 2.22 (0.29 to 16.90) RR 0.87 (0.36 to 2.11) RR 1.41 (0.50 to 4.00) RR 1.01 (0.49 to 2.08) RR 0.67 (0.25 to 1.81) RR 1.80 (0.42 to 7.70)	 RR 3.29 (0.44 to 24.73) RR 1.54 (0.60 to 4.02) RR 1.89 (0.25 to 14.5) RR 0.70 (0.29 to 1.70) RR 1.51 (0.40 to 5.03) RR 0.89 (0.41 to 1.92) RR 0.97 (0.28 to 3.31) RR 1.01 (0.23 to 4.47)	NR

Study Population (N/%) Quality	PPI Used	Primary Outcomes/Timing	PPI vs. No PPI Unadjusted Results	Adjusted HR/OR/RR (95% CI)	Propensity Score Matching HR/OR (95% CI)
Sarafoff, 2010[26] Total N: 3338 UA: 23% Stable angina: 66% Good	Pantoprazole, esomeprazole, omeprazole, lansoprazole, ransoprazole	<u>Composite 30 days</u> Total mortality, stent thrombosis <u>Individual 30 days</u> Stent thrombosis Total mortality Nonfatal MI Major bleeding	HR 2.7 (1.6 to 4.7) HR 2.3 (1.0 to 5.6) HR 3.0 (1.6 to 5.5) HR 1.5 (0.9 to 2.5) HR 4.0 (2.1 to 7.7)	HR 2.0 (1.1 to 3.7) HR 1.8 (0.7 to 4.7) HR 2.2 (1.1 to 4.3) HR 1.3 (0.8 to 2.3) HR 3.3 (1.7 to 6.7)	NR
Schmidt, 2012[27] Total N: 13,001 UA/NSTEMI: 31% STEMI: 29% Stable angina: 38% Poor	Esomeprazole, omeprazole, lansoprazole, pantoprazole, rabeprazole	<u>Composite 1 yr</u> Nonfatal MI, stroke, stent thrombosis, revascularization, CV mortality	HR 1.51 (1.26 to 1.81)	HR 1.40 (1.17 to 1.68)	NR
Simon, 2011[28] FAST-MI Study Total N: 2744 NSTEMI: % NR STEMI: % NR Good	Omeprazole, esomeprazole, lansoprazole, pantoprazole	<u>Composite 1 yr</u> Total mortality, nonfatal MI, stroke <u>Individual in-hospital</u> Total mortality Nonfatal MI Stroke Major bleeding <u>Individual 1 yr</u> Total mortality	N=125 vs. 100 N=32 vs. 49 N=13 vs. 24 N=11 vs. 7 N=16 vs. 23 N=77 vs. 94	OR 0.98 (0.90 to 1.08) OR 1.04 (0.61 to 1.77) OR 1.15 (0.57 to 2.32) OR 0.33 (0.12 to 0.92) OR 0.87 (0.44 to 1.74) OR 0.97 (0.87 to 1.08)	HR 1.24 (0.87 to 1.78) NR NR NR NR HR 1.15 (0.73 to 1.83)
Stockl, 2010[29] Total N: 7049 Population NR Good	Pantoprazole, rabeprazole, omeprazole, lansoprazole, esomeprazole	<u>Composite 1 yr</u> Nonfatal MI, revascularization <u>Individual 1 yr</u> Nonfatal MI	HR 1.64 (1.16 to 2.31) HR 1.94 (1.06 to 3.54)	HR 1.64 (1.16 to 2.32) HR 1.93 (1.05 to 3.54)	NR

Study Population (N/%) Quality	PPI Used	Primary Outcomes/Timing	PPI vs. No PPI Unadjusted Results	Adjusted HR/OR/RR (95% CI)	Propensity Score Matching HR/OR (95% CI)
Tentzeris, 2010[30] Total N: 1210 ACS: 45% Good	Pantoprazole, esomeprazole, omeprazole, lansoprazole, rabeprazole	<u>Composite 1 yr</u> Event-free survival from total mortality, rehospitalization for ACS, stent thrombosis <u>Individual 1 yr</u> Total mortality CV mortality Rehospitalization for ACS Stent thrombosis	HR 1.14 (0.59 to 2.21) HR 0.92 (0.42 to 1.99) HR 0.54 (0.21 to 1.38) HR 1.42 (0.36 to 5.70) HR 2.19 (0.44 to 10.9)	HR 1.08 (0.53 to 2.22) HR 0.78 (0.34 to 1.76) HR 0.56 (0.21 to 1.55) HR 1.27 (0.285 to 5.70) HR 2.56 (0.49 to 13.20)	NR
Tsai, 2011[31] Total N: 3580 ACS: 100% Good	Omeprazole, pantoprazole, rabeprazole, esomeprazole, lansoprazole	<u>Composite 1 yr</u> CV events: Coronary heart disease, nonfatal MI, peripheral vascular disease, stroke, transient ischemic attack GI events: GI hemorrhage, ulcer, bleeding, perforation	N=121 vs. 62 N=91 vs. 34	NR	NR
Valkhoff, 2011[32] Total N: 23,655 Population NR Nested case-control analysis Poor	Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	<u>Individual 1 yr</u> Nonfatal MI	N=4793 vs. 11,237	OR 1.62 (1.15 to 2.27)	OR 1.89 (1.37 to 2.63)
Van Boxel, 2010[33] Total N: 18,139 UA: 35% Fair	Omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole	<u>Composite 1 yr</u> Total mortality, nonfatal MI, stroke, UA <u>Individual 1 yr</u> Nonfatal MI UA Stroke Total mortality Peptic ulcer disease	HR 2.03 (1.84 to 2.24) HR 2.41 (1.77 to 3.28) HR 1.92 (1.70 to 2.18) HR 1.32 (0.91 to 1.89) HR 2.56 (2.08 to 3.16) HR 5.66 (1.80 to 17.84)	HR 1.75 (1.58 to 1.94) HR 1.93 (1.4 to 2.65) HR 1.79 (1.60 to 2.03) HR 1.13 (0.78 to 1.65) HR 1.79 (1.44 to 2.22) HR 4.76 (1.18 to 19.17)	NR

Study Population (N/%) Quality	PPI Used	Primary Outcomes/Timing	PPI vs. No PPI Unadjusted Results	Adjusted HR/OR/RR (95% CI)	Propensity Score Matching HR/OR (95% CI)
Wu, 2010[34] Total N: 5860 ACS: 100% Good	Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	<u>Composite 1 yr</u> Rehospitalization for ACS, or total mortality within 3 mo of rehospitalization <u>Individual 1 yr</u> Rehospitalization for ACS Revascularization Total mortality	33.2% vs. 11.6% 24.6% vs. 10.1% 11.4% vs. 4.0% 11.4% vs. 1.7%	HR 3.20 (2.56 to 4.01) NR NR NR	HR 3.07 (2.45 to 3.84) NR NR NR
Zairis, 2010[35] Total N: 588 STEMI: 37% Stable angina: 23% UA/NSTEMI: 40% Good	Omeprazole	<u>Composite 1 yr</u> CV mortality or nonfatal MI <u>Individual 1 yr</u> CV mortality Nonfatal MI Stent thrombosis Revascularization	10% vs. 9.7% 3.5% vs. 3.2% 6.5% vs. 6.5% 8.8% vs. 8.5% 9.4% vs. 8.9%	HR 1.1 (0.6 to 1.8) HR 1.1 (0.4 to 2.7) HR 1.0 (0.5 to 1.9) HR 1.1 (0.7 to 1.8) HR 1.0 (0.6 to 1.9)	NR

Abbreviations: ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; GI=gastrointestinal; HR=hazard ratio; MI=myocardial infarction; mo=month/months; N=number of patients; NR=not reported; NSTEMI=non-ST elevation myocardial infarction; OR=odds ratio; PCI=percutaneous coronary intervention; PPI=proton pump inhibitor; RR=relative risk; STEMI=ST elevation myocardial infarction; UA=unstable angina; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; vs=versus; yr=year/years

Unadjusted Results From Studies of Proton Pump Inhibitors

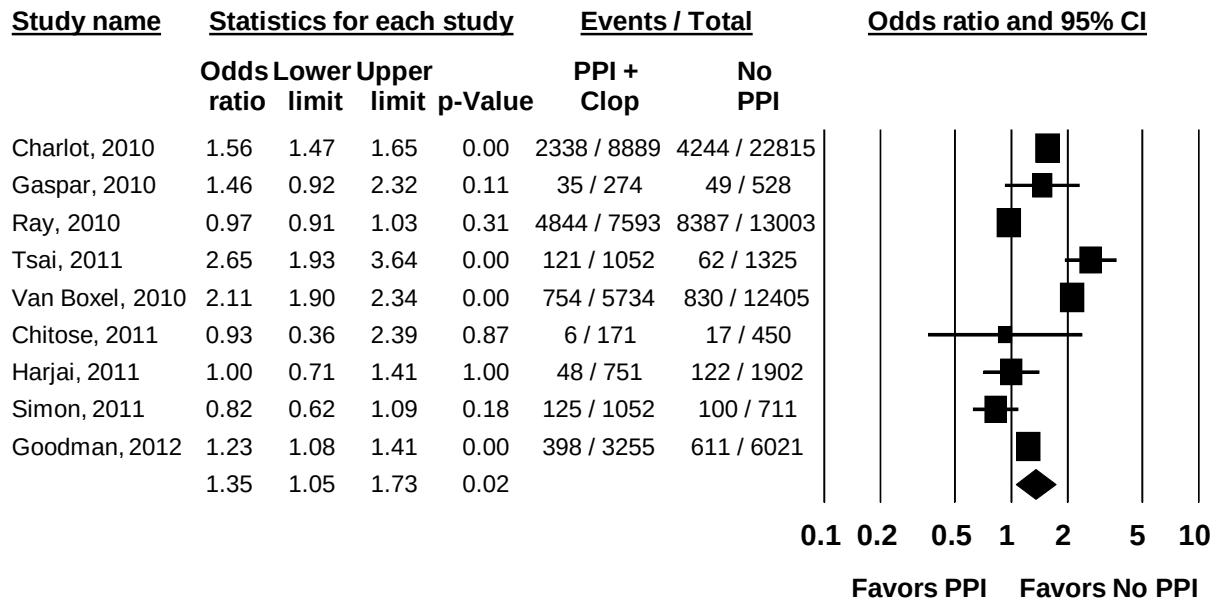
Effect on Composite Ischemic Endpoints Within 1 Year

Five observational studies (3 good quality, 1 fair, 1 poor; 29,403 patients) reported composite ischemic outcomes at 1 year.[4,25-27,34] One study[25] comparing the use of PPI versus no PPI found a nonsignificant difference in the rate of in-hospital composite outcomes (all-cause mortality, nonfatal MI, or stroke) between the two treatment arms (no PPI vs. PPI 0.6% vs. 2.5%; OR 3.29; 95% CI, 0.44-24.73, p=0.247). Another study[26] assessed the use of PPI versus no PPI and found a significant increase in the rate of composite outcomes (all-cause mortality or stent thrombosis) at 30 days among patients discharged with PPI treatment versus no PPI (PPI vs. no PPI 3.3% vs. 1.2%; adjusted OR 2.0; 95% CI, 1.1 to 3.7, p=0.02). Another study[34] evaluated the use of PPI versus no PPI found a significant increase in the rate of composite outcomes (all-cause mortality or rehospitalization for MI) at 3 months among patients discharged with PPI treatment versus without PPI (33.2% [PPI] vs.11.6% [no PPI]; adjusted HR 3.20; 95% CI, 2.56 to 4.01, p<0.0001). A study[4] evaluating the use of PPI versus no PPI found a significant increase in the rate of composite outcomes (rehospitalization for MI, percutaneous coronary intervention, or intermediate coronary syndrome) among patients discharged with PPI treatment versus without PPI treatment (PPI vs. no PPI HR 1.44; 95% CI, 1.24 to 1.68). Another study[27] evaluating the use of PPI versus no PPI, found a significantly higher rate of composite outcomes (cardiovascular mortality, MI, ischemic stroke, stent thrombosis, or target lesion revascularization) among patients concomitantly treated with clopidogrel (HR 1.40; 95% CI, 1.17 to 1.68) but not among those who did not receive clopidogrel (HR 1.16; 95% CI, 0.95 to 1.43). The strength of evidence was rated moderate for composite ischemic outcomes based on consistent but imprecise results from five observational studies.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal MI, or Stroke at 1 Year

A random-effects meta-analysis of 9 observational studies[5,7,10,11,13,23,28,31,33] (8 good quality, 1 fair) in 124,888 UA/NSTEMI patients reporting a composite outcome of all-cause mortality, nonfatal MI, or stroke between 6 and 18 months found an odds ratio of 1.35 (95% CI, 1.05 to 1.73), favoring no PPI use (Figure J-1). There was evidence of extreme heterogeneity, with a Q-value of 248.9 for 8 degrees of freedom, p<0.001. The strength of evidence was rated moderate for this composite outcome at 1 year based on good-quality studies and inconsistent findings of a direct outcome with a narrow confidence interval.

Figure J-1. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on composite of all-cause mortality, nonfatal myocardial infarction, or stroke at 1 year

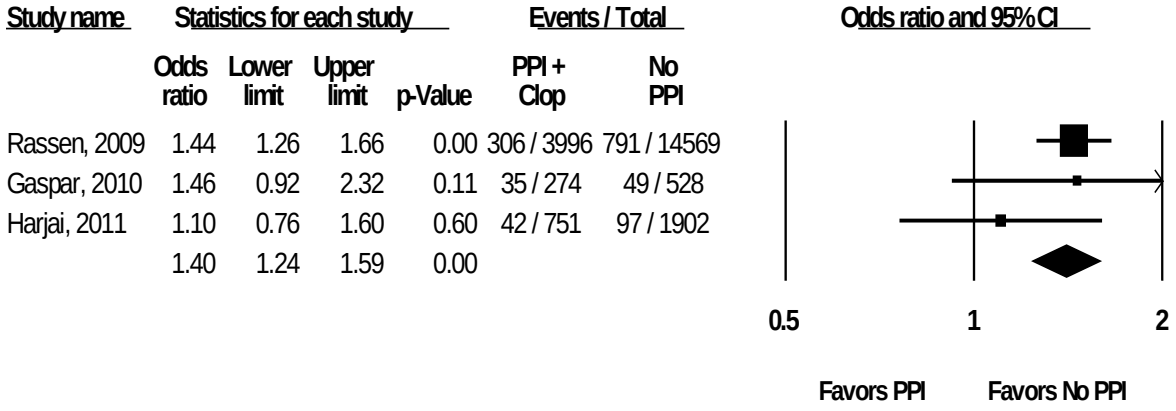


Abbreviations: CI=confidence interval; Clop=clopidogrel; PPI=proton pump inhibitor

Effect on Composite Endpoint of All-Cause Mortality or Nonfatal MI at 6 to 18 Months

A random-effects meta-analysis of three good-quality observational studies[10,13,22] in 22,094 UA/NSTEMI patients reporting all-cause mortality or nonfatal MI between 6 and 18 months found an odds ratio of 1.40 (95% CI, 1.24 to 1.59), favoring no PPI use (Figure J-2). There was no evidence of heterogeneity, with a Q-value of 1.80 for 2 degrees of freedom, p=0.41. Despite having good-quality studies and consistent findings of a direct outcome with a narrow confidence interval, the overall strength of evidence was reduced from high to moderate based on possible confounding by comorbid conditions in the patient population that was prescribed a PPI (selection bias).

Figure J-2. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on composite of all-cause mortality or nonfatal myocardial infarction at 6 to 18 months



Abbreviations: CI=confidence interval; Clop=clopidogrel; PPI=proton pump inhibitor

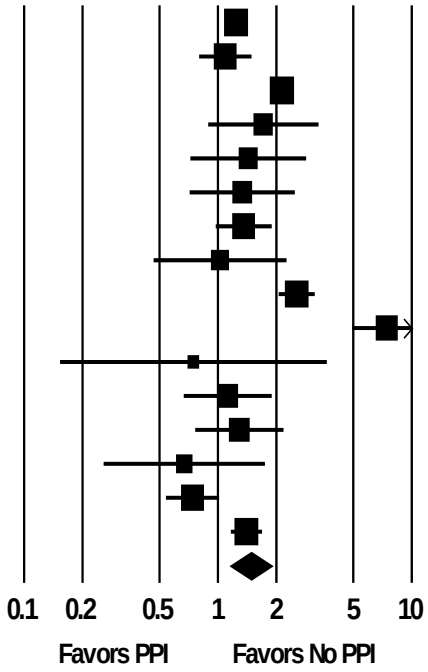
Effect on All-Cause Mortality After 1 Year

A random-effects meta-analysis of 16 observational studies[5,7,10-14,16,17,21,23,25,28,30,33,34] (14 good quality, 2 fair quality) in 141,474 UA/NSTEMI patients reporting all-cause mortality between 6 and 18 months found an odds ratio of 1.48 (95% CI, 1.16 to 1.89), favoring no PPI use (Figure J-3). There was evidence of extreme heterogeneity, with a Q-value of 151.0 for 15 degrees of freedom, $p<0.001$. The strength of evidence was rated moderate for all-cause mortality after 1 year based on predominately good-quality studies and inconsistent findings of a direct outcome with a narrow confidence interval.

One study was not included in the analysis since it presented data as adjusted RR only and event rates were not available. This study[22] comparing PPI use versus no PPI use in 18,565 UA/NSTEMI patients found no significant difference in the risk of all-cause mortality at 6 months (RR 1.20; 95% CI, 0.84 to 1.70).

Figure J-3. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on all-cause mortality after 1 year

Study name	Odds ratio	Lower limit	Upper limit	p-Value	PPI + Clop	No PPI
Ho, 2009	1.24	1.10	1.40	0.00	1042 / 5244	493 / 2961
Juurlink, 2009	1.09	0.80	1.49	0.58	71 / 323	188 / 916
Charlot, 2010	2.14	1.88	2.44	0.00	419 / 5986	551 / 16216
Gaspar, 2010	1.71	0.89	3.29	0.11	18 / 274	21 / 528
Gupta, 2010	1.43	0.72	2.85	0.30	14 / 72	35 / 243
Kreutz, 2010	1.33	0.72	2.49	0.36	19 / 6828	21 / 9862
Ray, 2010	1.36	0.98	1.89	0.07	64 / 7593	81 / 13003
Tentzeris, 2010	1.02	0.47	2.25	0.95	15 / 691	11 / 519
Van Boxel, 2010	2.55	2.06	3.15	0.00	189 / 5734	164 / 12405
Wu, 2010	7.44	4.96	11.15	0.00	35 / 311	94 / 5551
Chitose, 2011	0.75	0.15	3.63	0.72	2 / 171	7 / 450
Harjai, 2011	1.12	0.67	1.89	0.66	21 / 751	48 / 1902
Ortolani, 2011	1.29	0.77	2.17	0.34	190 / 3519	16 / 377
Rossini, 2011	0.67	0.26	1.74	0.41	24 / 1158	5 / 170
Simon, 2011	0.74	0.54	1.01	0.06	94 / 1453	77 / 900
Goodman, 2012	1.40	1.17	1.68	0.00	213 / 3255	286 / 6021
	1.48	1.16	1.89	0.00		



Abbreviations: CI=confidence interval; Clop=clopidogrel; PPI=proton pump inhibitor

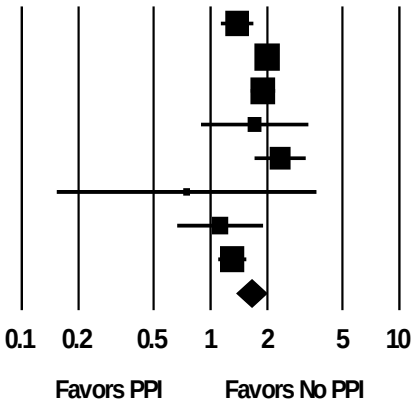
Effect on Nonfatal MI at 1 Year

A random-effects meta-analysis of 8 observational studies[5,7,8,11,13,16,17,33] (7 good quality, 1 fair quality) in 122,367 UA/NSTEMI patients reporting nonfatal MI between 6 and 18 months found an odds ratio of 1.65 (95% CI, 1.38 to 1.97), favoring no PPI use (Figure J-4). There was evidence of extreme heterogeneity, with a Q-value of 31.0 for 7 degrees of freedom, p<0.001. The I^2 value was 77.4. The strength of evidence was rated moderate for nonfatal MI at 1 year based on primarily good quality studies, inconsistent results of a direct outcome, and a narrow confidence interval.

Two studies were not included in the analysis because these studies reported adjusted OR/HR and actual event rates were not available. One study[32] looking at the effect of concomitant use of PPIs with clopidogrel on nonfatal MI found that UA/NSTEMI patients discharged on PPI were at higher risk of nonfatal MI at 1 year compared with those discharged without PPI (adjusted OR1.62; 95% CI, 1.15 to 2.27). In the second study[22] treatment with PPI resulted in a higher risk of nonfatal MI but did not reach statistical significance (HR 1.22; 95% CI, 0.99 to 1.51).

Figure J-4. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on nonfatal myocardial infarction at 1 year

Study name	Odds ratio	Lower limit	Upper limit	p-Value	PPI + Clop	No PPI
Juurlink, 2009	1.38	1.14	1.68	0.00	194 / 734	424 / 2057
Charlot, 2010	1.99	1.79	2.23	0.00	582 / 5596	861 / 15663
Evanchan, 2010	1.89	1.64	2.19	0.00	356 / 1369	693 / 4425
Kreutz, 2010	1.71	0.89	3.29	0.11	18 / 274	21 / 528
Van Boxel, 2010	2.34	1.71	3.19	0.00	84 / 5734	78 / 12405
Chitose, 2011	0.75	0.15	3.63	0.72	2 / 171	7 / 450
Harjai, 2011	1.12	0.67	1.89	0.66	21 / 751	48 / 1902
Goodman, 2012	1.30	1.10	1.54	0.00	245 / 3255	354 / 6021
	1.65	1.38	1.97	0.00		



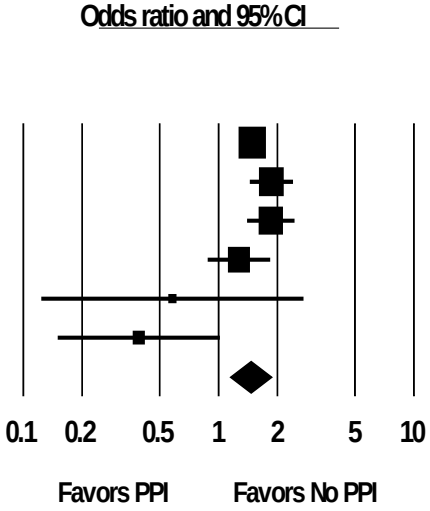
Abbreviations: CI=confidence interval; Clop=clopidogrel; PPI=proton pump inhibitor

Effect on Stroke at 1 Year

A random-effects meta-analysis of six good-quality observational studies[5,7,17,23,28,33] in 57,501 UA/NSTEMI patients reporting stroke between 6 and 18 months found an odds ratio of 1.46 (95% CI, 1.15 to 1.86), favoring no PPI use (Figure J-5). There was evidence of heterogeneity, with a Q-value of 14.7 for 5 degrees of freedom, p= 0.01. The strength of evidence was rated moderate for stroke outcomes at 1 year based on six good-quality studies with inconsistent results of a direct outcome and a narrow confidence interval.

Figure J-5. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on stroke at 1 year

Study name	Odds ratio	Lower limit	Upper limit	p-Value	PPI + Clop	No PPI
Charlot, 2010	1.49	1.29	1.72	0.00	297 / 6753	538 / 17949
Kreutz, 2010	1.86	1.45	2.40	0.00	140 / 6828	109 / 9862
Ray, 2010	1.85	1.40	2.44	0.00	105 / 7593	98 / 13003
Van Boxel, 2010	1.27	0.88	1.83	0.20	46 / 5734	78 / 12405
Chitose, 2011	0.58	0.12	2.71	0.49	2 / 171	9 / 450
Simon, 2011	0.39	0.15	1.01	0.05	7 / 1453	11 / 900
	1.46	1.15	1.86	0.00		



Abbreviations: CI=confidence interval; Clop=clopidogrel; PPI=proton pump inhibitor

Effect on Revascularization at 1 Year

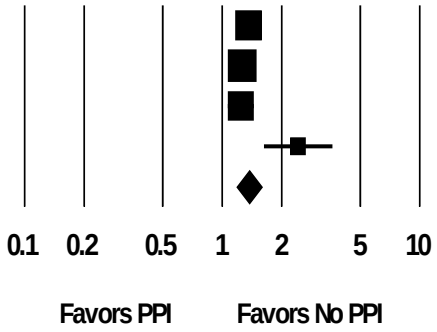
Two studies of omeprazole reported repeat revascularization—one RCT at 6 months[3] and one observational study at 1 year[35] after hospital discharge for UA/NSTEMI. Both studies found a

similar rate of revascularization among patients discharged on omeprazole compared with those discharged without omeprazole (4.0% vs. 4.6% and 9.4% vs. 8.9%). The strength of evidence was rated insufficient for assessing revascularization outcomes based on imprecise estimates and insufficient power to detect a difference.

A random-effects meta-analysis of four good-quality observational studies of any PPI[1,14,17,21] in 52,576 UA/NSTEMI patients reporting revascularization at 1 year found an odds ratio of 1.37 (95% CI, 1.19 to 1.58), favoring no PPI use (Figure J-6). There was evidence of heterogeneity, with a Q-value of 10.7 for 3 degrees of freedom, p=0.01.

Figure J-6. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on revascularization at 1 year

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Events / Total PPI	Events / Total No PPI
Ho, 2009	1.36	1.19	1.55	0.00	815 / 5244	353 / 2961
Kreutz, 2010	1.26	1.16	1.38	0.00	1109 / 6828	1312 / 9862
Banerjee, 2011	1.24	1.07	1.44	0.00	429 / 867	1622 / 3678
Ortolani, 2011	2.42	1.63	3.60	0.00	573 / 3519	28 / 377
	1.37	1.19	1.58	0.00		

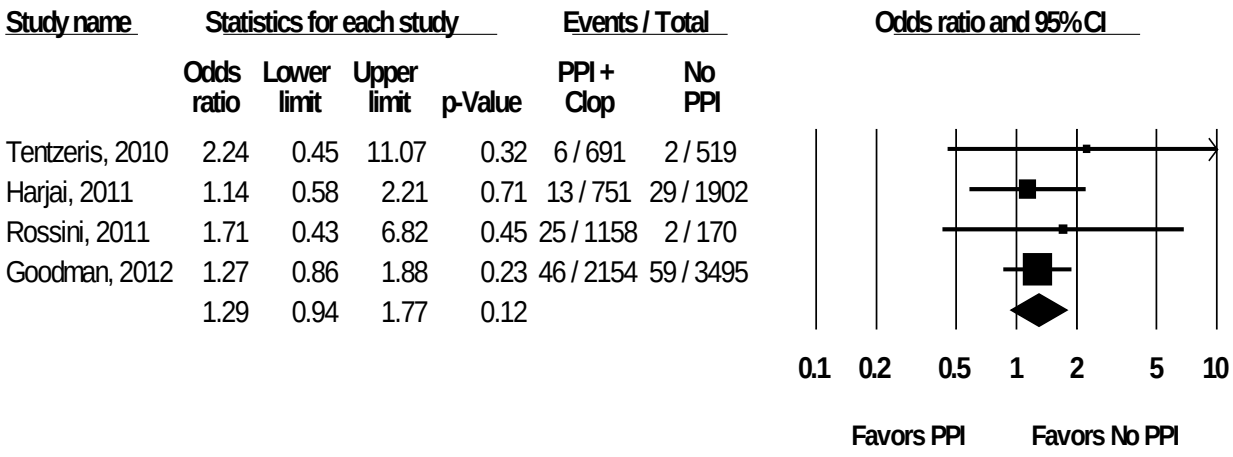


Abbreviations: CI=confidence interval; PPI=proton pump inhibitor

Effect on Stent Thrombosis at 1 Year

A random-effects meta-analysis of four good-quality observational studies[11,13,25,30] in 23,833 UA/NSTEMI patients reporting stent thrombosis between 6 and 18 months found an odds ratio of 1.29 (95% CI, 0.94 to 1.77) (Figure J-7). There was no evidence of heterogeneity, with a Q-value of 0.76 for 3 degrees of freedom, p=0.86. The strength of evidence was rated insufficient for stent thrombosis at 1 year based on good-quality studies with consistent results of a direct outcome and a wide confidence interval.

Figure J-7. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on stent thrombosis at 1 year

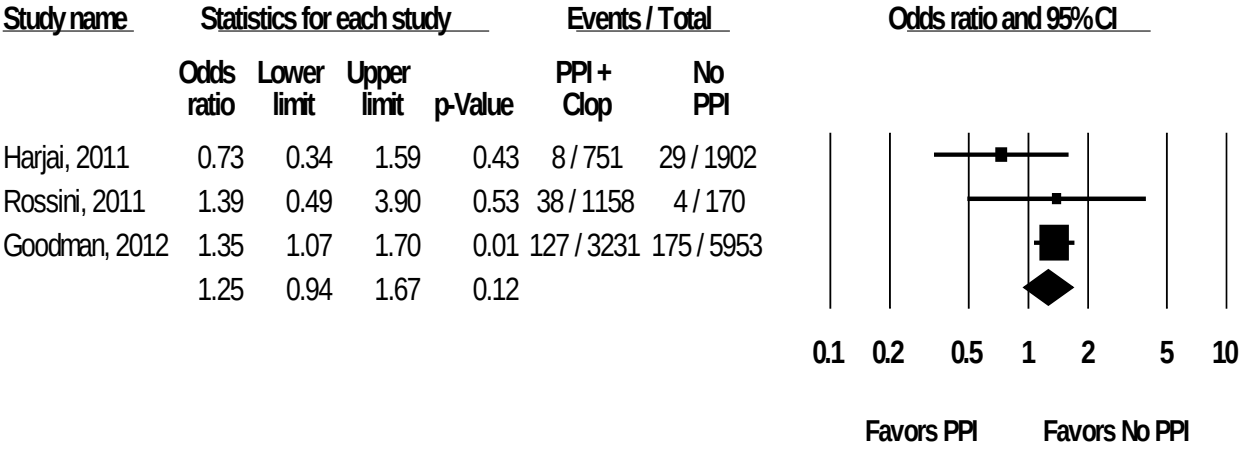


Abbreviations: CI=confidence interval; Clop=clopidogrel; PPI=proton pump inhibitor

Effect on Major Bleeding at 1 Year

A random-effects meta-analysis of three good-quality studies[11,13,25] in 22,138 UA/NSTEMI patients reporting major bleeding at 1 year found an odds ratio of 1.25 (95% CI, 0.94 to 1.67) (Figure J-8). There was no evidence of heterogeneity, with a Q-value of 2.22 for 2 degrees of freedom, p=0.33. The strength of evidence was rated insufficient for major bleeding at 1 year based on good-quality studies with inconsistent results of a direct outcome and a narrow confidence interval.

Figure J-8. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on major bleeding at 1 year



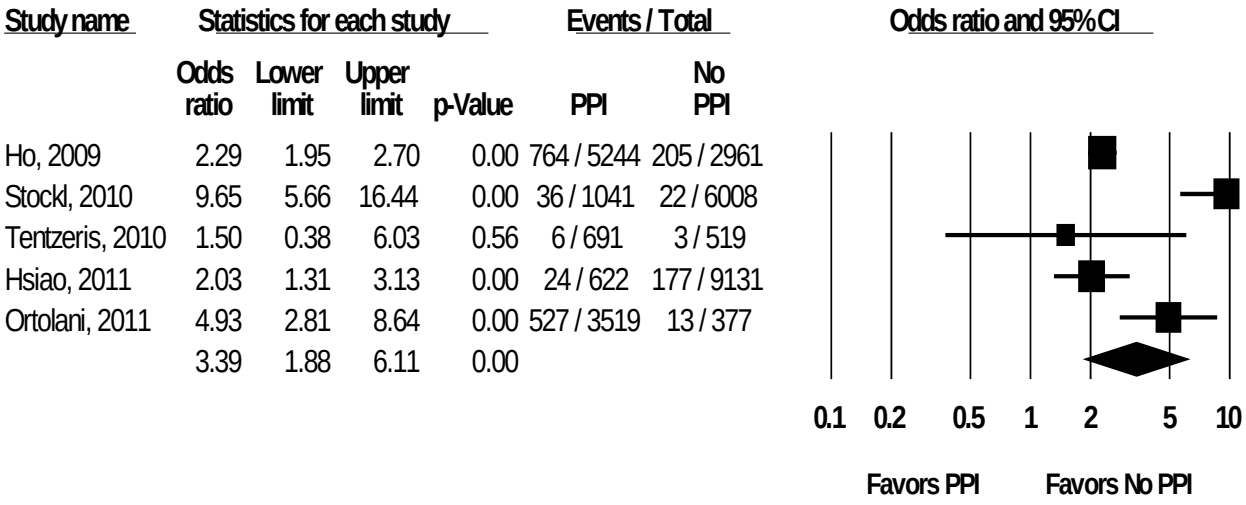
Abbreviations: CI=confidence interval; Clop=clopidogrel; PPI=proton pump inhibitor

Effect on Rehospitalization at 1 Year

A random-effects meta-analysis of five good-quality observational studies[14,15,21,29,30] in 25,715 UA/NSTEMI patients reporting rehospitalization at 1 year found an odds ratio of 3.39

(95% CI, 1.88 to 6.11), favoring no PPI use (Figure J-9). There was evidence of extreme heterogeneity, with a Q-value of 32.4 for 4 degrees of freedom, p<0.001. The strength of evidence was rated low for rehospitalization at 1 year based on good-quality studies with inconsistent results of an indirect outcome and a wide confidence interval.

Figure J-9. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on rehospitalization at 1 year



Abbreviations: CI=confidence interval; PPI=proton pump inhibitor

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