Comparative Effectiveness Review

Number xx

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

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Preface

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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 167 studies (291 articles); 90 studies were relevant to early invasive management, 32 were relevant to initial conservative management, and 63 were relevant to the postdischarge setting. Findings with moderate or high strength of evidence (SOE) ratings are reported here along with magnitude of effect.

For patients undergoing an *early invasive approach*, *upstream* (precatheterization) treatment using glycoprotein IIb/IIIa inhibitors (GPIs) was associated with lower rates of revascularization (odd ratio [OR] 0.77; 95% confidence interval [CI], 0.65-0.92) but higher risk of major bleeding events (OR 1.24; CI, 1.08-1.43) at 30 days compared with *deferred* (periprocedural) GPI treatment (high SOE). This higher risk of bleeding from upstream GPI administration also occurred with either pretreatment (OR 1.49; CI, 1.10-2.01; moderate SOE) or deferred clopidogrel administration (OR 1.27; CI, 1.08-1.50; high SOE). At 30 days, prasugrel reduced rates of death/myocardial infarction/stroke (4.8% prasugrel, 5.4% clopidogrel), and ticagrelor reduced the same composite endpoint (5.7% ticagrelor, 7.4% clopidogrel) compared with clopidogrel (moderate SOE). At 1 year, prasugrel reduced rates of the same composite endpoint (9.9% prasugrel, 12.1% clopidogrel) as did ticagrelor (10.6%) compared with clopidogrel (12.6%) (moderate SOE). With planned GPI use, bivalirudin reduced the rate of the composite outcome of all-cause mortality, nonfatal myocardial infarction, revascularization, or major bleeding compared with heparin at 30 days (OR 0.87; CI, 0.78-0.97; high SOE). Bivalirudin reduced major bleeding events at 30 days compared with heparin both without GPI use (OR 0.63; CI, 0.47-0.85) and with GPI use (OR 0.52; CI, 0.43-0.63); it also reduced minor bleeding events at 30 days compared to heparin with GPI use (OR 0.50; CI, 0.42-0.59) (all high SOE). Bivalirudin reduced major bleeding events (OR 0.65; CI, 0.49-0.85) at 30 days in patients who were treated with clopidogrel before undergoing percutaneous coronary intervention when compared with heparin-based treatment (moderate SOE).

In the analysis of a mostly *conservatively managed* population, enoxaparin reduced composite ischemic events (OR 0.84; CI, 0.76-0.93; high SOE) and myocardial infarction (OR 0.85; CI, 0.76-0.95; 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; CI, 0.67-0.96; high SOE) and also reduced composite ischemic events (risk ratios [RRs] ranging from 0.58 to 0.84) and nonfatal myocardial infarction (OR 0.79; CI, 0.61-1.02) up to 30 days, especially in trials of eptifibatide and tirofiban (moderate SOE).

In the *postdischarge* setting, dual antiplatelet therapy reduced the rates of composite ischemic outcomes (ORs/RRs ranging from 0.69 to 0.91) and nonfatal myocardial infarction (ORs/RRs ranging from 0.77 to 0.88) compared with single antiplatelet therapy (high SOE). Based on three randomized trials, all-cause mortality at 1 year was reduced for patients on omeprazole compared with placebo (low SOE). In the 26 observational studies comparing all types of proton pump inhibitor (PPI) medication with no PPI medication, findings suggest that patients on a PPI do worse. Although the findings from the observational trials are consistent and precise, possible confounding by comorbid conditions reduced the SOE to moderate. We were not able to reach a firm conclusion as to why large, well-done observational studies of PPIs as a class consistently found worse outcomes in patients who received PPIs with antiplatelet therapy while a smaller number of RCTs of one particular PPI (omeprazole) found no increase in overall mortality.

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

Conclusions: Evidence exists to help clinicians weigh the benefits and harms of various antiplatelet and anticoagulant treatments that can be used in invasive, conservative or postdischarge management of patients with UA/NSTEMI, but uncertainty remains about the optimal dosing, timing, duration, and combinations of many of the options, especially in subpopulations of interest (e.g., the elderly, diabetics, women, obese patients, and those with comorbid illness).

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Effective Health Care

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

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm

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 between the time of admission and 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 parenteral anticoagulants—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 their 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 this 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[a]

Drug Category	Early Invasive		Initial Conservative	Postdischarge
Aspirin	Aspirin (low or high dose)		Aspirin (low or high dose)	Aspirin (low or high dose)
Intravenous antiplatelet (glycoprotein IIb/IIIa inhibitor)	Upstream	Periprocedure		
	Epifibatide Tirofiban	Eptifibatide Tirofiban Abciximab		
Oral antiplatelet ($P2Y_{12}$ Inhibitor)	Clopidogrel Ticagrelor	Clopidogrel Prasugrel Ticagrelor	Clopidogrel Ticagrelor Prasugrel[a]	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

[a]TRILOGY ACS trial was published in NEJM August 26, 2012, and will be added to the final version of this report.
Abbreviations: PCI = percutaneous coronary intervention

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 P2Y12 inhibitor, is currently recommended for patients with UA/NSTEMI. Other oral P2Y12 inhibitors include prasugrel and ticagrelor. While there are 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, and it provides a more potent and faster acting antiplatelet effect when compared with clopidogrel and does not appear to be susceptible to genetic polymorphisms of the hepatic isoenzymes. Ticagrelor is a reversible P2Y12 receptor antagonist that, when compared with clopidogrel, provides a more rapid and more potent inhibition of platelets.

The antiplatelet agents belonging to the glycoprotein IIb/IIIa inhibitor (GPI) class are administered intravenously and 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.

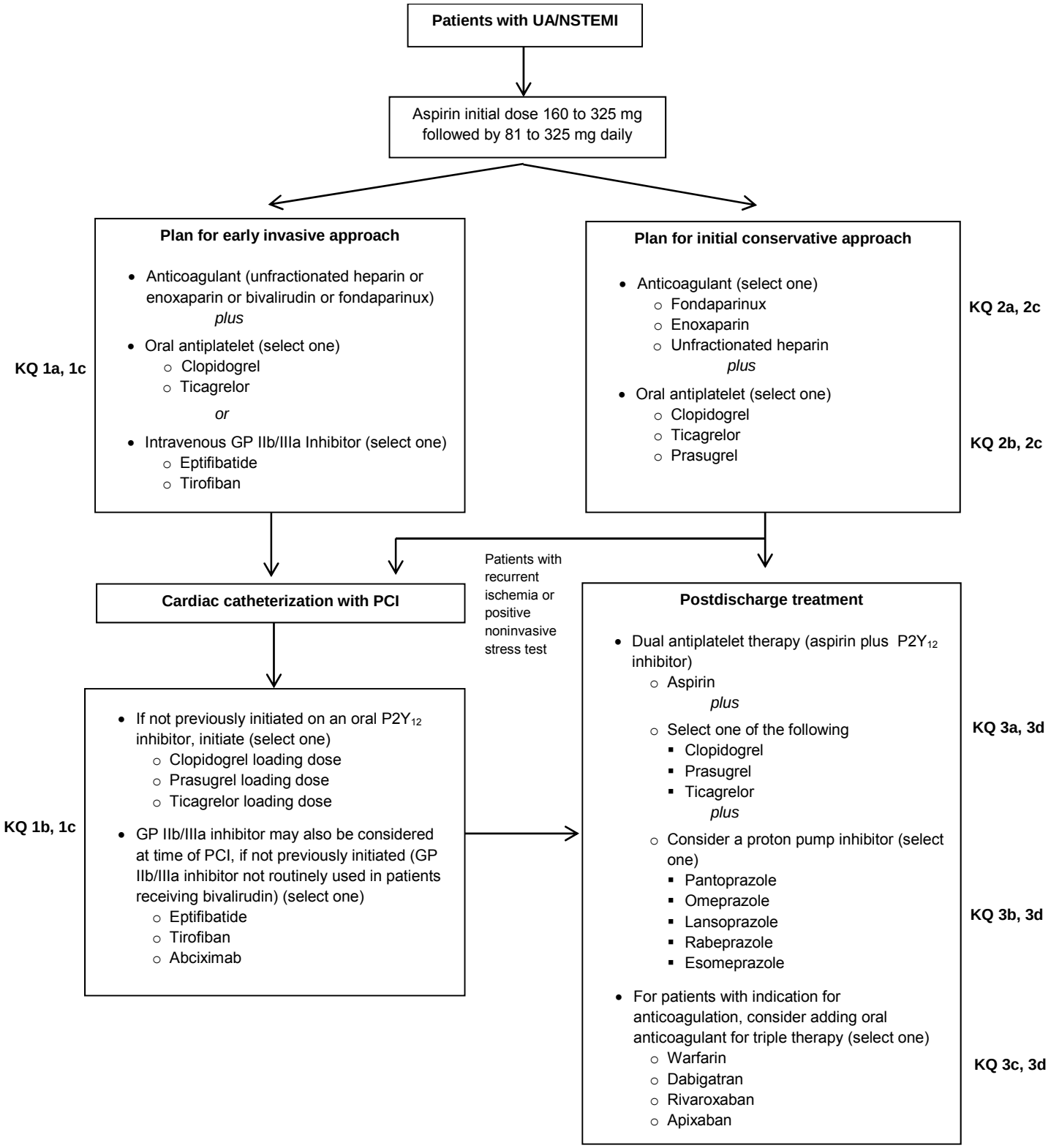
Treatment Strategy Algorithm

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 GPI as initial therapy prior to going to the cardiac catheterization laboratory. After catheterization with percutaneous coronary intervention, the next stage considers 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. 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 clinicians guidance, 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.

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



Scope and Key Questions

Scope of the 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, the interventions, comparators, outcomes, timing of outcomes, and settings. 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 on improving cardiovascular outcomes?
  b. What are the comparative effectiveness (dose and timing) and comparative safety of different antiplatelet agents on 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?

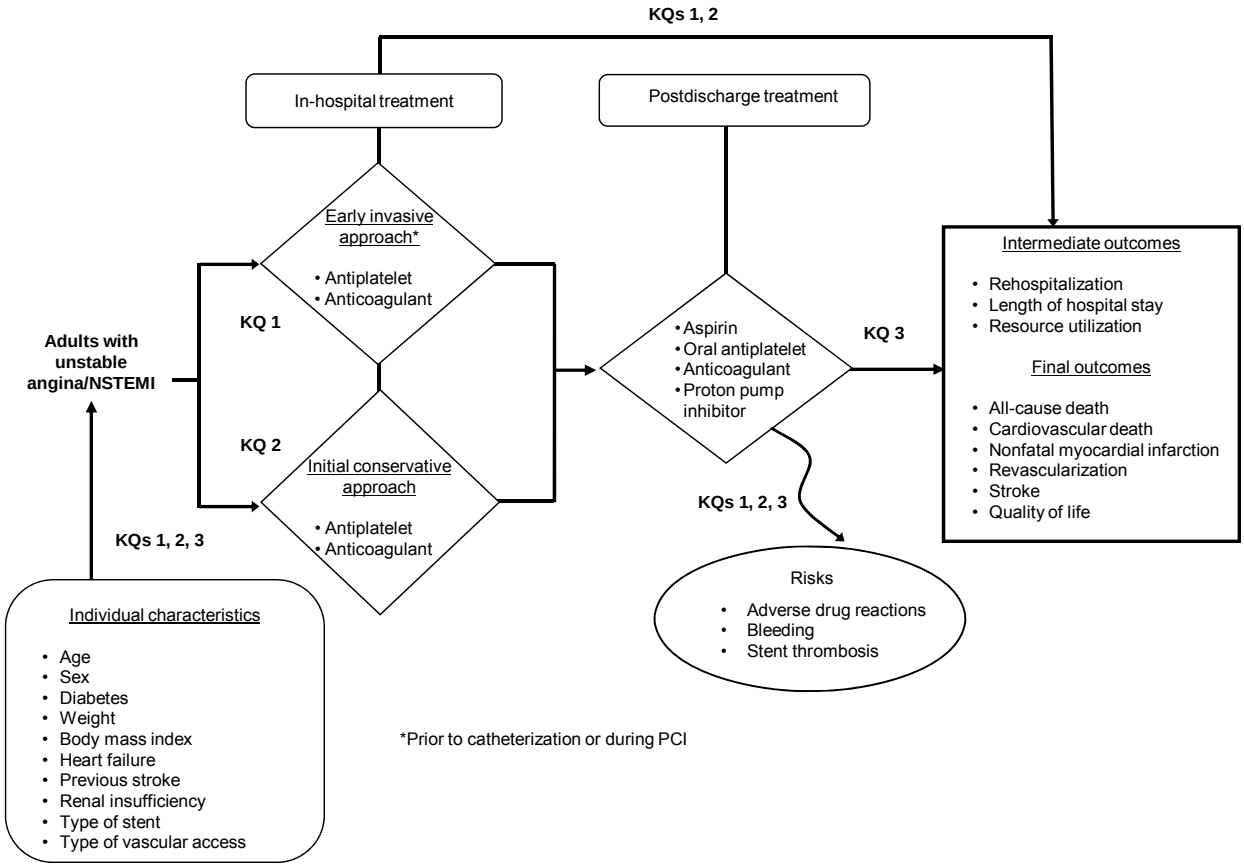
c. In patients with an indication for long-term anticoagulant therapy, what are the comparative effectiveness and comparative safety of adding an oral anticoagulant to aspirin and another antiplatelet agent for improving cardiovascular outcomes?

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



Abbreviations: KQ = key question; PCI = percutaneous coronary intervention; NSTEMI = non-ST elevation myocardial infarction; UA = unstable angina

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 considers whether there are subgroups of patients, based on demographic and other characteristics, for which 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, 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* (available at http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm; hereafter referred to as the *Methods Guide*).[15] The main sections in this chapter reflect the elements of the protocol established for the systematic review; certain methods map to the PRISMA checklist.[16] All methods and analyses were determined a priori.

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 key questions. The key questions were then posted for public comment for 30 days, 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 and did not contribute 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. 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 list for identified pivotal articles was 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; metaRegister of Controlled Trials; ClinicalStudyResults.org; WHO: International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. 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.

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 in Table 2 of the main 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). The following outcomes were considered: rehospitalization, hospital length of stay, resource utilization (e.g., emergency department visits), all-cause mortality, cardiovascular-related mortality, nonfatal myocardial infarction, revascularization, stroke, and quality of life. Also evaluated were individual characteristics such age, sex, weight, body mass index, diabetes, heart failure, previous stroke, renal insufficiency, type of stent, and type of vascular access.

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were examined independently by two reviewers for potential relevance to the key questions. 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, ON, 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*,[15] 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 was 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*.[15] To assess quality, we used the strategy to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive 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.[17]

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.

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 deviation, 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 where at least three studies reported the same outcome.

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. 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 strength of evidence for each outcome assessed because a given study may be of different quality for two individual outcomes reported within that study. The strength of evidence for each key question and outcome was assessed using the approach described in the *Methods Guide*.[15,19] In brief, the approach required assessment of four domains: risk of bias, consistency, directness, and precision. Additionally, when appropriate, the studies were evaluated for dose-response association, 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 strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make; for example, 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*.[15,20] In brief, the latter methods use the PICOTS format 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 (such as 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 acute coronary syndrome (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 including the UA/NSTEMI population but where the results were not reported separately. The investigative team felt that limiting our review to the pure UA/NSTEMI population would result in a narrow focus of 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 percutaneous coronary intervention 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 glycoprotein IIb/IIIa inhibitor (GPI), (2) different loading doses of clopidogrel, (3) clopidogrel versus ticagrelor versus prasugrel, (4) bivalirudin versus a heparin-based strategy, (5) enoxaparin versus unfractionated heparin versus fondaparinux, and (6) the timing of 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 that were not included in KQ 1. Thus we present the findings of studies comparing (1) enoxaparin versus unfractionated heparin versus fondaparinux in the conservatively managed or total population (if results by treatment strategy are not presented) and (2) GPI versus unfractionated heparin 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.

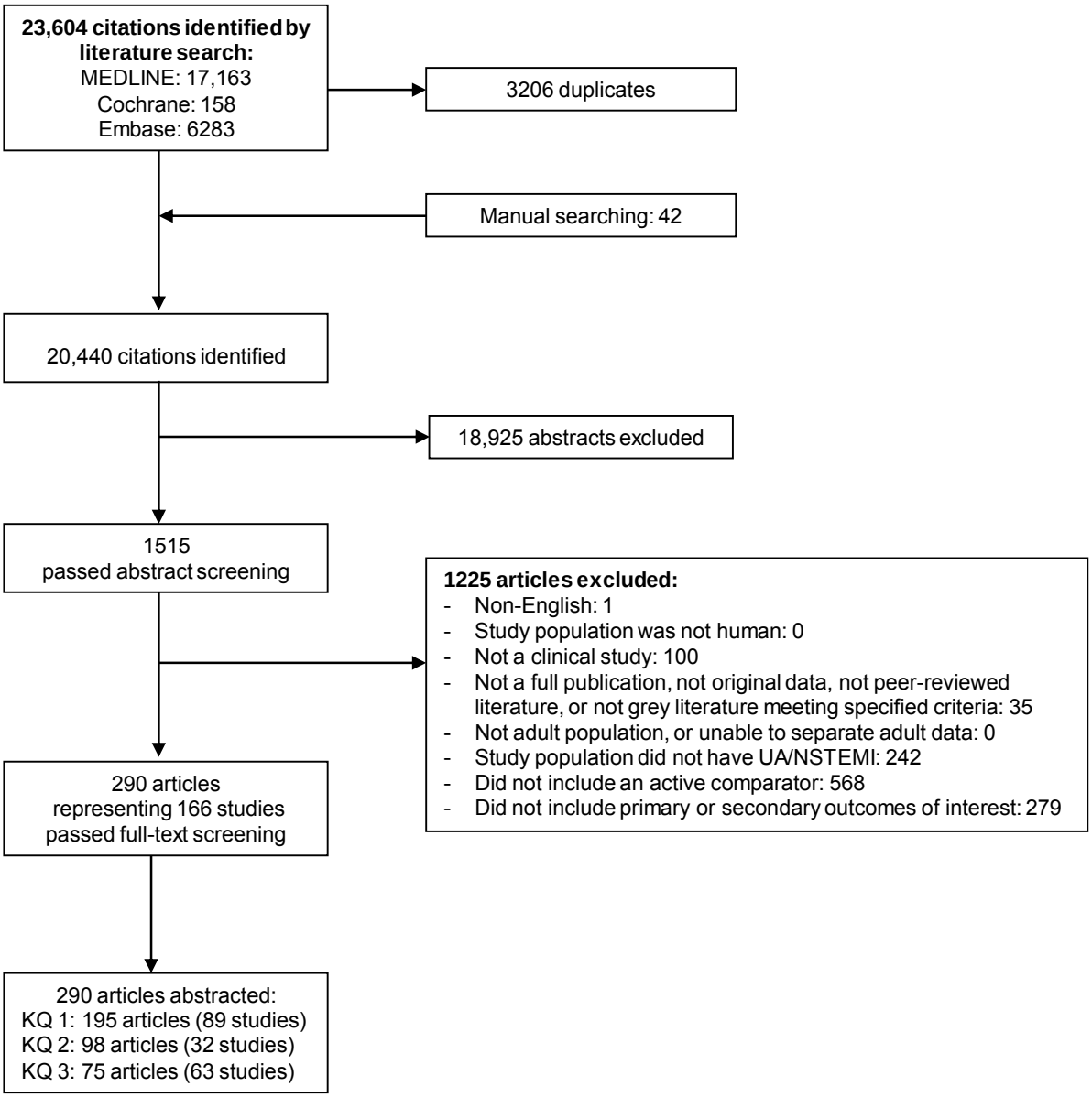
- In KQ 3 (*postdischarge*), we present the findings of studies comparing (1) low-dose versus high-dose aspirin, (2) single versus dual antiplatelet therapy, (3) short-term versus long-term clopidogrel, (4) antiplatelet therapy with or without the addition of proton pump inhibitors (PPIs), and (5) dual 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 December 2011 yielded 23,604 citations, 3206 of which were duplicates. Manual searching and contacts to drug manufacturers identified 42 additional citations, for a total of 20,440. After applying inclusion/exclusion criteria at the title-and-abstract level, 1515 full-text articles were retrieved and screened. Of these, 1225 were excluded at the full-text

screening stage, leaving 290 articles (representing 166 unique studies) for data abstraction. Note that several articles/studies were relevant to more than one KQ.

Figure C. Literature flow diagram



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

Key Question 1. Early Invasive Approach for UA/NSTEMI

We identified 89 unique studies that evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 439,261 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 means medications given at the same time as the PCI).

The following six comparisons were assessed in the included studies for KQ 1 and are detailed in this analysis:

1. Upstream versus deferred administration of glycoprotein IIb/IIIa inhibitor (GPI)
   - 18 studies (14 RCTs, 4 observational; 142,729 total patients)
2. Clopidogrel loading dose of 300 mg versus 600 mg
   - 11 studies (8 RCTs, 3 observational; 36,347 total patients)
3. Clopidogrel versus ticagrelor versus prasugrel
   - 3 studies (3 RCTs; 33,216 total patients)
4. Bivalirudin versus a heparin-based strategy (with or without GPI)
   - 11 studies (9 RCTs, 2 observational; 24,712 total patients)
5. Enoxaparin versus unfractionated heparin versus fondaparinux
   - 14 studies (11 RCTs, 3 observational; 44,372 total patients)
6. Timing of clopidogrel administration (before or after PCI) in studies that were designed to compare bivalirudin versus a heparin-based strategy or to compare upstream versus deferred GPI use
   - 4 studies (2 RCTs, 2 observational; 6325 patients)

For each comparison in KQ 1, we present the Key Points, followed by a table summarizing the strength of evidence (SOE) and estimates of the magnitude of effect.

Key Points For Upstream (Precatheterization) vs. Deferred (Periprocedural) GPI

- Upstream (precatheterization) treatment with glycoprotein IIb/IIIa inhibitors (GPIs) was associated with lower rates of revascularization (high SOE) but a higher risk of major bleeding events at 30 days compared with deferred (periprocedural) GPI administration (high SOE).

- Upstream treatment with GPIs was also associated with higher rates of major bleeding events at 30 days compared with deferred GPI treatment (high SOE),

Table B. Summary strength of evidence and effect estimates: upstream vs. deferred glycoprotein inhibitor[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor upstream GPI; ORs greater than 1 favor deferred GPI
Upstream vs. deferred GPI	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE=Low (6 studies, 19,662 patients) Summary OR 0.88 (0.77 to 1.01)
Composite of all-cause mortality, nonfatal MI, or revascularization after 6 months	SOE=Insufficient (4 studies, 773 patients) Summary OR 0.77 (0.46 to 1.28)
All-cause mortality at 30 days	SOE=Insufficient (10 studies, 20,521 patients) Summary OR 0.80 (0.57 to 1.11)
All-cause mortality after 6 months	SOE=Insufficient (3 studies, 673 patients) One study reported no deaths in both arms; one study reported 1 death in the upstream GPI arm; one study reported similar rates (2.0% upstream GPI, 3.6% deferred GPI)
Nonfatal MI at 30 days	SOE=Insufficient (9 studies, 20,263 patients) Summary OR 0.84 (0.65 to 1.10)
Nonfatal MI after 6 months	SOE=Insufficient (3 studies, 673 patients) One study reported 1 MI in the deferred GPI arm only; other studies reported MI rates of 12% upstream vs. 15% deferred; 10% upstream vs. 9% deferred
Revascularization at 30 days	SOE=High (6 studies, 19,454 patients) Summary OR 0.77 (0.65 to 0.92) favors upstream GPI
Revascularization after 6 months	SOE=Insufficient (3 studies, 673 patients) Summary OR 0.69 (0.34 to 1.39)
Major bleeding at 30 days	SOE=High (9 studies, 20,242 patients) Summary OR 1.24 (1.08 to 1.43) favors deferred GPI
Minor bleeding at 30 days	SOE=Insufficient (5 studies, 969 patients) Summary OR 1.58 (0.95 to 2.64)
Stent thrombosis at 30 days	SOE=Insufficient (0 studies, 0 patients)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: CI=confidence interval; GPI= glycoprotein IIb/IIIa inhibitor; MI=myocardial infarction; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence

Key Points for 300 mg vs. 600 mg Clopidogrel Loading Dose

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

Table C. Summary strength of evidence and effect estimates: 300 mg vs. 600 mg clopidogrel loading dose[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI)
300 mg vs. 600 mg clopidogrel loading dose	
Composite of cardiovascular mortality, nonfatal MI, or revascularization at 30 days	SOE=Insufficient (1 study, 119 patients) Lower rate in 600 mg group (10.4% vs. 23.8%)
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days	SOE=Low (1 study, 25,086 patients) No difference found, HR 0.94 (0.83 to 1.06), in this large, good-quality RCT sufficiently powered to assess this composite endpoint
Composite of cardiovascular mortality, nonfatal MI, or recurrent ACS at 30 days	SOE=Insufficient (1 study, 387 patients) 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 study, 103 patients) 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 study, 255 patients) 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 study, 256 patients) No difference in event rate between groups (13.3% vs. 13.2%)
All-cause mortality at 30 days	SOE=Low (3 studies, 25,444 patients) Two small studies reported no deaths in both groups; no difference found, HR 0.93 (0.83 to 1.05), in the large, good-quality RCT
All-cause mortality at 6 months	SOE=Insufficient (1 study, 256 patients) Three deaths in 300 mg group, 1 death in 600 mg group
Cardiovascular mortality at 30 days	SOE=Low (3 studies, 25,497 patients) No difference found, HR 0.95 (0.81 to 1.13), in the large, good-quality RCT
Nonfatal MI at 30 days	SOE=Low (5 studies, 25,821 patients) OR 1.74 (0.99 to 3.06)
Nonfatal MI at 6 months	SOE=Insufficient (1 study, 256 patients) 600 mg group 5.0% vs. 300 mg group 8.6%, p=0.26
Nonfatal stroke at 30 days	SOE=Insufficient (2 studies, 25,378 patients) 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 study, 256 patients) Only one stroke in overall cohort (600 mg group)
Revascularization at 30 days	SOE=Insufficient (3 studies, 477 patients) Low overall event rate ranging from 0 to 1.3% in 300 mg group, 0 to 4.8% in 600 mg group; disparate results
Revascularization after 6 months	SOE=Insufficient (1 study, 256 patients) 600 mg group 3.3% vs. 300 mg group 2.3%, p=0.64
Major bleeding at 30 days	SOE=Insufficient (6 studies, 26,206 patients) Three studies reported no bleeding events; inconsistent findings from three other studies with largest study reporting HR 1.09 (0.89 to 1.34)

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Minor bleeding at 30 days	SOE=Insufficient (5 studies, 25,819 patients) Inconsistent findings with incidence in 300 mg loading dose group ranging from 0.8% to 9.5% compared with 600 mg loading dose group ranging from 0.8% to 3.9%
Stent thrombosis at 30 days	SOE=Low (1 study, 17,263 patients) Large study reported HR 0.68 (0.55 to 0.85) favoring 600 mg loading dose

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; NA=not applicable; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence

Key Points for Clopidogrel vs. Ticagrelor vs. Prasugrel

- Ticagrelor was associated with lower rates of the composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke compared with clopidogrel at 30 days (moderate SOE) and 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 revascularization at 6 months (low SOE), but an increase in major bleeding events at 1 year (low SOE), compared with clopidogrel.

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

Table D. Summary strength of evidence and effect estimates: clopidogrel vs. ticagrelor vs. prasugrel[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Clopidogrel vs. ticagrelor vs. prasugrel	
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days	SOE=Moderate (3 studies, 33,216 patients) Ticagrelor (4.3% and 4.8%) and prasugrel (5.7%) were both associated with lower composite endpoints than clopidogrel (3.8%, 5.4%, and 7.4%).
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke after 1 year	SOE=Moderate (2 studies, 32,232 patients) Ticagrelor (10.6%) and prasugrel (9.9%) were both associated with lower composite endpoints than clopidogrel (12.6%).
Composite of cardiovascular mortality, nonfatal MI, or revascularization at 15 months	SOE=Low (1 study, 13,608 patients) HR (95% CI): 0.81 (0.73 to 0.87) favors prasugrel
All-cause mortality at 30 days	SOE=Insufficient (1 study, 984 patients) Clopidogrel: 0.6% Ticagrelor: 1.9% p=0.18
All-cause mortality after 1 year	SOE=Low (2 studies, 32,232 patients) Ticagrelor (4.5%) and prasugrel (3.0%) were both associated with fewer deaths than clopidogrel (5.9% and 3.2%)

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Cardiovascular mortality at 30 days	SOE=Insufficient (1 study, 984 patients) Clopidogrel: 0.6% Ticagrelor: 1.9% p=0.18
Cardiovascular mortality after 1 year	SOE=Low (2 studies, 32,232 patients) Ticagrelor (4.0%) and prasugrel (2.1%) were both associated with fewer CV deaths than clopidogrel (5.1% and 2.4%)
Nonfatal MI at 30 days	SOE=Insufficient (1 study, 984 patients) Clopidogrel: 3.5% Ticagrelor: 2.2% p=0.34
Nonfatal MI after 1 year	SOE=Low (2 studies, 32,232 patients) Ticagrelor (5.8%) and prasugrel (7.3%) were both associated with fewer MIs than clopidogrel (6.9% and 9.5%)
Nonfatal stroke at 30 days	SOE=Insufficient (1 study, 984 patients) Clopidogrel: 0.3% Ticagrelor: 0.6% p=0.57
Nonfatal stroke after 1 year	SOE=Insufficient (2 studies, 32,232 patients) One study: prasugrel 1.0% and clopidogrel 1.0%; other study: ticagrelor 1.5% and clopidogrel 1.3%
Revascularization at 30 days	SOE=Insufficient (0 studies, 0 patients)
Revascularization after 6 months	SOE=Low (1 study, 13,608 patients) HR 0.66 (0.54 to 0.81) favoring prasugrel over clopidogrel
Major bleeding at 30 days	SOE=Insufficient (1 study, 984 patients) Ticagrelor (7.1%) and clopidogrel (6.9%)
Major bleeding after 1 year	SOE=Low (2 studies, 32,232 patients) Ticagrelor (7.9%) and clopidogrel (7.7%) had similar event rates; prasugrel (2.4%) had higher events rates than clopidogrel (1.8%)
Minor bleeding at 30 days	SOE=Insufficient (1 study, 984 patients) Clopidogrel: 1.3% Ticagrelor: 2.7% p=0.18
Stent thrombosis after 1 year	SOE=Low (2 studies, 32,232 patients) Ticagrelor (1.3%) and prasugrel (1.1%) were both associated with lower individual endpoints than clopidogrel (1.9% and 2.4%)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: CI=confidence interval; CV=cardiovascular; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; NA=not applicable; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence

Key Points for Bivalirudin vs. Heparin-based Strategy With and Without Planned GPI Use

- With planned GPI use, bivalirudin reduced the rate of the composite outcome of all-cause mortality, nonfatal MI, revascularization, major bleeding, and minor bleeding compared with heparin at 30 days (high SOE).

- There was a statistically significant lower incidence in major and minor bleeding at 30 days favoring bivalirudin when compared with a heparin-based strategy without GPI use (high SOE for major bleeding; low SOE for minor bleeding).

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

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor bivalirudin; ORs greater than 1 favor heparin-based strategy
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 study, 4571 patients) Bivalirudin (8.4%) vs. heparin without GPI (8.7%)
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE=Insufficient (2 studies, 5420 patients) One study found no difference, OR 1.19 (0.92 to 1.54); another study found a statistically significant lowering in the bivalirudin group OR 0.42 (CI 0.21 to 0.84)
Composite of all-cause mortality, nonfatal MI, or revascularization after 1 year	SOE=Insufficient (2 studies, 5420 patients) One study found no difference, OR 0.97 (0.83 to 1.13); another study found a statistically significant lowering in the bivalirudin group OR 0.58 (0.37 to 0.92).
All-cause mortality at 30 days	SOE=Insufficient(3 studies, 5822 patients) Summary OR 0.46 (0.12 to 1.81)
All-cause mortality after 6 months	SOE=Insufficient (2 studies, 5420 patients) Disparate results in two RCTs: bivalirudin 1.2% vs. heparin 2.4%; bivalirudin 1.9% vs. heparin 1.7%
Nonfatal MI at 30 days	SOE=Insufficient (3 studies, 5822 patients) Summary OR 1.00 (0.64 to 1.55)
Nonfatal MI after 6 months	SOE=Insufficient (2 studies, 5420 patients) Disparate results in two RCTs: bivalirudin 3.3% vs. heparin 5.7%; bivalirudin 6.0% vs. heparin 5.3%
Revascularization at 30 days	SOE=Insufficient (3 studies, 5822 patients) Summary OR 1.10 (0.60 to 2.04)
Revascularization after 6 months	SOE=Insufficient (2 studies, 5420 patients) Bivalirudin-treated patients (4.1% and 11.2%) vs. heparin treated (5.7% and 12.5%)
Major bleeding at 30 days	SOE=High (3 studies, 5822 patients) Summary OR 0.63 (0.47 to 0.85) favoring bivalirudin
Minor bleeding at 30 days	SOE=Low (3 studies, 5822 patients) Summary OR 0.64 (0.43 to 0.95) favoring bivalirudin
Stent thrombosis at 30 days	SOE=Insufficient (3 studies, 5822 patients) Summary OR 1.42 (0.64 to 3.15)
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 studies, 12,287 patients) Summary OR 0.87 (0.78 to 0.97) favoring bivalirudin
Composite of all-cause mortality, nonfatal MI, or revascularization, at 30 days	SOE=High (3 studies, 12,287 patients) Summary OR 1.07 (0.95 to 1.22)
Composite of all-cause mortality, nonfatal MI, or revascularization after 1 year	SOE=Insufficient (2 studies, 10,566 patients) Both studies found no difference between treatments, OR 1.11 (0.74 to 1.63); and OR 1.08 (0.92 to 1..25)
All-cause mortality at 30 days	SOE=Insufficient (3 studies, 12,287 patients) Summary OR 1.21 (0.89 to 1.65)
All-cause mortality after 6 months	SOE=Insufficient (2 studies, 10,566 patients) One study (3.8% bivalirudin, 3.8% GPI); other study (0.9% bivalirudin, 1.3% GPI, p=0.46)
Nonfatal MI at 30 days	SOE=Moderate (3 studies, 12,287 patients) Summary OR 1.06 (0.92 to 1.23)

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor bivalirudin; ORs greater than 1 favor heparin-based strategy
Nonfatal MI after 6 months	SOE=Insufficient (2 studies, 10,566 patients) Bivalirudin-treated patients (7.8% and 8.1%) vs. heparin (6.9 and 7.6%)
Revascularization at 30 days	SOE=Insufficient (3 studies, 12,287 patients) Summary OR 1.11 (0.86 to 1.42)
Revascularization after 6 months	SOE=Low (2 studies, 10,566 patients) Higher event rate in bivalirudin-treated patients (8.7% and 11.7%) compared with heparin-treated patients (8.4% in both studies)
Major bleeding at 30 days	SOE=High (3 studies, 12,287 patients) OR 0.52 (0.43 to 0.63) favoring bivalirudin
Minor bleeding at 30 days	SOE=High (3 studies, 12,287 patients) OR 0.50 (0.42 to 0.59) favoring bivalirudin
Stent thrombosis at 30 days	SOE=Insufficient (2 studies, 10,936 patients) Bivalirudin 0.7 to 1.0%, heparin 0.6 to 0.8%)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: CI=confidence interval; CV=cardiovascular; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; NA=not applicable; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence

Key Points for Enoxaparin vs. UFH vs. 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 unfractionated heparin and enoxaparin versus fondaparinux (low SOE).
- There was a statistically significant lower incidence of major bleeding at 30 days favoring fondaparinux when compared with enoxaparin in the PCI cohort (low SOE).

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

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Enoxaparin vs. unfractionated heparin vs. fondaparinux	
Composite ischemic endpoints at 7 days	SOE=Low (1 study, 3987 patients) HR 0.89 (0.75 to 1.05), No difference between enoxaparin and UFH (adequately powered for noninferiority hypothesis)
Composite ischemic endpoints at 30 days	SOE=Low (4 studies, 34,022 patients) Similar rates of composite events in two studies of enoxaparin vs. UFH (14% vs. 14.5% and 14% vs. 16.1%), one study of fondaparinux vs. UFH (4.2% vs. 6%), and one study of enoxaparin vs. fondaparinux (7.4% vs. 7.4%)
Composite of all-cause mortality, nonfatal MI, or revascularization after 6 months	SOE=Low (1 study, 20,078 patients) No difference between enoxaparin (10.2%) and fondaparinux (10.1%) adequately powered for a noninferiority hypothesis
Major bleeding at 30 days	SOE=Low (4 studies, 69,908 patients) One RCT showed lower events with fondaparinux (3.1%)vs. enoxaparin (5.0%); one RCT showed lower events with UFH (7.6%) vs. enoxaparin (9.1%). Two observational studies of UFH v s. enoxaparin had conflicting results (2.7% UFH vs. 1.8% enoxaparin; 7% UFH vs. 6.7% enoxaparin)

Abbreviations: CI=confidence interval; CV=cardiovascular; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; NA=not applicable; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence; UFH=unfractionated heparin

Key Points for Timing of Clopidogrel Administration (Before or After PCI) in Studies of Bivalirudin vs. UFH and Upstream vs. Deferred GPI Use

- In patients pretreated with clopidogrel, there were no statistically significant differences in composite ischemic endpoints at 30 days or at 1 year, or in all-cause mortality at 30 days in bivalirudin-treated patients when compared with heparin-treated patients at 30 days (all insufficient SOE).

- In both clopidogrel pretreated and clopidogrel deferred patients, bivalirudin resulted in fewer major bleeding events at 30 days when compared with heparin-based treatment (moderate SOE for clopidogrel pretreated and insufficient SOE for clopidogrel deferred).

- 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).

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

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor bivalirudin or upstream GPI; ORs greater than 1 favor UFH or deferred GPI
Clopidogrel pretreatment: Bivalirudin vs. heparin-based strategy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE=Insufficient (2 studies, 2571 patients) Both studies showed no statistically significant difference in composite event rates ranging from OR 1.11 to 1.25
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE=Insufficient (1 study, 4570 patients) Bivalirudin 21.5%, heparin 20.1%
All-cause mortality at 1 year	SOE=Insufficient (1 study, 5126 patients) Bivalirudin 16.0%, heparin 16.3%
Major bleeding at 30 days	SOE=Moderate (3 studies, 6322 patients) Summary OR 0.65 (0.49 to 0.85) favoring bivalirudin
Clopidogrel pretreatment: Upstream vs. deferred GPI use	
Composite of all-cause mortality, nonfatal MI, revascularization, or thrombotic GPI bailout at 96 hours	SOE=Insufficient (1 study, 6895 patients) Upstream GPI: 8.7% Deferred GPI: 9.4%
Composite of all-cause mortality, nonfatal MI, or rehospitalization at 30 days	SOE=Insufficient (1 study, 300 patients) Upstream GPI: 9% Deferred GPI: 10%
Composite of all-cause mortality, nonfatal MI, or ischemia/revascularization at 30 days	SOE=Low (2 studies, 638 patients) Upstream GPI: 15.7% Deferred GPI: 20.3%
All-cause mortality at 30 days	SOE=Insufficient (5 studies, 8168 patients) Summary OR (95% CI): 0.56 (0.30 to 1.05)
Major bleeding at 30 days	SOE=Moderate (5 studies, 7416 patients) Summary OR 1.49 (1.10 to 2.01) favoring deferred GPI use

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor bivalirudin or upstream GPI; ORs greater than 1 favor UFH or deferred GPI
Clopidogrel deferred: Bivalirudin vs. heparin-based strategy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE=Insufficient (2 studies, 2571 patients) One study showed a significant reduction favoring bivalirudin, OR 0.42 (0.21 to 0.84, p=0.02), the other study showed no difference, OR 1.05 (0.80 to 1.40).
Major bleeding at 30 days	SOE=Insufficient (2 studies, 2571 patients) One study showed no statistical difference between the groups, OR 0.32 (0.10 to 1.01) ; the other study showed a statistically significant reduction favoring bivalirudin, OR 0.53 (0.31 to 0.91, p=0.02).
Clopidogrel deferred: Upstream vs. deferred GPI use	
Composite of all-cause mortality, nonfatal MI, revascularization, or thrombotic bailout with GPI at 96 hours	SOE=Insufficient (1 study, 2271 patients) Upstream GPI: 10.3% Deferred GPI: 11.2%
All-cause mortality at 30 days	SOE=Insufficient (4 studies, 11,858 patients) Summary OR 0.97 (0.80 to 1.18)
Major bleeding at 30 days	SOE=High (3 studies, 11,698 patients) Summary OR 1.27 (1.08 to 1.50) favoring deferred GPI use

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: CI=confidence interval; CV=cardiovascular; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; NA=not applicable; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence

Key Question 2. Initial Conservative Approach for UA/NSTEMI

Thirty-two studies evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 209,231 patients with UA/NSTEMI treated with an initial conservative approach or a mixed population where the approach (conservative or invasive) was not presented separately. The following two comparisons were assessed in the included studies and are detailed in this analysis:

1. Enoxaparin versus UFH versus fondaparinux (full UA/NSTEMI cohort)
   - 21 studies (12 RCTs, 9 observational; 161,506 total patients)
2. GPI plus UFH versus UFH alone
   - 11 studies (11 RCTs; 47,725 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.

Key Points for Enoxaparin vs. UFH vs. 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, but there was insufficient evidence to reach a conclusion on the comparative treatment effect on all-cause mortality and major bleeding.

- From 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 and all-cause mortality.

Table H. Summary strength of evidence and effect estimates: enoxaparin vs. unfractionated heparin vs. fondaparinux (full UA/NSTEMI cohort)[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor enoxaparin or fondaparinux; ORs greater than 1 favor UFH
Enoxaparin vs. UFH vs. fondaparinux	
Composite endpoint of all-cause mortality, nonfatal MI, revascularization, or recurrent ischemia at 48 hours to 43 days	Enoxaparin vs. UFH SOE=High (6 studies, 12,124 patients) Summary OR 0.84 (0.76 to 0.93) favoring enoxaparin
	Fondaparinux vs. UFH SOE=Low (7 studies, 32,202 patients) Summary OR 0.78 (0.67 to 0.90) favoring fondaparinux
Composite ischemic outcome at 6 months	Enoxaparin vs. fondaparinux SOE=Low (1 study, 20,078 patients) Event rate similar in enoxaparin and fondaparinux groups (10.2% vs. 10.1%) in this large, good-quality RCT adequately powered for a noninferiority hypothesis
All-cause mortality at 48 hours to 43 days	Enoxaparin vs. UFH SOE=Insufficient (8 studies, 23,015 patients) Summary OR 0.98 (0.84 to 1.14)
	Fondaparinux vs. UFH SOE=Insufficient (9 studies, 43,093 patients) Summary OR 0.93 (0.71 to 1.20),
Nonfatal MI at 48 hours to 43 days	Enoxaparin vs. UFH SOE=Moderate (9 studies, 22,970 patients) Summary OR 0.85 (0.76 to 0.95) favoring enoxaparin
	Fondaparinux vs. UFH SOE=Insufficient (10 studies, 43,048 patients) Summary OR 0.85 (0.69 to 1.04)
Major bleeding at 48 hours to 43 days	Enoxaparin vs. UFH SOE=Insufficient (8 studies, 22,901 patients) Summary OR 1.11 (0.81 to 1.51)
	Fondaparinux vs. UFH SOE=Low (9 studies, 42,979 patients) Summary OR 0.69 (0.49 to 0.97) favoring fondaparinux

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: CI=confidence interval; ECG=electrocardiogram; GPI= glycoprotein IIb/IIIa inhibitor; KQ=Key Question; MI=myocardial infarction; RCT=randomized controlled trial; SOE=strength of evidence; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

Key Points for GPI Plus UFH vs. UFH Alone

- Adding GPIs to unfractionated heparin reduced the rate of mortality at 30 days (high SOE), and reduced composite ischemic events and nonfatal MI, especially in trials of eptifibatide and tirofiban (moderate SOE). 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 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 listed above, the tradeoff is an increase in and 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 vs. unfractionated heparin alone[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor GPI plus UFH; ORs greater than 1 favor UFH alone
GPI vs. UFH	
Composite ischemic events up to 30 days	SOE=Moderate (11 studies, 47,725 patients) 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)
Mortality up to 30 days	SOE=High (9 studies, 24,699 patients) Summary OR 0.80 (0.67 to 0.96), favoring GPI
Nonfatal MI up to 30 days	SOE=Moderate (9 studies, 24,699 patients) Summary OR 0.79 (0.61 to 1.02)
Recurrent ischemia up to 30 days	SOE=Insufficient (6 studies, 5755 patients) Summary OR 0.81 (0.56 to 1.18)
Revascularization up to 30 days	SOE=Insufficient (2 studies, 279 patients) Low number of events reported in both trials, with fewer in GPI groups
Major bleeding at 30 days	SOE=Insufficient (4 studies, 18,855 patients) Summary OR 1.13 (0.80 to 1.59)
Minor bleeding up to 30 days	SOE=High (5 studies, 22,259 patients) Summary OR 1.62 (1.20 to 2.19), favoring heparin alone

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: CI=confidence interval; ECG=electrocardiogram; GPI= glycoprotein IIb/IIIa inhibitor; KQ=Key Question; MI=myocardial infarction; RCT=randomized controlled trial; RR=risk ratio; SOE=strength of evidence; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

Key Question 3. Postdischarge Treatment for UA/NSTEMI

Sixty-three studies evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 604,267 patients with UA/NSTEMI continued on treatment after hospitalization (postdischarge). The following five comparisons were relevant in the posthospitalization setting and were analyzed:

1. Low-dose versus high-dose aspirin
   - 4 studies (0 RCTs, 4 observational; 29,718 total patients)
2. Single versus dual antiplatelet therapy
   - 7 studies (2 RCTs, 5 observational; 207,745 total patients)
3. Short-term versus long-term dual antiplatelet therapy (clopidogrel)
   - 9 studies (4 RCTs, 5 observational; 21,410 total patients)
4. Antiplatelet therapy with PPI versus antiplatelet alone
   - 32 studies (4 RCTs, 28 observational; 308,790 total patients)
     a. Dual antiplatelet with and without omeprazole
     b. Dual antiplatelet with and without PPI
     c. Aspirin monotherapy with and without PPI
5. Dual antiplatelet therapy alone versus dual antiplatelet plus oral anticoagulant (i.e., triple therapy)
   - 11 studies (11 observational; 83,962 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.

Key Points for Low-dose vs. High-dose Aspirin

- In the postdischarge setting, high-dose aspirin was associated with fewer nonfatal MI events compared with low-dose aspirin at 6 months (low SOE).

- There were conflicting results on composite ischemic events and the individual outcomes of mortality, nonfatal MI at 1 year, stroke, revascularization, and major bleeding due to the different definitions of low-dose versus high-dose aspirin across the observational studies (all insufficient SOE).

Table J. Summary strength of evidence and effect estimates: low-dose vs. high-dose aspirin[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) HRs less than 1 favor high-dose aspirin; HRs greater than 1 favor low-dose aspirin
Low-dose vs. high-dose aspirin	
Composite of all-cause mortality, nonfatal MI, or stroke at 6 months	SOE=Insufficient (1 study, 20,469 patients) HR 0.92 (0.79 to 1.07)
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE=Insufficient (3 studies, 9249 patients) Low-dose ASA and high-dose ASA had similar rates of ischemic events in all 3 studies
All-cause mortality at 6 months	SOE=Insufficient (1 study, 20,469 patients) HR 0.89 (0.72 to 1.10)
All-cause mortality at 1 year	SOE=Insufficient (2 studies, 6409 patients) One study (ASA/clopidogrel) showed no difference between doses, the other found that high-dose ASA (monotherapy) reduced mortality
Nonfatal MI at 6 months	SOE=Low (1 study, 20,469 patients) HR 0.79 (0.64 to 0.98) favoring high-dose ASA
Nonfatal MI at 1 year	SOE=Insufficient (1 study, 4589 patients) HR 0.99 (0.66 to 1.48)
Stroke at 6 months	SOE=Insufficient (1 study, 20,469 patients) HR 1.59 (0.95 to 2.65)
Stroke at 1 year	SOE=Insufficient (1 study, 4589 patients) HR 1.37 (0.94 to 2.00)
Revascularization at 1 year	SOE=Insufficient (2 studies, 6429 patients) One study (ASA/clopidogrel) showed no difference between doses, the other study (ASA monotherapy) showed more events with high dose
Major bleeding at 1 year	SOE=Insufficient (2 studies, 7409 patients) One study had high bleeding rates in low-dose group; other study had high rates in high-dose group

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

Key Points for Single vs. Dual Antiplatelet Therapy

- Dual antiplatelet therapy reduces the rates of composite ischemic outcomes and nonfatal MI in-hospital to 1 year compared with single antiplatelet therapy (high SOE).

Table K. Summary strength of evidence and effect estimates: single vs. dual antiplatelet therapy[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Single vs. dual antiplatelet therapy	
Composite ischemic outcomes in-hospital to 1 year	SOE=High (4 studies, 152,601 patients) All studies showed statistically significant lowering of composite events in dual antiplatelet arm, ORs/RRs 0.69 to 0.91
Stroke in-hospital to 1 year	SOE=Insufficient (5 studies, 158,840 patients) 4 out of 5 studies showed no statistically significant difference in stroke rates
Nonfatal MI in-hospital to 1 year	SOE=High (4 studies, 152,601 patients) All studies showed fewer recurrent MIs in dual antiplatelet group, ORs/RRs 0.77 to 0.86

Outcome	Strength of Evidence and Effect Estimate (95% CI)
All-cause mortality in-hospital to 1 year	SOE=Moderate (6 studies, 160,171 patients) All studies showed fewer deaths in the dual antiplatelet group ranging from OR/RR 0.66 to OR/RR 0.93
Major bleeding in-hospital to 9 months	SOE=Insufficient (3 studies, 148,311 patients) 2 studies showed a reduction in major bleed in dual antiplatelet group (1 statistically significant [16% vs. 21%], 1 not statistically significant)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

Key Points for Short-term vs. Long-term Dual Antiplatelet Therapy

- Long-term dual antiplatelet therapy reduces the rates of composite ischemic events and all-cause mortality compared with short-term dual antiplatelet therapy (low SOE).
- Rates of stent thrombosis are similar between short- and long-term clopidogrel therapy (low SOE). The rates were higher when clopidogrel was stopped within 30 days or 6 months, but the difference beyond 6 months was nonsignificant.

Table L. Summary strength of evidence and effect estimates: short-term vs. long-term dual antiplatelet therapy[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Short-term vs. long-term dual antiplatelet therapy	
Composite of all-cause mortality and nonfatal MI within 2 years	SOE=Insufficient (2 studies, 3468 patients) One observational study showed discontinuation before 6 months increased events; other RCT showed no difference between 6- and 24-month therapy
Composite of all-cause mortality and stroke at 2 years	SOE=Insufficient (1 study, 2013 patients) One RCT reported no difference between 6- and 24-month therapy
Composite all-cause mortality, nonfatal MI and revascularization at 6 months and 1 year	SOE=Insufficient (2 studies, 3258 patients) Both studies (1 RCT, 1 observational) found similar rates between short- and long-term therapy
Composite all-cause mortality, nonfatal MI and stroke at 30 days, 1 year, and 2 years	SOE=Low (3 studies, 5133 patients) 2 RCTs found statistically significant reductions in events from long-term DAPT at 6 months and 1 year. One RCT found no difference between 6- and 24-month therapy
All-cause mortality at 6 months, 1 year, and 2 years	SOE=Low (5 studies, 6275 patients) 3 RCTs showed statistically significant reduction with longer therapy (2 studies comparing 30 days to 6 months; 1 study comparing 6 and 24 months); DES patients benefited more than BMS patients in an observational study; another observational study reported higher mortality in patients who discontinued DAPT within first 6 months of discharge
Cardiovascular mortality at 6 months and 2 years	SOE=Insufficient(2 studies, 3017 patients) Both RCTs found similar rates between short-and long-term therapy (30 day vs. 6 months and 6 months vs. 24 months)
Nonfatal MI at 6 months, 1 year, and 2 years	SOE=Insufficient (5 studies, 6275 patients) 4 studies (3 RCTs and 1 observational) showed similar rates of MI in short- and long-term therapy groups; One observational study showed statistically significant higher risk in DES patients who discontinue clopidogrel within first 6 months

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Stroke at 6 months and 2 years	SOE=Insufficient (2 studies, 3017 patients) Both RCTs found similar rates between short-and long-term therapy
Revascularization at 6 months and 1 year	SOE=Insufficient (3 studies, 4262 patients) Rates of revascularization were similar between short- and long-term therapy (30 day vs. 6 months and 6 months vs. 24 months)
Stent thrombosis at 6 months, 1 year, and 2 years	SOE=Low (5 studies, 11,255 patients) Rates of stent thrombosis were higher when clopidogrel was stopped within 30 days or 6 months from two observational studies. Three studies (2 RCTs and 1 observational) showed no statistically significant difference in event rates at 1 or 2 years.
Major bleeding at 1 and 2 years	SOE=Insufficient (2 studies, 4129 patients) One RCT showed a statistically significant lower rate of major bleed with clopidogrel with 6-month treatment; the other RCT showed no statistically significant difference in rates with 1-year treatment
Minor bleeding at 1 and 2 years	SOE=Insufficient (2 studies, 4129 patients) Both RCTs found no difference at 1 and 2 years

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

Key Points for Antiplatelet Therapy with PPI vs. Antiplatelet Alone

- In RCTs that evaluated the specific PPI omeprazole versus placebo given in combination with dual antiplatelet therapy, use of omeprazole reduced rates of upper gastrointestinal bleeding (moderate SOE) and all-cause mortality at 1 year (low SOE). There was insufficient evidence on the effect of omeprazole on composite ischemic events, nonfatal MI, stroke, revascularization, or stent thrombosis.

- From observational studies assessing the use of diverse PPIs with dual antiplatelet therapy, event rates are higher in patients who were receiving any type of PPI medication for the composite outcome (all-cause mortality/nonfatal MI) at 6 to 18 months, nonfatal MI at 1 year, and revascularization after 1 year. Possible confounding reduced the SOE to moderate. Note that we were not able to reach a firm conclusion as to why large, well-done observational studies of PPIs as a class consistently found worse outcomes in patients who received PPIs with antiplatelet therapy while a smaller number of RCTs of one particular PPI (omeprazole) found no increase in mortality.

- There was also insufficient evidence that the type of PPI affected any of the clinical outcomes (composite or individual).

- In observational studies assessing use of PPIs with aspirin monotherapy, there was a higher rate of composite ischemic events, all-cause mortality, and nonfatal MI at 1 year in the group receiving any type of PPI (moderate SOE).

Table M. Summary strength of evidence and effect estimates: antiplatelet therapies with and without proton pump inhibitor[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Dual antiplatelet therapy with and without omeprazole	
Composite of CV mortality, nonfatal MI and stroke within 1 year	SOE=Insufficient (2 RCTs, 1 observational, 4774 patients) No statistically significant difference between omeprazole vs. placebo on composite events
All-cause mortality at 1 year	SOE=Low (2 RCTs, 1 observational, 4698 patients) One study showed lower rates of death with omeprazole OR 0.31 (0.10 to 0.97); other two studies showed statistically nonsignificant differences in event rates
Nonfatal MI at 6 months and 1 year	SOE=Insufficient (1 RCT, 1 observational, 4461 patients) No statistically significant difference in MI rates with omeprazole
Stroke at 30 days and 6 months	SOE=Insufficient (2 RCTs, 4045 patients) No statistically significant difference in TIA or CVA rates with omeprazole
Revascularization at 1 year	SOE=Insufficient (1 RCT, 1 observational, 4461 patients) No statistically significant difference in revascularization rates with omeprazole
Stent thrombosis at 1 year	SOE=Insufficient (1 RCT, 1 observational, 4461 patients) No statistically significant difference in stent thrombosis in omeprazole group
GI bleeding	SOE=Moderate (4 RCTs, 4595 patients) 3 out of 4 RCTs found statistically significant lower rates of upper GI bleed in omeprazole group
Dual antiplatelet therapy with and without PPI **ORs less than 1 favor PPI use; ORs greater than 1 favor no PPI use**	
Composite ischemic outcomes within 1 year	SOE=Moderate (3 observational studies, 11,054 patients) All 3 studies showed higher event rates in PPI group (statistically significant in 2 studies: OR 2.0 (1.1 to 3.7); HR 3.2 (CI, 2.56 to 4.01)
Composite of all-cause mortality, nonfatal MI, or stroke at 1 year	SOE=Moderate (9 observational studies, 124,888 patients) Summary OR 1.35 (1.05 to 1.73) favoring no PPI group
Composite of all-cause mortality and nonfatal MI at 6 to 18 months	SOE=Moderate (3 observational studies, 22,094 patients) Summary OR 1.40 (1.24 to 1.59) favoring no PPI group
All-cause mortality within first 3 months	SOE=Insufficient (3 observational studies, 8941 patients) Two studies showed no differences in mortality rates; one study showed a statistically significant increase in mortality in PPI group (adjusted HR 2.2; 95% CI, 1.1 to 4.3)
All-cause mortality after 1 year	SOE=Moderate (16 observational studies, 141,474 patients) Summary OR 1.48 (1.16 to 1.89) favoring no PPI group
All-cause mortality at 6 years	SOE=Low (1 observational study, 23,200 patients) HR 1.32 (1.00 to 1.73)
Cardiovascular mortality at 1 year	SOE=Insufficient (3 observational studies, 69,296 patients) Two 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, 8941 patients) 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 1 year	SOE=Moderate (8 observational studies, 122,367 patients) Summary OR 1.65 (1.38 to 1.97), favoring no PPI group
Stroke at 1 year	SOE=Moderate (6 observational studies, 57,501 patients) Summary OR 1.46 (1.15 to 1.86), favoring no PPI group
Revascularization after 1 year	SOE=Moderate (4 observational studies, 52,576 patients) Summary OR 1.37 (1.19 to 1.58), favoring no PPI group
Revascularization at 6 months and 4 years	SOE=Insufficient (2 observational studies, 18,880 patients) Both studies showed no difference in revascularization rates
Stent thrombosis at 30 days	SOE=Insufficient (1 observational study, 3406 patients) No statistically significant difference in stent thrombosis rate between groups

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Stent thrombosis at 1 year	SOE=Insufficient (4 observational studies, 23,833 patients) Summary OR 1.29 (0.94 to 1.77)
Major bleeding at 30 days	SOE=Insufficient (3 observational studies, 7496 patients) OR 1.95 (0.59 to 6.49)
Major bleeding at 1 year	SOE=Insufficient (3 observational studies, 22,138 patients) OR 1.25 (0.94 to 1.67)
GI bleeding	SOE=Insufficient (4 observational studies, 23,555 patients) Conflicting results in in-hospital and 12-18 month time points with 2 studies showing no difference and 2 studies showing a statistically significant reduction in GI bleed in PPI group
Minor bleeding	SOE=Insufficient (1 observational study, 7346 patients) No difference in minor bleed in-hospital or at 1 year
Rehospitalization at 3 months	SOE=Low (1 observational study, 3406 patients) Significant increase in rehospitalization in PPI group at 3 months, HR 1.32 (1.00 to 1.73)
Rehospitalization at 1 year	SOE=Low (5 observational studies, 25,715 patients) Summary OR 3.39 (1.88 to 6.11), favoring no PPI group
Aspirin monotherapy with and without PPI **ORs less than 1 favor PPI use; ORs greater than 1 favor no PPI use**	
Composite of CV death, nonfatal MI, or stroke at 1 year	SOE=Moderate (3 observational studies, 108,602 patients) Summary OR 1.58 (1.45 to 1.73) favoring no PPI group
All-cause mortality (in-hospital)	SOE=Insufficient (1 observational study, 2744 patients) OR 1.47 (0.67 to 3.25)
All-cause mortality at 1 year	SOE=Moderate (3 observational studies, 108,602 patients) Summary OR 1.59 (1.43 to 1.76) favoring no PPI group
Nonfatal MI (in-hospital)	SOE=Insufficient (1 observational study, 2744 patients) OR 0.99 (0.18 to 5.53)
Nonfatal MI at 1 year	SOE=Moderate (2 observational studies, 105,858 patients) Both studies showed increased risk of events in PPI group HR 1.19 to 1.39
Stroke (in-hospital)	SOE=Insufficient (1 observational study, 2744 patients) OR 3.21 (0.24 to 42.5)
Stroke at 1 year	SOE=Insufficient (3 observational studies, 108,602 patients) Summary OR 1.13 (0.94 to 1.36)
Major bleeding (in-hospital)	SOE=Insufficient (1 observational study, 2744 patients) OR 2.16 (0.17 to 27.3)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

Key Points for Dual Antiplatelet vs. Triple Therapy

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

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

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor triple therapy; ORs greater than 1 favor DAPT
Dual antiplatelet vs. triple therapy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year or longer	SOE=Insufficient (4 studies, 4520 patients) 2 studies showed statistically nonsignificant differences; 2 studies showed statistically significant increases in events in DAPT group
Composite of all-cause mortality, nonfatal MI, within first year	SOE=Insufficient (3 studies, 51,658 patients) One study each showed a statistically significant increase, statistically significant decrease, or statistically nonsignificant increase in events in the TT group
All-cause mortality at 30 days to 6 months	SOE=Insufficient (2 studies, 7075 patients) One study found no difference, another found statistically significant lower deaths in in TT group
All-cause mortality at 1 to 5 years	SOE=Insufficient (6 studies, 32,134 patients) Summary OR 1.50 (0.076 to 2.95)
Nonfatal MI at 6 months	SOE=Insufficient (1 study, 800 patients) TT 3.3% Warfarin/ASA 4.5% (p=0.49)
Nonfatal MI at 1 to 5 years	SOE=Low (4 studies, 1,425 patients) Summary OR 1.85 (1.13 to 3.02) favoring DAPT
Stroke at 6 months	SOE=Low (1 study, 800 patients) TT 0.7% warfarin/ASA 3.4% (p=0.02), favoring TT
Stroke at 1 to 5 years	SOE=Insufficient (3 studies, 999 patients) Summary OR 1.57 (0.72 to 3.43)
Revascularization up to 5 years	SOE=Insufficient (4 studies, 2066 patients) No statistical difference between DAPT and TT groups
Major bleeding at 30 days	SOE=Insufficient(4 studies, 3476 patients) Summary OR 2.68 (0.80 to 8.99)
Major bleeding at 1 to 5 years	SOE=Insufficient (5 studies, 29,340 patients) Summary OR 1.79 (0.86 to 3.74)
Minor bleeding at 1 to 5 years	SOE=Insufficient (3 studies, 890 patients) Summary OR 1.33 (0.48 to 3.69)
Major and minor bleeding	SOE= Insufficient (2 studies, 21,545 patients) Both studies failed to show a difference between DAPT and TT in the combined endpoint of major and minor bleeding.
Stent thrombosis	SOE=Insufficient (2 studies, 840 patients) No significant difference in rates (triple therapy 1.4 to 4.1%; dual antiplatelet 1.3 to 3.6%)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.

Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

Discussion

Key Findings

This CER assessed many types of antiplatelet and anticoagulant therapies for UA/NSTEMI patients undergoing PCI, medical management, and postdischarge treatment. For patients undergoing an early invasive approach, the highest level of evidence was found for upstream (precatheterization) treatment with GPIs, which was associated with lower rates of revascularization but higher risk of major bleeding events at 30 days compared with deferred (periprocedural) GPI treatment. There was moderate evidence that the higher risk of bleeding from upstream GPI administration occurred with either pretreatment or deferred clopidogrel administration. There was low strength of evidence that a 600-mg loading dose of clopidogrel resulted in lower rates of nonfatal MI or stent thrombosis at 30 days compared with a 300-mg loading dose. In the short term, there was moderate evidence that prasugrel significantly reduced rates of death/MI/stroke and ticagrelor reduced the same composite endpoint at 30 days compared with clopidogrel. At 1 year, both agents were associated with a lower rate of composite ischemic events and individual endpoints of nonfatal MI and stent thrombosis, but the strength of evidence was rated low. Similarly, there was low strength of evidence that prasugrel increased major bleeding events, and ticagrelor had no difference in major bleeding events compared with clopidogrel.

Our findings are consistent with 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 ACCF/AHA guidelines update. Our major findings mirror other meta-analyses in that upstream GPI use is not associated with significant reduction of composite ischemic endpoints, the optimal loading dose of clopidogrel remains unclear, and prasugrel and ticagrelor are associated with a significant reduction in ischemic endpoints when compared with clopidogrel. The results of two RCTs evaluating ticagrelor versus clopidogrel were investigated in our analysis and evidence from these RCTs adds to what is already known about the use of antiplatelet medications in UA/NSTEMI patients. Ticagrelor is associated with a significant reduction in ischemic endpoints at 1 year (not at 30 days) when compared with clopidogrel, but unlike prasugrel, the incidence of major bleeding was not significantly higher in ticagrelor-treated patients.

Due to a paucity of data on the optimal timing of oral antiplatelet agents as initial treatment for UA/NSTEMI, we performed separate analyses evaluating the effect of a nonrandomized (i.e., specified in the study protocol) treatment with either clopidogrel pretreatment or clopidogrel treatment at the time of PCI in two groups of study patients: (1) those randomized to bivalirudin versus heparin-based strategy and (2) those randomized to upstream GPI use versus deferred GPI use. In the comparison of bivalirudin versus heparin *with planned GPI use*, there was high strength of evidence that bivalirudin reduced the rate of the composite outcome of all-cause mortality, nonfatal MI, revascularization, major bleeding, and minor bleeding at 30 days. In the comparison of bivalirudin *without planned GPI use*, there was high strength of evidence that bivalirudin reduced major bleeding at 30 days, but low strength of evidence that it reduced minor bleeding at 30 days. In patients who were treated with clopidogrel before undergoing PCI (*clopidogrel pretreatment strategy*), there was moderate strength of evidence that bivalirudin

reduced major bleeding events at 30 days when compared with heparin-based treatment, low strength of evidence that the use of deferred GPI is associated with higher rates of ischemic endpoints (all-cause mortality, nonfatal MI, ischemia, revascularization), and moderate strength of evidence that deferred GPI resulted in lower rates of major bleeding at 30 days than use of upstream GPI. In patients treated with clopidogrel at the time of PCI (*clopidogrel deferred strategy*), there was less major bleeding at 30 days with the use of deferred GPI compared with upstream GPI.

The comparisons of LMWH with UFH resulted in different findings in the invasively and conservatively managed populations. For patients undergoing PCI, there was low strength of evidence that enoxaparin versus UFH and enoxaparin versus fondaparinux showed no significant difference in composite ischemic endpoints at 30 days; but there was a significantly lower incidence of major bleeding at 30 days favoring fondaparinux when compared with enoxaparin. In contrast, in the analysis of the conservatively managed population at 30 days, there was high strength of evidence that enoxaparin reduced composite ischemic events compared with UFH, and insufficient strength of evidence for major bleeding. Fondaparinux also showed a significant reduction in composite ischemic events compared with UFH, but the strength of evidence was rated low since we used an indirect analysis and the estimate was imprecise. These results, based mostly on RCTs and supported by observational studies, are consistent with ACCF/AHA guideline recommendations of initial anticoagulant treatment among UA/NSTEMI patients undergoing an initial conservative approach where all three anticoagulants are recommended but enoxaparin and fondaparinux are preferred.

For the conservatively managed population, there was high strength of evidence that adding GPIs to UFH reduced the rate of mortality at 30 days and moderate strength of evidence that it also reduced composite ischemic events and nonfatal MI, especially in trials of eptifibatide and tirofiban. The addition of abciximab to UFH did not significantly reduce ischemic events compared with UFH alone. Data gained from these studies are more challenging to extrapolate and implement in the context of actual clinical practice due to the fact that the majority of these studies were performed prior to the time when an early invasive strategy was widely implemented, and they employed an initial conservative strategy followed by percutaneous revascularization after 18 to 72 hours. Furthermore, several GPI studies reported results with 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. Current ACCF/AHA UA/NSTEMI guidelines recommend adding a GPI (tirofiban or eptifibatide) for 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,[21] show no change in the recommendation of administering a GPI (tirofiban or eptifibatide) in addition to an anticoagulant or oral antiplatelet for patients in 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 or if after angiography a percutaneous revascularization is deemed not necessary or if they do not undergo diagnostic angiography (class IIa, level of evidence C).

In the postdischarge setting, there was insufficient strength of evidence to draw conclusions about the rates of composite ischemic events associated with low-dose aspirin compared with high-dose aspirin. There were conflicting results on the individual outcomes of mortality,

nonfatal MI, stroke, revascularization, and major bleeding; this was due to the different definitions of low-dose (81 mg, <150 mg, <162 mg) versus high-dose aspirin (161-325 mg, ≥150 mg, and ≥162 mg) across the observational studies. There was high strength of evidence that dual antiplatelet therapy reduced the rates of composite ischemic outcomes and nonfatal MI. There was low strength of evidence that rates of composite ischemic events (all-cause mortality, nonfatal MI, stroke), all-cause mortality, and stent thrombosis are reduced with long-term clopidogrel therapy. The rates of these events were higher when clopidogrel was stopped within 30 days or 6 months, but the differences between therapies beyond 6 months were nonsignificant. We have less confidence in the findings comparing 6 months to longer-term therapy since the RCTs had different durations of clopidogrel treatment (12 months in one trial and 24 months in another trial) and this is partly based on a qualitative assessment of five observational studies which assessed different time point comparisons (e.g., 6 months vs. 12 months and <12 months vs. ≥12 months).

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 versus dual antiplatelet therapy supported current recommendations, with evidence of better outcomes among patients treated with dual antiplatelet therapy. Only two studies examined treatment effect based on stent type, and again the worst outcomes were observed among patients who discontinue clopidogrel within the first 6 months with either bare metal or drug-eluting stents. Guidelines recommend duration of 1 year if there is no increased risk of bleeding.

In our analysis of the use of PPIs with dual antiplatelet therapies, three randomized trials of omeprazole versus placebo failed to show any difference in ischemic events. In the observational studies comparing all types of PPI medication to no PPI medication, findings suggest that patients on a PPI do worse but are likely confounded by comorbid conditions since these findings are not seen in the randomized trials. Indeed, a recent update of the AHA/ACCF guidelines has removed the recommendation to administer PPI among patients with a history of GI bleeding.

Finally, we assessed the use of triple therapy (dual antiplatelet plus anticoagulation) and found low strength of evidence that nonfatal MI rates are higher and stroke rates are lower with triple therapy. 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 AHA/ACC 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 (due to the lack of randomized trials for this comparison) to target oral anticoagulant therapy to a lower INR (e.g., 2.0 to 2.5) is reasonable in patients managed with dual antiplatelet therapy due to the lack of randomized trials for this comparison.

Applicability

Studies included in this review are primarily multicenter international studies, including the United States and Canada, so the applicability of our findings does span multiple geographic locations. While many studies are also conducted outside the United States, there are similarities in UA/NSTEMI treatments internationally and should therefore not be seen as a limitation in treatment setting. However, there are two factors that limit our findings; namely, 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 acute coronary syndrome (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 did exclude studies that focused exclusively in 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 were labeled as a conservatively managed approach. Many of those types of studies are older (mid-1990s), or are conducted in non-U.S. settings. We did not find any limits to applicability regarding the comparisons or outcomes reported.

Research Gaps

Acute coronary syndromes, including UA/NSTEMI, are widely studied as evidenced by the fact that we screened 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, and specifically related to dosage, timing, 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 (Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest) to identify gaps and classifies 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 key question.

KQ 1

In KQ 1, the primary research gap was the lack of direct comparisons of intravenous and oral antiplatelet and anticoagulant treatment strategies. While many studies investigated the use of one oral antiplatelet versus another oral antiplatelet, there was scant data on combinations of antiplatelet and anticoagulant medications used for UA/NSTEMI patients. Our review highlights that there is also a need for future studies to compare novel antiplatelet agents (ticagrelor, prasugrel) in a head-to-head manner. In clinical practice, the desire to minimize bleeding 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. Furthermore, given the importance of reducing ischemic events and bleeding events, the absence of studies measuring the effect of specific strategies to reduce bleeding (i.e., radial artery access, vascular closure devices) is a serious gap.

KQ 2

In KQ 2, the primary research gap is reporting the 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 LMWH and GPI analyses—and often the data were not concordant. Future studies can address this by either 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 dual antiplatelet treatment strategy requires further study, especially within subgroups of patients at risk for bleeding complications.

Second, more studies are needed on clopidogrel duration beyond one year of ongoing treatment. There were few RCTs on this subject, and the small number of observational studies showed no difference in treatment durations 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 long-term benefit is still uncertain with this review suggesting no differences in clinical outcome comparing 6 months or 1 year to longer. 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 use of these agents comparing effectiveness 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) show 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 if 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.

Conclusions

- Overall, the administration of GPIs prior to PCI is associated with a reduction in future ischemic events but an increase in major bleeding events, regardless of whether clopidogrel was administered prior to or during the PCI.
- Prasugrel and ticagrelor reduced rates of composite ischemic events (death/MI/stroke) at 30 days and 1 year in comparison to clopidogrel.

- Bivalirudin was associated with a lower incidence of major bleeding events compared with heparin-based treatment, regardless of whether a GPI administration was planned; bivalirudin also reduced rates of minor bleeding events compared to heparin with GPI use.
- Enoxaparin and fondaparinux are associated with a significant reduction in composite ischemic events when compared with unfractionated heparin 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 (any type) have been associated with worse clinical outcomes in observational studies, the results from a small number of RCTs of omeprazole show no significant difference in ischemic events compared with placebo. Therefore, observational studies are likely confounded by patient selection bias and coexisting comorbid conditions.

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, diabetics, women, obese patients and those with comorbid illness).

Glossary

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
TIA	transient ischemic attack
TIMI	thrombolysis in myocardial infarction
TT	triple therapy
UA	unstable angina
UFH	unfractionated heparin
wk	week/weeks
yr	year/years

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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 between the time of admission and 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 parenteral anticoagulants—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 their 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 this 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[a]

Drug Category	Early Invasive		Initial Conservative	Postdischarge
Aspirin	Aspirin (low or high dose)		Aspirin (low or high dose)	Aspirin (low or high dose)
Intravenous antiplatelet (glycoprotein IIb/IIIa inhibitor)	Upstream	Periprocedure		
	Epifibatide Tirofiban	Eptifibatide Tirofiban Abciximab		
Oral antiplatelet ($P2Y_{12}$ Inhibitor)	Clopidogrel Ticagrelor	Clopidogrel Prasugrel Ticagrelor	Clopidogrel Ticagrelor Prasugrel[a]	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

[a]TRILOGY ACS trial was published in NEJM August 26, 2012, and will be added to the final version of this report.
Abbreviations: PCI = percutaneous coronary intervention

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 there are 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, and it provides a more potent and faster acting antiplatelet effect when compared with clopidogrel and does not appear to be susceptible to genetic polymorphisms of the hepatic isoenzymes. Ticagrelor is a reversible $P2Y_{12}$ receptor antagonist that, when compared with clopidogrel, provides a more rapid and more potent inhibition of platelets.

The antiplatelet agents belonging to the glycoprotein IIb/IIIa inhibitor (GPI) class are administered intravenously and 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

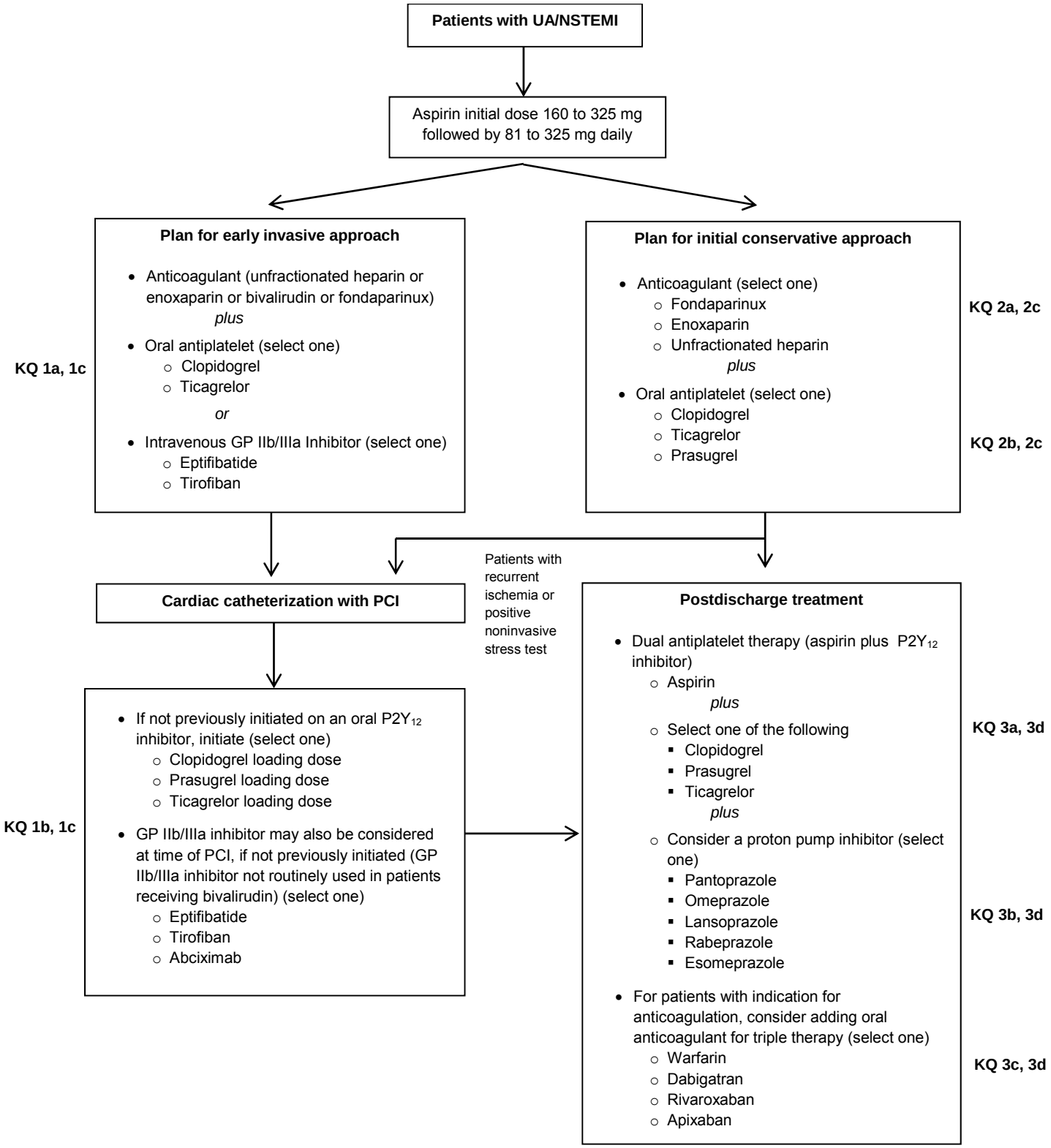
Figure 1 illustrates the treatment strategy algorithm for patients with UA/NSTEMI. First, all patients presenting with UA/NSTEMI are treated with an initial dose of aspirin, followed by either an early invasive or an initial conservative approach. An early invasive approach consists of an oral antiplatelet agent or intravenous GPI as initial therapy prior to going to the cardiac catheterization laboratory. After catheterization with percutaneous coronary intervention, the next stage considers 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. And 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 clinicians guidance, 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.

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



Scope and Key Questions

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

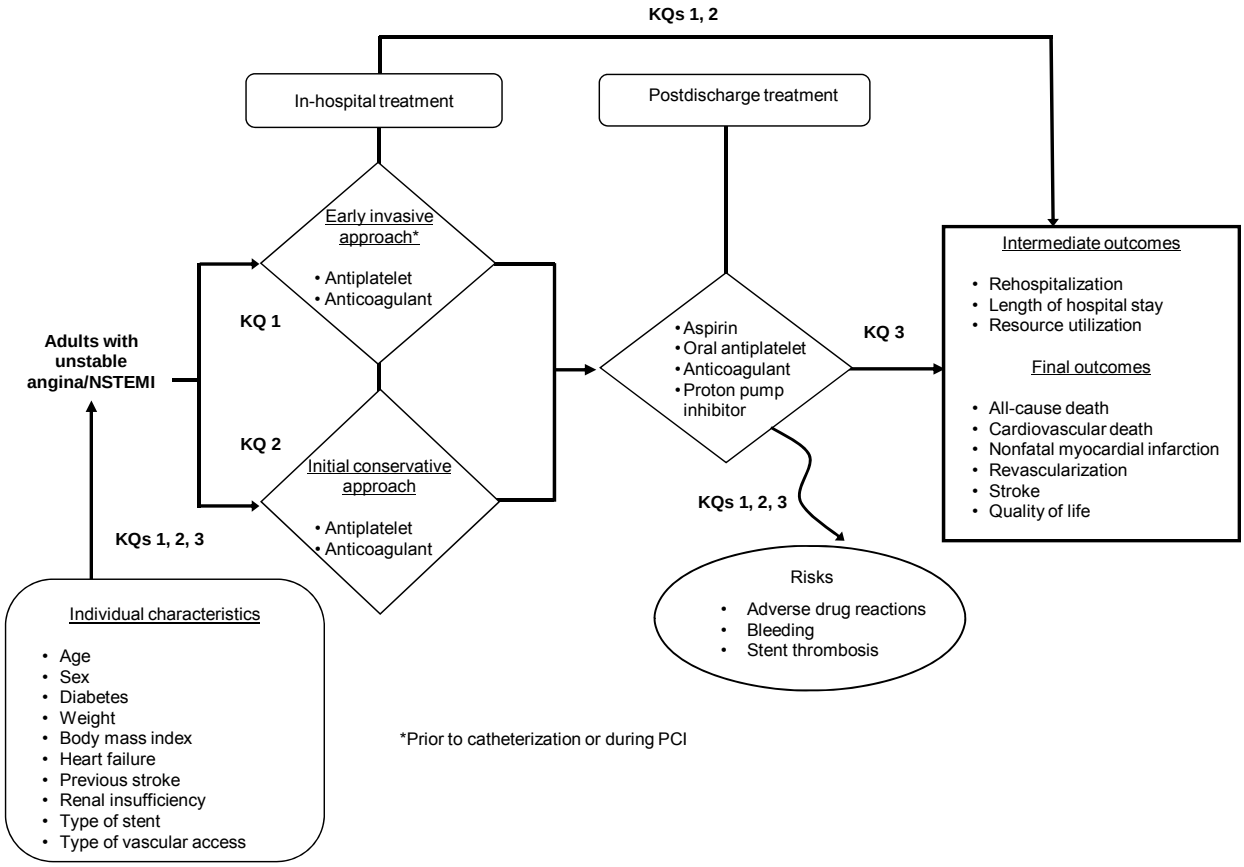
c. In patients with an indication for long-term anticoagulant therapy, what are the comparative effectiveness and comparative safety of adding an oral anticoagulant to aspirin and another antiplatelet agent for improving cardiovascular outcomes?

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



Abbreviations: KQ = key question; PCI = percutaneous coronary intervention; NSTEMI = non-ST elevation myocardial infarction; UA = unstable angina

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 considers whether there are subgroups of patients, based on demographic and other characteristics, for which 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, 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* (available at http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm; hereafter referred to as the *Methods Guide*).[15] The main sections in this chapter reflect the elements of the protocol established for the systematic review; certain methods map to the PRISMA checklist.[16] 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 key questions. The key questions were then posted for public comment for 30 days, 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 and did not contribute to the writing of the report.

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. 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 list for identified pivotal articles was 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; metaRegister of Controlled Trials; ClinicalStudyResults.org; WHO: International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. 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.

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 and comorbid or multimorbid disease	• 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) ○ Aspirin ○ Intravenous glycoprotein IIb/IIIa inhibitors ▪ Abciximab ▪ Eptifibatide ▪ Tirofiban ○ Oral antiplatelets ▪ Clopidogrel ▪ Prasugrel ▪ Ticagrelor ○ 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* ○ Aspirin ○ Oral antiplatelets ▪ Clopidogrel ▪ Prasugrel ▪ Ticagrelor ○ Anticoagulants ▪ Fondaparinux ▪ Enoxaparin ▪ Unfractionated heparin	• Study does not include any of the medications listed • Medications are not administered as part of an initial conservative strategy

Study Characteristic	Inclusion Criteria	Exclusion Criteria
	• KQ 3: *Postdischarge treatment* ○ Aspirin ○ Oral antiplatelets ▪ Clopidogrel ▪ Prasugrel ▪ Ticagrelor ○ Anticoagulants ▪ Warfarin ▪ Dabigatran ▪ Rivaroxaban ▪ Apixaban ○ 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 ○ Rehospitalization ○ Length of hospital stay ○ Resource utilization (e.g., emergency department visits) • Final outcomes ○ All-cause death ○ Cardiovascular-related death ○ Nonfatal myocardial infarction ○ Revascularization ○ Stroke ○ 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

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Outcomes (safety)	KQs 1–3: Adverse effects of treatments such as adverse drug reactions (thrombocytopenia, allergic drug reaction), bleeding, and stent thrombosis	None
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

Abbreviations: 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

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were examined independently by two reviewers for potential relevance to the key questions. 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, ON, 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*,[15] 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 was 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*.[15] To assess quality, we used the strategy to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive 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.[17]

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.[16] 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 deviation, 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 where at least three studies reported the same outcome.

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. 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 strength of evidence (SOE) for each outcome assessed; thus, a given study may be of different quality for two individual outcomes reported within that study. The SOE for each key question and outcome was assessed using the approach described in the *Methods Guide*.[15,19] In brief, the approach required assessment of four domains: risk of bias, consistency, directness, and precision (Table 4).

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

Abbreviation: RCT=randomized controlled trial

Additionally, when appropriate, the studies were evaluated for dose-response association, 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; for example, 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*.[15,20] In brief, the latter methods use the PICOTS format 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 (such as 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, have been invited to provide external peer review of this draft report; AHRQ and an associate editor will also provide comments. The draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revising the text as appropriate, and will document everything in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the AHRQ Web site. We will include a list of peer reviewers submitting comments on this draft in the final 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 key question (KQ). Under each of the KQs, 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 acute coronary syndrome (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 including the UA/NSTEMI population but where the results were not reported separately. The investigative team felt that limiting our review to the pure UA/NSTEMI population would result in a narrow focus of 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 percutaneous coronary intervention 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 glycoprotein IIb/IIIa inhibitor (GPI), (2) different loading doses of clopidogrel, (3) clopidogrel versus ticagrelor versus prasugrel, (4) bivalirudin versus a heparin-based strategy, (5) enoxaparin versus unfractionated heparin versus fondaparinux, and (6) the timing of 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 that were not included in KQ 1. Thus we present the findings of studies comparing (1) enoxaparin versus unfractionated heparin versus fondaparinux in the conservatively managed or total population (if results by treatment strategy are not presented) and (2) GPI versus unfractionated heparin 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.

- In KQ 3 (*postdischarge*), we present the findings of studies comparing (1) low-dose versus high-dose aspirin, (2) single 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 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 December 2011 yielded 23,604 citations, 3206 of which were duplicates. Manual searching and contacts to drug manufacturers identified 42 additional citations, for a total of 20,440. After applying inclusion/exclusion criteria at the title-and-abstract level, 1515 full-text articles were retrieved and screened. Of these, 1225 were excluded at the full-text screening stage, leaving 290 articles (representing 166 unique studies) for data abstraction. Note that several articles/studies were relevant to more than one KQ.

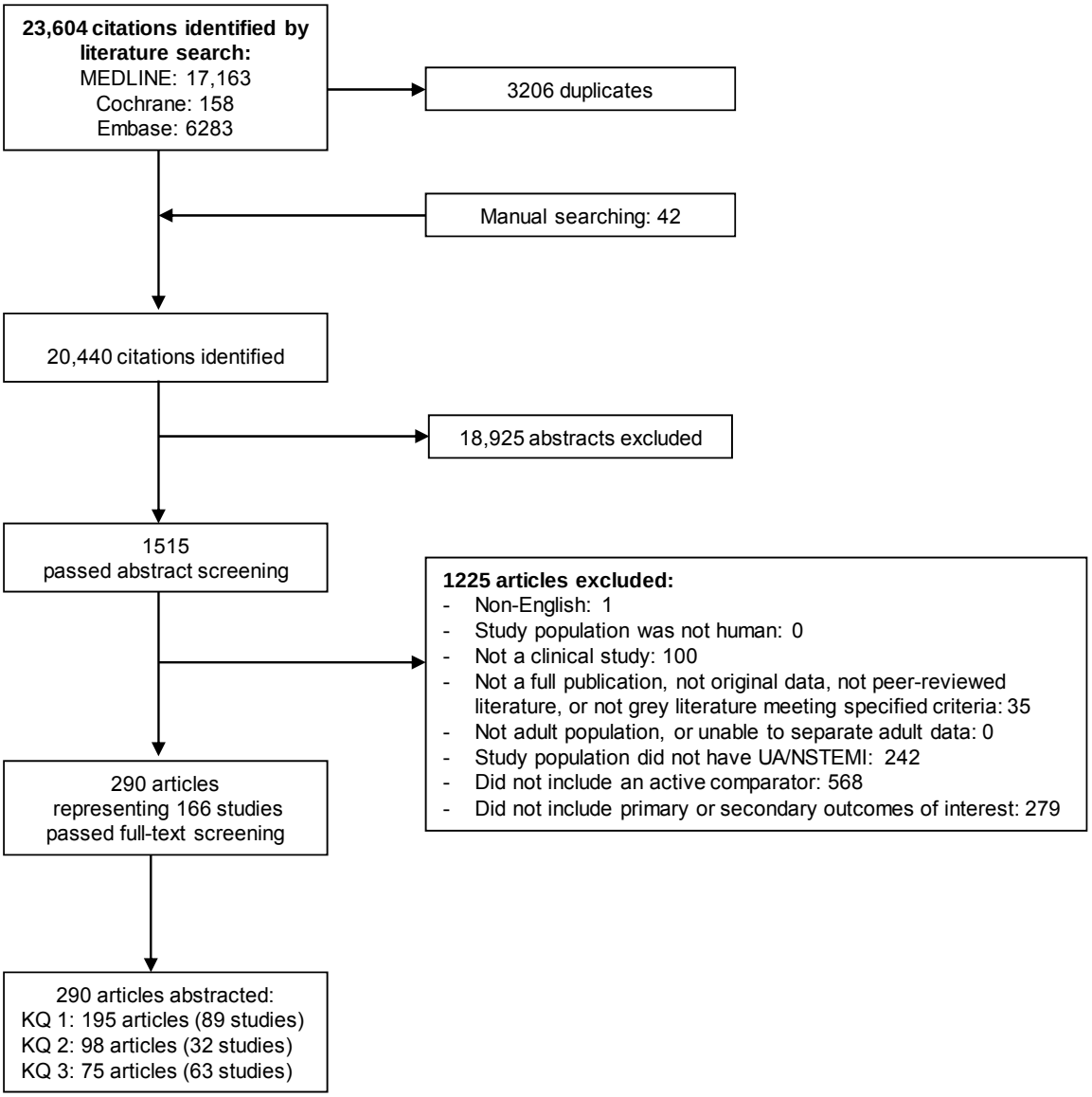
Description of Included Studies

Overall, we included 166 studies represented by 290 publications: 89 studies were relevant to KQ 1, 32 to KQ 2, and 63 to KQ 3. Studies were conducted wholly or in part in Europe (49.4%); Asia (17.8%); the United States or Canada (43.2%); Australia or New Zealand (14.4 %); and other locations (3.0 %). Further details are provided in the relevant KQ results sections that follow.

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



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

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 glycoprotein IIb/IIIa inhibitors (GPIs) was associated with lower rates of revascularization (high SOE) but a higher risk of major bleeding events at 30 days compared with deferred (periprocedural) GPI administration (high SOE).

- Upstream treatment with GPIs was also associated with higher rates of major bleeding events at 30 days compared with deferred GPI treatment (high SOE),

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

- Ticagrelor was associated with lower rates of the composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke compared with clopidogrel at 30 days (moderate SOE) and 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 revascularization at 6 months (low SOE), but an increase in major bleeding events at 1 year (low SOE), compared with clopidogrel.

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

- With planned GPI use, bivalirudin reduced the rate of the composite outcome of all-cause mortality, nonfatal MI, revascularization, major bleeding, and minor bleeding compared with heparin at 30 days (high SOE).

- There was a statistically significant lower incidence in major and minor bleeding at 30 days favoring bivalirudin when compared with a heparin-based strategy without GPI use (high SOE for major bleeding; low SOE for minor bleeding).

- At 30 days, there were no significant differences in the incidence of the composite ischemic endpoints in PCI patients treated with enoxaparin versus unfractionated heparin and enoxaparin versus fondaparinux (low SOE).

- There was a statistically significant lower incidence of major bleeding at 30 days favoring fondaparinux when compared with enoxaparin in the PCI cohort (low SOE).

- In patients pretreated with clopidogrel, there were no statistically significant differences in composite ischemic endpoints at 30 days or at 1 year, or in all-cause mortality at 30 days in bivalirudin-treated patients when compared with heparin-treated patients at 30 days (all insufficient SOE).

- In both clopidogrel pretreated and clopidogrel deferred patients, bivalirudin resulted in fewer major bleeding events at 30 days when compared with heparin-based treatment (moderate SOE for clopidogrel pretreated and insufficient SOE for clopidogrel deferred).

- 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 89 unique studies that evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 439,261 patients with UA/NSTEMI treated with an *early invasive approach* or PCI-based strategy.[21-109] Of these studies, 59 were RCTs (29 good quality, 24 fair, 6 poor) and 30 were observational (2 good quality, 21 fair, 7 poor) (Table E-1 in Appendix E).

The majority of studies were published from 2000 through 2012, with one study[70] published in 1997 and two studies[26,76] published in 1999. Thirty-six studies were single-center,[21,26,29,30,32,33,36,37,39,40,43,44,46,49,50,73,74,79,86,87,89-99,101,103-105,108] 43 were multicenter,[22,23,27,28,31,34,41,42,45,47,48,51-57,60,61,63-65,67-72,75-78,80,83-85,88,100,102,106,107,109] and in 10 studies[24,25,35,38,58,59,62,66,81,82] the number of sites was unclear or not stated. Forty-two studies included sites in the United States or Canada,[22,23,27,28,31,41,42,47,49,54-56,59-61,63,65,67-72,75-77,81-83,86-88,91,93-95,99,101-103,106,107] 49 included sites in Europe,[21,24,26,28-30,32,34,37,40-43,46,47,50-53,55,56,58,59,62,63,65,67,68,70-73,76-80,83-85,89,96-98,100,104,105,107,109] 10 included sites in Asia,[25,33,36,38,39,44,45,68,74,77] 8 included sites in Australia or New Zealand,[28,42,48,56,67,83,90,107] 1 was in Israel,[92] and 5 included locations that were either unreported or unclear.[35,57,64,66,108] A total of 39 studies used industry funding,[21-23,27,28,30,34,35,41,42,47,48,51,54-57,59-61,63-71,76,77,80-83,99,100,106,107] 1 was government-only funded,[24] 6 were funded by nongovernment/nonindustry sources,[31,53,58,78,84,96]

and funding was unclear or not reported in 43 studies.[25,26,29,32,33,36-40,43-46,49,50,52,62,72-75,79,85-95,97,98,101-105,108,109]

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 following six comparisons were assessed in the included studies for KQ 1 and are detailed in this analysis:

1. Upstream versus deferred administration of glycoprotein IIb/IIIa inhibitor (GPI)
    - 18 studies (14 RCTs, 4 observational; 142,729 total patients)
2. Clopidogrel loading dose of 300 mg versus 600 mg
    - 11 studies (8 RCTs, 3 observational; 36,347 total patients)
3. Clopidogrel versus ticagrelor versus prasugrel
    - 3 studies (3 RCTs; 33,216 total patients)
4. Bivalirudin versus a heparin-based strategy (with and without GPI)
    - 11 studies (9 RCTs, 2 observational; 24,712 total patients)
5. Enoxaparin versus unfractionated heparin versus fondaparinux
    - 14 studies (11 RCTs, 3 observational; 44,372 total patients)
6. Timing of clopidogrel administration (before or after PCI) in studies that were designed to compare bivalirudin versus a heparin-based strategy or to compare upstream versus deferred GPI use
    - 4 studies (2 RCTs, 2 observational; 6,325 patients)

Detailed Synthesis

1. Upstream Versus Deferred Glycoprotein Inhibitor Administration

GPI Administration

We abstracted 47 studies (26 RCTs, 21 observational) that evaluated the use of GPIs in patients with UA/NSTEMI.[21-46,80-99] Of these studies, 18 compared upstream versus deferred GPI administration and are the focus of this comparison.[21,34-46,80-83] The terms *upstream* and *pretreatment* both refer to the time before the PCI is begun, whereas *deferred* treatment means the GPI medications are given at the same time as the PCI. Studies that did not include this comparison are also discussed in this section.

Four observational studies (all fair quality and evaluating upstream GPI use versus no upstream GPI use) were not included in the meta-analysis due to the lack of clarity regarding

timing of PCI and early invasive management strategy.[80-83] In each study, eptifibatide, tirofiban and abciximab were used. The rate of composite ischemic endpoints in these studies 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.

Five RCTs and five observational studies of GPI use versus placebo (at the time of PCI) were not analyzed due to heterogeneity of the patient population and lack of clarity regarding an early invasive management strategy.[22-26,86,96-99] 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 of upstream GPI versus GPI at the time of PCI were not included in the analysis due to similar reasons of patient heterogeneity and lack of clarity regarding an early invasive management strategy.[27-29,89-95] 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 specific GPI. No conclusions were made based on these observations.

Two RCTs of differential GPI treatment duration after PCI were not included in the analysis of this key question.[30,31] One study[30] 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,[31] 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 other RCTs were not analyzed due to the study of high versus low tirofiban dose[33] and the study of GPI only in patients who had saphenous vein graft stenoses.[32] Multiple observational studies were not included in this analysis because of inclusion criteria of specific subgroups of patients: patients with diabetes mellitus,[85,86] patients undergoing saphenous vein graft PCI,[87] patients undergoing rotational atherectomy,[88] and patients on chronic warfarin treatment.[84] These studies will be discussed in the Findings by Subgroup subsection for each comparison of this Key Question.

Upstream (Precatheterization) Versus Deferred (Periprocedural) GPI Administration

Of the 47 studies evaluating GPI use in patients with UA/NSTEMI, 18 (14 RCTs, 4 observational) compared an upstream versus deferred use of GPI and included a total of 21,301 patients in the RCTs and 121,428 patients in the observational studies.[22-33,80-87,89-99] Of the 14 RCTs, 5 (36%) were rated good quality, 6 (43%) fair, and 3 (21%) poor. Of the four observational studies, all were rated fair quality. Sample sizes ranged from 83 to 9,378 patients for individual RCTs and 789 to 60,770 patients for individual observational studies. Study duration ranged from 3 days to 3 months, and (with the exception of three studies) all reported 30 day outcomes. The GPIs administered included eptifibatide in 9 studies, tirofiban in 12 studies, and abciximab in 6 studies.

The mean age of study participants ranged from 53 to 68 years. The proportion of female patients ranged from 25 to 54 percent. None of the studies reported the racial and ethnic demographics of study participants. Three studies (21%) were conducted within the United States or Canada, with the rest international. Funding source was reported in five studies (36%), all of which were funded by an industry source.

The following outcomes were quantitatively assessed (in the 18 studies in this comparison):

- Composite ischemic endpoints at 30 days and 6 months
- All-cause mortality at 30 days
- Nonfatal MI at 30 days
- Revascularization at 30 days
- Major bleeding at 30 days
- 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

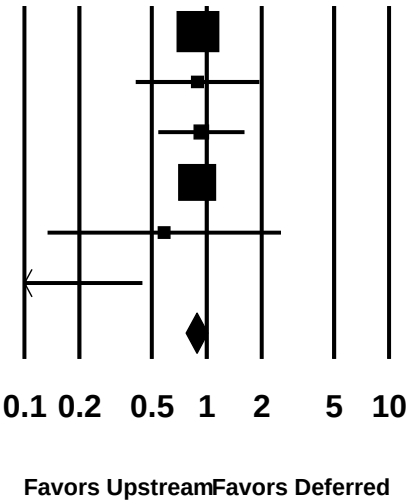
A random-effects meta-analysis of six RCTs[34,37-39,41,42] (two good quality, three fair, one poor) including 19,662 UA/NSTEMI patients reporting the composite outcome of all-cause mortality, nonfatal MI, or revascularization at 30 days found that the odds ratio was 0.88 (95% CI, 0.77 to 1.01), demonstrating 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[38] 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 (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.

The SOE was rated low for the composite endpoint at 30 days based on consistent results from two large RCTs that upstream GPI is not superior to deferred GPI.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Giugliano, 2005	0.895	0.794	1.009	0.069
Leoncini, 2005	0.890	0.411	1.928	0.768
Durand, 2007	0.934	0.547	1.596	0.803
Stone,2007	0.887	0.759	1.036	0.131
Liu, 2009	0.584	0.135	2.532	0.473
Momtahen, 2009	0.026	0.002	0.440	0.011
	0.883	0.771	1.012	0.073

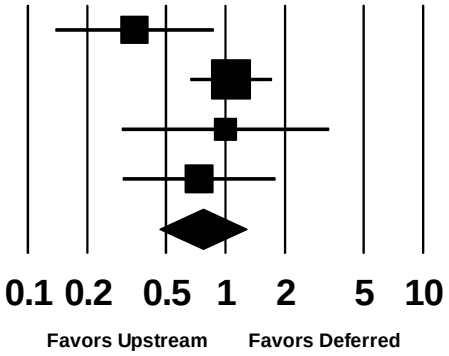


Effect on Composite Endpoint of All-Cause Mortality, Nonfatal Myocardial Infarction, or Revascularization After 6 Months

A random-effects meta-analysis of four RCTs[21,34,39,44] (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[44] 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 vs. deferred glycoprotein inhibitor use on composite endpoint of all-cause mortality, nonfatal myocardial infarction, or revascularization at 6 months

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Kim, 2005	0.347	0.138	0.871	0.024
Durand, 2007	1.067	0.664	1.715	0.788
Ivandic, 2008	1.000	0.299	3.341	1.000
Liu, 2009	0.736	0.302	1.793	0.500
	0.769	0.463	1.277	0.311

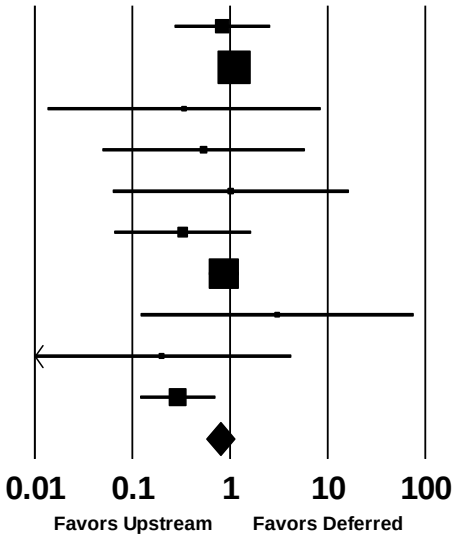


Effect on All-Cause Mortality at 30 Days

A random-effects meta-analysis of 10 RCTs[34,36-44] (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.[36-40,43,44] 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 statistically nonsignificant confidence interval.

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

Study name	Odds ratio	Lower limit	Upper limit	p-Value
van't Hof, 2003	0.835	0.271	2.572	0.753
Giugliano, 2005	1.104	0.860	1.416	0.438
Kim, 2005	0.339	0.014	8.484	0.510
Leoncini, 2005	0.535	0.049	5.802	0.607
Rasoul, 2006	1.016	0.063	16.406	0.991
Durand, 2007	0.328	0.065	1.643	0.175
Stone, 2007	0.865	0.610	1.226	0.414
Liu, 2009	3.038	0.122	75.693	0.498
Momtahen, 2009	0.199	0.009	4.221	0.300
Bhattacharya, 2010	0.291	0.120	0.706	0.006
	0.796	0.572	1.107	0.175



Effect on All-Cause Mortality at 6 Months

Of the three studies (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,[44] and one study involving 160 patients reported a single death in the upstream GPI arm.[39] The remaining study[34] 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.

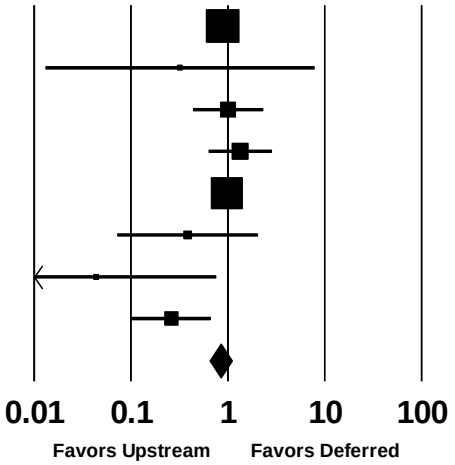
Effect on Nonfatal MI at 30 Days

A random-effects meta-analysis of nine RCTs (three good quality, five fair, one poor) including 20,263 UA/NSTEMI patients reporting nonfatal MI at 30 days found that the odds ratio was 0.84 (95% CI, 0.65 to 1.10) demonstrating no statistically significant difference between upstream GPI and deferred GPI (Figure 7). Of note, the Kim study[44] had no events in either treatment arm and was not included in the analysis. 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[36-39,43] likely contributed to the inconsistent results and heterogeneity. In the two largest studies (good quality)[41,42] 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 results in a fixed-

effects odds ratio of 0.91 (CI, 0.81 to 1.01, p=0.26) and a random-effects odds ratio of 0.88 (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 vs. deferred glycoprotein inhibitor use on nonfatal myocardial infarction at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Giugliano, 2005	0.885	0.773	1.013	0.076
Leoncini, 2005	0.320	0.013	7.825	0.485
Rasoul, 2006	1.007	0.439	2.313	0.986
Durand, 2007	1.343	0.634	2.847	0.441
Stone, 2007	0.979	0.811	1.182	0.825
Liu, 2009	0.385	0.072	2.044	0.262
Momtahen, 2009	0.044	0.003	0.758	0.032
Bhattacharya, 2010	0.261	0.102	0.668	0.005
	0.844	0.649	1.098	0.207



Effect on Nonfatal MI at 6 Months

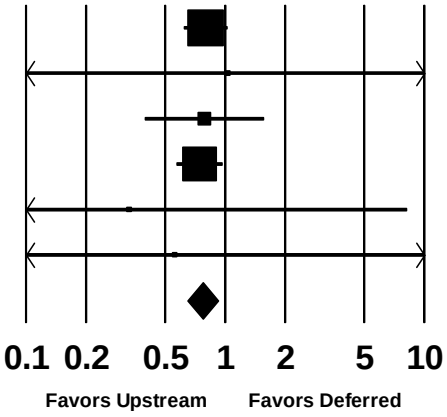
Of the three studies (all fair quality) that reported the incidence of nonfatal MI, one study involving 120 patients reported a single MI in the deferred GPI treatment arm.[44] The remaining two studies[34,39] included 553 UA/NSTEMI patients and reported similar nonfatal MI rates (12% vs. 15%, p=0.65;[39] 10% vs. 9%, p=0.59[34]) 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[34,38,39,41,42,44] (three good quality, three 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 vs. deferred glycoprotein inhibitor use on revascularization at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Giugliano, 2005	0.799	0.620	1.028	0.081
Kim, 2005	1.031	0.063	16.903	0.983
Durand, 2007	0.787	0.395	1.567	0.495
Stone, 2007	0.745	0.570	0.972	0.030
Liu, 2009	0.329	0.013	8.203	0.498
Momtahen, 2009	0.558	0.017	18.011	0.742
	0.772	0.647	0.921	0.004

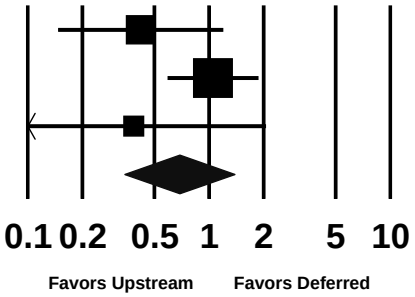


Effect on Revascularization at 6 Months

Of the three studies (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.[34,39,44] 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.

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

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Kim, 2005	0.420	0.148	1.190	0.103
Durand, 2007	1.051	0.594	1.859	0.864
Liu, 2009	0.385	0.072	2.044	0.262
	0.690	0.343	1.389	0.299

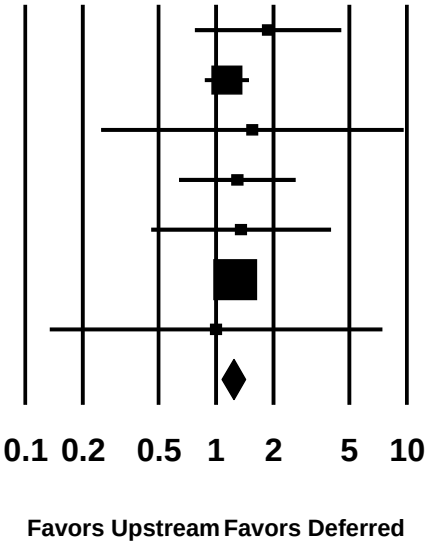


Effect on Major Bleeding at 30 Days

A random-effects meta-analysis of nine RCTs[21,34,37,38,40-44] (two good quality, five fair, two poor) including 20,242 UA/NSTEMI patients reporting major bleeding at 30 days found that the odds ratio was 1.24 (95% CI, 1.08 to 1.43) showing a statistically significant reduction in major bleeding favoring deferred GPI (Figure 10). Of note, two of the nine studies were excluded from the meta-analysis because no endpoints occurred in either treatment group.[38,44] 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 vs. deferred glycoprotein inhibitor use on major bleeding at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value
van't Hof, 2003	1.872	0.780	4.493	0.160
Giugliano, 2005	1.141	0.881	1.477	0.317
Leoncini, 2005	1.549	0.252	9.537	0.637
Rasoul, 2006	1.294	0.645	2.597	0.468
Durand, 2007	1.352	0.460	3.970	0.583
Stone, 2007	1.261	1.053	1.510	0.012
Ivandic, 2008	1.000	0.135	7.392	1.000
	1.239	1.077	1.427	0.003

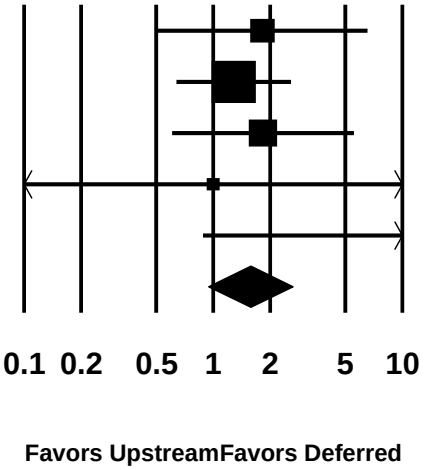


Effect on Minor Bleeding at 30 Days

A random-effects meta-analysis of five RCTs[21,34,38,39,44] (five 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[38] 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 vs. deferred glycoprotein inhibitor use on minor bleeding at 30 days

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Kim, 2005	1.822	0.512	6.486	0.354
Durand, 2007	1.285	0.645	2.561	0.476
Ivandic, 2008	1.833	0.611	5.502	0.280
Liu, 2009	1.000	0.061	16.270	1.000
Momtahen, 2009	15.822	0.889	281.434	0.060
	1.579	0.945	2.636	0.081



Findings by Subgroup

Two studies (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 one substudy 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 study, there was no difference in ischemic event rates in 2377 patients over age 75 who were treated with upstream GPI use (11.4%) or deferred GPI use (11.4%).[41]

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%).[42]

Sex

There were two studies of upstream versus deferred GPI use reporting subgroup results for men versus women. In one substudy 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 2975 female patients in this study who were treated with upstream GPI use (9.7%) versus deferred GPI use (10.4%).[41]

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%).[42]

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%).[41] 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%).[42]

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.[41] 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%).[42]

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%).[41] 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%).[42]

TIMI Risk Score

Two studies of upstream versus deferred GPI use reported results for patients' TIMI risk score on presentation. In 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).[41,42] 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.[42]

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, and the ones that did report outcomes 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.

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; those greater than 1 favor deferred GPI.

Table 5. Summary strength of evidence for UA/NSTEMI patients treated with upstream vs. deferred glycoprotein 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 all-cause mortality, nonfatal MI, or revascularization at 30 days					**Low SOE**
6 (19,662)	6 RCTs/2 good quality, 3 fair, 1 poor	Inconsistent	Direct	Precise	OR 0.88 (0.77 to 1.01)
Composite of all-cause mortality, nonfatal MI, or revascularization after 6 months					**Insufficient SOE**
4 (773)	4 RCTs/4 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)

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 after 6 months					**Insufficient SOE**
3 (673)	3 RCTs/3 fair quality	Inconsistent	Direct	Imprecise	One study reported no deaths in both arms; one study reported 1 death in the upstream GPI arm; one 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 after 6 months					**Insufficient SOE**
3 (673)	3 RCTs/3 fair quality	Inconsistent	Direct	Imprecise	One study reported 1 MI in the deferred GPI arm only. 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
Revascularization after 6 months					**Insufficient SOE**
3 (673)	3 RCTs/3 fair quality	Consistent	Direct	Precise	OR 0.69 (0.34 to 1.39)
Major bleeding at 30 days					**High SOE**
9 (20,242)	9 RCT/s2 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/5 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

Abbreviations: CI=confidence interval; GPI= glycoprotein IIb/IIIa 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 of 300 mg Versus 600 mg

Eleven studies (eight RCTs, three observational) compared loading doses of clopidogrel in 36,347 UA/NSTEMI patients undergoing an invasive strategy.[47-54,100-102] Outcomes that were 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.

Six of these RCTs compared clopidogrel 300 mg loading dose versus clopidogrel 600 mg loading dose and included a total of 26,206 patients. One RCT also randomly assigned patients to clopidogrel 900 mg loading dose. One RCT of clopidogrel loading dose (600 mg) versus placebo in 647 ACS and stable patients previously treated with clopidogrel was not included in this analysis.[53] 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 after initial clopidogrel loading dose versus placebo in patients with standard clopidogrel responsiveness was not included in this analysis.[54] 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.

There were three observational studies (one good quality, two fair) comparing clopidogrel loading doses that were screened and abstracted.[100-102] These studies were not included in the analysis due to lack of a standard loading dose (300 mg or 600 mg) in one treatment arm or heterogeneity of the patient population (an unselected PCI population). Instead, we chose to describe these studies below. One study[100] 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,[101] 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[102] 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.

Of the six RCTs included in the meta-analysis, two (33%) were rated good quality and four (66%) fair. Of the three observational studies, one (33%) was rated good quality and two (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

Five studies 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.[47,49-52] 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).[47] The SOE was rated low for this composite outcome at 30 days due to a large, good-quality RCT that was sufficiently powered to assess this endpoint.

Four single-center studies reported a lower incidence of a composite ischemic outcome with clopidogrel 600 mg loading dose. One 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%).[49] One 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%).[50]

Similarly, another 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%).[51] 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 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%).[52] The SOE was rated insufficient for the four other single-center studies at 30 days based on smaller sample sizes and imprecise estimates of effect.

Effect on Composite Ischemic Endpoints at 6 Months

Only one 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%).[48] 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

Of the three studies (two good quality, one fair) that report the incidence of all-cause mortality at 30 days, two studies report no deaths in either treatment arm.[51,52] The remaining study (good quality)[47] 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 all-cause mortality at 30 days based on a single large, good-quality RCT.

Effect on All-Cause Mortality at 6 Months

Only one study (fair quality) in 256 patients reported the incidence of all-cause mortality at 6 months.[48] 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

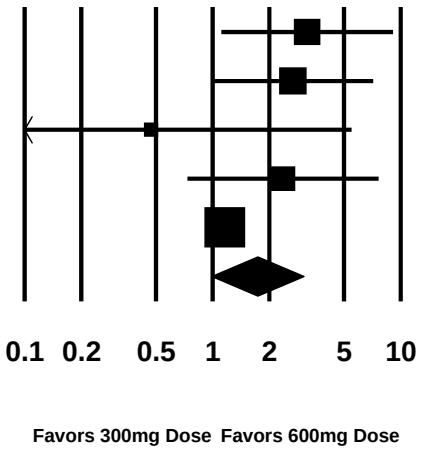
Of the three studies (one good quality, two fair) with 25,497 patients that reported the incidence of cardiovascular mortality at 30 days, there was one good-quality study[47] that included 25,086 patients and reported similar outcomes in the 300 mg loading dose group (2.2%) versus 600 mg loading dose (2.1%). 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.[50] The other fair-quality study included 387 patients and 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%).[49] The SOE was rated low for 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 (two good quality, three fair)[47,47,48,50,51] including 25,821 UA/NSTEMI patients reporting nonfatal MI at 30 days found that the odds ratio was 1.74 (95% CI, 0.99 to 3.06) 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 vs. 600 mg clopidogrel loading dose on nonfatal myocardial infarction at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Patti, 2005	3.184	1.121	9.044	0.030
Cuisset, 2006	2.672	1.006	7.092	0.049
Montalescot, 2006	0.471	0.041	5.445	0.546
Abuzahra, 2008	2.367	0.740	7.573	0.147
Mehta, 2010	1.161	0.975	1.384	0.094
	1.740	0.991	3.055	0.054



Effect on Nonfatal MI at 6 Months

Only one study (fair quality) in 256 patients reported the incidence of nonfatal MI at 6 months.[48] 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

Two studies (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.[47,50] In the largest study,[47] 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,[50] 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.

Effect on Nonfatal Stroke at 6 Months

Only one study (fair quality) in 256 patients reported the incidence of nonfatal stroke at 6 months.[48] 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

Three studies (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.[49,51,52] Overall, there was a low event rate that was different among the studies. In one study,[49] 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,[51] 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,[52] 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.

Effect on Revascularization at 6 Months

Only one study (fair quality) in 256 patients reported the incidence of revascularization at 6 months.[48] 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 studies that reported the incidence of major bleeding at 30 days, three studies reported no major bleeding in either treatment arm.[50-52] In two of the remaining studies,[48,49] 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%[48] and 1.3%[49]) which were not statistically significant. In the largest study[47] 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.[47-49,51,52] Of the five studies, three studies reported minor bleeding according to TIMI criteria[48,49,52] and two studies reported minor bleeding according to non-TIMI criteria.[47,51] 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%).[49] 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%).[48,52]

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).[47] 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%).[51] 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 RCT (a prespecified subgroup),[47] 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

Only one study (good quality) of 25,086 patients reported variations in treatment effectiveness by subgroup.[47] 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. Summary strength of evidence for UA/NSTEMI patients treated with 300 mg vs. 600 mg clopidogrel loading dose

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 cardiovascular mortality, nonfatal MI, or revascularization at 30 days					**Insufficient SOE**
1 (119)	RCT/Fair quality	NA	Direct	Imprecise	Lower rate in 600 mg loading dose group (10.4% vs. 23.8%)
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 recurrent ACS at 30 days					**Insufficient SOE**
1 (387)	RCT/Fair quality	NA	Direct	Imprecise	Lower rate in 600 mg loading dose 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 loading dose 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 loading dose 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	Two studies reported no deaths in both groups; Largest study reported HR 0.93 (0.83 to 1.05) No difference
All-cause mortality at 6 months					**Insufficient SOE**
1 (256)	RCT/1 fair quality	Insufficient	Direct	Imprecise	Three deaths in 300 mg group and 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 (25,821)	5 RCTs/2 good quality, 3 fair	Inconsistent	Direct	Imprecise	OR 1.74 (0.99 to 3.06)
Nonfatal MI at 6 months					**Insufficient SOE**
1 (256)	RCT/1 fair quality	NA	Direct	Unknown	Higher MI rate in 600 mg loading dose group (5.0% vs. 8.6%, 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

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Nonfatal stroke at 6 months					**Insufficient SOE**
1 (256)	RCT/1 fair quality	NA	Direct	Imprecise	Only one 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 300 mg group and 0 to 4.8% in 600 mg group; disparate results
Revascularization after 6 months					**Insufficient SOE**
1 (256)	RCT/1 fair quality	NA	Direct	Imprecise	Lower incidence in 600 mg loading dose group (3.3% vs. 2.3%, p=0.64)
Major bleeding at 30 days					**Insufficient SOE**
6 (26,206)	2 RCTs/2 good quality, 4 fair	Inconsistent	Direct	Imprecise	Three studies reported no bleeding events; inconsistent findings from three 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	Inconsistent findings with incidence in 300 mg loading dose group ranging from 0.8% to 9.5% compared with 600 mg loading dose group ranging from 0.8% to 3.9%
Stent thrombosis at 30 days					**Low SOE**
1 (17,263)	RCT/Good quality	NA	Direct	Precise	Large study reported HR 0.68 (0.55 to 0.85) favoring 600 mg loading dose

Abbreviations: 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 Versus Prasugrel

Three RCTs compared the use of clopidogrel, ticagrelor, or prasugrel in 33,216 patients with ACS undergoing an invasive strategy.[55-57] Of the three RCTs, two (66%) were rated good quality[55,56] and one (33%) fair.[57] Sample sizes for individual studies ranged from 984 to 18,624 patients. Study duration ranged from 3 to 15 months; all three studies 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.[55] 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.[55,56] Two studies compared ticagrelor to clopidogrel: one for 3 months duration[57] and the other for 277 days median duration.[55] The other study compared prasugrel to clopidogrel for a median duration of

15 months.[56] 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 Endpoint of Cardiovascular Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke at 30 Days and After 1 Year

All three studies[55-57] (two good quality, one fair) reported a composite outcome of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke at 30 days in the entire population of 33,216 patients studied (i.e., not strictly limited to UA/NSTEMI patients). In these studies, there were statistically significantly fewer major adverse cardiovascular events (MACE) in patients randomized to prasugrel (5.7%) when compared with clopidogrel (7.4%). There were mixed results in the two studies comparing ticagrelor (4.3%;[57] 4.8%[55]) and clopidogrel (3.8%;[57] 5.4%[55]). When subgroups of only UA/NSTEMI patients in two studies were evaluated for the occurrence of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke after 1 year, the lower rates of MACE events were statistically significant in patients treated with ticagrelor (10.6%) when compared with clopidogrel (12.6%), as well as with prasugrel (9.9%) when compared with clopidogrel (12.1%) (HR 0.81; 95% CI, 0.73 to 0.90; $p<0.001$).[55,56] The SOE was rated moderate for the composite endpoint at 30 days based on two good- and one fair-quality RCTs with inconsistent results of a direct outcome. The SOE was rated moderate for the composite endpoint after 1 year based on two good-quality RCTs with consistent results of a direct outcome.

One study comparing prasugrel to clopidogrel in 13,608 patients[56] reported the composite outcome of cardiovascular mortality, nonfatal MI, and revascularization at 15 months and found a statistically significant reduction in the group receiving prasugrel (HR 0.81; 95% CI, 0.73 to 0.87). The SOE was rated low for the composite endpoint at 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 study of 984 patients comparing ticagrelor with clopidogrel[57] 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.

In the entire population (not limited to UA/NSTEMI patients) of two studies (32,232 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, $p<0.001$); and statistically nonsignificant reduction in all-cause deaths in patients treated with prasugrel (3.0%) when compared with clopidogrel (3.2%) (HR 0.95; CI, 0.78 to 1.16, $p=0.64$).[55,56] The SOE was rated low for all-cause mortality after 1 year based on two good-quality RCTs with consistent results of a direct outcome.

Effect on Cardiovascular Mortality at 30 Days and After 1 Year

One fair-quality study of 984 patients comparing ticagrelor with clopidogrel[57] reported cardiovascular 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 cardiovascular mortality at 30 days based on one small, fair-quality RCT with an imprecise estimate.

In the entire population (not limited to UA/NSTEMI patients) of two studies (32,232 patients), lower incidence of cardiovascular deaths after 1 year was statistically significant in 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); and a statistically nonsignificant reduction in cardiovascular mortality in patients treated with prasugrel (2.1%) when compared with clopidogrel (2.4%) (HR 0.89; CI, 0.70 to 1.12, p=0.31).[55,56] The overall SOE was rated low for cardiovascular mortality after 1 year based on two good-quality RCTs with consistent results of a direct outcome.

Effect on Nonfatal MI at 30 Days and After 1 Year

One fair-quality study of 984 patients comparing ticagrelor with clopidogrel[57] reported nonfatal MI results at 30 days and found no difference between clopidogrel (3.5%) and ticagrelor (2.2%), p=0.34. The SOE was rated insufficient for nonfatal MI at 30 days based on one small, fair-quality RCT.

In all patients treated with ticagrelor and prasugrel (not limited to UA/NSTEMI patients) in two studies (32,232 patients), the lower incidence of nonfatal MI after 1 year was statistically significant in 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; and with prasugrel (7.3%) when compared with clopidogrel (9.5%) (HR 0.76; CI, 0.67 to 0.85, p<0.001).[55,56] The SOE was rated low for nonfatal MI after 1 year based on two large, good-quality RCTs with consistent results of a direct outcome.

Effect on Nonfatal Stroke at 30 Days and After 1 Year

One fair-quality study of 984 patients comparing ticagrelor with clopidogrel[57] reported nonfatal stroke results at 30 days and found no difference between clopidogrel (0.3%) and ticagrelor (0.6%), p=0.57. The SOE was rated insufficient for nonfatal stroke at 30 days based on one small, fair-quality RCT with an imprecise estimate.

The incidence of nonfatal stroke after 1 year was similar in all 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); as well as in patients treated with ticagrelor (1.5%) when compared with patients treated with clopidogrel (1.3%) (HR 1.17; CI, 0.91 to 1.52, p=0.22).[55,56] 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[56] reported revascularization events at 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 low 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 study of 984 patients comparing ticagrelor with clopidogrel[57] 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. The SOE was rated insufficient for major and minor bleeding at 30 days based on one small, fair-quality RCT.

The incidence of TIMI major bleeding after 1 year was similar in all patients treated with ticagrelor (7.9%) and clopidogrel (7.7%) (HR 1.03; 95% CI, 0.93 to 1.15, p=0.57); while all patients treated with prasugrel (2.4%) had a higher rate of TIMI major bleeding when compared with clopidogrel (1.8%) (HR 1.32; CI, 1.03 to1.68, p=0.03).[55,56] The SOE was rated low for major bleeding after 1 year based on two good-quality RCTs with inconsistent results of a direct outcome.

Effect on Stent Thrombosis After 1 Year

In the entire population of two trials (not limited to UA/NSTEMI patients), there was a lower incidence of stent thrombosis after 1 year in patients treated with ticagrelor (1.3%) when compared with clopidogrel (1.9%) (HR 0.67; 95% CI, 0.50 to 0.91, p=0.009); as well as with prasugrel (1.1%) when compared with clopidogrel (2.4%) (HR 0.48; CI, 0.36 to 0.64, p<0.001).[55,56] The SOE was rated low for stent thrombosis after 1 year based on two large, good-quality RCTs with consistent results of a direct outcome.

Findings by Subgroup

Two studies (good quality) of 32,232 patients reported variations in treatment effectiveness by subgroup.[55,56] Subgroups analyzed were age, sex, race, diabetes mellitus, chronic kidney disease, troponin positivity, TIMI risk score, weight, prior TIA/stroke, prior coronary revascularization, the performance of PCI after randomization, type of coronary stent, and geographic location. 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%).[56]

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.[55]

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%).[56]

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.[55]

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.[55]

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/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%).[56]

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.[55]

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/nonfatal stroke favoring prasugrel (15.1%) when compared with clopidogrel (17.5%).[56]

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%).[55]

Troponin Positivity

There was no subgroup analysis of troponin positivity or negativity in TRITON-TIMI 38.[56] 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.[55]

TIMI Risk Score

There was no subgroup analysis of TIMI risk score in TRITON-TIMI 38.[56] 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.[55]

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/nonfatal stroke favoring clopidogrel (6.5%) when compared with prasugrel (10.1%).[56]

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.[55]

Prior TIA 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/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 ticagrelor (5.0%).[56]

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.[55]

Prior Coronary Revascularization

There was no subgroup analysis of prior coronary revascularization in TRITON-TIMI 38.[56] 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.[55]

PCI After Randomization

All patients in TRITON-TIMI 38 underwent PCI, thus no subgroup analysis was performed.[56] There was no subgroup analysis of patients who underwent PCI after randomization in PLATO.[55]

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/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%).[56] There was no subgroup analysis of coronary stenting in PLATO.[55]

Geographic Region

There was no subgroup analysis of geographic region in TRITON-TIMI 38.[56] 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.[55]

Summary of Results for Clopidogrel Versus Ticagrelor Versus Prasugrel

In our analysis of studies comparing clopidogrel, ticagrelor, and prasugrel, three studies reported a lower incidence of the composite outcome of cardiovascular mortality, nonfatal MI and 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, and major 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 one 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/stroke, prior coronary revascularization, the performance of PCI after randomization, type of coronary stent, and geographic location. 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. Summary strength of evidence for UA/NSTEMI patients treated with clopidogrel vs. ticagrelor vs. prasugrel

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 cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days					**Moderate SOE**
3 (33,216)	3 RCTs/2 good quality, 1 fair	Inconsistent	Direct	Precise	Ticagrelor (4.3% and 4.8%) and prasugrel (5.7%) were both associated with lower composite endpoints than clopidogrel (3.8%, 5.4%, and 7.4%).
Composite of cardiovascular mortality, nonfatal MI, or revascularization at 15 months					**Low SOE**
1 (13,608)	RCT/Good quality	NA	Direct	Precise	HR (95% CI): 0.81 (0.73 to 0.87) Favors prasugrel
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke after 1 year					**Moderate SOE**
2 (32,232)	2 RCTs/2 good quality	Consistent	Direct	Precise	Ticagrelor (10.6%) and prasugrel (9.9%) were both associated with lower composite endpoints than clopidogrel (12.6%).
All-cause mortality at 30 days					**Insufficient SOE**
1 (984)	RCT/Fair quality	NA	Direct	Imprecise	Clopidogrel: 0.6% Ticagrelor: 1.9% p=0.18
All-cause mortality after 1 year					**Low SOE**
2 (32,232)	2 RCTs/2 good quality	Consistent	Direct	Precise	Ticagrelor (4.5%) and prasugrel (3.0%) were both associated with fewer deaths than clopidogrel (5.9% and 3.2%)
Cardiovascular mortality at 30 days					**Insufficient SOE**
1 (984)	RCT/Fair quality	NA	Direct	Imprecise	Clopidogrel: 0.6% Ticagrelor: 1.9% p=0.18

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Cardiovascular mortality after 1 year					**Low SOE**
2 (32,232)	2 RCTs/2 good quality	Consistent	Direct	Precise	Ticagrelor (4.0%) and prasugrel (2.1%) were both associated with fewer CV deaths than clopidogrel (5.1% and 2.4%)
Nonfatal MI at 30 days					**Insufficient SOE**
1 (984)	RCT/Fair quality	NA	Direct	Imprecise	Clopidogrel: 3.5% Ticagrelor: 2.2% p=0.34
Nonfatal MI after 1 year					**Low SOE**
2 (32,232)	2 RCTs/2 good quality	Consistent	Direct	Precise	Ticagrelor (5.8%) and prasugrel (7.3%) were both associated with fewer MIs than clopidogrel (6.9% and 9.5%)
Nonfatal stroke at 30 days					**Insufficient SOE**
1 (984)	RCT/Fair quality	NA	Direct	Imprecise	Clopidogrel: 0.3% Ticagrelor: 0.6% p=0.57
Nonfatal stroke after 1 year					**Insufficient SOE**
2 (32,232)	2 RCTs/2 good quality	Consistent	Direct	Imprecise	Prasugrel (1.0%) and clopidogrel (1.0%) had similar event rates; ticagrelor (1.5%) had higher event rates than clopidogrel (1.3%).
Revascularization at 30 days					**Insufficient SOE**
0	NA	NA	NA	NA	NA
Revascularization after 6 months					**Low SOE**
1 (13,608)	RCT/Good quality	NA	Direct	Precise	HR (95% CI): 0.66 (0.54 to 0.81) favoring prasugrel over clopidogrel
Major bleeding at 30 days					**Insufficient SOE**
1 (984)	RCT/fair quality	Consistent	Direct	Imprecise	Ticagrelor (7.1%) and clopidogrel (6.9%) had similar event rates
Major bleeding after 1 year					**Low SOE**
2 (32,232)	2 RCTs/2 good quality	Inconsistent	Direct	Precise	Ticagrelor (7.9%) and clopidogrel (7.7%) had similar event rates; prasugrel (2.4%) had higher event rates than clopidogrel (1.8%)
Minor bleeding at 30 days					**Insufficient SOE**
1 (984)	RCT/Fair quality	NA	Direct	Imprecise	Clopidogrel: 1.3% Ticagrelor: 2.7% p=0.18

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Stent thrombosis after 1 year					**Low SOE**
2 (32,232)	2 RCTs/2 good quality	Consistent	Direct	Precise	Ticagrelor (1.3%) and prasugrel (1.1%) were both associated with lower individual endpoints than clopidogrel (2.4%)

Abbreviations: 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 With and Without GPI

Eleven studies (nine RCTs, two observational) compared bivalirudin with a heparin-based strategy in 24,712 UA/NSTEMI patients undergoing an invasive approach.[58-66,103,104] 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.

Four RCTs compared bivalirudin with unfractionated heparin (UFH) or enoxaparin with provisional GPI and included a total of 5822 patients.[58-61] These four studies are quantitatively assessed below when data were available for the outcomes of interest. When data were not sufficient to meta-analyze, the results are qualitatively described. One RCT that compared bivalirudin with UFH or enoxaparin with provisional GPI was not analyzed due to a low use of invasive strategy and due to the fact that the sponsor terminated the study with 3 percent of patients enrolled.[61]

Four RCTs compared bivalirudin with UFH or enoxaparin with planned GPI and included a total of 17,748 patients.[63-66] These four studies are quantitatively assessed when data were available for the outcomes of interest. When data were not sufficient to meta-analyze, the results are qualitatively described. One RCT[66] reported outcomes in patients randomized to bivalirudin versus UFH plus GPI, but due to the fact that followup was limited to 48 hours, these results were not included in the meta-analysis. The results 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.

One additional RCT[62] compared the use of bivalirudin during PCI with the use of bivalirudin during PCI plus 4 hours post-PCI. This was not included in the analysis since both study arms contained bivalirudin.

Two observational studies (fair quality) evaluated the use of bivalirudin in ACS patients only, but there was not clarity on the use of an early invasive strategy, and both studies had differential utilization of GPI.[103,104] Therefore, these studies were not included in the meta-analysis. The remainder of the observational studies were excluded from this analysis because (1) an unselected patient population undergoing PCI was evaluated or (2) there was differential use of GPI, or (3) the use and timing of oral antiplatelet agents was unclear, thus limiting the estimation of effect of the treatment comparisons in UA/NSTEMI patients.

Of the seven RCTs included in the meta-analyses, five (71%) were rated good quality and two (29%) fair. Sample sizes for individual studies ranged from 401 to 13,819 patients. Study duration ranged from 48 hours to 6 months, with each RCT reporting 30 day outcomes except one study.

The mean age of study participants ranged from 60 to 70 years of age. The proportion of female patients ranged from 23 to 33 percent. One study (14%) reported the racial and ethnic demographics of study participants. Six studies (86%) were conducted within the United States or Canada, with the other conducted internationally. Funding source was reported in all seven studies, with 6 studies (86%) funded by industry source.

Across all outcomes, we present the results of the bivalirudin versus heparin-based strategy for the "without planned GPI" (i.e., provisional use) 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 All-Cause Mortality, Nonfatal Myocardial Infarction, Revascularization, or Major Bleeding at 30 Days

Without Planned GPI

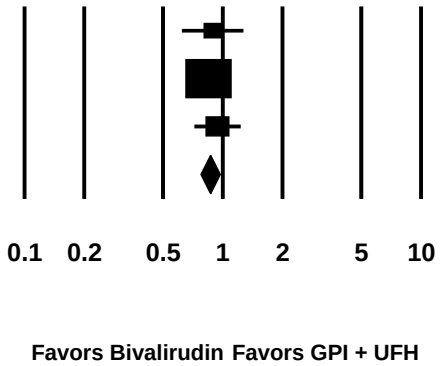
Only one study (good quality) reported the composite endpoint of all-cause mortality, nonfatal MI, revascularization, or major bleeding at 30 days in 4571 patients randomized to a bivalirudin versus heparin-based strategy without planned GPI.[59] In this study, there was a similar incidence of the composite endpoint for patients treated with bivalirudin (8.4%) and heparin without planned GPI (8.7%). The SOE was rated insufficient for this composite endpoint at 30 days without planned GPI based on one good-quality study that was underpowered to answer the question.

With Planned GPI

A random-effects meta-analysis of three RCTs[63-65] (three 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 endpoint at 30 days with planned GPI based on three good-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Rajagopal, 2006	0.889	0.627	1.261	0.509
Stone, 2006	0.848	0.744	0.967	0.014
Kastrati, 2011	0.941	0.725	1.221	0.647
	0.868	0.777	0.970	0.013



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

Without Planned GPI

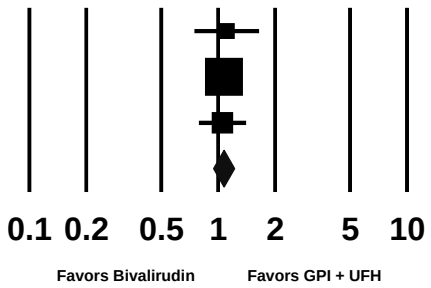
Two RCTs[58,59] (one good quality, one fair) including 5420 UA/NSTEMI patients reported the composite outcome of all-cause mortality, nonfatal MI, and revascularization at 30 days. The study by Kastrati reported an odds ratio of 1.19 (95% CI 0.92 to 1.54) with no statistically significant difference between treatment groups. The study by Parodi reported an odds ratio of 0.42 (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 the composite outcome of all-cause mortality, nonfatal MI and revascularization at 30 days without planned GPI based on one good- and one fair-quality RCT with inconsistent results of a direct outcome and imprecise results.

With Planned GPI

A random-effects meta-analysis of three RCTs[63-65] (three good quality) including 12,287 UA/NSTEMI patients reporting the composite outcome of all-cause mortality, nonfatal MI, and 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 the composite outcome of all-cause mortality, nonfatal MI and revascularization at 30 days with planned GPI based on three good-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Rajagopal, 2006	1.111	0.754	1.636	0.594
Stone, 2006	1.074	0.920	1.254	0.364
Kastrati, 2011	1.054	0.797	1.395	0.712
	1.074	0.945	1.220	0.274



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

Without Planned GPI

Two RCTs[58,59] (one good quality, one fair) including 5420 UA/NSTEMI patients reported the composite outcome of all-cause mortality, nonfatal MI, and revascularization at 1 year. The 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 study by Parodi reported an odds ratio of 0.58 (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 all-cause mortality, nonfatal MI, and revascularization at 1 year without planned GPI based on one good- and one fair-quality RCT with inconsistent and imprecise results of a direct outcome.

With Planned GPI

Two RCTs[64,65] (two good quality) including 10,566 UA/NSTEMI patients reported the composite outcome of all-cause mortality, nonfatal MI, and 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 (CI, 0.92 to 1.25). While both ORs favored GPI with UFH the findings were not statistically significant. The SOE was rated insufficient for all-cause mortality, nonfatal MI, and revascularization at 1 year with planned GPI based on two good-quality RCTs with consistent results of a direct outcome and imprecise estimates.

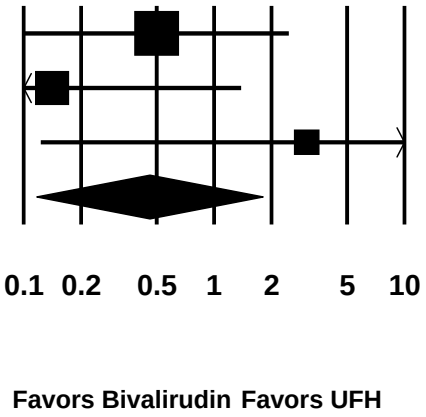
Effect on All-Cause Mortality at 30 Days

Without Planned GPI

A random-effects meta-analysis of three RCTs[58-60] (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) for 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 study with a significantly higher odds ratio[60] reported no deaths in one treatment arm, and this likely contributed to the inconsistent results. The SOE was rated insufficient for all-cause mortality at 30 days without planned GPI 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 vs. heparin-based strategy without glycoprotein inhibitor on all-cause mortality at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Kastrati, 2008	0.499	0.102	2.446	0.392
Parodi, 2010	0.141	0.014	1.375	0.092
Patti, 2012	3.070	0.124	76.025	0.493
	0.460	0.117	1.807	0.266

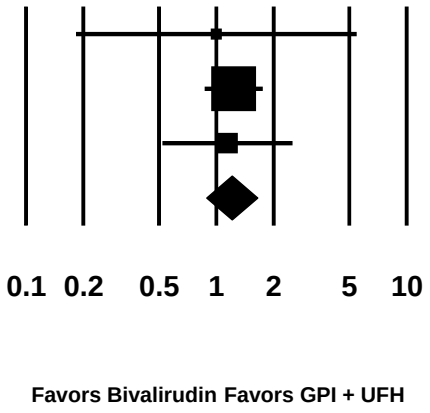


With Planned GPI

A random-effects meta-analysis of three RCTs[63-65] (three 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 for all-cause mortality at 30 days with planned GPI based on three good-quality RCTs with consistent results of a direct outcome and a wide confidence interval.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Rajagopal, 2006	1.000	0.185	5.418	1.000
Stone, 2006	1.235	0.876	1.740	0.229
Kastrati, 2011	1.145	0.525	2.496	0.733
	1.211	0.889	1.650	0.224



Effect on All-Cause Mortality After 6 Months

Without Planned GPI

Only two studies[58,59] (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.[58] 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.[59] The SOE was rated insufficient for all-cause mortality after 6 months without planned GPI based on one good- and one fair-quality RCTs with inconsistent results of a direct outcome.

With Planned GPI

Only two studies[64,65] (two 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.[65] 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.[64] The SOE was rated insufficient for all-cause mortality after 6 months with planned GPI based on two good-quality RCTs with consistent results of a direct outcome.

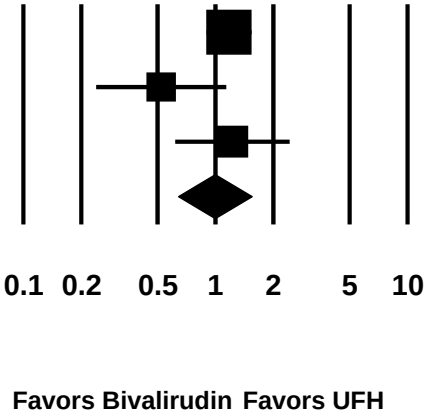
Effect on Nonfatal MI at 30 Days

Without Planned GPI

A random-effects meta-analysis of three RCTs[58-60] (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 for nonfatal MI at 30 days without planned GPI 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 vs. heparin-based strategy without glycoprotein inhibitor on nonfatal myocardial infarction at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Kastrati, 2008	1.177	0.905	1.529	0.224
Parodi, 2010	0.522	0.241	1.130	0.099
Patti, 2012	1.225	0.622	2.413	0.557
	0.997	0.642	1.548	0.989

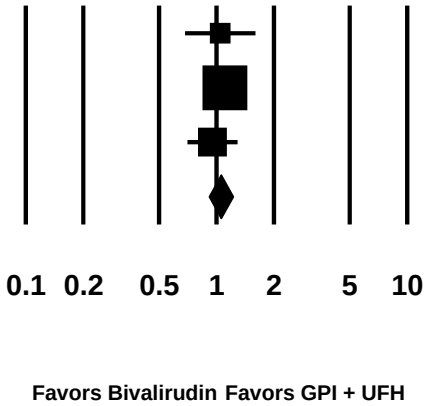


With Planned GPI

A random-effects meta-analysis of three RCTs[63-65] (three 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 nonfatal MI at 30 days with planned GPI 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 vs. heparin-based strategy with glycoprotein inhibitor on nonfatal myocardial infarction at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Rajagopal, 2006	1.047	0.690	1.588	0.829
Stone, 2006	1.108	0.921	1.333	0.278
Kastrati, 2011	0.953	0.710	1.279	0.747
	1.060	0.915	1.227	0.438



Effect on Nonfatal MI After 6 Months

Without Planned GPI

Only two studies[58,59] (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.[58] 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.[59] The SOE was rated insufficient for nonfatal MI after 6 months without planned GPI based on one good- and one fair-quality RCTs with inconsistent results of a direct outcome.

With Planned GPI

Only two studies[64,65] (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%;[64] 8.1%[65]) versus heparin plus GPI (6.9%;[64] 7.6%[65]) at 6 months and 1 year (p=NS for both studies). The SOE was rated insufficient for nonfatal MI after 6 months with planned GPI based on two good-quality RCTs with consistent results of a direct outcome.

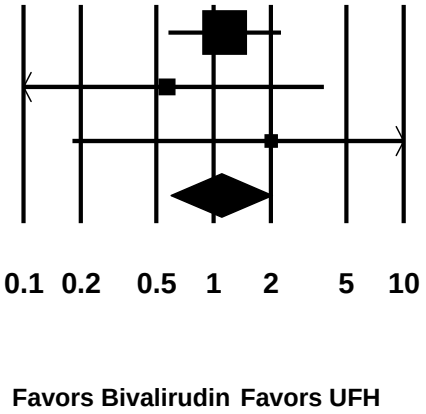
Effect on Revascularization at 30 Days

Without Planned GPI

A random-effects meta-analysis of three RCTs[58-60] (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 revascularization at 30 days without planned GPI 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 vs. heparin-based strategy without glycoprotein inhibitor on revascularization at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Kastrati, 2008	1.144	0.583	2.244	0.695
Parodi, 2010	0.570	0.086	3.768	0.559
Patti, 2012	2.010	0.182	22.174	0.569
	1.103	0.597	2.037	0.755

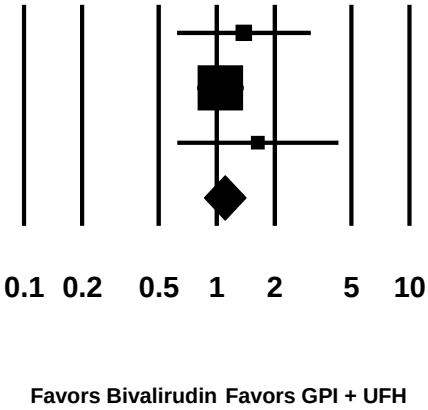


With Planned GPI

A random-effects meta-analysis of three RCTs[63-65] (three 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) for 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 insufficient for revascularization at 30 days with planned GPI based on three good-quality RCTs with inconsistent results of a direct outcome and a wide confidence interval.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Rajagopal, 2006	1.383	0.628	3.049	0.421
Stone, 2006	1.045	0.798	1.368	0.751
Kastrati, 2011	1.633	0.629	4.240	0.314
	1.106	0.864	1.415	0.423



Effect on Revascularization After 6 Months

Without Planned GPI

Only two studies[58,59] (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%[58] 11.2%[59]) versus heparin-based strategy (5.7%;[58] 12.5%[59]) at 6 months and 1 year (p=NS for both studies). The SOE was rated insufficient for revascularization after 6 months without planned GPI based on inconclusive findings.

With Planned GPI

Only two studies[64,65] (two 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%;[64] 11.7%[65]) 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 for revascularization after 6 months with planned GPI based on two good-quality RCTs with consistent results of a direct outcome.

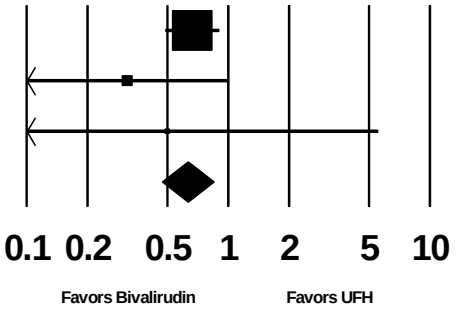
Effect on Major Bleeding at 30 Days

Without Planned GPI

A random-effects meta-analysis of three RCTs[58-60] (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 for major bleeding at 30 days without planned GPI use 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 vs. heparin-based strategy without glycoprotein inhibitor on major bleeding at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Kastrati, 2008	0.663	0.488	0.902	0.009
Parodi, 2010	0.315	0.099	1.006	0.051
Patti, 2012	0.497	0.045	5.543	0.570
	0.630	0.469	0.845	0.002

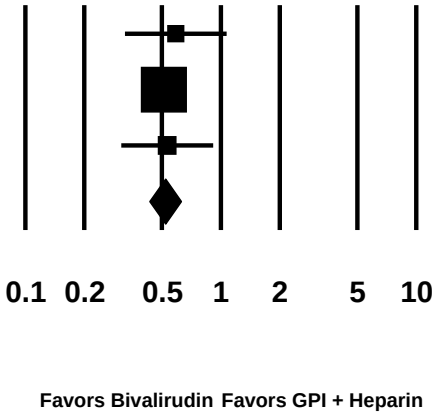


With Planned GPI

A random-effects meta-analysis of three RCTs[63-65] (three 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 for major bleeding at 30 days with planned GPI based on three good-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Rajagopal, 2006	0.589	0.326	1.064	0.079
Stone, 2006	0.512	0.415	0.631	0.000
Kastrati, 2011	0.532	0.312	0.907	0.020
	0.521	0.433	0.628	0.000



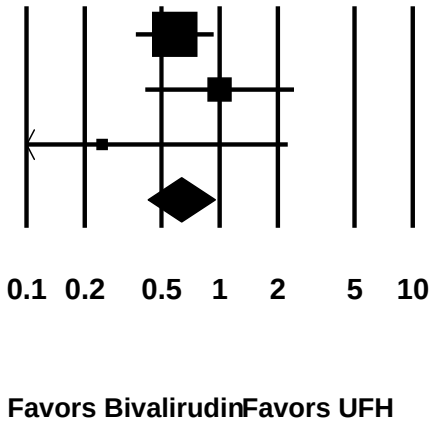
Effect on Minor Bleeding at 30 Days

Without Planned GPI

A random-effects meta-analysis of three RCTs[58-60] (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 for minor bleeding at 30 days without planned GPI use 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 vs. heparin-based strategy without planned glycoprotein inhibitor on minor bleeding at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Kastrati, 2008	0.586	0.371	0.925	0.022
Parodi, 2010	1.000	0.415	2.407	1.000
Patti, 2012	0.246	0.027	2.235	0.213
	0.636	0.427	0.947	0.026

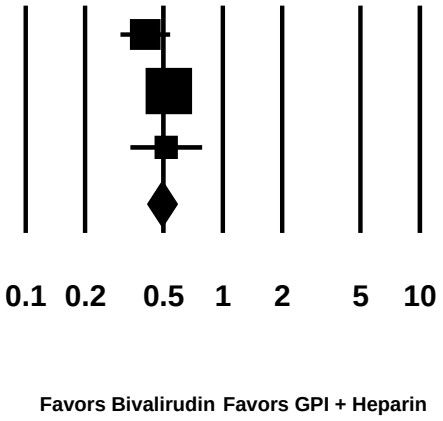


With Planned GPI

A random-effects meta-analysis of three RCTs[63-65] (three good quality) including 12,287 UA/NSTEMI patients reporting minor bleeding at 30 days found that the odds ratio was 0.50 (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 for minor bleeding at 30 days with planned GPI based on three good-quality RCTs with consistent results of a direct outcome and a narrow confidence interval.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Rajagopal, 2006	0.405	0.305	0.537	0.000
Stone, 2006	0.533	0.477	0.596	0.000
Kastrati, 2011	0.517	0.342	0.780	0.002
	0.495	0.416	0.588	0.000



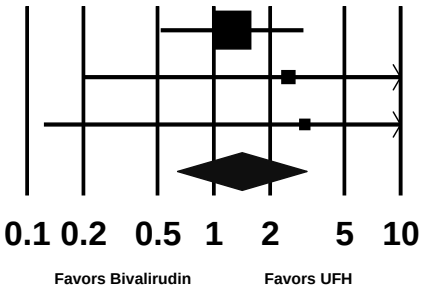
Effect on Stent Thrombosis at 30 Days

Without Planned GPI

Of the three RCTs[58-60] (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 for stent thrombosis at 30 days without planned GPI based on an imprecise estimate and a low total number of events.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Kastrati, 2008	1.251	0.523	2.992	0.614
Parodi, 2010	2.508	0.202	31.133	0.474
Patti, 2012	3.070	0.124	76.025	0.493
	1.418	0.639	3.150	0.391



With Planned GPI

Of the two RCTs[64,65] (two 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%;[64] 1.0%[65]) when compared with those treated with a heparin-based strategy plus GPI (0.6 %;[64] 0.8%[65]) which was not statistically significant .The SOE was rated insufficient for stent thrombosis at 30 days with planned GPI based on studies not sufficiently powered to detect a difference.

Findings by Subgroup

Three studies (good quality) of 15,494 patients reported variations in treatment effectiveness by subgroup.[59,63,64] The main report from an additional study reported subgroups, but due to the fact that data was abstracted from the subgroup report of UA/NSTEMI patients, this was not included in the findings by subgroup.[65] 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 will be 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).[59]

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.[64]

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).[63]

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%).[59]

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%).[64]

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%).[63] 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%).[59]

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%).[64]

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%).[63]

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%).[59]

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%).[64]

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%).[63]

Serum Biomarker Positivity

There was no subgroup analysis of serum biomarkers in ISAR-REACT 3.[59] 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.[64]

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%).[63]

TIMI Risk Score

There was no subgroup analysis of TIMI risk score in ISAR-REACT 3[59] or ISAR-REACT 4.[63] 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%).[64]

Weight

There was no subgroup analysis of weight or body-mass index in ISAR-REACT 3,[59] or ACUITY.[64] 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).[63]

PCI or CABG After Randomization

There was no subgroup analysis of PCI or CABG in ISAR-REACT 3[59] or ISAR-REACT 4.[63] 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%).[64]

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 insufficient after 1 year. 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 use although the SOE was rated insufficient for this outcome. For revascularization in the planned GPI group, at 30 days there was insufficient evidence, 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 a statistically nonsignificant higher incidence in stent thrombosis in patients treated with bivalirudin versus heparin-based strategy without planned GPI use at 30 days; there was insufficient evidence for this outcome in the planned GPI group.

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; those greater than 1 favor a heparin-based strategy.

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

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 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	One study OR 1.19 (0.92 to 1.54); another study OR 0.42 (0.21 to 0.84)
Composite of all-cause mortality, nonfatal MI, or revascularization after 1 year					**Insufficient SOE**
2 (5420)	2 RCTs/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	One study OR 0.97 (0.83 to 1.13); another study 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 two 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)
Nonfatal MI after 6 months					**Insufficient SOE**
2 (5420)	2 RCTs/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	Disparate results in two 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)

Abbreviations: CI=confidence interval; GPI= glycoprotein IIb/IIIa 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. Summary strength of evidence for UA/NSTEMI patients treated with bivalirudin vs. heparin-based strategy with planned glycoprotein inhibitor use

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 major bleeding at 30 days					**High SOE**
3 (12,287)	3 RCTs/3 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/3 good quality	Consistent	Direct	Precise	OR 1.07 (0.95 to 1.22)
Composite of all-cause mortality, nonfatal MI, or revascularization after 1 year					**Insufficient SOE**
2 (10,566)	2 RCTs/2 good quality	Consistent	Direct	Precise	Both studies found no difference between treatments, OR 1.11 (0.74 to 1.63); and OR 1.08 (0.92 to 1..25)
All-cause mortality at 30 days					**Insufficient SOE**
3 (12,287)	3 RCTs/3 good quality	Consistent	Direct	Imprecise	OR 1.21 (0.89 to 1.65)
All-cause mortality after 6 months					**Insufficient SOE**
2 (10,566)	2 RCTs/2 good quality	Consistent	Direct	Imprecise	Similar event rate in one study (3.8% bivalirudin, 3.8% GPI), slightly lower event rate in other study (0.9% bivalirudin,1.3% GPI, p=0.46)
Nonfatal MI at 30 days					**Moderate SOE**
3 (12,287)	3 RCTs/3 good quality	Consistent	Direct	Imprecise	OR 1.06 (0.92 to 1.23)
Nonfatal MI after 6 months					**Insufficient SOE**
2 (10,566)	2 RCTs/2 good quality	Consistent	Direct	Imprecise	Higher event rate in bivalirudin (7.8% and 8.1%) vs. heparin (6.9 and 7.6%)
Revascularization at 30 days					**Insufficient SOE**
3 (12,287)	3 RCTs/3 good quality	Inconsistent	Direct	Imprecise	OR 1.11 (0.86 to 1.42)
Revascularization after 6 months					**Low SOE**
2 (10,566)	2 RCTs/2 good quality	Consistent	Direct	Imprecise	Higher event rate in bivalirudin (8.7% and 11.7%) vs. heparin (8.4% in both studies)
Major bleeding at 30 days					**High SOE**
3 (12,287)	3 RCTs/3 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/3 good quality	Consistent	Direct	Precise	OR 0.50 (0.42 to 0.59) favors bivalirudin
Stent thrombosis at 30 days					**Insufficient SOE**
2 (10,936)	2 RCTs/2 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%)

Abbreviations: CI=confidence interval; GPI= glycoprotein IIb/IIIa 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)

Fourteen studies (11 RCTs, 3 observational) compared the use of enoxaparin, UFH, and fondaparinux in 44,372 UA/NSTEMI patients undergoing an invasive strategy.[67-77,105-107] Four RCTs compared enoxaparin with UFH prior to PCI and included a total of 17,931 patients.[67-70] One RCT (20,078 patients) compared enoxaparin with fondaparinux[71] and one RCT (350 patients) compared fondaparinux with UFH.[72] Three studies compared enoxaparin with UFH at the time of PCI;[73-75] 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 not included in the analysis. One study 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.[76] One additional study 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.[77]

Multiple observational studies were screened and abstracted. With the exception of four studies, most were excluded due to lack of clarity about an early invasive management strategy or heterogeneity in the study population. Of the four included studies, one study[105] 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. The remaining two studies[106,107] will be discussed below.

Of the six RCTs, five studies (86%) were rated good quality and one study (14%) fair. Of the two observational studies, both studies were rated moderate risk of bias. Sample sizes for included individual studies ranged from 350 to 20,078 patients. Study duration ranged from 48 hours to 30 days, with four 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 34 percent. Two studies (25%) reported the racial and ethnic demographics of study participants. All six RCTs and both observational studies were international, multi-center studies, including sites in the United States and Canada. All six 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,[68,71] 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 Endpoint Prior to 7 Days and at 30 Days

Three good-quality RCTs[67,69,71] (two studies evaluating enoxaparin versus UFH, one study evaluating enoxaparin versus fondaparinux) reported a composite ischemic endpoint at 30 days, while one good-quality RCT[68] comparing enoxaparin versus UFH reported a composite endpoint at 7 days, and one fair-quality RCT[72] 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.

Enoxaparin Versus UFH

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);[68] all-cause mortality or nonfatal MI at 30 days (enoxaparin 14.0% vs. 14.5%);[67] and all-cause mortality, nonfatal MI, or revascularization at 30 days (enoxaparin 14.0% vs. 16.1%).[69] In the two observational studies (two fair quality) of enoxaparin versus unfractionated heparin, Brieger et al.[107] reported a lower incidence of death during hospitalization in patients treated with enoxaparin when compared with unfractionated heparin. Singh et al.[106] reported similar composite ischemic endpoints in enoxaparin-treated and unfractionated heparin-treated patients (7.4% in each group).

Enoxaparin or UFH Versus Fondaparinux

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%).[71] 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%).[72]

The SOE was rated low for the composite ischemic endpoint at 7 days due to one RCT (A to Z study) which was adequately powered for a noninferiority hypothesis. In the A to Z study, enoxaparin was to be considered noninferior to unfractionated heparin if the upper 1-sided 95% confidence boundary for the enoxaparin effect relative to unfractionated heparin was less than 1.14. The SOE was rated low for the composite ischemic endpoint at 30 days based on 4 good-quality RCTs (two studies of enoxaparin vs. UFH, one study of fondaparinux vs. UFH, and one study of enoxaparin vs. fondaparinux) with consistent results of a direct outcome.

Effect on Composite Ischemic Outcome at 6 Months

Only one RCT[71] (good quality) of 20,078 patients in this comparison group evaluated the effect of treatment on the composite ischemic outcome 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 (two good quality) and two observational studies (two fair quality) of 69,908 patients in this comparison group evaluated the effect of treatment of enoxaparin versus unfractionated heparin versus fondaparinux on major bleeding.[67,71,106,107] In one of the RCTs, there was a significantly higher incidence of major bleeding in patients treated with enoxaparin (5.0%) when compared with fondaparinux (3.1%) at 30 days, $p<0.001$. These results were also statistically significant at 180 days (enoxaparin 5.8%; fondaparinux 4.3%, $p<0.001$).[71] 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 unfractionated heparin (7.6%), p=0.008.[67] In the observational studies, there was a statistically significant difference in major bleeding favoring enoxaparin (1.8%) versus unfractionated heparin (2.7%), p<0.001,[107] but no statistically significant difference in non–CABG-related transfusions (enoxaparin 6.7%; unfractionated heparin 7.0%) between treatments.[106] The SOE was rated low for major bleeding at 30 days based on inconsistent results of a direct outcome.

Findings by Subgroup

Three good-quality RCTs[67,68,71] (two studies evaluating enoxaparin versus UFH, one study evaluating enoxaparin versus 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 will be 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.[67]

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%).[68]

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.[71]

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%).[67]

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%).[68]

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.[71]

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%).[67] 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%).[68] There was no subgroup analysis presented in patients with diabetes mellitus from OASIS-5.[71]

Chronic Kidney Disease

No subgroup analysis data on kidney function or chronic kidney disease was presented in SYNERGY or A to Z.[67,68] 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%).[71]

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/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.[67]

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.[67] There was no subgroup analysis of prior coronary revascularization (including PCI or CABG) in A to Z or OASIS-5.[68,71]

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%).[67] 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%).[68] There was no subgroup analysis presented in patients with abnormal serum cardiac biomarkers from OASIS-5.[71]

TIMI Risk Score

No subgroup analysis data on TIMI risk score was presented in SYNERGY.[67] 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%).[68] There was no subgroup analysis of TIMI risk score from OASIS-5.[71]

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%).[67] 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%).[68] There was no subgroup analysis of geographic region presented in OASIS-5.[71]

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

In our analysis of studies comparing enoxaparin, unfractionated heparin, 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, unfractionated heparin, 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.

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. Summary strength of evidence for UA/NSTEMI patients treated with enoxaparin vs. unfractionated heparin vs. fondaparinux (percutaneous coronary intervention cohort)

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 prior to 7 days					**Low SOE**
1 (3987)	1 RCT/Good quality	NA	Direct	Precise	HR 0.89 (0.75 to 1.05), No difference between enoxaparin and UFH (adequately powered for noninferiority hypothesis)
Composite ischemic endpoints at 30 days					**Low SOE**
4 (34,022)	4 RCTs/4 good quality	Consistent	Direct	Precise	Similar rates of composite events in two studies of enoxaparin vs. UFH, one study of fondaparinux vs. UFH, and one study of enoxaparin vs. fondaparinux
Composite of all-cause mortality, nonfatal MI, or revascularization after 6 months					**Low SOE**
1 (20,078)	RCT/Good quality	NA	Direct	Precise	No difference between enoxaparin (10.2%) and fondaparinux (10.1%) adequately powered for a noninferiority hypothesis
Major bleeding at 30 days					**Low SOE**
4 (69,908)	2 RCTs/2 good quality 2 observational/2 fair	Inconsistent	Direct	Precise	One RCT showed lower events with fondaparinux vs. enoxaparin; one RCT showed lower events with UFH vs. enoxaparin. Two observational studies of UFH v s. enoxaparin had conflicting results

Abbreviations: 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. Timing of Clopidogrel for Patients Undergoing Percutaneous Coronary Intervention for UA/NSTEMI

A total of four studies—two RCTs[78,79] (fair quality; 735 patients) and two observational studies[108,109] (both fair quality; 5590 patients)—directly compared a pretreatment clopidogrel strategy with a deferred clopidogrel treatment strategy (Tables G-6, G-7, and G-8 in Appendix G). In one RCT,[78] 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,[79] 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 and delay in PCI (15.6%). In one observational study,[108] 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. In the other observational study[109] 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 analysis 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 and patients treated with clopidogrel at the time of PCI. While the assignment of clopidogrel timing was not random, the intention of these analyses is not to compare across strategies but to provide estimation of effects in those patients who underwent randomized assignment to one strategy compared with another.

Therefore, the remainder of this analysis presents results for the following approaches:

- Clopidogrel pretreatment strategy:
  - Studies of patients pretreated with clopidogrel prior to PCI with random assignment to bivalirudin versus a heparin-based strategy
  - Studies of patients pretreated with clopidogrel prior to PCI with random assignment to upstream versus deferred GPI use
- Clopidogrel deferred treatment strategy:
  - Studies of patients treated with clopidogrel at the time of PCI with random assignment to bivalirudin versus heparin-based strategy
  - Studies of patients treated with clopidogrel at the time of PCI with random assignment to upstream versus deferred GPI use

Clopidogrel Pretreatment Strategy

Nine RCTs compared different antithrombotic strategies in UA/NSTEMI patients pretreated with clopidogrel while undergoing an invasive strategy. Four of these studies involved patients who were pretreated with clopidogrel and underwent random assignment to bivalirudin versus a heparin-based strategy.[59,60,64,65] Five of these studies involved patients who were pretreated with clopidogrel and underwent random assignment to upstream versus deferred use of GPI.[21,34,36,37,41] 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 GPI use and other treatment options (i.e., enoxaparin, UFH).

Of the nine RCTs included in the meta-analysis, six studies (66%) were rated good quality, two (22%) fair, and one (11%) 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 (11%) reported the racial and ethnic demographics of study participants. Five studies (56%) were conducted within the United States or Canada, with the rest international. Funding source was reported in seven studies (78%) as an industry source.

Studies of Patients Pretreated With Clopidogrel—Random Assignment to Bivalirudin Versus Heparin-based Strategy

Effect on Composite Ischemic Endpoints at 30 Days

Two good-quality RCTs[64,65] including 2,571 UA/NSTEMI patients treated with clopidogrel prior to PCI reported the composite outcome of all-cause mortality, nonfatal MI, and 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; CI, 0.99 to 1.56), but neither were statistically significant. The SOE was rated insufficient for composite ischemic endpoints at 30 days based on two good-quality RCTs with consistent results of direct outcome and a wide confidence interval.

Effect on Composite Ischemic Endpoints at 1 Year

We identified one good-quality RCT[59] of 4,570 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 for composite ischemic endpoints at 1 year based on findings from only one moderate-sized, good-quality RCT.

Effect on All-Cause Mortality at 1 Year

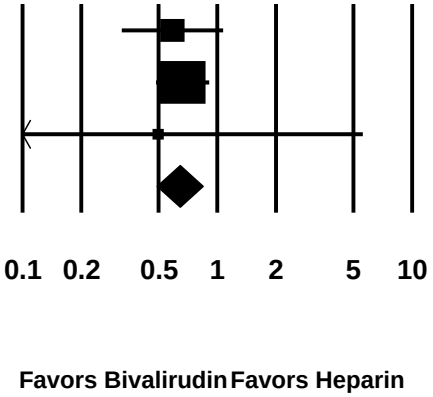
One good-quality study[64] of 5,126 patients reported the effect of treatment on all-cause mortality at 1 year in patients pretreated with clopidogrel who were randomly assigned to bivalirudin versus a heparin-based strategy. In these patients who were pretreated with clopidogrel, those treated with bivalirudin (16.0%) had a similar incidence of all-cause mortality to those treated with a heparin-based strategy (16.3%). The SOE was rated insufficient for all-cause mortality at 1 year based on findings from only one moderate-sized, good-quality RCT.

Effect on Major Bleeding at 30 Days

A random-effects meta-analysis of three RCTs[59,60,65] (two good quality, one fair) including 6,322 UA/NSTEMI patients pretreated with clopidogrel prior to PCI reporting the composite outcome of major bleeding at 30 days found that the odds ratio was 0.65 (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 for major bleeding at 30 days 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 vs. heparin-based strategy on major bleeding at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Rajagopal, 2006	0.589	0.326	1.064	0.079
Kastrati, 2008	0.663	0.488	0.902	0.009
Patti, 2012	0.497	0.045	5.543	0.570
	0.645	0.492	0.845	0.001



Studies of Patients Pretreated With Clopidogrel—Random Assignment to Upstream Versus Deferred GPI Use

Effect on Composite Ischemic Endpoints Prior to 30 days

Only one good-quality RCT[41] 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 but statistically nonsignificant difference in composite endpoint in those patients treated with upstream GPI (8.7%) versus deferred GPI (9.4%). The SOE for the composite endpoint of all-cause mortality, nonfatal MI, revascularization, or thrombotic GPI bailout at 96 hours was rated insufficient based on only one good-quality RCT.

One poor-quality RCT[37] 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 the composite endpoint of all-cause mortality, nonfatal MI, or rehospitalization at 30 days was rated insufficient based on only one, small sized, poor-quality RCT.

Two randomized studies (one good quality, one fair)[34,36] 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 (15.7%) had a reduction in the incidence of the composite outcome when compared with deferred GPI (20.3%). This effect was mainly driven by refractory ischemia in one of the studies.[36] The SOE for the composite outcome of all-cause mortality, nonfatal MI, or

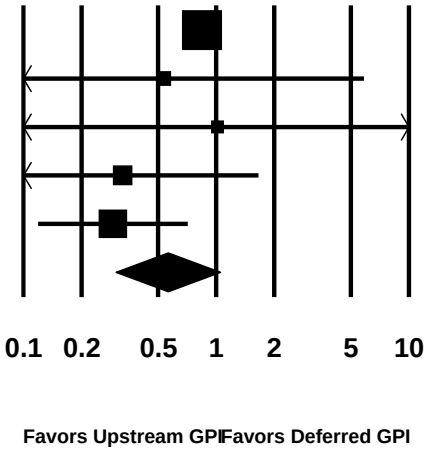
ischemia/revascularization at 30 days was rated low based on one good-and one fair-quality RCT with consistent results of unknown precision of a direct outcome.

Effect on All-Cause Mortality at 30 Days

A random-effects meta-analysis of five RCTs[34,36,37,41,43] (two good quality, two fair, one poor) including 8,168 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) (Figure 27). There was some evidence of heterogeneity, with a Q-value of 6.76 for 4 degrees of freedom, p=0.15. The inclusion of two good-, two fair-, and one poor-quality single-center studies[34,36,37,43] likely contributed to the inconsistent results and heterogeneity. The SOE was rated insufficient for all-cause mortality at 30 days based on two good-, two fair-, and one poor-quality RCTs with inconsistent results of a direct outcome and a wide confidence interval.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Giugliano, 2005	0.844	0.725	0.982	0.028
Leoncini, 2005	0.535	0.049	5.802	0.607
Rasoul, 2006	1.016	0.063	16.406	0.991
Durand, 2007	0.328	0.065	1.643	0.175
Bhattacharya, 2010	0.291	0.120	0.706	0.006
	0.564	0.302	1.051	0.071

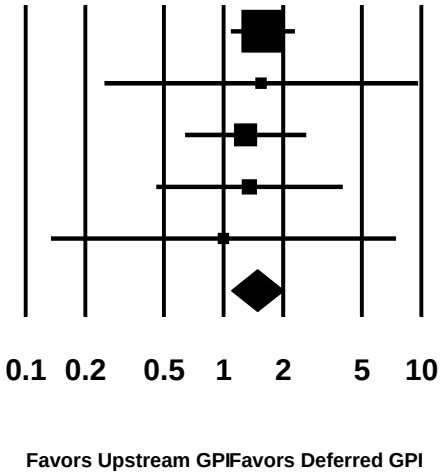


Effect on Major Bleeding at 30 Days

A random-effects meta-analysis of five RCTs[34,37,41,43] (two good quality, two fair, one poor) including 7,416 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 for major bleeding at 30 days based on two good-, two fair-, and one poor-quality RCTs with consistent results of a direct outcome and a wide confidence interval.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Giugliano, 2005	1.581	1.097	2.278	0.014
Leoncini, 2005	1.549	0.252	9.537	0.637
Rasoul, 2006	1.294	0.645	2.597	0.468
Durand, 2007	1.352	0.460	3.970	0.583
Ivandic, 2008	1.000	0.135	7.392	1.000
	1.488	1.100	2.012	0.010



Clopidogrel Deferred Treatment 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. 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.[58,63] 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.[39-42] 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.

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.

Studies of Patients Treated With Clopidogrel at the Time of PCI—Random Assignment to Bivalirudin Versus Heparin-Based Strategy

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

Two RCTs[58,63] (one good quality, one fair) including 2,571 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 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 showed no statistical difference between the groups, OR 1.05 (95% CI 0.80 to 1.40). The SOE was rated insufficient for composite endpoint at 30 days 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[58,63] (one good quality, one fair) including 2,571 UA/NSTEMI patients treated with clopidogrel at the time of PCI reported major bleeding at 30 days. The Parodi study showed no statistical difference between the groups, OR 0.32 (95% CI 0.10 to 1.01) and the Kastrati study showed a statistically significant reduction favoring bivalirudin, OR 0.53 (95% CI 0.31 to 0.91, p=0.02). 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.

Studies of Patients Treated With Clopidogrel at the Time of PCI—Random Assignment to Upstream Versus Deferred GPI Use

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

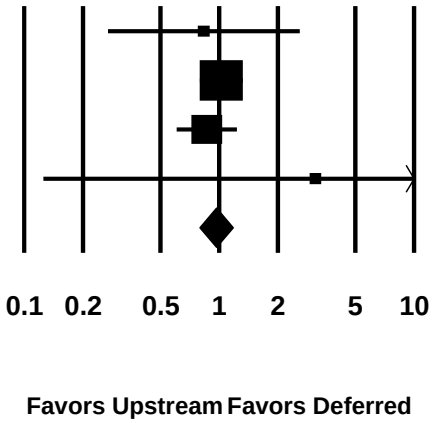
Only one RCT (good quality)[41] including 2271 UA/NSTEMI patients reported a composite endpoint of all-cause mortality, nonfatal MI, revascularization, thrombotic GPI bailout at 96 hours in patients treated with clopidogrel at the time of PCI randomly assigned to upstream versus deferred GPI use. This 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 for composite events at 96 hours 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[39-42] (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) (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 study[39] contributed to the inconsistent results. The SOE was rated insufficient for all-cause mortality at 30 days based on two good-, one fair-, and one poor-quality RCTs with inconsistent results of a direct outcome and a confidence interval that crosses 1.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
van't Hof, 2003	0.835	0.271	2.572	0.753
Giugliano, 2005	1.027	0.804	1.312	0.831
Stone, 2007	0.865	0.610	1.226	0.414
Liu, 2009	3.120	0.127	76.950	0.487
	0.970	0.797	1.181	0.762

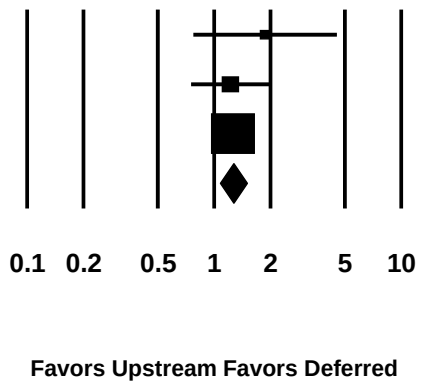


Effect on Major Bleeding at 30 Days

A random-effects meta-analysis of three RCTs[40-42] (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 for major bleeding at 30 days based on two good- and one fair-quality RCTs with consistent results of an indirect 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 vs. deferred glycoprotein inhibitor use on major bleeding at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
van't Hof, 2003	1.872	0.780	4.493	0.160
Giugliano, 2005	1.222	0.758	1.969	0.411
Stone, 2007	1.261	1.053	1.510	0.012
	1.274	1.080	1.503	0.004



Findings by Subgroup

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 Clopidogrel Pretreatment Versus Deferred Strategy

Two RCTs and two observational studies directly assessed a pretreatment and at the time of PCI (deferred) treatment of clopidogrel. These studies had mixed results; however, in the subgroup of patients with UA/NSTEMI, those pretreated with clopidogrel had fewer clinical events than those treated with in-laboratory clopidogrel.

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 when compared with patients randomized to deferred GPI use. There was insufficient SOE for the composite outcome at 96 hours, the composite of all-cause mortality, nonfatal MI, or rehospitalization at 30 days, and all-cause mortality 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 insufficient SOE for the effect on major bleeding at 30 days in those patients treated with deferred clopidogrel and randomized to bivalirudin. In studies of patients treated with deferred clopidogrel and randomized to upstream GPI, there was insufficient SOE for composite ischemic outcomes and 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; those greater than 1 favor a heparin-based strategy or deferred GPI use.

Table 11. Summary strength of evidence for UA/NSTEMI patients pretreated with clopidogrel randomized to bivalirudin vs. heparin-based strategy

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 revascularization at 30 days					**Insufficient SOE**
2 (2571)	2 RCTs/2 good quality	Consistent	Direct	Imprecise	Both studies showed no statistically significant difference in composite event rates ranging from OR 1.11-1.25
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year					**Insufficient SOE**
1 (4570)	RCT/good quality	NA	Direct	Unknown	bivalirudin 21.5%, heparin 20.1%
All-cause mortality at 1 year					**Insufficient SOE**
1 (5126)	RCT/Good quality	NA	Direct	Unknown	Similar incidence of endpoints between groups (16.0% bivalirudin, 16.3% heparin)
Major bleeding at 30 days					**Moderate SOE**
3 (6322)	3 RCTs/3 good quality	Consistent	Direct	Precise	OR 0.65 (0.49 to 0.85) favoring bivalirudin

Abbreviations: 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. Summary strength of evidence for UA/NSTEMI patients pretreated with clopidogrel randomized to upstream vs. deferred glycoprotein inhibitor use

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 thrombotic GPI bailout at 96 hours					**Insufficient SOE**
1 (6895)	RCT/Good quality	NA	Direct	Unknown	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	Unknown	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	Unknown	Upstream GPI: 15.7% Deferred GPI: 20.3%
All-cause mortality at 30 days					**Insufficient SOE**
5 (8168)	5 RCTs/2 good quality, 1 fair, 1 poor	Inconsistent	Direct	Imprecise	OR 0.56 (0.30 to 1.05)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Major bleeding at 30 days					**Moderate SOE**
5 (7416)	5 RCTs/2 good quality, 1 fair, 1 poor	Consistent	Direct	Imprecise	OR 1.49 (1.10 to 2.01) favoring deferred GPI use

Abbreviations: CI=confidence interval; GPI= glycoprotein IIb/IIIa 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. Summary strength of evidence for UA/NSTEMI patients treated with clopidogrel at time of percutaneous coronary intervention randomized to bivalirudin vs. heparin-based strategy

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 revascularization at 30 days					**Insufficient SOE**
2 (2571)	2 RCTs/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	One study showed a significant reduction favoring bivalirudin, OR 0.42 (95% CI 0.21 to 0.84, p=0.02), the other study showed no difference, OR 1.05 (0.80 to 1.40).
Major bleeding at 30 days					**Insufficient SOE**
2 (2571)	2 RCTs/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	One showed no statistical difference between the groups, OR 0.32 (95% CI 0.10 to 1.01) and the other study showed a statistically significant reduction favoring bivalirudin, OR 0.53 (0.31 to 0.91, p=0.02).

Abbreviations: 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. Summary strength of evidence for UA/NSTEMI patients treated with clopidogrel at time of percutaneous coronary intervention randomized to upstream vs. deferred glycoprotein inhibitor use

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 thrombotic bailout with GPI at 96 hours					**Insufficient SOE**
1 (2,271)	RCT/Good quality	NA	Direct	Unknown	Upstream GPI: 10.3% Deferred GPI: 11.2%
All-cause mortality at 30 days					**Insufficient SOE**
4 (11,858)	4 RCTs/2 good quality, 1 fair, 1 poor	Inconsistent	Direct	Imprecise	OR 0.97 (0.80 to 1.18)
Major bleeding at 30 days					**High SOE**

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
3 (11,698)	3 RCTs/2 good quality, 1 fair	Consistent	Direct	Precise	OR 1.27 (1.08 to 1.50) favoring deferred GPI use

Abbreviations: CI=confidence interval; GPI= glycoprotein IIb/IIIa 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 on improving cardiovascular outcomes?

b. What are the comparative effectiveness (dose and timing) and comparative safety of different antiplatelet agents on 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, but there was insufficient evidence to reach a conclusion on the comparative treatment effect on all-cause mortality and major bleeding.

- From 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 and 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 ECG.

- Adding GPIs to unfractionated heparin reduced the rate of mortality at 30 days (high SOE), and reduced composite ischemic events and nonfatal MI, especially in trials of

eptifibatide and tirofiban (moderate SOE). 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 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 listed above, the tradeoff is an increase in and minor bleeding rates (high SOE). There was insufficient evidence on the effect of GPIs on major bleeding.

Description of Included Studies

We identified 32 unique studies that evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 209,231 patients with UA/NSTEMI treated with an *initial conservative* approach or a mixed population where the approach (conservative or invasive) was not presented separately.[36,38,42,45,46,64,67-76,106,107,110-123] Of these studies, 23 were RCTs (13 good quality, 9 fair, 1 poor) and 9 were observational (4 good quality, 4 fair, 1 poor) (Table E-2 in Appendix E). 27 studies were multicenter,[42,45,64,67-72,74-76,106,107,110-117,119-123] four studies were single-center,[36,46,73,118] and in one study the number of sites was unclear or not reported.[38] Nineteen studies included sites in the U.S. or Canada,[42,67-72,75,76,106,107,113-117,119-121]16 included sites in Europe,[42,46,67,68,70-73,76,107,111,114,116,119,120,122] 9 included sites in Asia,[36,38,45,68,71,74,110,112,118] and in 2 studies the site location was unclear or not reported.[64,123] A total of 17 studies used industry funding,[42,64,67-72,74,76,106,107,113,115,119-121] zero studies were government-only funded, zero were funded by nongovernment/nonindustry sources, and in 15 studies the funding source was either not reported or unclear.[36,38,45,46,73,75,110-112,114,116-118,122,123] 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.

The following two comparisons were assessed in the included studies in KQ 2 and are detailed in this analysis:

1. Enoxaparin versus UFH versus fondaparinux (full UA/NSTEMI cohort)
   - 21 studies (12 RCTs, 9 observational; 161,506 total patients)
2. GPI plus UFH versus UFH alone
   - 11 studies (11 RCTs; 47,725 total patients)

Detailed Synthesis

1. Enoxaparin Versus Unfractionated Heparin Versus Fondaparinux (Full UA/NSTEMI Cohort)

Twenty-one studies (12 RCTs, 9 observational) compared the use of enoxaparin, UFH, or fondaparinux in 161,506 patients with UA/NSTEMI.[67-76,106,107,110-116,118,123] 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[69] to 63 percent.[71]

Six RCTs compared enoxaparin with UFH as an initial management strategy prior to PCI and included a total of 18,554 patients.[67-70,116,118] One RCT (20,078 patients) compared enoxaparin with fondaparinux[71] and one RCT (350 patients) compared fondaparinux with UFH.[72] Three studies compared enoxaparin with UFH at the time of PCI.[73-75] 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.[76] 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.

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.[106,107,110-115,123,124] A description of the observational studies follows our analysis of the RCTs. The Goodman 2006 article considered in this group is a prospective observational study on subgroups from the ESSENCE trial,[70] 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[113-115] 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.[123] Four of the nine studies were industry sponsored and will be discussed qualitatively below.

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[67,68] 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.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal Myocardial Infarction, Revascularization, or Recurrent Ischemia at 48 hours to 43 Days

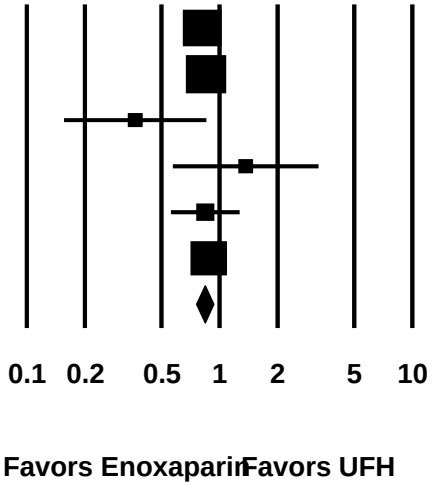
Six studies[68-70,75,76,118] (6 RCTs; 4 good quality, 2 fair) evaluated the effect of low molecular weight heparin and unfractionated heparin on a composite endpoint of total mortality, nonfatal MI, and recurrent ischemia/revascularization in a total of 12,124 UA/NSTEMI patients. These endpoints were reported for short-term outcomes ranging from 48 hours to 43 days, with the majority of studies reporting the composite outcome at 30 days. 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 six studies comparing the effect of treatment strategies incorporating enoxaparin versus unfractionated heparin 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 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 vs. unfractionated heparin on composite outcome of all-cause mortality, nonfatal myocardial infarction, revascularization, or recurrent ischemia at 48 hours to 43 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Cohen, 1997	0.814	0.687	0.964	0.017
Antman, 1999	0.852	0.725	1.002	0.052
Malhotra, 2001	0.365	0.157	0.849	0.019
Bhatt, 2003	1.367	0.577	3.238	0.478
Goodman, 2003	0.844	0.564	1.261	0.407
Blazing, 2004	0.880	0.733	1.057	0.170
	0.842	0.761	0.932	0.001



The effect of fondaparinux versus unfractionated heparin on the composite short-term endpoint was estimated using methods described by Hasselblad and Kong.[125] We created an indirect comparison of fondaparinux versus unfractionated heparin by combining the above estimate of enoxaparin versus unfractionated heparin with the results for fondaparinux versus enoxaparin in the study by Yusuf et al.[71] The uncertainty around the estimate is the sum of the variances of the meta-analysis and the results from Yusuf et al.[71] 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 Outcome at 6 Months

Only one RCT (good quality) of 20,078 patients in this comparison group evaluated the effect of treatment on the composite ischemic outcome at 6 months.[71] 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.

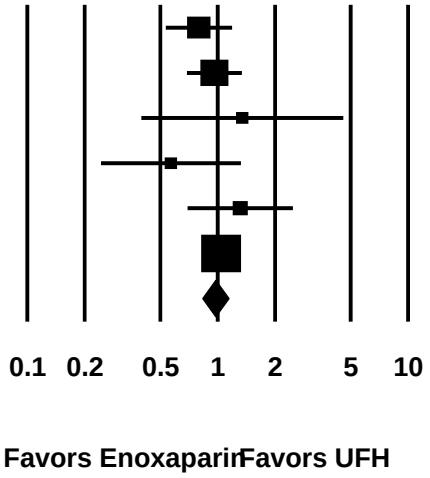
Effect on All-Cause Mortality at 48 Hours to 43 Days

Eight studies[67-70,75,76,116,118] (8 RCT, 5 good quality, 3 fair) reported the effect of low molecular weight heparin and unfractionated heparin on total mortality in a total of 23,015 UA/NSTEMI patients. Two studies[75,118] had no deaths and so were not included in the analysis.

A random-effects meta-analysis of the six studies comparing the effect of treatment strategies incorporating enoxaparin versus unfractionated heparin 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 insufficient for 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 unfractionated heparin.

Figure 32. Meta-analysis of enoxaparin vs. unfractionated heparin on all-cause mortality at 48 hours to 43 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Cohen, 1997	0.796	0.538	1.179	0.256
Antman, 1999	0.961	0.695	1.328	0.809
Cohen, 2002	1.346	0.400	4.531	0.632
Goodman, 2003	0.568	0.245	1.314	0.186
Blazing, 2004	1.314	0.700	2.465	0.395
Ferguson, 2004	1.044	0.833	1.307	0.709
	0.977	0.835	1.144	0.775



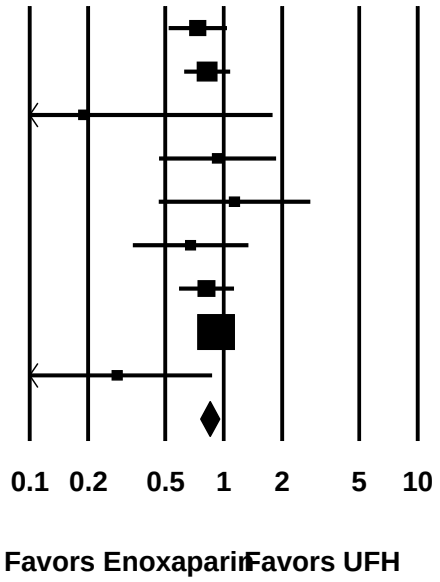
We created an indirect comparison of fondaparinux versus unfractionated heparin by combining the above estimate of enoxaparin versus unfractionated heparin with the results for fondaparinux versus enoxaparin in Yusuf et al.[71] The result is an estimated odds ratio of 0.93 (95% CI, 0.71 to 1.20), showing 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 Myocardial Infarction at 48 Hours to 43 Days

Nine studies[67-70,73,75,76,116,118] (9 RCTs; 5 good quality, 4 fair) reported the effect of low molecular weight heparin and unfractionated heparin on nonfatal (re)infarction in a total of 22,970 UA/NSTEMI patients. A random-effects meta-analysis of the nine studies comparing the effect of treatment strategies incorporating enoxaparin versus unfractionated heparin 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 vs. unfractionated heparin on nonfatal myocardial infarction at 48 hours to 43 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Cohen, 1997	0.735	0.524	1.031	0.074
Antman, 1999	0.822	0.631	1.070	0.146
Malhotra, 2001	0.190	0.020	1.771	0.145
Cohen, 2002	0.929	0.468	1.847	0.835
Bhatt, 2003	1.137	0.466	2.777	0.778
Goodman, 2003	0.675	0.343	1.331	0.257
Blazing, 2004	0.815	0.593	1.121	0.209
Ferguson, 2004	0.914	0.810	1.031	0.142
Bertel, 2010	0.283	0.092	0.865	0.027
	0.851	0.761	0.951	0.004



We created an indirect comparison of fondaparinux versus unfractionated heparin by combining the above estimate of enoxaparin versus unfractionated heparin with the results for fondaparinux versus enoxaparin in Yusuf et al.[71] 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.

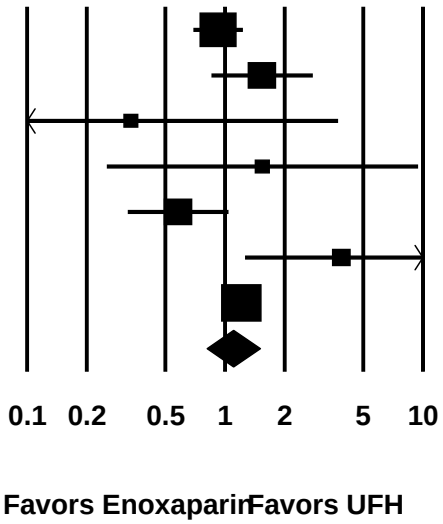
Effect on Major Bleeding at 48 Hours to 43 Days

Eight studies[67-70,75,76,116,118] (8 RCTs; 5 good quality, 3 fair) reported the effect of low molecular weight heparin and unfractionated heparin on major bleeding in a total of 22,901 UA/NSTEMI patients. The study by Malhotra et al.[118] 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 unfractionated heparin 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[116] was a double-blind, small-sized RCT with 30 percent of patients undergoing PCI. In contrast, the Blazing study[68] was an open-label, large-sized RCT with 60 percent of patients undergoing PCI. Accommodating for 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 vs. unfractionated heparin on major bleeding at 48 hours to 43 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Cohen, 1997	0.924	0.698	1.223	0.578
Antman, 1999	1.539	0.860	2.753	0.147
Cohen, 2002	0.335	0.030	3.695	0.372
Bhatt, 2003	1.546	0.255	9.383	0.636
Goodman, 2003	0.580	0.325	1.034	0.065
Blazing, 2004	3.872	1.272	11.784	0.017
Ferguson, 2004	1.211	1.050	1.396	0.008
	1.107	0.812	1.508	0.522



We created an indirect comparison of fondaparinux versus unfractionated heparin by combining the above estimate of enoxaparin versus unfractionated heparin with the Yusuf et al.[71] 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 (or 10 citations including 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.[106,107,110-115,123,124] Of the nine observational studies, only one[111] 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.[106,107,111,112,114,115] The Thai registry[112] 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 unfractionated heparin (16%) overall. The U.S.-based CRUSADE Registry of 11,358 patients[106] 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[114] noted that 37.9 percent of patients received enoxaparin in first 24 hours with continued use; 17.0 percent received unfractionated heparin in the first 24 hours with continued use; 12.7 percent received neither, and 31.7 percent had cross-over from enoxaparin to unfractionated heparin or vice versa. Over time intervals from 1999 to 2005 there was an increased use of enoxaparin alone, and more crossovers, with less unfractionated heparin 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 unfractionated heparin or to be in the crossover group.

Another GRACE article[107] evaluated heparin use in relation to GPI and invasive care. Enoxaparin was used in 51 percent, unfractionated heparin in 32 percent, and 17 percent received both unfractionated heparin and enoxaparin at some time. Patients given unfractionated heparin had more comorbidity than those given enoxaparin or both. A multicenter registry of 2874 patients in France[111] found that between 2006 and 2007, the use of fondaparinux increased considerably (5% to 25%) Patients given unfractionated heparin were older, with more comorbidities and fewer guideline-associated treatments. Finally, the NRMI (National Registry of Myocardial Infarctions) study[115] 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 unfractionated heparin.

Effect on Cardiovascular Events

Seven observational studies reported the effect on mortality, myocardial infarction, and/or recurrent ischemia. In the Thai registry[112] the unfractionated heparin group had more cardiac deaths than the enoxaparin group (9.3% vs. 5.2%, $p<0.0001$). Within the U.S.-based CRUSADE Registry[106] 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 unfractionated heparin. There

were particular benefits in this study to enoxaparin among those who did not undergo revascularization. The GRACE Registry[114] found that the adjusted ORs for death were not significant but favored enoxaparin over either unfractionated heparin 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[107] 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 unfractionated heparin in the subgroup receiving both GPI and PCI. The multicenter registry in France[111] found that fondaparinux was associated with lower adjusted mortality than unfractionated heparin and similar adjusted mortality to enoxaparin. Again, patients given unfractionated heparin in the French registry were older, with more comorbidities and fewer guideline-associated treatments. The KAMIR (Korean Acute MI registry) study[110] assessed the use of enoxaparin with low-dose unfractionated heparin compared with usual-dose unfractionated heparin 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 unfractionated heparin group (1.0, p=0.024). Finally, the NRMI study[115] found no differences recurrent MI or death in those treated with enoxaparin compared with unfractionated heparin. 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,[112] 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[106] showed similar bleeding risks between the enoxaparin and UFH groups. In the GRACE Registry,[114] the adjusted ORs for bleeding were not different in enoxaparin, unfractionated heparin, or crossover groups compared with no heparin. Another GRACE article[107] 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[111] reported rates of in-hospital bleeding of 2.1 percent in the enoxaparin group, 5.0 percent in the unfractionated heparin 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 unfractionated heparin group. The KAMIR study[110] did not find any significant differences in in-hospital major or minor bleeding rates. Finally, the NRMI study[115] noted no differences in major bleeding rates in those treated with enoxaparin compared with unfractionated heparin. 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,[112] reported a longer length of hospital stay in the unfractionated heparin 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).[116] 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).[118]

Findings by Subgroup

The subgroup findings for the RCTs of LMWH 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.[113,123,124] Among a CRUSADE Registry population who received enoxaparin, 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,[123] 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[124] found that enoxaparin was particularly beneficial over unfractionated heparin 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, unfractionated heparin, and fondaparinux, we present the findings of UA/NSTEMI patients who received primarily initial conservative treatment. From the comparison of enoxaparin and unfractionated heparin, there was a significant reduction in composite ischemic events and nonfatal MI at around 30 days with enoxaparin. There was insufficient SOE 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 LMWH is increasing over time in the conservatively managed population. Use of LMWH 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 to LMWH. 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; those greater than 1 favor UFH.

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

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite endpoint of all-cause mortality, nonfatal MI, revascularization, or recurrent ischemia at 48 hours to 43 days					
6 (12,124)	6 RCTs/4 good quality, 2 fair	Consistent	Direct	Precise	**High SOE** Enoxaparin vs. UFH OR 0.84 (0.76 to 0.93) favors enoxaparin
7 (32,202)	7 RCTs/5 good quality, 2 fair	NA	Indirect	Precise	**Low SOE** Fondaparinux vs. UFH OR 0.78 (0.67 to 0.90) favors fondaparinux
Composite ischemic outcome at 6 months					
1 (20,078)	RCT/Good quality	NA	Direct	Unknown	**Low SOE** Event rate similar in enoxaparin and fondaparinux groups (10.2% vs. 10.1%)
All-cause mortality at 48 hours to 43 days					
8 (23,015)	8 RCTs/5 good quality, 3 fair	Consistent	Direct	Imprecise	**Insufficient SOE** Enoxaparin vs. UFH OR 0.98 (0.84 to 1.14)
9 (43,093)	9 RCTs/6 good quality, 3 fair	NA	Indirect	Imprecise	**Insufficient SOE** Fondaparinux vs. UFH OR 0.93 (0.71 to 1.20)
Nonfatal MI at 48 hours to 43 days					
9 (22,970)	9 RCTs/5 good quality, 4 fair	Consistent	Direct	Imprecise	**Moderate SOE** Enoxaparin vs. UFH OR 0.85 (0.76 to 0.95) favors enoxaparin
10 (43,048)	10 RCTs/6 good quality, 4 fair	NA	Indirect	Imprecise	**Insufficient SOE** Fondaparinux vs. UFH OR 0.85 (0.69 to 1.04)
Major bleeding at 48 hours to 43 days					
8 (22,901)	8 RCTs/5 good quality, 3 fair	Inconsistent	Direct	Imprecise	**Insufficient SOE** Enoxaparin vs. UFH OR 1.11 (0.81 to 1.51)
9 (42,979)	9 RCTs/6 good quality, 3 fair	NA	Indirect	Imprecise	**Low SOE** Fondaparinux vs. UFH OR 0.69 (0.49 to 0.97) favors fondaparinux

Abbreviations: 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

2. GPI Plus UFH Versus UFH Alone

Eleven RCTs (8 good quality, 3 fair), and no observational studies, compared GPIs with unfractionated heparin in 47,725 patients with UA/NSTEMI.[36,38,42,45,46,64,117,119-122] 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. Proportions of patients proceeding to revascularization ranged from 0 percent[36,45,46] to 100 percent.[122] 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[119-121] reported the racial and ethnic demographics of study participants. The RCTs included nine 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[117,122]), eptifibatide (three studies[38,42,119]), tirofiban (five studies[36,45,46,120,121]), and any of the three GPIs with either unfractionated heparin or enoxaparin (1 study[64]). The full results across all outcomes are reported in Table G-10 in Appendix G.

Effect on Composite Outcome Up to 30 Days

Eleven RCTs (8 good quality, 3 fair) reported composite endpoints at 30 days in 47,725 patients with UA/NSTEMI.[36,38,42,45,46,64,117,119-122] 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,[119] rates of the composite outcome (death/nonfatal MI) were significantly lower in the eptifibatide group compared with heparin (14.2% vs. 15.7%, p=0.04). In the PRISM study,[120] the primary composite endpoint (death/MI/refractory ischemia/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/MI showed a nonsignificant reduction in event rates in the tirofiban group (RR 0.80; 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; CI, 0.65 to 1.10) and the secondary composite endpoint (RR 0.58; CI, 0.38 to 0.87).

In the PRISM-PLUS study,[121] the primary composite endpoint (death/MI/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/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; CI, 0.60 to 1.25) and secondary composite endpoint (RR 0.75; CI, 0.46 to 1.23).

The Bhattacharya study[36] 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. Likewise, Momtahen et al.[38] found that the composite

of total mortality/nonfatal MI/revascularization was significantly lower in the eptifibatide group (0%) compared with heparin (16%, p<0.01).

In the Okmen study,[46] the in-hospital rate of composite events (total mortality/nonfatal MI/revascularization/refractory angina) was significantly lower in the tirofiban group (26% vs. 54%, p=0.01) In the ACUITY TIMING study,[42] the medical therapy subgroup also had fewer composite events (death/MI/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 unfractionated heparin and GPI over bivalirudin (RR 1.24; CI, 0.83 to 1.85).

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). The odds ratio of the primary composite endpoint of total mortality or nonfatal MI was 1.0 in the 24-hour infusion group (95% CI, 0.83 to 1.24) and 1.1 in the 48-hour infusion group (CI, 0.94 to 1.39) compared with heparin.

In the RCT by Song et al.,[45] the frequency of the composite endpoint (total mortality/nonfatal MI/refractory ischemia) in the tirofiban plus UFH arm was lower than UFH alone (13,9% vs. 29.3%, p=0.01). Finally, the study by van den Brand et al.[122] showed lower rates of major events (total mortality/nonfatal MI/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)[117] showed no difference in events, but a small trial[122] 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.[36,38,45,46,117,119-122] In the PURSUIT study[119] the mortality rate was similar in the eptifibatide and heparin groups (3.5% vs. 3.7%). In the PRISM study[120] 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,[121] the mortality rate was nonsignificantly lower in the tirofiban plus heparin group (RR 0.79; CI, 0.48 to 1.30). The GUSTO-IV trial[117] showed no differences in mortality at 30 days for both the abciximab 24-hour infusion group (OR 0.90; CI, 0.64 to 1.50) and the 48-hour infusion group (OR 1.1; CI, 0.83 to 1.43) compared with heparin.

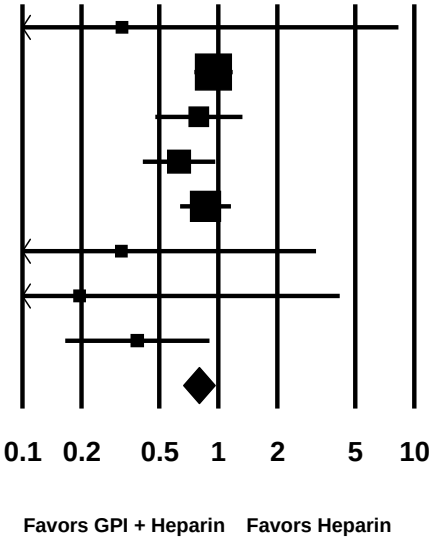
Fewer deaths were also seen in the smaller trials of GPIs compared with UFH. The Bhattacharya study[36] reported number of combined deaths due to unknown causes and fatal MI events (tirofiban 6%, heparin 14%) at 30 days. Momtahen et al.[38] reported no deaths in the eptifibatide group (n=98) and two deaths in the heparin group (n=98). No in-hospital deaths occurred in the Okmen study[46] for both the tirofiban (n=41) and no tirofiban (n=42) groups. Song et al.[45] reported one death in the tirofiban group (n=101) and three deaths in the heparin group (n=99). Similarly, van den Brand[122] 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[36,38,45,117,119-122] 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. Overall, the rates of mortality at 30 days were higher in the heparin group from these nine RCTs with consistent results of a direct outcome with precise results, thus leading us to conclude that the SOE was high.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Van den Brand, 1995	0.322	0.013	8.235	0.494
Harrington, 1998	0.944	0.760	1.173	0.604
Theroux, 1998	0.794	0.480	1.315	0.371
White, 1998	0.630	0.415	0.957	0.030
Simoons, 2001	0.861	0.644	1.151	0.311
Song, 2007	0.320	0.033	3.130	0.327
Momtahen, 2009	0.196	0.009	4.134	0.295
Bhattacharya, 2010	0.386	0.167	0.893	0.026
	0.800	0.665	0.961	0.017



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.[36,38,45,46,117,119-122] In the PURSUIT study[119] the rates nonfatal MI were nonsignificantly lower in the eptifibatide group compared with heparin (12.6% vs. 13.5%). In the PRISM study[120] 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,[121] the rate of MI events was lower in the tirofiban plus heparin group (RR 0.70; CI, 0.40 to 1.00). The GUSTO-IV trial[117] showed no differences in mortality at 30 days for both the abciximab 24-hour infusion group (OR 1.1; CI, 0.87 to 1.41) and the 48-hour infusion group (OR 1.2; CI, 0.91 to 1.46) compared with heparin.

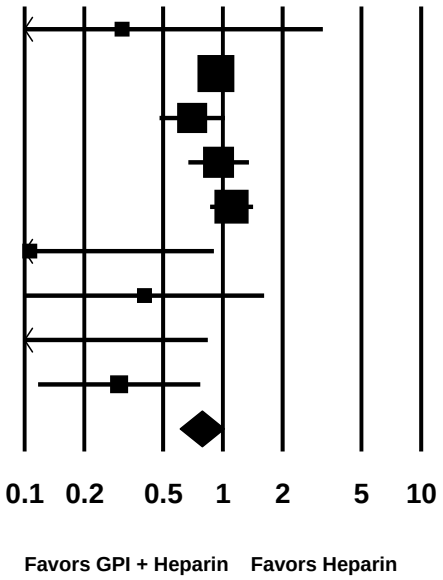
The smaller RCTs also reported lower nonfatal MI events in the GPI group compared with heparin. The Bhattacharya study[36] reported six nonfatal MI events in the tirofiban group and 22 MIs in the heparin group up to 30 days. Momtahen et al.[38] reported no MIs in the eptifibatide group (n=98) and five MIs in the heparin group (n=98). In the Okmen study[46] one MI occurred in the tirofiban and eight MIs occurred in the no tirofiban group. Song et al.[45] reported three MIs in the tirofiban group and seven deaths in the heparin group. Similarly, van den brand[122] 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. 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.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Van den Brand, 1995	0.310	0.030	3.168	0.324
Harrington, 1998	0.923	0.819	1.041	0.192
Theroux, 1998	0.701	0.483	1.017	0.061
White, 1998	0.951	0.675	1.342	0.777
Simoons, 2001	1.107	0.870	1.410	0.409
Okmen, 2003	0.106	0.013	0.893	0.039
Song, 2007	0.402	0.101	1.603	0.197
Momtahen, 2009	0.048	0.003	0.834	0.037
Bhattacharya, 2010	0.300	0.118	0.763	0.011
	0.787	0.610	1.016	0.066



Effect on Recurrent Ischemia at 30 Days

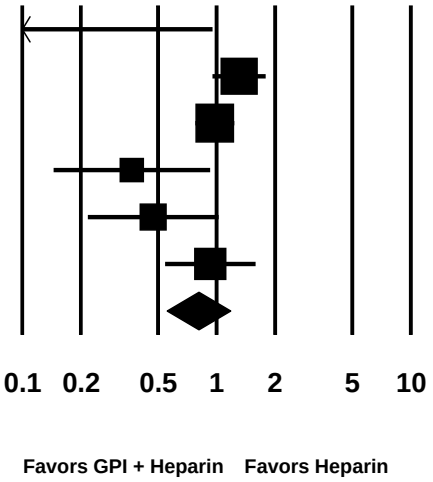
Six RCTs (4 good quality, 2 fair) with a total of 5,755 UA/NSTEMI patients reported recurrent or refractory ischemia either in-hospital or at 30 days.[36,45,46,120,122] In the PRISM study,[120] the rates of refractory ischemia were similar in the tirofiban and heparin groups, RR 0.98 (95% CI, 0.79 to 1.09). The PRISM-PLUS study[121] found a slight increase in refractory ischemia events in the heparin group compared with tirofiban plus heparin, (CI, 0.57 to 1.01; p=0.05).The Okmen study[46] reported an in-hospital recurrent angina rate of 27% in the tirofiban group and 50% in the heparin group. The Bhattacharya study[36] 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[45] 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[122] 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. 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.

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

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Van den Brand, 1995	0.051	0.003	0.946	0.046
Theroux, 1998	1.307	0.962	1.775	0.087
White, 1998	0.979	0.783	1.224	0.854
Okmen, 2003	0.367	0.146	0.918	0.032
Song, 2007	0.472	0.219	1.016	0.055
Bhattacharya, 2010	0.929	0.547	1.576	0.784
	0.811	0.558	1.181	0.275



Effect on Revascularization Up to 30 Days

Two fair-quality RCTs[38,46] with a total of 279 UA/NSTEMI patients reported the revascularization rates at up to 30 days. The Okmen study[46] found low numbers of in-hospital revascularization events (1 event in the tirofiban group and none in the heparin group). The Momtahen study[38] 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

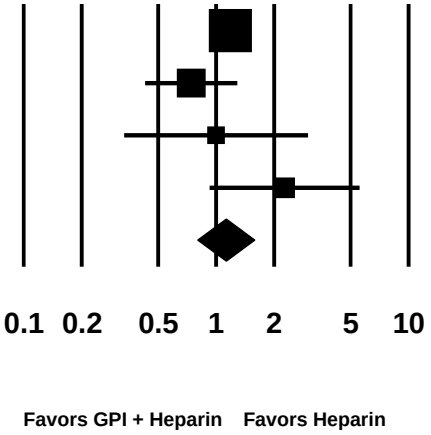
Eight RCTs (6 good quality, 2 fair) with a total of 30,118 UA/NSTEMI patients reported major bleeding events either in-hospital or at 30 days.[38,42,46,64,117,119-121] In the PURSUIT study[119] the rate of TIMI-criteria major bleeding was higher in the eptifibatide group (10.6%) compared with heparin (9.1%). In the PRISM study,[120] the rates of major bleeding were similar in the tirofiban and heparin groups (both 0.4%). In the PRISM-PLUS study,[121] 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[46] reported zero in-hospital major bleeding events in both the tirofiban and heparin groups. The GUSTO-IV study[117] 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[38] found no major bleeding events at 30 days in either the eptifibatide or heparin groups. In the ACUITY study[64] 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 unfractionated heparin (RR 0.57; 95% CI, 0.38 to 0.84) favoring bivalirudin. In the ACUITY TIMING[42] 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 18,855 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. 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 study compared deferred and upstream GPI use, so those studies were not included in this meta-analysis.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Harrington, 1998	1.185	1.034	1.358	0.014
Theroux, 1998	0.742	0.431	1.279	0.283
White, 1998	1.000	0.335	2.981	1.000
Simoons, 2001	2.269	0.932	5.525	0.071
	1.128	0.803	1.586	0.487



Minor Bleeding Up to 30 Days

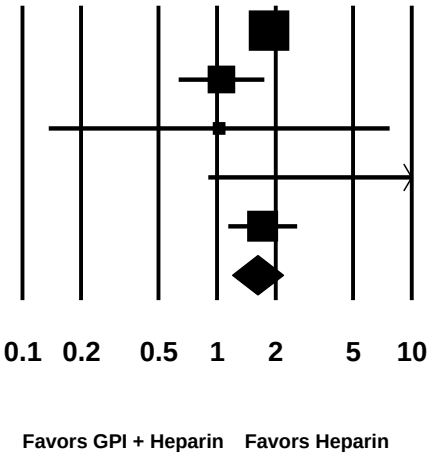
Five RCTs (three good quality, two fair)[38,46,117,119,120] with a total of 22,259 UA/NSTEMI patients reported minor bleeding events up to 30 days. In the PURSUIT study[119] the minor bleeding rate was higher in the eptifibatide group compared with heparin (12.9% vs. 7.4%). In the PRISM study[120] the rates of minor bleeding were similar in the tirofiban and heparin groups (2.0% and 1.9% respectively). The GUSTO-IV study[117] 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[46] reported an in-hospital minor bleeding rate of 5% in both the tirofiban and heparin groups. The Momtahen study[38] 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 43.92. Given the consistent results in five RCTs with narrow CIs, the SOE was rated high for the effect of GPIs on minor bleeding, with fewer minor bleeds in the heparin group.

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

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Harrington, 1998	1.852	1.612	2.127	0.000
White, 1998	1.054	0.640	1.735	0.837
Okmen, 2003	1.026	0.138	7.647	0.980
Momtahen, 2009	16.148	0.909	286.743	0.058
Simoons, 2001	1.716	1.151	2.559	0.008
	1.623	1.203	2.190	0.002



Findings by Subgroup

Four good-quality RCTs (PURSUIT, PRISM, PRISM PLUS, and GUSTO)[117,119-121] 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[119] 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[120] 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[121] 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[117] 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[119] 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[120] reported a reduction in composite ischemic events in both men and women treated with tirofiban. The PRISM-PLUS study[121] reported a statistically significant benefit of tirofiban plus heparin compared with heparin alone in male and female patients. The GUSTO-IV study[117] 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[119] 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[120] 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[121] 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[117] 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[119] 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[120] 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[120] 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[121] 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[117] 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 unfractionated heparin, 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. 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 LMWH). 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 16. Odds ratios less than 1 favor GPI plus UFH; those greater than 1 favor UFH alone.

Table 16. Summary strength of evidence for UA/NSTEMI patients treated with glycoprotein inhibitor plus unfractionated heparin vs. unfractionated heparin alone

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 events up to 30 days					**Moderate SOE**
11 (47,725)	11 RCTs/8 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).
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) favoring GPI

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
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)
Recurrent ischemia up to 30 days					**Insufficient SOE**
6 (5755)	6 RCTs/4 good quality, 2 fair	Consistent	Direct	Imprecise	OR 0.81 (0.56 to 1.18)
Revascularization up to 30 days					**Insufficient SOE**
2 (279)	2 RCTs/2 fair	Consistent	Direct	Imprecise	Low number of events reported in both trials, with fewer in GPI groups
Major bleeding at 30 days					**Insufficient SOE**
4 (18,855)	4 RCTs/4 good quality	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) favoring heparin alone

Abbreviations: CI=confidence interval; GPI= glycoprotein IIb/IIIa inhibitor; 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

- In the postdischarge setting, high-dose aspirin was associated with fewer nonfatal MI events compared with low-dose aspirin at 6 months (low SOE).

- There were conflicting results on composite ischemic events and the individual outcomes of mortality, nonfatal MI at 1 year, stroke, revascularization, and major bleeding due to the different definitions of low-dose versus high-dose aspirin across the observational studies (all insufficient SOE).

Single Versus Dual Antiplatelet Therapy

- Dual antiplatelet therapy reduces the rates of composite ischemic outcomes and nonfatal MI in-hospital to 1 year compared with single antiplatelet therapy (high SOE).

Short-Term Versus Long-Term Dual Antiplatelet Therapy

- Long-term dual antiplatelet therapy reduces the rates of composite ischemic events and all-cause mortality compared with short-term dual antiplatelet therapy (low SOE).

- Rates of stent thrombosis are similar between short- and long-term clopidogrel therapy (low SOE). The rates were higher when clopidogrel was stopped within 30 days or 6 months, but the difference beyond 6 months was nonsignificant.

Antiplatelet Therapy with PPI Versus Antiplatelet Alone

- In RCTs that evaluated the specific PPI omeprazole versus placebo given in combination with dual antiplatelet therapy, use of omeprazole reduced rates of upper gastrointestinal bleeding (moderate SOE) and all-cause mortality at 1 year (low SOE). There was insufficient evidence on the effect of omeprazole on composite ischemic events, nonfatal MI, stroke, revascularization, or stent thrombosis.

- From observational studies assessing the use of diverse PPIs with dual antiplatelet therapy, event rates are higher in patients who were receiving any type of PPI medication for the composite outcome (all-cause mortality/nonfatal MI) at 6 to 18 months, nonfatal MI at 1 year, and revascularization after 1 year. Possible confounding reduced the SOE to moderate. Note that we were not able to reach a firm conclusion as to why large, well-done observational studies of PPIs as a class consistently found worse outcomes in patients who received PPIs with antiplatelet therapy while a smaller number of RCTs of one particular PPI (omeprazole) found no increase in overall mortality.

- There was also insufficient evidence that the type of PPI affected any of the clinical outcomes (composite or individual).

- In observational studies assessing use of PPIs with aspirin monotherapy, there was a higher rate of composite ischemic events, all-cause mortality, and nonfatal MI at 1 year in the group receiving any type of PPI (moderate SOE)

Dual Antiplatelet Versus Triple Therapy

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

Description of Included Studies

We identified 63 unique studies that evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 604,267 patients with UA/NSTEMI continuing treatment *after hospitalization (postdischarge)*.[14,126-187] Of these studies, 13 were RCTs (9 good quality, 2 fair, 2 poor) and 51 were observational (36 good quality, 11 fair, 4 poor) (Table E-3 in Appendix E). Forty-seven studies were multicenter,[14,126,130,132,133,135-138,141-148,150,152,153,155,157,160-164,166,167,169-177,179,180,182-187] 15 were single-center,[127,129,134,139,140,149,151,154,156,158,159,165,168,178,181] and in two studies the number of sites was unclear or not reported.[128,131] Twenty-three studies included sites in the United States or Canada,[129,132,137,148-150,153,154,156,158-161,163,166,170,172,178-180,182,185,187] 27 included sites in Europe,[130,133-136,139-141,143-145,151,155,162,163,165,167,171-173,175,179,180,182,184-186] 13 included sites in Asia,[126-128,131,142,146,147,163,164,169,177,183,185] 5 studies contained sites in other locations,[157,168,174,176,181] and in 3 studies the site location was unclear or not reported.[14,138,152] A total of 11 studies used industry funding,[14,138,143,163,166,172,177,179,182,185,187] 6 studies were government-only funded,[146,150,153,160,170,178] 12 were funded by nongovernment/nonindustry sources,[126-128,130,135,136,139-141,156,173,186] 3 studies had a mix of government and private foundation funding,[161,175,184] and in 31 studies the funding source was either not reported or unclear.[129,131-134,137,142,144,145,147-149,151,152,154,155,157-159,162,164,165,167-169,171,174,176,180,181,183] The study characteristics table (Table F-3 in Appendix F) contains details about the study design, proportion of UA/NSTEMI patients, antiplatelet/anticoagulant comparison, concomitant therapy, outcomes measured, and study quality.

The following five comparisons were relevant in the posthospitalization setting in KQ 3 and are detailed in this analysis:

1. Low-dose versus high-dose aspirin
   - 4 studies (0 RCTs, 4 observational; 29,718 total patients)
2. Single versus dual antiplatelet therapy
   - 7 studies (2 RCTs, 5 observational; 207,745 total patients)
3. Short-term versus long-term dual antiplatelet therapy (clopidogrel)
   - 9 studies (4 RCTs, 5 observational; 21,410 total patients)
4. Antiplatelet therapy with PPI versus antiplatelet alone
   - 32 studies (4 RCTs, 28 observational; 308,790 total patients)
     a. Dual antiplatelet with and without omeprazole
     b. Dual antiplatelet with and without PPI
     c. Aspirin monotherapy with and without PPI

5. Dual antiplatelet therapy alone versus dual antiplatelet plus oral anticoagulant (i.e., triple therapy)
    - 11 studies (11 observational; 83,962 total patients)

Detailed Synthesis

1. Low-Dose Versus High-Dose Aspirin

Four observational studies compared low-dose with high-dose aspirin in the postdischarge treatment of UA/NSTEMI patients.[129,159,163,180] One study each compared:

- 81 mg versus 161 to 325 mg aspirin (Harjai study; clopidogrel use was 53% in each group)[129]
- 81 mg versus 325 mg aspirin (So study; clopidogrel use 99% in each group)[159]
- <162 mg versus ≥162 mg aspirin (Aronow study; ticlopidine/clopidogrel use not permitted except for after revascularization for 30 days or less)[163]
- <150 mg versus ≥150 mg aspirin (Quinn study; clopidogrel use not reported)[180]

Of the four observational studies, two (50%) were rated fair quality and two (50%) 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 62.4 to 64.3 years. The proportion of female patients ranged from 27 to 32 percent. Two studies (50%) reported the racial and ethnic demographics of study participants. Two studies (50%) were conducted within the United States or Canada, with the rest international. Funding source was reported in two studies, and both were funded by industry.

These four studies assessed a composite endpoint of all-cause mortality, nonfatal MI, or stroke in addition to individual endpoints of all-cause mortality, nonfatal MI, stroke, revascularization, and major bleeding. Table G-11 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 the results are discussed qualitatively by outcome below.

Effect on the Composite Endpoint of All-Cause Mortality, Nonfatal Myocardial Infarction, or Stroke at 6 Months

Only the Quinn study[180] reported the composite outcome of all-cause mortality, nonfatal MI, and 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.

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

Three studies[129,159,163] reported the composite outcome of all-cause mortality, nonfatal MI, and revascularization at 12 months. In general, low-dose aspirin had similar composite event rates as high-dose aspirin. The study by Harjai et al.[129] comparing 81 mg of aspirin with 162–325 mg found no significant difference in the composite of death/MI at 1 year (6.7% vs. 6.1%, respectively) or in the composite of death/MI/stent thrombosis or target vessel revascularization (8.6% vs. 9.2%). Similarly, in the study by So et al.[159] comparing 81 mg of aspirin with 325 mg, the risk of death/MI and death/MI/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; CI, 0.80 to 1.47). The third study, by Aronow et al.,[163] 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/stroke (HR 0.961; 95% CI, 0.76 to 1.21) and death/MI/stroke/revascularization and rehospitalization (HR 1.112; 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[180] 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[159,163] reported 1-year mortality risk. In the So study,[159] 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[163] found that high-dose aspirin (≥162 mg) was associated with a significant reduction of all-cause mortality (HR 0.552; 95% CI, 0.369 to 0.827) 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[163,180] reported nonfatal MI, one at 6 months and the other at 1 year. While the study by Quinn et al.[180] 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.[163] comparing similar doses of aspirin found no effect of high-dose versus low-dose (≥162 mg vs. <162 mg) in 1-year mortality (HR 0.984; CI, 0.655 to 1.478). 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/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,[163,180] 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[180] (≥150 mg vs. < 150 mg; HR 1.59; 95% CI, 0.95 to 2.65) and at 1 year in the Aronow study[163] (≥162 mg vs. <162 mg; HR 1.374; 95% CI, 0.944 to 2.001).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.[159,163] In the So study[159] repeat revascularization was not 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[163] patients treated with high-dose aspirin (≥162 mg) were more likely to undergo urgent revascularization (HR 1.343; 95% CI, 1.101 to 1.638). The inconsistent and imprecise findings for revascularization outcomes at 1 year resulted in an SOE rating of insufficient.

Effect on Major Bleeding at 1 Year

Two studies[129,163] reported major bleeding at 1 year. The Harjai study[129] 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[163] found a higher incidence of any bleeding among patients treated with high-dose aspirin (≥162 mg vs. <162 mg; adjusted HR 1.32; 95% CI, 1.12 to 1.55). The inconsistent and imprecise findings for major bleeding outcomes at 1 year resulted in an SOE rating of insufficient.

Findings by Subgroup

One fair-quality study by So et al.[159] comparing aspirin doses in patients also receiving clopidogrel, reported variations in treatment effectiveness by subgroup (Table H-3 in Appendix H). 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/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/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/MI (OR 1.12; 95% CI, 0.53 to 2.34) and of death/MI/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/MI (OR 1.25; 95% CI, 0.67 to 2.33) and of death/MI/revascularization (OR 1.38; 95% CI, 0.92 to 2.06) compared with the high-dose aspirin group.

Summary of Results 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 study reporting higher bleeding rates in the low-dose (81 mg) group and another study reporting higher rates in the high-dose group (162 mg). Differences in the consistency of the results may be due to the fact that the Harjai[129] and So[159] studies were smaller, single-center studies that had higher rates of clopidogrel use (53% and 99% respectively) , while the Aronow[163] and Quinn[180] studies were secondary analyses of larger RCTs (i.e., BRAVO, Gusto IIb and PURSUIT), one of which did not allow use of thienopyridines and the other study did not report its use. In addition, the doses of aspirin compared differed among the four 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. 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. Detailed SOE ratings are shown in Table 17.

Table 17. Summary strength of evidence for UA/NSTEMI patients treated with low-dose vs. 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	NA	Direct	Precise	HR 0.92 (0.79 to 1.07)
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	Low-dose ASA had similar rates of ischemic events in all 3 studies
All-cause mortality at 6 months					**Insufficient SOE**
1 (20,469)	Observational/Good	NA	Direct	Imprecise	HR 0.89 (0.72 to 1.10)
All-cause mortality at 1 year					**Insufficient SOE**
2 (6409)	2 observational/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	One study (ASA/clopidogrel) showed no difference between doses, the other found that high-dose ASA (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), favoring high-dose ASA
Nonfatal MI at 1 year					**Insufficient SOE**
1 (4589)	Observational/Good quality	NA	Direct	Imprecise	HR 0.99 (0.66 to 1.48)
Stroke at 6 months					**Insufficient SOE**
1 (20,469)	Observational/Good quality	NA	Direct	Imprecise	HR 1.59 (0.95 to 2.65)
Stroke at 1 year					**Insufficient SOE**
1 (4589)	Observational/Good quality	NA	Direct	Imprecise	HR 1.37 (0.94 to 2.00)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Revascularization at 1 year					**Insufficient SOE**
2 (6429)	2 observational/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	One study (ASA/clopidogrel) showed no difference between doses, the other study (ASA monotherapy) showed more events with high dose
Major bleeding at 1 year					**Insufficient SOE**
2 (7409)	2 observational/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	One study had high bleeding rates in low-dose group; other study had high rates in high-dose group

Abbreviations: ASA = 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 Versus Dual Antiplatelet Therapy

Seven studies (two RCTs, five observational) compared single antiplatelet with dual antiplatelet therapy in the postdischarge treatment of UA/NSTEMI patients.[138,147,166,171,177,179,182] 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.[147] The RCTs were rated good quality, and of the five observational studies, two were rated good quality, two fair, and one poor. In one RCT (COMMIT study[177]) the aspirin dose was 162 mg daily, and the other RCT (CURE study[182]) 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 and ethnic demographics of study participants. One study was conducted solely in the United States, two were conducted in Asia, and the other three were international. Funding source was reported in five studies, with all five studies funded by industry. Table G-12 in Appendix G contains the results reported by each study.

Effect on Composite Outcomes In-hospital to 1 Year

Two RCTs and two observational studies comparing aspirin alone with aspirin plus clopidogrel reported composite outcomes. In one RCT (CURE study[182]), the rate of cardiovascular mortality/nonfatal MI/stroke and cardiovascular mortality/nonfatal MI/stroke/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. The other RCT (COMMIT study[177]) showed a significantly lower rate of total mortality/nonfatal MI/stroke among patients receiving aspirin plus clopidogrel compared with those on aspirin alone (OR 0.91; 95% CI, 0.86 to 0.96) at 28 days followup. In

one observational study (CRUSADE registry[166]), 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[171]) showed significantly lower rates of total mortality/nonfatal MI/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 dual antiplatelet therapy result in a high SOE rating.

Effect on Stroke In-hospital to 1 Year

Five studies (3 observational, 2 RCTs) reported stroke events within the first 9 months postdischarge. An observational study[179] 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,[166] 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[171] 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[182] similarly 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 COMMIT RCT[177] showed a nonsignificant lower rate of stroke among patients receiving aspirin plus clopidogrel compared with those on aspirin alone (OR 0.86; 95% CI, 0.72 to 1.03) at 28 days followup. The SOE was rated insufficient for stroke outcomes based on inconsistent and imprecise findings from these five studies.

Effect on Nonfatal MI In-hospital to 1 Year

Four studies (2 RCTs, 2 observational) reported the effect of single versus dual antiplatelet therapy on nonfatal MI. The CURE RCT[182] 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). The COMMIT RCT[177] showed a lower rate of nonfatal MI among patients receiving aspirin plus clopidogrel compared with those on aspirin alone (OR 0.86; 95% CI, 0.76 to 0.97) at 28 days followup. In the CRUSADE registry,[166] 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[171] 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 dual antiplatelet therapy.

Effect on All-Cause Mortality In-hospital to 1 Year

Six studies (4 observational, 2 RCTs) reported the effect of single versus dual antiplatelet therapy on mortality. One observational study[179] 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[147] 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,[166] 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[171] 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[182] 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 COMMIT RCT[177] showed a lower rate of deaths among patients receiving aspirin plus clopidogrel compared with those on aspirin alone (OR 0.93; 95% CI, 0.87 to 0.99) at 28 days followup. The SOE was rated moderate based on consistent, but imprecise, findings that dual antiplatelet therapy reduces all-cause mortality.

Effect on Major Bleeding In-hospital to 9 Months

Three studies (1 observational, 2 RCTs) reported the effect of single versus dual antiplatelet therapy on major bleeding. In the CRUSADE registry,[166] 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[182] 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 COMMIT RCT[177] showed similar rates of major bleeding (both groups at 0.6%) among patients receiving aspirin plus clopidogrel compared with those on aspirin alone at 28 days followup. The SOE was rated insufficient for major bleeding outcomes based on inconsistent and imprecise findings.

Findings by Subgroup

Four studies[138,147,177,182] (two good-quality RCTs; 1 good- and 1 poor-quality observational study) reported variations in treatment effectiveness by subgroup. Subgroups analyzed were diabetes (1 study), sex (2), age (2), clinical presentation (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[182] comparing aspirin alone with aspirin plus clopidogrel in postdischarge UA/NSTEMI patients reported composite outcomes (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

Two studies assessed composite ischemic outcomes by sex. One RCT (CURE study[182]) comparing aspirin alone with aspirin plus clopidogrel in postdischarge UA/NSTEMI patients reported composite outcomes (cardiovascular death, nonfatal MI, or stroke) at 9 months by sex. Among men (n=7,726), 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. The other RCT (COMMIT study[177]) reported a composite outcome of death, MI, or stroke at 28 days. Among men, the rate was 7.7 percent in the aspirin plus clopidogrel arm and 8.6 percent in the aspirin-only arm. Among women, the rate was 13.3 percent in the aspirin plus clopidogrel arm and 14.0 percent in the aspirin-only arm.

Age

Two RCTs assessed composite ischemic outcomes by age. The CURE RCT[182] 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. The COMMIT RCT[177] reported a composite outcome of death, MI, or stroke at 28 days for patients under age 60, between 60 to 69, and over 70 years of age. Among patients under 60, the rate was 5 percent in the aspirin plus clopidogrel arm and 5.4 percent in the aspirin-only arm. Among patients age 60 to 69, the rate was 10.1 percent in the aspirin plus clopidogrel arm and 11.2 percent in the aspirin-only arm. Finally among patients 70 years of age or over, the rate was 14.9 percent in the aspirin plus clopidogrel arm and 16.2 percent in the aspirin-only arm.

Clinical Presentation

One RCT[182] 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.

Revascularization

One RCT[182] 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[182] 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=4,087), 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; 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; 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; 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; CI, 1.21 to 1.86).

Aspirin Dosing

One RCT[182] 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,[182] 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[171] 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 study[147] 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[138] 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 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 4 studies (2 RCTs and 2 observational registries). While 6 studies (2 RCTs 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, 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. 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 18.

Table 18. Summary strength of evidence for UA/NSTEMI patients treated with single vs. 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 outcomes in-hospital to 1 year					**High SOE**
4 (152,601)	2 RCTs/2 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/RR 0.69 to OR/RR 0.91
Stroke in-hospital to 1 year					**Insufficient SOE**
5 (158,840)	2 RCTs/2 good quality 3 observational/2 fair quality, 1 poor	Inconsistent	Direct	Imprecise	4 out of 5 studies showed no significant difference in stroke rates
Nonfatal MI in-hospital to 1 year					**High SOE**
4 (152,601)	2 RCTs/2 good quality 2 observational/1 fair quality, 1 poor	Consistent	Direct	Precise	All studies showed fewer recurrent MI in dual antiplatelet group, ranging from OR/RR 0.77 to OR/RR 0.86
All-cause mortality in-hospital to 1 year					**Moderate SOE**
6 (160,171)	2 RCTs/2 good quality 4 observational/1 good quality, 2 fair, 1 poor	Consistent	Direct	Imprecise	All studies showed fewer deaths in the dual antiplatelet group, ranging from OR/RR 0.66 to OR/RR 0.93
Major bleeding in-hospital to 9 months					**Insufficient SOE**
3 (148,311)	2 RCTs/2 good quality 1 observational/Fair quality	Inconsistent	Direct	Imprecise	2 studies showed a reduction in major bleed in dual antiplatelet group (1 statistically significant [16% vs. 21%], 1 not statistically significant)

Abbreviations: CI=confidence interval; 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

Nine studies (4 RCTs, 5 observational) compared short-term with long-term dual antiplatelet therapy (clopidogrel plus aspirin) in the postdischarge treatment of UA/NSTEMI patients.[155-158,170,174,181,186,187] Of the RCTs, two studies compared 1 month of dual antiplatelet therapy (DAPT) with 6 months;[174,181] another compared DAPT use for 6 months with 24 months;[186] and one compared 1 month of DAPT with 12 months.[187] In the observational studies, one evaluated planned duration of DAPT use for <3 months versus 6 months versus 12 months;[157] a second evaluated clopidogrel discontinuation by multivariable analysis at 6-month intervals;[170] one assessed patients with stent thrombosis for independent predictors;[158] one evaluated clopidogrel cessation by a competing risk approach;[155] and one compared dual antiplatelet therapy for more than 12 months with less than 12 months.[156]

Of the RCTs, two (50%) were rated good quality and two (50%) fair. Of the observational studies, one (20%) was rated good quality, three (60%) fair, and one (20%) poor quality. Sample

sizes for individual studies ranged from 278 to 6,816 patients. Study duration ranged from 30 days to 4 years.

The mean age of study participants ranged from 56.5 to 66.8 years. The proportion of female patients ranged from 2 to 43 percent. Two studies (22%) reported the racial and ethnic demographics of study participants. Three studies (33%) were conducted within the United States or Canada, with the rest international. Funding source was reported in 4 studies (44%), with 1 study (25%) funded by industry source. Table G-13 in Appendix G summarizes the results reported by each study.

Effect on Composite Endpoint of All-Cause Mortality and Nonfatal MI Within 2 Years

Two studies (one RCT[186] one observational[170]) reported the composite outcome of all-cause mortality and nonfatal MI. The RCT comparing DAPT for 6 months versus 24 months showed no differences in the rate of composite outcomes of all-cause mortality and nonfatal MI at 2 years between the two treatment arms (9.6% vs. 8.9%; OR 1.07; 95% CI, 0.80 to 1.43, p=0.62). The retrospective observational study assessing the effect of clopidogrel discontinuation on the composite outcomes 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 SOE was rated insufficient for the composite outcome of all-cause mortality and nonfatal MI based on inconsistent and imprecise findings between the observational study and randomized trial.

Effect on Composite Endpoint of All-Cause Mortality and Stroke at 2 Years

One RCT[186] comparing DAPT for 6 months versus 24 months showed no differences in the rate of the composite outcome of all-cause mortality and 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 and stroke based on one study with an imprecise estimate.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal MI, and Revascularization at 6 Months and 1 Year

Two studies[157,181] reported the composite outcome of all-cause mortality, nonfatal MI, and revascularization at 6 months and 1 year. In one observational study[157] assessing DAPT use for <3 months versus 6 months versus >12 months, the composite outcome of all-cause mortality, nonfatal MI, and revascularization at 1 year was reported based on type of stent (DES and BMS) used during percutaneous coronary intervention (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).

Another RCT[181] comparing 30-day 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%). 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, and Stroke at 30 Days, 1 Year, and 2 Years

Three RCTs[174,186,187] reported the composite outcome of all-cause mortality, nonfatal MI, and stroke at 30 days, 1 year and 2 years. One RCT[174] comparing 30-day with 6-month treatment with DAPT found that the rate of the composite outcome 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[187] comparing DAPT treatment for 28 days versus 12 months found a significant reduction in the risk of the composite outcome 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[186] comparing 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 low for this composite outcome (death/MI/stroke) based on significant findings favoring long-term DAPT from two out of three studies with imprecise estimates.

Effect on All-Cause Mortality at 6 Months, 1 Year, and 2 Years

Five studies[157,170,174,181,186] reported total mortality results. Two RCTs[174,181] comparing 30-day with 6-month treatment with DAPT found that the rate of all-cause mortality was lower among patients treated with DAPT for 6 months compared with those treated for 30 days. The difference in event rate was statistically different in only one study (0.87% vs. 2.6%, p=0.047[174] and 0.7% vs. 1.4%[181]).

In one observational study[157] comparing 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, 12-month 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=0.012), while in BMS-treated patients, 12-month mortality was similar among the three DAPT duration strategies (5.9% vs. 4.5% vs. 6.0%, 12 vs. 6 vs. 3 months, respectively).

An RCT[186] comparing 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)

A retrospective study[170] 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 month after discharge, the rate of all-cause mortality was higher compared with those who continue clopidogrel treatment (19.9% vs. 6.9%; HR 2.4; 95% CI, 1.61to 3.58).

The SOE was rated low for all-cause mortality based on statistically significant findings favoring long-term DAPT in 4 out of 5 studies and imprecise estimates.

Effect on Cardiovascular Mortality at 6 Months and 2 Years

Two RCTs[174,186] reported cardiovascular mortality results. One RCT[174] comparing 30-day 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).The other RCT[186] 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 SOE was rated insufficient for cardiovascular mortality based on imprecise and inconclusive findings from two studies.

Effect on Nonfatal MI at 6 Months, 1 Year, and 2 Years

Five studies (3 RCTs[174,181,186] and 2 observational[157,170]) reported nonfatal MI results. Two RCTs[174,181] comparing 30-day 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%[181] and 2.8% vs. 1.5%, p=0.18[174]).

In one observational study[157] 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%).

An RCT[186] 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).

A retrospective observational study[170] 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 month 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 and 2 Years

Two RCTs[174,186] reported stroke results. One[174] comparing 30-day 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 other,[186] comparing DAPT for 6 months versus 24 months, showed no difference in 2-year cardiovascular mortality between the two treatment arms (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 two studies.

Effect on Revascularization at 6 Months and 1 Year

Three studies (two RCTs[174,181] and one observational[157]) reported stent thrombosis results. Two studies[174,181] comparing 30-day 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[174] and 11.4% vs.12.3% in the other[181]).

In one observational study[157] evaluating DAPT use for less than 3 months versus 6 months versus more than 12 months, 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 studies.

Effect on Stent Thrombosis

Five studies (two RCTs[181,186] and three observational[155,156,158]) reported stent thrombosis results. One observational study[158] evaluated the temporal relation between clopidogrel cessation and stent thrombosis and found that clopidogrel cessation was an independent predictor of cumulative stent thrombosis at 30 days (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 12 months (OR 1.7; 95% CI, 0.9 to 3.1).

Another observational study[155] 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[156] comparing 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). One RCT[181] comparing 30-day 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[186] comparing 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).

The SOE was rated low since the findings were consistent that discontinuation of clopidogrel within 30 days or 6 months was associated with higher rates of stent thrombosis and 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

Two RCTs[186,187] reported major bleeding results. One[187] comparing DAPT for 28 days versus 12 months found no significant increase in the risk of major bleeding among patients treated with DAPT for 1 year (6.7% vs. 8.8%, p= 0.7). The other[186], comparing 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 SOE was rated insufficient for major bleeding outcomes based on inconsistent and imprecise results.

Effect on Minor Bleeding at 1 and 2 Years

Two RCTs[186,187] reported minor bleeding results. One[187] comparing DAPT for 28 days 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[186] 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

Three studies,[156,170,186] one RCT (good quality) and two observational (one good quality, one fair), reported variations in treatment effectiveness by subgroup. Subgroups analyzed were diabetes (2 studies), sex (1), age (1), chronic renal disease (1), stent type (2). Table H-3 in Appendix H presents the results data for these subgroups.

Diabetes

Two studies[156,186] reported a composite outcome in the diabetic subgroup. One RCT[186] comparing DAPT for 6 months versus 24 months showed no differences in the rate of composite outcomes (all-cause mortality, nonfatal MI, and 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; CI, 0.76 to 1.50). In the other study,[156] comparing 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, nonfatal MI) at 3 years between the two treatment groups among patients with diabetes (12% vs. 16%; HR 0.85; CI, 0.51 to 1.43, p=0.55).

Age

One RCT[186] comparing DAPT for 6 months versus 24 months reported composite outcomes (cardiovascular death, nonfatal MI, or stroke) at 2 years by age subgroups (<65 vs. ≥ 65 years). No significant differences in the rate of composite outcomes were observed in either age group (<65 years, HR 0.57; 95% CI, 0.28 to 1.16; and ≥ 65 years, OR 1.12; CI, 0.82 to 1.51).

Sex

One RCT[186] comparing DAPT for 6 months versus 24 months reported composite outcomes (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; CI, 0.77 to 1.29).

Chronic Kidney Disease

One RCT[186] comparing DAPT for 6 months versus 24 months reported composite outcomes (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; CI, 0.78 to 1.65).

Stent Type

Two studies[170,186] reported outcomes by stent type. One study,[170] 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; 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; CI, 0.58 to 2.74) and the DES group (HR 3.57; CI, 1.13 to 11.3).

One RCT[186] comparing DAPT for 6 months versus 24 months reported composite outcomes (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; CI, 0.67 to 1.30).

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. Our qualitative analysis showed that DAPT duration of either 6 months or 1 year reduces the rate of composite ischemic events (all-cause mortality, nonfatal MI, or stroke) compared with therapy less than 6 months 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 in 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 benefitted from longer dual antiplatelet therapy more than patients receiving a bare metal stent. Evidence was insufficient for the outcomes of cardiovascular mortality (2 studies), nonfatal MI (5 studies), stroke (2 studies), and revascularization (3 studies). Rates of stent thrombosis (5 studies), and were higher when DAPT was stopped within 30 days or 6 months, but the differences between therapies beyond 6 months were nonsignificant. 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, and the other RCT showing no significant increase in major bleed among patients treated with 28 days compared with 1 year. 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. Three studies (one good-quality RCT and two observational of good and fair quality) reported variations in treatment effectiveness by subgroup. Subgroups analyzed were diabetes (2 studies), sex (1), age (1), chronic renal disease (1), and stent type (2). No differences in composite ischemic events were found among the different subgroup comparisons. 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 19.

Table 19. Summary strength of evidence for UA/NSTEMI patients treated with short-term vs. 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 and nonfatal MI within 2 years					**Insufficient SOE**
2 (3468)	1 RCT/Good quality 1 observational/Fair quality	Inconsistent	Direct	Imprecise	One observational study showed discontinuation before 6 months increased events; other RCT showed no difference between 6- and 24-month therapy
Composite of all-cause mortality and stroke at 2 years					**Insufficient SOE**
1 (2013)	RCT/Good quality	NA	Direct	Imprecise	No difference between 6- and 24-month therapy in this RCT

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Composite all-cause mortality, nonfatal MI and revascularization at 6 months and 1 year					**Insufficient SOE**
2 (3258)	1 RCT/Fair quality 1 observational/Good quality	Inconsistent	Direct	Imprecise	Both studies (1 RCT, 1 observational) found similar rates between short- and long-term therapy
Composite all-cause mortality, nonfatal MI and stroke at 30 days, 1 year, and 2 years					**Low SOE**
3 (5133)	3 RCTs/2 Good quality, 1 fair	Inconsistent	Direct	Imprecise	2 RCTs found statistically significant reductions in events from long-term DAPT at 6 months and 1 year. One RCT found no difference between 6- and 24-month therapy
All-cause mortality at 6 months, 1 year, and 2 years					**Low SOE**
5 (6275)	3 RCTs/1 good quality, 1 fair 2 observational/1 good quality, 1 fair	Inconsistent	Direct	Imprecise	3 RCTs showed statistically significant reduction with longer therapy (2 studies comparing 30 days to 6 months; 1 study comparing 6 and 24 months); DES patients benefited more than BMS patients in an observational study; another observational study reported higher mortality in patients who discontinued DAPT within first 6 months of discharge
CV mortality at 6 months and 2 years					**Insufficient SOE**
2 (3017)	2 RCTs/1 good quality, 1 fair	Consistent	Direct	Imprecise	Both RCTs found similar rates between short-and long-term therapy (30 day vs. 6 months and 6 months vs. 24 months)
Nonfatal MI at 6 months, 1 year, and 2 years					**Insufficient SOE**
5 (6275)	3 RCTs/1 good quality, 1 fair 2 observational/1 good quality, 1 fair	Consistent	Direct	Imprecise	4 studies (3 RCTs and 1 observational) showed similar rates of MI in short- and long-term therapy groups; One observational study showed statistically significant higher risk in DES patients who discontinue clopidogrel within first 6 months

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 and 2 years					**Insufficient SOE**
2 (3017)	2 RCTs/1 good quality, 1 fair	Consistent	Direct	Imprecise	Both RCTs found similar rates between short-and long-term therapy
Revascularization at 6 months and 1 year					**Insufficient SOE**
3 (4262)	2 RCTs/Fair quality 1 observational/Good quality	Consistent	Direct	Imprecise	Rates of revascularization were similar between short- and long-term therapy (30 day vs. 6 months and 6 months vs. 24 months)
Stent thrombosis at 6 months, 1 year, and 2 years					**Low SOE**
5 (11,255)	2 RCTs/1 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 from two observational studies. Three studies (2 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**
2 (4129)	2 RCTs/2 good quality	Inconsistent	Direct	Imprecise	One RCT showed a statistically significant lower rate of major bleed with clopidogrel with 6-month treatment; the other RCT showed no statistically significant difference in rates with 1-year treatment
Minor bleeding at 1 and 2 years					**Insufficient SOE**
2 (4129)	2 RCTs/2 good quality	Consistent	Direct	Imprecise	Both RCTs failed to show a difference at 1 and 2 years

[a]Consistency cannot be determined because treatment durations were heterogeneous.
Abbreviations: 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

4. Antiplatelet Treatments With and Without Use of PPI

Thirty-two studies (4 RCTs, 28 observational) evaluated antiplatelet treatments with PPI versus antiplatelets alone in the postdischarge treatment of UA/NSTEMI patients.[14,126-128,130-137,139-146,148-151,153,154,160,161,164,168,169,185] Three of these studies compared esomeprazole with placebo and were included in the analysis; one study compared esomeprazole with famotidine. All other studies compared 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 28 observational studies, 23 (82%) were rated good quality, 3 (11%) fair, and 2 (7%) 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. 4 studies (13%) reported the racial and ethnic demographics of study participants. 10 studies (31%) were conducted within the United States or Canada, with the rest international. Funding source was reported in 17 studies (53%), with 4 studies (13%) funded by industry source. Table G-14 in Appendix G contains the results reported by each study.

The PPI studies were grouped into the following three comparisons:

a. Dual antiplatelet therapy with and without omeprazole (5 studies; 4 RCT, 1 observational)

b. Dual antiplatelet therapy with and without PPI (unspecified) (26 observational studies)

c. Aspirin monotherapy (i.e., no clopidogrel) with and without PPI (unspecified) (3 observational studies)

4a. Dual Antiplatelet Therapy With and Without Omeprazole

Five studies,[14,127,131,151,164] composed of four RCTs (2 good quality, 2 poor) and one good-quality observational study in 5,183 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 GI bleeding in patients with UA/NSTEMI.[127]

Effect on Composite Outcomes Within 1 Year

Three studies reported composite outcomes within one year of enrollment. One RCT[127] comparing omeprazole with famotidine reported a nonsignificant difference in the rate of composite outcomes (cardiovascular mortality, nonfatal MI, and 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, and 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[151] comparing omeprazole with placebo reported a nonsignificant difference in the rate of composite outcomes (cardiovascular mortality, nonfatal MI) at 12 months between the two treatment arms (10% vs. 9.7%; HR 1.1; CI, 0.6 to 1.8, p=0.89). The SOE was rated insufficient for this composite outcome based on imprecise findings.

Effect on All-Cause Mortality at 1 Year

Three studies reported all-cause mortality within one year of enrollment. One RCT[164] comparing omeprazole with placebo in an acute MI population reported a significant difference in the rate of all-cause mortality favoring omeprazole, OR 0.31 (95% CI, 0.10 to 0.97, p=0.05). One RCT[14] comparing omeprazole with placebo in a mixed population of ACS and PCI patients reported a nonsignificant difference in the rate of all-cause mortality at 6 months between the two treatment arms (HR 1.01; CI, 0.29 to 3.48, p=0.99). Similarly, an observational study[151] comparing omeprazole with placebo in a mixed population of stable angina and ACS patients reported a nonsignificant difference in the rate of all-cause mortality at 12 months between the two treatment arms (HR 1.10; CI, 0.44 to 2.84, p=0.84). The SOE was rated low based on the findings from one RCT that showed a significant reduction in mortality favoring omeprazole, while the other RCT and observational study reported nonsignificant differences in mortality.

Effect on Nonfatal MI at 6 Months and 1 Year

Two studies[14,151] 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 other study[151] found no effect of omeprazole versus placebo on nonfatal MI (6.5% vs. 6.5%; HR 1.0; CI, 0.5 to 1.9). The SOE was rated insufficient for nonfatal MI based on imprecise results.

Effect on Stroke at 30 days and 6 Months

Two studies reported cerebrovascular events; one reported a transient ischemic attack (TIA) at 30 days,[131] and the other reported stroke events at 6 months.[14] Nonsignificant differences were found in the rate of TIA events in the observational study[131] and in the rate of stroke events in the RCT[14] between patients treated with omeprazole versus those receiving placebo (TIA 2.3% vs. 1.0%; stroke 0.2% vs. 0.3%). The SOE was rated insufficient based on low number of stroke events in these studies which are underpowered to detect a difference.

Effect on Revascularization at 1 Year

Two studies reported repeat revascularization, one RCT at 6 months[14] and one observational study at 1 year[151] 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 SOE was rated insufficient for assessing revascularization outcomes based on imprecise estimates and insufficient power to detect a difference.

Effect on Stent Thrombosis at 1 Year

Two studies reported stent thrombosis (definite, possible, probable) at 6 months[14] and 1 year[151] 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.[151] The SOE was rated insufficient for stent thrombosis at 1 year based on inconsistent and imprecise findings.

Effect on GI Bleeding

Four RCTs reported gastrointestinal bleeding during the first year after hospital discharge.[14,127,131,164] One RCT[127] 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[164] 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[131] 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; CI, 0.18 to 0.63, p<0.001). Given the differences in the timing of followup (14 days, 30 days, 4 months, and 6 months), a meta-analysis was not performed, however the SOE was rated moderate for GI bleeding based on mostly consistent and precise findings from three out of four randomized trials.

Summary of Results for Dual Antiplatelet Therapy With and Without Omeprazole

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 studies that compared omeprazole to placebo or no omeprazole we found insufficient evidence for an effect of omeprazole on composite ischemic events (CV mortality/nonfatal MI/stroke) at 1 year, nonfatal MI at 6 months or 1 year, stroke at 30 days and 6 months, revascularization at 1 year, and stent thrombosis at 1 year. Use of omeprazole did not affect the rates of all-cause mortality; however, it significantly reduced the rates of upper GI bleeding from 4 randomized trials. Detailed SOE ratings are shown in Table 20.

Table 20. Summary strength of evidence for UA/NSTEMI patients treated with dual antiplatelet therapy with and without omeprazole

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 mortality, nonfatal MI and stroke within 1 year					**Insufficient SOE**
3 (4774)	2 RCTs/2 good quality 1 observational/Good quality	Consistent	Direct	Imprecise	No statistically significant difference between omeprazole vs. placebo on composite events
All-cause mortality at 1 year					**Low SOE**
3 (4698)	2 RCTs/1 good quality, 1 poor 1 observational/Good quality	Inconsistent	Direct	Imprecise	One study showed lower rates of death with omeprazole OR 0.31 (0.10 to 0.97); other two studies showed statistically nonsignificant differences in event rates

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Nonfatal MI at 6 months and 1 year					**Insufficient SOE**
2 (4461)	1 RCT/Good quality 1 observational/Good quality	Consistent	Direct	Imprecise	No statistically significant difference in MI rates with omeprazole
Stroke at 30 days and 6 months					**Insufficient SOE**
2 (4045)	2 RCTs/1 good quality, 1 poor	Consistent	Direct	NR	No statistically significant difference in TIA or CVA rates with omeprazole
Revascularization at 1 year					**Insufficient SOE**
2 (4461)	1 RCT/Good quality 1 observational/Good quality	Consistent	Direct	Imprecise	No statistically significant difference in revascularization rates with omeprazole
Stent thrombosis at 1 year					**Insufficient SOE**
2 (4461)	1 RCT/Good quality 1 observational/Good quality	Inconsistent	Direct	Imprecise	No statistically significant difference in stent thrombosis in omeprazole group
GI bleeding					**Moderate SOE**
4 (4595)	4 RCTs/2 good quality, 2 poor	Mostly consistent	Direct	Precise	3 out of 4 RCTs found statistically significant lower rates of upper GI bleed in omeprazole group

Abbreviations: CI=confidence interval; CV=cardiovascular; CVA=cardiovascular accident; GI=gastrointestinal; MI=myocardial infarction; NA=not applicable; NR=not reported; OR=odds ratio; RCT=randomized controlled trial; SOE=strength of evidence; TIA=transient ischemic attack; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction

4b. Dual Antiplatelet Therapy With and Without PPI

Twenty-six observational studies assessed the effect of antiplatelet treatments with PPI versus antiplatelets alone (no PPI) in the postdischarge treatment of UA/NSTEMI patients.

Effect on Composite Ischemic Outcomes Within 1 Year

Three observational studies (all good quality; 11,054 patients) reported composite ischemic outcomes at 1 year. One study[133] 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, and 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).

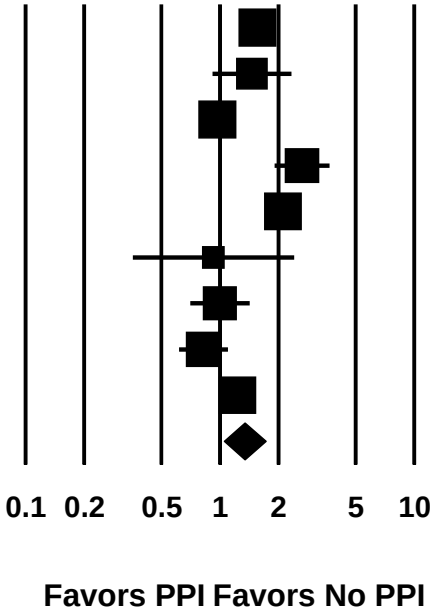
Another study[144] comparing the use of PPI versus no PPI found a significant increase in the rate of composite outcomes (all-cause mortality, stent thrombosis) at 30 days among patients discharged with PPI treatment versus without PPI treatment (PPI vs. no PPI 3.3% vs. 1.2%; adjusted OR 2.0; 95% CI, 1.1 to 3.7, p=0.02). Another study[146] comparing 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). The SOE was rated moderate for composite ischemic outcomes based on consistent but imprecise results from three good-quality observational studies.

Effect on Composite Endpoint of All-Cause Mortality, Nonfatal MI, and Stroke at 1 Year

A random-effects meta-analysis of 9 observational studies[126,132,134,135,141,143,150,185,188] (8 good and 1 fair quality) in 124,888 UA/NSTEMI patients reporting all-cause mortality between 6 and 18 months found that the odds ratio was 1.35 (95% CI, 1.05 to 1.73) favoring no PPI (Figure 40). There was evidence of extreme heterogeneity, with a Q-value of 248.9 for 8 degrees of freedom, p<0.001. The SOE 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 40. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on all-cause mortality, nonfatal myocardial infarction, and stroke at 1 year

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Charlot, 2010	1.562	1.474	1.655	0.000
Gaspar, 2010	1.462	0.922	2.316	0.106
Ray, 2010	0.970	0.914	1.029	0.312
Tsai, 2010	2.647	1.926	3.636	0.000
Van Boxel, 2010	2.112	1.903	2.343	0.000
Chitose, 2011	0.926	0.359	2.389	0.874
Harjai, 2011	1.000	0.708	1.412	1.000
Simon, 2011	0.824	0.621	1.093	0.179
Goodman, 2012	1.233	1.079	1.411	0.002
	1.348	1.053	1.726	0.018

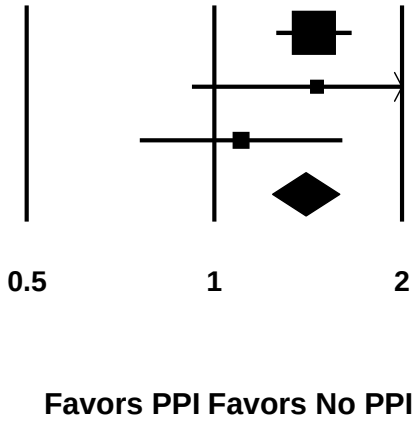


Effect on Composite Endpoint of All-Cause Mortality and Nonfatal MI at 6 to 18 Months

A random-effects meta-analysis of 3 good-quality observational studies[132,134,153] including 22,094 UA/NSTEMI patients and reporting all-cause mortality and nonfatal MI between 6 and 18 months found that the odds ratio was 1.40 (95% CI, 1.24 to 1.59), favoring no PPI use (Figure 41). There was no evidence of heterogeneity, with a Q-value of 1.80 for 2 degrees of freedom, p=406. Despite having good-quality studies and consistent findings of a direct outcome with a narrow confidence interval, the overall SOE 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 41. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on all-cause mortality and nonfatal myocardial infarction at 6 to 18 months

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Rassen, 2009	1.445	1.260	1.657	0.000
Gaspar, 2010	1.462	0.922	2.316	0.106
Harjai, 2011	1.104	0.761	1.602	0.603
	1.404	1.240	1.588	0.000



Effect on All-Cause Mortality Within First 3 Months

Three observational studies (all good quality; 8941 patients) reported the effect of PPI on all-cause mortality within the first 3 months after hospital discharge for a UA/NSTEMI event. One study[135] comparing PPI versus no PPI in patients with UA/NSTEMI 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[144] comparing PPI versus no PPI in patients with UA/NSTEMI 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[161] 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 (OR 0.82; 95% CI, 0.57 to 1.18). The SOE was rated insufficient for all-cause mortality within the first three months based on inconsistent and imprecise results.

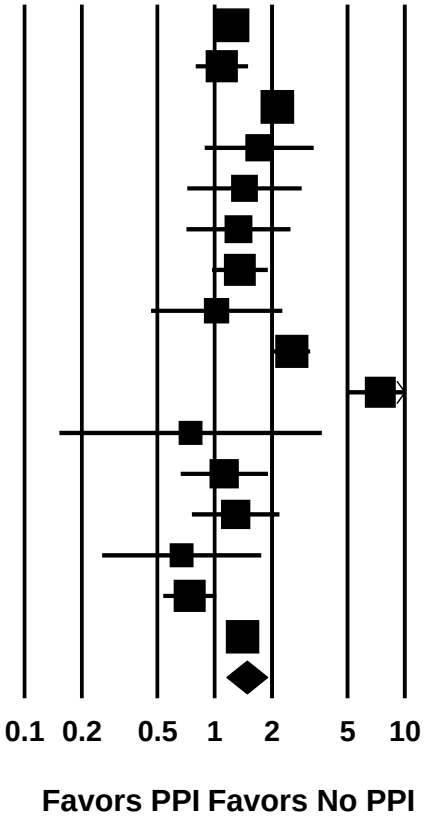
Effect on All-Cause Mortality After 1 Year

A random-effects meta-analysis of 16 observational studies[126,132-136,140,141,143,145,146,150,154,160,161,185] (14 good quality and 2 fair quality) including 141,474 UA/NSTEMI patients and reporting all-cause mortality between 6 and 18 months found that the odds ratio was 1.48 (95% CI, 1.16 to 1.89), favoring no PPI use (Figure 42). There was evidence of extreme heterogeneity, with a Q-value of 151.0 for 15 degrees of freedom, $p<0.001$. The SOE 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[153] 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, 0.84-1.70).

Figure 42. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on all-cause mortality at 1 year

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Ho, 2009	1.241	1.103	1.397	0.000
Juurlink, 2009	1.091	0.802	1.485	0.579
Charlot, 2010	2.139	1.877	2.437	0.000
Gaspar, 2010	1.713	0.893	3.287	0.106
Gupta, 2010	1.434	0.723	2.845	0.302
Kreutz, 2010	1.334	0.716	2.486	0.364
Ray, 2010	1.358	0.977	1.888	0.069
Tentzeris, 2010	1.024	0.466	2.249	0.953
Van Boxel, 2010	2.551	2.065	3.152	0.000
Wu, 2010	7.440	4.964	11.150	0.000
Chitose, 2011	0.747	0.154	3.629	0.718
Harjai, 2011	1.123	0.668	1.890	0.661
Ortolani, 2011	1.289	0.765	2.172	0.340
Rossini, 2011	0.670	0.258	1.744	0.412
Simon, 2011	0.739	0.540	1.011	0.058
Goodman, 2012	1.403	1.169	1.685	0.000
	1.483	1.161	1.894	0.002



Effect on All-Cause Mortality at 6 Years

Only one good quality observational study of 23,200 patients[137] reporting the effect of 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 for all-cause mortality at 6 years based on one large observational study.

Effect on Cardiovascular Mortality at 1 Year

Three observational studies[140,141,185] (two good quality, one fair) reported the effect of PPI use on cardiovascular mortality at 1 year in 69,296 total patients. Two studies comparing 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%, HR 1.42; 95% CI, 1.14 to 1.76[185] and HR 1.57; 95% CI, 1.36 to 1.82[141]). Another study[140] comparing 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%, 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 MI Within First 3 Months

Three observational studies (all good quality; 8941 patients) reported the effect of PPIs on nonfatal MI within the first 3 month after hospital discharge for a UA/NSTEMI event. Two studies[135,144] comparing PPI versus no PPI in patients with UA/NSTEMI reported a nonsignificant difference in the rate of nonfatal MI in-hospital[135] (2.0% vs. 1.4%, adjusted OR 1.15; 95% CI, 0.57 to 2.32) and at 30 days[144] (3.0% vs. 2.0%, adjusted HR 1.3; CI, 0.8 to 2.3). A case-control study[161] found an increased risk of nonfatal MI events at 3 months among UA/NSTEMI patients treated with PPI versus those not treated with PPI (OR 1.27; 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.

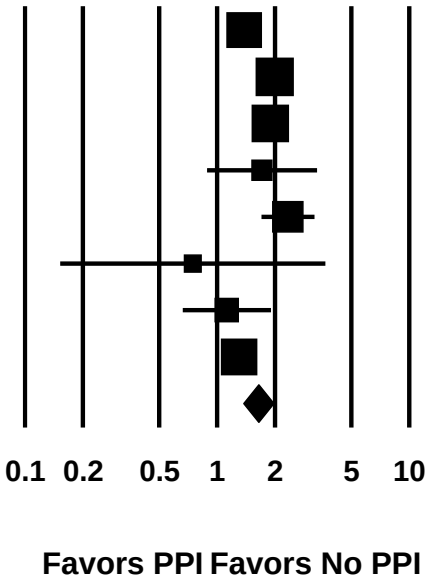
Effect on Nonfatal MI at 1 Year

A random-effects meta-analysis of 8 observational studies[126,132,141,143,145,149,161,185] (7 good quality and 1 fair quality) including 122,367 UA/NSTEMI patients reporting nonfatal MI between 6 and 18 months found that the odds ratio was 1.65 (95% CI, 1.38 to 1.97), favoring no PPI use (Figure 43). 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 SOE 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[139] 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,[153] treatment with PPI resulted in a higher risk of nonfatal MI but did not reach statistical significance (HR 1.22; CI, 0.99 to 1.51).

Figure 43. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on nonfatal myocardial infarction at 1 year

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Juurlink, 2009	1.384	1.138	1.683	0.001
Charlot, 2010	1.994	1.787	2.226	0.000
Evanchan, 2010	1.892	1.636	2.189	0.000
Kreutz, 2010	1.713	0.893	3.287	0.106
Van Boxel, 2010	2.337	1.714	3.186	0.000
Chitose, 2011	0.747	0.154	3.629	0.718
Harjai, 2011	1.123	0.668	1.890	0.661
Goodman, 2012	1.303	1.101	1.543	0.002
	1.648	1.376	1.974	0.000

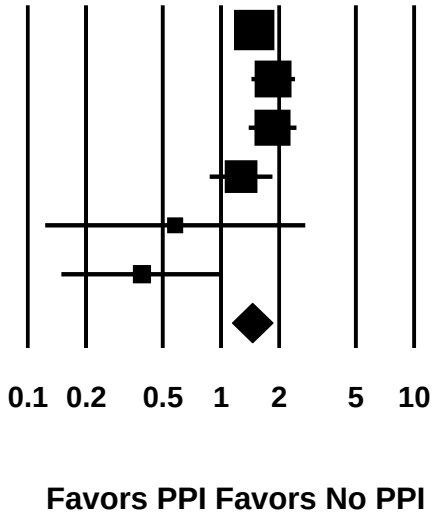


Effect on Stroke at 1 Year

A random-effects meta-analysis of six observational studies[126,135,141,143,145,150] (all good quality) including 57,501 UA/NSTEMI patients reporting stroke between 6 and 18 months found that the odds ratio was 1.46 (95% CI, 1.15 to 1.86), favoring no PPI use (Figure 44). There was evidence of heterogeneity, with a Q-value of 14.7 for 5 degrees of freedom, p= 0.01. The SOE was rated moderate for stroke outcomes at 1 year based on good-quality studies with inconsistent results of a direct outcome and a narrow confidence interval.

Figure 44. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on stroke at 1 year

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Charlot, 2010	1.488	1.288	1.719	0.000
Kreutz, 2010	1.865	1.449	2.399	0.000
Ray, 2010	1.852	1.403	2.443	0.000
Van Boxel, 2010	1.272	0.882	1.834	0.197
Chitose, 2011	0.580	0.124	2.712	0.489
Simon, 2011	0.391	0.151	1.012	0.053
	1.460	1.149	1.856	0.002



Effect on Revascularization at 6 Months and 4 Years

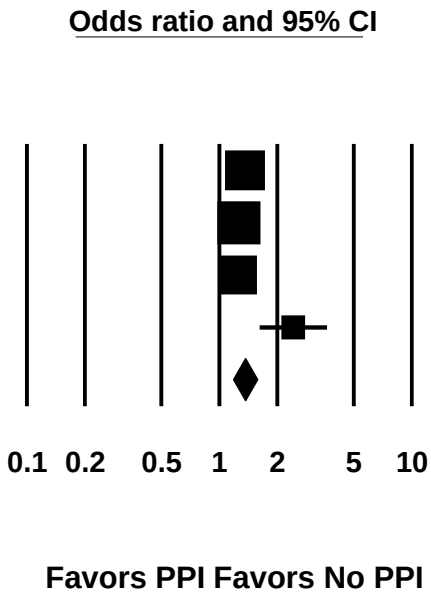
Two observational studies (one good quality, one fair; 18,880 patients) examined the effect of PPIs on revascularization at early and late followup. One study,[153] reporting the effect of PPIs on revascularization after hospital discharge for a UA/NSTEMI event, found no difference in the risk of revascularization 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). Similarly, another study[154] 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; CI, 0.80 to 3.03). The SOE was rated insufficient for revascularization at 6 months and 4 years based on imprecise findings.

Effect on Revascularization at 1 Year

A random-effects meta-analysis of four observational studies[136,137,145,160] (all good quality) including 52,576 UA/NSTEMI patients reporting revascularization at 1 year found that the odds ratio was 1.37 (95% CI, 1.19 to 1.58), favoring no PPI use (Figure 45). There was evidence of heterogeneity, with a Q-value of 10.7 for 3 degrees of freedom, p=0.01. Despite having good-quality studies with consistent results of a direct outcome and a narrow confidence interval, the overall SOE 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 45. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on revascularization at 1 year

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Ho, 2009	1.360	1.189	1.554	0.000
Kreutz, 2010	1.264	1.159	1.378	0.000
Banerjee, 2011	1.242	1.071	1.441	0.004
Ortolani, 2011	2.423	1.632	3.597	0.000
	1.370	1.187	1.581	0.000



Effect on Stent Thrombosis at 30 Days

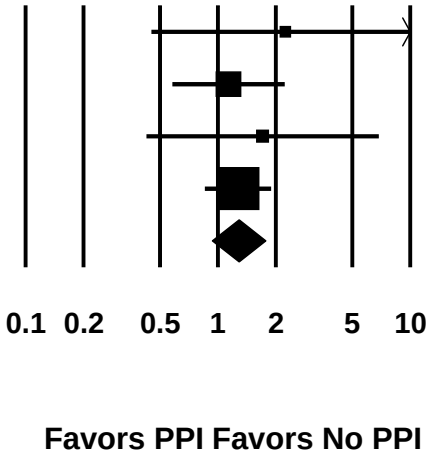
Only one good-quality observational study[144] of 3406 patients reporting the effect of PPI on stent thrombosis at 30 days after hospital discharge for a UA/NSTEMI event found no significant difference in the rate of stent thrombosis between the two treatment arms (PPI 1.1% vs. 0.5%, adjusted HR 1.8; 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 1 Year

A random-effects meta-analysis of 4 observational studies[132,133,140,185] (all good quality) including 23,833 UA/NSTEMI patients reporting stent thrombosis between 6 and 18 months found that the odds ratio was 1.29 (95% CI, 0.94 to 1.77) (Figure 46). There was no evidence of heterogeneity, with a Q-value of 0.76 for 3 degrees of freedom, p= 0.86. The SOE 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 46. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on stent thrombosis at 1 year

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Tentzeris, 2010	2.242	0.454	11.068	0.322
Harjai, 2011	1.136	0.584	2.209	0.708
Rossini, 2011	1.708	0.428	6.815	0.448
Goodman, 2012	1.272	0.862	1.877	0.225
	1.288	0.935	1.773	0.121

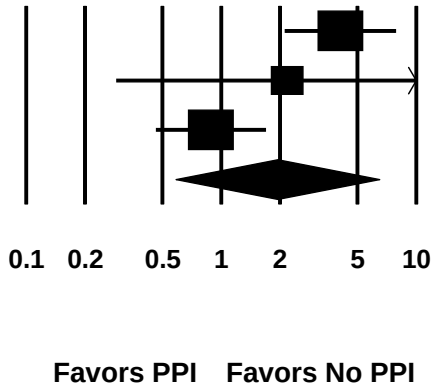


Effect on Major Bleeding at 30 Days

A random-effects meta-analysis of three good quality observational studies[133,135,144] including 7496 UA/NSTEMI patients reporting minor bleeding at 30 days found that the odds ratio was 1.95 (95% CI, 0.59 to 6.49) (Figure 47). There was evidence of heterogeneity, with a Q-value of 10.7 for 2 degrees of freedom, p=0.005. The SOE was rated insufficient for major bleeding at 30 days based on good-quality studies, inconsistent results of a direct outcome, and a wide confidence interval.

Figure 47. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on major bleeding at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Sarafoff, 2010	4.084	2.130	7.829	0.000
Rossini, 2011	2.182	0.292	16.315	0.447
Simon, 2011	0.886	0.465	1.686	0.712
	1.953	0.588	6.493	0.275

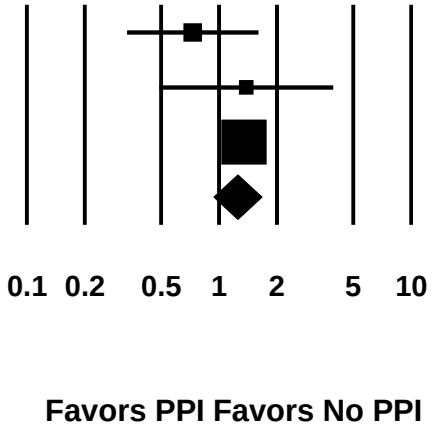


Effect on Major Bleeding at 1 Year

A random-effects meta-analysis of 3 good-quality studies[132,133,185] including 22,138 UA/NSTEMI patients reporting major bleeding at 1 year found that the odds ratio was 1.25 (95% CI, 0.94 to 1.67) (Figure 48). There was no evidence of heterogeneity, with a Q-value of 2.22 for 2 degrees of freedom, p=0.33. The SOE 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 48. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on major bleeding at 1 year

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Harjai, 2011	0.730	0.335	1.592	0.429
Rossini, 2011	1.388	0.494	3.902	0.534
Goodman, 2012	1.351	1.070	1.704	0.011
	1.254	0.944	1.666	0.118



Effect on GI Bleeding

Four observational studies reported gastrointestinal (GI) bleeding: two[168,169] in-hospital, and two[126,150] at long term in 23,555 patients. One study[168] comparing PPI use 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[169] 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[126] 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[150] 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).

The SOE was rated insufficient for GI bleeding outcomes based on inconsistent and insufficient results.

Effect on Minor Bleeding

One good-quality observational study[133] of 7346 UA/NSTEMI patients comparing 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

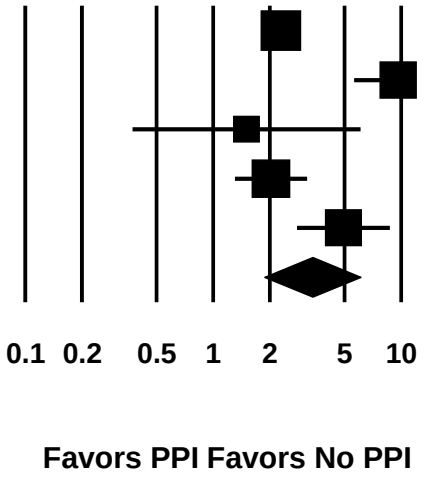
One good-quality observational study[146] of 3406 patients reporting the effect of PPI on rehospitalization after hospital discharge for a UA/NSTEMI event found a significant increase in the rate of rehospitalization at 3 months among patients treated with PPI compared with those not treated with PPI (24.6% vs. 10.1%, adjusted HR 1.32; 95% CI, 1.00 to 1.73). The SOE was rated low for rehospitalization at 3 months based on significant results of an indirect outcome.

Effect on Rehospitalization at 1 Year

A random-effects meta-analysis of five observational studies[128,136,140,148,160] (all good quality) including 25,715 UA/NSTEMI patients reporting rehospitalization at 1 year found that the odds ratio was 3.39 (95% CI, 1.88 to 6.11) favoring the no PPI group (Figure 49). There was evidence of extreme heterogeneity, with a Q-value of 32.4 for 4 degrees of freedom, p<0.001. The SOE 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 49. Meta-analysis of dual antiplatelet therapy with and without proton pump inhibitor on rehospitalization at 1 year

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Ho, 2009	2.294	1.952	2.696	0.000
Stockl, 2010	9.651	5.664	16.443	0.000
Tentzeris, 2010	1.504	0.375	6.031	0.564
Hsiao, 2011	2.029	1.315	3.133	0.001
Ortolani, 2011	4.931	2.814	8.639	0.000
	3.390	1.881	6.109	0.000



Summary of Results for Dual Antiplatelet Therapy With and Without PPI

In our analysis of dual antiplatelet treatment with and without concomitant PPI therapy, we present the findings from studies (all observational) that grouped patients given different PPI medications, and compared clinical outcomes to patients who did not receive a PPI. These patient populations were treated with aspirin plus clopidogrel. Event rates are lower in patients who are not receiving a PPI medication for the various composite outcomes, all-cause mortality after 1 year, nonfatal MI at 1 year, stroke at 1 year, revascularization at 1 year, and rehospitalization at 3 months and at 1 year. Findings based on observational studies may be confounded by selection bias, where sicker patients with more comorbidities are treated with a PPI and therefore have more adverse clinical outcomes. There was no difference between groups for all-cause mortality at 6 years. The findings were inconsistent (i.e., showing no differences between groups or showing increased event rates in the PPI group) and the evidence base insufficient for all-cause mortality within the first 3 months, cardiovascular mortality at 1 year, nonfatal MI within the first 3 months, revascularization at 6 months and 4 years, stent thrombosis at 30 days and 1 year, major bleeding at 30 days and at 1 year, GI bleeding, and minor bleeding. Detailed SOE ratings are shown in Table 21. Odds ratios less than 1 favor PPI use; those greater than 1 favor no PPI use.

Table 21. Summary 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 outcomes within 1 year					**Moderate SOE**
3 (11,054)	3 observational/3 good quality	Consistent	Direct	Imprecise	All 3 studies showed higher event rates in PPI group (statistically significant in 2 studies: OR 2.0 (1.1 to 3.7) HR 3.2 (2.56 to 4.01)
Composite of all-cause mortality, nonfatal MI, or stroke at 1 year					**Moderate SOE**
9 (124,888)	9 observational/7 good quality, 2 fair	Inconsistent	Direct	Precise	OR 1.35 (1.05 to 1.73) favoring no PPI group
Composite of all-cause mortality and nonfatal MI at 6 to 18 months					**Moderate SOE**
3 (22,094)	3 observational/3 good quality	Consistent	Direct	Precise	OR 1.40 (1.24 to 1.59) favoring no PPI group
All-cause mortality within first 3 months					**Insufficient SOE**
3 (8941)	3 observational/3 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 (adjusted HR 2.2; CI, 1.1 to 4.3)
All-cause mortality after 1 year					**Moderate SOE**
16 (141,474)	16 observational/14 good quality, 2 fair	Inconsistent	Direct	Precise	OR 1.48 (1.16 to 1.89) favoring no PPI group
All-cause mortality at 6 years					**Low SOE**
1 (23,200)	Observational/Good quality	NA	Direct	Imprecise	HR 1.32 (1.00 to 1.73)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Cardiovascular mortality at 1 year					**Insufficient SOE**
3 (69,296)	3 observational/2 good quality, 1 fair	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 (8941)	3 observational/3 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 1 year					**Moderate SOE**
8 (122,367)	8 observational/7 good quality, 1 fair	Inconsistent	Direct	Precise	OR 1.65 (1.38 to 1.97) favoring no PPI group
Stroke at 1 year					**Moderate SOE**
6 (57,501)	6 observational/6 good quality	Inconsistent	Direct	Precise	OR 1.46 (1.15 to 1.86), favoring no PPI group
Revascularization after 1 year					**Moderate SOE**
4 (52,576)	4 observational/4 good quality	Consistent	Direct	Precise	OR 1.37 (1.19 to 1.58) favoring no PPI group
Revascularization at 6 months and 4 years					**Insufficient SOE**
2 (18,880)	2 observational/1 good quality, 1 fair	Consistent	Direct	Imprecise	Both studies showed no difference in revascularization rates
Stent thrombosis at 30 days					**Insufficient SOE**
1 (3406)	Observational/Good quality	NA	Direct	Imprecise	No statistically significant difference in stent thrombosis rate between groups
Stent thrombosis at 1 year					**Insufficient SOE**
4 (23,833)	4 observational/4 good quality	Consistent	Direct	Imprecise	OR 1.29 (0.94 to 1.77)
Major bleeding at 30 days					**Insufficient SOE**
3 (7496)	3 observational/3 good quality	Inconsistent	Direct	Imprecise	OR 1.95 (0.59 to 6.49)
Major bleeding at 1 year					**Insufficient SOE**
3 (22,138)	3 observational/3 good quality	Inconsistent	Direct	Imprecise	OR 1.25 (0.94 to 1.67)
GI bleeding					**Insufficient SOE**
4 (23,555)	4 observational/4 good quality	Inconsistent	Direct	Imprecise	Conflicting results in in-hospital and 12-18 month time points with 2 studies showing no difference and 2 studies showing a significant reduction in GI bleed in PPI group
Minor bleeding					**Insufficient SOE**
1 (7346)	Observational/Good quality	NA	Direct	Unknown	No difference in minor bleed in-hospital or at 1 year
Rehospitalization at 3 months					**Low SOE**
1 (3406)	Observational/Good quality	NA	Indirect	Precise	Significant increase in rehospitalization in PPI group at 3 months (HR 1.32, CI = 1.00-1.73)

Number of Studies (Patients)	Domains				SOE and Magnitude of Effect Effect Estimate (95% CI)
	Risk of Bias: Study Design/Quality	Consistency	Directness	Precision	
Rehospitalization at 1 year					**Low SOE**
5 (25,715)	5 observational/5 good quality	Inconsistent	Indirect	Imprecise	OR 3.39 (1.88 to 6.11) favoring no PPI group

Abbreviations: 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

4c. Aspirin Monotherapy With and Without PPI

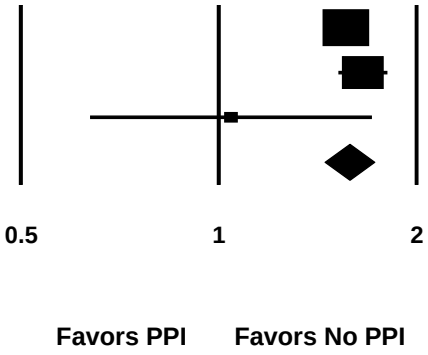
Three observational studies (2 good quality, 1 fair quality) reported the results of 108,602 UA/NSTEMI patients who were given aspirin monotherapy; i.e., not prescribed clopidogrel, and then either treated or not treated with PPIs.

Effect on the Composite of Cardiovascular Death, Nonfatal MI, or Stroke at 1 Year

A random-effects meta-analysis of 3 observational studies[130,135,141] (2 good quality and 1 fair quality) including 108,602 UA/NSTEMI patients reporting the composite of cardiovascular death, nonfatal MI, and stroke at 1 year found that the odds ratio was 1.58 (95% CI, 1.45 to 1.73), favoring no PPI use (Figure 50). There was no evidence of heterogeneity, with a Q-value of 4.12 for 2 degrees of freedom, p=0.12. The SOE was rated moderate for this composite endpoint at 1 year based on three observational studies with consistent results of a direct outcome and a narrow confidence interval.

Figure 50. Meta-analysis of aspirin monotherapy with and without proton pump inhibitor on composite outcome of cardiovascular death, nonfatal myocardial infarction, or stroke at 1 year

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Charlot, 2010	1.562	1.474	1.655	0.000
Charlot, 2011	1.657	1.524	1.801	0.000
Simon, 2011	1.044	0.639	1.706	0.863
	1.583	1.451	1.726	0.000



Effect on In-hospital Outcomes

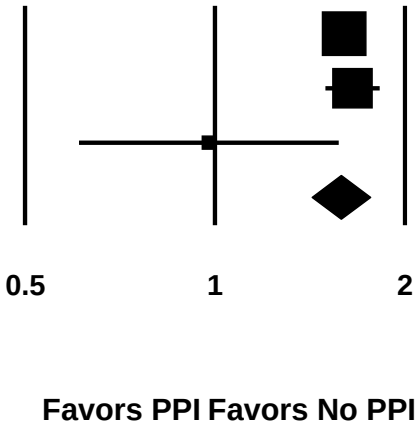
One good-quality study[135] comparing PPI with no PPI among UA/NSTEMI patients receiving aspirin monotherapy reported the in-hospital rate of individual components of the composite outcomes and major bleeding. The study found no differences in the rate of in-hospital death (13.0% vs.14%, OR 1.47; 95% CI, 0.67 to 3.25), nonfatal MI (2.5% vs.3.4%, HR 0.99; CI, 0.18 to 5.53), stroke (1.0% vs.1.0%, HR 3.21; CI, 0.24 to 42.5), or major bleeding (3% vs. 1%, OR 2.16; 95% CI, 0.17 to 27.3). 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

A random-effects meta-analysis of 3 observational studies[130,135,141] (2 good quality and 1 fair quality) including 108,602 UA/NSTEMI patients reporting all-cause mortality 1 year found that the odds ratio was 1.59 (95% CI, 1.43 to 1.76), favoring no PPI use (Figure 51). There was no evidence of heterogeneity, with a Q-value of 4.58 for 2 degrees of freedom, p=0.10. The overall SOE was moderate based on 3 observational studies with inconsistent results of a direct outcome and a narrow confidence interval.

Figure 51. Meta-analysis of aspirin monotherapy with and without proton pump inhibitor on all-cause mortality at 1 year

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Charlot, 2010	1.603	1.498	1.715	0.000
Charlot, 2011	1.652	1.500	1.819	0.000
Simon, 2011	0.978	0.610	1.567	0.926
	1.586	1.426	1.764	0.000



Effect on Nonfatal MI at 1 Year

Two observational studies,[130,141] one good quality and one fair, compared the effect of PPI versus no PPI among patients with UA/NSTEMI on nonfatal MI at 1 year. One study[130] showed an increased risk among patients receiving PPI at hospital discharge (11.5% vs.7.1%, HR 1.39; 95% CI, 1.20 to 1.62). Similarly, another study[141] showed an increased risk of nonfatal MI at 1 year among patients receiving PPI at hospital discharge (11.6% vs.7.9%; HR 1.19; 95% CI, 1.05

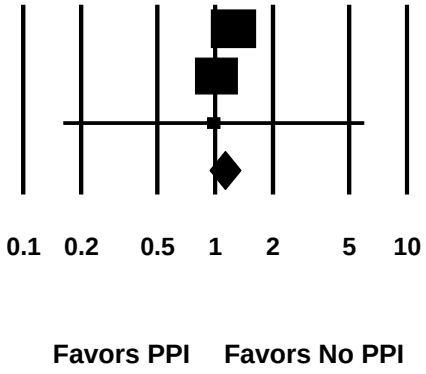
to 1.35). The SOE was rated moderate for nonfatal MI at 1 year based on consistent and precise results.

Effect on Stroke at 1 Year

A random-effects meta-analysis of 3 studies (2 good and 1 fair) including 108,602 UA/NSTEMI patients reporting stroke at 1 year found that the odds ratio for PPI use was 1.13 (95% CI, 0.94 to 1.36) (Figure 52). There was evidence of heterogeneity, with a Q-value of 6.62 for 2 degrees of freedom, p= 0.04. The SOE was rated insufficient for stroke at 1 year based on 3 observational studies with consistent results of a direct outcome and a wide confidence interval that crosses 1.

Figure 52. Meta-analysis of aspirin monotherapy with and without proton pump inhibitor on stroke at 1 year

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Charlot, 2010	1.247	1.137	1.368	0.000
Charlot, 2011	1.017	0.897	1.153	0.794
Simon, 2011	0.984	0.163	5.944	0.986
	1.131	0.941	1.358	0.189



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 studies that compared clinical outcomes between the grouping of patients given different PPI medications to patients who did not receive a PPI. In contrast to the previous section, these patient populations were not prescribed dual antiplatelet therapy; therefore the evaluation focuses on the addition of PPIs to aspirin monotherapy. All evidence comes from observational studies. Patients not receiving a PPI had fewer composite ischemic events (CV mortality, nonfatal MI, or stroke) and lower all-cause mortality at 1 year of followup. Two of these studies reported rates of nonfatal MI at 1 year and both showed an increased risk of MI events in the PPI group. There was insufficient evidence for the effect of PPIs on aspirin monotherapy for in-hospital outcomes; only one study of 2,744 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 was also insufficient evidence for stroke at 1 year. Detailed SOE ratings are shown in Table 22. Odds ratios less than 1 favor PPI use; those greater than 1 favor no PPI use

Table 22. Summary 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					**Moderate SOE**
3 (108,602)	3 observational/2 good quality, 1 fair	Consistent	Direct	Precise	OR 1.58 (1.45 to 1.73) favoring no PPI group
All-cause mortality (in-hospital)					**Insufficient SOE**
1 (2744)	Observational/good quality	NA	Direct	Imprecise	OR 1.47 (0.67 to 3.25)
All-cause mortality at 1 year					**Moderate SOE**
3 (108,602)	3 observational/2 good quality, 1 fair	Inconsistent	Direct	Precise	OR 1.59 (1.43 to 1.76) favoring no PPI group
Nonfatal MI (in-hospital)					**Insufficient SOE**
1 (2744)	Observational/good quality	NA	Direct	Imprecise	OR 0.99 (0.18 to 5.53)
Nonfatal MI at 1 year					**Moderate SOE**
2 (105,858)	2 observational/1 good quality, 1 fair	Consistent	Direct	Precise	Both studies showed increased risk of events in PPI group (HR 1.19-1.39)
Stroke (in-hospital)					**Insufficient SOE**
1 (2744)	Observational/good quality	NA	Direct	Imprecise	OR 3.21 (0.24 to 42.5)
Stroke at 1 year					**Insufficient SOE**
3 (108,602)	3 observational/2 good quality, 1 fair	Consistent	Direct	Imprecise	OR 1.13 (0.94 to 1.36)
Major bleeding (in-hospital)					**Insufficient SOE**
1 (2744)	Observational/Good quality	NA	Direct	Imprecise	OR 2.16 (0.17 to 27.3)

Abbreviations: 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)

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 (7), 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[133,141] comparing PPI versus no PPI in 57,752 UA/NSTEMI patients reported outcomes among patients with diabetes. One study[141] reported the rate of the composite outcome (cardiovascular death, nonfatal MI, 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; 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, CI, 1.06-1.45) and those without diabetes (HR 1.35; 95% CI, 1.26-1.44).

The other study[133] comparing PPI versus no PPI in UA/NSTEMI patients reported the rate of composite outcome (all-cause mortality, nonfatal MI, stroke and 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; CI, 0.61 to 4.88).

Sex

Only one good-quality observational study[141] comparing PPI versus no PPI in 56,406 UA/NSTEMI patients reported the rate of the composite outcome (cardiovascular death, nonfatal MI, 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; 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; CI, 1.21 to 1.44) and men (HR 1.34; CI, 1.23 to 1.46).

Age

Two good-quality observational studies[133,141] comparing PPI versus no PPI in 57,752 UA/NSTEMI patients reported outcomes by age group. One study[141] reported the rate of the composite outcome (cardiovascular death, nonfatal MI, 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; 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; CI, 1.24 to 1.43) but not the younger group (≤70 years HR 1.19; CI, 0.99 to 1.39).

The other study[133] reporting the rate of a composite outcome (all-cause mortality, nonfatal MI, stroke and 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; CI, 0.35 to 7.37).

Chronic Kidney Disease

Only one good-quality observational study[133] comparing PPI versus no PPI in 1346 UA/NSTEMI patients reported rate of composite outcome (all-cause mortality, nonfatal MI, stroke and 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; CI, 0.76 to 8.06).

Type of PPI

Seven observational studies[133,135,141,143,150,153,160] (6 good quality, 1 fair quality) comparing PPI versus no PPI in 126,586 UA/NSTEMI patients reported outcomes by type of PPI. Table 23 summarizes the results reported for each study for each PPI. The first study by Charlot et al.[141] reported the rate of a composite outcome (cardiovascular death, nonfatal MI, stroke) by concomitant clopidogrel use and by type of PPI (pantoprazole, omeprazole, lansoprazole, esomeprazole). The study found a significant increase in the risk of the composite outcome at 1 year among patients treated with PPI *and* concomitant clopidogrel for all types of PPI. Similarly, a significant increase in the risk of the composite outcome at 1 year was found among patients

treated with PPI but *no* concomitant clopidogrel for all types of PPI. A Cox proportional hazards regression analysis demonstrated no difference in risk associated with the type of PPI independent of clopidogrel treatment

A second study by Ho[160] found a significant increase in the composite of all-cause mortality and rehospitalization both with omeprazole and with rabeprazole. A third study by Rassen[153] found a nonsignificant increase in the composite of all-cause mortality and nonfatal MI both with omeprazole and with pantoprazole.

The fourth study by Ray[150] found a nonsignificant difference in the composite of cardiovascular mortality, nonfatal MI, and stroke with omeprazole, pantoprazole, esomeprazole, and lansoprazole. Only 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; CI, 0.33 to 0.63).

The fifth study by Rossini[133] 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 sixth study by Simon[135] 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/stroke (in-hospital and at 1 year), and individual outcomes of total mortality nonfatal MI, stroke, and bleeding compared with those not receiving those PPIs.

The seventh study by van Boxel[143] found a significant increase in the composite outcome (all-cause mortality, nonfatal MI, and stroke) with omeprazole, pantoprazole, esomeprazole and rabeprazole.

Table 23. Summary of findings by type of proton pump inhibitor prescribed

Study Details	Prescribed PPI				
	Esomeprazole	**Lansoprazole**	**Omeprazole**	**Pantoprazole**	**Rabeprazole**
Charlot, 2010[141] Total N: 56,406 Quality: Good	CV death/MI/CVA 1 yr With clopidogrel HR 1.29, 95% CI 1.09 to 1.48 Without clopidogrel HR 1.53, 95% CI 1.39 to 1.71	CV death/MI/CVA 1 yr With clopidogrel HR 1.47, 95%CI 1.21 to 1.81 Without clopidogrel HR 1.45, 95%CI 1.27 to 1.68	CV death/MI/CVA 1 yr With clopidogrel HR 1.40 95%CI 1.10 to 1.78 Without clopidogrel HR 1.25, 95%CI 1.09 to 1.41	CV death/MI/CVA 1 yr With clopidogrel HR 1.42 95%CI 1.22 to 1.67 Without clopidogrel HR 1.5, 95%CI 1.36 to 1.69	NR

Study Details	Prescribed PPI				
	Esomeprazole	**Lansoprazole**	**Omeprazole**	**Pantoprazole**	**Rabeprazole**
Ho, 2009[160] Total N: 8790 Quality: Good	NR	NR	Death/rehospital-ization Adjusted OR (95% CI): 1.24 (1.08 to 1.41)	NR	Death/rehospitali zation Adjusted OR (95% CI): 2.83 (1.96 to 4.09)
Rassen, 2009[153] Total N: 18,565 Quality: Good	NR	NR	Death/MI HR (95% CI): 1.17 (0.68 to 2.01)	Death/MI HR (95% CI): 1.26 (0.93 to 1.71)	NR
Ray, 2010[150] Total N: 20,596 Quality: Good	CV death/MI/CVA HR (95% CI): 0.71 (0.48 to 1.06) GI bleeding HR (95% CI): 0.43 (0.18 to 1.07)	CV death/MI/CVA HR (95% CI): 1.06 (0.77 to 1.45) GI bleeding HR (95% CI): 0.71 (0.43 to 1.18)	CV death/MI/CVA HR (95% CI): 0.79 (0.54 to 1.15) GI bleeding HR (95% CI): 0.43 (0.16 to 1.13)	CV death/MI/CVA HR (95% CI): 1.08 (0.88 to 1.32) GI bleeding HR (95% CI): 0.46 (0.33 to 0.63)	CV death/MI/CVA HR (95% CI): 0.54 (0.30 to 0.97) GI bleeding HR (95% CI): 0.25 (0.03 to 2.01)
Rossini, 2011[133] 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: 2.1% 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: 1.7% Minor bleeding in-hospital: 7.1% Minor bleeding 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: 3.1%; 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
Simon, 2011[135] FAST-MI Study Total N: 2744	Death/ MI/CVA in-hospital Adjusted OR (95% CI): 0.77 (0.41 to 1.46) Death/ MI/CVA	Death/ MI/CVA in-hospital Adjusted OR (95% CI): 0.59 (0.07 to 4.72) Death/ MI/CVA	Death/ MI/CVA in-hospital Adjusted OR (95% CI): 0.92 (0.59 to 1.43) Death/ MI/CVA	Death/ MI/CVA in-hospital Adjusted OR (95% CI): 1.31 (0.54 to 3.17) Death/ MI/CVA at 1	NR

Study Details	Prescribed PPI				
	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Quality: Good	at 1 yr Adjusted OR (95% CI): 1.05 (0.62 to 1.77) Total mortality Adjusted OR (95% CI): 0.72 (0.30 to 1.7) Nonfatal MI Adjusted OR (95% CI): 1.20 (0.44 to 3.30) Stroke Adjusted OR (95% CI): 0.54 (0.14 to 2.16) Bleeding Adjusted OR (95% CI): 0.97 (0.33 to 2.86)	at 1 yr Adjusted OR (95% CI): 0.40 (0.05 to 2.95) Total mortality Adjusted OR (95% CI): 1.30 (0.15 to 11.5) Nonfatal MI 0 Stroke 0 Bleeding Adjusted OR (95% CI): 1.82 (0.22 to 15.3)	at 1 yr Adjusted OR (95% CI): 0.82 (0.54 to 1.24) Total mortality Adjusted OR (95% CI): 1.16 (0.66 to 2.05) Nonfatal MI Adjusted OR (95% CI): 1.18 (0.55 to 2.52) Stroke Adjusted OR (95% CI): 1.18 (0.55 to 2.52) Bleeding Adjusted OR (95% CI): 0.94 (0.44 to 1.98)	yr Adjusted OR (95% CI): 1.79(0.95 to 3.37) Total mortality Adjusted OR (95% CI): 1.00 (0.27 to 3.68) Nonfatal MI Adjusted OR (95% CI): 1.22 (0.26 to 5.77) Stroke Adjusted OR (95% CI): 1.78 (0.36 to 8.83) Bleeding 0	
Van Boxel, 2010[143] Total N: 18,139 Quality: Fair	Death/MI/CVA HR (95% CI): 1.83 (1.52 to 2.21)	NR	Death/MI/CVA HR (95% CI): 1.62 (1.38 to 1.91)	Death/MI/CVA HR (95% CI): 1.83 (1.61 to 2.08)	Death/MI/CVA HR (95% CI): 1.76 (1.07 to 2.88)

Abbreviations: 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[139,145,161] (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[145] 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; CI, 0.98 to 1.71). Another study[161] found no difference in the rate of nonfatal MI among patients with both prior use (HR 0.86; CI, 0.63 to 1.19) and remote use (HR 0.81; CI, 0.46 to 1.41). Another study[139] comparing current PPI use with past PPI use found no difference in the rate of nonfatal MI among patients (OR 0.95; CI, 0.38 to 2.41).

Dose of PPI

One good-quality observational study[150] 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; 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; CI, 0.36 to 0.64 and high dose HR 0.53; CI, 0.32 to 0.89).

5. Dual Antiplatelet Versus Triple Therapy

Eleven studies (all observational) compared dual antiplatelet therapy (DAPT), defined as aspirin with oral antiplatelet, with triple therapy (TT), defined as dual antiplatelet therapy with an oral anticoagulant, in the postdischarge treatment of 83,962 total patients with UA/NSTEMI and a long-term indication for anticoagulation. The dual versus triple therapy comparisons studied included:

- Five studies comparing DAPT (with aspirin and clopidogrel) with TT (with oral anticoagulant, aspirin, and clopidogrel)[167,173,176,183,184,189]
- One study comparing warfarin versus no warfarin among patients with atrial fibrillation-complicating UA/NSTEMI event[152]
- One study comparing DT (aspirin with clopidogrel) with two TT arms—one consisting of oral anticoagulant, aspirin, and clopidogrel, and one consisting of low molecular weight heparin, aspirin, and clopidogrel[165]
- One study comparing TT (oral anticoagulant, aspirin, and clopidogrel) with warfarin plus aspirin or thienopyridine[172]
- One study comparing aspirin and /or thienopyridine versus oral anticoagulant with/without an antiplatelet agent[175]
- One five-treatment-arm study comparing aspirin, warfarin, aspirin plus warfarin, aspirin plus a thienopyridine (DAPT), and aspirin plus warfarin plus a thienopyridine (TT).[178]

Of the 11 observational studies, 1 (9%) was rated poor quality, 2 (18%) fair quality, and 8 (73%) good 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 60.1 to 77.7 years of age. The proportion of female patients ranged from 20 to 43 percent. Three studies (25%) reported the racial and ethnic demographics of study participants. One study (8.3%) was conducted within the United States or Canada, with the rest international. Funding source was reported in 6 studies (50%), with 1 study (17%) funded by industry source. Table G-15 in Appendix G contains the results reported by each study.

Effect on Composite Outcome of All-Cause Mortality, Nonfatal MI, and Revascularization or Stroke 1 Year or More

Four studies reported three 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 TT reported a composite of all-cause mortality, nonfatal MI, and revascularization at long-term followup. One study[167] showed a significant increase in the composite outcomes at 5 years among patients treated with DAPT compared with TT (38.7% vs.26.5%, HR 4.9; 95% CI, 2.17 to 11.1). The other study[183] showed a nonsignificant difference

in the rate of composite outcomes at 3 years between patients treated with DAPT and TT (15.5% vs.11.9%, HR 0.94; CI, 0.56 to 1.59).

One study reported a composite of all-cause mortality, nonfatal MI, and stroke at long-term followup.[162] This study comparing DAPT with TT 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[167] comparing DAPT with TT showed that patients discharged on DT were at higher risk of the composite outcomes of stroke, major bleeding, death, nonfatal MI and 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 of All-Cause Mortality and Nonfatal MI Within First Year

Three studies reported a composite endpoint of all-cause mortality and nonfatal MI during the first year of followup. One study,[152] comparing use of warfarin versus no warfarin among patients with atrial fibrillation complicating a UA/NSTEMI event, showed a significant reduction of the composite of all-cause mortality and 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[184] showed a higher incidence of the composite of all-cause mortality and nonfatal MI at 1 year among patients treated with warfarin (adjusted RR 1.20; CI, 1.00 to 1.45).

Another study[173] comparing TT versus DAPT found a nonsignificant difference in the rate of composite outcomes (all-cause mortality, nonfatal MI, revascularization and 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).

The SOE was rated insufficient for the composite outcome of all-cause mortality and nonfatal MI within the first year based on inconsistent and imprecise results.

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

Two studies reported mortality at 30 days and 6 months. One study[172] comparing TT 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[175] comparing DAPT versus TT found a significantly lower rate of all-cause mortality at 30 days among patients in the TT group (4.1% vs.6.1%, p=0.002). The SOE was rated insufficient for all-cause mortality at 30 days to 6 months based on inconsistent results and unknown precision.

Effect on All-Cause Mortality at 1 to 5 Years

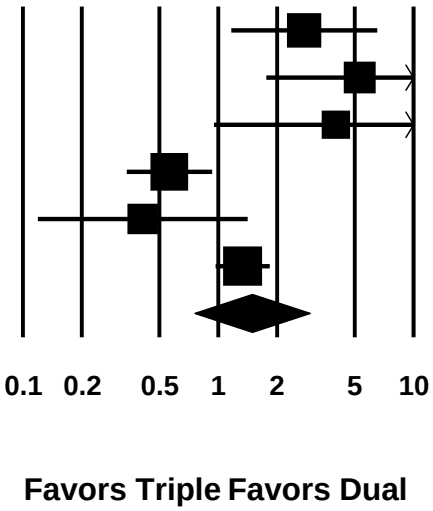
A random-effects meta-analysis of six observational studies[165,167,173,176,183,184] (3 good quality, 2 fair, 1 poor) including 32,134 UA/NSTEMI patients reporting all-cause mortality at 1 to 5 years found that the odds ratio for TT compared with DAPT was 1.50 (95% CI, 0.076 to 2.95) (Figure 53). There was evidence of heterogeneity, with a Q-value of 25.8 for 5 degrees of freedom, p=0.0001, I^2=80.62.

One study[175] reported all-cause mortality but was not included in the analysis because it had different treatment comparison groups.[175] This study comparing ASA and/or thienopyridine versus oral anticoagulant with or without platelet inhibitor 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 SOE was rated insufficient based on 6 observational studies with inconsistent results of a direct outcome and a wide confidence interval.

Figure 53. Meta-analysis of triple vs. dual therapy on all-cause mortality at 1 to 5 years

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Konstantino, 2006	2.755	1.174	6.463	0.020
Karjalainen, 2007	5.306	1.774	15.867	0.003
Maegdefessel, 2008	4.002	0.960	16.679	0.057
Ruiz-Nodar, 2008	0.562	0.343	0.923	0.023
Jang, 2011	0.411	0.120	1.404	0.156
Persson, 2011	1.334	0.978	1.819	0.069
	1.497	0.760	2.951	0.244



Effect on Nonfatal MI at 6 Months

Only one study[172] reported nonfatal MI at 6 months. This study comparing TT 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.

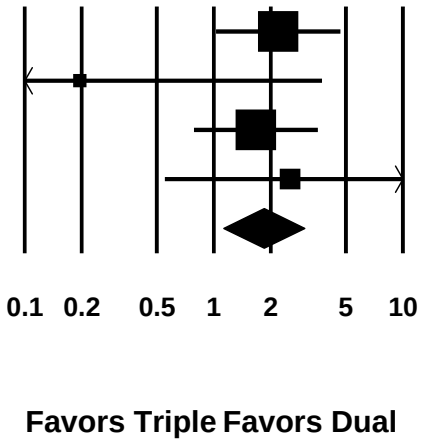
Effect on Nonfatal MI at 1 to 5 Years

A random-effects meta-analysis of four observational studies[165,167,173,183] (2 good quality, 1 fair, 1 poor) including 1425 UA/NSTEMI patients reporting nonfatal MI at 1-5 years found that the odds ratio for TT compared with DAPT was 1.85 (95% CI, 1.13 to 3.02), favoring DAPT (Figure 54). 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; 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 54. Meta-analysis of triple vs. dual therapy on nonfatal myocardial infarction at 1 to 5 years

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Karjalainen, 2007	2.192	1.037	4.635	0.040
Maegdefessel, 2008	0.196	0.010	3.705	0.277
Ruiz-Nodar, 2008	1.670	0.792	3.519	0.178
Jang, 2011	2.534	0.556	11.554	0.230
	1.848	1.130	3.022	0.014



Effect on Stroke at 6 Months

Only one study[172] reported stroke at 6 months. This study comparing TT versus warfarin plus single antiplatelet found a significantly lower rate of stroke at 6 months among patients treated with TT (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.

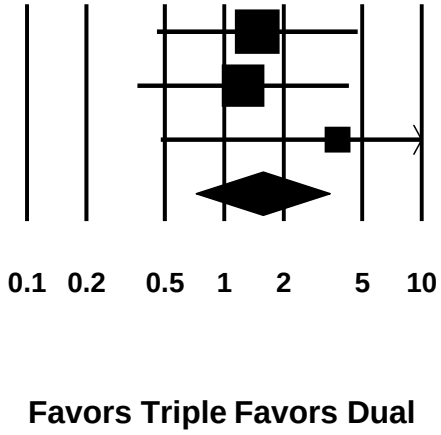
Effect on Stroke at 1 to 5 Years

A random-effects meta-analysis of three observational studies[165,173,183] (1 good quality, 1 fair, 1 poor) including 999 UA/NSTEMI patients reporting stroke at 1 to 5 years found that the odds ratio for TT compared with DAPT was 1.57 (95% CI, 0.72 to 3.43) (Figure 55). There was no evidence of heterogeneity, with a Q-value of 0.84 for 2 degrees of freedom, p=0.66.

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; CI, 0.28 to 0.98, p<0.03) as were those treated with warfarin compared with aspirin alone (RR 0.52; CI, 0.28 to 0.97, p=0.03). The SOE was rated insufficient on the basis 3 observational studies with consistent results of a direct outcome and a wide confidence interval that crosses 1.

Figure 55. Meta-analysis of triple vs. dual therapy on stroke at 1 to 5 years

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Karjalainen, 2007	1.470	0.459	4.702	0.517
Maegdefessel, 2008	1.246	0.366	4.243	0.725
Jang, 2011	3.749	0.480	29.272	0.208
	1.573	0.721	3.433	0.255



Effect on Revascularization Up to 5 Years

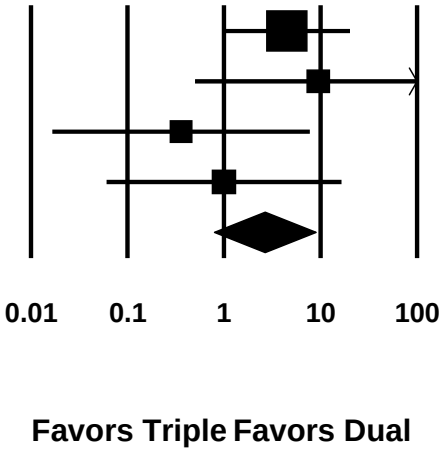
Four studies[167,172,173,183] reported revascularization between 6 months and 5 years of followup. One study[172] comparing TT versus warfarin plus single antiplatelet found no difference in the rate of repeat revascularization (unscheduled PCI) at 6 months between the two groups (10.6% vs.12.5%, p=0.50). Another study[173] comparing TT 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[183] comparing TT 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,[167] again comparing DAPT with TT 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 based on nonsignificant results from four observational studies.

Effect on Major Bleeding at 30 Days

A random-effects meta-analysis of four observational studies[133,165,173,176] (2 good quality, 2 fair) including 3476 UA/NSTEMI patients reporting major bleeding at 30 days found that the odds ratio for TT compared with DAPT was 2.68 (95% CI, 0.80 to 8.99) (Figure 56). There was no evidence of heterogeneity, with a Q-value of 3.31 for 3 degrees of freedom, p=0.35. The SOE was rated insufficient for major bleeding at 30 days based on four observational studies with inconsistent results of a direct outcome and a wide confidence interval.

Figure 56. Meta-analysis of triple vs. dual therapy on major bleeding at 30 days

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Konstantino, 2006	4.475	1.010	19.826	0.049
Karjalainen, 2007	9.518	0.510	177.787	0.131
Maegdefessel, 2008	0.360	0.017	7.622	0.512
Rossini, 2008	1.000	0.062	16.217	1.000
	2.676	0.796	8.993	0.112



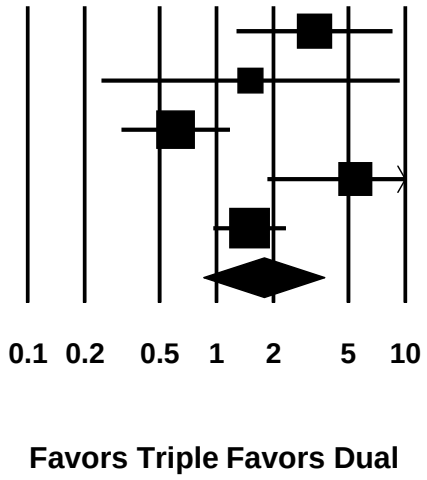
Effect on Major Bleeding at 1 to 5 Years

A random-effects meta-analysis of five observational studies[133,161,167,173,184] (4 good quality, 1 poor) including 29,340 UA/NSTEMI patients reporting major bleeding at 1 to 5 years found that the odds ratio for TT was 1.79 (95% CI, 0.86 to 3.74) (Figure 57). There was evidence of heterogeneity, with a Q-value of 15.7 for 3 degrees of freedom, p= 0.001. The I^2 value was 74.4.

Two observational studies[165,178] 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[165] 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[178] comparing aspirin to warfarin to 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 and aspirin compared with aspirin alone (OR 1.84; CI, 1.23 to 2.76). The SOE was rated insufficient for major bleeding outcomes at 1 to 5 years based on five observational studies with inconsistent results of a direct outcome and a wide confidence interval.

Figure 57. Meta-analysis of triple vs. dual therapy on major bleeding at 1 to 5 years

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Karjalainen, 2007	3.303	1.285	8.488	0.013
Rossini, 2008	1.515	0.248	9.267	0.653
Ruiz-Nodar, 2008	0.608	0.316	1.168	0.135
Jang, 2011	5.433	1.875	15.745	0.002
Persson, 2011	1.497	0.969	2.314	0.069
	1.790	0.856	3.744	0.122

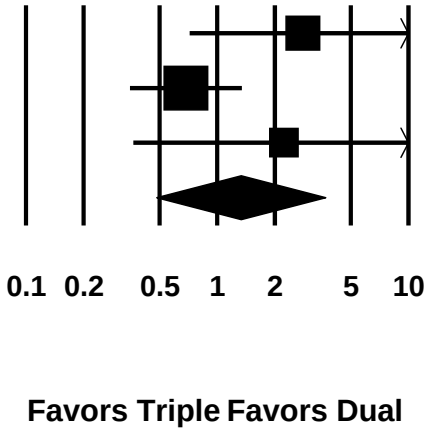


Effect on Minor Bleeding at 1 to 5 Years

A random-effects meta-analysis of three observational studies[133,167,183] (2 good quality, 1 poor) including 890 UA/NSTEMI patients reporting minor bleeding at 1 to 5 years found that the odds ratio for TT compared with DAPT was 1.33 (95% CI, 0.48 to 3.69) (Figure 58). 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 58. Meta-analysis of triple vs. dual therapy on minor bleeding at 1 to 5 years

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Rossini, 2008	2.808	0.723	10.908	0.136
Ruiz-Nodar, 2008	0.686	0.353	1.334	0.267
Jang, 2011	2.233	0.367	13.591	0.383
	1.334	0.483	3.688	0.578



Effect on Major and Minor Bleeding

One study[162] comparing DAPT with TT found a nonsignificant increase in major and minor bleeding at 18 months followup among UA/NSTEMI patients treated with TT after discharge (10.8% vs.4.9%, p=0.1). Another study[178] compared aspirin, warfarin, aspirin plus warfarin, aspirin plus a thienopyridine (DAPT), and aspirin plus warfarin plus a thienopyridine (TT). In the TT 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 TT 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 studies reported stent thrombosis at 1 and 3 years. One study[173] comparing TT 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). The other study[183] comparing TT 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 based on inconsistent and imprecise results.

Findings by Subgroup

One good-quality observational study[175] 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[175] 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; CI, 0.47 to 0.86).

Age

The same study reported all-cause mortality by age group (≤75 years vs. >75 years)[175] 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; CI, 0.53 to 0.96).

Sex

This study also reported all-cause mortality by sex[175] 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 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 11 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/revascularization, or all-cause mortality/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 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 and 1 to 5 years, minor bleeding at 1 to 5 years, major and minor bleeding, and stent thrombosis. 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. Detailed SOE ratings are shown in Table 24.

Table 24. Summary strength of evidence for UA/NSTEMI patients treated with dual antiplatelet vs. 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, or revascularization at 1 year or longer					**Insufficient SOE**
4 (4520)	1 RCT/Good quality 3 observational/2 good quality, 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 and nonfatal MI within first year					**Insufficient SOE**
3 (51,658)	3 observational/3 good quality	Inconsistent	Direct	Imprecise	One study each showed a statistically significant increase, statistically significant decrease, or statistically nonsignificant increase in events in the TT 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 30 days to 6 months					**Insufficient SOE**
2 (7075)	2 observational/2 good quality	Inconsistent	Direct	Unknown	One study found no difference, another found statistically significant lower deaths in in TT group
All-cause mortality at 1 to 5 years					**Insufficient SOE**
6 (32,134)	6 observational/3 good quality, 2 fair, 1 poor	Inconsistent	Direct	Imprecise	OR 1.50 (0.08 to 2.95)
Nonfatal MI at 6 months					**Insufficient SOE**
1 (800)	Observational/Good quality	NA	Direct	Unknown	TT 3.3% Warfarin/ASA 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) favoring DAPT
Stroke at 6 months					**Low SOE**
1 (800)	Observational/Good quality	NA	Direct	Unknown	TT 0.7% warfarin/ASA 3.4% (p=0.02), favoring TT
Stroke at 1 to 5 years					**Insufficient SOE**
3 (999)	3 observational/1 Good quality, 1 fair, 1 poor	Consistent	Direct	Imprecise	OR 1.57 (0.72 to 3.43)
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 TT groups
Major bleeding at 30 days					**Insufficient SOE**
4 (3476)	4 observational/2 good quality, 2 fair	Inconsistent	Direct	Imprecise	OR 2.68 (0.80 to 8.99)
Major bleeding at 1 to 5 years					**Insufficient SOE**
5 (29,340)	5 observational/4 good quality, 1 poor	Inconsistent	Direct	Imprecise	OR 1.79 (0.86 to 3.74)
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/2 good quality	Consistent	Direct	Imprecise	Both studies failed to show a difference between DAPT and TT 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%)

Abbreviations: ASA=aspirin; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; MI=myocardial infarction; NA=not applicable; OR=odds ratio; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction

Discussion

Key Findings and Strength of Evidence

In this comparative effectiveness review (CER), we reviewed 166 studies represented by 290 articles that directly compared antiplatelet and anticoagulant medications prescribed for the treatment of UA/NSTEMI. This included 89 studies in 439,261 patients treated with an early invasive approach or PCI-based strategy, 32 studies in 209,231 patients treated with an initial conservative strategy, and 63 studies with 604,267 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 glycoprotein IIb/IIIa inhibitors (GPIs), unfractionated heparin, enoxaparin, and dual antiplatelet therapy with clopidogrel. Numerous uncertainties remain in 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-nine unique studies evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 439,261 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 versus prasugrel, (4) bivalirudin versus a heparin-based strategy, (5) enoxaparin versus unfractionated heparin versus fondaparinux, and (6) the timing of 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, and the ones that did report outcomes 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. Table 25 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 25. Summary strength of evidence and effect estimates: upstream vs. deferred glycoprotein inhibitors[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor upstream GPI; ORs greater than 1 favor deferred GPI
Upstream vs. deferred GPI	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE=Low (6 studies, 19,662 patients) Summary OR 0.88 (0.77 to 1.01)
Composite of all-cause mortality, nonfatal MI, or revascularization after 6 months	SOE=Insufficient (4 studies, 773 patients) Summary OR 0.77 (0.46 to 1.28)
All-cause mortality at 30 days	SOE=Insufficient (10 studies, 20,521 patients) Summary OR 0.80 (0.57 to 1.11)
All-cause mortality after 6 months	SOE=Insufficient (3 studies, 673 patients) One study reported no deaths in both arms; one study reported 1 death in the upstream GPI arm; one study reported similar rates (2.0% upstream GPI, 3.6% deferred GPI)
Nonfatal MI at 30 days	SOE=Insufficient (9 studies, 20,263 patients) Summary OR 0.84 (0.65 to 1.10)
Nonfatal MI after 6 months	SOE=Insufficient (3 studies, 673 patients) One study reported 1 MI in the deferred GPI arm only; other studies reported MI rates of 12% upstream vs. 15% deferred; 10% upstream vs. 9% deferred
Revascularization at 30 days	SOE=High (6 studies, 19,454 patients) Summary OR 0.77 (0.65 to 0.92) favors upstream GPI
Revascularization after 6 months	SOE=Insufficient (3 studies, 673 patients) Summary OR 0.69 (0.34 to 1.39)
Major bleeding at 30 days	SOE=High (9 studies, 20,242 patients) Summary OR 1.24 (1.08 to 1.43) favors deferred GPI
Minor bleeding at 30 days	SOE=Insufficient (5 studies, 969 patients) Summary OR 1.58 (0.95 to 2.64)
Stent thrombosis at 30 days	SOE=Insufficient (0 studies, 0 patients)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations ; CI=confidence interval; GPI= glycoprotein IIb/IIIa inhibitor; MI=myocardial infarction; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence

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 26 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 26. Summary strength of evidence and effect estimates: 300 mg vs. 600 mg clopidogrel loading dose[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI)
300 mg vs. 600 mg clopidogrel loading dose	
Composite of cardiovascular mortality, nonfatal MI, or revascularization at 30 days	SOE=Insufficient (1 study, 119 patients) Lower rate in 600 mg group (10.4% vs. 23.8%)
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days	SOE=Low (1 study, 25,086 patients) No difference found, HR 0.94 (0.83 to 1.06), in this large, good-quality RCT sufficiently powered to assess this composite endpoint
Composite of cardiovascular mortality, nonfatal MI, or recurrent ACS at 30 days	SOE=Insufficient (1 study, 387 patients) 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 study, 103 patients) 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 study, 255 patients) 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 study, 256 patients) No difference in event rate between groups (13.3% vs. 13.2%)
All-cause mortality at 30 days	SOE=Low (3 studies, 25,444 patients) Two small studies reported no deaths in both groups; no difference found, HR 0.93 (0.83 to 1.05), in the large, good-quality RCT
All-cause mortality at 6 months	SOE=Insufficient (1 study, 256 patients) Three deaths in 300 mg group, 1 death in 600 mg group
Cardiovascular mortality at 30 days	SOE=Low (3 studies, 25,497 patients) No difference found, HR 0.95 (0.81 to 1.13), in the large, good-quality RCT
Nonfatal MI at 30 days	SOE=Low (5 studies, 25,821 patients) OR 1.74 (0.99 to 3.06)

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Nonfatal MI at 6 months	SOE=Insufficient (1 study, 256 patients) 600 mg group 5.0% vs. 300 mg group 8.6%, p=0.26
Nonfatal stroke at 30 days	SOE=Insufficient (2 studies, 25,378 patients) 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 study, 256 patients) Only one stroke in overall cohort (600 mg group)
Revascularization at 30 days	SOE=Insufficient (3 studies, 477 patients) Low overall event rate ranging from 0 to 1.3% in 300 mg group, 0 to 4.8% in 600 mg group; disparate results
Revascularization after 6 months	SOE=Insufficient (1 study, 256 patients) 600 mg group 3.3% vs. 300 mg group 2.3%, p=0.64
Major bleeding at 30 days	SOE=Insufficient (6 studies, 26,206 patients) Three studies reported no bleeding events; inconsistent findings from three other studies with largest study reporting HR 1.09 (0.89 to 1.34)
Minor bleeding at 30 days	SOE=Insufficient (5 studies, 25,819 patients) Inconsistent findings with incidence in 300 mg loading dose group ranging from 0.8% to 9.5% compared with 600 mg loading dose group ranging from 0.8% to 3.9%
Stent thrombosis at 30 days	SOE=Low (1 study, 17,263 patients) Large study reported HR 0.68 (0.55 to 0.85) favoring 600 mg loading dose

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ACS=acute coronary syndrome; CI=confidence interval; CV=cardiovascular; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; NA=not applicable; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence

Clopidogrel Versus Ticagrelor Versus Prasugrel

In our analysis of studies comparing clopidogrel, ticagrelor, and prasugrel, three studies reported a lower incidence of the composite outcome of cardiovascular mortality, nonfatal MI and 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, and major 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 one 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 27 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/stroke, prior coronary revascularization, the performance of PCI after randomization, type of coronary stent, and geographic location. 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 27. Summary strength of evidence and effect estimates: clopidogrel vs. ticagrelor vs. prasugrel[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Clopidogrel vs. ticagrelor vs. prasugrel	
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days	SOE=Moderate (3 studies, 33,216 patients) Ticagrelor (4.3% and 4.8%) and prasugrel (5.7%) were both associated with lower composite endpoints than clopidogrel (3.8%, 5.4%, and 7.4%).
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke after 1 year	SOE=Moderate (2 studies, 32,232 patients) Ticagrelor (10.6%) and prasugrel (9.9%) were both associated with lower composite endpoints than clopidogrel (12.6%).
Composite of cardiovascular mortality, nonfatal MI, or revascularization at 15 months	SOE=Low (1 study, 13,608 patients) HR (95% CI): 0.81 (0.73 to 0.87) favors prasugrel
All-cause mortality at 30 days	SOE=Insufficient (1 study, 984 patients) Clopidogrel: 0.6% Ticagrelor: 1.9% p=0.18
All-cause mortality after 1 year	SOE=Low (2 studies, 32,232 patients) Ticagrelor (4.5%) and prasugrel (3.0%) were both associated with fewer deaths than clopidogrel (5.9% and 3.2%)
Cardiovascular mortality at 30 days	SOE=Insufficient (1 study, 984 patients) Clopidogrel: 0.6% Ticagrelor: 1.9% p=0.18
Cardiovascular mortality after 1 year	SOE=Low (2 studies, 32,232 patients) Ticagrelor (4.0%) and prasugrel (2.1%) were both associated with fewer CV deaths than clopidogrel (5.1% and 2.4%)
Nonfatal MI at 30 days	SOE=Insufficient (1 study, 984 patients) Clopidogrel: 3.5% Ticagrelor: 2.2% p=0.34
Nonfatal MI after 1 year	SOE=Low (2 studies, 32,232 patients) Ticagrelor (5.8%) and prasugrel (7.3%) were both associated with fewer MIs than clopidogrel (6.9% and 9.5%)
Nonfatal stroke at 30 days	SOE=Insufficient (1 study, 984 patients) Clopidogrel: 0.3% Ticagrelor: 0.6% p=0.57
Nonfatal stroke after 1 year	SOE=Insufficient (2 studies, 32,232 patients) One study: prasugrel 1.0% and clopidogrel 1.0%; other study: ticagrelor 1.5% and clopidogrel 1.3%
Revascularization at 30 days	SOE=Insufficient (0 studies, 0 patients)
Revascularization after 6 months	SOE=Low (1 study, 13,608 patients) HR 0.66 (0.54 to 0.81) favoring prasugrel over clopidogrel
Major bleeding at 30 days	SOE=Insufficient (1 study, 984 patients) Ticagrelor (7.1%) and clopidogrel (6.9%)

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Major bleeding after 1 year	SOE=Low (2 studies, 32,232 patients) Ticagrelor (7.9%) and clopidogrel (7.7%) had similar event rates; prasugrel (2.4%) had higher events rates than clopidogrel (1.8%)
Minor bleeding at 30 days	SOE=Insufficient (1 study, 984 patients) Clopidogrel: 1.3% Ticagrelor: 2.7% p=0.18
Stent thrombosis after 1 year	SOE=Low (2 studies, 32,232 patients) Ticagrelor (1.3%) and prasugrel (1.1%) were both associated with lower individual endpoints than clopidogrel (1.9% and 2.4%)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: CI=confidence interval; CV=cardiovascular; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; NA=not applicable; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence

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 was insufficient after 1 year. 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 was insufficient evidence, 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 a statistically nonsignificant higher incidence in stent thrombosis in patients treated with bivalirudin versus heparin-based strategy without planned GPI use at 30 days; there was insufficient evidence for this outcome in the planned GPI group. Table 28 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 28. Summary strength of evidence and effect estimates: bivalirudin vs. heparin-based strategy without and with planned glycoprotein inhibitor use[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor bivalirudin; ORs greater than 1 favor heparin-based strategy
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 study, 4571 patients) Bivalirudin (8.4%) vs. heparin without GPI (8.7%)
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE=Insufficient (2 studies, 5420 patients) One study found no difference, OR 1.19 (0.92 to 1.54); another study found a statistically significant lowering in the bivalirudin group OR 0.42 (CI 0.21 to 0.84)
Composite of all-cause mortality, nonfatal MI, or revascularization after 1 year	SOE=Insufficient (2 studies, 5420 patients) One study found no difference, OR 0.97 (0.83 to 1.13); another study found a statistically significant lowering in the bivalirudin group OR 0.58 (0.37 to 0.92).
All-cause mortality at 30 days	SOE=Insufficient(3 studies, 5822 patients) Summary OR 0.46 (0.12 to 1.81)
All-cause mortality after 6 months	SOE=Insufficient (2 studies, 5420 patients) Disparate results in two RCTs: bivalirudin 1.2% vs. heparin 2.4%; bivalirudin 1.9% vs. heparin 1.7%
Nonfatal MI at 30 days	SOE=Insufficient (3 studies, 5822 patients) Summary OR 1.00 (0.64 to 1.55)
Nonfatal MI after 6 months	SOE=Insufficient (2 studies, 5420 patients) Disparate results in two RCTs: bivalirudin 3.3% vs. heparin 5.7%; bivalirudin 6.0% vs. heparin 5.3%
Revascularization at 30 days	SOE=Insufficient (3 studies, 5822 patients) Summary OR 1.10 (0.60 to 2.04)
Revascularization after 6 months	SOE=Insufficient (2 studies, 5420 patients) Bivalirudin-treated patients (4.1% and 11.2%) vs. heparin treated (5.7% and 12.5%)
Major bleeding at 30 days	SOE=High (3 studies, 5822 patients) Summary OR 0.63 (0.47 to 0.85) favoring bivalirudin
Minor bleeding at 30 days	SOE=Low (3 studies, 5822 patients) Summary OR 0.64 (0.43 to 0.95) favoring bivalirudin
Stent thrombosis at 30 days	SOE=Insufficient (3 studies, 5822 patients) Summary OR 1.42 (0.64 to 3.15)
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 studies, 12,287 patients) Summary OR 0.87 (0.78 to 0.97) favoring bivalirudin
Composite of all-cause mortality, nonfatal MI, or revascularization, at 30 days	SOE=High (3 studies, 12,287 patients) Summary OR 1.07 (0.95 to 1.22)
Composite of all-cause mortality, nonfatal MI, or revascularization after 1 year	SOE=Insufficient (2 studies, 10,566 patients) Both studies found no difference between treatments, OR 1.11 (0.74 to 1.63); and OR 1.08 (0.92 to 1..25)
All-cause mortality at 30 days	SOE=Insufficient (3 studies, 12,287 patients) Summary OR 1.21 (0.89 to 1.65)
All-cause mortality after 6 months	SOE=Insufficient (2 studies, 10,566 patients) One study (3.8% bivalirudin, 3.8% GPI); other study (0.9% bivalirudin, 1.3% GPI, p=0.46)
Nonfatal MI at 30 days	SOE=Moderate (3 studies, 12,287 patients) Summary OR 1.06 (0.92 to 1.23)
Nonfatal MI after 6 months	SOE=Insufficient (2 studies, 10,566 patients) Bivalirudin-treated patients (7.8% and 8.1%) vs. heparin (6.9 and 7.6%)

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor bivalirudin; ORs greater than 1 favor heparin-based strategy
Revascularization at 30 days	SOE=Insufficient (3 studies, 12,287 patients) Summary OR 1.11 (0.86 to 1.42)
Revascularization after 6 months	SOE=Low (2 studies, 10,566 patients) Higher event rate in bivalirudin-treated patients (8.7% and 11.7%) compared with heparin-treated patients (8.4% in both studies)
Major bleeding at 30 days	SOE=High (3 studies, 12,287 patients) OR 0.52 (0.43 to 0.63) favoring bivalirudin
Minor bleeding at 30 days	SOE=High (3 studies, 12,287 patients) OR 0.50 (0.42 to 0.59) favoring bivalirudin
Stent thrombosis at 30 days	SOE=Insufficient (2 studies, 10,936 patients) Bivalirudin 0.7 to 1.0%, heparin 0.6 to 0.8%)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: CI=confidence interval; CV=cardiovascular; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; NA=not applicable; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence

Enoxaparin Versus Unfractionated Heparin Versus Fondaparinux

In our analysis of studies comparing enoxaparin, unfractionated heparin, 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, unfractionated heparin, 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 29 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 29. Summary strength of and effect estimates: enoxaparin vs. unfractionated heparin vs. fondaparinux (percutaneous coronary intervention cohort)

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Enoxaparin vs. unfractionated heparin vs. fondaparinux	
Composite ischemic endpoints at 7 days	SOE=Low (1 study, 3987 patients) HR 0.89 (0.75 to 1.05), No difference between enoxaparin and UFH (adequately powered for noninferiority hypothesis)
Composite ischemic endpoints at 30 days	SOE=Low (4 studies, 34,022 patients) Similar rates of composite events in two studies of enoxaparin vs. UFH (14% vs. 14.5% and 14% vs. 16.1%), one study of fondaparinux vs. UFH (4.2% vs. 6%), and one study of enoxaparin vs. fondaparinux (7.4% vs. 7.4%)

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Composite of all-cause mortality, nonfatal MI, or revascularization after 6 months	SOE=Low (1 study, 20,078 patients) No difference between enoxaparin (10.2%) and fondaparinux (10.1%) adequately powered for a noninferiority hypothesis
Major bleeding at 30 days	SOE=Low (4 studies, 69,908 patients) One RCT showed lower events with fondaparinux (3.1%)vs. enoxaparin (5.0%); one RCT showed lower events with UFH (7.6%) vs. enoxaparin (9.1%). Two observational studies of UFH v s. enoxaparin had conflicting results (2.7% UFH vs. 1.8% enoxaparin; 7% UFH vs. 6.7% enoxaparin)

Abbreviations: CI=confidence interval; CV=cardiovascular; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; NA=not applicable; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence

Clopidogrel Pretreatment Versus Deferred Strategy

Two RCTs and two observational studies directly compared a clopidogrel pretreatment strategy with a deferred strategy (clopidogrel at the time of PCI). These studies had mixed results; however, in the subgroup of patients with UA/NSTEMI, those pretreated with clopidogrel had fewer clinical events than those treated with in-laboratory clopidogrel.

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 evidence. Patients pretreated with clopidogrel and randomized to upstream GPI use had a trend toward fewer composite ischemic outcomes at 30 days when compared with patients randomized to deferred GPI use. There was insufficient evidence for the composite outcome at 96 hours, the composite of all-cause mortality, nonfatal MI, or rehospitalization at 30 days, and all-cause mortality 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 evidence was insufficient. There was insufficient evidence for the effect on major bleeding at 30 days in those patients treated with deferred clopidogrel and randomized to bivalirudin. In studies of patients treated with deferred clopidogrel and randomized to upstream GPI, there was insufficient evidence for composite ischemic outcomes and 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. Table 30 shows the summary SOE and effect estimates for these outcomes.

Table 30. Summary strength of evidence and effect estimates: clopidogrel upstream (pretreatment) and deferred treatment strategies[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor bivalirudin or upstream GPI; ORs greater than 1 favor UFH or deferred GPI
Clopidogrel pretreatment: Bivalirudin vs. heparin-based strategy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE=Insufficient (2 studies, 2571 patients) Both studies showed no statistically significant difference in composite event rates ranging from OR 1.11 to 1.25
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE=Insufficient (1 study, 4570 patients) Bivalirudin 21.5%, heparin 20.1%
All-cause mortality at 1 year	SOE=Insufficient (1 study, 5126 patients) Bivalirudin 16.0%, heparin 16.3%
Major bleeding at 30 days	SOE=Moderate (3 studies, 6322 patients) Summary OR 0.65 (0.49 to 0.85) favoring bivalirudin
Clopidogrel pretreatment: Upstream vs. deferred GPI use	
Composite of all-cause mortality, nonfatal MI, revascularization, or thrombotic GPI bailout at 96 hours	SOE=Insufficient (1 study, 6895 patients) Upstream GPI: 8.7% Deferred GPI: 9.4%
Composite of all-cause mortality, nonfatal MI, or rehospitalization at 30 days	SOE=Insufficient (1 study, 300 patients) Upstream GPI: 9% Deferred GPI: 10%
Composite of all-cause mortality, nonfatal MI, or ischemia/revascularization at 30 days	SOE=Low (2 studies, 638 patients) Upstream GPI: 15.7% Deferred GPI: 20.3%
All-cause mortality at 30 days	SOE=Insufficient (5 studies, 8168 patients) Summary OR (95% CI): 0.56 (0.30 to 1.05)
Major bleeding at 30 days	SOE=Moderate (5 studies, 7416 patients) Summary OR 1.49 (1.10 to 2.01) favoring deferred GPI use
Clopidogrel deferred: Bivalirudin vs. heparin-based strategy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE=Insufficient (2 studies, 2571 patients) One study showed a significant reduction favoring bivalirudin, OR 0.42 (0.21 to 0.84, p=0.02), the other study showed no difference, OR 1.05 (0.80 to 1.40).
Major bleeding at 30 days	SOE=Insufficient (2 studies, 2571 patients) One study showed no statistical difference between the groups, OR 0.32 (0.10 to 1.01) ; the other study showed a statistically significant reduction favoring bivalirudin, OR 0.53 (0.31 to 0.91, p=0.02).
Clopidogrel deferred: Upstream vs. deferred GPI use	
Composite of all-cause mortality, nonfatal MI, revascularization, or thrombotic bailout with GPI at 96 hours	SOE=Insufficient (1 study, 2271 patients) Upstream GPI: 10.3% Deferred GPI: 11.2%
All-cause mortality at 30 days	SOE=Insufficient (4 studies, 11,858 patients) Summary OR 0.97 (0.80 to 1.18)
Major bleeding at 30 days	SOE=High (3 studies, 11,698 patients) Summary OR 1.27 (1.08 to 1.50) favoring deferred GPI use

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.

Abbreviations: CI=confidence interval; CV=cardiovascular; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; NA=not applicable; OR=odds ratio; PCI=percutaneous coronary intervention; RCT=randomized controlled trial; SOE=strength of evidence

Key Question 2. Initial Conservative Approach to UA/NSTEMI

Thirty-two studies evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 209,231 patients with UA/NSTEMI treated with an initial conservative approach or a mixed population where the approach (conservative or invasive) was not presented separately. Thus we present the findings of studies comparing (1) enoxaparin versus unfractionated heparin versus fondaparinux in the conservatively managed or total population (if results by treatment strategy are not presented) and (2) GPI versus unfractionated heparin 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. 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.

Enoxaparin Versus Unfractionated Heparin Versus Fondaparinux

In our analysis of studies comparing enoxaparin, unfractionated heparin, and fondaparinux, we present the findings of UA/NSTEMI patients who received primarily initial conservative treatment. From the comparison of enoxaparin and unfractionated heparin, 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 LMWH is increasing over time in the conservatively managed population. Use of LMWH 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 to LMWH. Table 31 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 31. Summary strength of evidence and effect estimates: enoxaparin vs. unfractionated heparin vs. fondaparinux (full UA/NSTEMI cohort)[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor enoxaparin or fondaparinux; ORs greater than 1 favor UFH
Enoxaparin vs. UFH vs. fondaparinux	
Composite endpoint of all-cause mortality, nonfatal MI, revascularization, or recurrent ischemia at 48 hours to 43 days	Enoxaparin vs. UFH SOE=High (6 studies, 12,124 patients) Summary OR 0.84 (0.76 to 0.93) favoring enoxaparin
	Fondaparinux vs. UFH SOE=Low (7 studies, 32,202 patients) Summary OR 0.78 (0.67 to 0.90) favoring fondaparinux

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor enoxaparin or fondaparinux; ORs greater than 1 favor UFH
Composite ischemic outcome at 6 months	Enoxaparin vs. fondaparinux SOE=Low (1 study, 20,078 patients) Event rate similar in enoxaparin and fondaparinux groups (10.2% vs. 10.1%) in this large, good-quality RCT adequately powered for a noninferiority hypothesis
All-cause mortality at 48 hours to 43 days	Enoxaparin vs. UFH SOE=Insufficient (8 studies, 23,015 patients) Summary OR 0.98 (0.84 to 1.14)
	Fondaparinux vs. UFH SOE=Insufficient (9 studies, 43,093 patients) Summary OR 0.93 (0.71 to 1.20),
Nonfatal MI at 48 hours to 43 days	Enoxaparin vs. UFH SOE=Moderate (9 studies, 22,970 patients) Summary OR 0.85 (0.76 to 0.95) favoring enoxaparin
	Fondaparinux vs. UFH SOE=Insufficient (10 studies, 43,048 patients) Summary OR 0.85 (0.69 to 1.04)
Major bleeding at 48 hours to 43 days	Enoxaparin vs. UFH SOE=Insufficient (8 studies, 22,901 patients) Summary OR 1.11 (0.81 to 1.51)
	Fondaparinux vs. UFH SOE=Low (9 studies, 42,979 patients) Summary OR 0.69 (0.49 to 0.97) favoring fondaparinux

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: CI=confidence interval; ECG=electrocardiogram; GPI= glycoprotein IIb/IIIa inhibitor; KQ=Key Question; MI=myocardial infarction; RCT=randomized controlled trial; SOE=strength of evidence; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

GPI Plus UFH Versus UFH Alone

In our analysis of studies comparing GPIs with unfractionated heparin, we present the findings of UA/NSTEMI patients who received primarily initial conservative treatment. Adding GPIs to unfractionated heparin 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. Table 32 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 LMWH). 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 32. Summary strength of evidence and effect estimates: glycoprotein inhibitor plus unfractionated heparin vs. unfractionated heparin alone[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor GPI plus UFH; ORs greater than 1 favor UFH alone
GPI vs. UFH	
Composite ischemic events up to 30 days	SOE=Moderate (11 studies, 47,725 patients) 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)
Mortality up to 30 days	SOE=High (9 studies, 24,699 patients) Summary OR 0.80 (0.67 to 0.96), favoring GPI
Nonfatal MI up to 30 days	SOE=Moderate (9 studies, 24,699 patients) Summary OR 0.79 (0.61 to 1.02)
Recurrent ischemia up to 30 days	SOE=Insufficient (6 studies, 5755 patients) Summary OR 0.81 (0.56 to 1.18)
Revascularization up to 30 days	SOE=Insufficient (2 studies, 279 patients) Low number of events reported in both trials, with fewer in GPI groups
Major bleeding at 30 days	SOE=Insufficient (4 studies, 18,855 patients) Summary OR 1.13 (0.80 to 1.59)
Minor bleeding up to 30 days	SOE=High (5 studies, 22,259 patients) Summary OR 1.62 (1.20 to 2.19), favoring heparin alone

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: CI=confidence interval; ECG=electrocardiogram; GPI= glycoprotein IIb/IIIa inhibitor; KQ=Key Question; 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

Sixty-three studies evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 604,267 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 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 versus triple antiplatelet 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 study reporting higher bleeding rates in the low-dose (81 mg) group and another study reporting higher rates in the

high-dose group (162 mg). Differences in the consistency of the results may be due to the fact that the Harjai[129] and So[159] studies were smaller, single-center studies that had higher rates of clopidogrel use (53% and 99% respectively) , while the Aronow[163] and Quinn[180] studies were secondary analyses of larger RCTs (i.e., BRAVO, Gusto IIb and PURSUIT), one of which did not allow use of thienopyridines and the other study did not report its use. In addition, the doses of aspirin compared differed among the four studies. Table 33 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. 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.

Table 33. Summary strength of evidence and effect estimates: low-dose vs. high-dose aspirin[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) HRs less than 1 favor high-dose aspirin; HRs greater than 1 favor low-dose aspirin
Low-dose vs. high-dose aspirin	
Composite of all-cause mortality, nonfatal MI, or stroke at 6 months	SOE=Insufficient (1 study, 20,469 patients) HR 0.92 (0.79 to 1.07)
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE=Insufficient (3 studies, 9249 patients) Low-dose ASA and high-dose ASA had similar rates of ischemic events in all 3 studies
All-cause mortality at 6 months	SOE=Insufficient (1 study, 20,469 patients) HR 0.89 (0.72 to 1.10)
All-cause mortality at 1 year	SOE=Insufficient (2 studies, 6409 patients) One study (ASA/clopidogrel) showed no difference between doses, the other found that high-dose ASA (monotherapy) reduced mortality
Nonfatal MI at 6 months	SOE=Low (1 study, 20,469 patients) HR 0.79 (0.64 to 0.98) favoring high-dose ASA
Nonfatal MI at 1 year	SOE=Insufficient (1 study, 4589 patients) HR 0.99 (0.66 to 1.48)
Stroke at 6 months	SOE=Insufficient (1 study, 20,469 patients) HR 1.59 (0.95 to 2.65)
Stroke at 1 year	SOE=Insufficient (1 study, 4589 patients) HR 1.37 (0.94 to 2.00)
Revascularization at 1 year	SOE=Insufficient (2 studies, 6429 patients) One study (ASA/clopidogrel) showed no difference between doses, the other study (ASA monotherapy) showed more events with high dose
Major bleeding at 1 year	SOE=Insufficient (2 studies, 7409 patients) One study had high bleeding rates in low-dose group; other study had high rates in high-dose group

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

Single 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 4 studies (2 RCTs and 2 observational registries). While 6 studies (2 RCTs 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. Table 34 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. SOE for subgroup findings was rated insufficient given the small number of studies reporting results for each subgroup.

Table 34. Summary strength of evidence and effect estimates: single vs. dual antiplatelet therapy[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Single vs. dual antiplatelet therapy	
Composite ischemic outcomes in-hospital to 1 year	SOE=High (4 studies, 152,601 patients) All studies showed statistically significant lowering of composite events in dual antiplatelet arm, ORs/RRs 0.69 to 0.91
Stroke in-hospital to 1 year	SOE=Insufficient (5 studies, 158,840 patients) 4 out of 5 studies showed no statistically significant difference in stroke rates
Nonfatal MI in-hospital to 1 year	SOE=High (4 studies, 152,601 patients) All studies showed fewer recurrent MIs in dual antiplatelet group, ORs/RRs 0.77 to 0.86
All-cause mortality in-hospital to 1 year	SOE=Moderate (6 studies, 160,171 patients) All studies showed fewer deaths in the dual antiplatelet group ranging from OR/RR 0.66 to OR/RR 0.93
Major bleeding in-hospital to 9 months	SOE=Insufficient (3 studies, 148,311 patients) 2 studies showed a reduction in major bleed in dual antiplatelet group (1 statistically significant [16% vs. 21%], 1 not statistically significant)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

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 reduces the rate of composite ischemic events (all-cause mortality, nonfatal MI, or stroke) compared with therapy less than 6 months 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 in 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 benefitted from longer dual antiplatelet therapy more than patients receiving a bare metal stent. Evidence was insufficient for the outcomes of cardiovascular mortality (2 studies), nonfatal MI (5 studies), stroke (2 studies), and revascularization (3 studies). Rates of stent thrombosis (5 studies) were higher when DAPT was stopped within 30 days or 6 months, but the differences between therapies beyond 6 months were nonsignificant. 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, and the other RCT showing no significant increase in major bleed among patients treated with 28 days compared with 1 year. 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 35 shows summary SOE and effect estimates for these outcomes.

Three studies (one good-quality RCT and two observational of good and fair quality) reported variations in treatment effectiveness by subgroup. Subgroups analyzed were diabetes (2 studies), sex (1), age (1), chronic renal disease (1), and stent type (2). No differences in composite ischemic events were found among the different subgroup comparisons. SOE was low based on the small number of studies that reported subgroup findings and the imprecise estimates of effect.

Table 35. Summary strength of evidence and effect estimates: short-term vs. long-term dual antiplatelet therapy[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Short-term vs. long-term dual antiplatelet therapy	
Composite of all-cause mortality and nonfatal MI within 2 years	SOE=Insufficient (2 studies, 3468 patients) One observational study showed discontinuation before 6 months increased events; other RCT showed no difference between 6- and 24-month therapy
Composite of all-cause mortality and stroke at 2 years	SOE=Insufficient (1 study, 2013 patients) One RCT reported no difference between 6- and 24-month therapy
Composite all-cause mortality, nonfatal MI and revascularization at 6 months and 1 year	SOE=Insufficient (2 studies, 3258 patients) Both studies (1 RCT, 1 observational) found similar rates between short- and long-term therapy

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Composite all-cause mortality, nonfatal MI and stroke at 30 days, 1 year, and 2 years	SOE=Low (3 studies, 5133 patients) 2 RCTs found statistically significant reductions in events from long-term DAPT at 6 months and 1 year. One RCT found no difference between 6- and 24-month therapy
All-cause mortality at 6 months, 1 year, and 2 years	SOE=Low (5 studies, 6275 patients) 3 RCTs showed statistically significant reduction with longer therapy (2 studies comparing 30 days to 6 months; 1 study comparing 6 and 24 months); DES patients benefited more than BMS patients in an observational study; another observational study reported higher mortality in patients who discontinued DAPT within first 6 months of discharge
Cardiovascular mortality at 6 months and 2 years	SOE=Insufficient(2 studies, 3017 patients) Both RCTs found similar rates between short-and long-term therapy (30 day vs. 6 months and 6 months vs. 24 months)
Nonfatal MI at 6 months, 1 year, and 2 years	SOE=Insufficient (5 studies, 6275 patients) 4 studies (3 RCTs and 1 observational) showed similar rates of MI in short- and long-term therapy groups; One observational study showed statistically significant higher risk in DES patients who discontinue clopidogrel within first 6 months
Stroke at 6 months and 2 years	SOE=Insufficient (2 studies, 3017 patients) Both RCTs found similar rates between short-and long-term therapy
Revascularization at 6 months and 1 year	SOE=Insufficient (3 studies, 4262 patients) Rates of revascularization were similar between short- and long-term therapy (30 day vs. 6 months and 6 months vs. 24 months)
Stent thrombosis at 6 months, 1 year, and 2 years	SOE=Low (5 studies, 11,255 patients) Rates of stent thrombosis were higher when clopidogrel was stopped within 30 days or 6 months from two observational studies. Three studies (2 RCTs and 1 observational) showed no statistically significant difference in event rates at 1 or 2 years.
Major bleeding at 1 and 2 years	SOE=Insufficient (2 studies, 4129 patients) One RCT showed a statistically significant lower rate of major bleed with clopidogrel with 6-month treatment; the other RCT showed no statistically significant difference in rates with 1-year treatment
Minor bleeding at 1 and 2 years	SOE=Insufficient (2 studies, 4129 patients) Both RCTs found no difference at 1 and 2 years

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

Dual Antiplatelet Therapy With and Without Omeprazole

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 studies that compared omeprazole to placebo or no omeprazole we found insufficient evidence for an effect of omeprazole on composite ischemic events (CV mortality/nonfatal MI/stroke) at 1 year, nonfatal MI at 6 months or 1 year, stroke at 30 days and 6 months, revascularization at 1 year, and stent thrombosis at 1 year (Table 36). Use of omeprazole did not affect the rates of all-cause mortality; however, it significantly reduced the rates of upper GI bleeding from 4 randomized trials.

Table 36. Summary strength of evidence and effect estimates: dual antiplatelet therapy with and without omeprazole[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI)
Dual antiplatelet therapy with and without omeprazole	
Composite of CV mortality, nonfatal MI and stroke within 1 year	SOE=Insufficient (2 RCTs, 1 observational, 4774 patients) No statistically significant difference between omeprazole vs. placebo on composite events
All-cause mortality at 1 year	SOE=Low (2 RCTs, 1 observational, 4698 patients) One study showed lower rates of death with omeprazole OR 0.31 (0.10 to 0.97); other two studies showed statistically nonsignificant differences in event rates
Nonfatal MI at 6 months and 1 year	SOE=Insufficient (1 RCT, 1 observational, 4461 patients) No statistically significant difference in MI rates with omeprazole
Stroke at 30 days and 6 months	SOE=Insufficient (2 RCTs, 4045 patients) No statistically significant difference in TIA or CVA rates with omeprazole
Revascularization at 1 year	SOE=Insufficient (1 RCT, 1 observational, 4461 patients) No statistically significant difference in revascularization rates with omeprazole
Stent thrombosis at 1 year	SOE=Insufficient (1 RCT, 1 observational, 4461 patients) No statistically significant difference in stent thrombosis in omeprazole group
GI bleeding	SOE=Moderate (4 RCTs, 4595 patients) 3 out of 4 RCTs found statistically significant lower rates of upper GI bleed in omeprazole group

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

Dual Antiplatelet Therapy With and Without PPI

In our analysis of dual antiplatelet treatment with and without concomitant PPI therapy, we present the findings from studies (all observational) that grouped patients given different PPI medications, and compared clinical outcomes to patients who did not receive a PPI (Table 37). These patient populations were treated with aspirin plus clopidogrel. Event rates are lower in patients who are not receiving a PPI medication for the various composite outcomes, all-cause mortality after 1 year, nonfatal MI at 1 year, stroke at 1 year, revascularization at 1 year, and rehospitalization at 3 months and at 1 year. Findings based on observational studies may be confounded by selection bias, where sicker patients with more comorbidities are treated with a PPI and therefore have more adverse clinical outcomes. There was no difference between groups for all-cause mortality at 6 years. The findings were inconsistent (i.e., showing no differences between groups or showing increased event rates in the PPI group) and the evidence base insufficient for all-cause mortality within the first 3 months, cardiovascular mortality at 1 year, nonfatal MI within the first 3 months, revascularization at 6 months and 4 years, stent thrombosis at 30 days and 1 year, major bleeding at 30 days and at 1 year, GI bleeding, and minor bleeding.

Table 37. Summary strength of evidence and effect estimates: dual antiplatelet therapy with and without PPI[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor PPI use; ORs greater than 1 favor no PPI use
Dual antiplatelet therapy with and without PPI	
Composite ischemic outcomes within 1 year	SOE=Moderate (3 observational studies, 11,054 patients) All 3 studies showed higher event rates in PPI group (statistically significant in 2 studies: OR 2.0 (1.1 to 3.7); HR 3.2 (CI, 2.56 to 4.01)
Composite of all-cause mortality, nonfatal MI, or stroke at 1 year	SOE=Moderate (9 observational studies, 124,888 patients) Summary OR 1.35 (1.05 to 1.73) favoring no PPI group
Composite of all-cause mortality and nonfatal MI at 6 to 18 months	SOE=Moderate (3 observational studies, 22,094 patients) Summary OR 1.40 (1.24 to 1.59) favoring no PPI group
All-cause mortality within first 3 months	SOE=Insufficient (3 observational studies, 8941 patients) Two studies showed no differences in mortality rates; one study showed a statistically significant increase in mortality in PPI group (adjusted HR 2.2; 95% CI, 1.1 to 4.3)
All-cause mortality after 1 year	SOE=Moderate (16 observational studies, 141,474 patients) Summary OR 1.48 (1.16 to 1.89) favoring no PPI group
All-cause mortality at 6 years	SOE=Low (1 observational study, 23,200 patients) HR 1.32 (1.00 to 1.73)
Cardiovascular mortality at 1 year	SOE=Insufficient (3 observational studies, 69,296 patients) Two 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, 8941 patients) 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 1 year	SOE=Moderate (8 observational studies, 122,367 patients) Summary OR 1.65 (1.38 to 1.97), favoring no PPI group
Stroke at 1 year	SOE=Moderate (6 observational studies, 57,501 patients) Summary OR 1.46 (1.15 to 1.86), favoring no PPI group
Revascularization after 1 year	SOE=Moderate (4 observational studies, 52,576 patients) Summary OR 1.37 (1.19 to 1.58), favoring no PPI group
Revascularization at 6 months and 4 years	SOE=Insufficient (2 observational studies, 18,880 patients) Both studies showed no difference in revascularization rates
Stent thrombosis at 30 days	SOE=Insufficient (1 observational study, 3406 patients) No statistically significant difference in stent thrombosis rate between groups
Stent thrombosis at 1 year	SOE=Insufficient (4 observational studies, 23,833 patients) Summary OR 1.29 (0.94 to 1.77)
Major bleeding at 30 days	SOE=Insufficient (3 observational studies, 7496 patients) OR 1.95 (0.59 to 6.49)
Major bleeding at 1 year	SOE=Insufficient (3 observational studies, 22,138 patients) OR 1.25 (0.94 to 1.67)
GI bleeding	SOE=Insufficient (4 observational studies, 23,555 patients) Conflicting results in in-hospital and 12-18 month time points with 2 studies showing no difference and 2 studies showing a statistically significant reduction in GI bleed in PPI group
Minor bleeding	SOE=Insufficient (1 observational study, 7346 patients) No difference in minor bleed in-hospital or at 1 year
Rehospitalization at 3 months	SOE=Low (1 observational study, 3406 patients) Significant increase in rehospitalization in PPI group at 3 months, HR 1.32 (1.00 to 1.73)
Rehospitalization at 1 year	SOE=Low (5 observational studies, 25,715 patients) Summary OR 3.39 (1.88 to 6.11), favoring no PPI group

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.

Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

Aspirin Monotherapy With and Without PPI

In our analysis of aspirin monotherapy with and without concomitant PPI therapy, we presented the findings from studies that compared clinical outcomes between the grouping of patients given different PPI medications to patients who did not receive a PPI. In contrast to the previous section, these patient populations were not prescribed dual antiplatelet therapy; therefore the evaluation focuses on the addition of PPIs to aspirin monotherapy. All evidence comes from observational studies (Table 38). Patients not receiving a PPI had fewer composite ischemic events (CV mortality, nonfatal MI, or stroke) and lower all-cause mortality at 1 year of followup. Two of these studies reported rates of nonfatal MI at 1 year and both showed an increased risk of MI events in the PPI group. 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 was also insufficient evidence for stroke at 1 year.

Table 38. Summary strength of evidence and effect estimates: aspirin monotherapy with and without PPI[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor PPI use; ORs greater than 1 favor no PPI
Aspirin monotherapy with and without PPI	
Composite of CV death, nonfatal MI, or stroke at 1 year	SOE=Moderate (3 observational studies, 108,602 patients) Summary OR 1.58 (1.45 to 1.73) favoring no PPI group
All-cause mortality (in-hospital)	SOE=Insufficient (1 observational study, 2744 patients) OR 1.47 (0.67 to 3.25)
All-cause mortality at 1 year	SOE=Moderate (3 observational studies, 108,602 patients) Summary OR 1.59 (1.43 to 1.76) favoring no PPI group
Nonfatal MI (in-hospital)	SOE=Insufficient (1 observational study, 2744 patients) OR 0.99 (0.18 to 5.53)
Nonfatal MI at 1 year	SOE=Moderate (2 observational studies, 105,858 patients) Both studies showed increased risk of events in PPI group HR 1.19 to 1.39
Stroke (in-hospital)	SOE=Insufficient (1 observational study, 2744 patients) OR 3.21 (0.24 to 42.5)
Stroke at 1 year	SOE=Insufficient (3 observational studies, 108,602 patients) Summary OR 1.13 (0.94 to 1.36)
Major bleeding (in-hospital)	SOE=Insufficient (1 observational study, 2744 patients) OR 2.16 (0.17 to 27.3)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

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 11 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/revascularization, or all-cause mortality/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 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 and 1 to 5 years, minor bleeding at 1 to 5 years, major and minor bleeding, and stent thrombosis. Table 39 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 39. Summary strength of evidence and effect estimates: dual antiplatelet vs. triple therapy[a]

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor triple therapy; ORs greater than 1 favor DAPT
Dual antiplatelet vs. triple therapy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year or longer	SOE=Insufficient (4 studies, 4520 patients) 2 studies showed statistically nonsignificant differences; 2 studies showed statistically significant increases in events in DAPT group
Composite of all-cause mortality, nonfatal MI, within first year	SOE=Insufficient (3 studies, 51,658 patients) One study each showed a statistically significant increase, statistically significant decrease, or statistically nonsignificant increase in events in the TT group
All-cause mortality at 30 days to 6 months	SOE=Insufficient (2 studies, 7075 patients) One study found no difference, another found statistically significant lower deaths in in TT group
All-cause mortality at 1 to 5 years	SOE=Insufficient (6 studies, 32,134 patients) Summary OR 1.50 (0.076 to 2.95)
Nonfatal MI at 6 months	SOE=Insufficient (1 study, 800 patients) TT 3.3% Warfarin/ASA 4.5% (p=0.49)
Nonfatal MI at 1 to 5 years	SOE=Low (4 studies, 1,425 patients) Summary OR 1.85 (1.13 to 3.02) favoring DAPT
Stroke at 6 months	SOE=Low (1 study, 800 patients) TT 0.7% warfarin/ASA 3.4% (p=0.02), favoring TT
Stroke at 1 to 5 years	SOE=Insufficient (3 studies, 999 patients) Summary OR 1.57 (0.72 to 3.43)
Revascularization up to 5 years	SOE=Insufficient (4 studies, 2066 patients) No statistical difference between DAPT and TT groups
Major bleeding at 30 days	SOE=Insufficient(4 studies, 3476 patients) Summary OR 2.68 (0.80 to 8.99)
Major bleeding at 1 to 5 years	SOE=Insufficient (5 studies, 29,340 patients) Summary OR 1.79 (0.86 to 3.74)
Minor bleeding at 1 to 5 years	SOE=Insufficient (3 studies, 890 patients) Summary OR 1.33 (0.48 to 3.69)
Major and minor bleeding	SOE= Insufficient (2 studies, 21,545 patients) Both studies failed to show a difference between DAPT and TT in the combined endpoint of major and minor bleeding.

Outcome	Strength of Evidence and Effect Estimate (95% CI) ORs less than 1 favor triple therapy; ORs greater than 1 favor DAPT
Stent thrombosis	SOE=Insufficient (2 studies, 840 patients) No significant difference in rates (triple therapy 1.4 to 4.1%; dual antiplatelet 1.3 to 3.6%)

[a]Gray highlights insufficient strength of evidence when no evidence is available or when available evidence was imprecise or inconsistent to reach a conclusion.
Abbreviations: ASA=aspirin; BMS=bare metal stent; CI=confidence interval; CV=cardiovascular; DAPT=dual antiplatelet; DES=drug-eluting stent; GI=gastrointestinal; GPI= glycoprotein IIb/IIIa inhibitor; HR=hazard ratio; MI=myocardial infarction; PPI=proton pump inhibitor; RCT=randomized controlled trial; SOE=strength of evidence; TT=triple therapy; UA/NSTEMI=unstable angina/non-ST elevation myocardial infarction; UFH=unfractionated heparin

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.[190] For each key question, we discuss the findings of this report in relationship to current guidelines and previous systematic reviews or meta-analyses.

Key Question 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 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 ACC/AHA guidelines update. Our major findings mirror other meta-analyses in that upstream GPI use is not associated with a significant reduction in ischemic endpoints, the optimal loading dose of clopidogrel remains unclear, and prasugrel and ticagrelor are associated with a significant reduction in ischemic endpoints when compared with clopidogrel.

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

Due to a paucity of data on the optimal timing of oral antiplatelet agents as initial treatment for UA/NSTEMI, we performed analyses evaluating the effect of a nonrandomized treatment with either clopidogrel pretreatment or clopidogrel treatment at the time of PCI in two groups of study patients: (1) those randomized to bivalirudin versus heparin-based strategy and (2) those randomized to 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 is associated with less major bleeding than a heparin-based strategy. In patients pretreated with clopidogrel, the use of deferred GPI is 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. In patients treated with clopidogrel at the time of PCI there was less major bleeding at 30 days with the use of deferred GPI.

Key Question 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 with 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. From an indirect comparison of fondaparinux and UFH, there were 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 initial conservative approach where 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 reduces 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 did increase 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 due to the fact that the majority of these studies were performed prior to the time when an early invasive strategy was widely implemented, and they employed an initial conservative strategy followed by percutaneous revascularization after 18 to 72 hours. Furthermore, several GPI studies reported results with 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.

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,[190] show no change in the recommendation of administering a GPI (tirofiban or eptifibatide) in addition to an anticoagulant or oral antiplatelet for patients in 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 or if after angiography a percutaneous revascularization is deemed not necessary or if they do not undergo diagnostic angiography (class IIa, level of evidence C).

Key Question 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 versus dual antiplatelet therapy 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 who discontinue clopidogrel (either stop taking it or are taken off it by their doctor) within the first 6 months with either bare metal or drug-eluting stents. Guidelines recommend duration of 1 year if there is no increased risk of bleeding.

In our analysis of the use of PPIs with dual antiplatelet therapies, three randomized trials of omeprazole versus placebo failed to show any difference in ischemic events. In the observational studies comparing all types of PPI medication to no PPI medication, findings suggest that patients on a PPI do worse but are likely confounded by comorbid conditions since these findings are not seen in the randomized trials. Indeed, a recent update of the AHA/ACCF guidelines has removed the recommendation to administer PPI among patients with a history of GI bleeding.

Applicability

Studies included in this review are primarily multicenter international studies, including the United States and Canada, so the applicability of our findings does span multiple geographic locations. While many studies are also conducted outside the United States, there are similarities in UA/NSTEMI treatments internationally and should therefore not be seen as a limitation in treatment setting. However, there are two factors that limit our findings; namely, 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 acute coronary syndrome (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 did exclude studies that focused exclusively in 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 were labeled as a conservatively managed approach. Many of those types of studies are older (mid-1990s), or are 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. Importantly, since the start of this comparative effectiveness review, clopidogrel has become available as a generic medication. While two new antiplatelet medications (prasugrel and ticagrelor) were superior to clopidogrel in terms of reduction of ischemic endpoints, the cost-

effectiveness of these novel agents is not currently known. Additionally, due to the different pharmacokinetic and pharmacodynamic properties of these novel agents, the effectiveness of these agents 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, we found a growing use of low molecular weight heparin (namely, enoxaparin) based on evidence of better effectiveness and similar bleeding rates compared with unfractionated heparin from our review of observational studies. The effectiveness of fondaparinux in comparison with enoxaparin requires further study; however, our indirect analysis comparing fondaparinux with unfractionated heparin 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 recommendations suggest that GPIs should only be administered prior to PCI or for recurrent symptoms. Most of this evidence comes from our findings in the invasively managed population (KQ1).

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 of durations of 6 months to 1 year are better than shorter duration of therapy. The addition of PPIs with DAPT appears to cause more ischemic events in observational studies, but the findings across RCTs show no significant difference in clinical outcomes. 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-only 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 did treat total mortality and cardiovascular mortality as essentially similar, since the event rates of cardiovascular mortality usually dominate the event rates for total mortality.

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. Furthermore, a calculation of net benefit across studies may be less 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. Bleeding definitions were also variable across studies. In our analyses of bleeding definition we used TIMI criteria when it was 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 considerably 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. 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, unfractionated heparin, 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 acute coronary syndrome (ACS) patients, including UA/NSTEMI and STEMI patients.

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 the fact that we screened 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, and specifically related to dosage, timing, type of administration (IV or oral), and combinations of therapy. We used the framework recommended by Robinson et al.[191] to identify gaps in evidence and describe the reasons why these gaps exist. This approach considers PICOTS (Populations, Interventions, Comparators, Outcomes, Timings, and Settings of interest) to identify gaps and classifies 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 key question.

Key Question 1

In KQ 1, the primary research gap was the lack of direct comparisons of intravenous and oral combination treatment strategies. While many studies investigated the use of one oral antiplatelet versus another oral antiplatelet, there was scant data on combinations of antiplatelet and anticoagulant medications used for UA/NSTEMI patients. Our review highlights that there is a 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. Furthermore, 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 the 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 LMWH and GPI analyses—and often the data were not concordant. Future studies can address this by either 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 dual antiplatelet treatment strategy requires further study, especially within subgroups of patients at risk for bleeding complications.

Second, more studies are needed on clopidogrel duration beyond one year of ongoing treatment. There were few RCTs on this subject, and the small number of observational studies showed no difference in treatment durations 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 long-term benefit 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 use of these agents comparing effectiveness 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) show 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 if 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.

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 was administered prior to or during the PCI.
- Prasugrel and ticagrelor reduced rates of composite ischemic events (death/MI/stroke) at 30 days and 1 year in comparison to clopidogrel.
- Bivalirudin was associated with a lower incidence of major bleeding events compared with heparin-based treatment, regardless of whether a GPI administration was planned; bivalirudin also reduced 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 unfractionated heparin 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 in observational studies, the results from a small number of RCTs of omeprazole show no significant difference in clinical events compared with placebo.

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, diabetics, 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
TT	triple therapy
UA	unstable angina
UFH	unfractionated heparin
wk	week/weeks
yr	year/years