Comparative Effectiveness Review
Number 129

Effective Health Care Program

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

Executive Summary

Background

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

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

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presence of myocardial necrosis or infarction as suggested by serum tests such as creatine kinase-myocardial band, troponin I, or troponin T in NSTEMI.

Treatment Strategies for UA/NSTEMI

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

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

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

Antiplatelet and Anticoagulant Medications for UA/NSTEMI

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

Aspirin and Antiplatelet Agents

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

The antiplatelet agents belonging to the glycoprotein IIb/IIIa inhibitor (GPI) class are administered intravenously. They include abciximab, eptifibatide,

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

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

and tirofiban. Eptifibatide and tirofiban are reversible platelet inhibitors, whereas abciximab, a selective antibody, is an irreversible platelet inhibitor.

Anticoagulant Agents

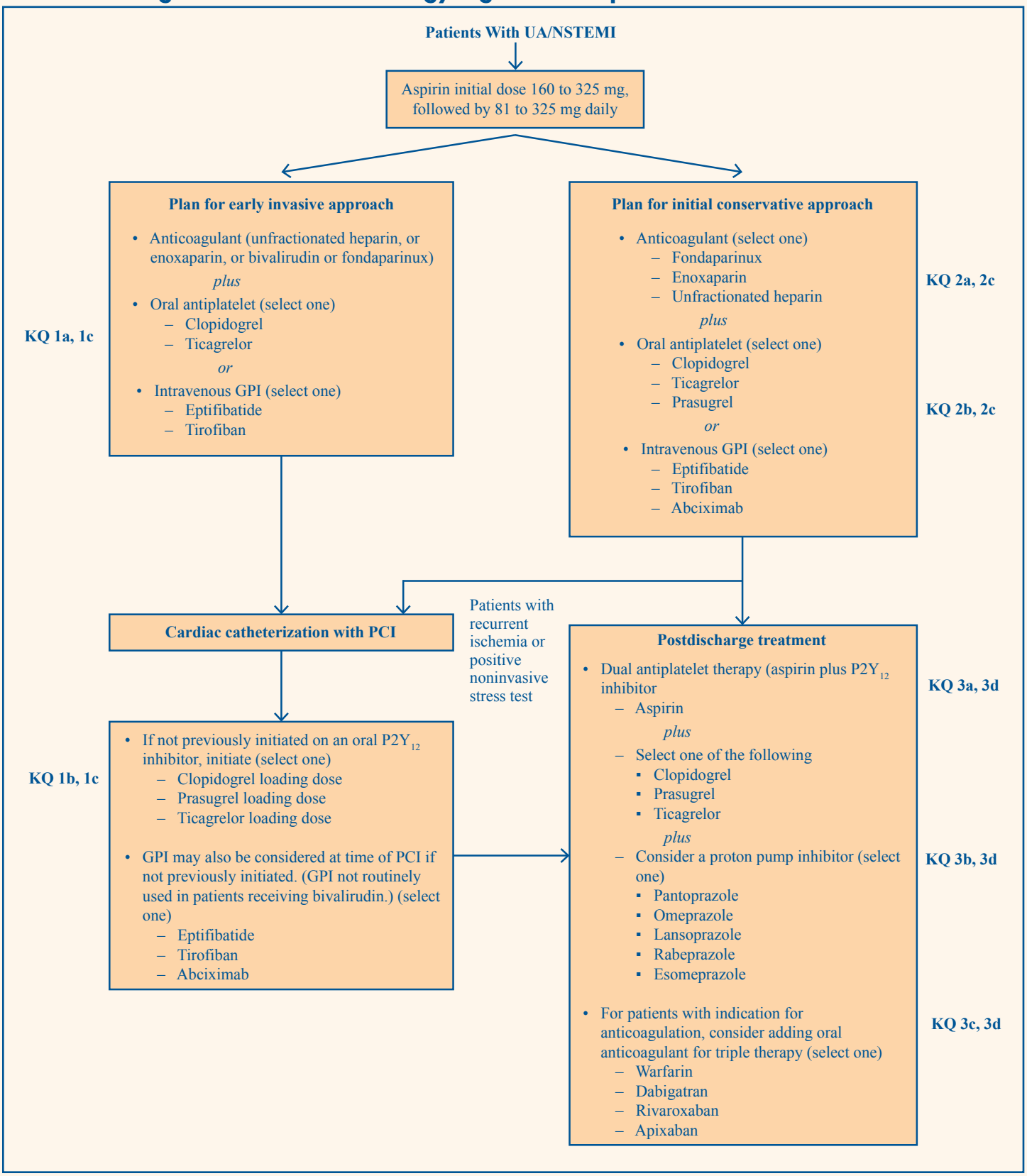
Anticoagulants used to manage patients with UA/NSTEMI include unfractionated heparin (UFH), low molecular weight heparin (enoxaparin), bivalirudin, and fondaparinux. Intravenous UFH is the traditional anticoagulant used to manage UA/NSTEMI. Because of its short biologic half-life of approximately 1 hour,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

Treatment Strategy Algorithm

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

For all patients with UA/NSTEMI, the postdischarge phase of treatment considers oral antiplatelet agents, aspirin for

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



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

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

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

Scope and Key Questions

Scope of Review

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

Key Questions

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

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

a. What are the comparative effectiveness (dose and timing) and comparative safety of an intravenous (IV) glycoprotein IIb/IIIa inhibitor versus oral antiplatelet agent as initial therapy before going to the catheterization laboratory?

b. What are the comparative effectiveness (dose and timing) and comparative safety of coadministration of IV or oral antiplatelet agents in patients undergoing percutaneous coronary intervention for improving cardiovascular outcomes? Do the effectiveness and safety vary based on which initial anticoagulant is used or the combination of anticoagulant and antiplatelet agents?

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

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

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

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

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

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

a. What are the comparative effectiveness (dose and duration) and comparative safety of the available oral antiplatelet agents given in combination with aspirin? Do the effectiveness and safety vary based on the dose of aspirin used?

b. What are the comparative effectiveness and comparative safety of proton pump inhibitors (PPIs) for reducing bleeding events in patients receiving dual antiplatelet therapy after UA/NSTEMI? Do the effectiveness and safety vary by oral antiplatelet therapy and PPI?

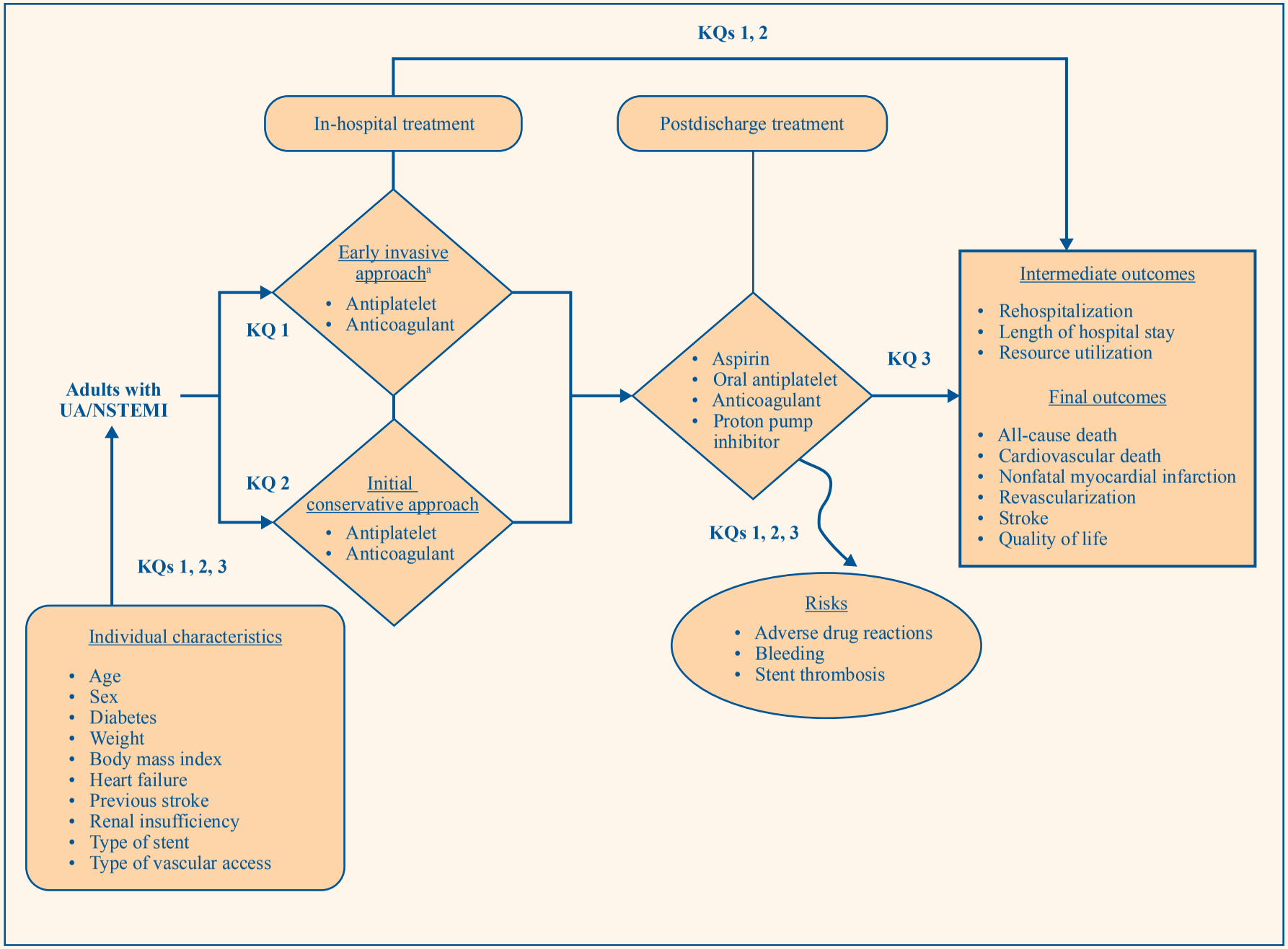
c. In patients with an indication for long-term anticoagulant therapy, what are the comparative effectiveness and comparative safety of adding an oral anticoagulant to aspirin and another antiplatelet agent for improving cardiovascular outcomes?

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

Analytic Framework

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

Figure B. Analytic framework



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

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

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

Methods

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

Input From Stakeholders

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

Literature Search Strategy

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

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

Inclusion and Exclusion Criteria

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

early invasive (KQ 1), initial conservative (KQ 2), and after hospitalization (KQ 3) with the outcomes listed in the analytic framework.

Study Selection

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

Data Extraction

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

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

Quality Assessment of Individual Studies

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

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

Data Synthesis

We summarized the primary literature by abstracting relevant continuous data (e.g., age) and categorical data (e.g., race, presence of coronary disease risk factors). Continuous variable outcomes reported by study authors included means, medians, standard deviations, interquartile ranges, ranges, and associated p-values. Dichotomous variable outcomes were summarized by proportions and associated p-values. We then determined the feasibility of completing a quantitative analysis (i.e., meta-analysis). Feasibility depended on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the reporting of results. For our main analyses, we considered meta-analysis for comparisons in which at least three studies reported the same outcome. For the KQ 2 sensitivity analyses, we grouped studies by trial size

(small, <1,000 patients; large, ≥1,000 patients) and by use (aspirin monotherapy vs. dual antiplatelet therapy) to help explain any heterogeneity, if present. Any subgroup summary estimate based on fewer than three studies is noted as such and should be interpreted with caution.

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

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

Strength of the Body of Evidence

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

Applicability

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

Results

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

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

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

Results of Literature Searches

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

Key Question 1. Early Invasive Approach for UA/NSTEMI

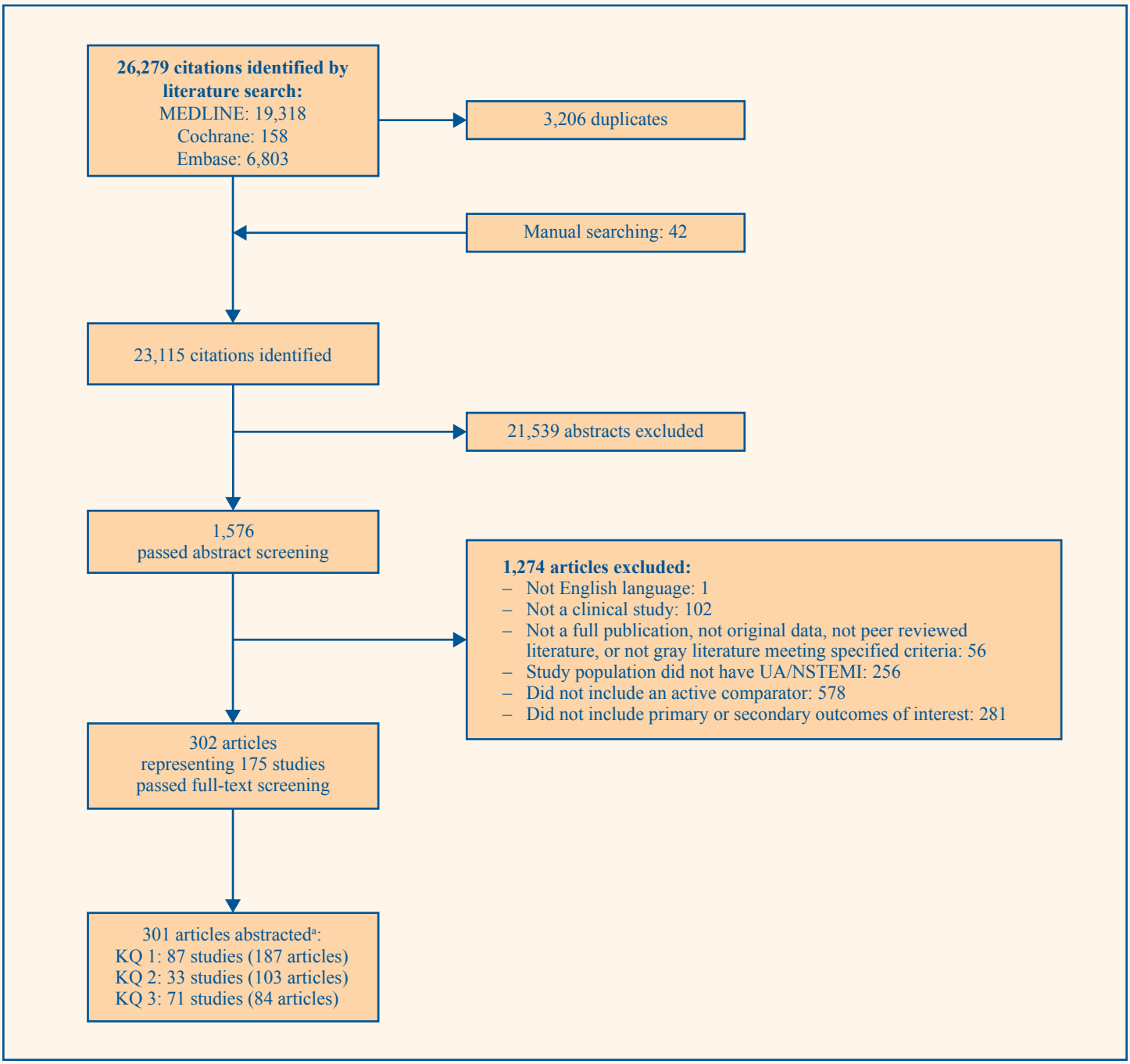
We identified 87 unique studies that evaluated the comparative effectiveness of antiplatelet medications and anticoagulant medications in 354,511 patients with UA/NSTEMI treated with an *early invasive approach* (PCI-based strategy). Six comparisons assessed dosage, timing, and combinations of antiplatelet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

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

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

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

Figure C. Literature flow diagram



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

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

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

Key Points: 300 mg Versus 600 mg Clopidogrel Loading Dose

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

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

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

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

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

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

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

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

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

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

Outcome and Timing	SOE[a] and Effect Estimate[b] (95% CI)
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Low (6 RCTs; 19,662 patients) OR 0.88 (0.77 to 1.01); no difference
Composite of all-cause mortality, nonfatal MI, or revascularization after 6 months	SOE = Insufficient (4 RCTs; 773 patients) Insufficient evidence due to imprecision: OR 0.77 (0.46 to 1.28)
All-cause mortality at 30 days	SOE=Insufficient (10 RCTs, 20,521 patients) Insufficient evidence due to inconsistency and imprecision, with a CI that crosses 1: OR 0.80 (0.57 to 1.11)

Table B. Summary strength of evidence and effect estimates: upstream versus deferred glycoprotein inhibitor (continued)	
Outcome and Timing	**SOE[a] and Effect Estimate[b] (95% CI)**
All-cause mortality at 6 months	SOE = Insufficient (3 RCTs; 673 patients) Insufficient evidence due to inconsistency and imprecision: 1 study reported no deaths in either arm; 1 study reported 1 death in the upstream GPI arm; 1 study reported similar rates (2.0% upstream GPI, 3.6% deferred GPI)
Nonfatal MI at 30 days	SOE = Insufficient (9 RCTs; 20,263 patients) Insufficient evidence due to inconsistency and imprecision: OR 0.84 (0.65 to 1.10)
Nonfatal MI at 6 months	SOE = Insufficient (3 RCTs; 673 patients) Insufficient evidence due to inconsistency and imprecision: 1 study reported 1 MI in the deferred GPI arm only; 2 other studies reported MI rates of 12% upstream vs. 15% deferred, and 10% upstream vs. 9% deferred
Revascularization at 30 days	SOE = High (6 RCTs; 19,454 patients) OR 0.77 (0.65 to 0.92); favors upstream GPI
Revascularization at 6 months	SOE = Insufficient (3 RCTs; 673 patients) Insufficient evidence due to inconsistency and imprecision: OR 0.69 (0.34 to 1.39)
Major bleeding at 30 days	SOE = High (9 RCTs; 20,242 patients) OR 1.24 (1.08 to 1.43); favors deferred GPI
Minor bleeding at 30 days	SOE = Insufficient (5 RCTs; 969 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.58 (0.95 to 2.64)
Stent thrombosis at 30 days	SOE = Insufficient (0 studies; 0 patients)

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

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

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

Table C. Summary strength of evidence and effect estimates: 300 mg versus 600 mg clopidogrel loading dose	
Outcome and Timing	**SOE[a] and Effect Estimate (95% CI)**
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days	SOE = Low (1 RCT; 25,086 patients) HR 0.94 (0.83 to 1.06) in this large good-quality RCT sufficiently powered to assess this composite endpoint; no difference
Composite of cardiovascular mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (1 RCT; 119 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (10.4% vs. 23.8%)
Composite of cardiovascular mortality, nonfatal MI, or recurrent ACS at 30 days	SOE = Insufficient (1 RCT; 387 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (4.8% vs. 12.3%)
Composite of all-cause mortality, nonfatal MI, revascularization, or rehospitalization at 30 days	SOE = Insufficient (1 RCT; 103 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (5.9% vs. 11.4%)
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (1 RCT; 255 patients) Insufficient evidence due to imprecision: lower rate in 600 mg group (4.0% vs. 11.6%)
Composite of all-cause mortality, nonfatal MI, nonfatal stroke, or rehospitalization at 6 months	SOE = Insufficient (1 RCT; 256 patients) Insufficient evidence due to imprecision: no difference in event rates between groups (13.3% vs. 13.2%)
All-cause mortality at 30 days	SOE = Low (3 RCTs; 25,802 patients) 2 small studies reported no deaths in either group; largest study reported HR 0.93 (0.83 to 1.05); no difference

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

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

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

Table D. Summary strength of evidence and effect estimates: clopidogrel versus ticagrelor or prasugrel (percutaneous coronary intervention cohort)	
Outcome and Timing	**SOE[a] and Effect Estimate (95% CI)**
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (2 RCTs; 19,608 patients) Insufficient evidence due to inconsistency and imprecision: compared with clopidogrel (3.8% and 5.4%), ticagrelor had mixed results (4.3% and 4.8%)
	Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) Compared with clopidogrel (7.4%), prasugrel (5.7%) was associated with lower composite endpoint; favors prasugrel

Table D. Summary strength of evidence and effect estimates: clopidogrel versus ticagrelor or prasugrel (percutaneous coronary intervention cohort) (continued)	
Outcome and Timing	**SOE[a] and Effect Estimate (95% CI)**
Composite of cardiovascular mortality, nonfatal MI, or nonfatal stroke after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (12.6%), ticagrelor (10.6%) was associated with lower composite endpoint; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) HR 0.81 (0.73 to 0.90) Compared with clopidogrel (12.1%), prasugrel (9.9%) was associated with lower composite endpoint at 15 months; favors prasugrel
Composite of cardiovascular mortality, nonfatal MI, or revascularization at 15 months	Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) HR 0.81 (0.73 to 0.87); favors prasugrel
All-cause mortality at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 0.6%, ticagrelor 1.9%; p = 0.18
All-cause mortality after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (5.9%), ticagrelor (4.5%) was associated with fewer deaths; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Low (1 RCT; 13,608 patients) Compared with clopidogrel (3.2%), prasugrel (3.0%) was associated with fewer deaths; favors prasugrel
Cardiovascular mortality at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 0.6%, ticagrelor 1.9%; p = 0.18
Cardiovascular mortality after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (5.1%), ticagrelor (4.0%) was associated with fewer cardiovascular deaths; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Low (1 RCT; 13,608 patients) Compared with clopidogrel (2.4%), prasugrel (2.1%) was associated with fewer cardiovascular deaths; favors prasugrel
Nonfatal MI at 30 days	Clopidogrel vs. ticagrelor: SOE = Insufficient (1 RCT; 984 patients) Insufficient evidence due to imprecision: clopidogrel 3.5%, ticagrelor 2.2%; p = 0.34
Nonfatal MI after 1 year	Clopidogrel vs. ticagrelor: SOE = Moderate (1 RCT; 18,624 patients) Compared with clopidogrel (6.9%), ticagrelor (5.8%) was associated with fewer MIs; favors ticagrelor Clopidogrel vs. prasugrel: SOE = Moderate (1 RCT; 13,608 patients) Compared with clopidogrel (9.5%), prasugrel (7.3%) was associated with fewer MIs; favors prasugrel

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

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

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

Table E. Summary strength of evidence and effect estimates: bivalirudin versus heparin-based strategy without and with planned glycoprotein inhibitor use	
Outcome and Timing	**SOE[a] and Effect Estimate[b] (95% CI)**
Bivalirudin vs. Heparin-Based Strategy Without Planned GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or major bleeding at 30 days	SOE = Insufficient (1 RCT; 4,571 patients) Insufficient evidence due to imprecision: bivalirudin 8.4% vs. heparin 8.7%
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: 1 study found no difference, OR 1.19 (0.92 to 1.54); 1 study found statistically significant lowering in the bivalirudin group, OR 0.42 (0.21 to 0.84)
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: 1 study found no difference, OR 0.97 (0.83 to 1.13); 1 study found statistically significant lowering in the bivalirudin group, OR 0.58 (0.37 to 0.92)
All-cause mortality at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to inconsistency and imprecision: OR 0.46 (0.12 to 1.81)
All-cause mortality after 6 months	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: disparate results in 2 RCTs: bivalirudin 1.2% vs. heparin 2.4%; bivalirudin 1.9% vs. heparin 1.7%
Nonfatal MI at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.00 (0.64 to 1.55)
Nonfatal MI after 6 months	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to inconsistency and imprecision: disparate results in 2 RCTs: bivalirudin 3.3% vs. heparin 5.7%; bivalirudin 6.0% vs. heparin 5.3%
Revascularization at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.10 (0.60 to 2.04)
Revascularization after 6 months	SOE = Insufficient (2 RCTs; 5,420 patients) Insufficient evidence due to imprecision: lower rate of revascularization in bivalirudin-treated patients (4.1% and 11.2%) vs. heparin-treated (5.7% and 12.5%)
Major bleeding at 30 days	SOE = High (3 RCTs; 5,822 patients) OR 0.63 (0.47 to 0.85); favors bivalirudin
Minor bleeding at 30 days	SOE = Low (3 RCTs; 5,822 patients) OR 0.64 (0.43 to 0.95); favors bivalirudin
Stent thrombosis at 30 days	SOE = Insufficient (3 RCTs; 5,822 patients) Insufficient evidence due to imprecision: OR 1.42 (0.64 to 3.15)
Bivalirudin vs. Heparin-Based Strategy With Planned GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or major bleeding at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 0.87 (0.78 to 0.97); favors bivalirudin
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 1.07 (0.95 to 1.22); no difference
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Low (2 RCTs; 10,566 patients) Both RCTs found no difference between treatments: OR 1.11 (0.74 to 1.63) and OR 1.08 (0.92 to 1.25); no difference
All-cause mortality at 30 days	SOE = Insufficient (3 RCTs; 12,287 patients) Insufficient evidence due to imprecision: OR 1.21 (0.89 to 1.65)
All-cause mortality after 6 months	SOE = Insufficient (2 RCTs; 10,566 patients) Insufficient evidence due to imprecision: similar event rate in 1 RCT (3.8% bivalirudin, 3.8% GPI); slightly lower event rate in other RCT (0.9% bivalirudin,1.3% GPI; p = 0.46)

Table E. Summary strength of evidence and effect estimates: bivalirudin versus heparin-based strategy without and with planned glycoprotein inhibitor use (continued)	
Outcome and Timing	**SOE[a] and Effect Estimate[b] (95% CI)**
Bivalirudin vs. Heparin-Based Strategy With Planned GPI Use (continued)	
Nonfatal MI at 30 days	SOE = Moderate (3 RCTs; 12,287 patients) OR 1.06 (0.92 to 1.23); no difference
Nonfatal MI after 6 months	SOE = Moderate (2 RCTs; 10,566 patients) Higher event rate with bivalirudin (7.8% and 8.1%) vs. heparin (6.9% and 7.6%); favors heparin
Revascularization at 30 days	SOE = Low (3 RCTs; 12,287 patients) OR 1.11 (0.86 to 1.42); favors bivalirudin
Revascularization after 6 months	SOE = Low (2 RCTs; 10,566 patients) Higher event rate with bivalirudin (8.7% and 11.7%) vs. heparin (8.4% in both studies); favors heparin
Major bleeding at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 0.52 (0.43 to 0.63); favors bivalirudin
Minor bleeding at 30 days	SOE = High (3 RCTs; 12,287 patients) OR 0.49 (0.42 to 0.59); favors bivalirudin
Stent thrombosis at 30 days	SOE = Insufficient (2 RCTs; 10,936 patients) Insufficient evidence due to imprecision: similar event rates between treatment arms in both studies (bivalirudin 0.7% to 1.0%; heparin 0.6% to 0.8%)

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

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

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

Table F. Summary strength of evidence and effect estimates: enoxaparin versus unfractionated heparin versus fondaparinux (percutaneous coronary intervention cohort)	
Outcome and Timing	**SOE[a] and Effect Estimate (95% CI)**
Composite ischemic endpoints prior to 7 days	Enoxaparin vs. UFH: SOE = Low (1 RCT; 3,987 patients) HR 0.89 (0.75 to 1.05); no difference (adequately powered for noninferiority hypothesis)
	Fondaparinux vs. UFH: SOE = Insufficient (1 RCT; 350 patients) Insufficient evidence due to imprecision: 4.2% vs. 6%
Composite ischemic endpoints at 30 days	Enoxaparin vs. UFH: SOE = Low (2 RCTs; 10,773 patients) 14% vs. 14.5% and 14% vs. 16.1%; no difference Enoxaparin vs. fondaparinux: SOE = Low (1 RCT; 20,078 patients) 7.4% vs. 7.4%; no difference
Composite of all-cause mortality, nonfatal MI, or revascularization at 6 months	Enoxaparin vs. fondaparinux: SOE = Low (1 RCT; 20,078 patients) Enoxaparin 10.2% and fondaparinux 10.1%; no difference (adequately powered for noninferiority hypothesis)

Table F. Summary strength of evidence and effect estimates: enoxaparin versus unfractionated heparin versus fondaparinux (percutaneous coronary intervention cohort) (continued)	
Outcome and Timing	**SOE[a] and Effect Estimate (95% CI)**
Major bleeding at 30 days	Enoxaparin vs. UFH: SOE = Moderate (1 RCT; 10,027 patients) Lower event rates with UFH (7.6%) vs. enoxaparin (9.1%); favors UFH Enoxaparin vs. UFH: SOE = Low (2 observational studies; 29,017 patients) Lower event rates with enoxaparin (2.7% UFH vs. 1.8% enoxaparin; 7% UFH vs. 6.7% enoxaparin); favors enoxaparin Enoxaparin vs. fondaparinux: SOE = Moderate (1 RCT; 20,078 patients) Lower event rates with fondaparinux (3.1%) vs. enoxaparin (5.0%); p <0.001; favors fondaparinux

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

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

Table G. Summary strength of evidence and effect estimates: clopidogrel upstream (pretreatment) and deferred treatment strategies	
Outcome and Timing	**SOE[a] and Effect Estimate[b] (95% CI)**
Upstream Clopidogrel: Bivalirudin vs. Heparin-Based Strategy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Low (2 RCTs; 7,104 patients) Both studies showed no statistically significant difference in composite event rates ranging from OR 1.11 to 1.25; no difference
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Insufficient (1 RCT; 4,570 patients) Insufficient evidence due to imprecision: bivalirudin 21.5%, heparin 20.1%
All-cause mortality at 1 year	SOE = Insufficient (1 RCT; 5,126 patients) Insufficient evidence due to imprecision: bivalirudin 16.0%, heparin 16.3%
Major bleeding at 30 days	SOE = Moderate (3 RCTs; 6,322 patients) OR 0.65 (0.49 to 0.85); favors bivalirudin
Upstream Clopidogrel: Upstream vs. Deferred GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or thrombotic bailout with GPI at 96 hours	SOE = Insufficient (1 RCT; 6,895 patients) Insufficient evidence due to imprecision: upstream GPI 8.7%, deferred GPI 9.4%
Composite of all-cause mortality, nonfatal MI, or rehospitalization at 30 days	SOE = Insufficient (1 RCT; 300 patients) Insufficient evidence due to imprecision: upstream GPI 9%, deferred GPI 10%
Composite of all-cause mortality, nonfatal MI, or ischemia/revascularization at 30 days	SOE = Low (2 RCTs; 638 patients) Upstream GPI 15.7%, deferred GPI 20.3%; favors upstream GPI
All-cause mortality at 30 days	SOE = Low (5 RCTs; 8,168 patients) OR 0.56 (0.30 to 1.05); favors upstream GPI
Major bleeding at 30 days	SOE = Moderate (5 RCTs; 7,416 patients) OR 1.49 (1.10 to 2.01); favors deferred GPI

Table G. Summary strength of evidence and effect estimates: clopidogrel upstream (pretreatment) and deferred treatment strategies (continued)	
Outcome and Timing	**SOE[a] and Effect Estimate[b] (95% CI)**
Deferred Clopidogrel: Bivalirudin vs. Heparin-Based Strategy	
Composite of all-cause mortality, nonfatal MI, or revascularization at 30 days	SOE = Insufficient (2 RCTs; 2,571 patients) Insufficient evidence due to inconsistency and imprecision: 1 RCT (fair) showed a significant reduction favoring bivalirudin, OR 0.42 (0.21 to 0.84; p = 0.02); the other RCT (good) showed no difference, OR 1.05 (0.80 to 1.40)
Major bleeding at 30 days	SOE = Low (2 RCTs; 2,571 patients) 1 RCT (fair) showed no statistical difference between the groups, OR 0.32 (0.10 to 1.01); the other RCT (good) showed a statistically significant reduction favoring bivalirudin, OR 0.53 (0.31 to 0.91, p = 0.02); favors bivalirudin
Deferred Clopidogrel: Upstream vs. Deferred GPI Use	
Composite of all-cause mortality, nonfatal MI, revascularization, or thrombotic bailout with GPI at 96 hours	SOE = Insufficient (1 RCT; 2,271 patients) Insufficient evidence due to imprecision: upstream GPI 10.3%, deferred GPI 11.2%
All-cause mortality at 30 days	SOE = Low (4 RCTs; 11,858 patients) OR 0.97 (0.80 to 1.18); no difference
Major bleeding at 30 days	SOE = High (3 RCTs; 11,698 patients) OR 1.27 (1.08 to 1.50); favors deferred GPI

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

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

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

Key Question 2. Initial Conservative Approach for UA/NSTEMI

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

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

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

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

- Compared with UFH, enoxaparin treatment showed a significant reduction in composite ischemic events (high SOE) and nonfatal MI (moderate SOE) at around 30 days. There was no difference in all-cause mortality at 30 days (low SOE), but there was insufficient evidence to reach a conclusion on the comparative treatment effect on all-cause mortality and major bleeding at 30 days.

- Based on an indirect comparison of fondaparinux and UFH, there was a significant reduction in composite ischemic events (low SOE) and major bleeding (low SOE) at around 30 days favoring fondaparinux, but there was insufficient evidence to reach a conclusion on the comparative treatment effect on nonfatal MI or all-cause mortality.
- Observational studies within subgroups showed that the use of enoxaparin was associated with lower rates of ischemic events in obese patients, those with renal impairment, and those with ST depression on electrocardiography.

Key Points: GPI Plus UFH Versus UFH Alone

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

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

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

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

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

Table H. Summary strength of evidence and effect estimates: unfractionated heparin versus enoxaparin or fondaparinux (full UA/NSTEMI cohort) (continued)	
Outcome and Timing	**SOE[a] and Effect Estimate[b] (95% CI)**
Major bleeding at around 30 days	Enoxaparin vs. UFH: SOE = Insufficient (8 RCTs; 22,901 patients) Insufficient evidence due to inconsistency and imprecision: OR 1.11 (0.81 to 1.51)
	Fondaparinux vs. UFH: SOE = Low (1 RCT; 20,078 patients) OR 0.69 (0.49 to 0.97); favors fondaparinux

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

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

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

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

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

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

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

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

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

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

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

Key Question 3. Postdischarge Treatment for UA/NSTEMI

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

1. Low-dose versus high-dose aspirin (KQ 3a)
   - 6 studies (all observational; 60,904 total patients)
2. Single antiplatelet versus dual antiplatelet therapy (KQ 3a)
   - 7 studies (1 RCT, 6 observational; 173,035 total patients)
3. Short-term versus long-term dual antiplatelet therapy (clopidogrel) (KQ 3a)
   - 11 studies (5 RCTs, 6 observational; 52,121 total patients)
4. Antiplatelet therapy with a PPI versus antiplatelet alone (KQ 3b)
   - 35 studies (4 RCTs, 30 observational; 340,559 total patients)
     - Dual antiplatelet with and without a PPI
     - Aspirin monotherapy with and without a PPI
5. Dual antiplatelet therapy alone versus dual antiplatelet plus oral anticoagulant (i.e., triple therapy) (KQ 3c)
   - 14 studies (all observational; 97,067 total patients)

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

Key Points: Low-Dose Versus High-Dose Aspirin

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

Key Points: Single Antiplatelet Versus Dual Antiplatelet Therapy

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

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

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

Key Points: Antiplatelet Treatments With and Without Use of PPI

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

Key Points: Dual Antiplatelet Versus Triple Therapy

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

Table K. Summary strength of evidence and effect estimates: low-dose versus high-dose aspirin	
Outcome and Timing	**SOE[a] and Effect Estimate[b] (95% CI)**
Composite of all-cause mortality, nonfatal MI, or stroke at 6 months	SOE = Insufficient (1 observational study; 20,469 patients) Insufficient evidence due to CI that crosses 1: HR 0.92 (0.79 to 1.07)
Composite of all-cause mortality, nonfatal MI, or stroke at 1 year	SOE = Insufficient (2 observational studies; 31,186 patients) Insufficient evidence due to inconsistency and imprecision: 1 study showed similar rates of composite events across 3 dosage categories for aspirin monotherapy and DAPT; the other study showed lower event rates when combining low-dose aspirin with ticagrelor and high-dose aspirin with clopidogrel
Composite of all-cause mortality, nonfatal MI, or revascularization at 1 year	SOE = Insufficient (3 observational studies; 9,249 patients) Insufficient evidence due to imprecision: low-dose aspirin and high-dose aspirin had similar rates of ischemic events in all 3 studies
All-cause mortality at 6 months	SOE = Insufficient (1 observational study; 20,469 patients) Insufficient evidence due to imprecision: HR 0.89 (0.72 to 1.10)
All-cause mortality at 1 year	SOE = Insufficient (2 observational studies; 6,429 patients) Insufficient evidence due to inconsistency and imprecision: 1 study (aspirin/clopidogrel) showed no difference between doses; the other found that high-dose aspirin (monotherapy) reduced mortality
Nonfatal MI at 6 months	SOE = Low (1 observational study; 20,469 patients) HR 0.79 (0.64 to 0.98); favors high-dose aspirin
Nonfatal MI at 1 year	SOE = Insufficient (1 observational study; 4,589 patients) Insufficient evidence due to imprecision: HR 0.98 (0.66 to 1.48)
Stroke at 6 months	SOE = Insufficient (1 observational study; 20,469 patients) Insufficient evidence due to imprecision: HR 1.59 (0.95 to 2.65)
Stroke at 1 year	SOE = Insufficient (1 observational study; 4,589 patients) Insufficient evidence due to imprecision: HR 1.37 (0.94 to 2.00)
Revascularization at 1 year	SOE = Insufficient (2 observational studies; 6,429 patients) Insufficient evidence due to inconsistency and imprecision: 1 study (aspirin/clopidogrel) showed no difference between doses; the other study (aspirin monotherapy) showed more events with high dose
Major bleeding at 1 year	SOE = Low (3 observational studies; 19,971 patients) 1 study had high bleeding rates in low-dose group; 2 studies had high bleeding rates in high-dose group; favors low-dose aspirin

CI = confidence interval; DAPT = dual antiplatelet therapy; HR = hazard ratio; MI = myocardial infarction; SOE = strength of evidence
[a]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.
[b]HRs less than 1 favor high-dose aspirin; HRs greater than 1 favor low-dose aspirin.

Table L. Summary strength of evidence and effect estimates: single antiplatelet versus dual antiplatelet therapy	
Outcome and Timing	**SOE[a] and Effect Estimate (95% CI)**
Composite ischemic endpoints, in-hospital to 1 year	SOE = High (1 RCT, 2 observational studies; 106,749 patients) All studies showed statistically significant lowering of composite events in DAPT arm, ranging from RR 0.69 to OR 0.80; favors DAPT
Stroke, in-hospital to 1 year	SOE = Insufficient (1 RCT, 3 observational studies; 116,136 patients) Insufficient evidence due to inconsistency and imprecision: 3 out of 4 studies showed no statistically significant difference in stroke rates
Nonfatal MI, in-hospital to 1 year	SOE = High (1 RCT, 2 observational studies; 106,749 patients) All studies showed fewer recurrent MIs in DAPT group (2.3% to 5.8%) vs. aspirin alone (3.0% to 8.5%); favors DAPT

Table L. Summary strength of evidence and effect estimates: single antiplatelet versus dual antiplatelet therapy (continued)	
Outcome and Timing	**SOE[a] and Effect Estimate (95% CI)**
All-cause mortality, in-hospital to 1 year	SOE = Moderate (1 RCT, 4 observational studies; 117,467 patients) All studies showed fewer deaths in DAPT group, ranging from OR/RR 0.66 to OR/RR 0.93; favors DAPT
Major bleeding, in-hospital to 9 months	SOE = Low (1 RCT, 1 observational study; 105,607 patients) 2 studies showed a reduction in major bleeding in DAPT group (1 statistically significant [16% vs. 21%]; 1 not statistically significant); favors DAPT

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

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

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

Table M. Summary strength of evidence and effect estimates: short-term versus long-term dual antiplatelet therapy (continued)	
Outcome and Timing	**SOE[a] and Effect Estimate (95% CI)**
Cardiovascular mortality at 6 months, 1 year, and 2 years	SOE = Insufficient (3 RCTs, 1 observational study; 33,728 patients) Insufficient evidence due to heterogeneity of DAPT duration, timing of endpoint measurement, and imprecision: all RCTs found similar rates between short- and long-term therapy (1 month vs. 6 months, 6 months vs. 12 months, and 6 months vs. 24 months); 1 observational study found no difference in CV mortality within the first 90 days of discontinuation after a 12-month treatment
Nonfatal MI at 6 months, 1 year, and 2 years	SOE = Insufficient (4 RCTs, 2 observational studies; 9,173 patients) Insufficient evidence due to imprecision: 5 studies (4 RCTs and 1 observational) showed similar rates of MI in short- and long-term therapy groups; 1 observational study showed statistically significant higher risk in DES patients who discontinued clopidogrel within first 6 months
Stroke at 6 months, 1 year, and 2 years	SOE = Insufficient (3 RCTs; 4,460 patients) Insufficient evidence due to imprecision: all RCTs (1 month vs. 6 months, 6 months vs. 12 months, and 6 months vs. 24 months) found similar rates between short- and long-term therapy, but heterogeneity of DAPT duration makes this inconclusive
Revascularization at 6 months and 1 year	SOE = Insufficient (3 RCTs, 1 observational study; 5,705 patients) Insufficient evidence due to imprecision: rates of revascularization were similar between short- and long-term therapy (1 month vs. 6 months and 6 months vs. 24 months)
Stent thrombosis at 6 months, 1 year, and 2 years	SOE = Insufficient (3 RCTs, 3 observational studies; 15,298 patients) Insufficient evidence due to heterogeneity of DAPT duration and imprecision: rates of stent thrombosis were higher when clopidogrel was stopped within 30 days or 6 months in 2 observational studies; 4 studies (3 RCTs and 1 observational) showed no statistically significant difference in event rates at 1 or 2 years
Major bleeding at 1 year and 2 years	SOE = Insufficient (3 RCTs; 5,572 patients) Insufficient evidence due to inconsistency and imprecision: 1 RCT (6 months vs. 24 months) showed a statistically significant lower rate of major bleeding with clopidogrel with 6-month treatment; the other 2 RCTs (1 month vs. 12 months and 6 months vs. 12 months) showed no statistically significant difference in rates with 1-year treatment
Minor bleeding at 1 year and 2 years	SOE = Insufficient (2 RCTs; 4,129 patients) Insufficient evidence due to imprecision: both RCTs (1 month vs. 12 months and 6 months vs. 24 months) found no difference at 1 and 2 years

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

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

Table N. Summary strength of evidence and effect estimates: antiplatelet therapies with and without proton pump inhibitor	
Outcome and Timing	**SOE[a] and Effect Estimate (95% CI)**
Dual Antiplatelet Therapy With and Without PPI[b]	
Composite ischemic endpoints at about 1 year	SOE = Low (2 RCTs, 21 observational studies; 272,311 patients) RCTs of omeprazole showed no difference; however, meta-analysis of observational studies of any PPI showed adj HR 1.35 (1.18 to 1.54), which favors no PPI. The discrepancy between the RCTs and the observational studies makes it difficult to draw a firm conclusion about the effect.
Composite of all-cause mortality or MI at about 1 year	SOE = Moderate (3 observational studies; 60,389 patients) Adj HR 1.27 (1.12 to 1.43); favors no PPI

Table N. Summary strength of evidence and effect estimates: antiplatelet therapies with and without proton pump inhibitor (continued)	
Outcome and Timing	**SOE[a] and Effect Estimate (95% CI)**
Dual Antiplatelet Therapy With and Without PPI[b] (continued)	
All-cause mortality within first 3 months	SOE = Insufficient (3 observational studies; 8,943 patients) Insufficient evidence due to inconsistency and imprecision: 2 studies showed no differences in mortality rates; 1 study showed a statistically significant increase in mortality in PPI group, adj HR 2.2 (1.1 to 4.3)
All-cause mortality at about 1 year	SOE = Moderate (2 RCTs, 18 observational studies; 264,172 patients) RCTs of omeprazole showed no difference or favored omeprazole, and the meta-analysis of observational studies of any PPI showed adj HR 1.17 (0.92 to 1.48); no difference
All-cause mortality at 6 years	SOE = Low (1 observational study; 23,200 patients) Adj HR 1.32 (1.00 to 1.73); favors no PPI
Cardiovascular mortality at 1 year	SOE = Insufficient (3 observational studies; 76,184 patients) Insufficient evidence due to inconsistency and imprecision: 2 out of 3 studies showed statistically significant increase in CV mortality in PPI group
Nonfatal MI within first 3 months	SOE = Insufficient (3 observational studies; 8,943 patients) Insufficient evidence due to inconsistency and imprecision: 2 studies showed no statistically significant difference in MI rates; 1 study showed statistically significant increase in MI events in PPI group
Nonfatal MI at about 1 year	SOE = Low (1 RCT, 11 observational studies; 225,687 patients) The RCT and observational study of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.33 (1.15 to 1.55), which favors no PPI. The discrepancy between the omeprazole studies and the observational studies of any PPI makes it difficult to draw a firm conclusion about the effect.
Stroke at about 1 year	SOE = Low (2 RCTs, 5 observational studies; 165,212 patients) RCTs of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.49 (1.20 to 1.84), which favors no PPI. The discrepancy between the RCTs and the observational studies makes it difficult to draw a firm conclusion about the effect.
Revascularization at 6 months	SOE = Low (1 RCT, 1 observational study; 22,326 patients) Both studies showed no difference in revascularization rates; no difference
Revascularization at 1 year	SOE = Low (5 observational studies; 53,164 patients) Observational study of omeprazole showed no difference; meta-analysis of observational studies of any PPI showed adj OR 1.48 (1.21 to 1.82); favors no PPI
Revascularization at 4 years	SOE = Insufficient (1 observational study; 315 patients) Insufficient evidence due to imprecision; no statistically significant difference in revascularization rate between groups
Stent thrombosis at 30 days	SOE = Insufficient (1 observational study; 3,408 patients) Insufficient evidence due to imprecision: no statistically significant difference in stent thrombosis rate between groups
Stent thrombosis at about 1 year	SOE = Low (1 RCT, 7 observational studies; 45,198 patients) The RCT and observational study of omeprazole showed no difference; however, the meta-analysis of observational studies of any PPI showed adj HR 1.34 (1.17 to 1.55), which favors no PPI. The discrepancy between the RCT and the observational studies makes it difficult to draw a firm conclusion about the effect.
Major bleeding at 30 days	SOE = Insufficient (3 observational studies; 7,498 patients) Insufficient evidence due to inconsistency and imprecision: adj HR 1.73 (0.61 to 4.88)
Major bleeding at about 1 year	SOE = Low (4 observational studies; 36,231 patients) Adj HR 1.26 (1.12 to 1.41); favors no PPI

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

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

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

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

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

[a]Triple therapy refers to aspirin plus antiplatelet plus anticoagulant.
[b]All SOE ratings of "Insufficient" (no evidence is available or available evidence is imprecise or too inconsistent to reach a conclusion) are shaded.
[c]ORs less than 1 favor triple therapy; ORs greater than 1 favor DAPT.

Discussion

Key Findings

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

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

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

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

For KQ 2, which addresses antiplatelet and anticoagulant treatment in patients undergoing an initial conservative approach for treating UA/NSTEMI, our findings were concordant with the recently published ACCF/AHA guideline recommendations. A direct comparison of enoxaparin and UFH showed a significantly lower incidence of composite ischemic endpoints, mostly driven by nonfatal MI reduction, among patients receiving enoxaparin, with no difference in the rate of major bleeding. An indirect comparison of fondaparinux and UFH showed significant reductions in composite ischemic events and major bleeding favoring fondaparinux. These results, based mostly on RCTs and supported by observational studies, are consistent with guideline recommendations of initial anticoagulant treatment among UA/NSTEMI patients undergoing an initial conservative approach, in which all three anticoagulants are recommended but with indication of a preferable option for enoxaparin and fondaparinux.

Our findings on the effectiveness and safety of GPIs when administered with UFH compared with UFH alone have shown that the use of tirofiban or eptifibatide reduced the rate of composite ischemic events, mortality, nonfatal MI, and recurrent ischemia. The administration of abciximab with UFH did not significantly reduce ischemic events compared with UFH alone. Use of GPIs increased the rates of major and minor bleeding. Data gained from

these studies are more challenging to extrapolate and implement in the context of actual clinical practice because the majority were performed before an early invasive strategy was widely implemented, and they employed an initial conservative strategy followed by percutaneous revascularization after 18 to 72 hours. Further, several GPI studies reported results from a combination of treatment approaches (both invasive and medically managed), and the proportion of patients receiving percutaneous revascularization ranged widely. Lastly, the treatment approach seems to vary by country, with greater use of conservative, medically managed approaches in countries with less access to cardiac catheterization laboratories than in more developed countries.

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

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

Effect of clopidogrel duration was assessed in nine studies; however, because of differences in the comparison of duration of treatment and outcomes that were assessed, a meta-analysis was not performed and only a qualitative assessment was possible. Significant differences in outcomes were observed when clopidogrel was discontinued early after discharge, and no differences in outcomes were observed when treatment comparisons were greater than 6 months. Only two studies looked at treatment effect based on stent type, and again the worst outcomes were observed among patients with either bare metal or drug-eluting stents who discontinued clopidogrel (either stopped taking it or were taken off it by their doctor) within the first 6 months. Guidelines recommend a treatment duration of 1 year if there is no increased risk of bleeding. Our findings support the recommendation not to treat beyond 1 year; however, there is uncertainty about whether discontinuation at an earlier time point (between 6 and 12 months) could be safely done, since the data are not clear about when exactly the benefit fades.

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

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

Applicability

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

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

Second, due to a change in terminology regarding treatment approach (i.e., early invasive strategy and initial conservative strategy), we had to make an assumption that trials that discouraged coronary angiography or PCI in the early phase of MI treatment could be labeled as a conservatively managed approach. Many of those types of studies are older (mid-1990s) or were conducted in non-U.S. settings. We did not find any limits to applicability regarding the comparisons or outcomes reported.

Implications for Clinical and Policy Decisionmaking

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

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

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

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

Limitations of the Review Process

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

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

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

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

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

Limitations of the Evidence Base

The main limitation was the change in terminology regarding treatment approach (i.e., early invasive strategy and initial conservative strategy) in the early 2000s. There is no MeSH search term for these types of treatment approaches; thus, it was difficult to group studies and patient populations into an early invasive treatment or initial conservative strategy. Some studies included both early invasive and early conservative treatment approaches, and some studies did not report which treatment approach was used. Fortunately, newer publications are starting to report findings by treatment approach, so future evidence reviews will benefit from further specification. However, in clinical practice the treatment approach for a UA/NSTEMI patient may not always be determined before the pharmacologic therapy is selected. For this review, we tried to separate the early invasive and initial conservative studies into a PCI-based strategy and a medically managed strategy. This led to some overlap in the comparisons of enoxaparin, UFH, and fondaparinux in both the KQ 1 and KQ 2 sections of this report. Another limitation was the patient population enrolled in these antiplatelet and anticoagulant studies. While the focus of this review was the UA/NSTEMI population, we found a lower proportion of studies (about 35%) that solely enrolled UA/NSTEMI patients. Instead, the majority of studies (65%) contained a mixed population of ACS patients, including UA/NSTEMI and STEMI patients. Also, improvements in diagnostic testing have altered the definition and classification of MI and UA over time, thus leading to variations in these definitions across studies.

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

Research Gaps

Acute coronary syndromes, including UA/NSTEMI, are widely studied, as evidenced by our screening of over 20,000 abstracts to identify 290 articles (166 studies) of antiplatelet and anticoagulant agents. In our review, we found research gaps involving both established and

newer therapies, particularly related to the comparative effectiveness of these treatments; issues related to dosage, timing, and type of administration (IV or oral), and combinations of therapy. We used the framework recommended by Robinson et al.[22] to identify gaps in evidence and describe the reasons why these gaps exist. This approach considers PICOTS criteria to classify gaps as due to (1) insufficient or imprecise information, (2) biased information, (3) inconsistency or unknown consistency, and (4) not the right information. Results are presented for each KQ.

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

Key Question 1

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

Key Question 2

In KQ 2, the primary research gap is reporting safety and effectiveness among the subgroup of conservatively managed patients within trials or observational studies of mixed treatment approaches. We found only a couple of studies presenting subgroup analysis by medically managed patients for both the low molecular weight heparin and GPI analyses—and often the data were not concordant. Future studies can address this either by stratification of the antiplatelet or anticoagulant therapy by treatment approach (invasive or conservative) or by reporting the subgroup findings for the conservatively managed population within a larger trial or observational study.

Key Question 3

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

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

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

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

Conclusions

- Overall, the administration of GPIs prior to PCI is associated with a reduction in revascularization rates but an increase in major bleeding events, regardless of whether clopidogrel is administered prior to or during the PCI.
- Prasugrel reduces rates of composite ischemic events (death, MI, or stroke) at 30 days and 1 year, but also results in an increase in major bleeding events at 1 year in comparison with clopidogrel. Ticagrelor reduces rates of composite ischemic events but has similar rates of major bleeding at 1 year compared with clopidogrel.
- Bivalirudin is associated with a lower incidence of major bleeding events compared with heparin-based treatment, regardless of whether a GPI administration is planned. Bivalirudin also reduces rates of minor bleeding events compared with heparin with GPI use.
- Enoxaparin and fondaparinux are associated with a significant reduction in composite ischemic events when compared with UFH in a conservatively managed population.
- Dual antiplatelet therapy of 6 months to 1 year reduces the rates of composite ischemic outcomes and nonfatal MI; however, the optimal dose of aspirin in combination with clopidogrel is less certain.
- While PPIs have been associated with worse clinical outcomes compared with no PPI use in observational studies, the results from a small number of RCTs of omeprazole show no significant difference in clinical events compared with placebo. Therefore PPIs should be used with caution in patients receiving clopidogrel with aspirin (DAPT).

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

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Glossary

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

Full Report

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Addendum

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

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