Evidence-based Practice Center Systematic Review Protocol
Project Title: Antiplatelet and Anticoagulant Treatments for Unstable Angina/Non-ST Elevation Myocardial Infarction

Amendment Date(s):

Amendment 1 – December 11, 2012

(Amendment Details – see Section VII)

I. Background and Objectives for the Systematic Review

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

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

Overview of Treatment Strategies

The standard treatment goals for patients with UA/NSTEMI involve the elimination of ischemia 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. 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 anticoagulants—traditionally heparin—is standard treatment for patients hospitalized with ACS, and newer anticoagulants have been developed that improve outcomes and reduce or have a bleeding risk similar to heparin.

By virtue of their ability to inhibit factors associated with thrombosis and to reduce ischemic

outcomes, each antiplatelet or anticoagulant agent has the potential to increase the risk of bleeding. The balance of ischemic risk and bleeding risk has been highlighted in a number of recent large clinical trials that evaluated antiplatelet and anticoagulant therapies as discussed below. Despite recent clinical 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. The first is the number of agents in each category and the complexity of assessing which combinations have the best outcomes. Second, optimal medical management may be affected by which revascularization strategy is chosen. For the majority of patients who are at higher risk of recurrent ischemia, MI, or death, an *early invasive treatment strategy*—defined as diagnostic angiography and coronary revascularization prior to 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, a *conservative treatment strategy* is often chosen and consists of angiography and revascularization only in patients who develop recurrent infarction, angina at rest, or inducible ischemia on stress testing.[1] Therefore, evidence for concurrent medical therapy needs to be considered separately for initial conservative and early invasive strategies. It is also important to consider the *after-hospitalization* (*postdischarge*) treatment strategies using antiplatelets and anticoagulants to reduce recurrent ischemic events.

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

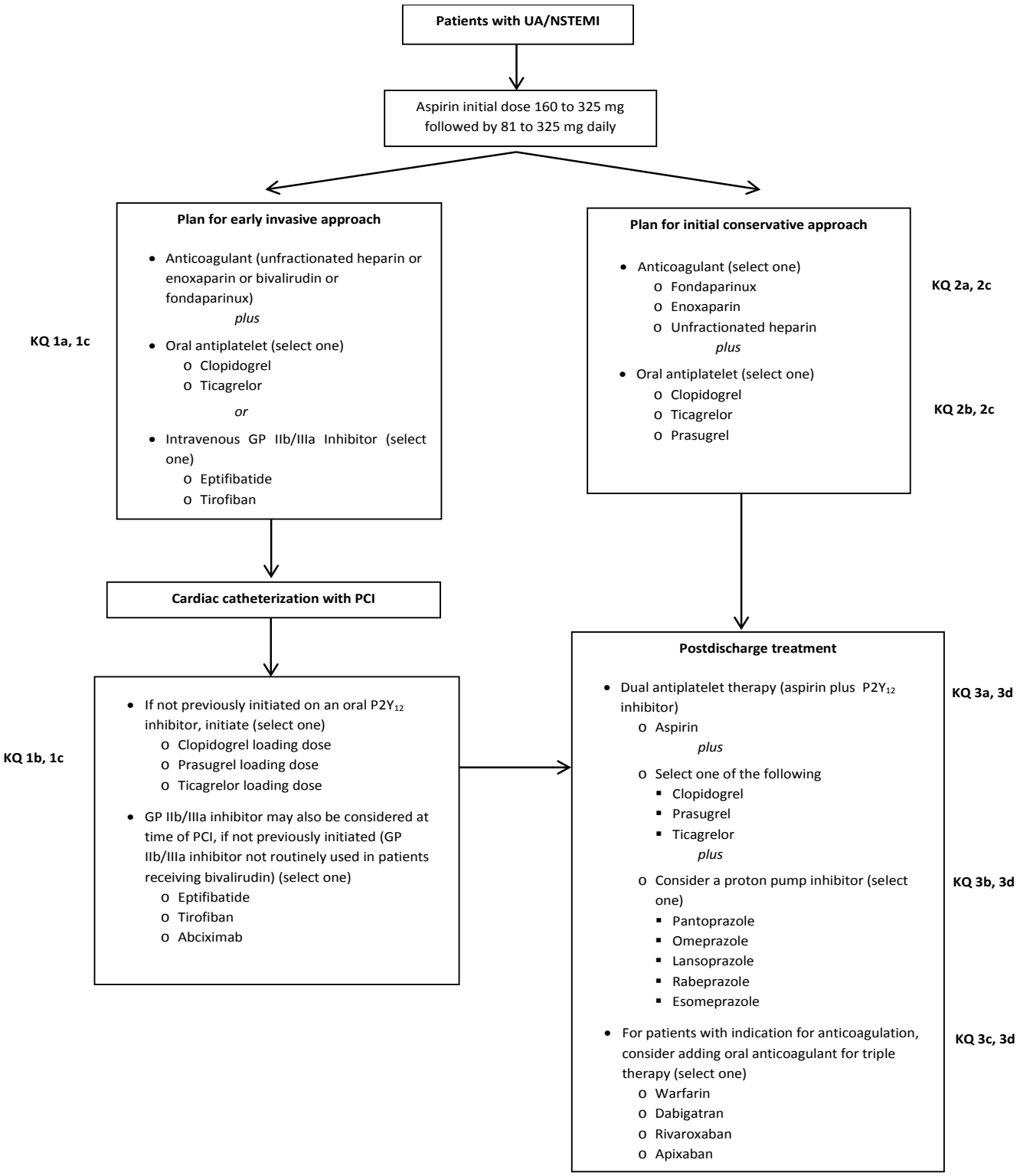
Table 1. Antiplatelet and anticoagulant therapies

<table>
<tr><th>Drug Category</th><th colspan="2">Early Invasive</th><th>Initial Conservative</th><th>Postdischarge</th></tr>
<tr><td>Aspirin</td><td colspan="2">Aspirin</td><td>Aspirin</td><td>Aspirin</td></tr>
<tr><td rowspan="2">Intravenous antiplatelet (glycoprotein IIb/IIIa inhibitors)</td><td>Upstream</td><td>Periprocedure</td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td>Epifibatide
Tirofiban</td><td>Eptifibatide
Tirofiban
Abciximab</td></tr>
<tr><td>Oral antiplatelet ($P2Y_{12}$ Inhibitor)</td><td>Clopidogrel
Ticagrelor</td><td>Clopidogrel
Prasugrel
Ticagrelor</td><td>Clopidogrel
Ticagrelor
Prasugrel (trial in progress)</td><td>Clopidogrel
Prasugrel
Ticagrelor</td></tr>
<tr><td>Anticoagulant</td><td colspan="2">Bivalirudin
Fondaparinux
Enoxaparin
Unfractionated heparin</td><td>Fondaparinux
Enoxaparin
Unfractionated heparin</td><td>Warfarin
Dabigatran
Rivaroxaban
Apixaban</td></tr>
<tr><td>Other considerations</td><td colspan="2">Dose and timing</td><td>Dose and timing</td><td>• Duration related to PCI vs. no PCI
• PPIs
• Patients requiring triple therapy</td></tr>
</table>

Abbreviations: PCI = percutaneous coronary intervention; PPI = proton pump inhibitor

Figure 1 shows the treatment strategy algorithm for patients with UA/NSTEMI.

Figure 1. Treatment strategy algorithm for UA/NSTEMI



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

Introduction to Antiplatelet and Anticoagulant Medications for UA/NSTEMI

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

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

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

Use of Antiplatelets and Anticoagulants in an Early Invasive Approach

Despite the routine use of aspirin for ACS, randomized data comparing doses of aspirin in this setting have been few until the recent publication of the CURRENT-OASIS 7 (clopidogrel and aspirin optimal dose usage to reduce recurrent events–seventh organization to assess strategies in ischemic syndromes) trial.[15] In this trial, higher doses of aspirin were associated with an increased incidence of minor bleeding and no difference in ischemic events at 30 days.

To more effectively prevent thrombotic or ischemic events, additional antiplatelet agents are also routinely used in the early invasive approach for patients with UA/NSTEMI and fall into two classes: oral $P2Y_{12}$ inhibitors and GP IIb/IIIa inhibitors. Oral $P2Y_{12}$ inhibitors are often administered before invasive cardiac catheterization (upstream) or at the time of catheterization when a decision has been made to perform percutaneous coronary intervention (PCI; periprocedure). A strategy using multiple antiplatelet agents has also been shown to increase the

patient's risk of bleeding. While bleeding is inherently higher with dual antiplatelet agents when compared with aspirin monotherapy, the timing and dose of antiplatelet agents are important determinants of clinical bleeding risk. Current clinical practice regarding the dose and timing of oral $P2Y_{12}$ treatment varies dramatically. Given the recent U.S. Food and Drug Administration (FDA) approval of prasugrel and ticagrelor and the absence of direct comparisons of these agents, clinical uncertainty also remains about which agent is ideal for individual patients.

While there is a well-established body of clinical evidence supporting the use of GP IIb/IIIa agents in combination with aspirin for the upstream management of high-risk patients with UA/NSTEMI who are undergoing PCI, much of this evidence comes from an era preceding routine early invasive management, the upstream use of $P2Y_{12}$ inhibitors, and the availability of newer antiplatelet and anticoagulant agents.[1,16-19] Given the increased frequency of upstream oral $P2Y_{12}$ inhibitor use, the upstream use of GP IIb/IIIa inhibitors (in combination with or in place of oral $P2Y_{12}$ inhibitors) has been questioned because of concerns about excessive bleeding risk. Therefore, further reviews are needed to identify certain subgroups of patients who are likely to derive a net clinical benefit from upstream GP IIb/IIIa inhibitor use in an early invasive strategy.

In addition to a recommendation for using multiple antiplatelet agents in patients with UA/NSTEMI, anticoagulant agents are currently recommended for managing patients who present with UA/NSTEMI. In the clinical guidelines for an early invasive strategy, multiple options exist, including UFH, enoxaparin, bivalirudin, and fondaparinux. While each agent differs in its modulation of the coagulation cascade, much of the recent focus of anticoagulant therapy in clinical trials has been on the balance between efficacy and safety. Despite the recent clinical data assessing anticoagulant therapy, a number of questions still remain about the preferred agents in selected populations and the optimal strategies for the combined use of anticoagulant and antiplatelet agents in an early invasive approach.

Use of Antiplatelets and Anticoagulants in an Initial Conservative Approach

As described above, aspirin is an essential component of the treatment regimen of patients with UA/NSTEMI who are treated with an initial conservative approach. Most patients are treated with dual antiplatelet therapy; however, the optimal timing, dose, and comparative effectiveness and safety of the newer $P2Y_{12}$ agents, when compared with clopidogrel, are poorly studied.

While bivalirudin is not currently used in an initial conservative approach, the main controversy about anticoagulation surrounds the use of UFH, enoxaparin, or fondaparinux. Current guidelines recommend fondaparinux as the preferred anticoagulant for patients with UA/NSTEMI who are being managed with a conservative strategy and are considered at high risk for bleeding.[1] However, there is uncertainty about which anticoagulant is preferred in certain subgroups of patients who are being managed with an initial conservative strategy and are not considered at high risk for bleeding.

Use of Antiplatelets and Anticoagulants After Hospitalization

Aspirin is routinely used in patients with UA/NSTEMI; however, the optimal dose for long-term use is less clear. While the CURRENT-OASIS 7 trial was an important randomized controlled trial (RCT), the results expanded knowledge about aspirin dose only out to 30 days. Currently, long-term management decisions are being made based on studies performed before

the era of oral $P2Y_{12}$ inhibitors and PCI. Additionally, guideline recommendations about the optimal duration of dual antiplatelet therapy (aspirin plus an oral P2Y12 inhibitor) have changed drastically over the past decade, specifically as development and implantation of drug-eluting stents in clinical practice have changed since their FDA approval. Significant uncertainty remains about the optimal duration of dual antiplatelet therapy in patients treated with an initial conservative strategy and in those treated with an early invasive strategy (stratified by the type of coronary stent that is implanted). Therefore, further research to better define the optimal duration of dual antiplatelet therapy in patients with UA/NSTEMI is needed to assist clinicians in making these common, everyday decisions.

The use of dual antiplatelet therapy has been associated with a significant increase in the risk of gastrointestinal (GI) bleeding than with aspirin alone. To reduce the occurrence of GI bleeding with dual antiplatelet therapy, medications such as proton pump inhibitors (PPIs), which are capable of suppressing gastric acid production, have been recommended. However, PPIs have the potential to inhibit the hepatic CYP2C19 pathway that is involved in the conversion of clopidogrel to its active metabolite; consequently, this mechanism has been the focus of much discussion in the literature, especially concerning clopidogrel initiation at the time of UA/NSTEMI. Initial pharmacokinetic/pharmacodynamic studies have suggested a reduction in the antiplatelet response when clopidogrel is coadministered with omeprazole.[20] While much research has been conducted in this area, questions still remain about whether there is a preferred PPI to use in patients receiving clopidogrel and about how PPI use with dual antiplatelet therapy might impact bleeding and cardiovascular events in a high-risk population.

A clinical scenario that is also becoming more frequently encountered is the use of *triple therapy*, defined as dual antiplatelet therapy in patients with UA/NSTEMI who also have an indication for oral anticoagulation (e.g., warfarin) such as atrial fibrillation or mechanical heart valves. The current evidence describing the combined use of warfarin and dual antiplatelet therapy is derived from registries, case series, and post hoc analyses of prospective trials. Overall, the observational data indicate an increased risk of bleeding with the combined use of dual antiplatelet therapy and oral anticoagulation. Furthermore, considerable variability exists in the reported rates of thromboembolic and ischemic events.[21] Given the aging population and the increased prevalence of conditions such as atrial fibrillation, the use of dual antiplatelet therapy in addition to an oral anticoagulant will be expected to increase. Identifying patients most likely to benefit from this triple therapy would be helpful in guiding clinical decisionmaking. Additionally, the introduction of a number of newer oral antiplatelet and anticoagulant agents will make selection of an optimal treatment strategy more uncertain.

Rationale for Evidence Review and Current Clinical Uncertainty

Although thousands of RCTs have been published about the medical management of patients with UA/NSTEMI, there remain notable uncertainties surrounding the use of antiplatelet and anticoagulant medications, as follows:

- What is the effectiveness of an intravenous GP IIb/IIIa inhibitor versus an oral antiplatelet agent as initial therapy before going to the catheterization laboratory within an early invasive strategy?
- What are the optimal timing, dosing strategy, and duration of antiplatelet agents (including aspirin, clopidogrel, prasugrel, and ticagrelor) in patients treated with an early

invasive strategy? In patients treated with an initial conservative strategy? Do these vary based on the anticoagulant strategy, specifically with use of bivalirudin?
- Which oral $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) provides the greatest clinical benefit in patients already treated with aspirin?
- In patients with an indication for oral anticoagulant therapy, what are the risks and benefits of triple therapy (dual antiplatelet therapy plus warfarin) versus dual antiplatelet therapy?
- In patients receiving dual antiplatelet therapy, what are the risks and benefits of adding a PPI? Are certain PPIs better than others?

II. The Key Questions

The draft Key Questions (KQs) developed during Topic Refinement were available for public comment from October 7, 2011, to November 3, 2011. Based on comments received in response to this posting, the following change was made to the KQs:

- Clarifying that the effectiveness and safety of anticoagulant and antiplatelet agents may vary based on the combination of agents used in the clinical studies

Other comments were received from the Technical Expert Panel (TEP) and considered for inclusion in the comparative effectiveness review protocol, including the following:

- The addition of body mass index and previous stroke as subpopulations of interest
- Inclusion of clinical trials comparing triple and dual antiplatelet therapy for the treatment of ACS, without requiring a long-term indication for anticoagulation

The KQs, revised after public comments, are found in the table below.

KQ 1:	In patients undergoing an *early invasive* approach for treating unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI): a. What are the comparative effectiveness (dose and timing) and comparative safety of an intravenous (IV) glycoprotein IIb/IIIa inhibitor versus oral antiplatelet agent as initial therapy before going to the catheterization laboratory? b. What are the comparative effectiveness (dose and timing) and comparative safety of coadministration of IV or oral antiplatelet agents in patients undergoing percutaneous coronary intervention for improving cardiovascular outcomes? Do the effectiveness and safety vary based on which initial anticoagulant is used or the combination of anticoagulant and antiplatelet agents? c. Based on demographic and other clinical characteristics, are there subgroups of patients for whom the effectiveness and safety differ?
KQ 2:	In patients undergoing an *initial conservative* approach for treating UA/NSTEMI: a. What are the comparative effectiveness (dose and timing) and comparative safety of different anticoagulants on improving cardiovascular outcomes? b. What are the comparative effectiveness (dose and timing) and comparative safety of different antiplatelet agents on improving cardiovascular outcomes? c. Based on demographic and other characteristics, are there subgroups of patients for whom the effectiveness and safety differ?

KQ 3:	In patients treated for UA/NSTEMI *after hospitalization (postdischarge)*: a. What are the comparative effectiveness (dose and duration) and comparative safety of the available oral antiplatelet agents given in combination with aspirin? Do the effectiveness and safety vary based on the dose of aspirin used? b. What are the comparative effectiveness and comparative safety of proton pump inhibitors (PPIs) for reducing bleeding events in patients receiving dual antiplatelet therapy after UA/NSTEMI? Do the effectiveness and safety vary by oral antiplatelet therapy and PPI? c. In patients with an indication for long-term anticoagulant therapy, what are the comparative effectiveness and comparative safety of adding an oral anticoagulant to aspirin and another antiplatelet agent for improving cardiovascular outcomes? d. Based on demographic and other characteristics, are there subgroups of patients for whom the effectiveness and safety differ?

PICOTS Criteria

- **Population(s):**
  - Adult patients with UA/NSTEMI and comorbid or multimorbid disease:
    - Subgroups by age, sex, weight, body mass index, diabetes, heart failure, previous stroke, renal insufficiency, type of stent, type of vascular access

- **Interventions:**
  - KQ 1: Early invasive strategy (before cardiac catheterization or during PCI)
    - Aspirin
    - Intravenous glycoprotein IIb/IIIa inhibitors
      - Abciximab
      - Eptifibatide
      - Tirofiban
    - Oral antiplatelets
      - Clopidogrel
      - Prasugrel
      - Ticagrelor
    - Anticoagulants
      - Bivalirudin
      - Fondaparinux
      - Enoxaparin
      - UFH
  - KQ 2: Initial conservative strategy
    - Aspirin
    - Oral antiplatelets
      - Clopidogrel
      - Prasugrel
      - Ticagrelor
    - Anticoagulants
      - Fondaparinux

        - Enoxaparin
        - UFH

    - KQ 3: Postdischarge treatment
        - Aspirin
        - Oral antiplatelets
            - Clopidogrel
            - Prasugrel
            - Ticagrelor
        - Anticoagulants
            - Warfarin
            - Dabigatran
            - Rivaroxaban
            - Apixaban
        - PPIs
            - Pantoprazole
            - Omeprazole
            - Lansoprazole
            - Rabeprazole
            - Esomeprazole

    See Appendix 1 for information on the medications and devices under consideration.

- **Comparators:**

    - KQ 1a: Before catheterization—dose and timing of intravenous or oral antiplatelets with anticoagulants plus aspirin
    - KQ 1b: During PCI—dose and timing of intravenous or oral antiplatelet with anticoagulants, plus aspirin
    - KQ 2a: Dose and timing of anticoagulants plus aspirin
    - KQ 2b: Dose and timing of oral antiplatelets plus aspirin
    - KQ 3a: Dose and duration of oral antiplatelets in combination with aspirin at different doses
    - KQ 3b: PPIs versus no PPIs
    - KQ 3c: Dual antiplatelet therapy (aspirin with oral antiplatelet) versus triple therapy (oral anticoagulant, aspirin, and oral antiplatelet)

- **Outcomes measures for KQs 1–3:**

    - Intermediate outcomes
        1. Rehospitalization
        2. Length of hospital stay
        3. Resource utilization (e.g., emergency department visits)

    - Final outcomes
        1. All-cause death

2. Cardiovascular disease-related death
3. Nonfatal MI
4. Revascularization
5. Stroke
6. Quality of life (validated instruments such as Short Form-36, EQ-5D, Seattle Angina Questionnaire, etc.)

- Adverse effects of treatments
  1. Adverse drug reactions (thrombocytopenia, allergic drug reaction)
  2. Bleeding (various definitions of minor and major bleeding have been used in published studies such as TIMI, GUSTO, PLATO, BARC, which are based on a decrease in hemoglobin levels or the number of transfusions administered)
  3. Stent thrombosis

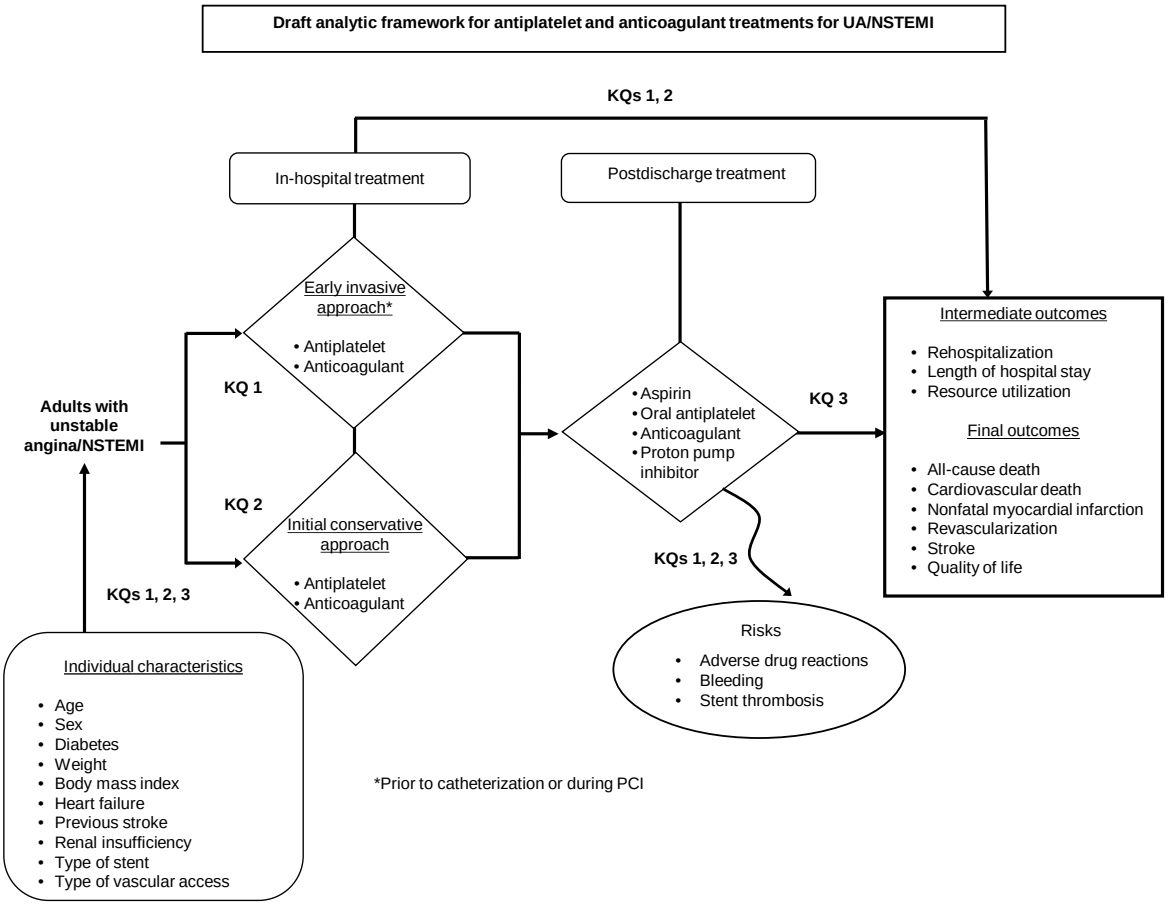
- **Timing:**

  - Studies with all durations of followup will be included in the review. The duration of treatment and followup will be considered when evaluating the benefits and risks for these therapies: short term (≤30 days), intermediate term (31 days to 1 year), and long term (>1 year).

- **Settings:**

  - Inpatient for early invasive and initial conservative therapies
  - Outpatient for after hospitalization (postdischarge) therapies

III. Analytic Framework



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

IV. Methods

In developing this comprehensive review, we will apply the rules of evidence and formulation of strength of evidence recommended by the Agency for Healthcare Research and Quality in its *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*).[22] We will solicit feedback regarding conduct of the work (such as development of search strategies and identifying outcomes of key importance) from the Task Order Officer and the Technical Expert Panel. We will follow the methodology recommended to the Evidence-based Practice Centers for literature search strategies, inclusion/exclusion of studies in our review, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each KQ.

A. Criteria for Inclusion/Exclusion of Studies in the Review

Table 2 lists the inclusion and exclusion criteria for this comparative effectiveness review.

Table 2. Inclusion and exclusion criteria

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

Study Characteristic	Inclusion Criteria	Exclusion Criteria

	• KQ 3: *Postdischarge treatment*
	  ○ Aspirin
	  ○ Oral antiplatelets
	  ▪ Clopidogrel
	  ▪ Prasugrel
	  ▪ Ticagrelor
	  ○ Anticoagulants
	  ▪ Warfarin
	  ▪ Dabigatran
	  ▪ Rivaroxaban
	  ▪ Apixaban
	  ○ PPIs
	  ▪ Pantoprazole
	  ▪ Omeprazole
	  ▪ Lansoprazole
	  ▪ Rabeprazole
	  ▪ Esomeprazole
		• Study does not include any of the medications listed
		• Medications are not administered as part of postdischarge treatment

Comparators	• KQ 1a: Before catheterization, dose and timing of intravenous or oral antiplatelets with anticoagulants plus aspirin • KQ 1b: During PCI, dose and timing of intravenous or oral antiplatelet with anticoagulants plus aspirin • KQ 2a: Dose and timing of anticoagulants plus aspirin • KQ 2b: Dose and timing of oral antiplatelets plus aspirin • KQ 3a: Dose and duration of oral antiplatelets in combination with aspirin at different doses • KQ 3b: PPIs versus no PPIs • KQ 3c: Dual antiplatelet therapy (aspirin with oral antiplatelet) versus triple therapy (oral anticoagulant, aspirin, and oral antiplatelet)	Studies without an active comparator

Outcomes	• Intermediate outcomes
	  o Rehospitalization
	  o Length of hospital stay
	  o Resource utilization (e.g., emergency department visits)
	• Final outcomes
	  o All-cause death
	  o Cardiovascular-related death
	  o Nonfatal myocardial infarction
	  o Revascularization
	  o Stroke
	  o Quality of life
		No intermediate or final outcomes of interest are reported

Outcomes (modifiers)	KQs 1–3: Individual characteristics including age, sex, weight, body mass index, diabetes, heart failure, previous stroke, renal insufficiency, type of stent, type of vascular access	None
Outcomes (safety)	KQs 1–3: Adverse effects of treatments such as adverse drug reactions (thrombocytopenia, allergic drug reaction), bleeding, and stent thrombosis	None

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

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

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

Our search strategy will use 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 will use PubMed®, EMBASE®, and the Cochrane Database of Systematic Reviews for our literature search. Our proposed search strategy for PubMed is included in Appendix 2; this strategy will be adapted as necessary for use in the other databases. We will date-limit our search to articles published since January 1995, corresponding to the period when contemporary studies on antiplatelet therapy, anticoagulant therapy, and combined therapies were published. The reference list for identified pivotal articles will be manually hand-searched and cross-referenced against our library, and additional manuscripts will be retrieved. All citations will be imported into an electronic database (EndNote® X4 or higher).

We will also search the gray literature of study registries and conference abstracts for relevant articles from completed studies. Gray literature databases will include ClinicalTrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; the World Health Organization's International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. Scientific information packets will be requested from

the manufacturers of medications and devices that are listed in Appendix 1 and reviewed for relevant articles from completed studies not previously identified in the literature searches.

C. Data Abstraction and Data Management

The research team will create data abstraction forms and evidence table templates for abstracting data for the KQs. Based on their clinical and methodological expertise, a pair of researchers will be assigned to the research questions to abstract data from the eligible articles. One of the pair will abstract the data, and the second researcher will over-read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements will be resolved by consensus or by obtaining a third reviewer's opinion if consensus cannot be reached between the first two researchers.

To aid in both reproducibility and standardization of data collection, researchers will receive data abstraction instructions directly on each form created specifically for this project with the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada). We will design 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 will be framed to help identify adverse events, including adverse drug reactions, contrast nephropathy, radiation, and bleeding.

Data necessary for assessing quality and applicability, as described in the *Methods Guide*,[22] will also be abstracted. Before they are used, abstraction form templates will be pilot tested with a sample of included articles to ensure that all relevant data elements are captured and that there is consistency/reproducibility between abstractors. Forms will be revised as necessary before full abstraction of all included articles.

D. Assessment of Methodological Quality of Individual Studies

The included studies will be assessed on the basis of the quality of their reporting of relevant data. We will evaluate the quality of individual studies by using the approach described in the *Methods Guide*.[22] To assess quality, we will employ the strategy to 1) classify the study design, 2) apply predefined criteria for quality and critical appraisal, and 3) arrive at a summary judgment of the study's quality. To assess the risk of bias/methodological quality of individual studies, we will use the key criteria for RCTs described in the *Methods Guide*[22] and adapted for this specific topic. These criteria include 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. These general criteria will be customized for each major outcome and listed in the appendix of the report.

For nonrandomized clinical trials, such as those with an observational control group that was not randomized, we will assess for any threats to the internal validity of the systematic review based on the individual study characteristics. Study-specific issues to be considered include 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 (see the section on "Selecting Observational Studies for Comparing Medical Interventions" in the *Methods Guide*[23]). To indicate the summary judgment of the quality of the individual studies, we will use the summary ratings of good, fair, and poor based on their adherence to well-accepted standard methodologies and adequate reporting.

Grading will be outcome-specific; thus, a given study may be graded to be of different quality for two individual outcomes reported within that study. Study design will be considered when grading quality. RCTs will be graded as good, fair, or poor. Observational studies will be graded separately, also as good, fair, or poor. We anticipate that any included retrospective studies would fall into a grading of fair or poor.

E. Data Synthesis

We will summarize the primary literature by abstracting relevant continuous (e.g., age) and categorical (e.g., race, presence of coronary disease risk factors) data. Continuous variable outcomes will be summarized by mean and standard deviation, median, and interquartile range; significance testing will be performed with t-tests (if normally distributed) or nonparametric tests (if non-normally distributed). Categorical variable outcomes will be summarized by proportions; significance testing will be performed by chi-squared analysis. We will then determine the feasibility of completing a meta-analysis for considered outcomes. Feasibility depends on the volume of relevant literature, conceptual homogeneity of the studies (e.g. study design, patient population, intervention, comparator, outcome), and completeness of the results reporting. When a meta-analysis is appropriate, we will use random-effects models to quantitatively synthesize the available evidence. We will test for statistical heterogeneity between studies (I^2) while recognizing that the power to detect such heterogeneity may be limited. Potential heterogeneity between studies will be reflected through the confidence intervals of the summary statistics obtained from a random-effects approach. For comparison, we will also perform fixed-effects meta-analysis. We will present summary estimates, standard errors, and confidence intervals. Analyses by subgroup (e.g., age, sex, weight, body mass index, diabetes, heart failure, previous stroke, renal insufficiency, type of stent, type of vascular access) will depend on the number of studies that report the results by subgroup.

F. Grading the Evidence for Each Key Question

The strength of evidence for each key question will be assessed by using the approach described in the *Methods Guide*.[24] The evidence will be evaluated by using the four required domains: risk of bias (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), and precision (precise or imprecise). Additionally, when appropriate, the studies will be evaluated for dose-response association, the presence of confounders that would diminish an observed effect, strength of association (magnitude of effect), and publication bias. The strength of evidence will also be assigned an overall grade of high, moderate, low, or insufficient according to the following four-level scale:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.

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

G. Assessing Applicability

We will use data abstracted on the population studied, the intervention and comparator, the outcomes measured, study settings, and timing of assessments to identify specific issues that may limit the applicability of individual studies or a body of evidence as recommended in the *Methods Guide*.[25] We will use these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population (such as age, ethnicity, and sex) in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use (such as specific components of treatments considered to be "optimal medical therapy," plus advancements in endovascular and surgical revascularization techniques that have changed over time), and clinical relevance and timing of the outcome measures. We will summarize issues of applicability qualitatively.

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VI. Definition of Terms

ACS	acute coronary syndrome
CV	cardiovascular
GP	glycoprotein
KQ	key question
MI	myocardial infarction
NSTEMI	non-ST elevation myocardial infarction
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
UA	unstable angina
UFH	unfractionated heparin

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
12/11/2012	II. Key Questions	Population: Adult patients with UA/NSTEMI and comorbid or multimorbid disease:	Population: Adult patients with UA or NSTEMI and comorbid or multimorbid disease:	This change is to make this sentence match the population inclusion criteria wording in Table 2.
12/11/2012	IV. Methods (Population)	Exclusion Criteria: Studies with a STEMI population only or acute coronary syndrome studies that do not report the UA/NSTEMI results separately	Exclusion Criteria: Studies with only a STEMI or stable angina population	We have included acute coronary syndrome populations due to limited data from UA/NSTEMI-only trials or trials where the UA/NSTEMI group was reported separately, resulting in too narrow of a focus for therapies that are used in clinical practice.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

The EPC team has no conflicts of interest to disclose.

XIII. Role of the Funder

This project was funded under Contract No. 290-2007-10066-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements, including the objectivity and independence of the research process and the methodological quality of the report. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix 1. Devices and Medications

Devices

Registered or Trademark Name	Type	Manufacturer	Comments
Balloons			
Sprinter®	PTCA	Medtronic	FDA approved
VOYAGER™	PTCA	Abbott Vascular	FDA approved
TREK®	PTCA	Abbott Vascular	FDA approved
Maverick®	PTCA	Boston Scientific Corporation	FDA approved
Flextome®	Cutting	Boston Scientific Corporation	FDA approved
AngioSculpt®	Cutting	Angioscore Inc.	FDA approved
Stents			
Driver®	Bare-metal stent	Medtronic	FDA approved

Registered or Trademark Name	Type	Manufacturer	Comments
Integrity®	Bare-metal stent	Medtronic	FDA approved
VISION™	Bare-metal stent	Abbott Vascular	FDA approved
VeriFlex™	Bare-metal stent	Boston Scientific Corporation	FDA approved
JoStent Graftmaster®	Closed-cell stent	Abbott Vascular	FDA approved
Express®	Open-cell stent	Boston Scientific Corporation	FDA approved
ACS Multi-Link®	Bare-metal stent	Abbott Vascular	FDA approved
OMEGA™	Bare-metal stent	Boston Scientific Corporation	FDA approved
CYPHER™	Drug-eluting stent	Cordis Corporation/Johnson and Johnson	FDA approved
Endeavor®	Drug-eluting stent	Medtronic	FDA approved
TAXUS™/ION™	Drug-eluting stent	Boston Scientific Corporation	FDA approved
XIENCE™/PROMUS™	Drug-eluting stent	Abbott Vascular	FDA approved
DESyne™ novolimus-eluting stent	Drug-eluting stent	Elixir Medical Corporation	Available only for export

Abbreviations: FDA = U.S. Food and Drug Administration; PTCA = percutaneous transluminal coronary angioplasty

Medications

Registered or Trademark Name	Generic Name (if applicable)	Manufacturer	Dosage	Frequency	Route of Administration	FDA Status	UA/NSTEMI-Related FDA Indications
Plavix®	Clopidogrel	Bristol Myers Squibb Sanofi Pharmaceuticals partnership	MD: 75 mg LD: 300-600 mg	Daily Once	Oral	Approved	Indicated for patients with non-ST-segment elevation ACS (UA/NSTEMI), including patients who are to be managed medically and those who are to be managed with coronary revascularization
Effient®	Prasugrel	Eli Lilly and Co	MD: 10 mg, 5 mg LD: 60 mg	Daily Once	Oral	Approved	Indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with ACS who are to be managed with PCI
Brilinta™	Ticagrelor	AstraZeneca LP	MD: 90 mg LD: 180mg	Twice daily Once	Oral	Approved	Indicated to reduce the rate of thrombotic CV events in patients with ACS (UA, NSTEMI, STEMI)
Arixtra®	Fondaparinux	GlaxoSmithKline Pharmaceuticals	2.5 mg	Daily	Subcutaneous	Approved	Not currently FDA approved for use as an anticoagulant in patients with UA/NSTEMI

Registered or Trademark Name	Generic Name (if applicable)	Manufacturer	Dosage	Frequency	Route of Administration	FDA Status	UA/NSTEMI-Related FDA Indications
Angiomax®	Bivalirudin	The Medicines Company	PCI: 0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/hr (if CrCl< 30 ml/min reduce infusion to 1.0 mg/kg/hr, if patient on hemodialysis reduce infusion to 0.25 mg/kg/hr) for the duration of the PCI procedure Continuation of the infusion for up to 4 hr postprocedure is optional Initial anticoagulant in UA/NSTEMI: 0.1 mg/kg bolus followed by 0.25 mg/kg/hr At the time of PCI a bolus of 0.5 mg/kg should be given followed by an increase in the infusion to 1.75 mg/kg/hr for the duration of the PCI procedure	Initiated at the time of the PCI procedure Initiated on presentation and continued through the PCI procedure or up to 72 hr following the procedure if a medical management strategy is selected	Intravenous	Approved	Indicated for use as an anticoagulant in patients with unstable angina undergoing PTCA and in patients undergoing PCI with the provisional use of a glycoprotein IIb/IIIa inhibitor
Lovenox®	Enoxaparin	Sanofi-Aventis US LLC	1 mg/kg For CrCl <30 ml/min: 1 mg/kg	Every 12 hr Daily	Subcutaneous	Approved	Indicated for prophylaxis of ischemic complications of unstable angina and non–Q-wave MI

Registered or Trademark Name	Generic Name (if applicable)	Manufacturer	Dosage	Frequency	Route of Administration	FDA Status	UA/NSTEMI-Related FDA Indications
Fragmin®	Dalteparin	Eisai Inc.	120 IU/kg (max 10,000 IU)	Every 12 hr	Subcutaneous	Approved	Indicated for prophylaxis of ischemic complications of unstable angina and non-Q wave MI
Fraxiparine®	Nadroparin	GlaxoSmithKline Inc.	86 anti-Xa IU/kg intravenous bolus followed by 86 anti-Xa IU/Kg subcutaneously every 12 hr A dose reduction of 25-33% should be considered in patients with CrCl <50 ml/min	Every 12 hr	Intravenous subcutaneous	Not Approved Available in Canada; not available in the US	Not FDA approved: In Canada, indicated for the treatment of unstable angina and non-Q wave MI
ReoPro®	Abciximab	Eli Lilly and Co.	As an adjunct to PCI: 0.25 mg/kg IV bolus followed by a continuous infusion of 0.125 mcg/kg/min (max =10 mcg/min) for 12 hr In UA patients when PCI planned within 24 hr: 0.25 mg/kg IV bolus followed by an 18-24 hr continuous IV infusion of 10 mcg/min, concluding one hr after the PCI	At the time of PCI procedure Initiated upstream and to be discontinued 1 hr after the PCI	Intravenous	Approved	Indicated as an adjunct to PCI for the prevention of cardiac ischemic complications in patients undergoing PCI and in patients with UA not responding to conventional medical therapy when PCI is planned within 24 hr

Registered or Trademark Name	Generic Name (if applicable)	Manufacturer	Dosage	Frequency	Route of Administration	FDA Status	UA/NSTEMI-Related FDA Indications
Integrilin®	Eptifibatide	Schering Corporation a Subsidiary of Merck & Co., Inc.	180 mcg/kg bolus followed by an infusion of 2.0 mcg/kg/min (reduce infusion to 1 mcg/kg/min for nondialysis patients with a CrCl <50 ml/min) for up to 72 hr If a patient is to undergo a percutaneous coronary intervention (PCI) while receiving eptifibatide, the infusion should be continued for up to 18 to 24 hr after the procedure	Initiated either upstream or at the time of PCI and continued for up to 24 hr after the PCI procedure	Intravenous	Approved	For the treatment of patients undergoing PCI, including those undergoing coronary stenting and in patients with ACS (UA/NSTEMI), including patients who are to be managed medically and those undergoing PCI
Aggrastat®	Tirofiban	Medicure Pharma	Initial infusion rate of 0.4 mcg/kg/min for 30 minutes and then continued at 0.1 mcg/kg/min for 12 to 24 hr following PCI Patients with severe renal insufficiency (CrCl <30 mL/min) should receive half the usual rate of infusion	Initiated either upstream or at the time of PCI and continued for up to 24 hr after the PCI procedure	Intravenous	Approved	Indicated, in combination with heparin, for the treatment of ACS, including patients who are to be managed medically and those undergoing PTCA or atherectomy

Registered or Trademark Name	Generic Name (if applicable)	Manufacturer	Dosage	Frequency	Route of Administration	FDA Status	UA/NSTEMI-Related FDA Indications
Coumadin®	Warfarin	Bristol Myers Squibb Pharma Co.	1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 6 mg 7.5 mg 10 mg	Daily	Oral	Approved	Indicated for the prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement and for the reduction in the risk of death, recurrent MI, and thromboembolic events such as stroke or systemic embolization after MI
Xarelto®	Rivaroxaban	Johnson & Johnson Pharmaceutical Research & Development, LLC and Bayer HealthCare	20 mg If CrCl 15-50 ml/min: 15 mg	Daily Daily	Oral	Approved	Indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
Pradaxa®	Dabigatran	Boehringer Ingelheim Pharmaceuticals	150 mg If CrCl 15-30 ml/min: 75 mg	Twice daily Twice daily	Oral	Approved	Indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
Eliquis™	Apixaban	Bristol Myers Squibb and Pfizer	2.5 mg 5 mg	Twice daily	Oral	Not currently FDA approved	
Protonix®	Pantoprazole	Wyeth Pharmaceuticals	20 mg 40 mg	Once to twice daily	Oral (an intravenous formulation is commercially available)	Approved	No approved indication in patients with ACS Frequently used in patients on dual antiplatelet therapy to reduce the risk of bleeding
Prilosec®	Omeprazole	AstraZeneca	10 mg 20 mg 40 mg	Once to twice daily	Oral	Approved	No approved indication in patients with Frequently used in patients on dual antiplatelet therapy to reduce the risk of bleeding

Registered or Trademark Name	Generic Name (if applicable)	Manufacturer	Dosage	Frequency	Route of Administration	FDA Status	UA/NSTEMI-Related FDA Indications
Nexium®	Esomeprazole	AstraZeneca	20 mg 40 mg	Once to twice daily	Oral (an intravenous formulation is commercially available)	Approved	No approved indication in patients with ACS Frequently used in patients on dual antiplatelet therapy to reduce the risk of bleeding
Aciphex®	Rabeprazole	Eisai Inc.	20 mg	Once to twice daily	Oral	Approved	No approved indication in patients with ACS Frequently used in patients on dual antiplatelet therapy to reduce the risk of bleeding
Prevacid®	Lansoprazole	Takeda Pharmaceuticals North America Inc.	15 mg 30 mg	Once to twice daily	Oral	Approved	No approved indication in patients with ACS Frequently used in patients on dual antiplatelet therapy to reduce the risk of bleeding
Dexilant™	Dexlansoprazole	Takeda Pharmaceuticals North America Inc.	30 mg 60 mg	Daily	Oral	Approved	No approved indication in patients with ACS Frequently used in patients on dual antiplatelet therapy to reduce the risk of bleeding
Bayer Aspirin®	Aspirin	Bayer Healthcare LLC	75 mg 81 mg 162 mg 324 mg 325 mg	Daily	Oral	Approved	Indicated for the management of an acute MI and in the secondary prevention of an MI

Abbreviations: ACS = acute coronary syndrome; CrCl = creatinine clearance; FDA = U.S. Food and Drug Administration; IU = international unit; IV = intravenous; LD = loading dose; MD = maintenance dose; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; STEMI = ST elevation myocardial infarction; UA = unstable angina

Appendix 2. Literature Search Strategy (11/11/11)

Broader ACS terms for systematic review search		
Set #	**Terms**	**Results**
#1	ACS[tw] OR acute coronary syndrome[MeSH Terms] OR (acute[tw] AND coronary[tw] AND syndrome[tw]) OR "acute coronary syndrome"[tw] OR non-st[tw] OR nstemi[tw] OR n-stemi[tw] OR non-stemi[tw] OR nonstemi[tw] OR nsteacs[tw] OR angina, unstable[MeSH Terms] OR (angina[tw] AND unstable[tw]) OR "unstable angina"[tw] OR (preinfarction[tw] AND angina[tw]) OR "preinfarction angina"[tw] OR "cardiovascular diseases"[MeSH Terms] OR ("cardiovascular"[tw] AND "diseases"[tw]) OR "heart diseases"[MeSH Terms] OR ("heart"[tw] AND "diseases"[tw]) OR "heart"[MeSH Terms] OR "heart"[tw] OR "coronary"[tw] OR cardiovas*[tw] OR cardiac*[tw] OR "myocardium"[MeSH Terms] OR "myocardium"[tw] OR "myocardial"[tw] OR myocardial infarction[mesh]	2283489
#2	platelet aggregation inhibitors[MeSH Terms] OR (platelet[tw] AND aggregation[tw] AND inhibitors[tw]) OR (antiplatelet[tw] AND agent*[tw]) OR "platelet aggregation inhibitors"[Pharmacological Action] OR Purinergic P2Y Receptor Antagonists[Pharmacological Action] OR purinergic p2y receptor antagonists[MeSH Terms] OR (purinergic[tw] AND p2y[tw] AND receptor[tw] AND antagonists[tw]) OR "ADP receptor antagonist"[tw] OR "ADP receptor antagonists"[tw] OR aspirin[mesh] OR aspirin[tw] OR clopidogrel[supplementary concept] OR clopidogrel[tw] OR plavix[tw] OR prasugrel[supplementary concept] OR prasugrel[tw] OR effient[tw] OR ticagrelor[supplementary concept] OR ticagrelor[tw] OR brilinta[tw]	121676
#3	factor xa[mesh] OR "factor xa inhibitor"[tw] OR "factor xa inhibitors"[tw] OR rivaroxaban[Supplementary Concept] OR rivaroxaban[tw] OR xarelto[tw] OR bivalirudin[Supplementary Concept] OR bivalirudin[tw] OR angiomax[tw] OR apixaban[Supplementary Concept] OR eliquis[tw] OR apixaban[tw] OR "2-(3-carbamimidoylbenzyl)-3-(4-(1-oxypyridin-4-yl)benzoylamino)butyric acid methyl ester"[Supplementary Concept] OR "2-(3-carbamimidoylbenzyl)-3-(4-(1-oxypyridin-4-yl)benzoylamino)butyric acid methyl ester"[tw] OR otamixaban[tw] OR "YM 60828"[Supplementary Concept] OR "YM 60828"[tw] OR "ym466"[tw]	5149
#4	heparin[MeSH] OR heparin[tw] OR (low[tw] AND molecular[tw] AND weight[tw] AND heparin[tw]) OR (unfractionated[tw] AND heparin[tw]) OR fondaparinux[Supplementary Concept] OR fondaparinux[tw] OR arixtra[tw] OR Dalteparin[tw] OR fragmin[tw] OR Enoxaparin[tw] OR lovenox[tw] OR Nadroparin[tw] OR fraxiparine[tw]	79834
#5	Vitamin K/antagonists and inhibitors[mesh] OR "vitamin k antagonist"[tw] OR "vitamin k antagonists"[tw] OR warfarin[mesh] OR warfarin[tw] OR Coumadin[tw] OR VKA[tw] OR coumarol[tw] OR dicoumarol[tw] OR coumarin[tw] OR dicoumarin[tw]	26593
#6	antithrombins[mesh] OR antithrombins[pharmacological action] OR "direct thrombin inhibitor"[tw] OR "direct thrombin inhibitors"[tw] OR "N-((2-(((4-(aminoiminomethyl)phenyl)amino)methyl)-1-methyl-1H-benzimidazol-5-yl)carbonyl)-N-2-pyridinyl-beta-alanine"[Supplementary Concept] OR "N-((2-(((4-(aminoiminomethyl)phenyl)amino)methyl)-1-methyl-1H-benzimidazol-5-yl)carbonyl)-N-2-pyridinyl-beta-alanine"[tw] OR dabigatran[tw] OR pradaxa[tw]	13704
#7	"Glycoprotein IIb/IIIa inhibitor"[tw] OR "GP IIb/IIIa inhibitor"[tw] OR "Glycoprotein IIb/IIIa inhibitors"[tw] OR "GP IIb/IIIa inhibitors"[tw] OR abciximab[Supplementary Concept] OR abciximab[tw] OR reopro[tw] OR eptifibatide[Supplementary Concept] OR eptifibatide[tw] OR integrilin[tw] OR tirofiban[Supplementary Concept] OR tirofiban[tw] OR aggrastat[tw]	4228
#8	Proton Pump Inhibitors[Mesh] OR Proton Pump Inhibitors[Pharmacological Action] OR Proton Pumps/antagonists and inhibitors[Mesh] OR omeprazole[MeSH] OR omeprazole[tw] OR esomeprazole[tw] OR lansoprazole[Supplementary Concept] OR lansoprazole[tw] OR pantoprazole[Supplementary Concept] OR pantoprazole[tw] OR rabeprazole[Supplementary Concept] OR rabeprazole[tw] OR dexlansoprazole[tw] OR "omeprazole, sodium bicarbonate drug combination"[Supplementary Concept] OR zegerid[tw] OR nexium[tw] OR aciphex[tw] OR protonix[tw] OR prevacid[tw] OR kapidex[tw] OR prilosec[tw]	16142

Broader ACS terms for systematic review search		
Set #	**Terms**	**Results**
#9	"Angioplasty, Balloon, Coronary"[Mesh] OR (Percutaneous[tw] AND Transluminal[tw] AND Coronary[tw] AND Angioplasty[tw]) OR "percutaneous transluminal coronary angioplasty"[tw] OR angioplasty[mesh] OR angioplasty[tw] OR PTCA[tw] OR PCI[tw] OR (percutaneous[tw] AND coronary[tw] AND intervention[tw]) OR ((coronary[tw] OR heart[mesh] OR heart[tw]) AND (stents[mesh] OR stent[tw] OR stents[tw] OR stenting[tw] OR stented[tw]))	75050
#10	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	146727
#11	#10 AND (systematic[sb] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw])	4305
#12	#11, Limits: English, 1995-	3672
#13	#12 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[MeSH] NOT humans[MeSH])	3546

Narrower ACS terms for trials search		
Set #	**Terms**	**Results**
#1	ACS[tw] OR acute coronary syndrome[MeSH Terms] OR (acute[tw] AND coronary[tw] AND syndrome[tw]) OR "acute coronary syndrome"[tw] OR non-st[tw] OR nstemi[tw] OR n-stemi[tw] OR non-stemi[tw] OR nonstemi[tw] OR nsteacs[tw] OR angina, unstable[MeSH Terms] OR (angina[tw] AND unstable[tw]) OR "unstable angina"[tw] OR (preinfarction[tw] AND angina[tw]) OR "preinfarction angina"[tw] OR myocardial infarction[mesh] OR "myocardial infarction"[tw] OR "heart attack"[tw]	191441
#2	platelet aggregation inhibitors[MeSH Terms] OR (platelet[tw] AND aggregation[tw] AND inhibitors[tw]) OR (antiplatelet[tw] AND agent*[tw]) OR "platelet aggregation inhibitors"[Pharmacological Action] OR Purinergic P2Y Receptor Antagonists[Pharmacological Action] OR purinergic p2y receptor antagonists[MeSH Terms] OR (purinergic[tw] AND p2y[tw] AND receptor[tw] AND antagonists[tw]) OR "ADP receptor antagonist"[tw] OR "ADP receptor antagonists"[tw] OR aspirin[mesh] OR aspirin[tw] OR clopidogrel[supplementary concept] OR clopidogrel[tw] OR plavix[tw] OR prasugrel[supplementary concept] OR prasugrel[tw] OR effient[tw] OR ticagrelor[supplementary concept] OR ticagrelor[tw] OR brilinta[tw]	121676
#3	factor xa[mesh] OR "factor xa inhibitor"[tw] OR "factor xa inhibitors"[tw] OR rivaroxaban[Supplementary Concept] OR rivaroxaban[tw] OR xarelto[tw] OR bivalirudin[Supplementary Concept] OR bivalirudin[tw] OR angiomax[tw] OR apixaban[Supplementary Concept] OR eliquis[tw] OR apixaban[tw] OR "2-(3-carbamimidoylbenzyl)-3-(4-(1-oxypyridin-4-yl)benzoylamino)butyric acid methyl ester"[Supplementary Concept] OR "2-(3-carbamimidoylbenzyl)-3-(4-(1-oxypyridin-4-yl)benzoylamino)butyric acid methyl ester"[tw] OR otamixaban[tw] OR "YM 60828"[Supplementary Concept] OR "YM 60828"[tw] OR "ym466"[tw]	5149
#4	heparin[MeSH] OR heparin[tw] OR (low[tw] AND molecular[tw] AND weight[tw] AND heparin[tw]) OR (unfractionated[tw] AND heparin[tw]) OR fondaparinux[Supplementary Concept] OR fondaparinux[tw] OR arixtra[tw] OR Dalteparin[tw] OR fragmin[tw] OR Enoxaparin[tw] OR lovenox[tw] OR Nadroparin[tw] OR fraxiparine[tw]	79834
#5	Vitamin K/antagonists and inhibitors[mesh] OR "vitamin k antagonist"[tw] OR "vitamin k antagonists"[tw] OR warfarin[mesh] OR warfarin[tw] OR Coumadin[tw] OR VKA[tw] OR coumarol[tw] OR dicoumarol[tw] OR coumarin[tw] OR dicoumarin[tw]	26593
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Narrower ACS terms for trials search		
Set #	**Terms**	**Results**
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#9	"Angioplasty, Balloon, Coronary"[Mesh] OR (Percutaneous[tw] AND Transluminal[tw] AND Coronary[tw] AND Angioplasty[tw]) OR "percutaneous transluminal coronary angioplasty"[tw] OR angioplasty[mesh] OR angioplasty[tw] OR PTCA[tw] OR PCI[tw] OR (percutaneous[tw] AND coronary[tw] AND intervention[tw]) OR ((coronary[tw] OR heart[mesh] OR heart[tw]) AND (stents[mesh] OR stent[tw] OR stents[tw] OR stenting[tw] OR stented[tw]))	75050
#10	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	35935
#12	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "case-control studies"[MeSH Terms] OR "case-control"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw]	5664894
#13	#10 AND #12	27003
#14	#13 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[MeSH] NOT humans[MeSH]) Limits: English, 1995 - Present	17163