Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Treatment Strategies for Women With Coronary Artery Disease

Amendment Date: 14Sep2011 (see Section VII for details)

I. Background and Objectives for the Systematic Review

Overview

Cardiovascular disease remains the leading cause of death among women in United States.[1] More than 500,000 women die of cardiovascular disease each year, exceeding the number of deaths in men and the next seven causes of death in women combined. This translates into approximately one death every minute.[1,2] Coronary artery disease (CAD), which includes coronary atherosclerotic disease, myocardial infarction (MI), acute coronary syndrome (ACS), and angina, is the most prevalent form of cardiovascular disease and is the largest subset of this mortality. The morbidity associated with this disease is also considerable. Each year, more than 1 million patients have an MI. Many more are hospitalized for unstable angina and for evaluation and treatment of stable chest pain syndromes. This report focuses on women because of the differences in clinical presentation and coronary anatomy, which affect the treatment options for CAD. Most of the currently available guidelines or systematic reviews assume that treatment options are equally effective for both sexes. However, women have a worse prognosis than men for manifestations of CAD such as acute MI, and some data suggest that women and men do not respond equally to the same treatments.[3] Therefore, a better understanding of the evidence for the effectiveness of medical treatment and revascularization therapies specifically in women is needed to reduce cardiovascular events in women.

Clinical presentations

CAD is the presence of atherosclerosis in the epicardial coronary arteries. Atherosclerotic plaques may either rupture and cause acute ischemia or progressively narrow the coronary artery lumen, resulting in chronic stable angina. Acute myocardial ischemia occurs when an atheromatous plaque ruptures or splits. The reasons for why a specific plaque ruptures when it does are unclear but probably relate to plaque morphology, plaque calcium content, and plaque softening due to an inflammatory process. Rupture exposes collagen and other thrombogenic material, which activates platelets and the coagulation cascade, resulting in an acute thrombus that interrupts coronary blood flow and causes some degree of myocardial ischemia. The consequences of acute ischemia depend on the location and degree of obstruction and range from reversible ischemia (unstable angina) through partial tissue damage (non–ST-elevation myocardial infarction [NSTEMI]) to transmural infarction of the heart muscle (ST–elevation myocardial infarction [STEMI]). The constellation of clinical symptoms that are compatible with acute myocardial ischemia is usually referred to as ACS.[4,5]

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Chronic stable angina resulting from progressive narrowing of the coronary arteries is the initial manifestation of ischemic heart disease in approximately one-half of patients.[6] Angina is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arm. It is typically aggravated by exertion or emotional stress and relieved by nitroglycerin. Angina usually occurs in patients with CAD that involves at least one large epicardial artery. However, angina can also occur in patients with valvular heart disease, hypertrophic cardiomyopathy, and uncontrolled hypertension. It can also be present in patients with normal coronary arteries and myocardial ischemia related to spasm or endothelial dysfunction. Most stable angina is a sign of significant CAD, defined angiographically as a stenosis with a ≥ 70 percent diameter in at least one major epicardial artery segment or with a ≥ 50 percent diameter in the left main coronary artery. However, some angina is caused by stenotic lesions of lesser diameters, which have much less prognostic significance.[6]

Treatment options

The purpose of this report is to evaluate the evidence for the comparative effectiveness of combinations of optimal medical therapies, percutaneous coronary intervention (PCI), and coronary artery bypass graft surgery (CABG) in women with CAD. In general, these treatments aim to reduce cardiac workload and improve coronary artery blood flow. In addition, some optimal medical therapies may halt or reverse the atherosclerotic process over the long term. However, optimal medical therapies, PCI, and CABG have very different approaches, risks, and potential benefits.

Chronic medical treatment of a patient with CAD should address all the elements in the following mnemonic:[7]

A = **A**ntiplatelet and **A**ntianginal therapy

B = **B**eta-blockers and **B**lood pressure control

C = **C**igarette smoking cessation and **C**holesterol management

D = **D**iet modification and **D**iabetes prevention or management

E = **E**xercise

The combinations of treatment listed above comprise optimal medical therapy of CAD to reduce future cardiovascular events. Patients may not be able to receive optimal medical therapy if they have allergies or adverse effects to individual medications (e.g., aspirin, β-blocker, or cholesterol-lowering drugs) or the combination of medications. In addition, the definition of optimal medical therapy continues to evolve as new drugs are developed and as studies are conducted to assess the optimal blood pressure, blood sugar, and lipid goals needed to reduce future cardiovascular events. For medical therapy to be optimized, the patient should be prescribed appropriate therapy to reach their therapeutic goal. Medication adherence can affect the latter.

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The mechanical approaches to coronary revascularization fall broadly into two categories: CABG and catheter-based PCI. Together, these coronary revascularization techniques are among the most common major medical procedures performed in North America and Europe. Since the introduction of bypass surgery in 1967 and PCI in 1977, it has become clear that both strategies can contribute to the effective treatment of patients with CAD—yet, both have weaknesses. CABG and PCI (with or without stents) are alternative approaches to mechanical coronary revascularization, so their comparative effectiveness in terms of patient outcomes has been of great interest. The comparative effectiveness of CABG and PCI is an open question primarily for those patients for whom either procedure would be technically feasible or whose CAD is neither too limited nor too extensive.

CABG is generally preferred for patients with left main CAD or severe triple-vessel disease with reduced left ventricular function because it has been previously shown in randomized trials to improve survival when compared with medical therapy. In contrast, PCI is generally preferred for patients with most forms of single-vessel disease when symptoms warrant coronary revascularization, in light of its lower procedural risk and the evidence that PCI reduces angina and myocardial ischemia in this subset of patients. The choice between PCI and CABG is most relevant for patients whose CAD lies in between these extremes; namely, patients with single-vessel disease of the proximal left anterior descending artery, most forms of double-vessel CAD, and less extensive forms of triple-vessel CAD. Most randomized controlled clinical trials (RCTs) of PCI and CABG have been conducted in this middle segment of the patient population with CAD. The major advantage of PCI is its relative ease of use and avoidance of general anesthesia, thoracotomy, extracorporeal circulation, central nervous system complications, and prolonged convalescence. Repeat PCI can be performed more easily than repeat bypass surgery, and revascularization can be achieved more quickly in emergency situations. The disadvantages of PCI are early restenosis and the inability to relieve many totally occluded arteries and/or vessels with extensive atherosclerotic disease. CABG has the advantages of greater durability (graft patency rates exceeding 90 percent at 10 years with arterial conduits) and more complete revascularization regardless of the morphology of the obstructing atherosclerotic lesion.[8]

Treatment options for CAD vary based on clinical presentation (i.e., ACS or chronic stable angina; see table below). For ACS, antithrombin and antiplatelet therapies should be administered to all patients regardless of the presence or absence of ST-segment elevation. Treatment for patients with persistent ST-segment elevation is well established. Patients with STEMI are candidates for reperfusion therapy (either pharmacological or catheter based) to restore flow promptly in the occluded epicardial infarct-related artery.[5] In general, patients with STEMI are not treated with CABG (unless emergent from PCI complications) but do receive optimal medical therapy.

Patients without ST-segment elevation (i.e., NSTEMI) are not candidates for immediate pharmacological reperfusion. The optimal management of NSTEMI has the twin goals of the immediate relief of ischemia and the prevention of serious adverse outcomes (i.e., death or MI). Optimal management is best accomplished with an approach that includes anti-ischemic therapy, antithrombotic therapy, ongoing risk stratification, and the use of invasive procedures. In addition to aggressive medical therapy, two treatment pathways have emerged for treating patients without ST-segment elevation.[4] An "initial conservative strategy" (also referred to as selective invasive management) calls for proceeding with an invasive evaluation only for those

patients whose medical therapy fails (refractory angina or angina at rest or with minimal activity despite vigorous medical therapy) or in whom objective evidence of ischemia (dynamic electrocardiographic changes, high-risk stress test) is identified. The "invasive strategy" triages patients to undergo an invasive diagnostic evaluation without first getting a noninvasive stress test or having medical treatment fail. Patients treated with an invasive strategy generally will undergo coronary angiography within 4 to 24 hours of admission; however, these patients also are treated with the usual NSTEMI medications, including appropriate anti-ischemic, antiplatelet, and anticoagulant therapy. Several randomized trials have demonstrated improved clinical outcome in patients with an invasive strategy, leading to guideline recommendations for invasive approaches to treat patients with NSTEMI and high-risk ACS. Patients with NSTEMI also receive optimal medical therapy.

The treatment of stable angina has two major purposes. The first is to prevent MI and death and thereby increase the quantity of life. The second is to reduce symptoms of angina and occurrence of ischemia, which should improve the quality of life.[6] All patients with stable angina are candidates for optimal medical therapy and may be candidates for PCI or CABG based on findings from coronary angiography and if symptoms persist despite optimal medical therapy. The following table shows the potential comparisons for the treatment of women with CAD.

Presentation	Treatment		
	Optimal medical therapy	PCI*	CABG*
STEMI	X	X	
NSTEMI/ unstable angina	X	X	X
Stable angina	X	X	X

*Delivered with optimal medical therapy.

Controversy or uncertainty about treatment of women with CAD

CAD is underdiagnosed, undertreated, and underresearched in women.[9] Multiple factors are likely to contribute to the lower use of evidence-based medicine (medical therapy and/or mechanical treatment) and the higher rate of cardiovascular complications among women with CAD. First, cardiovascular disease affects women later in life. For example, among patients with an NSTEMI, the mean age is 62 years for men versus 68 years for women, and among patients with a STEMI, the mean age is 57 years for men versus 66 years for women.[10-12] Second, at the time CAD is diagnosed, women are more likely to have comorbid factors such as diabetes mellitus, hypertension, hypercholesterolemia, peripheral vascular disease, and heart failure.[9] Women also tend to more often have atypical symptoms such as nausea, vomiting, fatigue, dyspnea, and abnormal pain location at the time of diagnosis when compared with men.[13] Third, the coronary vessels in women tend to be smaller than those of men, which makes them more difficult to revascularize percutaneously and surgically.[14] Microvascular disease of the coronary arteries is more common in women than in men.[15] Fourth, delay in hospitalization or in symptom recognition ultimately results in delay in diagnosis and effective treatment.[10,11] It also has been

hypothesized that a patient's sex may influence a physician's recommendation with respect to cardiac catheterization regardless of the patient's clinical characteristics.[16] Finally, a lack of solid data on cardiovascular disease in women because of their underrepresentation in RCTs leaves uncertainty about the risk-benefit ratio of treatment.[17,18]

A recent RCT comparing optimal medical therapy with or without PCI for patients with stable angina demonstrated that the addition of PCI to optimal medical therapy reduced the prevalence of angina but not the long-term rates of death or nonfatal MI.[19] However, the authors acknowledge that among the study limitations was the preponderance of men that reached 85 percent of the patients enrolled, thus making difficult any extrapolation of their finding to women. Similarly, in the American College of Cardiology/American Heart Association guidelines for the management of patients with chronic stable angina, important patient subgroups such as women and elderly were either not represented or were underrepresented in the randomized trials discussed. The trials of initial medical versus initial surgical management excluded patients older than 65 years and contained very few women. In the trials of percutaneous transluminal coronary angioplasty (PTCA) versus surgery, women were included and reasonably well represented, but few patients older than 70 years and none older than 80 years were included.[6] Additionally, the majority of these trials had few patients treated with newer drug-eluting stents.

There is also some evidence that appropriate treatment for women with ACS differs from the appropriate treatment for men.[4,5] A meta-analysis of contemporary randomized trials of patients with NSTEMI currently supports the benefit of using an early invasive strategy, as compared with an initial conservative strategy, for improved long-term mortality and morbidity.[20] However, available data on comparisons between the early invasive and the initially conservative treatment strategies are controversial with respect to sex. In FRISC-II and RITA-3, an improved outcome in the early invasive arm was seen only in men, whereas the benefit of early revascularization was equivalent in men and women in the TACTICS-TIMI 18 trial, provided that the troponin level was elevated.[21-23] In contrast, low-risk women tended to have worse outcomes, including a higher risk of major bleeding, with early revascularization therapy, whereas low-risk men were neither harmed nor benefited by this strategy.[24]

A meta-analysis of CABG versus stenting for the treatment of multiple-vessel disease—including different RCTs with a heterogeneous patient population (stable and unstable angina patients)—showed no difference in the primary composite end point of death, MI, and stroke and no difference in mortality between the CABG and the stent groups.[25] Results by sex are provided, but women represented only 23 percent of enrolled patients.

In summary, differences in presentation and coronary anatomy significantly affect treatment options in women. Women also continue to be underrepresented in research on heart disease, making it difficult to draw conclusive evidence on managing cardiovascular disease in women. Yet, available data are conflicting, and additional research is needed to further clarify the different responses to revascularization treatments in women.[26]

II. The Key Questions

The draft key questions (KQs) developed during Topic Refinement were available for public comment from August 5, 2010, to September 2, 2010. Based on comments received in response to this posting, the following changes were included in the key questions:

- Adding "adverse drug reactions" to the list of potential harms in KQ 3.

Other comments were received and considered for inclusion in the comparative effectiveness review protocol, including the following:

- Adding the time frame (long term or short term) for the impact of treatment.
- Adding the effect of different therapies on cognition.
- Adding adherence as important factor influencing optimal medical therapy.

The KQs, revised after public comments, are found in the table below. Consideration of public comments also resulted in minor changes to the analytic framework and population of interest. The KQs were further reorganized for clarity upon amendment of the protocol in September 2011 (see Section VII for details).

KQ 1:	In women presenting with ST elevation myocardial infarction (STEMI): 1a. What is the effectiveness of optimal medical therapy (i.e., fibrinolytics) versus percutaneous coronary intervention (PCI) on clinical outcomes (nonfatal MI, death, stroke, repeat revascularization, unstable angina, heart failure, repeat hospitalization, length of hospital stay, angina relief, quality of life, or cognitive effects)? 1b. Is there evidence that the comparative effectiveness of optimal medical therapy (i.e., fibrinolytics) and PCI varies based on characteristics such as: • Age, race, or other demographic and socioeconomic risk factors? • Coronary disease risk factors such as diabetes, chronic kidney disease, or other comorbid disease? • Angiographic-specific factors (number of diseased vessels, vessel territory stenoses, left ventricular function, access site, or prior PCI or coronary artery bypass graft surgery [CABG] revascularization procedure)? • Hospital characteristics (hospital volume, setting, guideline-based treatment protocols)? 1c. What are the significant safety concerns associated with each treatment strategy (i.e., adverse drug reactions, radiation exposure, access site complications, renal dysfunction, anaphylaxis, arrhythmias, stent thrombosis, bleeding, infections)?

KQ 2:	In women presenting with unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI): 2a. What is the effectiveness of initial conservative therapy versus early invasive therapy (PCI or CABG) on clinical outcomes (nonfatal MI, death, stroke, repeat revascularization, unstable angina, heart failure, repeat hospitalization, length of hospital stay, graft failure, angina relief, quality of life, or cognitive effects)? 2b. Is there evidence that the comparative effectiveness of initial conservative therapy and early invasive therapy varies based on characteristics such as: • Age, race, or other demographic and socioeconomic risk factors? • Coronary disease risk factors such as diabetes, chronic kidney disease, or other comorbid disease? • Angiographic-specific factors (number of diseased vessels, vessel territory stenoses, left ventricular function, access site, or prior PCI or CABG revascularization procedure)? • Hospital characteristics (hospital volume, setting, guideline-based treatment protocols)? 2c. What are the significant safety concerns associated with each treatment strategy (i.e., adverse drug reactions, radiation exposure, access site complications, renal dysfunction, anaphylaxis, arrhythmias, stent thrombosis, bleeding, infections)?
KQ 3:	In women with stable angina: 3a. What is the effectiveness of the following treatment strategies on clinical outcomes (nonfatal MI, death, stroke, repeat revascularization, unstable angina, heart failure, repeat hospitalization, length of hospital stay, graft failure, angina relief, quality of life, or cognitive effects)? • Optimal medical therapy versus mechanical revascularization (PCI or CABG) in women with stable angina • PCI versus CABG in women with stable or unstable angina 3b. Is there evidence that the comparative effectiveness of medical therapy and mechanical revascularization varies based on characteristics such as: • Age, race, or other demographic and socioeconomic risk factors? • Symptomatic versus asymptomatic? • Coronary disease risk factors such as diabetes, chronic kidney disease, or other comorbid disease? • Angiographic-specific factors (number of diseased vessels, vessel territory stenoses, left ventricular function, access site, or prior PCI or CABG revascularization procedure)? • CABG-specific factors such as type of surgery performed, cardiopulmonary bypass mode (normothermic versus hypothermic), on-pump versus off-pump, type of cardioplegia used (blood versus crystalloid), or use of saphenous vein grafts, single or bilateral internal mammary artery grafts, or other types of bypass grafts? • Hospital characteristics (hospital volume, setting, guideline-based treatment protocols)? 3c. What are the significant safety concerns associated with each treatment strategy (i.e., adverse drug reactions, radiation exposure, access site complications, renal dysfunction, anaphylaxis, arrhythmias, stent thrombosis, bleeding, infections)?

- **Population(s):**

  Adult women (age ≥18 years) with CAD and angiographically proven single- or multiple-vessel disease including STEMI, NSTEMI, and stable angina

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- **Interventions:**
  - Optimal medical therapy alone
  - Optimal medical therapy and percutaneous coronary intervention (bare metal and drug-eluting stents)
  - Optimal medical therapy and coronary artery bypass graft surgery

- **Comparators:**
  - Optimal medical therapy alone
  - Optimal medical therapy and percutaneous coronary intervention (bare metal and drug-eluting stents)
  - Optimal medical therapy and coronary artery bypass graft surgery

- **Outcomes for each question:**
  - Primary outcomes: Major adverse cardiovascular events such as death, nonfatal myocardial infarction, stroke, and repeat revascularization
  - Other clinical outcomes: Heart failure, repeat hospitalization, length of hospital stay, unstable angina, graft failure, angina relief, quality of life, cognitive effects
  - Adverse effects of intervention(s): Adverse drug reactions, radiation exposure, access site complications, renal dysfunction, anaphylaxis, arrhythmias, stent thrombosis, bleeding, infections

- **Timing:**

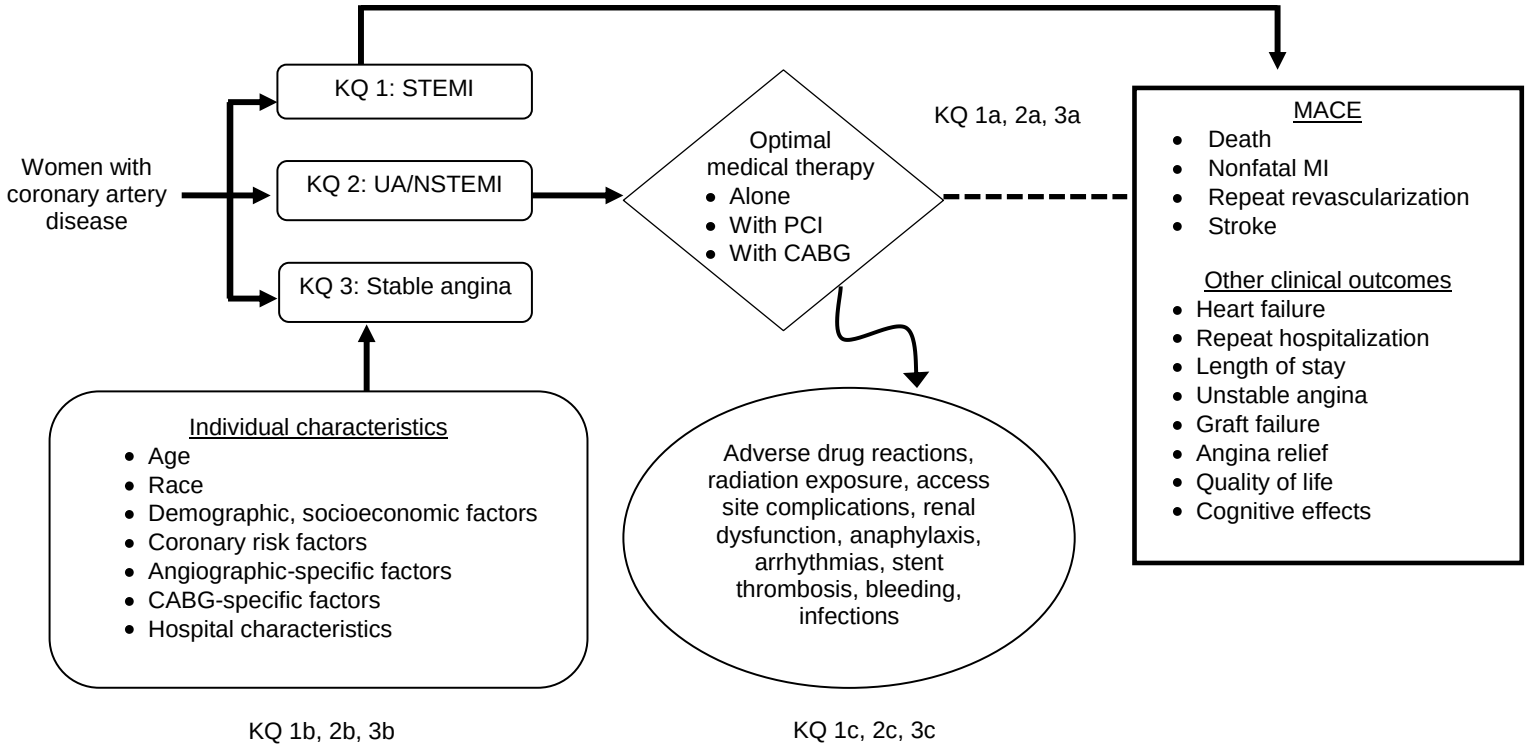
  Short (≤ 30 days), intermediate and/or long term (> 30 days)

- **Settings:**

  Inpatient or outpatient, primarily primary care and cardiology clinics

III. Analytic Framework

Analytic Framework for Treatment Strategies for Women with Coronary Artery Disease



Abbreviations: CABG = coronary artery bypass graft; CAD = coronary artery disease; KQ = key question; MACE = major adverse cardiovascular events; MI = myocardial infarction; NSTEMI = non–ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

Alternate text: This figure depicts the key questions within the context of the PICO (population, interventions, comparators, and outcomes) described elsewhere in this document. In general, the figure shows that the report will consider the effectiveness of one treatment option versus the others among symptomatic women presenting with STEMI, unstable angina/NSTEMI, or stable angina in reducing major cardiovascular outcomes and other relevant clinical outcomes (Key Questions 1a, 2a, 3a), possible individual characteristics that may influence effectiveness of treatment options (Key Questions 1b, 2b, 3b) and whether there are significant safety concerns or risks associated with the use of the different treatments including adverse drug reactions, radiation exposure, access site complications, renal dysfunction, anaphylaxis, arrhythmias, stent thrombosis, bleeding, infections (Key Questions 1c, 2c, 3c).

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IV. Methods

A. Input From Stakeholders

The KQs were refined with the help of an eight-person person Key Informant group representing doctors, patients, scientific experts, and Federal agencies. All participants were screened for conflicts of interests, and conflicts were either excluded or balanced. An eight-person Technical Expert Panel was assembled to provide input during the review process with experts knowledgeable in CAD, PCI, and CABG. All participants were screened for conflicts of interest, and conflicts were either excluded or balanced.

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

An article will be included if all of the following criteria apply:

- Study population includes women with angiographically proven CAD with a presentation of STEMI, NSTEMI, or stable angina
- Original data for any of the interventions listed in KQ 1
- Adults (age ≥ 18 years), human studies
- English language
- Randomized controlled trial, or relevant systematic review or meta-analysis

An article will be excluded if any of the following criteria apply:

- Study population is composed entirely of patients without CAD, or the population also includes patients with CAD but results are not reported separately for the subgroup with CAD
- Study does not include women, or results are not reported by sex
- All subjects under age 18, or some subjects under age 18, but results are not broken down by age
- Study does not report any of the primary or secondary outcomes of interest
- Not a clinical study (e.g., editorial, non–systematic review, letter to the editor, case series)

Prospective and retrospective observational studies or registries will be considered if a KQ cannot be adequately answered from available RCT data.

Given the high volume of literature available in English-language publications (including the majority of known important studies), non-English articles will be excluded. It is the opinion of the investigators that the resources required for translation of non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.

For all included studies, we will indicate the total number of patients enrolled and the longest length (weeks or months) of followup if relevant.

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Outcomes of interest

- Comparative effectiveness of different treatment options as defined by the following:
  - Clinical outcomes including major adverse cardiovascular events: death, nonfatal myocardial infarction, stroke, and repeat revascularization
  - Other clinical outcomes including: heart failure, repeat hospitalization, length of hospital stay, unstable angina, graft failure, angina relief, quality of life, and cognitive effects
- Individual characteristics including the following:
  - Age, race, or other demographic and socioeconomic risk factors
  - Coronary disease risk factors such as diabetes, chronic kidney disease, or other comorbid disease
  - Angiographic-specific factors such as access site (radial or femoral), number of diseased vessels, vessel territory stenoses, left ventricular function, or prior PCI or CABG revascularization procedure
  - CABG-specific factors such as type of surgery performed (traditional or robot-assisted), cardiopulmonary bypass mode (normothermic versus hypothermic), on-pump versus off-pump, type of cardioplegia used (blood versus crystalloid), or use of saphenous vein grafts, single or bilateral internal mammary artery grafts, or other types of bypass grafts
  - Hospital characteristics (hospital patient volume, setting, guideline-based treatment protocols)
- Safety and adverse effects, including adverse drug reactions, radiation exposure, access-site complications, renal dysfunction, anaphylaxis, arrhythmias, stent thrombosis, bleeding, and infections

Sample size

We will not exclude articles based on sample size.

C. 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 1; this strategy will be adapted as necessary for use in the other databases. We will limit our search to reports of

RCTs. If it becomes necessary and/or appropriate to do so in order to expand the base of available evidence for certain KQs, we may also consider data from observational studies. We will date-limit our search to articles published since January 2001. To capture relevant evidence from older studies, we will also review the included articles from a previous AHRQ evidence report on the diagnosis and treatment of coronary heart disease in women,[27] whose methodology included a systematic search of MEDLINE and the Cochrane Database for relevant literature published from January 1985 through July 2001. 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).

In developing this comprehensive review, we will apply the rules of evidence and formulation of strength of evidence recommended by AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*).[28] 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 throughout our evidence review. 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.

D. 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 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. Guidance documents will be drafted and provided to the researchers as reference material to perform this task, thus aiding in both reproducibility and standardization of data collection.

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, radiation exposure, access-site complications, renal dysfunction, anaphylaxis, arrhythmias, stent thrombosis, infections, and bleeding. Data necessary for assessing quality and applicability, as described in the *Methods Guide*, 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.

E. 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*.[28] 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 evaluate methodological quality, we will apply criteria for each study type derived from the core elements described in the *Methods Guide*. 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. If included, 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.

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*. 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 PCI or CABG techniques that have changed over time), and clinical relevance and timing of the outcome measures. We will summarize issues of applicability qualitatively.

F. Data Synthesis

We will summarize the primary literature by abstracting relevant continuous (e.g., age, event rates) and categorical data (e.g., race, presence of coronary disease risk factors). We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depends on the volume of relevant literature, conceptual homogeneity of the studies, 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 heterogeneity while recognizing that the ability of statistical methods to detect heterogeneity may be limited. For comparison, we will also perform fixed-effects meta-analysis. We will present summary estimates, standard errors, and confidence intervals.

The majority of outcomes within this report are expected to be binary or categorical; we will, therefore, summarize these outcomes by proportions. We will summarize inherently continuous variables such as age by mean, median, and standard deviation.

G. 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*.[28] 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.

V. References

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VI. Definition of Terms

ACS	Acute coronary syndrome
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CKD	Chronic kidney disease
FRISC-II	Fast Revascularization during Instability in Coronary Artery Disease trial
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NSTEMI	Non–ST-elevation myocardial infarction
PCI	Percutaneous coronary intervention
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomized controlled trial
RITA-3	Randomized Intervention Trial of unstable Angina 3
STEMI	ST-elevation myocardial infarction

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TACTICS-TIMI 18	Treat Angina with aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy – Thrombolysis In Myocardial Infarction 18

VII. Summary of Protocol Amendments

Amendment 1, 14Sep2011:

This amendment modifies the ordering of the key questions in Section II to reorganize the report findings by disease presentation (STEMI, UA/NSTEMI and stable angina). Each key question contains subquestions on (a) the effectiveness of treatment strategies (optimal medical therapy, PCI, or CABG), (b) modifiers of effectiveness, and (c) safety concerns. In addition, the term stable CAD was changed to stable angina to clarify that the patient population of interest has symptomatic, stable angina, as opposed to patients who have a known diagnosis of CAD who are angina-free. For the STEMI population, we clarify that the comparison of interest is fibrinolytic therapy versus PCI. For the UA/NSTEMI population, we clarify that the comparison strategy of interest is initial conservative versus early invasive (PCI or CABG). For the stable angina population, we outline two comparisons of interests: first, optimal medical therapy versus mechanical revascularization, and second, PCI versus CABG. Finally, the project title was modified to reflect the project's emphasis on comparison of treatment strategies rather than comparison between individual treatment elements.

Original protocol	Change	Justification	Date change went into effect
KQs were organized by treatment strategy comparison	KQs were realigned in order to present the findings by disease presentation	Presenting the report findings by disease presentation (STEMI, UA/NSTEMI, and stable angina) improves clarity and readability for end users of the report.	14Sep2011
Term stable CAD used to describe a patient population of interest	Term revised to stable angina	The original term could be interpreted to include an asymptomatic patient group; the revision adds specificity.	14Sep2011
Key treatment comparisons questions for each disease presentation not well defined	Clarification added to denote the key comparisons of interest for each disease presentation	The revision clearly indicates the treatment comparison decisions of emphasis for each disease presentation, improving the readability of the report.	14Sep2011
Title presented as "Comparative Effectiveness of Treatments for Women With Coronary Artery Disease"	Title revised to "Comparative Effectiveness of Treatment Strategies for Women With Coronary Artery Disease"	The revised title clarifies the report's focus on comparison of treatment strategies for this population.	14Sep2011

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VIII. Review of Key Questions

For Comparative Effectiveness Reviews (CERs), the key questions were posted for public comment and finalized 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 healthcare 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 task order officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Expert Panel (TEP)

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 health 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 peer or 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 Review

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 three months after the publication of the Evidence Report.

Appendix 1. Proposed Search Strategy

cardiovascular diseases OR heart diseases OR heart OR cardiovas* OR cardiac* OR coronary OR myocardial OR acute coronary syndrome OR myocardial infarction OR unstable angina

AND
(Coronary Artery Bypass OR CABG OR aortocoronary bypass OR coronary revascularization OR myocardial revascularization) OR (percutaneous transluminal coronary angioplasty OR PTCA OR percutaneous coronary intervention* OR PCI OR Stent* OR stents OR Balloon angioplasty OR Balloon dilatation OR Balloon dilation OR Transluminal angioplasty OR coronary atherectomy)

AND
women OR woman OR female OR females OR sex factors

AND
randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]

NOT
animals[mh] NOT humans[mh] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp]) OR (Animals[Mesh:noexp])

Limits: English, Publication Date from 2001/01/01