Comparative Effectiveness Review
Number 66

Effective Health Care Program

Treatment Strategies for Women With Coronary Artery Disease

Executive Summary

Background

Cardiovascular disease remains the leading cause of death among women in the 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, and angina—is the most prevalent form of cardiovascular disease and is the largest subset of this mortality. An estimated 16.3 million Americans 20 years of age and older have CAD, and the overall CAD prevalence is 7 percent in adults in the United States (8.3% for men, 6.1% for women). The prevalence of CAD is higher in men than in women across different age groups until they reach 75 years of age, giving the perception that CAD is a male-specific disease.[1]

This report focuses on women because of the differences in clinical presentation and coronary anatomy, which affect the treatment options for CAD.[3-5] Currently available guidelines and systematic reviews provide specific treatment recommendations for women only among a subset of treatment options and overall assume that treatment options are equally effective for both sexes when gender

Effective Health Care Program

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

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

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data are not available. However, women have a worse prognosis than men for manifestations of CAD such as acute myocardial infarction, and some data suggest that women and men do not respond equally to the same treatments. Further, women are more likely than men to experience bleeding complications.[6-9]

In women, CAD is misdiagnosed or not treated as aggressively as in men or is underresearched.[10-12] Multiple factors[13] are likely to contribute to the lower use of evidence-based medicine (medical therapy and/or coronary revascularization) and the higher rate of cardiovascular complications among women with CAD.[3] These factors include:

- Cardiovascular disease affects women later in life.[1,13-15]
- 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.[10]
- Women present with angina-equivalent symptoms such as dyspnea or atypical symptoms more often than men.[16,17]
- The coronary vessels in women tend to be smaller than those of men, which makes them more difficult to revascularize percutaneously and surgically,[18] and microvascular disease of the coronary arteries is more common in women than in men.[19]
- Women tend to have less extensive CAD and a higher proportion of nonobstructive CAD.[20,21]
- Delay in hospitalization, symptom pattern and recognition, and higher frequency of nonobstructive CAD ultimately results in delay in diagnosis and effective treatment.[13,14,22,23]
- Because of underrepresentation of women in randomized controlled trials (RCTs), a lack of solid data on cardiovascular disease in women leaves uncertainty about the risk–benefit ratio of treatment.[24,25]

Thus, a better understanding of the evidence for the effectiveness of medical treatment and revascularization therapies specifically in women is needed in order to reduce cardiovascular events in women.

Clinical Presentations of CAD

Coronary artery disease 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 obstruction and tissue damage (non-ST elevation myocardial infarction [NSTEMI]) to complete epicardial occlusions leading to possible 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 acute coronary syndrome.[26,27]

Angina resulting from progressive narrowing of the coronary arteries is the initial manifestation of ischemic heart disease in approximately one-half of patients.[28] 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 angina is a sign of significant CAD—defined angiographically as a stenosis with greater than 70 percent diameter in at least one major epicardial artery segment or with greater than 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.[28]

Unstable angina (UA) is defined as angina with at least one of three features: (1) it occurs at rest or with minimal exertion, (2) it is severe and of recent onset (within the past 4 to 6 weeks), and/or (3) it occurs in a crescendo pattern (i.e., more severe, more prolonged, or more frequent than previously experienced). UA and NSTEMI have a fairly similar pathophysiology, mortality rate, and management strategy when compared with STEMI; therefore they are often grouped together as UA/NSTEMI in clinical guidelines and trial populations. Chronic stable angina is classified as pain that classically occurs with moderate to severe exertion, is milder in nature, and is relieved with rest or sublingual nitroglycerin.

Treatment Options for Patients With CAD

Optimal Medical Therapy

All patients with CAD—regardless of clinical presentation—should receive aggressive management of risk factors for progression of atherosclerosis (smoking, hypertension, hyperlipidemia, and diabetes) combined with pharmacological treatment (antiplatelets, antianginals, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and lipid-lowering drugs).[29] Optimal medical therapy of CAD comprises the combinations of these treatments to reduce future cardiovascular events for all the clinical presentations outlined in the previous section. However, patients may not be able to receive optimal medical therapy if they have allergies to, or adverse effects from, individual medications (e.g., aspirin, beta blockers, or cholesterol-lowering drugs) or the combination of medications. Also, 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, patients should be prescribed appropriate therapy to reach their therapeutic goal. The effectiveness of medical therapy is also affected by how adherent the patient is to the prescribed therapy.

Coronary Revascularization

Coronary revascularization falls broadly into two categories: coronary artery bypass grafting (CABG) and catheter-based percutaneous coronary intervention (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. CABG and PCI (with or without stents) are alternative approaches in 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 very high CAD burden—often described as left main CAD or severe triple-vessel disease with reduced left ventricular function—because CABG has previously been shown in RCTs to improve survival when compared with medical therapy. In contrast, PCI is generally preferred for patients with milder CAD burden—described as single- or double-vessel disease—when symptoms warrant coronary revascularization, in light of its lower procedural risk and evidence that PCI reduces angina and myocardial ischemia in this subset of patients. Uncertainty exists about the choice between PCI and CABG for patients with moderate CAD burden; namely, patients with disease of the proximal left anterior descending artery and less extensive forms of triple-vessel CAD. Most 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 or vessels with extensive atherosclerotic disease. CABG has the advantages of greater durability (graft patency rates exceeding 90% at 10 years with arterial conduits) and more complete revascularization regardless of the morphology of the obstructing atherosclerotic lesion.[30]

Therefore, patients and clinicians have two or more major treatment approaches to consider for each presentation of CAD. In general, these fall into less invasive (i.e., more medical) approaches and more invasive approaches. Table A summarizes the major treatment options for each clinical scenario described in the sections that follow.

Table A. Comparisons of treatment strategies for women with CAD

CAD Presentation	Treatment Choices
STEMI	• PCI vs. fibrinolysis • PCI vs. conservative/supportive medical management
NSTEMI/unstable angina	Early invasive management (with PCI or CABG) vs. initial conservative management
Stable/unstable angina	PCI vs. CABG vs. optimal medical therapy

CABG = coronary artery bypass grafting; CAD = coronary artery disease; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction

STEMI

Treatment for patients with ST-segment elevation is well established. Patients with STEMI are candidates for reperfusion therapy (either pharmacological or catheter-based) to restore blood flow promptly in the occluded epicardial infarct-related artery. Pharmacological therapy consists of fibrinolysis or conservative/supportive therapy with facilitated antithrombotic medications.[27] Multiple randomized trials have demonstrated the benefit of PCI in reducing major cardiovascular adverse events when compared with fibrinolysis or conservative therapy; therefore, immediate revascularization with PCI is the preferred strategy when patients have close access to a catheterization facility. Otherwise, fibrinolysis is recommended (in facilities without access) since it also has been shown to improve cardiovascular outcomes. In older or unstable patients, the use of fibrinolytics can increase bleeding complications; therefore, trials comparing conservative medical therapy to PCI have been performed. In general, patients with STEMI are not treated with CABG (unless emergent from PCI complications) but do receive optimal medical therapy.

UA/NSTEMI

Patients with UA/NSTEMI are not candidates for immediate pharmacological reperfusion. The optimal management of UA/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 in some cases the use of invasive procedures. In addition to aggressive medical therapy, two treatment pathways have emerged for treating patients without ST-segment elevation.[26] 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. An early 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 early invasive strategy generally will undergo coronary angiography within 4 to 24 hours of admission; however, these patients also are treated with the usual UA/NSTEMI medications, including appropriate anti-ischemic, antiplatelet, and anticoagulant therapy. Several RCTs have demonstrated improved clinical outcomes in patients with an invasive strategy, leading to guideline recommendations for invasive approaches to treat patients with NSTEMI and high-risk acute coronary syndrome. Patients with UA/NSTEMI also receive optimal medical therapy.

Angina

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.[28] 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.

Objectives of This Review

Although CAD is the leading cause of death for women in the United States, treatment studies to date have primarily enrolled men and may not reflect the benefits and risks that women experience. We conducted this systematic review of the medical literature to assess the comparative effectiveness of the major treatment options for CAD specifically in women, evaluating these comparisons:

1. PCI versus fibrinolysis or PCI versus conservative/supportive medical management in women with STEMI
2. Early invasive versus initial conservative management in women with UA/NSTEMI
3. PCI versus CABG versus optimal medical therapy in women with stable or unstable angina

The endpoints assessed were clinical outcomes, modifiers of effectiveness by demographic and clinical factors, and safety outcomes. The following Key Questions (KQs) were considered in this review:

KQ 1. In women presenting with ST elevation myocardial infarction (STEMI):

a. What is the effectiveness of percutaneous coronary intervention (PCI) versus fibrinolysis/supportive therapy on clinical outcomes (nonfatal MI, death, stroke, repeat revascularization, recurrent unstable angina, heart failure, repeat hospitalization, length of hospital stay, angina relief, quality of life, or cognitive effects)?

b. Is there evidence that the comparative effectiveness of PCI versus fibrinolysis/supportive 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 coronary artery bypass graft surgery [CABG] revascularization procedure)?
- Hospital characteristics (hospital volume, setting, guideline-based treatment protocols)?

c. 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 or non-ST elevation myocardial infarction (UA/NSTEMI):

a. What is the effectiveness of early invasive (PCI or CABG) versus initial conservative therapy on clinical outcomes (nonfatal MI, death, stroke, repeat revascularization, recurrent unstable angina, heart failure, repeat hospitalization, length of hospital stay, graft failure, angina relief, quality of life, or cognitive effects)?

b. Is there evidence that the comparative effectiveness of early invasive versus initial conservative 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)?

c. 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 presenting with stable or unstable angina:

a. What is the effectiveness of the following treatment strategies on clinical outcomes (nonfatal MI, death, stroke, repeat revascularization, recurrent unstable angina, heart failure, repeat hospitalization, length of hospital stay, graft failure, angina relief, quality of life, or cognitive effects)?

- Revascularization (PCI or CABG) versus optimal medical therapy in women with stable angina
- PCI versus CABG in women with stable or unstable angina

b. Is there evidence that the comparative effectiveness of revascularization versus optimal medical therapy varies based on characteristics such as:

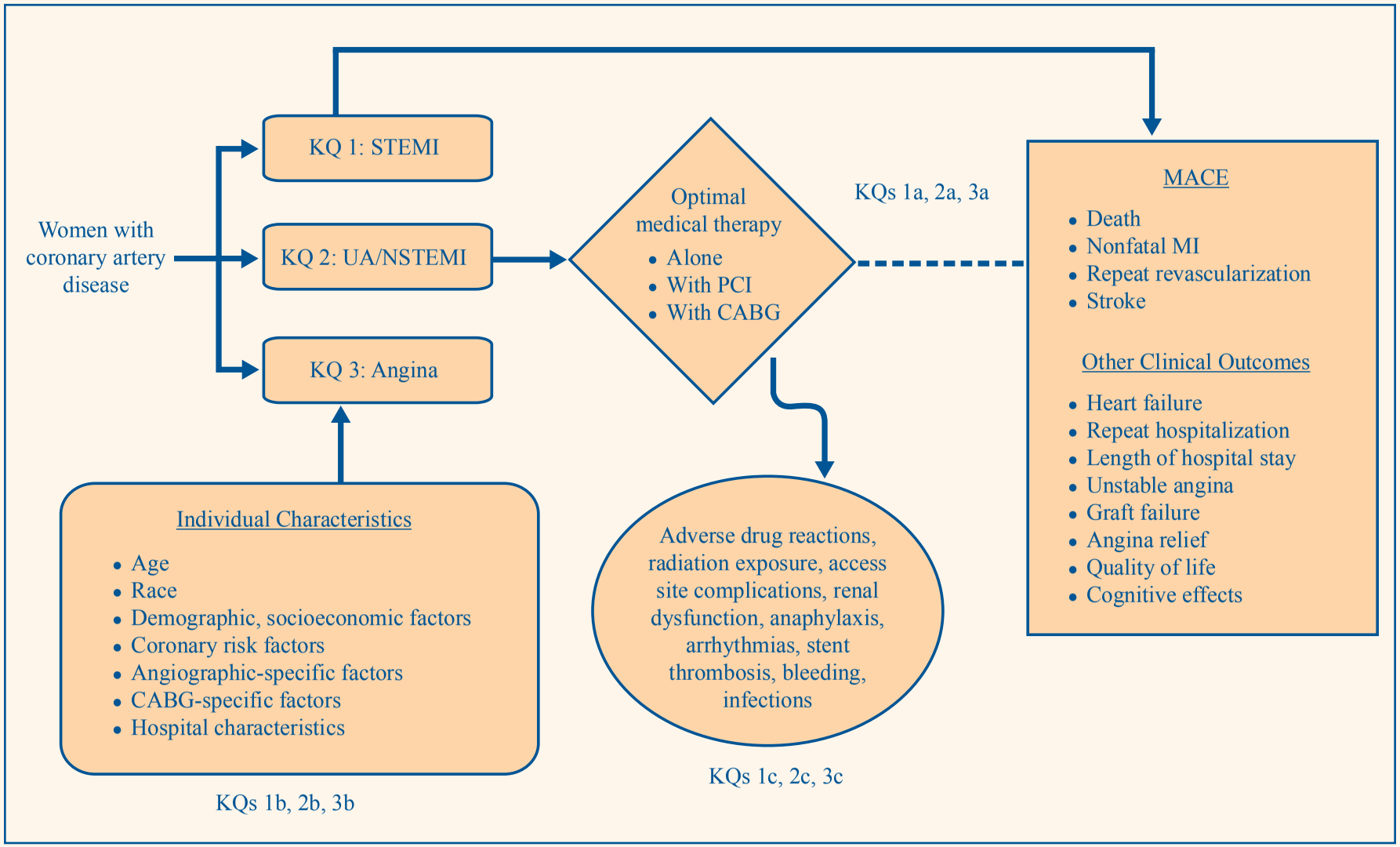
- Age, race, or other demographic and socioeconomic risk factors?
- Coronary disease risk factors such as diabetes, chronic kidney disease, or other comorbid disease?
- Angiographic-specific factors (number of diseased vessels, vessel territory stenoses, left ventricular function, access site, or prior PCI or CABG revascularization procedure)?
- 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 vs. 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)?

c. 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)?

Analytic Framework

Figure A shows the analytic framework for the systematic review of treatment strategies for women with CAD.

Figure A. Analytic framework



CABG = coronary artery bypass grafting; CAD = coronary artery disease; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction

Methods

Input From Stakeholders

During the topic refinement stage, the KQs were refined with the help of an eight-person Key Informant group representing clinicians (cardiology, primary care, cardiac surgery), patients, scientific experts, and Federal agencies. We solicited input from the Task Order Officer and an eight-person Technical Expert Panel (TEP) with experts knowledgeable in CAD, PCI, and CABG throughout our evidence review and followed, based on an a priori research protocol, the Effective Health Care Program's Methods Guide for Effectiveness and Comparative Effectiveness Reviews[31] (hereafter referred to as the Methods Guide) for literature search strategies, inclusion/exclusion of studies, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each KQ. All Key Informant and TEP participants were screened for conflicts of interest, and any potential conflicts were balanced or mitigated.

Data Sources and Selection

We included studies published in English from January 1, 2001, through December 12, 2011. Search strategies were specific to each database in order to retrieve the articles most relevant to the KQs. Our search strategy used the National Library of Medicine's medical subject headings (MeSH) keyword nomenclature developed for MEDLINE® and adapted for use in other databases. In consultation with our research librarians, we used PubMed®, Embase®, the Cochrane Database of Systematic Reviews, and the Cochrane Central Registry of Controlled Trials for our literature search. We also searched the grey literature of study registries and conference abstracts for relevant articles from completed RCTs. Grey literature databases included Clinicaltrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; WHO: International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index. The exact search strings used in our strategy are given in Appendix A of the full report. The reference lists of articles applicable to the relevant KQs of two previous Agency for Healthcare Research and Quality (AHRQ) reports related to this topic[32,33] and from identified systematic reviews and meta-analyses were manually hand-searched and cross-referenced against our library, and additional manuscripts were retrieved. All citations were imported into an electronic bibliographic database (EndNote® Version X4; Thomson Reuters, Philadelphia, PA).

We developed a list of article inclusion and exclusion criteria for the KQs (Table B). This review focused on randomized controlled studies, since this is the strongest study design for evaluating treatment effectiveness and since observational studies contain potential biases (e.g., patient selection bias, intervention bias) that could affect the clinical outcome. The TEP approved this approach given that the number of abstracts identified in PubMed exceeded 5,000. This review focused on comparisons of treatment strategies; therefore, differences in specific drugs or devices were not investigated and were considered beyond the scope. Using the prespecified inclusion and exclusion criteria, titles and abstracts were examined independently by two reviewers for potential relevance to the KQs. Articles included by any reviewer underwent full-text screening. At the full-text screening stage, two independent reviewers read each article to determine if it met eligibility criteria. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to "include" or "exclude" the article for data abstraction. When the paired reviewers arrived at different decisions about whether to include or exclude an article, they reconciled the difference through a third-party arbitrator. Articles meeting our eligibility criteria were included for data abstraction. Relevant review articles, meta-analyses, and methods articles were flagged for manual searching and cross-referencing against the library of citations identified through electronic database searching.

Data Extraction and Quality Assessment

The investigative team created forms for abstracting the data elements for the KQs. The abstraction forms were pilot tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors for accuracy. Based on their clinical and methodological expertise, two researchers were assigned to abstract data from the eligible articles pertaining to the research questions. One researcher abstracted the data, and the second overread the article and the accompanying abstraction form to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion if consensus was not reached by the first two researchers. Guidance documents were drafted and given to the researchers as reference material to perform data abstraction, thus aiding in both reproducibility and standardization of data collection.

Table B. Summary of inclusion and exclusion criteria		
Study Characteristic	**Inclusion Criteria**	**Exclusion Criteria**
Population	Adult women (≥18 years of age) with CAD and angiographically proven single- or multiple-vessel disease including STEMI, NSTEMI, and stable angina.	• Study population was composed entirely of patients without CAD, or the population also included patients with CAD but results were not reported separately for the subgroup with CAD. • Study did not include women, or results were not reported by sex. • All subjects under age 18, or some subjects under age 18, but results were not broken down by age. • Study did not report any of the primary or secondary outcomes of interest.
Interventions and comparators	Article reported original data for any of the interventions compared with another treatment category; or a related methodology paper of an included article. • Optimal medical therapy alone. • PCI (bare-metal and drug-eluting stents) with optimal medical therapy. • CABG with optimal medical therapy.	Intervention comparisons within the same treatment category such as: • Medical therapy with medical therapy (e.g., one type of fibrinolysis drug compared with another fibrinolysis drug). • PCI with PCI (e.g., bare-metal stent compared with drug-eluting stent). • CABG with CABG (e.g., open sternotomy compared with minimally invasive CABG).
Outcomes and effect modifiers	• 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 interventions: adverse drug reactions, radiation exposure, access site complications, renal dysfunction, anaphylaxis, arrhythmias, stent thrombosis, bleeding, infections. Effect modifiers—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.	• Outcomes of women not reported separately from total population. • Study did not report any of the primary or secondary outcomes of interest.

Table B. Summary of inclusion and exclusion criteria (continued)		
Study Characteristic	**Inclusion Criteria**	**Exclusion Criteria**
Outcomes and effect modifiers (continued)	• 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).	
Timing	Short-term (≤30 days), intermediate-term (1 year), or long-term (>1 year).	None.
Setting	Inpatient or outpatient, primarily primary care and cardiology clinics.	None.
Study design	Randomized controlled trial (strongest study design for evaluating treatment effectiveness).	• Observational (retrospective or prospective cohort) studies, due to potential biases that could affect the clinical outcome (e.g., patient selection bias, intervention bias). • Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series). Systematic reviews and meta-analyses were excluded from abstraction but hand-searched as potential sources of additional material if relevant to the topic.
Publication languages	English only.	Given the high volume of English-language publications (including the majority of known important studies), non-English articles were excluded.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction

To aid in both reproducibility and standardization of data collection, researchers received data abstraction instructions directly on each form created specifically for this project with the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada). We designed the data abstraction forms for this project to collect the data required to evaluate the specified eligibility criteria for inclusion in this review as well as to collect demographics and outcomes. The safety outcomes abstracted included adverse drug reactions, radiation exposure, access-site complications, renal dysfunction, anaphylaxis, arrhythmias, stent thrombosis, bleeding, and infections—the more common adverse events resulting from medical therapy and revascularization. Data on the total population and women and men subgroups were collected. Appendix B of the full report lists the elements used in the data abstraction form. Appendix C contains a bibliography of all studies included in this review, organized alphabetically by author. When appropriate, methods articles providing additional detail were considered when abstracting data for an included study. If a methods article was used as a source for information in the abstraction of a study, it was included in the review and is listed in the bibliography in Appendix C.

Study quality was assessed on the basis of the reported methods and results and performed by two reviewers. We evaluated the quality of individual studies using the approach described in the Methods Guide.[31] To evaluate methodological quality, we applied criteria for RCTs that were derived from the core elements described in the Methods Guide. To indicate the summary judgment of the quality of the individual studies, we used the summary

ratings of Good, Fair, and Poor based on the study's adherence to well-accepted standard methodologies and adequate reporting.

We used data abstracted on the population studied, the intervention and comparator, the outcomes measured, settings, and timing of assessments to identify specific issues that may have limited the applicability of individual studies or a body of evidence as recommended in the Methods Guide.[31] We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population (e.g., age, race/ethnicity, sex) in comparison with the target population, version or characteristics of the intervention used in comparison with therapies currently in use (e.g., 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 summarized issues of applicability qualitatively. Appendix D of the full report summarizes our assessment of the quality and applicability for each included study.

Data Synthesis and Analysis

We synthesized the primary literature by continuous data (e.g., age, event rates) and categorical data (e.g., race/ethnicity, presence of coronary disease risk factors). We determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). The feasibility of a meta-analysis depended on the volume of relevant literature (two or more studies), and clinical and methodological homogeneity of the studies. When a meta-analysis was appropriate, we used random-effects models to quantitatively synthesize the available evidence (Review Manager software Version 5.1.; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). We tested for heterogeneity while recognizing that the ability of statistical methods to detect heterogeneity may be limited. When feasible, we used similar composite outcomes in the meta-analysis for two reasons: (1) a majority of studies reported a composite outcome (e.g., death/MI/stroke/revascularization) as their primary endpoint and (2) many of the studies reported results for women for the primary composite outcome but not for each individual (secondary) outcome. We presented summary odds ratio estimates, standard errors, and confidence intervals for women and men separately to show any similarity or differences.

The majority of outcomes within this report were binary or categorical; therefore, we summarized these outcomes by proportions. We summarized inherently continuous variables, such as age, by mean, median, and standard deviation.

Grading the Body of Evidence

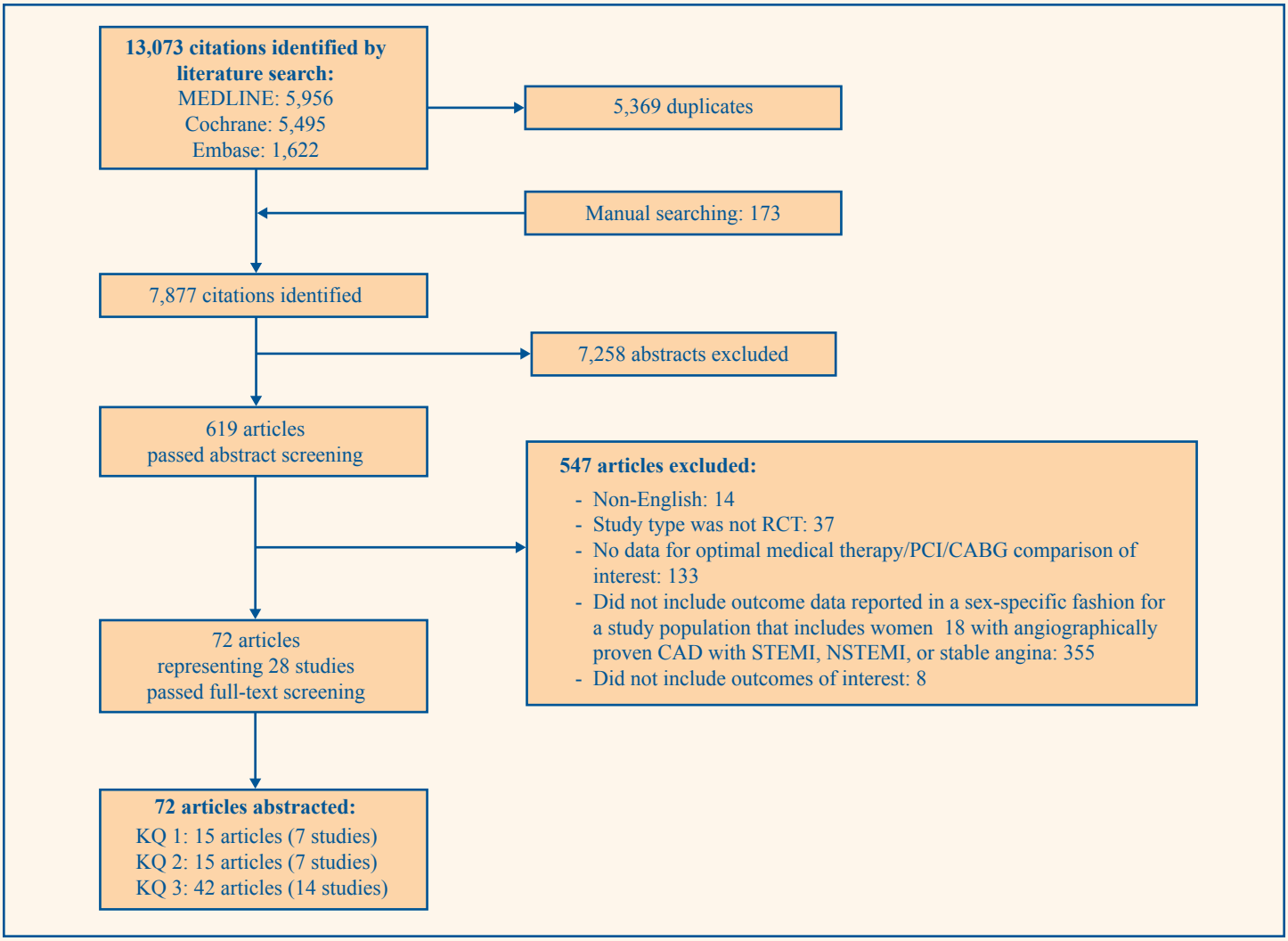
The strength of evidence for each KQ was assessed by using the approach described in the Methods Guide.[31] The evidence was evaluated by using the four required domains: risk of bias (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), and precision (precise or imprecise). Additionally, when appropriate, the studies were evaluated for the presence of confounders that would diminish an observed effect, the strength of association (magnitude of effect), and publication bias. The strength of evidence was 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.

Results

The flow of articles through the literature search and screening process is depicted in Figure B. Of the 13,073 citations identified by our searches, 5,369 were duplicates. Manual searching identified an additional 173 citations for a total of 7,877 citations. After applying inclusion/exclusion criteria at the title/abstract level, 619 full-text articles were retrieved and screened. Of these, 547 articles were excluded at the full-text screening stage, with 72 articles (representing 28 studies) remaining for data abstraction. Appendix E of the full report provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure B. Literature flow diagram



CABG = coronary artery bypass graft; CAD = coronary artery disease; KQ = Key Question; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; STEMI = ST elevation myocardial infarction

Summary of Key Findings

Our search identified 28 comparative studies (72 articles, including methodology and secondary analysis papers). Of the 28 studies, 24 were good quality and 4 were fair quality for their overall reporting of methodology and analysis. A total of 35,597 patients included 10,126 (28%) women. We grouped these by CAD presentation and type of comparison:

- KQ 1: seven studies (six good quality, one fair) comparing PCI with fibrinolysis/supportive (five fibrinolysis, two supportive) in patients with STEMI
- KQ 2: seven studies (six good quality, one fair) comparing early invasive (PCI or CABG) with initial conservative in patients with UA/NSTEMI
- KQ 3: 5 studies (all good quality) comparing revascularization (PCI or CABG) with optimal medical therapy in patients with stable angina (Strategy 1) and 10 studies (8 good quality, 2 fair) comparing PCI with CABG in patients with either stable or unstable angina (Strategy 2). There were a total of 14 studies with 1 study containing data for both comparative strategies.

Table C summarizes the key findings for each KQ, including the modifiers of effectiveness and safety concerns, and provides a grade for the strength of supporting evidence. Detailed reporting of the risk of bias, consistency, directness, precision, and limits to applicability are described in the Summary and Discussion section of the full report.

Table C. Summary of key findings		
Key Question	**Strength of Evidence**	**Conclusions**
KQ 1: Women with STEMI (PCI vs. fibrinolysis/ supportive therapy)	Effectiveness of intervention 1. High (women and men) for short-term (30-day) composite outcomes 2. Insufficient (women and men) for intermediate-term (1-year) composite outcomes Modifiers of effectiveness Insufficient Safety concerns Insufficient	7 studies (6 good quality, 1 fair) compared PCI with or without supportive therapy with fibrinolysis or other routine medical care for women with STEMI and contributed evidence about the comparative effectiveness, modifiers of effectiveness, or safety for these interventions. These studies included a total of 4,527 patients, of which 1,174 (26%) were women. • Effectiveness of interventions: A meta-analysis of 5 studies (all good quality) reporting 30-day composite outcomes (primarily death/MI/stroke) showed that PCI was better than fibrinolysis in women (OR, 0.50; 95% CI, 0.36 to 0.72) and men (OR, 0.54; CI, 0.42 to 0.70). However, there was insufficient evidence for assessing outcomes at 1 year. • Modifiers of effectiveness: 2 studies (1 good quality, 1 fair) reported subgroup analyses of demographic or clinical factors in women and included a total of 395 patients, of which 167 (32%) were women. 1 good-quality study evaluated the comparative effectiveness of PCI vs. fibrinolysis in patients <65 years of age and ≥65 and found no differences in in-hospital mortality among the treatment groups. 1 fair-quality study evaluated patients ≥80 years of age with STEMI. The study was limited by a small overall size, and it did not find significant differences in outcomes in patients ≥80 years with STEMI undergoing PCI compared with usual (supportive) medical care. • Safety concerns: 2 good-quality studies reported safety concerns in women with STEMI and included a total of 1,532 patients, of which 367 (24%) were women. 1 study reported a lower nadir hematocrit in women receiving PCI vs. fibrinolysis but no statistically significant differences in the requirement for blood transfusion. Another study reported the proportion of women with intracranial hemorrhage in women who received PCI vs. accelerated t-PA (0% vs. 4.1%). No studies systematically reported radiation exposure, contrast reactions, access site complications, or stent thrombosis in women with STEMI undergoing PCI.

Table C. Summary of key findings (continued)		
Key Question	**Strength of Evidence**	**Conclusions**
KQ 2: Women with UA/NSTEMI (early invasive vs. initial conservative)	Effectiveness of interventions 1. Low (women) and high (men) for short-term (6-month) composite outcomes 2. Low (women and men) for intermediate-term (1-year) composite outcomes 3. Insufficient (women) and low (men) for long-term (5-year) composite outcomes Modifiers of effectiveness Insufficient Safety concerns Insufficient	7 studies (6 good quality, 1 fair) compared early invasive (revascularization via PCI or CABG) with initial conservative therapy for women with UA/NSTEMI and contributed evidence about the comparative effectiveness, modifiers of effectiveness, or safety for these interventions. These studies included a total of 17,930 patients, of which 6,084 (34%) were women. • Effectiveness of interventions: A meta-analysis of 2 good-quality studies reporting 6-month composite outcomes (death/MI) suggested a benefit of early invasive compared with initial conservative therapy in women (OR, 0.77; 95% CI, 0.28 to 2.12) that, however, was not statistically significant; early invasive therapy was superior to initial conservative therapy in men at 6 months (OR, 0.65; CI, 0.52 to 0.82; p=0.0002). At 1 year, a meta-analysis of 5 good-quality studies showed that the composite outcome (primarily death/MI) suggested a similar benefit in women who received early invasive therapy (OR, 0.78; CI, 0.54 to 1.12) as well as in men (OR, 0.88; CI, 0.64 to 1.20); however, this was not statistically significant. A meta-analysis of 2 good-quality studies with 5-year followup between early invasive and initial conservative therapy for the composite outcome of death/MI in both sexes suggested a small benefit of initial conservative therapy in women (1.05; CI, 0.81 to 1.35) while suggesting a benefit of early invasive therapy in men (0.91; CI, 0.53 to 1.56). Given the small suggested benefit at 5 years in women, the wide confidence interval crossing 1, and the trend favoring early invasive therapy suggested at earlier time points and across time points in men — we cannot support firm conclusions. • Modifiers of effectiveness: 2 good-quality studies comparing initial conservative medical therapy with early invasive therapy with PCI reported a subgroup analysis by risk stratification and included a total of 4,030 patients, of which 1,439 (36%) were women. These studies revealed conflicting results—one showed no difference in treatment outcomes in the intermediate- and high-risk groups; the other showed a higher event rate in women in the groups with moderate-to-high risk for thrombolysis in myocardial infarction. • Safety concerns: 1 good-quality study (2,220 total patients, 757 [34%] women) reported the harms associated with treatment of UA/NSTEMI by sex group but not the rates of events by treatment group. Bleeding in women undergoing PTCA was higher compared with men (adjusted OR, 3.6; 95% CI, 1.6 to 8.3). However, bleeding related to CABG was similar in women and men, with rates of 12.6 and 15%, respectively. No studies systematically reported radiation exposure, contrast reactions, access site complications, stent thrombosis, or infection in women with UA/NSTEMI comparing early invasive with initial conservative therapy.

Table C. Summary of key findings (continued)		
Key Question	**Strength of Evidence**	**Conclusions**
KQ 3: Strategy 1—women with stable angina (revascularization vs. optimal medical therapy)	Effectiveness of interventions 1. With the PCI strategy: Moderate (women) and low (men) for long-term (4- to 5-year) composite outcomes 2. With the CABG strategy: Low (women and men) for long-term (4- to 5-year) composite outcomes 3. With both types of revascularization: Moderate (women) and low (men) for long-term (4- to 5-year) composite outcomes	5 studies (all good quality) compared revascularization (PCI or CABG) with optimal medical therapy for women with stable angina and contributed evidence about the comparative effectiveness, modifiers of effectiveness, or safety for these interventions. These studies included a total of 6,851 patients, of which 1,285 (19%) were women. • Effectiveness of interventions: A meta-analysis of 3 good-quality studies with long-term followup on the composite outcomes (death/MI/revascularization) comparing PCI or CABG with optimal medical therapy showed that revascularization was significantly better than optimal medical therapy in women with stable angina (OR, 0.64; 95% CI, 0.47 to 0.89; p=0.008 for PCI strategy trials; OR, 0.56; CI, 0.32 to 0.96; p=0.04 for CABG strategy trials; and OR, 0.59; CI, 0.43 to 0.81; p=0.001 for either PCI or CABG). However, for men with stable angina, the analysis suggested a small benefit for optimal medical therapy when compared with PCI (OR, 1.03; CI, 0.79 to 1.33). This suggested small benefit however has a wide confidence interval crossing 1 and is not supported by additional time periods or by the evidence in women. Analyses suggested a benefit of CABG (OR, 0.62; CI, 0.31 to 1.24) or either PCI or CABG (OR, 0.71; CI, 0.49 to 1.02) in men with stable angina. These findings were not statistically significant and had very wide confidence intervals.

Table C. Summary of key findings (continued)		
Key Question	**Strength of Evidence**	**Conclusions**
KQ 3: Strategy 2—women with stable/unstable angina (PCI vs. CABG)	Effectiveness of interventions 1. Low (women and men) for short-term (30-day) composite outcomes 2. Low (women and men) for intermediate-term (1-year) composite outcomes 3. Low (women) and high (men) for long-term (>2-year) composite outcomes Modifiers of effectiveness Insufficient Safety concerns Insufficient	10 studies (8 good quality, 2 fair) compared PCI with CABG in women with stable/unstable angina and contributed evidence about the comparative effectiveness, modifiers of effectiveness, or safety for these interventions. These studies included a total of 6,289 patients, of which 1,583 (25%) were women. • Effectiveness of interventions: A meta-analysis of 2 good-quality studies reporting a 30-day death outcome showed no statistically significant difference between PCI and CABG in either men or women. The summary odds ratio in women was 0.68 (95% CI, 0.24 to 1.93) and in men was 1.36 (CI, 0.44 to 4.24). The odds ratios suggest a possible sex effect, with PCI showing more benefit in women and CABG showing more benefit in men, but the confidence intervals are too wide to support firm conclusions. For 1-year composite outcomes (death/MI/stroke), a meta-analysis of 2 good-quality studies showed lower events in the CABG group for both sexes, but this benefit was not statistically significant. The summary odds ratio in women was 1.30 (CI, 0.69 to 2.45) and in men was 1.19 (CI, 0.84 to 1.70). For long-term (>2 years) composite outcomes (death/MI/stroke), a meta-analysis of 4 good-quality studies suggested lower events in the CABG group in women (OR, 1.17; CI, 0.90 to 1.54) although again this did not reach statistical significance; however in men, CABG was significantly better than PCI in lowering cardiovascular events (OR, 1.63; CI, 1.20 to 2.23; p=0.002). • Modifiers of effectiveness: 1 good-quality study evaluated the comparative effectiveness of PCI vs. CABG in diabetic patients with stable/unstable angina. The survival rate at 7 years was similar in diabetic women from both treatment groups. However in diabetic men, those treated with CABG had higher survival than those treated with PCI. • Safety concerns: 1 good-quality study reported harms associated with PCI compared with CABG among women with UA/NSTEMI and found that bleeding associated with PCI was higher in women compared with men (OR, 29.4; 95% CI, 5.3 to 500; p=0.001). No studies systematically reported radiation exposure, contrast reactions, access site complications, stent thrombosis or infection, in women with UA/NSTEMI undergoing PCI or CABG.

CABG = coronary artery bypass grafting; CI = confidence interval; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; SOE = strength of evidence; STEMI = ST elevation myocardial infarction; t-PA = tissue plasminogen activator; UA = unstable angina

Discussion

The findings from this systematic review on the treatment strategies for women across the spectrum of CAD presentations highlight areas for future research and for informing clinical practice. First, this review underscores the significant need for clinical researchers to provide study findings with women-specific data on the primary and secondary clinical outcomes. Overall, we were able to find only 28 relevant studies with data on either shorter term or longer term outcomes in women with CAD treated with invasive or conservative medical therapies. In addition, the representation of women enrolled in these trials was low. Melloni et al.[25] found similarly low rates with sex-specific results discussed in only 31 percent of the 156 primary trial publications cited by the American Heart Association's 2007 women's prevention guidelines. In addition, they found that enrollment of women in randomized clinical trials had increased over time (18% in 1970 to 34% in 2006) but remained low relative to their overall representation in disease populations (e.g., 25% women representation in RCTs of CAD compared with 46% women representation in the CAD population).

Second, our findings confirm current practice and evidence for care in one of the three areas evaluated. For women patients with STEMI, we found that an invasive approach with immediate PCI is superior to fibrinolysis in reducing cardiovascular events in women. These findings are similar to a meta-analysis[34] of 23 randomized trials comparing PCI with fibrinolysis for acute MI in combined populations of men and women. However, for patients with NSTEMI treated with an early invasive approach compared with a conservative or selective invasive approach, this review did not find statistically significant evidence about the benefit of an early invasive approach in reducing cardiovascular events in women—although our findings did suggest a benefit of early invasive therapy. In contrast, the meta-analysis for trials of early invasive versus conservative strategies in the overall population showed a statistically significant benefit of early invasive therapy.[35] The results from this review suggest that such a benefit may also be true in women, but the confidence intervals are too wide to support a firm conclusion.

In addition, for medical therapy alone versus revascularization plus medical therapy for patients with stable angina or high CAD burden, the findings from the current analysis suggest a benefit of revascularization in women. These findings should be viewed with caution because they are based on a limited number of studies with data on 704 (17%) women; these analyses often have both PCI and CABG together in the revascularization group, and the overall findings from these studies do not show a significant benefit beyond angina or symptom reduction for revascularization. In these studies, it is possible that women who present later in life with CAD, and with higher CAD burden, may be obtaining a greater benefit with revascularization, and the findings from this analysis should prompt further research in this area and again encourage researchers to provide data specific on women. In contrast, previous meta-analyses that combined results for men and women found similar outcomes for either treatment. The higher proportion of men enrolled in these trials (83%) may have led to the masking of the women's results by the men's results within a pooled analysis.

Our stakeholder group advised us to assess the effectiveness of these therapies by sex on multiple important clinical outcomes such as nonfatal MI, death, stroke, repeat revascularization, recurrent unstable angina, heart failure, repeat hospitalization, length of hospital stay, angina relief, quality of life, or cognitive effects. A majority of sex-specific reporting was on the composite outcome of major cardiovascular adverse events (death, MI, or revascularization). Individual outcomes by sex were rarely reported, especially on heart failure, repeat hospitalization, length of hospital stay, angina relief, quality of life, or cognitive effects.

Based on the small number of studies that looked at demographic and clinical factors that influence response to treatment strategies in women, there was insufficient evidence that clinicians can use to determine if age, race/ethnicity, socioeconomic status, coronary risk factors, angiographic-specific factors, CABG-specific factors, or hospital-level characteristics should be taken into consideration when deciding a treatment strategy for women with CAD. Unfortunately, more studies are needed that evaluate the subgroups and various demographic and clinical characteristics to fully understand this evidence gap.

In addition, the safety concerns or harms of these treatment strategies are underreported for women enrolled in RCTs. It appears that the bleeding risk may be higher in women receiving fibrinolysis or PCI. Careful consideration should be given to the dose, timing, and duration of antiplatelet, antithrombotic, and anticoagulant therapies administered to women.

Limitations of the Review Process

With 28 studies meeting the inclusion criteria, this systematic review has several limitations. First, our search

focused on comparative RCTs—the highest quality of evidence for determining the efficacy of different treatment modalities on cardiovascular outcomes. While this was adequate for evaluating the evidence to support the clinical outcomes by treatment strategy and by CAD presentation for the overall population, there were very few RCTs that reported subgroup analyses by demographic or clinical characteristics and also very few RCTs that reported the harms or risks of therapy. Most studies that reported results applicable to modifiers of effectiveness or safety did this for the overall population and did not separate the effects by sex. We are aware that there are several observational and noncomparator studies of each of the treatment modalities that address these issues in women. Because of the problems with confounding from observational studies and the difficulty of constructing reliable comparisons among single-arm studies, we did not include observational or noncomparator studies in our review.

Second, the sample size and low representation of women in most of the comparator studies may affect the study authors' ability to analyze the results by sex, therefore reducing the number of studies reporting these findings separately (i.e., reporting bias). We excluded 355 articles due to lack of sex-specific reporting of the study results, which resulted in low numbers of studies available for analysis for each clinical presentation (STEMI, UA/NSTEMI, stable angina). Of these 355 articles, 116 were associated with the same 28 studies included in our review, but they did not report data on women separately. The remaining 239 articles were associated with 173 studies that did not report data on women. Figure C presents a graph of the number of articles reporting data on women per year. The percentage ranges from 0 percent (in 1992 and 1993) to 75 percent in 1995. On average, 17 percent of the articles comparing treatment strategies for CAD reported sex-specific outcomes. Of note, many articles included a multivariate analysis that included sex as a covariate in the model; the majority found no evidence of a sex effect. The result of a multivariable model is insufficient for incorporating into a meta-analysis; thus these were excluded from the review. Reporting bias in these publications therefore resulted in selection bias in this review.

Third, the strength of our meta-analysis is limited by the different definitions of the primary composite outcome and by the timing (short term and long term) of those clinical endpoints. We used our best judgment in choosing which composite outcomes (e.g., death/MI/stroke and death/MI/stroke/revascularization) and time points (e.g., in hospital and 30 days) to combine in the meta-analysis.

A final limitation is the change in PCI techniques and definition of optimal medical therapy over time. Most of the studies involved balloon angioplasty or bare-metal stents. The current era of drug-eluting stents and the use of dual antiplatelet therapy may be underrepresented. Nevertheless, the findings represent the best available evidence. While the treatment options continue to evolve over time, these older therapies (bare-metal stents, balloon angioplasty) are still being used in clinical practice, and therefore we did not downgrade the strength of evidence based on the availability of newer technologies. Medication adherence to beta blockers, angiotensin-converting enzyme inhibitors, aspirin, antiplatelet agents, and lipid-lowering agents were not reported in the studies included in this review. There was also variable reporting on the implementation of optimal medical therapy.

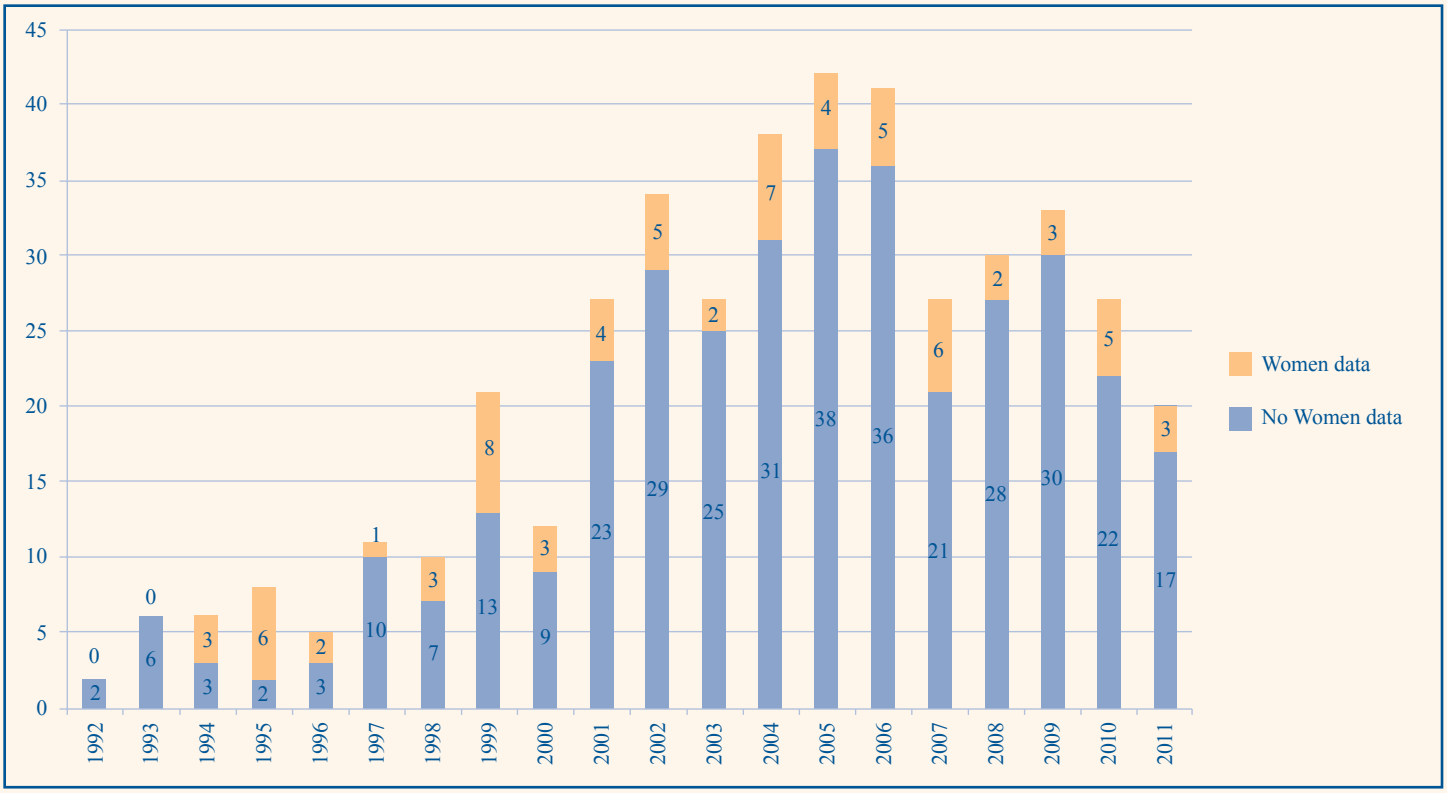
Many of these studies were multicenter, international RCTs with multiple countries represented. The generalizability of those studies to the United States may be of concern; however, the practice of revascularization and prescription of medical therapies are not dramatically different.

Conclusions

From a limited number of studies reporting results for women separately from the total study population, our findings confirm current practice and evidence for care in one of the three areas evaluated.

1. For women with STEMI, we found that an invasive approach with immediate PCI is superior to fibrinolysis for reducing cardiovascular events, which is similar to findings in previous meta-analyses combining results for both women and men.
2. For women with NSTEMI or unstable angina, we found that, although not statistically significant, the evidence suggests a benefit of an early invasive approach in reducing cardiovascular events, whereas previous meta-analyses of studies comparing early invasive with initial conservative strategies on a combined population of men and women showed a statistically significant benefit of early invasive therapy.
3. For women with stable angina, the few trials reporting sex-specific data on revascularization compared with optimal medical therapy showed a greater benefit with revascularization for women, while the men in the study fared equally well with either treatment. In contrast, previous meta-analyses that combined results for men and women found similar outcomes for either treatment.

Figure B. Literature flow diagram



Implications for Future Research

This comprehensive review of the comparative effectiveness of treatment modalities for women with CAD identified numerous gaps in evidence that would be suitable for future research and for improving the reporting of women findings of cardiovascular therapies in the published literature.

Studies With Sufficient Representation of Women

Sex subgroup analyses are often limited by the number of men or women in each treatment group to allow for adequate power to detect a statistically significant difference in outcome. While we were able to find RCTs that reported risk ratios in women, the enrollment numbers were insufficient to have adequate power to detect a difference, thus resulting in large confidence intervals that often crossed the null effect, with a potential type II error. To better understand the clinical outcomes of women treated by medical therapy or revascularization, trials should be either (1) women-only enrollment or (2) of large enough sample size with stratification of randomization by sex to allow for meaningful sex-based analyses. In order to assess sex differences in treatment modalities and their impact on clinical outcomes, a sufficient sample size is required in order to have adequate statistical power for subgroup analyses.

Patient-Level Meta-Analysis

Given the small representation of women in these RCTs, the heterogeneity of clinical outcomes (e.g., definition of composite outcome) and different measurement time points (e.g., 30 days or 6 weeks for short-term outcomes), we are aware that our group-level meta-analysis may be inadequate (when too few studies are available) to address the comparative effectiveness of medical therapy and revascularization. Therefore, patient-level analysis of trials comparing similar interventions for the same CAD presentation may be more appropriate for assessing the sex differences as well as for conducting subgroup analyses on demographic and clinical factors that influence treatment outcomes, or for evaluating safety concerns/harms of these treatment strategies. Subgroup analyses across trials can be done similarly to a previous AHRQ report on the comparative effectiveness of PCI and CABG, which included an addendum study that pooled individual patient data from 10 randomized trials to compare the effectiveness of CABG with PCI according to patients'

baseline clinical characteristics (e.g., age, diabetes, sex, individual cardiac risk factors, angioplasty versus bare metal stents).[32,36,37]

Reporting Sex by Treatment Results Separately

Our review excluded trials that looked for a sex effect yet failed to provide results of women and men by treatment arm. An example is a trial that did a multivariate analysis to assess factors that influenced clinical outcomes and included male (or female) sex in the model, with a finding that it was nonsignificant or significant. We did not contact the corresponding authors of the articles that did not report sex results separately. It would aid future comparisons of treatment modalities if study authors were to report the primary data for women and men separately either within the article itself or in an online supplementary appendix. The 2010 report by the Institute of Medicine on Women's Health Research recommended that funding agencies ensure adequate participation of women and reporting of sex-specific analyses in health research.[38]

Reporting of Demographic and Clinical Factors That Influence Cardiovascular Outcomes

We found a few studies that conducted subgroup analyses of age, diabetes, and risk stratification in women populations. We did not find any data specific to women on race/ethnicity, socioeconomic factors, chronic kidney disease, angiographic-specific factors, or CABG-specific factors that were listed in KQ 2. Knowing the influence of these factors on cardiovascular outcomes is important for determining the proper treatment strategy and prognosis of women patients who present with various risk factors and comorbidities.

Reporting of Safety Concerns/Risks by Sex

Medical therapy can result in adverse drug reactions, and use of fibrinolytics can result in bleeding or intracranial hemorrhage. PCI can cause access site complications, radiation exposure, contrast-related anaphylaxis, bleeding, and stent thrombosis. CABG can result in wound infections, renal dysfunction, and bleeding. Most studies reported the bleeding risk of revascularization strategies but not the other safety concerns. Systematic reporting of adverse events in publications—in total and by sex—should continue to clarify which treatment modalities are safe for use in clinical practice.

To summarize, these evidence gaps could be addressed in various ways. First, more primary research with adequate representation of women for any of the three CAD clinical presentations could be conducted to achieve adequate statistical power for a sex-based analysis. Second, authors of the comparative trials that were excluded for not reporting sex-based results could be contacted to provide results of women and men by treatment arm, and the group-level meta-analysis could be repeated with a larger number of trials. Alternatively, these authors could be contacted to provide compatible (deidentified) datasets that could be combined for a patient-level analysis to assess the comparative effectiveness, modifiers of effectiveness, and risks of the various treatment strategies available. Finally, the use of observational cohorts from electronic health records could inform the real-world effectiveness of the treatment strategies chosen by clinicians and patients in a nonrandom fashion.

Glossary

AHRQ	Agency for Healthcare Research and Quality
CABG	coronary artery bypass graft
CAD	coronary artery disease
CI	confidence interval
KQ	Key Question
MACE	major adverse cardiovascular events
MI	myocardial infarction
NSTEMI	non-ST elevation myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
SOE	strength of evidence
STEMI	ST elevation myocardial infarction
TEP	Technical Expert Panel
t-PA	tissue plasminogen activator
UA	unstable angina

References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart Disease and Stroke Statistics—2012 Update: A Report From the American Heart Association. Circulation. 2012;125(1):e2-e220. PMID: 22179539.
2. Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. Circulation. 2007;115(11):1481-501. PMID: 17309915.
3. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. J Am Coll Cardiol. 2009;54(17):1561-75. PMID: 19833255.
4. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. N Engl J Med. 1999;341(4):226-32. PMID: 10413734.
5. Berger JS, Elliott L, Gallup D, et al. Sex differences in mortality following acute coronary syndromes. JAMA. 2009;302(8):874-82. PMID: 19706861.

6. Mieres JH, Shaw LJ, Arai A, et al. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Circulation 2005;111(5):682-96. PMID: 15687114.

7. Alexander KP, Chen AY, Newby LK, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative. Circulation. 2006;114(13):1380-7. PMID: 16982940.

8. Pepine CJ. Ischemic heart disease in women: facts and wishful thinking. J Am Coll Cardiol 2004;43(10):1727-30. PMID: 15145090.

9. Vaccarino V, Abramson JL, Veledar E, et al. Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. Circulation. 2002;105(10):1176-81. PMID: 11889010.

10. Mikhail GW. Coronary heart disease in women. BMJ. 2005;331(7515):467-8. PMID: 16141136.

11. Vaccarino V, Parsons L, Every NR, et al. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med. 1999;341(4):217-25. PMID: 10413733.

12. Daly C, Clemens F, Lopez Sendon JL, et al. Gender differences in the management and clinical outcome of stable angina. Circulation. 2006;113(4):490-8. PMID: 16449728.

13. Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. J Am Coll Cardiol. 2005;45(6):832-7. PMID: 15766815.

14. Anand SS, Xie CC, Mehta S, et al. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. J Am Coll Cardiol. 2005;46(10):1845-51. PMID: 16286169.

15. Vaccarino V, Rathore SS, Wenger NK, et al. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. N Engl J Med. 2005;353(7):671-82. PMID: 16107620.

16. Milner KA, Funk M, Richards S, et al. Gender differences in symptom presentation associated with coronary heart disease. Am J Cardiol. 1999;84(4):396-9. PMID: 10468075.

17. Patel H, Rosengren A, Ekman I. Symptoms in acute coronary syndromes: does sex make a difference? Am Heart J. 2004;148(1):27-33. PMID: 15215788.

18. Klein J, Karawan A, Abeles-Raviv N, et al. Is there a gender difference in risk profile, attendance, and beneficial effects of a multidisciplinary cardiac rehabilitation program? J Am Coll Cardiol. 2002;39(Supplement 1):1088-1137.

19. Kaski J. Cardiac syndrome X. In: Wenger NK and Collins P, eds. Women and heart disease. 2nd ed. London: Informa Healthcare. 2005:205-216.

20. Clayton TC, Pocock SJ, Henderson RA, et al. Do men benefit more than women from an interventional strategy in patients with unstable angina or non-ST-elevation myocardial infarction? The impact of gender in the RITA 3 trial. Eur Heart J. 2004;25(18):1641-50. PMID: 15351164.

21. Hochman JS, McCabe CH, Stone PH, et al. Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIB. TIMI Investigators. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol. 1997;30(1):141-8. PMID: 9207635.

22. Kreatsoulas C, Natarajan MK, Khatun R, et al. Identifying women with severe angiographic coronary disease. J Intern Med. 2010;268(1):66-74. PMID: 20210841.

23. Wenger NK. Angina in women. Curr Cardiol Rep 2010;12(4):307-14. PMID: 20425162.

24. Lee PY, Alexander KP, Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA. 2001;286(6):708-13. PMID: 11495621.

25. Melloni C, Berger JS, Wang TY, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. Circ Cardiovasc Qual Outcomes. 2010;3(2):135-42. PMID: 20160159.

26. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/ Non ST-elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 2007;116(7):e148-304. PMID: 17679616.

27. Kushner FG, Hand M, Smith SC, Jr., et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009;120(22):2271-306. PMID: 19923169.

28. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina--summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Circulation. 2003;107(1):149-58. PMID: 12515758.

29. Sibley C, Rivera J, Blumenthal RS.'ABCDE' makes an effective prevention tool. Cardiology Today: approach translates guidelines into a comprehensive management plan for the primary and seconday prevention of CVD [commentary]. 2007 Jun 1. www.cardiologytoday.com/view.aspx?rid=39071.

30. Lansky AJ, Hochman JS, Ward PA, et al. Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association. Circulation. 2005;111(7):940-53. PMID: 15687113.

31. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0. Rockville, MD: Agency for Healthcare Research and Quality. Draft Posted October 2007. www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318.

32. Bravata DM, McDonald KM, Gienger AL, et al. Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease. Comparative Effectiveness Review No. 9. (Prepared by Stanford-UCSF Evidence-based Practice Center under Contract No. 290-02-0017.) Rockville, MD: Agency for Healthcare Research and Quality. October 2007. www.effectivehealthcare.ahrq.gov/ehc/products/15/55/CER_PCI_CABGMainReport.pdf. PMID: 20704052.

33. Grady D, Chaput L, Kristof M. Results of systematic review of research on diagnosis and treatment of coronary heart disease in women. Evid Rep Technol Assess (Summ). 2003(80):1-4. PMID: 12827897.

34. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003;361(9351):13-20. PMID: 12517460.

35. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. JAMA. 2005;293(23):2908-17. PMID: 15956636.

36. Hlatky MA, Boothroyd DB, Bravata DM, et al. Addendum to Coronary Artery Bypass Surgery Compared With Percutaneous Coronary Interventions for Multivessel Disease. Comparative Effectiveness Review No. 9 Addendum. (Prepared by Stanford-UCSF Evidence-based Practice Center under Contract No. 290-02-0017.) Rockville, MD: Agency for Healthcare Research and Quality. February 2010. www.effectivehealthcare.ahrq.gov/ehc/products/15/421/CER9%20Addendum%20Final.pdf.

37. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet. 2009;373(9670):1190-7. PMID: 19303634.

38. Women's Health Research: Progress, Pitfalls, and Promise. Institute of Medicine of the National Academies, Consensus Report. 2010. www.iom.edu/Reports/2010/Womens-Health-Research-Progress-Pitfalls-and-Promise.aspx.

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