Effective Health Care Program

Comparative Effectiveness Review
Number 66

Treatment Strategies for Women With Coronary Artery Disease

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Treatment Strategies for Women With Coronary Artery Disease

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Treatment Strategies for Women With Coronary Artery Disease

Structured Abstract

Objectives. Although coronary artery disease (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. Our systematic review of the medical literature assessed the comparative effectiveness of major treatment options for CAD specifically in women. The comparisons were (1) percutaneous coronary intervention (PCI) versus fibrinolysis/supportive pharmacologic therapy in ST elevation myocardial infarction (STEMI), (2) early invasive versus initial conservative management in non-ST elevation myocardial infarction (NSTEMI) or unstable angina, and (3) PCI versus coronary artery bypass surgery (CABG) versus optimal medical therapy in stable or unstable angina. The endpoints assessed were clinical outcomes, modifiers of effectiveness by demographic and clinical factors, and safety outcomes.

Data Sources. MEDLINE®, PubMed®, Embase®, and Cochrane Database of Systematic Reviews.

Review Methods. Randomized controlled trials published in English from January 1, 2001, to December 12, 2011, comparing the treatment options for CAD listed above and containing sex-specific outcomes. Clinical outcomes were classified as short term (≤30 days), intermediate term (1 year), or long term (>1 year). Random-effects meta-analysis was performed for studies with similar outcomes measured at similar time points.

Results. Twenty-eight comparative studies contributed evidence about effectiveness, modifiers of effectiveness, or safety for the comparisons described above. For women with STEMI, five studies showed a reduction in composite outcomes (primarily death/MI/stroke) at 30 days for PCI over fibrinolysis (odds ratio [OR] 0.50; 95% CI, 0.36 to 0.72; high strength of evidence [SOE]); there was insufficient evidence for assessing outcomes at 1 year. For women with NSTEMI or unstable angina, the included studies, although not showing statistical significance, suggested a benefit of early invasive over initial conservative management for the composite outcome of primarily death/MI at 6 months and 1 year (2 studies, OR 0.77; CI, 0.28 to 2.12; low SOE; 5 studies, OR 0.78; CI, 0.54 to 1.12; low SOE). Evidence, however, suggested a small benefit of initial conservative management at 5 years (2 studies, OR 1.05; CI, 0.81 to 1.35). Given the small suggested benefit at 5 years, 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 (insufficient SOE). For women with stable angina randomized to revascularization (PCI or CABG) or medical therapy, three studies showed a reduction in the composite outcome of death/ MI/repeat revascularization at 5 years for revascularization with either PCI (OR 0.64; CI, 0.47 to 0.89; moderate SOE) or CABG (OR 0.56; CI, 0.32 to 0.96; low SOE). For stable and unstable angina trials comparing PCI with CABG, two studies suggested a nonsignificant benefit of PCI in mortality at 30 days (low SOE). At 1 year and beyond, although suggestive of a benefit of CABG in for the composite outcomes

of death/MI/stroke for women, this finding was not statistically significant and represented wide confidence intervals (low SOE at 1 year and at >2 years).

Five studies assessed modifiers of effectiveness in women due to demographic factors (≥65 or ≥80 years of age) or clinical factors (risk stratification or diabetes). Strength of evidence for modifiers of effectiveness for STEMI, NSTEMI, and stable/unstable angina was insufficient.

Four studies assessed safety outcomes in women: two STEMI studies (PCI versus fibrinolysis) and two NSTEMI studies (PCI versus CABG) assessed transfusion rates, incidence of intracranial hemorrhage, and bleeding rates. Strength of evidence for safety outcomes for all the CAD presentations was insufficient.

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. 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. For women with NSTEMI or unstable angina, evidence suggested that an early invasive approach reduces cardiovascular events; however, it was not statistically significant. Previous meta-analyses of studies comparing early invasive with initial conservative strategies on a combined population of men and women showed a significant benefit of early invasive therapy. We also found that the few trials reporting sex-specific data on revascularization compared with optimal medical therapy for stable angina 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.

Limitations include a small number of trials with data for women available for meta-analysis, varying definitions of composite outcomes, and variable timing of followup. Future studies should collect and report clinical outcomes and harms in women by treatment strategy and at each followup time point—including subgroup data on important demographic and clinical factors that may modify clinical effectiveness—so that firmer conclusions can be reached about the risk and benefit of these therapies in women.

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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 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

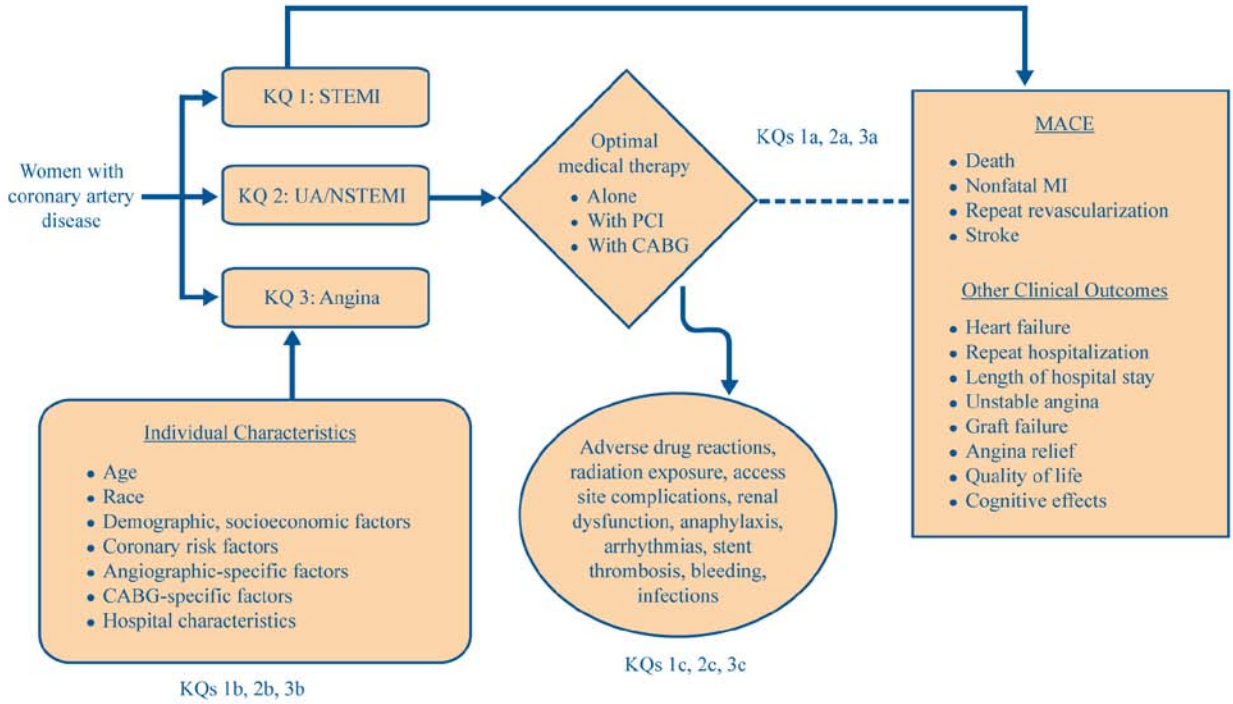
b. Is there evidence that the comparative effectiveness of revascularization versus optimal medical therapy varies based on characteristics such as:
   - Age, race, or other demographic and socioeconomic risk factors?
   - Coronary disease risk factors such as diabetes, chronic kidney disease, or other 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 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)?

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 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

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	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)	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 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)	Outcomes of women not reported separately from total population
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

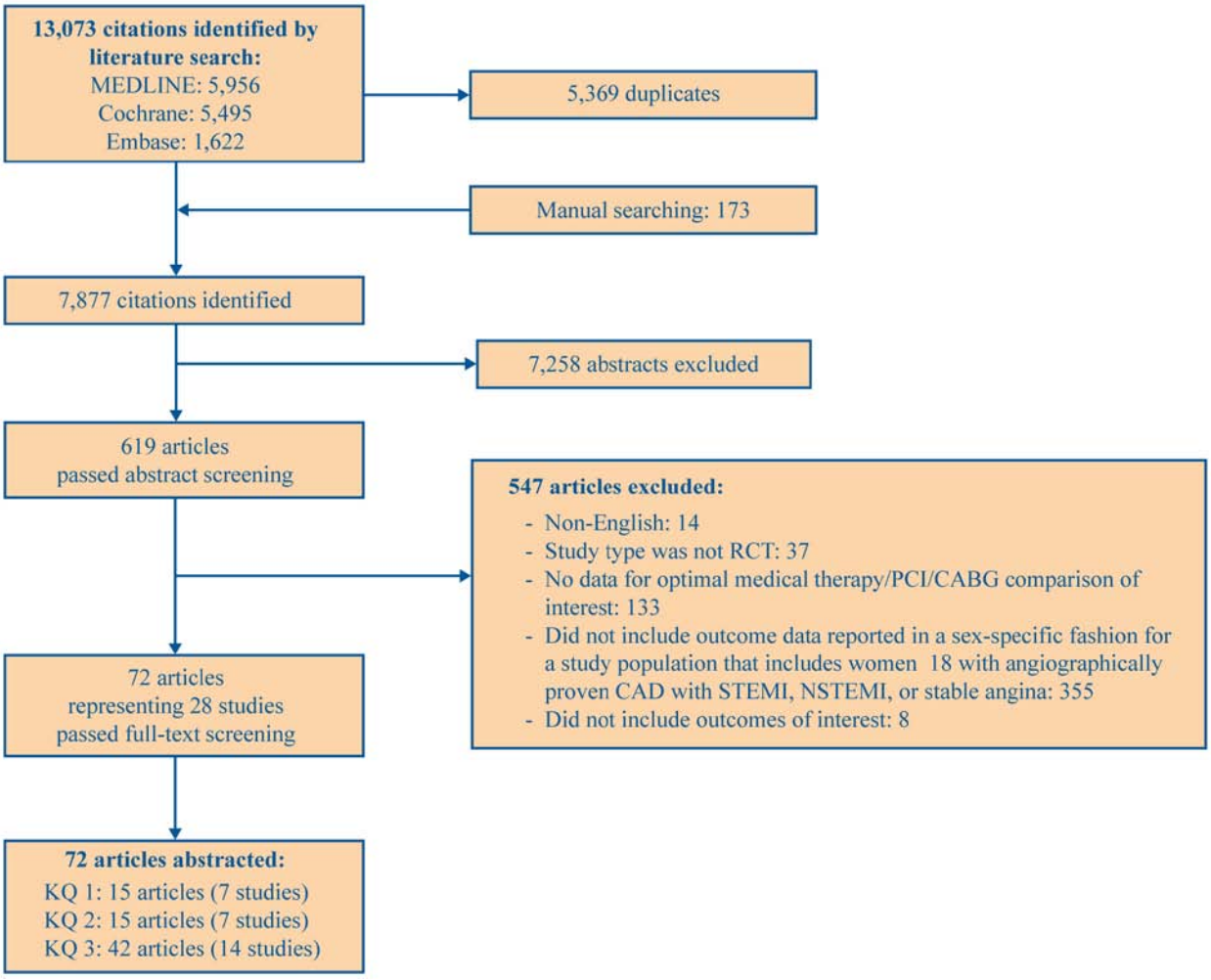
The strength of evidence for each KQ was assessed by using the approach described in the Methods Guide.[31] The evidence was evaluated by using the four required domains: risk of bias (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), 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:

b. High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
c. 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.
d. 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.
e. 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:

a. KQ 1: seven studies (six good quality, one fair) comparing PCI with fibrinolysis/supportive (five fibrinolysis, two supportive) in patients with STEMI
b. KQ 2: seven studies (six good quality, one fair) comparing early invasive (PCI or CABG) with initial conservative in patients with UA/NSTEMI
c. 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.

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.

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 1583 (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

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.

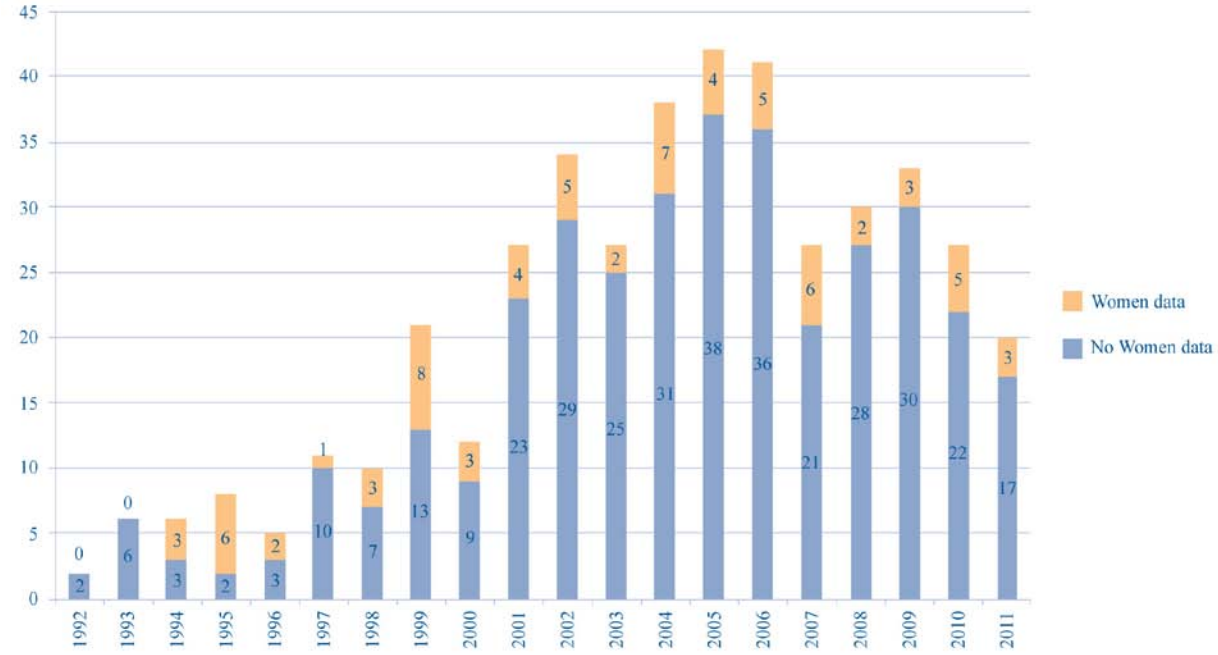
Limitations of the Review Process

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.

Figure C. Number of articles reporting data on women by year



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.

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

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Introduction

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, 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, thus giving the perception that CAD is a male-specific disease.[1]

The morbidity associated with this disease is also considerable. The estimated annual incidence of myocardial infarction is 610,000 new heart attacks; the average age at first myocardial infarction is 64.5 years for men and 70.3 for women. Many more individuals are hospitalized for unstable angina and for evaluation and treatment of stable chest pain syndromes. Recent data have shown a decrease in mortality rate in women, but reductions are well behind those obtained in men and are mainly in older women—still leaving the greater discrepancy in mortality rate limited to younger patients.[3-5]

This report focuses on women because of the differences in clinical presentation and coronary anatomy, which affect the treatment options for CAD.[6-8] 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 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.[9-12]

In women, CAD is misdiagnosed or not treated as aggressively as in men or is underresearched.[4,13,14] Multiple factors[15] 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.[6] These factors include:

- Cardiovascular disease affects women later in life.[1,15-17]
- 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.[13]
- Women present with angina-equivalent symptoms such as dyspnea or atypical symptoms more often than men.[18,19]
- The coronary vessels in women tend to be smaller than those of men, which makes them more difficult to revascularize percutaneously and surgically,[20] and microvascular disease of the coronary arteries is more common in women than in men.[21]
- Women tend to have less extensive CAD and a higher proportion of nonobstructive CAD.[22,23]

- Delay in hospitalization, symptom pattern and recognition, and higher frequency of nonobstructive CAD ultimately results in delay in diagnosis and effective treatment.[15,16,24,25]
- Because of underrepresentation of women in RCTs, a lack of solid data on cardiovascular disease in women leaves uncertainty about the risk-benefit ratio of treatment.[26,27]

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.[28,29]

Angina resulting from progressive narrowing of the coronary arteries is the initial manifestation of ischemic heart disease in approximately one-half of patients.[30] 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.[30]

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 typically occurs with moderate to severe exertion, is milder in nature, and 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).[31] 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 randomized controlled trials (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 or 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.[32]

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 1 summarizes the major treatment options for each clinical scenario described in the sections that follow.

Table 1. 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.[29] 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 with 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.[28] 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 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.[30] 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.

Scope and Key Questions

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 a 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 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)?
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)?

Methods

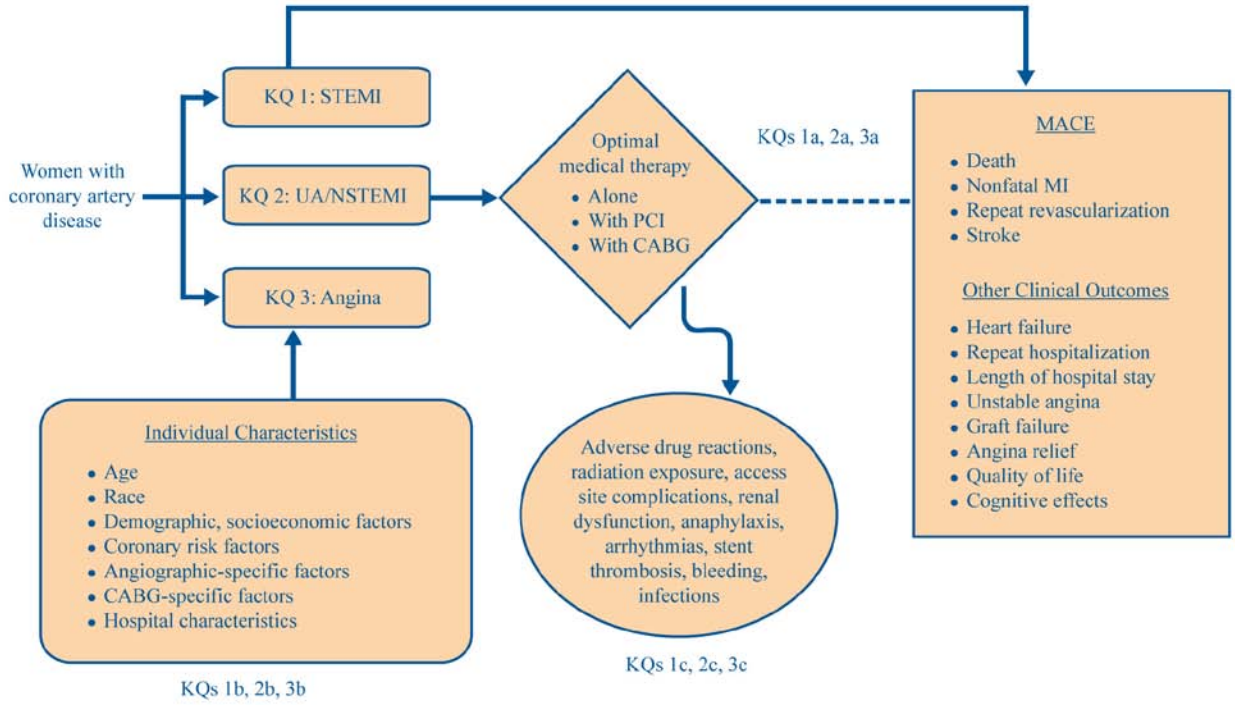
Topic Development and Refinement

During the topic refinement stage, the Key Questions (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[33] (hereafter referred to as 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.

Analytic Framework

Figure 1 shows the analytic framework for the systematic review of the comparative effectiveness of treatment strategies for women with CAD.

Figure 1. Analytic framework



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

Literature Search Strategy

Sources Searched

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. The reference list of articles applicable to the relevant KQs of two previous AHRQ reports related to this topic[34,35] and from identified systematic reviews and meta-analyses was 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).

Process for Study Selection

Screening for Inclusion and Exclusion

We developed a list of article inclusion and exclusion criteria for the KQs (Table 2). 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.

Table 2. 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	• Outcomes of women not reported separately from total population • Study did not report any of the primary or secondary outcomes of interest

Table 2. Summary of inclusion and exclusion criteria (continued)

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Outcomes and effect modifiers (continued)	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 • CABG-specific factors such as type of surgery performed (traditional or robot-assisted), cardiopulmonary bypass mode (normothermic vs. hypothermic), on-pump vs. 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 patient volume, setting, guideline-based treatment protocols)	Outcomes of women not reported separately from total population
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

Data Extraction and Data Management

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.

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—which are the more common adverse events resulting from medical therapy and revascularization.

Appendix B 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.

Individual Study Quality Assessment

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.[33] 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.[33] 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 summarizes our assessment of the quality and applicability for each included study.

Data Synthesis

We synthesized the primary literature by continuous (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 (2 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.

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.[33] 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). All the studies were randomized controlled trials and most were of good quality, resulting in a low risk of bias. To rate consistency, we looked at the test of heterogeneity and the I^2 value; any significant test of heterogeneity or I^2 value greater than 50 percent was rated as inconsistent. To rate directness, we looked at the composite outcome used in the meta-analysis; any inclusion of softer endpoints (e.g., revascularization or heart failure) in the composite outcome, or differences in the composite endpoint between studies, was rated as indirect. To rate precision, we looked at the effect sizes used in the power calculations of the trials to determine a clinically meaningful reduction in odds. For a negative finding, a confidence interval narrow enough to exclude a less than 30 percent reduction (or increase) was rated as precise. 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.

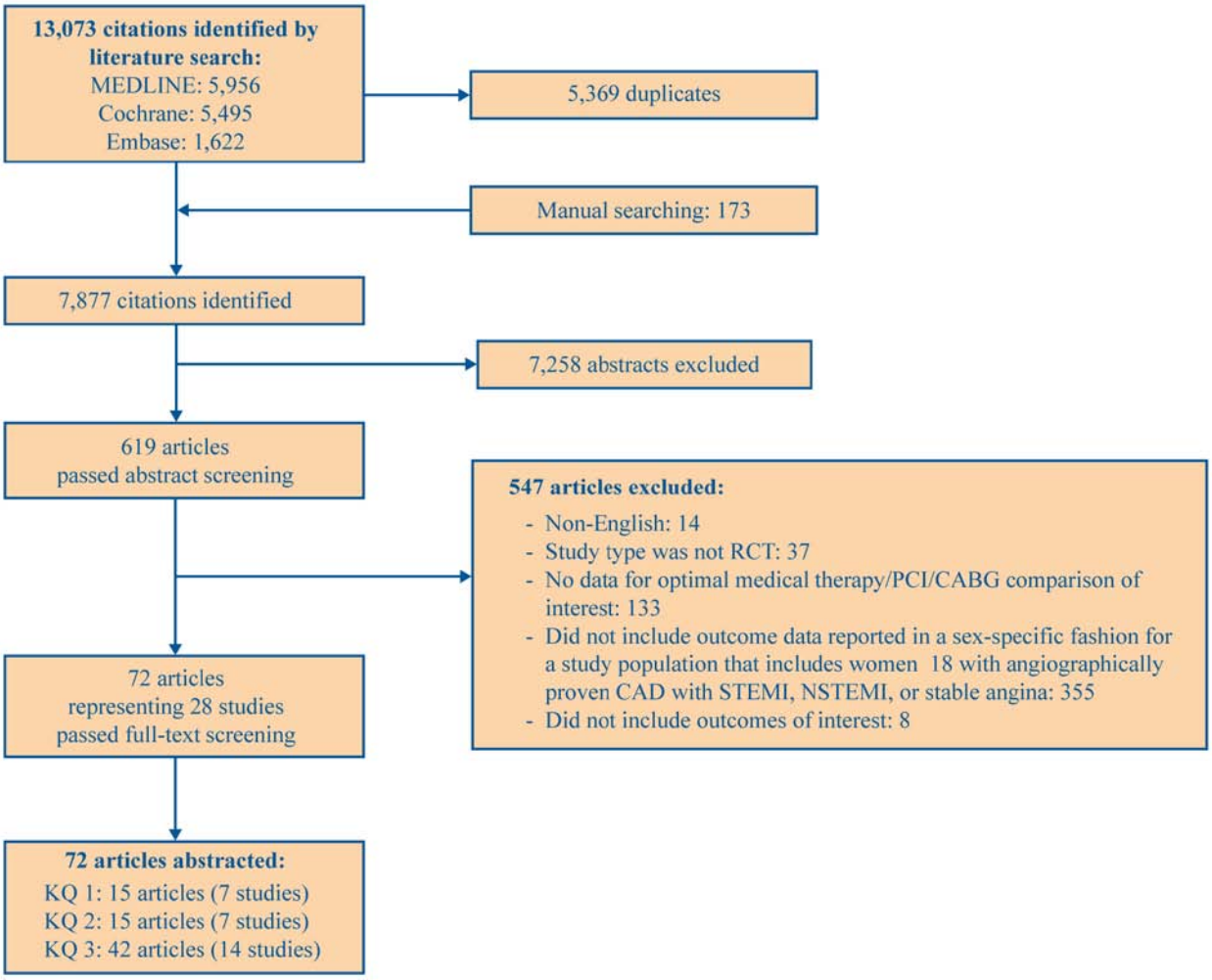
Peer Review and Public Commentary

The peer review process was our principal external quality-monitoring device. Nominations for peer reviewers were solicited from several sources, including the TEP and interested Federal agencies. The list of nominees was forwarded to AHRQ for vetting and approval. A list of reviewers submitting comments on the draft report is included in the Preface.

Results

The flow of articles through the literature search and screening process is depicted in Figure 2. 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 provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure 2. 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

Key Question 1: Women With STEMI (PCI Vs. Fibrinolysis)

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)?

Overview

STEMI is caused by the complete occlusion of an epicardial artery, leading to possible transmural infarction of the heart muscle. Treatment for patients with STEMI consists of 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 facilitated antithrombotic medications.[29] In general, patients with STEMI are not treated with CABG (unless emergent from PCI complications) but do receive optimal medical therapy in addition to treatment directed at removing the clot. Studies assessing the effectiveness of immediate PCI compared with fibrinolytics or immediate PCI compared with conservative/supportive therapy were evaluated for KQ 1.

Key Points

- **Description of included studies:** Seven studies (6 good quality, 1 fair) evaluated PCI with or without supportive pharmacologic therapy versus fibrinolysis or other routine medical care for women with STEMI and included a total of 4,527 patients, of which 1,174 (26%) were women.
- **Effectiveness of interventions:** A meta-analysis of five 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). Strength of evidence favoring PCI over fibrinolysis was high at 30-day followup. However, there was insufficient evidence for assessing outcomes at 1 year. These findings also are limited in that all the studies were conducted with either balloon angioplasty or bare-metal stents. The current use of drug-eluting stents may lead to different practice patterns and, potentially, increase the effectiveness of PCI. Individual outcomes by sex were rarely reported for heart failure, repeat hospitalization, length of hospital stay, angina relief, quality of life, or cognitive effects.
- **Modifiers of effectiveness:** Two 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. Both studies assessed the influence of age on in-hospital mortality or composite clinical outcomes (death/heart failure/MI/stroke) and showed no age-related differences in PCI compared with optimal medical therapy. Therefore, there was insufficient evidence of the comparative effectiveness of treatment strategies among subgroups of women with STEMI, which precludes any meaningful conclusions.
- **Safety concerns:** Two good-quality studies reported safety concerns in women with STEMI and included a total of 1,532 patients, of which 367 (24%) were women. One study reported a lower nadir hematocrit in women receiving PCI versus fibrinolysis but no statistically significant differences in the requirement for blood transfusion. Another study reported the proportion of women with intracranial hemorrhage who received PCI versus accelerated tissue plasminogen activator (t-PA) (0% vs. 4.1%). No studies systematically collected radiation exposure, contrast reactions, access site complications, or stent thrombosis in women with STEMI undergoing PCI. Strength of evidence for safety concerns in STEMI studies was insufficient.

Detailed Synthesis

We identified seven studies[36-42] that evaluated PCI with or without supportive pharmacologic therapy versus fibrinolysis or other routine medical care for women with STEMI. Of these seven studies, six were good quality, and one was fair quality. Table 3 presents a general description of these seven studies, including the study name, author, year, and related articles (i.e., study design and secondary papers); treatment comparisons evaluated; study population; and overall quality rating. Table 4 summarizes the women-specific outcomes (composite and individual) reported in these studies. Appendix F contains summary tables with sex-specific clinical outcomes for all followup time points.

Table 3. KQ 1: Study characteristics of RCTs evaluating women with STEMI

Study Author/Year Related Articles	Description of Study	# Subjects	Quality
CARESS-in-AMI Di Mario et al., 2008[36] and Di Mario et al., 2004[43]	**Title:** Immediate angioplasty vs. standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomized, multicentre trial **Comparator:** Immediate PCI with fibrinolysis (reteplase) vs. fibrinolysis (reteplase) with rescue PCI **Components of medical therapy:** Clopidogrel (300 mg bolus on arrival, then 75 mg once daily 1 to 12 months after stent implantation). Beta blockers, angiotensin-converting enzyme inhibitors, and statins were administered to all patients unless contraindicated.	Total: 600 Women: 128 (21%)	Good
DANAMI-2 Andersen et al., 2003[37] and Mortensen et al., 2007[44] Nielsen et al., 2010[45] Busk et al., 2009[46] Busk et al., 2008[47]	**Title:** A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction **Comparator:** PCI vs. fibrinolysis (accelerated t-PA) **Components of medical therapy:** Aspirin 300 mg, IV beta-blocker (20 mg of metoprolol), IV unfractionated heparin (5000 U bolus, then 1000 U/hr).	Total: 1,572 Women: 417 (27%)	Good
Dobrzycki et al., 2007[40]	**Title:** Transfer with GP IIb/IIIa inhibitor tirofiban for primary percutaneous coronary intervention vs. on-site thrombolysis in patients with ST elevation myocardial infarction (STEMI): a randomized open-label study for patients admitted to community hospitals **Comparator:** Transfer with tirofiban for primary PCI vs. onsite fibrinolysis (streptokinase) **Components of medical therapy:** Aspirin 325 mg daily. Additional treatment was administered at the discretion of the physician.	Total: 401 Women: 105 (26%)	Good
GUSTO II-B Tamis-Holland et al., 2004[39]	**Title:** Benefits of direct angioplasty for women and men with acute myocardial infarction: results of the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes Angioplasty (GUSTO II-B) Angioplasty Substudy **Comparator:** PCI vs. fibrinolysis (accelerated t-PA) **Components of medical therapy:** Not reported.	Total: 1,137 Women: 260 (23%)	Good

Table 3. KQ 1: Study characteristics of RCTs evaluating women with STEMI (continued)

Study Author/Year Related Articles	Description of Study	# Subjects	Quality
Minai et al., 2002[41]	**Title:** Long-term outcome of primary percutaneous transluminal coronary angioplasty for low-risk acute myocardial infarction in patients older than 80 years: a single-center, open, randomized trial **Comparator:** PCI vs. optimal medical therapy (without fibrinolysis) **Components of medical therapy:** IV heparin; IV nitroglycerin (0.5 mg/min/kg) for 24 hours after admission. Aspirin, other cardiovascular medications (calcium channel blockers, beta-blockers, and angiotensin-converting enzyme inhibitors administered at the discretion of the physician.	Total: 120 Women: 60 (50%)	Fair
PAMI Stone et al., 1995[42]	**Title:** Comparison of in-hospital outcome in men with outcome in women treated by either thrombolytic therapy or primary coronary angioplasty for acute myocardial infarction **Comparator:** PCI vs. fibrinolysis (t-PA) **Components of optimal medical therapy:** IV unfractionated heparin for 3 - 5 days, Nitroglycerin for at least 24 hours, followed by topic or oral nitrates. Aspirin 325 mg/daily, diltiazem 30 to 60 mg x 4 times a day; use of beta-blockers and IV lidocaine was left to investigator discretion.	Total: 395 Women: 107 (27%)	Good
SHOCK Hochman et al., 2001[38] and Hochman et al., 2006[48] Hochman et al., 1999[49] Hochman et al., 1999[50]	**Title:** One-year survival following early revascularization for cardiogenic shock **Comparator:** Early invasive revascularization (PCI or CABG within 6 hours) vs. initial medical stabilization (thrombolysis, IABP) **Components of optimal medical therapy:** Aspirin, IV unfractionated heparin, as recommended by AHA/ACC guidelines and at discretion of local investigator.	Total: 302 Women: 97 (32%)	Good

CABG = coronary artery bypass graft; IABP = intra-aortic balloon pump; IV = intravenous; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; STEMI = ST elevation myocardial infarction; t-PA = tissue plasminogen activator

Table 4. KQ 1: Outcomes reported in RCTs evaluating women with STEMI

Study	Composite Outcome[a] (Timing) Anticipated Effect Size	Death[a] (Timing)	MI (Timing)	Stroke (Timing)	Revascularization (Timing)	Other (Timing)
CARESS-in-AMI[36,43]	*Total mortality/reinfarction/refractory MI* (30 days) Powered to detect >50% RRR					
DANAMI-2[37,44-47]	*Total mortality/nonfatal MI/stroke* (30 days, 3 years; median 7.8 years) Powered to detect 40% RRR	Yes (30 days, 3 years)				Angina (30 days, 1 year) SF-36 (30 days, 1 year)
Dobrzycki et al.[40]	Total mortality/nonfatal MI/stroke (30 days, 1 year) Powered to detect 50% RRR	*Yes* (30 days, 1 year)				
GUSTO II-B[39]	*Total mortality/nonfatal MI/nonfatal disabling stroke* (30 days) Powered to detect 40% RRR	Yes (30 days)	Yes (30 days)	Yes (30 days)		Intracranial hemorrhage (30 days)
Minai et al.[41]	Total mortality/heart failure/repeat MI/stroke (3 years) Primary outcome & effect size not specified					
PAMI[42]	*Death/reinfarction* (in hospital) Powered to detect 50% RRR	Yes (in hospital)	Yes (in hospital)	Yes (in hospital)		Recurrent ischemia (in hospital) Length of stay (in hospital)
SHOCK[38,48-50]	Powered to detect 25% RRR				*Yes* (1 year)	

MI = myocardial infarction; RRR = relative risk reduction; STEMI = ST elevation myocardial infarction
[a]Primary outcome in italics.

KQ 1a: Effectiveness of Interventions

A meta-analysis was performed on studies with similar composite outcomes measured at similar time points. This meta-analysis was divided into followup intervals of short term (≤30 days) and long term (≥1 year). The SHOCK study,[38] evaluating early revascularization versus medical stabilization, did not report 1-year data by sex, except for noting the lack of a treatment-by-sex interaction, and therefore was not included in the meta-analysis. Similarly, in the Minai study[41] evaluating PCI versus no PCI, 3-year data reported no sex effect in a multivariate analysis; however, since the data were not reported by sex, this study also was excluded from the meta-analysis.

Short-Term Followup Studies

Five studies—CARESS-in-AMI,[36] DANAMI-2,[37] Dobrzycki,[40] GUSTO II-B,[39] and PAMI[42]—were included in the meta-analysis based on comparable composite outcomes (primarily death/MI/stroke) and followup time points of 30 days or in-hospital. The published results from Dobrzycki et al. were inverted to change the reference arm to fibrinolysis. The PAMI study event rates by treatment group and sex were converted into odds ratios. Table 5 presents the outcomes, odds ratios, and confidence intervals for the meta-analysis.

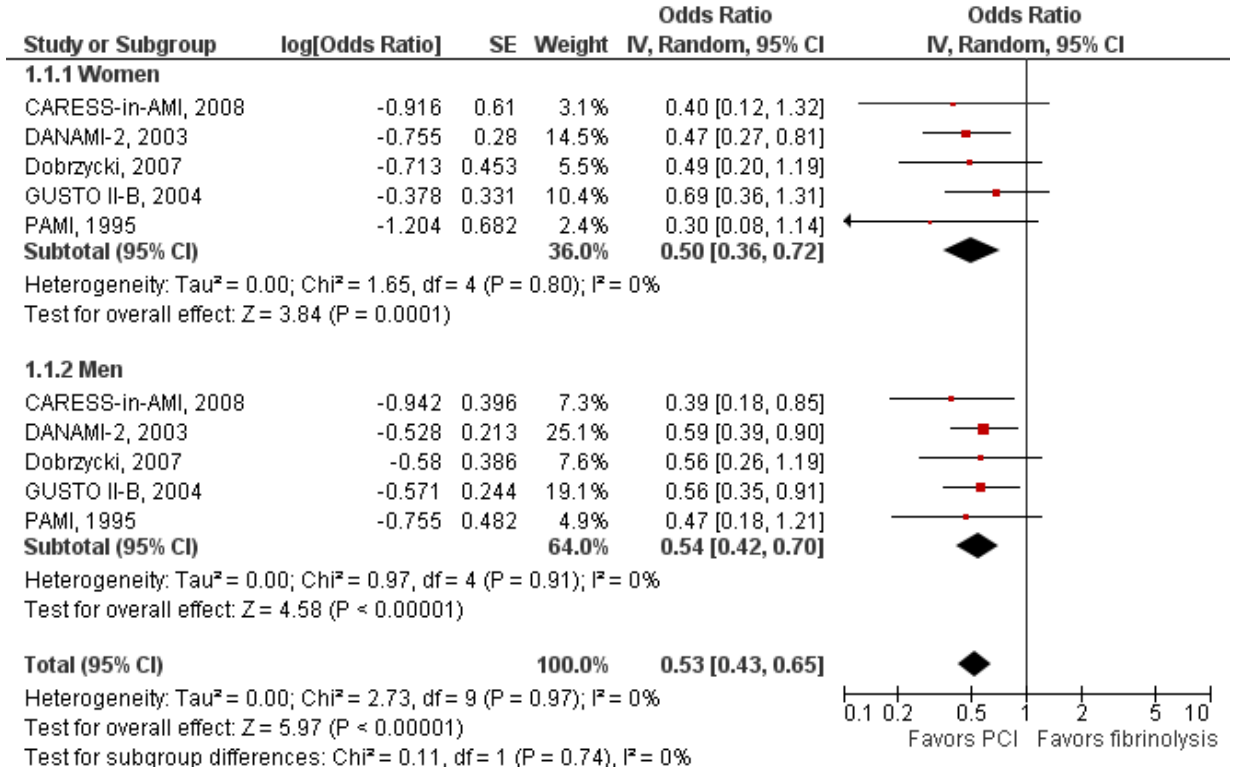
Table 5. Sex results for STEMI on composite outcomes (short-term)

Study (Comparison)	Outcome	Women (95% CI)	Men (95% CI)	Overall (95% CI)
CARESS-in-AMI (immediate PCI with reteplase vs. reteplase with rescue PCI)	Death/MI/refractory ischemia (30 days)	0.40 (0.12 to 1.31)	0.39 (0.18 to 0.85)	0.40 (0.21 to 0.76)
DANAMI-2 (immediate PCI vs. accelerated t-PA)	Death/MI/stroke (30 days)	0.47 (0.27 to 0.81)	0.59 (0.39 to 0.90)	0.55 (0.38 to 0.76)
Dobrzycki (transfer for primary PCI vs. onsite streptokinase)	Death/MI/stroke (30 days)	0.49 (0.20 to 1.18)	0.56 (0.26 to 1.18)	0.51 0.29 to 0.91)
GUSTO II-B (PCI vs. accelerated t-PA)	Death/MI/stroke (30 days)	0.69 (0.36 to 1.32)	0.56 (0.35 to 0.91)	0.67 (0.47 to 0.97)
PAMI (PCI vs.t-PA)	Death/MI (in-hospital)	0.30 (0.08 to 1.16)	0.47 (0.18 to 1.19)	0.40 (0.18 to 0.85)

CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention; t-PA = tissue plasminogen activator

Forest plots for the random-effects model are shown in Figure 3. The summary odds ratio in women was 0.50 (95% CI, 0.36 to 0.72) and in men was 0.54 (CI, 0.42 to 0.70). The test for heterogeneity was nonsignificant. These results show that PCI was better than fibrinolysis in reducing death/MI/stroke in both sexes (p=0.0001 women, p<0.00001 men) at 30 days.

Figure 3. STEMI short-term (30 days) PCI versus fibrinolysis



Intermediate-Term Followup Studies

Two studies—DANAMI-2[44] and Dobrzycki[40]—reported sex-specific clinical outcomes at 1 year. Table 6 presents the outcomes, odds ratios, and confidence intervals for PCI compared with fibrinolysis by sex. Due to the heterogeneous clinical outcomes, a meta-analysis was not conducted.

Table 6. Sex results for STEMI on clinical outcomes (intermediate-term)

Study (Comparison)	Outcome	Women (95% CI)	Men (95% CI)	Overall (95% CI)
DANAMI-2 (immediate PCI vs. accelerated t-PA)	Angina	0.86 (0.50 to 1.49)	0.86 (0.61 to 1.20)	NR
Dobrzycki (transfer for primary PCI vs. onsite streptokinase)	Death/MI/stroke	0.40 (0.17 to 0.94)	0.62 (0.35 to 1.09)	0.53 (0.33 to 0.84)

CI = confidence interval; NR = not reported; PCI = percutaneous coronary intervention; t-PA = tissue plasminogen activator

PCI Versus Fibrinolysis in High-Risk Groups

We identified two studies that evaluated a PCI or CABG strategy versus conservative/supportive medical therapy in high-risk groups.[38,41] These studies were not included in the meta-analysis since the actual results by sex were not reported in the manuscript; instead both papers report the results of a multivariate analysis with sex as a covariate in the model. The SHOCK study[38] was considered good quality and evaluated patients with cardiogenic shock and STEMI with a strategy of PCI or CABG within 6 hours versus initial medical stabilization that included fibrinolysis or insertion of an intra-aortic balloon pump (IABP). This study found that the early revascularization strategy was associated with a lower relative risk of death when compared with medical stabilization (risk ratio 0.72; 95% CI, 0.54 to 0.95). Analysis by sex did

not identify any significant interaction by treatment arm. The study by Minai et al.[41] was considered fair quality and evaluated PCI versus routine medical therapy without reperfusion in patients 80 years of age and older. There was no difference in the number of patients with the composite outcome of death/heart failure/repeat MI/stroke at 3 years between the treatment arms. No analysis by sex was done; however, in a multivariate analysis to evaluate factors associated with the composite outcome, sex was not found to be significantly associated with the outcome in the overall study population. This study was limited by the small sample size of 120 patients enrolled.

KQ 1b: Modifiers of Effectiveness

Two studies[41,42] evaluating women with STEMI assessed the characteristics of interest and included a total of 515 patients, of which 167 (32%) were women. The PAMI study[42] was considered good quality and evaluated patients randomized to PCI versus fibrinolysis with t-PA. No difference was found in in-hospital mortality among women receiving PCI versus t-PA who were under 65 years of age (0% vs. 4%; p=0.42) nor among women 65 and older (5.9% vs. 21.9%; p=0.58).

The study by Minai et al.[41] evaluated PCI versus routine medical therapy without reperfusion in patients 80 years of age and older. The results are noted above. Appendix G contains a summary table with study data related to modifiers of effectiveness (subgroup analyses).

KQ 1c: Safety Concerns

Two good-quality studies reported safety concerns in women with STEMI and included a total of 1,532 patients, of which 367 (24%) were women. In the PAMI study[42] evaluating PCI versus t-PA in STEMI patients, the mean nadir hematocrit in women with PCI was 30 ± 5 percent versus 33 ± 5 percent in women with t-PA (p=0.0002). However, there was no statistically significant difference in the requirement for blood transfusion in women with PCI versus t-PA (18% vs. 8.8%; p=0.16). In the GUSTO II-B study[39] the proportion of women with intracranial hemorrhage was reported in women who received PCI versus accelerated t-PA (0% vs. 4.1%), but statistical analysis for this comparison was not done. Appendix H contains a summary table with study data related to safety concerns (harms).

Key Question 2: Women With UA/NSTEMI (Early Invasive Vs. Initial Conservative Therapy)

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)?

Overview

Unstable angina is caused by reversible ischemia of the epicardial arteries, whereas NSTEMI is caused by the partial obstruction of the epicardial arteries and results in myocardial tissue damage. Patients with UA/NSTEMI are not candidates for immediate pharmacological reperfusion (i.e., fibrinolysis). The optimal management of UA/NSTEMI has the twin goals of immediate relief of ischemia and the prevention of serious adverse outcomes (i.e., death or MI). Optimal management is best accomplished with aggressive medical therapy that includes anti-ischemic therapy, antithrombotic therapy, ongoing risk stratification, and in some cases the use of invasive procedures.

Following initiation of aggressive medical therapy, two treatment pathways have emerged for treating patients without ST-segment elevation.[28] An "initial conservative strategy" 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 early invasive strategy triages patients to undergo an invasive diagnostic evaluation without first having 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. Therefore, studies assessing the effectiveness of early invasive versus initial conservative therapy were evaluated for KQ 2.

Key Points

- **Description of included studies:** Seven studies (6 good quality, 1 fair) compared early invasive therapy (PCI or CABG) with initial conservative therapy for women with UA/NSTEMI and included a total of 17,930 patients, of which 6,084 (34%) were women.
- **Effectiveness of interventions:** A meta-analysis of two 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), but early invasive therapy was superior to initial conservative therapy in men (OR 0.65; CI, 0.52 to 0.82; p=0.0002). At 1 year, a meta-analysis of five good-quality studies showed that composite outcomes (primarily death or MI) suggested a benefit for women who received early invasive therapy (OR 0.78; CI, 0.54 to 1.12) as well as for men (OR 0.88; CI, 0.64 to 1.20); however this benefit was not statistically significant. Finally, a meta-analysis of two good-quality studies with 5-year followup comparing early invasive and initial conservative therapy for the composite outcome of death or MI did not reach statistical significance in either sex. The summary odds ratio in women was 1.05 (CI, 0.81 to 1.35) and in men was 0.91 (CI, 0.53 to 1.56). The long-term analysis is limited by the low number of studies. Strength of evidence favoring an early invasive approach was low for women and high for men at 6-month followup; low for women and men at 1-year followup; and insufficient for women and low for men at 5-year followup. Similar to the STEMI studies, individual outcomes by sex were rarely reported for heart failure, repeat hospitalization, length of hospital stay, quality of life, or cognitive effects.
- **Modifiers of effectiveness:** Two good-quality studies comparing early invasive treatment with PCI with initial conservative treatment 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 (TIMI). Strength of evidence for modifiers of effectiveness for early invasive versus initial conservative treatments was insufficient.
- **Safety concerns:** One good-quality study (2,220 total patients, 757 women, 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).[51] However, bleeding related to CABG was similar in women and men with rates of 12.6 and 15 percent respectively. No studies systematically reported radiation exposure, contrast reactions, access site complications, stent thrombosis or infection, in women with UA/NSTEMI comparing initial conservative with early invasive therapy. Strength of evidence for safety concerns in these populations was insufficient.

Detailed Synthesis

We identified seven studies[22,52-57] that evaluated the effect of early invasive therapy compared with initial conservative therapy for UA/NSTEMI and reported results by sex. Of these seven studies, six were good quality, and one was fair. Table 7 presents a general description of these seven studies, including the study name, author, year, and related articles (i.e., study design and secondary papers); treatment comparisons evaluated; study population; and overall quality rating. Table 8 summarizes the women-specific outcomes (composite and individual) reported in these studies. Appendix F contains summary tables with sex-specific clinical outcomes for all followup time points.

Table 7. KQ 2: Study characteristics of RCTs evaluating women with UA/NSTEMI

Study Author/Year Related Articles	Description of Study	# of Subjects	Quality
FRISC II Lagerqvist et al., 2001[52] and Lagerqvist et al., 2006[58] Wallentin et al., 2000[59] Anonymous, 1999[60]	**Title:** Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators **Comparator:** Early invasive treatment with revascularization (PCI, type not specified, for 1- or 2-vessel CAD; CABG for 3-vessel CAD or left main disease) vs. initial conservative strategy **Components of optimal medical therapy:** Aspirin 300 to 600 mg (initial), then 75 to 320 mg daily. Beta blockade (unless contraindicated). Organic nitrates and calcium antagonists as needed. Lowering of cholesterol with statins, angiotensin converting-enzyme inhibitors for left-ventricular dysfunction, and aggressive antidiabetic treatment were recommended according to modern treatment guidelines.	Total: 2,457 Women: 749 (30%)	Good
GUSTO IV-ACS Ottervanger et al., 2004[53]	**Title:** Association of revascularisation with low mortality in non-ST elevation acute coronary syndrome, a report from GUSTO IV-ACS **Comparator:** Early invasive management vs. initial conservative treatment within 30 days. A total of 2265 (30%) patients underwent revascularization: 789 patients CABG, 1450 patients PCI, and 26 both CABG and PCI. Type of PCI was not specified. **Components of optimal medical therapy:** Aspirin for 30 days if not contraindicated. IV unfractionated heparin as bolus and infusion for 48 hours or low molecular weight heparin (dalteparin) subcutaneously every 12 hours for 5 to 7 days or until a revascularisation procedure or discharge. Continuation of antithrombin therapy with unfractionated or low molecular weight heparin was left at the discretion of the investigator.	Total: 7,800 Women: 2,896 (37%)	Good

Table 7. KQ 2: Study characteristics of RCTs evaluating women with UA/NSTEMI (continued)

Study Author/Year Related Articles	Description of Study	# of Subjects	Quality
ICTUS de Winter et al., 2005[56] and Damman et al., 2010[61]	**Title:** Early invasive vs. selectively invasive management for acute coronary syndromes **Comparator:** Early invasive therapy with revascularization vs. selective invasive strategy (initial conservative) **Components of optimal medical therapy:** Aspirin (300 mg at randomization then 75 mg daily); enoxaparin (1 mg/kg twice daily subcutaneously for 48 hours), Clopidogrel (300 mg immediately, followed by 75 mg daily) in combination with aspirin was recommended after the drug was approved in 2002 for the indication of acute coronary syndromes; intensive lipid-lowering therapy, preferably 80 mg of atorvastatin daily or the equivalent.	Total: 1,200 Women: 320 (27%)	Good
RITA-2 Anonymous, 1997[54]	**Title:** Coronary angioplasty vs. medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants **Comparator:** Early invasive therapy with PCI (primarily PTCA, but stent could be used if PTCA failed) vs. initial conservative **Components of optimal medical therapy:** Aspirin, unless contraindicated. Antianginal medication for symptom relief. Beta-adrenoceptor blocker with a calcium antagonist and/or long-acting nitrate in maximally tolerated doses. Lipid-lowering drugs prescribed at the discretion of the supervising clinician.	Total: 1,018 Women: 183 (8%)	Fair
RITA-3 Clayton et al., 2004[22] and Fox et al., 2002[62]	**Title:** 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 **Comparator:** Early invasive with PCI (type at discretion of investigator) vs. initial conservative **Components of optimal medical therapy:** Aspirin; enoxaparin 1 mg/kg twice daily subcutaneously for 2 to 8 days. Antianginal treatment chosen by the supervising clinician, including a beta-blocker unless contraindicated.	Total: 1,810 Women: 682 (38%)	Good

Table 7. KQ 2: Study characteristics of RCTs evaluating women with UA/NSTEMI (continued)

Study Author/Year Related Articles	Description of Study	# of Subjects	Quality
TACTICS TIMI-18 Cannon et al., 2001[55] and Glaser et al., 2002[51] Cannon et al., 1998[63]	**Title:** Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban **Comparator:** Early invasive with PCI (type not specified) vs. initial conservative **Components of optimal medical therapy:** Aspirin 325 mg daily (unless contraindicated); IV unfractionated heparin (5000 U bolus, then 1000 U/hour for 48 hours); tirofiban (loading dose 0.4 μg/kg per minute for a period of 30 minutes, then 0.1 μg/kg/min for 48 hours or until revascularization, and for at least 12 hours after PCI; beta blockers (82%), nitrates (94%), and lipid-lowering agents (52%).	Total: 2,220 Women: 757 (34%)	Good
TIMI III-B Anonymous, 1994[57] and Anderson et al., 1995[64]	**Title:** Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial **Comparator:** Early invasive with PCI (type not specified) vs. initial conservative **Components of optimal medical therapy:** Anti-ischemic therapy consisting of a beta-blocker (metoprolol 50 mg p.o. q 12 hours), a calcium antagonist (diltiazem 30 mg p.o. q 6 hours), and a long-acting nitrate (isosorbide dinitrate 10 mg p.o. q 8 hours) or larger doses and supplemented by sublingual nitroglycerin pm. IV heparin. Aspirin 325 mg daily was given on the second day and continued for 1 year.	Total: 1,425 Women: 497 (35%)	Good

CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; NSTEMI = non-ST elevation myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial; UA = unstable angina

Table 8. Outcomes reported in RCTs evaluating women with UA/NSTEMI

Study	Composite Outcome[a] (Timing) Anticipated Effect Size	Death (Timing)	MI (Timing)	Stroke (Timing)	Revascularization (Timing)	Other (Timing)
FRISC II[52,58-60]	*Death/MI or both* (6 months, 1 year, 5 years) Powered to detect 32% difference					
GUSTO IV-ACS[53]	Not reported by sex Powered to detect 25% reduction in primary endpoint of death/MI	Yes (1 year)				
ICTUS[56,61]	*Death/MI/rehospitalization for angina* (1 year) Death/spontaneous MI (5 years) Powered to detect 25% RRR					
RITA-2[54]	*Death/MI* (median followup of 2.7 years) Powered to detect 15% difference					Angina grade 2+ (6 months) Exercise time (6 months)
RITA-3[22,62]	*Death/MI* (1 year) Death/MI/refractory angina (4 months, 1 year) Powered to detect 33% RRR	Yes (1 year)				

Table 8. Outcomes reported in RCTs evaluating women with UA/NSTEMI (continued)

Study	Composite Outcome[a] (Timing) Anticipated Effect Size	Death (Timing)	MI (Timing)	Stroke (Timing)	Revascularization (Timing)	Other (Timing)
TACTICS TIMI-18[51,55,63]	*Death/MI/rehospitalization for acute coronary syndrome* (6 months) Death/MI (6 months) Powered to detect 25% difference	Yes (6 months)				
TIMI III-B[57,64]	*Death/MI/failed symptom-limited exercise treadmill test* (6 weeks) Death/MI (6 weeks, 1 year) Powered to detect 30% RRR					

MI = myocardial infarction; RRR = relative risk reduction; NSTEMI = non-ST elevation myocardial infarction; UA = unstable angina
[a]Primary outcome in italics.

KQ 2a: Effectiveness of Interventions

A meta-analysis was performed on studies with similar composite outcomes measured at similar time points. This meta-analysis was divided into followup intervals of short term (6 months), intermediate term (1 year) and long term (5 years).

Short-Term Followup Studies

Two studies reporting 6-month outcomes—FRISC II[60] and TACTICS TIMI-18[51]—were included in the meta-analysis. The TIMI III-B study[57] (good quality) reported a shorter followup time point of 6 weeks and therefore was not included in this meta-analysis. In TIMI III-B, the proportion of women with the composite outcome of death/MI at 6 weeks was 6.1 percent in the early invasive arm and 8.9 percent in the initial conservative arm (p=0.24). The proportion of men with the same composite outcome was 7.8 percent and 7.3 percent, respectively (p=0.73). The RITA-2 study[54] (fair quality) reported outcomes for angina grade 2+ or exercise time and likewise was not included in the meta-analysis. In RITA-2, the proportion of women with angina graded 2 or higher at 6 months was 22.8 percent for the early invasive arm, and 39.8 percent for the initial conservative arm. In men, the proportion with angina graded 2 or higher was 20.5 percent and 31.4 percent, respectively. For the TACTICS TIMI-18 study, we used the adjusted odds ratio for the composite outcome of death/MI. Table 9 presents the outcomes, odds ratios, and confidence intervals for the meta-analysis.

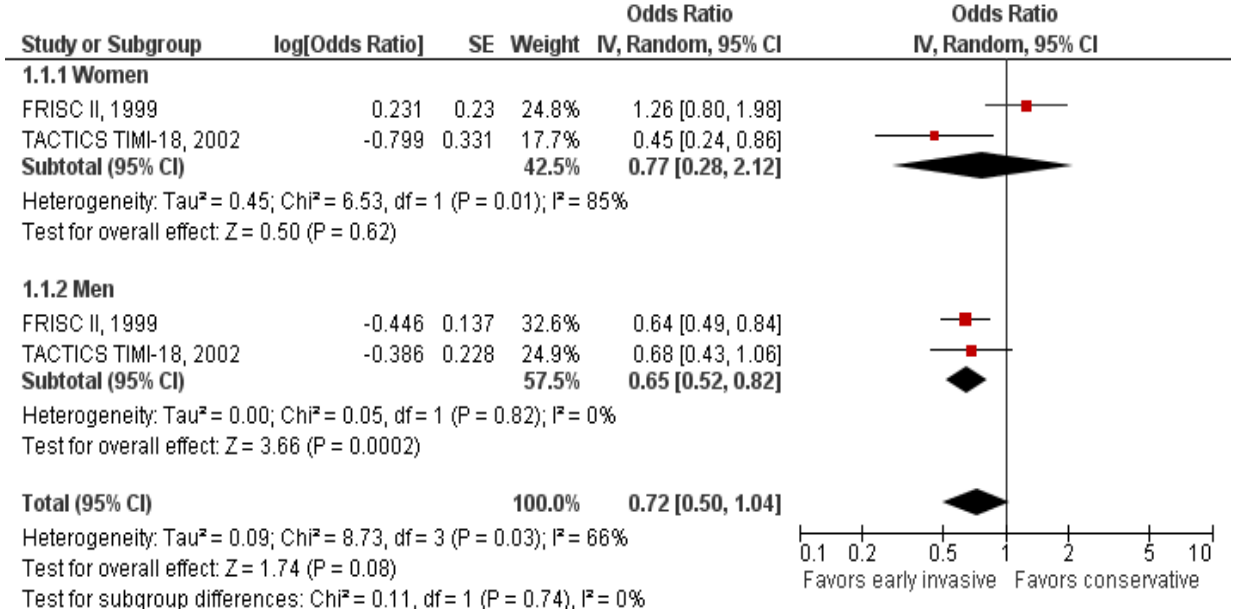
Table 9. Sex results for UA/NSTEMI on composite outcomes (short-term)

Study (Comparison)	Outcome	Women (95% CI)	Men (95% CI)	Overall (95% CI)
FRISC II (early invasive vs. initial conservative)	Death/MI	1.26 (0.80 to 1.97)	0.64 (0.49 to 0.84)	0.78 (0.62 to 0.98)
TACTICS TIMI-18 (early invasive vs. initial conservative)	Death/MI	0.45 (0.24 to 0.88)	0.68 (0.0.43 to 1.05)	0.74 (0.54 to 1.00)

CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention

Forest plots for the random-effects model are shown in Figure 4. The summary odds ratio in women was 0.77 (95% CI, 0.28 to 2.12) and in men was 0.65 (CI, 0.52 to 0.82). The test for heterogeneity was significant in women (p=0.01), but it was nonsignificant in men. These results for short-term outcomes suggested a non–statistically significant benefit of early invasive compared with initial conservative therapy in women but demonstrated that early invasive was superior to initial conservative therapy in men (p=0.0002). The two trials resulted in conflicting conclusions in women versus men, despite having similar results for the overall population.

Figure 4. UA/NSTEMI short-term (6 months) early invasive versus initial conservative



Intermediate-Term Followup Studies

Five studies with 1-year data—FRISC II,[59] GUSTO IV-ACS,[53] ICTUS,[56] RITA-3,[22] and TIMI III-B[64]—were included in the meta-analysis. For the RITA-3 study, the adjusted odds ratio for the composite outcome of death/MI was selected for this analysis. For the ICTUS and TIMI III-B studies, event rates were converted to odds ratios. Table 10 presents the outcomes, odds ratios, and confidence intervals for the meta-analysis.

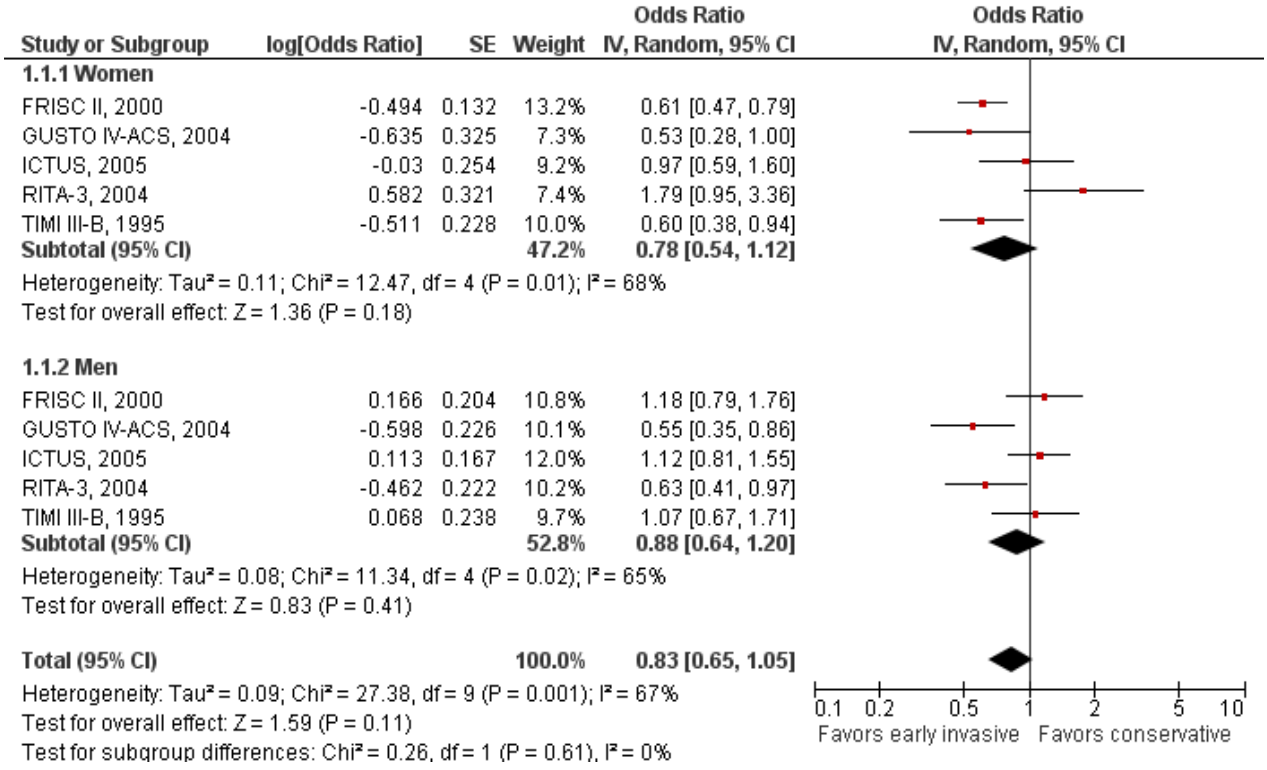
Table 10. Sex results for UA/NSTEMI on composite outcomes (intermediate-term)

Study (Comparison)	Outcome	Women (95% CI)	Men (95% CI)	Overall (95% CI)
FRISC II (early invasive vs. initial conservative)	Death/MI	0.61 (0.47 to 0.79)	1.18 (0.79 to 1.76)	0.74 (0.60 to 0.92)
GUSTO IV-ACS (revascularization in 30 days vs. initial conservative)	Death	0.53 (0.28 to 1.00)	0.55 (0.35 to 0.85)	0.53 (0.37 to 0.77)
ICTUS (early invasive vs. selective invasive)	Death/MI/rehospitalization for angina	0.97 (0.59 to 1.60)	1.12 (0.81 to 1.56)	1.07 (0.87 to 1.33)
RITA-3 (early invasive vs. initial conservative)	Death/MI	1.79 (0.95 to 3.35)	0.63 (0.41 to 0.98)	0.91 (0.67 to 1.25)
TIMI III-B (early invasive vs. initial conservative)	Death/MI	0.60 (0.38 to 0.93)	1.07 (0.67 to 1.70)	0.88 (0.64 to 1.21)

CI = confidence interval; MI = myocardial infarction

Forest plots for the random-effects model are shown in Figure 5. The summary odds ratio in women was 0.78 (95% CI, 0.54 to 1.12) and in men was 0.88 (CI, 0.64 to 1.20). The test for heterogeneity was significant in women (p=0.01) and men (p=0.02). These results show trends favoring early invasive therapy in 1-year outcomes although these benefits were not statistically significant in either women or men.

Figure 5. UA/NSTEMI intermediate-term (1 year) early invasive versus initial conservative



Long-Term Followup Studies

Two studies with 5-year, long-term data were included in the analysis: FRISC II[58] and ICTUS.[61] Table 11 presents the outcomes, odds ratios, and confidence intervals for the meta-analysis.

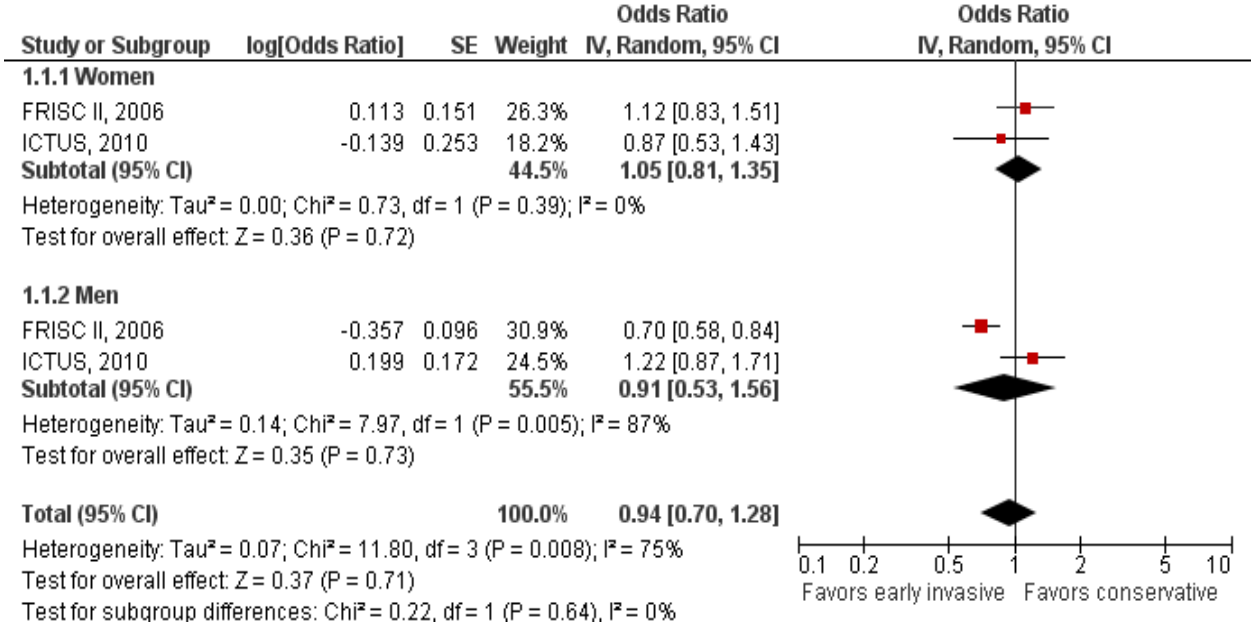
Table 11. Sex results for UA/NSTEMI on composite outcomes (long-term)

Study (Comparison)	Outcome	Women (95% CI)	Men (95% CI)	Overall (95% CI)
FRISC II (early invasive vs. initial conservative)	Death/MI	1.12 (0.83 to 1.50)	0.70 (0.59 to 0.86)	0.81 (0.69 to 0.95)
ICTUS (early invasive vs. selective invasive)	Death/MI	0.87 (0.53 to 1.43)	1.22 (0.87 to 1.71)	1.29 (1.00 to 1.66)

CI = confidence interval; MI = myocardial infarction

Forest plots for the random-effects model are shown in Figure 6. The summary odds ratio in women was 1.05 (95% CI, 0.81 to 1.35) and in men was 0.91 (CI, 0.53 to 1.56). The test for heterogeneity was significant in men (p=0.005) but not in women. Although these results demonstrate a slight trend favoring initial conservative therapy in women, given the small suggested benefit at 5 years, 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. There was no evidence of a sex effect. The analysis is limited by the low number of studies.

Figure 6. UA/NSTEMI long-term (5 years) early invasive versus initial conservative



Some of the analyses above showed heterogeneity in clinical outcomes between the FRISC II and ICTUS studies. The major heterogeneity in these studies arises from the rates and threshold of invasive treatment in the conservative arm. In the FRISC II study, more conservative strategies were used, thus leading to lower rates of invasive treatment in the conservative groups. In the ICTUS study, the selective invasive group was more liberal with the rates of invasive therapy and almost as high as the invasive arms of the other studies, thus explaining some of the potential differences in the results.

KQ 2b: Modifiers of Effectiveness

We identified two good-quality studies[22,55] examining the effect of early invasive therapy compared with initial conservative therapy in women by subgroup; these included a total of 4030 patients, of which 1439 (36%) were women. The TACTICS TIMI-18 study[55] found that there was no significant benefit to the treatment of women with intermediate-risk (3 to 4) or high-risk (5 to 7) TIMI scores on the primary composite outcome of death/MI/rehospitalization for acute coronary syndrome with early invasive therapy (OR 0.72; 95% CI, 0.45 to 1.16) compared with initial conservative therapy (OR 0.56; CI, 0.23 to 1.32).[51] There also was no significant benefit of early invasive therapy on the primary composite outcome for those presenting with ST-segment changes (OR 0.66; CI, 0.38 to 1.15). However, there did seem to be a reduced risk of the primary composite outcome among women who had an elevated troponin level and who underwent early invasive treatment compared with conservative treatment (OR 0.56; CI, 0.32 to 0.97). Men with ST-segment changes and elevated troponin levels also seemed to benefit from early invasive therapy but not those in intermediate- or high-risk groups based on TIMI risk scores.[51]

The RITA-3 study[22] also examined the effect of early invasive therapy compared with initial conservative therapy in women by subgroup based on risk, which was derived from components of the TIMI risk score and a couple other aspects of the participants' presentation at randomization, including aspirin use and angina severity. This study, unlike the TACTICS TIMI-

18 study, found a higher event rate among women in moderate- and high-risk groups who underwent early invasive therapy compared with initial conservative therapy, with event rates of 13.4 percent versus 3.4 percent for those in the moderate-risk group and 11.7 percent versus 8.2 percent for those in the higher risk group. Men with moderate and higher risk had lower event rates if they were in the early invasive arm compared with the initial conservative arm, with 5.4 percent versus 9.4 percent for those in the moderate-risk group and 10.3 percent versus 17.9 percent for those in the higher risk group. This study also examined the effect of intervention group by body mass index group and found no effect of body mass index on treatment effect in either women or men.[22] Appendix G contains a summary table with study data related to modifiers of effectiveness (subgroup analyses).

KQ 2c: Safety Concerns

We identified one good-quality study[55] (2,220 total patients, 757 women, 34% women) that reported the harms associated with treatment of UA/NSTEMI by sex group but not the rates of events by treatment group. The TACTICS TIMI-18 study, comparing early invasive therapy with initial conservative therapy, found that bleeding in women undergoing PTCA was higher than in men (adjusted OR 3.6; 95% CI, 1.6 to 8.3).[51] They found, however, that the bleeding related to CABG was similar in women and men with rates of 12.6 and 15 percent, respectively. Appendix H contains a summary table with study data related to safety concerns (harms).

Key Question 3: Women With Stable or Unstable Angina

In women 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)?

Strategy 1. Revascularization (PCI or CABG) versus optimal medical therapy in women with stable angina

Strategy 2. 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 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)?

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)?

Overview

Angina resulting from progressive narrowing of the coronary arteries is the initial manifestation of ischemic heart disease in approximately 50 percent of patients.[30] Most angina is a sign of significant CAD, defined angiographically as a stenosis with ≥70 percent diameter in at least one major epicardial artery segment or with ≥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.[30]

Chronic stable angina is classified as pain that classically occurs with moderate to severe exertion, is milder in nature, and relieved with rest or sublingual nitroglycerin. 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.

The treatment of 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.[30] All patients with stable or unstable angina are candidates for optimal medical therapy and also may be candidates for PCI or CABG based on findings from coronary angiography or if symptoms persist despite optimal medical therapy.

For KQ 3, we evaluated two sets of treatment strategies:

1. Revascularization (PCI or CABG) versus optimal medical therapy in women with stable angina
2. PCI versus CABG in women with either stable or unstable angina

Strategy 1: Revascularization Versus Optimal Medical Therapy in Stable Angina

Key Points

- **Description of included studies:** Five studies (all good quality) compared revascularization (PCI or CABG) with optimal medical therapy for women with stable angina and included a total of 6,851 patients, of which 1,285 (19%) were women.
- **Effectiveness of interventions:** A meta-analysis of three good-quality studies with long-term (4- to 5-year) 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 did not show statistically significant findings between revascularization and optimal medical therapy, though it demonstrated a trend favoring optimal medical therapy compared with PCI (OR 1.03; CI, 0.79 to 1.33 for PCI strategy trials). 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. Conversely, evidence suggested that CABG or either PCI or CABG reduced outcomes compared with optimal medical therapy in men (OR 0.62; CI, 0.31 to 1.24 for CABG strategy trials; and OR 0.71; CI, 0.49 to 1.02 for either PCI or CABG)—again these findings were not statistically significant. Strength of evidence favoring revascularization for women was moderate in the PCI strategy, low in the CABG strategy, and moderate for both types of revascularization combined. In men, the strength of evidence was low for the PCI, CABG, and combined revascularization strategies.
- **Modifiers of effectiveness:** No studies were identified that evaluated women presenting with stable angina; therefore data are insufficient.
- **Safety concerns:** No studies were identified that evaluated women presenting with stable angina; therefore data are insufficient.

Detailed Synthesis

We identified five studies[65-69] that reported outcomes for women with stable angina. Of these five studies, all were good quality. Two studies compared PCI with optimal medical therapy,[65,66] one compared CABG with optimal medical therapy,[67] and one compared medical management with transmyocardial revascularization (TMR).[69] Table 12 presents a general description of these five studies, including the study name, author, year, and related articles (i.e., study design and secondary papers); treatment comparisons evaluated; study population; and overall quality rating. Table 13 summarizes the women-specific outcomes (composite and individual) reported in these studies. Appendix F contains summary tables with sex-specific clinical outcomes for all followup time points.

Table 12. KQ 3 Strategy 1: Study characteristics of RCTs evaluating women with stable angina (PCI/CABG vs. optimal medical therapy)

Study Author/Year Related Articles	Description of Study	# of Subjects	Quality
Allen et al., 2004[69] and Allen et al., 1999[70]	**Title:** Transmyocardial revascularization: 5-year follow-up of a prospective randomized multicenter trial **Comparator:** Surgical revascularization (CABG with transmyocardial revascularization) vs. optimal medical therapy **Components of optimal medical therapy:** Not reported.	Total: 222 Women: 61 (27%)	Good
COURAGE Boden et al., 2007[65] and Mancini et al., 2009[71] Boden et al., 2006[72]	**Title:** Optimal medical therapy with or without PCI for stable coronary disease **Comparator:** PCI (type not specified) or CABG if PCI failed vs. optimal medical therapy **Components of optimal medical therapy:** Aspirin (81 to 325 mg per day) or 75 mg of clopidogrel per day, if aspirin intolerance was present. Metoprolol, amlodipine, and isosorbide mononitrate, alone or in combination, along with either lisinopril or losartan; aggressive therapy to lower low-density lipoprotein cholesterol levels (simvastatin alone or in combination with ezetimibe) with a target level of 60 to 85 mg per deciliter (1.55 to 2.20 mmol per liter).	Total: 2,287 Women: 338 (15%)	Good
MASS II Hueb et al., 2010[68] and Hueb et al., 2004[73] Hueb et al., 2007[74]	**Title:** Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease **Comparator:** PCI vs. optimal medical therapy; CABG vs. optimal medical therapy **Components of optimal medical therapy:** Nitrates, aspirin, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or a combination of these drugs unless contraindicated. Lipid-lowering agents, particularly statins, were also prescribed, along with a low-fat diet, on an individual basis.	Total: 611 Women: 196 (32%)	Good

Table 12. KQ 3 Strategy 1: Study characteristics of RCTs evaluating women with stable angina (PCI/CABG vs. optimal medical therapy) (continued)

Study Author/Year Related Articles	Description of Study	# of Subjects	Quality
OAT Hochman et al., 2006[66] and Hochman et al., 2005[75,76]	**Title:** Coronary intervention for persistent occlusion after myocardial infarction **Comparator:** PCI (or CABG if PCI failed) vs. optimal medical therapy **Components of optimal medical therapy:** Aspirin, anticoagulation if indicated, angiotensin-converting enzyme inhibition, beta blockade, and lipid-lowering therapy, unless contraindicated. Thienopyridine therapy was initiated before PCI and continued for 2 to 4 weeks after stenting. After reports of the efficacy of prolonged treatment with a thienopyridine after MI, the recommendation was changed to 1 year in both study groups.	Total: 2,166 Women: 476 (22%)	Good
STICH Velazquez et al., 2011[67] and Velazquez et al., 2007[77]	**Title:** Coronary-artery bypass surgery in patients with left ventricular dysfunction **Comparator:** CABG vs. optimal medical therapy **Components of optimal medical therapy:** Unless contraindicated, optimal medical therapy included angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or both; beta blocker; aldosterone antagonist; and antiplatelet agents adjusted to optimal doses within 30 days after randomization. Statin, diuretic, and digitalis use was individualized to patient-specific indications. The use of implantable defibrillators was encouraged as part of medical therapy and was used in compliance with standard guidelines.	Total: 1,212 Women: 148 (12%)	Good

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty

Table 13. KQ 3 Strategy 1: Outcomes reported in RCTs evaluating women with stable angina (PCI/CABG vs. optimal medical therapy)

Study	Composite Outcome[a] (Timing) Anticipated Effect Size	Death[a] (Timing)	MI (Timing)	CVA (Timing)	Revascularization (Timing)	Other[a] (Timing)
Allen et al.[69,70]	Effect size not reported	Yes (5.7 years)				*Angina relief* (5.7 years)
COURAGE[65,71,72]	*Death/MI* (median 4.6 years) Powered to detect 22% RRR					
MASS II[68,73,74]	*Death/MI/angina requiring revascularization* (10 years) Powered to detect 2-fold difference					
OAT[66,75,76]	*Death/MI/heart failure* (4 years, 7 years) Powered to detect 25% reduction					
STICH[67,77]	Powered to detect 25% reduction in mortality	*Yes* (5 years)				

CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; MI = myocardial infarction; PCI = percutaneous coronary intervention; RRR = relative risk reduction
[a]Primary outcome in italics.

KQ 3a: Effectiveness of Interventions

Long-Term Followup Studies

Three studies were included in a meta-analysis: COURAGE,[65] MASS II,[68] and STICH.[67] These studies had similar followup times (4 to 5 years, except a 10-year followup in the MASS II study) and comparable outcomes (composite, death). No results were available for the short- or intermediate-term outcomes. The TMR study by Allen et al.[69] was excluded since the results were reported in a different fashion (i.e., whether sex had an impact on outcome for the TMR patients) and could not be incorporated into the meta-analysis. The OAT study[66] was excluded from the meta-analysis since the study subjects were enrolled ≥7 days after an acute MI with revascularization or medical therapy for an occluded artery; the patient population was deemed to be quite different from those enrolled in the other studies. The MASS II study numbers were inverted to place PCI in the comparison group. Table 14 presents the outcomes, odds ratios, and confidence intervals for the meta-analyses.

Table 14. Sex results for stable angina on composite outcomes (long-term)

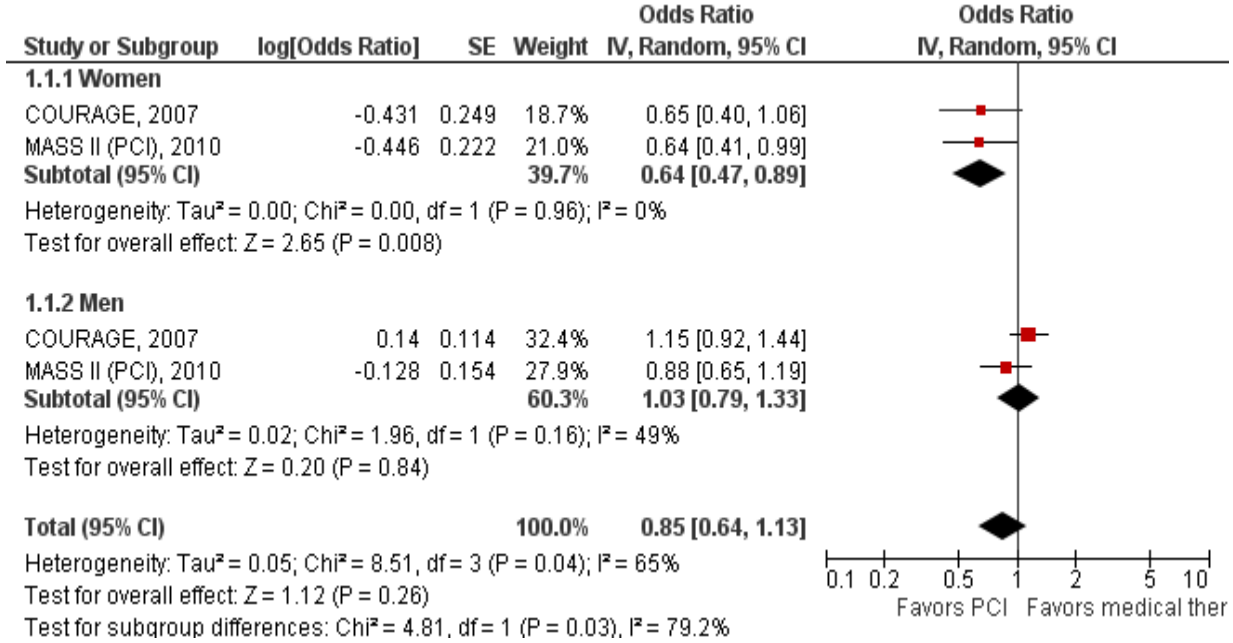
Study (Comparison)	Outcome	Women (95% CI)	Men (95% CI)	Overall (95% CI)
COURAGE (PCI [or CABG if PCI failed] vs. optimal medical therapy)	Death/MI	0.65 (0.40 to 1.06)	1.15 (0.91 to 1.42)	1.05 (0.87 to 1.27)
MASS II (PCI vs. optimal medical therapy)	Death/MI/revascularization	0.64 (0.41 to 0.98)	0.88 (0.65 to 1.19)	0.79 (0.62 to 1.01)
MASS II (CABG vs. optimal medical therapy)	Death/MI/revascularization	0.43 (0.26 to 0.72)	0.43 (0.31 to 0.61)	0.43 (0.32 to 0.56)
STICH (CABG vs. optimal medical therapy)	Death	0.75 (0.42 to 1.31)	0.87 (0.72 to 1.06)	0.86 (0.72 to 1.04)

CI = confidence interval; CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention

Forest plots for the random-effects model are shown in Figures 7, 8, and 9. Separate analyses were created for (a) primarily PCI strategy, (b) primarily CABG strategy, and (c) either type of revascularization strategy compared with optimal medical therapy for the purposes of creating a sensitivity analysis given the subtle differences in patient populations and revascularization methods used in those studies.

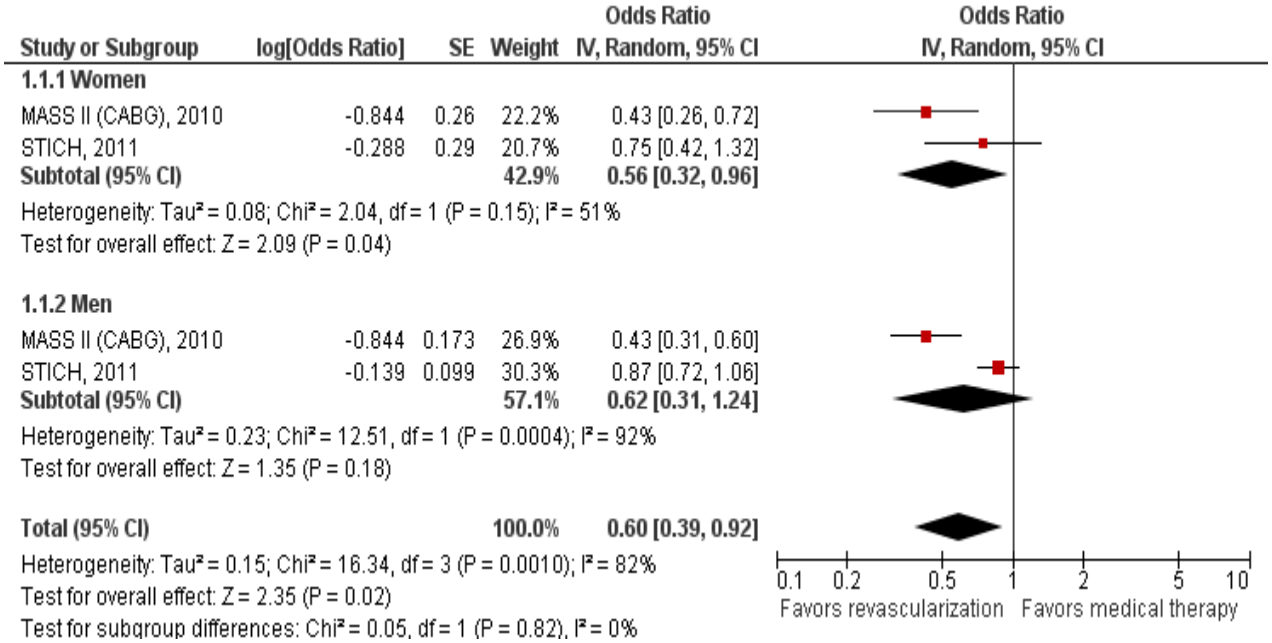
The primarily PCI strategy (Figure 7) studies included COURAGE and MASS II (PCI). The summary odds ratio in women was 0.64 (95% CI, 0.47 to 0.89) and in men was 1.03 (CI, 0.79 to 1.33). The test for heterogeneity was not significant for women and men. The results showed that PCI reduced death/MI in women but not in men.

Figure 7. Stable angina, revascularization (primarily PCI) versus medical therapy



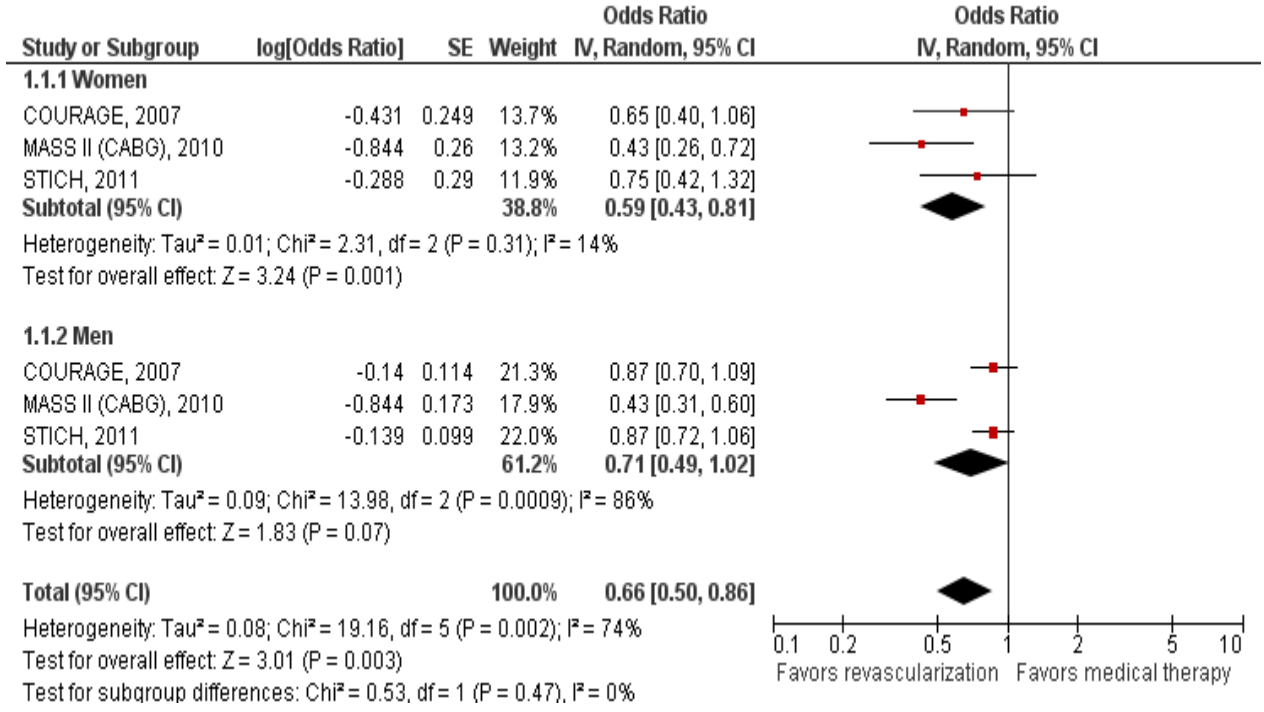
The primarily CABG strategy (Figure 8) studies included MASS II (CABG) and STICH. The summary odds ratio in women was 0.56 (CI, 0.32 to 0.96) and in men was 0.62 (CI, 0.31 to 1.24). The test for heterogeneity was not significant for women (p=0.15) but was significant for men (p=0.0004). These results show that CABG was significantly better in reducing cardiovascular events than optimal medical therapy was in women (effect size p=0.04) but not in men.

Figure 8. Stable angina, revascularization (primarily CABG) versus medical therapy



We then combined all studies utilizing both types of revascularization strategies (PCI or CABG)—COURAGE, MASS II, and STICH. Figure 9 shows the forest plot for the random-effects model using the MASS II (CABG) cohort. The summary odds ratio in women was 0.59 (CI, 0.43 to 0.81) and in men was 0.71(CI, 0.49 to 1.02). The test for heterogeneity was not significant in women, but was significant in men. These results showed that revascularization was significantly better in reducing cardiovascular events than optimal medical therapy in women. Similar results were obtained if the model was run with the MASS II (PCI) cohort (figure not shown). For men, revascularization and optimal medical therapy were not statistically different.

Figure 9. Stable angina, revascularization (combined) versus medical therapy



KQ 3b: Modifiers of Effectiveness

No studies were identified that evaluated women presenting with stable angina related to modifiers of the effectiveness of revascularization versus optimal medical therapy.

KQ 3c: Safety Concerns

No studies were identified that evaluated women presenting with stable angina related to safety concerns for revascularization versus optimal medical therapy.

Strategy 2: PCI Versus CABG in Stable/Unstable Angina

Key Points

- **Description of included studies:** 10 studies (8 good quality, 2 fair) compared PCI with CABG in women with stable/unstable angina and included a total of 6,289 patients, of which 1,583 (25%) were women.
- **Effectiveness of interventions:** A meta-analysis of two good-quality studies reporting 30-day death rates showed no statistically significant difference between PCI and CABG and therefore did not support evidence of a sex effect. 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). These two studies did, however, suggest a potentially greater benefit with PCI in women and with CABG in men. The low number of studies and wide confidence intervals made this a less robust finding and one that should be interpreted with caution. For 1-year outcomes (death/MI/stroke), a meta-analysis of two good-quality studies suggested potentially better outcomes in the CABG group for both sexes however this findings was not statistically significant (CI crosses 1). 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) outcomes (death/MI/stroke), a meta-analysis of four good-quality studies although not statistically significant, suggested better outcomes in the CABG group in women (OR 1.17; CI, 0.90 to 1.54); however in men, CABG was significantly better than PCI (OR 1.63; CI, 1.20 to 2.23, p= 0.002). Strength of evidence favoring CABG over PCI was low for women and men at 30-day and 1-year followups, and low for women and high for men at ≥2-year followup.
- **Modifiers of effectiveness:** One good-quality study (915 total patients, 249 [27%] women) evaluated the comparative effectiveness of PCI versus 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 who underwent PCI. Strength of evidence for modifiers of effectiveness for PCI versus CABG in stable/unstable angina was insufficient.
- **Safety concerns:** One good-quality study (1205 total patients, 283 [23%] women) reported harms associated with PCI compared with CABG among women with unstable angina or NSTEMI and found that bleeding associated with PCI was higher in women compared with men. Strength of evidence for safety concerns for PCI versus CABG in stable/unstable angina was insufficient.

Detailed Synthesis

We identified 10 studies[68,78-86] that evaluated PCI versus CABG for women presenting with unstable angina or NSTEMI. Of these 10 studies, 8 were good quality, and 2 were fair quality. Table 15 presents a general description of these 10 studies, including the study name, author, year, and related articles (i.e., study design and secondary papers); treatment comparisons evaluated; study population; and overall quality rating. Table 16 summarizes the women-specific outcomes (composite and individual) reported in these studies. Appendix F contains summary tables with sex-specific clinical outcomes for all followup time points.

Table 15. KQ 3 Strategy 2: Study characteristics of RCTs evaluating women with stable or unstable angina (PCI vs. CABG)

Study Author/Year Related Articles	Description of Study	# of Subjects	Quality
ARTS I Vaina et al., 2009[78] and van den Brand, et al., 2002[87] Serruys et al., 1999[88] Voudris et al., 2006[89] Anonymous, 1999[90]	**Title:** Effect of gender differences on early and mid-term clinical outcome after percutaneous or surgical coronary revascularisation in patients with multivessel coronary artery disease: insights from ARTS I and ARTS II **Comparator:** PCI (BMS) vs. CABG **Components of medical therapy:** Not reported.	Total: 1,205 Women: 283 (23%)	Good
BARI Jacobs et al., 1998[79] and Gibbons et al., 2001[91] Anonymous, 2007[92] Lombardero et al., 2002[93] Anonymous, 2000[94] Hlatky et al., 1995[95] Rogers et al., 1995[96] Sutton-Tyrrell et al., 1998[97] Mullany et al., 1999[98] Anonymous, 1996[99]	**Title:** Better outcome for women compared with men undergoing coronary revascularization: a report from the bypass angioplasty revascularization investigation (BARI) **Comparator:** PCI (type not specified) vs. CABG **Components of medical therapy:** Not reported.	Total: 915 Women: 249 (27%)	Good
CABRI Anonymous, 1995[80]	**Title:** First-year results of CABRI (Coronary Angioplasty vs. Bypass Revascularisation Investigation) **Comparator:** PCI (PTCA) vs. CABG **Components of medical therapy:** Aspirin; fish oils and lipid-lowering agent were allowed; individual patient management followed the established practice at each participating center.	Total: 1,054 Women: 234 (22%)	Good

Table 15. KQ 3 Strategy 2: Study characteristics of RCTs evaluating women with stable or unstable angina (PCI vs. CABG) (continued)

Study Author/Year Related Articles	Description of Study	# of Subjects	Quality
CARDia Kapur et al., 2010[84] and Kapur et al., 2005[100]	**Title:** Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial **Comparator:** PCI (BMS or DES) vs. CABG **Components of medical therapy:** Glycoprotein IIb/IIIa, clopidogrel, and aspirin.	Total: 510 Women: 132 (26%)	Good
EAST King et al., 2000[81] and King et al., 1995[101] King et al., 1994[102] Zhao et al., 1996[103]	**Title:** Eight-year mortality in the Emory Angioplasty vs. Surgery Trial (EAST) **Comparator:** PCI (type not specified) vs. CABG **Components of medical therapy:** Not reported.	Total: 392 Women: 103 (26%)	Good
GABI Kaehler et al., 2005[86] and Hamm et al., 1994[104]	**Title:** 13-year follow-up of the German angioplasty bypass surgery investigation **Comparator:** PCI (type not specified) vs. CABG **Components of medical therapy:** Not reported (discretion of treating provider).	Total: 359 Women: 66 (18%)	Good
MASS II Hueb et al., 2010[68] and Hueb et al., 2004[73] Hueb et al., 2007[74]	**Title:** Ten-year followup survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease **Comparator:** PCI (type not specified) vs. CABG **Components of medical therapy:** Nitrates, aspirin, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or a combination of these drugs unless contraindicated. Lipid-lowering agents, particularly statins, were also prescribed, along with a low-fat diet, on an individual basis.	Total: 611 Women: 196 (32%)	Good

Table 15. KQ 3 Strategy 2: Study characteristics of RCTs evaluating women with stable or unstable angina (PCI vs. CABG) (continued)

Study Author/Year Related Articles	Description of Study	# of Subjects	Quality
PRECOMBAT Park et al., 2011[85]	**Title:** Randomized Trial of Stents versus Bypass Surgery for Left Main Coronary Artery Disease **Comparator:** PCI (DES) vs. CABG **Components of medical therapy:** Before or during PCI: aspirin plus clopidogrel (loading dose, 300 mg) or ticlopidine (loading dose, 500 mg). After PCI: 100 mg/day aspirin indefinitely and 75 mg/day clopidogrel or 250 mg/day ticlopidine for at least 6 months. Medications after CABG were selected according to the policy of the institution or physician.	Total: 600 Women: 141 (24%)	Good
SOS Zhang et al., 2004[82] and Zhang et al., 2003[105] Stables et al., 1999[106]	**Title:** Relative benefit of coronary artery bypass grafting vs. stent-assisted percutaneous coronary intervention for angina pectoris and multivessel coronary disease in women vs. men (one-year results from the Stent or Surgery trial) **Comparator:** PCI (BMS) vs. CABG **Components of medical therapy:** Not reported.	Total: 908 Women: 206 (23%)	Fair
SYNTAX Morice et al., 2010[83]	**Title:** Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial **Comparator:** PCI (type not specified) vs. CABG **Components of medical therapy:** In the PCI arm, clopidogrel for 6 months, with aspirin therapy indefinitely.	Total: 705 Women: 185 (26%)	Fair

BMS= bare-metal stent; CABG = coronary artery bypass graft; CAD = coronary artery disease; DES = drug-eluting stent; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial

Table 16. KQ 3 Strategy 2: Outcomes reported in RCTs evaluating women with stable or unstable angina (PCI vs. CABG)

Study	Composite Outcome[a] (Timing) Anticipated Effect Size	Death[a] (Timing)	MI (Timing)	CVA (Timing)	Revascularization (Timing)	Other (Timing)
ARTS I[78,87-90]	*Death/CVA/MI/CABG/repeat PCI* (30 days, 1 year, 3 years, 5 years) Death/CVA (30 days, 1 year, 3 years) Death/MI/CVA (30 days, 1 year, 3 years, 5 years) MI/CVA/PTCA (5 years) Powered to detect 7% difference in favor of CABG	Yes (30 days, 1 year, 3 years, 5 years) MACE-free survival (30 days, 1 year, 3 years)	Yes (30 days, 1 year, 3 years, 5 years)	Yes (5 years) (30 days, 1 year, 3 years, 5 years)	Yes (30 days, 1 year, 3 years, 5 years)	Quality of life (3 years) Bleeding (in hospital)
BARI[79,91-99]	Effect size not reported	*Cumulative survival rate* (5 year, 7 years, 10 years)	Yes (in hospital)		Yes (10 years)	Angina status (4 years, 10 years) Congestive heart failure (in hospital)
CABRI[80]	Powered to detect 60% reduction in mortality in PCI group	*Yes* (1 year)				Angina (1 year)
CARDia[84,100]	*Death/MI/stroke repeat revascularization* (1 year) Death/MI/CVA (1 year) Powered for OR of 0.69 in favor of PCI (upper CI 1.3)					

Table 16. KQ 3 Strategy 2: Outcomes reported in RCTs evaluating women with stable or unstable angina (PCI vs. CABG) (continued)

Study	Composite Outcome[a] (Timing) Anticipated Effect Size	Death[a] (Timing)	MI (Timing)	CVA (Timing)	Revascularization (Timing)	Other (Timing)
EAST[81,101-103]	Powered for 25% reduction	*Survival* (3 years, 8 years)				
GABI[86,104]	Powered for 15% difference in success rates as therapeutically equivalent	Yes (13 years)				Primary outcome was freedom from angina (not reported by sex)
MASS II[68,73,74]	Death/MI/angina requiring revascularization (10 years) Powered to detect 2-fold difference					
PRECOMBAT[85]	*Death/MI/stroke/ischemia-driven target-vessel revascularization* (1 year, 2 years) Powered to detect 7% difference					
SOS[82,105,106]	Powered for event rate of 5% in CABG arm and 10% in PCI arm				Primary outcome not reported by sex	Quality of life (6 months, 1 year) Angina frequency (6 months, 1 year) Physical limitation (6 months, 1 year)
SYNTAX[83]	*Death/MI/CVA/repeat revascularization* (1 year) Powered for clinically relevant difference of 5%					

CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; MACE = major adverse cardiovascular event; MI = myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; RRR = relative risk reduction

[a]Primary outcome in italics.

KQ 3a: Effectiveness of Interventions

A meta-analysis of studies was performed on those with similar composite outcomes measured at similar time points. This meta-analysis was divided into followup intervals of short term (≤30 days), intermediate term (1 year), and long term (≥2 years).

Short-Term Followup Studies

Two studies with short-term (30-day or in-hospital) outcomes—ARTS I[78] and BARI[79]—were included in the meta-analysis. For both studies, the reported event rates/percentages were converted into odds ratios. Table 17 presents the outcomes, odds ratios, and confidence intervals for the meta-analysis.

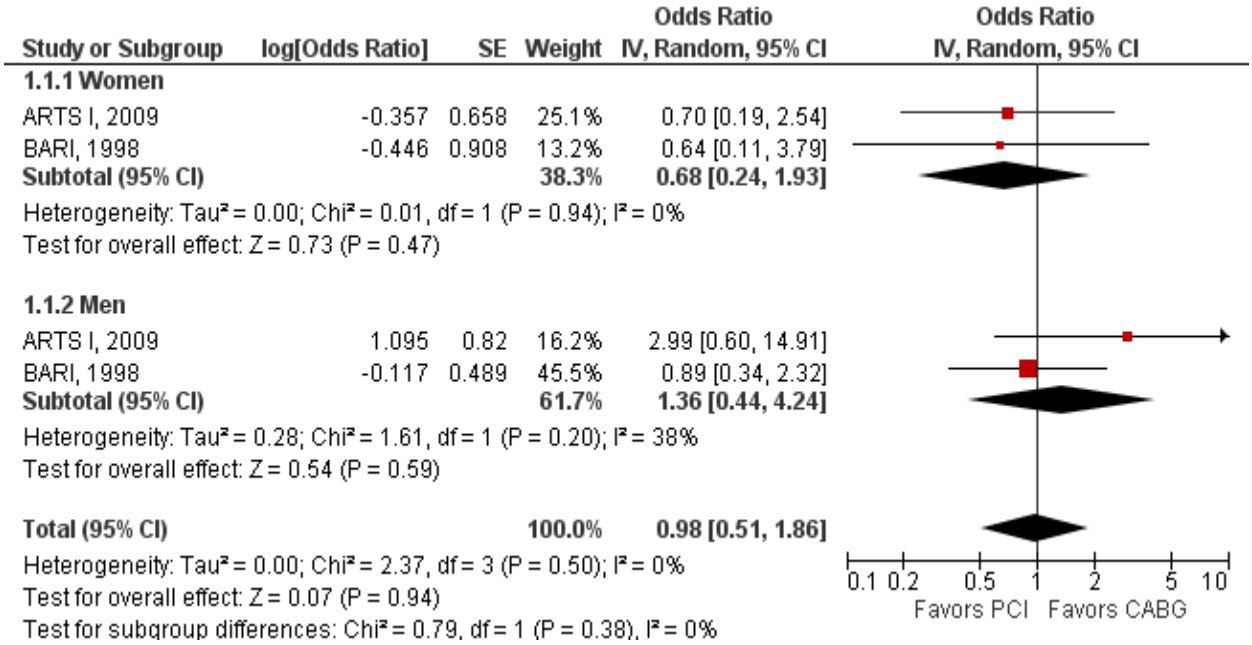
Table 17. Sex results for stable/unstable angina on composite outcomes (short-term)

Study (comparison)	Outcome	Women (95% CI)	Men (95% CI)	Overall (95% CI)
ARTS I (PCI vs. CABG)	Death (30 days)	0.70 (0.19 to 2.51)	2.99 (0.60 to 14.91)	NR
BARI (PCI vs. CABG)	Death (in-hospital)	0.64 (0.11 to 3.86)	0.89 (0.34 to 2.31)	0.83 (0.36 to 1.93)

CI = confidence interval; CABG = coronary artery bypass graft; NR = not reported; PCI = percutaneous coronary intervention

Forest plots for the random-effects model are shown in Figure 10. 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 test for heterogeneity was nonsignificant. The findings were not statistically significant for demonstrating a benefit in PCI and CABG, although the odds ratios suggested 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.

Figure 10. Stable/unstable angina short-term (30 days) PCI versus CABG



Intermediate-Term Followup Studies

Two studies with 1-year outcomes—ARTS I[78] and CARDia[84]—were included in the meta-analysis. In the SYNTAX study, [83] there was no difference in the primary composite outcome (death/MI/stroke, or repeat revascularization) at 1 year between patients undergoing CABG and PCI (13.6% vs. 15.8%). No sex data by treatment in this fair-quality study were provided, but being female was a significant predictor of 1-year major adverse cardiovascular events (OR 0.50; 95% CI, 0.27 to 0.91; p=0.02 [interaction effect not reported]). The SYNTAX study was excluded from the meta-analysis since it did not report subgroup results by sex. The PRECOMBAT study[85] did not report sex-specific data at 1 year, so this study was not included in this intermediate-term followup analysis (but data reported at 2 years are included in the long-term followup analysis below). Event data from the ARTS I study were transformed into risk ratios. Table 18 presents the outcomes, odds ratios, and confidence intervals for the meta-analysis.

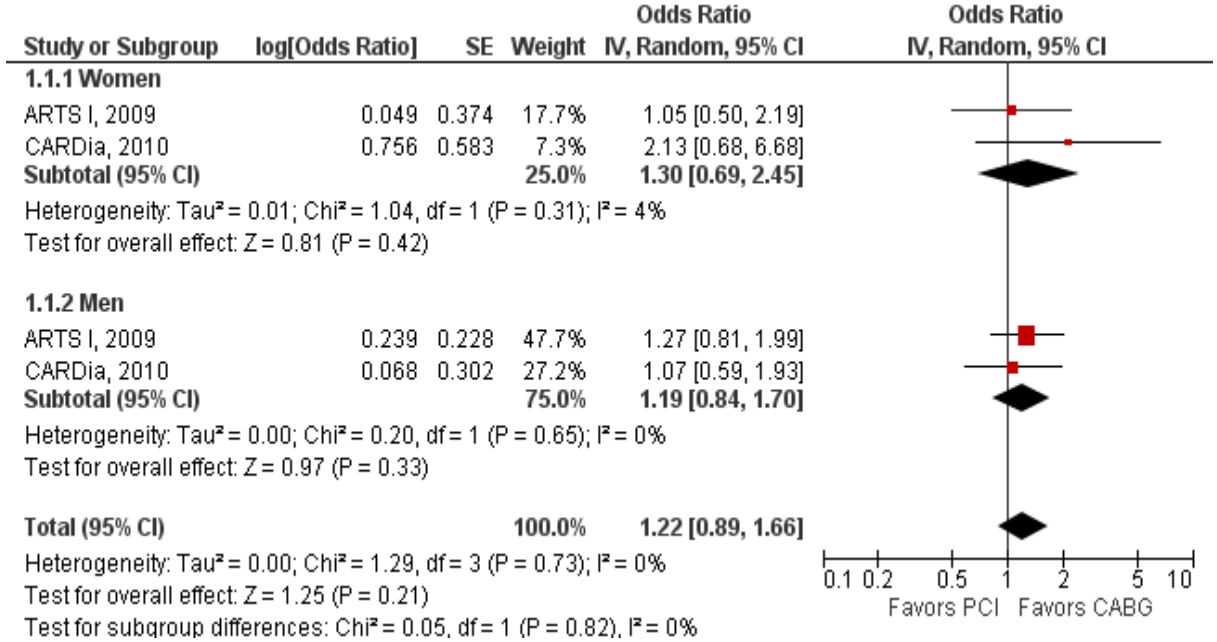
Table 18. Sex results for stable/unstable angina on composite outcomes (intermediate-term)

Study (Comparison)	Outcome	Women (95% CI)	Men (95% CI)	Overall (95% CI)
ARTS I (PCI vs. CABG)	Death/MI/stroke	1.05 (0.51 to 2.21)	1.27 (0.81 to 1.98)	NR
CARDia (PCI vs. CABG)	Death/MI/stroke	2.13 (0.68 to 6.68)	1.07 (0.59 to 1.93)	1.25 (0.75 to 2.09)

CI = confidence interval; CABG = coronary artery bypass graft; NR = not reported; PCI = percutaneous coronary intervention

Forest plots for the random effects model are shown in Figure 11. The summary odds ratio in women was 1.30 (95% CI, 0.69 to 2.45) and in men was 1.19 (CI, 0.84 to 1.70). The test for heterogeneity was nonsignificant. These results show lower events in the CABG group for both sexes, but this benefit was not statistically significant.

Figure 11. Stable/unstable angina intermediate-term (1 year) PCI versus CABG



Long-Term Followup Studies

To assess the long-term effect at ≥2 years, four studies were included in the meta-analysis: ARTS I (3-year),[78] BARI (5-year),[79] MASS II (10-year),[68] and PRECOMBAT (2-year).[85] Results of the ARTS I and BARI studies were transformed into risk ratios. For the BARI study, the survival rates were converted into death rates. For women, the death rates for CABG and PCI were 24 percent of 240 and 26 percent of 249, respectively. For men, survival rates by treatment group were not reported. The MASS II results were inverted to hazard ratios <1 favoring PCI and hazard ratios >1 favoring CABG. The GABI study[86] was excluded from the meta-analysis because it did not present data by sex. The GABI study randomized 359 patients (66 women) with angina CCS class II-IV, under age 75, and coronary multiple-vessel disease requiring revascularization of at least 2 major coronary vessels to either PCI or CABG. The authors report that the hazard ratio for death following PCI or CABG was not different between men and women at the 13-year followup. Table 19 presents the outcomes, odds ratios, and confidence intervals for the meta-analysis.

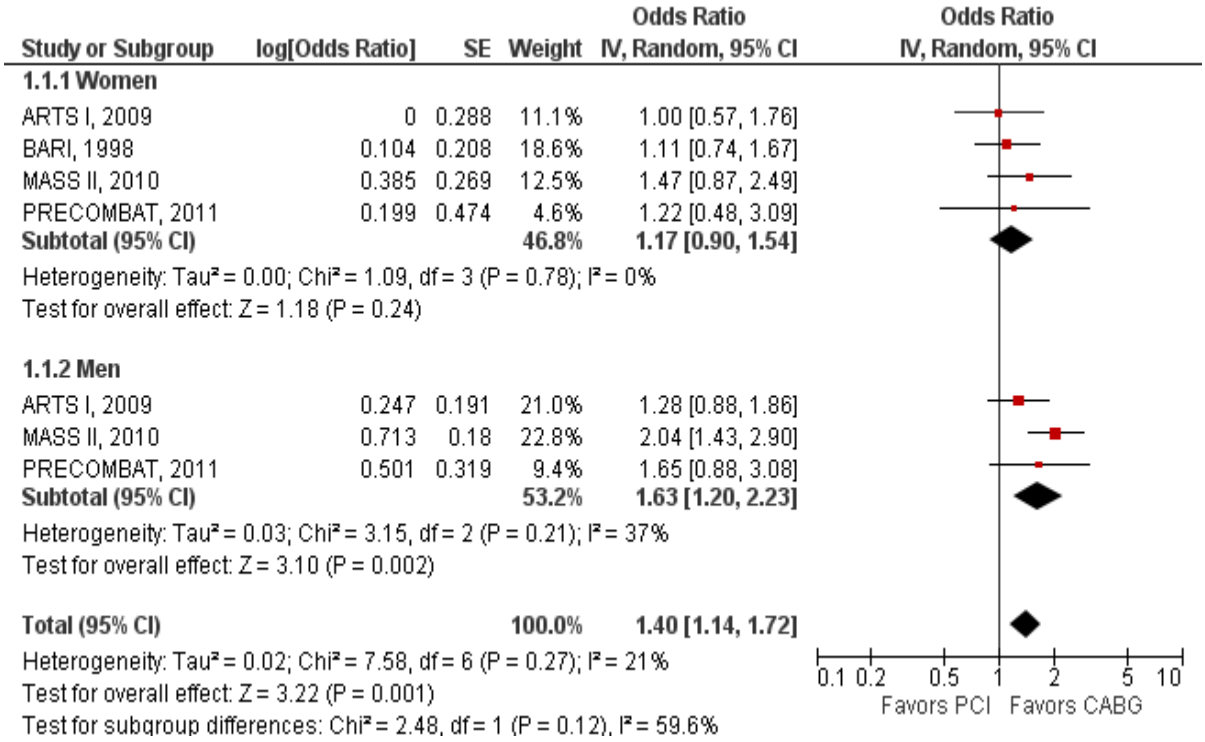
Table 19. Sex results for stable/unstable angina on composite outcomes (long-term)

Study (Comparison)	Outcome	Women (95% CI)	Men (95% CI)	Overall (95% CI)
ARTS I (PCI vs. CABG)	Death/MI/CVA/revascularization	1.00 (0.57 to 1.76)	1.28 (0.88 to 1.86)	NR
BARI (PCI vs. CABG)	Death	1.11 (0.74 to 1.67)	NR	1,20 (0.92 to 1.59)
MASS II (PCI vs. CABG)	Death/MI/revascularization	1.47 (0.87 to 2.50)	2.04 (1.45 to 2.94)	1.89 (1.38 to 2.56)
PRECOMBAT (PCI vs. CABG)	Death/MI/CVA/revascularization	1.22 (0.48 to 3.08)	1.65 (0.88 to 3.07)	1.50 (0.90 to 2.52)

CI = confidence interval; CABG = coronary artery bypass graft; NR = not reported; PCI = percutaneous coronary intervention

Forest plots for the random effects model are shown in Figure 12. The summary odds ratio in women was 1.17 (95% CI, 0.90 to 1.54) and in men was 1.63 (CI, 1.20 to 2.23). The test for heterogeneity was nonsignificant. Similar to the intermediate-term outcomes, there was no definitive evidence of a sex effect. In men, CABG was significantly better than PCI (p=0.002); in women, results suggest lower events in the CABG group, but it was not statistically significant (p=0.24).

Figure 12. Stable/unstable angina long-term (≥2 years) PCI versus CABG



KQ 3b: Modifiers of Effectiveness

We identified one good-quality study (915 total patients, 249 [27%] women) in which the long-term survival rate (7 years) in diabetic women was addressed. In the BARI study,[79] this subgroup analysis was not initially specified but was requested by the safety and monitoring board during the course of the trial on the basis of concurrent reports from another study. Survival rate at 7 years was significantly higher among diabetic patients (n=353) treated with CABG compared with those undergoing PCI (74.6% vs. 55.7%), a difference that remained significant in men (77.9% vs. 51.5%) but not in women (74.3% vs. 61.0%). Appendix G contains a summary table with study data related to modifiers of effectiveness (subgroup analyses).

KQ 3c: Safety Concerns

We identified one good-quality study[78] (1,205 total patients, 283 [23%] women) that addressed significant safety concerns and, specifically, risk of major bleeding in women (n=283). The ARTS I study was designed to compare CABG with PCI combined with stent implantation for the treatment of patients with multiple-vessel disease. Major bleeding was higher in women undergoing PCI compared with men (7.2% vs. 0.2%, p<0.001) but not among those assigned to CABG (1.4% vs. 2.8%). After adjusting for baseline characteristics, major bleeding complications remained higher among women in the PCI group (OR 29.4; 95% CI, 5.3 to 500; p=0.001 women vs. men) compared with the CABG group (OR 1.5; CI, 0.4 to 10.1, p=0.58 women vs. men). Appendix H contains a summary table with study data related to safety concerns (harms).

Summary and Discussion

For this report, we conducted a systematic review of the medical literature for the comparative effectiveness of optimal medical therapy, PCI, and CABG in women with CAD. CAD presentations included stable angina and acute coronary syndrome; i.e., STEMI, NSTEMI, and unstable angina. This review assessed the comparative effectiveness of the three treatment strategies on (1) clinical outcomes, (2) outcomes by modifiers such as demographic and clinical factors, and (3) safety outcomes.

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: 7 studies (6 good quality, 1 fair) comparing PCI with fibrinolysis/supportive medical therapy (5 fibrinolysis, 2 supportive) in patients with STEMI
- KQ 2: 7 studies (6 good quality, 1 fair) comparing early invasive (PCI or CABG) with initial conservative in patients with UA/NSTEMI
- KQ 3: 5 studies (all good quality) comparing revascularization 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.

Key Findings and Strength of Evidence

The main findings of the treatment strategies for women with CAD are summarized in the following sections. Table 20 summarizes the strength of evidence (SOE) by effectiveness outcome for the KQs.

Table 20. Strength of evidence by effectiveness outcome

KQ: Presentation Comparison Outcome Time Point (Forest Plot #)	# Studies	N Total N Women (%)	Effect OR (95% CI)	Conclusions	Limitations to Applicability	Strength of Evidence
KQ 1a: STEMI PCI vs. fibrinolysis Death/MI/stroke 30 days (Figure 3)	5[36,37,39,40,42]	Total: 4,105 Women: 1,017 (25%)	<u>Women</u> 0.50 (0.36 to 0.72); p=0.0001 <u>Men</u> 0.54 (0.42 to 0.70); p<0.00001	<u>Women</u> Favors PCI <u>Men</u> Favors PCI	PCI consisted of balloon angioplasty or bare-metal stents	Study design/quality: RCT/good <u>Women</u> Risk of bias : Low Consistency: Consistent Directness: Direct Precision: Precise ***SOE: High*** <u>Men</u> Risk of bias: Low Consistency: Consistent Directness: Direct Precision: Precise ***SOE: High***
KQ 1a: STEMI PCI vs. fibrinolysis 1 year (No figure)	2[40,44]	Total: 1,973 Women: 523 (26%)	<u>Women</u> No summary estimate due to heterogeneous outcomes <u>Men</u> No summary estimate due to heterogeneous outcomes	<u>Women</u> Insufficient <u>Men</u> Insufficient	PCI consisted of balloon angioplasty or bare-metal stents	Study design/quality: RCT/good <u>Women</u> Risk of bias: Low Consistency: N/A Directness: N/A Precision: N/A ***SOE: Insufficient*** <u>Men</u> Risk of bias: Low Consistency: N/A Directness: N/A Precision: N/A ***SOE: Insufficient***

Table 20. Strength of evidence by effectiveness outcome (continued)

KQ: Presentation Comparison Outcome Time Point (Forest Plot #)	# Studies	N Total N Women (%)	Effect OR (95% CI)	Conclusions	Limitations to Applicability	Strength of Evidence
KQ 2a: UA/NSTEMI Early invasive vs. initial conservative Death/MI 6 months (Figure 4)	2[51,60]	Total: 4,677 Women: 1,506 (32%)	Women 0.77 (0.28 to 2.12) Men 0.65 (0.52 to 0.82); p=0.0002	Women Trend favoring early invasive Men Favors early invasive	FRISC II study had lower rates of invasive treatment in the initial conservative group.	Study design/quality: RCT/good Women Risk of bias: Low Consistency: Inconsistent Directness: Direct Precision: Imprecise ***SOE: Low*** Men Risk of bias: Low Consistency: Consistent Directness: Direct Precision: Precise ***SOE: High***
KQ 2a: UA/NSTEMI Early invasive vs. initial conservative Death/MI/ rehospitalization 1 year (Figure 5)	5[22,53,56,59]	Total: 14,692 Women: 5,144 (35%)	Women 0.78 (0.54 to 1.12) Men 0.88 (0.64 to 1.20)	Women Trend favoring early invasive Men Trend favoring early invasive	FRISCII and RITA-3 studies had lower rates of invasive treatment in the initial conservative group. ICTUS allowed more liberal use of revascularization, therefore rates of invasive therapy were higher in initial conservative group.	Study design/quality: RCT/good Women Risk of bias: Low Consistency: Inconsistent Directness: Direct Precision: Imprecise ***SOE: Low*** Men Risk of bias: Low Consistency: Inconsistent Directness: Direct Precision: Imprecise ***SOE: Low***

Table 20. Strength of evidence by effectiveness outcome (continued)

KQ: Presentation Comparison Outcome Time Point (Forest Plot #)	# Studies	N Total N Women (%)	Effect OR (95% CI)	Conclusions	Limitations to Applicability	Strength of Evidence
KQ 2a: UA/NSTEMI Early invasive vs. initial conservative Death/MI/ rehospitalization 5 years (Figure 6)	2[58,61]	Total: 3,657 Women: 1,069 (29%)	<u>Women</u> 1.05 (0.81 to 1.35) <u>Men</u> 0.91 (0.53 to 1.56)	<u>Women</u> Slight trend favoring initial conservative therapy. Given the small suggested benefit at 5 years, 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. <u>Men</u> Trend favoring early invasive	At longer term followup, rate of PCI in initial conservative group approached that of early invasive group.	Study design/quality: RCT/good <u>Women</u> Risk of bias: Low Consistency: Inconsistent Directness: Direct Precision: Imprecise ***SOE: Insufficient*** <u>Men</u> Risk of bias: Low Consistency: Inconsistent Directness: Direct Precision: Imprecise ***SOE: Low***
KQ 3a: Stable angina PCI vs. medical therapy Death/MI/ revascularization 4–5 years (Figure 7)	2[65,68]	Total: 2,898 Women: 556 (19%)	<u>Women</u> 0.64 (0.47 to 0.89); p=0.008 <u>Men</u> 1.03 (0.79 to 1.33)	<u>Women</u> Favors PCI <u>Men</u> Slight trend favoring medical therapy. This suggested small benefit, however, has a wide confidence interval crossing 1 and is not supported by additional time points or by the evidence in women.	None	Study design/quality: RCT/good <u>Women</u> Risk of bias: Low Consistency: Consistent Directness: Indirect Precision: Precise ***SOE: Moderate*** <u>Men</u> Risk of bias: Low Consistency: Inconsistent Directness: Indirect Precision: Imprecise ***SOE: Low***

Table 20. Strength of evidence by effectiveness outcome (continued)

KQ: Presentation Comparison Outcome Time Point (Forest Plot #)	# Studies	N Total N Women (%)	Effect OR (95% CI)	Conclusions	Limitations to Applicability	Strength of Evidence
KQ 3a: Stable angina CABG vs. medical therapy Death/MI/ revascularization 4–5 years (Figure 8)	2[67,68]	Total: 1,823 Women: 344 (19%)	<u>Women</u> 0.56 (0.32 to 0.96); p=0.04 <u>Men</u> 0.62 (0.31 to 1.24)	<u>Women</u> Favors revascularization <u>Men</u> Trend favoring revascularization	STICH study consisted of CABG in low EF patients.	Study design/quality: RCT/good <u>Women</u> Risk of bias: Low Consistency: Inconsistent Directness: Indirect Precision: Imprecise ***SOE: Low*** <u>Men</u> Risk of bias: Low Consistency: Inconsistent Directness: Indirect Precision: Imprecise ***SOE: Low***
KQ 3a: Stable angina Revascularization (PCI or CABG) vs. medical therapy Death/MI/ revascularization 4–5 years (Figure 9)	3[65,67,68]	Total: 4,110 Women: 704 (17%)	<u>Women</u> 0.59 (0.43 to 0.81); p=0.001 <u>Men</u> 0.71 (0.49 to 1.02)	<u>Women</u> Favors revascularization <u>Men</u> Trend favoring revascularization	STICH study consisted of CABG in low EF patients.	Study design/quality: RCT/good <u>Women</u> Risk of bias: Low Consistency: Consistent Directness: Indirect Precision: Precise ***SOE: Moderate*** <u>Men</u> Risk of bias: Low Consistency: Inconsistent Directness: Indirect Precision: Imprecise ***SOE: Low***

Table 20. Strength of evidence by effectiveness outcome (continued)

KQ: Presentation Comparison Outcome Time Point (Forest Plot #)	# Studies	N Total N Women (%)	Effect OR (95% CI)	Conclusions	Limitations to Applicability	Strength of Evidence
KQ 3a: Stable/unstable angina PCI vs. CABG Death 30 days (Figure 10)	2[78,79]	Total: 2,120 Women: 530 (25%)	<u>Women</u> 0.68 (0.24 to 1.93) <u>Men</u> 1.36 (0.44 to 4.24)	<u>Women</u> Trend favoring PCI <u>Men</u> Trend favoring CABG	Type of PCI not specified in most studies.	Study design/quality: RCT/good <u>Women</u> Risk of bias: Low Consistency: Consistent Directness: Direct Precision: Imprecise ***SOE: Low*** <u>Men</u> Risk of bias: Low Consistency: Inconsistent Directness: Direct Precision: Imprecise ***SOE: Low***
KQ 3a: Stable/unstable angina PCI vs. CABG Death/MI/stroke 1 year (Figure 11)	2[78,80,84]	Total: 1,715 Women: 415 (24%)	<u>Women</u> 1.30 (0.69 to 2.45) <u>Men</u> 1.19 (0.84 to 1.70)	<u>Women</u> Trend favoring CABG <u>Men</u> Trend favoring CABG	Type of PCI not specified in most studies.	Study design/quality: RCT/good <u>Women</u> Risk of bias: Low Consistency: Consistent Directness: Direct Precision: Imprecise ***SOE: Low*** <u>Men</u> Risk of bias: Low Consistency: Consistent Directness: Direct Precision: Imprecise ***SOE: Low***

Table 20. Strength of evidence by effectiveness outcome (continued)

KQ: Presentation Comparison Outcome Time Point (Forest Plot #)	# Studies	N Total N Women (%)	Effect OR (95% CI)	Conclusions	Limitations to Applicability	Strength of Evidence
KQ 3a: Stable/unstable angina PCI vs. CABG Death/MI/stroke ≥2 years (Figure 12)	4[68,78,79,85]	Total: 3,331 Women: 866 (26%)	<u>Women</u> 1.17 (0.90 to 1.54) <u>Men</u> 1.63 (1.20 to 2.23); p=0.002	<u>Women</u> Trend favoring CABG <u>Men</u> Favors CABG	Type of PCI not specified in most studies.	Study design/quality: RCT/good <u>Women</u> Risk of bias: Low Consistency: Consistent Directness: Direct Precision: Imprecise ***SOE: Low*** <u>Men</u> Risk of bias: Low Consistency: Consistent Directness: Direct Precision: Precise ***SOE: High***

CABG = coronary artery bypass grafting; CI = confidence interval; MI = myocardial infarction; EF = ejection fraction; 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; UA = unstable angina

Modifiers of Effectiveness

Five studies (four good, one fair quality) assessed variations in clinical outcomes in women due to demographic or clinical factors. One good-quality study evaluated the comparative effectiveness of PCI versus fibrinolysis in women under 65 years of age and women 65 and older and found no differences in in-hospital mortality among the treatment groups. One fair-quality study evaluated patients 80 years of age and older with STEMI. The study was limited by a small overall size, and it did not find significant differences in the composite outcome (death/heart failure/repeat MI/stroke) at 3 years in patients 80 years of age and older with STEMI undergoing PCI compared with conservative/supportive medical care.

Two good-quality UA/NSTEMI studies of early invasive versus initial conservative therapy showed conflicting results on risk stratification—one showed no difference in treatment outcomes in the intermediate- and high-risk groups (risk was derived from components of the TIMI risk score and a couple other aspects of the participants' presentation at randomization, including aspirin use and angina severity). The other study showed a higher event rate in women in the groups at moderate-to-high risk for thrombolysis in myocardial infarction (TIMI).

One good-quality stable/unstable angina study comparing PCI with CABG showed no difference in survival rate in diabetic women receiving CABG although survival was higher for diabetic men and the total diabetic population (total population results were influenced by the higher proportion of men enrolled in the study).

Of note, we did not find any data specific to women on race, socioeconomic factors, chronic kidney disease, angiographic-specific factors, or CABG-specific factors. Strength of evidence for modifiers of effectiveness for all treatment comparisons was insufficient.

Safety Concerns

Four good-quality studies reported safety outcomes in women. Two good-quality STEMI studies comparing fibrinolysis with PCI showed no difference in transfusions and a higher incidence of intracranial hemorrhage in women who received accelerated t-PA versus PCI (4.1% vs. 0%), but statistical analysis for this comparison was not done. Two good-quality UA/NSTEMI studies showed higher in-hospital bleeding rates in women undergoing PCI (adjusted OR 3.6; 95% CI, 1.6 to 8.3) but not in those undergoing CABG. However, we did not find data specific to women on adverse drug reactions, radiation exposure, access site complications, renal dysfunction, anaphylaxis, arrhythmias, stent thrombosis, or infection. Strength of evidence for safety concerns for all treatment strategies was insufficient.

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.[27] 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. These findings are similar to a meta-analysis[107] 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, while finding a trend favoring early invasive strategies, does not demonstrate a statistically significant benefit of an early invasive approach in reducing cardiovascular events in women. In contrast, the overall meta-analysis for trials of early invasive versus conservative strategies including both men and women showed a benefit of early invasive therapy.[108] 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

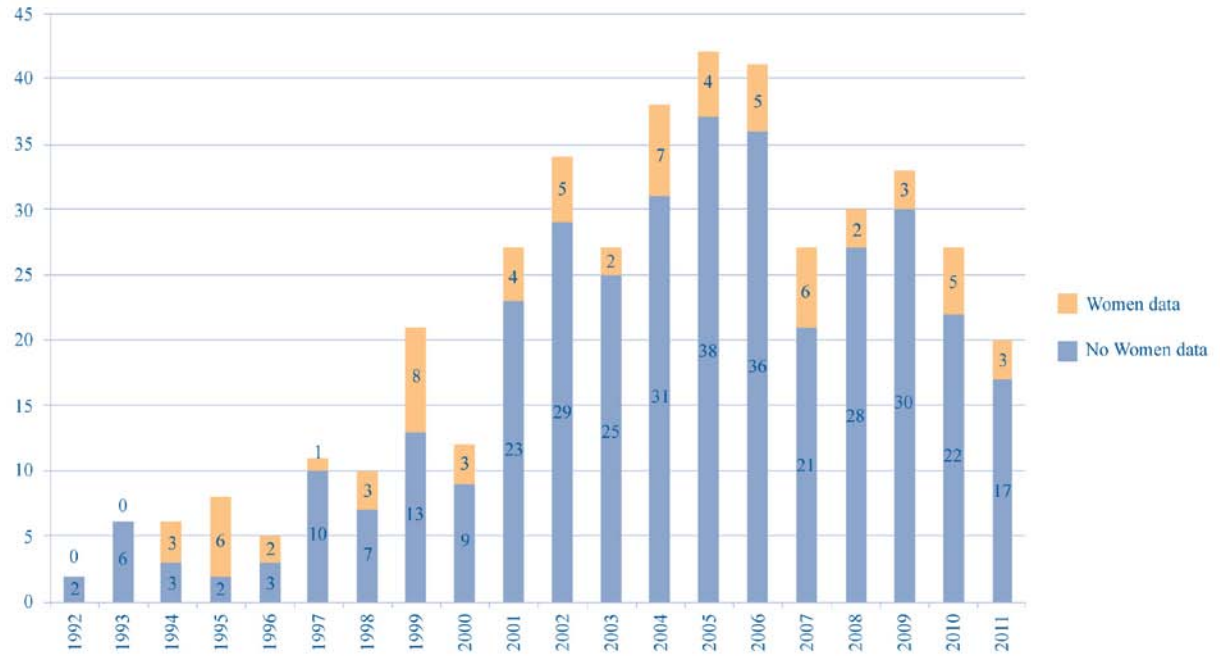
fibrinolysis or PCI. Careful consideration should be given to the dose, timing, and duration of antiplatelet, antithrombotic, and anticoagulant therapies administered to women.

Limitations of This Review

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 or 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 13 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 which included sex as a covariate in the model; the majority found no evidence of a gender 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.

Figure 13. Number of articles reporting data on women by year



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 was 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 evidence suggestive of a benefit of early invasive strategies for reducing cardiovascular events; however, this benefit was not statistically significant. Previous meta-analyses of studies comparing early invasive with initial conservative strategies on a combined population of men and women showed a 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.

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, 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).[34,109,110]

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.[111]

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, socioeconomic, 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.

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
BMS	bare-metal stent
CABG	coronary artery bypass graft
CAD	coronary artery disease
CI	confidence interval
CVA	cerebrovascular accident
DES	drug-eluting stent
EF	ejection fraction
HCT	Hematocrit
HR	hazard ratio
IABP	intra-aortic balloon pump
ICH	intracranial hemorrhage
IV	Intravenous
KQ	Key Question
MACE	major adverse cardiovascular events
MI	myocardial infarction
NSTEMI	non-ST elevation myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
PTCA	percutaneous transluminal coronary angioplasty
RCT	randomized controlled trial
RR	risk ratio
SOE	strength of evidence
STEMI	ST elevation myocardial infarction
TEP	Technical Expert Panel
TIMI	thrombolysis in myocardial infarction
TMR	transmyocardial revascularization
t-PA	tissue plasminogen activator
UA	unstable angina

Appendix A. Exact Search Strings

PubMed® Search Strategy (December 12, 2011)

Set #	Terms
#1	("cardiovascular diseases"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR "cardiovascular diseases"[All Fields]) OR ("heart diseases"[MeSH Terms] OR ("heart"[All Fields] AND "diseases"[All Fields]) OR "heart diseases"[All Fields]) OR ("heart"[MeSH Terms] OR "heart"[All Fields] OR "coronary"[All Fields]) OR cardiovas*[All fields] OR cardiac*[All fields] OR ("myocardium"[MeSH Terms] OR "myocardium"[All Fields] OR "myocardial"[All Fields]) OR ("acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields] AND "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields]) OR ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields]) OR ("angina, unstable"[MeSH Terms] OR ("angina"[All Fields] AND "unstable"[All Fields]) OR "unstable angina"[All Fields] OR ("unstable"[All Fields] AND "angina"[All Fields]))
#2	"angioplasty, balloon, coronary"[MeSH Terms] OR ("angioplasty"[All Fields] AND "balloon"[All Fields] AND "coronary"[All Fields]) OR "coronary balloon angioplasty"[All Fields] OR ("percutaneous"[All Fields] AND "transluminal"[All Fields] AND "coronary"[All Fields] AND "angioplasty"[All Fields]) OR "percutaneous transluminal coronary angioplasty"[All Fields] OR "ptca"[All Fields] OR percutaneous coronary intervention[All Fields] OR percutaneous coronary interventional[All Fields] OR percutaneous coronary interventions[All Fields] OR PCI[All Fields] OR stent[All Fields] OR stents[All Fields] OR stent*[All Fields] OR "stents"[MeSH Terms] OR ("balloon"[All Fields] AND "angioplasty"[All Fields]) OR "balloon angioplasty"[All Fields] OR "angioplasty, balloon"[MeSH Terms] OR "balloon dilation"[MeSH Terms] OR ("balloon"[All Fields] AND "dilation"[All Fields]) OR "balloon dilation"[All Fields] OR ("balloon"[All Fields] AND "dilatation"[All Fields]) OR "balloon dilatation"[All Fields] OR ("transluminal"[All Fields] AND "angioplasty"[All Fields]) OR "transluminal angioplasty"[All Fields] OR "angioplasty"[MeSH Terms] OR "angioplasty"[All Fields] OR "atherectomy, coronary"[MeSH Terms] OR ("atherectomy"[All Fields] AND "coronary"[All Fields]) OR "coronary atherectomy"[All Fields] OR ("coronary"[All Fields] AND "atherectomy"[All Fields]) OR ("coronary artery bypass"[MeSH Terms] OR ("coronary"[All Fields] AND "artery"[All Fields] AND "bypass"[All Fields]) OR "coronary artery bypass"[All Fields]) OR CABG[All Fields] OR ("coronary artery bypass"[MeSH Terms] OR ("aortocoronary"[All Fields] AND "bypass"[All Fields]) OR "aortocoronary bypass"[All Fields]) OR "coronary revascularization"[All Fields] OR "myocardial revascularization"[All Fields]
#3	"women"[MeSH Terms] OR "women"[All Fields] OR "woman"[All Fields] OR "female"[MeSH Terms] OR "female"[All Fields] OR "females"[All Fields] OR "sex factors"[MeSH Terms] OR ("sex"[All Fields] AND "factors"[All Fields]) OR "sex factors"[All Fields]
#4	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[MeSH Terms:noexp] OR randomly[tiab] OR trial[ti]
#5	#1 AND #2 AND #3 AND #4
#6	#5 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp]) NOT Animals[Mesh:noexp]
	Limits: Human, English, Publication Date: 2001- Present

Embase® Search Strategy (December 12, 2011)

Platform: Embase.com

Set #	Terms
#1	'cardiovascular disease'/exp OR 'heart disease'/exp OR 'heart'/exp OR 'acute coronary syndrome'/exp OR 'heart infarction'/exp OR 'unstable angina pectoris'/exp OR 'cardiovascular diseases':ab OR 'heart diseases':ab OR heart:ab OR cardiovasc*:ab OR cardiac*:ab OR coronary:ab OR myocardial:ab OR 'acute coronary syndrome':ab OR 'myocardial infarction':ab OR 'unstable angina':ab OR 'cardiovascular diseases':ti OR 'heart diseases':ti OR heart:ti OR cardiovasc*:ti OR cardiac*:ti OR coronary:ti OR myocardial:ti OR 'acute coronary syndrome':ti OR 'myocardial infarction':ti OR 'unstable angina':ti
#2	'transluminal coronary angioplasty'/exp OR 'percutaneous coronary intervention'/exp OR 'stent'/exp OR 'balloon dilatation'/exp OR 'percutaneous transluminal angioplasty'/exp OR 'atherectomy'/exp OR 'percutaneous transluminal angioplasty':ti OR ptca:ti OR ('percutaneous coronary' NEXT/1 intervention*):ti OR pci:ti OR stent*:ti OR 'balloon angioplasty':ti OR 'balloon dilation':ti OR 'balloon dilatation':ti OR 'transluminal angioplasty':ti OR 'coronary atherectomy':ti OR 'percutaneous transluminal angioplasty':ab OR ptca:ab OR ('percutaneous coronary' NEXT/1 intervention*):ab OR pci:ab OR stent*:ab OR 'balloon angioplasty':ab OR 'balloon dilation':ab OR 'balloon dilatation':ab OR 'transluminal angioplasty':ab OR 'coronary atherectomy':ab OR 'coronary artery bypass graft'/exp OR 'heart muscle revascularization'/exp OR 'coronary artery bypass':ti OR cabg:ti OR 'aortocoronary bypass':ti OR 'coronary revascularization':ti OR 'myocardial revascularization':ti OR 'coronary artery bypass':ab OR cabg:ab OR 'aortocoronary bypass':ab OR 'coronary revascularization':ab OR 'myocardial revascularization':ab OR 'coronary artery recanalization'/exp
#3	'female'/exp OR female OR women OR woman OR females OR 'sex difference'/exp
#4	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR cross NEAR/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*
#5	#1 AND #2 AND #3 AND #4
#6	#5 (AND [embase]/lim NOT [medline]/lim)
	Limits: Human, English, Publication Date: 2001- Present

Cochrane Search Strategy (December 12, 2011)

Platform: Wiley

Databases searched: Cochrane Central Registry of Controlled Trials and Cochrane Database of Systematic Reviews

Set #	Terms
#1	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 [in title-abstract-keywords]
#2	percutaneous transluminal coronary angioplasty OR PTCA OR "percutaneous coronary intervention" OR "percutaneous coronary interventions" OR "percutaneous coronary interventional" OR PCI OR Stent* OR stents OR Balloon angioplasty OR Balloon dilatation OR Balloon dilation OR Transluminal angioplasty OR coronary atherectomy OR Coronary Artery Bypass OR CABG OR aortocoronary bypass OR coronary revascularization OR myocardial revascularization [in title-abstract-keywords]
#3	women OR woman OR female OR females OR sex factors [in title-abstract-keywords]
#4	#1 AND #2 AND #3
	Limits: 2001- Present

Grey Literature Searches

ClinicalTrials.gov

Search date: 12/16/2011

Search #1: PCI vs. CABG
Expert Search String:
(NOT ("Recruiting" OR "Not yet recruiting" OR "Available")) [OVERALL-STATUS] AND (heart diseases OR cardiovascular diseases) [DISEASE] AND ((percutaneous transluminal coronary angioplasty OR PTCA OR percutaneous coronary intervention OR PCI OR balloon OR stent) AND (coronary artery bypass OR CABG)) [TREATMENT]

Search #2: CABG vs. Medical Therapy
Expert Search String:
(NOT ("Recruiting" OR "Not yet recruiting" OR "Available")) [OVERALL-STATUS] AND (heart diseases OR cardiovascular diseases) [DISEASE] AND ((coronary artery bypass OR CABG) AND (medical management OR medical therapy OR OMT OR standard of care OR medical treatment OR standard therapy OR usual care)) [TREATMENT]

Search #3: PCI vs. Medical Therapy
Expert Search String:
(NOT ("Recruiting" OR "Not yet recruiting" OR "Available")) [OVERALL-STATUS] AND (heart diseases OR cardiovascular diseases) [DISEASE] AND ((percutaneous transluminal coronary angioplasty OR PTCA OR percutaneous coronary intervention OR PCI OR balloon OR stent) AND (medical management OR medical therapy OR OMT OR standard of care OR medical treatment OR standard therapy OR usual care)) [TREATMENT]

Processing of results

1. Total number of results: 117
2. Duplicates removed: 10
3. All Status categories other than Completed, Terminated, and Withdrawn removed: 39 removed
4. Final number for screening: 68

WHO: International Clinical Trials Registry Platform Search Portal

Search date: 12/16/2011

Condition: heart OR cardiovascular OR coronary artery disease OR CAD
Intervention: percutaneous transluminal coronary angioplasty OR PTCA OR percutaneous coronary intervention OR PCI OR balloon OR stent OR coronary artery bypass OR CABG OR coronary revascularization

Processing of results

1. Total number of results: 1157
2. Removed all entries with "Recruiting" status; retained entries with "Not recruiting" status: 253 removed, 904 remaining
3. Removed all entries with NCT designations (covered by a separate search of clinicaltrials.gov with a more refined search strategy): 531 removed, 373 remaining
4. Final number for screening: 373

ProQuest COS Conference Papers Index

Search date: 12/12/2011

Set #	Terms
#1	(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) [in all fields + text]
#2	(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 or Coronary Artery Bypass or CABG or aortocoronary bypass or coronary revascularization or myocardial revascularization) [in all fields + text]
#3	women OR woman OR female OR females OR sex OR gender [in all fields + text]
#4	#1 AND #2 AND #3 AND #4
	Limits: 2001- Present

Appendix B. Data Abstraction Elements

I. Study Characteristics

- Study name and acronym
- Other articles used in this abstraction
- Study dates
- Date enrollment started (Mon and YYYY)
- Date enrollment ended (Mon and YYYY)
- Number of subjects screened/ approached for study participation: Total. Female, Male
- Study site
- Single center, Multicenter, Not reported/Unclear
- Geographic location
- If single center, enter City and State (if US) or City and Country (if outside US). If multicenter, enter number of sites. Enter NR if not reported.
- If multicenter, specify applicable geographic regions
- Funding source: Government, Private foundation, Industry, Not reported, Other.
- Setting: Academic centers, Community hospitals, Outpatient, VA, Not reported/unclear, Other
- Were patients transported from the site of presentation to another location to receive PCI?
- Were patients transported from the site of presentation to another location to receive CABG?
- Qualifications of the study surgeons: Not specified, Minimum case volume (specify), Maximum mortality (specify), Other (specify)
- Qualifications of the study interventional cardiologists: Not specified, Minimum case volume (specify), Maximum mortality (specify), Minimum success rates (specify), Other (specify)
- Qualifications of the sites involved in the trial: Not specified, Minimum case volume (specify), Maximum mortality (specify) , Minimum success rates (specify), Other (specify)
- Were guideline-based treatment protocols followed?
- Briefly describe use of guideline-based protocols.
- Length of followup
- Inclusion and exclusion criteria; Copy/paste criteria as reported in the article.
- Clinical presentation: STEMI NSTEMI/ Unstable angina Stable CAD
- Method for interpretation of angiograms: Central laboratory, Local site interpretation, Quantitative angiography, Unclear/ Not reported Other
- Were study patients systematically enrolled in cardiac rehabilitation?
- Does the study report a composite primary endpoint?
- Indicate the components of the composite primary endpoint (check all that apply): Total mortality, Cardiac mortality, Nonfatal myocardial infarction, Stroke, TIA, Unstable angina, Angina/ recurrent symptoms, Angina class, Angina relief, Repeat revascularization, Heart failure, Graft failure, Hospitalization, Length of hospital stay, Bleeding, Quality of life, Cognitive effects, Adverse drug reactions, Radiation exposure, Access site complications, Renal dysfunction, Anaphylaxis, Arrhythmias, Stent thrombosis, Infections, Cost, Employment/ productivity, Other (specify)
- Indicate timing of the components of the composite primary endpoint: Short-term (less than or equal to 30 days), Long-term (greater than 30 days), Mixture of short- and long-term outcomes
- Indicate all short-term (<30 days) primary and secondary endpoints separately reported (i.e. reported singly, rather than only reported as part of a composite primary endpoint): Total

mortality, Cardiac mortality, Nonfatal myocardial infarction, Stroke, TIA, Unstable angina, Angina/ recurrent symptoms, Angina class, Angina relief, Repeat revascularization, Heart failure, Graft failure, Hospitalization, Length of hospital stay, Bleeding, Quality of life, Cognitive effects, Adverse drug reactions, Radiation exposure, Access site complications, Renal dysfunction, Anaphylaxis, Arrhythmias, Stent thrombosis, Infections, Cost, Employment/ productivity, Other (specify)

- Indicate all long-term (>30 days) primary and secondary endpoints separately reported (i.e. reported singly, rather than only reported as part of a composite primary endpoint): Total mortality, Cardiac mortality, Nonfatal myocardial infarction, Stroke, TIA, Unstable angina, Angina/ recurrent symptoms, Angina class, Angina relief, Repeat revascularization, Heart failure, Graft failure, Hospitalization, Length of hospital stay, Bleeding, Quality of life, Cognitive effects, Adverse drug reactions, Radiation exposure, Access site complications, Renal dysfunction, Anaphylaxis, Arrhythmias, Stent thrombosis, Infections, Cost, Employment/ productivity, Other (specify)
- Describe how the short- and long-term outcome data is reported (e.g. Kaplan-Meier plots, Cox proportional hazards, hazard ratios, risk ratios, odds ratios, raw numbers, percentages, other methods), including whether p values, confidence intervals, etc. are provided.
- Include timing of outcomes (e.g. 1 yr, 5 yr)
- Comments (if needed)

II. Intervention characteristics

- Briefly indicate which population/intervention combination is reflected by the data abstracted on this instance of the form.
- PCI Procedural Characteristics
    - Describe the PCI intervention
    - Complete the below for Total, Female, and Male
        - Complete revascularization achieved
        - Vessels treated (mean): 1, 2, 3, or Unclear/ Not specified
        - Access site
            - Radial
            - Femoral
            - Unclear/ Not specified
        - Stents used (mean)
            - 0 stents
            - Bare metal stents
                - 1
                - 2
                - 3
                - More than 3
                - Unclear/ Not specified
            - Drug-eluting stents
                - 1
                - 2
                - 3
                - More than 3
                - Unclear/ Not specified
        - Interventional approach
            - Balloon
            - Atherectomy
            - Unclear/ Not specified

        - Timing
            - Initial conservative strategy
            - Invasive strategy
            - Unclear/ Not specified
    - If applicable, specify type of bare metal stent used
    - If applicable, specify type of drug-eluting stent used:
- CABG Procedural Characteristics
    - Describe the CABG intervention:
    - Complete the below for Total, Female, and Male
        - Bypass mode
            - None (beating heart)
            - Normothermic
            - Hypothermic
            - Unclear/ Not specified
        - Cardioplegia type
            - Blood
            - Crystalloid
            - Other
            - Mixed
            - Unclear/ Not specified
        - Incision type
            - Median sternotomy
            - Minimally invasive direct coronary bypass (Midcab)
            - Unclear/ Not specified
        - Grafts used
            - 0 grafts
            - Saphenous vein (mean)
                - 1
                - 2
                - Greater than 2
                - Unclear/ Not specified
            - Mammary arteries (mean)
                - Left internal mammary artery
                - Right internal mammary artery
                - Both mammary arteries
                - Unclear/ Not specified
            - Radial artery (mean)
                - 1
                - 2
                - Unclear/ Not specified
        - Transmyocardial laser revascularization (TMR)
            - Received
            - Not received
            - Unclear/ Not specified
    - If applicable, specify type of crystalloid cardioplegia agent used
    - If applicable, specify type of vein harvest (check all that apply): Endoscopic, Open, Unclear/ Not reported, Other (specify)
    - Mean cardiopulmonary bypass time
    - Mean cross-clamp time

    - Were concomitant procedures performed at the time of CABG surgery?
        - If yes, describe the concomitant procedures
- Medical Therapy Intervention Characteristics
    - Describe the medical therapy intervention received by patients in the PCI arm (if applicable)
    - Describe the medical therapy intervention received by patients in the CABG arm (if applicable)
    - Describe the medical therapy intervention received by patients in the OMT arm (if applicable)
    - Medications received in-hospital: record for PCI Subjects, CABG Subjects, and OMT Subjects; If 'yes' list drug name(s)/ dosage(s)
        - Acetylsalicylic acid (ASA)
        - Additional antiplatelet agents (e.g. clopidogrel, prasugrel, ticagrelor)
        - Antithrombin drugs (e.g. LMWH, unfractionated heparin, bivalirudin)
        - Glycoprotein IIb/IIIa inhibitors
        - Thrombolytic/ fibrinolytic drugs
        - Statins/ lipid-lowering drugs
        - Beta-blockers
        - ACEIs/ ARBs
        - Calcium channel blockers
        - Nitrates
        - Other #1 (specify)
        - Other #2 (specify)
        - Other #3 (specify)
- Discharge medications
    - Record for PCI Subjects, CABG Subjects, and OMT Subjects; If 'yes' list drug name(s)/ dosage(s)
        - Acetylsalicylic acid (ASA)
        - Additional antiplatelet agents (e.g. clopidogrel, prasugrel, ticagrelor)
        - Antithrombin drugs (e.g. LMWH, unfractionated heparin, bivalirudin)
        - Glycoprotein IIb/IIIa inhibitors
        - Thrombolytic/ fibrinolytic drugs
        - Statins/ lipid-lowering drugs
        - Beta-blockers
        - ACEIs/ ARBs
        - Calcium channel blockers
        - Nitrates
        - Other #1 (specify)
        - Other #2 (specify)
        - Other #3 (specify)
- Lifestyle modification
    - Indicate the components of lifestyle modification recommended to patients in the study (check all that apply): Smoking cessation, Diet modification, Exercise, Other (specify)
    - If lifestyle modifications recommended were not consistent across all patients in the study, specify which groups received these recommendations and which did not.
- Therapeutic targets
    - Did the study include consideration of therapeutic target goals?
        - If yes, describe the therapeutic targets considered and whether interventions were adjusted for the purpose of meeting those specific goals.

- Compliance
    - If reported, provide data on in-hospital medication compliance (and lifestyle modification compliance, if available)
    - If reported, provide data on post-discharge medication compliance (and lifestyle modification compliance, if available) at the first followup visit after discharge. Include the time point of this followup visit (including units)
- Comments (if needed)

III. Outcomes

- Outcomes definitions
    - Authors' definition of procedure-related outcomes
    - Authors' definition of post-CABG MI
    - Authors' definition of post-PCI MI
    - Check all outcomes for which gender-specific data is provided. Include an outcome if (1) data is reported specifically for women, or if (2) data is reported for men that can be used to calculate values for women (Total mortality, Cardiac mortality, Nonfatal myocardial infarction, Stroke, TIA, Unstable angina, Angina/ recurrent symptoms/ refractory angina/ refractory myocardial infarction, Angina class, Angina relief, Repeat revascularization (PCI or CABG),Heart failure, Graft failure, Hospitalization/ Re-hospitalization, Length of hospital stay, Bleeding, Quality of life, Cognitive effects, Adverse drug reactions, Radiation exposure, Access site complications, Renal dysfunction, Anaphylaxis, Arrhythmias, Stent thrombosis, Infections, Cost, Employment/ productivity, Other individual outcome #1 (e.g. CPR, cardioversion, respiratory failure, pulmonary edema) , Other individual outcome #2, Other individual outcome #3.)
    - Comments (if needed)
- Composite outcome data
    - Are one or more composite outcomes reported in such a way that data for women can be abstracted or derived?
    - Is this a Primary or Secondary composite outcome?
    - Refer to the Intervention Characteristics forms completed; indicate which one applies to the outcome data recorded on this form:
    - Indicate the components that make up this composite outcome (check all that apply): Total mortality, Cardiac mortality, Nonfatal myocardial infarction, Stroke, TIA, Unstable angina, Angina/ recurrent symptoms/ refractory angina/ refractory myocardial infarction, Angina class, Angina relief, Repeat revascularization (PCI or CABG),Heart failure, Graft failure, Hospitalization/ Re-hospitalization, Length of hospital stay, Bleeding, Quality of life, Cognitive effects, Adverse drug reactions, Radiation exposure, Access site complications, Renal dysfunction, Anaphylaxis, Arrhythmias, Stent thrombosis, Infections, Cost, Employment/ productivity, Other individual outcome #1 (e.g. CPR, cardioversion, respiratory failure, pulmonary edema) , Other individual outcome #2, Other individual outcome #3.
    - Complete tables to provide data for this outcome/ time point(s).
        - Timing of the outcome data reported in the table: Short term $\leq$ 30 days, Long-term > 30 days,
            - Specify timing of short-term outcome: 30 days, Other (specify)
            - Specify timing of long-term outcome: 6 weeks, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, Other (specify)

        - Indicate whether/ how the results reported were adjusted (check all that apply):Results are not adjusted , RCT that did not adjust for any baseline difference, Age, Sex, Race, Comorbidity(ies) (specify), Other (specify all)
        - For each reported group (OMT, PCI, CABG, and/or Mixed Revascularization) record the following for Total, Female, and Male:
            - N for Analysis
            - Result
                - Mean
                - Median
                - Number of patients with outcome
                - % of patients with outcome
                - Relative risk
                - Relative hazard
                - Odds ratio
                - Risk difference
                - Other (specify)
            - Variability
                - Standard Error (SE)
                - Standard Deviation (SD)
                - Other (specify)
            - Confidence Interval (CI) or Interquartile Range (IQR)
                - 95% CI
                - Other %CI
                - IQR
            - p-value between female and male data (within tx group)
            - p-value between tx groups
            - Reference group (for comparisons between tx groups)
    - Comments (if needed)
- Individual outcome data
    - Select the outcome reported: Total mortality, Cardiac mortality, Nonfatal myocardial infarction, Stroke, TIA, Unstable angina, Angina/ recurrent symptoms/ refractory angina/ refractory myocardial infarction, Angina class, Angina relief, Repeat revascularization (PCI or CABG),Heart failure, Graft failure, Hospitalization/ Re-hospitalization, Length of hospital stay, Bleeding, Quality of life, Cognitive effects, Adverse drug reactions, Radiation exposure, Access site complications, Renal dysfunction, Anaphylaxis, Arrhythmias, Stent thrombosis, Infections, Cost, Employment/ productivity, Other individual outcome #1 (e.g. CPR, cardioversion, respiratory failure, pulmonary edema) , Other individual outcome #2, Other individual outcome #3.
    - Complete tables to provide data for this outcome/ time point(s).
        - Timing of the outcome data reported in the table: Short term $\leq$ 30 days, Long-term > 30 days,
            - Specify timing of short-term outcome: 30 days, Other (specify)
            - Specify timing of long-term outcome: 6 weeks, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, Other (specify)
        - Indicate whether/ how the results reported were adjusted (check all that apply):Results are not adjusted , RCT that did not adjust for any baseline difference, Age, Sex, Race, Comorbidity(ies) (specify), Other (specify all)
        - For each reported group (OMT, PCI, CABG, and/or Mixed Revascularization) record the following for Total, Female, and Male:

- N for Analysis
- Result
    - Mean
    - Median
    - Number of patients with outcome
    - % of patients with outcome
    - Relative risk
    - Relative hazard
    - Odds ratio
    - Risk difference
    - Other (specify)
- Variability
    - Standard Error (SE)
    - Standard Deviation (SD)
    - Other (specify)
- Confidence Interval (CI) or Interquartile Range (IQR)
    - 95% CI
    - Other %CI
    - IQR
- p-value between female and male data (within tx group)
- p-value between tx groups
- Reference group (for comparisons between tx groups)

o Comments (if needed)

IV. Subgroup Analyses

- Does the article include subgroup analyses reported in a gender-specific way such that data for women can be abstracted or derived for any outcomes of interest?
- For each outcome record for Total, Female, and Male
- Indicate the nature of the subgroup analysis (i.e. the characteristic factor being considered): Age, Race, Other demographic or socioeconomic factor (specify), Diabetes, Chronic kidney disease, Other comorbid disease (specify), Angiographic-specific factor (specify), CABG-specific factor (specify), Hospital characteristic (specify)
- Specify the categories for this subgroup analysis. Columns are provided to capture up to 5 categories. Complete only the number needed to capture the data presented in the study.
    - Define the categories, then complete the tables with as much information as is provided in the study.
    - Provide data for each outcome. Clearly indicate units (number of patients, %, hazard ratio, etc.). Include values for confidence intervals, p values, standard error, standard deviation, etc. when available.
- Comments (if needed):

V. Quality Assessment

- Selection Bias
    - Was treatment adequately randomized (e.g. random number table, computer-generated randomization)?
    - Was the allocation of treatment adequately concealed (e.g. pharmacy-controlled randomization or use of sequentially numbered sealed envelopes)?
    - Did the strategy for recruiting participants into the study differ across study groups?
    - Are baseline characteristics similar between groups? If not, did the analysis control for differences?

- Performance Bias
    - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
    - Did variation from the study protocol compromise the conclusions of the study?
- Attrition Bias
    - Was there a high rate of differential or overall attrition?
    - Did attrition result in a difference in group characteristics between baseline (or randomization) and followup?
    - Is the analysis conducted on an intention-to-treat (ITT) basis?
- Detection Bias
    - Were the outcome assessors blinded to the intervention status of participants?
    - Are the inclusion/exclusion criteria measured using valid and reliable measures?
    - Are the inclusion/exclusion criteria implemented consistently across all study participants?
    - Are interventions/exposures assessed using valid and reliable measures?
    - Are interventions/exposures implemented consistently across all study participants?
    - Are primary outcomes assessed using valid and reliable measures?
    - Are primary outcomes implemented consistently across all study participants?
- Reporting Bias
    - Are the potential outcomes pre-specified by the researchers? Are all pre-specified outcomes reported?
- Additional Comments
- Summary Judgment. Assign the study an overall quality rating based on the following definitions:
    - Good (low risk of bias). These studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts.
    - Fair. These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
    - Poor (high risk of bias). These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

VI. Applicability

- Population (P) (select all that apply)
    - Study population not representative of community patients
    - Study population poorly specified
    - Key characteristics not reported
- Intervention (I) (select all that apply)
    - Monitoring practices or visit frequency not used in typical practice
    - Older versions of an intervention no longer in common use
    - Cointerventions that are likely to modify effectiveness of therapy

    - Highly selected intervention team or level of training/proficiency not widely available
- Comparator (C) (select all that apply)
    - Inadequate comparison therapy
- Outcomes (O) (select all that apply)
    - Composite outcomes that mix outcomes of different significance
    - Data not stratified or adjusted for key predictors
    - Only short-term or surrogate outcomes reported
- Timing (T) (n/a)
- Setting (S) (select all that apply)
    - Resources available to providers for diagnosis and treatment of condition vary widely
    - Provider type/specialty varies across settings
    - Comparability of care in international settings unclear
    - Standards of care differ markedly from setting of interest
    - Specialty population or level of care differs from that seen in community
- Comments (if needed)

Appendix C. List of Included Studies

Allen KB, Dowling RD, Angell WW, et al. Transmyocardial revascularization: 5-year follow-up of a prospective, randomized multicenter trial. Ann Thorac Surg. 2004;77(4):1228-34. PMID: 15063241.

Allen KB, Dowling RD, Fudge TL, et al. Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina. N Engl J Med. 1999;341(14):1029-36. PMID: 10502592.

Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med. 2003;349(8):733-42. PMID: 12930925.

Anderson HV, Cannon CP, Stone PH, et al. One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial. A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q wave myocardial infarction. J Am Coll Cardiol. 1995;26(7):1643-50. PMID: 7594098.

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Appendix D. Quality and Applicability of Included Studies

Table D-1. Quality and applicability for RCTs evaluating women with STEMI (KQ 1)

Study Name	Study Author/Year	Comparator	Quality	Limitations to Applicability
CARESS-in-AMI	Di Mario et al., 2008[1]	Immediate PCI with fibrinolysis (reteplase) vs. fibrinolysis (reteplase) with rescue PCI	Good	• None
DANAMI-2	Andersen et al., 2003[2]	PCI vs. fibrinolysis (accelerated t-PA)	Good	• None
Dobrzycki	Dobrzycki et al., 2007[3]	Transfer with tirofiban for primary PCI vs. onsite fibrinolysis (streptokinase)	Good	• Comparability of care in international settings unclear
GUSTO II-B	Tamis-Holland et al., 2004[4]	PCI vs. fibrinolysis (accelerated t-PA)	Good	• Comparability of care in international settings unclear
Minai	Minai et al., 2002[5]	PCI vs. optimal medical therapy (without fibrinolysis)	Fair	• Comparability of care in international settings unclear
PAMI	Stone et al., 1995[6]	PCI vs. fibrinolysis (t-PA)	Good	• Comparability of care in international settings unclear
SHOCK	Hochman et al., 2001[7]	Early invasive revascularization (PCI or CABG within 6 hours) vs. initial medical stabilization (thrombolysis, IABP)	Good	• None

Abbreviations: CABG = coronary artery bypass grafting; PCI = percutaneous coronary revascularization; STEMI = ST elevation myocardial infarction

Table D-2. Quality and applicability for RCTs evaluating women with UA/NSTEMI (KQ 2)

Study Name	Study Author/Year	Comparator	Quality	Limitations to Applicability
FRISC II	Lagerqvist et al., 2001[8]	Early invasive treatment with revascularization vs. initial conservative strategy	Good	• Comparability of care in international settings unclear
GUSTO IV-ACS	Ottervanger et al., 2004[9]	Early invasive management vs. initial conservative treatment within 30 days.	Good	• Older versions of an intervention no longer in common use • Resources available to providers for diagnosis and treatment of condition varied widely • Comparability of care in international settings unclear
ICTUS	de Winter et al., 2005[10]	Early invasive therapy with revascularization vs. selective invasive strategy	Good	• Comparability of care in international settings unclear
RITA-2	Anonymous, 1997[11]	Early invasive therapy with PCI vs. initial conservative	Fair	• Provider type/specialty varied across settings • Comparability of care in international settings unclear
RITA-3	Clayton et al., 2004[12]	Early invasive with PCI vs. initial conservative	Good	• None
TACTICS TIMI-18	Cannon et al., 2001[13]	Early invasive with PCI vs. initial conservative	Good	• None
TIMI III-B	Anonymous, 1994[14]	Early invasive with PCI vs. initial conservative	Good	• Older versions of an intervention no longer in common use

Abbreviations: CABG = coronary artery bypass grafting; PCI = percutaneous coronary revascularization

Table D-3. Quality and applicability for RCTs evaluating women with stable angina (KQ 3 Strategy 1)

Study Name	Study Author/Year	Comparator	Quality	Limitations to Applicability
Allen	Allen et al., 2004[15]	Surgical revascularization vs. optimal medical therapy	Good	• Older versions of an intervention no longer in common use • Cointerventions that were likely to modify effectiveness of therapy
COURAGE	Boden et al., 2007[16]	PCI (or CABG if PCI failed) vs. optimal medical therapy	Good	• None
MASS II	Hueb et al., 2010[17]	PCI vs. optimal medical therapy CABG vs. optimal medical therapy	Good	• Study population not representative of community patients • Cointerventions that were likely to modify effectiveness of therapy
OAT	Hochman et al., 2006[18]	PCI (or CABG if PCI failed) vs. optimal medical therapy	Good	• None
STICH	Velazquez et al., 2011[19]	CABG vs. optimal medical therapy	Good	• Cointerventions that were likely to modify effectiveness of therapy • Comparability of care in international settings unclear

Abbreviations: CABG = coronary artery bypass grafting; PCI = percutaneous coronary revascularization

Table D-4. Quality and applicability for RCTs evaluating women with stable/unstable angina (KQ 3 Strategy 2)

Study Name	Study Author/Year	Comparator	Quality	Limitations to Applicability
ARTS I	Vaina et al., 2009[20]	PCI vs. CABG	Good	• None
BARI	Jacobs et al., 1998[21]	PCI vs. CABG	Good	• Study population not representative of community patients • Older versions of an intervention no longer in common use • Cointerventions that were likely to modify effectiveness of therapy
CABRI	Anonymous, 1995[22]	PCI vs. CABG	Good	• None
CARDia	Kapur et al., 2010[23]	PCI vs. CABG	Good	• Key characteristics not reported • Provider type/specialty varied across settings
EAST	King et al., 2000[24]	PCI vs. CABG	Good	• Study population not representative of community patients • Older versions of an intervention no longer in common use • Cointerventions that were likely to modify effectiveness of therapy
GABI	Kaehler et al., 2005[25]	PCI vs. CABG	Good	• Cointerventions that were likely to modify effectiveness of therapy
MASS II	Hueb et al., 2010[17]	PCI vs. CABG	Good	• Study population not representative of community patients • Cointerventions that were likely to modify effectiveness of therapy
PRECOMBAT	Park et al., 2011[26]	PCI vs. CABG	Good	• Comparability of care in international settings unclear

Study Name	Study Author/Year	Comparator	Quality	Limitations to Applicability
SOS	Zhang et al., 2004[27]	PCI vs. CABG	Fair	• Study population not representative of community patients • Cointerventions that were likely to modify effectiveness of therapy
SYNTAX	Morice et al., 2010[28]	PCI vs. CABG	Fair	• Data not stratified or adjusted for key predictors • Comparability of care in international settings unclear

Abbreviations: CABG = coronary artery bypass grafting; PCI = percutaneous coronary revascularization

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27. Zhang Z, Weintraub WS, Mahoney EM, et al. Relative benefit of coronary artery bypass grafting versus stent-assisted percutaneous coronary intervention for angina pectoris and multivessel coronary disease in women versus men (one-year results from the Stent or Surgery trial). Am J Cardiol. 2004;93(4):404-9. PMID: 14969611.

28. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation. 2010;121(24):2645-53. PMID: 20530001.

Appendix E. List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded. Following each reference, in italics, is the reason for exclusion. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Aaberge L, Aakhus S, Nordstrand K, et al. Myocardial performance after transmyocardial revascularization with CO(2)laser. A dobutamine stress echocardiographic study. Eur J Echocardiogr. 2001;2(3):187-96. PMID: 11882452. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Aaberge L, Nordstrand K, Dragsund M, et al. Transmyocardial revascularization with CO(2) laser in patients with refractory angina pectoris. J Am Coll Cardiol. 2000;35(5):1170-1177. PMID: 10758957. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Aaberge L, Rootwelt K, Blomhoff S, et al. Continued symptomatic improvement three to five years after transmyocardial revascularization with CO(2) laser: a late clinical follow-up of the Norwegian Randomized trial with transmyocardial revascularization. J Am Coll Cardiol. 2002;39(10):1588-93. PMID: 12020484. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Aaberge L, Rootwelt K, Smith HJ, et al. Effects of transmyocardial revascularization on myocardial perfusion and systolic function assessed by nuclear and magnetic resonance imaging methods. Scand Cardiovasc J. 2001;35(1):8-13. PMID: 11354578. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Aasa M, Dellborg M, Herlitz J, et al. Risk reduction for cardiac events after primary coronary intervention compared with thrombolysis for acute ST-elevation myocardial infarction (five-year results of the Swedish early decision reperfusion strategy [SWEDES] trial). Am J Cardiol. 2010;106(12):1685-91. PMID: 21126610. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Aasa M, Henriksson M, Dellborg M, et al. Cost and health outcome of primary percutaneous coronary intervention versus thrombolysis in acute ST-segment elevation myocardial infarction-Results of the Swedish Early Decision reperfusion Study (SWEDES) trial. Am Heart J. 2010;160(2):322-8. PMID: 20691839. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Abizaid A, Costa MA, Centemero M, et al. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. Circulation. 2001;104(5):533-8. PMID: 11479249. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Acampa W, Petretta M, Spinelli L, et al. Survival benefit after revascularization is independent of left ventricular ejection fraction improvement in patients with previous myocardial infarction and viable myocardium. Eur J Nucl Med Mol Imaging. 2005;32(4):430-7. PMID: 15821962. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Adgey J, Fox K, Flather M. Gusto Iv Acs. Br J Cardiol. 2000;7(11):663. *Exclude - Study type is not RCT, prospective or retrospective observational study, or registry.*

Agati L, Funaro S, Madonna M, et al. Does coronary angioplasty after timely thrombolysis improve microvascular perfusion and left ventricular function after acute myocardial infarction? Am Heart J. 2007;154(1):151-7. PMID: 17584568. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes*

women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.

Anonymous. Arterial Revascularization Therapies Study (ARTS). Indian Heart J. 2001;53(2):239. PMID: 11428490. *Exclude - Study type is not RCT, prospective or retrospective observational study, or registry.*

Anonymous. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. N Engl J Med. 1997;336(23):1621-8. PMID: 9173270. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Anonymous. Coronary angioplasty versus coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. Lancet. 1993;341(8845):573-80. PMID: 8094826. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Anonymous. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. Lancet. 2002;360(9338):965-70. PMID: 12383664. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Anonymous. Does PCI added to drug therapy improve outcomes in stable CAD? J Fam Pract. 2007;56(7):529. PMID: 17612033. *Exclude - Study type is not RCT, prospective or retrospective observational study, or registry.*

Anonymous. Does the new angiotensin converting enzyme inhibitor cilazapril prevent restenosis after percutaneous transluminal coronary angioplasty? Results of the MERCATOR study: a multicenter, randomized, double-blind placebo-controlled trial. Multicenter European Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR) Study Group. Circulation. 1992;86(1):100-10. PMID: 1535568. *Exclude - No data for OMT/PCI/CABG comparison of interest.*

Anonymous. Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease. A multicenter randomized trial. Writing Group for the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. JAMA. 1997;277(9):715-21. PMID: 9042843. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Anonymous. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). Circulation. 1997;96(6):1761-9. PMID: 9323059. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Anonymous. Little benefit to revascularization over intensive medical treatment in diabetes mellitus with coronary artery disease. J Natl Med Assoc. 2009;101(9):975-976. *Exclude - Study type is not RCT, prospective or retrospective observational study, or registry.*

Anonymous. One-year survival following early revascularization for cardiogenic shock (SCHOCK trial). Indian Heart J. 2001;53(2):240. PMID: 11428491. *Exclude - Study type is not RCT, prospective or retrospective observational study, or registry.*

Anonymous. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. Lancet. 2001;358(9286):951-7. PMID: 11583747. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Aoki J, Ong AT, Arampatzis CA, et al. Comparison of three-year outcomes after coronary stenting versus coronary artery bypass grafting in patients with multivessel coronary disease, including involvement of the left anterior descending coronary artery proximally (a subanalysis of the arterial revascularization therapies study trial). Am J Cardiol. 2004;94(5):627-31. PMID: 15342295. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Aoki J, Ong AT, Hoye A, et al. Five year clinical effect of coronary stenting and coronary artery bypass grafting in renal insufficient patients with multivessel coronary artery disease: insights from ARTS trial. Eur Heart J. 2005;26(15):1488-93. PMID: 15860519. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Armstrong PW. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study. Eur Heart J. 2006;27(13):1530-8. PMID: 16757491. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Aversano T, Aversano LT, Passamani E, et al. Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. JAMA. 2002;287(15):1943-51. PMID: 11960536. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Baldus S, Köster R, Küchler R, et al. [Percutaneous revascularization of multivessel coronary disease using stents - a multicenter, prospective study]. Dtsch Med Wochenschr. 200211):547-52. PMID: 11894174. *Exclude - Non-English.*

Banning AP, Westaby S, Morice MC, et al. Diabetic and nondiabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with cardiac surgery and paclitaxel-eluting stents. J Am Coll Cardiol. 2010;55(11):1067-75. PMID: 20079596. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Barnett PG, Chen S, Boden WE, et al. Cost-effectiveness of a conservative, ischemia-guided management strategy after non-Q-wave myocardial infarction: results of a randomized trial. Circulation. 2002;105(6):680-4. PMID: 11839621. *Exclude - Does not include outcomes of interest.*

Bata I, Armstrong PW, Westerhout CM, et al. Time from first medical contact to reperfusion in ST elevation myocardial infarction: a Which Early ST Elevation Myocardial Infarction Therapy (WEST) substudy. Can J Cardiol. 2009;25(8):463-8. PMID: 19668780. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Bell MR, Grill DE, Garratt KN, et al. Long-term outcome of women compared with men after successful coronary angioplasty. Circulation. 1995;91(12):2876-81. PMID: 7796495. *Exclude - No data for OMT/PCI/CABG comparison of interest.*

Bell MR, Holmes DR, Jr., Berger PB, et al. The changing in-hospital mortality of women undergoing percutaneous transluminal coronary angioplasty. JAMA. 1993;269(16):2091-5. PMID: 8468762. *Exclude - No data for OMT/PCI/CABG comparison of interest.*

Ben-Gal Y, Moses JW, Mehran R, et al. Surgical versus percutaneous revascularization for multivessel disease in patients with acute coronary syndromes: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. JACC Cardiovasc Interv. 201010):1059-67. PMID: 20965465 *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Berger PB, Velianou JL, Aslanidou Vlachos H, et al. Survival following coronary angioplasty versus coronary artery bypass surgery in anatomic subsets in which coronary artery bypass surgery improves survival compared with medical therapy. Results from the Bypass Angioplasty Revascularization Investigation (BARI). J Am Coll Cardiol. 2001;38(5):1440-9. PMID: 11691521. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Berrocal DH, Cohen MG, Spinetta AD, et al. Early reperfusion and late clinical outcomes in patients presenting with acute myocardial infarction randomly assigned to primary percutaneous coronary intervention or streptokinase. Am Heart J. 2003;146(6):E22. PMID: 14661011. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes*

women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.

Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. N Engl J Med. 1998;338(25):1785-92. PMID: 9632444. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Bohmer E, Arnesen H, Abdelnoor M, et al. The NORwegian study on DIstrict treatment of ST-elevation myocardial infarction (NORDISTEMI). Scand Cardiovasc J. 2007;41(1):32-8. PMID: 17365975. *Exclude - Does not include outcomes of interest.*

Bohmer E, Hoffmann P, Abdelnoor M, et al. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). J Am Coll Cardiol. 2010;55(2):102-10. PMID: 19747792. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Bonnefoy E, Lapostolle F, Leizorovicz A, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. Lancet. 2002;360(9336):825-9. PMID: 12243916. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Bonnefoy E, Steg PG, Boutitie F, et al. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. Eur Heart J. 2009;30(13):1598-606. PMID: 19429632. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Bonnefoy E, Steg PG, Chabaud S, et al. Is primary angioplasty more effective than prehospital fibrinolysis in diabetics with acute myocardial infarction? Data from the CAPTIM randomized clinical trial. Eur Heart J. 2005;26(17):1712-8. PMID: 15840623. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Bonow RO, Maurer G, Lee KL, et al. Myocardial viability and survival in ischemic left ventricular dysfunction. N Engl J Med. 2011;364(17):1617-25. PMID: 21463153. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Booth J, Clayton T, Pepper J, et al. Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). Circulation. 2008;118(4):381-8. PMID: 18606919. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Borden WB, Redberg RF, Mushlin AI, et al. Patterns and intensity of medical therapy in patients undergoing percutaneous coronary intervention. JAMA. 2011;305(18):1882-9. PMID: 21558519. *Exclude - No data for OMT/PCI/CABG comparison of interest.*

Borges JC, Lopes N, Soares PR, et al. Five-year follow-up of angiographic disease progression after medicine, angioplasty, or surgery. J Cardiothorac Surg. 2010;5(91. PMID: 20977758. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Boudriot E, Thiele H, Walther T, et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. J Am Coll Cardiol. 2011;57(5):538-45. PMID: 21272743. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Bourassa MG, Kip KE, Jacobs AK, et al. Is a strategy of intended incomplete percutaneous transluminal coronary angioplasty revascularization acceptable in nondiabetic patients who are candidates for coronary artery bypass graft surgery? The Bypass Angioplasty

Revascularization Investigation (BARI). J Am Coll Cardiol. 1999;33(6):1627-36. PMID: 10334434. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Brener SJ, Galla JM, Bryant R, 3rd, et al. Comparison of percutaneous versus surgical revascularization of severe unprotected left main coronary stenosis in matched patients. Am J Cardiol. 2008;101(2):169-72. PMID: 18178401. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Brener SJ, Lytle BW, Casserly IP, et al. Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. Circulation. 2004;109(19):2290-5. PMID: 15117846. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Brener SJ, Murphy SA, Gibson CM, et al. Efficacy and safety of multivessel percutaneous revascularization and tirofiban therapy in patients with acute coronary syndromes. Am J Cardiol. 2002;90(6):631-3. PMID: 12231091. *Exclude - No data for OMT/PCI/CABG comparison of interest.*

Brooks MM, Chung SC, Helmy T, et al. Health status after treatment for coronary artery disease and type 2 diabetes mellitus in the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial. Circulation. 2010;122(17):1690-9. PMID: 20937978. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Brooks MM, Jones RH, Bach RG, et al. Predictors of mortality and mortality from cardiac causes in the bypass angioplasty revascularization investigation (BARI) randomized trial and registry. For the BARI Investigators. Circulation. 2000;101(23):2682-9. PMID: 10851204. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Buller CE, Rankin JM, Carere RG, et al. Percutaneous coronary intervention in the Occluded Artery Trial: procedural success, hazard, and outcomes over 5 years. Am Heart J. 2009;158(3):408-15. PMID: 19699864. *Exclude - No data for OMT/PCI/CABG comparison of interest.*

Buszman P, Tendera M, Bochenek A, et al. A prospective evaluation of early and late results of percutaneous and surgical revascularisation in patients with ischaemic left ventricular dysfunction. Kardiol Pol. 2002;56(1):57-61. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Buszman P, Wiernek S, Szymanski R, et al. Percutaneous versus surgical revascularization for multivessel coronary artery disease: a single center 10 year follow-up of SOS trial patients. Catheter Cardiovasc Interv. 2009;74(3):420-6. PMID: 19360866. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol. 2008;51(5):538-45. PMID: 18237682. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Campbell HE, Tait S, Buxton MJ, et al. A UK trial-based cost--utility analysis of transmyocardial laser revascularization compared to continued medical therapy for treatment of refractory angina pectoris. Eur J Cardiothorac Surg. 2001;20(2):312-8. PMID: 11463549. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Campbell HE, Tait S, Sharples LD, et al. Trial-based cost-utility comparison of percutaneous myocardial laser revascularisation and continued medical therapy for treatment of refractory angina pectoris. Eur J Health Econ. 2005;6(4):288-97. PMID: 16195897. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Cantor WJ, Burnstein J, Choi R, et al. Transfer for urgent percutaneous coronary intervention early after thrombolysis for ST-elevation myocardial infarction: the TRANSFER-AMI pilot feasibility study. Can J

Cardiol. 2006;22(13):1121-6. PMID: 17102829. *Exclude - No data for OMT/PCI/CABG comparison of interest.*

Cantor WJ, Fitchett D, Borgundvaag B, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med. 2009;360(26):2705-18. PMID: 19553646. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Cantor WJ, Goodman SG, Cannon CP, et al. Early cardiac catheterization is associated with lower mortality only among high-risk patients with ST- and non-ST-elevation acute coronary syndromes: observations from the OPUS-TIMI 16 trial. Am Heart J. 2005;149(2):275-83. PMID: 15846265. *Exclude - No data for OMT/PCI/CABG comparison of interest.*

Carrie D, Elbaz M, Puel J, et al. Five-year outcome after coronary angioplasty versus bypass surgery in multivessel coronary artery disease: results from the French Monocentric Study. Circulation. 1997;96(9 Suppl):II-1-6. PMID: 9386066. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Carver A, Rafelt S, Gershlick AH, et al. Longer-term follow-up of patients recruited to the REACT (Rescue Angioplasty Versus Conservative Treatment or Repeat Thrombolysis) trial. J Am Coll Cardiol. 2009;54(2):118-26. PMID: 19573727. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Chaitman BR, Hardison RM, Adler D, et al. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease: impact of treatment strategy on cardiac mortality and myocardial infarction. Circulation. 2009;120(25):2529-40. PMID: 19920001. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Chaitman BR, Rosen AD, Williams DO, et al. Myocardial infarction and cardiac mortality in the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial. Circulation. 1997;96(7):2162-70. PMID: 9337185. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Chauhan MS, Ho KK, Baim DS, et al. Effect of gender on in-hospital and one-year outcomes after contemporary coronary artery stenting. Am J Cardiol. 2005;95(1):101-4. PMID: 15619402. *Exclude - Study type is not RCT, prospective or retrospective observational study, or registry.*

Chen B, Wang W, Zhao H, et al. [Comparison of the clinical efficacy of recombinant tissue-type plasminogen activator thrombolysis with primary coronary stenting in acute myocardial infarction]. Zhonghua Nei Ke Za Zhi. 20021):21-3. PMID: 11940291. *Exclude - Non-English.*

Chew DP, Huang Z, Pieper KS, et al. Patients with non-ST-elevation acute coronary syndromes undergoing coronary artery bypass grafting in the modern era of antithrombotic therapy. Am Heart J. 2008;155(2):239-44. PMID: 18215592. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Chung SC, Hlatky MA, Faxon D, et al. The effect of age on clinical outcomes and health status BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes). J Am Coll Cardiol. 2011;58(8):810-9. PMID: 21835316. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Cisowski M, Drzewiecka-Gerber A, Ulczok R, et al. Primary direct stenting versus endoscopic atraumatic coronary artery bypass surgery in patients with proximal stenosis of the left anterior descending coronary artery--a prospective, randomised study. Kardiol Pol. 2004;61(9):253-61; discussion 262-4. PMID: 15531937. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Cisowski M, Drzewiecki J, Drzewiecka-Gerber A, et al. Primary stenting versus MIDCAB: preliminary report-comparision of two methods of revascularization in single left anterior descending coronary artery stenosis. Ann Thorac Surg. 2002;74(4):S1334-9. PMID: 12400812. *Exclude - Does not include outcome data reported in a gender-*

specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.

Claude J, Schindler C, Kuster GM, et al. Cost-effectiveness of invasive versus medical management of elderly patients with chronic symptomatic coronary artery disease. Findings of the randomized trial of invasive versus medical therapy in elderly patients with chronic angina (TIME). Eur Heart J. 2004;25(24):2195-203. PMID: 15589636. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

Cleland JG, Calvert M, Freemantle N, et al. The Heart Failure Revascularisation Trial (HEART). Eur J Heart Fail. 2011;13(2):227-33. PMID: 21156659. *Exclude - Does not include outcome data reported in a gender-specific fashion for a study population that includes women 18 or older with angiographically proven CAD w/ STEMI, NSTEMI, or stable CAD.*

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Appendix F. Summary Tables for Sex-Specific Clinical Outcomes

Table F-1. Summary of RCTs reporting clinical outcomes for STEMI (KQ 1)

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
CARESS-in-AMI **Di Mario et al., 2008**[1] **and** **Di Mario et al., 2004**[2]	STEMI	Fibrinolysis (reteplase) plus immediate PCI vs. fibrinolysis (reteplase) plus rescue PCI	Total: 600 Women: 128 (21%)	<u>1) Composite outcome</u> (total mortality/reinfarction/refractory MI within 30 days) HR (95%CI) Women: 0.4 (0.12 to 1.31) Men: 0.39 (0.18 to 0.85) Overall: 0.40 (0.21 to 0.76) <u>2) Cumulative event rate</u> (total mortality/reinfarction/refractory MI within 30 days) Women: 6.2 vs. 14.5 Men: 3.9 vs. 9.7 Overall: 4.4 vs.10.7	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
DANAMI-2 **Andersen et al., 2003**[3] **and** **Mortensen et al., 2007**[4] **Nielsen et al., 2010**[5] **Busk et al., 2009**[6] **Busk et al., 2008**[7]	STEMI	Primary PCI vs. fibrinolysis (accelerated t-PA)	Total: 1,572 Women: 417 (27%)	1) Composite outcome (total mortality/nonfatal MI/stroke) **30 days** OR (95% CI) Women: 0.47 (0.27 to 0.81) Men: 0.59 (0.39 to 0.90) Overall: 0.55 (0.39 to 0.76) **3 years** HR (95% CI) Women: 0.62 (0.42 to 0.90) Men: 0.81 (0.63 to 1.04) Overall: 0.74 (0.60 to 0.92) **Median 7.8 years** HR (95% CI) Women: 0.73 (0.53 to 0.99) Men: 0.80 (0.66 to 0.97) Overall: 0.78 (0.66 to 0.92) 2) Angina (angina/recurrent symptoms/refractory angina/refractory MI) **30 days** Women: 25.3% vs. 30.7% Men: 18.8% vs. 26.4% **1 year** Women: 18.5% vs. 21.3% Men: 15.5% vs. 17.6% 3) General health SF-36 **30 day**s Women: 62 vs. 61.1 Men: 69.2 vs. 65.1 **1 year** Women: 61.5 vs. 66.4 Men: 68.2 vs. 63.1	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
Dobrzycki et al., 2007[8]	STEMI	Fibrinolysis (streptokinase) onsite vs. tirofiban plus transfer for primary PCI	Total: 401 Women: 105 (26%)	1) Composite outcome (total mortality/nonfatal MI/stroke): **30 days** RR (95% CI) Women: 2.04 (0.85 to 4.90) Men: 1.79 (0.85 to 3.79) Overall: 1.95 (1.1 to 3.45) **1 year** Women: 2.48 (1.06 to 5.79) Men: 1.61 (0.92 to 2.85) Overall: 1.88 (1.18 to 3.00) 2) Total mortality **30 days** RR (95% CI) Women: 2.19 (0.73 to 6.53) Men: 1.41 (0.50 to 3.96) Overall: 1.81 (0.86 to 3.82) **1 year** Women: 2.41 (0.82 to 7.07) Men: 1.48 (0.68 to 3.22) Overall: 1.79 (0.96 to 3.35)	Good
GUSTO II-B Tamis-Holland et al., 2004[9]	STEMI	PCI vs. fibrinolysis (accelerated t-PA)	Total: 1,137 Women: 260 (23%)	1) Composite outcome (30-day): (total mortality/nonfatal MI/nonfatal disabling stroke) OR (95% CI) Women: 0.685 (0.36 to 1.32) Men: 0.562 (0.35 to 0.91) Overall: 0.67 (0.47 to 0.97) 2) Total mortality (30-day) Women: 10.9% vs. 11.6% Men: 4% vs. 5.8% 3) Nonfatal MI (30-day): Women: 6.5% vs. 6.6% Men: 3.8% vs. 6.4% 4) Nonfatal disabling stroke (30-day): Women: 0 vs. 2.5% Men: 0.2% vs. 0.4%	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
Minai et al., 2002[10]	STEMI age ≥ 80 years	PCI vs. conservative/supportive medical therapy (without fibrinolysis)	Total: 120 Women: 60 (50%)	Composite outcome (total mortality/heart failure/repeat MI/stroke) **3 years** 46 of the PCI subjects vs. 31 of the no PCI subjects; p = 0.06 Multivariate analysis was done to look at factors associated with the composite endpoint in the overall study (i.e., not treatment specific) and found that male gender was NOT a factor significantly associated with outcome in the overall population.	Fair
PAMI **Stone et al., 1995**[11]	STEMI	PCI vs. fibrinolysis (t-PA)	Total: 395 Women: 107 (27%)	1) In-hospital death or reinfarction Women: 6% vs. 17.5%; p = 0.07 Men: 4.8% vs. 9.8%; p = 0.11 Overall: 5.1% vs. 12%; p=0.02 2) In-hospital total mortality Women: 4.0% vs. 14%; p = 0.07 Men: 2.1% vs. 3.5%; p = 0.46 3) In-hospital nonfatal MI Women: 2.0% vs. 3.5%; p = 0.64 Men: 2.8% vs. 7.7%; p = 0.06 4) In-hospital recurrent ischemia Women: 16% vs. 28.1%; p = 0.14 Men: 8.2% vs. 28%; p = 0.001 5) In-hospital stroke Women: 0 vs. 5.3%; p = 0.10 Men: 0 vs. 2.8%; (p = 0.04 6) Length of stay Women: 7.8 ± 3.4 days vs. 8.5 ± 4.1 days; p = 0.34 Men: 7.4 ± 3.3 days vs. 8.3 ± 4.8 days; p = 0.05	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
SHOCK **Hochman et al., 2001**[12] **and** **Hochman et al., 2006**[13] **Hochman et al., 1999**[14] **Hochman et al., 1999**[15]	STEMI	Early revascularization (PCI or CABG within 6 hours) vs. initial medial stabilization (thrombolysis, IABP)	Total: 302 Women: 97 (32%)	Relative risk (95% CI) for death at 1 year with early revascularization vs. initial medical stabilization: 0.72 (0.54 to 0.95) There was no interaction between treatment effect and sex.	Good

Abbreviations: BMS = bare metal stent; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; IABP = intra-aortic balloon pump; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial; RR = relative risk; UA = unstable angina

Table F-2. Summary of RCTs reporting clinical outcomes for UA/NSTEMI (KQ 2)

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
FRISC II **Lagerqvist et al., 2001**[16] **and** **Lagerqvist et al., 2006**[17] **Wallentin et al., 2000**[18] **Anonymous, 1999**[19]	UA/NSTEMI	Early invasive treatment with revascularization vs. initial conservative strategy	Total: 2,457 Women: 749 (30%)	<u>Primary endpoint</u> (death/MI or both) **6 months** RR (95% CI) Invasive vs. conservative Women: 1.26 (0.80 to 1.97) Men: 0.64 (0.49 to 0.84) Overall: 0.78 (0.62 to 0.98); p = 0.031 **1 year** Women: 12.4% vs. 10.5%; p = not significant Men: 9.6% vs. 15.8%; p < 0.001 Overall: 0.74 (0.60 to 0.92); p = 0.005 Interaction by sex: p = 0.008 (significant) OR (95% CI) 0.91 (0.68 to 1.22) for effect of women on primary endpoint adjusted for treatment group Women did not benefit from early invasive strategy partly because of higher mortality related to CABG. **5 years** OR (95% CI) Women: 1.12 (0.83 to 1.50) Men: 0.70 (0.59 to 0.86) Overall: 0.81 (0.69 to 0.95); p = 0.009 Interaction by sex p = 0.010 (significant)	Good
GUSTO IV-ACS **Ottervanger et al., 2004**[20]	NSTEMI Acute coronary syndrome	Revascularization within 30 days (early invasive) vs. initial conservative strategy	Total: 7,800 Women: 2896 (37%)	<u>Death, 1 year</u> Women: adjusted HR (95% CI) 0.53 (0.28 to 1.00) Men: adjusted HR (95% CI) 0.55 (0.35 to 0.85) Overall: adjusted RR (95% CI) 0.53 (0.37 to 0.77)	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
ICTUS **de Winter et al., 2005**[21] **and** **Damman et al., 2010**[22]	NSTEMI-acute coronary syndrome	Early invasive therapy with revascularization vs. selective invasive strategy (initial conservative)	Total: 1,200 Women: 320 (27%)	1) Death/MI/rehospitalization for angina **1 year** Early invasive vs. selective Total: RR (95% CI) 1.07 (0.87 to 1.33); p = 0.33 No significant difference among sex groups 2) Death/spontaneous MI **5 years** HR (95% CI) Women: 0.87 (0.53 to 1.43); p = 0.59 Men: 1.22 (0.87 to 1.71); p = 0.24 Overall: 1.10 (0.83 to 1.45); p = 0.52	Good
RITA-2 **Anonymous, 1997**[23]	UA/stable CAD (no recent MI)	Early invasive therapy with PCI (PTCA) vs. initial conservative	Total: 1,018 Women: 183 (8%)	1) Death/MI **Median followup of 2.7 years** PTCA vs. optimal medical therapy Total: RR (95% CI) 1.92 (1.08 to 3.41); p = 0.02 No significant interaction by sex 2) Secondary outcomes **Angina grade 2+ at 6 months** Women: 22.8% vs. 39.8% Men: 20.5% vs. 31.4% 3) Exercise time **6 months mean (SE)** Women: 6.72 (0.25) vs. 6.52 (0.26); Men: 9.34 (0.13) vs. 8.90 (0.15)	Fair

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
RITA-3 **Clayton et al., 2004**[24] **and** **Fox et al., 2002**[25]	UA/NSTEMI	Early invasive (PCI) vs. initial conservative	Total: 1,810 Women: 682 (38%)	1) Primary outcome (death/MI/refractory angina) Early invasive vs. initial conservative **4 months** Women: 10.9% vs. 9.6% (similar) Men: 8.8% vs. 17.3% Overall: 9.6% vs. 14.5% p = 0.001 RR (95% CI) 0.66 (0.51 to 0.85) Significant interaction by sex: p = 0.004 **1 year** Women: adjusted OR (95% CI) 1.14 (0.74 to 1.76) Men: adjusted OR (95% CI) 0.48 (0.34 to 0.67) Overall: RR (95% CI) 0.72 (0.58 to 0.90); p = 0.003 2) Secondary outcomes (death/MI) Early invasive vs. initial conservative **1 year** Women: adjusted OR (95% CI) 1.79 (0.95 to 3.35) Men: adjusted OR (95% CI) 0.63 (0.41 to 0.98) Overall: RR (95% CI) 0.91 (0.67 to 1.25); p = 0.58 3) Death **1 year** Women: adjusted OR (95% CI) 2.43 (1.01 to 5.84) Men: adjusted OR (95% CI) 0.78 (0.44 to 1.41) Overall: RR (95% CI) 1.16 (0.75 to 1.80); p = 0.50 Significant interaction by sex for all 3 outcomes 4) Risk stratification by TIMI risk score (death/MI/refractory angina) Early invasive vs. initial conservative **Low risk** Women: 2.3% vs. 3.8% Men: 6.1% vs. 5.1% **Moderate risk** Women: 13.4% vs. 3.4% Men: 5.4% vs. 9.5%	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
RITA-3 (continued)				**High risk** Women: 11.7% vs. 8.2% Men: 10.3% vs. 17.9% Women in moderate- or high-risk TIMI groups had higher event rate in early invasive arm Men in moderate- or high-risk TIMI groups had benefit from early invasive therapy	
TACTICS TIMI-18 **Cannon et al., 2001**[26] **and** **Glaser et al., 2002**[27] **Cannon et al., 1998**[28]	UA./NSTEMI	Early invasive (PCI) vs. initial conservative	Total: 2,220 Women: 757 (34%)	1) Primary endpoint (death/MI/rehospitalization for acute coronary syndrome) Early invasive vs. initial conservative **6 months** Adjusted OR (95% CI) Women: 0.72 (0.47 to 1.11) Men: 0.64 (0.47 to 0.88) Overall: 0.78 (0.62 to 0.97) 2) Secondary outcomes (death/MI) Early invasive vs. initial conservative **6 months** Adjusted OR (95% CI) Women: 0.45 (0.24 to 0.88) Men: 0.68 (0.43 to 1.05) Overall: 0.74 (0.54 to 1.00); $p < 0.05$ 3) Death Early invasive vs. initial conservative **6 months** Adjusted OR (95% CI) Women: 0.94 (0.37 to 2.44) Men: 0.75 (0.36 to 1.56) Women less likely to undergo CABG even after adjustment for 3-vessel and left main disease	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
TIMI III-B **Anonymous, 1994**[29] **and** **Anderson et al., 1995**[30]	UA/NSTEMI	Early invasive vs. initial conservative	Total: 1,425 Women: 497 (35%)	1) Primary endpoint (death/MI/failed symptom-limited exercise treadmill test) **6 weeks** Overall: 16.2% vs. 18.1%; p = 0.33 2) Secondary outcomes (death/MI) Early invasive vs. initial conservative **6 weeks** Women: 6.1% vs. 8.9%; p = 0.24 Men: 7.8% vs. 7.3%; p = 0.73 **1 year** Women: 9.7% vs. 15.4%; p = 0.06 Men: 11.3% vs. 10.6%; p = 0.68 Overall: 10.8% vs. 12.2%; p = 0.42 No interaction by sex	Good

Abbreviations: CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; SE = standard error; t-PA = tissue plasminogen activator; UA = unstable angina

Table F-3. Summary of RCTs reporting clinical outcomes for stable angina (KQ 3 Strategy 1—revascularization vs. optimal medical therapy)

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
Allen et al., 2004[31] **and** **Allen et al., 1999**[32]	Stable angina	Surgical revascularization (CABG with transmyocardial revascularization) vs. optimal medical therapy	Total: 222 Women: 61 (27%)	1) Death **5.7 years** (SD 0.8) Men: OR (95% CI) 1.4 (0.4 to 5.0); p = 0.63 2) Angina relief **5.7 years** (SD 0.8) Men: OR (95% CI) 1.1 (0.7 to 1.8); p = 0.41	Good
COURAGE **Boden et al., 2007**[33] **and** **Mancini et al., 2009**[34] **Boden et al., 2006**[35]	Stable angina	PCI (type not specified) or CABG if PCI failed vs. optimal medical therapy	Total: 2,287 Women: 338 (15%)	1) Death/MI **4.6 years (median followup)** PCI vs. optimal medical therapy: Women: 18% vs. 26% Men: 19% vs. 18% p = 0.03 Women: HR (95% CI) 0.65 (0.40 to 1.06) Men: HR (95% CI) 1.15 (0.93 to 1.42) Overall: HR (95%CI) 1.05 (0.87 to 1.27)	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
MASS II **Hueb et al., 2010**[36] **and** **Hueb et al., 2004**[37] **Hueb et al., 2007**[38]	Stable angina with multiple-vessel CAD	PCI vs. Optimal medical therapy CABG vs. optimal medical therapy	Total: 611 Women: 196 (32%)	<u>Primary endpoint</u> (death/MI/angina requiring mechanical revascularization) **10 years** Adjusted HR (95% CI) Women: Optimal medical therapy vs. PCI: 1.57 (1.01 to 2.46); p = 0.047(favoring PCI) CABG vs. optimal medical therapy: 0.43 (0.26 to 0.72); p = 0.001 Men: Optimal medical therapy vs. PCI: 1.13 (0.84 to 1.53); p = 0.410 CABG vs. optimal medical therapy: 0.43 (0.31 to 0.60); p = 0.001 Overall: PCI vs. optimal medical therapy: 0.79 (0.62-1.01) CABG vs. optimal medical therapy: 0.43 (0.32 to 0.58) p < 0.001	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
OAT **Hochman et al., 2006**[39] **and** **Hochman et al., 2005**[40] **Hochman et al., 2011**[41]	Stable angina	PCI (or CABG if PCI failed) vs. optimal medical therapy	Total: 2,166 Women: 476 (22%)	<u>Primary endpoint</u> (death/MI/heart failure) **4 years** PCI vs. optimal medical therapy: Women: 18.3% vs. 22.9% Men: 16.8% vs. 13.5% p = 0.13 Women: HR < 1.0 (favoring PCI, but not significant) Men: HR > 1.0 (favoring optimal medical therapy, but not significant) Overall: HR 0.43 (0.32 to 0.56) **7 years** PCI vs. optimal medical therapy: Women: 25.5% vs. 28.6%; HR 0.89 (0.62 to 1.28) Men: 21.3% vs. 21.3%; HR 1.11 (0.89 to 1.39) p = 0.31	Good
STICH **Velazquez et al., 2011**[42] **and** **Velazquez et al., 2007**[43]	Stable angina	CABG vs. optimal medical therapy	Total: 1,212 Women: 148 (12%)	<u>Death</u> **5 years** HR (95% CI) Women: 0.75 (0.42 to 1.31) Men: 0.87 (0.72 to 1.06) Overall: 0.86 (0.72 to 1.04) p = 0.61	Good

Abbreviations: BMS = bare metal stent; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; DES = drug-eluting stent; HR = hazard ratio; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial; SD = standard deviation; UA = unstable angina

Table F-4. Summary of RCTs reporting clinical outcomes for stable/unstable angina (KQ 3 Strategy 2–PCI vs. CABG)

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
ARTS I **Vaina et al., 2009[44]** **and** **van den Brand, et al., 2002[45]** **Serruys et al., 1999[46]** **Voudris et al., 2006[47]** **Anonymous, 1999[48]**	Unstable angina	PCI (BMS) vs. CABG	Total: 1,205 Women: 283 (23%)	1) Composite outcome (death/CVA/MI/CABG/repeat PCI) **30 days** Women: PCI 13.0% vs. CABG 8.3% Men: PCI 8.0% vs. CABG 5.7% **1 year** Women: PCI 29.0% vs. CABG 14.5% Men: PCI 25.8% vs. CABG 10.7% **3 years** Women: PCI 35.5% vs. CABG 19.3% Men: PCI 33.5% vs. CABG 15.1% 2) Composite death/CVA **30 days** Women: PCI 4.3% vs. CABG 4.8% Men: PCI 1.9% vs. CABG 1.5% **1 year** Women: PCI 8.0% vs. CABG 7.6% Men: PCI 3.5% vs. CABG 3.5% **3 years** Women: PCI 10.9% vs. CABG 9.7% Men: PCI 5.8% vs. 5.9%	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
ARTS I (continued)				3) Composite death/MI/CVA **30 days** Women: PCI 7.2% vs. 6.9% Men: PCI 4.5% vs. 5.0% **1 year** Women: PCI 11.6% vs. 11.0% Men: PCI 8.9% vs. CABG 7.0% **3 years** Women: PCI 14.5% vs. CABG 14.5% Men: PCI 12.3% vs. CABG 9.6% 4) Death—5 years PCI: women 7.4% vs. men 9.0%; p = 0.29 CABG: women 7.2% vs. men 10.1%; p = 0.48 PCI: OR (95% CI) 1.1 (0.5 to 2.8); p = 0.86 CABG: OR (95% CI) 1.4 (0.5 to 4.1); p = 0.54 5) MI—5 years PCI: OR (95% CI) 1.4 (0.7 to 3.2); p = 0.44 CABG: OR (95%CI) 0.6 (0.3 to 1.3); p = 0.17 6) CVA—5 years PCI: OR (95% CI) 0.8 (0.3 to 2.2); p = 0.58 CABG: OR (95%CI) 0.6 (0.3 to 1.9); p = 0.39 7) Revascularization—5 years PCI: OR (95% CI) 1.0 (0.6 to 1.5); p = 0.92 CABG: OR (95%CI) 0.7 (0.4 to 1.4); p = 0.32	
ARTS I (continued)				8) Composite death/MI/CVA Men vs. women PCI: OR (95% CI) 1.2 (0.7 to 1.2); p = 0.57 CABG: OR (95%CI) 0.8 (0.5 to 1.5); p = 0.57 9) Composite MI/CVA/PTCA Men vs. women PCI : OR (95% CI) 0.9 (0.6 to 1.4); p = 0.77 CABG : OR (95% CI) 0.8 (0.5 to 1.3); p = 0.38	

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
ARTS I (continued)				10) In-hospital outcomes PCI: OR 95% CI 0.6 (0.3 to 1.2); p = 0.14 CABG: OR 95%CI 1.8 (0.7 to 6.2); p = 0.29 11) In-hospital MI PCI: OR 95% CI 0.7 (0.2 to 2.6); p = 0.58 CABG: OR 95%CI 1.2 (0.4 to 4.3); p = 0.72 12) In-hospital CVA PCI: OR 95% CI 0.6 (0.1 to 12.5); p = 0.65 CABG: OR 95%CI 1.8 (0.3 to 34.9); p = 0.57 13) Quality of life—3 years Euro-QoL summary: PCI: Men 86 ± 16 vs. women 83 ± 19 P = 0.08 CABG: Men 86 ± 20 vs. women 82 ± 20 P = 0.02 14) Composite outcome (death/CVA/MI/CABG/repeat CABG) **5 years** Men vs. women PCI: OR (95%CI) 0.9 (0.6 to 1.4); p = 0.77 CABG: OR (95%CI) 0.8 (0.5 to 1.3) p = 0.38	

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
ARTS I (continued)				<u>15) Individual outcomes</u> **30 days** Death: Women: PCI 2.9% vs. CABG 4.1% Men: PCI 1.3% vs. CABG 0.4% CVA: Women: PCI 2.2% vs. CABG 0.7% Men: PCI 0.6% vs. CABG 1.1% MI: Women: PCI 3.6% vs. CABG 4.1% Men: PCI 3.2% vs. CABG 3.7% Revascularization: Women: PCI 7.2% vs. CABG 1.4% Men: PCI 5.2% vs. CABG 0.7% Major cardiovascular adverse event- free survival: Women: PCI 87.0% vs. CABG 91.7% Men: PCI 92.0% vs. CABG 94.3%	

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
ARTS I (continued)				**1 year** Death: Women: PCI 5.8% vs. CABG 6.2% Men: PCI 1.7% vs. CABG 1.5% CVA: Women: PCI 2.9% vs. CABG 2.1% Men: PCI 1.7% vs. CABG 2.0% MI: Women: PCI 5.1% vs. CABG 5.5% Men: PCI 6.1% vs. CABG 3.7% Revascularization: Women: PCI 20.3% vs. CABG 4.1% Men: PCI 21.2% vs. CABG 4.2% Major cardiovascular adverse event- free survival: Women: PCI 71.0% vs. CABG 85.5% Men: PCI 74.2% vs. CABG 89.3%	
ARTS I (continued)				**3 years** Death: Women: PCI 7.2% vs. CABG 6.9% Men: PCI 3.0% vs. CABG 3.5% CVA: Women: PCI 4.3% vs. CABG 4.1% Men: PCI 3.0% vs. CABG 2.8% MI: Women: PCI 5.8% vs. CABG 7.6% Men: PCI 7.1% vs. CABG 4.2% Revascularization: Women: PCI 24.6% vs. CABG 6.2% Men: PCI 26.8% vs. CABG 6.6% Major cardiovascular adverse event- free survival: Women: PCI 64.5% vs. CABG 80.7% Men: PCI 66.5% vs. CABG 84.9%	

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
BARI **Jacobs et al., 1998[49]** **and** **Gibbons et al., 2001[50]** **Anonymous, 2007[51]** **Lombardero et al., 2002[52]** **Anonymous, 2000[53]** **Hlatky et al., 1995[54]** **Rogers et al., 1995[55]** **Sutton-Tyrrell et al., 1998[56]** **Mullany et al., 1999[57]** **Anonymous, 1996[58]**	Stable/unstable angina Diabetics	PCI (type not specified) vs. CABG	Total: 915 Women: 249 (27%)	<u>1) 5-year cumulative survival rate</u> Women: PCI 86.3% vs. CABG 89.3% Men: PCI 86% vs. CABG 89% Survival free of MI: Women: PCI 74% vs. CABG 76% In-hospital death: PCI 1.1% vs. CABG 1.3% Women: PCI 0.8% vs. CABG 1.3% Men: PCI 1.2% vs. CABG 1.4% Q-waves MI: Women : PCI 1.2% vs. CABG 4.7% Men : PCI 2.4% vs. CABG 4.6% Congestive heart failure: Women: PCI 4.8% vs. CABG 9.8% Men: PCI 1.4% vs. CABG 1.8% <u>2) 7-year survival rate</u> Women: PCI 79.2% vs. CABG 82.6% Men: PCI 81.6% vs. CABG 85.1%	Good
BARI (continued)				<u>3) 10-year survival rate</u> Women: PCI 70.2% vs. CABG 67.8% Men: PCI 71.3% vs. CABG 75.5% <u>4) 4-year angina status</u> Women: PCI 23.3% vs. CABG 18.8% Men: PCI 19.7% vs. CABG 13.2% At 5 years, anginal status was not significantly different between men and women <u>5) Repeat revascularization</u> CABG: Women RR 1.74 p = 0.043 PCI: Women RR 0.74 p = 0.011 Women were less likely than men to undergo repeat revascularization with an initial strategy of CABG compared with PTCA (11.2% vs. 51.9%, respectively; p < 0.001)	

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
CABRI **Anonymous, 1995**[59]	Stable/unstable angina with multiple-vessel disease	PCI (PTCA) vs. CABG	Total: 1,054 Women: 234 (22%)	1) Primary endpoint of mortality, 1 year PTCA 3.9% vs. CABG 2.7% RR 95%CI 1.42 (0.731 to 2.74); p = 0.297 Women had higher risk of 1-year mortality RR (95% CI) 2.07 (1.07 to 4.01); p=0.031 2) Angina, 1 year PTCA 13.9% vs. CABG 10.1% RR (95% CI) 1.54 (1.09 to 2.16) Women: 3.12 (1.41 to 6.54) p = 0.002 Men: 1.25 (0.85 to 1.85); p = 0.256 3) Crude absolute risk of angina, 1 year PTCA Women: 0.214 Men: 0.131 CABG Women: 0.069 Men: 0.104	Good
CARDia **Kapur et al., 2010**[60] **and** **Kapur et al., 2005**[61]	UA/NSTEMI Stable angina Diabetic Multiple-vessel disease or complex single lesion	PCI (BMS or DES) vs. CABG	Total: 510 Women: 132 (26%)	1) Primary endpoint, 1 year (death/MI/stroke) HR (95%CI) Women: 2.13 (0.68 to 6.68) Men: 1.07 (0.59 to 1.93) Overall: 1.25 (0.75 to 2.09) 2) Secondary endpoint, 1 year (death/MI/stroke/repeat revascularization) HR (95%CI) Women: 2.4 (0.87 to 6.61) Men: 1.62 (0.95 to 2.74) Overall: 1.77 (1.11 to 2.09)	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
EAST **King et al., 2000**[62] **and** **King et al., 1995**[63] **King et al., 1994**[64] **Zhao et al., 1996**[65]	Stable angina with multiple-vessel disease	PCI (type not specified) vs. CABG	Total: 392 Women: 103 (26%)	<u>Single outcome survival</u> **3 years** CABG 93.8% vs. PTCA 92.9% **8 years** CABG 82.7% vs. PTCA 79.3% Comparisons were made for other baseline variables including sex, and no survival differences by treatment assignment were seen	Good
GABI **Kaehler et al., 2005**[66] **and** **Hamm et al., 1994**[67]	Stable angina	PCI (type not specified) vs. CABG	Total: 359 Women: 66 (18%)	<u>Death</u> **13 years** No significant sex differences in hazard ratio for death	Good
MASS II **Hueb et al., 2010**[36] **and** **Hueb et al., 2004**[37] **Hueb et al., 2007**[38]	Stable angina with multiple-vessel coronary artery disease	PCI (type not specified) vs. CABG	Total: 611 Women: 196 (32%)	<u>Primary endpoint</u> (death/MI/angina requiring mechanical revascularization) **10 years** Adjusted HR (95% CI) Women: CABG vs. PCI: 0.68 (0.40 to 1.15); p = 0.015 Men: CABG vs. PCI: 0.49 (0.34 to 0.69); p = 0.001 Overall: CABG vs. PCI: 0.53 (0.39 to 0.72); p < 0.001	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
PRECOMBAT **Park et al., 2011**[68]	Stable/unstable angina	PCI (DES) vs. CABG	Total: 600 Women: 141 (24%)	<u>1) Composite endpoint, 1 year</u> (death/MI/stroke/ischemia-driven target-vessel revascularization) PCI 8.7% vs. CABG 6.7% <u>2) Composite endpoint, 2 years</u> PCI 12.2% vs. CABG 8.1% HR (95% CI) 1.50 (0.90 to 2.52); p = 0.12 Women: PCI 13.9% vs. CABG 11.7 % HR (95% CI) 1.22 (0.48 to 3.08); p = 0.68 Men: PCI 11.7% vs. CABG 7.0% HR (95%CI) 1.65 (0.88 to 3.07); p = 0.12 Overall : HR 1.50 (0.90 to 2.52)	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Outcomes	Quality
SOS **Zhang et al., 2004**[69] **and** **Zhang et al., 2003**[70] **Stables et al., 1999**[71]	Stable angina	PCI (BMS) vs. CABG	Total: 908 Women: 206 (23%)	1) Quality of life (adjusted relative difference of CABG vs. PCI) **6 months** Women: 39.3 Men: 18.3 **1 year** Women: 0.6 Men: 15.3 2) Angina frequency (adjusted relative difference of CABG vs. PCI) **6 months** Women: 43.2 Men: 31.3 **1 year** Women: 11.1 Men: 19.7 3) Physical limitation (adjusted relative difference of CABG vs. PCI) **6 months** Women: 11.6 Men: 54.7 **1 year** Women: 1.6 Men: 50.6	Fair
SYNTAX **Morice et al., 2010**[72]	Triple-vessel or left main coronary artery disease	PCI (type not specified) vs. CABG	Total: 705 Women: 185 (26%)	1) Primary endpoint , 1 year (death/MI/stroke/repeat revascularization) CABG vs. PCI 13.6% vs. 15.8% OR (95% CI) 2.1 (-3.2 to 7.4); p = 0.44 2) Predictors of 1-year major adverse cardiovascular events OR (95% CI) Women: 0.50 (0.27 to 0.91); p = 0.02	Fair

Abbreviations: BMS = bare metal stent; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; CVA = cerebrovascular accident; DES = drug-eluting stent; HR = hazard ratio; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial; UA = unstable angina

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Appendix G. Summary Table for Modifiers of Effectiveness

Table G-1. Summary of RCTs reporting modifiers of effectiveness (subgroup analyses)

Study Author/Year Related Articles	Population	Comparison	# Subjects	Subgroup Analyses	Quality
BARI **Jacobs et al., 1998**[1] **and** **Gibbons et al., 2007**[2] **Anonymous, 2007**[3] **Lombardero et al., 2002**[4] **Anonymous, 2000**[5] **Hlatky et al., 1995**[6] **Rogers et al., 1995**[7] **Sutton-Tyrrell et al., 1998**[8] **Mullany et al., 1999**[9] **Anonymous, 1996**[10]	Stable/unstable angina Diabetics	PCI vs. CABG	Total: 915 Women: 249 (27%)	<u>7-year survival rates</u> Women: PCI 61.0% vs. CABG 74.3% Men: PCI 51.5% vs. CABG 77.9%	Good
Minai et al., 2002[11]	STEMI age ≥ 80 years	PCI vs conservative/supportive therapy	Total: 120 Women: 60 (50%)	No difference in composite outcome (death/congestive heart failure/repeat MI/cerebrovascular accident at 3 years between treatment groups).	Fair
PAMI **Stone et al., 1995**[12]	STEMI	PCI vs. fibrinolysis (t-PA)	Total: 395 Women: 107 (27%)	<u>In-hospital mortality</u> Women aged <65: 0% vs. 4%; p = 0.42 Women aged ≥65: 5.9% vs. 21.9%; p = 0.58 Men aged <65: 0.9% vs. 0%; p = 0.74 Men aged ≥65: 5.6% vs. 10.4%; p = 0.42	Good

Study Author/Year Related Articles	Population	Comparison	# Subjects	Subgroup Analyses	Quality
RITA-3 **Clayton et al., 2004**[13] **and** **Fox et al., 2002**[14]	UA/NSTEMI	Early invasive (PCI) vs. initial conservative	Total: 1,810 Women: 682 (38%)	Lower TIMI risk scores, both men and women had similar event rates in early invasive vs. initial conservative treatment arms. In those with moderate to high risk, men had lower event rates in intervention arm compared with conservative arm while women had higher even rates in the intervention arm. Moderate risk (women) Invasive: 13.4% Conservative: 3.4% High risk (women) Invasive: 11.7% Conservative: 8.2% Moderate risk (men) Invasive: 5.4% Conservative: 9.4% High risk (men) Invasive: 10.3% Conservative: 17.9% No benefit of intervention was seen in any BMI group for women.	Good
TACTICS TIMI-18 **Cannon et al., 2001**[15] **and** **Glaser et al., 2002**[16] **Cannon et al., 1998**[17]	UA/NSTEMI	Early invasive (PCI) vs. initial conservative	Total: 2,220 Women: 757 (34%)	<u>Primary endpoint</u> (death/MI/rehospitalization for acute coronary syndrome by risk) Women with intermediate (3–4) and high (5–7) TIMI risk scores did not have significantly different outcomes in early invasive vs. initial conservative group. OR (95% CI) 0.72 (0.45 to 1.16) vs. 0.56 (0.23 to 1.32)	Good

Abbreviations: BMS = bare metal stent; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; DES = drug-eluting stent; HCT = hematocrit; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial; TIMI = thrombolysis in myocardial infarction; t-PA = tissue plasminogen activator; UA = unstable angina

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Appendix H. Summary Table for Safety Concerns

Table H-1. Summary of RCTs reporting safety concerns (harms)

Study Author/Year Related Articles	Population	Comparison	# Subjects	Harms	Quality
ARTS I **Vaina et al., 2009**[1] **and** **van den Brand, et al., 2002**[2] **Serruys et al., 1999**[3] **Voudris et al., 2006**[4] **Anonymous, 1999**[5]	UA/NSTEMI	PCI vs. CABG	Total: 1,205 Women: 283 (23%)	<u>Major bleeding</u> PCI (men vs. women): OR (95% CI) 29.4 (5.3 to 500); p = 0.001 CABG (men vs. women): OR (95%CI) 1.5 (0.4 to 10.1); p = 0.58	Good
GUSTO II-B **Tamis-Holland et al., 2004**[6]	STEMI	PCI vs. fibrinolysis (accelerated t-PA)	Total: 1,137 Women: 260 (23%)	<u>Intracranial hemorrhage</u> Women PCI: 0 Optimal medical therapy: 4.1% Men PCI: 0 Optimal medical therapy: 0.7%	Good
PAMI **Stone et al., 1995**[7]	STEMI	PCI vs. fibrinolysis (t-PA)	Total: 395 Women: 107 (27%)	<u>Nadir HCT (PCI vs. fibrinolysis)</u> Women: 30 ± 5% vs. 33 ± 5%; p = 0.002 Men: 35 ± 6% vs. 35 ± 6%; p = 0.17 <u>Requirement for blood transfusion (PCI vs. fibrinolysis)</u> Women: 18% vs. 8.8%; p = 0.16 Men: 9.7% vs. 8.4%; p = 0.71	Good
TACTICS TIMI-18 **Cannon et al., 2001**[8] **and** **Glaser et al., 2002**[9] **Cannon et al., 1998**[10]	UA/NSTEMI	Early invasive vs. initial conservative	Total: 2,220 Women: 757 (34%)	Bleeding in women undergoing PTCA was higher compared to men; adjusted OR (95% CI) 3.6 (1.6 to 8.3). Bleeding related to CABG was similar in women and men (12.6% vs. 15%). Occurrence of stroke at 30 days related to CABG also was similar in women and men (2.1% vs. 1.5%).	Good

Abbreviations: BMS = bare metal stent; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; DES = drug-eluting stent; HCT = hematocrit; NSTEMI = non-ST elevation myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial; t-PA = tissue plasminogen activator; UA = unstable angina

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