Results of Systematic Review of Research on Diagnosis and Treatment of Coronary Heart Disease in Women

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AHRQ is the lead Federal agency charged with supporting research designed to improve the quality of health care, reduce its cost, address patient safety and medical errors, and broaden access to essential services. AHRQ sponsors and conducts research that provides evidence-based information on health care outcomes; quality; and cost, use, and access. The information helps health care decisionmakers—patients and clinicians, health system leaders, and policymakers—make more informed decisions and improve the quality of health care services.
Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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Structured Abstract

Objectives. The Agency for Healthcare Research and Quality and several partner organizations charged the University of California, San Francisco-Stanford Evidence-based Practice Center to review the evidence on five key topics related to coronary heart disease (CHD) in women: (1) accuracy of noninvasive testing for diagnosis of CHD; (2) efficacy of treatments; (3) strength of risk factors and efficacy of risk factor reduction; (4) utilization of tests and treatments in men compared to women, and (5) accuracy of biomarkers for diagnosis of myocardial infarction. These five key questions included 42 discrete subtopics. We used standard methods to systematically review the medical literature to address each subtopic. The evidence identified was reviewed, graded and summarized for each subtopic and further research was recommended as appropriate.

Search Strategy. We identified 6,403 citations from searching electronic databases from 1985 through July 2001, reviewing bibliographies, and by recommendation from our peer reviewers.

Selection Criteria. After the titles were screened, abstracts were reviewed independently by two investigators who coded each abstract for eligibility for full text review. In order to be categorized as providing evidence regarding a research question, the article had to address the predictor variable and the clinical outcome and contain data to address the question specifically in women. Articles meeting inclusion criteria were abstracted independently on a standardized form by two investigators, and received a quality score based on predefined criteria. All studies rated good or fair were included in this review.

Data Collection and Analysis. The titles and abstracts were entered and coded in EndNote® files. Data from the standardized review form was entered into a Microsoft® Access database, which allowed tracking of the eligibility, quality and type of study of each article reviewed.

Main Results. We reviewed the full text of 819 articles and found 162 that provided evidence in women. We found no data in women to address 13 of the subtopics, weak data to address 15, fair data for eight and good data to address six.

- Fair evidence suggests that the accuracy of exercise EKG and exercise thallium testing for CHD in women is low. The accuracy of exercise echocardiography appears to be higher, but data are limited.
- Fair or good evidence suggests that beta-blockers, aspirin and angiotensin converting enzyme inhibitors reduce risk for CHD events and that nitrates are ineffective in women with known heart disease.
- Fair evidence suggests that glycoprotein IIb/IIIa inhibitor drugs given to women undergoing percutaneous revascularization result in a reduced risk of CHD events and need for revascularization, but treatment of women suffering acute coronary syndromes may result in increased mortality. This was the only treatment for which there was evidence of a possible interaction by gender: men treated with IIb/IIIa drugs during acute coronary syndromes appear to benefit.
• Fair or good evidence suggests that hyperlipidemia, diabetes, and hyperhomocysteinemia are risk factors for CHD in women.
• Fair or good evidence suggests that smoking cessation after MI and treatment of hypertension and hyperlipidemia lower risk for CHD events in women.
• We found little evidence to address the key questions in women of different races or ethnicities. The only evidence regarding differences by ethnicity suggests that African-American women may benefit more from treatment of hypertension than white women.

Conclusions. New or updated systematic reviews of the literature appear to be feasible and would likely provide clinically important information for 14 of the subtopics. The major limitation in performing these systematic reviews is that data stratified by gender and race/ethnicity from completed studies may not available. We recommend that, in addition to requiring participation of women and minorities in research, the National Institutes of Health, U.S. Food and Drug Administration and other funding and regulatory agencies insist that outcome data by subgroup be published or archived.
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Overview

Coronary heart disease (CHD) is the most common disease and cause of death in women, accounting for over 250,000 deaths in women per year. Over the last two decades, multiple important studies have helped define accurate clinical tests, risk factors, preventive interventions, and effective therapies for CHD. Unfortunately, many of these studies have either excluded women entirely or included only limited numbers of women and minorities. Thus, much of the evidence supporting contemporary recommendations for testing, prevention, and treatment of coronary disease in women is extrapolated from studies conducted predominantly in middle-aged men. The two best approaches to obtain additional evidence on diagnosis and treatment of CHD in women are to conduct large studies that include adequate numbers of women and minorities to answer the research question or to perform systematic reviews and meta-analyses summarizing effect estimates by subgroup.

The Agency for Healthcare Research and Quality (AHRQ) and several partner organizations charged the University of California, San Francisco (UCSF)-Stanford Evidence-based Practice Center (EPC) with the development of an initial review of evidence-based research on five key topics, including 42 subtopic areas related to the diagnosis and management of coronary heart disease in women and minority race/ethnic groups.

The three major aims of this project were to (1) determine whether any of the 42 specific subtopic areas have been adequately addressed in systematic reviews or definitive individual studies, (2) summarize the information from the evidence-based studies identified that address the subtopics, and (3) describe the feasibility of further research for each subtopic.

Key Questions

1. Are there accurate non-invasive approaches to evaluating suspected coronary disease in women? (3 subtopics, 1.01-1.03)
   1.01 exercise tolerance testing, with and without perfusion imaging
   1.02 exercise echocardiogram
   1.03 coronary artery calcification score

2. Are there effective treatments for women with coronary heart disease? (15 subtopics 2.01-2.12 with secondary and primary prevention considered separately as appropriate)
   2.01 aspirin
     a. secondary prevention
     b. primary prevention
   2.02 beta-blockers
     a. secondary prevention
     b. primary prevention
   2.03 angiotensin converting enzyme inhibitors
     a. secondary prevention
     b. primary prevention
   2.04 calcium channel blockers
   2.05 nitrates
   2.06 heparin, including low molecular weight heparin
   2.07 glycoprotein IIb/IIIa inhibitor drugs
   2.08 thrombolysis
   2.09 ticlopidine
   2.10 clopidogrel
2.11 angioplasty or stenting
2.12 coronary artery bypass surgery

3. What are the risk factors for coronary heart disease in women and does modifying these risk factors result in reduced risk for coronary heart disease events? (20 subtopics labeled 3.01-3.12 with subtopic as a risk factor for CHD or treatment/modification of a risk factor for CHD prevention considered separately where appropriate)
3.01 hypertension
   a. as a risk factor
   b. treatment
3.02 diabetes
   a. as a risk factor
   b. treatment
3.03 hyperlipidemia (LDL-, HDL-cholesterol, triglycerides, lipoprotein (a))
   a. as a risk factor
   b. treatment
3.04 elevated homocysteine
   a. as a risk factor
   b. treatment
3.05 C-reactive protein
   a. as a risk factor
   b. treatment
3.06 cigarette smoking
   a. as a risk factor
   b. smoking cessation
3.07 obesity
   a. as a risk factor
   b. weight reduction
3.08 inactivity
   a. as a risk factor
   b. exercise
3.09 age
3.10 age at menopause
3.11 ethnicity
3.12 socioeconomic status

4. Are accurate tests (defined in #1), effective treatments (defined in #2), or risk factor modifications (defined in #3) underutilized in women (or among women of various race/ethnic populations) compared to men?

5. What is the prognostic value of biochemical markers for diagnosis of acute myocardial infarction or unstable angina in women? (3 subtopics labeled 5.01-5.02)
5.01 troponin
5.02 creatinine kinase myocardial bands including isoforms
5.03 myoglobin

Methodology

Data Sources
To assemble a bibliographic database of systematic reviews and articles that might provide definitive primary data, we searched MEDLINE®, the Cochrane Database and DARE from 1985 to July 2001, reviewed the bibliographies of retrieved articles and sought suggestions for additional articles from an expert Advisory Board and Peer Reviewers.

Inclusion Criteria
To be categorized as an article that provided evidence regarding a key question, the article had to address the subtopic and contain data specific to women. For subtopics with CHD events as the outcome (effects of risk factors, risk factor modification, and treatment), we required that the outcome be CHD events or mortality. For key question 1, the gold standard test to which noninvasive test results were compared was required to be angiographic evidence of coronary disease. When systematic reviews were not available to address the subtopic, we also searched for clinical trials, prospective cohort, and cross-sectional studies as appropriate.

Search Terms
We conducted a separate search for evidence regarding each of the 42 subtopics using the same search terms for CHD outcomes (i.e., cardiovascular diseases or heart diseases or heart or cardiovas* or cardiac* or coronary or myocardial) and for systematic reviews (i.e., publication type: meta-analysis or meta-analy* or metaanaly* or metanaly* or review or overview and systematic or methodologic* or evidence*) and added terms specific to each subtopic.

Data Abstraction
One UCSF-Stanford EPC physician investigator reviewed all identified titles and excluded those that clearly did not meet inclusion criteria. The abstracts of remaining articles were reviewed by two UCSF-Stanford EPC physician investigators, who independently classified eligibility. The full text of remaining eligible articles was reviewed independently by two UCSF-Stanford EPC physician investigators using a standardized abstraction form to classify eligibility and rate quality as fair or good based on predefined criteria.

Evaluation of Evidence Provided by Identified Articles
We reviewed and summarized in detail the findings of each systematic review and clinical trial identified. A general summary of the overall findings from prospective cohort and cross-sectional studies pertinent to each subtopic is also
provided. Finally, we summarized the answer to each subtopic question, graded the evidence as none, weak, fair or good, compared results in women and men and recommended a new or updated systematic review if feasible.

**Results of Literature Searches**

The searches identified 6,403 citations. After review of titles and abstracts, 810 articles were retrieved and reviewed in full text. The 162 articles that provided evidence in women are characterized with regard to study design and quality as follows:

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Good Quality</th>
<th>Fair Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic review</td>
<td>32</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Randomized trial</td>
<td>25</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>66</td>
<td>59</td>
<td>7</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>39</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>162</td>
<td>118</td>
<td>44</td>
</tr>
</tbody>
</table>

In total, we reviewed the full text of 272 systematic reviews and 55 randomized trials; only 32 systematic reviews and 25 randomized trials contained evidence on the key question in women. In general, most authors of systematic reviews and randomized trials that we identified did not perform subgroup analyses in women or ethnic minorities, even though a substantial proportion of participants were women or minorities.

Of the articles that provide evidence to address one of the key questions in women, only 35 percent are systematic reviews or randomized trials. The remaining cohort and cross-sectional studies provide some evidence, but the study designs are susceptible to bias due to confounding.

**Findings**

**General**

- We found no data in women to address 13 of the subtopic questions, weak data to address 15, fair data for eight, and good data to address six.
- In general, no evidence addressed differences in the accuracy of diagnostic tests, strength of risk factors, effects of treatment, and prognostic value of markers for ischemia in women of different races or ethnicity. The only evidence regarding differences by ethnicity suggests that African-American women may benefit more from treatment of hypertension than white women.

**Non-invasive diagnostic testing**

Fair evidence suggests that the accuracy of exercise EKG and exercise thallium testing for CHD in women is low. The accuracy of exercise echocardiography appears to be higher, but data are limited.

Weak evidence suggests that the absence of coronary calcification may be useful for ruling out disease in both men and women.

**Treatments**

- Fair or good evidence suggests that beta-blockers, aspirin, and angiotensin converting enzyme inhibitors reduce risk for CHD events in women with known heart disease.
- Good evidence suggests that nitrates do not reduce risk for CHD events in women with known heart disease.
- Fair evidence suggests that glycoprotein IIb/IIIa inhibitor drugs given to women undergoing percutaneous revascularization result in a reduced risk of CHD events and need for revascularization, but treatment in women suffering acute coronary syndromes may result in increased mortality. This was the only treatment for which there was evidence of a possible interaction by gender: men treated with IIb/IIIa drugs during acute coronary syndromes appear to benefit.
- Evidence regarding the efficacy of important treatments such as calcium channel blockers, heparin, ticlopidine, clopidogrel, coronary artery bypass surgery, percutaneous angioplasty and coronary stenting in women is weak.

**Risk factors and risk factor modification**

- Fair or good evidence suggests that hyperlipidemia, diabetes and hyperhomocysteinemia are risk factors for CHD in women.
- Only weak evidence links most of the risk factors of interest and CHD risk in women. This is primarily because all of the studies addressing the strength of risk factors are observational and very few good-quality systematic reviews have been completed.
- Risk factors for CHD seem to be equally strong in men and women with the possible exceptions of age, diabetes, and certain lipoproteins.
- Fair or good evidence suggests that smoking cessation after MI and treatment of hypertension and of hyperlipidemia lower risk for CHD events in women.
- No evidence was found for the effectiveness of other interventions to modify risk factors in women.

**Differences in utilization**

- Weak evidence suggests that men are more likely than women to undergo diagnostic testing and treatment for CHD, but that women are more likely than men to be treated for hypertension.
• Differences in utilization of tests and treatment might be explained by differences in severity of disease or comorbidities between men and women or by overuse of tests and treatments in men.

**Biochemical Markers**

• No evidence was found to address the diagnostic value of troponins, creatine kinase or myoglobin in women with ischemia.

**Future Research**

We believe that a new or updated systematic review is feasible and would be provide clinically important information for the following subtopics:
• Exercise tolerance testing
• Exercise echocardiogram
• Aspirin for secondary prevention
• Beta-blockers for secondary prevention
• Hypertension as a risk factor
• Diabetes as a risk factor
• Hyperlipidemia as a risk factor
• Hyperlipidemia treatment
• Homocysteine as a risk factor
• Smoking as a risk factor
• Smoking cessation
• Obesity as a risk factor
• Age as a risk factor
• Differences in utilization between men and women

The major limitation in performing these systematic reviews will be the availability of data on women and minority populations. Women typically comprise 20 to 30 percent of participants in randomized trials, but risk estimates for women are infrequently published. Thus, investigators attempting to systematically review the medical literature must attempt to contact investigators and obtain unpublished risk estimates. For a variety of reasons, these subgroup analyses are often not available. Thus, even though the National Institutes of Health and other funding agencies appear to have succeeded in assuring that some proportion of women and minorities are included in randomized trials, data from such participation are not generally available. We recommend that, in addition to demanding participation of women and minorities in research, the National Institutes of Health, U.S. Food and Drug Administration and other funding and regulatory agencies insist that primary and secondary outcome data by subgroup be published or archived. Similarly, we recommend that funding agencies that support systematic reviews require inclusion of subgroup estimates in women and minorities whenever possible.

**Availability of the Full Report**

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of California, San Francisco-Stanford Evidence-based Practice Center, under Contract No. 290-97-0013. It is expected to be available in May 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 80, *Results of Systematic Review of Research on Diagnosis and Treatment of Coronary Heart Disease in Women*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.
Chapter 1: Introduction

Coronary Heart Disease in Women

Coronary heart disease (CHD) is the most common disease and the most common cause of death in women. Approximately one in two women develop CHD and one in three die from it,\(^1\) accounting for over 250,000 deaths in women per year.\(^2\) Despite the very high prevalence of CHD in women, it has traditionally been thought of as a disease of middle-aged men, perhaps because women tend to develop CHD about a decade later in life than men.\(^3\) Over the last two decades, multiple important studies have helped define accurate clinical tests, important risk factors, preventive interventions, and effective therapies for CHD. Unfortunately, many of these studies have either excluded women entirely or included only limited numbers of women.\(^4\) Thus, much of the evidence that supports contemporary recommendations for testing, prevention, and treatment of coronary disease in women is extrapolated from studies conducted predominantly in middle-aged men. Applying the findings of studies in men to management of CHD in women may not be appropriate, since the symptoms of CHD, natural history, and response to therapy differ in men and women.\(^2\)

The first symptoms of CHD in women are often atypical, and angina is less predictive of CHD in women than in men.\(^5\) Compared to men, early mortality following myocardial infarction is higher in women,\(^6\) perioperative complications and mortality after percutaneous angioplasty and coronary artery bypass surgery are higher,\(^7, 8\) and long-term prognosis is worse.\(^9, 10\) Mortality rates for CHD among African-American women are about double those in white women.\(^11\) It is uncertain if these unfavorable clinical outcomes are gender-specific, reflecting more advanced age, smaller body size, or more frequent and severe risk factors and comorbid illnesses in women, or whether it is the result of late diagnosis and less optimal care.

Some studies suggest that women and nonwhites are less likely to undergo intensive and invasive evaluation and treatment for cardiac disease than white men with similar symptoms.\(^12-14\) These differences might be the result of overuse of tests and treatments in men, older age and more comorbid illnesses in women, or gender and race bias among health care providers.
Approaches to Improving Evidence on Diagnosis and Treatment of CHD in Women

Because many studies of diagnosis and treatment for CHD have excluded women or included only a small proportion of women, clinicians have typically been forced to generalize the findings of studies conducted predominantly in middle-aged white men to women and minorities. There are three basic approaches to obtain better evidence regarding diagnosis and treatment of CHD in women and minority populations: 1) perform clinical studies that include adequate numbers of women and minorities to determine outcomes for these subgroups separately; 2) perform systematic reviews and meta-analyses using subgroup estimates by gender and ethnicity to calculate summary estimates of effect and determine if there are interactions by gender; 3) perform systematic reviews and multivariate meta-analyses to determine if gender and ethnicity are predictors of outcome. The first option may be feasible or even required in some cases, such as the role of postmenopausal hormone therapy to prevent CHD in women.\(^\text{15, 16}\) In general, however, this approach is not feasible because it is too expensive to study adequate numbers of women and minorities to answer each clinical question. Given this, the next best option is to conduct systematic reviews and meta-analyses to calculate summary estimates of outcome in women and minorities. This approach is limited because studies that include a substantial proportion of women often do not publish subgroup estimates of effect in women and minorities. Thus, performing a meta-analysis typically requires contacting the authors of studies and requesting estimates of the outcomes by subgroup. Authors are sometimes unable or unwilling to provide such subgroup estimates, limiting the completeness of meta-analyses. Performing multivariate meta-analysis to determine if gender or ethnicity is a predictor of outcome can yield information on whether the outcome differs by gender or ethnicity, however, it is often under-powered (because the sample size is equal to the number of studies in the meta-analysis) and does not provide specific estimates of the effects in women.

Key Questions

Recognizing the importance of the issues raised above, multiple groups have requested evidence-based research pertinent to diagnosis and management of CHD in women and minorities. The groups include an ad hoc women’s health coalition (American Heart Association, American College of Cardiology, American College of Obstetricians and Gynecologists, American Society of Echocardiography, Association of Black Cardiologists, Jacobs Institute of Women’s Health, Mayo Clinic Women’s Heart Clinic, Society for Women’s Health Research, and WomenHeart: National Coalition for Women with Heart Disease), the American Association for Clinical Chemistry and the NIH Office of Research in Women’s Health. The Centers for Medicare and Medicaid Services and Harvard Pilgrim Health Services have also expressed interest. Concern about sex and gender-based differences in diagnosis and treatment of CHD was also noted in the Senate
Appropriations Committee’s report accompanying the FY 2000 Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriations bill. Specifically, these groups have requested evidence related to: 1) the accuracy of noninvasive tests for diagnosis of CHD in women; 2) the value of traditional treatments for CHD in women; 3) the importance of risk factors for CHD in women; 4) appropriate utilization of tests, treatments and risk factor modification in women, and 5) the prognostic value of biologic markers for diagnosis of acute coronary syndromes in women.

The University of California, San Francisco (UCSF)-Stanford Evidence-based Practice Center (EPC) worked with staff at the Agency for Healthcare Research and Quality to refine these five areas of interest to include the specific questions listed in Table 1. Of note, these questions include 42 separate topic areas (e.g., the accuracy of exercise tolerance testing; the effect of treatment with aspirin, the strength of hypertension as a risk factor, the prognostic value of troponins) and multiple questions concerning each (what is the accuracy of exercise tolerance testing in women? does the accuracy of exercise tolerance testing differ in men and women? does the accuracy of exercise tolerance testing differ by ethnicity?). We assessed the strength of risk factors separately from the effect of modifying the same risk factor, and assessed the effect of treatments in primary and secondary prevention separately. Thus, the total number of specific questions is large, although many are related.

The major aim of this report is to determine if any of these specific questions have been adequately addressed in systematic reviews or in methodologically sound individual studies with adequate numbers of women and minorities. We identified evidence-based studies that address the key questions, assessed their quality, and described and summarized their findings.
Chapter 2: Methodology

Identification of Evidence

Data Sources

We searched MEDLINE®, the Cochrane Database and DARE from 1985 through July 2001. We also reviewed the bibliographies of articles fitting our inclusion criteria and asked our expert Technical Expert Advisory Board and Peer Reviewers (Appendix A) to notify us of articles that provide evidence to address the key questions. Articles outside of the above date parameters were included if recommended by our advisors or reviewers.

Search Terms

We developed search terms to identify the outcome variable (i.e., mortality and coronary disease events), the predictors (defined by the individual key questions), and the study design (systematic reviews, Appendix B). We defined coronary disease events as nonfatal myocardial infarction and CHD death. We conducted a separate search for evidence regarding each predictor using the specific search terms listed in Appendix B. Each search used the same search terms for the outcome variable and for systematic review.

For each topic, we searched the databases above for evidence from systematic reviews. To identify evidence regarding the accuracy of diagnostic tests for CHD in women (questions 1.01-1.03), we additionally reviewed large cross-sectional studies. To identify evidence regarding the efficacy of treatments for CHD in women (questions 2.01-2.12), we also sought large randomized clinical trials that provided data on outcomes in women. To identify evidence regarding the strength of the association of traditional risk factors and CHD in women (questions 3.01-3.12), we also sought large prospective cohort studies with multivariate adjustment for potential confounders. To identify evidence regarding the utilization of accurate tests, effective treatments, and risk factor modifications in women compared to men (question 4.0); we also reviewed large prospective cohort and cross-sectional studies with multivariate adjustment for potential confounders. To identify evidence regarding the prognostic value of troponins, creatine kinase myocardial bands, and myoglobin (questions 5.01-5.03); we also sought large prospective cohort studies with multivariate adjustment for potential confounders.

Inclusion Criteria

To be categorized as an article that provides evidence regarding a key question, the article had to address the predictor variable (as defined by the key questions and search terms listed in Appendix B) and the outcome of CHD events or mortality (with the exception of angiographic evidence of atherosclerosis for question 1) and contain data to address the question specifically in women.
**Article Identification**

An initial search using the terms listed in Appendix B identified articles that potentially provided evidence regarding the key questions. One UCSF-Stanford EPC physician investigator reviewed the titles and excluded those that clearly did not provide data on humans or clearly did not address the key question.

The abstracts of all remaining articles were reviewed independently by two UCSF-Stanford EPC physician investigators, who classified each article using the codes listed below. The two abstractors discussed each abstract and decided by consensus on the code that was entered into the database.

- **PV** – the article clearly does not address the correct predictor variable (as defined by the key question)
- **OV** - the article clearly does not address the correct outcome variable (CHD events or mortality, or for question 1, angiographic evidence of coronary atherosclerosis)
- **NSR** – the article is a review that is clearly not systematic
- **NH** - the article clearly does not include data on humans
- **NW** – the article clearly does not include data on women
- **E** – the article may contain evidence regarding the key question in women

All articles coded E were retrieved and the full text was reviewed independently by two UCSF-Stanford EPC physician investigators using a standardized abstraction form (Appendix C). If the article did not address the key question, did not include data to answer the question in women, or was a review that was not systematic, it was eliminated from further consideration. Articles that addressed a key question in women and were a systematic review, large prospective cohort or cross-sectional study with multivariate analysis, or a large randomized trial were classified as eligible for review. Large cohort studies, cross-sectional studies, and randomized trials were those that included 1000 or more participants.

**Quality Assessment**

We considered any article that addressed a key question in women and were a systematic review, large prospective cohort or cross-sectional study with multivariate analysis, or large randomized trial to be *fair quality*.

To be categorized as *good quality*, articles were required to meet the following additional parameters:

**Systematic Reviews** (questions 4-8 on the abstraction sheet in Appendix C)
- information source appropriate
- information source adequately searched
- inclusion/exclusion criteria clear and appropriate
- data abstraction performed by at least 2 independent reviewers
• principal measures of effect and the methods of combining results appropriate

Randomized Trials (questions 4-8 on the abstraction sheet in Appendix C)
• intervention randomized
• control group received placebo
• participants and research staff blinded to the intervention
• inclusion/exclusion criteria clear and appropriate
• more than 75 percent complete follow-up

Prospective Cohort Studies (questions 4-7 on the abstraction sheet in Appendix C)
• inclusion/exclusion criteria clear and appropriate
• more than 75 percent complete follow-up
• analysis includes multivariate adjustment for potential confounders
• outcome adjudicated blindly

Cross-sectional Studies
For Question 1: Non-invasive diagnostic tests (questions 7-8 on the abstraction sheet in Appendix C):
• all women who underwent the non-invasive test also underwent angiography
• diagnosis of CAD on angiography made by investigators blinded to results of the non-invasive test

For Question 4: Utilization differences in women and men (questions 4-5 on the abstraction sheet in Appendix C):
• inclusion/exclusion criteria clear and appropriate
• analysis includes multivariate adjustment for potential confounders

Our searches identified several articles that presented the pooled results of individual level data from multiple randomized trials or cohort studies. We treated these articles as fair quality systematic reviews. We did not rate the quality of cost-effectiveness analyses, decision analyses, evidence reports, or clinical practice guidelines.

Completeness

Determining whether evidence-based reports are complete and up-to-date is difficult. For example, if a good systematic review of randomized trials was completed in 1994 and no additional important randomized trial has been completed, the systematic review can be considered complete. However, if the results of several new trials have been published
and could alter the results of the systematic review, the review may be out-dated. Determination of completeness can only be definitively decided by a formal update of the systematic review.

**Data Management and Archive**

The titles and abstracts identified by each search were electronically transferred into separate EndNote\(^\text{17}\) files identified by key question. The code assigned to each article after review of the abstract was entered in the EndNote file as a keyword. Using the EndNote keyword, articles can be classified by reason for exclusion. Lists of excluded articles categorized by reason for exclusion can be provided on request.

We also constructed a Microsoft Access\(^\text{18}\) database that was used to enter data from the abstraction forms completed at review of the full text of articles. This database allows us to track and report the reasons for exclusion of each article for which the full text was reviewed, the type of study (systematic review, randomized trial, cohort, cross-sectional, cost-effectiveness or decision analysis, evidence report and clinical practice guideline), and the number or proportion of eligible articles that were judged good quality.

The full-text articles that were retrieved, along with the completed abstraction sheet and names of the two reviewers for each article are filed by key question in Dr. Grady’s offices at the Women’s Health Clinical Research Center at UCSF.

**Results of Literature Searches**

Our systematic reviews identified 6,403 articles that potentially addressed a key question (Figure 1). In addition, we reviewed articles that were recommended by our Technical Expert Advisory Group and Peer Reviewers (Appendix A) or were identified by review of the bibliographies of articles eligible for full text review. We searched the websites of large clinical trials and large cohort studies for additional publications. After review of the titles and abstracts of these articles, we eliminated 5,520 that did not address a key question, did not contain data on women or were a review that was not systematic. Thus, we reviewed the full text of 810 articles (Appendix D). Of these, 648 did not address the key question, did not include data to answer the question in women, or were reviews that were not systematic, leaving 162 articles that provide evidence to address the key questions (Evidence Table 1).
The 162 articles that provided evidence in women are characterized with regard to study design and quality as follows:

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Total</th>
<th>Good Quality</th>
<th>Fair Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic review</td>
<td>32</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Randomized trial</td>
<td>25</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>66</td>
<td>59</td>
<td>7</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>39</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>162</td>
<td>118</td>
<td>44</td>
</tr>
</tbody>
</table>

Good quality articles are denoted with the superscript “a” in Evidence Table 1. Our searches also identified 21 cost-effectiveness or decision analyses (Appendix E), 43 clinical practice guidelines (Appendix F) and nine evidence reports (Appendix G) which were not rated for quality or reviewed in detail.

Table 2 displays the key question number, the topic of the question, the total number of articles identified, the number of articles for which the full-text was reviewed, the number of articles that provide evidence regarding the key question in women and the number of good quality articles that provide evidence regarding the key question in women.

In total, we reviewed the full text of 272 systematic reviews and 55 randomized trials; only 32 systematic reviews and 25 randomized trials contained evidence on the key question in women. In general, most of authors of systematic reviews and randomized trials that we identified did not perform subgroup analyses in women or ethnic minorities, even though a substantial proportion of participants were women or minorities.

Of the articles that provide evidence to address one of the key questions in women, only 35 percent are systematic reviews or randomized trials. The remaining cohort and cross-sectional studies provide some evidence, but the study designs are susceptible to bias due to confounding.

**Summary of Evidence**

**Hierarchy of Evidence and Completeness of Searches**

We assumed that a systematic review of the literature provided the most evidence-based data to address a key question. Thus, we focused our searches by including terms to identify systematic reviews and are confident that we identified all systematic reviews published in English that provide data on any of the five key questions in women.

When systematic reviews were not available, we relied on the findings of individual large randomized trials to address key questions related to treatment (question 2.01-2.12) and risk factor modification (question 3.01b-3.08b). We reviewed articles that were recommended by our Technical Expert Advisory Board and Peer Reviewers (Appendix
A) or were identified by review of the bibliographies of articles eligible for full text review. We additionally searched the websites from large clinical trials for publications.

Key questions concerning the accuracy of non-invasive testing (1.01-1.03), the strength of CHD risk factors (3.01a-3.08a, 3.09-3.12), comparative utilization of diagnostic tests and treatments in men and women (4.0) and the prognostic value of biochemical markers (5.01-5.03) cannot be addressed by randomized trials. When systematic reviews were not available for these key questions, we relied on the findings of individual cohort or cross-sectional studies. We reviewed articles that were recommended by our Technical Expert Advisory Board and Peer Reviewers (Appendix A) or were identified by review of the bibliographies of articles eligible for full text review. We additionally searched the websites from large prospective cohort studies for publications.

For the question concerning utilization of tests and treatments (Question 4), we searched for systematic reviews. When these were not available, we relied on the findings of individual cohort or cross-sectional studies, which were identified during our database searches (Appendix B). We also consulted with our Technical Expert Advisory Board (Appendix A) to identify studies that our searches may have missed.

We tracked all decision and cost-effectiveness analyses (Appendix E), clinical practice guidelines (Appendix F) and evidence reports (Appendix G), that were identified by our searches and advisors, but we did not search specifically for these publication types and did not review these publications to determine if they address a key question in women or include evidence-based recommendations.

**Summary of Studies**

All good and fair quality studies are summarized. Each reference is preceded by either a “G”, indicating a good quality study, or “F”, indicating a fair quality study. The reasons that a study is rated only fair quality are stated at the end of each review.

If a randomized trial, prospective cohort study or cross-sectional study was summarized in a systematic review that was included in our analysis, we did not independently report the findings from the primary study.

For each systematic review and randomized trial, we describe the study design, participants, predictor and outcome variables, and the main findings. When possible, we present the findings as odds ratios (OR) or relative risks (RR) with 95 percent confidence intervals (CI) and p-values for all participants combined and for women separately. The general format for presenting the results is demonstrated in the following table:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Participants</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=x)</td>
<td>(N=x; y% women)</td>
</tr>
<tr>
<td>CHD Event</td>
<td>OR 95% CI p-value</td>
<td>OR 95% CI p-value</td>
</tr>
<tr>
<td></td>
<td>x.x x.x-y.y .xx</td>
<td>x.x x.x-y.y .xx</td>
</tr>
</tbody>
</table>
We elected to present data for all participants rather than for men. If there is no evidence of an interaction by gender, the outcome estimate for all participants is the most precise and accurate estimate for all subgroups, including women. When there was evidence of an interaction by gender, or when the manuscript presented only data for men and women separately, we included estimates in the tables for men rather than for all participants.

All identified good and fair quality prospective cohort and cross-sectional studies are listed by key question. The number of cohort studies was large, multiple publications from the same cohort were identified, definitions of the predictor variable were not uniform (i.e., socioeconomic status defined as level of income, education, postal code, etc), duration of observation varied markedly, definition of the outcomes were not uniform and the quality of the studies was much more variable than for randomized trials. Given these problems, we did not describe each cohort study individually, but present a general summary of the overall findings of the cohort studies. For most of the key questions where the evidence comes entirely from cohort studies, the number and size of the studies identified allows us to make clear recommendations concerning the feasibility of conducting a systematic review. Decision analyses and cost-effectiveness analyses, evidence reports and clinical practice guidelines were not reviewed or summarized, but are listed in Appendices E, F and G.

Evidence by Ethnicity

We found very little evidence to address the five key questions in minority populations of women. Where this information is available, it is included in the description of each study and in the summaries of the evidence for each key question.

Abbreviations

The abbreviations and acronyms that were used throughout the review are listed in Appendix H.
Chapter 3: Results

Results by Key Question

QUESTION 1

1. Are there accurate non-invasive approaches to evaluating suspected coronary disease in women? (3 subtopics, labeled 1.01-1.03)

Specifically, what are the summary estimates of sensitivity, specificity, and positive and negative likelihood ratios (using angiographic diagnosis of coronary artery disease as the gold standard) for the following tests, calculated separately for women, for men, and for women restricted to major ethnic groups (Caucasian, African-American, Hispanic, Asian):

<table>
<thead>
<tr>
<th>Subtopic</th>
<th>Test Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.01</td>
<td>exercise tolerance testing, with and without perfusion imaging (thallium)</td>
</tr>
<tr>
<td>1.02</td>
<td>exercise echocardiogram (ECHO)</td>
</tr>
<tr>
<td>1.03</td>
<td>coronary artery calcification score</td>
</tr>
</tbody>
</table>

1.01 Exercise testing


This is a systematic review of the English language literature published from 1966 to 1995 that provided separate estimates of the accuracy of exercise EKG and exercise thallium using planar or tomographic imaging for diagnosis of coronary atherosclerosis in women. Mean weighted estimates of accuracy are given below.

<table>
<thead>
<tr>
<th>Test</th>
<th>N Studies</th>
<th>N Women</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>likelihood Ratio+</th>
<th>likelihood Ratio-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise EKG</td>
<td>19</td>
<td>3,721</td>
<td>.61</td>
<td>.70</td>
<td>2.3</td>
<td>0.55</td>
</tr>
<tr>
<td>Exercise thallium</td>
<td>5</td>
<td>842</td>
<td>.78</td>
<td>.64</td>
<td>2.9</td>
<td>0.36</td>
</tr>
</tbody>
</table>

These non-invasive tests appear to be only moderately accurate for diagnosis of CHD in women. Exercise thallium appears to be more sensitive but less specific than exercise EKG, resulting in similar likelihood ratios.
From the ten studies that provided data on men, Kwok et al. also calculated the accuracy of exercise EKG in men and found a mean weighted sensitivity of 0.70 and specificity of 0.77, suggesting that exercise EKG is somewhat more accurate in men than in women. A prior meta-analysis,\textsuperscript{20} using similar selection criteria, identified 147 studies including 24,074 participants, most of whom were men, and calculated a mean weighted sensitivity and specificity for exercise EKG of 0.68 and 0.77, very similar to that calculated by Kwok, et al. These studies would suggest that the positive likelihood ratio for an abnormal exercise EKG in men is about 3, somewhat higher than the summary estimate of 2.3 reported from the Kwok et al. meta-analysis in women.

Kwok et al. did not calculate a summary estimate for the accuracy of exercise thallium in men, because only two studies included in their meta-analysis included men. A prior meta-analysis using similar inclusion criteria, that identified 56 studies with 6,038 mostly male participants, found a mean weighted sensitivity of exercise thallium of 0.85 and sensitivity of 0.85.\textsuperscript{21} Based on these findings, the positive likelihood ratio for an abnormal exercise thallium test in men is 5.7, substantially higher than the summary estimate of 2.9 reported from the Kwok et al. meta-analysis in women.


The systematic review by Fleischmann et al. reviewed the accuracy of exercise single photon emission computed tomography (SPECT) and exercise echocardiography (see 1.02). The authors searched Medline for English language articles published from 1990 to 1997. The main results are given below (likelihood ratios were calculated from the summary weighted sensitivity and specificity). The sensitivity was high, but the specificity of exercise SPECT was low, resulting in a low positive likelihood ratio.

\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
 & N & N & % Women & Sensitivity & Specificity & Likelihood Ratio+ & Likelihood Ratio- \\
\hline
Exercise SPECT & 27 & 3237 & 30 & .87 & .64 & 1.9 & 0.20 \\
\hline
\end{tabular}

\textit{Unfortunately, the analysis does not provide separate estimates of the accuracy of these tests among women.} Multivariate analyses suggested that fewer men (more women) in a study was associated with lower accuracy for exercise SPECT.

This cross-sectional study provides data on the accuracy of exercise single-photon emission computed tomography (SPECT) imaging with thallium-201 in 727 men (87 percent with CHD) and 266 women (81 percent with CHD). The definition of an abnormal exercise test was not provided. Coronary artery disease was defined as 50 percent or greater narrowing of one or more of the major coronary arteries.

### Exercise thallium SPECT

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Ratio+*</th>
<th>Ratio-*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>266</td>
<td>.72</td>
<td>.69</td>
<td>2.3</td>
<td>.41</td>
</tr>
<tr>
<td>Men</td>
<td>727</td>
<td>.92</td>
<td>.70</td>
<td>3.1</td>
<td>.11</td>
</tr>
</tbody>
</table>

*calculated from sensitivity and specificity

The sensitivity of exercise thallium SPECT imaging was lower in women than in men, while the specificity was similar. This resulted in both a lower positive likelihood ratio and a lower negative likelihood ratio for women than for men.

This study was rated fair quality because not all persons who underwent the stress tests had coronary angiography and the manuscript does not state that the angiographers were blinded to the results of the stress tests.


This cross-sectional study provides data on the accuracy of exercise EKG testing in 838 men (75 percent with CHD) and 205 women (60 percent with CHD). Patients exercised according to the Bruce or Naughton protocol to severe fatigue, moderate angina or >2 mm ST depression. An abnormal exercise test was defined as ≥1mm horizontal or downsloping ST depression. Coronary artery disease was defined as 50 percent or greater narrowing of one or more of the major coronary arteries.

### Exercise EKG

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Ratio+*</th>
<th>Ratio-*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>205</td>
<td>.53</td>
<td>.69</td>
<td>1.7</td>
<td>.68</td>
</tr>
<tr>
<td>Men</td>
<td>838</td>
<td>.63</td>
<td>.74</td>
<td>2.4</td>
<td>.50</td>
</tr>
</tbody>
</table>

*calculated from sensitivity and specificity

The sensitivity of exercise EKG was lower in women than in men, while the specificity was similar. This resulted in a lower positive likelihood ratio for women than for men.

This study was rated fair quality because not all persons who underwent the stress tests had coronary angiography and the manuscript does not state that the angiographers were blinded to the results of the stress tests.
Summary

The accuracy of exercise EKG and exercise thallium (with either conventional or SPECT imaging) for the diagnosis of CHD is lower in women than in men. The accuracy of these tests in women appears to be low due to both poor sensitivity and specificity with positive likelihood ratios ranging from 2 to 3 and negative likelihood ratios of .35 to .70.

1.02 Exercise echocardiogram


Summary estimates of the accuracy of exercise echocardiogram in men and women from the systematic review by Fleischmann et al. (also described in section 1.01) are given below.

<table>
<thead>
<tr>
<th>N</th>
<th>N</th>
<th>% Women</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Ratio+</th>
<th>Ratio-</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>2637</td>
<td>31</td>
<td>.85</td>
<td>.77</td>
<td>3.7</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Unfortunately, the analysis does not provide separate estimates of the accuracy of these tests among women. Multivariate analyses suggested that the average proportion of men in the study did not affect the summary accuracy estimates for exercise echocardiogram.


Summary estimates of the accuracy of exercise echocardiogram in women from the systematic review by Kwok et al. (also described in section 1.01) are given below.

<table>
<thead>
<tr>
<th>N</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Ratio+</th>
<th>Ratio-</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>296</td>
<td>.86</td>
<td>.79</td>
<td>4.29</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Summary

The accuracy of exercise echocardiogram in women appears to be better than either exercise EKG or exercise thallium, but this finding is based on limited data (3 studies including only 296 women). Estimates of the accuracy of exercise echocardiogram among both men and women from the systematic review by Fleischmann et al.22 are very similar to the estimates among women from the systematic review by Kwok et al.19 and Fleischmann et al.22 found no evidence of lower accuracy of exercise echocardiogram in studies that included a higher proportion of women.
### 1.03 Coronary artery calcification score


This cross-sectional study provides data on the accuracy of measures of coronary calcification in 280 symptomatic men and 211 symptomatic women. All participants underwent computed tomographic measures of coronary calcium (method for computing score and range not given) and coronary angiography. Abnormal coronary calcium was defined as a coronary calcium score >0 or <100. Coronary artery disease was defined as 50 percent or greater narrowing of one or more of the major coronary arteries.

<table>
<thead>
<tr>
<th>Calcium score &gt;0</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood Ratio+*</th>
<th>Likelihood Ratio-*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;55 years old</td>
<td>.98</td>
<td>.31</td>
<td>1.4</td>
<td>.06</td>
</tr>
<tr>
<td>≤55 years old</td>
<td>.93</td>
<td>.46</td>
<td>1.7</td>
<td>.15</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;55 years old</td>
<td>.97</td>
<td>.13</td>
<td>1.1</td>
<td>.03</td>
</tr>
<tr>
<td>≤55 years old</td>
<td>.92</td>
<td>.30</td>
<td>1.3</td>
<td>.27</td>
</tr>
<tr>
<td>Calcium score &gt;100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;55 years old</td>
<td>.77</td>
<td>.65</td>
<td>2.2</td>
<td>.35</td>
</tr>
<tr>
<td>≤55 years old</td>
<td>.60</td>
<td>.88</td>
<td>5.0</td>
<td>.45</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;55 years old</td>
<td>.86</td>
<td>.51</td>
<td>1.8</td>
<td>.27</td>
</tr>
<tr>
<td>≤55 years old</td>
<td>.49</td>
<td>.73</td>
<td>1.8</td>
<td>.70</td>
</tr>
</tbody>
</table>

*calculated from sensitivity and specificity

The overall accuracy of computed tomographic calcium score >0 was low in both men and women. Given the high sensitivity and low negative likelihood ratio of no calcium on computed tomography, a negative test might be useful to rule out CHD in both women and men. The accuracy of a calcium score greater than 100 appears to be low in both men and women. The positive likelihood ratio of a high calcium score in women under 55 appears to be higher than in any other group of men or women, but this probably occurred by chance or due to multiple comparisons.

This cross-sectional study provides data on the accuracy of measures of coronary calcification in 733 symptomatic men (70 percent with CHD) and 387 women (41 percent with CHD). All participants underwent computed tomographic measures of coronary calcium (method for computing score and range not given) and coronary angiography. Abnormal coronary calcium was defined as a coronary calcium score >0. Coronary artery disease was defined as 50 percent or greater narrowing of one or more of the major coronary arteries.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood Ratio+*</th>
<th>Likelihood Ratio-*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>.96</td>
<td>.57</td>
<td>2.2</td>
<td>.09</td>
</tr>
<tr>
<td>Men</td>
<td>.96</td>
<td>.46</td>
<td>1.8</td>
<td>.07</td>
</tr>
</tbody>
</table>

*calculated from sensitivity and specificity

The overall accuracy of computed tomographic calcium score is low in both men and women. Among women, 64 percent had a coronary calcium score of 0 compared to 44 percent of men. Given the high sensitivity and low negative likelihood ratio of a calcium score of 0, a negative test might be useful to rule out CHD in women.

Summary

The overall accuracy of computed tomographic calcium score is low in both men and women. For a calcium score of 0, the sensitivity is high and the negative likelihood ratio is low. Thus, a calcium score of 0 might be useful to rule out CHD in both women and men.

Overall Summary and Recommendations for Question 1

The accuracy of exercise EKG and exercise thallium for the diagnosis of coronary atherosclerosis in women appears to be low with positive likelihood ratios of 2 to 3 and negative likelihood ratios of .35 to .70. The accuracy of exercise echocardiogram appears to be higher than exercise EKG or exercise thallium imaging with a positive likelihood ratio of 4 and a negative likelihood ratio of .2. Based on the review of Fleischmann et al., exercise echocardiogram also seems to be superior to exercise SPECT.

Two good-quality studies of the accuracy of computed tomographic measures of coronary calcium suggest that a score of 0 has a high sensitivity and low negative likelihood ratio for angiographic coronary disease. Thus, while this test has a low positive likelihood ratio, it might be useful for ruling out disease in both men and women.

While we found two good quality systematic reviews, each is limited. The review by Kwok et al. included only studies published until 1995 using exercise EKG or exercise thallium with planar imaging and the review by Fleischmann, et al. did not estimate the accuracy of noninvasive tests separately for women. Importantly, the systematic reviews do not address the accuracy of current myocardial perfusion imaging technology using thallium and/or technetium agents with SPECT or gated SPECT imaging in women. A
systematic review of the accuracy of current myocardial perfusion imaging for the diagnosis of CHD in women is feasible and could contribute important clinical information.
QUESTION 2

2. Are there effective treatments for women with coronary heart disease? (15 subtopics labeled 2.01-2.12 with secondary and primary prevention considered separately where appropriate)

Specifically, what are the summary estimates of the relative risk or risk reduction for mortality or CHD events for the following potential treatments, calculated separately for women and for women restricted to major ethnic groups (Caucasian, African-American, Hispanic, Asian):

2.01 aspirin
   a. secondary prevention
   b. primary prevention

2.02 beta-blockers
   a. secondary prevention
   b. primary prevention

2.03 angiotensin converting enzyme (ACE) inhibitors
   a. secondary prevention
   b. primary prevention

2.04 calcium channel blockers

2.05 nitrates

2.06 heparin, including low molecular weight heparin

2.07 IIb/IIIa drugs

2.08 thrombolysis

2.09 ticlopidine

2.10 clopidogrel

2.11 angioplasty or stenting (PTCA)

2.12 coronary bypass surgery (CABG)

2.01a Aspirin: secondary prevention


The Antiplatelet Trialists’ Collaboration provides a systematic review of 145 randomized controlled trials published prior to 1990. Trial selection required that participants were randomized to aspirin and/or dipyridamole or sulphipyrazone for at least one-month.
The primary outcome was defined as vascular events, including non-fatal MI, nonfatal stroke, and vascular death.

While the systematic review included both primary and secondary prevention trials, gender stratified results for vascular events are only available for high-risk women, defined as those with unstable angina, acute myocardial infarction, prior MI, stroke, transient ischemic attack, or other high risk conditions.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular events</td>
<td>.78</td>
<td>NA</td>
<td>&lt;.0001</td>
<td>.81</td>
<td>NA</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

There was a similar 20 percent reduction in risk of vascular events among both men and women. Compared to high dose therapy (500 – 1500 mg daily), low and intermediate doses of aspirin (< 160 mg/day and 160 – 325 mg) were slightly more beneficial, but the 95 percent confidence intervals overlap. In the entire high-risk population (approximately 50,000 individuals), there was no evidence that aspirin increased the risk of non-vascular death or fatal stroke. Evidence on the risks associated with aspirin therapy was not provided separately for women.

**G.2. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2.**

The Second International Study of Infarct Survival (ISIS-2) was a randomized trial of the effect of low-dose aspirin and streptokinase on cardiovascular outcomes following acute myocardial infarction. Between 1985 and 1987, 17,187 hospitalized patients in 16 countries were randomized to receive either one hour of intravenous streptokinase or identical placebo. Participants were also randomized to aspirin (162.5 mg daily) or identical placebo (2x2 factorial design); thus, there were four treatment groups: streptokinase alone, aspirin alone, both, or neither. Randomization occurred within 24-hours after the onset of symptoms of an acute MI. The main outcome was vascular death (cardiac, cerebral, hemorrhagic and other vascular deaths) during 5 weeks of follow-up.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular death</td>
<td>.77</td>
<td>.70-.85</td>
<td>&lt;.00001</td>
<td>.83</td>
<td>NA*</td>
<td>NA</td>
</tr>
</tbody>
</table>

*figure demonstrates that the 95 percent confidence interval does not cross 1.0.
There appeared to be about a 20 percent reduction in risk of vascular events in women that was similar to the benefit observed in all participants. There were no statistically significant differences in the odds ratios for vascular death among men and women. For both genders combined, the risks of major bleeding and hemorrhagic stroke were not increased with aspirin use. There was a small excess risk of minor bleeding (0.6 percent).

2.01b Aspirin: primary prevention


The Primary Prevention Project was a randomized trial of the effect of low-dose aspirin (100 mg/day) on cardiovascular risk (nonfatal MI, nonfatal stroke and cardiovascular death). All participants were over age 50 years and had at least one major cardiovascular risk factor (hypertension, hypercholesterolemia, diabetes, obesity, family history of premature MI or age ≥ 65 years). The trial was prematurely concluded after 3.6 years due to new information from other studies on the benefits of aspirin therapy, primarily in men.

All Participants (N=3,012 men; 2,583 women)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td>.56</td>
<td>.31-.99</td>
<td>NA</td>
</tr>
<tr>
<td>Combined endpoint*</td>
<td>.71</td>
<td>.48-1.04</td>
<td>NA</td>
</tr>
<tr>
<td>MI</td>
<td>.69</td>
<td>.38-1.23</td>
<td>NA</td>
</tr>
</tbody>
</table>

*cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

The results included in the report were not stratified by gender, but the authors state that the direction and size of the effects were similar in men and women. None of the findings were statistically significant, likely due to early termination of the trial. Participants in the aspirin group were more likely to report major bleeding (1.1 percent vs. 0.3 percent; p< .001).


The Hypertension Optimal Treatment (HOT) trial was a randomized trial among 18,790 persons with hypertension (8,883 women) aged 50-80 years, who were randomized to 75 mg/day of aspirin or placebo and followed for 3.8 years. The main outcome was major cardiovascular events (fatal and nonfatal stroke, MI and all other cardiovascular deaths).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Participants (N=18,790)</th>
<th>Women (N=8,883; 47%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mortality</td>
<td>.93</td>
<td>.79-1.09</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>.85</td>
<td>.73-.99</td>
</tr>
<tr>
<td>MI</td>
<td>.64</td>
<td>.49-.85</td>
</tr>
</tbody>
</table>

There was a 15 percent reduction in risk of cardiovascular events and a 35 percent reduction in risk of MI in all participants. Risk of death was reduced 7 percent, but this finding was not statistically significant. Among women, mortality was not decreased. Risk of cardiovascular events and of MI was reduced about 20 percent, but these findings were not statistically significant. The risk of fatal bleeding was not increased by aspirin therapy in men or women, but the risk of non-fatal major bleeding was increased in both genders (RR in men 1.6, p-value .01; RR in women 2.1, p-value .006).


The Nurses Health Study is a prospective cohort study of risk factors for various diseases. Between 1980 and 1986, 87,678 women aged 34 to 65 years were followed prospectively to determine the association between aspirin therapy (assumed dose 325 mg) and the risk of a cardiovascular event. The primary outcomes were nonfatal MI and CHD death.

The multivariate adjusted relative risks (RR) for cardiovascular events among women taking various numbers of aspirin per week compared to nonusers are as follows:

<table>
<thead>
<tr>
<th>Number of Aspirin per Week</th>
<th>1-6</th>
<th>7-14</th>
<th>&gt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Mortality</td>
<td>.86 (.72-1.03)</td>
<td>1.14 (.89-1.47)</td>
<td>.97 (.76-1.23)</td>
</tr>
<tr>
<td>Nonfatal MI and CHD Death</td>
<td>.75 (.58-.99)</td>
<td>1.20 (.84-1.69)</td>
<td>.89 (.63-1.27)</td>
</tr>
<tr>
<td>Stroke</td>
<td>.99 (.71-1.36)</td>
<td>.83 (.49-1.42)</td>
<td>1.20 (.79-1.83)</td>
</tr>
</tbody>
</table>

Low-dose aspirin (1 to 6 aspirin/week) reduced risk of CHD events about 25 percent and mortality about 15 percent, but higher doses were not associated with benefit and there was no reduction in risk of stroke.
Summary and Recommendations

For secondary prevention, there is good evidence from a systematic review of randomized trials\textsuperscript{27} that aspirin therapy reduces risk of cardiovascular events about 20 percent in women with coronary disease or women at high risk for CHD and that the reduction in risk appears to be similar in men and women. This result is supported by the findings of one clinical trial that included a large number of women\textsuperscript{28} and found about a 20 percent reduction in risk of cardiovascular events among women admitted to the hospital for suspected MI. However, the systematic review\textsuperscript{27} searched the literature only up to 1990, and the authors did not provide detailed information on dose, duration of treatment, subgroups of women (those with prior acute MI, distant MI, unstable angina, etc), specific outcomes in women (MI, stroke, cardiac death, etc) or on the effect of aspirin in low-risk women (primary prevention). The clinical trial\textsuperscript{28} provides evidence only for women admitted to the hospital with suspected MI. A more detailed and current systematic review of the data in women is feasible and might provide clinically important information.

Evidence that aspirin is beneficial for primary prevention of cardiovascular disease among women is weak. The systematic review by the Antiplatelet Trialists’ Collaboration\textsuperscript{27} identified multiple small trials that included about 20,000 persons at “low risk” for vascular events for whom aspirin would be considered primary preventive therapy. However, no information on the number of women in the low risk group or the effect of aspirin in low-risk women was provided. Evidence from the Hypertension Optimal Treatment trial\textsuperscript{31} among men and women with hypertension suggests that risk for cardiovascular events was reduced about 20 percent in women taking aspirin but total mortality was not reduced. A second large randomized trial included over 2,500 women,\textsuperscript{29} but the results were not stratified by gender and the trial was stopped prematurely providing inadequate power. A large, well-conducted prospective cohort study among women\textsuperscript{32} found that aspirin therapy reduced risk of CHD events about 25 percent, but the findings of this study are susceptible to bias due to the observational design. Definitive evidence may be available from the Women’s Health Study, a clinical trial that is currently on-going among 40,000 postmenopausal women randomized to 100 mg daily of aspirin versus placebo.

A systematic review of aspirin for primary prevention could provide important evidence, assuming that data stratified by gender could be obtained from earlier small trials, the Primary Prevention Project\textsuperscript{29} and the Hypertension Optimal Treatment trial.\textsuperscript{31} However, a systematic review should likely await the results of the on-going Women’s Health Study, a randomized trial of aspirin therapy among women that may be definitive.
2.02a Beta-blockers: secondary prevention

*Outpatient Treatment in Patients with Congestive Heart Failure (CHF)*


This *systematic review* summarized the results of two randomized controlled trials of the effect of beta-blockers on risk for mortality in persons with CHF. All participants in the Cardiac Insufficiency Bisoprolol Study (CIBIS) and CIBIS II had symptomatic heart failure (New York Heart Association class III or IV) and ejection fraction of less than 40 percent. Participants were randomized to receive up to 10 mg of bisoprolol or identical placebo. The primary outcome was mortality during a mean follow-up of 1.9 years (CIBIS) and 1.3 years (CIBIS II).

<table>
<thead>
<tr>
<th>All Participants (N=3,288)</th>
<th>Women (N=627; 19%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>RR</strong></td>
</tr>
<tr>
<td>Mortality</td>
<td>.71</td>
</tr>
</tbody>
</table>

There was a 30 percent reduction in risk of death among all participants assigned to beta-blockers compared to those assigned to placebo and a similar reduction in risk of death among women.

This study was rated fair quality because there was no systematic review of the literature and inclusion and exclusion criteria were not described.


The Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF) was a *randomized trial* that assessed the effect of metoprolol on CHF mortality. Participants had New York Heart Association class II-IV heart failure with ejection fraction 40 percent or lower and all received diuretics and ACE inhibitors. Participants were randomized to controlled release/extended release metoprolol (12.5 mg or 25 mg daily) or identical placebo. The primary outcome was mortality during a mean follow-up of one year.

<table>
<thead>
<tr>
<th>Men (N=3,093)</th>
<th>Women (N=898; 22%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>RR</strong></td>
</tr>
<tr>
<td>Mortality</td>
<td>.66</td>
</tr>
<tr>
<td>Mortality or hospitalization</td>
<td>.82</td>
</tr>
</tbody>
</table>
Women appeared to have a smaller reduction in mortality associated with beta-blocker treatment compared to men, but a similar reduction in mortality or hospitalization.

This manuscript also presents a systematic review of data from 3 large randomized trials of beta-blocker therapy for CHF: MERIT-HF (described above in F.2), CIBIS II (described in F.1) and the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS). COPERNICUS randomized 2,289 participants with symptomatic heart failure and an ejection fraction of less than 25 percent to carvedilol or placebo. Carvedilol dose was titrated from 3.125 mg to 25 mg twice daily and placebo was similarly titrated. Most participants were also taking diuretics, digoxin and angiotensin converting enzyme inhibitors. The average length of follow-up was 10.4 months.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Men (N=7,044)</th>
<th>Women (N=1,883)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR 95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Mortality</td>
<td>.66 .58-.75</td>
<td>NA</td>
</tr>
</tbody>
</table>

In these three trials, there was a statistically significant 30 percent reduction in the risk of mortality associated with beta-blocker treatment in both men and women with CHF. Although the types of beta-blockers used differed in the three trials, there was little evidence of an effect on outcome.

This manuscript was rated fair quality because there was no systematic review of the literature, inclusion and exclusion criteria were not defined and the statistical methods were inadequately described.

**Treatment in the Setting of Acute MI**


The Beta-Blocker Pooling Project is a systematic review that included double-blinded, placebo-controlled trials with 200 or more participants who were randomized to beta-blockers within 1 to 45 days after acute MI and followed for at least one year. Nine eligible trials were identified. Beta-blockers differed by trial, and drug doses were within the range for treatment of angina or hypertension. All trials were published by the end of 1983.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Participants (N=13,679)</th>
<th>Women (N=2,281; 17%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI p-value</td>
<td>OR 95% CI p-value</td>
</tr>
<tr>
<td>Mortality</td>
<td>.76 .66-.87 &lt;.0001</td>
<td>.81 NA .17</td>
</tr>
</tbody>
</table>
Treatment with beta-blockers after MI reduced risk of death by about 25 percent in all participants. The risk reduction was similar in women, but the findings were not statistically significant, likely due to the small number of women included. The test for homogeneity of outcomes indicated that the results of the trials were not consistent (p = .05), possibly due to differences in the beta-blockers studied.

This systematic review was categorized as fair quality based on the lack of information regarding the methods used, including inclusion criteria, search strategy and data abstraction.


This is a systematic review that includes outcomes from five large double-blind, placebo controlled randomized trials to assess the effect of treatment with metoprolol on mortality after MI. Randomization occurred 1 to 14 days after MI, with follow-up between 3 months and 3 years.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Participants (N=5,474)</th>
<th>Women (N=1,121; 20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>OR 95% CI p-value</td>
<td>OR 95% CI p-value</td>
</tr>
<tr>
<td></td>
<td>.81 NA .04</td>
<td>.77 NA NA</td>
</tr>
</tbody>
</table>

Mortality was reduced about 20 percent in all participants. The reduction in mortality was similar among women, but the finding was not statistically significant, likely due to the small number of women included. The ORs were not significantly different in men and women.

This systematic review was categorized as fair quality based on the lack of information regarding the methods used, including inclusion criteria, search strategy and data abstraction.

**2.02b Beta-blockers: primary prevention**

No systematic reviews or randomized trial that addressed the value of beta-blockers for primary prevention of CHD in women were identified.
Summary and Recommendations

Two small meta-analyses\textsuperscript{33} that included data from 4 large randomized trials found that treatment with beta-blockers reduced the risk of mortality by about 30 percent in both men and women with heart failure. There have been approximately 20 randomized trials of the effect of beta-blockers in persons with CHF. Many of these included a small proportion of women, but did not report results specific to women. Since 1996 there have been approximately eleven other systematic reviews of the effect of treatment with beta-blockers in persons with CHF; however, none has presented data specific to women. A systematic review of the CHF literature is feasible and could provide a more accurate estimate of the effect on mortality, assess other outcomes such as hospitalizations and adverse effects, and evaluate outcomes in subgroups of women, such as those with severe CHF.

Based on evidence from two systematic reviews,\textsuperscript{35,36} treatment with beta-blockers shortly after MI in women appears to decrease mortality 20 to 25 percent. However, neither of these reviews was good quality. Both are over 10 years old and provide no data on long-term beta-blocker treatment after MI. It would be useful to update these systematic reviews using currently accepted methodologic standards.

No data addressed the value of beta-blockers for primary prevention of CHD in women.

2.03a Angiotensin converting enzyme (ACE) inhibitors: secondary prevention

Outpatient Treatment in Patients with Congestive Heart Failure (CHF)


The Collaborative Group on ACE Inhibitor Trials is a systematic review of findings from 32 trials (1985-1994) evaluating the effect of angiotensin-converting enzyme (ACE) inhibitors on CHD mortality. All study participants had New York Heart Association class II or greater CHF. The minimum length of follow-up was eight weeks. Twelve trials followed participants for greater than three months.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Men (N=5,399)</th>
<th>Women (N=1,587; 23%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Mortality</td>
<td>.76 .65-.88</td>
<td>NA</td>
</tr>
<tr>
<td>Combined endpoint*</td>
<td>.63 .55-.73</td>
<td>NA</td>
</tr>
</tbody>
</table>

*mortality or hospitalization for CHF
Risk for mortality was reduced about 20 percent in both men and women and risk for mortality or hospitalization was reduced about 30 to 40 percent. However, the results in women were not statistically significant, likely due to the small sample size. The analyses were primarily based on trials with the ACE inhibitor enalapril, although studies with captopril, lisinopril, quinapril, and ramipril were also represented in this review.


The ACE-inhibitor Myocardial Infarction Collaborative Group provides a systematic review of randomized trials with 1,000 or more participants with left ventricular dysfunction or heart failure after acute myocardial infarction. The five trials included in the pooled analyses are Survival and Ventricular Enlargement (SAVE), Acute Infarction Ramipril Efficacy (AIRE), Tandolapril in Patients with Reduced Left-ventricular Function after Acute Myocardial Infarction (TRACE), Studies of Left Ventricular Dysfunction (SOLVD) treatment and SOLVD prevention. The trial outcomes were mortality, readmission for CHF, and reinfarction.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Men (N=10,367)</th>
<th>Women (N=2,396; 19%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>.79 (.72-.87)</td>
<td>.85 (.71-1.02)</td>
</tr>
<tr>
<td>Combined endpoint*</td>
<td>.71 (.65-.77)</td>
<td>.79 (.67-.93)</td>
</tr>
</tbody>
</table>

*mortality, readmission for CHF or MI

Risk for mortality was reduced about 20 percent in both men and women. The estimate in men was highly statistically significant, while the estimate in women was only borderline significant, likely due to the smaller sample size. Women also had a statistically significant 20 percent reduction in risk of the combined endpoint.

Outpatient Treatment in Persons at High Risk for Coronary Events


All three of these manuscripts are based on findings from the Heart Outcomes Prevention Evaluation (HOPE) trial, a randomized trial to evaluate the effects of ramipril 10 mg/day and vitamin E on cardiovascular outcomes (2x2 factorial design). The first manuscript (Yusuf, et al.) focuses on the main findings, the second (Dagenais et al.) on findings in subgroups at high risk and the third (Lonn et al.) on the results in women. All participants were older than age 55 years, and had vascular disease or diabetes plus one other cardiovascular risk factor, but not congestive heart failure. The trial was terminated after 4.5 years of follow-up due to a beneficial effect of ramipril on CHD outcomes.

### Risk for the combined endpoint of cardiovascular mortality, MI or stroke

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>All Participants (N=9,297)</th>
<th>Women (N=2,480; 27%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined endpoint*</td>
<td>RR 95% CI p-value</td>
<td>RR 95% CI p-value</td>
</tr>
<tr>
<td></td>
<td>.78 .70-.86 &lt;.001</td>
<td>.77 .62-.96 &lt;.05</td>
</tr>
<tr>
<td>MI</td>
<td>.80 .70-.90 &lt;.001</td>
<td>.89 .69-1.17 NA</td>
</tr>
</tbody>
</table>

*cardiovascular mortality, MI, or stroke

Risk for the combined endpoint of cardiovascular mortality, MI or stroke was statistically significantly reduced about 20 percent in all participants and in women. Risk for MI was also about 20 percent lower in all participants and 10 percent lower in women. This finding in women was not statistically significant, likely due to the smaller sample size and lower rate of MI in women (9.4 percent among women in the placebo group vs. 13.2 percent among men).

### Inpatient Treatment in the Setting of Probable Acute MI

**G.6.** Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation 1998;97(22):2202-12.

The ACE Inhibitor Myocardial Infarction Collaborative Group analysis provides a systematic review of four randomized trials (Cooperative New Scandinavian Enalapril Survival Study (Consensus-II), Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI-3), Second International Study of Infarct Survival (ISIS-4), Chinese Cardiac Study (CCS-1)) in which ACE inhibitor treatment was initiated within 36 hours after onset of symptoms of MI. The primary outcome was mortality after 30 days of therapy. All of the trials were conducted between 1990 and 1995. The four included trials studied the ACE inhibitors captopril, enalapril, and lisinopril.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Participants (N= 98,496)</th>
<th>Women (N=24,834; 25%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 30-days</td>
<td>OR 95% CI p-value</td>
<td>OR 95% CI p-value</td>
</tr>
<tr>
<td></td>
<td>.93 .89-.98 NA</td>
<td>.95 NA* NA</td>
</tr>
</tbody>
</table>

*Figure demonstrates that the 95 percent CI overlaps 1.0.
There was a statistically significant but small (7%) reduction in risk of 30-day mortality among all participants. The reduction in risk among women was similar, but not statistically significant, likely due to the smaller number of women studied. Two known side effects of ACE inhibitors, persistent hypotension and renal dysfunction, were also evaluated by gender.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>2.11</td>
<td>1.99-2.23</td>
<td>NA</td>
<td>1.97</td>
<td>1.80-2.15</td>
<td>NA</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>2.11</td>
<td>1.73-2.57</td>
<td>NA</td>
<td>1.57</td>
<td>1.14-2.17</td>
<td>NA</td>
</tr>
</tbody>
</table>

Risk for hypotension and for renal dysfunction was increased about 2-fold in both men and women.

**Randomized trials not included in the systematic reviews**


Between 1991 and 1993, the GISSI-3 randomized trial enrolled 19,394 patients from 200 Italian hospitals. Participants were randomized to lisinopril, nitrates, or open control (2x2 factorial design) within 24-hours after the onset of symptoms of acute MI. Participants assigned to lisinopril received an initial 5 mg dose, which was titrated to 10 mg daily for 6 weeks. The primary outcomes were assessed after 6 weeks and 6 months of follow-up. The short-term results were included in the systematic review described above. This manuscript presents the 6-month findings.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Participants (N=19,318)</th>
<th>Women (N=4,276; 22%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>.95 (NA)</td>
<td>.89 (NA)</td>
</tr>
<tr>
<td>Combined endpoint*</td>
<td>.92 (.86-.99)</td>
<td>.87 (.76-1.00)</td>
</tr>
</tbody>
</table>

* mortality and clinical CHF

At 6 months, there was no reduction in risk of mortality among all participants or in women. There was a statistically significant 10 percent reduction in risk of mortality and clinical CHF among all participants and among women. Among all participants, persistent hypotension and renal dysfunction were significantly more likely to occur on ACE inhibitor therapy compared to controls (OR for hypotension = 2.48: 95 percent CI , 2.09 – 2.93; OR for renal dysfunction = 2.15; 95 percent CI, 1.58 – 2.92).

This study was given a fair quality rating based on the lack of a placebo control group.
2.03b Angiotensin converting enzyme (ACE) inhibitors: primary prevention

No systematic review or randomized trial that addressed the value of ACE inhibitors for primary prevention of CHD in women was identified.

Summary and Recommendations

Among women with documented CHF, two good systematic reviews\textsuperscript{37, 38} suggest that outpatient treatment with ACE inhibitors reduces the risk of mortality 15 to 20 percent.

Results of the HOPE trial\textsuperscript{39-41} suggest that outpatient treatment of women with cardiovascular disease or with multiple risk factors results in about a 20 percent reduction in risk of cardiovascular events.

Based on the results of 4 large randomized trials, treatment with ACE inhibitors within 36 hours of acute MI is probably associated with about a 7 percent reduction in risk of mortality in the 30 days after MI, but this small benefit is associated with about a 2-fold increased risk of both hypotension and renal dysfunction.

New systematic reviews of these topics are feasible, but unlikely to provide additional information on use of ACE inhibitors in women.

No data addressed the value of ACE inhibitors for primary prevention of CHD in women.

2.04 Calcium channel blockers

There were no systematic reviews, randomized trials, or cohort studies identified for this topic.

2.05 Nitrates

\textit{Inpatient Treatment for Probable Acute MI}


Between 1991 and 1993, 19,394 patients (4,191 women) from 200 Italian hospitals were enrolled in the GISSI-3 randomized trial. Participants were randomized to lisinopril or nitrates or open control (2x2 factorial design) within 24 hours of the onset of acute MI symptoms. Participants assigned to nitrates received an intravenous infusion (glyceryl trinitrates) for 24 hours, followed by a transdermal patch (10 mg daily) or isosorbide
mononitrate (50 mg daily). Tolerance to the drug was minimized by removal of the transdermal patch for 10 hours each day. The primary outcomes measured after 6 weeks of therapy included all cause mortality and development of clinical CHF.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Participants (N=19,394)</th>
<th>Women (N=4,191; 22%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mortality</td>
<td>.94</td>
<td>.84-1.05</td>
</tr>
<tr>
<td>Mortality and CHF</td>
<td>.94</td>
<td>.87-1.02</td>
</tr>
</tbody>
</table>

Among all participants, treatment with nitrates did not result in lower risk for mortality or mortality and CHF. Among women, there appeared to be a trend to reduced risk, but differences in the outcomes between women and all participants are small, suggesting that the effect of treatment with nitrates in women is no different from the overall effect. Women assigned to nitrates were not at a significantly increased risk for persistent hypotension (OR = 1.07; 95% CI, .95 – 1.20).

This study was given a fair quality rating based on the lack of a placebo control group.


Between 1991 and 1993, 58,050 patients were enrolled in the ISIS-4 randomized trial within 24 hours of the onset of symptoms of an acute MI. Treatment interventions included oral captopril, oral mononitrates, and IV magnesium sulfate (2x2x2 factorial design). Participants were assigned to one month of oral controlled-release mononitrate therapy (30 mg initial dose titrated to 60 mg daily) or placebo. Total mortality was assessed after 5 weeks of therapy.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Participants (N=58,050)</th>
<th>Women (N=14,990; 26%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mortality</td>
<td>.97</td>
<td>.91-1.03</td>
</tr>
</tbody>
</table>

*RR and 95 percent CIs for the main outcome stratified by gender are presented only in a figure and are thus estimated for women.

Nitrate therapy did not reduce risk for mortality among all patients or among women. Differences in the outcomes in all participants compared to women are small, suggesting that the effect of treatment with nitrates in women is no different from the overall effect.
Participants receiving mononitrate therapy were at increased risk for profound hypotension, requiring termination of study treatment (8.1 percent for treatment versus 6.7 percent for placebo; p < .0001).


This follow-up report from the GISSI-3 randomized trial\textsuperscript{43} indicates that there were no additional benefits associated with nitrate therapy in all participants or in women after six months of follow-up.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Participants</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=19,394)</td>
<td>(N=4,191; 22%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mortality and CHF</td>
<td>.97</td>
<td>.90-1.04</td>
</tr>
</tbody>
</table>

This study was given a fair quality rating based on the lack of a placebo control group.

**Summary and Recommendations**

Good evidence from two randomized trials suggests that mortality in women is not reduced after MI by early treatment with nitrates. Further systematic review of the literature related to this question is unlikely to provide clinically useful information.

**2.06 Heparin**

There were no systematic reviews, randomized trials, or cohort studies identified for this topic.

**2.07. Glycoprotein IIb/IIIa Drugs**

*To Reduce Risk of Coronary Events in Patients Undergoing Percutaneous Coronary Intervention*

In this systematic review, results from three trials, Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC), Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade (EPILOG), Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) were pooled to assess the effect of treatment with abciximab on CHD outcomes. Between 1994 and 1998, 1,701 women and 4,824 men were randomized to abciximab or placebo. All participants were undergoing elective or urgent percutaneous coronary intervention. The maximum duration of treatment with abciximab was 12 hours. All participants received aspirin and heparin (either weight-adjusted standard dose or low dose heparin). The primary endpoint was a composite of death, MI and urgent revascularization at 6 weeks and 6 months. The main results are listed below:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=4,824)</td>
<td>(N=1,771; 37%)</td>
<td></td>
</tr>
<tr>
<td>Mortality, 1 year</td>
<td>OR .70</td>
<td>OR .62</td>
</tr>
<tr>
<td></td>
<td>95% CI NA</td>
<td>95% CI NA</td>
</tr>
<tr>
<td></td>
<td>p-value .06</td>
<td>p-value .03</td>
</tr>
<tr>
<td>Combined endpoint*</td>
<td>OR .51</td>
<td>OR .51</td>
</tr>
<tr>
<td></td>
<td>95% CI NA</td>
<td>95% CI NA</td>
</tr>
<tr>
<td></td>
<td>p-value .001</td>
<td>p-value .001</td>
</tr>
<tr>
<td>6 weeks</td>
<td>.51 NA</td>
<td>.51 NA</td>
</tr>
<tr>
<td></td>
<td>p-value .001</td>
<td>p-value .001</td>
</tr>
<tr>
<td>6 months</td>
<td>.59 NA</td>
<td>.62 NA</td>
</tr>
<tr>
<td></td>
<td>p-value &lt;.001</td>
<td>p-value .01</td>
</tr>
</tbody>
</table>

*death, MI and urgent revascularization

Mortality was about 40 percent in women who received IIb/IIIa inhibitors compared to those who received placebo. Risk for coronary events was reduced about 50 percent six weeks after treatment and about 40 percent six months after treatment. There were no statistical differences in the RRs for men and women.

The incidence of major bleeding was not higher in women or men treated with abciximab compared to those treated with placebo.

Our reviewers classified this systematic review as fair because it lacked information regarding inclusion criteria, search strategy, and data abstraction.

**To Reduce Risk of Coronary Events in Persons with Acute Coronary Syndromes**


This systematic review included all randomized trials that: 1) included persons admitted to the hospital with acute coronary syndromes but without persistent ST elevation on EKG; 2) compared a glycoprotein IIb/IIIa inhibitor with placebo or control; 3) recommended against early coronary revascularization during study drug infusion and 4) enrolled at least 1000 patients. Six trials were identified that fit the inclusion criteria (PRISM, PRISM-PLUS, PARAGON-A, PARAGON-B, PURSUIT, GUSTO-IV ACS)
and individual patient data were obtained from each. The six trials enrolled 31,402 participants (10,991 women) from 41 countries and used 4 different glycoprotein IIb/IIIa inhibitors. In all trials, glycoprotein IIb/IIIa inhibitors were started within 12 to 24 hours of onset of symptoms and continued for 48 to 120 hours. In most of the trials, all participants were treated with aspirin and standard dose heparin. Outcomes at 30 days are given below:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>.83</td>
<td>.71-.96</td>
<td>NA</td>
</tr>
<tr>
<td>Death or MI</td>
<td>.81</td>
<td>.75-.89</td>
<td>NA</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.6</td>
<td>1.3-2.0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Among treated men, mortality was reduced 17 percent and death or MI 19 percent at 30 days. Among women, risk for death or MI was increased 15 percent. Risk for major bleeding was increased about 2-fold in both genders. The difference in ORs for mortality and death or MI between men and women was highly statistically significant. There were multiple differences between men and women participants at baseline: on average, women were older, more likely to have diabetes, heart failure and ST depression on admission, less likely to have elevated CKMB concentrations and less likely to have had coronary revascularization or MI. However, sex differences in the effect of glycoprotein IIb/IIIa inhibitors remained after adjusting for these baseline differences. There was no interaction with level of CKMB, but both men and women with elevated baseline troponins (measured on only 34 percent of men and 37 percent of women) appeared to benefit from treatment with glycoprotein IIb/IIIa inhibitors while those without elevated troponins did not.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>.75</td>
<td>.55-1.04</td>
<td>NA</td>
</tr>
<tr>
<td>Death or MI</td>
<td>.82</td>
<td>.65-1.03</td>
<td>NA</td>
</tr>
</tbody>
</table>

Glycoprotein IIb/IIIa inhibitors increased major bleeding complications, and this increased risk appeared to be higher in women than in men. There was no increased risk for intracranial hemorrhage or stroke.

PRISM = Platelet Receptor Inhibition in Ischemic Syndrome Management; PRISM-PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; PARAGON = Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome events in a Global Organization Network; PURSUIT = Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression using Integrilin Therapy; GUSTO-IV ACS = Global Utilization of Strategies to Open Occluded Coronary Arteries Trial IV in Acute Coronary Syndromes
Summary and Recommendations

A fair-quality, relatively recent systematic review\textsuperscript{46} that included data from 3 large randomized trials of the effect of glycoprotein IIb/IIIa inhibitors in women undergoing percutaneous coronary interventions found a 40 to 50 percent reduction in risk of death, MI and urgent revascularization at 6 weeks to 6 months, and a 40 percent reduction in mortality at one year. There appears to be no difference in the effect of these drugs in men and women who are undergoing percutaneous coronary intervention.

Among women admitted to the hospital for acute coronary syndromes, the effect of glycoprotein IIb/IIIa inhibitor treatment is not clear. A good quality, recent systematic review\textsuperscript{47} that included data from 6 large randomized trials of the effect of glycoprotein IIb/IIIa inhibitors in women admitted to the hospital with acute coronary syndromes found that women did not benefit from treatment. The risk of mortality or MI was statistically significantly increased by 15 percent at 30 days of follow-up and there was a highly statistically significant interaction between gender and the effect of glycoprotein IIb/IIIa inhibitors. In a subset of about 1/3 of both men and women in whom troponins were elevated, treatment appeared to reduce risk of mortality about 20 to 25 percent in both men and women. However, these findings are not statistically significant, are based on subset analyses in women with elevated troponins, and there does not appear to be a similar benefit in women with elevated CPKs.

New systematic reviews of these topics are feasible, but are unlikely to add important clinical information.

2.08 Thrombolysis

Thrombolysis compared to placebo or control

G.1. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists’ (FTT) Collaborative Group. Lancet 1994;343(8893):311-22.\textsuperscript{48}

This systematic review includes pooled data from nine trials including 58,600 patients (13,855 women) hospitalized for suspected myocardial infarction or unstable angina. The trials included in this analysis were published between 1986 and 1993. Participants were randomized to receive fibrinolytic therapy with streptokinase, anistreplase, tissue plasminogen activator or urokinase versus open control or placebo. In most trials participants received both aspirin and heparin. The primary outcome was mortality during the first 35 days after treatment.
In both women and men, thrombolysis was associated with excess mortality on the first day of treatment, but a statistically significant 20 percent reduction in risk of mortality by 35 days after treatment. There were no statistically significant differences between the risk reductions observed for women and men. Because the absolute risk of mortality was higher for women than for men (5.5 percent vs. 3.2 percent in the control group on the first day of treatment and 16.0 percent vs. 10.1 percent by 35 days after treatment), the absolute risk during the first day was higher in women (7 vs. 1 per 1000) and the absolute benefit by 35 days greater than in men (27 vs. 20 per 1000). Mortality may have been higher in women than in men because the women were older and were more likely to have experienced a delay in treatment, both major risk factors for mortality.

The overall risks of stroke and major bleeding were increased similarly in both men and women and were highest during the first day of therapy.

**Thrombolysis compared to PTCA for acute MI**


The Primary Angioplasty in Myocardial Infarction (PAMI) trial was a randomized trial to compare CHD outcomes in participants with acute MI randomized to tissue plasminogen activator (100 mg) and subsequent conservative therapy or immediate PTCA. Between 1990 and 1992, 395 participants (107 women) were enrolled within 12 hours of onset of anginal symptoms. The primary outcome was in-hospital mortality and acute MI. Major findings comparing immediate PTCA to thrombolysis are as follows:
Mortality and risk of MI were lower among both men and women with symptoms of acute MI treated with immediate PTCA compared to those treated with tissue plasminogen activator. However, none of the outcomes were statistically significant, probably because the trial was too small.

No strokes occurred among either men or women in the PTCA group, while 2.8 percent of men and 5.3 percent of women experienced a stroke in the tissue plasminogen activator group. All of the strokes in women were hemorrhagic. Among patients assigned to tissue plasminogen activator, mortality in women was higher than in men (14.0 vs. 4 percent); there was no difference in mortality rates among women and men assigned to PTCA. At baseline, women were, on average, 8 years older than men and more likely to have diabetes, hypertension, history of CHF and had a longer interval of time between onset of symptoms and randomization. After multivariate adjustment for these risk factors, gender was no longer predictive of mortality with tissue plasminogen activator (p = .25).

This trial was rated fair quality because it was not blinded.

**Summary and Recommendations**

A systematic review of 9 large randomized trials\(^48\) demonstrates that thrombolysis reduces the risk of 5-week mortality in women and men hospitalized with suspected acute MI about 15 percent. Thrombolysis resulted in about a 50 percent increased risk of stroke and a nearly 3-fold increased risk of major bleeding in both men and women.

One small trial suggested that PTCA may be more effective than thrombolysis for reducing in-hospital mortality in women and much less likely to cause hemorrhagic stroke,\(^49\) but none of the relative risk estimates were statistically significant.

The systematic review is somewhat out of date. An updated review might be useful by providing more complete estimates for the effects of thrombolysis in women, but is unlikely to alter the major findings.

**2.09 Ticlopidine**

There were no systematic reviews, randomized trials, or cohort studies identified for this topic.
2.10 Clopidogrel

To Reduce Risk of Coronary Events in Persons with Acute Coronary Syndrome


The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study was a randomized trial to assess the effect of clopidogrel among persons with acute coronary syndromes (hospitalization for ischemic symptoms without ST-elevation). Between 1998 and 2000 12,562 patients (38 percent women) were randomized to clopidogrel (300mg loading dose, followed by 75mg/day) or placebo within 24-hours of the onset of acute coronary symptoms. Treatment continued for 3 to 12 months. All participants also received daily treatment with aspirin (75-325 mg). The primary outcome was death from cardiovascular causes, nonfatal MI, or stroke.

<table>
<thead>
<tr>
<th></th>
<th>All (N=12,562)</th>
<th>Women (N=4,836; 38%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>RR  95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Primary Events*</td>
<td>.80 .72-.90</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Death from cardiovascular causes, nonfatal MI, or stroke
**figure demonstrates that 95 percent CI crosses 1.0.

Among all participants, there was a highly statistically significant 20 percent reduction in risk of cardiovascular death, nonfatal MI or stroke among those assigned to clopidogrel. The reduction in risk was about 10 percent in women and was not statistically significant. The risk of a major bleeding was 38 percent higher for participants receiving clopidogrel (p = .001); however risks for life-threatening bleeding complications and hemorrhagic strokes were not increased.

To Reduce Risk of Coronary Events in Patients Undergoing Percutaneous Coronary Intervention


PCI-CURE is a randomized trial comparing the effect of extended treatment with clopidogrel among a subset of CURE participants who underwent percutaneous coronary intervention (PCI). All participants received open-label treatment with aspirin (75-325 mg/day) and were randomized to clopidogrel (300mg loading dose, followed by
75mg/day) or placebo within 24-hours of the onset of acute coronary symptoms. Those who underwent PCI had blinded study medication stopped and received 2-4 weeks of open label treatment after PCI with either clopidogrel or ticlopidine. They were then restarted on blinded study medication that continued for 3 to 12 months. Thus, the main comparison is between short-term treatment with clopidogrel or ticlopidine (2 to 4 weeks) after PCI compared to long-term treatment (3 to 12 months). The risk of death from cardiovascular causes, nonfatal MI, or stroke was assessed among 2,658 participants (30 percent women) who underwent PCI.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Event*</td>
<td>.70</td>
<td>.50-.97</td>
<td>.03</td>
<td>.77</td>
<td>.52-1.15</td>
<td>NA**</td>
</tr>
</tbody>
</table>

*Death from cardiovascular causes, nonfatal MI, or stroke
**figure demonstrates that 95 percent CI crosses 1.0.

In this subgroup analysis, risk for death from cardiovascular causes, nonfatal MI or stroke was statistically significantly reduced 30 percent among all participants. Among women, the risk reduction was about 20 percent and was not statistically significant. The risk of bleeding following PTCA was not increased by treatment with clopidogrel.

**Summary and Recommendations**

Results from the CURE trial suggest that 2 to 4 weeks of treatment with clopidogrel among women with acute coronary syndromes probably reduces risk of cardiovascular events and death about 10 to 20 percent. This benefit was associated with about a 40 percent increased risk of major bleeding, but risks for life-threatening bleeding complications and hemorrhagic stroke were not increased. Prolonged treatment (3 to 12 months) with clopidogrel among women undergoing percutaneous coronary intervention also appears to reduce risk of cardiovascular events and death about 20 to 30 percent more than brief treatment (2 to 4 weeks). However, these estimates of benefit are based only on the results of one trial, the effects in women were uniformly lower than in men, and the results were not statistically significant. Treatment with clopidogrel among persons undergoing PCI was not associated with serious adverse side effects.

A systematic review of the effect of clopidogrel on CHD outcomes in women is not feasible given that only one major randomized trial has been published.
2.11 Percutaneous transluminal coronary angioplasty (PTCA) and stenting

Angioplasty compared to medical management in patients with CHD


RITA-2 was a randomized trial to compare long-term CHD outcomes following PTCA to medical management in patients with CHD. Patients were required to have coronary disease that was suitable for either PTCA or medical management and a significant stenosis of at least one major coronary vessel that appeared technically amenable to PTCA. Participants were not required to have symptoms of angina. Between 1992 and 1996, 1,018 participants (183 women) were enrolled. The primary outcome was death plus nonfatal MI after an average of 2.7 years of follow-up. Major findings, comparing PTCA to medical management are presented below:

<table>
<thead>
<tr>
<th></th>
<th>All (N=1,018)</th>
<th>Women (N=183; 18%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>OR 95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.6 NA</td>
<td>.32</td>
</tr>
<tr>
<td>Death + nonfatal MI</td>
<td>1.9 1.08-3.41</td>
<td>.02</td>
</tr>
<tr>
<td>CABG</td>
<td>1.4 NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Among all patients, risk of death or nonfatal MI was 90 percent higher among those randomized to PTCA compared to those randomized to medical therapy. The authors state that there were no differences in the primary outcome by gender, but no quantitative estimates are given. Both men and women were less likely to experience grade 2 or worse angina (Canadian Cardiovascular Society) during the first six months following PTCA (in women: 22.8 percent PTCA versus 39.8 percent medical management, in men: 20.5 percent PTCA versus 31.4 percent medical management). However, these differences in prevalence of angina in the treatment groups were markedly attenuated over time such that there was no difference in prevalence of angina by 3 years of follow-up.

This trial was rated fair quality because it was not blinded.

Angioplasty compared to CABG for treatment of symptomatic multivessel coronary disease

The Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI) was an international randomized trial comparing CABG and PTCA for 1,054 patients with symptomatic multivessel coronary disease. Recruitment began in 1988 and continued for 53 months. The primary outcomes were angina (Canadian Cardiovascular Society class >1) and mortality after one year of follow-up. Major findings comparing PTCA to CABG are presented below:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All (N=1,054)</th>
<th>Women (N=234; 22%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR 95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.42 (.73-2.76)</td>
<td>.30</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1.42 (.80-2.54)</td>
<td>.23</td>
</tr>
<tr>
<td>Angina</td>
<td>1.54 (1.09-2.16)</td>
<td>.01</td>
</tr>
<tr>
<td>Revascularization</td>
<td>5.23 (3.9-7.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

For both genders combined there were no significant differences in risk of death or nonfatal MI between the CABG and PTCA groups. Overall, PTCA was associated with an increased risk for clinically significant angina and with a marked increased risk of undergoing another revascularization procedure within one year. Among women, the prevalence of angina after 1 year was 3-fold higher with PTCA compared to CABG. In contrast, men were about 50 percent more likely to experience angina after PTCA compared to CABG but this difference between men and women was not statistically significant (p for interaction = .052). Other risk estimates for women were not presented.

**Angioplasty compared to thrombolysis for acute MI**


The Primary Angioplasty in Myocardial Infarction (PAMI) trial was a randomized trial to compare CHD outcomes in participants with acute MI randomized to tissue plasminogen activator (100 mg) and subsequent conservative therapy or immediate PTCA. Between 1990 and 1992, 395 participants (107 women) were enrolled within 12 hours of the onset of anginal symptoms. The primary outcome was in-hospital mortality and acute MI. Major findings comparing immediate PTCA to thrombolysis are as follows:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Men (N=288)</th>
<th>Women (N=107; 27%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>.60 NA</td>
<td>.46</td>
</tr>
<tr>
<td>MI</td>
<td>.36 NA</td>
<td>.06</td>
</tr>
</tbody>
</table>
Mortality and risk of MI were lower among both men and women with symptoms of acute MI treated with immediate PTCA compared to those treated with tissue plasminogen activator. However, none of the outcomes were statistically significant, probably because the trial was too small.

No strokes occurred among either men or women in the PTCA group, while 2.8 percent of men and 5.3 percent of women experienced a stroke in the tissue plasminogen activator group. All of the strokes in women were hemorrhagic. Among patients assigned to tissue plasminogen activator, mortality in women was higher than in men (14.0 vs. 4 percent); there was no difference in mortality rates among women and men assigned to PTCA. At baseline women were, on average, 8 years older than men and more likely to have diabetes, hypertension, history of CHF, and had a longer interval of time between onset of symptoms and randomization. After multivariate adjustment for these risk factors, gender was no longer predictive of mortality with tissue plasminogen activator (p = .25).

This trial was rated fair quality because it was not blinded.

**Prospective Cohort Studies**

We reviewed eight prospective cohort studies that assessed the association between PTCA and CHD outcomes. The findings from these studies indicate that women are at higher risk than men for in-hospital mortality following PTCA. Possible explanations for this observation include older age, more severe underlying disease and anatomical differences, such as smaller vessel size and decreased body surface area, which may predispose women to an increased risk of death in the post-procedure period. Longer term clinical success rates following PTCA were also measured in several cohorts. In these studies, the main measure of clinical success was the probability of survival following PTCA (1 year to 10 years). Between 70 and 90 percent of all patients survived during this time interval. Survival rates did not differ by gender; however, women were as much as 78 percent more likely than men to experience symptoms of angina during long-term follow-up.


**Coronary stenting**

No studies were identified that provided data on the efficacy of coronary stenting to reduce risk of CHD events in women.

**Summary and Recommendations**

Evidence regarding the efficacy of PTCA to reduce the risk of CHD events in women is weak. For treatment of patients with symptomatic coronary artery disease who are suitable for PTCA or medical therapy, one small trial including only 183 women suggests that PTCA is more likely to result in death or nonfatal MI at 3 years than medical management, but no specific estimates were given for women. PTCA did appear to be superior to medical management for relief of angina in the first 6 months, but there was no difference in symptoms after 3 years of follow-up.

One trial, including only 234 women, suggested that CABG and PTCA have similar effects on risk for CHD events at one year after the procedure among women with symptomatic multivessel coronary disease. In women, PTCA was associated with 3-fold higher rates of angina at one year compared to CABG, but quantitative estimates among women for other outcomes were not given.

For treatment of patients during acute MI, one small trial including only 107 women suggested that PTCA may be more effective than thrombolysis for reducing in-hospital mortality in women (70 percent reduction) than in men (40 percent reduction), and much less likely to cause hemorrhagic stroke, but none of the relative risk estimates were statistically significant.
Whether PTCA is superior to medical management or CABG for management of CHD in women is very important and currently unanswered. However, there appears to be insufficient data to conduct a definitive systematic review of these questions.

2.12 Coronary artery bypass graft surgery

CABG surgery compared to medical therapy for treatment of symptomatic coronary disease


This is a prospective cohort study based on the Coronary Artery Surgery Study Registry of men and women with operable symptomatic coronary disease who were treated with either medical therapy or CABG surgery at one of 15 medical centers in the US between 1974 and 1979. The main outcomes were 8 and 15-year survival, based on 6,018 men and 1,095 women who were initially managed medically, and 6,922 men and 1,291 women who were initially managed surgically. Operative mortality was 2.5 percent among men and 5.3 percent among women (P<.0001). Multivariate adjusted relative risks for 8-year survival comparing medical management to CABG surgery are given below:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (N=12,940)</td>
<td></td>
<td></td>
<td></td>
<td>Women (N=2,386; 16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-year survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>single vessel disease</td>
<td>1.07</td>
<td>NA</td>
<td>&lt;.05</td>
<td>1.05</td>
<td>NA</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>double vessel disease</td>
<td>1.17</td>
<td>NA</td>
<td>&lt;.05</td>
<td>1.13</td>
<td>NA</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>triple vessel disease</td>
<td>1.41</td>
<td>NA</td>
<td>&gt;.05</td>
<td>1.56</td>
<td>NA</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

At 8 years, both men and women with double or triple vessel CHD appear to have improved survival, with the largest benefit in those with triple vessel disease. At 15 years, there were no differences between survival rates for medical and surgical management in either men or women, but 75 percent of all of the men and 72 percent of the women had undergone CABG surgery at 15 years.

CABG surgery compared to angioplasty for treatment of symptomatic multivessel coronary disease

The Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI) was an international randomized trial comparing CABG surgery and PTCA for 1,054 patients with symptomatic multivessel coronary disease. Participant recruitment began in 1988 and continued for 53 months. The primary outcomes were angina (Canadian Cardiovascular Society class >1) and mortality after one year of follow-up. Major findings comparing PTCA to CABG surgery are presented below:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All (N=1,054)</th>
<th>Women (N=234; 22%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.42</td>
<td>.73-2.76</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1.42</td>
<td>.80-2.54</td>
</tr>
<tr>
<td>Angina</td>
<td>1.54</td>
<td>1.09-2.16</td>
</tr>
<tr>
<td>Revascularization</td>
<td>5.23</td>
<td>3.9-7.0</td>
</tr>
</tbody>
</table>

For both genders combined there were no significant differences in risk of death or nonfatal MI between the CABG surgery and PTCA groups. Overall, PTCA was associated with an increased risk for clinically significant angina and with a marked increased risk of undergoing another revascularization procedure within one year. Among women, the prevalence of angina after 1 year was 3-fold higher with PTCA compared to CABG surgery. In contrast, men were about 50 percent more likely to experience angina after PTCA compared to CABG surgery, but this difference between men and women in effect of the procedures on angina was not statistically significant (p for interaction = .052). Other risk estimates were for women were not presented.


The Bypass Angioplasty Revascularization Investigation (BARI) was a randomized trial to assess the effect of CABG surgery compared to PTCA among 1,829 participants (489 women; 27 percent) with angina or myocardial ischemia and multivessel coronary disease amenable to both CABG surgery and PTCA. The average length of follow-up was 5 years.

Data from this article are difficult to interpret because only crude rates are presented. Relative risk estimates, confidence intervals and p-values were not provided. The authors note that the risk for in-hospital MI was significantly reduced among women who underwent PTCA compared to CABG surgery (4.8 vs. 9.8 percent; p=.03). In men, rates of in-hospital MI were also lower among those randomized to PTCA compared to CABG surgery (2.4 vs. 4.6 percent), but this comparison was presumably not statistically significant, as no p-value was given. No information on 5-year outcomes among women is presented.
Summary and Recommendations

Evidence regarding the efficacy of CABG surgery to reduce the risk of CHD events and death in women is limited. One large cohort study suggests that despite a high perioperative mortality rate (5.3 percent), 8-year survival is improved in women with double or triple vessel coronary disease who undergo CABG surgery compared to initial medical management. By 15 years of observation, the majority of women (72 percent) had undergone CABG surgery and there was no difference in long-term survival among those initially treated surgically compared to those initially treated medically. The results of this study may be biased by differences in risk between patients who are chosen to undergo CABG surgery compared to those chosen to receive medical therapy.

Randomized trials to compare the effectiveness of CABG surgery and PTCA provide little evidence regarding the relative effectiveness of these procedures in women. The Coronary Angioplasty versus Bypass Revascularisation Investigation suggests that neither revascularization procedure is superior with regard to mortality or CHD outcomes in women, but that CABG surgery is more effective than PTCA in relieving angina and is less likely to be followed by additional revascularization procedures.

Coronary artery bypass surgery is a major procedure that is associated with substantial perioperative morbidity, mortality and expense. It is not clear that a systematic review of the data regarding the efficacy of this procedure for preventing CHD events in women is feasible. However, this topic is very important given the potential benefits and risks of bypass surgery in women. Given this, we recommend that a systematic review be attempted. If data are inadequate to provide definitive answers, additional research should be conducted.
QUESTION 3

3. What are the risk factors for coronary heart disease in women, does modifying these risk factors result in reduced risk for coronary heart disease events, and what are the most effective methods for modifying these risk factors? (20 subtopics labeled 3.01-3.12 with subtopic as a risk factor for CHD or treatment/modification of a risk factor for CHD prevention considered separately where appropriate)

3.01 hypertension:
   a. as a risk factor
   b. treatment
3.02 diabetes
   a. as a risk factor
   b. treatment
3.03 hyperlipidemia (high LDL, triglycerides, Lp(a), low HDL)
   a. as a risk factor
   b. treatment
3.04 homocysteine
   a. as a risk factor
   b. treatment
3.05 C-reactive protein
   a. as a risk factor
   b. treatment
3.06 cigarette smoking
   a. as a risk factor
   b. smoking cessation
3.07 obesity
   a. as a risk factor
   b. weight reduction to reduce risk
3.08 inactivity
   a. as a risk factor
   b. exercise
3.09 age
3.10 age at menopause
3.11 ethnicity
3.12 socioeconomic status
3.01a Hypertension as a risk factor for CHD in women

We identified no systematic reviews that addressed the strength of hypertension as a risk factor for CHD outcomes in women.

Prospective Cohort Studies

Data from the Nurses’ Health Study\textsuperscript{62} and from the Framingham Heart Study\textsuperscript{63} suggest a 2 to 3-fold increased risk of coronary heart disease events among women with hypertension, after adjustment for other CHD risk factors. However, the evidence from these two studies is not convincing. In the Nurses’ Health Study,\textsuperscript{62} hypertension was self-reported and blood pressure was not measured. The report from the Framingham Heart Study\textsuperscript{63} provides no definition of hypertension and no confidence intervals or p-values for the reported risk estimates. Among women in the Copenhagen City Heart Study,\textsuperscript{64} isolated systolic hypertension (SBP ≥ 160 mm Hg and DBP < 90 mm Hg) was not associated with an increased risk of MI (RR = 0.8; 95% CI, 0.3 – 2.0), but women with diastolic hypertension (DBP > 90 mm Hg) were 1.7 times more likely than normotensive women to have a MI (95% CI, 1.1 – 2.8). In the Walnut Creek Cohort,\textsuperscript{65} the risk of all-cause mortality (excluding accidental death) was 1.6 times higher among premenopausal women with high blood pressure compared to those without. The risk of all-cause mortality was not significantly higher among postmenopausal women with high blood pressure compared to those without.


3.01b Treatment of hypertension to reduce risk of CHD events in women

Systematic Reviews


This systematic review from the Individual Data Analysis of Antihypertensive intervention trials (INDANA) pooled data from seven large randomized trials that studied the effect of treatment for hypertension on CVD outcomes. All trials were conducted between 1972 and 1990. Only trials that enrolled both men and women were included. Results from only 7 of 15 published clinical trials were included in this review, but these 7 trials represent 97 percent of all participants in the 15 trials. Drug interventions included thiazide diuretics and/or beta-blockers. The primary outcomes were fatal and nonfatal cardiovascular events among hypertensive men and women aged 30 to 84 years.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>.88</td>
<td>.80-.97</td>
<td>.01</td>
<td>.91</td>
<td>.81-1.01</td>
<td>.09</td>
</tr>
<tr>
<td>Fatal CHD events</td>
<td>.83</td>
<td>.71-.97</td>
<td>.02</td>
<td>.92</td>
<td>.74-1.16</td>
<td>.48</td>
</tr>
<tr>
<td>Major CHD events</td>
<td>.82</td>
<td>.73-.92</td>
<td>&lt;.001</td>
<td>.85</td>
<td>.72-1.01</td>
<td>.06</td>
</tr>
</tbody>
</table>

Among treated hypertensive men, there was a statistically significant 12 percent reduction in risk of mortality, a 17 percent reduction in risk of fatal CHD events, and an 18 percent reduction in risk of major coronary events. While none of the risk estimates in women were statistically significant, there were strong statistical trends suggesting that the patterns of risk reduction for mortality (9 percent reduction) and major coronary events (15 percent reduction) were similar to those in men. There was no evidence of an interaction between treatment effect and gender (p >.10).

This manuscript was given a fair quality rating because it did not describe the search or data abstraction methods.


This is a systematic review of the findings of 11 randomized trials that studied the effect of treatment for hypertension on risk for CVD events in women. Clinical trials were included if they met the following criteria: publication between 1966 and 1998, more than 100 women, hypertension was defined, the intervention was a drug, the control group received a placebo or standard care, and the outcomes included CVD events. CHD outcomes included all cause mortality, fatal CHD events and all CHD events (fatal and nonfatal). Interventions included diuretics, beta-blockers, calcium channel blockers, and clonidine. After adjustment for baseline risk factors, the findings were as follows.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Women 30-54 years (N=8,565)</th>
<th>Women ≥ 55 years (N=17,604)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mortality</td>
<td>.92</td>
<td>.68-2.79</td>
</tr>
<tr>
<td>Fatal CHD</td>
<td>1.47</td>
<td>.78-4.76</td>
</tr>
<tr>
<td>CHD events*</td>
<td>.80</td>
<td>.56-2.86</td>
</tr>
</tbody>
</table>

*fatal and nonfatal events

None of the effects of treatment were statistically significant. However, there were strong trends to reduced risk of mortality, fatal CHD and CHD events in older women. Among younger women, the pattern of risk reduction for mortality and CHD events was similar to that among women 55 or older, but the confidence intervals were much wider. There was no statistical evidence of an interaction between treatment effect and age.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>White Women (N=22,963)</th>
<th>African-American Women (N=3,206)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mortality</td>
<td>.98</td>
<td>.85-1.13</td>
</tr>
<tr>
<td>Fatal CHD</td>
<td>.95</td>
<td>.73-1.23</td>
</tr>
<tr>
<td>CHD events</td>
<td>.88</td>
<td>.72-1.08</td>
</tr>
</tbody>
</table>

Among white women, there was no evidence that treatment reduced risk. In contrast, treatment was associated with a 30 to 40 percent reduction in the risk of mortality and CHD events among African-American women. These risk reductions were statistically significant among African-American women, despite the relatively small number included in the trials. There was statistical evidence of interaction of the effects of treatment and race on total mortality (p =.003).
Randomized Trials Not Included in the Systematic Reviews


Syst-China was a randomized trial to test the effect of treatment for isolated systolic hypertension on CVD outcomes. Between 1988 and 1991, 2,394 persons age 60 or older (36 percent women) with systolic blood pressures between 160 and 219 mm Hg, were randomized to active treatment (nitrendipine plus captopril, and/or hyrochlorothiazide) or placebo. The median follow-up time was 3 years.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR (N=1,541)</th>
<th>95% CI</th>
<th>P-value</th>
<th>RR (N=853)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>.74</td>
<td>.50-1.09</td>
<td>.12</td>
<td>.34</td>
<td>.16-.72</td>
<td>.005</td>
</tr>
</tbody>
</table>

The treatment-by-sex interaction approached statistical significance (p = .06), indicating that the mortality benefit associated with treatment of isolated systolic hypertension may be greater in women than in men.

Summary and Recommendations

Hypertension as a Risk Factor for CHD in Women

Results of four large cohort studies62-65 suggest that hypertension, especially diastolic hypertension, is associated with a 1.6 to 3-fold increased risk for coronary heart disease events in women. Substantial additional data regarding the association of high blood pressure and CHD outcomes in women could likely be obtained from the placebo groups followed in large clinical trials of treatment for hypertension. Based on these data, a systematic review and meta-analysis would likely be feasible. Summary estimates of the effect of blood pressure on CHD risk could be important in helping to identify the women who are most likely to benefit from therapy.

Treatment of Hypertension to Reduce Risk of CHD Events in Women

The best evidence regarding the effect of treatment of hypertension on risk for CHD events among women comes from two systematic reviews. The systematic review by the INDANA investigators66 suggests that treatment of hypertension in women results in small reductions in risk of mortality (9 percent) and CHD events (15 percent), but the findings were not statistically significant. The systematic review by Quan et al.67 found
strong statistical trends to reduced risk of mortality (11 percent), fatal CHD events (16 percent) and all CHD events (18 percent) among women over age 55 years, but not among younger women. These differences between younger and older women may be due to the small number of events that occurred in younger women. The systematic review by Quan et al.\textsuperscript{67} also provides the only evidence regarding treatment of hypertension in women by race. Although relatively few black women were included in the trials, they experienced a statistically significant reduction in risk of mortality (41 percent) and of CHD events (39 percent). There was no evidence of benefit among white women, and there was statistical evidence that the effect of treatment on mortality differed in white and black women. The findings of the Syst-China trial\textsuperscript{69} suggest that treatment of isolated systolic hypertension may reduce the risk of mortality by as much as 65 percent in elderly Chinese women. The reason for this difference in the effect of treatment of hypertension between races is not clear. Repeating the two relatively recent systematic reviews is unlikely to add additional clinical information.

### 3.02a Diabetes as a risk factor for CHD in women

#### Systematic Reviews


This is a systematic review of the results from 12 prospective cohort studies published between 1980 and 1993 that address the association between non-insulin dependent diabetes and CHD events in men and women. Diabetes was defined by glucose tolerance testing, medication use, or medical history. The main outcomes were CHD death and MI. Follow-up ranged from 2 to 30 years. The authors did not calculate summary estimates comparing risk for CHD death among diabetic and nondiabetic men and women. Instead, they calculated a summary relative risk comparing the risk for CHD events among women to that among men.

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td>1.47</td>
<td>1.09-1.99</td>
</tr>
<tr>
<td>Nondiabetics</td>
<td>2.52</td>
<td>1.91-3.34</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td>1.75</td>
<td>1.23-2.49</td>
</tr>
<tr>
<td>Nondiabetics</td>
<td>1.92</td>
<td>1.36-2.79</td>
</tr>
</tbody>
</table>
The findings suggest that men diabetics and non-diabetics have a higher risk for CHD events than women. The increased risk associated with male sex is about 2 to 2.5-fold for nondiabetics, but only 1.5 to 2-fold for diabetics. The narrowing of the male disadvantage with respect to CHD risk suggests that diabetes is a stronger risk factor for CHD in women than in men. These findings are limited because the outcomes of the individual studies were not adjusted for other predictors of CHD events, and there was significant between-study heterogeneity of the findings.

This study was rated fair quality based on the lack of a systematic literature search.


This is a systematic review of 10 prospective cohort studies published between 1966 and 1999 evaluating the association between diabetes and CHD risk. The criteria for inclusion were prospective cohort studies that provided data on the risk of CHD events in both men and women with diabetes. Diabetes was diagnosed by self-report, physician diagnosis, treatment with insulin or oral hypoglycemic agents, or random or fasting glucose measures. The primary outcome was CHD mortality. Follow-up time ranged from 4 to 36 years.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR* 95% CI p-value</td>
<td>RR* 95% CI p-value</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.85 1.47-2.33 NA</td>
<td>2.58 2.05-3.26 NA</td>
</tr>
</tbody>
</table>

*summary RR comparing risk for CHD death among diabetics to nondiabetics

These results suggest that risk for CHD death is increased 2.6-fold in diabetic women compared to nondiabetic women and 1.8-fold in diabetic men compared to nondiabetic men. While many of the individual studies provided outcomes adjusted for other predictors of CHD risk, the meta-analytic techniques used to calculate summary estimates included only unadjusted estimates.

**Cohort Studies Not Included in the Systematic Reviews**

We reviewed data from four cohort studies, including the Framingham Heart Study and the Nurses Health Study. The findings suggest that diabetes is associated with a 1.5 to 3-fold increased risk of CHD events in women after adjustment for other risk factors. The relative risk of CHD events among women with diabetes appears to be almost twice that of men with diabetes. However, there is considerable variation in the levels of other CHD risk factors among men and women in these studies making evaluations of gender differences difficult.
3.02b Treatment of diabetes to reduce risk of CHD events in women

There were no systematic reviews or randomized trials identified that addressed the effectiveness of treatment of diabetes to reduce risk of CHD events in women.

Summary and Recommendations

Diabetes as a Risk Factor for CHD in Women

The systematic review by Orchard et al. suggests that the relative risk for CHD events is higher among women than among men diabetics, but does not provide an estimate of the summary relative risk in women. The systematic review by Lee et al. reported that risk for CHD death was about 2.6-fold higher among women diabetics compared to non-diabetics. This increase in risk appears to be higher than that associated with diabetes in men (1.8-fold increased risk). One explanation for the higher risk among women than among men diabetics is that diabetes is, by mechanisms that are not clear, more harmful in women than in men. Alternatively, women diabetics may be more likely to have other CHD risk factors, or more severe CHD risk factors than men diabetics. The summary estimates calculated by Lee et al. were based on unadjusted findings and do not address this issue. In addition, the systematic review by Lee et al. does not include the results.
from several studies that were analyzed in the earlier systematic review by Orchard et al.\textsuperscript{70} It is feasible to update these systematic reviews and to calculate comparable, adjusted relative risk estimates in men and women diabetics. An adjusted analysis may provide clinically and scientifically important evidence to determine if diabetes has more harmful effects on CHD risk in women or is more likely to be associated with other risk factors in women.

Treatment of Diabetes to Reduce Risk of CHD Events in Women

There was no evidence regarding the efficacy of treatment of diabetes to reduce the risk of CHD events in women.

3.03.a Hyperlipidemia as a risk factor for CHD in women

Total, LDL- and HDL-cholesterol, and triglycerides


This systematic review includes the findings of 22 United States (US) and international cohort studies presented at a workshop at the National Heart Lung and Blood Institute in 1991. Inclusion criteria were measurement of serum cholesterol, follow-up for CHD events, explicit criteria for CHD outcomes and availability of results stratified by gender, age and ethnicity. The review includes 90,349 women, 891,882 men, and data stratified by ethnicity among approximately 348,600 men who were screened for the Multiple Risk Factor Intervention Trial (MRFIT) (316,000 white, 22,000 black, 6,600 Hispanic and 4,000 Asian men). Findings were summarized separately by gender, age at the time of lipid measurements (less than 65 years versus 65 years and older) and, where possible, ethnicity. The majority of the participants in these studies did not have CHD at the beginning of the study, but had either elevated cholesterol or other risk factors for CHD. Unadjusted relative risks for CHD mortality were summarized.
### Summary Relative Risk (95% CI)

<table>
<thead>
<tr>
<th>Sex and Age</th>
<th>Total Cholesterol*</th>
<th>LDL-C*</th>
<th>HDL-C*</th>
<th>Triglycerides*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>2.44†</td>
<td>3.27†</td>
<td>2.13†</td>
<td>1.98†</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>1.12</td>
<td>1.13</td>
<td>1.75†</td>
<td>1.39†</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>1.73†</td>
<td>1.92†</td>
<td>2.31†</td>
<td>1.16†</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>1.32†</td>
<td>1.51†</td>
<td>1.09</td>
<td>1.24†</td>
</tr>
</tbody>
</table>

*RR compares those with total cholesterol <200 to ≥ 240 mg/dL; those with LDL-cholesterol <140 to ≥ 160 mg/dL, those with HDL-cholesterol ≥ 60mg/dL to < 50, and those with triglycerides < 100 mg/dL to ≥ 130 mg/dL.

† p<.05 for unadjusted comparisons

For women less than 65 years old, risk for CHD death increased with higher total cholesterol, LDL-C and triglycerides and with lower HDL-C. For women and men less than 65 years old, the increased relative risk associated with elevated total cholesterol, LDL-C and triglycerides was higher for women than for men, while the increased risk associated with low HDL-C was similar. Among older men, CHD mortality was increased with higher total cholesterol, LDL-C and triglycerides, but not with lower HDL-C. Among older women, only low HDL-C and high triglycerides were associated with increased risk.

No specific risk estimates were given for minority populations, but relative risks associated with elevated total cholesterol were said to be similar for white, black, Hispanic and Asian middle-aged and older men based on data from the MRFIT screenees.

This study was rated as fair because it did not provide information on how the cohorts included were identified or selected for inclusion. In addition, the summary estimates may be biased because the comparisons are not adjusted for potential confounding factors.


This systematic review includes the findings of 11 US and international cohort studies presented at a workshop at the National Heart Lung and Blood Institute in 1992. The purpose of this workshop was to investigate the association of low blood cholesterol and risk for non-cardiovascular death. Inclusion criteria were not stated. The review includes 124,814 women and 523,737 men, most of whom did not have CVD at the start of the studies. The main outcomes were death, CVD death, cancer death, and non-CVD, non-cancer death. When possible, adjusted outcomes from each individual cohort were used.
to calculate the summary estimates. Results for the men included in the MRFIT screenees were presented separately because they constituted 67 percent of the population.

<table>
<thead>
<tr>
<th>Total Cholesterol (mg/dL)</th>
<th>All death</th>
<th>CVD death</th>
<th>Cancer death</th>
<th>Non-CVD, non-cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;160</td>
<td>1.17†</td>
<td>1.04</td>
<td>1.18†</td>
<td>1.32†</td>
</tr>
<tr>
<td>160-199</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>200-239</td>
<td>1.14†</td>
<td>1.16†</td>
<td>.95</td>
<td>0.89†</td>
</tr>
<tr>
<td>&gt;240</td>
<td></td>
<td>1.48†</td>
<td>.95</td>
<td>0.87†</td>
</tr>
<tr>
<td><strong>MRFIT MEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;160</td>
<td>1.17†</td>
<td>0.89</td>
<td>1.23†</td>
<td>1.48†</td>
</tr>
<tr>
<td>160-199</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>200-239</td>
<td>1.05†</td>
<td>1.31†</td>
<td>.95</td>
<td>0.87†</td>
</tr>
<tr>
<td>&gt;240</td>
<td>1.22†</td>
<td>1.86†</td>
<td>.91†</td>
<td>0.84†</td>
</tr>
<tr>
<td><strong>WOMEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;160</td>
<td>1.10</td>
<td>0.96</td>
<td>1.05</td>
<td>1.41†</td>
</tr>
<tr>
<td>160-199</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>200-239</td>
<td>0.94</td>
<td>0.95</td>
<td>1.01</td>
<td>0.92</td>
</tr>
<tr>
<td>&gt;240</td>
<td>0.97</td>
<td>1.09</td>
<td>0.97</td>
<td>0.82†</td>
</tr>
</tbody>
</table>

*comparing total cholesterol of 160-199 mg/dL to the other categories and excluding deaths that occurred in the first 5 years of follow-up
† p-value less than .05

Among men, risk for death was increased 15 to 20 percent and risk for CVD death was increased 50 to 80 percent among those with total cholesterol >240 mg/dL. Among men with cholesterol <160 mg/dL, risk for cancer death was increased about 20 percent and risk for non-CVD, non-cancer death was increased 30 to 50 percent. There were no statistically significant associations between total cholesterol levels and any cause of death among women, except that risk for non-CVD, non-cancer death was increased among women with cholesterol levels <160mg/dL.

This study was rated as fair because it did not provide information on how the cohorts included were identified or selected for inclusion.

These two manuscripts report the results of a systematic review of population-based international studies, published between 1965 and 1994, that assessed the correlation between triglyceride levels and risk for CVD (CVD death, CHD death, and MI). Inclusion criteria were prospective cohort design, population-based sampling, and a fasting triglyceride measurement. Seventeen studies provided data on men (N=46,413), with an average duration of follow-up of 8.4 years. Five studies provided data on women (N=10,864), with average duration of follow-up of 11.4 years. Six studies with men (N=22,293) and two studies with women (N = 6,345) provided risk estimates adjusted for other potential confounders, including HDL-cholesterol level. Most participants in these studies did not have CVD at the start of the studies.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Men (N=46,413/22,293)</th>
<th>Women (N=10,864; 19%/6,345; 22%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR* 95% CI p-value</td>
<td>OR* 95% CI p-value</td>
</tr>
<tr>
<td>CVD events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>unadjusted</td>
<td>1.32 1.26-1.39 NA</td>
<td>1.76 1.50-2.07 NA</td>
</tr>
<tr>
<td>adjusted</td>
<td>1.14 1.05-1.28 NA</td>
<td>1.37 1.13-1.66 NA</td>
</tr>
</tbody>
</table>

*per 1 mmol/L increase in triglyceride level

Risk of CVD events among men and women was correlated with triglyceride levels. The increased cardiovascular risk associated with elevated triglycerides appeared to be higher in women (about 40 percent increase in CVD risk per 1 mmol/L increase in triglyceride level) compared to men (about 15 percent increase per 1 mmol/L increase in triglyceride level).

**Lipoprotein (a)**


This is a systematic review of observational studies on the association between lipoprotein (a) (Lp(a)) and risk for CHD. The articles in this review were published between 1991 and 1997, and included persons without known CHD. The average length of follow-up was between 1 and 15 years. The outcomes were fatal and nonfatal CHD. The 12 cohort and nested case-control studies included in this review included 11,105 men. Three studies provided data on women (N = 547). The summary outcome was expressed as the ratio of Lp(a) level in mg/dL among cases and controls.

The overall association between Lp(a) and risk of ischemic heart disease was similar for males and females (case:control ratio = 1.42; 95% CI 1.21 – 1.63 in men, and case:control ratio = 1.32; 95% CI 1.19 – 1.45 in women). Adjustment for age, blood pressure, body mass index, smoking, and lipoprotein-related variables did not modify the significance of this relation. However, there was considerable between-study variability.
in Lp(a) case:control ratios (p for heterogeneity < .001). Among women, the dose response relation between Lp(a) and ischemic heart disease was equivocal.

This study was rated fair quality because it did not describe the inclusion criteria or methods for independent data abstraction.

3.03b Treatment of hyperlipidemia to reduce risk of CHD events in women


Primary and secondary prevention trials published between 1971 and 1994 were included in this systematic review of the effectiveness of interventions to lower cholesterol in women. The outcomes were total and CHD mortality. The authors identified three primary prevention trials and six secondary prevention trials. However, only two of the primary prevention trials, and three of the secondary prevention trials, included adequate data for inclusion in the meta-analyses. Interventions studied in the two primary prevention trials included low-saturated fat diet and colestipol. The interventions included in the three secondary prevention trials included clofibrate and simvastatin. Summary estimates of relative risks were calculated using standard meta-analytic methods.

<table>
<thead>
<tr>
<th></th>
<th>Primary Prevention (N=5,848)</th>
<th>Secondary Prevention (N=1,048)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.15</td>
<td>.90-1.46</td>
</tr>
<tr>
<td>CHD Mortality</td>
<td>1.03</td>
<td>.62-1.70</td>
</tr>
</tbody>
</table>

For primary prevention, there was no effect of treatment on CHD or total mortality. Given the small number of outcome events, there may have been inadequate power to detect differences. Also, two of the primary prevention trials were conducted in institutionalized populations that may not be representative of healthy women. For secondary prevention, there was a statistically significant 64 percent reduction in risk of CHD mortality among treated women, but no reduction in overall mortality.

This study was rated fair quality because it did not describe inclusion criteria or a blinded review of the findings.

This is a systematic review of the data from four randomized, blinded, placebo controlled trials using pravastatin for reduction of cholesterol among persons with CHD and mildly to moderately elevated cholesterol. Outcomes were mortality and MI.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>.54</td>
<td>.25-.109</td>
<td>.17</td>
<td>NA</td>
<td>NANA</td>
<td>NA</td>
</tr>
<tr>
<td>MI</td>
<td>.48</td>
<td>.20-.63</td>
<td>.001</td>
<td>NA</td>
<td>NA.04</td>
<td></td>
</tr>
</tbody>
</table>

Only 4 MIs occurred among the women assigned to pravastatin and none in the placebo group. Thus, these 4 randomized trials of pravastatin provide no information on the effect of lipid-lowering in women.

This review was rated fair quality because it did not provide a clear description of search methods, inclusion criteria or methods for extracting data.


This is a systematic review of lipid intervention trials. All trials were published between 1971 and 1994. Among the seven primary and secondary prevention trials included in the review, interventions were diet, clofibrate, colestipol, simvastatin, pravastatin, and ileal bypass surgery. Primary and secondary prevention trials were not analyzed separately.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>.81</td>
<td>.67-.98</td>
<td>.03</td>
<td>.89</td>
<td>.60-1.32</td>
<td>.56</td>
</tr>
</tbody>
</table>

The findings suggested a 20 percent reduction in risk of mortality among men treated with cholesterol-lowering interventions, but no benefit in women.

The results from the Program On Surgical Control of the Hyperlipidemias (POSCH) were also presented in this report. Treatment with partial ileal bypass surgery in women did not reduce the risk of overall mortality, CHD mortality, or CHD events (CHD mortality or
nonfatal MI). In contrast, risk of CHD death and CHD death or nonfatal MI were significantly reduced among men in the surgical intervention group.

This review was rated fair quality because it did not provide a clear description of methods for searching or extracting data from identified studies.


This is a systematic review of five clinical trials published between 1966 and 1998 on the effect of statin therapy on CHD risk. The criteria for inclusion were: treatment with statin drugs or placebo, at least 4 years of follow-up and clinical disease or death as the primary endpoint. The review included three secondary prevention trials (4S, CARE, LIPID) and two primary prevention trials (WOSCOPS and AFCAPS/TEXCAPS). Standard meta-analytic methods were used to calculate the following summary estimates.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All (N=30,817)</th>
<th>Women (N=3,916;13%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Mortality</td>
<td>.79</td>
<td>.72-.86</td>
</tr>
<tr>
<td>Major CHD events</td>
<td>.69</td>
<td>.64-.74</td>
</tr>
</tbody>
</table>

Results were not stratified by primary and secondary prevention. There was about a 30 percent reduction in risk of major CHD events in all participants and in women treated with statins. Risk for total mortality was decreased in men treated with statins, but no data regarding total mortality in women was provided, probably because the number of women studied was relatively small.

4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events trial; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; WOSCOPS = West of Scotland Coronary Prevention Study; AFCAPS/TEXCAPS = Air Force/Texas Coronary Artherosclerosis Prevention Study

**Clinical Trials Not Included in the Systematic Reviews**


This manuscript provides additional data on women included in the Scandinavian Simvastatin Survival Study (4S). Main findings of the 4S were included in each of the three systematic reviews described above. 4S was a randomized trial that studied the effect of treatment with simvastatin on the risk of coronary events in persons with CHD. Between 1988 and 1989, 4,444 high-risk patients (827 women) from 94 clinical centers were randomized to simvastatin or placebo. All participants (age 35 – 70 years) had a
history of angina pectoris or myocardial infarction, and elevated serum cholesterol. The treatments were titrated between 10 mg and 40 mg, to achieve the goal LDL-cholesterol levels of 115-200 mg/dL. Outcomes were total mortality and major coronary events (coronary death, nonfatal definite or probable MI, silent MI or resuscitated cardiac arrest). The trial was stopped prematurely after a mean follow-up of 5.4 years, due to evidence of benefit with treatment.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=3,617)</td>
<td>(N=827; 19%)</td>
</tr>
<tr>
<td>RR* 95% CI p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>.65 .53-.80 &lt;.001</td>
<td>1.16 .68-1.99 .58</td>
</tr>
<tr>
<td>CHD death</td>
<td>.55 .43-.71 &lt;.001</td>
<td>.86 .42-1.74 .67</td>
</tr>
<tr>
<td>Major CHD events</td>
<td>.66 .58-.75 &lt;.001</td>
<td>.66 .48-.91 .01</td>
</tr>
</tbody>
</table>

Both men and women had a statistically significant 34 percent reduction in risk of major CHD events. However, men also had a statistically significant 35 to 45 percent reduction in risk of CHD death and total mortality. Similar benefits were not observed in women. The interaction between treatment and gender for the mortality outcome was not statistically significant. Overall, there was no difference between the treatment groups in other causes of death or side effects.


The MRC/BHF Heart Protection Study was a randomized trial to assess the effect of cholesterol-lowering on CHD outcomes. Between 1994 and 1997, 20,536 participants (5082 women) with known CHD, other occlusive arterial disease or diabetes were randomly assigned to simvastatin (40 mg daily) or identical placebo. The average length of follow-up was 5 years.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=20,536)</td>
<td>(N=5,082; 25%)</td>
</tr>
<tr>
<td>RR 95% CI P-Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>.87 .81-.94 .0003</td>
<td>.81 NA NA**</td>
</tr>
<tr>
<td>Major vascular event*</td>
<td>.76 .72-.81 &lt;.001</td>
<td>.81 NA NA**</td>
</tr>
</tbody>
</table>

*Coronary death, nonfatal MI, stroke, coronary or non-coronary revascularization
**figure demonstrates that 95% CI does not cross 1.0.

The findings from this study indicate that, among men and women with known CHD or at high risk for CHD, treatment with simvastatin significantly lowers cardiovascular event rates by approximately 25 percent, regardless of pretreatment cholesterol levels. The risk of myopathy associated with treatment was about 0.01 percent.
Summary and Recommendations

Hyperlipidemia as a Risk Factor for CHD in Women

Evidence regarding the association of abnormal lipoprotein levels and CHD risk in women is inconclusive. The systematic review by Manolio et al.\(^7^9\) suggests that the pattern of risk associated with hyperlipidemia in middle-aged women is similar to that for middle-aged men (increased risk for CHD mortality with higher total cholesterol, LDL-C and triglycerides, and with lower HDL-C). However, the pattern of risk among older women appears to be different than in men (i.e., CHD risk was increased among older men with higher total cholesterol and LDL-C, but not in older women). In addition, CHD risk was increased among older women with low HDL-C and high triglycerides, but not among older men with these lipid abnormalities. There are several limitations to the review by Manolio et al.,\(^7^9\) including an outdated and incomplete literature search and the lack of adjusted results. Evidence provided by the systematic review by Jacobs et al.\(^8^0\) is not very helpful, as summary data was provided only for total cholesterol levels. The systematic review by Hokanson, et al.\(^8^1\) and Austin et al.\(^8^2\) strongly suggests that elevated triglyceride level is a risk factor for CVD, and that this elevated risk is higher in women than in men.

The suggestion that the pattern of risk associated with lipoprotein abnormalities in women is different than in men could be clinically important. This is especially true because statins, which are the most widely used lipid-lowering drugs, primarily reduce LDL-cholesterol. If elevated LDL-C is a weaker risk factor in women than low HDL-C, these drugs may be less effective for lowering risk in women than in men. A systematic review of the literature to address the association of lipoproteins and risk for CHD in women is feasible and would likely contribute important clinical information.

Treatment of Hyperlipidemia to Reduce Risk of CHD Events in Women

The best evidence concerning the effect of lipid-lowering on CHD risk in women is provided by the systematic review by LaRosa et al.\(^8^7\). Both women and men with hypercholesterolemia had a 30 percent reduction in risk of major CHD events. Men also experienced a 20 percent reduction in total mortality. The effect on total mortality in women was not provided, perhaps because only 13 percent of the participants in the five trials reviewed were women. A recent large randomized trial\(^8^9\) among persons with CHD or at high risk for CHD found that treatment with simvastatin reduced risk of major vascular events about 25 percent in both men and women, regardless of cholesterol level.

The review by LaRosa et al.\(^8^7\) included only clinical trials of statin drugs for lipid-lowering, only one quantitative estimate of the effect of lipid lowering on risk for CHD events in women and no separate assessments of the effectiveness for primary and secondary prevention. A systematic review focused on the effects of lipid-lowering in women could provide important clinical information.
3.04a Homocysteine as a risk factor for CHD in women

Systematic Reviews


In this systematic review, standard methods were used to determine the association between homocysteine and risk for CVD events. Overall, 27 observational studies were identified that fulfilled the inclusion criteria of providing data on the association of serum homocysteine level and risk for vascular disease. Nine of the 27 included studies were considered high quality because they were prospective cohorts or population-based case-control studies. Coronary disease was defined as fatal and nonfatal MI and angiographically confirmed occlusion of at least one major coronary artery. Only three studies provided data on women. Assuming a linear relation between homocysteine and outcomes, the summary odds ratios, based on a 5 $\mu$mol/L increase in homocysteine are given below:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All (N=NA)</th>
<th>Women (N=NA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>CHD events</td>
<td>1.7</td>
<td>1.5-1.9</td>
</tr>
</tbody>
</table>

Each 5 $\mu$mol/L increase in serum homocysteine level was associated with a 70 percent increased risk of CHD events among all participants and an 80 percent increased risk of CHD events in women.

This article was rated fair quality based on lack of information regarding analysis methods.

3.04b Treatment to reduce homocysteine levels to reduce risk of CHD events in women

There were no systematic reviews identified for this topic. Folate supplementation is known to reduce serum homocysteine levels in men.91 Whether reductions in homocysteine lead to a decreased risk of CHD events has not been tested in a randomized controlled trial.
Summary and Recommendations

Homocysteine as a Risk Factor for CHD in Women

A systematic review of observational studies suggests that higher serum homocysteine levels are strongly associated with higher risk for CHD events in both men and women. Each 5 µmol/L increase in serum homocysteine level was associated with a 70 percent higher risk of CHD events among both men and women. This systematic review is relatively old and did not rate studies by degree of statistical adjustment for potential confounding variables. An updated systematic review of this topic is feasible and could provide important evidence.

Treatment to Lower Homocysteine Levels to Reduce Risk of CHD Events in Women

There is insufficient evidence in women to address this question.

3.05a C-reactive protein as a risk factor for CHD events in women

There were no systematic reviews identified for this topic.

Prospective Cohort Studies

We reviewed two reports from the Women’s Health Study that evaluated the association between C-reactive protein and the risk of CVD events in 28,263 healthy postmenopausal women. After adjustment for markers of inflammation, lipoprotein measures and other coronary heart disease risk factors, the relative risk of a CVD event associated with a one-quartile increase in the concentration of C-reactive protein levels was 1.5 (95% CI, 1.1-2.1; p = .02).


3.05b Treatment to reduce C-reactive protein levels to reduce risk of CHD events in women

There were no systematic reviews, randomized trials, or cohort studies identified for this topic.
Summary and Recommendations

C-Reactive Protein as a Risk Factor for CHD Events in Women

One large cohort study\(^9\) suggests that higher C-reactive protein levels are associated with increased risk for CVD events in women. A systematic review of this topic is not feasible due to lack of data.

3.06a Smoking as a risk factor for CHD in women

There were no systematic reviews identified for this topic.

Prospective Cohort Studies

We identified six prospective cohort studies evaluating the relation between cigarette smoking and risk of CHD in women. Four studies reported that smoking was independently associated with increased risk of fatal or nonfatal CHD events with a RR of about 2.\(^94-98\) Smoking was associated with increased CHD risk in the Framingham Heart Study\(^99, 100\) and in a study of three communities,\(^101\) but the findings in these two cohorts were not statistically significant in women.

3.06b Smoking cessation to reduce risk of CHD in women

Systematic Reviews


This systematic review of observational studies evaluated the association between smoking cessation after MI and subsequent overall mortality. The twelve international studies included in this meta-analysis were published between 1966 and 1996 and included at total of 5,878 participants. Two of the studies provided data on 185 women. Smoking status was evaluated by self-report during the first year after MI. The duration of follow-up ranged from 2 to 10 years.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All (N=5,878)</th>
<th>Women (N=185; 3.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>OR 95% CI p-value</td>
<td>OR 95% CI p-value</td>
</tr>
<tr>
<td>Mortality</td>
<td>.54 .46-.62 NA</td>
<td>.36 .23-.54 NA</td>
</tr>
</tbody>
</table>

Mortality was reduced by 50 percent among all participants and about 65 percent among women who stopped smoking after their MI, compared to persons who continued to smoke. The findings from some of the individual studies included in this meta-analysis were not adjusted for differences in CHD risk factors between persons who quit and those who continued to smoke.

Prospective Cohort Studies Not Included in the Systematic Review

We reviewed eight manuscripts based on six prospective cohort studies. Compared to women who had never smoked cigarettes, women who were former smokers had as much as a 50 percent increased risk of fatal and nonfatal coronary heart disease events, although this finding was not significant.94, 97, 98 Among former smokers, CHD event rates approach that of non-smokers 10 to 20 years after cessation of smoking.95, 96, 101, 103, 104


Summary and Recommendations

Smoking and Risk for CHD among Women

Based on the findings of six cohort studies, smoking appears to be associated with an approximate 2-fold increased risk of CHD events in women, but no systematic review has quantified this increased risk or compared it to the increased risk among male smokers. A systematic review appears to be feasible and could provide important information.

Smoking Cessation to Reduce Risk of CHD Events among Women

A systematic review of prospective cohort studies found that smoking cessation after MI was associated with about a 50 percent lower risk of death during 2 to 10 years of observation. This evidence is observational and subject to the biases associated with this study design. Of particular concern, it is not clear that the results of the studies included in the systematic review were adjusted for differences in CHD risk factors between smokers who quit and those who continued to smoke. This systematic review, though published in 2000, included only studies published before 1996. Given that the systematic review is relatively old, and the fact that only 185 women are represented in the review, we recommend a systematic review of the literature to update this topic.

3.07a Obesity as a risk factor for CHD in women

There were no systematic reviews identified for this topic.
Prospective Cohort Studies

We reviewed data from five cohort studies. Among women in the Framingham Heart Study, the Nurses’ Health Study, Atherosclerosis Risk in Communities (ARIC), and the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Risk Development in Young Adults (CARDIA) studies, increased weight or body mass index were associated with 1.5 to 3-fold increases in the risk of fatal and nonfatal CHD events. Fluctuating weight patterns and increased waist-hip ratios were associated with a 1.5 to 2-fold increased risk for CHD events and mortality among participants in the Iowa Women’s Health Study and the Nurses’ Health Study. Compared to BMI and skinfold measurements, waist-hip ratio was a better predictor of CHD among African-American women in the ARIC and CARDIA studies.


3.07b Weight reduction to reduce risk of CHD events in women

There were no studies identified for this topic.

Summary and Recommendations

Obesity as a Risk Factor for CHD in Women

Findings of five cohort studies suggest that obesity increases risk of CHD events in women, but the measure of obesity (weight, body mass index, skinfold thickness, or waist-hip ratio) that best predicts CHD risk women is not clear. A systematic review of this topic is feasible and could be clinically useful.

Weight Reduction to Reduce Risk of CHD Events in Women

No evidence was identified to address this topic. A systematic review is not feasible due to lack of data.

3.08a Inactivity as a risk factor for CHD in women

No systematic reviews of this topic were identified.

Prospective Cohort Studies

We reviewed data from three cohort studies. Among healthy women in the Nurses’ Health Study, there was a 15 to 50 percent reduction in the risk of CHD events with physical activity. However, there appeared to be a threshold above which increasing levels of activity were not associated with increased benefit. Compared to healthy women with low fitness levels, healthy women with high fitness levels were at significantly less risk for a fatal event, but not for CVD death. Among healthy women in the Framingham Heart Study, increased physical activity was associated with an approximate 30 percent reduction in the risk of mortality, but not with a lower risk for CVD or CVD death.


3.08b Exercise to reduce risk of CHD events in women

There were no systematic reviews identified for this topic that provide separate data on women. We know of three systematic reviews of randomized trials that assessed the effect of exercise as part of a cardiac rehabilitation program following an acute ischemic event on risk for subsequent CHD events. However, the randomized trials included in these analyses were small and included few women.

Summary and Recommendations

Inactivity as a Risk Factor for CHD in Women

It is not clear that inactivity is a risk factor for CHD events in women. Three cohort studies suggest that risk for all-cause mortality is increased with inactivity, but the evidence regarding the association of inactivity and risk for CHD and CVD events is mixed. The limited number of studies that provide data on women and variations in measurement of activity level limit the feasibility of a systemic review of this topic.

Exercise to Reduce Risk of CHD Events in Women

There is insufficient evidence in women to address this question.
3.09 Age as a Risk Factor for CHD events in women

Systematic Reviews

**F.1.** Pocock SJ, McCormack V, Gueyffier F, Boutitie F, Fagard RH, Boissel JP. A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials. BMJ 2001;323(7304):75-81.\(^{125}\)

This is a systematic review of data from eight randomized controlled trials that studied the effect of treatment for hypertension on CVD risk and are included in the Individual Data Analysis of Antihypertensive intervention trials (INDANA) database. Pooled data from the trials were used in an prospective cohort design to determine the effect of various risk factors on CVD events and to develop a score for predicting risk of death from CVD. Baseline measures of 16 potential CVD risk factors (age, sex, height, body mass index, smoking, systolic and diastolic blood pressure, heart rate, total cholesterol, creatinine, uric acid, previous MI, stroke or diabetes, left ventricular hypertrophy on ECG and blood pressure treatment) were included in a multivariate Cox proportional hazards model. Regression coefficients from this model were used to develop a risk score for the probability of cardiovascular death within a five year interval. All participants had elevated blood pressure at entry in the trials. The primary outcomes were fatal CVD and fatal CHD events. Associations between age and fatal events are presented below:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR* (N=27,987)</th>
<th>95% CI</th>
<th>p-value</th>
<th>RR* (N=20,802)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonsmokers</td>
<td>1.43</td>
<td>NA</td>
<td>&lt;.0001</td>
<td>1.58</td>
<td>NA</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>smokers</td>
<td>1.33</td>
<td>NA</td>
<td>&lt;.0001</td>
<td>1.46</td>
<td>NA</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.35</td>
<td>NA</td>
<td>&lt;.0001</td>
<td>1.58</td>
<td>NA</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

* per 5 year increase in age
† interaction between age and smoking status required stratified estimates for the relative risk associated with age

The risk for CVD and CHD death increased 50 to 60 percent with each 5-year increase in age among women. The effect of age is similar, but slightly weaker in men, with a 30 to 40 percent increase in risk of CVD or CHD death with each 5-year increase in age.

This study was rated fair quality because inclusion was restricted to selected clinical trials among hypertensive persons.
Prospective Cohort Studies Not Included in the Systematic Review

These two articles present risk estimates for CHD events associated with increasing age among white men and women in the Framingham Heart Study. The article by D'Agostino et al.\textsuperscript{126} also presents associations between age and risk of CHD events stratified by race from seven other cohort studies. Data from each of the cohort studies was used to construct a multivariate Cox proportional hazards model that included age, race, sex, blood pressure, cholesterol, smoking, and diabetes as risk factors and CHD death or nonfatal MI as the outcome. Models were gender and race-specific. Multivariate relative risks for a one-year increase in age from these studies are presented below:

<table>
<thead>
<tr>
<th>Race and Study*</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR$^\dagger$</td>
<td>95% CI</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FHS</td>
<td>1.05</td>
<td>1.04-1.07</td>
</tr>
<tr>
<td>ARIC</td>
<td>1.05</td>
<td>1.02-1.07</td>
</tr>
<tr>
<td>PHS</td>
<td>1.01</td>
<td>1.00-1.02</td>
</tr>
<tr>
<td>CHS</td>
<td>1.07</td>
<td>0.99-1.16</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIC</td>
<td>1.05</td>
<td>1.01-1.10</td>
</tr>
<tr>
<td>Japanese-American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHP</td>
<td>1.06</td>
<td>1.04-1.08</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>1.03</td>
<td>1.00-1.05</td>
</tr>
<tr>
<td>Native American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHS</td>
<td>1.05</td>
<td>1.02-1.09</td>
</tr>
</tbody>
</table>

*FHS = Framingham Heart Study; ARIC = Atherosclerosis Risk in Communities; PHS = Physicians’ Health Study; CHS = Cardiovascular Health Study; HHP = Honolulu Heart Program; PR = Puerto Rico Heart Health Program, and SHS = Strong Heart Study.

† relative risk for CHD death and nonfatal MI for each one year increase in age

For each one-year increase in age, men of all races have about a 5 percent increase in risk of CHD events. There appears to be a greater increase in CHD risk with increasing age among women than in men, but the associations are difficult to interpret in women because the number of outcomes was small and none of the risk estimates are statistically significant. The small number of women studied also makes it difficult to determine if risk associated with increasing age differs with race.


Summary and Recommendations

Among men, cohort studies consistently show a 5 percent increase in risk of CHD events per year of age among white, black, Japanese-American, Hispanic and Native American men. Among women, increasing age seems to be a stronger risk factor for CHD events than among men, but the evidence is inconclusive due to the small number of women included in the studies.

A systematic review of this topic could provide important information regarding the effect of aging on CHD risk and on differences in this association between men and women. Such a review would be challenging because increasing age is also associated with higher prevalence and severity of other risk factors for CHD. In addition, as indicated by the results of Pocock et al., the effects of age and gender may interact with other risk factors, such as smoking.

3.10 Age at menopause and risk for CHD

There were no systematic reviews identified for this topic.

Prospective Cohort Studies

We reviewed data from three prospective cohort studies. The Nurses’ Health Study and the Diagnostisch Onderzoek Mammacarcinoom (Diagnostic Investigation of Mammary Cancer) found a 2 to 3 percent increased risk of CHD events with each one year decrease in age at menopause. Age at natural menopause was not a significant predictor of CHD deaths among women in the National Health and Examination Survey (NHANES). Inadequate adjustment for cigarette smoking may confound the association of age at menopause and CHD risk, as smokers have an increased risk for CHD events and earlier age at menopause.


Summary and Recommendations

Evidence that earlier age at menopause is associated with increased risk for CHD events is weak because the number of studies identified was small and their results are not consistent. Several large community-based studies may provide sufficient data to perform a systematic review.
3.11 Ethnicity as a risk factor for CHD in women

There were no systematic reviews identified for this topic.

Prospective Cohort Studies

We reviewed data from three cohorts, comparing risk for CHD outcomes between African-American and white women. Among participants in the Charleston Heart Study\textsuperscript{130} the risk of coronary heart disease death and mortality did not differ significantly by race. However, case fatality rates after myocardial infarction were 1.5 to 3-times higher among African-American women compared to white women in the Atherosclerosis Risk in Communities study\textsuperscript{131} and in the National Hospital Discharge Survey.\textsuperscript{132}


Summary and Recommendations

The three cohort studies that we reviewed provide conflicting evidence regarding the association between race/ethnicity and coronary heart disease risk in women.\textsuperscript{130-132} Several large community-based studies may provide sufficient data to perform a systematic review, but such a review would be challenging because relative risk estimates comparing CHD risk by ethnicity must be adjusted for other cardiovascular risk factors.

3.12 Socioeconomic status and risk for CHD

There were no systematic reviews identified for this topic.

Prospective Cohort Studies

We reviewed three cohort studies. After adjustment for age and other coronary heart disease risk factors, income,\textsuperscript{133} socioeconomic deprivation score,\textsuperscript{134} and postcode of residence\textsuperscript{135} correlated with risk for CHD events, such that women with lower socioeconomic status (SES) measures were at an approximate 2-fold increased risk for CHD events compared to women with higher SES. However, among women in the Charleston Heart Study, level of education was not a significant predictor of coronary
heart disease deaths for white or African-American women after adjustment for other CHD risk factors.\textsuperscript{130}


\textbf{Summary and Recommendations}

Three cohort studies suggest that socioeconomic status may be associated with an increased CHD risk, but the evidence is weak due to the small number of studies identified and differences in the definition of socioeconomic status.\textsuperscript{133-135} Several large community-based studies may provide sufficient data to perform a systematic review, but such a review would be challenging because relative risk estimates comparing CHD risk by ethnicity should be adjusted for other cardiovascular risk factors and definitions of socioeconomic status vary.
QUESTION 4

4. Are accurate tests (defined in #1), effective treatments (defined in #2), or risk factor modifications (defined in #3) underutilized in women (or among women of various race/ethnic populations) compared to men?

We searched the medical literature to identify studies that compared the use of tests, treatments and risk factor reduction for CHD in men and women. We have described results only for those subtopics for which studies were identified.

1.0 Non-invasive testing for CHD

Exercise Tolerance Testing

Cross-sectional Studies

Among patients hospitalized with ischemic chest pain, women were approximately 20-40 percent less likely than men to undergo exercise stress testing, even after adjustment for other risk factors.\textsuperscript{136,137} Men with positive exercise stress test results were 1.5 to 2-fold more likely to undergo invasive or non-invasive follow-up testing,\textsuperscript{14,136,137} despite the fact that risk of a subsequent MI or cardiac death was 5-fold higher in women than in men.\textsuperscript{14} Between 1995 and 1996, primary care providers in a major managed-care network were 2-fold more likely to refer men than women with ischemic symptoms for exercise stress testing (p<.0001).\textsuperscript{138} Among the oldest patients in this population (age > 70 years), rates of referral for exercise testing were similar in men and women.


2.0 Treatments for CHD

Aspirin

Cross-sectional Studies

Compared to women, men in six large cross-sectional studies were more likely than women to receive aspirin during hospitalization for an acute MI\textsuperscript{12,139-142} or as secondary prophylaxis for a CVD event.\textsuperscript{143} Rates of aspirin treatment among men compared to women were 38 percent higher at hospital admission,\textsuperscript{12} 10 to 20 percent higher during hospitalization,\textsuperscript{139,141,142} 6 percent higher on discharge,\textsuperscript{140} and 40 percent higher after a CVD event.\textsuperscript{143}

The Atherosclerotic Risk in Communities (ARIC) prospective cohort study reported similar rates of aspirin use between black women and black men (10 percent), but higher prevalence of use among white men than among white women (31 percent vs. 28 percent; \( p < .001 \)). Overall, the prevalence of aspirin use was almost 3-fold greater among whites compared to blacks.\textsuperscript{144} Between 1986 and 1990 the use of antiplatelet agents in women increased 4-fold in one study,\textsuperscript{139} but remained unchanged in another.\textsuperscript{144}


Beta-Blockers

Cross-sectional Studies

After adjustment for age, women were 10 to 30 percent less likely than men with symptoms of an acute MI to receive beta-blockers during hospitalization and approximately 45 percent less likely to be discharged on beta-blockers.

Several studies found no gender difference in beta-blocker use prior to or during hospitalization for an acute MI. Between 1986 and 1990, the use of beta-blockers increased by 15 percent in hospitalized women (48.4 percent) and by 17 percent in hospitalized men (60.0 percent).


Thrombolysis

Cross-sectional Studies

Six large cohort studies found that men were 1.5 to 2-fold more likely than women to receive thrombolytic therapy during hospitalization for symptoms of acute MI. However, among patients who had been admitted to a coronary care unit, men and women were equally likely to receive thrombolytic treatment. In the SAVE trial, the odds of receiving thrombolysis were 56 percent higher for men than women; however, after adjustment for other variables related to indication for thrombolysis, gender was not an independent predictor of thrombolytic therapy. Between 1986 and 1990, the use of thrombolytics in women increased 6-fold.

In contrast, two studies did not find a significant gender difference in thrombolytic therapy during hospitalization for acute MI.


Percutaneous Transluminal Coronary Angioplasty (PTCA) and Coronary Artery Bypass Graft Surgery (CABG)

Cross-sectional Studies

We reviewed 21 cross-sectional studies comparing gender differences in revascularization procedures (PTCA and CABG). Most studies included patients who were admitted to the hospital for evaluation of acute coronary symptoms. Because women appear to be less likely than men to undergo cardiac catheterization, we categorized studies that evaluated all patients admitted for acute coronary syndromes and those that provided data on procedures subsequent to cardiac catheterization.
Procedures among all patients evaluated for acute coronary syndromes

Two European studies found significant gender differences in revascularization procedure rates among patients with known CHD, including a 50 to 60 percent higher rate for men compared to women in the United Kingdom and a 36 percent higher rate for men in Austria. In 1995, the lowest PTCA rates in Austria were among women over the age of 64 years. These findings were similar to data from the United States, where CHD-adjusted rates of revascularization in men were 30 to 45 percent higher than in women. In the same study, revascularization rates remained higher in men than in women hospitalized for an acute MI, suggesting that potential biases in admitting practices could not explain the gender differences.

In adjusted models, men discharged from California hospitals in 1989 were 35 percent more likely to have undergone PTCA and 2-fold more likely to have undergone CABG than women. In Massachusetts, men were 2.5-fold more likely than women to undergo PTCA following acute MI, but equally likely to undergo CABG. Among patients referred for non-invasive testing, men were twice as likely as women to undergo a subsequent revascularization procedure. Data from the National Registry of Myocardial Infarction indicate that, among patients who did not receive thrombolytic therapy, 19 percent of men underwent PTCA compared with 13.8 percent of women, and 12.6 percent of men underwent CABG compared with 8.0 percent of women. However, after thrombolytic therapy, 28.3 percent of women vs. 30.6 percent of men underwent PTCA and 11.0 percent of women vs. 13.5 percent of men underwent CABG.

Race and gender rates of revascularization indicate that black and white women are as likely as white men to undergo PTCA, but white women are 35 percent less likely and black women 63 percent less likely to undergo CABG than white men, even after adjustment for multiple risk factors. Medicare data suggest that white men have the highest rates of CABG (40.4 per 10,000 persons) and black women the lowest (6.4 per 10,000 persons).

Procedures among patients who have had cardiac angiography

Among participants in the population-based Corpus Christi Heart Project, age-adjusted rates of PTCA and CABG were 1.5-times higher for men than women. However, after acute MI and coronary angiography, there was no evidence of differential revascularization rates between genders. After adjustment for CHD risk factors, there were only slight differences in rates of PTCA between Mexican-Americans and non-Hispanic Whites.

In similar analyses among persons who had coronary angiography, women were as likely as men to undergo PTCA but 40 percent less likely to undergo CABG. Gender differences in intervention rates were most significant among younger participants. Findings from several cohort studies indicate that after coronary angiography, women
were more likely to undergo PTCA\textsuperscript{159-161} while men more likely to undergo CABG.\textsuperscript{160, 161} After adjustment for CHD risk factors, gender was not a significant predictor of revascularization procedure in one,\textsuperscript{161} but not all\textsuperscript{159, 160} studies. In GUSTO-I, the rates of coronary angiography were similar in men and women (52 percent vs. 57 percent), but women were significantly more likely than men to undergo PTCA (35 percent vs. 32 percent; p < .001) and less likely to undergo CABG (7 percent vs. 9 percent; p < .001).\textsuperscript{160} Four studies found that men were 1.5 to 2-fold more likely than women to undergo revascularization (PTCA or CABG) subsequent to acute coronary symptoms; however, once a diagnostic procedure had been performed, gender was a non-significant predictor of revascularization.\textsuperscript{12, 146, 159, 162}

Three studies found no significant gender differences in the referral rates for PTCA or CABG after coronary angiography.\textsuperscript{60, 149, 163} However, men were more likely to undergo revascularization procedures during the early phases of infarction,\textsuperscript{149} or when the risk of cardiac death was low.\textsuperscript{163} In one study, women were half as likely to undergo early intervention for MI (thrombolysis, catheterization, PTCA, CABG).\textsuperscript{149}


Treatment of hypertension

Systematic Review

In this systematic review, data from 46 population-based studies published between 1966 and 1996 were analyzed to assess gender differences in the pharmacological treatment of hypertension. Data on 108,184 men and 59,575 women with hypertension are included. Crude differences in treatment practices were also evaluated by antihypertensive drug class and by country.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Female:Male</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any pharmacological treatment</td>
<td>1.33</td>
<td>1.32 – 1.34</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1.12</td>
<td>1.09 – 1.15</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>.82</td>
<td>.79 - .85</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>.67</td>
<td>.59 - .76</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>.85</td>
<td>.77 - .95</td>
</tr>
</tbody>
</table>

Women with hypertension were approximately 30 percent more likely than men to receive treatment for hypertension. Women were more likely than men to be treated with a diuretic, while men were more likely to be treated with beta-blockers, ACE inhibitors and calcium antagonists. Among participants aged 20-29, women were 2-fold more likely than men to receive treatment for hypertension. By age 60-69 the prevalence of treatment was only 22 percent higher in women than in men. Gender differences in treatment practices declined between 1970 and 1991.

**Lipid lowering**

**Cross-sectional Studies**

Three international cross-sectional studies document that rates of medication usage and gender differences in use rates vary by country.  


**Summary and Recommendations**

Available studies suggest that men are more likely than women to undergo diagnostic testing and treatment for CHD, but that women are more likely
to be treated for hypertension. Several theories have been proposed to explain these gender differences.

It is possible that women have less severe CHD symptoms or findings than men and more comorbidities that contraindicate tests and procedures. This theory is supported by the fact that gender differences appear to be minimized in studies with inadequate control for potential confounding. Coronary tests and procedures may not be underused in women, but overused in men. For example, lower rates of CABG among low risk women may indicate a more appropriate treatment referral pattern among women than men. A panel of nationally recognized experts assessed the appropriateness of coronary angiography, PTCA, and CABG based on hospital data from New York and found that the rate of inappropriate cardiovascular procedures was not significantly different by gender.

Women may be more reluctant than men to undergo invasive coronary procedures. Among patients scheduled for exercise stress testing, Saha et al. found that women were more willing than men to undergo coronary angiography and equally willing to undergo PTCA or CABG.

A systematic review of the literature is feasible and could provide clinically important information for treatment practice guidelines.
QUESTION 5

5. What is the prognostic value of biochemical markers for acute myocardial infarction or unstable angina in women? (3 subtopics labeled 5.01-5.02)

Specifically, does the prognostic value of the following markers differ in women and men? What is the incremental prognostic benefit of new cardiac markers in addition to history, physical exam, and other laboratory data including electrocardiography?

5.01 Troponin
5.02 Creatine kinase myocardial bands (CKMB) including isoforms
5.03 Myoglobin

5.01 Troponins

There were no systematic reviews identified for this topic.

5.02 Creatine kinase MB

There were no systematic reviews identified for this topic.

5.03 Myoglobin

There were no systematic reviews identified for this topic.
Chapter 4: Conclusions

Summary and Recommendations by Key Question

Table 3 presents a summary of the findings of the evidence review for each key question. We have classified the evidence as none, weak, fair or good, defined as follows:

<table>
<thead>
<tr>
<th>Classification</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>no publications that address the key question in women</td>
</tr>
<tr>
<td>Weak</td>
<td>some evidence, but no systematic review or definitive evidence from randomized trials</td>
</tr>
<tr>
<td>Fair</td>
<td>at least one systematic review, but the review is only fair quality or outdated or evidence from randomized trials, but the trials are small or have inconsistent findings</td>
</tr>
<tr>
<td>Good</td>
<td>at least one recent, good quality systematic review or several major randomized trials with consistent findings</td>
</tr>
</tbody>
</table>

As noted in Chapter 2, Methodology, Hierarchy of Evidence and Completeness of Searches, we are confident that we have identified all systematic reviews and major randomized trials, but some large cohort or cross-sectional studies may not have been identified. Importantly, we were only able to include the results of studies if the results were stratified by gender. Thus, many completed studies may have the potential to provide evidence on women if the study investigators are willing and able to produce stratified results.

A new systematic review was considered feasible when we identified at least 5 or more studies using similar methods that could likely be included in a systematic review. In some cases, even though a systematic review is feasible, it was not recommended if a recent, methodologically sound systematic review has already been completed or a definitive randomized trial has been completed or is under way.

Findings by Level of Evidence and Key Question

Assuming that the strength of a risk factor is a different question from the effect of modifying the same risk factor, and that the effects of a treatment in primary prevention are different from the effect in secondary prevention, we reviewed the medical literature related to 42 questions pertaining to CHD in women. We found no data in women to address 13 of the questions, weak data to address 15, fair data for eight and good data to address six questions (Table 4).

Summary of Major Findings

There was fair data suggesting that the accuracy of exercise EKG and exercise thallium testing (using either conventional or SPECT imaging) for CHD in women is poor and that exercise echocardiography might be more accurate.
While evidence for many treatments was lacking, we found fair or good data to suggest that beta-blockers, aspirin and angiotensin converting enzyme inhibitors reduce risk for CHD events in women with coronary disease. Good evidence suggests that nitrates do not reduce risk for CHD events in women with known heart disease. There was fair evidence to suggest that IIb/IIIa drugs given to women undergoing percutaneous revascularization result in a reduced risk of CHD events and need for repeat revascularization. Fair evidence also suggests that IIb/IIIa drugs given to women suffering acute coronary syndromes result in increased mortality. This was the only treatment for which there appeared to be an interaction by gender: men treated with IIb/IIIa drugs during acute coronary syndromes appear to benefit.

We found only weak evidence linking most of the risk factors of interest and CHD risk in women. For the most part, this is because all of the studies addressing the strength of risk factors are observational, and very few good quality systematic reviews have been completed. However, there was fair evidence to suggest that hyperlipidemia and hyperhomocysteinemia are risk factors for CHD in women and good evidence that diabetes is a risk factor. Risk factors seem to be equally strong in men and women with the possible exceptions of age, diabetes, and specific lipoproteins. Increasing age seems to be a stronger risk factor for CHD events in women than men, but the evidence is inconclusive due to the small number of women included in the studies. Diabetes may be a stronger risk factor for CHD in women than in men and patterns of risk associated with lipoprotein subfractions appear to differ in men and women.

There was fair or good evidence to suggest that smoking cessation after MI and treatment of hypertension and of hyperlipidemia lower the risk for CHD events in women. In contrast, we found no evidence for the effectiveness of other interventions to modify risk factors in women.

Available studies suggest that men are more likely than women to undergo diagnostic testing and treatment for CHD, but that women are more likely to be treated for hypertension. These observed differences may be due to inadequate control for differences in severity of disease and comorbidities in men and women or result from overtreatment in men.

We found no evidence to address the prognostic value of troponins, creatine kinase or myoglobin in women with ischemia.

In general, no evidence addressed differences in the accuracy of diagnostic tests, strength of risk factors, effects of treatment or prognostic value of markers for ischemia in women of different races or ethnicity. The only evidence regarding differences by ethnicity suggests that African American women may benefit more from treatment of hypertension than white women.
Chapter 5: Future Research

Based on our reviews of published studies that include data on women, we believe that a systematic review of the literature is probably not feasible for 19 of the 42 key questions (Table 3). However, systematic reviews of some of these questions might be feasible if unpublished gender-specific findings can be obtained. Systematic reviews of the remaining 23 topics are likely feasible. For some questions, however, we did not recommend a systematic review because the question appears to have been adequately addressed by completed clinical trials or a definitive clinical trial is currently in progress (Table 3).

We believe that a systematic review is feasible and should be recommended for the subtopics listed below (Table 3).

- Exercise tolerance testing
- Exercise echocardiogram
- Aspirin - secondary prevention
- Beta-blockers - secondary prevention
- Hypertension as a risk factor
- Diabetes as a risk factor
- Hyperlipidemia as a risk factor
- Hyperlipidemia treatment
- Homocysteine as a risk factor
- Smoking as a risk factor
- Smoking cessation
- Obesity as a risk factor
- Age as a risk factor
- Differences in utilization between men and women

The major limitation in performing these systematic reviews will be the availability of data on women and minority populations. Women typically comprise only 20 to 30 percent and minorities a substantially lower proportion of participants in randomized trials. For questions where several trials have been completed, data on women and minorities could be summarized in a systematic review. However, risk estimates for women and minorities are infrequently published. Thus, investigators attempting to systematically review the medical literature must attempt to contact investigators and obtain unpublished risk estimates. For a variety of reasons, these subgroup analyses are often not obtainable. Randomized trials of the benefit of beta-blockers in CHF provide an excellent example of this problem. At least 20 randomized trials of the effect of beta-blockers on mortality in persons with CHF have been published. Most of these have included women, but only 4 that we were able to identify included analyses among women and these data were generally limited to the primary outcome. Thus, even though the National Institutes of Health and other funding agencies appear to have succeeded in assuring that women and minorities are included in randomized trials, data from such participation is not generally available. We recommend that, in addition to demanding
participation of women and minorities in research, the National Institutes of Health, Federal Drug Administration and other funding sources should insist that primary and secondary outcome data by subgroup be published or archived.

Similarly, most systematic reviews of the literature do not provide subgroup estimates for women or minorities. This is due primarily to the difficulty of obtaining unpublished subgroup estimates, as noted above. However, as demonstrated by several excellent systematic reviews included in this report, it is possible with additional effort to obtain subgroup estimates for women and minorities. We recommend that funding agencies that support systematic reviews require inclusion of subgroup estimates in women and minorities whenever possible.

Table 5: Findings by Level of Evidence and Recommendation for Systematic Review

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Number of Key Questions</th>
<th>Systematic Review Feasible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>None</td>
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</tr>
<tr>
<td>Good</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>
References

42. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation 1998;97(22):2202-12.


Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality

1.01 Exercise tolerance testing

Systematic Review


Cross Sectional


1.02 Exercise echocardiogram

Systematic Review


1.03 Coronary artery calcification score

Cross-sectional


Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)

### 2.01 Aspirin

**Systematic Review**

**Clinical Trial**

**Prospective Cohort**

### 2.02 Beta-blockers

**Systematic Review**

*a* indicates “good quality” article
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)

Clinical Trial

2.03 Angiotensin converting enzyme (ACE) inhibitors

Systematic Review

\(^a\)Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation 1998;97(22):2202-12.


Clinical Trial


2.05 Nitrates

Clinical Trial

\(^a\)indicates “good quality” article
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)


2.07 Glycoprotein IIb/IIIa Drugs

Systematic Review


2.08 Thrombolysis

Systematic Review


Clinical Trial


2.10 Clopidogrel

Clinical Trial


Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)

2.11 Percutaneous transluminal coronary angioplasty (PTCA) and stenting

Clinical Trial


Prospective Cohort


a indicates "good quality" article
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)


**2.12 Coronary artery bypass surgery (CABG)**

**Clinical Trial**  


**Prospective Cohort**  

**3.01a Hypertension as a risk factor for CHD in women**

**Propsective Cohort**  


**3.01b Treatment of hypertension to reduce risk of CHD events in women**

**Systematic Review**  


\(^a\)indicates "good quality” article
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Type of Research Design</th>
<th>Level of Quality</th>
<th>Authors and Details</th>
</tr>
</thead>
</table>

*a* indicates "good quality" article
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)

### 3.03a Hyperlipidemia as a risk factor for CHD in women

**Systematic Review**


### 3.03b Treatment of hyperlipidemia to reduce risk of CHD events in women

**Systematic Review**


**Clinical Trial**

- **MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,538 high-risk individuals: a randomized placebo controlled trial.** Heart Protection Study Collaborative Group. Lancet 2002; 360:7-22.


*Indicates "good quality" article
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)

3.04a Elevated homocysteine as a risk factor for CHD in women

Systematic Review

3.05a C-reactive protein as a risk factor for CHD events in women

Prospective Cohort


3.06a Smoking as a risk factor for CHD in women

Prospective Cohort


*Indicates “good quality” article
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)


3.06b Smoking cessation to reduce risk of CHD in women

Prospective Cohort


Systematic Review


3.07a Obesity as a risk factor for CHD in women

Prospective Cohort


\(^a\)Folsom AR, Stevens J, Schreiner PJ, McGovern PG. Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and whites. Atherosclerosis
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Type of Research Design</th>
<th>Level of Quality</th>
<th>Article Details</th>
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</thead>
<tbody>
<tr>
<td>3.08a Inactivity as a risk factor for CHD in women</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


#### 3.08a Inactivity as a risk factor for CHD in women

**Prospective Cohort**


*Indicates "good quality" article
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)


3.09 Age as a risk for CHD events in women

Systematic Review

Prospective Cohort


3.10 Age at menopause and risk for CHD

Prospective Cohort


3.11 Ethnicity

Prospective Cohort
aKeil JE, Sutherland SE, Knapp RG, Lackland DT, Gazes PC, Tyroler HA. Mortality rates and risk factors for coronary disease in black as compared with white men and women. N
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of 
research design, and level of quality (continued)

<table>
<thead>
<tr>
<th>Article</th>
<th>Year</th>
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</table>

3.12 Socioeconomic status and risk for CHD

Prospective Cohort

<table>
<thead>
<tr>
<th>Article</th>
<th>Year</th>
</tr>
</thead>
</table>

4.0 Differences in utilization between women and men

Systematic Review

<table>
<thead>
<tr>
<th>Article</th>
<th>Year</th>
</tr>
</thead>
</table>

*indicates “good quality” article
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)

<table>
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<th>Key Question</th>
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<th>Level of Quality</th>
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<tbody>
<tr>
<td>Do women with acute myocardial infarction receive the same treatment as men?</td>
<td>BMJ 1994;309:563-566.</td>
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<td>Good Quality</td>
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*Indicates "good quality" article
Evidence Table 1: Articles containing evidence on key question arranged by key question, type of research design, and level of quality (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
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</table>

\*\*Indicates "good quality" article


Bibliography

45. Austin MA. Epidemiology of hypertriglyceridemia and cardiovascular disease. Am J Cardiol 1999;83(9B):13F-16F.
127. Cerqueira MD. Diagnostic testing strategies for coronary artery disease: special issues related to gender. Am J Cardiol 1995;75(11):52D-60D.


346. Holme I. Cholesterol reduction and its impact on coronary artery disease and total mortality. Am J Cardiol 1995;76(9):10C-17C.


436. Latini R, Tognoni G, Maggioni AP, et al. Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin:


529. Morris JL, Cowan JC. Nitrates in myocardial infarction: a current perspective. Can J Cardiol 1995;11(Suppl B):5B-10B.


Appendix A: Technical Expert Advisory Group and Expert Consultants

Technical Expert Advisory Group

Noel Bairey-Merz, MD  Cedars-Sinai Medical Center
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Advice was also solicited from representatives of Partner Organizations, including:

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Rosalind Fabunmi, Ph.D.  American Heart Association
Rose Marie Robertson, MD  American Heart Association
Mary Norine Walsh, MD  American College of Cardiology
Mary Winston, Ed.D.  American Heart Association
Appendix B: Literature Search Terms

The following terms were used to define the outcome for all questions.

<table>
<thead>
<tr>
<th>Search Terms</th>
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<tbody>
<tr>
<td>cardiovascular diseases or heart diseases or heart or cardiovas* or cardiac* or coronary or myocardial</td>
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Publication Type

<table>
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<tr>
<td>meta-analysis or meta-analy* or metaanaly* or metanaly* or review or overview and systematic or methodologic* or evidence* or Medline</td>
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Limits

<table>
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</thead>
<tbody>
<tr>
<td>publication date 1985 to 2002, English language, human</td>
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</table>

The following terms were used to define the predictor for each specific question.

Question

<table>
<thead>
<tr>
<th>Question</th>
<th>Search Terms</th>
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<tr>
<td>1.01 exercise test* or stress test* or exercise electrocardio* or exercise tolerance test*</td>
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</tr>
<tr>
<td>1.02 exercise echocardio* or coronary disease, ultrasonography or dobutamine, diagnostic or exercise test* or stress test*</td>
<td></td>
</tr>
<tr>
<td>1.03 coronary artery calcification or electron beam tomography or coronary arteriosclerosis, radiography or coronary disease, radionuclide imaging or heart radionuclide imaging or spect or tomography, x-ray computed</td>
<td></td>
</tr>
<tr>
<td>2.01 aspirin</td>
<td></td>
</tr>
<tr>
<td>2.02 adrenergic beta-antagonists or beta-blockers or beta blockers or B-blockers</td>
<td></td>
</tr>
<tr>
<td>2.03 angiotensin converting enzyme inhibitors or angiotensin-converting enzyme inhibitors or angiotensin receptor blockers</td>
<td></td>
</tr>
<tr>
<td>2.04 calcium channel blocker*</td>
<td></td>
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</tbody>
</table>
Appendix B: Literature Search Terms (continued)

2.05 nitrate* or isosorbide mononitrate or isosorbide dinitrate

2.06 heparin or low molecular weight heparin

2.07 glycoprotein IIb-IIIa or glycoprotein IIb/IIIa or abciximab or tirofiban or eptifibatide

2.08 fibrinolytic agents or thrombolytics or thrombolysis or myocardial infarction, drug therapy or streptokinase or tissue plasminogen activator or myocardial reperfusion, methods

2.09 ticlopidine

2.10 clopidogrel

2.11 angioplasty, transluminal, percutaneous coronary or stent

2.12 coronary artery bypass graft surgery or CABG

3.01 hypertension or antihypertensive agents or vascular resistance

3.02 diabetes or diabetic*

3.03a hyperlipidemia or cholesterol or LDL* or HDL* or VLDL or LPA or lipoprotein* or triglycerides or triglycerid*

3.03b lipid lowering agents or anticholesteremic agents or antilipemic agents or hyperlipidemia, therapy

3.04 homocysteine or folic acid or pyridoxine

3.05 c-reactive

3.06 tobacco or smoking or nicotine

3.07 obesity or body weight or weight
### Appendix B: Literature Search Terms (continued)

<table>
<thead>
<tr>
<th>Code</th>
<th>Term</th>
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<tbody>
<tr>
<td>3.08</td>
<td>inactiv* or sedentary</td>
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<tr>
<td>3.09</td>
<td>aging or age factors or age or ageing or aging</td>
</tr>
<tr>
<td>3.10</td>
<td>menopause</td>
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<td>3.11</td>
<td>racial stocks or ethnic groups or race</td>
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<td>3.12</td>
<td>socioeconomic factors or income*</td>
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<td>4.0</td>
<td>comparative study, male and female, sex factors or sex characteristics</td>
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<tr>
<td>5.01</td>
<td>troponin or troponin-t</td>
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<tr>
<td>5.02</td>
<td>creatine kinase or ck or ck-mb</td>
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<tr>
<td>5.03</td>
<td>myoglobin</td>
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Appendix C: Full Text Article Abstraction Form

<table>
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<tr>
<th>Question Code</th>
<th>Article:</th>
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<tr>
<td>INCLUSION CRITERIA</td>
<td>If answer is “NO” for any question 1-3 skip to #14.</td>
</tr>
<tr>
<td>1. Is the article a large randomized controlled trial, systematic review of the literature, a large prospective cohort (≥1000) with multivariable analysis, or X-sectional (for Key Q #1 &amp; 4)?</td>
<td>YES NO</td>
</tr>
<tr>
<td>2. Does the review article address the evidence-based question?</td>
<td>YES NO</td>
</tr>
<tr>
<td>3. Does the article contain data on women that address the research question?</td>
<td>YES NO</td>
</tr>
<tr>
<td>SYSTEMATIC REVIEW</td>
<td>YES NO</td>
</tr>
<tr>
<td>4. Was the information source appropriate?</td>
<td>YES NO</td>
</tr>
<tr>
<td>5. Was the information source adequately searched?</td>
<td>YES NO</td>
</tr>
<tr>
<td>6. Were the inclusion/exclusion criteria used to select articles clear and appropriate?</td>
<td>YES NO</td>
</tr>
<tr>
<td>7. Were the study assessments performed by at least 2 independent reviewers?</td>
<td>YES NO</td>
</tr>
<tr>
<td>8. Were the principal measures of effect and the methods of combining results appropriate? (summary effect size and CI)</td>
<td>YES NO</td>
</tr>
<tr>
<td>9. Was the methodological quality of the studies systematically assessed?</td>
<td>YES NO</td>
</tr>
<tr>
<td>10. Was the heterogeneity of the studies determined?</td>
<td>YES NO</td>
</tr>
<tr>
<td>11. Was there an assessment of publication bias?</td>
<td>YES NO</td>
</tr>
<tr>
<td>12. Was a sensitivity analysis included in the report?</td>
<td>YES NO</td>
</tr>
<tr>
<td>13. Years covered by review: ( ) to ( ) (go to Question #14)</td>
<td>YES NO</td>
</tr>
<tr>
<td>CLINICAL TRIAL</td>
<td>YES NO</td>
</tr>
<tr>
<td>4. Was the intervention randomized?</td>
<td>YES NO</td>
</tr>
<tr>
<td>5. Was there a control group that received placebo?</td>
<td>YES NO</td>
</tr>
<tr>
<td>6. Were the participants and research staff blinded to the intervention?</td>
<td>YES NO</td>
</tr>
<tr>
<td>7. Were the inclusion/exclusion criteria clear and appropriate?</td>
<td>YES NO</td>
</tr>
<tr>
<td>8. Was there &gt; 75% complete follow up? (go to Question #14)</td>
<td>YES NO</td>
</tr>
<tr>
<td>PROSPECTIVE COHORT</td>
<td>YES NO</td>
</tr>
<tr>
<td>4. Were the inclusion/exclusion criteria clear and appropriate?</td>
<td>YES NO</td>
</tr>
<tr>
<td>5. Was there &gt; 75% complete follow up?</td>
<td>YES NO</td>
</tr>
<tr>
<td>6. Did the analysis include multivariate adjustment for potential confounders?</td>
<td>YES NO</td>
</tr>
<tr>
<td>7. Was the outcome adjudicated blindly? (go to Question #14)</td>
<td>YES NO</td>
</tr>
<tr>
<td>ADDITIONAL INCLUSION CRITERIA (use for Key Question 1 only)</td>
<td>YES NO</td>
</tr>
<tr>
<td>4. Was coronary angiography the “gold standard” for measuring the accuracy?</td>
<td>YES NO</td>
</tr>
<tr>
<td>5. Was data on the accuracy of these tests in women included?</td>
<td>YES NO</td>
</tr>
<tr>
<td>6. Were non-invasive tests performed exclusively in patients after myocardial infarction, percutaneous angioplasty, coronary artery surgery or hospitalization for an unstable coronary syndrome (yes-exclude)</td>
<td>YES NO</td>
</tr>
<tr>
<td>CROSS-SECTIONAL QUALITY EVALUATION (use for Key Question 1 only)</td>
<td>YES NO</td>
</tr>
<tr>
<td>7. Did all women who undergo the non-invasive test also undergo angiography?</td>
<td>YES NO</td>
</tr>
<tr>
<td>8. Was the diagnosis of coronary artery disease on angiography made by investigators blinded to results of the non-invasive test? (go to Question #14)</td>
<td>YES NO</td>
</tr>
<tr>
<td>CROSS-SECTIONAL QUALITY EVALUATION (use for Key Question 4 only)</td>
<td>YES NO</td>
</tr>
<tr>
<td>4. Were the inclusion/exclusion criteria clear and appropriate?</td>
<td>YES NO</td>
</tr>
<tr>
<td>5. Did the analysis include multivariate adjustment for potential confounders? (go to Question #14)</td>
<td>YES NO</td>
</tr>
</tbody>
</table>

14. **Was this article a (check one only):** (required if Question 1-3 are ‘yes’)
________ Systematic Review
________ Prospective cohort
________ Pooling project
________ Interesting other finding
________ Randomized controlled trial
________ Evidence-based guideline
________ Cost effectiveness analysis
________ Other

15. Does this article contain data on women only? (required if Question 1-3 are ‘yes’)

16. Comments (continue on other side)
Appendix D: Articles Eligible for Full-Text Review by Key Question

1.01 Exercise tolerance testing


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


1.02 Exercise echocardiogram

Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


1.03 Coronary artery calcification score


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Raggi P. Coronary calcium on electron beam tomography imaging as a surrogate marker of coronary artery disease. Am J Cardiol 2001;87(4A):27A-34A.


2.01 Aspirin

Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


2.02 Beta-blockers


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Yusuf S. Interventions that potentially limit myocardial infarct size: overview of clinical trials. Am J Cardiol 1987;60(2):11A-17A.


2.03 Angiotensin converting enzyme inhibitors


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


2.04 Calcium channel blockers


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)

2.05 Nitrates


Morris JL, Cowan JC. Nitrates in myocardial infarction: a current perspective. Can J Cardiol 1995;11(Suppl B):5B-10B.


2.06 Heparin


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


2.07 Glycoprotein IIb/IIIa Drugs


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)

2.08 Thrombolysis


Fox KA. Comparative analysis of long-term mortality after thrombolytic therapy. Am J Cardiol 1991;68(16):38E-44E.

Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Topol EJ. Treatment of acute myocardial infarction: in which patients should primary percutaneous transluminal coronary angioplasty be preferred to thrombolysis? Cardiologia 1996;41(9):843-7.


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


2.09 Ticlopidine


Hankey GJ, Sudlow CL, Dunbabin DW. Thienopyridines or aspirin to prevent stroke and other serious vascular events in patients at high risk of vascular disease? A systematic review of the evidence from randomized trials. Stroke 2000;31(7):1779-84.


2.10 Clopidogrel


Hankey GJ, Sudlow CL, Dunbabin DW. Thienopyridines or aspirin to prevent stroke and other serious vascular events in patients at high risk of vascular disease? A systematic review of the evidence from randomized trials. Stroke 2000;31(7):1779-84.
Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


2.11 Percutaneous transluminal coronary angioplasty (PTCA) and stenting


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Topol EJ. Treatment of acute myocardial infarction: in which patients should primary percutaneous transluminal coronary angioplasty be preferred to thrombolysis? Cardiologia 1996;41(9):843-7.


Yusuf S, Pogue J. Primary angioplasty compared with thrombolytic therapy for acute myocardial infarction. JAMA 1997;278(23):2110-1.


2.12 Coronary artery bypass graft surgery (CABG)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.01 Hypertension


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.02 Diabetes


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.03a Hyperlipidemia as a risk factor for CHD in women


Austin MA. Epidemiology of hypertriglyceridemia and cardiovascular disease. Am J Cardiol 1999;83(9B):13F-16F.


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Cullen P. Evidence that triglycerides are an independent coronary heart disease risk factor. Am J Cardiol 2000;86(9):943-9.


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Holme I. Cholesterol reduction and its impact on coronary artery disease and total mortality. Am J Cardiol 1995;76(9):10C-17C.


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.03b Treatment of hyperlipidemia to reduce risk of CHD events in women


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Holme I. Cholesterol reduction and its impact on coronary artery disease and total mortality. Am J Cardiol 1995;76(9):10C-17C.


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.04 Elevated homocysteine


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.05 Elevated C-reactive protein


3.06 Smoking
Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.07 Obesity


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.08 Inactivity


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.09 Age


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.10 Age at Menopause


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.11 Ethnicity


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


3.12 Socioeconomic status


4.0 Difference in utilization between women and men


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Cerqueira MD. Diagnostic testing strategies for coronary artery disease: special issues related to gender. Am J Cardiol 1995;75(11):52D-60D.
Appendix D: Articles Eligible for Full-Text Review by Key Question
(continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


5.01 Troponins


5.02 Creatine kinase MB


Appendix D: Articles Eligible for Full-Text Review by Key Question (continued)


5.03 Myoglobin


Appendix E: Cost-effectiveness Analyses and Decision Analyses Articles (N = 21)

Appendix E: Cost-effectiveness Analyses and Decision Analyses Articles (continued)

Appendix F: Clinical Practice Guidelines (N = 43)


Appendix F: Clinical Practice Guidelines (continued)


Appendix F: Clinical Practice Guidelines (continued)


Appendix G: Evidence Reports (N = 9)


Appendix H: Abbreviations and Acronyms

ACE angiotensin converting enzyme
AHRQ Agency for Healthcare Research and Quality
β-blockers beta-blockers
CABG coronary artery bypass grafting
CHD coronary heart disease
CKMB creatinine kinase myocardial bands
CHF congestive heart failure
CVD cardiovascular disease
CI confidence interval
DTS Duke Treadmill Score
ECHO echocardiography
EKG electrocardiogram
EPC Evidence-based Practice Center
ETT exercise treadmill test
HDL high density lipoprotein
HDL-C high density lipoprotein cholesterol
LDL low density lipoprotein
LDL-C low density lipoprotein cholesterol
Lp(a) lipoprotein a
Mg milligrams
MI myocardial infarction
Mmol millimole
MRC/BHF Medical Research Council/British Heart Foundation
N number
NA not available
NHLBI National Heart Lung and Blood Institute
OR odds ratio
PCI percutaneous coronary intervention
PTCA percutaneous coronary angioplasty
SES socioeconomic status
SPECT single photon emission computed tomography
RR relative risk

Names of studies:
4S Scandinavian Simvastatin Survival Study
AFCAPS/TEXCAPS Air Force/Texas Coronary Artherosclerosis Prevention Study
AIRE Acute Infarction Ramipril Efficacy
ARIC Atherosclerosis Risk in Communities
BARI Bypass Angioplasty Revascularization Investigation
BENESTENT Belgian Netherlands Stent study
BBPP Beta Blocker Pooling Project
CABRI Coronary Angioplasty versus Bypass Revascularisation Investigation
### Appendix H: Abbreviations and Acronyms (continued)

#### Names of studies (continued):

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CARDIA</td>
<td>Coronary Artery Risk Development in Young Adults</td>
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<td>CARE</td>
<td>Cholesterol and Recurrent Events trial</td>
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<tr>
<td>CCS</td>
<td>Chinese Cardiac Study</td>
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<tr>
<td>CHS</td>
<td>Cardiovascular Health Study</td>
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<tr>
<td>CIBIS, CIBIS II</td>
<td>Cardiac Insufficiency Bisoprolol Study</td>
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<tr>
<td>COPERNICUS</td>
<td>Carvedilol Prospective Randomized Cumulative Survival Study</td>
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<tr>
<td>CURE</td>
<td>Clopidogrel in Unstable Angina to Prevent Recurrent Events Study</td>
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<tr>
<td>Consensus</td>
<td>Cooperative New Scandinavian Enalapril Survival Study</td>
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<tr>
<td>DOM</td>
<td>Diagnostisch Onderzoek Mammacarcinoom (Diagnostic Investigation of Mammary Cancer)</td>
</tr>
<tr>
<td>EPIC</td>
<td>Evaluation of 7E3 for the Prevention of Ischemic Complications</td>
</tr>
<tr>
<td>EPILOG</td>
<td>Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade</td>
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<tr>
<td>EPISTENT</td>
<td>Evaluation of Platelet IIb/IIIa Inhibitor for Stenting</td>
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<tr>
<td>FHS</td>
<td>Framingham Heart Study;</td>
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<tr>
<td>FTT</td>
<td>Fibrinolytic Therapy Trialists’ Collaborative Group</td>
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<tr>
<td>GISSI</td>
<td>Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico</td>
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<tr>
<td>GUSTO-I</td>
<td>Global Utilization of Strategies to Open Occluded Coronary Arteries Trial I</td>
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<tr>
<td>GUSTO-IV ACS</td>
<td>Global Utilization of Strategies to Open Occluded Coronary Arteries Trial IV in Acute Coronary Syndromes</td>
</tr>
<tr>
<td>HHP</td>
<td>Honolulu Heart Program</td>
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<tr>
<td>HOPE</td>
<td>Hypertension Optimal Treatment</td>
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<tr>
<td>INDANA</td>
<td>INIndividual Data ANalysis of Antihypertensive Intervention Trials</td>
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<tr>
<td>ISIS-2</td>
<td>Second International Study of Infarct Survival</td>
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<td>ISIS-4</td>
<td>Fourth International Study of Infarct Survival) Collaborative Group</td>
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<td>LIPID</td>
<td>Long-term Intervention with Pravastatin in Ischaemic Disease</td>
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<tr>
<td>MERIT-HF</td>
<td>Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure</td>
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<td>MRFIT</td>
<td>Multiple Risk Factor Intervention Trial</td>
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<tr>
<td>MUSIC</td>
<td>Multicenter Ultrasound Stenting In Coronary study</td>
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<tr>
<td>NHANES</td>
<td>National Health and Examination Survey</td>
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<td>NMRI</td>
<td>National Registry of Myocardial Infarction</td>
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<tr>
<td>OASIS</td>
<td>Organization to Assess Strategies for Ischemic Syndromes</td>
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<tr>
<td>PCI-CURE</td>
<td>Percutaneous Coronary Intervention Substudy of Clopidogrel in Unstable Angina to Prevent Recurrent Events Study</td>
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<tr>
<td>POSCH</td>
<td>Program on the Surgical Control of the Hyperlipidemias</td>
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<tr>
<td>PAMI</td>
<td>Primary Angioplasty in Myocardial Infarction</td>
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<tr>
<td>PARAGON</td>
<td>Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome events in a Global Organization Network</td>
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### Appendix H: Abbreviations and Acronyms (continued)

#### Names of studies (continued):

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<th>Acronym</th>
<th>Description</th>
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<td>PHS</td>
<td>Physicians’ Health Study</td>
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<tr>
<td>PR</td>
<td>Puerto Rico Heart Health Program</td>
</tr>
<tr>
<td>PRISM</td>
<td>Platelet Receptor Inhibition in Ischemic Syndrome Management</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
<td>Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression using Integrilin Therapy</td>
</tr>
<tr>
<td>RITA</td>
<td>Randomised Intervention Treatment of Angina</td>
</tr>
<tr>
<td>SAVE</td>
<td>Survival and Ventricular Enlargement</td>
</tr>
<tr>
<td>SHS</td>
<td>Strong Heart Study</td>
</tr>
<tr>
<td>SOLVD</td>
<td>Studies of Left Ventricular Dysfunction</td>
</tr>
<tr>
<td>Syst-China</td>
<td>Systolic Hypertension in China Study</td>
</tr>
<tr>
<td>TRACE</td>
<td>Trandolapril in Cardiac Evaluation</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>West of Scotland Coronary Prevention Study</td>
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</table>