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Diagnosis and Treatment of Coronary Heart Disease in Women: Systematic Reviews of Evidence on Selected Topics

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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 (AHRQ) and the National Institutes of Health Office of Research on Women's Health funded the University of California, San Francisco-Stanford Evidence-based Practice Center to perform systematic reviews and meta-analyses on four key topics related to coronary heart disease (CHD) in women: (1) accuracy of exercise myocardial perfusion imaging and echocardiography for diagnosis of CHD in women, (2) lipid lowering treatment to reduce risk of CHD in women, (3) diabetes as a risk factor for CHD in women, and (4) troponin as a prognostic factor for CHD in women. For each question, we also attempted to provide evidence stratified by race or ethnicity. We used standard methods to systematically review the medical literature to address each topic. The evidence identified was reviewed and graded, data were abstracted and the findings summarized for each topic.

Search Strategy. We developed specific search terms for each of the four key topics and performed standardized searches of electronic databases. We also reviewed bibliographies and sought suggestions from our peer reviewers. Authors of studies that met selection criteria but did not report findings by gender were contacted and asked to provide gender-specific outcomes.

Selection Criteria. Inclusion and exclusion criteria were defined for each of the four systematic reviews. Titles and abstracts were reviewed by investigators who coded each for eligibility. The full text of eligible articles was reviewed independently by two physician investigators using standardized forms to classify eligibility, rate quality and abstract data. The findings of all eligible studies rated good or fair quality were included in the summary estimates.

Data Collection and Analysis. Titles and abstracts were entered and coded using EndNote® (Niles Software, Inc). Data from the standardized review forms were entered in an Access (Microsoft® Corporation) database to allow tracking of eligibility, quality and study design. Abstracted data were also stored electronically in a database (EXCEL, Microsoft® Corporation).

Main Results

Overall

- Findings from 82 otherwise eligible studies could not be included in the systematic reviews because data were not stratified by gender. We contacted the author of these studies twice requesting data for women and received data from 19 studies (23 percent).
- Little evidence was available regarding the key questions as they pertain to women of different races/ethnicities. For this reason, only the review of diabetes as a risk factor for CHD provides summary findings by ethnicity.

Accuracy of exercise myocardial perfusion imaging and echocardiography for diagnosis of CHD in women

- We found 14 eligible studies that provided data on the accuracy of noninvasive tests in 893 women. Ten studies examined the accuracy of myocardial perfusion imaging and four examined the accuracy of exercise echocardiography.
- In women, the overall accuracy of both exercise myocardial perfusion imaging and exercise echocardiography for diagnosis of CHD is low with positive likelihood ratios of 2.5 to 3 and negative likelihood ratios of about 0.3.
- The accuracy of exercise myocardial perfusion imaging for diagnosis of CHD is not clinically different in women compared to men.
- There is little difference in the accuracy of exercise myocardial perfusion imaging and exercise echocardiography for diagnosis of CHD in women.
- The accuracy of exercise myocardial perfusion imaging for diagnosis of CHD is similar whether thallium or sestamibi is used as the imaging agent.

Efficacy of lipid lowering to reduce risk of CHD in women

- Although 20 clinical trials of the effects of lipid lowering therapy included women, only nine published results by gender. By contacting study investigators, we were successful in obtaining data on women from two additional trials. Thus, we were able to analyze results from 11 trials that included 15,917 women.
- In women with known CHD, treatment with lipid lowering therapy reduces risk of CHD mortality 26 percent, nonfatal myocardial infarction (MI) 36 percent and major CHD events 21 percent. There was insufficient evidence to show that lipid lowering reduces rates of revascularization procedures and no evidence of a reduction of risk in total mortality.
- For women without CHD, there is insufficient evidence to determine whether lipid lowering reduces risk for any clinical outcome.

Diabetes as a risk factor for CHD in women

- We found 17 eligible studies that included 43,944 women (4,522 with diabetes and 39,422 without diabetes).
- Adjusted summary odds ratios (ORs) for CHD mortality and nonfatal MI due to diabetes are higher among women than men, but summary ORs for all-cause mortality are slightly higher in men than women. All of the differences between men and women are modest and not statistically significant.
- The summary odds ratio for CHD mortality due to diabetes is 2.9 (95% confidence interval [CI], 2.2-3.8) for women and 2.3 (95% CI, 1.9-2.8) for men. The summary OR for nonfatal MI due to diabetes is 1.7 (95% CI, 1.3-2.3) for women and 1.6 (95% CI, 1.1-2.2) for men. The summary OR for all-cause mortality due to diabetes is 1.9 (95% CI, 1.7-2.3) for women and 2.1 (95% CI, 1.7-2.7) for men.

- Summary estimates for risk of CHD mortality due to diabetes for nonwhite men and women are similar to those for whites.
- The difference in relative risk for CHD outcomes between men and women is progressively attenuated with adjustment for major cardiovascular risk factors. This finding may be due to the fact that women with diabetes have more risk factors or more severe risk factor abnormalities in comparison to women without diabetes than is the case for men with and without diabetes.

Prognostic value of troponin for CHD in women

- We identified eight eligible cohort studies that provided data on 3,169 women and 4,070 men.
- Elevated troponin was observed in 35 percent of women and 39 percent of men with non-ST elevation acute coronary syndromes.
- Women with acute coronary syndromes were older and more likely to have diabetes and hypertension than men.
- An elevated troponin indicates a similar increase in risk of death for both women (summary OR 2.63; 95% CI 1.75-3.95) and men (OR 2.83; 95% CI 1.92-4.17).
- An elevated troponin indicates a greater increase in risk of nonfatal MI for women (summary OR 1.80; 95% CI 1.28-2.54) than men (OR 1.06; 95% CI 0.8-1.41).

Conclusions. The major problem in performing these systematic reviews was that data stratified by sex and race/ethnicity from completed studies are often 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 and made easily available to meta-analysts.

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Summary

Overview

Coronary heart disease (CHD) is a 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 the National Institutes of Health Office of Research on Women's Health funded the University of California, San Francisco (UCSF)-Stanford Evidence-based Practice Center (EPC) to review the evidence regarding prevention, diagnosis, and management of coronary heart disease in women and minorities. In an initial phase of this work, the UCSF-Stanford EPC conducted a preliminary review of evidence on 42 topics related to CHD in women, titled *Results of Systematic Review of Research on Diagnosis and Treatment of Coronary Heart Disease in Women.*[1] Based on these reviews, we identified four key questions for systematic review and meta-analysis. The results of these four reviews are presented in this report.

Key Questions

1. **What is the accuracy of noninvasive tests for diagnosis of CHD in women: exercise myocardial perfusion imaging (MPI) and exercise echocardiography?**
   a. What are the summary estimates of sensitivity, specificity and likelihood ratios for exercise MPI and exercise echocardiography in women?
   b. What is the accuracy of exercise MPI and exercise echocardiography in women compared to men?
2. **What is the effectiveness of treatment with lipid lowering drugs for reducing CHD risk in women with and without CHD?**
   a. What is the effectiveness of drug treatment in reducing total mortality, CHD mortality, CHD events or CHD procedures in women with known CHD and those without known CHD?
3. **What is the relative risk for CHD in women with type 2 diabetes?**
   a. What is the relative risk for CHD in women with type 2 diabetes compared to women without diabetes?

[1] Grady D, Chaput L, Kristof M. Results of Systematic Review of Research on Diagnosis and Treatment of Coronary Heart Disease in Women. Evidence Report/Technology Assessment No. 80. (Prepared by the University of California, San Francisco-Stanford Evidence-based Practice Center under Contract No 290-97-0013.) AHRQ Publication No. 03-0035. Rockville, MD: Agency for Healthcare Research and Quality. May 2003.

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b. Does the relative risk for CHD differ between women and men with type 2 diabetes?

4. **What is the prognostic value of troponin for CHD in women?**
   a. What is the impact of troponin on risk for death among women with non-ST elevation acute coronary syndromes?
   b. Does the prognostic value of troponin for mortality differ between men and women?
   c. What is the impact of troponin on risk for death or myocardial infarction for women with non-ST elevation acute coronary syndromes?
   d. Does the prognostic value of troponin for mortality or myocardial infarction differ between men and women?

For each of the four questions, we also attempted to identify and summarize evidence stratified by race or ethnicity.

Methodology

We performed standardized searches of electronic databases of publications relevant to the topic areas. We developed specific search terms for each of the four key topics and conducted a separate search for evidence regarding each. We also reviewed the bibliographies of retrieved articles and sought suggestions for additional articles from our expert peer reviewers. For each topic area, we established clear inclusion criteria that required that studies provide data regarding the research question specific to women.

For three of the key questions (noninvasive diagnostic tests, lipid lowering and diabetes), two UCSF-Stanford EPC investigators reviewed all identified titles and excluded those that 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 the remaining eligible articles was reviewed independently by two UCSF-Stanford EPC physician investigators using standardized abstraction forms to classify eligibility, rate quality as *fair* or *good* based on predefined criteria, and abstract data for eligible studies. For the key question regarding troponin, titles and abstracts were reviewed by one UCSF-Stanford EPC investigator. Data were abstracted from each eligible article by two independent reviewers and entered on standardized electronic data forms.

Accuracy of exercise myocardial perfusion imaging and echocardiography for diagnosis of CHD in women

We searched PubMed®, the Cochrane Database, and DARE for articles in English and other languages published from 1990 through January 2002. We used the following search terms to identify cross-sectional studies in which the accuracy of the exercise MPI or exercise echocardiography was compared to angiographic findings:

(Note: An asterisk indicates truncation of the search term.)

- Exercise MPI: thallium radioisotopes, radiopharmaceuticals, tomography emission-computed single-photon, technetium TC 99M sestamibi, organotechnetium compounds, Spect, Cardiolite, Mibi AND exercise, exercise test, exercise tolerance, exercise*, exercising, "stress test" AND diagnosis, diagnoses, diagnostic, diagnosing, predictive values of test
- Exercise echocardiography: echocardio*, ultrasound, ultrasonography AND exercise, exercise test, exercise tolerance, exercise*, exercising, "stress test" AND diagnosis, diagnoses, diagnostic, diagnosing, predictive values of test
- Outcomes: cardiovascular diseases, heart diseases, myocardial ischemia, coronary disease

Searches for noninvasive diagnostic tests identified 3,136 titles. After eliminating ineligible studies by review of titles and abstracts, we reviewed the full text of 326 articles and found 14 eligible cross-sectional studies with data on women that were included in the systematic review. Ten studies examined the accuracy of MPI and four examined the accuracy of exercise echocardiography.

Efficacy of lipid lowering to reduce risk of CHD in women

We searched PubMed®, the Cochrane Database, and DARE for articles in English and other languages published from 1966 through January 2002. We used the following search terms to identify clinical trials:

- Lipid lowering: hyperlipidemia and anticholesteremic agents, antilipemic agents, simvastatin, lovastatin, pravastatin, atorvastatin, fluvastatin, gemfibrozil, cholestyramine, cholestpol, niacin
- Outcomes: cardiovascular diseases, heart diseases, myocardial ischemia, coronary disease

Searches for clinical trials of lipid lowering treatment identified 1,335 titles. After eliminating ineligible studies by review of titles and abstracts, we reviewed the full text of 120 articles and found 11 eligible randomized trials that provided data on women and were included in the systematic review.

Diabetes as a risk factor for CHD in women

We searched PubMed®, the Cochrane Database, and DARE for articles in English and other languages published from 1966 through January 2002. We used the following search terms to identify cohort and cross-sectional studies:

- Diabetes: diabetes
- Outcomes: cardiovascular disease, myocardial infarction, ischemic heart disease

Searches for diabetes as a risk factor for CHD in women identified 4,578 titles. After eliminating ineligible studies by review of titles and abstracts, we reviewed the full text of 233 articles. We found 17 studies that fulfilled all inclusion criteria; 12 were prospective cohort studies and five were cross-sectional analyses.

Prognostic value of troponin for CHD in women

We searched MEDLINE® for articles in English and other languages published from 1966 through January 2002. We used the following search terms to identify clinical trials or cohort studies:

- The text word troponin, and
- The text words angina or unstable or myocardial infarction or ischemia.

We also performed a search of EMBASE from 1990-1998, but did not find any additional articles fulfilling the study criteria.

Searches identified 1,049 articles. We excluded 878 articles based on title or abstracts and reviewed the full text of 171 articles. Of these, eight eligible studies provided data on women and were included in the systematic review; six were clinical trials and two were cohort studies.

Findings

Overall

- Data from many otherwise eligible studies could not be included in the systematic reviews because the findings were not stratified by sex. We identified 82 studies that included women, but did not stratify the data by sex. We contacted authors of these studies twice requesting data on women but received data from only 19 studies (23 percent).
- Little evidence was available regarding the key questions as they pertain to women of different races/ethnicities. For this reason, only the review of diabetes as a risk factor for CHD provides summary findings by ethnicity.

Accuracy of exercise myocardial perfusion imaging and echocardiography for diagnosis of CHD in women

- Although 34 eligible studies of the accuracy of exercise myocardial perfusion imaging or exercise echocardiography included women, only nine published results by sex. By contacting study investigators, we were successful in obtaining data on women from five additional studies. Thus, we were able to analyze results from 14 studies that included 893 women. Ten studies examined the accuracy of myocardial perfusion imaging and four examined the accuracy of exercise echocardiography.
- In women, the overall accuracy of both exercise myocardial perfusion imaging and exercise echocardiography for diagnosis of CHD is low with positive likelihood ratios of 2.5 to 3 and negative likelihood ratios of about 0.3.
- The accuracy of exercise myocardial perfusion imaging for diagnosis of CHD is not clinically different in women compared to men.
- There is little difference in the accuracy of exercise myocardial perfusion imaging and exercise echocardiography for diagnosis of CHD in women.
- The accuracy of exercise myocardial perfusion imaging for diagnosis of CHD is similar whether thallium or sestamibi is used as the imaging agent.

Efficacy of lipid lowering to reduce risk of CHD in women

- Although 20 clinical trials of the effects of lipid lowering therapy included women, only nine published results by sex. By contacting study investigators, we were successful in obtaining data on women from two additional trials. Thus, we were able to analyze results from 11 trials that included 15,917 women.
- In women with known CHD, treatment with lipid lowering therapy reduces risk of CHD mortality 26 percent, nonfatal myocardial infarction (MI) 36 percent and major CHD events 21 percent. There was insufficient evidence to show that lipid lowering reduces rates of revascularization procedures and no evidence of a reduction of risk in total mortality.
- For women without CHD, there is insufficient evidence to determine whether lipid lowering reduces risk for any clinical outcome.

Diabetes as a risk factor for CHD in women

- Although 36 eligible studies included women, only 10 published results by sex. By contacting study investigators, we were successful in obtaining data on women from seven additional studies. Thus, we were able to analyze results from 17 studies that included 43,944 women (4,522 with diabetes and 39,422 without diabetes).
- Adjusted summary odds ratios (ORs) for CHD mortality and nonfatal MI due to diabetes are higher among women than men, but summary ORs for all-cause mortality are slightly higher in men than women. All of the differences are modest and not statistically significant.
- The summary OR for CHD mortality due to diabetes is 2.9 (95% confidence interval [CI], 2.2-3.8) for women and 2.3 (95% CI, 1.9-2.8) for men. The summary OR for nonfatal MI due to diabetes is 1.7 (95% CI, 1.3-2.3) for women and 1.6 (95% CI, 1.1-2.2) for men. The summary

OR for all-cause mortality due to diabetes is 1.9 (95% CI, 1.7-2.3) for women and 2.1 (95% CI, 1.7-2.7) for men.
- Summary estimates for risk of CHD mortality due to diabetes for white men and women are similar to those for all ethnicities combined.
- The difference in relative risk for CHD outcomes between men and women is progressively attenuated with adjustment for major cardiovascular risk factors. This finding may be due to the fact that women with diabetes have more risk factors or more severe risk factor abnormalities in comparison to women without diabetes than is the case for men with and without diabetes.

Prognostic value of troponin for CHD in women

- We reviewed the full text of 171 articles and found three eligible studies with data on women. Nine additional large studies of the prognostic value of troponin included women, but did not provide data stratified by sex. After contacting authors, we obtained data for women from five of these studies. Thus, we identified eight eligible studies that provided data on 3,169 women and 4,070 men.
- Elevated troponin was observed in 35 percent of women and 39 percent of men with non-ST elevation acute coronary syndromes.
- Women with acute coronary syndromes were older and more likely to have diabetes and hypertension than men with acute coronary syndromes.
- Elevated troponin indicates a similar increase in risk of death for both women (summary OR 2.63; 95% CI, 1.75-3.95) and men (summary OR 2.83; 95% CI, 1.92-4.17).
- Elevated troponin indicates a greater increase in risk of nonfatal MI for women (summary OR 1.80; 95% CI, 1.28-2.54) than men (summary OR 1.06; 95% CI, 0.8-1.41).

Future Research

The major problem in performing these systematic reviews was lack of availability of data on women and minority populations. Many studies that include women did not provide estimates stratified by sex. Attempts to obtain unpublished data from women were time-consuming and only modestly successful.

Recommendations for future research follow.

Overall

- Future studies that include women should publish or make available outcomes stratified by sex and ethnicity.

Accuracy of exercise myocardial perfusion imaging and echocardiography for diagnosis of CHD in women

- The quality of future studies of the accuracy of noninvasive tests for the diagnosis of CHD should be improved by excluding persons with known CHD, performing both the noninvasive test and angiography in all participants and assuring that the outcome of the noninvasive test is assessed by personnel blinded to the results of angiography.
- Future research should address ways to improve accuracy of noninvasive tests for CHD in both men and women.

Efficacy of lipid lowering to reduce risk of CHD in women

- Future clinical trials should include adequate numbers of women to determine the effect of lipid lowering in women at high risk but without known CHD.

Diabetes as a risk factor for CHD in women

- Future prospective studies should present sex- and race/ethnicity-specific fatal and nonfatal coronary disease endpoints before and after adjustment for established CHD risk factors.
- Future studies should attempt to clarify the effect of established risk factors, which cluster in women with diabetes, compared to the effect of diabetes itself in increasing risk for CHD among women with diabetes.

Prognostic value of troponin for CHD in women

- Future studies are needed to verify and explore why the prognostic value of elevated troponin results for nonfatal MI is different in women compared to men.

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. 81, *Diagnosis and Treatment of Coronary Heart Disease in Women: Systematic Reviews of Evidence on Selected Topics.* In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Evidence Report

Chapter 1: Introduction

Coronary heart disease (CHD) is the most common cause of death in women. Approximately 1 in 2 women develop CHD and 1 in 3 die from it,[1] accounting for over 250,000 deaths in women per year.[2] Despite the 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] During the last two decades, multiple important studies have helped define accurate clinical tests, important risk factors, preventive interventions and effective therapies for CHD. Unfortunately, the majority 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 in women differ from that in men.[5] Because large studies that include adequate numbers of women and minorities to answer the research question are generally not feasible, systematic reviews of the literature may be the best option for maximizing management of CHD in women.

The Agency for Healthcare Research and Quality (AHRQ) and the National Institutes of Health Office of Research on Women's Health funded the University of California, San Francisco (UCSF)-Stanford Evidence-based Practice Center (EPC) for 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.[6] Based on the results of the initial report, four key questions were identified for systematic review and meta-analysis: (1) the accuracy of exercise myocardial perfusion imaging and exercise echocardiography for diagnosis of CHD in women; (2) the efficacy of lipid lowering to reduce risk of CHD in women; (3) the strength of diabetes as a risk factor for CHD in women, and (4) the prognostic value of elevated troponin for CHD in women. This report presents the results of these four systematic reviews.

Organization

The methods of conducting these systematic reviews were similar. However, the appropriate study designs, inclusion criteria, clinical outcomes and statistical methods differed. In addition, the audience for each of these systematic reviews will likely differ. For these reasons, we present the four systematic reviews sequentially to allow each systematic review to stand alone.

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 minority populations. 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 National Institutes of Health Office of Research on Women's Health. The Centers for Medicare & 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 U.S. 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 the following four key questions:

1. **What is the accuracy of noninvasive tests for diagnosis of CHD in women: exercise myocardial perfusion-imaging (MPI) and exercise echocardiography?**
   a. What are the summary estimates of sensitivity, specificity and likelihood ratios for exercise MPI and exercise echocardiography in women?
   b. What is the accuracy of exercise MPI and exercise echocardiography in women compared to men?

2. **What is the effectiveness of treatment with lipid lowering drugs for reducing CHD risk in women with and without CHD?**
   a. What is the effectiveness of drug treatment in reducing total mortality, CHD mortality, CHD events or CHD procedures in women with known CHD and those without known CHD?

3. **What is the relative risk for CHD in women with type 2 diabetes?**
   a. What is the relative risk for CHD in women with type 2 diabetes compared to women without diabetes?
   b. Does the relative risk for CHD differ between women and men with type 2 diabetes?

4. **What is the prognostic value of troponin for CHD in women?**
   a. What is the impact of troponin on risk for death among women with non-ST elevation acute coronary syndromes?
   b. Does the prognostic value of troponin for mortality differ between men and women?
   c. What is the impact of troponin on risk for death or myocardial infarction for women with non-ST elevation acute coronary syndromes?

d. Does the prognostic value of troponin for mortality or myocardial infarction differ between men and women?

For each of the four questions, we also attempted to identify and summarize evidence stratified by race or ethnicity.

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Chapter 2. Systematic Review of the Accuracy of Exercise Myocardial Perfusion Imaging and Echocardiography for Diagnosis of Coronary Heart Disease in Women

Introduction

Multiple studies suggest that the accuracy of diagnostic testing for coronary heart disease (CHD) may be different in women compared to men.[1-6] Many factors may account for a differential accuracy, including differences in the pre-test probability of disease, chest wall anatomy, left ventricular chamber size, ability to exercise maximally, catecholamine response to exercise or hormone levels.

One systematic review of the studies of the diagnostic accuracy of exercise electrocardiogram (ECG), exercise thallium and exercise echocardiogram in women included literature published up to 1995. The review examined five myocardial perfusion imaging (MPI) studies that included 842 women and three echocardiography studies that included 296 women.[7] MPI studies all used thallium as the radionuclide; two studies used planar imaging and three used single photon emission computed tomography (SPECT). Weighted mean sensitivity and specificity for exercise ECG in women were 61 and 70 percent; for exercise MPI 78 and 64 percent; and for exercise echocardiography 86 and 79 percent. The findings suggested that exercise stress testing without imaging has limited accuracy in women and that planar MPI is more specific than SPECT. Exercise echocardiography appeared to be the most accurate test, but data were available from only three studies. This systematic review is now outdated and provides little information on the accuracy of currently used MPI techniques that almost universally employ SPECT with technetium or technetium plus thallium imaging.

Another systematic review examined the accuracy of exercise echocardiography and exercise SPECT imaging in men and women based on literature published up to 1997.[8] Weighted mean sensitivity and specificity for exercise MPI were 87 and 64 percent and for exercise echocardiography 85 and 77 percent. The authors concluded that exercise echocardiography and exercise SPECT have similar sensitivities for the detection of coronary artery disease, but exercise echocardiography has slightly higher specificity. The total number of subjects in this study was 5,436; 70 percent were men and separate estimates for accuracy in women were not provided.

The purpose of this systematic review is to evaluate the accuracy of exercise echocardiography and MPI in women, to determine if there are differences in accuracy of these tests in men and women, and to assess test characteristics of exercise MPI with thallium compared to technitium sestamibi imaging.

Methodology

Data sources

We searched PubMed®, the Cochrane Database, and DARE for articles in English and other languages published from 1990 through January 2002. We also reviewed bibliographies and asked peer reviewers (Appendix A) to identify additional articles. The date limits of the search were chosen because both exercise echocardiography and exercise MPI using SPECT with thallium and sestamibi were in widespread use during this period.

Search Terms

We used the following search terms to identify cross-sectional studies in which the accuracy of the diagnostic tests of interest were compared to angiographic findings:

Limits	publication dates 1990 to January 2002, human *Not:* practice guideline, letter, editorial, review, meta-analysis Infant newborn, infant, preschool child, child
Predictor 1:	thallium radioisotopes, radiopharmaceuticals, tomography emission-computed single-photon, technetium TC 99M sestamibi, organotechnetium compounds, Spect, Cardiolite, Mibi *AND* exercise, exercise test, exercise tolerance, exercise*, exercising, "stress test" *AND* diagnosis, diagnoses, diagnostic, diagnosing, predictive values of test
Predictor 2:	echocardio*, ultrasound, ultrasonography *AND* exercise, exercise test, exercise tolerance, exercise*, exercising, "stress test" *AND* diagnosis, diagnoses, diagnostic, diagnosing, predictive values of test Note -- all of the commas represent "OR" statements.
Outcomes	cardiovascular diseases, heart diseases, myocardial ischemia, coronary disease

Inclusion Criteria

To be included, articles were required to fit the following criteria:

1) Contained primary data on at least 10 women who underwent exercise ECG with radionuclide injection and SPECT imaging or exercise echocardiography.
2) Estimated accuracy of noninvasive tests using angiographic evidence of CHD as the gold standard.
3) Provided data to calculate true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) for the noninvasive tests.
4) Clear definition of positive noninvasive test and positive angiogram provided.
5) Published between 1990 and January 2002. Articles published outside this date range that were recommended by peer reviewers were included.

We excluded studies that met the following criteria:

1) Noninvasive tests performed exclusively in patients after myocardial infarction (MI), percutaneous angioplasty, coronary artery bypass surgery or hospitalization for an unstable coronary syndrome. In these patients, noninvasive tests are done for the purpose of risk assessment rather than diagnosis.
2) Tests in which pharmacologic agents rather than exercise were used as the stressor. Use of pharmacologic stressors may significantly affect the accuracy of noninvasive testing; many different agents are used and protocols for their use vary substantially.

Article Identification

An initial search using the terms listed above identified articles that potentially provided evidence. Two University of California, San Francisco (UCSF)-Stanford Evidence-based Practice Center (EPC) investigators reviewed the titles and excluded those that clearly did not provide data on humans or clearly did not address the question.

The abstracts of the remaining articles were reviewed independently by two UCSF-Stanford EPC physician investigators and coded using the categories listed below. Disagreements were discussed and consensus codes were entered into a database (Access, Microsoft Corporation).

T	Test – the study clearly does not include data on exercise ECG with imaging or exercise echocardiography.
A	Angiogram - the study clearly does not compare the results of the noninvasive test with the results of angiography.
ND	Not diagnostic - The study assesses noninvasive tests performed exclusively in patients after myocardial infarction, percutaneous angioplasty, coronary artery bypass surgery or hospitalization for an unstable coronary syndrome.
R	Review – the study is a review that does not contain primary data.

NH No humans - the study clearly does not include data on humans.

E_1 Eligible – the study may contain primary evidence regarding the research questions in women and will be reviewed in full-text.

Articles coded E_1 were retrieved and the full text was reviewed independently by two UCSF-Stanford EPC physician investigators. Names of authors and titles of journals were obscured before articles were reviewed.

Obtaining Unpublished Results in Women

Some eligible studies included women in the study population, but did not report findings separately by gender. In these instances we attempted to contact authors of these studies to obtain estimates in women. If we did not receive a response after the first contact, a second attempt was made. We contacted 34 authors[2, 9-41] and received data from five.[11, 15, 17, 18, 24]

Quality Assessment

The full text of each eligible study was reviewed independently by two UCSF-Stanford EPC physician investigators who completed a quality evaluation form (Appendix B). The studies included in this systematic review are cross-sectional. The three major quality issues affecting these studies are verification bias, biased outcome measurement and spectrum effect. Verification bias occurs when the decision to proceed to the gold standard is in part dependent on the results of the noninvasive test. Since positive noninvasive test results are more likely to be followed by an invasive test, this tends to increase the chance of detecting a true positive (TP) relative to a false negative (FN) and tends to increase the chance of detecting a false positive (FP) relative to a true negative (TN). Therefore, sensitivity may appear to be higher and specificity lower in the verified sample. Biased outcome measurement occurs when personnel performing or reading the results of the noninvasive test already know the results of angiography. Spectrum effect refers to the variation in test performance depending on the severity of disease in the population studied. Sensitivity and specificity appear higher when the persons studied either have severe disease or are healthy. For instance, in participants with significant coronary disease and healthy volunteers, the spectrum of disease is clear-cut, and both sensitivity and specificity will be higher compared to a population with intermediate prior probability of coronary disease, such as those with angina. Our quality assessment addresses verification bias and biased outcome measurement, and we recorded spectrum of disease to allow subgroup analyses.

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

- All participants who had the noninvasive test also had angiography.
- The diagnosis of coronary artery disease on angiography was made by investigators blinded to the results of the noninvasive test

Studies that did not meet these criteria were considered *fair* quality.

Data Abstraction

Two UCSF-Stanford EPC physician investigators independently reviewed the full text of each eligible study and completed a data abstraction form (Appendix C). Data abstracted included characteristics of the study (design, inclusion and exclusion criteria, noninvasive tests performed, and setting), participant characteristics (number of women and men, mean age of participants, number with prior MI, number with revascularization, cardiac risk factors in the population, and indications for cardiac testing), and test characteristics (type of exercise, average duration of exercise, percent with adequate exercise, radionuclide and imaging protocols used, criteria for positive noninvasive test, and criteria for positive coronary angiogram). For each eligible study, the numbers of true positive, true negative, false positive and false negative tests were recorded or calculated as necessary. We also abstracted accuracy measures for all subgroups evaluated. Disagreements between abstractors were discussed and decided by consensus. For studies with multiple publications, only data from the most comprehensive or recent publication were used.

Data Management and Archive

We entered all identified titles and abstracts in an EndNote® file (Niles Software, Inc.) that includes searchable key words as codes for eligibility. Information on all articles that were reviewed in full text was transferred from EndNote® to a database (Access, Microsoft® Corporation) that allows us to categorize each article by reason for exclusion. Quality assessment data for each eligible study were also entered in the database, allowing us to categorize eligible articles by quality.

Abstracted data were entered into a database (EXCEL, Microsoft® Corporation) for preparation of evidence tables and calculation of summary estimates, confidence intervals and tests of heterogeneity.

The full-text articles that were retrieved, and the abstraction forms for each article are filed in Dr. Grady's offices at the UCSF Mt. Zion Women's Health Clinical Research Center.

Data Analyses

The primary outcomes of each study were expressed as sensitivity, specificity, positive likelihood ratio and negative likelihood ratio comparing the results of the noninvasive test to angiographic findings. Summary results were calculated as the mean of the appropriate proportion (sensitivity, specificity, likelihood ratios) weighted by the sample size of each individual study. The significance level for all p-values for the weighted means was set at 0.05. All findings were assessed for heterogeneity using Z-tests. The significance level for tests of heterogeneity was 0.10. To avoid calculation problems associated with zero cells, 0.5 was added to all cells to calculate variances and standard deviations.[42] Results for women vs. men were compared using the Q* statistic, the point on the summary ROC curve where sensitivity equals specificity.[43]

Publication bias usually occurs if small studies with unremarkable findings (poor accuracy) are not published while small studies with markedly positive findings (high accuracy) are published. We calculated the correlation between individual study sample size and sensitivity using Kendall's Tau to assess potential publication bias.

Results

Study Identification

Our searches identified 3,136 titles. After eliminating ineligible studies by review of titles and abstracts, we reviewed the full text of 326 articles and found 14 eligible for inclusion in the systematic review.[2, 6, 17, 18, 23, 24, 41, 44-50] Of the 10 studies included that examined exercise MPI as the noninvasive test, five used thallium,[17, 41, 44-46] four used sestamibi[18, 23, 47, 48] and one used both[6] as radionuclide agents.

Nine MPI studies that provided accuracy estimates in women were excluded from the systematic review: four used pharmacologic agents in addition to exercise;[51-54] four reported some measures of accuracy, but did not report adequate data to allow calculation of all required estimates,[5, 55-57] and one did not provide definitions of a positive noninvasive test or positive coronary angiogram.[58]

Four eligible studies examined the accuracy of exercise echocardiography as the noninvasive test.[2, 24, 49, 50] One study of exercise echocardiography that provided accuracy estimates for women was excluded because it was published outside our date range.[59]

Description of Eligible Studies

The characteristics of the 10 studies assessing the accuracy of MPI that were included in the systematic review are shown in Evidence Table 1. The number of participants in each

study ranged from 41 to 371 and 14 to 100 percent were women. The total number of participants was 1,249, including 549 women and 700 men. Three of the studies included only women. One study included both men and women, but provided data that allowed calculation of accuracy estimates only in women.[48] The mean age of participants ranged from 51 to 62 years. Eight of the studies included participants with prior MI. All 10 studies used SPECT imaging; five used thallium only, four sestamibi only and one used both radionuclides. The definition of an abnormal test was very similar in nine of the studies (fixed or reversible perfusion defects, perfusion defects at rest or after exercise or decreased uptake at rest or after exercise). One study defined a positive test as reversible uptake defects in more than one of 22 coronary segments. All but one of the 10 studies defined 50 percent stenosis of one or more major coronary artery at angiography as the gold standard for the presence of coronary artery disease. Eight studies used treadmill exercise and two used bicycle exercise. Six of the MPI studies were judged fair quality and four were judged good quality.

The characteristics of the four studies assessing the accuracy of echocardiography that were included in the systematic review are shown in Evidence Table 2. The number of participants in each study ranged from 70 to 340 and 15 to 100 percent were women. The total number of participants was 689, including 344 women and 345 men. Two of the studies included both men and women and 2 included only women.[2, 49] The mean age of participants ranged from 55 to 66 years. One of the studies included participants with prior MI. Two of the studies defined an abnormal test as new or worse regional wall motion abnormalities after exercise and two defined a positive as regional wall motion abnormalities at rest or after exercise. All studies defined 50 percent stenosis of at least one major coronary artery at angiography as the gold standard for the presence of coronary artery disease. Two of the echocardiography studies were judged fair quality and two were judged good quality.

Findings

Exercise Myocardial Perfusion Imaging

In women, sensitivity of exercise MPI using either thallium or sestamibi ranged from 0.61 to 1.0 with a mean weighted sensitivity of 0.77 (95% CI 0.72-0.83) (Evidence Table 3). Specificity of exercise MPI in women ranged from 0.40-1.0, with a mean weighted specificity of 0.69 (95% CI 0.62-0.75). The mean weighted positive likelihood ratio for exercise MPI in women was 2.46 (95% CI 2.00-3.04) and the mean weighted negative likelihood ratio was 0.33 (95% CI 0.26-0.41).

Based on the findings of the six studies that included men, the mean weighted sensitivity of exercise MPI in men was 0.93 (95% CI 0.90-0.95) (Evidence Table 3) and the mean weighted specificity was 0.57 (95% CI 0.47-0.67). The mean weighted positive likelihood ratio for exercise MPI in men was 2.17 (95% CI 1.73-2.73) and the mean weighted negative likelihood ratio was 0.13 (95% CI 0.09-0.19).

We performed a subgroup analysis limited to the findings of the four good quality studies (Evidence Table 1). Mean weighted accuracy estimates from these analyses were not materially different from the overall mean summary estimates (Evidence Table 3).

We performed two sensitivity analyses. One eligible study evaluated the accuracy of both thallium and sestamibi.[6] The overall mean weighted results included only the accuracy estimates for sestamibi. A sensitivity analysis substituting the results for thallium produced similar overall results. We also repeated the analysis for women including the findings of one study that was excluded because no definitions of an abnormal test or abnormal angiogram were provided.[58] Including the results of this study did not materially change the accuracy estimates.

We calculated mean weighted accuracy estimates for men and women from studies that used sestamibi separately from those that used thallium (Evidence Table 4). Accuracy estimates in women for studies using sestamibi and those using thallium were very similar (p-value for the comparison of Q* statistics = 0.84)

Exercise Echocardiography

In women, sensitivity for exercise echocardiography ranged from 0.77 to 0.88 with a mean weighted sensitivity of 0.81 (95% CI 0.74-0.87) (Evidence Table 5). Specificity for exercise echocardiography in women ranged from 0.37 to 0.84, with a mean weighted specificity of 0.73 (95% CI 0.66-0.79). The mean weighted positive likelihood ratio for exercise echocardiography in women was 2.95 (95% CI 2.28-3.79) and the mean weighted negative likelihood ratio was 0.26 (95% CI 0.19-0.36).

Based on the findings of two studies of the accuracy of echocardiography that included men, the mean weighted sensitivity was 0.84 (95% CI 0.79-0.88) and the mean weighted specificity was 0.45 (95% CI 0.32-0.59) (Evidence Table 5). The mean weighted positive likelihood ratio for exercise echocardiography in men was 1.54 (95% CI 1.20-1.98) and the mean weighted negative likelihood ratio was 0.36 (95% CI 0.24-0.53).

We performed subgroup analyses limited to the findings of the two good quality studies of the accuracy of exercise echocardiography in women (Evidence Table 1). The mean weighted sensitivity estimate from the good quality studies was similar to the overall mean sensitivity (0.82 vs. 0.81), but specificity was lower (0.60 vs. 0.73) (Evidence Table 5). These differences resulted in a lower mean weighted positive likelihood ratio based on the good quality studies compared to the estimate based on all eligible studies (2.06 vs. 2.95). Mean estimates of negative likelihood ratios did not differ when results were restricted to the good quality studies (Evidence Table 5).

We performed a sensitivity analysis by adding the results of one study of the accuracy of exercise echocardiography that was published before our date range.[59] Including the results of this study did not materially change the overall accuracy estimates.

Accuracy of Exercise MPI vs. Echocardiography in Women

Based on 10 studies of the accuracy of exercise MPI and four of exercise echocardiography, the accuracy of each test for the diagnosis of CHD in women is similar (Evidence Tables 3 and 5). The mean weighted sensitivity, specificity and positive likelihood ratio for MPI are slightly lower than for echocardiography (sensitivity 0.77 vs. 0.81; specificity 0.69 vs. 0.73, positive likelihood ratio 2.46 vs. 2.95), but the differences are small and not statistically different (p-value for the Q* statistic = 0.10). The accuracy of the two tests is also similar when analyses are restricted to good quality studies (Evidence Tables 3 and 5). The use of sestamibi instead of thallium also did not change the accuracy of MPI studies in women (Evidence Table 4).

Accuracy of Noninvasive Testing in Women Compared to Men

The mean weighted sensitivity of MPI in women is somewhat lower than in men (0.77 vs. 0.93), but the specificity is higher (0.69 vs. 0.57) (Evidence Table 3). The positive likelihood ratio is slightly higher in women compared to men (2.46 vs. 2.17) as is the negative likelihood ratio (0.33 vs. 0.13). These differences in the accuracy of MPI between men and women were statistically significant (p-value for the comparison of Q* statistics 0.028), but it is not clear whether higher sensitivity or higher specificity is preferable.

Comparison of mean weighted accuracy estimates between women and men may be biased if these data are derived from different studies that may have used somewhat different methods and definitions of positive tests. To avoid this problem, we calculated mean weighted accuracy estimates for men and women restricted to the findings of studies that included both genders (Evidence Table 3). Based on the findings of these studies, sensitivity of MPI is lower in women than in men (0.86 vs. 0.93), but specificity is the same (0.57 for both genders; p-value for the comparison of Q* statistics 0.012). This analysis suggests that exercise MPI is more accurate in men than in women, but the differences are small and not clinically meaningful.

The mean weighted sensitivity of echocardiography in women is similar to that in men (0.81 vs. 0.84), but the specificity is higher (0.73 vs. 0.45) (Evidence Table 5). The positive likelihood ratio was substantially higher in women than in men (2.95 vs. 1.54), and the negative likelihood ratio was slightly lower (0.26 vs. 0.36). However, given the small numbers of men included in the analyses, we could not calculate a Q* statistic or determine any statistically significant differences between men and women with regard to exercise echocardiography.

Assessments for Heterogeneity and Publication Bias

There was no heterogeneity in any of the mean weighted estimates of accuracy. Publication bias usually occurs if small studies with unremarkable findings (poor accuracy) are not published while small studies with markedly positive findings (high

accuracy) are published. We calculated the correlation between individual study sample size and sensitivity using Kendall's Tau to assess potential publication bias. There was no evidence of publication bias in any of the summary estimates of accuracy.

Conclusions

In the last decade, both exercise echocardiography and exercise MPI have become widely available and commonly used for noninvasive diagnosis of coronary disease. It is important for both patients and providers to understand the accuracy of these tests and their limitations. We obtained results from 14 studies published between 1990 and 2002 on the accuracy of these tests in women. Based on these data, the overall accuracy of both tests in women is low with positive likelihood ratios of 2.5 to 3 and negative likelihood ratios of about 0.3.

There are several advantages of estimating accuracy of a diagnostic test using likelihood ratios rather than sensitivity and specificity. First, it is possible to achieve a high sensitivity for most diagnostic tests by accepting a low specificity; similarly, high specificity can be achieved by accepting low sensitivity. In contrast, both sensitivity and specificity must be high to achieve good likelihood ratios (positive LR = sensitivity/(1-specificity) and negative LR = (1-sensitivity)/specificity). Secondly, likelihood ratios are a powerful tool to apply clinically using Bayes' theorem; the post-test odds that a patient has the disease are estimated by multiplying the pre-test odds by the positive likelihood ratio. For instance, in a 55 year old woman with probable angina, the prior probability of CHD is about 30 percent.[60] If her exercise MPI is positive, her posterior probability of CHD would be about 50 percent (prior odds 1:2.3 multiplied by positive LR of 2.5 equal posterior odds of 2.5:2.3 which is equivalent to posterior probability of about 50 percent). Similarly, if her exercise echocardiogram is positive, her posterior probability of having CHD would be about 55 percent. If either of these studies were negative, her posterior probability would be about 10 percent. Small differences in the posterior probabilities based on exercise MPI or echocardiogram do not have different clinical implications and suggest that the value of these tests is equivalent.

The common conception that exercise testing in women should always be combined with imaging may not be true. A prior meta-analysis that evaluated the accuracy of exercise EKG in women found a mean weighted positive likelihood ratio of 2.25 and a negative likelihood ratio of 0.55.[7] These accuracy estimates are very similar to those that we calculated for exercise MPI and echocardiogram and would result in very similar estimates of posterior probability of CHD. However, women who receive exercise EKG testing without imaging are more likely to have a normal EKG at baseline and thus may be less likely to have significant CHD. Thus, comparison of the accuracy of exercise EKG with exercise imaging studies or exercise echocardgiography may be biased unless patients are randomized to receive the different tests.

The value of a diagnostic test result depends on the accuracy of the test, the prior probability of disease and the threshold for treatment. In women with low to intermediate prior probability of CHD, a positive exercise MPI or echocardiogram result in similar posterior probabilities that may warrant further testing. Our 55 year-old woman with angina, for example, has about a 50 percent probability of having CHD if she has a positive noninvasive test. Before labeling her as having CHD and beginning treatment, many clinicians may want to pursue angiography. An older woman in her mid sixties with angina has about a 50 percent prior probability of having CHD. If she has a negative noninvasive test, her posterior probability of having CHD is about 25 percent. Many clinicians may prefer a more accurate test (such as angiography) before declaring that this woman does not have CHD and forgoing treatment.

Our analysis found that the sensitivity of exercise MPI in women was lower than in men. While this difference was statistically significant, it was small and not clinically meaningful. Most of the studies included in our review reported a higher prevalence of CHD in men than in women. The prevalence of prior MI also was higher in men compared to women. This spectrum effect could account for the apparent lower sensitivity of MPI in women compared to men. Alternatively, the lower sensitivity in women may be due to differences in chest wall anatomy, left ventricular chamber size, ability to exercise maximally, catecholamine response to exercise or hormone levels. Comparison of the accuracy of exercise echocardiography in women and men was limited by the small number of studies that reported separate data for men.

Evaluation of the accuracy of noninvasive tests requires a dichotomous outcome. The conventional "gold standard" for the presence of CHD is 50 percent or more stenosis of one or more of the major coronary arteries at angiography, and this is the definition that we used. However, coronary heart disease represents a continuum of disease that may not be best measured by angiography.

In addition to diagnosis of CHD, exercise MPI and exercise echocardiography are also performed to localize disease and to determine the extent of disease. Our analysis provides no data on the accuracy of noninvasive tests for these purposes.

The value of our review is limited by the quality of the studies included and the number of persons included. Many of the studies included in this systematic review were rated only fair quality, often because it was not clear that personnel who interpreted the noninvasive test were blinded to the results of the angiogram. Prior knowledge of angiographic results could falsely increase the accuracy of the noninvasive test. In many of the studies included, only persons with a positive noninvasive test went on to have angiography. This verification bias may result in higher sensitivity and lower specificity than in studies in which all subjects undergo both tests.

Unfortunately, most studies did not report the percent of maximum predicted heart rate achieved by subjects. Failure to achieve 85 percent of maximum predicted heart rate would likely result in a higher number of false negatives and lower sensitivity. Sensitivity might be lower in women if they are less likely than men to exercise adequately.

Most of the studies of MPI and one of the studies of echocardiography included a substantial proportion of persons with prior myocardial infarction. Including persons with diagnosed disease likely increases sensitivity at the cost of specificity. Finally, we identified only 14 studies that met our inclusion criteria and the number of women included was limited. We identified many additional studies that included some women, but were unable to obtain data stratified by gender from the authors.

Future Research

Studies of the accuracy of noninvasive tests should publish all estimates of accuracy stratified by sex, or make these estimates available to public access. Stratification by sex would allow more precise estimates of the accuracy of noninvasive tests for CHD in women, but it is unlikely that this would result in a substantial improvement in the estimated accuracy of the tests. The major finding of this systematic review is that the accuracy of noninvasive tests for CHD in both men and women is low and that future research should address ways to improve accuracy. The quality of future studies of the accuracy of noninvasive tests for the diagnosis of CHD would be improved by excluding persons with known CHD, performing both the noninvasive test and angiography in all participants and assuring that the outcome of the noninvasive test is assessed by personnel blinded to the results of angiography. Finally, assessment of the value of diagnostic tests for estimating risk of future CHD events would have important long-term clinical implications.

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Chapter 3. Systematic Review of Lipid Lowering Treatment to Reduce Risk of Coronary Heart Disease in Women

Introduction

Coronary heart disease (CHD) is the leading cause of death in the United States and half of all deaths from CHD occur in women.[1, 2] Among white women, the cumulative risk of developing CHD between 50 and 94 years of age is 46 percent and the cumulative risk of dying from CHD is 31 percent.[3]

Elevated total cholesterol, low density lipoprotein-C (LDL-C) and triglycerides, and low high density lipoprotein-C (HDL-C) are risk factors for CHD in women.[4-6] Lipid lowering may be achieved with either diet or drugs, but few studies have addressed the effects of dietary interventions on clinical outcomes. Several randomized clinical trials have evaluated the effect of lipid lowering with drugs on risk of CHD events, both in persons with known cardiovascular disease and in those without CHD.[7-11] Unfortunately, many of the clinical trials of lipid lowering treatments did not include women and others did not include adequate numbers of women to allow sex-specific analyses. Finally, some of the trials that did include women reported aggregate events (e.g. major coronary events) but did not report specific outcomes such as CHD death or nonfatal myocardial infarction (MI) separately.

A previous systematic review of lipid lowering therapy in women included only studies published before 1995 and is now outdated.[12] A more recent systematic review that included only trials of statin drugs found that both women and men treated with statins had a 30 percent reduction in risk of major CHD events.[13] However, this review did not address outcomes other than major CHD events in women, did not stratify by primary or secondary prevention and did not include data from recent large trials.

The goal of this systematic review is to critically assess the available clinical trial evidence regarding drug treatment of hyperlipidemia for the prevention of CHD events and death in women. We will assess the effects of lipid lowering on total mortality, CHD mortality, nonfatal myocardial infarction (MI), CHD events and revascularization procedures in women with and without prior CHD.

Methodology

Data sources

We searched PubMed®, the Cochrane Database, and DARE for articles published in English and other languages from 1966 through January 2002. We also reviewed bibliographies and asked peer reviewers (Appendix A) to identify additional articles.

Search Terms

Search terms were developed in collaboration with a medical librarian and included the following:

Limits	publication dates 1966 to January 2002, human *Not:* practice guideline, letter, editorial, review, meta-analysis, infant, newborn, preschool child, child
Predictor	hyperlipidemia and anticholesteremic agents, antilipemic agents, simvastatin, lovastatin, pravastatin, atorvastatin, fluvastatin, gemfibrozil, cholestyramine, cholestpol, niacin
Outcomes	cardiovascular diseases, heart diseases, myocardial ischemia, coronary disease

Inclusion Criteria

To be included, articles were required to fit the following criteria:

1) Randomized clinical trials of outpatients with or without known CHD.
2) Treatment duration of at least one year.
3) Study population classified as either primary (participants without prior CHD) or secondary prevention (participants with prior CHD).
4) Data on women provided.
5) Impact of lipid lowering with drug treatment assessed for at least one of the following clinical outcomes: total mortality, CHD mortality, nonfatal MI, CHD events or revascularization procedures. Coronary events included ischemic coronary syndromes and nonfatal myocardial infarction. CHD procedures included coronary bypass graft surgery and percutaneous coronary angioplasty or stenting.
6) Published between January 1, 1966 and January 30, 2002. Articles published outside this date range recommended by peer reviewers were included.

We excluded studies that only provided evidence on the effect of treatment on changes in lipids, angiographic findings or other intermediate outcomes. For studies with multiple publications, only data from the most comprehensive or most recent publication were used.

Article Identification

An initial search using the terms listed above identified articles that potentially provided evidence. Two University of California, San Francisco (UCSF)-Stanford Evidence-based Practice Center (EPC) physician investigators reviewed the titles and excluded those that clearly did not provide data on humans or clearly did not address the question.

The abstracts of the remaining articles were reviewed independently by two UCSF-Stanford EPC physician investigators and coded using the categories listed below. Disagreements were discussed and the following consensus codes were entered into a database (Access, Microsoft Corporation):

RQ	Research question - the article clearly does not address the research question.
R	Review – the study is a review that does not contain primary data.
NSD	Not appropriate study design - The article is not a randomized clinical trial.
NH	No humans - the study clearly does not include data on humans.
E_1	Eligible – the study may contain primary evidence regarding the research question in women and will be reviewed in full-text.

Articles coded E_1 were retrieved and the full text was reviewed independently by two UCSF-Stanford EPC investigators. Names of authors and titles of journals were obscured before articles were reviewed.

Obtaining Unpublished Results

Some eligible studies included women in the study population, but did not report findings separately by gender. In these instances we attempted to contact authors to obtain these data. If we did not receive a response after the first contact, a second attempt was made. We contacted 13 authors[11, 14-27] and received data from two.[16, 25, 26]

Quality Assessment

The full text of each eligible study was reviewed independently by two UCSF-Stanford physician investigators, who completed a quality evaluation form (Appendix B). All of the studies included in this systematic review are randomized clinical trials. To be categorized as *good quality*, articles were required to meet the following additional parameters:

- Inclusion/exclusion criteria clear and appropriate.
- Randomization allocation concealed.
- Control group received placebo.
- Participants and research staff blinded to intervention.
- More than 75 percent complete followup.

All other trials were considered *fair quality*. Disagreements between reviewers regarding quality parameters were decided by discussion and consensus.

Data Abstraction

Two UCSF-Stanford EPC physician investigators independently reviewed the full text of each eligible study and completed a data abstraction form (Appendix C). We abstracted information on the study population (primary prevention trials were defined as those that included individuals without known CHD; secondary prevention trials included individuals with known CHD), inclusion criteria, length of followup, numbers of men and women, participant characteristics such as age, other cardiovascular risk factors and cardiac medication use, baseline and followup lipoprotein values and all clinical outcomes that were measured. When possible, data were abstracted for men and women separately. Disagreements were discussed and decided by consensus.

Data Management and Archive

We entered all identified titles and abstracts in an EndNote® file (Niles Software, Inc.) that includes searchable key words as codes for eligibility. Information on all articles that were reviewed in full text was transferred from EndNote® to a relational database (Access, Microsoft® Corporation) that allows us to categorize each article by reason for exclusion. Quality assessment data for each eligible study were also entered in the Access database, allowing us to categorize eligible articles by quality. Selected data were transferred to a flatfile database (EXCEL, Microsoft® Corporation) for preparation of evidence tables and calculation of summary estimates, confidence intervals and tests of heterogeneity.

The full-text articles that were retrieved, and the abstraction forms for each article are filed by topic and question in Dr. Grady's offices at the UCSF Mt. Zion Women's Health Clinical Research Center.

Data Analyses

The primary outcome of each clinical trial was expressed as the relative risk (RR) among treated compared to untreated study participants. Summary estimates of RR and 95 percent confidence intervals (CI) were calculated using the Mantel-Haenszel method and both fixed and random effects models. Results of the fixed and random effects models were similar, and we report only the findings of the random effects model. To avoid calculation problems associated with zero cells, 0.5 was added to all cells to calculate variances and standard deviations.[28] The significance level for all tests of outcome was set at 0.05. All findings were assessed for heterogeneity using a standard Chi-square test and Q statistic with critical value set at 0.10. All analyses were performed separately for the findings of primary and secondary prevention studies. Subgroup analyses were performed by type of drug treatment (statins vs. others), and by good vs. fair quality.

Publication bias usually occurs if small studies with unremarkable findings (relative risks about 1.0) are not published while small studies with markedly positive findings (in this case, low relative risks) are published. We calculated the correlation between individual study weight (1/variance) and relative risk using a nonparametric correlation coefficient (Kendall's Tau) with critical value set at 0.10 to assess potential publication bias. Statistically significant correlation of study weight and relative risk suggests publication bias.

Results

Results of Study Identification

Our searches identified 1,335 titles. After eliminating ineligible studies by review of titles and abstracts, we reviewed the full text of 120 articles. We identified 20 studies that fit all inclusion criteria, but only 9 provided outcomes stratified by sex.[7-9, 11, 27, 29-39] We contacted the principal investigators of the studies that did not provide data for women to request this information.[11, 14-27] We received data on women from two investigators.[16, 25, 26] Thus, 11 studies (represented by 19 articles) were found to be both eligible and to contain data stratified by sex for inclusion in the systematic review.[7-9, 11, 16, 25-27, 29-39] One additional study did not meet inclusion criteria because it did not provide data on any of the clinical outcomes of interest and the study population was equally divided between persons with prior CHD and those without prior CHD and separate estimates for the effects of lipid lowering in primary and secondary prevention were not published.[40]

Description of Eligible Studies

Characteristics of the 11 eligible trials are described in Evidence Table 6. The numbers of participants in each trial ranged from 151 to 20,536 and 15 to 50 percent of participants were women. The total number of women included in the trials was 15,917, but almost two thirds were from two studies.[11, 39]Information on the ethnicity of participants was not provided in most trials. Duration of treatment ranged from 2.8 to 6.1 years and averaged 4.7 years. Seven of the trials were classified as secondary prevention and four were classified as primary prevention (Evidence Table 6). Eligibility criteria for 5 trials required at least mild hyperlipidemia,[7, 16, 25, 26, 31, 39] four required a range of cholesterol levels that would include some participants in the normal range[9, 11, 27, 34] and 2 included participants regardless of cholesterol levels.[29, 30] Three trials assessed the effects of clofibrate[29, 30] or colestipol[31] and eight assessed the efficacy of treatment with statins (lovastatin,[9, 25, 26] simvastatin,[7, 11, 39]pravastatin[16, 27, 34]).

All but one of the 11 trials included a placebo control group[39] and all but two were adequately blinded.[31, 39] In all but one of the trials,[31] followup was greater than 75 percent complete. Overall, seven of the trials were rated good quality and four were rated fair (Evidence Table 6).

The clinical outcomes evaluated were total mortality, CHD mortality, nonfatal MI, CHD events and revascularization (Evidence Tables 7 and 8). Most trials were designed to address clinical outcomes, but two were designed to evaluate change in intimal medial thickness of the carotid artery[16, 25, 26] and included clinical events only as secondary outcomes.

For studies with mixed populations (e.g. some participants had CHD and some did not), the trial was classified as primary or secondary prevention based on the status of the majority of participants. Participants in most of the trials classified as primary prevention were at high risk for CHD outcomes due to presence of CHD risk factors.

Three trials included participants with and without CHD. In the colestipol trial, only 20 percent of participants had CHD and this trial was classified as a primary prevention study.[31] In the Heart Protection Study, 65 percent of participants had known CHD and remaining 35 percent had peripheral vascular disease, cerebrovascular disease or diabetes.[11] Because the majority of participants had CHD and those without CHD were also at very high risk for CHD events, this trial was classified as a secondary prevention study. A recently published trial included older participants with CHD and those at high risk for CHD in approximately equal numbers[40] and did not present results stratified by history of CHD. Because of the equal distribution, we are unable to classify this study as either primary or secondary prevention. In addition, we could not include the results of this trial for any specific coronary disease endpoint because the results for women were only given for the composite outcome of cardiovascular events (CHD mortality, nonfatal MI, fatal stroke and nonfatal stroke).

Findings

For each outcome, we assessed the effects of lipid lowering separately for primary and secondary prevention studies. We also calculated summary estimates based on the findings of all eligible studies, those that used a statin as the lipid lowering agent and those that were rated good quality (Evidence Table 8).

Seven trials assessed the effects of lipid lowering among women with CHD (secondary prevention)[7, 8, 11, 16, 27, 29, 30, 32-37] and included a total of 8,244 women. Two of these trials used clofibrate as the intervention,[29, 30] while five used a statin.[7, 8, 11, 16, 27, 32-37] Both of the trials of clofibrate were rated fair,[29, 30] while all of the statin trials were rated good quality. While seven trials provided data, three were small (22 to 124 women),[16, 29, 30] two were mid-sized (576[8, 34, 35] and 827 women[32, 33]) and only two included more than 1,000 women (1,516[27, 36, 37] and 5,082[11]). Evidence was also limited because several of the trials reported results among women for only one or two of the five outcomes of interest (total mortality, CHD mortality, nonfatal MI, CHD events and revascularization).

Four trials assessed the effects of lipid lowering among women without prior CHD (primary prevention)[9, 25, 26, 31, 38, 39] and included 7,673 women. One of these trials used colestipol as the intervention[31] and the rest used a statin. Two trials[31, 39] were rated fair and the other two good quality.[9, 25, 26, 38] Three of these trials included about 1,000 women or less (441,[25, 26] 997,[9, 38] and 1,184[31]) and one included 5,051.[39] As with the secondary prevention trials, many of these trials reported results among women for only one or two of the five outcomes of interest.

Secondary Prevention

Total mortality. Two trials,[7, 16, 32, 33] both using a statin as the intervention, reported the effect of lipid lowering on mortality among a total of 899 women with CHD (Evidence Table 7). One of these trials[16] enrolled only 22 women, so that essentially all of the data regarding the effects of lipid lowering for secondary prevention of mortality in women comes from one trial that used a statin as the intervention.[7, 32, 33] Neither of the two trials found a reduction in risk of mortality among women (Evidence Table 7), and the summary relative risk was 1.11 (95% CI 0.66-1.87) (Evidence Table 8).

CHD mortality. Five trials reported the effect of lipid lowering on CHD mortality among 1,646 women with CHD (Evidence Table 7). However, three of these trials were small,[16, 29, 30] and two,[7, 8, 32-35] both using a statin as the intervention, provide most of the evidence regarding the effect of lipid lowering on CHD mortality in women with CHD. The findings of these two trials were consistent in showing a reduced risk of CHD death among women treated with lipid lowering compared to controls. The summary relative risk for secondary prevention of CHD mortality was 0.74 (95% CI 0.57-0.96), suggesting a 26 percent reduction in risk of CHD mortality (Evidence Table 8).

Nonfatal MI. Five trials reported the effect of lipid lowering on risk for nonfatal MI in 1,646 women with CHD (Evidence Table 7). Three of these trials were small[16, 29, 30] and two trials, both using a statin as the intervention,[7, 8, 32-35] provide most of the evidence regarding the effect of lipid lowering for secondary prevention of nonfatal MI in women. Both of these two trials showed a reduced risk for nonfatal MI and the summary relative risk was 0.64 (95% CI 0.50-0.82), suggesting a 36 percent reduced risk (Evidence Table 8).

CHD events. Four trials, all using a statin as the intervention, reported the effect of lipid lowering on CHD events in 8,001 women with CHD (Evidence Table 7). These trials consistently found a reduced risk of CHD events among women,[7, 8, 11, 27, 32-37] with a summary relative risk of 0.79 (95% CI 0.72-0.88), suggesting a 21 percent reduced risk of CHD events among women with CHD (Evidence Table 8).

Revascularization. Two trials, both using a statin as the intervention, reported the effect of lipid lowering for secondary prevention of revascularization procedures in 1,403 women with CHD (Evidence Table 7). Both of these trials found a reduction in risk among treated women and the summary relative risk was 0.70 (95% CI 0.42-1.16). Although the summary relative risk suggests a 30 percent reduction in risk of revascularization, this finding was not statistically significant (Evidence Table 8).

Drug class and study quality. Only two studies, including a total of 221 women, addressed the impact of lipid lowering drugs other than statins.[29, 30] Thus, evidence on the effect of non-statin drugs is limited. However, the summary ORs were similar for all outcomes when findings were restricted to those studies using a statin. Both of the studies that used a non-statin drug were rated fair quality,[29, 30] and all five of the trials that used a statin were rated good quality. Thus, the summary ORs are also unchanged when the results are restricted to good quality studies.

Sensitivity analyses. One trial that we included with the secondary prevention studies enrolled a mixed population of persons with and without CHD and reported the effect of statin treatment on risk for CHD events.[11] Because 65 percent of the participants had prior CHD and the rest had vascular disease or diabetes, we included the results of this trial as secondary prevention. We also performed a sensitivity analysis excluding the results of this trial. The summary relative risk for secondary prevention of CHD events excluding the results of this trial was essentially unchanged (summary relative risk 0.74; 95% CI 0.61-0.91). We also performed a sensitivity analysis by adding the results of the cardiovascular disease outcomes from the PROSPER trial to the summary results for secondary prevention of CHD events.[40] The summary relative risk for secondary prevention of CHD events including the results of this trial was essentially unchanged (summary relative risk 0.76; 95% CI 0.72-0.87).

Primary Prevention

Total mortality. Four trials[9, 25, 26, 31, 38, 39] reported the effect of lipid lowering on mortality among 7,673 women without prior CHD (Evidence Table 7). One of these trials[31] used colestipol as the intervention, while the rest used a statin. One of the trials reported a lower risk of mortality in women treated with lipid lowering compared to controls, but the other three did not (Evidence Table 7). The summary relative risk for primary prevention of mortality was 0.95 (95% CI 0.62-1.46) (Evidence Table 8).

CHD mortality. Three trials[9, 25, 26, 31, 38] reported the effect of lipid lowering on CHD mortality among 2,622 women without prior CHD (Evidence Table 7). One of these trials[31] used colestipol as the intervention, while the other two used a statin. One of the three trials reported a lower risk of CHD mortality in women treated with lipid lowering compared to controls,[25, 26] but the others did not. The summary relative risk for primary prevention of CHD mortality was 1.07 (95% CI 0.47-2.40).

Nonfatal MI. Two trials[9, 25, 26, 38] reported the effect of lipid lowering on risk for nonfatal MI in 1,646 women without prior CHD (Evidence Table 7). Both of these trials used a statin as the intervention, and both found a reduced risk of nonfatal MI among women treated with lipid lowering. The summary relative risk for primary prevention of nonfatal MI was 0.61 (95% CI 0.22-1.68). Although the summary relative risk suggests a 39 percent reduction in risk of nonfatal MI among treated women, this finding was not statistically significant.

CHD events. Two trials, both using a statin as the intervention,[9, 38, 39] reported the effect of lipid lowering on risk for CHD events in 6,048 women without prior CHD (Evidence Table 7). The results of these trials are inconsistent, and the summary relative risk for primary prevention of CHD events was 0.87 (95% CI 0.50-1.49).

Revascularization. Only one trial reported the effect of statin therapy for primary prevention of revascularization procedures in women[9, 38] (Evidence Table 7). This trial found a relative risk of 0.87 (95% CI 0.33-2.31).

Drug class and study quality. Evidence on the primary prevention effects of drugs other than statins is limited as only one trial addressed the impact of a non-statin drug.[31] The summary ORs were similar for all outcomes when findings were restricted to those studies using a statin or to studies rated good quality.

Sensitivity analyses. We performed a sensitivity analysis by adding the results of the cardiovascular disease outcomes from the PROSPER trial to the summary results for primary prevention of CHD events.[40] The summary relative risk for primary prevention of CHD events including the results of this trial was essentially unchanged (summary relative risk 0.97; 95% CI 0.84-1.12).

Assessments for Heterogeneity and Publication Bias

There was no statistical evidence of heterogeneity in any of the overall summary estimates of the effect of lipid lowering on any outcome except for secondary prevention of revascularization (Evidence Table 8). There was no evidence of publication bias in any of the summary estimates.

Conclusions

Although 20 clinical trials of the effects of lipid lowering therapy included women, only nine published results by gender. By contacting study investigators, we were successful in obtaining data on women from two additional trials. Thus, we were able to analyze results from 11 trials that included 15,917 women. However, complete data on the five outcomes of interest were not available from each trial, limiting our ability to assess the effect of lipid lowering on some outcomes. Only three studies, including a total of 1,405 women, addressed the impact of lipid lowering drugs other than statins. Thus, evidence on the effect of non-statin drugs is limited.

In the secondary prevention setting, treatment with lipid lowering therapy reduced risk of CHD mortality, nonfatal MI and CHD events in women. Summary estimates suggest a 26 percent reduction in risk of CHD mortality, a 36 percent reduction in risk of nonfatal MI and a 21 percent reduction in risk of a CHD event. There was no evidence of a reduction in risk of total mortality and insufficient evidence to document a reduction in risk of revascularization procedures. In the primary prevention setting, there was insufficient evidence of reduced risk of any clinical outcome in women. The summary relative risk for nonfatal MI was similar to that for secondary prevention (39 percent reduction vs. 36 percent reduction for secondary prevention), but was not statistically significant.

A prior systematic review of the findings of clinical trials of the effects of lipid lowering among persons without CHD used inclusion criteria and methods very similar to ours, but did not stratify the results by gender.[41] Since 90 percent of the participants included in that review were men, the results primarily reflect the effects of lipid lowering in men. Among (mostly) men, primary prevention with lipid lowering resulted in about a 30 percent reduced risk for both CHD events and CHD mortality[41] Our findings suggest that, among persons without CHD, lipid lowering may not be as effective in women as in men without CHD. However, our power to observe a modest reduction in CHD risk was limited because the findings of only four primary prevention trials were available for inclusion in the meta-analysis.

We were unable to include findings from a recently published clinical trial of the effect of lipid lowering among 2,804 men and 3,000 women aged 70 to 82 years randomized to pravastatin or placebo and followed for a mean of 3.2 years.[40] About half of the participants in this trial had vascular disease and the others had vascular risk factors. Results were reported for the effect of lipid lowering on cardiovascular events in women (CHD mortality, nonfatal MI, fatal stroke and nonfatal stroke); the relative risk among women treated with pravastatin was 0.96 (95% CI 0.79-1.18). We could not include these data because we could not categorize the trial as primary or secondary prevention and results in women were only given for cardiovascular events. Given the timeline for this review, we did not have time to contact the authors to request findings stratified by sex, primary vs. secondary prevention and clinical outcomes. However, in sensitivity analyses that included the results of this trial as either primary or secondary prevention of CHD events did not alter the findings.

There were no clinical differences in the summary odds ratios when studies included were restricted to those that used a statin as the intervention or to good quality studies. This is likely because eight of the 11 included trials used a statin as the intervention, and seven of the 11 trials were rated good quality.

In summary, lipid lowering therapy appears to reduce risk of CHD mortality, nonfatal MI and CHD events 25 to 35 percent in women with prior CHD. There was inadequate evidence to document a reduction in risk of any clinical outcome among women without prior CHD. Data were limited, but the risk for total mortality was not lower in women

treated with lipid lowering, regardless of whether they had prior CHD or not. The lack of reduction in risk for mortality in either primary or secondary prevention settings may be because lipid lowering does not affect total mortality in women or because there were few deaths, even after summarizing study findings.

Future Research

Future randomized trials should include women in adequate numbers to assess the effects of lipid lowering on clinical outcomes. Studies that include women should report the effects of lipid lowering on all clinical outcomes stratified by sex and primary vs. secondary prevention.

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Chapter 4. Systematic Review of Diabetes as a Risk Factor for Coronary Heart Disease in Women

Introduction

Studies suggest that there may be a stronger association between type 2 diabetes and coronary heart disease (CHD) risk in women than in men. Estimates of coronary heart disease mortality in diabetic men have varied from 1 to 3-fold the rate in nondiabetic men,[1-10] while estimates in diabetic women have ranged from 2 to 5-fold the rate in nondiabetic women.[2, 5, 8, 10-12] Variations in study population, design, quality and findings make it difficult to evaluate the strength of diabetes as a risk factor for CHD in either sex. Two previous meta-analyses that included studies that did not adjust for major cardiovascular risk factors concluded that diabetes is a stronger risk factor for CHD mortality in women than in men.[13, 14] However, it is unclear whether these reported sex differences are real or attributable to differences in other major risk factors for CHD between diabetic men and women.

The goal of this systematic review is to establish an accurate estimate of CHD risk among women with type 2 diabetes and to compare the risk of CHD in diabetic women to that in diabetic men. Our main analyses will include only studies that provide multivariate-adjusted comparisons to determine the independent association between diabetes and coronary disease outcomes.

Methodology

Data Sources

We searched PubMed®, the Cochrane Database, and DARE for studies in English or other languages published from 1966 through January 2002 . We also reviewed bibliographies and asked peer reviewers (Appendix A) to identify additional articles. In the case of multiple publications from a single study, we used the most comprehensive or recent publication.

Search Terms

Search terms were developed in collaboration with a medical librarian and include the following:

Limits	publication dates 1966 to 2002, peer-reviewed articles
Predictor	diabetes
Outcomes	cardiovascular disease, myocardial infarction, ischemic heart disease

Inclusion Criteria

To be included, articles were required to fit the following criteria:

1) Include both men and women and provide an estimate of the CHD risk associated with diabetes in both sexes.
2) Followup of the cohort for at least six months.
2) Data on one of the following outcomes: total mortality, CHD mortality, cardiovascular disease (CVD) mortality or nonfatal myocardial infarction (MI).
3) Inclusion of primarily type 2 diabetic participants (defined by self-report, use of diabetic medication, medical record diagnosis, positive oral glucose tolerance test or an elevated fasting glucose).
4) Inclusion of multivariate adjustment for confounders, including at least age, hypertension, hypercholesterolemia and smoking.
5) Inclusion of a nondiabetic, concurrent control group.
6) Published between January 1, 1966 and January 1, 2002. Articles published outside this date range that were recommended by peer reviewers (Appendix A) were included.

Definition of Outcomes

All included studies defined CHD mortality by the International Classification of Diseases, Ninth Revision (ICD-9) codes of 410 through 414 or by physician documentation of sudden cardiac death. Nonfatal MI was defined by definite electrocardiographic criteria using the Minnesota code, enzyme levels consistent with MI, self-report (with or without Rose questionnaire criteria), or medical record documentation.

Article Identification

An initial search using the terms listed above identified articles that potentially provided evidence. Two University of California, San Francisco (UCSF)-Stanford Evidence-based Practice Center (EPC) investigators reviewed the titles and excluded those that clearly did not provide data on humans or clearly did not address the question.

The abstracts of the remaining articles were reviewed independently by two UCSF-Stanford EPC physician investigators and coded using the categories listed below. Disagreements were discussed and consensus codes were entered into a database (Access, Microsoft Corporation).

RQ	Research question: the article clearly does not address the research question
R	Review – the study is a review that does not contain primary data
NH	No humans - the study clearly does not include data on humans
O	Outcome- the study clearly does not address the outcomes of interest
P	Predictor- the study clearly does not include type 2 diabetics
E_1	Eligible – the study may contain primary evidence regarding the research questions in women and will be reviewed in full-text

Articles coded E_1 were retrieved and the full text was reviewed independently by two UCSF-Stanford EPC physician investigators. Names of authors and titles of journals were obscured before articles were reviewed.

Obtaining Unpublished Results in Women

Some eligible studies included women in the study population, but did not report findings separately by gender. In these instances we twice attempted to contact the authors of these studies to obtain these data. We contacted the authors of 26 articles, requesting the required information.[4, 5, 8, 11, 15-36] Authors of seven studies[15-21] provided the data necessary to satisfy inclusion criteria. Some authors were unable to recreate their original analyses [4, 11, 22, 23] or did not have the necessary variables in the dataset,[24-26] and others did not provide the requested data.[5, 8, 27-36]

Quality Assessment

The full text of each eligible study was reviewed independently by two UCSF-Stanford physician investigators who completed a quality evaluation form (Appendix B). Most of the studies included in this systematic review are prospective cohort studies. The major quality issues with this study design are lack of information on potential confounders, inadequate duration of followup, non-blinded outcome adjudication and loss to followup.

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

- Prospective cohort design (vs. retrospective cohort or cross-sectional design)
- Type 2 diabetes defined by fasting plasma glucose or oral glucose-tolerance test (vs. other definitions of diabetes)
- Multivariate adjustment for potential confounders in addition to age, hypertension, hypercholesterolemia, and smoking
- At least 14 years of followup time (the median length of followup of all studies)
- Less than 10 percent loss to followup

Studies were considered to be of *fair quality* if they met the following parameters:

- Retrospective or cross-sectional study design
- Criteria other than fasting plasma glucose or oral glucose-tolerance test used to define diabetes
- Adjusted for age, hypertension, hypercholesterolemia, and smoking only
- Follow-up time of less than 14 years
- More than 10 percent loss to followup

Data Abstraction

Two UCSF-Stanford EPC physician investigators independently reviewed the full text of each eligible study and completed a data abstraction form (Appendix C). One author reviewed titles and abstracts of articles retrieved from the search and excluded case reports, letters, comments, reviews, and reports without primary data. Two UCSF-Stanford EPC physician investigators reviewed the 50 remaining manuscripts to determine study eligibility. Data were extracted on study quality, participant characteristics, length of followup, and outcomes (CHD mortality, nonfatal MI, and cardiovascular or all-cause mortality). Discrepancies between reviewers were resolved by consensus. For studies with multiple publications, only data from the most comprehensive or recent publication were used.

Data Management and Archive

We entered all identified titles and abstracts in an EndNote® (Niles Software, Inc) file that includes searchable key words as codes for eligibility. Information on all articles that were reviewed in full text was transferred from EndNote® (Niles Software, Inc) to a database (Access, Microsoft® Corporation) that allows us to categorize each article by reason for exclusion. Quality assessment data for each eligible study were also entered in the database (Access, Microsoft® Corporation), allowing us to categorize eligible articles by quality.

Abstracted data were entered into a database (EXCEL, Microsoft® Corporation) for preparation of evidence tables and calculation of summary estimates, confidence intervals and tests of heterogeneity.

The full-text articles that were retrieved, and the abstraction forms for each article are filed by topic and question in Dr. Grady's offices at the UCSF Mt. Zion Women's Health Clinical Research Center.

Data Analysis

The primary outcome of each study was expressed as the most adjusted odds ratio (and 95 percent confidence interval) for CHD events among persons with diabetes compared to those without diabetes. Summary estimates of odds ratio and 95 percent confidence

intervals were calculated using a general variance-based (confidence interval) method[37] that retains adjustment for confounding. We calculated summary odds ratios using both a fixed and random effects model.[38] Results were similar using both models and we report only summary odds ratios based on the random effects model. The significance level for all summary relative risks was set at 0.05. All estimates were assessed for heterogeneity using a Chi square test with the significance level set at 0.10.

Publication bias usually occurs if small studies with unremarkable findings (odds ratios for the association of diabetes and CHD risk around 1.0) are not published while small studies with markedly positive findings (high odds ratios) are published. We calculated the correlation between individual study weight (1/variance) and odds ratio using Kendall's Tau (a nonparametric correlation coefficient) to assess potential publication bias.

Summary estimates for men and women were compared using the Z-test, with a two-tailed five percent level of significance. The main comparisons were repeated in subgroups defined by race/ethnicity (white, black, Latino, Japanese American, and Native American) and by study design (prospective cohort and cross-sectional analyses). Sensitivity analyses were performed to assess the effects of study quality and degree of adjustment for confounding on the outcome.

Results

Results of Study Identification

Our searches identified 4,578 titles. Of the 233 articles that contained primary data, 50 were duplicative publications, 46 did not include a nondiabetic control group, 44 did not provide information about the outcomes of interest and 26 did not perform analyses based on diabetes status. Eight studies did not provide data stratified by sex and used ineligible study designs,[39-46] seven were hospital-based studies with followup less than six months,[47-53] nine included only patients with prior MI.[54-62] Seven studies were excluded because the study population consisted of a single sex only.[63-69]

Of the 36 remaining studies, ten met all inclusion criteria.[12, 70-78] Twenty-two did not publish adequately adjusted risk estimates,[4, 5, 15-31, 33-35] two did not report 95 percent confidence intervals or p-values for adjusted results,[2, 8] and two provided only combined outcomes of nonfatal and fatal CHD.[11, 36] We contacted the authors of these 26 articles twice requesting the required information.[4, 5, 8, 11, 15-36] Authors of seven studies[15-21] provided the data necessary to satisfy inclusion criteria. Some authors were unable to recreate their original analyses [4, 11, 22, 23] or did not have the necessary variables in the dataset,[24-26] and others did not provide the requested data.[5, 8, 27-36]

Description of Eligible Studies

After receiving additional information from authors, 17 studies fulfilled all inclusion criteria (Evidence Table 9); 12 were prospective cohort studies[12, 15, 20, 70-78] and five were cross-sectional analyses.[16-19, 21] More than one publication provided data from the same cohort [70, 77] such that the meta-analysis includes adjusted findings from 14 distinct study populations.

Followup time in the 12 prospective cohort studies ranged from 5 to 32 years (mean approximately 14 years). Most of the studies enrolled middle-aged participants; one study enrolled only subjects older than 65.[19] The 14 study populations included 6,235 diabetic participants (48 percent women) and 71,306 nondiabetic control subjects (52 percent women). In 7 of the 17 studies,[12, 15, 16, 18, 19, 71, 79] all diabetics were type 2; the remainder of the studies included a few type 1 diabetics, but the majority were type 2.[20, 21, 70, 72, 144, 73-78]

Summary of Results

Evidence Table 10 presents the multivariate-adjusted odds ratios (OR) by gender and ethnicity for CHD mortality, nonfatal MI, and all-cause mortality for each included study. Most of the studies show a higher OR for CHD mortality and for nonfatal MI due to diabetes among women compared to men. Outcomes for cardiovascular and all-cause mortality are mixed with approximately half of the studies showing a higher odds ratio for women than men.

CHD Mortality

The overall summary OR for CHD mortality due to diabetes was 2.3 (95% CI, 1.9 - 2.8) for men and 2.9 (95% CI, 2.2 - 3.8) for women for all race/ethnic groups combined (Evidence Table 11). Although the overall summary OR for CHD mortality from diabetes for women was somewhat higher than for men, the summary estimates were not statistically different (p=0.19 for the comparison of ORs). In sensitivity analyses that included only studies of whites, a trend to statistically significant differences between the summary odds ratios for men and women was observed only when outcomes were inadequately adjusted for potential confounders (Evidence Table 12). For example, based on the results of studies that provided age-adjusted estimates, the summary OR was higher in women compared to men (3.42 vs. 2.07; p-value for difference = .05).

Most studies that reported CHD mortality were performed in white subjects, limiting subgroup analyses by race to whites. Summary estimates for CHD mortality from eligible studies for white men and women were similar to those for all ethnicities combined 2.2 (95% CI, 1.8-2.7) for men and 2.8 (95% CI, 2.1–3.7) for women.

Nonfatal Myocardial Infarction and All-Cause Mortality

The summary OR for nonfatal MI due to diabetes was 1.6 (95% CI, 1.1-2.2) for men and 1.7 (95% CI, 1.3-2.3) for women, a difference that was not statistically significant (p=.68 for comparison of ORs in men and women) (Evidence Table 11).

The summary OR for all-cause mortality due to diabetes was 2.1 (95% CI, 1.7-2.7) for men and 1.9 (95% CI, 1.7-2.3) for women, a difference that was not statistically significant (p=.50 for comparison of ORs in men and women) (Evidence Table 11).

Despite summarizing estimates from 14 distinct study populations, we lacked power to perform subgroup analyses by race/ethnicity for CHD mortality and total mortality. We were able to derive summary estimates for nonfatal MI for Latinos only from two cross-sectional analyses.[18, 19] Diabetes did not significantly increase risk of nonfatal myocardial infarction for Latino men (summary OR 1.2; 95% CI, 0.6-2.4) or for Latina women (1.4; 95% CI, 0.9-2.1). The summary estimates for Latino men and women were lower than those for non-Latino whites (OR 1.7; 95% CI 1.1-2.6 for men and 2.8; 95% CI 1.7-4.4 for women).

Assessments for Heterogeneity and Publication Bias

There was no heterogeneity in the findings of the individual studies for CHD death, nonfatal MI and total mortality in women. There was no hetereogeneity in the findings of the studies for CHD mortality in men, but there was significant heterogeneity of the findings among men for nonfatal MI and total mortality (Evidence Table 11) that was not explained in subgroup analyses.

There was no evidence of publication bias in any of the summary odds ratios.

Conclusions

Using estimates adjusted for age, hypertension, hypercholesterolemia and smoking, summary ORs for CHD mortality and nonfatal MI due to diabetes were higher among women than men, but ORs for all-cause mortality were slightly higher in men than women. All of the differences were modest and not statistically significant.

Two prior meta-analyses have addressed the question of whether there is a sex-specific difference in risk for coronary outcomes related to diabetes.[13, 14] The first meta-analysis included the results of 25 prospective, population-based studies that provided unadjusted data to examine gender differences in relative risk of CHD mortality and myocardial infarction associated with type 2 diabetes.[13] The risk of CHD death was higher for diabetic women compared to men. However, many of the cohort studies included in this meta-analysis did not control for established risk factors for coronary disease. The second and more recent meta-analysis included the results of 10 studies and found that women

with diabetes were at significantly higher risk of CHD mortality compared with men (2.58 vs. 1.85, p=.045 for the comparison of ORs)[14]. This meta-analysis included studies that adjusted only for age and included subjects with prior coronary disease. In a subgroup analysis excluding studies of patients with existing coronary disease, there was no significant difference between summary ORs for CHD death between men and women (1.9 in men vs. 2.4 in women, p=0.18). A third systematic review based on this evidence report was recently published.[80]

These results of the two prior systematic reviews are consistent with our findings, except that we found no statistically significant differences between summary ORs for CHD for men and women. This disparity is likely due to the fact that the prior reviews included studies in which outcomes were unadjusted, while our inclusion critieria required adjustment for major CHD risk factors. Our subgroup analyses suggest that the difference in relative risk for CHD mortality between men and women is attenuated with adjustment for major cardiovascular risk factors. This may be due to the fact that diabetic women have more risk factors or more severe risk factor abnormalities compared to nondiabetic women than do diabetic men compared to nondiabetic men.[81] Alternatively, cardiac risk factors may have a stronger impact on CHD risk in women than in men or risk factors may be managed less aggressively in women than in men.[82, 83] Adjustment for additional risk factors that were not included in most of the analyses in studies in our meta-analysis, (HDL cholesterol, triglycerides, exercise, body mass index) or more specific adjustment using continuous measures of risk rather than risk categories, might eliminate the remaining disparity between men and women. These data suggest that most of the observed difference in risk for CHD due to diabetes in men and women is mediated by traditional cardiac risk factors that are likely modifiable.

Four large prospective cohort studies did not meet criteria for inclusion in our meta-analysis.[4, 8, 11, 36] These four studies had conflicting results; one showed a higher diabetes-associated relative risk for CHD mortality in men compared to women,[36] another showed a higher relative risk among women,[4] and the two remaining studies found no difference between the sexes.[8, 11] It is unlikely that the addition of the results of these four studies would have changed our summary estimates significantly. The results of one large prospective cohort study in the United States was not included, since participants were all women.[66] In a sensitivity analysis, we added the results of this study to our summary estimate for CHD mortality in white women. The resulting summary OR for CHD mortality was 2.83 (95% CI, 2.27-3.53), very similar to the summary estimate restricted to the results of studies that included both men and women (OR = 2.79; 95% CI, 2.11-3.69).

It is now recommended that cardiovascular risk factors be treated as aggressively in diabetic patients without a history of CHD as in nondiabetic patients with a prior myocardial infarction.[84] Based on the results of the present review, diabetes independently increases the risk of fatal CHD in both men and women without pre-existing CHD by 2- to 3-fold. The fact that the summary OR for CHD mortality is

attenuated more with adjustment for major risk factors in women than in men diabetics suggests that women with diabetes might benefit more from aggressive risk factor management than diabetic men.

As with any systematic review, we are limited to the variables measured and endpoints reported in each eligible study. We required that outcomes be adjusted for major CHD risk factors, but these variables were defined differently in the studies. Likewise, there were differences in definition of outcomes among studies. Some studies differentiated patients with impaired glucose tolerance from those with frank diabetes, while others included those with impaired glucose tolerance with nondiabetic subjects. Some studies did not completely distinguish participants with type 1 diabetes from those with type 2. These errors of misclassification may have caused us to underestimate summary ORs. Lastly, we were unable to analyze results based on race/ethnicity for most of the outcomes due to the absence of studies meeting our inclusion criteria in nonwhite populations.

The advantage of the present systematic review is that it is restricted to the findings of studies controlled for age, hypertension, hypercholesterolemia, and smoking. The most accurate adjusted summary odds ratio for coronary heart disease mortality due to diabetes for all race/ethnic groups combined is 2.3 for men and 2.9 for women. The difference in odds ratios between men and women is modest and not statistically significant.

Future Research

Future prospective studies should present sex- and ethnicity-specific fatal and nonfatal coronary disease endpoints before and after adjustment with established CHD risk factors. Analyzing the effect of specific risk factors separately and in combination will help to clarify their role in the cardiovascular protection observed in women without diabetes. In addition, much remains to be learned about coronary outcomes among ethnic minority groups with diabetes.

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Chapter 5. Systematic Review of Troponin as a Prognostic Factor for CHD in Women

Introduction

Patients with acute coronary syndromes (defined as myocardial infarction (MI) or unstable angina) are at increased risk for subsequent acute myocardial infarction and death. Managing patients with known or suspected acute coronary syndromes consumes a large amount of resources. Approximately five million people undergo evaluation for acute coronary syndromes in emergency departments annually in the United States at an estimated cost of over six billion dollars.[1] Several tests have been used to identify patients at high risk of a major cardiac event, including the electrocardiogram, blood tests of proteins (cardiac markers) released with myocardial injury and clinical characteristics obtained from the history and physical exam. Several characteristics were recently combined in a risk score by the Thrombolysis in Myocardial Infarction (TIMI) study group.[2] These characteristics include age of 65 or greater, known coronary artery disease, at least three risk factors for coronary artery disease (family history, hypertension, diabetes, hypercholesterolemia, current smoker), ST-segment deviation of at least 0.5 mm, recent severe angina, aspirin use in the last seven days and elevated cardiac markers (troponin, creatine kinase-MB fraction). In a recently published study based on data from Evidence Report Number 31 (Prediction of Risk for Patients with Unstable Angina),[3] we found that troponin cardiac markers indicate substantial risk for death or subsequent myocardial infarction.[4]

Cardiac troponin immunoassays (troponin T and I) were approved in 1994 by the Food and Drug Administration as markers of acute myocardial infarction and risk stratification. The troponin complex is comprised of three proteins (C, I, and T) which together regulate the contraction of striated muscle (cardiac and non-cardiac). Troponin C binds calcium and regulates contraction, troponin I inhibits actomyosin adenosine triphosphatase, and troponin T binds the troponin complex to tropomyosin. Because cardiac troponin C has the same amino acid sequence as skeletal muscle it is not a specific marker for cardiac injury. In contrast, cardiac troponins I and T are easily distinguished from skeletal troponin I and T, and the detection of cardiac troponin in serum is highly specific for cardiac injury. Both I and T have a small molecular mass and are thus released rapidly following cellular injury. They typically are detected four to six hours following injury and peak at 12 to 18 hours. Troponin I assays are produced by multiple companies and there is no standard threshold for an elevated test. Although the troponin T assay is standardized (produced by a single company), there are several generations of assays that are progressively more sensitive. The American College of Cardiology currently recommends that each lab report a positive troponin if the value is greater than the 99th percentile for normal controls.

Although all elevated troponin levels are now considered diagnostic of myocardial infarction in the appropriate clinical setting (per the American College of Cardiology and European Society of Cardiology), little is known about the prognostic value of an elevated troponin level for women. Because women with acute coronary syndromes are often older than men, they may be more likely to have congestive heart failure which often results in elevated troponin levels independent of acute coronary syndromes. Thus, the prognostic value of troponin for women may differ from the value for men.[5] One recently published study found that women suspected of acute coronary syndromes but with a negative troponin test (<0.06 ng/ml) had a very low six month risk (1 percent) of future death or myocardial infarction.[6] This was not the case for a similar group of men whose risk of events was 9 percent in those with a negative troponin test.

Thus we sought to answer the following question:

- What is the impact of troponin on risk for death or myocardial infarction for women and men with non-ST elevation acute coronary syndromes?

Women with suspected acute coronary syndromes are often older than men and are likely to have more risk factors for coronary disease.[6, 7] Thus, it is possible that the prognostic value of troponin will be different for men and women. If substantial differences between men and women exist, then different risk assessments should be considered for men and women.

Methodology

Data Sources

We used the results of a previous search of troponin articles in unstable angina (through 1999)[3] and supplemented this with a second search (through 2002) to identify gender specific rates of cardiac outcome (death or myocardial infarction) for patients with non-ST elevation acute coronary syndromes with and without elevated troponin levels. Because few published studies provided sex specific data, we also contacted a selected group of study authors directly. Peer reviewers (Appendix A) were asked to submit articles that provide evidence to address the questions.

Search Terms

We searched MEDLINE® (1966-2002) and reviewed cited references of retrieved articles to identify relevant published studies. Our search criteria were (1) the text word troponin, and (2) the text words angina or unstable or myocardial infarction or ischemia. We also performed a search of the EMBASE database from 1990-1998, but did not find any additional articles fulfilling the study criteria. We contacted experts in the field of cardiac markers to identify large unpublished cohort studies.

Inclusion and Exclusion Criteria

To be included, articles were required to fit the following inclusion criteria:
1) Clinical trial or cohort study
2) Evaluate patients with suspected myocardial ischemia
3) Evaluate the prognostic value of troponin levels in patients with non-ST elevation acute coronary syndromes
4) Published between January 1, 1966 and January 30, 2002.

We excluded studies that only included patients with myocardial infarction. We also excluded case-control studies, articles that did not report mortality, and articles with followup limited to hospitalization.

Article Identification

Study selection was performed initially by title review (PAH). Candidate abstracts were then reviewed and selected for data retrieval.

Data Abstraction

Two independent reviewers abstracted data for each article on standardized electronic data forms. A third reviewer compared their results and settled any differences. At least one reviewer of the pair had clinical cardiology expertise and one had experience in critical appraisal. We recorded the outcomes of nonfatal myocardial infarction and death. These were combined to form the outcome of death or myocardial infarction. If outcomes at more than one time period were reported, we used the value closest to 30 days following presentation.

Obtaining Unpublished Results

A number of eligible studies included women in the study population, but did not report findings separately by sex. In these instances we attempted to contact authors of all large studies (defined as >300 patients or >10 deaths during followup) to obtain this data. We contacted ten authors regarding nine studies[8-17] and received data from five studies.[8-10, 12, 13, 16]

Quality Assessment

We performed double abstractions for each article. For data obtained directly from authors we asked for confirmation of the data we received. We determined if the following quality indicators were present for the studies: clear listing of exclusion criteria, statement of whether providers were or were not blinded to the troponin results (for clinical trials), clear definition of myocardial infarction, classification of death outcome as cardiac death or total death. If less than three of these indicators (or the two applicable to cohort studies) were present, a study was classified as poor; otherwise it was considered to be good quality.

Data Management and Archive

All abstracted and author provided data were entered and stored electronically (EXCEL, Microsoft® Corporation). A citation of each article reviewed was archived using EndNote® (Niles Software Inc.).

Data Analysis

We used standard random (DerSimonian-Laird) and fixed (Peto) effects methods to estimate summary odds ratios for the outcomes of death and myocardial infarction.[18, 19] Because both fixed and random-effects summary estimates were similar, we report only the random-effects results. For studies with no events in a patient group, we added 0.5 to each cell of the study for the random-effects calculation. We tested homogeneity of study effect size using a standard Chi-square test with the Q statistic.[19] Summary estimates for men and women were compared using the z statistic. Data are presented as summary odds ratios with 95% confidence intervals, with two-tailed P-values and statistical significance set at $P < 0.05$.

Results

Results of study identification

A total of 1,049 articles were identified with the MEDLINE® and EMBASE databases and citation reviews. We excluded 878 articles based on title or abstract because they did not evaluate the prognostic value of troponin in patients with non-ST elevation acute coronary syndromes. The remaining 171 articles were retrieved and reviewed, and 78 of these articles met all of the inclusion/exclusion criteria.

Eligible articles were then reviewed to determine whether they reported relevant data for women. Only three of the 78 articles reported sex and troponin specific outcomes of death or myocardial infarction following hospitalization. The three included studies reported data for 407 women and 774 men.

Since so few studies reported data for an analysis of prognostic value of troponin by sex, we contacted the authors of the nine largest of the 78 studies to request outcomes data partitioned by sex and troponin test results. We obtained unpublished gender specific

data for 2,762 women and 3,296 men from the authors of five of the nine large studies. [8-10, 12, 13, 16] Two investigators reported on different topics for the same population.[10, 16]

Patient Characteristics

Patient characteristics are displayed by sex in Evidence Table 13. Women were consistently older than men. Women were less likely to be smokers and have a history of myocardial infarction, but were more likely to have hypertension and diabetes than men.

Study Report Characteristics

Evidence Table 14 shows characteristics of the studies and the source of data used in the analysis (i.e., abstraction of data from publication or supplied directly by a study author). Most studies used the highest troponin value to determine if the threshold was reached. The thresholds used for troponin T ranged from 0.1 to 0.2 ng/ml. The majority of studies were clinical trials where the troponin evaluation was a sub-study.

Quality of Study Reports

All eight included studies were rated as "good" quality. One study did not clearly list exclusion criteria.[20] All trials noted that health care providers were blinded to the troponin results. All studies stated how myocardial infarction was defined and all reported whether deaths referred to total or cardiac deaths.

Findings

Troponin Values

The frequency of elevated troponin and outcomes for women and men for each study are listed in Evidence Tables 15 and 16. Among 3,169 women, troponin was elevated in 1,118 (35 percent). This value ranged from 18 percent in the 1998 study report by Antman[9] to 49 percent for the study by Safstrom.[6] Among 4,070 men, the troponin was elevated in 1,571 (39 percent). This value ranged from 18 percent in the study by Galvani[21] to 64 percent for the study by Safstrom.[6]

Death

There were 103 deaths among 3,169 women (3.3 percent). Among 2,051 women with a negative troponin, 42 died (2.0 percent) compared to 61 (5.5 percent) who died following a positive troponin value (Figure 1). There were 129 deaths among 4,070 men (3.2 percent). Among 2,499 men with a negative troponin, 47 died (1.9 percent) compared to 82 (5.2 percent) who died following a positive troponin value (Figure 2). The summary odds ratio for death with an elevated troponin was 2.63 (95 % CI 1.75-3.95) for women and 2.83 (95% CI 1.92-4.17) for men (p=0.8 for difference in odds ratio between men and women).

Death or Myocardial Infarction

There were 256 deaths or nonfatal myocardial infarctions among 3,169 women (8.1 percent). Among women with a negative troponin, 117 died or had a myocardial infarction (5.7 percent) compared to 139 (12.4 percent) who died or had a myocardial infarction following a positive troponin value (Figure 3). There were 366 deaths or myocardial infarctions among 4,070 men (9.0 percent). Among men with a negative troponin, 180 died or had a myocardial infarction (7.2 percent) compared to 186 (11.8 percent) who died or had a myocardial infarction following a positive troponin value (Figure 4). The summary odds ratio for the combined endpoint of death or MI for patients with an elevated troponin was for 2.16 (95% CI 1.65-2.81) women and 1.50 (95% CI 1.20-1.88) for men (p=0.04 for difference in odds ratio between men and women).

Nonfatal Myocardial Infarction

There were 153 nonfatal myocardial infarctions among 3,169 women (4.8 percent). Among women with a negative troponin, 75 had a nonfatal myocardial infarction (3.7 percent) compared to 78 (7.0 percent) who had a nonfatal myocardial infarction following a positive troponin value (Figure 5). There were 237 nonfatal myocardial infarctions among 4,070 men (5.8 percent). Among men with a negative troponin, 133 had a nonfatal myocardial infarction (5.3 percent) compared to 104 (6.6 percent) who had a nonfatal myocardial infarction following a positive troponin value (Figure 6). The odds ratio for death with an elevated troponin was for 1.80 (95% CI 1.28-2.54) women and 1.06 (95% CI 0.8-1.41) for men (p=0.02 for difference in odds ratio between men and women).

Comparisons Between Men and Women

The summary odds ratios for death (Figure 7), death or myocardial infarction (Figure 8) and nonfatal myocardial infarction (Figure 9) were computed separately for women and men. There was no significant heterogeneity ($p<0.05$) for any of the six summary estimates (three per gender). These results show that women and men had a similar increase in risk of death associated with a positive troponin. However, the relationship between death or myocardial infarction and elevated troponin was stronger for women (p=0.05). This was due to a stronger risk of nonfatal myocardial infarction with a positive troponin for women than for men (p=0.02).

Conclusions

Few published data are available comparing the prognostic value of troponin for men and women. Although many analyses of troponin have included a large number of women, we identified only three studies that reported sex specific outcome data. Because several of the investigators from the larger studies provided sex specific data, we were able to calculate a more robust estimate of the impact of troponin on outcome for men and women.

Our study is consistent with prior investigations that found that women with acute coronary syndromes are older and have more comorbidities (hypertension, diabetes) than men. In addition, we found that women were less likely to have a prior history of myocardial infarction and less likely to be smokers. Unlike other studies we found that the frequency of elevated troponin levels was similar for men and women.

We found that the prognostic value of troponin for predicting death was the same for both men and women (odds ratio near 3). However, for the combined outcome of death or MI, troponin had greater prognostic value in women than men. This was due to a smaller number of nonfatal myocardial infarctions in troponin negative women than troponin negative men.

How does one reconcile the similar troponin prognostic value for death but a difference in prognostic value for nonfatal MI? One possibility is that men and women are treated differently. In the study by Safstrom,[6] low risk women (troponin <0.06 ng/ml) were less likely to undergo revascularization with percutaneous coronary interventions or bypass grafting than men (22 percent vs. 46 percent, $p<0.01$). However for higher levels of troponin, the rate of revascularization in men and women was similar. In fact, revascularization was more common for women than for men (though not significantly) with a troponin value >= 0.2 ng/ml (39 percent vs. 36 percent). If revascularization is frequently complicated by small myocardial infarctions, there will be more nonfatal myocardial infarctions in men than in women due to higher rates of revascularization in men, yet fatal events would be similar. Unfortunately, we do not have data on revascularization by gender and troponin level for most of the included studies.

Another possibility is that men are at an increased risk for nonfatal myocardial infarction (but not fatal infarction) compared to women. Men are known to have more severe coronary artery disease than women among those presenting with chest pain. Men may be more likely to develop myocardial infarction at a site unrelated to the culprit lesion responsible for the initial coronary syndrome. These infarctions would not be preceded by a positive troponin level. Our findings could be explained if these new infarctions are more likely to be survived than the initial coronary syndrome. If men are simply at higher risk of events in general, we would have expected to observe similar gender specific risk with elevated troponin for death and nonfatal myocardial infarction.

Our ability to observe differences between men and women in their risk associated with an elevated troponin would not have been possible without the data provided directly from authors of past studies. Less than a third of the patients' data used in the analysis were available from published studies. Because each study had limited power to detect differences between men and women, the authors may be reluctant to use limited resources to analyze and publish inconclusive sub-group data. Thus, obtaining data directly from authors is often critical to determine results for sub-populations.

Limitations

Although we observed a difference between men and women in the relationship between troponin and risk of nonfatal myocardial infarction, the cause of this difference could not be determined. The borderline statistical significance indicates that this difference may have occurred by chance.

Future Research

Future studies will be needed to verify and explore possible causes for the finding that troponin results prognosticate nonfatal MI differently in women compared to men. In addition, authors should be encouraged to report outcomes data by sex and ethnic sub-groups or to make these analyses easily available.

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Evidence Table 1. Diagnostic Testing: Characteristics of studies of exercise myocardial perfusion imaging

Reference	Total N (% women)	Mean age (years)	Prior MI N (% women)	Radionuclide	Definition of abnormal test	Definition of CHD[a] (%)	Exercise	Quality[b]
Kiat et al, 1990[23]	53 (26)	56	24 (NA)	MIBI	Fixed or reversible PD	50	Treadmill	Fair
Van Train et al, 1990[41]	371 (14)	NA	130 (NA)	TI	PD at rest or after exercise	50	Treadmill	Fair
Gupta et al, 1992[17]	93 (17)	58	37 (NA)	TI	Fixed or reversible PD	50	Treadmilll	Fair
Sciammarella et al, 1992[47]	56 (20)	55	42 (45)	MIBI	Fixed or reversible PD	50	Treadmill	Good
Chae et al, 1993[44]	243 (100)	62	102 (42)	TI	PD at rest or after exercise	50	Treadmill	Good
Mak et al, 1995[48]	139 (18)	51	90 (NA)	MIBI	Fixed or reversible PD	50	Treadmill	Good
Hambye et al, 1996[18]	123 (31)		0 (0)	MIBI	Fixed or reversible PD	50	Bicycle	Fair
Laurienzo et al, 1997[45]	82 (100)	51	NA (NA)	TI	Fixed or reversible PD	70 or 50 LM	Treadmill	Good
Taillefer et al, 1997[6]	48 (100)	58	8 (17)	TI & MIBI	Decreased uptake at rest or after exercise	50	Treadmill	Fair
Astarita et al, 1998[46]	41 (48)	59	0 (0)	TI	Reversible uptake defects in $\geq$ 2/22 segments	50	Bicycle	Fair

N, number; MI, myocardial infarction; CHD, coronary heart disease; NA, not available; TI, thallous chloride TI 201 (thallium); PD, perfusion defect; MIBI, technetium Tc 99m sestamibi; LM, left main coronary artery

[a]Percent stenosis of any one major coronary artery at or above this cut-off used to define angiographic evidence of coronary disease.

[b] Quality classification described in section on quality assessment.

Note: Superscripted numbers correspond with citations on reference list for Chapter 2.

Evidence Table 2. Diagnostic Testing: Characteristics of studies of exercise echocardiography

Reference	Total N (% women)	Mean age (years)	Prior MI N (% women)	Definition of abnormal test	Definition of CHD (%)[a]	Exercise Used	Quality[b]
Williams et al, 1994[49]	70 (100)	60	0 (0)	New or worse RWMA after exercise	50	Bicycle	Good
Marwick et al, 1995[2]	161 (100)	60	0 (0)	RWMA at rest or after exercise	50	Treadmill & bicycle	Fair
Luotolahti et al, 1996[24]	118 (15)	55	57 (39)	New or worse RWMA after exercise	50	Bicycle	Fair
Roger et al, 1997[50]	340 (28)	66	0 (0)	RWMA at rest or after exercise	50	Treadmill	Good

N, number; MI, myocardial infarction; CHD, coronary heart disease; RWMA, regional wall motion abnormality
[a] Percent stenosis of any one major coronary artery at or above this cut-off used to define angiographic evidence of coronary disease.
[b] Quality classification described in section on quality assessment.
Note: Superscripted numbers correspond with citations on reference list for Chapter 2.

Evidence Table 3. Diagnostic Testing: Findings of studies of exercise myocardial perfusion imaging and summary estimates of accuracy.

Reference	Women				Men			
	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Kiat et al, 1990[23]	1.00 (0.72-1.00)	0.67 (0.09-0.99)	3.00 (0.82-11.00)	[a]	0.92 (0.78-0.98)	0.50 (0.01-0.99)	1.84 (0.58-5.86)	0.16 (0.03-0.75)
Van Train et al, 1990[41]	0.95 (0.83-1.00)	0.62 (0.32-0.87)	2.47 (1.27-4.82)	0.08 (0.02-0.30)	0.95 (0.92-0.97)	0.43 (0.29-0.58)	1.67 (1.31-2.13)	0.12 (0.06-0.22)
Gupta et al, 1992[17]	0.85 (0.55-0.99)	0.67 (0.09-0.99)	2.54 (0.68-9.46)	0.23 (0.06-0.92)	0.81 (0.69-0.90)	0.86 (0.57-0.99)	5.67 (1.78-18.1)	0.22 (0.12-0.39)
Sciammarella et al, 1992[47]	1.00 (0.54-1.00)	0.40 (0.05-0.96)	1.67 (0.81-3.43)	[a]	0.95 (0.83-1.00)	0.33 (0.04-0.78)	1.42 (0.80-2.51)	0.15 (0.03-0.75)
Chae et al, 1993[44]	0.71 (0.63-0.78)	0.65 (0.54-0.75)	2.03 (1.47-2.79)	0.44 (0.33-0.59)	[b]	[b]	[b]	[b]
Mak et al, 1995[48]	0.83 (0.62-0.95)	1.00 (0.02-1.00)		0.17 (0.05-0.55)	[b]	[b]	[b]	[b]
Hambye et al, 1996[18]	0.61 (0.39-0.80)	0.67 (0.39-0.89)	1.83 (0.85-3.93)	0.59 (0.30-1.10)	0.94 (0.85-0.99)	0.82 (0.60-0.95)	5.15 (2.20-12.0)	0.08 (0.03-0.20)
Laurienzo et al, 1997[45]	0.86 (0.65-0.97)	0.80 (0.68-0.89)	4.32 (2.53-7.37)	0.17 (0.06-0.46)	[b]	[b]	[b]	[b]
Taillefer et al, 1997[6] (using sestamibi)	0.72 (0.53-0.86)	0.81 (0.54-0.96)	3.83 (1.44-10.2)	0.35 (0.19-0.64)	[b]	[b]	[b]	[b]
(using thallium)	0.75 (0.57-0.89)	0.50 (0.25-0.50)	1.50 (0.89-2.54)	0.50 (0.23-1.07)	[b]	[b]	[b]	[b]

Evidence Table 3. Diagnostic Testing: Findings of studies of exercise myocardial perfusion imaging and summary estimates of accuracy. (continued)

Reference	Women				Men			
	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Astarita et al, 1998[46]	1.00 (0.29-1.00)	0.47 (0.23-0.72)	1.89 (1.05-3.39)	[a]	1.00 (0.77-1.00)	0.50 (0.16-0.84)	2.00 (1.02-3.92)	[a]
SUMMARY								
All eligible studies[c]	0.77 (0.72-0.83)	0.69 (0.62-0.75)	2.46 (2.00-3.04)	0.33 (0.26-0.41)	0.93 (0.90-0.95)	0.57 (0.47-0.67)	2.17 (1.73-2.73)	0.13 (0.09-0.19)
Good quality studies	0.75 (0.69-0.81)	0.71 (0.69-0.78)	2.54 (1.95-3.32)	0.36 (0.28-0.46)	[d]	[d]	[d]	[d]
Studies including men and women	0.86 (0.77-0.92)	0.57 (0.43-0.70)	2.01 (1.46-2.76)	0.24 (0.14-0.42)	0.93 (0.90-0.95)	0.57 (0.47-0.67)	2.17 (1.73-2.37)	0.13 (0.09-0.19)

CI, confidence interval; LR+, likelihood ratio for a positive test; LR- likelihood ratio for a negative test

[a] Estimates not calculable because sensitivity or specificity = 100%.

[b] Estimates not available because these studies did not include men.

[c] Includes results from the study by Taillefer for sestamibi.[6]

[d] Estimates not available because only one good quality study included men.

Note: Superscripted numbers correspond with citations on reference list for Chapter 2.

Evidence Table 4. Diagnostic Testing: Summary estimates of accuracy of myocardial perfusion imaging from studies using sestamibi compared to studies using thallium

Radionuclide	Women				Men			
	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Sestamibi[6, 18, 23, 47, 48]	0.77 (0.67-0.85)	0.70 (0.53-0.83)	2.57 (1.58-4.17)	0.33 (0.22-0.50)	0.94 (0.89-0.97)	0.70 (0.51-0.85)	3.12 (1.82-5.37)	0.09 (0.05-0.18)
Thallium[6, 17, 41, 44-46]	0.77 (0.72-0.82)	0.67 (0.60-0.74)	2.32 (1.87-2.88)	0.34 (0.27-0.44)	0.92 (0.89-0.95)	0.52 (0.40-0.64)	1.93 (1.51-2.46)	0.14 (0.09-0.22)

CI, confidence interval; LR+ = likelihood ratio for a positive test; LR- = likelihood ratio for a negative test
Note: Superscripted numbers correspond with citations on reference list for Chapter 2.

Evidence Table 5. Diagnostic Testing: Findings of studies of exercise echocardiography and summary estimates of accuracy

Reference	Women				Men			
	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
Williams et al, 1994[49]	0.88 (0.72-0.97)	0.84 (0.68-0.94)	5.42 (2.62-11.2)	0.14 (0.06-0.35)	[a]	[a]	[a]	[a]
Marwick et al, 1995[2]	0.80 (0.68-0.89)	0.81 (0.72-0.88)	4.28 (2.79-6.57)	0.25 (0.15-0.42)	[a]	[a]	[a]	[a]
Luotolahti et al, 1996[24]	0.77 (0.46-0.95)	0.80 (0.28-0.99)	3.85 (0.91-16.4)	0.29 (0.10-0.82)	0.96 (0.90-0.99)	0.60 (0.14-0.95)	2.39 (0.91-6.29)	0.07 (0.02-0.22)
Roger et al, 1997[50]	0.79 (0.66-0.89)	0.37 (0.22-0.54)	1.26 (0.95-1.67)	0.56 (0.32-1.08)	0.78 (0.71-0.84)	0.44 (0.30-0.59)	1.39 (1.07-1.80)	0.50 0.33-0.76)
SUMMARY								
All eligible studies	0.81 (0.74-0.87)	0.73 (0.66-0.79)	2.95 (2.28-3.79)	0.26 (0.19-0.36)	0.84 (0.79-0.88)	0.45 (0.32-0.59)	1.54 (1.20-1.98)	0.36 (0.24-0.53)
Good quality studies	0.82 (0.73-0.89)	0.60 (0.48-0.71)	2.06 (1.53-2.77)	0.29 (0.18-0.47)	[b]	[b]	[b]	[b]
Studies including men and women	0.79 (0.68-0.88)	0.42 (0.27-0.58)	1.36 (1.02-1.81)	0.50 (0.28-0.89)	0.84 (0.79-0.88)	0.45 (0.32-0.59)	1.54 (1.20-1.98)	0.36 (0.24-0.53)

CI, confidence interval; LR+ = likelihood ratio for a positive test; LR- = likelihood ratio for a negative test
[a]Estimates not available because these studies did not include men.
[b]Estimates not available because only one good quality study included men and women.
Note: Superscripted numbers correspond with citations on reference list for Chapter 2.

Evidence Table 6. Lipids: Characteristics of Included Clinical Trials

Study Name, Year	N Women/ Total (% Women)	Mean Age of Women	Percent with CHD[a]	Lipid Entry Criterion	Intervention	Mean Follow Up (years)	Outcomes in Women	Quality Rating[b]
Scottish Society of Physicians, 1971[29]	124/717 (17)	54	100%	None	Clofibrate	6	CHD mortality nonfatal MI	Fair
Newcastle Upon Tyne, 1971[30]	97/497 (20)	54	100%	None	Clofibrate	5	CHD mortality nonfatal MI	Fair
Colestipol Study, 1978[31]	1184/2278 (52)	57	20%	TC >250 mg/dl	Colestipol	3	total mortality CHD mortality	Fair
4S, 1994[7, 32, 33]	827/4444 (19)	61	100%	TC 213-309 mg/dl	Simvastatin	5.4	total mortality CHD mortality nonfatal MI revascularization CHD events[c]	Good
ACAPS, 1994[25, 26]	441/919 (48)	61	0%	LDL 130-159 mg/dl with any number of risk factors; LDL 160-189 mg/dl with no or one risk factor	Lovastatin	2.8	total mortality CHD mortality nonfatal MI	Good
PLAC II, 1994[16]	22/151 (15)	NA	100%	LDL in 60-90th percentile for age and gender	Pravastatin	3	total mortality CHD mortality nonfatal MI	Good
CARE, 1998[8, 34, 35]	576/4159 (14)	61	100%	TC <240 mg/dl and LDL-C 115-174 mg/dl	Pravastatin	5	total mortality CHD mortality nonfatal MI revascularization CHD events[c]	Good
LIPID, 1998[27, 36, 37]	1516/9014 (17)	62	100%	TC 155-271 mg/dl	Pravastatin	6.1	CHD events[c]	Good

Evidence Table 6. Lipids: Characteristics of Included Clinical Trials (continued)

Study Name, Year	N Women/ Total (% Women)	Mean Age of Women	Percent with CHD[a]	Lipid Entry Criterion	Intervention	Mean Follow Up (years)	Outcomes in Women	Quality Rating[b]
AFCAPS/ TEXCAPS, 1998[9, 38]	997/6605 (15)	62	0%	TC 180-264 mg/dl LDL 130-190 mg/dl and HDL <47 mg/dl	Lovastatin	5.2	total mortality CHD mortality nonfatal MI revascularization CHD events[c]	Good
HPS, 2002[11]	5082/20,536 (25)	NA	65%	TC >135 mg/dl	Simvastatin	5	CHD events[c]	Good
ALLHAT, 2002[39]	5051/10,355 (49)	NA	14%	LDL 100-189 mg/dl	Pravastatin	4.8	total mortality CHD events[c]	Fair

4S, Scandinavian Simvastatin Survival Study; ACAPS, Asymptomatic Carotid Artery Progression Study; PLAC II, Pravastatin, Lipids and Atherosclerosis in the Carotid Arteries; CARE, Cholesterol and Recurrent Events trial; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease; AFCAPS/TEXCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; HPS, Heart Protection Study; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent heart Attack Trial.

N, number; CHD, coronary heart disease; mg/dl, milligrams per deciliter; MI, myocardial infarction; NA, not available; CVD, cardiovascular disease; TC total cholesterol; LDL, low density lipoprotein

[a]CHD defined as history of myocardial infarction or angina.

[b]see Quality Assessment section in text.

[c] CHD events in, CARE, LIPID and ALLHAT defined as CHD mortality or nonfatal MI; in 4S as CHD mortality, non fatal MI or resuscitated cardiac arrest and in AFCAPS as CHD mortality, nonfatal MI or unstable angina or sudden cardiac death; in HPS as CHD mortality, nonfatal MI, stroke or revascularization.

Note: Superscripted numbers correspond with citations on reference list for Chapter 3

Evidence Table 7. Lipids: Outcomes of Eligible Studies

Outcome	Study	RR (95% CI)	
Secondary Prevention			
Total Mortality	4S[7, 32, 33] PLAC II[16]	1.11 1.18	(0.66, 1.5) (0.03, 54.81)
CHD Mortality	Scottish Society of Physicians[29] Newcastle Upon Tyne[30] 4S[7, 32, 33] PLAC II[16] CARE[8, 34, 35]	0.17 0.20 0.79 1.18 0.80	(0.02, 1.34) (0.04, 1.13) (0.39, 1.6) (0.03, 54.81) (0.61, 1.05)
Nonfatal MI	Scottish Society of Physicians[29] Newcastle Upon Tyne[30] 4S[7, 32, 33] PLAC II[16] CARE[8, 34, 35]	0.75 0.43 0.66 1.18 0.51	(0.42, 1.33) (0.08, 2.25) (0.48, 0.90) (0.48, 54.81) (0.27, 0.94)
CHD events[a]	4S[7, 32, 33] CARE[8, 34, 35] LIPID[27, 36, 37] HPS[11]	0.68 0.60 0.87 0.81	(0.51, 0.91) (0.37, 0.97) (0.67, 1.13) (0.72, 0.92)
Revascularizaion	4S[7, 32, 33] CARE[8, 34, 35]	0.52 0.82	(0.31, 0.86) (0.64, 1.20)
Primary Prevention			
Total Mortality	Colestipol[31] ACAPS[25, 26] AFCAPS/TEXCAPS[9, 38] ALLHAT[39]	0.92 0.09 1.53 0.98	(0.51, 1.69) (0.01, 1.7) (0.62, 3.81) (0.83, 1.17)
CHD Mortality	Colestipol[31] ACAPS[25, 26] AFCAPS/TEXCAPS[9, 38]	1.08 0.35 2.99	(0.44, 2.63) (0.01, 8.47) (0.12, 73.3)
Nonfatal MI	ACAPS[25, 26] AFCAPS/TEXCAPS[9, 38]	0.35 0.69	(0.04, 3.31) (0.21, 2.28)
CHD events[a]	AFCAPS/TEXCAPS[9, 38] ALLHAT[39]	0.54 1.02	(0.22, 1.34) (0.81, 1.28)
Revascularization	AFCAPS/TEXCAPS[9, 38]	0.87	(0.33,2.31)

CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; NA not available; RR, relative risk; 4S, Scandinavian Simvastatin Survival Study; ACAPS, Asymptomatic Carotid Artery Progression Study; PLAC II, Pravastatin, Lipids and Atherosclerosis in the Carotid Arteries; CARE, Cholesterol and Recurrent Events trial; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease; AFCAPS/TEXCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; HPS, Heart Protection Study; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

[a]CHD events in CARE, LIPID and ALLHAT defined as CHD mortality or nonfatal MI; in 4S as CHD mortality, non fatal MI or resuscitated cardiac arrest; in AFCAPS as CHD mortality, nonfatal MI, unstable angina or sudden cardiac death, and in HPS as CHD mortality, nonfatal MI, stroke or revascularization.

Note: Superscripted numbers correspond with citations on reference list for Chapter 3.

Evidence Table 8. Lipids: Summary Results

Outcome	Secondary Prevention		Primary Prevention	
	References	RR (95% CI)	References	RR (95% CI)
Total mortality				
All studies	7, 16, 32, 33	1.11 (0.66 1.87)	9, 25, 26, 31, 38, 39	0.95 (0.62, 1.46)
Statin drugs	7, 16, 32, 33	1.11 (0.66 1.87)	9, 25, 26, 38, 39	0.87 (0.37, 2.00)[a]
Good quality	7, 16, 32, 33	1.11 (0.66 1.87)	9, 25, 26, 38	0.45 (0.03, 7.00)[a]
CHD mortality				
All studies	7, 8, 16, 29, 30, 32-35	0.74 (0.57, 0.96)	7, 16, 32, 33	1.07 (0.47, 2.40)
Statin drugs	7, 8, 16, 32-35	0.78 (0.60, 1.01)	7, 16, 32, 33	1.02 (0.11, 9.76)
Good quality	7, 8, 16, 32-35	0.78 (0.60, 1.01)	7, 16, 32, 33	1.02 (0.11, 9.76)
Nonfatal MI				
All studies	7, 8, 16, 29, 30, 32-35	0.64 (0.50, 0.82)	9, 25, 26, 38	0.61 (0.22, 1.68)
Statin drugs	7, 8, 16, 32-35	0.63 (0.48, 0.83)	9, 25, 26, 38	0.61 (0.22, 1.68)
Good quality	7, 8, 16, 32-35	0.63 (0.48, 0.83)	9, 25, 26, 38	0.61 (0.22, 1.68)
CHD events[b]				
All studies	7, 8, 11, 27, 32-37	0.79 (0.72, 0.88)	9, 38, 39	0.87 (0.50, 1.49)
Statin drugs	7, 8, 11, 27, 32-37	0.79 (0.72, 0.88)	9, 38, 39	0.87 (0.50, 1.49)
Good quality	7, 8, 11, 27, 32-37	0.79 (0.72, 0.88)	9, 38	0.54 (0.22, 1.30)
Revascularization				
All studies	7, 8, 32-35	0.70 (0.42, 1.16)[a]	9, 38	0.87 (0.33,2.31)[c]
Statin drugs	7, 8, 32-35	0.70 (0.42, 1.16)[a]	9, 38	0.87 (0.33,2.31)[c]
Good quality	7, 8, 32-35	0.70 (0.42, 1.16)[a]	9, 38	0.87 (0.33,2.31)[c]

RR, relative risk; CI, confidence interval; CHD, coronary heart disease; MI, myocardial infarction; statin drugs included lovastatin, pravastatin or simvastatin; good quality is defined in the methods section.

[a] P-value for heterogeneity <0.10

[b] CHD events in CARE, LIPID and ALLHAT defined as CHD mortality or nonfatal MI; in 4S as CHD mortality, non fatal MI or resuscitated cardiac arrest; in AFCAPS as CHD mortality, nonfatal MI, unstable angina or sudden cardiac death, and in HPS as CHD mortality, nonfatal MI, stroke or revascularization. See Tables 1 and 2 for full names of studies.

[c] Only one trial provided data on this outcome [9, 38]

Note: Superscripted numbers correspond with citations on reference list for Chapter 3.

Evidence Table 9. Diabetes: Characteristics of studies of coronary heart disease risk in diabetics vs. nondiabetic subjects

Source	Study Name or Location	Quality Score	Mean Followup (years)	Mean Age (Range), y	Number of Subjects			
					Diabetic		Nondiabetic	
					M	F	M	F
Barrett-Connor et al, [70] 1991[a]	Rancho Bernardo, CA	good	14.4	63(50-89)	207	127	893	1244
Collins et al, [71] 1996	Asian Indian, Fiji	fair	11	20+	102	129	1077	1236
Fujimoto et al, [16, 17] 1987, 1991	King County, WA	fair	NA	62- 64	78	52	79	72
Howard et al, [21] 1995	Strong Heart Study	fair	4.8	55-57	797	1412	1049	1291
Jousilahti et al, [72] 1999	WHO-MONICA	fair	7-12	25-64	262	254	6828	7442
Keil et al, [73] 1993	Charleston Heart Study	fair	30	50(35-74)	30	42	956	1153
Kleinman et al, [74] 1988	NHANES I	fair	9	57,63[b](40-77)	189	218	3151	3823
Lindeman et al, [19] 1998	Bernalillo County, NM	fair	NA	$\geq$ 65	115	73	330	321

Evidence Table 9. Diabetes: Characteristics of studies of coronary heart disease risk in diabetics vs. nondiabetic subjects (continued)

Source	Study Name or Location	Quality Score	Mean Followup (years)	Mean Age (Range), y	Number of Subjects Diabetic M	Diabetic F	Nondiabetic M	Nondiabetic F
Lowe et al, [75] 1997[a] and Pan et al, [76]1986[a]	Chicago, IL	fair	9-22	45,52[b](35-64)	926	170	7975	7860
Niskanen et al, [15] 1998	Finland-Kuopio	fair	15	55(45-64)	70	63	62	82
Rewers et al, [18] 1992	San Luis Valley, CO	fair	NA	25-74	186	521	243	571
Scheidt-Nave et al, [77] 1990[a]	Rancho Bernardo, CA	good	14.4	50-89	159	157	591	732
Sievers et al, [20] 1998	Gila River, AZ	fair	12.1	≥ 15	630	813	1542	1552
Vilbergsson et al, [12] 1998	Reykjavik Study	good	17	52(34-79)	267	210	8861	9549
Wei et al, [78] 1998	San Antonio Heart Study	fair	7.5	43,53[b] (25-64)	190	281	1910	2494

CI indicates confidence interval; NA indicates not available; WHO-MONICA indicates World Health Organization-Monitoring of Trends and Determinants in Cardiovascular Disease; NHANES I indicates National Health and Nutrition Examination Survey I

[a]Duplicate publication, but separate outcomes or subgroups reported in each article.

[b]Values represent mean age for nondiabetic and diabetic subjects, respectively.

Note: Superscripted numbers correspond with citations on reference list for Chapter 4.

Evidence Table 10. Diabetes: Adjusted odds ratios (95% confidence intervals) for coronary heart disease mortality, nonfatal myocardial infarction (NFMI), and all-cause mortality by sex

Source	Race/ Ethnicity	CHD Mortality		Nonfatal MI		All-Cause Mortality	
		Male	Female	Male	Female	Male	Female
		OR (95% CI)		OR (95% CI)		OR (95% CI)	
Barrett-Connor, [70]1991	W	1.9(1.3-2.8)	3.3(2.0-5.6)				
Scheidt-Nave, [77]1990	W			1.3 (0.8-2.1)	1.8 (1.0-3.0)		
Collins, [71]1996	I	3.2(1.3-2.0)	20.7 (2.5-171)			4.4 (2.7-6.9)	3.1 (1.7-5.8)
	Me	1.6(0.4-6.0)	5.4(1.2-24.3)			1.3 (0.7-2.5)	2.3 (1.2-4.6)
Fujimoto[a], [16]1987	JA			2.1 (1.3-3.3)			
Fujimoto[a], [17]1991	JA				1.2 (0.8-1.9)		
Howard[a], [21]1995	NA			1.59 (.74-3.21)	7.11(2.24-22.58)		
Jousilahti, [72]1999	W	2.4 (1.6-3.4)	4.3 (2.4-7.6)				
Keil, [73]1993	W	0.8 (0.5-2.4)	1.3 (0.4-4.5)			1.2 (0.7-2.0)	2.2 (1.1-4.2)
	B	2.5(0.3-18.7)	2.0 (0.9-4.5)			3.1 (1.4-7.2)	1.8 (1.1-2.8)
Kleinman,[74]1988	W	2.8 (2.0-3.8)	2.5 (1.6-3.8)			2.3 (1.8-2.8)	2.0 (1.6-2.6)
Lindeman[a], [19]1998	W			3.4 (1.2-5.5)	3.6 (1.3-10)		
Lindeman[a], [19]1998	L			1.7 (0.9-3.3)	1.4 (0.5-3.7)		
Lowe, [75]1997	W					1.9 (1.6-2.2)	
	B					1.8 (1.0-3.3)	
Pan, [76]1986	W	3.8 (1.7-8.4)	4.7 (1.9-11.9)				
Niskanen[a], [15]1998	W					5.4(1.7-14.7)	5.2(1.8-15)
Rewers[a], [18]1992	W			1.7 (1.0-2.8)	2.7 (1.5-4.7)		
	L			0.9 (0.5-1.4)	1.4 (0.9-2.1)		
Sievers[a], [20]1992	P	5.3 (2.2-13)	6.3 (0.8-50)			1.8 (1.4-2.4)	1.4 (1.0-2.0)
Vilbergsson, [12]1998	W	2.0 (1.5-2.6)	2.2 (1.7-2.8)			1.9 (1.6-2.3)	1.7 (1.3-2.1)
Wei, [78]1998	M					2.1 (1.3-3.5)	3.2 (1.9-5.4)

[a]Multivariate results received via personal communication with authors; OR indicates odds ratio; CI indicates confidence interval; W=white, B=black, I=East Indian, Me=Melanesian, JA=Japanese- American, L=Latino, P=Pima Indian, M=multiple races, INA=Native American

Note: Superscripted numbers correspond with citations on reference list for Chapter 4.

Evidence Table 11. Diabetes: Summary odds ratios for coronary heart disease (CHD) mortality, nonfatal myocardial infarction (NFMI), and all-cause mortality by sex (comparing diabetics to nondiabetics)

Outcome	Men Summary OR (95%CI)	Women Summary OR (95%CI)	References	p-value[a]
CHD Mortality: (n=8)	2.33 (1.91-2.85)	2.92 (2.22-3.84)	12, 20, 70-74, 76	0.19
White (n=6)	2.22 (1.79-2.75)	2.79 (2.11-3.69)	12, 70, 72-74, 76	0.20
Black (n=1)	2.5 (0.3-18.7)	2.0 (0.9-4.5)	73	0.87
East Indian (n=1)	3.2 (1.3-2.0)	20.7 (2.5-171)	71	0.11
Melanesian (n=1)	1.6 (0.4-6.0)	5.4 (1.2-24.3)	71	0.24
Pima India (n=1)	5.3 (2.2-13)	6.3 (0.8-50)	20	0.88
Nonfatal MI: (n=5)	1.55 (1.11-2.17)[b]	1.70 (1.27-2.28)	16-19, 21, 77	0.68
White (n=3)	1.65 (1.06-2.56)	2.29 (1.59-3.30)	18,19,77	0.26
Native American (n=1)	1.59 (0.74-3.21)	7.11 (2.24-22.58)	21	0.03
Japanese American (n=1)	2.1 (1.3-3.3)	1.2 (0.8-1.9)	16,17	0.08
Latino (n=2)	1.2 (0.6-2.4)	1.4 (0.9-2.1)	18,19	0.71
Mortality: (n=7)	2.13 (1.71-2.65)[b]	1.94 (1.65-2.28)	12,15, 20, 71, 73, 74,75, 78	0.50
White (n=5)	2.01 (1.59-2.54)	1.98 (1.65-2.38)	12,15, 73-75	0.92
Black (n=2 male; n=1 female)	2.19 (1.28-3.73)	1.8 (1.1-2.8)	73,75	0.60
East Indian (n=1)	4.4 (2.7-6.9)	3.1(1.7-5.8)	71	0.37
Melanesian (n=1)	1.3 (0.7-2.5)	2.3 (1.2-4.6)	71	0.21
Pima Indian (n=1)	1.8 (1.4-2.4)	1.4 (1.0-2.0)	20	0.24

OR indicates odds ratio; CI indicates confidence interval.
[a] *P* Value for comparison of odds ratio estimates between men and women.
[b] *P* Value for heterogeneity < .10.
Race-ethnicity groups with only one study (n=1), were not meta-analyzed.
Note: Superscripted numbers correspond with citations on reference list for Chapter 4.

Evidence Table 12. Diabetes: Summary odds ratios (95% confidence intervals) for coronary heart disease mortality by sex (diabetes vs. no diabetes) quality of studies and sensitivity analysis (white race only)

Subgroup	Summary Odds Ratios (95% Confidence Interval) Men	Women	*P*-value[a]	References
Quality of Studies[b]				
Good (n=2)	1.96 (1.56-2.47)	2.54 (1.73-3.72)	.26	12,70
Fair (n=4)	2.42 (1.71-3.42)	3.07 (1.97-4.80)	.41	72,73,74,76
Level of Adjustment for Potential Confounding[b]				
Age Adjusted only (n=4)	2.07 (1.39-3.08)	3.42 (2.55-4.59)	.05	12,70,73,76
Unadjusted only (n=3)	2.16 (1.56-2.98)	3.22 (2.39-4.34)	.08	70,73,74

OR indicates odds ratio; CI indicates confidence interval

[a] *P* value for comparison of odds ratio estimates between men and women.

[b] The studies included in these subgroup analyses were eligible for inclusion because they provided outcomes adjusted for at least age, hypertension, hyperlipidemia and smoking; these studies also provided unadjusted and/or age-adjusted estimates which are used to calculate these summary estimates.

Note: Superscripted numbers correspond with citations on reference list for Chapter 4.

Evidence Table 13. Troponin: Characteristics of the Study Populations by Gender

Author	Year	Patient Cohort	Age[a] (years)		History of MI (%)		Hypertension (%)		Diabetes Mellitus (%)		Smoking (%)	
			M	F	M	F	M	F	M	F	M	F
Antman 1996[8]	1996	ACS	58	61	45	30	35	56	12	20	39	34
Antman 1998[9]	1998	ACS	61	64	42	35	59	68	29	41	31	19
Christenson[10, 16]	1996	ACS	62	69	25	25	39	60	16	26	38	23
Galvani[21]	1997	Unstable Angina	66		48		na		na		na	
Hamm[12]	1999	Unstable Angina	61		20		37		12		41	
Heeschen[13]	1999	ACS	64		46		55		21		69	
Ravkilde[20]	1993	Unstable Angina	68		28		9		9		na	
Safstrom[6]	2000	ACS	69	72	29	29	30	37	12	16	22	16

na=not available; ACS=suspected acute coronary syndrome (non-ST elevation); UA=unstable angina (MI excluded). MI=myocardial Infarction.
[a]Mean or median.
Note: Superscripted numbers correspond with citations on reference list for Chapter 5.

Evidence Table 14. Troponin: Characteristics of the Study Reports

Study	Data Source	Definition of Positive Troponin	Study Type	Troponin	Troponin Threshold (ng/ml)	Exclusions Listed	Providers Blinded to Troponin
Antman 1996[8]	Author	Any positive	Clinical Trial	I	0.4	Yes	Yes
Antman 1998[9]	Author	Any positive	Clinical Trial	T	0.2	Yes	Yes
Christenson[10, 16]	Author	Initial Positive	Clinical Trial	T	0.1	Yes	Yes
Galvani[21]	Publication	Any positive	Cohort	I	3.1	Yes	Yes
Hamm[12]	Author	Any positive	Clinical Trial	T	0.1	Yes	Yes
Heeschen[13]	Author	Any positive	Clinical Trial	I	0.1	Yes	Yes
Ravkilde[20]	Publication	Any positive	Cohort	T	0.2	No	Yes
Safstrom[6]	Publication	Any positive	Clinical Trial	T	0.2	Yes	Yes

I=Troponin I protein; T=Troponin T protein; ng/ml=nanogram per milliliter
Note: Superscripted numbers correspond with citations on reference list for Chapter 5.

Evidence Table 15. Troponin: Outcomes for Women

Author	Total	Troponin Positive (%)	Death (%) Troponin Negative	Death (%) Troponin Positive	Death or MI (%) Troponin Negative	Death or MI (%) Troponin Positive
Antman 1996[8]	471	179 (38)	5 (1.7)	10 (5.6)	18 (6.2)	19 (10.6)
Antman 1998[9]	194	35 (18)	3 (1.9)	2 (5.7)	6 (3.8)	7 (20.0)
Christenson[10, 16]	251	102 (41)	8 (5.4)	13 (12.7)	14 (9.4)	15 (14.7)
Galvani[21]	29	11 (38)	0 (0)	1 (9)	2 (11)	2 (18)
Hamm[12]	333	149 (45)	2 (1.1)	3 (2.0)	16 (8.7)	26 (17.4)
Heeschen[13]	1513	464 (31)	20 (1.9)	19 (4.1)	51 (4.9)	30 (8.2)
Ravkilde[20]	36	12 (33)	0 (0)	0 (0)	0 (0)	2 (17)
Safstrom[6]	342	166 (49)	4 (2.3)	13 (7.8)	10 (5.7)	30 (18.1)
Total	3169	1118 (35)	42 (2.0)	61 (5.5)	117 (5.7)	139 (12.4)

MI = myocardial infarction
Note: Superscripted numbers correspond with citations on reference list for Chapter 5.

Evidence Table 16. Troponin: Outcomes for Men

Author	Total N	Total Positive (%)	Death (%) Troponin Negative	Death (%) Troponin Positive	Death or MI (%) Troponin Negative	Death or MI (%) Troponin Positive
Antman 1996[8]	933	394 (42)	7 (1.3)	11 (2.8)	44 (8.2)	27 (6.9)
Antman 1998[9]	344	75 (22)	3 (1.1)	1 (1.3)	7 (2.6)	4 (5.3)
Christenson[10, 16]	554	187 (34)	12 (3.2)	20 (10.7)	33 (9.0)	25 (13.4)
Galvani [21]	62	11 (18)	0 (0)	1 (9.1)	2 (3.9)	3 (27.3)
Hamm[12]	756	297 (39)	5 (1.1)	12 (4.1)	33 (7.2)	35 (11.8)
Heeschen[13]	709	180 (25)	14 (2.6)	8 (4.4)	32 (6.0)	18 (10.0)
Ravkilde[20]	91	32 (35)	1 (1.7)	3 (9.4)	3 (5.1)	4 (12.5)
Safstrom[6]	621	395 (64)	5 (2.2)	26 (6.6)	26 (11.5)	70 (17.7)
Total	4070	1571 (39)	47 (1.9)	82 (5.2)	180 (7.2)	186 (11.8)

MI = myocardial infarction
Note: Superscripted numbers correspond with citations on reference list for Chapter 5.

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Appendix A
Peer Reviewers

Appendix A: Peer Reviewers

Expert Peer Reviewers

Overall Reviewers

Elizabeth Barrett-Connor, MD	University of California, San Diego
JoAnn Manson, MD, DrPH	Harvard Medical School, Brigham and Women's Hospital
Lori Mosca, MD, MPH, PhD	Columbia University

Noninvasive Diagnostics:

C. Noel Bairey Merz, MD	Cedars-Sinai Medical Center
Pamela S. Douglas, MD	University of Wisconsin, Madison

Lipid lowering:

Vera Bittner, MD, MSPH	University of Alabama at Birmingham
Robert H. Knopp, MD	Northwest Lipid Research Clinic, University of Washington School of Medicine

Diabetes as a risk factor:

Trevor Orchard, MBBCh, MMedSi	University of Pittsburgh

Troponin:

E. Magnus Ohman, MD	University of North Carolina at Chapel Hill

Advice was also solicited from representatives of Partner Organizations, including:

Robert Christenson, PhD	American Association for Clinical Chemistry
Sharonne N. Hayes, M.D., F.A.C.C.	American College of Cardiology
Rosalind Fabunmi, Ph.D.	American Heart Association
Mary Norine Walsh, MD	American College of Cardiology
Mary Winston, Ed.D.	American Heart Association

Appendix B
Quality Assessment Forms

Appendix B: Quality Assessment Forms

Noninvasive Diagnostics: Exercise MPI and Echocardiography Quality Evaluation Form

Reviewer 1: **«Reviewer1»**
Reviewer 2: **«Reviewer2»**
Topic Team: «Question»
Article: «Article»
Name:

INCLUSION/EXCLUSION CRITERIA **If answer is "NO" for any question 1-5 or "YES" for Q 6, skip to Q 7.** **(Note: you may not be able to complete Q 4 until later if PI needs to be contacted)**	**YES**	**NO**
1. a Is the study design cross sectional? b Does it address the research question?		
2. Does the article contain primary data on ≥ 10 women who underwent exercise EKG with radionuclide injection and SPECT imaging or exercise echocardiography.		
3. Does the article include coronary angiography as the "gold standard" for measuring the accuracy of these tests?		
4A. Does the article present data on the accuracy of these tests that allow calculation of sensitivity, specificity, or likelihood ratios in women (one measure acceptable if all are not given, but raw data TP, TN, FP, FN preferred) (If YES, go to Q.5)		
If NO to 4A: 4B. Will PI be contacted, or has PI already been contacted? (if NO, go to Q.7)		
If YES to 4B: 4C. Was data received from PI? (if YES, include in review)		
5. Was the paper published between January 1, 1990 and January 1, 2002?		
6. Were non-invasive tests performed exclusively in patients after myocardial infarction, percutaneous angioplasty, coronary artery surgery or hospitalization for an unstable coronary syndrome? (If yes, exclude)		
7. Based on your responses to questions 1-6, is this article eligible for the systematic review? **IF YES,** complete Question 8 - 10 and Quality Evaluation. **IF NO,** complete Questions 8 - 10 only.		
MISCELLANEOUS 8. Does this article contain data on women only?		
9. Does the investigator need to be contacted to receive further data on women?		
10. Comments (*continue on other side*)		

QUALITY EVALUATION	**Yes**	**No**	**Unclear**	**Likely**
11. Did all women who undergo the non-invasive test also undergo angiography?				
12. Did only women with abnormal non-invasive tests undergo angiography?				
13. Was the diagnosis of coronary artery disease on angiography made by investigators blinded to results of the non-invasive test?				

Appendix B: Quality Assessment Forms (continued)

Treatment: Lipid Lowering Quality Evaluation Form

Reviewer 1: **«Reviewer1»**
Reviewer 2: **«Reviewer2»**
Topic Team: «Question»
Article: **«Article»**

INCLUSION/EXCLUSION CRITERIA **If answer is "NO" for any question 1-5, STOP after completing Q 6, article does not qualify for review. One "no" response will disqualify article.**	**YES**	**NO**
1. Does the article assess the impact of lipid lowering on clinical outcomes: total mortality, CHD mortality, CHD events or CHD procedures?		
• Is the study a randomized clinical trial? • Is this publication a sub-study? __yes __no • IF YES, which paper will be reviewed for this systematic review? __substudy __main __ both __ neither • What is the ID# (or author/year/journal) of main paper? _____		
3. Does the article contain data on women that address the research question?		
4. Does the study include treatment duration of at least one year?		
5. Was the article published between January 1, 1966 and January 1, 2002?		
6. Based on your responses to questions 1-5, is this article eligible for the systematic review? IF YES, proceed to Question 7. IF NO, stop here.		
MISCELLANEOUS		
7. Is the study: *(select one only)* ( ) primary prevention ( ) mixed ( ) secondary prevention ( ) cannot determine		
8. Were any references found in this article that need to be reviewed? IF YES: list information on back of this page so that article can be obtained.		
9. Does the investigator need to be contacted to receive further data on women?		

10. Comments: (continue on other side)			
QUALITY EVALUATION	**YES**	**NO**	**NOT CLEAR**
11. Was there a control group that received placebo?			
12. Were the participants blinded to the intervention?			
13. Were the providers blinded to intervention?			
14. Were the staff who assessed outcome blinded to intervention?			
15. Was randomization allocation concealed?			
16. Were the inclusion/exclusion criteria clear?			
17. Was there > 75% complete follow up?			

Appendix B: Quality Assessment Forms (continued)

Risk Factors: Diabetes Quality Evaluation Form

Reviewer 1: **«Reviewer1»**

Reviewer 2: **«Reviewer2»**

Topic Team: «Question»

Article: **«Article»**

INCLUSION/EXCLUSION CRITERIA	**YES**	**NO**
1. Is the study design a prospective or retrospective cohort, or cross sectional study?		
2. Does the article address the risk/rates of CHD mortality, a CHD event, or angiographic evidence of CHD in diabetic persons?		
3. Does the article include data specific to Type II diabetic participants?		
4.a. Does the article include data on women, with outcomes specified by gender?		
4. b. **If NO**, should PI be contacted?		
5. Does the article include multivariate adjustment for confounders, including age, hypertension, hypercholesterolemia and tobacco use?		
6. Does the article include a nondiabetic control group (studies with historical controls or standardized mortality ratios will be excluded)?		
7. Was the paper published between January 1, 1966 and January 1, 2002?		
If the answer to any of the above questions is NO, STOP.		

QUALITY EVALUATION	YES	NO	NA
8. Were the inclusion/exclusion criteria clear?			
9. If article is a prospective cohort study, was there less than 25% loss to follow-up?			
10. Did the analysis include multivariate adjustment for potential confounders beyond the specified 4 variables: age, hypertension, hypercholesterolemia, tobacco?			
11. Was the outcome adjudicated blindly *?*			
12. If a prospective cohort, was the length of follow up time at least 6 months?			
13. Was diabetes defined based on any formal glucose testing (fasting plasma glucose or OGTT)?			

Appendix C
Data Abstraction Forms

Appendix C: Data Abstraction Forms (continued)

DATA ABSTRACTION FORM: DIAGNOSTICS

REVIEWER *DATE*

ARTICLE NUMBER
Author
Title
Journal
Year
Country
Institution
Is there another article from this same database? Y or N

STUDY CHARACTERISTICS
Setting (University/Community/Both/Emergency Room?/Pre-op?)
Study design (prospective, retrospective)
Exercise Echo done (Y/N)
Exercise SPECT done (Y/N)
Other tests done (Y/N), if Y, which?_____

POPULATION
Consecutive? Y N Unclear
Total n_____
Number of Women_____
% follow up, all_____% follow up, women_____
Mean age of all _____and of women_____
Clinical indications, all: angina_____atypical chest pain____ asymptomatic____other_
Clinical indic, women: angina_____atypical CP_____asymptomatic_____other_____
Inclusion criteria:

Exclusion criteria:

BL Characteristics	Women	Men	All
Age Range			
Cardiac Risks (%) Diabetes Smokers HTN Dyslipidemia (definition)			
Cardiac Hx (%) Angina Prior MI Prior CABG Prior PTCA			

TEST FACTORS
Exercise preformed: Bruce____Other treadmill_____Bike_____Step____Other_____
Percent with Adequate exercise: Women_____ All_____
Radionuclide used (if applicable): Tl_____MIBI_____Both_____Other_____

Imaging used: SPECT_____Echo_____Planar_____Other_____
Criteria for positivity_____

Appendix C: Data Abstraction Forms (continued)

For Nuclear med	Women	Men	All
+ ECG Criteria + Imaging Criteria			
# w/ +ECG/+image #w/+ECG/-image # w/-ECG/+image # w/-ECG/-image			

_
Positive reported at rest (Y/N) at exercise (Y/N)
If echo, WMA new (Y/N) or worse (Y/N)
If echo, cine loop or videotape reading?
If SPECT, visual (Y/N) quantitative (Y/N)
Number of non-diagnostic tests, all_____ women_____
Reasons for non-diagnostic tests, all: inadequate HR_____technically difficult_____
Inadequate double product____ image uninterpretable (rest/stress/both)_____
Reasons for non-diag, women: inadequate HR_____technically difficult_____
Inadequate double product____image ininterpretable (rest/stress/both)_____
Reversibility examined (Y/N)
Protocol: Time _____Return for repeat images (Y/N) and if Y, when?
Baseline ECG abnormalities: LBBB_____RBBB____dig effect_____LVH____ST/T__

GOLD STANDARD
Cath done on all (Y/N), if N # who received cath_____# of women who received cath___
Angiographic definition of dz: < 50%___>50%____>70%____>50% LM____other____
Time between exercise test and cath_____

Cath data	Women	Men	All
% normal % w/ single vessel			
% w/ 2 vessel			
% w/3 vessel % w/ L Main			

SUBGROUPS
Was severe disease a subgroup (Y/N), and if so, how was it defined?_____

Other subgroups and definitions?

Data for Sens/Spec	Women	Men	All
Participants # with cath results			
TP (+cath+test) FP (-cath+test)			
TN (-cath-test) FN (-cath-test)			

Appendix C: Data Abstraction Forms (continued)

Subgroup:

Data for Sens/Spec	Women	Men	All
Participants # with cath results			
TP (+cath+test) FP (-cath+test)			
TN (-cath-test) FN (-cath-test)			

Subgroup:

Data for Sens/Spec	Women	Men	All
Participants # with cath results			
TP (+cath+test) FP (-cath+test)			
TN (-cath-test) FN (-cath-test)			

Comments:

Data Abstraction Form: Lipid Lowering

Reviewer_____
First Author _____
Study Number_____
Year of Publication_____

Directions: Complete this form after completing the quality review form which assesses study eligibility. Form does not need to be filled out on studies that are not eligible.

METHODS

Study Design

Randomized Clinical Trial Y _____ N_____

Participants

Source (eg community, hospital) _____
Inclusion criteria
- Age range_____
- Total cholesterol _____
- LDL cholesterol_____
- HDL cholesterol_____
- Known CHD?_____
- Other_____

Exclusion criteria
- (eg cancer, dementia)_____

Primary/secondary prevention

Primary _____
Secondary _____
Mixed (if mixed, what is the % of each) _____

Location (city, state, country) _____
Recruitment Start Date _____

Intervention

Drug
- Name(s)_____
- Starting dose_____
- Was the dose titratable?_____

Diet
- Type of diet(s)_____
  _____

Interventions common to control and intervention group
_____

Outcomes

Primary outcome IF INDIVIDUAL

Total mortality _____
CHD mortality _____
Non-fatal MI _____
Angina _____
Revascularization _____
Cardiovascular death_____
Stroke_____
Other _____

Primary Composite Outcome(s) MARK ALL THAT APPLY

Total mortality _____
CHD mortality _____
Non-fatal MI _____
Angina _____
Revascularization _____
Cardiovascular death_____
Stroke_____
Other _____

Secondary outcomes

Total mortality _____
CHD mortality _____
Non-fatal MI _____
Angina _____
Revascularization _____
Cardiovascuar death_____
Stroke_____
Other (Individual) _____
Other (Composite) _____

Follow-up strategy and how often	Frequency
Patient examination/clinic visit	_____
Questionnaire	_____
Telephone contact	_____
Medical records	_____
Death registry	_____
Other_____	_____

Over what period of time were outcomes assessed (mean, range)
Exact dates of follow-up_____
Mean length of follow-up_____
Follow up rate or percent_____

RESULTS

Participant Information

	Women	Men
Intervention		
Control		
Total number of patients		

Appendix C: Data Abstraction Forms (continued)

Age

Average age intervention (I) _____
Avg age I women _____
Average age I men_____
Average age placebo (P) _____
Average age P women_____
Average age P men_____

Angina

	Total (%)	Women	Men
Intervention			
Control			

Hypertension

	Total (%)	Women	Men
Intervention			
Control			

Anti-hypertensives

	Total (%)	Women	Men
Intervention			
Control			

Diabetes

	Total (%)	Women	Men
Intervention			
Control			

Current smokers

	Total (%)	Women	Men
Intervention			
Control			

Aspirin use

	Total (%)	Women	Men
Intervention			
Control			

ACE inhibitor use

	Total (%)	Women	Men
Intervention			
Control			

Beta blocker use

	Total (%)	Women	Men
Intervention			
Control			

Baseline Lipids

	Total	LDL	HDL	Triglycerides
Intervention				
Control				

Baseline Lipids in women

	Total	LDL	HDL	Triglycerides
Intervention				
Control				

Outcomes

Follow-up Lipids

	Total	LDL	HDL	Triglycerides
Intervention				
Control				

Follow-up Lipids in women

	Total	LDL	HDL	Triglycerides
Intervention				
Control				

All cause mortality

OVERALL	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

WOMEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

MEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

Relative Risk_____
Relative risk in women_____
Absolute risk reduction_____
Absolute risk reduction in women_____
NNT_____

CHD death

OVERALL	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

WOMEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

MEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

Relative Risk_____
Relative risk in women_____
Absolute risk reduction_____
Absolute risk reduction in women_____
NNT_____

Nonfatal MI

OVERALL	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

WOMEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

MEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

Relative Risk_____
Relative risk in women_____
Absolute risk reduction_____
Absolute risk reduction in women_____
NNT_____

Angina

OVERALL	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

WOMEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

MEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

Relative Risk_____
Relative risk in women_____
Absolute risk reduction_____
Absolute risk reduction in women_____
NNT_____

Revascularization

OVERALL	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

WOMEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

MEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

Relative Risk_____
Relative risk in women_____
Absolute risk reduction_____
Absolute risk reduction in women_____
NNT_____

Cardiovascular death

OVERALL	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

WOMEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

MEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

Relative Risk_____
Relative risk in wo men_____
Absolute risk reduction_____
Absolute risk reduction in women_____
NNT_____

Stroke

OVERALL	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

WOMEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

MEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

Relative Risk_____
Relative risk in women_____
Absolute risk reduction_____
Absolute risk reduction in women_____
NNT_____

Other

OVERALL	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

WOMEN	**Number of events**	**Event rate (eg # per 1000 years)**	**Number at risk**
Intervention			
Control			

MEN	Number of events	Event rate (eg # per 1000 years)	Number at risk
Intervention			
Control			

Relative Risk_____
Relative risk in women_____
Absolute risk reduction_____
Absolute risk reduction in women_____
NNT_____

Other

OVERALL	Number of events	Event rate (eg # per 1000 years)	Number at risk
Intervention			
Control			

WOMEN	Number of events	Event rate (eg # per 1000 years)	Number at risk
Intervention			
Control			

MEN	Number of events	Event rate (eg # per 1000 years)	Number at risk
Intervention			
Control			

Relative Risk_____
Relative risk in women_____
Absolute risk reduction_____
Absolute risk reduction in women_____
NNT_____

Adverse event(s)

LFT abnormality
How defined_____
Number (%) Intervention_____
Number (%) Control_____
Liver failure
How defined_____
Number (%) Intervention_____
Number (%) Control_____
CK abnormality
How defined_____
Number (%) Intervention_____
Number (%) Control_____
Rhabdomyolysis
How defined_____
Number (%) Intervention_____
Number (%) Control_____

Renal failure

How defined_____
Number (%) Intervention_____
Number (%) Control_____

Breast cancer

How defined_____
Number (%) Intervention_____
Number (%) Control_____

Other

How defined_____
Number (%) Intervention_____
Number (%) Control_____

Other

How defined_____
Number (%) Intervention_____
Number (%) Control_____

Data Abstraction Form: Diabetes

Reviewer: _____ First Author: _____
Study #: _____ Year of Publication: _____

METHODS:

Study design:
_____ Prospective cohort study
_____ Retrospective cohort study
_____ Cross-sectional analysis
_____ Case-Control study
_____ Randomized Clinical Trial, intervention type: _____

Study name (acronym):_____
Patient Population (clinic, survey, volunteers…): _____
Location (City/State/Country): _____
Recruitment start date: _____

Type of diabetics studied:
_____ Type 1 (Insulin-Dependent DM)
_____ Type 2 (NIDDM)

Type 2 diabetes defined by (check all that apply):
_____ self-report
_____ use of diabetic medication
_____ medical record diagnosis
_____ Positive Oral Glucose Tolerance Test, cut-off: _____
_____ Elevated fasting Glucose, cut-off: _____
_____ Elevated HbA1c or glycohemoglobin, cut-off: _____
_____ other:

<u>Outcomes</u>:

Primary endpoint(s):
1.
2.

Secondary endpoints(s):
1.
2.
3.
4.

Endpoint Definition: (check all that apply)

- Coronary heart disease death defined by:
  _____ ICD-9 code 410-414
  _____ sudden CHD death
  _____ Other:
- MI defined by:
  _____ EKG changes
  _____ Enzyme levels consistent with MI
  _____ Other:

Cardiovascular disease death defined by:
_____ ICD-9 code 400-459
_____ physician documentation
_____ other:

Stroke death defined by:
_____ ICD-9 code 430-438
_____ physician documentation
_____ Other:

Follow-up strategy (Check all that apply):
_____ patient examination/clinic visit
_____ questionnaire returned
_____ telephone contact
_____ medical records search
_____ death registry
_____ other:

Within what period of time were outcomes assessed (mean, range): _____
Exact dates of follow-up: _____
Follow-up rate or percent: _____

RESULTS:
Participant Information:

	Women	**Men**
Number of (type 2) diabetics		
Number of nondiabetic patients		
Total number of patients		
Race: (list all: # with DM, # without DM) • •		
Age (mean, range): Diabetics Non-diabetics		

- Are outcomes reported with crude numbers (y/n):
- Are outcomes adjusted by age alone (y/n)?
- Are outcomes adjusted for other variables (y/n)?
  List all variables:

Outcome: Coronary heart disease death Race: _____

	WOMEN	MEN
With Diabetes		
Without Diabetes		

Women:
Crude RR: _____ 95% CI or p-value: _____
Age-adjusted RR: _____ " _____
Multiply-adjusted RR: _____ " _____
Men:
Crude RR: _____ 95% CI or p-value: _____
Age-adjusted RR: _____ " _____
Multiply-adjusted RR: _____ " _____

Outcome: Non-fatal Myocardial Infarction

	WOMEN	MEN
With Diabetes		
Without Diabetes		

Women:
Crude RR: _____ 95% CI or p-value: _____
Age-adjusted RR: _____ " _____
Multiply-adjusted RR: _____ " _____
Men:
Crude RR: _____ 95% CI or p-value: _____
Age-adjusted RR: _____ " _____
Multiply-adjusted RR: _____ " _____

Outcome: Cardiovascular Death

	WOMEN	MEN
With Diabetes		
Without Diabetes		

Women:
Crude RR: _____ 95% CI or p-value: _____
Age-adjusted RR: _____ " _____
Multiply-adjusted RR: _____ " _____
Men:
Crude RR: _____ 95% CI or p-value: _____
Age-adjusted RR: _____ " _____
Multiply-adjusted RR: _____ " _____

Outcome: All-cause mortality

	WOMEN	MEN
With Diabetes		
Without Diabetes		

Women:
Crude RR: _____ 95% CI or p-value: _____
Age-adjusted RR: _____ " _____
Multiply-adjusted RR: _____ " _____
Men:
Crude RR: _____ 95% CI or p-value: _____
Age-adjusted RR: _____ " _____
Multiply-adjusted RR: _____ " _____
Other outcome: _____

	WOMEN	MEN
With Diabetes		
Without Diabetes		

Women:
Crude RR: _____ 95% CI or p-value: _____
Age-adjusted RR: _____ " _____
Multiply-adjusted RR: _____ " _____
Men:
Crude RR: _____ 95% CI or p-value: _____
Age-adjusted RR: _____ " _____
Multiply-adjusted RR: _____ " _____

Appendix C: Data Abstraction Forms (continued)

Other outcome: ____

	WOMEN	MEN
With Diabetes		
Without Diabetes		

Women:
Crude RR: _____________________ 95% CI or p-value: ___________________________
Age-adjusted RR: ___________________ " ___________________________
Multiply-adjusted RR: ________________ " ___________________________
Men:
Crude RR: _____________________ 95% CI or p-value: ___________________________
Age-adjusted RR: ____________________ " ___________________________
Multiply-adjusted RR: ________________ " ___________________________

If Race information is provided, enter each outcome with crude number and RR per race:
Race: ____
Outcome: ____

	WOMEN	MEN
With Diabetes		
Without DM		

Women: Men:
Age-adj RR(CI): ______________________ Age-adj RR(CI): ________________________
Mult.-adj RR(CI): ______________________ Mult-adj RR(CI): ________________________

Race: ____
Outcome: ____

	WOMEN	MEN
With Diabetes		
Without DM		

Women: Men:
Age-adj RR(CI): ______________________ Age-adj RR(CI): ________________________
Mult.-adj RR(CI): ______________________ Mult-adj RR(CI): ________________________

Race: ____
Outcome: ____

	WOMEN	MEN
With Diabetes		
Without DM		

Women: Men:
Age-adj RR(CI): ______________________ Age-adj RR(CI): ________________________
Mult.-adj RR(CI): ______________________ Mult-adj RR(CI): ________________________

Race: ____
Outcome: ____

	WOMEN	MEN
With Diabetes		
Without DM		

Women: Men:
Age-adj RR(CI): ______________________ Age-adj RR(CI): ________________________
Mult.-adj RR(CI): ______________________ Mult-adj RR(CI): ________________________

Appendix D
Abbreviations and Acronyms

Appendix D: Abbreviations and Acronyms

ACE	angiotensin converting enzyme
AHRQ	Agency for Healthcare Research and Quality
CABG	coronary artery bypass grafting
CHD	coronary heart disease
CKMB	creatine 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
ICD-9	International Classification of Diseases, Ninth Revision
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LM	Left main coronary artery
Lp(a)	lipoprotein a
mg	milligrams
MI	myocardial infarction
MIBI	technetium Tc 99m sestamibi
mm	millimeter
mmol	millimole
MPI	myocardial perfusion-imaging
MRC/BHF	Medical Research Council/British Heart Foundation
MB	myocardial bands
N	number
NA	not available
NFMI	nonfatal myocardial infarction
ng	nanograms
NHLBI	National Heart Lung and Blood Institute
OR	odds ratio
PCI	percutaneous coronary intervention
PD	perfusion defect
PTCA	percutaneous coronary angioplasty
RWMA	regional wall motion abnormality
RR	relative risk
SPECT	single photon emission computed tomography
TI	thallous chloride TI 201 (thallium)

Names of studies:

4S	Scandinavian Simvastatin Survival Study
ACAPS	Asymptomatic Carotid Artery Progression Study
AFCAPS/TEXCAPS	Air Force/Texas Coronary Artherosclerosis Prevention Study
ALLHAT-LLT	Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial - Lipid-Lowering Trial
CARE	Cholesterol and Recurrent Events trial
HPS	Heart Protection Study
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease
NHANES I	National Health and Nutrition Examination Survey I
PLAC I	Pravastatin Limitation of Atherosclerosis in the Coronary Arteries
PLAC II	Pravastatin, Lipids and Atherosclerosis in the Carotid Arteries
PROSPER	PROspective Study of Pravastatin in the Elderly at Risk
TIMI	Thrombolysis in Myocardial Infarction
WHO-MONICA	World Health Organization-Monitoring of Trends and Determinants in Cardiovascular Disease