Agency for Healthcare Research and Quality

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

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.

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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