Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment
Number 80

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

Summary

Overview

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

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

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

Key Questions

1. **Are there accurate non-invasive approaches to evaluating suspected coronary disease in women? (3 subtopics, 1.01-1.03)**
   - 1.01 exercise tolerance testing, with and without perfusion imaging
   - 1.02 exercise echocardiogram
   - 1.03 coronary artery calcification score
2. **Are there effective treatments for women with coronary heart disease? (15 subtopics 2.01-2.12 with secondary and primary prevention considered separately as appropriate)**
   - 2.01 aspirin
     - a. secondary prevention
     - b. primary prevention
   - 2.02 beta-blockers
     - a. secondary prevention
     - b. primary prevention
   - 2.03 angiotensin converting enzyme inhibitors
     - a. secondary prevention
     - b. primary prevention
   - 2.04 calcium channel blockers
   - 2.05 nitrates
   - 2.06 heparin, including low molecular weight heparin
   - 2.07 glycoprotein IIb/IIIa inhibitor drugs
   - 2.08 thrombolysis
   - 2.09 ticlopidine
   - 2.10 clopidogrel

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2.11 angioplasty or stenting
2.12 coronary artery bypass surgery

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

3.01 hypertension
a. as a risk factor
b. treatment
3.02 diabetes
a. as a risk factor
b. treatment
3.03 hyperlipidemia (LDL-, HDL-cholesterol, triglycerides, lipoprotein (a))
a. as a risk factor
b. treatment
3.04 elevated homocysteine
a. as a risk factor
b. treatment
3.05 C-reactive protein
a. as a risk factor
b. treatment
3.06 cigarette smoking
a. as a risk factor
b. smoking cessation
3.07 obesity
a. as a risk factor
b. weight reduction
3.08 inactivity
a. as a risk factor
b. exercise
3.09 age
3.10 age at menopause
3.11 ethnicity
3.12 socioeconomic status

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

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

5.01 troponin
5.02 creatinine kinase myocardial bands including isoforms
5.03 myoglobin

Methodology

Data Sources

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

Inclusion Criteria

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

Search Terms

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

Data Abstraction

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

Evaluation of Evidence Provided by Identified Articles

We reviewed and summarized in detail the findings of each systematic review and clinical trial identified. A general summary of the overall findings from prospective cohort and cross-sectional studies pertinent to each subtopic is also

provided. Finally, we summarized the answer to each subtopic question, graded the evidence as none, weak, fair or good, compared results in women and men and recommended a new or updated systematic review if feasible.

Results of Literature Searches

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

	Total	Good Quality	Fair Quality
Systematic review	32	17	15
Randomized trial	25	17	8
Prospective cohort	66	59	7
Cross-sectional	39	25	14
Total	162	118	44

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

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

Findings

General

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

Non-invasive diagnostic testing

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

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

Treatments

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

Risk factors and risk factor modification

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

Differences in utilization

- Weak evidence suggests that men are more likely than women to undergo diagnostic testing and treatment for CHD, but that women are more likely than men to be treated for hypertension.

- Differences in utilization of tests and treatment might be explained by differences in severity of disease or comorbidities between men and women or by overuse of tests and treatments in men.

Biochemical Markers

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

Future Research

We believe that a new or updated systematic review is feasible and would be provide clinically important information for the following subtopics:

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

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

Availability of the Full Report

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

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