Chapter 1: Introduction

Coronary Heart Disease in Women

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

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

Some studies suggest that women and nonwhites are less likely to undergo intensive and invasive evaluation and treatment for cardiac disease than white men with similar symptoms.[12-14] These differences might be the result of overuse of tests and treatments in men, older age and more comorbid illnesses in women, or gender and race bias among health care providers.

Approaches to Improving Evidence on Diagnosis and Treatment of CHD in Women

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

Key Questions

Recognizing the importance of the issues raised above, multiple groups have requested evidence-based research pertinent to diagnosis and management of CHD in women and minorities. The groups include an ad hoc women's health coalition (American Heart Association, American College of Cardiology, American College of Obstetricians and Gynecologists, American Society of Echocardiography, Association of Black Cardiologists, Jacobs Institute of Women's Health, Mayo Clinic Women's Heart Clinic, Society for Women's Health Research, and WomenHeart: National Coalition for Women with Heart Disease), the American Association for Clinical Chemistry and the NIH Office of Research in Women's Health. The Centers for Medicare and Medicaid Services and Harvard Pilgrim Health Services have also expressed interest. Concern about sex and gender-based differences in diagnosis and treatment of CHD was also noted in the Senate

Appropriations Committee's report accompanying the FY 2000 Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriations bill. Specifically, these groups have requested evidence related to: 1) the accuracy of noninvasive tests for diagnosis of CHD in women; 2) the value of traditional treatments for CHD in women; 3) the importance of risk factors for CHD in women; 4) appropriate utilization of tests, treatments and risk factor modification in women, and 5) the prognostic value of biologic markers for diagnosis of acute coronary syndromes in women.

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

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