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Evidence-Based Medicine in the Assessment of Women at Risk for Cardiovascular Disease

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The diagnosis and treatment of cardiovascular disease (CVD) in women is perhaps one of the greatest clinical dilemmas in medicine. Coronary heart disease (CHD), including congestive heart failure (CHF), hypertensive disease, and other forms of atherosclerotic diseases, is an all-encompassing challenge that is a major cause of death and disability for women in most Westernized countries. The lifetime risk of coronary disease is substantial with approximately one in four women being at risk (1). Although CVD is manifested earlier for men, nearly 250,000 women die from ischemic heart disease every year. As a result of greater longevity, further growth in the number of deaths is anticipated (2).

Only in the last several decades has research focused on the CVD risk in women. A number of challenges and contradictions exist within the evaluation of the disease and in the risk estimation of women that currently hinder effective care for females. Despite the burden of the disease, dramatic improvements in therapeutic and surgical interventions have led to substantive declines in cardiovascular mortality. Since peaking in the 1960s, recent trends in mortality have revealed a 35–50% decline in CVD mortality (Fig. 1; 3). Declines in mortality have been less for lower socioeconomic, racial, ethnic, and female subsets of the population.

These data should be considered within our current era of evidence-based medicine, where optimal medical management is structured based on a substantial body of clinical effectiveness research on the diagnosis and treatment of at-risk women. Evidence-based medicine is divergent from prior clinical reasoning, where decision making was based on an accumulation of varied clinical experiences. Evidence-based medicine stands in contrast to the decision-making processes of the past in that patient outcomes data (in this case, derived from female populations) from published, peer-reviewed literature would be used to develop high-quality clinical guidelines for various clinical scenarios. Thus, for women, high-quality health care would require a threshold level of evidence such that effective guidelines of care could be established, including a sufficient (statistically powered sample) representation of women in large multicenter, observational series and randomized clinical trials in order to make definitive state-

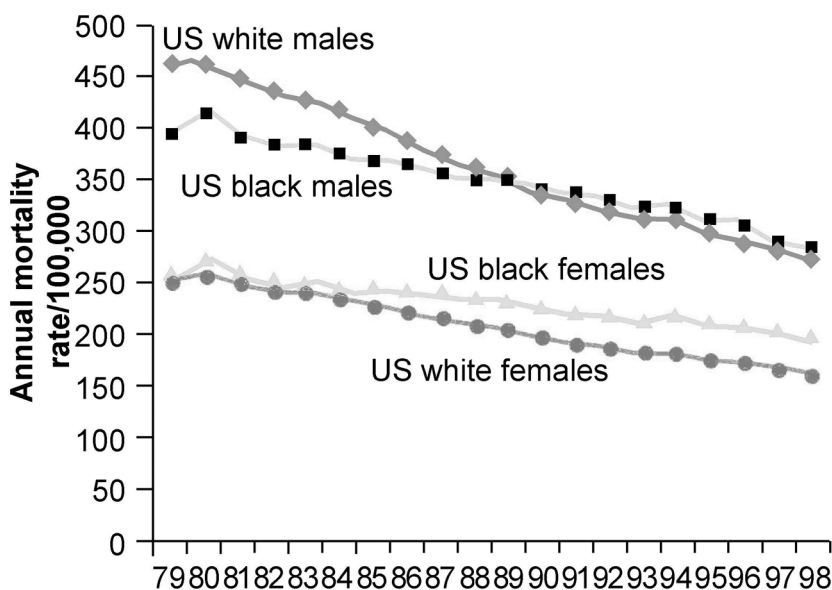


Fig. 1. CHD mortality trends by race and gender in United States 1979–1998. (From ref. 3.)

ments about the diagnosis and treatment of women in both the primary and secondary prevention setting. This volume provides a present-day understanding of the epidemiological evidence of the disease, asymptomatic screening and diagnosis of symptomatic women, primary and secondary prevention strategies, as well as health care policy evaluations, including developing cost-effective care for women.

Within the area of women's health, evidence has grown dramatically over the last decade. In many cases, developments in the field have substantially outpaced educational efforts for patients, consumers, and clinicians. This chapter serves to orient the reader as to the depth of knowledge on women's cardiovascular health as well as a theoretical framework for current and future standards required for evidence in order to effectively guide care for women. Historically, women have been underrepresented in clinical trials and observational studies (4,5), despite the mandate from the US Food and Drug Administration (FDA) in 1990 to assure equivalent inclusion of women (6). Furthermore, in 1990, the National Institutes of Health (NIH) began requiring documentation of recruitment strategies for women and minority subsets of the population. The lack of available evidence is one factor that has hindered wide-scale reductions in morbidity and mortality for women.

To further compound the challenge of diagnosing at-risk women, current data suggest that women more often present atypically with a greater frequency of nonexertional chest pain (or an equivalent, e.g., dyspnea) (7–10). The women who present atypically have often been considered to be at a decidedly lower risk when compared to their male counterparts (7). In the primary prevention setting, there are marked differences in the incidence, prevalence, and outcome of women with traditional risk factors, including hypertension, hyperlipidemia, family history of premature coronary disease, and diabetes (11–18). Accumulating risk using a global risk score often classifies a disproportionate frequency of women as low risk (Fig. 2; 16). Furthermore, women

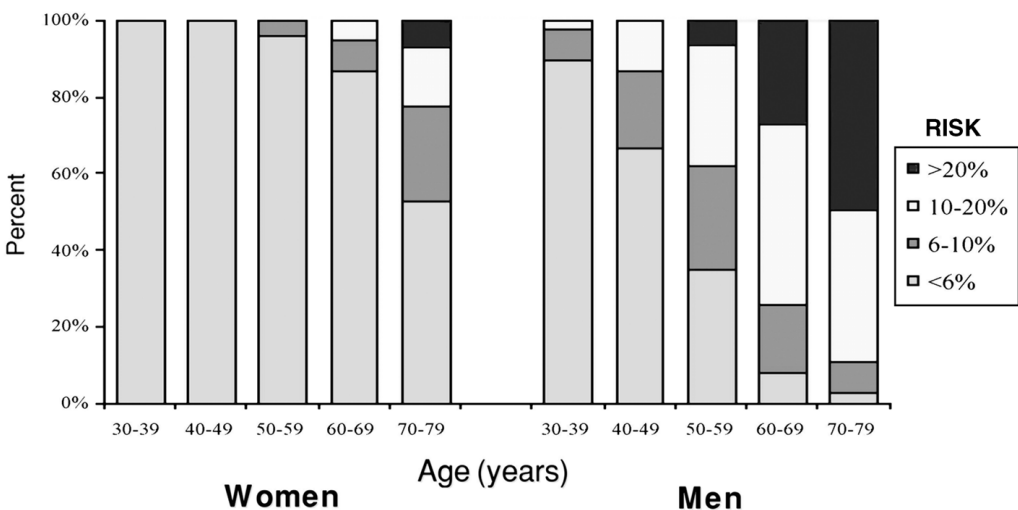


Fig. 2. Estimated 10-year hard CHD risk Framingham offspring and cohort. (From ref. 16.)

generally have a lower prevalence of ischemia and obstructive coronary disease (i.e., approx 40–60% rate of normal coronaries), contributing to less intensive management patterns for women (19–23). Gender differences in risk factor profiles, symptom presentation, and reports on reduced noninvasive test accuracy for women may contribute to greater case female fatality rates and challenge appropriate selection of at-risk women (24–28).

New evidence reveals that there is a more complex interaction of risk factors and reproductive hormones that affect both vascular function and metabolism (2). This includes new evidence on the role of conditional risk markers, such as high sensitivity C-reactive protein (CRP), an indicator of inflammation that both mediate and mark vascular disease abnormalities (29,30). Additional challenges in the diagnosis and risk assessment of women is further challenged by the smaller artery size and evidence that microvascular abnormalities or subclinical disease may be more of a risk factor for CHD in women than in men (31,32).

Evidence suggests that there may be gender-based differences in pain perception that may be acting on differential clinical presentation and evaluation of symptomatic women (33). The perception of pain is further compounded by differences in societal roles and expectations for women that may constrain early and optimal health care-seeking behavior. Despite this, in the evaluation of a patient with new onset of chest pain symptoms, women report more anginal symptoms. Approximately 4 million women were evaluated for chest pain symptoms in 2000 in comparison to 2.4 million men. Women are also more often hospitalized for chest pain. However, at diagnostic cardiac catheterization, women have lower rates of obstructive coronary disease (34). A large majority of women without a significant lesion in one of their epicardial coronary arteries have persistent symptoms and continue to consume large amounts of health care resources. Thus, for this large subset of women, few diagnostic strategies have been elucidated, but preliminary evidence suggests that a proportion of this group may have evidence of subendocardial flow heterogeneity or shifts in anaerobic metabolism

that is suggestive of myocardial ischemia (35–38). Additionally, very recent evidence suggests that when large subsets of women with chest pain symptoms are evaluated, cardiac imaging using stress echocardiographic or nuclear perfusion-based techniques may risk stratify women with normal and abnormal test results (39–41).

For women with obstructive coronary disease, an abundance of evidence suggests a worsening short- and/or long-term prognosis, including acute coronary syndromes or myocardial infarction, poststent or coronary bypass surgery, and, in some cases, CHF (42–52). Although women have less extensive disease and more often have normal left ventricular function, greater in-hospital and 30-day outcomes have been reported (42–52). The acuity of presentation and greater comorbidity promotes differences in early outcome, especially for women with diabetes mellitus. For surgical interventions, such as percutaneous coronary interventions or bypass surgery, smaller body and artery size contributes to variations in procedural success and outcome differences, including a greater need for recurrent intervention and less symptom relief (42), although overall procedural success rates are equally high for both men and women (i.e., >90–95%). Additionally, symptomatic women (especially diabetics) with evidence of provocative ischemia on conventional stress testing have a substantially worse event-free survival when compared to men with ischemia (39).

For years, the reason for the worsening outcomes has been related to the older age of clinical presentation for women. However, recent evidence suggests younger women may be those at greatest risk (48). This increase in risk may be the result of delays from chest pain onset to treatment-seeking, underrecognition of the disease in young women, a greater acuity of female presentation, a greater degree of comorbidity, and a less aggressive treatment pattern for women. Recent evidence suggests that greater mortality risk in women may be most likely driven by a greater degree of risk factor burden and comorbidity than to sex-related differences per se (49).

Women with CHD also have worse functional capacity, a greater degree of physical disability, greater symptom burden, and an overall lower quality of life when compared to men (2). As such, for female subsets of the population, there is a greater amount of health care resources consumed throughout the course of the disease process (2). The reasons for the higher costs of care are most likely multifactorial and related to less intensive prevention management, resulting in greater use of higher cost hospitalization (2), as well as less gender-tailored therapies and a lower evidence-base of female-oriented guidelines of care. As such, there is a need for considerations of strategies aimed at cost efficiency and cost-effectiveness analysis. The development of cost-effective diagnosis and treatment patterns for women is hampered by a lack of knowledge in the pathophysiology of the disease, the role of reproductive hormones, and the transition state into menopause, as well as influential factors that contribute to varying atherogenic processes in women.

Despite rapid advances in the field of gender-based evaluations in CVD, the pathophysiology of myocardial ischemia and CHD in women remains poorly understood and underdeveloped (2). There is still a need to develop more wide-ranging strategies for research, diagnosis, management, and education oriented toward female patients. In particular, there is a growing body of evidence that the atherosclerotic disease process may vary by gender and may be mediated by sex hormones, an area of research that is vastly underdeveloped. For example, pathological evidence suggests that positive remodeling may occur more often in women (53,54). From the Armed Forces Institute

of Pathology registry, plaque erosion is a more common presentation for sudden cardiac death in women in comparison to plaque rupture in men (53,54). This latter point is mediated by age, where older women present more typically with plaque rupture (53,54). Additionally, there are NIH-sponsored studies, such as the Women's Ischemia Syndrome Evaluation (WISE), that may provide a theoretical model for the interplay between traditional risk factors, conditional risk markers, vascular function and abnormalities, as well as signs and symptoms suggestive of myocardial ischemia in a relatively large cohort of women.

Despite our research gap, there are also misunderstandings on the part of patients and clinicians alike. Although most women are at risk of developing CHD, most women still consider coronary disease only a remote health risk. In fact, many patients do not realize that mortality for men and women is higher than from all cancers combined (CVD deaths in 2002: women = 512,904, men = 445,871; cancer-related deaths: women = 264,006, men = 445,871). For women, awareness of higher morbidity and mortality in females dictates the need for early detection strategies and more aggressive therapeutic interventions. Thus, a paradigm shift in screening and diagnostic testing should be promoted. Currently, the evaluation of new or worsening coronary disease is prompted by an evaluation of symptoms. Typical symptoms, occurring less often in women, provide the mainstay for aggressive care of at-risk patients. If we allow symptoms to drive the testing and treatment of women, then we will be less accurate in risk detection. Thus, a broadened definition of symptoms or more female-specific symptom evaluation tools will need to be developed to foster efficient care for women. Chapter 17 provides a state-of-the-heart evidence primer for the work-up of women with stable chest pain symptoms and is based on strategies currently utilized in the Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE) randomized trial. Strategies developed and aimed at improving outcomes in women provide a cornerstone for reducing the heavy clinical and economic burden of the disease in most Westernized societies. Furthermore, the development of female-oriented strategies offers a huge opportunity for improving the quality of care for women, as well as enhanced community goodwill, which translates into improved health care for women and their families, as women are often the gatekeepers for their family's health, making approximately two-thirds of all health care decisions. There are also economic benefits to targeting high-risk women that could result in increased early detection of the disease and aversion of costly downstream care that will impact improved societal productivity and the economic load of the disease.

In this era of evidence-based medicine, our current aim for the evaluation of at-risk women is to provide a solid base of research to guide both the diagnosis and management of this large subset of the population. For diagnostic decision making, this would include the fact that results from a noninvasive or laboratory test may be reliably used to determine the necessity for cardiac catheterization and determine the underlying disease burden. Chapters 12 and 13 discuss current evidence for the evaluation of asymptomatic and symptomatic women, including the detection of subclinical disease and tests for myocardial ischemia. For therapeutic decision making, clinical decision making would then be aimed at risk reduction using an array of medical and surgical interventions that have shown to be efficacious and effective in adequately studied female samples from rigorously controlled clinical trials.

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