

VIEWPOINTS

Women and Cardiovascular Heart Disease: Clinical Implications From the Women's Ischemia Syndrome Evaluation (WISE) Study

Are We Smarter?

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Review of the trend in cardiovascular disease mortality for males and females clearly demonstrated that whereas the trend shows a decline in males this decline is not observed in females. Multiple important reports emerged from the initial phases of the Women's Ischemic Syndrome Evaluation (WISE) study that may have significant clinical implications for our approach to cardiovascular disease in women. The data derived from the WISE study certainly provided important information to our understanding of the approach to women with cardiovascular disease. The clinical presentation may be different, and a gender-oriented questionnaire may enhance our diagnosis. In a multivariable model, low hemoglobin was associated with significantly higher risk of adverse outcomes. The risk factor assessment and the risk factor profiles in women that are associated with coronary artery disease may be different. Based on the studies from the WISE study, metabolic syndrome is a leading and a major risk factor in women. Moreover, the data further support the concept that the mechanism of ischemia in women may be localized in the microvascular coronary arteries. Therefore, the diagnoses of coronary microvascular dysfunction or endothelial dysfunction should be considered in women with chest pain who do not have obstructive coronary artery disease. It may be advantageous to add such diagnostic tests when the conventional tests are nondiagnostic. A revised clinical approach to cardiovascular disease in women may be designed and tested based on these findings. (J Am Coll Cardiol 2006;47:59S–62S) © 2006 by the American College of Cardiology Foundation

Coronary heart disease (CHD) is the leading cause of mortality and morbidity in the U.S. More women than men have died annually from ischemic heart disease (IHD) since 1984, and coronary artery disease (CAD) is the cause of over 250,000 deaths in women each year. The evaluation of IHD in women presents a unique and sometimes difficult challenge for clinicians, owing to the greater symptom burden, greater functional disability, and lower prevalence of obstructive coronary disease as compared to men. Objective evidence of ischemia, whether symptomatic or asymptomatic, identifies individuals with an adverse prognosis. The results of older trials largely defined the relative places of medical therapy and coronary surgery for the era in which they were conducted. A number of significant changes in selection of patients for surgery, in surgical methods, and in medical therapies have occurred. New pharmacologic and revascularization strategies are now available to relieve ischemia. However, the diagnosis and treatment of CHD have been primarily based on research conducted in men,

either excluding women entirely or including only limited numbers of women and minorities.

Beginning in the early 1970s, with the popularization of revascularization, a number of studies reported on the experience of coronary artery bypass surgery. The Coronary Artery Surgery Study (CASS) was a landmark multicenter study conducted in the 1970s that influenced clinical practice in CAD for many years to come. In that seminal study, which prospectively enrolled patients referred for coronary angiography, only 24% of the more than 24,959 patients (registry and randomized trial) enrolled were women. This represented one of the largest, if not the largest, cohort of women who had angiography to document CAD at that time. Despite the relatively small proportion of women in the CASS trial, important conclusions regarding gender differences in coronary artery disease were evident. First, a high proportion of women with the clinical diagnosis of angina "failed" to show evidence of CAD at angiography. Second, the use of the traditional risk factor assessment was limited in prediction of CAD in individual patients and specifically in women (1,2). The study also generated a number of interesting findings. Women were 4.5 times more likely to have false-positive exercise test response even in the presence of normal coronary angiography. However, positive exercise testing was potentially more helpful in predicting the diagnosis of CAD in women than in men (2).

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Abbreviations and Acronyms

BMI	= body mass index
CAD	= coronary artery disease
CASS	= Coronary Artery Surgery Study
CHD	= coronary heart disease
Hgb	= hemoglobin
IHD	= ischemic heart disease
NHLBI	= National Heart, Lung, and Blood Institute
WISE	= Women's Ischemia Syndrome Evaluation

Subsequent reports describing these CASS trial results implied that these paradoxical findings might be explained by the relatively lower incidence of CAD among women compared to men; however, critical inquiry was not undertaken.

It has been only recently realized that it may not be appropriate to extrapolate clinical decisions regarding women from studies performed in exclusively or predominantly male cohorts. This realization is underscored by the alarming epidemiologic data demonstrating that IHD is the leading cause of morbidity and mortality for women, and that the gap between women and men in terms of incidence and mortality narrows with advancing age. Review of the trends in cardiovascular disease mortality for males and females clearly demonstrates declines in males, which is not observed in females. These data suggest that our concept and understanding of CAD in women are clearly far from complete.

In response to a need for sex-specific IHD research, the National Heart, Lung, and Blood Institute (NHLBI)-funded a number of clinical studies. In 1996, NHLBI funded the Women's Ischemia Syndrome Evaluation (WISE) to improve the reliability of diagnostic testing for IHD in women, and to develop safe, efficient, and cost-effective new diagnostic approaches for women with suspected IHD. A number of important reports continue to emerge from the study that may have significant clinical implications for our approach to cardiovascular disease in women. Moreover, a revised clinical approach to IHD in women may be designed and tested based on these findings.

Clinical evaluation. One of the fundamental steps in the accurate diagnosis of CAD is a thorough history and physical examination. The typical textbook symptoms of substernal chest pain or pressure radiating to the arms may not be the primary symptoms in women presenting with CAD. Other symptoms such as dyspnea, fatigue, and lack of energy may be predominant (3). The new onset of the symptoms and their relationship to activity has more clinical relevance than their physical location (4,5). Women report symptoms more often during daily activities and mental stress than during exercise (6). Special attention should be given to the woman's social history, particularly to the presence of stressful environment or situations. Recent reports suggest that the incidence of transient global myocardial ischemia in response to mental stress may be higher in women than in men (7). Because, among premenopausal

women undergoing coronary angiography for suspected myocardial ischemia, disruption of ovulatory cycling characterized by hypoestrogenemia of hypothalamic origin appears to be associated with angiographic CAD (8), a detailed history should include this information for the global assessment. Thus, a female-specific questionnaire based on the data from the WISE study may enhance our diagnosis.

One of the laboratory tests that is often overlooked as a potential risk factor is hemoglobin (Hgb). Low hemoglobin levels are associated with higher risk for adverse cardiovascular outcomes in women evaluated for suspected ischemia in the absence of acute myocardial infarction or congestive heart failure. However, the prognostic significance of Hgb in women with suspected ischemia is unclear. Recent evidence from the WISE study demonstrated that women with low Hgb (<12 g/dl) have a higher risk of death from any cause and total adverse outcomes (9). In a multivariable model, low Hgb was associated with significantly higher risk of adverse outcomes. Also, anemic women had shorter survival time free of adverse outcome. These findings may not only be relevant for understanding the mechanism of CAD in women, but also have potential therapeutic implications.

Although women are generally at lower risk than men, the combination (i.e., clustering of novel risk markers) acts additively and/or multiplicatively to increase risk and therefore risk assessment in female cohorts. The metabolic syndrome is a leading and a major risk factor in women. In the WISE study, the presence of the metabolic syndrome was independently associated with increased risk of death and major cardiovascular events as opposed to increased body mass index (BMI) (10). Because the metabolic syndrome but not BMI predicts future cardiovascular risk in women, it may be more important to assess the whole spectrum of the metabolic syndrome rather than the BMI alone and to recommend control of all modifiable risk factors in both normal and overweight persons to prevent transition to the metabolic syndrome (11). For example, among women with the metabolic syndrome and high levels of high sensitivity C-reactive protein, the risk of cardiovascular events was similar to that of diabetic women.

Noninvasive functional testing. The lack of correlation between the symptoms in women and conventional functional testing may again indicate that these tests were developed in studies that were predominately male, and may be less applicable for the diagnosis of CAD in women. Although women have less extensive obstructive disease than do men, but a similar or worse prognosis (12), this renders important the need to diagnose such CAD in women but poses a challenge for further development of noninvasive diagnostic methods. It may be speculated that functional tests based on differential perfusion between vascular territories may be less beneficial for the diagnosis of myocardial ischemia in women, compared with global measures of ischemia or risk.

Among the WISE study women with suspected myocardial ischemia in the absence of obstructive CAD, the abnormal phosphorus-31 nuclear magnetic resonance cardiac stress test was a significant predictor of poor cardiovascular outcomes in women with chest pain, independent of the presence of CAD and CAD risk factors. The test was able to identify women who were more likely to have persistent and worsening angina requiring catheterization and hospitalization resulting in greater functional limitations and higher health care costs. These results suggest that magnetic resonance can have wide utility in evaluating women with chest pain, reducing the number of women undergoing repeated coronary angiography, and facilitating treatment before the ischemia worsens (13). The data further support the concept that the mechanism of the myocardial ischemia in women may be localized in the microvascular coronary arteries.

Coronary angiography. The conventional sequence of noninvasive functional tests followed by diagnostic coronary angiography was derived from large multicenter studies that were based on the hypothesis that the cause of the myocardial ischemia is secondary to epicardial obstructive CAD. However, it has become apparent that women who present with angina have less severe and frequent obstructive CAD on coronary angiography (12). These observations led to the notion that women had increased false-positive results in function tests. The WISE study results have advanced our understanding of the nature of myocardial ischemia in women. Functional rather than structural abnormalities of the coronary circulation may be the hallmark of the disease in women. Reis et al. (14) demonstrated that coronary microvascular dysfunction can be identified in approximately half of women with chest pain in the absence of obstructive CAD and cannot be predicted by risk factors for atherosclerosis or by hormone levels. Moreover, coronary flow reserve is lower in women than in men, suggesting potential primary abnormalities in the coronary microcirculation as a source of ischemia in women (15). Furthermore, in women in the WISE study, coronary endothelial dysfunction was independently associated with adverse cardiovascular outcomes regardless of CAD severity (16). Thus, the diagnoses of coronary microvascular dysfunction or endothelial dysfunction should be considered in women with chest pain who do not have obstructive CAD.

Summary and clinical implications. The WISE study provides new information to our understanding of the clinical presentation, diagnosis, and prognosis of IHD in women. With the use of careful traditional risk factor data collection, state-of-the-art technology, and comprehensive analyses, the study has a wealth of data applicable to the diagnosis and management of women with suspected IHD.

A seminal finding from the WISE study relevant to the practice of cardiology is that among women referred for evaluation of suspected myocardial ischemia, approximately 50% do not have obstructive coronary disease, and the prognosis for these women is intermediate in terms of future

adverse cardiac events and persistent symptoms. Practitioners should no longer ignore nonobstructive coronary angiograms in women nor call evidence of clear ischemia in this setting, such as a positive troponin or an abnormal stress perfusion test, a false positive.

The WISE study has further demonstrated that microvascular ischemia is frequently associated with the signs and symptoms of ischemia for this large cohort of women with nonobstructive coronary arteries. Because this abnormal vascular function is often concomitant with abnormal endothelial function, prudent treatment of these women should involve aggressive medical therapy directed at improving endothelial function, atherosclerosis, and established risk factors, including statin lipid-lowering, angiotensin-converting enzyme inhibitors, and aspirin. Future WISE and non-WISE clinical trials will be directed at testing these strategies for reduction of adverse events in these women.

The predictive value of novel risk markers demonstrated in the WISE study may provide us with additional insight into the sex-specific differences in the pathophysiology of IHD. For example, because women in general have lower hemoglobin levels compared to men, due to decades of menstrual cycling and pregnancy-associated losses, it may also be prudent to initiate treatment for low hemoglobin levels in the presence of IHD sooner than current practices among women. Clearly, prospective randomized trials will need to address the utility, risks, and benefits of this approach.

The results of the older trials largely defined the relative places of medical therapy and revascularization based primarily on experience from studies consisting largely of men. In the current pace of the rapid evolution and expansion of invasive and noninvasive interventions, there is a need to address the optimal therapy suitable for women. Recent studies suggest that gender-specific approaches could be beneficial in preventing future events. Based on results from these studies, it is logical to pose the hypothesis that sex improves long-term prognosis. However, many uncertainties remain. Clearly, new studies are needed to prospectively test and validate the WISE study results in a new population and to establish the long-term morbidity and mortality benefits, and quality of life and health care economics, of practice-based sex-targeted strategies. There is no doubt that the investment in the WISE study was a “WISE” move.

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