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INTRODUCTION

Ischemic Heart Disease in Women

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This supplement is intended to provide a specialized forum to overview new information on the pathophysiology, diagnosis, and outcomes of women with suspected ischemic heart disease (IHD). Led by Women's Ischemic Syndrome Evaluation (WISE) study investigators and other experts, the scientific summaries contained in this supplement will permit sharing of current knowledge about this important clinical problem. Improved understanding in these areas will advance the prevention and treatment of IHD in women. These comments by the investigators and experts, as well as those from a recent National Heart, Lung, and Blood Institute consensus conference, should also provide direction for future studies in this critical area. (J Am Coll Cardiol 2006;47:1S–3S) © 2006 by the American College of Cardiology Foundation

This *Journal of the American College of Cardiology* supplement is developed to share new information on the problem of ischemic heart disease (IHD) in women, a topic that has received inadequate attention (1). The new data are a result of an initiative by the National Heart, Lung, and Blood Institute (NHLBI). The NHLBI, through sponsorship of the Women's Ischemic Syndrome Evaluation (WISE) study, created the opportunity to investigate some of the deficiencies in our knowledge base about the clinical aspects of this critically important problem. Specifically, these studies were directed to focus on diagnostic testing and pathophysiology of IHD in women and how sex hormones and other gender-specific findings influence the clinical aspects of this disease (2). The overall design was a prospective cohort recruited at four sites with expertise in all aspects of IHD. The general approach was to screen women referred for diagnostic coronary angiography to further evaluate signs and symptoms suggesting IHD. Data were collected on conditions present at entry, and standard as well as novel tests were then applied. Entry data and test findings were examined for links with the presence and severity of coronary artery obstruction, assessed qualitatively and quantitatively by a core laboratory. The project was divided into a one-year pilot phase (~256 women) and a three-year full study phase (~680 additional women) to prospectively evaluate test findings. The initial results focused on diagnosis and pathophysiological mechanisms. The later results evaluate the relationship of test findings with adverse outcomes in all 936 participants. The project also has a number of substudies, and ancillary studies focused on specific areas of interest.

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CONTRIBUTIONS FROM THE WISE STUDY

In this unique supplement, we have assembled pertinent results from the WISE clinical scientists and also included subject matter experts and opinion leaders to provide overviews on selected aspects of IHD in women. These contributions have shaped, and will continue to shape, the many diagnostic and therapeutic facets of this challenging area.

The supplement begins with a cluster of articles summarizing the results of this ongoing effort in three parts by WISE investigators. In Part I of the "Ischemic Heart Disease in Women: Insights From the NHLBI-Sponsored WISE Study," Shaw et al. (3) review findings dealing with gender differences in risk factors, symptom evaluation, and gender-specific optimized diagnostic strategies. They conclude that variability in onset and risks, along with the synergy of traditional and novel risk conditions in women, creates a challenge for clinicians leading to suboptimal management. They emphasize that some unique risk profiles in women, like hypoestrogenemia and protracted dysmetabolic state, may promote an inflammatory milieu that provokes symptoms and ischemia without obstructive coronary artery disease (CAD). Further, they suggest that, in a growing portion of such women, symptoms and functional limitations may relate to metabolic alterations. Thus, tests to detect obstructive CAD (e.g., stress echocardiography and stress single-photon emission computed tomographic imaging) are better utilized to guide decision making by identifying women at risk.

In Part II, Bairey Merz et al. (4) review how vascular disease may affect gender-specific differences in metabolic alterations, vascular wall findings, plaque deposition, and expression of adverse outcomes. They conclude that new investigative strategies encompassing symptoms, functional disability, diminished quality of life, risk factors, and new imaging techniques for vascular dysfunction need to be

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Abbreviations and Acronyms

CAD = coronary artery disease
DASI = Duke Activity Status Index
IHD = ischemic heart disease
NHLBI = National Heart, Lung, and Blood Institute
WISE = Women's Ischemic Syndrome Evaluation

developed to improve IHD risk assessments and interventions for women.

The third article provides an overview of the coronary vascular findings underlying IHD in women (5). This includes a summary of some risk conditions unique to women that, in addition to traditional risk factors, may promote IHD. This article concludes with a first description of a female-specific vasculopathy that is characterized by a prevalent underlying non-endothelial-dependent microvascular dysfunction superimposed upon endothelial dysfunction. These features contribute to a very defuse involvement by the disease process throughout the entire coronary vascular tree of many postmenopausal women.

NEW FINDINGS FROM THE WISE STUDY

The next cluster of articles deals with specific new findings from the WISE. These begin with a report on the value of estimated functional capacity in predicting outcome (6). Shaw et al. (6) conclude that estimated functional capacity derived from the Duke Activity Status Index (DASI), a 12-question self report, provides valid information predictive of adverse cardiovascular outcomes in these women. Perhaps this instrument, if validated in other female populations, should be administered in the office as a part of our diagnostic evaluation.

Also, the estimated functional capacity from the DASI appears to be linked to impaired coronary vascular reactivity to adenosine as detailed in the following manuscript by Handberg et al. (7). From these results, they conclude that coronary flow reserve may be decreased in response to sedentary lifestyle in these women. Alternatively, the sedentary lifestyle could result from activity limitations caused by an inadequate vasodilator response.

Next, Gierach et al. (8) present new data on hypertension, menopause, and CAD risk from detailed analyses of women in the WISE study. They conclude that identification of elevated systolic blood pressure and/or pulse pressure defines a subgroup of symptomatic premenopausal women that could potentially benefit from additional risk assessment and more intense management.

IMPLICATIONS FROM THE WISE STUDY AND OTHER STUDIES

The last cluster of articles deals with implications from the results reported from the WISE and other studies. Lerman and Sopko (9) provide viewpoints on clinical evaluation, non-invasive functional tests, and coronary angiography findings in women with suspected IHD. They conclude that about one-half of the women referred to a cardiology practice for suspected ischemia do not have obstructive coronary disease, yet their prognosis is not benign in terms of future events and persistent symptoms. They advocate more aggressive therapy including statins, angiotensin-converting enzyme inhibitors, and aspirin, but they emphasize need for randomized trials to assess the utility, as well as risks and benefits, of this approach. Next, Alice Jacobs (10) provides her perspective on "Revascularization and the Gender Gap: What Are We Missing?" From her long career as an interventional cardiologist, she discusses the current status of revascularization in women with acute coronary syndromes and cardiogenic shock, as well as the poor outcomes observed in young women. She concludes with suggestions about how the pathophysiology findings that the WISE investigators have delineated may help to explain some of the well recognized gender differences in IHD. Finally, Arshed Quyyumi (11) provides views on the "Pathophysiological Implications From the WISE Study and Future Research Steps." His topics include ischemia and microvascular dysfunction, risk factors and vascular disease, oxidative stress, endothelial function, inflammation, obesity, insulin resistance and metabolic syndrome, ethnicity and genetics. He concludes with the suggestion that defective repair of continuing vascular injury from an exhausted or senescent progenitor cell pool may be a central paradigm defining vascular disease among women at risk.

SUMMARY

Ischemic heart disease in women represents as an important problem that is difficult to identify early owing to our incomplete understanding of early stage symptoms and mechanisms. A heightened awareness of women at risk of IHD and a different approach than that used in men is necessary to allow for diagnosis before late stages develop. By then, significant pathophysiological changes in the coronary vasculature may result in sudden death, myocardial infarction, congestive heart failure, or need for revascularization. As with most, if not all vascular disease, inflammation and endothelial dysfunction are key elements of the pathophysiology, and both processes are linked with adverse outcomes. But women also are likely to have non-endothelial-dependent microvascular dysfunction, particularly in the early stages of IHD. Limitations to the prevailing diagnostic evaluation of women are now more clearly defined. With more data from the WISE, as well as new studies, consensus needs to be reached on an algorithm of diagnostic testing to better assure an accurate early diagnosis of IHD. Improved understanding of this earlier phase of disease should lead to innovative management approaches to prevent or limit the morbid consequences of IHD in women.

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