The WISE workshop was convened to review results from the Women’s Ischemic Syndrome Evaluation (WISE) study and other studies of ischemic heart disease to examine the nature and scope of gender differences in both chronic and acute cardiac ischemia, in terms of clinical manifestations, detection, and treatment. This section addresses research needs in improved diagnosis of myocardial ischemia in women.

Pathology and Pathophysiology
The chronic stable ischemia syndrome was traditionally viewed as reversible myocardial ischemia and obstructive macrovascular coronary artery disease (CAD) that limits blood flow during periods of increased myocardial oxygen demand. The symptom, typical angina pectoris, usually had a predictable, effort-induced threshold for provocation and a characteristic chest discomfort. Unless they had diabetes, women were thought to be generally spared from this syndrome until they became elderly.\(^1\) Relatively “fixed” stenoses were central to this syndrome, and dynamic changes in coronary size were believed infrequent and contributing to only occasional variability in the threshold for ischemia provocation. Finally, the smaller arteries and arterioles were thought to be relatively spared from disease, and hence, they were not likely to participate in the pathophysiology of the ischemic syndrome.

Our more contemporary view includes both men and women (with the latter being more prevalent\(^2,3\)) who have variable thresholds for ischemia and symptoms that may be typical or atypical for angina pectoris. This view also includes patients (more frequently women, but also men) who have symptoms but no flow-limiting large-vessel coronary stenoses. The pathophysiology of this variability, as well as of ischemia without flow-limiting stenoses, has now been confirmed to be due to dynamic changes in coronary size that also include the microcirculation.\(^4\) These findings often involve dysfunctional endothelium and have the potential to limit flow, causing ischemia and related symptoms that may be somewhat different (eg, lesser in magnitude, limited to subendocardium, patchy distribution, prolonged duration) from those seen with a large-vessel obstruction. Endothelial dysfunction has been linked to oxidative stress resulting from many atherosclerosis risk factor conditions, particularly hypertension, diabetes, and dyslipidemia,\(^5\) which are prevalent in women.

Clinical Application and Evidence
Symptom Recognition
The sensitivity and specificity of symptom assessment depends on the prevalence of obstructive CAD by coronary angiography.\(^6\) This concept limits symptom assessment as...
well as other diagnostic tests developed in angiography populations because it is now recognized that disorders of the coronary circulation other than fixed obstructions on angiography, as summarized above, may cause myocardial ischemia. Furthermore, symptoms occur very late in atherosclerosis, and events often result from destabilization of nonobstructive plaque with subsequent thrombosis, which is not detectable by tests for ischemia. Finally, results cannot be applied to nonangiography populations without adjusting for distorting effects of verification bias.

Clinical Diagnosis of Angina

Prior literature demonstrates that women referred for angiography have a lower likelihood of obstructive CAD than anticipated from angiography in men. Only 39% of the women have CAD, defined as >50% stenosis in >1 coronary artery. Women also appear to have different symptom presentations than men. The Coronary Artery Surgery Study (CASS) study demonstrated that the symptom constellation of typical angina (substernal pain, precipitated by emotional or physical stress, relieved within 10 minutes by rest or nitroglycerin) was predictive of CAD in both men and women. However, the higher prevalence of nonobstructive CAD among the CASS women compared with the CASS men suggested symptoms were less diagnostic in women. WISE investigators found that a classification of “typical” angina missed 65% of the women who actually had CAD. Symptoms experienced by women without CAD may be symptoms of microvascular ischemia or ischemia related to coronary constriction.

Absence of a reliable symptom tool for women is costly in terms of mortality, morbidity, and healthcare utilization. According to recent estimates in the American College of Cardiology National Cardiovascular Disease Registry, approximately 300,000 diagnostic left heart catheterizations are performed annually in the United States each year, with 40% of these performed in women. Given that 48% of these studies in women demonstrate nonobstructive coronary arteries, this excessive normal coronary artery rate will result in an estimated $280 million in potentially unnecessary healthcare costs annually. This estimate does not include the costs of continued medical evaluation and care for the 65% of women found to have normal coronary arteries who have persistent or worsening symptoms, test abnormalities, and disability at 5 years after catheterization.

Critical Pathway for Diagnosis of Myocardial Ischemia

Critical pathways are based on evidence-based guidelines, which mainly address care after a decision to perform a procedure and emphasize focused quality and efficiency; are multidisciplinary in development and execution; and are designed along a timeline. There are currently no critical pathways specifically developed for women with CAD.

Ischemia Tests: Past, Present, and Future Reference Standards

Several studies demonstrate that standard stress testing evaluating inducible electrocardiographic changes, myocardial perfusion defects, and regional wall motion abnormalities are of limited value in women undergoing evaluation for CAD. Specifically, the WISE study has documented low sensitivity of dobutamine echocardiography testing for significant multivessel disease in women with suspected myocardial ischemia. Perfusion imaging with magnetic resonance imaging, recently shown to be feasible in women with chest pain, has shown evidence of subendocardial hypoperfusion in the absence of large-vessel obstruction. Magnetic resonance spectroscopy also has potential to detect myocardial ischemia by demonstrating transient reduction in myocardial high-energy phosphates and increases in inorganic phosphate during stress testing. These exciting new methods deserve additional study to determine their diagnostic accuracy and potential role in evaluating women with chest pain.

New Invasive Diagnostic Strategies: Angiography/Intravascular Ultrasound and Endothelium

Coronary angiography is limited in terms of visualizing only the coronary lumen, whereas intravascular ultrasound (IVUS) also visualizes the arterial wall. A qualitative study of donor hearts for cardiac transplantation indicates that atherosclerosis is at least as prevalent in “normal” hearts of women as in men. Positive remodeling (vessel enlargement to accommodate plaque growth while lumen size is maintained) may be an anatomic explanation for absence of luminal narrowing on angiography. Preliminary data from the WISE IVUS substudy suggest that the majority of women studied in WISE without flow-limiting lesions have abnormalities of coronary endothelial function and/or microvascular flow reserve. In many instances, these abnormalities are of such severity that they have the potential to limit coronary perfusion. Although IVUS indices of plaque burden do correlate with traditional atherosclerosis risk factors and with endothelial dysfunction, the links with microvascular abnormalities are not yet clear.

Office-Based Screening: Role of New Technologies for Subclinical Atherosclerosis

Technologies to detect atherosclerosis in its earliest stages have not been widely used in the office. Coronary artery calcium, carotid ultrasound, magnetic resonance imaging, and endothelial function testing may have advantages over other invasive technologies, but they also require sophisticated equipment and significant expertise. Measurement of arterial compliance may be a useful method to detect individuals with subclinical atherosclerosis that avoids the expense, inconvenience, and risks associated with these other tests. Further work is needed in this area.

Section 1 Recommendations

1. Future research should be targeted to better characterize symptoms in women with CAD. Is there a “female pattern” of angina?

2. Research should better characterize relationships between symptoms and coronary vascular dysfunction in women. Are there relationships between vascular function and symptoms?
3. Gender differences in atherosclerotic and ischemic heart disease pathology and pathophysiology should be investigated. What are the pathological basis, risk factors, and mechanisms for coronary vascular dysfunction in women, as well as mechanisms for vascular remodeling? Could vascular dysfunction be a very early manifestation of ischemic heart disease in the absence of large epicardial vessel obstruction in women?

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Carl J. Pepine, Robert S. Balaban, Robert O. Bonow, George A. Diamond, B. Delia Johnson, Paula A. Johnson, Lori Mosca, Steven E. Nissen and Gerald M. Pohost

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