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EDITORIAL COMMENT

Ischemic Heart Disease in Women

A Need for Sex-Specific Diagnostic Algorithms*

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The decades-long research focus on the pathophysiology of coronary artery disease (CAD) has provided insights into sex-specific factors that are uniquely important in the noninvasive diagnosis of myocardial ischemic syndromes in women. Evidence gained from the landmark WISE (Women's Ischemic Syndrome Evaluation) study (1) indicates that the full spectrum of CAD in women extends beyond atherosclerotic stenoses in the epicardial coronary arteries to include dysfunction of the coronary microvasculature and endothelium. Additional conditions contributing to the full pathophysiologic spectrum of acute and chronic ischemic heart disease (IHD) in women include coronary vasospasm and coronary artery dissection which mainly affect the epicardial coronary arteries and often develop in younger women (2). The implications of these diverse conditions are substantial. They create diagnostic challenges and limit the application of traditional testing strategies which, while adequate to detect obstructive epicardial CAD, may be insufficient for many women presenting with symptoms of chest discomfort.

Considering the spectrum of IHD, additional investigation beyond standard stress tests is often necessary to define the etiology of symptoms in women. This is important as recent studies have demonstrated that dysfunction in the smaller coronary arterioles can cause chronic ischemia, acute myocardial infarction, or stress-induced cardiomyopathy (3). Although women have a lower burden of obstructive CAD on traditional coronary angiography compared to men, women have a higher prevalence of angina and a worse prognosis (1,4). This emphasizes the diagnostic conundrum in confronting the spectrum of possible IHD etiologies in women with chest pain. To improve the diagnosis, treatment, and follow-up in female populations, sex-specific biomarker thresholds and risk stratification tools are needed (3,5).

The secondary analysis by the investigators of the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial presented by Hemal et al. (6) in this issue of *iJACC* adds considerably to our understanding of the sex-specific differences in clinical presentation and management of stable symptomatic outpatients undergoing evaluation for suspected chronic CAD. This analysis reports the demographics, risk factor profiles, clinical presentation, and risk estimates in men and women in the 8,966 stable outpatients with suspected CAD in PROMISE. As all patients enrolled in the PROMISE trial were candidates for noninvasive testing, the data also provide insights into the sex-specific decisions by their providers regarding the choice of functional test, as well as the test results themselves and subsequent management decisions.

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Hemal et al. (6) identify significant differences in the clinical presentation, diagnostic evaluation, and noninvasive testing results between men and women, with a higher prevalence of traditional cardiac risk factors, and a higher likelihood of chest pain characteristics of typical angina, in the 4,720 women compared to the men. Despite the symptomatic presentation, greater family history of premature CAD, and higher risk factor burden, including older age and greater prevalence of hypertension and dyslipidemia, the women in PROMISE were more likely to be characterized as low risk based on standard cardiovascular risk assessment scores and thus, not surprisingly, were also considered to be at lower risk by their providers. These findings add credence to the ongoing concerns that women are preferentially likely to receive less intensive management of CAD than their male counterparts. Women in the PROMISE trial were less likely to have a positive test, and key

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predictors of test positivity also varied by sex. Additionally, women were more frequently referred for imaging stress tests, specifically nuclear stress testing with single-photon emission computed tomography (SPECT), compared to men, but were less likely to have a test result interpreted as positive. This referral pattern is likely driven by prior reports of a diminished accuracy of the exercise electrocardiogram in women (7). It is important to note that this persistent pattern of testing among women fails to consider recent randomized trial evidence noting equal effectiveness of the exercise electrocardiogram compared to myocardial perfusion SPECT for women in diagnosis of CAD (8). Hemal et al. (6) also report that the predictors of test positivity differ between women and men. PROMISE is the first large-scale study of diagnostic testing in a stable outpatient population being evaluated for symptoms of suspected CAD, and hence these findings have important implications by emphasizing the need for sex-specific approaches to CAD evaluation.

Although these data add further to our understanding of the sex differences in the presentation and standard evaluation of patients with suspected CAD who are referred for noninvasive testing, the focus on the use of diagnostic testing for the identification of focal epicardial coronary stenoses underestimates the full pathophysiologic spectrum of IHD that appears to be unique in women. Emerging data underscore the importance of adverse prognosis in symptomatic women with coronary microvascular and endothelial dysfunction in the absence of focal epicardial stenosis (4,9,10). Women with stable angina and nonobstructive CAD are 2 to 3 times more likely than men to experience a cardiac event and have persistent chest pain symptoms within the first year following cardiac catheterization (11). The evolving research on sex-specific vascular biology has provided insight into the mechanisms by which atherosclerotic lesions degenerate to cause acute coronary syndromes. Specifically, the erosion of plaque underneath an incompletely healed or damaged endothelium, which is more likely to occur in younger women, deviates from the characteristic mechanism whereby active inflammatory processes cause degradation of the extracellular matrix and thinning of the fibrous cap of atherosclerotic plaque, leading to plaque rupture and thrombus formation (12).

Therefore, the findings of Hemal et al. (6) of an increased burden of traditional cardiovascular disease risk factors despite a lower frequency of positive tests, does not provide a complete diagnostic picture of all of the possible components of symptomatic IHD in the women patients enrolled in PROMISE. This underestimation of future IHD risk could have profound implications, resulting in the potential of a false sense of security (on the part of the physician as well as the patient) in symptomatic women with negative noninvasive tests.

The 2014 American Heart Association Consensus Statement on noninvasive diagnostic testing in women with suspected IHD (13) highlighted the development of novel diagnostic tools that have an expanded role in the evaluation of symptomatic female patients to detect not only focal epicardial coronary stenosis, but also nonobstructive atherosclerosis as well as the identification of ischemia resulting from microvascular dysfunction. Such methods using advanced imaging are making steady progress in the understanding of microvascular disease and its consequences (14–16).

We agree with the PROMISE investigators that focused sex-specific diagnostic strategies are needed to reduce the cardiovascular mortality and morbidity in women. With emerging data on the full pathophysiologic spectrum of IHD in women, diagnostic algorithms must include functional and anatomic cardiac tests as well as physiologic assessments of endothelial and microvascular function, for accurately establishing the diagnosis and prognosis of women with suspected IHD.

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