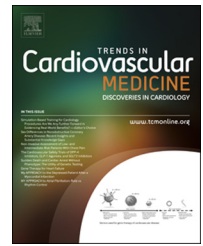


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Sex differences in nonobstructive coronary artery disease: Recent insights and substantial knowledge gaps

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ABSTRACT

The existence of sex differences in the epidemiology, presentation, diagnosis, and management of coronary artery disease (CAD) has been a subject of growing inquiry for the past several decades. The prevailing paradigm is that the prevalence of anatomically obstructive disease of the epicardial coronary arteries is less common in women than similarly aged men, while nonobstructive and microvascular ischemic disease is more prevalent in women. Although both “patterns” of coronary atherosclerosis are associated with angina and cardiovascular events, the dominant diagnostic and therapeutic tools used in cardiology have focused on the male-predominant pattern of anatomically obstructive epicardial CAD. This has raised justified concerns about the under-diagnosis and under-treatment of symptomatic women with nonobstructive CAD. However, as recent research has begun to highlight the importance of nonobstructive CAD and coronary physiology in men as well as women, adjustments to this paradigm and greater attention to nonobstructive CAD are necessary. The present article seeks to review key insights as well as substantial knowledge gaps regarding sex differences and nonobstructive CAD.

Key words: Sex differences, Coronary artery disease.

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Background

Ischemic heart disease (IHD) is the leading cause of mortality of women in all age groups [1]. At 50 years of age, the average lifetime risk of developing IHD in women is approximately 40% [2]. Overall, despite mortality from IHD in the United States steadily declining from the 1960s, the rate of mortality reduction in women has down-trended more slowly than that of men [1]. The exact factors contributing to poorer outcomes for women diagnosed with IHD have yet to be fully elucidated, but there are several prevailing hypotheses including differences in coronary vasoreactivity, inappropriate risk factor

stratification, the sensitivity and specificity of noninvasive imaging modalities for IHD diagnosis, and treatment.

Overall, numerous studies have consistently demonstrated that the burden of atherosclerosis is higher in men than in women at all stages of the disease process [1]. For example, a study of 142 patients (53 men and 89 women) with “early CAD” found that men had significantly more epicardial atheroma burden by intravascular ultrasound (IVUS) in the left main artery (median, 23.0% vs 14.1%, $p = 0.002$) and eccentricity of plaque in the proximal left anterior descending artery (median, 0.89 vs 0.80, $p = 0.04$) [3]. At the other end of the CAD spectrum, there appear to be additional sex

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differences in the pathophysiology of acute coronary syndrome (ACS), with coronary plaque rupture more prevalent in men and plaque erosion and less necrotic core volume more prevalent in women [4]. Nevertheless, though women with ACS typically have less anatomically obstructive coronary artery disease, they still experience roughly similar mortality rates when compared to men [5].

The observation of sex differences has been the impetus for considerable research efforts over the past several decades, most notably the Women's Ischemic Syndrome Evaluation (WISE) study [6]. An important finding of this work is the adverse prognosis associated with nonobstructive CAD in women with chest pain symptoms and ischemia by non-invasive testing [6]. Nonobstructive CAD can be considered as the lack of flow-limiting atherosclerotic epicardial coronary plaque, but unfortunately, there has been no consistent definition of what qualifies as nonobstructive CAD. Previous studies and trials have used widely varying definitions, most of which are built upon anatomic assumptions from invasive coronary angiography (ICA). For example, the Veteran's Administration CART National Registry defines nonobstructive CAD as any epicardial arterial stenosis $\geq 20\%$, but $\leq 70\%$, except for the left main artery, which was defined as $\geq 20\%$, but $\leq 50\%$ stenosis [7,8]. The lower 20% threshold reflects limitations of measuring luminal irregularities by ICA [6]. However, more recent studies using coronary-computed tomographic angiography (CCTA) have overcome this limitation and defined the presence of any coronary plaque as nonobstructive CAD [9,10]. It is unclear the degree to which this re-categorizes patients who may have been defined as "normal" ICA.

Additionally, neither conventional ICA nor CCTA can detect coronary microvascular disease (CMD), an entity that

nosologically overlaps with nonobstructive CAD. CMD is a complex entity defined by reduced coronary flow reserve (CFR) and coronary endothelial dysfunction with impaired vasoreactivity at the microvascular level. The major function of the coronary microvasculature is to ensure appropriate oxygen and myocardial blood supply match through modulation of endothelial shear stress and coronary vasodilation [11]. Mismatch of oxygen and myocardial blood supply owing to microvascular dysfunction can lead to small, discrete areas of focal ischemia. Many mechanisms have been proposed to contribute to CMD, and the degree to which it is a discrete entity rather than a phenotype of nonobstructive CAD remains unclear [6]. Although patients with CMD may have "normal" angiograms, they frequently suffer from anginal symptoms [12] and have an increased risk of major adverse cardiac events (MACE) [13]. For instance, Taqueti and coauthors found that patients with CMD (defined as a CFR < 2) had a more than twofold-increased risk of MACE compared to those with normal microvascular function (adjusted hazard ratio = 2.25; 95% CI: 1.31–3.86; $p = 0.003$). Studies have consistently found that women are more likely to have abnormal coronary microvascular function than men [1,11,12]. However, in light of recent observations that women have higher resting coronary flow and lower CFR than men with similar microvascular function [14], it is possible that sex differences in microvascular dysfunction are overstated [15].

The definitional inconsistency of nonobstructive CAD has limited retrospective analyses of prior literature to more fully understand the impact of sex on the diagnosis, prevalence, treatment, and morbidity associated with nonobstructive CAD (Fig.). Until fairly recently, nonobstructive CAD has often

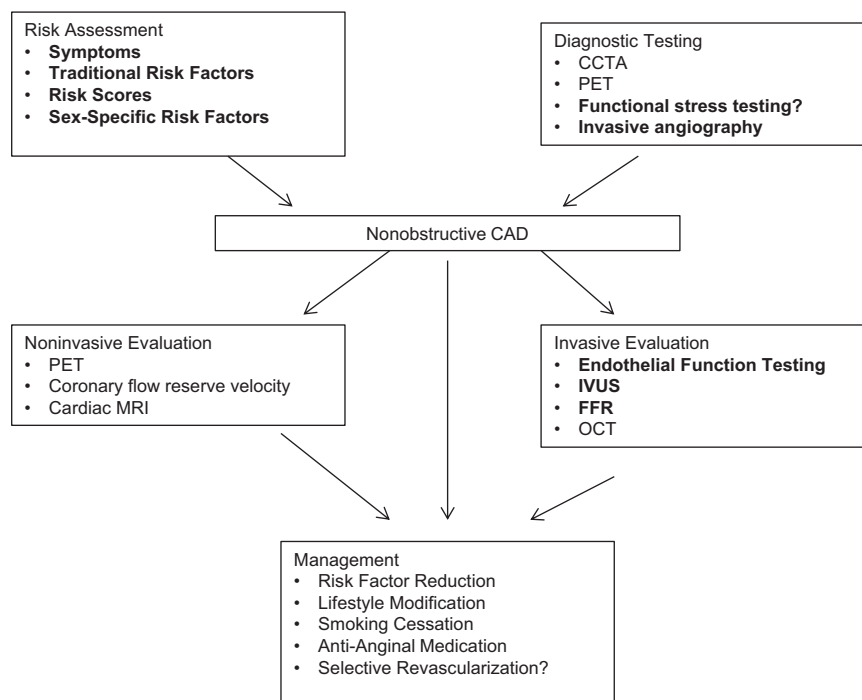


Fig – Sex Differences in nonobstructive CAD. Elements in bold signify where sex differences have been reported. Abbreviations: CCTA, coronary-computed tomographic angiography; FFR, fractional flow reserve; IVUS, intravascular ultrasound; MRI, magnetic resonance imaging; OCT, optical coherence tomography; PET, positron emission tomography.

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