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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Emergence of Nonobstructive Coronary Artery Disease

A Woman's Problem and Need for Change in Definition on Angiography

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ABSTRACT

Recognition of ischemic heart disease (IHD) is often delayed or deferred in women. Thus, many at risk for adverse outcomes are not provided specific diagnostic, preventive, and/or treatment strategies. This lack of recognition is related to sex-specific IHD pathophysiology that differs from traditional models using data from men with flow-limiting coronary artery disease (CAD) obstructions. Symptomatic women are less likely to have obstructive CAD than men with similar symptoms, and tend to have coronary microvascular dysfunction, plaque erosion, and thrombus formation. Emerging data document that more extensive, nonobstructive CAD involvement, hypertension, and diabetes are associated with major adverse events similar to those with obstructive CAD. A central emerging paradigm is the concept of nonobstructive CAD as a cause of IHD and related adverse outcomes among women. This position paper summarizes currently available knowledge and gaps in that knowledge, and recommends management options that could be useful until additional evidence emerges. (J Am Coll Cardiol 2015;66:1918–33) © 2015 by the American College of Cardiology Foundation.

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Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Recognition of ischemic heart disease (IHD) is often delayed or deferred in women. Consequently, many at risk for related adverse outcomes are not provided specific diagnostic, preventive, and/or treatment strategies. In part, this lack of recognition is related to sex-specific cardiovascular disease (CVD) pathophysiology in women that differs from the traditional male-pattern model. The latter model is based largely upon studies in which the majority of subjects were men with flow-limiting atherosclerotic coronary artery disease (CAD). The current state centers on the emerging paradigm of nonobstructive CAD relationships to myocardial ischemia and related adverse outcomes among women. Women are less likely to have flow-limiting obstructive CAD compared with men presenting with similar symptoms (1). This nonobstructive CAD pattern and the tendency among women to have plaque erosion with subsequent thrombus formation, along with coronary microvascular dysfunction (CMD), are not well recognized. Importantly, data are emerging to show that more extensive nonobstructive CAD involvement is associated with a rate of major adverse cardiovascular events (MACE) that may approximate that of obstructive CAD (2). However, there are many limitations to our understanding of nonobstructive CAD, a consequence of numerous gaps in current knowledge.

This position paper summarizes the available knowledge and important gaps in knowledge, and recommends management options that could be useful for the clinician until additional evidence becomes available. We expect this report to raise awareness of clinical presentations, adverse outcomes, diagnostic strategies, and therapeutic options, and to help guide efforts to further improve outcomes among patients with acute and chronic ischemia syndromes (e.g., IHD) and nonobstructive CAD, who are predominantly women.

THE PROBLEM OF NONOBSTRUCTIVE CAD: DEFINITION, PREVALENCE, AND PATHOPHYSIOLOGICAL IMPLICATIONS FOR MANAGEMENT

Nonobstructive CAD may be considered in patients with symptoms/signs of IHD where atherosclerotic epicardial CAD does not limit coronary blood flow, but other processes may adversely influence myocardial supply/demand relationships. Nonobstructive CAD is highly prevalent in women, including those presenting with typical symptoms of IHD (e.g., angina).

HISTORICAL CONSIDERATIONS AND TERMINOLOGY. Although it has long been recognized that selected conditions other than obstructive CAD may cause ischemia and related symptoms and signs, the prevailing opinion was that these situations were relatively infrequent and had no clinical implications beyond those associated with the selected condition (e.g., severe aortic valve stenosis, hypertrophic cardiomyopathy, pulmonary hypertension). However, several factors have contributed to a change in that position.

For example, approximately 20% to 30% of angina patients with technically successful coronary revascularization, by either coronary bypass graft or percutaneous coronary intervention, have persistent signs and/or symptoms of IHD (3,4). Explanations for ischemia among these patients include incomplete revascularization, unrecognized remaining obstructive disease, coronary spasm, and/or CMD. Next, a large cohort of patients with chronic angina and objective evidence of ischemia at stress testing have no demonstrable obstructive CAD by angiography (5,6). This was initially explained as false-positive findings for ischemia, despite the documentation of ischemia by methods ranging from the electrocardiogram (6), positron emission tomography (PET) imaging (7), contrast cardiac magnetic resonance imaging (cMRI) (8), and cardiomyocyte metabolism (9–11). Then, ischemia with nonobstructive CAD was viewed as a benign form because these patients generally had normal left ventricular (LV) systolic function and good short-term outcomes. However, patchy areas of ischemia in the subendocardium and/or midwall of the LV are often not associated with major reductions in systolic function (7). Additionally, issues such as survival bias, high rates of variability in quality and/or interpretation of angiograms related to lack of core labs, and incomplete follow-up limit much of this past outcomes literature. Indeed, many well-designed, more recent cohorts document a heightened rate of adverse outcomes among patients with symptoms and signs of ischemia and no obstructive CAD versus similar patients without symptoms and signs of ischemia (1,12–25). Importantly, multiple cohorts link other mechanisms for ischemia, such as coronary endothelial and microvascular dysfunction, and risk for adverse outcomes among symptomatic patients with nonobstructive CAD (2,19,26–28).

Definitions for nonobstructive CAD vary in the literature, in part from variable methods used to

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ACS = acute coronary syndrome(s)

CAD = coronary artery disease

CI = confidence interval

CMD = coronary microvascular dysfunction

cMRI = cardiac magnetic resonance imaging

CTA = computed tomography angiography

CVD = cardiovascular disease

HR = hazard ratio

IHD = ischemic heart disease

IVUS = intravascular ultrasound

LV = left ventricular

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

NSTE = non-ST-segment elevation

NSTEMI = non-ST-segment elevation myocardial infarction

PET = positron emission tomography

STEMI = ST-segment elevation myocardial infarction

TCFA = thin-cap fibroatheromas