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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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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

interpret coronary angiograms (individual operator or group consensus readings using simple visual estimation, differing methods to quantify narrowings, dedicated core lab, and so on). Experience from the WISE (Women's Ischemic Syndrome Evaluation) angiographic core lab, using standardized qualitative and quantitative methods, indicates that essentially any observed luminal irregularity, measured quantitatively, yields at least a 20% diameter reduction versus the most completely normal-appearing reference segment in the same part of the coronary artery under evaluation (23). In addition, as a result of vessel tapering, it is common to obtain narrowing ranging from 0% to 19% when measuring such "normal" segments. Thus, it follows that a patient with no apparent CAD or normal-appearing coronary arteries may be defined as having normal-appearing coronary arteries and, when measured, no stenosis ≥20% diameter narrowing in any epicardial coronary artery. *Nonobstructive CAD* may be defined as at least 1 stenosis ≥20, but <50%, whereas *obstructive* (single-, double-, or triple-vessel) *CAD* may be defined as at least 1 stenosis ≥50%.

Recently, the Veterans Administration CART National Registry (16) defined nonobstructive CAD as any stenosis ≥20%, but <70%, narrowing in any epicardial artery, or ≥20%, but <50%, in the left main artery. Normal coronary anatomy was defined as <20% stenosis in all coronary arteries, consistent with the definition for normal used in the WISE.

PATHOPHYSIOLOGY. From the pathophysiology standpoint, a number of different terms have been used to describe these patients: nonobstructive CAD; IHD patients without obstructive CAD; open artery IHD; myocardial infarction (MI) with no coronary artery obstruction; CMD; microvascular angina; and cardiac syndrome X. The latter term has been unfortunate, as there is no consensus in the literature on its definition, and there is now sufficient knowledge to sunset this terminology (28,29).

Coronary intravascular ultrasound (IVUS) and, to some extent, cardiac computed tomography angiography (CTA) studies indicate that essentially all patients (within the limitations of sampling by these techniques) with suspected IHD reported to date with "normal-appearing coronary arteries by angiography" have some evidence for atherosclerosis (plaque). Thus, it seems most appropriate to endorse the descriptive term *nonobstructive CAD* in the absence of another cause for the syndrome.

Another concern is exclusion of concealed obstructive CAD due to diffuse epicardial coronary artery narrowing. The only study (19) addressing this in a prospective, systematic approach found that 5% of cases (7 of 139) had a fractional flow reserve ≤0.80 among patients otherwise thought to have normal or nonobstructive CAD by quantitative angiography. Interestingly, most of the cases (4 of 7) had other, coexisting reasons for ischemia (myocardial bridging and/or severe endothelial dysfunction), as all 7 had some evidence for endothelial dysfunction. So, it seems reasonable to conclude that diffuse or concealed obstructive CAD alone rarely explains this syndrome of symptoms/signs of ischemia.

Approximately 60% to 70% of women and 30% of men undergoing coronary angiography to further evaluate suspected clinically stable IHD have nonobstructive CAD (1). Thus, this nonobstructive pattern is common, but more highly prevalent among women. This is despite the fact that symptomatic women are generally 10 to 15 years older than symptomatic men when they present, and often have greater density (number) and magnitude of risk factors (hypertension, diabetes, smoking, dyslipidemia). In the presence of nonobstructive CAD, microvascular and/or endothelial dysfunction, and many other processes (e.g., epicardial and microvascular spasm, myocardial bridging, conduit vessel stiffening) may contribute to myocardial ischemia (30) (**Table 1**). These features appear to be much more frequent in women than in men. The presence of coronary microvascular and/or endothelial coronary dysfunction predicts adverse outcomes (26,31), although specific mechanisms responsible for these mortality/morbidity outcomes are not fully understood. Our limited understanding of these nonobstructive disease patterns is particularly relevant for young women, who have an unfavorable prognosis compared with men of the same age (32,33). Clearly, nonobstructive CAD requires better recognition and investigation if we are to develop effective prevention, diagnosis, and treatment approaches for this population, which includes large numbers of women.

CLINICAL MANAGEMENT IMPLICATIONS. Numerous guideline-recommended strategies target prevention of atherosclerosis progression in obstructive CAD to improve outcomes, and promising innovative therapies that target obstructive CAD are under development. Although most nonobstructive CAD patients likely have coronary atherosclerosis, no guideline-recommended therapy is available (except for symptom relief and CVD risk factor management) for the large proportion of patients with signs and symptoms of IHD and nonobstructive CAD, and none appear on the horizon. As a result, these patients are often dismissed from specialty care and even general care, and the majority are women. It is noteworthy that guideline-directed care for patients with

nonobstructive CAD was not included in the recent stable IHD practice guideline that focused on obstructive CAD as the pathophysiology of ischemia (34). The evidence reviewed here can inform the clinical community and support a focused guideline update for clinicians facing dilemmas regarding diagnosis and management of patients (particularly women) with nonobstructive CAD.

To recapitulate, patients with nonobstructive CAD encompass all of the acute and chronic IHD syndromes. This disease pattern is associated with heightened risk for adverse outcomes, yet current guidelines do not inform clinicians regarding assessment and management of these patients. The foregoing has generated several important questions.

IS CORONARY ATHEROSCLEROSIS PRESENT?

Without an obvious focal epicardial stenosis, remodeling renders the angiogram insensitive to the presence of atherosclerosis and invalidates use of a so-called "normal reference segment" to estimate stenosis severity. Studies using IVUS (19,35,36) or CTA (13) have documented that coronary artery remodeling makes it very challenging to determine whether or not atherosclerosis is present from the "lumenogram" presented by selective coronary angiography. Some have proposed developing a method for quantifying angiographic estimates of coronary artery segmental size and shape (e.g., tapering) compared with sex- and segment-specific, population-derived, normal values (37). Registry data report that positive or expansive remodeling is associated with an elevated risk of acute coronary syndrome (ACS) (38–41). In the absence of obstructive stenosis, coexisting low-attenuation plaque on CTA or echolucent plaque on IVUS are also noted, which further increase ACS risk (42).

Coronary artery IVUS confirmed that >80% of the women evaluated in a WISE substudy had evidence for atherosclerotic plaque (36,43). Lee et al. (19) found IVUS evidence for atherosclerosis in all 139 patients with angina in the absence of obstructive CAD, of whom 107 (77%) were women.

Thus, atherosclerosis is present in most of the cases included in reports to date, but this may be influenced by selection bias related to atherosclerosis risk factor threshold contributing to referral for invasive studies.

IS MYOCARDIAL ISCHEMIA REALLY PRESENT?

Findings of normal global LV systolic function and good short-term clinical outcomes led to speculation that ischemia might not be present. Yet, there is uniformity of data supporting risk stratification across conventional stress imaging procedures, concluding that identification of ischemia in women

TABLE 1 Proposed Mechanisms for Stable IHD Syndromes

Type	Location of Defect	Potential Mechanisms
Vascular		
	Coronary macrovessels	Flow-limiting stenosis (e.g., atherosclerosis) Non–flow-limiting stenosis (e.g., atherosclerosis) Endothelial dysfunction (e.g., athero RFs, viruses) VSM dysfunction/spasm (e.g., athero RFs, ANS, drugs, viruses) Thrombotic (e.g., hypercoagulation, enhanced platelet activation, plaque rupture/erosion/fissuring) Embolic (e.g., AF, prosthetic valve, LV thrombus, SBE) Inflammation (atherosclerosis, transplant, col dis [e.g., SLE, PAN, RA]) Congenital (muscle bridge, aberrant origin) Dissection (e.g., pregnancy, chest trauma, Marfan) Misc.
	Coronary microvessels	Microvascular dysfunction (VSM dysfunction/spasm (e.g., athero RFs, ANS, viruses, drugs) Endothelial dysfunction (e.g., athero RFs, viruses) Endothelial cell-x cell "crosstalk" (e.g., EC-VSM, mononuclear cell, cardiomyocyte) Microparticle occlusion (e.g., atheroma, cells, platelet microaggregation, cholesterol) Thrombotic (e.g., hypercoagulable state, platelet activation, plaque rupture/erosion) Microembolic (e.g., atheroma, AF, prosthetic valve, SBE) Inflammation (athero, transplant, col dis [e.g., SLE, PAN, RA]) Capillary insufficiency (e.g., LVH) Misc.
	Other vessels	
	Capacitance	Increased aortic-femoral arterial stiffness (e.g., aging, calcification, hypertension, CRI)
Nonvascular		
	Cardiomyocyte	
	Transcellular	Oxygen transport (reduced diffusion [e.g., infiltrate, amyloid]) Energy substrate (e.g., depleted FFA, glucose) ?
	Intracellular	Oxygen transport (e.g., defective myoglobin) Energy substrate (e.g., depleted FFA, glucose) ?
	Mitochondria	Mitochondrial dysfunction/adaptation (ischemic injury/protection, HF, DM, aging) ?
	Adventitia/matrix	Stroma-connective tissue proliferation Adipocytes-estrogens (from androgens), leptins, and so on. Leukocytes-cytokines, angiotensin II, and so on. Mast cells, histamine, serotonin, proteoglycans, serine proteases, eicosanoids, and so on. Sympathetic nerve activation Vasa vasorum-capillary leak ?
	Other	CNS dysfunction/disease, defective bone marrow-derived cells (e.g., CD34/CD133), T cells, among others. Adipose-derived cells, among others. ?

AF = atrial fibrillation; ANS = autonomic nervous system; athero RF = atherosclerosis risk factors; CNS = central nervous system; col dis = collagen vascular disease; CRI = chronic renal insufficiency; DM = diabetes mellitus; EC = endothelial cell; FFA = free fatty-acid; HF = heart failure; IHD = ischemic heart disease; LV = left ventricular; LVH = left ventricular hypertrophy; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; SBE = subacute bacterial endocarditis; SLE = systemic lupus erythematosus; VSM = vasomotor; ? = unknown.

(and men) is associated with elevated risk for cardiac events (34). Specifically, in cohorts of women with prevalent nonobstructive CAD, as the extent and severity of inducible ischemia increases, so do IHD-related event rates (17,21,24). Furthermore, because most clinical methods to assess ischemia rely on detecting relatively large regional differences in LV perfusion and/or wall motion in epicardial coronary territories, it became apparent that most patients without obstructive CAD do not have major global perfusion differences. Instead, with pharmacological vasodilator stress, perfusion of the subendocardium and/or mid-ventricular wall fails to increase appropriately (7,8,44). The most useful methods for these cases are those that measure coronary blood flow reserve (directly with Doppler or PET or cMRI with gadolinium) and/or myocardial metabolism (^{31}P magnetic resonance spectroscopy).

IS CORONARY MICROVASCULAR DYSFUNCTION PRESENT?

Without a more proximal flow-limiting stenosis, coronary resistance vessels (e.g., arterioles <100-μm diameter), the microcirculation, predominantly modulates myocardial perfusion. Considerable data document that CMD contributes to myocardial perfusion abnormalities in regions supplied by vessels without epicardial stenosis (45–48) in patients with risk factors and/or angina, but without epicardial stenosis (49–52). In the MESA (Multi-Ethnic Study of Atherosclerosis), both myocardial flow (cMRI) during adenosine-induced hyperemia and flow reserve were inversely associated with risk factor burden (53). CMD has been documented among symptomatic women without flow-limiting coronary stenosis in the WISE (26,54) by directly measured (Doppler flow wire) coronary flow, by cMRI (44), and by PET (20). These studies have linked CMD and atherosclerosis risk factors with adverse outcomes over follow-up. CMD has also been replicated in another female cohort (55), providing additional support for its link with several risk factors. Thrombolysis In Myocardial Infarction frame counts and some noninvasive measures to assess contrast flow as an index of myocardial blood flow have also been used (56–58).

Even among individuals with obstructive CAD, noninvasive imaging has documented abnormal perfusion in myocardial regions supplied by vessels without apparent obstructive CAD (48). Histology of nonischemic LV myocardium, remote from vessels with obstructive CAD, shows that women have less interstitial fibrosis, but similar perivascular fibrosis versus men (59). The arteriolar wall area/circumference ratio, a measure of arteriolar wall thickness, was almost 50% greater in these women versus men. Cardiomyocyte width, capillary length density, diffusion radius, and cardiomyocyte width/body surface area ratio were similar for men and women, but women had greater diffusion radius/body surface area ratio and diffusion radius/cardiomyocyte width ratio, with lower plasma vascular endothelial growth factor (VEGF) receptor-1 levels and VEGF receptor-1/VEGF-A ratios. These findings imply that women have greater arteriolar wall thickness and diffusion radius relative to body surface area and to cardiomyocyte width than men, which may predispose them to ischemia. Studies of larger numbers of women with less extensive CAD are required to confirm these findings and elucidate mechanisms of underlying CMD.

SYNDROMES ASSOCIATED WITH NONOBSTRUCTIVE CAD AND ADVERSE OUTCOMES

CHRONIC STABLE ANGINA. So-called "normal coronary arteries" and "no obstructive CAD" by selective angiography may be reported in as many as 60% to 70% of symptomatic women referred to angiography for evaluation of chronic stable symptoms (principally angina) (1). Much of this information originated from the WISE, a prospective cohort study of 936 women presenting to coronary angiography to further evaluate symptoms (chest pain) and/or signs of IHD. One a priori objective was to determine the frequency and impact of ischemia in the absence of significant coronary stenosis. All underwent a baseline physical examination with collection of demographic, medical history, and symptom data using standardized questionnaires. Angiograms were quantitatively and qualitatively evaluated for presence and extent of CAD by the core laboratory (masked to all other data). Among the 883 completing the angiogram and available for follow-up, no obstructive CAD was found in 547 (62%, mean age 56 years), defined as no stenosis ≥50% in any artery (60). Outcome data were collected by a scripted interview 6 weeks after initial assessment and annually thereafter. The initial follow-up analysis was done at a mean of 5.2 years (18). Death certificates, clinical data, and hospital summaries were reviewed by the Events Committee masked to angiographic data, to determine the cause of death (cardiac vs. noncardiac). Another analysis, which also included a National Death Registry search, extended the follow-up to 10 years (23). The

same Events Committee, masked to angiographic information, also reviewed these additional deaths to determine the cause of death.

The WISE data indicated that about two-thirds of the women referred for angiography to further evaluate symptoms/signs of IHD had nonobstructive CAD. At 5 years, the nonobstructive CAD cohort had a 2.5% yearly risk of MACE (first occurrence of death [all-cause], nonfatal MI, nonfatal stroke, or heart failure hospitalization) that was 3-fold higher than the case-matched asymptomatic reference cohort (18). At 10 years, cardiovascular death or MI had occurred in 6.7% of women with "no obstructive CAD" (e.g., ≤20% diameter reduction) versus 12.8% of those with nonobstructive CAD (e.g., >20%, but <50%, narrowing) (23). Limitations of these findings were largely related to the design: absence of men, small sample size, and selection bias by the respective centers.

However, multiple larger studies, free of selection bias, from the United States, Canada, and Europe, have replicated the high prevalence of nonobstructive CAD among angina patients, the adverse prognosis in women, and extended these findings to men (1,22,25). Some have found that the outcomes associated with nonobstructive CAD are worse for women.

One study included all patients ≥20 years with stable angina undergoing coronary angiography (N = 13,695) in British Columbia, Canada, from July 1999 to December 2002 (22). Using the WISE angiographic definitions, outcomes were assessed to 3 years follow-up. Among women with stable angina, 42%, versus 14% of men, had no obstructive CAD. Women with no obstructive CAD were ~3 times more likely than men to experience a MACE (same definition as WISE) within the first year of angiography.

A larger registry study of all patients with suspected stable angina in Eastern Denmark having a "first" coronary angiography between 1998 and 2009 (1) identified 11,223 patients and 5,705 participants from the Copenhagen City Heart Study for reference. Within the symptomatic population (4,711 women and 6,512 men), significantly more women (65%) than men (32%) had no obstructive CAD (<50% stenosis). Interestingly, this fraction progressively increased over the 10-year study period. Although event rates were higher among women, in models adjusted for age, body mass index, diabetes, smoking, and lipid-lowering or antihypertensive medication use, risks associated with no obstructive CAD were similar in women and men. In a pooled analysis (women plus men), the risks for MACE (as cardiovascular death, MI, stroke, or heart failure), and all-cause death increased with increasing degrees of nonobstructive CAD: adjusted hazard ratios (HRs) were 1.52 (95% confidence interval [CI]: 1.27 to 1.83) for patients with normal coronary arteries and 1.85 (95% CI: 1.51 to 2.28) for those with diffuse nonobstructive CAD versus the reference population. For all-cause mortality, normal coronary arteries and diffuse nonobstructive CAD were associated with HRs of 1.29 (95% CI: 1.07 to 1.56) and 1.52 (95% CI: 1.24 to 1.88), respectively. It is noteworthy that these stable angina patients with nonobstructive CAD also had higher rates of cardiovascular hospitalization versus reference individuals, after adjustment for cardiac risk factors and exclusion of cardiovascular comorbidities.

Among all veterans undergoing elective angiography from 2007 to 2012, ~75% of 3,181 women had no obstructive CAD (e.g., either "normal" or "nonobstructive CAD") and among 36,590 men only ~44% had these findings (16). But, as noted previously, "nonobstructive CAD" was defined as any stenosis ≥20%, but <70% narrowing, in any epicardial artery or ≥20%, but <50%, in the left main artery. Relative to patients with no apparent CAD, those with 1-vessel nonobstructive CAD had a hazard ratio (HR) of 2 for MI at 1 year, which increased to 4.6 for 2-vessel nonobstructive CAD.

In community-based, predominantly symptomatic (angina) patients (N = 23,854) without known CAD, the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) found that about a third had nonobstructive CAD by CTA (14), which occurred more frequently in symptomatic women versus men. All-cause mortality risk associated with nonobstructive CAD was similar among women and men (HR: 1.67 and 1.52, respectively), but these risks were similar or higher compared with those with obstructive 1-vessel CAD (HR: 1.17). Importantly, when stratified by age, older (≥65 years) women with nonobstructive CAD experienced a more than 5-fold higher all-cause mortality risk (adjusted HR: 8.08) versus younger women (HR: 1.59) that was greater than the risk observed for older men (HR: 7.79).

Referral for another coronary angiogram is costly, is associated with additional risk, and adversely impacts quality of life. In the WISE cohort of women having an angiogram to evaluate stable angina symptoms, those with nonobstructive CAD had rates of repeat angiography of 3.7%, 12.3%, and 15.7% at 1, 3, and 5 years, respectively (60). These findings have been confirmed and extended to men (61). Over 7.8 years, 23% of women and 30% of men had at least

1 additional angiogram. In both women and men, those with no obstructive CAD had 3- to 5-fold higher rates of repeat angiography per 1,000 years at risk versus asymptomatic reference individuals. Overall, the risk for repeat angiography was >2-fold higher in patients with "angiographically normal" coronary arteries and ~6-fold higher for those with diffuse nonobstructive CAD.

Our studies comparing WISE participants with nonobstructive CAD and a reference group of asymptomatic, apparently healthy women matched for age, height, and body mass index identified significant differences related to indexes of increased arterial stiffness, reflected by aortic pulse wave velocity, augmentation index, systolic blood pressure, and pulse pressure. These observations suggest that these factors may contribute to the development of nonobstructive CAD, but additional studies are clearly warranted (62).

In summary, about 30% to 60% of patients with stable angina undergoing selective coronary angiography have no obstructive CAD. This frequency appears higher in women (40% to 60%) versus men. Using CTA, this frequency of nonobstructive CAD is about one-third. It is also clear that those with nonobstructive CAD have considerably greater risk burdens in terms of CVD hospitalization, disability, repeat angiography, and MACE versus reference individuals. It is unclear whether these adverse outcomes associated with nonobstructive CAD are significantly higher among women with stable angina versus men. However, contrary to common perception, excluding obstructive CAD by angiography in stable angina patients does not ensure a benign cardiovascular prognosis.

ACUTE CORONARY SYNDROMES. Women with ACS are less likely than men to have obstructive CAD, suggesting that different ACS mechanisms operate among women compared with men (63). More than one-third of women with MI and nonobstructive CAD have plaque rupture or ulceration when examined with IVUS (64,65). Within 180 days of an ACS presentation, women with normal-appearing coronary arteries by angiography are 4 times more likely than men to be readmitted for ACS/chest pain (66,67). Over 1 to 5 years, they have a 40% risk of rehospitalization for chest pain and a 30% rate of repeat coronary angiography. Details of patient characteristics and outcomes are provided in 2 large datasets summarized in the subsequent discussion.

Relative to non-ST-segment elevation (NSTE) ACS, data from 37,101 patients, 3,555 with no obstructive CAD, were reported in a patient-level meta-analysis of 8 randomized trials (68). Overall, ~10% had nonobstructive CAD; they were younger (60 vs. 66 years), more frequently women (56% vs. 29% men), and fewer had diabetes (15% vs. 26%), prior MI (15% vs. 32%), or percutaneous coronary intervention (10% vs. 20%) compared with those with obstructive CAD. Patients with nonobstructive CAD were treated less often with guideline-recommended drugs before angiography and this difference increased after angiography. Death or MI at 30 days was less frequent among patients with nonobstructive (2.2%) versus obstructive CAD (13.3%; odds ratio: 0.15; 95% CI: 0.11 to 0.20); 6-month mortality was also lower (0.19 [95% CI: 0.14 to 0.25] and odds ratio: 0.37 [95% CI: 0.28 to 0.49], respectively). In the nonobstructive CAD group, patients with 30-day death/MI had higher GRACE (Global Registry of Acute Coronary Events) risk scores and elevated cardiac markers at presentation versus those without these events. These data are limited by wide variability across trials in fractions of patients undergoing angiography (52% to 97%) and with findings of nonobstructive CAD (6.9% to 13%), and adverse outcomes that generally related to refractory ischemia or urgent revascularization. These data are also limited by bias related to different entry criteria and treatments mandated by each trial.

Such limitations are not present in the population-based CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) registry of 51,608 NSTE ACS patients (69). Overall, no obstructive CAD was found in 4,903 (9.5%, 60% women), but was twice as likely among women (15.1% vs. 6.8% of men). Women were older (63 vs. 53 years of age), and more likely to have hypertension (65% vs. 52%), diabetes (19% vs. 16%), dyslipidemia (35% vs. 31%), heart failure (11% vs. 8.7%), or stroke (6.4% vs. 3.6%), and less likely to be smokers (23% vs. 36%) versus men. There were no significant differences in medications given in the initial 24 h by sex. Although women were as likely as men (89% vs. 87%) to have troponin elevation, they were less likely to undergo early angiography. At discharge, women were more likely to receive calcium antagonists and either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. Similar percentages of women and men died or had reinfarction or stroke. The strongest predictors of nonobstructive CAD were female sex and younger age (70).

From these datasets, it is appropriate to conclude (**Table 2**) that ~10% of NSTE ACS patients have nonobstructive CAD, and death or MI occurred in ~2% of them by 30 days. Sex differences in characteristics

and outcomes were similar to those found with obstructive CAD. Although women with NSTE ACS are about twice as likely to have nonobstructive CAD than men, those with nonobstructive CAD have lower event rates than patients with obstructive CAD. But their death and MI rates are not negligible. Furthermore, ACS patients, like those selected for these analyses (e.g., reaching hospital alive and undergoing early angiography), usually have lower event rates than those seen in the general, all-inclusive ACS population. Women were less likely than men to undergo angiography within 48 h of admission and to receive guideline recommended therapies, despite similar proportions with troponin elevation, suggesting opportunities for improved management. Therefore, the presence of nonobstructive CAD alone does not justify dismissing opportunities for secondary prevention.

TABLE 2 Tabulation of Findings in NSTE ACS Patients With Nonobstructive CAD

- Overall, ~10% of NSTE ACS patients have nonobstructive CAD.
- Sex differences in patient characteristics and outcomes are similar to those with obstructive CAD.
  - Women are twice as likely to have nonobstructive CAD than men.
  - Those with nonobstructive CAD have lower event rates than patients with obstructive CAD.
  - Women are less likely to undergo early angiography and to receive guideline-recommended therapies, suggesting opportunities for improved management.
- Death or MI occurs in ~2% of these patients by 30 days.
- Although death/MI rates are low, they are not negligible. Furthermore, patients such as those selected for analyses (e.g., reaching hospital alive and undergoing early angiography and/or consenting to a randomized trial) are recognized to have lower events rates than those in the all-inclusive ACS population.
- The presence of nonobstructive CAD alone does not justify dismissing opportunities for secondary prevention.

ACS = acute coronary syndrome(s); CAD = coronary artery disease; MI = myocardial infarction; NSTE = non-ST-segment elevation.

Relative to ST-segment elevation myocardial infarction (STEMI), at the time of hospitalization, it is known that women are generally older than men and less frequently have chest pain/discomfort, which, in addition to social factors, contributes to delayed treatment and delayed symptom-to-balloon time versus men (71). Optimal recognition and timely management of STEMI is important, especially reducing delay in seeking care and physician decision making. Although presence of chest pain/discomfort is the hallmark of acute MI, it is important to account for age when considering sex differences in presentation and mortality. Relationships between sex and symptom presentation and hospital mortality, before and after accounting for age, were examined in registry patients (481,581 women and 661,932 men) with MI (71). The proportion presenting without pain in the chest, arm, neck, or jaw was higher for women than men (42.0% vs. 30.7%); this sex-related difference was larger in younger (<45 years) versus older patients.

Among patients hospitalized with MI, women are more likely to present without chest pain, and this is linked with higher mortality versus men of the same age. However, sex differences in clinical presentation without chest pain and in mortality are attenuated with increasing age.

The effect of sex on incidence of acute MI without obstructive CAD was assessed among 95,849 patients undergoing angiography in the Swedish Coronary Angiography and Angioplasty Registry (72). Analyses in 2,268 STEMI and 10,904 non-ST-segment elevation myocardial infarction (NSTEMI) patients without obstructive CAD (<50% stenosis) revealed the presence of nonobstructive CAD in 7% of STEMI (6% men, 10% women) and 17% of NSTEMI patients (11% men, 28% women). During 2.6 years follow-up, 8% of STEMI and 5% of NSTEMI patients died. Sex-associated differences in risk were observed in NSTEMI patients, with HRs for mortality (HR: 0.90; 95% CI: 0.50 to 0.73) and heart failure (HR: 0.61; 95% CI: 0.52 to 0.72) lower in women than in men. Women also had less revascularization. They concluded that nonobstructive CAD was more common in NSTEMI versus STEMI patients, as well as in women versus men. Mortality in patients with nonobstructive CAD was higher after STEMI than NSTEMI. These differences in outcomes support the suggestion that there are important sex-related differences in underlying pathogenesis of MI without obstructive CAD.

There has been controversy concerning the incidence of nonobstructive disease leading to STEMI on the basis of angiograms. However, recent IVUS studies (PROSPECT [Providing Regional Observations to Study Predictors of Events in the Coronary Tree] and VIVA [virtual histology IVUS (VH-IVUS) in Vulnerable Atherosclerosis]) have shown that responsible lesions are usually only mild (on the basis of adjacent reference segment lumens), but severe by IVUS on the basis of large atheroma volume with severe cross-sectional area narrowing (73). Mechanistically, other studies have noted that a greater atheroma burden is linked with a greater burden of lipid and necrotic core, and a thinner fibrous cap, more inflammation, more deranged vaso vasorum, and more abnormal stress-strain relationships (23,27). That nonobstructive lesions can lead to STEMI has also been confirmed after thrombus aspiration (74).

Details on the extent and composition of atherosclerosis contributing to ACS (n = 697, 24% women) were provided in the multicenter PROSPECT study (75). Three-vessel multimodality intracoronary imaging (quantitative coronary angiography,

grayscale, and radiofrequency IVUS) was performed after culprit lesion(s) treatment. Women were older and had more comorbid disease than men. By angiography, women had a similar number of culprit lesions, but fewer nonculprit lesions, and fewer vessels with nonculprit lesions than men. By IVUS, women had fewer nonculprit lesions, but similar plaque burden per lesion, and female sex was not predictive of severe (>70%) plaque burden. Plaque rupture was significantly less frequent among women (6.6% vs. 16.3% in men), even after adjusting for comorbidities, and their total necrotic core volume was also less. Frequencies of pathological intimal thickening, thin-cap fibroatheromas (TCFA), and thick-cap fibroatheromas were similar in women and men. Rates of MACE attributed to culprit and nonculprit lesions during follow-up were not significantly different between women and men, although women were rehospitalized more frequently due to culprit lesion–related angina. For men, nonculprit lesion minimal lumen area ≤4.0 mm^2, plaque burden ≥70%, and TCFA predicted nonculprit MACE at 3 years, but for women, only TCFA and plaque burden were predictive. These data lead to the conclusion that among ACS patients, women have more comorbid risk factors, but less extensive CAD by angiographic and IVUS measures than men. Furthermore, women have less plaque rupture, less necrotic core and calcium, and similar plaque burden, but smaller coronary lumens, and TCFA may be a stronger marker of plaque vulnerability versus men.

A more thorough understanding is needed of the complex interplay among procoagulant, antiplatelet, and fibrinolytic properties of normal and diseased endothelium to provide additional insight into mechanisms and directions for management of ACS associated with sudden coronary thrombosis in the absence of obstructive coronary atherosclerosis.

CARDIAC SUDDEN DEATH. Interestingly, an alternative explanation for the relative lack of severely obstructive CAD among women versus men presenting with ACS could be that women with obstructive CAD are more likely to die before reaching the hospital versus women with nonobstructive CAD.

Overall, women have a lower incidence of cardiac sudden death than men, even when adjusted for predisposing conditions such as coronary heart disease, MI, and heart failure. Additionally, their percentage of cardiac sudden deaths due to obstructive CAD is lower: CAD is found in approximately one-half of women versus 80% to 90% of men (76). But details relative to nonobstructive CAD by angiography are unclear.

Pathological findings have been described in many fatal cases with nonobstructive CAD (64,77-79). The most complete evaluations of sex differences in the extent and severity of coronary and myocardial findings in fatal IHD are from autopsy reports on people aged 21 to 54 years (78,79). According to the medical examiner, obstructive CAD (≥75% cross-sectional area stenosis in an epicardial vessel or ≥50% left main) was significantly less likely among women (63% vs. 77% of men). Yet, pathological evidence of MI was present in almost one-half of the cases, 17% with nonobstructive CAD. The frequency of MI did not vary by sex overall or among those without significant CAD (~23%) versus those with obstructive CAD. Thus, among younger adults determined at autopsy to have died of IHD, fewer women have obstructive CAD, consistent with angiographic data from other IHD syndromes. Furthermore, pathological evidence of MI exists in many without obstructive CAD.

These findings do not support the notion that the relative lack of severely obstructive CAD among women versus men with ACS is related to higher prehospital death risk among women with obstructive CAD. Yet, the mechanisms for these deaths are unknown.

PREDICTORS OF ADVERSE OUTCOMES WITH NONOBSTRUCTIVE CAD: ROLE OF HYPERTENSION, DIABETES, AND RELATED INSULIN-RESISTANT STATES

Predictors of adverse outcomes among individuals with nonobstructive CAD appear similar to those documented among the population with obstructive CAD, with some exceptions. The strong association with LV systolic function observed in those with obstructive CAD is not present, as LV systolic function is usually preserved among those with nonobstructive CAD. Measures of the extent and severity of CAD also appear important in the nonobstructive cohort but, as discussed later, are not well developed. Patient characteristics, including hypertension, diabetes, and smoking, have been identified in the WISE study (23) and other nonobstructive CAD cohorts as important. Because of the high and increasing prevalence of hypertension, diabetes, and metabolic syndrome among women, and the known associations with microvascular disease, these areas will be addressed in more detail.

In the large prospective CONFIRM registry, hypertension was present in the majority with nonobstructive, as well as obstructive, CAD (14). Furthermore, hypertension (HR: 1.93), diabetes (HR:

2.13), and smoking (HR: 1.47) were all significantly associated with increased risk. The multivariable adjusted risk for all-cause mortality, stratified by sex, found nonobstructive CAD was associated with a 67% excess risk among women with versus without CAD. These findings are consistent with hypertension being the major risk factor for atherosclerosis that underlies most nonobstructive and obstructive CAD. Hypertensive postmenopausal women have abnormal endothelium-dependent vascular function, and hypertension is a known cause of microvascular complications in the heart, brain, eye, and kidney. Antihypertensive treatment improves endothelial and other microvascular functions, which identifies patients who possibly have a more favorable prognosis (80). Effective control of hypertension in women is proven to decrease CVD risks, but it is unclear if the benefit is the same among women with nonobstructive CAD versus obstructive CAD.

Elevated glucose (type 2 diabetes and pre-diabetes) is highly prevalent among women and is associated with insulin resistance. Insulin resistance is strongly linked with both microvascular and macrovascular disorders, resulting in organ and tissue damage. Numerous studies document that these disorders convey higher risk for CVD morbidity and mortality in women versus men (81–83). Even women with type 1 diabetes have 40% excess risk of fatal and nonfatal CVD events versus men with type 1 diabetes (84). Accordingly, nonobstructive CAD is more prevalent among those with diabetes versus those without, and coronary microvascular abnormalities are highly prevalent and progress with worsening glucose intolerance. Vascular damage associated with insulin resistance has long been recognized (85–90).

Coronary endothelial dysfunction occurs with hypertension and diabetes, and is associated with increased risk for CVD events. Stress myocardial blood flow by PET has characterized CMD in various states of insulin resistance. Compared with insulin-sensitive individuals, endothelium-dependent coronary dilation is progressively diminished in insulin-resistant (−56%), impaired glucose-tolerant (−85%), and normotensive (−91%), as well as hypertensive diabetic subjects (−120%). Thus, progressive worsening of CMD occurs with increasing severity of insulin resistance and carbohydrate intolerance.

These observations are important because CMD is an independent predictor for mortality among patients with diabetes, providing incremental risk stratification (91). Patients with diabetes and normal coronary flow reserve have low annual CVD mortality, similar to patients without diabetes or obstructive CAD who had normal myocardial perfusion with stress. But patients with diabetes and impaired coronary flow reserve have CVD mortality similar to that of patients with obstructive CAD, but no diabetes.

Early detection of CMD among women without obstructive CAD and insulin resistance is particularly important given their increased prevalence of hypertension and the worsening worldwide epidemic of diabetes. In addition, CMD in hypertension and diabetes can be normalized with blood pressure control and insulin, as well as with many insulin-sparing drugs.

PROPOSED MECHANISTIC CLASSIFICATION OF IHD SYNDROMES WITH NONOBSTRUCTIVE CAD

In addition to CMD, many other potential etiologies exist beyond the traditional “flow-limiting stenosis” (**Table 1**). Each of these mechanisms may operate alone, but they more frequently operate in concert (19). Nevertheless, the specific mechanisms operating in any given patient are likely to remain elusive unless the diagnostic approach moves beyond the coronary angiogram currently done as usual care for evaluation of IHD. Several reports, including one limited to women (36), document that the additional testing required can safely be conducted in experienced hands.

KNOWLEDGE GAPS

Although the need for cardiovascular research focusing on women has recently been emphasized by the American College of Cardiology, American Heart Association, European Society of Cardiology, and other organizations, none have specifically addressed the issue of IHD with nonobstructive CAD. Clearly, there are many important gaps in our existing knowledge. Information about the following is essential:

1. Identify specific mechanism(s). Whether the underlying pathophysiology of IHD without documentation of obstructive CAD is different in women and men, or is different from those with obstructive CAD, requires further investigation. The current focus is on nonobstructive CAD associated with limitations in flow reserve at the coronary microvascular level or CMD. However, evolving data suggest that CMD also occurs among patients with obstructive CAD and carries a particularly poor prognosis (92). Does CMD contribute to the development or characteristics of upstream plaque in large coronary arteries? If so, does this contribute to plaque vulnerability to erosion or

rupture? Is microvascular flow limited due to microvascular spasm (93)? If so, is this spasm due to endothelial dysfunction (e.g., loss of nitrous oxide [insufficient production/excessive inactivation or both]), intrinsic heightened vascular smooth muscle activation state, sympathetic nervous system activation, platelet microaggregates with direct plugging or release of vasoactive substances, and so on? What about the complex interplay among white blood cells and the procoagulant, antiplatelet, and fibrinolytic properties of a diseased coronary endothelium? Many other possibilities exist (see **Table 1**) alone or in combination. Finally, why does CMD seem to be more prevalent in women?

2. Define optimal diagnostic approaches. It is unclear how to best identify nonobstructive CAD. Additional information on its clinical predictors is needed. The incidence of nonobstructive CAD in women with complications of pregnancy could be important. The need for lower radiation doses is obvious, and the effective dose with CTA overall is ≈10 mSv, but is <2 to 5 mSv with current dose-reduction techniques (94). Data comparing different imaging modalities for identification of nonobstructive plaque and ischemia in patients with nonobstructive CAD are lacking. This is clearly an important knowledge gap for future study. Most of the evidence for nonobstructive CAD with CMD as a mechanism for ischemia was obtained using directly measured coronary flow, either by catheter (Doppler flow or thermal dilution to calculate microvascular resistance) or PET. Although the latter provides flow/g of LV muscle, both methods are costly, have radiation and other hazards, and are not applicable to large studies, particularly where repeated measurements are needed. The WISE study has advanced adenosine-stimulated gadolinium perfusion cMRI, which can be quantified using available techniques, has no radiation hazard, and can be repeated. The challenge is its lack of widespread availability.

   Biomarkers, such as circulating endothelial and bone marrow–derived cells and ischemia metabolites, are under current evaluation. The study of noncoronary microvascular beds thus far appears to have limited applicability to the coronary circulation, although the retina holds promise.

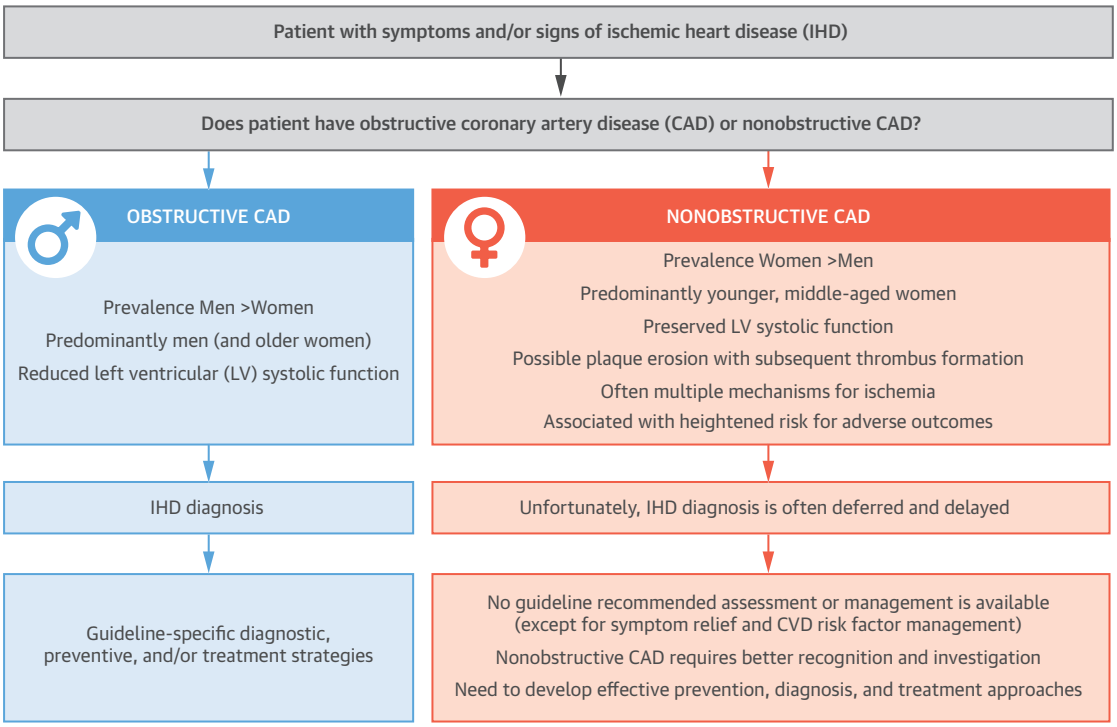
   It should also be noted that the previously mentioned studies all required either selective coronary angiography or CTA as an imaging method to exclude obstructive CAD and quantify functional changes of the large coronary vessels. To this end, new functional imaging modalities that do not require radiation are clearly needed.

3. Discover novel treatment strategies and their follow-up. Most treatment strategies and current IHD guidelines center on identification of high risk, which is code for finding flow-limiting stenosis, identifying candidates for revascularization, and then deciding the most appropriate revascularization strategy among percutaneous and surgical approaches. This is followed by lifetime modification of lifestyle and medical management directed at prevention of atherosclerosis progression. It would be truly useful to discover novel treatment strategies for women that do not begin with finding flow-limiting stenosis, searching for candidates for revascularization, and end with lifetime medical treatments and repeated hospitalizations and/or costly testing. Also important is the need to follow atherosclerosis progression in patients treated for nonobstructive disease. To this end, evolving lower-dose CTA and cMRI techniques may offer promise, but this is an important knowledge gap.

CLINICAL TRIALS TO PROVIDE EVIDENCE-BASED GUIDELINE DEVELOPMENT

Prior, short-term, single-agent studies of symptomatic subjects with ischemia and nonobstructive CAD testing antiatherosclerotic and/or anti-ischemic therapies suggest benefit in patients with nonobstructive CAD. Briefly, statins and ACE inhibitors counteract oxidative stress and improve endothelial function (95,96), and CMD (97) may benefit (96,98). Beneficial effects of statins on CMD are also documented (99), and many trials in patients with obstructive CAD show prevention of atherosclerosis progression in nonobstructed segments. Drug combinations (e.g., statins with ACE inhibitors) may potentially amplify benefits (96). Calcium antagonists fail to ameliorate CMD in these patients (100), but may prevent spasm. Conversely, beta-blockers appear effective for management of angina (101), and superior to calcium antagonists (101,102). Few controlled studies have been done with nitrates. Exercise training beneficially modulates adrenergic and nitric oxide pathways (103). Imipramine improves angina, possibly through visceral analgesic, anticholinergic, and alpha-antagonist effects (104). L-Arginine improved angina and vascular function (105), but was adverse in an obstructive CAD trial (106). Post-menopausal hormone therapy improved emotional well-being, but had no effect on angina or exercise tolerance (107). Several studies reported symptom and ischemia

CENTRAL ILLUSTRATION **Nonobstructive CAD in Women: Sex-Specific CAD and Need for Ischemic Cardiac Disease Definition Changes**



Pepine, C.J. et al. J Am Coll Cardiol. 2015; 66(17):1918–33.

Among patients presenting with symptoms/signs suspect for IHD, the presence of obstructive CAD (e.g., identifying a flow-limiting lesion, FFR <0.80) is highly prevalent in men (and older women), and often associated with reduced LV systolic function. Diagnosis and risk stratification are prompt because guideline-specific diagnostic, preventive, and/or treatment strategies are available. By contrast, nonobstructive CAD (e.g., FFR ≥80) is highly prevalent among women (mostly younger and middle-aged women) with preserved LV systolic function. Additionally, pharmacological testing with acetylcholine and adenosine distinguishes those with macrovascular or microvascular spasm, endothelial dysfunction, and/or coronary microvascular dysfunction (CMD). These latter findings are associated with increased risk of adverse outcomes that include heart failure with preserved systolic function, acute coronary syndromes, and cardiovascular-related hospitalizations, as well as repeated testing. Unfortunately, no guideline-recommended assessment or management is available, except for symptom relief and CVD risk factor management. CAD = coronary artery disease; CVD = cardiovascular disease; FFR = fractional flow reserve; IHD = ischemic heart disease; LV = left ventricular.

improvement with less coronary vascular dysfunction (97,108). However, appropriately powered outcome trials testing various strategies have not been performed in such patients. Existing guidelines focus on reassurance and symptom management (109,110). This is inappropriate because of the elevated MACE rate (1,18,22,23,25,26), symptom recurrence, and health resource consumption comparable to that of obstructive CAD (60). Pragmatic trials testing real-world strategies of antiatherosclerotic and anti-ischemic therapies are needed to advise guidelines for this growing population with nonobstructive CAD.

Even without definitive information about mechanisms, it may be possible to use the limited information currently available to test new strategies to improve outcomes. To accelerate development of new diagnostic and therapeutic regimens, an integrated approach to phase II and III clinical trials that incorporates multiple efficacy variables, including angiography, biomarkers of microvascular dysfunction, and other factors should be considered.

SUMMARY AND CONCLUSIONS

Nonobstructive CAD is relatively common in women in acute or chronic coronary syndromes (**Central Illustration**). Reassurance of an excellent prognosis is inappropriate among symptomatic patients with no or minimal epicardial coronary artery obstruction (>0%, but <50%, stenosis). Suboptimal clinical outcomes of

patients with symptoms and/or signs of ischemia and nonobstructive CAD must be better understood so that a near-normal or "normal" angiogram does not drive diagnostic and therapeutic complacency (30,92). Importantly, given their impaired prognosis, a search for cause(s) of ischemia must be much more comprehensive than simply a diagnostic angiogram. Additional testing must be considered to attempt to identify some of the processes reviewed earlier (endothelial and/or microvascular dysfunction, coronary spasm, angiographically nonevident plaques causing diffuse narrowing, and so on) followed by additional research to fully understand the pathophysiology, treatments, and outcomes for this condition.

This information should foster: 1) development of more precise tools to better risk stratify patients with nonobstructive CAD; 2) prospective trials to assess benefits of intensive medical therapy directed at ischemia and atherosclerosis progression in these patients; and 3) discovery of novel management strategies for these patients, most of whom are women. In the future, if we aim at preventing these events, the paradigm of risk stratification for prevention must move from identification of obstructive atherosclerosis to an earlier stage that includes nonobstructive coronary disease.

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