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# Noninvasive Imaging to Evaluate Women With Stable Ischemic Heart Disease

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## JACC: CARDIOVASCULAR IMAGING CME

**CME Editor:** Ragavendra R. Baliga, MD

This article has been selected as this issue's CME activity, available online at http://www.acc.org/jacc-journals-cme by selecting the CME tab on the top navigation bar.

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**CME Objective for This Article:** After reading this article the reader should be able to provide an updated review on advances in noninvasive stress imaging and noninvasive coronary angiography in the evaluation of women presenting with stable, suspected ischemic heart disease.

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# Noninvasive Imaging to Evaluate Women With Stable Ischemic Heart Disease

## ABSTRACT

Declines in cardiovascular deaths have been dramatic for men but occur significantly less in women. Among patients with symptomatic ischemic heart disease (IHD), women experience relatively worse outcomes compared with their male counterparts. Evidence to date has failed to adequately explore unique female imaging targets and their correlative signs and symptoms of IHD as major determinants of IHD risk. We highlight sex-specific anatomic and functional differences in contemporary imaging and introduce imaging approaches that leverage refined targets that may improve IHD risk prediction and identify potential therapeutic strategies for symptomatic women. (J Am Coll Cardiol Img 2016;9:421–35) © 2016 by the American College of Cardiology Foundation.

For more than 2 decades, population case fatality rates for cardiovascular (CV) disease have been higher for women compared with men [1]. Recent declines in CV deaths in men have been dramatic; yet declines are significantly less for women than men [2,3]. The term ischemic heart disease (IHD) now broadly includes higher risk status associated with symptomatic patients with obstructive and nonobstructive coronary artery disease (CAD), including coronary microvascular disease (CMD) [4]. Among patients with IHD, women experience relatively worse outcomes ranging from stable angina to acute coronary syndromes (ACS) and heart failure compared with men [5-8]. Determining sex-specific causality has been elusive because series often include only women [9], are invasive coronary angiographic series [6,10], or include cohorts of women with attempted case-matching to men, thus limiting identification of a unique female risk profile [11]. For example, the National Institutes of Health National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) included only symptomatic women undergoing a variety of ischemia and other physiological testing without

comparative assessments of male patients [9]. The ensuing selection and other biases represent sizable challenges to uncover sex-specific findings that may explain the higher risk status of women with IHD compared with men. Evidence to date fails to explore unique female imaging targets and their correlative signs and symptoms of IHD as major determinants of IHD risk. This paper highlights sex-specific anatomic and functional differences across imaging targets and introduces contemporary imaging approaches that leverage refined targets that may improve IHD risk prediction and identify potential therapeutic strategies for symptomatic women.

## LIMITATIONS OF DEMAND ISCHEMIA TESTING IN WOMEN

Traditional diagnostic approaches for the assessment of risk associated with IHD are derived from the notion that identification of the consequences of flow-limiting stenosis(es) in major epicardial coronary arteries represents the major mechanism for ischemia. Accordingly, this concept is extended to clinical practice guidelines and appropriate use

criteria (12,13). Furthermore, these approaches depend on a patient's ability to exercise and an accurate assessment pre-test probability of obstructive CAD to guide test selection. Most integrated risk scores poorly categorize women as to their pre-test CAD likelihood, with variable point values assigned to risk factors resulting in an over- or underestimation of CV risk (14). Moreover, women commonly present with more atypical, less exertional symptoms, which confound candidate selection and accurate assessment of pre-test risk. Importantly, a sizable proportion of women are unable to exercise maximally (those with prevalent obesity, diabetes, and orthopedic limitations), which may contribute to the lower reported sensitivity of the stress electrocardiogram (29 studies, 62% sensitivity) than stress imaging tests such as stress echocardiography (14 studies, 79% sensitivity) and single-photon emission computed tomography (SPECT) (14 studies, 81% sensitivity) from a recent meta-analysis (15). In addition to a reduced diagnostic accuracy of the exercise electrocardiogram alone for epicardial CAD, equivocal results are frequent and lead to physician uncertainty and contribute to further, perhaps unnecessary, testing of women (16).

Moreover, the traditional diagnostic goal for symptomatic women and men in whom IHD is suspected has been the detection of obstructive CAD requiring revascularization. It is now clear that this search for a functionally limiting obstructive stenosis is at a mismatch with the much greater prevalence of nonobstructive CAD in women versus men (17). For many years, this has led to the misperception of a high rate of "false-positive" (i.e., abnormal stress test results with nonobstructive CAD) findings for women. According to a recent systematic review, the range of abnormal test findings in the setting of nonobstructive CAD is 16% to 32% for stress testing using electrocardiography, nuclear, echocardiography, and cardiac magnetic resonance (CMR) (18). Conventional stress imaging also has technical artifact issues related to breast tissue, obesity, and lung disease with poor exercise capacity, further contributing to reduced test accuracy (4). For women, the misperception of a high "false-positive" rate may prompt greater uncertainty and inaction on the part of the treating physician. Documented ischemia on stress testing for women is rarely followed by intensification or alterations in anti-ischemic therapies or referral to coronary angiography (19). Compared with men, women consistently receive less intensive care, including fewer antianginal medications, less frequent coronary angiography or revascularization, and fewer lifestyle or risk factor-modifying
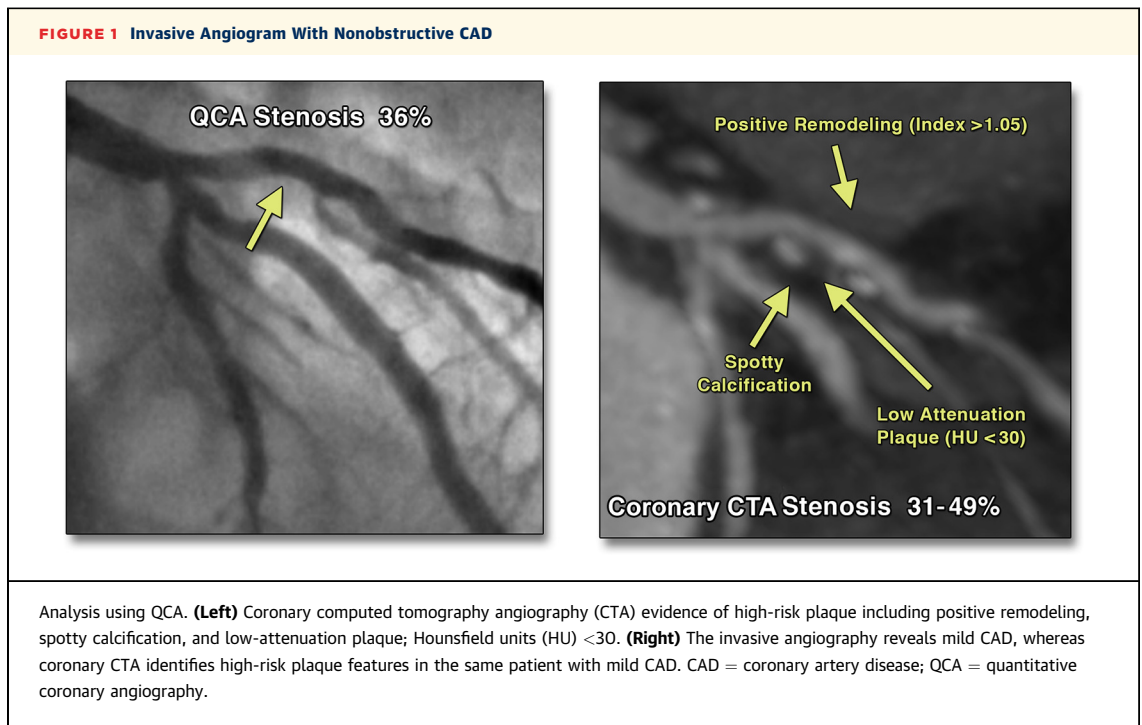
treatments (20-23). Even when accounting for sex differences in risk factor prevalence, smaller body size, higher bleeding risk, and other factors, women have decidedly worse outcomes after coronary revascularization, particularly in the near term. The lack of symptom-driven care for women with demonstrable ischemia is a contributor to their worsening IHD outcomes. In addition, at 1 year after the index evaluation, nearly 40% of symptomatic women have persistent or worsening symptoms (24). The extent to which our diagnostic evaluation is not tailored to women may be at the core of suboptimal care. However, there also likely remains an unexplained residual gap in knowledge with regard to treatment effectiveness and strategies of care optimized for women with IHD. Additional imaging markers not in use in our contemporary diagnostic evaluation may hold promise to improve identification of high-risk women.

## SEX-SPECIFIC ATHEROSCLEROTIC PLAQUE VULNERABILITY

Decades of data demonstrate that the culprit ACS lesion often occurs in a previously documented nonobstructive stenosis, revealing that there is much to learn regarding ischemia and atherosclerotic plaque as contributors to symptoms and future IHD risk (25). Coronary thrombosis is the most common precursor of ACS (26,27), and evidence supports unique sex-specific mechanisms of ACS, including differences in plaque rupture, erosion, and calcified nodules (26,28,29). Plaque rupture is more common in men with culprit lesions exhibiting atherosclerotic plaque features including thin-cap fibroatheroma (thin fibrous caps with a large thrombogenic lipid-rich necrotic core), positive remodeling, and a high plaque burden (27,28,30-32). More unique to women is the plaque erosion as a precursor of ACS (33-36), which has been variably associated with more fibrous plaque (p < 0.001), less thin-cap fibroatheroma (p < 0.001), a lower plaque burden (p = 0.003), and a reduced remodeling index (p = 0.003) (26,33-37). These data support a sex-specific etiology for ACS, underscoring the importance of varying plaque features unique to women compared with men. Results identifying unique atherosclerotic plaque features as precursors of worsening or unstable symptoms have direct applicability to the pool of female candidates undergoing evaluation for suspected IHD. Importantly, atherosclerotic plaque features

**FIGURE 1   Invasive Angiogram With Nonobstructive CAD**



Analysis using QCA. **(Left)** Coronary computed tomography angiography (CTA) evidence of high-risk plaque including positive remodeling, spotty calcification, and low-attenuation plaque; Hounsfield units (HU) <30. **(Right)** The invasive angiography reveals mild CAD, whereas coronary CTA identifies high-risk plaque features in the same patient with mild CAD. CAD = coronary artery disease; QCA = quantitative coronary angiography.

associated with ACS are also reported in ~50% of stable IHD patients (38,39). The extent to which other imaging markers may be female specific and whether the totality of risk is uniquely defined in women are unknown.

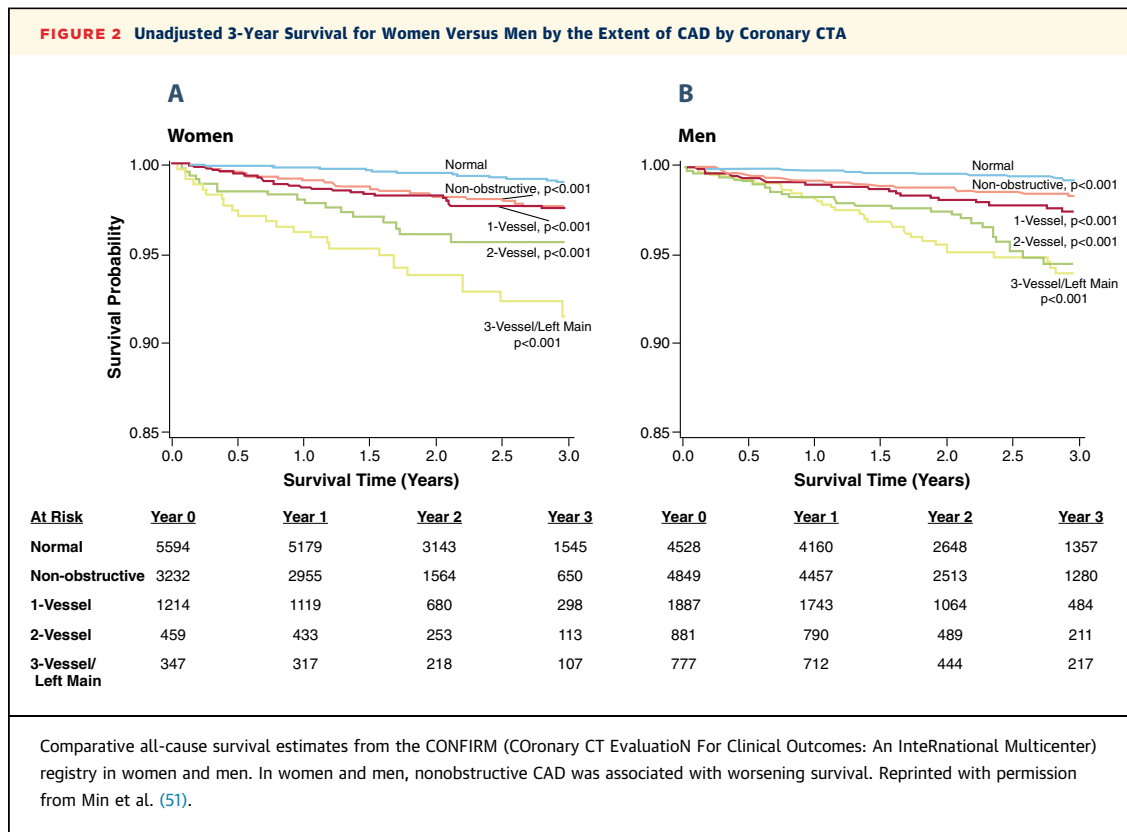## ADVANCED IMAGING APPROACHES TO UNIQUELY IDENTIFY RISK IN WOMEN

A plethora of novel technology was introduced in the past decade that may improve IHD risk assignment in women. These approaches are reviewed as anatomic visualization of atherosclerotic plaque and the extent and severity of obstructive CAD and provocative imaging to demonstrate myocardial ischemia. Ancillary markers as well as combined anatomic with functional parameters imaged sequentially or using hybrid technology are also discussed.

## ANATOMIC IMAGING TO DETECT IHD RISK IN WOMEN

**X-RAY ANGIOGRAPHY.** Invasive coronary angiography has been the traditional endpoint of a diagnostic evaluation for IHD patients. Nonobstructive CAD (i.e., <50% stenosis) is more common in symptomatic women than men (4,17,40). From the American College of Cardiology CathPCI Registry (N = 375,886 [~50% women] from >600 hospitals), nearly one-half of black, Hispanic, Native American, Asian, and white women with stable IHD had nonobstructive CAD (6).

A recent statement from the American College of Cardiology CV Disease in Women Committee focused on redefining the term nonobstructive CAD to incorporate the burden of atherosclerotic plaque and vascular dysfunction, which is increasingly cited as contributory to symptom provocation in women (17).

Our current strategy for women and men with demonstrated ischemia has been to obtain a follow-up invasive angiogram. Yet the high rate of nonobstructive CAD on invasive angiography coupled with infrequent clinical measurement of atherosclerotic plaque provides an opportunity for alternative noninvasive approaches that may be more efficient and effective. Invasive coronary angiography yields greater inefficiency as it is reimbursed at a rate substantially higher than coronary computed tomography angiography (CTA) or magnetic resonance angiography (MRA) and is ineffective because there is a low diagnostic yield with invasive angiography (41) (frequent documentation of <50% stenosis) and a 3% to 4% procedural complication rate (e.g., vascular bleed, heart failure, ACS, or death) (6). Given the low diagnostic yield of current approaches leading to invasive angiography (41) and the limitations of lumenography, particularly for women, the concept of noninvasive angiography examining beyond coronary stenosis to include prevalent atherosclerotic plaque features (38,39,42,43) is worthy of exploration. Coronary CTA and MRA may detail atherosclerotic plaque extent and severity more easily than routine x-ray

**FIGURE 2**  Unadjusted 3-Year Survival for Women Versus Men by the Extent of CAD by Coronary CTA



| At Risk | Year 0 | Year 1 | Year 2 | Year 3 | Year 0 | Year 1 | Year 2 | Year 3 |
|---|---|---|---|---|---|---|---|---|
| Normal | 5594 | 5179 | 3143 | 1545 | 4528 | 4160 | 2648 | 1357 |
| Non-obstructive | 3232 | 2955 | 1564 | 650 | 4849 | 4457 | 2513 | 1280 |
| 1-Vessel | 1214 | 1119 | 680 | 298 | 1887 | 1743 | 1064 | 484 |
| 2-Vessel | 459 | 433 | 253 | 113 | 881 | 790 | 489 | 211 |
| 3-Vessel/ Left Main | 347 | 317 | 218 | 107 | 777 | 712 | 444 | 217 |

Comparative all-cause survival estimates from the CONFIRM (COronary CT EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry in women and men. In women and men, nonobstructive CAD was associated with worsening survival. Reprinted with permission from Min et al. (51).

angiography (**Figure 1**), an important advantage when recognizing the distinct vascular biology of CAD in women.

**CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY.** Coronary CTA has emerged as a noninvasive option for coronary angiography and atherosclerotic plaque characterization (30,44) including a host of features from luminal narrowing and plaque location, burden, remodeling, and composition. Contemporary coronary CTA technology has improved spatial and temporal resolution and volume coverage, allowing for acquisition of motion-free images of the heart. Coronary CTA has demonstrated excellent accuracy for the detection of obstructive CAD (45-47) and coronary plaque compared with intravascular ultrasound with sensitivity and specificity measures ≥90 (44,48-50).

There is now well-established evidence of the proportional increase in major adverse event risk by the number of arteries with obstructive CAD seen on coronary CTA (51,52), consistent with invasive data (53). From a large series (N = 23,854), coronary CTA nonobstructive CAD was associated with an elevated mortality risk (**Figure 2**) (51). In several large registries, the number of vessels with nonobstructive plaque had a 2- to 6-fold elevated risk of death (52,54-56). Thus, there is also a graded increase in risk based on the number of vessels or segments with identifiable nonobstructive plaque observed with coronary CTA or invasive coronary angiography (57,58). Among patients with evidence of calcified plaque, major adverse events were reported more often in those with co-occurring noncalcified plaque (59,60). Moreover, in 1,102 patients with nonobstructive CAD, the 6-year death rate was 1.4% for calcified plaque, 3.3% for mixed plaque, and 9.6% for noncalcified plaque (p < 0.0001) (61). Similar to invasive series, women have less obstructive CAD seen on coronary CTA (6,14,62,63) but have a higher mortality risk with multivessel CAD (51). Data are available with regard to sex differences in atherosclerotic plaque (11,51,63,64), with most using visual (nonquantitative) plaque assessment (11,51,64). The number of nonobstructive plaques predicted death in women (p = 0.003), even when adjusting for obstructive CAD, findings not replicated in men (65). From the CONFIRM (COronary CT EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry, nonobstructive CAD was associated with an approximately 2-fold increased major adverse event risk in women (11). As well, 5-year outcomes were

higher for women than men with 2 to 3 vessels with plaque (51). Coronary artery calcium (CAC) scoring was also recently evaluated in a subset of symptomatic CONFIRM patients with nonobstructive CAD (64). The vast majority (86%) of patients with no luminal stenosis (i.e., 0%) had a CAC score <10. By comparison, among patients with a stenosis >0% but <50%, mortality increased in proportion with the CAC score, ranging from 0.8% to 9.8% for CAC scores of 0 to ≥400 (p < 0.0001). The CAC score in this symptomatic patient subset of 2,820 was independently predictive of all-cause mortality (p < 0.0001) and death or myocardial infarction (MI) (p < 0.0001), even in models controlling for CAD risk factors and presenting symptoms. These pioneering coronary CTA investigations added to intravascular ultrasound data (66-68) by examining patients with no previous CAD and identifying atherosclerotic plaque from coronary CTA akin to that defined invasively. This evidence supports a largely unmeasured plaque burden and a lack of detail on sex-specific patterns of atherosclerosis. However, it is unknown whether high-risk atherosclerotic plaque features (e.g., low-attenuation plaque, noncalcified plaque, arterial remodeling) are uniquely different in women compared with men.

**MAGNETIC RESONANCE ANGIOGRAPHY.** Contemporary MRA techniques for atherosclerotic imaging have advanced considerably (69). In addition to anatomic imaging, Hays et al. (70) optimized phase contrast magnetic resonance (MR)–based coronary artery flow measurement coupled with simple hand grip exercise to demonstrate abnormal coronary endothelial function compared with control subjects in a majority female cohort with nonobstructive CAD. Remarkably little has been published to date on advanced MRA-based plaque characterization to analyze sex differences in CAD, highlighting opportunities to fill important knowledge gaps (71).

**ADVANCES IN STRESS IMAGING FOR WOMEN.** Evidence is robust regarding the role of inducible perfusion or wall motion abnormalities, impaired flow reserve, and other imaging markers as predictive of major adverse event risk, with more limited evidence of unique risk estimates among women (7,40,72,73). In this section, we highlight recent advances in imaging, including echocardiography, CMR, SPECT, and positron emission tomography (PET) that have incorporated a multiparametric approach to uniquely identify women at elevated IHD risk.

**ECHOCARDIOGRAPHY.** In women presenting acutely with chest pain, in the absence of diagnostic electrocardiographic or biomarker evidence of ischemia,

echocardiography remains a valuable and readily available bedside test, facilitated by progressive miniaturization (74). In addition to ruling out wall motion abnormalities, echocardiography is valuable for screening for disease entities including hypertensive, hypertrophic, and Takotsubo cardiomyopathies. The use of myocardial contrast echocardiography may help to facilitate recognition of the latter, reflecting the contribution of microvascular disease (75).

Most of the work on sex-specific benefits of echocardiography has focused on the ability of stress echocardiography to recognize anatomically defined coronary disease with a higher sensitivity and specificity than nonimaging tests (15). Although the use of myocardial perfusion stress echocardiography increases the accuracy of this test, event rates (driven by revascularization) were significantly higher in men after an abnormal real time myocardial contrast echocardiography (men, 35%; women, 16%, p = 0.02) (76). In a small series, Doppler-derived measures of impaired coronary flow velocity reserve (77) have been shown to be prognostically significant, although not specifically studied in women (78). In 1 report of 369 octogenarians (58% women), the all-cause mortality rates were 9.8% and 3.7% among patients with a coronary flow velocity reserve ≤1.93 and >1.93 (p = 0.001) (79).

Exercise echocardiography as an initial screening test can also be particularly beneficial for the recognition of noncoronary heart disease. The assessment of diastolic dysfunction and especially the recognition of a likely abnormal filling pressure response to exercise may explain nonspecific symptoms, including dyspnea, which may be attributable to coronary as well as noncoronary heart disease (80). The detection of abnormal myocardial mechanics (assessed using tissue Doppler imaging and speckle-tracking echocardiography) may facilitate the recognition of myocardial dysfunction as an explanation of exercise intolerance (81). The extent to which this finding may be due to CMD in women remains undefined.

**CARDIAC MAGNETIC RESONANCE.** Due to high spatial resolution, a lack of limitation by body habitus and windows, a lack of ionizing radiation, and high diagnostic accuracy, stress MR is well suited to evaluate suspected IHD in women.

Dobutamine CMR remains a useful test for ischemia (82,83), with particular utility for women with poor acoustic windows (84). Increasing availability of rapid high-resolution techniques has made vasodilator perfusion imaging the first-line stress CMR modality. In the CMR and SPECT for diagnosis of

coronary heart disease (CE-MARC [Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease]) single center trial (n = 752) (85), CMR demonstrated accuracy superior to that of SPECT. From a predefined secondary analysis of CE-MARC, the CMR examination, which included as MRA, function, perfusion, and scar imaging, had high sensitivity for CAD detection in both women and men (89% vs. 86%, p = 0.57), with similar specificity measurements (>80%) (86). However, the sensitivity of SPECT was significantly lower in women than men in this study (51% vs. 71%, p = 0.007). The higher diagnostic performance of stress CMR compared with SPECT (area under the curve, 0.76 ± 0.04 vs. 0.63 ± 0.05; p = 0.033) was also demonstrated by the MR-IMPACT II (A Study of Gadodiamide Injection in Myocardial Perfusion Magnetic Resonance Imaging) study (87). Specifically in women, stress perfusion CMR has a high accuracy (87%, n = 147) (88) and prognostic value (hazard ratio: ∼50, n = 168) (89).

Advanced techniques to evaluate perfusion and metabolism appear promising. Semiquantitative evaluation can generate a myocardial perfusion reserve index whose lower value in 118 symptomatic women and 21 reference subjects from the WISE (Women's Ischemia Syndrome Evaluation) project predicted ≥1 abnormal invasive coronary reactivity testing variable (90). Abnormal myocardial flow reserve on vasodilator stress CMR in symptomatic women may indicate CMD (91). Dark rim artifact can be problematic when distinguishing from true perfusion defects in microvascular disease, which may be subendocardial. Advances in perfusion imaging may eliminate this artifact (92); until there is widespread clinical availability of such techniques, one must follow interpretive guidelines that emphasize transmurality and persistence of the perfusion defect beyond the initial frames of the first-pass acquisition to distinguish true-positive from false-positive results (93).
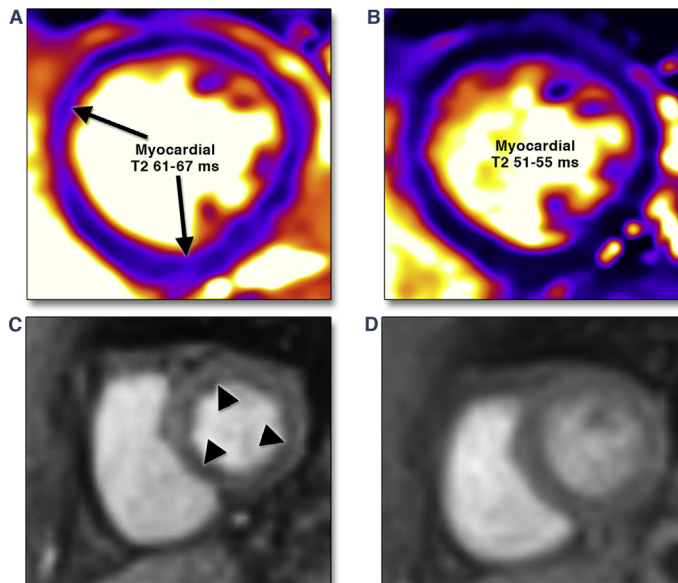
Mordini et al. (94) showed that fully quantitative assessment of stress perfusion MR images outperforms both semiquantitative and qualitative methods of interpretation for identification of obstructive CAD in a cohort of patients (n = 67, 33% women) referred for coronary angiography, with an endocardial-to-epicardial ratio <0.50, identifying segments with abnormal perfusion. This may be due to the ability of fully quantitative perfusion to increase linearly over a range of flow rates, enabling this method to yield even better diagnostic accuracy (95). The increase in signal-to-noise ratios and higher spatial resolution with higher field strength 3-T scanners may further increase the sensitivity of stress MR perfusion testing (96).

Blood oxygenation level–dependent (BOLD) imaging can be used to assess regional myocardial oxygenation as an assessment of microvascular dysfunction and ischemia by measuring paramagnetic deoxyhemoglobin, as reflected in the difference in signal intensity of the myocardium at rest and stress when imaged with this sequence. A study of 22 patients with obstructive CAD (≥50% stenosis on quantitative coronary angiography) showed cutoff values of stress myocardial blood flow (MBF) of <2.45 ml/min/g and a BOLD signal intensity change of <3.74% to correlate with ischemic segments on 3-T imaging. There was good correlation of ischemia using BOLD CMR and $^{15}$O-water PET (97). Many BOLD-CMR studies have limited sample sizes and lack invasive coronary reactivity testing data (98).

Exercise CMR is on the horizon as a promising modality for women who can perform exercise stress testing. A recent study evaluated 115 subjects (38% women) with treadmill exercise stress CMR and found that the presence of inducible regional wall motion abnormalities identified those at risk of future IHD events (99).

CMR spectroscopy uses MR signals from nuclei, such as phosphorus-31, to provide insights into metabolic activity. In women with chest pain and no epicardial CAD, a subgroup of subjects demonstrated an abnormal decrease in myocardial phosphocreatine-to-adenosine triphosphate ratios with hand-grip exercise, similar to that seen in those with obstructive CAD (100). At 3 years of follow-up, abnormal hand-grip testing on phosphorus-31 MR spectroscopy stress testing was predictive of increased IHD events, the majority of which were chest pain hospitalization (101). Further technological advances may enable cardiac MR spectroscopy to further elucidate metabolic dyscrasias in women with suspected IHD, affording targeted therapy.

Late gadolinium enhancement imaging is routinely included as part of the CMR examination, adding powerful diagnostic and prognostic value. In a cohort of subjects (50% women) with a low prevalence of CAD, unrecognized subendocardial or transmural MI on late gadolinium enhancement CMR was detected in 20% of subjects (102). More women had unrecognized MI (45%) compared with recognized MI (18%). In a prospective study of suspected IHD patients (34% women), CMR-detected unrecognized MI was an independent predictor of CAD mortality with a hazard ratio of 17.4 (103). Importantly, older individuals (52% women) with unrecognized MI by CMR were *less* likely to use anti-ischemic or risk factor–modifying therapies compared with those with recognized MIs (104). Underdetected MIs with undertreatment and

**FIGURE 3**  Myocardial Inflammation and Impaired Myocardial Perfusion Reserve by CMR

A 37-year-old female was admitted with visual changes. Serologic testing and neuro-imaging yielded a diagnosis of lupus cerebritis. Significant resting tachycardia (heart rate 120 to 130 beats/min) raised concern of lupus myocarditis, confirmed by CMR examination that showed significantly elevated myocardial T2 values **(A)**. Immunomodulatory therapy was initiated, with both improvement visual symptoms and normalization of heart rate. She returned to the hospital approximately 5 months later with chest pain and lack of inflammatory markers with a resting heart rate of 75 beats/min. ECG and serial troponin-I measurements were negative for myocardial injury. CMR showed normalized T2 values **(B)**; vasodilator stress adenosine infusion produced severe chest pain, and concomitant first-pass perfusion imaging showed diffuse subendocardial hypoperfusion **(C)**. Minimal residual chest pain was present upon termination of adenosine, with near-complete normalization of perfusion **(D)**. Chest pain attributed to impaired myocardial perfusion reserve has reduced with angiotensin converting enzyme inhibitor therapy.

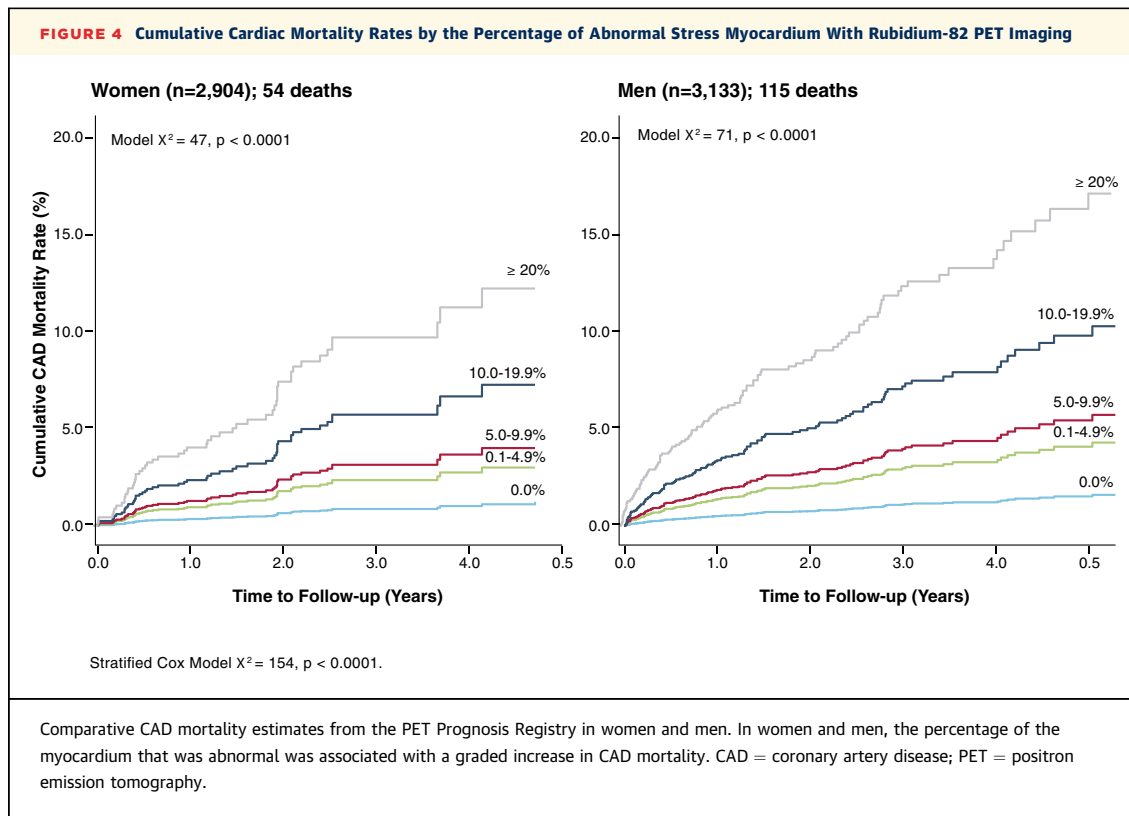intervention highlight opportunities to improve worse IHD outcomes in female patients.

Advances in CMR-based parametric mapping are rapidly being translated to assess ischemic or at-risk myocardium (105). Myocardial edema and inflammation can be targeted with quantitative T2 mapping (**Figure 3**) (106) to delineate ischemic and injured myocardium more reliably, overcoming the limitations of traditional T2-weighted imaging (107). T1 mapping has also been proposed as a useful technique to image myocardium at risk (108), with recent reports raising the intriguing possibility of non-contrast stress CMR with native T1 alone (109).

**STRESS MYOCARDIAL PERFUSION SPECT AND PET.** There is abundant evidence of the utility of stress myocardial perfusion SPECT imaging in women

(4,7,19,110-115). False-positive findings in women who are obese or with large breasts reduce the diagnostic accuracy of myocardial perfusion SPECT (81% sensitivity and 78% specificity in women) (18). Studies have reported improved interpretive accuracy when integrating multiple parameters from the SPECT study, including gated left ventricular ejection fraction and wall motion findings, with the perfusion findings, which can aid in discerning true- from false-positive findings. Moreover, use of validated attenuation correction algorithms or the addition of 2-position supine/prone imaging has been reported to improve diagnostic specificity in numerous studies (116-118). Despite the limitations of SPECT, data support equivalent risk stratification by sex across population cohorts, whereby risk ranges from low for normal findings to high for moderate to severe myocardial perfusion SPECT abnormalities, and this pattern is similar for women and men (4,7,115). Evidence is also available of risk stratification in diverse cohorts of African-American and Hispanic women using myocardial perfusion SPECT (119,120). The newly introduced high-speed SPECT camera technology is capable of measuring blood flow (similar to PET) and reduced radiation exposure, marked improvements in nuclear imaging over conventional SPECT technology, which may disproportionately benefit women.

In women, stress myocardial perfusion PET has several advantages over the more commonly performed SPECT imaging including the following: 1) improved spatial and temporal resolution; 2) high diagnostic and prognostic accuracy (121-124); 3) segmentation of subepicardial and epicardial perfusion; and 4) quantification of absolute MBF and CFR (125). Computed tomography is used to generate an attenuation map of the chest for correction of breast tissue attenuation, the latter of which is a notable limitation of SPECT in women. The safety profile of PET is markedly beneficial with an effective radiation dose of ~2 to 3 mSv using the perfusion tracers rubidium-82 and ammonia-13N versus ~14 mSv for technetium-99 m SPECT (126).

There is a growing evidence base with vasodilator stress myocardial perfusion PET, and evidence supports a high diagnostic and prognostic accuracy for both women and men (122,123). The diagnostic accuracy of PET is decidedly higher than that of SPECT (88% vs. 67%, $p = 0.009$) (122). The evidence with stress myocardial perfusion PET reveals a directly proportional relationship between the extent and severity of stress abnormalities and major adverse CAD events including CAD mortality (**Figure 4**) (123,127,128). These data reveal a similar prognostic

**FIGURE 4** Cumulative Cardiac Mortality Rates by the Percentage of Abnormal Stress Myocardium With Rubidium-82 PET Imaging

Comparative CAD mortality estimates from the PET Prognosis Registry in women and men. In women and men, the percentage of the myocardium that was abnormal was associated with a graded increase in CAD mortality. CAD = coronary artery disease; PET = positron emission tomography.
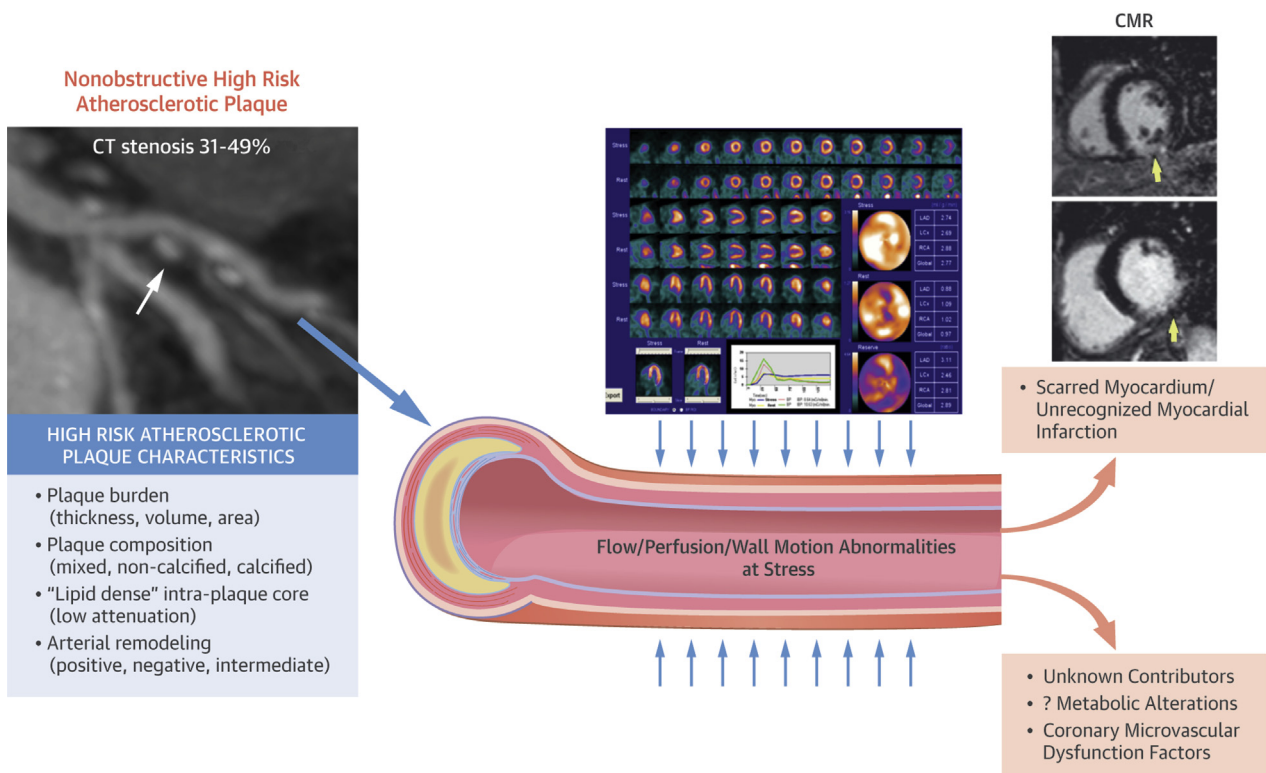
pattern with PET and SPECT, although no formal comparison has been performed.

PET CFR measures absolute MBF into the perfused myocardium and is affected by the extent and severity of atherosclerotic plaque within the epicardial coronary arteries, arterial remodeling, and CMD. In patients with a reduced CFR, the frequency of nonobstructive CAD is greater in women, whereas obstructive CAD is more common in men (127). A PET CFR of ∼2 or lower is a consistent threshold of higher adverse events (129,130). In short-term follow-up of ∼1 year, a higher hazard ratio (∼5) for a reduced CFR suggests a temporal relationship to CAD events (129). Importantly, there is a synergistic relationship among ischemia severity, CFR, and major CAD events (128,130). In patients with ischemia, a reduced CFR doubles their CAD death rate (128). CMD has been the focus of attention (131) due to the high rate of nonobstructive CAD in women compared with men. CMD is defined as chest pain and reduced CFR occurring without an obstructive epicardial stenosis (often including mild CAD and normal coronaries) and largely occurs in women. From the literature, there is an unclear distinction between atherosclerotic microvascular dysfunction with mild epicardial CAD compared with "pure" microvascular dysfunction with normal epicardial coronary arteries. These are

likely 2 different manifestations of CMD but have been incompletely defined heretofore. From the WISE study, ∼80% of 200 women with nonobstructive CAD had mild but notable nonstenotic atherosclerosis (132). Similarly, Lee et al. (133) reported detectable atherosclerotic plaque in 139 patients with nonobstructive CAD and evidence of endothelial dysfunction by invasive coronary reactivity testing. Thus, the extent to which epicardial nonobstructive CAD has been excluded from published findings focusing on CMD remains unclear. In 1 recent report, no prognostic difference was identified between women and men without obstructive CAD and a PET CFR <2.0 (134). This latter definition included a fair number of patients with demonstrable atherosclerotic plaque, and in a secondary analysis of patients with a CAC score of 0, no prognostic differences were identified between women and men with a PET CFR <2.0 (134). To date, no sufficiently powered series has clearly delineated flow impairment in the coronary microvasculature in the absence of nonobstructive epicardial CAD and noted sex differences.

The data are unfolding on the added parameters of absolute MBF and incorporation of coronary CTA findings as additive or interactive with myocardial perfusion parameters. Importantly, separation of the influence of nonobstructive atherosclerosis on

CENTRAL ILLUSTRATION  A Working Model of Imaging Targets Identifying Ischemic Heart Disease Risk in Women



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Potential influential factors contributing to high rates of nonobstructive coronary artery disease (CAD) in women. Investigations have implicated altered flow reserve and provocative ischemia as determinants of risk, even in women with nonobstructive CAD. Other factors may further refine risk including scarring and unrecognized myocardial infarction. Each of these proposed parameters may differentially affect short- or long-term outcomes in women.

reduced flow reserve remains an important differentiator of epicardial CAD versus CMD. If the primary determinant of risk from reduced CFR is derived from epicardial atherosclerotic plaque, then guided anti-ischemic and risk factor-modifying management approaches may prove useful for the millions of women presenting for evaluation with suspected IHD with documented nonobstructive CAD. This would allow for more fruitful research toward the use of contemporary anti-ischemic regimens as reducing IHD risk in women. Moreover, the prognostic significance of PET subepicardial ischemia, an early manifestation of ischemia specific to IHD risk in women, has not been adequately explored in the scientific literature.

Myocardial perfusion imaging technology includes a focus on expanded applications for PET CFR but also a substantial role for PET-CT imaging. Minimal data are available on the correlation of coronary CTA findings with stress myocardial perfusion ischemia, reporting that calcified and noncalcified plaque are more often associated with an abnormal myocardial perfusion scan or reduced CFR on PET (135-137). Stress myocardial perfusion abnormalities and reduced CFR occur commonly with obstructive CAD but also occur in 20% to 40% of patients with nonobstructive CAD (135-137). Thus, the burden of atherosclerotic plaque is quite substantial in patients with suspected IHD but is uncommonly measured in tandem. The evidence is robust that there is a directly proportional relationship between stress-induced abnormalities and the major adverse event risk for women and men alike (4,7,114,132). Yet, for women with documented ischemia, major adverse event rates range widely from 3% to 10% per year, supporting our contention that undetected atherosclerotic plaque

features may contribute to the varying clinical event rates observed for women (7,138-140). Data suggest that the interplay of calcified, noncalcified, or mixed plaque coupled with reduced CFR may improve IHD risk detection (141). Multimodality image fusion integrating myocardial segmentation of coronary anatomy, myocardial perfusion imaging, and MBF is possible and has tremendous promise in the identification of functionally limiting atherosclerosis.

## NOVEL PARADIGMS AND KNOWLEDGE GAPS

Women are differentially affected by IHD through the evolution of their symptoms from initial chest pain to ACS (Central Illustration). Although many of the data on atherosclerotic plaque features focus on its relationship with ACS, sex-specific patterns in stable IHD as links to persistent/worsening symptoms represent sentinel changes, and, perhaps, as intermediate links to ACS. More evidence is needed to support novel paradigms using state-of-the-art imaging strategies to detect and characterize IHD in women. Novel evidence is needed to develop sex-specific profiles of atherosclerotic plaque correlating with perfusion, MBF, fractional flow reserve, CFR, and other physiological measures such as shear stress (142). The emergence of fractional flow reserve computed tomography (143,144) suggests a "game-changing" approach that combines CAD imaging with hemodynamic assessment of plaque; a similar case is being made for coronary CTA with vasodilator perfusion imaging (145,146). Evidence of smaller coronary arteries and higher resting coronary artery flow in women compounds the challenges for CAD imaging and should be addressed. With integrated imaging strategies that deliver anatomic and physiological targets in diagnosis, evidence is needed to direct specific treatment strategies.

Demonstration of improved precision in diagnosis and refined imaging-guided treatment may be insufficient to support the incorporation of advanced techniques into novel evaluation paradigms without comparative effectiveness research that includes the perspectives of all relevant stakeholders including patients, advocacy experts, and clinicians. The ongoing CE-MARC 2 trial will evaluate across multiple centers the comparative effectiveness of multiparametric CMR versus SPECT (147). The randomized MR-INFORM (MR Perfusion Imaging to Guide Management of Patients With Stable CAD) trial will test the hypothesis that CMR perfusion is non-inferior to invasive angiography with fractional flow reserve, based on the endpoints of death, MI, or repeat revascularization (148). Moreover, the National Institutes of Health National Heart, Lung, and Blood Institute-sponsored ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial is randomizing patients with moderate to severe ischemia (on CMR, nuclear, and echocardiography) to an initial invasive or optimal medical therapy approach. These trials are imaging-guided therapeutic strategies that target sufficient enrollment of women and will add tremendously to inform the diagnostic evaluation and treatment of women with IHD. Nevertheless, these trials focus on diagnosis and treatment of obstructive CAD and do not address the needs of women and men with nonobstructive CAD. Additional clinical trials focusing on standardized non-invasive approaches and therapeutic strategies of care for IHD women with nonobstructive CAD are warranted. One such example is the ongoing iPOWER (*Imp*roving diagnosis and treatment of *w*omen with angina p*e*ctoris and microvascular disease) registry, which examines transthoracic echocardiography during rest and dipyridamole stress with measurement of CFR by Doppler imaging of the left anterior descending artery in IHD women with nonobstructive CAD (149).

All of these questions must be addressed across the expanse of presentations associated with IHD, from stable IHD to ACS. Establishing temporal relationships among plaque characteristics, myocardial ischemia, and clinical sequelae is needed to inform our understanding of drivers of worse outcomes for women with IHD and to define allocation of societal resources toward improving outcomes for our female patients.

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