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"Coronary Arterial Function and Disease in Women with No Obstructive Coronary Arteries"

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Abstract

Ischemic heart disease (IHD) is the leading cause of mortality in women. While traditional cardiovascular risk factors play an important role in the development of IHD in women, women may experience sex-specific IHD risk factors and pathophysiology, and thus female-specific risk stratification is needed for IHD prevention, diagnosis and treatment. Emerging data from the last two decades have significantly improved the understanding of IHD in women, including mechanisms of ischemia with no obstructive coronary arteries (INOCA) and myocardial infarction with no obstructive coronary arteries (MINOCA). Despite this progress, sex-differences in IHD outcomes persist, particularly in young women. This review highlights the contemporary understanding of coronary arterial function and disease in women with no obstructive coronary arteries, including coronary anatomy and physiology, mechanisms of INOCA and MINOCA, noninvasive and invasive diagnostic strategies, and management of IHD.

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INTRODUCTION

Ischemic heart disease (IHD) is estimated to affect 67 million women globally and is the leading cause of mortality in women.[1] IHD has traditionally been considered a problem of postmenopausal women, but the annual incidence of acute MI hospitalizations has been increasing in young women <55 years.[2] While traditional cardiovascular risk factors play an important role in the development of IHD in women, women may experience sex-specific IHD risk factors and pathophysiology. Thus female-specific risk stratification is needed for IHD prevention, diagnosis, and treatment. Recently, a clinical practice guideline for the evaluation and diagnosis of chest pain underscored the "uniqueness" of chest pain in women.[3]

Emerging data from the last two decades have significantly improved the understanding of IHD in women, including mechanisms of ischemia with no obstructive coronary arteries (INOCA) and myocardial infarction with no obstructive coronary arteries (MINOCA). This review highlights the contemporary understanding of coronary arterial function and disease in women with no obstructive coronary arteries, including risk perception and stratification, coronary anatomy and physiology, mechanisms of INOCA and MINOCA, noninvasive and invasive diagnostic strategies, and management of IHD.

RISK PERCEPTION AND STRATIFICATION

In the past decade, the conventional "typical" vs "atypical" distinction of angina has been a source of controversy in the evaluation of IHD in women vs men, given gendered sociocultural language differences in symptom expression[4] as well as gender bias in chest pain diagnosis and treatment.[5] Atypical angina may be more prevalent than typical angina in women with INOCA.[6] Determination of "atypical angina" may thus contribute to misdiagnosis and delayed recognition and treatment of ischemia in women.[3, 6] In recognition of this, the recently published chest pain guidelines recommend the term "atypical" should be avoided.[3] Additional challenges to the diagnosis and prognosis of IHD based on symptom presentation include poor correlation of angina with evidence of myocardial ischemia in women and men.[7, 8]

Furthermore, commonly used primary prevention cardiovascular risk scores fail to predict cardiovascular event rates in women with INOCA,[9] compared to secondary prevention risk scores which either over- or underestimate observed INOCA risk.[10] Ongoing efforts to improve risk factor stratification has led to national guideline addition of women-specific cardiovascular risk enhancing conditions, such as premature menopause, autoimmune inflammatory diseases, and history of pregnancy-associated conditions such as hypertensive disorders of pregnancy (including preeclampsia), preterm labor, gestational diabetes, and small for gestational age delivery.[11] Rigorous studies are needed to determine whether

incorporation of these risk enhancers improve cardiovascular risk prediction and outcomes in women.

CORONARY ANATOMY AND PHYSIOLOGY

Women have smaller epicardial coronary arteries than men, even when adjusted for smaller body habitus and left ventricular mass.[12–14] Women also have lower prevalence of obstructive coronary atherosclerosis,[15, 16] even with comparable levels of ischemia[17, 18] and are less likely to have adverse plaque characteristics and less atherosclerotic plaque of all subtypes compared to men.[19] Interestingly, sex differences in CAD severity and plaque composition are most evident among young adults and attenuated in older adults,[20–22] thought to be related to the protective role of endogenous estrogen in premenopausal women. These sex differences in coronary size and atherosclerosis development appear to contribute to higher prevalence of INOCA in women.[23]

Increasing recognition of INOCA and MINOCA has shifted the focus from identifying epicardial coronary artery disease (CAD) to understanding coronary anatomy and physiology (Figure 1).[3, 24, 25] The proximal epicardial coronary arteries (>400 μm) are the conduit vessels, providing low resistance to coronary flow under physiologic conditions and dilating in response to arterial wall shear stress, an endothelium-dependent mechanism. The epicardial arteries represent only 10% of the coronary circulation volume, while the microvasculature (pre-arterioles and arterioles) represents approximately 90%. The pre-arterioles (100 to 400 μm) and intramural arterioles (<100 μm) interface directly with the coronary capillary bed (<10 μm) and control the majority of coronary vascular resistance. These resistance vessels are responsible for the dynamic regulation and distribution of coronary blood flow; the pre-arterioles and proximal arterioles maintain a steady level of shear stress and pressure by endothelial-dependent and non-endothelial dependent dilatation, while the distal arterioles play a critical role in the metabolic regulation of coronary blood flow.[26] Arterioles dilate in response to changes in intramyocardial concentration of metabolites as a result of increased oxygen consumption, decreasing coronary vascular resistance and triggering further dilation of upstream vessels.[26, 27] These arterioles are also responsive to the effects of vasoactive drugs.

In healthy vessels, coronary blood flow remains constant over a wide range of coronary perfusion pressures through dynamic changes in resistances within the different microvascular territories via distinct regulatory mechanisms.[27] An increase in metabolic demand must be met by an increase in coronary blood flow. Based on studies in men, coronary blood flow can increase at least three to five-fold in normal conditions,[28, 29] primarily regulated by the coronary endothelium by releasing vasodilator substances such as nitric oxide, which then produces a guanylyl-cyclase-mediated relaxation of the vascular smooth muscle cells.[30] A normal functioning endothelium is needed not only for appropriate dilation of the coronary arteries but also for vascular growth, repair and thromboresistance.[31] Nonendothelial-dependent coronary microvascular dilatation also occurs due to a myogenic response to reduced pressure.[26] In addition, adrenergic and muscarinic receptors regulate vasoconstriction or vasodilation of the coronary arterioles in response to sympathetic and parasympathetic innervation.[24]

Invasive and noninvasive interrogation studies of coronary flow and myocardial perfusion have suggested sex differences in coronary physiology. Middle-aged women have higher resting coronary blood flow compared to men,[32–35] possibly related to sex differences in autonomic function.[7] Higher resting coronary blood flow may explain lower coronary flow reserve (CFR) values, defined as the ratio of maximal hyperemic coronary blood flow to resting blood flow, in women compared to men in invasive studies,[34, 36] although noninvasive studies suggest similar CFR distribution in women and men.[17, 35] On the other hand, premenopausal women have nearly two-fold better coronary blood flow response than postmenopausal women and age-matched men,[37, 38] consistent with evidence linking estradiol with the production of nitric oxide and estradiol receptor mediated vasodilation.[39] Another coronary physiologic measure is fractional flow reserve (FFR), the ratio of mean distal coronary pressure to mean aortic pressure and a measure of the physiologic significance of an epicardial coronary stenosis; FFR is dependent not only on the severity of the stenosis and subtended myocardium but also on hyperemic microvascular resistance.[40, 41] For a given epicardial stenosis severity, FFR tends to be higher in women than men.[42] Higher FFR in women could possibly related to sex differences in microvascular resistance or vasomotion although the finding of similar index of microvascular resistance (IMR) by sex in INOCA may refute this explanation.[34]

ISCHEMIA WITH NO OBSTRUCTIVE CORONARY ARTERIES (INOCA)

The definition of INOCA is broad and refers to ischemia with stable or unstable symptoms in the setting of normal or nonobstructive coronary arteries (<50% stenosis). INOCA is a common but heterogenous condition associated with elevated risk for cardiovascular events in both women and men.[24] In a large retrospective Danish cohort study, compared to an asymptomatic reference population without IHD, INOCA was associated with an increased risk of all-cause mortality even after adjusting for traditional cardiac risk factors and similar in women and men (normal coronary arteries, adjusted HR 1.29; non-obstructive CAD, adjusted HR 1.52).[16] Among symptomatic women in the Women's Ischemia Syndrome Evaluation (WISE), cardiac mortality rates were 6% (for no CAD) and 11% (for minimal CAD) within 10 years of their angiographic evaluation, again demonstrating that INOCA is not benign.

Standardized diagnostic criteria have been proposed by the Coronary Vasomotor Disorders International Study Group (COVADIS) for the two primary mechanisms of INOCA: coronary microvascular dysfunction (CMD) and coronary vasospasm.[43, 44] In the absence of obstructive CAD, CMD has an estimated prevalence of up to 53% in individuals undergoing non-invasive stress tests.[35, 45] In patients with suspected INOCA undergoing invasive evaluation, CMD and/or coronary vasospasm are diagnosed in up to 4 in 5 patients;[46–50] these patients are often female (50–80%).[47, 48, 50–52] Prevalence estimates may change over time as more centers adopt invasive evaluation of INOCA. Long-term prognosis is impaired in women with CMD and/or vasospasm,[35, 53–57] with a 5% annualized major adverse cardiac event (MACE) rate (including death, nonfatal MI, heart failure hospitalization, late revascularization or nonfatal stroke) in INOCA women with CMD.[35, 53–58] When microvascular angina and epicardial vasospastic angina co-exist, this combination is associated with worse prognosis.[59] An international cohort study recently found no sex or

ethnic difference in prognosis of patients with microvascular angina, but women had lower quality of life scores.[60]

Coronary Microvascular Dysfunction (CMD): Definition and Pathophysiology

CMD should be suspected when exertional or rest angina is present in the absence of obstructive CAD (<50% diameter reduction or FFR>0.80), particularly in the presence of objective evidence of myocardial ischemia, such as 1) dynamic ischemic electrocardiographic changes during an episode of angina or 2) stress-induced angina and/or ischemic electrocardiographic changes in the presence of absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality.[43] CMD is diagnosed in the setting of impaired CFR<2.0 or 2.5, coronary microvascular spasm, abnormal coronary microvascular resistance indices (IMR<25 or hyperemic vascular resistance [hMR]<2.0), or coronary slow flow phenomenon.[43] Although traditional cardiovascular risk factors are associated with CMD,[47, 58, 61] they account for less than 20% of the observed variability in CFR in women with suspected CMD.[61, 62] Postmenopausal status does not appear to significantly contribute to CFR, while systemic inflammation, prior adverse pregnancy outcomes, and prior breast cancer chemotherapy may play a role.[62–65]

CMD pathophysiology may be characterized by structural and functional abnormalities. Structural abnormalities may include luminal obstruction (e.g., microembolization during acute coronary syndrome or revascularization), vascular-wall infiltration (e.g., infiltrative heart disease such as Anderson-Fabry disease), vascular remodeling (e.g., arterial hypertension, hypertrophic cardiomyopathy), perivascular fibrosis (e.g., arterial hypertension, aortic stenosis), and capillary rarefaction (e.g., arterial hypertension, aortic stenosis, heart failure), while functional abnormalities include endothelial dysfunction, smooth-muscle dysfunction, and autonomic dysfunction.[26] Sex differences in structural CMD pathophysiology have not been well studied in humans, although estrogen effects on preventing inflammation-induced apoptosis of vascular endothelial cells and perivascular fibrosis have been hypothesized to cause postmenopausal women to be more vulnerable to capillary rarefaction and impaired hypoxia-induced angiogenesis than premenopausal women.[66] In the presence of atherosclerosis, the endothelium becomes dysfunctional and there may be blunted coronary vasodilation or increased vasoconstriction, resulting in blunted coronary blood flow augmentation or frank reduction in blood flow.[67, 68] In response to increased oxidative stress, the endothelium may release vasoconstrictive substances (endothelin, thromboxane A2, prostaglandin H2, superoxide) that counter the endothelium's vasodilating, anti-proliferative, and antithrombotic mediators (nitric oxide, prostacyclin, endothelium-derived hyperpolarizing factor).[69] Diffuse nonobstructive epicardial CAD may result in a longitudinal pressure gradient, compensatory microvascular vasodilation to maintain myocardial perfusion, and a diminished coronary vasodilatory reserve.[70] Furthermore, presence of positive remodeling, serial stenoses, and high-risk plaque such as large necrotic core can also contribute to ischemia in the absence of obstructive coronary stenosis.[71, 72]

Recently, CMD has been further characterized by structural vs functional endotypes based on vascular tone at rest and stress (Figure 2).[73] Patients with functional CMD endotype

tend to have low vascular tone as reflected by elevated resting flow, normal microvascular resistance and higher nitric oxide synthase activity, while patients with structural CMD endotype tend to have high vascular tone as reflected by low resting flow, elevated microvascular resistance and endothelial dysfunction.[74] The prognostic and therapeutic implications of each endotype, including any potential sex-specific implications, warrant further study.

Epicardial Coronary Vasospasm: Definition and Pathophysiology

Vasospastic angina should be suspected in the presence of nitrate-responsive angina, often occurring at rest between night and early morning, and suppressed by calcium channel blockers.[44] Epicardial coronary vasospasm is defined as transient total or subtotal coronary artery occlusion (>90% constriction) with angina and ischemic electrocardiographic (ECG) changes either spontaneously or in response to a provocative stimulus.[44] Compared to men, women were approximately two times more likely to be found to have inducible coronary vasospasm in an European study.[48] However, coronary vasospasm has been found to be more common in Japanese men than women.[75] Coronary vasospasm mechanisms include smooth muscle cell hyperreactivity (including through rho-kinase activation), inflammation, oxidative stress, deficiency of endogenous nitric oxide activity (including e-NOS polymorphisms), deficient variant aldehyde dehydrogenase genotype, and endothelial dysfunction.[76–78] Vasospasm may be triggered in the setting of sex-specific factors, such as menstruation, and factors that affect both sexes, including sympathetic activity, non-selective beta-blockers, hyperventilation, allergic reactions (such as mast cell activation syndrome), alcohol, muscarinic agonists, ergot alkaloids, prostaglandins, exposure to cold or to smoke, and abnormal platelet activation.[76, 77]

Long-term prognosis of patients with coronary artery spasm on medical therapy are generally favorable (>95% survival over 5 years).[56, 57] However, if comorbid obstructive CAD (FFR>0.80) is present, a high incidence of MACE has been reported in patients with coronary artery vasospasm despite calcium channel blockade treatment.[79] Predictors of MACE include smoking, significant CAD, ST-elevation, multivessel spasm, reduction or withdrawal of anti-spasm medications, and history of cardiac arrest.[57]

NONINVASIVE RISK STRATIFICATION AND DIAGNOSIS

The evaluation of IHD in women can present unique challenges to clinicians.[80–82] The accuracy of standard noninvasive ischemia testing can vary significantly when evaluated against a gold standard of finding anatomic obstructive CAD. This may be particularly problematic for female patients, whose symptoms are less likely to be explained by findings on invasive coronary angiography (ICA), and whose abnormal stress tests in the absence of obstructive CAD are more likely to be interpreted as ‘false positives’ when in fact they may represent INOCA.[83] Over the last two decades, we have witnessed falling diagnostic yields for noninvasive stress testing[84] and ICA,[85] reflecting the referral of patients with lower risk and less prevalent obstructive CAD. The current American Heart Association (AHA)/ American College of Cardiology (ACC) chest pain guidelines provide clinical pathways that

may begin with anatomic or functional imaging, and either pathway may lead to a diagnosis of INOCA.[3]

Standard stress tests have low sensitivity for detecting CMD, although the presence of ischemic ECG changes, specifically ST depression that persists for at least 1 minute into recovery, in the absence of obstructive CAD should raise suspicion for CMD.[86, 87] Exercise echocardiography may be preferred in women with myocardial bridging, to assess for end-systolic to early-diastolic septal wall buckling with apical sparing, a sign of dynamic focal ischemia of a compressed segment.[88] The limited accuracy of conventional noninvasive testing for the diagnosis of CMD and its increased prevalence in women underscores the importance and complementary value of assessing both the macro- and microcirculation in symptomatic women with suspected coronary disease (Figure 3). Identification of women with INOCA should trigger evaluation of CMD with referral for specialized testing, such as with cardiac stress positron emission tomography (PET) and stress cardiac magnetic resonance (CMR) imaging, to confirm ischemia that, in the absence of epicardial CAD or artifact, represents coronary microvascular dysfunction.[3, 25, 83] While transthoracic Doppler echocardiography has been used to diagnose CMD by assessing CFR in the left anterior descending artery in eligible patients with favorable anatomy, it is not commonly performed.[3, 89] Additional assessments of atherosclerotic plaque burden using coronary computed tomography angiography (CCTA) may also further refine risk assessment and help focus preventive care strategies in women with INOCA.[3]

Coronary Computed Tomography Angiography (CCTA)

In asymptomatic patients, non-contrast computed tomography measurement of coronary artery calcium (CAC) score is highly predictive of MACE in women and men.[90] However, women have significantly lower CAC scores than men, with 83–95% of women <50 years old demonstrating a zero CAC score.[91] Measures beyond the CAC score have provided important insight to sex differences in atherosclerotic plaque and cardiovascular risk. The Coronary Artery Calcium Consortium found an increase in the proportion of women with detectable CAC occurring at approximately 46 years of age, which is nearly 10 years older than in men.[92] Despite having lower CAC scores, women had greater calcified plaque volume and higher calcified plaque density than men within CAC subgroups. In addition, more extensive diffuse calcification across multiple vessels or larger calcified plaque volume was associated with higher cardiovascular mortality among women than men, despite women having less obstructive disease.[92] Although noncalcified plaque is missed by CAC scores, a zero CAC score represents very low annual MACE rates in both women and men.[90, 93] Since statin therapy might be withheld or deferred in patients with zero CAC scores, this impact on long-term cardiovascular prevention in women is currently poorly understood.

CCTA has dramatically increased test sensitivity for CAD diagnosis and enabled early characterization of plaque morphology. Mounting evidence supports that: (1) the presence of any atherosclerotic plaque, obstructive or not, portends increased risk of events, and (2) the higher the overall plaque burden present, the higher the risk.[94, 95] From the international multicenter CONFIRM registry, nonobstructive CAD was associated with increased MACE

in both women and men.[96] Women and men with comparable risk and extent of CAD had comparable prognosis, as there was no interaction of sex on the association between per-vessel extent of obstructive CAD and MACE.[96] Nonetheless, prevalent patterns of disease do differ between women and men, with more symptomatic women than men manifesting nonobstructive rather than obstructive CAD.[15–17] Subsequent analysis of the CONFIRM data demonstrated that women with nonobstructive left main disease had a nearly 80% higher risk for MACE than men with nonobstructive left main disease, potentially due to smaller luminal area size and more positive remodeling associated with vulnerable plaque in women.[97] In a secondary analysis of the International Study of Comparative Health Effectiveness of Medical and Invasive Approaches (ISCHEMIA) trial, among those who had obstructive CAD on CCTA, women demonstrated less extensive CAD as compared to men (36% vs. 47% with 3-vessel disease), despite experiencing more frequent angina.[18]

In nonobstructive CAD, CCTA also allows for characterization of high-risk plaque features, including positive remodeling, low-attenuation plaque, or napkin-ring sign. In an observational substudy[98] of the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, the presence of high-risk plaque in patients with nonobstructive CAD increased the adjusted risk of adverse events by 1.6-fold, and high-risk plaque was more strongly associated with events in women than in men. Nonetheless, the positive predictive value of high-risk plaque detection in these patients was low (only 4.8% for future events), limiting its current clinical applicability. Although the PROMISE trial found that a strategy of initial CCTA, as compared with functional testing, did not improve clinical outcomes over a median follow-up of 2 years, half of the cardiovascular events occurred in patients with no obstructive CAD or negative stress testing, highlighting the clinical impact of INOCA.[99] PROMISE investigators found that women were more likely to have positive stress tests than positive CCTA for obstructive CAD compared to men, again suggesting the role of INOCA in these women.[100] More recently, among patients with nonobstructive CAD followed with serial CCTA over >2 years in the Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging (PARADIGM) study, baseline percent atheroma volume independently predicted the development of obstructive CAD, whereas presence of high-risk plaque (positive remodeling, spotty calcification, low-attenuation plaque) did not.[101] Analysis of sex differences in PARADIGM demonstrated that women had greater calcified plaque volume progression but slower noncalcified plaque progression and less development of high-risk plaques than men, suggesting that CCTA may provide additional sex-specific risk stratification in patients with nonobstructive CAD.[102] In patients presenting with known or suspected angina, a higher proportion of women than men will have a normal angiogram or no obstructive atherosclerosis.[103] Yet a substantial number of these patients may have underlying CMD microvascular angina.

Cardiac Positron Emission Tomography (PET)

Neither conventional ICA nor CCTA can detect CMD, which is defined as a reduced CFR in the absence of flow-limiting CAD.[25] Global CFR, calculated as the ratio of hyperemic to rest absolute myocardial blood flow averaged over the left ventricle, is an integrated marker of coronary vasomotor dysfunction that measures the hemodynamic effects of focal, diffuse,

and small-vessel CAD on myocardial tissue perfusion[104, 105]. Observational data have shown that CFR measurements using cardiac PET distinguish patients at low or high risk for MACE and cardiac mortality,[106–109] beyond other clinical variables.[110–112] Evidence now supports that: (1) the existence of impaired CFR, whether in the presence or absence of obstructive CAD, portends increased risk of cardiovascular events, and (2) the more severely impaired the overall global CFR, the higher the risk. Whereas a CFR≥2 effectively excluded high-risk angiographic CAD and was associated with low rates of annualized cardiac death,[113] event rates for patients with CFR<2 increased steeply as CFR decreased, even in the absence flow-limiting CAD.[35, 108] As such, noninvasive quantification of myocardial blood flow may be particularly useful for diagnosis and risk assessment of symptomatic women with suspected CMD.

PET evidence supports that women with ischemia and very low CFR<1.6 may be at an especially increased risk for MACE. In symptomatic patients referred for ICA after cardiac PET, women had a lower burden of obstructive CAD relative to men and still experienced worse outcomes, which were found to be mediated by impaired CFR, not obstructive CAD.[17] Therefore, patients with impaired CFR and less obstructive CAD may be at significantly increased risk of MACE despite having access to revascularization, which is fundamentally targeted at management of obstructive CAD. Compounding this risk is the recognition that many of these patients may receive falsely reassuring (or perceived “false positive”) evaluations using conventional diagnostic testing approaches. This phenomenon may be especially relevant in women with obesity,[114] cardiometabolic and inflammatory disease risk factors,[115] heart failure and preserved ejection fraction,[111] and INOCA.[116]

Cardiac Magnetic Resonance Imaging (CMR)

Stress-rest CMR myocardial perfusion reserve and coronary sinus flow reserve have been emerging tools for CMD diagnosis and prognosis over the last decade.[117, 118] CMR semiquantitative myocardial perfusion reserve index (MPRI) <1.84 and quantitative myocardial perfusion reserve <2.19 have been shown to have high sensitivity and specificity for CMD in women and men.[119, 120] In addition, MPRI has been found to be an independent predictor of MACE in patients with INOCA, with MPRI≤1.47 as the optimal cutoff value.[121] CMR-derived coronary sinus flow reserve has also been found to be prognostic in patients with known or suspected CAD even in the absence of ischemic perfusion abnormalities, supporting its predictive role in INOCA patients.[119] CMR’s strength lies in its superior spatial resolution allowing for the comprehensive assessment of cardiovascular structure and function, including the quantification of myocardial scar using late gadolinium enhancement (LGE). In women with INOCA, the prevalence of LGE has been reported to be 8%, with one-third of affected women lacking a prior diagnosis of MI despite the majority of patients demonstrating a scar pattern typical of CAD.[122] As such, CMR is useful in the identification of MINOCA.[123, 124]

INVASIVE CORONARY ANGIOGRAPHY (ICA)

ICA remains a cornerstone for investigation of patients with suspected CAD. ICA allows for diagnosis of high-risk coronary anatomy needing revascularization but can also reveal

non-obstructive causes of ischemia or infarction with additional specialized testing.[89, 124] ICA can also identify lesions that may benefit from further interrogation using advanced imaging and physiological techniques. There are specific challenges that are associated with ICA in women, as they are more likely to experience access site complications and access site crossover from the radial to femoral approach.[125] This is likely related to smaller caliber radial arteries and subsequent predisposition to radial spasm.[126] Nevertheless, the use of radial access is associated with a reduction in vascular complications, with a greater absolute reduction seen in women when compared with men.[127]

ICA is limited by the two-dimensional depiction of the vascular lumen and does not provide information regarding plaque characteristics or the result of PCI.[128] The use of advanced coronary imaging techniques such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have allowed for visualization of the coronary vasculature and coronary plaque, which is particularly useful when evaluating women with MINOCA.[124] Furthermore, imaging guidance for stent implantation has been shown to reduce MACE and cardiovascular death.[129]

Intravascular Ultrasound (IVUS)

IVUS utilizes a miniature ultrasound transducer on a monorail catheter to visualize the coronary lumen and vascular wall. IVUS can assess for the presence of plaque disruption (encompassing plaque rupture, erosion and calcific nodules) of non-obstructive plaque.[124] Interestingly, disruption rarely occurs in the largest, eccentric or remodeled plaques; highlighting the need for imaging assessment to identify the culprit lesion.

Optical Coherence Tomography (OCT)

OCT uses the backscattering of infrared light to produce an image of the coronary vascular wall, allowing a higher spatial resolution but lower penetration depth than IVUS.[130] OCT requires the use of contrast media to clear blood from the vessel to ensure optimal image quality, which may preclude some patients who cannot tolerate large contrast volumes. OCT can be used in a similar fashion to IVUS to assess plaque morphology, optimal stent sizing and the post-PCI result, and has been shown to be non-inferior to IVUS in this context.[131] The higher spatial resolution can help identify subtle plaque disruptions such as plaque erosion.[124]

Invasive Coronary Artery Function Testing—Invasive coronary function testing is recommended for selected patients with frequent or persistent stable chest pain and suspected INOCA for the comprehensive evaluation of CMD and coronary vasospasm.[3, 89]

Coronary Flow Reserve (CFR)

CFR describes the ratio between hyperemic coronary blood flow velocity and resting coronary flow velocity which can be measured invasively using a coronary Doppler wire.[58] A thermodilution method using coronary pressure wires has also been validated.[132] Although initially devised to analyze intermediate epicardial stenoses, CFR has been adapted to assess for CMD as it can interrogate the entire coronary circulation including epicardial arteries and the microvasculature.[43]

CFR measurements in healthy asymptomatic subjects are usually greater than 3.0, indicating that the coronary circulation can triple coronary blood flow when required.[104] CFR is generally lower in women compared to men, possibly due to sex differences in resting coronary flow.[34, 36] A CFR cutoff of <2.0 has been identified as significantly correlated with ischemia identified on SPECT imaging, with high sensitivity and specificity.[133, 134] Therefore, this is often considered the threshold for abnormal microcirculatory function.[89, 135] Among women with suspected INOCA, CFR<2.32 was found to be the best discriminating threshold for MACE.[58]

Index of Microcirculatory Resistance (IMR)

IMR is a measurement of coronary microvascular function by using a coronary pressure wire as a thermistor to calculate overall microcirculatory resistance at maximal hyperemia.[136] This is calculated based on Ohm's Law, as microvascular resistance is proportional to the pressure differential between the distal coronary bed and the venous pressure; and inversely proportional to coronary flow as measured by thermodilution.[137] IMR is potentially more useful for assessing CMD as it is specific to the microvasculature and does not incorporate measurements from the epicardial vessels. IMR is also not affected by changes in patient hemodynamics. A normal IMR is considered <25.[137] Doppler-derived hMR correlates modestly with IMR and CFR, and an hMR threshold <2 is considered normal.[36, 138]

An abnormal IMR or hMR has been reported in 21–35% of patients with suspected INOCA, suggestive of a microvascular cause of symptoms.[36, 50, 139] Elevated IMR in concert with low CFR has been associated with increased MACE in patients with INOCA; however, an isolated elevated IMR did not portend worse outcomes.[139]

Coronary endothelial dysfunction

Coronary endothelial dysfunction is characterized by an attenuated increase or decrease in coronary blood flow and coronary artery diameter in response to low dose acetylcholine.[68] Impaired endothelial-dependent CMD is often defined as a percentage increase in coronary blood flow ≤50%, while endothelial-dependent epicardial dysfunction is typically defined as coronary artery dilation <5% or any significant vasoconstriction.[47, 49] Although endothelial dysfunction may affect both the epicardial and microvascular coronary circulation,[49] there may be a dissociation between the epicardial and microvascular function such that coronary blood flow may be preserved or even increased in the setting of coronary epicardial vasoconstriction in response to acetylcholine.[68] Invasively determined coronary endothelial dysfunction portends increased MACE and mortality risk in women with INOCA.[55]

Coronary vasospasm

Epicardial or microvascular vasospasm is assessed using intracoronary injection of sequentially higher doses of acetylcholine or ergonovine and can be found in up to 60% of patients with suspected INOCA.[56] Epicardial vasospasm is typically defined as ≥90% angiographic vasoconstriction from baseline[44] with reproduction of angina and transient ischemic ECG changes, while microvascular vasospasm is defined as angina and transient ischemic ECG changes in the absence of epicardial vasospasm.[56] When performed by experienced operators, no fatal or irreversible nonfatal complications of

intracoronary acetylcholine provocation testing have been reported, but testing may be associated with arrhythmias, including self-limiting pause, symptomatic bradycardia and atrial fibrillation.[46, 140]

Myocardial bridging

Myocardial bridging is an intramyocardial segment of an epicardial coronary artery with a prevalence of approximately 25% in women and men by autopsy studies, although reported prevalence differs based on method of evaluation.[141] During ICA, myocardial bridge is often diagnosed when there is evidence of systolic compression, often appearing worse after nitroglycerin administration. IVUS can play an important role in confirming myocardial bridging by detecting a characteristic “half-moon” appearance in the bridged segment and identifying concomitant atherosclerosis..[142]. While myocardial bridging is generally considered benign, it can be associated with angina and adverse cardiovascular outcomes.[141, 143, 144] Concomitant endothelial dysfunction or vasospasm may contribute to symptoms in those who present in adulthood.[50, 145] Beta-blocker and calcium-channel blocker therapy are usually recommended medical therapy for symptomatic patients, with surgical unroofing the preferred surgical strategy in refractory cases.[146]

Doppler measurements in bridged coronary segments show a characteristic pattern that reflects abrupt early diastolic flow acceleration, mid-to-late diastolic plateau and retrograde flow in systole.[147] CFR measurements have been shown to be abnormal distal to the bridged segment, despite being normal or slightly reduced in the proximal coronary segment, and vasospasm may often be provoked at bridge sites.[147, 148] Invasive hemodynamic assessment is typically performed using inotropic stimulation with dobutamine. Diastolic FFR ≤0.76 during dobutamine provocation has the best sensitivity and specificity for identifying myocardial bridging associated with stress-induced myocardial ischemia.[149] Another diastole-specific index, instantaneous wave-free ratio (iFR), has been shown to be superior to conventional-FFR in the assessment of myocardial bridging, although the ischemic cut-off values of iFR are unknown.[150]

STRATIFIED MEDICAL THERAPY OF INOCA

Currently, the therapeutic strategy for INOCA remains unclear due to a paucity of clinical trial evidence.[151] Considering patients presenting with stable angina, clinical trials and practice guidelines have historically focused on obstructive CAD. However, this narrow focus promulgates under-recognition and undertreatment of INOCA, widening gender inequalities in cardiovascular care.[89] Novel personalized therapeutic approaches are urgently needed. Stratified medicine is relevant to INOCA, since patients with initially undiagnosed disease may pass through clinical services that are providing care for relatively unselected (undifferentiated) populations.

Evidence from CorMicA

The British Heart Foundation Coronary Microvascular Angina (CorMicA) trial was a randomized, controlled, blinded clinical trial of stratified medical therapy versus usual care in patients with angina undergoing clinically indicated ICA (Figure 4). Patients with no

obstructive CAD were randomized (n=151) to stratified medicine or standard, angiography-guided management. Baseline characteristics were notable for a median age 61 years, majority female (73.5%), and moderate angina frequency. Coronary function testing using thermodilution and acetylcholine vasoreactivity testing were undertaken in all patients and the results were disclosed in the intervention group but not in the blinded control group. The diagnostic options for all patients were 1) a non-cardiac diagnosis, 2) microvascular angina, 3) vasospastic angina, or 4) both microvascular and vasospastic angina. The treatment options aligned with the diagnosis and contemporary practice guidelines for the management of stable IHD and for coronary artery spasm.

Stratified medicine informed by coronary function testing significantly improved angina and quality of life at six months and one year as compared to a usual care approach without knowledge of coronary reactivity test findings.[152] There was no difference in MACE at 6 months or after a median follow-up duration of 19 months.[46, 152] Evidence from CorMicA supported Class IIA guideline recommendations for invasive coronary function testing in patients with suspected INOCA.[3, 89]

Pharmacologic Treatment of INOCA

Multiple factors have contributed to a paucity of clinical evidence for pharmacotherapy in INOCA. The reasons include limitations in the accuracy of traditional diagnostic tests (noninvasive stress tests, CCTA and ICA) for coronary vasomotor disorders. The tests with comparatively high accuracy for INOCA (PET, CMR and invasive coronary function tests) may have limited adoption because of costs, logistics, education, and training. Finally, the clinical evidence pertaining to INOCA has mainly been developed in observational studies (with the notable exception of a small WISE clinical trial of angiotensin-converting enzyme inhibition [ACE-I]).[153] Therefore, lack of clinical evidence and, relatedly, limitations in practice guideline recommendations, has underpinned an empirical approach to the management of INOCA, and sometimes, therapeutic nihilism. Since most patients with microvascular and/or vasospastic angina are female, these evidence gaps underpin sex-related disparities in healthcare.[154] Sex-specific therapeutic trials are lacking, thus the following treatment options are generalized for women and men.

Guideline-indicated, preventive pharmacological therapies to control cardiovascular risk factors is a key part of management of INOCA.[3, 89] For symptomatic patients with nonobstructive CAD, intensification of preventive therapies is recommended.[3] Statins and ACE-I/angiotensin receptor blocker therapy is suggested to improve microvascular function. Lifestyle counseling, including stress management, should be also supported as outlined in the stable IHD guidelines.[155]

Microvascular angina can be treated with a beta-blocker, calcium channel blockers, nicorandil, and lifestyle modification.[89] If vasospasm is diagnosed or suspected, a calcium channel blocker should be prescribed in preference to a beta-blocker. A low dose should be prescribed initially to give the best chance of tolerance and adherence. The dose can then be titrated to enhance efficacy and symptom relief, as clinically appropriate.

Coronary artery spasm should be treated with calcium channel blockade. The choice of calcium channel blocker should be personalized according to heart rate, blood pressure, and drug interactions. In patients with persisting symptoms, dual calcium channel blocker therapy may be helpful. Long-acting oral nitrate therapy is also indicated, with short acting nitrates on demand for chest pain.[89, 156]

Emerging Pharmacological Therapies in INOCA

Ongoing randomized clinical trials may expand pharmacologic therapies or strategies in INOCA and will provide critically needed evidence regarding the potential impact of treatment on cardiovascular events. Novel therapies include a selective, potent endothelin receptor A antagonist zibotentan (NCT04097314) and intracoronary autologous CD34+ cell treatment (NCT04614467). The *W*omen's Ischemi*A* Trial to *R*educe Events in Non-Obst*R*uct*I*ve C*OR*onary Artery Disease (WARRIOR) is a multicenter, prospective, randomized, open blinded end-point trial evaluating the effect of an intensive statin/ACE-I (or ARB)/aspirin treatment strategy vs. usual care strategy on first occurrence of MACE in women with suspected INOCA (NCT03417388).

Non-pharmacologic Options and Emerging Clinical Strategies in INOCA

Lifestyle measures represent the cornerstone of management for patients with INOCA.[89] Non-pharmacological approaches should be personalized according to the needs and preferences of the individual. A shared-care approach should consider different forms of exercise, stress management, yoga, meditation and dietary modification for weight loss, including referral to cardiac rehabilitation.

Device therapy is an emerging new paradigm for INOCA patients with refractory symptoms. Percutaneously implantable coronary sinus devices mechanically narrow the coronary sinus to achieve an increase in coronary sinus pressure and redistribution of coronary blood flow to reduce myocardial ischemia. An ongoing randomized trial will assess improvement in microvascular angina at six months after coronary sinus reducer implantation versus optimal medical therapy (NCT04606459).

Novel clinical strategies are also being investigated in randomized controlled trials, comparing standard CCTA- or ICA-guided therapy with invasive coronary function testing-guided stratified medicine in patients with suspected INOCA (CorCTCA, NCT03477890; iCorMicA, NCT04674449). Similarly, CorCMR is a randomized controlled trial of stratified medicine informed by stress perfusion CMR or standard, angiography-guided care in patients with suspected INOCA (NCT04805814).

MYOCARDIAL INFARCTION IN WOMEN

Risk stratification, diagnosis, and treatment of women with IHD (including INOCA) are targeted to prevent MACE, including MI. In the United States, approximately 430,000 women are hospitalized with acute coronary syndromes each year.[157] Compared with men, women tend to be older at the time of first MI presentation (72.0 vs. 65.6 years).[157] Atypical MI symptoms in women may not be promptly recognized and may contribute to pre-hospital delays in care.[158, 159] Women age <55 years were more likely than men to

present >6 hours after the onset of MI symptoms.[160] Sex-specific decision limits of high sensitivity troponin improve the accuracy of diagnosis of MI in women.[161] Among patients with non-ST segment elevation MI (NSTEMI), women are less likely to undergo ICA within the first 24 hours of admission compared to men.[162] Similarly, in STEMI, door-to-device times are longer in women versus men.[163, 164] Guideline-directed medical therapies for MI are underused in women compared with men, both in the acute setting and at hospital discharge.[162, 165, 166] Clinical outcomes reflect these disparities in care. In-hospital mortality is higher in women than in men with MI.[157, 167] The greatest sex differences in MI mortality are observed among younger individuals, and differences attenuate with older age.[168] Sex disparities in MI outcomes may improve using standardized protocols.[169]

The pathophysiology, management, and outcomes of MI in women vary considerably by subtype, which are broadly stratified based on the presence or absence of obstructive CAD and coronary dissection at the time of coronary angiography (Figure 6).

Myocardial Infarction with No Obstructive Coronary Arteries (MINOCA):

MINOCA is reported in ~6% of spontaneous MI, and is more common among women than men.[168, 170] In a large national registry of acute MI in the United States, MINOCA was identified in approximately 1 of every 9 women without a history of established obstructive CAD.[168] MINOCA is defined based on a <50% diameter stenosis in all major epicardial coronary arteries, in the absence of a specific alternative cause for the clinical presentation, such as pulmonary embolism or myocarditis.[124] Among women with MINOCA, relatively few (14%) present with STEMI, but ST elevation is associated with higher risk of adverse outcomes.[168] Although MINOCA confers a more favorable prognosis than MI with obstructive CAD (MI-CAD), it can be fatal, and pre-hospital deaths have been reported.[171] Mortality associated with MINOCA is ~1% in-hospital, 2–5% at 1 year, and ~11% at 5 years.[168, 170, 172–174] MACE occur in nearly 25% of individuals with MINOCA at 4-year follow-up.[175] The risk of adverse outcomes is higher in patients aged 65 and older, with up to 12% 1-year mortality and nearly 19% 1-year rate of MACE.[173]

The pathogenesis of MINOCA is heterogeneous and can include atherosclerotic plaque rupture, plaque erosion, coronary spasm, coronary thromboembolism, and rarely, coronary dissection.[124, 176] Patients with Takotsubo Syndrome, acute myocarditis, or non-ischemic cardiomyopathy are not considered to have MINOCA once the alternate diagnosis has been established.[124] Since the optimal management of MINOCA may vary based on the underlying mechanism of infarction, a systematic approach to diagnosis is critical. Clinical algorithms for the diagnosis of MINOCA (Figure 5)[124] highlight the importance of a careful review of coronary angiographic findings for clinically overlooked diagnoses, left ventricular functional assessment to evaluate for wall motion abnormalities characteristic for Takotsubo Syndrome, and contrast CMR to diagnose myocarditis or identify the territory of acute infarction or injury.[124, 177] Intracoronary imaging with OCT or IVUS to identify atherosclerotic culprit lesions, and coronary functional assessments to diagnose epicardial or microvascular coronary spasm, should also be considered to enhance diagnostic sensitivity and potentially tailor therapy.[124] These additional tests may be undertaken at the time of initial diagnostic angiography or during a subsequent cardiac catheterization. CCTA may be

useful to identify the presence of coronary atherosclerosis but does not currently provide imaging resolution sufficient to identify plaque rupture or erosion.

Invasive coronary imaging and pathology data demonstrate women to exhibit a higher prevalence of plaque erosion, lower prevalence of plaque rupture, less necrotic core and calcium, but similar plaque burden.[178–180] Thin-cap fibroatheroma and plaque burden have been found to predict nonculprit MACE in women over time.[180]

A multi-modality imaging approach has a high likelihood of identifying abnormalities that provide insight into pathophysiology of MINOCA.[123, 181–183] For example, in the largest multicenter observational study of women with MINOCA, 84.5% of patients undergoing multivessel OCT and CMR had an identifiable cause of the clinical presentation, of which 75.5% were ischemic and 24.5% of which were non-ischemic.[123] The majority of non-ischemic presentations were due to myocarditis diagnosed solely on CMR. In general, myocarditis is more frequent among men.[184] A coronary culprit lesion was identified in 46.2%, with atherosclerotic mechanisms, including intraplaque hemorrhage, layered plaque, and plaque rupture, most common.[123] Thrombus without plaque rupture was also observed in a small number of cases.

Coronary artery spasm is common in patients with MINOCA. In studies of MINOCA in which patients underwent provocative testing with intracoronary acetylcholine or ergonovine, 24% to 65% of individuals had evidence of coronary spasm.[181, 185–187] Despite concerns about provocative testing in the setting of acute MI, this approach was safe, with procedure-related arrhythmias reported in ~5% of patients, without any recurrent infarction or major adverse events reported.[185]

Mechanisms of MINOCA have been defined in small studies that predominantly enroll female participants; investigations to identify potential sex differences in MINOCA pathophysiology are currently ongoing (NCT02905357).

The preferred treatment of MINOCA is medical therapy, and there is no established role for coronary stents in the setting of non-obstructive coronary plaque disruption. However, impact of medical therapy for secondary prevention of MINOCA is unknown. Current clinical practice guidelines for the secondary prevention of MI are based largely on data from patients with obstructive CAD. Though it stands to reason that prognosis and best treatment may vary according to the underlying cause of MINOCA, this has yet to be proven. Consequently, although typical secondary prevention medications for MI are often administered at the time of discharge after a diagnosis of MINOCA, they are used less often than in MI-CAD, with substantial heterogeneity in clinical practice, reflecting provider equipoise.[188, 189]

In the absence of randomized controlled trials, observational studies provide some key insights into the effects of medical therapy in MINOCA, but few studies report sex specific findings.[175] In a propensity-matched analysis of men and women with MINOCA, statins and angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARB) were associated with lower rate of MACE. Beta blockers were associated with a trend toward benefit, while no reduction in adverse events was observed with dual

antiplatelet therapy.[175] These findings were consistent in the subgroup of women with MINOCA. Still, observational data such as these are hypothesis generating and require confirmation in randomized trials. The ongoing Randomized evaluation of Beta blocker and ACE-I/ARB Treatment in patients with MINOCA trial (MINOCA-BAT) seeks to provide additional insights into effects of these two treatments on cardiovascular events (NCT03686696).[190] Although calcium channel blocker use is reasonable in patients with presumed or documented coronary spasm as the mechanism of MI and is recommended in society statements, its role in unselected patients with MINOCA remains to be established. Additional efforts to define optimal medical therapy in patients with MINOCA are needed.

Spontaneous Coronary Artery Dissection (SCAD)

MI due to SCAD has a unique pathogenesis, in which spontaneous development of intramural hematoma, with or without an intimal tear, narrows the vessel lumen and limits myocardial perfusion.[191] Dissection can occur between any of the three layers of arterial wall; specifically the intima, media or adventitia.[192] SCAD is a non-atherosclerotic problem but causes narrowing that may be mistaken for MI due to atherosclerosis and thrombosis. Among patients with SCAD, the overwhelming majority (90%) are women, the average age is ~50 years, and few have traditional cardiovascular risk factors.[193] Although often overlooked, SCAD may account nearly 35% of MI occurring in women age ≤50 years[191] and is a leading cause of pregnancy-associated MI.[194] Diagnosis of SCAD requires careful attention to the angiogram with a high index of suspicion, and intracoronary imaging may be considered in selected cases when a definitive diagnosis cannot be established although care must be taken to avoid propagation of further dissection.[195]

The preferred management of SCAD is conservative, with careful monitoring and medical therapy as the mainstay of treatment. This is both because angiographic healing of SCAD occurs in 70–97% cases in the weeks to months after the initial episode and because of the higher rate of PCI and bypass graft failure in the setting of SCAD as compared to MI due to CAD.[191] Thus, coronary revascularization for SCAD should be reserved for patients with ongoing ischemia despite medical therapy or hemodynamic instability. When SCAD occurs in large-caliber, proximal vessels, CCTA may be useful for subsequent re-imaging to confirm angiographic resolution of the dissection.

Optimal medical management of SCAD has not been established. Some observational data indicate that beta-blockers reduce the risk of SCAD recurrence, but randomized trials have not been performed.[191] The role of antiplatelet therapy also remains to be defined in clinical trials. Though dual antiplatelet therapy is prescribed commonly,[196, 197] it increases bleeding risks and carries a potential for harm related to propagation of the intramural hematoma. Randomized trials evaluating medical therapy for SCAD are an area of unmet need in IHD with a disproportionate impact to women.

Myocardial Infarction with Obstructive Coronary Artery Disease (MI-CAD)

Despite the higher prevalence of MINOCA and SCAD in women versus men with MI, most women with MI have obstructive CAD (MI-CAD) due to atherosclerosis even if they did not have pre-existing obstructive lesions.[168] Atherosclerotic MI-CAD are typically ascribed

to plaque rupture or plaque erosion. Although a greater prevalence of plaque erosion was observed in young women than young men in autopsy studies, a prospective multicenter study of intracoronary OCT in age-matched men and women with STEMI found similar prevalence of plaque rupture (~50%) and plaque erosion (25%) in women and men.[198,199]

Women with atherosclerotic MI-CAD may be candidates for coronary revascularization, either by PCI with stent placement or coronary artery bypass grafting. Although few technical aspects of PCI are specific to women, women are at greater risk of major vascular access site complications after PCI for acute coronary syndromes.[127] Women who undergo bypass surgery are less likely to receive guideline concordant revascularization with multiple arterial grafts or complete revascularization,[200] and have a greater frequency of post-operative complications and early hospital readmission than men.[201, 202]

Takotsubo Syndrome

Takotsubo Syndrome is a reversible left ventricular dysfunction syndrome that presents as acute MI. Takotsubo Syndrome is characterized by wall motion abnormalities that are out of proportion to peak troponin, the absence of culprit coronary artery stenoses, frequent triggering by physical or emotional stress, and a predilection for postmenopausal women.[203] Pathophysiology has not yet been identified as primarily vascular, though microvascular or epicardial spasm may contribute and may impact sex differences in treatment. Medical therapy with ACE-I/ARB is associated with improved 1-year survival in a large Takotsubo Syndrome registry (1750 patients; 90% women).[204] Thus, Takotsubo Syndrome will not be discussed in depth in this compendium of coronary function and disease.

KNOWLEDGE GAPS

The Cardiovascular Disease in Women Committee of the ACC, in conjunction with interested parties (from the National Heart, Lung, and Blood Institute, AHA, and European Society of Cardiology), previously convened a working group to develop a consensus on the syndromes of INOCA.[24] The report identified research gaps with recommendations addressing three overarching investigation goals: 1) formulate phenotypic classification of patients with INOCA based on clinical presentation, pathophysiological mechanisms, and prognosis; 2) develop diagnostic algorithms based on this classification system; 3) develop management approaches to reduce or prevent symptoms and to modify risk for adverse outcomes.

Expanded research recommendations from the prior report,[24] to improve the understanding, diagnosis and management of coronary arterial dysfunction and disease in women include:

1. Discover markers for mechanisms of epicardial and/or microvascular coronary dysfunction to investigate environmental and biological determinants that may account for individual differences in vasomotor function, plaque micro-disruption, enhanced thrombus formation, sympathetic nervous system activation, and other potential triggering mechanisms for acute coronary syndromes.

2. Identify markers of risk that include clinical and advanced technology variables (e.g., proteomic, gene expression, cell-based, exosomes, miRNAs). Validate them in clinical settings and develop informatics platforms for prediction modeling that may require monitoring specific biological “signatures” periodically to discern which are perturbed before a clinical event (e.g., angina, HF hospitalization) and will be useful for predicting risk and directing new therapies. This should include, but not be limited to, new methods for predictive modeling using multidimensional data sets.

3. Using traditional and novel risk markers, new IHD risk scores can be developed in women and validated from ICA and CCTA and other sources to estimate near-term risk that also include clinical and behavioral variables, existing biomarkers, genetic, ‘omic, and imaging markers.

4. Test developed scores for use as targeted screening tools for women deemed to be at intermediate or higher cardiovascular risk by traditional risk scores to determine who would benefit from more intensive testing, monitoring, and therapeutic interventions.

5. Conduct adequately powered clinical trials in women, using standardized MINOCA/INOCA, epicardial and/or microvascular dysfunction definitions, on risk outcomes with existing strategies effective in obstructive CAD.

6. Conduct exploratory trials in the same populations using novel interventions based on new phenotypic and mechanistic understanding on risk outcomes.

7. Construct evidence-based therapeutic guidelines for INOCA, epicardial and/or microvascular coronary dysfunction. Develop physician education and fellowship training programs to enhance the understanding of these conditions and to encourage the use of novel risk assessment and management strategies. Develop programs to understand and overcome barriers to clinical implementation of these guidelines.

CONCLUSIONS

IHD remains the leading cause of death in women, and sex-differences in IHD outcomes persist. Evidence to date have established that coronary arterial function and disease are not limited to obstructive CAD in women. Increased understanding of female specific IHD risk factors and pathophysiology of INOCA and MINOCA has led to changes in guidelines for atherosclerotic cardiovascular disease prevention and for the diagnosis and management of acute and chronic coronary syndromes over the past five years. Next steps needed to address knowledge gaps in women include evidence-based approaches to IHD risk stratification and management, including conducting large randomized clinical trials for women with INOCA and MINOCA to inform therapeutic strategies.

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Nonstandard Abbreviations and Acronyms

ACE-I	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker
CAD	coronary artery disease
CCTA	coronary computed tomography angiography
CMD	coronary microvascular dysfunction
CFR	coronary flow reserve
CMR	cardiac magnetic resonance
ECG	electrocardiographic
FFR	fractional flow reserve
HMR	hyperemic microvascular resistance
ICA	invasive coronary angiography
IFR	instantaneous wave-free ratio
IHD	ischemic heart disease
IMR	index of microcirculatory resistance
INOCA	ischemia with no obstructive coronary arteries
IVUS	intravascular ultrasound
LGE	late gadolinium enhancement
MACE	major adverse cardiac events
MI	myocardial infarction

MINOCA	myocardial infarction with no obstructive coronary arteries
MPRI	myocardial perfusion reserve index
NSTEMI	non-ST elevation myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
PET	positron emission tomography
SCAD	spontaneous coronary artery dissection
STEMI	ST elevation myocardial infarction

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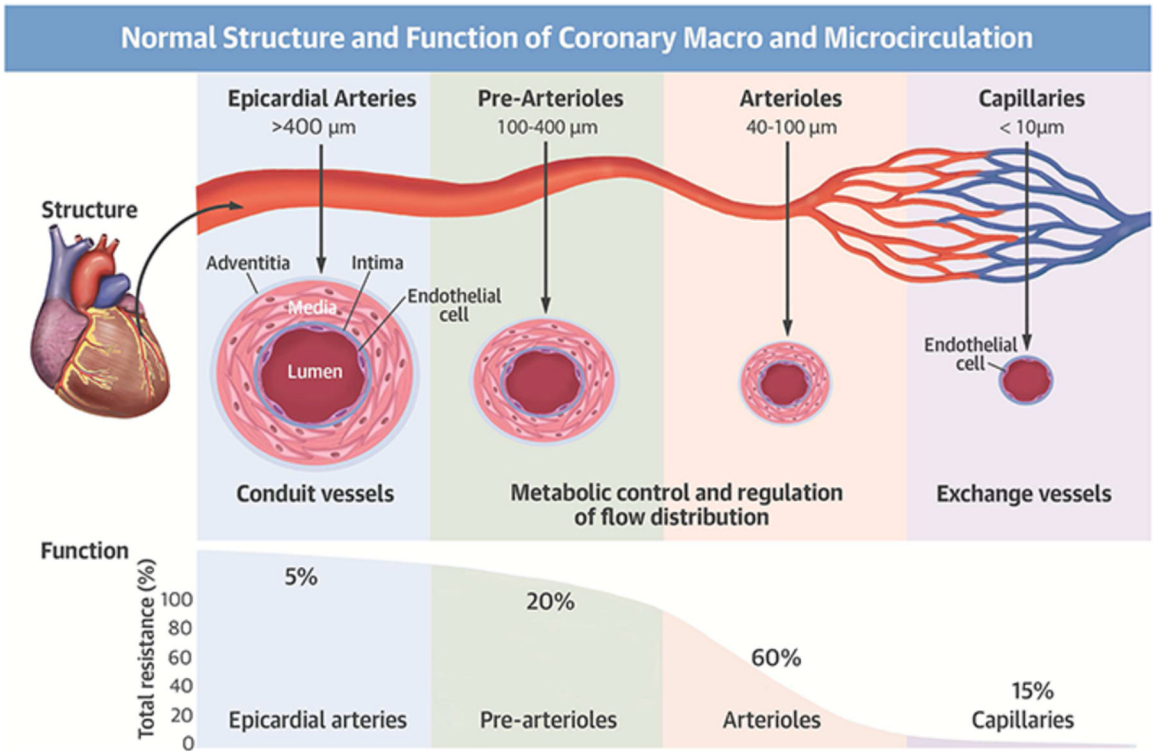

Figure 1. Normal Structure and Function of Coronary Macro- and Microcirculation.
Reprinted from Taqueti VR et al[25] with permission.

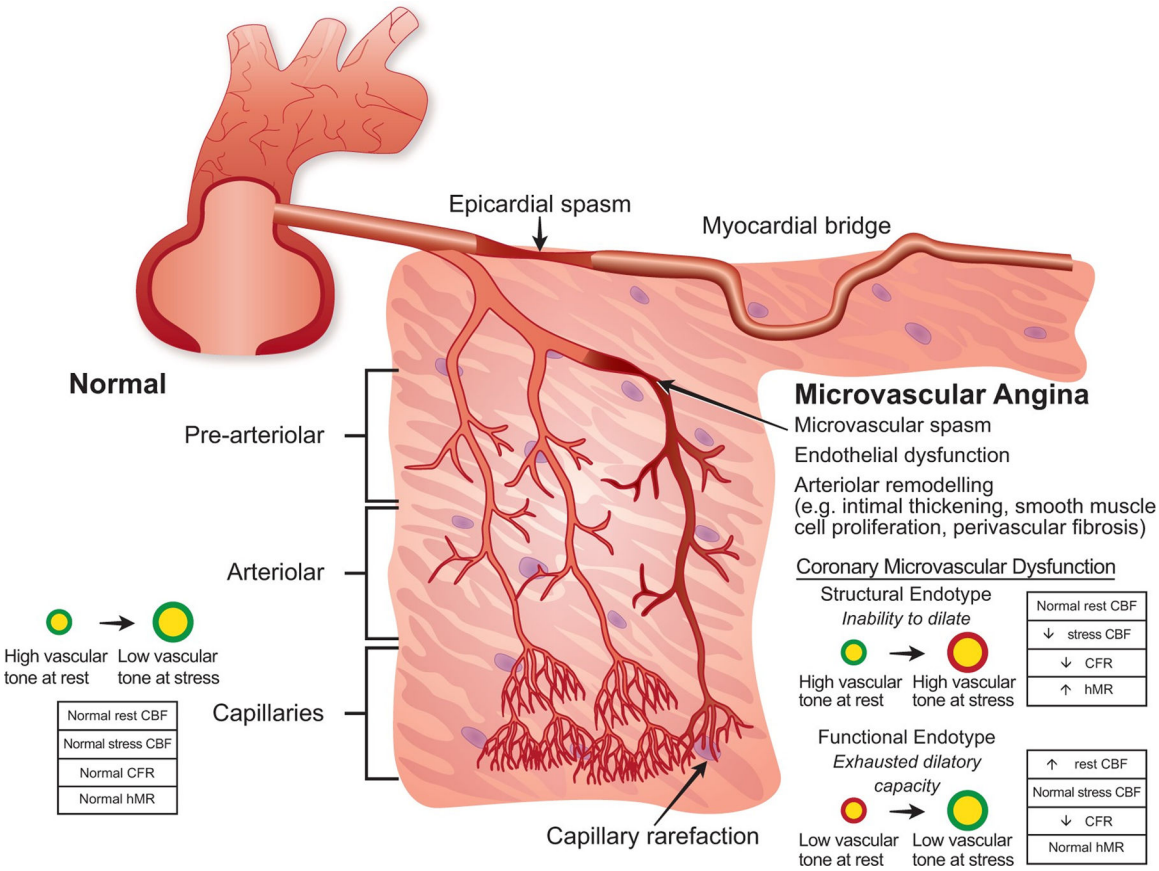

Figure 2. Coronary Vascular Dysfunction Mechanisms in Ischemia and No Obstructive Coronary Artery Disease.

CBF, coronary blood flow; CFR, coronary flow reserve; hMR, hyperemic index of microcirculatory resistance. Reprinted from de Silva R et al[73] with permission.

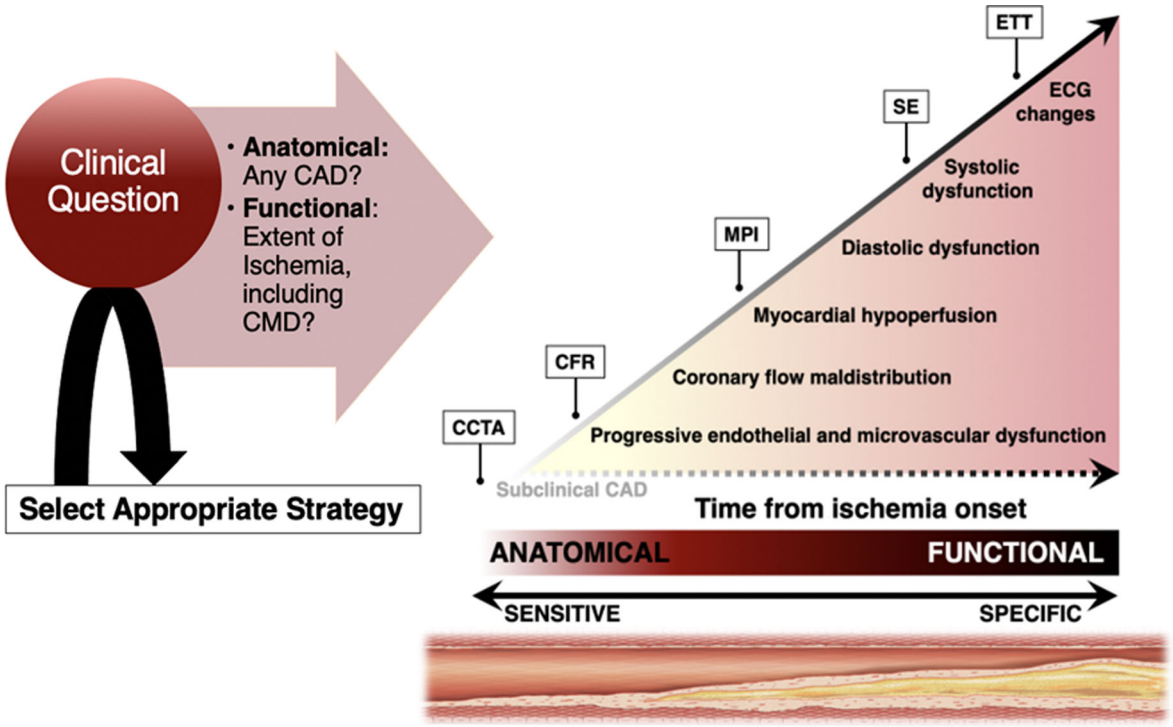

Figure 3. Noninvasive Diagnosis of Ischemic Heart Disease in Women.

Schematic of the ischemic cascade, a sequence of pathophysiologic events associated with CAD, and noninvasive multimodality imaging approaches for the evaluation of IHD in women. Anatomy-based (CCTA) and quantitative functional (CFR) imaging probes earlier events in the cascade than dose conventional testing, and as such may be especially useful in the evaluation of women. CCTA, coronary computed tomography angiography; CFR, coronary flow reserve; MPI, myocardial perfusion imaging; SE, stress echocardiography; ETT, exercise treadmill testing. Adapted from Taqueti VR et al[81] with permission.

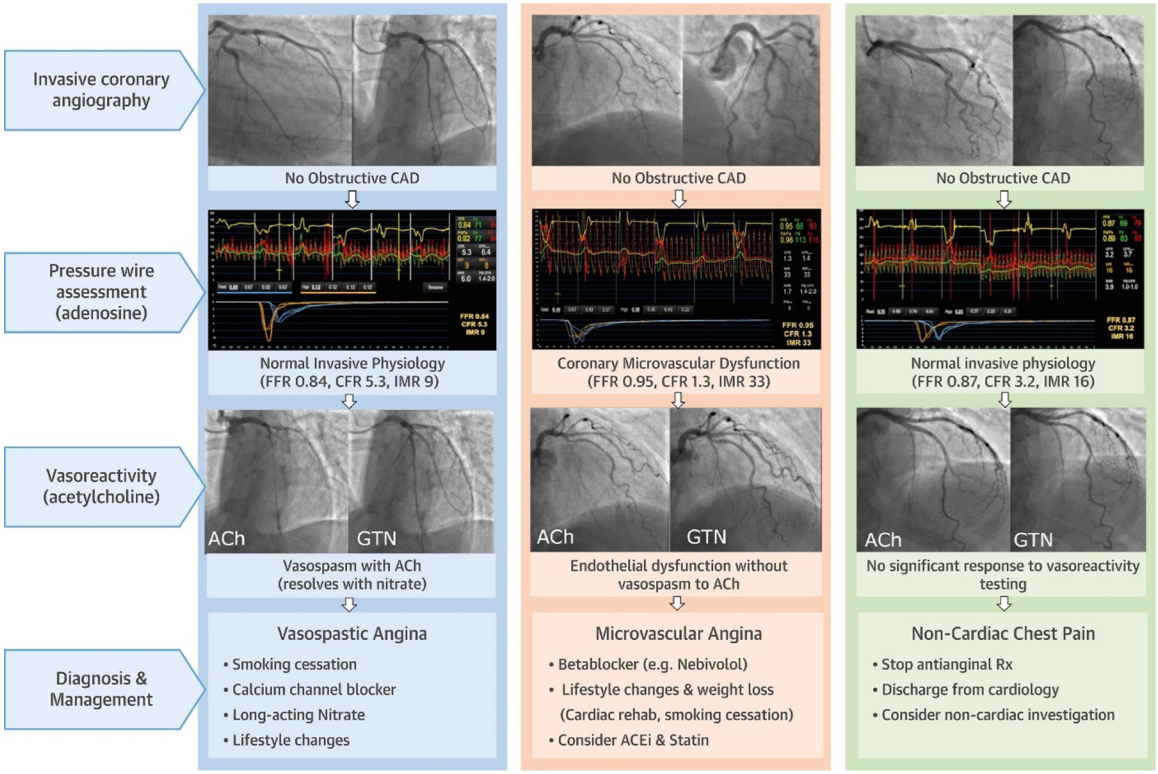

Figure 4. Stratified Medical Therapy Using Invasive Coronary Function Testing in INOCA.

The Coronary Microvascular Angina (CorMicA) Trial randomized patients with angina and no obstructive CAD to invasive coronary function testing linked to stratified medical therapy or standard care. Invasive coronary function testing included assessment of coronary flow reserve (CFR), index of microcirculatory resistance (IMR), fractional flow reserve (FFR), and vasoreactivity testing with acetylcholine (Ach) and nitroglycerin (GTN). Stratified medical therapy based on diagnosis of microvascular angina, vasospastic angina, vs noncardiac chest pain was associated with improved angina and quality of life. Reprinted from Ford TJ et al[46] with permission.

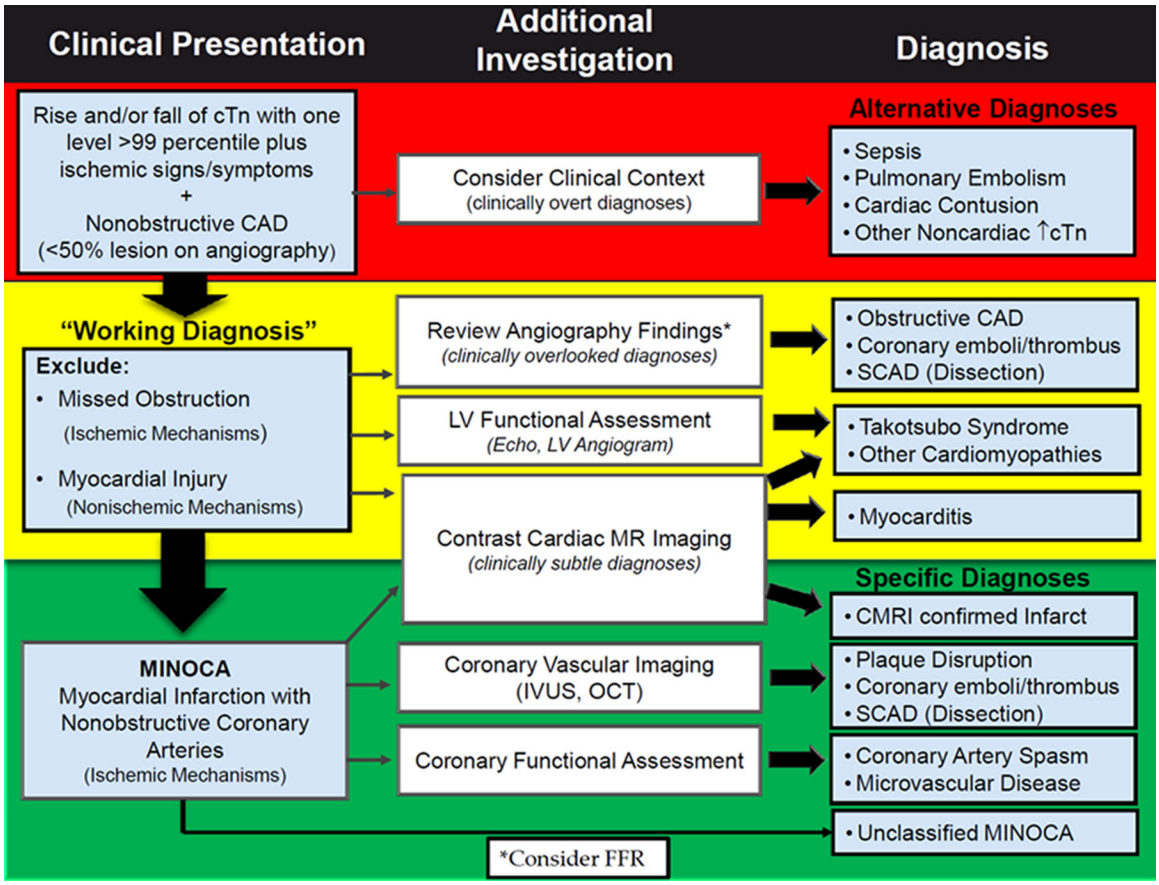

Figure 5. "Traffic light" clinical algorithm for the diagnosis of MINOCA.

CAD, coronary artery disease; FFR, fractional flow reserve; LV, left ventricular; MINOCA, myocardial infarction with no obstructive coronary arteries; SCAD, spontaneous coronary artery dissection. Reprinted from Tamis-Holland JE et al[124] with permission.

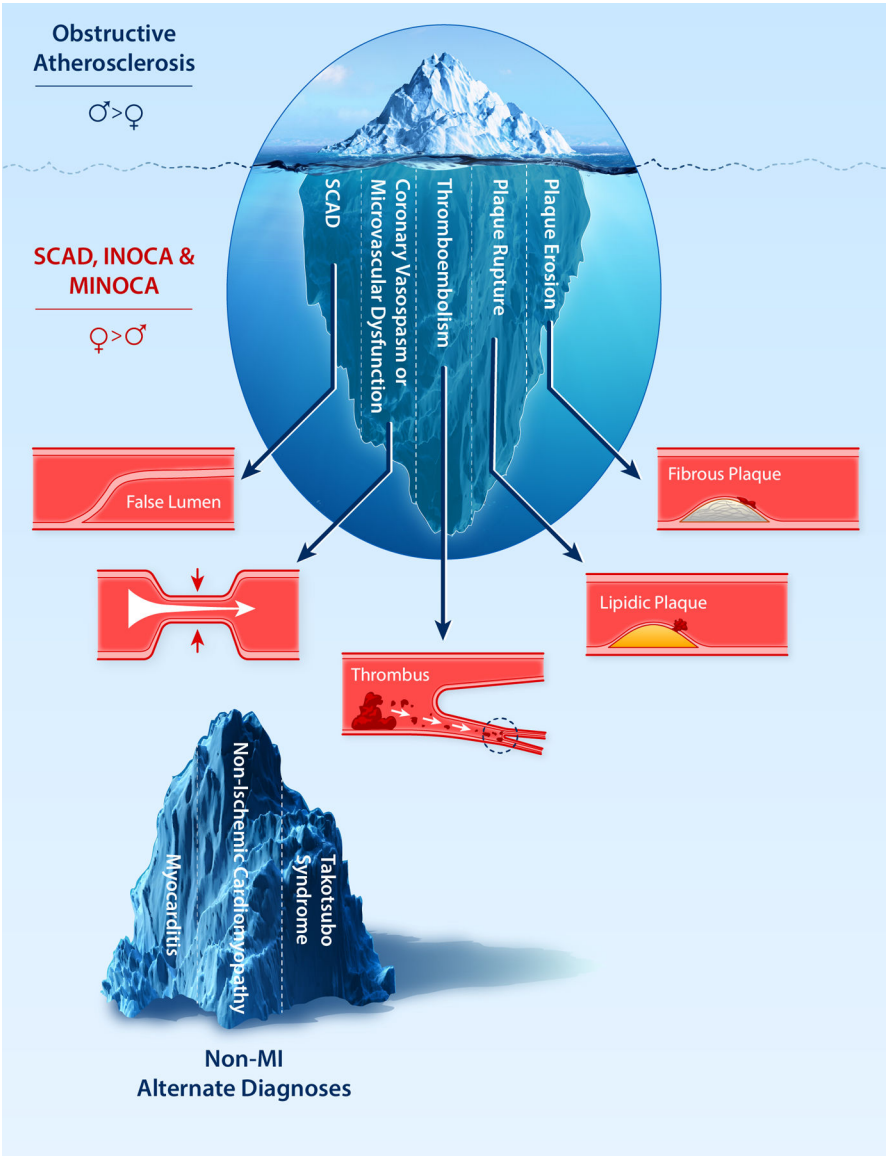

Figure 6. The Diverse Pathogenesis of Myocardial Infarction and Ischemia in Women.

While obstructive atherosclerosis is the most common etiology of MI and ischemia in women, it is just the tip of the iceberg when considering the diverse pathological mechanisms of coronary arterial function and disease in women. Coronary microvascular dysfunction and coronary vasospasm are common causes of ischemia with no obstructive coronary arteries (INOCA). Spontaneous coronary artery dissection (SCAD) is a cause of MI that can have an obstructive or nonobstructive angiographic appearance. MI in the setting of no obstructive coronary arteries (MINOCA) can be attributed to coronary vasospasm (epicardial or microvascular), thromboembolism, plaque rupture, or plaque erosion. Elevated troponin in women may also be due to non-MI etiologies, including myocarditis, nonischemic cardiomyopathy, and Takotsubo Syndrome. INOCA, ischemia with no obstructive coronary arteries; MI, myocardial infarction; MINOCA, myocardial

infarction with no obstructive coronary arteries; SCAD, spontaneous coronary artery dissection. (Illustration credit: Julia Huang and Ben Smith).