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SPOTLIGHT REVIEW

Sex differences in non-obstructive coronary artery disease

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Ischaemic heart disease is a leading cause of morbidity and mortality in both women and men. Compared with men, symptomatic women who are suspected of having myocardial ischaemia are more likely to have no obstructive coronary artery disease (CAD) on coronary angiography. Coronary vasomotor disorders and coronary microvascular dysfunction (CMD) have been increasingly recognized as important contributors to angina and adverse outcomes in patients with no obstructive CAD. CMD from functional and structural abnormalities in the microvasculature is associated with adverse cardiac events and mortality in both sexes. Women may be particularly susceptible to vasomotor disorders and CMD due to unique factors such as inflammation, mental stress, autonomic, and neuroendocrine dysfunction, which predispose to endothelial dysfunction and CMD. CMD can be detected with coronary reactivity testing and non-invasive imaging modalities; however, it remains underdiagnosed. This review focuses on sex differences in presentation, pathophysiologic risk factors, diagnostic testing, and prognosis of CMD.

Keywords Coronary microvascular dysfunction • Angina • Women

This article is part of the Spotlight Issue on Coronary Microvascular Dysfunction.

1. Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide in both men and women, and ischaemic heart disease (IHD) accounts for the majority of these deaths.[1] The prevailing paradigm for diagnosis and treatment of IHD relies on identification of obstructive coronary artery disease (CAD) in symptomatic patients. However, approximately two-thirds of women and one-third of men with stable IHD have no obstructive CAD on angiography.[2–7] No obstructive CAD is typically defined as <50% stenosis in any major epicardial coronary artery. Ischaemia with No Obstructive Coronary Arteries (INOCA) is associated with adverse cardiovascular outcomes despite absence of flow-limiting epicardial stenosis.[8–12] Over the past two decades, it has become increasingly clear that a large proportion of INOCA subjects, who are predominantly women, have coronary vasomotor disorders or coronary microvascular dysfunction (CMD). In CMD, vascular dysregulation due to endothelium-dependent and/or endothelium-independent mechanisms leads to a higher microvascular resistance and reduced coronary blood flow. It is estimated that approximately half of patients with INOCA have CMD, a condition that is associated with adverse cardiac events. CMD remains underdiagnosed and undertreated, partly because our diagnostic and therapeutic algorithms have focused on obstructive CAD detection and treatment (*Figure 1*).

Persistent and recurrent chest pain presentations in women is a major clinical problem that not only impacts prognosis but also contributes to anxiety from not having a clear diagnosis, impacts quality of life, and leads to elevated cardiovascular and estimated lifetime costs that rival that for obstructive CAD (*Figure 2*).[13] Women are also more likely to present with myocardial infarction with no obstructive CAD (MINOCA).[15,16] Data from >750 hospitals in the USA from 2007 to 2014 indicate that MINOCA occurs in 10.5% of women presenting with a myocardial infarction (MI) compared with 3.4% of men.[17] Furthermore, it is more common in patients <55 years of age and in African Americans and is less likely to be associated with traditional CAD risk factors including dyslipidaemia, hypertension, and diabetes mellitus.[18] In patients presenting with an ST-segment elevation MI (STEMI), 3.6% of women and 1.6% of men had MINOCA compared with 15% of women and 5.1% of men presenting with a non-STEMI.[19] Mechanistic studies reveal that plaque disruption may be present in up to 38% of cases.[20] Other coronary causes of MINOCA besides CMD include coronary vasomotor disorders, non-atherogenic spontaneous coronary artery dissection,[21] and coronary thrombi/emboli. It has been speculated that conditions of

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INOCA and MINOCA are expressions of an 'atherosclerotic continuum'.[22] Patients who have CAD (even if not obstructive) have worse outcomes compared with those with normal coronary arteries by angiography, and atherosclerotic burden is an important prognostic factor.[6,23] This review focuses on sex differences in presentation, risk factors, pathophysiology, and prognosis of CMD.

2. Definition and prognosis

There has been some confusion in the literature regarding the definition of CMD. The combination of angina, electrocardiogram (ECG) changes, and no obstructive CAD was previously referred to in the literature as 'cardiac syndrome X', although this term is now considered outdated as it included heterogeneous groups who did not always have assessments of coronary flow reserve (CFR) or endothelial function.[14] In order to clarify definitions and terminology, and advance international collaborative research, the International Coronary Vasomotor Study Group (COVADIS) has defined criteria for diagnosis of coronary vasomotor disorders and CMD.[24,25]

Coronary vasomotor disorders, endothelial dysfunction, and CMD can be integrally assessed by invasive coronary reactivity testing (CRT), using vasoactive agents such as adenosine, acetylcholine, and nitroglycerine.[26–28] A comprehensive CRT protocol involves using a Doppler flow wire or a thermodilution wire to assess the microvasculature. Doppler-derived measures of CFR and hyperaemic microvascular resistance are used to diagnose CMD.[29] Thermodilution technique is used to measure CFR and index of microcirculatory resistance (IMR), which is considered a more accurate measure of microvasculature, since CFR is influenced by epicardial disease[30] (*Figure 3*). CMD by the COVADIS criteria is defined as (i) symptoms suggestive of myocardial ischaemia, (ii) objective evidence of ischaemia, (iii) absence of obstructive CAD, and (iv) impaired CFR and/or evidence of coronary microvascular spasm, which is defined as reproduction of symptoms and ischaemic ECG changes, but no visible epicardial coronary spasm during acetylcholine testing.[24] Per COVADIS criteria, if there is reproduction of symptoms and ischaemic ECG shifts with transient total or subtotal coronary artery occlusion, then vasospastic angina due to epicardial vasospasm is diagnosed.[25] These definitions do have limitations in that often vasomotor disorders and CMD can present with no objective evidence of ischaemia on conventional stress testing, and clinicians should consider these in the differential diagnosis of patients with recurrent chest pain.

While there are no specific US guidelines on diagnosis and management of CMD, the European guidelines on stable IHD recommend testing for vasomotor disorders and CMD in symptomatic patients.[31] In the WISE study, a CFR of <2.3 was prognostic of future cardiovascular events in women with INOCA.[8] CMD is highly prevalent in both men and women,[32] and a low CFR is associated with adverse cardiovascular outcomes in both sexes. Evidence from WISE suggests that women with CMD have an adverse prognosis, with a 2.5% per year rate of major adverse cardiovascular events (MACE) (hospitalization for acute coronary syndrome, heart failure, stroke, or cardiovascular death).[10] Another study showed that women with severely decreased CFR (<1.2) were at a significantly increased risk of CVD events [hazard ratio (HR) 2.49, 95% confidence interval (CI) 1.16–5.38] compared with men.[33] Although CRT is considered safe and effective,[27] non-invasive imaging with echocardiography, positron emission tomography (PET), and cardiac magnetic resonance (CMR) can be used to diagnose CMD.[31,34]

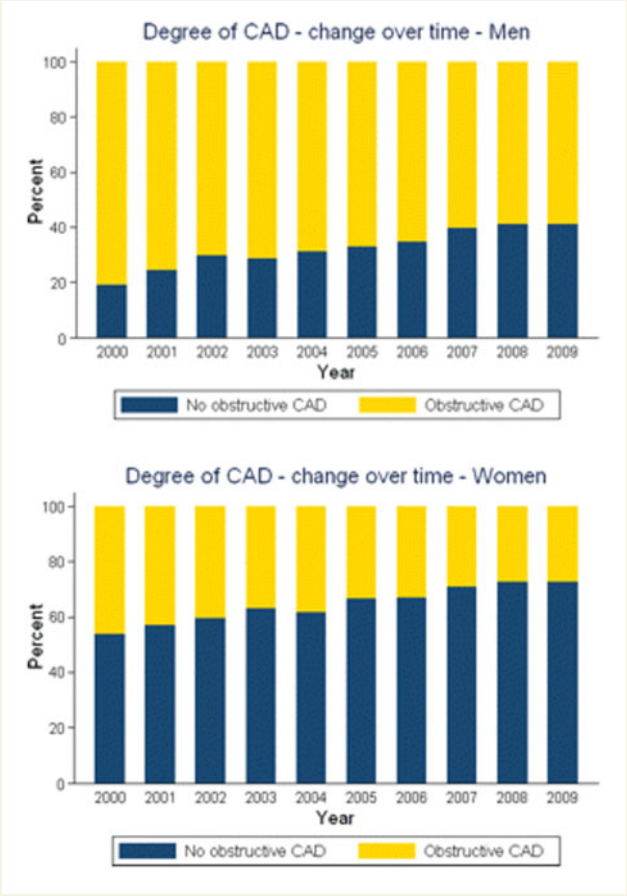

Figure 1 Degree of CAD by examination year and gender. Reprinted with permission from Jespersen *et al.*[7]

It is important to note that patients with significant CAD can also have CMD; sex differences in relationships between CMD and epicardial atherosclerosis are under investigation. In patients presenting with a STEMI, no sex differences in acute reperfusion injury have been found as measured by IMR or CFR.[35] IHD due to obstructive CAD usually is treated with anti-anginal, anti-atherosclerotic medications, and percutaneous coronary intervention, given clear guideline recommendations, but INOCA is undertreated. Furthermore, testing to detect vasomotor disorders or CMD in INOCA patients is not routinely done, and therefore, CMD remains underdiagnosed. Provocative testing may be underused due to concerns related to safety and adverse outcomes, but a systematic review including 9444 patients showed that major (0.8%) and minor (4.7%) complications from pharmacologic testing were low. Thus, provocative testing is not only effective but also safe and should be used for diagnosis when it is done at experienced centres.[27,36,37] Usual care for patients with INOCA is not well-defined and rates of prescription use are low.[7,38,39] An analysis of medication use for all patients ≥20 years with stable angina who underwent index coronary angiography in British Columbia, Canada, in 2008–2010 revealed that only 26% of patients with INOCA were prescribed anti-anginal medication (beta-blockers and/or calcium channel blockers) or endothelial modifying agents [angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and/or statins] within 90 days of angiography.[40] In the Cath-PCI registry of 1 489 745 patients undergoing coronary angiography in the

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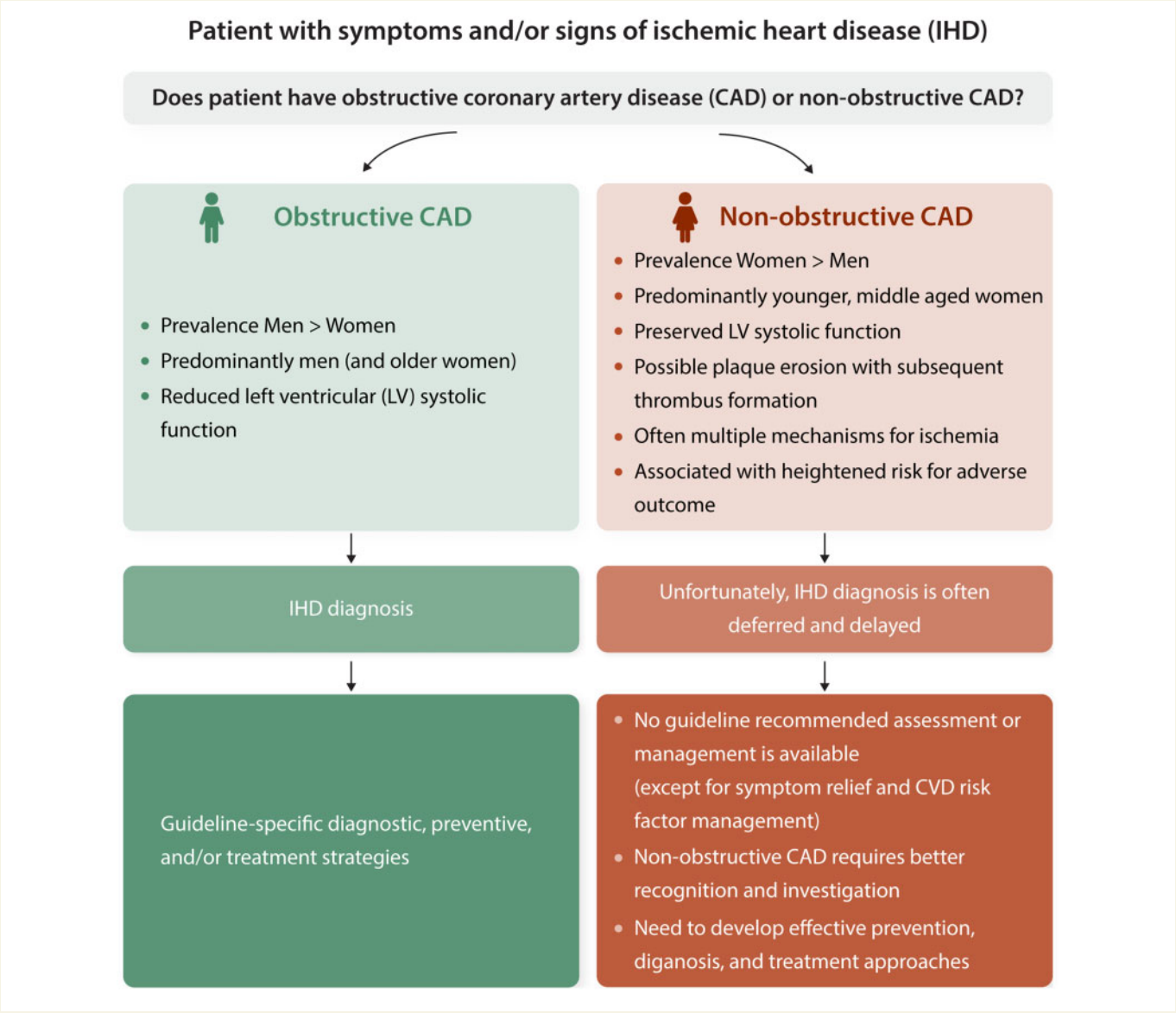

Figure 2 Comparison of obstructive vs. non-obstructive CAD. Reprinted with permission from Pepine *et al.*[14]

USA, 15.9% had no obstructive CAD. Compared to those with obstructive CAD, those with no obstructive CAD were less likely to receive secondary prevention therapies.[41] The Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR) is an ongoing multi-site, randomized clinical trial of medical therapy vs. usual care in women with no obstructive CAD. The medical therapy arm includes intensive statin therapy (atorvastatin or rosuvastatin), in addition to ACE inhibitors/ARBs and aspirin.[42]

3. Symptoms

Both men and women can present with typical and atypical symptoms of IHD, although women are more likely to present more with a variation in symptoms, such as shortness of breath, nausea, weakness, fatigue, and jaw pain.[43] For women, angina is often different in location and milder in intensity, with more subtle, non-specific symptoms which can be commonly misdiagnosed. It should be noted that the labelling 'typical' angina fits best in obstructive CAD, whereas non-obstructive CAD and vasomotor disorders provokes more variable symptoms, often with a crescendo decrescendo pattern that may change over time. Effort-induced, retrosternal chest pain or discomfort, with or without dyspnoea, is also characteristic of CMD.[24] These symptoms can also present during hours after physical exercise. Extreme tiredness is a frequently occurring additional complaint that interferes with daily activities and work ability. The term 'microvascular angina' was coined to describe the clinical syndrome of angina or ischaemic symptoms in the absence of flow-limiting CAD.[24] Today, this term is commonly used to describe symptoms in patients with CMD. It should be noted that CMD patients seem to respond less dramatically to short-acting nitrates, whereas long-acting nitrates may aggravate symptoms due to a 'stealing' effect.

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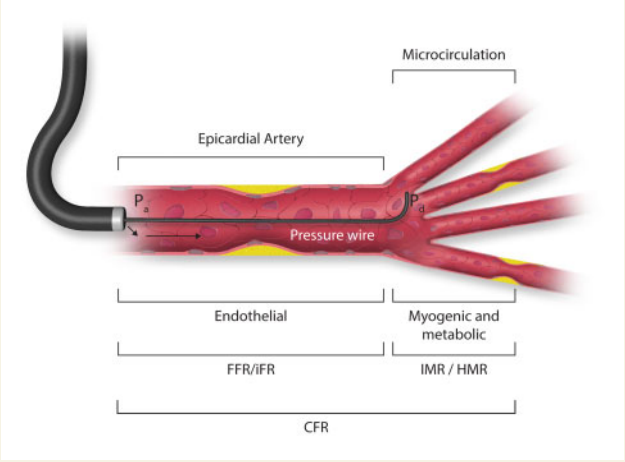

Figure 3 Coronary microcirculation assessment. CFR and IMR/HMR are used to detect CMD. CFR is an integrative measure that is influenced by epicardial atherosclerosis. CFR, mean hyperaemic flow velocity/mean resting flow velocity and resting Tmn/hyperaemic Tmn; FFR, Pd/Pa during maximum hyperaemia; HMR, Pd/mean hyperaemic flow velocity; iFR, Pd wave-free period/Pa wave-free period; IMR, Pd at maximal hyperaemia X hyperaemic Tmn; Tmn, an inverse correlate to absolute coronary flow.

4. Sex differences in risk factors

4.1 Traditional risk factors

Traditional risk factors such as hypertension, hyperlipidaemia, and diabetes mellitus are associated with CMD, endothelial dysfunction, and progression of atherosclerosis.[44] Women typically have a greater burden of these risk factors, despite less obstructive CAD.[45–47] While risk factor control is the cornerstone in CMD treatment, these factors are not always predictive of CMD. CMD may be one manifestation of a more generalized, systemic process that impacts the microvasculature in multiple organ systems leading to nephropathy, retinopathy, lacunar stroke, and so on.[48]

In hypertension, remodelling of arterioles as well as capillary rarefaction contribute to a diminished CFR.[44,49–51] Premenopausal women are at a higher risk of hypertension-induced end organ damage compared with age-matched men.[52] During the menopause transition, blood pressure begins to rise and load-dependent changes as well as diastolic dysfunction begin to contribute to dyspnoea on exertion.[53,54] Pathophysiologic links between CMD and future development of heart failure, and particularly heart failure with preserved ejection fraction (HFpEF), are under investigation.[55–57] Dyslipidaemia has also been associated with decreased CFR, with an inverse relationship between CFR and low-density lipoproteins,[58,59] whereas high levels of high-density lipoproteins and low levels of triglycerides were associated with improved resting microvascular blood flow.[60] Statins, as either monotherapy or in combination with other agents, have beneficial effects in patients with coronary endothelial dysfunction.[61–63]

Among both type 1 and type 2 diabetics, there is similarly reduced myocardial blood flow (161 ± 18% vs. 185 ± 19%, respectively) compared with controls (351 ± 43%).[64] Diabetic women are found to have a lower CFR and impaired diastolic function compared with diabetic men.[65] A study of 462 patients with metabolic syndrome demonstrated a lower CFR (2.5 ± 1.0) than those without metabolic syndrome (3.0 ± 0.9, $P = 0.004$).[66] Bajaj *et al.*[67] followed 827 obese patients for 5.6 years to describe the role of obesity on CFR and adverse events. This study found that CFR decreased with increasing body mass index, and patients with impaired CFR had adverse CVD events, such as MI, heart failure, or death (5.7% vs. 2.6%; $P = 0.002$). Another study in 959 patients (70% female) showed an inverse relationship between CFR and metabolic impairment, and this was also associated with major adverse cardiac events.[68]

The role of physical activity has also been investigated in patients with CMD. Women with angina and non-obstructive CAD have been found to have markedly reduced exercise capacity compared with controls. In one study, peak VO_2 in patients with CMD was 17.3 vs. 27.3 mL/kg/min in controls ($P = 0.001$).[69] In four small randomized controlled trials of cardiac rehabilitation in patients with non-obstructive CAD and angina, completion of exercise training led to symptom benefit and increased exercise capacity, although data are limited to a small number of predominantly female patients.[70] Given the beneficial role of supervised exercise training on cardiac risk factors, improvement in angina, as well as cardiac morbidity and mortality,[71–74] exercise is an important component in CMD management.

4.2 Unique sex-specific risk factors

In 2011, the American Heart Association published guidelines on prevention of heart disease in women that included adverse pregnancy outcomes (i.e. pre-eclampsia, eclampsia, pregnancy-induced hypertension, gestational diabetes) and autoimmune disorders [i.e. systemic lupus erythematosus (SLE), rheumatoid arthritis] as IHD risk factors.[75,76] Current risk stratification tools such as the Framingham risk score, Reynolds risk score,[77] and atherosclerotic CVD pooled-cohorts risk assessment underestimate IHD risk in women due to their exclusion of risk factors unique to women.[78] Compared with Framingham risk score, the Reynold risk score provides a modestly better prediction among a diverse sample of US women.[79] Due to lack of current risk prediction models incorporating women-specific risk factors, clinicians should recognize the limitations of the risk scores.

4.2.1 Autoimmune/inflammatory disorders

Inflammation is a factor that contributes to CMD. Elevated high-sensitivity C-reactive protein has been associated with impaired CFR in CMD patients.[80,81] In a retrospective study including 150 MINOCA patients, elevated C-reactive protein level at admission was an independent predictor for major adverse cardiac events (HR 1.47, 95% CI 1.06–2.07; $P = 0.005$).[82] Moreover, the role of inflammation in the pathophysiology of coronary spasm has been rigorously demonstrated by ^{18}F-labelled fluoro-2-deoxyglucose (^{18}F-FDG) PET/CT in the ADIPO-VSA trial.[83] These findings are in keeping with significant cardiovascular events reduction yielded by targeted anti-inflammatory therapies, as by interleukin-1β inhibition.[84] For chronic autoimmune inflammatory conditions, CMD is likely related to both endothelial dysfunction and inflammatory status and should be considered on the differential when women present with chest pain and no obstructive CAD.[85,86] Patient with SLE, a chronic inflammatory disorder that disproportionately affects women, have increased rates of CMD compared with healthy controls.[87] In a case–control study, CFR (2.44 ± 0.78 vs. 3.87 ± 0.92; $P < 0.001$) was severely decreased in patients with SLE or rheumatoid arthritis in the absence of significant epicardial disease compared with controls.[86] Patients in this study were deemed to have low levels of disease activity, but still had

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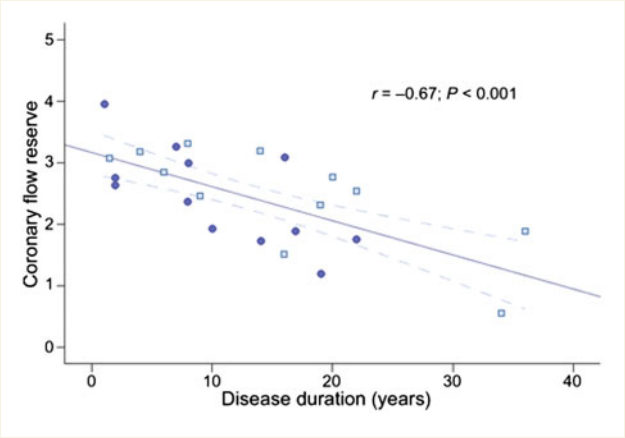

Figure 4 Relation between CFR and autoimmune disease duration in years. Reprinted with permission from Recio-Mayoral *et al.*[86]

reduced CFR.[85,88] Patients with SLE who have persistent chest pain and no obstructive CAD were also shown to have abnormal myocardial flow reserve by CMR imaging[89] (*Figure 4*).

Patients with ankylosing spondylitis, a condition more common in men,[90] also have significantly lower CFR than healthy controls (2.20 ± 0.46 vs. 3.02 ± 1.50, $P \leq 0.0001$).[91] Batko *et al.*[92] demonstrated that time to peak hyperaemia was almost twice as long in patients with ankylosing spondylitis in comparison with healthy controls [9.4 s (6.8–12.5) vs. 5.2 s (3.8–6.1), $P = 0.001$]. With capillaroscopy, it was found that ankylosing spondylitis was associated with increased neo-angiogenesis and perivascular oedema. Both perivascular oedema and microvascular function improved after patients were treated with a tumour necrosis factor-alpha inhibitor for 3 months.

4.2.2 Adverse pregnancy outcomes

Pregnancy-related complications, such as hypertensive pregnancy disorders and gestational diabetes, have been associated with premature endothelial dysfunction and CVD risk. In several meta-analyses, it was found that pre-eclampsia, occurring in 3–5% of all pregnancies, has the highest risk with a more than two-fold increased risk for IHD.[93,94] Levels of inflammatory markers often remain elevated even decades after index pregnancies and at least 30% of women show signs of premature subclinical atherosclerosis.[95–97] In large population-based studies recurrent miscarriages (≥2) have also been linked to a higher CVD risk and genetic involvement.[98,99] Women with a history of pre-eclampsia have a higher risk of developing diabetes (HR 1.82, 95% CI 1.26–2.62) compared with women with no history of pre-eclampsia after adjusting for age, primigravidity, and gestational diabetes.[100] It has been shown that women with a history of pre-eclampsia have impaired brachial artery flow-mediated dilation immediately postpartum[101] as well as 15–25 years from the index event.[102] The obstetric history is therefore crucial to optimize risk prediction and to start timely prevention in middle-aged women.

4.2.3 Polycystic ovarian syndrome

Women with polycystic ovarian syndrome (PCOS) are at increased risk for developing diabetes, dyslipidaemia, metabolic syndrome, and hypertension.[103–105] Insulin resistance and hyperandrogenism lead to more than four-fold increased risk of diabetes in women with PCOS and subsequent endothelial dysfunction.[106–108] Multiple studies have indicated that women with PCOS have endothelial abnormalities.[109–111] A case–control study found that skin microvascular perfusion was decreased in response to acetylcholine in patients with PCOS compared with healthy controls.[112] However, there is conflicting evidence as to whether peripheral measurements of skin blood flow are related to CMD in patients with PCOS.[113,114]

Usselman *et al.*[115] investigated whether hyperandrogenism was related to endothelin-B receptor-mediated microvascular endothelial dysfunction in women with PCOS, independent of the effects of insulin resistance and obesity. This study demonstrated a reduced vasodilatory response to endothelin-1 in lean women with androgen excess PCOS (AE-PCOS) compared with lean controls (0.59 ± 0.08 nM vs. 0.49 ± 0.09, $P < 0.05$), but not compared with obese AE-PCOS women, indicating that obesity does not worsen the effects of PCOS on the microvasculature. In both lean and obese women with PCOS, administering ethinyl oestradiol increased endothelin-1-mediated vasodilatation (0.29 ± 0.21 nM, 0.47 ± 0.09 nM) for lean and obese PCOS women, respectively by improving the impaired endothelin-B receptor signalling and nitric oxide availability.

4.2.4 Sex hormones and menopause

Sex steroid hormones are increasingly acknowledged as being relevant to immune response and vascular inflammation, having an importantly different impact on women and men throughout their lifetime.[116–118] Whereas in adulthood men tend to have a higher inflammatory predisposition than women, the opposite accounts for women after menopause.[119,120] Physiological levels of oestradiol (E2) are generally protective against inflammation. However, they also have paradoxically pro-inflammatory roles under different circumstances, depending on timing in the disease process and reproductive status.[121] Reduced oestrogen levels after menopause are associated with altered vascular function, enhanced inflammation and up-regulation of other systems such as the renin–angiotensin system and the sympathetic nervous system.[122]

Cardiovascular risk factors such as diabetes, hypertension, and hyperlipidaemia increase after menopause, and women who present with CMD are more likely to be mid-life women, who also have high plaque burden on intravascular ultrasound (IVUS).[123] With declining oestrogen levels, an altered ratio of testosterone/oestrogen may be contributing to the pathogenesis of vascular dysfunction and increased CVD risk. Oestrogen has beneficial effects on the vasculature as shown in basic science and observational studies. Transdermal oestrogen improved coronary reactivity in women with angina and no obstructive CAD,[124] and 17-β-oestradiol in women decreased coronary vasoconstriction in the non-stenotic segments in women with CAD.[125] However, in the Women's Health Initiative, which tested oestrogen with progestin vs. placebo, hormone therapy was associated with adverse outcomes.[126] Current recommendations by the North American Menopause Society recommend that if hormone therapy is needed, it should be used for the shortest duration and for treatment of menopausal symptoms only and not for primary CVD prevention.

4.2.5 Psychological risk factors and mental stress

Psychological risk factors such as depression and anxiety are highly prevalent in women with INOCA and may contribute to abnormal vascular reactivity, predominantly through autonomic dysfunction and inflammation.[127] CMD may be a contributor to mental stress-associated adverse outcomes since myocardial ischaemia from mental stress is independent

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of CAD severity. Mental stress has been associated with coronary endothelial dysfunction, and women may be more susceptible to mental stress.[128] Vaccarino et al.[129] reported a sex difference in mental stress-induced myocardial ischaemia (MSIMI) in younger women (≤50 years old) with a history of MI compared with age-matched men. These women had a higher summed difference score (SDS) on perfusion imaging (3.1 in women vs. 1.5 in men, $P = 0.029$) and had twice the rate of MSIMI (SDS ≥ 3; 52% vs. 25%). It also appears that women and men have distinct cardiovascular reactivity mechanisms for MSIMI. Sullivan et al.[130] showed that women with MSIMI have a proclivity towards vasoconstriction-induced MSIMI, whereas men with MSIMI is driven by supply-demand mismatch due to increased haemodynamic workload. A study of 53 middle-age male twin pairs (106 twins) assessed the relationship between depression and CFR using PET imaging.[131] No difference in myocardial ischaemia between twins with and without depression was observed. However, among dizygotic twin pairs, CFR was 14% lower in twins with depression than in their brothers without depression (2.36 vs. 2.74, $P < 0.03$). This relationship suggests there may be a shared genetic pathway between depression and microvascular dysfunction.

Women are more susceptible to stress-induced myocardial ischaemia and takotsubo syndrome after a significant emotional or physical stressor.[132,133] CMD has been implicated in the pathogenesis of takotsubo syndrome in multiple studies.[134–136] In a prospective study of women with a history of stress-induced cardiomyopathy, 228 cases were evaluated for coronary epicardial and microvascular responses to acetylcholine, nitroglycerine, and adenosine. The median increase in peak coronary blood flow (CBF) in women with stress-induced cardiomyopathy receiving acetylcholine was 13.1% [interquartile range (IQR) -18.6 to 55] compared with 103% (IQR 75–149) in the control group.[134]

4.3 Non-invasive diagnostic techniques for CMD

Stress echocardiography, Doppler echocardiography, cardiac PET, and cardiac magnetic resonance imaging (MRI) can be used to diagnose CMD. Single-photon emission computed tomography (SPECT) does not provide CFR, but an abnormal SPECT in a patient with no obstructive CAD may indicate endothelial dysfunction or CMD. In a study of 59 postmenopausal women, 21 showed perfusion defects by SPECT imaging and were more likely to exhibit endothelial dysfunction (57% vs. 29%) than those without perfusion defects.[137] Cardiac PET is able to quantify myocardial blood flow and CFR, and thus is a preferred method for the evaluation of CMD.[138] Recently, PET was used to compare sex differences in the frequency and severity of CMD. This study showed that the frequency of CFR < 2.0, which was used as the diagnostic threshold for CMD, was similar in both men ($n = 206$, 51%) and women ($n = 435$, 54%).[32] PET-derived CFR has been shown to be highly reproducible,[139] and this study highlighted its utility for diagnosing CMD as part of routine clinical practice.

CMR imaging can also be used to assess CMD using semi-quantitative myocardial perfusion reserve index; as software processing improves and availability of CMR increases, this may be a preferred test in women due to lack of radiation exposure and its ability to identify oedema, fibrosis, and scar.[140–143] Liu et al.[144] evaluated whether CMR could be used to diagnose CMD in patients with angina. The optimal myocardial perfusion index threshold was found to be 1.4 among patients with obstructive CAD and this threshold was shown to also accurately detect inducible ischaemia due to CMD [area under the curve (AUC) 0.90, 95% CI 0.80–0.96; $P < 0.0001$], with a specificity of 95% (95% CI 82–99%), and a sensitivity of 89% (95% CI 78–98%).

4.4 Invasive techniques

Intravenous infusion of adenosine and intracoronary injections of acetylcholine and nitroglycerine allow assessment of microvascular and macrovascular, endothelium- and non-endothelium-dependent pathways.

4.4.1 Endothelium-dependent mechanisms

Endothelium-dependent microvascular function is commonly assessed by acetylcholine. Normal coronary endothelial function results in an approximately three- to four-fold increase in coronary blood flow in response to acetylcholine. An abnormal response would be an attenuated increase, no change, or a decrease in CBF after intracoronary acetylcholine administration.[145] After acetylcholine infusion, vessels with intact endothelium vasodilate, whereas dysfunctional vessels or disrupted endothelium will result in vasoconstriction due to activation of muscarinic receptors on vascular smooth muscle cells.[146] Change in coronary blood flow in response to acetylcholine can be calculated to detect CMD.

4.4.2 Endothelium-independent mechanisms

Adenosine tests for endothelial-independent microvascular function. Endothelium-independent microvascular function is associated with structural vascular alterations and changes in smooth muscle cells.[147] Nitroglycerine directly acts on vascular smooth muscle. It results in an endothelium-independent evaluation of the coronary epicardial arteries as the coronary microvasculature lacks the enzyme needed to convert nitroglycerine to its active form, nitric oxide. Therefore, nitroglycerine administration produces dilation of coronary vessels greater than 0.2 mm in diameter and has no effect on smaller coronary vessels.[145] Adenosine stimulates the adenosine A2 receptor on smooth muscle cells and primarily acts on vessels less than 0.15 mm in diameter.[148] It therefore mainly assesses changes in coronary microvasculature resistance defined as CMD, with a CFR of <2.0 or 2.5 or IMR ≥25, depending on the methodology and cut-off used.[8,24,30,149]

4.4.3 Sex differences in coronary vasomotor disorders by invasive testing

Various studies have investigated sex differences in invasive CRT. Sara et al.[150] studied 1498 patients presenting with chest pain and non-obstructive CAD (34.9% males, mean age 51.1 years). This study evaluated impaired CFR (≤2.5) and coronary vascular dysfunction defined as either microvascular dysfunction (maximal percentage increase in coronary blood flow in response to acetylcholine of ≤50%) or epicardial dysfunction (a decrease in coronary artery diameter of ≥20% in response to acetylcholine). Two-thirds of all patients had coronary vascular dysfunction and women were more prevalent in both the microvascular dysfunction and epicardial dysfunction groups. In a multivariable analysis, age was the only variable that independently predicted abnormal microvascular function, but female sex was associated with abnormal microvascular function, with an odds ratio of 1.21 (95% CI 0.98–1.40) compared with men. A recent study followed 224 women over a median of 9.7 years and showed that low CFR was a predictor of MACE (HR 1.06, 95% CI 1.01–1.12; $P = 0.02$) and low CBF was associated with both increased mortality (HR 1.12, 95% CI 1.01–1.24; $P = 0.04$) and MACE (HR 1.11, 95% CI 1.03–1.20; $P = 0.006$)[151] (*Figure 5*).

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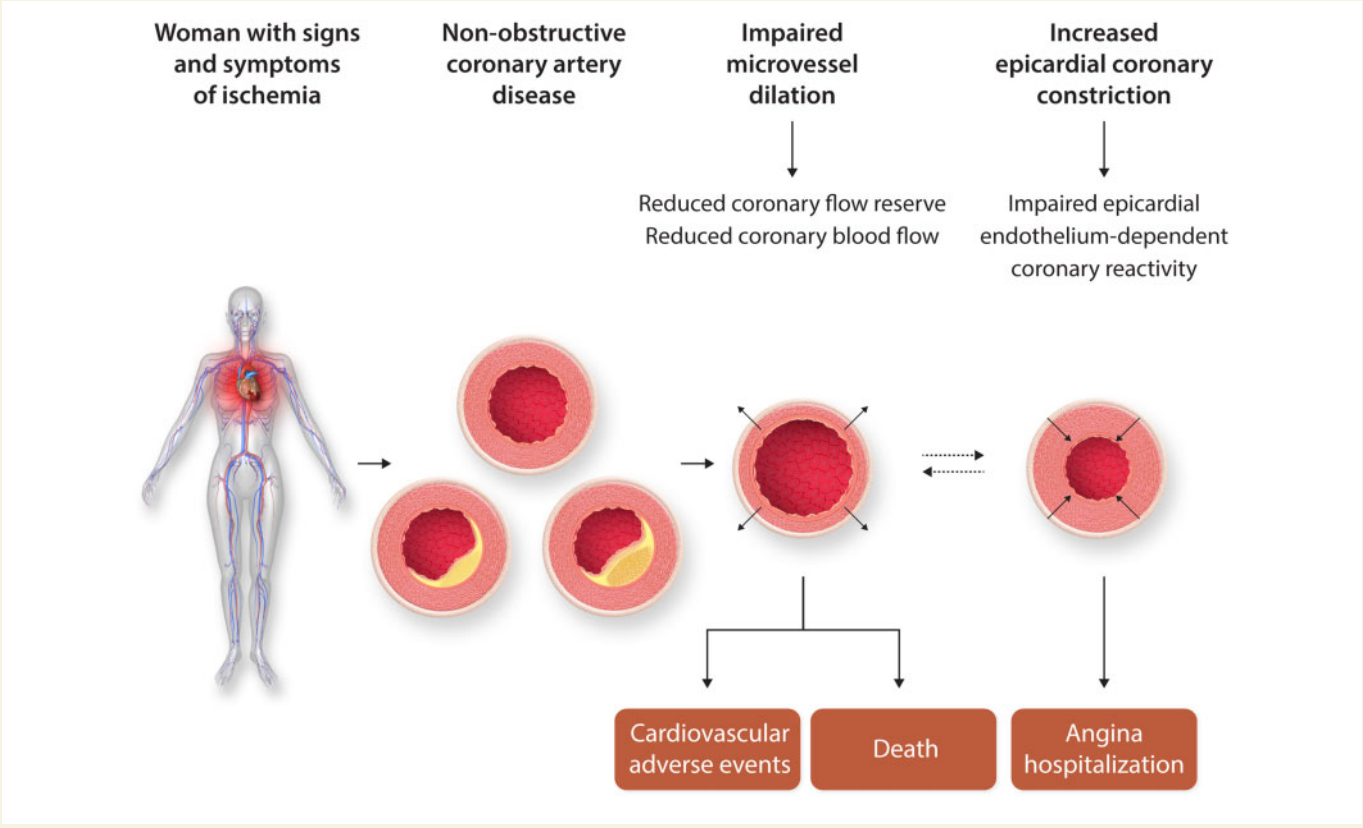

Figure 5 Women with signs and symptoms of INOCA have abnormal coronary reactivity and adverse outcomes. Reprinted with permission from AlBadri *et al.*[151]

Aziz *et al.*[152] evaluated 1379 patients with stable angina and non-obstructive CAD (42% males, mean age 62 years) and found that a pathological acetylcholine test is more common in women compared with men (70% vs. 43%; $P < 0.001$). A pathological test was either defined as having reproducible symptoms, ischaemic ECG changes, and diffuse or focal vasoconstriction of an epicardial vessel of ≥75% or reproduction of symptoms, ischaemic ECG shift, but no criteria for epicardial vasospasm (CMD). In a multivariable logistic regression model, the sex difference was significant with a female to male odds ratio for CMD and epicardial vasospasm of 4.2 (95% CI 3.1–5.5; $P < 0.001$) and 2.3 (95% CI 1.7–3.1; $P < 0.001$), respectively. Women were more sensitive to acetylcholine with vasomotor dysfunction occurring at lower doses compared with men. Patients with effort-related symptoms and a mix of effort and resting symptoms were more likely to have CMD than epicardial vasospasm. In this study, a total of 763 patients (55%) had undergone a non-invasive stress test before vasomotor testing. Non-invasive stress tests consisted of SPECT with pharmacologic stress, cardiac stress MRI, exercise stress echocardiography, and exercise ergometry. Of the 763 tests, 210 (27.5%) were abnormal. There was no association between an abnormal non-invasive stress test and an overall positive acetylcholine test, for either CMD or epicardial vasospasm.[152] Sara *et al.*[150] also did not find a correlation between invasive vasomotor test results and non-invasive ischaemia detection.

In a study of 718 patients (mean age 56.3 years, 49.7% males) with angina-equivalent symptoms and no CAD, 60% had coronary vasomotor dysfunction. A total of 33% had CMD, 20% had epicardial vasospasm (defined as a luminal narrowing of ≥ 50% with reproduction of symptoms) and 7% had a combination of both. Patients with CMD were more likely to be women (39.3% vs. 25.5%; $P < 0.001$) and have effort-related symptoms. Patients with epicardial vasospasm were more likely to be men with angina at rest.[153]

In a study of 139 patients (77% women) with angina and no obstructive CAD who underwent comprehensive CRT and IVUS, coronary vascular abnormalities were found in 77% of the patients. Endothelial dysfunction (defined as a decrease in coronary diameter of >20% after acetylcholine) was present in 44%, while 21% had an abnormal IMR of ≥25. A myocardial bridge (MB) was present in 58% of patients.[149] A subsequent study showed that IMR was similar between women and men (20.7 ± 9.8 vs. 19.1 ± 8.0; $P = 0.45$), but CFR was lower in women (3.8 ± 1.6 vs. 4.8 ± 1.9; $P = 0.004$).[37] Baseline characteristics were similar, except women were more likely to have hypertension and a history of early-onset CAD. Compared with men, women in this study had a shorter mean transit time, suggesting increased resting coronary flow, while there were no sex differences in hyperaemic transit time.[37] Recently, it has been shown that CMD (diagnosed by PET-derived CFR) is highly prevalent in both men and women,[32] and associated with adverse outcomes in both groups. When CMD is diagnosed or there is high clinical suspicion of this condition appropriate treatment of cardiovascular risk factors, as well as anti-anginal, anti-atherosclerotic, and anti-ischaemic medications can be initiated.

4.4.4 Sex differences in coronary vasomotor disorders

In a retrospective Japanese analysis of 1670 consecutive patients undergoing acetylcholine provocation testing for epicardial vasospasm (defined

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Table 1 Anatomical and haemodynamic characteristics of myocardial bridging by sex, assessed using IVUS and diastolic FFR during dobutamine stress

Characteristics	Women ($n = 101$)	Men ($n = 53$)	*P*-value
Halo thickness (mm)	0.48 (0.17–2.2)	0.58 (0.14–2.32)	0.001
MB length (mm)	20.3 (3.0–59.7)	25.8 (6.57–68.9)	0.002
MB muscle index	10.2 (1.6–56.9)	16.7 (0.92–72.2)	<0.001
Arterial compression (%)	28.6 (8–58.6)	36.7 (16.7–57)	<0.001
Number of septal branches within the MB segment	2 (0–7)	3 (1–7)	0.008
Proximal MPB (%)	26.9 (13.5–56.5)	44 (10–72)	<0.001
Distance of MPB from the proximal entrance of the MB (mm)	22.7 (3.4–57.5)	20.9 (7.1–55.2)	0.79
dFFR during dobutamine stress	0.70 (0.24–0.90)	0.63 (0.20–0.86)	0.02

Variable are expressed as median (minimum and maximum values).
MB muscle index, MB length × halo thickness; MB, myocardial bridge; MPB, maximum plaque burden.

as ≥90% constriction in one coronary segment or >75% in two adjacent coronary segments), 50% of patients had a positive test of which 56% males. Of the patients with a positive test, 59% had focal spasm, whereas 41% had diffuse spasm, most likely multivessel spasm. There was a clear sex difference between the type of spasm with a predominance of women (60%) in the group having diffuse spasm and a minority (33%) women in the group with focal spasm. The patients with diffuse spasm had less coronary risk factors than those with focal spasm, and diffuse spasm was not likely to be accompanied by significant coronary epicardial stenosis. Therefore, this pattern might be the consequence of endothelial dysfunction rather than coronary atherosclerosis.[154]

In a study comparing intracoronary acetylcholine- and ergonovine-provoked spasm (221 patients, 72% males, mean age 64.4 years), acetylcholine provoked spasm (defined as transient luminal narrowing >99% and usual chest pain or ischaemic ECG findings) in 96.7% of female patients, while ergonovine provoked spasm in only 32.8% of female patients. In male patients, spasm was provoked in 80.6% by acetylcholine and in 60.6% by ergonovine. Thus, acetylcholine is more sensitive than ergonovine as a spasm provocation test, especially in women.[155]

Various studies on sex-related differences in results of invasive coronary vasomotor function tests indicate that women have more CMD and epicardial vasospasm compared with men. Furthermore, women are more likely to have diffuse spasm as opposed to focal spasm and are more sensitive to acetylcholine than ergonovine. Irrespective of sex, results of invasive vasomotor testing do not seem to correlate well with those of non-invasive ischaemia detection tests.

4.4.5 Sex differences in myocardial bridging

Myocardial bridging should also be considered in patients with persistent angina and no obstructive CAD.[149] The overall prevalence of an MB varies greatly, depending on the cohort studied and the type of imaging test performed.[156] Some studies have reported a higher prevalence of MBs in men than women,[157] while others have shown no sex difference in prevalence.[158,159] In a study of 154 patients with angina and an MB undergoing invasive assessment with intravascular ultrasound and diastolic fractional flow reserve (dFFR) during dobutamine stress,[160] there were several sex differences in the anatomical characteristics of MBs (*Table 1*). However, these anatomical differences did not translate into sex differences in haemodynamic significance, with no difference found between women and men in dFFR or Doppler flow velocity during stress. This would suggest that haemodynamic testing, rather than relying solely on anatomical characteristics, is important in both women and men.

4.5 Abnormal cardiac nociception

A subgroup of patients with CMD, particularly women, demonstrate significant and persistent chest pain that is out of proportion to objective evidence of ischaemia. They may have a cardiac nociceptive abnormality and enhanced pain perception from a variety of stimuli. Cannon *et al.*[161] showed that 29 of 36 patients (81%) with no CAD had provoked chest pain with right ventricular catheter manipulation, right-sided pacing, and injection of intracoronary contrast. In contrast, only 6% of symptomatic patients with CAD experienced chest pain with these tests. Other studies have also described abnormal, heightened pain perception in patients with persistent chest pain, especially in women with non-obstructive CAD.[162–164] Further research is needed to elucidate whether this heightened pain sensitivity is due to abnormal cardiac nerve function or problems with central pain processing.[165–167]

Tricyclic medications, such as amitriptyline and imipramine, have been effective in treating some patients with chest pain and normal coronary arteries.[168–171] Non-pharmacological treatments for patients with persistent chest pain include cognitive behavioural therapy,[172] transcutaneous electrical nerve stimulation,[173] spinal cord stimulation,[174] and transcendental meditation.[175]

5. Conclusion

CMD is associated with an adverse cardiovascular prognosis in both women and men with INOCA. Risk factors for CMD are similar to those for obstructive CAD, including hypertension, hyperlipidaemia, and diabetes but unique risk factors in women such as pregnancy-related disorders, autoimmune dysfunction, chronic inflammation, and psychological risk factors contribute to CMD. Large-scale clinical trials are required to evaluate candidate therapies for CMD and expand therapeutic options for this challenging condition that impacts not only quality of life, healthcare costs but also cardiovascular mortality.

Conflict of interest: none declared.

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