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Coronary Artery Disease in Women—Review of Risk Factors and Emerging Concepts

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Abstract

Purpose of Review Coronary artery disease (CAD) in women is an evolving area of interest in cardiovascular medicine. This review seeks to provide a summary of contemporary insights into the gender-specific pathophysiology of CAD, particularly focusing on emerging risk factors and hormonal biology in women. In addition, we make our observations on gender differences in guideline-based management, highlighting the gaps in care and joining others in expounding the need for further research and gender-specific recommendations in the management of CAD.

Recent Findings Recent publications have brought into focus gender-based differences in the diagnosis and management of CAD with a demonstrable bias that adversely affects women. Since the recognition of such bias, contemporary clinical trials are designed to pay particular attention to equal representation in research studies as well as specifically evaluate gender-based outcomes. It has come to light that INOCA or ischemia with non-obstructive coronaries disproportionately affects women. Additionally, women are prone to more complications with interventions. Investigations are underway to understand the gender discrepancies better to address women's cardiovascular needs. There is a need for further studies to fully understand the unique hormonal biology and life stages of women, which affect coronary physiology. Additionally, socio-psychological factors that have a disproportionate influence on women need further study. Advances in cardiac imaging, particularly in coronary CT angiography and cardiac MRI, have the potential to accurately and non-invasively diagnose cardiovascular pathology so that care for women can be individualized in the era of precision medicine.

Summary Gender-specific care of women with cardiovascular disease starts early in life by recognizing the complex interplay between vascular and neuro-hormonal biology as well as psycho-social, environmental, and cultural factors. In this review, we discuss the less well-recognized risk factors, conditions prevalent in women that affect coronary biology, and the current management gaps in addressing the needs of women with CAD.

Keywords Coronary artery disease in women · Gender differences in coronary artery disease · Ischemia with obstructive disease · Ischemia with non-obstructive disease (INOCA) · Vasospastic angina · Microvascular angina

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Introduction

Coronary artery disease (CAD) in women is an area of increasing academic interest and research focus since the recognition of gender disparities in care and outcomes worldwide. In the past two decades, there has been a dedicated focus from national and international organizations to increase awareness of the bias in the care of women with CAD [1]. Data collected over the years reveal the prime contributor to be the atypical presentation in women, which often leads to a delay in diagnosis. Gender differences in heart disease for many decades were unexplored and unacknowledged as women were underrepresented in or excluded from clinical trials and research.

Although there has been steady scientific progress in understanding gender differences in CAD in recent years, there still remains a wide gap in care with many unanswered questions and unexplored therapeutic strategies. CAD in women poses not just a diagnostic challenge but also a management perplexity. The traditional management approaches may be less effective in women compared to men.

In this contemporary review, we focus on female-specific risk factors and pathophysiology and propose a tailored diagnostic and management approach for women. There is a necessity for guidelines-based treatment and prevention specific to women. In addition, a need exists for directed efforts to improve education, socioeconomic status, access to care, and public policy to improve women's heart health.

Brief History

In 1908, heart disease officially became the number 1 killer of women in the USA, and it has remained that way ever since. In 1976, the Framingham Heart Study found that menopause increased the risk of heart disease in women. The concept of "Yentl syndrome" was first described by Dr Bernardine Healy in 1991 [2]. Yentl syndrome refers to the phenomenon of treating women with CAD only when they present with obstructive CAD, sometimes referred to as "male pattern" disease, a simile to the character Yentl who pretended to be a man to study Talmud. It is now well recognized that, despite the absence of obstructive CAD, both women and men can have ischemia. In 1999, the American Heart Association published the first gender-specific clinical recommendations for heart disease in women, which started to address the issue. After years of tireless work by pioneering leaders in the field, Heart Centers for Women is now a contemporary practice, as supported in the 2018 American Heart Association's white paper [3].

Burden of CAD in the United States

The recent Heart and Stroke Statistics – 2022 update from the American Heart Association shows that 6.2% of women over the age of 20 are diagnosed with coronary heart disease. Among them, the prevalence was highest in Black women (7.2%), followed by Hispanic (6.4%), White (6.0%), and Asian women (3.2%) (Fig. 1). Though the overall prevalence has not changed much from the previous update (2019), a significant increase in prevalence was seen in non-Hispanic black and Hispanic women (previously 6.5% and 6.0%, respectively) [4]. Regional disparities in prevalence are observed, with the highest burden of CAD in women reported in West Virginia (8.3%), followed by Arkansas (6.4%) and Kentucky (6.3%), while the least prevalence was in Utah (2.4%) and Colorado (2.7%) [5].

Gender-Specific Risk Factors—Contemporary Understanding and Prevailing Practice Patterns

The widely known Framingham Heart Study from 1974 established the traditionally recognized risk factors for coronary artery disease such as age, dyslipidemia, diabetes, smoking, and hypertension. In contemporary clinical practice, the ASCVD risk score is widely used to assess CAD risk. Even while a report in 1998 emphasized the consideration of female-specific risk factors, particularly physical activity, postmenopausal hormonal therapy, family history of CAD, and fibrinogen levels in gender-specific risk assessment, such a gender-specific approach is not widely adopted even today [6].

Recently, the 2019 ACC/AHA primary prevention of cardiovascular disease guidelines incorporated the following risk-enhancing factors: pre-eclampsia, family history of premature coronary artery disease (women < 65 years) and premature menopause (< 40 years) in the risk assessment. Additional gender-specific factors that should be considered are shown in Table 1.

Connective tissue disorders, physical inactivity, anxiety, and depression are more prevalent in women. For the same risk factor, the relative risk in women is higher with smoking, obesity, and psychological factors.

Life Stages of Women and CAD

Women go through distinctive life stages with different biological processes that affect the cardiovascular system compared to men (Fig. 2). In general, cardiologists are not

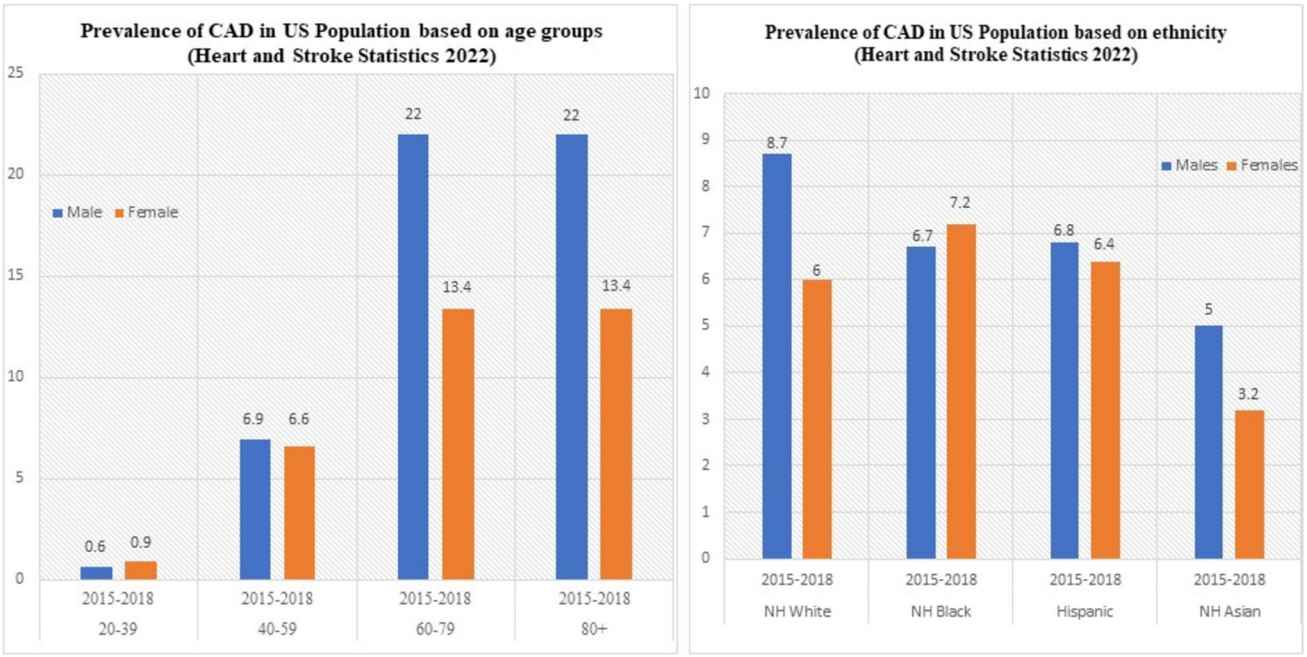

Fig. 1 Prevalence of CAD in US population as per *Heart and Stroke statistics 2022*

trained to pay attention to hormonal status during menarche, pregnancy, and menopause. Yet, these stages play a vital role in cardiovascular physiology and pathology.

Age at menarche and menopause are important cardiovascular risk factors. Menarche before age 12 is associated with increased adiposity (waist circumference), BMI, early-onset hypertension, and dyslipidemia [9]. The WISE (Women's Ischemic Syndrome Evaluation) researchers found a significant association between age at menarche (early and late) and adverse cardiovascular outcomes. The highest risk for major adverse cardiovascular events (MACE) was found in women with menarche age < 10 years of age (HR 4.21) and in women with menarche at age > 15 years with HR 2.52 [10].

Menopause has been linked to accelerated atherosclerosis in women, especially without hormone replacement therapy (HRT). This can be explained by the loss of cardioprotective effects of estradiol E2 and the presence of less effective estrone E1 following menopause. Premature menopause, natural or surgical, before age 40 was found to be associated with a 36% increased risk of cardiovascular diseases (CVD) after adjusting for conventional risk factors. The risk is higher, especially in those not on HRT [11]. In another subset of patients who underwent bilateral oophorectomy before age 45, the hazard ratio is equivalent to premature menopause (1.84) in patients with no HRT and much lesser (0.65) with HRT [12]. Each

Table 1 Prevalence and relative risk of CAD in women compared to men of known risk factors (non-specific and gender specific) [7, 8•]

Risk factors	Prevalence in women vs men	Relative risk in women vs men
Smoking	↔	↑↑
Physical inactivity/poor fitness	↑↑	↑
Obesity	↑	↑↑
Anxiety and depression	↑↑↑	↑↑
Connective tissue diseases (SLE/RA/scleroderma)	↑↑↑	↑
PCOS	Women-specific risk factors With significantly increased CAD risk	
Pregnancy associated (gestational diabetes, gestational hypertension, pre-eclampsia, post-partum weight gain)		

PCOS, polycystic ovarian syndrome; *CAD*, coronary artery disease

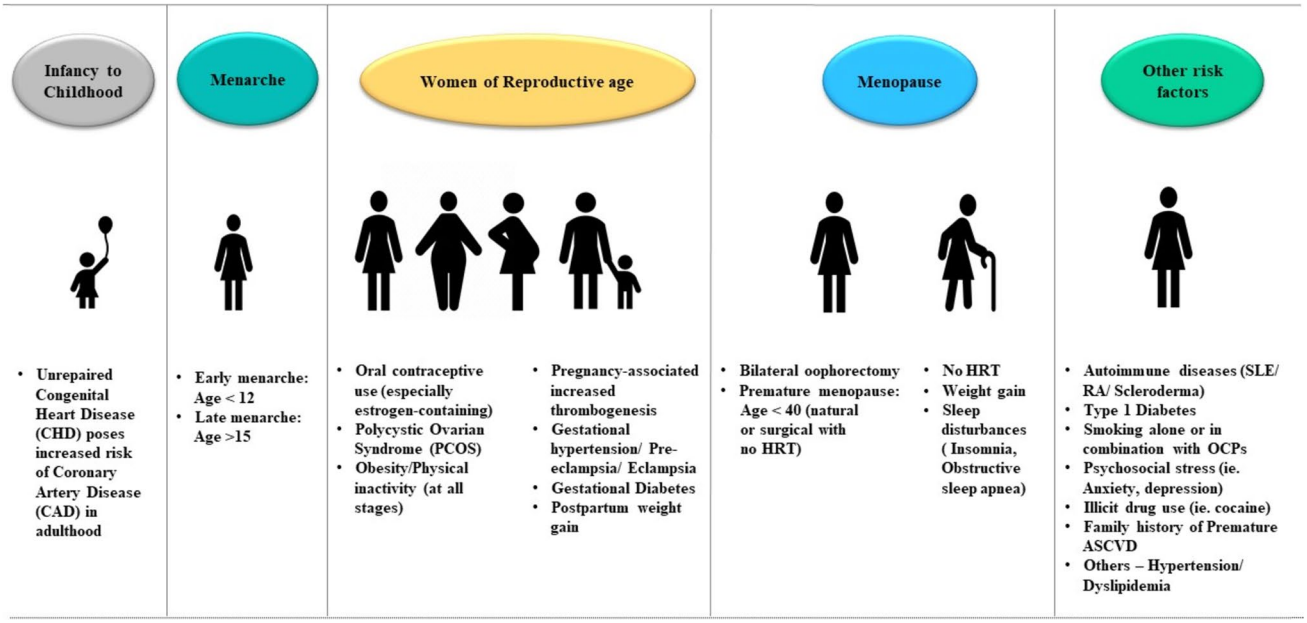

Fig. 2 Life stages of women and associated factors. HRT, hormonal replacement therapy; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; OCP, oral contraceptive pills; ASCVD, atherosclerotic cardiovascular disease

year following early menopause is associated with a 3% increased risk of CVD [13].

Polycystic Ovarian Syndrome (PCOS)

There is a high prevalence of metabolic syndrome (37.5%) in patients with PCOS. Women with PCOS have an equivalent male risk-factor profile due to hyperandrogenism, anovulation, and insulin resistance [14]. International guidelines in 2018 strongly recommended a close follow-up of PCOS patients to screen for CVD risk with annual or biennial weight check, fasting lipid panel, glycemic control, and social history, including smoking and physical activity [15].

Contraception

Often not regarded as a risk factor, it should be emphasized that all hormonal contraceptives have some adverse cardiovascular effects. While the appropriate use of contraceptives is the key to reducing the morbidity and mortality from complications of unplanned pregnancy, especially in the current political climate of pregnancy termination laws, it is vital to be aware of the cardiovascular side effects. Hypertension is a common side effect. The newer fourth-generation combined oral contraceptive pills containing low-dose estrogen have been found to increase ambulatory hypertension up to 8 mmHg in healthy normotensive women [16].

Oral contraceptive pills are also linked to developing venous/arterial thrombosis resulting in myocardial infarction and stroke. In patients with combined smoking and OCP use, the risk increases up to sevenfold.

In general, copper-containing intrauterine devices (Cu-IUD) are advantageous in most patients with cardiovascular diseases, including ischemic heart disease, thromboembolism, and cardiomyopathy, and those at high risk of other CVDs. In the case of hormonal contraceptives, progesterone-only pills or implants such as levonorgestrel-IUD and etonogestrel (Nexplanon) are considered cardio-safe. While both these agents can be continued post-myocardial infarction (MEC 2), they are not advisable to initiate following an event.

To assist and guide health care providers, the Centers for Disease Control and Prevention (CDC) have updated recommendations for the use of specific and most safe contraception in women with various risk factors and medical conditions. Recommendations specific for cardiovascular diseases are collated in Table 2.

Many women with CVD, as well as physicians, are often found to lack knowledge regarding safer and effective options of contraception. In a small survey conducted at our institution, which included 60 female medical students of reproductive age, 88% of the women were following some form of contraception. Of those, the majority (79%) preferred hormonal contraceptive methods. In general, many women who took the survey were unaware of the cardiovascular effects associated with their choices. Most participants preferred contraceptives with an estrogen component (42/53) which they have chosen from peer experience.

Table 2 Available contraceptives in the US—CDC safety profile in cardiovascular diseases [17]

	DVT	Ischemic heart disease	Stroke	Vascular disease	HTN (140–159/90–99)	Hx of HTN during pregnancy	Superficial venous thrombosis	Peripartum cardiomyopathy	Smoking
Nexplanon (etonogestrel implant)	2	2 if beginning 3 if continuing	2 if beginning 3 if continuing	1	1	1	1	1	1
Depo-Provera (medroxyprogesterone acetate injectable)	2	3	3	1	2	1	1	1	1
Ortho Tri-Cyclen (oral norgestimate ethinyl estradiol)	4	4	4	2/4**	3	2	3	4	2–4*
Mirena IUD (levonorgestrel)	2	2 if beginning 3 if continuing	2	1	1	1	1	2	1
Camila (norethindrone)	2	2 if beginning 3 if continuing	2 if beginning 3 if continuing	1	1	1	1	1	1
Nuvaring (etonogestrel/ethinyl estradiol vaginal ring)	4	4	4	2/4**	3	2	3	4	2–4*
Junel, Loestrin (norethindrone/ethinyl estradiol)	4	4	4	2/4**	3	2	3	4	2–4*
Aviane, Lessina, Levora (levonorgestrel/ethinyl estradiol)	4	4	4	2/4**	3	2	3	4	2–4*
Gianvi, Lorynza, Ocella (drospirenone/ethinyl estradiol)	4	4	4	2/4**	3	2	3	4	2–4*
Norethisterone (Micronor)	2	2 if beginning 3 if continuing	2 if beginning 3 if continuing	1	1	1	1	1	1
Xulane (norelgestromin/ethinyl estradiol transdermal patch)	4	4	4	2/4**	3	2	3	4	2–4*
Paragard (copper IUD)	2	1	1	1	1	1	1	2	1

(Medical eligibility criteria

1: No restriction on use; use method in any circumstance. 2: Benefits outweigh risks; generally used. 3: Risks outweigh benefits; use not usually recommended unless other appropriate methods are not available. 4: Unacceptable level of risk; method not to be used)

DVT, deep venous thrombosis; HTN, hypertension; IUD, intrauterine device

*2 for age < 35, 3 for age > 35 and < 15 cigarettes/day, 4 for age > 35 and > 15 cigarettes/day

**2 for uncomplicated valvular heart disease and 4 for complicated valvular heart disease

The majority of the women in the reproductive age group with cardiovascular risks are sexually active. It is essential to balance the side effects with efficacy when using contraception [18•]. The copper IUD can last longer, up to 10 years, but can increase menstrual bleeding and pain. This is the preferred method of contraception post-MI. Even while IUDs last longer and are safer and more effective, combined hormonal contraceptives (CHC) remain the most widely used contraceptive option. The cardiovascular effects of estrogen and progesterone are described in Table 3.

Cardiologists should become more familiar with contraceptive methods and their cardiovascular effects. Discussing contraception with every woman of reproductive age with CVD is imperative.

Pregnancy and CAD

Multiple factors are responsible for the increasing prevalence of coronary artery disease (CAD) in pregnant women [21]. These include advanced maternal age at the time of pregnancy, increased survival in adult congenital heart disease (ACHD), vasculitis, e.g., Kawasaki's disease, connective tissue disorders such as Marfan syndrome, Ehlers-Danlos type IV syndrome, systemic lupus erythematosus, polyarteritis nodosa, and fibromuscular dysplasia, and prevalence of cardiovascular risk factors including smoking, substance use, hypertension, hyperlipidemia, and diabetes. Both stable CAD and new-onset acute myocardial infarction (AMI) are seen during pregnancy. The etiology of AMI in pregnancy includes atherosclerosis, spontaneous coronary artery dissection (SCAD), coronary artery embolism, coronary spasm, and microvascular disease [22].

Although AMI is infrequent during pregnancy and postpartum (2.8 to 6.2/100,000 deliveries), complicating about 1:16,000 pregnancies, it is responsible for a large number of maternal cardiac deaths and increased long-term maternal and fetal morbidity in survivors [23–26]. Several pregnancy-related body adaptations contribute to this risk, including prothrombotic state, hemodynamic changes of reduction in systemic vascular resistance, increased heart rate, stroke volume, cardiac output, and overall oxygen consumption. Dyslipidemia may be worsened during pregnancy because HDL is significantly decreased during gestation. In addition, hormonal changes occur, including an increase in estrogen, progesterone, and relaxin levels leading to the altered architecture of coronary vessels and thus the increased risk of intramural hematoma and SCAD [27–29]. SCAD is estimated to contribute up to 27 to 43% of AMI and is reported at any time during pregnancy, predominantly in the first month postpartum [23, 30]. Predisposing factors for coronary spasms include hypovolemia in the setting of severe obstetrical hemorrhage, use of ergot-derived medications, smoking, and cocaine use.

Table 3 Summary of the cardiovascular effects of estrogen and progesterone [19, 20]

Cardiovascular effects	Estrogen	Progesterone
Thrombotic risks: • Risk of myocardial infarction: 1.6-fold higher risk • Risk of venous thrombosis: 2–4 times higher risk • Risk of stroke: risk higher with use of estrogen. Progesterone on the stroke risk lacks evidence	↑↑ Coagulation factors ↑↑ Platelet aggregation	↑↑ Coagulation factors ↑↑ Platelet aggregation May ↓ nitric oxide
Effects on CAD risk factors: • Blood pressure • Lipids • Glucose tolerance	↑↑ Coagulation factors (↑ inflammatory state) ↓LDL, ↑ HDL, ↑ triglycerides Increase in systolic BP up to 7–8 mmHg No change in fasting blood glucose, but can increase insulin resistance	
Electrophysiological effects: • Introduction of arrhythmias: easier at certain times of menstrual cycle • Increased risk of QT prolongation in post-menopausal women and in those with DMPA use • No specific increased event rate with CHC use	↑ QT interval ↓ Platelet aggregation	↓ or ↑ QT interval
Anticoagulation and contraception • Use of warfarin	Both estrogen and progesterone interfere with warfarin metabolism, unknown mechanism Heavy menstrual bleeding is expected (agents that reduce bleeding or induce amenorrhea can be beneficial)	

LDL, low-density lipoprotein; *HDL*, high-density lipoprotein; *DMPA*, depot medroxy progesterone acetate

Patients with known CAD (WHO class III) or at high risk of CAD should be screened non-invasively before conception. In case of any concern for angina during pregnancy, a sub-maximal exercise stress test is recommended. The accuracy of exercise stress electrocardiogram is lower, and fetal bradycardia has been reported during maximum exercise. Nuclear stress imaging should be avoided, particularly in the first trimester, due to the risk of teratogenesis in this organogenesis period. Stress echocardiography can be used to assess ischemia during pregnancy.

Chest pain is reported in > 90% of pregnant women with MI with associated symptoms of palpitations and nausea. If suspected, prompt EKG and consideration of echocardiography to assess for biventricular function and wall motion abnormalities are prudent. Pulmonary embolism (PE), peripartum cardiomyopathy, and pre-eclampsia/eclampsia/HELLP syndrome should also be ruled out. A multidisciplinary approach involving the obstetrician, maternal–fetal medicine team, cardiologist, and anesthetist should be adapted for management, including plans for emergent delivery of a viable fetus in the setting of sudden clinical deterioration of the mother. Coronary vasospasm should be addressed with nitrates, calcium channel blockers, and avoidance of inciting factors such as smoking and cocaine [31]. Paradoxical embolus should be evaluated with TTE or TEE to assess for shunt, which may require closure [32].

The management of STEMI or NSTEMI should be guideline-based, as for a nonpregnant patient, considering short-term use of heparin. Low-dose ASA is safe. The antiplatelet of choice is clopidogrel since data published of it being used without harm as early as 18 weeks gestation. Heparin should be discontinued 24 h before delivery; in case of spontaneous labor, protamine sulfate may be required to reduce bleeding risk and allow safe local and epidural anesthesia. Heparin can be resumed following delivery once adequate homeostasis has been achieved. Beta-blockers are generally safe. Statins, unfortunately, are teratogenic and are contraindicated in pregnant women. Cardiac catheterization with limited timing of fluoroscopy with concurrent abdominopelvic shielding should be performed to assess coronary anatomy and for coronary intervention if indicated.

In the presence of high-risk coronary anatomy or multivessel CAD, CABG during the late second trimester or early third trimester should be avoided to minimize the risk of preterm labor and delivery. CABG during the first trimester is associated with a high risk of congenital fetal abnormalities. If the fetus is > 28 weeks gestation, consideration must be given to delivering the child immediately before and during the same operation as the cardiac operation. In the presence of SCAD, early recognition is crucial due to variable presentation of EKG and cardiac enzymes; conservative management should be done in most cases to allow the coronary arteries to self-heal. Optical coherence tomography (OCT) or intravascular ultrasound (IVUS) can be used to enhance diagnostic capability during cardiac catheterization. There is data that one in six patients in this group may have progression of dissection in a week; thus, these patients should be monitored closely for an extended time. In some cases, PCI or CABG can be considered [33, 34].

Experts recommend delaying delivery 2–3 weeks post-MI for myocardial recovery. In the case of vaginal delivery, assistance during the second stage of delivery is recommended. Early, continuous epidural anesthesia is essential to minimize pain, which can increase maternal heart rate and myocardial oxygen demand. Tachycardia and hypertension should be promptly addressed. Ephedrine is usually the vasopressor of choice for hypotension associated with regional anesthesia as it helps maintain placental perfusion.

The postpartum and post-MI periods are independent risk factors for the development of major depression, which needs to be monitored [35, 36]. This may increase the risk of non-compliance with cardiac medications worsening the existing situation.

Connective Tissue Disease and CAD

The prevalence of connective tissue disease (CTD), primarily systemic lupus erythematosus (SLE), rheumatoid arthritis, and psoriasis, is reported in up to 18% of the total world population. With the higher incidence of CTD in women, the associated increased risk of CAD should be emphasized [37]. The risk of premature coronary artery disease in women of age < 55 is heightened in the setting of chronic inflammatory conditions like SLE, systemic vasculitis, rheumatoid arthritis (RA), psoriasis, primary antiphospholipid syndrome (PAPS), and other related conditions [38, 39]. There is a prominent role of chronic inflammation in the development of early-onset and accelerated atherosclerosis in these patients. Apart from the disease itself, the choice of treatment also has implications. Steroids are usually the mainstay, the chronic use of which itself predisposes to multiple CAD risk factors such as weight gain, hypertension, and diabetes, which in turn worsens the existing risk further.

A "lipid paradox" occurs in chronic inflammatory conditions, where the CAD risk remains elevated despite this population's low LDL and HDL [40•, 41]. The underlying mechanisms contributing to the pathogenesis of CAD in connective tissue disorders are summarized in Fig. 3. It is important to address the CAD risk in women with connective tissue disorders and focus on long-term remission of the underlying disease. C-reactive protein (CRP) and high-sensitivity CRP are commonly used biomarkers to assess active systemic inflammation. Elevated biomarkers are known to correlate with an increased risk of coronary artery disease. This correlation was observed in SLE and RA than in other CTD. Research on novel risk factors and modulation of

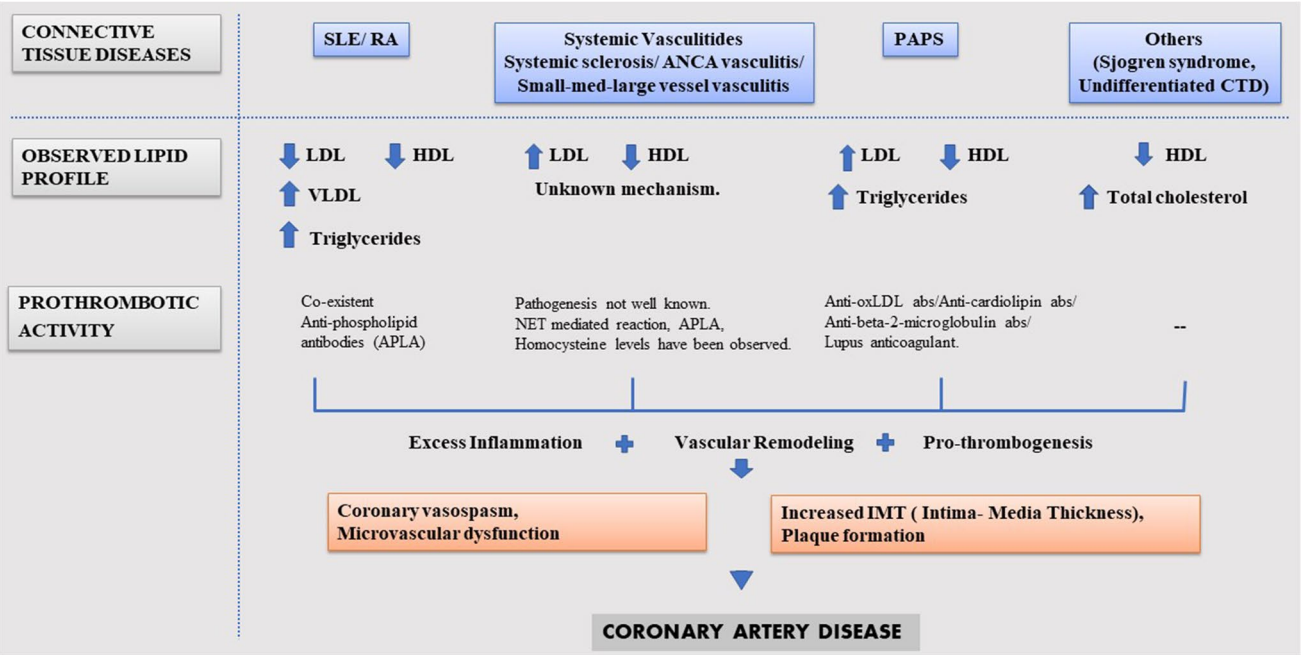

Fig. 3 Observed pathogenesis of coronary artery disease in patients with connective tissue diseases [42–46]. SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; ANCA, antineutrophil cytoplasmic antibodies; PAPS, primary antiphospholipid syndrome; CTD, connective tissue disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; NET, neutrophil extracellular traps; Anti-oxLDL abs, anti-oxidized LDL antibodies

inflammation is ongoing, and much remains to be learnt. Recently, GlycA measurement using NMR spectroscopy was found to be more sensitive than hs-CRP. It has the potential to be used broadly in multiple systemic inflammatory conditions to monitor underlying disease activity and treatment with anti-inflammatory therapies.

In addition to the above, coronary artery dissection in fibromuscular dysplasia is more prevalent in women. The exact pathophysiology is still debated.

Other Gender-Specific Considerations

Emotional Triggers—Gender Differences

Women often develop ischemia in response to mental, emotional, and psychological triggers relative to men, who generally respond to physical triggers. Compared to men, women have a different activation of their limbic system and hypothalamic-adrenocortical axis, which can explain their increased cardiovascular susceptibility to emotional stress [47]. Stress activates the sympathetic nervous system and induces a catecholamine surge that can result in coronary spasms and direct myocardial injury. Several patients with stable coronary artery disease with no inducible ischemia in exercise can still suffer from major ischemia in response to mental stress. MSIMI (mental stress-induced myocardial ischemia) is an unexplored target in current clinical cardiology practice [48]. Studies on integrated management focusing on psychological health are needed to understand better the impact on cardiovascular health care [49].

Gender Differences in Nociception

Factors contributing to the gender differences in pain pathways include autonomic nervous system reactivity, psychosocial susceptibility, and visceral innervation. Psychosocial factors such as anxiety, depression, and post-traumatic disorder have been seen to exacerbate angina. This is seen in a high number of INOCA subjects showing chest pain during a mental stress test compared to a control group. Further research into central, visceral, and autonomic pain processing in patients with and without angina should be investigated to better address this discrepancy [50].

Hormone Replacement Therapy

Hormone replacement therapy (HRT) was initially implemented in the 1960s; however, clinical trials to assess HRT and their effect on cardiovascular disease (CVD) were not initiated until the 1990s [51]. In 2002, as a direct result of a large prospective randomized control study called the Women's Health Initiative (WHI), women with known CVD were recommended discontinuation of HRT, fearing the increased risk of CVD, as it appeared that HRT had more negative than positive effects [52]. A re-analysis of the WHI data revealed that using HRT in early menopause benefited cardiovascular health [50, 51]. However, public opinion on the safety and efficacy of HRT has not changed, and HRT in cardiovascular disease remains controversial.

Re-evaluation of the data from WHI and the Early versus Late Intervention Trial with Estradiol (ELITE) supports a timing hypothesis suggesting that HRT has more favorable effects on the progression of cardiovascular disease in women close to the onset of menopause or younger women [53]. A recent systematic review from 2015 evaluated women older than 60 or under 60 and concluded that hormone replacement therapy provides little or no protection and actually increases the risk of stroke or venous thromboembolic events [54]. Others have suggested that drops in estrogen levels render postmenopausal women more vulnerable to microvasculature dysfunction and that combination HRT may be considered a novel and therapeutic treatment for cardiac dysfunction in patients when started at a younger age [55, 56]. In its totality, the currently available data supports two opinions on HRT: (1) HRT should be applied using a timing hypothesis, in which HRT should be started in early postmenopausal women who are younger, and (2) HRT should not be applied as a primary treatment for the prevention of CVD and should only be used for traditional symptomatic treatment in menopause, but opinions and conclusions are heavily mixed [57–60].

Of the current data, a great deal of support has been given to the HRT "timing hypothesis" in one capacity or another. It concludes that younger menopausal women using HRT to treat vasomotor symptoms are not at an increased risk of death or CAD event [56, 58, 61]. *Menopause*: The Journal of the North American Menopause Society 2017 position statement on the use of hormone therapy states that more research is needed, but "For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome vasomotor symptoms, and those at elevated risk for bone loss or fracture. For women who initiate HRT more than 10 or 20 years from menopause onset or those 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia" [61]. Hence, our current understanding is that HRT, when initiated in an appropriate manner in relation to age and/or time since menopause, may now be considered a potential therapeutic for microvascular dysfunction in postmenopausal women as long as it is applied using a timing hypothesis, and only prescribed to treat the symptoms associated with menopause.

Gender Differences in the Pathogenesis of Coronary Artery Disease: Ischemia with Obstructive Coronary Artery Atherosclerosis (IOCA) and Ischemia with Non-obstructive Coronaries (INOCA).

Traditionally, ischemia has been equated with obstructive coronary disease. Obstructive CAD refers to epicardial vessel stenosis ≥ 50% and is generally due to coronary atherosclerosis. The hallmark of clinically significant stenosis is impairment of myocardial perfusion reserve. Severe luminal narrowing on quantitative analysis of invasive quantitative coronary angiography (QCA) (> 70% stenosis) is always associated with decreased perfusion reserve and can cause ischemia at stress. However, the physiological effects of mild to moderate stenosis (40–70%) on QCA are less predictable, with a wide range of variability in perfusion reserve for the same apparent stenosis severity.

A detailed discussion of gender differences in obstructive CAD is beyond the scope of this review; however, certain pathophysiological differences are worth bearing in mind when evaluating women with acute coronary syndromes. An increased incidence of plaque erosion has been reported in younger women, while plaque rupture is the dominant mechanism in ACS for men and older women [62–64]. While the underlying mechanisms may vary, no significant mortality difference was found in the study population at the end of 2 years of follow-up [65, 66].

A third of women with chest pain syndromes have non-obstructive coronaries defined as luminal stenosis < 50% and are included in the broad category of INOCA.

A variety of pathophysiological mechanisms can affect the coronary vasculature, such that the coronary perfusion is unable to meet the oxygen demand resulting in ischemia. INOCA can occur at the epicardial coronary or microvascular level (microvascular angina). Individual variability in nociception can cause chest pains of varying presentation. INOCA syndromes not only cause morbidity but also increase mortality [67].

There may be multiple overlapping mechanisms causing INOCA in a given patient. In the WISE (Women's Ischemia Syndrome Evaluation) studies, comprehensive invasive physiological testing yielded abnormal coronary function in more than 60% of women with chest pain and "normal" coronary arteries [68, 69]. Figure 4 shows the invasive coronary physiology protocol used in the WISE study.

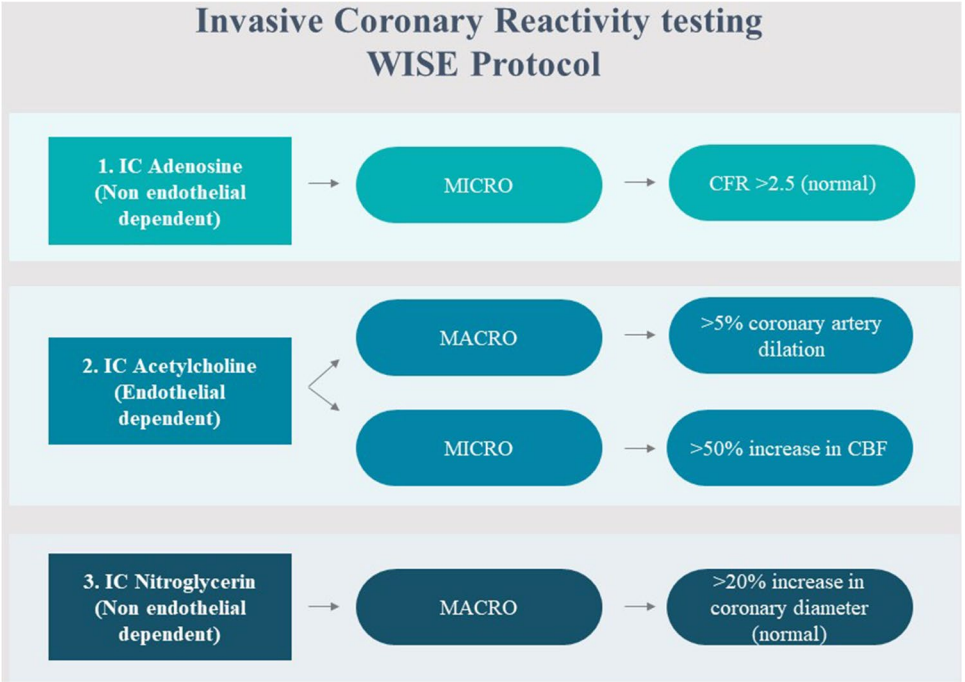

Fig. 4 The invasive coronary physiology protocol used in the WISE (Women's Ischemia Syndrome Evaluation) study. IC, intracoronary; CFR, coronary flow reserve; CBF, coronary blood flow

Vasospastic Angina (Prinzmetal Angina)

Vasospastic angina (VA) is a reversible, intense coronary vasoconstriction in the epicardial coronary vasculature causing angina. As a cause of INOCA, VA can be challenging to diagnose with standard diagnostic testing. The true incidence of vasospastic angina is difficult to estimate; however, on invasive physiology testing in 151 patients, isolated vasospastic angina was noted in 20% (*n* 25), isolated microvascular angina was seen in 52% (*n* 78), and mixed physiology was seen in 17% [70]. Provocable vasospasm was noted more frequently in women and can occur at lower doses of acetylcholine than in men.

A definitive diagnosis of coronary spasm relies on assessing coronary vasomotion and provocative testing with acetylcholine or ergonovine in the invasive coronary physiology lab. Although ideal, invasive testing is not routinely available and is infrequently done in clinical practice. Generally, the diagnosis is made based on history, clinical evaluation, presence of characteristic ST changes during symptomatic episodes, and response to nitroglycerin (Fig. 6).

Viral syndromes (parvovirus B19), psychosomatic factors (anxiety, panic attacks), drugs including amphetamines, ephedrine, 5-fluorouracil, cocaine, ethanol, marijuana, medroxyprogesterone, estrogen deficiency, anti-migraine medications, magnesium deficiency, withdrawal of calcium channel blockers, and adenosine have been implicated in inducing or worsening coronary VA. Mechanisms involved in coronary vasospasm include vagal withdrawal, abrupt change in sympathetic activity, endothelial dysfunction, smooth muscle cell hypersensitivity, inflammation, and genetic polymorphisms. Gender and ethnic disparities have also been noted.

VA can cause ischemia resulting in myocardial stunning, MINOCA, tachyarrhythmias, and atrioventricular block. A case of severe transient apical ballooning in a middle-aged woman with INOCA, primarily due to VA, is shown in Fig. 5 [71].

Microvascular Angina

Microvascular angina is diagnosed in symptomatic patients without obstructive coronary artery disease (CAD) but with objective evidence of ischemia and impaired coronary microvascular function. Microvascular angina can be due to:

- Microvascular spasm
- Increased microvascular resistance
- Reduced coronary flow reserve

The *Coronary Vasomotion Disorders International Study Group* (COVADIS) consortium's proposed criteria [72, 73] for diagnosing vasospastic and microvascular angina are summarized in Fig. 6.

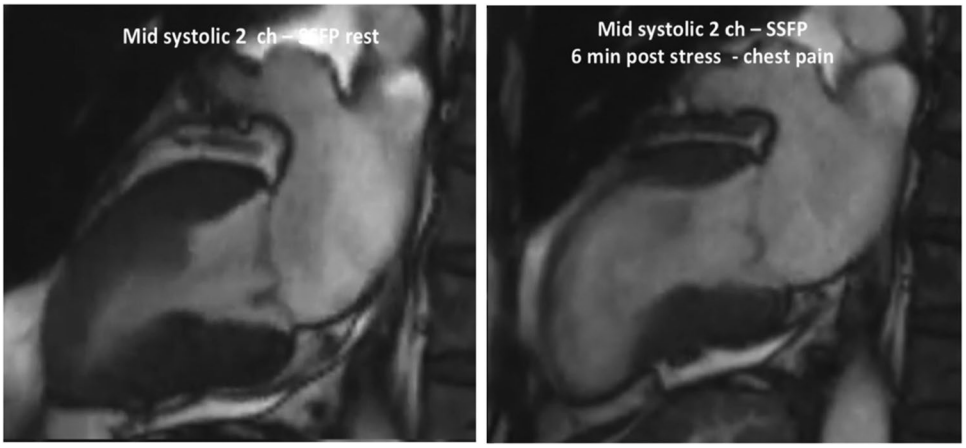

Fig. 5 Apical ballooning, severe sudden reduction in ejection fraction, and ST elevation were noted during an episode of chest pain after Adenosine withdrawal during stress perfusion cardiac MRI in a perimenopausal woman with disabling episodes of cramping chest pain and fainting spells. Standard diagnostic testing was non-diagnostic besides mild non-obstructive CAD. The episodes were due to coronary vasospastic angina. Patient also had reduced myocardial perfusion reserve

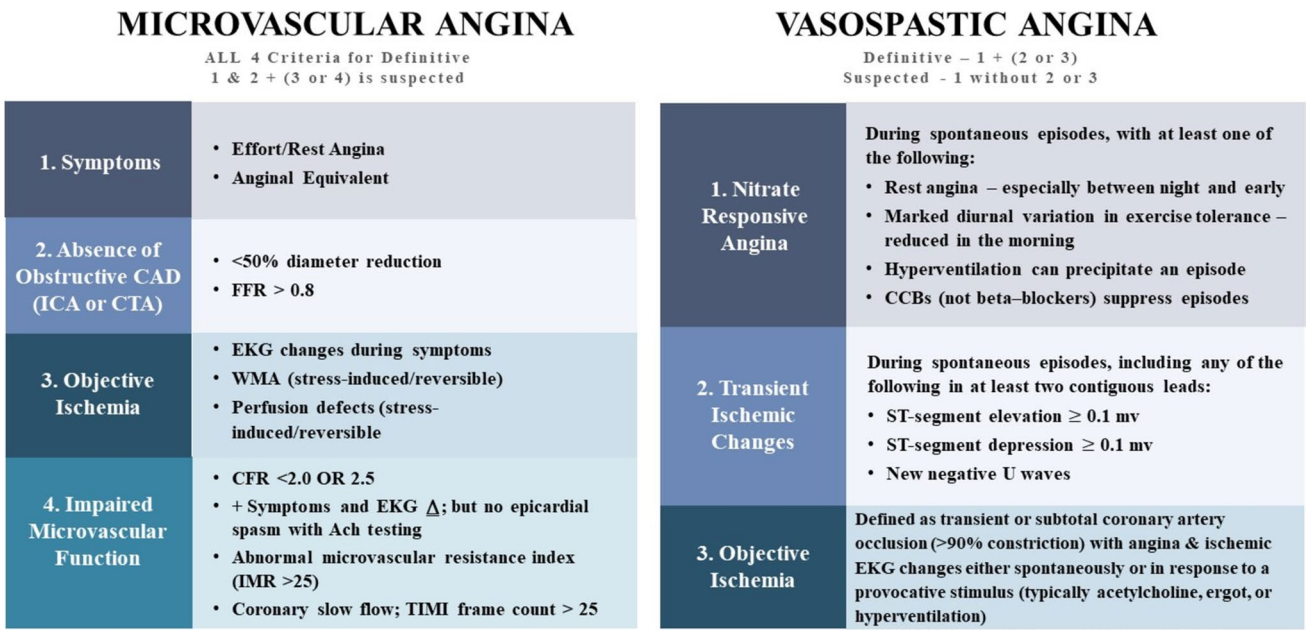

Fig. 6 The criteria to diagnose microvascular angina (based on clinical symptoms, diagnostic testing) and vasospastic angina (based on history, clinical evaluation, presence of characteristic ST changes during symptomatic episodes, and response to nitroglycerin). COVADIS diagnostic criteria 2017. ICA, invasive coronary angiography; CTA, computed tomography angiography; FFR, fractional flow reserve; CFR, coronary flow reserve; IMR, myocardial resistance index; CCBs, calcium channel blockers; WMA, wall motion abnormalities; Ach, acetylcholine

Myocardial Bridging

Myocardial bridging (MB) is a congenital anomaly with an abnormal intra-myocardial course of a segment of the epicardial coronary artery. The reported prevalence of MB was 6% on coronary angiography, 22% on computed tomography, and 42% on autopsy [74].

The clinical significance of MB has been debated. MB is associated with myocardial infarction, MINOCA, myocardial ischemia, sudden death, and other cardiovascular outcomes. The "milking" or compression of the coronary artery occurs primarily during systolic myocardial contraction, which is generally thought to be benign as the majority of coronary perfusion occurs during diastole. In reality, a complex interplay between anatomy and physiology can result in ischemia [75, 76]. A deeper (> 2 mm) and longer bridge (2.5 cm long) in the mid-left anterior descending artery (LAD) is more likely to cause ischemia than a superficial bridge in a small vessel. The location, length, depth of the bridge, associated atherosclerosis which often occurs in the proximal segment of the bridge, coexistent spasm, sympathetic tone, and heart rate should

be considered when assessing a patient with bridging-related ischemia.

Treatment is based on the clinical presentation and can include reassurance, rate-lowering medications (beta-blockers, calcium channel blockers, ivabradine), coronary stents, bypass surgery, and unroofing of the bridging segments. The invasive management approach should be carefully considered after a detailed assessment of anatomy and physiology [74]. Nitrates are generally avoided as they can worsen systolic narrowing and cause reflex tachycardia unless a significant vasospasm component is present.

MINOCA (Myocardial Infarction with Non-obstructive Coronary Arteries)

Myocardial infarction in the absence of obstructive coronary artery disease (MINOCA) is an entity used to describe patients presenting with AMI but without any evidence of obstructive CAD on coronary angiography [77]. It has an estimated 5–6% prevalence among patients with AMI referred to coronary angiography [78]. Although it has been broadly applied to include various clinical entities in the past, it is now a diagnosis of exclusion after ruling out other causes of elevated troponin and non-ischemic etiologies of troponin elevation. The first international position statement from the European Society of Cardiology proposed a standardized definition for MINOCA as:

1. AMI as defined by the third universal definition of MI,
2. Non-obstructive CAD (<50% stenosis or FFR > 0.80),
3. No other identifiable cause for acute presentation.

However, the third universal definition of MI was limited by the lack of distinction between ischemic and non-ischemic etiologies for troponin elevation. With the most recent fourth universal definition of MI, the term "MINOCA" is reserved only for patients with an ischemic basis for clinical presentation [79]. The demographic and clinical characteristics of MINOCA patients differ from those patients presenting as traditional AMI-CAD. Women are disproportionately affected, accounting for at least 60% of cases. Furthermore, MINOCA patients are younger and have a lower prevalence of traditional cardiac risk factors than the AMI-CAD population. MINOCA is more likely to occur among Black, Maori, and Hispanic ethnic groups [78]. It is estimated that one-third of MINOCA patients present initially as STEMI. MINOCA patients also have a lower prevalence of traditional CAD risk factors such as dyslipidemia, hypertension, diabetes mellitus, and smoking than the AMI-CAD population [80]. Plaque disruption, including rupture and erosion, remains the most common etiology for MINOCA in at least one-third of cases [79]. Other non-atherosclerotic mechanisms implicated include coronary vasospasm, microvascular dysfunction, coronary embolism, spontaneous coronary artery dissection, and demand–supply mismatch. Non-invasive diagnostic modality, especially cardiac magnetic resonance imaging (CMRI), remains an inevitable tool in arriving at the final diagnosis of MINOCA. The late gadolinium enhancement (LGE) patterns can help differentiate ischemic and non-ischemic etiologies for myocardial injury [81].

The prognosis of MINOCA appears to be similar to the AMI-CAD counterparts [82]. At least one in four patients with MINOCA experiences angina in the subsequent 12 months post presentation. As such, medical therapy and risk factor modification remain inevitable in managing these patients. Aspirin remains the mainstay treatment similar to AMI-CAD. Although no randomized trial data evaluate the effectiveness of other medical therapies, long-term clinical registries support the use of statins and ACE inhibitors [83].

Diagnostic Considerations for Coronary Artery Disease in Women

The 2008 INTERHEART study highlighted the late presentation of women with first-onset angina over men by a minimum of 9 years [84]. Even though women are often reported as presenting with atypical symptoms, chest pain remains the most common presenting symptom in both men and women [85, 86]. A retrospective study between 2009 and 2013 in 54,138 patients (49% women) showed that the time to clinical examination within the first hour and time to troponin testing was delayed in women presenting with non-traumatic chest pain (16% and 20% less likely compared to men) which contributed to the significant in-house and in-ER mortality [86]. Many women presenting with atypical symptoms like shortness of breath, dizziness, fatigue, and jaw/neck pain continue to be misdiagnosed and are prone to a delay in diagnosis.

There are no gender-specific guidelines regarding diagnostic testing of CAD; however, the following concepts should be considered while evaluating women for CAD in stable patients.

- Exercise stress testing is preferred for symptomatic patients, including women who can exercise (≥ 5 METS), as the information on functional capacity has prognostic value. Improved sensitivity with diagnostic accuracy was noted in the WOMEN trial when treadmill exercise ECG was combined with SPECT MPI [87].
- The use of ionizing radiation (CTA/SPECT/PET) for younger women or women of reproductive age is less ideal for diagnosing CAD and should be avoided in low-risk women. Studies have shown that the breast tissue

during the reproductive age is more radiosensitive and prone to increased progression to carcinogenesis with a stimulating estrogen effect [88, 89]. On the other hand, such risk is low in postmenopausal women, and the use of ionizing radiation can be justified.

- Structurally, smaller epicardial coronary arteries in women can theoretically make it challenging to assess the distal segments in CTA [90]. Similarly, thinner myocardial walls can be a challenge in accurately assessing ischemia with CMR [91].
- Myocardial perfusion reserve (MPR) is a robust prognosticator of ischemic CAD. MPR is a non-invasive measure that can indicate overall coronary vascular health, including epicardial and microvasculature, and has an emerging role in patients with INOCA. MPR with adenosine/regadenoson stress can be non-invasively assessed by positron emission tomography and cardiac magnetic resonance imaging. Further studies are needed to determine the integration of this measure in clinical practice.

A gender-specific diagnostic pathway customized to address CAD in women is proposed in Fig. 7.

Management of Coronary Artery Disease

The management of CAD is mainly based on the underlying mechanism of the disease itself. Coronary atherosclerosis and associated obstructive coronary artery disease are the dominant mechanisms. The 2014 ACC/AHA guideline for stable CAD and 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes direct the current practice of CAD management [93, 95]. Several studies have shown that women are less likely to be on guideline-directed medical therapy than men. We defer to the published guidelines for specific management algorithms. Current guidelines do not make specific gender-based recommendations saving some exceptions as mentioned below.

The primary and secondary prevention of CAD in women follows the same recommendations as men except for a few special considerations. The use of statin is warranted when 10-year ASCVD risk ≥ 7.5%. Women with lower ASCVD risk (< 7.5%) with other risk-enhancing factors such as premature menopause < 40 years, pre-eclampsia, and chronic inflammatory diseases (RA, psoriasis,

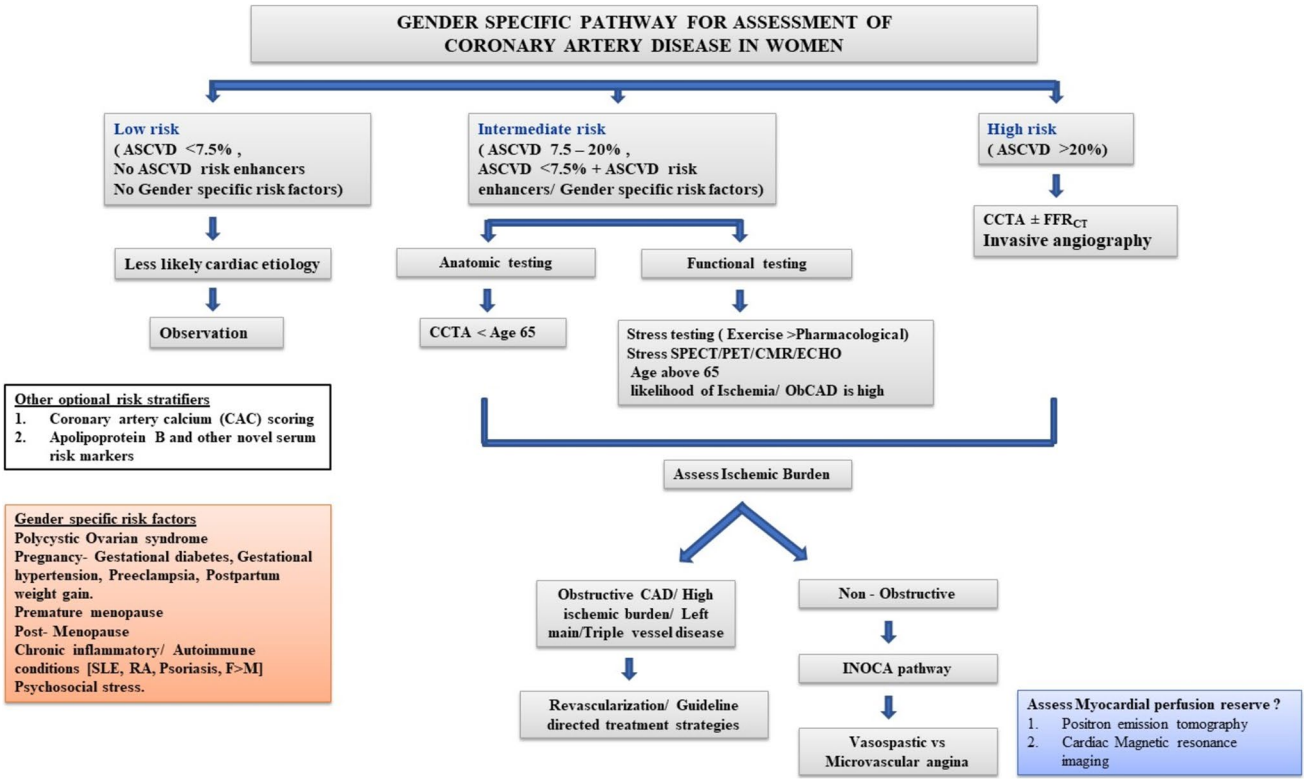

Fig. 7 Proposed diagnostic algorithm for detection of coronary artery disease in women [91, 92••, 93, 94••]. CCTA, coronary computed tomography angiography; FFRCT, fractional flow reserve–computed tomography; SPECT, single-photon emission computerized tomography; PET, positron emission tomography; CMR, cardiac magnetic resonance; ECHO, echocardiography; ObCAD, obstructive coronary artery disease; INOCA, ischemia with non-obstructive coronaries

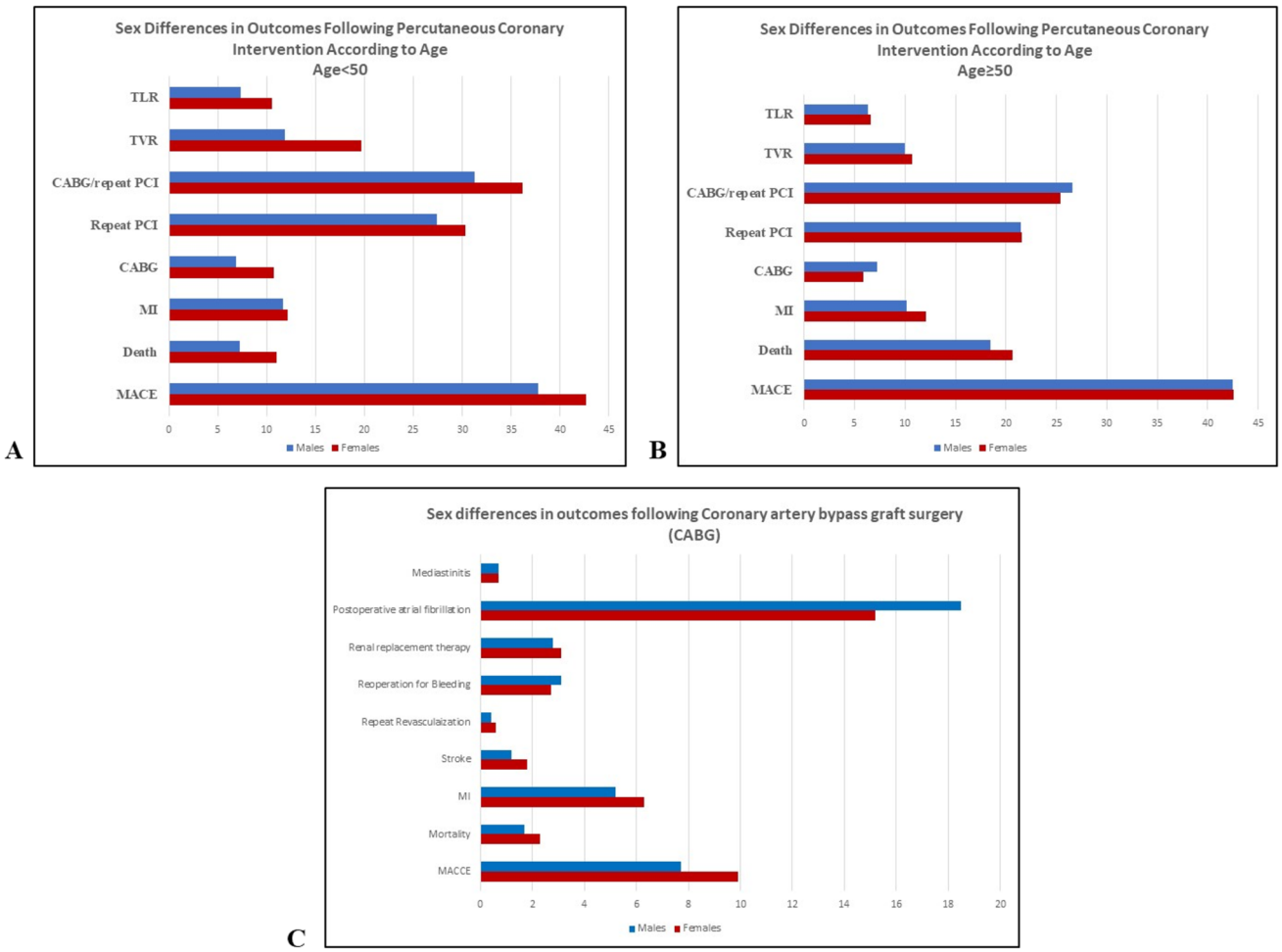

Fig. 8 **A**, **B** The sex differences in outcomes following percutaneous coronary intervention women of age groups below and above 50. **C** The sex differences in outcomes following CABG in a pooled analysis of 4 major CABG trials (ART/CORONARY/GOPCABE/PREVENT IV). TLR, target vessel revascularization; TVR, target vessel revascularization; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; MI, myocardial infarction; MACE, major adverse cardiovascular events

SLE, HIV) should still be considered for early initiation of statin treatment in a shared decision model.

Low-dose aspirin (ASA) 75–100 mg/day use is controversial in primary prevention [96]. In a study involving 39,876 US women over the age of 45 randomized to ASA 100 mg/day every other day vs placebo with a follow-up of 10 years to the first CV event, results showed significant benefit in lowering the risk of stroke but not MI. A subgroup analysis in women > 65 years showed a beneficial effect on preventing both stroke and myocardial infarction [97]. The last updated ACC/AHA 2019 guidelines on primary prevention recommended using ASA in men and women between 40 and 70 years with a high risk of ASCVD and no risk of bleeding.

Gender Differences in Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Graft (CABG) Surgery

While guidelines do not make recommendations based on gender, the following observations have been made in managing CAD. In STEMI-ACS, thrombolytic therapy in women was associated with increased morbidity and mortality compared to men [98].

Women less than 50 years of age, despite having less severe angiographic CAD, are at higher risk of requiring repeat PCI, CABG, TVR, and TLR compared to women over 50, as noted in a large multi-center observational study (Fig. 8A, B). The incidence of MACE was higher in

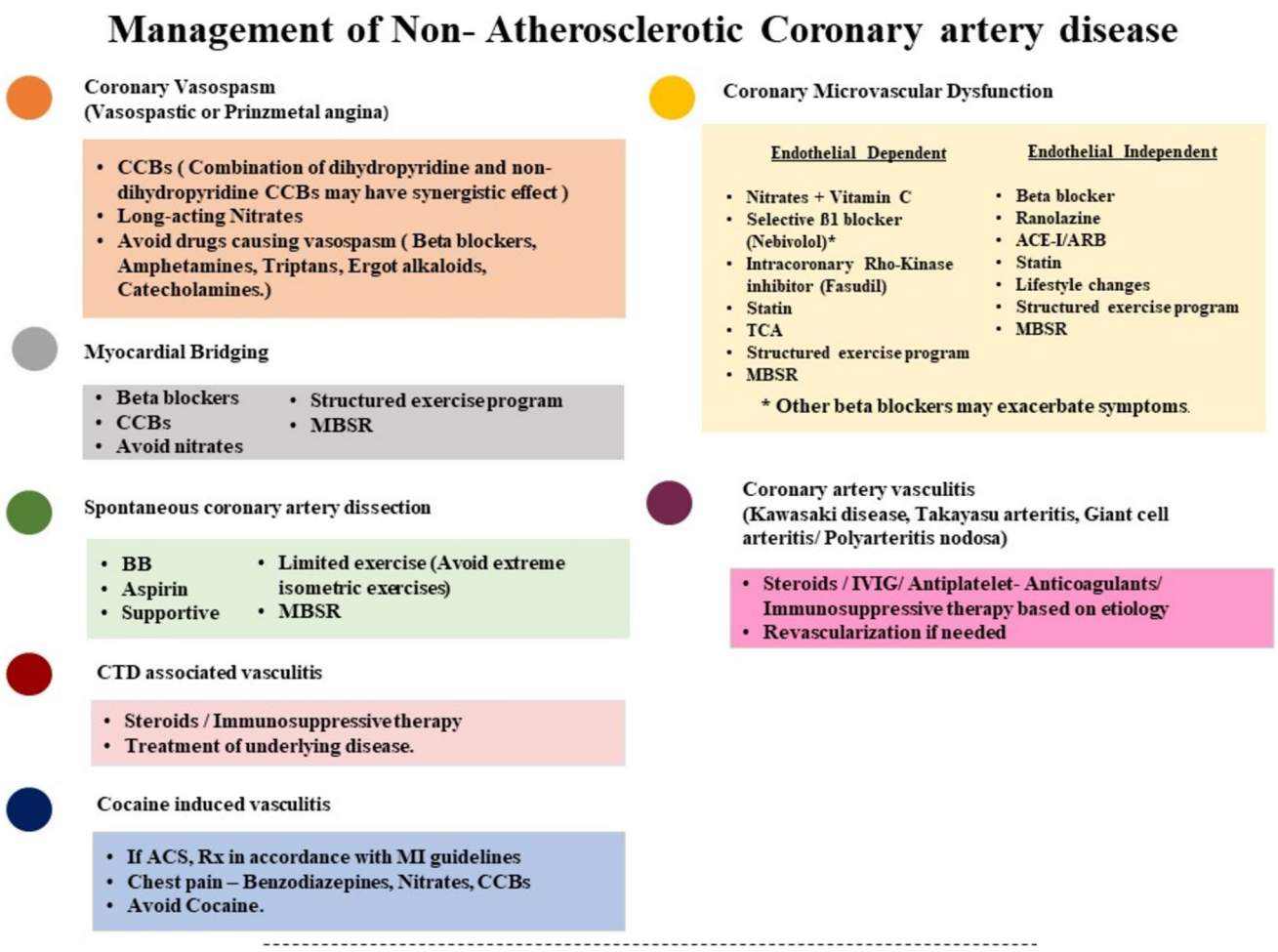

Fig. 9 Management considerations in INOCA (non-atherosclerotic coronary insults) [93, 95, 105]. CCBs, calcium channel blockers; MBSR, mindfulness-based stress reduction; BB, beta-blocker; TCA, tricyclic antidepressant; ACE-I/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ACS, acute coronary syndrome; Rx, treatment; IVIG, intravenous immunoglobulin

women than in men < 50 years (42.7% vs 37.8%) [99]. PCI in women is associated with a higher incidence of periprocedural bleeding and vascular complications following the intervention. In addition, women were also noted to have increased rates of post-procedural stroke/transient ischemic attack, infection, and death. Smaller body sizes and renal dysfunction were found to primarily contribute to these adverse effects in women [100].

CABG remains the preferred approach in patients with complex multivessel coronary artery disease and left main disease in both genders. A higher incidence of MACCE, MI, and repeat revascularization was noted in women (HR 1.12) after CABG in a pooled analysis of four major CABG trials (ART/CORONARY/GOPCABE/PREVENT IV trials) with a median follow-up of 5 years (Fig. 8C). However, all-cause mortality rates were similar at 5 years [101]. Another contemporary analysis involving 31 Midwestern hospitals revealed that the female gender was an independent predictor of increased in-hospital operative mortality in those undergoing CABG (risk-adjusted operative mortality 3.81% women vs 2.43% men) [102]. Overall, several of the adverse effects in women following any type of intervention were attributed to their delayed presentation, comorbidities, small body mass index, and delayed time of intervention due to their atypical symptoms [103•].

It should be remembered that patients with misdiagnosed coronary vasospasm and SCAD who later establish coronary flow can lead to early graft closure and atresia due to competitive flow in native circulation [104].

As previously discussed, women have a higher prevalence of non-atherosclerotic mechanisms of ischemia. While well-established guidelines exist for obstructive CAD, the management of the non-atherosclerotic disease is evolving. We summarize the management approach based on the underlying mechanism in Fig. 9.

Conclusion

Women are not men with pesky hormones. Hormonal changes throughout a woman's life significantly affect cardiovascular biology. In this contemporary review, we emphasized the life stages of women in relation to coronary artery disease and other gender-specific conditions. Dedicated research and emphasis on understanding gender differences in coronary biology are needed to better address the discrepancies in care. Future diagnostic and therapeutic algorithms should be tailored to incorporate gender-based biological differences.

Data Availability Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Declarations

Conflict of Interest Dhivya Velu, Abhiram Challa, Yasmin Hamirani, Varunsiri Atti, Anhthu Trinh, Roberta Renzelli-Cain, and Madhavi Kadiyala declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human and animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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