Chapter 1
Gender-Related Differences in the Pathogenesis and Diagnosis of Ischemic Heart Disease

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Abstract Gender plays an important role in the pathophysiology, clinical presentation, and outcomes of various medical illnesses. Among those, special interest is directed towards ischemic heart disease, being the most common cause of mortality in the United States and the developed world. The prevalence and pathogenesis of traditional cardiovascular risk factors differ between women and men, including hypertension, diabetes, dyslipidemia, as well as smoking and psychosocial risk factors such as depression, emotional stress, and low socioeconomic status. However, the difference in the pathophysiology of atherosclerosis represents the hallmark of gender-related discrepancies in ischemic heart disease. While men are more likely to have obstructive coronary artery disease (CAD), women have a higher prevalence of endothelial dysfunction, more tendency for vasospasm, lower coronary flow reserve, and higher incidence of plaque erosion than rupture compared with men. These differences are, at least in part, attributed to variations in sex hormones. Not only that gender affects the pathophysiology of CAD, but also impacts the difference in its clinical presentation. Women are more likely to present with atypical symptoms, and hence are more likely to present late or to be misdiagnosed. This has been shown to adversely impact the outcomes of CAD in women compared with men. Further, the utilization of various modalities for the diagnosis of CAD in women may be

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challenging due to multiple factors including limited exercise capacity, lower sensitivity of exercise-induced changes in electrocardiogram, higher prevalence of single-vessel disease, attenuation artifacts from breast tissue, and the higher likelihood of endothelial dysfunction rather than obstructive CAD. Clinicians should pay special attention to such differences aiming to improve outcomes in women with ischemic heart disease.

Keywords Gender · Sex · Women · Ischemic heart disease

Introduction

Among both women and men, ischemic heart disease remains the most common cause of mortality in the United States and the developed world [1]. Furthermore, it represents a heavy burden on the healthcare system in the United States with more than 1.4 million hospitalizations per year [1]. There is emerging evidence that ischemic heart disease presentation and outcome differ between women and men. In this chapter, we highlight the gender-related differences in the pathogenesis and diagnosis of ischemic heart disease.

Gender-Related Differences in the Pathogenesis of Ischemic Heart Disease

(A) Risk factors for coronary artery disease

Hypertension

Among the traditional risk factors for coronary artery disease (CAD), there are important differences in the prevalence and pathogenesis of hypertension between men and women. While the overall prevalence of hypertension appears to be similar among women and men, the prevalence is higher among women over the age of 65 [2], especially black women [3], and could be attributed to hormonal changes [4]. Estrogen plays a beneficial role in systemic blood pressure regulation through vascular vasodilation (either via a direct effect on the endothelial cells or indirectly through promoting nitric oxide release), as well as modulation of the renin-angiotensin system (via increasing the synthesis of angiotensinogen and suppressing the activity of pro-hypertensive angiotensin type 1 receptor and reducing the activity of angiotensin type 2 receptor) [5]. The drop in estrogen levels after menopause may be the basis of higher prevalence of hypertension in elderly women. Higher prevalence of hypertension in women > 65 years may relate to higher rates of CAD in elderly women.

Diabetes, obesity, and insulin resistance

Diabetes is among the most important risk factors for CAD. Diabetic women have comparable outcomes as age-matched men, indicating that diabetes may counteract the advantage of female sex hormones in the pathogenesis of CAD [6]. The peripheral adipose tissue distribution as well as the higher levels of adiponectin in women are associated with improved insulin sensitivity and provides some protection from insulin resistance, the hallmark of metabolic syndrome, compared to men [7–10]. Obesity is an important risk factor for diabetes and CAD. While the burden of obesity affects women and men equally, women above the age of 60 years have higher prevalence of metabolic syndrome [11–13], and among women, black women have the highest prevalence [14]. On the other hand, it is important to recognize that polycystic ovarian syndrome, which is present in about 10% of women, and includes a constellation of obesity, diabetes, and metabolic syndrome-like picture may relate to the higher prevalence of CAD. Treatment of this disease may reverse these risk factors and reduce the risk of cardiovascular disease [15].

Dyslipidemia

While pre-menopausal women (age 20–55 years) have lower cholesterol levels compared to men, the levels increase significantly after the age of 55 years in women. That is usually linked, at least in part, to the increased cardiovascular risk in elderly women [16]. On the cellular level, not only that women have higher levels of high-density lipoprotein (HDL) cholesterol and lower levels of low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, total plasma triglyceride and VLDL triglyceride compared to age-matched men [5], their circulating VLDL particles are smaller in size, while HDL are larger in size, which appears to be inversely associated with cardiovascular disease [17, 18]. Furthermore, hepatic lipase activity in women is much lower compared with men, leading to relatively larger size of HDL and LDL particles. Small HDL and LDL were found to be linked to increased cardiovascular disease risk [19, 20]. Further, low HDL and high triglyceride levels are more predictive of the risk of cardiovascular disease in women compared with men [21–23].

Smoking

Smoking is the single most important modifiable risk factor for CAD and contributed to 480,000 premature deaths in the U.S. from 2005–2009 [2], one-third of which were a result of secondhand smoke. The prevalence of smoking remains higher in men than women, however, the recent decline in tobacco use is less pronounced in women than in men [16]. Tobacco is known to be a major cause of endothelial dysfunction. It promotes inflammatory environment, stimulates platelet aggregation, increases oxidative stress, and induces vasospasm [24, 25]. Interestingly, the impact of smoking as a risk factor for cardiovascular disease was found to be at least 25% greater in women than age-matched men [26]. Smoking cessation is associated with a decline in the risk of cardiovascular disease to the levels of non-smokers in 5–10 years [27, 28].

Psychosocial risk factors

Psychosocial stress plays a role in the pathophysiology of CAD [29]. Among the important psychosocial factors, depression is more prevalent in women and was found to be present in up to 40% of young women presenting with acute myocardial infarction [30]. Not only depression increases the risk of cardiac events in women by at least 50% [31–33], it is also related to poor adherence to medical therapy after cardiac events and worse overall outcomes. In addition, emotional stress, either acute or chronic, is a known risk factor for acute coronary syndromes in women. Multiple studies have shown a relationship between anxiety and marital dissatisfaction with the risk of cardiac events and progression of CAD [34–37]. Importantly, low level of education, poor socioeconomic status, smoking, obesity, metabolic syndrome, and lack of exercise, all of which are highly associated with CAD [38], may be more pronounced in women than in men. The gender differences among different risk factors are summarized in Table 1.1.

(B) **Plaque burden and morphology**

While atherosclerosis is an inflammatory process that involves multiple factors such as dyslipidemia, endothelial dysfunction and oxidative stress [39–43], the resultant atherosclerotic plaques differ in morphology and burden between women and men [13, 44]. Men have been shown to have more obstructive CAD than women

Table 1.1 Gender differences in cardiovascular risk factors

Risk factor	Compared with men, women have
Hypertension	• Higher prevalence of hypertension above age of 65
Diabetes	• More peripheral adipose tissue distribution and higher levels of adiponectin which is associated with improvement in insulin sensitivity
Obesity and metabolic syndrome	• Higher prevalence of obesity and metabolic syndrome above age of 65
	• Polycystic ovarian syndrome associated with obesity and diabetes and metabolic syndrome-like picture
Dyslipidemia	• Lower levels of Cholesterol at age 20–55 years
	• Higher levels of HDL cholesterol
	• Lower levels of LDL cholesterol, VLDL cholesterol, and total plasma triglyceride
	• Smaller VLDL particles
	• Larger HDL particles
	• Less hepatic lipase activity
Smoking	• The recent decline in tobacco use is less pronounced in women than in men
Psychosocial risk factors	• Depression, anxiety, and emotional stress are more prevalent in women than men and are all known risk factors of coronary artery disease and acute coronary syndrome

in multiple studies [45–47]. Atheromatous plaques in men have more volume, are more commonly eccentric [13, 44], more likely to have calcification [48], with more structural and functional abnormalities in epicardial coronary arteries than women [11], while women have less dense fibrous tissue in their plaques [49, 50], and are more likely to have angiographically normal coronaries on angiogram. Women have higher prevalence of endothelial dysfunction, more tendency for vasospasm [2, 4, 51, 52], and lower coronary flow reserve compared with men [11, 44]. Furthermore, compared with men, women exhibit higher incidence of plaque erosion than rupture [53], and increased hyaluronan deposition, as well as elevated levels of serum myeloperoxidase [54, 55].

The differences in plaque burden and morphology among women and men are summarized in Table 1.2.

(C) Vascular biology and microvascular disease

Studies relating to vascular biology have led to better understanding of the pathogenesis of atherosclerosis. As mentioned above, while the burden of epicardial CAD may be less in women compared with men, coronary microvasculature plays a major role in the development of atherosclerosis and CAD is women. Women have higher incidence of impaired NO-dependent vasodilation of the coronary microvasculature, resulting in more microvascular spasm and vasospastic angina [56]. Microvascular dysfunction is considered an important part of the pathophysiology of chest pain in the absence of significant coronary obstruction, also known as microvascular

Table 1.2 Gender differences in atherosclerotic plaque burden, plaque morphology, and Pathophysiology of acute coronary syndrome

Criteria	Compared with men, women have
Plaque burden	• Less obstructive CAD and more likely to have normal coronaries on angiogram
	• Higher prevalence of endothelial dysfunction
	• More tendency for vasospasm
	• Lower coronary flow reserve
Plaque morphology	• Less volume
	• Less calcification
	• Less dense fibrous tissue
	• More centrally oriented
	• Increased hyaluronan deposition
	• Elevated levels of serum myeloperoxidase
Pathophysiology of ACS	• Higher incidence of plaque erosion than rupture
	• Higher incidence of SCAD

ACS = acute coronary syndrome
CAD = coronary artery disease
SCAD = spontaneous coronary artery dissection

angina [57, 58]. The authors of the WISE (Women's Ischemia Syndrome Evaluation) study [59], showed a clear role for estrogen in mediating vasodilation of coronary microvasculature through myocyte hyperpolarization, increase in prostacyclin production, and inhibition of myocyte-mediated vasoconstriction induced by calcium and endothelin-1 [59]. Of note, other studies showed that part of estrogen-induced coronary vasodilation is independent of these classical pathways and is mediated through changes in ATP-sensitive potassium or calcium channels [60]. As levels of estrogen decrease, women become more predisposed to microvascular dysfunction. Further etiologies of microvascular dysfunction in women without obstructive CAD include abnormal response of phosphocreatine/ATP to exercise indicating a shift to anaerobic metabolism consistent with myocardial ischemia [2, 52], as well as impairment of coronary flow velocity reserve [61].

Estrogen plays multiple other roles at the cellular level. For example, it accelerates the catabolism of reactive oxygen species through up-regulation of multiple enzymes such as superoxide dismutase and catalase. Thus, it reduces oxidative stress and increases free NO levels [9, 62]. Besides the classic NO/cGMP mediated pathway for vasodilation, estrogen also causes direct smooth muscle relaxation via endothelium derived hyperpolarizing factor (EDHF) [9, 63]. Furthermore, estrogen plays an important role in modulating the shear stress-mediated regulation in arteriolar diameter through G-protein-coupled estrogen receptors (GPER) in the vascular endothelium [18, 64, 65].

The role of estrogen and androgen in vascular biology and pathogenesis of atherosclerosis is shown in Fig. 1.1.

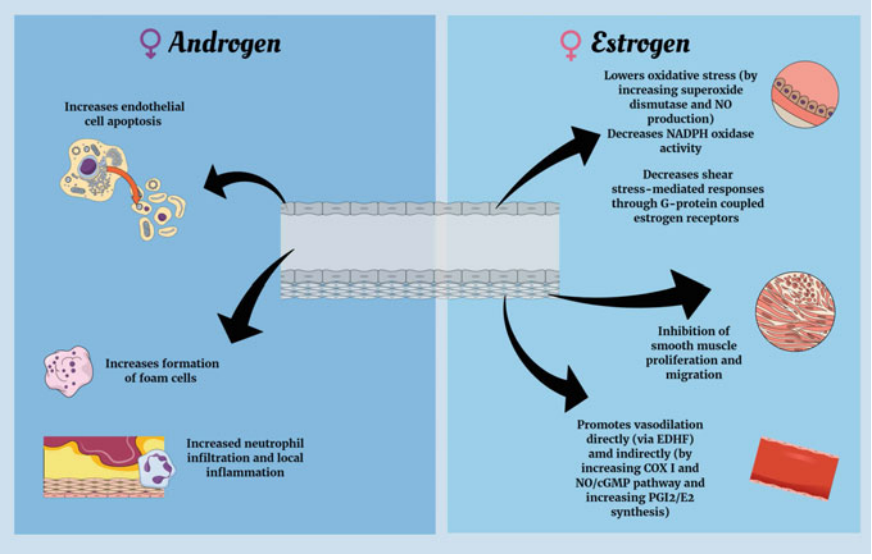

Fig. 1.1 The role of estrogen and androgen in the vascular biology and pathogenesis of atherosclerosis

(D) Coronary artery dissection

Although spontaneous coronary dissection (SCAD) was considered to be a rare cause of acute coronary syndrome, evidence is emerging that SCAD is the underlying etiology in 10–25% of patients with myocardial infarction, predominantly in women younger than 50 years of age [66–68] without atherosclerotic CAD. SCAD most commonly affects the left anterior descending artery [68], and is caused either by an intimal tear or bleeding of vasa vasorum leading to intramural hematoma and false lumen between the media and adventitia [69, 70]. While the underlying trigger remains unclear, hormonal changes with subsequent weakening of the arterial walls are among the main theories behind SCAD [71]. Multiple other factors include inflammatory disorders, hemodynamic stress during pregnancy or peripartum period, coronary vasospasm, and connective tissue disorders [72, 73]. In a recent National Inpatient Sample analysis of 7,347 women with SCAD in the period from 2009–2014, in-hospital mortality with acute myocardial infarction in the setting of SCAD was 6.8%, and outcomes appeared to favor conservative management especially in patients with non-ST-segment elevation myocardial infarction (NSTEMI) [74].

(E) Acute myocardial infarction

Acute myocardial infarction is a leading cause of death in the United States, with more than 610,000 deaths annually [75]. Development of atherosclerotic plaque is usually the initial step in the pathophysiology of AMI. Disruption of the endothelium overlying these plaques triggers a cascade of pro-inflammatory events that in turn lead to activation of multiple pro-thrombotic factors. Ann et al. described gender-related differences in plaque morphology in patients with STEMI [76]. Yahagi et al. [77] observed that AMI in men was more often associated with thin cap vulnerable plaques than in women. Hence, men are more likely to present with a ruptured plaque than women. Ruptured plaques are characterized by abundant foamy macrophages which are potent stimulator of the coagulation cascade, resulting in more frequently in an occlusive thrombus [78]. Although plaque rupture remains the main etiology of AMI in women, it is more prevalent in men than women [79]. In contrast, plaque erosions are seen more commonly in women than men and are associated with a less dramatic coronary obstruction and micro-embolization [80].

Another gender-related difference is the severity of CAD at the time of AMI. Early studies showed less plaque burden and obstructive CAD in women by angiogram in the setting of acute coronary syndrome, and normal appearing coronaries are not uncommon [47]. Intravascular ultrasound (IVUS) examination of plaques showed less eccentric location, more fibrous tissue, and less prevalence of thin-cap fibroatheromas [80, 81]. Women are more likely to have microvascular dysfunction and impaired coronary flow reserve [82, 83], which may explain acute coronary syndromes in women without significant CAD. SCAD is another major entity resulting in AMI that predominantly occurs in women as mentioned before.

These differences in plaque burden and morphology as well as the pathophysiology of AMI are, at least in part, attributed to variations in sex hormones. On

the cellular level, estrogen promotes re-endothelialization, reduces leukocyte adhesion molecules, and inhibits smooth muscle proliferation as well as matrix deposition in response to any vascular injury, hence acts as a major protective agent against atherosclerosis [84–86]. Estrogen also enhances vasodilation of coronary arteries through the production of NO and vasodilator prostaglandins PGE2 and PGI2 through estrogen receptors ERa and ERb [84]. These protective effects of estrogen are believed to be the main reason for the reduced burden of atherosclerosis and the lower incidence of AMI in premenopausal women.

Gender-Related Differences in the Diagnosis of Ischemic Heart Disease

The Symptomatic Conundrum

The symptomatic conundrum is a common term in the current cardiology literature. It describes the fact that women present with different CAD symptoms compared with men. Reasons for higher CAD mortality in women include older age at initial presentation and relatively smaller use of diagnostic tools [87]. Symptoms in women are often "atypical" and may include dyspnea, heartburn, bloating, or generalized fatigue. The symptomatic conundrum often leads to underappreciation of presenting symptoms and feeds the unawareness of association of these symptoms with CAD [88]. In ACS, despite the fact that most women present with typical symptoms including chest and/or arm pain, the likelihood of presenting with atypical symptoms is still high [89, 90].

The symptomatic conundrum not only leads to underappreciation of the symptoms by medical practitioners, but also leads to significant delay of care as the symptoms are also underappreciated by the patient. In a study by Rosenfeld et al. in 2005, 52 US women who presented with AMI were investigated; a large proportion of them attributed their symptoms to alternative causes or minimized their importance [91]. This could be partly explained by the common underestimation of CAD risk in women. In The Berlin Female Risk Evaluation (BEFRI) study, only half of urban women correctly estimated their CAD risk [92].

The symptomatic conundrum can have serious consequences. In stable CAD patients, it might lead to delay of care and lack of appropriate therapy that could help with the patients' symptoms and improve their quality of life. On the other hand, it might lead to late presentation in AMI, especially STEMI, delaying effective reperfusion therapy and leading to more serious long-term sequelae [93].

It is also important to understand that despite the underestimation of CAD risk, women actually have about 20% higher prevalence of angina compared with men. Women also report persistent or worsening symptoms at a rate that is double that of men [94–97]. There is a much larger pool of women with nonobstructive and obstructive CAD who report a heavy burden of symptoms compared with men [98]. Younger women tend to present with absence of chest pain and suffer worse outcomes

in comparison with their male counterparts. But, this is attenuated by age, with the difference between genders in the absence of chest pain narrowing or disappearing as age advances [99].

The impact of symptomatic conundrum has led to gender-based differences in the work-up of CAD. Women presenting with CAD symptoms might not be thoroughly investigated as men. Data from Euro Heart Survey in the management and clinical outcomes of stable angina (3779 patients, 42% women) showed that women were less likely to be referred for an exercise test or coronary angiography [100]. Another cross-sectional survey of 1162 patients with angina showed that physicians were more likely to note the risk factors in men and refer them for further work-up [88]. However, an Italian study investigating the use of cardiac procedures in relation to age and sex found that there was an age bias but no gender bias in referral to cardiac catheterization [101]. It is not unreasonable to assume that the underappreciation of CAD because of atypical symptoms in women would result in incorrectly reassuring patients without appropriate diagnostic tests.

Diagnostic Modalities

(A) **Exercise EKG test**

The choice of diagnostic testing and risk stratification in women suspected to have CAD can be challenging. Patients with low pretest probabilities of CAD, both men and women, are less likely to benefit from the addition of stress imaging test [102]. Therefore, for most patients at low-risk, exercise treadmill testing (ETT) without imaging is the initial test of choice for diagnosis and risk stratification. In the low-risk cohort who were able to exercise, the WOMEN trial [What is the Optimal Method of Ischemia Elucidation in Women] showed that the ETT alone was equivalent to ETT plus myocardial perfusion imaging (MPI) [103]. This is supported by guidelines and consensus statements of the ACC (American College of Cardiology) and American Society of Nuclear Cardiology (ASNC) [87, 94, 104, 105].

Exercise stress testing is physiologic and provides a constellation of clinical, electrocardiographic (EKG) and hemodynamic data; therefore, it is generally preferred over pharmacological testing [106]. However, exercise-induced ST depression may be less sensitive in women compared with men [107]. Exercise-induced ST depression in the absence of CAD could be secondary to changes in estrogen levels during the menstrual cycle [108, 109] or due to menopausal hormone therapy which renders EKG changes less accurate in women compared to men [110]. A recent study by Fitzgerald et al. found that the prevalence of false-positive exercise ST depression might be equal in men and women but with less predictable causes in women such as left ventricular hypertrophy and hypertension [111] Although endothelial dysfunction is thought to be a hallmark of atherosclerosis, a study found no relationship between endothelial dysfunction and exercise-induced ST depression in women [112].

Most women referred for stress testing often have limited exercise capacity as they are typically older with significant comorbidities. This is one of the major difficulties as they are often unable to reach a sufficient workload, resulting in submaximal tests of limited sensitivity. In women who are unable to exercise adequately, pharmacological stress testing is reasonable (e.g., adenosine MPI or dobutamine stress echocardiogram).

(B) **Stress imaging**

In symptomatic women who are at intermediate to high risk for CAD and have baseline EKG ST-T abnormalities, stress imaging with echocardiography, radionuclide single-photon emission computed tomography (SPECT), and positron emission tomography (PET) are recommended as the initial diagnostic modality. It is also reasonable to consider stress imaging as the initial modality in women who have poor exercise capacity or an abnormal stress EKG [113–116]. In the WOMEN trial, women with intermediate to high pretest risk, use of myocardial perfusion imaging (MPI) along with ETT was associated with higher accuracy to detect obstructive CAD [103].

Radionuclide single-photon emission computed tomography

Several studies have reported gender-based differences in the diagnostic accuracy of SPECT MPI. The diagnostic accuracy has been reported to be lower in women than men [117–119]. There are multiple reasons for this which include lower exercise capacity, higher prevalence of single-vessel disease, and anterior wall attenuation artifacts from breast tissue. Women also have a smaller heart size which often results in a blurred image affecting the sensitivity of the test [120]. Women also have higher left ventricular ejection fraction (LVEF) [121] leading to higher normal limits of transient ischemic dilation ratio [122]. The use of attenuation correction significantly improves the specificity of SPECT MPI, especially in women with high probability of breast tissue attenuation but does not typically affect the sensitivity of SPECT MPI [123, 124]. Another method to increase accuracy in women is using gender-based normal limits and software interpretation [125]. It is currently recommended by American Society of Nuclear Cardiology (ASNC) to use gender-based normal limits for reporting of LVEF and volumes [104].

The prognostic value SPECT MPI in women has also been debated. However, in a large meta-analysis, women with normal SPECT MPI had prognosis comparable to men with 99% event-free survival over 36 months [126]. A normal study with both normal SPECT MPI and stress EKG has excellent prognosis regarding CAD death or MI [127]. On the other hand, abnormal studies are associated with increases in adverse CAD events and worse prognosis in women [128]. Left ventricular volumes and LVEF on SPECT MPI also provide an added prognostic value in predicting CAD death or MI. Other studies have confirmed the excellent prognostic value of SPECT MPI in women, including elderly women [130] and women of diverse racial and ethnic subsets [131]. It is also important to note that some women have a normal

SPECT with ischemic EKG changes [132]; these patients have worse outcomes with more cardiovascular events despite normal perfusion pattern [133].

Positron emission tomography

The use of PET has been associated with improved diagnostic accuracy compared with SPECT [134, 135]. The use of PET has provided multiple advantages over SPECT including depth-independent attenuation correction, higher spatial and temporal resolution, lower radiation dose with radiopharmaceuticals that have short half-lives. PET also provides the ability to perform absolute quantification of myocardial perfusion [136]. These advantages render PET preferable in women as it negates the higher risk of both false positive and false negative studies given breast tissue attenuation, and amplified partial volume effects in small left ventricles, respectively. The ability to measure absolute myocardial blood flow is specifically relevant in women who have higher incidence of microvascular ischemia that is increasingly recognized to be associated with significant cardiovascular morbidity and mortality [137–139].

Regarding prognosis, a normal PET scan carries an excellent prognosis with 0.4% annual event rate [140] An abnormal PET study is associated with worse prognosis with more perfusion defects being associated with a graded increase in risk [141]. The prognostic value was found to be similar in men and women in the PET Prognosis Multicenter Registry sex-specific sub-analysis [142].

Stress echocardiography

Similar to stress MPI, stress echocardiography significantly improves the specificity and sensitivity for CAD diagnosis. Echocardiography has its limitations in women which include the variability in acoustic windows with breast tissue and being operator-dependent, which affects the ability to capture images at maximal stress. The diagnostic accuracy of stress echocardiography is generally comparable in men and women [143] The echocardiographic evidence of ischemia on pharmacologic stress echocardiography was found to be the only independent predictor of cardiovascular events in 456 women in the study by Cortigiani et al. [144]. Despite its limitations, stress echocardiography is preferred in pregnant and young women due to the absence of ionizing radiation needed for the test.

(C) **CT coronary angiography**

CT coronary angiography (CTCA) has evolved as a reliable gatekeeper of invasive coronary angiogram. A negative CT study reliably excluded obstructive CAD with a high degree of certainty in two independent studies [145, 146]. In patients at low to intermediate risk of CAD, CTCA is highly accurate in excluding the presence of obstructive disease [147], and the accuracy of CTCA is similar in men and women [147–149]. With advancing techniques and the development of CT-derived fractional flow reserve, future application of CTCA might improve outcomes in women suspected to have CAD. The main limitations of CTCA in women include radiation

exposure and lower positive predictive value leading to increased downstream testing with invasive testing.

(D) Coronary angiography in women

Coronary angiography remains the gold-standard for diagnosis of CAD. In women, a limitation of coronary angiography is the higher prevalence of non-obstructive CAD [150]. Significant obstructive lesion may not be identified in the cardiac catheterization laboratory unless coronary flow reserve is measured [151]. Women generally have smaller left ventricles and small coronary artery sizes. The smaller size along with breast tissue attenuation leads to partial inability to assess smaller mid and distal coronary segments [152, 153]. Moreover, interpretation of the severity of lesions might be different between men and women due to the difference in the area of myocardium supplied. In the FAME trial sub-study, angiographic lesions with similar severity in men and women were less likely to be ischemia-producing in women [154].

The use of fractional flow reserve (FFR) assessment of undetermined lesions have been evolving because of the superiority over angiography-guided PCI [155] However, using similar FFR values to guide therapy in women and men have been debated. In 2014, a study by Lin et al. in 1,090 patients, women who underwent FFR-guided PCI had less favorable long-term outcomes compared with men [156]. This study raised the issue to consider gender-based FFR-guided treatment protocols. More studies are required to further characterize the best women-specific FFR-guided treatment strategy.

The gender-related differences in utilization of various diagnostic modalities for CAD are summarized in Table 1.3.

Table 1.3 Gender differences in clinical presentation and role of diagnostic modalities in coronary artery disease

Criteria	Compared with men, women have the following characteristics
Clinical presentation	• Older age at presentation
	• More likely to present with atypical symptoms (ex. dyspnea, heartburn, bloating, or generalized fatigue) leading to late presentation and significant delay of care
	• Less likely to be referred for an exercise test or coronary angiography
Diagnostic modalities	
1. Exercise stress EKG	• Exercise-induced ST depression may be less sensitive
	• Similar prevalence of false positive exercise ST depression but with less predictable causes in women (e.g. left ventricular hypertrophy, hypertension, etc.)
	• Limited exercise capacity (typically older with significant comorbidities)

(continued)

Table 1.3 (continued)

Criteria	Compared with men, women have the following characteristics
2. SPECT MPI	• Diagnostic accuracy has been reported to be lower in women than men due to (a) lower exercise capacity, (b) higher prevalence of single-vessel CAD, (c) attenuation artifacts from breast tissue, (d) smaller heart size, (e) higher normal limits of transient ischemic dilation ratio
3. PET	• Improved diagnostic accuracy with PET in women as it
	(a) Overcomes the disadvantages of SPECT
	(b) Measures absolute myocardial blood flow (important to detect microvascular ischemia)
	(c) Normal PET carries an excellent prognosis
4. Stress echocardiogram	• Diagnostic accuracy may be affected by poor acoustic windows with breast tissue, however in general is comparable with men
	• Preferred in pregnant and young women (avoid ionizing radiation)
5. CT coronary angiography	• Diagnostic accuracy of CTCA is similar in men and women
	• Limitations in women include radiation exposure
6. Coronary angiogram	• Higher prevalence of non-obstructive CAD
	Small coronary artery size in women leads to partial inability to assess smaller mid and distal coronary segments
	• Possible differences in the outcomes of FFR-guided PCI in women versus men

ACS = acute coronary syndrome
CAD = coronary artery disease
SCAD = spontaneous coronary artery dissection
EKG = Electrocardiogram
SPECT MPI = Single-photon emission computed tomography myocardial perfusion imaging
PET = Positron emission tomography
CTCA = Computed tomography coronary angiography
FFR = functional flow reserve
PCI = percutaneous coronary intervention

Summary

Women have a significant burden of coronary atherosclerosis. This burden increases in post-menopausal years and is ascribed to a decline in estrogen levels; however, the precise etiology is not known. In addition to the atherosclerotic burden, women tend to have a higher prevalence of microvascular angina. Women generally present late and with atypical symptoms of ischemia and hence diagnostic strategies are employed late. There are also variabilities in the use and result of diagnostic strategies in men and women. Reperfusion strategies are used less often in women resulting in adverse outcomes. It is likely that better recognition of these unique gender differences in CAD will lead to improved outcomes in women.

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