

Stable ischemic heart disease in women: current perspectives

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Abstract: Cardiovascular disease is the leading cause of death in women accounting for 1 in every 4 female deaths. Pathophysiology of ischemic heart disease in women includes epicardial coronary artery, endothelial dysfunction, coronary vasospasm, plaque erosion and spontaneous coronary artery dissection. Angina is the most common presentation of stable ischemic heart disease (SIHD) in women. Risk factors for SIHD include traditional risks such as older age, obesity (body mass index [BMI] >25 kg/m²), smoking, hypertension, dyslipidemia, cerebrovascular and peripheral vascular disease, sedentary lifestyle, family history of premature coronary artery disease, metabolic syndrome and diabetes mellitus, and nontraditional risk factors, such as gestational diabetes, insulin resistance/polycystic ovarian disease, pregnancy-induced hypertension, pre-eclampsia, eclampsia, menopause, mental stress and autoimmune diseases. Diagnostic testing can be used effectively to risk stratify women. Guidelines-directed medical therapy including aspirin, statins, beta-blocker therapy, calcium channel blockers and ranolazine should be instituted for symptom and ischemia management. Despite robust evidence regarding the adverse outcomes seen in women with ischemic heart disease, knowledge gaps exist in several areas. Future research needs to be directed toward a greater understanding of the role of nontraditional risk factors for SIHD in women, gaining deeper insights into the sex differences in therapeutic effects and formulating a sex-specific algorithm for the management of SIHD in women.

Keywords: stable ischemic heart disease, women

Introduction

Heart disease is the leading cause of death in women in the USA, killing 289,758 women in 2013 – that is about 1 in every 4 female deaths, according to National Vital Statistics Report.¹ Despite increases in awareness about the high risk of heart disease, in one study, it was shown that only 56% of women recognize that heart disease is their number one killer.² The absolute numbers of women living with cardiovascular disease and stroke, as well as the number of hospital discharges for heart failure and stroke, exceeded those of men.³ Although women are generally under-tested and undertreated for coronary artery disease (CAD) with increased morbidity and worse prognosis,⁴⁻⁶ it is only recently in 2013, for the first time since 1984, that the mortality from cardiovascular diseases has been shown to be lesser for women than men.⁷ The onset of ischemic heart disease (IHD) in women is typically about 10 years later than men, with the prevalence increasing rapidly post menopause.⁸ Stable IHD (SIHD) includes a spectrum of presentations notably:

1. Patients who have suspected IHD with stable chest pain or ischemic equivalent symptoms such as dyspnea, exertional arm or jaw pain.

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2. Patients on chronic medical therapy after revascularization.
3. Patients with positive stress tests.⁹

The symptoms, risk factors, pathophysiology, management and prognosis of SIHD differ significantly between men and women. In this review, we aim to provide a concise overall summary of SIHD in women with emphasis on current practices.

Pathophysiology

It is known that women have smaller coronary arteries per 100 g of left ventricular mass after correcting for body surface area,¹⁰ and their arteries have increased stiffness. But beyond these underlying anatomic differences, the pathophysiology of IHD in women is unique and extends beyond just anatomic epicardial coronary artery stenosis. In the Women's Ischemia Syndrome Evaluation (WISE) study, nearly 60% of women with chest pain who underwent coronary angiography did not have a critical lesion (defined to be >50% luminal stenosis in a coronary artery).¹¹ Shaw et al¹² postulate that coronary microvascular and endothelial dysfunction plays a more important role in women as compared with men. Hormonal alterations coupled with pro-atherogenic risk factors result in higher prevalence of coronary microvascular dysfunction in women and are responsible for the observed ischemia paradox; despite having higher prevalence of angina, they tend to have lower prevalence of obstructive CAD and worse prognosis when compared with men.¹³ Any factor in addition to the underlying atheroma that diminishes the luminal flow further due to abnormal coronary reactivity such as coronary artery vasospasm, endothelial/microvascular dysfunction, autonomic nervous system adrenergic pathways or inflammation^{12,14,15} can be detrimental to myocardial perfusion. It has been shown that women have more diffuse non-obstructive coronary atherosclerosis and a greater frequency (twice as likely) of coronary plaque erosion and distal embolization compared with men.^{16–19} In the postpartum female, hormonal, vascular and shear-stress-related factors have been shown to be associated with increased risk for spontaneous coronary artery dissections.²⁰ Hence, when evaluating women with ischemic symptoms and non-obstructive epicardial CAD, alternate mechanisms for ischemia such as endothelial dysfunction and microvascular angina should be considered.

Clinical presentation

Women typically present more commonly with symptoms of angina than men but are less likely to have anatomic obstructive CAD.^{21–23} Among 10,003 study subjects with stable

angina (5,270 women and 4,733 men) with intermediate probability of CAD enrolled in the PROMISE (Prospective Multicenter Imaging Study for evaluation of Chest Pain) trial, chest pain was equally common in men and women; however, women were more likely to characterize their chest pain as “crushing/pressure/squeezing/tightness” as opposed to men who characterized their pain as “aching/dull.”²⁴ In addition, women were more likely to describe pain in the neck and throat than men. Younger women are less likely to report chest pain/discomfort than men, this difference declines with increasing age.²⁵ The VIRGO study was a prospective cohort study of 2,349 (67%) women and 1,152 (33%) men aged ≤55 years hospitalized for acute myocardial infarction (MI; n=3,501) in the USA and Spain, evaluating sex differences in demographics, access to health care, cardiovascular risk and psychosocial factors, clinical presentation, pre-hospital delay and hospital management for acute MI. In this study, women presented with more symptoms, waited more than a week to seek health care than men and were more likely to not think that their symptoms were heart related.²⁶ Because of these features, it was hypothesized that women who present to the emergency department with new-onset angina undergo less rigorous evaluation than men.²⁷ Women usually present with higher clinical risk scores on average, but men present with higher levels of cardiac biomarkers and more classic electrocardiogram (ECG) findings.²⁶ In the PROMISE trial, women were less likely to have a positive stress test even though they had a high burden of cardiovascular risk factors.²⁴ This false sense of a “negative” stress test in symptomatic women with risk factors can lead to underestimating and possibly undertreating women with SIHD.²⁴ Similarly, it has been shown that ECGs are less frequently ordered in women, resulting in misdiagnosis of MI.²⁸ In addition, they are less likely to be admitted to a coronary care unit or to receive inpatient or outpatient cardiology consultations.²⁹

Despite having a higher prevalence of non-obstructive CAD, women even in the absence of critical lesions not only continue to have symptoms while on anti-ischemic therapy but also have 2.5% yearly risk of major adverse cardiac events (MACEs), ie, first occurrence of death (all-cause), nonfatal MI, nonfatal stroke or heart failure hospitalization that is threefold higher than the case-matched asymptomatic reference cohort.^{23,30}

Risk factors and risk stratification

Among participants of the PROMISE trial, women had a higher prevalence of traditional risk factors for CAD such as

older age, overweight (BMI >25 kg/m²), hypertension, dyslipidemia, cerebrovascular and peripheral vascular disease, sedentary lifestyle and family history of premature CAD. The prevalence of diabetes mellitus (DM) and metabolic syndrome was similar among both sexes, while smoking was greater in men than women.²⁴ Type II DM imparts a greater risk of IHD in women than men, primarily due to more favorable survival rates of women (than men) without DM.³¹ Nontraditional risk factors for IHD in women include gestational diabetes, insulin resistance/polycystic ovarian disease, pregnancy-induced hypertension, pre-eclampsia, eclampsia, menopause and autoimmune disease (systemic lupus erythematosus (SLE), rheumatoid arthritis and psoriasis; Table 1).³²

Rheumatoid arthritis and SLE are linked to a significant increase in the risk of CAD.³³ In the Framingham Offspring study, women with SLE between ages 34 and 44 years were 50 times more likely to have an acute MI than women without SLE.^{34,35} Currently, with advances in cancer therapy, there are many breast cancer survivors who are also at higher risk for CAD. Women who survive breast cancer are also at higher risk for cardiovascular disease-related mortality compared with women without breast cancer, and this increase in risk is encountered approximately 7 years after diagnosis.³⁶

Mental stress has adverse prognostic implication in cardiovascular disease and is increasingly being recognized as a modifiable nontraditional CVD risk factor particularly in women. In the randomized, double-blind, placebo-controlled, REMIT trial that evaluated the effect of escitalopram on mental stress-induced myocardial ischemia, compared with men, women had a greater rate of myocardial stress-induced myocardial ischemia and collagen-stimulated platelet reactivity to mental stress.³⁷ The data from REMIT suggested that women were at higher cardiovascular risk from mental

stress and also highlighted the gap in current risk prediction algorithms that fail to measure an entire facet of risk.

Women with stable angina can be stratified as low, intermediate or high risk based on their age and risk factors. Women without high-risk features at the age of ≥50 years are considered low risk, ≥60 years are considered intermediate risk and those ≥70 years are considered high risk. However, the addition of risk factors such as uncontrolled DM, peripheral arterial disease (PAD), chronic kidney disease, cerebrovascular disease, chronic obstructive lung disease, functional disability or exercise capacity <5 metabolic equivalents (METS) can reclassify patients from low- to intermediate- or intermediate- to high-risk status.³⁸ Many middle-aged women are shown to have low 10-year risk but high lifetime risk for cardiovascular disease.³⁹ Overall, mortality rates increase with increasing number of traditional risk factors from 1.5% for low-risk patients to 9% for high-risk patients with 2 or more risk factors.⁴⁰

The impact of the risk factors is much more adverse in women and thus places them at a higher CAD risk, as compared with men. For example, the risk of MI is much higher in women who are smokers and diabetic compared with men.⁴¹⁻⁴³ Diabetes also provides greater prognostic information in women than any of the other classic risk factors and is the only risk factor predictive of angiographic coronary lesions in women presenting with chest pain.⁴⁴ Hypertension is differentially related to IHD according to menopausal status: it is predictive of higher risk in premenopausal women than in postmenopausal women.⁴⁵ Overall, the evidence for menopause as a risk factor for IHD in women is weak.⁴⁶ As opposed to men, for whom low-density lipoprotein (LDL) cholesterol is more predictive, low high-density lipoprotein (HDL) cholesterol is a stronger coronary risk factor in women, and levels below 30 mg/dL are strongly associated with increased cardiovascular mortality.⁴⁷ In women,

Table 1 Risk factors for coronary artery disease in women

Major risk factors	Nontraditional risk factors
Hypertension	Chronic inflammatory autoimmune disease (SLE, RA, psoriasis)
Age	Menopause
Diabetes mellitus	Pregnancy-induced HTN, eclampsia, pre-eclampsia
Smoking	Gestational diabetes
Family history of premature CVD (men <age 55 or women <age 65)	Polycystic ovarian syndrome
Dyslipidemia (HDL-C <40 in men or <50 in women)	Mental stress/depression
Physical inactivity/obesity	

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Abbreviations: CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

fasting triglyceride levels greater than 400 mg/dL and the total cholesterol (TC) and HDL cholesterol ratio of ≥ 3.2 indicate increased risk.⁴⁸ A family history of premature CAD is also seen more frequently in women than in men with CAD.³⁰ Even mildly reduced renal function is associated with increased CAD risk in women: 5% increase in risk for every 10 mL/min decrease in glomerular filtration rate.⁴⁹

Screening for CAD in women

The Framingham risk score underestimates risk stratification in women, and classified greater than 90% women as low risk.⁵⁰ The Reynold risk score was later utilized for risk stratification in women and improved risk re-stratification in women.⁵¹ The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend using pooled cohort equations every 4–6 years as the screening test to estimate 10-year risk for atherosclerotic cardiovascular disease among African-American and White men and women aged 40–79 years.⁵² Using the risk factors of age, total and HDL cholesterol, systolic BP, DM and current smoking status, 10-year risk is considered low if the estimated risk is calculated to be $< 7.5\%$ and high if $\geq 7.5\%$. Those considered at high risk should undergo vigorous prevention management strategies (lipid management, weight reduction and exercise). If, after quantitative risk assessment, treatment decision still remains ambiguous, family history, hs-CRP, coronary artery calcium (CAC) score or Ankle Brachial Index can be taken into account to help with management.

Selection of diagnostic testing in women

A large array of diagnostic tests is available to the treating clinician to exclude significant CAD in the low-to-intermediate pretest probability patient. Test choice is mainly driven by the patient's ability to exercise, the interpretability of the electrocardiogram and the additional ancillary data required for a cardiac imaging examination. An [algorithm](#) from the AHA consensus statement highlights the basic diagnostic approach to women with stable angina.³⁸

Exercise ECG

For symptomatic women who are at intermediate risk with a normal baseline ECG and can exercise (> 5 METS), an exercise ECG stress test should be the initial diagnostic test (class I recommendation).³⁸ Exercise ECG has a lower sensitivity and specificity for the detection of obstructive CAD in women compared with men;⁵³ however, with integration of the Duke Treadmill Score, exercise ECG stress test becomes

highly accurate in predicting IHD in women.^{12,54,55} In a cohort of women, every unit increase in the Duke Treadmill Score is associated with lower mortality by 9% and each increase in MET exercise capacity lowers mortality by 17%.^{54,55}

Role of echo stress and myocardial perfusion imaging (MPI)

Stress echocardiography (with exercise or dobutamine) can be utilized as a diagnostic and prognostic tool among patients with either abnormal ECGs at baseline or those who cannot exercise (class I recommendation). In women, compared with exercise ECG stress testing alone, exercise echocardiography is more sensitive and specific.^{53,56,57} The overall diagnostic accuracy and prognostic value of stress echocardiography and stress MPI are very similar.^{58,59} Breast tissue artifacts can decrease the specificity of single-photon emission computerized tomography (SPECT) MPI among women when compared with men (94% for men and 74% for women, $P < 0.01$).^{60,61} However, use of attenuation correction, prone imaging, evaluation of left ventricular ejection fraction (LVEF) and wall motion can improve diagnostic accuracy in women.³⁸

Stress MPI positron emission tomography (PET) has improved spatial resolution, better image quality and increased diagnostic accuracy for the detection of obstructive CAD in obese women.⁶² In addition to perfusion imaging, PET gives insight into the absolute coronary blood flow and calculation of myocardial flow reserve (MFR). Diminished MFR (defined as < 1.9 – 2.0) indicates vascular abnormality and microvascular dysfunction particularly in women with non-obstructive CAD.⁶³ In premenopausal young women, the concern for radiation exposure should lead to either stress imaging via echocardiogram or perfusion CMR. High IHD risk women with stable symptoms may also be referred for stress imaging for functional assessment of ischemic burden and to guide post-test, anti-ischemic therapeutic decision-making.

CAC score and coronary computed tomography angiography (CCTA)

CAC score has a sensitivity of 96%–100% and specificity of 40%–66% in detecting obstructive CAD in women.^{41,42} It provides incremental value to the Framingham risk equation and pooled cohort equation in the evaluation of asymptomatic women who may benefit from aggressive lipid-targeted therapy.⁵⁰ The diagnostic accuracy of CCTA is similar among men and women, with a sensitivity of 85%–99% and specificity of 64%–90%.^{64–66} For symptomatic

women at intermediate IHD risk who have equivocal or intermediate ECG stress test results, CCTA is a valuable diagnostic modality. In premenopausal young women, CCTA dose reduction to <3 mSv should be considered.

Invasive coronary angiography

According to the 2014 ACC/AHA guidelines,⁶⁷ coronary angiography is useful for patients with presumed SIHD who have limiting ischemic symptoms despite guideline-directed medical therapy (GDMT) and who are candidates for coronary revascularization. Patients with SIHD with high-risk features on noninvasive testing should be considered for cardiac catheterization to define coronary anatomy.⁶⁷ This is especially important since the 10-year mortality in women increases with increasing CAD severity.⁶⁸ However, there are a number of studies demonstrating lower utilization rates of coronary angiography and revascularization in women, thus resulting in lower rates of aggressive evaluation and management leading to poorer outcomes.^{69,70} Among patients with stable chest pain, white women with 1- to 3-vessel CAD have 1.67- to 2.02-fold higher in-hospital mortality than white men.⁷¹

Despite worse symptoms, women referred for coronary angiography for suspected CAD usually have less extensive coronary disease than men, as judged by the number of diseased vessels, suggesting greater degree of microvascular disease in women.⁷² Hence, tests of vascular dysfunction such as magnetic resonance spectroscopy might be more helpful in women to demonstrate vascular dysfunction and identify those at high risk for poor cardiovascular outcomes.^{73,74} Nevertheless, the exclusion of significant epicardial CAD with a high level of confidence can be important for high-quality diagnosis and patient management. The diagnosis of IHD in women poses unique challenges to physicians, and further study is needed to identify appropriate diagnostic and therapeutic strategies for women with normal angiograms but persistent chest pain.

Management

Despite strong evidence that the pathophysiology of SIHD differs between the sexes, studies specifically geared toward answering clinical questions about the management of SIHD in women are lacking.⁶⁷ The same GDMT is recommended for both men and women, with the goal of improving survival and quality of life. Unfortunately, multiple studies have shown that women receive less GDMT than men, in particular, aspirin and beta-blockers. This disparity probably contributes to greater risk associated with IHD in women than men.^{75,76}

Lifestyle changes such as daily exercise, weight loss and dietary restrictions including reduced intake of saturated fats (<7% of total calories), trans-fatty acid (<1% of total calories) and cholesterol (<200 mg/day) are pivotal for decreasing IHD risk. A moderate-to-high dose of a statin therapy should be started in addition to lifestyle modifications, especially among intermediate- and high-risk women.⁶⁷ Statins in addition to reducing lipids also have a pleiotropic effect. They improve endothelial dysfunction^{77,78} and have proven benefit in coronary microcirculation.⁷⁹ Statins and angiotensin-converting enzyme inhibitors (ACEIs) together potentiate these effects. ACEIs have also shown to improve coronary flow reserve (CFR) particularly in women with low CFR.⁸⁰ Aspirin therapy should be used indefinitely in patients with SIHD but is not recommended for primary prevention of IHD among women aged <65 years.

Beta-blockers should be prescribed as initial therapy for relief of symptoms in patients with SIHD. Long-term beta-blocker therapy reduces ischemic burden and threshold in patients with SIHD and improves survival in patients with left ventricular dysfunction or history of MI.⁸¹⁻⁸³ Other anti-ischemic agents include calcium channel blockers, long-acting nitrates and ranolazine should be prescribed for relief of symptoms when beta-blockers are contraindicated or cause unacceptable side effects. Patients on beta-blockers have been shown to have an average of 0.31 fewer angina episodes per week than patients on calcium channel blockers⁸⁴ and lower risk of discontinuation due to adverse effects. If there is persistent anginal symptoms despite being on maximum tolerated dosage of beta-blockers, then add-on therapy with other anti-ischemic agents is recommended.⁶⁷ In a pilot randomized control trial, ranolazine in particular has shown improvement in angina and possibly myocardial ischemia particularly among women with low CFR.⁸⁵

Hormone replacement therapy has shown benefit in reducing perimenopausal symptoms, emotional well-being and osteoporosis in postmenopausal women; however, it is not recommended for reducing cardiovascular risk or improving clinical outcomes in women.^{86,87} In fact, a recent meta-analysis including 22 studies involving 43,637 women showed that in relatively healthy postmenopausal women, combined continuous hormone therapy increased the risk of a coronary event, venous thromboembolism and stroke. Estrogen-only therapy increased the risk of venous thromboembolism and stroke but did not increase the risk of coronary events.⁸⁸ Hormone replacement therapy, selective estrogen receptor modulators, antioxidant vitamins (vitamins C and E, beta

carotene) and folic acid do “not” prevent IHD in women and may be harmful. Revascularization with coronary artery bypass graft or percutaneous coronary intervention is recommended if maximum GDMT fails.

Pregnancy and CAD

CAD occurs 3–4 times more often in pregnant women than the age-matched nonpregnant women. The incidence of acute coronary syndrome (ACS) in pregnancy is 1 in 10,000 but this increases to 3 per 10,000 deliveries in women 40 years or older.⁸⁹ Coronary atherosclerosis is the primary etiology of ACS in the antepartum period, and coronary artery dissection is the dominant etiology in the postpartum period. Literature regarding SIHD in pregnancy is limited, but with increasing maternal age more and more pregnant patients with SIHD might be encountered, warranting practitioners to recognize and carefully manage these patients.

Gaps in knowledge and future directions

Women undergo hormonal changes throughout their lifespan starting from menarche to menopause and pregnancy. Many of these biological changes may affect the vulnerability of women for CAD and are incompletely understood currently. Other disease states such as autoimmune disease and vascular dysfunction that alter risk for CAD in women are interconnected with these changes. Future discovery work must be targeted toward unraveling these complex interactions and developing disease-modifying targets.

At the same time, we need to gain deeper insights into factors accounting for disparities in care of women with SIHD and implementation of science research addressing those factors. Finally, improved enrollment of women in large cardiovascular prevention and intervention trials is needed to gain a greater understanding of sex differences in therapeutic effects and perhaps a more nuanced sex-specific approach to managing SIHD in men and women.

Conclusion

Cardiovascular disease is the leading cause of death in women. Pathophysiology of IHD in women includes epicardial coronary artery, endothelial dysfunction, coronary vasospasm, plaque erosion and spontaneous coronary artery dissection. Angina is the most common presentation of SIHD in women. Diagnostic testing can be used effectively to risk stratify women. GDMT should be used effectively for symptom and ischemia management. Despite robust evidence regarding the adverse outcomes seen in women

with IHD, there still remains a knowledge gap in sex-specific cardiovascular diagnostics and therapeutics.

Disclosure

The authors report no conflicts of interest in this work.

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