Coronary Artery Disease in Women: A Review and Update

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Coronary artery disease is the leading cause of death in women in the United States. In fact, coronary events are responsible for one of every six deaths per year in the United States. Since 1984, more women than men have died of heart disease. Research has shown that there are significant differences in pathophysiology, screening, and treatment between men and women with coronary disease. Future research is needed to explain the sex-specific issues that have led to assumptions about the screening and treatment of coronary artery disease in women, which in turn have led to undertreatment and suboptimal care.
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Cardiovascular disease (CVD) remains the leading killer of women in the United States and in most developed countries in the world.[1] Nearly one-third of all deaths of women are from heart disease.[2] Of the 500,000 annual deaths from CVD in the United States, 267,000 women die of heart attacks. The Centers for Disease Control and Prevention (CDC) estimates that 38% of all deaths in women are due to coronary artery disease (CAD), compared with 22% of all deaths due to cancer.[3] Heart disease is often perceived as an "older woman's disease," and it is indeed the leading cause of death among women aged 65 and older. However, heart disease is the third leading cause of death among women aged 25 to 44 and the second leading cause of death among women aged 45 to 64.[2] Because only one in five physicians knows the disease is responsible for the deaths of more women than men each year, there is much

to be done to fill the knowledge gap about CAD in women.[4]

Within 1 year of a heart attack, 38% of women will die compared with 25% of men; of those that survive, 35% of women will have a second heart attack compared with 18% of men.[5] Heart disease was historically presumed to be a "man's disease" due to the earlier age at which CAD presents in men and due to the enrollment primarily of men in cardiology studies in the past. The enrollment of women in clinical trials for coronary disease is improving, and with it more sex-specific recommendations have been suggested for CVD prevention in women. The manifestations, risk factors, screening, prognosis, and response to medical therapy for heart disease all show sex-specific differences. As physicians, we need to recognize these differences to better treat women with heart disease. Unfortunately, only approximately one-third of women recall discussing heart disease risk with their physicians and fewer women than men receive preventative recommendations from their primary care providers.[6]

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Pathophysiology of CAD in Women

Women appear to develop and manifest arterial disease differently than men. The reason for this is poorly understood. Research shows that girls and young women have less extensive atherosclerotic involvement than males of the same age.[7] Coronary artery calcification (CAC) is less prevalent in young women than young men.[8] CAC increases with age in both sexes, but women lag behind men by approximately 10 to 15 years.[9,10] Women have smaller coronary arteries compared with men; smaller arterial size is likely a contributor to the increased mortality that women experience after coronary artery bypass graft (CABG) surgery and is an independent predictor of postoperative mortality, irrespective of sex in patients who undergo CABG.[11,12] The coronary arteries of older women tend to have more diffuse atherosclerosis and stiffer aortas than those of older men, and their microvasculature appears to be more frequently dysfunctional.[13]

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Plaque composition also differs in men and women. Women tend to have less scar tissue and more lipid-containing foam cells.[9] Autopsy data demonstrated that women were less likely to have plaque rupture (63% vs 82%) and twice as likely as men to have plaque erosion (37% vs 18%).[9,14] The Women's Ischemia Syndrome Evaluation (WISE) study documented lesser degrees of epicardial CAD among women than among their age-matched male counterparts.[9,13] Research has shown that women develop CAD throughout the vessels, instead of primarily epicardially, as is the case in men.[9] The prevalence of obstructive CAD in premenopausal women is relatively low; however, men and women have equal prevalence rates after age 75.[4]

Risk Assessment and Risk Factor Management

Women and physicians both often have the misperception that women are at a low risk for development of CAD.[6,15] With assessment of risk based on Framingham risk score, calculated by a sum of points for risk given to age, sex, blood pressure, cholesterol, and cigarette smoking, 4%, 13%, and 47% of women between the ages of 50 and 59 years, 60 and 69 years, and 70 and 79 years, respectively, are at intermediate to high risk for CAD or nonfatal myocardial infarction (MI).[4] The risk of CAD and nonfatal MI increases dramatically after the seventh decade and the prevalence of CAD in men and women becomes comparable.[4] Postmenopausal women commonly have more atherosclerotic risk factors for CAD than men, which include obesity, the metabolic syndrome, inactivity, hypertension, and diabetes.[13]

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It is of interest that although central obesity is considered to be a risk factor for CAD, this measurement

alone did not increase CAD risk in the WISE study, in which the metabolic syndrome, but not obesity, was associated with significant CAD.[16,17] Other studies have shown increased risk with anthropomorphic measurements such as body mass index, waist circumference, and waist to height ratio that can be used to determine risk of CVD.[18] In a study by Ley and colleagues,[19] it was determined that in postmenopausal women body fat distribution becomes more similar to that of a man, with more android fat. An increased waist to hip ratio, or increased android to gynecoid fat, has been shown to be a significant risk factor for CAD.[20] Android body fat has been linked to diabetes, increased low-density lipoproteins (LDL) cholesterol, and increased total cholesterol, all known risk factors for CAD.[19]

Studies have shown that hypertension, dyslipidemia, and diabetes are more common risk factors for women than men. Hypertension has been a greater risk in women because they live longer than men and blood pressure rises with age.[15] Abnormal levels of lipids are important predictors for CAD in all populations. LDL cholesterol, believed to be the primary lipoprotein involved in the formation of atherosclerosis, has been the foremost target of drug therapy for the prevention of CVD. The US National Health and Nutrition Examination Survey (NHANES) has shown that LDL levels plateau in men after age 50 but continue to increase in women between ages 40 and 60.[21] Research has shown that diabetes greatly increases the risk of developing heart disease.[22-24] The Framingham Study found that diabetes triples the age-adjusted risk of CVD in women and doubles the risk in men.[23] Diabetes eliminates the cardioprotective effect of endogenous estrogen in premenopausal women by impairing endothelium-dependent vasodilatation.[25,26]

Epidemiologic studies have documented the risk of CVD in association with smoking in both sexes. Like diabetes, tobacco has been shown to cause endothelial dysfunction that is antecedent to atherosclerosis.[27,28] It was determined in the Nurses' Health Study that women who smoked one to four cigarettes per day were 2.5 times more likely to experience fatal CAD and nonfatal MI than women who didn't smoke.[29] The prevalence of smoking has been declining in both men and women for decades; however, the rate of smoking cessation has been four times greater for men than for women and the rate of smoking initiation among women was more than three times that observed for men.[30]

Recent studies have expressed doubts over the accuracy of the Framingham Risk Score, which has been validated by numerous studies over many years.[31,32] In 2007, Ridker and colleagues[33] developed a new risk assessment scale for women, the Reynolds Risk Score.[10,34] The Reynolds Risk Score introduces high-sensitivity C-reactive protein (CRP) levels and parental history of MI at age < 60 years as risk factors, in addition to traditional markers such as age, blood pressure, total and high-density lipoprotein (HDL) cholesterol levels, and smoking.[10,33,34] CRP, a biomarker of inflammation, has been shown to predict MI and other vascular events.[35,36]

Fortunately, the cluster of risk factors for CAD in women can be modified. With changes in diet, activity, and smoking, women can decrease their risk for heart disease. Lifestyle modifications (Table 1) and major risk factor interventions (Table 2) are included.[37]

Depression as a Risk Factor

Depression is a nontraditional risk factor for the development and expression of CAD, arrhythmia, and death in both men and women.[38-44] It has been suggested that depression

Table 1
Lifestyle Modifications

1. Smoking cessation.
2. Physical activity to include 30 minutes of moderate intensity physical activity on most but preferentially all days of the week.
3. Cardiac rehabilitation in women with a recent acute coronary syndrome or coronary intervention or angina.
4. Heart healthy diet including fruits vegetables, grains, low-fat or nonfat dairy products, fish, legumes, and protein sources low in fat. Saturated fat intake should be less than 10% of all calories, cholesterol intake should be < 300 mg/d, and intake of trans fatty acids should be limited.
5. Weight maintenance and reduction. Goal body mass index between 18.5 and 24.9, with a waist circumference < 35 inches.
6. Psychosocial factor screening to include screening for depression and refer for treatment if indicated.
7. Omega-3 fatty acids in high-risk women.
8. Folic acid supplementation in women with elevated homocysteine levels (except after procedures).

Data from Danesh J et al.[35]

Table 2
Major Risk Factor Interventions

1. Blood pressure < 130/80 mm Hg through lifestyle approaches.
2. Pharmacotherapy is indicated in women with blood pressures > 140/90 mm Hg or even lower in patients with evidence of end-organ damages or diabetes. Thiazide diuretics should be part of the regimen for most patients.
3. Optimal lipid profiles (LDL < 100 mg/dL in this document, later recommendations suggest that an LDL goal in patients with coronary artery disease, diabetes mellitus, or cardiovascular disease should be < 70 mg/dL. HDL goal is > 50 mg/dL, and triglycerides < 150 mg/dL, non-HDL cholesterol < 130 mg/dL.
4. Lipid reduction through dietary therapy; saturated fat should be limited to < 7% of calorie intake.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Data from Danesh J et al.[35]

or depressive symptoms carry a similar mortality risk in patients with CAD as cigarette smoking.[41] It is also a known risk factor for recurrent events in patients with established CVD and for adverse outcomes after CABG surgery.[40,42] In a cohort of women who were being evaluated for the presence of CAD, depression was associated with 15% to 53% increase in 5-year cardiovascular costs, and cost differences were present using three definitions of depression.[43] At the time of presentation with acute MI, women (but not men) who assessed themselves as not having a good quality of life had higher rehospitalization rates.[44]

Antidepressant use was not associated with recurrent MI in the Nurses' Health Study; however, it was associated with an elevated risk of sudden cardiac death (SCD).[38] Depressive symptoms alone also did not predict increased SCD. Prior studies have suggested that the etiology of increased SCD is related to increased arrhythmias with antidepressant medications.[39] In the Time to Ventricular Arrhythmias (TOVA) study, moderate to severe depression was associated with appropriate implantable cardioverter defibrillator shocks.[39]

Diagnostic and Prognostic Evaluation of Women With CAD

Screening for CAD

Early detection of women at risk for CAD is of critical importance, as SCD is the first expression of CAD in 50% of women with the disease.[45] Unfortunately, most of the current clinical trials supporting noninvasive imaging are composed of a majority of male participants. Despite a lack of good sex-specific evidence, noninvasive imaging for the diagnosis of CAD has been recommended in women with endorsement by the American Heart Association (AHA).[46]

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The sensitivity and specificity of noninvasive studies differ between sexes. Exercise stress testing continues to be the first-line of screening for CAD in symptomatic women.[46] For exercise electrocardiography (ECG,) the sensitivity and specificity in women is reduced when compared with that of their male counterparts. Sensitivity and specificity in women is 61% and 71% compared with 72% and 77% in men, respectively.[47] This discrepancy may be due to the increased frequency of ST segment changes in women, and the lower ECG voltage in women compared with men.[47] The Duke treadmill score has been validated in women and helps with prognosis.[10] One-minute heart rate recovery, maximal heart rate, and functional capacity are better prognostic indicators in women compared with the presence of cardiac symptoms.

Compared with ECG stress testing, stress echocardiography (ECHO) does not seem to show a sex-specific difference in sensitivity and specificity; however, for women with less advanced CAD, stress ECHO may underestimate risk.[48] Gated myocardial perfusion single-photon emission computed tomography (SPECT) improves the specificity and sensitivity of this study to similar levels as men and has been shown to detect perfusion abnormalities earlier than stress ECHO.[48-49] Myocardial perfusion imaging using radiopharmaceuticals has the limitation of breast artifact and small left chamber ventricular size, especially in women undergoing thallium radionuclide testing.[34,46]

Two developing modalities of cardiac imaging are cardiac magnetic resonance imaging (CMRI) and computed tomography (CT). CMRI is being studied and may offer a unique and cost-effective way to image CAD in women without radiation exposure. It also has the added advantage of being able to diagnose subendocardial ischemia, which may be more prevalent in women.[10,47,50,51] Cardiac CT detects the amount of CAC, a marker for atherosclerosis.[52]

Screening for CAC has been suggested for women at intermediate to high risk for CAD.[1]

Women are less likely than men to undergo invasive screening for CAD with cardiac catheterization. This may be due, in part, to the fact that women present with symptoms at older ages than men and are likely to have more comorbidities, or possibly other unrecognized factors.[25,53-56] Noninvasive stress testing before catheterization is recommended to enhance the diagnosis of CAD.[57]

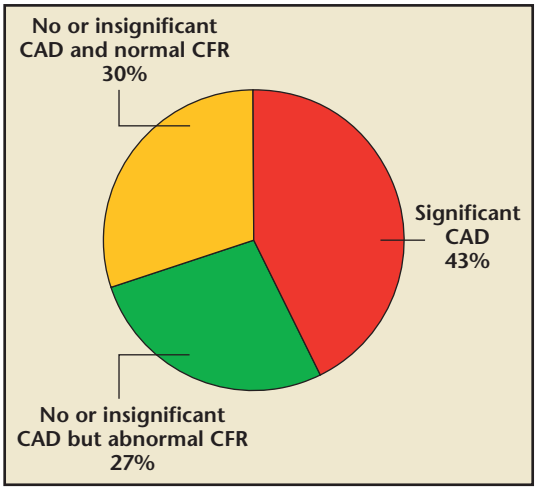

Figure 1. *Approximate percentages of findings at cardiac catheterization in women derived from Women's Ischemia Syndrome Evaluation (WISE) publications. CAD, coronary artery disease; CFR, coronary flow reserve. Data from Reis SE et al[50] and Sharaf BL et al.[51]*

Symptomatic Women With Nonobstructive Disease

Despite angina symptoms, only half of women undergoing coronary angiography have obstructive CAD and approximately 25% of women who present with acute coronary syndrome (ACS) have no evidence of obstructive CAD, compared with 9.5% of men.[57] This sex-based discrepancy holds true after stratification by symptoms (typical angina, atypical angina, nonanginal chest pain) and in asymptomatic subjects undergoing coronary angiography in preparation for valvular surgery.[58] Chest pain without normal coronary angiograms (CPNCA), or cardiac syndrome X, is a heterogeneous disorder that does seem to affect more women than men.[59] In some older studies, increased myocardial lactate production (indicative of ischemia and anaerobic metabolism) was seen in some but not all patients with CPNCA.[47] This led to the hypothesis that CPNCA is caused in at least some cases by dysfunction of the coronary microcirculation. A review of WISE publications and data suggests that a substantial percentage of women with chest pain who undergo cardiac catheterization and are found to have nonsignificant (< 50% stenosis) CAD have abnormal coronary flow reserve suggestive of abnormalities of the coronary microcirculation (Figure 1).[50,51]

In women suffering angina symptoms without epicardial coronary disease, coronary reactivity testing is an invasive way to evaluate endothelial dysfunction with both macrovascular and microvascular pathways and endothelium-dependent and non–endothelium-dependent vasodilatation, using adenosine, nitroglycerin, and acetylcholine.[60-61] Patients without risk factors had a normal vasoconstrictor response (10%-15% constriction in epicardial coronary arteries and 15%-20% reduction in coronary blood flow) versus patients who had risk factors and had less of a constrictor effect, suggesting a surrogate marker for endothelial dysfunction as a cause for CPNCA. Vasodilator response to adenosine is also impaired in up to 47% of patients with CPNCA.[47] This has also been described and demonstrated with CMRI. In a study by Vermeltfoort and colleagues,[62] 15 women who had ischemic ECGs and/or reversible nuclear perfusion defects had an increase in subendocardial signal intensity suggestive of subendocardial ischemia. ^{31}P-NMR spectroscopy is a noninvasive technique used to measure high-energy phosphates, adenosine triphosphate (ATP), and phosphocreatinine in the myocardium. A ratio of phosphocreatinine to ATP is then used to identify myocardial ischemia. In a study by Buchthal and associates,[63] approximately 20% of women with chest pain and nonobstructive coronary arteries had abnormal phosphocreatinine to ATP ratios, showing evidence of a metabolic change in women with CPNCA. Interestingly, the ratios in these women were similar to ratios in women with > 70% angiographic stenosis. Future studies are underway to further investigate the relationship between CMRI and coronary reactivity testing.

Current guidelines by the AHA and American College of Cardiology (ACC) recommend medical therapy for the management of cardiac syndrome X, including the use of nitrates, β-blockers, and calcium channel blockers.[64] CPNCA tends to have a better prognosis for cardiovascular death or MI, but results in many repeat hospitalizations and cardiac catheterizations.[47,57] The economic impact of CPNCA is tremendous; an estimated lifetime cost for women with nonobstructive CAD is over $750,000 and these women have 1.8 more heart catheterizations than women with single-vessel CAD.[49]

Asymptomatic Women and Risk Assessment

In asymptomatic women, use of the Framingham risk score helps to identify risk.[46,52] The Framingham risk score helps determine which women will benefit from more intense lipid-lowering therapy. This risk score, however, has many limitations. According to the NHANES data, over 95% of American women < age 70 are considered low risk (< 10% risk of CHD over 10 years). The Framingham risk score, however, can underestimate risk for women—especially women with a strong family history of early CAD. In the population of women with a strong family history, a coronary calcium score may be beneficial. The Multi-Ethnic Study of Atherosclerosis (MESA) study and other studies have shown that approximately one-third of women classified as having a low Framingham risk score had evidence of subclinical calcification on cardiac calcium scoring and therefore deserved more intense lipid-lowering therapy.[65,66] Cardiac imaging is also advocated in diagnosis in asymptomatic patients with CAD risk equivalents, such as diabetes and peripheral vascular disease.[46] Recently, CAC detection by cardiac CT has been shown to enhance prognostic value to traditional risk factors in women without symptoms for CAD.[52] CAC scores are significantly lower in premenopausal women than men, due to the difference in development of atherosclerosis in men versus women.[46] Interpretation of calcium scores by sex is recommended.[67]

The use of carotid ultrasonography to estimate intima-media thickness has been advocated in assessing risk of CAD in asymptomatic patients, though more evidence is needed to define its role in screening for CAD.[1,68] It has been shown that increased thickness in individuals is associated with a 3.3-fold increased risk of a coronary heart disease event.[69] Research has shown up to a fivefold increase in the risk of CVD in patients over the age of 50.[68]

Treatment of ACS in Women

Most studies suggest that women who present with unstable angina symptoms but without troponin elevation do not benefit from early invasive strategy, as men do.[55] Recently published trials have looked at using an early invasive strategy versus a selective invasive strategy in women presenting with unstable angina or non–ST-segment elevation MI (NSTEMI). Analysis of the Organization to Assess Strategies in Ischemic Syndromes (OASIS) 5, Randomized Intervention Trial of Unstable Angina (RITA) III, Thrombolysis In Myocardial Infarction (TIMI) IIIB, Fast Revascularization during Instability in Coronary Artery Disease (FRISC) II, and Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) studies failed to show benefit with an early invasive strategy in women.[34,55,56,70] Although the Treat Angina with Aggrastat and Determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS)-TIMI 18 trial did not show significant sex differences between the outcomes of early invasive and early conservative treatment, there was benefit of early invasive strategy incorporating intracoronary stents in women.[55] Further analysis of the TACTICS-TIMI 18 study noted harm in women who presented without troponin elevation and underwent invasive strategy.[34] ACC/AHA guidelines for management of unstable angina/NSTEMI in women recommend individual risk assessment. Women at low risk benefit from an initial conservative strategy and women at high risk benefit from an initial invasive strategy. The definition of high risk included women with any positive biomarker and that of low risk included those without elevated CRP, B-type natriuretic peptide, or troponin.

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It has been noted that women have a higher incidence of bleeding complications from left heart catheterizations.[53,71] Women also suffer from increased complication rates from femoral artery vascular closure devices. Smaller arterial sizes have been implicated as the cause of the increased risk with these devices.[72] Women constitute a high-risk group for bleeding in patients undergoing left heart catheterization, despite using smaller sheaths and having an overall reduced use of glycoprotein (GP) IIb/IIIa inhibitors.[72-77] Women also have an increased incidence of late major bleeding complications after coronary stenting with dual antiplatelet drugs. Recent studies have shown an 84% decrease in minor bleeding in women who undergo left heart catheterization using radial access as compared with femoral access.[77]

Women undergoing invasive treatment of ACS are most likely to first receive percutaneous coronary intervention (PCI).[54] CABG is performed less often in women than in men. Early mortality in women who undergo the surgery is 2.5 times higher

than that of men.[76] Cardiovascular mortality has recently been declining for both sexes, but lags behind in women. In women who are < 50 years old, the hospital mortality rate for MI was more than twice that for age-matched men (6.1% vs 2.9%).[78,79]

Compared with men, women with CAD are likely to receive less aggressive and less favorable care.[15] Revascularization is performed less often in women presenting with ACS.[80] Research by Jneid and associates[25] showed that women receive less timely care for treatment of MI. Men underwent fibrinolysis, PCI, and CABG more often than women. Women were less likely to undergo timely treatment, with rates of meeting ACC- and AHA-recommended perfusion times with fibrinolysis (28.3% vs 35.2%) and PCI (39.0% vs 44.8%) less often than men.[25]

Medical Management of CAD in Women

Women with CAD benefit from medical management with β-blockers, statins, and angiotensin-converting enzyme (ACE) inhibitors. Cross-sectional studies have shown that women are less likely to be prescribed β-blockers, aspirin, ACE inhibitors, and statins than men after an MI.[15,25,80] Statins are known to be beneficial in women as well as in men. In the Heart and Estrogen/Progestin Replacement Study (HERS) trial, a retrospective examination of statin use among postmenopausal women randomized to estrogen and progesterone therapy, statin therapy was associated with lower rates of cardiovascular events, venous thromboembolic events, and total mortality.[81] The use of ACE inhibitors for prevention of CVD is beneficial, as evidenced by a study published by Lonn and colleagues.[58] This study showed a 23% reduction in the risk of nonfatal MI, stroke, or cardiovascular death, a 38% reduction in the risk of cardiovascular death, and a 36% reduction in the risk of stroke in women over the age of 55 with a history of CVD or diabetes in the presence of at least one additional cardiovascular risk factor, which included smoking, dyslipidemia, microalbuminuria, or hypertension, and who took ramipril as compared with placebo.[58]

However, women differ in response to certain cardiac medications and interventions when compared with men. Women are known to have increased body fat, which could raise concerns regarding lipophilic drug bioavailability. Women are also known to have lower creatinine clearance than men.[73] Concern has recently been brought forward with regard to the increased bleeding risk in women with GP IIb/IIIa inhibitors, clopidogrel, aspirin, and warfarin. Meta-analyses have found a 32% increased risk of moderate to major bleeding in patients treated with GP IIb/IIIa antagonists, with an increased incidence of hemorrhagic events in women compared with men (3.0% vs 2.2%).[74,75,82,83] The cause of this increased risk is unknown. In the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) study, women were less likely to be treated with GP IIb/IIIa inhibitors than men, but, when treated, were more likely to be treated with an excessive dose and were more likely to suffer major bleeding complications (15.7% in women vs 7.3% in men).[75] Up to 25% of the bleeding complications could have been attributed to the excess dose of drug given to women.[73] The increased bleeding risk may be because of inherent differences in hemostasis and vascular reactivity in men versus women.[73] These differences are complex and in premenopausal women are cyclical, which raises concern over estrogen effects on the vascular endothelium. Mediators such as nitric oxide have antiplatelet actions and women have higher levels of circulating nitric oxide than men.[73]

Women with CAD benefit from medical management with β-blockers, statins, and angiotensin-converting enzyme inhibitors.

Conclusions

Women develop and express CAD differently than men and have unique characteristics relating to screening and intervention. This may be due to many factors including artery size, hormonal milieu, and lipid metabolism, as well as unrecognized variables. As noted above, a gap in care exists between men and women with CAD. Undertreatment may be a result of hesitancy in treating coronary disease in women because a lack of evidence-based diagnostic certainty exists.

It must be recognized that CAD is the leading killer of postmenopausal women. Public health campaigns to increase awareness of heart disease in women are indicated. Differences in prevention, screening, and treatment strategies in women compared with men should be recognized by cardiologists and physicians in general. Future research could focus on improvements in the diagnosis and management of cardiac syndrome X, determining why women have increased bleeding risks with certain cardiac interventions and medications, and what constitutes the best

therapy for ACS in women. In women as well as men, population-based prevention programs are strongly recommended. The writing committee for current evidence-based guidelines for prevention of CVD in women has suggested specific lifestyle and major risk factor interventions. ■

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Main Points

- Women develop and manifest coronary artery disease (CAD) differently than men.
- Depression is a risk factor for adverse outcomes in women with CAD. The pathophysiology of why depression is related to adverse outcomes is poorly understood.
- Cardiac magnetic resonance stress perfusion imaging may be one of the best ways to assess women for CAD because it enables the cardiologist to look for subendocardial ischemia as well as macrovascular disease with radiation-free imaging without breast tissue attenuation.
- Coronary reactivity testing is a good way to assess endothelial-dependent and non–endothelial-dependent vasoreactivity. Coronary endothelial dysfunction is related to adverse outcomes.

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