

Cardiovascular Disease in Special Populations

Improving
Diagnosis and
Management

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Despite advances in the detection and management of cardiovascular disease (CVD) in recent years, CVD risk remains underrecognized in many special populations, including women, African Americans, Hispanics, and diabetic and obese individuals. To discuss challenges in CVD diagnosis, management, and outcomes in these populations, a panel of experts recently held a roundtable meeting in New York, NY. The meeting included members of the Association of Black Cardiologists and was sponsored by Astellas Pharma US, Inc.

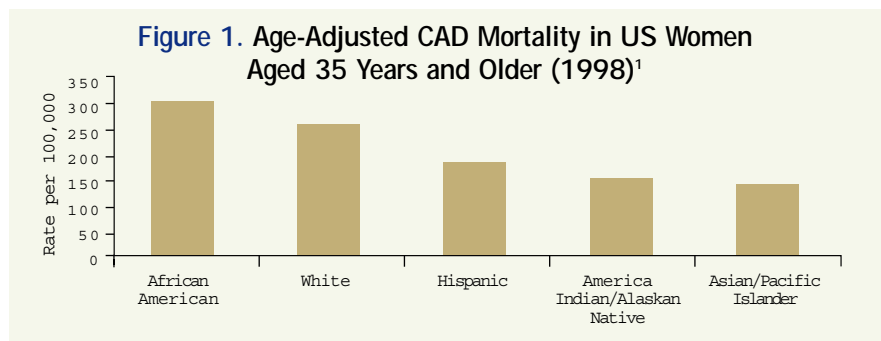
CAD in Women: Special Considerations

By Paula Johnson, MD

African American women are at higher risk for, and have a higher prevalence of, CVD—specifically coronary artery disease (CAD), myocardial infarction (MI), stroke, and congestive heart failure (CHF)—than women of other races. They also experience higher CAD mortality rates (Figure 1).¹

Data from HERS (Heart and Estrogen/Progestin Replacement Study), which assessed the effects of hormone therapy (HT) as secondary prevention for heart disease, showed that the African American women were at a 50% increased risk of having a cardiac event and an almost 80% increased risk of having a nonfatal MI than the white women. Interestingly, a review of baseline therapies in HERS showed that African American women were less likely to receive aspirin and less likely to receive a statin when a statin was indicated. Such a disparity among women already in the healthcare system would not be expected.

Key coronary heart disease (CHD) risk factors in African American women include hypertension, diabetes, obesity, smoking, physical inactivity, and stress. Diabetes is a strong CAD risk factor in women, and minority women tend to develop the condition at an earlier age, are less likely to monitor their glucose



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For more information on heart disease in women, visit www.cadinwomen.com

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Peripheral Vascular Disease and CAD in Women

By Donna Mendes, MD

All of the traditional risk factors for heart disease (Table 1) can lead to atherosclerosis, which can cause various cardiovascular (CV) conditions, including peripheral vascular disease (PVD). Peripheral vascular disease is a narrowing of blood vessels that supply the extremities and bodily organs other than the heart or brain. It is a marker of other atherosclerotic diseases and is closely linked with CAD.

Peripheral arterial disease (PAD) is a common type of PVD that affects the arteries that supply blood to the arms and, primarily, the legs. The risk factors for PAD include smoking, diabetes, hypercholesterolemia, and advancing age.^{1,2} A recent study—PARTNERS (PAD Awareness, Risk and Treatment: New Resources for Survival)—found that of almost 7000 patients screened in a primary care setting using noninvasive flow studies, 29% had PAD. Patients with PAD are often asymptomatic at first. They then begin to experience intermittent claudication that begins during ambulation and subsides only after a few minutes of resting. These patients eventually develop pain during rest, followed by tissue loss due to non-healing ulcers and, ultimately, gangrene (Figure 2).

Diagnosing PAD begins with a pulse exam of the lower extremities. Loss of hair growth over the dorsum of

Figure 2. Tissue Loss and Gangrene in the Later Stages of PAD



the foot and toes can indicate PAD, as the hair will stop growing due to a lack of oxygen. Shiny, scaly, and extremely emaciated feet also can be signs of PAD. Delayed capillary refill, dependent rubor, and pallor on elevation are also physical symptoms of PAD. Later in PAD, tissue loss and gangrene can occur (Figure 2).

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Table 1. Major Risk Factors for Heart Disease

Modifiable	Nonmodifiable	Emerging
High blood pressure	Family history	Homocysteine levels
Abnormal cholesterol levels	Age	Elevated lipoprotein(a) levels
Diabetes	Sex	Clotting factors
Cigarette smoking		Markers of inflammation
Obesity		(eg, C-reactive protein)
Physical inactivity		

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Gender- and Race-Based Differences in CVD

By Jennifer H. Mieres, MD

Cardiovascular disease is the leading cause of death among women in the United States, accounting for almost 499,000 deaths in 2001—a mortality rate 87% higher than that of cancer.¹ The prevalence of MI among women aged 65 to 69 years is 9.7%; for women 85 years and older, it increases to 17.9%.² More than 2.5 million women are hospitalized with CVD each year. While CVD mortality rates declined in men between 1979 and 2001, they actually increased in women (Figure 3).¹

CVD impact on African American women. African American women have a higher prevalence of CVD than white or Mexican American women—39.6% vs 23.8% and 26.6%, respectively.¹ Of all US

deaths due to CVD, 54% are attributable to CAD.¹ The prevalence of CAD is also higher among African American than white or Mexican American women (9.0% vs 5.4% and 6.8%, respectively),¹ and the CAD mortality rate is higher among African American than white women (176.7 per 100,000 vs 137.4 per 100,000, respectively, in 2001).¹

Lack of CVD awareness affects prevention. In 2003, 35% of women surveyed named breast cancer as their greatest health threat. Only 13% named heart disease as their greatest health threat (which was actually up from 8% in 2000), even though 55% of white women and 30% of African American women were aware that heart disease is

the leading cause of death among women. The awareness problem extends to CVD prevention. Although \$200 million is spent annually on CV healthcare in the United States, only 6¢ on the dollar is spent on prevention. To better address CVD disease in women, education and greater awareness are needed for women and their healthcare providers, including internists, family practitioners, obstetricians-gynecologists, and physician assistants.

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Figure 3. CVD Mortality Trends in the United States (1979–2001)¹

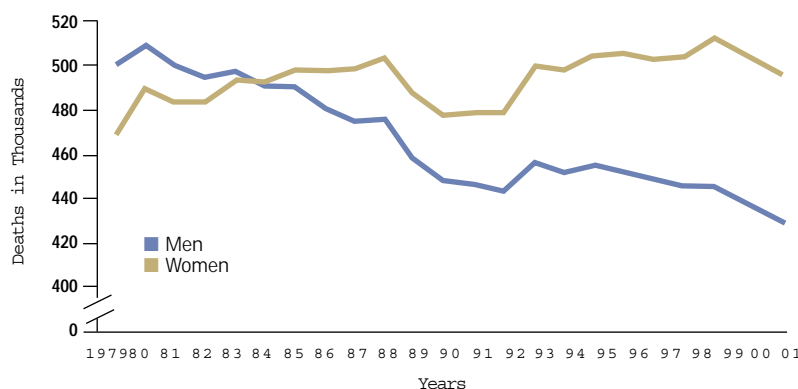


Table 2. Gender Differences in CAD

- Women generally present with CAD at an older age (10-15 years later than men)
- Women generally can have less-specific symptomatic manifestations
- CAD is more difficult to diagnose in women
- MI has more severe consequences in women
- African American women are at greatest risk of morbidity and mortality from CAD

CAD in Women: Special Considerations

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levels, are more likely to have higher HbA_{1C} levels, and are less likely to have hyperlipidemia diagnosed or treated. African American women in the Atherosclerosis Risk in Communities (ARIC) study were 85% more likely to develop diabetes than white women.

CVD and diabetes

Additionally, the rate of type 2 diabetes has been increasing among youths in

the US, especially among females and minority populations. Risk factors for diabetes in children and adolescents include overweight, insulin resistance, family history of diabetes, and acanthosis nigricans.²

Metabolic syndrome is an independent risk factor for CAD and may be diagnosed if a patient has 3 or more of the following 5 factors: (1) abdominal obesity, (2) high triglyceride levels, (3) low

high density lipoprotein cholesterol level (HDL-C), (4) high blood pressure, and/or (5) elevated fasting glucose level.

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The Role of Noninvasive Testing in the Diagnosis and Prognosis of Women With Suspected CAD

By Leslee J. Shaw, PhD, and Jennifer H. Mieres, MD

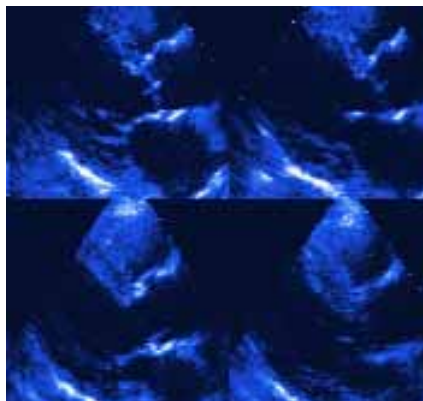
Noninvasive techniques to identify CAD in at-risk patients include stress electrocardiography (ECG), stress echocardiography, stress myocardial perfusion imaging (MPI), and electron beam computed tomography (EBCT).

Stress ECG—diagnosis. Stress ECG is a commonly used noninvasive test for the detection of ischemic heart disease.¹ Ischemia is identified by ST-segment depression. While several stress ECG protocols are available, the goal is achievement of 85% of maximal predicted heart rate. A number of factors can affect the results of exercise ECG, including hormonal influences (menstrual cycle, hormone replacement therapy), functional capacity, and resting ST-T wave changes. A 1999 study found the diagnostic sensitivity and specificity of 1 mm or more ST-segment depression to be only 61% and 70%, respectively, for detecting CAD.²

Stress ECG—prognosis. The Duke Treadmill Score (DTS) is a simple tool for risk-stratifying patients based on exercise ECG. Patients with high risk per DTS should be considered for catheterization, and patients with low risk likely require no immediate intervention. Patients identified as intermediate risk by the DTS should be referred for diagnostic imaging to gain more information on their coronary status.

Functional status is an important prognostic indicator that can be assessed during treadmill exercise.³ Patients who cannot reach 5 metabolic equivalents (METs)—the measure of a person's capacity to exercise—are at higher cardiac risk, regardless of the presence or absence of symptoms. Based on the Bruce protocol for exercise ECG, patients must reach 4.7 METs to get adequate test results. Results

Figure 4. Stress Echocardiography Images



obtained from lower levels of exercise, in which central myocardial stress is not provoked, are usually indeterminate and can lead to further indecision in the management of such patients. Therefore, patients who are unable to exercise to 5 METs should be considered for pharmacologic stress imaging.⁴

Stress echocardiography—diagnosis. Stress echocardiography (Figure 4) is a technique commonly used to detect ischemic heart disease by using ultrasound to detect the presence of wall motion abnormalities (a marker of CAD) with exercise or pharmacologic stress. Ultrasound is performed at rest and with exercise or pharmacologic stress. The sensitivity of echocardiography has been reported to be 81% to 85%, and the specificity has been reported to be 73% to 85%.^{2,5-7} Ischemia is recognized by the presence of wall-motion abnormalities.

Stress echocardiography—prognosis. Recent evidence supports the use of stress echocardiography to estimate event-free survival in women. Stress echocardiography with exercise or dobutamine is an effective and highly accurate noninvasive means of detecting ischemic heart disease and risk-stratifying women with symptoms of

Figure 5. Myocardial Perfusion Images



ischemic heart disease and an intermediate-to-high pretest likelihood of CHD. Stress echocardiography provides incremental value over exercise ECG and clinical variables in assessing women with suspected or known ischemic heart disease.

Stress MPI—diagnosis. Stress MPI is a commonly used noninvasive test that employs radioisotopes for detecting and evaluating the prognosis of ischemic heart disease. Imaging of the myocardial accumulation of the radio-tracer in proportion to blood flow can reveal the area of hypoperfused myocardium. Myocardial perfusion images (Figure 5) are obtained both at rest and with exercise or pharmacologic stress. Ischemic areas are identified by diminished perfusion on stress images compared with rest images. The sensitivity of MPI using contemporary techniques has been reported as 77% to 87%, and the specificity as 80% to 90%.^{2,5,7,8}

Stress MPI—prognosis. Reports from several large studies have noted that for both Tc-99m sestamibi (rest and exercise) and dual-isotope myocardial perfusion single-photon emission computed tomography (SPECT),

myocardial perfusion data add incremental prognostic value compared with clinical and exercise variables in women.⁹⁻¹¹ Gated stress SPECT MPI is an effective noninvasive means of evaluating women with an intermediate to high pretest likelihood of CAD. Data so far have confirmed the higher diagnostic and prognostic accuracy of both exercise and pharmacologic stress MPI compared with exercise ECG in the diagnosis and risk assessment of ischemic heart disease in women.

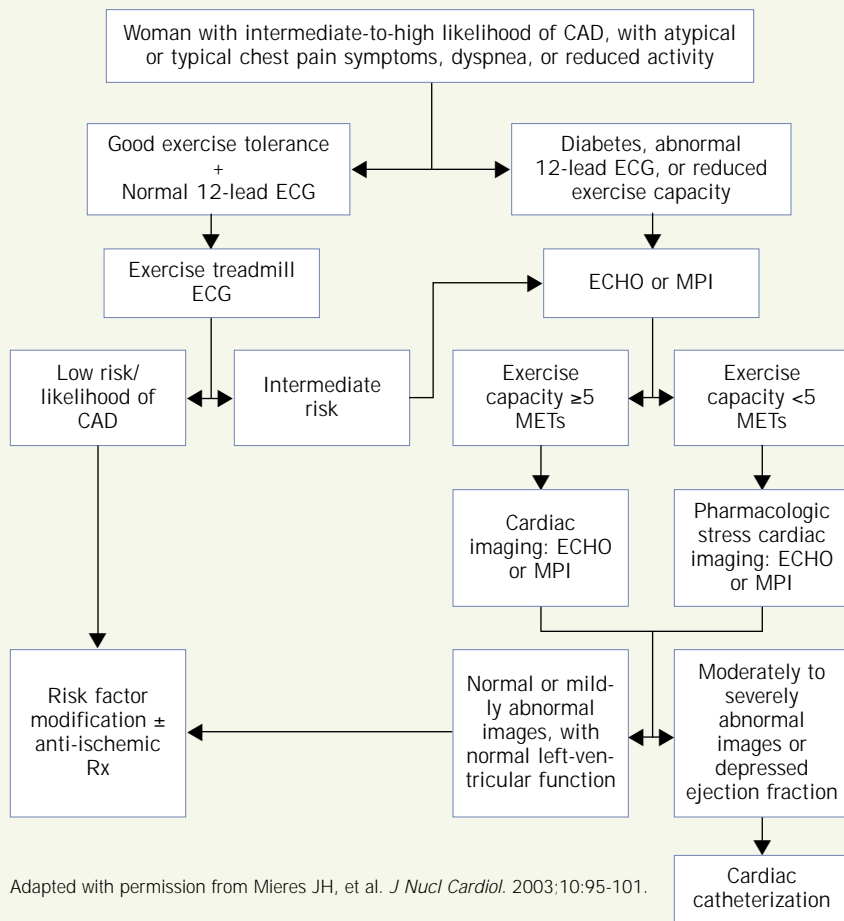
EBCT—diagnosis. EBCT images help detect coronary calcification, a marker of CAD. Cardiac computed tomography (CT), either EBCT or multidetector CT, can detect and quantify the amount of coronary artery calcium (CAC), a marker of atherosclerotic disease burden.^{7,12} While the presence of calcification indicates the presence of atherosclerosis, it is not specific for luminal obstruction. Coronary calcium scores approximate the total atherosclerotic plaque burden.

Data on CAC and symptomatic women include a report on a cohort of 539 women (mean age, 60±16 years) undergoing clinically indicated angiography.¹³ None of the 220 women (41%) who had a normal coronary angiogram had detectable CAC, yielding a negative predictive value of 100%. In contrast, women with moderate (100-399) or higher (≥400) calcium scores had a greater prevalence of obstructive coronary disease.¹³

EBCT—prognosis. Calcium scores have also been studied for risk stratification in asymptomatic women with an intermediate likelihood of CHD. Currently available data indicate that low calcium scores are associated with a low risk for adverse events, and high calcium scores are associated with worse event-free survival.^{7,14,15}

Conclusion. Exercise ECG is generally less accurate than echocardiography or MPI for identifying CAD in women. Visualization of wall motion, perfusion, and function with echocardiography and MPI provides better detection and prognostication than does ECG. However, ECG is still an

Figure 6. Algorithm for Noninvasive Evaluation of Women With Suspected CAD⁴



Adapted with permission from Mieres JH, et al. *J Nucl Cardiol.* 2003;10:95-101.

appropriate diagnostic measure for some women with suspected CAD. **Figure 6** presents an algorithm for the noninvasive evaluation of symptomatic women.

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Acute Coronary Syndrome in Women

By Elizabeth Ofili, MD

Gender differences in presentation. In women, angina is usually the initial manifestation of CAD, as opposed to men, in whom it is MI.¹ While chest pain is the typical presentation of MI in both men and women, there is a high prevalence of atypical symptoms (eg, abdominal pain, neck pain, shoulder pain, dyspnea) in women compared with men. This atypical presentation in women can present a challenge in the early identification of acute coronary syndrome in the emergency room. **Table 3** shows the typical symptoms, shared by both men and women, and the more atypical symptoms seen generally only in women.

Women with CAD are generally older than men at the time of presentation and more often have angina, hypertension, and diabetes. They are less likely than men to have had previous MI or revascularization procedures.

Prognosis after acute coronary syndrome. Regarding outcomes, women experience more complications and a higher 30-day mortality rate during hospitalization for an MI.² Women with ST-elevation MI (STEMI) do worse than men, while those with non-STEMI have similar outcomes. Women can experience better outcomes with primary percutaneous transluminal coronary angioplasty (PTCA) vs thrombolysis.

However, women experience an increased mortality rate related to PTCA and coronary artery bypass graft (CABG), likely due to baseline comorbidities.³ The benefits of pharmacologic MI management are similar for both women and men.

The 6-month survival rate after MI has been shown to be significantly lower in women than in men—74% vs 89%, respectively ($P < .001$).² Thirty-eight percent of women vs 24% of men will die by 1 year post-MI. Less aggressive diagnostic and treatment measures may contribute to this disparity.

While it is not as common an initial presentation of CAD in women as it is

Congestive Heart Failure in Women

By Judith Mitchell, MD, and Ann Taylor, MD

Coronary artery disease is the most common cause of heart failure,¹ and is the number 1 cause of heart failure in women with predominately systolic dysfunction. Signs of congestion, such as rales and dyspnea, are not common in most heart failure patients, and most die suddenly and unexpectedly, despite apparent clinical compensation.² Risk factors for heart failure are shown in **Table 4**.

For women and African Americans, hypertension is the most common cause of heart failure and is an antecedent to heart failure in 75% of cases.² This is a major concern for African American women, as that population has a higher prevalence of hypertension after age 45 years than any other demographic group.³

Diabetes is also an important risk factor for heart failure, particularly in women. The Framingham Heart Study found that, in patients younger than 65 years, diabetes increases the risk for heart failure 4 times in men and 8 times in women. Poor glycemic control increases the risk for heart failure by

15% for each 1% increase in HbA1c. Insulin resistance also contributes to heart failure in patients with diabetes.

Anemia is common among patients with heart failure and is associated with an increased risk for mortality. Patients with anemia generally also have a decreased tolerance for exercise and more hospitalizations than nonanemic patients. In the ARIC study, 9% of middle-aged patients were anemic.⁴

Recent clinical trials in heart failure. The African American Heart Failure Trial (A-HeFT) lists the causes of CHF among this population as hypertensive

(37.4%), idiopathic (27.2%), ischemic (22.6%), valvular (2.9%), and other (9.9%). The results of A-HeFT indicate that endothelial dysfunction may play an even greater role in heart failure among African Americans than among whites, contributing more to vascular dysregulation. Nitric oxide (NO) is an important regulator of endothelial function, and evidence has shown diminished NO release and increased NO inactivation in CHF. Therefore, A-HeFT is studying hydralazine/isosorbide dinitrate therapy, which improves endothelial function and increases NO availability.

Table 4. Risk Factors for Heart Failure

- CAD or history of MI
- Hypertension
- Valvular heart disease
- Asymptomatic LV dysfunction
- Alcoholism
- Chemotherapy
- Diabetes
- Congenital heart defects
- Other
 - ▶ Obesity
 - ▶ Age
 - ▶ Reduced or falling vital capacity
 - ▶ Smoking
 - ▶ High or low hematocrit level
 - ▶ LVH

in men, sudden cardiac death does occur in women. Younger women who die suddenly are generally cigarette smokers and have plaque erosion and little or no recognized CAD or elevated CAC levels (ie, calcium buildup on the inner vessel walls, which is a marker of atherosclerotic plaque burden). Older women who die suddenly generally do have significant CAD, elevated CAC and cholesterol levels, and ruptured plaques.⁴ Of women who die suddenly from CAD, 64% have no prior warning symptoms.⁵ Therefore, early recognition of symptoms, accurate diagnosis, and appropriate treatment are the keys to reduce CAD mortality among women.

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Table 3. Gender Differences in MI Symptoms⁵

Typical Symptoms in Both Sexes

- Pain, pressure, squeezing, or stabbing pain in the chest
- Pain radiating to the neck, shoulder, back, arm, or jaw
- Pounding heart, change in rhythm
- Difficulty breathing
- Heartburn, nausea, vomiting, or abdominal pain
- Cold sweats or clammy skin
- Dizziness

Less Classic Symptoms in Women

- Milder symptoms (without chest pain)
- Sudden onset of weakness, shortness of breath, fatigue, body aches, or overall feeling of illness (without chest pain)
- Unusual feeling or mild discomfort in the back, chest, arm, neck, or jaw (without chest pain)

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The Role of Noninvasive Testing

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Guidelines for Prevention of CVD in Women

By Karol Watson, MD

Relatively comprehensive, evidence-based guidelines for the prevention of CVD in women have been developed (*page 8*).¹ The guidelines are prioritized based on divisions of class, level of evidence, and generalizability index (**Table 5**). Adhering to these evidence-based guidelines is an important step toward improving women's healthcare and decreasing CVD mortality in women.

Tables 6-10 list the lifestyle modifications and major risk factor interventions outlined in the prevention guidelines.

Much improvement is necessary in the diagnosis and management of women with CVD. Education is the first step in improving CV health care for women. Physicians and women must recognize that heart disease is the number 1 killer of women, and they must become familiar with the risks and symptoms.

Early detection and more accurate diagnosis are key to improving out-

comes in women with CVD. Because women generally do not always present with the traditional symptoms of CVD usually seen in men, there is often confusion regarding the diagnosis of cardiac events or CVD.

Improvements in the treatment of women diagnosed with CVD must also be made. Women are generally undertreated compared with men, and the medical community must ensure that women are given every opportunity to obtain the appropriate treatments for their conditions.

Finally, more gender-specific research is needed. Because of the unique diagnostic and pathophysiologic issues related to CV health in women, continued research in female study populations is necessary to gain an improved understanding of CVD in women.

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Table 5. Classification and Levels of Evidence: Strength of Recommendation

Classification	Description	Level of Evidence
Class I	Intervention is useful and effective	A Sufficient evidence from multiple randomized trials B Limited evidence from single randomized trial or other nonrandomized studies C Based on expert opinion, case studies, standard of care
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy	
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	
Class III	Intervention is not useful/effective and may be harmful	
		Generalizability Index (GI)
		1 Very likely that results generalize to women 2 Somewhat likely that results generalize to women 3 Unlikely that results generalize to women 0 Unable to project if results generalize to women

Table 6. Class I Lifestyle Interventions

Intervention	Class	Level	GI	Description
Cigarette smoking cessation	I	B	1	
Physical activity	I	B	1	30 minutes of moderate-intensity activity (eg, brisk walking) on most (preferably all) days of the week
Cardiac rehabilitation in women with recent MI	I	B	2	
Heart-healthy/therapeutic diet	I	B	1	Fruits, vegetables, grains, low-fat/nonfat dairy products, fish, legumes, protein sources low in saturated fat: • Limit saturated fat to <10% of calories • Limit cholesterol to <300 mg/day • Low trans fatty acids
Weight reduction/maintenance	I	B	1	BMI 18.5-24.9 kg/m ² Waist circumference <35 inches

BMI = body mass index

Table 7. Class II Lifestyle Recommendations

Intervention	Class	Level	GI	Description
Psychosocial factors	IIa	B	2	Women with CVD should be evaluated for depression and referred/treated when indicated
Omega-3 fatty acids	IIb	B	2	Omega-3 fatty acid supplementation should be considered in high-risk women
Folic acid	IIb	B	2	Folic acid supplementation should be considered in high-risk women (except after revascularization) if a higher-than-normal homocysteine is present

Table 8. Class III Lifestyle Recommendations

Intervention	Class	Level	GI	Description
Hormone therapy	III	A	0	Estrogen + progestin should not be initiated to prevent CVD in post-menopausal women
Hormone therapy (additional recommendations)	III	C	0	Estrogen + progestin should not be continued to prevent CVD in post-menopausal women Other forms of menopausal hormone therapy should not be initiated or continued to prevent CVD in post-menopausal women, pending results of ongoing trials
Antioxidant supplements	III	A	1	Antioxidant supplementation should not be used to prevent CVD, pending results of ongoing trials
Aspirin	III	B	2	Routine aspirin use in lower-risk women is not recommended, pending results of ongoing trials

Table 9. Major Risk Factor Interventions: Blood Pressure and Diabetes

Intervention	Class	Level	GI	Description
Blood pressure (BP)—lifestyle	I	B	1	Encourage optimal BP of <120/80 mm Hg through lifestyle approaches
Blood pressure—drugs	I	A	1	Pharmacotherapy is indicated if BP is ≥140/90 mm Hg, or lower in the presence of BP-related target-organ damage or diabetes Thiazide diuretics should be part of drug regimens unless contraindicated
Diabetes	I	B	1	Lifestyle and pharmacotherapy should be used to reach HbA1c levels <7%

Table 10. Major Risk Factor Interventions: Lipids/Lipoproteins

Intervention	Class	Level	GI	Description
Lipids/ lipoproteins = general	I	B	1	Optimal levels should be encouraged through lifestyle approaches: • LDL-C <100 mg/dL • HDL-C >50 mg/dL • Triglycerides <150 mg/dL • Non-HDL-C <130 mg/dL
Lipids = diet therapy	I	B	1	In high-risk women or if LDL-C is elevated: • Limit saturated fats to <7% of calories • Total cholesterol <200 mg/dL • Limit trans fatty acids
Lipids—pharmacotherapy				
High risk + LDL-C ≥100 mg/dL	I	A	1	Initiate lipid-lowering therapy (preferably a statin) and lifestyle modification
High risk + LDL-C <100 mg/dL	I	B	1	Initiate statin therapy unless contraindicated
Low HDL-C or high risk + elevated non-HDL-C	I	B	1	Initiate niacin or fibrate therapy
Intermediate risk + LDL-C ≥130 mg/dL on lifestyle measures	I	A	1	Initiate LDL-C-lowering therapy (preferably a statin)
Low HDL-C or elevated non-HDL-C after LDL-C goal is reached	I	B	1	Initiate niacin or fibrate therapy
Low risk + LDL-C ≥190 mg/dL or multiple risk factors + LDL-C ≥160 mg/dL	IIa	B	0	Consider LDL-C-lowering therapy
Low HDL-C or elevated non-HDL-C after LDL-C goal is reached	IIa	B	1	Initiate niacin or fibrate therapy