Update on Cardiovascular Disease Prevention in Women

The latest American Heart Association guidelines shift the focus from 'evidence based' to 'effectiveness based.'

OVERVIEW: In 2008, more women in the United States died from cardiovascular disease (CVD) than from all forms of cancer, chronic lower respiratory disease, and Alzheimer's disease combined. One in three deaths in women was from CVD. While many women have come to recognize CVD as the leading cause of death in women, more education is needed to convey this message to others, especially high-risk groups like black and Hispanic women. In addition, recent American Heart Association (AHA) surveys have shown that a majority of women believe they can reduce their risk of heart disease through therapies with no established benefit (such as multivitamins and antioxidants, or aspirin in young women), just over half of women said they would call 9-1-1 if experiencing symptoms of heart attack, and few respondents were aware of atypical symptoms of heart attack.

Persistent misunderstandings about CVD in women; new epidemiologic data; and increased awareness of sex differences in the way CVD presents, is evaluated, and responds to treatment prompted the AHA to update its 2007 guidelines for preventing CVD in women, stressing interventions described as "effective" in women, not only "evidence based." This article explains the shift in emphasis and reports on the highlights of the updated guidelines.

Keywords: cardiovascular disease, cardiovascular health, coronary artery disease, coronary heart disease, effectiveness-based guidelines, heart disease, women, women's health

Cardiovascular disease (CVD) is the number-one killer of women, as well as men, in the United States.[1,2] More than one in three American women today has some form of CVD,[1,2] an umbrella term that includes coronary artery disease (often referred to as "coronary heart disease"), cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism.[3] In 2008, CVD was responsible for the death of more women in the United States than all forms of cancer, chronic lower respiratory disease, and Alzheimer's disease combined.[2] Whereas one in 31 women died of breast cancer, one in three died from CVD.

Women also accounted for more than half of all CVD deaths in 2008,[1,2] dispelling any notion that CVD is a "man's disease." Nevertheless, a 2009 cross-sectional survey of 2,300 U.S. women found that only 54% of respondents recognized CVD as the leading cause of death in women, and this realization was shared by fewer black and Hispanic women than white women (43% and 44%, respectively, versus 60%),[4] although CVD prevalence is greater in black and Hispanic populations than in whites (6.5% and 6.1%, respectively, versus 5.8%).[5] In addition, a majority of the women surveyed believed they could reduce their risk of heart disease through the use of therapies that have no established

Women veterans and U.S. Department of Veterans Affairs employees work out together at a recent "VA Goes Red—Healthy Heart Day" in Washington, DC, to raise awareness of women's risk of CVD. Photo courtesy of the Department of Veterans Affairs.

benefit (such as multivitamins and antioxidants, or aspirin in young women), only 53% said they would call 9-1-1 if experiencing symptoms of a heart attack, and few were aware of atypical heart attack symptoms.[4]

Within the year following a first heart attack, more women die than men (26% versus 19% in 2008).[1,2] It's been suggested that outcome disparities between men and women may be related to sex differences in the way CVD presents (in terms of age at symptom onset, characteristic symptoms, and electrocardiographic and angiographic findings), as well as in the way it is evaluated and treated and the way it responds to treatment.

In light of these epidemiologic data, these common misunderstandings, and a growing awareness of potentially relevant sex differences, the American Heart Association (AHA) has updated its guidelines for preventing CVD in women. The purpose of this article is to report on the highlights of the updated guidelines and to discuss the new AHA construct of "ideal cardiovascular health."

POTENTIAL SEX DIFFERENCES

For decades, it has been suggested that men and women should be treated for various diseases and conditions in much the same way. As increasing numbers of women participate in clinical trials, however, it's become apparent that both physiologic and pathologic functions may be affected by sex—a fact highlighted in a landmark report published by the Institute of Medicine in 2001.[6] In CVD, as in other conditions, sex differences have been described in the areas of presentation, evaluation, treatment, benefits, and risks.

Presentation. Compared with men, women have a 10-to-20-year lag in the initial presentation of coronary artery disease.[2,7,8] Additionally, women do not always present with the "characteristic" pattern of chest pain.[9] Other typical symptoms for women during their initial presentation include shortness of breath, diaphoresis, nausea, epigastric pain, and fatigue.[9,10] These differences in symptom onset often cause women to delay seeking emergency care and lifesaving interventions such as thrombolysis, coronary revascularization,

and angioplasty.[8-10] In addition, electrocardiograms and exercise electrocardiograms are less sensitive to changes in women, making it more difficult for providers to diagnose coronary artery disease.[8, 11, 12] As seen on angiography, plaque in women tends to be distributed diffusely, rather than in clumps, causing women's angiographic studies to be misinterpreted as "normal."[8, 12] A recent autopsy study showed that, among people who died from ischemic heart disease, fewer women than men had obstructive coronary artery disease.[13] There are also a number of coronary risk factors that affect men and women at different ages. For example, men tend to develop hypertension at younger ages than women; women's low-density lipoprotein (LDL) cholesterol levels tend to be lower than men's at younger ages but exceed those of men in advanced age; and while triglyceride levels decline in men of middle and older age, they rise in women of comparable ages.[12]

Evaluation and treatment. Over the past 20 years, studies have shown that women are less likely than men to be evaluated for coronary risk factors or to be treated aggressively for coronary artery disease.[8, 14, 15] Cardiac catheterization, coronary angioplasty, and coronary artery bypass graft surgery have been less frequently performed on women than on men,[10, 14-16] and such drugs as β-blockers, aspirin, and lipid-lowering agents are underprescribed in women.[16]

Benefits and risks. Because women have been underrepresented in most clinical trials, the degree to which findings from such studies can be generalized to women is unclear.[17] The realization that there may be "differences in the magnitude of the relative and absolute potential benefits and risks of preventative interventions" prompted the AHA to review the evidence and identify potential concerns.[18] Based on this review, the AHA shifted the focus of its guidelines from "evidence based" to "effectiveness based"—moving from an exclusive reliance on "evidence that documents efficacy (benefits observed in clinical research)" to consideration of the "effectiveness (benefits and risks observed in clinical practice) of preventive therapies."[18]

UPDATE HIGHLIGHTS

Like the 2007 guidelines, the 2011 update includes three categories of cardiovascular risk, but the definitions have been modified, and the category formerly called "optimal risk" is now referred to as "ideal cardiovascular health" (Table 1).[18, 19]

'Ideal cardiovascular health' redefined. In 2009, the AHA approved the development of the 2020 Impact Goal, which is "to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%" by the year 2020.[20] In redefining cardiovascular health, the AHA considered three precepts that influenced its understanding of how heart health should be monitored and improved[20]:

- Primordial prevention (focusing on prevention at all levels of risk) is of paramount importance.
- Evidence that CVD and associated risk factors develop early in life is overwhelming.
- Health promotion and disease prevention require both population-level and individual high-risk approaches to cardiovascular health.

Studies have shown that women are less likely than men to be evaluated for coronary risk factors or to be treated aggressively for coronary artery disease.

Ideal cardiovascular health was defined in terms of both ideal health behaviors (such as smoking abstinence, maintaining a body mass index [BMI] of less than 25 kg/m^2, keeping physical activity at goal level, and following a DASH [Dietary Approaches to Stop Hypertension] diet) and ideal health factors (such as untreated total cholesterol of less than 200 mg/dL, untreated blood pressure below 120/80 mmHg, and untreated fasting blood glucose below 100 mg/dL).[20] Individuals who maintain an ideal cardiovascular health status into middle age have greater longevity, better quality of life, lower health care usage, and a dramatic reduction in lifetime risk of CVD.

Assessing risk. Risk assessment algorithms may be used to raise awareness of CVD, educate patients about cardiovascular risk, prompt lifestyle changes, guide therapy, and predict both 10-year and lifetime risk of CVD.[21] Whereas the previous AHA guidelines defined "high risk" as having a greater than 20% 10-year risk of coronary artery disease, the current update defines high risk as having a 10% or greater 10-year risk of any CVD. The updated guidelines also recommend the use of several 10-year global cardiovascular risk algorithms, including the updated Framingham cardiovascular risk profile and the Reynolds risk score for women.[18] As before, evaluating a woman's risk of CVD includes obtaining a detailed medical, family, and pregnancy-complication history;

Table 1. Classification of CVD Risk in Women

Risk Status	Criteria
High risk (≥ 1 high-risk states)	Clinically manifest CHD Clinically manifest cerebrovascular disease Clinically manifest peripheral arterial disease Abdominal aortic aneurysm End-stage or chronic kidney disease Diabetes mellitus 10-y Predicted CVD risk ≥ 10%
At risk (≥ 1 major risk factor[s])	Cigarette smoking SBP ≥ 120 mmHg, DBP ≥ 80 mmHg, or treated hypertension Total cholesterol ≥ 200 mg/dL, HDL-C < 50 mg/dL, or treated for dyslipidemia Obesity, particularly central adiposity Poor diet Physical inactivity Family history of premature CVD occurring in first-degree relatives in men < 55 y of age or in women < 65 y of age Metabolic syndrome Evidence of advanced subclinical atherosclerosis (such as coronary calcification, carotid plaque, or thickened IMT) Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise Systemic autoimmune collagen-vascular disease (such as lupus or rheumatoid arthritis) History of preeclampsia, gestational diabetes, or pregnancy-induced hypertension
Ideal cardiovascular health (all of these)	Total cholesterol < 200 mg/dL (untreated) BP < 120/< 80 mmHg (untreated) Fasting blood glucose < 100 mg/dL (untreated) Body mass index < 25 kg/m^2 Abstinence from smoking Physical activity at goal for adults > 20 y of age: ≥ 150 min/wk moderate intensity, ≥ 75 min/wk vigorous intensity, or combination Healthy (DASH-like) diet

BP = blood pressure; CHD = coronary heart disease; CVD = cardiovascular disease; DASH = Dietary Approaches to Stop Hypertension; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; IMT = intima-media thickness; SBP = systolic blood pressure.

noting signs and symptoms of CVD; conducting a thorough physical exam, including measurement of blood pressure, BMI, and waist circumference; obtaining laboratory tests, including lipoprotein and glucose levels; in the absence of CVD or diabetes, applying a risk assessment algorithm, such as the Framingham risk profile; and, when there is a history of CVD, screening for depression.[18]

Pregnancy considerations. The updated AHA guidelines recognize that the metabolic and cardiovascular stresses of pregnancy provide a unique opportunity to assess a woman's lifetime risk of CVD. For example, such pregnancy complications as preeclampsia may be viewed as a "failed stress test," potentially revealing endothelial dysfunction or metabolic disease.[18] Women who develop such pregnancy complications should be referred for postpartum cardiovascular evaluation, and the cardiovascular evaluation of women should always include a detailed history of preeclampsia, gestational diabetes, preterm birth, or birth of an infant small for gestational age.

Diversity and international applicability. The updated guidelines acknowledge the changing demographics of U.S. and worldwide populations.[18] Whereas in 2005, the non-Hispanic white population accounted for 67% of U.S. residents, by 2050, it's expected to drop to 47%.[22] Over the same period, it's anticipated that the Hispanic population will rise from 14% to 29%, the black population will remain proportionally the same at about 13%, and the Asian population will rise from 5% to 9%.[22] To deliver

equitable health care to all, providers need to take into account such aspects of diversity as age, sex, language, culture, literacy, socioeconomic status, religious affiliation, disability, frailty, and occupational status—in addition to race, ethnicity, and geographic origin.[18]

Since CVD affects women worldwide, the international applicability of CVD prevention guidelines is a critical consideration. The World Health Organization has proposed four criteria for evaluating the international applicability of guidelines: efficacy and safety, cost-effectiveness, affordability, and population benefits.[18] The updated AHA guidelines note that some of the recommendations for preventing CVD in women may not be generalizable worldwide because they are based on studies with relatively small numbers of female participants, making it difficult to determine their usefulness to women of widely varying cultural, racial, and ethnic backgrounds.[18]

Blood pressure control, diabetes management, and achieving optimal lipid levels are central to AHA recommendations for major risk factor intervention.

INTERPRETING THE RECOMMENDATIONS

The AHA's updated guidelines recommend three types of interventions: lifestyle interventions, which are appropriate for all women; major risk factor interventions, which are directed at women considered to be "at risk" or at "high risk," as defined in Table 1; and preventive drug interventions, developed to prevent stroke and delay heart failure progression in women with predisposing conditions. Each intervention is classified (I, IIa, IIb, or III) based on the strength of the recommendation and assigned a level (A, B, or C) according to the type and quality of available supporting evidence.[18] Interventions are thus classified as follows:

- Class I—general agreement of usefulness and efficacy
- Class IIa—most evidence or opinion favors usefulness and efficacy
- Class IIb—some evidence or opinion favors usefulness and efficacy
- Class III—general agreement of *no* proven benefit; potentially harmful

Evidence is weighted on the basis of its source:

- Level A—supported by multiple randomized trials
- Level B—based on a single randomized trial or on nonrandomized studies
- Level C—derived from expert opinion, case studies, or standard of care

LIFESTYLE INTERVENTIONS

Encourage all women to follow the AHA recommended lifestyle interventions, which are universally beneficial.

Class I recommendations. AHA lifestyle interventions for women focus on smoking cessation, physical activity, cardiac rehabilitation, dietary intake, and weight maintenance or reduction. Women are advised to maintain an appropriate BMI (less than 25 kg/m^2) and waist size (less than 35 inches) through balancing caloric intake with physical activity, and with the addition of behavioral programs if needed. Physical activity recommendations include[18]

- performing at least 150 minutes per week of moderate exercise, 75 minutes per week of vigorous exercise, or an equivalent combination of both, with at least 10 minutes of aerobic activity per episode spread throughout the week.
- increasing aerobic activity to 300 minutes per week at a moderate intensity, 150 minutes per week at a vigorous intensity, or an equivalent combination of both, for additional cardiovascular benefits.
- engaging in muscle-strengthening activities, involving all major muscle groups, two or more days per week.
- accumulating 60 to 90 minutes of at least moderate-intensity physical activity on most or all days of the week if weight loss or weight loss maintenance is needed.

Cardiac rehabilitation, emphasizing CVD risk reduction and/or a physician-guided home- or community-based exercise training program, should be recommended for women who have had a recent cardiovascular or cerebrovascular event and for those with peripheral artery disease or symptoms of heart failure and a left ventricular ejection fraction at or below 35%.

Advise women to eat a diet rich in fruits and vegetables, whole grains, and fiber; to consume fish, preferably oily fish, at least twice a week; to limit saturated fat, cholesterol, alcohol, sodium, and sugar; and to avoid trans-fatty acids. Pregnant women should avoid eating fish associated with high levels of mercury contamination.[18]

Class IIb recommendations. For women with hypercholesterolemia or hypertriglyceridemia, consider omega-3 fatty acids (from fish or in the form of a daily supplement, such as 1,800 mg of EPA) for primary and secondary prevention of CVD.[18]

MAJOR RISK FACTOR INTERVENTIONS

Blood pressure control, diabetes management, and achieving optimal lipid levels are central to AHA recommendations for major risk factor intervention, intended for women who are either "at risk" or at

Table 2. AHA Recommended Preventive Drug Interventions for Women[18]

Drug	Indication	Recommendation	Strength of Evidence
Aspirin	At high risk for CV event, with CAD	75–325 mg/d, unless contraindicated	Class I, Level A
Clopidogrel	At high risk for CV event, with CAD, and intolerant of aspirin	Should be substituted for aspirin	Class I, Level B
Aspirin	At high risk for CV event, with diabetes	75–325 mg/d, unless contraindicated	Class IIa, Level B
Aspirin	At risk for CV event or healthy, ages 65 or older with controlled BP, for prevention of MI and ischemic stroke	81 mg/d or 100 mg every other day if CV benefit outweighs risk of GI bleeding and hemorrhagic stroke	Class IIa, Level B
Aspirin	At risk for CV event or healthy, under age 65 with controlled BP, for prevention of ischemic stroke	81 mg/d or 100 mg every other day	Class IIb, Level B
Warfarin	Chronic or paroxysmal AF	Use to maintain an INR of 2 to 3, unless at low risk for stroke or at high risk for bleeding	Class I, Level A
Aspirin	Chronic or paroxysmal AF, contraindicated for warfarin or at low risk for stroke (< 1%/y or CHADS2 score < 2)	75–325 mg/d	Class I, Level A
Dabigatran	Paroxysmal or permanent AF and risk factors for stroke or embolism	Use as alternative to warfarin in patients without prosthetic heart valve, significant valve disease, severe renal failure (CrCl < 15 mL/min), or advanced liver disease (impaired clotting)	Class I, Level B
β-blocker	After MI or ACS if LVF is normal	Use unless contraindicated for up to 12 months	Class I, Level A
β-blocker	After MI or ACS if LVF is normal	Use unless contraindicated for up to three years	Class I, Level B
β-blocker	Left ventricular failure	Use indefinitely unless contraindicated	Class I, Level A
β-blocker	Coronary or vascular disease and normal LVF	Long-term use may be considered	Class IIb, Level C
ACE inhibitor	After MI or with clinical evidence of HF, LVEF ≤ 40%, or diabetes	Use unless contraindicated	Class I, Level A
ARB	After MI or with clinical evidence of HF, LVEF ≤ 40%, or diabetes and intolerant of ACE inhibitors	Use instead of ACE inhibitor	Class I, Level B
Aldosterone antagonist	After MI, in the absence of significant hypotension, renal dysfunction, or hyperkalemia	Use in patients already receiving ACE inhibitor or ARB therapy and a β-blocker, who have symptomatic HF with LVEF ≤ 40%	Class I, Level B

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; AF = atrial fibrillation; AHA = American Heart Association; ARB = angiotensin receptor blocker; BP = blood pressure; CAD = coronary artery disease; CHADS2 = congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke or transient ischemic attack; CrCl = creatinine clearance; CV = cardiovascular; GI = gastrointestinal; HF = heart failure; INR = international normalized ratio; LVEF = left ventricular ejection fraction; LVF = left ventricular function; MI = myocardial infarction.

"high risk" for cardiovascular events, owing to such factors as established CVD, hypertension, hypercholesterolemia, diabetes, and other medical or behavioral concerns.

Class I recommendations. Encourage women to achieve an optimal blood pressure of less than 120/80 mmHg through lifestyle measures such as weight control, physical activity, alcohol moderation, sodium restriction, and a healthy intake of fruits, vegetables, and low-fat dairy products. For those whose blood pressure is 140/90 mmHg or higher—or 130/80 mmHg or higher in the presence of chronic kidney disease or diabetes—drug therapy is indicated. First-line drug therapy should include a thiazide diuretic unless contraindicated. Women at high cardiovascular risk who have acute coronary syndrome or a history of myocardial infarction should initially be treated with a β-blocker, an angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker (ARB).[18]

First-line drug therapy for women with high blood pressure should include a thiazide diuretic unless contraindicated.

Women are advised to maintain LDL cholesterol levels below 100 mg/dL, high-density lipoprotein (HDL) cholesterol levels above 50 mg/dL, triglyceride levels below 150 mg/dL, and non-HDL cholesterol levels below 130 mg/dL through weight control, physical activity, and a healthful diet. In addition to lifestyle modification, drug therapy may be helpful in women with the following risk factors[18]:

- coronary artery disease, other atherosclerotic CVD, diabetes, or a 10-year absolute CVD risk of more than 20%
- LDL cholesterol levels at or above 130 mg/dL, multiple risk factors, and a 10-year absolute coronary artery disease risk of 10% to 20%
- LDL cholesterol levels at or above 160 mg/dL and multiple risk factors, even if the 10-year coronary artery disease risk is less than 10%
- LDL cholesterol levels at or above 190 mg/dL, regardless of the presence or absence of other risk factors or CVD

Class IIa recommendations. Women with diabetes may aim to maintain a glycated hemoglobin level below 7% through lifestyle modification and drug therapy if they can do so without significant hypoglycemia.[18]

For women with coronary artery disease who are at very high CVD risk because of a recent acute coronary syndrome or several poorly controlled cardiovascular risk factors, it may be prudent to reduce LDL cholesterol levels to below 70 mg/dL, which may require an LDL-lowering drug combination.[18]

Class IIb recommendations. Women over age 60 who have a greater than 10% estimated coronary artery disease risk may use lipid-lowering therapy with statins if no acute inflammation is present and high-sensitivity C-reactive protein levels are greater than 2 mg/dL after lifestyle modification. Women at high risk for CVD, whose HDL cholesterol levels are below 50 mg/dL or whose non-HDL cholesterol levels are above 130 mg/dL, even after their LDL cholesterol goal has been achieved, may benefit from niacin or fibrate therapy.[18]

Class III recommendations. The updated AHA guidelines did not revise the previous (2007) Class III recommendations because no evidence supported altering them. For the primary or secondary prevention of CVD, the following therapies are *not* recommended: menopausal hormone therapy, antioxidant supplements, folic acid, or routine aspirin use in women under age 65.[18]

PREVENTIVE DRUG INTERVENTIONS

The AHA preventive drug interventions focus on preventing thromboembolism or stroke and delaying the progression of heart failure in vulnerable women through the use of such pharmacologic agents as aspirin, warfarin (Coumadin), dabigatran (Pradaxa), β-blockers, ACE inhibitors, and aldosterone antagonists (Table 2).[18]

Class I recommendations. Women with coronary artery disease should use aspirin therapy unless contraindicated. In women at high risk for CVD but intolerant of aspirin, clopidogrel (Plavix) can be substituted for aspirin. Women with chronic or paroxysmal atrial fibrillation who are at low risk for stroke and for whom warfarin is contraindicated should use aspirin.[18]

Women with chronic or paroxysmal atrial fibrillation should use warfarin to maintain an international normalized ratio of 2 to 3, unless they are considered to be at low risk for stroke. As an alternative to warfarin, dabigatran may be used to prevent stroke and thromboembolism in patients with atrial fibrillation and risk factors for stroke or embolization who do not have a prosthetic heart valve, significant valve disease, severe renal failure, or advanced liver disease.[18]

Following a myocardial infarction or acute coronary syndrome, women with normal left ventricular function should use β-blockers for 12 months to three years unless contraindicated. Women with left ventricular failure should use long-term β-blocker therapy indefinitely unless contraindicated.[18]

ACE inhibitors should be used in women with a history of myocardial infarction, clinical evidence of heart failure, a left ventricular ejection fraction at or below 40%, or diabetes, unless contraindicated. If ACE inhibitors are contraindicated or not tolerated, ARBs may be used instead.[18]

After myocardial infarction, aldosterone blockade is indicated in women who have no significant hypotension, renal dysfunction, or hyperkalemia; are receiving therapeutic doses of an ACE inhibitor and a β-blocker; and have a left ventricular ejection fraction at or below 40% with symptomatic heart failure.[18]

Class IIa recommendations. Women at high risk for CVD who have diabetes can use aspirin therapy unless contraindicated. At ages 65 or older, both healthy women and women at risk for CVD can use aspirin therapy if blood pressure is controlled and the benefits of preventing ischemic stroke and myocardial infarction outweigh the risks of gastrointestinal bleeding and hemorrhagic stroke.[18]

Class IIb recommendations. Aspirin therapy may be appropriate for women younger than 65 if blood pressure is controlled and the benefits of preventing ischemic stroke and myocardial infarction outweigh the risks of gastrointestinal bleeding and hemorrhagic stroke.[18]

Unless contraindicated, long-term β-blocker therapy may be considered for women with coronary or vascular disease and normal left ventricular function, even if they have no history of myocardial infarction or acute coronary syndrome.[18]

IMPLICATIONS FOR NURSES

Despite a growing awareness of the threat women face from CVD, they are still less likely than men to be recognized as being at risk for CVD or to receive a thorough risk evaluation and appropriate intervention. Understanding potential sex differences in CVD presentation and response to treatment, as well as current recommendations for risk assessment and intervention, prepares nurses to raise awareness of CVD among patients and caregivers, teach them about preventive strategies, and encourage lifestyle changes that promote cardiovascular health. To further this endeavor, advanced practice nurses should consider participating in related cardiovascular research and public policy debate. ▼

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