Cardiovascular disease in women: A journey toward a focus on prevention

By Tamera Lea Pearson, PhD, MSN, FNP, ACNP

Intended audience
Nurse practitioners (NPs), certified nurse-midwives (CNMs), and other advanced practice clinicians who care for women.

Continuing education (CE) approval period
Now through August 31, 2015

Estimated time to complete this activity
This activity will take 1 hour to complete.

Program description/identification of need
This CE program presents practical strategies to meet the needs of NPs, CNMs, and other advanced practice clinicians who provide primary care for women. The program will help clinicians identify women who have increased risk for cardiovascular disease (CVD) and help clinicians reduce these patients' CVD risk.

Cardiovascular disease remains the No. 1 cause of death in women worldwide, despite years of research and advances in diagnosis and treatment. One-third of women in the United States have some form of CVD, and more women than men die of CVD-related causes. Although notable improvements in understanding CVD in women have been made over the past three decades, much still needs to be done to reduce CVD morbidity and mortality in this patient population. New effectiveness-based recommendations from the American Heart Association (AHA) emphasize methods shown to reduce CVD risk or treat early heart disease in women—to save lives.

Educational objectives
- Discuss the prevalence of CVD and CVD-related mortality in women versus men.
- Describe the AHA's effectiveness-based recommendations for CVD risk reduction in women.
- Delineate recommendations for lifestyle changes and medication use to reduce CVD risk factors and prevent CVD development in women.

Approval statement
This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH) for 1 contact hour of CE credit, including 0.25 contact hours of pharmacology content. Each participant should claim only those contact hours that he/she actually spent in the educational activity.

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Tamera Lea Pearson, PhD, MSN, FNP, ACNP, has disclosed that she has not served on a speaker's bureau and that she has no financial disclosures to make related to this article.

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Successful completion of this activity
Successful completion of this activity, J-14-08, requires participants to (a) read the learning objectives, disclosures, and disclaimers; (b) study the material in the learning activity; (c) during the approval period (now through August 31, 2015), 1. click on the link to the course and log on to the NPWH Online Continuing Education Center; 2. complete the online posttest and evaluation; 3. earn a score of 70% or better on the posttest; 4. print out the CE certificate.

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Much progress has been made in terms of diagnosing and treating cardiovascular disease (CVD) in women, but more women in the United States are still dying of CVD than any other disease. The author briefly reviews the progress that has been made regarding CVD in women, examines the current state of the science, discusses the new effectiveness-based guidelines that focus on prevention, and considers implications for nurse practitioners.

KEY WORDS: **cardiovascular disease, coronary heart disease, stroke, CVD prevention**

Cardiovascular disease (CVD) remains the No. 1 cause of death in women worldwide, despite years of research and advances in diagnosis and treatment.[1] One-third of women in the United States have some form of CVD, and more women than men die of CVD-related causes.[2] Although notable improvements in understanding CVD in women have been made over the past three decades, much still needs to be done to reduce CVD morbidity and mortality in this patient population.[3]

Advancements and challenges

An appreciation of the nature of CVD in women has been evolving since the late 1990s, when gender inequity in CVD research was recognized to be a problem. Legislation for the Women's Cardiovascular Disease Research and Prevention Act was passed in 1996 in an effort to rectify this situation. Subsequently, women have been included in many CVD studies, which highlight differences between women and men in terms of the presentation and the treatment of CVD. In 1999, the American Heart Association (AHA) issued its first recommendation guidelines focused on CVD in women.[4] Updated evidence-based practice guidelines were released in 2004[5] and 2007.[6] Most recently, the AHA published *effectiveness-based guidelines for CVD prevention in women*.[7] These new guidelines define CVD as an encompassing term referring to both coronary heart disease (CHD) and stroke.[7] Inclusion of women in CVD research studies and accumulation of clinical experience provide an evolving body of knowledge that is reflected in the new guidelines. Nevertheless, CVD in women continues to be a major challenge.

Here are the facts in 2014: CVD is the leading cause of death among women worldwide, resulting in a societal burden projected to worsen over the next 10 years.[1] Within the U.S., a woman dies of CVD every minute, and overall mortality statistics indicate that one of every two women will die of CHD or stroke.[3,8] Most women (64%) who die suddenly of CHD did not have previous symptoms.[9] Women now experience more strokes than do men, and will likely suffer major physical, emotional, and cognitive consequences of these strokes.[8,10,11]

Despite numerous campaigns over the past decade that have focused on educating U.S. women about their CVD risk, about half are uninformed about it.[3,12] This lack of knowledge is more common among African-American women than among white women.[3] Healthcare practitioners (HCPs) themselves underestimate CVD risk in women, resulting in inadequate preventive therapy for appropriate candidates and missed diagnoses.[3,7,9,11,13,14] In addition, treatment discrepancies persist; compared with men, women are less likely to undergo coronary revascularization procedures or be discharged on recommended medications after suffering an acute cardiovascular event.[15] Overall CVD-related mortality among women has decreased since 1997, which Wenger has ascribed to improved management of established CVD and reduction of risk factors.[3] However, over the past 5 years, the number of CVD-related deaths in women aged 35-44 years has increased.[7,16]

The ongoing problem of CVD in women (including the increased number of CVD deaths in younger women) is related, at least in part, to the increased prevalence of chronic disorders such as hypertension (HTN), hypercholesterolemia, diabetes mellitus (DM), and obesity. For example, HTN prevalence among women has increased in the past 10 years, especially among African Americans.[9,11] In persons older than 65, HTN affects more

women than men.[9] With regard to hypercholesterolemia, the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) may have substantially underestimated lifetime CVD risk, possibly precluding initiation of statin therapy in many high-risk women.[7,17,18] Hypertriglyceridemia is associated with increased CVD-related mortality in women, but not in men.[19] DM now affects more than 12 million U.S. women, with double the impact on Hispanics versus whites.[7,9,12] Two-thirds of U.S. women are overweight or obese, a major CVD risk factor.[3,7,20] Autoimmune collagen diseases such as lupus erythematosus are another class of chronic diseases recently found to be associated with CVD risk in women.[3,21] The pervasiveness of these chronic conditions contributes to overall CVD risk in women and reinforces the need for sustained research to improve outcomes.

State of the science

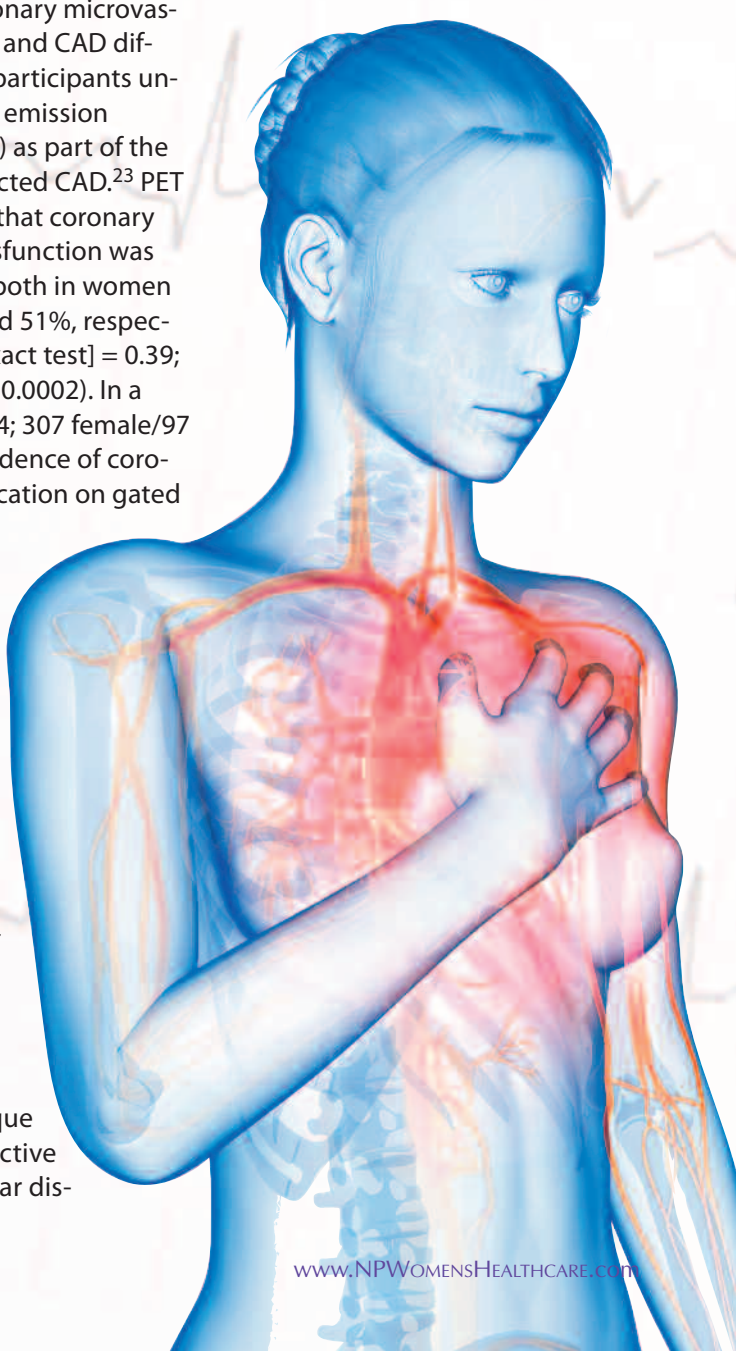
Researchers are advancing understanding of CVD in women through investigations aimed at recognizing gender differences. Inquiries into CVD pathophysiology and novel risk factors are essential steps in the process of improving outcomes for women.

Biological gender differences—Studies reveal differences between the genders in terms of the physiologic development and clinical presentation of CVD. In particular, women tend to develop microvascular coronary artery disease (CAD)—now termed *female pattern heart disease*.[13] This microvascular dysfunction leads to more varied clinical symptoms, or in some cases, no symptoms.[13,15] Fifty percent of women who present with angina have no evidence of ischemia or coronary artery obstruction on traditional stress tests or cardiac catheterization; other tests (see next section) show that these women have microvascular dysfunction.[22]

Of note, not all studies have demonstrated a major gender difference with regard to microvascular CAD. In a recent study conducted on 405 men and 813 women to ascertain whether the link between coronary microvascular dysfunction and CAD differed by gender, participants underwent positron emission tomography (PET) as part of the workup for suspected CAD.[23] PET imaging showed that coronary microvascular dysfunction was highly prevalent both in women *and* men (54% and 51%, respectively; *P* [Fisher exact test] = 0.39; *P* [equivalence] = 0.0002). In a subgroup (n = 404; 307 female/97 male) without evidence of coronary artery calcification on gated computed tomographic imaging, coronary microvascular dysfunction was common in both genders, despite normal stress perfusion imaging and zero coronary artery calcification (44% of men vs. 48% of women; *P* [Fisher exact test] = 0.56; *P* [equivalence] = 0.041).

Unlike the plaque buildup in obstructive CAD, microvascular disease involves small arteries and diffuse atherosclerosis, wherein plaque forms evenly throughout the artery wall. Another pathophysiologic aspect of microvascular disease is endothelial dysfunction, wherein coronary flow is affected by contraction of the vessel wall. Neither of these phenomena is seen clearly on traditional cardiac catheterization and is often not evident on stress tests.[13,24]

Novel factors and tests—Bairey Merz[13,15] has stated that women with positive cardiac



stress test results but negative obstructive findings by traditional angiography are particularly worrisome with regard to having female pattern heart disease. Researchers have developed innovative tests to identify microvascular disease, which they are promoting as the new gold standard to evaluate for CAD in women.[13,22-26] One option is an invasive coronary reactivity test, which involves introduction of adenosine during cardiac catheterization to detect endothelial dysfunction.[27] Another option is a coronary flow reserve test, in which intravascular ultrasonography of the coronary arteries is performed to detect endothelial dysfunction.[24] These novel approaches to detecting CAD were developed through the Women's Ischemia Syndrome Evaluation (WISE) study.[24] Although these diagnostic tests are continuing to be studied and may not be routinely available, the results are promising.

Additional CVD diagnostic tests may be indicated based on a woman's health history or reported symptoms. A cardiac calcium scan may be helpful to discern presence of calcium in the coronary arteries, which is associated with CVD in women.[7] Carotid ultrasonography and ankle brachial index tests are both correlated with presence of CAD and are indicated in a subgroup of women.[28,29] Elevated C-reactive protein level is another factor that has been associated with increased CVD risk in women.[7] Although routine use of these tests is not suggested at this time, their overall utility to improve CVD outcomes in women continues to be investigated.[7]

Table 1. Gender-sensitive cardiovascular disease risk profiles[3]

Updated Framingham: Includes these gender-specific variables	Reynold's Risk Score: Adds identified gender factors to Framingham
Age	High sensitivity C-reactive protein
Total cholesterol	Systolic blood pressure
High-density lipoprotein cholesterol	Family history
Systolic blood pressure	Hemoglobin A_{1C} (if patient has diabetes)
Hypertension treatment (if applicable)	
Smoking history	
Diabetes status	

The transformation from evidence-based to effectiveness-based guidelines denotes a shift from pure clinical research.

The new "effectiveness-based" guidelines

Research continues to improve understanding of the complexity of gender differences and the unique approach needed to alter outcomes of CVD in women. In response to this challenge, the new AHA guidelines focus on prevention in what are termed *effectiveness-based* guidelines.[7] The transformation from evidence-based to effectiveness-based guidelines denotes a shift from pure clinical research as the basis of recommendations to an approach that encompasses benefits and risks observed in clinical practice.[3] The focus is on recognizing lifetime risk for CHD and stroke in women and prevention of disease development. Early screening and a complete CVD risk assessment are advised to reduce the pervasiveness of CVD in women.[7,30]

CVD risk assessment

The effectiveness-based guidelines denote specific information that should be included in a CVD risk assessment in women.

History—Although family history was not part of the original Framingham assessment, research shows that women are at increased risk for CVD if they have a first-degree relative who experienced premature CVD (i.e., if this person was younger than 55 [male] or 65 [female] when first diagnosed with CVD).[7] Details of CVD in family members is obtained along with a woman's own health history. A history of pregnancy problems such as preeclampsia or gestational diabetes is now recognized as potential unique precursor of CVD risk in later years.[7,8,31] A personal

Table 2. New classification categories of cardiovascular disease risk in women[3]

High risk (≥1 high-risk states): Clinically manifest CHD, cerebrovascular disease, or PAD; abdominal aortic aneurysm; end-stage or chronic kidney disease; diabetes mellitus; 10-year predicted CVD risk ≥10%

At risk (≥1 major risk factors): Family history of premature CVD occurring in first-degree relatives (i.e., in men <55 years or in women <65 years); history of pre-eclampsia, gestational diabetes, or pregnancy-induced HTN; TC ≥200 mg/dL, HDL-C <50 mg/dL, or treated for dyslipidemia; SBP ≥120 mm Hg, DBP ≥80 mm Hg, or treated HTN; metabolic syndrome; cigarette smoking; poor diet; obesity, particularly central adiposity; physical inactivity; systemic autoimmune collagen-vascular disease; evidence of advanced subclinical atherosclerosis; poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise

Ideal cardiovascular health (all of these): No family history of CVD at premature age; no history of pregnancy problems; TC <200 mg/dL; BP <120/80 mm Hg; fasting blood glucose <100 mg/dL; abstinence from smoking; healthy diet; BMI <25 kg/m^2; regular physical activity

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; PAD, peripheral arterial disease; SBP, systolic blood pressure; TC, total cholesterol.

history of smoking or current tobacco use is noted. A history of paroxysmal atrial fibrillation (AF) in women is a specific problem that increases stroke risk and requires particular attention.[2,3,7]

Specific elements—Elements delineated as essential to include in a comprehensive CVD risk assessment are exercise routine, dietary habits, and measurements of blood pressure (BP), body mass index (BMI), waist circumference, lipoprotein levels, and glucose.[3,7] Existing health problems of DM, kidney disease, HTN, hypercholesterolemia, and autoimmune collagen disease are risk status determinants that must be identified.[2,3] Screening for depression is recommended as an essential part of the CVD risk evaluation, not because of a direct effect on CVD but because of the possible influence on a woman's ability to address her risks.[7]

Gender-sensitive risk assessment tools—CVD risk assessment in women includes use of gender-sensitive tools. The original Framingham profile underestimates CVD risk in women, which led to modification of the tool to create an instrument that is accurate in women.[32] Another group of researchers designed a new gender-specific instrument incorporating novel factors to appraise CVD risk in women.[33] Current guidelines suggest using either the updated Framingham Heart Study risk assessment tool or the Reynold's Risk Score as part of a comprehensive CVD risk assessment.[32,33] Details of variables built into each score calculation are noted in *Table 1*.[3] The Framingham Heart Study website includes ***risk score calculators*** based on lipids or BMI.[34] An ***interactive calculator*** for assessing cardiac and stroke risk can be found at the Reynolds Risk Score website.[35]

New risk categories—Another substantial change in the effectiveness-based guidelines is the classification of three specific CVD risk categories for women, which include *high risk, at risk,* and *ideal cardiovascular health*.[3] Findings from the comprehensive CVD risk assessment and results from a gender-sensitive risk tool are compiled to determine a woman's individual risk category. *Table 2* lists the determinants of each new risk classification category.[3] Women with clinical manifestations of CHD, cerebrovascular disease, peripheral arterial disease (PAD), abdominal aortic aneurysm, kidney disease, DM, or a 10-year predicted CVD risk of 10% are in the *high risk* category. The *at risk* category represents women who have one or more major CVD risk factors as defined in the guidelines and noted in the comprehensive assessment. Women who report a healthy lifestyle, including regular physical activity and a wholesome diet, with no CVD history or identified risk factors, meet the criteria for the *ideal cardiovascular health* category. All women are encouraged to achieve or maintain ideal cardiovascular health through prevention. Aggressive treatment and risk reduction strategies are indicated for women who are in the other two risk categories or who have a history of paroxysmal AF.[3,7]

Application of CVD guidelines based on risk category

Lifestyle interventions are recommended for women in every CVD risk category to maximize prevention.[3,7] Smoking cessation, tobacco avoidance, and a

low-fat diet rich in fruits, vegetables, and weekly fish are recommended. Limited intake of sugar, salt, and alcohol is advised. Regular physical activity is essential at a frequency of 150 minutes of moderate exercise or 75 minutes of vigorous workouts per week.[3] Following healthful lifestyle principles in order to maintain a BMI <25 kg/m^2 with a waist circumference <35 inches is suggested. Women who have had a cardiac event or are in the *high risk* category because of known CVD or PAD should be referred to a formal cardiac rehabilitation program.[7]

Preventive medication—Preventive drug therapy is individualized based on a woman's personal history and CVD risk classification. For example, routine use of aspirin in healthy women younger than 65 years is not recommended but may be useful in women older than 65 to prevent stroke and myocardial infarction.[3,7] Aspirin (75-325 mg/d) is prescribed for women with CHD and DM unless contraindicated.[3,7] Estrogen therapy, antioxidant supplements, and folic acid should not be used for primary or secondary prevention of CVD.[3,7]

Aggressive treatment—Interventions aimed at reducing major CVD risks are crucial for women classified as *high risk* or *at risk*.[3] Aggressive treatment of HTN and hypercholesterolemia and meticulous management of DM, if present, are imperative. History of paroxysmal AF is noted as a distinct category of CVD risk that must be addressed consistently. Studies show that, compared with men, women are undertreated for these major CVD risks and do not receive the equivalent pharmacotherapy for diagnosed CAD or cerebrovascular disease.[12,13] Therefore, aggressive treatment of identified CVD risks and prevention of CVD development are priorities.

Hypertension is addressed by diet, exercise, and medications to achieve a BP <120/80 mm Hg. A thiazide diuretic is typically indicated, although additional medication may be required to reach goal. Women in the *high risk* category (unless pregnant), with evidence of clinical CVD, heart failure, and/or DM, are routinely given beta blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers.[3,7] Diet modification and omega-3 fatty acid supplements are endorsed for primary and secondary CVD prevention in women with hyperlipidemia and hypertriglyceridemia.[7]

Regular physical activity is essential at a frequency of 150 minutes of moderate exercise or 75 minutes of vigorous workouts per week.

Hypercholesterolemia is managed aggressively according to individual CVD risk. Based on ATP III guidelines, lipid goals are low-density lipoprotein cholesterol (LDL-C) <100 mg/dL, high-density lipoprotein cholesterol >50 mg/dL, and triglycerides <150 mg/dL.[3,7] If implementation of lifestyle interventions (e.g., dietary changes, exercise) does not achieve adequate results, statins, niacin, and fibrates are all appropriate pharmacotherapy—depending on the component of the lipid profile being addressed.[7] For women older than 60 in the *high risk* category who have hypercholesterolemia, statin therapy is indicated to reach an LDL-C goal as low as <70 mg/dL to reduce CVD risk.[12-14]

Recently, the AHA published a risk calculator tool designed to determine indication for statin therapy based on global CVD risk; a 30%-50% reduction of LDL-C is recommended if LDL-C exceeds 190 mg/dL.[36] Based on use of this new tool, the threshold for instituting statin therapy would be much lower for many men and women (the risk calculator is not gender specific). Although use of this particular tool is controversial, evidence indicates that women, regardless of which guideline is followed, need to lower their cholesterol levels in order to reduce their CVD risk.

Presence of DM automatically places a woman in the *high risk* category for CVD. Glycemic control in women with DM aims to maintain hemo-

globin A_{1C} under 7% through lifestyle changes and/or pharmacotherapy.[7]

Women with a history of paroxysmal AF are at a 4- to 5-fold increased risk for ischemic stroke. Because of the documented undertreatment of AF, the 2011 guidelines for CVD prevention in women specifically addressed this risk factor.[7] Women with AF require specific anticoagulation treatment with warfarin, aspirin, or one of the newer oral anticoagulants (e.g., dabigatran, rivaroxaban, apixaban).[7]

Implications for NPs

Nurse practitioners caring for women are in a key position to address CVD prevention. Being cognizant of gender differences in CVD pathophysiology may influence both diagnostic workup and treatment of women who present with symptoms that may otherwise be discounted as noncardiac in origin.[25] NPs must be familiar with the new effectiveness-based guidelines and develop implementation methods within their individual practices. Routinely utilizing one of the interactive gender-sensitive CVD risk assessment tools as part of a woman's comprehensive evaluation may increase identification of women at risk and may influence treatment or referral decisions.

To reduce CVD risk in women, HTN, hyperlipidemia, DM, and obesity must be managed persistently to reach recommended goals. NPs can increase other HCPs' and patients' awareness about CVD in women by sharing their knowledge in practice and in community settings. Participating in clinical research aimed at furthering understanding of CVD in women is another way NPs can support the effort to reduce CVD prevalence and improve outcomes. NPs can serve as role models to patients by pursuing a healthy lifestyle and aiming for ideal cardiovascular health.

Although the problem of CVD in women is global, some NPs may find it helpful to access information about the problem in their own community. The CDC provides an ***interactive website*** with data for state and county CVD incidence levels.[37] Progress has been made in recognizing gender differences. The new effectiveness-based guidelines from the AHA are a prime example of translating the past two decades of research regarding CVD in women into clinical practice. Now the focus is on CVD prevention through comprehensive assessment of risk, encouraging a healthy lifestyle, and careful management of major health risks. As the principles espoused in the guidelines are implemented, and as better diagnostic and therapeutic options for women continue to be studied and verified, the problem of CVD in women is likely to be mitigated.

> Nurse practitioners caring for women are in a key position to address CVD prevention.

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