Prevention of Cardiovascular Disease in Women

Anum Saeed, M.D.[b]; *June Kampangkaew*, M.D.[b]; *Vijay Nambi*, M.D., Ph.D.[a,b]

[a]MICHAEL E. DEBAKEY VA MEDICAL CENTER, HOUSTON, TEXAS; [b]BAYLOR COLLEGE OF MEDICINE, HOUSTON, TEXAS

ABSTRACT: Cardiovascular diseases are the leading cause of morbidity and mortality among women worldwide. The pathophysiological basis of cardiovascular health among men and women is not identical. This leads to variable cardiovascular responses to stimulus and presentation of cardiovascular disease symptoms, both of which can have a direct effect on treatment outcomes.

Traditionally, the enrollment of women in clinical trials has been minimal, resulting in a lack of gender-specific analysis of clinical trial data and, therefore, the absence of concrete risk factor assessment among women. However, scientific progress in the past decade has identified a spectrum of risk factors for cardiovascular diseases that may be specific to women. These risk factors, which may include menopause, hypertensive disease of pregnancy, and depression, confer additional risk in women besides the traditional risk factors. The current state of knowledge and awareness about these risk factors is suboptimal at this time. Therefore, although the treatment of cardiovascular diseases is similar in both genders, appropriate risk stratification may be limited in women compared to men.

The purpose of this review is to describe the recent trends in identifying female-specific risk factors for cardiovascular diseases, their utility in risk stratification, and current pharmacological options for women with regard to cardiovascular disease prevention.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality in women in the United States.[1] Although the overall management of CVD is similar for both genders, gender-based variations exist in the pathophysiology,[2,3] symptoms,[4] presentation, efficacy of diagnostic tests, and response to pharmacological interventions. Some relevant differences between men and women are summarized in Table 1.

Research has shown that women have less obstructive but more diffuse coronary artery disease (CAD) and a higher 1-year mortality rate after acute myocardial infarction when compared to men.[5] Among women, black women seem to have the highest CAD death rates. Finally, both women and physicians are less aware of and less proficient in identifying CVD in women. Prevention and management of CVD in women, therefore, should begin with awareness of the problem and an understanding of the disease's unique characteristics and challenges in women.

The first guidelines for CVD prevention tailored to women were published in 2004 and later updated in 2007 and 2011.[6] Although the general CVD risk factors in men and women are similar, some exceptions unique to women were detailed in these guidelines. The following reviews some of the important risk factors for CVD and the current state of prevention, guidelines, and management of CVD in women.

TRADITIONAL RISK FACTORS

Non-Modifiable

Age. Age is one of the most powerful risk factors for developing CVD. The cardioprotective effect of estrogen for premenopausal women results in a roughly 8- to 10-year lag in the onset of CAD in women. After the age of 55, the risk for CAD increases similarly in both men and women.[7]

Modifiable

Smoking. According to the American Heart Association (AHA), 13% of women in the United States who are over 18 years of age are current smokers. Although the percentage of women smokers is lower than men, a recent meta-analysis of 75 cohort studies (approximately 2.4 million individuals) showed a 25% greater risk of CAD in women smokers compared with male smokers (RR, 1.25; 95% CI, 1.12-1.39).[1] In a report from the Nurses' Health Study of 85,941 women with a 14-year follow-up, reduction in smoking accounted for a 13% decline in the incidence of CAD.[8]

As in men, women should be advised not to smoke and to avoid environmental tobacco smoke. Smoking cessation counseling at each encounter, nicotine replacement, and other pharmacotherapy options as indicated in conjunction with a formal smoking cessation program should be considered.[2]

PARAMETERS	GENDER-BASED DIFFERENCES
Anatomical features	Vessel sizes are smaller in women than men. Women have smaller left ventricular size than men. Women have greater systolic function and less diastolic compliance than men.
Hormonal differences	Estrogen is predominantly influential in women and testosterone in men.
Cardiovascular function differences	Women have reduced sympathetic and higher parasympathetic activity than men. Women have 10% lower stroke volume than men.
Cardiovascular adaptions	Women have an increased pulse rate with increased cardiac output versus men, who have higher blood pressure in response to high stress.
Electrocardiographic findings	Women have a longer corrected QT interval than men. Women have a shorter PR interval than men.

Table 1.
Differences in clinical parameters and manifestations in women compared to men.

Obesity. According to the 2013 National Health and Nutrition Examination Survey (NHANES) among U.S. adults aged ≥ 20 years, 37.7% were obese (35% of men and 40.4% of women).[3] The impact of obesity on the development of CAD seems to be greater in postmenopausal women and is thought to be due to redistribution of fat around the abdominal area and predisposition to metabolic syndrome.[9] The guidelines on CVD prevention recommend that women should maintain or lose weight through appropriate physical activity, caloric intake, and formal behavior programs with a goal body mass index (BMI) of < 25 kg/m^2 in women or waist size < 35 inches.[6] Currently, the recommended exercise time for women and men for prevention of CVD is at least 150 minutes/week of moderate exercise or 75 minutes/week of vigorous exercise.

Hypertension. Endogenous estrogens maintain vasodilation and contribute to blood pressure (BP) control in premenopausal women. Hypertension risk increases more in elderly women than in elderly men. Compared with white women, black and Hispanic women have a significantly higher prevalence of hypertension independent of other factors.[7] There is currently no evidence that antihypertensive treatments differentially affect BP response, as many trials of antihypertensive agents do not report sex-specific analysis for efficacy or adverse effect profiles. The Eighth Joint National Committee recommended a BP target of < 140/90 mm Hg in most individuals except those aged 60 years and older without diabetes or chronic kidney disease, for whom the BP target recommendation was < 150/90 mm Hg.[10]

Dyslipidemia. The prevalence of elevated total cholesterol (TC) ≥ 200 mg/dL and ≥ 240 mg/dL is 42% and 13%, respectively, in women ≥ 20 years in the United States. Similarly, 30% of women ≥ 20 years have an LDL-cholesterol (LDL-C) of ≥ 130 mg/dL, and 10% of these women have an HDL-cholesterol (HDL-C) < 40 mg/dL. Elevated LDL-C, triglycerides, and non-HDL-C and low HDL-C have all been associated with an increased risk for CVD in women as in men. However, the Centers for Disease Control and Prevention recently reported that women are less likely to be prescribed statin therapy than men who are at equal risk of CVD despite equal efficacy of statin therapy among both genders.

The 2013 American College of Cardiology (ACC)/AHA cholesterol guidelines recommend statin therapy (moderate to high intensity, depending on the indication) for all individuals with established CVD, LDL-C ≥ 190 mg/dL, diabetes, or an established 10-year CVD risk ≥ 7.5% based on the pooled cohort risk equation, which calculates the 10-year and lifetime atherosclerotic cardiovascular disease (ASCVD) event risk.[11] Additionally, consideration of statin therapy (based on physician-patient discussion) was recommended for (1) those with a 10-year ASCVD risk of 5% to 7.5%, (2) those with other factors such as an elevated calcium score or a family history of premature ASCVD, or (3) those with an elevated high-sensitivity C-reactive protein (hs-CRP) or an abnormal ankle-brachial index (ABI).[11]

Diabetes Mellitus. Substantial evidence supports the association of diabetes mellitus (DM) and hemoglobin A1c

(HbA1c) with adverse CV outcomes.[12] Mortality due to heart disease-related causes in adults with DM is two to four times higher than in those without DM.[13]

There is a significant gender difference in CVD mortality in patients with type 1 DM, although type 1 DM affects women and men equally. Even when adjusted for comorbidities and glycemic control, women with type I DM have a 37% increased risk of all-cause mortality and twice the excess risk of fatal and nonfatal vascular events compared to men with type I DM.[14] Furthermore, data indicate that women with DM are less likely to have appropriate glycemic control and receive less aggressive treatment for many modifiable CAD risk factors than diabetic men. Clinical trial interventions to lower HbA1c have failed to demonstrate ASCVD benefit with intensive versus standard glycemic control; however, recent trials with newer agents such as SGLT-2 inhibitors have started to show some benefit with respect to CVD. The current applicable guidelines recommend an HbA1c of < 7%, if achieved without causing significant hypoglycemia, for ASCVD risk reduction.

NONTRADITIONAL RISK FACTORS

Hypertensive Disorders of Pregnancy

Pregnancy is a cardiometabolic stressor that may unmask underlying vascular and metabolic abnormalities. Hypertension affects approximately 10% of pregnancies and is one of the leading causes of maternal and fetal morbidity and mortality.[15] Gestational hypertensive disorders and diabetes have been linked to increased risk of developing hypertension as well as cardiovascular disease later in life.

The mechanism behind the increased risk of CVD in women with gestational hypertension disorders is poorly understood. However, the leading hypothesis is that preeclampsia in particular and CVD both have a state of endothelial dysfunction, oxidative stress, inflammatory response, and increased expression of procoagulants. Preeclampsia and CVD also share similar risk factors including obesity, insulin resistance, and renal disease. Meta-analyses have shown that preeclampsia has an increased relative risk for incidence of ischemic heart disease and may be independently associated with CVD in women.[16-18]

The AHA has recognized preeclampsia as a risk factor for CVD, and the American College of Obstetrics and Gynecology has recommended yearly assessment of blood pressure, lipids, fasting blood glucose, and body mass index following a medical history of recurrent preeclampsia or preeclampsia with preterm birth. Beyond more aggressive screening, women with a history of hypertensive disorders during pregnancy should be advised to focus on lifestyle modifications including diet, weight, exercise, and smoking cessation.

Gestational Diabetes

Gestational diabetes mellitus (GDM) is defined as new-onset impaired glucose tolerance during the third trimester of pregnancy. Normal glucose metabolism typically returns after pregnancy. However, despite glucose metabolism returning to normal, patients with a history of GDM have an elevated risk for developing diabetes mellitus.[19,20] Thus, more aggressive screening and lifestyle modification should be considered.

Autoimmune Diseases

Systemic autoimmune disorders, which have been shown to be associated with CVD, tend to affect women more often than men. Patients with rheumatoid arthritis are reported to have a 2- to 3-fold higher risk of myocardial infarction (MI) and a 50% higher risk of stroke.

In case control studies, systemic lupus erythematosus has been reported to increase the risk of MI between 9- and 50-fold over the general population.[21] It has been postulated that these inflammatory diseases affect the microvasculature and can also result in plaque instability, both of which can increase the risk of acute CV events.[22]

Depression

Depression has been described as an antecedent to heart disease. According to the NHANES I study, women with depression had a higher relative risk of CAD incidence compared to women without depression.[23] Depression is also associated with other CV risk factors such as smoking and physical inactivity. Women experience depression at approximately twice the rate of men.[24] Studies have also suggested that depressed women have a higher risk for CVD compared to non-depressed women.

It is important to keep in mind that in some women, chest pain and tachycardia are the presenting features of depression and anxiety disorders. In all, a thorough, clinically appropriate cardiac evaluation should be performed in women with such symptoms. Currently, it is not known if treatment of depression will improve cardiac outcomes; therefore care should follow the same standards as when managing any patient with depression.

RADIATION THERAPY IN BREAST CANCER

Radiation therapy has been associated with an increased risk of cardiac mortality and morbidity in patients with breast cancer.

LIFESTYLE	INTERVENTION
Cigarette smoking	Counselling for cessation, nicotine replacement, and pharmacotherapy as indicated in conjunction with a behavioral program for smoking cessation
Physical activity	At least 150 min/week of moderate exercise At least 75 min/week of vigorous exercise Muscle strengthening activities at least 2 days/week
Cardiac rehabilitation	Recommended for women with recent acute coronary syndrome, revascularization, CVA, PAD
Weight	BMI < 25 kg/m^2, waist size < 35 inches, or other target metric of obesity should be maintained by exercise and appropriate diet
CLINICAL RISK FACTORS	**TARGETS AND USES IN RISK ASSESSMENT**
Blood pressure	< 140/90 mm Hg recommended If higher, consider therapy from one of the indicated classes of antihypertensive drugs.
LDL-C	If between 70-189 mg/dL at baseline without clinical ASCVD in ages 40-75 years, consider statins for ASCVD risk score ≥ 7.5%. Concomitant ASCVD risk factors, 10-year ASCVD risk ≥ 7.5%, CKD, albuminuria, retinopathy, evidence of subclinical atherosclerosis, elevated lipoprotein(a), or elevated hs-CRP indicate higher risk and warrant high-intensity statin therapy ± ezetimibe (or colesevelam). Statin use of moderate to high intensity recommended at any LDL-C level in patients of ages < 75 years with established ASCVD
Triglycerides	< 100 mg/dL optimal, < 150 mg/dL normal ≥ 150 mg/dL elevated Treat if ≥ 500 mg/dL (after ruling out secondary causes)
Diabetes mellitus	Lifestyle and pharmacotherapy are recommended to achieve an HbA1c of < 7%. Concomitant use of statin is recommended.
HDL-C	< 50 mg/dL in women is a risk marker of ASCVD.
Hs-CRP	> 3.0 mg/dL high relative risk
CAC scoring	0: no identifiable disease; 1-99: mild disease; 100-399: moderate disease; ≥ 400: severe disease Recommended for risk stratification*
CIMT	Not recommended for routine ASCVD risk assessment
THERAPIES	**RECOMMENDATIONS**
Aspirin	USPTF recommends for women aged 50-59 years with 10% or greater 10-year CVD risk without an increased risk of bleeding.

* Per expert opinion in 2013 ACC/AHA Guidelines

Table 2.
Risk factor assessment and interventions for prevention of cardiovascular diseases in women based on the current guidelines. CVA: cerebrovascular accident (includes stroke or transient ischemic attack); PAD: peripheral arterial disease; BMI: body mass index; ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CAC: coronary artery calcium; CIMT: carotid intima–media thickness; USPTF: United States Preventive Services Task Force

Radiation injury can cause constrictive pericarditis, myocardial fibrosis, and valvular and coronary artery lesions.[25] The increased risk of cardiovascular mortality is proportional to the dose volume of exposure to the heart, beginning just a few years after exposure and continuing for at least 20 years.[26]

A trial that randomized subjects to preoperative radiation therapy, postoperative radiation therapy, or surgery alone found that cardiac mortality was positively correlated with the cardiac radiation dose-volume. Furthermore, patients receiving high-dose volumes exhibited an increased mortality related to ischemic heart disease but not to MI, which may suggest radiation-induced microvascular damage to the heart. Women with preexisting cardiac risk factors also have been noted to have a greater absolute increase in risk from radiotherapy.

Although radiotherapy regimens for breast cancer have changed since the women in these trials were irradiated, radiation still remains a consideration in women with breast cancer who have undergone therapy.

MENOPAUSE AND HORMONE REPLACEMENT THERAPY

Estrogen is thought to act through estrogen receptors expressed both in vascular endothelial and smooth muscle cells. It improves the arterial wall response to injury, promotes re-endothelialization,[27] and inhibits smooth muscle cell proliferation and matrix deposition following vascular injury.[28] Estrogen also prevents coronary artery spasm through vasodilation mediated by both rapid increases in the production of nitric oxide (NO) and the induction of NO genes. In addition to its impact on the endothelium and smooth muscle cells, estrogen also affects cardiomyocytes. In vitro studies suggest that estrogen prevents cardiomyocyte apoptosis[29] and inhibits cardiomyocyte hypertrophic response,[30] although the data on hypertrophic response is conflicting.[31] Hence, postmenopausal women lose the cardioprotective effects of estrogen and have an elevated risk for CVD.

Although the ACC and AHA recognize menopause as a risk factor for CAD, the evidence for promoting hormone replacement therapy (HRT) is controversial. In the Women's Health Initiative (WHI) study, estrogen-progestin replacement had no cardioprotective effect and may have produced harm. Similar results in a secondary prevention cohort of women were seen in the Heart and Estrogen/progestin Replacement Study (HERS) trials. As a result, HRT is not recommended for primary or secondary prevention of CVD,[6] and its use has decreased as much as 80% since the WHI findings were published.[32] These findings have also affected treatment decisions regarding perimenopausal women in their 40s and 50s with distressing vasomotor symptoms[33]; this is despite the United States Preventive Services Task Force (USPSTF) statement that the recommendations do not apply to women under age 50 who have had surgical menopause, nor do they apply to the use of HRT for treatment of menopausal symptoms.[34] Currently, this topic is undergoing reassessment; until further data emerges, the risks and benefits should be considered and discussed with the patient.[33]

RISK STRATIFICATION

As previously noted, the current recommendation in the United States is to use the pooled cohort risk equation to assess 10-year CVD risk.[11] However, in the future, nontraditional risk factors and markers such as depression, radiation exposure, pregnancy complications, depression, and history of autoimmune disease should also be considered. Furthermore, whether or not the treatment thresholds should be similar in men and women will need to be further explored. The 2011 effectiveness-based guidelines directed towards women recommended different CVD prevention and treatment strategies specific to women compared to men,[6] but the 2013 ACC/AHA lipid guidelines have similar recommendations for men and women.[11]

CAROTID INTIMA-MEDIA THICKNESS, CORONARY CALCIUM SCORE, AND OTHER RISK MARKERS

Ten-year risk assessments still have room for improvement; thus genetic biomarkers, serum biomarkers, and imaging such as carotid ultrasound and coronary computed tomography (CT) have been extensively studied in risk stratification.[2] Several studies have shown that carotid intima-media thickness (CIMT)/plaque information on a carotid ultrasound improves risk prediction for CVD.

Although CIMT/plaque was endorsed by the 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults,[2] it was not recommended by the 2013 ACC/AHA lipid guidelines.

On the other hand, a CT-based coronary calcium score (CAC) > 300 Agatson units or a CAC score that is > 75th percentile, when adjusted for age and gender, has been suggested by the expert opinion in the ACC/AHA 2013 lipid guidelines as a threshold for initiating statin therapy. The ACC/AHA 2013 guidelines also recommend considering hs-CRP and ankle brachial index as tools to assist treatment decisions if there is still uncertainty after quantitative risk assessment.

THERAPIES FOR PRIMARY PREVENTION OF CVD

Statins in Prevention

The JUPITER trial,[35] which included individuals with a C-reactive protein > 2 mg/dL and an LDL-C < 130 mg/dL, and the

HOPE-3 trial, which included intermediate-risk subjects without known CVD, both demonstrated that statins help in the primary prevention of CVD. Prespecified analyses have shown that the benefit occurs in both men and women. Therefore, statins are valuable in both men and women in the primary and secondary prevention of CVD. Given the lack of statin safety data in pregnancy, women of childbearing age need to be thoroughly counseled on contraceptive use to avoid pregnancy while on statin therapy.

Role of Aspirin

Like statin therapy, secondary prevention of CVD with the use of aspirin is well established. Prior to 2005, the data supporting aspirin use in primary prevention was mainly reported in men. However, in 2005, the Women's Health Study randomized 40,000 healthy women > 45 years old to 100 mg alternate-day dosing of aspirin or placebo. After a 10-year follow-up, low-dose aspirin reduced the risk of stroke without reducing MI. However, age was found to be the most important determinant, as low-dose aspirin significantly reduced the risk of major cardiovascular events, ischemic stroke, and MI in women > 65 years old. However, those assigned to aspirin therapy had a higher bleeding risk; therefore, the risk and benefits of aspirin therapy should be weighed, particularly if a patient has risk factors for bleeding.[36]

A recently published study evaluated the long-term safety and efficacy of low-dose aspirin in patients with type 2 DM for primary prevention of CVD.[37] After a median follow-up period of 10.3 years, low-dose aspirin did not improve CV outcomes but did increase the risk of gastrointestinal bleeding. A postulated hypothesis for this negative result is that statin use among these individuals and a lower LDL-C may have reduced the previously known aspirin benefit.

Nevertheless, the U.S. Preventive Services Task Force recommended the use of low-dose aspirin for primary prevention in both women and men aged 50 to 59 years who have a 10% or greater 10-year CVD risk without an increased risk of bleeding (Grade B recommendation). Other preventive recommendations, including management of hypertension and diabetes and smoking cessation, are similar in women and men.

RESEARCH ENROLLMENT OF WOMEN

Women in cardiovascular clinical trials have been underrepresented, resulting in therapeutic strategies that have been mostly extrapolated from studies on men.[38] With large single-sex studies like the WHS and the WHI, female participation has increased substantially; however, in mixed-gender trials, women on average represent less than a third of all participants.

Some of the most commonly postulated reasons for low female enrollment include underestimated cardiac risk in women and atypical cardiac disease presentation, which results in reduced referrals to cardiology practices where recruitment for CV clinical trials is performed.

In addition, women manifest CVD later in life, and an age-gender bias may be present during the study enrollment process.[39] Other possible barriers to the recruitment of women that have been outlined by the NIH are fear and distrust of the research enterprise, lack of knowledge, lack of transportation, interference with work or family responsibilities, subject burden as a result of study participation, and financial costs.

CONCLUSION

Preventive therapies for CVD are essential in reducing mortality and preserving cardiovascular health in women. Although several advances have been made in primary and secondary prevention, CVD is still the leading cause of death among women in the United States. The scientific community has made robust progress in recognizing the clear differences in pathophysiology of CVD in women. However, there currently are no differences in treatment approaches between women and men. This hopefully will change as we move into an era of personalized medicine.

KEY POINTS

- Female patients are likely to be treated less aggressively and have fewer coronary interventions performed for similar presentations compared to men despite the similarity of overall risk in postmenopausal women and men.
- Comprehensive understanding of the hormonal and genomic basis for the pathophysiologic differences of CVD and symptom presentation in women is key to providing gender-specific care.
- Encouraging more research participation by women will help clarify gender-based risk factors and aid in discovery of beneficial treatments.

Conflict of Interest Disclosure:
Dr. Nambi receives research funding from Merck through Baylor College of Medicine, served on a regional advisory board for Sanofi-Regeneron, received an honorarium from Siemens Healthcare Diagnostics, and holds a provisional patent entitled "Biomarkers to Improve Prediction of Heart Failure Risk" filed by Baylor College of Medicine and Roche.

Keywords:
cardiovascular disease, cardiovascular risk factors, women and CVD, postmenopausal CVD

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