Curr Treat Options Cardio Med (2019) 21: 47
DOI 10.1007/s11936-019-0753-0

Women's Health (M Wood, Section Editor)

Addressing the Gap in Physician Preparedness To Assess Cardiovascular Risk in Women: a Comprehensive Approach to Cardiovascular Risk Assessment in Women

Nino Isakadze, MD[1,*]
Puja K. Mehta, MD[2,3]
Karen Law, MD[3]
Mary Dolan, MD[4]
Gina P. Lundberg, MD[2,3]

Address
[*,1]Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, 600 N. Wolfe St./Halsted 500, Baltimore, MD, 21287, USA
Email: nisakad1@jhmi.edu
[2]Department of Medicine, Division of Cardiology, Emory Women's Heart Center, 1462 Clifton Rd NE, Suite 505, Atlanta, GA, 30322, USA
[3]Department of Medicine, Emory University School of Medicine, 201 Dowman Drive, Atlanta, GA, 30322, USA
[4]Department of Obstetrics and Gynecology, Emory University School of Medicine, Ste 700, Atlanta, GA, 30342, USA

Published online: 29 July 2019

This article is part of the Topical Collection on *Women's Health*

Keywords Women · Heart disease · Risk assessment · Menopause · Lipids · Hypertension · Risk factors

Abstract

Purpose of review Increased recognition of risk factors and improved knowledge of sex-specific presentations has led to improved clinical outcomes for women with cardiovascular disease (CVD) compared to two decades ago. Yet, CVD remains the leading cause of death for women in the USA. Women have unique risk factors for CVD that continue to go under-recognized by their physicians.

Recent findings In a nationwide survey of primary care physicians (PCPs) and cardiologists, only 22% of PCPs and 42% of cardiologists reported being extremely well prepared to

assess CVD risk in women. A presidential advisory from the American Heart Association (AHA) and American College of Obstetrics and Gynecologist (ACOG) recommends that cardiologists and obstetricians and gynecologists (Ob/Gyns) collaborate to promote CVD risk identification and reduction throughout a woman's lifetime.
Summary We suggest a comprehensive approach to identify unique and traditional risk factors for CVD in women, address the gap in physician knowledge, and improve cardiovascular care for women.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in women in the USA [1]. Although overall mortality is declining compared to previous decades, one woman dies every 79 s from CVD (or 399,028 deaths per year), killing more women than all cancers combined [1]. While men and women share many traditional risk factors for CVD, there are differences in prevalence of these risk factors and they carry different weight in women compared to men [2]. After age 65, women are more likely to have hypertension (HTN) than men, with less than 30% achieving adequate management for blood pressure [1, 3•]. Women with diabetes mellitus (DM), regardless of the type, are at higher cardiovascular (CV) risk than men with diabetes [4•, 5, 6]. Similarly, smoking confers a greater CVD risk for 68 women than men (19.1% versus 10.1%) [7]. Additional sex-based risk factors and mechanisms of disease have been shown to be unique in women [8, 9]. Table 1 lists the CVD risk factors that are unique, more common, and more impactful in women.

In spite of numerous studies identifying sex-specific differences in CVD, a lack of recognition of sex disparities among health care providers continues. A national study of physician awareness and adherence to CVD prevention guidelines showed that providers assigned women lower perceived risk for CVD despite similar calculated risk for men, and providers underestimated women's probability of CVD [10]. In addition, multiple studies have shown that women often receive suboptimal care for CVD prevention [11, 12•]. Several factors are likely contributors to this knowledge gap. First, nearly 70% of postgraduate trainees reported no or minimal training of sex-based medical concepts in their training. As a result, providers do not feel prepared to provide sex-specific CVD risk assessment. A nationwide survey conducted by the Women's Heart Alliance (WHA) showed that only 22% of primary care physicians (PCPs) and 42% of cardiologists ($p = 0.0477$) felt extremely well prepared to assess CVD risk in women [13]. Women

Table 1. CVD risk factors that are sex specific, predominant, and more impactful in women

Female-specific risk factors	Female-predominant risk factors	Increased risk in females compared to males	Equal risk in females and males
Early menarche (≤ 11 years old)	Systemic lupus erythematosus	Hypertension	Hyperlipidemia
Early menopause (< 40 years old)	Rheumatoid arthritis	Diabetes	Sedentary lifestyle
History of PCOS	Depression	Smoking	Obesity
History of hypothalamic amenorrhea			
History of premature delivery, low birth weight, or high birth weight fetus	Psychological stress		Family history of CVD
Gestational diabetes			
Hypertensive disorders of pregnancy			

PCOS polycystic ovarian syndrome, *CVD* cardiovascular disease

receive health care from numerous specialty fields, including primary care and obstetricians and gynecologist (Ob/Gyn) [14, 15], in addition to cardiology, each with varying degrees of attention to CVD prevention guidelines and a varying scope of practice. Thus, despite established knowledge of sex-specific differences in CVD, concerning gaps remain in physicians' self-perception of preparedness to assess CVD risk, physician practice, medical society guidelines, and collaboration between specialties treating women [16].

Addressing this gap in physician knowledge, preparedness, and collaboration is a critical step in mitigating the adverse CVD mortality women continue to experience. The 2018 American Heart Association (AHA)/American College of Obstetricians and Gynecologists (ACOG) joint presidential advisory underscores the need for Ob/Gyns and cardiologists to work together to offer sex-specific CVD risk identification and reduction [17•]. We propose a comprehensive step-wise approach for screening women for cardiovascular disease for use by all specialties, including Ob/Gyns, PCPs, and cardiologist. It is critical for all health care providers to identify the sex-specific, unique, and traditional CVD risk factors in women (Fig. 1).

Sex-specific risk assessment made easy

To date, risk factor assessment for CVD has been driven by population-based scoring algorithms that have not included CVD risk factors unique to women. The Framingham Risk Score (FRS) underestimated risk in women, classifying 90% of females as low risk [18]. Similarly, the 10-year or lifetime atherosclerotic CVD (ASCVD) risk score recommended by the 2019 American College of Cardiology (ACC)/AHA Guideline on the Primary Prevention of CVD does not incorporate female-specific or female-predominant risk factors that have been identified to increase women's CVD risk. Female-specific risk factors include early menopause (defined as premature ovarian failure before the age of 40 years) [19] and early menarche (often defined as ≤ 11 years old) [20], complications of pregnancy (gestational diabetes, hypertensive disorder of pregnancy (HDP), low birth weight for gestational age, preterm delivery), or a history of polycystic ovarian syndrome (PCOS). Female-predominant risk factors include depression and rheumatologic disorders, which are clearly associated with adverse CVD outcomes (Table 1).

An important step in evaluation for ASCVD per the 2019 ACC/AHA Guideline on the Primary Prevention of CVD is to obtain 10-year absolute ASCVD risk using the pooled cohort equation (PCE) for adults 40–75 years of age (Fig. 2). ASCVD risk evaluation can be considered every 4–6 years for adults 20–39 years of age. If the ASCVD risk is high (> 20% 10-year risk), aggressive risk factor modification should be pursued. If the risk is borderline (5 to < 7.5% 10-year risk) or intermediate (≥ 7.5 to 20% 10-year risk) guideline suggests that it is reasonable to use additional ASCVD risk-enhancing factors to guide decisions about preventive interventions. Risk-enhancing factors include family history of premature ASCVD, primary hypercholesterolemia, metabolic syndrome, chronic kidney disease (CKD), chronic inflammatory conditions, history of premature menopause, and history of pregnancy-associated conditions such as preeclampsia, high risk race/ethnicity, persistently elevated triglycerides (TG), elevated lipoprotein(a) (Lp(a)), elevated apoprotein B (ApoB), and ankle-brachial index (ABI) < 0.9 [21•]. If the calculated ASCVD risk is low or intermediate as above, we suggest using this comprehensive pathway to further personalize risk and more appropriately identify females at risk who would benefit from early

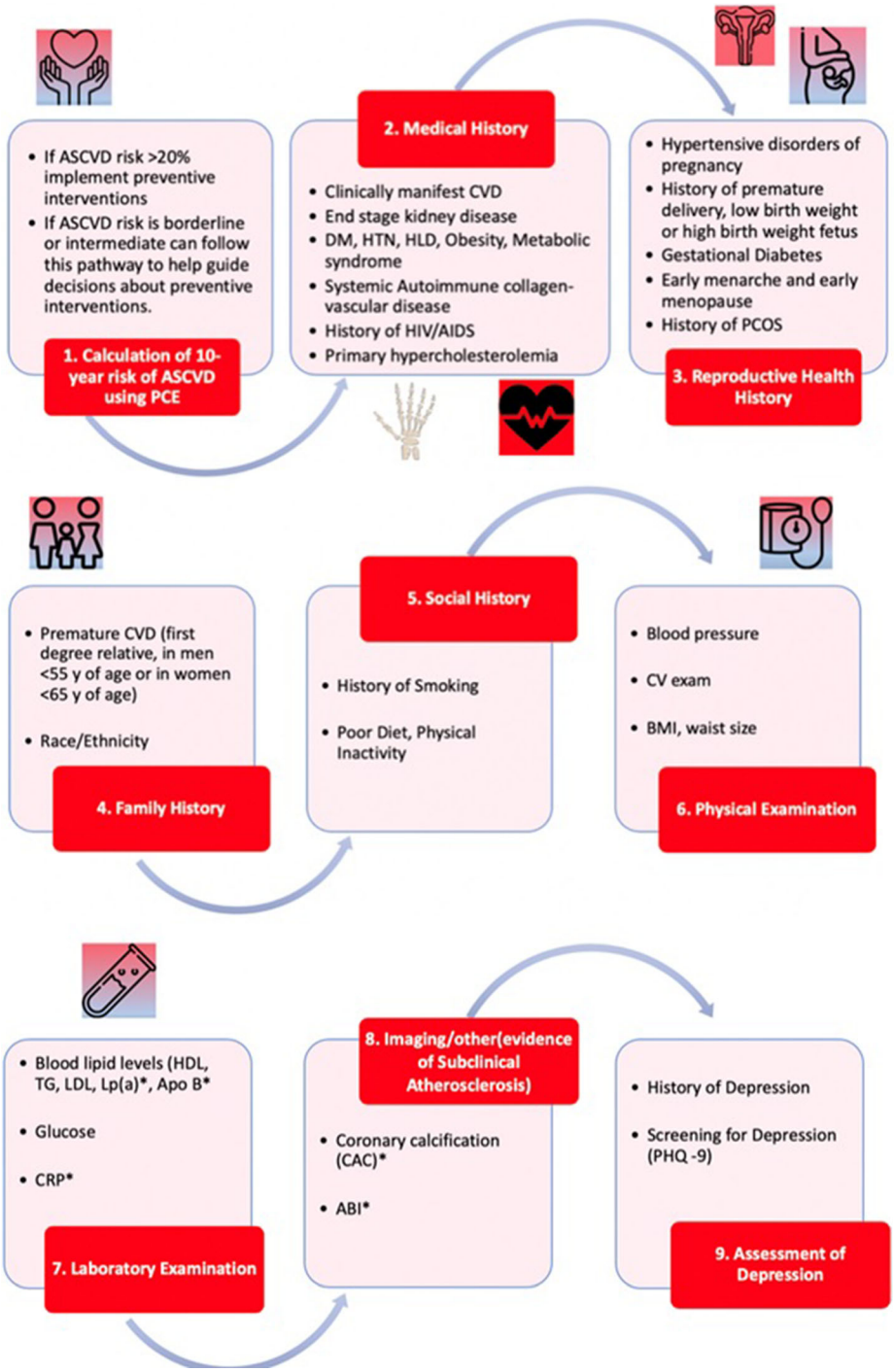

Fig. 1. Approach to cardiovascular risk assessment in women. CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; HLD, hyperlipidemia; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); Apo B, apolipoprotein B; ABI, ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; PHQ-9, Patient Health Questionnaire-9. The asterisk indicates those which are obtained only in selected patients.

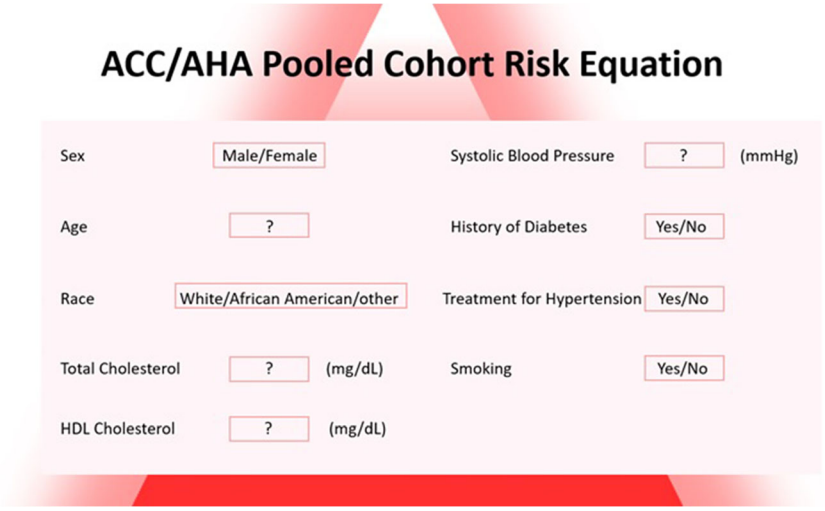

Fig. 2. American College of Cardiology (ACC)/American Heart Association (AHA) pooled cohort risk equation. ACC, American College of Cardiology; AHA, American Heart Association.

preventative measures (Fig. 1). In addition to helping make the risk assessment easy, this approach includes risk factors that are yet not included among risk-enhancing factors and have been associated with increased CVD risk in females as well as highlight female-predominant risk factors and risk factors that carry more significant risk in females then males.

CVD risk assessment begins with a careful history. Traditional CVD risk factors include HTN, DM, blood cholesterol disorders, and tobacco use. Rheumatologic and inflammatory chronic conditions are under-recognized risk factors in women and are associated with a significantly increased relative risk for CVD (Fig. 1). Women have a higher incidence of autoimmune and rheumatologic disorders [22•, 23]. Rheumatoid arthritis (RA) elevates CVD risk to a similar extent as DM [24], and young women (aged 35–45) with systemic lupus erythematosus (SLE) have a 50-fold increased risk of myocardial infarction (MI) compared with the general population [25]. Similarly, inflammatory disorders such as gout, ankylosing spondylitis, Takayasu arteritis, psoriatic arthritis, and vasculitis predispose women to premature atherosclerosis and increased CVD risk [23]. Women of all ages who have these inflammatory conditions should be considered at increased risk for CVD, regardless of clinically evident CVD. The 2019 ACC/AHA Guideline on the Primary Prevention of CVD and the 2018 Multi-society Guidelines of Management of Blood Cholesterol have listed chronic inflammatory conditions such as psoriasis, RA, SLE, or HIV/AIDs as risk-enhancing factors [21•, 26].

A woman's past medical history should always include a detailed reproductive health history. Menarche and menopause mark important cardiovascular biological transitions in women. Early menarche has been related to increased CVD risk; however, research is hindered by the lack of a standard definition. It is unclear whether early menarche is a marker of other risk factors and/or exposure to sex hormones across the lifespan but documenting early menarche should be included in a CVD risk assessment. Data shows a stronger relationship on the timing of menopause and CVD risk. Estrogen loss with menopause causes an

increase in low-density lipoprotein cholesterol (LDL-C) and decrease in high-density lipoprotein cholesterol (HDL-C) and has negative effects on arterial function [27•, 28]. Thus, early menopause, whether natural or surgically induced, significantly increases CVD risk [29].

PCOS is also associated with increased cardiovascular risk, a more atherogenic lipid profile, and higher blood pressure [30]. There is evidence of increased CVD risk in lean women with PCOS as well as women with central obesity, supporting its independent role in contributing to CVD risk [31].

A careful and detailed history of pregnancy complications, such as gestational DM, HDP, and preterm birth, should be included on the initial clinical encounter. HDP and gestational DM are abnormal responses to the CV and metabolic stress of pregnancy, disrupting vascular, metabolic, and inflammatory pathways. Some experts consider pregnancy complications a "failed cardiac stress test" and these conditions as early indicators of cardiovascular dysfunction unmasking early or preexisting endothelial dysfunction, vascular, or metabolic disease [32, 33].

A history of preeclampsia and HDP in women doubled the risk of CVD and tripled the risk of developing hypertension [34, 35]. A recent study showed that pregnant women with preeclampsia with severe features have higher rates of diastolic dysfunction, cardiac chamber remodeling, higher pulmonary pressures (estimated by echocardiography) and higher incidence of pulmonary edema in peripartum period [36]. Gestational DM is associated with an approximately 60% higher risk of myocardial infarction and 4-fold increased risk of DM [4•]. In addition, spontaneous preterm birth has been found to be an independent risk factor for CVD and marker of endothelial dysfunction, which is likely a precursor of CVD [37].

A detailed family history of early CVD (aortic aneurysm, MI, percutaneous coronary intervention, coronary artery bypass surgery, stroke), and familial hypercholesterolemia should be included in CV risk assessment. Careful social history of alcohol, tobacco use, sedentary vs active lifestyle, and life stressors should also be documented. As part of the physical exam, blood pressure, body mass index (BMI), and waist measurement should be assessed. In addition to a detailed CV exam, patients with family history of premature ASCVD or high cholesterol should be evaluated for arcus cornealis, xanthelasma, and tendon xanthomas. Laboratory evaluation should include measuring blood cholesterol and blood glucose level. Further blood testing such as hemoglobin A1C (HgbA1C), advanced lipids such as Lp(a), and high sensitivity C-reactive protein (hs-CRP) may be indicated in selected patients.

Lp(a) is a low-density lipoprotein-like particle containing an additional highly heterogeneous apolipoprotein(a). Expression of Lp(a) is genetically determined. Lp(a) levels increase with menopause, and elevated levels of Lp(a) over 125 nmol/L or 50 mg/dL are associated with an increased risk of premature CVD [26, 38, 39]. The National Lipid Association recommends measuring Lp(a) in patients with a family history of premature coronary artery disease (CAD) or with established coronary heart disease (CHD) with a history of recurrent events despite appropriate therapy [40]. Because Lp(a) is entirely inherited, most women only need this test performed once. Borderline levels will rise after menopause so selected women may need reevaluation after menopause. Lp(a), if measured is listed as ASCVD risk enhancer in the 2019 ACC/AHA Guideline on the Primary Prevention of CVD and the 2018 ACC/

AHA Guidelines for the Management of the Blood Cholesterol [21•, 26]. Synthetic oligonucleotides have shown to lower Lp(a), specifically AKCEA-APO(a) L_{Rx} has showed to lower Lp(a) by 50–80% in phase 2 clinical trial. Whether lowering Lp(a) has role in reducing CVD risk is unclear and phase 3 study of AKCEA-APO(a)-L_{Rx} is planned to provide answer to this question [41]. In the meantime, in patients with elevated Lp(a) aggressive risk factor modification should be implemented. The current guidelines recommend statin therapy to lower LDL-C in patients with elevated Lp(a).

High sensitive C-reactive protein (hs-CRP) has been shown to independently predict cardiovascular events [42]. Statins reduce CVD among patients who are otherwise considered at low risk and have elevated hs-CRP [43]. We have known for over a decade that women have significantly higher levels of hs-CRP compared to men, even after adjusting for estrogen use, CVD risk factors, and other variables [44, 45]. Therefore, inflammation may play an important role in contributing to CVD risk in women compared to men [46]. The 2013 ACC/AHA guidelines recommend measurement of hs-CRP to further risk stratify individuals at intermediate risk (10–20% 10-year risk) for heart disease and if measured, the 2019 ACC/AHA Guideline on the Primary Prevention of CVD and the 2018 ACC/AHA Guidelines for the Management of the Blood Cholesterol listed hs-CRP ≥ 2 mg/L as a risk-enhancing factor [21•, 26]. Given women have higher levels of hs-CRP, more studies are needed to establish optimal gender-specific values which will improve accuracy of CVD risk prediction. Obesity and inflammation are also related to elevated levels of hs-CRP which can be reduced through weight loss and medical therapy [47, 48].

Use of non-invasive tests for early attention and risk stratification can be used in selected patients and clinical scenarios. Coronary artery calcium (CAC) [49] and ABI [50] are measures of subclinical cardiovascular disease. CAC is measured by non-contrast cardiac computed tomography (CT), with very low levels of radiation, generally under 2 mSV [51]. CAC serves a marker for total coronary atherosclerosis burden and can be considered a surrogate measure for the biological age of the artery [49]. The 2019 ACC/AHA guidelines suggest that CAC testing in is reasonable in subjects with no clinical ASCVD and intermediate or borderline risk for CVD to aid with clinician-patient risk discussion, if risk-based decisions for preventive interventions remain unclear [21•].

Analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) data, which included 3601 women aged 45 to 84 years, found that 32% of low-risk patients had an abnormal CAC. This was predictive of future CHD and CVD events and allowed reclassification of an otherwise low-risk population [52]. Similarly, a meta-analysis of 5 large studies analyzing data from 6739 women with low ASCVD risk showed that abnormal CAC was present in nearly one third of subjects and was associated with increased CVD risk [53]. A large multicenter study of asymptomatic women and men showed that compared to men, women with detectable CAC had higher hazard for CV death and that larger size plaques and more numerous CAC lesions were associated with higher CV mortality among women compared to men [54].

ABI is a surrogate marker for advanced systemic atherosclerosis and future cardiovascular complications and is listed among risk-enhancing factors in 2019 ACC/AHA Primary Prevention Guidelines [21•]. Measuring ABI can be used for further risk stratification in intermediate risk patients. Abnormal ABI has been shown to be associated with increased CV events and mortality [50, 55].

Lastly, a large body of evidence links psychological factors such as history of depression, anxiety, and post-traumatic stress disorder with adverse CVD risk and outcomes. Women in particular appear to be more vulnerable to mental stress-induced myocardial ischemia [56]. Women suffer with a higher burden of depression and anxiety, at younger ages when compared with men, which is strongly associated with an increased risk of CVD and poor CV outcomes [57–59]. Depression is considered a risk factor for adverse outcomes in patients with a history of MI, and screening for depression with Patient Health Questionnaire (PHQ-9) should be performed. When psychosocial stress is suspected, patients should be referred to a mental health provider. Other psychosocial factors and social determinants of health, such as socio-economic status, income, and education, all play a role in CVD risk [60], and currently there are no risk assessment tools that incorporate these factors to more precisely estimate CVD risk (Fig. 1 illustrates suggested comprehensive risk assessment pathway).

In summary, CVD remains the leading cause of mortality in females. Female-specific and female-predominant risk factors are under-recognized by many front-line providers. PCPs, Ob/Gyns, and cardiologists should provide coordinated care delivery to facilitate timely CVD risk assessment, primary prevention, and early interventions to improve cardiovascular outcomes in women. Female-specific and female-predominant risk factors should be included in risk assessment to allow identification of more women at risk. We propose the following 9-step approach to increase provider awareness of these unique CVD risk factors and facilitate comprehensive CVD risk assessment in women. Patients identified at risk for CVD by Ob/Gyns should be referred to an internist or a preventive cardiologist for optimal management.

Funding

This work was supported by Emory Women's Heart Center.

Compliance with Ethical Standards

Conflict of Interest

Nino Isakadze, Karen Law, Mary Dolan, and Gina P. Lundberg each declare no potential conflicts of interest. Puja K. Mehta reports research support from Sanofi Aventis.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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