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WOMEN AND ISCHEMIC HEART DISEASE (P. KOHLI, SECTION EDITOR)

The Role of Sex-Specific Risk Factors in the Risk Assessment of Atherosclerotic Cardiovascular Disease for Primary Prevention in Women

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Abstract

Purpose of Review Robust evidence is emerging regarding the contribution of sex-specific risk factors to a woman's unique risk of atherosclerotic cardiovascular disease (ASCVD). This review summarizes the available literature regarding the association of sex-specific risk factors and ASCVD in women.

Recent Findings The American College of Cardiology and American Heart Association Guidelines recommend estimation of 10-year risk of a first ASCVD event using the 2013 Pooled Cohort Equations. This can be further personalized by identifying sex-specific risk factors present in a woman's history. There are multiple vulnerable periods across a woman's life course that are associated with increased risk of ASCVD. Risk factors across the reproductive life course that have been shown to correlate with higher risk for future ASCVD include early menarche, adverse pregnancy outcomes (such as pre-eclampsia or preterm birth), and early natural or surgical menopause. In addition, certain conditions that are more common among women, including autoimmune diseases, history of chest irradiation, and certain chemotherapies, also need to be considered. Finally, risk assessment can be refined with subclinical disease imaging (coronary calcium score) if there remains uncertainty about clinical management with lipid-lowering therapies for primary prevention after inclusion of these risk enhancers.

Summary Risk assessment for ASCVD in women requires a personalized approach that incorporates sex-specific risk factors to guide primary prevention measures, such as lipid-lowering therapies. Coronary calcium score imaging may also help further refine risk assessment, but no clinical trials conducted to date have addressed this question.

Keywords Sex-specific risk factors · Risk prediction · Primary prevention · Atherosclerotic cardiovascular disease · Adverse pregnancy outcomes

Introduction

Cardiovascular disease (CVD) is the leading cause of death in men and women in the USA and worldwide [1]. Though CVD is often thought to be a disease predominantly of males, it is nearly equally as common in women in the USA and worldwide. In the year 2017, heart disease accounted for 24.2% of deaths in males in the USA and 21.8% of deaths in US females [1]. Furthermore, the World Health Organization reports 9.4 million deaths worldwide from ischemic heart disease in 2016; 4.9 million of these were men and 4.8 million were women. The worldwide rate of death from stroke was also equal among sexes—with 2.9 million deaths in both men and women [2]. Though a large portion of the atherosclerotic CVD (ASCVD) burden can be attributed to traditional risk factors such as hyperlipidemia, hypertension, diabetes, and obesity, there is emerging evidence of sex-specific risk factors that also contribute to a woman's unique risk of developing ASCVD. In this article, the data on the role of these sex-specific risk factors, and how to incorporate them into personalized ASCVD risk assessment, will be reviewed, and strategies to optimize prevention for women will be discussed.

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Sex-Specific Risk Prediction of Atherosclerosis

The American College of Cardiology (ACC) and American Heart Association (AHA) recommend prediction of 10-year risk of a first hard ASCVD event using the 2013 Pooled Cohort Equations, which were derived from longitudinal data in non-Hispanic black and non-Hispanic white men and women 40–79 years of age [3]. These equations have been validated broadly, and recommendations for their use in the general population and specific subgroups have been updated recently[4••, 5, 6].

Numerous studies have demonstrated higher rates of ASCVD among women with a history of certain sex-specific risk factors (such as adverse pregnancy outcomes and early-onset menopause). However, parity and hypertensive disorders of pregnancy including pre-eclampsia have not demonstrated additional clinical utility for risk prediction, as measured by net reclassification index, beyond currently existing risk prediction tools. Data in those available studies, such as one conducted in the Nurses' Health Study, are limited by the use of self-report of a history of hypertensive disorder of pregnancy [7]. There is a need for prospective, well-adjudicated data to examine whether sex-specific risk factors may enhance the personalization of 10-year and lifetime risk ASCVD risk prediction models.

We propose that the clinical workflow for assessment of ASCVD risk for primary prevention in women should begin with quantitative risk calculation, followed by personalization based on sex-specific risk enhancers. Finally, in cases where uncertainty remains, the use of subclinical disease imaging such as a coronary artery calcium (CAC) score should be considered [4••, 5]. (Fig. 1).

Race/Ethnicity

An important advance in the 2013 ACC/AHA Cholesterol guidelines was the recognition with the Pooled Cohort Equations (PCE) of greater 10-year ASCVD risk for black women than for their white counterparts at the same levels of risk factors [8]. For example, a 55-year-old non-smoking, non-diabetic, but hypertensive woman on anti-hypertensive therapy with systolic BP of 135 mmHg, total cholesterol of 220 mg/dL, and an HDL-C of 45 mg/dL has a 10-year risk of 4% if she is white and a risk of 7.7% if she is black. Distribution of estimated 10-year risk of a first hard ASCVD event in the CVD-free, nonpregnant US population, 40 to 79 years of age, indicated that 67.5% of white women had a low predicted 10-year ASCVD risk of less than 5%, whereas only 55.2% of black women had low risk [8].

Vulnerable Periods of Cardiovascular Risk Across a Woman's Life Course

Early Life/Adolescence

Timing of Menarche

Early age at menarche (defined as prior to 12 years of age) has been associated with a higher future risk of CVD [9–11]. In a large cohort of greater than 1.2 million women in the UK without underlying CVD, the average age of menarche was reported to be 13 years of age. Compared with women who experienced menarche at 13 years, those who had menarche at

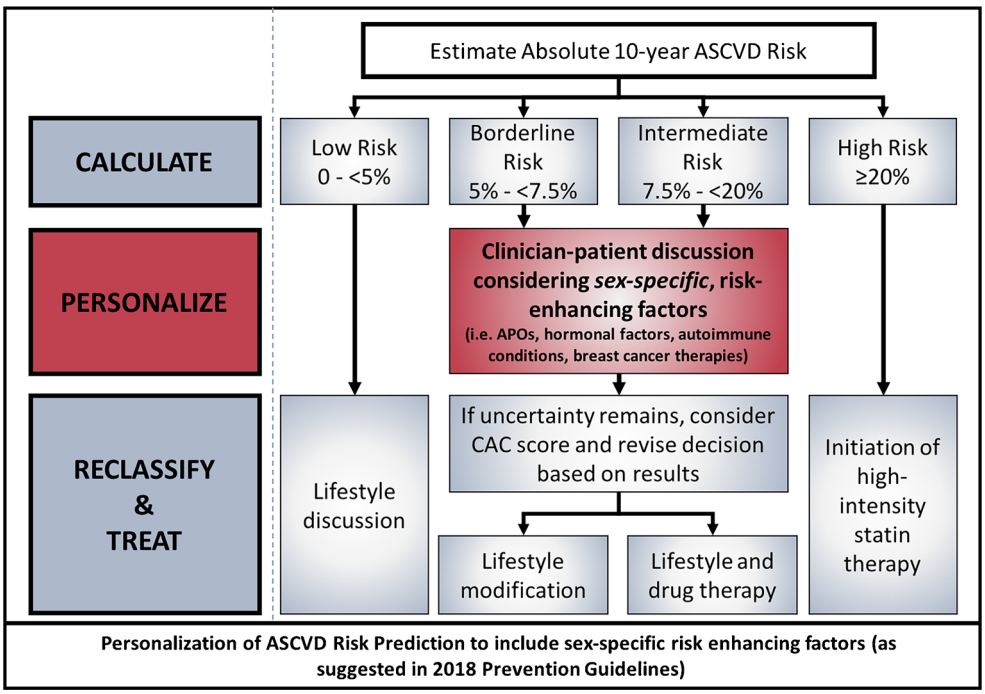

Fig. 1 Personalization of ASCVD risk prediction to include sex-specific risk-enhancing factors (as suggested in 2018 Prevention Guidelines)

10 years or younger had a significantly higher relative risk of coronary heart disease (CHD) (relative risk 1.27, 95% confidence interval 1.22–1.31, $p < 0.0001$) [11]. In a US cohort, the Women's Ischemia Syndrome Evaluation (WISE) study, of 648 middle-aged women, those with early menarche (≤ 10 years) were found to have a 4.53-fold higher risk (95% CI 2.13, 9.63) of cardiovascular disease as well as those with late menarche (≥ 15 years, HR 2.58; 1.28, 5.21) [12].

Premenstrual Syndrome

Premenstrual syndrome (PMS) is a constellation of physical and emotional symptoms that can occur in the window of time between ovulation and menses, and is associated with development of subsequent hypertension. In the Nurses' Health Study II, 1257 women with clinically significant PMS symptoms were compared with 2463 age-matched controls and followed for 6–20 years for incident hypertension. Women with PMS were more likely to have incident hypertension (adjusted hazard ratio 1.4; 95% CI 1.2–1.6) and especially more likely to develop hypertension before the age of 40 years (adjusted hazard ratio 3.3, 95% CI 1.7–6.5) [13].

Reproductive Years

Pregnancy-Related Factors

Parity In a meta-analysis of ten cohort studies, with over 3 million women included in the analysis, ever parity is associated with higher CVD risk compared with nulliparous status, with an even higher risk of CVD with greater number of pregnancies [14]. In an analysis of 8583 white and black women from the Atherosclerosis Risk in Communities Study, a history of 5 + live births was associated with higher CHD risk, specifically hospitalized myocardial infarctions (MI), compared with women with 1–2 prior births [15]. A cohort study of 100,387 women found that women with twin pregnancies do not have increased CVD risk when compared with women with singleton pregnancies [16].

Lactation Adverse metabolic changes occur during pregnancy, including accumulation of fat mass, hyperinsulinemia, insulin resistance, and hyperlipidemia. Breastfeeding is thought to reverse the metabolic syndrome-like changes faster and more completely than no breastfeeding. In an analysis of 63,260 Danish women from the Danish National Birth Cohort, breastfeeding for greater than 4 months was associated with a 30% and 20% lower risk of hypertension and CVD, respectively, when compared with breastfeeding for less than 4 months or not at all [17].

Adverse Pregnancy Outcomes

Hypertensive Disorders of Pregnancy (Pre-Eclampsia, Gestational HTN) Hypertensive disorders of pregnancy (HDP) are defined as either pre-eclampsia or gestational hypertension (GH). Women with HDP have a nearly two-fold higher risk of CVD than women without HDP [18–20]. HDP are associated with cardiovascular aging and contribute to a more diverse group of cardiovascular conditions than previously recognized, including coronary artery disease, heart failure, aortic stenosis, and mitral regurgitation—all partially mediated by chronic hypertension [21••].

The more severe the HDP, the worse the risk for CVD, as seen in one study where nearly half of women with early-onset pre-eclampsia went on to develop hypertension with higher average blood pressures, compared with 25% of women with late-onset pre-eclampsia [22]. Furthermore, risk of future CVD is higher when women have recurrent pre-eclampsia compared with a single episode [23, 24]. Interestingly though, women with pre-eclampsia in a multiple pregnancy do not appear to have a higher CVD risk compared with women in a singleton pregnancy, suggesting that their pre-eclampsia may be related to the larger burden of pregnancy on the cardiovascular system rather than the woman's underlying cardiovascular phenotype [25].

A portion of the excess CVD risk in women with HDP is associated with conventional cardiovascular risk factors, such as hypertension, diabetes, obesity, and hypercholesterolemia, indicating that these are important targets for prevention [26•, 27]. However, the portion of CVD risk *not* attributable to these traditional risk factors in post-HDP women is not well understood and deserves further study [28]. Given the known higher risk for long-term ASCVD, the American Heart Association (AHA) and American Stroke Association (ASA) recommend that women with pre-eclampsia should have 6-month and 1-year post-partum follow-up visits for blood pressure and CVD risk monitoring. The uptake of this recommendation appears to be poor, however, as shown in a study examining the discharge planning for women with pre-eclampsia at an urban academic women's hospital—out of 561 women, only 39% had documented follow-up visits specifically addressing blood pressure within the first year following delivery [29].

Several studies have tested adding HDP to the already existing ASCVD risk prediction models—in some, this has not been shown to improve discrimination or reclassification [7, 30•], and in others, the addition of HDP to these models only mildly improved CVD prediction [31]. However, these models relied on self-report of HDP and one study that manually adjudicated that self-report and birth records of HDP identified a very poor sensitivity and specificity for self-report. This degree of misclassification of HDP status undermines its utility as a risk predictor. It is not known if pregnancy

complications will enhance prediction of ASCVD risk in women, but newer risk prediction models in young women should be considered in more contemporary cohorts with more prospective, well-adjudicated pregnancy health and complication data [32]. However, it is unlikely that addition of adverse pregnancy outcome (APO) will improve risk prediction in middle-aged women once risk factors, such as hypertension and diabetes, have already developed.

Gestational Diabetes The rate of gestational diabetes (GDM) has significantly increased over the past several decades, from 0.3 in 1979–1980 to 5.8% in 2008–2010 [33]. Women with GDM have a 7- to 13-fold higher risk of developing type 2 diabetes mellitus (T2DM) later in life than women without GDM [34•]. An analysis of 89,000 women in the Nurses' Health Study II showed that women with history of GDM have a modestly elevated risk for CVD, particularly MI events, when compared with parous women without GDM. Much of the increased CVD risk in this analysis was attenuated by subsequent weight gain and healthy lifestyle behaviors, with a small remaining absolute rate increase of 0.3 CVD events per 1000 person-years [35]. Other studies have found that the risk of CVD is in greater part attributable to GDM, citing that women with GDM have a two-fold higher risk for CVD even when corrected for the subsequent development of T2DM or metabolic syndrome [36, 37]. Furthermore, women with GDM and high pre-pregnancy maternal weight (> 200 lb) have a compounded risk of CVD compared with women with GDM alone [38]. Finally, in a Canadian study, even women who did not have GDM but had an abnormal glucose challenge test result had higher risk for CVD [39].

Low Offspring Birth Weight Women who deliver a low birth weight (LBW) infant may be at higher risk for future cardiovascular disease. In an analysis from the Health, Aging, and Body Composition Study, women who had a history of a pregnancy complicated by LBW (defined as < 2500 g) were more likely to have risk factors of ASCVD such as hypertension and insulin resistance [40]. However, conflicting reports have been published with a recent meta-analysis examining 4 studies that did not identify a different risk of ASCVD for women with or without a LBW infant [41].

Preterm Delivery Women who give birth before 37 weeks of gestation have a greater risk of CVD when compared with women who give birth at term. In a study of 47,908 Israeli women who gave birth between 1988 and 1999 and were followed for more than a decade, preterm delivery (PTD) was present in 12.5% of women and was found to be independently associated with a higher risk of future cardiovascular hospitalizations [42]. Furthermore, a systematic review of 10 studies including over 2 million women found that women with history of PTD were significantly more likely to develop future CVD [43]. The severity and number of PTDs cause a dose-dependent increase on maternal CVD risk [44]. In an analysis of nearly 200,000 women with a history of PTD who were followed for three decades, approximately 25% of the association between PTD and future maternal cardiovascular hospitalization could be attributed to vascular disorders of pregnancy, particularly pre-eclampsia [45]. Though the association of PTD and future maternal CVD is well-documented, many studies have been unable to adjust for the common link of maternal smoking that is a risk factor for both. In an Australian study of > 700,000 women, association of preterm birth and maternal CVD risk was found to be independent of smoking status during pregnancy [46].

Spontaneous Pregnancy Loss Early spontaneous abortion (< 12 weeks), late pregnancy loss (12–19 weeks), and stillbirth (> 20 weeks) are all associated with later maternal development of hypertension, diabetes mellitus, and hyperlipidemia [47•, 48]. Recurrent miscarriage (> 3) was associated with five times higher risk of MI, and the history of a stillbirth increased the risk for MI by 2.3 times, after adjusting for other ASCVD risk factors [49]. This risk factor is especially important given how common it is—in data from 79,121 women from the Women's Health Initiative (WHI), approximately 35% experienced a history of a pregnancy loss [50].

Hormonal Factors

Oral Contraceptive Use The use of combined estrogen-progestin oral contraceptives has been associated with a two-fold higher rate of MI and thrombotic stroke, with even greater risk at higher estrogen doses [51]. However, given that MI and stroke in healthy reproductive age women are so rare, even a doubling of risk in this group still results in a very low absolute risk. The use of these agents should be carefully considered and likely avoided for reproductive age women with multiple other risk factors that put them at higher risk for ASCVD, such as smoking, obesity, diabetes, hyperlipidemia, and hypertension.

Post-menopausal Hormonal Therapy Over the past two decades, there has been significant controversy regarding the role of hormonal therapy (HT) in post-menopausal women in the primary prevention of ASCVD. In the 1980s, suggestions of benefit based on observational data supporting the antiatherogenic effects of estrogen (e.g., favorable lipid profiles, insulin sensitivity, and endothelial function) led to widespread use. However, subsequent large clinical trials have suggested minimal benefit or harm, depending on their design. A series of publications from the WHI suggested that HT after menopause is not beneficial for primary prevention and in fact demonstrated an increased risk of stroke in the estrogen therapy arm compared with placebo among 10,000 healthy post-

menopausal women aged 50–79 years, with prior hysterectomy, randomized to estrogen versus placebo [52]. Furthermore, a Cochrane review including 19 trials and greater than 40,000 post-menopausal women found a high-quality evidence that women who started hormone treatment more than 10 years after the menopause showed similar findings that treatment with HT for primary or secondary prevention of CVD is not effective and causes increased risk of stroke and venous thromboembolism. Therefore, HT should be used in caution for those with predisposing risk factors for CVD events seeking relief from menopausal symptoms [53].

Polycystic Ovarian Syndrome Women with polycystic ovarian syndrome (PCOS) have a higher prevalence of concomitant CVD risk factors: insulin resistance, T2DM, and metabolic syndrome [54, 55]. Pre- and peri-menopausal women with PCOS have been shown to have higher rates of CVD [56], which is largely thought to be caused by their underlying risk factor burden. Given that women with PCOS have a high prevalence of metabolic syndrome and exhibit adverse cardiometabolic risk factors, they warrant early screening and regular monitoring throughout their reproductive lifespan.

Menopause

The association between menopause and CVD has been studied for many years. Premature natural and surgical menopause (< 40 years) are associated with higher risk for a variety of CVD events in the long term, even when adjusted for HT use after menopause. This risk has been demonstrated repeatedly to be even higher in those who have premature surgical menopause compared with those who have premature natural menopause [57••, 58]. Furthermore, even premenopausal women with low ovarian reserve (expressed by unmeasurable serum AMH levels) may have a greater risk of CVD [59]. Conversely, women with a very early CVD event (< 35 years) had twice as high of likelihood to go on to experience early menopause (< 45 years) [60]. Some women experience a distinctive increase in lipids in the year before and after their final menstrual period, so monitoring of lipids should be performed diligently in peri-menopausal women to enhance primary prevention targets for ASCVD [61].

Disease-Specific Risk Enhancers in Women

Autoimmune Conditions

Systemic Lupus Erythematosus

Women are 9 times more likely to develop systemic lupus erythematosus (SLE) than their male counterparts. Patients with SLE have been shown to have higher rates of subclinical atherosclerosis, in terms of both coronary plaque [62] and carotid plaque [63], which appear to be independent of traditional risk factors. In addition, women with SLE are more likely to have HDP (20%) than women without SLE (7%). In this population, HDP is associated with a two-fold higher rate of CVD and three-fold higher rate of incident hypertension [64].

Rheumatoid Arthritis

Women are 2–3 times more likely to develop rheumatoid arthritis (RA) than men. Given that the inflammatory milieu is thought to play a role in atherosclerotic plaque development and progression in this population, those with RA who have frequent inflammatory flares have a greater burden of ASCVD than those who are in remission for longer [65].

In women with autoimmune conditions, aggressive control of inflammation along with identification and treatment of other traditional cardiovascular risk factors should be implemented to reduce ASCVD. Further studies are needed to understand if there is an increased ASCVD risk in less common autoimmune conditions such as systemic sclerosis, Sjogren's syndrome, polymyalgia rheumatica, antiphospholipid syndrome, and giant cell arteritis, all of which are autoimmune inflammatory states that are more prevalent in women than in men [66].

Breast Cancer

Chemotherapy and Radiation

Though breast cancer can affect both sexes, this disease is female-predominant, with a 100 times higher likelihood of occurring in women than in men [67]. Cancer survivorship has improved dramatically in recent decades with improvement in understanding of disease pathophysiology and mechanisms as well as emergence of targeted therapies. With cancer survivorship, however, comes other long-term medical conditions. There are greater than 3.8 million breast cancer survivors in the USA, and the number one cause of death in this group is CVD. Given the shared risk factor burden and various short-term and long-term cardiometabolic toxic effects known to result from breast cancer treatment, the American Heart Association recently issued a Scientific Statement highlighting the need to focus on cardiovascular prevention [68••] in all breast cancer survivors and to pursue appropriate diagnostics and/or cardiology consultation to address the high rates of coronary artery disease, congestive heart failure, and thromboembolic disease.

Anthracycline-based chemotherapies and trastuzumab have been repeatedly demonstrated to lead to left ventricular dysfunction and heart failure. In addition, these

chemotherapeutic agents can also contribute to a decline in exercise tolerance and cardio-pulmonary reserve despite preserved ejection fraction [69].

Radiation therapy administered as adjuvant therapy or breast cancer elevates the risk of CVD [70]. In particular, radiation therapy for left-sided breast cancer has been associated with higher rates of ischemic heart disease [69].

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is an autosomal co-dominant monogenic condition. It results in lifelong elevated total and low-density lipoprotein (LDL) cholesterol, associated often with corneal arcus and tendon xanthomas in adults before age 50, a family history of premature CHD, and if untreated, an increased risk for premature CHD and death [71]. An analysis of 116 kindreds, whose probands were diagnosed at the National Heart, Lung, Blood institute (NHLBI) in the pre-statin era, showed an increase in CHD occurring in women more than a decade after affected men. Affected women had a risk of nonfatal or fatal CHD by age 60 of 32.8% compared with only 9.1% in non-affected women. Perak et al. [72] showed substantially elevated 30-year CHD risks in those with an FH phenotype defined as LDL-C ≥ 190 mg/dL with hazard ratios up to 5.0 (95% CI 1.1–21.7). Moreover, CHD risk was accelerated across index ages in those with the FH phenotype by 10 to 20 years in men and 20 to 30 years in women. The EOMI (Early-Onset Myocardial Infarction) study found that approximately 2% of cases of early MI in women ≤ 60 years and men ≤ 50 years had a pathogenic variant in one of the three main genes associated with FH, the LDL receptor (LDLR) gene [73]. Genetic testing is recommended in those with a clinical diagnosis of FH, given that a pathogenic variant in LDLR, apo B, or PCSK9 confirms monogenic FH that is associated with a higher risk of premature CAD than polygenic FH [74].

Diagnosis at a young age is crucial, since effective lipid-lowering therapy is associated with reduced rates of CAD and improved survival [75]. Statin therapy should not be deferred in women until a threshold 10-year risk of 7.5% is achieved, as this algorithm does not apply in FH [76]. Pregnancy poses a specific hazard for women with FH as cholesterol rises with each trimester. Statin therapy is recommended to be stopped before pregnancy to avoid the potential for teratogenic effects [4••] and can be resumed after cessation of breast feeding.

Transgender Medicine

Female Hormonal Supplementation in Men

Clinicians are more frequently encountering transgender people in their practice; however, they often lack formal training or experience in the assessment and management of the potential complications of transgender therapies. Data on the effects of estrogen therapy on rates of myocardial infarction are mixed [77]. However, there is clear evidence of increased rates of venous thromboembolic disease and possible increase in stroke in cisgender and transgender women taking oral supplemental estrogen therapy [77, 78]. Therefore, it is prudent to ensure that other cardiovascular risk factors—such as smoking, hypertension, hyperlipidemia, and obesity—are well managed prior to initiation of oral estrogen therapy in transgender women. Clinicians who counsel both cis- and transgender women 60 years and older must communicate the documented higher CVD risks from estrogen therapy in this age group. Thus, a decision regarding estrogen usage should consider benefits/all harms (some not cardiovascular) and be individualized in the context of a clinician-patient risk discussion.

Role of Preventive Testing to Risk Stratify Women

For those with borderline to intermediate 10-year ASCVD risk, the 2018 AHA/ACC/Multi-Society Cholesterol Guidelines [4••] recommend a clinician-patient risk discussion based on quantitative risk assessment and consideration of personal risk-enhancing factors, and for those in whom risk status remains uncertain, the use of CAC scoring to help facilitate decision-making was recommended.

A consideration of enhancing factors (see Fig. 2) is especially pertinent to women since they often present with multiple such factors that allow the clinician to personalize both their short and long-term ASCVD risk. Single enhancing factor as noted above may not increase 10-year ASCVD risk substantially over the risk determined by the PCE for women, but when multiple enhancing factors are present, they have the potential to reclassify risk. For example, a 62-year-old non-diabetic, non-hypertensive, non-smoker black woman with a total cholesterol of 172 mg/dL, HDL of 55 mg/DL, and systolic blood pressure of 112 mmHg who would ordinarily have a 10-year ASCVD risk score of 3.7% should have a very different clinician-patient discussion than her counterpart with all of the same demographic and comorbidity profile, but with the addition of a prior pregnancy complicated by pre-eclampsia, followed by early menopause at age 39 and a history of chest irradiation for breast cancer. At a minimum, incorporating sex-specific risk-enhancing factors into the clinician-patient discussion allows the patient and clinician to see clearly the stable elements of risk that characterize her propensity to ASCVD. In addition, bringing sex-specific risk-enhancing factors to the forefront of the primary prevention discussion also has the potential to improve patient adherence to lipid-lowering therapy when recommended, as this allows the

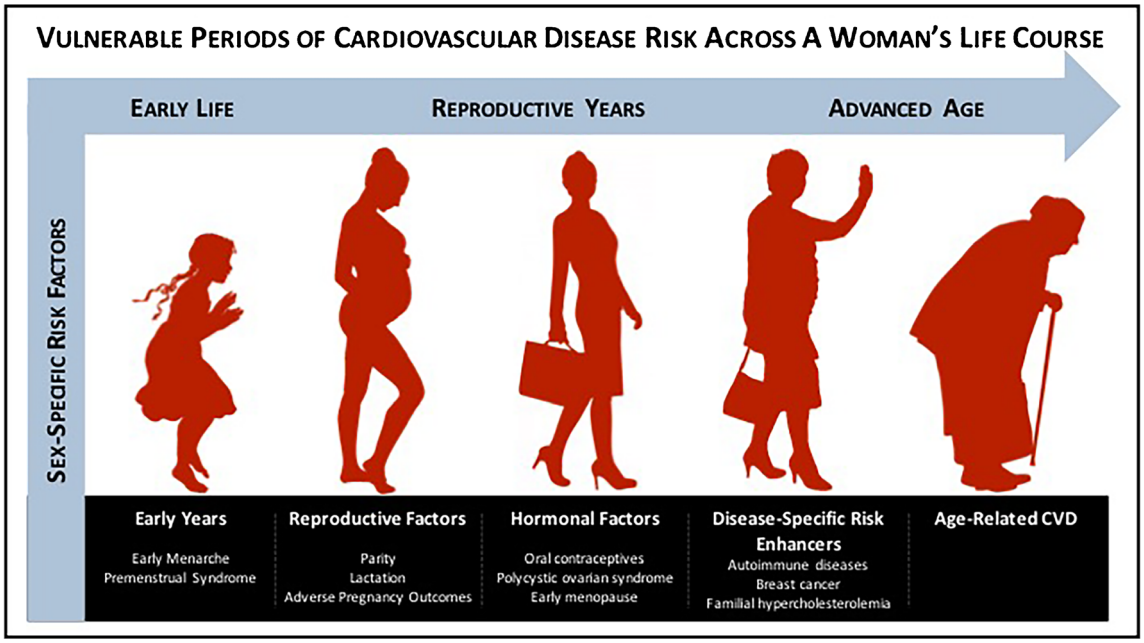

Fig. 2 Vulnerable periods of cardiovascular disease risk across a woman's life course

patient to better understand her personalized risk, as contrasted with simply being given a risk percentage and told to start a therapy based on a number alone. We await studies that are needed to see if this improvement in adherence to therapy is, in fact, the case.

Coronary Artery Calcium Scoring

The Multi-Ethic Study of Atherosclerosis (MESA), a prospective cohort study of 6814 participants (51% women), found CAC to be robustly associated with fatal and nonfatal MI and stroke over a 10-year period [79•]. Multiple studies have shown that although men have higher CAC burden, women have a larger proportion of mixed and non-calcified plaques, which portend higher acute and long-term cardiovascular mortality [80, 81]. Using MESA data, a validated ASCVD risk score is available for those patients who have undergone a CAC test to estimate 10-year CHD risk using traditional risk factors and CAC [82]. Furthermore, the absence of coronary calcium, or a CAC score = 0, is clinically very meaningful in reclassifying risk. In a study of more than 4500 MESA participants, approximately half of those who would have traditionally been recommended a statin based on their PCE 10-year ASCVD risk score had a CAC = 0 and an extremely low ASCVD event risk (1.5 per 1000 patient years) [83]. Thus, these patients would be reclassified to not be recommended to initiate statin therapy. The significant improvement in risk prediction obtained could be especially helpful in women who prefer not to take a statin despite having a 10-year risk of ≥ 7.5% and enhance the clinician-patient risk discussion.

Breast Arterial Calcification

Breast arterial calcification (BAC) is another surrogate marker that may demonstrate utility for ASCVD screening for women. BAC can be assessed from mammograms and reflects calcification of the breast arteries in the media of the artery (Mönckeberg medial calcific sclerosis). While BAC is in earlier stages of development and discovery, and limited data on clinical applications are available, early studies, albeit small in size and mostly retrospective, demonstrate a strong association between BAC and CAC [84–86]. BAC can be obtained without additional cost or radiation to women during mammograms that are already routinely performed starting at age 40 for breast cancer screening and therefore are an appealing potential tool to leverage. Currently, limitations of the translation of BAC into routine clinical practice are hampered by the lack of reproducible and quantitative assessment as well as prospective studies for validation.

Conclusions

Women at every stage of the life cycle after menarche have characteristics that require a woman-centered determination of their risk of ASCVD. Moreover, even among women, race and ethnicity factors further affect absolute global

Table 1 Key research questions/gaps in evidence

Question	Current evidence	Gaps in evidence/future directions
Does inclusion of sex-specific risk factors in short-term and long-term ASCVD risk prediction have clinical utility and inform initiation of preventive therapies?	Multiple sex-specific risk factors (premature menarche, adverse pregnancy outcomes, premature menopause) are associated with higher risk of ASCVD, independent of traditional risk factors.	Prospective, adjudicated, epidemiological studies incorporating pregnancy and non-pregnancy cohorts and electronic health record data are needed to understand the potential additional predictive utility of these risk factors.
What are the pathways and mechanisms that underlie the transition from adverse pregnancy outcomes to ASCVD?	Adverse pregnancy outcomes constitute a spectrum of placental vascular disorders that are associated with higher risk of ASCVD risk factors in follow-up.	Dissemination and implementation of collaborative care beginning in the early post-partum period focusing on lifestyle behavior modification and optimization of CVH to assess best strategies to assess, modify, and prevent a woman's risk of ASCVD need to be studied. Discovery of unique biomarkers that may predict risk or be targeted to prevent ASCVD may enhance personalized care.
Should subclinical imaging tools (CAC) be employed in women with a sex-specific risk factor to identify women at risk earlier in life and inform guideline-recommended initiation of evidence-based therapy?	Sequential screening with CAC can reclassify risk for ASCVD in intermediate and high predicted risk middle-aged women.	Randomized controlled trial evidence to assess the impact of CAC on ASCVD events may complement the available robust epidemiological data to guide decisions on statin therapy initiation when there is uncertainty.

cardiovascular risk. Recent guidelines have recommended a consideration of risk-enhancing factors in primary prevention clinician-patient risk discussions. These factors should be included in a detailed obstetric and gynecological history in order to personalize the assessment of ASCVD risk for each individual woman. The most powerful factor, however, to allow for reclassification of ASCVD risk is a CAC score. This may be especially useful in older women who do not want to take cholesterol-lowering medications such as statins to determine more precisely if they would, in fact, benefit. Many such patients with a calcium score of 0 have a lower overall risk that puts them beneath the treatment threshold. This review of sex-specific factors should be considered a first step on the route to the precision medicine that is eagerly awaited in the future (Table 1).

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Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- • Of importance
- •• Of major importance

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