Circulation

PRIMER

The Use of Sex-Specific Factors in the Assessment of Women's Cardiovascular Risk

ABSTRACT: Cardiovascular disease (CVD) is the leading cause of death among women in the United States. As compared with men, women are less likely to be diagnosed appropriately, receive preventive care, or be treated aggressively for CVD. Sex differences between men and women have allowed for the identification of CVD risk factors and risk markers that are unique to women. The 2018 American Heart Association/American College of Cardiology Multi-Society cholesterol guideline and 2019 American College of Cardiology/American Heart Association guideline on the primary prevention of CVD introduced the concept of risk-enhancing factors that are specific to women and are associated with an increased risk of incident atherosclerotic CVD in women. These factors, if present, would favor more intensified lifestyle interventions and consideration of initiation or intensification of statin therapy for primary prevention to mitigate the increased risk. In this primer, we highlight sex-specific CVD risk factors in women, stress the importance of eliciting a thorough obstetrical and gynecological history during cardiovascular risk assessment, and provide a framework for how to initiate appropriate preventive measures when sex-specific risk factors are present.

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Cardiovascular disease (CVD) is the leading cause of death among women in the United States. Women are less likely to be diagnosed appropriately, receive preventive care, or be treated aggressively for CVD.[1,2] This may be attributable to a lower perceived risk in women by patients and clinicians, even when traditional risk factors are present.[1,3]

In addition to screening for and managing traditional risk factors, sex-specific differences between men and women allow for the identification of CVD risk factors unique to women. A woman's lifespan offers several opportunities to identify additional CVD risk factors beyond traditional risk factors. We have learned that a one-size-fits-all model of cardiovascular risk stratification is no longer an acceptable way to deliver health care to 51% of the population.[4] We must capitalize on sex-specific differences to deliver optimal preventive medical care.

The 2011 American Heart Association (AHA) guideline for the prevention of CVD in women considered the presence of preeclampsia, gestational diabetes mellitus (GDM), gestational hypertension, or systemic autoimmune collagen-vascular disease (ie, lupus or rheumatoid arthritis) as factors associated with an increased risk of CVD.[5] The 2018 AHA/American College of Cardiology Multi-Society cholesterol guideline and the 2019 American College of Cardiology/AHA guideline

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on the primary prevention of CVD introduced the concept of risk-enhancing factors that can be applied to patients who are at borderline- and intermediate-risk, after estimating their 10-year atherosclerotic CVD risk using the pooled cohort equations.[6,7] The presence of 1 or more of these factors could elevate patients to a higher risk category and may favor initiation or intensification of statin therapy.[6,8] Notably, these guidelines have raised awareness of risk-enhancing factors specific to women that may increase a woman's risk of CVD.[6,7] The risk-enhancing factors mentioned in these guidelines were premature menopause and preeclampsia. However, several additional factors are also associated with increased CVD risk in women: adverse pregnancy outcomes such as gestational hypertension, GDM, preterm delivery (PTD), and delivery of small for gestational age (SGA) infants.[5]

This primer highlights features that may increase a woman's CVD risk, discusses the evidence and rationale behind them, and provides a framework for how to incorporate these factors when making lifestyle and treatment recommendations.

ADVERSE PREGNANCY OUTCOMES

The gestational window is a natural stress test on a woman's body and a time that is ripe for gathering data on cardiovascular risk. Adverse pregnancy outcomes such as preeclampsia, hypertensive disorders of pregnancy, and GDM afflict between 3% to 20% of pregnancies. Each of these conditions has been associated with an increased CVD risk.[9–14]

Preeclampsia and Gestational Hypertension

The hallmark of preeclampsia is the combination of elevated blood pressure and proteinuria after 20 weeks gestation. Gestational hypertension is characterized by the development of hypertension after 20 weeks of gestation in the absence of proteinuria or preeclampsia. It is defined by a blood pressure >140/90 mmHg on 2 separate occasions. Hypertensive disorders of pregnancy are thought to confer not only an elevated risk for the subsequent development of hypertension and diabetes mellitus, but notably for incident CVD and heart failure.[14] A meta-analysis of >6.4 million women (258 000 with preeclampsia) demonstrated that preeclampsia was independently associated with a 4-fold increased risk of incident heart failure (relative risk [RR] 4.19 [95% CI, 2.09–8.38]) and a 2-fold increased risk of coronary heart disease (CHD; RR 2.50 [95% CI, 1.43–4.37]).[14] A study that included 1 033 559 women without preexisting CVD before their first pregnancy showed that women who experienced a placentally-mediated condition during pregnancy (7% of the cohort), such as gestational hypertension, preeclampsia, placental abruption, or placental infarction, were twice as likely to develop CVD (hazard ratio [HR] 2.0 [95% CI, 1.7–2.2]) after a median follow up of 8.7 years. Adjusted HRs for incident CVD for women with gestational hypertension and preeclampsia were 1.8 (95% CI, 1.4–2.2) and 2.1 (95% CI, 1.8–2.4), respectively.[15] The composite outcome of CVD was highest in women with maternal placental syndrome and either poor fetal growth or intrauterine fetal death concurrently.[15] Another meta-analysis evaluated 146 748 women during their first pregnancy for hypertensive disorders and the development of CVD and hypertension later in life. Women with hypertensive disorders of pregnancy had higher rates of CVD (HR 2.2 [95% CI, 1.7–2.7]), and hypertension (HR 5.6 [95% CI, 5.1–6.3]).[11] Hypertensive disorders of pregnancy manifest via multiple phenotypes that are thought to arise from an interplay of underlying contributing factors including endothelial dysfunction, insulin resistance, and thrombophilia.[16] Studies are ongoing to understand the molecular mechanisms that determine the phenotypic heterogeneity in these disorders.[17–19]

Gestational Diabetes Mellitus

GDM is the development of elevated blood sugars during pregnancy, typically secondary to insulin resistance. Women with GDM have an 8-fold increased risk of developing type 2 diabetes mellitus (T2DM) after pregnancy compared with normoglycemic women.[20] GDM is also associated with future risk of CVD.[21,22] According to one study, GDM confers 63% higher odds (1.02–2.62) of developing incident CVD and an absolute risk increase of 2.8%.[23] A recent meta-analysis demonstrated that women with GDM have a 2-fold greater risk for future cardiovascular events compared with those without GDM (RR 1.98 [95% CI, 1.57–2.50]).[21] After restricting the sensitivity analysis to women who did not subsequently develop T2DM, the relative risk of future CVD was attenuated but remained significant (RR 1.56 [95% CI, 1.04–2.32]). These findings suggest an independent association between the development of GDM and future CVD risk. It is thought that women who develop dysglycemia have an underlying cardiometabolic phenotype that predisposes them to GDM and CVD. Glucose screening during pregnancy could identify women at risk for CVD.

Preterm Delivery

PTD is the birth of a baby at fewer than 37 weeks gestational age. In the Nurses' Health Study, a history of PTD, particularly one that occurred very prematurely (ie, <32 weeks), was independently associated with increased

maternal CVD risk.[24,25] The Nurses' Health Study II demonstrated that PTD during the first pregnancy was associated with an increased CVD risk compared with a term delivery (HR 1.42 [95% CI, 1.16–1.72]).[24] Women with a history of PTD are at an increased risk of developing chronic hypertension, T2DM, and hypercholesterolemia, particularly within the first decade after the pregnancy, and are more likely to have subclinical atherosclerosis.[26,27] These factors account for about 25% of the association between PTD and CVD. Though other pathways are thought to be involved, our understanding of the mechanism behind this is currently limited.

Small for Gestational Age

Infants who are SGA are characterized as being below the 10th percentile in weight for their gestational age. Delivery of an SGA infant is associated with future maternal CVD in a dose-response fashion related to severity of SGA and the number of SGA deliveries.[28] It is thought that women who are at higher risk for CVD may be less likely to accommodate the hemodynamic changes during pregnancy and this may manifest as fetal growth restriction. While SGA infants and future maternal CVD appear to be associated, it is unclear as to whether this association is independent of maternal placental syndromes including hypertensive disorders of pregnancy as many of these factors are interrelated.[28,29] Women who deliver SGA infants should be monitored carefully for the development of hypertension.

Hypertensive disorders of pregnancy portend a greater risk of incident hypertension, while GDM is associated with a substantially increased risk of T2DM. PTD is associated with an array of downstream effects including hypertension, hyperlipidemia, and T2DM. When a history of adverse pregnancy outcomes is elicited during risk stratification, aggressive lifestyle interventions should be implemented early on along with careful screening to prevent or mitigate the development of downstream intermediate phenotypes associated with an increased CVD risk.

OVARIAN FAILURE

Premature ovarian failure (POF) and early onset menopause are characterized by loss of ovarian function before the age of 40 or 45, cessation of menstruation, hypergonadotropism, and hypoestrogenism and an increased CVD risk.[30–32] The average age for the onset of menopause is 51 years. Women who experienced menopause at an age younger than 45 years, compared with those ≥45 years, had an increased risk of CHD (RR 1.50 [95% CI, 1.28–1.76]), according to one meta-analysis.[30] Women who experienced menopause between the ages of 50 and 54 years had a decreased risk of fatal CHD (RR 0.87 [95% CI, 0.80–0.96]), but not stroke, compared with those who experienced it at younger than 50 years.[30,32] Another meta-analysis assessed the relationship between POF and CHD among 190 588 women with 9440 cardiovascular events. Women with POF had an increased risk of CVD mortality (HR 1.69 [95% CI, 1.29–2.21]) and of overall incident CVD (HR 1.61 [95% CI, 1.22–2.12]).[30,32] A prospective cohort from the NHS, including 73 814 participants, showed that a reproductive lifespan of <30 years compared with that of ≥42 years was associated with an increased risk for incident CVD (RR 1.32 [95% CI, 1.16–1.49]). Age at menopause <40 years compared with 50 to <55 years was also associated with an increased CVD risk (RR 1.32 [95% CI, 1.16–1.51]).[31] Age at menopause is thought to be a marker for reproductive aging and general health, and a shorter reproductive lifespan mediated by early loss of estrogens has been associated with a higher CVD risk.

Regardless of the cause, whether spontaneous or iatrogenic, women with estrogen deprivation secondary to POF are at higher risk of cardiovascular morbidity and mortality.[33] Estrogens help regulate blood flow and assist in the relaxation of blood vessels. Early loss of ovarian function with associated changes in sex hormones is also associated with long-term activation of the renin-angiotensin-aldosterone system. These effects lead to endothelial dysfunction, inflammation, and immune dysfunction, all of which contribute to vascular damage.[34] Loss of estrogens also leads to a loss of their beneficial effects on cholesterol metabolism and atherosclerotic plaque formation and thereby contributes to the increased CVD risk. A higher testosterone to estradiol ratio in postmenopausal women is associated with a greater risk for incident CVD, CHD, and heart failure.[35] While it is currently unknown whether estrogen therapy is beneficial in women with POF, women with this condition should be monitored closely and treated with aggressive lifestyle modifications to prevent the development of CVD.

ADDITIONAL CVD RISK FACTORS IN WOMEN OUTSIDE OF PREGNANCY AND MENOPAUSE

Several factors beyond pregnancy and menopause are thought to confer an elevated CVD risk and should be considered during risk stratification: premature menarche, polycystic ovarian syndrome (PCOS), hormone-based contraceptive use, multiple spontaneous miscarriages, and breast cancer.

Premature Menarche

Premature menarche is associated with increased CHD and CVD risk. The average age of menarche is 13 years,

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and menarche is considered premature when it occurs at age 10 years or younger. A meta-analysis showed a 3% reduction in the relative risk of all-cause mortality for every 1-year increase in age at menarche, pooled HR 0.97 (0.96–0.98). Women who experienced menarche at age <12 versus ≥12 years were at an increased risk of all-cause mortality (HR 1.23 [95% CI, 1.10–1.38]).[36] Another study suggests that both early and late menarche increase the relative risk of CHD; the RR in women with menarche age ≤10 years was 1.27 (1.22–1.31) and for women with menarche age ≥17 years was 1.23 (1.16–1.30).[37] Premature menarche is associated with the development of hypertension and components of metabolic disease including T2DM and hypercholesterolemia, all of which increase CVD risk. Adjusting for these factors slightly attenuated CVD risk estimates, however, the risk remained significant, suggesting the possibility of additional shared risk factors between premature menarche and CVD.[37]

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is the most common cause of infertility in women and frequently manifests during adolescence. Key features include excess androgens, ovulatory dysfunction, and polycystic ovaries on imaging. There is an associated higher prevalence of hypertension, central adiposity, insulin resistance, dyslipidemia, and metabolic syndrome. PCOS has notable shared risk factors with CVD. Women with PCOS have a higher degree of subclinical atherosclerosis noted by a greater carotid intima-media thickness and greater coronary artery calcium.[38] In some studies, PCOS was associated with future risk of CVD; however, there is heterogeneity of risk based on PCOS phenotype.[39,40] Higher body mass indices, waist circumferences, blood pressure, glucose levels, and hyperlipidemia at the time of PCOS diagnosis are associated with greater CVD risk. Understandably, these features associated with PCOS are also independent risk factors for CVD.

Pregnancy Loss

Pregnancy loss, particularly recurrent miscarriages, is associated with an increased CVD risk. Women with a history of 2 or more miscarriages, regardless of whether they were consecutive or not, are at a higher risk for CHD. In one study, women who experienced 2 miscarriages or 3 or more miscarriages were at higher risk for CHD as compared with women who did not experience miscarriage (HR 1.75 [95% CI, 1.22–2.52]; and HR 3.18 [95% CI, 1.49–6.80], respectively).[41] While the emotional aspects of pregnancy loss and concerns regarding fertility are understandably the immediate focus after a miscarriage, the cardiovascular burden of recurrent miscarriages also merits careful consideration.

Premature menarche, PCOS, and recurrent pregnancy loss are all associated with an underlying higher risk cardiometabolic phenotype. Women with this medical history should be closely monitored for signs of metabolic dysregulation, and preventive lifestyle measures ought to be implemented early on.

Hormone-Based Contraceptive Methods

Hormone-based contraceptive methods can affect the lipid profile and thereby cardiovascular risk. Estrogen-based contraceptives typically elevate triglycerides and high-density lipoprotein cholesterol levels while decreasing low-density lipoprotein cholesterol levels and should be used with caution, particularly among women with elevated triglycerides. Some contraceptive methods contain norgestrel or levonorgestrel, both of which have androgenic components that elevate low-density lipoprotein cholesterol levels and decrease high-density lipoprotein cholesterol levels. Progesterone- based contraceptive methods tend to have neutral effects on the lipid profile. Obtaining information on the type and duration of hormone-based contraceptive use as well as identifying potential contraindications to their use is of clinical value when implementing preventive strategies.

Breast Cancer

Breast cancer history and associated treatments may portend an increased risk of incident CVD. Radiation to the left breast is associated with an increased risk of CHD and treatment with chemotherapeutic agents such as anthracyclines and trastuzumab increase the risk of cardiomyopathy and heart failure.[42] Given several shared risk factors between cancer and CVD, such as smoking, obesity, hypertension, and oxidative stress to name a few, there are opportunities for shared preventive strategies to reduce the risk for and morbidity and mortality from both conditions.[43] These include education and awareness on shared risk factors for cancer and CVD using public health campaigns, collaborative screening initiatives, and emphasis on lifestyle modifications.

Inflammatory Disorders

Inflammatory disorders such as rheumatoid arthritis, psoriasis, and systemic erythematous lupus have robust associations with CVD.[44–46] These conditions are considered risk-enhancing factors in the 2018 Cholesterol Guideline, and their presence in intermediate or select borderline risk patients should yield consideration of initiation or intensification of statin therapy.[6] Given their substantially higher prevalence in women, careful screening and preventive measures should be utilized in women with a history of these conditions.

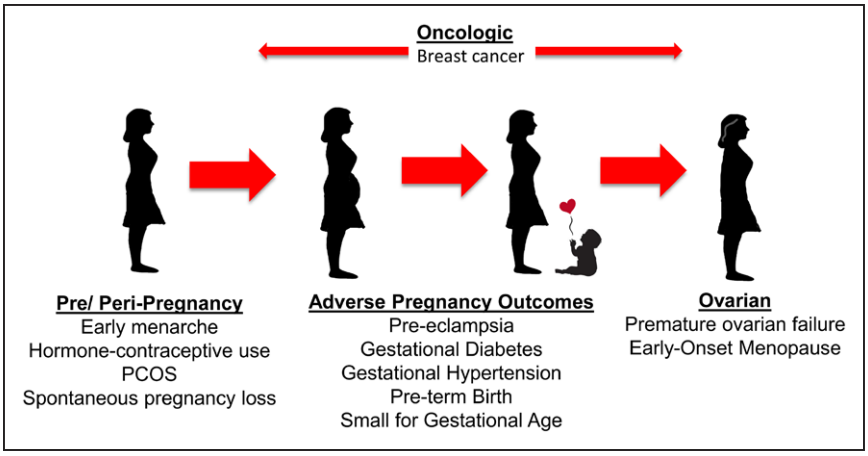

Figure 1. Sex-specific cardiovascular disease (CVD) risk factors in women.
PCOS indicates polycystic ovarian syndrome.

LACTATION

Lactation is an important factor in the reproductive continuum and is associated with lower maternal cardiovascular risk. Breastfeeding is thought to aid in reversing the metabolic changes of insulin resistance, dyslipidemia, and accumulation of fat mass that take place during pregnancy.[47] Lactation has been associated with a lower risk of hypertension and metabolic dysfunction, both of which are risk factors for CVD. In a cohort of roughly 63 000 Danish women followed up to 7 years postpartum, breastfeeding ≥4 months was associated with a 30% and 20% lower risk of hypertension and CVD, respectively, compared with breastfeeding <4 months.[48] The protective effects of breastfeeding were noted both in women who were normal/underweight and overweight/obese before pregnancy. While further studies are needed to determine how the interplay of lactation with traditional and sex-specific factors affect CVD risk, clinicians should highlight the protective effects of breastfeeding concerning maternal CVD risk.

PUTTING IT ALL TOGETHER: COMPREHENSIVE CARDIOVASCULAR RISK STRATIFICATION IN WOMEN

As we have reviewed, factors unique to women can have a substantial impact on a woman's cardiovascular health (Figure 1). We assert that cardiovascular risk stratification in women is incomplete without a thorough obstetrical and gynecological history. The Table outlines the elements that comprise a comprehensive history for cardiovascular risk stratification in women.

We recommend a 4-fold approach to cardiovascular risk stratification in women (Figure 2). First and most importantly is eliciting a thorough history of CVD risk factors that includes a comprehensive obstetrical and gynecological history. Second, if sex-specific risk factors are present, early and frequent screening for traditional CVD risk factors is crucial in addition to screening for, preventing, and treating intermediate phenotypes related to the sex-specific risk factors (ie, hypertension, diabetes mellitus, hyperlipidemia, and metabolic syndrome). Many reproductive conditions including GDM, early menarche, PTD, PCOS, and recurrent pregnancy loss, are associated with intermediate phenotypes of T2DM and metabolic syndrome. Additionally, maternal placental syndromes and hypertensive disorders of pregnancy portend a higher risk of hypertension. Vigilant screening and early detection and treatment of these intermediate phenotypes can substantially reduce future CVD risk. Third, the implementation of aggressive lifestyle changes is key. Lifestyle modifications can be approached using AHA's Life's Simple 7 to approach ideal cardiovascular health. The 7 metrics include managing blood pressure, controlling cholesterol, reducing blood sugar, becoming and

Table. Elements of a Comprehensive Cardiovascular History in Women

Phases of Life/ Categories	Elements to be Addressed
Birth	Prematurity/gestational age
	Birth weight/born small for gestational age
Puberty/Adolescence	Age at menarche
	Diagnosis of polycystic ovarian syndrome
Contraception	Use of contraception, type, duration, and inclusion of hormonal components
Childbearing peripartum period	Miscarriage(s)
	Gestational diabetes mellitus
	Gestation hypertension
	Preeclampsia
	Preterm delivery
	Delivery of a small for gestational age infant
	Lactation
Comorbidities	Autoimmune disorders (ie, rheumatoid arthritis, lupus, Crohn's disease)
	Cancer history including history of radiation or chemotherapy (ie, anthracycline or trastuzumab)
Menopause	Age at menopause/ premature ovarian failure
	Use of hormone therapy

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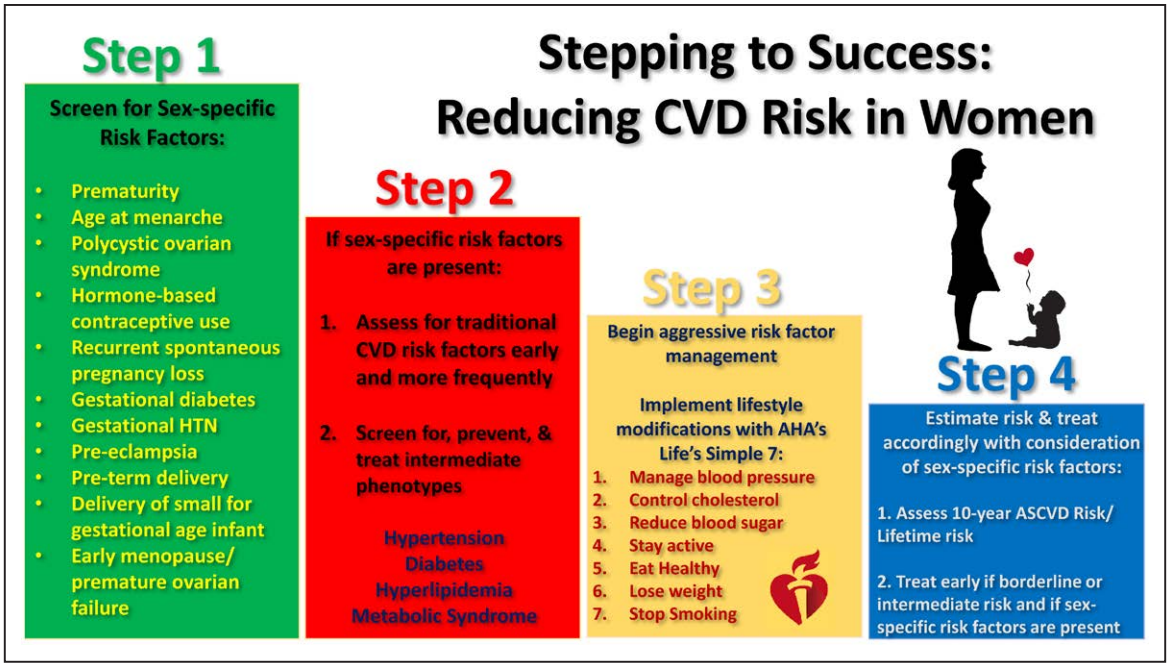

Figure 2. Stepping to success.
Reducing cardiovascular disease (CVD) risk in women when sex-specific risk factors are encountered. AHA indicates American Heart Association; ASCVD, atherosclerotic cardiovascular disease; and HTN, hypertension.

remaining active, healthy eating, weight loss, and smoking cessation. These 7 steps, when implemented early on, can have lasting effects on CVD risk reduction.[49,50] Finally, for patients between the ages of 40 and 75, the 10-year atherosclerotic CVD risk calculator can be used to estimate risk; for those aged 20 to 59, lifetime risk can be assessed. Individuals with low 10-year risk, but high lifetime risk, may be treated with aggressive lifestyle modifications as recommended by the 2018 AHA/American College of Cardiology Multi-Society cholesterol management guideline and the 2019 American College of Cardiology/AHA Prevention of CVD guideline.[6] In individuals at borderline or intermediate risk with the presence of these risk markers, early statin initiation or intensification could be considered to reduce atherosclerotic risk in addition to lifestyle modifications. For some sex-specific phenotypes, clinicians could follow these patients vigilantly for the development of heart failure and institute therapies to further reduce this risk.

Future studies are needed to understand whether sex-specific risk factors allow risk reclassification beyond traditional risk scoring algorithms and how best to assess high-risk phenotypes. As we await a more formalized framework of how to incorporate sex-specific risk factors into current risk stratification algorithms, clinical judgment concerning the number of risk factors and phenotype severity must be incorporated during risk stratification and shared decision making about treatment. Collaborative efforts among primary care clinicians, obstetricians, gynecologists, and cardiologists are key to streamlining early identification of sex-specific risk factors and the institution of preventive care for women.

CONCLUSION

The current state of cardiovascular care for women is far from ideal. It is our duty as the cardiovascular community to change the paradigm of underdiagnosing and undertreating CVD in women, and doing so will require a concerted effort. Together, we can optimize cardiovascular care for women.

ARTICLE INFORMATION

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

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