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REVIEW

A Woman's Heart: Improving Uptake and Awareness of Cardiovascular Screening for Middle-Aged Populations

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Abstract: Mid-life, the years leading up to and following the menopause transition, in women is accompanied by a change in cardiometabolic risk factors, including increases in body weight, changes in body composition, a more insulin-resistant state, and a shift towards a more atherogenic dyslipidemia pattern. Cardiovascular disease (CVD) risk assessment should be performed continually throughout the lifespan, as risk is not stagnant and can change throughout the life course. However, mid-life is a particularly important time for a woman to be evaluated for CVD risk so that appropriate preventive strategies can be implemented. Along with assessing traditional risk factors, ascertainment of a reproductive history is an integral part of a comprehensive CVD risk assessment to recognize unique female-specific or female-predominant factors that modify a woman's risk. When there is uncertainty about CVD risk and the net benefit of preventive pharmacotherapy interventions (such as statins), measuring a coronary artery calcium score can help further refine risk and guide shared decision-making. Additionally, there should be heightened sensitivity around identifying signs and symptoms of ischemic heart disease in women, as these may present differently than in men. Ischemia from coronary microvascular disease and/or vasospasm may be present even without obstructive coronary artery disease and is associated with a heightened risk for major cardiovascular events and reduced quality of life. Therefore, correctly identifying CVD in women and implementing preventive and treatment therapies is paramount. Unfortunately, women are underrepresented in cardiovascular clinical trials, and more data are needed about how to best incorporate novel and emerging risk factors into CVD risk assessment. This review outlines an approach to CVD screening and risk assessment in women using several methods, focusing on the middle-aged population.

Keywords: women's health, mid-life, risk assessment, cardiovascular disease, prevention, menopause

Introduction

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality for women in the United States (US), as well as internationally, contributing to 48% of deaths among women in the US in 2020.[1,2] Furthermore, rates of myocardial infarction (MI) and CVD mortality have been rising in younger and middle-aged women (ages <65) in the past decade.[3–5] A recent US analysis showed that ST elevation MI is on the rise even in women <45 years of age over an 11-year time frame.[6] Globally, while there has been a decrease in the age-standardized prevalence of CVD in most areas of the world since 1990, with an overall decrease of 4.3%, this reduction has stagnated in recent years. Additionally, some countries have seen increased CVD prevalence, particularly China, India, and Indonesia.[7] In Europe, there are large disparities between high and middle-income countries, and for premature mortality (before age 70) due to CVD causes (vs non-CVD), this socioeconomic disparity is even greater for women.[8] In women, the proportion of premature mortality due to CVD was 36% in middle income

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countries compared to 16% in high income countries. For men, the corresponding rates are 36% and 24% in middle and high-income countries, respectively.[8]

To decrease CVD mortality, a deeper understanding of the contributing risk factors is needed, and individualized, tailored care for each patient is advocated for, particularly for women's cardiovascular health. Dr. James Herrick's models of MI, which began circulating in the early 1900s, typically used middle-aged men as the archetype to study CVD.[9] Dr. Herrick advocated for individualized, tailored care for each patient. Despite this, an approach focused explicitly on women's cardiovascular health did not gain prominence until several decades later, in the early 1990s.[9]

The 1992 National Heart, Lung, and Blood Institute (NHLBI) Conference on Cardiovascular Health and Disease in Women posed an important question: what are the differences in CVD between men and women? Research in the area primarily focused on hormone replacement therapy (HRT) in postmenopausal women and, as a consequence, largely ignored CVD in younger women.[9] The Heart and Estrogen/Progestin Replacement Study (HERS) and Women Health Initiative (WHI) studies that came shortly after that showed that HRT was not the universal answer for preventing CVD in women. This finding pivoted discussions about women's CVD to the modern-day search for differences in traditional risk factors and risk factors unique to women. The 2007 American Heart Association (AHA) Women's CVD prevention guideline[10] and Institute of Medicine (IOM) report[11] emphasized the need for more sex-specific research in CVD and shed light on differences between subgroups of women, particularly those who experience a more significant burden of CVD due to social disadvantages because of their race, ethnicity, income or education levels.

The 2020 American College of Cardiology (ACC) Summary of Updated Recommendations for Primary Prevention of CVD in Women further emphasized the prior discrepancies in CVD risk models between men and women.[12] It underscored the influence of unique female-specific factors on future CVD risk. These include the age of onset of menarche and menopause, total reproductive years, premenstrual syndrome, severe or persistent vasomotor symptoms (VMS), history of polycystic ovary syndrome (PCOS), infertility, use of assisted reproductive technology (ART), spontaneous pregnancy loss, grand multiparity, lack of breastfeeding, and adverse pregnancy outcomes (APOs) such as gestational diabetes mellitus (GDM), preterm delivery, and hypertensive disorders of pregnancy.[13–16] There are also female-predominant conditions, such as autoimmune diseases and depression, that independently increase the risk of CVD. The impact of these non-traditional factors is particularly salient in younger to middle-aged women, who may not present with signs of elevated CVD risk until later in life. Additionally, even among the more traditional risk factors of diabetes, hypertension, smoking, and obesity, there are differences in risk conferred between the sexes, as further discussed below.[13]

This review outlines an approach to CVD screening and risk assessment in women using several methods, focusing on the middle-aged population. First, we will review the initial approach to risk assessment using equations that estimate 10-year risk for atherosclerotic CVD (ASCVD) as a starting framework. We will then discuss how the ascertainment of female-specific or female-predominant risk factors can be used as "risk-enhancing" or "risk-modifying" factors to modify those estimated risks. Next, we will discuss how the selective use of imaging for subclinical atherosclerosis, specifically the coronary artery calcium (CAC) score, can be useful when there is uncertainty about the risk to refine risk estimation further and then guide shared decision-making about preventive therapies. Finally, we will discuss the impact of menopause, specifically on women's cardiometabolic risk, and an approach to risk assessment when considering menopausal HRT for managing VMS.

Initial Approach to Risk Assessment in Women – Risk Estimator Tools

Following a healthy lifestyle across the lifespan is the foundation for all CVD prevention strategies. However, when making decisions about preventive pharmacotherapies, assessment of CVD risk is a central tenet across all preventive guidelines to match the intensity of therapy with the absolute risk of the patient.[16–20]

The pooled cohort equations (PCE) were developed by the ACC and AHA in 2013 as tools for estimating 10-year risk of ASCVD events [fatal and non-fatal coronary heart disease (CHD) and stroke events] in the primary prevention setting (ie, to be applied to individuals without established ASCVD).[21] The PCE derive a risk estimate based on several established cardiovascular risk factors, including age, sex, race, blood pressure, cholesterol, diabetes, and smoking for individuals aged 40–79 years. The PCE are best calibrated for non-Hispanic White and Black adults living in the United States. Even then, the PCE may overestimate or underestimate ASCVD risk in specific populations.[22] The PCE may also

not estimate risk accurately in other global populations, leading to the need to develop regional-specific risk scores. For example, in their prevention guidelines, the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) use the SCORE2 risk score to estimate 10-year risk, which has modifications for four different risk regions in Europe.[16,23]

Notably, the PCE do not incorporate nontraditional emerging and female-specific cardiovascular risk factors, limiting their accuracy in specific populations, such as middle-aged women.[24,25] A comprehensive cardiovascular risk assessment in middle-aged women requires careful evaluation of their unique risk-enhancing factors. These are especially crucial in women at borderline or intermediate cardiovascular risk, as they may provide insight into their appropriate stratification and counseling. An important aspect is evaluating reproductive history regarding parity, pregnancy (including complications), hormonal therapies, and menopause.

Thus, the PCE are an initial starting framework for risk assessment but not the end of risk assessment. The 2019 ACC/AHA Guideline for the primary prevention of CVD acknowledged the limitation of PCE.[17] They further outline a list of "risk-enhancing" factors, which, if present, would place an individual who would otherwise only be estimated to be a borderline or intermediate risk into a higher risk category that would favor the initiation of statin therapy for primary prevention. These risk enhancers include the female-specific factors of early menopause (before age 40) and APOs such as pre-eclampsia, as well as additional risk-enhancing factors such as having a family history of premature ASCVD, chronic kidney disease (CKD), chronic inflammatory conditions, South Asian ethnicity, metabolic syndrome, persistently elevated triglycerides, and if measured, high levels of high-sensitivity C-reactive protein (hsCRP), lipoprotein (a) [Lp(a)], or apolipoprotein B (apoB). We will discuss some of these below, focusing on the female-specific or female-predominant conditions.

Sex Differences in Traditional Risk Factors

When assessing CVD risk in women, it is important to note that multiple traditional risk factors for ischemic heart disease (IHD) have a differential risk between the sexes. For example, hypertension, diabetes mellitus, and smoking confer a greater relative risk for MI in women than men, with odds ratios of 1.5, 1.6, and 1.3, respectively.[26]

Although diabetes is more prevalent in men at a given age, the presence of diabetes is associated with a significantly greater relative risk for CHD and vascular mortality in women compared to men.[27–30] This may be partly because compared to men, women have higher body mass index (BMI) and worse cardiometabolic risk profiles at the time of diabetes diagnosis.[27,31] Excess circulating glucose can diminish estrogen-related cardiovascular protection by decreasing vascular and platelet nitric oxide production, thereby increasing vascular tone, platelet aggregation, and vascular proliferation.[27]

Obesity increases the risk of CVD for both men and women. However, the prevalence of obesity and its impact on cardiovascular risk factors are further influenced by sex. Data from the Framingham study showed that women with obesity had a risk of CHD greater than 64% compared to 46% among men with obesity.[32] Menopause increases the prevalence of metabolic syndrome and redistribution of adipose tissue in the visceral cavity.[33] Obesity also increases the risk of maternal complications in pregnancy, such as hypertensive disorders of pregnancy, GDM, and heart failure.[34]

Smoking also confers a greater relative risk in women than in men. Compared with nonsmokers, women who smoke may have a 25% greater relative risk of CHD than male smokers, independent of other cardiovascular risk factors.[35] This female vulnerability in the setting of smoking may be related to genes involved in thrombin signaling, while other studies state that it is unclear if related to biological differences or smoking behaviors.[35]

Hypertension is more prevalent and less well-controlled in older women than in men.[36,37] Although, on average, the rise in blood pressure throughout a woman's lifespan appears linear, consistent with an aging effect rather than an ovarian effect,[38] there are differences in the patterns of blood pressure changes during the menopause transition across the population with some women experiencing an acceleration in blood pressure rise later in life.[39] Women also have unique considerations throughout their life course that influence blood pressure and/or its treatment. These include pregnancy, PCOS, the use of oral contraceptives or menopausal HRT, and predominant female conditions such as autoimmune disease and fibromuscular dysplasia.

Sleep disorders are well-recognized risk factors for CVD,[40] and women have been described as especially sensitive to the negative effects of those at different stages of life.[41] The proposed physiological mechanisms include complex interactions that are not fully understood. Sleep disorders include insomnia and short sleep duration (<5 hours), which are highly associated with an increased incidence of MI in a similar proportion to other risk factors.[42] A meta-analysis reported that females were at higher risk of MI among people with insomnia. Additionally, it was described that a shorter sleep-onset latency might be a protective factor against stroke and that females experienced a greater reduction in CVD risk from this factor.[43]

Female-Specific Risk Enhancing Factors

In addition to the sex differences in traditional CVD risk factors, female-specific factors uniquely elevate women's CVD risk throughout their lifespan, as discussed below.

Menarche, the onset of the 1st menstrual period, hallmarks the entry into a women's reproductive period of life. In the US, the average age of menarche is approximately 12 years.[44] However, both early onset of menarche ≤10 years or late onset menarche ≥17 years have been associated with incident future CVD.[45–47]

PCOS is the most common endocrine abnormality found in reproductive-age women and is diagnosed by the Rotterdam criteria if at least two of the following three criteria are present: androgen excess, ovarian dysfunction, and cystic morphology of the ovaries.[48] Women with PCOS have a worse cardiometabolic risk profile compared to women without PCOS, including insulin resistance, atherogenic dyslipidemia, elevated blood pressure, and elevated BMI.[48,49] PCOS has also been associated with an approximate 2-fold increased risk of subclinical CVD[50] and 30–50% higher risk of incident CVD events.[51,52] Menstrual irregularity is common among women with PCOS due to anovulatory cycles. Growing evidence supports an association between menstrual cycle length and/or cycle irregularity with cardiometabolic risk factors and CVD risk.[53,54] Thus, a menstrual history is an essential but underrecognized vital sign of cardiometabolic health. Interestingly, only a tiny proportion of the association between menstrual cycle regularity and length and CVD risk was driven by hypercholesterolemia, chronic hypertension, and type 2 diabetes (T2D),[55] suggesting that menstrual cycle dysfunction may be a useful early life marker for future CVD risk.

Parity, the number of live births, and gravidity, the number of pregnancies, are important factors in middle-aged women's cardiovascular risk assessment. A "J"-shaped relationship between parity and future CVD risk has been described.[56–59] It should be noted that higher parity is also a CVD risk factor in men, suggesting confounding by cultural and socioeconomic factors.[56] However, there is greater risk associated with multiparity seen in women, suggesting additional biological mechanisms such as those potentially mediated by adverse cardiometabolic and adipokine profiles and a more androgen sex hormone profile.[60–62]

Notably, pregnancy is another critical time in a person's life that could adversely affect their future cardiovascular outcomes, even decades after an index pregnancy with an APO. Several pregnancy complications are now recognized to confer long-term cardiovascular risk: hypertensive disorders of pregnancy, GDM, preterm births, and small-for-gestational-age newborns.[63] The association of preeclampsia with later-life CVD has been thoroughly studied, with several systematic reviews and meta-analyses showing at least a twofold increase in heart failure, CHD, stroke, and cardiovascular death.[64–66] Pre-term delivery before 37 weeks is also associated with a 2-fold risk of future CVD.[67] In a nationwide Swedish study, preterm or small-for-gestational-age infant delivery was associated with later-life maternal hospitalization or death from CVD.[68] Similarly, in a systemic review and meta-analysis, women with GDM had a twice higher risk of cardiovascular events, even without progressing to T2D post-partum.[69] In the Coronary Artery Risk Development in Young Adults (CARDIA) Study, women with a history of GDM also have a nearly twofold higher prevalence of subclinical atherosclerosis as detected by the CAC score approximately 15 years after their index pregnancy, even among those who returned to euglycemia after delivery.[70]

Other pregnancy-related factors have been associated with CVD. A history of infertility has been associated with an increased risk of ASCVD[71] and heart failure with preserved ejection fraction, even after accounting for traditional CVD risk factors.[72] Spontaneous pregnancy loss has also been associated with incident future ASCVD.[73] Breastfeeding, on the other hand, is thought to be a protective factor associated with decreased risk of incident diabetes[74] and CVD,[75] and well

as associated with a lower CVD risk among women with a hypertensive disorder of pregnancy compared to women with a hypertensive disorder of pregnancy who did not breastfeed.[76]

The premenstrual syndrome is another emerging risk factor in reproductive age women. The premenstrual syndrome is characterized by symptoms that may be physical, behavioral, or affective/psychological and is estimated to occur in up to 80% of women.[77] The premenstrual syndrome correlates with fluctuations in arterial stiffness and monthly blood pressures.[78] Additionally, moderate to severe premenstrual symptoms may be associated with an increased risk of developing hypertension before age forty.[79]

The menopause transition hallmarks the end of a woman's reproductive lifespan. The risk of CVD is higher in women after menopause compared to premenopausal women of the same age.[80] The onset of menopause that occurs early (before 45 years) or premature (before 40 years) has also been demonstrated to be a risk factor for adverse cardiovascular outcomes in women.[45,81,82] Additionally, shorter total reproductive years (from menarche to menopause) have also been linked to increased CVD risk.[83,84] This may be due to significant changes in lipid profiles that occur at the menopause transition, as longer duration since menopause is linked to lower high-density lipoprotein cholesterol (HDL-C), higher low-density lipoprotein cholesterol (LDL-C), higher triglycerides, higher total cholesterol, higher apoB and potentially higher Lp(a) levels.[85,86]

Vasomotor symptoms (ie, "hot flashes") are experienced by 70–80% of women transitioning through menopause, but less than 25% of women seek help for them. Many patients and clinicians are unaware of the link between VMS and CVD risk. Very severe, frequent, or persistent VMS are associated with an increased risk of future CVD, even after accounting for traditional CVD risk factors.[87,88]

Auto-immune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, are also more prevalent in women and have been associated with excess CVD risks beyond traditional risk factors.[89–94] The presence of an inflammatory state is emerging to be a separate causal mechanism in atherothrombotic pathogenesis and may be a therapy target in and of itself.[95]

Finally, social determinants of health should be ascertained as part of comprehensive CVD risk assessment.[96] Socioeconomic disparities at each stage of life disproportionately affect a woman's future cardiovascular health. They encompass multiple factors and include, but are not limited to, family income, education, literacy, language barriers, health care systems (health insurance, quality of care), marital status, social support, physical environment, economic stability, structural racism, culture, sexual orientation and gender identity.[96–99]

In sum, these studies highlight the uniqueness of CVD risk factors in women, compared to men, and emphasize the importance of taking a comprehensive reproductive history to identify these "red flags" of risk that may not capture through traditional risk factor assessment alone (Figure 1). Many pregnancy-associated factors are harbingers of short- and long-term CVD risks. Additionally, special intensive prevention efforts are needed to address individuals with inflammatory conditions.[95] Unfortunately, to date, there has been limited success in changing the C-statistic in risk prediction by trying to incorporate these factors directly into traditional risk assessment tools such as the PCE, likely because the cohorts that these risk calculators were derived were generally older and more data are needed to derive risk equations specific to the younger cohorts to which these equations would be applied. These risk calculators also work better on a population level (ie, reflecting an average risk across a group) but less well on an individual level. Better risk stratification tools and tailored prevention strategies for the individual are sorely needed to figure out how to incorporate these emerging factors, which are currently not captured in traditional 10-year risk estimator tools. In the meantime, as mentioned above, these factors, particularly early menopause and APOs, are considered "risk enhancers" that modify risk estimates generated by the risk equations like the PCE, placing women into a higher category where statin therapy may be considered for prevention.

Subclinical Atherosclerosis Assessment

The 2019 ACC/AHA Guideline on the Primary Prevention of CVD acknowledges that in many cases that even after estimating 10-year risk with the PCE and considering the "risk-enhancing factors" described above, there can still be uncertainty about an individual's risk and the net benefit for preventive pharmacotherapies, notably statins, and aspirin.[17] In these cases of risk uncertainty, the guideline recommends using the CAC score to help refine risk estimation (for ages

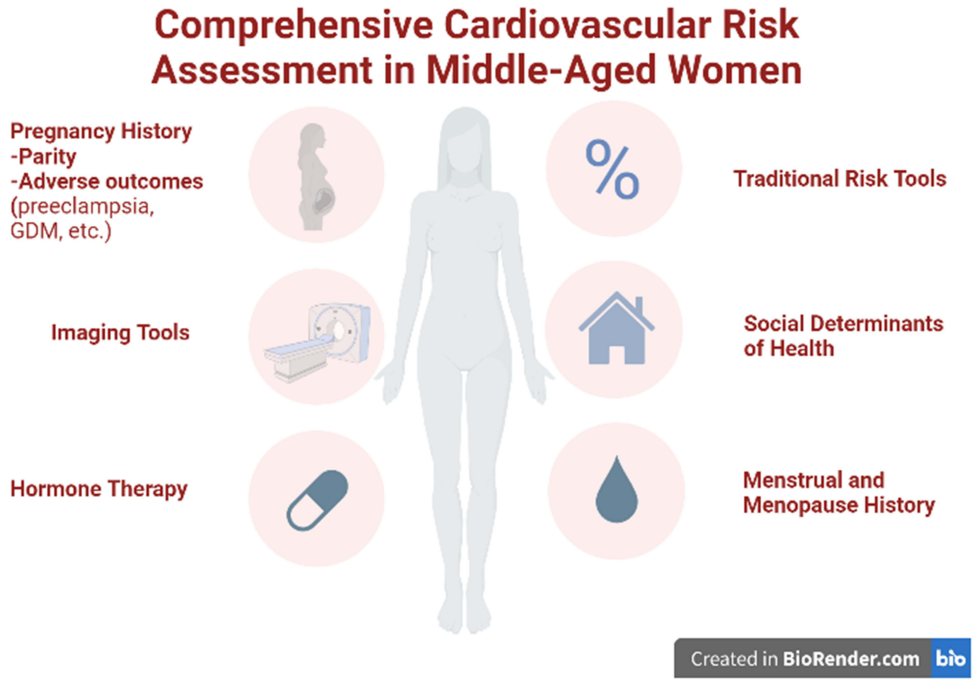

Figure 1 Comprehensive Cardiovascular Risk Assessment in Middle-Aged Women. (Figure was created with Biorender.com).

40-75 years). CAC scoring is a noninvasive imaging technique widely used in CVD risk stratification and guides shared decision-making regarding statin initiation in patients who would otherwise be considered at low or intermediate risk according to traditional risk factors.[100] Women are less likely to have prevalent CAC than men at a given age. However, for a given CAC score, the presence of CAC is associated with a greater risk for future ASCVD in women than in men.[101,102] In other words, CAC is equally (if not more so) prognostic in women when it is present.

CVD risk is on a continuum. The detection of subclinical atherosclerosis offers a window of opportunity to detect disease before it has become clinically manifest so that more intensive preventive efforts can be implemented.[103] The CAC score has emerged as a superior risk marker for clinical ASCVD events. It predicts risk better than age, LDL-C, or traditional risk score because it directly captures the presence of atherosclerotic disease.[100,104] Furthermore, the absence of CAC (ie, CAC=0) is associated with a low risk for ASCVD events in the next 5–10 years and, as such, has the potential to "de-risk" an individual into a lower-risk category where potentially statin therapy could be deferred.[100,105]

However, the CAC score has limitations and should be applied appropriately, not superseding clinical judgment. A CAC score of 0 is "low risk" but not "no risk". It is meant to be applied to asymptomatic individuals for risk assessment. Thus, a CAC score of 0 should not deter further cardiac investigation in a person with signs and symptoms of IHD. In patients with symptoms suggestive of IHD, using a CAC of 0 to avoid perfusion stress imaging could miss coronary microvascular dysfunction (CMD) in up to 4 out of 10 patients.[106] Also, as it takes time for plaques to become calcified, a CAC score of 0 has reduced prognostic utility in younger individuals (such as men <40 and women <50 years of age). In one study of symptomatic patients <60 years of age, a sizeable proportion still had coronary artery disease (CAD) despite having a CAC score of 0.[107]

For women with symptoms concerning for CHD (stable angina) whose coronary anatomy is unknown, a coronary CT angiography (CCTA) is a good initial test to determine the presence and extent of CAD burden.[108,109] Not only can a CCTA exclude obstructive CAD, but it can also identify the presence of non-obstructive CAD, offering the opportunity to initiate or intensify preventive therapy once identified. The benefit of this approach was highlighted in the SCOT-Heart trial, which enrolled patients with stable chest pain and demonstrated a significant reduction in major adverse cardiovascular events (MACE) at five years in the CCTA-guided arm compared to a usual care arm, with no significant interaction by sex.[110] This benefit was likely driven by the 40% greater uptake in preventive therapies such as statins in the CCTA arm.

The detection of non-obstructive plaque on CCTA is similarly prognostic in women and men. In CONFIRM, a large, multi-national, observational registry of individuals undergoing CCTA, non-obstructive CAD was associated with a similar increased risk of MACE in both women [aHR 1.96 (95% CI, 1.17–3.28)] and men [aHR 1.77 (1.07–2.83)] after adjustment for age and traditional risk factors, compared to no CAD.[111] Additionally the finding of non-obstructive plaque in the left main coronary artery conferred an increased risk of MACE in women [aHR 1.48 (1.21–1.75)] but not in men [aHR 0.98 (0.81–1.18)]. High-risk coronary plaque features, which are defined as positive remodeling, low CT attenuation, or napkin-ring sign, detected on CCTA were also associated with a greater risk for MACE in women [aHR 2.41 (1.25–4.64)] than in men [aHR 1.40 (0.81–2.39)].[112]

Additionally, there can be sex-specific differences in the pathophysiology of IHD, and women can still have ischemia with non-obstructive coronary arteries (INOCA).[113] In the setting of angina, non-obstructive CAD is more common in women than men. However, INOCA is not benign but rather is associated with an increased 5-year ASCVD event rate compared to asymptomatic women without angina[114] and can have a similarly reduced quality of life compared with patients with ischemia from obstructive CAD.[115] Thus, for patients with signs and symptoms of IHD, the workup should not end with the exclusion of obstructive CAD by coronary angiography or CCTA; additional testing for the INOCA phenotypes of CMD and vasospastic angina should be considered.[116] In the absence of obstructive CAD, the presence of reduced coronary flow reserve (CFR) <2 hallmarks coronary microvascular impairment; this is the inability of the coronary arteries to dilate properly in the setting of stress or vasodilator.[117] The detection of CMD identifies an individual at higher risk for MACE, even in the absence of obstructive CAD.[118] A severely impaired CFR (<1.6) conferred an even greater prognostic risk in women than in men.[119] In the CorMICA trial of patients with suspected INOCA, invasive coronary function testing to examine for INOCA endotypes and to tailor therapy accordingly was associated with a reduction in angina and improved quality of life compared to a control group with invasive angiography but no coronary function testing.[120] Non-invasively, CMD can be evaluated by a stress positron emission tomography (PET) or stress cardiac magnetic resonance imaging (CMR) with an assessment of myocardial blood flow reserve. Invasive coronary functional testing, stress PET, and stress CMR were all given a class IIa recommendation in the US Chest Pain guidelines for additional work-up when INOCA is suspected.[116]

In sum, in women with symptoms of suspected IHD, focusing on evaluating just for the obstructive disease is not enough. CMD is common and associated with poor outcomes, and making the diagnosis and implementing preventive, and treatment strategies is paramount. While INOCA and angina with non-obstructive coronary arteries (ANOCA) are stable presentations, in the setting of acute coronary syndromes, women are also more likely than men to have a myocardial infarction with non-obstructive coronary arteries (MINOCA).[121,122] MINOCA, although usually considered a more benign phenomenon, still carries significant morbidity and mortality compared to the general population. Intravascular imaging such as coronary optical coherence tomography, along with CMR, are essential steps in diagnosing these patients, allowing the proper differential diagnosis, targeted treatment, and prognosis.[121,123]

Furthermore, women have been historically underrepresented in cardiovascular clinical trials compared to their disease burden in the population, limiting the data on the efficacy of cardiovascular therapies in women compared to men.[124–128] Adequate representation of women and diverse populations in future cardiovascular trials is critical to ensure that the results from the trial apply to the broad groups of patients being cared for in clinical practice.

Physiological Changes of Perimenopause and Menopause

When considering CVD risk assessment in mid-life, perhaps the most significant influence that comes to mind is the impact of the menopausal transition. The average age of menopause in the US is approximately 51 years of age. Perimenopause is when physiologic changes relating to a decline in follicle number indicate progress toward a woman's final menstrual period. Perimenopause, on average, lasts around four years but can be as short as a few months or as long as up to 10 years. Perimenopause begins with the onset of menstrual irregularities and continues until a woman reaches menopause, diagnosed after 12 months of amenorrhea.[129,130]

Perimenopause can be divided into two stages: the early stage, characterized by occasionally skipped cycles and menstrual cycle lengths varying by seven days or more, and the late stage, defined by more significant menstrual irregularity, with periods of amenorrhea ranging from 60 days to 12 months. The symptoms associated with

perimenopause are caused by multiple hormonal changes during this time, resulting from a decline in ovarian function. As the number of ovarian follicles decreases, inhibin B levels decline, leading to a loss of pituitary inhibition and an increase in follicle-stimulating hormone (FSH) secretion.[131] In the late menopausal transition, estradiol levels decrease as the number of anovulatory cycles increases. As women approach menopause, anti-Müllerian hormone levels decrease and directly reflect the ovarian follicular reserve.[131]

Menopause is characterized by the complete or near-complete exhaustion of the ovaries' follicles, leading to low estrogen (estradiol) levels and significantly increased FSH levels.[131] After menopause, the withdrawal of endogenous estrogen levels can worsen traditional CVD risk factors. It can accelerate CVD, including body fat redistribution into the visceral cavity, impairment of glucose tolerance, adverse changes in lipid profile, elevations in blood pressure, endothelial dysfunction, and increased sympathetic tone, all of which have detrimental effects on arterial and cardiovascular function.[13]

Menopausal Hormone Therapy

The ACC/AHA prevention guidelines do not recommend initiating menopausal HRT for the sole purpose of CVD prevention after the landmark HERS and WHI demonstrated increased CVD risks rather than benefits.[17] However, it should be noted that WHI enrolled participants aged 50–70 years, and the mean age was 63 years, indicating that most women were quite far out from their final menstrual period. In addition, many women in the HRT trials were not symptomatic with VMS.[132,133] The risks associated with HRT likely depend on the age of initiation of HRT, time since menopause, age at menopause, duration of HRT therapy, type of HRT, a dose of HRT, and route of administration. For women with only the genitourinary symptoms of menopause, topical (vaginal) estrogen is not thought to have much systemic absorption and therefore can be safely used even in women at elevated CVD risk.

For systemic HRT (oral or transdermal preparations), HRT is still indicated for women <60 years or within ten years of menopause who have symptomatic VMS or other menopausal symptoms. For women with early menopause without contraindications, HRT is recommended until at least the average age of natural menopause. Generally, HRT is not recommended if >10 years from menopause or age >65 years. Oral estrogens should be avoided in women with a history of CVD, blood clots, high triglycerides, gallbladder disease, or prior breast or endometrial cancer. A cardiovascular risk assessment should be done before the initiation of HRT.[14,134] Generally women at low CVD risk (<5% 10-year ASVCD risk), HRT is acceptable for VMS management but should generally be avoided in women at high CVD (≥20% 10-year risk) or established ASCVD. For those at intermediate estimated ASCVD risk, the use of a CAC score can help determine the presence and burden of coronary atherosclerosis and guide risk-based decisions about HRT safety. Shared decision-making about the benefits and risks of HRT tailored for an individual patient transitioning through menopause should be made between the patient and her clinician.

Tactics to Increase Uptake and Awareness

Screening is vital for the early detection and management of CVD women. Several strategies can be implemented to improve CVD screening in this population. First, increasing CVD awareness through public health campaigns and targeted educational materials is essential. Engaging gynecology and primary care clinicians in the screening process of middle-aged women are also crucial. Furthermore, tailored screening methods and risk assessments should be developed: general screening guidelines are helpful. Still, they do not account for women's unique risks and disease presentations, so an individualized approach incorporating reproductive history is essential. Finally, the need for dedicated research funding to develop new screening modalities and guidelines cannot be stressed enough.

Conclusion

The road to improving women's cardiovascular health is long and multifaceted, requiring a combination of education, tailored screening, and risk assessment. A growing body of evidence currently supports the limitations of current cardiovascular risk assessment tools. It encourages the additional incorporation of female-specific or female-predominant risk factors in the cardiovascular evaluation of women, including their history of menstrual cycles, parity, pregnancy complications, hormone therapy, menopause, and/or the presence of autoimmune diseases. Proper identification of CVD in women and implementation

of preventive and treatment therapies is paramount, as understanding the uniqueness of how IHD may present in women, with INOCA being more common than in men. More data from future studies are necessary to understand how to best incorporate novel and emerging risk factors into CVD risk assessment. Finally, further efforts are strongly needed to ensure women are adequately represented in cardiovascular clinical trials.

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