MAYO CLINIC

Focused Cardiovascular Care for Women: The Need and Role in Clinical Practice

Mariana Garcia, MD; Virginia M. Miller, PhD; Martha Gulati, MD, MS; Sharonne N. Hayes, MD; JoAnn E. Manson, MD, DrPH; Nanette K. Wenger, MD; C. Noel Bairey Merz, MD; Rekha Mankad, MD; Amy W. Pollak, MD; Jennifer Mieres, MD; Juliana Kling, MD, MPH; and Sharon L. Mulvagh, MD

Abstract

Over the past decade, an emerging clinical research focus on cardiovascular (CV) disease (CVD) risk in women has highlighted sex-specific factors that are uniquely important in the prevention and early detection of coronary atherosclerosis in women. Concurrently, a 30% decrease in the number of female deaths from CVD has been observed. Despite this, CVD continues to be the leading cause of death in women, outnumbering deaths from all other causes combined. Clinical practice approaches that focus on the unique aspects of CV care for women are needed to provide necessary resources for the prevention, diagnosis, and treatment of CVD in women. In addition to increasing opportunities for women to participate in CV research, Women's Heart Clinics offer unique settings in which to deliver comprehensive CV care and education, ensuring appropriate diagnostic testing, while monitoring effectiveness of treatment. This article reviews the emerging need and role of focused CV care to address sex-specific aspects of diagnosis and treatment of CVD in women.

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From the Division of Cardiovascular Diseases (M.G., S.N.H., R.M., S.L.M.), Department of Surgery (V.M.M.), Department of Physiology (V.M.M.), and Department of Biomedical Engineering (V.M.M.), Mayo Clinic, Rochester, MN; Division of Cardiovascular Medicine, The Ohio State University Wexner Medical Center, Columbus, OH (M.G.); Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (J.E.M.); Division of Cardiology, Emory University School of Medicine, Atlanta, GA (N.K.W.); Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Institute, Los Angeles, CA (C.N.B.M.); Division of Cardiovascular Diseases, Mayo Clinic, Jacksonville, FL (A.W.P.); Department of Cardiology, Hofstra North Short-LIJ School of Medicine, Hempstead, NY (J.M.); and Department of Internal Medicine, Mayo Clinic, Scottsdale, AZ (J.K.).

According to the most recent US annual mortality statistics, cardiovascular (CV) disease (CVD) accounted for 398,035 female deaths, exceeding the number of female lives lost to malignant neoplasms, chronic lower respiratory tract diseases, and diabetes mellitus combined.[1] During the past 2 decades, CVD mortality rates have decreased in both men and women. Unfortunately, this rate has not decreased in parallel in women, especially those in midlife (ages 35-50 years), in whom CVD mortality has slightly increased or stagnated.[2-6] At the last assessment, only 56% of American women were aware that CVD is the primary cause of death in women and only 13% perceived this as the major risk to their personal health.[7-9] Moreover, marked racial, ethnic, and age disparity exists, with fewer black, Hispanic, and younger women possessing this awareness.[7] This knowledge gap persists despite the fact that a focused effort to rectify this situation was initiated in 2004 through the launch of major national awareness programs including the National Heart, Lung, and Blood Institute's "*Heart Truth*" and the American Heart Association (AHA)'s "*Go Red*®" campaigns.

Beyond routine CVD prevention, diagnosis, treatment, and education, Women's Heart Clinics can address CVD conditions and risks that *exclusively affect* women, including adverse pregnancy outcomes, peripartum cardiomyopathy (PPCM), polycystic ovary syndrome (PCOS), menopause, and menopausal hormone therapy (MHT) concerns, as well as CVD conditions that *disproportionately affect* women, including coronary microvascular dysfunction (CMD), spontaneous coronary artery dissection (SCAD), apical ballooning syndrome, inflammatory conditions associated with autoimmune disorders, peripheral arterial disease (PAD), heart failure with preserved ejection fraction (HFpEF), and postural orthostatic tachycardia syndrome (POTS). Lack of physician awareness and understanding of pathophysiological differences in heart disease in women have underscored a profound knowledge gap about optimal prevention strategies, diagnostic methods, and responses to both medical and surgical therapies for CVD in women. Existing guidelines for the prevention

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of heart disease in women have been endorsed by major professional associations, yet are not routinely being translated into practice, generating a marked difference between what is currently being achieved in clinical practice and what could potentially be achieved.[10]

This article was conceived at a satellite symposium held in conjunction with the 2012 Scientific Sessions of the AHA, "Women and Heart Disease: New Insights Across the Lifespan," and includes additional updates to serve as a review of the contemporary status of CV care for women. The purpose of this communication was to provide guidance on CV care for women and to encourage the establishment of focused centers for this care. These focused centers are often termed *Women's Heart Clinics* and are staffed by providers who are familiar with sex- and gender-specific CV issues, resulting in better outcomes for women at risk of and living with CVD. The care model that we have found most effective is a team-based approach, consisting of CV subspecialty physicians and certified nurse practitioners, with available multidisciplinary and collaborative consultative resources to provide nutritional, physical activity, behavioral, rehabilitative, complementary, and integrative medical, interventional, and surgical support. MEDLINE and PubMed databases were searched for literature published from September 1, 1994 to September 1, 2015. Searches included CVD in women plus the following terms: adverse pregnancy outcomes, polycystic ovary syndrome, menopause, and menopausal hormone therapy, autoimmune disorders, peripheral arterial disease. Other relevant searches included Women's Heart Clinics, peripartum cardiomyopathy, coronary microvascular dysfunction, spontaneous coronary artery dissection, apical ballooning syndrome, heart failure with preserved ejection fraction, and postural orthostatic tachycardia syndrome. Publications were classified as English-only original data, reviews, and clinical guidelines. Nonpublished data were excluded.

ARTICLE HIGHLIGHTS

- The emerging recognition of sex-based disparities in the treatment of, and survival from, heart disease has underscored a knowledge gap in the awareness, prevention, diagnosis, and treatment of heart disease in women.
- This review article provides an overview of our current understanding of cardiovascular physiology and pathophysiology across a woman's life span, identifying those cardiovascular disease entities that are either uniquely or more often seen in women. Novel approaches to the evaluation and treatment of these disorders are discussed. The identification of newly recognized cardiovascular risk factors unique to women is addressed.
- The concept of focused sex-specific cardiovascular care for women is new. We review the need for integrated multidisciplinary programs in women's heart health and disease. Unique approaches to primary and secondary preventive strategies, diagnostic testing, and treatment of ischemic heart disease in women are introduced.

ASPECTS OF CV PHYSIOLOGY UNIQUE TO WOMEN

The 2010 publication of the Institute of Medicine "Women's Health Research: Progress, Pitfalls, and Promise"[11] highlighted the fact that women's health involves both sex- and gender-specific differences. A number of factors contribute to the sex-specific differences in CVD morbidity and mortality, including biological variances due to sex chromosomes and complex effects that sex steroid hormones have on the CV system. These differences result in variations in the prevalence and presentation of CV conditions including those associated with autonomic regulation, hypertension, diabetes, and vascular and cardiac remodeling. Thus, CV conditions fall into 3 general categories: those unique to a single sex, those occurring in both sexes but with sex-specific differences in prevalence, and those that present differently in women than in men.[12] Modulation of physiological control mechanisms is most apparent in 2 conditions that are unique to women and are characterized by changes in the hormonal environment: pregnancy and menopause.

CV CONDITIONS AND PREGNANCY

CV Adaptations to Normal Pregnancy: A "Natural Stress Test" for Women

In normal pregnancy, the female body undergoes remarkable physiologic, metabolic, and hemodynamic changes needed to support fetal health.

Pregnancy has been described as a *natural stress test* on the CV system of women.[13,14] Normally, pregnancy-related hemodynamic variations are well tolerated by the mother; however, CVD may be initially manifested during pregnancy because of increased cardiac output demands that either expose the underlying genetic phenotypes or exacerbate minor preexisting CVD symptoms and conditions.

Adverse Pregnancy Outcomes and Maternal CV Risk

Women with a history of adverse pregnancy outcomes, including gestational hypertension and diabetes, preeclampsia, eclampsia, and preterm delivery, are at an increased risk of future CVD.[15-19] Pregnancy-related CV complications including gestational hypertension, preeclampsia, eclampsia, and gestational diabetes are now accepted as CV risk factors unique to women and were included as such in the 2011 AHA guidelines for the prevention of heart disease in women.[20] Gestational hypertension and preeclampsia-eclampsia confer risks of developing subsequent hypertension of 2.7 and 3.0 times, respectively.[21] Similarly, the risk of subsequent stroke is 2.3 to 3.4 times higher.[21] Women who have persistent hypertension after preeclampsia have a 2-fold risk of developing CVD.[22]

Gestational diabetes is associated with a hazard ratio of 1.71 for future CV events, mainly but not entirely attributed to the subsequent development of diabetes.[23] In a large meta-analysis,[24] it was reported that between 3% and 70% of women with a history of gestational diabetes will develop type 2 diabetes within 3 decades after pregnancy. Thus, women with gestational diabetes should be counseled on appropriate preventive strategies primarily focused on achieving and maintaining a healthy weight, with routine screening to assess for the development of diabetes.

Although cumulative evidence supports that women with pregnancy complications should be made aware of their increased risk of the subsequent development of CVD, conventional CV risk scoring algorithms do not currently include this new information. Patient-centric discussions with women must be undertaken to educate and aggressively modify and monitor traditional risk factors so as to mitigate the increased risk conferred by adverse pregnancy outcomes.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is defined on the basis of 4 criteria: (1) the development of cardiac failure in the last month of pregnancy or within 5 months of delivery; (2) the absence of an identifiable cause of heart failure (HF); (3) the absence of recognizable heart disease before the last month of pregnancy; and (4) left ventricular (LV) systolic dysfunction exhibited by echocardiography.[25] Peripartum cardiomyopathy occurs more frequently in multifetal pregnancies, multiparous women, women older than 30 years, African American women, women with preeclampsia, and women treated with tocolytic therapy.[26] The etiology of PPCM remains unknown and is a diagnosis of exclusion; therefore, all patients should be thoroughly investigated to identify alternative causes of HF.

Although relatively rare, PPCM has mortality rates between 18% and 56% (mostly because of heart failure or ventricular arrhythmias) and is recognized as an important cause of pregnancy-related deaths in the United States.[25] Improvement in LV function within 6 months of childbirth is expected in 54% of the cases.[26]

The main consideration should be maternal CV benefit. In advanced HF with hemodynamic instability, urgent delivery, irrespective of gestation, may need to be considered.[27] After delivery, the principles of managing acute HF due to PPCM are no different from those applying to acute HF due to other causes and include the use of diuretics (to manage volume overload), β-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ARBs), and hydralazine/nitrates.[28] Long-acting metoprolol is safe during both pregnancy and lactation. Newborns can be sensitive to angiotensin-converting enzyme inhibitors, and these agents should not be used during the first few weeks postpartum. ARBs have not been studied during lactation and should be avoided. Loop diuretics have also not been well studied during lactation, but thiazide diuretics appear to be safe.[29,30] Inotropes may be considered in patients with severely reduced cardiac output state; anticoagulation may be indicated if ejection fraction falls below 35%. According to the published data, heart

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transplant occurs in 0% to 11% of patients with PPCM.[28]

On the basis of postulated negative effects of prolactin subfragments related to the pathogenesis of PPCM, some have advocated avoidance of breast-feeding in mothers with PPCM.[28] However, this is highly controversial, especially given the importance of breast-feeding for infant survival in developing countries, where PPCM is more prevalent. Moreover, in a recent study,[27] breast-feeding did not affect the rate of recovery from PPCM, and a previous retrospective study[31] suggested better outcomes for lactating women than for those who did not breast-feed. Lastly, most drugs used in the management of HF are compatible with breast-feeding, but additional research in this area is needed before firm breast-feeding recommendations can be made for patients with PPCM.

At present, no consensus exists on general recommendations for the possibility of future pregnancy in women with a history of PPCM; individualized expert counseling in the setting of a high-risk pregnancy and/or Women's Heart Clinic is suggested. In a recent prospective study of 92 women with PPCM,[27] predictors of recovery included an LV diastolic diameter of less than 6 cm and an ejection fraction of more than 35% at presentation. Although women with complete recovery of LV systolic function have a better chance of having an uneventful pregnancy, there is still a 20% risk of relapse.[32] The management of women with PPCM should be a joint effort between high-risk fetal/maternal obstetricians and cardiologists with special expertise in high cardiac risk pregnant/postpartum women.

POLYCYSTIC OVARY SYNDROME: A METABOLIC DISORDER SPECIFIC TO WOMEN

Polycystic ovary syndrome is the most common endocrinopathy in women of reproductive age. The prevalence of PCOS has been estimated to be 6% to 10%, depending on which diagnostic criteria are used.[33] Classic features of PCOS include anovulatory infertility, menstrual irregularities, and hirsutism. Other important manifestations include metabolic derangements such as insulin resistance, dyslipidemia, low-grade inflammation, and a higher risk of type 2 diabetes; therefore, all women with PCOS should be screened for the presence of modifiable CV risk factors.[34]

MENOPAUSE AND THE DILEMMA OF MENOPAUSAL HORMONE THERAPY

Many women seen in Women's Heart Clinics are peri- or postmenopausal, experiencing menopausal symptoms and expressing concerns about the use of MHT and CV risk. The average age of menopause in American women is 51 years.[35] Epidemiological data have indicated the onset of coronary artery calcification (CAC) on computed tomography and are, on average, a decade later than in men, coinciding with a "10-year lag time" after menopause.[36,37] Conversely, women with hypoestrogenic states, as seen in primary ovarian failure and/or premature (occurring before the age of 40 years) menopause, experience an earlier onset of CAC and acute coronary syndromes than do their peers who experience menopause later.[38] These observations lead to the concept of a "biological plausibility" in associating female hormonal protection with the development of CVD.[39,40] The suggestion of estrogen having a protective effect on CVD and a related beneficial effect on mortality arose initially from observational studies of women receiving MHT.[41] In contrast, past randomized controlled trials (RCTs) such as the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) that examined the effects of conjugated equine estrogens in older women with overt CVD (HERS) or at usual risk of CVD (WHI) failed to exhibit protective vascular effects with MHT. However, the average age of participants in the WHI (primary prevention trial) was 63 years and the average age in the HERS (secondary prevention trial) was 67 years, over a decade beyond the average age of natural menopause. Indeed, when the WHI results were stratified by age and time since menopause, more favorable results were apparent in younger than in older women and in those who had experienced menopause more recently, especially in the conjugated equine estrogen—alone (ie, no progestogen component) arm of the study.[42,43]

Persisting evidence supports the concept of a "timing hypothesis," in which MHT may have

protective effects on CVD in younger women during the early menopausal period but may have neutral or adverse effects on vascular risk if started after the onset of menopause.[44] The majority of adverse effects seen in RCTs occurred in women who did not begin MHT until well after (>5 years) the onset of menopause whereas women who began MHT immediately after surgical menopause exhibited reductions in coronary atherosclerosis.[44]

Favorable effects of oral estrogens on CV biomarkers include modification of the composition of circulating lipoproteins (decreased low-density lipoprotein cholesterol and lipoprotein(a)[45,46] levels and increased low-density lipoprotein cholesterol levels). However, oral, but not transdermal, administration of estrogen is associated with adverse effects on blood coagulation and triglycerides. Estrogen, either oral or transdermal preparations, decreases insulin resistance[47] and lipid peroxidation,[48] inhibits intravascular accumulation of collagen, decreases vascular smooth muscle proliferation, and promotes vasodilation of blood vessels.[49] Many of the vascular effects of estrogen are mediated through vascular estrogen receptors. The failure to observe beneficial effects of MHT in women who are well past menopause may be due to age-related changes in the integrity, quantity, and distribution of downstream estrogen receptor signaling mechanisms, as well as vascular structural changes.[50]

These mixed findings from randomized hormone trials have resulted in a clinical dilemma when advising our female patients as to risks and benefits of MHT. According to the US Preventive Services Task Force,[51] MHT reduces the risk of fractures but may increase the risk of stroke, thromboembolic events, and gallbladder disease (depending on the formulation, dose, and time of initiation of the treatment). Moreover, conjugated estrogen alone (without progestogen) decreased the risk of breast cancer, whereas estrogen combined with a synthetic progestogen (medroxyprogesterone acetate) is associated with small increases in the risk of dementia and breast cancer.[51] Thus, MHT is currently not recommended to prevent chronic conditions, despite the positive effects on preventing osteoporosis, and is considered a class III indication (contraindicated) for the primary and secondary prevention of CVD in women. US Preventive Services Task Force recommendations and Food and Drug Administration indications for MHT endorse short-term (<5 years) use for the treatment of menopausal symptoms, such as vasomotor hot flashes and genitourinary syndromes (the latter may alternatively be treated with low-dose vaginal estrogen, which has minimal systemic absorption). The North American Menopause Society[52] shares similar recommendations and states that it is reasonable to prescribe MHT for women with moderate to severe vasomotor and/or other menopausal symptoms such as insomnia or mood alterations if no contraindications exist.

These guidelines make no distinction between various formulations of estrogenic products in terms of active components, dose, or mode of delivery. Given the complexities in metabolism of estrogen, it is indeed difficult to apply the various recommendations to each woman, making MHT one of the most complex health care decisions for menopausal symptom management, magnified by an expanded assortment of pharmacological options. Indeed, newer formulations and lower doses of products now used in clinical practice may not provide appropriate comparisons with those used in past observational studies or RCTs such as the WHI and HERS. Several contemporary studies have aimed to address this dilemma. The Kronos Early Estrogen Prevention Study conducted in recently (<3 years) menopausal women comparing placebo with transdermal or oral conjugated equine estrogen, in conjunction with oral micronized progesterone, did not find adverse effects on the vascular end points of carotid intima media thickness or CAC after 4 years.[53] The Early versus Late Intervention Trial with Estradiol is another recent study that provides further support for the "timing hypothesis." Preliminary data have indicated a slower progression of atherosclerosis measured by carotid intima media thickness in early menopausal women randomized to receive oral 17β-estradiol than that in women randomized to placebo. These differences were not seen in older women.[54] In conclusion, the role of MHT in relation to the progression of CVD remains debated. Additional research is needed to assess, through long-term follow-up in recently menopausal women, the consequences of different doses, formulations, and delivery modes of products currently used in clinical practice.

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ISCHEMIC HEART DISEASE IN WOMEN

Sex- and gender-specific CVD research has led to a new understanding of the pathophysiology of coronary disease in women, which includes, but is not limited to, our conventional understanding of atherosclerosis. Ischemic heart disease (IHD) in women includes not only atherosclerotic obstructive coronary artery disease (CAD) but also an expanded spectrum of coronary disease, including CMD, endothelial dysfunction, vasomotor abnormalities, SCAD, and stress-induced cardiomyopathy.[3]

Certainly, there are marked differences in the prevalence, incidence, and burden of IHD between women and men.[55] The 3 most important characteristics are as follows: women have (1) a higher prevalence of angina, (2) a lower burden of obstructive CAD on angiography, and (3) a poorer prognosis than do men.[56] In addition, current risk scores, based on acute coronary syndrome thresholds determined in predominantly male populations, do not accurately predict risk in women, indicating the need for sex-specific biomarker ranges and risk stratification tools to improve the diagnosis, treatment, and follow-up in female populations.[57]

"Female-Specific" IHD

According to the Women's Ischemia Syndrome Evaluation study, two-thirds of women failed to exhibit typical angiographic findings of obstructive coronary disease during clinically ordered coronary angiography for signs and symptoms of ischemia and often exhbited CMD, yet these symptomatic women had poorer outcomes.[58] Coronary computed tomography angiography in women has confirmed lower rates of obstructive CAD and also smaller coronary artery diameters than those in men, despite adjustment for body surface area.[59] The pathophysiology of IHD can vary, depending on the portion of the coronary vasculature affected. Ischemic heart disease that mainly affects the epicardial coronary arteries includes CAD, coronary vasospasm, and SCAD. In contrast, CMD refers to dysfunction in the smaller coronary arterioles that can cause chronic ischemia, acute myocardial infarction (MI), or stress-induced cardiomyopathy (also known as *apical ballooning syndrome*, *takotsubo cardiomyopathy*, and *broken heart syndrome*). The risk factor profile for the development of ischemic disease should include risk factors unique to women such as ovarian function, MHT, and pregnancy history in addition to traditional risk factors.

Coronary Vasospasm

Coronary vasospasm has also been implicated as a cause of MI or injury in the absence of obstructive CAD. Although coronary spasm usually occurs in the epicardial vessels, coronary microvascular spasm can also occur.[60] Its pathogenesis is likely multifactorial, involving endothelial dysfunction and smooth muscle hyperreactivity, which may be initiated by such modifiable environmental factors such as smoking. As smoking cessation removes one of the triggers for variant angina and leads to a significant decrease in the frequency of episodes, at least in the short term, smoking cessation should be highly encouraged.[61] Traditional antiischemic drugs are the first step in medical treatment. Calcium channel blockers and long-acting nitrates are effective as long-term therapies for variant angina, preventing vasoconstriction and promoting vasodilation in the coronary vasculature Short-acting nitrates can also be used in the short term to manage angina attacks. The angiographic confirmation of coronary vasospasm may be challenging and often requires provocative testing because of the transient nature of the condition.

Stress-Induced Cardiomyopathy

Stress-induced cardiomyopathy was first reported in Japan in 1990 and is characterized by transient systolic and diastolic LV dysfunction. In its acute phase, the clinical presentations, biomarker profiles, and electrocardiographic findings can mimic an MI because of obstructive CAD, but normal coronary arteries are seen on coronary angiography. The majority of patients presenting with this condition are postmenopausal women (mean age, 61-76 years),[62] and in a recently published large international registry,[63] they were found to more likely present with neurologic and psychiatric comorbidities. The accompanying symptoms of chest pain and dyspnea are often, yet not always, preceded by intense physical or emotional stress.[63,64] Although a hallmark feature of this acute heart failure syndrome is usually spontaneous improvement and resolution of LV dysfunction

within several months, substantial morbidity and mortality can occur.

Spontaneous Coronary Artery Dissection

Spontaneous coronary artery dissection, previously considered rare, is emerging as an important cause of MI and sudden death, especially in young women. Spontaneous coronary artery dissection is a strongly female predominant condition; approximately 80% of the affected are women, and conventional CVD risk factors are not typically present. Although true prevalence is uncertain, in reports that have used careful angiographic evaluation or advanced intracoronary imaging to detect intramural hematoma and more subtle dissections, incidence has been reported to be as high as 1% to 4% of acute coronary syndromes overall,[65,66] a factor in up to 30% of MIs in women younger than 50 years, and is the most common cause of pregnancy-associated MI.[67] Limited data exist on the pathogenesis and natural history of SCAD, but recent studies have found associations with fibromuscular dysplasia and other systemic vasculopathies, many of which also have a female predominance.[68,69] Other associations include extreme physical or emotional stress and, less commonly, genetic mutations such as Ehlers-Danlos syndrome type IV or Loeys-Dietz syndrome. Familial cases have also been reported.[70] Although presenting symptoms are similar to those of atherosclerotic MI, diagnosis is often delayed and the optimal approach to short- and long-term management of SCAD is different.[71] It is important to make an accurate diagnosis because an initial invasive treatment strategy of percutaneous coronary revascularization in SCAD is associated with reduced technical success and more frequent complications than in atherosclerotic coronary obstructions. Vessel healing is common,[72,73] and as a result, those treated with coronary artery bypass grafting have a high rate of subsequent bypass graft failure, likely because of competitive flow from the healed artery. Thus, in stable patients with SCAD and thrombolysis in myocardial infarction flow grade greater than 0 in the involved vessel, medical stabilization without revascularization is usually the preferable short-term treatment strategy.[74]

Although survival and LV function in women after SCAD are typically better than those after atherosclerotic MI, 10-year SCAD recurrence rates have been reported to be as high as 29%, supporting a role of appropriate longitudinal follow-up.[72] To date, the most appropriate long-term therapy has not yet been determined, but should not be assumed to be the same as secondary prevention of atherosclerotic MI. Indeed, a retrospective evaluation of 87 patients with SCAD identified an unexpected increase in recurrent SCAD in those taking statins.[72] As such, statins are not recommended unless concomitant clinical characteristics support guideline-indicated therapy for CVD prevention.[72] Cardiac rehabilitation has been shown to be safe and effective[75] and should be recommended. Reproductive counseling considerations are an important part of care, because most patients are premenopausal women for whom pregnancy and hormonal contraception is not advised.[76] Specialized centers such as a Women's Heart Clinic can provide a referral base for genetic and vascular screening and counseling.

PERIPHERAL ARTERIAL DISEASE IN WOMEN

Atherosclerotic lower extremity PAD impairs walking performance[77] and is associated with not only a reduced quality of life[78,79] but also a markedly increased risk of CVD events and mortality.[80] Although male sex was traditionally believed to be a risk factor for PAD, recent studies[81,82] have reported compelling results on the high prevalence of PAD in women. At the extremes of ages <40 and >80 years), women represent a greater estimated population burden of PAD, affecting the lower extremities.[81] Moreover, PAD in women may be asymptomatic,[83] or present with atypical symptoms,[84] and is associated with comorbidities or situations more common or exclusively found in the female sex, such as the use of oral contraceptives[85] and a history of gestational hypertension.[86]

The identification of patients with PAD on the basis of symptoms alone is misleading because only a minority (~10%) of patients will have *classic intermittent claudication*, defined as cramping calf discomfort that occurs with exertion and is relieved by rest.[87] Despite the often lack of traditional "symptoms" of intermittent claudication, women have a greater functional impairment than do men with reduced walking distance and speed.[78]

Lower extremity PAD can be easily diagnosed on the basis of a noninvasive ankle-brachial index (ABI).[88] An ABI of less than

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0.90 is abnormal and indicates the presence of PAD, whereas an ABI of 0.90 to 1.0 is borderline for PAD[88] but represents an increased risk of CVD.[81] Likewise, when more significant PAD is present (ABI<0.70), women are at a higher risk of MI and CV death than are men.[81] Overall, mortality is higher in women with PAD than in men (58% vs 42%),[1] as well as in-hospital mortality is higher after revascularization procedures.[89,90] The American Heart Association/American College of Cardiology guidelines[91] recommend screening for PAD in all adults older than 65 years, or if there is a history of any tobacco use or diabetes, screening should commence earlier (at >50 years). However, the US Preventive Services Task Force gives screening for asymptomatic PAD an indeterminate recommendation.

OTHER CV ENTITIES OBSERVED MORE OFTEN IN WOMEN

Heart Failure

Although heart failure can manifest with reduced or preserved ejection fraction, women are more likely than men to develop heart failure in the setting of preserved left ventricular ejection fraction. Differences in prevalence of comorbidities also exist between men and women with HFpEF. Women are generally older and have a higher likelihood of having diabetes and systemic hypertension.[92] Estrogen receptors in the heart modulate hypertrophy and subsequently the progression of HF.[93] It is hypothesized that activational and organizational effects of hormones on cardiac remodeling that are adaptive to increases in cardiac output during pregnancy may be detrimental later in life, possibly contributing to the subsequent pathophysiology observed in HFpEF.[94] These unique differences in the composition of vascular and cardiac extracellular matrices may contribute to the higher incidence of HFpEF in women, a poorly understood entity without focused therapy, and in great need of additional research. There is no specific treatment of HFpEF. Blood pressure control concordant with existing hypertension guidelines remains the most important recommendation in treating patients with HFpEF (recommendation class I-B); in addition, the use of diuretics to relieve volume overload symptoms (recommendation class I-C), coronary revascularization for CAD with angina/ischemia despite optimal medical therapy (recommendation class IIa-C), management of atrial fibrillation (AF) (recommendation class IIa-C), and ARBs might also be considered to reduce hospitalizations (recommendation class IIb-B). Unfortunately, trials of specific agents to treat HFpEF (Phosphdiesterasr-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure [RELAX] trial) have not reported significant effect.[95] Obstructive sleep apnea and obesity are commonly associated with HFpEF, contributing to a proinflammatory state and cardiac hypertrophy.[96] Screening overnight oximetry is useful in guiding the need for formal sleep study consultations.

Postural Orthostatic Tachycardia Syndrome

Postural orthostatic tachycardia syndrome is a clinical syndrome defined by a 6 months or more of history of (1) heart rate increases by 30 beats/min or more from supine to standing, (2) symptomatic exacerbation upon standing and improvement with recumbence, and (3) absence of other overt causes of orthostatic symptoms or tachycardia.[97] The overwhelming majority of patients with POTS are women of childbearing age.[98] The etiology is multifactorial, and no clear cause has been identified. Common symptoms include light-headedness, blurred vision, weakness, cognitive difficulties, and fatigue and are often accompanied by palpitations, shortness of breath, syncope, or gastrointestinal symptoms. Proposed pathophysiological mechanisms include peripheral denervation, hypovolemia, venous pooling, β-receptor supersensitivity, psychological mechanisms, and impairment of brain stem regulation.[99] Therapies targeting hypovolemia and excess sympathetic nervous system activation may help relieve symptoms.[97] Exercise training and reconditioning is emerging as an important strategy to improve the quality of life of these women.

Atrial Fibrillation and Increased Stroke Risk

The incidence of AF is lower in women than in men[100]; however, women who have AF show a different prognosis, with a higher incidence of stroke and a higher mortality rate than those observed in men.[100] Risk assessment of women for stroke should take into account age- and sex-specific differences. The $CHADS_2$-Vasc

score is an extension of the $CHADS_2$ score that adds an extra point for female sex. In the 2014 American Heart Association/American Stroke Association guidelines for the prevention of stroke in women,[101] a summary of the current evidence and gaps for stroke prevention focused on risk factors that are either unique to or more common in women than in men, including reproductive factors, migraine with aura, obesity, and metabolic syndrome. Studies have found that female sex is substantially associated with stroke, especially in women 75 years and older,[102] even in the presence of adequate anticoagulation.[100] Therefore, active screening for AF, especially in women older than 75 years, in primary care settings using vital sign assessment followed by confirmatory electrocardiogram when heart rate irregularity is detected is recommended (class I; level of evidence B).[101] Given that AF increases with age and that women have a higher life expectancy, it is anticipated that there will be an increasing number of elderly women with AF. At present, women with AF are slightly less likely to receive anticoagulation therapy than are men (88% vs 89.7%; adjusted odds ratio, 0.93; 95% CI, 0.88-0.98).[103]

The bleeding risk while receiving anticoagulation treatment is similar or possibly lower than that in men, and when appropriate stroke risk stratification indicates the need for anticoagulation (in the absence of significant contraindications), women should receive treatment. Women are frequently affected by several modifiable risk factors for stroke, such as hypertension, obesity, and metabolic syndrome,[104] and controlling these risk factors will potentially help to optimize stroke prevention.

Autoimmune Disorders: An Emerging Risk Factor for CVD

Numerous population studies have found a sex-specific association between inflammatory diseases and increased mortality, mainly as a consequence of CVD.[105,106] For example, autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are far more prevalent in women (RA has a 4% prevalence in women vs 2% in men and SLE has a 10:1 predominance in women) and are associated with an increased risk of CV death,[107,108] proposed to be related to accelerated atherogenesis associated with chronic inflammation.[109,110] The increase in CVD mortality observed in patients with RA and SLE occurs even in the absence of traditional CV risk factors. Interestingly, disease-modifying antirheumatic drugs appear to reduce the progression of atherosclerosis in patients with RA.[111-113] Traditional risk factors for CVD, when present, tend to be underrecognized and undertreated in this population.[114] Perplexing though is the fact that some of these risk factors, such as hyperlipidemia and obesity, appear to impart paradoxical risk, supporting the concept that the chronic inflammatory burden may alter the effect of traditional risk factors.[115,116] It has been recognized that CV risk scoring systems underestimate the burden of CV risk in patients with RA and SLE, and an empirical "EULAR" (European League Against Rheumatism) multiplier of 1.5 has been suggested.[117,118]

It is extremely important for rheumatologists and cardiologists to recognize autoimmune disorders such as RA and SLE as significant risk factors for CVD and to apply this knowledge to patient care.[119] Because women are more often afflicted with these disorders, their optimal CV care especially demands an understanding of this amplified risk.

DISPARITIES IN CVD TREATMENT IN WOMEN

Sex-specific differences in underlying physiological mechanisms affect not only manifestations of CVD but also the response to treatment. Treatment of hypertension is generally more effective in women, however, at older ages blood pressure control is more likely to be achieved in men than in women. Thus, stroke risk may not be managed as efficiently in women. Antiarrhythmic drugs have different effects, interactions, and need for dosing adjustments in women than in men.[120,121] Similarly, RCTs of pharmacological strategies for antiplatelet therapies have found higher rates of bleeding complications in women,[122] suggesting the need for dose adjustments according to sex. Unfortunately, a significant paucity of data exists in the area of sex-specific CV pharmacological recommendations, in large part because of a lack of both women enrollees in clinical trials and sex-specific data analysis and reporting.

Although the current recommended treatment for atherosclerotic CAD is similar for both

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men and women, women are less likely to receive guideline-based therapy for chronic stable CAD or acute coronary syndromes.[123-125] Moreover, after a CVD diagnosis has been made, women are less likely to be referred for cardiac rehabilitation.[126,127]

In recent years, there has been increasing research and information related to sex-specific differences in traditional treatments of CVD. For example, aspirin shown to be efficacious in the primary prevention of MI in men older than 45 years may not be so in women older than 65 years,[128] although it is efficacious for stroke prevention in younger women.

Many studies have looked at the benefits of statin therapy in women. Women have similar low-density lipoprotein–lowering effects and reduction in myocardial reinfarction occurrence as observed in men, when exposed to statin therapy for secondary prevention.[129] Thus, statin therapy should be used for the secondary prevention of CAD in both men and women.[130] Lastly, women tend to benefit more than do men from the use of β-blockers.[131] However, because evidence is lacking, there are no specific guidelines for the management of women with signs and symptoms of ischemia but no obstructive CAD, who comprise approximately 20% of the 20.8 million Americans with IHD.[132] Even more challenging, and less well studied, is why fewer women undergo CV revascularization interventions (percutaneous and surgical) as well as device implantation as compared with men. Intriguing is the observation that women may indeed benefit greatly from interventions, as seen with the effect of cardiac resynchronization therapy, through which women experienced greater recovery of LV systolic function than did men.[133]

Clinical studies indicate that the perioperative risk of carotid stenting compared with carotid endarterectomy may be higher in women than in men. The studies disagree as to whether the perioperative risk associated with carotid artery stenting is more prevalent in symptomatic or asymptomatic women. Moreover, in terms of the management of carotid stenosis, carotid endarterectomy (CEA) is performed less often in women, likely because of the lower incidence of high-grade symptomatic stenosis.[134] A retrospective cohort study of patients identified as having had either a transient ischemic attack or symptomatic carotid stenosis found that women were less likely to undergo CEA.[134] In patients who underwent CEA, the time to surgery was longer in women whereas the current recommendations are to perform CEA within 2 weeks of symptoms of transient ischemic attack or mild stroke.[101,134]

Lastly, in regard to elderly women with symptomatic severe aortic stenosis, female sex is associated with better short- and long-term survival after transcatheter aortic valve replacement (TAVR), although women present more vascular and stroke complications and major/life-threatening bleeds.[135] The PARTNER 1A subgroup analysis revealed a greater survival benefit with TAVR relative to surgery in women (risk ratio, 0.68; 95% CI, 0.44-1.04) than in men (risk ratio, 1.17; 95% CI, 0.84-1.63). Within the TAVR arm, mortality was lower in women (18.4%) than in men (28.4%) (P=.03); after surgical aortic valve replacement, the mortality rates in men (24.2%) and women (27.2%) were similar.[135]

CONCLUSION

The CV health of women is strongly affected by sex-specific factors, including hormonal and metabolic disorders, pregnancy-related adverse CV outcomes, menopausal status, and associated autoimmune diseases. Women are predisposed to certain types of CVD, including CMD, SCAD, PAD, HFpEF, POTS, and apical ballooning syndrome. Awareness and recognition that women are at a significant risk of CVD is crucial to provide appropriate care and avoid reflexive misattribution of symptoms to noncardiac causes. The medical community in general, and women specifically, lack information on CV health and disease in women, making it less likely that they receive guidance on preventive strategies and referral for needed diagnostic testing, treatment, and cardiac rehabilitation. The public health cost of misdiagnosed or undiagnosed cardiac disease in women is significant. Moreover, although awareness of heart disease as the leading cause of death in women is increasing, minority and younger women are less often aware, resulting in inadequate or nonexistent medical care and decreased likelihood of adopting necessary lifestyle changes.

Specialized centers of focused CV care for women, such as can be achieved in Women's Heart Clinics, are uniquely capable of identifying, characterizing, treating, and preventing heart disease in women, while also addressing important research gaps and developing new diagnostic tools and treatments. Women's Heart Clinics have the potential to help correct gender inequalities as well as educate women on how to recognize CV disease symptoms and entities either unique to or more common in women. The disparities in CVD treatment and survival rates between men and women clearly indicate the need for integrated multidisciplinary women's heart programs to provide sex-specific CV care for those women with existing CVD and those at risk of developing it. Cardio-oncology and cardio-rheumatology subspecialty focused clinics have been set up in conjunction with Women's Heart Clinics because of the increased frequency of women presenting with conditions that are recognized to occur more commonly in women (eg, breast cancer and autoimmune disorders), which have a CV effect.

Very few clinics offered focused cardiac care for women before 2000, and the concept of their formation as Women's Heart Clinics or Women's Heart Centers was met with hesitation from many cardiologists. However, the need and value of this specialized care for women is now recognized, and such clinics are present in virtually every major city and many teaching hospitals. Cardiologists in training are frequently seeking special training and experience in the care of women's hearts at teaching hospitals that offer these programs. Importantly, road maps to integrate sex- and gender-based evidence into medical and interprofessional education are needed for effective translation into better outcomes for all patients. Lastly, Women's Heart Clinics may also serve as centers to organize and communicate with lay advocates for female heart health who serve as invaluable resources to bridge the gap between health care services and the community.

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Abbreviations and Acronyms: **ABI** = ankle-brachial index; **AF** = atrial fibrillation; **AHA** = American Heart Association; **ARB** = angiotensin II receptor blocker; **CAC** = coronary artery calcification; **CAD** = coronary artery disease; **CEA** = carotid endarterectomy; **CMD** = coronary microvascular dysfunction; **CV** = cardiovascular; **CVD** = cardiovascular disease; **HERS** = Heart and Estrogen/progestin Replacement Study; **HF** = heart failure; **HFpEF** = heart failure with preserved ejection fraction; **IHD** = ischemic heart disease; **LV** = left ventricular; **MHT** = menopausal hormone therapy; **MI** = myocardial infarction; **PAD** = peripheral arterial disease; **PCOS** = polycystic ovary syndrome; **POTS** = postural orthostatic tachycardia syndrome; **PPCM** = peripartum cardiomyopathy; **RA** = rheumatoid arthritis; **RCT** = randomized controlled trial; **SCAD** = spontaneous coronary artery dissection; **SLE** = systemic lupus erythematosus; **TAVR** = transcatheter aortic valve replacement; **WHI** = Women's Health Initiative

Correspondence: Address to Sharon L. Mulvagh, MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (smulvagh@mayo.edu).

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