

This Review is in a thematic series on **Cardiovascular Disease in Women**, which includes the following articles:

**Cardiovascular Disease in Women: Clinical Perspectives**

The Importance of Biological Sex and Estrogen in Rodent Models of Cardiovascular Health and Disease

## Cardiovascular Disease in Women Clinical Perspectives

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**Abstract:** Cardiovascular disease continues to be the leading cause of death among women in the United States, accounting for  $\approx 1$  of every 3 female deaths. Sex-specific data focused on cardiovascular disease have been increasing steadily, yet is not routinely collected nor translated into practice. This comprehensive review focuses on novel and unique aspects of cardiovascular health in women and sex differences as they relate to clinical practice in the prevention, diagnosis, and treatment of cardiovascular disease. This review also provides current approaches to the evaluation and treatment of acute coronary syndromes that are more prevalent in women, including myocardial infarction associated with nonobstructive coronary arteries, spontaneous coronary artery dissection, and stress-induced cardiomyopathy (Takotsubo Syndrome). Other cardiovascular disease entities with higher prevalence or unique considerations in women, such as heart failure with preserved ejection fraction, peripheral arterial disease, and abdominal aortic aneurysms, are also briefly reviewed. Finally, recommendations for cardiac rehabilitation are addressed. (*Circ Res.* 2016;118:1273-1293. DOI: 10.1161/CIRCRESAHA.116.307547.)

**Key Words:** acute coronary syndromes ■ cardiovascular disease ■ primary prevention ■ risk factors ■ women

Cardiovascular disease (CVD) remains the leading cause of death in women and, according to the most recently released United States statistics, accounted for 398 086 female deaths in 2013.<sup>1</sup> For the past 3 decades, dramatic declines in heart disease mortality for both men and women have been observed, especially in the >65 years age group. However, recent data suggest stagnation in the improvements in incidence and mortality of coronary heart disease, specifically among younger women (<55 years).<sup>2</sup> It is imperative that we understand the mechanisms that contribute to worsening risk factor profiles in young women to reduce future atherosclerotic cardiovascular disease (ASCVD) morbidity and mortality. Increased recognition of the prevalence of traditional ASCVD risk factors, and their differential impact in women, as well as emerging, nontraditional risk factors unique to or more common in women, contribute to new understanding of mechanisms leading to these worsening outcomes for women (Figure 1). Finally, diagnosis of acute coronary syndromes

(ACS) is often challenging in women, especially young women, and it is important to recognize differences in the signs and symptoms at presentation to improve patient management and outcomes.

Awareness of CVD as the primary cause of mortality in women has been slowly increasing. In 1997, only 30% of American women surveyed were aware that CVD was the leading cause of death in women; this increased to 54% in 2009 and has subsequently plateaued when last surveyed in 2012.<sup>3</sup> Women are less likely to receive preventive treatment or guidance, such as lipid-lowering therapy, aspirin (ASA), and therapeutic lifestyle changes, than are men at similar ASCVD risk.<sup>4,5</sup> When medications are prescribed, treatment is less likely to be aggressive or to achieve optimal effects, for example, women with hypertension are less likely to have their blood pressure (BP) at goal, and hyperlipidemic women, especially those with coexisting diabetes mellitus (DM), are less likely to be treated with statins to lower low-density

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**Nonstandard Abbreviations and Acronyms**

<b>AAA</b>	abdominal aortic aneurysms
<b>ACC</b>	American College of Cardiology
<b>ACS</b>	acute coronary syndromes
<b>AF</b>	atrial fibrillation
<b>AHA</b>	American Heart Association
<b>ASA</b>	aspirin
<b>ASCVD</b>	atherosclerotic cardiovascular disease
<b>BP</b>	blood pressure
<b>BSO</b>	bilateral salpingo-oophorectomy
<b>CAC</b>	coronary artery calcium
<b>CAD</b>	coronary artery disease
<b>CI</b>	confidence interval
<b>CMD</b>	coronary microvascular dysfunction
<b>CR</b>	cardiac rehabilitation
<b>CT</b>	computed tomography
<b>CVD</b>	cardiovascular disease
<b>DM</b>	diabetes mellitus
<b>ELITE</b>	Early Versus Late Intervention Trial With Estradiol
<b>EULAR</b>	European League Against Rheumatism
<b>HERS</b>	Heart and Estrogen/Progestin Replacement Study
<b>HFpEF</b>	heart failure with preserved ejection fraction
<b>HR</b>	hazard ratio
<b>IHD</b>	ischemic heart disease
<b>JNC8</b>	Eighth Joint National Committee
<b>JUPITER</b>	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin
<b>KEEPS</b>	Kronos Early Estrogen Prevention Study
<b>LDL</b>	low-density lipoprotein
<b>MHT</b>	menopausal hormone therapy
<b>MI</b>	myocardial infarction
<b>NHIS</b>	National Health Interview Survey
<b>PAD</b>	peripheral arterial disease
<b>PPCM</b>	peripartum cardiomyopathy
<b>PROMISE</b>	Prospective Multicenter Imaging Study for Evaluation of Chest Pain
<b>PTD</b>	preterm delivery
<b>ROMICAT</b>	Rule Out Myocardial Infarction using Computer Assisted Tomography
<b>SCAD</b>	spontaneous coronary artery dissection
<b>T2DM</b>	type 2 DM
<b>USPSTF</b>	United States Preventive Services Task Force
<b>VIRGO</b>	Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients
<b>WHI</b>	Women's Health Initiative
<b>WISE</b>	Women's Ischemia Syndrome Evaluation

lipoprotein (LDL) cholesterol.<sup>6–8</sup> Also, cardiac rehabilitation (CR) is underused,<sup>9–11</sup> with women being 55% less likely to participate in CR than men,<sup>9</sup> the reasons for which are multifactorial, but partly as a result of lack of referral by their treating physician.<sup>12</sup>

Coronary artery disease (CAD) can be defined as vascular disease limited to the epicardial coronary arteries and should not be confused with ischemic heart disease (IHD), which includes ischemic disease originating in the coronary arteries,

the microcirculation, or from an imbalance in myocardial oxygen supply and demand. Particularly in women, use of the terminology IHD has advantages over CAD because of the lower prevalence of anatomically obstructive CAD, yet greater rates of myocardial ischemia and associated mortality in females, compared with similarly aged males.<sup>13–17</sup> The Women's Ischemia Syndrome Evaluation (WISE) and other related studies have implicated abnormal coronary reactivity,<sup>18</sup> microvascular dysfunction,<sup>19</sup> and plaque erosion/distal microembolization<sup>20,21</sup> as causative to female-specific IHD pathophysiology. Women with IHD have a persistent suboptimal treatment pattern, higher mortality, and poorer CVD outcomes compared with men.<sup>22–25</sup> In an environment where cardiologists have traditionally been trained to equate IHD with angiographically defined obstructive CAD, failure to recognize those unique aspects of IHD in women has contributed to less aggressive lifestyle and medical preventive interventions in women relative to men and may contribute to the observed sex-based mortality gap. Thus, a paradigm shift beyond solely an anatomic description of obstructive CAD is needed to translate into earlier IHD risk detection and treatment for women.

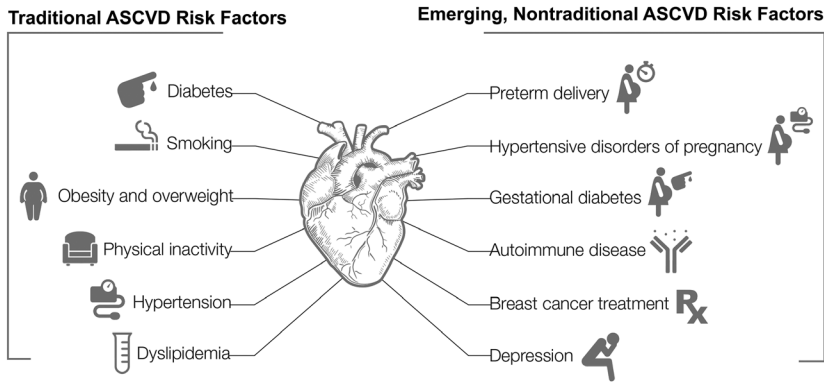
Biological variances among women and men are called sex differences and are frequently reproducible in animal models. Sex differences in the cardiovascular system are as a result of differences in gene expression from the sex chromosomes, which may be further modified by sex differences in hormones, resulting in sex-unique gene expression and function. These differences result in variations in prevalence and presentation of cardiovascular conditions, including those associated with autonomic regulation, hypertension, DM, and vascular and cardiac remodeling. In contrast, gender differences are unique to the human and arise from sociocultural practices (behaviors, environment, lifestyle, nutrition). To facilitate quality improvement in sex- and gender-specific care, this review will examine the latest clinical perspectives on CVD in women, focusing on novel and unique aspects of cardiovascular health in women and sex and gender differences as they relate to clinical practice in the prevention, diagnosis, and treatment of CVD. This review will also provide current approaches to the evaluation and treatment of ACS and other CVD entities that have greater prevalence or unique considerations in women.

## Traditional ASCVD Risk Factors in Women

### Diabetes Mellitus

More than 13.4 million US women have a diagnosis of DM, and 90% to 95% of these women have type 2 DM (T2DM).<sup>26</sup> The rate of T2DM in Hispanic women is more than double when compared with non-Hispanic white women (12.7% versus 6.45%, respectively).<sup>27</sup> The increasing prevalence of T2DM is concerning because it is a potent risk factor for ASCVD and has long been recognized to confer greater risk for ASCVD death in women compared with men (Table 1).<sup>28</sup>

There is a 3-fold excess fatal CAD risk in women with T2DM compared with nondiabetic women (95% confidence interval [CI], 1.9–4.8).<sup>29</sup> Women with T2DM have a higher adjusted hazard ratio (HR) of fatal CAD (HR=14.74; 95% CI, 6.16–35.27) compared with T2DM men (HR=3.77; 95% CI,









**Figure 1. Traditional and nontraditional atherosclerotic cardiovascular disease (ASCVD) risk factors in women.** Increasing among women and more impactful traditional ASCVD risk factors include diabetes mellitus, hypertension, dyslipidemia, smoking, obesity, and physical inactivity. Emerging, nontraditional ASCVD risk factors include preterm delivery, hypertensive pregnancy disorders, gestational diabetes mellitus, breast cancer treatments, autoimmune diseases, and depression.

2.52–5.65).<sup>30</sup> In a meta-analysis of over 850 000 individuals, the relative risk for CVD was 44% greater in women with DM than in similarly affected men.<sup>31</sup>

The presence of DM thus represents an imperative for aggressive CVD prevention strategies in women. Growing evidence suggests that diabetic women have more adverse

**Table 1. Traditional ASCVD Risk factors: Sex-Based Differences and Recommendations**

Risk Factor	Sex-Based Differences	Recommendation
 Diabetes mellitus	DM: women with DM have a 3-fold excess risk of fatal CAD compared with nondiabetic women.	Both women and men with DM should have aggressive management of their CVD risk factors. Observational studies suggest that women may require greater frequency/intensity of physical activity than men to reduce CVD events.
	MI: earlier occurrence and higher mortality in diabetic women compared with diabetic men. Lower revascularization rates in diabetic women compared with diabetic men.	
	HF: diabetic women have a higher risk of developing HF compared with diabetic men.	
	Stroke: DM is a stronger risk factor for stroke in women compared with men.	
	PAD: DM is a stronger risk factor for the development of claudication in women compared with men. Decreased long-term survival in women undergoing revascularization and increased postsurgical mortality are seen in diabetic women with PAD compared with diabetic men with PAD.	
 Hypertension	Higher prevalence of HTN in women over age 60 than in men.	Encourage optimal BP through diet, exercise, and avoidance of excess alcohol and sodium.
	Less well controlled in women than men.	Pharmacotherapy is indicated when blood pressure is >140/90 mm Hg.
 Dyslipidemia	Among women, dyslipidemia has the highest PAR at 47.1%, compared with all other known risk factors for CVD.	Statins are equally effective for secondary CVD prevention in both men and women; however, statins may contribute to a greater likelihood of developing DM and myalgias in women. Statins are recommended for primary prevention in women; however, randomized trial evidence in women is limited.
	Atheroma regression and LDL lowering may be even greater among women on statins than in men.	
 Obesity	The impact of obesity on the development of CAD appears to be greater in women than in men. In the Framingham Heart Study, obesity increased the risk of CAD by 64% in women compared with 46% in men.	Women should maintain or lose weight through an appropriate balance of physical activity and diet. Women who need to lose weight should be advised to accumulate a minimum of 60 to 90 min of at least moderate-intensity physical activity preferably all days of the week.
 Physical inactivity	The prevalence of inactivity and sedentary behaviors is higher among women than men.	Overwhelming evidence indicates that regular physical activity is one of the most powerful health-promoting practices that clinicians can recommend for patients.
		Women should be advised to accumulate at least 150 min/wk of moderate exercise, 75 min/wk of vigorous exercise, or an equivalent combination.
 Smoking	In a recent meta-analysis by Huxley et al, it was reported that in all age groups with the exception of the youngest (30–44 y), women had a significant 25% increased risk for CAD conferred by cigarette smoking compared with men	Smoking is associated with a decade of lost life, and cessation reduces that loss by about 90%.
		Women should be advised not to smoke and to avoid environmental tobacco smoke. Provide counseling at each encounter, nicotine replacement, and other pharmacotherapy/behavioral therapy as indicated.

BP indicates blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; IHD, ischemic heart disease; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral arterial disease; and PAR, population attributable risk.

ASCVD risk factor status than diabetic men, consisting of impaired endothelium-dependent vasodilation, a hypercoagulable state, worse atherogenic dyslipidemia, and more metabolic syndrome.<sup>32–34</sup> As the detrimental effects of glucose already occur at glycemic levels below the threshold for the diagnosis of DM, the transition from normoglycemia to impaired glucose tolerance and overt DM may be more detrimental in women than in men. Accumulating evidence suggests that these adverse changes in metabolic and vascular risk factor profile in prediabetic individuals are greater in women than they are in men.<sup>35,36</sup>

### Smoking

Although there are fewer adult ( $\geq 18$  years) women smokers (15% versus 19% of men),<sup>37</sup> a recent meta-analysis reported that in all age groups, with the exception of the youngest (30–44 years), women had a 25% increased risk for CAD conferred by cigarette smoking compared with men.<sup>38</sup> The combination of smoking with oral contraceptive use has a synergistic effect on risk of acute myocardial infarction (MI), stroke, and venous thromboembolism.<sup>39,40</sup>

### Obesity and Overweight

More than 2 in 3 adults in the United States are considered to be overweight or obese, and the prevalence of obesity is higher among women than among men (Figure 2).<sup>45</sup> The impact of obesity on the development of CAD seems to be greater in women than in men. In the Framingham Heart Study, obesity increased the relative risk of CAD by 64% in women, as opposed to 46% in men.<sup>46</sup> Weight gain during adult years is highly related to developing a greater ASCVD risk factor burden, and this has been observed with relatively modest weight gain in prospective studies, such as the Framingham Offspring Study.<sup>47</sup>

### Physical Inactivity

The Physical Activity Guidelines for Americans recommend that adults get at least 150 minutes/week of moderate-intensity aerobic activity, such as walking, or 75 minutes/week of

vigorous-intensity aerobic activity, such as jogging, or a combination of both. Muscle strength training activities are also recommended on  $\geq 2$  days per week.<sup>48</sup> According to data from a 2011 National Health Interview Survey (NHIS) in adults, inactivity was higher among women than men (33.2% versus 29.9%, age-adjusted) and increased with age from 26.1% to 33.4%, 40.0%, and 52.4% among adults 18 to 44, 45 to 64, 65 to 74, and  $\geq 75$  years of age, respectively.<sup>49</sup> Observational data demonstrate an association between higher levels of physical activity and lower rates of many chronic diseases, including CVD, as well as enhanced longevity. Furthermore, an inverse dose–response relation exists, with higher levels of activity associated with commensurately lower rates of ASCVD in a curvilinear fashion.<sup>50,51</sup>

### Hypertension

Endogenous estrogens maintain vasodilation and contribute to BP control in premenopausal women. Women develop hypertension about a decade after men, becoming more prevalent in elderly women than in elderly men.<sup>52</sup> No sex differences in the clinical manifestation of hypertension, outside of pregnancy-related hypertension, have been described.<sup>53</sup> Hypertension is often poorly controlled in older women; only 23% of women versus 38% of men  $>80$  years have a BP  $<140/90$  mm Hg.<sup>54</sup> There is currently no evidence that antihypertensive treatments differentially affect BP response, but many trials of antihypertensive agents do not report sex-specific analysis for efficacy or adverse effect profiles.

In 2013, the Eighth Joint National Committee (JNC8) released new guidelines on the management of adult hypertension and recommended treating all hypertensive people  $\geq 60$  years to a BP goal of  $<150/90$  mm Hg and hypertensive people aged 30 to 59 year or with presence of DM or chronic kidney disease at any age to a goal of  $140/90$  mm Hg.<sup>55</sup>

More recently, the most appropriate targets for systolic BP to reduce CVD morbidity and mortality among people without DM were analyzed in a randomized controlled

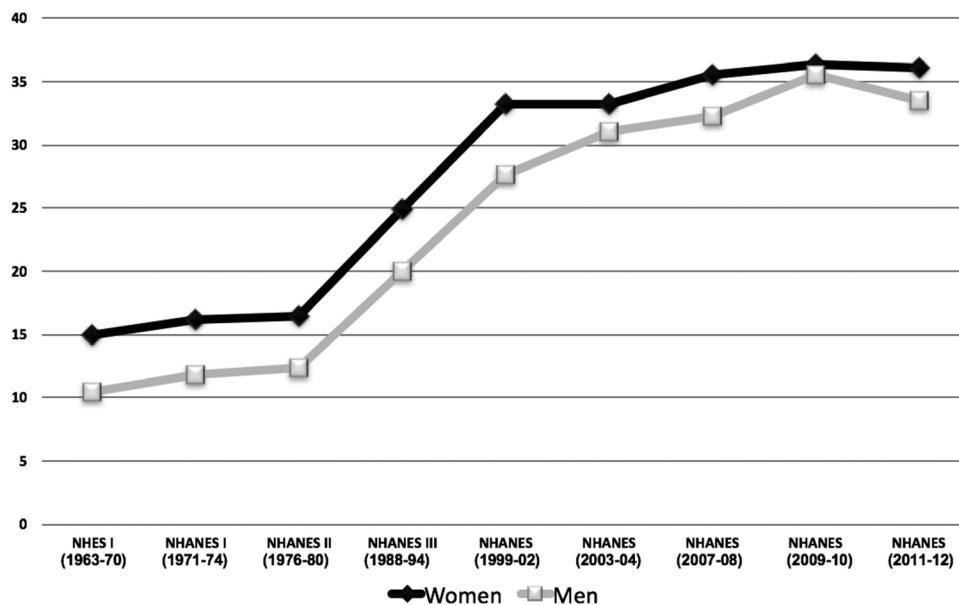


Figure 2. Percentage of US adults classified as obese (BMI  $\geq 30$  kg/m<sup>2</sup>) in health surveys from 1963 to 2012.<sup>41–44</sup>



multicenter clinical trial, Systolic Blood Pressure Intervention Trial (SPRINT). Subjects with a systolic BP of  $\geq 130$  mmHg and increased CVD risk, but without DM, were randomly assigned to an intensive treatment group (BP target of  $< 120$  mmHg achieved with an average of 3 medications) or to a standard treatment group (BP target of  $< 140$  mmHg achieved with an average of 2 medications). The intensive treatment group resulted in 25% lower relative risk of fatal and nonfatal major CVD events and death from any cause HR=0.75 (95% CI 0.64–0.89;  $P < 0.001$ ), although with notably higher rates of adverse events.<sup>56</sup> These results may lead to a reassessment of the current JNC8 guidelines.

### Dyslipidemia

Dyslipidemia has the highest population-adjusted risk among women, at 47.1%, compared with all other known risk factors for ASCVD.<sup>57</sup> However, this greater ASCVD risk is typically not observed before menopause, even if cholesterol levels are elevated. Lifestyle modifications, including diet and exercise, are of critical importance in the primary and secondary prevention of ASCVD. Pharmacological therapy of hyperlipidemia for secondary prevention has clearly been shown to be equally effective in women and men for reduction of recurrent cardiac events and ASCVD mortality.<sup>58,59</sup> In primary prevention, data in women are more limited. Primary prevention guidelines for statin initiation have recently been tailored to be sex-specific, with inclusion of sex in the American Heart Association (AHA)/American College of Cardiology (ACC)-pooled cohort formula for ASCVD risk determination. Statins should be used in subjects with moderate or high ASCVD risk according to the new AHA/ACC guidelines.<sup>60</sup> Of note, many more women will now qualify for treatment with statins according to these guidelines. In a Dutch study of 4854 people (mean age 65 years), of which 54% were women, the ACC/AHA guidelines recommended statin therapy in 66% of women, in contrast to the older Adult Treatment Panel III (ATP III) guidelines which would have recommended treatment in 36% of women.<sup>61</sup> However, the ACC/AHA pooled cohort risk score guidelines were developed specifically for the American population, and we can therefore expect this tool to perform differently in other populations.

Recent data from the Center for Disease Control and Prevention indicated that between 2005 and 2012, only 45% of 78.1 million adults eligible for cholesterol-lowering medications actually took them.<sup>62</sup> Of even more concern though is that recent reports have identified sex-specific differences in both treatment and adherence to lipid-lowering medications; women are less likely to be prescribed statin therapy,<sup>63,64</sup> and compliance is variable.<sup>65</sup> Reasons for this disparity are unclear at the present time, but underscore the need for additional physician and patient awareness of the benefits of lipid-lowering therapy in women. In a recent review, there was a suggestion that women had a greater likelihood of developing DM on statins,<sup>66</sup> which may contribute to some uncertainty, and needs further exploration. Evolving insights into the impact of sex and ethnicity on indication for, and interpretation of, advanced lipid testing (such as Lp-PLA2 [lipoprotein-associated phospholipase A2] activity determined by PLAC testing<sup>67</sup>) in the prediction of ASCVD events may play a role in refinement of

risk stratification of certain individuals considered for statin therapy.<sup>68</sup> Indeed, for the first time ever, the Food and Drug Administration advised that labeling for the PLAC test contains separate performance data for black women, black men, white women, and white men. The sex-specific aspects of other biomarkers and imaging studies, such as coronary artery calcium measurements, and roles in ASCVD risk stratification continue to be debated.

## Nontraditional ASCVD Risk Factors in Women

### Pregnancy-Related Disorders and CVD Risk Association

#### Preterm Delivery

Preterm delivery (PTD) defined as birth at  $< 37$  weeks' gestation complicates 5% to 12.7% of deliveries worldwide.<sup>69</sup> The underlying causes and mechanisms of PTD delivery are not yet completely understood. The main mechanisms that have been suggested are inflammation, infection, and vascular diseases. A recent study concluded that PTD is an independent risk factor for subsequent long-term cardiovascular morbidity and cardiovascular-related hospitalizations. The risk for ASCVD was further increased with a history of early PTD ( $< 34$  weeks' gestation).<sup>70</sup>

#### Hypertensive Pregnancy Disorders

Hypertensive pregnancy disorders include gestational hypertension, chronic hypertension, and preeclampsia. Gestational hypertension is defined as new onset hypertension ( $> 140/90$  mmHg) after 20 weeks' gestation in a woman who was originally normotensive. Women who develop hypertension before 20 weeks of gestation are diagnosed with chronic hypertension. Women who suffer severe hypertension ( $> 160/110$  mmHg) are at greater risk of progressing to preeclampsia. Preeclampsia is defined as new onset hypertension ( $> 140/90$  mmHg) after 20 weeks' gestation and proteinuria (0.3 g/24 hours) and end-organ dysfunction. There is growing consensus that the associated CVD risk persists into later life, far beyond the affected pregnancy period. In a meta-analysis with 198 252 preeclamptic women, it was concluded that in comparison to women with normotensive pregnancies, women with preeclampsia had a 3.7-fold (95% CI, 2.70–5.05) relative risk for developing hypertension 14 years after pregnancy, a 2.16-fold (95% CI, 1.86–2.52) relative risk for IHD after 12 years, a 1.81-fold (95% CI, 1.45–2.27) relative risk of stroke after 10 years, and a 1.79-fold (95% CI, 1.37–2.33) relative risk for venous thromboembolism after 5 years.<sup>71</sup> Earlier occurrence of preeclampsia in pregnancy is associated with poorer outcomes; in addition, the severity of preeclampsia is correlated with the severity of CVD later in life.

#### Gestational Diabetes Mellitus

For many years, gestational DM was defined as any degree of glucose intolerance with onset or first recognition during pregnancy.<sup>72</sup> However, the ongoing epidemic of obesity and DM has led to more T2DM in women of childbearing age, resulting in an increase in the number of women with undiagnosed T2DM at pregnancy, and thus, women found to have DM in the first trimester are classified as having T2DM.<sup>73</sup> Gestational DM is defined as newly diagnosed DM beyond

the first trimester of pregnancy.<sup>74</sup> Gestational DM increases the risk of developing T2DM by 7-fold, which is a major risk factor for subsequent ASCVD, but also raises CVD risk (2-fold for stroke and 4-fold for MI) independently of the overt development of T2DM.<sup>75,76</sup>

#### **Persistence of Weight Gain After Pregnancy**

Pregnancy is the only normal physiological setting in which body weight increases by  $\geq 20\%$  during a 9-month period. After delivery, maternal capacity for restoring normal weight regulation is enhanced by breastfeeding, but may be disrupted by lifestyle factors, including lack of time for exercise, dietary changes, and limited sleep duration. Weight at 1 year postpartum is a stronger predictor of the likelihood of being overweight 15 years later than the weight gained during the pregnancy itself.<sup>77</sup> A recent study observed that weight trend in the first year postpartum reported that an adverse cardiometabolic profile emerges as early as 1 year postpartum in women who do not lose weight between 3 and 12 months after delivery.<sup>78</sup>

#### **Autoimmune Diseases: Rheumatoid Arthritis and Systemic Lupus Erythematosus**

Numerous population studies have demonstrated an association between inflammatory diseases and increased mortality, in both men and women, mainly as a consequence of ASCVD.<sup>79</sup> In autoimmune diseases, the immune response to self-antigens results in damage or dysfunction of tissues, which can occur systemically or affect specific organs or body systems. For most systemic autoimmune disorders, there is a clear sex difference in prevalence, making this a more common ASCVD risk factor in women. The microvasculature in women may play an important role in the predisposition of women with autoimmune diseases to develop accelerated CVD.<sup>80</sup> The female to male ratio for rheumatoid arthritis is 2.5:1 and for systemic lupus erythematosus is 9:1. Patients with rheumatoid arthritis have a 2- to 3-fold higher risk of MI and a 50% higher risk of stroke.<sup>81</sup> For systemic lupus erythematosus, recent case-control series has indicated that the risk of MI is increased between 9- and 50-fold over that in the general population.<sup>82,83</sup> It has been recognized that well-known cardiovascular risk scoring systems underestimate the burden of cardiovascular risk in patients with rheumatoid arthritis and systemic lupus erythematosus, and an empirical European League Against Rheumatism (EULAR) multiplier of 1.5 has been suggested.<sup>84</sup>

#### **Radiation and Chemotherapy for Breast Cancer**

Radiotherapy for breast cancer often involves incidental exposure of the heart to ionizing radiation, increasing the subsequent rate of IHD. The increase is proportional to the mean dose to the heart, beginning within a few years after exposure, and continuing for at least 20 years.<sup>85</sup> Women with preexisting cardiac risk factors have greater absolute increases in risk from radiotherapy. In a recent population-based case-control study, women irradiated for cancer of the left breast had higher rates of CAD events than women receiving radiation to the right breast. Moreover, the rate of CAD events increased by 7.4% per gray of the mean radiation dose delivered.<sup>85</sup>

Radiation-induced heart disease can also manifest as valvular and cardiomyopathic processes.

There has been a tremendous improvement in the survival rates of breast cancer. Unfortunately, this improvement in outcome has been associated with chemotherapy dose-dependent acute, subacute, and late cardiotoxicity. Breast cancer patients treated with chemotherapy may be at risk for either or both Type I (anthracycline-like agents) and Type II (Trastuzumab-like agents) cardiotoxicity, for which prevention and monitoring is a contemporary issue of recent significant controversy and attention.<sup>86</sup> Patients with breast cancer who have undergone anthracycline-based therapy and patients who have had mediastinal radiation therapy are candidates for long-term cardiac surveillance programs. An expert consensus statement from the European Association of Cardiovascular Imaging and the American Society of Echocardiography recommends evaluation based on signs and symptoms and echocardiographic surveillance continuing 5 years after treatment in high-risk patients and 10 years in all other patients. It has also been recommended that high-risk patients should receive a functional noninvasive stress test within 5 to 10 years of completion of chest radiation therapy.<sup>87</sup>

#### **Depression**

Depression is a prevalent and increasingly recognized risk factor for development of CAD; its presence also portending unfavorable outcomes after a CAD event.<sup>88</sup> Limited evidence suggests that depression and other psychosocial risk factors might be more powerful risk factors in younger individuals,<sup>89</sup> and especially in young women.<sup>90-92</sup> Although few women develop CVD at a young age,<sup>93</sup> the lifetime risk in women at age 50 years is  $\approx 40\%$ , and therefore, identification of risk factors in young populations may provide long-term benefit by facilitating early prevention.<sup>94</sup> Furthermore, young women have been underrepresented in studies of CVD,<sup>95</sup> have higher rates of depression,<sup>96,97</sup> and have higher mortality rates after acute MI compared with men.<sup>98</sup> Although CVD mortality rates have declined in the United States, this decline is less pronounced among young women in recent years,<sup>2</sup> a time period when rates of depression have been increasing.

#### **Menopause and CVD**

Premenopausal women are relatively protected against CVD, compared with age-matched men. However, this sex gap narrows after menopause. This long-standing observation led to a hypothesis that ovarian steroid hormones and, in particular, estrogens, were cardioprotective, initially supported by retrospective observational studies.<sup>99-104</sup> However, such conclusions were refuted by randomized clinical trials of both primary and secondary prevention of ASCVD.<sup>105,106</sup> The discordance was surprising in light of the beneficial physiological effects of estrogen on the vascular endothelium at the cellular and molecular levels, on blood vessels in animal CVD models, and on lipids and insulin-resistance biomarkers; as such, menopausal hormone therapy (MHT) became one of the most controversial areas in women's health.<sup>107,108</sup> The results of the major randomized clinical trials, the Women's Health Initiative (WHI) and the Heart Estrogen/Progestin Replacement Study (HERS), led to dramatic

changes in clinical practice in the mid-2000s, with marked declines in the use of MHT worldwide

Since then, clinicians and scientists have reviewed the randomized clinical trials with a critical eye, attempting to explain the discordance with the observational studies. The average WHI enrollment age was 63 years, 12 years older than the age at which MHT is commonly initiated in clinical practice for the indication of postmenopausal vasomotor symptom management. When the WHI investigators analyzed the results by age groups (50–59, 60–69, and 70–79 years), CAD outcomes with MHT were found to be more favorable in younger than in older women, especially in the E-alone trial.<sup>106,109</sup> Consistent with these trends, a meta-analysis of >39 000 women enrolled in 23 clinical trials concluded that MHT reduces CAD risk in women <60 years, but not in older women.<sup>110</sup> Debate about the timing hypothesis continues, with recent randomized clinical trials focused on surrogate end points, such as carotid intimal medial thickness and coronary artery calcium. These trials have also yielded inconsistent findings, including null results for carotid intimal medial thickness and coronary artery calcium in the Kronos Early Estrogen Prevention Study (KEEPS)<sup>111</sup> and evidence supportive of the timing hypothesis in the Early Versus Late Intervention Trial with Estradiol (ELITE) (Figure 3).<sup>112</sup> Overall, a consensus has emerged that MHT, at the lowest effective dose, remains an appropriate treatment for menopausal symptoms in early (ie, within 5 years) menopause, in the absence of contraindications, but

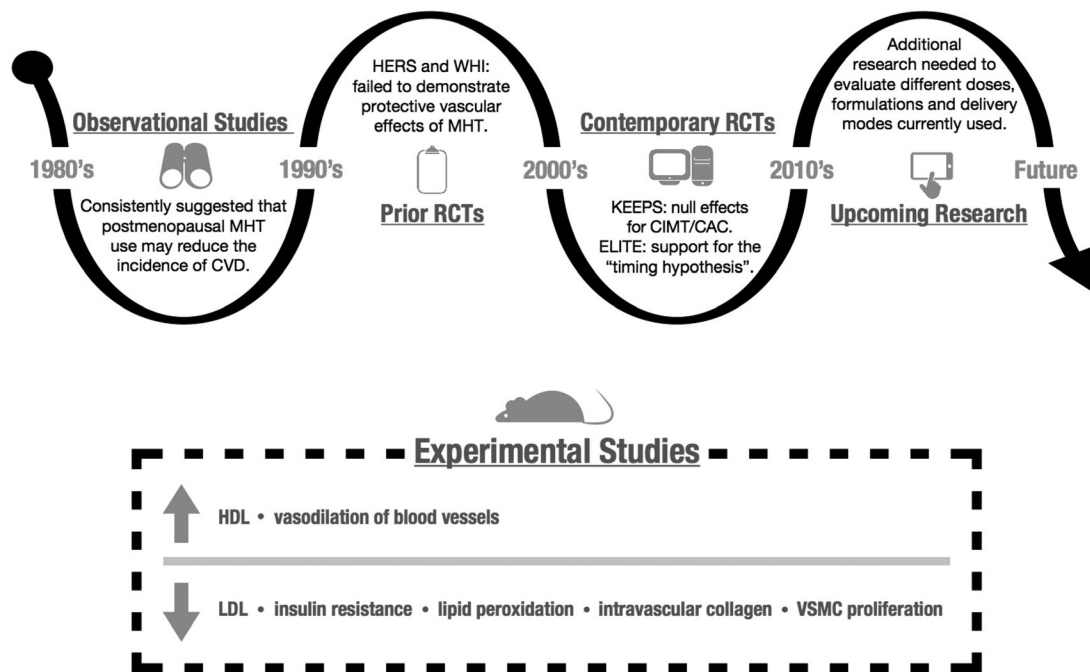
should never be prescribed for the express purpose of preventing CVD.<sup>113,114</sup>

**BRCA Carriers, Prophylactic Salpingo-Oophorectomy, and Menopause: Clinical Management Considerations and Recommendations**

Women who inherit a mutation in either the *BRCA1* or *BRCA2* gene have greatly elevated lifetime risks of ovarian cancer, fallopian tube cancer, and breast cancer. Risk-reducing surgery with mastectomies and bilateral salpingo-oophorectomy (BSO) is recommended, often before natural menopause, to prevent cancer.<sup>115</sup>

There are no published guidelines specifically for the management of *BRCA* mutation carriers after prophylactic BSO. In the general population, studies of surgical menopause in young women have demonstrated increased risk for development of premature CVD, low bone density, and an increase in cognitive impairment.<sup>116–119</sup> A positive association between BSO and increased risk of CVD has been observed in several observational studies, including the Nurse’s Health Study and the Mayo Clinic Cohort of Oophorectomy and Aging.<sup>117,120,121</sup>

The appropriate management of *BRCA*-positive women who elect to undergo prophylactic BSO is an important clinical issue. The National Comprehensive Cancer Network guidelines state that the increased risk of osteoporosis and CVD associated with premature menopause should be addressed, as well as possible effects of cognitive changes and



**Figure 3. Menopausal hormone therapy timeline.** Experimental studies have consistently demonstrated beneficial physiological effects of estrogen on the vascular endothelium at the cellular and molecular level. This long-standing observation led to a hypothesis that estrogens were cardioprotective, which was initially supported by retrospective and prospective observational studies, followed by disappointment from Heart Estrogen/Progestin Replacement Study (HERS), Women’s Health Initiative (WHI), and other randomized clinical trials (RCTs) that failed to demonstrate reduced risks of clinical cardiovascular disease (CVD) events with menopausal hormone therapy (MHT). More recent RCTs include Kronos Early Estrogen Prevention Study (KEEPS; null results) and Early Versus Late Intervention Trial with Estradiol (ELITE; which has supported the timing hypothesis). MHT is contraindicated for the primary and secondary prevention of CVD. CAC indicates coronary artery calcium; CIMT, carotid intimal medial thickness; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.



vasomotor symptoms on quality of life; counseling also includes a discussion of possible short-term MHT up to the average age of natural menopause. Specific guidelines for the appropriate care of *BRCA*-positive women after prophylactic BSO are needed. Further studies are required to determine the optimal management of young *BRCA*-positive women who elect to undergo prophylactic BSO.

### Primary Prevention Guidelines

Over the last decade, substantial progress has been made in improvement of the awareness of CVD as the major cause of morbidity and mortality in women. Concurrently, an emerging understanding of the sex-unique approaches required to recognize, diagnose, treat, and ideally prevent CVD has evolved. The focus is on recognizing lifetime risk for CVD in women and prevention of disease development. For the first time in 2007, the AHA published evidence-based guidelines focused on the primary prevention of CVD in women, which were subsequently updated in 2011 as effectiveness-based guidelines.<sup>122</sup> Early screening and a complete CVD risk assessment were advised to reduce the pervasiveness of CVD in women who were previously largely excluded or minimally represented in cardiovascular research. The transformation from evidence-based to effectiveness-based guidelines denoted a shift from pure clinical research as the basis of recommendations to an approach that encompasses benefits and risks observed in clinical practice.

Findings from the longitudinal, observational Nurses' Health Study highlighted the critical importance of lifestyle modifications in CAD prevention, demonstrating that women can reduce their risk of coronary events by >80% by not smoking, maintaining healthy body weight (body mass index <25 kg/m<sup>2</sup>), consuming a healthy diet, participating in moderate to vigorous exercise for 30 minutes a day, and consuming no more than a moderate amount of alcohol.<sup>123,124</sup> The Effect of Potentially Modifiable Risk Factors Associated With Myocardial Infarction in 52 Countries (INTERHEART) study was a large case-control study that screened all patients admitted to the coronary care unit or equivalent cardiology ward for a first MI at 262 participating centers in 52 countries. INTERHEART identified 9 easily measured risk factors (smoking, lipids, hypertension, DM, obesity, diet, physical activity, alcohol consumption, and psychosocial factors) that account for over 90% of the risk for acute MI.<sup>57</sup> Importantly, the magnitude of the ASCVD risks for men and women were similar, but the impact of modifying the risks was greater in women. Thus, large studies have demonstrated that lifestyle intervention for primary prevention can decrease the incidence of ASCVD as well as the associated mortality rates in both women and men.

### Aspirin

ASA has proven to be effective for both men and women in the secondary prevention of CVD and in the treatment of acute MI. However, for primary prevention of CVD in women, data have been more limited. In the large-scale Women's Health Study (WHS), almost 40 000 healthy women over the age of 45 years were randomly assigned to low dose ASA (100 mg every other day) or to placebo for 10 years, and major CVD events were evaluated.

Overall, the trial showed a statistically nonsignificant 9% reduction in the primary composite outcome of major CVD events with low-dose ASA.<sup>125</sup> ASA significantly lowered the risk of total stroke by 17% (CI, 0.01–0.31) and the risk of ischemic stroke by 24% (CI, 0.07–0.37) in women, but did not lower the risk of MI or cardiovascular death.<sup>125</sup> This contrasts to the significant reduction in MI and neutral effect on stroke for primary prevention in men observed in the Physicians' Health Study.<sup>126</sup> Moreover, as with men, ASA increased gastrointestinal bleeding risks and the risk of hemorrhagic stroke. However, in subgroup analyses, the CVD risk/benefit ratio appeared to be directly linked to a woman's age; in WHS participants over age 65 years, ASA was clearly associated with evidence of benefit for both ischemic stroke and MI. The AHA effectiveness-based guideline recommendations for the prevention of CVD in women were thus derived to state that for primary prevention, ASA therapy (81 mg daily or 100 mg every other day) can be useful in women ≥ 65 years of age if BP is controlled, and benefit for stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke (Class IIa, Level of Evidence B) and may be reasonable for women <65 years of age for ischemic stroke prevention (Class IIb, Level of Evidence B). The US Preventive Services Task Force (USPSTF) is reviewing their prior 2007 and 2009 recommendations (for ASA use in the prevention of colorectal cancer and CVD, respectively) and have proposed a draft of primary prevention guidelines. In the present format, a pragmatic approach is suggested, without sex-specific differentiation, using 81 mg of ASA in both men and women aged 50 to 59 years (grade B=offer to all) and 60 to 69 years (grade C=selective offering) who have a ≥10% 10-year ASCVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low dose ASA for at least 10 years. It is the judgment of the USPSTF that there is some certainty that the net benefit of ASA use is at least moderate for adults aged 50 to 59 years who are at average risk for bleeding; adults who have little potential of benefit or high risk for GI bleeding should be discouraged from ASA use.

### ASA in Women With Diabetes Mellitus

The use of ASA to prevent ASCVD events in women with DM is controversial, and the evidence for benefit is far from conclusive. There have been several meta-analyses of ASA use in DM; most did not show a benefit for ASA treatment in DM for primary CVD prevention.<sup>127–130</sup> Moreover, 3 trials that have examined ASA use among patients with DM demonstrated no overall benefit in the treatment group.<sup>131–133</sup> However, in the subgroup of DM in the Women's Health Study, women who received ASA had a lower risk of stroke, compared with those without DM.<sup>125</sup> A 2010 consensus by the AHA, the ACC Foundation, and the American Diabetes Association made the following recommendations<sup>134</sup> for adults with DM and without preexisting CVD:

- Low-dose ASA (75–162 mg/d) should be considered for individuals with a 10-year risk of CVD of at least 10% who do not have an increased risk of bleeding; this group consists of men at least 50 years of age and women at least 60 years of age with at least 1 additional CVD risk factor.



- ASA should not be recommended for adults with DM at low risk (men <50 years of age and women <60 years of age with no additional CVD risk factors).

It is important for physicians to be aware that, despite the increased risk for ASCVD in female patients with DM, having DM alone does not qualify them for ASA therapy. Physicians must still perform a proper ASCVD and bleeding risk assessment before making recommendations.

**Statins**

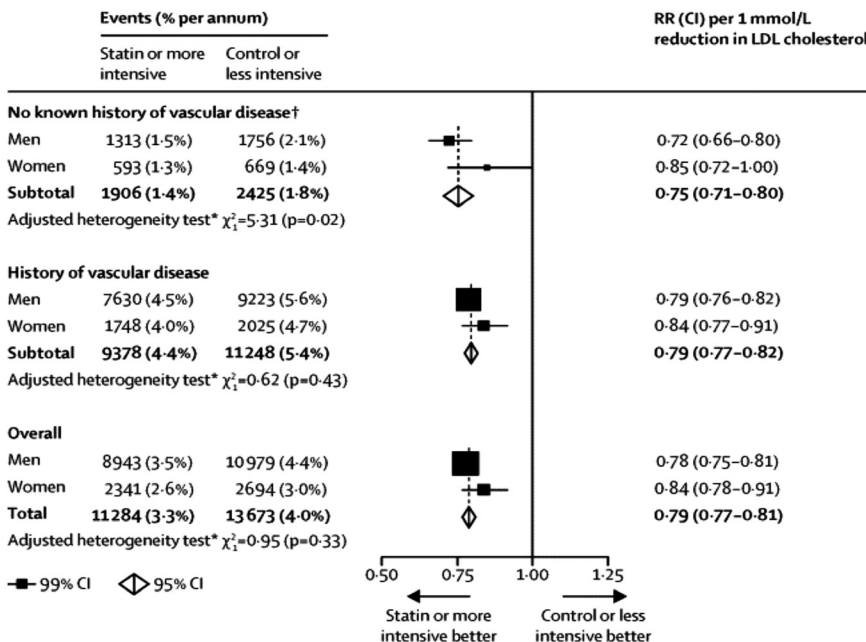
It is well established that statin therapy is as effective in women as in men for secondary prevention of ASCVD.<sup>135</sup> What has been more controversial is the effectiveness of statins in primary prevention in women.<sup>136</sup> A recent meta-analysis of 27 trials of statin therapy concluded that the proportional reduction in major vascular events per 1.0 mmol/L reduction in LDL cholesterol was similar for men and women (risk ratio for women 0.84 [99% CI 0.78–0.91]; risk ratio for men 0.78 [99% CI 0.75–0.81]), irrespective of the baseline level of ASCVD risk or subtype of ASCVD outcome assessed.<sup>137</sup> Although the results were slightly more favorable for men than for women (*P* for heterogeneity by sex <0.05), the guidelines for statin use are the same for both sexes (Figure 4).

In 2013, ACC/AHA jointly released new guidelines on the treatment of cholesterol to reduce ASCVD in adults, recommending statin use in asymptomatic adults aged 40 to 75 years without a history of CVD who have (1) LDL cholesterol level >189, (2) LDL cholesterol level of 70 to 189 mg/dL, if they also have DM (moderate-to-high dose statin use is recommended, depending on 10-year ASCVD event risk), or (3) an estimated 10-year ASCVD event risk of ≥7.5%, as calculated on the pooled cohort equation risk calculator. Moderate-to-high dose statin use occurs only after clinician–patient risk/benefit discussion that addresses other risk factors and optimal lifestyle, the potential for benefit versus potential for adverse effects, and drug–drug interactions. Instead of treating to a

specific LDL cholesterol target, the ACC/AHA recommends fixed-dose statin therapy.<sup>60</sup> In response, the Mayo Clinic established a task force and concluded similar recommendations, although emphasizing lifestyle modifications over immediate initiation of statin therapy in those adults aged ≥40 years with an LDL cholesterol level of 70 to 189 mg/dL, without DM, yet with and ASCVD event risk >7.5%, in cases where the patient is sufficiently motivated to reduce their ASCVD event risk to <7.5%, especially if the LDL cholesterol level is <100 mg/dL.<sup>60,138</sup> Critics of the new guidelines have suggested that the risk score overestimates risk. Nonetheless, the ASCVD risk calculator was based on >1 population and was validated in Caucasian and African American men and women. Therefore, when applied in Hispanic American, Asian American, and South Asian American populations, misclassification of risk category may be more likely.

The USPSTF is reviewing their prior 2008 guideline recommendations on statin use for primary prevention of ASCVD. The draft USPSTF recommendation (grade B=offer to all) includes that all adults without a history of ASCVD (ie, symptomatic CAD or thrombotic stroke) use a low-to-moderate dose statin for the prevention of ASCVD events when all of the following criteria are met: aged 40 to 75 years, ≥1 ASCVD risk factors (ie, dyslipidemia, DM, hypertension, or smoking) and a calculated 10-year ASCVD risk of ≥10%. At a lower level of recommendation (grade C=selective offering), a calculated 10-year ASCVD risk of 7.5% to 10% is suggested.

A recent report from the Center for Disease Control and Prevention found that there were significant differences in the percentage of men (40.8%) and women (32.9%) on or eligible for statin treatment. Among people on or eligible for treatment, there were major differences in the proportion of men (52.9%) and women (58.6) taking cholesterol-lowering medication.<sup>62</sup> There is no compelling evidence to support that statins are less safe in women than in men. The guidelines recommend baseline ALT level assessment, but unless there is suspected hepatic



**Figure 4. Effects on major vascular events per 1.0 mmol/L reduction in low-density lipoprotein (LDL) cholesterol, subdivided by history of vascular disease and sex.** Proportional reduction in major vascular events per 1.0 mmol/L reduction in LDL cholesterol was similar for men and women irrespective of the baseline level of atherosclerotic cardiovascular disease (ASCVD) risk or subtype of ASCVD outcome assessed. The results were slightly more favorable for men than for women (*P*, heterogeneity by sex <0.05). Reused with permission from the Cholesterol Treatment Trialists (CTT) Collaboration.<sup>137</sup>

dysfunction, monitoring is not needed. In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), which enrolled more women than any other statin trial to date, no differences in the rates of myopathies between men and women were found. The JUPITER trial, however, demonstrated that women taking rosuvastatin had a greater increase in their HbA1c compared with placebo (HbA1c 5.9 versus 5.8;  $P=0.001$ ) in addition to a greater risk of developing new DM (1.53 versus 1.03 per 100 person-years, respectively; HR=1.49; 95% CI, 1.11–2.01;  $P=0.008$ ) compared with men (1.36 versus 1.20 per 100 person-years, respectively; HR=1.14; 95% CI, 0.91–1.43;  $P=0.24$ ).<sup>139</sup> Of note, 80% of incident DM occurred in those with impaired fasting glucose at study entry. In the WHI, reported statin use was associated with an increased risk of self-reported new-onset DM in postmenopausal women (HR=1.48, 95% CI, 1.38–1.59).<sup>140</sup> A recent meta-analysis, including 13 statin trials with 91 140 participants, found that statin therapy was associated with a 9% increased risk of developing incident DM, odds ratio 1.09 (95% CI, 1.02–1.17); however, no sex-specific analysis was performed.<sup>141</sup> Overall, the benefit of statins from reduction in coronary events seems to exceed the risk related to DM in both men and women.

### Ischemic Heart Disease in women

In medicine, the proper distinction between sex and gender effects is usually unachievable, which is why these are often compiled for clinical purposes.<sup>53</sup> 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. IHD in women includes not only atherosclerotic obstructive CAD, but also an expanded spectrum of coronary disease, including coronary microvascular dysfunction (CMD), endothelial dysfunction, vasomotor abnormalities, spontaneous coronary artery dissection (SCAD) and stress-induced cardiomyopathy.<sup>142</sup>

Certainly, there are marked differences in the prevalence, incidence, and burden of IHD in women when compared with men,<sup>143</sup> such that an awareness of uniquely female-pattern of IHD is emerging, although some have suggested that the Yentl syndrome is alive and well 15 years after these initial observations.<sup>144</sup> This literature described that when women look like men (with male-pattern obstructive CAD), they are more likely to be diagnosed and treated like men. Dr Bernadine Healy used the term Yentl syndrome in 2001, as depicted in the Barbra Streisand movie of the same name, to call attention to the paradox of adverse outcomes of women with IHD, as well as the underdiagnosis and undertreatment of women.

The 3 most important characteristics of IHD in women are that they have (1) a higher prevalence of angina, (2) a lower burden of obstructive CAD on angiography, and (3) a poorer prognosis in comparison to men.<sup>145</sup> Additionally, current risk scores, based on ACS thresholds determined in predominantly male-based populations, do not accurately predict risk in women, showing the need for sex-specific biomarker ranges and risk stratification tools to improve the diagnosis, treatment, and follow-up in female populations.<sup>146</sup> In a recent prospective cohort study, the high-sensitivity troponin I assay

noticeably increased the diagnosis of MI in women (from 11% to 22%,  $P<0.001$ ) but had a minimal effect on men (from 19% to 21%,  $P=0.002$ ).<sup>147</sup> Other biomarkers, such as proneurotensin, are also found to be sex-specific and related to incident CVD only in women, affirming the need for more research in this area.<sup>148</sup>

### Clinical Presentation

Optimal recognition and timely management of acute MI, especially for reducing patient delay in seeking acute medical care, is critical. In a comprehensive review of the presenting symptoms of ACS in women, women were more likely than men to present without chest pain and had higher mortality than men, especially among younger age groups; sex differences in clinical presentation without chest pain and in mortality were attenuated with increasing age.<sup>149</sup>

Although it has been recognized that a wide range of atypical symptoms occur more frequently in women, including weakness, fatigue, nausea, dyspnea, as well as unconventional descriptors, triggers, and locations of chest-related symptoms, such as in the neck, jaw, and back, the most common presenting symptom of ACS is chest pain in both men and women.<sup>150,151</sup>

### Obstructive Versus Nonobstructive CAD

Recognition of IHD, both acute and chronic, is often delayed or deferred in women. Consequently, many women at risk for related adverse outcomes are not provided specific diagnostic, preventive, and treatment strategies. In part, this lack of recognition is related to sex-specific CVD pathophysiology in women that differs from the traditional male-pattern model (flow-limiting atherosclerotic CAD). This nonobstructive CAD pattern and the tendency among women to have plaque erosion with subsequent thrombus formation, along with CMD, are not well recognized. Importantly, data are emerging to show that more extensive nonobstructive CAD involvement is associated with a rate of major adverse cardiovascular events that may approximate that of obstructive CAD.<sup>152</sup> However, there are many limitations to our understanding of nonobstructive CAD and gaps in current knowledge.

With the widespread use of coronary angiography in the early clinical management of MI, multicenter MI registries have evolved and reported that as many as 10% of MI patients have no evidence of obstructive CAD.<sup>153</sup> These patients with MI and nonobstructive coronary arteries<sup>154</sup> represent an enigma because the underlying cause of the MI is not immediately apparent. In a recent systematic review, it was determined that MI and nonobstructive coronary arteries is characterized by (1) a 6% prevalence of all MI presentations (95% CI, 5%–7%), with a median patient age of 55 years and 40% women; (2) no diagnostic distinguishing clinical presentation features compared with MI with obstructive CAD; (3) a better 12-month all-cause mortality compared with MI with obstructive CAD, although its prognosis should be considered as guarded; and (4) structural dysfunction, coronary spasm, and thrombotic disorders as potential underlying causes. Given that MI and nonobstructive coronary arteries has similar features to MI with obstructive CAD, it should be considered a

working diagnosis that requires further evaluation of potential underlying causes.<sup>155</sup>

### Acute Coronary Syndromes in Women

ACS refers to a spectrum of clinical presentations, including ST-segment–elevation MI, non–ST-segment–elevation MI, and unstable angina. Symptoms of ACS in women may differ from those in men, which may lead to delays and misdiagnosis. Young women with acute MI represent a relatively large yet understudied population. Nearly 16000 US women  $\leq 55$  years die from IHD each year. These women account for 40000 hospitalizations for acute MI annually and have greater risks for morbidity and mortality compared with both young men and older women with acute MI.<sup>23,156</sup> The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study is an observational study of acute MI patients aged  $\leq 55$  years in the United States and Spain. In this study, young women with ST-segment–elevation MI were less likely to receive reperfusion therapy and more likely to have reperfusion delays than similarly aged men. Sex disparities were more pronounced among patients transferred to percutaneous coronary intervention institutions or who received fibrinolytic therapy.<sup>157</sup>

### Coronary Microvascular Dysfunction

CMD is defined as limited coronary flow reserve and coronary endothelial dysfunction and is associated with worse outcomes, with increased rate of cardiac death, stroke, or heart failure.<sup>158,159</sup> An annual major adverse cardiovascular event rate of 2.5% is present in women with CMD, and risk factors for CMD have not been fully elucidated.<sup>160</sup> CMD is characterized by a decrease in the size of epicardial vessels and microvasculature, diffuse atherosclerotic disease, increased arterial stiffness and fibrosis, altered remodeling, and the presence of endothelial or smooth muscle dysfunction.<sup>161</sup> The microcirculation cannot be investigated by angiogram; thus, several techniques for functional assessment of coronary flow reserve (noninvasive and invasive) have evolved; however, the gold standard is an invasive coronary reactivity test. The WISE study highlighted the importance of CMD in women<sup>145</sup> and supported the use of invasive coronary vasomotor testing as a safe method for definitive diagnosis and assessment of prognosis in high-risk women.<sup>160</sup> Early detection of endothelial dysfunction, measured by brachial artery flow-mediated vasodilation, has also been associated with a substantial increase in IHD in women.<sup>162</sup> Additional simpler noninvasive techniques have emerged, with specially designed fingertip probes to measure the peripheral reactive hyperemia index, a measure thought to reflect endothelial function.<sup>163</sup> Positron emission tomography and cardiac magnetic resonance imaging are growing noninvasive modalities to detect subendocardial ischemia. It is now well established that the prognosis is worse in women with CMD and should not be underestimated by clinicians.<sup>164</sup>

Treatment of microvascular angina in women starts with risk factor modification and lifestyle changes to achieve optimal coronary risk factor control. Exercise training and CR is often recommended. Statins, by their anti-inflammatory properties, are especially beneficial in improving endothelial

function. The first step in medical treatment includes traditional antiischemic drugs such as nitrates,  $\beta$ -blockers, angiotensin-converting enzyme inhibitor, and calcium channel blockers. Nontraditional antiischemic medications such as ranolazine or aminophylline (xanthine derivative) have been evaluated, but do not show consistent benefit. Xanthines and tricyclic antidepressants may be helpful for altered cardiac pain perception.<sup>165</sup>

### Spontaneous Coronary Artery Dissection

SCAD is defined as a sudden separation between the layers of a coronary artery wall, creating an intimal flap and intramural hematoma, thus obstructing intraluminal blood flow distally and resulting in acute myocardial ischemia.<sup>166</sup> Eighty percent of SCAD patients are female with average age of 42 years, with 20% to 25% of cases occurring in the peripartum period.<sup>167</sup> An association with occult fibromuscular dysplasia has been observed in  $\approx 50\%$  of patients, leading to routine screening with computed tomographic (CT) angiography from base of skull to pelvis, as well as magnetic resonance or CT screening for detection of occult cerebral aneurysms.<sup>166</sup> The classic presentation is of a young healthy woman, without traditional ASCVD risk factors, and sudden onset of ACS. Ongoing substantial progress of SCAD research is taking place because of recent increases in patient engagement through social media and creation of disease-specific online communities. The establishment of a large registry database<sup>168</sup> provided preliminary evidence that there may be a genetic predisposition to SCAD.<sup>169</sup>

The diagnosis of SCAD most importantly requires a high degree of suspicion with careful angiographic study. Accurate differentiation of ACS as a result of SCAD from ACS because of atherosclerosis is crucial because the approaches to both acute and long-term management are different. The most important reasons for accurately diagnosing SCAD are that acute SCAD patients undergoing percutaneous coronary intervention have markedly reduced technical success rates compared with percutaneous coronary intervention success rates for atherosclerotic ACS (62% versus 92%).<sup>166</sup> Moreover, the substantial rate of spontaneous vascular healing<sup>166,170</sup> suggests a role for conservative management in stable SCAD patients with preserved distal coronary flow. Conservative management has generally been associated with favorable outcomes<sup>170</sup>; however, careful inpatient monitoring (4–5 days) is needed because of a small early threat of dissection progression and the consequent need for acute intervention.

Ten-year recurrence rates of  $\leq 20\%$ , predominantly in women,<sup>166</sup> underscore the need for close and long-term follow-up, as well as the imperative for more research. In a retrospective case series, statins were associated with recurrent SCAD; therefore, statins are discouraged and recommended only when hyperlipidemia is documented.<sup>166</sup> Although evidence of benefit is lacking, the administration of low-dose ASA is routinely recommended. CR should be recommended to all SCAD patients.<sup>171</sup>



### Stress Cardiomyopathy (Takotsubo/Broken Heart Syndrome)

Stress-induced cardiomyopathy was first described in Japan in 1990 and was named after the octopus trapping pot with a round bottom and narrow neck, which resembles the left ventriculogram during systole in these patients. It is characterized by transient systolic and diastolic left ventricular dysfunction with a variety of wall motion abnormalities, but classically noted is mid to apical akinesis and basal hyperdynamic function.<sup>172</sup> It mainly affects postmenopausal women and is often preceded by extreme physical or emotional triggers.<sup>173</sup> The clinical presentation, electrocardiographic findings, and biomarker profiles are often similar to those of ACS, but the coronary artery anatomy is found to be without significant obstructive disease at angiography.<sup>173</sup>

The cause of Takotsubo cardiomyopathy remains unknown, but is thought to be related to a disproportionate distribution and activation of myocardial sympathetic receptors. The ventricular dysfunction, which usually involves the left, but may also involve the right ventricle, generally resolves within several weeks with supportive therapy, including  $\beta$ -blockade; however, especially in the presence of significant comorbidities, the outcome may not be benign. Patients remain at risk for recurrence, even years after the first event.<sup>174–176</sup>  $\beta$ -Blockers have been proposed as a therapeutic strategy.<sup>177</sup> In a recently published large international registry, patients with stress-induced cardiomyopathy were found to more likely present with neurological and psychiatric comorbidities.<sup>173</sup>

### Medical Antiischemic Therapy

Despite their beneficial effect, medical therapies such as ASA, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers,  $\beta$ -blockers, aldosterone inhibitors, and statins are frequently delayed in women. The EuroHeart Survey demonstrated that in the treatment of stable angina, women were significantly less likely to receive ASA.<sup>22</sup> On hospital discharge for non-ST-elevation MI, women were  $\approx 3\%$  less likely to receive ASA and  $\beta$ -blockers and  $\approx 13\%$  less likely to receive statin therapy compared with men.<sup>25</sup> Recent evidence suggests that many drugs that we commonly use to treat CVD in women, including especially antithrombotic and antiarrhythmic agents, are metabolized differently in women and put them at risk for increased adverse effects and potential need for dose adjustment, a neglected area of understanding which requires further research.

### Invasive Testing for IHD

In women and men with a high probability of CAD or with evidence of ACS, coronary angiography is indicated for diagnosis and, when appropriate, catheter-based therapy. Large-scale observations from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) initiative showed that despite these recommendations, women with ACS are treated less aggressively, with fewer cardiac catheterizations, catheter-based interventions, fibrinolytic and bypass surgical procedures, resulting in less favorable clinical outcomes with higher mortality and lower health-related

quality of life compared with men.<sup>25</sup> A recent meta-analysis comparing early invasive versus conservative treatment strategies in men and women with non-ST-segment-elevation MI and unstable angina ACS showed a comparable benefit of an early invasive strategy in men and high-risk women for reducing the composite end point of death, MI, or rehospitalization with ACS; however, lower risk women, without biomarker elevation, did not show a benefit.<sup>178</sup> Regarding potential risks associated with invasive procedures, women have been shown to have more bleeding complications. However, dose-adjusting of antithrombotic/antiplatelet therapies and newer technical approaches (radial access) may result in reduced bleeding and vascular complications in women.<sup>179,180</sup>

### Noninvasive Testing for IHD

The 2014 AHA Consensus Statement on the Role of Noninvasive Testing in the Clinical Evaluation of Women with Suspected Ischemic Heart Disease provides evidence-based guidelines on diagnosis of IHD in women by noninvasive testing.<sup>181</sup> The options for noninvasive tests are similar for both men and women and pretest probability must be taken into account when Choosing Wisely according to testing appropriateness (Table 2).<sup>181</sup> In women unable to perform activities of daily living or to perform adequately on exercise treadmill testing, a pharmacological stress test is the preferred method of risk assessment. Stress imaging tests provide information about wall motion abnormalities or perfusion and provide assessment of ventricular function.

### Functional Testing

Functional tests include exercise treadmill testing with ECG, exercise/pharmacological stress echocardiography, exercise/pharmacological cardiac nuclear imaging with single-photon emission computed tomography or positron emission tomography, pharmacological stress cardiac magnetic resonance, CT perfusion, and CT or Doppler ultrasound-derived flow reserve measurements.<sup>143</sup> Exercise treadmill testing is the most common method of diagnosing CAD in women despite a higher false-positive rate compared with men. Exercise treadmill testing is recommended as the diagnostic test of choice in symptomatic, intermediate risk women who are able to exercise and have a normal resting ECG. Exercise stress testing provides valuable information about exercise capacity and hemodynamic response to exercise and recovery.

### Anatomic Testing

Evidence regarding the usefulness of cardiac CT has grown. Coronary CT angiography and coronary artery calcium score provide additional tools for the clinical assessment of CAD. Recently published studies include the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial comparing functional versus anatomic assessment tests, demonstrating no significant differences in outcomes by test used.<sup>183</sup> The Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT) trial demonstrated that coronary CT angiography predicts major cardiovascular events.<sup>184</sup> ROMICAT II trial found that women who undergo coronary CT angiography compared with standard cardiac evaluation had less hospital admissions, shorter



**Table 2. Pretest Probability for Coronary Artery Disease by Age, Sex, and Symptoms\***

Age, y	Sex	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

High indicates >90%; intermediate 10% to 90%; low <10%; very low <5%. Reused with permission from Gibbons et al.<sup>182</sup>

\*No data exists for patients <30 or >69 y but it can be assumed that prevalence of coronary artery disease increases with age. In a few cases, patients with ages at the extremes of the decades listed may have probabilities slightly outside the high or low range.

length of hospital stay, and lower total radiation dose compared with men.<sup>185</sup>

## Heart Failure in Women

### Heart Failure With Preserved Ejection Fraction

Heart failure is major health threat in the United States. In most studies, heart failure in women occurs in older age and with less ischemic causes. Women are  $\approx 2\times$  more likely than men to develop heart failure with preserved ejection fraction (HFpEF). This syndrome was historically considered to be caused exclusively by left ventricular diastolic dysfunction, as demonstrated on echocardiography, but research has identified several other contributory factors, including limitations in left ventricular systolic reserve, systemic and pulmonary vascular function, coronary microvascular endothelial inflammation and reduction of nitric oxide bioavailability, chronotropic reserve, right heart function, autonomic tone, left atrial function, and peripheral impairments.<sup>186,187</sup> These impairments in cardiac, vascular, and peripheral reserve can be caused by common risk factors for HFpEF, such as aging, adiposity, hypertension, and metabolic stress. HFpEF is a clinical diagnosis and is subject to underdetection because of the lack of specific diagnostic biomarkers.

In contrast to heart failure with reduced ejection fraction, unfortunately no treatment has been proven effective for HFpEF in clinical trials.<sup>188,189</sup> BP control concordant with existing hypertension guidelines remains the most important recommendation in treating patients with HFpEF (Recommendation Class I-B); in addition, 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 angiotensin receptor blockers may also be considered to reduce hospitalizations (Recommendation Class IIb-B).<sup>190</sup> Women exhibit a worse quality of life after diagnosis of HF and more frequently exhibit depression.<sup>53</sup> As this poorly understood entity disproportionately affects women, and particularly elderly women, it is in dire need of research efforts to elucidate pathophysiology and treatment strategies.

### Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM), also known as pregnancy-associated cardiomyopathy,<sup>191</sup> is an uncommon condition in which an idiopathic form of left ventricular systolic dysfunction develops during pregnancy or the postpartum period in women without previous heart disease.<sup>192</sup> The incidence of this condition in the United States is  $\approx 1$  in 3000 deliveries, with a significantly higher incidence in African Americans, women >30 years of age, those with a history of pregnancy-associated hypertension, and in those with multifetal pregnancies.<sup>193</sup> The pathogenesis of PPCM remains unknown and is a diagnosis of exclusion; therefore, all patients should be thoroughly investigated.

The majority of women demonstrate a partial or complete recovery within 2 to 6 months after the diagnosis of PPCM. A recurring concern is the potential risk during or after subsequent pregnancies, even if LV function returns to normal. Despite the critical importance of this issue, it is only briefly discussed in the most recent guidelines for the management of pregnancy-related heart disease.<sup>194</sup> In advanced HF with hemodynamic instability, urgent delivery irrespective of gestation may need to be considered.<sup>195</sup>

On urgent delivery, the principles of managing acute HF because of PPCM do not differ than those applying to acute HF from other causes, including diuretics (thiazide diuretics seem to be safe<sup>196</sup>),  $\beta$ -blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and hydralazine/nitrates.<sup>192</sup> Inotropes may be considered in patients with severely reduced cardiac output states; anticoagulation may be indicated if ejection fraction falls <35%. Further research is needed before subsequent pregnancy recommendations and firm breastfeeding recommendations can be made for PPCM patients.

### Cardiac Rehabilitation in Women

CR is a multidisciplinary outpatient program that reduces overall and cardiovascular-related mortality by 13% and 26%, respectively, when compared with usual care.<sup>197</sup> CR is indicated after ACS, intervention (percutaneous coronary intervention and CABG), and heart failure diagnoses. Despite women-specific clinical practice guideline recommendations

for CR referral as a Class 1, Level A indication,<sup>197,198</sup> a recent meta-analysis showed that men were a third more likely to be enrolled in CR compared with women ( $P < 0.00001$ ).<sup>199</sup>

The reasons for women being underrepresented in CR programs are multifactorial. Physician referral patterns, program structure, and patient preferences influence the degree of CR participation among women.<sup>122,200</sup> Recommendations to attend CR programs need to be consistently offered to all women and reinforced by all health staff, including physicians.

## Other Vascular Diseases in Women

### Stroke

In the United States, 53.5% of the estimated new or recurrent strokes occur among women annually, resulting in  $\approx 55\,000$  more stroke events in women than in men.<sup>48</sup> Women have an increased lifetime incidence of stroke compared with men, largely because of a sharp increase in stroke risk in older postmenopausal women. Women also have an increased lifetime prevalence of stroke risk factors, including hypertension, as well as abdominal obesity and metabolic syndrome, especially in middle-aged women. Incidence of AF is lower in women compared with men<sup>201</sup>; however, women having AF show a higher incidence of stroke and a higher mortality rate with respect to men. A recently published meta-analysis evaluated 30 studies with 4371714 participants addressed whether AF is a stronger risk factor for stroke, CVD death, all-cause mortality, and other outcomes in women compared with men. This analysis found that the pooled relative risks for stroke was associated with twice the relative risk of stroke in women than in men (relative risk ratio 1.99, 95% CI 1.46–2.71). AF was associated with a higher relative risk of all-cause mortality, stroke, cardiovascular mortality, cardiac events, and heart failure in women compared with men.<sup>202</sup> Active screening for AF, especially in women  $>75$  years of age, in primary care settings using vital sign assessment followed by confirmatory ECG when heart rate irregularity is detected is recommended (Class I; level of evidence B).<sup>203</sup> Although female sex is incorporated as a risk factor for stroke in the widely used CHA<sub>2</sub>DS<sub>2</sub>-VASc score, AF seems to affect women and men differently.<sup>202</sup> The AHA recently recommended the development of a specific risk score for stroke in women as some risk factors for stroke are unique to, more prevalent, or differently impact women.<sup>203</sup> Finally, when stroke risk stratification indicates the need for anticoagulation, women should receive treatment. Pregnancy and the postpartum period represent a time of increased risk of stroke, presenting challenges for stroke management. Recognition of these issues is critical to improving acute care and functional recovery after stroke in women.

### Peripheral Arterial Disease in Women

Atherosclerotic lower extremity peripheral arterial disease (PAD) is now known to be associated with equal morbidity and mortality to CAD and stroke and is associated with significantly reduced quality of life.<sup>204–206</sup> Recent studies have shown a high prevalence of PAD in women,<sup>207</sup> particularly women at the extremes of ages ( $>80$  years and  $<40$  years), who represent a greater estimated population burden of PAD.<sup>207</sup> Intermittent claudication has been considered the hallmark feature of PAD; women may often be asymptomatic<sup>208</sup> or present with

atypical symptoms.<sup>209</sup> Noninvasive ankle-brachial index can diagnose lower extremity PAD,<sup>210</sup> and AHA/ACC guidelines recommend screening for PAD in all adults  $>65$  years, or if there is a history of any tobacco use or DM, screening should commence earlier (at  $>50$  years).<sup>211</sup> An ankle-brachial index  $<0.90$  is abnormal and indicates the presence of PAD. An ankle-brachial index of 0.90 to 1.0 is borderline for PAD,<sup>210</sup> but represents an increased risk for CVD.<sup>207</sup>

### Abdominal Aortic Aneurysms

Abdominal aortic aneurysms (AAAs) are 4 to 6 times more common in men than in women.<sup>212,213</sup> In addition, AAAs develop in women  $\approx 10$  years later than in men.<sup>214</sup> As with coronary heart disease, there is evidence that women with AAA also have a worse prognosis. Even in the absence of adjustment for AAA diameter, a meta-analysis showed that the annual risk of rupture of large AAA ( $\geq 5$  cm in diameter) was 18% (95% CI, 8%–26%) in women versus 12% (95% CI, 5%–20%) in men.<sup>215</sup>

In a population-based study, it was reported that in the event of rupture, men were more likely to be treated with surgery than women (odds ratio, 1.4; 95% CI, 1.14–1.9).<sup>216</sup> Women with ruptured AAAs, irrespective of age, were less likely to be admitted to the hospital.<sup>217</sup> Female sex was also an independent predictor (HR, 1.69; 95% CI, 1.28–2.22) of in-hospital death after surgery for ruptured AAA.<sup>218</sup> As is the case for CAD, AAAs are underdiagnosed and undertreated in women. All clinicians need to be aware that although women are inherently less likely than men to develop an AAA, those who develop an AAA fare worse than men.

## Conclusions

CVD continues to be the leading cause of death for women in the United States. The average lifetime risk of developing CVD in women at 50 years of age is  $\approx 40\%$ , and this percentage rises as the number of risk factors increases. A focus on primary prevention of CVD is necessary to reduce CVD mortality and the overall CVD burden. Identifying and treating risk factors, including hypertension, dyslipidemia, DM, smoking, obesity, and physical inactivity, has become a major focus of the AHA to accomplish this goal. Unfortunately, many of these risk factors are increasing in prevalence and severity, especially in young women. Further research into the mechanisms responsible for the observed sex differences in traditional risk factor effects would not only improve our understanding of the pathogenesis of CVD, but could also inform health policy makers and clinical guideline committees in tailoring sex-specific interventions for the treatment and management of these risk factors. Moreover, there are additional, female-specific risk factors (PTD, hypertensive pregnancy disorders, gestational DM, menopausal transition) that can be identified during reproductive life that may improve current risk assessment strategies for primary prevention of CVD. However, considerable challenges remain in incorporating this information into current risk assessment tools.

Frequently unrecognized and often undiagnosed CVD presentations that are either more prevalent in or unique to women include CMD, spontaneous coronary artery dissection, stress-induced cardiomyopathy, and HFpEF. There is yet

much more to learn, and this requires sex- and gender-specific approaches to research, with appropriate representation of women in clinical cardiovascular trials.

For many decades, CVD research has focused primarily on men, thus leading to an underappreciation of sex differences from an etiologic, diagnostic, and therapeutic perspective. As long as women are underrepresented in clinical trials, we will continue to lack data to make accurate clinical decisions on 51% of the world's population. Recent initiatives have raised awareness that CVD and its optimal management may differ between men and women. We encourage a new era in research where cardiovascular studies are designed with adequate power for sex-specific analysis to understand mechanisms and develop optimal treatments for cardiovascular diseases in both sexes.

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