AHA Scientific Statement

Preventing and Experiencing Ischemic Heart Disease as a Woman: State of the Science

A Scientific Statement From the American Heart Association

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The Institute of Medicine has defined sex as "the classification of living things, generally as male or female according to their reproductive organs and functions assigned by the chromosomal complement."[1] The term sex means biological differences between women and men, including chromosomes, sex organs, and hormonal contributions.[2] Sex differences result from true biological differences in the structure and function of the cardiovascular systems of men and women. In contrast, gender differences ensue from a person's self-representation, resulting in psychosocial roles and behaviors imposed by society; gender implies social roles, behaviors, and cultural norms.

Gender differences play a role in the treatment of cardiovascular disease (CVD) and affect outcomes, but they are very different from sex differences that arise from the genetic differences between men and women. Sex differences are a result of a single chromosomal difference between men (XY) and women (XX). Gender, however, is a social construct that differentiates men from women in a society as they assume their social roles. Gender develops on the basis of cultural norms and is articulated through values, perceptions, psychosocial characteristics, and behaviors.[1,3,4] Sex- and gender-specific science addresses how experiences of the same disease, for example, ischemic heart disease (IHD), are similar and different with respect to biological sex and gender. For instance, women tend to have smaller coronary arteries than men, and women have less obstructive IHD than men.[5–7] However, gender differences, which are influenced by ethnicity, culture, and socioeconomic environment, are intimately involved in risk factors and risk behaviors (eg, psychosocial risk factors, physical inactivity [PI], cardiac rehabilitation participation, obesity, and tobacco use) that play a far greater role in outcomes among women with IHD than biological sex differences, given that 80% of heart disease is preventable. These differences affect the mechanism and expression of CVD between the sexes. Sex differences in the cardiovascular system are summarized in Table 1.

During the past 2 decades, we have learned that sex differences exist in the pathophysiology of coronary heart disease, symptom presentation, efficacy of diagnostic tests, response to pharmacological interventions, and clinical outcomes of IHD. We have also learned that gender variations exist, such as delay in seeking treatment, which may also contribute to differences in clinical outcomes and mortality rates. Several milestones have contributed to the progress that has been made thus far (Table 2). These important milestones are instrumental

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Table 1. Sex-Related Differences in the Cardiovascular System

Parameter	Manifestations
Anatomy	Dimensions that are smaller in women (adjust for age and race): left ventricular mass, ventricular wall thickness, left atrial dimension, left ventricular end-diastolic dimension, and vessel size
Hormonal influences	Estrogen and progesterone are most influential in women; testosterone is predominant in men
	Menstruation can affect hematologic and electrocardiographic indexes
Cardiovascular function	Stroke volume is women is 10% less
	Pulse rate in women is 3–5 bpm faster
	Ejection fraction is higher in women
Physiology	Women have reduced sympathetic and enhanced parasympathetic activity
	Women have lower plasma concentrations of norepinephrine
Cardiovascular adaptations	In response to stress, women experience an increased pulse rate, resulting in increased cardiac output; men have increased vascular resistance, resulting in increased BP
	Women are more sensitive to altitude or body positioning changes and experience more orthostatic hypotension and syncope
Hematologic indexes	Women have a lower number of circulating red blood cells per unit volume of plasma (resulting in a lower hematocrit)
	Because of a lower hemoglobin, women have a lower oxygen-carrying capacity; this is balanced by women having a lower oxygen consumption
Electrocardiographic and electrophysiological indexes	Women on average have a longer corrected QT interval and a shorter sinus node recovery time
	Drug-induced torsades de pointes is more common in women
	Sudden cardiac death and atrial fibrillation are less common in women

BP indicates blood pressure. Reprinted with permission from Finks S. Cardiovascular Disease in Women. In Richardson M, Chant C, Cheng JWM, et al, eds. Pharmacotherapy Self-Assessment Program, ed 7 (PSAP-VII). Book 1 (*Cardiology*). Lenexa, KS: American College of Clinical Pharmacy, 2010;182.[8] Copyright © 2010, American College of Clinical Pharmacy.

in laying the foundation for evidence-based interventions to decrease the IHD burden in women to promote their cardiovascular health. However, this knowledge has accumulated slowly and often in isolation, resulting in women continuing to experience difficulty in receiving a diagnosis of IHD and timely appropriate treatment. This document presents a thorough compilation of the most current research related to IHD in women. Importantly, it focuses on studies that document women's experiences and influential factors that affect their receiving a correct diagnosis and timely treatment for IHD. In this article, IHD is inclusive of coronary heart disease.

Table 2. Milestones in Sex and Gender Differences in Research

1985	Public Health Service Task Force on Women's Health was established. Recommendations for a greater focus on women's health issues led to guidelines for inclusion of women in NIH-funded extramural research (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1424718/).
1990	The NIH created the Office of Research on Women's Health to ensure that women's health issues were appropriately addressed and that women were represented in NIH-supported research (http://orwh.od.nih.gov/about/AMIssion.asp).
1993	The NIH Revitalization Act included a Clinical Equity Provision to confirm that treatment effectiveness for women is not merely extrapolated from studies in men but instead is based on research in women (http://orwh.od.nih.gov/about/pdf/NIH-Revitalization-Act-1993.pdf).
2001	The Institute of Medicine report "Exploring the Biological Contributions to Human Health: Does Sex Matter?" states that sex is a key biological variable that must be considered when designing and analyzing both basic and clinical research (http://www.iom.edu/Reports/2001/Exploring-the-Biological-Contributions-to-Human-Health-Does-Sex-Matter.aspx).

NIH indicates National Institutes of Health.

Methods

Writing group members were nominated by the committee chair and co-chair on the basis of their previous work in relevant topic areas and were approved by the American Heart Association (AHA) Cardiovascular and Stroke Nursing Council's Leadership Committee and the AHA's Manuscript Oversight Committee. The writers searched PubMed and Medline searches using the search terms listed in Table 3. We searched primarily literature from 2000 to 2015 but included earlier seminal studies as appropriate. All members of the writing group had the opportunity to comment on and approved the final version of this document. The document underwent extensive external peer review and approval by the AHA Science Advisory and Coordinating Committee.

Table 3. Search Terms

1. Chest pain OR myocardial infarction OR angina OR myocardial ischemia OR heart attack OR heart infarction OR heart muscle ischemia OR ischemic heart disease OR cardiovascular disease OR coronary heart disease OR coronary artery disease OR acute coronary syndrome
2. Women OR woman OR gender OR sex OR sex factors OR female OR sex difference
3. Time-to-treatment OR delay OR delayed OR time OR early diagnosis OR emergency medical services OR delayed diagnosis OR patient acceptance of health care OR therapy delay
4. Ethnic groups OR ethnicity OR racial OR race
5. Risk factors OR smoking OR hypertension OR diabetes mellitus
6. Behavior OR risk self-assessment OR cardiac risk awareness OR risk awareness OR awareness OR perception OR understanding OR symptom recognition OR symptom interpretation OR psychosocial
7. Bias OR stereotyping OR prejudice OR gender attitudes OR disparities
8. Outcomes
9. Healthcare provider OR doctor OR clinician

Scope of the Problem: Epidemiology of IHD in Women

The epidemiology of IHD is multifactorial and includes the contribution of risk factors such as age, race, genomics, ethnicity, culture, social, lifestyle, and environmental influences that may negatively affect the disease process. These factors may behave singly or interact multiplicatively to influence IHD. Pooled data from cohort studies support that women have substantially worse outcomes than men after acute IHD events, including greater levels of disability.[9,10] Thus, diagnosing and treating IHD in women are costly and contribute to escalating healthcare expenditures.

Age

IHD is vast, affecting ≈15.5 million Americans ≥20 years of age, with a lower prevalence rate for women (5.0%) compared with men (7.6%).[11] However, after 45 years of age for men and 55 years of age for women, the risk for IHD increases similarly in both groups. Although it has been assumed that premenopausal women (usually before 55 years of age) possess cardioprotective effects of estrogen, surprisingly, hormone replacement therapy (HRT) has not been shown to be effective in protecting against IHD in postmenopausal women and in fact may be harmful.[12]

The life expectancy for women is greater than that of men, contributing to an increased aged female population with greater IHD risk.[13] However, it is particularly worrisome that the IHD death rate in younger women 35 to 44 years of age continues to increase, while it is decreasing in their male counterparts.[11,14,15] Although risk factors such as obesity, diabetes mellitus, hypertension, smoking, and metabolic syndrome in younger women are thought to be the primary culprit in these troubling IHD trends, lack of recognition of prodromal symptoms and failure to assess for IHD in these younger women may contribute to this disturbing trend.[14]

Race

Race is construed as a biological factor determined by genetics. However, science indicates that race is best described as social rather than biological because there is more variation of genes within than between races. Genetically, the DNA sequence in all people is 99.9% identical, making race indistinguishable.[16–18] However, despite scientific evidence, a social stratum exists that distinguishes groups of people according to phenotypic characteristics (eg, skin color, body shape, and hair texture) that imposes social concerns.[18]

Interestingly, racial/ethnic variations in IHD exist in the United States, and black women have higher prevalence rates (7.0%) of IHD compared with Hispanic (5.9%) and white (4.6%) women. The same trend is noted with myocardial infarction (2.2%, 1.7%, and 1.8%, respectively) and angina (5.0%, 3.8%, and 2.9%).[15] The AHA statistical data for Asian and American Indian/Alaska Native women either are not listed or did not meet the standards of reliability.[11] According to the Centers for Disease Control and Prevention,[19] the leading cause of death for black (23.4%) and white (22.9%) women is IHD, whereas IHD is considered the second leading cause of death for Hispanic (20.5%), Asian/Pacific Islander (20.8%), and American Indian/Alaska Native (16.9%) women. Cancer is regarded as the leading cause of death for Hispanic, Asian/Pacific Islander, and American Indian/Alaska Native women. However, when Asian subgroups (Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese) are further delineated, IHD is the leading cause of death for Asian Indian and Filipino women.[20] A plausible explanation for higher death rates in these racial/ethnic groups is that these women have more risk factors for CVD.

Genomics

Although there is no genetic basis for racial classification, there may be genetic and genomic influences that place some women at increased risk of developing IHD.[21,22] A more detailed review of genetic and genomic concepts in CVD is found in an AHA scientific statement.[23] IHD is considered a complex, multifactorial disease because it is influenced by multiple genes and the environment. With multifactorial diseases, a woman may inherit ≥1 alleles that put her at increased risk, but environmental factors also influence disease development and progression. Environmental factors can influence the development or prevention of multifactorial disease even in the presence or absence of genetic risk factors, depending on the health behaviors of the individual. In other words, a woman may inherit ≥1 alleles that increase susceptibility to IHD, but if she is never exposed to environmental risk factors such as a high-fat diet or sedentary lifestyle, she may never develop IHD. Therefore, inheriting alleles that place a woman at increased risk does not mean that she is destined to develop a multifactorial disease. Interventions, even for women at great risk of developing IHD and associated complications, may prevent disease and prolong years and quality of life. Women with increased susceptibility to IHD as a result of genetic or environmental risk factors should receive education on how to reduce their risk.

Ethnicity and Culture

Identification with an ethnic group often implies shared cultural traditions. Although ethnicity is frequently associated with culture, the 2 terms are distinct. Ethnicity refers to ancestry and a person's country of origin or place of parental or ancestor birth[24] and is used to distinguish racial groups.[16] On the other hand, culture denotes a learned pattern of behavior in which beliefs, values, norms, and practices are shared from 1 generation to the next and influence thoughts and actions of a particular group.[16]

Women are influenced by their ethnicity and cultural background and thus are not considered to be a homogeneous group. A woman's ethnic or culture background creates complex norms and expectations that affect all aspects of life, including marital status, childbearing, caregiving roles, food preparation, educational level, job choices, wage rates, health beliefs/practices, amount of political power, and degree of social influence.[25] Therefore, healthcare providers must be prepared to address the influence of ethnicity and culture on women's health and well-being. The striking differences in

IHD prevalence rates in which black women have the highest prevalence rates compared with Hispanic and White women[11] are evidence that ethnicity and culture identify groups of women who are known to suffer a disproportionate burden of IHD and CVD.

Social and Environmental Influences

Social and physical environments have been implicated as major determinants of cardiovascular health. Certain social and physical environments tend to promote a cause-and-effect chain of events that contribute to developing CVD, including IHD.[26] Social conditions that affect cardiovascular health may include health behaviors (eg, smoking and alcohol use), lack of social support, low educational levels, low income, menial jobs, and racial discrimination.[26] Physical environments that may contribute to poor cardiovascular health include low-income neighborhoods, substandard housing, high-level noise pollution, living by high-traffic freeways and other sources of air pollution,[27] food deserts (fast food restaurants and convenience stores with limited access to supermarkets and full-service grocery stores), crime-ridden neighborhoods, and lack of access to quality health services. Moreover, women are more likely to live in these undesirable neighborhoods, especially minority women.[26] In the Well-Integrated Screening and Evaluation for Women Across the Nation (WISEWOMAN) study,[28] the authors noted how community characteristics (eg, racial segregation, community-level education, income characteristics, employment opportunities, and neighborhood safety) influenced CVD risk behaviors in different racial/ethnic groups. Blacks displayed the most CVD risk, whereas Hispanic and Alaska Native women displayed the least. Interestingly, some racial/ethnic disparities in CVD risk factors were explained by differences in individual and community characteristics, but other disparities persisted even after controlling for these factors. Thus, the impact of social and environment influences on women's health deserves further attention.

Outcomes: Rates of Repeat Acute Myocardial Infarctions, Rehospitalization, Disability, and Mortality

Although the annual death rate from IHD between 2000 and 2010 declined 39.2%,[15] disparities exist and women have notably poorer outcomes than men after the initial IHD presentation. Pooled data from the National Heart, Lung, and Blood Institute–sponsored cohort studies (1986–2007) indicate substantial disparities between men and women: 1 year after acute myocardial infarction (AMI), 19% of men and 26% of women ≥45 years of age will die. Within 5 years after a first AMI, 36% of men and 47% of women will die. Higher in-hospital mortality rates have also been reported for women with stable angina and acute coronary syndrome (ACS) compared with men.[9,10] This disparity in deaths after a first AMI preferentially affects older women because women tend to present with IHD at older ages, but as stated earlier, IHD death rates in younger women continue to escalate.[11] Clearly, these startling disparities must be addressed.

Additionally, women have more complications after having a first AMI such as increased bleeding risk after a first AMI treated with percutaneous coronary intervention (2.4% versus 1.2% for men).[29] At 45 to 64 years of age, 15% of men and 22% of women have a recurrent AMI or fatal cardiovascular event within 5 years. Furthermore, 8% of men and 18% of women develop heart failure within 5 years of a first AMI. As women and men age, the rates of a subsequent AMI and heart failure equalize.[15]

Sex differences also exist with ACS symptoms. A greater proportion of women than men with anginal symptoms and ACS have nonobstructive IHD[30]; however, more women than men have adverse outcomes. Women with nonobstructive IHD and stable angina have greater major adverse event rates than men with nonobstructive IHD (adjusted hazard ratio, 2.43, 95% confidence interval [CI], 1.08–5.49).[31] Furthermore, data from the Women's Ischemia Syndrome Evaluation (WISE) study showed 5-year annualized event rates for cardiovascular events of 16% and 7.9% in symptomatic women with nonobstructive IHD and normal coronary arteries, respectively.[32] Adverse outcomes continue over the long term for women in the WISE cohort with cardiovascular death or AMI at 10 years in 6.7%, 12.8%, and 25.9% of women with no, nonobstructive, and obstructive IHD ($P<0.0001$), respectively.[5]

Women with suspected ACS are less likely to be diagnosed with ACS, which has often been attributed to atypical symptoms and less reliable ECG findings.[33] However, a recent investigation reported that the use of a high-sensitivity troponin assay with sex-specific cutoffs increased diagnostic accuracy for women. In a study of 1126 patients with ACS (46% women), the high-sensitivity troponin I assay increased the diagnosis of AMI in women (from 11% to 22%; $P<0.001$) but had a minimal effect in men (from 19% to 21%; $P=0.002$) compared with contemporary assays with a single diagnostic threshold.[33,34] Additional studies are needed to determine whether the use of a high-sensitivity troponin I assay with sex-specific diagnostic thresholds will improve outcomes for women with ACS.

Finally, women with documented IHD and those who have experienced an AMI have poorer self-reported health-related quality of life and depression compared with men.[35–37] In the WISE study, depression, symptom severity, and history of depression treatment were associated with a greater risk of mortality and hospitalization.[38]

Costs

The estimated direct and indirect cost for IHD in 2010 was $108.9 billion and is projected to more than double by 2030.[39] Investigators from the WISE study estimated the average lifetime cost for women with nonobstructive IHD at $767 288 (95% CI, 708 480–826 097).[40] The estimated cost ranged from $1 001 493 to $1 051 302 for women with 1-vessel to 3-vessel IHD ($P=0.0003$). The volume of repeat catheterizations or hospitalizations for angina in 1 year was almost 2-fold higher in women with nonobstructive versus 1-vessel IHD ($P<0.0001$). Interestingly, women with nonobstructive or 1-vessel IHD required more drug treatment ($P<0.0001$).[40]

Trends in Public Awareness

In response to women's increasing mortality rates, the AHA has conducted a series of surveys to ascertain awareness of CVD by American women.[41] The first survey, conducted in 1997, revealed that only 30% of women recognized that CVD was the leading cause of death for women.[42] Despite aggressive campaigns such as Go Red for Women to raise women's awareness, a repeat survey in 2012 indicated that only 56% of white women currently recognized CVD as the leading cause of death, with even lower recognition in black and Hispanic women.[41] Until a greater number of women are aware of IHD as the leading cause of death in women, it will remain difficult to convince women to undertake necessary behavior changes to prevent the development of IHD. Although almost half of women in 2012 consider themselves very well or well informed about heart disease in women, they had difficulty identifying symptoms of IHD. Notably, chest pain was less frequently cited as a warning sign of a heart attack in 2012 compared with 1997 (56% versus 67%); however, awareness of less typical signs of a heart attack remained very low (fatigue, 10%; nausea, 18%; shortness of breath, 38%).[41] Awareness of calling 9-1-1 if experiencing symptoms of a heart attack was also low (65%).[41]

How Women Experience IHD

Risk Factors

Increasing age is a significant risk factor for the development of IHD in both men and women. Women are typically 10 years older than men when their heart disease is diagnosed. Epidemiological studies suggest that the increased prevalence of IHD risk factors with aging explains up to 50% of the age-related increased risk of IHD in women.[43] By midlife, >80% of women have ≥1 traditional cardiac risk factors.[44] Traditional risk factors for IHD in women are similar to those in men and include obesity, dyslipidemia, diabetes mellitus, older age, hypertension, inactivity, family history, and smoking.[45] It is important to note that IHD risk factors are commonly seen in conjunction with one another and that the rate of IHD in women increases with the number of these traditional risk factors.[46–48] Among women 18 to 39 years of age, those with no IHD risk factors had 88% lower rates of cardiovascular mortality over an average of 31 years of follow-up compared with women of a similar age with ≥2 risk factors.[47] Prevention of major cardiovascular risk factors in female individuals must occur at an early age, preferably early childhood, to significantly affect these trends. Because 80% of IHD is preventable, risk factor modification is an essential component of preventing IHD in women.

Although the overall number of risk factors is prognostic in both sexes, the prevalence and outcomes associated with individual risk factors differ in women and men.[46,49–52] Furthermore, the use of traditional risk factors alone has been criticized for underestimating IHD risk in women, particularly among women with subclinical disease.[44,53,54] Given this concern, several novel risk factors have been identified that may improve risk estimation and IHD detection in women.[46] The following is a brief review of both the traditional and novel IHD risk factors for women.

Women's Psychosocial Risks

As noted previously, women lag behind men in the manifestation and presentation of IHD. There are several other gender differences, for example the higher prevalence among women of some psychosocial states such as depression, which itself is a major risk factor for IHD and is twice as common in women compared with men.[55] Low and colleagues[56] conducted a review of the literature on psychosocial risk and protective factors for IHD among women. Results of the review revealed that depression is a reasonably consistent predictor of IHD among women, both incident and recurrent IHD events. Although anxiety was associated with increased IHD risk among healthy women, a longitudinal study conducted by Stewart and colleagues[57] found that anxiety was not associated with the common carotid artery intima-media thickness for women or men. Two studies[58,59] reported that hostility was a significant predictor of increased risk for IHD events among women.

Stress is frequently thought to be associated with IHD. Low et al[56] identified 11 studies that examined stress that was based on the conventional measure of perceived high demand and low control and suggested that this measure may be less important for women compared with men. What may be more important is the exposure to psychological stress in both the work and home settings. Lack of social relationships in women with existing IHD[60,61] is associated with an increased risk for IHD mortality and recurrent events; specifically, loneliness has been shown to be associated with increased IHD incident risk.[62] In summary, the empirical literature suggests that for primary and secondary IHD prevention, positive reciprocal social relationships may be important for women, and from a negative perspective, psychological stress in the interpersonal domains may create an important risk for IHD among women.[56] Few studies have focused on positive states or traits.[63,64] The Women's Health Initiative (WHI)[63] found that an optimistic disposition was associated with reduced risk, whereas the National Health and Nutrition Examination Survey (NHANES)[64] reported that emotional control and vitality and positive well-being were associated with lower coronary heart disease risk.

Obesity, Metabolic Syndrome, Diabetes Mellitus, and Dyslipidemia

The increased incidence of obesity has been recognized for the past 20 years as an epidemic in all industrialized countries and is associated with increased CVD risk.[65] The incidence of obesity is greatest in the middle of the United States, with 24 states having a prevalence of >30%.[66] CVD prevalence and mortality are the highest in these same states.[67] With no other risk factors for CVD, Cerhan and colleagues[68] reported that waist circumference was associated with greater risk of mortality than any other variable.

Women are particularly at risk for CVD and especially IHD if they are obese. The incidence of obesity may be as high as 40% in postmenopausal women.[69] There are also ethnic differences in the incidence of obesity in the United States. For example, in 2007 to 2008, 33% of non-Hispanic white women were obese, whereas 49.6% of non-Hispanic black women were obese.[69,70] Obesity increases after surgical menopause

and is increased in women who start HRT within 12 months of amenorrhea.[71] There is also evidence that even if women do not gain additional weight after menopause, there is a redistribution of body fat, favoring an increase in abdominal fat waist circumference gain rather than lower-hip weight gain.[72] This is significant because weight that accumulates in the abdominal area is associated with a higher incidence of CVD than weight that is accumulated in the lower body.[73]

Obesity (particularly central obesity) is 1 component of the cluster of features known as the metabolic syndrome, which also includes insulin resistance or type 2 diabetes mellitus, dyslipidemia, and hypertension.[69,70] Women with metabolic syndrome have an increased prevalence of subclinical atherosclerotic disease and higher all-cause and cardiovascular mortality compared with women without metabolic syndrome.[46,74–76] Horvei and colleagues[77] reported that waist-to-hip ratios and waist-to-height ratios had the greatest risk for AMI in women who participated in the Tromsø Study (1994–1995) and were evaluated up to 2011. In another study in patients with IHD and hypertension, the majority of obese individuals were women (67.1%), and they had a higher prevalence of diabetes mellitus, dyslipidemia, left ventricular hypertrophy, and heart failure than normal-weight women.[78] In addition, hypertension was controlled in only <35% of obese individuals compared with 52% of normal-weight individuals, and diabetes mellitus was controlled in only 18% of obese individuals compared with 43% of normal-weight individuals. The investigators concluded that chronic IHD worsens as body mass index increases.

Currently, it is unknown whether body weight alone or the combination of obesity and parameters of the metabolic syndrome increases the risk of CHD.[79,80] In the Louisiana State University Hospital–based Longitudinal Study with 7414 subjects (2926 men and 4488 women), there was a positive correlation between body mass index at baseline and increased risk of IHD in individuals with type 2 diabetes mellitus at follow-up for both men (P_{trend}<0.001) and women (P_{trend}<0.001).[80] In contrast, comparison of data from the Framingham Offspring, Atherosclerosis Risk in Communities, and Cardiovascular Health cohorts, assessed for ≥8 years, indicated that abdominal obesity alone was not significantly associated with increased risk of CVD.[73] However, inclusion of 1 or 2 components of metabolic syndrome plus type 2 diabetes mellitus did significantly increase the odds ratio of developing CVD and IHD in both men and women.

Women with diabetes mellitus have a >6-times higher risk of dying of CHD compared with women without diabetes mellitus.[81] Numerous studies suggest that diabetes mellitus conveys a higher risk for cardiovascular mortality in women compared with men.[82–90] Even women with type 1 diabetes mellitus have been shown to have a 40% excess risk of fatal and nonfatal cardiovascular events compared with men with type 1 diabetes mellitus.[91] The increased risk from diabetes mellitus may be partially related to the greater burden of cardiovascular risk factors seen in women compared with men, differences in their pathophysiology, and lower rates of recognition, treatment, and control of diabetes mellitus in women compared with men.[83,85–88,92] Although mortality rates among diabetic women and men have been declining in recent years, the magnitude of decline has been greater in men than in women.[93] Therefore, continued research is needed to better understand how to improve cardiovascular outcomes among diabetic women.

Dyslipidemia is a significant risk factor for IHD in women and men.[49,94–97] High total cholesterol, high low-density lipoprotein, high triglycerides, and low high-density lipoprotein all have been shown to be associated with increased cardiovascular risk in women.[98,99] All major international guidelines on the treatment of dyslipidemia recommend similar approaches to the management of dyslipidemia in both men and women.[94–96] High triglycerides have been shown to be a stronger predictor of IHD risk in women compared with men, although whether this relationship is related to the ratio of triglycerides to high-density lipoprotein is debated.[99,100] Reiner and colleagues[97] assessed individuals who had IHD and reported that the majority of both men and women had elevated total cholesterol, especially low-density lipoprotein cholesterol, and 37% had reduced levels of high-density lipoprotein. Data from the 14-year follow-up of the Nurse's Health Study showed a significantly increased risk for nonfatal AMI and IHD among women with higher intake of saturated dietary fat.[101] Despite a similar recommended approach to the treatment of dyslipidemia, many studies have shown that women are less likely to be prescribed lipid-lowering therapies or to achieve recommended cholesterol goals when treated compared with the outcomes for men.[102–107] Clearly, the lack of following treatment guidelines and failure to obtain recommended treatment goals contribute to women's poorer outcomes. This disparate treatment enhances the perception of bias in treating women with known cardiac risk factors or IHD.

Physical Inactivity

PI negatively affects several modifiable major risk factors for IHD in both sexes. PI in women is often associated with obese and overweight states, hypertension, diabetes mellitus, and certain abnormal blood lipids. Overall, older women, who are more at risk for IHD, tend to be more physically inactive than men. Many older women lack experience in team activities and group exercise, contributing to their PI.[108] However, this is changing as more baby boomers age and participate in group activities such as water aerobics, yoga, and Pilates. The National Institute on Aging has excellent step-by-step instructional material to encourage safe activity in the older population, *Your Everyday Guide from the National Institute on Aging, Exercise and Physical Activity*.[107a] Silver Sneakers and other local programs are increasing opportunities for both older men and women to participate in physical activity. However, despite these educational materials tailored to older adults and increasing opportunities for age-related group exercise activities, women continue to have higher rates of PI than men (33.2% compared to 29.9%), perhaps because health professionals are not encouraging them to increase activity.[109,110] Unfortunately, high-risk minority women have the highest rate of PI.[109]

Research on the effectiveness of cardiac rehabilitation has consistently concluded that it is beneficial to all IHD patients in reducing cardiovascular risk factors after the occurrence of a cardiac event.[110–115] Some of these benefits are improved exercise capacity, improvement in lipids, reduction in body mass

index, reduction in morbidity and mortality, and improved psychological factors.[111,113–116] Historically, referral rates by healthcare providers to cardiac rehabilitation have been low for both sexes but substantially lower in women (≤50%).[110] Additionally, current referral rates remain severely suboptimal, with a greater disparity in referrals for women compared with men (31.1% versus 42.2%; $P<0.0001$),[112] with the lowest referral rates in minority women.[110,112–114]

If women are fortunate enough to be referred to cardiac rehabilitation, they do not fare as well as men. They typically have very low attendance rates, particularly minority women.[110–115] They report difficulty completing the recommended program because of their social roles of caretaker or single-parent head-of-household employment responsibilities.[110–115] Other barriers that may account for the disparity among women and minorities related to cardiac rehabilitation attendance and completion include lack of awareness among women about their IHD risk, low education level, psychological stress, financial barriers, language barriers, cultural differences, geographic inaccessibility, lack of transportation, physical deconditioning, and lack of significant social support system.[110–113,115]

Completion rates for women are significantly lower than for their male counterparts (50.1% versus 60.4%; $P<0.0001$), and minorities have decreased completion rates compared with whites.[112,113] In a study that compared younger women <55 years of age (n=65) with older women >55 years of age (n=187) enrolled in cardiac rehabilitation, data indicated that women who did not complete cardiac rehabilitation were significantly younger with more risk factors for IHD and increased levels of anxiety and depression.[115]

Another potential contributing factor for younger women is that when premenopausal women exercise, differences in pain perception may exist with regard to the effects of the menstrual cycle.[117] In addition, among women with angina, ischemia may be induced more easily in the early follicular phase (a low-estrogen state). Pain exacerbated by exercise in women with IHD may frighten them if they do not understand how pain may be affected by the menstrual cycle and may contribute to lower completion rates in younger women. There are other sex differences in exercise dynamics: Peak heart rate decreases more gradually in women than men, and exercise maximal heart rate is often different.[117]

Although there are mixed results in terms of who benefits the most from completion of cardiac rehabilitation, all studies conclude that women benefit from attendance, regardless of age. For instance, a study found that women (n=6374) who complete cardiac rehabilitation experienced the highest reduction in mortality (hazard ratio, 0.36; 95% CI, 0.28–0.45) with a relative benefit higher than men (n=19 584; hazard ratio, 0.51; 95% CI, 0.46, 0.56).[112] Another study demonstrated that although blacks (n=169) significantly benefited from cardiac rehabilitation, they did not benefit to the same degree as their white counterparts (n=927).[114] That study also concluded that women and diabetic patients had the least improvement after completing cardiac rehabilitation, but their improvements were significant.[114] Therefore, women with known IHD, regardless of age or race, benefit from referral to and completion of a cardiac rehabilitation program. Interventions need to be developed that address the social constraints that prevent many women from benefitting from cardiac rehabilitation.

Tobacco Use

Cigarette smoking remains the leading cause of preventable death in the United States.[45,118–121] In the United States, it is estimated that ≈17% of adult women currently smoke cigarettes.[118] Smoking is a potent risk factor for women in that it imparts a 25% greater risk of IHD than in male smokers, independently of smoking intensity or other cardiovascular risk factors.[49,122,123] In all age groups, women who smoke have a significantly higher risk of IHD events (fatal and nonfatal) compared with women who do not smoke.[124] The largest difference in risk for IHD events between smokers and nonsmokers was seen in young women or those 40 to 49 years of age; however, the absolute rate of IHD events was significantly higher in older women (≥60 years old) who smoked compared with nonsmokers.[124] Women who stop smoking at any age experience an immediate benefit and further longer-term declines in excess risk of IHD to the level of those who never smoked.[125–128] Therefore, promoting smoking cessation is vital to discuss with women of all ages to prevent the development of IHD.

Aging and Hypertension

Systolic blood pressure (BP) is the most important modifiable risk factor contributing to the excess IHD risk that occurs with aging in men and women.[43] Aging in both men and women is characterized by increases in BP, and the prevalence of hypertension in postmenopausal women is higher than in men.[129–132] Hypertension is a major risk factor for CVD in men and women.[129,131]

Worldwide, 25% of women are hypertensive, and in the United States, >75% of women >60 years of age are hypertensive.[133,134] The NHANES IV (1999–2002) showed that more women with high BP went undiagnosed compared with men (11.7% versus 9.9%).[135] Furthermore, in a study that compared the NHANES III cohort (ending in 1994) with the NHANES IV cohort (ending in 2002), hypertension was less well controlled in women than men who were taking antihypertension medications (14.6% versus 8.3%).[135] This finding is similar to the lower number of women receiving optimal treatment and achieving recommended lipid levels. It is possible that sex bias contributes to both of these treatment outcomes.

Nondipping of BP at night is associated with increased target-organ damage in both men and women,[136] but there is evidence that nondipping in women in general is associated with greater target-organ damage than in men[137,138] and that postmenopausal women are more likely than premenopausal women to exhibit nocturnal nondipping of BP.[137] Thus, although antihypertensive guidelines are no different for men and women[139] and women are more likely to have their BP measured, hypertension may be less well controlled in women. This suggests that women may not be as aggressively treated for their hypertension as men and that the mechanisms responsible for hypertension in aging women may differ from the mechanisms in men.

Roles of Estradiol and the Consequences of HRT

Whether the presence of estrogens protects against CVD is controversial. Estradiol has been shown to be cardiovascular

protective mainly in experimental settings or when intermediate markers for CVD were used as end points.[140,141] Whether the lack of estrogens contributes to CVD in postmenopausal women is also controversial and unknown. Early observational studies suggested an association between the use of HRT such as estradiol and lower cardiovascular risk in postmenopausal women.[142,143] However, large clinical trials of the effect of HRT in postmenopausal women have not supported these previous findings. The results of the WHI studies,[144] the Heart and Estrogen/Progestin Replacement Study (HERS) I and HERS II[145,146] trials, have not supported a role for HRT in the primary or secondary prevention of IHD, respectively. It is unknown if the mode of delivery of HRT, the dose of HRT, or the preparation of the HRT itself may play a role in the efficacy. For example, conjugated equine estrogen is a common estrogenic HRT, but because of the source (urine of pregnant mares), there are a significant number of other steroids in the preparation such as androgens. Conjugated equine estrogen was the preparation used in the WHI.[144] Ichikawa and colleagues[147] found that transdermal HRT for 12 and 24 months reduced diastolic and mean BPs in normotensive postmenopausal women. In contrast, Prelevic and colleagues[148] studied healthy postmenopausal women who had taken HRT for at least 5 years and reported either no effect or that BP was in fact higher in some women using HRT. Age at beginning HRT and the length of time after the last menstrual period when HRT is begun may also contribute to the efficacy and the occurrence of adverse effects. For example, postevaluation of women in the WHI study who were younger and randomized to the estrogen-only arm showed that there was a significant reduction in IHD after years 7 to 8.[149]

The prevalence of hypertension is higher in postmenopausal women, suggesting a possible role of sex hormones. Olszanecka and colleagues[150] measured ambulatory BP in normotensive and hypertensive women 40 to 60 years of age and found that BP was similar in the normotensive and hypertensive groups regardless of the presence or absence of menopause. Unfortunately, to the best of our knowledge, there have been no studies in which ambulatory BP has been measured serially over the perimenopausal transition to correlate and document any BP change with menopausal transition. Thus, whether the presence of estrogens protects young women from hypertension or loss of estrogens promotes coronary disease in postmenopausal women is not clear.

There is evidence that loss of estrogens at any age contributes to endothelial dysfunction, which is common in individuals with hypertension. Reduced endothelial function is more prevalent in postmenopausal women with hypertension, especially nighttime hypertension, compared with normotensive postmenopausal women.[151] Taddei and colleagues[152] reported that in response to acetylcholine, an index of endothelial dysfunction, endothelium-dependent flow-mediated vasodilation (FMD), was attenuated less with aging in hypertensive premenopausal women than men, but after menopause, the FMD response was attenuated to the same extent in both women and men. Attenuated FMD is prognostic of CVD risk factors, including hypertension, in postmenopausal women.[153] Women with premature ovarian failure before 40 years of age also exhibit reduced brachial FMD compared with age-matched cycling women, but in these women, HRT with conjugated equine estrogen and medroxyprogesterone for 6 months reversed the endothelial dysfunction.[154] In contrast, in the Women's Angiographic Vitamin and Estradiol (WAVE) trial, HRT had no beneficial effect on FMD in postmenopausal women.[155] The fact that HRT protected against endothelial dysfunction in young postmenopausal women but not in older postmenopausal women supports the contention that aging may change the response to HRT and thus may independently contribute to increases in BP.

Endothelial dysfunction is characterized by reductions in nitric oxide (NO). Estradiol stimulates NO production acutely by increasing intracellular calcium, which activates endothelial NO synthase.[156] In addition, estradiol increases NO chronically because it upregulates synthesis of endothelial NO synthase via estrogen response elements that would promote vasodilation and thus reductions in BP.[157] Estradiol is a modest antioxidant because it upregulates superoxide dismutase,[158] which removes superoxide, which reduces oxidative stress. Superoxide binds to NO with high affinity and thus renders NO unavailable for vasodilation.[159] Because an intact NO system is necessary for antioxidants to reduce BP, in situations of chronic hypertension when endothelial dysfunction is present and NO levels have been reduced for long periods, estradiol may lose the ability to affect BP. Furthermore, with an estrogen-mediated increase in superoxide dismutase, it is possible that there may be an increase in hydrogen peroxide, also a powerful oxidant that offsets any beneficial effect of removing superoxide.

Reductions in estradiol with menopause could also affect the renin-angiotensin system (RAS). Estradiol downregulates angiotensin type I receptors and angiotensin-converting enzyme,[160,161] thus protecting against activation of the RAS and subsequent vasoconstriction. Reductions in estradiol would therefore tend to promote activation of the RAS. However, in normotensive postmenopausal women, HRT with transdermal 17β-estradiol and oral medroxyprogesterone reduced BP but had no effect on levels or expression of RAS components such as plasma renin activity, angiotensin I or II, aldosterone, or angiotensin-converting enzyme activity.[147] In contrast, treatment of postmenopausal women with angiotensin type 1 receptor antagonists improved endothelial dysfunction measured by FMD, whereas calcium channel blockers did not,[162] supporting a role for the RAS in contributing to postmenopausal CVD.

Emerging Risk Factors for CVD

Inflammatory Markers

Research shows that there is a correlation between inflammation and IHD.[163–166] This correlation may be useful for early diagnosis of IHD because multiple biomarkers can be used to detect inflammation, including high-sensitivity C-reactive protein (hs-CRP), interleukin-1, interleukin-6, and tumor necrosis factor-α. In fact, some of these biomarkers have been used to aid in the diagnosis of IHD.[164,166,167] However, some of the biomarkers are not specific for IHD, which may limit their diagnostic usefulness. In addition, the exact mechanism of how biomarkers function is not clear. Therefore, the usefulness of biomarkers alone as screening tools for IHD is controversial.

Lipoprotein(a) [Lp(a)] has also been shown to be a risk factor for IHD and other CVDs. For instance, a 15-year prospective study (n=826; 52% female) found that Lp(a) level was associated with the occurrence of CVD. The hazard ratio per 1-SD-higher Lp(a) for women was 1.32 (95% CI, 1.10–1.58). Interestingly, the addition of Lp(a) to the Framingham Risk Score and Reynolds Risk Score improved prediction of CVD in this study.[168] The exact mechanisms are not known, but the association of Lp(a) with IHD may be due in part to its proinflammatory properties. Another mechanism may be its low-density lipoprotein component. Clinical utility of Lp(a) is controversial, but the US National Lipid Association and the European Atherosclerosis Society recommend its use in select populations such as those with intermediate or high risk of developing CVD to assist in identifying their risk.[169,170]

hs-CRP is the most commonly studied inflammatory marker for the detection of IHD. However, it is unknown whether it is an independent risk factor for CVD. Data support that it may improve risk detection in women.[163,171,172] In the Women's Health Study, a global risk predication model that included hs-CRP improved cardiovascular risk prediction in women.[171] Furthermore, hs-CRP has been shown to be a stronger predictor of cardiovascular events in women than low-density lipoprotein cholesterol.[172] For women with metabolic syndrome, hs-CRP may add prognostic information on future cardiac risk. In a study of apparently healthy women, those with metabolic syndrome and hs-CRP levels >3.0 mg/L had almost twice the risk of a future cardiovascular event as those with metabolic syndrome and an hs-CRP <3.0 mg/L.[173] Measuring hs-CRP is not recommended in routine risk assessment of women but rather as an option in those with intermediate risk.[174] The benefits of assessing hs-CRP or any treatment based on this strategy remain uncertain.

Autoimmune Disease

Atherosclerosis may be accelerated by the presence of systemic inflammation.[175] Rheumatoid arthritis and systemic lupus erythematosus (SLE) are associated with a significantly increased risk for CVD.[175] In the "Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update," systemic autoimmune collagen-vascular disease was listed as a criterion for the status of "at risk."[176] Examination of the California Hospital Discharge Database indicated that young women between 18 and 44 years of age with SLE (n=3851) were 2.27 times more likely than their age-matched peers without SLE (n=19 228) to be hospitalized because of AMI, 3.80 times more likely to be hospitalized because of congestive heart failure, and 2.05 times more likely to be hospitalized because of cerebrovascular accident.[177] Women in the Framingham Offspring Study 35 to 44 years of age with SLE were an astonishing 50 times more likely to have an AMI than women of the same age without SLE.[178] Traditional risk factors such as smoking, family history of premature disease, hypertension, and elevated cholesterol do not completely account for the increased risk of IHD in patients with SLE.

Preeclampsia and Pregnancy-Associated Hypertension

Women with a history of preeclampsia have a 3.6- to 6.1-fold greater risk of developing hypertension and a 3.1- to 3.7-fold higher risk of developing diabetes mellitus, depending on whether the preeclampsia is mild or severe.[179] Preeclampsia is also a risk factor for future ischemic stroke.[180] One large cohort study in Northern Finland (n=12 055) found that any elevated BP during pregnancy, regardless of type, signaled a greater risk of developing CVD, chronic kidney disease, and diabetes mellitus than in women without elevated BP during pregnancy.[181] A number of meta-analyses have demonstrated that women with a history of preeclampsia have approximately double the risk for subsequent IHD, stroke, and venous thromboembolic events over the 5 to 10 years after the pregnancy.[182,183] The "Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update" lists history of preeclampsia or pregnancy-induced hypertension as a criterion for the status of at risk.[176]

Gestational Diabetes Mellitus

Unique to women is the IHD risk factor of gestational diabetes mellitus. A history of gestational diabetes mellitus doubles the risk of developing diabetes mellitus in the following 4 months postpartum and remains a lifelong risk factor.[184] Fasting glucose levels ≥121 mg/dL during pregnancy increase the risk for diabetes mellitus in the early puerperium by an astounding 21-fold.[185] Studies have also shown at least 1.5 times greater risk of CVD in women with a history of gestational diabetes mellitus compared with women without gestational diabetes mellitus.[183] "Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update" incorporated a history of gestational diabetes mellitus as an at-risk criterion, requiring attention to CVD risk factors and the implementation of therapeutic lifestyle changes in these women throughout their lives.[176] Women must be educated about their ongoing risk imparted by experiencing gestational diabetes mellitus.

Reproductive Hormones

Oral Contraceptive Therapy. The American College of Obstetricians and Gynecologists and the World Health Organization have published guidelines on medical eligibility for contraceptive use.[186] For most women who are healthy and free of CVD and cardiovascular risk factors, the use of combination estrogen-progestin oral contraceptives is associated with low relative and absolute risks of developing CVD.[187] However, women who are smokers and >35 years of age, women with uncontrolled hypertension, and women with a history of IHD have an unacceptably high risk associated with oral contraceptive use.[187,188]

Postmenopausal Hormone Therapy. A majority of CVD occurs after menopause in older women, which is associated with an increased burden of risk factors for CVD.[189] As stated earlier, it was thought that postmenopausal HRT should reduce the risk of CVD, and initial observational data supported this hypothesis. Nonetheless, randomized trials such as HERS I, HERS II, WHI, and Raloxifene Use for the Heart (RUTH) did not support that HRT or selective estrogen receptor modulators prevented CVD, regardless of use for primary or secondary prevention.[144,146,190,191] The AHA "Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update" states that HRT and selective estrogen receptor modulators should not be used for the primary

or secondary prevention of CVD and are a Class III, Level of Evidence A intervention.[176]

Polycystic Ovarian Syndrome

Unique to women, polycystic ovarian syndrome (PCOS) is associated with the development of metabolic syndrome and insulin resistance. A meta-analysis concluded that women with PCOS have an increased prevalence of impaired glucose tolerance, metabolic syndrome, and diabetes mellitus compared with women without PCOS.[192] It remains unclear whether PCOS is an independent risk factor for premature CVD in women, but recent data suggest an elevated risk in women with PCOS that is independent of established risk factors in older postmenopausal women.[193] Furthermore, in the WISE study of postmenopausal women with PCOS, cumulative 5-year CVD event–free survival was 79% for women with PCOS compared with 89% for women without PCOS.[193]

Functional Hypothalamic Amenorrhea

It is estimated that up to 10% of premenopausal women have documented ovarian dysfunction, with a larger proportion having subclinical hormonal dysfunction that may result in an increased risk of developing CVD. Functional hypothalamic amenorrhea is a cause of a premenopausal ovarian dysfunction and occurs when gonadotropin-releasing hormone increases, thereby increasing luteinizing hormone in a pulse frequency causing both amenorrhea and hypoestrogenemia. Functional hypothalamic amenorrhea can be induced by psychological stressors or a metabolic insult such as caloric restriction or excessive exercise. In a large cohort study, women with menstrual irregularities had a 50% increased risk of nonfatal and fatal IHD compared with women with regular menstrual cycling.[194] Data suggest an association between functional hypothalamic amenorrhea and premature coronary atherosclerosis in women undergoing coronary angiography[195] and that the use of oral contraceptive therapy may offer protection.[196] These findings suggest that amenorrhea and cycling irregularity may be risk factors for CVD in women, but further research is still needed to understand this association.

Breast Cancer Therapy

As a result of advancements made in breast cancer treatment, there has been improved survival in women with breast cancer, yet these women have an elevated risk of developing CVD.[197] Breast cancer therapies (including anthracycline therapies, trastuzumab, and radiation therapy) are associated with various degrees of direct cardiovascular injury, in addition to significant indirect lifestyle changes that also reduce cardiovascular reserve.[197] It remains unclear whether it is the presence of breast cancer itself or the specific therapies for treatment of breast cancer that increase the risk for CVD. The risks to the heart can be related to many cardiovascular issues, but radiation therapy seems to have an established association with the development of IHD. Exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the rate of developing IHD. The risk is directly proportional to the mean dose of radiation to the heart, with an increase in CVD events of 7.4% per 1 Gy of radiation (95% CI, 2.9–14.5; $P<0.001$).[198] The mean radiation dose to the heart in a study of 2168 women who received radiotherapy treatment for breast cancer was 4.9 Gy. The risk of IHD begins within a few years after exposure and appears to continue for at least 20 years after the exposure. As expected, the absolute risk for IHD is highest in those women with preexisting CVD risk factors.[198] This increased risk for IHD may be underappreciated. Nonetheless, this is an increasingly important issue in the management of women surviving breast cancer. Further work is needed to determine the relative and absolute risk of breast cancer and its specific therapies to guide cardiovascular healthcare providers who will increasingly be called on to evaluate and treat these women.

Sleep Apnea

Although sleep apnea is more prevalent in men than in women, it is a very common issue in women and underrecognized in terms of its impact on CVD. In women, untreated obstructive sleep apnea is associated with an increased risk of hypertension, coronary artery disease, stroke, and atrial fibrillation.[199] Central sleep apnea occurs mainly in patients with heart failure. Regardless of type, sleep apnea is believed to induce severe intermittent hypoxemia and carbon dioxide retention during sleep, with oxygen saturation sometimes dropping to ≤60%, disrupting the normal autonomic and hemodynamic responses to sleep.[200] Apnea often occurs repetitively through the night, and toward the end of an apneic episode, BP can reach levels as high as 240/130 mm Hg.[201] This hemodynamic stress occurs simultaneously with severe hypoxemia, hypercapnia, and adrenergic activation, which in turn act to promote CVD. Importantly, untreated sleep apnea in women is associated with 3.5-times greater risk of dying of CVD, yet this risk was reduced to the same degree as in a woman without sleep apnea with appropriate treatment with continuous positive airway pressure.[199]

Assessing Women's IHD Risk

A gap in racial/ethnic awareness of IHD as the number 1 cause of death in women was noted in 1997 and again in 2012, with white women's awareness (65%) superseding that of black (36%) and Hispanic (34%) women.[41] Although awareness of heart disease has improved over the past 15 years, the gap in awareness is alarming. Clearly, efforts to inform minority women of their risk for developing IHD are insufficient. Further research is needed to determine the most effective ways to reduce this disparity. Because IHD is the leading cause of mortality, morbidity, and disability among women in the United States,[15] it is vital that women have an accurate perception of their risk for IHD. Major causative factors for heart disease are credited to modifiable risk factors (eg, hypertension, dyslipidemia, diabetes mellitus, and smoking). Rarely do cardiac risk factors occur in isolation; rather, there is a synergistic action among several risks factors that exacerbates the disease burden. Therefore, treatment should be holistic and not singly focused on individual risk factors.[202]

It is vital that healthcare providers accurately use cardiovascular risk assessment tools and effectively treat cardiac risk using recommended guidelines. It is equally vital that healthcare providers teach all patients about their cardiac risk in simple terms they can understand and provide lifestyle management counseling.[52] In a systematic review, intervention intensity and repetitive presentations improved risk

perception accuracy and intent to adhere to preventive strategies.[203] Whether this intent translated into action is not known. Longitudinal studies that focus on repetitive risk presentation at delivery levels are needed to determine suitable impact on cardiac outcomes.

Even when clinicians suspect IHD, accurately estimating women's risk is challenging. Perhaps the most used risk assessment tool is the Framingham Risk Score, which includes traditional risk factors such as age, sex, BP, tobacco use, and cholesterol levels. However, it does not include family history, pregnancy-related problems such as preeclampsia, and other emerging risk factors discussed earlier in this article. Therefore, it may underestimate IHD risk in women. The Reynolds Risk Score was developed to detect the risk of CVD[204] and includes the Framingham components but adds family history, hemoglobin A_{1c} in diabetics, and 1 inflammatory marker, hs-CRP. Inflammatory markers may be especially important in the detection of IHD in women, who tend to have more microvascular disease than men. A more recent risk score published jointly by the AHA and the American College of Cardiology is the Atherosclerotic Cardiovascular Disease Risk Estimator.[52] This risk score includes age, sex, BP, tobacco use, cholesterol, race, and diabetes mellitus status and was developed with Pooled Cohort Equations from several large cohort studies of white and black men and women. A mobile application is available that includes the risk score and most recent cardiovascular prevention guidelines so that clinicians can easily access this information. These risk scores can aid in decisions about the prevention and treatment of IHD. However, healthcare providers tend to underestimate the risk of IHD in women regardless of the risk assessment used.

Currently, risk assessment tools are available for 5-year, 10-year, or lifetime risk estimate of coronary disease electronically,[52,202] and the risk estimate is relevant for vulnerable populations such as women and blacks. However, modifications to current risk assessment tools are needed because most underestimate or overestimate risk for nonwhite racial/ethnic groups.[52]

The Diagnostic Experience

Recognizing IHD in women is a long-standing, 2-pronged problem for both women and health professionals. First, women have to recognize symptoms as indicative of potential disease and seek treatment. Second, when they seek treatment, health professionals must recognize symptoms as potential prodromes of heart disease or acute symptoms indicative of impending AMI and respond appropriately.[205,206] Although progress is evident on both fronts, too many women continue to have difficulty recognizing symptoms as potentially indicative of heart disease, and many of those who do recognize symptoms and seek medical attention continue to report that providers ignore their concerns or minimize the importance of their symptoms. This in turn undermines women's confidence in their ability to recognize the importance of their symptoms and may deter women from seeking additional health care for prodromal symptoms.[207] Prodromal symptoms are defined as symptoms that are new and intermittent before an acute cardiac event and resolve after the event.[208] This lack of recognition of symptoms leads to delays in seeking treatment and contributes to women's disability and mortality rates.

Women's Viewpoint

Early qualitative studies of women's experiences in seeking medical assistance for troubling symptoms of unknown origin, later diagnosed as IHD when women experienced an AMI, began appearing in the literature in the late 1990s.[209] At this time, research on women's IHD symptoms was in its infancy, and women's mortality rates were increasing at alarming rates and eventually surpassed men's rates.[15] In recognition of these statistics, a concerted effort was initiated to improve women's IHD outcomes. These early qualitative studies reported that women were often recognizing symptoms as not normal, but they did not attribute them to potential IHD because they thought it was a disease that occurred primarily in men. Additionally, elusive and vague intermittent prodromal symptoms made it difficult for women to recognize these symptoms as indicative of IHD. The AHA embarked on a project, Go Red for Women, to increase women's awareness of heart disease as the number 1 killer of women so that women would suspect it and seek prompt medical attention. However, studies continue to report that many women frequently attribute symptoms to noncardiac reasons, minimize the importance of symptoms, or put meeting social and role responsibilities ahead of their seeking medical attention for themselves.[205,207,210] Equally troubling, when women recognize that something is not right and they seek timely medical attention, they often report difficulty receiving a diagnosis and accurate treatment. Unfortunately, this is not just a problem in the United States. Similar experiences have been reported by women in a variety of studies conducted worldwide, making this a universal problem.[207,210–213]

Two recently published, small, qualitative studies[207,210] (n=10 and 20) conducted in different countries reported similar accounts of women's diagnostic experiences. In both studies, more than one half of women sought medical care during the prodromal period for troubling symptoms. Although a few received recommended diagnostic tests and treatments, many reported that their symptoms were not taken seriously or downplayed, which contributed to their delaying seeking treatment when symptoms became more severe. They doubted their ability to recognize important symptoms requiring immediate attention. Even when health professionals correctly identified symptoms as needing immediate treatment, some women were instructed to go to a hospital emergency department by private automobile or taxi, not by emergency transportation. This further decreased women's confidence in healthcare providers. These experiences are not remarkably different than those reported by McSweeney et al[214] more than a decade earlier in a sample of women in the United States. That study was conducted with 40 women 27 to 79 years of age (58.5±12.5 years) who had previously experienced an AMI.[214] Most women were unaware that they were at risk for IHD but sought medical attention when troubling symptoms appeared. When the women sought treatment for their prodromal symptoms, they reported trouble with getting diagnosed, perceived that they were not taken seriously by providers, and were often

treated for depression or indigestion.[214] This delay in treatment and diagnosis led many of the women to grow frustrated with seeking treatment for their symptoms and angry with the delay in receiving a diagnosis before their AMI.[214] Some women expressed relief at receiving the diagnosis of AMI because they finally understood what was wrong with them. These studies document a trend of missed opportunities to prevent and/or delay AMI resulting from a lack of recognition of prodromal symptoms. Unfortunately, this lack of recognition of prodromal symptoms in women continues to persist despite studies identifying women's most frequent prodromal symptoms.

Healthcare Providers' Viewpoint

Although awareness about the prevalence of IHD among women has improved in recent years, many healthcare providers still view it primarily as a man's disease or one that affects older women after menopause, and others are uncertain even when they correctly diagnose IHD.[215–217] This uncertainty often results in less aggressive or less timely treatment for women with possible IHD. In fact, research shows that women are consistently treated less intensely than men before and after the diagnosis of IHD in the United States and other countries.[217–221] There are many reasons for this such as bias and lack of education related to the nontraditional symptom presentation often described by women to their healthcare providers. For instance, many clinicians do not entertain IHD as a diagnosis when a woman complains of fatigue or shortness of breath. In addition, many women who undergo coronary angiography are negative for obstruction. In fact, among women who present with "chest symptoms," only ≈50% have obstructive IHD.[5,6] This procedure is not without risk and expense, and clinicians may be reluctant to offer it for women who are typically older at the time of diagnosis of IHD. The diagnosis of IHD may be missed or delayed when coronary angiography is not performed in a timely manner.

Symptoms/Presentation

Women's decision to seek care for possible IHD is directly related to their symptoms. Research shows that women are less likely to experience chest pain than men,[222] but the majority experience prodromal symptoms such as shortness of breath or unusual fatigue for weeks or even months before an acute cardiac event. McSweeney et al[223] have published a series of studies identifying US women's most frequently reported prodromal symptoms (Table 4) and racial/ethnic differences in these symptoms.

A study in Korea reported that 145 of 271 women experienced prodromal symptoms before their first AMI.[211] The most common reported prodromal symptoms were chest symptoms (34.5%), indigestion (19.3%), shortness of breath (9.7%), and fatigue (8.3%). Almost 64% of those who experienced fatigue or weakness and ≈38% of those who experienced chest or epigastric symptoms recognized that something was wrong but either did not think it was serious or attributed it to their age or other comorbidities. Only 40% of the women with prodromal symptoms visited a clinic or hospital for those early symptoms.

A prospective, longitudinal study conducted in the United States with 1097 women indicated 4 prodromal symptoms that were significantly associated with an increased risk of experiencing a cardiac event[212]: discomfort in the jaw/teeth, unusual fatigue, discomfort in the arms, and shortness of breath.[212] Additionally, women reporting ≥1 of these prodromal symptoms were 4 times more likely to experience a cardiac event within the 2-year follow-up.[212] Recognition of these prodromal symptoms by women and healthcare providers could improve the diagnosis of IHD and thus promote timely treatment to prevent/delay progression to AMI.

Recognition of Symptoms as Cardiac

Women may have difficulty identifying prodromal symptoms as cardiac because they may not experience chest pain, the most publicized symptom of heart disease. A meta-analysis of 26 studies examining sex differences in IHD symptom presentation reported that women with AMI had lower odds of presenting with chest pain than men (odds ratio, 0.63; 95% CI, 0.59–0.68).[224] Instead, women were more likely to present with fatigue, nausea, neck pain, right arm pain, jaw pain, dizziness, and syncope than men. Other differences were that women were older than men at symptom presentation by a mean of 6.58 years (95% CI, 5.42–7.74) and that women were more likely to have a history of congestive heart failure than men (relative risk, 1.64; 95% CI, 1.44–1.88).

Two qualitative studies examined women's recognition of IHD symptoms. One study included 9 women (4 black, 5 white) with recently diagnosed IHD who were interviewed within 2 weeks after hospital discharge.[225] Five of the 9 women experienced atypical symptoms of IHD and had difficulty identifying the cause of the symptoms. The women reported a lack of acute symptoms and did not initially realize the need to seek care. Four of the women had what they recognized as IHD symptoms. All women tried to identify a symptom pattern, and only when they were able to do so did they recognize their symptoms as cardiac in nature.

A descriptive study using vignettes in Lima, Peru, examined sex differences in health care–seeking behavior for AMI (n=90; 54.4% women).[213] Women in this sample were 4 times less likely than men to identify chest pain as a symptom of IHD in the vignette labeled typical chest pain after adjustment for demographic variables (odds ratio, 0.23; 95% CI, 0.063–0.87). After watching the same vignette, women were more likely to respond that a man would seek help (odds ratio, 4.54; 95% CI, 1.21–16.90) and that a woman would be less likely to seek help (odds ratio, 3.26; 95% CI, 1.13–9.41 after adjustment). Both of these studies demonstrate that women may be reluctant to attribute symptoms to heart disease even when they experience typical chest symptoms.

Women also underestimate their risk of IHD,[226] which can influence their decision to seek care. Most women still view IHD as a man's disease and perceive breast cancer as a greater health threat for them than IHD. One integrative review found that lack of communication between women and their healthcare providers about the risk of IHD contributes to this misunderstanding.[206]

Delay in Seeking Treatment

Obtaining timely treatment for AMI is crucial for survival and optimal clinical outcomes, yet women continue to delay longer than men.[227] Delay is defined as the time between symptom

Table 4. Significant Differences in Frequency of Women's Prodromal Symptoms by Race

	Black (n=545), n (%)	Hispanic (n=186), n (%)	White (n=539), n (%)	Raw *P* value	Adjusted *P* Value
Generalized symptoms					
Unusual fatigue	421 (77.2)	124 (66.7)	385 (71.4)	0.009	0.174
Anxious	27 (51.2)	95 (51.1)*	199 (36.9)†	<0.001	<0.001
Frequent indigestion	235 (43.1)*	50 (26.9)†	209 (38.8)*	<0.001	0.004
Heart racing	233 (42.8)*	68 (36.6)*†	153 (28.4)†	<0.001	<0.001
New vision problems	217 (39.8)*	43 (23.1)†	132 (24.5)†	<0.001	<0.001
Change in thinking or remembering	202 (37.1)*	60 (32.3)*†	135 (25.0)†	0.001	0.001
Loss of appetite	183 (33.6)*	50 (26.9)*†	124 (23.0)†	<0.001	0.006
Difficulty breathing at night	182 (33.4)*	38 (20.4)*†	107 (19.9)†	<0.001	<0.001
Tingling in hands/arms	172 (31.6)	47 (25.3)	125 (23.2)	0.007	0.064
Numbness or burning in hands/fingers	171 (31.4)*	45 (24.2))*†	104 (19.3)†	<0.001	<0.001
Cough	147 (27.0)*	59 (31.7)*	98 (18.2)†	<0.001	<0.001
Increased frequency of headaches	109 (20.0)	29 (15.6)	68 (12.6)	0.005	0.055
Increased intensity of headaches	91 (16.7)*	36 (19.4)*	48 (8.9)†	<0.001	<0.001
Discomfort/pain symptoms					
Centered high in chest	102 (18.7)*†	46 (24.7)*	76 (14.1)†	0.004	0.004
Leg(s)	61 (11.2)*	29 (15.6)*	22 (4.1)†	<0.001	<0.001
Both arms	30 (5.5)	24 (12.9)	33 (6.1)	0.003	0.014
Right arm or shoulder	24 (4.4)*†	16 (8.6)*	13 (2.4)†	0.002	0.004
Jaw/teeth	17 (3.1)†	20 (10.8)*†	23 (4.3)†	<0.001	0.001

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onset and accessing health care for those symptoms, referred to here as treatment-seeking delay. This difference is often attributed to the difference in symptoms or women's interpretation of symptoms compared with men. Although much success has been achieved in reducing the components of delay once a patient enters the healthcare system, little has changed in treatment-seeking delay times for women. This behavior is universal across cultures, including women in Saudi Arabia,[228] China,[229] Brazil,[230] and Norway,[231] and across racial groups, including black women.[232] Recent studies continue to demonstrate that treatment-seeking delay is associated with worse outcomes.[233] Clearly, new methods to educate women are urgently needed to assist women to recognize symptoms earlier and to immediately seek medical assistance.

Numerous studies have attempted to elicit causes of why women delay seeking treatment longer than men. Many attribute this to misinterpretation of symptoms by women[234] or their providers,[235] as well as differences in symptoms.[236] Qualitative studies have helped to elucidate the types and reasons for women's symptom behaviors during the treatment-seeking delay time. Rosenfeld et al[237] described 2 main decision trajectories that women used when responding to AMI symptoms: knowing (knowing almost immediately that they would seek help) and managing (treating an alternative hypothesis or minimizing their symptoms). Davis et al[225] described a process that women went through when making decisions about seeking care. This process included noticing symptoms, forming a symptom pattern, using a frame of reference, finding relief, and assigning causality. Some women who were uncertain delayed seeking care, whereas others who were certain also delayed seeking care.

Women who report prodromal symptoms often experience the same symptoms during an acute event.[212] Prodromal symptoms by definition are intermittent and resolve spontaneously.[212] In a recent study comparing prodromal and acute symptoms in women, >50% reported experiencing the same prodromal and acute symptoms.[208] Two of the symptoms from this study had >80% agreement: chest pain/discomfort and shortness of breath.[208] Additionally, the prodromal and acute symptom of weak and heavy arms had >65% agreement.[208] These women may delay seeking treatment until they determine that symptoms are unrelenting.[212]

The state of the science of intervention research to decrease delay has been disappointing. Neither the Rapid Early Action for Coronary Treatment (REACT) study[238] of a community-level intervention nor An Intervention to Reduce Prehospital Delay to Treatment in Acute Coronary Syndrome (PROMOTION)[239] trial of an individual intervention for both men and women resulted in a decrease in delay time. No effective interventions have been tested for women.

Differences in IHD Pattern (Obstructive Versus Nonobstructive)

Initially, women who did not fit the classic (or male) pattern of IHD were diagnosed with cardiac syndrome X, which has a female predominance of ≈70%.[240] Cardiac syndrome X is defined as the triad pattern of chest pain, abnormal stress test consistent with ischemia, and the absence of significant obstructive IHD on angiography.[241] In stable IHD, women are 5 times more likely to be diagnosed with normal coronary arteries than men.[242] Recent data from the Dallas Heart Study demonstrated that angina in the general population is not associated with subclinical atherosclerosis as measured by coronary artery calcification scores on cardiac electron beam computed tomography.[243] Normal to nonobstructive IHD is twice as likely in women who present with ACS, unstable angina, non–ST-segment–elevation myocardial infarction, or ST-segment–elevation myocardial infarction compared with men.[244–248] Several paradoxes are identified in women: Despite lower rates of obstructive disease, less extensive IHD, and decreased incidence of AMI compared with men, women tend to have increased prevalence of angina, higher rates of myocardial ischemia, and more adverse cardiac events (rehospitalization and death).[10,243–248]

The current characterization of angina (typical chest pain) is based largely on data in men; this definition has been generalized to women as well. However, sex differences exist in terms of the type, pattern, and quality of symptoms.[249] Until recently, the diagnosis and treatment of IHD in women have largely centered on whether their symptoms fit the typical angina definition and pattern. Regardless of sex disparities in symptoms on presentation to the emergency room, typical angina symptoms in women are predictive of AMI and warrant further investigation.[250] Data from 69 AMI/ACS studies that assessed IHD symptoms indicated that women frequently present with typical angina, but when atypical symptoms are present, the prevalence of these symptoms is higher in women than men.[251] Higher rates of atypical chest pain in women may be explained partly by the increased prevalence of ischemia from vasospastic and microvascular disease in women. Additionally, women experience angina during periods of mental stress or rest, whereas angina in men is most frequently related to exertion.[249]

There appears to be an interaction with age and symptom presentation in patients hospitalized for chest pain. Older women often present similarly to men with typical angina patterns, and rates of ACS are similar between the sexes. Younger women (<65 years of age) are more likely to be discharged with a diagnosis of unstable angina compared with a similar age-matched cohort of men. Regardless of age, women have less atherosclerotic burden compared with men, which may contribute to these differences.[252]

In a study by McSweeney et al[223] of 1270 ethnically diverse women, 545 black (43%), 186 Hispanic (15%), and 539 white (42%), the most frequent prodromal symptom among all women was unusual fatigue (73%). The other most commonly reported prodromal symptoms among all women were sleep disturbances (50%), anxiety (45%), shortness of breath (44.5%), and frequent indigestion (38.9%).[223] Chest discomfort/pain was reported by only 37.7% of women in the prodromal period.[223] During the acute phase of AMI, shortness of breath was reported most often (62.8%), then weakness (54.9%), unusual fatigue (48.3%), dizziness (44%), and cold sweat (40%).[223] When 4 locations of chest discomfort/pain were combined, chest discomfort/pain was frequently reported during the AMI. When women reported chest discomfort/pain, they frequently used terms other than pain to describe their symptoms: pressure (44.8%), tightness (28.9%), ache (28.5%), sharpness (27.7%), fullness (14.7%), burning (10.5%), crushing (8.9%), spasm (8.5%), soreness (8.1%), and tingling (7.3%).[212] Importantly, 42% of whites, 38% of blacks, and 28% of Hispanics did not report any chest discomfort/pain when experiencing their AMI[223] (Table 5 gives women's acute symptoms that were significantly different by race). Thus, there is research to support both differences[46,253,254] and similarities[255] in symptoms of IHD in men and women.

Women report angina more frequently than men despite women having lower rates of obstructive IHD.[10] Interestingly, in the WISE study, >50% of women with angina were found to have no IHD or minimal IHD on coronary angiography.[256] In patients without obstructive IHD, women with persistent chest pain had worse cardiac outcomes compared with asymptomatic women,[257] including higher rates of repeat hospitalization and repeat coronary angiography, which in turn results in higher healthcare resource consumption.[40] Additionally, those women from the WISE study who had persistent chest pain despite no obstructive IHD had higher mortality rates than asymptomatic women. This highlights the importance of recognizing and treating the signs and symptoms of ischemia in patients without obstructive IHD because ongoing ischemia is not a benign entity and places these women at increased CVD risk. Equally important, lack of chest pain as a presenting symptom of AMI contributes to missed diagnoses and is associated with higher in-hospital mortality rates.[222,258]

Subsequent researchers have since identified a subset of patients with cardiac syndrome X who have microvascular angina, also called female pattern of IHD.[44,259] There are several features of microvascular angina or the female pattern of IHD: angina, abnormal stress testing indicative of ischemia, no obstructive IHD on angiography, and abnormal coronary microcirculation dysfunction.[260] Microvascular angina can be secondary to endothelium-dependent or -independent microvascular coronary dysfunction, which can be detected on coronary angiography.[44,260]

The WISE study was instrumental to our current understanding of IHD in women, and subsequent ancillary studies will provide more insight.[46,261] More than half of the patients in this study cohort had no or minimal IHD, and persistent chest pain despite no obstructive IHD was associated with worse prognosis (increased rehospitalization, revascularization, death).[256,257,262] Microvascular angina is neither benign

Table 5. Significant Differences in Frequency of Women's Acute Symptoms by Race

	Black (n=545), n (%)	Hispanic (n=186), n (%)	White (n=539), n (%)	Raw *P* Value	Adjusted *P* Value
Generalized symptoms					
Unusual fatigue	277 (50.8)*†	109 (58.6)*	227 (42.1)†	<0.001	0.003
Dizzy or faint	269 (49.4)	76 (40.9)	214 (39.7)	0.004	0.028
Hot, flushed	252 (46.2)*	51 (27.4)†	173 (32.1)†	<0.001	<0.001
Indigestion	224 (41.1)*	48 (25.8)†	154 (28.6)†	<0.001	<0.001
Heart racing	194 (35.6)*	67 (36.0)*†	125 (23.2)†	<0.001	0.005
Numbness in hands/fingers	149 (27.3)*	50 (26.9)*†	97 (18.0)†	<0.001	0.007
Vomiting	149 (27.3)*	42 (22.6)*†	101 (18.7)†	0.004	0.014
Loss of appetite	145 (26.6)	53 (28.5)	106 (19.7)	0.008	0.076
New vision problems	145 (26.6)*	37 (19.9)*†	77 (14.3)†	<0.001	<0.001
Headache	125 (22.9)*†	50 (26.9)*	80 (14.8)†	<0.001	0.005
Coughing	89 (16.3)*	36 (19.4)*	52 (9.6)†	<0.001	0.002
Choking sensation	83 (15.2)	34 (18.3)	50 (9.3)	0.001	0.016
Discomfort/pain symptoms					
Centered high in chest	177 (32.5)†	87 (46.8)*	166 (30.8)†	<0.001	<0.001
Left breast	133 (24.4)*	44 (23.7)*†	73 (13.5)†	<0.001	<0.001
Back/between shoulder blades	84 (15.4)‡	70 (37.6)*	112 (20.8)†	<0.001	<0.001
Neck/throat	71 (13.0)†	44 (23.7)*	87 (16.1)†	0.003	0.001
Generalized chest	70 (12.8)†	41 (22.0)*†	110 (20.4)*	0.001	0.003
Leg(s)	40 (7.3)*	27 (14.5)*	9 (1.7)†	<0.001	<0.001
Both arms	38 (7.0)†	34 (18.3)*	77 (14.3)*	<0.001	<0.001
Top of shoulders	36 (6.6)†	33 (17.7)*	57 (10.6)*†	<0.001	<0.001
Right arm or shoulder	34 (6.2)†	24 (12.9)*	25 (4.6)†	<0.001	0.001
Jaw/teeth	26 (4.8)‡	36 (19.4)*	54 (10.0)†	<0.001	<0.001

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nor inexpensive. Care of the symptomatic female with nonobstructive IHD is costly and places an economic burden on the healthcare system.[40] The pathophysiology, presentation, evaluation, and treatment of microvascular angina are complex and challenging. Further research is needed to help clarify many unanswered questions about this entity.

Disparities in Guideline-Based Diagnosis of IHD

When the Bayes theorem is used to assess myocardial ischemia, the pretest likelihood of angiographic IHD in symptomatic women is lower than in men, regardless of typical or atypical symptoms.[263] Women are less likely to be assessed for cardiac symptoms, but when assessment is performed, sex-based differences exist. Exercise ECG is the first-line diagnostic tool to evaluate for IHD in symptomatic women who have a normal resting ECG, an intermediate pretest probability, and an ability to perform maximal exercise.[264] The sensitivity and specificity for the detection of obstructive IHD with exercise ECG are lower in women than in men, but the negative predictive value of the exercise ECG is very high.[265,266] The reduced accuracy in women is related to increased functional impairment that inhibits women in achieving maximal levels of exercise, lower QRS voltage, and hormonal factors (endogenous estrogen in younger women and HRT in postmenopausal women).[264,267–269] The Duke treadmill score provides additional diagnostic and prognostic information in women undergoing evaluation for IHD.[270]

The addition of cardiac imaging to assess for stress-induced wall motion or myocardial perfusion abnormalities supports the evaluation of IHD in women with an abnormal resting ECG, diabetes mellitus, questionable functional capacity, or intermediate-risk treadmill findings.[264] In women, stress echocardiography provides better specificity and diagnostic accuracy than standard exercise electrocardiography.[265,271] The diagnostic accuracy of exercise and dobutamine echocardiography appears to be comparable in women and men (ie, sex-neutral accuracy).[264] Prognostic information with stress echocardiography is also similar between men and women.[272,273]

Stress gated myocardial perfusion single-photon emission computed tomography with contemporary nuclear imaging

agents provides high specificity and diagnostic accuracy[274–276] and high prognostic accuracy regardless of sex.[277] In patients with left bundle-branch block, pharmacological nuclear stress testing is more accurate than exercise perfusion imaging, regardless of sex.[278] Challenges of single-photon emission computed tomography imaging in women include breast attenuation artifact and possible unobserved minor perfusion defects in women with smaller hearts, in addition to radiation exposure.[279] The labeling of false-positive stress tests in women with nonobstructive IHD on angiography should be avoided if there are any objective signs or symptoms of ischemia during the stress portion of the test.

Only a few specialized centers currently perform stress magnetic resonance imaging to assess for subendocardial ischemia or wall motion abnormalities in the evaluation of IHD.[280,281] Stress magnetic resonance demonstrated diffuse subendocardial perfusion defects in patient with cardiac syndrome X.[280] In the WISE study,[147] phosphorus-31 nuclear magnetic resonance spectroscopy identified women with metabolic myocardial ischemia, which also provided important prognostic information.[262,282] Stress cardiac magnetic resonance imaging is a relatively newer imaging test. The hope is that with further research it will provide promising diagnostic and prognostic data for IHD.

Even after an appropriate diagnosis of IHD, disparities exist in the treatment of IHD in women despite guidelines for CVD prevention designed specifically for women.[176] With the use of the AHA's Get With The Guidelines–Coronary Artery Disease Database, it has been demonstrated that after multivariate analysis there are no sex differences in in-hospital mortality in all AMI patients; however, sex differences exist in patients with ST-segment–elevation myocardial infarction. In this large cohort of >78 000 patients, women were less likely to receive aspirin or β-blocker therapy within 24 hours compared with men. Women were also less likely to undergo invasive procedures, and when acute reperfusion therapy was provided, women were less likely to be treated in a timely fashion compared with men.[283] Additionally, younger women demonstrated decreased quality of care and increased in-hospital mortality compared with young men.[284]

Disparities also exist in regard to physician adherence to evidence-based guidelines in the treatment of CVD at the time of hospital discharge. Prescribing patterns have shown that women are less likely to be prescribed lipid-lowering medications, antiplatelet agents, and β-blockers at the time of hospital discharge than men.[285–288] Hospitals participating in AHA's Get With The Guidelines–Coronary Artery Disease program have had increased rates of guideline adherence over a 5-year period regardless of sex and age.[289] This demonstrates the powerful impact that quality-improvement projects can have on adherence, yet more data are necessary to determine whether they will affect clinical outcomes.

Emotional/Affective Response and Behavior Change

When women receive a diagnosis of IHD or AMI, they often express disbelief. Even when women are able to identify common CVD risk factors, they often do not personalize this information, meaning that they do not perceive themselves at risk even though they have multiple risk factors.[226] An integrative review of the literature supported these findings, in particular that women underestimate their cardiovascular risks and that communication between the female patient and physician is less than therapeutic. These perceptions can influence a patient's decision-making process related to making healthy behavior changes and seeking health care.[206] Thanavaro et al[290] examined the best predictors of risk-reducing and health-promoting behaviors among women without a prior history of CHD in a cross-sectional study of 119 women. Results indicated that women had low levels of knowledge related to IHD and did not regularly practice health-promoting behaviors, although they perceived that benefits to these behaviors were good. Those who were more likely to engage in healthful behaviors perceived fewer barriers to reducing risk of IHD and had greater knowledge of IHD and a negative history for smoking.

Moore et al[291] used qualitative methods to examine perceptions of risk for IHD and perceptions of risk-reducing behaviors among 7 women with known CVD. Three major themes emerged from the data: that an absence of symptoms was interpreted as an absence of disease, that women desired a relationship with their physician in which they could have an open discussion, and an expressed fear of the effects of the disease on their daily lives and relationships. To further elaborate on the 3 themes, the women did not interpret their IHD as a chronic disease but rather one that was corrected by the acute intervention and thus did not necessitate a change in behavior to reduce their risk of a recurrent event. They did not see their patient-provider relationship as one that fostered dialogue with the physician and reported that there was no discussion of risk reduction. This lack of discussion about risk reduction supported the women's ideas that behavior changes were not necessary. The fear the women expressed was manifested in various ways. One woman expressed fear about unknown dangerous changes occurring in her heart, whereas others feared the effects of IHD on their relationships. One woman reported that being diagnosed with IHD served as a motivator for her to make behavior changes, targeting her specific risks.

Other studies have linked specific personal CVD risk factors with behavior change in women. Murphy and colleagues[292] conducted studies among 239 women after AMI and monitored self-initiated changes in diet. Using the Short Fat Questionnaire, they demonstrated over 4 time points that the women significantly reduced their dietary fat intake, and although there was some regression over the subsequent months, the 12-month score remained significantly lower than at baseline. In addition, the scores were lower than the scores of a randomly selected sample of healthy women and older adults in the same time period.

Although the Murphy et al[292] study was conducted in Australia and revealed positive self-initiated behavior changes in post-AMI women's diets, increasing physical activity is often a more problematic self-initiated behavior change before or after AMI. Adults in several countries have received and adopted the low-fat diet message to some extent[293,294]; however, <50% of adults in the United States are physically active at the recommended level.[295] Mozumdar and colleagues[296] examined the relationship of occupational and leisure physical activity with IHD risk among working women. They did not find a

relationship between IHD risk and occupational physical activity, but they reported a greater prevalence of high risk for IHD among those with low levels of leisure-time physical activity. This study was conducted in India, a country where there may be more physically demanding occupations for women compared with the United States. Thus, these reported relationships might not be the same among women in the United States.

An area where attention is needed for both primary and secondary prevention of IHD is medication adherence, particularly for the control of hypertension and dyslipidemia. Moss and Crane[297] studied the financial burden of cardiac medications among older women after AMI. Results of the cross-sectional study revealed that 89% of a sample of 83 were taking at least 1 cardiac medication, that costs per day varied ($0.13–$6.75), and that the total number of pills taken per day was between 1 and 19. Providers need to be sensitive to the financial burden of medications to enhance adherence. Other factors that contribute to nonadherence are frequency of medications and perceived and actual side effects. Still other studies have shown that medication frequency may be related to low adherence rates and recommend that providers consider daily dosing formulas to increase medication adherence.[298,299] Multiple medications (polypharmacy) prescribed to patients and the increased accompanying cost are associated with decreased adherence.[300] Other reasons for nonadherence to medication are that the patient chooses to make lifestyle changes instead of taking prescribed preventive medications and previous experience with CVD.[301] Increased income and education levels have been well established as associated with increased compliance rates. Inversely, lower socioeconomic status and education levels are associated with decreased compliance levels. Adherence is a multifactorial concern that requires assessment of the patient's abilities and willingness to participate in the plan of care.

Explanations for the Unique Experience: The Role of Sex

Clinician Behavior as a Source of Gender/Sex Disparities

The Institute of Medicine's Unequal Treatment report defines disparities as differences in treatment that remain after accounting for patient characteristics, including clinically appropriate needs, the demands of coexisting conditions, and patient preferences.[302,303] Determinants of residual gender/sex disparities include health system and clinician factors.[302] From the clinician perspective, greater clinical uncertainty when interacting with female patients, beliefs or stereotypes about the behavior or health of female patients, and bias or prejudice toward women have all been proposed as potential contributors to health disparities.[302–310] Physician uncertainty about a CVD diagnosis has been shown to vary by patient sex and to influence clinical decisions.[215,217,311] Indirect evidence also indicates that healthcare clinicians' interpretation of symptoms is influenced by patient demographics, including sex/gender.[312–314] For example, physicians are more likely to interpret a man's symptoms as organic and a woman's symptoms as psychosocial.[215,315] Importantly, clinicians' beliefs about a patient may directly influence their clinical decision making. Clinician sex/gender bias has been commonly inferred when sex/gender differences in care persist after adjustment for different patient, clinician, and health system characteristics.[103,316,317] For example, Schulman et al[316] demonstrated that physicians were less likely to refer hypothetical female than male patients with the same symptoms and stress test results for cardiac angiography. Although these studies indirectly suggest that clinician gender/sex bias explains the observed variation in clinician recommendations, to the best of our knowledge, no studies have directly measured clinician gender/sex beliefs and the extent to which these attitudes are associated with clinical decisions.

Explicit (conscious) stereotypes about the traits that women and men possess are common. Women are traditionally felt to be more selfless and concerned with others, and men are viewed as being self-assertive and motivated to master.[318–321] The unjust application of these stereotypes, or gender bias, is also felt to be common and primarily implicit.[319,321,322] As its name suggests, implicit gender bias is less intentional, even unconscious, and it operates in a relatively automatic manner.[319,323,324] Clinicians are not immune to bias; levels of implicit bias among clinicians toward different groups have been shown to be similar to those seen in the general population.[325–330] Tools have been developed in other fields that measure explicit gender attitudes such as the Trait Stereotype measure and implicit gender attitudes such as the Implicit Association Test.[331–335] These tools have been widely used to explain gender differences in social outcomes, including hiring decisions, job promotions, and performance evaluations, but they have less widely been applied to the study of healthcare disparities.[336–339] A few studies have used these tools among clinicians to examine the role of race and ethnicity bias in clinical decisions and outcomes.[340–344] Further work is needed to understand whether clinician gender/sex attitudes and bias play a role in treatment decisions and potentially contribute to disparities in care of women.

As discussed earlier, many other factors may make it more difficult to diagnose IHD in women. Lack of appropriate risk assessment tools that do not incorporate women's novel risk factors and vague intermittent symptoms compound the diagnostic problem. Furthermore, women's terms to describe symptoms such as chest pressure or burning or fatigue may not match the provider's expectations of IHD symptoms. In addition, because women are often older at the time of initial IHD diagnosis, they frequently have other comorbid conditions, confounding the diagnosis. Even when providers suspect IHD in women, many diagnostic tools are not as sensitive and specific in women. Combined, these factors make diagnosing IHD in women challenging. Studies cited in this document should assist clinicians in recognizing IHD in women.

Gaps in Science of IHD in Women

Although there is clear evidence that women experience IHD differently from men because of both sex and gender differences, significant gaps in scientific knowledge of the risks, mechanisms, assessment, interventions, and symptoms for women with IHD remain.

Risks, Mechanisms, and Assessment

The reasons for women's worse outcomes are likely multifactorial, and studies are needed that incorporate

comprehensive theoretical frameworks. Inadequate information is available about hypertension across the life span in women. Whether the presence of estrogens protects young women from hypertension or loss of estrogens promotes coronary disease is unclear. Additionally, data are needed to explain why hypertension in aging women differs from that in men. Exciting findings about emerging risk factors for heart disease in women are emerging, but the precise use of biomarkers such as hs-CRP and other novel risk factors needs further study. Commonly used risk scores may not be as sensitive for women; thus, clinicians may not have adequate knowledge to accurately assess women's risks. Furthermore, the existence of clinician gender bias and its influence on clinicians' decisions are not fully understood. Significant gaps in our understanding of the pathophysiology, presentation, evaluation, and treatment of microvascular angina exist, despite that fact that this is a predominantly female phenomenon. The impact of the use of sex-specific troponin cutoff values on diagnostic accuracy for women is a crucial question.

Interventions

Women, particularly younger women, receive less evidence-based care for ST-segment–elevation myocardial infarction than men.[283,284] Many studies show that women do not benefit as much as men in intervention trials related to depression, physical activity, cardiac rehabilitation, diabetes mellitus, treatment-seeking delay, and other outcomes. Interventions developed for women only are more effective,[111] and thus, more trials are needed to test interventions tailored for women with IHD. Interventions targeted to specific racial and ethnic groups of women also are needed. Regardless, interventions that have proven beneficial in women need to be offered to all women for both primary and secondary prevention. Population-based interventions focused on women for primordial prevention of risk factors are needed.

Symptoms

There is strong evidence about the typical and atypical symptoms that women experience. The precise mechanisms for those symptoms are not fully understood. Identification of symptom phenotypes in women is needed.

Future Directions

Although tremendous progress has been made in building the science of how women experience IHD, much remains to be done to translate the science into practice and education and to continue to expand the science.

Practice

- Increased education for providers and women on emerging risks for IHD and routine assessment of individual risk of IHD
- Routine assessment of sex-specific risks for IHD in screening, history, and physical examination by all primary care providers and gynecologists
- Population health approaches to decreasing women's and girls' risks
- Assessment of risk factors for IHD and ways to reduce risk as part of every clinic visit for women

Research

- Powering clinical trials to allow analysis by sex/gender and reporting of sex-specific differences
- Encouraging the use of common data elements to allow data sharing across studies and analysis of treatment effects by sex with big data sets
- Broadening inclusion criteria that focus on IHD symptoms to include more than chest pain
- Testing interventions tailored for women and women of different ethnicities, in particular cardiac rehabilitation programs designed to increase women's participation and completion
- Using community-based participatory research methods to develop culturally sensitive approaches to meeting the needs of underserved populations of women

Policy

- Research funding targeted to improving the evidence for guidelines for the prevention of IHD in women
- Randomized, clinical trials of the diagnosis, treatment, and outcomes of IHD in women with nonobstructive coronary artery disease
- Interventions to identify and eliminate sex bias in treatment and the use of clinical guidelines
- Devise measures to assess the effectiveness of guidelines for the prevention, diagnosis, and treatment of women with or at risk for IHD

Public Health Education

- Improved methods to disseminate information about women's risk, symptoms, and behaviors and necessary responses to symptoms of ischemia

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*Modest.

†Significant.

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KEY WORDS: AHA Scientific Statements ■ myocardial ischemia ■ prevention and control ■ women

Preventing and Experiencing Ischemic Heart Disease as a Woman: State of the Science: A Scientific Statement From the American Heart Association

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