Sex Differences in Ischemic Heart Disease

Advances, Obstacles, and Next Steps

ABSTRACT: Evolving knowledge of sex-specific presentations, improved recognition of conventional and novel risk factors, and expanded understanding of the sex-specific pathophysiology of ischemic heart disease have resulted in improved clinical outcomes in women. Yet, ischemic heart disease continues to be the leading cause of morbidity and mortality in women in the United States. The important publication by the Institute of Medicine titled "Women's Health Research—Progress, Pitfalls, and Promise," highlights the persistent disparities in cardiovascular disease burden among subgroups of women, particularly women who are socially disadvantaged because of race, ethnicity, income level, and educational attainment. These important health disparities reflect underrepresentation of women in research, with the resultant unfavorable impact on diagnosis, prevention, and treatment strategies in women at risk for cardiovascular disease. Causes of disparities are multifactorial and related to differences in risk factor prevalence, access to care, use of evidence-based guidelines, and social and environmental factors. Lack of awareness in both the public and medical community, as well as existing knowledge gap regarding sex-specific differences in presentation, risk factors, pathophysiology, and response to treatment for ischemic heart disease, further contribute to outcome disparities. There is a critical need for implementation of sex- and gender-specific strategies to improve cardiovascular outcomes. This review is tailored to meet the needs of a busy clinician and summarizes the contemporary trends, characterizes current sex-specific outcome disparities, delineates challenges, and proposes transformative solutions for improvement of the full spectrum of ischemic heart disease clinical care and research in women.

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Ischemic heart disease (IHD) represents the leading cause of death in women. It accounts for a third of all female deaths globally and affects nearly 48 million women in the United States.[1,2] The landmark 2010 Institute of Medicine's publication, "Women's Health Research—Progress, Pitfalls, and Promise," highlights the fact that women's health involves 2 aspects: (1) sex differences because of the biological factors and (2) gender differences, those affected by broader social, environmental, and community factors.[3] The emphasis on sex- and gender-specific cardiovascular disease (CVD) research and our improved understanding of sex-specific pathophysiology for coronary atherosclerosis in women have resulted in important insights into an expanded spectrum of IHD in women to include obstructive coronary artery disease as well as dysfunction of the coronary microvasculature and endothelium.[4] The focus on sex and gender research in CVD has resulted in a nearly 30% decline in the number of women dying from CVD, and for the first time, in 2014, more men than women died of CVD in the United States since 1984.[2] The decreased mortality rate, specifically because of IHD, has been attributed to increased awareness, greater focus on women and their IHD risk, and the application of evidence-based treatments for established IHD.[2,5] Despite this progress, women with IHD experience relative-

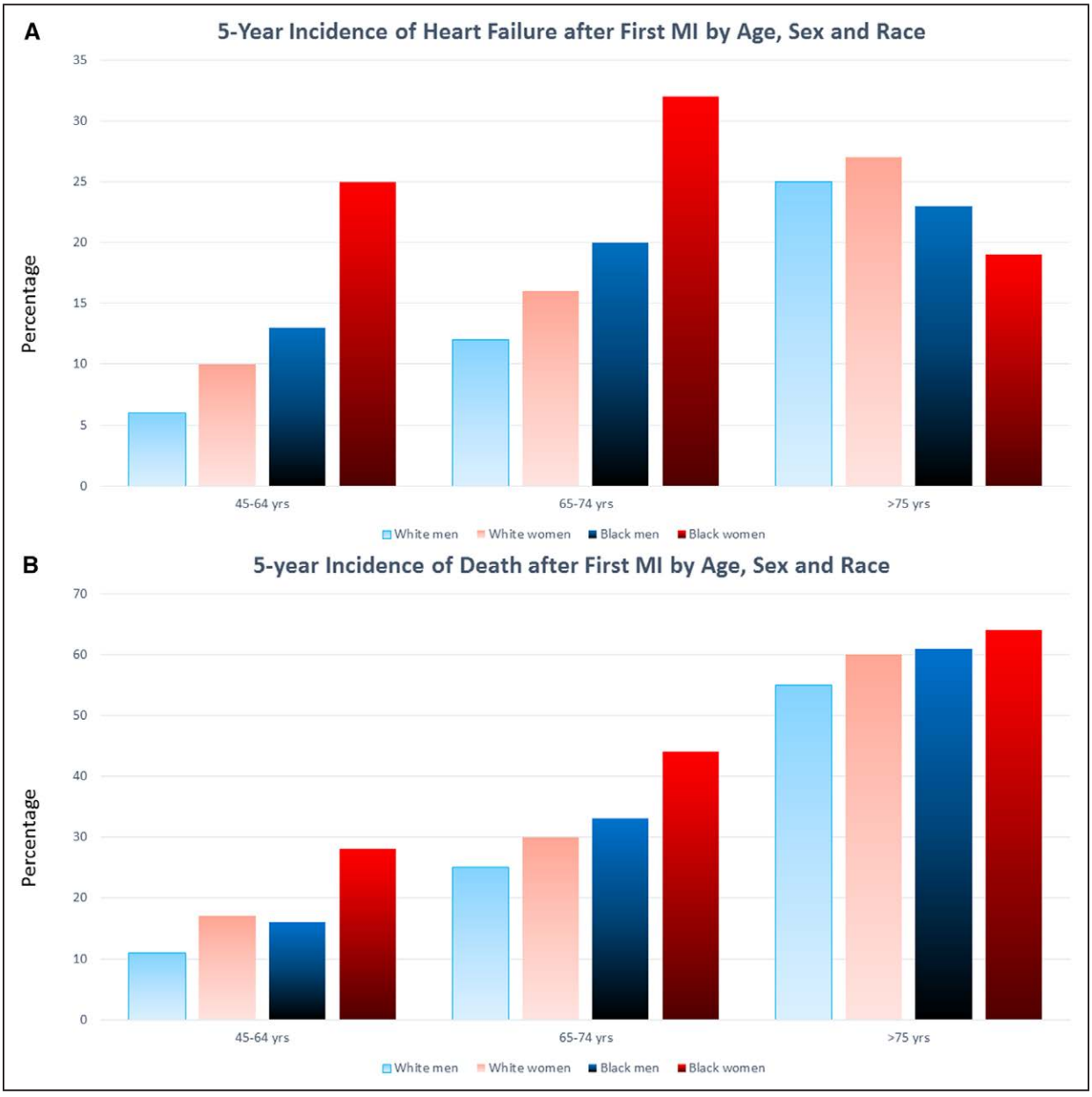

Figure 1. Five-year risk of heart failure and death after first MI by age, sex, and race.
Percentage of patients having (**A**) heart failure and (**B**) death 5 years after their first myocardial infarction, by age, sex and race. MI indicates myocardial infarction. Adapted from Benjamin et al.[2]

ly worse outcomes compared with men, and younger women (<55 years) and subgroups of women defined by race, ethnicity, socioeconomic status, and educational level still show striking disparities in cardiovascular health (Figure 1).[6,7] These disparities reflect our limited understanding of the sex differences in physiology, which is substantially related to lack of female-specific data.[8] An expanded view of the multifactorial epidemiology of IHD in women has identified important risk factors, including age, race, culture, ethnicity, and lifestyle influences that adversely impact cardiovascular outcomes.[5] This review, customized to meet the needs of a busy clinician, highlights the contemporary data on sex-specific differences in traditional and novel risk factors, clinical presentation, diagnostic workup, and management of the full spectrum of IHD in women, including acute myocardial infarction (MI), chronic epicardial stenosis, and microvascular and endothelial dysfunction. It summarizes the underlying biological differences in IHD, sex- and gender-based disparity in outcomes, and contemporary challenges for equitable health care and proposes transformative solutions for improvement of clinical care and research in women.

UNDERLYING BIOLOGICAL DIFFERENCES IN ISCHEMIC HEART DISEASE

Biological sex and socio-cultural gender are often indistinguishably coupled together. Contemporary research highlights the impact of these variables on many observed sex-differences in presentation, natural history, pathophysiology, diagnosis, and outcomes of IHD.[9–11] While men and women share many traditional risk factors for IHD, additional sex-based risk factors and mechanisms of disease have been shown to be important in women.[12–14] Menopause marks an important cardiovascular biological transition, with a significantly increased CVD risk in women aged ≥55 years, and equals the risk of men aged ≥45 years. Estrogen loss seems to have a negative effect on arterial function and adversely alters the cholesterol profile.[15] Menopause increases the prevalence of metabolic syndrome and truncal obesity.[16] Early menopause, whether natural or surgically induced, significantly increases a woman's risk for IHD.[16] Sex differences in risk factors, presentation, and pathophysiology of IHD are listed.

Risk Factors

There is increasing evidence that biological differences may impact the expression of cardiovascular risk factors and impart a differential risk for women compared with men (Figure 2). Hypertension, diabetes mellitus, and smoking are more potent risk factors for MI in women than in men, with an odds ratio (OR) of 1.5, 1.6, and 1.3, respectively.[17] Additionally, there are several non-traditional cardiac risks unique to or predominant in women, including early menopause or menarche, gestational diabetes mellitus, hypertension, preeclampsia and eclampsia during pregnancy, and systemic inflammatory disorders (Figure 2).[18–21] The 2013 American College of Cardiology/American Heart Association (AHA) guidelines on assessment of CVD risk recommend the use of ASCVD risk calculator, which accounts for sex and ethnic diversity but not the emerging risk factors prevalent in women.[22]

Presentation

Differences exist in the presentation of IHD in women compared with men. Fewer women present with the classic symptoms of chest pain (31% compared with 42% men), particularly in young patients.[23,24] Women often exhibit dyspnea, weakness, arm, back or jaw pain, palpitations, lightheadedness, or loss of appetite.[23,24] The historic limited interpretation of women's symptoms based on the traditional approaches such as the Diamond and Forrester risk model results from under-recognition of the sex-specific presentation of IHD and contributes to misdiagnosis and delayed recognition of ischemia.[25–28]

Pathophysiology

The distribution and burden of coronary plaque differs by sex, with nearly 60% of symptomatic women having no flow-limiting stenosis.[4,15,29,30] Emerging data have significantly contributed to our understanding of the full spectrum of IHD in women, which includes obstructive epicardial disease, microvascular disease, coronary spasm, and spontaneous coronary artery dissection. The role of microvascular dysfunction, vascular inflammation, coronary reactivity, endothelial function, hormonal influences, oxidative stress, and coronary size on the development of IHD in women is being increasingly recognized.[4,31] Similarly, there are pathophysiologic differences in MI, with women having a higher prevalence of plaque erosion compared with more plaque rupture in men.[31] These observations support a need for an in-depth and integrated understanding of the factors accounting for the varying mechanisms and presentation of IHD in women.

SEX-SPECIFIC ROLE OF DIAGNOSTIC IMAGING

Vascular dysfunction in absence of obstructive coronary disease is more prevalent in women and associated with increased use of healthcare resources, higher symptom burden, and importantly a 2-fold higher mortality, indi-

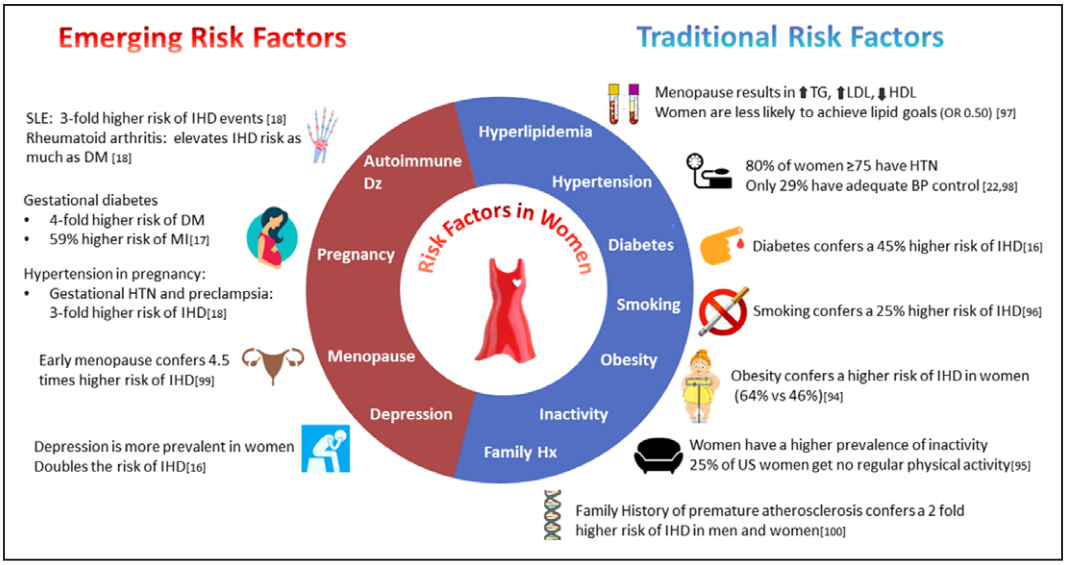

Figure 2. Traditional and emerging risk factors.
Many traditional risk factors for ischemic heart disease in women impart a differential risk for women compared with men. The role of emerging nontraditional cardiac risks unique to or predominant in women are also being increasingly recognized. BP indicates blood pressure; DM, diabetes mellitus; HDL, high-density lipoprotein; HTN, hypertension; IHD, ischemic heart disease; LDL, low-density lipoprotein; MI, myocardial infarction; SLE, systemic lupus erythematosus; and TG, triglycerides.

cating that nonobstructive disease is not benign.[4,31–33] Among 10 003 subjects with stable angina and intermediate probability of atherosclerosis in the The Prospective Multicenter Imaging Study for Evaluation of Chest Pain trial, women were less likely to have positive stress tests.[34] The higher burden of nonobstructive atherosclerosis in women may result in negative stress tests and obscure the diagnosis of IHD, underscoring the need for additional diagnostic imaging that reveals the nonobstructive pathophysiological mechanisms of IHD.[30,35] Consequently, the 2014 AHA consensus statement for noninvasive evaluation of woman at risk for IHD recommends testing for the full spectrum of IHD (Figure 3).[35] Contemporary cardiac imaging techniques

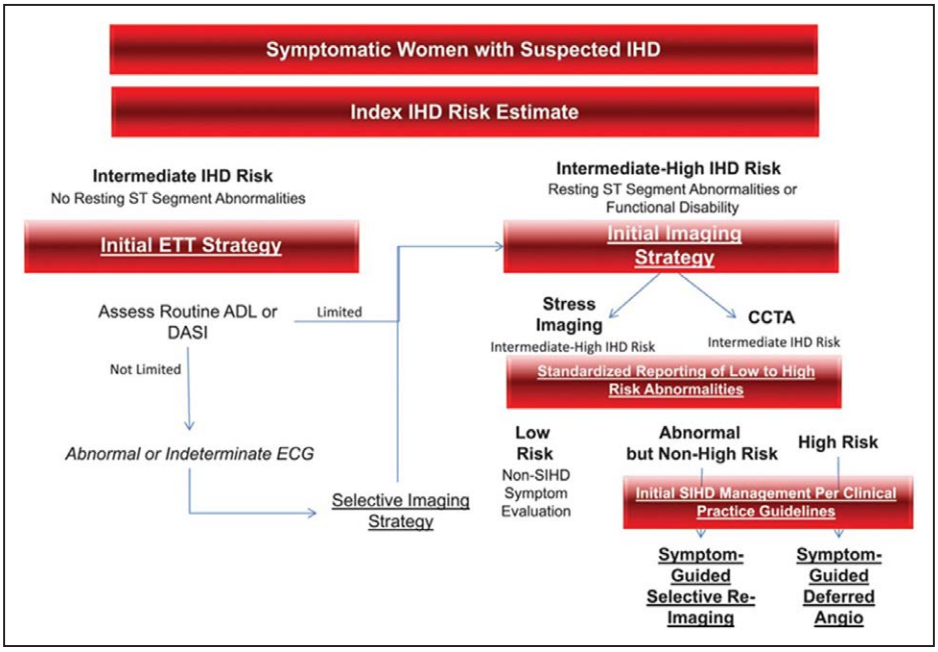

Figure 3. Diagnostic algorithm for women presenting with suspected ischemic heart disease (IHD).
ADL indicates activities of daily living; angio, angiography; CCTA, coronary computed tomography angiography; DASI, Duke Activity Status Index; ETT, exercise treadmill testing; and SIHD, stable ischemic heart disease. Reprinted with permission from Mieres et al.[35]

include detecting the extent and severity of myocardial ischemia resulting from obstructive coronary artery disease, visualizing the nonobstructive plaque burden on coronary computed tomography, and evaluating small vessel disease by use of myocardial perfusion coronary flow reserve (positron emission tomography and stress magnetic resonance imaging).[36] Guidelines for diagnosis and management of symptomatic women with suspected IHD comprise both the determination of a woman's risk status for IHD (including a pretest evaluation based on AHA guidelines) and shared decision-making regarding the need for and choice of diagnostic testing.[35]

SEX-BASED DISPARITIES IN OUTCOMES AND QUALITY OF CARE

A growing body of evidence supports a lack of recognition, inadequate medical resource utilization, and suboptimal application of evidence-based guidelines as factors resulting in higher case fatality rates among women with IHD (Table 1).[12,37] Women with IHD use more cardiac resources and incur greater healthcare costs because of greater symptom burden, frequent office visits, and hospitalizations.[31,62] Subgroups of women who experience worse outcomes for IHD include younger women (aged <55 years) and those of Black, Latino, and South Asian descent.[2,7]

Higher Morbidity and Mortality

Although the mortality of IHD in women has sharply declined over the last 4 decades, sex-based differences in outcomes persist (Table 1). Paradoxically, women presenting with acute coronary syndrome have less obstructive disease but exhibit higher in-hospital (OR, 1.85) and 1-year (OR, 1.6) mortality compared with men.[59–61] Additionally, women also experience a higher incidence of cardiogenic shock (5.8% versus 4.0%) and heart failure (5.8% versus 3.4%) compared with men (Figure 1).[2,39,63] These differences in outcome were ameliorated after adjusting for baseline comorbidities. These disparate outcomes are potentially caused by a combination of less-intensive hospital and postdischarge care[44,48,64] and underlying biological differences in response to pharmacological and reperfusion therapies. Similar trends are noted in sex-specific outcomes of nonobstructive IHD, which is now recognized to be far from benign, and associated with recurrent angina, and frequent cardiac events compared with women with normal coronaries (Table 1).[65,66]

Delayed Presentation

Recognizing the delays in door-to-balloon time and its association with decreased likelihood of survival in patients with an acute ST-segment–elevation MI, the American College of Cardiology and AHA launched the door-to-balloon alliance in 2006 and partnered with hospitals, medical personnel, third-party payers, and hospital quality alliance to standardize systemic approaches for timeliness of percutaneous coronary intervention.[67] However, a decade later, significant disparities persist in timeliness of revascularization, with women experiencing longer median first medical contact-to-device times (80 versus 75 minutes; $P<0.001$) and a lower propensity to achieve the recommended contact-to-device times ≤90 minutes target than men (67.5% versus 75.6%; $P<0.001$).[39] This delay was secondary to differences in both prehospital presentation times and in getting crucial admission procedures, with longest delays in young women (aged 18–55 years).[39,41] These findings underscore the need for improved symptom recognition and triage strategies used by first responders, particularly in young women.

Fewer Revascularization

Despite the proven efficacy of revascularization, women are less likely than men to be referred for revascularization for ST-segment–elevation MI,[41] non–ST-segment–elevation MI,[42] and stable angina (Table 1).[44] This inequality in referral was more profound in younger women[6,41,44] and might be explained by increased technical complexity related to smaller coronary arteries,[68] less obstructive coronary plaque,[29] and a perceived higher rate of postprocedural complications in women.[48] Studies have demonstrated a higher rate of in-hospital complications after percutaneous and surgical revascularization and higher rates of bleeding in women. These sex differences in clinical outcomes were resolved after adjusting for the higher prevalence of comorbidities, smaller body habitus, and lower renal function seen in women compared with those in men.[42,69–71] Furthermore, most women are diagnosed with IHD later than men, and have more comorbidities resulting in a higher surgical risk profile, which may preclude them from getting surgical revascularization.[72]

Less Cardiac Rehabilitation

Despite documented benefits and corresponding American College of Cardiology/AHA recommendation for cardiac rehabilitation post-MI, women are substantially less likely to be referred and participate in cardiac rehabilitation compared with men.[53,54,73] Sex-based attrition occurs at each step of cardiac rehabilitation: referral, enrollment, and adherence (Table 1). Potential barriers for suboptimal enrollment of women in cardiac rehabilitation included inadequate reinforcement by healthcare professionals, financial constraints, inadequate patient awareness, perception of exercise being painful, suboptimal social support system, transportation issues, family responsibilities, and higher comorbidities.[73]

Table 1. Sex-Based Disparities in Outcomes and Quality of Care

Factors	Setting	Sex-Specific Outcomes
Diagnostic testing	Stable IHD	1. Less than 1 in 10 women with angina and abnormal stress test had any change in pharmacotherapy or referral to diagnostic angiography.[38]
Delay in reperfusion	STEMI	1. Women had longer median first medical contact-to-device times compared with men (80 vs 75 min).[39]
		2. Women experienced a 30-minute prehospital delay from symptom onset to hospital presentation compared with men.[40]
		3. Young women were more likely to exceed door-to-needle time guidelines for PCI during STEMI compared with age-matched men (67% vs 32%). (OR, 2.62).[41]
Fewer revascularizations	ACS	1. Women were less likely to undergo revascularization after STEMI[41]and NSTEMI.[42]
		2. Women with documented 1-vessel disease were less likely to undergo PCI compared with men (OR, 0.78).[42]
		3. Women were less likely to be referred for surgical revascularization (OR, 0.81).[42]
		4. Young women were particularly less likely to have revascularization compared with men (28% vs 13%).[6]
		5. Despite known survival benefits of arterial grafts over vein grafts as conduits, women undergoing coronary artery bypass graft surgery (CABG) were less likely to receive arterial grafts compared with men.[43]
	Stable IHD	1. Despite higher angina class, women were less likely to undergo coronary angiography (31% vs 49% men).[44]
		2. Women with stable angina and confirmed CAD were less likely to undergo PCI compared with men (OR, 0.70).[44]
Less pharmacotherapy	Primary prevention	1. Women were less likely to have IHD risk factors measured, and young women (aged 35–54 y) were 37% less likely to be prescribed guideline-recommended medications.[45]
		2. Women were 65% less likely to have assessment of their smoking status, body habitus, blood pressure, and lipid profile.[46]
	ACS	1. In the CRUSADE study, women were less likely to received aspirin, ACE inhibitors, and statins on hospital discharge, even after adjustment for higher comorbidities in women.[47,48]
		2. Black women were significantly less likely to receive appropriate secondary prevention measures compared with age-matched White patients after MI, despite having ≥3 risk factors.[49]
		3. Medicare claims data demonstrated similar prescriptions patterns at hospital discharge but reported a 30% to 35% lower 12-month medication adherence after MI among Black and Hispanic women compared with White men.[50]
	Stable IHD	1. Women report a significantly lower use of statin and aspirin therapy compared with men.[44]
		2. Women were less likely to achieve guideline-directed secondary prevention targets for lipid (OR, 0.5), glucose (OR, 0.78), physical activity (OR, 0.74), or body mass index (OR, 0.82).[47] Similar findings were confirmed by the EUROASPIRE III and IV surveys in Europe.[51,52]
Cardiac rehabilitation		1. Despite higher event rates and worse outcomes after MI, women were less likely to access cardiac rehabilitation.
		2. Women were 32% less likely to be referred to cardiac rehabilitation (39.6% vs 49.4%).[53]
		3. Women were 36% less likely to enroll in cardiac rehabilitation (38.5% vs 45.0%).[54]
		4. Women adhered to median of 71.9% cardiac rehabilitation sessions compared with 75.6% men.[55]
Morbidity after MI	ACS	1. All women with acute MI had a 26% higher 1-year rate of rehospitalization even after adjusting for comorbidities, with even higher rehospitalizations in Black women.[56,57]
		2. Women with NSTEMIs had a higher in-hospital risk of recurrent MI (OR, 1.1) and heart failure (OR, 1.4).[48] Similar outcome disparities were noted in STEMI.[39]
		3. Black women were more likely to have angina at 1 y after MI treated with PCI (49% vs 31% in white men).[56]
		4. Young women with acute MI experienced more angina and depression, had worse quality of life, and were less likely to return to work within 12-months after their MI.[11,57]
	Stable IHD	1. Women with suspected angina, but angiographically normal vessels had more hospitalizations and repeat catheterizations for chest pain or ACS (OR 4.1).[58]
		2. These women exhibited a decreased quality of life.[58]
		3. 57% of women with confirmed CAD reported recurrent angina (compared with 47% men).[44]
Mortality	ACS	1. Women with STEMI had higher in-hospital mortality compared with men (10.2% vs 5.5%).[59]
		2. Women with ACS had higher in-hospital mortality after coronary angiography.[60]
		3. Men and women have similar 30-day post-MI mortality after adjusting for comorbidities and angiographic severity of disease.[2]
		4. Younger women (<55 y) had a 2-fold higher post-infarct in-hospital and 1-year mortality.[6]
	Stable IHD	1. Women with stable chest pain had higher in-hospital mortality at time of angiography (OR 1.25) and higher 1-year mortality compared with men.[60,61]
		2. Women with angiographic CAD had a 2-fold higher risk of 1-year death, even after adjusting for severity of disease and comorbidities.[44]

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; C2D, contact-to-device time; CABG, coronary artery bypass graft; CAD, coronary artery disease; CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines; EUROASPIRE, European Action on Secondary Prevention Through Intervention to Reduce Events; IHD, ischemic heart disease; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation MI; OR, odds ratio; PCI, percutaneous coronary intervention; and STEMI, ST-segment-elevation MI.

Less Intense Pharmacotherapy

Since the release of AHA's first women-specific clinical recommendations for the prevention of CVD in 1999,[74] with growing sex-specific CVD knowledge, 4 sets of guidelines and statements exclusively focused on CVD in women have now been published.[14,35,75,76] The efficacy of aspirin, statins, and β-blockers for secondary prevention are equally established in both men and women and endorsed by guidelines.[14,77] Additionally, data from Women's Ischemia Syndrome Evaluation (WISE) Study demonstrated that angiotensin-converting enzyme inhibitors improved coronary flow reserve and angina symptoms in women with microvascular coronary disease.[78] Despite documented efficacy and guideline endorsement, women are less likely to receive guideline-based primary and secondary prevention. Women are less likely than men to have their cardiac risks assessed, with the majority not adhering to appropriate primary prevention guidelines and instead resorting to nonevidence-based therapies.[45,46,79] Similarly, EUROASPIRE III and IV surveys demonstrated that despite the higher burden of comorbidities at time of presentation of MI, women are less likely to receive recommended pharmacotherapies (Figure 4)[47,48] and less likely to achieve secondary prevention targets for hyperlipidemia (OR, 0.5), hyperglycemia (OR 0.78), physical activity (OR, 0.74), or body mass index (OR, 0.82).[47,51,52] These disparities are most prominent in Black women, the majority of whom have ≥3 traditional risk factors and yet are significantly less likely to receive appropriate secondary prevention compared with age-matched White women after hospitalization for MI.[49] Decreased adherence was present in the Medicare claims data with a 30% to 35% lower likelihood of medication adherence in Black and Hispanic women 12 months post-MI. This decreased adherence was postulated to be secondary to lack of social support, community resources, cognitive deficiencies, and physician follow-up.[50] Disparities in medication prescription and adherence might explain the sex differences for suboptimal outcomes post-MI.

SUBGROUPS WITH HIGHER DISPARITY IN OUTCOMES

The improved mortality from IHD in women conceals significant disparities across subsets of population, particularly in racial minorities and young women. The age-adjusted death rate for IHD was highest in Black women (89 per 100 000 compared with 72 per 100 000 in White women; Figure 1).[2] South Asian women also exhibit a greater prevalence of severe and extensive coronary artery disease compared with those of European and Chinese descent.[7]

Analysis of temporal trends is notable for deceleration in the rate of decline of IHD death in young women (<55 years) in the United States (annual percent decline of −1.9% in women versus −2.8% in age-matched men).[80] Two large prospective trials focused on young women with acute MI [VIRGO (Variation in recovery: Role of gender on outcomes of young acute myocardial infarction patients) and GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: From bench to beyond-Premature Acute Coronary Syndrome)] showed that these women were less likely to receive perfusion therapy, be referred for cardiac rehabilitation, experienced more angina and depression, had higher mortality, had worse quality of life, and were less likely to return to work at 12 months.[6,11,57]

CONTEMPORARY CHALLENGES AND SOLUTIONS FOR EQUITABLE HEALTHCARE FOR WOMEN

Public Awareness

Since the launch of the Red Dress Campaign, dedicated to increasing recognition of CVD in women, awareness of IHD as the leading cause of death in women has risen from 30% to 56%.[79] Awareness, however, has plateaued as the most recent survey demonstrated nearly 45% of women are still unaware of IHD being the leading cause of death, with even lower awareness rates in women with lesser education, low income, and racial

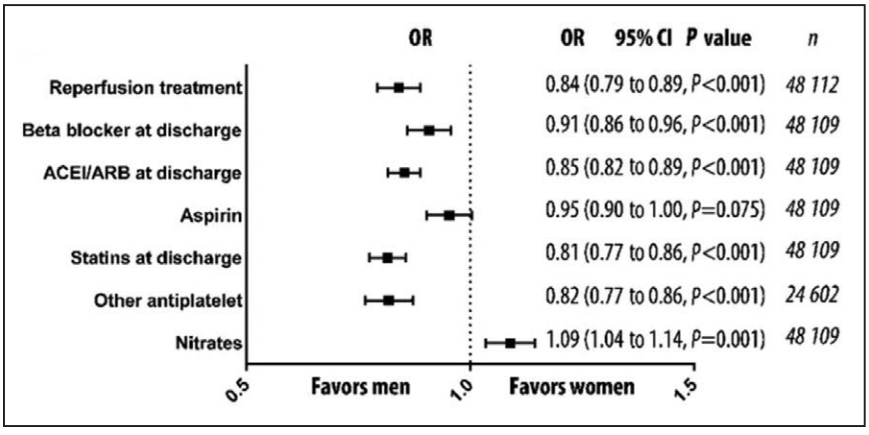

Figure 4. Likelihood of receiving evidence-based treatment by sex. Likelihood of women receiving evidence-based treatment, compared with men, as assessed by logistic regression models adjusted for risk factors. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSTEMI, non–ST-segment–elevation myocardial infarction; OR, odds ratio; STEMI, ST-segment–elevation myocardial infarction. Adapted from Redfors et al.[63]

and ethnic minorities.[13] Most women did not recognize the typical risk factors for IHD. Although most women had ≥3 risk factors, only 52% considered themselves at risk at the time of their index MI (Figure 5).[26] To date, there is suboptimal recognition of the atypical presentation of MI in women.[13] Of concern, even when the symptoms were recognized, only half would seek medical attention.[13,79] Given the perceived social stigma and anxiety associated with CVD, 63% put off visiting their physician.[13] Potential barriers to healthcare aversion include social stigma regarding body weight, caretaking responsibilities, inadequate financial resources, limited personal confidence, and insufficient time.[79]

Improved awareness of risk for IHD are paramount for improving outcomes in women. Public education campaigns and tailored social media messages need to include young women and minorities. Collaboration between local faith–based organizations, local gyms, schools, community leaders, and work-place wellness sites to engender heart-healthy behaviors, improved health literacy, and improved adherence to lifestyle-based primary prevention in a manner that is culturally acceptable, affordable, and readily accessible may be helpful. Expanding the partnership to include patient-centered organizations, like WomenHeart,[81] to identify female IHD survivors from lower socioeconomic status and ethnic and racial minorities, who understand the challenges of their communities and can serve as community leaders, liaisons, and media spokeswomen may help reduce sex disparities in outcomes. Reducing the social stigma of IHD and integrating the tenets of health literacy and affordable heart-healthy lifestyle choices with cultural awareness are pivotal for improving IHD care.

Use of Sex- and Gender-Specific Guidelines

Inadequate recognition of the full spectrum of IHD in women by the medical community continues to be a barrier. In a recent survey, only 22% of primary care physicians and 42% of cardiologists felt adequately prepared to assess women's cardiovascular risk.[13] Nearly 70% of postgraduate trainees report insufficient discussion of sex-based medical concepts in their training.[82] Integration of a formal sex-based cardiovascular curriculum in medical, nursing, public health and pharmacy schools, and residencies and fellowships is needed for integration of guidelines into day-to-day practice. Case-based learning modules can effectively promote cultural awareness and expose learners to the unique challenges of delivering care to women. Fostering a partnership with healthcare teams that are most in contact with women—Primary Care, Obstetrics and Gynecology, Women's Health and Emergency Department—may enhance the delivery of guideline-directed care for women.[83] Inclusion of credentialing policies that mandate continuing medical education credits devoted to detection and management of IHD in women, along with the promotion of sex- and gender-based modules in scientific meetings, will further promote medical awareness.

The identification of at-risk women is presently substandard. Increasing the utilization of the ASCVD Risk Calculator for female patients, currently used by only 44% primary care physicians and 53% cardiologists, would be helpful.[13] A multidisciplinary team approach to treatment with improved inclusion of advanced practice providers has demonstrable effectiveness with improved risk factor modification, medication adherence, and

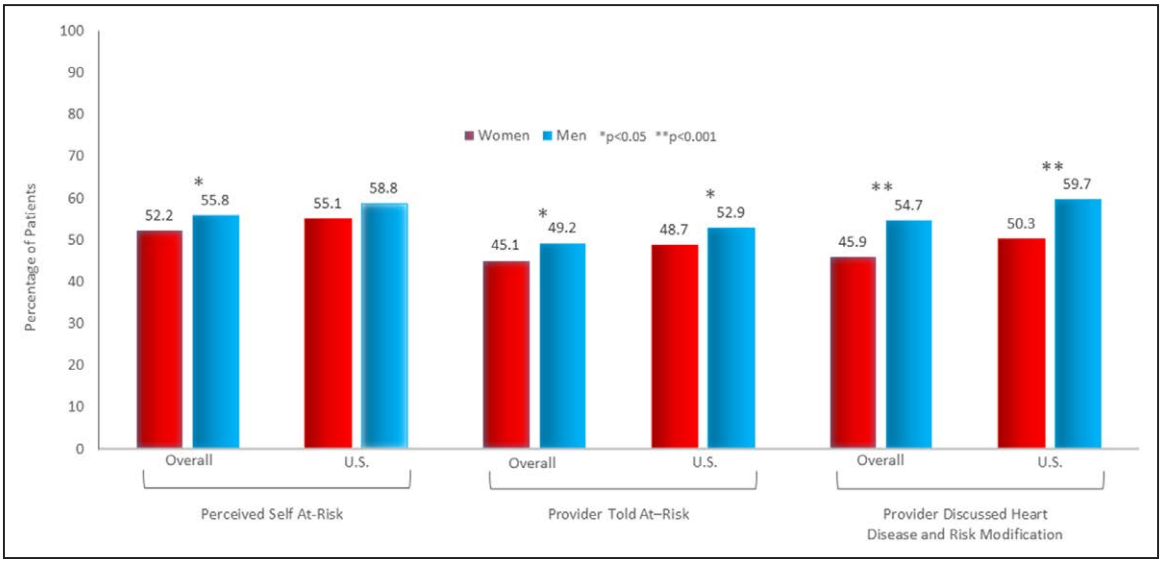

Figure 5. Perceptions and discussions of risk by sex.
Percentage of women and men reporting their self-perception of being at risk, being told by a healthcare professional that they were at risk, or had a healthcare professional discuss risk factor modification for ischemic heart disease, prior to their index myocardial infarction. Adapted from Leifheit-Limson et al[26] with permission. Copyright ©2017, Elsevier.

implementation of guidelines.[84] Systematic approaches such as automated referral for cardiac rehabilitation or computerized physician reminders for diagnostic and therapeutic considerations when patients meet criteria will likely increase adherence to guidelines.

Inclusion of Women in Research

Recognition of sex differences in presentation, pathophysiology, treatment, and outcomes accentuates the need for sex-specific research. Underrepresentation of women results in male outcomes being extrapolated to females, which does not consider sex and gender differences. Despite mandates by the National Institute of Health and the major funding body for Europe (Horizon 2020) on inclusion of women in trials,[85,86] women continue to be grossly underrepresented in IHD trials (only 34% in 2006).[87] Analysis of the 2007 women's CVD prevention guidelines revealed that women comprised only 25% of the participants of the 156 IHD trials.[87] Recognizing these disparities, the 2010 report published by the Institute of Medicine called for ongoing efforts to enhance the inclusion of women in clinical trials.[3] Ongoing enforcement by federal, industrial, and professional regulatory bodies and by journal editors for mandatory reporting of adequately powered sex-based analysis would help. A thorough implementation of National Institute of Health mandates that ensure transparent and publicly available publication of sex-specific research data will be key. Novel strategies such as oversampling, focused recruitment of women subgroups, better incentives for researchers for inclusion of women, and social networking-enabled recruitment may be beneficial.[88]

Recognition of Other Important Determinants of Health

Beyond the biological differences, gender roles encompassing a multifaceted, complex construct of cultural norms, psychosocial attributes, and environmental factors are increasingly recognized as having a strong influence on health-seeking behaviors and outcomes in women. In a study of 3500 patients across 24 centers, women had a 29% increased likelihood of rehospitalization within 1 year after an acute MI compared with age-matched men.[57] This increased risk of readmission was largely attributed to baseline health and psychosocial factors like perceived social support and stress.[57] Presence of anxiety and depression after a cardiac event was strongly associated with an unhealthy lifestyle and poor compliance with medications and risk factor modification.[89] Similarly, analysis of risk factors in the INTERHEART study (n=29 972) revealed that psychosocial stress was twice as common in women and a more significant predictor of risk of future MI (OR, 3.49 versus 2.58 in men).[9,17] Interventions that enhance perceived social support, psychosocial factors, and emotional state by reassurance, support groups, stress–reduction intervention programs, health coaches, church support, and psychotropic medications might result in improved clinical outcomes.[90] Furthermore, women, particularly of ethnic minorities, experience a greater demand for family caregiving responsibilities, which in turn is associated with chronic stress, time constraints for self-care, and ultimately poor health outcomes.[91] Improved recognition of barriers to seeking care including time constraints, primary caretaker responsibilities, and psychosocial stress is important. Alternate modes of delivery such as telemedicine or web-based approaches that offer flexible hours and personalized treatment options may be better embraced by women.[73]

Other gendered determinants of health, including access to education and economic opportunities, access to community resources and healthcare, social support, language and literacy, significantly contribute to differences in delivery of care for women, particularly racial and ethnic minorities.[15] These often overlooked factors expose patients to unique risks, may restrict access to care, and make them vulnerable to worse outcomes. Training a more culturally and linguistically competent and diverse workforce along with improved awareness of unconscious bias, stereotyping, and prejudice by healthcare providers may help reverse gender, ethnic, and racial disparities prevalent in IHD care.

Dedicated Heart Centers for Women

Most heart centers for women offer a personalized approach with a sex- and gender-specific care model and address risks that predominantly affect women, including pregnancy outcomes, hormonal changes, breast cancer therapies, and autoimmune disorders. With a multidisciplinary team of clinicians versed in cardio-oncology, cardio-rheumatology, pregnancy disorders, and medically, culturally, and linguistically aware nursing and allied health professionals, these centers can be well positioned to identify at-risk women and prevent IHD. In addition, their role reaches beyond prevention by identifying and phenotyping women with specific forms of IHD and promoting women-specific research.[92] They may improve the cardiovascular health of women by advancing research and the implementation of sex- and gender-specific prevention, diagnostic, and treatment strategies that can lead to the elimination of CVD disparities in women.[93]

Legislative Measures, Policies, and Advocacy

Unique partnerships between advocacy groups, policy makers, and researchers have resulted in landmark

actions which have advanced women's cardiovascular health. An example is the 2014 FDA action plan of 27 points to enhance the collection and availability of sex-specific data and development of a new women's health research plan to answer specific sex-specific concerns and promote enrollment of a diverse subpopulations.[94] In spite of these recommendations and legislations addressing the gaps in sex- and gender-based disparities in CVD, these are inadequately implemented.[95] Policies supporting the health of women to include access to high quality care, and address aspects of financing and payment models, must be expanded and adopted. These include addressing the social determinants of health as barriers to care and the built environment (eg, access to safe spaces to exercise) contribute to disparities and challenges facing women, particularly racial and ethnic minorities, immigrants, and those living in rural areas.[96] Addressing these issues is critical and will require policy changes, investments, and collaboration among an array of stakeholders.[96] These recommendations made at the 2015 WomenHeart policy and science summit should lead to healthier women, families, and communities.[95] Federal agencies, researchers, clinicians, patients, women advocates, and policy makers must commit to work together to fully implement and expand existing policies (Figure 6).[95,97]

CONCLUSIONS

Despite dramatic improvements in mortality from IHD in women, it continues to be the leading cause of death. Sex- and gender-specific disparities in outcome persist, particularly, in subsets of women disadvantaged by race, ethnicity, income level, and educational attainment. There is a need for improved recognition of the unique biological risk factors, differences in pathophysiology of IHD, and unique challenges of sex- and gender-specific delivery of care in women. Increasing awareness of the unique aspects of women's IHD in the public and medical community to include the tenets of health and cultural literacy and improve adherence to prevention, diagnostic, and treatment guidelines are instrumental to improving women's heart health. Advancing the focus on sex- and gender-specific CVD research beyond conventional biomedical models to incorporate the social determinants that affect a woman's health and establishment of health policies which facilitate a sex- and gender-based patient-centered personalized model will result in equitable IHD outcomes and care for women.

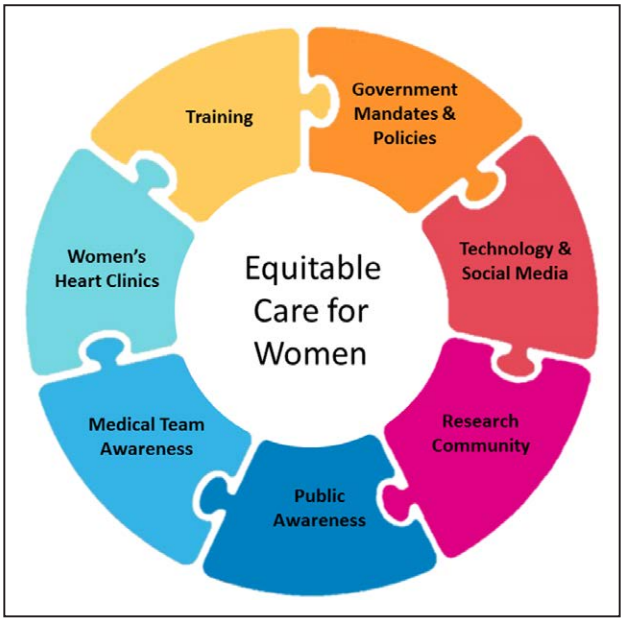

Figure 6. Solutions to equitable care for women. A multifaceted approach is required to achieve equitable cardiac care for women.

Take-Home Points for the Clinician

- Sex-specific risk of traditional and novel risk factors for ischemic heart disease should be considered for improved risk stratification of at-risk women.
- Diagnostic imaging should evaluate the full spectrum of ischemic heart disease and include assessment with stress testing and coronary computed tomography for epicardial stenosis and with positron emission tomography and magnetic resonance imaging for microvascular disease.
- Psychosocial variables, including perceived social support, depressive symptoms, and caretaking responsibilities, play an important role in influencing health-seeking behaviors and clinical outcomes in women.
- Increased awareness of ischemic heart disease in women, attention to social determinants of health, health and cultural literacy, improved adherence to sex-specific guidelines, and adequate inclusion of women in trials are needed to address the existing disparities in research and clinical care.

DISCLOSURES

Dr Sanghani is consultant for Astellas, Inc. Dr Mehta is a site principal investigator for an American Heart Association research grant. Dr Wood is a consultant for Boerhinger Ingelheim and Abbvie. The other authors report no conflicts.

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FOOTNOTES

Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org.

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