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Sex-Specific Disparities in Risk Factors for Coronary Heart Disease

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Abstract In the past two decades, focused research on women at risk for cardiovascular disease (CVD) has helped to clarify our understanding of some of the sex-specific factors that are important in the prevention and early detection of coronary atherosclerosis with a resultant 30 % decrease in the number of women dying from CVD. In spite of these advances, CVD, specifically, ischemic heart disease due to coronary atherosclerosis is the leading cause of cardiovascular death of women in the USA. The 2010 landmark Institute of Medicine (IOM) report, "Women's Health Research—Progress, Pitfalls and Promise," highlighted the fact that although major progress had been made in reducing cardiovascular mortality in women, there were disparities in disease burden among subgroups of women, particularly those women who are socially disadvantaged because of race, ethnicity, income level, and educational attainment [1]. The IOM recommended targeted research on these subpopulations of women with the highest risk and burden of disease. Causes of disparities are multifactorial and are related to differences in risk factor prevalence, access to care, use of evidence-based guidelines, and social and environmental factors. In this article, we review a few of the contributing factors to the disparities in ischemic heart disease in women with a focus on the subgroups of women of Black, Latino, and South Asian descent who are at high risk for morbidity and mortality from CVD.

Keywords Cardiovascular disease in women · Gender-based approach to heart disease · Disparities in healthcare

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Introduction

Cardiovascular (cardiovascular disease (CVD)), which includes coronary atherosclerosis, myocardial infarction, and stroke, is the leading cause of death of women in the USA and the western world [2]. The landmark 2010 Institute of Medicine (IOM) publication, "Women's Health Research Progress, Pitfalls, and Promise," highlights the fact that women's health involves two aspects: (1) sex differences due to the biological factors and (2) gender differences, those affected by broader social, environmental, and community factors [1]. The emphasis on sex-specific CVD research and our improved understanding of sex-specific pathophysiology for coronary disease in women have resulted in important insights into an expanded spectrum of coronary atherosclerosis in women to include obstructive coronary artery disease (CAD) as well as dysfunction of the coronary microvasculature and endothelium as contributors to ischemic heart disease [3]. Marked reductions in cardiovascular mortality in women have occurred for the first time this decade as a result of an increase in awareness, greater focus on women and their

cardiovascular risk, and the application of evidence-based treatments for established coronary heart disease (CHD) [4, 5••]. The IOM report also highlights the fact that although major progress had been made in reducing cardiovascular mortality in women, many subgroups of women defined by race, ethnicity, gender, socioeconomic status, and educational level still show striking disparities in cardiovascular health [1]. The IOM called for greater research and focus on the elimination of disparities in CV mortality and morbidity among the subpopulations of women with the highest risks and burdens of disease. Possible causes of CHD disparities are multifactorial and are related to differences in risk factor prevalence and control, access to and use of evidence-based treatments, and social and environmental factors.

We review a few of the contributing factors to the gender disparities in ischemic heart disease and discuss disparities among the subgroups of women who are at the highest risk for morbidity and mortality from CVD.

The Scope of the Problem: Women at Higher Risk for CHD

The disparity in CVD mortality between women and men prompted sex-specific research, the development of specific guidelines, and the initiation of awareness campaigns. Since the call to action to focus research on the sex-specific aspects of CVD in 1992 at the first National Heart, Lung, and Blood Institute (NHLBI) Conference on Cardiovascular Health and Disease in Women, we have seen a 39 % decline in overall mortality rates for CVD in women in the USA from 1999 to 2011. Despite this decline, the burden of disease and risk factor prevalence remain high and evidence suggests that women with myocardial infarction have a worse outcome and a higher incidence of congestive heart failure (CHF) compared to men with MI. Recent clinical trials have provided evidence that there are sex differences in the presentation, pathophysiology, diagnosis, and treatment of CAD. While men and women share many of the traditional CHD risk factors, different risk factors and mechanisms of disease may be present in women [3, 4]. The evolving evidence supports a multifactorial pathophysiology of coronary atherosclerosis that includes obstructive CAD and dysfunction of the coronary microvasculature and endothelium, and therefore, the term ischemic heart disease (IHD) best describes the pathophysiology in women. Annual CHD population statistics continue to report a greater number of deaths annually for women than men [1]. Evidence supports a lack of recognition of IHD, undertreatment, and undertesting of women, leading to higher case fatality rates and increased morbid complications among women [4, 6]. Women with IHD use more cardiac resources and incur greater health care costs due to (1) more frequent diagnoses of angina, office visits, and hospitalizations; (2) greater myocardial infarction (MI) mortality; and (3) greater rates of heart failure hospitalization as compared with men [3]. Early recognition of symptoms and accurate diagnosis of the full spectrum of coronary atherosclerosis are critical to decreasing the mortality and morbidity of CHD in women.

Gender Disparities in Risk Factors for CHD

Research has demonstrated that although men and women share similar modifiable risk factors for CHD (smoking, elevated cholesterol, diabetes, sedentary lifestyle, hypertension, obesity), several of these traditional risk factors are more potent in women. Also, certain unique sex-specific risk factors such as early onset of menopause, inflammatory diseases such as lupus and rheumatoid arthritis, and complications of pregnancy such as preeclampsia and gestational diabetes are associated with an increased incidence of heart disease. Fifty percent of the reduction in CVD mortality is attributed to reducing these major risk factors [7], and the continued focus on raising awareness and early detection is needed to continue to further lower the mortality rates.

Traditional Risk Factors for CHD

Diabetes Mellitus

Data from the Framingham study highlighted the greater relative impact of diabetes on women compared with men [8], with diabetic women having a 3-fold risk of CAD over non-diabetic women [9]. A gender-specific analysis from the INTERHEART study [10], which highlights the nine factors responsible for 90 % of all MI, found that several risk factors including diabetes mellitus (DM) are more potent in women than men, particularly below the age of 60 years and are more strongly associated with MI. A meta-analysis of ten prospective trials demonstrated a higher risk of CVD death among diabetic women than diabetic men. Also of concern is data demonstrating that women are less likely to be treated aggressively with regard to glucose control [11]. The Rancho Bernado Study—a single-site, >40-year cohort trial studying gender differences in heart disease—data support the fact that diabetes appears to eradicate women's usual cardioprotection. Women with diabetes were also shown to have more classic CVD risk factors than men, and it is suggested that "excess risk factor clustering" may partially explain the fact that diabetes eliminates any cardioprotection women are felt to have related to the lag in average first appearance of CVD [12]. The increased burden that DM has on a women's risk for CVD has also been shown to be particularly important for women who are diagnosed with DM at a later age [13].

Hypertension

The prevalence of hypertension (HTN) in men <45 years exceeds that in women, the prevalence equalizes from 45 to 64 with the prevalence of women with hypertension exceeding that of men from age 65 years onward [1]. While women are more likely to have hypertension and benefit from drug therapy similarly to men, women are less likely than men to achieve adequate blood pressure control [14]. Women are at higher risk of left ventricular hypertrophy and symptomatic heart failure with preserved ejection fraction [15]. Estrogen influences the vasculature maintaining endothelial function through nitric oxide production and reduction in sympathetic nervous system activity. This may help explain the higher rates of hypertension seen in post-menopausal women, given their reduced amounts of estrogen. Conversely, the chronic use of oral contraceptives (OCP) increases the risk of CVD by 2–3-fold via its increased effect on BP. This was shown in a meta-analysis of 14 studies published between 1980 and 2003 in patients who used <50 mcg of ethinyl estradiol daily [16]. The main concern with an OCP-induced rise in BP is the development of persistent hypertension and subsequent premature CVD, especially in women who smoke. The hypertensive effect may be attributed to estrogen's effect on the renin-angiotensin system, since estrogen stimulates the hepatic production of the renin substrate angiotensinogen [17].

Hyperlipidemia

Premenopausal women tend to have lower low-density lipoprotein (LDL) cholesterol levels and higher high-density lipoprotein (HDL) cholesterol and apo A-I levels when compared to men or their post-menopausal counterparts. A meta-analysis of 17 prospective population-based studies revealed a 37 % increased risk for CVD events in women with higher concentrations of triglycerides compared with a 14 % increased risk in men [18]. Cross-sectional data from a large-scale population study suggests that around the time of menopause, LDL-cholesterol levels increase by approximately 15 to 25 % [19]. Because this increase is larger than that observed in men over the same age span and closely approximates that observed in women after oophorectomy, it is likely that reduced circulating estrogen levels associated with menopause play a role in the adverse changes in both blood lipid levels and CHD incidence.

Obesity, Inactivity, and the Metabolic Syndrome

Early data from the Nurses' Health Study confirmed that being even mild to moderately overweight increased the risk of coronary disease in middle-aged women [20]. Most recent data from the American Heart Association reports that 65 % of women are overweight or obese, including 82 % of African American women. Obesity is noted in 35 % of women overall with a much higher prevalence of 58 % in African American women [1].

In June of 2013, the American Medical Association officially recognized obesity as a disease. Body weight may increase during the first years following menopause, and body fat distribution shifts from a gynoid to a more android (central) pattern. This central obesity with an increase in visceral fat occurs with a higher presence of comorbid risk factors and components of the metabolic syndrome in women compared with aging men, including a higher prevalence of DM [21].

Inactivity has been shown to be an important risk factor for women and compounds risk related to being overweight or obese. Fewer women than men report performing the recommended 150 min of exercise each week. Interestingly, the EPIC-Norfolk study showed that women with abdominal obesity and features of the metabolic syndrome who were physically active were shown to have a 50 % lower risk of CHD than those with abdominal obesity who were sedentary [22].

The metabolic syndrome is characterized by abdominal obesity, insulin resistance, atherogenic dyslipidemia, and HTN. In the general population, women with the metabolic syndrome have a 2-fold increased risk of major adverse cardiovascular events and death. In addition to the cardiovascular risk factors that comprise the metabolic syndrome, there is a 3-fold increase in DM [23]. Although studies have shown that the prevalence of obesity and metabolic syndrome is similar between men and women, a meta-analysis of prospective studies has concluded that metabolic syndrome confers a greater overall CVD risk in women, resulting in a 30 % higher relative risk than men [18]. In women, elevated BMI, low HDL cholesterol, increased waist circumference, and hyperglycemia were significantly larger contributors to the metabolic syndrome while, in men, hypertension and elevated triglycerides contributed most [24].

An additional risk for metabolic syndrome in women is the diagnosis of polycystic ovarian syndrome (PCOS), and 40 % of women with PCOS have metabolic syndrome. The risk is even higher for Black women [25]. The association between PCOS and cardiovascular comorbidities is well recognized with a higher incidence of obesity, a 5-fold risk of developing type 2 diabetes compared to age- and weight-matched controls and dyslipidemia being noted in 70 % of patients with PCOS [26]. In addition, women with PCOS have an increased prevalence of subclinical atherosclerosis, as demonstrated by endothelial dysfunction, increased carotid intima media thickness, and increased coronary artery calcium scores [27].

Non-Traditional and Sex-Specific Risk Factors

Hormonal Issues

The effects of hormonal changes over a women's lifetime have important implication for the risk of CHD, and, at the time of natural menopause, women are more likely to develop lipid abnormalities, changes in blood pressure, and increased BMI. Several large-scaled studies have shown an association between early menopause or primary ovarian failure and CVD. Results from the Nurses' Health Study showed a significant association between the age of menopause and the risk of MI, although the strength of the association was decreased when adjusted for smoking [28].

Cardiovascular Complications of Pregnancy

Complications in pregnancy such as pregnancy-induced hypertension, gestational diabetes, and preeclampsia/eclampsia add to the cardiac risk profile of a woman. Mosca referred to these complications of pregnancy as representing a "failed stress test," unmasking endovascular or metabolic dysfunction [29•]. Robbins et al. evaluated 301 women with gestational hypertension and found higher rates of obesity, CVD, and DM compared with women without a history of hypertension [30]. Up to 70 % of women with gestational diabetes will develop type 2 DM within 5 years of the pregnancy. Women with preeclampsia or eclampsia, often called the "metabolic syndrome of pregnancy," are 3.8 times more likely to develop diabetes and 11.6 times more likely to develop hypertension requiring drug treatment. In a recent large study, preeclampsia/eclampsia doubled the risk for subsequent IHD, stroke, and venous thromboembolic events over the 5–15 years after pregnancy [31, 32].

Inflammatory Disorders

Chronic inflammation and endothelial injury are a cardinal feature of many autoimmune diseases like SLE and rheumatoid arthritis (RA) (more common in women than men), which have been shown to be associated with CHD. Women with SLE and RA are at five to eight times greater risk for heart disease [33]. Women in the Framingham Offspring study aged 34–44 years with SLE have a 50-fold likelihood of sustaining an acute MI than those similarly aged women without lupus [34]. A longitudinal study of women with SLE showed progressive atherosclerotic changes in the carotid arteries with a 10 % annual progression [35]. Approximately 35 % of patients with SLE have evidence of atherosclerosis, and the risk of MI in these patients is significant with the overall prevalence of clinical CHD in SLE patients ranging from 6 to 10 % in many cohorts [36]. Evidence suggests that traditional risk factors alone do not explain the increase in CHD observed and that chronic inflammation with endothelial cell injury and antiphospholipid antibodies may also contribute [37].

Depression, Acute Stress, and CVD in Women

Depression is associated with a 70 % increased risk for heart disease and is twice as common in women than men [38]. Depression results in elevated atherosclerotic and inflammatory markers which impair vascular function and also cause impaired platelet activation. Depression leads to nonadherence to medication and follow-up, apathy, poor diet, increased smoking, and increased physical inactivity. Collectively, the physiological and behavioral responses of depression contribute to negative outcomes.

Depression is significantly linked to heart disease in women younger than 55 years of age. Data on over 7000 patients from Johns Hopkins showed a significantly high risk of CHD in women aged 17–39 with depression [39]. A recent study by Shah and colleagues from Emory looked at 3237 women with established or suspected heart disease and found that young women with moderate to severe depression had double the risk of heart attack in the next 2 years and increased risk of death [40]. These findings were not the same for men or woman older the 55. Shah theorized that depression can interfere with normal ovulation and therefore interrupt the normal hormonal cardio protection of the premenopausal state [40]. Similar to diabetes or any CVD risk, primary prevention of depression is particularly important in women, and therefore, screening is paramount [41].

The effects of acute stress have been shown to induce myocardial ischemia in women but not men after MI. The Myocardial Infarction and Mental Stress (MIMS) study compared middle-aged men and women after MI and showed a dramatic difference in myocardial ischemia produced by mental stress as documented on nuclear perfusion study in women younger than 50 years old. Induced ischemia related to physical stress did not show a gender-based difference [42].

Sleep Disorders

Obstructive sleep apnea (OSA) and sleep disorders are now recognized as an important cardiac risk factor in women. Recent studies have shown that OSA is independently associated with high blood pressure and increased arterial stiffness in perimenopausal women [43]. Sleep disorders have also been found to be independently associated with atherosclerosis and heart remodeling [44]. Campos and colleagues have recently shown that women <65 years of age with severe untreated OSA have an increased incidence of serious cardiovascular outcomes, particularly incidence of stroke [45]. Adequate CPAP treatment seems to reduce this risk. Unfortunately, OSA and sleep disorders are underdiagnosed and undertreated in women [46].

Recent investigation has described that women who report poor sleep have elevated levels of inflammatory markers including C-reactive protein, fibrinogen, and interleukin 6, but this has not been noted in men [47]. More women than men reported sleep disturbances in this study, and it was hypothesized that low estrogen levels might explain the link between poor sleep habits and elevated markers of inflammation in this predominantly post-menopausal female population. Miller and colleagues showed that levels of inflammatory markers varied with sleep duration in women but not in men [48]. Also, poor sleep has been linked to resistant hypertension in women but not men and an increased association between poor sleep, resistant hypertension, and depression was also noted in women but not men in this study.

Subgroups of Women at Higher Risk for CHD: the Impact of Race and Ethnicity

Disparities in CVD exist by race and ethnicity with significantly higher rates, morbidity, and mortality in racial and ethnic minority groups compared to their White counterparts [49]. In 2010, the prevalence of CHD was more than 50 % higher among Black women and approximately 15 % higher among Mexican American women compared to non-Hispanic White women, respectively [50]. The comparisons are similar for the prevalence of angina, the incidence of MI, and for CHD death rates. Over age 64, the incidence of MI in Black women is even higher than that of White men [51]. Studies in migrant South Asian populations have shown MI and CHD deaths at up to four times the rate of the general world's population with higher rates of premature CHD even with similar levels of risk factors [52]. South Asian women have high overall heart disease rates, approaching those of South Asian men and their CAD mortality rate a much higher than that of White women [53]. Angiographic studies have also shown high rates of severe and extensive multivessel disease in Indian women when compared to White women [54, 55].

Despite significant improvements in CVD quality of care and declines in cardiovascular mortality, racial/ethnic disparities in care and outcomes have persisted and the contributing factors to these disparities are complex and multifactorial [56]. The increased burden of cardiovascular risk factors among racial and ethnic minorities is definitely one significant contributor to the disparities. Hypertension is much more common among Black women compared to non-Hispanic White and Mexican American women, and diabetes is much higher in Black and Mexican American women compared to non-Hispanic White women [50, 57, 58]. Of modifiable risk factors, while smoking is higher among non-Hispanic White women, other risk factors such as overweight, obesity, and physical inactivity are much more common among Black and Hispanic women. While much of the data on CVD in the Hispanic/Latino population has focused on Mexican Americans, this is a very heterogeneous group with diverse backgrounds. A study of CVD risk factors in Hispanic/Latino groups in the US showed variation of CVD risk factors by specific country of origin, with women of Puerto Rican background having the highest rates of obesity (31.7 %), current smoking (51.4 %), hypercholesterolemia (41 %), and ≥3 risk factors compared to their Cuban, Dominican, Mexican, Central American, and South American counterparts. There was also a higher prevalence of ≥3 risk factors with higher degrees of acculturation as assessed by place of birth (US or abroad), time living in the USA, and preferred language of English or Spanish. These differences by background were not seen among the Hispanic/Latino men studied [59].

South Asians, a population that is growing in the USA, experience CAD at up to four times the rate of the general world's population [52]. Except for diabetes, South Asians do not have a higher incidence of smoking, obesity, or hypertension and many are vegetarians who exercise regularly. The overall heart disease rates among South Asian women are as high as or higher than South Asian men. South Asian women also have one of the highest mortality rates due to CAD. Angiographic studies in these women have shown high prevalence of severe and extensive disease, including three-vessel disease, despite the fact that majority of these women (56 %) were premenopausal [54]. In a Canadian angiographic study, Asian Indian women were twice as likely to have left main or three-vessel CAD compared to White women [55]. In the Study of Health Assessment and Risk in Ethnic groups (SHARE), South Asians were found to have a higher prevalence of subclinical atherosclerosis, and South Asian ethnicity was an independent predictor of CVD [54]. Unfortunately, conventional screening and management do not address the high rates of premature heart attacks. Atherogenic dyslipidemia characterized by high triglycerides and low HDL, low HDL2B concentrations, small dense LDL, and apolipoprotein B, which in turn is related to insulin resistance, is highly prevalent among Asian Indian women and appears to be a major contributor to the high incidence of CAD/MI [53]. Perhaps, the strongest contributor is high levels of lipoprotein (a) found in 35–40 % of Asian Indians worldwide [60].

Another contributing factor may be lower awareness of CVD among racial and ethnic minorities. In surveys conducted by the American Heart Association, low levels of awareness persisted with a minority of Black and Hispanic women citing heart disease as the leading cause of death, levels similar to those of White women 15 years ago and almost half of those of White women in 2012 [61]. Beyond awareness and health literacy, the racial and ethnic disparities in CVD are further impacted and confounded to varying degrees by a myriad of other factors including socioeconomic status, education, geographical location, social and environmental

factors, access to care, differences in care provider characteristics, and adherence to guideline-based treatment, all areas of ongoing investigation and targets for intervention [56].

Gender Disparities in the Presentation of CHD

Disparities in the manner that women and men present with CHD have been noted. Women less often report chest pain and diaphoresis and more often complain of back or jaw pain, palpitations, lightheadedness, or loss of appetite [62, 63]. Data from the National Registry of Myocardial Infarction (NRMI) demonstrated that 42 % of men vs. 31 % of women presented with chest pain in the setting of MI with in-hospital mortality of 14.6 vs. 10.3 % for men. Younger women without chest pain in the NRMI were at highest risk [64].

This "atypical presentation" in women has been linked to the delay in diagnosis and delivery of life-saving treatment strategies, with poorer outcomes [65, 66]. The recent VIRGO trial which confirmed that young middle-aged women with MI have poor outcomes at 1 year than men suggested that one of the multiple factors resulting in this finding is the less-frequent reporting of typical chest pain [67].

Diagnosis and Prognostic Assessment of IHD

Historically, the diagnosis of ischemic heart disease (IHD) has focused on the identification of obstructive CAD as measured by degree of stenosis and candidacy for revascularization. Sex-specific research has resulted in an expanded understanding of the pathophysiology of IHD with a greater appreciation of the contributing roles of vascular endothelial dysfunction and microvascular disease as well as the prognostic importance and implications in the setting of non-obstructive CAD [5••]. In women, non-obstructive CAD is more often found on angiography, but among symptomatic women, especially among women ≤75, this has been shown to be associated with an elevated risk of adverse outcomes [3, 68–71]. Contemporary cardiac imaging techniques work well to investigate all components implicated in the spectrum of IHD in symptomatic women by illustrating inducible ischemia due to obstructive CAD and by identifying the extent and severity of myocardial ischemia resulting from coronary vascular dysfunction in the setting of non-obstructive CAD which is associated with an increase in IHD risk [3, 5••].

In the evaluation of symptomatic women with suspected IHD, the determination of a woman's risk status (low, intermediate, or high risk for IHD) should guide shared decision-making between the woman and her healthcare professional as to the need for and appropriate selection of diagnostic tests. Low-risk women generally require no further testing and should be assessed for an etiology of their symptoms. An evaluation of symptoms should be incorporated into the risk assessment, as studies have shown that women are more likely than men to report a wider range of symptoms such as epigastric pain, nausea, and dyspnea that is unrelated to exertion. In general, premenopausal women ≤50, with no CHD equivalent conditions such as diabetes or peripheral artery disease, are considered to be at low risk. Women in their 50s are classified as low or intermediate risk based on level of functional capacity with lower functional capacity conferring higher risk. Women in their 60s are considered intermediate risk, and women ≥70 are considered high risk. The presence of comorbidities and multiple other risk factors may adjust the assessment of risk up to one category. As previously mentioned, women with peripheral arterial disease and long-standing diabetes are high risk [5••, 72].

After a pretest risk classification, the next step is the decision for further diagnostic testing. As per the American Heart Association consensus statement [73], shared decision-making involving the at-risk woman is recommended. For premenopausal women, an important consideration is radiation exposure which varies widely depending on the type of test chosen and the test protocols available. Exercise ECG testing is recommended as the initial test of choice for symptomatic women with at least a low-intermediate pretest risk who have a normal interpretable baseline ECG and are able to exercise sufficiently. In women with lower levels of fitness, there should be consideration for using alternatives to the standard Bruce protocol that start at lower workloads and have smaller incremental increases. Important prognostic information obtained from the ECG stress test includes functional capacity, fitness level, chronotropic competence, blood pressure response to exercise, heart rate recovery, and evidence of ischemia by ST segment changes. Lower accuracy of the ECG response in women has been reported; however, this may be mostly attributed to more frequent resting ST segment abnormalities at baseline. Despite the higher false-positive rate, the negative predictive value is similar to men, and therefore, a negative maximal ECG test is as good a predictor of having no obstructive coronary disease as in men [73–75]. The exercise treadmill test provides important diagnostic and prognostic information, and its accuracy in at-risk women can be improved by the incorporation of parameters such as exercise capacity, chronotropic response, heart rate recovery, blood pressure response, and the Duke treadmill score, in addition to ST segment changes with exercise [73].

Symptomatic women at intermediate to high risk for IHD with an abnormal 12-lead resting ECG, those who are unable to exercise sufficiently, and those with an indeterminate exercise treadmill testing (ETT) should be referred for stress imaging with echocardiography, myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT) or PET, cardiac magnetic resonance (CMR) imaging, or coronary computed tomographic angiography (CCTA)

[73]. Physiologically significant coronary atherosclerosis can be accurately detected by the presence of stress-induced wall motion abnormalities with exercise or perfusion abnormalities noted on pharmacologic stress echo or SPECT or PET pharmacologic testing. Risk stratifications based on the extent of wall motion abnormalities or extent and severity of stress myocardial perfusion abnormalities are effective at improving delineation of symptomatic women for cardiac events and provide incremental and improved risk reclassification over and above clinical and ETT parameters [73]. Contemporary techniques of CCTA can provide information on the obstructive and non-obstructive burden of CAD and can guide post-test management approaches for women. CMR with vasodilator stress can be useful for the identification of obstructive CAD as well as the detection of subendocardial ischemia in women with non-obstructive CAD [73]. Stress PET MPI, with the ability to calculate absolute blood flow across the coronary vessels and the resultant calculation of PET myocardial flow reserve (MFR), is useful for the detection of microvascular CAD, with diminished MFR correlating with vascular dysfunction [76]. An algorithmic approach can be followed for the use of non-invasive testing in symptomatic women at risk for IHD (Fig. 1).

Women are less likely than men to receive appropriate treatment after a MI. An analysis of the CRUSADE ACS registry of 35,875 patients (41 % women) demonstrated higher mortality in women (5.6 vs. 4.3 %, $P<0.01$) with acute coronary syndrome (ACS) [66]. Once diagnosed, women are more often managed medically and undergo less percutaneous coronary intervention and coronary artery bypass grafting than men. When adjusted for confounders, the use of invasive management and guideline-recommended medication was lower for women when compared to men except for the use of beta blockers. Acutely, women were less likely to receive heparin, ACE inhibitors, and glycoprotein IIb/IIIa inhibitors and, at discharge, were less likely to be prescribed aspirin, ACE inhibitors, and statin drugs [66].

There are a few notable favorable strategies, reflected in the ACC/AHA guidelines in treating ACS in women that should be mentioned. First, an invasive approach in women with ACS and positive biomarkers derives more benefit than for women with negative biomarkers [77] Also, the use of GP IIb/IIIa inhibitors incurs a risk reduction for women with positive biomarkers where women receive no benefit when the biomarkers are negative [78] Outcomes in the use of DES are similar in men and women [79, 80].

Most studies of outcomes after MI demonstrate that women have poorer outcomes compared to men. Unadjusted mortality rates are higher in women in most studies as well. Post-PCI, women have higher in-hospital bleeding rates than men. In CRUSADE ACS, women had inappropriately excessive dosing of anti-platelet and antithrombin agents with resultant increased bleeding, length of stay, and mortality [66].

Women comprise less that 30 % of patients who are referred for CABG [81]. Female sex is found to be an

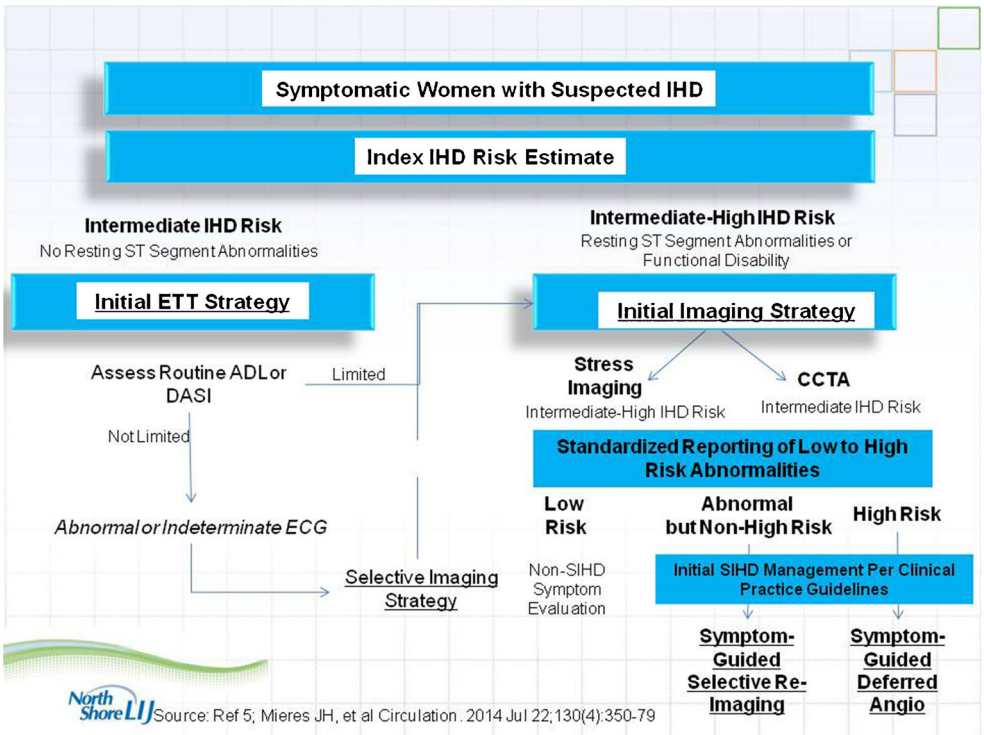

Fig. 1 Diagnostic evaluation algorithm for women presenting with suspected ischemic heart disease (IHD) symptoms and intermediate IHD risk and intermediate-high IHD risk. *ADL* activities of daily living, *Angio* angiography, *CCTA* coronary computed tomography angiography, *DASI* Duke activity status index, *ETT* exercise treadmill testing, *SIHD* stable ischemic heart disease. Reprinted with permission from [5]

independent risk factor for morbidity and mortality [82]. Also, women experience less relief from pain after CABG as compared to men [83].

Treatment and Outcomes of Non-Obstructive IHD in Women

Sex-specific research has demonstrated that non-obstructive CAD is not a benign diagnosis. In a cohort of WISE women, with chest pain and an abnormal stress test without an angiographic flow-limiting lesion, there was an intermediate risk of cardiovascular events at 5-year follow-up. In these women, there was an increased rate of cardiac mortality, MI, stroke, and hospitalization for CHF compared with a similarly matched cohort of women without symptoms [84]. Endothelial dysfunction and microvascular disease are felt to be the cause of persistent symptoms and abnormal stress tests in this group [3]. The goal of treatment of non-obstructive CAD is symptom control and improved endovascular function.

It is demonstrated that angina can be effectively treated with beta blockers [85]. Long-term angiotensin-converting enzyme inhibitor has been shown to improve endothelial function and symptoms by improving nitric oxide bioavailability [86]. Statins have also been demonstrated to improve microcirculation [87]. One study notes that the combination of ACE and statin improves endothelial dysfunction [88]. Imipramine has been shown to improve symptoms in women with chest pain and non-obstructive CAD, perhaps related to a visceral analgesic effect [89]. L-Arginine, a precursor for nitric oxide, has been shown to improve small vessel endothelial function. Through this mechanism, it is believed to improve symptoms in patients with non-obstructive CAD [90]; however, recent safety concerns that need further investigation have come up with L-arginine in post-infarct patients [91]. Lastly, a recent promising study by Mehta et al. demonstrated that women with angina, myocardial ischemia, and no obstructive CAD had an improvement in chest pain with ranolazine [92].

Conclusion and Proposed Future Directions

The 2012 American Heart Association awareness survey [61] demonstrated that although awareness of heart disease among women has improved in the past 15 years, a significant racial/ethnic minority gap persists. In spite of the overall increase in awareness, almost 50 % of US women currently fail to recognize heart disease as their major health problem and fail to partner with their health care professionals to adopt heart-healthy lifestyles. Additionally, many of the gains made in advancing the prevention of CHD in women are in jeopardy of being reversed as recent statistics demonstrate an increase in the death rate for younger women ages 35–54 and a growing epidemic of obesity, hypertension, diabetes, and sedentary lifestyle among US women.

Therefore, a model which empowers women to personalize and translate the awareness and knowledge about heart disease into heart-healthy living is essential. For this to occur, the medical community and organizations committed to improving the heart health of women must change the narrative to focus on heart health and wellness and away from a discussion on heart disease. A "woman-centered" holistic approach should be seen as an ongoing process fostering a lifestyle and personal commitment to heart health and wellness combined with risk factor modification and appropriate gender-specific diagnostic and treatment approaches customized for the unique physical, mental, and social well-being of individual women. The incorporation of heart-healthy messages that are culturally customized to the individual woman is essential to promote the elimination of cardiovascular health care disparities, particularly important for African-American and Latino women who are at high risk for heart disease [2].

Compliance with Ethics Guidelines

Conflict of Interest SE Rosen, S Henry, R Bond, C Pearte, and JH Mieres all declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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testing highlighting new data and new techniques as well as an understanding that ischemic heart disease in women is a heterogeneous condition including both traditional obstructive coronary artery disease as well as those with other etiologies for IHD. The importance of shared decision making is also an important aspect of this publication.

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