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The Challenges of Prevention, Diagnosis and Treatment of Ischemic Heart Disease in Women

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Abstract

Increasing evidence suggests that there are significant differences in the presentation, diagnosis and treatment of ischemic heart disease in women compared to men. Women often present with atypical symptoms, and this, in association with a consistent underestimation of their risk for ischemic heart disease, leads to underdiagnosis and undertreatment in women. Cardiovascular risk factors unique to women have only recently been recognized, and moreover, traditional risk factors have recently been shown to have greater impacts on women. Consequently, women suffer more disability and poorer clinical outcomes, with higher cardiovascular morbidity and mortality. These discrepancies may in part be secondary to the higher prevalence of nonobstructive coronary artery disease in women with persistent chest pain symptoms as compared to men when evaluated invasively. Focused diagnostic and therapeutic strategies unique to women are thus needed, but unfortunately, such sex-specific guidelines do not yet exist, largely due to lack of awareness, both on the part of providers and patients, as well as a paucity of evidence-based research specific to women. Although underutilized in women, diagnostic modalities, including functional and anatomic cardiac tests as well as physiologic assessments of endothelial and microvascular function, are useful for establishing the diagnosis and prognosis of suspected ischemic heart disease in women. This review discusses the current challenges of prevention, diagnosis and treatment of ischemic heart disease in women.

Keywords

Women; Ischemic heart disease; Cardiovascular risk; Diagnosis; Treatment

Introduction

The Current State of Ischemic Heart Disease in Women

The number of men and women who are affected by and die from coronary artery disease (CAD) outnumber all other conditions including all forms of cancer in the US [1]. However, there are distinct differences in the experience of CAD among women in comparison to men. Several studies have demonstrated perplexing diagnostic and management dilemmas in

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women due to their lower prevalence of angiographically obstructive CAD, greater symptom burden and rate of functional disability in comparison to their male counterparts [2]. These discrepancies have called for a more inclusive term, “ischemic heart disease” (IHD), in women to capture a wider spectrum and definition of a sex-specific pattern of CAD in women [3]. There is consistent evidence that adverse outcomes in women with IHD may be fueled by underestimation of cardiovascular disease (CVD) risk, leading to underdiagnosis and undertreatment. The reasons for these gender disparities are uncertain; therefore it is crucial to elucidate the interplay of key clinical, pathophysiological and psychosocial determinants in the evolution of IHD. It is essential that a focus be placed on the primary and secondary prevention of CVD in women to not only alleviate the exuberant economic burden of associated health care costs, but to also to reduce its associated effects on mortality and well-being.

Most of our knowledge and guidelines directing the prevention, management and treatment of IHD and its risk factors are based on data from randomized clinical trials with small proportions of women participants. This underrepresentation was confirmed by an assessment of females in clinical trials from 1997 to 2006 which was estimated at only 27 % [4]. Furthermore, the substantial heterogeneity across studies and lack of consideration of sex-specific factors in study design and implementation, limit the ability to draw more conclusive inferences [5]. In addition, there are a disproportionately small number of studies addressing CVD in women, but studies have instead overwhelmingly targeted reproductive concerns, termed “bikini medicine” [6]. As such, there remains uncertainty in women-specific clinical manifestations and management of IHD as many algorithms that we use today are derived from predominantly male populations.

This review outlines the current challenges in the primary and secondary prevention, diagnosis and management of IHD in women. We present a comprehensive selection of key evidence highlighting the epidemiology, risk factors, screening, diagnosis and treatment of IHD in women. We identify gaps in knowledge of IHD in women which in turn may spur further sex-specific studies and interventions towards the improvement of cardiac care and outcomes in women.

Epidemiology of Ischemic Heart Disease

Incidence and Prevalence

The view of CAD as a “man’s disease” is slowly dissipating as it has emerged as a major cause of morbidity and mortality amongst women. Among Americans aged 20 years or older, 15.4 million have CAD with 5 % of these individuals being women [1]. Black women have a higher prevalence of 7 % compared to 4.6 % among white women. Overall, the prevalence of CAD is lower in middle-aged women than in men according to the most recent iteration for the National Heart, Lung, and Blood Institute (NHLBI), National Health and Nutrition Examination Survey (NHANES); however there exists an overall upward trend in women [7], especially younger women. This data is likely an underestimation as it only accounts for obstructive CAD (angiographically-determined stenosis >50 %) and does not include other forms of IHD.

As women age, the incidence of all initial coronary events including myocardial infarction (MI), angina pectoris, unstable coronary syndromes and coronary deaths) increases and eventually approaches that of men by age 60 [8–10]. There is a lag time period of about 10 years in the incidence of all coronary events in women behind men which increases to about 20 years for critical events such as MI and sudden death [1]. Notably, the incidence of total coronary events triples in women over age 65 compared to younger women [11]. There is evidence of a racial disparity as black women aged 45 to 64 within the Atherosclerosis Risk in Communities (ARIC) study were significantly more likely than their white counterparts to experience CVD death as a first event [12]. Discouragingly, recent statistics indicate that although the overall CVD mortality is decreasing for both men and women, it is accelerating in younger women, especially those in mid-life [13, 14].

Clinical Presentation

The clinical assessment of women with IHD has been traditionally viewed through the lens of “typical” angina symptoms characteristic of primarily male study cohorts. Interestingly, effort angina is of similar or increased prevalence among women in comparison to their male counterparts [15, 16]. Yet, a wide range of “atypical” symptoms occur more frequently in women including nausea, fatigue, dyspnea, weakness as well as unconventional descriptors, triggers and locations of chest-related symptoms [17, 18]. Some have suggested that lack of existence of a female-specific characterization of IHD symptoms has resulted in suboptimal care and outcomes among women as an emphasis has been placed on identifying noncardiac etiologies to chest pain that is not “typical.” [17] Of clinical relevance is the fact that the presence of symptoms alone, whether “typical” or “atypical” places women at a greater risk of future cardiovascular events [19]. Black and white women differ in their symptom presentation and this difference is associated with a worse prognosis among black women [18]. Strikingly, women are more likely to not report anginal symptomatology as it seems as if a disconnect exists between perception of symptoms and health status [20].

Obstructive versus Nonobstructive CAD

Despite having more symptomatology and debility than men, women have less anatomical obstructive CAD [21, 22]. Several studies have confirmed the clinical observation that women have a lower plaque burden than men, including atheroma within the media and luminal plaque [21]. In an effort to tackle this issue of clinicopathophysiological differences of IHD in women, the NHLBI-sponsored Women’s Ischemia Syndrome Evaluation (WISE) study sought to better elucidate the complexity of IHD in women. Of over 800 women in the cohort who underwent clinically-indicated angiograms, 62 % were not found to have obstructive CAD at catheterization [23]. These findings were further corroborated within the American College of Cardiology (ACC)-National Cardiovascular Data Registry (NCDR), as 51 % of women with stable angina referred for coronary angiography had nonobstructive disease compared with 32 % of men [24]. Approximately two-thirds of the black women studied within the Coronary Artery Surgery Study (CASS) registry had nonobstructive CAD in comparison to slightly over half of their white counterparts [25]. The issue remains whether women experience myocardial ischemia by a different pathophysiology than men, as they more commonly do not have obstructive CAD. The lack of “significant stenosis” approach to management has been a serious detriment to women as the absence of

demonstrable obstructive CAD in women with persistent IHD symptoms is not benign [15, 26].

Cardiovascular Mortality

Positively speaking, the US mortality rate from CVD in men and women has had a 39 % decline over the past decade [1]. However, the leading cause of death among women remains CAD. Despite innovations in cardiac medical therapies and care, greater than 250,000 women in the US die annually from CAD-related deaths-five-fold higher than women with breast cancer [1, 2, 27]. There is an even greater disparity among middle-aged black women as they have a 2.5 times higher mortality from CAD than similarly-aged white women [2, 27, 28]. It is also striking that women are more likely to die after their first MI whereas men have four times more coronary events than women [1]. Nevertheless, nearly half of all American women, especially those younger than 50 and/or of ethnic diversity, remain unaware that IHD is their greatest health threat [29].

There is equipoise in the current evidence regarding mortality rates in women after an acute coronary event with some studies revealing higher death rates or even a survival advantage in women [5, 30]. The longer term outcomes are even more inconclusive [5]. However, the vast majority of studies have reported higher mortality rates for women compared with men after an acute MI [5], but this trend may be explained by age, higher prevalence of cardiac risk factors, poorer clinical presentation and treatment differences. Older age and increased comorbidities at presentation such as diabetes, hypertension and heart failure, may further clarify this differential. There is also evidence suggesting worse mortality rates in younger women following an acute MI [5, 31–35]. Fortunately, differences in mortality risk following percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) appear to be narrowing between men and women [5, 35]. This has been attributed to advances in revascularization techniques and therapies and improved guideline adherence.

A puzzling paradox exists when examining cardiac event and mortality rates among women with nonobstructive CAD. Among the WISE cohort, there is a trend towards increased fatal and nonfatal cardiovascular event rates (MI, stroke, and congestive heart failure) with age, with the major difference emerging after age 54 [19]. Most salient is the fact that the risk of cardiac events for symptomatic women with nonobstructive CAD is almost double that of symptomatic women with normal coronaries. Correspondingly, among women without CAD, those with persistent chest pain in spite of medical therapy had twice the rate of future cardiac events than asymptomatic women [36].

Healthcare Cost Burden

CVD constitutes 17 % of the national health expenditures, with the annual direct and indirect costs of care for women at an estimated $130 billion [1, 28]. Much of these exuberant healthcare costs are associated with the diagnosis and management of persistent angina in women without obstructive CAD. An annual excess expenditure of $280 million has resulted from the over half a million coronary angiograms completed in women which in only half of the cases are revealing of actual flow-limiting stenoses [37]. This estimate does not account for the incurred continued longitudinal medical assessments including increased

office visits, procedures and hospitalizations for women with persistent chest pain [37]. The average lifetime cost estimate is approximately $770,000 and ranged from $1.0 to $1.1 million for women with nonobstructive CAD which approaches that of women with obstructive CAD [23]. This presents an enormous challenge to clinicians in treating these women with a greater symptom burden but no evidence of the classically described male pattern of obstructive CAD (>50 % stenosis).

Quality of Life

Persistently symptomatic women with IHD require more hospitalizations and repeat invasive procedures in comparison to men which undoubtedly lead not only to increased health care costs but more importantly, lower ratings of quality of life, general well-being and productivity among women. Despite similar lifestyle and pharmacologic management strategies, women with angina have been shown to have inferior functional status scores than men even after adjustment for confounders such as CAD severity and comorbid conditions [20]. Women with IHD are likely to have higher rates of depression, anxiety and inadequate social support which may have a detrimental effect on physical functioning [20, 38–40]. Clearly, the implications of this disparity in psychosocial well-being are substantial and deserve further attention in the clinical care of women with IHD.

Risk Factors for Ischemic Heart Disease

Traditional Risk Factors

Traditional risk factors including family history of premature CAD, age, smoking, hypertension, diabetes, dyslipidemia, obesity and physical inactivity are well-documented in the etiological IHD pathway in women. Over 80 % of middle-aged women have ≥1 traditional cardiac risk factor [3]. The majority of risk factors for black women are attributed to diabetes, hypertension, overweight/obesity, and physical inactivity, as compared to white women who proportionally have more smoking and hypercholesterolemia [1].

Unfortunately, most “traditional” CVD risk factors are associated with proportionally greater risk in women. Female relatives with premature CAD confer a more potent risk to family members than male relatives with premature CAD [41]. Hypertension is a major risk factor in women which becomes more prevalent with age and is particularly prevalent in black women [1]. Diabetic women have a 3-fold higher risk for CAD in comparison to nondiabetic women and have significantly greater IHD mortality rate than diabetic men. Lipid profiles in women deteriorate in the perimenopausal and postmenopausal phases of life, with reductions in “good” (HDL) and increases in “bad” (LDL) cholesterol; indeed women develop higher cholesterol levels than men after the fifth decade of life [42–14]. Higher triglyceride levels are a more prevalent and potent, independent risk factor for IHD in women than in men [45–47]. Moreover, smoking has been identified as a stronger risk factor for IHD among middle-aged women in comparison to men [48, 49], conferring approximately twice the risk in women.

The so-called “graying” or aging of America projected for 2020 and beyond will undoubtedly influence patterns in CVD epidemiology and healthcare costs, particularly for

women. Women experience a more exponential increase in IHD after age 60, whereas men have a more linear increase [50]. Despite the clear evidence that both men and women with optimal risk factor profiles have lower risks of IHD compared to those with suboptimal profiles, less than 2 % of the US population in NHANES (75 % women) actually met the seven simple ideal cardiovascular health metrics [51, 52]. Although women are increasingly aware of CVD as the “number one killer of women” there remain significant disconnects between this awareness and perceived individual risk [53] which is especially significant for women who are younger and of diverse ethnicity [29].

Unique and Emerging Risk Factors

There are several newly-identified cardiac risk factors for women. The examination of those unique to, or more common in, women may offer insight into the tailoring of current risk assessment algorithms for women. Metabolic syndrome has emerged as a clustering of cardiometabolic risk factors [glucose intolerance, central obesity, hypertension, dyslipidemia (low HDL, high triglycerides)] and is more common after menopause [26]. Thus, it is often linked with hormonal alterations [26, 54] and is associated with a markedly higher risk of IHD and cardiac events. Furthermore, high-sensitivity C-reactive protein (hsCRP) may improve risk stratification for IHD in women, particularly those with metabolic syndrome [55, 56]. High-sensitivity C-reactive protein has consistently been higher in women than in men after puberty and there is clear variation with estrogen levels in postmenopausal women [57]. Recent evidence has emerged suggesting a connection between autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, which are more common in women, and increased risk of IHD [58].

Hormonal fluxes over a woman’s lifespan also influence IHD risk, and provide unique risk factors, seen only in women. It has been observed that early menarche (<12 years at onset) increases subsequent risk of cardiac events and both CVD and overall mortality [59]. Entities causing ovarian dysfunction, such as functional hypothalamic amenorrhea, have been associated with premature coronary atherosclerosis and associated CVD events [60]. Moreover, polycystic ovarian syndrome (PCOS) is coupled with risk factor clustering including diabetes, obesity and the metabolic syndrome, thus leading to heightened IHD risk [3]. The recent effectiveness-based prevention guidelines for women have identified pre-eclampsia and gestational diabetes as “at risk” categories for IHD [61] and there is further supportive evidence linking these entities to a 2-fold increased CVD risk [62].

Microvascular and Endothelial Dysfunction

The astonishing prevalence of “normal” or “near-normal” epicardial arteries in women with chest pain, suggests alternative pathophysiological mechanisms from the classic demand-supply mismatch of flow-limiting coronary artery stenosis. Possible explanations for this chest pain syndrome, often termed “nonobstructive CAD”, include abnormal coronary reactivity, plaque erosion/distal microembolization and microvascular or endothelial dysfunction as contributory to a female-specific IHD pattern [21]. These mechanisms are characterized by impairment in vasomotor tone and vascular homeostasis which lead to characteristic ischemic symptoms [20, 63]. Close to one half of the women presenting with chest pain in the presence of nonobstructive CAD within the WISE study had coronary

microvascular dysfunction as determined by invasive [64] and noninvasive methods such as magnetic resonance imaging [65, 66]. Further evidence suggests the clinical and prognostic importance of impaired coronary vasomotion, as its detection was associated with adverse cardiovascular outcomes irrespective of CAD severity in the same cohort of women [67].

Traditional cardiovascular risk factors of increased prevalence and impact in women have been implicated in the development of endothelial dysfunction [20]. These conditions, whether alone or in conglomerate, lead to vascular endothelial injury and increased oxidative stress which further promote coronary atherogenesis [9]. Investigators have theorized that the higher prevalence of left ventricular hypertrophy and obesity in black women results in “microvascular angina” from decreased coronary vascular reserve [68]. There is also evidence of a higher risk of progression to atherosclerotic CAD in patients with endothelial dysfunction [69].

Risk Assessment for Prevention

Given the alarmingly high burden of cardiac risk factors in our population, there has been a timely shift toward primary and secondary prevention of IHD through enhanced risk stratification and assessment. Thus, the notion is to significantly reduce the prevalence of risk factors through therapeutic and lifestyle intervention with an anticipated alleviation of CVD events and mortality [28]. In terms of primary prevention, the classic Framingham risk score (FRS) has historically been the most prominent and widely used tool for estimating 10-year cardiovascular risk; however it has inherent limitations of underestimating risk in women. In women who sustained their first MI, the majority were classified in the low risk category by FRS score (95 %), with the remaining in the intermediate category (5 %) [70, 71]. Given the FRS shortcomings, a number of other global risk score calculators have debuted from different study cohorts including SCORE [72], QRISK [73]), the 2001 ATP-III Risk estimator (FRS-based) [74] in addition to the Reynold’s risk score. Ideally, scoring systems have the highest accuracy in the population from which they were developed [71]. This presents substantial room for inaccuracies in women and ethnic groups whom are disproportionately understudied. The Reynold’s risk score, which includes hsCRP, was derived from and validated in women cohorts and in comparison with the FRS resulted in improved risk prediction with reclassification in 15 % of intermediate-risk FRS women to high risk [75, 76].

The unveiling in 2013 of the new guidelines on treatment of cholesterol to reduce atherosclerotic cardiovascular risk (ASCVD) by the ACC and American Heart Association (AHA) generated much controversy though its aim was to avail to clinicians a more straightforward, evidence-based tool [77]. The vanguard instrument eliminates the use of a target cholesterol level, recommends a fixed statin intensity based on classified risk group, includes stroke as an endpoint and allows for estimates by sex and race. The guideline’s pooled cohort equation was originated and validated in men and women within geographically and racially representative populations including blacks [78]. Critics suggest that the novel score calculator overestimates risk by 75 to 150 % in at least seven external validation cohorts which could lead to excessive statin therapy [79, 80]. There remains disagreement among polarized academicians regarding the performance of the pooled cohort

equation and conventional scoring systems. Nevertheless, with certainty, the outstanding issue remains-intermediate to high risk groups, including women, are in dire need of lifestyle and risk factor optimization for CVD risk reduction, and refined IHD detection to ideally prevent, or treat adverse CVD events.

Diagnosis of Ischemic Heart Disease

The diagnosis of IHD in women is more challenging and is frequently delayed as women commonly present with delayed onset of frequently atypical symptoms. Women are usually evaluated for CAD about 10–20 years later than men. Although the majority of women present with the same symptoms of CAD as men, a significant number also experience atypical symptoms. For example, in a large study of patients diagnosed with myocardial infarction, 58 % of women compared to 69 % of men were reported to describe chest pain as their presenting symptom [81]. Moreover, when women with acute coronary syndromes (ACS) undergo cardiac catheterization, at least twice as many women as compared to men, will have no significant obstructive CAD, yet their prognosis is worse than that of both men and women who do not have chest pain syndromes [36]. This makes the diagnosis of IHD in women more challenging. Most often, those individuals with other than the characteristic “male” pattern of obstructive CAD at coronary angiography, are simply reassured, and not offered additional testing or treatments, nor guidance on reduction of ASCVD risk. Even more complex are those women who present with ACS that represent manifestations of coronary disease that are very poorly understood, but far more common in women, including stress-induced (Takotsubo, left ventricular apical ballooning) cardiomyopathy, spontaneous coronary artery dissection, coronary vasospasm and coronary embolism. These entities once thought “rare” are increasingly being diagnosed in women. Additional imaging techniques, including MRI with late gadolinium enhancement [82] echocardiography with ultrasound enhanced cardiac perfusion [83] intravascular ultrasound and optical coherence tomography [84, 85] are assisting in establishing the diagnosis and pathophysiologic understanding of these less common acute cardiovascular entities, in order to determine and guide the most appropriate therapy.

Unfortunately, current guidelines on the management of acute and stable cardiac ischemic syndromes do not include a sex-based diagnostic approach. It is important to underscore that the majority of available multicenter clinical studies and trials used to support current guidelines are based on predominantly male populations. Within these limitations, we will review the current noninvasive and invasive approaches to the diagnosis of IHD in women, including functional testing (stress testing), anatomic imaging (coronary computed tomography (CT), and endothelial function assessments).

Noninvasive Testing

The 2014 AHA Consensus Statement on the “Role of Noninvasive Testing in the Clinical Evaluation of Women with Suspected Ischemic Heart Disease,” provides evidence-based guidelines on diagnosis of IHD in women by noninvasive testing [86]. The choices of non-invasive testing are similar between men and women. However, women are more likely to have “false positive” results, and due to a lack of confidence in accuracy, these non-invasive

diagnostic tests are often improperly utilized [86]. Pretest probability must be taken into account when determining the need for ASCVD assessment. Initial pretest assessment for exercise capacity is important to ascertain whether a woman can exercise to an adequate level at which ischemia may develop. In women unable to perform activities of daily living or to perform adequately on exercise treadmill testing (ETT), a pharmacological stress test is the preferred method of risk assessment. Stress imaging tests provide information about wall motion abnormalities or perfusion, and provide assessment of ventricular function.

Functional Testing

Functional tests include ETT with electrocardiogram (ECG), exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with single-photon emission computed tomography (SPECT) or positron emission tomography (PET), pharmacologic stress cardiac magnetic resonance imaging (CMR), CT perfusion and CT or Doppler ultrasound-derived flow reserve measurements.

ETT is the most common method of diagnosing CAD in women despite a higher false-positive rate compared to men. ETT is recommended as the diagnostic test of choice in symptomatic, intermediate risk women who are able to exercise and have an interpretable resting ECG. Exercise stress testing provides valuable information about exercise capacity, and hemodynamic response to exercise and recovery, all markers of cardiovascular risk. Women who are unable to exercise beyond stage 1 of a standard Bruce protocol, achieving <4–5 metabolic equivalents, are at the highest risk of cardiovascular events and this portends worse clinical outcome [87]. This is in contrary to women achieving exercise workloads of >10 metabolic equivalents which predicts a very low risk of inducible ischemia [88]. Lack of appropriate blood pressure and heart rate increase with exercise, or a drop of blood pressure with exertion, are concerning for IHD in both men and women [89]. Regardless of gender, high risk patients identified by ETT demonstrate symptom limited angina and marked ST segment changes of ≥2 mm or downsloping ST segments in multiple leads. This threshold is however less accurate for detection of ischemia in women. Lower sensitivity and specificity of ST-segment responses with exercise has been documented [90]. Exercise capacity is further reflected by the Duke Treadmill Score, calculated as exercise time – (5 × ST segment changes in mm) – (4 × angina index). This scoring tool not only identifies high risk patients for CAD, but also provides prognostic information [91]. However, ETT testing can be limited by both reduced specificity and sensitivity in both women and men, and is not interpretable if there are resting ECG abnormalities, or the patient is unable to exercise.

A frequent reason for performing ETT in women is the high negative predictive value. In order to explore whether myocardial perfusion imaging (MPI) with SPECT could provide incremental information for diagnosis in symptomatic women at low to intermediate pretest probability over ETT alone, the “What is the Optimal Method for Ischemia Evaluation in Women” (WOMEN) trial was performed [92]. Similar 2-year clinical outcomes were observed, with no difference in major adverse cardiac events (MACE) (<3 %). Overall, the cumulative diagnostic cost savings was 48 % for ETT compared with exercise MPI. Thus, for symptomatic women with low to intermediate risk who are capable of exercising, ETT is the recommended initial test of choice to provide diagnostic and prognostic information.

As previously noted, the prevalence of obstructive CAD in women is lower than in men. The pretest probabilities of CAD are lower in women, and more false positive results for stress imaging have been reported. In women, the accuracy of stress echocardiography and its diagnostic sensitivity and specificity in detecting CAD is higher compared to exercise ECG [93–95]. In comparison, exercise echocardiography has higher sensitivity in men [96]. Despite these differences, the prognostic value of exercise echocardiography is comparable between men and women [97]. Women with low-risk stress imaging findings, have <1 % risk of CAD. Women with moderate to severe wall motion or perfusion abnormalities are at higher risk, and may have annual CAD event rates as high as 5–10 % per year, depending on the vascular territory and the choice of stress imaging used [97, 98]. Additionally, reaching a workload of >6 metabolic equivalents during exercise echocardiography was associated with decreased risk of cardiac events and cardiac death in both men and women [97].

Challenges in interpretation of stress imaging tests in women are technique-dependent. Nuclear stress testing challenges can occur due to breast tissue artifacts and smaller hearts of females. The smaller LV size may not allow detection of small perfusion abnormalities. New techniques however are currently used to overcome the frequency of attenuation artifacts. Questions about radiation safety associated with radionuclide stress tests have been raised [99], and tests utilizing ionizing radiation are frequently avoided or used cautiously in young women due to increased lifetime risk of cancer.

Anatomic Testing

In the last decade, the evidence regarding the utility of cardiac CT has grown exponentially. Coronary computed tomographic angiography (CCTA) and coronary artery calcium (CAC) score provide additional tools for assessing diagnosis and prognosis of CAD. CCTA can risk-stratify patients with acute chest pain and intermediate likelihood of ACS. CCTA shows the extent of both calcified and non-calcified plaque, obstructive and nonobstructive atherosclerosis, with increasingly lower radiation exposure and improved image quality. Data from the “Coronary CT Angiography Evaluation for Clinical Outcomes” (CONFIRM) trial showed that the presence of multi-vessel CAD in women by CCTA predicted a 3–1 fold higher risk of death [100]. The “Rule Out Myocardial Infarction using Computer Assisted Tomography” trial (ROMICAT), comprised of 40 % women, demonstrated that half of patients with acute chest pain at low to intermediate likelihood of ACS had no CAD by CCTA, with very high negative predictive value [101]. Two-year follow up of the ROMICAT study cohort revealed that CCTA predicts MACE and has incremental prognostic value in patients with acute chest pain. The probability of MACE within 2 years increased in parallel with increased burden of coronary disease (plaque, stenosis, left ventricular wall motion abnormalities) [102]. The subsequent ROMICAT II trial sought to examine gender differences in outcomes and found that women undergoing CCTA compared to standard cardiac evaluation had fewer hospital admissions, shorter length of hospital stay and lower total radiation dose compared with men. Thus, CCTA is a viable alternative for women undergoing assessment of CAD. Assessment of CAC score and its prognostic value in both men and women is rapidly evolving. CAC increases with age and is more substantial in men [103]. Women tend to have a less severe burden of atherosclerosis, with very low prevalence in premenopausal women. CAC scoring was shown to have similar predictive value for

arteriographic CAD in men and women. The sensitivity of CAC for detection of obstructive disease is >95 % in women, and specificity of the test is significantly higher in women compared to men [104]. Therefore, CAC scoring also adds value in assessment of CAD in women, with minimal radiation exposure.

The recent "Prospective Multicenter Imaging Study for Evaluation of Chest Pain" (PROMISE) trial comparing functional tests (ETT, stress echocardiography, MPI) to anatomic assessment (CCTA), which had excellent female representation (50 % women), showed no significant differences in outcomes by strategy used [105]. Several additional multicenter clinical trials are underway comparing the role of different noninvasive tests which will further help in the diagnostic and therapeutic decision-making in stable patients with suspected IHD. The "Randomized Evaluation of Patients with Stable Angina" (RESCUE) trial compares CCTA with SPECT MPI. The NHLBI-sponsored "International Study of Comparative Health Effectiveness and Invasive Approaches" (ISCHEMIA) trial plans to randomize patients with chronic IHD with moderate to severe ischemia on stress imaging to therapy with invasive angiography or medical management. These studies will further expand our understanding of the diagnosis and treatment of suspected IHD in both men and women.

Microvascular Testing

Coronary microvascular disease (MVD), defined as limited coronary flow reserve and/or coronary endothelial dysfunction are the presumed mechanisms of ischemia in women with persistent angina, variable evidence of ischemia on stress testing, and no evidence of obstructive CAD on angiography. MVD is characterized by a decrease in the size of epicardial vessels and microvasculature, increased arterial stiffness, increased fibrosis, altered remodeling, more diffuse atherosclerotic disease, and the presence of endothelial or smooth muscle dysfunction [106]. MVD portends a worse prognosis in women with an estimated 2.5 % annual MACE rate in women [107]. In the last few decades, non-invasive and invasive techniques have evolved to adequately assess coronary physiology.

Noninvasive techniques such as PET, CMR and transthoracic echocardiography Doppler allow for the assessment of myocardial blood flow and coronary flow reserve. Decreased flow reserve in women is associated with worse outcomes, with increased rate of cardiac death, stroke or heart failure [19, 108]. Early detection of endothelial dysfunction, measured by brachial artery flow-mediated vasodilation, has also been associated with a 1.3 to 4.4-fold increase in IHD in women [109]. Additional simpler noninvasive techniques have emerged, with specially-designed fingertip probes to measure the peripheral reactive hyperemia index (PRHI), a measure thought to reflect endothelial function [110] and has been shown to be significantly reduced in the setting of persistent chest pain syndromes associated with nonobstructive CAD in women [111].

PET and CMR are growing noninvasive modalities to detect sub-endocardial ischemia; the gold standard is an invasive coronary reactivity test. The WISE study highlighted the importance of MVD in women [64] and supported the use of invasive coronary vasomotor testing as a safe method for definitive diagnosis and assessment of prognosis in high risk

women [107]. It is now well established that the prognosis is worse in women with MVD and should not be underestimated by clinicians [112].

Invasive Testing

In women and men with a high pretest probability of CAD, coronary angiography is the mainstay of diagnosis and permits catheter-based therapy when indicated. As outlined above, evidence from the NCDR and the WISE studies, indicate that over 50 % of women with chest pain referred for coronary angiography do not have significant (>50 % stenosis of any one major coronary artery) obstructive CAD [2]. In the absence of significant obstructive CAD, strong consideration of coronary physiologic testing should be done, to evaluate for MVD and endothelial dysfunction. Although noninvasive techniques, as described above, are evolving for this, the gold standard remains catheter-based [113]. Pharmacologic assessment of coronary blood flow and flow reserve by cardiac catheterization, permits evaluation of both endothelium-dependent (using acetylcholine) and non-endothelium dependent (using adenosine, nitroglycerin or ergot alkaloids) mechanisms. [114] Endothelial dysfunction is defined as lack of increase in coronary blood flow after administration of endothelium-dependent vasodilators such as acetylcholine. Endothelial dysfunction is also one of the earliest markers of atherosclerotic disease. Coronary flow reserve is defined as the ratio of augmented to baseline blood flow after intracoronary administration of a vasodilator (adenosine, dipyridamole or regadenoson); normally, the ratio is >2.0. Although coronary physiologic testing does have potential risks and limitations, the evaluation for coronary vascular dysregulation, either invasively, or noninvasively, is recommended in women with persistent chest pain syndromes without obstructive CAD for proper diagnosis and effective treatment.

Treatment of Ischemic Heart Disease

Although our emerging understanding of IHD in women points to a differing pathophysiology than men, the recommended treatment of CVD in women is similar to that of men, with respect to both primary and secondary prevention, and ACS. According to the current ACC/AHA guidelines for management of ACS, indications for non-invasive/invasive diagnostic procedures and the treatment strategies should be implemented similarly for both men and women [115] with the overarching goal to improve quality of life and outcomes. However, despite these recommendations and goals of care, women continue to be treated less aggressively than men, with less intensive use of evidence-based medical and procedural therapy, less enrollment in cardiac rehabilitation, and less intensive therapeutic lifestyle counseling [116–119]. In a large international prospective study of over 30,000 men and women (22.6 %) with stable CAD, it was found that although risk profiles of men and women differed substantially, their one-year outcomes were similar, although fewer women underwent revascularization [120]. Further research is needed to better understand gender determinants of outcome and devise strategies to minimize bias in the management and treatment of women.

Therapeutic Lifestyle Intervention

Lifestyle modification, risk factor control and overall CVD prevention is paramount in women. Lifestyle interventions include smoking cessation, regular moderate intensity physical activity, dietary counseling for a heart healthy diet, weight reduction and maintenance, and treatment of depression if indicated. Major risk factor interventions include optimization of blood pressure, lipids, and glycemic control, as well as weight management through appropriate lifestyle interventions and medical therapy.

Medical Anti-Ischemic Therapy

Anti-ischemic medical therapy including aspirin, the angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), beta blockers, aldosterone inhibitors and statins are frequently delayed in women due to delay in symptom presentation and are less intensively used, despite their beneficial effects. These treatment differences in gender are possibly attributed to lower prevalence of obstructive CAD in women. The Euro Heart Survey showed that women were significantly less likely to receive aspirin and statin for treatment of stable angina [118]. After hospital discharge for non-ST-elevation MI, women received about 3 % less aspirin and beta blockers and about 13 % less statin therapy compared to men [116]. These are concerning findings, considering that statins and ACEI were shown to improve endothelial dysfunction, which is so prevalent in women.

Aspirin is recommended as part of management of ACS in both men and women. Although it has been shown to be equally beneficial for secondary prevention in both genders [121], it is less consistently used for primary prevention of CVD in women. In regards to primary prevention, it has been shown that aspirin prevents stroke in women older than 45 years old, and prevents MI in those over age 65 years [122]. Reduction in platelet reactivity in women after intake of low dose aspirin is at least similar to that of men [123] and based on the results from the Women's Health Study, the reduction of thromboxane and prostacyclin is also similar between men and women [124]. Recent clinical trials, including the "Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin" (JUPITER) trial [125], Heart Protection Study [126], "The Cholesterol and Recurrent Events" (CARE) trial [127] and "The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22" (PROVE IT-TIMI 22) trial [128], focused on cholesterol-lowering in patients with CVD and demonstrated at least similar reduction in cardiovascular morbidity and mortality for both men and women.

Therapies for Acute Coronary Syndromes

According to the 2014 ACC/AHA guideline for management of ACS, it is recommended that women be treated in a similar manner to men with the same indications for noninvasive and invasive testing. Large scale observation from the CRUSADE initiative [116] showed that despite these recommendations, women are treated less aggressively, with less cardiac catheterizations, PCIs, fibrinolysis procedures or CABG, which may contribute to different clinical outcomes. Recent metaanalysis comparing early invasive versus conservative treatment in men and women with unstable angina [129] showed similar reductions of death, MI or recurrent ACS using invasive therapy in men and women. However, the risk of composite end-point was lower in biomarker (creatinine kinase-MB or troponin) positive

women. Regarding potential risks associated with these invasive procedures, women have been shown to have more bleeding complications. Taken together with the less aggressive medical management, women overall have higher mortality after MI with lower health-related quality of life compared to men [116].

Women are less frequently referred for appropriate diagnostic procedures and thus may receive less therapy. Moreover, women are less often referred for cardiac rehabilitation after ACS, despite the clear benefits on overall well-being and reduction of future cardiac events [130, 131].

Therapies of Specific Conditions in Women

Treatment of microvascular angina in women starts with risk factor modification and therapeutic lifestyle changes. Exercise training and cardiac rehabilitation is often recommended. Statins, by their anti-inflammatory properties, are especially beneficial in improving endothelial function. Traditional anti-ischemic drugs, including nitrates, beta blockers, ACEI and calcium channels blockers are first line therapy. L-arginine, a precursor of nitric oxide, improves angina and improves small vessel endothelial function in nonobstructive CAD [132], although its long-term use in certain situations is being questioned. The non-traditional anti-ischemic medications including ranolazine (an anti-anginal agent) or xanthine derivatives such as aminophylline have also shown to benefit. Xanthines and tricyclics are effective also on abnormal cardiac pain perception [133]. Isolated reports of the use of cGMP phosphodiesterase inhibitors have emerged, but no consistent studies have been done.

Strategies for long-term management of coronary microvascular dysfunction in women are challenging and not well established. This is partially due to our still incomplete understanding of the pathophysiology of microvascular dysfunction and limited effectiveness of current conventional therapies. Large, randomized outcome clinical trials testing the efficacy of currently available medical therapies or novel therapies in women with refractory symptoms are lacking. Further research is needed to evaluate the best long-term treatment strategy and to provide treatment guidelines.

The role of menopausal hormone therapy (MHT) in primary prevention of CAD in women has not been confirmed and data is insufficient to recommend its use [134, 135] for the prevention (primary or secondary) of CAD. However, a recent study, Kronos Early Estrogen Study (KEEPS), exploring the use of MHT in recently menopausal women (mean age of 50, in contrast to the mean age of 63 in the Women's Health Initiative (WHI) trial) found that there was no acceleration of atherosclerosis as detected by carotid intima media thickness and CAC score [136]. This suggests that MHT is not harmful to the cardiovascular system when clinically-indicated for treatment of vasomotor menopausal symptoms. Indeed, in perimenopausal and early menopausal women with refractory chest pain symptoms due to MVD, observational experience suggests that a trial of MHT may be beneficial in symptom relief. One could postulate that the fluctuation and withdrawal of estrogen levels at time of perimenopause could provoke untoward vasomotor effects upon the endothelium in the coronary microvasculature. However, there is currently no clear evidence base for this suggestion. Interestingly, the Danish Osteoporosis Prevention Study (DOPS) [137] provided

indirect evidence for a beneficial effect of MHT on CAD risk reduction when started early in menopause. A subset analysis of the WHI data showed similarly that the youngest tertile of patients actually had a significant reduction in cardiac events and in CAC scoring [138].

There is no role for MHT in secondary prevention. The Heart and Estrogen/Progestin Replacement Study (HERS) showed no evidence of cardiovascular benefit in women with established obstructive CAD. The rate of coronary events increased in the first two years with the use of hormone replacement therapy, while in subsequent two years, the risk decreased, with no net benefit [139, 140].

Conclusions

Although we have made great strides in the reduction of CVD mortality in women through advanced medical care, state-of-the-art medical technologies and health awareness campaigns, we still have more tread to cover. The prevention, diagnosis and treatment of women with IHD remain a great challenge which ultimately leads to healthcare inequities. A complex interplay of variables contribute to this conundrum including unique risk factors and pathophysiology for IHD among women, particularly the amassed number of women with nonobstructive CAD and dysfunction of the coronary microvasculature and endothelium [2]. Our review provides a synthesis of key evidence highlighting gender disparities in the epidemiology, presentation, risk assessment, mortality and clinical diagnosis and management of women with IHD. Women have an increase in incidence of CVD events with age, although there is an emergence of events in younger women. Furthermore, women have a high CVD risk factor burden, particularly those of African-descent and are more prone to present with atypical symptomatology which contributes to underdiagnosis and increased mortality rates. Our current diagnostic strategies are inherently tailored towards identification of “classical” obstructive CAD, with subsequent catheter-based or surgical interventions. Although some women do fit into this “accepted” algorithm, they are not consistently receiving guideline-based therapy. Moreover, we do not yet have a clear understanding of what to do with the patients, the majority of whom are women, who do not fit neatly into this standard algorithm, yet have persistent symptoms, and increased morbidity and mortality.

These persistent disparities provide a framework for clinicians and researchers to “refashion” and remodel current practices in the evaluation of women with IHD with the overarching goal of providing efficient and cost-effective healthcare for improved clinical outcomes. The fundamental hurdle remains to build credible sex-specific evidence on CVD mechanisms through better representation of women in cardiovascular clinical trials. In this era of health care reform, future guidelines for the assessment of IHD in women must include gender-specific risk assessment models as well as diagnostic and therapeutic algorithms for obstructive and nonobstructive CAD.

Abbreviations used in the paper

ACC	American College of Cardiology
ACS	acute coronary syndromes

ACEI	ACE inhibitors
AHA	American Heart Association
ARB	angiotensin receptor blockers
ARIC	Atherosclerosis Risk in Communities
ASCVD	atherosclerotic cardiovascular risk
CABG	coronary artery bypass grafting
CAC	coronary artery calcium
CAD	coronary artery disease
CASS	Coronary Artery Surgery Study
CCTA	coronary computed tomographic angiography
CMR	cardiac magnetic resonance imaging
CVD	cardiovascular disease
CT	computed tomography
ETT	exercise treadmill test
FRS	Framingham risk score
hsCRP	high-sensitivity C-reactive protein
IHD	ischemic heart disease
MACE	major adverse cardiac events
MHT	menopausal hormone therapy
MI	myocardial infarction
MPI	myocardial perfusion imaging
MVD	microvascular disease
NCDR	National Cardiovascular Data Registry
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
PCI	percutaneous coronary intervention
PCOS	polycystic ovarian syndrome
PET	positron emission tomography
PRHI	peripheral reactive hyperemia index

SPECT	single-photon emission computed tomography
WHI	Women's Health Initiative
WISE	Women's Ischemia Syndrome Evaluation

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