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WOMEN AND ISCHEMIC HEART DISEASE (A. MARAN, SECTION EDITOR)

Gender Disparities in CAD: Women and Ischemic Heart Disease

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Abstract

Purpose of Review The goal of this article is to review the disparities that exist for women who present for treatment of ischemic heart disease.

Recent Findings It is well known that women are more likely to present with ischemic heart disease at an advanced age with more comorbidities when compared to male counterparts. Despite correction of risk factors, women experience worse outcomes, even in the absence of obstructive coronary artery disease. A review of the literature highlights the importance of a thoughtful approach to medical therapy and revascularization.

Summary While most recommendations applied to women are derived mostly from male data, further study of sex-specific differences may lead to approaches which can ultimately reduce disparities for the treatment of ischemic heart disease in women.

Keywords Women · Acute coronary syndrome · Ischemic heart disease · Gender disparities

Introduction

Cardiovascular disease remains the leading cause for morbidity and mortality in women. Despite improvements in care, more mortalities occur in women annually from ischemic heart disease compared to men. The reasons for this disparity are multifactorial and may include lack of awareness, institution of guideline-directed therapy, and appreciation of sex-specific differences. Women are less likely to present and receive guideline-directed therapy. In addition, sex-specific differences exist that are poorly understood. Women are underrepresented in clinical trials. Even when included in clinical trials, many studies do not include analysis for gender differences. The hope is that with improved knowledge of prevalence, novel risk factors, and sex-specific pathophysiology, gender disparities would continue to decline.

This article is part of the Topical Collection on *Women and Ischemic Heart Disease*

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Burden of Cardiovascular Disease in Women

Many people do not realize the discrepancies between men and women in regard to their cardiovascular health. There has been obvious improvement with both diagnostic modalities and treatment options resulting in decreased mortality rate from ischemic heart disease, but there are still more women not only being diagnosed but also succumbing to cardiovascular disease [1, 2]. Cardiac death continues to be the leading cause of death amid women of all ages, leading to approximately one death per minute in the USA [1, 3]. There has been an actual increase in mortality seen among women aged 35–54 years from cardiovascular disease [2]. The CDC noted a greater proportion of women dying from sudden cardiac death (52%) when compared to men (42%) [2].

Discrepancies become even more apparent when comparing different races; in particular, it has been noted by the American Heart Association that black females are at a statistically increased risk for cardiovascular disease compared to white females [2, 3]. Cardiovascular disease is not just becoming an increasing burden to females living within the USA but it is also increasing in every major developed country and many economies that are just emerging [4]. Therefore, it is imperative for physicians, not only cardiologists but also general practitioners, internists, and other sub-specialty physicians, to realize the importance of making a diagnosis of cardiovascular disease if patients are showing concerning

symptoms. It is also important that these patients are referred for the appropriate testing or referred to a cardiologist in order to get the assessment initiated.

Lack of Inclusion in Clinical Trials

Many of the guidelines that have been developed for women are the result of data obtained mostly from men. Among the 801,198 patients enrolled in over 150 trials, only 245,525 (approximately 31%) were women [5•]. Therefore, with the lack of representation of women within randomized clinical trials, the data has been extrapolated for clinical decision-making in women. Unfortunately, this does not address the many additional risk factors, such as pregnancy and hormone changes over the course of woman's lifespan, which may or may not increase their risk of heart disease.

Recently, there has been increasing emphasis on recruiting more women into clinical trials. Future studies should continue to strive not only to enroll women but also to look at differences within them, such as ethnic variations, hormonal changes, and age to see if there are in fact other risk factors that may be leading to the increasing number of women being diagnosed or dying from cardiovascular disease. It would also be helpful to see more analysis of treatment management strategies and their respective short- and long-term outcomes [5•].

Differences in Risk Factors

We realize that traditional risk factors and the Framingham risk score (FRS) underestimate ischemic heart disease in women [5•, 6–10]. The FRS classifies 90% of women at low risk, with very few assigned to high risk under the age of 70 years [6]. There are other risk factor score calculators, such as the Reynolds score, which has been used and resulted in reclassification of 40–50% of intermediate risk by the FRS into higher or lower risk categories [7, 11]. Therefore, it is obvious that this is still a work in progress, but is improving as more factors are being looked at, such as age, systolic blood pressure, hemoglobin A1C (if diabetic), current smoking, HDL, hsCRP, and family history of premature coronary disease [11, 12]. The 2013 ACC/AHA guidelines have introduced the use of the pooled cohort equation. Further research will identify the accuracy of this score to predict events in women.

Risk Factors

As mentioned previously, there are many risk factors that are known to be associated with cardiovascular disease. Hypertension, which is underdiagnosed and therefore undertreated, is an ever-increasing risk factor for women, with a lifetime risk of developing hypertension to be approximately 90% [2, 13]. It is believed that by the time a woman is 65 years of age, they have a higher prevalence of hypertension with less than half of them receiving adequate treatment if any treatment at all [14, 15].

The prevalence of hypertension among black females within the USA was found to be among the highest and continues to increase [2]. Hypertension is not the only a risk factor that continues to increase. There is also a growth seen among those suffering from type 2 diabetes mellitus, especially in Hispanic females [2, 3]. Having hypertension alone increases a woman's risk of developing many other comorbidities, including myocardial infarction, heart failure, atrial fibrillation, stroke, and renal failure [13].

Hyperlipidemia is also a significant risk factor, of which the INTERHEART study showed that low-density lipoprotein cholesterol (LDL-C) reduction with statins leads to improved overall cardiovascular outcomes with similar proportional benefits for both men and women [16–18]. Unfortunately, again, it is seen that women are 20% less likely to actually take a statin [19]. It is unclear as to why this is but likely results from lack of prescription or from side effects, such as statin-induced myopathy [19, 20].

Diabetes mellitus is believed to not only be a stronger prognostic predictor of mortality in women when compared to men, but it is also associated with a four to six times increased risk of developing ischemic heart disease [21–24].

Underlying these risk factors is the increasing rate of obesity. Sadly, nearly two out of every three women over the age of 20 years have been diagnosed with increased body weight [3]. This is where the education should start, but often does not. Physicians have to be engaged and speak to their patients about the importance of regular exercise several times per week for at least 30 min, eating a heart-healthy diet such as the DASH diet in addition to smoking cessation [2]. If patients have already developed hyperlipidemia, initiation of an anti-cholesterol medication may need to be initiated to gain control of their LDL [2].

We are all very aware of the literature behind tobacco use, but regrettably many women continue to smoke cigarettes. They do not realize or choose to not acknowledge its association with progression of atherosclerosis, myocardial infarction, and sudden cardiac death [25]. Smoking as little as two to three cigarettes daily increases a woman's risk of cardiovascular problems, and it is now recognized to be more strongly associated with MI in middle-aged women when compared to men [25, 26].

It is important to ask patients about family history. Premature coronary disease in a family member is an independent prognostic indicator of increased ischemic heart disease in both men and women [27]. Women with family history were found to have increased major adverse cardiovascular events in a multivariate analysis of traditional FRS risk factors, but oddly there was no significant increased risk seen in men [27, 28].

A physician must also consider other risk factors that may also impart risk of adverse cardiovascular health. Peripheral arterial disease is believed to be an equivalent to ischemic heart disease and often is associated with many of the same risk factors as those seen in cardiovascular disease, including hypertension, diabetes, and smoking. In fact, a lower ankle-brachial index has been associated with coronary artery calcification according to the Jackson Heart Study [29, 30].

Emerging Risk Factors

Chronic kidney insufficiency is now considered an equivalent to ischemic heart disease. According to the WISE (Women's Ischemia Syndrome Evaluation) study, women with a baseline creatinine between 1.2 and 1.9 mg/dl were found to have an increased risk of significant angiographic disease (defined in this study as any coronary stenosis of at least 50%) when compared to woman with normal renal function [29]. There is an increased risk of mortality among patients with renal disease and 50% of these deaths are thought to be secondary to cardiovascular causes [31, 32].

Pregnancy is considered a metabolic stress test. It can actually serve to provide information to a physician about the health and cardiovascular outcomes for a particular patient [2]. If a woman develops pre-eclampsia, eclampsia, gestational diabetes, or pre-term delivery, it can actually be an early predictor of risk for cardiovascular disease in the future [33–36]. Therefore, these patients should be referred on to see a cardiologist because there is an increased risk for development of ischemic heart disease, stroke, and venous thromboembolism [37, 38].

Other risk factors, which are now being associated to cardiovascular disease, are systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [2, 38]. In fact, cardiovascular disease is a leading cause of morbidity and mortality among patients with SLE, while RA is associated with a two- to threefold increased risk of myocardial infarction and cardiovascular disease [2, 38].

Additionally, treatment for Hodgkin's lymphoma or breast cancer with radiation to the chest wall or mediastinum has been recognized to have increased risk of not only atherosclerosis and ischemic heart disease but also pericardial and valvular disease [29]. In particular, left breast and chest wall radiation is associated with mid-left anterior descending, distal diagonal, and proximal right coronary artery atherosclerosis [39]. Lastly, underdiagnosed obstructive sleep apnea among women has also been associated with development of both pulmonary and systemic hypertension that may ultimately lead to the development of cardiovascular disease [40, 41].

Differences in Clinical Presentation

Women tend to present with atypical symptoms. This is thought to be a strong reason why women are more likely to have a delay in seeking care and experience an increased risk of sudden cardiac death [42, 43]. Interestingly, 64% of women who die from sudden cardiac death as a result of cardiovascular heart disease had no prior symptoms [44]. In a study of 515 women, 43% did not have chest pain at presentation [42]. The most common acute symptoms seen within this study were dyspnea (58%), weakness (55%), and fatigue (43%). Additionally, they were found to have prodromal symptoms beginning roughly 1 month prior that include fatigue (71%), sleep disturbance (71%), and dyspnea (42%) [42].

Within the National Registry of Myocardial Infarction (NRMI) from 1994 to 2006, there were over 1,000,000 patients of which 481,581 were women [43]. Within this registry, it was discovered that women had a higher in-hospital mortality after presentation with coronary syndrome when compared to men (14.6% vs. 10.3%) [43]. Women found to be at greatest risk tended to be younger at presentation and were without chest pain [43, 44]. The women who were younger and without chest pain also tended to be sicker overall with known diabetes mellitus, delay in presentation, higher Killip class (III or IV), and elevated troponins. As a result, many women presenting without chest pain during coronary syndrome were less likely to receive timely therapies including fibrinolytics or primary percutaneous intervention [43, 44]. Additionally, these women were less likely to receive aspirin, other antiplatelet agents, heparin, and beta-blocker therapies during their hospitalization [43, 44].

Sex-Specific Pathophysiology

Understanding is needed regarding the paradoxical result of worse outcomes despite the absence of obstructive CAD [45•]. Several studies and registries cite advanced age, comorbidities, and less use of guideline-directed medical therapy as a cause for this difference in outcomes. Other studies demonstrate differences that exist after adjustment for covariates [46, 47]. Some proposed mechanisms of female-specific pathophysiology and ischemic heart disease include distal microembolization, abnormal coronary vasoreactivity, and microvascular dysfunction [48–54].

Microvascular dysfunction is poorly understood. It is estimated to be present in 50 to 65% of patients who present with angina without epicardial coronary disease or microvascular angina (MVA) [55]. Similar pathophysiology is also thought to be responsible for the development of stress (takotsubo) cardiomyopathy that is more prevalent in postmenopausal

women [56–58]. The only difference is that stress cardiomyopathy usually occurs in association with a catecholamine surge as a result of physical or emotional stress. The diagnosis of coronary microvascular dysfunction (CMD) can be made by evaluation of coronary flow reserve (CFR) or myocardial perfusion reserve (MPR). CFR and MPR compare the increase in coronary flow or perfusion at both resting and stress states. Because resistance is determined primarily by microvasculature, CFR and MPR allow assessment of microvascular dysfunction. CFR can be evaluated invasively through techniques such as thermodilution and intracoronary Doppler ultrasound. The downsides of this approach include risk of procedural complications and ability to interrogate one coronary distribution at a time. Conversely, microvascular dysfunction can be evaluated noninvasively with PET and CMR. PET has become the gold standard for evaluation of microvascular dysfunction [55]. CMR is thought to produce MPR levels that are lower compared to PET MPR values [59]. Disadvantages of PET include availability, the need for an onsite cyclotron, and radiation exposure. CMR is more available and does not expose patients to radiation. The cons of CMR include lack of patient comfort and contraindication in patients who have metallic hardware and are at risk for nephrogenic systemic fibrosis due to low GFR. The ideal cutoff for CFR/MPR has not been established. Prognostic benefit has been shown in several studies inpatient without epicardial CAD with CFR/MPR values of 1.5–2.6 [60••]. There is limited data available on the treatment of MVA. A systematic review by Marinescu et al. evaluated therapies for MVA which defined CMD as a CFR or MPR < 2.5 using invasive, PET, or CMR methods [55]. Although numerous treatments have been evaluated, the only treatments that showed potential benefit in improving CMD after meeting the review inclusion criteria were sildenafil, quinapril, estrogen (not recommended for secondary prevention of coronary events in patients with NSTE-ACS), and use of transcutaneous electrical nerve stimulation (TENS) [55]. While treatment of CMD is a potential target for both improving symptoms and outcomes in women, several barriers exist. The goals of future research should aim to standardize the definition of CMD and evaluate outcomes in studies with adequate size and duration of follow-up. Identification of the ideal treatment regimens could reduce disparities by treating this sex-specific pathophysiologic mechanism.

Differences in Treatment

The importance of medical therapy cannot be underestimated given worse outcomes in women even in the absence of significant epicardial coronary disease. Even in the absence of obstructive stenosis, women who present with NSTE-ACS have a 2% risk of MI or death at 30 days [61]. Several studies have documented the fact that women are less likely to receive guideline-directed medical therapy, which is proven to improve outcomes, both in the hospital and after discharge for presentation with acute coronary syndrome. Simply correctly diagnosing acute coronary syndrome and instituting appropriate guideline-directed medical therapy could improve outcomes in women. Given women are more likely to present with advanced age and comorbidities, prevention and optimal control of risk factors is important in improving outcomes.

While women receive the same benefit from PCI, they are more likely to experience periprocedural complications [62–64]. The frequency of complications has again been attributed to increased age and presence of comorbidities in women. Women who have low-risk features (low TIMI score) and negative troponin are more likely to be harmed than benefit from revascularization [65–70]. While thoughtful procedural risk reduction strategies should be employed for all patients, they are more important for women. A few suggested strategies include careful patient selection, access management (radial access, use of ultrasound-guided access, vascular closure devices, pharmacology management (renal and weight-based dosing), and CIN prevention (pre/post-hydration and contrast minimization). While women benefit from revascularization with CABG after presentation with ACS, they are more likely to experience periprocedural complications [70–74]. Risk reduction strategies such as appropriate use of hemodynamic support, pharmacology, and use of optimal conduits for grafting should also be used to minimize complications in patients who are undergoing surgical revascularization.

Conclusions

Women continue to represent a significant amount of the annual cardiovascular mortalities. While women are underrepresented in clinical trials, clinical approaches have been extrapolated to treat women. Improved recognition of ACS, implementation of guideline-directed medical therapy, treatment of risk factors, and careful patient selection for revascularization can achieve reduction in disparities. Future research should address gaps in knowledge including emerging sex-specific risk factors, pharmacology, and pathophysiology (vascular remodeling and function). As we strive to increase our focus on heart disease in women, we can continue to improve overall cardiovascular outcomes.

Compliance with Ethical Standards

Conflict of Interest Rhian E. Davies and Jeremy D. Rier declare no conflict 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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