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

Gender Differences in Ischemic Cardiomyopathy

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Abstract

Purpose of Review Cardiovascular disease remains the leading cause of death among women globally, majority of which are due to ischemic heart disease. Despite the recent advances in the overall management of CVD, there are unique challenges in the diagnosis and management of women as well as poorer outcomes.

Recent Findings Women with ischemic cardiomyopathy experience significant morbidity and mortality. Differences in underlying pathology, delays in presentation, diagnosis, and treatment as well as the under-representation of women in clinical trials contribute to these poor outcomes.

Summary In this review, we discuss the nuances of gender-specific differences in the burden, clinical presentation, and outcomes of ischemic cardiomyopathy in women, in addition to discussion of areas needing further research.

Keywords Women · Gender · Coronary artery disease · Heart failure · Ischemic cardiomyopathy · Gender disparities

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide for both women and men [1]. In the USA, ischemic cardiomyopathy (ICM) and hypertension are the leading etiologies of CVD and for the development of heart failure (HF) [2••]. Women often present with atypical symptoms and are prone to several non-traditional risk factors, which are often under recognized by patients themselves as well as their treating physicians, leading to delays in diagnosis and treatment. Women have less obstructive coronary artery disease (CAD) than men and are more prone to the development of symptomatic HF after an acute myocardial infarction [3]. Here, we review contemporary literature that highlights these differences and describes recent advances in our understanding of ischemic cardiomyopathy in women.

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

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Prevalence of Ischemic Heart Disease

Ischemic heart disease (IHD) affects over 23 million worldwide and over 15.5 million in the USA with a lower prevalence in women (5%) as compared to men (7.5%) [4••]. Over 6.6 million women in the USA suffer from IHD annually, including 2.7 million who have a history of myocardial infarction (MI) [5••]. The risk of HF increases once women are diagnosed with CAD. In the Framingham cohort, women had a greater risk of development of symptomatic HF after an acute MI, than men [3]. In the first National Health and Nutrition Examination Survey (NHANES I), CAD accounted for > 60% of incident HF, with hypertension and diabetes contributing to 10% and 3% respectively [6]. The 2017 American Heart Association (AHA) Heart Disease and Stroke Statistics reported an increase in prevalence of HF to 6.5 million in Americans > 20 years of age and this is only expected to increase [1]. Thus, the early identification and management of CAD and preventing its progression to HF are of vital importance.

The prevalence of HF varies between gender and race. The Chicago Heart Association Detection Project in Industry, the Atherosclerosis Risk in Communities (ARIC study), and the Cardiovascular Health Study demonstrated that the lifetime risk of HF was 30–42% in white men, 20–29% in black men, 32–39% in white women, and 24–46% in black women through 95 years of age [7]. The burden of HF is split almost

evenly between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) [1, 8], although white females had the highest proportion of hospitalization for HFpEF.

Risk Factors for Ischemic Heart Disease

Traditional Risk Factors

Women develop IHD typically a decade after men and the incidence of CAD increases dramatically after menopause [9]. This is believed to be due to the cardio-protective effect of estrogen in pre-menopausal women, although studies have failed to demonstrate cardiovascular protection with estrogen therapy, for both primary and secondary prevention [10–12]. The INTERHEART study identified numerous traditional risk factors for IHD including diabetes mellitus, hypertension, hyperlipidemia, waist-hip ratio, high-risk diet, physical activity, tobacco, and alcohol consumption that apply to both women and men; however hypertension, diabetes, physical activity, and alcohol consumption had a greater impact on the development of MI in women less than 60 years of age, than in men [13]. The Framingham study found that diabetes in women was associated with a threefold increased risk of CAD as compared to non-diabetic women and a sixfold higher risk of dying from IHD. In addition, women were treated less aggressively in this study [14]. It has been proposed that women with diabetes have excess clustering of risk factors, eliminating the cardio-protective effect of younger age [15]. Obesity and metabolic syndrome increase the risk of subclinical atherosclerotic disease in women, and obese women have higher risk of left ventricular hypertrophy and HF [4]. Dyslipidemia is a significant risk factor for IHD in men and women, but high triglycerides is a stronger risk for IHD in women, as compared to men [16, 17]. Despite similar guidelines to treat dyslipidemia in men and women, women are less likely to be prescribed lipid-lowering therapies or achieve recommended cholesterol levels as compared to men [18]. Similar discrepancies exist for the diagnosis and treatment of hypertension in women [19]. Moderate alcohol consumption has been associated with decreased risk of CVD in women, including MI and HF [20]. Tobacco use is a stronger risk factor for women imparting a 25% greater risk of IHD as compared to male smokers. Tobacco use is also a strong risk factor for HF conveying an 88% greater risk in women and a 45% greater risk in men as compared to nonsmokers [6, 20].

Non-traditional Risk Factors

There is growing literature on sex-specific risk factors for women (Fig. 1). Inflammatory markers such as high sensitivity C-reactive protein (hs-CRP) have been used for risk stratification of CAD in men and women. Women with metabolic syndrome and hs-CRP levels > 3 mg/L have been shown to have twice the risk for CVD as compared to those with lower levels [21]. Autoimmune disorders associated with chronic inflammation such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) as are also associated with increased risk of CVD, including acute MI and HF. Women aged 35 to 44 years in the Framingham offspring study with SLE had a 50-fold higher risk of acute MI than women of the same age group and without SLE. [22]

Preeclampsia, pregnancy-associated hypertension, and gestational diabetes confer a 1.5- to 2-fold increased risk of IHD, as compared to women without such complications [23]. Preeclampsia and CVD share similar risk factors including obesity, insulin resistance, and dyslipidemia and are both characterized by endothelial dysfunction, oxidative stress, and upregulation of inflammatory response. Polycystic ovarian syndrome (PCOS) is associated with metabolic syndrome and insulin resistance. PCOS, functional hypothalamic amenorrhea, and oophorectomy confer a higher risk of CVD and premature CAD [24]. The use of combination estrogen-progestin oral contraceptives is associated with low risk of CVD in healthy women but there is a high risk of IHD in those women who are smokers, age > 35, or who have uncontrolled hypertension [25]. Clinical depression affects hormonal and menstrual cycles and increases risk of CVD by 70% in women less than 55 years of age [26]. Breast cancer and CVD share several overlapping risk factors and breast cancer therapies including chemotherapy and radiation raise CVD risk for many years following treatment [27]. Lastly, untreated sleep apnea, although more prevalent in men, is associated with increased risk of hypertension, CAD, HF, atrial fibrillation, and 3.5 times increased risk of dying of CVD in women [28].

Symptoms and Clinical Presentation of Ischemia

From 1997 to 2012, women's awareness that CVD is the leading cause of death rose from 30 to 56% [29]. Although chest pain is the predominant symptom of acute MI, women are more likely to report multiple non-chest pain symptoms as compared to men, which may increase the difficulty in making a timely and accurate diagnosis [30••]. A majority of women presenting with an acute MI, experience prodromal symptoms of shortness of breath, unusual fatigue, or arm/jaw discomfort for weeks prior [31•]. According to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the Management of ST-Elevation Myocardial Infarction (STEMI), there is a 1.5 to 2-h delay in patients with STEMI seeking medical care which is further prolonged in women, African Americans, the elderly, and Medicaid-only recipients [32]. Stable angina is a more frequent clinical presentation for women with IHD as opposed to acute MI or sudden death [33].

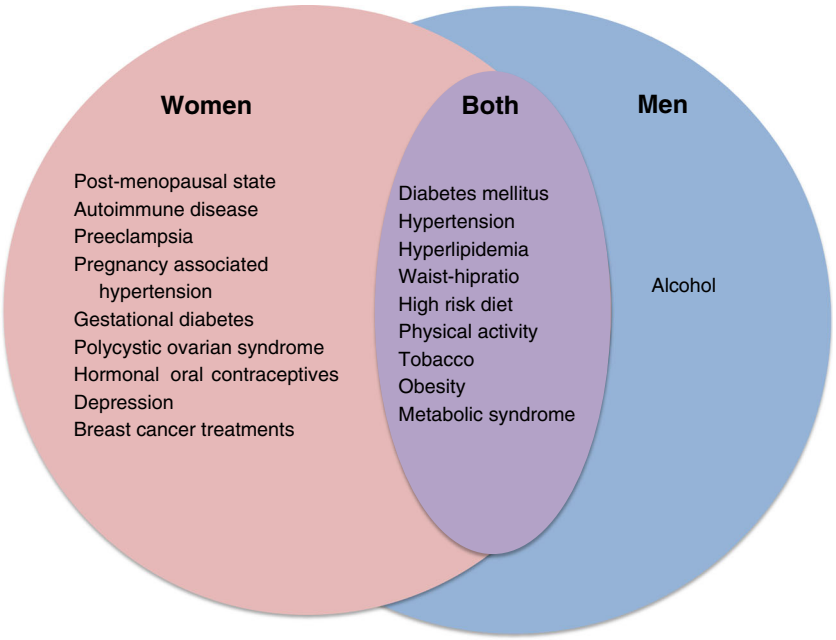

Fig. 1 Risk factors for ischemic heart disease in women and men

Pathophysiology of Ischemia

Despite similar coronary anatomy, women have smaller diameters of the left anterior descending and right coronary arteries and have overall smaller atheromatous burden than men [34]. Men have higher sympathetic activity while women have higher parasympathetic activity, and autonomic dysfunction is believed to play a role in syndromes more common in women including cardiac syndrome X (triad pattern of chest pain, abnormal stress test consistent with ischemia, and the absence of significant obstructive IHD on angiography) and Takotsubo cardiomyopathy [35]. Men and women have varying estrogen and testosterone levels, which may play a role in the handling of calcium by the cardiomyocyte in response to ischemia and reperfusion [36]. Plaque rupture is the most common etiology of fatal MI in women (55%) and men (76%) but is particularly less common in premenopausal women [5]. As compared to men, women with acute MI more commonly present with Non-STEMI (NSTEMI) and non-obstructive CAD. The Women's Ischemic Syndrome Evaluation (WISE) study demonstrated a 2.5% annual risk of major adverse CV events (MACE) during 5-year follow-up in women diagnosed with non-obstructive CAD on angiograms performed to evaluate symptoms of IHD [37].

Spontaneous coronary artery dissection (SCAD) and coronary artery spasm (CAS) are also more common in women [38]. A large series of SCAD patients from the Mayo Clinic has demonstrated a high risk of recurrence as well as increased MACE and CV mortality in these patients [39]. Coronary microvascular dysfunction (CMD) due to abnormalities of the structure and function of the coronary microvasculature that limits myocardial perfusion as detected by reduced coronary flow reserve (CFR) is increasingly recognized as a cause of ischemia in women without obstructive CAD [40•]. In the WISE study, an abnormally reduced CFR < 2.32 (defined as an invasive Doppler time-averaged peak hyperemic coronary flow velocity/resting flow velocity) predicted increased 5-year MACE of 27% versus 9.3% in those with higher CFR [41]. It has also been recently demonstrated that excess cardiovascular risk in women relative to men is due to severely reduced CFR and not obstructive CAD [42]. Takotsubo cardiomyopathy, more frequently seen in females, has been thought to be associated with CMD [43].

Cardiac Remodeling in Response to Ischemia

The female heart is less maladaptive as compared to the male heart in response to ischemic injury, with less apoptosis, cell death, and greater myocardial salvage [44, 45]. This leads to smaller infarct size as well as less left ventricular dilation and hypertrophy, as demonstrated in mice studies [46]. In a study of 100 patients (72 men, 28 women) undergoing cardiac transplantation, including 50 patients with ischemic cardiomyopathy, direct measurement of cardiac mass revealed significant increase in LV mass, myocyte volume, and resting cell length in men, as compared to women. This difference was not seen in idiopathic cardiomyopathy, suggesting gender may influence local myocardial adaptation to ischemic injury [47].

Gender Difference in Outcomes of Acute Myocardial Infarction and Ischemic Cardiomyopathy

Women have overall worse outcomes as compared to men [1], including worse health status scores, all cause re-

hospitalization, and mortality after acute MI [48]. Mortality rates are higher for women than men at both 1 year (26% vs 19%) and 5 years (47% vs 36%) following an acute MI [4••]. In particular, young women with acute MIs have more comorbidities, longer length of stay, and higher in-hospital mortality as compared to young men, although their mortality rates are decreasing [49].

Women have higher rates of complications with acute coronary syndromes than men. Despite the ACC/AHA recommendations that women with high-risk features undergo early invasive strategy, they are less likely to undergo appropriate revascularization and are under treated with guideline-directed medical therapies [5, 50, 51]. Young women with STEMI are also less likely to receive reperfusion therapies and more likely to have reperfusion delays exceeding current guidelines [32]. They also are more likely to experience delays in transfer to percutaneous coronary intervention capable institutions [52].

Those women who do undergo percutaneous or surgical revascularization are more likely to have complications including bleeding, HF, cardiogenic shock, need for ventilator or vasopressor support, renal failure with or without the need of dialysis, repeat MI, stroke, and hospital readmissions [5••, 32].

Women have higher incidence of symptomatic HF after acute MI and this increases with age [1, 3]. The National Registry of Myocardial Infarction and the Global Registry of Acute Cardiac Events (GRACE) registry demonstrated that among patients presenting with acute MI, women were more likely to present with or develop HF and have a higher Killip class at presentation [53–55]. Female sex was an independent predictor of HF and cardiogenic shock after acute MI, despite presenting with smaller infarct size and less extensive CAD [56, 57]. In an analysis from the SHOCK registry, women with cardiogenic shock complicating acute MI had lower cardiac index and higher risk of mechanical complications as compared to men [58]. Early revascularization, the use of diuretics, vasodilators, and inotropes as well as appropriate mechanical circulatory support are recommended for women who develop HF or cardiogenic shock due to pump failure after acute MI [32, 51, 56, 59].

The increased risk of development of HF after acute MI also extends beyond the initial MI episode in women, as compared to men [60]. Despite better left ventricular ejection fraction (LVEF) and lower burden of obstructive CAD, women with CAD and ischemic cardiomyopathy have lower functional capacity, worse quality of life scores as compared to men but similar mortality [61, 62]. Sudden cardiac death (SCD) after acute MI accounts for 50% of post-MI mortality and is attributed to recurrent MI, cardiac rupture, and HF as the leading causes [63]. A greater proportion of women die of SCD before their arrival at a hospital as compared to men (52% vs 42%) [64]. Improvement in rates of SCD in recent years in men has not been observed in women [65].

Gender Difference in Response to Therapies in Ischemic Cardiomyopathy

Women with ICM are less likely to be prescribed guideline-directed medical therapies (GDMT) and are less likely to adhere to their prescribed regimen [5, 55]. While randomized clinical trials have established the benefit of antiplatelet agents, statins, beta-blockers, angiotensin converting enzymes (ACE) inhibitors or angiotensin receptor blockers (ARB) and aldosterone antagonists in the medical management of post MI and ICM in both men and women, sex-specific differences are limited due to inadequate enrollment of women in these trials [32, 51, 66] (Table 1). To understand sex-specific differences, several post hoc analyses have been conducted in clinical trial populations and their data have to be interpreted with caution. Current guidelines for HF therapies are not sex-specific and are uniformly applied to both men and women [8].

Antiplatelet Agents and Anticoagulation

Aspirin and other anti-platelets are recommended for acute management of ACS and secondary prevention of CAD in men and women, with dose adjustment for weight and renal function in women, due to higher risk of bleeding [51]. In a 2009 meta-analysis of anti-platelet therapies, primarily aspirin as compared to placebo, low dose aspirin led to significant reduction in vascular events, primarily driven by reduction in ischemic stroke (RR 0.77, 95% CI 0.59–0.99) without major reduction in coronary events in women (RR 0.88 95% CI 0.77–1.17), as compared to men [91]. Aspirin is recommended for primary prevention of CAD only in women who are considered high risk (10-year risk of CV events > 10%) or older than 65 years of age [92]. In secondary prevention trials, aspirin has demonstrated similar benefit in men and women, and decreases further CV events by ~ 25% [91]. Clopidogrel treatment as compared to placebo, has been associated with significant reduction in MI in women, while men also experienced reduction in stroke and all-cause mortality [93]. Studies on prasugrel and ticagrelor have not demonstrated sex-specific differences on MACEs [94, 95].

In a retrospective analysis of the Studies of LV dysfunction, (SOLVD) trial, reduced ejection fraction was independently associated with thromboembolic risk in women, and women were less likely to be taking antiplatelet agents or anticoagulation therapy [96].

Statins

The 2013 ACC/AHA Blood Cholesterol Guidelines recommend fixed dose statins for primary prevention of CAD based on low density lipoprotein cholesterol (LDL-

Table 1 Female participation and mortality reduction in subgroup analysis of chronic heart failure trials

Therapy	Trial	Women (%)	Mortality reduction
Beta-blocker			
Bucindolol	BEST [67]	22	HR 0.82 (0.60–1.13)
Carvedilol	COPERNICUS [68]	20	NA
Bisoprolol	CIBIS II [69]	19	RR 0.52 (0.30–0.89)
Metoprolol succinate	MERIT-HF [70]	23	RR 0.93 (0.58–1.49)
Carvedilol	U.S. Carvedilol [68]	23	HR 0.23 (0.07–0.69)
Carvedilol	COMET [71]	20	HR 0.97 (0.73–1.27)
ACE inhibitor			
Enalapril	CONSENSUS [72]	20	RR 1.14 (0.68–1.90)
Enalapril	SOLVD [73, 74]	20	RR 0.86 (0.67–1.09) treatment
			RR 1.15 (0.74–1.78) prevention
ARBs			
Losartan	ELITE-II [75]	31	HR: 1.14
Valsartan	Val-HeFT [76]	20	NA
			Hospital stay only - HR 0.74 (0.55–0.98)
Candesartan	CHARM-low LVEF [77]	26	NA
Vasodilators			
Hydralazine/isosorbide dinitrate or prazosin or placebo	V-HeFT I [78]	0	
Hydralazine/isosorbide dinitrate vs Enalapril	V-HeFT II [79]	0	
Hydralazine/isosorbide dinitrate	AHeFT [80]	40	HR 0.33 (0.16–0.71)
ARNI	PARADIGM-HF [81]	21	HR 0.92 (0.6–1.1)
Aldosterone antagonist			
Spironolactone	RALES [82]	27	NA
Eplerenone	EPHESUS [83]	29	NA
Eplerenone	EMPHASIS-HF [84]	22	HR 0.65 (0.4–0.9)
Spironolactone	TOPCAT [85]	51	HR 0.89 (0.71–1.12)
Ivabradine	SHIFT [86]	23	NA
Digoxin	DIG [87]	22	HR 1.23 (1.02–1.47)
ICD/CRT			
CRT	CARE-HF [88]	26	HR 0.64 (0.42–0.97) Mortality + hospital stay
CRT ± ICD	COMPANION [89]	32	NA
ICD	MADIT II [88]	16	HR 0.57 (0.28–1.16)
ICD	SCD HeFT [90]	24	HR 0.96 (0.58–1.61) ICD arm
			HR 1.17 (0.72–1.90) amiodarone

c) levels, comorbidities, and the atherosclerotic CV disease (ASCVD)-pooled cohort risk equations, for both men and women [16]. Multiple secondary prevention studies of statins have demonstrated benefit in both men and women [97, 98]. Women experience similar reduction in lipid levels as compared to men [99]. The guidelines also recommend statins for secondary prevention of CVD in both men and women with clinical CAD [16].

Beta-Blockers

Beta-blockers are recommended post-MI to improve outcomes and reduce the risk of recurrent ischemia, infarct size, ventricular arrhythmias, and mortality.

Beta-blocker treatment is associated with a 25% reduction in re-infarction rate, 30% reduction in SCD, and a 21% reduction in mortality, with similar benefit in women and men [5••].

Non-selective beta-blockers should be avoided in women with coronary vasospasm due to unopposed α-adrenergic action, which can exacerbate vasospasm [100].

Three beta-blockers are proven to improve outcomes and reduce morbidity and mortality in HFrEF including carvedilol, metoprolol succinate, and bisoprolol [8]. Metoprolol succinate and bisoprolol are β1 selective adrenergic antagonists. The MERIT-HF (Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure) trial that enrolled 898 women, with LVEF < 40% and NYHA class II to IV, metoprolol succinate reduced HF hospital stay by 42% ($p = 0.021$) and by 72% in women with LVEF < 25% ($p = 0.004$), without a survival benefit for women (6.9% vs 7.5%, p = NS) [70]. Bisoprolol improved survival in 515 women with LVEF ≤ 35% and NYHA class III or IV (relative hazard 0.37, 95% CI 0.19 to 0.69) in the Cardiac Insufficiency Bisoprolol Study or CIBIS II study [69]. Carvedilol is a nonselective β-adrenergic antagonist with α-blocking properties. In the U.S. Carvedilol HF study, carvedilol improved survival in 256 women with LVEF ≤ 35% and HF symptoms (HR 0.23, 95% CI 0.07 to 0.69) [101]. Carvedilol reduced combined end point of death or hospital stay in 469 women with LVEF < 25% and severe HF symptoms in the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Study) study, primarily driven by reduction in hospital stay [68]. A meta-analysis that included data from five beta-blocker trials in HF found both women and men had reduced mortality (RR for women 0.63, men 0.66) [102].

Angiotensin Converting Enzymes Inhibitors

ACE-inhibitors have morbidity and mortality benefits and are recommended for all patients with HFrEF, who can tolerate the drug [8]. Few women participated in major trials of these drugs [73, 103]. A meta-analysis that included data from 30 ACE-I trials that included 1587 women with HF demonstrated a trend towards improved survival (13.4% vs 20.1%, $p < 0.001$) and a favorable trend in the combined end point of survival and HF hospitalization in women who took an ACE-I as compared to those who did not (20.2% vs 29.5%, $p < 0.001$) [104]. Another meta-analysis of 2373 women demonstrated similar trends in women who had symptomatic HF (RR 0.90, 95% CI 0.78–1.05), but achieved less benefit than symptomatic men (RR 0.80, 95% CI 0.68–0.93) [102]. However, the results did not reach statistical significance in either meta-analysis. In a meta-analysis of patients with acute MI and HF, there was improved mortality and HF outcomes in women treated with ACE-I [105]. The Heart Outcomes Prevention Evaluation (HOPE) trial found no sex-specific differences in the effect of ramipril in prevention of HF in high-risk individuals with vascular disease or diabetes [106]. In the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study, ACE-I use in women with known CAD did not result in a mortality benefit, although women constituted only 18% of the study population [107].

Angiotensin Receptor Blockers (ARBs)

ARBs are used in ACE intolerant HF patients. Pooled data from CHARM-Alternative (ARB for patients intolerant of ACEI) and CHARM-Added (ARB added to an ACEI) trials, that included 1188 women with LVEF < 40% with NYHA class II to IV, candesartan reduced risk of CV death and HF hospitalization in women (HR 0.82; 95% CI 0.74–0.90; $p < 0.001$) [77]. The Val-HeFT trial (Valsartan Heart Failure Trial), demonstrated that valsartan as compared to placebo, reduced HF hospital stay (HR 0.74, 95% CI 0.55 to 0.98) in 1003 women with LVEF < 40% and NYHA class II to IV, but did not reduce mortality in women [76]. There were no sex-specific differences in mortality in patients with post-MI LV dysfunction, in two studies with ARBs [108, 109].

Angiotensin Receptor- Nepirlysin Inhibitor (ARNI)

In ARNI, an angiotensin receptor blocker is combined with an inhibitor of nepirlysin that degrades natriuretic peptides, bradykinin, and other vasoactive peptides. In the PARADIGM-HF trial valsartan/sacubitril was compared to enalapril in > 8000 symptomatic HFrEF patients, including 60% with ICM and 21% women [110•]. The ARNI reduced the composite endpoint of cardiovascular death or HF hospitalization by 20%. It is now recommended that ACE-I or ARB be replaced with ARNI, in chronic HFrEF patients with NYHA class II or III symptoms [8].

Aldosterone Antagonists

Aldosterone antagonists have been shown to have a mortality benefit in women with HF in subgroup post hoc analysis of RALES (Randomized Aldactone Evaluation Study) and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trials [82, 83]. RALES trial included 446 women with both ICM and non-ischemic cardiomyopathy with LVEF ≤ 35% and NYHA class III or IV. The EPHESUS trial included 1918 women with LVEF < 40% and signs of HF and demonstrated that the addition of eplerenone to standard medical therapies including aspirin, statins, beta-blockers, and ACE-I decreased 30-day mortality by 32% and SCD by 37%.

Women with IHD often present with HFpEF, where there is a paucity of data on beneficial therapies. In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, spironolactone was shown to decrease HF hospitalizations in symptomatic HFpEF patients, especially in those with elevated brain natriuretic peptides

(BNP) without survival benefit, and this is now a Class IIb recommendation for symptomatic HFpEF patients, who meet criteria based on renal function and potassium levels [2••, 85].

Hydralazine/Isosorbide Dinitrate

The combination of hydralazine and isosorbide dinitrate is used in HFrEF patients who are ACE/ARB intolerant. In the A-HeFT trial (African-American Heart Failure Trial) that included 40% women with HFrEF and NYHA class III to IV, the addition of hydralazine/isosorbide dinitrate to standard HF therapies demonstrated survival benefits for both women (HR 0.33, 95% CI 0.16 to 0.71, $p = 0.003$) and men (HR 0.79, 95% CI 0.46 to 1.35, $p = 0.385$) as well as fewer hospital stays, without treatment interactions by gender [80].

Ivabradine

Ivabradine is a selective sinus-node inhibitor, which results in heart rate reduction. In the SHIFT trial (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) enrolled 6558 patients, including 23% women with HFrEF, in sinus rhythm with resting heart rate > 70 beats per minute, LVEF ≤ 35% and NYHA class II to IV, and prior HF hospitalization on standard medical therapies, were randomized to ivabradine vs placebo [86]. Patients who received ivabradine had reduction in composite end point of death or HF hospitalization, driven primarily by HF hospitalization. However, only 25% of patients were on optimal doses of beta-blocker therapy. The trial excluded patients with a MI within the past 2 months. The 2017 ACC/AHA HF guidelines recommend addition of ivabradine (Class IIa) for symptomatic HFrEF patients on maximal standard HF therapies, in sinus rhythm, and heart rate > 70 bpm [2••].

Digoxin

Digoxin reduces HF hospitalizations without affecting survival [87]. In a post hoc subgroup analysis of the Digitalis Investigation Group (DIG) trial, women with HFrEF had an increased mortality, which was attributed to digoxin toxicity [111]. Serum digoxin levels between 0.5 and 0.9 ng/ml are considered safe for men and women based on a retrospective analysis [112].

Implantable Cardioverter-Defibrillators (ICDs) and Cardiac Resynchronization Therapy (CRT)

Multiple studies have demonstrated the benefit of ICDs in reducing SCD; however, few have provided sex-specific data. The MADIT II trial (Multicenter Automatic Defibrillator Implantation Trial) that included 16% women with ICM and LVEF ≤ 30% demonstrated a trend towards lower mortality in women with ICD, suggesting that women with ICM may benefit from this therapy [88]. In contrast, in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), that included 588 women with both ICM and non-ICM, LVEF ≤ 35% and NYHA class II to III, the benefits of ICD in women were not as clear [90].

CRT is recommended for HFrEF patients with LVEF ≤ 35% and NYHA class III to IV with a wide QRS ≥ 120 ms, on optimal medical therapies, to improve functional class and mortality [8]. Women who meet criteria, have improved outcomes including mortality, when they receive CRT as compared to women who receive only optimal medical therapies [113]. The Multicenter Automatic Defibrillator Implantation Trial Cardiac Resynchronization Therapy (MADIT CRT) and Multicenter In-Sync Randomized Clinical Evaluation (MIRACLE) trials suggested that women may have a greater benefit from CRT than men, while the Comparison of Medical Therapy, Defibrillation, and Heart Failure (COMPANION) trial and the Cardiac Resynchronization-HF (CARE-HF) trial demonstrated similar benefit in both sexes [89, 113–115].

In the Get with the Guidelines Program that included > 13,000 patients hospitalized with HF, less ICD implants were performed in eligible women with HF and LVEF ≤ 30% as compared to men (29% vs 41%) [45, 116]. The MADIT II and Multicenter Unsustained Tachycardia Trial (MUSTT) trials demonstrated women have a lower incidence of ventricular tachycardia that may be related to their higher parasympathetic tone, but similar ICD effectiveness as men [117]. The incidence of adverse events during device implantation is also higher for women [118].

Counseling on the indications and need for an ICD prior to hospital discharge happen less frequently for women as compared to men (19.3 vs 24.6%), but women are just as likely to consent for an ICD when counseled (63.1 vs 62.3%) [119]. MADIT-II, MUSTT, SCD-HeFT, Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE), and COMPANION trials had a total of 7229 patients including 1630 (23%) women with ischemic cardiomyopathy and showed that women have less appropriate ICD therapies [120]. The Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Cardiac Resynchronization Therapy (RAFT-CRT) trial found lower reduction in death or heart failure rates in women as compared to men (45% vs 20%) [121, 122]. Myocardial scar burden, which plays a role in the amount of ventricular arrhythmia and ICD therapies, is higher in men resulting in a larger survival benefit with an ICD [27].

Cardiac Rehabilitation

Cardiac rehabilitation has been shown to reduce CV mortality and hospitalizations in women and men who have had an ACS or HF, as well as improves functional capacity, exercise duration and quality of life [8, 51]. Yet, < 80% of eligible women

are enrolled in a program post hospital discharge and they are less likely to attend if they are referred [4, 5••].

Advanced Heart Failure Therapies

Ventricular assist devices (VADs) are used as bridge-to-heart transplant or destination therapy for patients with end-stage HF, who are ineligible for heart transplant [123]. Women are more likely than men to be hospitalized with advanced HF but are less likely to receive a VAD [124, 125]. In a recent study of 966 patients that included 151 women from the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) registry, women were often sicker at the time of VAD implantation (Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] profile 1 and 2) (51.7 vs 41.6% in men) and experience more complications including major bleeding ($p = 0.0012$), arrhythmias ($p = 0.022$), and right ventricular (RV) failure ($p < 0.001$) with need for additional RV support, as well as worse 1-year survival (75.5 vs 83.2%) as compared to men [126•].

Heart transplantation remains the gold standard for the treatment of end-stage HF. ICM accounts for ~35% of adult heart transplantations and 75% of heart transplant recipients remain men [127]. The criteria for matching a heart based on height, weight, blood type, tissue typing, and quantification of panel reactive antibodies, account for lower rates of transplantation in women. Women have a higher mortality than men while awaiting heart transplantation [128•]. Women may also be at higher risk of post-heart transplant complications including antibody-mediated rejection and coronary allograft vasculopathy. [129, 130]

Conclusion

Cardiovascular disease is the leading cause of death in women in the USA and worldwide. Women with IHD are more likely to present later in life and with an atypical cluster of symptoms. Both traditional and non-traditional risk factors play a role in the development of IHD in women. Coronary microvascular disease, spontaneous coronary artery dissection, and Takotsubo cardiomyopathy are more common in women. Women are also less likely to have obstructive CAD. The female heart is relatively protected to ischemic insults with less maladaptive remodeling and relative preservation of LV size and function. Women are more likely to develop HF as a result of IHD with less robust response to therapies such as ACE-inhibitors and ICD, but may have better response to beta-blockers, aldosterone antagonists, and CRT, as demonstrated in retrospective analysis. Women continue to be underrepresented in HF clinical trials, resulting in the lack of sex-specific recommendations. Areas for further research include identifying better treatment options for coronary microvascular disease, improved recognition and treatment of risk factors specific to women, and inclusion of sex-specific data in clinical trials.

Compliance with Ethical Standards

Conflict of Interest Laura Divoky, Anbukarasi Maran, and Bhavadharini Ramu 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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- • Of importance
- •• Of major importance

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