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Gender Differences in the Pathophysiology, Clinical Presentation, and Outcomes of Ischemic Heart Failure

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Abstract

Despite advances in the treatment of acute myocardial infarction (MI), heart failure (HF) remains a frequent acute and long-term outcome of ischemic heart disease (IHD). In response to acute coronary ischemia, women are relatively protected from apoptosis, and experience less adverse cardiac remodeling than men, frequently resulting in preservation of left ventricular size and ejection fraction. Despite these advantages, women are at increased risk for HF-complicating acute MI when compared with men. However, women with HF retain a survival advantage over men with HF, including a decreased risk of sudden death. Sex-specific treatment of HF has been hindered by historical under-representation of women in clinical trials, though recent work has suggested that women may have a differential response to some therapies such as cardiac resynchronization. This review highlights the sex differences in the pathophysiology, clinical presentation and outcomes of ischemic heart failure and discusses key areas worthy of further investigation.

Keywords

women; gender; coronary disease; heart failure; myocardial infarction; ischemic heart disease; disparities

Introduction

Ischemic heart disease (IHD), the most common form of cardiovascular disease (CVD), is the leading cause of death in both men and women worldwide. Along with hypertension, IHD is responsible for the largest proportion of the 770,000 newly diagnosed cases of heart failure (HF) each year in the United States. However, recent research efforts have highlighted distinct sex differences in the epidemiology, pathophysiology, and prognosis of ischemic heart disease and HF. While great strides have been made in identifying the gender disparities that exist, the reasons for these differences remain largely unexplained, and represent a prominent area of ongoing research and evolving knowledge. Herein, we review the existing literature with a focus on examining the burden of ischemic heart disease, and clinical presentation and outcomes of ischemic HF in men and women.

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Burden of Ischemic Heart Disease in Men and Women. Prevalence

CVD remains the leading cause of death in both men and women worldwide, and claims more lives each year in the United States (U.S) than cancer, chronic lung disease, and accidents combined [1]. Ischemic heart disease (IHD) is the most common form of CVD, and accounted for 49.9 % of cardiovascular deaths in the U.S. in 2008. The prevalence of IHD is higher in men than in women (8.3% in men vs. 6.1% in women in 2008) [1]. In the Multi-Ethnic Study of Atherosclerosis (MESA) study, 36.0 % of women < 75 years old had detectable coronary calcium on computed tomography, compared with 58.2% of men [2]. Among elderly patients with IHD who survive their first acute myocardial infarction (MI), 76% develop HF within 5 years [3].

The prevalence of IHD in patients with HF has varied across published reports, and has been particularly difficult to assess due to the lack of consistent coronary angiography in patients presenting with HF in the general population. In the National Health and Nutrition Examination Survey (NHANES), which relied on self-report to define coronary disease, it was estimated that more than 60 % of HF cases may be attributable to IHD [4]. In the Framingham Heart Study, 52 % of HF cases were attributable to coronary heart disease [5]. In Olmsted County, hypertension and IHD were equally responsible for the highest proportion of new HF cases in the population (population-attributable risk 20 % for each), though hypertension played a greater role in women, and IHD in men [6].

Risk factors for Ischemic Heart Disease

There are a number of identifiable risk factors for IHD in the population. The INTERHEART study pinpointed nine potentially modifiable risk factors for acute MI including smoking, diabetes, waist/hip ratio, diet, physical activity, alcohol consumption, hypertension, plasma apolipoproteins, and psychosocial factors that accounted for 90 % of the population attributable risk of acute MI in men and 94 % in women [7]. While a decrease in the burden of some IHD risk factors in the U.S. population in recent years has been reported to account for 44 % of the decrease in mortality from IHD in the population [8], the prevalence of diabetes mellitus and obesity has risen. Both men and women with optimal risk factor profiles have markedly decreased lifetime risks of MI, stroke, and death from cardiovascular disease compared with those with suboptimal risk factor profiles [9,10]. However, among adults in NHANES, < 2% of the population (75 % of whom were women) met 7 simple cardiovascular health metrics (not smoking, being physically active, having normal blood pressure glucose and cholesterol levels, normal weight, and eating a healthy diet) [10].

There are important sex differences in risk factors for IHD in men vs. women. Women have higher levels of total cholesterol than men after the fifth decade of life [11]. Further, hypertriglyceridemia appears to play a greater role in IHD risk in women than in men [11]. Hypertension is more common in women than men after age 55 years. Diabetic women have greater IHD mortality rates than diabetic men [12], and there were no declines in cardiovascular mortality for women with diabetes from 1971 to 2000, though improvements were noted in diabetic men [13].

Pathophysiology

Women have less coronary atherosclerotic burden than men in the setting of acute coronary syndrome (ACS) and when referred for percutaneous coronary intervention [14-17]. In a pooled sample of patients from 11 ACS trials, women presenting with ACS more often had non-obstructive CAD than men (15% vs. 8%, respectively), and less frequently had 3-vessel disease (23% vs. 26%) [15]. In the recent Providing Observations to Study

Predictors of Events in the Coronary Tree (PROSPECT) study, despite having more comorbidities than men, women with ACS had less extensive CAD by both coronary angiography and intravascular ultrasound [17].

Endothelial and microvascular dysfunction has been hypothesized as one potential mechanism to explain why women frequently have chest pain without obstructive CAD and may have adverse outcomes compared with men despite less CAD. This hypothesis has been controversial, as endothelial function has been demonstrated to be worse in men than women in some evaluations. In a recent article, Han et al. performed intravascular ultrasound and coronary reactivity assessment in patients with non-obstructive CAD, and found that men had longer segments of the coronary arteries with endothelial dysfunction, while women had lower maximal coronary flow reserve (indicative of microvascular dysfunction) [18]. In addition, in the recent evaluation from the Women's Ischemia Syndrome Evaluation (WISE) study, abnormal coronary flow reserve after intracoronary adenosine injection was associated with an increase in adverse outcomes (death, MI, stroke, or HF hospitalization, HR 1.20, 95% CI 1.05-1.38) in women without obstructive CAD [19].

Response to Acute Coronary Ischemia—In response to prolonged acute coronary ischemia, cardiomyocytes develop cell edema, apoptosis, and necrosis (Figure). Even if successful reperfusion is achieved with primary percutaneous coronary intervention, females have been demonstrated to have greater myocardial salvage compared with males [20]. The female heart has been demonstrated to be protected, compared with males, from apoptosis and cell death [21]. Female adult mouse cardiomyocytes have improved survival compared with male cardiomyocytes when challenged with oxidative stress [22]. In a mouse model of acute MI, males have delayed myocardial healing, higher infarct re-expansion, and an increased risk of cardiac rupture [23]. In females, endogenous estrogens (biologically active 17- β -estradiol) have been demonstrated to aid in limiting cardiac apoptosis, thereby resulting in reduced infarct size in response to ischemia/ reperfusion injury [24,25]. While this is an area of intense ongoing investigation, estrogens may mediate a large portion of the observed sex differences in response to acute coronary ischemia and reperfusion.

Sex Differences in Cardiac Remodeling—As previously noted, in response to acute coronary ischemia, females appear to be relatively protected from programmed cell death and have smaller infarct sizes when faced with similar circumstances. Sex differences in response to acute MI extend beyond the acute period, as men tend to have greater adverse remodeling than women. In a mouse model, in the 12 week period following acute MI, male mice had more maladaptive remodeling, including a greater degree of ventricular dilatation and hypertrophy compared with females (Figure) [23].

Gender Differences in the Clinical Presentation of Ischemic Heart Failure

Heart Failure Post Myocardial Infarction

Despite advances in the treatment of acute MI, HF post MI remains frequent (Table 1). Most of the literature has demonstrated that women are at increased risk of HF complicating acute MI. However, as more men than women have acute MI, the absolute number of patients with HF complicating acute MI may still be greater in men. In the National Registry of Myocardial Infarction (NRMI) which included 606,500 cases of MI from 1994-2000, women were more likely to have HF at the time of acute MI presentation or complicating their MI hospitalization. In total, 48 % of those developing HF were women compared with 36 % of those without HF [26]. A similar increased risk of HF complicating acute MI was found in women in the second round of NRMI [27]. In the Global Registry of Acute Coronary Events (GRACE), among patients admitted with acute MI, women were more likely to present with or develop HF during the hospitalization (adjusted OR 1.25 comparing

women to men) [28]. In the APEX-AMI trial, which randomized patients with acute STEMI undergoing PCI to pexelizumab or placebo, 3.4 % developed cardiogenic shock and 4.4% had HF during acute MI hospitalization. In total, 34 % of patients with cardiogenic shock or HF complicating ST-segment elevation MI (STEMI) were female compared with 22 % of those without, and female sex was an independent predictor of cardiogenic shock or HF after STEMI (OR 1.40, 95% CI 1.19-1.78) [29]. While most studies have shown an increased risk of HF complicating acute MI in women vs. men, a recent study by Ezekowitz et al examining patients in Alberta Canada with acute MI (International Classification of Diseases, 9th revision [ICD-9] code 410) found that women were less likely than men to develop HF during hospitalization for acute MI (RR 0.86, 95 % CI 0.78-0.95, $p=0.002$) [3].

The increased risk of HF in women vs. men may extend beyond the MI hospitalization period. In VALIANT (Valsartan in Acute Myocardial Infarction Trial), among patients with EF < 40 % who survived hospitalization for MI without HF, women were more commonly admitted for HF during follow-up than men (39 % of those readmitted for HF were women, compared with 27 % of those who were not admitted for HF), though the difference was not significant after adjustment [30]. Similarly, in an Australian cohort of patients with acute MI or unstable angina (ICD-9 codes 410, 411), women were more likely to develop acute HF during admission or within 28 days of the coronary event [31].

Sex differences in remodeling may contribute to an increased risk of cardiogenic shock and HF complicating MI in women vs. men. As previously discussed, women are less likely to develop ventricular dilatation during remodeling than men. While this may have some protective effects by aiding in the preservation of left ventricular EF in the long run, it may also contribute to deleterious short-term effects including an increased risk of cardiogenic shock [32]. Women with cardiogenic shock complicating acute MI have been demonstrated to have lower cardiac indices and higher rates of mechanical complications compared with men [33]. In Olmsted County, Minnesota, among patients who developed HF following MI, preserved EF was more common in women than in men (37 % vs. 23 %) [34].

Gender Differences in the Outcomes of Ischemic Heart Failure

Mortality

Sex differences in the risk of HF post MI is of particular importance as the development of HF post MI has been associated with a markedly increased mortality risk. In the National Registry for Myocardial Infarction (NORMI), in-hospital mortality was 24 % for those with HF vs. 6.2 % for those without [26]. The risk of death imposed by HF complicating MI extends beyond the index admission; patients remain at increased risk of death [3] and readmission even after hospital discharge [28]. Further, the development of HF during follow-up post-MI discharge is associated with increased risk of death [30]. In the VALIANT trial, patients developed HF at a rate of 3.4 % per year during follow-up, and HF markedly increased the risk of death (HR 8.22, 95% CI 7.49-9.01) [30]. Therefore, HF complicating MI places patients at extraordinarily high risk of adverse outcomes.

While most data would suggest that women with HF have a better long-term prognosis than their male counterparts, this issue has been controversial, with some [35-38], but not all [39,40] studies demonstrating that females fared better. Further, much of the data on prognosis in HF comes from randomized clinical trials, where women have been historically underrepresented, which may limit the ability to perform sex-specific comparisons. The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) group recently published important data compiled from 31 studies that included 41,949 patients (33 % women) [41]. Women with HF were older than men and more frequently had preserved EF. After 3 years of follow-up and following adjustment for potential confounders such as age and EF, men

were at increased risk of death compared with women (adjusted HR 1.23, 95 % CI 1.18-1.28). The sex difference in survival was not specific to those with reduced EF; men with preserved EF still did worse than women with preserved EF. Interestingly, the sex difference in mortality was most marked in patients with a non-ischemic etiology for their HF, with the survival differences between men and women attenuated for those with ischemic HF (adjusted HR men vs. women 1.17, 95% CI 1.10-1.24). Similarly, the Beta-Blocker Evaluation of Survival Trial (BEST), which randomized patients with an EF $\geq$ 35 % to bisoprolol or placebo found that coronary disease was a stronger predictor of prognosis in women than in men [42].

Men are at increased risk of sudden cardiac death compared with women. In the VALIANT study, which included 14,609 patients with HF or left ventricular dysfunction after MI, men were at increased risk of sudden death compared with women [43]. In Olmsted County, women were at 25 % less risk of sudden cardiac death after MI after adjustment for potential confounders [44]. Using US Mortality Vital Statistics Data from 1989-1998, Zheng et al. examined the sudden death rate among U.S. adults and found that rates were higher in men than in women < 85 years of age [45]. However, while sudden cardiac death rates declined for other groups over the time period, they increased by 21% among younger women (21-34 years of age) for reasons that are unclear. In patients with coronary disease who have an implantable cardioverter defibrillator (ICD), men experienced more ventricular arrhythmias and received more ICD shocks during follow-up [46,47]. While there may be many reasons for the increased male propensity for ventricular arrhythmias, potential contributing factors may include some of those previously discussed including decreased ventricular dilatation with remodeling after MI and protection from apoptosis/ decreased infarct size. Furthermore, it is easier to induce sustained ventricular arrhythmia in men than women who have post-MI scarring [48].

Morbidity

While women may have a survival advantage after HF diagnosis, they experience increased morbidity. Women with HF experience worse quality of life [49] and are more likely to have depression [50]. Whether women with HF are more likely to be hospitalized has been controversial with some studies demonstrating an increased risk of hospitalization in women [51,52], while others have found that men are at higher risk [37,53]. It appears that some of the increased risk of hospitalization in women with HF found in some studies is mediated by the older age of women with HF, and studies that have accounted for these differences have found that women are at similar or even lower risk for hospitalization after HF diagnosis. A recent Dutch study examining factors associated with delay in presentation for care in 911 patients hospitalized with acute decompensated HF found that men were more likely to present to the hospital more than 48 hours after the onset of symptoms [54], a finding that has been corroborated in a Worcester cohort [55]. This is in contrast to the acute coronary syndrome population, where women have been demonstrated to more frequently delay seeking medical care [56]. Perhaps a portion of this is mediated by the fact that women who present with HF typically experience more symptoms than men and have more signs of HF such as peripheral edema, jugular venous distension, and a third heart sound [57]. In contrast, women with acute coronary syndromes may stereotypically present with “atypical” symptoms that may result in confusion about the diagnosis and a delay in seeking therapy.

Response to Therapies

The female sex advantage for survival in HF is particularly impressive given that women may be less likely to receive many of the guideline-proven therapies for HF, and many HF therapies have less proven benefit in women. Women have been historically underrepresented in clinical trials (Table 2), and there are no sex-specific guidelines for the

management of patients with HF. In order to examine whether women experience a similar clinical benefit compared with men in response to medical therapies for HF with reduced EF, several post hoc analyses with their inherent interpretation problems have been conducted in clinical trial populations. One meta-analysis which included 2373 women from the seven largest angiotensin-converting enzyme (ACE) inhibitor trials found that women with HF (symptomatic LV dysfunction) may experience a mortality benefit when treated with ACE inhibitors (RR 0.90, 95 % CI 0.78-1.05), though the confidence interval did cross 1 and the benefit for women may not be as great as for men (RR for men 0.80, 95% CI 0.68-0.93) [58]. Further, women with asymptomatic LV dysfunction experienced no survival benefit when treated with ACE inhibitors (RR 0.96, 95 % CI 0.75-1.22), though the male mortality benefit of ACE inhibitors persisted even when asymptomatic (RR 0.83, 95 % CI 0.71-0.96). While sex-specific data on the efficacy of angiotensin receptor blockers (ARB) in women are limited, data would suggest that candesartan, losartan and valsartan may be beneficial [59]. Data from the CHARM-Alternative and CHARM-Added trials that included patients with an EF $\geq$ 40 % demonstrated that candesartan reduced the risk of cardiovascular death or hospitalization in women [60]. The recently published study analyzing the effect of candesartan vs. losartan on outcomes in Danish patients discharged on an ARB following hospitalization for HF found that women taking losartan were at similar risk of all-cause mortality compared with those taking candesartan [61]. Given the suggested benefit of candesartan in women with HF in clinical trials, this suggests that losartan may offer similar benefit in women. Post hoc analyses of trial data for each of the three beta blockers demonstrated to improve mortality in HF (bisoprolol, carvedilol, metoprolol succinate) have shown to improve outcomes in women [62-64], though the majority of reduction in outcomes is related to hospitalizations and not mortality. In a large meta-analysis, which included data from the five largest beta blocker trials, both men and women treated with beta blockers with HF had reduced mortality (RR for women 0.63, men 0.66) [58].

As no sex-specific guidelines for the management of HF exist, women with systolic dysfunction should be treated similar to men. Historically, a gender gap has existed whereby women are less likely to be treated with evidence-based medical therapies compared with men [65,66]. While use of evidence-based therapies has improved in both sexes, there remains room for improvement.

Implantable Cardioverter Defibrillator (ICD)/ Cardiac Resynchronization Therapy (CRT)

ICDs are a class I indication in patients with a prior MI (at least 40 days ago) with an EF $\leq$ 35 % (NYHA functional class II-III) or EF $\leq$ 30 % (NYHA functional class I) or in those who have survived cardiac arrest due to ventricular arrhythmia. Similarly, ICD is indicated for patients with non-ischemic HF and an EF $\leq$ 35 %. CRT with or without ICD is a class I recommendation in patients with an EF $\leq$ 35 %, a wide QRS ($\geq$ 120 ms), and who have NYHA functional class III-IV symptoms [67].

Similar to trials of pharmaceutical therapies, women have been underrepresented in trials of ICD and CRT. For example in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), only 16 % of the 1232 randomized patients were women [68]. ICDs have also been underutilized in women who are eligible for these therapies in clinical practice. Among 13,034 patients hospitalized with HF and an EF $\leq$ 30% in the Get With the Guidelines Program, rates of planned or current ICD use were lower in eligible women (29%) compared with men (41%) [69]. While women were older and may therefore be less likely to warrant an ICD for prevention of sudden death, the disparity in ICD use persisted after adjustment for age and other potential confounders. Similarly, in a 5 % sample of U.S. Medicare and Medicaid beneficiaries in 2005, men were three-fold more likely to receive ICDs for primary or secondary prevention than women (HR 3.15, 95% CI 2.46-3.47) [70]. However,

rates of implantation appear to be similar for both sexes after a referral to an electrophysiologist is made [47]. Following ICD implantation, women are more likely to experience a complication, and, as previously noted, are less likely to be treated appropriately for a ventricular arrhythmia [47]. While women are less likely than men to receive appropriate ICD shocks, both sexes appear to derive a similar mortality benefit after ICD implantation, which could possibly be due to a greater risk of noncardiac death in women compared to men [71].

There has been some evidence suggesting that women may derive greater benefit from CRT than men. In the MADIT-CRT trial, which randomized 453 women and 1367 men with ischemic or non-ischemic cardiomyopathy and an EF $\geq 30\%$ to CRT-ICD or ICD, CRT was associated with a greater reduction in the combined endpoint of HF or death in women compared with men (HR 0.31 vs. 0.72, respectively, p -value for interaction < 0.01) [72]. Men were more likely to have ischemic cardiomyopathy and right bundle branch block pattern, which may explain some of the difference in response to CRT. While post-hoc analysis of the Multicenter In-Sync Randomized Clinical Evaluation (MIRACLE) trial (randomized 453 HF patients with EF $\geq 35\%$ to CRT or usual care) suggested that there may be a greater benefit to CRT in women [73], the Comparison of Medical Therapy, Defibrillation, and Heart Failure (COMPANION) trial (randomized 1520 HF patients with an EF $\geq 35\%$ to CRT, CRT + ICD, or usual care) [74] and the Cardiac Resynchronization-HF (CARE-HF) trial (randomized 813 HF patients with EF $< 35\%$ to CRT or usual care) [75] demonstrated equal benefit in both sexes.

While we are left performing post-hoc analyses of clinical trial data to examine whether women benefit from medical therapies in a similar fashion to men, one caveat is that women with HF, even of an ischemic etiology, are more likely to have preserved EF [5,76], a complex clinical entity for which beneficial therapies are currently lacking.

Conclusion

Women develop IHD at an older age than men, and have less atherosclerotic burden when presenting with acute coronary syndromes. The female heart is relatively protected from apoptosis in response to acute coronary ischemia, and remodels differently, with a tendency to maintain normal left ventricular size and preserved EF. Women have a survival advantage over men after diagnosis with ischemic HF, and have been underrepresented in clinical trials, with analyses indicating that they may respond differently to some therapies such as ACE inhibitors and CRT. Promising areas for future research include continuing to investigate the reasons that women are protected from adverse remodeling following acute MI, to advance our understanding of HF with preserved EF, and to further delineate whether there is differential benefit by sex with therapies such as CRT.

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Fig 1. Left Ventricular Remodeling Following Myocardial Infarction

This schematic depicts the conventional model of left ventricular remodeling following acute myocardial infarction

Table 1

Selected Studies Reporting Sex Differences in the Risk of Heart Failure Complicating Acute Myocardial Infarction Hospitalization

Study (Reference #)	Women in Study (%)	Patients With HF Post MI (%)		Risk of HF in Women vs. Men
		Men	Women	
Observational Studies				
Alberta Canada (3)	40 %	38 %	35 %	0.86 (0.78-0.95)
^b Australia (31)	16 %	21 %	28 %	1.36 (1.16-1.69)*
GRACE (28)	32 %	11 %	16 %	1.25 (1.08-1.39)
NRMI (26)	43 %	25 %	35 %	1.42 (1.41-1.43)*
NRMI-2 (27)	36 %	16 %	26 %	1.64 (1.61-1.67)*
^c VALIANT (77)	33 %	39 %	48 %	1.28 (1.19-1.38)*
Worcester (78)	37 %	33 %	45 %	1.34 (1.26-1.42)*
Clinical Trials				
APEX-AMI (29)	23 %	7 %	11 %	1.40 (1.19-1.78)
^d Fibrinolysis Trials (79)	24 %	27 %	36 %	1.33 (1.30-1.37)
InTime II (80)	25 %	21 %	28 %	1.33 (1.26-1.42)*

^aUnadjusted relative risk (95 % CI) calculated given information in citation

^bIncluded patients with HF within 28 days of acute MI hospitalization

^cIncluded patients with asymptomatic left ventricular dysfunction (ejection fraction <40 %)

^dGUSTOI, GUSTOIIb, GUSTOIII, and ASSENT II

Table 2

Proportion Female Participants in Selected Heart Failure Trials

Type of Therapy	Trial (Ref)	Ejection Fraction (%)	Proportion Females (%)
Beta blocker			
Bucindolol	BEST (81)	35	22
Carvedilol	Copernicus (63)	<20	20
Bisoprolol	CIBIS-II (64)	35	19
Metoprolol succinate	MERIT-HF (82)	40	23
Carvedilol	US Carvedilol (83)	35	23
ACE inhibitor			
Enalapril	CONSENSUS (84)	NS	30
Enalapril	SOLVD (85)	35	20
Angiotensin Receptor Blocker			
Losartan	ELITE-II (86)	40	31
Valsartan + ACE	VAL-HEFT (87)	<40	20
Candesartan	CHARM-Alternative (88)	40	32
ICD/ CRT			
CRT	CARE-HF (75)	35	26
CRT ± ICD	COMPANION (74)	35	32
CRT	MIRACLE (89)	35	32
ICD	MADIT-II (68)	30	16
CRT	MADIT-CRT (72)	30	33
ICD	SCD-HeFT (90)	35	23