PREVENTION

Heart Failure in Women

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ABSTRACT

Heart failure (HF) has steadily increased in prevalence and affects both males and females equally. Despite this, there has been a significant underrepresentation of women in large scale HF trials. This disparity has lead to a deficit in understanding important gender-based differences in pathophysiology, diagnosis and treatment strategies.

We review these gaps and explore a biological basis for varying outcomes. Endogenous estrogen plays an important role in epidemiology and outcome. The administration of exogenous estrogen has had varied success in treatment and is outlined extensively below. Additionally, we highlight unique HF syndromes through pregnancy and important sex-specific issues concerning transplant and mechanical circulatory support. A central theme remains: there is a clear need for increased female recruitment in clinical trials, and more studies exploring the role of gender-based biology in HF treatment.

Introduction

The prevalence of heart failure (HF) has steadily increased and is now the leading cause of hospital admissions in the adult population in the United States.[1] Women constitute approximately one half of the patients hospitalized for HF, and deaths from HF contribute 35% of the total cardiovascular disease (CVD) mortality in women.[1–3] Despite this, women have been historically under-represented in clinical HF trials. Although the population estimate of women among patients with HF in the Unites States is about 50%, only 17% to 23% of HF randomized controlled trials enrolled women.[4] This disparity has limited our understanding of gender-related differences in HF. The objective of this article is to review the relationships between sex and the epidemiology, etiology, clinical characteristics, therapeutic management, and outcomes in patients with HF.

Epidemiology

The most recently available figures indicate that HF in the United States affects 3.1 million males and 2.6 million females with an annual incidence of 550,000 cases, affecting men and women in near equal numbers.[5] The prevalence of HF increases with age for both men and women, with more women than men having a diagnosis of HF after 79 years of age. Women also develop HF later in life than men. Although HF hospitalization rates are similar between men and women, women overall have been shown to have better survival than men.[5] However, women with ischemic heart disease resulting in left ventricular dysfunction may have a mortality similar to men with ischemic disease.[6,7] The Olmsted County data showed that the incidence of HF did not decline between 1979 and 2000, but the survival rate improved overall, with less improvement among women and elderly persons.[5] Previous studies have shown that women treated for chronic HF are more likely than men to have HF with preserved ejection fraction (HFPEF).[5,8] A large proportion of women who are admitted for acute decompensated HF have preserved systolic function with many comorbidities.[9] In addition, clinical outcomes among women with HF have not improved at the same rate as those seen in men.[10] It is unclear whether this is due to sex-related differences in pathophysiology, disparities in the application of evidence-based HF therapies, or a difference in response to treatment.

Morbidity and Mortality

Despite improvements in therapy, the morbidity and mortality rate in patients with HF has remained high. HF has become the leading cause of hospitalization in the United States for Medicare recipients, and the estimated direct and indirect cost of HF for 2010 was $39.2 billion.[10] The investigation of outcomes in women with HF has been limited by the smaller proportion of women than men enrolled in trials.[4] Generally, women appear to have better survival than men, for reasons that are not entirely clear.[11] In both men and women, the prognosis is better in nonischemic disease causes.[6] The mortality disparity between women and men may be due to the higher incidence of HFPEF in women, with a suggestion that HFPEF patients overall have a better prognosis than HF patients with impaired systolic function.[12]

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The difference in survival may also be related to sex-related differences in HF etiology, as women have less ischemic cardiomyopathy compared to men.[6,13] Among patients with reduced ejection fraction (EF), women have more frequent and prolonged hospitalizations than men.[14] The relative roles of risk factors influencing the development of HF, such as age, coronary disease, diabetes, and hypertension, are different in men and women. Regarding comorbidities, women with HF tend to have more hypertension and thyroid disease, whereas men tend to have more coronary disease, peripheral vascular disease, and chronic obstructive lung disease,[13,15,16] Compared to men, women are older and have greater clinical severity of HF, as evidenced by worse New York Heart Association (NYHA) functional class, more frequent symptoms and signs of HF, and more treatment with diuretics.[17] In addition, women with HF have consistently demonstrated a lower quality of life, more functional capacity impairment, and more symptoms of depression than men.[2,10,15,18,19] Diabetes appears to be a particularly strong risk factor for the development of HF in women.[1,20]

The investigation of outcomes in women with HF has been limited by the smaller proportion of women (17%–23%) than men enrolled in clinical trials.[4] Of the two most common causes of death in patients with HF, progressive HF and sudden cardiac death (SCD), men are more likely than women to die from SCD.[21] Readmission for HF is a significant healthcare burden and has recently come under scrutiny as a measure of hospital performance. In 2009, The Center for Medicare and Medicaid Services began to publicly report 30-day readmission rates for beneficiaries across US hospitals. Analysis of this data over a 2-year span revealed that readmission rates are approximately 25% in this population.[22] Retrospective and observational studies have shown similar readmission rates among the genders, but women tended to have longer lengths of stay,[23] although the data regarding length of stay are conflicting.[15] Prior studies suggest that women have higher rates of nonischemic etiologies, normal EFs, and improved survival compared to men; thus, it is somewhat perplexing that readmission rates are similar between the two groups.[24] Further studies are warranted to better elucidate this trend.

Gender Differences in Presentation

Prior epidemiological studies have suggested important gender-related differences in presentation, baseline characteristics, and the prognosis of HF. The Framingham Heart Study population found that women may have a better prognosis than men with HF. Experience from the Beta-Blocker Evaluation of Survival Trial (BEST) echoed this finding and additionally noted several other important observations.[6] Women had a higher prevalence of nonischemic etiology (which in turn conferred an improved survival), higher left ventricular EF, a lower occurrence of atrial fibrillation, and a higher prevalence of left bundle branch block.

The largest clinical database set of around 105 000 HF patients comes from the Acute Decompensated Heart Failure National Registry (ADHERE), which provides important insight into the effects of gender on treatment and outcomes in all patients admitted with acute decompensated HF, regardless of EF.[15] Over half of all admissions (52%) are women, thus confirming the apparent disparity in clinical trial enrollment. Importantly, there were no gender differences in in-hospital mortality, and contrary to prior studies, length of stay was not significantly different between the two sexes. Of note, significant treatment gaps occurred in both sexes (roughly 50% of both populations were on β-blockers), with women receiving less evidence-based therapies than their male counterparts. Additionally, women were less likely to undergo invasive testing or procedures. These disparities in care, including implantable cardioverter-defibrillator (ICD) placement, have been reported in other HF registries, such as the American Heart Association's Get With the Guidelines-Heart Failure registry.[25]

Women who present with HF typically exhibit more symptoms than men, such as decreased exercise tolerance, and have more physical signs of HF (edema, S3 gallop, jugular venous distension).[23,26] The presentation of acute coronary syndrome also differs among genders. For example, women with acute ischemia often have atypical symptoms such as fatigue, back pain, palpitations, and indigestion.[27] This is often misleading and can lead to delayed diagnosis. Women are usually older than men at diagnosis, perhaps related to the protective effects of estrogen in early midlife and the subsequent decrease in protection in late menopause. The ADHERE registry suggests that acute heart syndromes are similar in presentation in both genders, with a predominance of dyspnea, fatigue, and edema.[15]

Pregnancy and Peripartum Cardiomyopathy

Pregnancy is associated with substantial hemodynamic changes, including a 30% to 50% increase in cardiac output, which is accomplished by sodium and water retention leading to blood volume expansion, and reductions in systemic vascular resistance and systemic blood pressure, in addition to a rise in the maternal heart rate by 10 to 15 beats/minute. These changes begin early in pregnancy, reach their peak during the second trimester, and then remain relatively constant until delivery. In women with a history of HF or other CVDs, these demands can lead to clinical deterioration.[28]

Peripartum cardiomyopathy (PPCM) is a rare but potentially lethal complication of pregnancy occurring in approximately 1:4000 live births in the United States.[29] PPCM is a form of dilated cardiomyopathy that is defined as deterioration in cardiac function presenting typically between the last month of pregnancy and up to 5 months postpartum with no other etiology evident.[30] Approximately 75% of cases are diagnosed within the first month postpartum and 45% present in the first week after birth.[31] The incidence of PPCM in the United States is difficult to estimate as the diagnosis overlaps with other cardiomyopathies. The highest incidence of PPCM occurs in African American women compared to other racial groups.[32] Other reported risk factors include older age, pregnancy-induced hypertension or preeclampsia, multiparity, multiple gestations, obesity, chronic hypertension, usage of tocolytics, and poverty.

The hemodynamic changes during pregnancy can cause several signs and symptoms during normal pregnancy that may mimic the signs and symptoms of HF. Dyspnea, lightheadedness, orthopnea, and decreased exercise capacity often are normal symptoms in pregnant women. This may

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lead to a delay in the diagnosis of PPCM.[33] Echocardiography is a valuable tool for the diagnosis and evaluation of suspected cardiac disease in the pregnant patient. Other clinical findings reported include displaced apical impulse, gallop, and electrocardiogram abnormalities.[34] The etiology of PPCM remains unknown, but potential causes that have been investigated include myocarditis, abnormal immune response to pregnancy, increased myocyte apoptosis, genetic predisposition, excessive prolactin production, viral antigen persistence, and stress-activated cytokines.[35]

The treatment for PPCM includes standard recommended HF therapies until the systolic function recovers or the patient stabilizes. Of note, the use of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are contraindicated in pregnancy. In a small prospective single-center study in South Africa, Sliwa et al[36] studied the use of bromocriptine as treatment in PPCM patients, based on the hypothesis that prolactin may be responsible for the development of the disease.[37] In these reported results, 10 patients with PPCM who were treated with bromocriptine and standard HF therapy had a significantly larger rate of systolic recovery at 6 months compared with a group of 10 women with PPCM treated with standard HF therapy alone. However, large prospective studies aimed at evaluating the therapeutic potential of bromocriptine as the first specific therapy for patients with PPCM are needed.

Recovery of systolic function occurs in roughly 50% of affected women and usually occurs within 6 months of symptom onset. Approximately 20% deteriorate and either die or require heart transplantation.[38,39] A left ventricular end-diastolic dimension >5.6 cm, the presence of intracardiac thrombus, and African American race may be predictive of lack of recovery in PPCM patients.[40] It may be safe to withdraw HF medications in those PPCM that recover ventricular function. Eventual recovery of left ventricular systolic function occurred more frequently in women who had an EF of >30% at original diagnosis of PPCM.[31] However, the safety of subsequent pregnancies remains a concern. Elkayam et al report that women with PPCM exhibit a significant decline in left ventricular function with subsequent pregnancies.[31] In summary, PPCM is an HF diagnosis specific to women that is not well understood and remains an area that requires further investigation.

HF Therapies

Previous studies have shown that women treated for HF are significantly less likely to be prescribed certain evidence-based pharmacological therapies, and when these are prescribed for women, they tend to be prescribed at suboptimal doses, although recently this treatment gap appears to be closing.[41] Most large multicenter trials of systolic dysfunction HF have not included sufficient numbers of women to allow conclusions about the efficacy and safety of their treatment.[11] Over recent years, there has been an increased awareness for gender-specific issues surrounding cardiovascular pharmacotherapy. Due to the under-representation of women in most HF clinical trials, important observations have been made in a pooled meta-analysis fashion. The variability in drug response may be explained by inherent differences of cellular and biological processes in women.

The American Heart Association's Get With the Guidelines–Heart Failure (GWTG-HF) registry is the most recent data set that includes nearly 100 000 hospitalized patients.[42] Analysis of this database suggests that although there are significant disparities in trial enrollment, women and men are treated equally with most guideline-based HF therapy. Specifically, β-blocker and ACE-inhibitor or angiotensin-receptor blocker use between the 2 sexes peaked at around 90%. This demonstrates a significant improvement since the ADHERE database, in which only 50% to 55% of both sexes were treated appropriately.[41]

Sex hormones play an important role in the regulation of β receptors, thus differing responses would be reasonably expected. The major β-blocker trials in HF have consistently recruited around 20% female-gendered patients. Pooled data from 3 large studies—Metoprolol CR/XL Randomised Intervention Trial in Heart Failure (MERIT-HF), Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS), and the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) suggest that β blockade leads to similar decreases in mortality among men and women.[6] If each trial is examined separately, this similarity is not evident, and it may be concluded that women do not fare as well as men with β-blocker therapy. Only in combining the data is there a significant benefit noted, a fact that again highlights the need for greater enrollment of women.

ACE inhibition is a key part of the HF regimen. As is true for β-blockers, data on women and ACE inhibition are similarly less well founded. A combined analysis of more than 30 trials established a 37% decrease in mortality for men, with only a 22% decrease in women.[43] Other pooled analyses have echoed the finding that there is a trend toward less benefit for women treated with ACE inhibitors.[44] It may be that estrogen causes a natural inhibition of the renin-angiotensin system, which is a cardioprotective benefit that is lost after menopause.

In 1997, the Digitalis Investigation Group (DIG) outlined the benefit of digoxin in an HF population. They showed that there was a significant decrease in rehospitalization with therapy, but failed to reveal any mortality benefit.[45] Subsequently, there were subtle hints of limited efficacy in women; the HERS trial even suggested an increased cardiovascular event rate in women on digoxin and hormone replacement therapy.[46] A subsequent post hoc subgroup analysis of the DIG population was performed to examine the benefit of digoxin in women. The results of the analysis showed that women on digoxin had an increased risk of death compared to men. Furthermore, there was a smaller digoxin-associated reduction in rate of hospitalization.[47] This analysis raised important concerns regarding the use of digoxin in women, namely, a risk of increased mortality may not outweigh the marginal benefit in rehospitalization rates.

Clinical trials in aldosterone antagonism have not detected a sex-based difference in pharmacology. Although there were only 27% and 28% female enrollments in the Randomized ALdactone Evaluation Study (RALES) and Eplerenone Post-myocardial infarction Heart failure Efficacy and Survival Study (EPHESUS) studies, respectively, both nonspecific and specific aldosterone antagonism seem to carry equal prognostic benefit in both men and women.[48,49]

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Device therapy is underutilized in both genders. The GWTG-HF registry confirms that only 40% of patients qualifying for ICD therapy actually receive implantation.[41] Women are even less likely to undergo device implantation, with 40% lower odds of receiving the therapy compared to men. There is no difference in efficacy of ICD therapy between sexes; therefore, this gender-based disparity is unfounded.

Finally, cardiac resynchronization therapy (CRT) is one of the latest mortality improving interventions in the HF population. Data from the Healthcare Cost and Utilization Project suggest a significant disparity in utilization of resynchronization therapy in women. In this population, women comprised the majority of all heart failure (HF) hospitalizations, yet only 25% of CRT implants were in women compared to 75% in men.[50] Of significant note is the fact that prior studies have shown significantly more women than men with HF have a left bundle branch block,[6] which is an important criteria for CRT therapy. Some possible explanations are that the overall prevalence of HF in women is lower, or that more women suffer from HF with preserved EF. Further studies are warranted to investigate the cause of such a large gender disparity in this life-saving therapy. More recently, important differences have been noted in men and women in regard to response to CRT. Generally, around 30% of the people implanted are labeled as responders, which is defined as an improvement in left ventricular EF, reduction in left ventricular volume, and an improvement in NYHA class. A recent substudy of the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) population found 7 different patient characteristics that were most predictive of this positive response, with female gender conferring a greater degree of reverse remodeling and better outcomes with resynchronization therapy.[51]

Menopause and Hormone Replacement Therapy

After menopause, a woman's risk of HF rises exponentially. The loss of endogenous estrogen plays an important role in this increased risk. Receptors to estrogen are present in cardiac cells, reproductive organs, liver cells, bone, and vasculature. Hepatic gene expression is altered with estrogen, leading to a favorable lipid profile such as decreases in serum total cholesterol and low-density lipoprotein along with an increase in high-density lipoprotein. Estrogen is responsible for a wide range of vascular effects, from rapid vasodilation via nitric oxide, to a protective response to injury that prevents the development of atherosclerosis.[52]

Initial observational studies combined with this physiological data suggested a benefit with hormone replacement therapy (HRT). The largest observational sample is the Nurses' Health Study, which included 28 263 healthy postmenopausal women. The trial reported a 51% reduction in all-cause death in those taking HRT and a 40% decrease in cardiovascular deaths.[53] Since then, there have been several large randomized trials that have failed to confirm the cardioprotective benefit of HRT. In fact, HRT has been linked to an increase in the risk of CVD.[5] These data have changed the prescribing practice and led to guidelines cautioning against the routine use of HRT to decrease CVD risk in postmenopausal women.[54]

The increased risk of HRT on CVD has been clearly defined with several randomized trials; however, the effects of HRT in women with HF are not well established. A few observational studies suggested that this subpopulation may actually benefit with HRT, but randomized studies are conflicting.[20,55,56] Several HF-specific benefits of estrogen are noted. For instance, afterload reduction via the vasodilatory properties of estrogen can theoretically improve outcomes in HF. Also, estrogen abrogates several inflammatory cytokine pathways (including -tumor necrosis factor-α), which are abnormally elevated in the failing myocyte. This, in combination with the well-defined antiatherosclerotic and antifibrotic pathways on estrogen, may contribute to the positive effects noted in this population. The data examining HRT in women with HF remain an area that requires further scientific exploration.

Transplant and Mechanical Circulatory Support

According to a recent report on heart transplantation from the International Society for Heart and Lung Transplantation, 23% of patients who underwent heart transplantation between 2005 and 2010 were women.[57] Survival rates post-transplant were similar between men and women. The lower rates of transplantation in women may be partly explained by higher levels of panel reactive antibody in parous women, which makes identifying suitable donors more challenging. There is also a higher acceptance of patients for transplantation with an ischemic cause of cardiomyopathy, regardless of gender, which increases the proportion of men who undergo transplantation compared to women.[58] Female patients are also less likely to accept the option for heart transplantation.[59] Peak oxygen uptake (PVO_2) has traditionally been used to determine the timing of heart transplantation. Mancini et al showed that patients with a $PVO_2 \leq$ 14 mL/kg/min had poor outcomes and benefited from cardiac transplantation.[60] It has been demonstrated, however, that women have a significantly lower peak VO_2 than men, but better survival at all levels of exercise capacity.[61,62] This finding is most likely explained by the influence of muscle mass on peak VO_2, as well as a lower baseline metabolic rate and lower hemoglobin levels in women. Women with HF also tend to be of older age, as women develop HF later in life than men, and age may be impacting on lower PVO_2 findings. For women, the predicted peak VO_2 percentage may be a better prognostic marker.[23] Based on these findings, the International Society for Heart and Lung Transplantation has recommended using $\leq$50% predicted peak VO_2 as a listing criteria for heart transplantation in women.[23]

Implantable left ventricular assist devices (LVADs) have emerged as an important treatment option for patients with end-stage HF. Enrollment of women in trials involving first generation pulsatile-flow LVADs has ranged between 8% and 20%, primarily because many women did not have the body size to allow for implantation of the large pump housing of the pulsatile-flow LVADs.[63–65] Previous studies showed that pulsatile-flow LVADs showed worse survival rates and an increased need for right ventricular assist device implantation due to right HF in women compared to men.[66,67] With the development of smaller continuous-flow devices, slightly more women (19%–24%) were implanted in

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the initial trials,[5,68] with similar survival rates in both women and men.[69]

Conclusion

HF remains a significant healthcare concern for women in the United States. Large HF trials have under-represented women in their enrollment numbers, and this has limited our understanding of gender-related differences in HF pathophysiology, diagnosis, and treatment. Distinct differences in sex hormones and their effects on cardiovascular pathophysiology likely account for the differences between women and men with HF. Women with HF tend to be older and exhibit better left ventricular function compared to men. Women are also more likely to have hypertension and diabetes, and less likely to have coronary disease. In addition, at presentation, women are more symptomatic and describe worse quality of life than men with similar HF disease severity. In general, survival appears to be better for women with HF, with the possible exception of those patients with ischemic disease. Our current guidelines are not sex specific because of insufficient data, but as the therapeutic options for HF expand, sex-based differences in treatment may need to be considered. Further studies examining sex differences in HF are clearly warranted to confirm or establish benefits of existing and future treatments in women. Exclusion of potential pregnancy has limited enrollment of younger women in randomized clinical trials of medical therapy with concerns about fetal outcomes. Nonetheless, investigators must strive to include women in clinical trials at a rate commensurate with the prevalence of HF. The National Institutes of Health have a policy of inclusion of minorities in clinical trials; investigators need to formulate specific plans for the balanced recruitment of women as well. Further studies are needed to identify sex-specific differences and the role of endogenous estrogen in the evolution of the syndrome and perhaps as a basis for the differences that have been highlighted in this review.

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