abstract

Heart failure (HF) is an increasing problem in the older adult population, specifically among women. The majority of health care expenses are generated in the last few years of life, and hospitalization for HF is one of the major medical conditions influencing the expenditure. The nature of women's HF differs from men: coronary artery disease is the most common etiologic factor for HF in men while women more often suffer from hypertensive heart disease, which results in stiffness of the left ventricle with relaxation problems, and diastolic HF. Most commonly there is a long history of poorly controlled hypertension. In acute situations these patients often present with florid edema and congestion along with significantly elevated blood pressure levels, which are both challenging to treat.

This short review covers issues related to gender differences in etiology and epidemiology of HF, and evaluates current evidence for drug therapies.

Key words: *epidemiology, heart failure, gender, myocardial infarction, hypertension*

Gender and Congestive Heart Failure

Silja Majahalme, MD, PhD, FESC, *Cardiologist and Clinical Hypertension Specialist, Appleton Heart Institute/Appleton Cardiology Associates, Appleton, WI, USA.*

Introduction

Despite improvement of treatment options and understanding of the pathophysiology of heart failure (HF) the prevalence is still increasing. Estimates of the prevalence of symptomatic HF in the general European population range from 0.4% to 2%.[1] Based on the recent U.S. statistics,[2] the prevalence of HF among older women (>75 years) reached 10.9% and in men of the same age prevalence is 9.8%. Hospitalization for HF occurs more commonly in women. There were about one million hospital discharges due to HF in 2003 in the U.S., and women represented almost 60% of the patient population. In the U.S. the cost of HF in 2006 is estimated to reach almost 30 billion dollars. Guidelines for the treatment of HF are continuously updated as results from new clinical trials are incorporated into the dynamic process. Two important guidelines for diagnosis and treatment of HF were published in 2001: one by the ESC (European Society of Cardiology)[3] and a joint set of recommendations by the ACC/AHA (American College of Cardiology/American Heart Association), which was updated 2005.[4]

However, as with most guidelines, there are gaps between them and clinical practice. There are also gaps between guidelines and trial results published after the guidelines' publication. This article emphasizes the findings of the treatment gaps, and also evaluates the latest research results in HF treatment through a gender perspective.

Practice guideline recommendations for HF are summarized in Table 1.

Epidemiology and Etiology

HF is a growing problem among women, partially due to the rising number of older persons, more of whom are female. Based on recently published data from the Framingham Heart Study, subjects at age 40 (independent of gender) without HF had a one in five lifetime risk for developing congestive HF.[6] In the same study, at the age of 40, the lifetime risk of HF without myocardial infarction was 1 in 9 in men and 1 in 6 for women. This difference is attributed to hypertension being the most common etiology for HF in women, whereas myocardial infarction is the most common factor causing HF in men.[6] Unfortunately, hypertension—specifically systolic hypertension—is a very common problem in the older population, with prevalence reaching 83.4% in women aged 75 years and older and 69.2% in men 75 years and older. Hypertension is a treatable risk factor of congestive HF. Hypertension is adequately controlled in only 17.3% to 29.8% of U.S. adults. Even more concerning is that target blood pressure is achieved in only 17.6% of young adults (ages 20–39 years) compared to 31.4% in persons aged 60 years and older.[2]

The etiology of HF influences both the selection and outcome of the treatment. For example, when valvular disease is the cause of HF, surgery is considered curative. However, timing of the surgery and patient selection (including gender and comorbidities) play a major role in long-term outcomes. Women tend to be older and have more comorbities at the time of the cardiac surgery, resulting in a poorer outcome.[7] The benefit of drug therapy may also be related to etiology. For example, patients with nonischemic systolic HF may benefit from amlodipine while ischemic HF patients do not.[7]

Etiology of HF seems to influence

the mortality and morbidity differences between genders. Myocardial infarction as an etiologic factor for HF is detrimental for both genders, but especially for women: within six years of acute myocardial infarction 46% of women are disabled because of HF compared to a 22% rate of disability in men. HF is killing one in five during the first year of diagnosis independent of the gender. However, less than 15% of women live longer than 8–12 years after the diagnosis.[2]

There are variations between genders in mortality in different studies, probably reflecting etiology. In the Studies of Left Ventricular Dysfunction (SOLVD), which mostly included patients with previous myocardial infarction, mortality was higher in women.[8] In the Framingham Study women's survival was higher, probably because hypertension was more common as an etiologic factor among them and men more often had HF due to myocardial infarction.[9] In the post-hoc analysis of Systolic HF Trial with Valsartan (Val-HeFT),[10] mortality was lower in women than in men in the overall population. However, women had 8.8% increased risk of nonfatal morbidity compared to men. Furthermore, this risk was dramatically more elevated for women with primary etiology of coronary artery disease (26.6%) or with history of diabetes (21.1%). Differences between women and men in mortality and morbidity may also be related to differences in left ventricular function. Women tend to have better-preserved left ventricular systolic function despite having more frequent HF symptoms.[11]

Research Results of Treatment Differences

There continue to be significant gaps between clinical practice and guidelines. Large clinical trials have clearly shown the benefit of drug therapies in HF, particularly angiotensin-converting enzyme (ACE) inhibitors;[12] however, fewer than half of patients with HF in the community based surveys receive an ACE inhibitor.[13,14] Those receiving treatment are prescribed doses that are lower than shown to be effective in clinical trials. Furthermore, studies have demonstrated that women are less likely to be prescribed an ACE inhibitor than men[15,16] and women are less likely to be prescribed an optimal dose.[17] In the Val-HeFT trial, 89.5% of women and 93.5% of men were prescribed an ACE inhibitor. However, this difference in prescription rates was not statistically significant ($p<0.001$).[18]

Older adults of both genders, and women of all ages, tend to have HF with preserved systolic function. A study by Dauterman *et al.*[19] evaluated the effects of ACE inhibitor treatment in 1,720 patients hospitalized for HF, 45% of whom had reduced systolic function (ejection fraction <40%) and 55% had systolic function preserved (ejection fraction >40%). The preserved systolic function group had lower one-year mortality rates, but hospital readmission rates were similar for both groups. Further analyses found that

Table 1: Practice Guideline Recommendations for Heart Failure

	Heart failure stages			
	Stage A High risk	**Stage B** Structural disease No symptoms	**Stage C** Structural disease symptoms	**Stage D** Highly symptomatic All medications used
Patients	Hypertension Diabetes Atherosclerosis Obesity Metabolic syndrome	Myocardial infarction Hypertrophy Poor LV function Valvular disease	As stage B plus symptoms (shortness of breath, fatigue, poor exercise tolerance)	As C, but symptoms require ongoing hospitalization
Treatment Options	Optimization of risk factors with medications and life style modification	As in Stage A and ACEI/ARB always if no contraindications (renal failure, significant aortic stenosis, intolerance)	As in stage A and B Salt restriction Diurectics for fluid retention Selected patients: Aldosterone antagonists Digitalis, Hydralazine/nitrates	As in stages A–C End stage disease Consider: Hospice Selected patients: Biventricular pacers Transplantation Assisted devices Experimental drugs
	ACE inhibitor/ARB in Diabetes or with specific indications	Beta-blockers (postinfarction, LV dysfunction, valvular disease)		

ACE inhibitor = angiotensin converting enzyme, ARB = angiotensin receptor blockers, LV = left ventricular
Source: Modified from AHA/ACC.[4]

Key Points

- Heart failure (HF) is slightly more prevalent among older women (75 years and older) than men (10.9% vs. 9.8% in one U.S. study); hospitalization for HF occurs more commonly in women.
- Hypertension is the most common etiology for HF in women, whereas myocardial infarction is the most common factor causing HF in men.
- Etiology of HF seems to influence the mortality and morbidity differences between genders.
- Women tend to have better-preserved left ventricular systolic function despite having more frequent HF symptoms.
- Evidence supports the use of drug therapies such as ACE inhibitors, yet studies have demonstrated that women are less likely to be prescribed an ACE inhibitor than men and are more likely to be prescribed suboptimal doses.
- Many major clinical trials do not include an analysis by gender, and most HF studies underrepresent women.
- Current evidence supports that the majority of recommended drug therapies show equal efficacy for both genders, although women (specifically older women) are more prone to side effects.

the treatment with ACE inhibitors in patients with preserved systolic function was not associated with either a reduction in mortality or hospital readmissions for HF. Other studies have reported benefits in patients with preserved systolic function, so this issue must be considered unresolved at present.[20] No large-scale prognostic studies of preserved systolic function without acute myocardial infarction exist, and similarly no randomized treatment studies of HF with hypertension have been done.

One of the limitations in reaching any conclusions about gender differences in cardiovascular disease is that many major clinical trials do not include a gender analysis. In addition, women are under-represented in most of the HF studies that do include such an analysis. (One analysis found that only about 21% of study participants were women,[21] yet almost 60% of patients hospitalized for HF are women.[2])

It is possible, however, to draw some conclusions. Metoprolol CR/XL (slow release) has been shown to reduce mortality in men but not in women with congestive HF.[22] Likewise, digoxin may be associated with a higher risk of death among women than men with HF.[23] However, in the Val-Heft post-hoc analysis[10] valsartan reduced the adjusted relative risk of the combined mortality/morbidity end point by 16.1% (p=0.044) in women and by 12.8% (p=0.053) in men. Significant risk reductions with valsartan treatment were demonstrated for nonfatal morbid events in both women (25.8%, p=0.0129) and men (28.3%, p<0.001), primarily due to the decreased risk of HF hospitalizations (women: 21.9%, p=0.035; men: 29.4%, p<0.001).

Although no gender analyses of post–myocardial infarction HF studies exist, it seems that women get equal benefit from angiotensin receptor blockers (candesartan and valsartan) and selective aldosterone blockers. In the study evaluating eplerenone, a selective aldosterone blocker, almost 1,000 women were enrolled (30% of the study population). Eplerenone, in addition to standard HF therapy (guideline-based standard therapy includes ACEI, diuretics, and beta-blockers) showed a significant benefit over placebo for both men and women.[24] These findings confirm the results found with another aldosterone blocker, spironolactone (RALES study).[25] In this study only 27% of the study population were women. There were fewer side effects in eplerenone trial than in spironolactone trial, but caution is needed because this was not a head-to-head comparison. The most common side effect in both trials was hyperkalemia, which was more common in older adults and persons with lower body weight. This observation emphasizes the importance of careful follow-up of potassium, particularly in these patient populations. In the CHARM (Candesartan in Heart Failure) preserved trial 3,023 patients were randomly assigned to candesartan or placebo in addition to existing HF medications.[26] Patients had acute myocardial infarction and HF with preserved systolic function. This study included more women than the majority of other postmyocardial infarction HF studies—almost 40%. Hypertension as an additional etiologic factor (no gender-specific information was available) was found in 65%, and previous myocardial infarction in 45%. Although there was a trend for better primary outcome in the composite endpoint (cardiovascular mortality or HF hospital admissions) in the candesartan group, it did not reach statistical significance. Candersartan, however, reduced hospital admissions. Unfortunately no separate analysis comparing women and men was done.[26]

Conclusion

HF is a complex syndrome, and etiology influences both treatment options and outcomes. Similarly, gender has an impact on outcome, and etiology and comorbidities influence gender-specific outcomes. Current evidence suggests that the majority of recommended drug therapies are equally effective in both men and women, although older women are the group most prone to side effects.

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