EDITORIAL COMMENT

A Better Survival for Women With Heart Failure? It’s Not So Simple…*

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The value of experience is not in seeing much, but in seeing wisely.

—William Osler (1)

Good news! The incidence of heart failure (HF) in women has dropped by one-third from the 1950s through the 1990s but has remained unchanged in men over the same time period (2). This decline may be due to in part to the availability of antihypertensive medications and the increased recognition of elevated blood pressure levels among physicians, given that hypertension predominates in women as a risk factor for HF. Another possible explanation is the decrease in the incidence of rheumatic heart disease after the 1970s in the U.S., which had affected more women than men (3–5).

More good news! The 30-day mortality rate among women dropped from 18% in the 1950 to 1969 decades to 11% in 1990 to 1999. Moreover, the one- and five-year mortality in women also declined in the years 1950 to 1999 from 28% to 24% and from 57% to 45%, respectively (2). Therefore, women have an overall better survival than men with HF.

HF PRESENTATION IN WOMEN

Information about HF in women can be acquired from registries, from large group data (insurers/health plans), from statistical data of large organizations, or from clinical trials such as the Beta Blocker Evaluation of Survival Trial (BEST) about which Ghali et al. (6) report in this issue of the Journal. If we were only to review clinical trials, however, the number of women would appear to barely reach one-third of all HF patients (7–23) (Table 1). Yet in registries, health plans, and national statistics, such as the American Heart Association Statistics, the number of women with HF approaches one-half of all diagnosed patients (24). Rather than speculate on the reasons for the under-representation of women in trials, there is a lot to be learned from these same clinical trials.

Discrepancies between the presentation of men and women with HF are worth noting (25). Women with HF present at an older age and have a lower prevalence of ischemic heart disease and previous myocardial infarction than men and are more likely to have systemic hypertension (26). When controlling for ischemic disease, women are less likely to have undergone coronary bypass surgery. When suffering a myocardial infarction, women are more likely than men to develop HF (26,27). More women than men with HF also have diabetes as an additional comorbidity (28). In addition, diabetic women have two to four times the cardiovascular mortality than women without diabetes (24).

On presentation, women with HF are more symptomatic than men with a greater degree of edema, a third heart sound, murmurs, and more noticeable jugular venous distension (29). In addition, health-related quality of life is low in women who are admitted with HF when compared with men and has a smaller improvement over the hospitalization (30). When controlling for New York Heart Association functional class, women have a greater impairment in daily living activities, which usually require low level effort and, therefore, are less functional than men (31).

In the U.S., hospitalization rates for HF have increased from 377,000 in 1979 to 962,000 in 1999 (24). When hospitalized for HF, women have a longer length of stay, leading to higher costs, less involvement by cardiology specialists, and a higher in-patient mortality (32). In the Studies Of Left Ventricular Dysfunction (SOLVD) trials, female gender was one of the factors associated with hospitalization for HF and one-year mortality (28,33).

HF THERAPY IN WOMEN

Given the discrepancies of presentation, burden of disease, etiology, and hospitalizations between men and women, it is necessary to assess the benefits of medical therapy and its impact on disease progression and mortality. Although HF trials have underrepresented women, they do provide important data, in subgroup analysis, which should help clinicians recommend therapy to their female patient population.

Angiotensin-converting enzyme (ACE) inhibitors. Preliminary analysis of the SOLVD data suggested that women had a lesser benefit from the ACE inhibitor, enalapril, than the men in the treatment arm of the trial (34). A recent meta-analysis of ACE inhibitors in both treatment and prevention trials reported that women did benefit from ACE inhibition in treatment trials, although the benefits...
were attenuated (35). However, a significant mortality benefit from ACE inhibitors in prevention trials was not noted for women. The differences, however, did not reach statistical significance and may be attributable to the small number of women in the trials. Although ACE inhibitors should be the standard of care for HF patients, less women may be receiving these agents in practice. In the Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF), fewer women were receiving an ACE inhibitor at entry into the trial than their male counterparts (MERIT-HF women). This difference was not observed in the BEST trial (36).

**Beta-blockers.** Beta-blockers have become important therapeutic agents in patients with HF who are on ACE inhibitors. Although the number of women in the large beta-blocker trials with carvedilol or metoprolol succinate (extended release) has been limited, the benefits have been definitive in mortality reduction and equal for both men and women (36,37).

**Digoxin.** In the Digitalis Investigation Group trial, digoxin failed to show an improvement in overall survival but did result in a reduction in hospitalization rates when compared with placebo (23). However, a recent post-hoc analysis of the data showed that women may have an increased risk of death with digoxin and a smaller improvement in hospitalization rate (38). This difference could be due to a smaller body mass in women and, therefore, a higher comparable blood level of digoxin (39).

### Table 1. Women in Heart Failure Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Number of Women</th>
<th>Percentage of Women</th>
</tr>
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<tbody>
<tr>
<td>V-HeFT-I (7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>V-HeFT-II (8)</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>CONSENSUS-I (9)</td>
<td>253</td>
<td>75</td>
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<tr>
<td>SOLVD-T (10)</td>
<td>2,569</td>
<td>504</td>
<td>23</td>
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<tr>
<td>SOLVD-P (11)</td>
<td>4,228</td>
<td>476</td>
<td>31</td>
</tr>
<tr>
<td>ELITE-I (12)</td>
<td>722</td>
<td>240</td>
<td>31</td>
</tr>
<tr>
<td>ELITE-II (13)</td>
<td>3,152</td>
<td>966</td>
<td>30</td>
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<td>MERIT-HF (14)</td>
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<td>CIBIS II (15)</td>
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<td>COPERNICUS (16)</td>
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<td>Val-HeFT (17)</td>
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<td>RALES (18)</td>
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<td>SAVE (19)</td>
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<td>TRACE (20)</td>
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<td>SCD HeFT (22)</td>
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<td>DIG (23)</td>
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<tr>
<td>Total</td>
<td>47,422</td>
<td>10,907</td>
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</table>

CHARM = Candesartan in Heart Failure-Assessment of Reduction in mortality and morbidity; CIBIS II = Cardiac Insufficiency Bisoprolol Study II; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; DIG = Digitalis Investigation Group; ELITE = Evaluation of Losartan in the Elderly; MERIT-HF = Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure; RALES = Randomized Aldactone Evaluation Study; SAVE = Survival and Ventricular Enlargement; SCD HeFT = Sudden Cardiac Death Heart Failure Trial; SOLVD-T = Studies of Left Ventricular Dysfunction Prevention trial; SOLVD-P = Studies of Left Ventricular Dysfunction Treatment trial; TRACE = Trandolapril Cardiac Evaluation; Val-HeFT = Valsartan Heart Failure Trial; V-HeFT = Vasodilator Heart Failure Trial I and II.

**Figure 1.** Cardiovascular disease mortality trends for males and females, U.S., 1979 to 2000. Reprinted with permission from the American Heart Association. Source: CDC/CHS. Black line = males; white line = females.

### THE BEST TRIAL

Ghali et al. (6) describe the female cohort in the BEST trial. Features of the women in BEST are consistent with those of other reports, such as a higher ejection fraction, lower prevalence of atrial fibrillation, and a lower presence of ischemic disease. As in the parent trial, the women in the bucindolol group did not have an improvement in survival when compared with placebo. The crude mortality in women was overall lower when compared with the men. Nonetheless, those women with ischemic disease did not enjoy the same survival benefits over men as those with non-ischemic disease. The investigators should be congratulated in going beyond the simple mortality rates and examining in more detail the women with ischemic disease. Taken separately, women with an ischemic etiology for HF had a different course, with a 2.5-fold increase in the risk of death compared with a 1.5-fold increase in men. Ghali et al. (6) offer various hypotheses for this mortality difference. The answer is not clear but should stimulate more research into gender differences in HF. Adams et al. (40) had already reported that the mortality was similar for men and women when HF was due to ischemic disease and that the mortality benefit for women was only in the dilated cardiomyopathy group. Their data, however, were derived from a HF clinic experience where selection bias due to referrals could exist. The current findings in the BEST trial confirm the observations of Adams et al. (40) in a larger number of women enrolled in a multicenter, randomized, double-blind trial.

### WHAT DOES THE FUTURE HOLD?

With the continuing increase in the prevalence of obesity (41), the already high prevalence of smoking among women, the prevalence of hypertension in women, and an ever increasing number of diabetics in the U.S. (33% increase in men and women from 1990 to 1998) (24), the number of women with ischemic disease will only continue to grow. Today, cardiovascular disease claims the lives of more women than men, and the gap is widening even further (Fig. 1). Clinicians cannot afford to be less aggres-
sive in prescribing medical therapy to their women patients with HF when compared with the men. Furthermore, we can no longer be complacent in attempting to stem the tide by using measures of prevention, although efforts in this arena have been traditionally focused on men. These primary prevention measures need to be implemented in women as well. Extensive national campaigns, for example, the American Heart Association "Women's Heart Day," need to be supported by local communities. Other such measures could include the dissemination of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (42) to the female lay public, programs that address weight reduction coupled to information on exercise and targeting of these programs to women groups, and community-based smoking cessation programs, among others. The advocates for dissemination of breast cancer awareness have been highly successful in spreading their message. Should we not do the same?

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