Gender Differences in Survival in Advanced Heart Failure

Insights From the FIRST Study

Kirkwood F. Adams, Jr, MD; Carla A. Sueta, MD, PhD; Mihai Gheorghiade, MD; Christopher M. O’Connor, MD; Todd A. Schwartz, BA; Gary G. Koch, PhD; Barry Uretsky, MD; Karl Swedberg, MD; William McKenna, MD; Jordi Soler-Soler, MD; Robert M. Califf, MD, for the FIRST Investigators

Background—Previous natural history studies in broad populations of heart failure patients have associated female gender with improved survival, particularly in patients with a nonischemic etiology of ventricular dysfunction. This study investigates whether a similar survival advantage for women would be evident among patients with advanced heart failure.

Methods and Results—The study analysis is based on the Flolan International Randomized Survival Trial (FIRST) study which enrolled 471 patients (359 men and 112 women) who had evidence of end-stage heart failure with marked symptoms (60% NYHA class IV) and severe left ventricular dysfunction (left ventricular ejection fraction 18±4.9%). A Cox proportional-hazards model, adjusted for age, gender, 6-minute walk, dobutamine use at randomization, mean pulmonary artery blood pressure, and treatment assignment, showed a significant association between female gender and better survival (relative risk of death for men versus women was 2.18, 95% CI 1.39 to 3.41; \(P\) < 0.001). Although formal interaction testing was negative (\(P\) = 0.275), among patients with a nonischemic etiology of heart failure, the relative risk of death for men versus women was 3.08 (95% CI 1.56 to 6.09, \(P\) = 0.001), whereas among those with ischemic heart disease, the relative risk of death for men versus women was 1.64 (95% CI 0.87 to 3.09, \(P\) = 0.127).

Conclusions—Women with advanced heart failure appear to have better survival than men. Subgroup analysis suggests this finding is strongest among patients with a nonischemic etiology of heart failure. (Circulation. 1999;99:1816-1821.)

Key Words: sex ■ heart failure ■ survival

Natural history studies have suggested important differences in survival between men and women in patient populations with a broad spectrum of heart failure severity.1–4 The population-based Framingham Heart Study found that the prognosis of women was significantly better than men after the onset of symptomatic heart failure.5,6 Previous work using the UNC Heart Failure Database also demonstrated better survival during follow-up in women than men with heart failure.7,8 Additional analysis of the UNC dataset indicated that the improved outcome in women was restricted to patients with heart failure resulting from nonischemic causes.

Although this previous work suggested a gender difference in survival, whether women would have a mortality advantage in specific subsets of heart failure patients has not been well studied. The present study used data from the Flolan International Randomized Survival Trial (FIRST) to determine if a survival advantage for women would be present in patients with advanced heart failure. Better prognostic models are needed in advanced heart failure, an important subset of patients with circulatory dysfunction, characterized not only by severe biventricular dysfunction but also by unrelenting clinical symptoms, a high mortality rate, and frequent hospitalization.

In addition, controversy continues concerning the origin of the gender difference in prognosis in heart failure. Given the nature of previous patient populations, discordant outcomes could simply reflect disparities between men and women in duration of heart failure, medical compliance, or prognostic factors not determined at baseline. Use of the FIRST data seems likely to reduce the influence of these clinical factors. Because of the complicated nature of epoprostenol therapy, the study enrolled patients who were predominantly NYHA functional class IV with noninvasive and invasive evidence of profound cardiac dysfunction. Heart failure was typically longstanding and severe by multiple entry criteria that were the same for both men and women. Careful and frequent

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From the University of North Carolina at Chapel Hill (K.F.A., C.A.S., T.A.S., G.G.K.); Northwestern University Medical School (M.G.), Chicago, Ill; Duke University Medical Center (C.M.O., R.M.C.), Durham, NC; The University of Texas Medical Branch at Galveston (B.U.); Ostra University Hospital and Goteborg University (K.S.), Goteborg, Sweden; St. George’s Hospital Medical School (W.M.), London, UK; Hospital Universitari Vall D’Hebron (J.S.-S.), Barcelona, Spain.

Reprint requests to Kirkwood F. Adams, Jr, MD, Division of Cardiology, University of North Carolina at Chapel Hill, CB# 7075, Burnett-Womack Building, Chapel Hill, NC 27599-7075. E-mail kfa@med.unc.edu

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follow-up was built into the protocol for all study patients. Although specific formal measures of compliance were not determined, this study design would work to maximize similar medical treatment and compliance in both genders. The extensive clinical and functional evaluation at baseline allowed many characteristics of heart failure to be considered in the statistical analyses of male-female differences in survival. Thus, the present study was able to carefully investigate the relationship between gender and survival in patients with advanced heart failure. In addition, the relationship between etiology and any gender-associated difference in survival was examined using traditional interaction testing and stratified analysis.

Methods

Design of Protocol
The design of the FIRST study has been reported in detail elsewhere. Briefly, a total of 471 patients with NYHA functional class IIIB or IV heart failure for at least 1 month on a regimen including a loop diuretic, digitalis glycoside, and angiotensin converting enzyme inhibitor, unless contraindicated, were randomized in the study. Additional entry criteria included a left ventricular ejection fraction of <25% (or <30% if on an inotropic infusion) obtained within 3 months of enrollment and a cardiac index <2.2 L min⁻¹ m⁻²; a pulmonary artery wedge pressure >15 mm Hg was required in all patients except those on intravenous vasoactive medications. Before randomization, patients underwent a battery of baseline noninvasive tests, including a 6-minute walk test. On the basis of clinical findings, each patient was assigned 1 of 4 potential factors (ischemic, hypertensive, idiopathic, or other) as the primary cause of heart failure. Patients were randomized to receive either intravenous epoprostenol (flolan) plus standard management for heart failure or standard management for heart failure alone. Patients returned for follow-up at 2 weeks and 1 month after randomization and at monthly intervals after that time. Home health care visits occurred on a monthly basis in both placebo- and epoprostenol-treated patients and were staggered with the clinic follow-up so that patients were seen at least twice a month throughout the study. Vital status was known for all patients, as none were lost to follow-up.

Statistical Methods

Data are presented as the mean±SD unless otherwise indicated. Differences in categorical and continuous variables between men and women were assessed by the χ² test or Student’s t test, as appropriate. Data on the 6-minute walk test were analyzed using the 457 patients who had actual values for distance walked (n=25, 65%). The results of the 6-minute walk test were also related to exercise capacity, determined by the 6-minute walk test, and were staggered with the clinic follow-up so that patients were seen at least twice a month throughout the study. Vital status was known for all patients, as none were lost to follow-up.

Characteristics to survival. Each significant predictor identified by this analysis was subsequently tested in a backward selection process with all candidate variables forced into the model. The following baseline clinical characteristics were considered along with gender in the modeling procedure: age, race, indices of habitus (height, weight, body surface area, body mass), geographic location (by continent), primary cause of heart failure, NYHA functional class, use of dobutamine at baseline, history of diabetes, duration of heart failure, atrial fibrillation, serum sodium, serum creatinine, cardiac index, pulmonary artery wedge pressure, right atrial pressure, systolic blood pressure, mean pulmonary artery pressure, heart rate, left ventricular ejection fraction, 6-minute walk test results, and randomized treatment assignment to epoprostenol plus standard therapy or standard therapy alone. The final multivariate analysis included the 430 study patients who had data available for all the significant baseline characteristics. Unadjusted Cox analysis was also undertaken to assess the univariate relationship between gender and survival. To permit comparison with the multivariate modeling, this unadjusted analysis was based on the 430 study patients with complete data as survival analysis; interaction testing indicated that baseline data were not missing at random. This testing revealed significantly poorer survival in the 41 study patients with missing data versus the 430 patients with complete data. The influence of cause on gender-related differences in survival was assessed by formal interaction testing and by stratified analysis. In the stratified analysis, the predictive model developed for the entire study population was tested in subgroups of study patients defined by an ischemic or nonischemic cause of heart failure.

Results

Patient Characteristics
A variety of invasive and noninvasive measurements demonstrated the advanced nature of the heart failure present in patients enrolled in the FIRST trial. The majority were NYHA functional class IV (60%) with severe reduction in resting left ventricular ejection fraction (18±4.9%), marked depression of cardiac index (1.8±0.3 L min⁻¹ m⁻²), and elevation of pulmonary artery wedge pressure (26±7.4 mm Hg).

Analysis of demographic and clinical characteristics of men and women in the FIRST trial revealed several differences (Table 1). Men were more likely than women to be white and to have ischemic heart disease as the primary cause of their heart failure. There were trends for NYHA functional class and dobutamine use tended to be lower in men. Left ventricular ejection fraction was similar in the 2 genders. Invasive hemodynamic measurements demonstrated a lower cardiac index and higher pulmonary artery wedge pressure in men, but the absolute differences were minor. There was no difference in the reported duration of heart failure between men and women.

Exercise capacity, determined by the 6-minute walk test, was significantly greater in men than in women (Table 1). The results of the 6-minute walk test were also related to differences in habitus between men and women. Walk test results correlated significantly with body weight, but the strength of the relationship was weak (r=0.142, P=0.003). Regression modeling to determine the role of habitus and gender as predictors of the 6-minute walk results revealed that gender (P=0.001) but not weight (P=0.522), height (P=0.382), body mass (P=0.997), or body surface area (P=0.454) were significant independent predictors of 6-minute walk results.

Survival for Men Versus Women

Unadjusted analysis by the Cox proportional-hazards method found a strong trend for poorer survival in men compared with women (relative risk of death for men versus women 1.48, 95% CI 0.96 to 2.28, P=0.074; Figure 1).

Results of multivariate modeling of survival in the study population by the Cox method are shown in Table 2. Female gender was found to be a significant independent predictor of better survival after consideration of numerous baseline clinical characteristics (relative risk of death for men versus women 2.18, 95% CI 1.39 to 3.41, P<0.001). Figure 2 shows the survival curve for men and women in the FIRST study.
after adjustment for age, 6-minute walk, dobutamine use at randomization, mean pulmonary artery blood pressure, and treatment assignment—characteristics demonstrated to be independent predictors of survival in the FIRST study population (Table 2). The association between female gender and better survival persisted when characteristics that differed at baseline between men and women but were not present in the final survival model (Table 1) were forced into a multivariate analysis (relative risk of death for men versus women 2.47, 95% CI 1.43 to 4.25, \( P < 0.001 \)).

Additional analyses supported the finding in the multivariate modeling that female gender was associated with better survival. Although distance walked normalized for body weight is imperfect as a correction for gender-related differences, men remained at increased risk of death (relative risk of death for men versus women 1.96, 95% CI 1.25 to 3.06, \( P < 0.003 \)). Female gender was also found to be a predictor of better survival in several analyses which did not adjust for differences between men and women in the 6-minute walk test. Multivariate modeling was performed with all the significant independent predictors of survival (Table 2) except the 6-minute walk test results. Men still had poorer survival than women in this analysis (relative risk of death for men versus women 1.63, 95% CI 1.05 to 2.53, \( P = 0.031 \)).

**TABLE 1. Baseline Characteristics of Men and Women**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
<th>( n )</th>
<th>( n )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64 ± 10</td>
<td>64 ± 11</td>
<td>331</td>
<td>99</td>
<td>0.666</td>
</tr>
<tr>
<td>White, %</td>
<td>86</td>
<td>74</td>
<td>331</td>
<td>99</td>
<td>0.004</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III, %</td>
<td>44</td>
<td>35</td>
<td>147</td>
<td>35</td>
<td>0.110</td>
</tr>
<tr>
<td>IV, %</td>
<td>56</td>
<td>64</td>
<td>184</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>HF, yrs</td>
<td>5.3 ± 4.8</td>
<td>5.7 ± 4.7</td>
<td>329</td>
<td>97</td>
<td>0.484</td>
</tr>
<tr>
<td>Cause of HF IHD primary, %</td>
<td>67</td>
<td>44</td>
<td>331</td>
<td>99</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dobutamine use, %</td>
<td>14</td>
<td>21</td>
<td>331</td>
<td>99</td>
<td>0.093</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>34</td>
<td>36</td>
<td>330</td>
<td>99</td>
<td>0.697</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>24</td>
<td>15</td>
<td>327</td>
<td>98</td>
<td>0.082</td>
</tr>
<tr>
<td>CI, L/min⁻¹·m²</td>
<td>1.8 ± 0.5</td>
<td>1.9 ± 0.5</td>
<td>328</td>
<td>98</td>
<td>0.058</td>
</tr>
<tr>
<td>PAWP, mm Hg</td>
<td>27 ± 7.6</td>
<td>25 ± 7.1</td>
<td>314</td>
<td>95</td>
<td>0.023</td>
</tr>
<tr>
<td>PAPm, mm Hg</td>
<td>38 ± 9.1</td>
<td>35 ± 8.6</td>
<td>331</td>
<td>99</td>
<td>0.004</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>86 ± 16</td>
<td>90 ± 17</td>
<td>330</td>
<td>99</td>
<td>0.050</td>
</tr>
<tr>
<td>LVEF, U</td>
<td>18 ± 4.8</td>
<td>18 ± 5.3</td>
<td>331</td>
<td>99</td>
<td>0.954</td>
</tr>
<tr>
<td>6-minute walk, m</td>
<td>192 ± 127</td>
<td>129 ± 113</td>
<td>331</td>
<td>99</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174 ± 12</td>
<td>158 ± 13</td>
<td>329</td>
<td>99</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76 ± 17</td>
<td>64 ± 14</td>
<td>328</td>
<td>98</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.9 ± 0.2</td>
<td>1.6 ± 0.2</td>
<td>328</td>
<td>98</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26 ± 13</td>
<td>26 ± 14</td>
<td>328</td>
<td>98</td>
<td>0.741</td>
</tr>
</tbody>
</table>

\( n \) was based on the 430 patients used for the unadjusted and adjusted survival analysis. Results shown as mean ± SD where appropriate.

HF indicates heart failure; IHD, ischemic heart disease; CI, cardiac index; PAWP, pulmonary artery wedge pressure; PAPm, mean pulmonary artery pressure; HR, heart rate; LVEF, left ventricular ejection fraction; BSA, body surface area; BMI, body mass index.

**TABLE 2. Significant Predictors of Survival in the FIRST Study Population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted ( \chi^2 )</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>11.5</td>
<td>2.18</td>
<td>1.39–3.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6-minute walk*</td>
<td>49.5</td>
<td>0.995</td>
<td>0.993–0.996</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dobutamine use</td>
<td>20.6</td>
<td>2.47</td>
<td>1.67–3.65</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PAPm†</td>
<td>9.7</td>
<td>1.03</td>
<td>1.01–1.05</td>
<td>0.002</td>
</tr>
<tr>
<td>Age/year‡</td>
<td>7.4</td>
<td>1.03</td>
<td>1.01–1.04</td>
<td>0.007</td>
</tr>
<tr>
<td>Epoprostenol use</td>
<td>6.3</td>
<td>1.52</td>
<td>1.09–2.11</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*Risk ratio is for each meter increase in 6-minute walk distance.
†Risk ratio is for each mm Hg increase in PAPm.
‡Risk ratio is for each year increase in age.
The survival advantage for women persisted after follow-up, after adjusting for a number of baseline clinical characteristics that were significant independent predictors of survival in the study population.

Two alternative approaches analyzed gender differences in subgroups of men and women from the study population without adjustment for 6-minute walk results. First, adjusted modeling tested for gender differences in survival in the lowest sex-specific tertiles for distance walked (<37 m for women and <125 m for men). In this analysis, all significant predictors in the survival model were included except for distance walked. The relative risk of men for death was 1.95 with a strong trend toward significance (95% CI 0.96 to 3.98, P = 0.065). In the second approach, a risk score for each patient was computed on the basis of parameter estimates for each of the 5 main effects in a Cox proportional-hazards model (dobutamine use, age, 6-minute walk, mean pulmonary artery blood pressure, and epoprostenol use). These risk scores were divided into tertiles and the possibility of a gender effect was tested in an unadjusted manner in the highest risk tertile using the log-rank statistic. In this analysis, a significant effect of gender was again noted with men having poorer survival (P = 0.002).

Formal interaction testing of the relationship between clinical cause of heart failure and the association of gender with outcome was not significant (P = 0.275). A stratified analysis, performed on the basis of whether the primary cause of heart failure was ischemic or nonischemic, yielded results shown in Figure 3. Among patients with a nonischemic etiology of heart failure, the relative risk of death for men versus women was 3.08 with a 95% CI of 1.56 to 6.09; P = 0.001. In contrast, in patients with an ischemic cause, the relative risk of men versus women was 1.64 with a 95% CI of 0.87 to 3.09; P = 0.127.

**Discussion**

Our results suggest, for the first time, a significant gender-related difference in survival between men and women with advanced heart failure. Using data from the FIRST study, we found that men were more likely than women to die during follow-up, after adjusting for a number of baseline clinical characteristics that influenced mortality risk in this population. The survival advantage for women persisted after modeling that considered other clinical characteristics, including race, that differed between the genders at baseline. Our analysis also suggests that the better prognosis of women is related, in part, to the underlying cause of heart failure. On the basis of our previous work, we performed a stratified analysis of the relationship between gender and survival based on whether an ischemic or nonischemic cause of heart failure was present. The survival advantage of female gender was evident in the nonischemic but not the ischemic subgroup (Figure 3). However, we believe our findings concerning the influence of cause must be viewed with some caution. Formal interaction testing concerning the influence of cause on the gender association with survival was not statistically significant. Additional studies of larger groups of patients with advanced heart failure will be necessary to reach definitive conclusions concerning the role that cause might play in modulating gender differences in survival.

There are several unique aspects of the FIRST study population which enhance the likelihood that biological differences are an important cause of the survival difference we observed between men and women. In contrast to previous studies, mortality in women was lower despite an advanced degree of heart failure which was long-standing in both sexes. This clinical picture argues that our study findings did not result from differences in the timing of presentation with heart failure between men and women. Disparities in the intensity of care and compliance among men and women in the FIRST study cannot be fully ruled out. However, the close follow-up built into the design of the FIRST study seems to make this a less likely explanation for the survival advantage of women than might be the case for standard database studies.

**Gender and Cardiac Physiology**

A growing body of basic and clinical data points to fundamental gender-related differences in the nature and extent of myocardial hypertrophy and adaptation, which might account for the survival advantage for women. Early studies of
spontaneously hypertensive rats by Pfeffer et al suggested that the adverse influence of hypertrophy on cardiac function was greater in male than female rats.\textsuperscript{14} Currently, several preliminary but novel basic laboratory studies using classic techniques and methods from molecular biology are providing new support for gender differences in cardiac hypertrophy and function. Typical of this work, Lorell and Weinberg reported gender differences in upregulation of left ventricular angiotensin-converting enzyme activity during pressure overload hypertrophy.\textsuperscript{15} Pelzer et al found that male neonatal rat cardiomyocytes had a significantly greater increase in total protein synthesis and upregulation of several hypertrophic marker genes in response to norepinephrine compared with female neonatal cardiomyocytes.\textsuperscript{16}

Several studies of human cardiac hypertrophy and heart failure have produced clinical correlates for the gender differences in cardiac growth and adaptation observed in the laboratory. Carrol et al suggest that gender may influence the nature of left ventricular adaptation in patients with aortic stenosis.\textsuperscript{17} They found that elderly women with severe aortic stenosis tended to have well-preserved systolic function with less ventricular dilatation and hypertrophy than their male counterparts. Devereux et al reported that hypertensive women are more likely than hypertensive men to have left ventricular hypertrophy when a sex-specific 97th-centile upper limit of normal is used to define increased myocardial mass.\textsuperscript{18} Although many patients had preserved systolic function, Echeverria et al found that left ventricular function was better in women than men in 50 consecutive patients presenting for echocardiographic evaluation of congestive heart failure.\textsuperscript{19} Thus, a growing body of basic and clinical evidence points to fundamental differences in cardiac physiology and hypertrophy that could possibly account for the survival advantage for women with heart failure.

Previous Work
The findings reported here extend and are consistent with previous work suggesting (1) gender differences in survival in broad populations of men and women with heart failure\textsuperscript{2,3,9} and (2) that the gender-related difference is dependent on the underlying cause of heart failure.\textsuperscript{4,10} In contrast to previous reports,\textsuperscript{4,11} we did not find resting left ventricular ejection to be higher in women versus men in the FIRST population. Invasive hemodynamic data revealed only minor differences in cardiac index and filling pressure between men and women.

Potential Limitations
Several potential limitations concerning our study findings need to be addressed. Our study presents a post hoc analysis of gender differences among patients in a trial that was stopped prematurely. The subjects included in the study were not consecutive patients with heart failure but were selected because they met specific criteria for advanced heart failure. Use of the FIRST study population creates the potential for bias. However, the trial structure does have the advantage of applying a uniform criteria for the diagnosis of advanced heart failure in both men and women. Definitions of advanced heart failure may vary; however, entry criteria for the FIRST study documented the presence of end-stage heart failure on the basis of multiple clinical characteristics. Statistical significance for the association of gender and survival was evident in multivariate modeling. Multivariate analysis is classically used to demonstrate the prognostic importance of the characteristic of interest (in this case gender) through adjustment for baseline imbalances in other important prognostic factors. The present multivariate analysis adjusts, in part, for 6-minute walk results, which would be inappropriate if intrinsic differences in exercise performance on the walk test existed between men and women. However, the strong association between 6-minute walk results and survival in the FIRST population suggests that disease severity, not gender, was the prime determinant of walk test results. In addition, a variety of statistical approaches (detailed in Results) demonstrates that the association between gender and survival was not solely dependent on adjustment for the walk test results.

There are potential limitations concerning the stratified analysis comparing survival of men and women in ischemic versus nonischemic etiologic groups. The etiologic classification in the FIRST study was based on the clinical assessment of the study investigators. Specific data on coronary angiography were not collected. The possibility exists that an ischemic cause for heart failure went undetected in some of study patients, causing their misclassification into the nonischemic subgroup. However, such misclassification might be assumed to create bias against the detection of a survival difference based on ischemic versus nonischemic cause.

Information on neurohormonal and menopausal status was not available in the FIRST study patients. Thus, gender differences in activation of the renin-angiotensin or sympathetic systems that might account for the survival advantage of women cannot be excluded. Given the advanced age of the women in the study, most were likely postmenopausal. However, specific data on this point were not collected nor was the frequency of hormonal replacement therapy noted. Further studies will be needed to determine the relationship, if any, between menopausal status or hormonal replacement therapy and the survival advantage of women with advanced heart failure.

Conclusions
Women with advanced heart failure appear to have better survival than men. Subgroup analysis suggests this finding is strongest among patients with a nonischemic cause of heart failure. Better understanding of the biological and psychosocial factors which contribute to the survival advantage of women with heart failure may ultimately allow improved management of patients with this deadly syndrome.

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References


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