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Gender Differences in Advanced Heart Failure: Insights From the BEST Study

Jalal K. Ghali, MD,* Heidi J. Krause-Steinrauf, MS,† Kirkwood F. Adams, JR, MD,‡ Steven S. Khan, MD,§ Yves D. Rosenberg, MD,† Clyde W. Yancy, JR, MD,‖ James B. Young, MD,¶ Steven Goldman, MD,# Mary Ann Peberdy, MD,** JoAnn Lindenfeld, MD††

Shreveport, Louisiana; Bethesda, Maryland; Chapel Hill, North Carolina; Los Angeles, California; Dallas, Texas; Cleveland, Ohio; Tucson, Arizona; Richmond, Virginia; and Denver, Colorado

OBJECTIVES The goal of this study was to determine the influence of gender on baseline characteristics, response to treatment, and prognosis in patients with heart failure (HF) and impaired left ventricular ejection fraction (LVEF).

BACKGROUND Under-representation of women in HF clinical trials has limited our understanding of gender-related differences in patients with HF.

METHODS The impact of gender was assessed in the Beta-Blocker Evaluation of Survival Trial (BEST) which randomized 2,708 patients with New York Heart Association class III/IV and LVEF ≤0.35 to bucindolol versus placebo. Women (n = 593) were compared with men (n = 2,115). Mean follow-up period was two years.

RESULTS Significant differences in baseline clinical and laboratory characteristics were found. Women were younger, more likely to be black, had a higher prevalence of nonischemic etiology, higher right and left ventricular ejection fraction, higher heart rate, greater cardiothoracic ratio, higher prevalence of left bundle branch block, lower prevalence of atrial fibrillation, and lower plasma norepinephrine level. Ischemic etiology and measures of severity of HF were found to be predictors of prognosis in women and men. However, differences in the predictive values of various variables were noted; most notably, coronary artery disease and LVEF appear to be stronger predictors of prognosis in women. In the nonischemic patients, women had a significantly better survival rate compared with men.

CONCLUSIONS In HF patients with impaired LVEF, significant gender differences are present, and the prognostic predictive values of some variables vary in magnitude between women and men. The survival advantage of women is confined to patients with nonischemic etiology. (J Am Coll Cardiol 2003;42:2128–34) © 2003 by the American College of Cardiology Foundation

The differential impact of gender on the occurrence, presentation, prognosis, and response to treatment in cardiovascular diseases has received considerable attention in the past decade (1–3). Under-representation of women, however, has been a consistent finding in clinical trials (4,5),

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including heart failure (HF) (6–8) trials, which has resulted in several challenges to clinicians and investigators including lack of appreciation of the differences in clinical characteristics between men and women, and limitation on the ability to analyze various clinical and laboratory variables that could serve as markers and, potentially, determinants of survival in women with HF.

The Beta-Blocker Evaluation of Survival Trial (BEST), following National Heart, Lung, and Blood Institute guidelines (9), placed special emphasis on recruitment of women, and randomization was stratified by etiology, left ventricular ejection fraction (LVEF), ethnicity, and gender. The large number of women enrolled in BEST, the extensive characterization of many important baseline clinical and laboratory characteristics, and randomization by gender provide an opportunity to delineate gender differences in HF. This report details the BEST experience in women with HF.

METHODS

The study design was reported (10). All patients had New York Heart Association (NYHA) class III or IV HF with an LVEF ≤0.35, and gave written informed consent. The protocol was approved by each participating site's institutional review board.

Randomization to the beta-blocker bucindolol or placebo was stratified at each clinical site by etiology of HF (presence or absence of coronary artery disease [CAD]),

From the *Cardiac Centers of Louisiana, Shreveport, Louisiana; †National Heart, Lung, and Blood Institute, Bethesda, Maryland; ‡University of North Carolina, Chapel Hill, North Carolina; §Cedars-Sinai Medical Center, Los Angeles, California; ‖University of Texas Southwestern, Dallas, Texas; ¶Cleveland Clinic Foundation, Cleveland, Ohio; #Tucson Veteran Affairs Medical Center, Tucson, Arizona; **Virginia Commonwealth University, Medical College of Virginia, Richmond, Virginia; and ††University of Colorado Health Science Center, Denver, Colorado.
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Abbreviations and Acronyms

Afib = atrial fibrillation
BEST = Beta-Blocker Evaluation of Survival Trial
BMI = body mass index
CAD = coronary artery disease
CTR = cardiothoracic ratio
HF = heart failure
LBBB = left bundle branch block
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
PNE = plasma norepinephrine
RVEF = right ventricular ejection fraction
VA = Veteran's Administration

LVEF (>0.20 vs. ≤0.20), gender, and ethnicity (black vs. non-black).

The trial was conducted at 30 Veterans Administration Hospital (VA) sites, and 60 non-VA sites. A total of 24,933 patients were screened, including 20,343 males and 4,590 females. Of those, 2,708 (11%) were randomized, including 2,115 (10%) males and 593 (13%) females. Enrollment of women was 22% overall and 32% at non-VA sites. Etiology was defined as ischemic by the primary investigator in each center in the presence of documented CAD or prior myocardial infarction.

The primary end point of BEST was all-cause mortality. Secondary end points included cardiovascular mortality, all-cause and HF hospitalization, the combination of death and heart transplantation, and LVEF at 3 and 12 months.

Statistical analysis. Gender and treatment group comparisons were conducted. For continuous variables, the *t* test was used except when the data were non-normal. This was the case with plasma norepinephrine (PNE), and Wilcoxon rank-sum test was used. For categorical variables, the chi-square test was used. The log-rank test was used to compare survival distributions (mortality rates) by gender and treatment group. Kaplan-Meier methods were used to construct survival curves. Cox regression models were used to examine the effect of covariates of interest on overall survival and in gender subgroups, and to estimate hazard ratios and 95% confidence intervals. Univariate analysis of associations with mortality were conducted within gender for each hypothesized predictor, followed by multivariate analyses within gender, with reduction of variables by backwards elimination of those found not significant at the $p = 0.05$ level (all models were adjusted for randomized treatment group assignment). Cox regression analysis was also used to examine potential interactions between gender, presence of CAD, and treatment group. The p values are reported from the paired *t* test comparing treatment response from baseline, at 3 and 12 months, and overall mean estimates, respectively.

A type I error of 0.05 was used to denote statistical significance, and p values reported are unadjusted.

RESULTS

Baseline characteristics. Baseline characteristics are presented in Table 1. Women were younger than men, were more likely to be black, had a higher prevalence of nonischemic etiology, higher left and right ventricular ejection fraction (RVEF), higher heart rate, greater cardiothoracic ratio (CTR), higher blood urea nitrogen/creatinine ratio, higher prevalence of left bundle branch block (LBBB), lower prevalence of atrial fibrillation (Afib), current and past smoking, lesser use of anticoagulants and aspirin, and lower PNE compared with men.

Response to treatment. In women receiving bucindolol, a clinically significant slowing of the heart rate was noted at three months from 83 (beats/min) to 75 (beats/min) that was sustained at 12 months ($p < 0.05$). The slowing of the heart rate was significantly greater with bucindolol compared with placebo ($p < 0.0001$). Both RVEF and LVEF improved at three and 12 months in the study participants. In the bucindolol group, LVEF increased from 25 ± 7% at baseline, to 33 ± 13% at 12 months ($p < 0.05$), which was significantly higher than LVEF in the placebo group measured at 12 months, 28 ± 12% ($p = 0.0004$). Right ventricular ejection fraction was measured at 38 ± 14% at baseline, 42 ± 15% at 12 months in the placebo group ($p \leq 0.05$). In the bucindolol group, the corresponding figures were 37 ± 14% and 47 ± 13% ($p = 0.05$), respectively. Right ventricular ejection fraction was significantly higher at 12 months in the bucindolol group ($p = 0.0006$).

Survival. No improvement in survival was noted in the bucindolol group compared with placebo (mortality 26% vs. 29%, respectively, $p = 0.44$). This finding was consistent in all subgroups regardless of etiology, ethnicity, or the presence of diabetes.

Analyzing crude mortality by gender demonstrated lower mortality in women compared with men (27% vs. 33%, respectively, $p = 0.02$) due to the significant difference in the nonischemic compared with ischemic group (19% vs. 27%, respectively, $p = 0.009$) (Table 2). New York Heart Association class III women had lower overall mortality than men (25% vs. 32%, respectively, $p = 0.004$), and a lower mortality in nondiabetic women compared with nondiabetic men (25% vs. 31%, respectively, $p = 0.03$) was noted as illustrated in Figure 1, which also displays the hazard ratios by gender for the prespecified variables.

Variables related to prognosis. The following preselected clinical characteristics and laboratory values were related to prognosis in a Cox proportional hazards regression model: NYHA functional class (class IV vs. III), CAD (presence vs. absence of CAD), ethnicity (black vs. non-black), age, body mass index (BMI), diabetes history, systolic blood pressure, LVEF, CTR, QRS duration, Afib (presence vs. absence), blood urea nitrogen/creatinine ratio, and treatment. Regression analyses were conducted separately for women and men.

In women, all the above-mentioned variables were found to be univariate predictors of survival with the exception of

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Table 1. Baseline Clinical Characteristics by Gender

Characteristics	Women (n = 593)	Men (n = 2,115)	p Value
Age (yrs) mean (range)	58 ± 13.3 (19–93)	61 ± 12.0 (21–90)	< 0.001
Ethnicity			
White, non-Hispanic	367 (62%)	1,529 (72%)	0.001
Black, non-Hispanic	180 (30%)	447 (21%)	
Other	46 (8%)	139 (7%)	
NYHA functional class			
III	549 (93%)	1,933 (91%)	0.356
IV	44 (7%)	182 (9%)	
Etiology			
Ischemic	228 (38%)	1,359 (64%)	< 0.001
Nonischemic	365 (62%)	756 (36%)	
Diabetes mellitus	214 (36%)	750 (35%)	0.778
Hypertension	340 (57%)	1,256 (59%)	0.370
Physical exam			
HR (beats/min)	84 ± 12.8	81 ± 13.3	< 0.001
BMI (kg/m^2)	28 ± 6.8	28 ± 5.8	0.318
SBP (mm Hg)	117 ± 18.1	117 ± 18.0	0.883
Baseline medications			
ACE inhibitor	536 (90%)	1,934 (91%)	0.423
Digitalis	550 (93%)	1,951 (92%)	0.684
Anticoagulant	246 (41%)	969 (46%)	0.061
Aspirin	214 (36%)	1,001 (47%)	< 0.001
Afib	29 (5%)	274 (13%)	< 0.001
LBBB	202 (34%)	478 (23%)	< 0.001
LVEF (%)	25 ± 7.1	23 ± 7.3	< 0.001
RVEF (%)	38 ± 13.8	34 ± 13.3	< 0.001
CTR	59 ± 7.6	55 ± 6.8	< 0.001
BUN/creatinine	21 ± 9.3	19 ± 7.8	< 0.001
Sodium (mEq/l)	139 ± 3.2	139 ± 3.4	0.862
PNE (pg/ml) median	398	442	0.007
Current smoker	68 (11%)	406 (19%)	< 0.001
History of smoking	314 (53%)	1,638 (77%)	0.001

Mean ± 1 SD.

ACE = angiotensin-converting enzyme; Afib = atrial fibrillation; BMI = body mass index; BUN = blood urea nitrogen; CTR = cardiothoracic ratio; HR = heart rate; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PNE = plasma norepinephrine; RVEF = right ventricular ejection fraction; SBP = systolic blood pressure.

ethnicity, QRS duration, and treatment (Table 3). A parallel analysis was carried out in men (Table 4) with similar results. QRS duration, but not Afib, was found to be a univariate predictor of survival in men.

Table 2. Crude Mortality by Gender

	Women (n = 593)	Men (n = 2,115)	Log Rank p Value
Death	163 (27%)	697 (33%)	0.02
CAD	92/228 (40%)	494/1,359 (36%)	0.15
Non-CAD	71/365 (19%)	203/756 (27%)	0.009
LVEF			
≤20	67/178 (38%)	342/847 (40%)	0.62
>20	96/415 (23%)	355/1,268 (28%)	0.07
NYHA class			
III	136/549 (25%)	613/1,933 (32%)	0.004
IV	27/44 (61%)	84/182 (46%)	0.15
Ethnicity			
Black	52/180 (29%)	156/447 (35%)	0.11
Non-black	111/413 (27%)	541/1,668 (32%)	0.05
Diabetes	68/214 (32%)	279/750 (37%)	0.39
No diabetes	95/379 (25%)	418/1,365 (31%)	0.03

CAD = coronary artery disease; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Ischemic etiology and measures of the severity of HF were found to be predictors of survival in multivariate regression models in both women and men (Tables 5 and 6). These include CAD, LVEF, systolic blood pressure, CTR, and blood urea nitrogen/creatinine ratio. Coronary artery disease and LVEF appeared to be stronger predictors of prognosis in women (Table 5). Atrial fibrillation and NYHA were predictors in women, but not in men. QRS duration, BMI, age, heart rate, diabetes history, and treatment (bucindolol vs. placebo) were found to be predictors of survival in men only (Table 6).

A multivariate model (Table 7) comparing survival of females to males and adjusting for major risk factors indicates that gender is a significant predictor of outcome ($p = 0.0046$). There was a significant CAD by gender interaction ($p = 0.011$). The effect of gender on survival is modified by etiology (ischemic vs. nonischemic). In the nonischemic group, women have a better survival than men ($p = 0.0093$); however, in the ischemic group, there was a trend for a better survival in men ($p = 0.1516$) (Fig. 2).

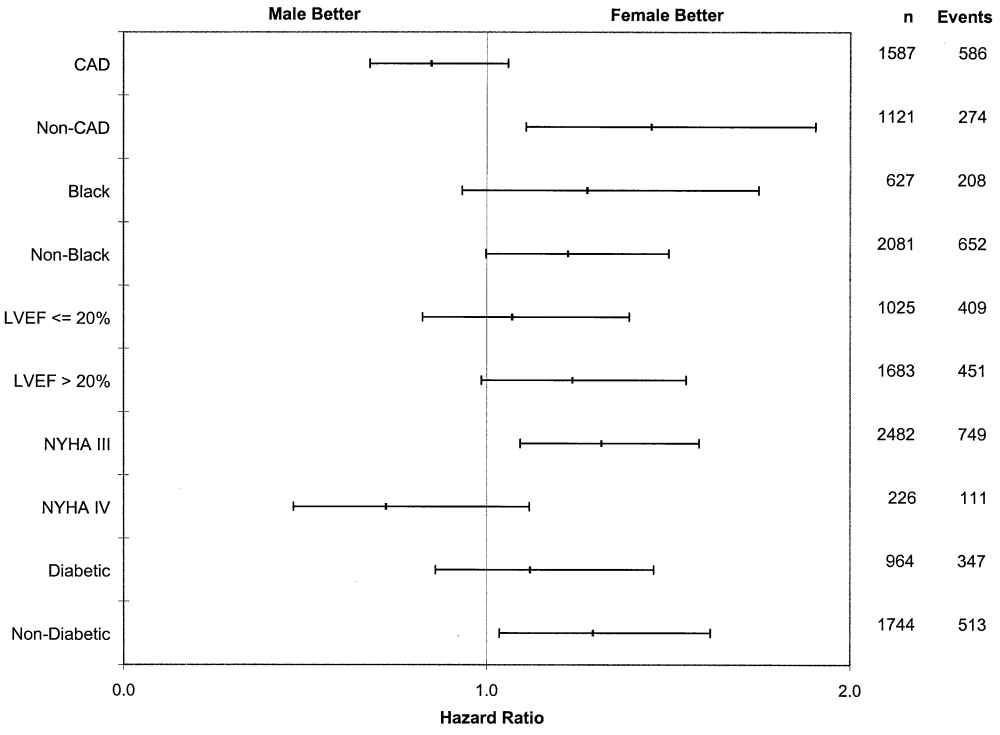

Figure 1. Hazard ratios for mortality comparing genders for prespecified patient subgroups adjusted for treatment group. CAD = coronary artery disease; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

DISCUSSION

The large number of women enrolled in BEST coupled with the detailed assessment of their baseline characteristics and follow-up data provide an opportunity to address major issues related to women with HF.

Baseline characteristics and prognostic variables. Several baseline clinical and laboratory features were found to differ significantly between women and men. Some characteristics are expected to confer better prognosis, namely having a higher prevalence of nonischemic etiology, higher LVEF (11), lower occurrence of Afib (12), and lower PNE (11). Some other features, however, have been related to worse outcome including higher heart rate (13), CTR (11), and higher prevalence of LBBB (14).

A review of prior studies addressing gender differences in patients with advanced HF reveals certain common features in women consistent with our findings including a lower percentage of ischemic etiology (15–18) a higher percentage of African Americans (15,16), a higher heart rate (16,18), LVEF (15,18), CTR (19), higher prevalence of LBBB (17,19), and lower prevalence of Afib (15,18).

A more favorable outcome among women may theoret-

Table 3. Univariate Predictors of Mortality in Women

Covariate	Hazard Ratio	95% CI	p Value
CAD (CAD vs. no CAD)	2.45	(1.80–3.34)	0.0001
NYHA (class IV vs. class III)	3.27	(2.16–4.95)	0.0001
LVEF (per 1%)	0.95	(0.93–0.97)	0.0001
BUN/creatinine (per 1 U)	1.03	(1.01–1.04)	0.0001
CTR (per 1 U)	1.05	(1.03–1.08)	0.0001
Age (per 1 year)	1.02	(1.01–1.04)	0.0003
SBP (per 1 mm Hg)	0.99	(0.98–0.994)	0.0016
Afib (presence vs. absence)	2.20	(1.29–3.74)	0.0037
BMI (per 1 kg/m^2)	0.97	(0.95–0.995)	0.0178
Diabetes (Hx vs. no Hx)	1.45	(1.06–1.97)	0.0209
HR (beats/min)	0.99	(0.98–0.999)	0.0383
QRS duration (per 1 ms)	1.00	(0.999–1.01)	0.1642
Treatment (bucindolol vs. placebo)	0.89	(0.65–1.21)	0.4423
Ethnicity (black vs. non-black)	1.08	(0.78–1.50)	0.6447

For continuous variables, the hazard ratio represents the risk of dying per 1 U increase in the covariate. Women: 593 total participants, 163 deaths.

CI = confidence interval; Hx = history of. Other abbreviations as in Tables 1 and 2.

Table 4. Univariate Predictors of Mortality in Men

Covariate	Hazard Ratio	95% CI	p Value
CAD (CAD vs. no CAD)	1.47	(1.25–1.73)	0.0001
NYHA (class IV vs. class III)	1.80	(1.43–2.26)	0.0001
LVEF (per 1%)	0.97	(0.96–0.98)	0.0001
BUN/creatinine (per 1 U)	1.04	(1.03–1.05)	0.0001
SBP (per 1 mm Hg)	0.986	(0.98–0.99)	0.0001
CTR (per 1 U)	1.05	(1.03–1.06)	0.0001
QRS duration (per 1 ms)	1.006	(1.00–1.01)	0.0001
Age (per 1 year)	1.02	(1.01–1.03)	0.0001
BMI (per 1 kg/m^2)	0.96	(0.95–0.97)	0.0001
Diabetes (Hx vs. no Hx)	1.27	(1.09–1.48)	0.0019
HR (beats/min)	1.006	(1.00–1.01)	0.0430
Treatment (bucindolol vs. placebo)	0.89	(0.77–1.04)	0.1366
Ethnicity (black vs. non-black)	1.14	(0.95–1.36)	0.1516
Afib (presence vs. absence)	1.13	(0.91–1.40)	0.2636

For continuous variables, the hazard ratio represents the risk of dying per 1 U increase in the covariate. Men: 2,115 total participants, 697 deaths.

Abbreviations as in Tables 1, 2, and 3.

Table 5. Multivariate Predictors of Mortality in Women

Covariate	Hazard Ratio	95% CI	p Value
CAD (CAD vs. no CAD)	2.47	(1.80–3.41)	0.0001
NYHA (class IV vs. class III)	2.63	(1.72–4.04)	0.0001
BUN/creatinine (per 1 U)	1.02	(1.01–1.04)	0.0025
CTR (per 1 U)	1.04	(1.01–1.06)	0.0027
LVEF (per 1%)	0.96	(0.94–0.99)	0.0043
Afib (presence vs. absence)	2.07	(1.16–3.69)	0.0137
SBP (per 1 mm Hg)	0.99	(0.98–0.999)	0.0294
Treatment (bucindolol vs. placebo)	0.82	(0.60–1.13)	0.2216

For continuous variables, the hazard ratio represents the risk of dying per 1 U increase in the covariate. Women: 593 total participants, 163 deaths. Final model based on 580 participants, 158 deaths.
Abbreviations as in Tables 1 and 2.

ically be explained on the basis of the effects of sex hormones. Women with late menopause were found to have larger end-systolic volumes, lower LVEF, and lower filling rates as compared with early menopausal women (20). Similarly, premenopausal women have lower blood pressure compared with men of similar age, a pattern that is no longer seen after menopause (21). Estrogen decreases endothelin levels in postmenopausal women (22), and estrogen replacement in perimenopausal women results in reduction of systolic and diastolic blood pressure, and in total body norepinephrine spillover in response to mental stress (23). The potential vasodilator effect of estrogen may be mediated through the renin-angiotensin system, bradykinin, or nitric oxide (24–26). Moreover, sex hormones exhibit a favorable effect on hemostasis and thrombolysis. Significantly lower levels of plasminogen activator inhibitor were found in premenopausal women as compared with postmenopausal women or to men of similar age (27).

Gender-related differences in geometric remodeling and earlier onset of impaired LV systolic function in males was noted in animal models (28) as well as in humans with aortic stenosis (29) and hypertension (30). Myocyte cell loss pattern favoring females (31) and gender differences in gene expression have also been reported (32), and, very recently, reduced hypertrophy in women in postinfarction remodeling was speculated to reflect fundamental differences in cellular remodeling (33).

Table 6. Multivariate Predictors of Mortality in Men

Covariate	Hazard Ratio	95% CI	p Value
BUN/creatinine (per 1 U)	1.02	(1.015–1.03)	0.0001
CTR (per 1 U)	1.03	(1.02–1.05)	0.0001
Age (per 1 year)	1.02	(1.01–1.023)	0.0004
CAD (CAD vs. no CAD)	1.33	(1.12–1.59)	0.0015
BMI (per 1 kg/m^2)	0.98	(0.96–0.99)	0.0026
SBP (per 1 mm Hg)	0.99	(0.988–1.00)	0.0033
HR (beats/min)	1.01	(1.00–1.02)	0.0054
Diabetes (Hx vs. no Hx)	1.25	(1.06–1.47)	0.0081
LVEF (per 1%)	0.99	(0.98–1.00)	0.0225
QRS duration (per 1 ms)	1.002	(1.00–1.01)	0.0381
Treatment (bucindolol vs. placebo)	0.85	(0.73–0.99)	0.0386

For continuous variables, the hazard ratio represents the risk of dying per 1 U increase in the covariate. Final model based on 2,035 participants, 676 deaths.
Abbreviations as in Tables 1, 2, and 3.

Table 7. Multivariate Predictors of Mortality in Women and Men

Covariate	Hazard Ratio	95% CI	Adjusted p Value
Creatinine (per 1 mg/dl)	2.18	(1.87–2.55)	< 0.0001
NYHA (class IV vs. class III)	1.51	(1.23–1.85)	< 0.0001
SBP (per 1 mm Hg)	0.99	(0.985–0.993)	< 0.0001
LVEF (per 1%)	0.97	(0.96–0.98)	< 0.0001
CAD (CAD vs. no CAD)	1.91	(1.40–2.63)	< 0.0001
Age (per 1 year)	1.01	(1.005–1.02)	0.0005
Diabetes (Hx vs. no Hx)	1.25	(1.08–1.44)	0.0026
Body mass index (per 1 kg/m^2)	0.98	(0.97–0.99)	0.0029
Gender (male vs. female)	1.09	(0.83–1.43)	0.0046
Treatment (bucindolol vs. placebo)	0.81	(0.69–0.94)	0.0233
Ethnicity (black vs. non-black)	0.93	(0.74–1.18)	0.1818
CAD-by-gender interaction			0.0107
Ethnicity-by-treatment interaction			0.0980

For continuous variables, the hazard ratio represents the risk of dying per 1 U increase in the covariate. Final model based on 2,705 participants, 859 deaths.
Abbreviations as in Tables 1, 2, and 3.

However, a more likely explanation is that these variables were derived from studies that have enrolled predominantly men. Our data indicate a differential prognostic value for some characteristics. For example, Afib was found to be a predictor in women but not in men. On the other hand, QRS duration and BMI were predictors only in men. Because of the relatively limited sample size, one should be cautious not to over-interpret these differences. However, two interesting findings should be mentioned. For every 1% increase in LVEF, there was a corresponding 4% decrease in mortality in women compared with a 1% decrease in men. Similarly, CAD conferred a 2.5-fold increase in the risk of mortality in women compared with a 1.5-fold increase in men. Thus, LVEF and CAD appear to be stronger predictors of prognosis in women.

Comparison with previous survival studies. A study in a young population of 65 women and 238 men with idiopathic dilated cardiomyopathy who were enrolled consecutively found no difference in survival rates between men and women (19). Adams et al. (15) reported their experience with 177 women and 380 men with HF and impaired left ventricular systolic function consecutively enrolled in an outpatient HF clinic. They found a significantly better survival rate for women with nonischemic etiology. Similar findings were reported from the Flolan International Randomized Survival trial, in 112 women and 359 men (16). Recently, Simon et al. (17) reported the survival rates in 515 female and 2,132 men in the Cardiac Insufficiency Bisoprolol study. Although they confirmed better survival for women compared with men, this difference was predominantly noted in the undefined etiology, and no difference in survival was seen between women and men in the nonischemic group. Likewise, in Metoprolol CR/XL Randomized Intervention Trial In Heart Failure, women had a 37% lower risk of dying than men after adjusting for baseline differences including ischemic etiology (18). Findings from

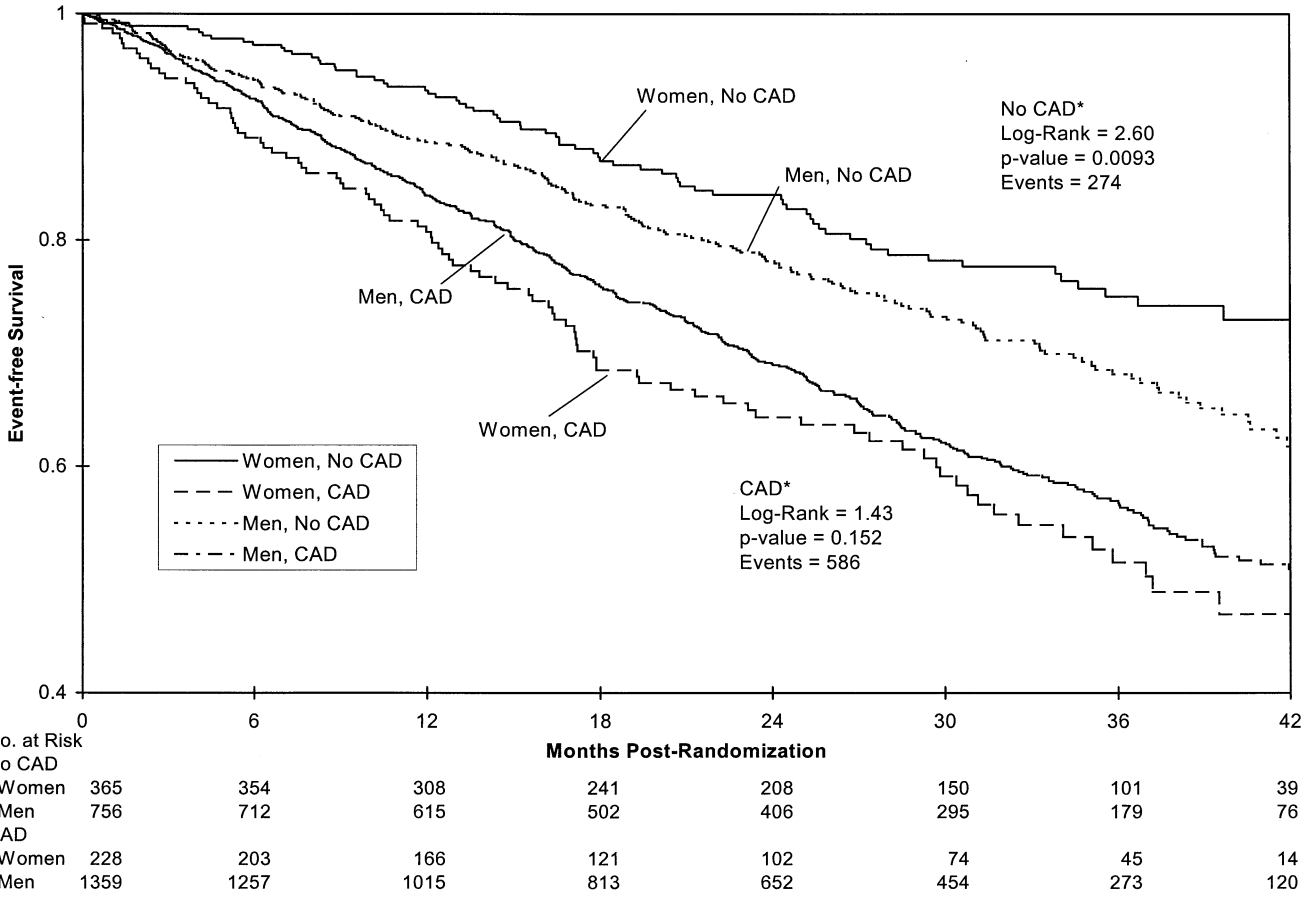

Figure 2. Survival curves by gender within ischemia status. CAD = coronary artery disease.

BEST, however, indicate that the survival advantage of women was confined to the nonischemic patients. Therefore, one has to conclude that the survival advantage of women cannot be explained entirely on the basis of higher prevalence of nonischemic etiology. It is likely that other confounders not identified by measured baseline clinical and laboratory characteristics play a role.

Study limitations. Despite the attempt to maximize enrollment of women and to collect all pertinent information relevant to gender differences, this effort is by no means complete. The sample size is limited, and there are several factors that have not been measured. For example, gender-related differences in pharmacokinetics have been identified for a number of drugs including beta-blockers (34), and socioeconomic status has not been addressed. We consider our findings exploratory in nature and hypothesis-generating.

Conclusions. Major baseline differences in clinical and laboratory characteristics exist between men and women. The prognostic role of various predictors may vary in magnitude between genders, and the survival advantage of women in our study was confined to the nonischemic etiology. These data indicate that information collected on men with HF cannot be assumed to apply similarly or with the same magnitude to women, emphasize the importance of accounting for these differences in designing clinical trials, and highlight the need for both stratifying entry by gender and enrolling more women in HF trials.

Reprint requests and correspondence: Dr. Jalal K. Ghali, Cardiac Centers of Louisiana, L.L.C., 2551 Greenwood Road, Suite 350, Shreveport, Louisiana 71103. E-mail: jkgalt@shreve.net.

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