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Associations of Gender and Etiology With Outcomes in Heart Failure With Systolic Dysfunction

A Pooled Analysis of 5 Randomized Control Trials

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Objectives This study sought to explore the gender-related differences in etiology and outcomes in chronic heart failure (HF) patients from 5 randomized trials.

Background Each year, 550,000 new cases of HF are identified; however, there remain limited data on gender-related differences in etiology and outcomes among patients with HF with systolic dysfunction.

Methods We analyzed data from 8,791 men and 2,851 women randomized in 5 clinical trials (PRAISE [Prospective Randomized Amlodipine Survival Evaluation], PRAISE-2, MERIT-HF [Metoprolol Extended Release Randomized Intervention Trial in Heart Failure], VEST [Vesnarinone Trial], and PROMISE [Prospective Randomized Milrinone Survival Evaluation]) to explore gender-related differences in etiology (ischemic vs. nonischemic) and outcomes (all-cause mortality and death or all-cause hospitalization). Hazard ratios (HR), 95% confidence intervals (CIs), and Kaplan-Meier survival curves were generated by gender and etiology.

Results A total of 18% of ischemic and 31% of nonischemic patients were women. Irrespective of etiology, women were older, more ethnically diverse, and had higher systolic blood pressures, more diabetes, and severe HF symptoms, but less often smoked or had prior myocardial infarctions than men. Mean ejection fractions were similar between women (23.6%) and men (23.2%). The 1-year Kaplan-Meier survival estimates varied by gender and etiology (female nonischemics, HR 0.88 [95% CI 0.85 to 0.89]; female ischemics, HR 0.83 [95% CI 0.81 to 0.85]; male nonischemics, HR 0.84 [95% CI 0.83 to 0.85]; male ischemics, HR 0.79 [95% CI 0.78 to 0.81]). After adjustment, female gender (HR 0.77 [95% CI 0.69 to 0.85]) and nonischemic etiology (HR 0.80 [95% CI 0.72 to 0.89]) were associated with longer survival time. Time to death or hospitalization was longer among nonischemics (HR 0.83 [95% CI 0.78 to 0.89], $p < 0.0001$); however, female gender was not significantly associated with the composite outcome (HR 1.01 [95% CI 0.95 to 1.08]).

Conclusions Our data clarify that outcomes differ by both gender and etiology among patients with HF with systolic dysfunction. Understanding these differences may lead to better management of HF patients and improved overall prognosis. (J Am Coll Cardiol 2007;49:1450–8) © 2007 by the American College of Cardiology Foundation

Heart failure (HF) affects 5 million people in the U.S., with estimated direct and indirect costs reaching $29.6 billion in 2006 (1). Each year, 550,000 new cases of congestive HF are diagnosed. Advances in medical management have improved the prognosis of HF patients; however, survival remains poor (2–12). Although 5-year mortality with HF is lower among women than men (45% vs. 59%), women now account for the majority (62.5%) of deaths from HF in the U.S. because of shifting demographics (1,2).

Subset analyses of large-scale trials have attempted to provide insight into gender-related differences in clinical profiles and predictors of outcome, but individually, these analyses are limited by small numbers of female participants and differences in systolic function and definitions of etiology (13–16). A pooled analysis of multiple trials provides an opportunity to further explore gender-related differences in etiology, clinical profiles, and outcomes among patients with HF with depressed left ventricular (LV) ejection fraction (LVEF). Therefore, we combined the databases from 5 randomized clinical trials in chronic HF with LV

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systolic dysfunction (Metoprolol Extended Release Randomized Intervention Trial in Heart Failure [MERIT-HF], Prospective Randomized Amlodipine Survival Evaluation Study [PRAISE], PRAISE-2, Prospective Randomized Milrinone Survival Evaluation [PROMISE], and Vesnarinone Trial [VEST]) in order to: 1) explore differences in clinical profiles by gender and etiology (ischemic vs. nonischemic); 2) investigate characteristics associated with mortality and hospitalization; and 3) examine differences in these clinical outcomes by gender and etiology. In so doing, we sought to better understand the independent associations of gender and HF etiology with clinical outcomes among patients with LV systolic dysfunction.

Abbreviations and Acronyms

CI = confidence interval
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
MI = myocardial infarction
NYHA = New York Heart Association

Methods

Trials. We pooled data from the MERIT-HF, PRAISE, PRAISE-2, PROMISE, and VEST trials, which represent a convenience sample of chronic HF trials coordinated through the authors and their institutions. Protocol design, entry criteria, and baseline characteristics for each trial are displayed in Table 1 (17–20). Etiology of HF was used as classified on each trial's case report form. Ischemic etiology was defined as the presence of coronary artery disease confirmed by coronary arteriography or radionuclide scanning, or suspected based on a history of myocardial infarction (MI). Nonischemic etiology was defined as HF with systolic dysfunction in the absence of history of MI or significant coronary artery disease on angiography. Enrollment medications collected from the case report forms included aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, nitrates, digoxin, diuretics, warfarin, anti-arrhythmics, and hormone replacement therapy. Studies varied slightly in the variables collected and their definitions. Shared variables with similar definitions were chosen to be combined across trials to create a common data set for pooling patient-level data. Each common variable had <5% missing information in any one trial. For the Cox proportional hazards models presented here, only variables that were collected in all studies were included as covariates.

Pooled patient-level data. From the pooled population of 11,719 patients, those missing information on HF etiology (n = 77) were excluded, leaving a final study population of 11,642 patients (8,791 men and 2,851 women). The median duration of follow-up was 352 (range 222 to 901) days.

All-cause mortality and all-cause hospitalization. The primary outcome of interest was time to all-cause mortality. A secondary outcome was time to first event of all-cause mortality or all-cause hospitalization as a composite end point. We also assessed time to all-cause hospitalization. End points were accepted as collected by the individual studies without reclassification or further validation.

Statistical analysis. Baseline characteristics and outcomes were compared across subgroups by gender (female vs. male) and HF etiology (ischemic vs. nonischemic). Continuous variables are presented using means with standard deviations and categorical variables as percentages. Comparisons were made using Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables.

Kaplan-Meier survival curves were created for mortality, the composite of mortality or hospitalization, and hospitalization alone. Stratified multivariable Cox proportional hazards regression models were used to test the association among gender, HF etiology, and outcomes. The Cox models were stratified by study and treatment to allow for differing baseline hazard rates between studies. Results are displayed as hazard ratios (HR) (95% confidence intervals). Variables included in the modeling process were age, race/ethnicity, LVEF, New York Heart Association (NYHA) functional class, ischemic (vs. nonischemic) etiology, systolic blood pressure, heart rate, and weight. Gender-by-etiology interaction terms were evaluated in separate models including all of the aforementioned covariates. The Cox models developed on the overall population were compared with similar models, stratified by study, and fit to placebo patients only. These models resulted in effects for the terms in common, which were similar in direction and magnitude in the placebo-only and all-randomized groups. The robustness of results was also assessed by systematically dropping each study from the pooled data. The hazard ratios for all included covariates in the resulting models were reassuringly consistent for mortality, the composite end point of death or hospitalization, and hospitalization alone. In addition, the gender-by-etiology interaction terms were examined in covariate-adjusted models fit to each study. For all analyses and the modeling, a p value of <0.05 was considered statistically significant. No adjustments were made for multiple comparisons. The summary statistics and Cox models were done using SAS/STAT software, version 9 of the SAS System for Linux (SAS Institute, Cary, North Carolina). Graphics were created using version 2.1 of the R software (R Development Core Team, Vienna, Austria).

Results

Study Population

The pooled study population included 24% women, mean LVEF was 23%, and 85% had NYHA functional class III or IV symptoms at enrollment. Median follow-up was 352 (range 222 to 901) days. Baseline characteristics are shown by gender and HF etiology in Table 2. Among women, 39.8% had ischemic and 60.2% had nonischemic etiology. Among men, 57.1% were ischemic and 42.9% nonischemic. Compared with men, women were older; more ethnically diverse; and had higher systolic blood pressure, more dia-

Table 1 Description of Pooled Trials

	MERIT	PRAISE	PRAISE-2	PROMISE	VEST	Combined
Protocol design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	N/A
Clinical centers	313 centers	Not stated	240 centers	119 centers	189 centers	N/A
Countries	U.S. and Europe	U.S.	U.S. and Canada	U.S. and Canada	U.S. and Canada	N/A
Enrollment (n)	3,991	1,153	1,654	1,088	3,833	11,719
Female (%)	23	24	34	22	25	24
Ejection fraction (mean)	28	21	21	21	21	23
NYHA functional class II (%)	41	0	0	0	0	14
NYHA functional class III (%)	55	81	80	58	85	71
NYHA functional class IV (%)	4	19	20	42	15	14
Mean follow-up duration (days)	364	454	901	222	285	410
Randomized treatment	Metoprolol CR/XL	Amlodipine	Amlodipine	Oral milrinone	Vesnarinone	N/A
Ischemic (%)	65	63	0	54	58	53
Primary outcome	All-cause mortality; all-cause mortality and all-cause hospitalization	All-cause mortality and cardiovascular morbidity	All-cause mortality	All-cause mortality	All-cause mortality	N/A

MERIT = Metoprolol Extended Release Randomized Intervention Trial; N/A = not applicable; NYHA = New York Heart Association; PRAISE = Prospective Randomized Amlodipine Survival Evaluation Study; PROMISE = Prospective Randomized Milrinone Survival Evaluation Study; VEST = Vesnarinone Trial.

betes, and more advanced HF symptoms. Women less often had a history of smoking or prior MI. The mean LVEF was similar among women and men (23.6% vs. 23.2%, respectively).

Compared with an ischemic etiology, nonischemic HF patients were younger, more often black and female, and had higher body mass index and lower systolic blood pressure. They had less diabetes and tobacco use. The group mean QRS duration was prolonged, >120 ms in all subgroups, but duration varied by etiology and gender.

Medication use at enrollment differed by etiology (Table 2). Diuretic use was high regardless of gender or etiology (range 92% to 96%). Patients with nonischemic etiology reported more use of angiotensin-converting-enzyme inhibitors and digoxin, whereas nitrates, aspirin, and calcium channel blockers were used less often. Beta-blocker use was low overall, and use of anti-arrhythmics was more frequent among men regardless of etiology. Hormone replacement therapy was used by 17% of women with ischemic and 21% of women with nonischemic HF.

Clinical Outcomes

Primary outcome. Death occurred in 2,400 patients during follow-up. Kaplan-Meier 1-year survival estimates varied by gender and etiology (female nonischemics HR 0.88 [95% confidence interval (CI) 0.85 to 0.89], female ischemics HR 0.83 [95% CI 0.81 to 0.85], male nonischemics HR 0.84 [95% CI 0.83 to 0.85], male ischemics HR 0.79 [95% CI 0.78 to 0.81]. The unadjusted survival curves for men and women diverged early, and the difference persisted among nonischemic patients, but the difference was less prominent among ischemic patients. Compared with men, women had better survival, whether ischemic or nonischemic etiology. Kaplan-Meier probabilities for mortality by gender and etiology are shown in Figure 1.

Secondary outcomes. Crude survival curves for the composite of mortality or hospitalization differed by etiology, but not by gender. Ischemic patients did worse than nonischemic patients. Figure 2 shows the Kaplan-Meier probabilities for the composite of mortality or hospitalization by gender. Nonischemic patients had shorter time to hospitalizations than ischemic patients. Gender differences were not apparent among nonischemic patients; however, among ischemic patients, time to hospitalization was shorter among women (Fig. 3).

Multivariable Associations With Clinical Outcomes

Primary outcome. Baseline characteristics associated with survival time are shown in Table 3. Characteristics associated with worse survival included advancing age, higher heart rate, and NYHA functional class IV symptoms. Female gender, nonischemic etiology, non-Caucasian ethnicity, higher systolic blood pressure, and higher LVEF were associated with better survival.

In assessing associations with time to mortality among ischemic and nonischemic groups independently, among ischemic patients, higher heart rates, NYHA functional

Table 2 Demographics and Clinical Profiles by Gender

	Male		Female	
	Ischemic (n = 5,021) 57%	Nonischemic (n = 3,770) 43%	Ischemic (n = 1,134) 40%	Nonischemic (n = 1,717) 60%
Age variables				
Age (mean/SD)	65.4 (9.2)	58.3 (12.5)	66.7 (9.6)	60.3 (12.5)
Age, yrs (groups %)				
<65	43%	65%	38%	60%
65–74	41%	25%	40%	28%
75+	16%	9%	22%	12%
Race/ethnicity (%)				
Caucasian	93	75	86	73
Black	5	20	11	23
Asian	<1	<1	<1	<1
Other	1	4	2	4
Baseline measurements				
Weight, kg (mean/SD)	81.9 (15.7)	87.4 (20.2)	64.7 (15.2)	72.9 (19.3)
Body mass index, kg/m^2 (mean/SD)	26.8 (4.4)	28.0 (5.9)	26.2 (5.3)	27.7 (6.7)
Cardiothoracic ratio (mean/SD)	0.55 (0.07)	0.56 (0.08)	0.59 (0.08)	0.60 (0.09)
QRS width (mean/SD)	132 (49.7)	126.8 (44.8)	126.7 (60.9)	130.8 (40.4)
NYHA functional class of heart failure (%)				
II	17	13	15	9
III	70	73	69	74
IV	13	14	16	17
Medical history (%)				
Prior myocardial infarction	83	9	77	8
Diabetes mellitus	32	32	42	35
Prior tobacco	84	77	55	52
Clinical presentation (mean/SD)				
Systolic blood pressure	121 (19.7)	119 (19.0)	126 (21.2)	121 (19.3)
Diastolic blood pressure	73 (11.0)	75 (11.5)	74 (11.7)	73 (11.2)
Heart rate	80 (12.1)	84 (14.6)	82 (11.6)	85 (13.6)
Ejection fraction (%)	23.9 (7.2)	22.3 (7.1)	24.7 (7.3)	22.9 (6.8)
Medications (%)				
Angiotensin-converting enzyme inhibitor	89	94	86	94
Beta-blocker	3	4	3	4
Diuretic	92	95	94	96
Digoxin	80	90	79	91
Nitrates	59	33	62	33
Calcium channel blockers	12	8	12	9
Aspirin	51	24	48	24
Warfarin	40	44	37	38
Antiarrhythmics	15	13	9	10
Hormone replacement therapy	<1	<1	17	21

Abbreviations as in Table 1.

class IV symptoms, and greater age were associated with shorter time to death. Higher systolic blood pressure and LVEF, non-Caucasian ethnicity, female gender, and greater weight were associated with better survival among ischemic patients. Among nonischemic patients, increasing age, NYHA functional class IV symptoms, and higher heart rate were associated with shorter survival time, while female gender and increased systolic blood pressure and LVEF were associated with improved survival. The individual predictors were similar for men and women, except that non-Caucasian ethnicity was not significant for women.

A gender-by-etiology interaction term was significant in the Cox model for time to death ($p = 0.048$). Descriptively, time to death was longer for women than men among patients with both ischemic and nonischemic etiologies, but the difference between men and women was greater in the nonischemic group.

Secondary outcomes. TIME TO DEATH OR HOSPITALIZATION. Baseline characteristics associated with time to death or hospitalization are shown in Table 4. Characteristics associated with shorter time to death or hospitalization for both ischemic and nonischemic patients included increasing

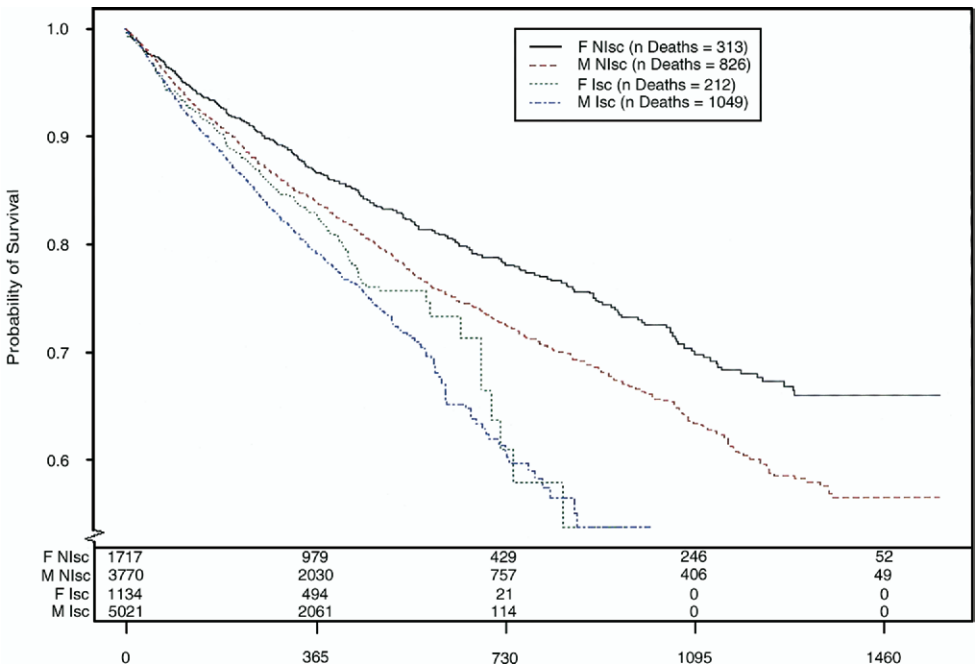

Figure 1 Kaplan-Meier Probabilities of Survival by Etiology of Heart Failure and Gender

F = female; Isc = ischemic; M = male; NIsc = nonischemic.

age, NYHA functional class IV symptoms, and higher heart rate. Higher systolic blood pressure and LVEF were associated with greater time to hospitalization or death. Female gender was not significantly associated with the composite end point among ischemic patients (HR 1.05, 95% CI 0.95 to 1.16) or among nonischemic patients (HR 0.97, 95% CI 0.90 to 1.06). In assessing gender-related differences in factors associated with death or hospitalization, NYHA functional class IV symptoms and increased heart rate were associated with increased morbidity and mortality among both genders, but age was only significantly associated among men (HR 1.13, 95% CI 1.09 to 1.16). Nonischemic etiology, higher systolic blood pressure, and higher ejection fraction were associated with longer time to events for both genders. A gender-by-etiology interaction term was not significant in the Cox model for time to death or hospitalization ($p = 0.06$); however, a trend was evident. Descriptively, for this interaction, time to hospitalization or death was shorter for women than men among patients with ischemic etiology but was longer in women than men in nonischemics. For men and women, nonischemics had longer time to the composite, but for women, time to event was longer than among men.

TIME TO HOSPITALIZATION. Characteristics associated with shorter time to hospitalization included NYHA functional class IV symptoms and higher heart rates. Female gender was not significantly associated with time to hospitalization (HR 1.04, 95% CI 0.97 to 1.11), but when examined by etiology, female gender was a significant predictor of hospitalization for ischemic patients (HR 1.15, 95% CI 1.04 to 1.27). Older age was associated with shorter time to hospitalization among men but not among women. Nonischemic etiology and higher systolic blood pressure and LVEF were associated with greater time to hospitalization overall and among both women and men.

Discussion

The 2,851 women enrolled in these trials of advanced chronic HF with systolic dysfunction were older, more likely to have nonischemic HF, and more ethnically diverse compared with men. Women also had more severe HF symptoms, higher systolic blood pressure, and more diabetes. In addition, whereas female gender was associated with better survival across HF etiologies, gender was not associated with time to hospitalization or the composite outcome of death or hospitalization. For the end point of mortality, advanced age, ischemic etiology, and advanced NYHA symptoms were equally strong predictors of death among women and men. However, advanced NYHA symptoms and ischemic etiology were among the variables most strongly associated with composite end point of death or hospitalization among women, whereas older age, ischemic etiology, and advanced symptoms had the strongest associations with earlier death or hospitalization among men. Nonischemic etiology was associated with lower mortality and greater time to hospitalization in both genders. Thus,

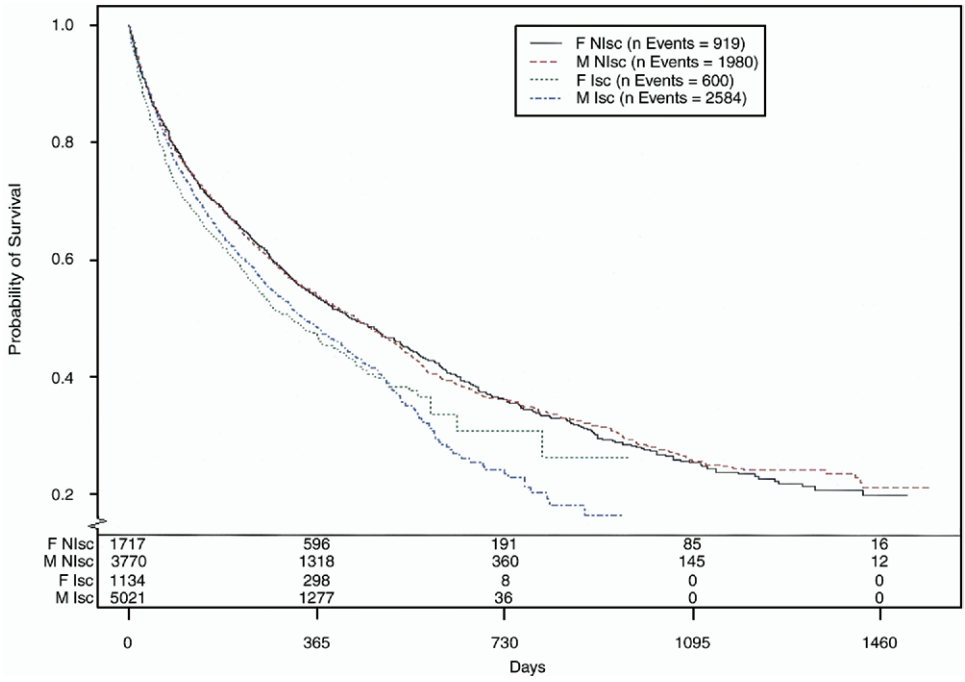

Figure 2 **Kaplan-Meier Probabilities of the Composite of Death or Hospitalization by Etiology of Heart Failure and Gender**

Abbreviations as in Figure 1.

differences exist in symptom severity and clinical characteristics, as well as event-free survival, by patient gender and HF etiology among chronic HF patients with systolic dysfunction included in these analyses. This may have important implications for understanding prognosis and guiding management in patients with HF with LV systolic dysfunction.

The women in this analysis were more likely to have a nonischemic etiology compared with men (60.2% vs. 42.8%, respectively). This predominance of nonischemic etiology among women is similar to previous reports (14–16,21). Women in our analysis had higher blood pressure and more diabetes, suggesting that chronic hypertension and diabetes may be important contributing mechanisms to the development of systolic HF among women. Adaptation to pressure overload and remodeling from cardiac hypertrophy to dilation and its progression to systolic dysfunction as a result of hypertension in addition to microvascular disease and differences in hypertrophic response associated with diabetes may differ among women and men (22–27).

Although the trials in our pooled database recruited for severe HF, the higher prevalence of NYHA functional class III and IV symptoms among women also may relate to differences in HF etiology or differences in hemodynamics in women compared with men. Hemodynamic studies have shown higher end-diastolic pressures despite lower volumes in women, suggesting greater alterations in the pressure-volume relation in women (28–31). In addition, perception of disease, description of symptoms, and adaptation differ among women and men and may influence these characteristics and contribute to symptom severity and hospitalizations among women, particularly with ischemic disease (32–37). Lastly, reports have indicated that pharmacologic therapy differs between women and men (38,39). In our analysis, women more frequently received diuretic therapy and less frequently received angiotensin-converting enzyme inhibitors before enrollment, which may contribute to persistent symptoms. These mechanisms may either explain the variance in etiology of HF observed between the genders in this symptomatic population or suggest opportunities for clinical care across the spectrum of HF with systolic dysfunction.

Unlike previous analyses in HF indicating that women had higher LVEF than men, which was used to explain their relatively better survival (13–16,21,32), our data demonstrated better survival among women compared with men in a population with similar LVEF. This persisted even after adjusting for covariates. The greatest gender-related survival difference was observed between nonischemic women and men; however, a difference was also evident among ischemic patients. Although additional risk factors not addressed may contribute to these differences, our data provide new insight into gender-related differences in HF by etiology among patients with marked systolic dysfunction that should be explored further.

Whether gender is associated with hospitalization in HF has been controversial. Many studies suggest that women

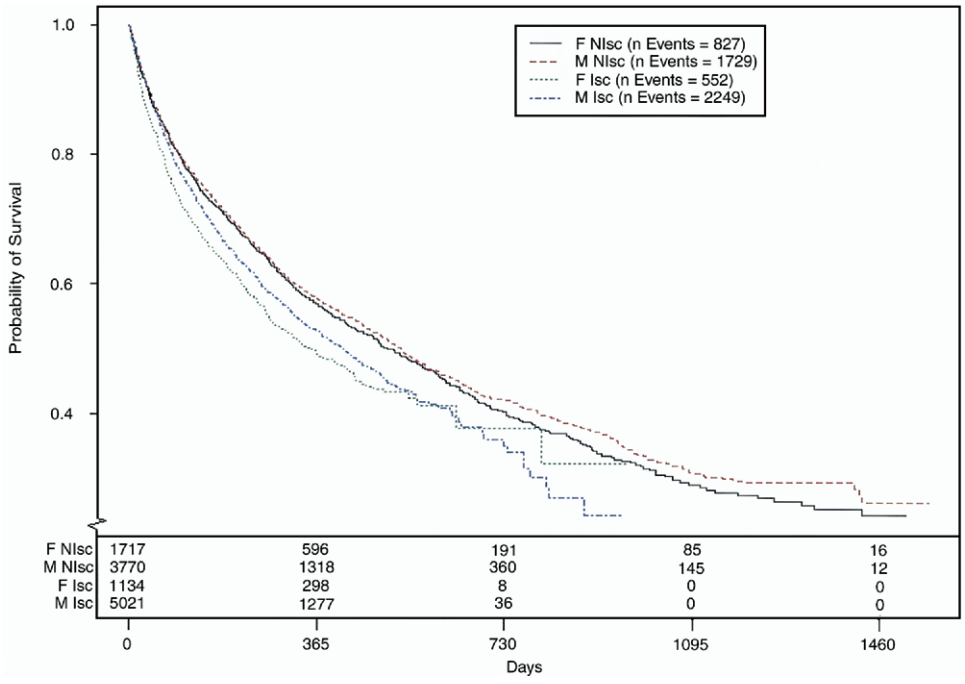

Figure 3 Kaplan-Meier Probabilities of Hospitalization by Etiology of Heart Failure and Gender

Abbreviations as in Figure 1.

are hospitalized more frequently and have shorter time to hospitalization compared with men (13–16,21,32). However, other analyses suggest there are no differences by gender (40,41). In our analysis, we found that female gender was not significantly associated with hospitalizations or the composite death or hospitalization outcome. Heart failure etiology appeared to better discriminate these outcomes. After adjustment for comorbidities, our study demonstrated that female gender was not a significant predictor of time to hospitalization alone or the combined end point of death or hospitalization among patients with severe LV systolic dysfunction. Only after accounting for etiology was female gender significantly associated with earlier hospitalizations. The differing results in other studies may relate to the proportion of patients with ischemic etiology or preserved systolic function.

We also found that women had a longer time to death compared with men, but the protective effect of gender was greater among nonischemic patients. The existence of such an interaction between HF etiology and gender has only rarely been evaluated previously. Adams et al. (42) evaluated gender and etiology of HF in 557 HF patients. This long-term observational study noted a significant association between gender and survival, but through further analysis, HF etiology was the strongest predictor of survival, with a significant gender-by-etiology interaction. These authors concluded that the variance in survival was mostly due to etiology of HF rather than gender.

Table 3 Multivariable Predictors of Death: Hazard Ratios With 95% Confidence Intervals

	Overall (n = 11,487)	Male (n = 8,682)	Female (n = 2,805)
Age (per 10-yr increase)	1.20 (1.15–1.25)	1.19 (1.13–1.25)	1.22 (1.12–1.33)
Ethnicity (non-Caucasian)	0.86 (0.77–0.97)	0.86 (0.76–0.99)	0.85 (0.67–1.06)
Female	0.77 (0.69–0.85)	—	—
Nonischemic etiology	0.80 (0.72–0.89)	0.81 (0.72–0.91)	0.76 (0.61–0.94)
NYHA functional class IV	1.80 (1.63–1.99)	1.78 (1.60–2.00)	1.87 (1.54–2.29)
Heart rate (per 10-beats/min increase)	1.05 (1.02–1.08)	1.05 (1.01–1.08)	1.07 (1.00–1.14)
Weight (per 10-kg increase)	0.96 (0.94–0.99)	0.97 (0.94–1.00)	0.95 (0.89–1.00)
Systolic blood pressure (per 10-mm Hg increase)	0.85 (0.83–0.88)	0.86 (0.83–0.88)	0.84 (0.80–0.89)
Left ventricular ejection fraction (per 10% increase)	0.71 (0.67–0.76)	0.72 (0.67–0.78)	0.69 (0.60–0.80)

NYHA = New York Heart Association.

Table 4 Multivariable Predictors of Death or Hospitalization: Hazard Ratios With 95% Confidence Intervals

	Overall	Female	Male	Ischemic	Nonischemic
Age (per 10-yr increase)	1.10 (1.08–1.13)	1.05 (1.00–1.11)	1.13 (1.09–1.16)	1.09 (1.04–1.13)	1.12 (1.08–1.16)
Ethnicity (non-Caucasian)	1.06 (0.99–1.13)	1.08 (0.95–1.23)	1.05 (0.96–1.13)	1.02 (0.90–1.15)	1.08 (0.98–1.17)
Female	1.01 (0.95–1.08)	—	—	1.05 (0.95–1.16)	0.97 (0.89–1.05)
Nonischemic	0.83 (0.79–0.89)	0.74 (0.65–0.83)	0.87 (0.81–0.93)	—	—
NYHA functional class IV	1.54 (1.44–1.65)	1.54 (1.35–1.76)	1.55 (1.43–1.68)	1.50 (1.37–1.66)	1.58 (1.44–1.74)
Heart rate (per 10-beats/min increase)	1.06 (1.04–1.08)	1.09 (1.04–1.13)	1.05 (1.03–1.07)	1.05 (1.02–1.08)	1.06 (1.03–1.09)
Weight (per 10-kg increase)	1.00 (0.98–1.01)	0.99 (0.96–1.02)	1.00 (0.98–1.02)	0.98 (0.96–1.01)	1.01 (0.99–1.03)
Systolic blood pressure (per 10-mm Hg increase)	0.94 (0.92–0.95)	0.94 (0.91–0.96)	0.94 (0.92–0.95)	0.95 (0.93–0.97)	0.92 (0.89–0.94)
Left ventricular ejection fraction (per 10% increase)	0.82 (0.78–0.85)	0.85 (0.78–0.92)	0.80 (0.77–0.84)	0.84 (0.79–0.89)	0.79 (0.75–0.84)

NYHA = New York Heart Association.

Study limitations. Potential limitations in this observational study include heterogeneity of the included studies, selection bias, treatment effect, and time period and duration and follow-up of included trials. The MERIT-HF study included more NYHA functional class II patients (41%) than the other four studies, and the PRAISE II trial studied exclusively nonischemic cardiomyopathy patients and had a higher mean LVEF than the other studies. Therefore, the pooled analysis methodology could introduce heterogeneity in the large group evaluation. However, this was addressed by merging the data at the patient level to allow use of and adjustment for enrolling demographics, patient profiles, medication use, and outcomes from the original randomized controlled trials. In addition, we employed analyses stratified by trial. Also, all the pooled studies enrolled patients with chronic HF with depressed EF. Because a substantial portion of women with HF have preserved systolic function, this could lead to underrepresentation of women in the included studies. Despite this concern, our pooled analyses included 24% women.

Another potential limitation in this analysis was including all patients enrolled in the studies. Differential response to experimental treatments by gender could bias our results. To address this, we developed Cox proportional hazards models stratified by study drug treatment and also analyzed the data, pooling only the placebo groups, and found similar results as for our overall analyses (data not shown). Median follow-up in the pooled trials was 352 days. This short duration of follow-up could limit the number of recorded events, potentially affecting our ability to detect differences if they exist. However, with a total of 2,400 deaths, we do not believe power to detect differences was a substantial limitation. Lastly, the time period of the trials we pooled spanned more than a decade. This was addressed by merging data at the patient level, stratifying the analyses by trial, and testing concomitant therapies in our adjustment models.

Conclusions

This analysis of pooled data from five large, randomized, controlled trials in HF with LV systolic dysfunction adds clarity to existing research on gender-related differences in etiology and outcomes in this population. Previously, better survival among women had been attributed to better systolic function, and women were thought to have more hospitalization over time. Our study demonstrates that, even with systolic dysfunction, women have better survival compared with men and that hospitalization over time is influenced more by etiology than gender. These observations should lead to clearer understanding of the management and outcomes of patients with HF and systolic dysfunction.

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