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Relation Between Gender, Etiology and Survival in Patients With Symptomatic Heart Failure

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Objectives. **This study investigated the relation between gender, etiology and survival in patients with symptomatic heart failure.**

Background. **Previous work provides conflicting results concerning the relation between gender, clinical characteristics and survival in patients with heart failure.**

Methods. **We examined the relation of these factors in 557 patients (380 men, 177 women) who had symptomatic heart failure, predominantly nonischemic in origin (68%) and typically associated with severe left ventricular dysfunction.**

Results. **Follow-up data were available in 99% of patients (mean follow-up period 2.4 years, range 1 day to 10 years) after study entry, and 201 patients reached the primary study end point of all-cause mortality. By life-table analysis, women were significantly less likely to reach this primary end point than men ($p < 0.001$). A significant association was found between female gender and better survival ($p < 0.001$), which depended on the primary etiology of heart failure ($p = 0.008$ for the gender–etiology interaction) but not on baseline ventricular function. Women survived longer than men when heart failure was due to nonischemic causes (men vs. women: relative risk [RR] 2.36, 95% confidence interval [CI] 1.59 to 3.51, $p < 0.001$). In contrast, outcome appeared similar when heart failure was due to ischemic heart disease (men vs. women: RR 0.85, 95% CI 0.45 to 1.61, $p = 0.651$).**

Conclusions. **Women with heart failure due to nonischemic causes had significantly better survival than men with or without coronary disease as their primary cause of heart failure.**

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Cardiovascular disease in women has attracted increasing attention because epidemiologic and clinical trial data suggest potential differences in natural history and response to therapy between women and men. Most work has concentrated on ischemic heart disease, and gender differences in risk of ischemic complications have been found by some investigators (1,2). However, the possibility of gender differences in heart failure now assumes importance, given the emergence of this condition as a major cardiovascular problem (3). Women, as well as men, with heart failure still have high mortality and morbidity rates despite treatment advances (4). Studies suggest that the clinical expression of heart failure could be affected by gender-related disparities in cardiac function and adaptation that have been observed in the laboratory (5–8), during aging (9) and in patients with aortic stenosis (10), hypertension (11) and heart failure (12). Whether these physiologic differences significantly alter the clinical expression and outcome of heart failure in men versus women continues to be debated.

Many previous studies (13–19) have related a variety of demographic, clinical and physiologic characteristics to poor or favorable long-term prognosis in patients with heart failure. However, there is significant conflict between the two most important studies concerning the relation between gender and outcome. The population-based Framingham Heart Study (20,21) results suggest that the prognosis of women is significantly better than men after the onset of symptomatic heart failure. In contrast to these epidemiologic data, Bourassa et al. (22) reported a poorer outcome in women than men presenting with symptomatic heart failure during short-term (1 year) follow-up based on the Studies of Left Ventricular Dysfunction (SOLVD) Registry experience. Additional studies to resolve these discrepant findings have not been reported.

To readdress this controversy, we studied whether the clinical expression and outcome of heart failure differed between men and women and whether gender was an independent risk factor for mortality after adjustment for gender differences in left ventricular function and ischemic etiology. We addressed these questions using information from the UNC Heart Failure Database, University of North Carolina. This prospective, long-term study observed the natural history

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Abbreviations and Acronyms

CI = confidence interval
ECG = electrocardiogram
RR = relative risk

of patients with heart failure at our institution, approximately a third of whom were women.

Methods

The UNC Heart Failure Program, a referral practice at the University of North Carolina devoted to the evaluation and management of patients with heart failure, was initiated in 1984 by one of the authors (K.F.A.). Since that time, selected data on baseline clinical characteristics and outcome in patients seen by the program have been prospectively collected into the UNC Heart Failure Database. Collection methods for the study data were approved by the institutional Committee for the Protection of the Rights of Human Subjects. Entry into this data base required a diagnosis of heart failure based on at least one of the following: shortness of breath at rest or on exertion or fluid retention (edema, orthopnea or paroxysmal dyspnea) that was believed to originate from cardiac causes (23).

Patients had a clinical examination to determine demographics, New York Heart Association functional class and assignment of a primary etiology for their left ventricular dysfunction. Signs and symptoms of heart failure and current medications were recorded from history and physical examination performed in our Heart Failure Clinic or during a previous hospital admission for heart failure. A standard 12-lead electrocardiogram was available within 6 months of study entry for 96% of patients. Patients enrolled from July 1984 through November 1994 who had data on left ventricular ejection fraction obtained by radionuclide ventriculography within 6 months of study entry (91% within 1 month) were considered for this report. Two patients whose heart failure was complicated by other medical diseases (one with advanced scleroderma and another with severe obstructive lung disease) likely to significantly limit their longevity were subsequently excluded.

The majority of patients received their chronic heart failure care in our clinic. Their therapy was optimized according to general guidelines used in heart failure centers at the time of the patient's enrollment. However, treatment varied in individual cases and was not rigorously standardized as in a clinical trial. Beginning in September of 1986, heart transplantation was considered as a therapeutic option in patients who met standard criteria for this procedure. Vital status and the occurrence of heart transplantation were ascertained at last follow-up from contact with the patient, a family member or the referring physician. All heart transplantation procedures and hospital admissions resulting in urgent transplantation occurred at our institution. Information concerning the patient's demise, obtained from available medical records and the patient's attending physician or the family, was used by the study physicians to assign a cause of death. Sufficient follow-up data for determining vital status were available for 99% of patients (six women and one man were lost to follow-up). The cause of death was unknown in one female and three male patients. The mean length of follow-up was 2.4 years (range 1 day to 10 years).

Documentation of coronary disease. Angiographic, autopsy and clinical data were used to establish the presence (188 patients) or absence (369 patients) of coronary artery disease in the study cohort. Coronary artery disease was identified in 156 patients on the basis of angiographic (147 patients) or autopsy (9 patients) evidence of ≥70% stenosis of at least one major epicardial coronary artery. Previous myocardial infarction documented by standard ECG or enzymatic criteria established the diagnosis of coronary disease in another 29 patients. In three patients, the diagnosis of ischemic heart disease was based on the presence of typical angina and a stress radionuclide examination consistent with ischemia. Coronary artery disease was judged absent in the remaining 369 study patients. In 194 of these patients, coronary angiography revealed no significant obstructive lesions, and autopsy results were negative in another 16. The remaining 159 patients were judged not to have coronary artery disease according to the following clinical criteria: no evidence of previous myocardial infarction by history or ECG findings; no history of angina pectoris; and the presence of an alternative etiology of heart failure.

Assignment of etiology. Available clinical, laboratory and autopsy data were utilized to assign a primary etiology for heart failure in each patient. When multiple etiologic factors were present, the one judged to be predominant was identified as the primary cause. Ischemic heart disease was assigned as the primary etiology in 162 of 188 patients with the diagnosis of coronary artery disease. All 129 patients assigned hypertension as the primary etiology of their heart failure had a history of this disorder and evidence of either 1) antihypertensive pharmacologic treatment, or 2) documentation of blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic on at least three separate occasions before or within 3 months after their entry date (24). A primary etiology of hypertension was assigned only after exclusion of other specific causes of cardiomyopathy detailed later. Alcohol-related cardiomyopathy was designated in 70 patients with a history of excessive ethanol intake documented by a daily ingestion of 75 g of alcohol for ≥1 year (25). Another 13 patients, with heavy but unquantifiable alcohol use and social evidence of serious ethanol abuse (traffic violation or attendance at Alcoholics Anonymous) were also assigned alcohol as a primary etiology. Valvular heart disease was denoted as the primary etiology in 29 patients on the basis of the presence of longstanding tricuspid, mitral or aortic regurgitation documented by physical examination and echocardiography or angiography. Peripartum cardiomyopathy was diagnosed in 14 patients in whom the symptoms of heart

failure developed at delivery (2 patients) or within 6 months of delivery (12 patients).

Other rare causes of heart failure, including familial (11 patients), myocarditis (9 patients), chemotherapy (6 patients) and congenital heart disease (5 patients), were assigned as the primary etiology in 43 patients. Idiopathic cardiomyopathy was designated as the primary etiology in the 97 study patients in whom no apparent cause of heart failure was found. Coronary angiographic (63 patients) or autopsy data (8 patients) ruled out ischemic heart disease as the primary etiology in 71 of these patients. The following primary etiologic groups were thus identified: ischemic heart disease (162 patients), hypertension (129 patients), alcohol related heart disease (83 patients), valvular heart disease (29 patients), idiopathic cardiomyopathy (97 patients) and other (57 patients).

Radionuclide ventriculography. Patients underwent rest equilibrium radionuclide ventriculography by techniques previously described in our laboratory (26,27), and the majority (92%) also underwent first-pass imaging by standard methods, as described by others (28). First-pass left ventricular images were analyzed to determine left ventricular end-diastolic volume by a geometric method (28). This technique was shown in our laboratory to correlate well ($r = 0.95$) with angiographic left ventricular end-diastolic volume determined in our cardiac catheterization laboratory.

Statistical analysis. Data are presented as mean value ± SEM, unless otherwise indicated. Various demographic factors and indexes of cardiac function were compared between men and women by Student *t* test or the chi-square test. The primary study end point was all-cause mortality, and the principal secondary end point was death related to cardiovascular causes. The cause of death was considered to be cardiovascular in the four study patients whose reason for death was unknown. In analyses using the primary and secondary end points, patients undergoing heart transplantation were considered alive and were censored at the time of operation. Because a substantial number of patients underwent heart transplantation during the follow-up period, the following complementary composite secondary end points were also examined: all-cause mortality plus urgent heart transplantation and cardiovascular death plus urgent heart transplantation. Heart transplantation was defined as urgent if the patient developed worsening heart failure requiring hospital admission and inotropic support before this surgical procedure. Cumulative survival curves based on gender were constructed by Kaplan-Meier methods, with differences between the curves tested for significance by the log-rank statistic (29). The Cox proportional hazards regression method was used to determine the relation of gender and other baseline characteristics to outcome (30,31). The following variables, determined from the baseline evaluation, were considered potential predictors of study end points: gender, functional class, ischemic versus nonischemic primary etiology of heart failure, race, age, left ventricular ejection fraction, left ventricular end-diastolic volume index, left ventricular end-systolic volume index, height, weight, body surface area, body mass, presence of atrial fibrillation and use of antiplatelet therapy. A method similar to that reported by Harrell et al. (31) was followed by grouping baseline characteristics related to cardiac function and patient morphology into clusters likely to be intercorrelated and relevant to the same clinical phenomenon. A stepwise regression identified any variables within each cluster that were likely to be significant. These variables and other baseline characteristics shown to be univariate predictors of outcome with a significance level ≤ 0.10 were then analyzed in a stepwise fashion to develop Cox models of the study end points and to create an adjusted survival curve for men and women. In addition, the effect of race on the final model was also evaluated by proportional hazard methods. The uniformity of the association between gender and outcome in various etiologic groups was assessed by the likelihood ratio test from the proportional hazards model (29).

Study patients. A total of 557 patients who met the criteria for study entry were identified in the data base. The mean (±SD) age of the study patients was 51 ± 14 years, (range 13 to 87), and approximately one-third were female (32%), and 53% were white. The majority of the patients were functional class II (30%) or III (49%). Only 14 patients (2.5% of 557) were assigned to functional class I at their baseline evaluation. All patients met the study definition of heart failure, and 90% had symptoms of both fluid retention and dyspnea. A left ventricular third heart sound was a common finding on physical examination (77%), and congestion, as evidenced by jugular venous distension (46%) or rales (35%), was frequently present. The primary cause of heart failure was judged to be nonischemic in 68% of patients. Severe left ventricular dysfunction was typically present, with a mean (±SD) left ventricular ejection fraction of 25 ± 13 in the study cohort and an ejection fraction <40% in 86%.

Results

Baseline patient data. Men and women did not differ with regard to functional class, but men were significantly more likely than women to be white, to have atrial fibrillation on the baseline ECG and to have ischemic heart disease as the primary etiology of heart failure (Tables 1 and 2). Rest left ventricular ejection fraction was significantly higher in women than men (Table 1). At baseline (Table 2), a similar proportion of men and women were receiving angiotensin-converting enzyme inhibitors (69% vs. 72%, $p = 0.419$) and digoxin (69% vs. 68%, $p = 0.834$), whereas total diuretic use in men tended to be higher than in women (82% vs. 75%, $p = 0.056$). Men were receiving antiplatelet therapy more frequently than women (22% vs. 13%, $p = 0.016$).

Table 3 compares selected baseline characteristics in men and women by ischemic versus nonischemic etiology. Left ventricular ejection fraction did not differ in men and women when ischemic heart disease was the primary etiology of heart failure, but women had a higher left ventricular ejection fraction than men in the nonischemic group. Women were older than men when the primary etiology was ischemic heart

Table 1. Baseline Characteristics of Male and Female Study Patients

Characteristic	Men (n = 380)	Women (n = 177)	p Value
Age (yr)	52 ± 0.7	49 ± 1.1	0.031
White	58% (219)	44% (78)	0.003
History of			
HTN	53% (202)	51% (91)	0.701
DM	21% (80)	24% (42)	0.477
CABG	16% (60)	5% (8)	<0.001
Etiology of HF			
Idiopathic	13% (48)	28% (49)	<0.001
Alcohol	21% (78)	3% (5)	<0.001
Ischemic	37% (142)	11% (20)	<0.001
Valvular	4% (14)	9% (15)	0.018
Hypertensive	20% (76)	30% (53)	0.010
Other	5% (22)	19% (35)	<0.001
IHD primary	37% (142)	12% (20)	<0.001
AF	12% (45)	5% (9)	0.012
Body habitus			
Height (cm)	178 ± 0.42 (n = 361)	163 ± 0.54 (n = 171)	<0.001
Weight (kg)	84 ± 1.0 (n = 361)	72 ± 1.5 (n = 170)	<0.001
Body mass (kg/ht^2)	27 ± 0.3 (n = 361)	27 ± 0.6 (n = 170)	0.340
LVEF (U)	24 ± 0.6 (n = 380)	29 ± 1.1 (n = 177)	0.001
LVEDVI (ml/m^2)	191 ± 3.6 (n = 357)	185 ± 4.9 (n = 168)	0.324
LVESVI (ml/m^2)	149 ± 3.5 (n = 357)	137 ± 4.9 (n = 168)	0.048

Data presented are mean value ± SD or percent (number) of patients. AF = atrial fibrillation; CABG = coronary artery bypass graft surgery; DM = diabetes mellitus; HF = heart failure; HTN = hypertension; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; LVESI = left ventricular end-systolic volume index.

Table 2. Historical Data on Signs, Symptoms and Therapy for Heart Failure in Male and Female Patients

Characteristic	Men (%)	Women (%)	p Value (chi-square)
NYHA functional class			0.343
I	2	4	
II	30	29	
III	50	46	
IV	18	21	
Symptoms of			
Dyspnea on exertion	90	92	0.475
Edema	51	59	0.085
Orthopnea	61	71	0.023
PND	48	48	0.974
Physical exam			
Rales	36	32	0.337
JVD	45	47	0.527
S3	77	77	0.926
Pedal edema	39	46	0.119
Medication			
Digitalis	69	68	0.834
Diuretic	82	75	0.056
ACE inhibitor	69	72	0.419
Long-acting nitrate	26	21	0.210
Hydralazine	7	8	0.650
Dobutamine	4	5	0.779
Calcium antagonist	8	6	0.413
Antiplatelet	22	13	0.016
Anticoagulant	27	31	0.444
Amiodarone	3	2	0.458

ACE = angiotensin converting enzyme; JVD = jugular venous distension; NYHA = New York Heart Association; PND = paroxysmal nocturnal dyspnea; S3 = left ventricular S3 gallop.

disease but ages were similar in patients with a nonischemic etiology.

Outcome of men versus women. During the follow-up period, 201 patients reached the primary study end point of all-cause mortality (156 men, 45 women). In 180 patients (41 women, 139 men), death was attributed to cardiovascular causes. Heart transplantation was deemed urgent in 57 (42 men, 15 women) of the 65 patients undergoing this procedure. Life-table analysis demonstrated that female patients were significantly less likely to have a mortal event during follow-up than male patients ($p < 0.001$) (Fig. 1). Women survived longer than men when the end point was cardiovascular mortality ($p < 0.001$). In addition, the composite end points of all-cause mortality plus urgent heart transplantation, and cardiovascular mortality plus urgent heart transplantation were more likely to be reached by men than women during follow-up ($p < 0.001$ for both).

Predictors of outcome. A number of baseline characteristics, in addition to gender, were univariate predictors of all-cause mortality in the study cohort (Table 4). Atrial fibrillation but not use of antiplatelet medication tended to be a univariate predictor of outcome. Although indexes of body habitus differed between men and women, proportional hazards analysis of this cluster of variables and gender demonstrated that only gender was significantly related to outcome ($p < 0.001$). Initial multivariate analysis demonstrated that female gender was associated with a better outcome after all other significant univariate predictors were accounted for (adjusted relative risk [RR] of men vs. women for all-cause mortality was 2.37, 95% confidence interval [CI] 1.37 to 3.51, $p < 0.001$). Multivariate analysis also demonstrated that functional class, age, left ventricular ejection fraction and primary ischemic etiology of heart failure were independently associated with all-cause mortality after adjustment for all other significant univariate variables (Table 5). In addition, the final predictive model was not altered when race was included as part of the multivariate Cox analysis.

Further multivariate Cox proportional hazards analysis demonstrated that the favorable association between female gender and all-cause mortality was dependent on the etiology of heart failure ($p = 0.008$) (Tables 5 and 6). The risk of death was similar for the subset of men and women with ischemic heart disease as the primary cause of heart failure (n = 162). The relative risk of males versus females in this etiologic group was <1, but this difference was not significant (men vs. women:

Table 3. Comparison of Selected Clinical Characteristics in Men Versus Women by Ischemic or Nonischemic Etiology*

	IHD Primary Etiology			Non-IHD Primary Etiology		
	Men (n = 142)	Women (n = 20)	p Value	Men (n = 238)	Women (n = 157)	p Value
Age (yr) (mean ± SD)	58 ± 0.9	64 ± 2.0	0.025	48 ± 0.9	47 ± 1.1	0.529
NYHA functional class (%)			0.189			0.541
I	2	0		2	4	
II	23	20		34	30	
III	50	40		50	47	
IV	25	40		14	19	
LVEF (U) (mean ± SD	23 ± 0.8	24 ± 2.9	0.575	24 ± 0.8	29 ± 1.2	<0.001

*Men versus women within each etiologic group; p values reflect Student *t* test, except those for functional class, which were computed using the chi-square statistic. Abbreviations as in Tables 1 and 2.

RR 0.85, 95% CI 0.45 to 1.61, p = 0.651). In contrast, men had a significantly greater risk of death than women in the subset of patients judged to have a nonischemic etiology of heart failure (n = 395; men vs. women: RR 2.36, 95% CI 1.59 to 3.51, p < 0.001). These findings are reflected in the adjusted survival curves for men and women with ischemic and nonischemic etiologies shown in Figure 2. The confidence limit for the relative risk of men versus women with heart failure primarily associated with ischemic heart disease was distinct from that found in patients with nonischemic heart failure (Fig. 3).

Because of the interrelation between etiology, gender and outcome, additional analyses were undertaken using different definitions of ischemic heart disease. Multivariate Cox proportional hazards analysis was repeated, with ischemic heart disease defined as the presence (n = 188) or absence (n = 369) of significant coronary artery disease, whether this disease was considered the primary cause of heart failure. The predictors included in this model were gender, ischemic heart disease (as previously defined) functional class, left ventricular ejection fraction and age (Table 5). Using this categorization, male gender was associated with an increase in risk similar to that observed in the principal study analysis (n = 557; men vs. women: RR 1.94, 95% CI 1.35 to 2.78, p < 0.001). Again as in the principal analysis, the relation between gender and outcome tended to be linked to the primary etiology of heart failure (p = 0.162 for the gender–etiology interaction). Outcome was similar in men and women with evidence of coronary artery disease (n = 188; men vs. women: RR 1.08, 95% CI 0.58 to 2.00, p = 0.812). In contrast, men without coronary artery disease had a greater risk than women (n = 369; men vs. women: RR 2.38, 95% CI 1.58 to 3.58, p < 0.001).

Proportional hazards analysis was also performed in study patients (n = 395) in whom the presence or absence of coronary artery disease was determined on the basis of invasive methods (coronary angiography or autopsy) or the occurrence of myocardial infarction. Male gender was associated with poorer survival in this subset (men vs. women: RR 1.86, 95% CI 1.11 to 3.15, p = 0.020). Male gender was also associated with an unfavorable prognosis in the remaining 162 patients whose coronary artery disease status was determined by clini-

Figure 1. Kaplan-Meier estimates of survival for male and female patients. p < 0.001 by log-rank test. Women (**circles**) had a significantly better outcome during follow-up. **Squares** = men.

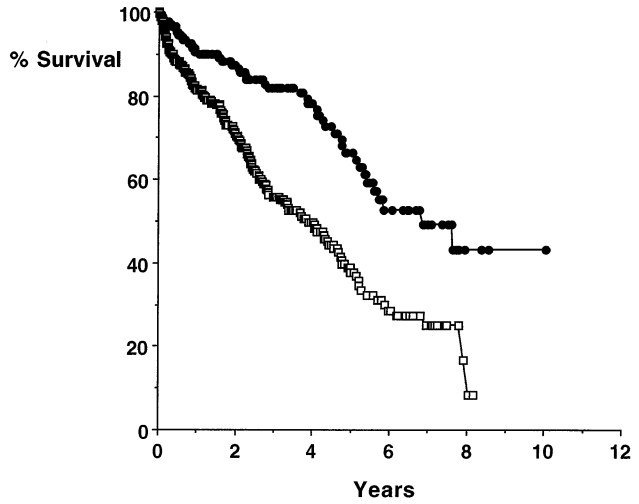


Table 4. Univariate Relation of Individual Baseline Characteristics to All-Cause Mortality

Variable	Chi-Square	RR (95% CI)	p Value*
NYHA functional class	30.2	1.76 (1.44–2.15)	<0.001
LVEF (per 5 U)	24.5	0.85 (0.80–0.91)	<0.001
Type of CM (IHD)	31.8	2.32 (1.73–3.11)	<0.001
Gender (male)	24.7	2.23 (1.67–3.26)	<0.001
Age (decade)	25.2	1.31 (1.18–1.46)	<0.001
LVESVI (per 50 ml/m^2)	23.8	1.30 (1.17–1.45)	<0.001
LVEDVI (per 50 ml/m^2)	14.2	1.23 (1.10–1.37)	<0.001
Height (per 10 cm)	10.4	1.25 (1.09–1.42)	0.001
BSA	3.0	1.66 (0.94–2.93)	0.083
Body mass	1.7	0.98 (0.96–1.01)	0.195
Weight (per 5 kg)	0.2	1.01 (0.97–1.04)	0.666
Race (white)	1.0	1.15 (0.88–1.52)	0.322
AF	3.2	0.68 (0.45–1.03)	0.070
Antiplatelet therapy	0.1	0.98 (0.67–1.44)	0.924

*Cox proportional hazards model. BSA = body surface area; CI = confidence interval; CM = cardiomyopathy; RR = relative risk; other abbreviations as in Tables 1 and 2.

Table 5. Baseline Characteristics With Independent Prognostic Value

Variable	Adjusted Chi-Square	RR (95% CI)	p Value*
Gender (male)	13.0	1.90 (1.28–1.99)	<0.001
Type of CM (IHD)†	7.8	1.58 (1.15–2.17)	<0.001
NYHA functional class	17.6	1.60 (1.28–1.99)	<0.001
LVEF (per 5 U)	11.7	0.89 (0.83–0.95)	<0.001
Age (decade)	11.3	1.22 (1.09–1.37)	<0.001
Interaction, type of CM and gender	7.0	0.36 (0.17–0.77)	0.008

*Cox proportional hazards model. †Significant predictor when modeling was done before an interaction between gender and ischemic heart disease (IHD) was considered. Abbreviations as in Tables 1, 2 and 4.

cal criteria alone (men vs. women: RR 2.80, 95% CI 1.55 to 5.07, $p < 0.001$).

Discussion

Clinical investigation suggests that the natural history and response to therapy may differ in men and women with cardiovascular disease (1,2). Although most work has concentrated on gender differences in ischemic heart disease, heart failure of any cause is an important cardiovascular condition in women. By conservative estimate, there are ~1 million female patients with heart failure in the United States today (3). Both women and men continue to have high mortality and morbidity from symptomatic failure despite treatment advances. An increasing body of laboratory (5–8), and clinical research (9–12) suggests there are gender-related differences in cardiac function and myocardial adaptation to injury or stress. Available studies disagree as to whether these physiologic factors result in different clinical characteristics and survival in men and women with heart failure. Our investigation addresses these conflicting results.

We found that women—not men—survived longer with symptomatic heart failure. To clarify this association, we examined the relation between gender and a number of clinical characteristics of heart failure. We found two major differences. Men were more likely than women to have an ischemic etiology of their heart failure, and left ventricular ejection fraction was higher in nonischemic women than nonischemic men.

Table 6. Relative Risk of Men Versus Women in Subsets Defined by Interaction of Gender and Ischemic–Nonischemic Etiology

Subset	Adjusted Chi-Square	RR (95% CI)	p Value
IHD vs. non-IHD			
Women	14.1	3.82 (1.90–7.69)	<0.001
Men	3.3	1.37 (0.98–1.92)	0.067
Men vs. women			
IHD	0.3	0.85 (0.45–1.61)	0.615
Non-IHD	18.0	2.36 (1.59–3.51)	<0.001

Abbreviations as in Tables 1 and 4.

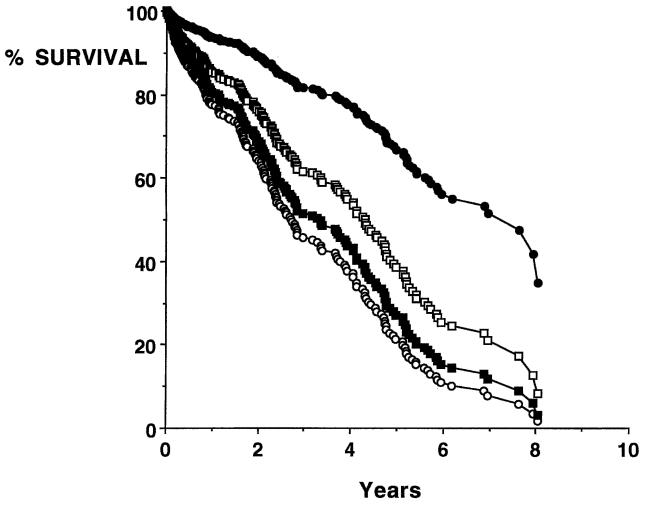
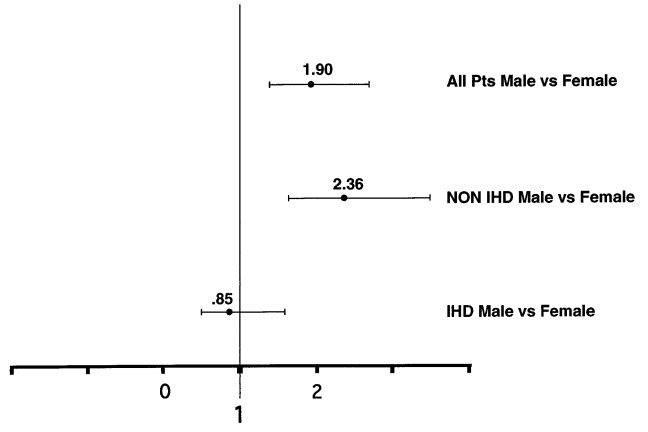


Figure 2. Adjusted survival curves for male and female patients with and without ischemic heart disease as the primary etiology of heart failure. Cox proportional hazards method revealed a significant interaction between ischemic etiology and the association between gender and survival ($p = 0.008$). Women without coronary artery disease as the primary cause of heart failure had a significantly better outcome during follow-up. **Open circles** = women with ischemic cardiomyopathy; **solid circles** = women with nonischemic cardiomyopathy; **open squares** = men with nonischemic cardiomyopathy; **solid squares** = men with ischemic cardiomyopathy.

The survival advantage of women could have been due to better left ventricular function. However, mortality was still lower in women after Cox proportional hazards modeling adjusted for baseline differences in left ventricular function. In contrast, the association between gender and outcome was related to the primary etiology of heart failure (Fig. 2). Modeling revealed that survival was significantly better in

Figure 3. Relative risks and 95 percent confidence intervals for all-cause mortality of men versus women in various patient groups. Relative risks are adjusted for the variables shown in Table 5. An interaction between gender, etiology and outcome is revealed. The risk of men with nonischemic etiologies of heart failure is significantly greater than that of women with a similar etiology. In contrast, the relative risk is similar in men and women with an ischemic etiology of heart failure. IHD = ischemic heart disease; Pts = patients.



women than men when heart failure was due to nonischemic causes but was similar in the two genders when the principal etiology was ischemic heart disease. The confidence interval of the relative risk of women versus men with nonischemic cardiomyopathy was well above unity and distinct from that of patients with ischemic cardiomyopathy (Fig. 3). In contrast, the survival of women with heart failure due to ischemic cardiomyopathy did not appear to be longer than that for men with this cause of heart failure.

Various causal factors were present in our patients with a primary nonischemic origin of heart failure. Differences in outcome between men and women may be limited to specific etiologic factors within this broad group. Additional studies in a larger cohort of men and women with specific etiologies of heart failure will be needed to resolve this issue.

Origin of differences. Although our investigation does not identify the reasons for the difference in outcome between men and women with heart failure, a number of possibilities, both demographic and physiologic, can be considered. Interestingly, despite previous findings in coronary artery disease, our survival analysis did not suggest an association between body habitus and prognosis. Women may have survived longer simply because they were identified earlier in the course of their disease. They appeared to have a similar degree of symptomatic heart failure but a better baseline level of left ventricular function than men. We cannot rule out differences in follow-up treatment or compliance with treatment that may have influenced the occurrence of different outcomes in men and women.

Fundamental physiologic differences in the nature and extent of myocardial hypertrophy and adaptation might also play a role in the gender differences that we found (7,8). Animal studies by Pfeffer et al. (6) suggest that the adverse influence of a given degree of hypertrophy on cardiac function is different in male and female spontaneously hypertensive rats. Despite a similar degree of concentric hypertrophy, peak stroke volume and end-diastolic volume indexes were similar in control and 18 month old affected female rats. In contrast, similarly aged affected male rats showed a significant reduction in peak stroke volume index and an increase in end-diastolic volume index compared with age-matched control rats. Recent work by Carroll et al. (10) suggests that gender may influence left ventricular adaptation to the abnormal cardiac loading conditions present in patients with aortic stenosis. In their study of elderly patients with severe aortic stenosis, women tended to have well preserved systolic function with less ventricular dilation and hypertrophy than their male counterparts, even when indexes of cardiac function were normalized for body surface area. Devereux et al. (11) have reported that hypertensive women are more likely than hypertensive men to have left ventricular hypertrophy when a gender-specific 97th percentile upper limit of normal is used to define increased myocardial mass. Echeverria et al. (12) also found that left ventricular function is better preserved in women than men presenting with congestive heart failure. The autopsy study of Olivetti et al. (9) in patients free of cardiovascular disease found that aging is associated with cardiac myocyte cell loss and reactive hypertrophy in men but not women. Their findings suggest that the myocardium of men may be more vulnerable to the effects of cardiac damage than that of women. Although these laboratory findings are intriguing, additional studies of the relation between outcome and ventricular structure and function in men and women will be required.

Previous work: gender and survival. Our data may help to reconcile the conflicting results of previous studies concerning gender-related differences in the outcome of heart failure. Early and recent epidemiologic data from the Framingham cohort (20,21) suggest that prognosis in women is better than that in men after the development of heart failure. These results are consistent with our findings because the majority of Framingham study patients appear to have developed heart failure primarily from nonischemic causes. In addition, our data suggesting an influence of etiology on the association between gender and survival may help to explain the results of Bourassa et al. (22). Their study showed that female gender was associated with a poor prognosis but in a population of older patients with heart failure primarily due to coronary artery disease. Several other previous series (32–38) in patients with symptomatic heart failure have found an inconsistent relation between gender and outcome. However, the majority of these studies lacked statistical power to detect a gender-related difference in mortality and did not take into account the association between etiology and the influence of gender on outcome observed in our work.

Limitations of the study. There are several potential limitations to our study. The presence or absence of coronary artery disease was determined in a number of patients on the basis of clinical criteria alone. However, our analysis suggests that the association between gender, etiology and survival did not depend on the method of defining ischemic heart disease. Female gender predicted better survival when ischemic heart disease was expanded to include the presence or absence of coronary artery disease without regard for the patient's primary etiology of heart failure. Additionally, a favorable association between female gender and outcome was found in those study patients in whom angiography and autopsy results or the occurrence of myocardial infarction was used to determine the presence or absence of ischemic heart disease.

The small number of women with ischemic heart disease limits the strength of our conclusions concerning survival in men and women in this etiology group. Although the point estimate in this subset was close to 1, the confidence interval was wide, and we cannot fully rule out a survival difference between the two genders in this etiologic group. The higher early mortality of women after myocardial infarction might have been expected to select a group of women who would have a better outcome than men with chronic ischemic heart failure (2). Clearly, additional long-term investigation of a larger cohort of patients with heart failure due to ischemic heart disease is warranted to determine whether risk is indeed similar in men and women.

The generalizability of our results could be questioned because our investigation was conducted at a single center and

enrolled patients who were relatively young. We cannot rule out the possibility that a different relation between gender and outcome would have been found in a wider geographic area or among geriatric patients. Acknowledging this potential limitation, our study did enroll a relatively high proportion of women and African-Americans, constituting a demographic spectrum not commonly found in clinical trial data sets. Data concerning other important prognostic factors, including plasma norepinephrine and exercise capacity, would be of great interest but were not consistently available in our patients. Additional investigation is needed to determine whether these factors account for the gender difference in survival that we observed.

Conclusions. Our study results support the hypothesis that survival differs between women and men with symptomatic heart failure. Our data suggest a relation between female gender and better outcome but one that depends on the primary etiology of heart failure. Women survived longer than men when heart failure was due to nonischemic causes, but mortality did not appear to differ substantially when heart failure was due to coronary artery disease. Further studies in larger groups of men and women are needed to clarify gender differences in survival in specific nonischemic etiologies of heart failure. Better understanding of the mechanisms contributing to the improved prognosis of women with nonischemic cardiomyopathy may enhance future clinical investigation and drug development for symptomatic ventricular dysfunction.

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