Prognostic Stratification of Women With Chronic Heart Failure Referred for Heart Transplantation: Relevance of Gender as Compared With Gender-related Characteristics

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Background: Few studies are available regarding prognostic stratification of women with severe chronic heart failure (CHF). Although women seem to have a better outcome than men, this may be due to favorable baseline characteristics.

Methods: We analyzed a cohort of CHF patients referred for heart transplantation (HT) who underwent clinical/laboratory/instrumental evaluation. Women and men were frequency matched for baseline age (53 ± 14 vs 53 ± 9 years, $p = 0.92$), left ventricular ejection fraction (33 ± 10 vs $31 \pm 8\%$, $p = 0.90$) and ischemic etiology (17 vs 22% , $p = 0.50$).

Results: A total of 198 patients were analyzed (109 women matched to 89 men). In addition to matching parameters, prevalence of severe symptoms, diabetes and hypertension were also comparable ($p \geq 0.25$). After 3 years, cardiovascular death or need for HT (CD/HT) event-free survival was $78 \pm 4\%$ in women and $50 \pm 6\%$ in men ($p = 0.005$). On multivariate analysis, female gender was associated with a lower risk of CD/HT (relative risk [RR] 0.52; 95% confidence interval [CI] 0.30 to 0.89; $p = 0.017$), independently of symptoms, blood pressure (BP), left ventricular end-diastolic diameter (LVEDD) and mitral regurgitation (MR). Nevertheless, CD/HT event-free survival at 3 years was $49 \pm 9\%$ for women with New York Heart Association (NYHA) Class III or IV status, who presented with either severe MR, mean BP ≤ 60 mm Hg or LVEDD ≥ 35 mm/m².

Conclusions: In advanced CHF, women patients seem to have a better prognosis irrespective of baseline characteristics, supporting the hypothesis that female gender is protective against myocardial injury. However, women with severe symptoms accompanied by either hypotension, severe left ventricular enlargement or MR are at high risk and deserve cautious follow-up and consideration for HT. *J Heart Lung Transplant* 2006;25:648–52. Copyright © 2006 by the International Society for Heart and Lung Transplantation.

Reliable risk stratification in chronic heart failure (CHF) is mandatory to deliver the most appropriate therapeutic strategies, including heart transplantation (HT). Few studies are available to help stratify the prognosis of women with severe CHF,¹ largely because female patients have been consistently under-represented both in

clinical trials and in studies on prognostic stratification.^{1,2} Most studies^{1,3–6} but not all⁷ indicate that women seem to have a better outcome than men. However, these results may have been influenced by profound gender-related differences in baseline characteristics.⁸ Indeed, women were almost invariably older at baseline,^{5–7} and had (when assessed) better preserved left ventricular ejection fraction (LVEF),³ lower prevalence of ischemic etiology^{3–7} and higher prevalence of diabetes.^{6,7} Furthermore, because the original data included only select clinical/instrumental parameters,^{1,3–7} it was not possible to adjust for the confounding influence of several important predictors of outcome.^{2,9}

We analyzed and compared the outcome of women and men within a cohort of CHF patients receiving optimized medical treatment who were referred to the outpatient clinic of our institution, which offers an HT program. Frequency matching was performed accord-

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ing to gender for baseline age, LVEF and prevalence of ischemic etiology to ensure similarity of major determinants of outcome at baseline. Independent prognostic significance of gender was also tested using multivariate analysis.

METHODS

Eligibility Criteria and Setting

All consecutive patients with an established diagnosis of CHF, who were referred to the heart failure clinics of our institutions for prognostic stratification and evaluation for HT from March 1, 1996 through December 31, 2003, were screened for this study. The single eligibility criterion was concomitant availability at index evaluation of a clinical, laboratory, electrocardiographic (ECG) and echocardiographic assessment. To increase the statistical power of the study,¹⁰ all eligible women were matched to eligible men for 3 strong confounders: age (baseline); LVEF (baseline); and underlying ischemic etiology of CHF (as confirmed at coronary angiography). Because the matching process involved multiple variables, frequency matching was selected.^{11,12} The computerized matching process was conducted in a fully blinded fashion (and done before any outcome information was obtained). A 2-dimensional standard transthoracic echocardiogram (Sonos 5500, Hewlett Packard) was performed as previously described.¹³ Severity of mitral regurgitation was evaluated semi-quantitatively from the area of the regurgitant jet by color Doppler assessment.¹⁴ All patients had provided written consent to confidential use of their data. The study was conducted in accordance with our institutional guidelines and national legal requirements.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD or as otherwise reported, and categoric variables as numbers (percentages). Group comparisons were performed using the *t*-test or chi-square test, as appropriate. The combined end-point was cardiovascular death or need for heart transplantation (CD/HT)¹⁵⁻²¹; analysis was performed with censoring at the time of cardiac surgery (other than HT), whenever this was performed ($n = 1$). Event rates were estimated using the Kaplan-Meier method. Each baseline variable was individually tested by univariate Cox proportional hazards analysis (because frequency matching was necessarily conducted using categoric definitions of LVEF and age, these 2 parameters were also tested as continuous variables).¹⁰ Variables that reached $p < 0.10$ were then used to create a multivariate model. The variable "gender" was then added into this model. $p < 0.05$ was considered statistically significant. All tests were performed using

Table 1. Principal Baseline Characteristics of the Study Population According to Gender

	Women (<i>n</i> = 109)	Men (<i>n</i> = 89)	<i>p</i>
Age (years)	53 $\pm$ 14	53 $\pm$ 9	0.92
NYHA Class III or IV	38 (35%)	33 (37%)	0.77
Ischemic etiology of			
congestive heart failure	19 (17%)	20 (22%)	0.50
Mean blood pressure (mm Hg)	57 $\pm$ 6	56 $\pm$ 9	0.65
Hypertension	49 (45%)	32 (36%)	0.25
Diabetes	18 (16%)	13 (15%)	0.85
Atrial fibrillation	9 (8%)	14 (16%)	0.12
QRS duration (ms)	136 $\pm$ 37	140 $\pm$ 38	0.37
Left atrial diameter (mm/m ²)	28 $\pm$ 7	26 $\pm$ 5	0.053
Left ventricular end-diastolic diameter (mm/m ²)	38 $\pm$ 5	38 $\pm$ 7	0.60
Left ventricular end-systolic diameter (mm/m ²)	31 $\pm$ 6	33 $\pm$ 7	0.082
Left ventricular ejection fraction (%)	33 $\pm$ 10	31 $\pm$ 8	0.90
Severe mitral regurgitation	37 (34%)	33 (37%)	0.66

STATVIEW 5.0.1 software (SAS Institute, Inc.) for Windows.

RESULTS

Study Population

A total of 198 patients entered the analysis (all 109 eligible women, frequency matched to 89 eligible men). Table 1 indicates the main baseline characteristics of the study population: these major determinants of prognosis appeared mostly comparable in men and women. The impairment in clinical/instrumental parameters indicates that CHF was generally severe. The young mean age likely reflects the institutional availability of an HT program. With regard to medications, 87 (80%) women and 70 (79%) men were taking beta-blockers ($p = 0.90$); angiotensin-converting enzyme (ACE) inhibitors were taken by 96 (88%) female patients and by 83 (93%) male patients ($p = 0.24$). The 2 most common ACE inhibitors used were enalapril (66 patients; mean dosages in women and men: 15 $\pm$ 7 vs 19 $\pm$ 15 mg/day; $p = 0.19$) and ramipril (43 patients; mean dosages in women and men: 6 $\pm$ 3 vs 5 $\pm$ 2 mg/day; $p = 0.21$). Eighty-seven (80%) women and 70 (79%) men were taking beta-blockers ($p = 0.90$). The most common beta-blocker prescribed was carvedilol (138 patients; dosages in women and men: 25 $\pm$ 16 vs 22 $\pm$ 17 mg/day; $p = 0.15$). Use of implantable cardioverter defibrillators appeared comparable in men ($n = 11$) and women ($n = 8$) ($p = 0.33$).

Incidence of Adverse Cardiac Events According to Gender

During a mean medical follow-up of 24 $\pm$ 18 months (in 99% of patients followed up to 2004 or death), 17

Figure 1. CD/HT event-free survival according to gender among 198 CHF patients with similar baseline characteristics.

patients died from cardiovascular death (CD) and a further 47 required HT due to worsening clinical conditions. Cardiovascular deaths were attributed to CHF in 13 of 17 (76%) patients. Ten (58%) of the deaths were sudden. **Figure 1** shows CD/HT event-free survival curves according to gender. CD/HT event-free survival at 3 years turned out to be significantly more favorable in women ($78 \pm 4\%$ vs $50 \pm 6\%$; $p = 0.005$), although the matching process (for age, LVEF and ischemic etiology) led to similarities in most other major baseline characteristics.

Analysis of Predictors of Adverse Cardiac Events

Non-gender-related predictors. The following variables reached $p < 0.1$ according to univariate analysis, with CD/HT as the end-point: New York Heart Association (NYHA) Class III or IV status ($p < 0.0001$); mean blood pressure (BP; $p < 0.0001$); QRS duration ($p = 0.009$); left ventricular end-systolic and end-diastolic diameter (LVEDD); LVEF; left atrial diameter; and presence of severe functional mitral regurgitation (MR) (all $p < 0.001$). Non-gender-related variables that turned out to be independent predictors of CD/HT according to multivariate analysis are reported in **Table 2**.

Effect of gender. On univariate analysis, the risk ratio (RR) for female gender was 0.49, with a 95% confidence interval (95% CI) of 0.29 to 0.81 ($p = 0.006$). **Table 3** reports multivariate predictors of CD/HT after female

Table 3. Multivariate Predictors of CD/HT Factoring the Variable "Gender" Into the Model

	Risk ratio ^a	95% confidence interval	<i>p</i>
NYHA Class III or IV	3.04	1.72–5.38	<0.001
Mean blood pressure (mm Hg)	0.95	0.92–0.98	0.002
Left ventricular end-diastolic diameter (mm/m ²)	1.06	1.02–1.11	0.004
Severe mitral regurgitation	1.96	1.11–3.47	0.020
Female gender	0.52	0.30–0.89	0.017

^aExpressed per unit of each determinant.

gender was factored into the multivariate Cox proportional hazards model. Female gender was independently associated with a reduced risk of adverse cardiac events (RR 0.52; 95% CI 0.30 to 0.89; $p = 0.017$). The independent prognostic significance of female gender was retained even when the following variables were individually forced into the model: presence of multivessel disease by coronary angiography ($n = 25$; RR 0.46; $p = 0.018$); age (RR 0.53; $p = 0.022$); and LVEF (RR 0.50; $p = 0.013$). CD/HT event-free survival at 3 years in women with NYHA Class III or IV status, with either severe MR, mean BP ≤ 60 mm Hg (corresponding to the approximation of the median value of mean BP) or LVEDD ≥ 35 mm/m² (corresponding to the to the approximation of the median value of LVEDD), was $49 \pm 9\%$ ($n = 37$; $p < 0.001$ vs the other women). Notably, the use of ACE inhibitors was not significantly different between female patients with and without mean BP ≤ 60 mm Hg ($p = 0.13$).

DISCUSSION

Limited data are available to help stratify the prognosis of female patients with CHF.¹ Furthermore, it remains unclear whether the reportedly more favorable outcome of women is related to gender per se or depends on favorable baseline characteristics.^{9,22,23} The present study was specifically designed not only to help prognostic stratification of female CHF patients, but also to analyze, for the first time, the influence of gender in the presence of largely comparable baseline characteristics.

All the patients had been submitted to a very extensive set of concomitant clinical, instrumental and laboratory assessments.^{2,9} To increase the statistical power of the study,¹⁰ we adopted frequency matching for 3 major determinants of outcome. This decision allowed us to take into account the possible influence of a wide range of possible confounders.^{10–12} Despite largely similar medical treatment and baseline values for a series of prognostically relevant variables⁹ (**Table 1**), the women had a better outcome in terms of a lower incidence of major adverse cardiac events (**Figure 1**). Moreover, gender retained independent prognostic significance for these adverse events even after adjusting

Table 2. Non-gender-related Predictors of CD/HT at Multivariate Analysis

	Risk ratio ^a	95% confidence interval	<i>p</i>
NYHA Class III or IV	2.80	1.58–4.97	<0.001
Mean blood pressure (mm Hg)	0.94	0.91–0.97	<0.001
Left ventricular end-diastolic diameter (mm/m ²)	1.07	1.03–1.12	0.002
Severe mitral regurgitation	1.77	1.00–3.12	0.051

^aExpressed per unit of each determinant.

at multivariate analysis for all of the independent predictors of outcome deriving from the comprehensive set of clinical, instrumental and laboratory variables.

Evidence of better survival among women (derived from analyses of populations with heterogeneous baseline characteristics) has often been explained in terms of their higher mean baseline values of LVEF.⁸ Notably, the Framingham study²⁴ and NHANES 1 study,²⁵ neither of which assessed LVEF, showed more favorable survival in women with CHF. However, these findings were not confirmed in the SOLVD study, which enrolled only patients with established low LVEF.⁷ More recent reports^{1,5,6} supporting a protective effect of female gender involved disputable adjustments for major differences at baseline—including LVEF, age and ischemic etiology—sometimes in the presence of a different medical treatment. It has been hypothesized that gender could influence the pathophysiologic response to myocardial injury. Clinical and biologic studies have indicated that a protective effect of female gender could be due to a more favorable response of the left ventricle to pressure overload,²⁶ attenuated sympathetic activation and parasympathetic withdrawal,²⁷ reduced myocyte necrosis and apoptosis²⁸ or a protective effect of gender hormones on the renin-angiotensin system.²⁹

In the present study, NYHA class, BP, LVEDD and presence of severe functional MR turned out to be independent predictors of serious adverse cardiac events even when adjusted for gender. While providing useful confirmation of the prognostic value of some previously identified predictors of outcome,^{1,2} our results suggest a novel combination of commonly available indicators of prognosis, which may be useful for prognostic stratification of female patients. Notably, female patients who presented with severe symptoms associated with either hypotension, severe left ventricular enlargement or MR turned out to be at high risk, with an event-free survival at 3 years comparable to male patients. Taken together these findings indicate that female patients presenting these factors are at high risk and therefore deserve cautious follow-up. Of note, the broad similarity of use of ACE inhibitors in women with and without mean BP ≤ 60 mm Hg suggests that outcome differences were more likely due to the underlying severity of CHF rather than to beneficial effects of this class of drugs.²

Regarding study limitations, in this retrospective analysis of prospectively collected data, CD and need for HT were considered as a combined end-point—a highly relevant clinical outcome measure that has been used widely in previous studies on CHF.^{15–21} Furthermore, even when the analysis was repeated censoring the follow-up at the time of HT and considering acute heart failure or CD as the end-point, the RR related to female gender remained similar (RR 0.40, $p = 0.002$). The

clinical/instrumental assessment was obtained at a given timepoint, and it is possible that studies analyzing time-related changes in prognostic parameters could provide a further relevant contribution to the topic of gender and CHF.²¹ Unfortunately, information on the duration of CHF was not available.

Although prevalence of ischemic heart disease was similar in men and women ($p = 0.50$), the event-free survival was more favorable in female patients (Figure 1). Furthermore, the lower risk of adverse events that characterized female gender was confirmed on multivariate analysis independently from the presence of ischemic etiology of CHF (RR 0.52, $p = 0.018$). Taken together, these findings suggest that the survival advantage of female gender is not affected by the presence of coronary artery disease, although the relatively low prevalence of CHF due to ischemic heart disease in the present series does not allow firm conclusions with respect to this issue.¹

In conclusion, in advanced CHF, female patients seem to have a better prognosis irrespective of baseline characteristics, supporting the hypothesis that female gender exerts a protective effect against myocardial injury. Nevertheless, women with severe symptoms and either hypotension, severe left ventricular enlargement or MR are at high risk and deserve cautious follow-up and consideration for HT.

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