No gender survival difference in a population of patients with chronic heart failure related to left ventricular systolic dysfunction and receiving optimal medical therapy

P. de Groote*, N. Lamblin, F. Mouquet, C. Bauters

Pôle de cardiologie et maladies vasculaires, Hôpital Cardiologique, Centre hospitalier universitaire, Lille.

KEYWORDS
Chronic heart failure; Systolic dysfunction; Gender; Woman; Prognosis.

Summary
Introduction. — Controversial results have been published concerning a possible gender survival difference in patients with chronic heart failure (CHF).

Methods. — We analysed data from consecutive patients with stable CHF admitted to our department for prognostic evaluation. Patients underwent coronary angiography, echocardiography, radionuclide angiography and a cardiopulmonary exercise test.

Results. — We included 613 consecutive patients of whom 115 (19%) were women. The major difference in clinical characteristics was a higher proportion of ischaemic cardiomyopathy in men compared to women (51% vs 28%, p<0.0001) and a lower left ventricular ejection fraction (35±9 vs 38±9, p=0.001). Therapeutic management was similar in men and women. A total of 140 cardiovascular-related deaths and 4 urgent transplantations occurred during a median follow-up of 1.234 days. There was no gender difference in cardiac survival. Cardiovascular mortality rates at 2 years were 11% in men and 13% in women.

Conclusions. — Despite a lower percentage of ischaemic cardiopathy in women, no gender survival benefit was found in our population of CHF patients receiving optimal medical therapy.

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Introduction

Previous studies have shown gender differences in clinical characteristics, therapeutic management and survival in patients with cardiac diseases. Although some specific aspects of metabolism could explain these differences, gender difference in survival in patients with chronic heart failure (CHF) remains controversial. Some studies clearly demonstrate better survival in women with CHF, particularly in post-hoc analyses of large mortality trials [4-6]. However, other studies have failed to demonstrate a gender survival benefit [7, 8]. In the SOLVD (Studies Of Left Ventricular Dysfunction) registry and the DIG (Digitalis Investigation Group) trial, women had a greater mortality than men [7, 8]. These controversial results could be related to selection bias in mortality trials and gender differences in the management of CHF.

The aim of the present study was to compare gender differences in clinical characteristics, therapeutic management and survival in a large cohort of patients with CHF related to left ventricular systolic dysfunction from a tertiary hospital, who was receiving contemporary treatment including high doses of renin inhibitors and beta-blockers.

Methods

All patients referred to our department for non-invasive evaluation of left ventricular systolic dysfunction were considered for inclusion in the study. Before inclusion, treatment of the patients was optimized with the introduction and/or up-titration to maximal tolerated doses of renin inhibitors and/or beta-blockers. The non-invasive evaluation was performed 3 months after maximal tolerated doses of both renin inhibitors and beta-blockers were reached. During this treatment optimization, patients had systematic coronary angiography to help define the aetiology of left ventricular systolic dysfunction. Patients were included in the study if they were ambulatory, stable for at least 2 months and had an echocardiographic left ventricular ejection fraction (LVEF) ≤45%. Patients were excluded if they had an acute coronary syndrome or had undergone coronary revascularization or cardiac surgery in the previous 3 months.

All of the patients underwent echocardiography, radionuclide angiography, and a cardiopulmonary exercise test as described previously [9]. Blood samples were drawn in the morning with the patient in the supine position for standard measurements and brain natriuretic peptide (BNP) determination. BNP samples were immediately put on ice, centrifuged at 4°C within 20 minutes and the supernatant was immediately stored at -70°C until assayed. Plasma BNP concentrations were measured by radio-immunoassay (Shionoria BNP kit, Shionogi & Co. Ltd., Osaka, Japan). Normal values were <21.1 pg/mL with inter-assay and intra-assay coefficients of variation of 4.2% and 2.7%, respectively, for the concentration of 21.1 pg/mL, and 2.1% and 2%, respectively, for the concentration of 520 pg/mL.

Definitions

Patients with ischaemic cardiomyopathy were defined as those with a proven history of myocardial infarction (significant Q waves on the electrocardiogram and/or significant increase in creatinine kinase levels during a previous hospitalization) and/or stenosis >50% in one of the major coronary arteries. Patients who did not fulfill these criteria were considered to have non-ischaemic cardiomyopathy. If coronary angiography was not performed or if the patient did not have a proven history of myocardial infarction, they were considered as having undetermined cardiomyopathy (7 men and 3 women), except for young patients (<30 years’ old) without any risk factor for atherosclerosis. These patients were considered to have non-ischaemic cardiomyopathy.

Qualitative classification of doses of angiotensin-converting enzyme (ACE) inhibitor was defined using the recommendations of the European Society of Cardiology. High doses were defined as the highest recommended doses, intermediate as the lowest recommended doses, and low as non-recommended doses of ACE inhibitor [10].

Statistics

Results are expressed as mean±SD except for BNP values, which are presented as median with interquartile range. Discrete variables were compared using χ² analysis or with Fisher’s exact test, when indicated. Continuous variables were compared by the unpaired Student’s t test or by the non-parametric Mann-Whitney test. Follow-up was performed either by direct examination or by contact with the general practitioner. Cardiac mortality was defined as cardiac-related death or urgent cardiac transplantation (United Network for Organ Sharing [UNOS] status 1); patients who had non-urgent transplantation (UNOS status 2) were censored at the time of transplantation. A cardiac event was defined as cardiac-related death or cardiac transplantation (UNOS1 and 2). A Kaplan-Meier method was performed to

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estimate the cumulative survival. Differences in survival were compared with a log-rank test. A P value ≤0.05 was considered statistically significant. Statistics were performed with the SPSS software version 15.01 (Chicago, Illinois).

Results

Clinical characteristics and treatment

The present analysis is based on 613 patients with stable CHF, of whom 115 were women (19%). Major clinical characteristics of the study population are summarized in Table 1. Women were less likely to have ischaemic cardiomyopathy than men (28% vs 51%, p<0.0001). LVEF and right ventricular ejection fraction were significantly higher in women compared to men. Other differences were related to differences in weight and height between men and women.

| Table 1 | Women were less likely to have ischaemic cardiomyopathy than men (28% vs 51%, p<0.0001). LVEF and right ventricular ejection fraction were significantly higher in women compared to men. Other differences were related to differences in weight and height between men and women. |

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>Gender differences in major characteristics of the study population.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=498)</td>
</tr>
<tr>
<td>Age, years</td>
<td>56±12</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81±16</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172±9</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.94±0.2</td>
</tr>
<tr>
<td>NYHA III, n (%)</td>
<td>89 (18%)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>65 (13%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>131 (26%)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>190 (38%)</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy, n (%)</td>
<td>248 (51%)</td>
</tr>
<tr>
<td>Heart rate at rest, bpm</td>
<td>67±13</td>
</tr>
<tr>
<td>Systolic blood pressure at rest, mmHg</td>
<td>118±19</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>117±34</td>
</tr>
<tr>
<td>Complete LBBB,%</td>
<td>100 (20%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction,%</td>
<td>35±9</td>
</tr>
<tr>
<td>Right ventricular ejection fraction,%</td>
<td>41±12</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>44±8.7</td>
</tr>
<tr>
<td>Left atrial diameter/m²</td>
<td>22.9±4.5</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>63.5±10.4</td>
</tr>
<tr>
<td>LVEDD/m²</td>
<td>33±5.7</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.48±1.4</td>
</tr>
<tr>
<td>Mitral deceleration time, ms</td>
<td>192±76.6</td>
</tr>
<tr>
<td>Peak VO₂, mL/min/kg</td>
<td>16.1±5.4</td>
</tr>
<tr>
<td>% maximal predicted VO₂</td>
<td>60±16.7</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>138±3.1</td>
</tr>
<tr>
<td>Creatinine, mg/L</td>
<td>11.7±5.4</td>
</tr>
<tr>
<td>Creatinine clearance, ml/min</td>
<td>54.5±18.2</td>
</tr>
<tr>
<td>Uric acid, mg/L</td>
<td>78.8±21.6</td>
</tr>
<tr>
<td>Haemoglobin, g/dL</td>
<td>13.9±2.4</td>
</tr>
<tr>
<td>BNP, pmol/L</td>
<td>38 [3-99]</td>
</tr>
</tbody>
</table>

* exclusion of the 10 patients who did not have coronary angiography

BNP, B-type natriuretic peptide; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association; VO₂, oxygen consumption.
carvedilol remained higher in men than women, but the difference was not significant (43±18 vs 36±15 mg/d, p=0.08).

Survival analysis

A total of 140 cardiovascular-related deaths and 29 non-cardiac related deaths occurred over a median follow-up of 1.234 days; four patients had an urgent transplantation and 27 a non-urgent transplantation (table 3). One patient was lost to follow-up. Survival was similar in women and men. Cardiovascular mortality rates at 1 year were 6% in men and 7% in women. At 2 years, these rates were 11% and 13%, respectively. Figure 1 shows survival curves according to gender. Figure 2 shows survival curves in ischaemic and non-ischaemic patients according to gender. Similar results were obtained when the analysis included all cardiovascular events (cardiovascular-related deaths and all transplantations) as the major end-points (data not shown).

Table 2  Treatment of the study population according to gender.

<table>
<thead>
<tr>
<th></th>
<th>Men (n=498)</th>
<th>Women (n=115)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor, n (%)</td>
<td>460 (92%)</td>
<td>104 (90%)</td>
<td>NS</td>
</tr>
<tr>
<td>% at maximal recommended doses</td>
<td>314 (68%)</td>
<td>66 (63%)</td>
<td>NS</td>
</tr>
<tr>
<td>% at minimal recommended doses</td>
<td>73 (16%)</td>
<td>16 (15%)</td>
<td>NS</td>
</tr>
<tr>
<td>ARB, n (%)</td>
<td>35 (7%)</td>
<td>9 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitor or ARB, n (%)</td>
<td>484 (97%)</td>
<td>111 (97%)</td>
<td>NS</td>
</tr>
<tr>
<td>Bisoprolol, n (%)</td>
<td>328 (66%)</td>
<td>63 (55%)</td>
<td>NS</td>
</tr>
<tr>
<td>Doses of bisoprolol, mg/d</td>
<td>8.4±3.8</td>
<td>8.3±3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Carvedilol, n (%)</td>
<td>102 (20%)</td>
<td>35 (30%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Doses of carvedilol, mg/d</td>
<td>52.5±27</td>
<td>40±18</td>
<td>0.01</td>
</tr>
<tr>
<td>Diuretic, n (%)</td>
<td>369 (74%)</td>
<td>80 (70%)</td>
<td>NS</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>139 (28%)</td>
<td>29 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>150 (30%)</td>
<td>35 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Amiodarone, n (%)</td>
<td>76 (15%)</td>
<td>19 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>223 (45%)</td>
<td>48 (42%)</td>
<td>NS</td>
</tr>
<tr>
<td>Oral anticoagulant, n (%)</td>
<td>177 (36%)</td>
<td>41 (36%)</td>
<td>NS</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>236 (47%)</td>
<td>37 (32%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Allopurinol, n (%)</td>
<td>53 (11%)</td>
<td>6 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Implantable cardio-defibrillator, n (%)</td>
<td>65 (13%)</td>
<td>10 (9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Resynchronization therapy, n (%)</td>
<td>19 (4%)</td>
<td>5 (4%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Discussion

The results of the present study demonstrate no gender survival difference in our population of patients with CHF related to left ventricular systolic dysfunction, despite modest differences in clinical characteristics. Women were less
likely to have ischaemic cardiomyopathy and had higher LVEF and right ventricular ejection fraction. We have also shown that our therapeutic management was similar irrespective of gender, and that survival was similar in men and in women.

Gender-related clinical characteristics

As expected, and as reported in previous studies, the major gender difference in clinical characteristics was the lower proportion of ischaemic cardiomyopathy in women compared with men [3, 11]. This significant difference was highlighted by the fact that in the present study, coronary angiography was performed systematically. Thus, we are sure of the coronary status of most of our patients, with the exception of 10 who did not have an angiography. As in previous studies [11, 12], we found modest but significant differences in LVEF and right ventricular ejection fraction between men and women. Other differences in clinical characteristics in our study population were related to differences in body surface area. Left ventricular end diastolic and left atrial diameters were slightly higher in men compared to women, as was serum creatinine concentration. However, these differences were not significant after adjustment for body surface area. Moreover, adjusted left ventricular end diastolic diameter was significantly greater in women compared with men. As expected, peak VO₂ was higher in men, even after adjustment for predicted values. Previous studies clearly demonstrated that peak VO₂ is related to muscle mass, which is higher in men. Predicted values of VO₂ have been determined in large cohorts of male subjects but have to be interpreted with caution in women and in overweight or underweight patients [13]. Previous studies have shown other significant gender differences: women are often older than men, with a higher proportion of diabetic women, in atrial fibrillation, and with a history of hypertension [2, 14-16]. All of these differences in previous studies could be explained by selection bias [3, 11] but also by the inclusion of CHF patients with or without depressed LVEF [14, 16]. In our population, all consecutive CHF patients with left ventricular systolic dysfunction were included and, except for ischaemic cardiomyopathy, women and men had a similar clinical presentation, particularly the same mean age. Of interest, BNP levels - a powerful prognostic parameter - were similar in men and women [17, 18]. Moreover, while studies have shown that women undergo fewer invasive procedures such as coronary angiography [16], this was not the case in the present study.

Gender differences in therapeutic management

Most previous large mortality trials have demonstrated the same efficacy of CHF drugs in men and women, including ACE inhibitors, angiotensin receptor blockers, beta-blockers and aldosterone antagonists [2, 19]. One exception is digoxin, which in a post-hoc analysis from the DIG trial showed a greater mortality rate in women receiving digoxin versus men [8]. Despite the lack of a gender difference in therapeutic efficacy, previous studies have demonstrated under-treatment of women versus men [3, 20, 21], even in acute heart failure [12]. In the present study, women had the same rate of coronary angiography and the same therapeutic management, except for a minor difference concerning carvedilol, which was more often given to women. Recent studies also suggest that women are less likely to receive implantable cardioverter-defibrillators for primary and secondary prevention of sudden cardiac death [22, 23]. This difference in therapeutic management and in clinical characteristics could explain the controversial results concerning the gender impact on survival in CHF.

Gender impact on survival

This gender impact on survival in CHF is controversial, with some studies demonstrating a survival benefit in women [1-3, 11, 16, 24-27], others showing no benefit [21, 28] and a
few reporting a worse prognosis [7, 8], especially after myocardial infarction [29]. As for clinical characteristics, these controversial results could be explained by selection bias or the inclusion of CHF patients with preserved LVEF. Studies from tertiary hospital, as ours, with the selection of CHF patients, could explain the previous controversial results. Moreover, some studies were conducted several years ago, before the modern treatment era [26, 27]. Differences in therapeutic management could also explain the gender survival difference in previous studies [20]. In some reports, the benefit appears restricted to subgroups such as non-ischaemic patients [11, 24] and non-diabetic patients [30]. A post-hoc analysis of the BEST (Beta-blocker Evaluation of Survival Trial) trial found no gender survival difference in patients with ischaemic cardiomyopathy, but a significantly better survival in women with non-ischaemic cardiomyopathy [11].

Several studies have suggested pathophysiological gender-related differences that could explain the survival benefit in women. For example, the remodelling process during arterial hypertension is different in men and women, with a major impact of diabetes mellitus [31, 32]. Heart rate variability also differs [33], which could explain the discrepancy in incidence of sudden cardiac death.

Study limitations

Although we included all consecutive patients, the present study was not prospective. As in many previous cardiovascular studies, the number of women was limited, particularly those with ischaemic cardiomyopathy. Because of the limited number of patients, we did not perform multivariate analyses. We enrolled selected patients in a tertiary hospital so our results cannot be extended to the whole CHF population, especially to older patients or those with preserved left ventricular systolic function. There were few significant gender differences in clinical characteristics, suggesting a lack of selection bias in our study population. CHF treatment was similar in men and women, with similar doses prescribed, but information regarding treatment modification during the follow-up period was not collected. These changes may influence the outcome of our patients. However, therapeutic optimization, with maximal tolerated doses of ACE inhibitors and beta-blockers, was performed in all of our patients before they were enrolled. We have shown in a previous study with the same inclusion criteria that limited changes in CHF treatment and doses occur during follow-up [34]. Finally, we do not have any information on re-hospitalization rates during the follow-up period and on the quality of life of our patients. Our study was focused on hard end-points, such as total mortality, cardiovascular mortality and cardiac transplantation.

Conclusions

We demonstrate no gender survival difference in this large population of patients from a tertiary hospital with stable CHF related to left ventricular systolic dysfunction receiving high doses of renin inhibitors and beta-blockers. Although fewer women had ischaemic cardiomyopathy, this result could be partly explained by similar therapeutic management in men and women.

No author has any conflict of interest.

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