Clinical research

Female sex is associated with a better long-term survival in patients hospitalized with congestive heart failure

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Aims Results of previous studies on the influence of gender on prognosis in heart failure have been conflicting and most studies have been conducted in selected populations. The aim of this study was determine whether mortality risk in women and men hospitalized with congestive heart failure is different.

Methods and results Survival analysis of 5491 consecutive patients admitted with congestive heart failure to 34 Danish hospitals between 1993–1996. Follow-up time was 5–8 years. Forty percent of the patients were female. Females were older, had less evidence of ischaemic heart disease and their left ventricular systolic function was preserved to a greater extent than in males. Men were more often treated with ACE inhibitors. During the follow-up period 1569 women (72%) and 2386 (72%) of the men died. When the age difference between men and women was adjusted for, male gender was associated with an increased risk of death (RR 1.25 (1.17–1.34)) and the increased risk was confirmed in a multivariate model containing several covariates.

Conclusion In patients hospitalized with congestive heart failure male gender is an independent predictor of mortality. Female heart failure patients may be under-treated with ACE inhibitors.

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The aim of the present study was to evaluate the effect of gender on the long-term survival in patients hospitalized with CHF, and to assess potential interaction with common clinical covariates.

Methods

Patients

The DIAMOND-CHF registry comprises consecutive heart failure patients admitted to 34 Danish Hospitals between November 1993 and July 1996. University hospitals as well as medium and small sized county hospitals participated in the study. Patients were included in the DIAMOND-CHF registry if a clinical diagnosis of heart failure was made and if the patient had experienced at least one episode within the preceding month of shortness of breath, either on minimal exertion or at rest (New York Heart Association (NYHA) functional class III or IV), or paroxysmal nocturnal dyspnoea. In Denmark, this covers practically all heart failure related admissions since patients with less severe heart failure symptoms are not likely to be admitted but will be managed in an out-patient facility. The local investigators made the decision on whether the underlying cause of the symptoms was cardiac or not. Patients with acute myocardial infarction within the last 7 days were not included in the DIAMOND-CHF screening registry. Twenty-seven percent of the patients in the registry were subsequently randomized in the DIAMOND-CHF study, which was a multicentre, randomized, double blind, placebo controlled trial of the efficacy of the class III antiarrhythmic agent dofetilide on mortality in patients with CHF. The study showed no significant effect of dofetilide when compared with placebo.

All patients in the registry were screened by obtaining a clinical history, a physical examination and an ECG. An echocardiogram was recorded on videotape and evaluated in a central laboratory. Left ventricular systolic function was assessed by calculation of wall motion index (WMI) as described previously. Using a 16-segment model of the left ventricle. A WMI of 1.2 is approximately equivalent to an ejection fraction of 35%. Furthermore, LV systolic function and geometry were characterized by measurements of mitral E-point ventricular septum separation (EPSS) and LV end-diastolic diameter (LVEDD) obtained from 2-D recordings (parasternal longitudinal axis view). Creatinine clearance was estimated using serum creatinine values.

Survival status was obtained from the Danish Central Personal Registry. In Denmark all residents are given a central person registry number and all deaths in the country are registered within 2 weeks from the time of death. Follow-up time ranged from 5 to 8 years. Including the patients who died the median follow-up time was 1307 days (interquartile range: 2136 days). For the surviving patients the median follow-up was 2722 days (interquartile range 314 days). During the study 5548 patients were registered. Survival status was not available in 57 patients who were lost to follow-up either due to immigration or because their central personal registry number was not recorded. Thus, the study population comprised 5491 patients.

The study was conducted in accordance with the Declaration of Helsinki II and approved by the Central Danish Ethics Committee.

Statistics

Baseline characteristics for men and women were compared using continuity adjusted Chi-square tests for discrete variables and Wilcoxon rank sum tests for continuous variables. Differences in time to death between men and women were analysed by a two-sided log-rank test. Life table plots were constructed using the Kaplan–Meier method. Relative risk (hazard ratio) (RR), confidence limits and the associated P-value were calculated from maximum likelihood estimates of proportional hazard models. Multivariate analysis was performed using a backward selection procedure. The model contained the baseline variables seen in Table 1 except baseline drug treatment. We anticipated that the treatment pattern with for instance ACE inhibitors and diuretics for men and women would differ for reasons not explained by differences in the prevalence of indication for treatment between the sexes. Adding such information into the model would not contribute to the determination of sex as a risk factor, but would be more likely to bias this particular analysis. Therefore baseline drug treatment was not included in the model. The presented RR values are based on the final Cox regression model containing only the variables, which had not been excluded by the backward selection procedure. Linearity of continuous variables was tested by plotting parameter estimates of quintiles versus means of each quintile and by demonstrating that parameter estimates of quintiles did not differ significantly from zero in a model containing the continuous variable. The proportional hazard assumption was tested by visual inspection of log(-log(survival)) curves. All calculations were performed on Statistical Analysis System software (SAS Institute, Cary, NC). A P value <0.05 was considered significant.

Results

Of the 5491 patients included in the present study 2189 (40%) were female. Baseline characteristics according to sex are presented in Table 1. Females were older and had less evidence of ischaemic heart disease. In the population as a whole an acute coronary syndrome within the last 8 weeks was reported only in 3%. Females more often had a history of arterial hypertension, valve disease and impaired renal function. Smoking and chronic obstructive pulmonary disease were more frequent in males. Men and women were equally distributed with regard to NYHA functional class but LV systolic function, evaluated by WMI or EPSS, and LV cavity dimensions were preserved to a greater extent in the female population. WMI was obtained in 95% of the patients with the missing values (n=251) distributed equally among men and women. Other missing data were (n): Creatinine: 362, previous MI: 1, NYHA class: 41, LVEDD: 584, duration of CHF: 437, EPSS 1075.

More men than women were being treated with ACE inhibitors at discharge, partly reflecting the higher proportion of males with systolic dysfunction (Table 1). However, even among patients with LV systolic dysfunction (WMI ≤1.2) more males (79%) than females (70%) were treated with ACE inhibitor at discharge (P=0.001, Table 2). The difference in treatment with ACE inhibitors between women and men was found in all age groups but ranged from an absolute 7% lower use in patients above 80 years to only 1% lower use in patients below 60 years. Few patients (13%) were treated with beta-blockers, and treatment rates were similar for men and women, irrespective of LV systolic function.

Baseline characteristics according to sex for the subgroup of patients with systolic heart failure (WMI
During the follow-up period 1569 women (72%) and 2386 (72%) of the men died (log rank, \( P = 0.23 \), Fig. 1). However, when the age difference between men and women was adjusted for, male gender was associated with an increased risk of death (RR 1.25 (1.17–1.34), \( P = 0.001 \)). A similar risk ratio for men (RR 1.26 (1.17–1.36)) was found in the multivariate analysis, which included the variables listed in Table 1 except for drug treatment. In this model also increasing age (RR 1.04 (1.03–1.05), per year increase), decreasing LV systolic function (RR 0.60 (0.56–0.64), per unit increase), diabetes (RR 1.42 (1.30–1.56), the presence of significant valve disease (RR 1.40 (1.18–1.65), duration of heart failure (RR 1.02 (1.00–1.003) per month), chronic obstructive pulmonary disease (RR 1.36 (1.25–1.47)) and creatinine clearance (RR 0.73 (0.69–0.77) per 20 ml/min increase) emerged to have independent, negative influence on survival after admission to hospital with CHF. The remaining variables in the multivariate model did not meet the significance criteria, and were therefore found not to have any independent predictive value. Performing the analysis using fixed determinants instead of the backward selection procedure did not significantly alter the results.

Finally, we conducted formal tests of interaction between sex and the remaining covariates from the multivariate model mentioned above. Interaction between sex and history of ischaemic heart disease was marginally statistically significant (\( P = 0.03 \)), but for no variable was an interaction of clinical relevance found.

**Discussion**

To our knowledge the present study is the first large investigation of the effect of gender on long-term survival to include data on LV function in consecutive heart failure patients admitted to hospital. Results of
univariate analysis did not suggest any difference in mortality between men and women. However, when the analysis was corrected for various covariates (particularly age) male gender emerged as a potent predictor of death.

In the present study the patients were elderly with a mean age above 70 years which is a general finding in unselected heart failure populations irrespectively of whether they are community or hospital based. The finding that the men included in this registry were younger than the women is consistent with previous data from the Framingham study\(^3\) as well as investigations of hospitalized subjects with CHF.\(^6,8\) More men than women were admitted with heart failure in accordance with most epidemiological heart failure studies\(^19,20\) although a predominance of female patients has been reported in some series.\(^21,22\)

Ischaemic heart disease appeared to be the most common cause of heart failure in the present population which is in accordance with most earlier large-scale analyses.\(^2,23\) except the Framingham study in which hypertension was the most important single cause.\(^24\) As expected, evidence of ischaemic heart disease was more prevalent in the male population.\(^4,5,23–26\) In the current analysis we found that even though the functional status (NYHA class) among men and women was comparable, the left ventricle was more dilated and the impairment of systolic function was greater in the male population. Hence, females seem less likely to have systolic dysfunction as the principal cause for their heart failure symptoms. This appears to be compatible with the finding that males more frequently had evidence of ischaemic heart disease and previous myocardial infarction.

Few and mostly smaller studies of patients with stable CHF (i.e. not immediately post MI) have previously addressed the issue of gender related differences in LV systolic function. In a population of 557 consecutive patients with severe heart failure referred to a specialized heart failure clinic, Adams et al found a higher ejection fraction in women, whereas no significant difference in end-diastolic diameter was detected.\(^4\) This is supported by data obtained both in a community setting\(^27\) and in hospitalized patients.\(^28,29\) In contrast, two studies of patients with severe LV dysfunction enrolled in a clinical trial or referred for invasive evaluation have not reported gender related differences in ejection fraction.\(^5,8\) From pathophysiological studies in humans as well as in laboratory animals it is known that females adapt to pressure overload with a greater degree of concentric hypertrophy than male individuals. In contrast the left ventricle in males is prone to dilation and progressive impairment of contractile properties.\(^30,31\) Thus at least for the patients with heart failure due to hypertension, experimental data are in line with the findings of the present study. Based on the epidemiological data it seems reasonable to say that in unselected

| Table 2 Baseline characteristics for 2147 women and men with WMI ≤1.2 admitted with congestive heart failure |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Females (n=639)\(^a\) | Males (n=1508)\(^a\) | P |
| Age (years) | 74 (68–80) | 70 (63–77) | <0.0001 |
| Duration of CHF (months) | 12 (0.2–36) | 12 (0.5–48) | 0.05 |
| History of: | | | |
| IHD | 364 (57%) | 982 (65%) | 0.0004 |
| Angina pectoris | 248 (39%) | 637 (42%) | 0.15 |
| MI | 249 (39%) | 760 (50%) | <0.0001 |
| Hypertension | 168 (26%) | 317 (21%) | 0.009 |
| Valve disease | 31 (5%) | 59 (4%) | 0.04 |
| Smoking | 175 (28%) | 566 (38%) | <0.0001 |
| COPD | 107 (17%) | 325 (22%) | 0.01 |
| Diabetes | 127 (20%) | 279 (19%) | 0.5 |
| Atrial fibrillation | 114 (18%) | 376 (25%) | 0.0004 |
| During hospitalization: | | | |
| NYHA III–IV | 384 (61%) | 952 (63%) | 0.2 |
| Drug treatment | | | |
| ACEI | 449 (70%) | 1196 (79%) | <0.0001 |
| Digoxin | 398 (62%) | 974 (65%) | 0.3 |
| Beta-blockers | 66 (10%) | 140 (9%) | 0.5 |
| Diuretics | 589 (92%) | 1398 (93%) | 0.7 |
| Creatinine clearance | | | |
| <20 ml/min | 33 (5%) | 21 (1%) | |
| 20–60 ml/min | 551 (75%) | 832 (57%) | |
| >60 ml/min | 118 (20%) | 604 (41%) | <0.0001 |

IHD: ischaemic heart disease; MI: myocardial infarction; EPSS: E-point ventricular septum separation; LVEDD: left ventricular end diastolic diameter; COPD: Chronic obstructive pulmonary disease or asthma; WMI: Wall motion index; ACEI: angiotensin converting enzyme inhibitors.

\(^a\)Number of patients (%) or median (interquartile range).
heart failure patients a greater degree of preserved LV systolic function and diastolic dimensions is to be expected in the female population.

Previous studies have raised the concern that women with heart failure are treated less intensively with documented life saving intervention than men. In the present study this hypothesis could be confirmed with regard to ACE inhibitor therapy at discharge. Adding to that, it has been shown that ACE inhibitor therapy is more frequently discontinued in females, implying that the true difference in treatment rates could be substantial for the patients in the present registry. A difference in treatment frequency between the sexes was found in all age groups but it was clearly greater in the elderly patients. The reason for the lower frequency of ACE inhibitor treatment in the elderly patients of present study is not clear. Although renal dysfunction generally should not preclude treatment with ACE inhibitors it may constitute a contraindication (for instance in the case of bilateral renal artery stenosis). In the present study renal dysfunction was more common in women with systolic dysfunction than in men (Table 2), and this may have caused a lower frequency of ACE inhibitor treatment in females. However, the number of patients with severe renal dysfunction was low and this finding cannot completely explain the difference in ACE inhibitor treatment, meaning that other factors must have played a role as well. Since the data for the DIAMOND-CHF registry were collected before the emergence of solid documentation for mortality benefit of beta blocker therapy in systolic heart failure, few patients in the current cohort were treated with this class of agents. However, recently published data have shown that beta blocker therapy is equally effective in men and women with heart failure. Therefore, the fact that the number of patients on beta blocker therapy in the DIAMOND CHF-registry is lower than one would expect from a contemporary heart failure population, should not decrease the relevance of the outcome data from this population.

The present study showed that male gender per se was associated with a lower survival rate in patients hospitalized with heart failure. Previous studies on intermediate or long-term (>6 months) survival in men and women with heart failure are conflicting. Several studies have reported a poorer outcome in men either in univariate analyses or after controlling for the influence of covariates (particularly age). In contrast, a number of other studies have reported a higher mortality in men, which did not persist in a multivariate analysis controlling for one or more factors. Furthermore a number of studies have shown no difference in mortality in univariate analysis or even higher mortality in women as described for the patients in the SOLVD registry. The reasons for the different outcomes of these analyses are not clear, but likely candidates are differences in study populations, especially with regards to the degree of heart failure, exclusion of patients with non-systolic heart failure and the prevalence of ischaemic heart disease in the population. It should be recognized that several of the studies cited above included 20% females or less, which could imply that the size of the female population was simply too small to detect any differences in mortality. The DIAMOND registry overcomes some of these difficulties in being a consecutive database with a large number of female patients and by having data on systolic function on almost all individuals.

It is important to underline that although ischaemic heart disease was more common in males, ischaemic heart disease was very frequent in the female population as well. This may be different from other populations, for instance Afro-Americans, where hypertension may be a leading cause of heart failure, which may again lead to a different effect of sex on the survival pattern. Therefore, the results of the present analysis may only be applicable to a Caucasian population.

It should be noted that although ischaemic heart disease was more common in males, the life expectancy of females with heart failure is much reduced. The median survival time for the women in the DIAMOND CHF registry was 1364 days or less than 4 years. In comparison the expected lifetime for women aged 74 years in Denmark is more than 12 years.

Fig. 1 Mortality rate in 2189 women and 3302 men hospitalized with congestive heart failure (Log rank: ns).
The mechanism behind the difference in mortality in men and women with CHF is not clear. Most previous studies addressing this issue have focused on differences in the change in LV geometry and function in CHF in the two sexes as previously discussed. In the present study, the poorer survival in men was not merely a consequence of a lower LVEF in the male population since this was corrected for in the multivariate model. Others have suggested that a higher prevalence of myocardial ischaemia in the male population might be responsible for the difference in outcome.\(^4\) In our study the mortality difference between men and women persisted even if history of ischaemic heart disease and previous MI were added to the model, which would argue against ischaemia as a principal explanation. However, ischaemia was presumably under-diagnosed and therefore this conclusion may not necessarily be correct. Possibly, a greater understanding of the difference may come from molecular studies, some of which have recently shown that myocyte apoptosis is increased in female patients with CHF.\(^{30}\) It seems clear, however, that further studies are required to shed light on the mechanism behind the unequal outcome in male and female heart failure patients.

In conclusion, it seems reasonable to state that in a population with a relatively high prevalence of ischaemic heart disease in both sexes, female gender per se is associated with a better long-term survival in hospitalized patients with CHF. This finding obviously implies that an effort should be made to improve prognosis in the male CHF population. However, it certainly should not remove the attention from a potential under-treatment of women with CHF, who even if their prognosis is superior to that of men, still face a substantial reduction in life expectancy.

References


