

Comparison of the outcome in men and women with chronic heart failure

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Recent studies have suggested some gender-related differences in the incidence, quality of care, response to therapy, and outcome in heart failure patients.

The majority of studies have proposed a better survival for women compared to men. However, the under-representation of women in clinical trials leads to some uncertainty regarding the survival benefit. Some data suggest the possibility that ACE-inhibitors may be less beneficial in women as compared to men. Beta-blockers seem to be effective both in women and men. Further studies are needed to clarify whether these differences may have a pathophysiological basis.

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Although nearly half of the patients affected by heart failure (HF) are women, clinical trials involving HF patients have predominantly included men. In recent years, epidemiological and clinical studies have highlighted some differences between men and women in the occurrence, quality of care, response to therapy, and prognosis of HF.

With regard to prognosis, data from the two major US epidemiological studies show a better survival for women compared to men. In the Framingham study, the average survival rate, after a diagnosis of HF, was 1.7 years in men and 3.2 years in women (relative risk-RR 0.64, 95% confidence interval-CI 0.054-0.77). The survival at 1, 2, 5 and 10 years after the diagnosis was significantly higher in women, despite their greater average age (72 vs 68 years)^{1,2}; this survival advantage persisted even after the data were adjusted for age and etiology. Similarly, the NHANES-I study also reported a better 10- and 15-year survival of women compared with men: in the group aged ≥ 55 years, the 15-year total mortality rate was respectively 39.1% for women and 71.8% for men³. It should be noted that these data were obtained before ACE-inhibitors and beta-blockers were shown to be beneficial in the treatment of HF. Besides, these two studies did not assess the left ventricular function.

More recently, the MERIT-HF⁴ and the CIBIS II⁵ trials have enrolled a relatively large number of women thus offering the opportunity for some comments. More-

over, the patients enrolled were already receiving optimal treatment with ACE-inhibitors. In both trials, women showed a lower total mortality than men, even after adjustment for the differences in baseline characteristics (in the MERIT-HF: RR 0.63, 95% CI 0.43-0.91, $p = 0.015$; in the CIBIS II: RR 0.64, 95% CI 0.47-0.86, $p = 0.003$).

Even another population survey⁶⁻⁹ as well as other studies of patients admitted to hospitals¹⁰⁻¹² reported a more favorable prognosis in women.

Some hypotheses have been proposed to explain this difference in the outcome between women and men. It has been supposed that the etiology has an influence on the association between gender and survival. Data from the FIRST study, that enrolled patients in NYHA functional class IV with evidence of severe cardiac dysfunction, showed that women survived longer only when non-ischemic HF was present (RR 3.08, 95% CI 1.56-6.09, $p = 0.001$); however, in patients with an ischemic etiology no significant difference in survival rate was found⁸.

Philbin and DiSalvo¹¹ evaluated 45 894 patients hospitalized during 1995 in the New York State: in comparison with men, women had a longer length of stay (9.2 vs 9.8 days, $p = 0.0001$) and in-hospital mortality (RR 0.878, 95% CI 0.813-0.947, $p = 0.0008$); similar results were obtained after adjustment for age and co-morbidities. The authors proposed some explanations: again, the different prevalence of the is-

chemic disease, but also the higher trigger of sudden death¹³ – confirmed by the observation of a lower incidence of ventricular arrhythmias during Holter monitoring¹⁴ – and the higher incidence of high-frequency heart rate fluctuations. These reflect a greater degree or responsiveness to vagally-mediated respiratory sinus arrhythmias¹⁵, and the different gender adaptation to pressure overload¹⁶, that may result in a more frequent diastolic dysfunction among women.

Different baseline characteristics were considered as being at the origin of the better survival among women in the study conducted by Vaccarino et al.¹², who observed among 2445 consecutive patients, admitted to different hospitals across Connecticut, a 20% lower 6-month mortality controlled for age in women (RR 0.81, 95% CI 0.68-0.95, $p = 0.01$), and a similar reduction in the 1-year mortality (RR 0.82, 95% CI 0.71-0.95, $p = 0.007$).

Opposite results have been reported in the SOLVD trial: a higher survival was found in men as compared to women (1-year non-adjusted mortality rate 17 vs 22%, $p = 0.05$)¹⁷. Some reasons have been proposed to explain this difference: the enrolled population was younger than in other studies (44% of men and 32% of women, ≤ 60 years of age), but women were significantly older than men and presented more co-morbidities; patients with left ventricular systolic dysfunction were enrolled, whereas the Framingham and the NHANES studies did not assess the ventricular function, and the ischemic etiology was prevalent.

No differences in the 1-year survival have been reported in the Italian Network-CHF Registry, a database that collected the data of 3327 consecutive outpatients referred to 133 cardiological centers in Italy: gender was not an independent predictor of death (15.9% in women and 16.4% in men in the 1-year total mortality, RR 0.93, 95% CI 0.75-1.14). Moreover, the survival according to gender was not influenced by the etiology of HF¹⁸.

Finally, a different responsiveness to therapy has been proposed. The survival benefit with ACE-inhibitors in patients with HF seems to be lower in women than in men. In the CONSENSUS trial, the 6-month mortality was reduced by 51% in enalapril-treated men ($p < 0.001$), while enalapril-treated women presented only a 6% reduction ($p = \text{NS}$)¹⁹. In the SOLVD trial, men and women treated with enalapril showed a reduction in mortality and hospitalization, but the benefit was less evident in women²⁰. In the SAVE trial, women treated with captopril showed a 4% risk reduction in morbidity and mortality, whereas men presented a 28% risk reduction, although captopril was reported to reduce the all-cause mortality, independently of sex²¹. An overview of 30 randomized trials of ACE-inhibitors, with a total of 5399 men and 1991 women enrolled, showed a significant reduction in mortality and in the combined endpoint of all-cause mortality and hospitalizations for worsening HF only in men (RR

0.63 for men and 0.78 for women)²². However, owing to the small number of women enrolled which might have caused an apparent lack of treatment benefit, the significance of these findings is not clear.

With regard to beta-blocker therapy, the US Carvedilol Group found a similar survival benefit in women and men (RR 0.52, 95% CI 0.32-0.85), even though only 14 deaths occurred among women ($n = 1024$, 768 men, 256 women)²³. In the MERIT-HF trial, the treatment with metoprolol reduced the combined endpoint of all-cause mortality and hospitalization by 21%. In detail, a significant reduction in mortality, cardiovascular death and death caused by worsening HF was observed in men, while a non-significant difference for the total mortality was seen in women⁴. In the CIBIS II trial, women treated with bisoprolol had a higher unadjusted protective effect than men for all-cause mortality (RR 0.53, 95% CI 0.42-0.67 in men; RR 0.37, 95% CI 0.19-0.69 in women)⁵. Pooling of the total-mortality data from the MERIT-HF, CIBIS II and COPERNICUS trials, which provided a larger number of deaths for analysis, showed very similar and statistically significant survival benefits in women (RR 0.69, 95% CI 0.51-0.93) and men (RR 0.66, 95% CI 0.58-0.75)⁴.

In summary, the majority of studies suggests a better long-term prognosis for women with HF. However, the small number of women and the lack of a direct comparison with men may limit the ascertainment of a survival benefit. Some data suggest the possibility that ACE-inhibitors may be less beneficial in women as compared with men. Beta-blockers seem to be effective both in women and in men.

Future research should be aimed at achieving a deeper understanding of the pathophysiology of HF in women, so as to clarify whether the above-mentioned gender differences reflect a true biological gender difference or whether they depend on one or more of the following issues: the under-representation of women in clinical studies, the different age, the different etiology, stage and management of disease, and the lack of any distinction between patients with a preserved or impaired left ventricular systolic function.

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