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Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis†

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Aim The aim of this study was to investigate the relationship between gender and survival of patients with heart failure, using data from both randomized trials and observational studies, and the relative contribution of age, left ventricular systolic function, aetiology, and diabetes to differences in prognosis between men and women.

Methods and results Data from 31 studies (41 949 patients; 28 052 men, 13 897 women) from the Meta-Analysis Global Group In Chronic Heart Failure (MAGGIC) individual patient meta-analysis were used. We performed survival analysis to assess the association of gender with mortality, adjusting for predictors of mortality, including age, reduced or preserved ejection fraction (EF), and ischaemic or non-ischaemic aetiology. Women were older [70.5 (standard deviation 12.1) vs. 65.6 (standard deviation 11.6) years], more likely to have a history of hypertension (49.9% vs. 40.0%), and less likely to have a history of ischaemic heart disease (46.3% vs. 58.7%) and reduced EF (62.6% vs. 81.6%) compared with men. During 3 years follow-up, 3521 (25%) women and 7232 (26%) men died. After adjustment, male gender was an independent predictor of mortality, and the better prognosis associated with female gender was more marked in patients with heart failure of non-ischaemic, compared with ischaemic, aetiology (*P*-value for interaction = 0.03) and in patients without, compared with those with, diabetes (*P*-value for interaction <0.0001).

Conclusion This large, individual patient data meta-analysis has demonstrated that survival is better for women with heart failure compared with men, irrespective of EF. This survival benefit is slightly more marked in non-ischaemic heart failure but is attenuated by concomitant diabetes.

Keywords Heart failure • Prognosis • Sex • Ejection fraction • Diabetes • Aetiology

Introduction

While the populations of patients with heart failure (HF) studied in clinical trials are dominated by men, in routine clinical practice half or more of all patients with HF are women.[1,2] Whether prognosis differs for men and women with HF is controversial. Many studies have associated female sex with better survival,[1–14] although several failed to identify such an association[15–18] and one study

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has reported worse prognosis for women.[19] Moreover, in HF populations, sex is strongly associated with a number of clinical variables that influence prognosis such as age, aetiology, and in particular left ventricular ejection fraction (EF), associations which may confound the independent effect of sex on survival. Assessment of the relationship between sex and prognosis is further complicated by the relatively small numbers of women in randomized, controlled trials involving patients with HF, in large part due to the exclusion from these trials of older patients and patients with HF with preserved EF, both of which are more prevalent among women with HF.

The potential reasons for differences in survival for men and women with HF are uncertain. Differences in survival between men and women with HF fail to show a consistent relationship to either aetiology (ischaemic or non-ischaemic)[2,3,9] or to whether patients had reduced or preserved EF.[1,10–12] The greater prevalence of diabetes[20–23] and the relative under-use of evidence-based therapies among women compared with men with HF[14,24,25] may theoretically contribute to worse prognosis for women. However, HF with preserved EF is more common among women than men, and this may be expected to lead to better survival for these patients.[26]

The main results from the Meta-Analysis Global Group In Chronic Heart Failure (MAGGIC) meta-analysis demonstrated that HF patients with preserved EF have a lower risk of death than patients with reduced EF, regardless of age, sex, and aetiology of HF.[27] The main analysis also showed that male sex was an independent predictor of mortality [hazard ratio (HR) 1.23, 95% confidence interval (CI) 1.18–1.28].[27] The aim of the current analysis was to assess comprehensively the relationship between sex and survival in patients with HF, using a large individual patient data set. Our hypothesis was that age, left ventricular EF, aetiology, and diabetes would have a different impact on survival for men and women with HF.

Methods

The methods and main results from the MAGGIC meta-analysis have already been described.[26,27] In brief, we searched online databases using the key words: incidence, prognosis, outcome, mortality, clinical trials, HF, ventricle, EF, systolic, and diastolic. We also searched reference lists of articles obtained during the online search, as well as conference abstracts, and utilized personal communication. Eligible studies were those that included patients with HF and reported outcome (death from any cause). Studies that applied a left ventricular EF entry criterion were excluded. The meta-analysis was approved by The University of Auckland Human Subjects Ethics Committee.

Fifty-six potentially suitable studies were identified, and individual patient data were provided from 31 studies on a pre-defined set of variables including demographics, medical history, medical treatment, symptomatic status, clinical variables, laboratory variables, and outcome. Data from the individual studies were re-coded into a uniform format at the Central Co-ordinating Centre at the University of Auckland and incorporated into one database. The data from the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM)[6] trial were made available for this meta-analysis, but the data set from this study was added at the London School of Hygiene and Tropical Medicine and the final analyses run again incorporating these data. The results from the MAGGIC meta-analysis demonstrated that patients with HF with preserved left ventricular EF have lower risk of death from any cause than patients with reduced left ventricular EF.

Statistical analysis

For the current analyses, Cox proportional hazards models were used to estimate the risk of death from any cause within 3 years for men compared with women. All models were adjusted for age, aetiology (ischaemic vs. non-ischaemic), left ventricular EF [reduced (defined as EF $<$50%) vs. preserved], history of hypertension, diabetes, and atrial fibrillation, and stratified by study. Cox models adjusted for age were used to plot mortality curves.

Interactions between sex and the remaining covariates were explored. All covariates were dichotomous except for age, which was left as a continuous variable. Statistically significant interactions (interaction *P*-value <0.05) prompted subgroup analyses that focused on the relationship between sex and the covariate, within the EF group. For clarity, these models were only adjusted for age and stratified by study.

The correlation between scaled Schoenfeld residuals and length of follow-up showed that there was no violation of the proportional hazards assumption for all analyses. Analyses were performed using SAS v 9.2 (SAS Institute Inc., Cary, NC, USA).

Role of the funding source

The sponsors of the study had no role in the study design, data analysis or interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Results

Data were available from 31 studies involving a total of 54 416 patients. Of these, 1179 patients were excluded from the analysis due to irresolvable dates or having died during an index hospital admission, 2246 based on aetiology of HF (either valvular heart disease or hypertrophic cardiomyopathy), 9019 due to missing information on left ventricular EF, and 23 due to missing information on sex. Thus, the main analysis was based on 41 949 patients; 28 052 (67%) men and 13 897 (33%) women.

The baseline characteristics of the study population are shown in *Table 1*. When compared with men, women were older {70.5 [standard deviation (SD) 12.1] vs. 65.6 [SD 11.6] years}, more commonly had a history of hypertension (49.9% vs. 40.0%), and less commonly had a reduced EF (62.6% vs. 81.6%). Women had more severe functional limitation than men, with a greater proportion of women than men in New York Heart Association (NYHA) class III or IV. Mean heart rate was also higher in women. Overall, women were prescribed angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and beta-blockers less frequently than men. The under-use in women of these treatments was particularly evident in patients with reduced EF (ACE inhibitors or ARBs 79.0% vs. 84.6%; beta-blocker 36.2% vs. 39.7%).

Survival

During 3 years follow-up, 3521 (25.3%) women and 7232 (25.7%) men died. There were 137 [95% confidence interval (CI) 133–140] deaths per 1000 patient-years in men and 135 (95% CI

Table 1 Baseline characteristics of 41 949 patients included in 31 studies by gender

	Men	Women	*P*-value
n (31 studies)	28 052	13 897	
Age, years (SD)	65.6 (11.6)	70.5 (12.1)	<0.001
Medical history			
Hypertension	40.0	49.9	<0.001
Myocardial infarction	51.0	33.3	<0.001
Atrial fibrillation	19.7	21.6	<0.001
Diabetes	22.8	25.4	<0.001
Ischaemic aetiology	58.7	46.3	<0.001
Medication			
ACE inhibitor or ARB	80.3	71.1	<0.001
Beta-blocker	38.5	34.7	<0.001
Diuretic	80.2	83.6	<0.001
Spironolactone	22.5	20.9	0.004
Digoxin	44.2	41.2	<0.001
Clinical status			
Functional class (I/II/III/IV)	11.1/47.4/34.7/6.8	9.1/45.2/36.7/9.0	<0.001
Heart rate, b.p.m.	78.0 (17.5)	81.4 (19.6)	<0.001
SBP, mmHg	128.6 (21.7)	135.0 (24.5)	<0.001
DBP, mmHg	76.9 (12.2)	77.0 (13.2)	0.3245
Left ventricular EF, %	33.0 (24.5–44.0)	42.0 (30.0–57.0)	<0.001
Preserved EF, %	18.4	37.4	<0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; EF, ejection fraction; SBP, systolic blood pressure; SD, standard deviation.

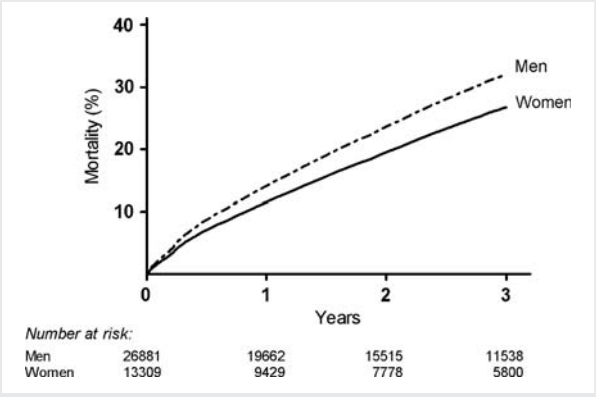

Figure 1 All-cause mortality for men and women adjusted for age ($P < 0.001$).

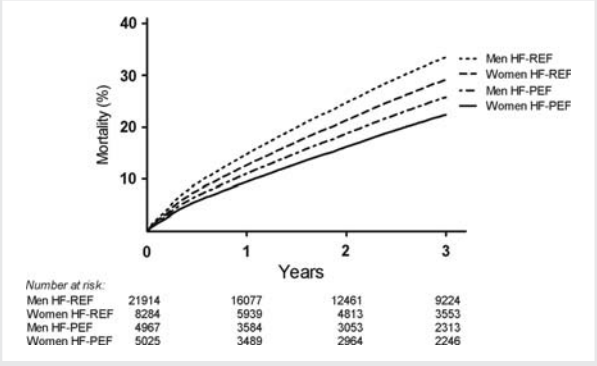

Figure 2 All-cause mortality for men and women with heart failure and preserved ejection fraction (HF-PEF) or reduced ejection fraction (HF-REF) adjusted for age (EF group × gender interaction $P = 0.72$).

131–139) deaths per 1000 patient-years in women. On analysis only adjusted for age, men were at higher risk of death than women [hazard ratio (HR) 1.31, 95% CI 1.25–1.36] (*Figure 1*). As previously reported, on multivariable analysis, male sex showed an independent association with the risk of death at 3 years (HR 1.23, 95% CI 1.18–1.28).[27] When the randomized controlled trials of pharmacotherapy (three trials, 20 878 patients) were excluded from the analysis, the risk of death remained higher among men (fully adjusted HR 1.27, 95% CI 1.19–1.36).

Age, left ventricular ejection fraction, and hypertension

The excess mortality risk associated with male sex was of similar magnitude in patients with reduced or preserved EF (*Figure 2*). Neither age ($P = 0.63$) nor history of hypertension ($P = 0.10$) altered the differential relationship between sex and outcome. However, both diabetes ($P < 0.001$) and aetiology of HF ($P = 0.03$) did appear to modify this relationship.

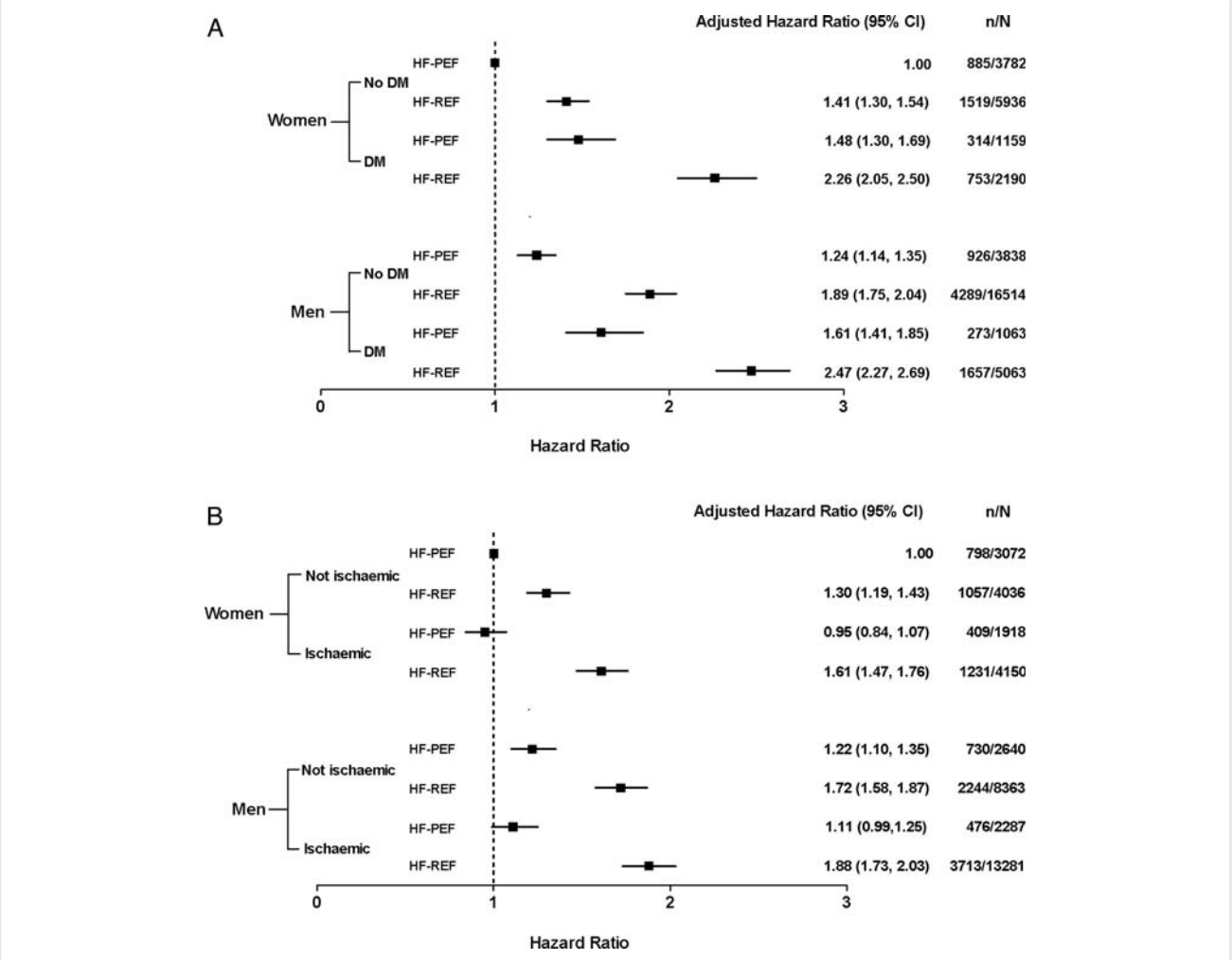

Figure 3 (*A*) Risk of death of heart failure (HF) patients by sex, diabetes mellitus (DM), and ejection fraction group (preserved HF-PEF or reduced HF-REF) adjusted for age and stratified by study (gender × EF group × diabetes interaction $P = 0.208$). (*B*) Risk of death of HF patients by sex, aetiology, and ejection fraction group (HF-PEF or HF-REF) adjusted for age and stratified by study (gender × EF group × ischaemic aetiology interaction $P = 0.0008$). CI, confidence interval.

Diabetes

Diabetes was present more frequently in women (25.4%) than in men (22.8%, $P < 0.001$). In patients with reduced EF, diabetes was present among 26.6% of women and 23.1% of men ($P < 0.001$), and in patients with preserved EF, among 23.6% of women and 21.7% of men ($P = 0.03$). There were 2997 deaths among 9776 patients (30.7%) with, and 7366 deaths among 31 513 patients (23.4%) without, diabetes. After adjustment for covariates, diabetes retained an independent association with death from any cause (adjusted HR 1.41, 95% CI 1.35–1.47) and with cardiovascular death (HR 1.51, 95% CI 1.41–1.62).

Concomitant diabetes attenuated the lower risk of death associated with female sex (risk of death for men vs. women: diabetes HR 1.11, 95% CI 1.03–1.20; no diabetes 1.37, 95% CI 1.30–1.45, *P*-value for interaction <0.0001). Diabetes also appeared to modify the relationship between sex and mortality, irrespective of left ventricular EF. Among patients with diabetes, there was no statistically significant difference in the HR for death from any cause between men and women in either the preserved or reduced EF groups. However, for patients without diabetes, men had a higher risk of death from any cause compared with women, in both the preserved and reduced EF groups. The adjusted HR for different subgroups, with women with preserved EF and no diabetes as the comparator, is shown in *Figure 3A*. The three-way interaction for gender × EF × diabetes was not statistically significant ($P = 0.208$).

Aetiology

Ischaemic aetiology was less frequent among women (46.3%) than men (58.7%, $P < 0.001$). Ischaemic aetiology was recorded in 61.4% of men and 50.9% of women ($P < 0.001$) with reduced EF, and in 46.9% of men and 38.6% of women ($P < 0.001$) with preserved EF. Ischaemic aetiology showed an independent

association with death from any cause (adjusted HR 1.07, 95% CI 1.03–1.12), and cardiovascular death (HR 1.11, 95% CI 1.04–1.19).

The aetiology of HF appeared to modify the association between sex and outcome: risk of death for men vs. women with ischaemic HF, adjusted HR 1.17 (95% CI 1.10–1.24); non-ischaemic aetiology HR 1.28 (95% CI 1.21–1.37), *P*-value for interaction = 0.03. Although there was a trend to worse prognosis in men with ischaemic aetiology, this did not reach statistical significance in either the preserved or reduced EF groups. For patients with non-ischaemic aetiology, men had a higher risk of death from any cause compared with women, in both the preserved and reduced EF groups. The adjusted HR for the different subgroups compared with women with preserved EF and no ischaemic HF is shown in *Figure 3B* (three-way gender × EF × ischaemic aetiology interaction $P = 0.0008$).

Discussion

This large-scale meta-analysis, based upon patient-level data from almost 42 000 individuals, represents the largest assessment of the association between sex and survival for patients with HF. The main finding of our study is that compared with men, women with HF have lower all-cause mortality over 3 years, irrespective of EF. Our analysis confirms that women with HF are on average older, are more likely to have a history of hypertension and diabetes, but are less likely to have HF of ischaemic aetiology. We also found that women had more severe functional limitation than men as reflected by NYHA class. Importantly, women were less likely than men to be prescribed evidence-based therapies, particularly among those patients with HF with reduced EF, for which there is unequivocal evidence of benefit from these agents.

Previous studies assessing potential differences in survival among men and women with HF have presented conflicting results, with some suggesting better survival for women[1–14] and others failing to identify such an association.[15–18] Many of these studies have been limited by relatively small numbers of patients and have presented mortality risks for men and women with wide and overlapping confidence intervals, preventing definitive conclusions from being drawn. Moreover, consideration of specific interactions of sex with aetiology of HF or with reduced/preserved EF has been limited. Our study, using a large individual patient data set, is appropriately powered to ascertain the prognostic significance of sex in patients with HF.

The current analysis suggests that while crude unadjusted mortality rates in men and women were very similar, when adjusted for age the risk of death was higher in men than in women with HF. Further, the influence of age on survival was similar in men and women (*P* for gender × age interaction = 0.63), suggesting that better survival in women is associated with factors other than age. While women have a higher prevalence of HF with preserved EF which was associated with a better prognosis in this study, we observed a higher risk of death in men, irrespective of whether they had HF with reduced or preserved EF (*Figure 2*).

There are a number of alternative potential explanations for the better outcomes in women with HF. The female heart appears to respond to injury differently from the male heart. For example, women have been reported to have less ventricular remodelling, preservation of right ventricular function, and protection against ventricular arrhythmias, neurohormonal activation, genetic mutations, myocyte necrosis, and apoptosis.[28] Some of these advantages could be related to pregnancy[28] and to sex-specific differences in gene expression.[29]

In accordance with previous studies,[13,14] we found lower prescription of ACE inhibitors or ARBs in women than in men. Perhaps surprisingly, this was particularly evident in patients with reduced EF, where the evidence for these therapies is strongest. In fact, for all age groups with reduced EF, women received ACE inhibitors or ARBs less frequently than men (data not shown). Given this pattern of prescribing, the lower risk of death for women compared with men is all the more remarkable.

The reported prevalence of diabetes in patients with HF is highly variable, with figures between 13% and 29%,[20–23]probably due to the definitions of both diabetes and HF used and the heterogeneous nature of the populations studied. Our data are consistent with previous reports of higher risk of death among patients with HF with co-existing diabetes.[20–23] In the current analysis we have extended these previous observations to a large population that included patients with reduced or preserved EF. In both groups we observed diabetes to be a strong independent risk factor for mortality in patients with HF. This association was particularly evident among women, especially those with reduced EF, where the presence of diabetes attenuates the apparently protective 'effect' of female sex on prognosis. A similar interaction has been described for patients with ischaemic heart disease, where diabetes also attenuates the gender gap in mortality.[30] In contrast, female gender has been suggested to be associated with greater likelihood of pre-clinical diabetic cardiomyopathy.[31]

Our finding that the association between female sex and better survival appears to be stronger in patients with non-ischaemic HF is in agreement with several previous studies.[2,3,8] Importantly, we have shown clearly that this sex-related difference in prognosis is seen regardless of whether EF is reduced or preserved. A single previous report, from the second Cardiac Insufficiency Bisoprolol Study (CIBIS II), suggested no sex-related difference in mortality in patients with non-ischaemic aetiology.[9] However, in CIBIS II, the aetiology of HF was undefined in 36% of men and 47% of women, limiting markedly the ability of this trial to compare prognosis between ischaemic and non-ischaemic HF.

Our analysis is constrained by the underlying limitations of the original individual studies. However, by incorporating large amounts of data from both randomized trials and observational studies, resulting in a wide range of patients, with long follow-up and a large number of clinical events, the results are likely to be an accurate reflection of patients with the syndrome of HF seen in routine clinical practice. The interaction between diabetes status and sex-related outcomes is robust, whereas the interaction with aetiology is less certain.

Conclusion

This analysis from a large, individual patient data meta-analysis has demonstrated that women with HF have lower risk of death when compared with men with HF, in both preserved and reduced EF. This survival benefit may be more marked in HF of non-ischaemic

aetiology but is clearly attenuated by concomitant diabetes. Further study is required to determine the biological reasons for this better prognosis in women.

Conflict of interest: none declared.

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Appendix

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References

1. Martínez-Sellés M, García Robles JA, Prieto L, Domínguez Muñoa M, Frades E, Díaz-Castro O, Almendral J. Systolic dysfunction is a predictor of long term mortality in men but not in women with heart failure. *Eur Heart J* 2003;**24**:2046–2053.
2. Adams KF Jr, Sueta CA, Gheorghiade M, O'Connor CM, Schwartz TA, Koch GG, Uretsky B, Swedberg K, McKenna W, Soler-Soler J, Califf RM. Gender differences in survival in advanced heart failure. Insights from the FIRST study. *Circulation* 1999;**99**:1816–1821.
3. Adams KF Jr, Dunlap SH, Sueta CA, Clarke SW, Patterson JH, Blauwet MB, Jensen LR, Tomasko L, Koch G. Relation between gender, etiology and survival in patients with symptomatic heart failure. *J Am Coll Cardiol* 1996;**28**:1781–1788.
4. Parashar S, Katz R, Smith NL, Arnold AM, Vaccarino V, Wenger NK, Gottdiener JS. Race, gender, and mortality in adults ≥65 years of age with incident heart failure (from the Cardiovascular Health Study). *Am J Cardiol* 2009; **103**:1120–1127.
5. Ruigómez A, Johansson S, Wallander MA, García Rodríguez LA. Gender and drug treatment as determinants of mortality in a cohort of heart failure patients. *Eur J Epidemiol* 2001;**17**:329–335.
6. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Piña IL, Granger CB, Ostergren J, Michelson EL, Solomon SD, Pocock S, Yusuf S, Swedberg K, Pfeffer MA; CHARM Investigators. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation* 2007;**115**:3111–3120.
7. Martínez-Sellés M, Martínez E, Cortés M, Prieto R, Gallego L, Fernández-Avilés F. Determinants of long-term survival in patients hospitalized for heart failure. *J Cardiovasc Med (Hagerstown)* 2010;**11**:164–169
8. Martínez-Sellés M, Domínguez M, Martínez E, García Fernández MA, García E. Women with left ventricular ejection fraction ≤20% have better prognosis than men. *Int J Cardiol* 2007;**120**:276–278.
9. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Circulation* 2001;**103**:375–380.
10. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;**355**:251–259.
11. Berry C, Hogg K, Norrie J, Stevenson K, Brett M, McMurray J. Heart failure with preserved left ventricular systolic function: a hospital cohort study. *Heart* 2005;**91**: 907–913.
12. Gustafsson F, Torp-Pedersen C, Brendorp B, Seibaek M, Burchardt H, Køber L; DIAMOND Study Group. Long-term survival in patients hospitalized with congestive heart failure: relation to preserved and reduced left ventricular systolic function. *Eur Heart J* 2003;**24**:863–870.
13. Sheppard R, Behlouli H, Richard H, Pilote L. Effect of gender on treatment, resource utilization, and outcomes in congestive heart failure in Quebec, Canada. *Am J Cardiol* 2005;**95**:955–959.
14. Nicol ED, Fittall B, Roughton M, Cleland JG, Dargie H, Cowie MR. NHS heart failure survey: a survey of acute heart failure admissions in England, Wales and Northern Ireland. *Heart* 2008;**94**:172–177.
15. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;**355**:260–269.
16. Tribouilloy C, Rusinaru D, Mahjoub H, Soulière V, Lévy F, Peltier M, Slama M, Massy Z. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. *Eur Heart J* 2008;**29**:339–347.
17. Vazquez R, Bayes-Genis A, Cygankiewicz I, Pascual-Figal D, Grigorian-Shamagian L, Pavon R, Gonzalez-Juanatey JR, Cubero JM, Pastor L, Ordonez-Llanos J, Cinca J, de Luna AB; MUSIC Investigators. The MUSIC Risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure. *Eur Heart J* 2009;**30**:1088–1096.

18. Rusinaru D, Mahjoub H, Goissen T, Massy Z, Peltier M, Tribouilloy C. Clinical features and prognosis of heart failure in women. A 5-year prospective study. *Int J Cardiol* 2009;**133**:327–335.
19. Bourassa MG, Gurné O, Bangdiwala SI, Ghali JK, Young JB, Rousseau M, Johnstone DE, Yusuf S. Natural history and current practices in heart failure. *J Am Coll Cardiol* 1993;**22**:14A–19A.
20. MacDonald MR, Jhund PS, Petrie MC, Lewsey JD, Hawkins NM, Bhagra S, Munoz N, Varyani F, Redpath A, Chalmers J, MacIntyre K, McMurray JJ. Discordant short- and long-term outcomes associated with diabetes in patients with heart failure: importance of age and sex: a population study of 5.1 million people in Scotland. *Circ Heart Fail* 2008;**1**:234–241.
21. Ahmed A, Aban IB, Vaccarino V, Lloyd-Jones DM, Goff DC Jr, Zhao J, Love TE, Ritchie C, Ovalle F, Gambassi G, Louis J. A propensity matched study of the effect of diabetes on the natural history of heart failure: variations by sex and age. *Heart* 2007;**93**:1584–1590.
22. Gustafsson I, Brendorp B, Seibaek M, Burchardt H, Hildebrandt P, Kober L, Torp-Pedersen C. Influence of diabetes and diabetes–gender interaction on the risk of death in patients hospitalized with congestive heart failure. *J Am Coll Cardiol* 2004;**43**:771–777.
23. Tribouilloy C, Rusinaru D, Mahjoub H, Tartière JM, Kesri-Tartière L, Godard S, Peltier M. Prognostic impact of diabetes mellitus in patients with heart failure and preserved ejection fraction: a prospective five-year study. *Heart* 2008;**94**: 1450–1455.
24. Yancy CW, Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN. Influence of patient age and sex on delivery of guideline-recommended heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. *Am Heart J* 2009;**157**:754–762.e2.
25. Frankenstein L, Clark AL, Ribeiro JP. Influence of sex on treatment and outcome in chronic heart failure. *Cardiovasc Ther* 2011; in press.
26. Somaratne JB, Berry C, Mcmurray JJV, Poppe K, Doughty RN, Whalley GA. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. *Eur J Heart Fail* 2009;**11**:855–862.
27. Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2011;in press.
28. Martínez-Sellés M. What do women have in their hearts? *Rev Esp Cardiol* 2007;**60**: 1118–1121.
29. Heidecker B, Lamirault G, Kasper EK, Wittstein IS, Champion HC, Breton E, Russell SD, Hall J, Kittleson MM, Baughman KL, Hare JM. The gene expression profile of patients with new-onset heart failure reveals important gender-specific differences. *Eur Heart J* 2010;**31**:1188–1196.
30. Dale AC, Nilsen TI, Vatten L, Midthjell K, Wiseth R. Diabetes mellitus and risk of fatal ischaemic heart disease by gender: 18 years follow-up of 74,914 individuals in the HUNT 1 Study. *Eur Heart J* 2007;**28**:2924–2929.
31. Kiencke S, Handschin R, von Dahlen R, Muser J, Brunner-LaRocca HP, Schumann J, Felix B, Berneis K, Rickenbacher P. Pre-clinical diabetic cardiomyopathy: prevalence, screening, and outcome. *Eur J Heart Fail* 2010;**12**: 951–957.