The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis

Meta-analysis Global Group in Chronic Heart Failure (MAGGIC)

Aims	A substantial proportion of patients with heart failure have preserved left ventricular ejection fraction (HF-PEF). Previous studies have reported mixed results whether survival is similar to those patients with heart failure and reduced EF (HF-REF).
Methods and results	We compared survival in patients with HF-PEF with that in patients with HF-REF in a meta-analysis using individual patient data. Preserved EF was defined as an EF $\geq$ 50%. The 31 studies included 41 972 patients: 10 347 with HF-PEF and 31 625 with HF-REF. Compared with patients with HF-REF, those with HF-PEF were older (mean age 71 vs. 66 years), were more often women (50 vs. 28%), and have a history of hypertension (51 vs. 41%). Ischaemic aetiology was less common (43 vs. 59%) in patients with HF-PEF. There were 121 [95% confidence interval (CI): 117, 126] deaths per 1000 patient-years in those with HF-PEF and 141 (95% CI: 138, 144) deaths per 1000 patient-years in those with HF-REF. Patients with HF-PEF had lower mortality than those with HF-REF (adjusted for age, gender, aetiology, and history of hypertension, diabetes, and atrial fibrillation); hazard ratio 0.68 (95% CI: 0.64, 0.71). The risk of death did not increase notably until EF fell below 40%.
Conclusion	Patients with HF-PEF have a lower risk of death than patients with HF-REF, and this difference is seen regardless of age, gender, and aetiology of HF. However, absolute mortality is still high in patients with HF-PEF highlighting the need for a treatment to improve prognosis.
Keywords	Heart failure • Prognosis • Meta-analysis

Introduction

Heart failure is a leading cause of cardiovascular morbidity and mortality and arises as a consequence of many cardiovascular conditions, including coronary artery disease (CAD), valve disease, and hypertension. Heart failure has been traditionally viewed as a failure of contractile function and left ventricular (LV) ejection fraction (EF) has been widely used to define systolic function, assess prognosis, and select patients for therapeutic interventions. However, it is recognized that heart failure can occur in the presence of normal or near-normal EF: so-called 'heart failure with preserved EF (HF-PEF)' which accounts for a substantial proportion of clinical cases of heart failure.[1-4]

There are many differences between patients with heart failure with reduced EF (HF-REF) and patients with HF-PEF. The latter are older and more often women, are less likely to have CAD, and more likely to have underlying hypertension.[1,2,5] In addition, patients with HF-PEF do not obtain similar clinical benefits from angiotensin-converting enzyme (ACE) inhibition or angiotensin receptor blockade compared with patients with HF-REF.[6-8] Several comparisons of survival between patients with HF-PEF and those with HF-REF have been reported but have given inconsistent results.[1,2] Although a recent literature-based meta-analysis demonstrated that patients with HF-PEF may have lower mortality than those with HF-REF,[9] lack of patient-level data precluded careful adjustment for differences between these patient groups in potentially important prognostic variables such as age, gender, co-morbidity, and aetiology of HF.

Therefore, we undertook a meta-analysis using individual patient data to examine mortality rates in patients with HF-PEF and HF-REF.

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Methods

A comprehensive search was undertaken for a literature-based meta-analysis of observational studies and randomized controlled trials (RCTs) published to the end of 2006, and the details of this have been reported.[9] The same search process was repeated to the end of 2008. In brief, we searched online databases including Embase, Medline, Medline In-progress, and PubMed using the key words: *prognosis*, *outcome*, *heart failure*, *left ventricle*, and *preserved*. We also searched reference lists of articles obtained during the search and conference abstracts and made personal communication with investigators and authors. Abstracts, unpublished studies, and articles published in languages other than English were not excluded. Eligible studies were those that included patients with heart failure and reported the outcome of interest (death from any cause) and where EF criterion was not used for entry into the study. All the individual studies were approved by Ethics Committees. The meta-analysis was approved by The University of Auckland Human Subjects Ethics Committee.

Study selection and data extraction

We identified 56 potentially suitable studies: principal investigators for each of these studies were invited to participate in this meta-analysis. An executive group was formed to oversee the data management and analysis, and the steering group involved the principal investigator from each study. Investigators from 31 studies (3 pharmacotherapy RCTs, 4 management intervention RCTs, and 24 observational studies)[10–40] provided individual patient data on a pre-defined set of variables including demographics (age, sex, and ethnicity), medical history (history of myocardial infarction, coronary revascularization, diabetes, hypertension, stroke, lung disease, peripheral artery disease, and smoking), medical treatment (ACE-inhibitor, angiotensin receptor blocker, β-blocker, diuretic, and aldosterone antagonist), symptom status [New York Heart Association (NYHA) functional class, dyspnoea, paroxysmal nocturnal dyspnoea, and oedema], clinical variables (heart rate, blood pressure, and pulmonary rales), laboratory variables (serum sodium, creatinine, and EF), and outcome (deaths and follow-up duration). Data from 30 of the individual studies were re-coded at the Central Coordinating Centre at the University of Auckland into a uniform format. Data were checked and queries resolved, and the summary data from each study compared against the original published data prior to incorporation into a single database. This data set was then sent to the London School of Hygiene and Tropical Medicine finally where the CHARM trial data were incorporated to create the final data set (31 studies) within which these analyses were undertaken.

Our primary hypothesis was that patients with HF-PEF would have a lower mortality rate than patients with HF-REF, even after adjustment for other prognostic variables.

Ejection fraction

In 18 studies, a preference for rounding EF to the nearest 5% was observed. In these studies, EF at these rounded values was reallocated within 2.5% either side of the rounded value by random selection from a uniform distribution. For example, EF values of 20% were randomly reallocated to values between 17.5 and 22.4%. Preserved EF was pre-specified as EF $\geq$50%.

Statistical analysis

The baseline variables for the HF-PEF and HF-REF groups were compared using Student's *t*-test for continuous variables and the χ^2 tests of proportions for categorical variables. For all analyses, the outcome was the rate of death from any cause at 3 years from hospital discharge or baseline study visit. Three-year death rates and deaths per 1000 patient-years were calculated. Cox's proportional hazard models were used to estimate the hazard of HF-PEF compared with HF-REF, adjusted for age, gender, ischaemic aetiology, a history of hypertension, diabetes, and atrial fibrillation, and stratified by study. These variables chosen for the model were selected for clinical relevance and where data were available for that variable in more than 90% of the patients in the MAGGIC data set. Data on NYHA functional class and medications (ACE-inhibitor and/or angiotensin receptor antagonist and/or β-blockers) were available on fewer patients in the MAGGIC data set. However, due to the importance of these variables in relation to outcome, the Cox proportional hazards model was repeated with incorporation of these variables in turn into the above model. In the whole group, within age groups and within gender, EF < 50% was the referent; when comparing mortality across 10% bands of EF, EF $\geq$ 60% was the referent. The correlation between the scaled Schoenfeld residuals and length of follow-up showed that there was no violation of the proportional hazards assumption for all analyses. Mortality curves were created of adjusted models that were not stratified by study. Analyses were performed using R version 2.9.0.[41]

Results

Thirty one of the 56 identified studies contributed data on 54 416 patients (*Figure 1*). One thousand one hundred and seventy-nine patients were excluded due to irresolvable dates or death during an index hospital admission and 2246 excluded as heart failure was secondary to severe valvular heart disease or hypertrophic cardiomyopathy. Ejection fraction data were not available for 9019 patients, and thus the main analysis was based on 41 972 patients for whom EF data were available. Ejection fraction was assessed using echocardiography in 33 717 (80.4%), scintigraphy in 6899 (16.4%), and angiography in 1356 (3.2%). Quantitative EF data were available for 38 484 (92%) patients and the remainder (3488, 8%) had semi-quantitative EF assessment: 10 347 (24.7%) patients had HF-PEF and 31 625 (75.3%) had HF-REF. The baseline
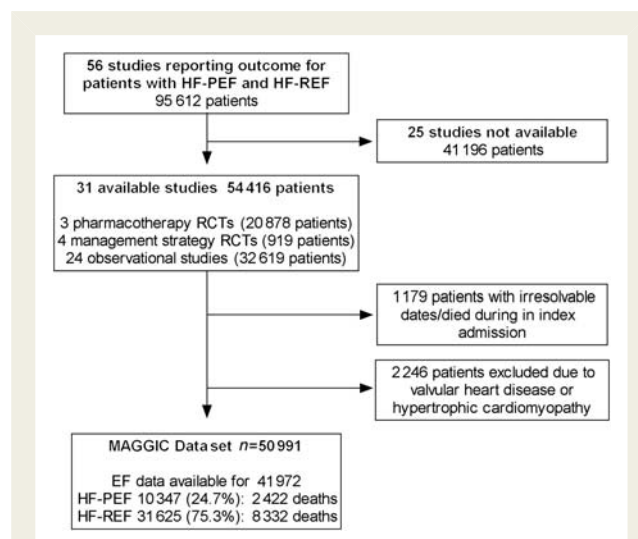

Figure 1 Flow chart of studies for meta-analysis.

Table 1   **Baseline characteristics of the groups**

	Whole group	HF-PEF	HF-REF	Missing LVEF	*P*-value (HF-PEF vs. HF-REF)
n (31 studies)	50 991	10 347	31 625	9019	—
Age [years (SD)]	68 (12)	71 (12)	66 (12)	71 (13)	<0.001
Women (%)	35%	50%	28%	44%	<0.001
Medical history					
Hypertension	43%	51%	41%	40%	<0.001
Myocardial infarction	43%	27%	51%	31%	<0.001
Atrial fibrillation	21%	27%	18%	23%	<0.001
Diabetes	23%	23%	24%	21%	0.005
Ischaemic aetiology	54%	43%	59%	49%	<0.001
Medication					
ACE-inhibitor or ARB	67%	44%	75%	64%	<0.001
β-Blocker	34%	33%	39%	23%	<0.001
Diuretic	82%	78%	83%	83%	<0.001
Spironolactone	21%	16%	24%	17%	<0.001
Digoxin	43%	32%	47%	44%	<0.001
Clinical status					
NYHA class (I/II/III/IV) (%)	11/47/34/8	14/48/29/9	10/46/37/7	19/48/25/8	All <0.004
Heart rate (b.p.m.)	79 (18)	78 (21)	79 (18)	79 (17)	0.019
SBP (mmHg)	131 (23)	141 (25)	128 (22)	135 (24)	<0.001
DBP (mmHg)	77 (13)	79 (14)	76 (12)	80 (13)	<0.001
LVEF % (median, IQR)	36 (27, 48)	60 (55, 61)	31 (24, 39)	—	—

Values represent mean (standard deviation) unless stated. ARB, angiotensin receptor blocker; IQR, inter-quartile range; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction.

characteristics are shown in *Table 1*. When compared with the HF-REF patients, those with HF-PEF were older (mean age 71 years SD 12 vs. 66 years SD 12), were more often women (50 vs. 28%), more often had a history of hypertension (51 vs. 41%) and atrial fibrillation (27 vs. 18%), and less often ischaemic aetiology (43 vs. 59%). Patients with HF-REF were more commonly receiving treatment with an ACE-inhibitor (75 vs. 44%), β-blocker (39 vs. 33%), and spironolactone (24 vs. 16%) compared with those with HF-PEF. For the 25 studies for which patient data were not available, the weighted mean from published data showed that these patients were slightly older (mean age 71 years), fewer were women (34%), and the proportion of patients with missing EF was higher (33%) than the included studies.

The median duration of follow-up for patients with a missing EF was only 121 days [inter-quartile range (IQR) 85, 365] compared with those with an available EF: HF-PEF group 1024 (IQR 246, 1546) days and HF-REF group 933 (IQR 346, 1348) days. Due to the large difference in duration of follow-up, the group with missing EF was not considered further in this analysis. The primary outcome of death from any cause occurred in 2422 (23.4%) patients with HF-PEF and in 8332 (26.3%) in those with HF-REF. There were 121 [95% confidence interval (CI): 117, 126] deaths per 1000 patient-years in those with HF-PEF and 141 (95% CI: 138, 144) deaths per 1000 patient-years in those with HF-REF. In univariate
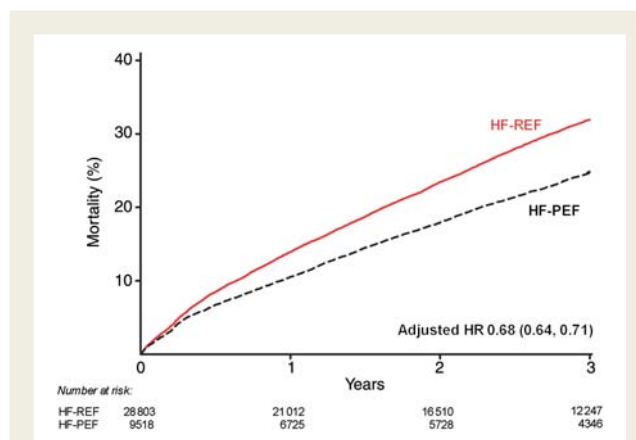

Figure 2 Mortality for patients with HF-PEF (heart failure with preserved left ventricular ejection fraction) and HF-REF (heart failure with low left ventricular ejection fraction), adjusted for age, gender, aetiology of heart failure, hypertension, diabetes, atrial fibrillation.

analysis, patients with HF-PEF were at lower risk of death than those with HF-REF, hazard ratio (HR) 0.71 (95% CI: 0.67, 0.74). In the adjusted Cox proportional hazards model, patients with HF-PEF had lower mortality than those with HF-REF, adjusted HR

0.68 (95% CI: 0.64, 0.71; *Figure 2* and *Table 2*). When the RCTs of pharmacotherapy (three trials, 20 878 patients) were excluded from the analysis, there were 146 (95% CI: 138, 154) deaths per 1000 patient-years in those with HF-PEF and 159 (95% CI: 154, 165) deaths per 1000 patient-years in those with HF-REF, and the risk of death remained lower in the patients with HF-PEF compared with those with the HF-REF group: adjusted HR 0.76 (95% CI: 0.71, 0.82). Correspondingly, in the randomized trials alone, there were 101 (95% CI: 96, 107) deaths per 1000 patient-years in those with HF-PEF and 131 (95% CI: 127, 134) deaths per 1000 patient-years in those with HF-REF and the risk of death remained lower in the patients with HF-PEF compared with those with HF-REF, adjusted HR 0.61 [95% CI: 0.57, 0.65; interaction EF × study design (RCT or non-RCT), $P = 0.0007$]. For studies that recruited patients who were hospitalized at baseline ($n = 18\,108$), the adjusted HR for death from any cause for patients with HF-PEF compared with those with HF-REF was 0.70 (95% CI: 0.66, 0.74) and was 0.59 (95% CI: 0.54, 0.66) for studies involving patients who were not

hospitalized ($n = 20\,213$). Thus, irrespective of whether hospitalized or not, patients with HF-PEF had a lower risk of death than patients with HF-REF. However, this difference appeared to be greater in ambulatory than in hospitalized patients.

Data on cardiovascular death were available for 26 725 patients from 14 studies; in an adjusted Cox proportional hazards model, patients with HF-PEF had lower risk of cardiovascular death than those with HF-REF, adjusted HR 0.55 (95% CI: 0.49, 0.61; *Table 2*). When the adjusted Cox proportional hazards model was repeated with inclusion of either NYHA functional class (16 592 patients) or medications (11 908 patients), similar results were seen for both death from any cause and cardiovascular death: NYHA included in model HR for death from any cause 0.68 (95% CI: 0.60, 0.77) and for cardiovascular death HR 0.62 (95% CI: 0.52, 0.75); medications included in model HR for death from any cause 0.66 (95% CI: 0.62, 0.69) and for cardiovascular death HR 0.47 (95% CI: 0.33, 0.68).

Risk of death from any cause and cardiovascular death by EF category is shown in *Figure 3*. The HR for death in patients with an EF 50−59% and in those with an EF between 40 and 49% was not increased compared with patients with an EF of 60% or above. However, the HR for death increased steadily below an EF of 40%. The rate of death increased with age: 847 (12.8%) deaths among 6624 patients aged <55 years, 5617 (21.7%) deaths among 25 882 patients aged 55−75 years, and 5510 (36.0%) deaths among 15 280 patients aged >75 years. In all three age groups, patients with HF-PEF had a lower risk of death than patients with HF-REF, with no differences in HR for men and women (*Figure 4*). There was no interaction between gender and age for death from any cause ($P = 0.604$). However, the HR for the difference in mortality between patients with HF-PEF and those with HF-REF appeared to differ according to age (age/EF group interaction, $P < 0.0001$). For example, for women aged ≥75 years, the adjusted HR comparing risk of death among women with HF-PEF and those with HF-REF was 0.79 (95% CI: 0.72, 0.87) compared with 0.38 (95% CI: 0.22, 0.65) for women aged <55 years. Similarly, for men aged ≥75 years, the adjusted

Table 2 Cox's proportional adjusted hazards ratios for all-cause death and cardiovascular death

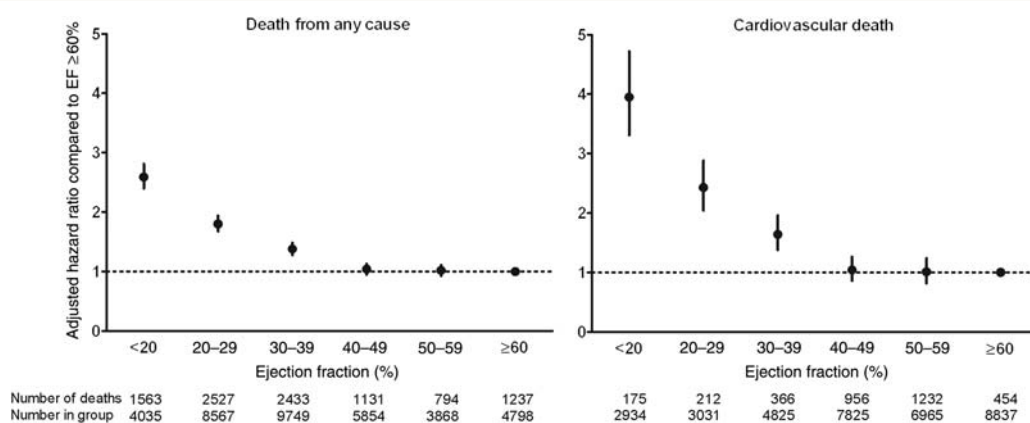| Variable	Death from any cause Hazard ratio (95% CI)	Cardiovascular death Hazard ratio (95% CI)
HF-PEF	0.68 (0.64, 0.71)	0.55 (0.49, 0.61)
Male gender	1.23 (1.18, 1.28)	1.23 (1.14, 1.33)
Age (years)	1.04 (1.04, 1.04)	1.03 (1.03, 1.04)
Ischaemic aetiology	1.07 (1.02, 1.12)	1.11 (1.03, 1.19)
Hypertension	0.93 (0.89, 0.97)	0.94 (0.88, 1.00)
Diabetes	1.41 (1.35, 1.47)	1.51 (1.41, 1.62)
Atrial fibrillation	1.10 (1.05, 1.16)	1.28 (1.16, 1.41)

Figure 3 Adjusted hazard ratios comparing death from any cause and cardiovascular death by groups of left ventricular ejection fraction (with LVEF ≥ 60% as the reference group).
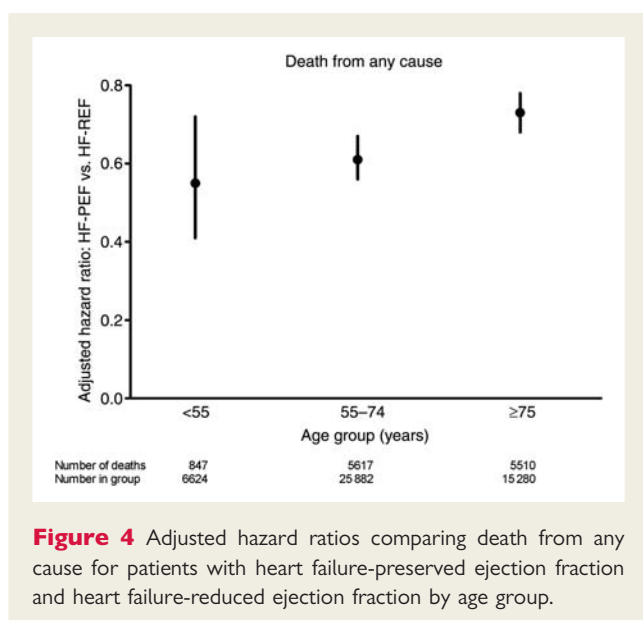
Figure 4 Adjusted hazard ratios comparing death from any cause for patients with heart failure-preserved ejection fraction and heart failure-reduced ejection fraction by age group.

HR comparing risk of death among men with HF-PEF and those with HF-REF was 0.74 (95% CI: 0.67, 0.81) compared with 0.50 (95% CI: 0.37, 0.69) for men aged <55 years. This indicates that the difference in the risk of death among patients with HF-PEF and HF-REF was less among older patients than in younger patients.

Discussion

This large systematic review of over 40 000 patients evaluating the survival of patients with HF-PEF or HF-REF has three principal findings. First, patients with HF-PEF had a 32% lower risk of death over 3 years compared with those with HF-REF. Secondly, the phenotype of patients in this study with HF-PEF confirms early studies demonstrating striking gender and age differences between the two syndromes. Compared with those with HF-REF, patients with HF-PEF were typically 5 years older, half were women but were less likely to have ischaemic heart disease as the aetiology of their heart failure. Thirdly, even after adjusting for these and other prognostic variables using individual patient data in this meta-analysis, the difference in mortality remained in both men and women and was present irrespective of aetiology of heart failure and age. Similar results were also observed whether the patients were hospitalized or not at baseline and whether involved in RCTs of pharmacotherapy or observational studies. These results, obtained by analysing more than 10 000 deaths among more than 40 000 patients, provide clear evidence that survival is different for these two distinct phenotypes of the heart failure syndrome.

While a number of studies have reported on outcome for patients with HF-PEF compared with those with HF-REF, the individual results have been conflicting. Two large retrospective community-based studies reported that mortality was similar for patients with HF-PEF and HF-REF.[1,2] Several sources of bias exist in studies reporting outcome, for example, ideally any such study for patients with heart failure utilizing a cut-off of EF would have EF measurements available for all patients, although this is rarely the case. If missing EF measurements were to occur across all patient groups, then this would not introduce bias. However, EF measurement is undertaken less frequently in some patient groups such as the elderly[42] and patients with missing EF measurement have worse outcome than those with EF measurements.[43] Consequently, exclusion of patients due to missing EF measurements can introduce systematic bias. While the current meta-analysis was not able to obtain individual patient data from all prior studies, the proportion of patients missing EF data was only 18% from the studies providing data, while the studies not contributing data had EF missing in 42% of the patients, thus the potential effects of missing EF data are likely to be lessened in the current analyses.

Characterization of patients with HF-PEF has been hampered by lack of a consistent definition of this condition. Earlier recommendations advocating the application of detailed assessment of LV diastolic function were complicated and effectively unworkable in clinical practice.[44] Furthermore, diastolic dysfunction is unlikely to be the sole underlying cardiac abnormality in all such patients, and other factors, such as atrial fibrillation, valve disease, and myocardial ischaemia, as well as non-cardiac conditions such as renal impairment, anaemia, obesity, and diabetes, are likely to contribute. A simple approach, as used in this current meta-analysis, is to define this symptomatic group of patients by an EF cut-off. This is attractive in that EF is commonly utilized in clinical practice to guide application of evidence-based therapies.[45] However, this approach is effectively one of 'exclusion' and likely results in a heterogeneous group of patients with multiple underlying cardiac abnormalities contributing to the heart failure despite preserved EF, including some with subtle abnormalities of LV systolic function.[46–48] In addition, there has been concern that with this approach patients with non-cardiac causes of breathlessness, exercise intolerance, and oedema may erroneously be labelled as having heart failure.[49]

Furthermore, the optimal EF cut-off for the simple classification of heart failure (HF-PEF or HF-REF) remains uncertain. Our data demonstrate that mortality risk does not increase substantially until EF falls below 40%, consistent with prior arbitrary use of this cut-point in trials of pharmacological treatment. More recently, recommendations have been made to incorporate LV size, and other echocardiographic and neurohormonal variables in this definition,[50] although these remain to be prospectively evaluated in large groups of patients with heart failure.

The current data are based on a large group of patients for whom one measurement of EF was available at the baseline assessment, which was used to define the group of patients with preserved or reduced EF. Prior studies suggest that EF measurements are similar whether obtained at the time of acute heart failure decompensation or at a later time when compensated and symptoms improved.[51] However, it remains uncertain whether the group of patients with HF-PEF will develop progressive worsening of EF in the longer-term as their disease progresses in association with subsequent events, although there are some data to suggest that patients with HF-PEF may only develop progressive LV remodelling if inter-current myocardial infarction occurs.[52] As a result, for some patients, the clinical outcomes

may be influenced by progressive LV remodelling, and in others may be influenced by vascular or other effects. Much remains to be learned as to why some patients with similar co-morbid conditions develop progressive remodelling, whereas others have worsened diastolic function.

The extensive study of patients with HF-REF has developed an understanding of the importance of mechanisms of death among patients with heart failure. In particular, the relative contributions of sudden death or death due to progressive heart failure have become of particular importance in the era of device-based therapies.[53] While it is now clear that patients with HF-PEF have lower total mortality than those with HF-REF, understanding the mode of death among patients with HF-PEF is of importance. Recent pharmacotherapy trials have reported that cardiovascular deaths account for 60% of all deaths in those with HF-PEF, with sudden death and death due to progressive heart failure appearing to be less common among patients with HF-PEF compared with those with HF-REF.[54–56] Community-based observational studies may involve older patients with a wider range of co-morbidities than patients in RCTs, and this may contribute to the lower proportion of cardiovascular deaths (49%) reported in these studies.[57,58] The difference in mortality between patients with HF-PEF and HF-REF in the current meta-analysis was less pronounced with more advanced age which would be consistent with a greater influence of non-cardiovascular deaths among older patients. Further understanding of the mode of death in a wide range of patients with HF-PEF will further assist with the development of appropriate strategies to improve outcome for these patients.

Our meta-analysis has some limitations. While we combined the data from a large number of studies and individual patients, their value is still determined by the underlying limitations of the original individual studies. However, incorporating 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 commonly seen in clinical practice with the syndrome of heart failure. Data were only incorporated from studies that enrolled patients without an EF inclusion criterion at baseline; thus, studies such as I-PRESERVE and PEP-CHF and the numerous individual studies of patients with HF-REF were not included in this meta-analysis. Data on clinical, echocardiographic, and laboratory variables were not universally available in all studies. The variables incorporated into the Cox proportional hazards model were selected for clinical relevance and being available in the majority of patients. Other variables which may have prognostic importance were not selected due to the amount of missing data. A relatively low proportion of the patients with HF-REF were receiving β-blockers and spironolactone, which may reflect the time that the studies were conducted, and could influence the overall difference in mortality seen in this analysis.

In summary, in combining individual patient data from multiple studies, we have demonstrated that patients with HF-PEF have lower total mortality when compared with patients with HF-REF. In particular, risk of death appears to increase in patients with EF below 40%. Further detailed study is required of outcome in patients with HF-PEF to determine new therapeutic strategies to improve outcome for these patients.

Appendix

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