



Mortality in heart failure with preserved ejection fraction: an unacceptably high rate

Daniel Burkhoff*

Columbia University, New York City, NY, USA

This editorial refers to ‘The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis’, by Meta-analysis Global Group in Chronic Heart Failure (MAGGIC), doi:10.1093/eurheartj/ehr254

One important factor that has contributed to our thinking about heart failure in patients with normal or preserved ejection fraction (HFpEF) has been the perception that mortality in this group of patients is similar to that in those of heart failure patients with reduced ejection fraction (HFrEF). This may derive largely from the results of two prior independent epidemiological studies that showed that mortality in these two groups of patients did not differ substantially (Figure 1A and B).^{1,2} Furthermore, the study by Owan *et al.*¹, which collected patient outcome data spanning the time period from 1987 to 2001, showed that there was no improvement in HFpEF mortality trends over each successive 4 year time period. This contrasted to the improvement in 5-year survival of patients with HFrEF from ~27% to ~35%, which was interpreted as reflecting the introduction and adoption of new medical therapies and implantable cardioverter-defibrillators (ICDs) over this time period.

However, the concept of similar mortality in HFpEF and HFrEF was recently challenged in a literature-based meta-analysis that included 17 studies with a total of 24 501 patients.³ That analysis showed a 32.1% mortality after an average of ~4 years of follow-up compared with a 40.6% mortality in HFrEF. To overcome some of the limitations inherent in a literature-based meta-analysis and to be able to delve deeper into factors contributing to mortality, the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) now report an individual patient data meta-analysis addressing the same question.⁴ The final analysis included data from 41 972 individual patients (10 347 with HFpEF and 31 625 with HFrEF) obtained from 31 studies. One of the main advantages of an individual patient data meta-analysis is that mortality rates can be adjusted for imbalances between important and well-known baseline characteristics between the groups. Another interesting and key feature of this analysis was that data were only included from studies in which there was no

baseline EF inclusion criterion. This was intended to avoid selection bias that could have been introduced in the enrolment of patients into the individual studies. Thus, data from several important and well-known studies were not included (see, for example, Massi *et al.*⁵). The main finding (Figure 1C) of this study confirmed the prior literature-based meta-analysis result that patients with HFpEF have a lower mortality rate than patients with HFrEF. At 3 years, the adjusted mortality was ~32% in HFrEF and ~25% in HFpEF. These findings complement the results of the prior meta-analysis in that they arrived at a similar conclusion (qualitatively and quantitatively) despite the fundamentally different statistical methods and despite having included a much greater number of patients derived from a larger number and different array of publications.

Prior prospective studies have shown that unlike HFrEF, as many as 30–40% of deaths in HFpEF are non-cardiovascular in nature.^{5,6} One additional important issue addressed by the new meta-analysis by the MAGGIC investigators was demonstration that in addition to reduced total mortality, the risk of cardiovascular mortality was also less in HFpEF compared with HFrEF. Also, and very interestingly, the difference in mortality between HFrEF and HFpEF patients decreased with increasing age, a finding that was considered to be related to a progressively greater contribution of non-cardiovascular deaths with age.

The significance of the findings in the new study by the MAGGIC investigators relates to the current emphasis on filling in as many gaps as possible in our understanding of HFpEF to guide development of new treatments. While several effective pharmacological and device-based treatments have become available over the past decades for patients with HFrEF, no therapy has yet been shown to improve survival in HFpEF. Why is that? Initial large-scale investigations of treatments for HFpEF focused on drugs known to be effective in HFrEF. From a very simplistic perspective, this may have been because it was assumed that since treatments for HFrEF are generally effective regardless of the underlying aetiology (ischaemic, non-ischaemic) they might also be effective in heart failure due to another aetiology, especially since so many of the HFpEF patients suffer from other conditions commonly treated by angiotensin-converting enzyme (ACE) inhibition and β -blockade.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +1 201 294 6081, Fax: +1 914 422 1549, Email: db59@columbia.edu

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2011. For permissions please email: journals.permissions@oup.com

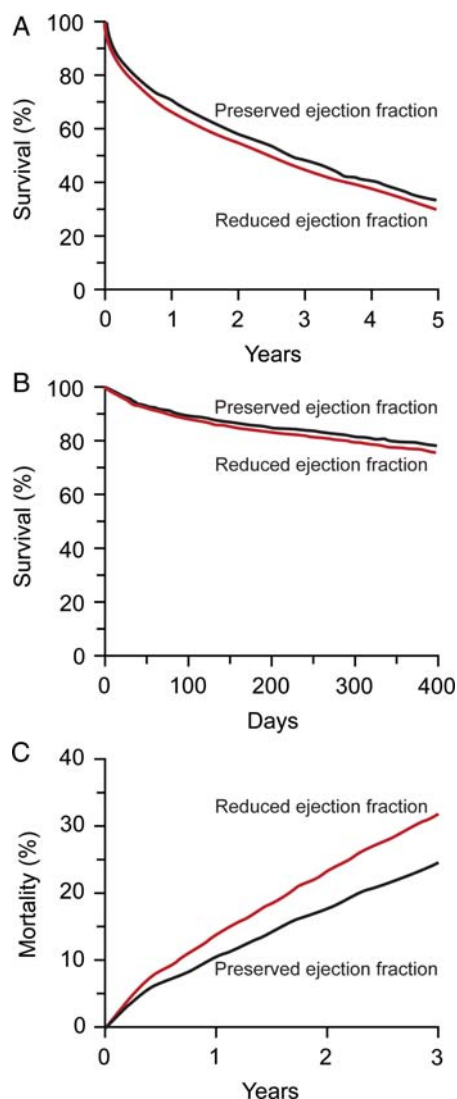


Figure 1 Comparison of survival between HFpEF and HFrEF from two epidemiological studies^{1,2} and an individual patient data meta-analysis including results of randomized studies.⁴ Note that although the differences in survival in A were statistically significant ($P = 0.03$, with >4500 patients included in the analysis) the difference at any time point is small. Adapted from 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, and 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. with permission from the *New England Journal of Medicine*.

Two additional, widely accepted principles may have also influenced thinking of how to develop treatments for HFpEF. First has been the longstanding belief that HFpEF is a disease due to ventricular diastolic dysfunction; indeed, until very recently this syndrome was universally referred to as ‘diastolic heart failure’. This concept led to testing some drugs aimed at enhancing the rate of myocardial relaxation (to improve active relaxation) and drugs

to reduce myocardial hypertrophy and fibrosis (to improve passive diastolic compliance). Second is the notion that the mechanism(s) that underlies HFpEF is the same in all affected patients. However, with each failed therapeutic clinical trial and the appearance of new basic studies (both animal and human) that delve deeper into the pathophysiology, some investigators are becoming more open minded to the possibility that both of these principles may not be true.

Several well acknowledged consequences arise if these two principles are relaxed.^{7,8} First is the need to identify and address new therapeutic targets. Identification of chronotropic incompetence during exercise⁹ and the presence of certain types of amyloidosis in some patients with HFpEF¹⁰ are two recent examples. Second is the need to rethink clinical trial strategies for HFpEF. For example, study inclusion and exclusion criteria may need to be refined to achieve enrolment of more homogenous populations likely to have common underlying disease pathophysiologies and who are more likely to respond to specific forms of therapy. In this regard, there is recent evidence that the pathophysiology of HFpEF may be influenced significantly by the number and type of co-morbidities present in an individual patient.¹¹ So, for all we know, there may actually be a subgroup of HFpEF patients that respond well to ACE inhibition or β -blockade, but this would not have been detectable from prior studies that included patients with widely different numbers and types of co-morbidities. Similarly, the interesting age-related differences in the rate of cardiovascular death in HFpEF suggested by the MAGGIC study investigators imply that it may be important to factor age into study inclusion criteria and statistical analysis plans. One already existing example of this is the PEP-HF study, which studied the effects of perindopril on mortality and heart failure hospitalizations in older patients, though this study also failed to show long-term benefits.¹²

One additional and interesting observation that is borne out by comparison of the results presented in *Figure 1* is that mortality rates are substantially higher in the retrospective epidemiological studies^{1,2} as compared with what is reported in the prospective randomized studies;⁴ both for HFrEF and for HFpEF. As pointed out by Cleland *et al.*¹³ this could reflect the fact that patients having significant but common serious co-morbidities such as severe renal disease, pulmonary disease, etc. which have a significant detrimental impact on mortality are excluded from entering studies but could exist in a significant portion of the heart failure population at large.

Irrespective of whether mortality in HFpEF is less than or the same as in HFrEF, results of all studies reveal that this rate is unacceptably high (*Figure 1*), that a large proportion of mortality and morbidity is due to heart failure,^{5,6} and that specific therapies for HFpEF are needed. Though not widely accepted, it has been suggested previously that development of new therapies might be facilitated if focus is shifted away from the assumption that diastolic dysfunction is the underlying pathophysiology in all HFpEF patients and that it be recognized that HFpEF may encompass different diseases with common signs and symptoms but that may have different underlying aetiologies requiring different therapies. Similarly, taking full advantage of knowing how patient characteristics impact on outcome, as demonstrated in the

individual patient data meta-analysis of the MAGGIC investigators, can also factor importantly in strategies to develop and test badly needed therapies for patients with HFpEF.

Conflict of interest: none declared.

References

- 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.
- 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.
- Somaratne JB, Berry C, McMurray JJ, Poppe KK, 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.
- 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* doi:10.1093/eurheartj/ehr254. Published online ahead of print 6 August 2011.
- Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;**359**:2456–2467.
- Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;**362**:777–781.
- Burkhoff D, Maurer MS, Packer M. Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? *Circulation* 2003;**107**:656–658.
- Bench T, Burkhoff D, O'Connell JB, Costanzo MR, Abraham WT, St John SM, Maurer MS. Heart failure with normal ejection fraction: consideration of mechanisms other than diastolic dysfunction. *Curr Heart Fail Rep* 2009;**6**:57–64.
- Kass DA, Kitzman DW, Alvarez GE. The restoration of chronotropic competence in heart failure patients with normal ejection fraction (RESET) study: rationale and design. *J Card Fail* 2010;**16**:17–24.
- Bhuiyan T, Helmke S, Patel AR, Ruberg FL, Packman J, Cheung K, Grogan D, Maurer MS. Pressure–volume relationships in patients with transthyretin (ATTR) cardiac amyloidosis secondary to V122I mutations and wild-type transthyretin: Transthyretin Cardiac Amyloid Study (TRACS). *Circ Heart Fail* 2011;**4**:121–128.
- Abramov D, He KL, Wang J, Burkhoff D, Maurer MS. The impact of extra cardiac comorbidities on pressure volume relations in heart failure and preserved ejection fraction. *J Card Fail* 2011;**17**:547–555.
- Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–2345.
- Cleland JG, Taylor J, Tendera M. Prognosis in heart failure with a normal ejection fraction. *N Engl J Med* 2007;**357**:829–830.