European Heart Journal (2012) **33**, 1750–1757
doi:10.1093/eurheartj/ehr254

CLINICAL RESEARCH
Heart failure/cardiomyopathy

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)

Received 18 March 2011; revised 30 May 2011; accepted 4 July 2011; online publish-ahead-of-print 6 August 2011

See page 1718 for the editorial comment on this article (doi:10.1093/eurheartj/ehr339)

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.

Corresponding author: Robert Neil Doughty, Department of Medicine, The University of Auckland, Private Bag 92019, Auckland Mail Centre, Auckland 1142, New Zealand. Tel: +64 9 923 9804, Fax: +64 9 367 7146, Email: r.doughty@auckland.ac.nz

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

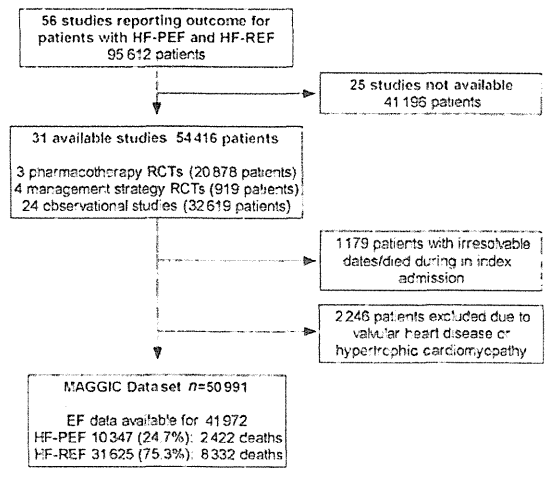

Figure 1 Flow chart of studies for meta-analysis.

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

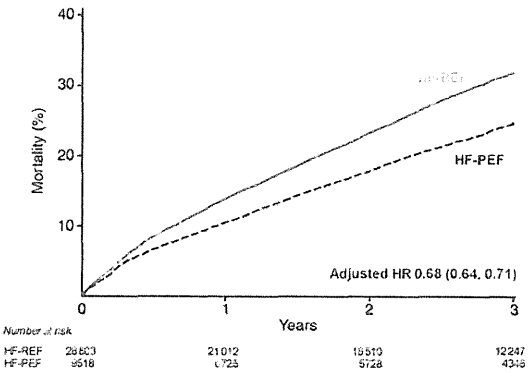

Figure 2 Mortality for patients with HF-PEF (heart failure with preserved left ventricular ejection fraction) and HF-REF (heart failure with low left ventricular ejection fraction), adjusted for age, gender, aetiology of heart failure, hypertension, diabetes, atrial fibrillation.

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)

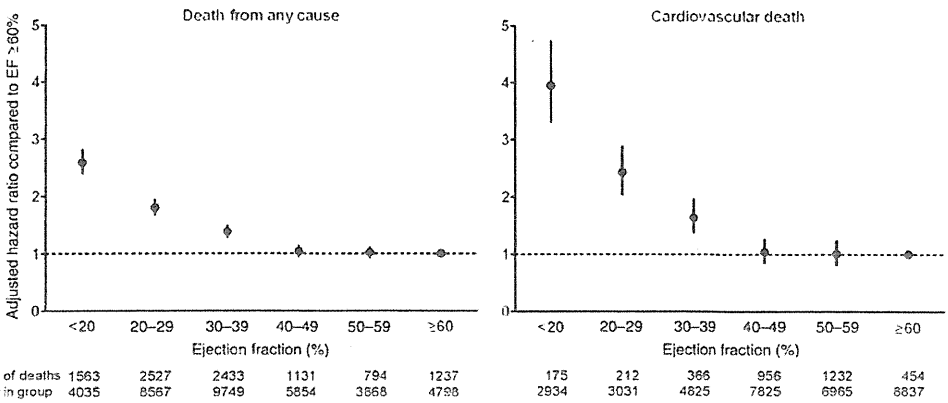

Figure 3 Adjusted hazard ratios comparing death from any cause and cardiovascular death by groups of left ventricular ejection fraction (with LVEF ≥ 60% as the reference group).

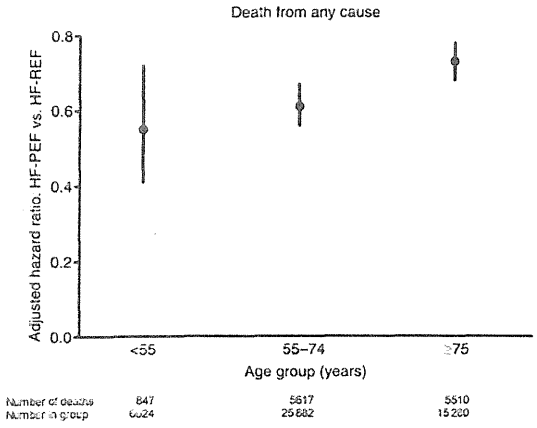

Figure 4 Adjusted hazard ratios comparing death from any cause for patients with heart failure-preserved ejection fraction and heart failure-reduced ejection fraction by age group.

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.

Funding

The MAGGIC meta-analysis was supported by grants from the New Zealand National Heart Foundation, The University of Auckland and The University of Glasgow. These sponsors had no role in the design, conduct, data management, and analysis; or in the manuscript preparation or review; or in the authorization for submission.

Conflict of interest: Dr Komajda is a member of the Executive Committee of the I-PRESERVE trial and is an ESC officer. Dr Rich has received research funding from Astellas Pharma US (small grant) and Sanofi-aventis (consultant, moderate).

Appendix

MAGGIC Executive Group (responsible for the oversight and overall conduct of the meta-analysis): C. Berry, R.N. Doughty, C. Granger, L. Køber, B. Massie, F. McAlister, J. McMurray, S. Pocock, K. Poppe, K. Swedberg, J. Somaratne, and G.A. Whalley.

MAGGIC Steering Group: The Steering Group included investigators from the original studies that provided individual patient data: A. Ahmed, B. Andersson, A. Bayes-Genis, C. Berry, M. Cowie, R. Cubbon, R.N. Doughty, J. Ezekowitz, J. Gonzalez-Juanatey, M. Gorini, I. Gotsman, L. Grigorian-Shamagian, M. Guazzi, M. Kearney, L. Køber, M. Komajda, A. di Lenarda, M. Lenzen, D. Lucci, S. Macín, B. Madsen, A. Maggioni, M. Martínez-Sellés, F. McAlister, F. Oliva, K. Poppe, M. Rich, M. Richards, M. Senni, I. Squire, G. Taffet, L. Tarantini, C. Tribouilloy, R. Troughton, H. Tsutsui, and G.A. Whalley.

MAGGIC Coordinating Centre: R.N. Doughty, N. Earle, K. Perera, K. Poppe, and G.A. Whalley, The University of Auckland, New Zealand.

MAGGIC Statistical Group: J. Dobson, S. Pocock, and K. Poppe.

The MAGGIC Studies and Investigators: The following investigators kindly provided the individual patient data from their studies: *AHFMS:* R.N. Doughty, and G. Whalley; *Andersson (two data sets)*: B. Andersson, C. Hall; *BATTLESCARRED* and *Richards*: A.M. Richards, R. Troughton, and J. Lainchbury; *Berry*: C. Berry, K. Hogg, J. Norrie, K. Stevenson, M. Brett, and J. McMurray; *CHARM*: M.A. Pfeffer, K. Swedberg, C.B. Granger, P. Held, J.J.V. McMurray, E.L. Michelson, B. Olofsson, J. Östergren, and S. Yusuf for the CHARM Investigators and Committees; *Diamond* and *ECHOS*: L. Køber, and C. Torp-Pedersen; *DIG Trial*: DIG limited access data, Ali Ahmed; *Euro HF Survey*: M.J. Lenzen, W.J.M. Scholte op Reimer, E. Boersma, P.J.M.J. Vantrimpont, F. Follath, K. Swedberg, J. Cleland, and M. Komajda; *Gotsman*: I. Gotsman, D. Zwas, D. Planer, T. Azaz-Livshits, D. Admon, C. Lotan, and A. Keren; *Grigorian-Shamagian*: L. Grigorian-Shamagian, A. Varela-Roman, P. Mazón-Ramos, P. Rigeiro-Veloso, M.A. Bandin-Dieguez, and J.R. Gonzalez-Juanatey; *Guazzi*: M. Guazzi, J. Myers, and R. Arena; *Heart Failure Clinic Edmonton*: F.A. McAlister, J. Ezekowitz, P.W. Armstrong, Bibiana Cujec, and Ian Paterson; *Hillingdon*: M.R. Cowie, D.A. Wood, A.J.S. Coats, S.G. Thompson, V. Suresh, P.A. Poole-Wilson, and G.C. Sutton; *HOLA*: M. Martínez-Sellés, J.A.G. Robles, L. Prieto, M.D. Muñoa, E. Frades, O. Díaz-Castro, and J. Almendral; *Italian HF Registry (IN-CHF)*: L. Tarantini, P. Faggiano, M. Senni, D. Lucci, D. Bertoli, M. Porcu, C. Opasich, L. Tavazzi, and A.P. Maggioni; *Kirk*: V. Kirk,

M. Bay, J. Parner, K. Krogsgaard, T.M. Herzog, S. Boesgaard, C. Hassager, O.W. Nielsen, J. Aldershvile, H. Nielsen, and L. Kober; *Macin*: S.M. Macín, E.R. Perna, J.P. Cimbaro Canella, P. Alvarenga, R. Pantich, N. Ríos, E.F. Farias, and J.R. Badaracco; *Madsen*: B.K. Madsen, J.F. Hansen, K.H. Stokholm, J. Brons, D. Husum, and L.S. Mortensen; *MUSIC*: A. Bayes-Genis, R. Vazquez, T. Puig, C. Fernandez-Palomeque, A. Bardají, D. Pascual-Figal, J. Ordoñez-Llanos, M. Valdes, A. Gabarrus, R. Pavon, L. Pastor, J.R. Gonzalez-Juanatey, J. Almendral, M. Fiol, V. Nieto, C. Macaya, J. Cinca, and A. Bayes de Luna; *Newton*: J.D. Newton, H.M. Blackledge, and I.B. Squire; *NPC I*: S.P. Wright, G.A. Whalley, and R.N. Doughty; *Rich (data set 1)*: R. Kerzner, B.F. Gage, K.E. Freedland, and M.W. Rich; *Rich (data set 2)*: B.C. Huynh, A. Rovner, K.E. Freedland, R.M. Carney, and M.W. Rich; *Taffet*: G.E. Taffet, T.A. Teasdale, A.J. Bleyer, N.J. Kutka, and R.J. Luchi; *Tribouilloy*: C. Tribouilloy, D. Rusinaru, H. Mahjoub, V. Soulière, F. Lévy, and M. Peltier; *Tsutsui*: H. Tsutsui, M. Tsuchihashi, and A. Takeshita; *UK Heart Study*: P.A. MacCarthy, M.T. Kearney, R. Cubbon, J. Nolan, A.J. Lee, R.J. Prescott, A.M. Shah, W.P. Brooksby, and K.A.A. Fox; *Varela-Roman*: A. Varela-Roman, J.R. Gonzalez-Juanatey, P. Basante, R. Trillo, J. Garcia-Seara, J.L. Martinez-Sande, and F. Gude.

References

1. 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.
2. 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.
3. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006;**47**:76–84.
4. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry. *J Am Coll Cardiol* 2007;**50**:768–777.
5. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004;**43**:317–327.
6. Cleland JGF, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, on behalf of PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–2345.
7. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A, the IPI. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;**359**:2456–2467.
8. 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.
9. 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. *Euro J Heart Fail* 2009;**11**:855–862.
10. Andersson B, Hall C. N-terminal proatrial natriuretic peptide and prognosis in patients with heart failure and preserved systolic function. *J Cardiac Fail* 2000;**6**:208–213.
11. Andersson B, Kjörk E, Brunlöf G. Temporal improvement in heart failure survival related to the use of a nurse-directed clinic and recommended pharmacological treatment. *Int J Cardiol* 2005;**104**:257–263.
12. Bayes-Genis A, Vazquez R, Puig T, Fernandez-Palomeque C, Fabregat J, Bardají A, Pascual-Figal D, Ordoñez-Llanos J, Valdes M, Gabbarrús A, Pavon R, Pastor L, Juanatey JRG, Almendral J, Fiol M, Nieto V, Macaya C, Cinca J, de Luna AB. Left atrial enlargement and NT-proBNP as predictors of sudden cardiac death in patients with heart failure. *Eur J Heart Fail* 2007;**9**:802–807.
13. 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.
14. Cowie MR, Wood DA, Coats AJS, Thompson SG, Suresh V, Poole-Wilson PA, Sutton GC. Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 2000;**83**:505–510.
15. Curtis J, Sokol S, Wang Y, Rathore S, Ko D, Jadbabaie F, Portnay E, Marshalko S, Radford M, Krumholz H. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. *J Am Coll Cardiol* 2003;**42**:736–742.
16. Doughty RN, Wright SP, Pearl A, Walsh HJ, Muncaster S, Whalley GA, Gamble G, Sharpe N. Randomised, controlled trial of integrated heart failure management: the Auckland Heart Failure Management Study. *Euro Heart J* 2002;**23**:139–141.
17. Gotsman I, Zwas D, Planer D, Azaz-Livshits T, Admon D, Lotan C, Keren A. Clinical outcome of patients with heart failure and preserved left ventricular function. Am J Med 2008;**121**:997–1001.
18. Grigorian Shamagian L, Roman AV, Ramos PM, Veloso PR, Bandin Dieguez MA, Gonzalez-Juanatey JR. Angiotensin-converting enzyme inhibitors prescription is associated with longer survival among patients hospitalized for congestive heart failure who have preserved systolic function: a long-term follow-up study. *J Cardiac Fail* 2006;**12**:128–133.
19. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol* 2005;**46**:1883–1890.
20. Gustafsson F, Torp-Pedersen C, Brendorp B, Seibaek M, Burchardt H, Kober L, for the Diamond Study Group. Long-term survival in patients hospitalized with congestive heart failure: relation to preserved and reduced left ventricular systolic function. *Euro Heart J* 2003;**24**:863–870.
21. Kerzner R, Gage BF, Freedland KE, Rich MW. Predictors of mortality in younger and older patients with heart failure and preserved or reduced left ventricular ejection fraction. *Am Heart J* 2003;**146**:286–290.
22. Kirk V, Bay M, Parner J, Krogsgaard K, Herzog TM, Boesgaard S, Hassager C, Nielsen OW, Aldershvile J, Nielsen H. N-terminal proBNP and mortality in hospitalised patients with heart failure and preserved vs. reduced systolic function: data from the prospective Copenhagen Hospital Heart Failure Study (CHHF). *Eur J Heart Fail* 2004;**6**:335–341.
23. Lainchbury JG, Troughton RW, Strangman KM, Frampton CM, Pilbrow A, Yandle TG, Hamid AK, Nicholls MG, Richards AM. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. *J Am Coll Cardiol* 2009;**55**:53–60.
24. Lenzen MJ, Scholte op Reimer WJM, Boersma E, Vantrimpont PJMJ, Follath F, Swedberg K, Cleland J, Komajda M. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. *Eur Heart J* 2004;**25**:1214–1220.
25. MacCarthy PA, Kearney MT, Nolan J, Lee AJ, Prescott RJ, Shah AM, Brooksby WP, Fox KAA. Prognosis in heart failure with preserved left ventricular systolic function: prospective cohort study. *BMJ* 2003;**327**:78–79.
26. Macín SM, Perna ER, Cimbaro Canella JP, Alvarenga P, Pantich R, Rios N, Farias EF, Badaracco JR. Differences in clinical profile and outcome in patients with decompensated heart failure and systolic dysfunction or preserved systolic function. *Rev Esp Cardiol* 2004;**57**:45–52.
27. Madsen BK, Hansen JF, Stokholm KH, Brøns J, Husum D, Mortensen LS. Description and survival of 190 consecutive patients with a diagnosis of chronic congestive heart failure based on clinical signs and symptoms. *Eur Heart J* 1994;**15**:303–310.
28. Martinez-Selles M, Robles JAG, Prieto L, Munoa MD, Frades E, Diaz-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.
29. McAlister FA, Teo KK, Taher M, Montague TJ, Humen D, Cheung L, Kiaii M, Yim R, Armstrong PW. Insights into the contemporary epidemiology and outpatient management of congestive heart failure. *Am Heart J* 1999;**138**:87–94.
30. Newton JD, Blackledge HM, Squire IB. Ethnicity and variation in prognosis for patients newly hospitalised for heart failure: a matched historical cohort study. *Heart* 2005;**91**:1545–1550.
31. Pfeffer M, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EI, Olofsson B, Ostergren J, Yusuf S, for the CHARM Investigators and Committees. Effects of candesartan on mortality and mobidity in patients with chronic heart failure: the CHARM-Overall Programme. *Lancet* 2003;**362**:759–766.
32. Pilbrow AP, Palmer BR, Frampton CM, Yandle TG, Troughton RW, Campbell E, Skelton L, Lainchbury JG, Richards AM, Cameron VA. Angiotensinogen M235T and T174M gene polymorphisms in combination doubles the risk of mortality in heart failure. *Hypertension* 2007;**49**:322–327.

33. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med* 1995;**333**:1190–1195.
34. Taffet GE, Teasdale TA, Bleyer AJ, Kutka NJ, Luchi RJ. Survival of elderly men with congestive heart failure. *Age Ageing* 1992;**21**:49–55.
35. Tarantini L, Faggiano P, Senni M, Lucci D, Bertoli D, Porcu M, Opasich C, Tavazzi L, Maggioni AP. Clinical features and prognosis associated with a preserved left ventricular systolic function in a large cohort of congestive heart failure outpatients managed by cardiologists. Data from the Italian Network on Congestive Heart Failure. *Ital Heart J* 2002;**3**:656–664.
36. Torp-Pedersen C, Kober L, Carlsen JE, Akkan D, Bruun NE, Dacoronias D, Dickstein K, Haghfelt T, Ohlin H, McMurray JJV. A randomised trial of a presynaptic stimulator of DA2-dopaminergic and α2-adrenergic receptors on morbidity and mortality in patients with heart failure. *Eur J Heart Fail* 2008;**10**:89–95.
37. Tribouilloy C, Rusinaru D, Mahjoub H, Souliere V, Levy 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.
38. Tsutsui H, Tsuchihashi M, Takeshita A. Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function. *Am J Cardiol* 2001;**88**:530–533.
39. Varela-Roman A, Grigorian L, Barge E, Bassante P, de la Pena MG, Gonzalez-Juanatey JR. Heart failure in patients with preserved and deteriorated left ventricular ejection fraction. *Heart* 2005;**91**:489–494.
40. Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ, Gordon G, Bagg W, Oxenham H, Yandle T, Richards AM, Sharpe N. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. *J Am Coll Cardiol* 2003;**42**:1793–1800.
41. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing, 2009.
42. Lindenfeld J, Fiske KS, Stevens BR, Debuhr J, Havranek EP, Abrams FR. Age, but not sex, influences the measurement of ejection fraction in elderly patients hospitalized for heart failure. *J Cardiac Fail* 2003;**9**:100–106.
43. McDermott MM, Feinglass J, Lee PI, Mehta S, Schmitt B, Lefevre F, Gheorghiade M. Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. *Am Heart J* 1997;**134**:728–736.
44. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *Eur Heart J* 1998;**19**:990–1003.
45. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;**29**:2388–2442.
46. Kono M, Kisanuki A, Takasaki K, Nakashiki K, Yuasa T, Kuwahara E, Mizukami N, Uemura T, Kubota K, Ueya N, Miyata M, Tei C. Left ventricular systolic function is abnormal in diastolic heart failure: re-assessment of systolic function using cardiac time interval analysis. *J Cardiol* 2009;**53**:437–446.
47. Zile MR. Heart failure with preserved ejection fraction: is this diastolic heart failure? *J Am Coll Cardiol* 2003;**41**:1519–1522.
48. Petrie MC, Caruana L, Berry C, McMurray JJV. 'Diastolic heart failure' or heart failure caused by subtle left ventricular systolic dysfunction? *Heart* 2002;**87**:29–33.
49. Caruana L, Petrie MC, Davie AP, McMurray JJV. Do patients with suspected heart failure and preserved left ventricular function suffer from 'diastolic heart failure' of from misdiagnosis? A prospective descriptive study. *BMJ* 2000;**321**:215–219.
50. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;**28**:2539–2550.
51. Gandhi SK, Powers JC, Nomeir A-M, Fowle K, Kitzman DW, Rankin KM, Little WC. The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001;**344**:17–22.
52. Desai RV, Ahmed MI, Mujib M, Aban IB, Zile MR, Ahmed A. Natural history of concentric left ventricular geometry in community-dwelling older adults without heart failure during seven years of follow-up. Am J Cardiol 2011;**107**:321–324.
53. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH, the Sudden Cardiac Death in Heart Failure Trial Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237.
54. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, Lopez-Sendon J, Teerlink JR, White M, McMurray JJ, Komajda M, McKelvie R, Ptaszynska A, Hetzel SJ, Massie BM, Carson PE, for the IPI. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) Trial. *Circulation* 2010;**121**:1393–1405.
55. Solomon SD, Wang D, Finn P, Skali H, Zornoff L, McMurray JJV, Swedberg K, Yusuf S, Granger CB, Michelson EL, Pocock S, Pfeffer MA. Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Program. *Circulation* 2004;**110**:2180–2183.
56. Solomon SD, Anavekar N, Skali H, McMurray JJV, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA, for the Candesartan in Heart Failure Reduction in Mortality Investigators. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005;**112**:3738–3744.
57. Henkel D, Redfield MM, Weston S, Gerber Y, Roger V. Death in heart failure: a community perspective. *Circ: Heart Fail* 2008;**1**:91–97.
58. Grigorian-Shamagian L, Raviña FO, Assi EA, Perez RV, Teijeira-Fernandez E, Roman AV, Sayagues LM, Gonzalez-Juanatey JR. Why and when do patients with heart failure and normal left ventricular ejection fraction die? Analysis of >600 deaths in a community long-term study. *Am Heart J* 2008;**156**:1184–1190.

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Heart Failure

Clinical Efficacy of Cardiac Resynchronization Therapy With an Implantable Defibrillator in a Japanese Population

– Results of the MIRACLE-ICD Outcome Measured in Japanese Indication (MOMIJI) Study –

Shin-ichi Momomura, MD; Hiroyuki Tsutsui, MD, PhD; Yoshitaka Sugawara, MD; Makoto Ito, MD; Takeshi Mitsuhashi, MD; Seiji Fukamizu, MD; Mahito Noro, MD; Naoki Matsumoto, MD; Tomoyuki Tejima; Kaoru Sugi, MD, PhD for the MOMIJI Study Investigators

Background: Cardiac resynchronization therapy (CRT) is effective in reducing morbidity and mortality in systolic heart failure patients with cardiac dyssynchrony as demonstrated in studies with primarily Western populations. Although CRT devices with a defibrillator (CRT-D) became available in Japan since 2006, their efficacy remains uncertain in Japanese patients. In this prospective, multicenter study, the efficacy of CRT-D therapy in an all-Japanese population was compared with the study conducted in the US, Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD).

Methods and Results: Ninety-three patients were evaluated according to the subject selection criteria of the MIRACLE-ICD study, and 80 patients were enrolled. Results at baseline and 6-month post-CRT-D implantation were compared in terms of composite clinical response (CCR) and other secondary endpoints. Quality of life (QOL) was assessed with a validated Japanese version of the Minnesota Living with Heart Failure questionnaire. CCR was improved in 55 patients (68.8%), unchanged in 14 (17.5%), and worsened in 11 patients (13.7%) (MIRACLE-ICD general phase: 62.0%, 13.4% and 24.6%, respectively). Non-inferiority was verified by 1-sided test with 10% equivalence margin. QOL score improved significantly (50.0±26.2 vs. 23.6±20.2, P<0.01).

Conclusions: The MOMIJI study demonstrated that CRT-D effectiveness as assessed with CCR was non-inferior to the trials conducted outside Japan, thus suggesting that the benefits of CRT-D are similar between Japanese and non-Japanese patients. (*Circ J* 2012; **76:** 1911–1919)

Key Words: Biventricular pacing; Cardiac resynchronization therapy; Defibrillators; Heart failure; Minnesota Living with Heart Failure

A number of large-scale randomized clinical studies demonstrated that cardiac resynchronization therapy (CRT) with or without an implantable cardioverter defibrillator (CRT-D) could improve symptoms, quality of life (QOL), functional status, exercise capacity, and mortality in patients with moderate to severe heart failure (HF), a wide QRS, and life-threatening arrhythmias.[1–3] More recent studies suggested that long-term CRT-D therapy could prevent the progression of disease and reduce the mortality also in patients with asymptomatic or mild HF.[4–8] CRT-D devices have been available since 2006, and their use is gradually gaining acceptance in Japan. Japanese patients have been included in multinational studies of CRT[9] and the results for Japanese patients have been reported in single-center studies, registries, and case reports.[10–13] However, clinicians have been uncertain as to whether the prognosis of Japanese patients with HF is compa-

Received November 21, 2011; revised manuscript received March 26, 2012; accepted April 9, 2012; released online May 30, 2012
Time for primary review: 65 days

Division of Cardiovascular Medicine, Saitama Medical Center, Jichi Medical University, Saitama (S.M., Y.S.); Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Sapporo (H.T.); Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu (M.I.); Department of Cardiovascular Medicine, Jichi Medical University, Shimotsuke (T.M.), Department of Cardiology, Tokyo Metropolitan Hiroo Hospital, Tokyo (S.F.); Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo (M.N., K.S.); Department of Pharmacology, St. Marianna University School of Medicine, Kawasaki (N.M.); and Cardiac Rhythm Disease Management, Medtronic Japan Co, Ltd, Tokyo (T.T.), Japan

Participants are listed in the Appendix.

Mailing address: Shin-ichi Momomura, MD, Division of Cardiovascular Medicine, Saitama Medical Center Jichi Medical University, 1-847 Amanuma, Omiya-ku, Saitama 330-8503, Japan. E-mail: momoshin@omiya.jichi.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-11-1341

Table 1. Inclusion and Exclusion Criteria

Inclusion

1. Age ≥20 years
2. Heart failure patients whose symptoms have not improved despite optimal pharmacological therapy and who meet all the criteria listed in (A) below as well as the criteria in either (B) or (C) with the exception of patients with disease of transient or reversible cause.
   (A) Indicated heart failure patients:
   - NYHA class III or IV
   - LVEF ≤35%
   - Intrinsic QRS duration ≥130 ms

   (B) Patients with one of the following risks for sudden cardiac death:
   - History of resuscitation from cardiac arrest following fatal arrhythmia (clear loss of consciousness)
   - VT or VF that disrupts hemodynamics
   - Confirmed NSVT, as well as VT or VF induced by electrophysiological testing

   (C) Patients who meet the Japanese criteria for implantation of an ICD
3. Patients signed the informed consent and permission for access to and use of health information.
4. Patients who are willing to visit the hospital in accordance with the follow-up schedule

Exclusion

1. Estimated survival <6 months
2. Bradycardia requiring pacemaker
3. Unstable angina, myocardial infarction, coronary angioplasty, cerebral vascular accident, or transient ischemic attack within the previous 3 months
4. >2 infusions of inotropic drug per week
5. Systolic blood pressure <80 mmHg or >170 mmHg
6. Resting heart rate >140 beats/min
7. Serum creatinine >3 mg/dl (265 μmol/L)
8. Hepatic enzymes >3-fold upper normal values
9. Severe lung disease
10. Chronic AF defined using the following classification:
    - Permanent: long-standing episode for which cardioversion did not take effect.
    - Persistent: recurrent episodes that are sustained but could be cardioverted.
    - Paroxysmal: recurrent episodes that stopped spontaneously.
11. Heart transplant recipient
12. Severe valvular heart disease (decision on severity made by a medical doctor)
13. Existing CRT or CRT-D device

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; VT, ventricular tachycardia; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator; AF, atrial fibrillation; CRT, cardiac resynchronization therapy; CRT-D, CRT with an implantable cardioverter defibrillator.

rable to that seen in the large-scale clinical trials conducted in Western countries.[14,15]

Editorial p1830

We conducted the MIRACLE-ICD Outcome Measured in Japanese Indication (MOMIJI) Study to compare the efficacy of CRT-D therapy in a population of Japanese patients with advanced HF, an intraventricular conduction delay, and an indication for implantable cardioverter defibrillator (ICD) therapy. The aim of the study was to examine the non-inferiority to the results of the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) general phase study conducted in the United States with regard to a composite clinical response (CCR) that classified patients as being improved, unchanged, or worsened. The MOMIJI study is the first prospective multicenter clinical trial of CRT-D therapy in an all-Japanese population seeking to evaluate equivalency of therapy to that in Western countries and the first usage of the officially validated Japanese language version of the Minnesota Living with Heart Failure (MLHF) questionnaire.

Methods

Study Population

The MOMIJI study was conducted at 22 centers in Japan between March 12, 2007 and March 31, 2009. Enrollment criteria were similar to those of the MIRACLE-ICD study,[1] except for left ventricular end-diastolic diameter (LVEDD) ≥55 mm and 6-min walk distance >450 m, which were an inclusion and an exclusion criterion, respectively, for MIRACLE-ICD. Table 1 lists the inclusion and exclusion criteria. No particular medications were required, and the medication status of patients was collected at baseline. The study protocol was approved by the institutional review board/medical ethics committee of each participating center, and all patients provided signed informed consent.

Patients meeting the enrollment criteria underwent a baseline evaluation prior to implant that included New York Heart Association (NYHA) class assessment, echocardiography, most recent documented intrinsic QRS interval, and B-type natriuretic peptide (BNP) measurement. Patients were also asked to complete 2 QOL assessment tools: the MLHF questionnaire in the Japanese language and the Specific Activity Scale (SAS) questionnaire. Patients then underwent implantation of a com-

mercially available CRT-D device manufactured by Medtronic, Inc (Minneapolis, MN, USA) and a right atrial pacing lead, a right ventricular pacing/defibrillator lead, and a left ventricular lead. A variety of leads not limited to those manufactured by Medtronic were used in the study.

Device Programming

General device programming was left to physician discretion. However, optimization of the sensed and paced atrioventricular (AV) delays was required. Use of the Ritter Method[16] was encouraged though other methods were allowed. Interventricular (V-V) timing optimization was recommended, and was required to be performed prior to AV delay optimization. Additionally, programming antitachycardia pacing (ATP) according to the PainFREE Rx II algorithm was recommended.[17]

Study Design and Endpoints

The MOMIJI study was a prospective, multicenter, observational study characterizing outcomes of CRT-D therapy in a Japanese population. The primary endpoint was non-inferiority to the CCR seen in the general phase of the MIRACLE-ICD study. The CCR was a secondary endpoint in both the intensive and general phases of the MIRACLE-ICD study. The CCR, which assesses patients more globally, is an accepted outcome measure in HF trials and has been used as an endpoint in studies such as the MIRACLE-ICD II and Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) studies.[4–6,18]

Patients in the MOMIJI study were classified as worsened, improved, or unchanged using definitions of those in the MIRACLE-ICD study. In the MOMIJI study, a patient was classified as worsened if he or she died, was hospitalized due to or associated with worsening HF, permanently discontinued CRT-D due to or associated with worsening HF, treatment failure, or lack of/insufficient therapeutic response, withdrew or was withdrawn from study and had worsening HF at the time of study withdrawal; demonstrated worsening in NYHA class at last observation carried forward (LOCF) or moderate-marked worsening of patient global assessment score at LOCF. Only hospitalizations that were due to worsening HF and would have resulted in the patient being hospitalized under standard medical practice were included in the CCR analysis. To minimize bias in comparison of hospitalization data between the MOMIJI and MIRACLE-ICD studies, a hospitalization events review committee composed of Japanese and US HF physicians adjudicated hospitalizations to determine if a Japanese admission would have been managed on an outpatient basis had the case been managed in the USA or if the patient would have been hospitalized. A patient was classified as improved if he or she had not worsened (as defined above) and demonstrated improvement in NYHA class at LOCF and/or moderate to marked improvement in patient global assessment score at LOCF. A patient was unchanged if he or she was neither improved nor worsened.

Secondary outcomes in the MOMIJI study included QOL assessment using the MLHF and SAS. The MLHF questionnaire is a validated[19,20] and well established assessment tool that has been used to assess patient QOL in a number of major trials of CRT.[1,5,6,21,22] The Japanese translation of the MLHF questionnaire was validated linguistically by the Health Outcome Group (San Francisco, CA, USA) with permission from Minnesota University (Minneapolis, MN, USA). The SAS assessment tool[23] is recommended by the Japanese Circulation Society and is widely used in Japan. Other secondary outcomes included characterization of the effectiveness of ATP in terminating ventricular tachycardia (VT) episodes and plasma BNP levels, echocardiographic parameters, and HF hospitalizations. The mitral regurgitant fraction was assessed by calculating the percentage of the color-Doppler area relative to the left atrial area in the apical 4-chamber view. Patients were followed at 1, 3, and 6 months. Full interrogation of the CRT-D device and NYHA assessment were performed at each visit. QOL evaluation using the MLHF and SAS questionnaires and echocardiography were performed at 6-month follow-up only.

MIRACLE-ICD General Phase

The general phase of the MIRACLE-ICD study was a continuation of the intensive phase which evaluated the safety and efficacy of the Medtronic Model 7272 InSync ICD system. All patients were programmed to CRT ON and both physicians and patients were unblinded to therapy delivery. Study inclusion and exclusion criteria were the same as in the intensive phase.[1] The general phase of the MIRACLE-ICD study was chosen as a comparative reference point for the therapeutic efficacy of CRT-D in the MOMIJI study because the inclusion criteria were similar to the CRT-D indication in Japan and because the study was unblinded. The intensive phase of the MIRACLE-ICD study was a prospective randomized double-blind study during which both physicians and patients were unaware of whether CRT was turned ON or OFF.[1] Results of the general phase of the MIRACLE-ICD study have not been published previously. However, the study authors have granted the MOMIJI investigators full access to the data and permission to publish the results of the general phase of the MIRACLE-ICD study as needed.

Statistical Analysis

All successfully implanted patients were included in the analysis. In terms of the primary endpoint, 62% (88/142) of the patients with NYHA class III or IV in the MIRACLE-ICD study had a response of improved on the CCR. We evaluated the non-inferiority with an equivalent margin of 10% on the CCR and a P-value <0.05 using an exact proportion test. An odds ratio analysis with and without a propensity score was also performed. The propensity score was computed using logistic regression with the study (MIRACLE-ICD or MOMIJI) as a response variable and 13 baseline parameters (sex, age, NYHA class (III or IV), QRS duration, left ventricular ejection fraction (LVEF), LVEDD, non-ischemic or ischemic etiology, hypertension, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, and diuretic) as explanatory variables. The odds ratio and 95% confidence interval (CI) of improved CCR between both studies were calculated directly and with the adjusted quintile propensity score.

For the secondary endpoints, descriptive statistics were used. The paired t-test was used to compare changes from baseline to 6 months. The success rate of ATP therapy was analyzed using detected VT/ventricular fibrillation (VF) episodes treated by ATP. ATP was considered successful if the episode terminated prior to a cardioversion or defibrillation shock. Geometric means were used for the analysis of BNP.

Adverse events were not collected. However, centers were required to report events in the same manner required for any commercially available device in Japan. The study was coordinated by Medtronic Japan. All data were collected on case report forms. Information was forwarded via a DataFax system and automatically stored into a database. Device interrogation data were saved to disk and forwarded to Medtronic Japan.

Table 2. Baseline Characteristics of the MIRACLE ICD and MOMIJI Study Groups*

Characteristic	MIRACLE ICD General phase (n=142)	MOMIJI (n=80)	P value
Age, (years) (SD)	67.3 (10.2)	64.7 (13.2)	0.10
Male sex, n (%)	109 (76.8)	63 (78.8)	0.87
NYHA class, (%)			0.65
III	126 (88.7)	73 (91.3)	
IV	16 (11.3)	7 (8.8)	
QRS interval, (ms) (SD)	166.4 (25.0)	160.9 (27.6)	0.13
BNP, pg/ml (SD)	–	626.8 (713.8)	–
LVEF, (%) (SD)	21.2 (6.5)[a]	23.0 (6.4)	0.04
LVEDD, (mm) (SD)	68.2 (8.6)	70.2 (10.3)[b]	0.13
MLHF score (SD)	56.9 (23.7)	51.8 (26.2)[c]	0.14
Underlying heart disease, n (%)			
Ischemic	82 (58.6)	24 (30.0)	<0.01
Non-ischemic	58 (41.4)	56 (70.0)	
Hypertension, n (%)	19 (13.4)	23 (28.8)	<0.01
Atrial tachyarrhythmias, n (%)			
Atrial flutter	5 (3.6)	3 (3.8)	>0.99
Paroxysmal AF	19 (13.6)	16 (20.0)	0.25
Ventricular tachyarrhythmias, n (%)			
Non-sustained VT	42 (30.0)	47 (58.8)	<0.01
Sustained VT	50 (35.7)	20.0 (25.0)	0.13
VF	14 (10.0)	7 (8.8)	0.82
Indication for ICD, n (%)			
Cardiac arrest*	–	9 (11.3)	–
Sustained VT*	–	22 (27.5)	–
Induced VF and SVT*	–	24 (30.0)	–
Low EF and advanced NYHA class alone	–	39 (48.8)	
Baseline medications, n (%)			
ACE inhibitor or ARB	126 (88.7)	64 (80)	0.11
β-blocker	91 (64.1)	58 (72.5)	0.23
Diuretic	137 (96.5)	76 (95.0)	0.73
Antiarrhythmic	46 (32.4)	42 (52.5)	<0.01

[a]n=141, [b]n=79, [c]n=76.
*More than 1 per patient possible.
P values were calculated by Fisher exact test or Student's t-test. All differences between the MIRACLE ICD and MOMIJI groups are not statistically significant, except categories with P<0.05.
MIRACLE ICD, Multicenter InSync ICD Randomized Clinical Evaluation; MOMIJI, MIRACLE-ICD Outcome Measured in Japan Indication; BNP, B-type natriuretic peptide; LVEDD, left ventricular end-diastolic dimension; MLHF, Minnesota Living with Heart Failure; EF, ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker. Other abbreviations as in Table 1.

Results

Through August 31, 2008, 93 patients were enrolled in the MOMIJI study. Of these patients, 13 were withdrawn (7 patients did not meet the eligible criteria for this study; 3 patients underwent an implant attempt but a device was not implanted; 2 patients had their device explanted; and 1 patient died prior to implantation). The remaining 80 patients comprise the MOMIJI study population described in this report. The baseline characteristics of the patients in the MOMIJI and the MIRACLE-ICD general phase are summarized in **Table 2**. There was a significant difference (P<0.05) between the 2 populations in terms of LVEF and the percentage of patients with an ischemic etiology, hypertension, non-sustained VT, and antiarrhythmic drugs. For all other baseline categories, the clinical characteristics of patients in both studies were similar.

Primary Endpoint

CRT-D treatment exerted favorable effects on the CCR. At 6-month follow-up, CCR was improved in 68.8% (n=55), unchanged in 17.5% (n=14), and worsened in 13.8% (n=11). These results demonstrated the non-inferiority compared with the MIRACLE-ICD general phase data (**Figure 1**). The difference in the percentage of patients improved at 6-month follow-up was 6.78 (95% CI: −6.14 to 19.70). Non-inferiority was verified by 1-sided test with the equivalent margin of 10% (P=0.01).

Non-inferiority with the MIRACLE-ICD CCR was also confirmed in the odds ratio analysis to adjust for the differences in the baseline characteristics between 2 studies. For improved CCR, the unadjusted odds ratio between MIRACLE-ICD and MOMIJI was 1.350 (95% CI: 0.755 to 2.415, P=0.3119). The odds ratio adjusted by propensity score was 1.309 (95% CI: 0.684 to 2.507, P=0.42). These odds ratios were comparable, and both lower interval values were greater than 0.668 dem-

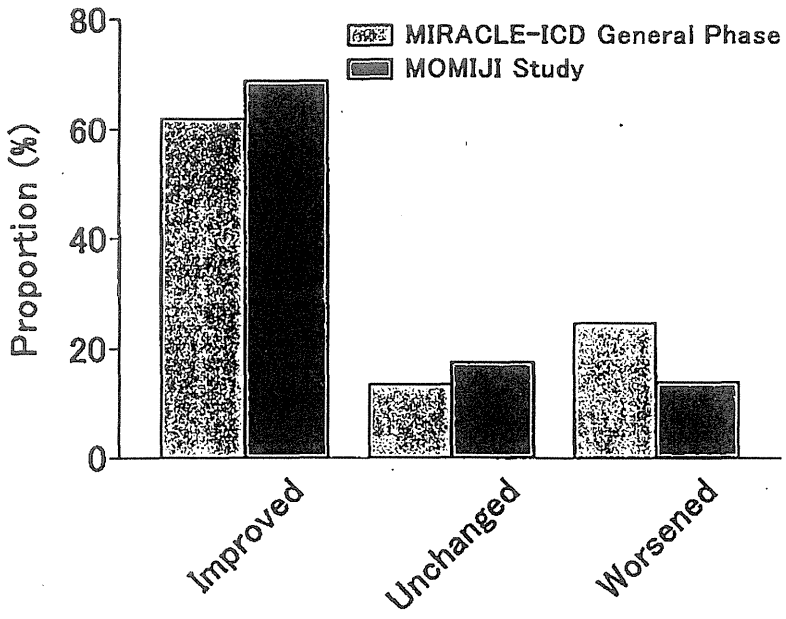

Figure 1. Clinical composite response in MOMIJI (n=80) and MIRACLE-ICD general phase (n=142) patients. There was a 6.8% (SD 6.59%) difference in the proportion that improved between the MOMIJI study and the MIRACLE-ICD general phase study. The 95% confidence interval was −6.14 to 19.70, demonstrating a non-inferiority margin of more than −10%.

Table 3. Secondary Endpoint Analysis Between Baseline and 6-Month Follow-up

	n	Baseline (mean±SD)	6 months (mean±SD)	P value
MLHF	67	50.0±26.2	23.6±20.2	<0.01
SAS	67	2.8±1.9	4.0±2.0	<0.01
LVEF (%)	54	23.6±6.4	31.6±12.0	<0.01
LVESV (ml)	49	163.1±81.1	135.0±78.8	<0.01
MRF (%)	32	24.8±14.8	18.4±14.9	0.03
BNP (pg/ml)	75	383.2±302.0	176.4±132.8	<0.01

SAS, Specific Activity Scale; LVESV, left ventricular end-systolic volume; MRF, mitral regurgitant fraction. Other abbreviations as in Tables 1,2.

onstrating lower limit corresponding to the non-inferiority margin of 10%.

Secondary Endpoints

The results of the secondary endpoints are summarized in Table 3. The improvement with MLHF scores between the baseline visit and 6-month follow-up were comparable to those seen with MIRACLE-ICD study (Figure 2). SAS scores also improved significantly confirming that the QOL of the patients were enhanced. Significant improvements were also observed with echocardiographic parameters as well as with the BNP level.

Arrhythmic Events

During the 6-month study period, a total of 80 episodes of VT (cycle length (CL): >320 ms) or fast VT (FVT, CL: 240–320 ms) were detected in 11 patients. Of these episodes, 50 were appropriate detections and 30 were inappropriate detections. Atrial tachycardia (AT) or atrial fibrillation was the reason for inappropriate detections in 15 (50%) of the total inappropriate detections, and the remaining supraventricular tachycardia was the reason for the other 15 (50%). A total of 5 patients experienced inappropriate detections with 3 patients experiencing 20 shocks. Considering the appropriate detections, 8 patients experienced a total of 50 episodes of VT or FVT. Of these episodes, 48 (96.0%) were VT and 2 were FVT (4%). Two FVT episodes occurred in 1 patient and were terminated with a total of 3 shocks.

The efficacy of ATP is shown in Figure 3. ATP was attempted in a total of 48 VT episodes and successfully terminated 79.2% (n=38) on the first attempt. In all, ATP was successful in 93.8% of the episodes (n=45) (Figure 3). The efficacy of ATP by CL is shown in Figure 4. ATP was successful in 100% of episodes with CLs >360 ms and in 81% of episodes with CLs from 320 to 360 ms.

HF Hospitalization and Deaths

There were 12 HF-related hospitalizations in 10 patients during the study. Adjudication by the Hospitalization Events Review Committee composed of 3 Japanese and 2 US HF specialists concurred that 4 (33.3%) of the HF hospitalizations would not have occurred if US practice guidelines had been applied. A total of 4 patients died during the follow-up period: 3 patients died due to progressive HF and 1 due to pneumonia.

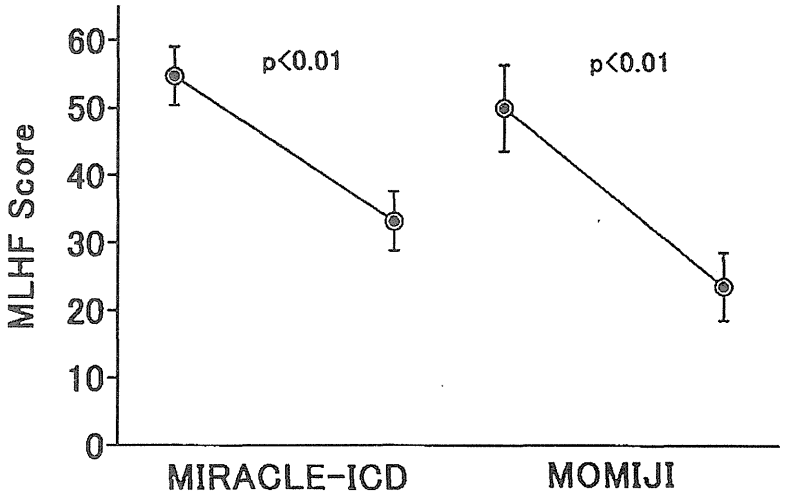

Figure 2. Minnesota Living with Heart Failure (MLHF) score at baseline and after treatment in MOMIJI (n=67) and MIRACLE-ICD general phase (n=120) patients. There was a significant decrease in MLHF scores, showing an improvement of quality of life in both the MOMIJI and the MIRACLE-ICD general phase studies. At 6-month follow-up, there was a 26.4 point decrease in the MOMIJI study compared with a 21.5 point decrease in the MIRACLE-ICD general phase compared with baseline.

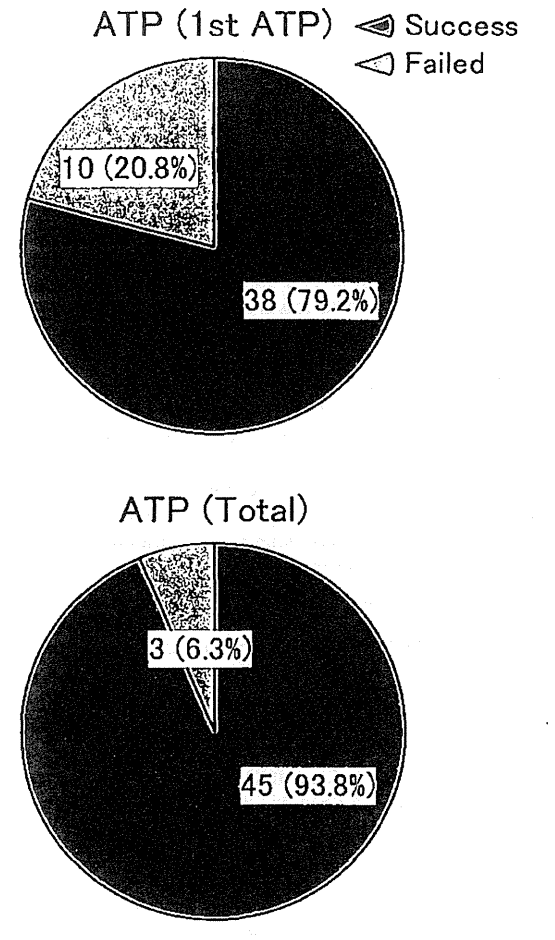

Figure 3. Terminating therapy for ventricular tachycardia (VT) episodes for first antitachycardia pacing (ATP) and total ATP. The number of episodes and percentages are shown.

Discussion

The improvements in the CCR observed in the MOMIJI study were non-inferior to those in the MIRACLE-ICD general phase. Compared with the patients in the MIRACLE-ICD study, those in the MOMIJI study had a higher LVEF, a higher proportion of non-ischemic cardiomyopathy and history of hypertension, and a higher rate of antiarrhythmic drug prescription. However, non-inferiority of the CCR was confirmed in the MOMIJI study after adjustment of these differences of baseline characteristics between the studies with propensity score analysis.

The results in the CCR score in the MOMIJI study were also similar to those in the PROSPECT study, which also assessed the performance of CRT in a predominately NYHA class III population (96% in the PROSPECT vs. 88.7% in the MOMIJI study) conducted in 53 centers in Europe, Hong Kong, and the USA.[18] In the PROSPECT study, the clinical composite score improved in 69% of 426 patients at 6-month follow-up compared with 68.8% in MOMIJI. This finding strengthens the evidence that the benefits of CRT observed in Western patients are transferable to Japanese patients with similar indications.

The morbidity and mortality benefits of CRT have been documented in prior large-scale landmark trials, however, Japanese patients were not included in the creation of this clinical evidence. The randomized controlled Cardiac Resynchronization-Heart Failure (CARE-HF) study, which included 813 patients with NYHA III or IV HF at 82 centers in Europe and a mean follow-up of 29.4 months, established the mortality benefit of CRT.[3] The CARE-HF study supported the recommendation that CRT devices should be considered in indicated patients to improve their prognosis. More recently, the efficacy of CRT and CRT-D has been studied in patients with less severe HF (NYHA class I and II). The European cohort of the REVERSE study demonstrated that CRT improved the CCR in a total of 287 patients from 35 European centers at 24 months.[5] The Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT) of 1,798 patients in Canada, Europe, Turkey, and Australia with NYHA class II or III HF and a mean follow-up of 40 months found that CRT-D therapy resulted in a 25% reduction in the relative risk of death and in

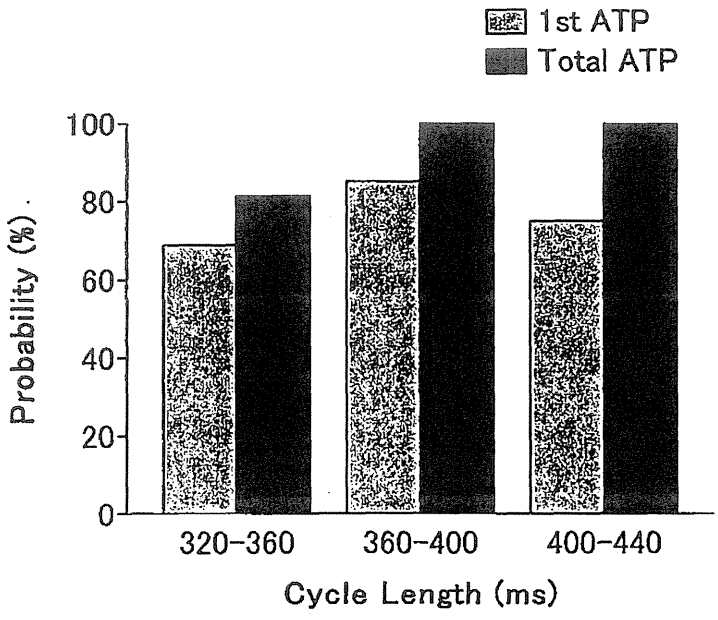

Figure 4. Distribution of ventricular tachycardia (VT) episodes by cycle length successfully terminated by antitachycardia pacing (ATP).

the composite endpoint of mortality or HF hospitalization compared with ICDs and optimal medical therapy.[8] These findings support the use of CRT-D in patients with mild to moderate HF, left ventricular dysfunction, and a wide QRS. In light of the favorable results in the MOMIJI study, the results of these landmark large-scale randomized controlled studies of CRT and CRT-D therapy may merit consideration when developing treatment strategies for Japanese patients with similar HF characteristics.

In terms of QOL evaluation, the MOMIJI study represents the first use of the MLHF questionnaire validated for Japanese patients. As such it provides a valuable assessment tool in studies examining the effects on patient QOL of various therapeutic modalities including CRT and CRT-D. MLHF score, a secondary endpoint in the MOMIJI and MIRACLE-ICD general phase, decreased in both studies, demonstrating improved QOL by CRT-D. MLHF score was a primary endpoint in the MIRACLE study, and patients receiving CRT demonstrated improvements at 6-month follow-up compared with the control group (median changes −18 vs. −9, P=0.001).[21] In the PATH-HF study, QOL score was unchanged in patients receiving CRT compared with univentricular pacing (25.2±3.3, 28.1±3.5, P=0.069); however, the follow-up period was very short.[22]

The MOMIJI study also evaluated cardiac functional parameters, which significantly improved as in the Western studies (Table 3). Although we could not perform statistical comparisons between them, the change in LVEF appeared to have improved more in the present patient population when compared with patients enrolled in the MIRACLE-ICD intensive phase[1] (median LVEF absolute change at 6 months +6.0% vs. +2.1%, respectively). This might be due to the higher proportion of non-ischemic patients among the MOMIJI study patients than that of the MIRACLE-ICD intensive phase (70.0 vs. 36.0%, P<0.01). Of note, the degree of LV reverse remodeling has been shown to be greater in non-ischemic than ischemic patients.[24,25] On the other hand, the mean changes in BNP at 3 months were comparable between the MOMIJI and the CARE-HF[3] studies: −186 pg/ml (95% CI: −366 to −7 pg/ml) and −225 pg/ml (95% CI: −705 to 255 pg/ml), respectively.

Among other secondary endpoints, the MOMIJI study examined the efficacy of ATP to terminate VT and prevent unnecessary defibrillation shocks. There were 50 episodes of ventricular tachyarrhythmia in 8 patients in the MOMIJI study, and the incidence rate was lower than that of MIRACLE-ICD intensive phase (10 vs. 22%, P=0.02).[1] One explanation could be that the patients in the MOMIJI study were prescribed antiarrhythmic drug more frequently than those in the MIRACLE-ICD intensive phase (52.5 vs. 32.4%, P<0.01). In the MOMIJI study, 93.8% of treated VT or FVT episodes were successfully terminated with ATP without the need for shocks. A lower incidence of shocks could improve QOL and increase the acceptability and tolerability of ICD therapy without compromising efficacy. Several studies have found that patients receiving defibrillation shocks have rather an increased mortality risk even though ICDs could terminate life-threatening ventricular arrhythmias.[26–28] Defibrillation shocks may cause myocardial damage and have negative inotropic effects, and those patients may be more susceptible to harm from shocks.[29–31] A combination of known and unknown factors may be involved, requiring further study to elucidate.

The MOMIJI study, which confirmed the therapeutic noninferiority to the MIRACLE-ICD study conducted in North America, advances the need of CRT-D therapy based on the broader clinical experience.

Study Limitations

First, the number of analyzed patients was as few as 80 in the MOMIJI study. In addition, the non-inferiority of the present analysis was based on a comparison between the MOMIJI and MIRACLE-ICD general phase populations. Therefore, the differences in baseline characteristics between them may have introduced bias into the results. However, non-inferiority was confirmed by the propensity score. Therefore, we consider that

the non-inferiority was meaningful in this study. Second, the prescription rate of β-blockers might be relatively low in light of current clinical practice and may have affected the results of this study;[32] however, there were no statistical difference between the MIRACLE-ICD study and the MOMIJI study with respect to the prescription rate. Third, the MOMIJI study was not designed or powered to detect mortality or morbidity difference and the follow-up period of 6 months may have been too short to detect the effects of CRT-D on cardiac function and QOL.

Conclusions

The MOMIJI study demonstrated the non-inferiority of the clinical efficacy of CRT-D in Japanese patients compared with a similar trial conducted in the USA. The results suggest that the benefits of CRT-D previously demonstrated in Western patient populations can be extrapolated to Japanese patients.

Acknowledgments

This work was supported by Medtronic Japan Co, Ltd. We thank William T. Abraham, MD, the Ohio State University, Columbus, OH, USA, and James B. Young, MD, the Cleveland Clinic Foundation, Cleveland, OH, USA, who agreed to share the MIRACLE-ICD general phase results used as the comparator in the MOMIJI study.

Disclosures

Grants: This study was supported by Medtronic Japan Co, Ltd. Staff from Medtronic Japan assisted in the design and coordination of the MOMIJI study. Specialists employed by the sponsor reviewed the manuscript prior to submission.

Conflict of Interest: Shin-ichi Momomura is the principal investigator of this study supported by Medotronic Japan.

References

1. Young JB, Abraham WT, Smith AI, Leon AR, Lieberman R, Wilkoff B, et al; for the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: The MIRACLE-ICD Trial. *JAMA* 2003; **289:** 2685–2694.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al; for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; **350:** 2140–2150.
3. Cleland JGF, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al; for the Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; **352:** 1539–1549.
4. Abraham WT, Young JB, Leon AR, Adler S, Brank AJ, Hall SA, et al; for the Multicenter InSync ICD II Study Group. Effects of cardiac resynchronization therapy on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter defibrillator, and mildly symptomatic chronic heart failure. *Circulation* 2004; **110:** 2864–2868.
5. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C; for the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008; **52:** 1834–1843.
6. Daubert C, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, et al; on behalf of the REVERSE Study Group. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: Insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. *J Am Coll Cardiol* 2009; **54:** 1837–1846.
7. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al; for the MADIT-CRT Trial Investigators. Cardiac resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; **361:** 1329–1338.
8. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al; for the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010; **363:** 2385–2395.
9. Crossley GH, Aonuma K, Haffajee C, Shoda M, Meijer A, Bauer A, et al; for the Concerto-AT Study Investigators. Atrial fibrillation therapy in patients with a CRT defibrillator with wireless telemetry. *Pacing Clin Electrophysiol* 2009; **32:** 13–23.
10. Seo Y, Ito H, Nakatani S, Takami M, Naito S, Shiga T, et al. The role of echocardiography in predicting responders to cardiac resynchronization therapy. *Circ J* 2011; **75:** 1156–1163.
11. Tanaka Y, Tada H, Yamashita E, Sato C, Irie T, Hori Y, et al. Change in blood pressure just after initiation of cardiac resynchronization therapy predicts long-term clinical outcome in patients with advanced heart failure. *Circ J* 2009; **73:** 288–294.
12. Inage T, Yoshida T, Hiraki T, Ohe M, Takeuchi T, Nagamoto Y, et al. Chronic cardiac resynchronization therapy reverses cardiac remodelling and improves invasive haemodynamics of patients with severe heart failure on optimal medical treatment. *Europace* 2008; **10:** 379–383.
13. Fujii B, Takami M. Normalization of left ventricular function following cardiac resynchronization therapy: Left bundle branch block as a potential etiology of dilated cardiomyopathy. *Circ J* 2008; **72:** 1030–1033.
14. Tsuchihashi M, Tsutsui H, Kodama K, Kasagi F, Takeshita A. Clinical characteristics and prognosis of hospitalized patients with congestive heart failure. *Circ J* 2000; **64:** 953–959.
15. Shiba N, Watanabe J, Shinozaki T, Koseki Y, Sakuma M, Kagaya Y, et al; for the CHART investigators. Analysis of chronic heart failure registry in the Tohoku district: Third year follow-up. *Circ J* 2004; **68:** 427–434.
16. Ritter P, Dib JC, Mahaux V, Lelievre T, Soyeur D, Lavergne T, et al. New method for determining the optimal atrio-ventricular delay in patients paced in DDD mode for complete atrio-ventricular block [NASPE abstract 237]. *Pacing Clin Electrophysiol* 2005; **18:** 855.
17. Wathen MS, DeGroot PJ, Sweeney MO, Stark AJ, Otterness MF, Adkisson WO, et al; for the PainFREE Rx II Investigators. *Circulation* 2004; **110:** 2591–2596.
18. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, et al. Results of the Predictors of response to CRT (PROSPECT) Trial. *Circulation* 2008; **117:** 2608–2616.
19. Rector TS, Cohn JS. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: Reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. *Am Heart J* 1992; **124:** 1017–1025.
20. Guyatt GH. Measurement of health-related quality of life in heart failure. *J Am Coll Cardiol* 1993; **22**(Suppl A): 185A–191A.
21. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al; for the MIRACLE Study Group. Cardiac resynchronization in heart failure. *N Engl J Med* 2002; **346:** 1845–1853.
22. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, et al; for the Pacing Therapies in Congestive Heart Failure (PATH-CHF) Study Group. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002; **39:** 2026–2033.
23. Sasayama S, Asanoi H, Ishizaka S, Miyagi K. Evaluation of functional capacity of patients with congestive heart failure. *In*: Yasuda H, Kawaguchi H, editors. New aspects in the treatment of failing heart. Tokyo: Springer-Verlag, 1992; 113–117.
24. Woo GW, Petersen-Stejskal S, Johnson JW, Conti JB, Aranda JA Jr, Curtis AB. Ventricular reverse remodeling and 6-month outcomes in patients receiving cardiac resynchronization therapy: Analysis of the MIRACLE study. *J Interv Card Electrophysiol* 2005; **12:** 107–113.
25. Wikstrom G, Blomström-Lundqvist C, Andren B, Lönnerholm S, Blomström P, Freemantle N, et al. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. *Eur Heart J* 2009; **30:** 782–788.
26. Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, et al; for the MADIT II Investigators. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: Frequency, mechanisms, predictors, and survival impact. *J Am Coll Cardiol* 2008; **51:** 1357–1365.
27. Sweeney MO, Sherfesee L, DeGroot P, Wathen MS, Wilkoff BL. Differences in effects of electrical therapy for ventricular arrhythmias on mortality in implantable cardioverter-defibrillator patients.

Heart Rhythm 2010; 7: 353–360.
28. Poole JE, Johnson GW, Hellkamp AS, Anderson JA, Callans DJ, Raitt MH. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med* 2008; 359: 1009–1017.
29. Barker-Voelz MA, Van Vleet JF, Tacker WA Jr, Bourland JD, Geddes LA, Schollmeyer MP. Alterations induced by a single defibrillating shock applied through a chronically implanted catheter electrode. *J Electrocardiol* 1983; 16: 167–179.
30. Tokano T, Bach D, Chang J, Davis J, Souza JJ, Zivin A, et al. Effect of ventricular shock strength on cardiac hemodynamics. *J Cardiovasc Electrophysiol* 1998; 9: 791–797.
31. Stoddard MF, Labovitz AJ, Stevens LL, Buckingham TA, Redd RR, Kennedy HL. Effects of electrophysiologic studies resulting in electrical countershock or burst pacing on left ventricular systolic and diastolic function. *Am Heart J* 1988; 116: 364–370.
32. Tsuchihashi-Makaya M, Kinugawa S, Yokoshiki H, Hamaguchi S, Yokota T, Goto D, et al; for the JCARE-CARD Investigators. Beta-blocker use at discharge in patients hospitalized for heart failure is associated with improved survival. *Circ J* 2010; 74: 1364–1371.

Appendix

Investigators and Institutions Participating in the MOMIJI Trial
Hiroyuki Tsutsui, MD, PhD, Hokkaido University Graduate School of Medicine; Shinya Shimoshige, MD, Sapporo Medical University School of Medicine; Joji Nitobe, MD, Yamagata University School of Medicine; Takashi Komatsu, MD, Iwate Medical University School of Medicine; Takeshi Mitsuhashi, MD, Jichi Medical University; Shin-ichi Momomura, MD, DMSc, Saitama Medical Center Jichi Medical University; Masayuki Inagaki, MD, Funabashi Municipal Medical Center; Kaoru Sugi, MD, PhD, Toho University Ohashi Medical Center; Seiji Fukamizu, MD, Tokyo Metropolitan Hiroo Hospital; Kaoru Tanno, MD, Showa University School of Medicine; Sugao Ishiwata, MD, Toranomon Hospital; Naoki Matsumoto, MD, St. Marianna University School of Medicine; Shinichi Sumita, MD, Yokohama City University Medical Center; Lee Jong-dae, MD, Faculty of Medical Sciences, University of Fukui; Takeshi Tomita, MD, Shinshu University School of Medicine; Eiichi Watanabe, MD, Fujita Health University School of Medicine; Makoto Ito, MD, Shiga University of Medical Science; Ryuji Otani, MD, Tokushima Red Cross Hospital; Osamu Igawa, MD, Tottori University Hospital; Masahiro Ogawa, MD, Fukuoka University School of Medicine; Ryusuke Tsunoda, MD, Japanese Red Cross Kumamoto Hospital; Toshihiro Honda, MD, Saiseikai Kumamoto Hospital.
Hospitalization Events Review Committee
Marc J. Semigran, MD, Massachusetts General Hospital, Boston, MA, USA; Mohamad R El-Zaru, MD, Cardiology Division, Tufts Medical Center, Boston, MA, USA; Shin-ichi Momomura, MD, DMSc, Division of Cardiovascular Medicine, Saitama Medical Center, Jichi Medical University, Saitama, Japan; Kaoru Sugi, MD, PhD, Toho University Ohashi Medical Center, Tokyo, Japan; Hiroyuki Tsutsui, MD, PhD, Hokkaido University Graduate School of Medicine, Hokkaido, Japan.
Additional Contributions
The investigators also thank the following physicians for their assistance in the MOMIJI study: Masaomi Chinushi, MD, Niigata University School of Medicine; Masahito Sato, MD, Tachikawa General Hospital; Koichi Mizumaki, MD, Toyama Medical and Pharmaceutical University; Satoru Sakagami, MD, Kanazawa Medical Center; Akira Miyazaki, MD, Chiba Cardiovascular Center; Satoshi Ohnishi, MD, NTT East Kanto Medical Center; Akihiko Nogami, MD, Yokohama Rosai Hospital; Takahisa Noma, MD, Kagawa University School of Medicine; Hiroshi Ogawa, MD, Tokuyama Central Hospital.
Additional Contributions
Harriet Guthertz, Medical Marketing and Communications, St. Paul, MN, USA assisted with the preparation of the manuscript.

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Heart Failure

Loop Diuretic Use at Discharge Is Associated With Adverse Outcomes in Hospitalized Patients With Heart Failure

– A Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) –

Sanae Hamaguchi, MD, PhD; Shintaro Kinugawa, MD, PhD; Miyuki Tsuchihashi-Makaya, PhD; Daisuke Goto, MD, PhD; Satoshi Yamada, MD, PhD; Hisashi Yokoshiki, MD, PhD; Akira Takeshita, MD, PhD; Hiroyuki Tsutsui, MD, PhD; The JCARE-CARD Investigators

Background: Loop diuretics are commonly used in patients with heart failure (HF) to remove retained fluid and improve symptoms. However, they may potentially worsen outcomes in HF. It remains unknown whether the use of loop diuretics is associated with adverse HF outcomes in routine clinical practice. We thus determined the effects of loop diuretic use at discharge on long-term mortality and rehospitalization among patients hospitalized with HF.

Methods and Results: The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) prospectively studied the characteristics and treatments of a broad sample of patients hospitalized with worsening HF and followed for 2.1 years. Among a total of 2,549 HF patients, loop diuretics were used by 2,015 patients (79%), but not 534 patients (21%). The mean age was 70.7 years and 60% were male. Etiology was ischemic in 32% and mean left ventricular ejection fraction was 42%. After adjustment for covariates, discharge use of loop diuretics was associated with significant adverse risks of cardiac death (adjusted hazard ratio [HR] 2.348, 95% confidence interval [CI] 1.246–4.423, P=0.008) and rehospitalization (adjusted HR 1.427, 95% CI 1.040–1.959, P=0.027).

Conclusions: Among patients hospitalized with worsening HF, loop diuretic use at discharge was associated with long-term adverse outcomes, which suggests that routine chronic use of loop diuretics may be harmful for patients with HF. (*Circ J* 2012; **76**: 1920–1927)

Key Words: Diuretics; Heart failure; Outcomes; Prognosis

Loop diuretics are the only drugs that can effectively control fluid retention in patients with heart failure (HF) and fluid overload.[1,2] However, loop diuretics can reduce the glomerular filtration rate (GFR), further worsen neurohormonal activation, and cause electrolyte disturbances.[3,4] Furthermore, they increase myocardial fibrosis,[5,6] which may be associated with disease progression and poor prognosis of HF. There have been no randomized clinical trials to determine the chronic effects of loop diuretics on HF outcomes. Previous subanalyses of randomized clinical trials demonstrated that the use of diuretics was associated with adverse outcomes in patients with HF and reduced left ventricular ejection fraction (LVEF).[4,7,8] In the Studies Of Left Ventricular Dysfunction (SOLVD), baseline use of a non-potassium-sparing diuretic was associated with an increased risk of arrhythmic death, after controlling for other variables of disease severity.[4] Similarly, analysis of the data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE) trial demonstrated that higher doses of diuretics were associated with increased mortality over 6 months of follow-up among patients hospitalized with advanced HF.[7] However, these analyses used the data for HF patients enrolled in randomized clinical trials, clearly different from those in the "real world" under current standard practice for HF treatment, who are more elderly and have more comorbidities. In fact, in those trials, patients with HF and preserved LVEF or renal dysfunction were excluded. Thus, the effect of loop diuretics on long-term outcomes needed to be assessed in an unselected population of HF patients.

The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) prospectively studied the characteristics, treatments and outcomes, including death and rehospitaliza-

Received October 17, 2011; revised manuscript received April 9, 2012; accepted April 10, 2012; released online May 26, 2012 Time for primary review: 20 days

Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Dr Akira Takeshita died in March 2009.

Mailing address: Hiroyuki Tsutsui, MD, PhD, Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan. E-mail: htsutsui@med.hokudai.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-11-1196

Table 1. Patients' Characteristics

Characteristics	Total (n=2,549)	Loop diuretic use (n=2,015)	No loop diuretic use (n=534)	P value
Age, years (mean±SD)	70.7±13.3	70.9±13.2	69.8±13.7	0.090
Male, %	60.0	60.9	56.6	0.066
BMI, kg/m²	22.4±4.1	22.4±4.1	22.2±4.1	0.262
Causes of HF, %				
Ischemic	32.0	33.1	28.1	0.029
Valvular	27.7	28.8	23.6	0.016
Hypertensive	24.2	23.5	26.8	0.118
Dilated cardiomyopathy	18.4	18.4	18.4	0.975
Medical history, %				
Hypertension	52.8	52.7	53.4	0.778
Diabetes mellitus	30.0	31.4	24.6	0.002
Dyslipidemia	25.1	26.1	21.4	0.028
Hyperuricemia	46.2	48.3	37.9	<0.001
Prior stroke	14.4	14.9	12.7	0.211
COPD	6.5	6.7	5.9	0.545
Smoking	38.1	38.8	35.6	0.191
Prior myocardial infarction	27.0	28.7	20.9	<0.001
Atrial fibrillation	35.2	36.8	29.1	0.001
Sustained VT/VF	6.0	6.3	4.7	0.163
Procedures, %				
PCI	17.8	18.4	15.2	0.085
CABG	9.5	10.2	6.8	0.020
Valvular surgery	6.7	7.2	4.9	0.061
PPM	0.9	1.0	0.6	0.349
ICD	2.0	1.9	2.6	0.285
CRT	1.6	1.6	1.5	0.820
Vital signs at discharge				
NYHA functional class, %				0.043
1	36.5	35.3	41.2	
2	57.2	58.0	53.9	
3	6.2	6.5	4.9	
4	0.2	0.2	0	
Heart rate, beats/min	70.3±11.8	70.2±11.6	70.7±12.6	0.652
SBP, mmHg	117.3±18.3	116.7±18.1	119.2±19.2	0.017
DBP, mmHg	66.2±10.4	66.0±11.6	66.9±11.3	0.138
Laboratory data at discharge				
eGFR, $ml \cdot min^{-1} \cdot 1.73m^{-2}$	51.5±24.7	50.8±24.1	54.2±26.8	0.005
Serum uric acid, mg/dl	7.4±2.9	7.4±2.3	7.0±4.5	<0.001
Hemoglobin, g/dl	12.1±3.3	12.1±3.3	12.3±2.9	0.240
Plasma BNP, pg/ml	375±474	377±411	369±658	0.010
Echocardiographic data				
LVEDD, mm	56.3±10.4	56.8±10.4	54.6±10.3	<0.001
LVESD, mm	53.0±9.4	54.0±9.4	52.2±9.3	<0.001
LVEF, %	42.2±17.5	41.8±17.6	43.3±17.1	0.059

Data are percent or means±SD.
BMI, body mass index; HF, heart failure; COPD, chronic obstructive pulmonary disease; VT/VF, ventricular tachycardia/fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction.

tion, in a broad sample of patients hospitalized with HF in Japan.[9–20] The JCARE-CARD enrolled 2,675 patients admitted with HF and an average of follow-up of 2.2 years at 164 participating hospitals in a web-based registry.

The aim of the present study was to analyze the prognostic value of loop diuretics on mortality and rehospitalization rates by evaluating the relationship between the drugs' use at discharge and clinical outcomes among patients hospitalized with HF and registered in the JCARE-CARD database.

Table 2. Medication Use at Hospital Discharge

	Total (n=2,549)	Loop diuretic use (n=2,015)	No loop diuretic use (n=534)	P value
ACEI, %	37.4	38.6	32.8	0.013
ARB, %	44.4	43.7	47.2	0.146
ACEI or ARB, %	76.5	76.8	75.5	0.511
ACEI and ARB, %	5.3	5.5	4.5	0.374
β-blocker, %	48.6	47.8	51.9	0.093
ACEI or ARB and β-blocker, %	39.9	39.8	40.6	0.710
Thiazide, %	3.6	2.9	6.4	<0.001
Spironolactone, %	41.6	47.6	18.7	<0.001
Digitalis, %	30.9	31.7	27.7	0.075
Calcium-channel blocker, %	25.2	24.2	28.8	0.029
Nitrates, %	23.3	24.4	19.1	0.010
Antiarrhythmics, %	16.6	16.9	15.5	0.463
Aspirin, %	47.2	47.6	45.5	0.390
Warfarin, %	40.8	41.5	37.8	0.121
Statin, %	19.9	20.4	17.6	0.143

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

Methods

Patients

The details of the JCARE-CARD have been described previously.[9,10,14,15,19] Briefly, eligible patients were those hospitalized with worsening HF as the primary cause of admission. The study hospitals were encouraged to register the patients as consecutively as possible. For each patient, baseline data included (1) age, sex, and body mass index; (2) cause of HF; (3) medical history; (4) prior procedures; (5) vital signs at discharge; (6) laboratory data; (7) echocardiographic data; and (8) medication use at discharge. The data were entered using a web-based electronic data capture (EDC) system licensed by the JCARE-CARD (www.jcare-card.jp).

From the database of a total cohort of 2,675 patients registered in JCARE-CARD, the present analysis used the data of 2,549 patients for whom information of the loop diuretic use could be obtained. The patients were divided into 2 groups according to loop diuretic use (n=2,015; 79.1%) or no loop diuretic use (n=534; 20.9%) at the time of discharge from the index hospitalization.

Outcomes

The status of all patients was surveyed and the following information about outcomes was obtained from participating cardiologists using the web-based EDC system: (1) all-cause death, (2) cardiac death, defined as death due to HF, myocardial infarction or other causes such as pulmonary embolism, (3) rehospitalization due to an exacerbation of HF that required more than continuation of the patient's usual therapy on prior admission, and (4) a composite endpoint of all-cause death and rehospitalization due to HF. The endpoints were adjudicated by the cardiologists in each participating hospital. Of the 2,549 patients, 244 (9.6%), missed during follow-up, were excluded from the follow-up analysis. Follow-up data could be obtained for 2,305 of the 2,549 patients (90.4%). Of these 2,305 patients, 1,814 were in the group of loop diuretic use and 491 were in that of no loop diuretic use. Mean postdischarge follow-up was 781±315 days (2.1±0.9 years).

The hypothesis being tested was whether loop diuretic use at hospital discharge would be associated with higher mortality and rehospitalization rates during the follow-up compared with no loop diuretic use.

Statistical Analysis

Patients' characteristics and treatments were compared using χ^2 test for categorical variables, Student's t-test for normally distributed continuous variables, and Mann-Whitney U test for continuous variables not normally distributed. We analyzed the data excluding the patients with missing data. Only patients who survived the index hospitalization were included in the follow-up analysis. Cumulative event-free rates during the follow-up were derived using the method of Kaplan and Meier. The relationship between loop diuretic use at discharge and outcome was evaluated among patients with multivariable adjustment. The covariates of age, sex, estimated GFR (eGFR) at discharge, systolic blood pressure (SBP) at discharge, LVEF, B-type natriuretic peptide (BNP), New York Heart Association (NYHA) functional class at discharge, cause of HF (ischemic, valvular), medical history (diabetes, dyslipidemia, hyperuricemia, prior myocardial infarction, and atrial fibrillation) and medication use (angiotensin-converting enzyme inhibitor [ACEI], β-blocker, spironolactone, thiazide, calcium-channel blocker (CCB), nitrate, and statins), were used in developing the postdischarge Cox proportional hazard models. The same variables were included in a multivariable logistic regression model and the propensity score (PS) for loop diuretic use was estimated for each patient. Using a greedy matching protocol, we matched each patient with no loop diuretic use to a patient with loop diuretic use who had a very similar PS; thus we used 465 pairs matched with PS for PS matching. We performed a formal sensitivity analysis for unmeasured confounding factors.[21]

The results were reported as hazard ratio (HR), 95% confidence interval (CI), and P value. HR for outcomes when loop diuretics were used was compared with no use of diuretics. A P value of <0.05 was used as the criterion for variables to stay in the model. SPSS version 16.0J for Windows was used for all statistical analyses (Chicago, IL, USA).