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Appendix

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Letter to the Editor

Predictive value of high-molecular weight adiponectin in subjects with a higher risk of the development of metabolic syndrome: From a population based 5-year follow-up data

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Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors on the basis of obesity and insulin resistance. Although the pathophysiology and optimal diagnostic criteria remain controversial, there are evidences that MetS is associated with the prevalence, mortality, and development of cardiovascular disease and type 2 diabetes mellitus [1–3]. Subjects who already have two MetS risk factors at the time of screening test are considered to be likely to develop MetS. Some specific biomarkers may be helpful for selecting subjects at higher risk for the development of MetS from these 'potential MetS patients', and provide clues to prevent development of MetS.

High-molecular weight (HMW)-adiponectin is thought to be the major active form of adiponectin and more useful for predicting insulin resistance [4]. The present study aimed to investigate whether the plasma HMW-adiponectin levels could have an additional diagnostic value to using the conventional MetS risk factors to predict future development of MetS.

This study was originally designed to investigate the efficacy of several biomarkers to predict cardiovascular events in participants in an annual health-check program in Kashima-City, a rural community in Japan. The initial health-check program was carried out from August 2005 to July 2006, and the follow-up survey was conducted after 5 years. Of the 1110 initial study participants, 434 subjects (217 men and 217 women) were eligible for the analysis. All participants provided their written informed consent and the study protocol was conformed to the ethical guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Saga University Faculty of Medicine. MetS was defined based on the National Cholesterol Education Program Adult Treatment Panel III criteria modified by the National Heart, Lung and Blood Institute and the American Heart Association [5]. Blood samples were collected from subjects more than 10 h after the last dietary intake. Plasma HMW-adiponectin levels were measured using a sandwich ELISA kit [6]. All statistical analyses were performed using the SPSS 16.0 Japanese edition for Windows. A P value less than 0.05 was considered to be statistically significant.

A gender-stratified analysis was performed because of the considerable gender differences in plasma HMW-adiponectin levels. Seventy-eight (36.4%) men and 34 (15.9%) women have already had two MetS risk factors at the initial health check program. Among these participants, twenty-six (33.3%) men and 12 (35.3%) women developed MetS during the 5-year follow-up period. In contrast, only 8 (9.4%) men and 5 (6.3%) women with only one MetS risk factor, and 2 (3.7%) men and 0 (0%) women with no MetS risk factor developed MetS, respectively. Therefore we compared between participants with and without development of MetS in the subgroup of the participants with two MetS risk factors at baseline. A multivariate logistic regression model without variable selection to adjust confounding factors showed that plasma HMW-adiponectin level was significantly associated with the development of MetS only in men. By contrast, no significant associations were observed between any variables and development of MetS in women (Table 1). A stepwise multivariate logistic regression model after adjustment for body weight, waist circumference, blood pressure, triglyceride, high-density lipoprotein cholesterol, γ-glutamyl transpeptidase (γ-GTP), and HMW-adiponectin showed that HMW-adiponectin was independently associated with the development of MetS in men (coefficients −0.611, odds ratio 0.543, 95% confidence interval 0.336–0.878, $P=0.013$, data not shown).

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Table 1
Results from a multivariate logistic regression model for predicting the development of MetS in participant with two MetS risk factors.

	Men			Women		
Variables	Coefficients	OR (95%CI)	*P* value	Coefficients	OR (95%CI)	*P* value
Age (years)	−0.042	0.959 (0.874–1.052)	N.S.	−0.266	0.767 (0.509–1.154)	N.S.
Body weight (kg)	−0.083	0.920 (0.818–1.034)	N.S.	0.006	1.006 (0.456–2.220)	N.S.
Waist circumference (cm)	0.126	1.135 (0.955–1.349)	N.S.	0.316	1.371 (0.670–2.809)	N.S.
Systolic BP (mmHg)	−0.001	0.999 (0.936–1.066)	N.S.	−0.050	0.951 (0.723–1.250)	N.S.
Diastolic BP (mmHg)	0.044	1.045 (0.945–1.155)	N.S.	−0.082	0.921 (0.713–1.191)	N.S.
Fasting glucose (mg/d1)	0.010	1.010 (0.947–1.077)	N.S.	−0.619	0.539 (0.131–2.218)	N.S.
TC (mg/dl)	0.010	1.010 (0.947–1.077)	N.S.	0.170	1.185 (0.909–1.545)	N.S.
HDL-C (mg/dl)	0.048	1.049 (0.971–1.133)	N.S.	0.066	1.068 (0.871–1.310)	N.S.
TG (mg/dl)	0.002	1.002 (0.996–1.009)	N.S.	−0.123	0.885 (0.722–1.084)	N.S.
ALT (IU/l)	0.000	1.000 (0.961–1.041)	N.S.	−0.983	0.374 (0.057–2.475)	N.S.
γ-GTP (IU/l)	−0.020	0.980 (0.959–1.002)	N.S.	0.746	2.109 (0.686–6.489)	N.S.
UA (mg/dl)	−0.139	0.870 (0.452–1.675)	N.S.	0.701	2.016 (0.025–162.364)	N.S.
Current smoking (n)	−0.209	0.811 (0.177–3.726)	N.S.	NA	NA	NA
HMW-adiponectin (μg/ml)	−0.896	0.408 (0.224–0.743)	0.003	−1.547	0.213 (0.013–3.577)	N.S.
NT-proBNP (pg/ml)	−0.005	0.995 (0.965–1.025)	N.S.	0.053	1.055 (0.949–1.172)	N.S.
hsCRP (mg/l)	0.006	1.006 (0.602–1.681)	N.S.	−0.793	0.452 (0.105–1.947)	N.S.

BP = blood pressure; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglyceride; ALT = alanine aminotransferase; γ-GTP = γ-glutamyl transpeptidase; UA = uric acid; HMW-adiponectin = high molecular weight adiponectin; NT-proBNP = N-terminal pro-B-type natriuretic peptide; hs-CRP = high sensitivity C-reactive protein; OR = odds ratio; and CI = confidence interval.

The study participants were separated into 3 groups in ascending order of the plasma HMW-adiponectin levels prior to the analysis. More subjects developed MetS during the 5-year follow-up period in proportion to the decreased plasma HMW-adiponectin levels in men with two MetS risk factors. However, this low was not applicable to men who have one or less MetS risk factor (Fig. 1a). On the other hand, plasma HMW-adiponectin levels were not useful for predicting future development of MetS in women in any stratum of the number of MetS component (Fig. 1b).

The present study demonstrated that the low plasma HMW-adiponectin level was independently associated with the development of MetS in men with two MetS risk factors. Seino et al. have already reported that HMW-adiponectin levels predicted the progression to MetS in a 6-year follow-up study of Japanese men [7]. The present study confirmed their findings, and, additionally, provided information that plasma HMW-adiponectin levels were of little use in predicting the risk of development of MetS in women. Sattar et al. reported that HMW-adiponectin is not associated with the incidence of coronary heart disease in older women [8], and Himbergen et al. recently reported that elevated plasma adiponectin levels are an independent risk factor for the development of all-cause dementia and Alzheimer disease in women [9]. The authors found a threshold effect above which the adiponectin level becomes a risk factor. Previous population-based studies and the current study found that women have significantly higher plasma HMW-adiponectin levels than that of men [10]. It is conceivable that the plasma HMW-adiponectin levels are compensatory increased in some women with the development of MetS; however, it seems to be difficult to distinguish between these subjects.

This study has potential limitations. The prevalence of MetS was 2.5% in women in the present study cohort at baseline. Also relatively small number of subjects developed MetS during the 5-year follow-up period in women. Therefore, the interpretation of the statistical measures, especially in women, could be associated with a potential bias.

In conclusion, a decreased concentration of plasma HMW-adiponectin was independently associated with the development of MetS only in men with two MetS risk factors. It is worth investigating the gender differences in the mechanism of the development of MetS, and the role of HMW-adiponectin.

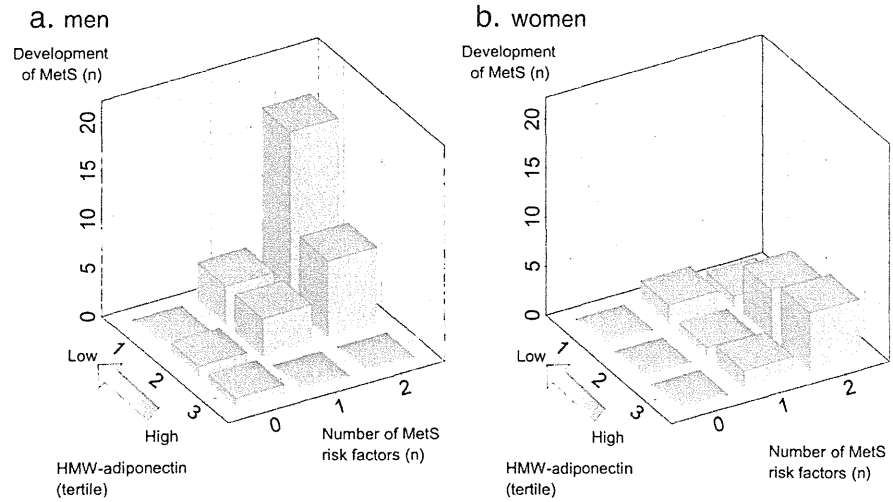

Fig. 1. The incidence of the development of MetS in relation to HMW-adiponectin tertile and number of MetS components. More subjects developed MetS in proportion to the decreased plasma HMW-adiponectin levels in men with two MetS risk factors. However, this low was not applicable to men with one or less MetS risk factor (a). On the other hand, HMW-adiponectin levels were not useful for predicting the development of MetS in women in any stratum of the number of MetS risk factor (b).

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ORIGINAL ARTICLE
Heart Failure

Mode of Death in Patients With Heart Failure and Reduced vs. Preserved Ejection Fraction

– Report From the Registry of Hospitalized Heart Failure Patients –

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Background: The mode of death has not been investigated in the registry data of patients with heart failure and reduced ejection fraction (HFREF) vs. preserved ejection fraction (HFPEF). The aim of the present study was therefore to carry out this comparison.

Methods and Results: The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) prospectively studied the characteristics and treatments in a broad sample of 2,675 patients hospitalized with worsening HF, and followed them for an average of 2.1 years. This study included 323 patients in whom information on both the mode of death and left ventricular EF on echocardiography could be obtained. The mode of death was cardiovascular (CV) in 63% (including 17% sudden, 36% HF, 3% myocardial infarction, and 3% stroke), non-CV in 23%, and unknown in 14%. The prevalence of CV death including sudden death was high in patients with HFREF compared to HFPEF (68% vs. 58%, P=0.020). HF death, the most common mode of death, was similar between groups (37% vs. 35%, P=0.694). In contrast, non-CV mortality was significantly higher in HFPEF than those with HFREF (28% vs. 18%, P=0.021).

Conclusions: In 60–70% of deaths the mode was CV, and HF death was the most common mode of death in either HFREF or HFPEF. The prevalence of sudden death was lower, and that of non-CV death higher, in HFPEF compared with HFREF. (*Circ J* 2012; **76:** 1662–1669)

Key Words: Cardiovascular death; Ejection fraction; Heart failure; Outcome; Sudden death

Approximately half of all patients with chronic heart failure (HF) have been reported to have a normal or nearly normal, preserved, left ventricular ejection fraction (LVEF).[1–4] The clinical characteristics and outcomes in patients with HF and a preserved EF (HFPEF) differ significantly from those with HF and a reduced EF (HFREF).[1–7] Previous studies have demonstrated that patients with HFPEF had a similar mortality risk and equally high rates of rehospitalization as those with HFREF.[3,5–9] In contrast, other studies found that the mortality rate was significantly lower in patients with HFPEF than HFREF.[1,2,4,10] One possible explanation for these discrepancies might be the differences in the mode of death between HFREF and HFPEF, making 1 group more or less vulnerable to specific mode. There have been several limitations in previous studies, however, in which the mode or cause of death was assessed.[11–18] First, they characterized the mode or cause of death in patients with HFREF and little is known about this critical issue in patients with HFPEF. Second, most previous studies merely distinguished between cardiovascular (CV) and non-CV death and no detailed analysis of the mode of death has been performed. Finally, 2 studies with detailed information on these modes were conducted, using a community-based cohort of HF patients from Olmsted Country,[17] and a subgroup of patients enrolled in a randomized clinical trial (RCT), the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-Preserve).[18] Therefore, selection bias and influence of therapy could not be completely excluded. To improve the understanding of the pathophysiology and to establish effective management strategies in HFPEF, it is of critical importance to identify the mode of death in these patients and compare it with that in HFREF. In particular, such an analysis needs to be performed in HF patients encountered in routine clinical practice.

The Japanese Cardiac Registry of Heart Failure in Cardiol-

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ogy (JCARE-CARD) studied prospectively the characteristics and treatments in a broad sample of 2,675 patients hospitalized with HF, and followed up the outcomes including death and rehospitalization due to worsening HF for an average of 2.1 years.[7,19–22] The aim of the present study was to examine the mode of death in HF patients registered in JCARE-CARD and compare the distribution of the specific mode of death in patients with HFPEF vs. HFREF.

Methods

Patients

The details of the JCARE-CARD have been described previously.[7,19,21–25] Briefly, eligible patients were those hospitalized due to worsening HF as the primary cause of admission. For each patient, baseline data included (1) age, sex, and body mass index (BMI); (2) causes of HF; (3) medical history; (4) prior procedures; (5) vital signs; (6) laboratory data; (7) echocardiographic data; and (8) medication use at discharge. The data were registered using a Web-based electronic data capture system licensed by JCARE-CARD (www.jcare-card.jp).

A total cohort of 2,675 patients was registered in JCARE-CARD at the time of the index hospitalization. A total of 126 patients (4.7%) died during the index hospitalization and 244 patients (9.1%) were missed during the follow-up. Follow-up data could thus be obtained in 2,305 out of 2,675 patients (86.2%), and 474 patients (20.6%) died during follow-up. Out of 2,305 patients, information on LVEF was obtained on echocardiography at the time of index hospitalization in 2,020 patients, and 393 patients (19.5%) died during the follow-up. Information on both mode of death and LVEF could be obtained in 323 patients (68% of all deaths).

Definitions of Mode of Death

The mode of death was assigned by the cardiologists in the participating hospitals based on the information including case records, discharge summary, and autopsy reports, and information on all the deaths and mode of death were reviewed by the steering committee. According to the previous study, mode of death categories were defined as follows: (1) sudden death; (2) HF death; (3) myocardial infarction (MI) death; (4) cerebrovascular accident death; (5) CV procedure death; (6) other cardiac death; (7) other vascular death; (8) non-CV death; and (9) unknown death.[18]

Sudden death was defined as an unexpected death in a previously clinically stable patient. Patients in this category had recent human contact before the event. This category includes patients who after attempted resuscitation became comatose and then died. For patients who died and who had been out of contact for prolonged (generally >1 week) or unknown periods of time, the death was classified as unknown. When sufficient information was available, sudden death was subcategorized as with or without preceding CV symptoms. In the absence of such information, the sudden death event was subcategorized as unknown.

HF death was defined as a death that occurred as a result of worsening or intractable HF. Terminal arrhythmias associated with HF deaths were classified as a HF death. HF secondary to a recent MI was classified as an MI death. Patients with worsening HF had many of the following features: symptoms of HF, signs on physical examination of HF, and diagnostic evidence of HF such as an abnormal chest X-ray, significant increase in B-type natriuretic peptide or N-terminal prohormone B-type natriuretic peptide, or prerenal azotemia. When sufficient information was available, HF death was subcategorized as with or without low output and/or congestion. In the absence of such information, the HF death event was subcategorized as unknown. Low output was indicated by symptoms (confusion, weakness, and cold periphery) and signs (poor peripheral perfusion, systolic blood pressure <90 mmHg, and anuria or oliguria).[26] Congestion was indicated by symptoms and signs on physical examination, chest X-ray, and non-invasive and invasive measurements.

MI death was defined as a death that occurred after a verified definite acute MI. In cases of death occurring outside the hospital, a death was classified as an MI death if the autopsy findings showed a recent MI or a recent coronary thrombus. The criteria necessary to satisfy the diagnosis for an acute, evolving, or recent acute MI included the following: positive changes or exceeding the upper limits of normal in biochemical markers of myocardial necrosis (troponin or creatine kinase-MB) and ischemic cardiac symptoms, electrocardiogram changes indicating the new onset ischemia or development of abnormal Q wave, and/or evidence of myocardial necrosis or a new appearance of wall motion abnormalities on the imaging tests.[27] Cerebrovascular accident death was defined as a death that occurred after a hospital-verified definite stroke. In cases of death occurring outside the hospital, a death was classified as a cerebrovascular accident death if autopsy findings showed a recent stroke. Stroke was defined as a persistent disturbance (≥24 h) of focal neurological function resulting in symptoms thought to be due to atherothrombotic or thrombotic cerebral infarction, embolus, or evidence of hemorrhage or for which there was no certain cause. Diagnosis required characteristic history, physical examination, imaging techniques, and/or autopsy data. CV procedure death was defined as a death that occurred during the operative or perioperative period that could be directly attributed to the procedure itself. Other cardiac death was defined as a death that could be attributed to a cardiac reason but was not 1 of the other modes listed here. For example, deaths resulting from valvular heart disease were considered other cardiac deaths. Other vascular death was defined as a death that could be attributed to a vascular reason. These included such events as pulmonary embolism, aortic dissection, or aortic rupture.

Non-CV death was defined as a death that could be attributed to a non-CV cause. These included subcategories such as renal, respiratory, cancer, trauma, infection/sepsis, suicide, and other. Unknown death was defined as a death in which no specific morbid event classification could be assigned.

Statistical Analysis

Patient characteristics and treatments were compared using Pearson chi-squared test for categorical variables, Student's t-test for normally distributed continuous variables, and Mann-Whitney U test for continuous variables not normally distributed. Cumulative event-free rates and incidence of outcomes during the follow-up were derived using the method of Kaplan and Meier. The relationship between predictors and outcomes was evaluated using multivariate adjustment. The covariates age, sex, BMI, diabetes mellitus, New York Heart Association (NYHA) functional class, estimated glomerular filtration rate (eGFR), hemoglobin, and LVEF, were used to develop the post-discharge Cox proportional hazard models.

The results are reported as hazard ratio, 95% confidence interval, and P-value. $P<0.05$ was used as a criterion for variables to stay in the model. SPSS version 16.0J for Windows was used for all statistical analysis.

Table 1. Patient Characteristics vs. LVEF

Characteristics	Total (n=323)	HFREF (n=154)	HFPEF (n=169)	P-value
Age (years)	75.5±12.6	73.4±12.6	77.5±12.2	0.001
Male (%)	62.5	70.8	55.0	0.003
BMI (kg/m²)	21.2±3.4	21.2±3.3	21.2±3.5	0.557
Causes of heart failure (%)				
Ischemic	37.5	46.8	29.0	0.001
Valvular	29.1	18.2	39.1	<0.001
Hypertensive	20.1	11.0	28.4	<0.001
Cardiomyopathy	17.3	25.3	10.1	<0.001
Medical history (%)				
Hypertension	47.8	36.6	58.0	<0.001
Diabetes mellitus	29.8	34.4	25.6	0.084
Dyslipidemia	21.8	25.5	18.5	0.127
Prior stroke	18.1	15.4	20.5	0.245
COPD	7.3	7.9	6.7	0.684
Smoking	37.2	41.0	33.8	0.196
Prior MI	32.8	45.7	20.9	<0.001
Atrial fibrillation	36.2	28.6	43.4	0.006
Sustained VT/VF	11.7	14.6	8.9	0.123
Procedures (%)				
PCI	19.9	27.6	12.8	0.001
CABG	11.0	15.8	6.6	0.009
Valvular surgery	4.4	3.3	5.4	0.354
PPM	1.9	3.2	0.6	0.078
ICD	3.2	5.4	1.2	0.036
CRT	2.9	4.8	1.2	0.064
Vital signs at discharge				
NYHA functional class 1/2 (%)	87.2	81.0	92.8	0.002
Heart rate (beats/min)	70.6±12.3	72.5±13.5	68.9±10.9	0.017
SBP (mmHg)	115.4±19.1	110.9±17.9	119.4±19.3	<0.001
DBP (mmHg)	64.0±11.1	62.3±11.0	65.5±11.0	0.008
Laboratory data at discharge				
eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	42.4±24.8	42.6±24.7	42.3±25.0	0.820
Serum uric acid (mg/dl)	7.9±2.5	8.1±2.5	7.7±2.4	0.306
Hemoglobin (g/dl)	11.1±2.4	11.5±2.5	10.8±2.3	0.055
Plasma BNP (pg/ml)	579±695	637±774	523±608	0.166
Echocardiographic data				
LV EDD (mm)	56.0±11.5	61.6±10.6	51.0±9.8	<0.001
LV ESD (mm)	43.8±13.2	53.0±10.3	35.5±9.6	<0.001
IVST (mm)	10.4±2.9	9.6±3.1	11.0±2.5	<0.001
LV PWT (mm)	10.7±2.7	10.2±2.8	11.2±2.6	<0.001
LVEF (%)	43.0±18.1	27.0±7.6	57.5±11.3	<0.001
Medications at discharge (%)				
ACE inhibitor	38.4	44.9	32.5	0.025
ARB	36.5	40.8	32.5	0.129
ACE inhibitor or ARB	69.4	76.2	63.2	0.013
β-blocker	41.9	51.7	33.1	0.001
Diuretics	90.3	89.8	90.8	0.766
Loop diuretics	84.5	83.7	85.3	0.697
Spironolactone	38.1	39.5	36.8	0.632
Digitalis	34.5	38.1	31.3	0.208
Ca channel blocker	23.2	13.6	31.9	<0.001
Nitrates	23.9	26.5	21.5	0.297
Anti-arrhythmics	21.6	31.3	12.9	<0.001
Aspirin	51.9	53.7	50.3	0.546
Warfarin	36.1	40.8	31.9	0.103
Statin	17.4	19.7	15.3	0.309

(Table 1 continued the next page.)

Data given as % or as mean±SD.
LV, left ventricular; EF, ejection fraction; HFREF, heart failure with reduced EF; HFPEF, heart failure with preserved EF; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; VT/VF, ventricular tachycardia/fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; PPM, permanent pacemaker; 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; EDD, end-diastolic diameter; ESD, end-systolic diameter; IVST, interventricular septal thickness; PWT, posterior wall thickness; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

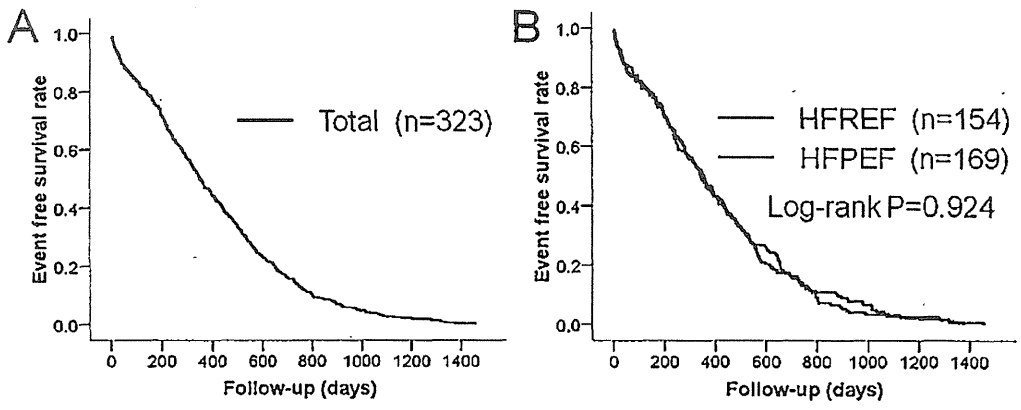

Figure 1. Kaplan-Meier curves for survival rate in (A) total patients (n=323) and (B) heart failure and reduced ejection fraction (HFREF; red line, n=154) vs. HF and preserved EF (HFPEF; black line, n=169).

Table 2. Mode of Death vs. LVEF

Mode of death	Total (n=323)	HFREF (n=154)	HFPEF (n=169)	P-value
Sudden death, n (% of total death)	54 (17)	36 (23)	18 (11)	0.002
With preceding CV symptoms, n (% of sudden death)	30 (56)	21 (58)	9 (50)	
Without preceding CV symptoms, n (% of sudden death)	4 (7)	3 (8)	1 (6)	0.714
Unknown, n (% of sudden death)	20 (37)	12 (33)	8 (44)	
HF death, n (% of total death)	116 (36)	57 (37)	59 (35)	0.694
Low output, n (% of HF death)	15 (13)	6 (11)	9 (15)	
Congestion, n (% of HF death)	16 (14)	2 (4)	14 (24)	0.006
Low output+congestion, n (% of HF death)	74 (64)	44 (77)	30 (51)	
Unknown, n (% of HF death)	11 (9)	5 (9)	6 (10)	
MI death, n (% of total death)	11 (3)	3 (2)	8 (5)	0.168
Cerebrovascular accident death, n (% of total death)	11 (3)	4 (3)	7 (4)	0.445
CV procedure death, n (% of total death)	1 (0)	1 (1)	0 (0)	0.294
Other cardiac death, n (% of total death)	4 (1)	2 (1)	2 (1)	0.925
Other vascular death, n (% of total death)	6 (2)	2 (1)	4 (2)	0.478
Non-CV death, n (% of total death)	75 (23)	27 (18)	48 (28)	0.021
Renal, n (% of non-CV death)	11 (15)	4 (15)	7 (15)	
Respiratory, n (% of non-CV death)	9 (12)	2 (7)	7 (15)	
Cancer, n (% of non-CV death)	28 (37)	12 (44)	16 (33)	
Trauma, n (% of non-CV death)	0 (0)	0 (0)	0 (0)	0.778
Infection/sepsis, n (% of non-CV death)	20 (27)	6 (22)	14 (29)	
Suicide, n (% of non-CV death)	0 (0)	0 (0)	0 (0)	
Other, n (% of non-CV death)	7 (9)	3 (11)	4 (8)	
Unknown death, n (% of total death)	45 (14)	22 (14)	23 (14)	0.861

CV, cardiovascular. Other abbreviations as in Table 1.

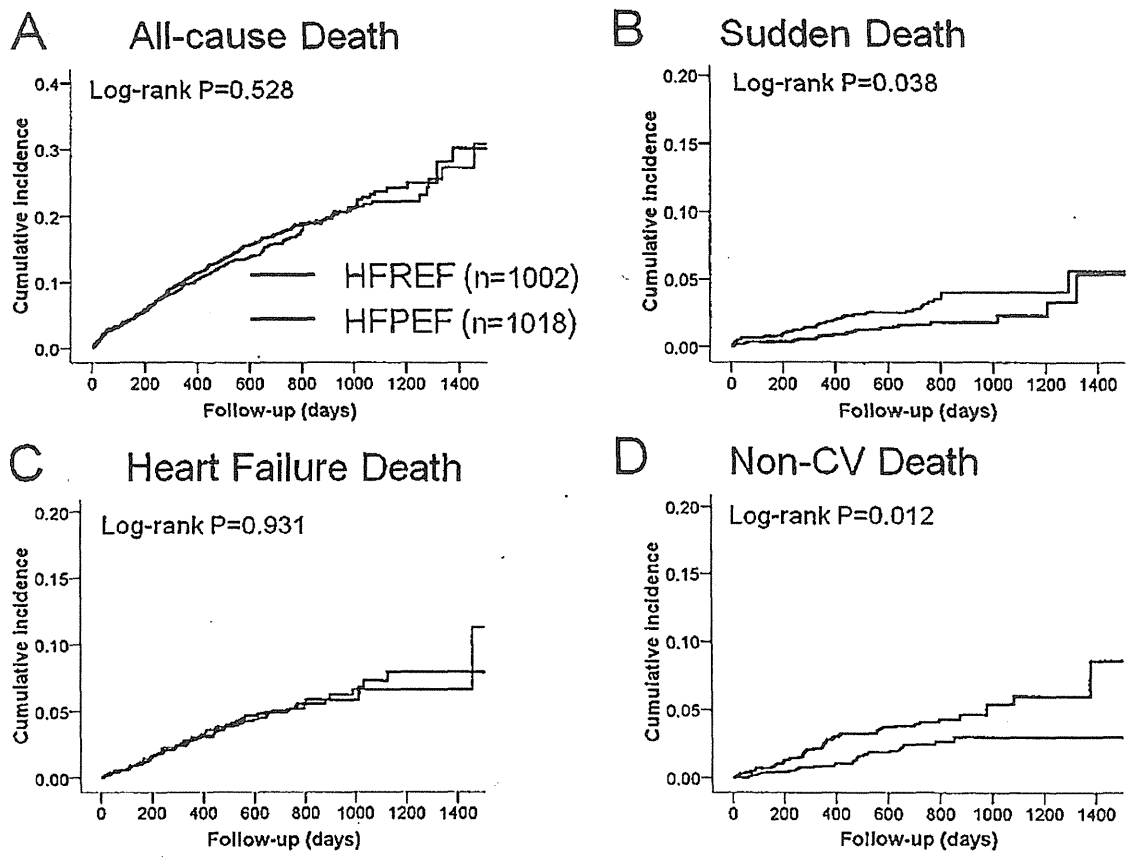

Figure 2. Kaplan-Meier curves for (**A**) all-cause death, (**B**) sudden death, (**C**) heart failure (HF) death, and (**D**) non-cardiovascular (CV) death in HF patients with reduced ejection fraction (HFREF) (red line, n=1,002) vs. those with preserved ejection fraction (HFPEF; black line, n=1,018).

Results

Patient Characteristics

Among a total cohort of 323 patients, the mean age was 75.5±12.6 years, 62.5% were men, 37.5% had ischemic heart disease for HF etiology, and 87.2% had mild HF symptoms at discharge (NYHA functional class I or II). The mean LVEF on echocardiography was 43% (**Table 1**).

Patients were divided into 2 groups according to LVEF: <40% (HFREF group; n=154, 48%) or ≥40% (HFPEF group; n=169. 52%; **Table 1**). Patients with HFPEF were significantly older and more frequently female. The prevalence of valvular and hypertensive etiology was higher, and that of ischemic heart disease and cardiomyopathy lower, compared to HFREF. The HFPEF patients had a higher prevalence of comorbidities including hypertension and atrial fibrillation, whereas prior MI was more common in patients with HFREF. The HFPEF patients underwent fewer percutaneous coronary interventions and coronary artery bypass grafts, and had fewer implantable cardioverter defibrillators. Patients with HFPEF had milder symptoms according to NYHA functional class at discharge. Systolic blood pressure and diastolic blood pressure at discharge were significantly higher in patients with HFPEF. As expected, echocardiography showed that LVEF was higher, and LV end-diastolic and end-systolic diameters were smaller in patients with HFPEF. LV wall thickness was greater in these patients.

The use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, and anti-arrhythmic drugs at hospital discharge was significantly lower in patients with HFPEF. Conversely, Ca channel blocker was more commonly prescribed for them.

All-Cause Death and Mode of Death

There was no significant difference in Kaplan-Meier curves for survival rates between patients with HFPEF and HFREF (P=0.924; **Figure 1**). **Table 2** lists the mode of death measured as number of patients and percentage of total mortality or categories. Out of total 323 deaths, 203 deaths (63%) were CV, 75 (23%) were non-CV, and 45 (14%) were unknown. HF death was the most common mode of death and HF death with low output plus congestion was the most common subcategory.

Among CV death, distribution of subcategories differed between HFREF and HFPEF. Sudden death was less frequent in patients with HFPEF than HFREF (11% vs. 23%, P=0.002). The distribution of subcategories of sudden death was similar between HFPEF and HFREF (P=0.714).

Table 3. Predictors of Sudden Death and HF Death

	Predictors	Adjusted HR	95%CI	P-value
Sudden death				
HFREF	Hemoglobin (per 1-g/dl decrease)	1.234	1.011–1.505	0.038
HFPEF	eGFR (per 1-ml·min^{-1}·1.73m^{-2} decrease)	1.026	1.001–1.051	0.040
HF death				
HFREF	eGFR (per 1-ml·min^{-1}·1.73m^{-2} decrease)	1.035	1.013–1.057	0.002
	Age (per 1-year increase)	1.046	1.003–1.091	0.035
	NYHA functional class (per 1-class increase)	2.437	1.214–4.892	0.012
HFPEF	Age (per 1-year increase)	1.033	1.002–1.065	0.038
	Hemoglobin (per 1-g/dl decrease)	1.165	1.009–1.346	0.037

The Cox regression model was used in the analysis adjusted for the following covariates; age, sex, BMI, diabetes mellitus, NYHA functional class, eGFR, hemoglobin, and LVEF.
HF, heart failure; HR, hazard ratio; CI, confidence interval. Other abbreviations as in Table 1.

HF death was the most common mode of death in patients with HFPEF as well as HFREF (35% vs. 37%, P=0.694). For HF death, there were more deaths in HFREF patients due to low output plus congestion than in the HFPEF patients (P=0.006). The mode of death distribution was similar even when the patients were divided into 2 groups according different definition; to LVEF <40% or ≥50% (data not shown).

Figure 2 shows Kaplan-Meier curves for the cumulative incidence of all-cause death, sudden death, HF death, and non-CV death in patients with HFREF and HFPEF during follow-up. Again, the incidence of sudden death was higher in HFREF than in HFPEF (P=0.038), and that of non-CV death was higher in HFPEF than in HFREF (P=0.012), while those of all-cause death and HF death were similar between the groups.

The independent predictor for sudden death was lower hemoglobin in patients with HFREF and lower eGFR in patients with HFPEF (**Table 3**). HF death was independently associated with lower eGFR, higher age, and higher NYHA functional class in patients with HFREF and with higher age and lower hemoglobin in patients with HFPEF (**Table 3**).

Other CV death including MI, cerebrovascular accident, and others was similar between groups. Non-CV death was significantly higher in patients with HFPEF than HFREF (28% vs. 18%, P=0.021). Distribution of subcategories of non-CV death was similar between groups (P=0.778). Unknown death was similar between HFREF and HFPEF (14% vs. 14%, P=0.861; **Table 2**).

Discussion

Using the registry data of hospitalized HF patients, the present study has made the following findings. First, 63% of the deaths among HF patients during the follow-up were CV, 23% non-CV, and 14% unknown. Second, HF death was the most common mode of death in patients with HFPEF as well as HFREF. Third, the distribution of the mode of death categories in patients with HFPEF differs from that in patients with HFREF. There were fewer sudden deaths and more non-CV deaths in HFPEF patients than in HFREF patients.

In our previous study using the same registry data, patients with HFPEF had a similar mortality risk and equally high rate of rehospitalization as those with HFREF.[7] The rate of in-hospital death (6.5% vs. 3.9%, P=0.030) and death during long-term follow-up after discharge (22.7% vs. 17.8%, P=0.058) were slightly higher in patients with HFPEF, which, however, did not differ after multivariate adjustment. Patients with HFPEF had a similar rate of rehospitalization due to worsening HF compared with patients with HFREF (36.2% vs. 33.4%, P=0.515).[7]

The present study shows that there are differences in the distribution of the mode of death categories between HFREF and HFPEF (**Table 2**). The most common mode of death was HF death in both HFREF and HFPEF patients (37% vs. 35%, P=0.694). This might be due to the fact that the present study included patients hospitalized due to worsening HF. HF death was subcategorized as with or without low output and/or congestion in the present study. Combined low output and congestion was the most common subcategory in HFREF. In contrast, patients with HFPEF had congestion more frequently than in HFREF. Sudden death was higher in HFREF than in HFPEF (23% vs. 11%, P=0.002). Non-CV death was lower in HFREF than in HFPEF (18% vs. 28%, P=0.021), consistent with the previous study based on results from the I-Preserve trial (15% vs. 30%)[18] and a community-based cohort study of HF patients from Olmsted Country (36% vs. 49%).[17] These findings indicate that patients with HFPEF carry a lower risk of sudden death, but not overall and HF death. This might be due to higher age and extensive comorbidities in HFPEF patients (**Table 1**). This underscores the importance of the identification and management of comorbidities among patients with HF, especially with HFPEF. Moreover, this also highlights the difficulties in the development of effective treatment strategies in patients with HFPEF because non-cardiac comorbid conditions may interfere with HF treatment and adversely affect outcomes.[28]

The present study demonstrated that, in patients with HFPEF, the mode of death was non-CV in 28% and CV in 63% (including 11% sudden, 35% HF, 5% MI, and 4% stroke). In the I-Preserve trial, it was non-CV in 30% and CV in 60% (including 26% sudden, 14% HF, 5% MI, and 9% stroke).[18] Therefore, the prevalence of sudden death was lower (11% vs. 26%), whereas that of HF death was higher (35% vs. 14%) in the present study than in the I-Preserve trial. The rate of HF death was reported to be 21% in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved, and 28% in the Digitalis Investigator Group (DIG)-Preserved.[13,15] Therefore, the rate of HF death in the present study was higher than in the previous studies. These differences may relate in part to the differences in LVEF cut-offs, the severity of HF, and the type of patients studied (outpatients vs. hospitalized patients). Moreover, the differences between the present registry and the clinical trial data illustrate the limitations of extrapolating the findings obtained from RCT into the real world. Even though the recent study from the I-

Preserve trial provided a detailed analysis regarding the mode of death, it included only patients with HFPEF and could not compare patients with HFPEF vs. those with HFREF.[18] In contrast, the present study analyzed HF patients independently of LVEF and could compare the mode of death in both HFREF and HFPEF patients enrolled within the registry. Regardless of the type of patients studied, HF death and sudden death were the most common CV death not only in HFREF but also in HFPEF. These results clearly demonstrate that effective treatment strategies against HF and sudden death are also critically needed in patients with HFPEF.

Study Limitations

Several limitations inherent in the design of the registry should be considered. First, this study included only patients who could be followed and whose data for both mode of death and LVEF were obtained. Thus 68% of all deaths could be included in the analysis, leading to a substantial selection bias. But this underscores the importance and relevance of the present findings to routine clinical practice. Second, the data were dependent on the accuracy of documentation and abstraction by the individual medical centers that participated in the study. Even though we could not completely exclude the possibility that some deaths could be misclassified, it would occur in both the HFPEF and the HFREF patients, therefore it should not affect the primary findings of the present study. Moreover, it is sometimes difficult to identify the mode of death only by clinical findings, even when complete information was obtained. Therefore, unknown death was defined as a death in which no specific morbid event classification could be assigned. Further, misclassification should not be a major problem because the present study used detailed and well-defined categories of mode of death.

Conclusions

In the patients hospitalized with worsening HF, the mode of 60–70% of death was CV, and HF death was the most common mode of death in either HFREF or HFPEF. In HFPEF the prevalence of sudden death was lower, and that of non-CV death higher, compared with HFREF. More widespread use of the standard medication for HF might reduce the risk of death also in patients with HFPEF. Effective management strategies are critically needed for HFPEF.

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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)

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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.

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Methods

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

Study selection and data extraction

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

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

Ejection fraction

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

Statistical analysis

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

Results

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

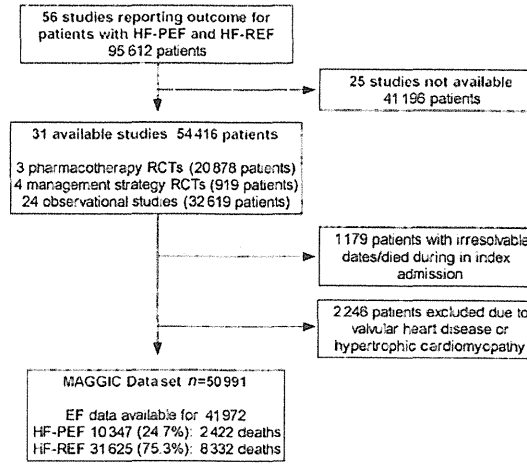

Figure 1 Flow chart of studies for meta-analysis.

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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 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

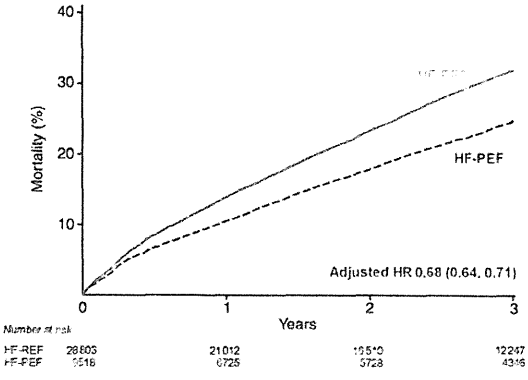

Figure 2 Mortality for patients with HF-PEF (heart failure with preserved left ventricular ejection fraction) and HF-REF (heart failure with low left ventricular ejection fraction), adjusted for age, gender, aetiology of heart failure, hypertension, diabetes, atrial fibrillation.

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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)

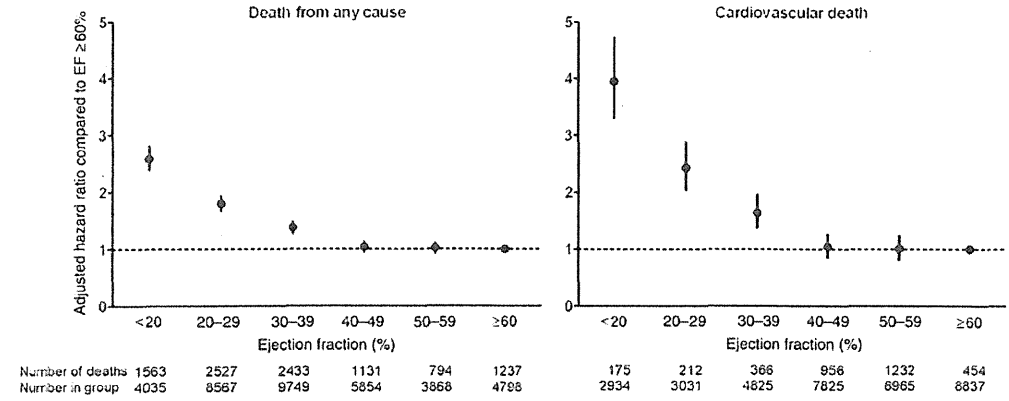

Figure 3 Adjusted hazard ratios comparing death from any cause and cardiovascular death by groups of left ventricular ejection fraction (with LVEF ≥ 60% as the reference group).

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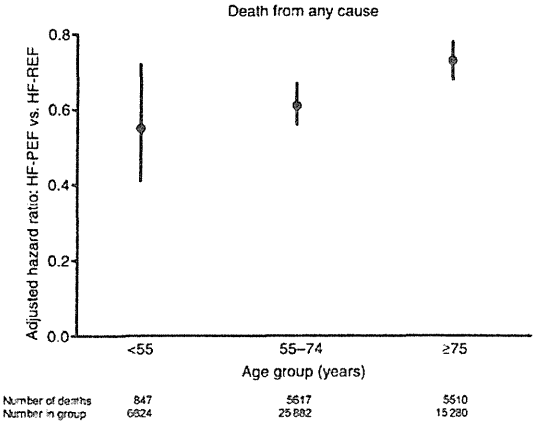

Figure 4 Adjusted hazard ratios comparing death from any cause for patients with heart failure-preserved ejection fraction and heart failure-reduced ejection fraction by age group.

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

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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.

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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

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