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 County,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.

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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 pro-hormone B-type natriuretic peptide, or prerenal azotemia. When sufficient information was available, HF death was subcatego-

rized 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.

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·min ⁻¹ ·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 $\geq 40\%$ (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 · 1.73 m ⁻² decrease)	1.026	1.001–1.051	0.040
HF death					
HFREF		eGFR (per 1-ml · min ⁻¹ · 1.73 m ⁻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 $\geq 50\%$ (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 worsen-

ing 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 County (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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