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ORIGINAL RESEARCH ARTICLE

Spironolactone use is associated with improved outcomes in heart failure with mid-range ejection fraction

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Abstract

Aims Spironolactone has been shown to improve outcomes in patients with heart failure (HF) with reduced ejection fraction (EF). We investigated whether the discharge use of spironolactone could be associated with better long-term outcomes among patients with HF with mid-range EF (HFmrEF).

Methods and results We analysed HFmrEF (left ventricular EF 40–49%) patients enrolled in the Japanese Cardiac Registry of Heart Failure in Cardiology, which prospectively studied the clinical characteristics, treatments, and long-term outcomes of patients hospitalized due to HF. Patients were divided into two groups according to the use of spironolactone at discharge. The primary outcome was a composite of all-cause death or HF rehospitalization. A total of 457 patients had HFmrEF. The mean age was 69.3 years and 286 (62.6%) were male. Among them, spironolactone was prescribed at discharge in 158 patients (34.6%). Chronic kidney disease (7.6% vs. 16.8%, $P = 0.007$) was less prevalent and loop diuretics (89.2% vs. 70.2%, $P < 0.001$) were more often prescribed in patients with spironolactone. During a mean follow-up of 2.2 years, patients with spironolactone had a lower incidence rate of the primary outcome than those without it (171.5 vs. 278.8 primary outcome per 1000 patient-years, incidence rate ratio 0.61, 95% confidence interval 0.44–0.86; $P = 0.004$). After multivariable adjustment, spironolactone use at discharge was associated with a significant reduction in the composite of all-cause death or HF rehospitalization (adjusted hazard ratio 0.63, 95% confidence interval 0.44–0.90, $P = 0.010$).

Conclusions Among patients with HF hospitalized for HFmrEF, spironolactone use at discharge was associated with better long-term outcomes.

Keywords Spironolactone; Heart failure with mid-range ejection fraction; Outcomes; Rehospitalization

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Introduction

Heart failure (HF) with left ventricular ejection fraction (LVEF) of 40–49% was first proposed in 2013 American College of Cardiology/American Heart Association guidelines as an intermediate group.[1] In 2016, the European Society of Cardiology HF guidelines defined this distinct group as HF with mid-range ejection fraction (HFmrEF)[2] and indicated the need for more research on this clinical entity because patients with LVEF of 40–49% were traditionally excluded from most of the previous randomized controlled clinical trials. Recent studies have investigated the clinical characteristics, outcomes, and prognostic factors in HFmrEF in comparison with HF with preserved EF (HFpEF) or HF with reduced EF (HFrEF).[3,4] However, an effective therapeutic strategy for HFmrEF remains to be established.

Several prospective randomized controlled clinical trials have demonstrated effects of mineralocorticoid receptor

antagonists (MRA) including spironolactone and eplerenone on outcomes in patients with HFrEF. Spironolactone reduced morbidity and mortality in patients with HFrEF.[5] Eplerenone, a more selective MRA, was also shown to reduce the risk of mortality and hospitalization among patients with LV systolic dysfunction after myocardial infarction[6] and HFrEF.[7] TOPCAT trial, a multinational randomized controlled trial of spironolactone, demonstrated that spironolactone reduced the composite outcome of cardiovascular mortality or HF re-hospitalization in patients who were diagnosed with HFpEF by elevated brain natriuretic peptide (BNP) levels and had a higher event rate.[8,9] To date, it has not been determined whether spironolactone could improve outcomes of patients with HFmrEF. The aim of the present study was to analyse the prognostic impact of spironolactone on mortality and rehospitalization due to worsening HF among patients with HFmrEF by using the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) database.

Methods

Patient selection

The JCARE-CARD is a multicentre registry of patients hospitalized for the worsening HF in Japan.[10] Baseline data were collected during the episode of index hospitalization from January 2004 to June 2005. Follow-up data were collected at least 1 year after the index admission. The baseline data include (i) demography; (ii) cause of HF; (iii) precipitating cause; (iv) co-morbidities; (v) complications; (vi) clinical status; (vii) electrocardiographic and echocardiographic findings; and (viii) treatment including discharge medications.

From the database of JCARE-CARD, those with LVEF of $\geq$40% and $<$50% were registered in this study. Of these, patients who died during the index hospitalization were excluded. These patients were divided into two groups according to the use of spironolactone at discharge from the index hospitalization.

Outcomes

The primary outcome of this study was a composite of all-cause death or HF rehospitalization. Secondary outcomes were a composite of cardiovascular death or HF rehospitalization, all-cause death, and cardiovascular death.

Statistical analysis

Patients with spironolactone were compared with those without it. The patient characteristics, including age, gender, New York Heart Association (NYHA) functional class at discharge, previous HF admission, echocardiographic data, co-morbidities, previous procedures, and therapeutic agents, were compared with Pearson χ^2 test for categorical variables, Student's *t*-test, or Wilcoxon rank sum test for continuous variables where applicable and were presented as mean ± SD or median with interquartile range (IQR). For analysis of associations between spironolactone and outcomes, incidence rates per 1000 patient-years and incidence rate ratio were calculated for each outcome. Cumulative incidence of outcomes was estimated by using regression estimates from a Cox proportional hazards model including covariates that were either statistically significant on univariate analysis or clinically relevant. Adjusted hazard ratios (HRs) were estimated by Cox regression model and were presented with 95% confidence interval (CI) and *P* value. Patient characteristics and prognostic factors in those with LVEF $\geq$50% were tested by same methods for comparison. For the purpose of the sensitivity analysis, a propensity score was estimated by fitting a logistic-regression model that adjusted for age ($\geq$70 years vs. $<$70 years), sex, previous HF admission, NYHA functional class (I–II vs. III–IV), ischaemic heart disease, hypertension, diabetes mellitus, chronic kidney disease, stroke, anaemia, history of percutaneous coronary intervention, chronic atrial fibrillation or atrial flutter, ventricular tachycardia or fibrillation, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, loop diuretics, oral inotropes, and warfarin. One-to-one pair matching between the two groups was performed by nearest neighbor matching without replacement. The same analysis was performed for the propensity matched cohorts. All tests were two tailed, and $P < 0.05$ was considered to be statistically significant. All analyses were performed with the SAS statistical package (version 9.4, SAS Institute, Cary, North Carolina).

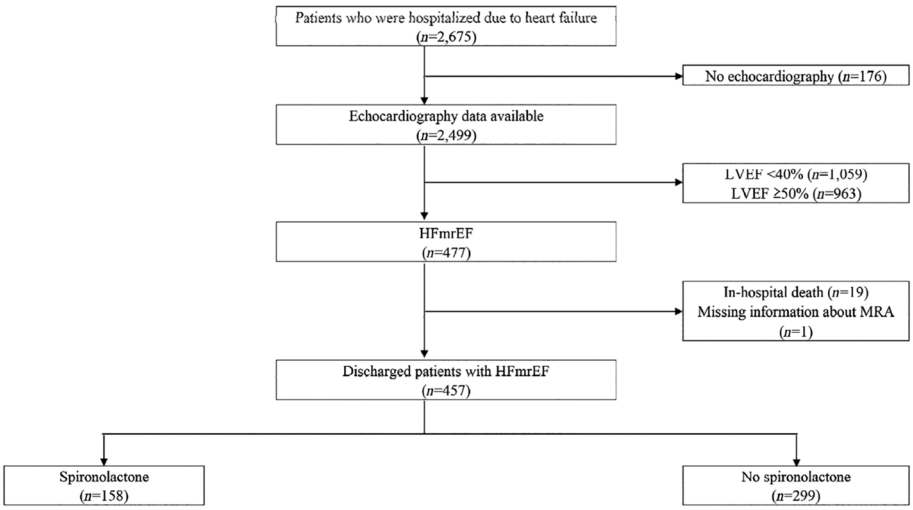
The JCARE-CARD protocol conforms with the principles outlined in the Declaration of Helsinki and the Guidelines for the Epidemiological Research published by the Japanese Ministry of Health, Labour and Welfare. The original study protocol was approved by the Institutional Review Board at Kyushu University. Institutional Review Board approval from each participating hospital was also required. Informed consent was given by each patient. The authors had full access to and take full responsibility for the integrity of the data.

Results

Patient characteristics

Figure 1 shows the method of patient selection in this study. Of the 2675 patients in this registry, 2499 patients were assessed with echocardiography during the index hospitalization, of whom 477 patients were defined as HFmrEF. Of them, 457 patients who survived to discharge were included in this

Figure 1 Patient selection. HFmrEF, heart failure with mid-range ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists.



study. Among them, 158 patients were treated with spironolactone. Baseline characteristics are shown in *Table 1*. The mean age was 69.3 years and 286 (62.6%) were male. Patient demographics, cause of HF, rates of previous HF diagnosis, previous HF hospitalization, and smoking were comparable between groups. Co-morbidities were also comparable except for lower prevalence of chronic kidney disease in the spironolactone group (7.6% vs. 16.8%, $P = 0.007$). The echocardiography demonstrated that LVEF was significantly but slightly lower in the spironolactone group (44.0 [IQR 41.0–46.0] vs. 44.7 [IQR 42.0–47.0]%; $P = 0.031$). Although BNP value at discharge was lower in the spironolactone group (190.4 [IQR 73.9–393.0] vs. 258.5 [IQR 127.2–545.0] pg/mL; $P = 0.005$), it was available only in 49.7% of the study cohort. Loop diuretics were more frequently prescribed in the spironolactone group (89.2% vs. 70.2%, $P < 0.001$), while nitrate was less frequently prescribed in the spironolactone group (19.6% vs. 29.4%, $P = 0.023$).

Clinical outcomes

During a mean follow-up of 2.2 years, the incidence rate of primary outcome was lower in patients with spironolactone than those without it (48 [30.4%] vs. 123 [41.1%]). The incidence rates of composite outcome of all-cause death or HF rehospitalization, composite outcome of cardiovascular death or HF rehospitalization, all-cause death, and cardiovascular death per 1000 patient-years were 171.5 vs. 278.8, 150.0 vs. 249.4, 65.0 vs. 91.5, and 27.8 vs. 53.8 for the spironolactone and no spironolactone groups, respectively (*Table 2*). The incidence rate ratios were 0.61 (95% CI 0.44–0.86; $P = 0.004$), 0.60 (95% CI 0.42–0.86; $P = 0.005$), 0.71 (95% CI 0.43–1.18; $P = 0.19$), and 0.52 (95% CI 0.25–1.09; $P = 0.083$) for each outcome (*Table 2*). Univariate analysis for the composite of all-cause death or HF rehospitalization by Cox regression hazard model demonstrated that spironolactone use at discharge, age, previous HF admission, NYHA functional class III–IV at discharge, chronic kidney disease, anaemia, ischaemic heart disease, the history of sustained ventricular tachycardia or ventricular fibrillation, oral inotrope, and warfarin was significantly associated with the primary outcome. Multivariate analysis including these factors showed that spironolactone was independently associated with better prognosis (adjusted HR 0.63, 95% CI 0.44–0.90; $P = 0.010$). Age (≥70 years) (adjusted HR 1.56, 95% CI 1.10–2.21; $P = 0.012$), prior HF admission (adjusted HR 2.59, 95% CI 1.84–3.65; $P < 0.001$), chronic kidney disease (adjusted HR 1.98, 95% CI 1.29–3.04; $P = 0.002$), and sustained ventricular tachycardia or fibrillation (adjusted HR 2.12, 95% CI 1.24–3.62; $P = 0.006$) were independently associated with poor prognosis (*Table 3*). *Figure 2* demonstrates the cumulative incidence of each outcome adjusted by covariates. The covariates were selected from the factors that were either statistically significant on univariate analysis (age, previous HF admission, NYHA functional class, chronic kidney disease, anaemia, ischaemic heart disease, sustained ventricular tachycardia or fibrillation, oral inotrope, and warfarin in *Table 3*) or clinically relevant (sex). The cumulative incidence of the composite of all-cause death or HF rehospitalization ($P = 0.012$; *Figure 2A*), the composite of cardiovascular death or HF rehospitalization ($P = 0.011$; *Figure 2B*), and cardiovascular death ($P = 0.030$; *Figure 2D*) were significantly decreased in the spironolactone group, except for all-cause death $P = 0.24$; *Figure 2C*). Patient characteristics before and after propensity score matching as a sensitivity analysis were shown in Supporting Information, *Tables S1* and *S2*. Spironolactone

Table 1 Patient characteristics

Variables	Spironolactone (n = 158)	No spironolactone (n = 299)	P value
Demographics			
Age, years	68.1 ± 15.0	70.0 ± 13.1	0.17
Male	99 (62.7)	187 (62.5)	0.98
BMI, kg/m^2	22.9 ± 4.6	22.3 ± 4.2	0.17
Previous HF diagnosis	91 (57.6)	169 (56.5)	0.83
Previous HF admission	66 (43.4)	123 (43.9)	0.92
NYHA III–IV at discharge	7 (4.4)	12 (4.0)	0.83
Smoking	63 (42.6)	113 (40.4)	0.66
Causes of HF			
Ischaemic	58 (36.7)	119 (39.8)	0.52
Hypertensive	37 (23.4)	75 (25.1)	0.69
Cardiomyopathic, dilated	25 (15.8)	45 (15.1)	0.83
Cardiomyopathic, hypertrophic	0 (0.0)	4 (1.3)	0.14
Other or unknown etiology	48 (30.4)	85 (28.4)	0.66
Co-morbidities			
Hypertension	81 (51.6)	160 (54.1)	0.62
Diabetes mellitus	49 (31.0)	110 (36.8)	0.22
Dyslipidaemia	39 (24.8)	92 (31.0)	0.17
Chronic kidney disease	12 (7.6)	50 (16.8)	0.007
Hyperuricemia	73 (48.3)	136 (46.9)	0.77
Stroke	22 (14.0)	42 (14.2)	0.95
Anaemia	24 (15.2)	63 (21.2)	0.12
COPD	9 (5.8)	19 (6.4)	0.78
Previous heart disease			
Myocardial infarction	54 (34.2)	100 (34.1)	0.99
Previous PCI	25 (16.0)	67 (22.7)	0.094
Previous CABG	18 (11.5)	34 (11.5)	0.996
Pacemaker implantation	2 (1.3)	3 (1.0)	0.80
CRT implantation	3 (1.9)	2 (0.7)	0.23
ICD implantation	6 (3.8)	4 (1.3)	0.087
Chronic AF, AFL	55 (34.8)	95 (32.2)	0.57
Sustained VT, VF	9 (5.8)	15 (5.2)	0.77
ECG			0.11
Left bandle branch block	11 (7.0)	35 (11.7)	
Pacing	10 (6.3)	10 (3.3)	
Echocardiography			
LVDd, mm	55.8 ± 8.7	55.1 ± 7.9	0.44
LVDs, mm	43.7 ± 7.4	42.7 ± 7.2	0.19
IVS, mm	10.1 ± 2.2	10.6 ± 2.5	0.025
LVPW, mm	10.0 ± 2.0	10.7 ± 2.3	0.001
LVEF, %	44.0 (IQR: 41.0–46.0)	44.7 (IQR: 42.0–47.0)	0.031
MR (moderate–severe)	30 (19.2)	52 (17.9)	0.74
BNP (admission), pg/mL	609.5 (IQR: 313.5–1230.0)	616.5 (IQR: 302.0–1202.0)	0.82
BNP (discharge), pg/mL	190.4 (IQR: 73.9–393.0)	258.5 (IQR: 127.2–545.0)	0.005
Medications			
ACE-I	66 (41.8)	117 (39.1)	0.58
ARB	79 (50.0)	135 (45.2)	0.32
Beta-blocker	80 (50.6)	157 (52.5)	0.70
Thiazide	5 (3.2)	6 (2.0)	0.44
Loop diuretics	141 (89.2)	210 (70.2)	<0.001
CCB	34 (21.5)	88 (29.4)	0.069
Nitrate	31 (19.6)	88 (29.4)	0.023
Digitalis	49 (31.0)	85 (28.4)	0.56
Oral inotrope	10 (6.3)	17 (5.7)	0.78
Aspirin	83 (52.5)	148 (49.5)	0.54
Anti-platelet	19 (12.0)	53 (17.7)	0.11
Warfarin	63 (39.9)	108 (36.1)	0.43
Statin	30 (19.0)	69 (23.1)	0.31

Data are shown as n (per cent), median (IQR), or mean ± SD. ACE-I, angiotensin-converting enzyme inhibiter; AF, atrial fibrillation; AFL, atrial flutter; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; IVS, interventricular septum thickness; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior wall thickness; MR, mitral regurgitation; PCI, percutaneous coronary intervention; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2 Incidence rate and incidence rate ratio

Outcomes	Spironolactone (n = 158)		No spironolactone (n = 299)			
	Patients with event, n (%)	Incidence/1000 person-years at risk	Patients with event, n (%)	Incidence/1000 person-years at risk	Rate ratio (95% CI)	P value
Primary outcome						
All-cause death or HF rehospitalization	48 (30.4)	171.5	123 (41.1)	278.8	0.61 (0.44–0.86)	0.004
Secondary outcomes						
CV death or HF rehospitalization	42 (26.6)	150.0	110 (36.8)	249.4	0.60 (0.42–0.86)	0.005
All-cause death	21 (13.3)	65.0	51 (17.1)	91.5	0.71 (0.43–1.18)	0.19
CV death	9 (5.7)	27.8	30 (10.0)	53.8	0.52 (0.25–1.09)	0.083

CV, cardiovascular; HF, heart failure.

Table 3 Unadjusted and adjusted hazard ratio for primary outcome

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Spironolactone	0.62	0.44–0.87	0.005	0.63	0.44–0.90	0.010
Age (≥70 years)	1.73	1.26–2.36	<0.001	1.56	1.10–2.21	0.012
Male	1.02	0.74–1.38	0.93	0.95	0.67–1.34	0.76
Previous HF admission	3.20	2.30–4.39	<0.001	2.59	1.84–3.65	<0.001
NYHA III–IV at discharge	2.22	1.20–4.10	0.011	1.70	0.90–3.23	0.10
Smoking	0.96	0.70–1.32	0.79			
SBP (per 10 mmHg), mmHg	0.99	0.91–1.08	0.84			
LVEF (per 10%), %	1.52	0.89–2.60	0.13			
LVDd (per 10 mm), mm	0.89	0.73–1.07	0.21			
LVDs (per 10 mm), mm	0.89	0.72–1.11	0.30			
Hypertension	1.05	0.77–1.42	0.77			
Diabetes mellitus	1.16	0.85–1.59	0.35			
Dyslipidaemia	1.04	0.75–1.45	0.82			
Chronic kidney disease	2.70	1.89–3.86	<0.001	1.98	1.29–3.04	0.002
Hyperuricemia	1.35	0.99–1.83	0.055			
Stroke	1.34	0.91–1.98	0.14			
Anaemia	1.67	1.18–2.36	0.004	0.95	0.63–1.45	0.82
COPD	1.71	0.99–2.96	0.054			
Ischaemic heart disease	1.45	1.07–1.97	0.015	0.84	0.60–1.17	0.30
Previous PCI	1.24	0.87–1.78	0.24			
Previous CABG	1.31	0.85–2.01	0.23			
Chronic AF, AFL	1.08	0.79–1.49	0.64			
Sustained VT, VF	2.36	1.41–3.97	0.001	2.12	1.24–3.62	0.006
ACE-I or ARB	0.71	0.50–1.02	0.065			
Beta-blocker	0.92	0.68–1.24	0.58			
Thiazide	1.07	0.40–2.87	0.90			
Loop diuretics	1.16	0.80–1.68	0.43			
Nitrate	1.24	0.89–1.74	0.21			
Digitalis	0.91	0.65–1.28	0.60			
Oral inotrope	1.76	1.05–2.95	0.032	1.64	0.93–2.89	0.087
Aspirin	0.98	0.73–1.33	0.90			
Warfarin	0.66	0.48–0.92	0.014	0.79	0.55–1.14	0.21
Statin	0.91	0.63–1.31	0.60			

Abbreviations as in *Table 1*. CI, confidence interval; HR, hazard ratio.

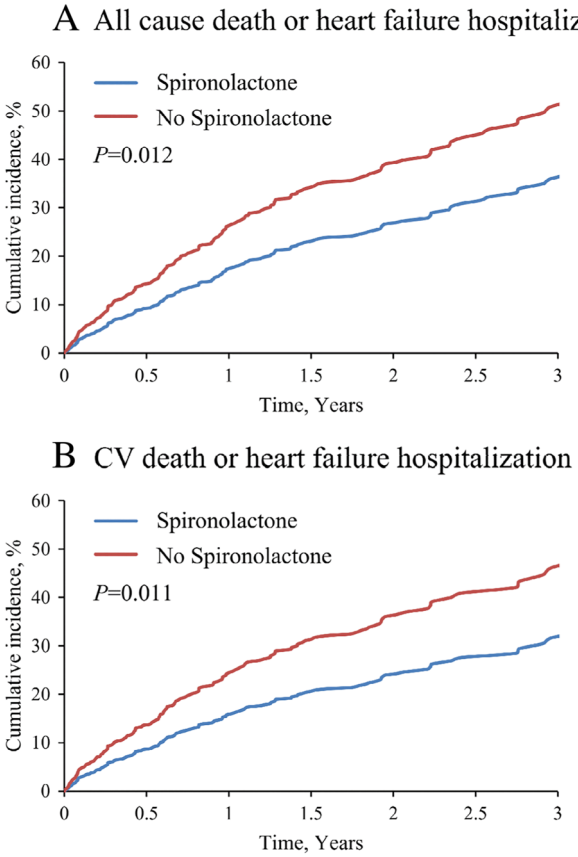
reduced the composite of all-cause death or HF rehospitalization also in propensity score-matched cohorts (P = 0.048; Supporting Information, *Figure S1*).

For comparison, the primary outcome of patients with LVEF ≥50%, so called HFpEF, in the JCARE-CARD cohort was also tested. Patient characteristics of HFpEF were shown in Supporting Information, *Table S3*. Spironolactone was not associated with the better outcome among patients with HFpEF (P = 0.20; Supporting Information, *Table S4*).

Discussion

The major finding of the present study was that spironolactone use at discharge was independently

Figure 2 Covariate-adjusted cumulative incidence of each outcome. Covariate-adjusted cumulative incidence of composite of all-cause death or heart failure rehospitalization (A), composite of cardiovascular death or heart failure rehospitalization (B), all-cause death (C), and cardiovascular death (D). The covariates were selected from the factors that were either statistically significant on univariate analysis (age, previous heart failure admission, New York Heart Association functional class, chronic kidney disease, anaemia, ischaemic heart disease, sustained ventricular tachycardia or fibrillation, oral inotrope, and warfarin in *Table 3*) or clinically relevant (sex).



associated with a significant reduction in the composite of all-cause death or HF rehospitalization among the patients with HFmrEF. This is the first report to demonstrate the beneficial effects of spironolactone on long-term outcomes in HFmrEF.

The 2016 European Society of Cardiology HF guidelines defined HFmrEF in patients with EF of 40–49%.[2] Recent observational studies extensively described characteristics of patients with HFmrEF in comparison with HFpEF and HFrEF[3,4,11–16]; however, it remains unknown whether patients with HFmrEF represent a transitional phenotype between HFpEF and HFrEF or a distinct pathophysiological entity. Furthermore, effective treatment strategies for these patients have not been established.

In the present study, patients with HFmrEF accounted for 19.1% of the total cohort in JCARE-CARD, which was consistent with previous studies.[3,4,11–16] We have previously reported characteristics of HFrEF and HFpEF.[17] In comparison with the present study and our previous study, the characteristics of patients with HFmrEF were, in part, similar to those of patients with HFrEF. Patients with HFmrEF or HFrEF are younger than those with HFpEF (HFmrEF vs. HFrEF vs. HFpEF; 69.3 ± 13.8 vs. 66.6 ± 13.8 vs. 73.6 ± 12.6 years old), more frequent in men (62.6% vs. 72.2% vs. 52.7%), and more likely to have a history of ischaemic heart disease (38.7% vs. 39.8% vs. 25.4%). On the other hand, the HFmrEF occupied an intermediate position between the other two categories regarding chronic atrial fibrillation or atrial flutter (HFmrEF vs. HFrEF vs. HFpEF; 33.1% vs. 24.5% vs. 38.3%) These features were compatible with a recent study.[18] Prognosis in these distinct groups is controversial. The composite outcome of all-cause death or HF rehospitalization was not different among these distinct groups.[17,19] On the other hand, a meta-analysis demonstrated that HFmrEF had a lower rate of cardiac mortality than HFrEF.[20] This discrepancy might be due to the difference in patient characteristics and treatment in each cohort.

The efficacy of MRA for patients with HFrEF has been already established based on previous randomized controlled clinical trials such as RALES and EMPHASIS-HF. The RALES

demonstrated that spironolactone significantly improved outcomes in patients with LVEF less than 35% and NYHA functional class III or IV.[5] In the EPHESUS, eplerenone on top of the conventional treatment including angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and beta-blocker significantly reduced the risk of death.[6] EMPHASIS-HF and J-EMPHASIS-HF demonstrated that eplerenone reduced the risk of death and rehospitalization in patients with LVEF no more than 35% and NYHA functional class II.[7,21]

The beneficial effects of spironolactone for patients with HFpEF have been also reported. TOPCAT trial showed that spironolactone reduced the composite outcome of hospitalization for HF or cardiovascular mortality among patients with LVEF ≥45% and elevated BNP who were enrolled in North and South America but not in Eastern Europe.[8,9,22] Given the stratified nature of TOPCAT, this result is randomized evidence.[23] The regional difference in clinical outcomes was explained as follows. Patients from Eastern Europe, who did not have BNP measured, had a very low event rate similar to the healthy population of the same age. Canrenone (an active metabolite of spironolactone) concentrations were undetectable in 30% of patients in Eastern Europe, compared with 3% of patients in North and South America.[24]

Another subgroup analysis of the TOPCAT trial demonstrated that spironolactone tended to be associated with better outcomes among patients with LVEF 45–50%, implicating that the potential efficacy of spironolactone was greatest at the lower end of the LVEF spectrum.[25] Consistent with these findings, the present study confirmed the clinical efficacy of spironolactone in HFmrEF (*Figure 2* and *Tables 2* and *3*).

Renin–angiotensin system inhibitors and beta-blockers have been reported to be associated with a reduced risk of all-cause mortality in HFmrEF.[26,27] In the present study, renin–angiotensin–aldosterone system inhibitors tended to lower all-cause death and HF rehospitalization in patients with HFmrEF and beta-blockers was not associated with better outcomes (*Table 2*). A meta-analysis of 11 randomized controlled trials, which investigated the effect of beta-blockers on LVEF and prognosis by stratifying according to the baseline LVEF and heart rhythm, showed that beta-blockers significantly reduced all-cause death and cardiovascular death in patients with HFmrEF only if the patient did not have atrial fibrillation.[28] In our study, 32.8% of the patients had chronic atrial fibrillation or atrial flutter. Thus, the high rate of atrial arrhythmias might explain why beta-blockers were ineffective. Importantly, even after adjusted for several factors including atrial fibrillation, spironolactone use was independently associated with a better prognosis (*Table 2*).

HFmrEF is composed of the following three types: HFmrEF recovered (previously HFrEF with LVEF <40%), HFmrEF deteriorated (previously HFpEF with LVEF ≥50%), and HFmrEF unchanged (previously HFmrEF with LVEF 40–50%).[11] HFmrEF is known to transit into HFpEF or HFrEF, by 44% or 16% at 1 year, respectively.[3] Those who transited into HFrEF had worse outcomes similar to HFrEF at registry. The present study did not have follow-up echocardiographic data. The types of HFmrEF benefited by spironolactone and its impact on changes in LVEF cannot be inferred from our study.

We found that age, the history of HF hospitalization, chronic kidney disease, and the history of sustained ventricular tachycardia or fibrillation were independently associated with a poor prognosis. These factors are well known as poor prognostic predictors of HFrEF and HFpEF, suggesting the overlap in predictors of HFmrEF with those of other HF categories.

Taken together, our data suggest that the characteristics of patients with HFmrEF were, in part, similar to those of patients with HFrEF and spironolactone was independently associated with better outcomes in HFmrEF.

Study limitations

Several limitations in this study using the JCARE-CARD database should be acknowledged. First, the dose of spironolactone and the information whether spironolactone was initiated before or during index hospitalization were not collected. In addition, the number of patients who stopped spironolactone during the follow-up period was not recorded. Second, a recent study showed discrepancies of treatment effect on HF patients between non-randomized studies and randomized controlled trials.[29] The present study suggests the efficacy of spironolactone in patients with HFmrEF; however, it is based on the subgroup analysis of an observational study. Thus, stronger evidence by randomized controlled trials is definitely needed to recommend the use of spironolactone for patients with HFmrEF. Finally, there may be unmeasured biases that affect the results.

Conclusions

Among patients with HF hospitalized for HFmrEF, discharge use of spironolactone was independently associated with better long-term outcomes. Spironolactone might be useful for the patients with HFmrEF.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patient characteristics before propensity score matching

Table S2. Patient characteristics after propensity score matching

Table S3. Patient characteristics of HFpEF

Table S4. Unadjusted hazard ratio for primary outcome according to spironolactone use in HFpEF patients

Figure S1. Cumulative incidence curve for primary outcome in propensity matched cohorts

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