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ORIGINAL ARTICLE

Comparison of effects of aldosterone receptor antagonists spironolactone and eplerenone on cardiovascular outcomes and safety in patients with acute decompensated heart failure

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Abstract

Differences in the clinical impacts of the aldosterone receptor antagonists spironolactone and eplerenone in patients with heart failure (HF) are unclear. Among 838 prospectively enrolled patients hospitalized for HF, 90 treated with eplerenone were compared with 90 treated with spironolactone. The primary endpoint was a composite of cardiovascular death and hospitalization. A serial evaluation of the clinical parameters was performed 1 year after discharge. The mean dose of spironolactone was 27 ± 8 mg and of eplerenone was 34 ± 15 mg. During follow-up (mean 594 ± 317 days), primary endpoints occurred in 27 patients in the eplerenone group (30.0%) and 25 patients in the spironolactone group (27.8%). There were no significant intergroup differences in the primary endpoint (log-rank, $p = 0.956$). Serial changes in left ventricular ejection fraction, serum brain natriuretic peptide, systolic blood pressure, and estimated glomerular filtration rate did not differ significantly between groups. Although gynecomastia in men was common in the spironolactone group ($p = 0.018$), the discontinuation rates due to adverse events were similar in the two groups ($p = 0.135$). Subgroup analyses suggested that eplerenone was associated with a lower hazard rate of the primary endpoint in female patients (interaction, $p = 0.076$). Among patients with HF, eplerenone and spironolactone have similar impacts on cardiovascular outcomes and safety.

Keywords Aldosterone receptor antagonist · Spironolactone · Eplerenone · Heart failure

Introduction

Aldosterone receptor antagonists are an established medical treatment in patients with heart failure (HF) with reduced ejection fraction (HFrEF). Guidelines recommended the use of aldosterone receptor antagonists for patients with HFrEF who remain symptomatic despite treatment with an angiotensin-converting enzyme inhibitor and a beta-blocker to reduce the risk of HF hospitalization and death [1, 2]. Two agents, spironolactone and eplerenone, are currently available that competitively inhibit aldosterone. Both agents have proven better prognostic effects on cardiovascular outcomes in randomized large clinical trials targeting HFrEF [3–5]. Eplerenone is a spironolactone derivative that was designed to enhance selective binding to the mineralocorticoid receptor. Eplerenone reportedly has a 20-fold lower affinity for the mineralocorticoid receptor in vitro than spironolactone although the in vivo dosage of eplerenone required to inhibit aldosterone binding by 50% was only approximately half

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that of spironolactone [6]. Eplerenone was both efficacious and safe when carefully monitored, even in subgroups at high risk of developing hyperkalemia or worsening renal function [7]. Based on these pharmacological advantages, eplerenone has been expected to be well tolerated and have higher effects on HF outcomes than spironolactone. However, no study to date has compared the effects of the aldosterone receptor antagonists spironolactone and eplerenone on cardiovascular outcomes in patients with HF, and no guideline mentions which aldosterone receptor antagonist should we select in individual case.

Accordingly, the aim of this study was to compare the effects of the aldosterone receptor antagonists spironolactone and eplerenone on cardiovascular outcomes and safety in patients with HF using data from a prospective observational multi-center registry.

Methods

Study population and protocol

The subjects were 838 patients who were hospitalized for acute decompensated HF and enrolled in the Ibaraki Cardiac Assessment Study-Heart Failure Registry (ICAS-HF registry). The ICAS-HF is a prospective observational multicenter registry pulling data from 11 institutions. This study was a post hoc analysis from ICAS-HF registry. The registration period was June 2012 through March 2015. Observation period has been continued up to March 2016 so that all patients had been followed for at least 1 year. The diagnosis of HF was made according to Framingham criteria [8]. Patients were divided into two groups based on eplerenone or spironolactone administration at hospital discharge. The exclusion criteria were as follows: age < 20 years, refusal to provide informed consent to the attending physician, limited life expectancy due to malignant neoplasms, a 1-year observation was predicted to be impossible, and deemed medically inappropriate to participate by the attending physician. The class I recommendation of the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guideline for the use of aldosterone receptor antagonists was defined as use by patients with New York Heart Association (NYHA) class II–IV HF who have a left ventricular ejection fraction (LVEF) ≤ 35%, serum creatinine level ≤ 2.5 mg/dL in men and ≤ 2.0 mg/dL in women, and serum potassium level < 5.0 mEq/L [1].

To minimize the risk of hyperkalemia, all investigators were instructed to observe strategies written in recommendation of the ACCF/ AHA guideline [1]. In patients, aldosterone receptor antagonist was newly introduced during hospitalization, each drug was started at a dose of 25 mg once daily. Patients should have initial serum creatinine < 2.5 mg/dL without a history of severe hyperkalemia. Aldosterone antagonists would not be initiated in patients with baseline serum potassium > 5.0 mEq/L. In patients, aldosterone receptor antagonist has already introduced on admission, dose of each drug was carefully controlled so that serum potassium level did not exceed 5.0 mEq/L. Measurement of potassium and creatinine levels was performed at every outpatient visit. Each drug was increased to target dose of 50 mg or more once daily, provided the serum potassium level was no more than 5.0 mEq/L. Investigators were instructed to reduce or discontinue the study drug if the serum potassium level was > 5.5 mEq/L.

Echocardiographic examination including two-dimensional pulse-wave, continuous-wave, and color Doppler imaging was performed with the patients in a stable condition prior to hospital discharge. Standard echocardiographic measurements for the evaluation of left atrial size and LV geometry and function were performed according to American Society of Echocardiography guidelines [9]. LVEF and LA volume were measured using the modified Simpson's method from the apical view. HF with preserved ejection function (HFpEF) was defined as an LVEF ≥ 45% [10]. A longitudinal assessment of echocardiography, blood tests, and blood pressure were performed 1 year after discharge. The primary endpoint was a composite of cardiovascular death and hospitalization, while the secondary endpoint was all-cause mortality. Clinical events were classified according to the ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials [11]. Cardiovascular event included HF, acute myocardial infarction, stroke, or arrhythmia. Cardiovascular death was considered of cardiovascular origin if it was caused by HF, acute myocardial infarction, stroke, or was sudden. Adjudication of the outcomes was carried out by an independent adjudication committee. The investigation conformed with the principles outlined in the Declaration of Helsinki. Our institution's ethical committee approved the protocol. Written informed consent was provided by all patients before enrollment.

Propensity score matching

Because the patients were not randomly assigned to receive spironolactone or eplerenone, we matched them according to their propensity for spironolactone and eplerenone administration. A multivariate logistic regression model (i.e., propensity model) was fitted to calculate the probability of spironolactone or eplerenone administration according to the 24 baseline variables listed in Table 1 [age; sex; de novo hospitalization; NYHA class; systolic blood pressure; heart rate; body mass index; LVEF; ischemic etiology; hypertension; atrial fibrillation; smoking; brain natriuretic peptide (BNP); hemoglobin; sodium

Table 1 Baseline patient characteristics according to aldosterone-receptor antagonist use

Variable	Total ($n=797$)	Aldosterone-receptor antagonist use		p value
		Yes ($n=475$)	No ($n=322$)	
Sociodemographic characteristic				
Age	72 ± 13	71 ± 14	74 ± 12	< 0.001
Sex (male)	492 (62)	299 (63)	193 (60)	0.499
De novo hospitalization	576 (72)	363 (76)	213 (66)	0.003
Clinical characteristic				
NYHA class III or IV	51 (11)	37 (10)	14 (13)	0.427
Systolic blood pressure (mmHg)	148 ± 38	146 ± 36	150 ± 40	0.076
Heart rate (bpm)	98 ± 29	99 ± 29	96 ± 29	0.185
Body mass index (kg/m^2)	22.4 ± 4.0	22.7 ± 4.2	22.0 ± 3.7	0.025
LVEF (%)	46 ± 15	44 ± 15	48 ± 16	< 0.001
Comorbidity				
Ischemic etiology	283 (36)	171 (36)	112 (35)	0.806
Hypertension	459 (58)	259 (54)	200 (63)	0.021
Diabetes	354 (44)	214 (45)	140 (44)	0.756
Atrial fibrillation	254 (32)	155 (32)	99 (31)	0.643
Smoking	418 (52)	260 (55)	158 (49)	0.155
Biochemical				
BNP (pg/mL)	402 ± 455	398 ± 462	381 ± 482	0.745
Hemoglobin (g/dL)	12.2 ± 2.3	12.6 ± 2.3	11.6 ± 2.1	< 0.001
Serum sodium (mEq/L)	139.0 ± 3.4	138.7 ± 3.5	139.5 ± 3.3	0.002
Serum potassium (mEq/L)	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	0.729
eGFR (mL/min/1.73 m^2)	50 ± 23	53 ± 21	47 ± 25	< 0.001
HbA1c (%)	6.3 ± 1.0	6.4 ± 1.3	6.4 ± 1.2	0.857
Medical treatment				
β-Blocker use	594 (75)	370 (78)	224 (70)	0.017
ACEI/ARB use	535 (67)	342 (72)	193 (60)	< 0.001
Loop diuretics use	619 (78)	419 (88)	200 (63)	< 0.001
Loop diuretics (mg)	23 ± 22	27 ± 20	18 ± 14	< 0.001
Tolvaptan use	60 (8)	41 (9)	19 (6)	0.158
CCB use	277 (28)	109 (23)	118 (37)	< 0.001
Statin use	293 (37)	167 (35)	126 (39)	0.211

Data are expressed as mean ± SD or as n (%)

LVEF left ventricular ejection fraction, *eGFR* estimated glomerular filtration rate, *BNP* B-type natriuretic peptide, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker

and potassium concentrations; estimated glomerular filtration rate (eGFR); HbA1c; dose of loop diuretics and β-blocker, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, calcium channel blocker, tolvaptan, or statin use]. The resultant probabilities were then transformed into propensity score logits. Propensity score matching was performed for the spironolactone or eplerenone groups with one-to-one caliper matching using a caliper width equal to 20% of the standard deviation of the logit of the calculated propensity score [12]. SPSS version 24 for Windows (SPSS Inc., Chicago, IL, USA) was used to perform the propensity score matching.

Subgroup analyses

In exploratory hypothesis-generating analyses, we compared the impacts of spironolactone and eplerenone on the primary outcome in predefined subgroups of sex, age, de novo HF, hypertension, ischemic etiology, NYHA functional class (I or II vs. III or IV), HF with reduced versus preserved ejection fraction, serum potassium and BNP concentrations, eGFR, and use of key HF medications before the primary outcome events. Using multivariate Cox regression models in the propensity-matched cohort, we tested the impact of an interaction between

spironolactone and eplerenone and each of the aforementioned subgroup strata on the primary outcome.

Statistical analysis

The results are expressed as number (%) or mean ± standard deviation as appropriate. Unpaired and paired Student *t* tests were conducted for normally distributed data, while skewed data were tested using nonparametric tests. Categorical data were compared using the Chi-square test or Fisher's exact test as appropriate. The risk of reaching a clinical endpoint was determined using Cox proportional hazard models. We also used the Kaplan–Meier analysis to determine the effects of spironolactone or eplerenone administration on the primary and secondary endpoints. The primary comparison between the two groups used a log-rank test. Adverse events leading to permanent study drug withdrawal were tabulated and analyzed using Fisher's exact test. p values < 0.05 were considered statistically significant. All analyses were performed with SPSS version 24 for Windows (SPSS Inc.).

Results

Baseline characteristics

Among the 838 patients, 41 were excluded: 13 who had undergone hemodialysis and 28 who died in-hospital. Thus, the analysis included 797 patients. The median follow-up period was 505 days, while the maximum follow-up period was 1232 days. During a median follow-up of 505 days, there were 137 (17.2%) deaths and 264 (33.5%) cardiovascular deaths or hospitalization events. Among them, 475 patients (59.6%) were treated with an aldosterone receptor antagonist at discharge. Eligible patients according to class I indication of the ACCF/AHA guideline were 188 of 797 patients (23.6%); of them, 124 (66.0%) were treated with either aldosterone receptor antagonist in practice. The breakdown by medications was spironolactone in 366 (45.9%) and eplerenone in 109 (13.7%). The mean dose of each aldosterone receptor antagonist was 28 ± 10 mg for spironolactone and 34 ± 15 mg for eplerenone. In the spironolactone group, most patients (86%) took spironolactone 25 mg. In the eplerenone group, most took 25 mg (69%), while 29% took 50 mg.

Table 1 shows the patients' baseline characteristics according to aldosterone receptor antagonist use. Patients who used an aldosterone receptor antagonist tended to: be younger; have a higher body mass index and eGFR; have a lower LVEF and lower serum hemoglobin and sodium levels; be more likely to have been treated with a β-blocker, angiotensin-converting enzyme inhibitor, or angiotensin II receptor blocker; and receive higher doses of loop diuretics. The rate of the primary endpoint, death of cardiovascular causes or hospitalization for cardiovascular events was lower in patients treated with aldosterone receptor antagonists than those not treated with them in the overall, HFrEF, and HFpEF cohorts (log-rank test; $p = 0.004$, 0.031, and 0.026, respectively) (Fig. 1a). The rate of the secondary endpoint, all-cause mortality, was lower in patients treated with aldosterone receptor antagonists than in those not treated with them in the overall cohort only (log-rank $p = 0.048$) (Fig. 1b).

The patient characteristics according to aldosterone receptor antagonist type used are summarized in Table 2. Notably, the prevalence of new-onset HF and dose of loop diuretics were higher; the mean sodium concentration of the spironolactone group was lower than that of the eplerenone group. Hospitalization duration did not differ significantly between the spironolactone and eplerenone groups (16 ± 8 days vs. 17 ± 7 days, $p = 0.671$). The rates of cardiovascular death, hospitalization, and all-cause mortality were similar between the spironolactone and eplerenone groups (Fig. 2a). Eplerenone use was not associated with a statistically significant increase in the likelihood of cardiovascular death or hospitalization [32.1% vs. 28.1%; hazard ratio (HR), 1.049; 95% confidence interval (CI), 0.706–1.524; $p = 0.806$] or all-cause mortality (11.0% vs. 11.7%; HR, 0.803; 95% CI, 0.438–1.384; $p = 0.443$) compared with spironolactone use (Table 3).

Propensity score-matched cohort

Ninety patients in the spironolactone group could be propensity score matched to the patients in the eplerenone group, resulting in a propensity-matched cohort of 180 patients (90 each in the spironolactone and eplerenone groups). After matching, there was no significant difference in the mean propensity score between the matched groups ($p = 0.401$) and the balance between the study groups improved markedly since none of the baseline characteristics differed significantly (Table 2). The mean dose was 27 ± 8 mg in the spironolactone group and 34 ± 15 mg in the eplerenone group. In the propensity-matched cohort, there were 22 (12.2%) deaths and 52 (28.9%) cardiovascular deaths or hospitalization events during follow-up. The rates of cardiovascular death and hospitalization and all-cause mortality were similar between the groups (Fig. 2b). Eplerenone use was not associated with a statistically significant increase in the likelihood of cardiovascular death or hospitalization (30.0% vs. 27.8%; HR, 1.016; 95% CI, 0.567–1.764; $p = 0.956$) or all-cause mortality (13.3% vs. 11.1%; HR, 1.106; 95% CI, 0.477–2.621; $p = 0.814$) compared with spironolactone use (Table 3).

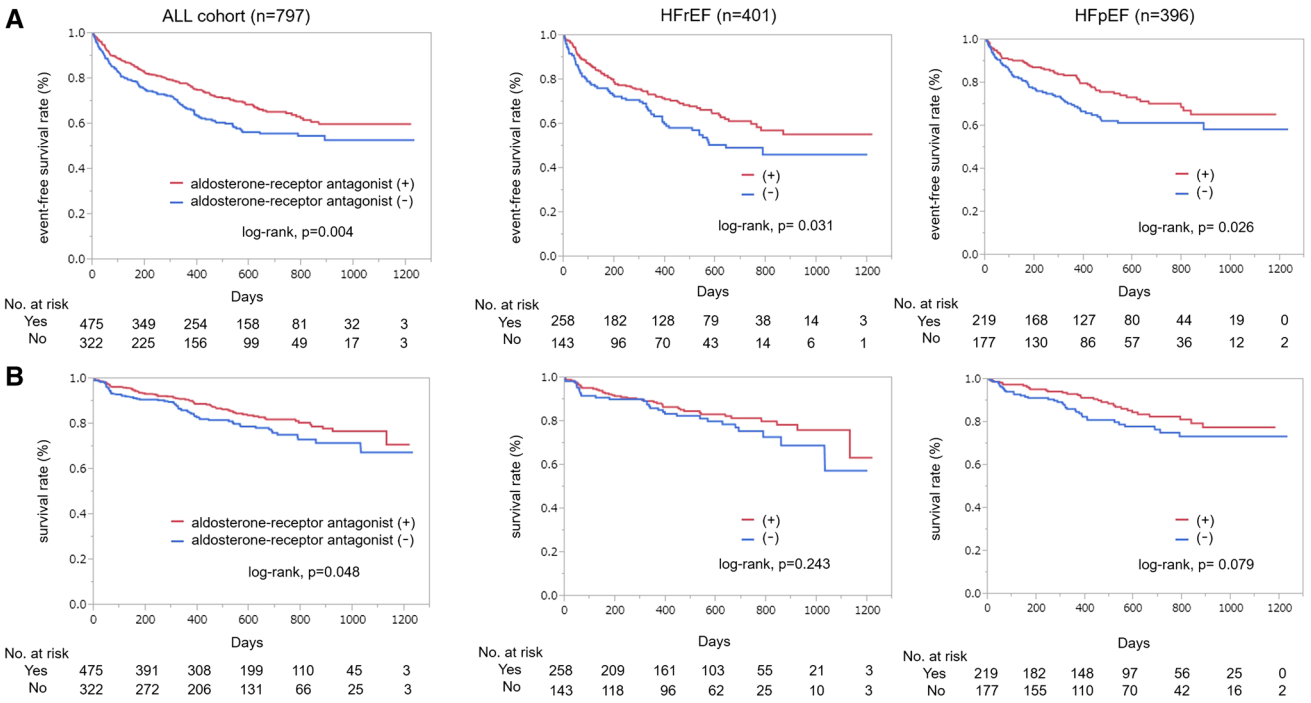

Fig. 1 Kaplan–Meier survival curves by use of aldosterone receptor antagonists. Composite of cardiovascular death and hospitalization (**a**) and all-cause mortality (**b**)

Adverse events and discontinuation of study drug

During the study, 22 patients (24%) receiving spironolactone and 15 patients (17%) receiving eplerenone discontinued the study drug in the propensity matching cohort ($p = 0.135$) (Table 4). Four patients (4%) discontinued the study drug because of improved HF in each group. In the spironolactone group, the major reason for discontinuation was hyperkalemia (15 patients, 17%). Two patients (2%) discontinued spironolactone because of gynecomastia and changed to eplerenone. In the eplerenone group, nine patients (10%) discontinued because of hyperkalemia. The prevalence of severe hyperkalemia ($p = 0.549$) and renal failure ($p = 0.402$) did not differ between the two groups. Mean serum potassium level at discontinuation was 6.0 ± 0.6 mEq/L in the spironolactone group and 5.8 ± 0.6 mEq/L in the eplerenone group. Gynecomastia was not observed in the eplerenone group, and its prevalence was significantly higher in the spironolactone group ($p = 0.018$).

Subgroup analysis

We performed a subgroup analysis of the propensity-matched cohort according to the status at hospital discharge (Fig. 3). There were no significant interactions between the aldosterone receptor antagonists in any of the subgroups. Notably, there was a trend toward a significant interaction between aldosterone receptor antagonist selection and sex (interaction $p = 0.076$) in that eplerenone was associated with a lower hazard of better outcomes in female patients, whereas the association was weaker in male patients.

Longitudinal change in clinical parameters

In patients among the propensity-matched cohort who underwent a 1-year follow-up examination, we assessed temporal changes in echocardiographic and other clinical parameters (Table 5). We included 52 patients in the spironolactone group and 72 in the eplerenone group who underwent follow-up examinations. In the echocardiography examinations, significant improvement of LVEF (spironolactone, 43 ± 15 to 51 ± 13%; eplerenone, 46 ± 16 to 50 ± 17%) and decreased LV end-diastolic volume (spironolactone, 116 ± 53 to 103 ± 49; eplerenone, 142 ± 75 to 118 ± 68 ml) and left atrial volume index (spironolactone, 48 ± 29 to 39 ± 30; eplerenone, 55 ± 43 to 44 ± 24 mL/m^2) were observed in both groups during follow-up. Mean systolic blood pressure was significantly elevated in both groups (spironolactone, 113 ± 20 to 129 ± 28 mmHg; eplerenone, 116 ± 21 to 128 ± 29 mmHg). On the other hand, significant changes in intraventricular septum, BNP level, and serum potassium level were not observed in either group. No significant difference in any parameter was seen between the spironolactone and eplerenone groups.

Table 2 Baseline patient characteristics by aldosterone-receptor antagonist type

Variable	Before propensity matching ($n=475$)			After propensity matching ($n=180$)		
	Spironolactone ($n=366$)	Eplerenone ($n=109$)	p value	Spironolactone ($n=90$)	Eplerenone ($n=90$)	p value
Propensity score logit	−0.93 ± 0.05	−0.98 ± 0.10	0.640	−1.07 ± 0.09	−0.97 ± 0.09	0.401
Sociodemographic characteristic						
Age	70 ± 14	71 ± 10	0.337	71 ± 14	71 ± 11	0.944
Sex (male)	224 (61)	73 (67)	0.272	54 (60)	61 (68)	0.277
De novo hospitalization	288 (79)	75 (69)	0.037	63 (70)	64 (71)	0.870
Clinical characteristic						
NYHA class III or IV	37 (10)	14 (13)	0.427	13 (14)	11 (12)	0.661
Systolic blood pressure (mmHg)	145 ± 40	148 ± 34	0.495	147 ± 39	148 ± 33	0.862
Heart rate (bpm)	71 ± 16	71 ± 15	0.607	72 ± 18	70 ± 13	0.378
Body mass index (kg/m^2)	22.5 ± 4.1	23.2 ± 4.7	0.142	23.6 ± 4.1	22.9 ± 4.7	0.355
LVEF (%)	44 ± 15	45 ± 16	0.645	46 ± 15	45 ± 16	0.757
Comorbidity						
Ischemic etiology	126 (34)	44 (40)	0.259	56 (62)	56 (62)	1.000
Hypertension	192 (52)	65 (60)	0.186	52 (60)	50 (56)	0.546
Diabetes	161 (44)	53 (49)	0.370	47 (52)	43 (48)	0.551
Atrial fibrillation	110 (30)	43 (39)	0.069	35 (39)	34 (38)	0.878
Smoking	193 (53)	66 (61)	0.149	50 (56)	53 (59)	0.651
Biochemical						
BNP (pg/mL)	398 ± 462	381 ± 482	0.745	404 ± 530	385 ± 489	0.804
Hemoglobin (g/dL)	12.5 ± 2.4	12.7 ± 2.1	0.333	13.0 ± 2.3	12.8 ± 2.1	0.484
Serum sodium (mEq/L)	138.6 ± 3.5	139.4 ± 3.5	0.033	139.6 ± 2.8	139.6 ± 3.1	0.978
Serum potassium (mEq/L)	4.4 ± 0.5	4.4 ± 0.5	0.364	4.4 ± 0.5	4.3 ± 0.5	0.888
eGFR (mL/min/1.73 m^2)	53 ± 22	53 ± 21	0.876	56 ± 20	55 ± 21	0.833
HbA1c (%)	6.3 ± 1.1	6.4 ± 1.0	0.737	6.6 ± 1.3	6.4 ± 1.0	0.387
Medical treatment						
β-Blocker use	282 (77)	87 (80)	0.539	74 (82)	72 (80)	0.703
ACEI/ARB use	259 (71)	82 (75)	0.359	69 (77)	65 (72)	0.494
Loop diuretics use	332 (91)	85 (80)	<0.001	81 (90)	73 (81)	0.088
Loop diuretics (mg)	29 ± 19	23 ± 12	0.007	27 ± 14	23 ± 12	0.079
Tolvaptan use	28 (8)	13 (12)	0.178	9 (10)	8 (9)	0.799
CCB use	86 (24)	22 (20)	0.464	27 (30)	17 (19)	0.083
Statin use	126 (34)	41 (38)	0.542	35 (39)	34 (38)	0.878

Data are expressed as mean ± SD or as n (%)

LVEF left ventricular ejection fraction, *eGFR* estimated glomerular filtration rate, *BNP* B-type natriuretic peptide, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker

Discussion

To our knowledge, the present study is first to compare the impacts of the aldosterone receptor antagonists spironolactone and eplerenone on cardiovascular outcomes and safety in patients with HF. The results of our study showed that spironolactone and eplerenone have similar prognostic impacts and effects on major clinical parameters such as LVEF, BNP level, and systolic blood pressure, except, it was possible that eplerenone was associated with a lower hazard of a better outcome in female patients.

The main purpose of this study was to compare the impacts of spironolactone and eplerenone on cardiovascular outcomes, and patients with various backgrounds were included for comparisons among many subgroups. The administration rate of aldosterone receptor antagonists in patients according to the class I indication of the ACCF/AHA guideline was approximately two-thirds in this study, and the rate was quite higher than that reported in a previous study (32.5%) [13.] Although some clinical backgrounds differed between patients with or without aldosterone receptor antagonist use, the rates of primary and secondary endpoints

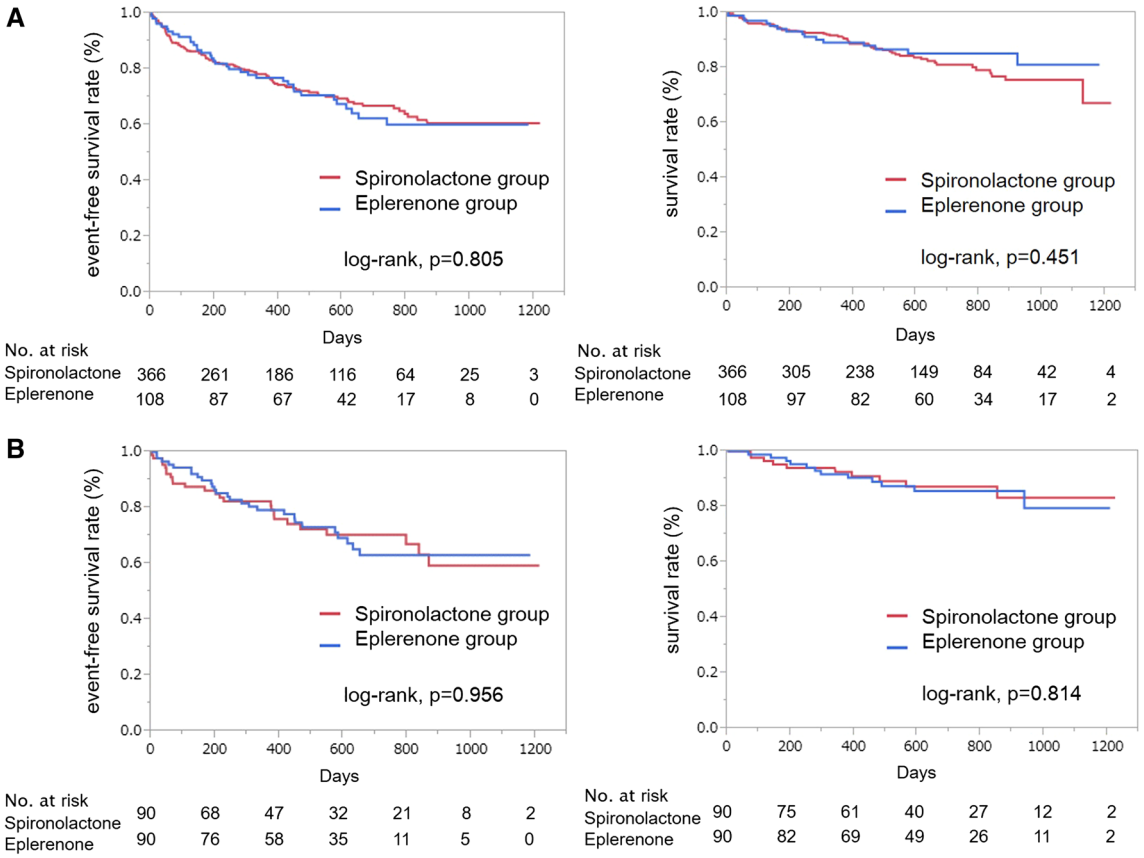

Fig. 2 Kaplan–Meier survival curves by aldosterone receptor antagonist type. Before propensity-matched cohort (**a**) and after propensity-matched cohort (**b**)

Table 3 Impact of aldosterone-receptor antagonist on clinical outcomes

	Event rates			Cox proportional hazard model	
	Total	Spironolactone	Eplerenone	HR (95% CI) vs. spironolactone	*p* value
Entire cohort ($n=475$)					
Cardiovascular death and hospitalization	138/475 (29.1)	103/366 (28.1)	35/109 (32.1)	1.049 (0.706–1.524)	0.806
All-cause mortality	55/475 (11.6)	43/366 (11.7)	12/109 (11.0)	0.803 (0.438–1.384)	0.443
Propensity-matched cohort ($n=180$)					
Cardiovascular death and hospitalization	52/180 (28.9)	25/90 (27.8)	27/90 (30.0)	1.016 (0.567–1.764)	0.956
All-cause mortality	22/180 (12.2)	10/90 (11.1)	12/90 (13.3)	1.106 (0.477–2.621)	0.814

HR hazard ratio, *CI* confidence interval

achieved in patients treated with an aldosterone receptor antagonist were lower than those of patients who were not treated with an aldosterone receptor antagonist. Thus, in this study, most patients received HF guideline-recommended aldosterone receptor antagonist therapy, which showed an effective influence on prognosis regardless of LVEF.

The landmark studies of aldosterone receptor antagonists were the Randomized Aldactone Evaluation Study (RALES) for spironolactone and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study for eplerenone (EPHESUS) for eplerenone, which targeted patients with HFrEF [3, 4]. In those studies, while the mortality rate was reduced by 30% with spironolactone and 15% with eplerenone, EPHESUS included patients with greater use of β-blockers and a higher baseline LVEF. Additionally, since EPHESUS targeted patients with myocardial infarction, there were some differences in the clinical backgrounds between the two studies. Therefore, we could not simply compare the results of EPHESUS and RALES. The present study compared spironolactone and eplerenone in patients

Table 4 Adverse events in after propensity matching cohort

	Spironolactone ($n=90$)	Eplerenone ($n=90$)	p value
Total adverse events	24 (27)	15 (17)	0.102
Gynecomastia in man or breast pain	4 (4)	0 (0)	0.018
Severe hyperkalemia (> 6 mEq/ml)	7 (8)	5 (6)	0.549
Total discontinuation	26 (29)	19 (21)	0.228
Discontinuation because of adverse event	22 (24)	15 (17)	0.135
Hyperkalemia	15 (17)	9 (10)	0.186
Hypotension	0 (0)	2 (2)	0.095
Renal failure	4 (4)	2 (2)	0.402
Gynecomastia in man or breast pain	2 (2)	0 (0)	0.095
Other	1 (1)	2 (2)	0.557
Discontinuation because of improved heart failure	4 (4)	4 (4)	1.00

Data are expressed as n (%)

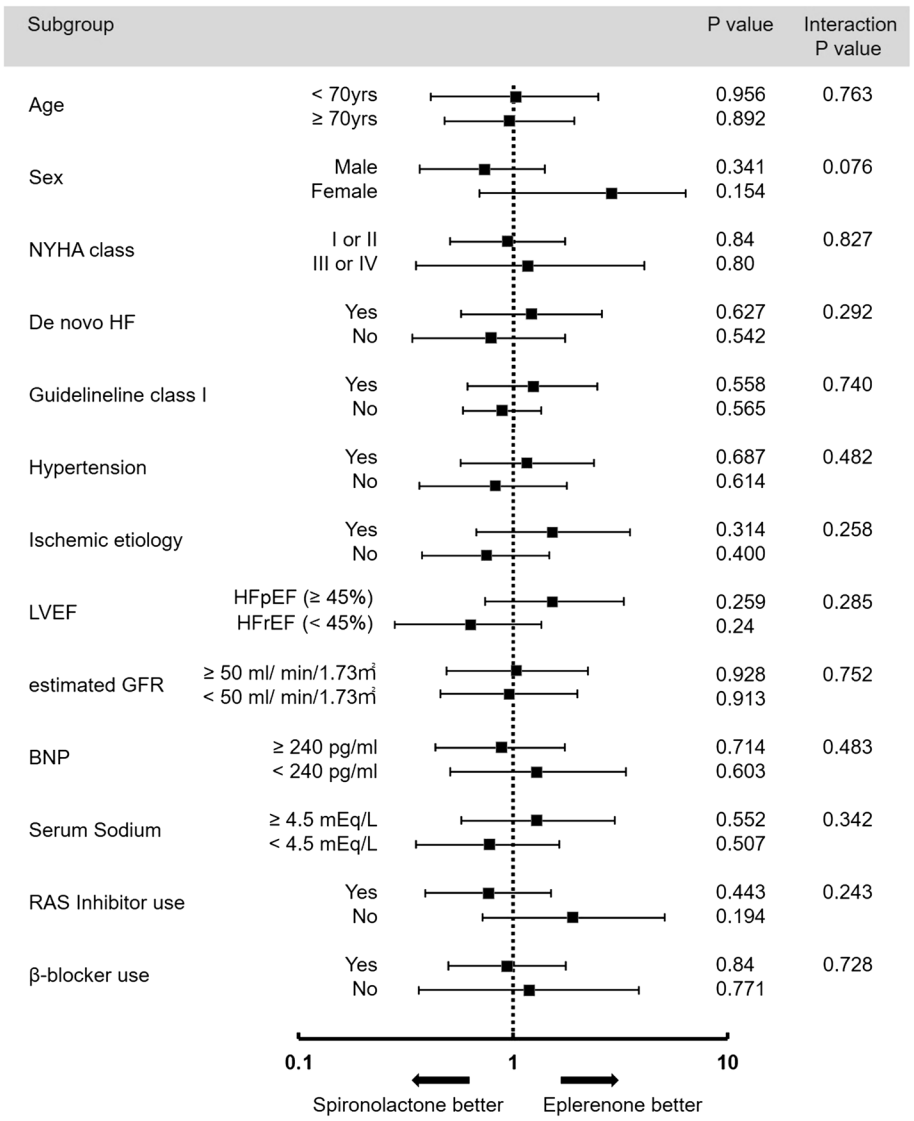

Fig. 3 Impact of aldosterone receptor antagonists on cardiovascular death and hospitalization by propensity-matched cohort subgroup

Table 5 Serial change in clinical parameters

	Spironolactone ($n=52$)			Eplerenone ($n=72$)			p value vs. change in spironolactone
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	
LV end-diastolic volume (mL)	116 ± 53	103 ± 49*	− 13 ± 28	142 ± 75	118 ± 68*	− 25 ± 39	0.126
LV ejection fraction (%)	43 ± 15	51 ± 13*	6 ± 14	46 ± 16	50 ± 17*	5 ± 12	0.765
Intraventricular septum thickness (mm)	9.3 ± 2.9	9.6 ± 2.4	0.3 ± 1.3	10.7 ± 2.5	10.5 ± 2.5	− 0.2 ± 1.6	0.127
Left atrial volume index (mL/m^2)	48 ± 29	39 ± 30*	− 9 ± 25	55 ± 43	44 ± 24*	− 11 ± 23	0.619
Systolic blood pressure (mmHg)	113 ± 20	129 ± 28*	16 ± 26	116 ± 21	128 ± 29*	12 ± 24	0.462
BNP (pg/mL)	475 ± 530	311 ± 352	− 163 ± 644	398 ± 489	342 ± 913	− 55 ± 58	0.372
eGFR (mL/min/1.73 m^2)	54 ± 20	48 ± 19*	− 6 ± 16	56 ± 21	50 ± 19*	− 6 ± 16	0.846
Serum Potassium (mEq/L)	4.4 ± 0.5	4.5 ± 0.6	0.0 ± 0.6	4.3 ± 0.7	4.4 ± 0.5	0.1 ± 0.5	0.510

Data are presented as mean ± SD

LV left ventricular, *BNP* B-type natriuretic peptide, *eGFR* estimated glomerular filtration rate

*$p < 0.05$ vs baseline

with the same clinical background and demonstrated that the effect of aldosterone receptor antagonist type on the primary outcome was consistent across the subgroups except for a trend that eplerenone was associated with a lower hazard of better outcomes in female patients, although the association was weaker in male patients. Although the underlying mechanism is unclear, it might reflect the low affinity of eplerenone for progesterone and androgen receptors compared with spironolactone. We cannot draw a conclusion from this finding based on the present study because of the small sample size.

Our preliminary data about the temporal change in clinical parameters showed that a significant decrease in LV end-diastolic volume and LA volume index and improvement in LVEF was observed in both groups. However, there are few reports about the effects of aldosterone receptor antagonists on cardiac function in human studies. In the present study, no significant decrease in BNP level was observed; however, significant reverse remodeling of LV was similarly observed in both groups. These results indicate that both drugs not only improved patient prognosis, but cardiac function similarly in HFrEF.

Some clinical trials have raised the possibility that aldosterone receptor antagonist use improves mortality and/or morbidity in patients with HFpEF, but the better prognostic impact of aldosterone receptor antagonists for HFpEF is not as clear as that of a β-blocker or ACE inhibitor in the treatment of HFpEF [10, 13–15]. The TOPCAT trial, which evaluated the effect of spironolactone on prognosis in HFpEF, has demonstrated that in the Americas, the rates of the primary outcome, cardiovascular death, and hospitalization for HF were significantly reduced by spironolactone [16]. Although the aim of the present study was not to evaluate the effect of aldosterone receptor antagonists on prognosis in HFpEF group, our preliminary subgroup analysis showed no difference in the effect of spironolactone and eplerenone on prognosis in HFpEF group. Previous studies reported BNP level, age, systolic blood pressure, renal function, and left atrial function as prognostic factors in HFpEF [17–19]. Increased left atrial pressure due to the elevation of LV and arterial stiffness is the main pathophysiological feature that distinguishes it from HFrEF. The present study demonstrated similar impacts of spironolactone and eplerenone on blood pressure, atrial size, LV wall thickness, and renal function, all of which were reported as prognostic factors for HFpEF. These facts strengthen the conclusion that the impacts of the two agents on prognosis were similar; however, additional data about the prognostic impact of aldosterone receptor antagonists, especially eplerenone, is needed.

Regarding the safety of aldosterone receptor antagonists, the persistent rate excluding discontinuation because of improved HF was 76% in the spironolactone group and 83% in the eplerenone group. These results are quite similar to those of reports in which the persistent rate was 74% in RALES and 85% in EMPHASIS. The major risk associated with aldosterone receptor antagonist use is hyperkalemia due to the inhibition of potassium excretion, ranging from 2–5% in large clinical trials [3–5] to 24–36% in population-based registries [20–22]. In the present study, the discontinuation rate because of hyperkalemia was 13%, much lower than that reported in previous population-based registries. The mean eGFR of this study population was 53 mL/min/1.73 m^2, and most of our patients had chronic kidney disease. This study demonstrated the safety of aldosterone-receptor antagonist use when carefully monitored, even in subgroups at relatively high risk of developing hyperkalemia. Gynecomastia was observed only in the spironolactone group. Among the four patients who had gynecomastia, two could continue using spironolactone and only two changed to eplerenone. In a subgroup analysis of sex, no better prognostic value of eplerenone compared with spironolactone was observed in male patients. These facts indicated that there is no need to avoid using spironolactone

to avoid gynecomastia in male patients. Discontinuation due to hypotension was observed in only two patients of the eplerenone group. There was no significant difference in the change of blood pressure between the eplerenone and spironolactone groups in the follow-up data. However, much evidence about the antihypertensive effect of eplerenone has been established [23–26]. Therefore, eplerenone should be used carefully in HF patients with low blood pressure. On the other hand, further studies are needed to determine whether eplerenone is more preferable than spironolactone in HF patients with hypertension.

Study limitations

Our study has some potential limitations. First, although aldosterone receptor antagonists use was not withdrawn from most patients in a short period of time, some patients withdrew its use in the chronic phase and crossover from spironolactone to eplerenone was observed in two patients due to gynecomastia. Second, this was not a randomized controlled study in which we used propensity score matching to adjust for parameters between the two groups, and the sample size after propensity score matching was relatively small. Since 24 variables were used for the propensity score matching, matching between the two groups was considered optimal. However, potential bias cannot be entirely excluded. To resolve this issue, a randomized clinical study targeting a large number of patients with HF is necessary.

Conclusions

The present study concluded that eplerenone and spironolactone have similar impacts on cardiovascular outcomes and safety among patients with HF. However, a large randomized clinical study will be needed in the future to decide the proper selection of each aldosterone receptor antagonist in individual patient.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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