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Association of renin-angiotensin system inhibitors with long-term outcomes in patients with systolic heart failure and moderate-to-severe kidney function impairment

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ABSTRACT

Purpose: Although guidelines recommend that patients with heart failure with reduced ejection fraction (HFrEF) should be treated with renin-angiotensin system (RAS) inhibitors, the long-term efficacy of RAS inhibitors in HFrEF patients with moderate-to-severe chronic kidney disease (CKD) remains unclear.

Methods: The present study included consecutive patients hospitalized for acute heart failure across five Japanese teaching hospitals. The impact of RAS inhibitors on 2-year all-cause mortality was evaluated in patients with an ejection fraction ≤40% and CKD, defined as an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2, at discharge. Its severity was subclassified from 3B to 5 according to eGFR.

Results: Overall, 553 patients (age, 76 ± 11 years; 68% male) were included. RAS inhibitors were prescribed more frequently in 227 patients with stage 3B (71.2%) than in 107 patients with stage 4 or 5 CKD (45.7%). All-cause mortality was recorded in 119 patients (23.4%) (55 [18.5%] patients with stage 3B; 64 [30.3%] patients with stage 4 or 5 CKD), within the median follow-up period of 609 (220–983) days. After many-to-one propensity score matching (87 pairs in stage 3; 60 pairs in stage 4 or 5 CKD), those with RAS inhibitors had reduced mortality rate in stage 3B (hazard ratio [HR], 0.39; 95% confidence interval [CI], 0.19–0.83) but not in stage 4 or 5 CKD (HR, 1.08; 95% CI, 0.57–2.03).

Conclusions: In HFrEF patients with CKD, RAS inhibitors are associated with reduction in mortality in stage 3B CKD, but the association is less clear in stage 4 or 5 CKD.

1. Introduction

The renin angiotensin system (RAS) blockade with angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor-II blockers (ARB) plays a pivotal role in contemporary therapies for heart failure with reduced ejection fraction (HFrEF) [1]. RAS inhibitors are concurrently effective in slowing the disease progression of chronic kidney disease (CKD), regardless of etiology [2]. These agents have also been prescribed extensively worldwide; they were prescribed in approximately 80% of heart failure cases in Spain in 2000 [3].

However, despite beneficial anti-proteinuric effects observed in patients with severely impaired kidney function, there remains a concern that RAS inhibitors may accelerate CKD stage progression [4]: withdrawal of these inhibitors in older patients with advanced CKD led to an improved estimated glomerular filtration rate (eGFR) after 12 months [5]. RAS inhibitors may therefore be harmful in patients with severely impaired kidney function. In addition, the long-term efficacy of RAS inhibitors in HFrEF patients with concomitant advanced CKD (i.e. stage 3B, 4, or 5 CKD) remains unclear [6,7].

The 2016 ESC Guidelines for diagnosis and treatment of acute and chronic heart failure referred to a gap in evidence regarding the efficacy of RAS inhibitors in severely impaired kidney function cases, especially wherein the eGFR is < 30 mL/min/1.73 m^2 [8]. Accordingly, the present study was designed to investigate whether the use of RAS

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inhibitors has an association with long-term clinical benefits to patients with HFrEF and concomitant moderate-to-severe CKD.

2. Methods

2.1. Ethical statement

This study protocol conforms to the 1975 Declaration of Helsinki and is in line with the Ethical Guidelines for Epidemiological Research established by the Japanese government. The study was approved by the ethics committee at each institution and registered on the University Medical Information Network (UMIN 000001171). Written or oral informed consent was obtained from each subject before the study.

2.2. Study population

The design of the West Tokyo Heart Failure (WET-HF) registry has been previously reported [9]. Briefly, WET-HF is a large, prospective, multicenter registry designed to collect data on the clinical characteristics and outcomes of patients hospitalized for acute heart failure (AHF). The clinical diagnosis of heart failure was made by cardiologists with a special interest in heart failure at each institution. A diagnosis of AHF is defined as rapid-onset heart failure or a change in the signs and symptoms of heart failure requiring urgent therapy and hospitalization, based on the Framingham criteria [10]. Consecutive AHF patients across five academic hospitals were registered from 2006 to 2017.

The present study included AHF patients with an ejection fraction (EF) of ≤40% and an eGFR at discharge of < 45 mL/min/1.73 m^2, equivalent to CKD stages 3B, 4, or 5. Ultrasound cardiography was evaluated by highly experienced cardiologists or clinical technologists during hospitalization. EF was calculated by the modified Simpson's method. The CKD stage was determined according to eGFR, which was calculated using the following formula for Japanese patients: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ (× 0.739 if female). Stage 3B CKD was defined as an eGFR < 45 mL/min/1.73 m^2 and ≥ 30 mL/min/1.73 m^2, stage 4 CKD was defined as an eGFR < 30 mL/min/1.73 m^2 and ≥ 15 mL/min/1.73 m^2, and stage 5 CKD was defined as an eGFR < 15 mL/min/1.73 m^2. Patients who developed acute coronary syndrome or had undergone dialysis at the time of discharge were excluded.

2.3. Data collection

Data on patient background (including age, sex, body mass index, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation/flutter, chronic obstructive pulmonary disease, past history of stroke and transient ischemic attack, vital signs, New York Heart Association (NYHA) classification, an etiology of AHF, laboratory data, medication, and device therapy) and outcomes (including all-cause, cardiac, and non-cardiac mortality) were collected by medical doctors and well-trained clinical research personnel. All deaths were reviewed and then categorized into cardiac or non-cardiac death. Central committee members (S·K., Y·S., T.K., Y.N., A.M., A.G., and T.Y.) reviewed the abstracted records and determined the mode of death. Oral medication for HF (including diuretics, RAS inhibitors including angiotensin-converting enzyme inhibitors [ACEI] and angiotensin II receptor blockers [ARB], beta-blockers, mineralocorticoid receptor antagonists [MRA], antihypertensives, vasoactive/inotropic agents, or other cardiovascular medications) was extracted at the time of discharge. It should be noted that angiotensin receptor-neprilysin inhibitors were not approved for clinical use in Japan during the study period.

The data were entered into an electronic data-capturing system, which has a robust data query engine and system validations for data quality. Exclusive on-site auditing by the investigators (Y.S. and S.K.) ensured proper registration of each patient.

2.4. Endpoint

The primary endpoint was all-cause mortality after discharge. The WET-HF registry is supported by a central study committee that adjudicates all death events.

2.5. Statistical analysis

Numerical data are presented as mean ± standard deviation (SD) if the data followed a normal distribution. Otherwise, data are displayed as median and interquartile range (Q1–Q3) values. Categorical variables are expressed as absolute numbers or percentages. Continuous variables were analyzed using unpaired Student's *t*-tests or Mann–Whitney *U* tests, while the chi-squared (χ^2) test was used for categorical variables. The cumulative incidence of long-term outcomes was assessed using Kaplan-Meier statistics. The risk of mortality was assessed using Cox regression analysis and expressed as hazard ratio (HR), 95% confidence interval (CI), and *P* value. Variables with a *p*-value < .10 in univariate analyses were retained for multivariate logistic regression analysis with least absolute shrinkage and selection operator.

Propensity score (PS) matching was used to assess the comparability of the treated (i.e., patients prescribed RAS inhibitors) and untreated (i.e., patients not prescribed RAS inhibitors) groups with respect to potential confounding factors. Variables used for the PS were decided using a logit model. Variables with a *P* value < .10 and/or that are known to be possible confounding factors associated with prognosis were selected. Clinical variables at the time of discharge used to generate the PS included the following: age [10]; gender [11]; etiology of heart failure (ischemic or non-ischemic); NYHA classification; body mass index (BMI); systolic blood pressure; heart rate; history of diabetes mellitus, chronic obstructive pulmonary disease [12], atrial fibrillation/flutter [13], and stroke; hemoglobin, albumin, and sodium levels; EF; prescription of beta blockers, loop diuretics [14], MRAs [8], and tolvaptan; and history of implantable cardioverter defibrillator/cardiac resynchronization therapy [15,16]. Continuous variables were classified into 3 groups divided by tertiles. Many-to-one matching was conducted within a caliper width of 0.25 multiplied by the SD of the PS. Cross-terms and doublets of variables were calculated if necessary for appropriate matching. Balance between the two groups was assessed by standardized difference, variance ratio, and PS distribution. The non-parametric bootstrap method, resampling with replacement 1000 times on the matched dataset, was conducted to provide inner validation.

Statistical significance was defined as *P* < .05. All statistical analyses were carried out using Stata version 14 (Stata Corp; College Station, TX, USA) and R version 3.4.3 (R Foundation for Statistical Computing; Vienna, Austria).

3. Results

3.1. Patient characteristics

A total of 3634 AHF patients were registered, of whom 2224 were excluded because their EF was > 40% or because they had a history of hemodialysis. Another 857 patients with an eGFR ≥ 45 mL/min/1.73 m^2 were also excluded. Finally, the present study included 553 patients with an EF ≤ 40% and eGFR < 45 mL/min/1.73 m^2 (mean age, 76 ± 11 years; 68% male). Patient characteristics before and after PS matching are shown in Table 1. Higher age, a higher prevalence of an NYHA classification of ≥III, and a lower value of hemoglobin and albumin levels were noted in stage 4 or 5 than that in stage 3B CKD patients, whereas the EF was similar. Concerning guideline-directed medical therapies, there were obvious differences between the groups; RAS inhibitors were more frequently prescribed in the patients with stage 3B CKD (227 [71%]) than those with stage 4 or 5 CKD (107 [46%]) (*P* < .001), as was the rate of MRA prescription (stage 3B, 153

Table 1
Patients characteristics.

	ALL			Stage 3B						Stage 4 or 5					
				Before PS match			After PS match			Before PS match			After PS match		
	RAS inhibitors	No RAS inhibitors	p value	RAS inhibitors	No RAS inhibitors	p value	RAS inhibitors	No RAS inhibitors	p value	RAS inhibitors	No RAS inhibitors	p value	RAS inhibitors	No RAS inhibitors	p value
	n = 334	*n* = 219		*n* = 227	*n* = 92		n = 87	*n* = 87		*n* = 107	*n* = 127		*n* = 60	n = 60	
Age, years	76 ± 11	77 ± 11	0.220	75 ± 11	78 ± 9	0.050	76 ± 11	76 ± 10	0.693	77 ± 11	76 ± 12	0.616	77 ± 10	78 ± 13	0.193
Male, n (%)	225 (67)	150 (68)	0.781	148 (65)	64 (70)	0.454	57 (66)	54 (62)	0.636	77 (72)	86 (68)	0.482	41 (68)	40 (67)	0.845
Body mass index, kg/m^2	22 ± 4	20 ± 3	< 0.001	22 ± 4	20 ± 3	< 0.001	22 ± 4	21 ± 3	0.247	21 ± 4	21 ± 3	0.333	22 ± 4	20 ± 3	0.108
Hypertension, n (%)	244 (74)	151 (70)	0.292	168 (75)	58 (64)	0.044	67 (77)	45 (52)	< 0.001	76 (71)	93 (74)	0.482	43 (72)	46 (77)	0.532
Dyslipidemia, n (%)	149 (46)	102 (47)	0.779	103 (47)	40 (43)	0.613	36 (41)	35 (40)	0.877	46 (43)	62 (49)	0.377	25 (42)	35 (58)	0.068
Diabetes mellitus, n (%)	142 (43)	106 (48)	0.183	88 (39)	44 (48)	0.145	38 (44)	35 (40)	0.645	54 (50)	62 (49)	0.802	36 (60)	34 (57)	0.711
Atrial fibrillation/flutter, n (%)	156 (47)	92 (42)	0.277	115 (51)	46 (50)	0.915	42 (48)	47 (54)	0.448	41 (38)	46 (32)	0.741	23 (38)	24 (40)	0.852
COPD, n (%)	22 (7)	9 (4)	0.211	18 (8)	3 (3)	0.096	5 (6)	2 (2)	0.247	4 (4)	6 (5)	0.485	2 (3)	1 (2)	0.500
Past history of stroke/TIA	58 (17)	40 (18)	0.792	39 (17)	17 (19)	0.433	15 (17)	12 (14)	0.530	19 (18)	23 (18)	0.568	10 (17)	11 (18)	0.500
Blood pressure at discharge, mmHg	107 ± 17	113 ± 19	< 0.001	109 ± 17	110 ± 18	0.721	109 ± 16	107 ± 17	0.116	104 ± 18	115 ± 20	< 0.001	105 ± 19	111 ± 16	0.023
Heart rate at discharge, bpm	70 ± 12	74 ± 14	0.006	70 ± 12	73 ± 13	0.114	69 ± 12	70 ± 10	0.298	70 ± 12	74 ± 15	0.060	72 ± 12	71 ± 13	0.871
NYHA classification at discharge			0.029			0.030			0.622			0.437			0.533
I	23 (7)	27 (12)		16 (7)	11 (12)		5 (6)	8 (9)		7 (7)	16 (13)		4 (7)	5 (8)	
II	227 (69)	125 (58)		163 (73)	53 (58)		63 (72)	63 (72)		64 (62)	72 (57)		36 (60)	38 (63)	
III	72 (22)	61 (28)		41 (18)	27 (30)		19 (22)	16 (18)		31 (30)	34 (27)		18 (30)	17 (28)	
IV	5 (2)	4 (2)		3 (1)	0 (0)		0 (0)	0 (0)		2 (2)	4 (3)		2 (3)	0 (0)	
≥ III	84 (25)	67 (31)	0.160	48 (21)	28 (30)	0.078	10 (22)	16 (18)	0.570	36 (34)	39 (31)	0.632	20 (33)	17 (28)	0.553
Ischemic heart disease	148 (44)	96 (44)	0.912	95 (42)	42 (46)	0.534	30 (34)	33 (38)	0.636	53 (50)	54 (43)	0.283	30 (50)	19 (32)	0.041
Laboratory data															
Sodium, mmol/L	138 ± 4	138 ± 4	0.978	139 ± 3	138 ± 4	0.251	139 ± 3	139 ± 3	0.654	137 ± 4	138 ± 4	0.041	137 ± 4	139 ± 3	0.007
Potassium, mmol/L	4.5 ± 0.5	4.4 ± 0.5	0.062	4.4 (4.1–4.7)	4.3 (4–4.6)	0.140	4.4 (4.1–4.7)	4.4 (4.2–4.6)	0.525	4.5 (4.2–4.8)	4.4 (4.0–4.8)	0.124	4.5 (4.2–4.9)	4.5(4.2–4.8)	0.634
Creatinine, μmol/L	141 ± 71	177 ± 97	< 0.001	1.3 ± 0.2	1.3 ± 0.2	0.902	1.3 ± 0.2	1.3 ± 0.3	0.898	2.3 ± 1.0	2.5 ± 1.1	0.068	2.2 ± 1.0	2.4 ± 0.9	0.031
eGFR, mL/min/1.73m^2	33 ± 8	28 ± 10	< 0.001	38 ± 4	38 ± 4	0.908	37 ± 4	38 ± 4	0.741	23 ± 6	21 ± 6	0.045	23 ± 5	21 ± 6	0.070
Hemoglobin, g/L	119 ± 21	114 ± 18	0.012	122 ± 21	118 ± 19	0.144	122 ± 17	127 ± 20	0.109	112 ± 18	111 ± 16	0.916	111 ± 16	111 ± 19	0.987
Albumin, g/L	35 ± 5	33 ± 6	0.003	35 ± 5	34 ± 5	0.051	36 ± 4	36 ± 5	0.956	34 ± 5	33 ± 6	0.218	34 ± 5	35 ± 4	0.559
Ejection fraction (%)	30 ± 7	29 ± 7	0.989	30 ± 7	29 ± 8	0.259	29 ± 7	30 ± 8	0.414	29 ± 7	30 ± 7	0.360	30 ± 7	30 ± 7	0.921
Medication															
MRA, n (%)	154 (46)	75 (34)	0.005	113 (50)	40 (43)	0.291	40 (46)	44 (51)	0.544	41 (39)	35 (28)	0.071	23 (38)	7 (12)	0.001
Beta blocker, n (%)	288 (86)	175 (80)	0.063	201 (89)	68 (75)	0.002	78 (90)	79 (91)	0.798	87 (81)	107 (84)	0.551	49 (82)	51 (85)	0.624
Furosemide, n (%)	274 (82)	177 (81)	0.664	182 (80)	66 (72)	0.101	67 (77)	62 (71)	0.387	92 (87)	111 (87)	0.890	55 (92)	54 (90)	0.752
Tolvaptan, (%)	22 (7)	22 (11)	0.148	15 (8)	8 (10)	0.573	10 (11)	10 (11)	1.000	7 (7)	14 (12)	0.187	1 (2)	1 (2)	1.000
Device															
ICD, n (%)	27 (8)	26 (12)	0.092	13 (6)	14 (15)	0.007	7 (8)	6 (7)	0.773	14 (13)	12 (9)	0.378	9 (15)	9 (15)	1.000
CRT, n (%)	18 (5)	11 (5)	0.507	10 (4)	6 (7)	0.299	4 (5)	3 (3)	0.700	8 (7)	5 (4)	0.239	5 (8)	2 (3)	0.243
ICD/CRT, n (%)	35 (10)	29 (13)	0.195	18 (8)	15 (16)	0.026	9 (10)	8 (9)	0.798	17 (16)	14 (11)	0.274	11 (18)	9 (15)	0.624

CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronization therapy; eGFR: estimated glomerular filtration rate; ICD: implantable cardioverter defibrillator. MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; PS: propensity score; RAS: renin-angiotensin system; TIA: transient ischemic attack.

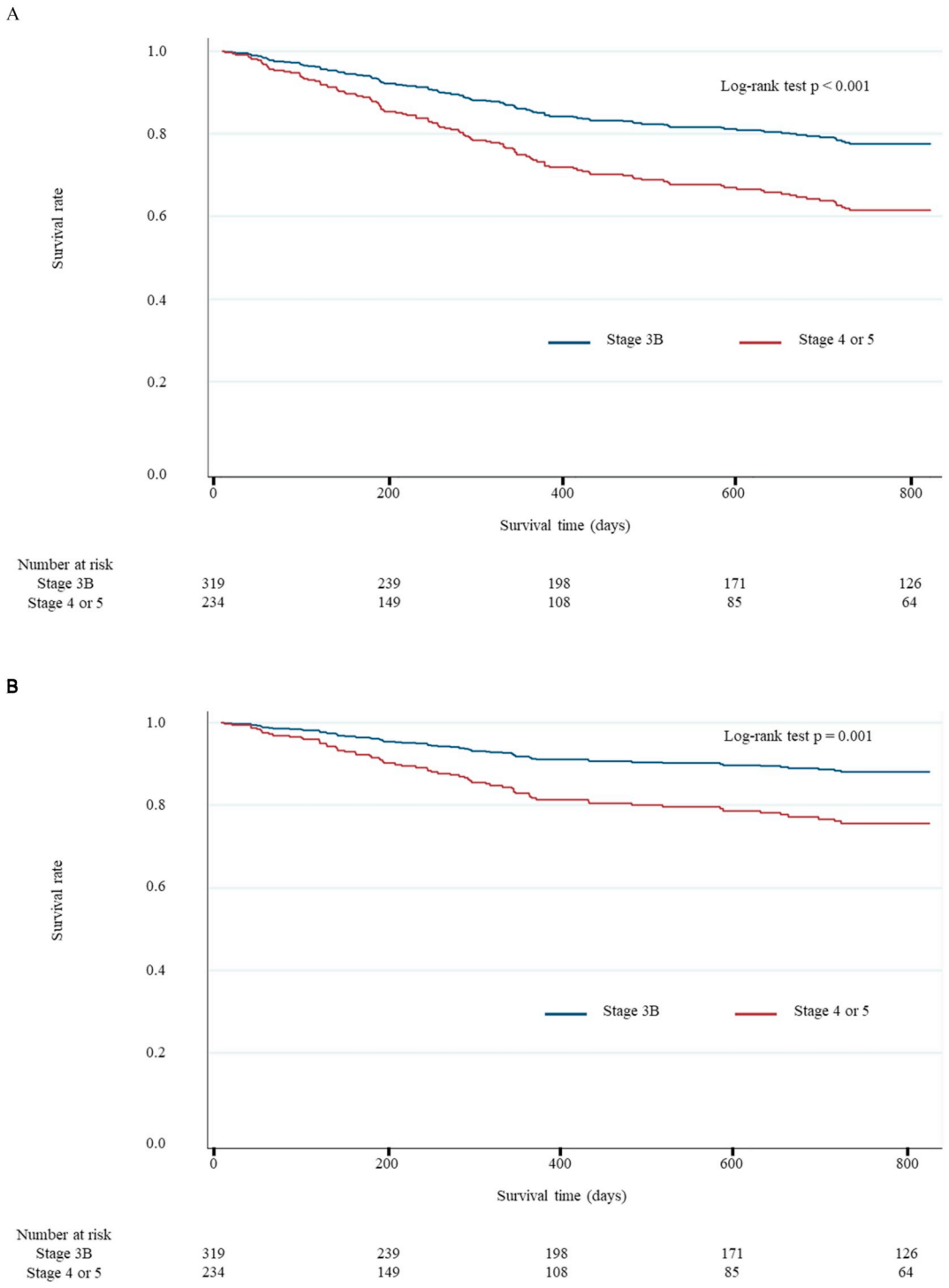

Fig. 1. Association between long-term mortality and the CKD stage.
A: All-cause mortality was higher in the stage 4 or 5 CKD. B: Cardiac death was also higher in the stage 4 or 5 CKD. CKD: chronic kidney disease.

[48%] patients; stage 4 or 5, 76 [33%] patients; $P < .001$). In contrast, beta blockers were commonly prescribed in > 80% of the patients regardless of the CKD stage. The combination of ACE-I and ARB prescriptions was observed in 6 of all the patients.

3.2. Long-term outcomes

The median follow-up duration was 609 days (interquartile range, 220–983 days). All-cause death at 2 year occurred in 119 (23.4%) patients and was frequently observed in stage 4 or 5 CKD patients (64 [30.3%] patients) rather than in stage 3B CKD patients (55 [18.5%] patients) ($P = .002$). In addition, the rate of cardiac death after discharge was higher in patients with stage 4 or 5 CKD (38 [18.0%]) than in those with stage 3B CKD (28 [9.4%] ($p = .004$) (Fig. 1A and B).

Regarding clinical variables associated with all-cause mortality, older age, higher NYHA classification, greater serum creatinine levels, and tolvaptan prescription were the predictors of increased post-discharge mortality. Conversely, higher BMI, systolic blood pressure, serum sodium, hemoglobin, and albumin levels, as well as RAS inhibitor and beta blocker prescription, were inversely associated with

Table 2
Analysis of risk factors for 2-year all-cause mortality.

Variables	HR (95% CI)	p value
Age, years (Increase of 1 year)	1.06 (1.04–1.08)	< 0.001
Male	1.08 (0.73–1.59)	0.699
Body mass index, kg/m^2 (Increase of 1 kg/m^2)	0.90 (0.85–0.95)	< 0.001
Systolic blood pressure, mmHg (Increase of 10 mmHg)	0.87 (0.78–0.97)	0.011
NYHA	2.12 (1.52–2.96)	< 0.001
NYHA II (vs NYHA I)	1.15 (0.50–2.67)	0.737
NYHA III or IV (vs NYHA I)	2.79 (1.19–6.50)	0.018
Sodium, mmol/L (Increase of 1 mmol/L)	0.92 (0.88–0.96)	< 0.001
Potassium, mmol/L (Increase of 1 mmol/L)	1.31 (0.93–1.86)	0.125
Creatinine, μmol/L (Increase of 50 μmol/L)	1.12 (1.01–1.24)	< 0.001
Hemoglobin, g/L (Increase of 10 g/L)	0.77 (0.70–0.86)	< 0.001
Albumin, g/L (Increase of 10 g/L)	0.65 (0.47–0.90)	0.009
Ejection fraction (%) (Increase of 5%)	0.89 (0.79–1.01)	0.081
RAS inhibitors	0.59 (0.41–0.85)	< 0.001
MRA	0.78 (0.54–1.13)	0.186
Beta blocker	0.46 (0.30–0.70)	< 0.001
Furosemide	1.22 (0.74–2.01)	0.44
Statin	0.81 (0.56–1.18)	0.279
Tolvaptan	2.37 (1.37–4.11)	0.002
Aspirin	1.11 (0.77–1.59)	0.567
Anticoagulation	1.31 (0.91–1.89)	0.144

CI: confidence interval; HR: hazard ratio; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; RAS: renin-angiotensin system.

mortality (Table 2). Univariate Cox regression analysis demonstrated that RAS inhibitors were associated with lower all-cause mortality in patients with stage 3B CKD (HR, 0.32; 95% CI, 0.19–0.54; $p < .001$), but not in patients with stage 4 or 5 CKD (HR, 1.37, 95% CI, 0.84–2.25; $p = .212$) (Table 3). After adjustment for age, systolic blood pressure, NYHA classification, sodium and hemoglobin levels, EF, and prescription of beta blocker, the result persisted in patients with stage 3B CKD (HR, 0.38; 95% CI, 0.21–0.69; $p = .002$).

After PS matching, a Cox regression model demonstrated that RAS inhibitors were associated with a reduced all-cardiac mortality in patients with stage 3B CKD (HR, 0.39; 95% CI, 0.19–0.83; $P = .015$), but not in those with stage 4 or 5 CKD (HR, 1.08; 95% CI, 0.57–2.03; $P = .820$). Notably, RAS inhibitors were significantly related to a reduced non-cardiac mortality (HR, 0.35; 95% CI, 0.12–0.99; $p = .50$) in those with stage 3B CKD (Table 3). The bootstrap method provided similar results. Kaplan-Meier curves depicting the effect of RAS inhibitors on all-cause mortality are shown in Fig. 2A and B.

3.3. Variables related to the prescription of RAS inhibitors

A 10-mL/min/1.73 m^2 increase in eGFR at discharge was related to a 1.78-fold increase in the rate of RAS inhibitor prescription (95% CI, 1.47–2.16; $P < .001$). This relationship is demonstrated in a cubic spline curve (Fig. 3A). Conversely, there was no relationship between RAS inhibitor prescription rate and serum potassium level (Fig. 3B).

4. Discussion

The present study demonstrated that RAS inhibitors were associated with reduced all-cause mortality after discharge in HFrEF patients with stage 3B CKD, while their impact was not apparent in those with stage 4 or 5 CKD. The insufficient prescription rate was also revealed in those with stage 3B CKD. Accordingly, promoting the prescription of RAS may contribute to improved long-term prognosis. Conversely, the positive relationship was obscure in a subset of patients with severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2), although current clinical practice guidelines strongly recommend that patients with HFrEF be treated with RAS inhibitors. Our findings may contribute to fill a gap in evidence regarding the efficacy of RAS inhibitors in patients with severely impaired kidney function.

Table 3
The clinical impact of RAS inhibitor on 2-year all-cause mortality.

	All-cause mortality				Cardiac mortality				Non-cardiac mortality			
	Before PS match		After PS match		Before PS match		After PS match		Before PS match		After PS match	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
All the patients ($n = 553$)	0.59 (0.41–0.85)	0.005	NA	NA	0.60 (0.38–0.92)	0.021	NA	NA	0.63 (0.37–1.09)	0.100	NA	NA
CKD 3B ($n = 319$)	0.32 (0.19–0.54)	< 0.001	0.39 (0.19–0.83)	0.015	0.27 (0.14–0.51)	< 0.001	0.89 (0.37–2.15)	0.801	0.47 (0.22–1.04)	0.062	0.35 (0.12–0.99)	0.050
CKD 4 or 5 ($n = 234$)	1.37 (0.84–2.25)	0.212	1.08 (0.57–2.03)	0.820	1.63 (0.88–3.00)	0.118	0.49 (0.61–3.04)	0.459	1.07 (0.50–2.31)	0.862	0.70 (0.27–1.82)	0.468

CI: confidence interval; CKD: chronic kidney disease; HR: hazard ratio; NA: not applicable; PS: propensity score; RAS: renin-angiotensin system.

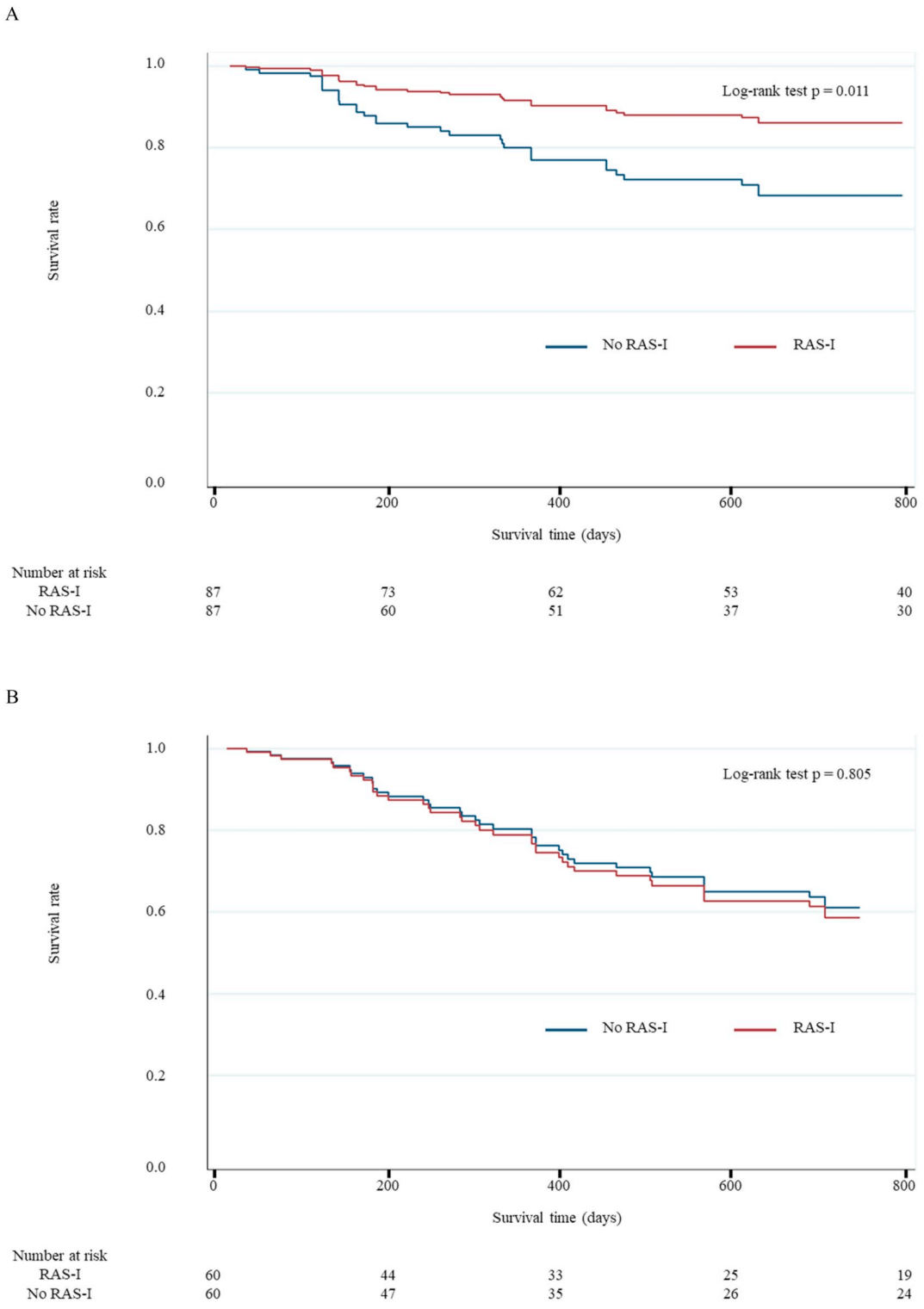

Fig. 2. Impact of RAS inhibitors on 2-year mortality at each CKD stage.
A: RAS inhibitors were associated with better prognosis in stage 3B CKD. B: Patients with stage 4 or 5 CKD appeared to receive no benefit from RAS inhibitors. CKD: chronic kidney disease; RAS: renin-angiotensin system.

4.1. RAS inhibitor and CKD stage

Our study demonstrated that RAS inhibitors may still be the cornerstone of therapies for heart failure even in patients with concomitant moderate renal dysfunction (e.g., CKD stage 3B [eGFR 30–45 mL/min/1.73 m^2]). Conversely, our results regarding stage 4 or 5 CKD are in conflict with those of previous reports. This contradiction might be attributable to the different analysis methods and event rates. For example, Ahmed et al. reported that RAS inhibitors were associated with a significant modest reduction in all-cause mortality in patients with an eGFR < 45 mL/min/1.73 m^2 [17]. It should be noted that Ahmed et al. did not differentiate patients with stage 3B CKD from stage 4 or 5 CKD patients, and did not demonstrate differences in the effect of RAS inhibitors between different CKD stages; hence, the positive effects of RAS

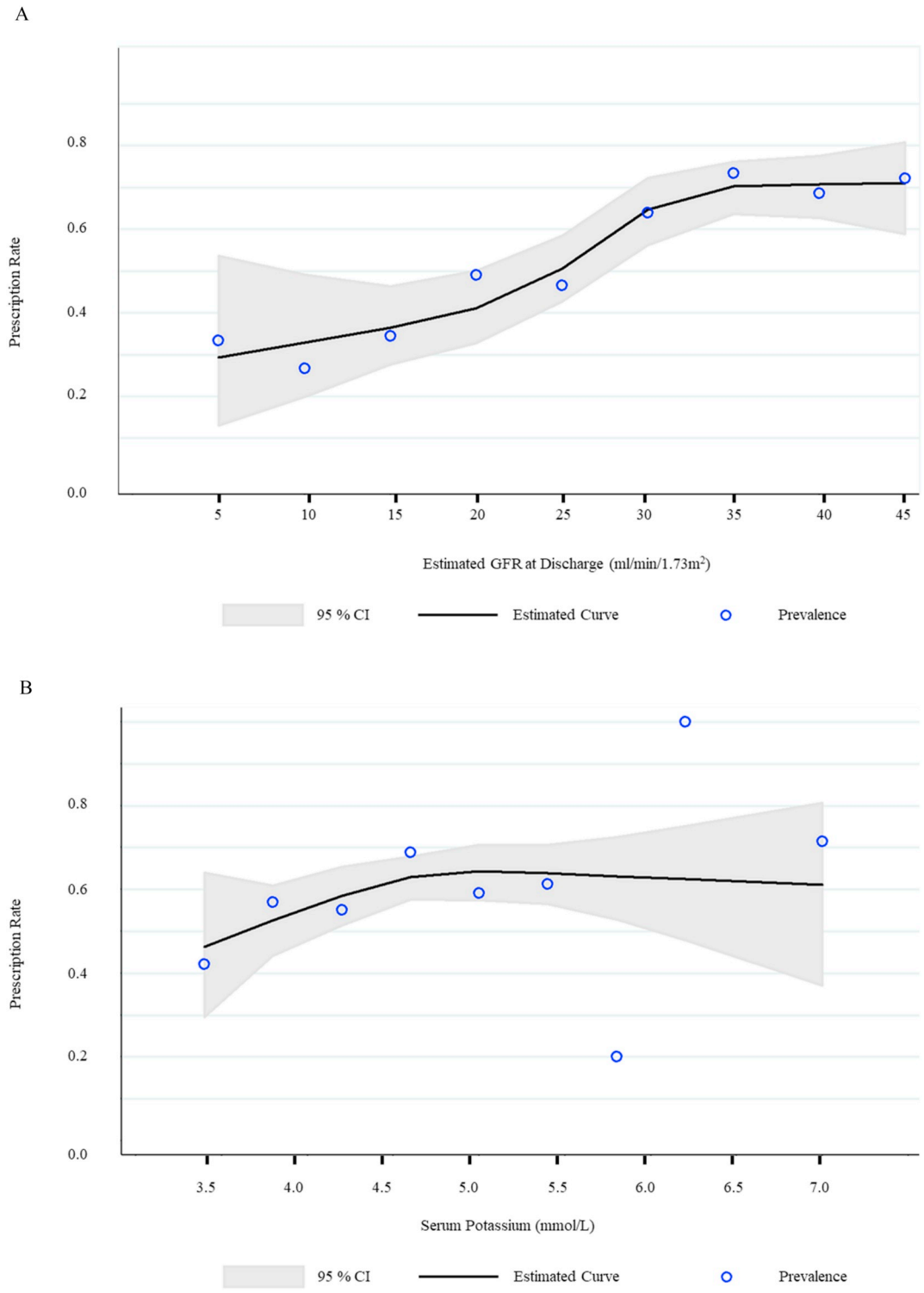

Fig. 3. Cubic spline curve representing the rate of RAS inhibitor prescription. A: Patients with a higher eGFR took RAS inhibitors more frequently. B: There was no relationship between RAS inhibitor prescription rate and serum potassium levels. CI: confidence interval; eGFR: estimated glomerular filtration rate; RAS: renin-angiotensin system.

inhibitors in stage 3B CKD patients might have masked a negative effect in stage 4 or 5 CKD patients.

More recently, Edner et al. found a positive effect of RAS inhibitors on all-cause mortality in patients with stage 4 or 5 CKD [18]. It should be noted that 1-year mortality rates significantly differed between Edner et al.'s study (treated, 39%; untreated, 58%) and ours (treated, 22%; untreated, 17%; data not shown), which might have led to the inconsistency in the long-term outcome. In addition, the applied dose of RAS inhibitors should be considered. Previously, the administration of < 50% of the recommended dose was reported to be associated with a greater risk of mortality than that with the administration of ≥100% of the recommended dose [19]. In Asian populations, a higher dose of the agents was related to lower mortality [20]. It was also noted that the prevalence of the prescription of 50% or more of the recommended

dose was much lower in Japan when compared with that in the other countries [21].

As for evaluating the effects of RAS inhibitors in advanced non-hemodialysis patients [22], there is some speculation as to why this nullification may occur. The impact of RAS inhibitors would be minimal in patients with stage 4 or 5 CKD, as they would develop severe glomerular sclerotic changes that would not improve by inhibition of the RAS. Moreover, tubulo-interstitial damage in the advanced stages of CKD would not be influenced by RAS inhibitors [5,23]. Thus, since the continuation of these agents in advanced CKD patients seemed not to improve eGFR, the long-term reduction of eGFR in severe CKD might have outweighed the positive effects of RAS inhibitors on cardiac function, including the prevention of dilatation, remodeling, and heart failure [24,25]. It should be noted that discontinuation of RAS inhibitors has been shown to delay the onset of renal replacement therapy [5].

4.2. Recommendations for the treatment of complicated AHF patients

The higher prevalence of comorbidities in an aging population complicates the process of devising a treatment strategy for heart failure in older patients. Current clinical knowledge is not sufficient for the management of AHF patients with comorbidities. The prevalence of moderate-to-severe kidney impairment was > 30% in our cohort. The clinical features concerning the modest numbers of AHF patients with CKD should be elucidated to improve their prognosis. We believe that our study provides some important knowledge and implications regarding better prognosis in such patients. However, a randomized controlled study would be needed to confirm the clinical efficacy of RAS inhibitors in terms of the prognosis of AHF patients with stage 3B, 4, or 5 CKD, in the future.

Along with the possible attenuated efficacy of RAS inhibitors in advanced CKD patients, some comorbidities such as frailty [26], sarcopenia [27], and malignancy [28] may also limit their efficacy. Furthermore, such comorbidities could lead to a decrease in the rate of drug prescription; for example, reduced eGFR was associated with a lower rate of RAS inhibitor prescription in the present study. We believe the first step in devising a treatment plan in patients with these conditions is to confirm that conventional evidence-based strategies, including pharmacological and device therapy, have been optimally provided. Treatment strategies should then be individualized in accordance with the other clinical conditions present. Palliative care, which focuses on improving patient quality of life, should also be provided.

4.3. Limitations

Despite the insights provided by the present study, it does have some limitations. First, the rate of MRA prescription was not matched sufficiently in patients with stage 4 or 5 CKD. However, despite its more frequent prescription in patients taking RAS inhibitors, mortality was similar between those who were administered MRA and those who were not. Thus, it is unlikely that different rates of MRA prescription would have masked a possible positive effect of RAS inhibitors in stage 4 or 5 CKD patients. Moreover, univariate Cox regression analysis demonstrated no association between MRA and long-term mortality in our dataset. Second, the interruption rate of RAS inhibitor administration was unknown. It is possible that higher CKD stages were associated with a higher prevalence of discontinuation, which may have resulted in an apparent reduction in drug efficacy. Down-titration might similarly occur in higher CKD stages. Third, our cohort did not include information regarding urinalysis as well as the other previous AHF registries. An important clinically-relevant factor with the use of RAS inhibitors is the level of protein in patients' urine. While RAS inhibitors do not appear to be more beneficial than other hypertensive drugs in patients with non-proteinuric CKD [29], this may not be the case in proteinuric CKD. Finally, the number of patients with HFrEF and CKD stage ≤3B was small. The result regarding RAS inhibitor inefficacy in stage 4 or 5 CKD patients may therefore have been due to beta error. However, a similar result derived from the bootstrap method reinforced the reliability of this finding.

5. Conclusions

In HFrEF patients with CKD, RAS inhibitors are associated with lower mortality in stage 3B CKD; however, the association is less clear in patients with stage 4 or 5 CKD. These findings may have important implications regarding the prognosis in these high-risk patients. Further studies including randomized clinical trials are needed to clarify this association in patients with complicated backgrounds.

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