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Efficacy of Renin-angiotensin-aldosterone-system inhibitors for heart failure with preserved ejection fraction and left ventricular hypertrophy
-from the KUNIUMI Registry Acute Cohort-

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Abstract

Background: Heterogeneity of heart failure (HF) with preserved ejection fraction (HFpEF) would contribute to the difficulty in identifying effective treatments, and interest in the phenogrouping of HFpEF as a potential means for predicting patients who respond to cardioprotective drugs has been increasing.

Methods: We studied 468 first-hospitalized HFpEF patients among 1971 acute-hospitalized HF patients from KUNIUMI Registry Acute Cohort. The primary endpoint was defined as HF-rehospitalization and cardiovascular death over a median follow-up period of 508 days.

Results: In HFpEF patients with left ventricular hypertrophy (LVH), patients prescribed renin-angiotensin-aldosterone-system (RAAS) inhibitors had similar outcomes compared to those without (HR, 0.77; 95% CI 0.51-1.16; P=0.21), and the outcome was also similar between patients with and without RAAS inhibitors prescription in HFpEF patients without LVH. Moreover, in HFpEF patients with LVH and mild-moderate chronic kidney disease (CKD), which was determined as an estimated glomerular filtration rate (eGFR) of 30-60 mL/min/1.73 m^2, patients prescribed RAAS inhibitors had significantly favorable outcomes compared to those without (HR 0.39; 95% CI 0.19-0.80; P=0.01). In HFpEF patients with LVH and severe CKD, which was defined as eGFR < 30 mL/min/1.73 m^2, the outcome was similar between patients with and without RAAS inhibitor prescription. Multivariable Cox regression analysis showed that the prescription of RAAS inhibitors was the only independent predictor of outcome in HFpEF patients with LVH and mild-moderate CKD (HR 0.49; 95% CI 0.25–0.94; P=0.03).

Conclusions: Our findings showed the importance of HFpEF phenogrouping for identifying effective pharmacological treatments.

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for approximately one-half of the prevalence of HF and is increasing in prevalence[1-3]. HFpEF is associated with excess mortality and similar morbidity following HF hospitalization for HF with a reduced ejection fraction[4, 5]. The major cause of poor outcome in HFpEF patients is that there is no proven pharmacological therapy to improve patient survival. It is well known that HFpEF is a heterogeneous disease, and a variety of clinical risk factors and abnormal left ventricular (LV) structures have been identified[6-8]. Since heterogeneity contributes to the difficulty in identifying effective treatments for HFpEF as well as disease complexity, interest in phenogrouping HFpEF as a potential means for predicting patients who respond to cardioprotective drugs has been increasing.

LV hypertrophy (LVH) is a targeted response to chronic arterial hypertension and other cardiovascular disorders and an independent risk factor for various types of HF, arrhythmias, including sudden cardiac death, stroke, and other major cardiovascular morbidity and mortality[9-13]_ENREF_4. Moreover, LVH is a common structural abnormality of HFpEF and is independently predictive of incident HF hospitalization or cardiovascular death[14]. The renin-angiotensin-aldosterone system (RAAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs), did not reduce the incidence of the primary endpoint in their prospective interventional studies on HFpEF[15-17]. However, large-scale observational studies and meta-analyses have indicated that RAAS inhibitors reduce HF hospitalization in patients with HFpEF [18]. Furthermore, a meta-analysis showed that RAAS inhibitors reduced LV mass in patients with essential hypertension[19], but the effect of RAAS inhibitors on HFpEF patients with LVH is unclear. Since the effectiveness of RAAS inhibitors for phenogrouping of HFpEF patients to predict outcomes has remained uncertain, we investigated the impact of RAAS inhibitors on outcomes in HFpEF patients with LVH from the Kobe University Heart Failure Registry in Awaji Medical Center (KUNIUMI) Registry acute cohort.

Materials and Methods

Study population

This study is a part of the KUNIUMI Registry acute cohort, which is a population-based registry of acute HF in Awaji Island in Japan and has been described previously[20]. Briefly, Awaji Island is one of the largest isolated islands in Japan and also has one of the most aging populations in the country, and it has a low migration rate with a relatively stable population. Therefore, higher-quality incidence and follow-up data in this study can be compared with previous registry data. This study was approved by the ethics committee of Awaji Medical Center (No. 20-11) and was conducted in accordance with the Declaration of Helsinki.

Study Population and Eligibility Criteria

In this study, a total of 1971 consecutive hospitalized HF patients who met the Framingham criteria[21] on Awaji Island between April 2013 and March 2020 were retrospectively enrolled (Figure 1). Among 1500 hospitalized HF patients after exclusion of 471 patients with recurrent hospitalization, we excluded 591 patients with HFrEF or HF with mildly reduced ejection fraction (HFmrEF), 274 with insufficient echo data, and 90 with an in-hospital death; thus, 545 hospitalized HFpEF patients were finally enrolled. In-hospital care and post-discharge care for HF were based on the method of attending physicians, including senior cardiologists. Echocardiography was performed using commercially available ultrasound systems. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the European Association of Cardiovascular Imaging[22]. All echocardiographic examinations were performed by senior echocardiologists or sonographers. HF phenotypes such as HFrEF, HFmrEF, and HFpEF were determined in accordance with the current European Society of Cardiology guidelines[23]. Patients who were prescribed RAAS inhibitors were defined as time point at discharge.

Comorbidities in this study were defined as follows. Hypertension was defined as >140 mmHg systolic or >90 mmHg diastolic blood pressure or being treated with anti-hypertensive drugs. Diabetes mellitus was defined as HbA1c > 6.5% or fasting glucose >126mg/dL, with or without the use of anti-diabetic drugs. Atrial fibrillation was defined as an irregular rhythm with a fluctuating baseline and no discernible P waves by means of 12-lead electrocardiogram. Ischemic heart disease was defined as previous history of percutaneous coronary intervention, coronary artery bypass grafting, or presence of myocardial ischemia by means of stress testing. Valvular heart disease was defined as more than moderate mitral or aortic valve disease by means of transthoracic echocardiography. Lung disease was defined as previous history of chronic obstructive pulmonary disease or bronchial asthma.

Definition of LVH

LV mass was estimated using the formula proposed by Devereux et al., and LV mass index (LVMI) was calculated for each subject by dividing LV mass by body surface area[24]. LVH was defined as LVMI >95 g/m^2 for females and >115 g/m^2 for males according to current guidelines of the European Association of Cardiovascular Imaging [22].

Definition of Primary Endpoint

The primary endpoint was defined as HF rehospitalization and cardiovascular death after discharge over a median follow-up period of 508 days (435-569 days).

Statistical Analysis

Continuous variables were expressed as mean values with standard deviation for normally distributed data and as medians with interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of the two subgroups were compared using Student's t-test or Mann–Whitney U test according to data distribution. Proportional differences were evaluated using Fisher's exact test. Survival curves of freedom from all-cause death and HF rehospitalization were determined using the Kaplan-Meier

method, and cumulative event rates were compared using the log-rank test. The associations of parameters with cardiovascular death were identified using a Cox proportional hazards model in univariate and multivariable analyses. Variables with a univariate value of $P < 0.05$ were incorporated into the stepwise selection. For all steps, a P value of <0.05 was considered statistically significant. All analyses were performed using a commercially available software (MedCalc software version 19.0.7; MedCalc Software, Mariakerke, Belgium).

Results

Patient Characteristics

The baseline characteristics of the patients with HFpEF are summarized in Table 1. Among 591 hospitalized patients with HFpEF, 63 were excluded due to insufficient patient data, and 14 were also excluded due to lost follow-up (Figure 1). Therefore, a total of 468 hospitalized patients with HFpEF were included in this study. The mean age was 81.5 ± 10 y, and 244 patients (52%) were female. Seventeen patients (3.6%) were New York Heart Association class II, 110 (23.5%) were class III, and 341 (75.8%) were class IV.

Impact of LVH on Patients with HFpEF

Two-hundred and seventy-four patients (58.5%) were classified as patients with LVH, and the remaining 194 (41.5%) were classified as those without LVH. A comparison of the baseline characteristics of HFpEF patients with and without LVH is shown in Table 1. Patients with LVH were more likely to be female (58.4% vs 43.3%, P<0.01), have higher prevalence of hypertension (73.4% vs. 63.9%, P=0.03), have more than moderate valvular disease (46.4% vs 33.0%, P=0.04), use ACE-Is or ARBs (71.5% vs 60.8%, P=0.02) and higher blood urea nitrogen (29.2±16.7 mg/dL vs. 25.2±18.5 mg/dL, P=0.02), have higher creatinine (1.6±1.5 mg/dL vs 1.2±0.9 mg/dL, P<0.01), have larger size (LV end-diastolic dimension: 47.9±7.2 mm vs. 42.2±6.5 mm, P<0.01, LV end-systolic dimension: 31.8±6.4 mm vs. 27.8±5.7 mm, P<0.01) and larger left atrial dimension

(44.7±8.5 mm vs 41.7±7.9 mm, P<0.01), and have lower prevalence of atrial fibrillation (53.6% vs 62.9%, P=0.04), lower LVEF (58.3±6.0 % vs 59.4%±5.7, P=0.03), lower hemoglobin (10.9±2.0 mg/dL vs. 11.6±2.0 mg/dL, P<0.01), and lower estimated glomerular filtration rate (eGFR; 44.2±24.5 mL/min/1.73 m^2 vs 53.5±22.8 mL/min/1.73 m^2).

Of the 468 hospitalized patients with HFpEF, the primary endpoint occurred in 179 (38%) during a median follow-up period of 508 days. As expected, HFpEF patients with LVH had significantly unfavorable outcomes compared to those without LVH, as shown in Figure 2 (hazard ratio [HR], 1.49; 95% confidence interval [CI], 1.11-2.00; P<0.01).

Efficacy of RAAS Inhibitors in HFpEF Patients with LVH

One hundred ninety-six patients with HFpEF and LVH (71.5%) were prescribed RAAS inhibitors, such as angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, whereas 118 (60.8%) HFpEF patients without LVH were prescribed RAAS inhibitors. Figure 3 shows that in HFpEF patients with LVH, those who were prescribed RAAS inhibitors had similar outcome compared to those without RAAS inhibitors (HR, 0.77; 95% CI, 0.51–1.16; P=0.21). In addition, the outcome was similar between patients with and without the prescription of RAAS inhibitors in HFpEF patients without LVH as shown in Figure 4 (HR, 1.28; 95% CI, 0.76–2.17; P=0.35). In contrast, outcome in HFpEF patients with LVH with RAAS inhibitor prescription was similar compared to that in HFpEF patients without LVH with RAAS inhibitor prescription (HR, 1.27; 95% CI 0.89-1.28; P=0.18; Supplementary file 1). Table 2 shows the association of RAAS inhibitors with each endpoint in all HFpEF patients, HFpEF patients with LVH and HFpEF patients without LVH.

Next, we evaluated the impact of RAAS inhibitors on outcomes in HFpEF patients with LVH and chronic kidney disease (CKD). In HFpEF patients with LVH and mild-moderate CKD, which was determined as an eGFR of 30-60 mL/min/1.73 m^2, patients prescribed RAAS inhibitors had significantly favorable outcomes compared to those without RAAS inhibitor prescription (HR,

0.39; 95% CI, 0.19-0.80; P=0.01; Figure 5). In HFpEF patients with LVH and severe CKD, which was defined as eGFR < 30 mL/min/1.73 m^2, the outcome was similar between patients with and without the prescription of RAAS inhibitors (HR, 0.81; 95% CI, 0.43–1.50; P=0.50). Conversely, in HFpEF patients without LVH, the outcome was similar between patients with and without the prescription of RAAS inhibitors regardless of CKD severity (mild-moderate CKD: HR, 0.84; 95% CI, 0.40-1.80; P=0.67; and severe CKD: HR, 1.39; 95% CI, 0.39–5.00; P=0.61).

Table 3 shows the univariable and multivariable Cox regression analyses for predicting the primary endpoint of 120 HFpEF patients with LVH and mild-moderate CKD. An important finding of the multivariable Cox regression analysis showed that the prescription of RAAS inhibitors was the only independent predictor of the primary endpoint (HR, 0.49; 95% CI, 0.25-0.94; P=0.03).

Discussion

The findings of our study indicate that HFpEF patients with LVH who were prescribed RAAS inhibitors tended to have favorable outcomes compared to those without RAAS inhibitors. Moreover, HFpEF patients with LVH and mild-moderate CKD who were prescribed RAAS inhibitors had significantly favorable outcomes compared to those without the RAAS inhibitors, and the prescription of RAAS inhibitors was the only independent predictor of the primary endpoint in HFpEF patients with LVH and mild-moderate CKD.

Utility of Phenogrouping of HFpEF for Better Understanding Its Heterogeneity

HFpEF is widely known as a heterogeneous disease. A variety of clinical risk factors for HFpEF have been identified, such as old age, female sex, hypertension, diabetes mellitus, obesity, atrial fibrillation, CKD, and coronary artery disease[3, 7]. In addition, HFpEF has highly variable underlying cardiac structural and functional abnormalities[6-8]. A wide range of abnormal LV structures, such as LV diastolic dysfunction, LVH, left atrial enlargement, and LV longitudinal myocardial dysfunction identified as low global longitudinal strain, were strongly associated with

HFpEF. This heterogeneity would contribute to the difficulty in identifying effective treatments for HFpEF as well as disease complexity. Therefore, previous studies have proposed that several different phenotypes of HFpEF exist[25], encompassing relatively discrete phenogroups with distinct clinical features[8]. Although few data exist regarding differences in underlying biological processes or responses to therapies between HFpEF phenogroups, these phenogroups may be linked to important differences in disease prognosis [8, 25]. Phenogroupings by risk factors or cardiac structural and functional abnormalities may suggest phenogroup-specific mechanisms that can be targeted for therapeutic purposes. No prospective interventional study on cardioprotective drugs for the treatment of HFpEF has demonstrated a clear reduction in the risk of death or clinical events. However, large-scale observational studies and meta-analyses have indicated that cardioprotective drugs such as RAAS inhibitors, β-blockers, and mineralocorticoid receptor antagonists significantly reduced HF hospitalization in patients with HFpEF [18, 26, 27]. Treatment of preserved cardiac function heart failure with an aldosterone antagonist trial (TOPCAT), which is a large multicenter international trial evaluating the efficacy of spironolactone therapy in patients older than 50 years with symptomatic HFpEF, did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF[26]. The sub-analysis of TOPCAT divided into three phenogroupings, and HFpEF patients with obesity, diabetes, CKD, concentric LVH, high renin, and biomarkers of tumor necrosis factor-alpha-mediated inflammation, liver fibrosis, and tissue remodeling had significantly better primary composite outcomes [28]. Thus, this study of sub-analysis of TOPCAT indicates the importance of HFpEF phenogrouping for predicting better response to pharmacological therapy in patients with HFpEF.

Effect of RAAS Inhibitors on HFpEF Patients with LVH

LVH is an independent cardiovascular risk factor in the general population and occurs in various types of patients with HF [9-12]. Development of LVH has been associated with progression

to HF, as characterized by increased LV end-diastolic pressure and diminished LV contractility. LVH is also a common structural abnormality of HFpEF and is independently predictive of incident HF hospitalization or cardiovascular death[14]. A meta-analysis of the effects of treatment on LV mass in essential hypertension reported that RAAS inhibitors reduced LV mass by approximately 10 %-13 %[19]. RAAS plays a key role in LVH, and angiotensin II (Ang II) is a major determinant of this process[29]. Ang II stimulates LVH and fibrosis in patients with HF, whereas Ang II blockade prevents the development of LVH[27, 30]. We showed that HFpEF patients with LVH who were prescribed RAAS inhibitors tended to have favorable outcomes compared to those without RAAS inhibitors. Moreover, the prescription of RAAS inhibitors in HFpEF patients with LVH and mild-moderate CKD (eGFR of 30-60 mL/min/1.73 m^2) was further associated with favorable outcomes, whereas that in HFpEF patients with LVH and severe CKD (eGFR < 30mL/min/1.73 m^2) was not. Bidirectional negative effects of heart and kidney dysfunction, such as cardiorenal syndrome, cause a potential vicious cycle. Renal dysfunction contributes to the exacerbation of HF by reducing sodium excretion and volume expansion and upregulating neurohormonal pathways as well as inflammatory and other potential mechanisms, while HF aggravates CKD by reducing renal perfusion and activating the sympathetic nervous and renin-angiotensin-aldosterone systems[31, 32]. Therefore, the association between CKD and HF is multifactorial and causal in nature, and meticulous treatment is needed. It is well known that RAAS inhibitors are the best-studied agents for slowing the progression of CKD. Kim et al. investigated the effects of RAAS inhibitors on long-term clinical outcomes in various phenotypes of patients with HF and CKD[33]. They showed that patients with HF treated with RAAS inhibitors had significantly better outcomes than those treated without RAAS inhibitors. However, this beneficial effect of RAAS inhibitors was not observed in HF patients with severe CKD (<15 mL/min/1.73 m^2). According to these findings, the importance of phenogrouping HFpEF patients is further underlined for pharmacological therapy.

Clinical Implications

The main problem with HFpEF is that there is no proven pharmacological therapy to improve survival. The use of novel cardioprotective medications such as sacubitril/valsartan and sodium-glucose cotransporter 2 inhibitors for patients with HFpEF has been discussed; however, phenogrouping HFpEF patients is still important for predicting better response to cardioprotective drugs. Based on our findings, patients with HFpEF and LVH, especially those with mild to moderate CKD, are recommended to use RAAS inhibitors for better outcomes.

Study Limitations

This was a retrospective study; therefore, there were some missing data. Further prospective studies with less missing data are needed to validate our findings. In addition, the number of patients in the subgroup was small for the Kaplan-Meier method, especially CKD subgroup analysis. Thus, the studies with larger patient populations are needed to further assess our findings.

Conclusions

LVH was associated with outcomes in patients with HFpEF, and patients with HFpEF and LVH who were prescribed RAAS inhibitors tended to have favorable outcomes compared to those without RAAS inhibitors. Moreover, HFpEF patients with LVH and mild-moderate CKD prescribed RAAS inhibitors had significantly more favorable outcomes than those without RAAS inhibitor prescription. Our findings showed the importance of HFpEF phenogrouping for identifying effective pharmacological treatments.

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Disclosures

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The remaining authors have no conflicts of interest to declare.

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Disease- Propensity Score Matching Analysis. Circ J 2019; 84 1:83-90.

Figure Legends

Figure 1: Flowchart of patient recruitment in this study.

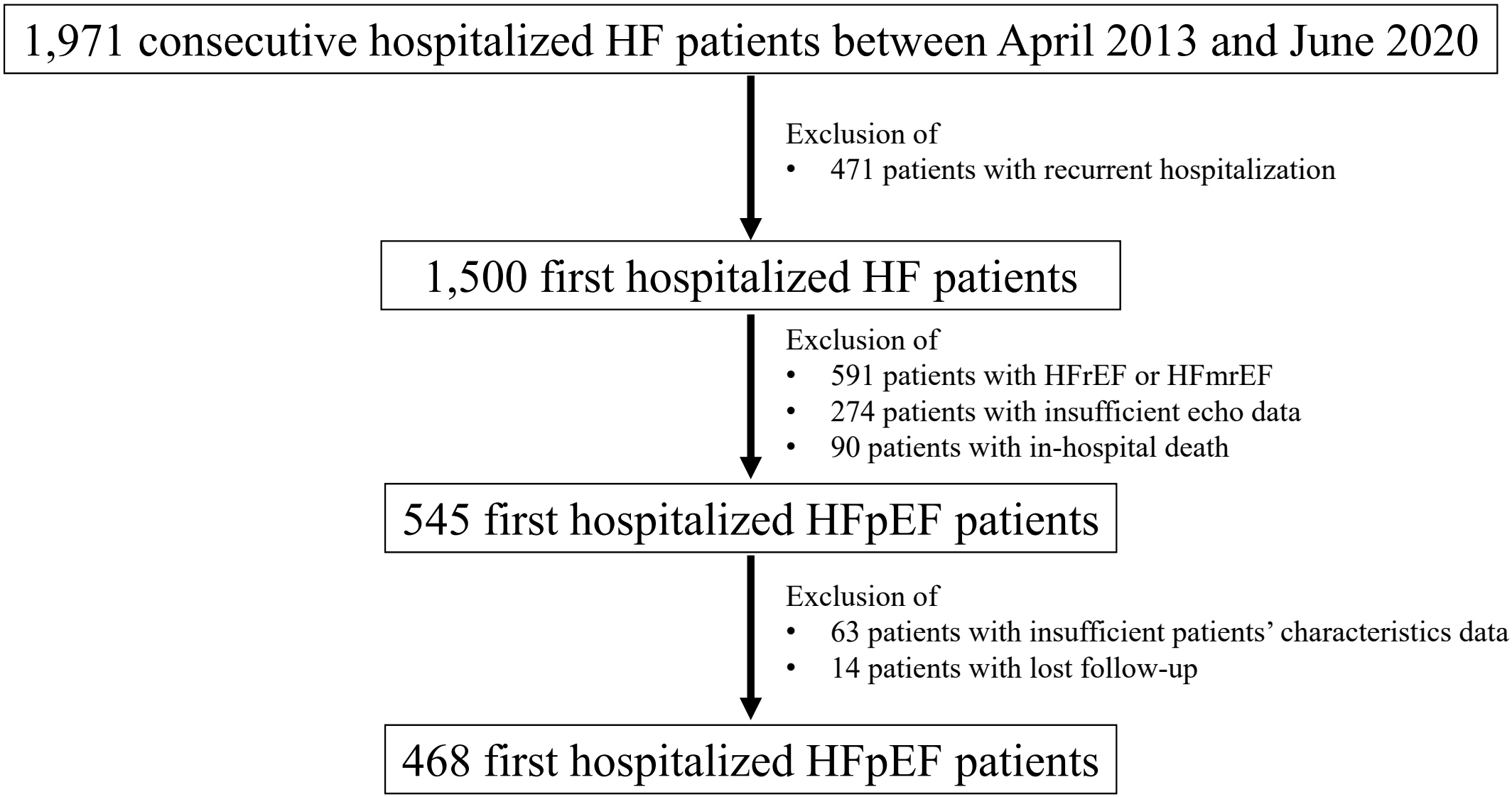
Figure 2: Kaplan-Meier curve indicating the influence on primary endpoint of HFpEF patients with or without LVH.

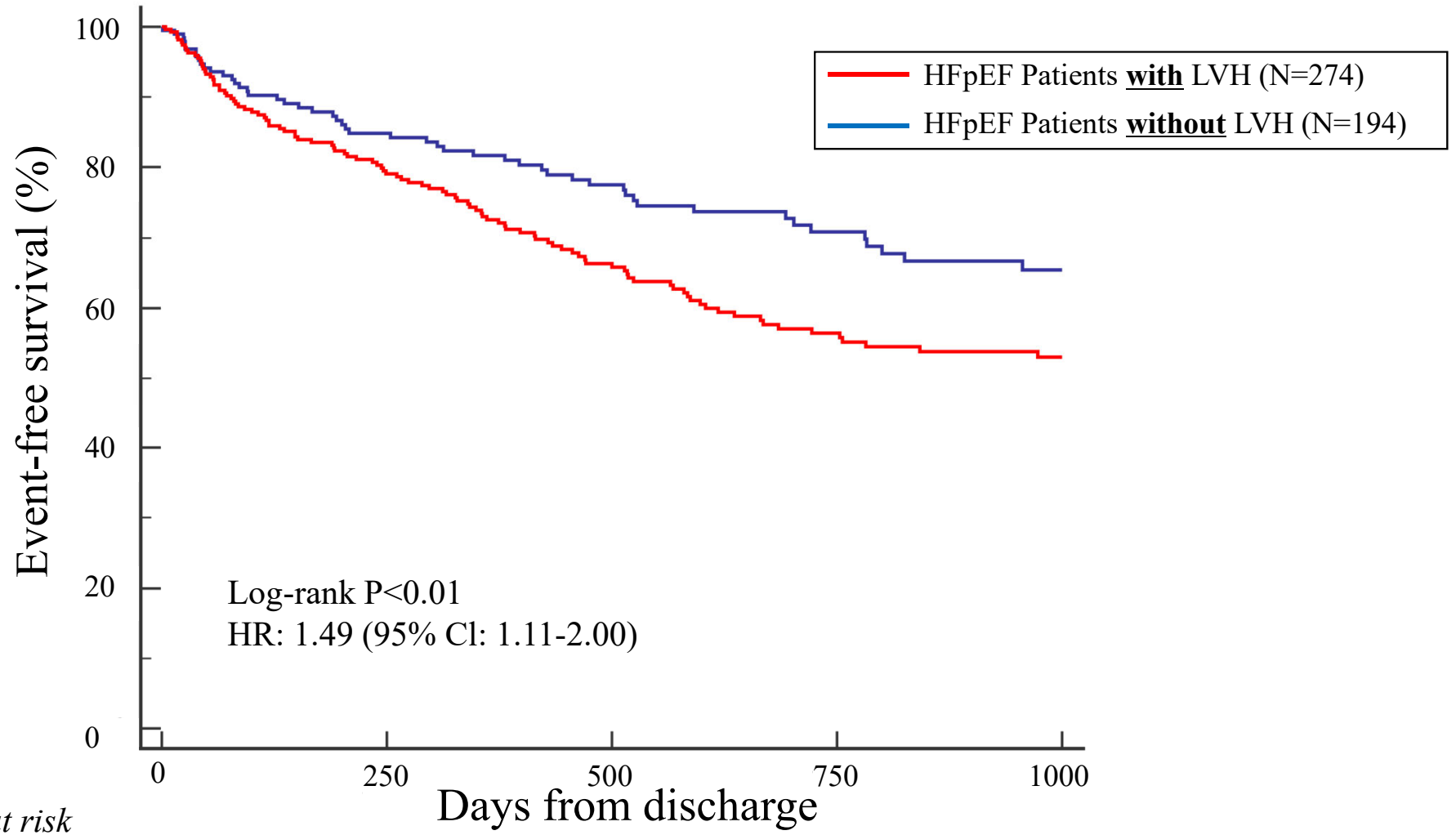
Figure 3: Kaplan-Meier curve indicating the primary endpoint of HFpEF patients with LVH, with and without RAAS inhibitors, showing that patients with RAAS inhibitors had similar outcome compared to those without.

Figure 4: Kaplan-Meier curve indicating the primary endpoint of HFpEF patients without LVH, with and without RAAS inhibitors, which show similar outcomes.

Figure 5: Kaplan-Meier curve indicating the primary endpoint of HFpEF patients with LVH and mild-moderate CKD, with and without RAAS inhibitors, showing that patients prescribed RAAS inhibitors had significantly better outcomes.

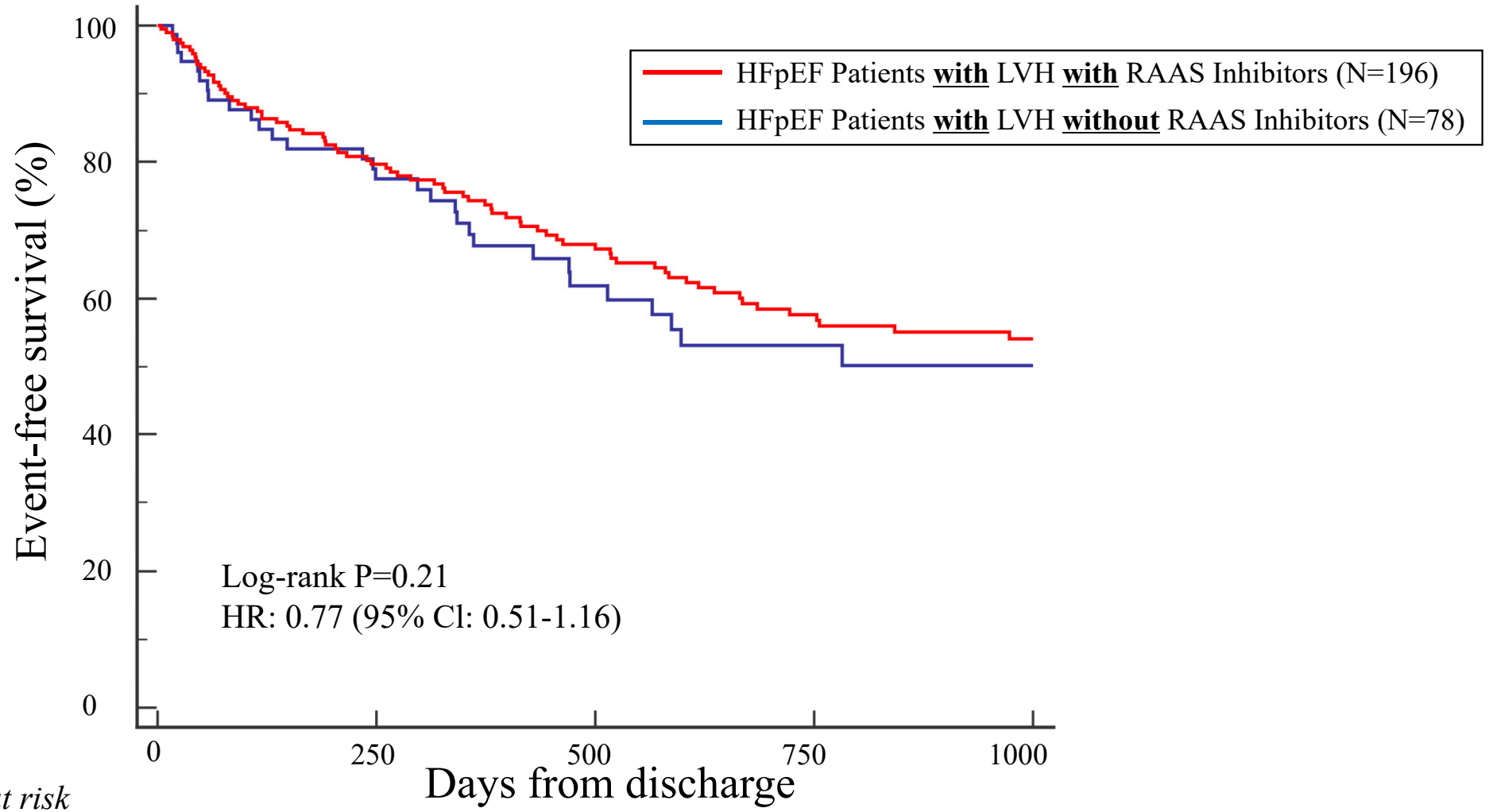
Supplementary file 1: Kaplan-Meier curve indicating the primary endpoint of HFpEF patients with and without LVH, with RAAS inhibitors, which show similar outcomes.


1,971 consecutive hospitalized HF patients between April 2013 and June 2020
Exclusion of
• 471 patients with recurrent hospitalization
1,500 first hospitalized HF patients
Exclusion of
• 591 patients with HFrEF or HFmrEF
• 274 patients with insufficient echo data
• 90 patients with in-hospital death
545 first hospitalized HFpEF patients
Exclusion of
• 63 patients with insufficient patients' characteristics data
• 14 patients with lost follow-up
468 first hospitalized HFpEF patients



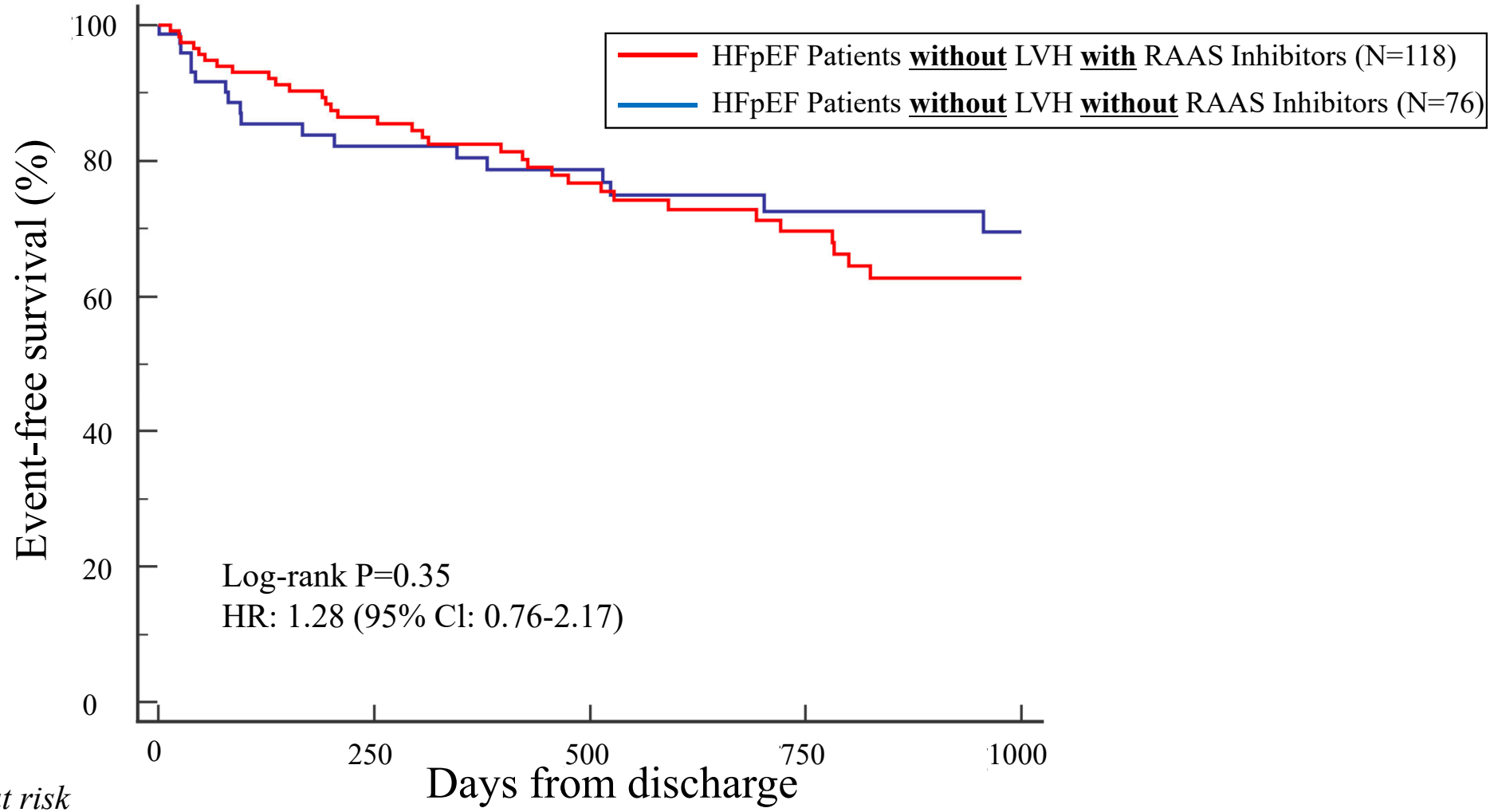
Number at risk

HFpEF Patients **with** LVH	274	220	191	174	169
HFpEF Patients **without** LVH	194	167	156	148	143



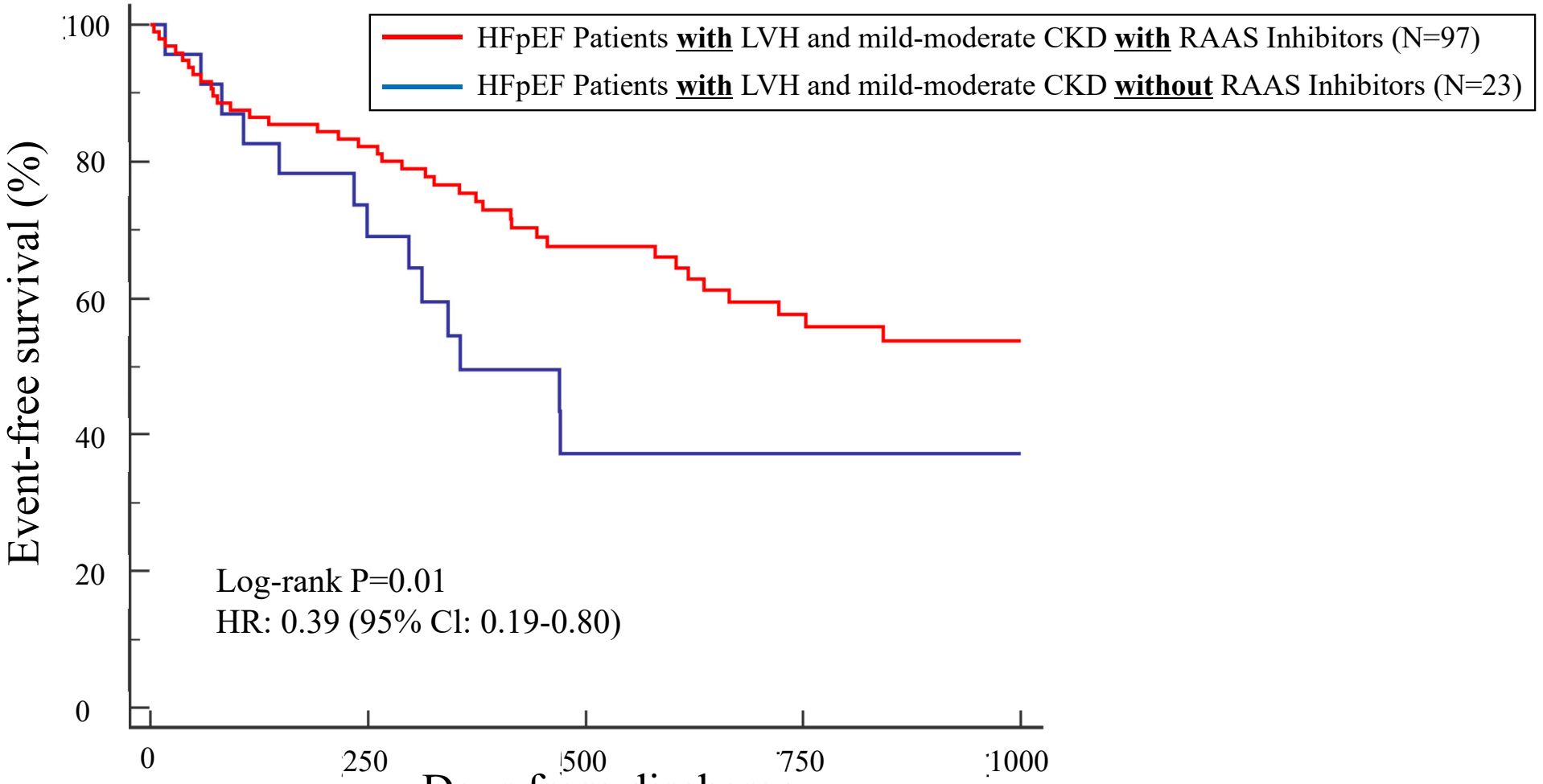
Number at risk

HFpEF Patients **with** LVH **with** RAAS Inhibitors	196	158	138	124	121
HFpEF Patients **with** LVH **without** RAAS Inhibitors	78	62	53	49	48



Number at risk

HFpEF Patients **without** LVH **with** RAAS Inhibitors	118	103	92	87	83
HFpEF Patients **without** LVH **without** RAAS Inhibitors	76	64	62	59	58



Number at risk

HFpEF Patients **with** LVH and mild-moderate CKD **with** RAAS Inhibitors	97	80	68	62	60
HFpEF patients **with** LVH and mild-moderate CKD **without** RAAS Inhibitors	23	17	11	11	11

Table 1
Baseline Characteristics of Patients

	Overall patients (N=468)	Patients **with** LVH (N=274)	Patients **without** LVH (N=194)	P-value
Clinical characteristics				
Age, years	81.5±10.5	81.9±10.1	80.9±11.0	0.30
Gender (Male), n (%)	224 (47.9)	114 (41.6)	110 (56.7)	<0.01
Body mass index, kg/m^2	21.3± 4.4	21.2±4.3	21.4±4.6	0.62
NYHA class, n (%)				
II	17 (3.6)	14 (5.1)	3 (1.5)	0.04
III	110 (23.5)	57 (20.8)	53 (27.3)	0.10
IV	341 (75.8)	203 (74.1)	138 (71.1)	0.18
Comorbidities, n (%)				
Hypertension	325 (69.4)	201 (73.4)	124 (63.9)	0.03
Diabetes mellitus	125 (26.8)	67 (24.5)	58 (29.9)	0.20
Atrial fibrillation	269 (57.7)	147 (53.6)	122 (62.9)	0.04
Ischemic heart disease	77 (16.5)	42 (15.3)	35 (18.0)	0.43
Valvular disease	188 (40.2)	127 (46.4)	61 (33.0)	<0.01
Lung disease	86 (18.4)	45 (16.4)	41 (21.1)	0.19
Blood examination				
Hemoglobin, mg/dL	11.2±2.0	10.9±2.0	11.6±2.0	<0.01
Albumin, mg/dL	3.1±0.5	3.1±0.5	3.1±0.5	0.54
Blood urea nitrogen, mg/dL	27.6±17.5	29.2±16.7	25.2±18.5	0.02
Creatinine, mg/dL	1.4±1.3	1.6±1.5	1.2±0.9	<0.01

eGFR, mL/min/1.73m^2	48.0±24.2	44.2±24.5	53.5±22.8	<0.01
Brain natriuretic peptide, pg/mL	221 (191-246)	366 (304-429)	277 (216-339)	0.05
Medications, n (%)				
ACE-Is/ARBs	314 (67.1)	196 (71.5)	118 (60.8)	0.02
β-blockers	314 (67.1)	184 (67.2)	130 (67.0)	0.97
MRAs	163 (34.8)	91 (33.2)	72 (37.1)	0.38
Loop diuretics	346 (73.9)	203 (74.1)	143 (73.7)	0.93
Tolvaptan	99 (21.2)	62 (22.6)	37 (19.1)	0.35
Echocardiographic data				
LV end-diastolic dimension, mm	45.6±7.4	47.9±7.2	42.2±6.5	<0.01
LV end-systolic dimension, mm	30.1±6.4	31.8±6.4	27.8±5.7	<0.01
LVMI, g/m^2 (men)	120.7±39.0	150.8±30.1	89.7±15.8	<0.01
LVMI, g/m^2 (women)	112.4±38.9	132.2±32.7	74.8±14.2	<0.01
LVEF, %	58.7±5.9	58.3±6.0	59.4±5.7	0.03
Left atrial diameter, mm	43.5±8.4	44.7±8.5	41.7±7.9	<0.01

Data are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%)

BMI; body mass index, NYHA; New York Heart Association

ACE-Is; angiotensin converting enzyme inhibitors, ARBs; angiotensin II receptor blockers, MRAs; mineralocorticoid receptor antagonists

LV; left ventricular, LVMI; Left ventricular mass index, EF; ejection fraction

Table 2

Association of RAAS inhibitors with each endpoint in all HFpEF patients, HFpEF patients with LVH and HFpEF patients without LVH

(A) All HFpEF patients

	All HFpEF patients **with** RAAS inhibitor prescription (N=314)	**All HFpEF** patients **without** RAAS inhibitor prescription (N=154)	HR (95% CI)	P value
Cardiovascular death or HF rehospitalization	124 (39.5)	55 (35.7)	0.99 (0.72-1.36)	0.96
Cardiovascular death	23(7.3)	16 (10.4)	0.62 (0.31-1.23)	0.17
HF rehospitalization	101 (32.2)	39 (25.3)	1.13 (0.79-1.62)	0.50

(B) HFpEF patients with LVH

	HFpEF patients **with LVH with** RAAS inhibitor prescription (N=196)	**HFpEF** patients **with LVH without** RAAS inhibitor prescription (N=78)	HR (95% CI)	P value
Cardiovascular death or HF rehospitalization	84 (42.9)	36 (46.2)	0.77 (0.51-1.16)	0.21
Cardiovascular death	17 (8.7)	12 (15.4)	0.43 (0.19-0.99)	0.05
HF rehospitalization	67 (34.2)	24 (30.8)	0.92 (0.57-1.49)	0.74

(C) HFpEF patients without LVH

	HFpEF patients **without LVH** **with** RAAS inhibitor prescription (N=118)	**HFpEF** patients **without LVH** **without** RAAS inhibitor prescription (N=76)	HR (95% CI)	P value
Cardiovascular death or HF rehospitalization	40 (33.9)	19 (25.0)	1.28 (0.76-2.17)	0.35
Cardiovascular death	6 (5.1)	4 (5.3)	0.88 (0.24-3.17)	0.84
HF rehospitalization	34 (28.8)	15 (19.7)	1.38 (0.78-2.46)	0.27

HR=hazard ratio; CI=confidential interval; RAAS= renin-angiotensin-aldosterone-system

Other abbreviation as in Table 1

Table 3

Univariate and Multivariate Cox Proportional-hazards Analysis for Predicting Primary Endpoint in HFpEF patients with LVH with mild-moderate CKD

Covariate	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.04	1.00-1.07	0.02			
Gender (Female)	0.83	0.48-1.44	0.50			
Body mass index	0.94	0.88-1.00	0.06			
Hypertension	0.85	0.49-1.49	0.58			
Diabetes mellitus	0.67	0.33-1.36	0.26			
Atrial fibrillation	1.30	0.74-2.29	0.35			
LVEF	0.93	0.95-1.05	0.93			
Left atrial diameter	1.00	0.98-1.04	0.59			
Albumin	0.54	0.29-1.01	0.05			
Hemoglobin	0.87	0.76-0.99	0.04			
Prescription of β-blockers	1.21	0.69-2.16	0.49			
Prescription of MRAs	0.70	0.41-1.19	0.18			
Prescription of RAAS inhibitors	0.47	0.26-0.84	0.02	0.49	0.25-0.94	0.03

Abbreviation as in Table 1 and 2