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ORIGINAL ARTICLE

Association between prognosis and the use of angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers in frail patients with heart failure with preserved ejection fraction

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Abstract

Aims The effectiveness of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) has not been demonstrated in patients with heart failure with preserved ejection fraction (HFpEF). We recently reported significant interaction between the use of ACE-I and/or ARB (ACE-I/ARB) and frailty on prognosis in patients with HFpEF. In the present study, we examined the association between ACE-I/ARB and prognosis in patients with HFpEF stratified by the presence or absence of frailty.

Methods and results We examined the association between the use of ACE-I/ARB and prognosis according to the presence [Clinical Frailty Scale (CFS) $\geq$ 5] or absence (CFS $\leq$ 4) of frailty in patients with HFpEF in a post hoc analysis of registry data. Primary endpoint was the composite of all-cause mortality and heart failure admission. Secondary endpoints were all-cause mortality and heart failure admission. Of 1059 patients, median age was 83 years and 45% were male. Kaplan–Meier analysis showed that the risk of composite endpoint (log-rank P = 0.001) and all-cause death (log-rank P = 0.005) in patients with ACE-I/ARB was lower in those with CFS $\geq$ 5, but similar between patients with and without ACE-I/ARB in patients with CFS $\leq$ 4 (composite endpoint: log-rank P = 0.830; all-cause death: log-rank P = 0.192). In a multivariable Cox proportional hazards model, use of ACE-I/ARB was significantly associated with lower risk of the composite endpoint [hazard ratio (HR) = 0.52, 95% confidence interval (CI) = 0.33–0.83, P = 0.005] and heart failure admission (HR = 0.45, 95% CI = 0.25–0.83, P = 0.010) in patients with CFS $\geq$ 5, but not in patients with CFS $\leq$ 4 (composite endpoint: HR = 1.41, 95% CI = 0.99–2.02, P = 0.059; heart failure admission: HR = 1.43, 95% CI = 0.94–2.18, P = 0.091). The association between ACE-I or ARB and prognosis did not significantly differ by CFS (CFS $\leq$ 4: log-rank P = 0.562; CFS $\geq$ 5: log-rank P = 0.100, for with ACE-I vs. ARB, respectively). Adjusted HRs for CFS 1–4 were higher than 1.0 but were $<$1.0 at CFS 5.

Conclusions In patients with HFpEF, use of ACE-I/ARB was associated with better prognosis in patients with frailty as assessed with the CFS, but not in those without frailty.

Keywords Heart failure with preserved ejection fraction; Clinical Frailty Scale; ACE-I; ARB

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Introduction

The number of patients with heart failure with preserved ejection fraction (HFpEF) is rapidly increasing with the development of the aging society.[1–3] However, optimal management of HFpEF remains largely unknown. Several large-scale randomized controlled trials that tested treatments effective in patients with heart failure with reduced ejection fraction (HFrEF) failed to demonstrate effectiveness.[4–7] One reason proposed to explain this outcome is the heterogeneity found among patients with HFpEF: not only cardiac abnormalities but also various extracardiac comorbidities contribute to the pathophysiology of HFpEF.[8–12] Accordingly, establishing effective treatments in patients with HFpEF may depend on the selection of appropriate treatments for appropriate populations stratified by pathophysiological factors.

Frailty is one important prognostic factor in patients with HFpEF.[9,13] Our previous study demonstrated that frailty—as assessed by the Clinical Frailty Scale (CFS)—and use of angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin II receptor blockers (ARB) (ACE-I/ARB) showed significant interaction on prognosis: among those with a high CFS score, prognosis was better in those who received ACE-I/ARB than in those who did not.[9] Although previous trials could not demonstrate the effectiveness of ACE-I or ARB in overall patients with HFpEFs,[4,5] stratification by the presence or absence of frailty may be useful in identifying populations that would benefit from the use of ACE-I/ARB.

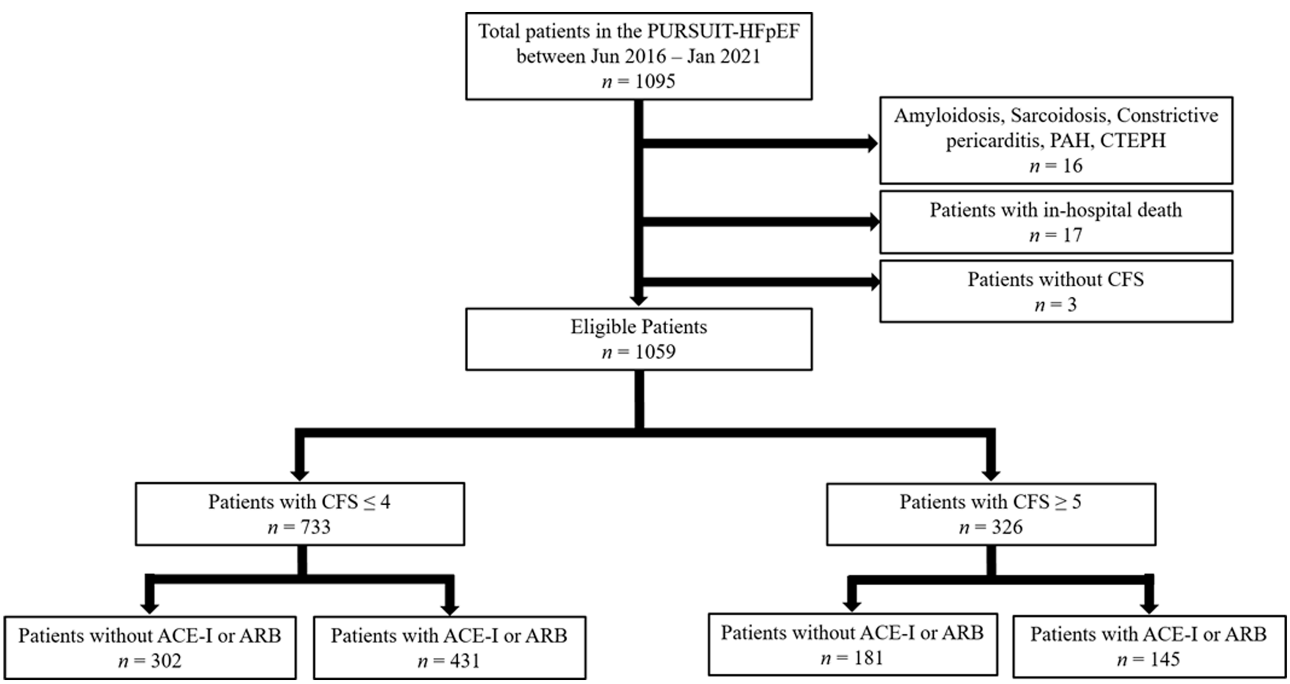
The purpose of this study was to examine the association between ACE-I/ARB and prognosis in patients with HFpEF stratified by the presence or absence of frailty using data from a prospective, multicentre, observational study of patients with HFpEF (the PURSUIT-HFpEF study).[14]

Methods

Study patients

Of 1095 patients registered in the PURSUIT-HFpEF study, a prospective, multicentre, observational study of patients with HFpEF, between June 2016 and January 2021, 3 patients without CFS, 17 patients with in-hospital death, and 16 patients with amyloidosis, pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, pericarditis, or sarcoidosis were excluded (*Figure 1*), leaving a total of 1059 patients for analysis. The PURSUIT-HFpEF registry has been described in detail elsewhere.[14] The registry was started in June 2016 and enrolled patients hospitalized with a diagnosis of decompensated heart failure based on the Framingham criteria and who met the criteria of (1) left ventricular ejection fraction (LVEF) $\geq$ 50%[15] on a transthoracic cardiac echocardiographic (TTE) test on admission and (2) N-terminal pro-brain natriuretic peptide (NT-proBNP) $\geq$ 400 pg/mL or brain natriuretic peptide $\geq$ 100 pg/mL on admission, regardless of the

Figure 1 Patient selection. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CFS, Clinical Frailty Scale; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary artery hypertension.



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presence or absence of atrial fibrillation (AF). We excluded patients with severe aortic stenosis, aortic regurgitation, mitral stenosis, or mitral regurgitation due to structural changes in the valve detected by TTE on admission. We also excluded patients under 20 years old, as well as those with acute coronary syndrome on admission, poor life prognosis of $<$6 months due to non-cardiac diseases, heart transplantation, and those considered inappropriate for the study by the attending physician. Thirty-one facilities participated in this study.

We collected data such as detailed past history, comorbidities, CFS, medication history, laboratory, and echocardiographic data. We followed each patient and collected outcome data on mortality, number and cause of hospitalization, and cause of death. All patients provided written informed consent to participate. The study was conducted in accordance with the ethical guidelines outlined by the Helsinki Declaration and was approved by the institutional review board of all participating facilities.

Data collection

Research cardiologists and specialized research nurses recorded the patients' data during their hospital stay. Medical history and CFS were obtained on admission. Vital signs, body mass index (BMI), New York Heart Association (NYHA) classification, echocardiography, laboratory data, and medication use were obtained both on admission and at discharge; however, the data at discharge were used in this study.

In echocardiography, tricuspid annular plane systolic excursion (TAPSE) and inferior vena cava (IVC) diameter were measured using the standard method. LVEF was measured using the Simpson method. Left ventricular mass was measured, and left ventricular mass index (LVMI) was calculated by dividing left ventricular mass by body surface area. Ratio of early diastolic velocity on transmitral Doppler and early diastolic velocity of mitral valve annulus (E/e′) was the mean of septal E/e′ and lateral E/e′. Tricuspid pressure gradient (TRPG) was measured using the simplified Bernoulli equation.

Clinical Frailty Scale

Frailty was assessed using the CFS, a rapid screening tool for frailty. The CFS classified patient condition as (1) very fit, (2) well, (3) managing well, (4) vulnerable, (5) mildly frail, (6) moderately frail, (7) severely frail, (8) very severely frail, and (9) terminally ill.[16] Details of the assessment of CFS score in this study are described elsewhere.[9] Briefly, we evaluated the CFS in the stable phase prior to admission based on interviews with the patients and their family.

Statistical analysis

We divided patients into four groups to compare baseline characteristics and outcomes. First, we divided them into two groups, CFS $\leq$ 4 and CFS $\geq$ 5, based on the fact that many previous studies on CFS used a cut-off of CFS = 5.[17] Each group was then further divided into two groups based on the use of ACE-I/ARB at discharge (*Figure 1*). Continuous variables are expressed as median [interquartile range]. Categorical data are presented as percentages unless otherwise specified. Tests for significance were conducted using the unpaired *t*-test or the Mann–Whitney *U* test for continuous variables, and the χ^2 test or the Fisher exact test for categorical variables. The primary endpoint of this study was a composite of all-cause mortality and heart failure admission. Secondary endpoints were all-cause mortality and heart failure admission. Endpoints were estimated using Kaplan–Meier curves, and statistical significance was determined using the log-rank test. Univariable and multivariable analyses were conducted using Cox proportional hazards regression models. In multivariable analysis, we adjusted for age, sex, diabetes mellitus, hypertension, estimated glomerular filtration rate, haemoglobin, albumin, cholinesterase,[18] prior heart failure admission, NYHA $\geq$ 2, NT-proBNP, LVMI, and E/e′. We selected these variables based on previous reports that examined prognosis in patients with HFpEF.[3,18–20] Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each endpoint using Cox proportional hazards regression models. The risk of either ACE-I or ARB for the composite endpoint was estimated by Kaplan–Meier analysis, comparing patients with ACE-I, ARB, or neither, in which patients taking both ACE-I and ARB (n = 7 in patients with CFS $\leq$ 4 and n = 1 in those with CFS $\geq$ 5, respectively) were excluded. We also calculated adjusted HRs in patients with each CFS class. All statistical analyses were performed using SPSS Version 25 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a $P < 0.05$.

Results

Baseline characteristics

Of 1059 patients, 733 were CFS $\leq$ 4 and 326 were CFS $\geq$ 5. We divided the 733 patients with CFS $\leq$ 4 into 302 patients without ACE-I/ARB and 431 patients with ACE-I/ARB, and the 326 patients with CFS $\geq$ 5 into 181 patients without ACE-I/ARB and 145 patients with ACE-I/ARB. Patient baseline characteristics among these four groups are shown in *Table 1*. Among the entire study population, median age was 83 [77, 87] years and 45% were male. In patients with CFS $\leq$ 4, patients with ACE-I/ARB had a higher BMI and systolic blood pressure at discharge, higher prevalence of hypertension, diabetes and

Table 1 Baseline characteristics

Variable	CFS ≤ 4 n = 733			CFS ≥ 5 n = 326		
	Without ACE-I/ARB n = 302	With ACE-I/ARB n = 431	P	Without ACE-I/ARB n = 181	With ACE-I/ARB n = 145	P
Clinical data						
Age, years	81 [75, 85]	81 [75, 85]	0.715	88 [83, 91]	85 [82, 88]	0.004
Male, n (%)	140 (46)	241 (56)	0.013	54 (30)	41 (28)	0.807
BMI at discharge, kg/m^2	21.3 [18.7, 23.8]	22.2 [19.6, 24.6]	<0.001	20.4 [17.5, 23.6]	21.1 [18.6, 25.0]	0.127
SBP at discharge, mmHg	117 [106, 129]	121 [109, 133]	0.010	115 [105, 129]	118 [102, 132]	0.667
Heart rate at discharge, b.p.m.	70 [62, 79]	68 [60, 77]	0.039	72 [65, 82]	71 [60, 80]	0.090
NYHA classification ≥ 2, n (%)	178 (60)	240 (56)	0.285	145 (82)	96 (67)	0.002
Prior HF admission, n (%)	68 (23)	96 (23)	1.000	57 (33)	38 (27)	0.324
Hypertension, n (%)	230 (76)	393 (91)	<0.001	139 (78)	131 (90)	0.002
Diabetes mellitus, n (%)	85 (28)	159 (37)	0.017	62 (35)	46 (32)	0.635
Stroke, n (%)	31 (10)	63 (15)	0.092	31 (18)	28 (19)	0.667
Atrial fibrillation, n (%)	140 (46)	201 (47)	1.000	84 (46)	66 (46)	0.911
Echocardiography at discharge						
LVEF (Simpson), %	61 [56, 66]	61 [56, 66]	0.775	60 [53, 64]	61 [56, 65]	0.069
LVMI, g/m^2	101.9 [80.4, 126.8]	103.7 [89.0, 124.9]	0.407	97.2 [78.9, 113.5]	100.9 [82.8, 120.4]	0.128
E/e′	11.0 [9.0, 15.1]	12.6 [10.0, 16.4]	0.001	13.3 [10.3, 17.4]	13.7 [10.6, 17.9]	0.965
TAPSE, mm	17 [14, 20]	18 [15, 21]	0.083	17 [14, 19]	18 [15, 20]	0.009
IVC diameter, mm	14 [11, 17]	14 [11, 17]	0.52	13 [11, 17]	13 [11, 17]	0.829
TRPG, mmHg	26 [21, 31]	27 [22, 33]	0.105	29 [23, 35]	27 [22, 33]	0.048
Laboratory data at discharge						
Sodium, mEq/L	139 [137, 141]	140 [138, 142]	0.002	139 [137, 141]	140 [137, 141]	0.343
Haemoglobin, g/dL	11.4 [10.2, 13.1]	11.5 [10.3, 12.9]	0.714	10.9 [9.8, 12.2]	10.9 [9.8, 12.1]	0.784
Creatinine, mg/dL	1.1 [0.9, 1.7]	1.1 [0.9, 1.5]	0.797	1.1 [0.8, 1.5]	1.0 [0.8, 1.4]	0.912
eGFR, mL/min/1.73 m^2	41 [27, 54]	44 [32, 56]	0.205	40 [29, 55]	40 [32, 52]	0.995
Albumin, g/dL	3.4 [3.2, 3.8]	3.5 [3.2, 3.7]	0.981	3.2 [2.9, 3.5]	3.4 [3.1, 3.6]	0.034
Cholinesterase, IU/L	201 [169, 252]	218 [184, 265]	0.003	195 [148, 220]	194 [163, 258]	0.131
NT-proBNP, pg/mL	1275 [575, 2795]	820 [424, 1661]	<0.001	1655 [705, 2853]	1290 [612, 2405]	0.138
Medications at discharge						
ACE-I, n (%)	0 (0)	139 (32)	<0.001	0 (0)	48 (33)	<0.001
ARB, n (%)	0 (0)	299 (69)	<0.001	0 (0)	98 (68)	<0.001
Ca channel blocker, n (%)	113 (37)	265 (62)	<0.001	62 (34)	72 (50)	0.004
Beta-blocker, n (%)	180 (60)	242 (56)	0.363	83 (46)	82 (57)	0.058
Diuretics, n (%)	241 (80)	346 (80)	0.874	154 (85)	122 (84)	0.814
Aldosterone antagonist, n (%)	117 (39)	162 (38)	0.751	80 (44)	59 (41)	0.524
Statin, n (%)	97 (32)	174 (40)	0.023	40 (22)	49 (34)	0.017

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CFS, Clinical Frailty Scale; eGFR, estimated glomerular filtration rate; HF, heart failure; IVC, inferior vena cava; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.
Continuous variables are expressed as median [interquartile range].

use of calcium channel blockers, higher level of E/e′ and cholinesterase, and lower NT-proBNP than those without ACE-I/ARB. In patients with CFS ≥ 5, patients with ACE-I/ARB had a lower age, lower prevalence of NYHA classification ≥ 2, higher prevalence of hypertension and use of calcium channel blockers, higher level of TAPSE and albumin, and lower TRPG than those without ACE-I/ARB (*Table 1*).

Outcomes

Median follow-up duration was 415 [202, 773] days. Incidence rates of the composite endpoint, all-cause death, cardiac death, non-cardiac death, and heart failure admission in the groups stratified by CFS and use of ACE-I/ARB are shown in *Table 2*. Incidence rates of the composite endpoint and each of all-cause death, heart failure admission, cardiac death, and non-cardiac death did not significantly differ between patients with and without ACE-I/ARB among those with CFS ≤ 4 (*Table 2*). In patients with CFS ≥ 5, in contrast, incidence rates of the composite endpoint and all-cause death were lower in patients with ACE-I/ARB, whereas that of heart failure admission did not significantly differ between those with and without ACE-I/ARB (*Table 2*). On Kaplan–Meier analysis, patients with ACE-I/ARB had a significantly lower risk of composite endpoint and all-cause death than those without ACE-I/ARB among patients with CFS ≥ 5, whereas the risks were not significantly different between patients with and without ACE-I/ARB in patients with CFS ≤ 4 (*Figure 2*). Univariable and multivariable analyses with Cox proportional hazard models for composite endpoint, all-cause mortality, and heart failure admission are shown in *Table 3*. Multivariable analysis revealed that the use of ACE-I/ARB was significantly associated with risk reduction of the

Table 2 Incidence rate of endpoints

	CFS ≤ 4			CFS ≥ 5		
	Without ACE-I/ARB	With ACE-I/ARB	*P*	Without ACE-I/ARB	With ACE-I/ARB	*P*
Composite endpoint, 100 person-years	24.2 (91)	25.0 (140)	0.830	54.7 (86)	29.5 (50)	0.001
All-cause death, 100 person-years	10.0 (45)	7.7 (54)	0.193	29.2 (60)	15.6 (31)	0.006
Cardiac death, 100 person-years	4.0 (18)	3.3 (23)	0.487	13.1 (27)	7.5 (15)	0.089
Non-cardiac death, 100 person-years	6.0 (27)	4.4 (31)	0.265	16.0 (33)	8.0 (16)	0.027
Heart failure admission, 100 person-years	16.5 (62)	19.3 (108)	0.332	30.5 (48)	19.5 (33)	0.059

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CFS, Clinical Frailty Scale.
Incidence rates (event number) are shown.

Figure 2 Kaplan–Meier analysis of outcomes for patients stratified by CFS and ACE-I/ARB. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CFS, Clinical Frailty Scale.

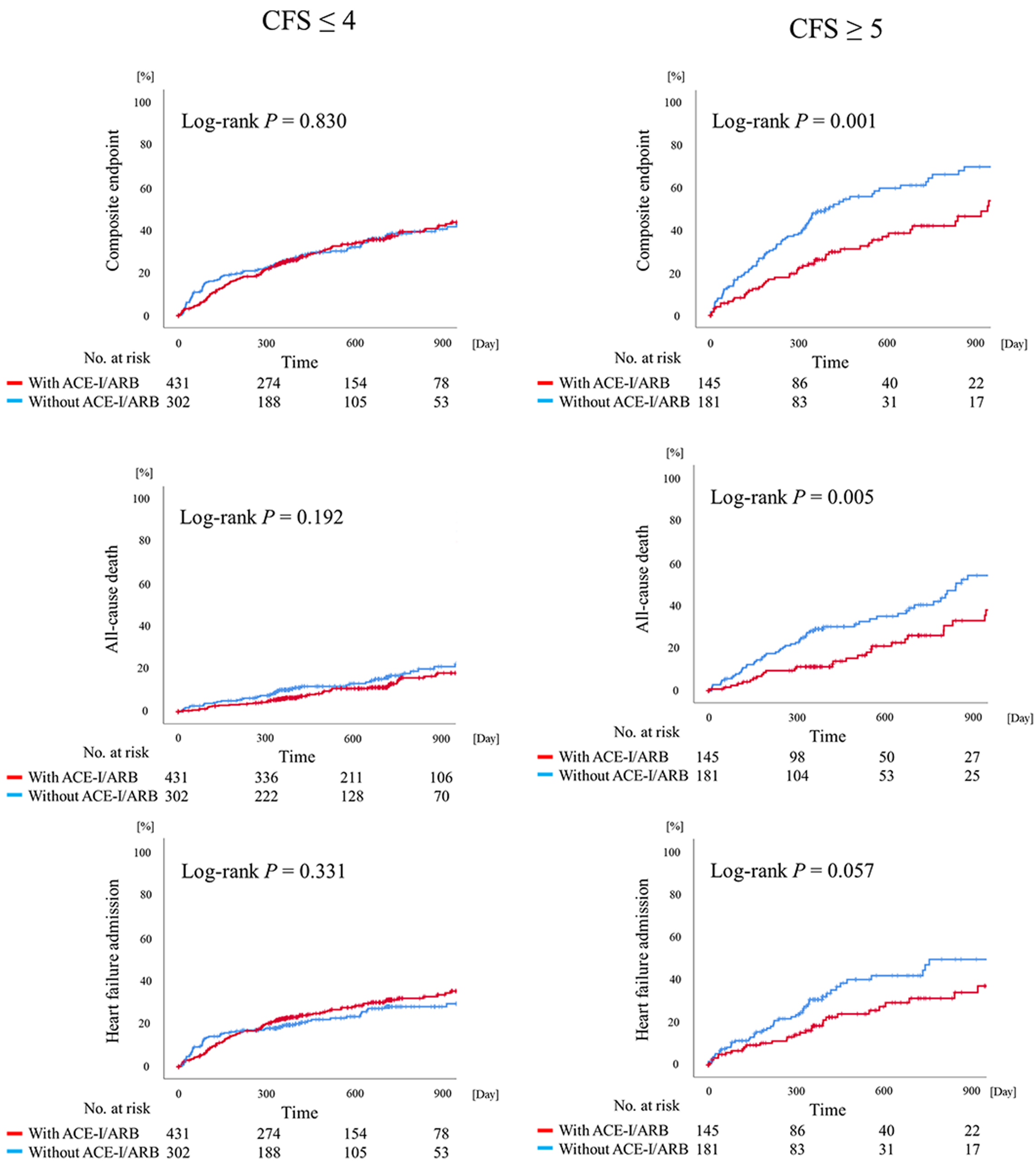

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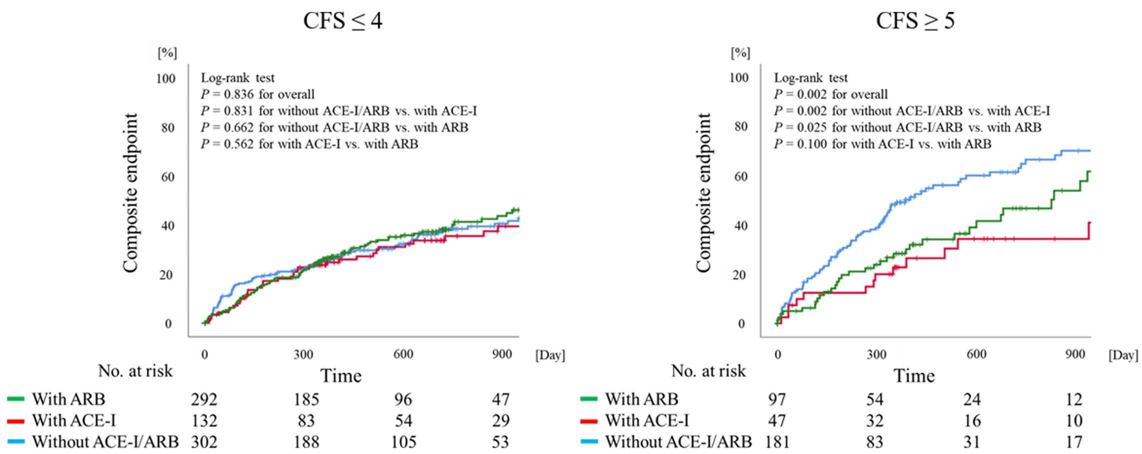
Table 3 Hazard ratio of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker for outcomes in patients with or without frailty

	Unadjusted			Adjusted[a]		
	HR	95% CI	*P*	HR	95% CI	*P*
CFS ≤ 4						
Composite endpoint	1.03	0.79–1.34	0.830	1.41	0.99–2.02	0.059
All-cause mortality	0.77	0.52–1.14	0.193	1.05	0.61–1.82	0.847
Heart failure admission	1.17	0.85–1.60	0.332	1.43	0.94–2.18	0.091
CFS ≥ 5						
Composite endpoint	0.56	0.39–0.79	0.001	0.52	0.33–0.83	0.005
All-cause mortality	0.54	0.35–0.83	0.006	0.64	0.37–1.12	0.120
Heart failure admission	0.65	0.42–1.02	0.059	0.45	0.25–0.83	0.010

CFS, Clinical Frailty Scale; CI, confidence interval; HR, hazard ratio.
Patient number included in the multivariable model was 500 cases for CFS ≤ 4, 200 cases for CFS ≥ 5.
[a]Adjusted for age, sex, diabetes mellitus, hypertension, estimated glomerular filtration rate, haemoglobin, albumin, cholinesterase, prior heart failure admission, New York Heart Association ≥ 2, N-terminal pro-brain natriuretic peptide, E/e′, and left ventricular mass index.

Figure 3 Kaplan–Meier analysis of composite endpoint for patients stratified by CFS according to the use of ACE-I, ARB, or neither. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CFS, Clinical Frailty Scale.



composite endpoint and heart failure admission in patients with CFS ≥ 5, but not in patients with CFS ≤ 4, even after adjustment for covariates (*Table 3*). There was significant interaction on composite endpoint between the use of ACE-I/ARB and CFS ≤ 4 or CFS ≥ 5 (*P* for interaction = 0.006). The association between ACE-I and ARB and prognosis did not significantly differ in both patients with CFS ≥ 5 and those with CFS ≤ 4 (*Figure 3*). We also examined HRs with the use of ACE-I/ARB for the composite endpoint in each CFS class (*Figure 4*). Adjusted HRs for CFS 1–4 were higher than 1.0, but were <1.0 at CFS 5.

Discussion

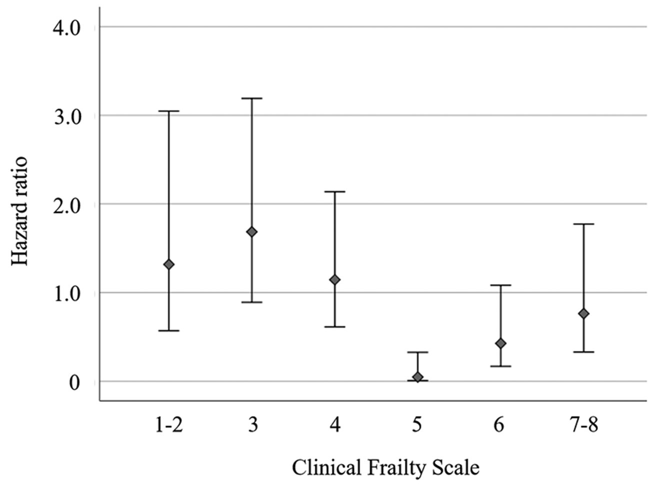
Main findings

In this post hoc analysis of the PURSUIT-HFpEF study, a prospective multicentre registry of East Asian patients with HFpEF, we clarified that patients with ACE-I/ARB showed a better composite endpoint and heart failure admission than those without ACE-I/ARB in patients with high CFS, but not in those with low CFS, after adjustment for major clinical variables. The associations of ACE-I and ARB with prognosis were similar. This study is the first report to suggest that the use of ACE-I/ARB improves the prognosis of patients with HFpEF stratified by the presence or absence of frailty.

Importance of stratifying patients with heart failure with preserved ejection fraction

Our data demonstrated that the stratification of patients with HFpEF possibly identified a population in which a specific medication may be effective. A number of previous randomized trials were unable to demonstrate the effectiveness of medications that are effective in patients with HFrEF, including ACE-I, ARB, mineralocorticoid receptor an-

Figure 4 Adjusted hazard ratios of the use of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker for composite endpoint in patients with each Clinical Frailty Scale class.



tagonist, and angiotensin receptor neprilysin inhibitor.[4,5,7,21] Heterogeneity of pathophysiology in patients with HFpEF has been postulated as a reason for these unfavourable results, and appropriate stratification of HFpEF patients has been considered important. Several sub-analyses of clinical trials revealed the presence of subgroups in which specific treatment may be effective. The effects of spironolactone showed significant interaction with the level of NT-proBNP on prognosis, and possible effectiveness was shown in patients with low NT-proBNP level.[22] Similarly, spironolactone and sacubitril/valsartan showed effectiveness in women but not in men.[23,24] Regarding ACE-I or ARB, only one report has appeared, showing that irbesartan may be effective in patients with a lower level of NT-proBNP.[25] Our study identified the novel combination of a specific subgroup and a possibly effective treatment and suggested a possible therapeutic option in patients with HFpEF. Although our results cannot be applied to overall HFpEF patients, considering the pathophysiological heterogeneity of this condition, the strategy of using a specific treatment targeted to a specific population may be important in the treatment of HFpEF.

Significance of frailty in patients with heart failure with preserved ejection fraction

A number of previous studies have reported that frailty is associated with mortality in patients with cardiovascular diseases.[26–30] Regarding HFpEF, we and another group reported the prognostic importance of frailty.[9,13] In a sub-analysis of data from the TOPCAT trial, higher frailty index was associated with poorer prognosis.[13] We recently reported that the prevalence of CFS ≥ 4 (more than vulnerable) was high (48%) in patients with HFpEF and that the presence of frailty as assessed with the CFS was significantly associated with poor prognosis.[9] These findings suggest that the assessment of frailty is critical to the management of patients with HFpEF and that interventions for frail patients may have a prognostic impact in patients with HFpEF. In our previous study, we observed significant interaction between frailty and the use of ACE-I or ARB for prognosis.[9] The present study examined the details of this interaction and more clearly demonstrated the possible effectiveness of ACE-I or ARB in frail patients with HFpEF.

Relationship among the renin-angiotensin-aldosterone system, frailty, and heart failure with preserved ejection fraction

Our study revealed that patients receiving ACE-I/ARB had a better composite endpoint and heart failure admission in HFpEF patients with high CFS. However, the mechanisms of the association between ACE-I/ARB and prognosis in patients with frailty remain unknown in detail. In addition, the relationship among the renin-angiotensin-aldosterone system (RAAS), frailty, and HFpEF remains to be elucidated. First, regarding the relationship between HFpEF and frailty, reduced physical activity, which is a characteristic of frailty, may increase the risk of HFpEF.[31] Frailty is also associated with malnutrition, which can cause a deterioration in immune function[32] and is an important prognostic factor in HFpEF.[33–35] These findings suggest that the presence of frailty may promote the progression of HFpEF, increase cardiac events, and cause a poor prognosis.

On the other hand, several mechanisms have been hypothesized to explain the potential association of the RAAS and frailty. First, inhibition of the RAAS leads to an improvement in cardiac and vascular function,[36] which is consequently associated with an improvement in physical function and a lower risk of frailty. Second, inhibition of the RAAS can attenuate inflammation,[37] which plays an important role in the development of frailty and poor muscle function.[38–40] Inflammation is also a well-known contributing factor in the development of HFpEF.[41–43] Finally, inhibition of RAAS can prevent age-related mitochondrial dysfunction, further contributing to improved muscle function.[44] These findings may suggest that ACE-I or ARB has a positive impact on improving frailty.

Taking these results together, we speculate that the inhibition of RAAS may improve prognosis in HFpEF patients with frailty at least partially through an improvement of frailty. In addition, RAAS may also directly improve HFpEF through the attenuation of inflammation, which is a common pathophysiology in HFpEF and frailty, particularly in patients who have both HFpEF and frailty. Further investigation to clarify the mechanism of this effect is warranted.

Clinical implications

Our results imply that the use of ACE-I/ARB may improve outcomes in patients with HFpEF and frailty, but not in those without frailty. Accordingly, CFS assessment of frailty in patients with HFpEF is useful in identifying patients who are eligible for treatment with ACE-I/ARB. ACE-I and ARB seem to be similarly associated with prognosis. On the other hand, ACE-I/ARB might not improve prognosis in HFpEF patients with low CFS. Considering that HRs in patients with low CFS were higher than 1.0 (*Figure 4*), administration of these drugs in this population may require careful attention. Prospective studies are necessary to clearly demonstrate these effects of ACE-I or ARB in patients with HFpEF.

Limitations

This study has several limitations. First, assessment of CFS was performed on admission but not at discharge or during hospitalization. It is possible that the severity of frailty may have changed during hospitalization. A previous study reported that 74.1% of patients showed an increase in CFS by ≥1 grade during hospitalization compared with CFS before admission.[45] Second, because we studied patients recovering from acute decompensated heart failure, generalization of the results to other populations should be performed with caution. Third, the CFS was recently updated.[46] Because this study was started in 2016, we used a previous version of the CFS in this study, and scoring in this study may therefore differ from that of the updated CFS. Finally, it is unclear whether the use of ACE-I/ARB in patients with frailty will lead to better outcomes. Prospective trials are needed to investigate this point.

Conclusions

In patients with HFpEF, the use of ACE-I/ARB was associated with better prognosis in patients with frailty assessed with the CFS, but not in those without frailty. The assessment of frailty with the CFS may be useful in identifying possible candidates for the administration of ACE-I/ARB in patients with HFpEF.

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Conflict of interest

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