Renin–angiotensin system inhibitors and clinical outcomes in patients with atrial fibrillation and heart failure: a propensity score-matched study from the Chinese Atrial Fibrillation Registry

Jing Lin[1] ⓘ, Liu He[1], Qing Qiao[1], Xin Du[1], Chang-Sheng Ma[1] and Jian-Zeng Dong[1,2] ⓘ

Abstract

Objective: The effect of renin–angiotensin system inhibitors (RASIs) in patients with heart failure (HF) and atrial fibrillation (AF) remains unclear. This study aimed to investigate associations between RASI use and all-cause mortality and cardiovascular outcomes in patients with AF and HF.

Methods: Using data from the China Atrial Fibrillation Registry study, we included 938 patients with AF and HF with a left ventricular ejection fraction $<50\%$. Cox regression models for RASIs vs. non-RASIs with all-cause mortality as the primary outcome were fitted in a 1:1 propensity score-matched cohort. A sensitivity analysis was performed by using a multivariable time-dependent Cox regression model. As an internal control, we assessed the relation between β-blocker use and all-cause mortality.

Results: During a mean follow-up of 35 months, the risk of all-cause mortality was similar in RASI users compared with non-users (hazard ratio: 0.92; 95% confidence interval: 0.67–1.26). Similar results were obtained in the sensitivity analysis. In contrast, β-blocker use was associated with significantly lower all-cause mortality in the same population.

[1]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University; National Clinical Research Center for Cardiovascular Diseases; Beijing Advanced Innovation Center for Big Data-Based Precision Medicine for Cardiovascular Diseases, Beijing, China

[2]Cardiovascular Hospital, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China

Corresponding author:
Jian-Zeng Dong, Beijing Anzhen Hospital, No. 2 Anzhen Street, Chaoyang District, Beijing, 100029, China.
Email: jzdong@ccmu.edu.cn

Conclusions: RASI use was not associated with better outcomes in patients with AF and HF in this prospective cohort, which raises questions about their value in this specific subset.
Trail Registration: ChiCTR-OCH-13003729.

Introduction

Chronic heart failure (HF) and atrial fibrillation (AF) are two common illnesses associated with a substantial morbidity and risk of death. AF and HF frequently coexist, and up to 50% of patients with HF develop AF throughout their disease.[1] HF promotes ultrastructural changes and neuroendocrine processes, which eventually lead to atrial remodeling and increase the risk of developing AF.[2–4] However, AF impairs cardiac function, leading to worsening symptoms of HF.[5,6] Patients with both AF and HF have an even higher mortality and hospital admission rates compared with having only one of these conditions, irrespective of which illness arises first.[7–9]

Oral therapies for HF, including β-blockers, renin–angiotensin system inhibitors (RASIs), and mineralocorticoid receptor antagonists, markedly improve outcomes in heart failure and reduced ejection fraction (HFrEF).[10–13] According to recent European and American guidelines, using these cardiovascular medications in patients with HFrEF has a class I recommendation.[14–16] Nonetheless, the efficacy of using these medications in patients with HF who have a comorbidity of AF remains unclear. Previous analyses in this patient subset have lacked statistical power, but further large randomized studies are

unlikely because most of these drugs are no longer patented. There is little incentive in the pharmaceutical industry to sponsor such trials. In the absence of such randomized evidence, evaluating the treatment effect from observational cohorts using specific methods to decrease attribution bias would be helpful. Post-hoc analysis of the Atrial Fibrillation and Congestive Heart Failure trial showed that β-blocker therapy was associated with a significantly lower mortality, but not hospitalization rate, in patients with HFrEF and AF.[17] These data enriched current evidence-based recommendations in patients with HF and added to the limited current evidence about treatment in patients with HF and AF.

With regard to RASIs, large randomized, controlled trials have established the benefits of angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers in reducing morbidity and mortality in HFrEF.[11–13,18] Recently, HF with a left ventricular ejection fraction (LVEF) of 40% to 49% was defined as a distinct phenotype of HF, namely HF with a mid-range left ventricular ejection fraction (HFmrEF).[15] Observational studies have shown that RASI use is associated with a better prognosis in patients with HFmrEF.[19,20] Therefore, this study aimed to investigate the association between routine RASI use and mortality and other

cardiovascular outcomes in patients with HF and AF, specifically those with HFrEF and HFmrEF.

Materials and methods

Study population

The current analysis is based on the China Atrial Fibrillation Registry (CAFR) study, which was a prospective, multicenter, hospital-based, ongoing registry study of patients diagnosed with AF. Details of the cohort have been described previously.[21] This observational study aimed to understand the current clinical practice patterns, prognoses, and related factors in Chinese patients with AF and to compare different treatments in real-world practice. This study was approved by the Human Research Ethics Committee of Beijing Anzhen Hospital (approval number: D111107300000). The study is 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. Written informed consent was obtained from all patients. The reporting of this study conforms to the STROBE statement.[22] Between August 2011 and December 2018, patients with AF were prospectively recruited from outpatient clinics and those in the hospital patients in 31 hospitals located in Beijing.

Patients with AF were included in the present analysis if they had an LVEF <50%, and they had symptomatic congestive heart failure and/or a medical history of HF.

RASI use was defined as the use of an angiotensin–converting enzyme inhibitor or angiotensin-II receptor blocker at baseline or during the follow-up. Patients who never used an RASI were classified as non-users at baseline and throughout the follow-up period (until death or 31 December 2018).

Information on angiotensin receptor-neprilysin inhibitor (ARNI) therapy was not collected in this registry because the use of an ARNI was recommended for patients with HFrEF in 2014.[10] RASIs and data on other medications were collected at every follow-up.

We excluded patients aged younger than 18 years (n = 17), those with valvular AF (n = 626), and those who had <6 months' follow-up (n = 3226). The following information on the patients' baseline characteristics was collected: age, sex, smoking and drinking status, the medical history, including hypertension, diabetes mellitus (DM), myocardial infarction, stroke/transient ischemic attack (TIA), peripheral artery disease, the presence of a permanent pacemaker or implantable cardioverter-defibrillator (ICD), and catheter ablation, and the CHA_2DS_2-VASc score (HF, hypertension, age ≥75 years, DM, previous stroke/TIA, vascular disease, age 65–74 years, female sex). We also collected results of a physical examination, laboratory and imaging tests, and medication. All data were entered into a specific electronic data capture system. Data elements and definitions of each variable were in accordance with the American College of Cardiology/American Heart Association recommendations on AF clinical data standards.[14,16,23,24]

Follow-up and outcomes

Each enrolled patient was followed up at 3 months, 6 months, and every 6 months thereafter at an outpatient clinic or by a telephone interview by trained staff. Information on medical or interventional therapies, events of hospitalizations, and deaths was collected at each follow-up. The primary outcome was all-cause mortality. The secondary outcomes were cardiovascular mortality, cardiovascular hospitalization, and a composite endpoint

of all-cause mortality or cardiovascular hospitalization.

Statistical analysis

Data are expressed as mean (standard deviation) for normally distributed continuous variables and number (%) for categorical variables. We compared patients' characteristics between baseline RASI users and non-RASI users using the t test for continuous variables and the χ^2 test for categorical variables.

For the main analysis, we carried out a propensity score-matched Cox proportional hazard analysis. Propensity score-matching (1:1) was performed using a greedy algorithm with a caliper of 0.2 to adjust for measured confounders between patients receiving and those not receiving an RASI at baseline before comparison. Propensity scores were calculated using a logistic regression model in which RASI use at baseline was treated as the dependent variable. Twenty-one baseline variables were included as covariates (Table 1). These covariates were selected on the basis of considering substantive knowledge and statistical associations. Improvements in balance across covariates were measured by absolute values of standardized differences in means or proportions of each covariate across exposure groups and expressed as a percentage of the pooled standard deviation. An absolute standardized difference <10%, as applied in our approach, was generally accepted as indicative of inconsequential residual bias.[25,26] Drug use (i.e., use of RASIs, digoxin, β-blockers, oral anticoagulants, and statins) was treated as a time-dependent covariate.

Sensitivity analysis was performed with multivariate Cox regression models to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs) for RASI use in clinical outcomes, in which drug use was also treated as a time-varying variable.

The following variables that were included in the multivariable adjustment were as follows: age, sex, smoking, drinking, estimated glomerular filtration rate (eGFR), heart rate, systolic blood pressure, New York Heart Association (NYHA) class, LVEF, medical history (stroke/TIA, peripheral arterial thrombosis, hypertension, DM, MI, peripheral artery disease, permanent pacemaker or ICD, and CA), and drug use (i.e., RASIs, digoxin, β-blockers, oral anticoagulants, and statins).

With observational data, there needs to be evaluation of whether methodological limitations or decisions could bias findings. As an internal validity check of the present analyses, we assessed the association between β-blocker use and clinical outcomes in the same non-HF with preserved ejection fraction population using the same analytical methods as those described above.

To investigate whether any particular feature modulated the effects of an RASI on the primary outcome, subgroup analyses were performed in the main analysis. Patients were stratified by age (age ≥65 years or age <65 years), the eGFR (eGFR ≥60 mL/minute or eGFR <60 mL/minute), the LVEF (LVEF ≥40% or LVEF <40%), or the AF pattern (persistent AF or non-persistent AF). Heterogeneity across subgroups was tested by introducing interaction terms of RASI use and stratification variables into the Cox proportional hazard regression models.

All statistical tests were two-tailed with a significance level of 0.05. Data were analyzed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

A total of 25,512 patients were prospectively enrolled in the CAFR study. Of these,

Table 1. Baseline characters according to RASI use before and after propensity score matching

Characteristics	Before propensity matching			After propensity matching		
	RASI user (n = 568)	Non-RASI user (n = 370)	p value	RASI user (n = 295)	Non-RASI user (n = 295)	p value
Age, mean (SD), years*	66.2 (12.6)	65.1 (14.0)	0.215	65.8 (13.8)	66.0 (12.9)	0.819
Male sex*	400 (68.4)	253 (70.4)	0.510	202 (68.5)	199 (67.5)	0.791
Smoking*	112 (19.7)	82 (22.2)	0.366	50 (19.6)	59 (23.1)	0.331
Drinking*	118 (20.8)	70 (18.9)	0.488	52 (17.6)	56 (19.0)	0.670
Medical history						
Stroke/TIA*	112 (19.7)	62 (16.8)	0.254	53 (18.0)	60 (20.3)	0.463
Peripheral arterial thrombosis*	15 (2.6)	7 (1.9)	0.459	7 (2.4)	7 (2.4)	1.000
Hypertension*	434 (76.4)	195 (52.7)	<0.001	173 (58.6)	194 (65.8)	0.075
Diabetes mellitus*	198 (34.9)	107 (28.9)	0.058	97 (32.9)	106 (35.9)	0.435
Myocardial infarction*	114 (20.1)	56 (15.1)	0.055	50 (17.0)	60 (20.3)	0.291
Coronary artery disease	138 (24.3)	76 (20.5)	0.180	67 (22.7)	67 (22.7)	1.000
Peripheral arterial disease*	13 (2.3)	5 (1.4)	0.306	5 (1.7)	6 (2.0)	0.761
Permanent pacemaker or ICD*	38 (6.7)	24 (6.5)	0.902	22 (7.5)	27 (9.2)	0.456
Catheter ablation*	98 (20.3)	75 (17.3)	0.244	62 (21.0)	53 (18.0)	0.350
Clinical examinations						
eGFR, mean (SD), mL/minute/1.73 m^2*	100.6 (58.1)	94.8 (34.4)	0.063	94.6 (35.4)	92.3 (29.4)	0.377
BMI, mean (SD), kg/m^2	25.2 (3.9)	25 (3.5)	0.298	25.0 (3.4)	25.0 (4.0)	0.953
NYHA class III or IV*	112 (19.7)	82 (22.2)	0.366	132 (44.8)	145 (50.0)	0.211
Systolic blood pressure, mean (SD), mm Hg*	129.2 (19.8)	122 (16.7)	<0.001	123.6 (17.1)	124.7 (20.2)	0.446
Heart rate, mean (SD), beats/minute*	92.3 (25.9)	88.1 (25.0)	0.0137	89.1 (25.4)	87.8 (25.4)	0.518
LVEF, mean (SD), %*	38.7 (6.9)	39.2 (7.1)	0.282	39.0 (7.1)	38.7 (6.8)	0.573
CHA$_2$DS$_2$-VASc score, mean (SD)	3.9 (1.9)	3.4 (2.0)	<0.001	3.6 (3.4)	3.8 (3.6)	0.147
Outpatient clinic	114 (20.1)	126 (34.1)	<0.001	66 (46.5)	76 (53.5)	0.386
Hospitalized setting	454 (79.9)	244 (65.9)	<0.001	229 (51.5)	219 (48.9)	0.386
Baseline medications						
OAC*	257 (47.0)	174 (45.3)	0.593	131 (44.4)	133 (45.1)	0.869
β-blocker*	360 (63.4)	211 (57.0)	0.051	173 (62.5)	182 (61.7)	0.449
Digoxin*	239 (42.1)	120 (32.4)	0.003	101 (34.2)	111 (37.6)	0.391
Statin*	310 (54.6)	141 (38.1)	<0.001	125 (42.4)	145 (49.2)	0.098
AF type						
Newly diagnosed AF	75 (13.4)	45 (12.2)	0.065	39 (13.2)	36 (12.2)	0.659
Paroxysmal AF	146 (26.0)	122 (33.1)		96 (32.5)	88 (29.8)	0.659
Persistent AF	341 (60.7)	202 (54.7)		160 (54.2)	171 (58.0)	0.659

Values are mean ± SD or n (%).

*Covariates included in the propensity score matching analysis.

RASI, renin–angiotensin system inhibitor; SD, standard deviation; TIA, transient ischemic attack; ICD, implantable cardioverter-defibrillator; eGFR, estimated glomerular filtration rate; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CHA$_2$DS$_2$-VASc, HF, hypertension, age ≥75 years, diabetes mellitus, previous stroke/TIA, vascular disease, age 65 to 74 years, female sex; OAC, oral anticoagulant; AF, atrial fibrillation.

938 patients with AF and HF with an LVEF <50% were included in the analysis, with a mean follow-up of 35 months. The baseline characteristics of the patients are shown in Table 1. Before matching, 568 (60.6%) patients were RASI users and 370 (39.4%) were non-RASI users. RASI users had a higher systolic blood pressure ($p < 0.001$), heart rate ($p < 0.05$), CHA_2D_2-VASc score ($p < 0.001$), and prevalence of hypertension ($p < 0.001$) compared with non-RASI users. Furthermore, RASI users were more likely to be receiving digoxin ($p < 0.01$) and to be on statins ($p < 0.001$) than non-RASI users.

After propensity matching, the population was restricted to 590 patients among whom 295 (50%) were RASI users and 295 (50%) were non-RASI users. A flow chart showing the patients' selection is shown in Figure 1. After propensity matching, there were no significant differences in baseline characteristics between those who received an RASI and those who did not receive an RASI (Table 1). Post-matching standardized differences for all 21 baseline covariates were <10%. Matched patients had a mean age of 65.9±13.3 years, 70.0% were men, and the mean LVEF was 38.9% ± 6.9%.

Primary and secondary outcomes

In the total population, 294 patients died during the follow-up. A total of 177 (9.06/100 patient-years) RASI users and 117 (9.64/100 patient-years) non-RASI users died. In the propensity score-matched population, 205 patients died during the follow-up, and these comprised 101 (9.98/100 patient-years) RASI users and 104 (11.37/100 patient-years) non-RASI users. The rate of the primary outcome (all-cause mortality) was similar in RASI users compared with non-RASI users (HR: 0.92; 95% CI: 0.67–1.26) (Table 2). Analyses of secondary outcomes yielded similar results. The HR was 1.02 (95% CI: 0.68–1.52) for

cardiovascular mortality, 0.99 (95% CI: 0.72–1.36) for cardiovascular hospitalization, and 0.89 (95% CI: 0.69–1.14) for the composite endpoint of all-cause mortality or cardiovascular hospitalization.

Similar results were obtained in sensitivity analysis with multivariate Cox regression models (HR: 0.93 for all-cause mortality, HR: 0.92 for cardiovascular mortality, HR: 1.07 for cardiovascular hospitalization, HR: 1.07 for cardiovascular hospitalization, and HR: 0.94 for the composite outcome).

Subgroup analyses

The main analyses by the propensity score-matching approach were repeated in key patient subgroups. There were no significant interactions between RASI use and AF patterns (i.e., persistent AF or non-persistent AF), age (i.e., age ≥65 years or <65 years), the eGFR (i.e., eGFR ≥60 mL/minute or <60 mL/minute), or the LVEF (i.e., LVEF ≥40% or <40%) regarding all-cause mortality (Figure 2).

Internal control

The associations of β-blocker use and all-cause mortality and cardiovascular outcomes were analyzed with the same population as that used for investigating RASI use. There were substantial differences in baseline characteristics between patients who received β-blockers and those who did not receive β-blockers before propensity matching (Table 3). After propensity matching, there were no significant differences in baseline characteristics between patients who received and those who did not receive β-blockers.

β-blockers were associated with significantly lower all-cause mortality in the propensity-matched population (HR: 0.69; 95% CI: 0.51–0.93; $p = 0.016$) and in the total population after analysis with
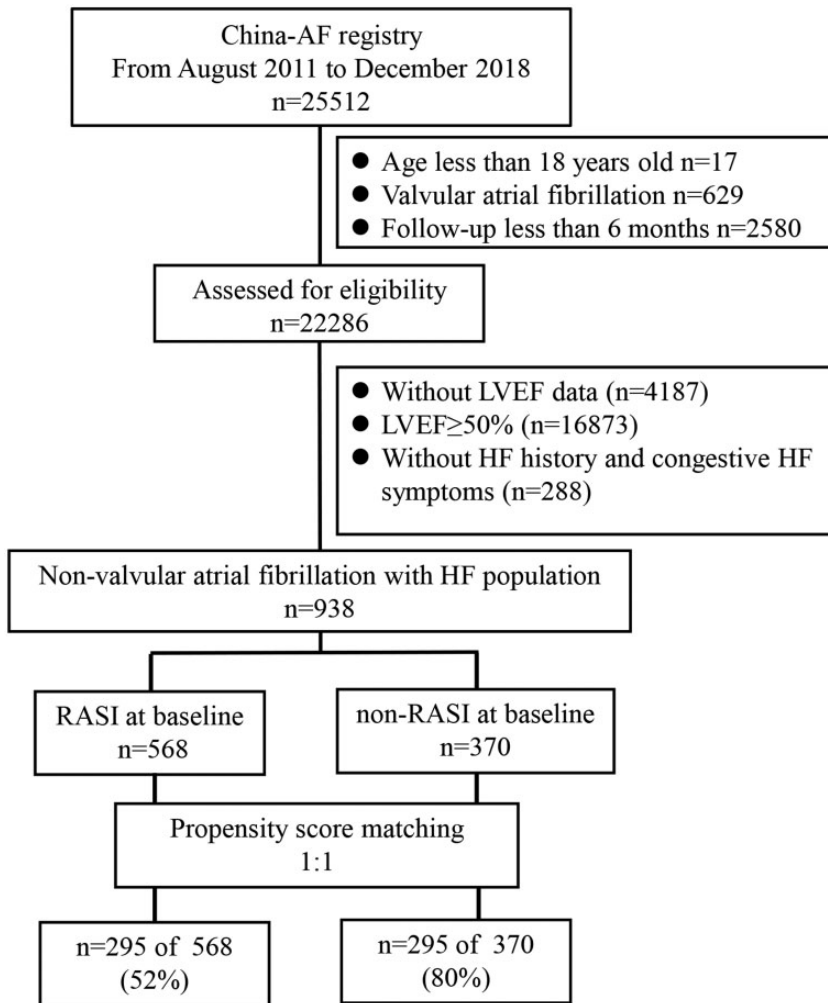
Figure 1. Overview of the study cohort
AF, atrial fibrillation; LVEF, left ventricular ejection fraction; HF, heart failure; RASI, renin–angiotensin system inhibitor.

multivariate Cox regression (HR: 0.68; 95% CI: 0.50–0.92; $p = 0.012$) (Table 4). However, β-blockers were not associated with any secondary outcomes in different analytical methods.

Discussion

In this prospective cohort, we did not find any significant associations between the routine use of RASIs and better outcomes in patients with AF and HFrEF or HFmrEF. These findings were consistent across propensity score-matching analysis and sensitivity analysis with multivariate Cox regression models. Sub-group analyses showed similar results, regardless of the age, eGFR, type of AF, or LVEF. However, with similar methodological approaches, β-blocker use was significantly

Table 2. Incidence rates and associations between RASI use and outcomes with propensity score matching analyses and sensitivity analyses

| | Events No. (/100 patient-years)[a] | | | |
Characteristics	RASI user (n = 295)	Non-RASI user (n = 295)	HR (95% CI)	p value
Propensity score matching analysis				
All-cause mortality	101 (9.98)	104 (11.37)	0.92 (0.67–1.26)	0.602
Cardiovascular mortality	57 (5.43)	62 (6.51)	1.02 (0.68–1.52)	0.931
Cardiovascular hospitalization	88 (9.78)	93 (11.46)	0.99 (0.72–1.36)	0.903
All-cause mortality or cardiovascular hospitalization	145 (17.07)	159 (21.30)	0.89 (0.69–1.14)	0.340
Sensitivity analysis (modeling with multivariate Cox regression)[b]				
All-cause mortality	177 (9.06)	117 (9.64)	0.93 (0.71–1.22)	0.606
Cardiovascular mortality	102 (5.03)	68 (7.99)	0.92 (0.65–1.31)	0.651
Cardiovascular hospitalization	171 (10.10)	115 (11.02)	1.07 (0.82–1.39)	0.637
All-cause mortality or cardiovascular hospitalization	274 (16.99)	188 (19.32)	0.94 (0.76–1.16)	0.576

[a]Data for RASI users and non-RASI users are shown as the incidence rate (number of events/100 patient-years).
[b]Multivariate time-varying Cox regression was performed in the 938 patients with non-heart failure with preserved ejection and adjusted for age, sex, smoking, drinking, the estimated glomerular filtration rate, heart rate, systolic blood pressure, New York Heart Association class, the left ventricular ejection fraction, the medical history (stroke/transient ischemic attack, peripheral arterial thrombosis, hypertension, diabetes mellitus, myocardial infarction, peripheral artery disease, permanent pacemaker or implantable cardioverter-defibrillator, and catheter ablation), and use of β-blockers, digoxin, oral anticoagulants, and statins.
RASI, renin–angiotensin system inhibitor; HR, hazard ratio; CI, confidence interval.
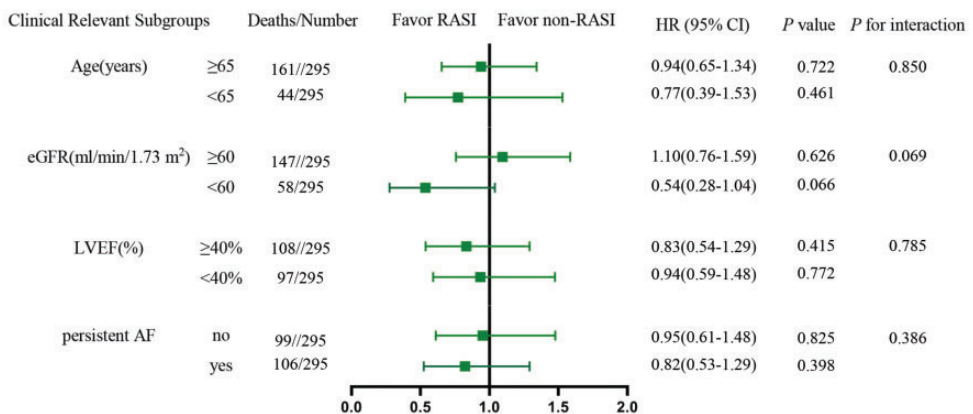
Figure 2. RASI use and outcomes in clinically relevant subgroups
RASI, renin–angiotensin system inhibitor; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; AF, atrial fibrillation.

Table 3. Baseline characters according to β-blocker use before and after propensity score matching

	Before propensity matching			After propensity matching		
Characteristics	β-blocker (n = 571)	Non-β-blocker (n = 367)	p value	β-blocker (n = 316)	Non-β-blocker (n = 316)	p value
Age, mean (SD), years*	65.8 (12.6)	65.8 (14.0)	0.975	65.8 (13.2)	66.2 (13.7)	0.694
Male sex*	400 (70.05)	253 (68.9)	0.717	217 (68.7)	217 (68.7)	1.000
Smoking*	134 (23.5)	60 (16.4)	0.009	58 (18.4)	56 (17.7)	0.836
Drinking*	125 (21.9)	63 (17.2)	0.078	60 (19.0)	56 (17.7)	0.681
Medical history						
Stroke/TIA*	102 (17.9)	72 (19.6)	0.500	66 (19.0)	65 (20.6)	0.922
Peripheral arterial thrombosis*	13 (2.3)	9 (1.9)	0.862	11 (3.5)	8 (2.5)	0.465
Hypertension*	394 (69.0)	235 (64.0)	0.114	219 (69.3)	208 (65.8)	0.350
Diabetes mellitus*	195 (34.2)	110 (30.0)	0.183	104 (32.9)	102 (32.3)	0.865
Myocardial infarction*	114 (20.0)	56 (15.2)	0.068	55 (17.4)	53 (16.8)	0.833
Coronary artery disease	152 (26.6)	62 (16.9)	0.001	74 (23.4)	59 (18.7)	0.143
Peripheral arterial disease*	12 (2.1)	6 (1.6)	0.611	8 (1.9)	6 (2.5)	0.589
Permanent pacemaker or ICD*	38 (6.7)	24 (2.5)	0.013	23 (7.3)	15 (4.8)	0.181
Catheter ablation*	82 (14.4)	91 (24.8)	<0.001	62 (19.6)	76 (24.1)	0.178
Clinical Examinations						
eGFR, mean (SD), mL/minute/1.73 m^2*	96.3 (53.6)	101.8 (45.2)	0.107	94.6 (35.4)	92.3 (29.4)	0.377
BMI, mean (SD), kg/m^2	25.3 (3.7)	24.8 (3.7)	0.105	25.2 (3.8)	24.9 (3.7)	0.341
NYHA class III or IV*	267 (46.8)	174 (47.4)	0.118	153 (48.4)	163 (51.6)	0.575
Systolic blood pressure, mean (SD), mm Hg	125.6 (18.3)	127.6 (20.0)	0.132	127.9 (19.0)	128.2 (20.3)	0.880
Heart rate, mean (SD), beats/minute	91.5 (24.1)	89.3 (27.8)	0.211	91.9 (24.6)	90.3 (27.8)	0.465
LVEF, mean (SD), %*	39.1 (7.1)	38.5 (6.8)	0.187	38.9 (7.3)	38.8 (6.7)	0.868
CHA$_2$DS$_2$-VASc score, mean (SD)	3.7 (1.9)	3.7 (2.0)	0.979	3.8 (3.6)	3.8 (3.6)	0.905
Baseline medications						
OAC*	284 (49.4)	147 (40.1)	0.004	131 (41.5)	123 (38.9)	0.516
RASI*	360 (63.1)	208 (56.7)	0.051	197 (62.3)	189 (59.8)	0.514
Digoxin*	218 (38.2)	141 (38.4)	0.941	116 (36.7)	124 (39.2)	0.512
Statin*	299 (52.4)	152 (41.4)	0.001	152 (48.1)	136 (43.0)	0.201
AF type						
Newly diagnosed AF	77 (13.5)	43 (11.9)	0.192	47 (14.9)	41 (13.0)	0.789
Paroxysmal AF	152 (26.7)	116 (32.1)		89 (28.2)	91 (28.8)	
Persistent AF	341 (59.8)	202 (56.0)		180 (57.0)	184 (58.2)	

Values are mean ± SD or n (%).

*Covariates included in the propensity score-matching analysis.

SD, standard deviation; TIA, transient ischemic attack; ICD, implantable cardioverter-defibrillator; eGFR, estimated glomerular filtration rate; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CHA$_2$DS$_2$-VASc, HF, hypertension, age $\geq$75 years, diabetes mellitus, previous stroke/TIA, vascular disease, age 65 to 74 years, female sex; OAC, oral anticoagulant; RASI, renin–angiotensin system inhibitor; AF, atrial fibrillation.

Table 4. Incidence rates and associations between β-blocker use and outcomes with multivariate time-varying Cox regression and propensity score matching analyses

Characteristics	Events No. (/100 patient-years)[a]		HR (95% CI)	p value
	β-blocker (n = 316)	Non-β-blocker (n = 316)		
Propensity score matching analysis				
All-cause mortality	95 (9.98)	108 (11.37)	0.69 (0.51–0.93)	0.016
Cardiovascular mortality	57 (5.43)	62 (6.51)	0.78 (0.52–1.17)	0.228
Cardiovascular hospitalization	88 (9.78)	93 (11.46)	1.09 (0.80–1.47)	0.589
All-cause mortality or cardiovascular hospitalization	145 (17.07)	159 (21.30)	0.82 (0.65–1.05)	0.112
Modeling with multivariate Cox regression[b]				
All-cause mortality	181 (9.19)	113 (9.74)	0.68 (0.50–0.92)	0.012
Cardiovascular mortality	107 (5.26)	63 (5.19)	0.77 (0.52–1.15)	0.204
Cardiovascular hospitalization	183 (10.65)	103 (10.17)	1.13 (0.82–1.56)	0.468
All-cause mortality or cardiovascular hospitalization	289 (117.51)	173 (18.56)	0.8 2(0.64–1.05)	0.113

[a]Data for RASI use and non-RASI use are shown as the incidence rate (number of events/100 patient-years).
[b]Multivariate Cox regression was performed as described previously.
HR, hazard ratio; CI, confidence interval; RASI, renin–angiotensin system inhibitor.

associated with a lower rate of all-cause mortality. This internal control reinforced the validity of the current analytical strategy. Therefore, a benefit of routine RASI use was not found in patients with AF and HFrEF and/or HFmrEF in this prospective, observational cohort.

In our study, 3.8% of the cohort of the patients had HF with HFrEF and HFmrEF. This rate is much lower than that in Western world cohorts. More than 50% of patients with HF will experience AF at some time. A meta-analysis on individual-level data on the efficacy of β blockers showed that 17% of patients with HF had AF at baseline.[17] However, we did not include HF with preserved ejection fraction in our study. More than two thirds of patients with HF with preserved ejection fraction have AF, and most AF occurs before a diagnosis of HF with preserved ejection.[27] Furthermore, the severity of patients in our study was much lower than that in patients who only have HF.

An example of this difference is that only approximately 20% of patients had NYHA class III/IV cardiac function in our study, whereas 60% of patients had NYHA class III/IV cardiac function in the previous meta-analysis.[17] AF is more likely to develop throughout illness as the severity of HF increases. This finding could be the reason for the prevalence of AF being much higher in a HF cohort than in our study.

HF with AF is a specific subset population; when one of these shows an increase in its prevalence and incidence, the prognosis of the other worsens. Their frequent coexistence raises several challenges, especially regarding how best to treat them with routine medication. Our study showed that the prognostic benefit identified in patients with HFrEF and HFmrEF should not be extrapolated to HF subsets with AF rhythm. Therefore, the benefit of RASI use might be different between HFmrEF with AF and HFrEF with AF. To address this hypothesis, interactions were tested

between RASI use and the LVEF ($\geq 40\%$ vs. $< 40\%$). However, this interaction was nonsignificant. More specifically, we did not find any benefit of RASI use in improving all-cause mortality when we compared patients with an LVEF $< 40\%$ or $\geq 40\%$ in subgroup analysis.

Notably, our results are in contrast to a secondary analysis of the Candesartan in Heart Failure-Assessment of Reduction in Mortality and morbidity (CHARM) trial.[28] This trial reported that candesartan led to a significant 30% risk reduction in all-cause mortality (HR: 0.70; 95% CI: 0.50–0.90) in patients with AF and HFrEF (i.e., LVEF $< 40\%$). Because of the nature of a secondary analysis, the conclusion of the CHARM trial may be not reliable owing to not following the randomized control principle and introducing bias. The primary analysis of this trial was based on the diagnosis of AF using a baseline electrocardiogram. Patients in sinus rhythm at baseline, but with a history of AF or new development of AF during follow-up, were categorized as no AF in the CHARM trial. Therefore, our study probably underestimated the true relationship between AF and mortality.

The reason for the lack of an association between RASI and better outcomes in patients with AF and HF might be due to several physiological and characteristic differences. First, unlike sinus rhythm, an irregular rhythm in AF is associated with a detrimental effect on cardiac function,[4,29] which might offset the benefit of RASI on mortality. Second, the statistical results should be evaluated with caution by fully understanding the detailed information and underlying biases of a study. An example of this required understanding is that a meta-analysis published in 2014 showed no evidence that β-blockers improved the prognosis in patients with HF concomitant with AF.[30] However, later studies found the opposite conclusion.[17,31] In this previous meta-analysis, more patients with NYHA

III/IV cardiac function may have weakened the therapeutic benefit of β-blockers. Fewer patients with HF had NYHA III/IV cardiac function in our study compared with previous trials in patients with HFrEF and HFmrEF.[30] Therefore, β-blocker use was associated with significantly lower all-cause mortality in patients with AF and HF, whereas RASI use was not associated with lower all-cause mortality in the same population. We speculate that the benefits of RASI are limited in this population. Third, there are also structural and cellular consequences of AF that might affect the treatment efficacy.[32] These reasons cannot fully explain why RASI was not associated with a prognostic benefit in patients with AF and HF. Therefore, this issue requires further investigation.

Even though we did not find evidence of a benefit from RASI use in this analysis, several factors suggest that these results are valid. First, we used data from the CAFR study.[22,33] These prospective data reduced the number of misclassifications, helped to avoid recall bias, and increased the accuracy of the potential confounder measurements. Second, we used different analytical approaches to control confounding. To balance potential confounders, we adopted the propensity score matching approach. Among observational studies, using the propensity score ensures the closest design to a clinical trial.[34] We also adjusted for an extensive array of clinical variables (21 clinical covariates) in a multivariable Cox model. Time-varying coefficients are capable of addressing the time-varying nature of treatment and reducing potential immortal time bias.[35] We modeled medication use as a time-dependent covariate in the propensity score matching approach and multivariable Cox model analysis to account for treatment changes during the follow-up. We confirmed our conclusion across various subgroups. Third, the contrast between the lack effects of RASI on all-cause mortality and the

marked consistent benefit of β-blocker use in our analysis suggested that drugs, rather than analytical methods or study design, may have accounted for our results.

Our study has several limitations. First, although we adjusted for many significant factors and used sensitivity analysis to examine the "true" association, residual confounding effects may have been present. Second, this was an observational study in nature. A causal relationship between RASI use and all-cause mortality or cardiovascular outcomes should not be ruled out unless randomized, controlled trials can confirm our findings. Third, we lacked information about ARNI use in this cohort, which may have had a role in the prognostic outcome. However, this potential bias is likely to be minimal because ARNI therapy is comparatively low in China.[36] Despite these limitations, our study provides essential data on the relationship between RASI use and clinical outcomes in patients with AF and HF.

Conclusions

In this prospective CAFR study, RASI use was not associated with better outcomes in patients with AF and HF with an LVEF <50%. In contrast, in the same population, identical methods showed a lower rate of all-cause mortality in patients on β-blockers than in those without β-blockers. These results suggest that RASIs are not useful in this specific subset, but their effects need to be critically evaluated in randomized trials.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Key Research and Development Program of China (2016YFC0900901, 2016YFC1301002).

ORCID iDs

Jing Lin https://orcid.org/0000-0002-9328-0480
Jian-Zeng Dong https://orcid.org/0000-0001-7299-7805

References

1. Desai AS and Stevenson LW. Rehospitalization for heart failure. *Circulation* 2012; 126: 501–506.
2. Sanders P, Morton JB, Davidson NC, et al. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. *Circulation* 2003; 108: 1461–1468.
3. Li D, Fareh S, Leung TK, et al. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation* 1999; 100: 87–95.
4. Clark DM, Plumb VJ, Epstein AE, et al. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol* 1997; 30: 1039–1045.
5. Byrne M, Kaye DM and Power J. The synergism between atrial fibrillation and heart failure. *J Card Fail* 2008; 14: 320–326.
6. Anter E, Jessup M and Callans DJ. Atrial fibrillation and heart failure treatment considerations for a dual epidemic. *Circulation* 2009; 119: 2516–2525.
7. Agarwal V, Briasoulis A and Messerli FH. Effects of renin-angiotensin system blockade on mortality and hospitalization in heart failure with preserved ejection fraction. *Heart Fail Rev* 2013; 18: 429–437.
8. Dries DL, Exner DV, Gersh BJ, et al. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. *J Am Coll Cardiol* 1998; 32: 695–703.
9. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint

influence on mortality. *Circulation* 2003; 107: 2920–2925.

10. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371: 993–1004.

11. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; 316: 1429–1435.

12. SOLVD Investigators; Yusuf S, Pitt B, Davis CE, et al. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; 325: 293–302.

13. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003; 362: 759–766.

14. Writing Committee Members, Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; 128: e240–e327.

15. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur Heart J* 2016; 37: 2129–2200.

16. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart failure society of America. *J Card Fail* 2017; 23: 628–651.

17. Cadrin-Tourigny J, Shohoudi A, Roy D, et al. Decreased mortality with beta-blockers in patients with heart failure and coexisting atrial fibrillation. *JACC Heart Fail* 2017; 5: 99–106.

18. Vermes E, Tardif J-C, Bourassa MG, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction. *Circulation* 2003; 107: 2926–2931.

19. Koh AS, Tay WT, Teng THK, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail* 2017; 19: 1624–1634.

20. Tsuji K, Sakata Y, Nochioka K, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. *Eur J Heart Fail* 2017; 19: 1258–1269.

21. Du X, Ma C, Wu J, et al. Rationale and design of the Chinese atrial fibrillation registry study. *BMC Cardiovasc Disord* 2016; 16: 130.

22. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Bull World Health Organ* 2007; 85: 867–872.

23. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol* 2016; 68: 1476–1488.

24. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. *Circulation* 2019; 140: e125–e151.

25. Edner M, Benson L, Dahlstrom U, et al. Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study. *Eur Heart J* 2015; 36: 2318–2326.

26. Thomas L, Li F and Pencina M. Using propensity score methods to create target

populations in observational clinical research. *Jama* 2020; 323: 466–467.

27. Saczynski JS, Go AS, Magid DJ, et al. Patterns of comorbidity in older adults with heart failure: the Cardiovascular Research Network PRESERVE study. *J Am Geriatr Soc* 2013; 61: 26–33.

28. Olsson LG, Swedberg K, Ducharme A, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006; 47: 1997–2004.

29. Daoud EG, Weiss R, Bahu M, et al. Effect of an irregular ventricular rhythm on cardiac output. *Am J Cardiol* 1996; 78: 1433–1436.

30. Kotecha D, Holmes J, Krum H, et al. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* 2014; 384: 2235–2243.

31. Nielsen PB, Larsen TB, Gorst-Rasmussen A, et al. β-Blockers in atrial fibrillation patients with or without heart failure. *Circ Heart Fail* 2016; 9: e002597.

32. Neilan TG, Shah RV, Abbasi SA, et al. The incidence, pattern, and prognostic value of left ventricular myocardial scar by late gadolinium enhancement in patients with atrial fibrillation. *J Am Coll Cardiol* 2013; 62: 2205–2214.

33. Lan DH, Jiang C, Du X, et al. Female sex as a risk factor for ischemic stroke and systemic embolism in Chinese patients with atrial fibrillation: a report from the China-AF study. *J Am Heart Assoc* 2018; 7: e009391.

34. Austin PC. Assessing balance in measured baseline covariates when using many-to-one matching on the propensity-score. *Pharmacoepidemiol Drug Saf* 2008; 17: 1218–1225.

35. Fisher LD and Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. *Annu Rev Public Health* 1999; 20: 145–157.

36. Li L, Liu R, Jiang C, et al. Assessing the evidence–practice gap for heart failure in China: the Heart Failure Registry of Patient Outcomes (HERO) study design and baseline characteristics. *Eur J Heart Fail* 2019; 22: 646–660.