

# ARNI versus ACEI/ARB in Reducing Cardiovascular Outcomes after Myocardial Infarction

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## Abstract

**Aims** This study aimed to compare the efficacy of angiotensin receptor-neprilysin inhibitor (ARNI) therapy with angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB) therapy for cardiovascular outcomes in patients with acute myocardial infarction (AMI).

**Methods and results** Data were collected from the Biobank of the First Affiliated Hospital of Xi'an Jiaotong University between January 2016 and December 2020. A total of 7556 AMI patients were screened for eligibility. Propensity score matching based on age, sex, blood pressure, kidney function, baseline left ventricular ejection fraction (LVEF), and cardiovascular medication were conducted, resulting in 291 patients with AMI being assigned to ARNI, ACEI, and ARB group, respectively. Patients receiving ARNI had significantly lower rates of the composite cardiovascular outcome than ACEI {hazard ratio [HR] 0.51, [95% confidence interval (CI), 0.27–0.95],  $P = 0.02$ }, and ARB users [HR 0.47, (95%CI, 0.24–0.90),  $P = 0.02$ ]. Patients receiving ARNI showed lower rates of cardiovascular death than ACEI [HR 0.37, (95%CI, 0.18–0.79),  $P = 0.01$ ] and ARB users [HR 0.41, (95%CI, 0.18–0.95),  $P = 0.04$ ]. Subgroup analysis indicated that patients with LVEF no more than 40% tend to benefit more from ARNI as compared with ACEI [HR 0.30, (95%CI, 0.11–0.86),  $P = 0.01$ ] or ARB [HR 0.21, (95%CI, 0.04–1.1),  $P = 0.05$ ]. Patients aged no more than 60 years exhibited reduced composite endpoints [HR for ARNI vs. ARB: 0.11, (95%CI, 0.03–0.46),  $P = 0.002$ ].

**Conclusions** In patients with AMI, ARNI was superior to ACEI/ARB in reducing the long-term adverse cardiovascular outcomes. Subgroup analysis further indicates that ARNI is more likely to benefit patients with LVEF less than 40% and aged less than 60 years.

**Keywords** Acute myocardial infarction; Sacubitril/valsartan (LCZ696); Angiotensin converting enzyme inhibitor (ACEI); Angiotensin receptor blockers (ARB)

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## Introduction

Ventricular remodelling after acute myocardial infarction (AMI) has been proven to be correlated to the occurrence of heart failure (HF) and the incidence of long-term cardiac events after AMI.<sup>1–3</sup> Despite advances in the treatment regime of cardiovascular disease, ventricular remodelling after AMI remains a major public health problem worldwide and exerts a substantial economic burden. Prompt initiation of guideline-proven therapies, including utilization of angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor

blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI), has resulted in reduced in-hospital mortality.<sup>4,5</sup> However, although a number of clinical trials indicate the superiority of ARNI compared with ACEI or ARB among patients with HF with reduced ejection fraction (HFrEF), evidence is still lacking for the long-term benefits of ARNI over ACEI or ARB among AMI patients.

Patients surviving an AMI, particularly those with features of higher risk of subsequent HF development, constitute an expanding population of individuals in jeopardy of developing symptomatic HF or premature death.<sup>6</sup> It is well established

that the mechanisms of ventricular remodelling after AMI involve activation of neuroendocrine system including renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and natriuretic peptide system.<sup>7</sup> SNS augments RAAS activity, while natriuretic peptides-atrial natriuretic peptide and brain natriuretic peptide antagonize the RAAS and SNS by natriuresis and vasodilation. Conventionally, RAAS inhibition has focused on clinical utilization of ACEI and ARB, and recently, ARNI brings the latest addition to this armamentarium.<sup>8</sup>

Sacubitril/valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor combining the valsartan with sacubitril, a neprilysin inhibitor. In the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, ARNI therapy significantly reduced the risk of death and hospitalization for worsening HF compared with enalapril.<sup>9</sup> Additionally, a number of studies have confirmed that in HF patients with reduced ejection fraction, sacubitril/valsartan can reduce N-terminal B-type natriuretic peptide levels, increase left ventricular ejection fraction (LVEF), and reverse ventricular remodelling, exerting more clinical and symptomatic benefits as compared to ACEI/ARB.<sup>10–14</sup> Although increasing evidence support the use of ARNI therapy instead of ACEI or ARB for patients with HF, the evidence for AMI patients is still lacking. The Prospective ARNI vs. ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction (PARADISE-MI) trial has been recently published with regard to the study design and baseline characteristics.<sup>15</sup> Yet more evidence based on real-world practice is still urgently needed.

As a result, the primary objective of the present study is to assess the long-term cardiovascular outcome of ARNI vs. ACEI/ARB among the AMI patients based on the real-world experience.

## Methods

### Data collection and study design

This is a triple-arm retrospective study. We collected the retrospective electronic medical records from the Biobank of the First Affiliated Hospital of Xi'an Jiaotong University, which contains de-identified data derived from raw medical records. The project was approved by the Institutional Ethical Board of the First Affiliated Hospital of Xi'an Jiaotong University. The disease was identified using International Classification of Diseases, Ninth Revision, Clinical Modification before 2015 and International Classification of Diseases, Tenth Revision, Clinical Modification diagnostic code after 2016.

*Figure 1* shows the flow chart of patient inclusion. A total of 7556 AMI patients from the biobank database between January 2016 and December 2020 were screened for eligibility. A total of 2085 patients without revascularization or without ARNI, ACEI, or ARB therapy were excluded to avoid potential treatment bias. The cohort entry date was the date of the first prescription of ARNI regardless of previous ACEI/ARB prescription. Propensity score matching (PSM) (1:1:1) based on age, sex, blood pressure, kidney function, baseline LVEF, and cardiovascular medication were conducted, resulting in 291 patients with AMI being assigned to each group. Patients with incomplete clinical data were excluded during the PSM. Patients switching to ACEI/ARB as indicated by the biobank database were also excluded from the subsequent analysis. Moreover, those patients without follow-up data were excluded, and the remaining patients were included in the clinical outcome analyses.

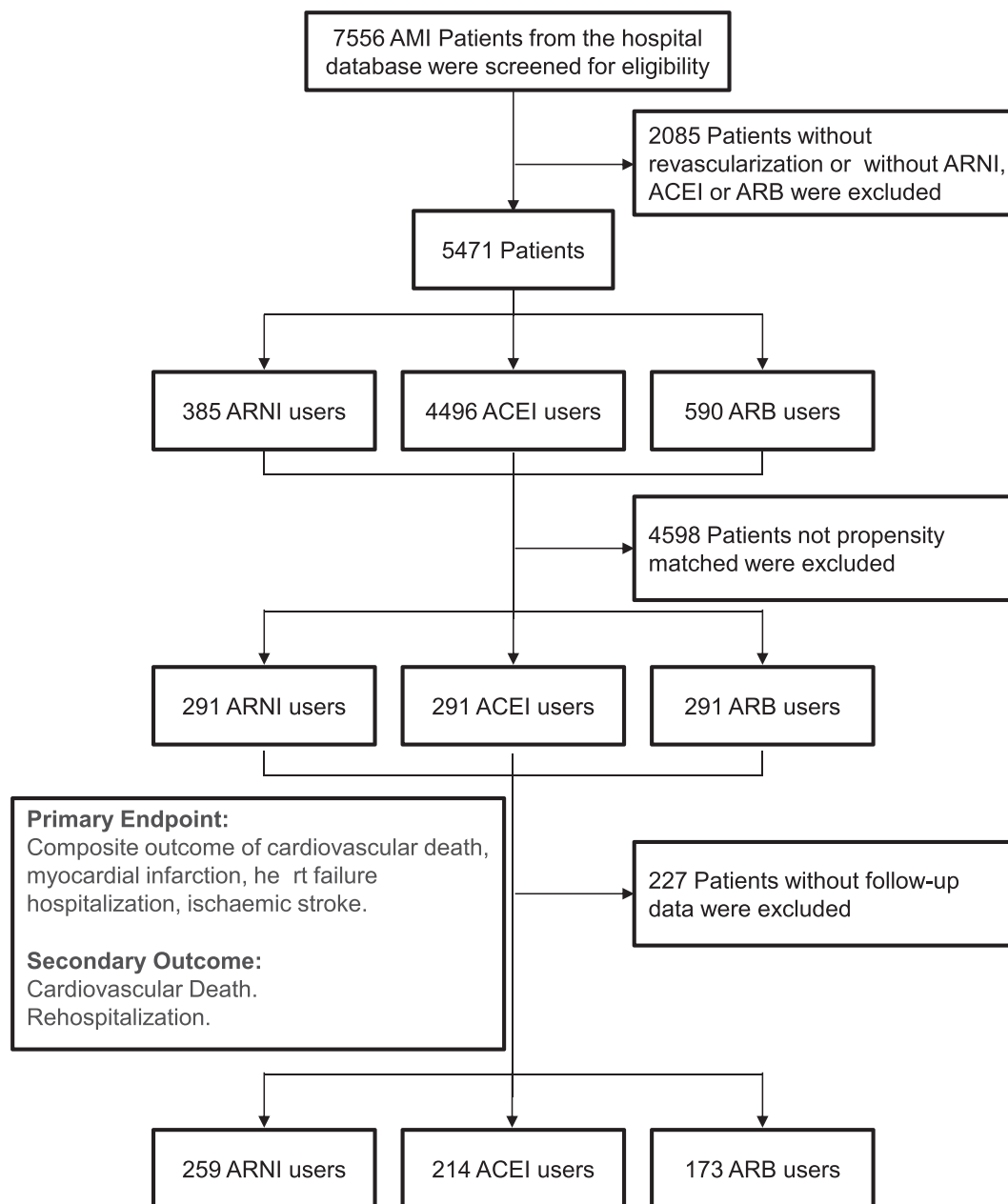
### Study cohorts and treatment

Participants were allocated into ARNI vs. ACEI or ARB treatment groups, contingent on whether they began ARNI during hospitalization. Patients were prescribed with ARNI either due to evidence of left ventricular systolic dysfunction (LVEF  $\leq$  50%) and/or large area myocardial infarction with pulmonary congestion requiring intravenous treatment based on the Chinese Expert Consensus on Prevention and Treatment of Ventricular Remodelling after Acute Myocardial Infarction.<sup>16</sup> The other two propensity score matched cohorts received ACEI or ARB therapy based on the present guidelines for the treatment of AMI.<sup>5</sup>

### Endpoints

The primary endpoint was to determine whether sacubitril/valsartan would be non-inferior to ACEI or ARB in reducing the incidence of the composite outcome including cardiovascular death, myocardial infarction, HF hospitalization, and ischaemic stroke, based on a time-to-first event analysis. The first of the secondary outcomes was cardiovascular death. Additionally, secondary objectives were to assess the rehospitalization for worsening HF. The occurrence of myocardial infarction and stroke was diagnosed using the biobank data or from the patients' follow-up claim. The definition of hospitalization for worsening HF was hospitalization with a combination of a diagnosis of HF. Each patient was followed until the day of outcome occurrence or death within 2 years after the cohort entry date or 31 March 2021, whichever came first.

**Figure 1** Patients selection, propensity score matching, and follow-up. ACEI, angiotensin converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors.



**Statistical analysis**

Because patients receiving ARNI, ACEI, or ARB varied a lot on baseline characters, PSM was employed and covariates were age, sex, admission blood pressure, respiration rate, temperature, LVEF, baseline creatine, uric acid and haemoglobin levels, and eight types of cardiovascular medication. All eligible participants were propensity-matched 1:1:1 of ARNI: ACEI: ARB. The propensity score was

calculated using the values of the covariates (Supporting Information, *Figure S1*).

The time from the first dose of ARNI, ACEI, or ARB to the first occurrence of a primary safety endpoint event was analysed with the use of a Cox proportional-hazards model, with ARNI as a covariate and with stratification to ACEI or ARB (no stratification for the comparison of ACEI with ARB), to provide a point estimate hazard ratio (HR) and a two-sided 95% confidence interval (CI). Cumulative event

Table 1 Baseline characteristics among the ARNI, ACEI, and ARB groups before and after propensity score matching

	Pre-match			Post-match			P value
	ARNI	ACEI	ARB	ARNI	ACEI	ARB	
Number	385	4496	590	291	291	291	
Age	62.45 ± 12.056	61.44 ± 11.90	63.59 ± 6.36	61.82 ± 11.90	61.98 ± 12.52	62.13 ± 12.53	NS
Sex							
Female	89, 23.1%	865, 19.2%	153, 25.9%	68.00, 23.4%	63.00, 21.6%	65.00, 22.3%	NS
Male	296, 76.9%	3631, 80.8%	437, 74.1%	223.00, 76.6%	228.00, 78.4%	226.00, 77.7%	NS
Medications							
β-Blockers	78.4%	87.1%	77.3%	82.1%	80.1%	75.3%	<0.05
Loop diuretics	52.5%	44.5%	42.2%	58.1%	60.1%	45.7%	<0.05
Aldosterone antagonist	48.1%	37.9%	35.8%	55.0%	56.4%	38.5%	<0.05
Aspirin	95.1%	98.3%	95.4%	97.6%	97.6%	96.2%	NS
Ticagrelor	54.8%	52.5%	46.9%	57.0%	55.3%	50.2%	NS
Clopidogrel	54.8%	62.0%	66.6%	56.4%	56.4%	61.9%	NS
Systolic BP (mmHg)	125.26 ± 23.90	125.65 ± 21.60	128.77 ± 24.44	117.33 ± 25.37	135.20 ± 14.48	119.83 ± 28.88	NS
Diastolic BP (mmHg)	79.03 ± 15.34	78.80 ± 14.57	77.46 ± 14.12	79.71 ± 15.80	78.95 ± 15.15	77.17 ± 14.31	NS
Creatine (μmol/L)	72.88 ± 48.41	71.40 ± 57.62	84.76 ± 46.17	73.34 ± 48.33	71.23 ± 51.14	78.19 ± 60.95	NS
Uric acid (μmol/L)	338.92 ± 107.97	332.25 ± 92.18	340.80 ± 95.91	342.93 ± 108.52	341.59 ± 98.83	333.79 ± 99.71	NS
Hb (g/L)	137.81 ± 20.08	141.52 ± 18.87	135.30 ± 17.32	138.41 ± 19.74	138.81 ± 20.40	138.88 ± 17.57	NS
LVEF (%)	50% ± 12%	52% ± 10%	54% ± 12%	50% ± 12%	50% ± 12%	53% ± 11%	NS
HbA <sub>1c</sub> (%)	6.64 ± 1.72	6.29 ± 1.46	6.54 ± 1.40	6.65 ± 1.75	6.33 ± 1.41	6.48 ± 1.35	NS
NT-proBNP (pg/mL)	1287.00 [347.78, 3677.75]	280.10 [87.91, 664.57]	435.75 [168.35, 1434.75]	956.78 [234.65, 3355.25]	890.95 [180.28, 1984.50]	610.65 [166.38, 1920.50]	NS
D-dimer (mg/L)	1.58 ± 1.91	0.95 ± 2.50	1.10 ± 2.53	1.58 ± 1.92	1.35 ± 2.79	1.23 ± 3.78	NS
TG (mmol/L)	1.42 ± 0.81	1.61 ± 1.21	1.51 ± 0.59	1.39 ± 0.77	1.57 ± 1.06	1.55 ± 1.14	NS
LDL-C (mmol/L)	2.29 ± 0.86	2.41 ± 0.84	2.23 ± 0.80	2.33 ± 0.86	2.50 ± 0.92	2.34 ± 0.95	NS
HDL-C (mmol/L)	0.93 ± 0.23	0.95 ± 0.23	0.93 ± 0.24	0.94 ± 0.24	0.98 ± 0.24	0.94 ± 0.23	NS
TC (mmol/L)	4.01 ± 1.13	4.13 ± 1.08	3.88 ± 1.02	4.08 ± 1.13	4.24 ± 1.15	4.08 ± 1.15	NS
Lp(a) (mg/L)	331.35 ± 296.21	255.51 ± 234.51	280.19 ± 254.42	320.84 ± 286.51	276.32 ± 255.33	252.03 ± 226.42	<0.05
Homocysteine (μmol/L)	25.65 ± 17.59	24.18 ± 15.97	23.62 ± 13.57	25.42 ± 17.78	25.05 ± 16.46	24.82 ± 16.97	NS

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors; BP, blood pressure; Hb, haemoglobin; HbA<sub>1c</sub>, haemoglobin A<sub>1c</sub>; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Lp(a), lipoprotein a; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal B-type natriuretic peptide; TC, total cholesterol; TG, triglyceride. Data were presented mean ± standard deviation, number (%), or median [25th, 75th percentile].

rates were estimated at the 24 month follow-up with the use of the Kaplan–Meier method, and *P* values were calculated with the use of the two-sided log-rank test. One-way ANOVA was used to compare continuous variables or  $\chi^2$  test for categorical variables. Data were presented as frequencies and percentages for categorical variables and mean  $\pm$  SD. for continuous variables, unless otherwise indicated. A two-sided *P* values of less than 0.05 were considered to indicate statistical significance. All the statistical analyses were performed using SPSS Version 25.0 (SPSS Inc, Chicago, IL).

## Results

### Study cohort and baseline characteristics

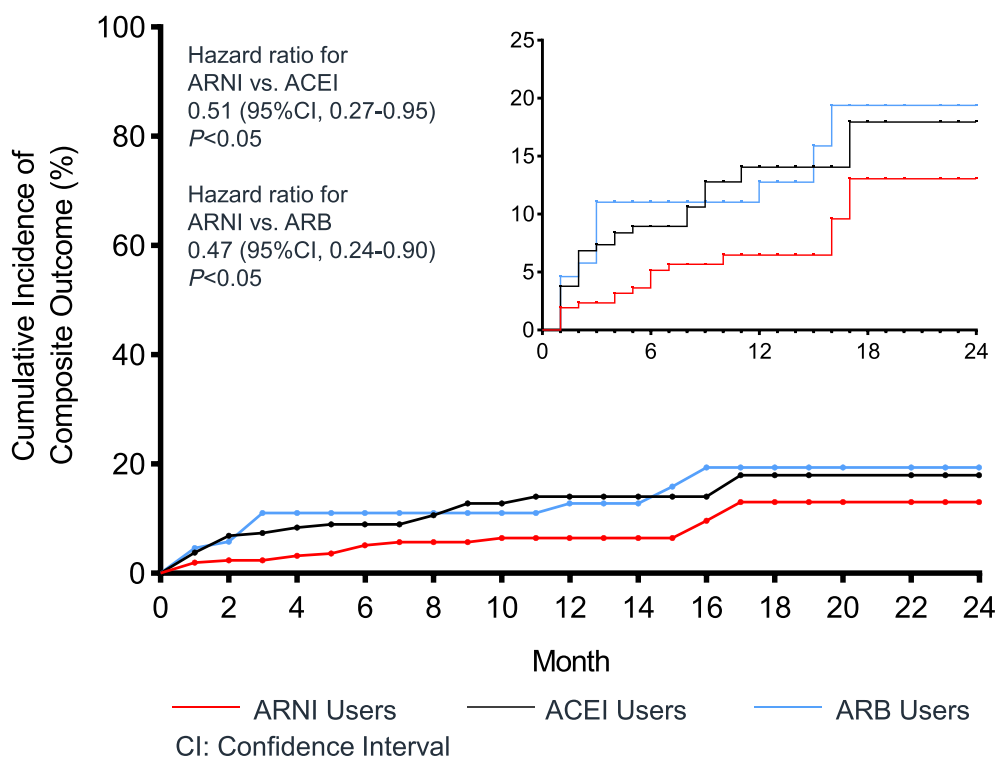
A total of 7556 AMI patients from the biobank database between January 2016 and December 2020 were screened for eligibility. After excluding those without revascularization or without ARNI, ACEI, or ARB therapy, the remaining 358 ARNI users, 4496 ACEI users and 590 ARB users were selected for PSM. Of these, 291 ARNI were successfully matched with 291 ACEI and ARB users, respectively. Characteristics of the

cohorts before and after PSM are presented in *Table 1*. The matched groups were well-balanced in demographic and clinical characteristics, with the exception of other cardiovascular medications and lipoprotein a level. The mean duration of follow-up was  $9.35 \pm 25.74$ ,  $8.63 \pm 34.91$ , and  $9.21 \pm 33.37$  months, respectively. The mean ages were  $61.82 \pm 11.90$ ,  $61.98 \pm 12.52$ , and  $62.13 \pm 12.53$  years among the ARNI, ACEI, and ARB users, respectively. For other cardiovascular medications, beta-blockers were prescribed in 82.1%, 80.1%, and 75.3%; loop diuretics 58.1%, 60.1%, and 45.7%; and aldosterone antagonist 55.0%, 56.4%, and 38.5% of patients, respectively. The baseline brain natriuretic peptide levels were 956.78, 890.95, and 610.65 mg/dL. The baseline LVEF levels were  $50 \pm 12\%$ ,  $50 \pm 12\%$ ,  $50 \pm 12\%$ , and  $53 \pm 11\%$  (*Table 1*).

### Primary endpoints

The primary composite endpoint, including cardiovascular death, myocardial infarction, HF hospitalization, and ischaemic stroke, occurred in 16 (6.18%) ARNI users, 24 (11.21%) ACEI users, and 22 (12.72%) ARB users. Patients receiving ARNI had significantly lower rates of the composite outcome

**Figure 2** Cumulative event rate of the primary composite endpoint (cardiovascular death, myocardial infarction, heart failure hospitalization, & ischaemic stroke) during the 2 year follow-up among the ARNI, ACEI, and ARB groups. ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors.



than ACEI users [HR for ARNI vs. ACEI: 0.51, (95%CI, 0.27–0.95),  $P = 0.02$ ] and ARB users [HR for ARNI vs. ARB: 0.47, (95%CI, 0.24–0.90),  $P = 0.02$ ] (Figure 2, Table 1).

## Secondary endpoints

Death from cardiovascular causes occurred in 9 (3.47%) patients in the ARNI group, 19 (8.88%) in the ACEI group, and 14 (8.09%) in the ARB group. Patients receiving ARNI had significantly lower rates of cardiovascular death than ACEI and ARB users [HR for ARNI vs. ACEI: 0.37, (95%CI, 0.18–0.79),  $P = 0.01$ ; HR for ARNI vs. ARB: 0.41, (95%CI, 0.18–0.95),  $P = 0.04$ ] (Figure 3). Cardiovascular death contributed most to the primary outcome benefits. But rates for myocardial infarction, HF hospitalization, ischaemic stroke, and rehospitalization showed no statistical difference (Table 2).

## Subgroup analysis

The lower rate of primary composite endpoints was consistent across multiple subgroups. It is indicated that patients with cardiac ejection fraction no more than 40% tend to

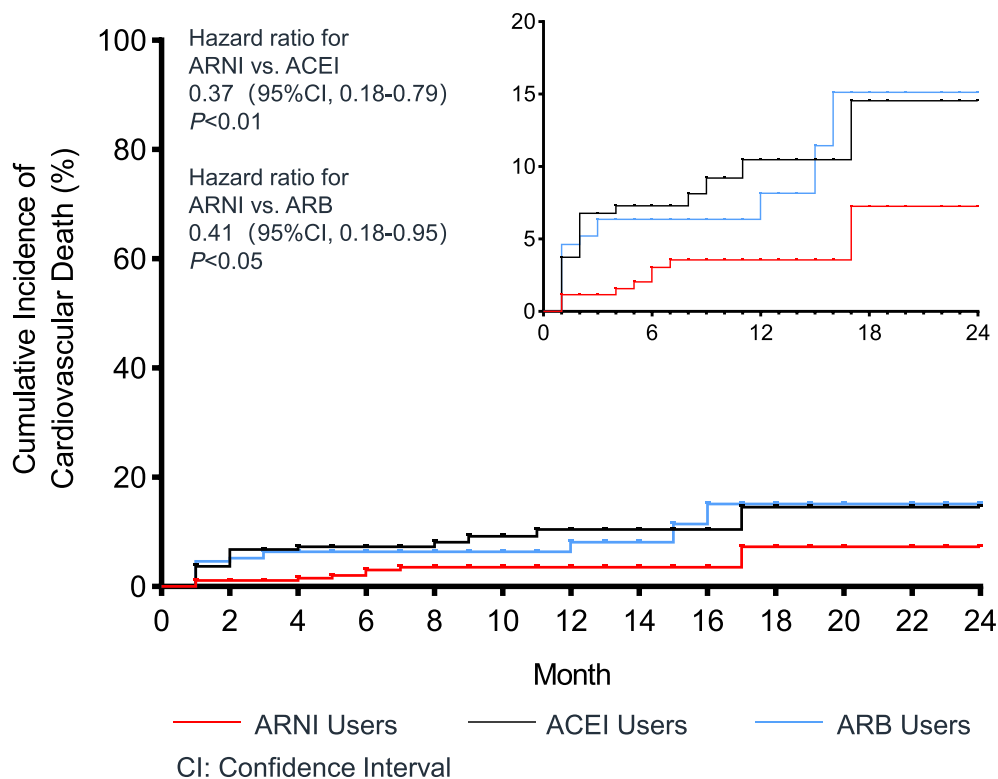
benefit more from ARNI as compared with ACEI [HR for ARNI vs. ACEI: 0.30, (95%CI, 0.11–0.86),  $P = 0.01$ ] or ARB [HR for ARNI vs. ARB: 0.21, (95%CI, 0.04–1.1),  $P = 0.05$ ]. Additionally, patients aged no more than 60 years also exhibited reduced composite endpoints [HR for ARNI vs. ACEI: 0.21, (95%CI, 0.04–1.03),  $P = 0.06$ ; HR for ARNI vs. ARB: 0.11, (95%CI, 0.03–0.46),  $P = 0.002$ ]. Interestingly, female patients benefit more from ARNI than ACEI female patients [HR for ARNI vs. ACEI: 0.24, (95%CI, 0.08–0.74),  $P = 0.004$ ] (Figure 4 and Table 3).

## Discussion

In the present study to compare the long-term outcome of AMI patients using ARNI vs. ACEI/ARB, we found that ARNI was associated with less composite outcomes and cardiovascular death during the 2 year follow-up. Subgroup analysis indicated that AMI patients with LVEF no more than 40%, aged no more than 60 years or female tend to benefit more from taking ARNI. To our knowledge, this is the first study to investigate the long-term outcomes of ARNI vs. ACEI/ARB among AMI patients focusing on the real-world evidence.

Ventricular remodelling after AMI are the factors that determine the incidence of cardiac events and long-term

**Figure 3** Cumulative event rate of the cardiovascular death during the 2 year follow-up among the ARNI, ACEI, and ARB groups. ACEI, angiotensin converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors.

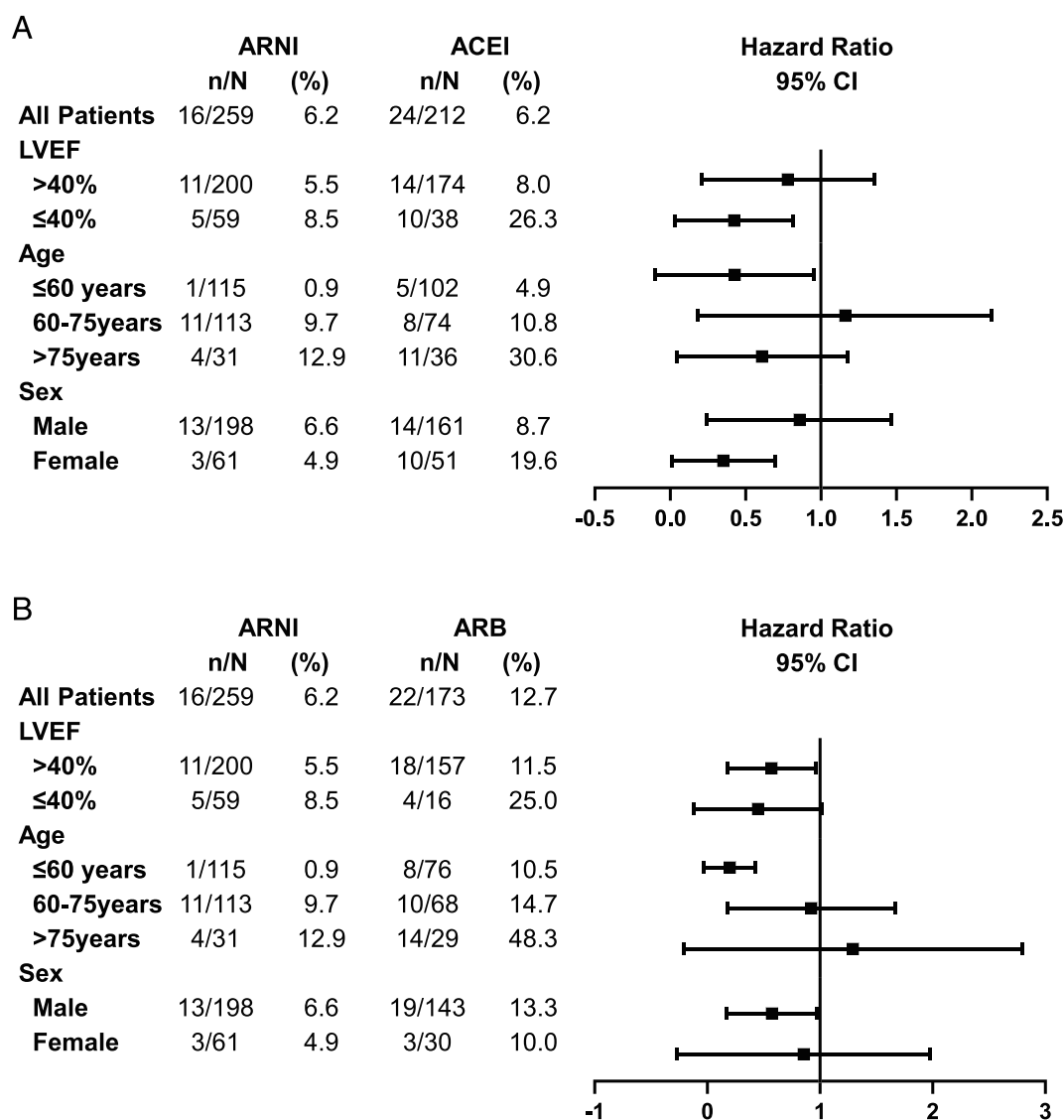


**Table 2** Cumulative incidence of primary and secondary endpoints among the ARNI, ACEI, and ARB groups

	ARNI	ACEI	ARB	ARNI vs. ACEI		ACEI vs. ARB	
	No. of participants with events (Kaplan–Meier event rate)			Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value
All participants—no.	259	214	173				
Composite endpoint	16 (6.18%)	24 (11.21%)	22 (12.72%)	0.51 (0.27–0.95)	0.02	0.47 (0.24–0.90)	0.02
Cardiovascular death	9 (3.47%)	19 (8.88%)	14 (8.09%)	0.37 (0.18–0.82)	0.01	0.41 (0.18–0.95)	0.04
Myocardial infarction	9 (3.47%)	5 (2.34%)	8 (4.62%)	1.37 (0.48–3.97)	0.88	0.75 (0.28–1.99)	0.56
Heart failure hospitalization	8 (3.09%)	5 (2.34%)	8 (4.62%)	1.19 (0.39–3.57)	0.78	0.66 (0.24–1.80)	0.42
Ischaemic stroke	5 (1.93%)	5 (2.34%)	8 (4.62%)	0.76 (0.22–2.68)	0.43	0.42 (0.14–1.26)	0.10
Rehospitalization	22 (8.49%)	18 (8.41%)	14 (8.09%)	0.95 (0.50–1.79)	0.76	1.10 (0.56–2.14)	0.63

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors; CI, confidence interval.

**Figure 4** The primary composite endpoint in the pre-specified subgroups between the ARNI and ACEI/ARB groups. ACEI, angiotensin converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors; LVEF, left ventricular ejection fraction.



CI: Confidence Interval

**Table 3** Cumulative incidence of primary composite endpoint in the pre-specified subgroups between the ARNI, ACEI, and ARB groups

	ARNI		ACEI		ARB		ARNI vs. ACEI		ACEI vs. ARB	
	n/N	(%)	n/N	(%)	n/N	(%)	Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value
All patients	16/259	6.18	24/212	6.18	22/173	12.72				
LVEF										
>40%	11/200	5.50	14/174	8.05	18/157	11.46	0.64 (0.29–1.41)	0.27	0.48 (0.23–1.00)	0.03
≤40%	5/59	8.47	10/38	26.32	4/16	25.00	0.30 (0.11–0.86)	0.01	0.21 (0.04–1.1)	0.05
Age										
≤60 years	1/115	0.87	5/102	4.90	8/76	10.53	0.21 (0.04–1.03)	0.06	0.11 (0.03–0.46)	0.002
60–75 years	11/113	9.73	8/74	10.81	10/68	14.71	0.89 (0.35–2.24)	0.80	0.72 (0.30–1.75)	0.37
>75 years	4/31	12.90	11/36	30.56	14/29	48.28	0.44 (0.15–1.24)	0.06	0.71 (0.17–3.00)	0.69
Sex										
Male	13/198	6.57	14/161	8.70	19/143	13.29	0.71 (0.33–1.53)	0.45	0.48 (0.23–1.01)	0.03
Female	3/61	4.92	10/51	19.61	3/30	10.00	0.24 (0.08–0.74)	0.004	0.37 (0.06–2.14)	0.23

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors; CI, confidence interval; LVEF, left ventricular ejection fraction.

prognosis after AMI.<sup>17</sup> Multiple factors, including sex, age, smoking, obesity, type of vascular lesions, and comorbidities, all contribute to the progression of HF after AMI, making the HF rate after myocardial infarction continued to increase event after percutaneous coronary intervention.<sup>18</sup> Recently, the application of ARNI for reversing cardiac remodelling has attracted a great deal of attention. Sacubitril/valsartan simultaneously blocks the effects of the angiotensin type 1 receptor through valsartan and inhibits the breakdown of several vasoactive peptides that are degraded by neprilysin.<sup>19</sup> Meta-analysis also indicates that ARNI can improve functional capacity and cardiac reverse remodelling in HFrEF patients compared with ACEI/ARB.<sup>20</sup> Although previous controlled trials validated the benefits of ARNI compared with ACEI/ARB to reduce morbidity and mortality in HFrEF patients, the real-world data for AMI patients are still inadequate.

The major novelty is that the present study innovatively investigated the long-term cardiovascular effect of ARNI vs. ACEI or ARB among AMI patients based on a real-world experience. It is speculated that sacubitril/valsartan could benefit MI and HF by simultaneously blocking the up-regulated RAAS in MI while augmenting the salutary effects of the natriuretic peptides. Animal studies have indicated that sacubitril/valsartan averts adverse post-infarction ventricular remodelling and preserves systolic function.<sup>21</sup> The PARADISE-MI trail, aiming to ascertain whether sacubitril/valsartan prevents the development of HF and reduces cardiovascular deaths when compared with a previously proven ACEI/ARB among AMI patients, has also been recently released, although without reaching its primary endpoint.<sup>15</sup> In our study, it is shown that ARNI offers incremental clinical value for the prevention of cardiovascular death. The difference of our results might be because the primary endpoints of our study include the first onset as well as the recurrence of heart failure. As a result, we suggest that, it is valuable to further in-depth investigate whether ARNI could 'rescue' the MI-induced HFrEF and reverse the ventricular remodelling as evaluated by the

echocardiography. In addition, long-term follow-up study as well as subgroup analysis from PARADISE-MI are also needed.

When comparing the primary composite endpoint in the pre-specified subgroups, it is indicated that patients with cardiac ejection fraction no more than 40% and aged no more than 60 years tend to benefit more from ARNI as compared with ACEI/ARB. Clinical trials have proved that the benefits of ARNI are most clearly evident in patients with LVEF below normal.<sup>10–14</sup> These subgroup data should be taken with caution and warrant large sample validation but might indicate preference for clinical treatments. Interestingly, it is also shown that female AMI patients utilizing ARNI exhibited a better long-term outcome as compared with ACEI users. This correlates to the findings from the PARAGON study<sup>22</sup> that ARNI treatment reduced the primary endpoint (total hospitalization for HF and risk of cardiovascular death) by 27% among female patients with HF with preserved ejection fraction. This indicates that ARNI might exert long-term cardiovascular benefits on female patients, and the exact mechanism remains to be explored.<sup>23</sup>

## Study limitations

Our findings should be interpreted in the context of several potential limitations. As this is a retrospective study, the follow-up data of echocardiography and New York Heart Association functional class are not complete, although these variables have been shown to contribute to the prognostic information in HF and AMI. Next, the achieved dose levels of ARNI, ACEI, or ARB are not available so that it is not possible to match the dose levels of the three groups. The incomplete information about the patients' medication compliance, especially to the ARNI or ACEI/ARB, might also affect the endpoints. As this is a single-centre study, the follow-up results are not broadly representative.



## Conclusion

This retrospective study based on real-world data suggests that ARNI can reduce the long-term adverse cardiovascular outcomes as compared with ACEI or ARB users. These improvements were largely driven by a substantial reduction of cardiovascular death after ARNI initiation. Subgroup analysis further indicates that ARNI are more likely to benefit patients with LVEF less than 40% and aged less than 60 years.

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## Conflict of interest

None declared.

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## Authors' contributions

JS, HL, and ZY participated in the design of the study. JS, BL, and HL collected the patients' data and did the follow-up. BZ, BL, and GTJ performed the statistical analysis. YL, HW, and CW finished the patients' follow-up. JS and BL drafted the manuscript. All authors approved the final manuscript.

## Ethics approval and consent to participate

Written informed consent was obtained from all study participants, with ethnic committee approval at the First Affiliated Hospital of Xi'an Jiaotong University.

## Consent for publication

All authors have reviewed the final version of the manuscript and approve it for publication.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Propensity Score Matching.

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