Original Article

Comparing the efficacy of angiotensin receptor-neprilysin inhibitor and enalapril in acute anterior STEMI patients after primary percutaneous coronary intervention: a prospective randomized trial

Youzheng Dong[1], Yan Xu[1], Congcong Ding[1,2], Zuozhong Yu[1], Zhide Yu[1], Xin Xia[1], Yang Chen[1], Xinghua Jiang[1]

[1]Department of Cardiovascular Medicine, The Second Affiliated Hospital of Nanchang University, Nanchang, China; [2]Center for Prevention and Treatment of Cardiovascular Diseases, The Second Affiliated Hospital of Nanchang University, Nanchang, China

Contributions: (I) Conception and design: Y Dong, X Jiang; (II) Administrative support: Y Xu; (III) Provision of study materials or patients: C Ding, Z Yu, Z Yu; (IV) Collection and assembly of data: Y Chen, X Xia; (V) Data analysis and interpretation: Y Dong, X Jiang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xinghua Jiang, MD. Department of Cardiovascular Medicine, the Second Affiliated Hospital of Nanchang University, No. 1 of Minde Road, Donghu District, Nanchang 330006, China. Email: xinghua__jiang@163.com.

Background: For patients with heart failure (HF), the effect of angiotensin receptor-neprilysin inhibitors (ARNIs, sacubitril/valsartan) on cardiac remodeling has been found to be superior to angiotensin-converting enzyme inhibitors (ACEI). However, little data have described the impact of early-initiation ARNI in patients with acute anterior ST-segment elevation myocardial infarction (STEMI).

Methods: In this prospective, randomized, double-blind, parallel-group trial, we enrolled 131 anterior STEMI patients who were treated with primary percutaneous coronary intervention (PCI) between February 2019 and December 2019. All patients received standard STEMI management and were divided into 2 groups (ARNI/enalapril). Primary efficacy outcomes were the between-group difference in change (from baseline to 4-, 12-, and 24-week) in N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, left ventricular ejection fraction (LVEF), and left ventricular end-systolic volumes and end-diastolic volumes (LVESV and LVEDV). Secondary outcomes were determined by a composite of death, reinfarction, outpatient HF or HF hospitalization, malignant arrhythmia, and stroke. Safety outcomes included worsening renal function, hypotension, hyperkalemia, angioedema and cough.

Results: We found that NT-proBNP concentration decreased more in the ARNI group than in the enalapril group [4 weeks: ratio of ARNI *vs.* enalapril 0.36, 95% confidence interval (CI): 0.24 to 0.52, P<0.001; 12 weeks: 0.54, 95% CI: 0.35 to 0.79, P<0.001; 24 weeks: 0.53, 95% CI: 0.32 to 0.83, P<0.001). When compared to the enalapril group, the ARNI group patients had a significant reduction in LVEDV (P<0.001) and LVESV (P<0.001), and an improvement in LVEF (P=0.011) at 24 weeks. Secondary outcomes occurred in 13 participants (20.3%) in the ARNI group and 22 participants (34.4%) in the enalapril group [hazard ratio (HR), 0.56; 95% CI: 0.28 to 1.12; P=0.102]. The incidence of outpatient HF or HF hospitalization in the ARNI group was significantly lower than that in the enalapril group (HR, 0.36; 95% CI: 0.14 to 0.94; P=0.037). There were no significant differences in the safety between the 2 groups.

Conclusions: For patients with acute anterior STEMI undergoing primary PCI, early initiation of ARNI provided significant clinical benefits.

Trial Registration: Chinese Clinical Trial Registry (ChiCTR2100042944) registered on February 1, 2021.

Keywords: Angiotensin receptor-neprilysin inhibitor (ARNI); sacubitril/valsartan; enalapril; segment elevation myocardial infarction (STEMI); cardiac remodeling

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Introduction

Even with the advent of coronary intervention techniques and progress in medication, acute myocardial infarction (AMI) remains the main cause of death from coronary artery disease. Other major adverse cardiovascular event following AMI, such as heart failure (HF) and reinfarction, can also impose a heavy economic burden. Ventricular remodeling plays an important role in the poor prognosis after AMI.

In spite of opening of the infarct-related artery as early as possible and the application of the best medical treatment, about 41.5% of ST-segment elevation myocardial infarction (STEMI) patients still experience ventricular remodeling at 6 months (1). Ventricular remodeling after AMI is affected by many risk factors, such as gender, age, smoking, obesity, diabetes, hypertension, dyslipidemia, location of MI, infarct size, and the presence of multivessel or chronic total occlusion disease (2-6). Among these factors, anterior wall myocardial infarction has been found to raise the risk of ventricular remodeling 1.9-fold compared with other localizations of the infarct (4).

Sacubitril/valsartan, a combination angiotensin receptor-neprilysin inhibitor (ARNI), is a new single-molecule treatment composed of valsartan and a neutral endopeptidase (NEP) inhibitor prodrug, sacubitril (1:1 ratio) (7). The pharmacological effect of sacubitril/valsartan is achieved by inhibiting the enkephalinase and angiotensin II type 1 (AT1) receptor at the same time, thereby exerting an anti-cardiac remodeling effect. Previous clinical trials have confirmed that sacubitril/valsartan is superior to angiotensin-converting enzyme inhibitors (ACEI) in improving cardiac structural and functional parameters and reducing the risk of HF rehospitalization and cardiovascular death in HF patients with reduced ejection fraction (8,9). In research on MI, several animal experiments have also demonstrated that when compared with enalapril, ARNI therapy could attenuate the scar area after infarction and improve left ventricular (LV) systolic function (10-12). Moreover, in the recent PARADISE-MI trial study (13), the main result adjudicated by the clinical endpoint committee (CEC) showed that, when compared with ramipril, ARNI significantly reduced total (first and recurrent) primary endpoint events by 21% [rate ratio 0.79; 95% confidence interval (CI): 0.65–0.97; P=0.02].

Given that ARNI is superior to ACEI in anti-cardiac remodeling, and may therefore help delay the progression of HF after AMI, we undertook this trial to assess the safety and efficacy of immediate ARNI initiation in patients with acute anterior STEMI after primary percutaneous coronary intervention (PCI). We present the following article in accordance with the CONSORT reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-386/rc).

Methods

Study population

We conducted a single-center, prospective, randomized, double-blind and parallel-group study. The protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University (No. 2019005), and informed consent was taken from all the patients. All methods were performed in accordance with the principles of the Declaration of Helsinki (as revised in 2013) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. Patients were screened by 2 researchers according to inclusion and exclusion criteria. The main eligibility criteria included the following: (I) participants aged ≥18 years; (II) typical history of chest pain and diagnosed with acute anterior STEMI based on admission electrocardiogram, serum markers of myocardial injury, and invasive coronary angiography; (III) systolic blood pressure ≥100 mmHg without symptoms of dizziness/vertigo during the last 12 hours before randomization; and (IV) provision of informed consent. Patients were excluded based on the following criteria: (I) previous history of MI or chronic HF; (II) previous revascularization (PCI, coronary artery bypass graft, CABG), implantation of ventricular assist devices, or heart transplantation; (III) estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or serum potassium >5.2 mmol/L at randomization; (IV) known history of liver disease (acute and chronic hepatic impairment, liver cirrhosis); (V) previous use of ARNI; (VI) history of allergy or contraindications to the study drugs

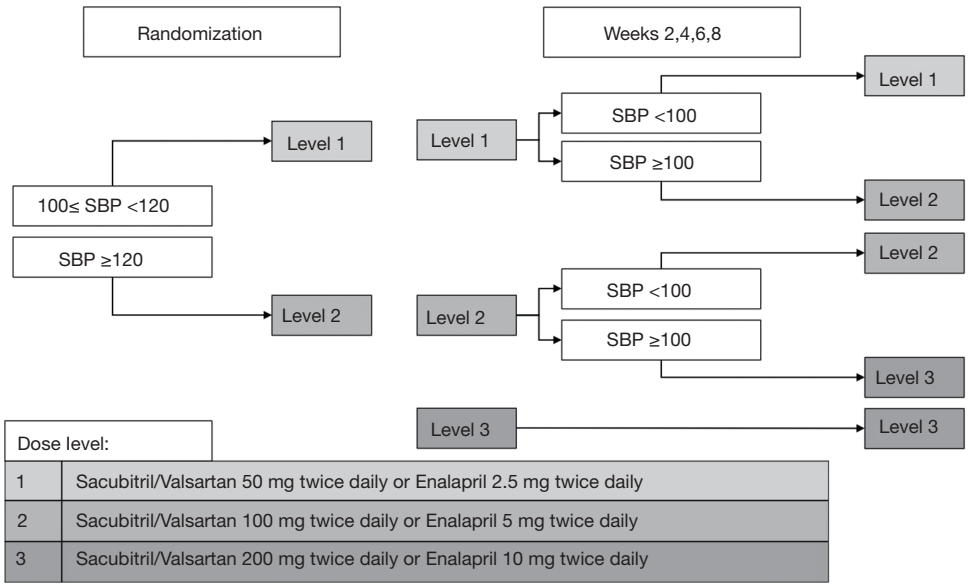

Figure 1 Dose titration algorithm. SBP, systolic blood pressure.

including ARNI, ACEI, and angiotensin receptor blocker (ARB); and (VII) life expectancy <1 year.

Study procedure

After the primary PCI operation, patients were admitted to the coronary care unit (CCU) for continuous medical monitoring and specialist nursing. Drug therapy mainly included dual antiplatelet, statins, beta blockers and enalapril. Mineralocorticoid receptor antagonists (MRAs), diuretics, and inotropes were used according to the patient's condition. Within 24 hours after PCI, the patients were randomly divided (1:1) into 2 groups (ARNI/enalapril) using R software-based random functions. Patients randomized to the enalapril group continued to receive enalapril, while patients randomized to the ARNI group ceased to receive enalapril with a minimum 36-hour washout period prior to receiving the sacubitril/valsartan. An independent researcher generated the randomization sequence by using randomized permuted blocks and assigned the participants to the interventions. For allocation concealment, medications are placed in sequentially numbered, opaque, sealed containers. All study personnel and patients were blind to treatment allocation and had no way of influencing whether a participant would receive sacubitril/valsartan or enalapril. A dose titration algorithm was used to select the initial dose (sacubitril/valsartan 24/26 or 49/51 mg and enalapril 2.5 or 5 mg) at the beginning of hospitalization and subsequent dose (sacubitril/valsartan 97/103 mg and enalapril 10 mg) changes during the drug titration (*Figure 1*) (14). Patients had follow-ups at 4, 12, and 24 weeks after discharge from the hospital. This involved a blood test and echocardiograph.

Echocardiography and laboratory assessment

We used the MS-Fast N-terminal pro-B-type natriuretic peptide (NT-proBNP) automatic chemiluminescence immunoassay analyzer and supporting reagent card (Sophonix Co., Ltd., Beijing, China) to carry out NT-proBNP quantitative detection. NT-proBNP levels were obtained from all patients before primary PCI and at 4, 12, and 24 weeks after discharge. Echocardiographic measurements were performed immediately after PCI and at 12 and 24 weeks with a Philips IE33 ultrasound system (Philips Medical System, Bothell, WA, USA). LV ejection fraction (LVEF), LV end-systolic volumes (LVESV), and LV end-diastolic volumes (LVEDV) were measured using the biplane Simpson method in the apical 4-chamber heart and 2-chamber heart view according to the recommendations issued by the American Society of Echocardiography and the European Cardiovascular Imaging Association (15).

Endpoints and definitions

The primary efficacy outcomes included differences

between groups in change from baseline to week 4, 12, and 24 in NT-proBNP concentration as well as change from baseline to week 12 and 24 in LVEF, LVESV and LVEDV. Secondary outcomes were the time-to-first event analysis of the composite risk of death, reinfarction, outpatient HF or HF hospitalization, malignant arrhythmia, and stroke. HF hospitalization was defined as a patient exhibiting new or worsening symptoms, objective evidence of HF, and the need for initiation or intensification of HF-specific treatment. Symptoms included at least 1 of the following: dyspnea, decreased exercise tolerance, fatigue, or other symptoms of worsened end-organ perfusion or volume overload. Objective evidence needed to consist of at least 2 physical examination findings or a combination of at least 1 physical examination finding and 1 laboratory criterion. Physical examination findings included peripheral edema, bloating or ascites (without any other underlying causes of hepatic disease), pulmonary rales/crackles/crepitations, jugular venous pressure elevation and/or hepatojugular reflux, S3 gallop, or rapid body weight gain due to fluid retention. The main laboratory evidence included increased brain natriuretic peptide (BNP)/NT-proBNP concentration consistent with decompensation of HF (such as BNP >500 pg/mL or NT-proBNP >2,000 pg/mL). Outpatient HF was defined as an emergent/unscheduled visit to an emergency department/outpatient clinic or a non-emergent visit for the primary diagnosis of HF (which did not require an overnight stay in a hospital ward). Malignant arrhythmia was defined as a composite event, including cardiac arrest, persistent ventricular tachycardia, and ventricular fibrillation. Safety outcomes were the incidence of worsening renal function, hypotension, hyperkalemia angioedema, and cough.

Statistical analysis

All data analyses were completed using R software version 3.6.1 (https://www.r-project.org/) and Empower (http://www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA). To evaluate the primary and secondary outcomes, we used per-protocol (PP) analyses. The targeted sample size was mainly driven by the LVEF of the primary outcomes. With an assumed increase in LVEF of 3%±6%, the patients were included in a ratio 1:1 if α=0.05, the test power was 80%, and the sample size for each group was predicted to be 64 cases. Outcome variables were tested for normality using the Shapiro-Wilk test. Continuous variables are expressed using mean and standard deviation (SD) or geometric means and 95% CI. Categorical variables are expressed in frequency and percentage. Comparison of baseline characteristics was carried out by using 2-sample *t*-test and Fisher's exact test. The 2-sided significance level for all final tests was set to 0.05. The change in the primary outcomes was tested suing a covariance analysis model adjusted for baseline values. Logarithmic transformation was used for NT-proBNP, due to its skewed distribution. Secondary outcomes data were evaluated suing Kaplan-Meier method and Cox proportional hazards models. The hazard ratio (HR), 95% CI, and 2-sided P values were calculated using the model to adjust the following baseline prognostic factors: age, gender, body mass index, total cholesterol, triglycerides, history of hypertension, diabetes, and previous history.

Results

Study participants and follow-up

Among the 171 participants screened between February 17, 2019 and December 28, 2019, 131 patients met all the inclusion and exclusion criteria and were randomized (*Figure 2*). The baseline characteristics of the patients are shown in *Table 1*. In the total study population, the mean age was 60.3 (SD, 9.9) years, 104 (79.4%) were males, 62 (47.3%) had a history of hypertension, 33 (25.2%) had a history of diabetes, and 50 (38.2%) had previously received an ACEI or ARB treatment. The average time from symptom onset to balloon inflation was 3.2 (SD, 1.2) hours. Furthermore, 64 patients in the ARNI group and 64 patients in the enalapril group completed a laboratory examination and cardiac ultrasound during follow-up; 52 (81.3%) patients in the enalapril group and 48 (75.0%) in the ARNI group successfully titrated to the target dose.

Study outcomes

After treatment, NT-proBNP levels were significantly reduced in both groups from the baseline to week 24. However, the NT-proBNP concentration of the ARNI group had decreased more significantly than had that of the enalapril group at each follow-up time (4 weeks: ratio of ARNI *vs.* enalapril 0.36, 95% CI: 0.24 to 0.52, P<0.001; 12 weeks: 0.54, 95% CI: 0.35 to 0.79, P<0.001; and 24 weeks: 0.53, 95% CI: 0.32 to 0.83, P<0.001; *Figure 3A* and *Table 2*). Compared with the enalapril group, the ARNI group also had a significant reduction in LVEDV

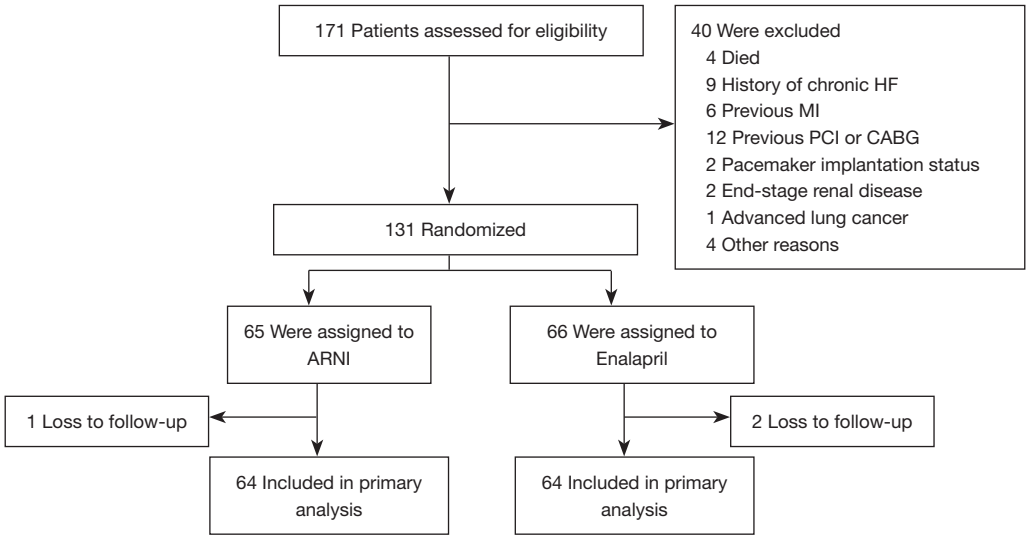

Figure 2 Study flow diagram. HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ARNI, angiotensin receptor-neprilysin inhibitor.

(ARNI: from 124.55±21.4 to 114.36±21.3 mL; enalapril: from 121.08±21.2 to 129.30±19.0 mL; difference −15.41 mL; 95% CI: −17.27 to −13.54 mL; P<0.001) and LVESV (ARNI: from 69.06±22.5 to 55.30±18.8 mL; enalapril: from 65.00±20.0 to 64.23±16.0 mL; difference −11.5 mL; 95% CI: −16.06 to −6.94 mL; P<0.001). In addition, at 24 weeks the ARNI group also had an improvement in LVEF (ARNI: from 45.75%±9.7% to 51.77%±8.8%; enalapril: from 46.97%±9.1% to 50.59%±8.5%; difference 3.39%; 95% CI: 1.12% to 6.66%; P=0.011; *Figure 3B-3D*, and *Table 3*).

After a median follow-up of 261 (interquartile range: 226 to 311) days, secondary outcomes (death, reinfarction, outpatient HF or HF hospitalization, malignant arrhythmia, or stroke) occurred in 13 participants (20.3%) in the sacubitril/valsartan group and 22 participants (34.4%) in the enalapril group. When compared with the enalapril group, the HR for secondary outcomes in the ARNI group was 0.56 (95% CI: 0.28 to 1.12; P=0.102; *Figure 4A* and *Table 4*). Outpatient HF or HF hospitalization occurred in 6 ARNI patients (2 outpatient HF and 4 HF hospitalization, 9.4%) compared to 17 enalapril patients (8 outpatient HF and 9 HF hospitalization, 26.6%; HR 0.36; 95% CI: 0.14 to 0.94; P=0.037; *Figure 4B* and *Table 4*). The effect of ARNI on this outcome was consistent in an unadjusted analysis (HR 0.35; 95% CI: 0.14 to 0.89; P=0.027).

During the treatment period, the incidence of hypotension in the ARNI group was higher than that in enalapril group, but the difference between the 2 groups was not significant (18.8% *vs.* 7.8%, P=0.068). No angioedema was found in the 2 groups. The incidence of worsening renal function, hyperkalemia, and cough was low, and there was no difference between the 2 groups (*Table 5*).

Discussion

This prospective, randomized, double-blind study was conducted to examine and compare the effect of early initiation ARNI and enalapril in patients with acute anterior STEMI after PCI. The most important findings of this trial were the following: (I) the timely application of ARNI led to a greater reduction in NT-proBNP than did enalapril; (II) compared to enalapril, ARNI was associated with an improvement in echocardiographic parameters including LVEF, LVESV, and LVEDV after 24 weeks; (III) ARNI was superior to enalapril in reducing the risk of outpatient HF or HF hospitalization; and (IV) ARNI had the tendency to increase the occurrence of hypotension, but it was well tolerated by most patients.

After AMI, myocardial mechanical stretch, secondary to LV dysfunction, is considered as one of the most important stimuli contributing to the increase of NT-proBNP (16). We observed a relatively rapid reduction of NT-proBNP concentration, apparent as early as 4 weeks, in patients with ARNI. The pharmacological action of the drug is not entirely clear, but possible mechanisms are outlined as follows: (I) compared with renin-angiotensin-aldosterone

Table 1 Baseline characteristics of the study population

Variables	Total (n=131)	ARNI (n=65)	Enalapril (n=66)	P value
Age, years	60.3±9.9	60.2±9.8	60.4±10.0	0.869
Gender (male)	104 (79.4%)	51 (78.5%)	53 (80.3%)	0.794
Body mass index, kg/m^2	24.1±2.8	23.9±3.1	24.3±2.5	0.489
Previous medical history, n (%)				
Hypertension	62 (47.3%)	29 (44.6%)	33 (50.0%)	0.537
Diabetes mellitus	33 (25.2%)	15 (23.1%)	18 (27.3%)	0.580
Smoking	57 (43.5%)	26 (40.0%)	31 (47.0%)	0.421
Blood pressure, mmHg				
Systolic	110.7±9.4	111.6±9.9	109.7±8.9	0.242
Diastolic	68.8±6.6	69.1±6.9	68.5±6.3	0.591
Heart rate, /min	75.4±8.4	75.3±8.9	75.4±7.9	0.904
Total cholesterol, mmol/L	4.88±1.05	5.00±1.07	4.77±1.02	0.204
Triglyceride, mmol/L	1.38±0.54	1.43±0.54	1.32±0.54	0.235
HbA1c, %	5.9±0.6	5.9± 0.6	5.9±0.6	0.581
LDL-C, mmol/L	2.95±0.81	3.07±0.85	2.83±0.76	0.097
Serum creatinine, μmol/L	88.5±27.6	85.2±28.2	91.8±26.9	0.173
Serum Potassium, mmol/L	4.1±0.4	4.1±0.4	4.1±0.4	0.518
eGFR, mL/min per 1.73 m^2	81.9±24.2	84.4±24.8	79.6±23.6	0.260
Hs-cTnI, ng/mL	11.3±12.6	12.0±13.3	10.5±11.8	0.504
Onset to balloon, h	3.18±1.15	3.29±1.15	3.08±1.15	0.291
Killip classification, n (%)				0.713
I	95 (72.5%)	46 (70.8%)	49 (74.2%)	
II	26 (19.9%)	15 (23.1%)	11 (16.7%)	
III	6 (4.6%)	2 (3.1%)	4 (6.1%)	
IV	4 (3.1%)	2 (3.1%)	2 (3.0%)	
TIMI flow grade, n (%)				0.581
3	110 (84.0%)	54 (83.1%)	56 (84.9%)	
2	17 (13.0%)	8 (12.3%)	9 (13.6%)	
1	4 (3.1%)	3 (4.6%)	1 (1.5%)	
Medications at discharge, n (%)				
Aspirin	123 (93.9%)	61 (93.9%)	62 (93.9%)	0.982
Clopidogrel	14 (10.7%)	6 (9.2%)	8 (12.1%)	0.592
Ticagrelor	118 (90.1%)	60 (92.3%)	58 (87.9%)	0.397
Statins	125 (95.4%)	63 (96.9%)	62 (93.9%)	0.414
Beta-blockers	123 (93.9%)	61 (93.9%)	62 (93.9%)	0.982

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total (n=131)	ARNI (n=65)	Enalapril (n=66)	P value
MRA	67 (51.2%)	30 (46.2%)	37 (56.1%)	0.257
Diuretics	41 (31.3%)	19 (29.2%)	22 (33.3%)	0.613
Digoxin	4 (3.1%)	2 (3.1%)	2 (3.0%)	0.988

Data are presented as n (%) or the mean ± SD. HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; Hs-cTnI, high sensitivity cardiac Troponin I; TIMI, thrombolysis in myocardial infarction; MRA, mineralocorticoid receptor antagonist.

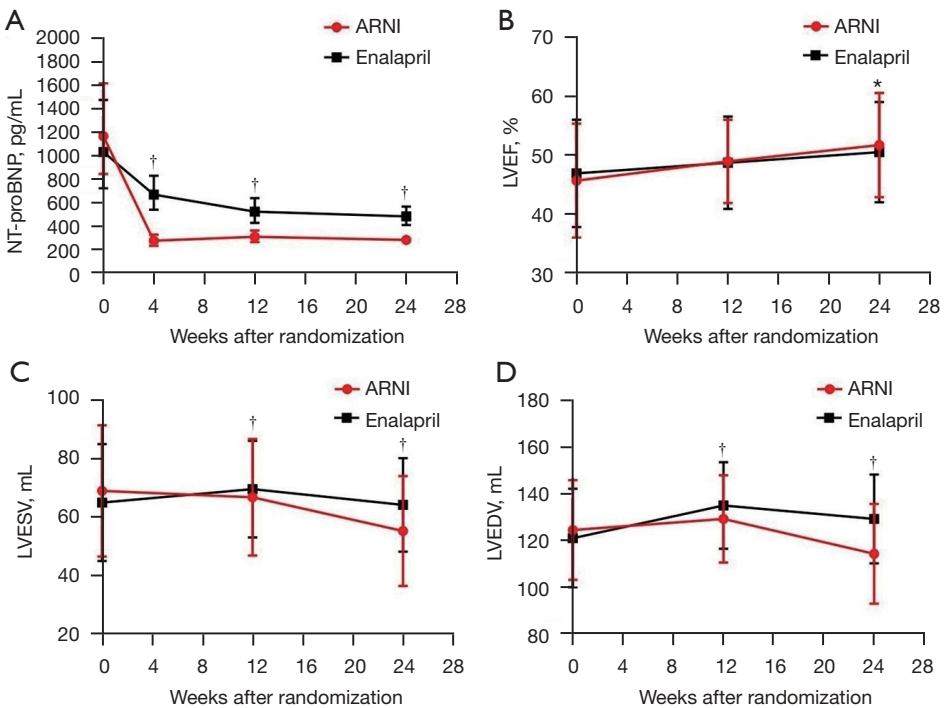

Figure 3 NT-proBNP (A) at baseline, 4, 12 and 24 weeks in the ARNI and Enalapril groups; LVEF (B), LVESV (C), and LVEDV (D) at baseline, 12, and 24 weeks in the ARNI and enalapril groups. *, P<0.05 compared with the enalapril group; †, P<0.001 compared with the enalapril group; ARNI, angiotensin receptor-neprilysin inhibitor; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume.

system (RAAS) inhibitors, early application with ARNI after AMI might have a cardioprotective effect through the further inhibition of the expression and release of inflammation-associated cytokines in the infarcted area (11); (II) the natriuretic, diuretic, and vasodilating effects of natriuretic peptides (NPs) lead to a decrease in pre- and after-load, thereby inhibiting ventricular wall tension and ventricular dilatation in the early stage of AMI; and (III) by inhibiting the angiotensin II receptor, ARNI inhibits the expression of pro-cardiac hypertrophy and fibrosis factors, such as soluble suppression of tumorigenesis-2 (sST2) (17), matrix metalloproteinase 9 (MMP9) (11) and transforming growth factor β (TGF-β) (18). ARNI can also lower the expression of β-myosin heavy chain (β-MHC) genes (19), as well as down-regulate the expression of exosomal miR-181a (regulates cell proliferation and apoptosis) (20) and connective tissue growth factor (CTGF, a strong marker pro-fibrotic remodeling) (19). Moreover, in animal experiments (10,19), sacubitril/valsartan was found to improve the blood supply of the infarcted myocardium

Table 2 Change in NT-proBNP (pg/mL) from baseline to 4, 12 and 24 weeks

Variables	ARNI	Enalapril	Ratio of ARNI *vs.* Enalapril, geometric mean (95% CI)	P value between groups
Baseline	1,168 [845–1,616]	1,033 [724–1,474]		
4 weeks	279 [236–331]	671 [542–831]		
Ratio of geometric means, 4 weeks/baseline (95% CI)	0.24 (0.20–0.29)	0.65 (0.55–0.77)	0.36 (0.24–0.52)	<0.001
12 weeks	313 [268–366]	525 [430–640]		
Ratio of geometric means, 12 weeks/baseline (95% CI)	0.27 (0.21–0.34)	0.51 (0.42–0.62)	0.54 (0.35–0.79)	<0.001
24 weeks	285 [251–323]	485 [413–569]		
Ratio of geometric means, 24 weeks/baseline (95% CI)	0.24 (0.19–0.31)	0.47 (0.37–0.59)	0.53 (0.32–0.83)	<0.001

Data for NT-proBNP are geometric mean (95% CI). ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval.

and significantly attenuate the size of the LV scar after MI, whereas RAAS blocker were found to have no statistical significance in reducing the scar. It is widely acknowledged that NT-proBNP is an important predictor of adverse events after AMI (21-23). Heeschen *et al.* reported that in patients with high levels of NT-proBNP at baseline, the slow decline of NT-proBNP after myocardial injury was associated with a short-term adverse prognosis (22). Another study found a close correlation between the concentration of NT-proBNP and the long-term all-cause mortality and rate of rehospitalization for HF after MI (23). The results of 4 previous large-scale clinical trials showed that sacubitril/valsartan reduced the NT-proBNP in patients with HF and the full-range of ejection fraction and acute decompensated HF (9,14,24,25). A similar effect was observed with ARNI in this acute anterior STEMI population, suggesting that sacubitril/valsartan may provide a beneficial prognosis in patients with this disorder.

In the analyses of echocardiographic parameters, treatment with sacubitril/valsartan was associated with improvements in LVEF, as well as a lower LVESV and LVEDV. Our results are in line with those in many other animal and clinical studies (10,12,19) and suggest the superiority of ARNI in cardiac remodeling. Compared with a single RAAS blocker, the improvement of cardiac ultrasound parameters observed with ARNI may be attributed to an increase in circulating NP levels. Previous clinical and animal studies have shown that the administration of NPs can provide cardioprotection and improve cardiac function and hemodynamic parameters (26).

In this study of acute anterior STEMI patients who underwent primary PCI, the inhibition of both the angiotensin II receptor and neprilysin was more effective in reducing the risk of outpatient HF or HF hospitalization than was ACE inhibition. However, the recently reported PARADISE-MI study (13) showed that compared with enalapril, ARNI failed to further reduce the combined events of cardiovascular death, HF hospitalization, and outpatient HF. Interestingly, when the primary endpoint was set as the total (first and recurrent) event adjudicated by the CEC, the rate ratio of the primary endpoint was 0.79 (95% CI: 0.65 to 0.97; P=0.02), and when considering the use of the primary endpoint reported by the investigator, the overall HR was 0.85 (95% CI: 0.75 to 0.96; P=0.01) while the HR for outpatient HF was 0.69 (95% CI: 0.54 to 0.88; P=0.003). The results of the PARADISE-MI trial were unexpected, but reasonable. At present, guideline-directed medical therapy (GDMT), which includes early reperfusion therapy and dual antiplatelet, statins, β-receptor blockers, and ACEI/ARB as its core methods, has reduced the 3-year mortality rate in AMI patients with LV insufficiency from 30% to 10% or less. It is indeed very difficult for ARNI to further obtain superior results on the basis of this optimized treatment. Unlike in the PARADISE-MI study, the patients included in the present trial were those with acute anterior STEMI, whose baseline NT-proBNP was at a relatively high level (geometric mean 1,168 pg/mL). There are some signs that reversal of LV remodeling with ARNI may be requisite on elevated LV wall stress (such as a high concentration of NT-proBNP at baseline) (9,27,28).

Table 3 Change in echocardiographic parameters from baseline to 12 and 24 weeks

Variables	12 weeks							24 weeks						
	ARNI			Enalapril				ARNI			Enalapril			
	Baseline	12 weeks	Δ from baseline	Baseline	12 weeks	Δ from baseline	Between-group difference in change from baseline (95% CI) P	Baseline	24 weeks	Δ from baseline	Baseline	24 weeks	Δ from baseline	Between-group difference in change from baseline (95% CI) P
LVEF (%)	45.75 (9.7)	49.00 (7.1)	3.25 (4.5)	46.97 (9.1)	48.77 (7.9)	1.80 (6.7)	1.45 (−0.54 to 3.45) 0.215	45.75 (9.7)	51.77 (8.8)	7.02 (8.3)	46.97 (9.1)	50.59 (8.5)	3.62 (10.3)	3.39 (1.12 to 6.66) 0.011
LVESV (mL)	69.06 (22.5)	66.83 (19.9)	−2.23 (7.9)	65.00 (20.0)	69.64 (16.5)	4.64 (11.8)	−6.88 (−10.38 to −3.37) <0.001	69.06 (22.5)	55.30 (18.8)	−12.27 (10.9)	65.00 (20.0)	64.23 (16.0)	−0.77 (14.9)	−11.5 (−16.06 to −6.94) <0.001
LVEDV (mL)	124.55 (21.4)	129.33 (18.7)	4.78 (5.8)	121.08 (21.2)	135.00 (18.6)	13.92 (10.9)	−9.14 (−6.08 to −12.20) <0.001	124.55 (21.4)	114.36 (21.3)	−7.19 (4.2)	121.08 (21.2)	129.30 (19.0)	8.22 (6.3)	−15.41 (−17.27 to −13.54) <0.001

Data are presented as mean (SD). ARNI, angiotensin receptor-neprilysin inhibitor; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volumes; LVEDV, left ventricular end-diastolic volumes.

This may explain why the findings of this study saw ARNI significantly reduce the cumulative risk of outpatient HF or HF hospitalizations. Furthermore, there was no statistically significant difference in the overall incidence of cardiovascular events between the 2 groups, which may be due to the follow-up time or sample size being insufficiently long or large, respectively. However, the benefit of sacubitril/valsartan, which were also apparent in this study, could be seen in patients who had already received all other drugs known to improve prognosis among STEMI patients.

Our research shows that sacubitril/valsartan is well tolerated. Very few patients stopped the study drug, and 75% of the ARNI patients were successfully titrated to the target dose. The PARADIGM-HF (8) trial reported that the incidence of hypotension in the ARNI patients was significantly higher than that of the enalapril patients. In our study, ARNI also had the tendency to increase the occurrence of hypotension, which may be due to its powerful vasodilator effect. Although the greater hypotensive effect of ARNI may impair renal perfusion, there were no statistically significant differences in the incidence of deterioration of renal function or hyperkalemia between the 2 groups in our study. Contrary to concerns surrounding ARNI, several studies have shown that it can delay renal function decline and slow down the eGFR decline (29,30). Therefore, based on current research, ARNI is more suitable for HF patients with renal insufficiency. In addition to, no angioedema occurred during the treatment, the incidence of cough was low, and there was no difference between the groups.

We used a per protocol analysis and therefore only data from patients with complete follow-up were analyzed. An intention-to-treat analysis would make the intervention less effective if patients assigned to the intervention group were lost to follow-up after randomization (31). With regard to follow-up, we do not expect a large difference in outcomes between a per-protocol analysis and an intention-to-treat analysis because of the number of patients lost to follow-up was low in our study. In summary, we found that the use of ARNI in patients with acute anterior STEMI is safe and effective, which indicates that treatment with sacubitril/valsartan in the early stages of myocardial remodeling after AMI will provide greater benefit for patients.

Limitations

This study has the following limitations: (I) the patients we included did not include all types of AMI patients, but only

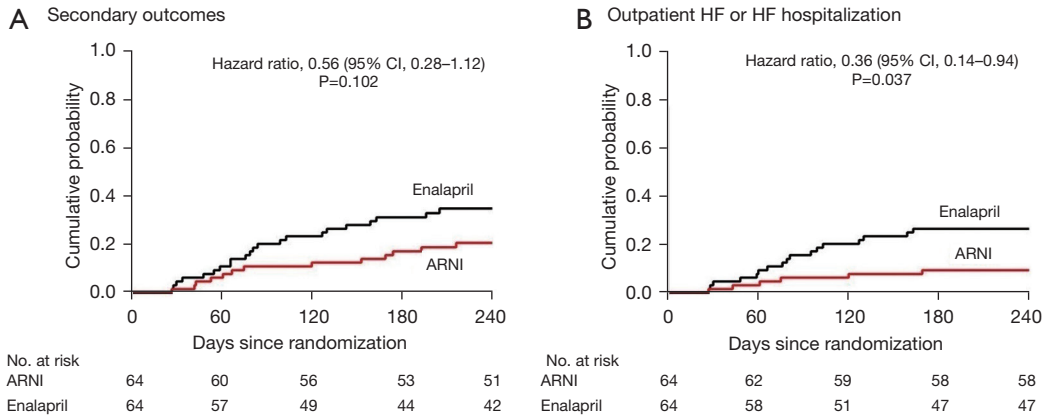

Figure 4 Cumulative Kaplan-Meier estimates of rates of secondary outcomes (according to study group. The hazard ratios for ARNI *vs.* enalapril are shown for the composites of death, reinfarction, outpatient HF or HF hospitalization, malignant arrhythmia, and stroke (A), HF or HF hospitalization (B). ARNI, angiotensin receptor-neprilysin inhibitor.

Table 4 Secondary outcomes

Variables	Events, n (%)	Adjusted		Unadjusted	
		HR (95% CI)	P value	HR (95% CI)	P value
Composite outcomes					
Enalapril	22 (34.4%)	Ref.		Ref.	
ARNI	13 (20.3%)	0.56 (0.28, 1.12)	0.102	0.53 (0.27, 1.06)	0.071
Death					
Enalapril	0 (0.0%)	Ref.		Ref.	
ARNI	1 (1.6%)	Inf. (0.00, inf)	1.000	Inf. (0.00, inf)	0.999
Outpatient HF or HF hospitalization					
Enalapril	17 (26.6%)	Ref.		Ref.	
ARNI	6 (9.4%)	0.36 (0.14, 0.94)	0.037	0.35 (0.14, 0.89)	0.027
Reinfarction					
Enalapril	3 (4.7%)	Ref.		Ref.	
ARNI	3 (4.7%)	0.84 (0.14, 5.04)	0.848	1.00 (0.20, 4.95)	0.999
Malignant arrhythmia					
Enalapril	4 (6.3%)	Ref.		Ref.	
ARNI	2 (3.1%)	0.29 (0.04, 2.26)	0.236	0.48 (0.09, 2.62)	0.396
Stroke					
Enalapril	1 (1.6%)	Ref.		Ref.	
ARNI	2 (3.1%)	2.21 (0.15, 31.81)	0.561	2.00 (0.18, 22.04)	0.572

Adjusted results were adjusted for prespecified baseline characteristics: age, gender, body mass index, total cholesterol, triglycerides, history of hypertension, diabetes and previous smoking. ARNI, angiotensin receptor-neprilysin inhibitor.

Table 5 Safety outcomes

Variables	ARNI (n=64)	Enalapril (n=64)	P value
All events	16 (25.0%)	17 (26.6%)	0.840
Worsening renal function	3 (4.7%)	6 (9.4%)	0.300
Hypotension	12 (18.8%)	5 (7.8%)	0.068
Hyperkalemia	3 (4.7%)	4 (6.2%)	0.697
Cough	1 (1.6%)	3 (4.7%)	0.310

Data are presented as n (%). ARNI, angiotensin receptor-neprilysin inhibitor.

acute anterior STEMI patients, with the culprit vessel being the anterior descending branch, and thus the efficacy of sacubitril/valsartan in other types of MI therefore requires further exploration; (II) this study only measured the changes in NT-proBNP, but not many other biomarkers related to neprilysin inhibition, neurohumoral activation, or cardiac remodeling; and (III) the data from this study were derived from a small sample at a single-center, and thus further verification will be needed with data from future studies using multiple centers and large samples.

Conclusions

For patients with acute anterior STEMI undergoing primary PCI, we found that when compared with enalapril, ARNI significantly decreases the concentration of NT-proBNP, improves LV systolic function, and reduces the risk of outpatient HF or HF hospitalization.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-386/rc

Trial Protocol: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-386/tp

Data Sharing Statement: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-386/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-386/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University (No. 2019005) and informed consent was taken from all the patients

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