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ORIGINAL ARTICLE

Sacubitril/valsartan role in patients with resistant hypertension: a systematic review

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ABSTRACT

BACKGROUND Sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor (ARNI), shows promising result in treating resistant hypertension (RH) but lacks comprehensive evaluation. We performed a systematic review to assess and compare the efficacy of ARNI in managing RH.

METHODS We conducted a systematic search on multiple databases such as Cochrane, ProQuest, PubMed, and Google Scholar. Studies comparing the effects of ARNI on blood pressure in adult RH patients were included in the review. Data extraction and synthesis followed PRISMA guidelines, and the risk of bias was assessed using Cochrane tools. The primary outcome is to determine the effect of ARNI on blood pressure in RH patients, and the secondary outcome was to assess the safety of ARNI in RH patients.

RESULTS Four studies involving 915 RH patients were included in the systematic review. The sacubitril/valsartan dose used ranged between 100 and 400 mg/day. All studies reported a statistically significant reduction in blood pressure, with 24-h blood pressure reduction ranging from 15.8/6.5 to 16.6/9.3 mmHg and office systolic blood pressure reduction ranging from 24.7 to 10.3 mmHg. Additionally, two studies reported improvements in cardiac remodeling and left ventricular function associated with sacubitril/valsartan. The most common adverse events were hypotension and elevated serum potassium levels, though these were minimal and did not require discontinuation of ARNI therapy.

CONCLUSION Sacubitril/valsartan is a promising alternative to ARB or ACEi in managing RH, offering superior blood pressure reductions and potential benefits in reversing cardiac remodeling, while maintaining a favorable safety profile with minimal risk of serious adverse events. (Hellenic Journal of Cardiology 2025;■:■-■) © 2025 Hellenic Society of Cardiology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. INTRODUCTION

Hypertension is well recognized as a significant modifiable risk factor for cardiovascular diseases (CVD). According to Yusuf et al. (2020), 22.3% of CVD cases are attributed to hypertension.[1] Despite the widely established association between hypertension and CVD, many cases remain poorly controlled, particularly those classified as resistant hypertension (RH). RH constituted 10.3% of the population receiving hypertension treatment.[2] RH is persistently elevated systolic blood pressure (SBP ≥ 140 mmHg)

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and/or diastolic blood pressure (DBP ≥ 90 mmHg) despite adherence to the maximum tolerated doses of at least three different classes of antihypertensive medications, including a calcium channel blocker (CCB), a diuretic, and either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB). True RH is confirmed using ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM).[3] The American Heart Association (AHA) expands this definition to include patients requiring four or more antihypertensive medications to achieve target blood pressure. In cases where elements such as medication doses, adherence, or out-of-office blood pressure measurements are unavailable, the condition is referred to as apparent treatment-resistant hypertension (aTRH).[4] Subsequently, uncontrolled RH can cause organ damage, including cardiac, macrovascular, microvascular, and renal damage.[5]

Currently, the European Society of Cardiology (ESC) strongly recommends a treatment approach for RH that includes lifestyle modifications, especially sodium restriction in combination with low-dose spironolactone to the current medication. Alternatively, additional diuretic therapy with eplerenone or amiloride, or the use of bisoprolol or doxazosin, may also be considered.[3] Despite the availability of an effectively designed treatment pathway for RH, the use of additional medicines has failed in controlling RH under real-world circumstances. Therefore, another potential therapy, such as angiotensin receptor neprilysin inhibitor (ARNI), is still being investigated. Sacubitril/valsartan, a drug combination earlier known as LCZ696, is an ARNI that combines ARB (valsartan) with neprilysin inhibitor (sacubitril). Sacubitril/valsartan simultaneously blocks the angiotensin II type 1 (AT_1) receptor with valsartan and inhibits the breakdown of natriuretic peptides, which are degraded by neprilysin.[6] Inhibition of the AT_1 receptor and natriuretic peptide breakdown leads to vasodilation, natriuresis, diuresis, and inhibits fibrosis.[6] Furthermore, neprilysin inhibition increases generation of myocardial cyclic guanosine 3'5' monophosphate, improving myocardial relaxation and reducing hypertrophy.[6]

Prior trials such as PARAMOUNT and PARADIGM HF further established the antihypertensive efficacy of sacubitril/valsartan, especially in heart failure patients. The PARAMOUNT trial, conducted in patients with heart failure with preserved ejection fraction (HFpEF), revealed significant reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, reflecting decreased cardiac stress, along with improvements in diastolic function, left atrial size, and blood pressure control.[6] Similarly, the PARADIGM HF trial, focusing on patients with heart failure with reduced ejection fraction (HFrEF), demonstrated that sacubitril/valsartan was superior to enalapril in reducing cardiovascular mortality and heart failure hospitalizations while also achieving greater reductions in SBP.[7] These findings highlight the dual action mechanism of ARNI, which both enhances natriuretic peptide levels and inhibits the renin-angiotensin system, offering substantial antihypertensive and cardioprotective benefits, particularly in managing hypertension and heart failure.[6,7]

Although some studies have demonstrated that switching to ARNI offers superior management of RH compared to ARB or ACEi, a thorough evaluation of ARNI's overall superiority is still lacking.[8,9] Therefore, this study aims to address this gap by providing a comprehensive review to evaluate and compare the efficacy and safety of ARNI with that of ACEi and ARB in managing RH.

2. MATERIAL AND METHODS

2.1. LITERATURE SEARCH STRATEGY. Three reviewers (HL, HA, VF) independently searched for eligible studies from August 2013 to August 2023 in the following databases: Cochrane, PubMed, Google Scholar, and ProQuest. The search strategy employed utilized medical subject heading (MeSH) terms combined with Boolean logical operators. Randomized controlled trials (RCTs) and observational studies published in the English language were included for review. Search terms included "sacubitril/valsartan," "angiotensin receptor neprilysin inhibitor," "neprilysin inhibitor," "ARNI," "refractory hypertension," and "resistant hypertension." The complete list of search terms used is outlined in Supplementary Material 1.

2.2. SELECTION CRITERIA. The inclusion criteria for the study were as follows: 1) Studies comparing the effects of ARNI on blood pressure in adult patients with true RH or aTRH. True RH is defined as uncontrolled blood pressure ≥ 140/90 mmHg while on optimal doses of at least three antihypertensives, one of which must be a diuretic, or when blood pressure control requires four or more medications. White coat hypertension and medication nonadherence should be excluded. aTRH is used when ≥1 of the following data elements are missing (medication dose, adherence, or out-of-office blood pressure). 2) Selected studies had to report SBP or DBP measurements both before and after the interventions or report changes in blood pressure following the interventions.

2.3. DATA EXTRACTION AND SYNTHESIS. Data in this study was extracted according to PRISMA

guidelines. The extracted data from the included studies comprised the year of publication, study design, study location, follow-up duration, participant characteristics, intervention details, blood pressure measurements, adverse events, and echocardiographic findings. The primary outcome of our study was to analyze the available data and determine the effect of ARNI on blood pressure in RH patients, comparing their efficacy to ARB and ACEi. Additionally, we reviewed the safety profile of ARNI. However, due to the limited number of studies, a meta-analysis could not be performed.

2.4. ETHICS CONSIDERATIONS. This study did not require Institutional Review Board approval, as the data involved was collected from publicly available and deidentified sources.

3. RESULTS

Titles and abstracts screening, followed by full-text article reviews, yielded six studies that met the inclusion criteria. Two full-text articles were excluded from our study due to insufficient data, resulting in a total of four studies being included (Fig. 1)[8-11]

The risk of bias in all studies included in our research was assessed using the Cochrane method. Two studies were assessed using ROBINS-I (Risk of Bias in Non Randomized Studies of Interventions),[9,10] while the others used RoB 2 (Cochrane risk of bias tool for randomized trials, version 2).[8,11] The overall risk of bias was low in three studies and of concern in one study (see Supplementary Material 2).

3.1. STUDY CHARACTERISTICS. The included studies, published between 2021 and 2022, were predominantly conducted in China, with only one being multicentered. A total of 915 patients with either true RH or aTRH were involved in this study. The majority of the studies showed that patients with resistant hypertension tend to have a higher prevalence of obesity and diabetes, a higher body mass index (BMI), and are associated with multiple adverse outcomes from cardiovascular disease.

The study characteristics, as shown in Table 1, indicate that Wang et al. conducted a single-center, 12-week, before-and-after prospective study assessing sacubitril/valsartan in 18 hemodialysis patients with RH. In this study, RH is defined as persistent hypertension (mean sitting SBP [msSBP] $\geq$ 140 mmHg) despite three or more antihypertensive drugs or SBP $<$ 140 mmHg despite taking more than three antihypertensives. Furthermore, patients were given sacubitril/valsartan at a dose of 50 mg twice daily, which was titrated to 100 mg twice daily based on tolerance and blood pressure control, switching out ARB/ACEi in their baseline regimen. For patients previously taking ACEi or ARB as part of their regimen, these medications were discontinued at least 72 h before initiating sacubitril/valsartan.[10]

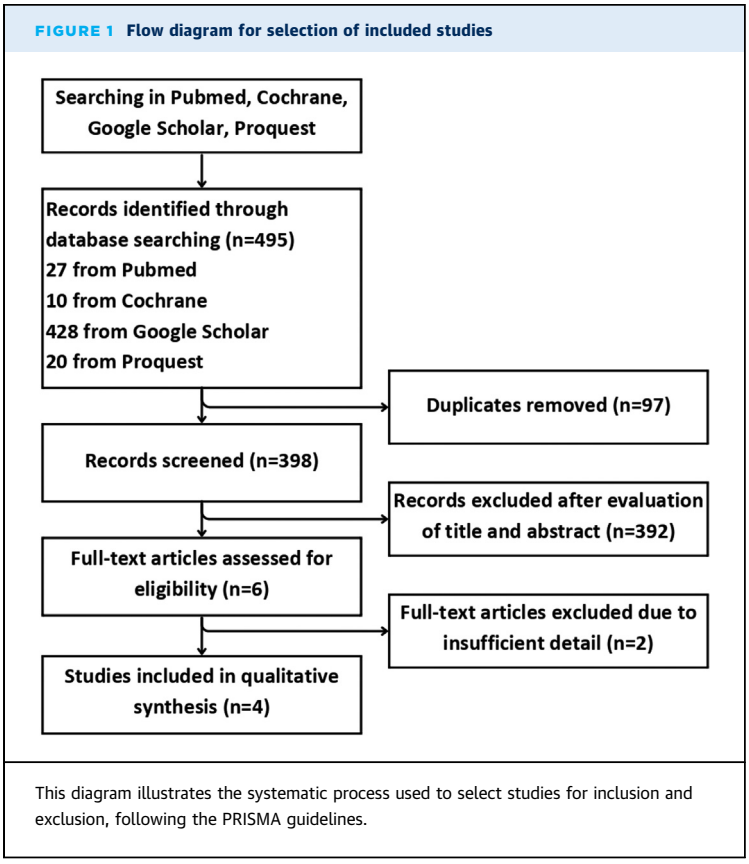

FIGURE 1 Flow diagram for selection of included studies

This diagram illustrates the systematic process used to select studies for inclusion and exclusion, following the PRISMA guidelines.

On the other hand, Li et al. conducted a multicenter, 8-week prospective study to evaluate sacubitril/valsartan's efficacy in managing refractory hypertension among 66 Asian patients. RH in this study was defined as inadequate blood pressure control despite the use of three antihypertensive agents (including a thiazide diuretic) for at least four weeks, along with lifestyle modifications, or the need for four or more drugs to achieve blood pressure control. Additionally, white coat hypertension and secondary hypertension causes were excluded. Similar to Wang et al.'s study, patients were transitioned from an ARB or ACEi in their baseline regimen to sacubitril/valsartan, starting at 200 mg daily, with an increase to 400 mg if blood pressure remained uncontrolled after four weeks. When switching from an ACEi, a 36-h washout period was implemented before initiating sacubitril/valsartan. Blood pressure outcomes were assessed through office and 24-h ambulatory monitoring.[9]

In contrast, the study by Lyu et al. was a single-center, 8-week randomized controlled trial to

TABLE 1 Study characteristics

Study/Location	Design	Follow-up duration (weeks)	Mean age (years)		Patients (n) (Male/Female)			Intervention description	Comorbidities	
			Intervention	Control	Overall	Intervention	Control		Intervention	Control
Wang et al. (2021)/ China	Prospective study	12	53.6 ± 14.5	-	18 (15/3)	18 (15/3)	-	SV 100–200 mg/day replacing ARB/ACEi in the baseline regimen[b]	Diabetes (44.4%), Stroke (11.1%), CAD (5.6%), CKD (100%), HFpEF (77.8%), HFmEF (16.7%), HFrEF (5.5%)	-
Jackson et al. (2021)/ Multicenter[a]	Post hoc analysis of a multiple centers prospective study	16	72.5 ± 8.2		731 (361/370)	NI	NI	SV 2 × 200 mg/day + CCB + diuretic (intervention) Val 2 × 160 mg/day + CCB + diuretic (control)	Cigarette smoking (37.8%), obesity (57.7%), diabetes (60.5%), Stroke (12.4%),	
Lyu et al. (2022)/ China	Single-center prospective randomized control trial	8	70.08 ± 9.29	70.56 ± 7.12	100 (49/51)	50 (24/26)	50 (25/25)	SV 200 mg/day, Amlo 5 mg, HCT 12.5 mg (intervention) Val 80 mg/day, Amlo 5 mg, HCT 12.5 mg (control)	Diabetes (24%), Stroke (14%), CAD (24%), AFib (12%), HF (22%)	Diabetes (22%), Stroke (12%), CAD (26%), AFib (10%), HF (24%)
Li et al. (2022)/ China	Multiple centers prospective study	8	55.1 ± 12.6	-	66 (52/14)	66 (52/14)	-	SV 200–400 mg/day replacing ARB/ACEi in the baseline regimen[b]	Diabetes (25.8%), CKD (NI)	-

NI: no information, only informed that patients are randomized into 1:1; SV: sacubitril/valsartan; Val: valsartan; ARB: angiotensin receptor blocker; ACEi: angiotensin-converting enzyme inhibitor; Amlo: amlodipine; HCT: hydrochlorothiazide; CAD: coronary artery disease; CKD: chronic kidney disease; AFib: atrial fibrillation; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFmEF: heart failure with midrange ejection fraction; HFrEF: heart failure with reduced ejection fraction. [a]No information of patient characteristics between groups. [b]The baseline regimen includes a maximally tolerated dose of either an angiotensin receptor blocker or an angiotensin-converting enzyme inhibitor, along with other maximally tolerated antihypertensives such as beta-blockers, calcium channel blockers, diuretics, sympathetic nervous system inhibitors, sodium-glucose cotransporter-2 inhibitors, alpha-blockers, or vasodilators.

evaluate the efficacy of sacubitril/valsartan in managing RH among 100 patients. The RH definition used in this study was uncontrolled blood pressure (≥140/90 mmHg) despite adherence to a triple therapy regimen including valsartan (80 mg), amlodipine (5 mg), and hydrochlorothiazide (12.5 mg) for at least four weeks, alongside lifestyle modifications.[9] Specifically, the conditions of secondary hypertension, severe liver, and renal impairment were excluded. Patients in this study were randomized into two groups: the research group replaced valsartan with sacubitril/valsartan (200 mg daily) while continuing other medications, whereas the control group maintained the original regimen.[8]

Ultimately, Jackson et al.'s study was a post hoc analysis of the PARAGON HF trial to evaluate the efficacy of sacubitril/valsartan in treating aTRH in patients with HFpEF. The study included 4795 participants, with 731 (15.2%) categorized as having aTRH. In this study, aTRH is defined as an SBP ≥ 140 mmHg (≥135 mmHg in patients with diabetes) despite treatment with valsartan, a calcium channel blocker, and a diuretic. Patients underwent sequential run-in periods with valsartan followed by sacubitril/valsartan before randomization to sacubitril/valsartan (97/103 mg twice daily) or valsartan (160 mg twice daily) while continuing other antihypertensive medications.[11] A key limitation in this study was the reliance on office blood pressure measurements without ambulatory or out-of-office monitoring, limiting the ability to confirm true RH.

3.2. COMPARISON OF BLOOD PRESSURE DATA ACROSS STUDIES. Our research, outlined in Table 2, demonstrated that in all randomized controlled trials (RCTs) or case-control studies, ARNI consistently showed greater reductions in blood pressure, especially in cases of RH, compared to ARB (valsartan) and ACEi. As shown in Wang et al.'s study, a significant reduction in msSBP and mean sitting DBP (msDBP) by 22.4 mmHg and 8.3 mmHg, respectively, from baseline was observed.[10] Additionally, the study by Li et al. demonstrated significant reductions in office blood pressure (mean reduction of 19.4/11.8 mmHg, $p < 0.001$) and ABPM over 24 h (16.6/9.3 mmHg, $p < 0.001$), with consistent improvements observed during both daytime and nighttime periods.[9]

Moreover, the research group in Lyu et al.'s study was also in line with the other studies mentioned above. They demonstrated significantly greater reductions in office blood pressure (24.78/17.86 mmHg vs. 14.1/13.3 mmHg in the control group, $p < 0.001$). In their study, ABPM also showed notable improvements, with significant decreases in 24-h, daytime,

and nighttime systolic and diastolic pressures ($p < 0.001$).[8] Finally, Jackson et al.'s study also supported the evidence of the superiority of sacubitril/valsartan in controlling blood pressure in aTRH (47.9% vs. 34.3%; OR 1.78, 95% CI 1.30-2.43). In addition, the subset with mineralocorticoid receptor antagonist-resistant hypertension in Jackson et al.'s study also showed a more pronounced SBP reduction (−6.3 mmHg), with a higher proportion achieving controlled SBP (43.6% vs. 28.4%; OR 2.63, 95% CI 1.18-5.89).[11]

3.3. CARDIAC REMODELING PARAMETERS AND ADVERSE EVENTS DATA ACROSS STUDIES. Two studies recorded cardiac remodeling parameters before and after the intervention with sacubitril/valsartan, as shown in Table 3. The first study is by Wang et al., who found that cardiac remodeling parameters showed improvement, with the left ventricular ejection fraction (LVEF) increasing from 53.2% to 56.3%, albeit not statistically significant ($p = 0.125$). Additionally, other cardiac remodeling parameters were observed, including a reduction in NT-proBNP levels from 8119.5 to 3130.5 pg/ml ($p = 0.037$), an enhancement in global myocardial work index (GWI) from 2045.31 ± 133.32 to 2185.69 ± 117 mmHg% ($p = 0.026$), and a significant improvement in quality of life ($p = 0.000$).[10] Secondly, the study by Lyu et al. supported the evidence of LVEF improvement in sacubitril/valsartan group, as they found a significant increase in LVEF from 48.36% to 55.08% ($p < 0.001$). Furthermore, they also found another cardiac remodeling parameter, left atrial diameter, which significantly decreased from 38.94 ± 4.54 to 37.04 ± 5.91 mm ($p < 0.05$).[8]

Moreover, adverse events associated with ARNI were also reported in two studies, as shown in Table 4. Wang et al., who found that hypotension occurred in 11% of patients, while Jackson et al. reported a rate of 4.5%.[10,11] Furthermore, Jackson et al.'s study recorded that elevated serum potassium (>5.5 mmol/L) occurred in 14.5% of the intervention group, although this rate was lower compared to the control group (17.7%). Ultimately, an increase of ≥3.0 mg/dl in serum creatinine was observed, which was doubled in the control group (3.4%) compared to the intervention group (1.7%), although it was not statistically significant.[11]

4. DISCUSSION

ARNI, originally identified as LCZ696 and later known as sacubitril/valsartan, have been rigorously studied since their discovery. One of the pioneering studies evaluating their antihypertensive effects was

TABLE 2 Blood pressure changes

Study/Location	24 h ABPM [SBP (mmHg)/DBP (mmHg)]				Office BP [msSBP (mmHg)/msDBP (mmHg)]				Home BP [msSBP (mmHg)/msDBP (mmHg)]	
	ARNI		Non-ARNI		ARNI		Non-ARNI			
	Baseline	Post intervention	Baseline	Post intervention	Baseline	Post intervention	Baseline	Post intervention	Baseline	Post intervention
Wang et al. (2021)/China	-	-	-	-	-	-	-	-	161.6 ± 10.6/ 83.9 ± 8.2	138.8 ± 7.0/ 74.8 ± 9.7
Jackson et al. (2021)/ Multicenter[a]	-	-	-	-	148.9 ± 11.1	138.6 ± 10.1	149.4 ± 11.0	143.0 ± 10.1	-	-
Lyu et al. (2022)/China	144.84 ± 22.53/ 79.82 ± 9.38	128.96 ± 11.11/ 73.32 ± 7.16	-	-	-	Changes. −24.78/−17.86	-	Changes −14.1/−13.3	-	-
Li et al. (2022)/China	146.2 ± 18.1/ 89.1 ± 13.0	129.6 ± 13.6/ 79.8 ± 9.1	-	-	150.0 ± 19.5/ 95.0 ± 18.3	130.6 ± 15.1/ 83.2 ± 9.9	-	-	-	-

ABPM: ambulatory blood pressure monitor; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; msSBP: mean sitting systolic blood pressure; msDBP: mean sitting diastolic blood pressure; ARNI: angiotensin receptor neprilysin inhibitor.
[a]Only systolic blood pressure.

TABLE 3 Cardiac remodeling parameters

Cardiac Remodeling Parameters	Wang et al. (2021)/China			Lyu et al. (2022)/China		
	Baseline	Post intervention	p value	Baseline	Post intervention	p value
LVEF (%)	53.2 ± 5.9	56.3 ± 4.7	0.125	48.36 ± 6.89	55.08 ± 8.17	<0.001
LVM (g)	416.5 ± 107.3	390.0 ± 106.8	0.137			
LVM index ($g/m^{2)}$	206.2 ± 30.4	192.0 ± 39.6	0.198			
NT proBNP (pg/ml)	8119.50 [3710.75, 29,300]	3130.50 [2244.50, 9565.70]	0.037			
GWI (mmHg%)	2045.31 ± 133.32	2185.69 ± 117	0.026			
LA (mm)				38.94 ± 4.54	37.04 ± 5.91	<0.05

LVEF: left ventricular ejection fraction; LVM: left ventricular mass; NT proBNP: N-terminal pro-B-type natriuretic peptide; GWI: global myocardial work index; LA: left atrium.

conducted by Ruilope et al., in 2010. This randomized controlled trial included 1215 patients with mild to moderate hypertension, comparing the efficacy and safety of LCZ696 to valsartan based on reductions in mean sitting SBP and DBP. The study demonstrated that LCZ696, a dual-acting agent, provided complementary and fully additive blood pressure reductions compared to valsartan, with a favorable safety profile. These findings suggested LCZ696's potential in treating hypertension and cardiovascular disease.[12]

As far as we know, there has not been a comprehensive review examining the potential of ARNI in reducing blood pressure among patients with RH. Our research demonstrated that ARNI consistently showed greater reductions in blood pressure in patients with RH compared to ARB (valsartan) or ACEi. This result remained consistent across the different methods of blood pressure monitoring used in each study. This finding aligns with the results of a study done by Rakugi et al., which demonstrated SBP reductions between baseline and week 8 with ARNI 200 mg, ARNI 400 mg, and olmesartan 20 mg at 18.78, 19.52, and 11.51 mmHg, respectively, in elderly participants.[13] Furthermore, in a study conducted by Izzo et al., comparing SBP reduction with ARNI 400 mg, valsartan 320 mg, and placebo, there were reductions of 14.00, 9.60, and 2.20 mmHg, respectively, at week 8.[14] These collective findings underscore the superior efficacy of ARNI in lowering blood pressure. Notably, the PARAMETER study also demonstrated the superior efficacy of sacubitril/valsartan over olmesartan in reducing central aortic pressures and arterial stiffness, particularly in elderly patients with systolic hypertension, further highlighting its role in managing RH.[15] Therefore, sacubitril/valsartan offers a viable alternative to ACEi or ARB for patients whose blood pressure remains inadequately controlled despite the use of three or four antihypertensive medications.[16]

The therapeutic impact of sacubitril and valsartan in managing RH might arise from their novel antihypertensive mechanism. These substances function as dual inhibitors of neprilysin and angiotensin receptors in blood vessels, acting on two pathways to mitigate neuroendocrine overactivity and suppress the release of renin and aldosterone. By boosting the levels of carboxy-terminal ANP, ARNI promotes their interaction with particulate guanylate cyclase (GC)/cyclic guanylate monophosphate (cGMP)-coupled receptors, thereby inducing vasodilation, diuresis, and natriuresis. This mechanism effectively counteracts the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), endothelin, and vasopressin, leading to a comprehensive antihypertensive effect.[17-19]

Another significant aspect found in this study is ARNI's ability to reverse left ventricle (LV) remodeling,

TABLE 4 Adverse events

Adverse Events	Jackson et al. (2021)/Multicenter			Wang et al. (2021)/China
	Intervention, n (%)	Control, n (%)	p value	Intervention, n (%)
Hypotension	16 (4.5)	11 (2.9)	0.55	2 (11.1)
Elevated serum creatinine (mg/dl)				
≥2.0	51 (14.5)	74 (19.5)	0.71	
≥2.5	22 (6.2)	31 (8.2)	0.41	
≥3.0	6 (1.7)	13 (3.4)	0.09	
Elevated serum potassium (mmol/L)				0 (0)
>5.5	51 (14.5)	67 (17.7)	0.87	
>6.0	14 (4.0)	21 (5.5)	0.91	

described by Lyu et al. and Wang et al. In Lyu et al.'s research, a statistically significant increase in LVEF was observed in the ARNI group, reaching 6.71% by week 8.[8] Although Wang et al. also reported a 3.1% increase in LVEF by week 12 in their study, the increase in LVEF was not statistically significant. Furthermore, Wang et al. also observed a decrease in LVM and LVMI, although the data were not statistically significant. This finding in Wang et al.'s study might be caused by the brief follow-up period (12 weeks) and the small sample size (18 patients).[10] The study by Chen et al. also supports this hypothesis, depicting the increase in LVEF percentage (7.0%; $p < 0.001$ in 1 year). Furthermore, other studies also reported the reverse LV remodeling ability of ARNI by using the LV mass index (LVMI) as their indicator; Chen et al. found a decrease in LVMI of 7.23 g/m^2 at week 24 ($p < 0.000$), while Schmieder et al. showed a reduction of 6.36 g/m^2 at week 56 ($p < 0.01$).[20,21] Hence, the increase of LVEF and the decrease of LVMI in these studies give a perspective on the ability of ARNI to reverse LV remodeling, leading to further experiments for determining the potential of ARNI as a reverse cardiac remodeling medication and its underlying mechanism.

It is worth noting that not all studies provided information on adverse events associated with ARNI. Two studies did report adverse events, with hypotension being the most commonly observed, followed by elevated serum potassium levels.[10,11] However, the adverse effects do not necessitate discontinuation of ARNI use. An RCT indicates that ARNI's safety profiles were comparable with olmesartan in hypertensive patients. The study found no difference in adverse events between the groups (23.4% vs. 21.9%, respectively), with headache and dizziness as the most common adverse events.[22] Similar findings were reported in the PARAMOUNT study, which demonstrated that the incidence of adverse events, including hypotension, hyperkalemia, and renal dysfunction, was comparable between ARNI and ARB treatment groups.[6] Thorough evaluation and ongoing monitoring are necessary to accurately assess and manage these effects in clinical practice.

It is also worth noting that the baseline antihypertensives used in each study differ in type and dosage, thus hindering us from accurately assessing the effect of ARNI on patients with RH across these studies. Nevertheless, Lyu et al. attempted to mitigate the bias by ensuring that patients in each group were prescribed the same baseline and concomitant antihypertensive drugs.[8] The reduction in blood pressure is significantly higher compared to RH patients who took valsartan, indicating that ARNI might be more effective.

While the existing research consistently supports the blood pressure-lowering effects of ARNI, it is essential to acknowledge that a significant portion of these studies involve a limited number of participants, with the majority having fewer than 100 patients. Moreover, the largest study available is based on a post hoc analysis. Notably, this study used the definition of apparent resistant hypertension, which necessitates careful interpretation of its findings. Nevertheless, the proportion of patients categorized in this group aligns with that observed in other studies involving patients classified as having true resistant hypertension.[11]

Furthermore, the majority of the research is conducted within the Asian population, predominantly of Chinese descent.[8–10] In contrast to these studies, Jackson et al.'s research primarily focuses on the white population.[11] Despite the difference, the reduction in blood pressure appears to be similar in both populations. The lack of standardized blood pressure measurement in these studies also warrants further investigation to provide more precise and robust data. Additionally, the study populations and comparators were considered too heterogeneous to allow for a quantitative meta-analysis.

4.1. FUTURE DIRECTION. Future research comparing the efficacy and safety of ARNI to placebo and other antihypertensive drugs in patients with RH should be conducted through long-term multicenter randomized controlled trials, incorporating 24-h ABPM to establish the superiority of ARNI. Additionally, studies aiming to observe RH patients with specific comorbidities can offer new insights into ARNI's effectiveness in lowering blood pressure in these specific populations. Furthermore, research utilizing various cardiac remodeling parameters over a prolonged follow-up period could enhance our comprehension of ARNI's ability to reverse cardiac remodeling and its underlying mechanisms.

5. CONCLUSION

In conclusion, ARNI represents a promising alternative to ARB or ACEi in the standard management of resistant hypertension, offering superior blood pressure reductions without an increased risk of serious adverse events comparable to the standard management. Furthermore, our study emphasizes the potential for the cardiac remodeling reversal effect of ARNI beyond mere blood pressure reduction. Nevertheless, to validate these findings, comprehensive, extensive-scale studies, preferably an RCT, remain crucial.

AUTHOR CONTRIBUTION

All authors have contributed equally to this work, including conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing (original draft, review, and editing).

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DECLARATIONS OF INTEREST

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KEYWORDS Sacubitril/valsartan, Angiotensin receptor neprilysin inhibitor, Neprilysin inhibitor, ARNI, Refractory hypertension, Resistant hypertension

APPENDIX A. SUPPLEMENTARY DATA Supplementary data related to this article can be found at https://doi.org/10.1016/j.hjc.2025.01.004.