

A RETROSPECTIVE COMPARISON OF ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITORS VERSUS ANGIOTENSIN RECEPTOR BLOCKERS IN PATIENTS WITH CARDIOVASCULAR DISEASES

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Abstract

Background: Cardiovascular diseases (CVDs), including coronary artery disease (CAD), hypertension (HTN), and heart failure (HF), remain leading causes of morbidity and mortality worldwide. Angiotensin receptor blockers (ARBs) are well-established therapies for these conditions; however, angiotensin receptor–neprilysin inhibitors (ARNIs) have emerged as a promising alternative by providing dual inhibition of the renin–angiotensin–aldosterone system and neprilysin pathway. Although randomized clinical trials have demonstrated the benefits of ARNIs in heart failure, evidence comparing ARNI and ARB therapy across a broader cardiovascular disease population remains limited.

Methods: A retrospective observational study was conducted in the Department of Cardiology at Pushpagiri Medical College Hospital, Thiruvalla. Electronic medical records of 320 eligible patients were reviewed, including 160 patients receiving ARNI therapy and 160 patients receiving ARB therapy. Clinical outcomes, symptom improvement, adverse drug reactions, treatment discontinuation, left ventricular ejection fraction (LVEF), serum creatinine, glycemic control, and systolic blood pressure were assessed. Statistical analyses included Chi-square tests, Mann–Whitney U tests, and Wilcoxon signed-rank tests.

Results: The mean age of participants was 65.3 ± 11.9 years, with males accounting for 62.5% of the study population. CAD was the most common diagnosis (31.3%). Compared with ARB therapy, ARNI therapy was associated with significantly lower rates of rehospitalization (33.8% vs 58.8%, $p < 0.001$), myocardial infarction (6.9% vs 24.4%, $p < 0.001$), syncope (8.8% vs 21.9%, $p = 0.001$), dizziness (13.8% vs 27.5%, $p = 0.002$), gastrointestinal discomfort (8.1% vs 23.1%, $p < 0.001$), and drug discontinuation (9.4% vs 41.9%, $p < 0.001$). Symptom improvement was significantly greater in the ARNI group, particularly for breathlessness, chest pain, edema, and cough. LVEF improvement was observed predominantly among ARNI-treated patients (70.0% vs 11.3%, $p < 0.001$). Both groups achieved significant reductions in systolic blood pressure, although ARNI therapy demonstrated superior blood pressure stability and glycaemic control.

Conclusion: The present study demonstrated that ARNI therapy was associated with better clinical outcomes than ARB therapy in patients with cardiovascular diseases. ARNI-treated patients showed lower rates of rehospitalization and major cardiovascular events, greater symptom improvement,

enhanced recovery of left ventricular function, better treatment adherence, and a favorable safety profile.

Keywords: Coronary Artery Disease; Hypertension; Heart Failure; Angiotensin Receptor Blockers; Angiotensin Receptor–Neprilysin Inhibitors

1. Introduction

Cardiovascular diseases (CVDs), including coronary artery disease (CAD), hypertension (HTN), and heart failure (HF), remain leading causes of morbidity and mortality worldwide. Despite advances in pharmacological therapy, the burden of cardiovascular complications, recurrent hospitalizations, and reduced quality of life continues to pose significant healthcare challenges. Angiotensin receptor blockers (ARBs) are commonly used in the management of cardiovascular diseases through inhibition of the renin–angiotensin–aldosterone system (RAAS), resulting in reduced vasoconstriction, blood pressure, and cardiac remodeling. More recently, angiotensin receptor–neprilysin inhibitors (ARNIs), particularly sacubitril/valsartan, have emerged as an important therapeutic option by combining RAAS blockade with neprilysin inhibition, thereby enhancing the beneficial effects of natriuretic peptides.

Several clinical trials and real-world studies have reported that ARNIs improve cardiac function, reduce heart failure hospitalizations, and provide superior blood pressure control compared with conventional ARB therapy. In addition, evidence suggests potential benefits in renal protection and overall cardiovascular outcomes. However, most studies have focused primarily on patients with heart failure, while comparative data across a broader range of cardiovascular diseases remain limited. Therefore, the present study was conducted to compare the clinical efficacy and safety profile of ARNI and ARB therapy among patients with cardiovascular diseases in a real-world tertiary care setting.

MATERIALS AND METHODS

A single centered, hospital based, retrospective study was conducted in the Department of Cardiology, Pushpagiri Medical College Hospital, Thiruvalla, Kerala, India for a duration of 6 months, including a total of 320 patients.

Inclusion Criteria

- Patients aged 18 years and above.
- Patients with cardiovascular diseases receiving ARNI or ARB therapy.
- Patients with complete electronic medical records.
- Matched ARNI and ARB treatment populations.

Exclusion Criteria

- Pregnant and lactating women.
- Severely ill patients.

The sample size obtained was $n = 320$ patients using the formula;

$$n = \frac{[Z_{(1-\alpha/2)}\sqrt{2pq} + Z_{(1-\beta)}\sqrt{p_1q_1 + p_2q_2}]^2}{(p_1 - p_2)^2}$$

STUDY PROCEDURE

Following Institutional Ethics Committee approval, a retrospective review of electronic medical records was conducted in the Department of Cardiology, Pushpagiri Medical College Hospital. A total of 320 patients with cardiovascular diseases receiving either ARNI therapy ($n=160$) or ARB therapy ($n=160$) were included based on the eligibility criteria. Demographic data, clinical characteristics, cardiovascular outcomes, symptom improvement, laboratory parameters, adverse drug reactions, and drug discontinuation details were collected using a structured data collection form. The efficacy and safety outcomes of ARNI and ARB therapies were compared using appropriate statistical methods, with a p -value <0.05 considered statistically significant.

STATISTICAL ANALYSIS

Data were analyzed using descriptive and inferential statistics. Chi-square tests were used for categorical variables. Mann–Whitney U tests compared continuous variables between groups, while Wilcoxon signed-rank tests assessed within-group changes. A p-value <0.05 was considered statistically significant.

RESULTS

Distribution of Patients According to Study Medication Group

A total of 320 patients were included in the study. Of these, 160 patients (50%) received Angiotensin Receptor–Neprilysin Inhibitors (ARNI), while 160 patients (50%) received Angiotensin Receptor Blockers (ARB). The equal distribution of patients between the two treatment groups provides a balanced comparison for evaluating the outcomes and effectiveness of ARNI versus ARB in patients with cardiovascular diseases.

Distribution of Study Participants According to Demographic Characteristics and Clinical Assessment

Among the 320 study participants, the majority were aged 60–74 years (47.2%), followed by 45–59 years (24.1%) and ≥75 years (23.8%). Only 5.0% of participants were younger than 45 years, indicating that cardiovascular diseases were predominantly observed in older adults. With respect to gender, males (62.5%) outnumbered females (37.5%), suggesting a higher representation of male patients in the study population. Regarding clinical assessment, coronary artery disease (CAD) was the most common diagnosis, accounting for 31.3% of patients, followed by Hypertension (HTN) (20.3%) and CAD with HTN (17.8%). Heart Failure with Reduced Ejection Fraction (HFrEF) was present in 15.6% of patients, while Congestive Cardiac Failure (CCF), Dilated Cardiomyopathy (DCM), and Acute Decompensated Heart Failure (ADHF) accounted for 6.3%, 5.6%, and 3.1% of cases, respectively. These findings indicate that CAD and hypertension were the predominant cardiovascular conditions among the study participants. The mean age of the study participants was 65.3 years, with a standard deviation of 11.9 years, indicating that most patients were elderly with a moderate variation in age distribution.

Distribution of Study Participants According to Comorbidities

Among the study participants, diabetes mellitus was the most prevalent comorbidity, affecting 182 patients (56.9%), while 138 patients (43.1%) did not have diabetes. Dyslipidaemia was present in 116 patients (36.3%), whereas 63.7% of participants did not have dyslipidaemia. Hypothyroidism was the least common comorbidity, observed in only 13 patients (4.1%), with the vast majority (95.9%) being free from the condition.

Distribution of Cardiovascular Outcomes Among Study Participants

Among the cardiovascular outcomes assessed, rehospitalization was the most frequently observed event, occurring in 148 patients (46.3%), while 53.8% of patients did not require rehospitalization. Myocardial infarction (MI) was reported in 50 patients (15.6%), and syncope occurred in 49 patients (15.3%), making them the next most common adverse cardiovascular outcomes. Atrial fibrillation was observed in 28 patients (8.8%), whereas stroke and cardiovascular death were less common, affecting 5.3% and 5.0% of participants, respectively. The majority of patients did not experience these adverse events during the study period.

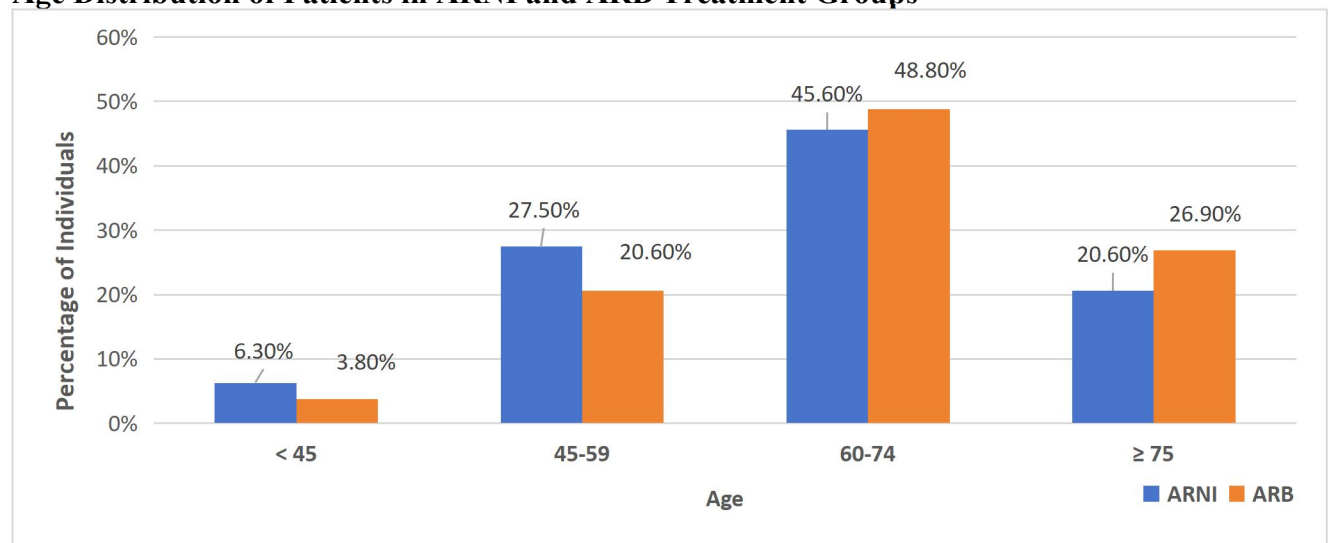
Cardiovascular outcomes		Frequency	Percent
Rehospitalization	yes	148	46.3
	no	172	53.8
MI	yes	50	15.6
	no	270	84.4
Stroke	yes	17	5.3
	no	303	94.7

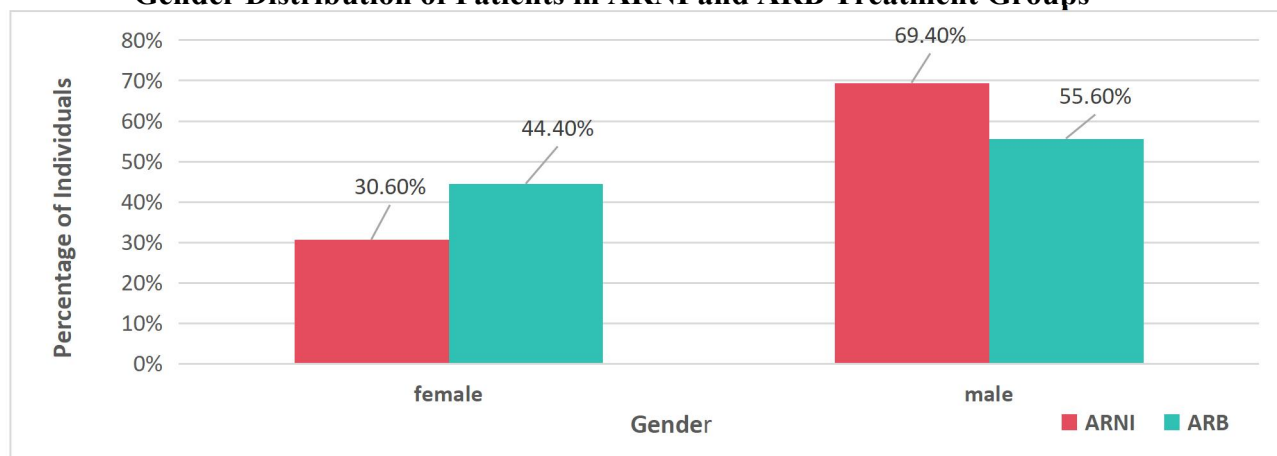
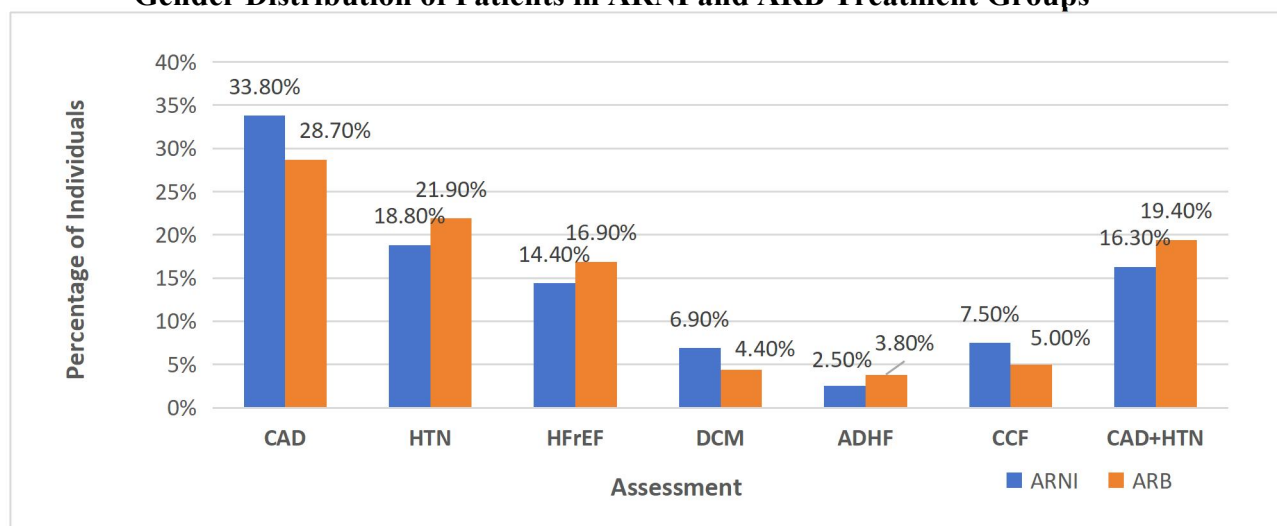
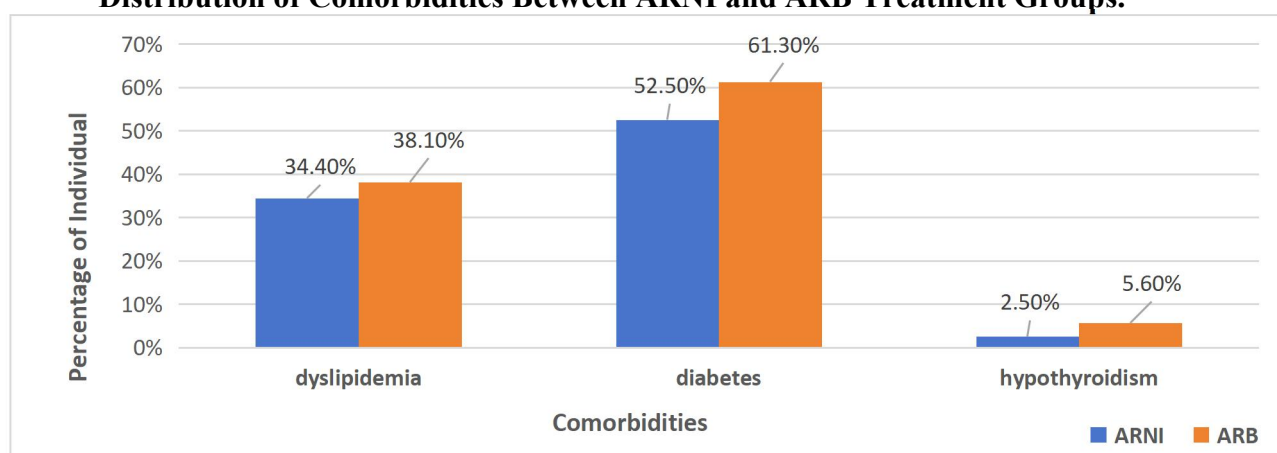
Atrial Fibrillation	yes	28	8.8
	no	292	91.3
Cardiovascular Death	yes	16	5
	no	304	95
Syncope	yes	49	15.3
	no	271	84.7

Distribution of Symptom Improvement Among Study Participants

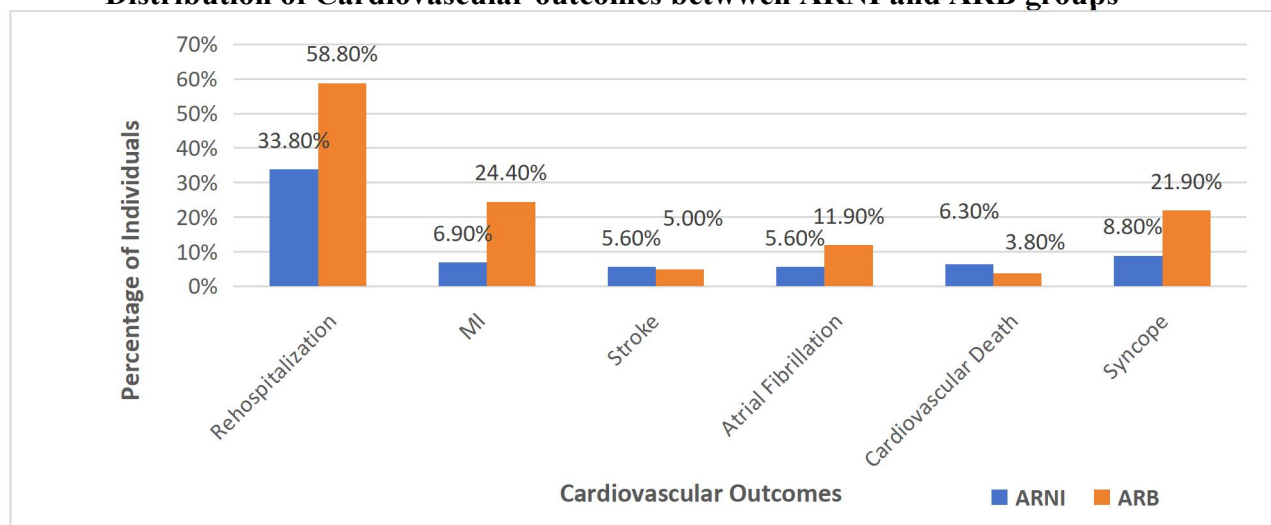
Symptoms Improvement		Frequency	Percent
Breathlessness	improved	137	42.8
	no change	96	30
	worsened	13	4.1
	nil	74	23.1
Fatigue	improved	56	17.5
	no change	56	17.5
	worsened	7	2.2
	nil	201	62.8
Cough	improved	66	20.6
	no change	46	14.4
	worsened	4	1.3
	nil	204	63.7
Edema	improved	74	23.1
	no change	53	16.6
	worsened	3	0.9
	nil	190	59.4
Chest pain	improved	96	30
	no change	65	20.3
	worsened	11	3.4
	nil	148	46.3

Age Distribution of Patients in ARNI and ARB Treatment Groups



Gender Distribution of Patients in ARNI and ARB Treatment Groups

Gender Distribution of Patients in ARNI and ARB Treatment Groups

Distribution of Comorbidities Between ARNI and ARB Treatment Groups.


Dyslipidaemia was present in 34.4% of ARNI patients and 38.1% of ARB patients, indicating a slightly higher prevalence in the ARB group. Diabetes mellitus was more common in the ARB group (61.3%) compared to the ARNI group (52.5%), suggesting a relatively higher burden of glycaemic comorbidity among ARB recipients. Hypothyroidism was the least prevalent comorbidity in both groups, affecting 2.5% of ARNI patients and 5.6% of ARB patients.

Distribution of Cardiovascular outcomes between ARNI and ARB groups


Rehospitalization was significantly lower in the ARNI group (33.8%) compared to the ARB group (58.8%), indicating fewer repeat hospital admissions among patients receiving ARNI therapy. Similarly, myocardial infarction (MI) occurred less frequently in the ARNI group (6.9%) than in the ARB group (24.4%). The incidence of atrial fibrillation and syncope was also lower in the ARNI group (5.6% and 8.8%, respectively) compared to the ARB group (11.9% and 21.9%). However, stroke rates were comparable between both groups (ARNI: 5.6%, ARB: 5.0%). Interestingly, cardiovascular death was slightly higher in the ARNI group (6.3%) compared to the ARB group (3.8%), though the overall numbers were low.

Comparison of Symptom Improvement According to Medication Group (ARNI vs ARB)

Patients receiving ARNI therapy demonstrated greater symptomatic improvement than those receiving ARB therapy. Improvement in breathlessness was markedly higher in the ARNI group (58.8% vs. 26.9%), while chest pain (32.5% vs. 27.5%) and edema (25.0% vs. 21.3%) also improved more frequently. Fatigue showed similar improvement in both groups (17.5%), whereas cough improved at comparable rates; however, the ARNI group had fewer patients with persistent symptoms and no reported worsening of cough or edema.

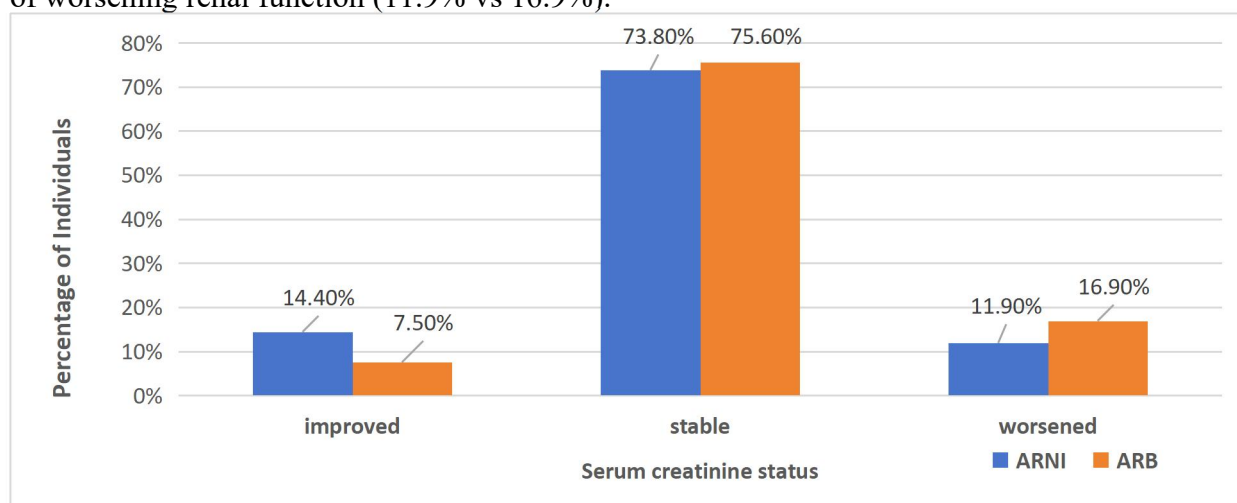
Symptoms Improvement		Medication	
		ARNI	ARB
Breathlessness	improved	94	43
		58.80%	26.90%
	no change	27	69
		16.90%	43.10%
	worsened	3	10
Fatigue	improved	36	38
		22.50%	23.80%
	no change	28	28
		17.50%	17.50%
	worsened	13	43
		8.10%	26.90%
		3	4
		1.90%	2.50%

Cough	nil	116	85
		72.50%	53.10%
	improved	32	34
		20.00%	21.30%
	no change	11	35
		6.90%	21.90%
	worsened	0	4
		0.00%	2.50%
Edema	nil	117	87
		73.10%	54.40%
	improved	40	34
		25.00%	21.30%
	no change	19	34
		11.90%	21.30%
	worsened	0	3
		0.00%	1.90%
Chest pain	nil	101	89
		63.10%	55.60%
	improved	52	44
		32.50%	27.50%
	no change	11	54
		6.90%	33.80%
	worsened	4	7
		2.50%	4.40%
	nil	93	55
		58.10%	34.40%

Comparison of Clinical Parameter Status According to Medication Group

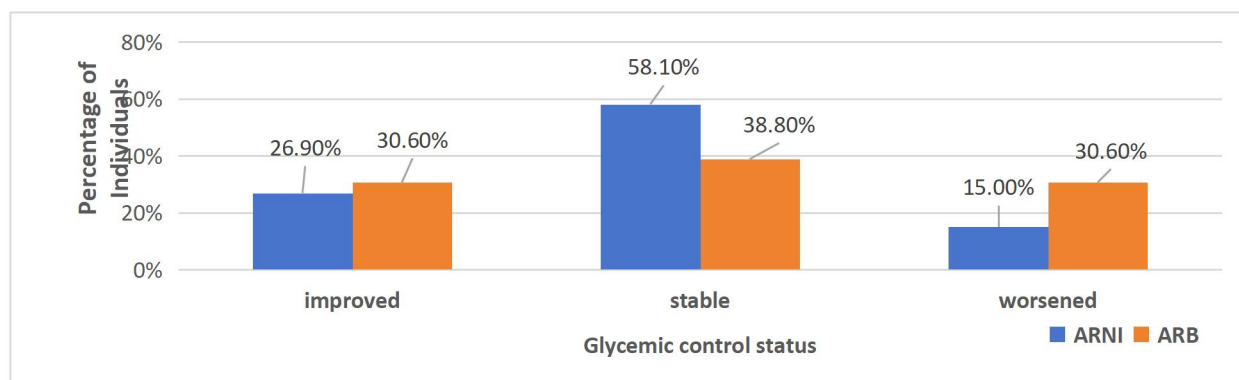
Comparison of Serum Creatinine Status Between ARNI and ARB Treatment Groups

For serum creatinine, both groups had a majority of patients remaining stable, but the ARNI group showed a slightly higher proportion of improvement (14.4% vs 7.5%) and fewer cases of worsening renal function (11.9% vs 16.9%).



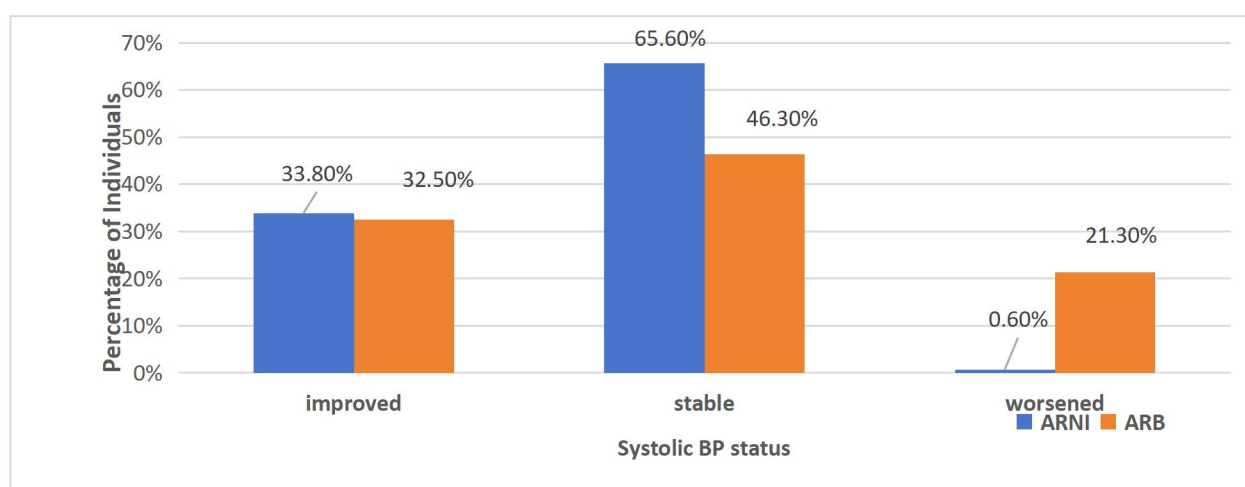
Comparison Glycemic control Status Between ARNI and ARB Treatment Groups

In glycemic control, ARNI patients demonstrated better stability (58.1%) and lower worsening rates (15.0%) compared to the ARB group, where a higher proportion of patients worsened (30.6%).



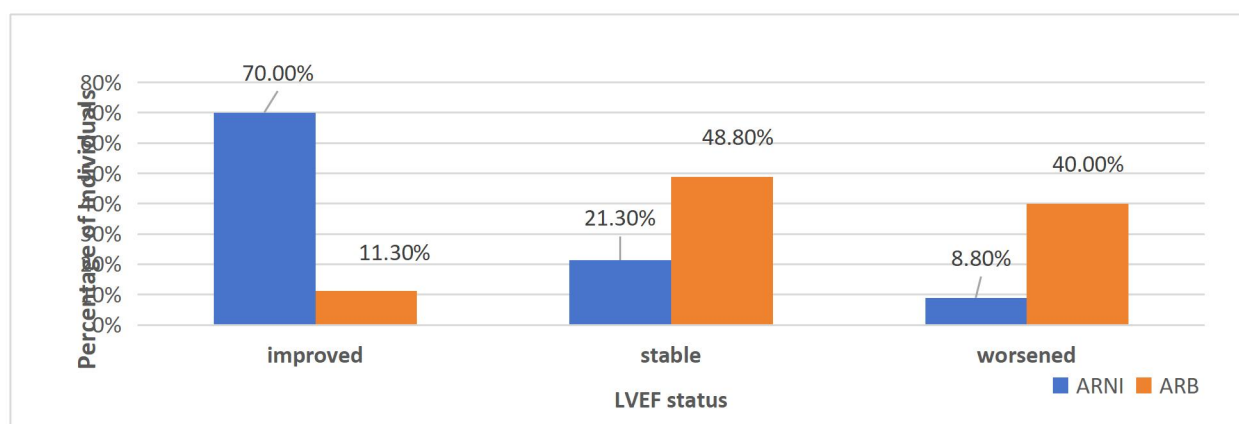
Comparison of Systolic BP Status Between ARNI and ARB Treatment Groups

For systolic blood pressure, both groups showed similar improvement rates; however, worsening was significantly higher in the ARB group (21.3%) compared to the ARNI group (0.6%), indicating better BP stability with ARNI therapy.



Comparison of LVEF Status Between ARNI and ARB Treatment Groups

The most striking difference was observed in LVEF status, where the ARNI group showed marked improvement in 70.0% of patients, compared to only 11.3% in the ARB group. Additionally, the ARB group had a substantially higher proportion of patients with worsening LVEF (40.0% vs 8.8%).



Comparison of Adverse Drug Reactions According to Medication Group

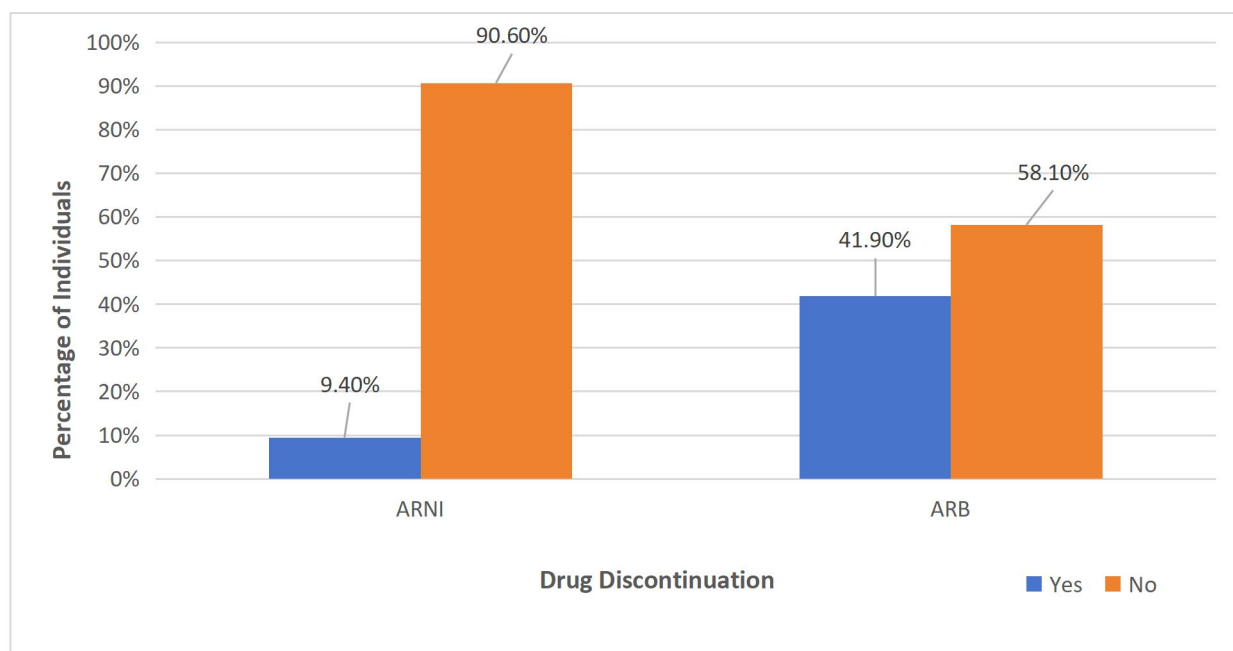
ADR		Medication	
		ARNI	ARB
Hypotension	present	42	32

	not present	26.30%	20.00%
		118	128
Hyperkalemia	present	7	5
		4.40%	3.10%
	not present	153	155
		95.60%	96.90%
Dizziness	present	22	44
		13.80%	27.50%
	not present	138	116
		86.30%	72.50%
GI discomfort	present	13	37
		8.10%	23.10%
	not present	147	123
		91.90%	76.90%

Hypotension was slightly more frequent in the ARNI group (26.3%) compared to the ARB group (20.0%). However, both groups showed a majority of patients without hypotension. Hyperkalemia was rare in both groups, with comparable low incidence (ARNI: 4.4%, ARB: 3.1%), indicating similar safety in terms of potassium imbalance. In contrast, dizziness and gastrointestinal (GI) discomfort were significantly more common in the ARB group (27.5% and 23.1%, respectively) compared to the ARNI group (13.8% and 8.1%).

Comparison of Drug Discontinuation According to Medication Group (ARNI vs ARB)

Drug discontinuation was significantly lower in the ARNI group (9.4%) compared to the ARB group (41.9%). The majority of patients in the ARNI group (90.6%) continued therapy without interruption, whereas less than two-thirds of patients in the ARB group (58.1%) maintained treatment.



DISCUSSION

The present retrospective study evaluated the clinical effectiveness and safety of Angiotensin Receptor–Neprilysin Inhibitors (ARNIs) compared with Angiotensin Receptor Blockers (ARBs) in patients with cardiovascular diseases managed at a tertiary care hospital. The study

population was predominantly elderly, with coronary artery disease and hypertension being the most common cardiovascular conditions. Overall, ARNI therapy was associated with more favorable clinical outcomes, including lower rates of rehospitalization, myocardial infarction, syncope, and atrial fibrillation. Patients receiving ARNIs also demonstrated greater symptomatic improvement, particularly in breathlessness, chest pain, and edema-related symptoms, along with greater improvement in left ventricular ejection fraction (LVEF). These findings are consistent with previous studies by Po-Cheng Chang et al. and Estrellita Uijl et al., supporting the beneficial effects of sacubitril/valsartan in reducing cardiovascular events and improving cardiac function.

Both treatment groups showed improvement in blood pressure control; however, ARNI therapy was associated with better overall clinical status and glycemic stability. Renal function remained largely stable in both groups, consistent with the findings of Alexander Peikert et al., supporting the renal safety of ARNIs. Hypotension was the most frequently observed adverse event, while hyperkalemia remained uncommon. Although some patients required dose reduction because of hypotension, treatment discontinuation was lower in the ARNI group, suggesting good long-term tolerability and treatment persistence in routine clinical practice.

A slightly higher number of cardiovascular deaths was observed in the ARNI group; however, this finding should be interpreted cautiously because ARNIs were often prescribed to patients with more advanced heart failure and lower baseline LVEF, making confounding by indication likely. Despite the limitations of its retrospective, single-center design and reliance on electronic medical records, this study provides valuable real-world evidence supporting the effectiveness and safety of ARNI therapy across a broad spectrum of cardiovascular diseases. Larger prospective multicenter studies with longer follow-up are needed to further validate these findings.

CONCLUSION

The findings of this study support the expanding role of Angiotensin Receptor–Neprilysin Inhibitors in contemporary cardiovascular care. In routine clinical practice, ARNI therapy demonstrated meaningful clinical benefits and maintained an acceptable safety profile across a broad spectrum of cardiovascular diseases. These results suggest that ARNIs may offer advantages beyond conventional RAAS blockade and represent a valuable therapeutic option for improving patient outcomes. Future large-scale prospective studies are warranted to further clarify their long-term impact on cardiovascular morbidity, mortality, and quality of life.

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Conflict of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/publication of this article.

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Ethical consideration

Institutional Research/ Human Ethics Committee approval was obtained.

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