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ORIGINAL ARTICLE

Angiotensin receptor-neprilysin inhibitors in concurrent heart failure with reduced ejection fraction and kidney failure

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Abstract

Aims Angiotensin receptor-neprilysin inhibitor (ARNI) therapy has demonstrated improved outcomes in heart failure with reduced ejection fraction (HFrEF). However, its benefits in patients with concomitant kidney failure undergoing replacement therapy remain uncertain.

Methods and results Using the National Health Insurance Service database, we identified individuals with HFrEF and kidney failure receiving replacement therapy who were prescribed either ARNI or renin-angiotensin system (RAS) blockers between 2017 and 2021. After applying inverse probability of treatment weighting, we compared 2104 patients on ARNI with 2191 on RAS blockers. The primary endpoint was a composite of all-cause mortality and any hospitalization. Secondary endpoints included all-cause mortality, any hospitalization and cardiovascular mortality. During a median follow-up of 19.1 months, ARNI use was associated with a significantly lower risk of the primary endpoint (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.75–0.97) compared with RAS blockers. ARNI also showed a reduced risk of all-cause mortality (HR 0.68, 95% CI 0.54–0.86), any hospitalization (HR 0.86, 95% CI 0.75–0.98) and cardiovascular mortality (HR 0.68, 95% CI 0.52–0.89). Subgroup analyses demonstrated consistent associations across age, sex, comorbidities and medications. Good adherence to ARNI was linked to a lower risk of the primary outcome, whereas non-adherence showed no benefit.

Conclusions Among HFrEF patients with kidney failure receiving replacement therapy, ARNI use was associated with lower risks of all-cause mortality, any hospitalization and cardiovascular mortality compared with RAS blockers, particularly in those with good adherence to therapy.

Keywords Heart failure, systolic; Hospitalization; Kidney failure, chronic; Mortality; Renin-angiotensin system; Treatment outcome

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Introduction

Patients with heart failure often have coexisting chronic kidney disease (CKD), with prevalence ranging from 26% to 64%, and approximately 5–6% of heart failure patients are on kidney replacement therapy.[1–4] In heart failure, deteriorating kidney function is associated with increased mortality, and this risk is even more pronounced in patients with kidney failure.[1,4,5] Unfortunately, most medications for heart failure with reduced ejection fraction (HFrEF) lack strong evidence in patients with estimated glomerular filtration rate (eGFR) $<$ 30 mL/min/1.73 m^2, particularly those receiving

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kidney replacement therapy.[4,6,7] This underscores significant risks for patients with HFrEF and kidney failure, highlighting unmet needs in treatment.

The angiotensin-receptor neprilysin inhibitor (ARNI) is considered a foundational medication for HFrEF due to its efficacy in reducing all-cause mortality and heart failure hospitalization, thereby forming one of the four pillars of treatment.[8,9] However, patients with an eGFR $<$ 30 mL/min/1.73 m^2 were excluded from the trial, and the efficacy of ARNI in patients with kidney failure receiving replacement therapy remains unclear. Previous studies demonstrated that ARNI improved cardiac function and ST2 levels in HFrEF with kidney failure on replacement therapy, without increasing predialysis potassium.[10,11] However, these studies did not evaluate clinical outcomes such as mortality or hospitalization. Subsequent studies have investigated the impact of ARNI on clinical outcomes, but results have been inconsistent, likely due to small sample sizes and follow-up periods limited to within 1 year.[12–14]

Therefore, we conducted this cohort study to elucidate the association between ARNI use and clinical outcomes compared with conventional treatment in patients with combined HFrEF and kidney failure receiving replacement therapy. Furthermore, we aimed to examine whether adherence to the medication differentially affects the clinical outcomes in this population.

Methods

Data source and study population

This study utilized data from the Korean National Health Insurance System (NHIS), a comprehensive and mandatory health insurance program managed by the Korean government. The NHIS provides healthcare coverage to nearly the entire population of South Korea, ensuring a vast and inclusive database. This system operates on a fee-for-service model, enabling the collection of detailed medical expense claims for all insured individuals nationwide.[15–17] Specifically, the NHIS database includes: (1) a qualification database, which contains basic information about enrollees such as age and sex; (2) a claims database, which includes diagnostic information classified by the International Classification of Diseases, Tenth Revision (ICD-10), and records of prescriptions and procedures for both inpatient and outpatient services; and (3) mortality data, which are linked to the database of Statistics Korea using unique identification numbers.

The eligible study population included individuals aged 18 years or older diagnosed with HFrEF who were taking either ARNI or traditional renin-angiotensin system (RAS) blockers (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) while also receiving kidney replacement therapy for kidney failure between July 2017 and December 2021. HFrEF diagnosis was confirmed using the following criteria: (1) initiation of ARNI, indicating no previous use of ARNI for at least 3 years before the index date, or (2) at least two claims for RAS blockers under the following ICD-10 codes for heart failure (heart failure with systolic dysfunction [I50.04], left ventricular failure [I50.1], dilated cardiomyopathy [I42.0], or ischaemic cardiomyopathy [I25.5]), along with examination of natriuretic peptide or echocardiography within 6 months of the RAS blocker prescription. For reference, ARNI is approved only for HFrEF patients with a left ventricular ejection fraction of $\leq$40% in Korea. The Health Insurance Review and Assessment Service strictly evaluates ARNI prescriptions, making it a reliable indicator for HFrEF diagnosis. We excluded individuals who were diagnosed with cancer within the past 5 years, had undergone heart transplantation or left ventricular assist device implantation, had a human immunodeficiency virus infection, were admitted to a nursing hospital at the index date, had a total prescription duration for ARNI or RAS blockers of less than 90 days, or had a follow-up duration of less than 6 months. We further excluded those who only underwent short-term dialysis, specifically continuous renal replacement therapy (CRRT), typically performed in hemodynamically unstable patients. The final cohort comprised 853 individuals on ARNI and 1389 individuals on RAS blockers. After applying inverse probability treatment weighting (IPTW) using the propensity score for each subject, the final analysis included a weighted sample of 2104 individuals on ARNI and 2191 individuals on RAS blockers. The study flowchart is depicted in *Figure S1*. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The local institutional review board reviewed and approved the study protocol (IRB No. CR321358). Participant consent was waived because anonymized data were provided by the NHIS under a strict confidentiality protocol.

Study outcomes

The primary outcome was a composite of all-cause mortality and any hospitalization within 2 years. Secondary outcomes included all-cause mortality, any hospitalization or cardiovascular mortality within 2 years. Cardiovascular mortality was defined as death occurring within 30 days after a diagnosis of the following diseases: myocardial infarction (I21–I23), unstable angina (I20.0), heart failure (I11.0, I13.0, I13.2 and I50), cardiomyopathy (I42), stroke (I60–I64), sudden cardiac arrest (I46.9), cardiogenic shock (R57.0), other cerebrovascular events (I65–I69) and other cardiovascular events (I24-25, I30-49 and I51-52). The index date was defined as the first prescription of either ARNI or a RAS blocker during the study period. From the index date, patients were monitored for up to 2 years or until the outcome occurred, following a 90-day supply of medication.

Covariates

As covariates, we collected data on the cohort entry year, age, sex, socioeconomic status, region, duration of RAS blocker prescription before the index date, comorbidity burden, medication and healthcare utilization. The cohort entry year was divided based on the COVID-19 period (pre-COVID-19 and amid-COVID-19), considering the potential impact of COVID-19 on clinical outcomes. Socioeconomic status was categorized into three groups (low, middle and high) based on insurance premiums. The Charlson comorbidity index was calculated to assess the comorbidity burden.[18]

Statistical analyses

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), while categorical variables were presented as number (percentage). To reduce confounding, we adopted the IPTW method. The goal of IPTW is to estimate treatment causal effects more accurately by creating a weighted sample where the distribution of confounding variables or prognostically important covariates is approximately equal between the comparison groups.[19] A multiple logistic regression model was used to estimate the propensity score, with the treatment group as the dependent variable and all baseline characteristics presented in *Table 1* as independent variables. Baseline characteristics were summarized descriptively both before and after applying IPTW to evaluate comparability. Covariates were considered well-balanced if the absolute standardized difference was less than 0.1. Incidence rates were calculated as the weighted number of events by the weighted total person-time at risk and were presented as events per 100 person-years. The cumulative incidence of outcomes was graphically presented using a weighted Kaplan–Meier curve and compared between groups.[20] The relationship between treatments and clinical outcomes was assessed using Cox proportional hazards regression with a robust sandwich-type variance estimator to account for the weights.[19] The results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption of the Cox regression was tested based on Schoenfeld residuals. Subgroup analyses were conducted based on cohort entry year, age, sex, socioeconomic status, region, Charlson comorbidity index (divided into two groups based on its median value in our cohort), presence of diabetes, hypertension, ischaemic heart disease, cerebrovascular disease, atrial fibrillation and use of beta-blockers and aldosterone antagonists. The results were presented as forest plots. Additionally, we analysed the potential differences in clinical outcomes based on drug adherence. Drug adherence was evaluated using the proportion of days covered (PDC), which measures the percentage of days a patient has access to their prescribed medications over a specific period. A cutoff value of 80% was used to define adequate adherence, with good adherence defined as PDC $\geq$ 80% and non-adherence as PDC $<$ 80%.[16] Furthermore, we performed the same analyses using a cutoff value of 90%. All statistical analyses were performed using SAS Enterprise Guide software, version 7.1 (SAS Institute Inc., Cary, NC, USA) and R software, version 4.1 (R Foundation for Statistical Computing, Vienna, Austria), with a two-sided *P*-value of $<$0.05 set as the threshold for statistical significance.

Results

Baseline demographic findings

After applying IPTW, baseline characteristics were well balanced between the groups (*Table 1*). We compared 2104 patients on ARNI with 2191 on RAS blockers. Overall, the mean age was 62.5 ± 18.8 years, with males accounting for 70% of the study population. In our cohort, the Charlson Comorbidity Index was relatively high, with a median (interquartile range) value of 7 (6–9).

Association between ARNI use and clinical outcomes

During a median follow-up of 19.1 months (interquartile range 9.5–24.0), ARNI use was associated with a 14% lower risk of the primary outcome compared with the use of RAS blockers at 2 year (HR 0.86, 95% CI 0.75–0.97, *P* = 0.018, *Table 2*). Specifically, ARNI use was linked to a lower risk of any hospitalization (HR 0.86, 95% CI 0.75–0.98, *P* = 0.021) and all-cause mortality (HR 0.68, 95% CI 0.54–0.86, *P* = 0.001). Additionally, ARNI use was associated with a decreased risk of cardiovascular mortality (HR 0.68, 95% CI 0.52–0.89, *P* = 0.004). In parallel with these findings, Kaplan–Meier curves also showed a lower risk of adverse outcomes in the ARNI group compared with the RAS blocker group (*Figure 1*).

Subgroup analyses

The ARNI group exhibited a lower risk for the primary outcome than the RAS blocker group across various subgroups, including age, sex, cohort entry year categorized by the COVID-19 period, socioeconomic status, region, comorbidity burden, underlying cardio-cerebrovascular disease, atrial fibrillation and other HFrEF medications (*P* for interaction $>$ 0.05, *Figure 2*). Similar patterns were observed for any hospitalization, all-cause mortality and cardiovascular mortality regardless of its subgroups (Figures S2–S4).

Table 1 Study population characteristics

	Before IPTW			After IPTW		
	ARNI (n = 853)	RAS blocker (n = 1389)	ASD	ARNI (weighted n = 2104)	RAS blocker (weighted n = 2191)	ASD
Cohort entry year			0.772			0.037
2017–2019 (pre-COVID-19)	338 (39.6)	1045 (75.2)		1258 (59.8)	1270 (58.0)	
2020–2021 (amid COVID-19)	515 (60.4)	344 (24.8)		846 (40.2)	921 (42.0)	
Age	62.8 ± 12.3	63.1 ± 13.7	0.029	62.3 ± 19.9	62.8 ± 17.6	0.030
Sex			0.137			0.004
Female	235 (27.5)	470 (33.8)		628 (29.8)	657 (30.0)	
Male	618 (72.5)	919 (66.2)		1476 (70.2)	1534 (70.0)	
Socioeconomic status			0.047			0.045
Low	367 (43.0)	571 (41.1)		873 (41.5)	916 (41.8)	
Middle	231 (27.1)	376 (27.1)		614 (29.2)	599 (27.3)	
High	255 (29.9)	442 (31.8)		617 (29.3)	676 (30.9)	
Region			0.136			<0.001
Metropolitan	151 (17.7)	310 (22.3)		418 (19.9)	430 (19.6)	
City	231 (27.1)	303 (21.8)		521 (24.8)	545 (24.9)	
Rural	471 (55.2)	776 (55.9)		1166 (55.4)	1216 (55.5)	
Duration of RAS blocker before the index date, month	32.2 ± 41.8	36.2 ± 41.7	0.085	34.8 ± 68.8	35.0 ± 54.4	0.003
Comorbidities, n (%)						
Charlson comorbidity index	7 (6–9)	7 (6–9)	0.018	7 (6–9)	7 (6–9)	0.006
Diabetes mellitus	266 (31.2)	409 (29.4)	0.038	587 (27.9)	653 (29.8)	0.042
Hypertension	582 (68.2)	955 (68.8)	0.011	1443 (68.6)	1505 (68.7)	0.002
Dyslipidaemia	393 (46.1)	592 (42.6)	0.070	915 (43.5)	967 (44.1)	0.012
Pacemaker	6 (0.7)	9 (0.6)	0.007	11 (0.5)	14 (0.6)	0.012
ICD	7 (0.8)	7 (0.5)	0.039	12 (0.6)	12 (0.5)	0.004
CRT	4 (0.5)	5 (0.4)	0.017	8 (0.4)	18 (0.8)	0.059
Coronary revascularization	176 (20.6)	241 (17.4)	0.084	404 (19.2)	413 (18.8)	0.009
Ischaemic heart disease	612 (71.7)	970 (69.8)	0.042	1428 (67.9)	1538 (70.2)	0.050
Angina	513 (60.1)	785 (56.5)	0.074	1192 (56.7)	1281 (58.5)	0.037
Myocardial infarction	144 (16.9)	179 (12.9)	0.112	299 (14.2)	315 (14.4)	0.006
Other ischaemic heart disease	333 (39.0)	590 (42.5)	0.070	810 (38.5)	877 (40.0)	0.031
Cerebrovascular disease	92 (10.8)	184 (13.2)	0.076	247 (11.7)	264 (12.0)	0.010
Ischaemic stroke	76 (8.9)	157 (11.3)	0.080	206 (9.8)	224 (10.2)	0.013
Haemorrhagic stroke	12 (1.4)	20 (1.4)	0.003	34 (1.6)	31 (1.4)	0.015
Transient ischaemic attack	12 (1.4)	20 (1.4)	0.003	27 (1.3)	29 (1.3)	0.006
Peripheral artery disease	57 (6.7)	93 (6.7)	0.001	149 (7.1)	146 (6.7)	0.015
Thromboembolism	40 (4.7)	56 (4.0)	0.032	91 (4.3)	108 (4.9)	0.029
Atrial fibrillation	152 (17.8)	199 (14.3)	0.095	357 (17.0)	370 (16.9)	0.003
Sick sinus syndrome	2 (0.2)	9 (0.6)	0.062	8 (0.4)	10 (0.5)	0.007
Medications, n (%)						
Diabetes medications						
Metformin	42 (4.9)	66 (4.8)	0.008	95 (4.5)	97 (4.4)	0.005
Sulfonylurea	208 (24.4)	332 (23.9)	0.011	509 (24.2)	512 (23.4)	0.020
DPP-4 inhibitor	377 (44.2)	570 (41.0)	0.064	886 (42.1)	937 (42.8)	0.013
Thiazolidinedione	16 (1.9)	36 (2.6)	0.049	57 (2.7)	46 (2.1)	0.040
GLP1-RA	13 (1.5)	4 (0.3)	0.131	17 (0.8)	18 (0.8)	0.005
Insulin	243 (28.5)	410 (29.5)	0.023	599 (28.5)	644 (29.4)	0.020
Hypertension medications						
Calcium channel blocker	450 (52.8)	938 (67.5)	0.305	1253 (59.6)	1306 (59.6)	0.001
Diuretics	522 (61.2)	763 (54.9)	0.127	1204 (57.2)	1251 (57.1)	0.003
Beta-blocker	601 (70.5)	935 (67.3)	0.068	1440 (68.4)	1515 (69.1)	0.015
Alpha-blocker	148 (17.4)	265 (19.1)	0.045	328 (15.6)	388 (17.7)	0.057
Digoxin	36 (4.2)	70 (5.0)	0.039	89 (4.2)	95 (4.3)	0.004
Nitrate	140 (16.4)	248 (17.9)	0.038	327 (15.5)	369 (16.8)	0.036
Lipid lowering agents						
Statin	506 (59.3)	791 (56.9)	0.048	1199 (57.0)	1250 (57.1)	0.001
Others	94 (11.0)	138 (9.9)	0.035	241 (11.5)	237 (10.8)	0.021
Anticoagulants	99 (11.6)	118 (8.5)	0.104	220 (10.5)	225 (10.3)	0.007
Antiplatelet agent	661 (77.5)	1037 (74.7)	0.066	1577 (75.0)	1656 (75.6)	0.015
Healthcare utilization						
No. of outpatient clinic visits, median (IQR)	102 (33–169)	86 (32–168)	0.048	104 (31–170)	95 (33–169)	0.008
Hospitalization within prior 1 year	745 (87.3)	1135 (81.7)	0.156	1760 (83.7)	1836 (85.0)	0.037
ER visit	25 (2.9)	35 (2.5)	0.025	47 (2.3)	66 (3.0)	0.047

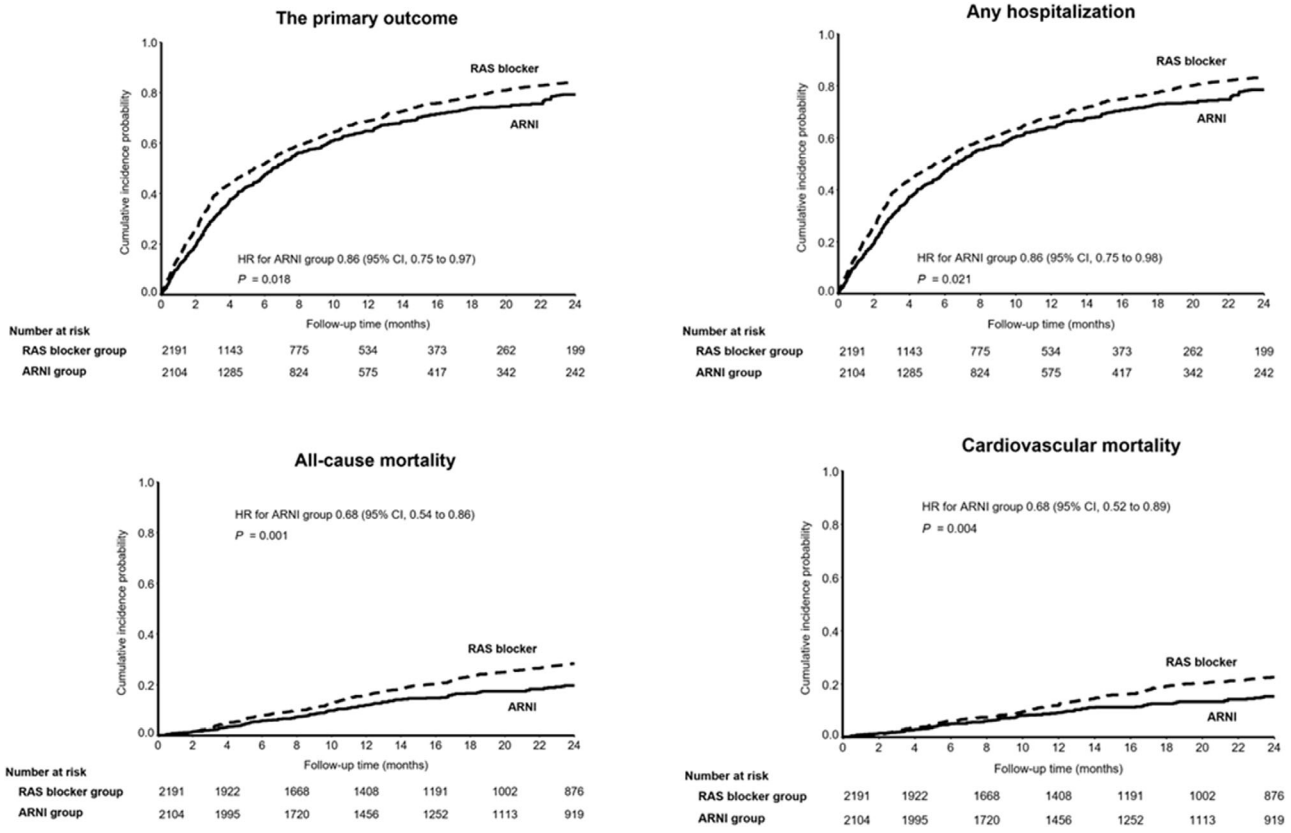
Descriptive data were expressed as mean ± standard deviation or median (interquartile range).
ARNI, angiotensin receptor-neprilysin inhibitor; ASD, absolute standardized difference; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; ER, emergency room; GLP1-RA, glucagon-like peptide 1 receptor agonist; ICD, implantable cardioverter-defibrillator; IPTW, inverse probability treatment weighting; IQR, interquartile range; RAS, renin-angiotensin system.

Table 2 The primary and secondary outcomes in the propensity score-matched population at 2 years

Outcomes	RAS blocker (weighted n = 2191)	ARNI (weighted n = 2104)	P
The primary outcome			
No. of event (incidence rate per 100 PY)	1648 (118.50)	1516 (99.33)	
Hazard ratio (95% confidence interval)	1 (reference)	0.86 (0.75–0.97)	0.018
The secondary outcome			
All-cause mortality			
No. of event (incidence rate per 100 PY)	485 (16.69)	340 (11.29)	
Hazard ratio (95% confidence interval)	1 (reference)	0.68 (0.54–0.86)	0.001
Any hospitalization			
No. of event (incidence rate per 100 PY)	1604 (115.34)	1480 (96.99)	
Hazard ratio (95% confidence interval)	1 (reference)	0.86 (0.75–0.98)	0.021
Cardiovascular mortality			
No. of event (incidence rate per 100 PY)	372 (12.81)	259 (8.59)	
Hazard ratio (95% confidence interval)	1 (reference)	0.68 (0.52–0.89)	0.004

ARNI, angiotensin receptor-neprilysin inhibitor; IPTW, inverse probability treatment weighting; RAS, renin-angiotensin system.

Figure 1 Weighted Kaplan–Meier curves for the primary and secondary outcomes. After IPTW, individuals on ARNI demonstrated a decreased risk of the primary outcome (a composite of all-cause mortality and any hospitalization) and the secondary outcomes (individual all-cause mortality, any hospitalization and cardiovascular mortality) compared with those on RAS blockers in patients with concomitant HFrEF and kidney failure receiving replacement therapy. ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; IPTW, inverse probability of treatment weighting; RAS, renin-angiotensin system.

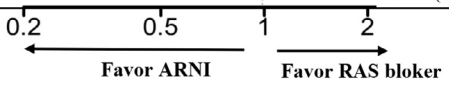


Exploring clinical outcomes based on drug adherence

We explored whether differences in drug adherence might affect clinical outcomes. Good adherence to ARNI was clearly associated with a greater decrease in the primary outcome compared with good adherence to RAS blockers (HR 0.78, 95% CI 0.67–0.90, P = 0.001). However, non-adherence to ARNI, defined as a PDC below 80%, did not show the same clinical benefit over non-adherence to RAS blockers (HR

Figure 2 Subgroup analyses for the primary outcome. The forest plot displays hazard ratios for the primary outcome—a composite of all-cause mortality and any hospitalization at 2 years—comparing ARNI to RAS blockers across predefined subgroups in patients with HFrEF and kidney failure receiving replacement therapy. Generally, ARNI is associated with a lower risk of adverse outcomes across various subgroups, with no significant interaction observed between treatment effects and the subgroups analysed. ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; RAS, renin-angiotensin system.

	RAS blocker Event/Total	ARNI Event/Total	The primary outcome at 2Y Hazard ratio (95% CI)	*P* for interaction
All patients	1648 / 2191	1516 / 2104	0.86 (0.75 -0.97)	
Cohort entry year				0.922
2017-2019 (Pre-COVID)	3510 / 8163	3124 / 8163	0.85 (0.73 -1.001)	
2020-2021 (Amid COVID)	2015 / 5320	1602 / 5320	0.84 (0.70 -1.02)	
Age				0.659
<75	1282 / 1725	1218 / 1730	0.84 (0.73 -0.97)	
≥75	366 / 466	297 / 374	0.90 (0.71 -1.13)	
Sex				0.817
Male	496 / 657	461 / 628	0.83 (0.67 -1.03)	
Female	1152 / 1534	1055 / 1476	0.86 (0.74 -0.997)	
Socioeconomic status				0.892
Low	702 / 916	636 / 873	0.83 (0.68 -0.995)	
Middle	458 / 599	455 / 614	0.89 (0.70 -1.13)	
High	488 / 676	425 / 617	0.84 (0.67 -1.06)	
Region				0.849
Metropolitan or City	712 / 975	670 / 939	0.86 (0.71 -1.04)	
Rural	935 / 1216	846 / 1166	0.84 (0.72 -0.99)	
Charlson comorbidity index				0.618
<7	550 / 803	490 / 754	0.81 (0.66 -1.003)	
≥7	1097 / 1388	1026 / 1350	0.87 (0.75 -1.01)	
Diabetes mellitus				0.685
No	1121 / 1538	1087 / 1517	0.87 (0.75 -1.01)	
Yes	527 / 653	428 / 587	0.82 (0.66 -1.02)	
Hypertension				0.491
No	507 / 686	455 / 661	0.80 (0.64 -0.99)	
Yes	1141 / 1505	1060 / 1443	0.88 (0.75 -1.02)	
Ischemic heart disease				0.229
No	465 / 653	429 / 676	0.76 (0.59 -0.97)	
Yes	1182 / 1538	1086 / 1428	0.90 (0.79 -1.04)	
Cerebrovascular disease				0.823
No	1447 / 1927	1335 / 1857	0.85 (0.75 -0.97)	
Yes	201 / 264	180 / 247	0.82 (0.57 -1.18)	
Atrial fibrilation				0.350
No	1372 / 1822	1230 / 1747	0.83 (0.72 -0.95)	
Yes	276 / 370	286 / 357	0.95 (0.74 -1.23)	
β-blocker				0.188
No	493 / 676	485 / 664	0.96 (0.77 -1.19)	
Yes	1154 / 1515	1030 / 1440	0.81 (0.69 -0.93)	
Aldosteron antagonist				0.896
No	1512 / 2013	1392 / 1923	0.85 (0.75 -0.96)	
Yes	136 / 178	123 / 181	0.87 (0.56 -1.36)	



1.00, 95% CI 0.79–1.26, P = 0.995), although the P-value for interaction was 0.075 (*Table 3*). Particularly for all-cause mortality, there was a statistically significant interaction based on drug adherence (P-value for interaction 0.044), indicating that the decreased risk in all-cause mortality was only evident in the good adherence to ARNI group (*Table 3*).

This trend became even more pronounced when the good adherence group was defined with a PDC cutoff of 90%, as illustrated in *Table 4*. Across all outcomes, there was a significant interaction between the good adherence group and the non-adherence group (P-value for interaction < 0.05). Good adherence to ARNI was associated with a significantly decreased risk in both the primary and secondary outcomes. In contrast, non-adherence (PDC $< 90\%$) resulted in similar outcomes between the ARNI and RAS blocker groups.

Discussion

In our cohort of patients with concomitant HFrEF and kidney failure receiving replacement therapy, ARNI was associated with a reduced risk of all-cause mortality, any hospitalization and cardiovascular mortality, underscoring its potential benefits in this under-evaluated population. This finding was consistent across various subgroups, including those defined by age, sex, cohort entry year, comorbidity burden, coexisting conditions and other HFrEF medication use. Notably, good adherence to ARNI was linked to significant reductions in adverse clinical outcomes, whereas non-adherence did not confer the same benefits (*Figure 3*). Collectively, our data suggest a potential clinical benefit of ARNI among patients with combined HFrEF and kidney failure, particularly emphasizing the importance of maintaining adherence to optimize therapeutic outcomes.

Traditionally, individuals with kidney failure receiving replacement therapy have been in a therapeutic blind spot when it comes to HFrEF treatment. Despite being a high-risk population with significant mortality risk[1] and challenges in volume control compared with patients with preserved kidney function, they have had very few medications available, aside from RAS blockers and beta-blockers.[4,7] Recently, ARNI has been established as a cornerstone in HFrEF treatment after demonstrating its ability to reduce mortality and lower the risk of heart failure-related hospitalizations.[8,21,22] Moreover, several studies have confirmed that ARNI provides similar benefits across a broader range of patients than those included in randomized clinical trials, with early initiation of ARNI demonstrating effectiveness in improving clinical outcomes and left ventricular remodelling.[23–27] However, the effects of ARNI in patients with kidney failure remain under-evaluated.

In this regard, our study provides valuable insight into this critical evidence gap. We found that patients prescribed ARNI had a significantly lower risk of the composite endpoint of all-cause mortality and any hospitalization, as well as a reduction in cardiovascular mortality, compared with those receiving traditional treatment with RAS blockers. Notably, the clinical benefit of ARNI was only evident in patients who were highly adherent to their medication, emphasizing the crucial role of adherence in achieving the full benefits of ARNI. Supporting our findings, previous studies have demonstrated that ARNI significantly reduces cardiac biomarkers and improves left ventricular systolic function in patients with concomitant HFrEF and kidney failure receiving replacement therapy. One study reported a reduction in high-sensitive troponin T levels and soluble ST2 levels, alongside an increase in left ventricular ejection fraction (LVEF)[10] Another study further corroborated these results, showing significant reverse cardiac remodelling in ARNI-treated patients, including

Table 3 Clinical outcomes according to adherence to medication with a proportion of days covered (PDC) of 80%

Outcomes	RAS blocker (Ref.)		ARNI		Hazard ratio (95% CI)	P	P for interaction
	Total	Event (IR)	Total	Event (IR)			
The primary outcome							
Good adherence	1468	1299 (153.90)	1439	1186 (115.19)	0.78 (0.67–0.90)	0.001	0.075
Non-adherence	723	349 (63.86)	655	329 (66.38)	1.00 (0.79–1.26)	0.995	
The secondary outcome							
All-cause mortality							
Good adherence	938	294 (20.48)	1077	202 (11.14)	0.55 (0.40–0.74)	<0.001	0.044
Non-adherence	1253	191 (13.00)	1027	138 (11.53)	0.88 (0.62–1.25)	0.474	
Any hospitalization							
Good adherence	1468	1266 (149.97)	1439	1163 (112.91)	0.79 (0.68–0.91)	0.002	0.101
Non-adherence	723	338 (61.88)	655	317 (63.90)	0.99 (0.78–1.26)	0.953	
Cardiovascular mortality							
Good adherence	938	232 (16.17)	1077	160 (8.82)	0.55 (0.39–0.77)	0.001	0.111
Non-adherence	1253	140 (9.54)	1027	99 (8.23)	0.86 (0.56–1.31)	0.474	

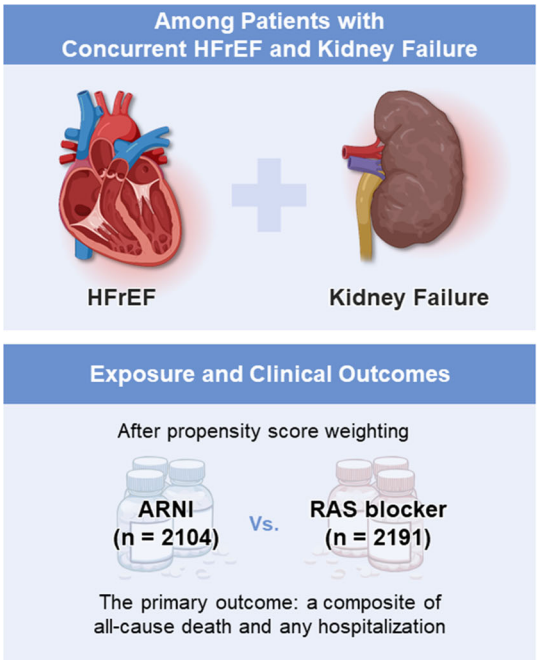
Drug adherence was defined by the proportion of days covered (PDC) for either a RAS blocker or ARNI, with a cutoff value of 80% (good adherence for PDC $\geq 80\%$, non-adherence for PDC $< 80\%$).
ARNI, angiotensin receptor-neprilysin inhibitor; IPTW, inverse probability treatment weighting; IR, event rate per 100 person year; RAS, renin-angiotensin system.

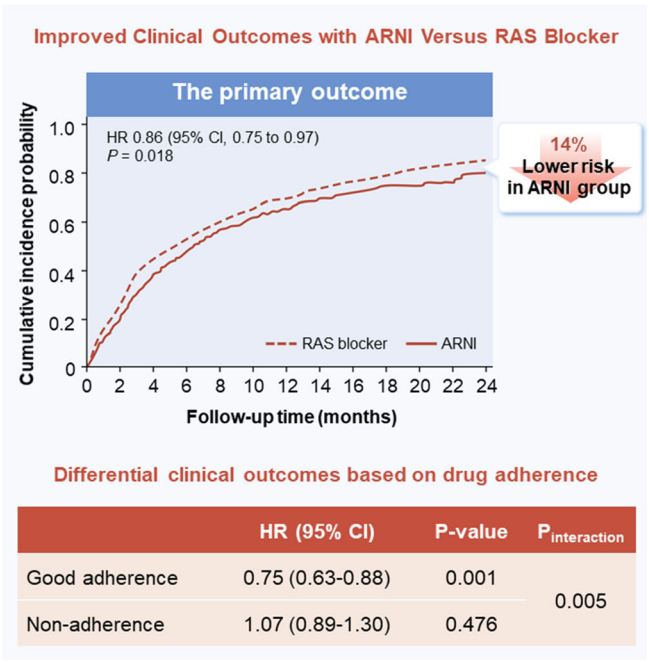
Table 4 Clinical outcomes according to adherence to medication with a proportion of days covered (PDC) of 90%

Outcomes	RAS blocker (Ref.)		ARNI		Hazard ratio (95% CI)	*P*	*P* for interaction
	Total	Event (IR)	Total	Event (IR)			
The primary outcome							
Good adherence	1281	1145 (157.72)	1171	954 (111.28)	0.75 (0.63–0.88)	0.001	0.005
Non-adherence	910	503 (75.68)	933	562 (84.01)	1.07 (0.89–1.30)	0.476	
The secondary outcome							
All-cause mortality							
Good adherence	705	225 (20.56)	825	145 (10.14)	0.49 (0.34–0.71)	<0.001	0.023
Non-adherence	1486	260 (14.36)	1279	190 (12.33)	0.85 (0.63–1.15)	0.300	
Any hospitalization							
Good adherence	1281	1123 (154.70)	1171	936 (109.14)	0.75 (0.63–0.88)	0.001	0.004
Non-adherence	910	481 (72.37)	933	544 (81.40)	1.08 (0.89–1.32)	0.412	
Cardiovascular mortality							
Good adherence	705	178 (16.31)	825	113 (7.94)	0.49 (0.33–0.74)	0.001	0.044
Non-adherence	1486	194 (10.70)	1279	146 (9.17)	0.85 (0.60–1.21)	0.370	

Drug adherence was defined by the proportion of days covered (PDC) for either a RAS blocker or ARNI, with a cutoff value of 90% (good adherence for PDC ≥ 90%, non-adherence for PDC < 90%).
ARNI, angiotensin receptor-neprilysin inhibitor; IPTW, inverse probability treatment weighting; IR, event rate per 100 person year; RAS, renin-angiotensin system.

Figure 3 Summary of the study. In this real-world study of patients with HFrEF and kidney failure on replacement therapy, the use of ARNI was associated with a significant reduction in the risk of all-cause mortality and any hospitalization compared with RAS blockers. These benefits were particularly evident in patients who adhered well to their medication. ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; RAS, renin-angiotensin system.





Differential clinical outcomes based on drug adherence

	HR (95% CI)	P-value	$P_{interaction}$
Good adherence	0.75 (0.63-0.88)	0.001	0.005
Non-adherence	1.07 (0.89-1.30)	0.476	

improvements in LVEF, left ventricular end-systolic volume, E/A ratio and medial E/e' ratio after 1 year of treatment, effects not observed in the conventional treatment group.[11] More recently, three additional studies have investigated the clinical impact of ARNI in this population, yielding heterogeneous results.[12–14] A single-center study in China found that ARNI reduced heart failure rehospitalizations (43.3% vs. 73.5%) but showed no difference in all-cause mortality over a one-year follow-up.[12] This study was limited by a small sample size (67 in the ARNI group and 49 in the control group) and the absence of RAS blocker use in the control group. A multi-center study in Taiwan, involving 89 patients (42 in the ARNI group and 47 in the RAS blocker group), found no significant difference in the composite outcome of heart failure hospitalization or all-cause mortality during the one-year follow-up.[13] Conversely, a larger study conducted in the

United States, including 1434 ARNI users and 1434 RAS blocker users, reported reductions in all-cause mortality (HR 0.82, 95% CI 0.73–0.92) and all-cause hospitalization (HR 0.86, 95% CI 0.79–0.93) over a median follow-up of 0.9 years.[14] These findings are consistent with our results. However, while that study found no significant difference in cardiovascular mortality (HR 1.01, 95% CI 0.86–1.19), our study demonstrated a significant reduction in cardiovascular mortality with ARNI use (HR 0.68, 95% CI 0.52–0.89), aligning with the cardiovascular mortality benefit observed in prior ARNI randomized clinical trials.[8,21] The precise reason for the inconsistent results is not entirely clear. However, our study included a larger cohort (2104 for ARNI and 2191 for RAS blockers) with an extended follow-up period of 2 years, providing more comprehensive data on clinical outcomes. Furthermore, we adjusted for multiple comorbidities and external factors, including COVID-19-related disruptions, to enhance the reliability of our findings.

A plausible explanation for ARNI's favourable effects may lie in its dual action of augmenting the natriuretic peptide system and suppressing the over-activated renin-angiotensin-aldosterone system, mechanisms that are also relevant in patients with advanced CKD, including those with kidney failure receiving replacement therapy.[28] By enhancing natriuretic peptides, ARNI improves cardiovascular and renal outcomes through several pathways, including promoting vasodilation, lowering blood pressure, reducing sympathetic nervous system activity and increasing diuresis and natriuresis. Collectively, these effects reduce cardiac stress, prevent further remodelling and protect renal function.[28] The renal benefits of ARNI are especially significant in the context of the complex cardio-renal interaction.[29–31] Previous research has demonstrated that ARNI slows the decline in glomerular filtration rate compared with enalapril, while consistently providing cardiovascular benefits in patients with or without CKD or albuminuria.[29] Moreover, the more pronounced clinical benefits of ARNI in patients with good adherence, as shown in our study, further supports the efficacy of this medication in improving clinical outcomes.

Several limitations of this study should be acknowledged. First, although we applied IPTW for possible confounders, the cohort design inherently limits the ability to establish causality. However, our study addresses a clinically significant and challenging patient population for whom randomized controlled trials are often impractical. Second, we lacked detailed echocardiographic, biomarker and laboratory data, as well as information on the aetiology and duration of heart failure or kidney failure, which could have provided deeper insights into the underlying mechanisms and potential side effects. Third, we focused on any hospitalization rather than heart failure-specific hospitalization because, in patients with concomitant heart failure and kidney failure, it is challenging to determine whether volume overload arises from heart failure or kidney failure, as these conditions are often interconnected. Finally, we did not have information on dosage of the drug, limiting our ability to investigate potential dose–response relationships. Despite these limitations, our findings suggest the potential benefit of ARNI in this underserved subgroup and underscore the importance of medication adherence in optimizing its effectiveness in real-world settings.

Conclusions

In patients with HFrEF and kidney failure receiving replacement therapy, ARNI use was associated with a significant reduction in all-cause mortality, all-cause hospitalization and cardiovascular mortality compared with RAS blockers. These benefits were most pronounced in patients with good medication adherence, highlighting the critical role of adherence in optimizing therapeutic outcomes. Our findings suggest that ARNI could be a valuable treatment option for this high-risk population.

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Conflict of interest

None declared.

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Supporting information

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

Figure S1. Flowchart of the study population.
Figure S2. Subgroup analyses for any hospitalization.
Figure S3. Subgroup analyses for all-cause mortality.
Figure S4. Subgroup analyses for cardiovascular mortality.

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