

Monitoring angiotensin receptor-neprilysin inhibitor usage and clinical outcomes in heart failure patients: Real-world evidence from a tertiary care center in Thailand

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ABSTRACT

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This retrospective study investigated the real-world usage patterns, effectiveness, and safety of the angiotensin receptor–neprilysin inhibitor (ARNI) in patients with heart failure with reduced ejection fraction (HFrEF) at a tertiary care center in Thailand. A total of 249 patients who initiated ARNI between January 1, 2018, and June 30, 2022, were included. The average age was 61.3 ± 11.1 years, and 69.1% were male. The mean BMI was 25.7 ± 13.4 kg/m², and the average body weight was 66.4 ± 13.8 kg. The baseline left ventricular ejection fraction (LVEF) was $28.4\% \pm 8.7\%$. Most patients (57.4%) were administered ARNI at a dose of 100 mg/day. The average follow-up was 18.5 months, and the maximum tolerable dose was 179.0 ± 98.7 mg/day, with 12.0% attaining the target dose. No deaths were recorded; however, 8.8% of the patients were hospitalized for heart failure. LVEF improved significantly at 6, 12, 18, 24, and 30 months, with 67.2% achieving LVEF $\geq 40\%$. Discontinuation of ARNI occurred in 20.9%, primarily due to hyperkalemia (9.3%), hypotension (6.0%), and a decrease in renal function (5.2%). These findings confirm ARNI's effectiveness in improving cardiac function in Thai HFrEF patients while emphasizing the need for close monitoring to manage adverse effects and optimizing dosing strategies.

Keywords: angiotensin receptor–neprilysin inhibitor; ARNI; heart failure; real-world; sacubitril/valsartan

1. INTRODUCTION

The angiotensin receptor–neprilysin inhibitor (ARNI), a combination of sacubitril and valsartan, plays a crucial role in the treatment of heart failure, particularly in patients

with reduced ejection fraction (HFrEF). Major treatment guidelines recommend guideline-directed medical therapy (GDMT) for HFrEF, with ARNI as a key component alongside angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid

receptor antagonists (MRAs), evidence-based beta-blockers, and sodium-glucose co-transporter-2 (SGLT-2) inhibitors (Maddox et al., 2024; McDonagh et al., 2021). The clinical benefits of ARNI in HFrEF patients were demonstrated in a large randomized controlled trial (PARADIGM-HF), in which ARNI significantly reduced cardiovascular death, heart failure hospitalizations, and all-cause mortality compared with enalapril (McMurray et al., 2014).

Although randomized controlled trials, such as PARADIGM-HF, have provided strong evidence because of their controlled environments and randomization, they lacked patient diversity that is observed in routine clinical practice. In contrast, real-world studies encompass a broader range of patient populations, comorbidities, and treatment approaches, thus offering a more comprehensive view of the challenges encountered during routine daily care. Notably, only 18% of the participants in the PARADIGM-HF trial were Asian (McMurray et al., 2014), which highlight potential limitations in the study of a representative population.

Data from real-world studies of ARNI indicate that Asian patients generally have lower blood pressure, reduced body mass index, and different comorbidity profiles compared with those who were enrolled in the PARADIGM-HF trial (Cheang et al., 2022; Cho et al., 2025; Hsiao et al., 2022; Oh et al., 2019; Rattanaivanon et al., 2021). For example, a Korean study found that only 12% of participants met the inclusion criteria for the PARADIGM-HF trial (Oh et al., 2019). Moreover, several studies indicated that Asian patients did not achieve the recommended target dose of ARNI (sacubitril/valsartan 400 mg/day) (Hsiao et al., 2020; Rattanaivanon et al., 2021). A study in Taiwan found that only 30% of the patients reached the target dose (Hsiao et al., 2020). Despite these differences, ARNI administration in Asian populations is associated with significant reductions in cardiovascular mortality and heart failure hospitalizations compared with ACEI/ARB therapy in real-world settings (Chang et al., 2019; Rattanaivanon et al., 2021). In addition, adverse effects such as hypotension, increased serum creatinine, and hyperkalemia are frequently observed in real-world studies, which is consistent with the findings of the PARADIGM-HF trial (Chng et al., 2021; McMurray et al., 2014).

In Thailand, ARNI has been available since 2017 as a non-national formulary drug; however, only one real-world study has been conducted in the country, specifically, in a tertiary care setting, where its efficacy was compared with that of conventional therapy (ACEIs or ARBs) (Rattanaivanon et al., 2021). The results indicated that ARNI significantly improved clinical outcomes and symptoms. Despite these findings, data on ARNI usage patterns and dose titration in the Thai population remain limited. Therefore, in this study, we investigated the treatment patterns, clinical effectiveness, and safety of ARNI in HFrEF patients at the Queen Sirikit Heart Center of the Northeast, a tertiary care center in Northeastern Thailand.

2. MATERIALS AND METHODS

2.1 Study design

This retrospective observational study was conducted at the Queen Sirikit Heart Center of the Northeast, a tertiary care university-affiliated hospital in Khon Kaen Province. Outpatients with HFrEF who were newly administered ARNI between January 1, 2018, and June 30, 2022, were

identified from the electronic hospital database. The study protocol was approved by the Center for Ethics in Human Research, Khon Kaen University, in 2021 (HE651545).

2.2 Participants and procedures

Individuals aged 18 and older who were diagnosed with HFrEF and newly initiated on ARNI at the Queen Sirikit Heart Center of the Northeast between January 1, 2018, and June 30, 2022 were enrolled in the study. Patients were excluded if they met any exclusion criteria, including loss to follow-up within 12 months after receiving ARNI or missing medical records.

2.3 Data extraction and collection

Data for this study were extracted from the hospital's electronic database. A search was conducted for 100 mg and 200 mg sacubitril/valsartan tablets dispensed between January 1, 2018, and June 30, 2022, regardless of the patient's symptoms or signs. The date of the first ARNI prescription was designated as the index date, and the 12 month preceding the index date was designated the pre-index period. Data collected during these periods included demographic information, comorbidities, initial ARNI dose, concomitant medications, laboratory test results, and baseline LVEF.

Follow-up data were collected until either a treatment outcome occurred (all-cause mortality or hospitalization from heart failure) or until June 30, 2023. Data were gathered at 6, 12, 18, 24, 30, 36, and 42 months following the index date. If data from a patient visit were unavailable for a specific analysis time point, data obtained within 45 days before or after the target date were used as a substitute. The collected data included the ARNI dosage regimen, time to first ARNI titration, the maximum ARNI dose achieved, the time to reach the maximum or target ARNI dose, and treatment outcomes related to ARNI treatment. Treatment effectiveness was evaluated based on outcomes including all-cause mortality, hospitalization due to heart failure, and LVEF. Adverse events related to ARNI use, including hypotension, elevated serum creatinine, elevated serum potassium, cough, and angioedema, were also recorded.

2.4 Data analysis

Descriptive statistics were used and presented as the mean $\pm$ standard deviation and percentages. Interval changes in LVEF were analyzed using Student's t-test, and changes in the laboratory results were analyzed using either Student's t-test or a Wilcoxon signed-rank test, depending on the data distribution assessed by the Kolmogorov-Smirnov test. A chi-square test was used to assess categorical variables potentially associated with treatment outcomes. Differences between cohorts were considered statistically significant if the p-value was less than 0.05. All statistical analyses were conducted using SPSS Statistics software (version 27.0, SPSS, Inc., Chicago, IL, USA).

3. RESULTS

A total of 407 patients newly administered ARNI were identified from the Queen Sirikit Heart Center of the Northeast's computerized database for sacubitril/valsartan prescriptions. Of these, 158 were excluded for the following reasons: baseline LVEF > 40% (75 patients), loss to follow-up within 12 months (71 patients), initiation of ARNI at

another hospital (11 patients), and age <18 years (1 patient). As a result, 249 patients were enrolled, with ARNI initiation as follows: 45 patients in 2018, 44 patients in 2019, 53 patients in 2020, 72 patients in 2021, and 35 patients between January and June 2022.

The baseline characteristics for the enrolled patients are listed in Table 1. The average patient age was 61.3 ± 11.1 years, and 69.1% were male. The patients had an average body weight of 66.4 ± 13.8 kg and a BMI of $25.7 \pm$

13.4 kg/m^2 . They were diagnosed with HFrEF; however, pre-index LVEF data were available for 154 patients (61.8%), with an average LVEF of $28.4 \pm 8.7\%$. The N-terminal pro-B-type natriuretic peptide (NT-pro BNP) levels were determined for 38 patients (15.2%), which showed an average of $3,476 \pm 4,712$ pg/mL. Coronary artery disease, diabetes, and atrial fibrillation (AF) were the three most common underlying conditions. In addition, 56.2% of the patients had dilated cardiomyopathy.

Table 1. Baseline characteristics

Variables		
Demographics		Valid N
Age (years; mean $\pm$ SD)	249	61.3 ± 11.1
Male gender (%)	249	69.1
Body weight (kg; mean $\pm$ SD)	249	66.4 ± 13.8
Body mass index (kg/m^2 ; mean $\pm$ SD)	249	25.7 ± 13.4
Systolic blood pressure (mmHg; mean $\pm$ SD)	200	124.4 ± 20.2
BUN (mg/dL; mean $\pm$ SD)	147	17.6 ± 6.9
sCr (mg/dL; mean $\pm$ SD)	231	1.1 ± 0.3
GFR (ml/min; mean $\pm$ SD)	229	72.6 ± 18.5
Serum sodium (mEq/L; mean $\pm$ SD)	202	138.1 ± 10.2
Serum potassium (mEq/L; mean $\pm$ SD)	216	4.2 ± 0.5
NT-pro BNP (pg/mL; mean $\pm$ SD)	38	3476 ± 4712
Left ventricular ejection fraction (%)	154	28.4 ± 8.7
Comorbidities		N (%)
Coronary artery disease	101 (40.6)	
Diabetes	76 (30.5)	
Atrial fibrillation	68 (27.3)	
Chronic kidney disease	54 (21.7)	
Hypertension	45 (18.1)	
Valvular heart disease	40 (16.1)	
Dyslipidemia	34 (13.7)	
Myocardial infarction	23 (9.2)	
Stroke	6 (2.4)	
Others	33 (13.3)	
Type of cardiomyopathy		N (%)
Dilated cardiomyopathy	140 (56.2)	
Ischemic cardiomyopathy	59 (23.7)	
Intracardiac devices		N (%)
AICD	19 (7.6)	
CRT	14 (5.6)	

Note. AICD, automated implantable cardioverter-defibrillator; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate

Before being prescribed sacubitril/valsartan, 40.2% of the patients were renin-angiotensin-aldosterone system (RAAS) blocker-naïve, whereas 29.7% and 28.5% had been prescribed ACEIs and ARBs, respectively. Of the RAAS-blocker prescriptions, enalapril was the most frequently used medication (51.0%), with an average daily dose of 7.64 mg. This was followed by losartan (33.6%) with an average daily dose of 57.5 mg. Diuretics were prescribed to 66.7% of the patients, with furosemide accounting for 98.8% of the prescriptions. Beta blockers were prescribed to 211 patients (84.7%), with carvedilol being the most frequently prescribed medication (66.8%), with an average

daily dose of 15.4 mg. Spironolactone, a mineralocorticoid receptor antagonist (MRA), was prescribed to 130 patients (52.2%) at an average daily dose of 21.0 mg. SGLT-2 inhibitors were prescribed to 20.9% of the patients, with empagliflozin being the most common (57.7%).

As shown in Table 2, two types of GDMT were prescribed alongside ARNI in 43.8% of the cases. Notably, the most common combination included beta-blockers and MRA, which accounted for 35.3% of the prescriptions. ARNI was also prescribed with a single type of GDMT in 41.0% of the cases, most frequently beta-blockers (34.5%); however, only a few patients (5.2%) received ARNI monotherapy.

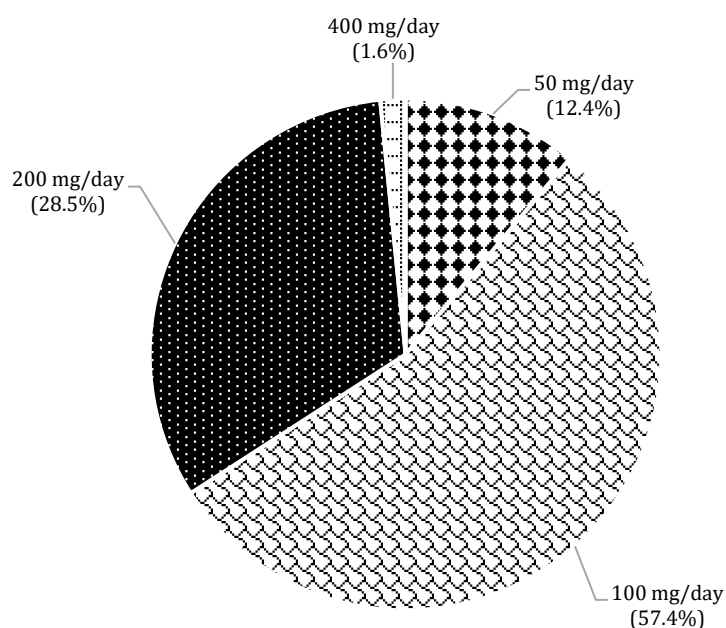
Table 2. Baseline pattern of ARNI and GDMT use on index date

	N = 249
ARNI monotherapy	13 (5.2)
ARNI + GDMT 1 type	102 (41.0)
Beta-blockers	86 (34.5)
SGLT2 inhibitors	5 (2.0)
MRA	11 (4.4)
ARNI + GDMT 2 types	109 (43.8)
Beta-blockers + MRA	88 (35.3)
Beta-blockers + SGLT2 inhibitors	19 (7.6)
MRA + SGLT2 inhibitors	2 (0.8)
ARNI + GDMT 3 types	25 (10.0)
Beta-blockers + MRA + SGLT2 inhibitors	25 (10.0)

Note. ARNI, Angiotensin receptor neprilysin inhibitor; GDMT, guideline-directed medical therapy; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose cotransporter 2

The initial ARNI doses for 249 patients were as follows: 12.4% initiated ARNI at 50 mg/day, 57.4% at 100 mg/day, 28.5% at 200 mg/day, and 1.6% at 400 mg/day (Figure 1). During the follow-up period with an average time of 18.5 months, ARNI doses were up-titrated in 44.2% of the patients. However, a down-titration to a lower dose was observed in 52 patients (20.9%). The average time to achieve the first upward-titration was

133.5 ± 15.6 days. The average maximal tolerable dose was 179.0 ± 98.7 mg/day, with 200 mg/day the most frequently prescribed (41.8%), followed by 100 mg/day (38.2%) (Figure 2). Only 12.0 % of the patients achieved the target dose of 200 mg twice daily, which required an average time of 229.3 ± 49.1 days. Furthermore, following an average of 283.6 ± 44.5 days, 20.9% discontinued ARNI treatment.

**Figure 1.** Percentage of patients at each initial daily ARNI dose

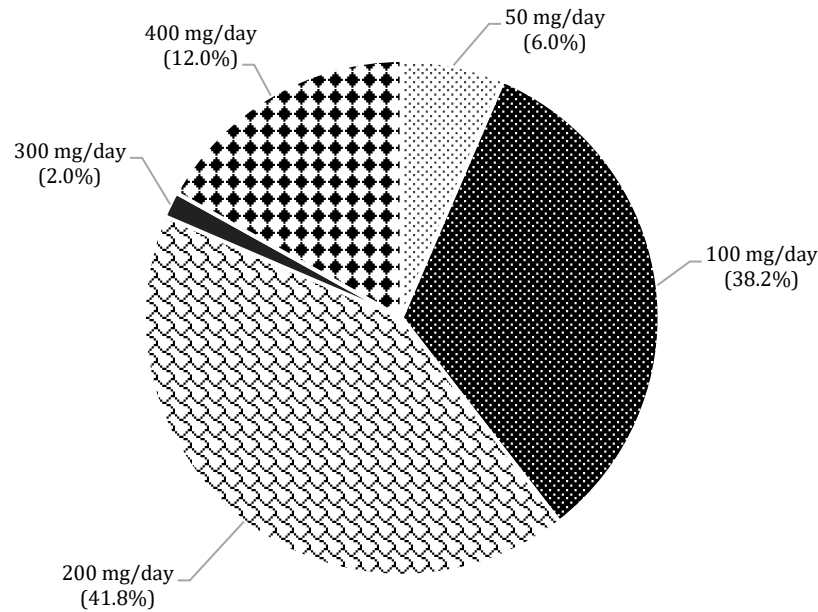


Figure 2. Percentage of patients at each achieved maximum daily ARNI dose

Of the 249 patients enrolled from January 1, 2018, to June 30, 2022, the average follow-up time was 18.5 months. Treatment outcomes were observed in 22 patients (8.8%), all of whom were hospitalized due to heart failure; however, no deaths occurred. Univariate analysis was conducted to assess the factors associated with hospitalization due to heart failure (Supplemental Table 1). The results indicated that patients with a baseline systolic blood pressure (SBP) below the mean (<124 mmHg) had a significantly higher hospitalization rate compared with those exhibiting a higher SBP ($p = 0.029$). In addition, patients without AF had a significantly higher hospitalization rate compared with those experiencing AF ($p = 0.047$).

There was a considerable increase in LVEF at 6, 12, 18, 24, and 30 months following ARNI treatment (Table 3). LVEF significantly improved over time: at 6 months (28.8% to 46.9%, $p < 0.001$; $N = 30$), 12 months (26.8% to 44.3%, $p < 0.001$; $N = 26$), 18 months (27.2% to 49.9%, $p < 0.001$; $N = 21$), 24 months (29.1% to 48.2%, $p = 0.019$; $N = 9$), and 30 months (24.6% to 45.5%, $p = 0.006$; $N = 10$). However, there was no notable change in LVEF at 36 and 42 months following ARNI therapy. Of the 249 patients, 154 (61.8%) had echocardiographic data for the pre-index period, and 134 (53.8%) underwent at least one repeat echocardiographic examination after initiating ARNI therapy, with follow-up extending up to 42 months. During the observation period, 90 of 134 patients (67.2%) showed an increase in LVEF to 40% or higher.

Table 3. Percentage of LVEF at baseline and during follow-up period (mean $\pm$ SD)

	Baseline	Follow-up	<i>p</i> -value
Index and Pre-index date ($N = 154$)	28.4 $\pm$ 8.6	-	
6 months ($N = 30$)	28.8 $\pm$ 10.0	46.9 $\pm$ 16.6	<0.001
12 months ($N = 26$)	26.8 $\pm$ 9.0	44.3 $\pm$ 13.8	<0.001
18 months ($N = 21$)	27.2 $\pm$ 7.7	49.9 $\pm$ 12.0	<0.001
24 months ($N = 9$)	29.1 $\pm$ 7.0	48.2 $\pm$ 16.0	0.019
30 months ($N = 10$)	24.6 $\pm$ 9.3	45.5 $\pm$ 18.6	0.006
36 months ($N = 7$)	28.4 $\pm$ 6.6	33.8 $\pm$ 14.7	0.274
42 months ($N = 4$)	26.7 $\pm$ 17.0	50.8 $\pm$ 15.8	0.106

Note. LVEF, left ventricular ejection fraction; SD, standard deviation

Patient parameters, including SBP, BUN, sCr, eGFR, serum Na, serum K, and BNP, were collected at 6, 12, 18, 24, 30, 36, and 42 months following the index date. Significant changes were observed in SBP, eGFR, sCr, and serum K levels. A remarkable decrease in SBP at 6 and 12 months was observed, with SBP decreasing from 123.5 $\pm$ 19.9 mmHg to 119.9 $\pm$ 17.7 mmHg ($p = 0.006$; $N = 176$) and

from 124.2 $\pm$ 19.9 mmHg to 119.3 $\pm$ 19.5 mmHg ($p < 0.001$; $N = 175$), respectively. Renal function decreased significantly at 6, 12, and 18 months following the index date. At 6 months the eGFR declined significantly from 71.6 $\pm$ 18.6 ml/min to 68.9 $\pm$ 20.4 ml/min ($p = 0.002$; $N = 204$), whereas sCr increased from 1.08 $\pm$ 0.25 mg/dL to 1.11 $\pm$ 0.29 mg/dL ($p = 0.002$; $N = 210$). At 12 months, the eGFR

decreased from 73.3 ± 18.6 ml/min to 69.6 ± 19.2 ml/min ($p < 0.001$; $N = 164$), whereas sCr levels increased from 1.07 ± 0.25 mg/dL to 1.13 ± 0.31 mg/dL ($p < 0.001$; $N = 180$). After 18 months, the eGFR decreased from 73.6 ± 18.6 ml/min to 69.7 ± 19.4 ml/min ($p < 0.001$; $N = 123$), whereas sCr increased from 1.06 ± 0.25 mg/dL to 1.11 ± 0.31 mg/dL ($p < 0.003$; $N = 132$). In addition, serum K levels increased at 36 months, from 4.1 ± 0.3 mEq/L to 4.4 ± 0.4 mEq/L ($p = 0.006$; $N = 16$).

The most frequently observed adverse effects during ARNI treatment were elevated serum potassium (serum potassium higher than 5.5 mEq/L), which affected 23 patients (9.3%). This was followed by hypotension (SBP less than 90 mmHg), which occurred in 15 patients (6.0%). Nine patients experienced vertigo or dizziness despite having normal blood pressure. One case of syncope was recorded. Regarding renal function, 5.2% of patients exhibited elevated serum creatinine levels (sCr higher than 2.5 mg/dL), and one patient experienced decreased eGFR despite having normal creatinine levels. Furthermore, angioedema and cough were observed in four (1.6%) and two (0.8%) patients, respectively.

4. DISCUSSION

This retrospective, single-arm, observational study was conducted at a cardiac specialist hospital in northeast Thailand. It only included Thai patients, and their characteristics in this real-world study were similar to those reported in a previous study conducted in Thailand (Rattanaivanon et al., 2021). In addition, the demographic characteristics, such as average age (61.3 years), serum creatinine levels (1.1 mg/dL), and LVEF (28.4%), were comparable to those reported in the PARADIGM-HF randomized controlled trial (McMurray et al., 2014). Notable differences were observed, however, including a higher percentage of female patients (30.9% vs. 21.0%), a lower body mass index (25.7 kg/m^2 vs. 28.10 kg/m^2), and lower prevalence rates of coronary artery disease (40.6% vs. 63.1%), ischemic cardiomyopathy (23.7% vs. 59.9%), and hypertension (18.1% vs. 70.9%). The lower body mass index and lower prevalence of coronary artery disease in the present study are consistent with the findings of other real-world studies, particularly those involving Asian populations (Cheang et al., 2022; Cho et al., 2025; Hsiao et al., 2022; Oh et al., 2019; Rattanaivanon et al., 2021). Moreover, dilated cardiomyopathy was the predominant type (56.2%), which was consistent with the finding of a previous study in a Thai population (Rattanaivanon et al., 2021).

During the pre-index period, 40.2% of patients were RAAS blocker-naïve, which was consistent with other real-world studies conducted in Asian countries, including Korea (Oh et al., 2019), Taiwan (Chang et al., 2019), and China (Cheang et al., 2022). In contrast, real-world studies in Singapore and Europe reported a remarkably lower proportion of RAAS blocker-naïve patients (<20%) (Chng et al., 2021; Giovannazzo et al., 2021). This discrepancy may be attributed to differences in the criteria used to define the RAAS blocker-free status among the studies. The present study classified patients as RAAS blocker-naïve if they had not received any RAAS blockers during the 12 months before ARNI initiation. In addition, variations in adherence to treatment guidelines across different countries may have contributed to these differences.

Because most patients in the present study were RAAS blocker-naïve or on a low-to-medium dose of RAAS blockers, they were initially administered ARNI at 50 mg twice daily, in accordance with major treatment guidelines (Maddox et al., 2024; McDonagh et al., 2021); however, 12.4% of the patients were started on a lower dose (25 mg twice daily), which is a regimen not specified in any guidelines or studies. Further analysis revealed that these patients were older (69.1 vs. 62.9 years), had lower baseline SBP (108.7 vs. 124.4 mmHg), and most (51.6%) were RAAS blocker-naïve. This suggests that initiating ARNI at a lower dose may represent a precautionary measure to minimize the risk of hypotension, which is a common adverse event in this population.

During the follow-up period, ARNI was combined with at least one GDMT, primarily beta-blockers and MRAs, which is consistent with other real-world studies (Chang et al., 2020b; Cheang et al., 2022; Chng et al., 2021; Hsiao et al., 2020; Rattanaivanon et al., 2021). The average time to the first ARNI dose escalation was 134 days, consistent with the typical 3-month follow-up schedule; however, only 12.0% of the patients achieved the target dose (200 mg twice daily), with an average maximum tolerable dose of 179.0 mg/day. This challenge in reaching the target dose was observed in other real-world studies, although with varying degrees. The percentage observed in this study is consistent with the results of a study in Taiwan (Hsiao et al., 2020), whereas higher achievement rates were observed in some studies, including 35% in European patients (Giovannazzo et al., 2021) and 55% in another tertiary-care setting in Thailand (Rattanaivanon et al., 2021).

Treatment outcomes for the present study focused on the all-cause mortality rate and hospitalization due to heart failure; however, no patient deaths from all causes occurred during the study period, which is consistent with the results from another setting in Thailand (Rattanaivanon et al., 2021). Our results indicated that 8.8% of the patients required hospitalization for heart failure over an average follow-up period of 18.5 months. One year after receiving ARNI, the cumulative hazard was approximately 3%, which was lower than the rates reported in the PARADIGM-HF trial and other real-world studies (6.9–10%) (Atallah et al., 2019; Hsiao et al., 2020; McMurray et al., 2014; Rattanaivanon et al., 2021); however, because the study lacked a control group, direct comparisons should be interpreted with caution because of differences in patient demographics and study designs.

In the present study, chronic kidney disease (CKD) patients comprised 21.7% of the cohort, which was comparable to that reported in another tertiary care center in Thailand (18.4%) (Rattanaivanon et al., 2021), but lower compared with those reported in Taiwan (35.8%) (Hsiao et al., 2020) and PARADIGM-HF (36.8%). Interestingly, a post hoc analysis from previous studies (Damman et al., 2018; Hsiao et al., 2022) reported that patients with CKD had a higher risk of the primary outcome (cardiovascular death or HF readmission) compared with patients without CKD; however, this association was not observed in the present study. We found that patients with SBP below the median and those without AF had a significantly higher rate of hospitalization due to heart failure.

We observed a statistically significant increase in LVEF at 6, 12, 18, 24, and 30 months following the initiation of ARNI therapy. This is consistent with several real-world studies (Chang et al., 2020a; Hsiao et al., 2020; Rattanaivanon et al.,

2021; Yang et al., 2024). Moreover, at 12 months, 71.4% of patients who underwent echocardiography achieved an LVEF of 40% or higher, which was greater than the 29.3% reported previously (Chang et al., 2020a). This may be explained by the higher baseline LVEF and the greater average ARNI dosage administered in our study population compared with the cohort described in Chang et al. (2020a).

In the present study, a remarkable increase in serum creatinine and a reduction in SBP were observed between months 6 and 12 following ARNI initiation, which is consistent with findings from previous studies (Hsiao et al., 2020; McMurray et al., 2014). These results highlight the importance of careful patient selection and close monitoring when administering ARNI therapy, particularly in those at risk for renal impairment or hypotension. Regarding serum potassium levels, we observed a remarkable increase at 36 months post-ARNI administration, whereas Hsiao et al. (2020) reported a significant increase at 12 months. Notably, both studies had similar proportions of MRA use and patients with CKD, which may contribute to an increased risk of hyperkalemia associated with ARNI treatment.

The most common adverse effects of ARNI observed in the present study were elevated serum potassium, hypotension, and elevated serum creatinine, which are consistent with the results from randomized controlled trials and real-world studies (Chng et al., 2021; McMurray et al., 2014; Rattanaivanon et al., 2021). Interestingly, bradykinin-related side effects, including cough and angioedema, were also observed. This study reported an ARNI discontinuation rate of 20.9%, with an average time to discontinuation of 283.61 days. In contrast, the randomized controlled study had a much lower discontinuation rate of only 1.9% (McMurray et al., 2014). The real world study by Chng et al. (2021) had an outpatient ARNI discontinuation rate of 10.3%. The lower discontinuation reported by Chng et al. (2021) may be attributed to fewer RAAS-naïve patients and a lower prevalence of CKD in the patient population, which likely increased ARNI tolerance.

Despite our study demonstrating favorable outcomes with ARNI in real-world settings, it is important to address several limitations. First, as this research was a retrospective study, we were unable to control the data received, such as laboratory tests required at specific time points. For example, NT-pro BNP was ordered in relatively few patients. Moreover, LVEF measurements were limited and irregular, as they are not a routine hospital test and are expensive, making data collection at consistent intervals challenging. In addition, there were limitations in tracking patient compliance. Finally, because of the observational nature of this study, our results are subject to potential confounding factors.

5. CONCLUSION

This retrospective study demonstrates the real-world effectiveness and safety of ARNI in Thai patients with HFrEF. Significant improvements in LVEF were also observed. Most patients who initiated ARNI were either RAAS blocker-naïve or previously on a low-to-medium dose of RAAS blockers, with initial doses that were consistent with guideline recommendations. Nonetheless, challenges in dose titration were observed, with a considerable percentage of patients unable to reach the target dose and a notable

discontinuation rate. Regarding safety, hyperkalemia was the most common adverse effect, followed by hypotension and elevated serum creatinine. Overall, these results highlight the benefits of ARNI for HFrEF management in a Thai population, while emphasizing the need for careful patient monitoring and individualized dosing strategies to optimize clinical outcomes.

AUTHOR CONTRIBUTIONS

V.U., S.J., and C.W. Conceptualization and Study Design. P.K. and S.J. Data collection. V.U., P.K., and S.J. Data Analysis and Interpretation. P.K. and V.U. Writing the manuscript.

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