ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 3003–3012
Published online 28 July 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12924

ORIGINAL RESEARCH ARTICLE

Sacubitril/valsartan vs. angiotensin receptor inhibition in heart failure: a real-world study in Taiwan

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Abstract

Aims This study aimed to compare the efficacy of angiotensin receptor–neprilysin inhibitor (ARNI) therapy with angiotensin receptor blocker (ARB) therapy for cardiovascular outcomes in patients with heart failure (HF) with reduced ejection fraction.
Methods and results Data were obtained from the Chang Gung Research Database. The cohort entry date of the ARB group was assigned as that of the ARNI group to avoid immortal time bias. Additionally, 1:1 propensity score matching based on age, sex, and baseline left ventricular ejection fraction was conducted. The expectation–maximization imputation method with inverse probability of treatment weighting was used to compare outcomes between the two groups. The primary outcome was a composite of cardiovascular death and hospitalization for worsening HF. Patients who received ARNI therapy had a significantly lower risk of the primary composite outcome occurring than patients who received ARBs (hazard ratio, 0.74; 95% confidence interval, 0.57–0.96). The reduction of hospitalization for worsening HF contributed most to the primary outcome benefits. In addition to the primary outcome, the ARNI group had a significantly lower risk of non-fatal myocardial infarction. The improvement of ejection fraction was not significantly different between the groups. The medication doses of ARNI were lower than in clinical trials.
Conclusions In patients with HF with reduced ejection fraction, sacubitril/valsartan was superior to ARB therapy in reducing the occurrence of the primary outcome endpoint of hospitalization for worsening HF and cardiovascular death.

Keywords Heart failure; Sacubitril/valsartan (LCZ696); Angiotensin receptor blockers

Received: 14 April 2020; Revised: 8 June 2020; Accepted: 13 July 2020
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Introduction

In the PARADIGM-HF trial, angiotensin receptor–neprilysin inhibitor (ARNI) therapy significantly reduced the risk of death and hospitalization for worsening heart failure (HF) compared with enalapril.[1] That trial provided extraordinary evidence to support the use of ARNI therapy instead of angiotensin-converting enzyme inhibitor (ACEI) therapy for patients with HF with reduced ejection fraction (HFrEF). ACEIs inhibit kininase and increase bradykinin levels, which can induce cough and angioedema. Dry cough was reported in 5–20% of patients treated with ACEI. That is especially common in Asian populations, with a prevalence rate that approaches 50%.[2] Because of intolerance related to ACEI-associated cough, most physicians favour prescribing angiotensin receptor blockers (ARBs) rather than ACEIs in Asian countries. Although clinical trials have demonstrated the comparable potential of ARBs to reduce rates of cardiovascular death and hospitalization for worsening HF,[3–6] evidence is still lacking for the superiority of ARNIs over ARBs.

A recent real-world study demonstrated that patients who received ARNI therapy had a lower composite risk of cardiovascular death and HF hospitalization than patients who did not receive ARNI therapy.[7] In the group without ARNI therapy, ACEIs/ARBs were only prescribed in 71% of patients; therefore, evidence may be inadequate to prove the superior efficacy of ARNIs over ARBs. In addition, medication underdosing is common in real-world clinical practice. Most

eligible patients with HFrEF do not receive target doses of related medication at any point during follow-up, and ~40–50% of patients received less than half of the standard dose.[8,9] Those real-world data revealed underdosing of ARNI prescriptions as well as other standard medications for HFrEF, including beta-blockers, ACEIs, ARBs, and mineralocorticoid receptor antagonists (MRAs).

Although ARBs are the ideal first choice for Asian patients with HFrEF, no clinical data have been made available to compare the benefits of ARNIs with those of ARBs. Therefore, we investigated the benefits of ARNIs over ARBs. In this study, patients who received ARNI and ARB therapy were selected using propensity score matching, and the two groups were compared using inverse probability of treatment weighting (IPTW). This paper also presents the real-world experience of ARNI and ARB underdosing and evaluates the relationship of underdosing with clinical benefits.

Methods and materials

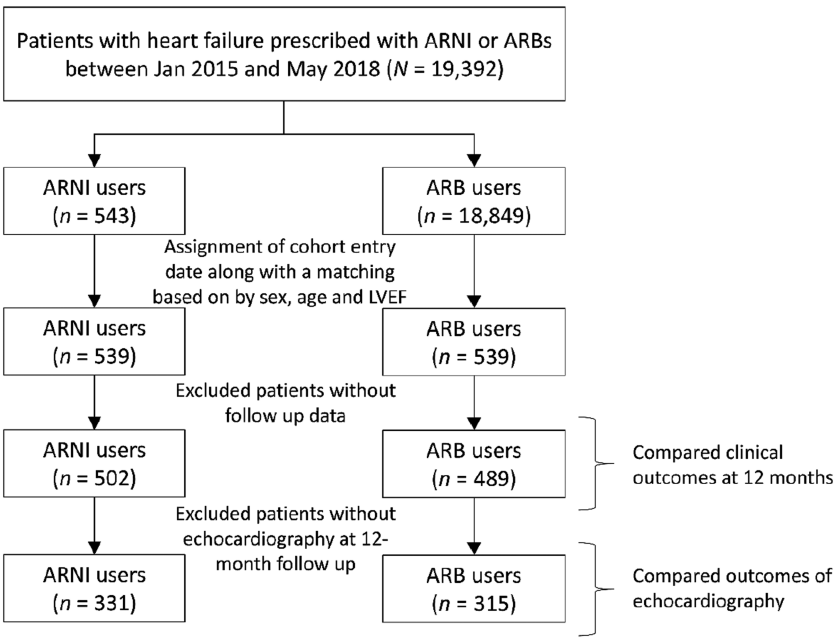
Data source

This double-arm prospective study used retrospective collected data from electronic medical records. The data were obtained from the Chang Gung Research Database (CGRD), which contains de-identified data derived from raw medical records of Chang Gung Memorial Hospital. More information about the CGRD can be obtained by referring to previous publications.[10,11] The project was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No. 201801032B0). The data were collected from the three medical institutes of Chang Gung Memorial Hospital in northern Taiwan (Linkou, Taipei, and Taoyuan branches). The disease was identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) before 2015 and ICD-10-CM diagnostic code after 2016.

Study design

Figure 1 shows the flow chart of patient inclusion. Patients with HFrEF, which was defined as left ventricular ejection fraction (LVEF) of <40%, who received ARNI or ARB (valsartan, losartan, and candesartan) therapy for at least 30 days between January 2016 and May 2018, were included. For the ARNI group, the cohort entry date was the date of the first prescription of ARNI regardless of previous ARB prescription. Because of many patients in the ARNI group previously receiving ARB therapy, we assigned the cohort entry date of one patient in the ARNI group to one or more counterparts

FIGURE 1 Flow chart for patient inclusion. Patients with heart failure with reduced ejection fraction and prescribed with angiotensin receptor–neprilysin inhibitors (ARNIs) or angiotensin receptor blockers (ARBs, including valsartan, losartan, and candesartan) were included. After the assignment of the cohort entry date and matching by sex, age, and left ventricular ejection fraction (LVEF), 539 patients were included in each group. Patients without follow-up data were excluded, and the remaining patients with complete follow-up data were included in the clinical outcome analyses. Among the patients, only 331 ARNI users and 315 ARB users had echocardiographic follow-up at 12 months and were included in the analyses of the echocardiographic results.



DOI: 10.1002/ehf2.12924

in the ARB group to avoid immortal time bias.[12] Patients were not included in the ARB group if they were eligible for the ARNI group. In conjunction with assigning the cohort entry date, propensity score matching (1:1) based on age, sex, and baseline LVEF were conducted, resulting in 539 patients with HFrEF being assigned to each group. Those patients without follow-up data were excluded, and the remaining patients were included in the clinical outcome analyses. Finally, patients without echocardiographic data at the 12 month follow-up were excluded, and the remaining patients were included in the echocardiographic result analysis.

Covariates and outcomes

Covariates were age, sex, 11 co-morbidities, eight types of medication, seven types of laboratory data, and echocardiographic results at baseline. Co-morbidity was defined as having at least two outpatient diagnoses or anyone inpatient diagnosis before the cohort entry date. Medication and laboratory data were extracted within 3 months before the cohort entry date.

The primary composite outcome included hospitalization for worsening HF and cardiovascular death. The secondary outcomes included all-cause death, cardiovascular death, hospitalization for worsening HF, non-fatal myocardial infarction, non-fatal stroke, and new renal replacement therapy. The occurrence of myocardial infarction and stroke was identified using the principal or the secondary diagnoses from inpatient claims data. The definition of myocardial infarction was a combination of the diagnosis of myocardial infarction and increased troponin I. The definition of hospitalization for worsening HF was hospitalization with a combination of a diagnosis of HF and at least one treatment for acute decompensated HF. The treatment for acute decompensated HF included additional dosages of diuretics, nitrites, and inotropic agents during the hospitalization. The baseline echocardiographic and laboratory data were collected within 3 months prior to the cohort entry date, and the 12 month echocardiographic and laboratory data were collected between 9 and 15 months after the cohort entry date. Only patients who had echocardiographic data at 12 months were included in the echocardiographic analyses. The baseline medication doses were the starting doses on the cohort entry date, and the 12 month doses were the doses for the 12th month. Each patient was followed until the day of outcome occurrence or death within 1 year after the cohort entry date or 31 May 2018, whichever came first.

Statistical analyses

With the cohort matched by age, sex, and baseline LVEF (n = 539 in each group), we further assigned an IPTW cohort based on propensity scores derived from the multivariable logistic regression. The propensity score was calculated using the values of the covariates (*Table 1*) except the follow-up duration was replaced with the cohort entry date. We used a stabilized weight to mitigate the influence of outliers on the estimated propensity scores. The quality of weighting was checked using the absolute value of the standardized difference (STD) between the groups after weighting, where a value of <0.1 was considered a negligible difference. Because of a substantial number of missing observations in the laboratory data, we first imputed the missing values using single expectation–maximization (EM) imputation method and then created the IPTW cohort.

The risks of time-to-event outcomes between the ARNI and ARB groups were compared using the Cox proportional hazard model where the study group (ARNI vs. ARB) was the only explanatory variable. The echocardiographic and laboratory data at the 12 month follow-up between the groups were compared using either independent sample t-test for continuous variables or χ^2 test for categorical variables. Finally, we compared the risk of the primary composite outcome in the ARNI users between those who could tolerate higher doses (≥200 mg/day) and those who could not by employing a Cox model using the EM imputation cohort without IPTW adjustment. Because several large randomized controlled trials, including the PARADIGM-HF trial, have demonstrated the benefit of ARNI on the primary composite outcome, the analysis of the primary composite outcome was prespecified as a one-sided test. The other outcome analyses were two-sided tests. A two-sided P value of <0.05 was statistically significant, and no adjustment for multiple testing (multiplicity) was applied in this study. All the statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient inclusion

A total of 19 392 patients with HFrEF who received ARNI (543 patients) or ARB therapy (18 849 patients) were identified between January 2016 and May 2018 in the CGRD (*Figure 1*). Cohort entry dates were assigned along with the propensity score matching by sex, age, and LVEF, resulting in 539 patients being included in each group. The patients without follow-up data were excluded, and the remaining 502 ARNI users and 489 ARB users were included in the clinical outcome analyses.

Baseline characteristics

Table 1 shows the baseline characteristics of the two groups. After EM imputation and IPTW were applied, all parameters

DOI: 10.1002/ehf2.12924

Table 1 Baseline characteristics between the ARNI and ARB groups before and after EM imputation and IPTW adjustment

		Before EM imputation and IPTW[a]				After EM imputation and IPTW[b]		
Variable	Valid *N*	Total (*n* = 991)	ARNIs (*n* = 502)	ARBs (*n* = 489)	STD	ARNIs	ARBs	STD
Demographics								
Age (years)	991	62.4 ± 15.2	62.1 ± 15.4	62.6 ± 15.0	0.03	62.8 ± 15.0	62.2 ± 14.8	−0.04
Male	991	761 (76.8)	391 (77.9)	370 (75.7)	−0.05	74.6%	76.8%	0.05
Co-morbidity								
Coronary artery disease	991	468 (47.2)	245 (48.8)	223 (45.6)	−0.06	45.9%	46.5%	0.01
Myocardial infarction	991	204 (20.6)	88 (17.5)	116 (23.7)	0.15	19.5%	20.8%	0.03
Hypertension	991	596 (60.1)	297 (59.2)	299 (61.1)	0.04	60.5%	59.9%	−0.01
Dyslipidaemia	991	509 (51.4)	248 (49.4)	261 (53.4)	0.08	51.7%	52.1%	0.01
Diabetes mellitus	991	366 (36.9)	185 (36.9)	181 (37.0)	<0.01	37.0%	37.1%	<0.01
Chronic kidney disease	991	376 (37.9)	181 (36.1)	195 (39.9)	0.08	38.0%	37.3%	−0.02
Dialysis	991	54 (5.4)	16 (3.2)	38 (7.8)	0.20	4.1%	5.1%	0.05
Stroke	991	75 (7.6)	37 (7.4)	38 (7.8)	0.02	8.2%	8.0%	−0.01
Atrial fibrillation	991	197 (19.9)	104 (20.7)	93 (19.0)	−0.04	22.1%	20.5%	−0.04
Chronic obstructive pulmonary disease	991	95 (9.6)	51 (10.2)	44 (9.0)	−0.04	9.1%	9.7%	0.02
Peripheral arterial disease	991	64 (6.5)	28 (5.6)	36 (7.4)	0.07	6.4%	5.6%	−0.03
Medication								
Beta-blocker	991	860 (86.8)	452 (90.0)	408 (83.4)	−0.20	86.7%	87.2%	0.02
MRAs	991	497 (50.2)	302 (60.2)	195 (39.9)	−0.41	50.4%	51.0%	0.01
Ivabradine	991	121 (12.2)	72 (14.3)	49 (10.0)	−0.13	12.2%	12.6%	0.01
Loop diuretics	991	670 (67.6)	362 (72.1)	308 (63.0)	−0.20	67.3%	67.1%	<0.01
Digoxin	991	207 (20.9)	111 (22.1)	96 (19.6)	−0.06	20.6%	20.9%	0.01
Amiodarone	991	110 (11.1)	60 (12.0)	50 (10.2)	−0.06	11.8%	11.7%	<0.01
Oral hypoglycaemic agents	991	330 (33.3)	159 (31.7)	171 (35.0)	0.07	33.4%	32.6%	−0.02
Insulin	991	150 (15.1)	53 (10.6)	97 (19.8)	0.26	16.6%	15.2%	−0.04
Laboratory data								
BNP (mg/dL)	422	791.7 [246.9, 1921.0]	613 [173, 1935]	933 [385, 1767]	NA	939 [549, 1308]	1006 [672, 1317]	NA
BUN (mg/dL)	632	30.5 ± 22.6	30.0 ± 21.5	31.1 ± 23.6	0.05	28.5 ± 17.6	28.7 ± 18.0	0.01
Creatinine (mg/dL)	873	1.8 ± 2.3	1.6 ± 2.0	2.0 ± 2.6	0.16	1.7 ± 2.1	1.7 ± 2.1	0.03
eGFR (mL/min/1.73 m^2)	873	66.1 ± 40.7	66.2 ± 38.1	66.0 ± 43.3	<0.01	65.9 ± 39.0	66.4 ± 35.7	0.01
Sodium (Na) (mEq/L)	679	139.5 ± 3.9	139.5 ± 4.2	139.5 ± 3.7	<0.01	139.6 ± 3.4	139.5 ± 3.0	−0.02
Potassium (K) (mEq/L)	793	4.2 ± 0.6	4.2 ± 0.6	4.2 ± 0.6	−0.10	4.2 ± 0.5	4.2 ± 0.5	0.01
Uric acid (mg/dL)	596	7.4 ± 2.6	7.4 ± 2.5	7.4 ± 2.6	−0.01	7.4 ± 2.0	7.3 ± 2.0	−0.03
Echocardiographic result								
LVEF (%)	991	32.0 ± 10.1	31.8 ± 10.2	32.2 ± 10.0	0.04	32.1 ± 10.8	32.4 ± 10.2	0.03
LVEDD (mm)	967	60.5 ± 9.0	61.7 ± 9.1	59.4 ± 8.8	−0.26	60.2 ± 9.1	60.3 ± 9.0	0.01
LVESD (mm)	967	50.5 ± 10.1	52.0 ± 10.0	48.9 ± 9.8	−0.31	50.2 ± 10.2	50.1 ± 9.9	−0.01
LA (mm)	965	45.6 ± 8.0	46.2 ± 8.2	45.0 ± 7.8	−0.15	45.4 ± 7.8	45.4 ± 7.9	<0.01
MR severity	954							
Severe		9 (0.9)	6 (1.3)	3 (0.6)	−0.07	1.0%	1.6%	0.05

(*Continues*)

Table 1 (continued)

Variable	Before EM imputation and IPTW[a]					After EM imputation and IPTW[b]		
	Valid *N*	Total (n = 991)	ARNIs (n = 502)	ARBs (n = 489)	STD	ARNIs	ARBs	STD
Moderate		103 (10.8)	56 (11.8)	47 (9.8)	−0.07	10.0%	9.6%	−0.01
Mild		659 (69.1)	326 (68.8)	333 (69.4)	0.01	68.8%	68.8%	<0.01
Trivial/none		183 (19.2)	86 (18.1)	97 (20.2)	0.05	20.3%	20.0%	−0.01
Follow-up duration (months)	991	7.4 ± 3.8	7.5 ± 3.9	7.2 ± 3.7	−0.06	7.7 ± 5.5	7.1 ± 5.1	−0.11

ARBs, angiotensin receptor blockers; ARNIs, angiotensin receptor–neprilysin inhibitors; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; EM, expectation–maximization; IPTW, inverse probability of treatment weighting; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NA, not available; STD, standard difference.

[a]Data were presented as *n* (%), mean ± standard deviation, or median [25th, 75th percentile].

[b]Data were presented as %, mean ± standard deviation, or median [25th, 75th percentile].

were not substantially different between the groups. The mean ages were 62.8 ± 15.0 and 62.2 ± 14.8 years (STD = −0.04) in the ARNI and ARB groups, respectively; the ratios of male patients were 74.6% and 76.8% (STD = 0.05). In the ARNI and ARB groups, respectively, 45.9% and 46.5% of patients (STD = 0.01) had a history of coronary artery disease, 19.5% and 20.8% of patients (STD = 0.03) had a history of myocardial infarction, 22.1% and 20.5% of patients (STD = −0.04) had a history of atrial fibrillation, and 8.2% and 8.0% of patients (STD = −0.01) had a history of stroke. Beta-blockers were prescribed in 86.7% and 87.2% of patients (STD = 0.02), respectively, and MRAs were prescribed in 50.4% and 51.0% of patients (STD = 0.01). The baseline brain natriuretic peptide level was 939 and 1006 mg/dL, and the median duration of follow-up was 7.7 ± 5.5 and 7.1 ± 5.1 months (STD = −0.11) in the ARNI and ARB groups, respectively.

Clinical outcomes

Death from cardiovascular causes or hospitalization for worsening HF (the primary composite endpoint) occurred in 95 patients in the ARNI group (18.0%, with IPTW) and 113 patients in the ARB group (22.2% with IPTW). The absolute composite endpoint reduction was 4.2% [hazard ratio, 0.74; 95% confidence interval (CI), 0.57–0.96, *Figure 2*]. Hospitalization for worsening HF contributed most to primary outcome benefits, with a hazard ratio of 0.75 (95% CI, 0.55–1.02). The ARNI group also demonstrated a lower risk of non-fatal myocardial infarction than the ARB group [2.0% (10 patients) in the ARNI group vs. 4.6% (25 patients) in the ARB group; hazard ratio, 0.41; 95% CI, 0.19–0.88]. Comparisons on all-cause death, cardiovascular death, HF death, non-fatal stroke, and new renal replacement therapy between the groups did not reveal significant differences. The summarized results are shown in *Table 2*.

Echocardiographic and laboratory outcomes

For cardiac function evaluation, only patients who received echocardiography at 12 months after the index entry date were included. In total, 331 ARNI users and 315 ARB users were included in the analyses. *Table 3* reports the results of echocardiographic parameters and laboratory data. In the ARNI and ARB groups, the baseline LVEF was 32.1 ± 10.8% and 32.4 ± 10.2% (STD = 0.03), and severe mitral regurgitation was noted in 1.0% and 1.6% (STD = 0.05) of patients, respectively. Echocardiography at 12 month follow-up demonstrated no significant differences in LVEF (39.1 ± 13.8% vs. 39.9 ± 14.4%, P = 0.294), left ventricular chamber sizes, and mitral regurgitation severity between the ARNI and ARB groups. Besides, renal function, potassium

FIGURE 2 Inverse probability of treatment weighting-adjusted cumulative event rate of the primary composite endpoint (heart failure hospitalization or cardiovascular death) during the 1 year follow-up between the angiotensin receptor–neprilysin inhibitor (ARNI) group and the angiotensin receptor blocker (ARB) group in the expectation–maximization-imputed cohort. The ARNI group had a lower risk of a negative outcome than did the ARB group. CI, confidence interval.

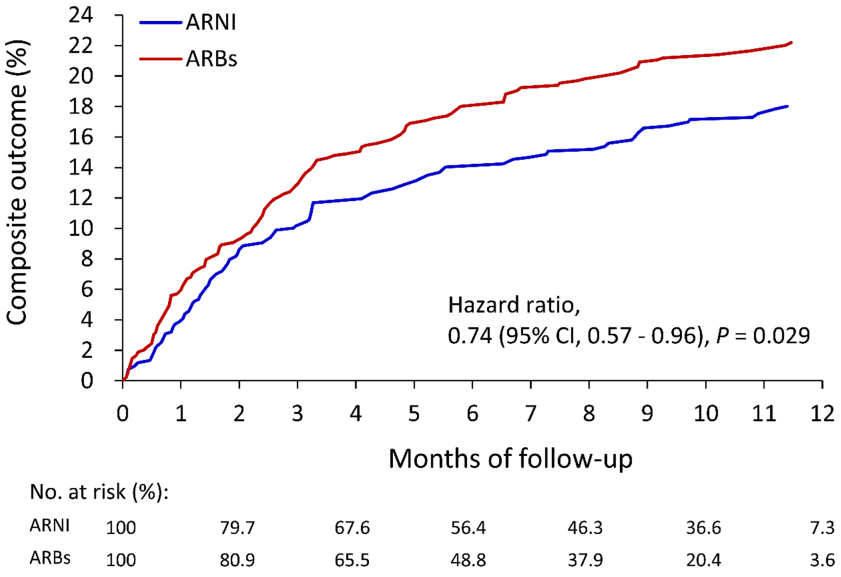


Table 2 Clinical outcomes between the ARNI and ARB groups at 12 month follow-up in the EM-imputed and IPTW-adjusted cohort

	Data before IPTW[a]		Data after IPTW[b]			
					ARNIs vs. ARBs	
Outcome variable	ARNIs (n = 502)	ARBs (n = 489)	ARNIs	ARBs	HR (95% CI)	P value
Primary outcome: composite of heart failure hospitalization and cardiovascular death	95 (18.9)	113 (23.1)	18.0%	22.2%	0.74 (0.57–0.96)[c]	0.029[c]
Secondary outcome						
All-cause death	15 (3.0)	18 (3.7)	3.3%	3.3%	0.90 (0.43–1.89)	0.774
Cardiovascular death	6 (1.2)	5 (1.0)	0.8%	0.8%	0.94 (0.27–3.26)	0.922
Heart failure death	6 (1.2)	3 (0.6)	0.8%	0.5%	1.50 (0.35–6.51)	0.590
Hospitalization due to heart failure	95 (18.9)	111 (22.7)	18.0%	21.9%	0.75 (0.55–1.02)	0.070
Hospitalization due to any cause	123 (24.5)	159 (32.5)	27.4%	29.8%	0.86 (0.65–1.13)	0.270
Non-fatal myocardial infarction	10 (2.0)	25 (5.1)	2.0%	4.6%	0.41 (0.19–0.88)	0.022
Non-fatal stroke	10 (2.0)	15 (3.1)	2.9%	2.7%	0.97 (0.36–2.61)	0.958
New renal replacement therapy	11 (2.2)	16 (3.3)	3.5%	2.8%	1.20 (0.49–2.95)	0.694

ARBs, angiotensin receptor blockers; ARNIs, angiotensin receptor–neprilysin inhibitors; CI, confidence interval; EM, expectation–maximization; HR, hazard ratio; IPTW, inverse probability of treatment weighting.
[a]Values are given as n (%).
[b]Values are presented as %.
[c]Prespecified one-sided test.

concentration, and uric acid were not significantly different between the groups at baseline and 12 month follow-up (*Table 3*).

Medication dosage

At the end of the data assessment, patients had medication discontinuation rates of 19.1%, 33.9%, 59.7%, and 24.9% for ARNI, valsartan, losartan, and candesartan, respectively (*Table 4*). Among patients taking ARNIs and ARBs, the mean daily doses of ARNI, valsartan, losartan, and candesartan at 12 months were 192 ± 110, 172 ± 97, 42 ± 22, and 7.3 ± 4.1 mg, respectively. Patients who could not tolerate higher doses (<200 mg/day) of ARNI had a slightly less favourable primary composite endpoint than the patients who could tolerate higher doses (≥200 mg/day) of ARNI (hazard ratio, 0.62; 95% CI, 0.38–1.03; two-sided P = 0.066; *Figure 3*). The LVEF and mitral regurgitation severity were not substantially different between the lower ARNI-dose

Table 3 Echocardiographic and laboratory data for the ARNI and ARB groups at 12 month follow-up in the IPTW-adjusted cohort

Parameter	Valid *N*	ARNIs (n = 331)	ARBs (n = 315)	*P* value
Echocardiographic data				
LVEF (%)	646	39.1 ± 13.8	39.9 ± 14.4	0.294
LVEDD (mm)	449	59.0 ± 10.1	59.2 ± 10.5	0.760
LVESD (mm)	449	47.1 ± 11.7	47.2 ± 12.0	0.908
LA (mm)	449	44.4 ± 7.9	44.7 ± 8.5	0.696
MR severity	441			0.062
Severe/moderate		9.0%	13.6%	
Mild		67.0%	60.9%	
Trivial/none		24.0%	25.5%	
Laboratory data				
BUN (mg/dL)	478	35.3 ± 30.3	34.5 ± 24.8	0.664
Creatinine (mg/dL)	749	1.9 ± 2.4	1.8 ± 2.4	0.660
Potassium (K) (mEq/L)	642	4.3 ± 0.6	4.3 ± 0.6	0.475
Uric acid (mg/dL)	469	7.0 ± 2.2	7.0 ± 2.4	0.921

ARBs, angiotensin receptor blockers; ARNIs, angiotensin receptor–neprilysin inhibitors; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; IPTW, inverse probability of treatment weighting; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation.

and higher ARNI-dose groups (see Supporting Information, *Table S1*). The higher ARNI-dose group had a higher prevalence of hypertension (70.0% vs. 54.4%, with an STD 0.33) than the lower ARNI-dose group. On the other hand, the lower ARNI-dose patients used more MRAs, ivabradine, and digoxin than the higher ARNI-dose group.

Discussion

In this study, patients who received ARNI therapy had a significantly lower risk of the primary composite endpoint of cardiovascular death and hospitalization for worsening HF than patients who received ARB therapy. The hazard ratio and absolute reduction of the primary endpoint were close to those detailed in the results of the PARADIGM-HF trial.[1] In terms of primary endpoint outcomes, the reduction in hospitalization for worsening HF contributed most to the related outcome benefits. Patients who received ARNI therapy and those who received ARB therapy had similar improvements of LVEF at 12 month follow-up. In this study, the mean medication doses of ARNIs and ARBs were lower than the values in the clinical trial[1,3–6]; however, underdosing is common in most real-world experiences.[8,9] In this study, underdosing of ARNI was associated with a borderline poor primary composite outcome.

Clinical benefits of angiotensin receptor–neprilysin inhibitor therapy over angiotensin receptor blocker therapy

Previous randomized controlled trials have clearly established the benefits of ACEIs to reduce morbidity and mortality in HFrEF patients.[13] Until the publication of the PARADIGM-HF trial results, ACEI administration was the recommended pharmacological therapy for patients with HFrEF owing to benefits indicated in previous clinical trials. In the PARADIGM-HF trial, enalapril was selected as the conventional pharmacological therapy to test the beneficial effects of sacubitril/valsartan.[1] ARNI therapy significantly reduced the risk of death and hospitalization for worsening HF compared with enalapril, leading to ARNI becoming the recommended therapy for patients with chronic symptomatic HFrEF New York Heart Association Class II or III who could tolerate ACEIs.[13,14] In most clinical trials currently recruiting patients with HFrEF for ARNI therapy (according to information from ClinicalTrials.gov), ACEIs are still chosen as a comparison to test the clinical outcome benefits. The prevalence of ACEI-induced cough is especially common in Asian populations, and most physicians favour prescribing an ARB rather than an ACEI. Although some clinical trials have indicated comparable benefits of ARBs and ACEIs in reducing rates of cardiovascular death and hospitalization for worsening HF,[3–6] evidence is still lacking for the superiority of ARNIs over ARBs.

In this study, we compared the clinical outcomes in patients with HFrEF who received ARNI therapy with those in patients who received ARB therapy. In accordance with previous large-scale clinical trials, which showed adequate evidence of outcome benefits from ARB therapy,[3–6] we selected only those patients who received valsartan, losartan, and candesartan therapy in the ARB group. ARNI therapy remained superior in reducing the primary composite endpoint of cardiovascular death and hospitalization due to worsening HF (hazard ratio 0.74 and absolute risk reduction 4.2%) when compared with the guideline-recommended ARBs. The primary endpoint results were similar to those of the PARADIGM-HF trial, in which the hazard ratio was 0.80 (95% CI, 0.73–0.87) with the absolute risk reduction of 4.7%

DOI: 10.1002/ehf2.12924

Table 4 The daily prescribed dose of ARNIs and ARBs at baseline and 12 month follow-up

	ARNI			Valsartan			Losartan			Candesartan	
	Baseline	12 month		Baseline	12 month		Baseline	12 month		Baseline	12 month
Valid *N*	499	414		149	112		116	72		225	181
Dose per day											
25 mg	3 (0.6)	2 (0.5)	40 mg	3 (2.0)	1 (0.9)	12.5 mg	3 (2.6)	2 (2.8)	2 mg	14 (6.2)	10 (5.5)
50 mg	31 (6.2)	25 (6.0)	80 mg	41 (27.5)	26 (23.2)	25 mg	48 (41.4)	31 (43.1)	4 mg	94 (41.8)	71 (39.2)
100 mg	315 (63.1)	141 (34.1)	160 mg	82 (55.0)	67 (59.8)	50 mg	58 (50.0)	33 (45.8)	8 mg	91 (40.4)	73 (40.3)
200 mg	130 (26.1)	172 (41.6)	320 mg	22 (14.8)	16 (14.3)	100 mg	6 (5.2)	6 (8.3)	12 mg	1 (0.4)	1 (0.6)
400 mg	20 (4.0)	74 (17.9)	640 mg	1 (0.7)	2 (1.8)	200 mg	1 (0.9)	—	16 mg	25 (11.1)	26 (14.4)
Mean dosage (mg)	135 ± 72	192 ± 110		162 ± 86	172 ± 97		43 ± 24	42 ± 22		6.9 ± 3.9	7.3 ± 4.1
Drug stopping (%)	—	79 (19.1)		—	38 (33.9)		—	43 (59.7)		—	45 (24.9)

ARBs, angiotensin receptor blockers; ARNIs, angiotensin receptor–neprilysin inhibitors.

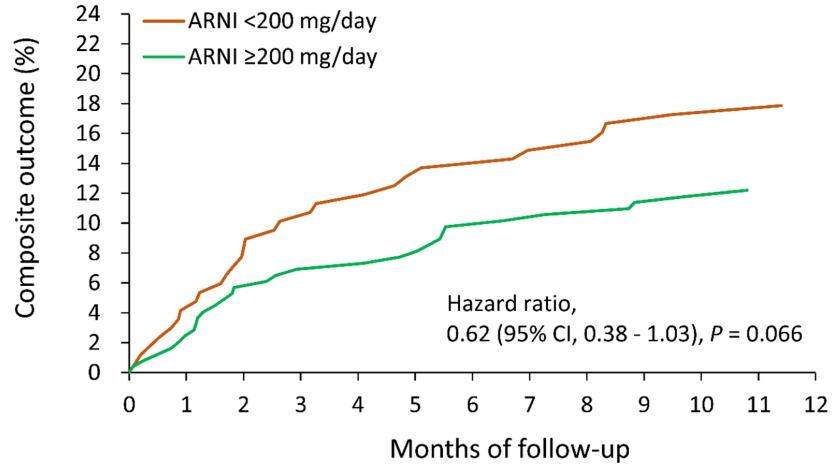
for the primary endpoint. Besides, we noted a significantly lower risk of non-fatal myocardial infarction in the ARNI group. That is compatible with the results of the PARADIGM-HF trial, in which ARNI reduced the risk of the coronary composite outcomes compared with enalapril.[15] However, a reduction in the risk of myocardial infarction may require further confirmation by other clinical trials (such as the PARADISE-MI trial).

The current study demonstrated similar patient demographics to the PARADIGM-HF trial, with some baseline characteristics, such as patient age, female sex ratio, history of diabetes and stroke, and use of beta-blockers and MRAs being comparable between the two studies. However, the patients in this study cohort had a lower prevalence of ischaemic cardiomyopathy, previous history of myocardial infarction and atrial fibrillation, and a higher baseline creatinine level than patients in the PARADIGM-HF trial. The pattern of a lower prevalence of ischaemia, previous history of myocardial infarction and atrial fibrillation, and a higher baseline creatinine level in patients with HFrEF was also observed in a large national registry study for patients with decompensated HFrEF in Taiwan (the TSOC-HFrEF Registry).[16]

Effect of medication underdosing on clinical outcomes

In this study, the underdose of ARNI was associated with a higher risk of the composite endpoint of cardiovascular death and hospitalization for worsening HF. Medication underdosing is one of the most critical issues in clinical practice. Evidence suggests considerable underdosing and physician underuse of recommended drugs in real-world conditions. Studies have demonstrated that most patients with HFrEF did not receive target doses of medical therapy at any point during follow-up.[8,9] Moreover, 40–50% of patients received less than half of the standard medication dose. The underdosing of medications may lead to less favourable clinical outcomes. A report indicated that the risk of hospitalization for worsening HF has an inverse relationship with the ACEI dose.[17] In this study, the doses of sacubitril/valsartan and ARBs were less than half of the recommended standard dose for HFrEF therapy. A possible explanation is that some patients did not tolerate the standard dosage of ARNI, leading to underdosing. The situation of underdosing might lead to a less favourable outcome, which emphasizes the need for greater awareness regarding this issue. However, in this study, the causal relationship between underdosing and the slightly less favourable outcome was not strong. The association might also be explained by the fact that patients with higher blood pressure tolerated a higher dose of ARNI.

FIGURE 3 Unadjusted cumulative event rate of primary composite endpoints during the 1 year follow-up in the 431 angiotensin receptor–neprilysin inhibitor (ARNI) users stratified by the ability to tolerate higher doses (≥200 mg/day). The patients who could not tolerate higher doses (<200 mg/day) of ARNI therapy had a slightly less favourable primary composite endpoint outcome. CI, confidence interval.



No. at risk:

ARNI <200	168	141	123	112	104	97	86
ARNI ≥200	246	225	202	182	171	160	138

Study limitations

In this study, the risks of cardiovascular death and all-cause death were lower than expected, and the lower risks made the statistical comparison of death between the groups problematic. Two possible factors may explain the relatively low risk of mortality. During the relatively short follow-up duration, fewer patients met the endpoint of cardiovascular death. Second, some patients who met the endpoint of cardiovascular death were not admitted to those hospitals in which CGRD collected data. Therefore, we were not able to estimate the exact risk of death, and the numbers of cardiovascular deaths and all-cause deaths were too small to reach statistical significance.

The maximum follow-up duration of this cohort was only 12 months, which was considerably shorter than the PARADIGM-HF trial. The Kaplan–Meier survival curve for death due to worsening HF showed that the curves of the two groups separated after 360 days,[18] indicating that differences between the two groups might not be significant within 12 months. Some clinical outcomes might not be significantly different within 12 months, including mortality and LVEF.

Among the patients included in the outcome analyses, approximately one-third of patients in both groups did not receive follow-up echocardiography. The echocardiographic outcomes were compared using the currently existing results. The echocardiographic follow-up duration might be too short for use in evaluating LVEF improvements.

At last, this is a not a randomized trial, and the results may be confounded by the unmeasured confounders. Therefore, caution should be used to interpret the results.

Conclusions

In this propensity-matched cohort study investigating the primary outcome endpoints of cardiovascular death and hospitalization for worsening HF, sacubitril/valsartan therapy was superior to ARB therapy for patients with HFrEF. In terms of primary endpoints, most benefits derived were related to hospitalization for worsening HF. Patients who received ARNI therapy and those who received ARB therapy had similar improvements of LVEF at 12 month follow-up. The patients in this cohort had smaller medication doses than those in previous clinical trials. Underdosing of ARNI was associated with a slightly less favourable primary composite outcome.

Acknowledgements

We thank Mr Alfred Hsing-Fen Lin and Mrs Zoe Ya-Jhu Syu for their assistance with the statistical analysis during the completion of this manuscript. Wallace Academic Editing edited this manuscript.

Conflict of interest

None declared.

Funding

This study was supported by the Chang Gung Research Database and the Chang Gung Medical Foundation (BMRP D62 and CMRPG3D0341 to P-C.C.).

Supporting information

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

Table S1. Baseline characteristics of the patients with different dose of ARNI at baseline.

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