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Original article

Sacubitril/valsartan in heart failure with reduced ejection fraction patients: Real world experience on advanced chronic kidney disease, hypotension, and dose escalation

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ABSTRACT

Background: Angiotensin receptor and neprilysin inhibition (ARNI) has been shown to reduce cardiovascular mortality by 20% as compared with enalapril in a randomized controlled trial. However, there is a paucity of real-world data on the effects of ARNI in heart failure patients with reduced ejection fraction (HFrEF), especially those with concurrent renal impairment or hypotension.

Methods: Between 2016 and 2017, we recruited 466 HFrEF patients treated with sacubitril/valsartan (Group A) and 466 patients managed with standard HF treatment without ARNI (Group B) in a HF referral center. Baseline characteristics and clinical outcomes were collected between both groups.

Results: Baseline characteristics were comparable between the two groups. During a follow-up period of 15 months, death from cardiovascular causes or first unplanned hospitalization for HF occurred in 100 patients in Group A (21.5%) and 144 in Group B (30.9%, hazard ratio 0.66; 95% CI 0.51–0.85; $p = 0.001$). The incidences of deaths from any causes, cardiovascular death, sudden death, and HF re-hospitalization were all significantly lower in Group A than Group B patients. Among patients with different chronic kidney disease stages and normotensive patients, treatment with sacubitril/valsartan showed more favorable outcomes than treatment with standard HF care without ARNI. However, in patients with baseline systolic blood pressure lower than 100 mmHg, there were no significant differences of outcomes in both groups. Among Group A patients, escalation of sacubitril/valsartan was associated with better outcomes.

Conclusions: Our study demonstrated the effectiveness of sacubitril/valsartan on HFrEF patients in real world practice, including those with advanced renal impairment.

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Introduction

Heart failure (HF) is a leading cause of morbidity and mortality and a global burden of the healthcare system [1–3]. Over-activations of neurohumoral systems are central to the pathophysiology of HF. Since the publication of the CONSENSUS trial in 1987 and SOLVD-Treatment trial in 1991, the angiotensin-converting enzyme inhibitors (ACEIs) have been shown to reduce overall HF mortality by 16–40% [4,5]. Angiotensin-receptor blockers (ARBs) have similar effects as ACEIs but work by blocking AT1 receptor and interfere with the action of angiotensin II. The Val-HeFT trial in 2001 established the usage of ARB therapy for HF [6]. Three beta-blockers for HF namely bisoprolol, carvedilol, and sustained-release metoprolol can block the adrenergic activation and lead to a substantial reduction in mortality [7–9]. The mineralocorticoid receptor antagonist (MRAs) spironolactone has been proven to reduce mortality by 30% among patients already receiving ACEIs in the RALES trial [10]. The EMPHASIS-HF trial in 2011 confirmed and extended the usage of MRA eplerenone

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in patients with mild symptomatic HF [11]. These neurohumoral antagonists are the cornerstones of modern HF therapy.

Despite extensive treatments targeting neurohumoral blockade, HF remains a substantial cause of morbidity and mortality. Another paradigm shift in HF therapy occurred after the publication of the PARADIGM-HF trial in 2014 [12]. The study showed that a novel approach to HF therapy, angiotensin-receptor and neprilysin inhibition (ARNI) with a combination of sacubitril and valsartan, reduced cardiovascular mortality by 20% and all-cause mortality by 16%, as compared with enalapril. According to this study, the American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology (ESC) have updated evidence-based guidelines for the treatment of HF recently [13,14]. Both guidelines provided class I, level of evidence B recommendation to replace ACEIs by sacubitril/valsartan in patients with chronic symptomatic HF with reduced ejection fraction (HFrEF) despite optimal treatment.

To date, there is a paucity of real-world data on the effects of ARNI on patients with HFrEF. To confirm the effectiveness of sacubitril/valsartan in the broad range of HFrEF patients in real-world clinical practice, we enrolled patients receiving ARNI and compared their baseline characteristics, treatment, and outcomes to control patients treated with standard HF therapy between 2016 and 2017.

Methods

Definition, study design, and study population

This study aimed to evaluate the effectiveness of sacubitril/valsartan in HFrEF patients receiving it (Group A) versus HFrEF patients not receiving it (Group B) in addition to standard HF management. The definition of HF used in our study is consistent with that in the ESC guideline: presentation of typical HF symptoms accompanied by HF signs caused by a structural and/or functional cardiac abnormality [13]. The definition of HFrEF patient is a patient with New York Heart Association (NYHA) class II, III, or IV HF symptoms, and with left ventricular ejection fraction (LVEF) of 40% or less.

The inclusion criteria for the current study included: (1) male or female, age more than 20 years old; (2) fulfill the diagnosis of HF with documented LVEF less than 40% by echocardiography. The exclusion criteria for the current study included: (1) patients refused medical advice or lost to follow up; (2) HF with echocardiographic LVEF $\geq$40%; (3) HF primarily resulting from right ventricular failure, pericardial disease, or congenital heart disease; (4) for Group B patients, switching to sacubitril/valsartan within 15 months of follow-up period. The study protocol was approved by the Institutional Review Board.

Between June 2016 and October 2017, our study involved 1563 patients from HF database in the Cheng Hsin General Hospital, which is a tertiary referral center for HF management and cardiac transplant in Taiwan. After applying both the inclusion and exclusion criteria, we included 466 consecutive HFrEF patients treated with sacubitril/valsartan in addition to standard HF treatment (Group A). For comparison between the two treatment strategies, we included another 466 consecutive HFrEF patients receiving only the standard HF treatment without ARNI (Group B). The flowchart of our study design is shown in Fig. 1. Baseline characteristics, vital signs, and concomitant medications before initiation of sacubitril/valsartan were collected. There were no specific protocols for management of HF and up-titrating of medication. The follow-up period is 15 months, until the end of January 2019.

Echocardiography studies

Echocardiographic images were acquired at baseline. Left ventricular end-diastolic diameter was measured at end-diastole, and left ventricular end-systolic diameter and left atrial anteroposterior dimension were measured at end-systole on parasternal views. The LVEF was calculated using the biplane Simpson's method on apical 4-chamber and 2-chamber views. Continuous wave Doppler of the tricuspid regurgitation trace is used to measure and estimate pulmonary artery systolic pressure.

Prescription pattern of sacubitril/valsartan

Prescription of sacubitril/valsartan was classified into three patterns: Dose escalation: defined as up-titration of sacubitril/valsartan to at least 50% target dose of PARADIGM-HF trial (49/51 mg twice a day); dose stationary: defined as no increase of sacubitril/valsartan dosage, or up-titration of sacubitril/valsartan to less than 50% target dose of PARADIGM-HF trial; dose de-escalation: defined as down-titration of sacubitril/valsartan or shift sacubitril/valsartan to ACEI or ARB.

Outcomes

Death from cardiovascular causes or a first unplanned hospitalization for HF was set as the primary outcome of the current study. In addition, death from cardiovascular causes alone, death from any cause, sudden cardiac death, unplanned re-hospitalization for HF, and frequencies of HF re-hospitalization were collected.

Statistical analysis

Quantitative data were expressed as mean $\pm$ standard deviation or as median and interquartile range, and categorical variables were presented as percentages. Descriptive summaries were presented for different groups of patients. The Student's *t*-test or the Mann–Whitney *U* test was used for comparisons between continuous data, and a chi-square test was used for comparisons between categorical data. A Kaplan–Meier survival analysis was used to plot the survival curves. Multivariate Cox regression analysis with forward selection was performed to assess the predictability of variables on the primary outcome presented as hazard ratios (HRs) and 95% confidence intervals (CIs) using $p < 0.1$ in univariate analyses for inclusion. A *p*-value of <0.05 was considered to be statistically significant. All tests were two-sided. All the statistical analyses were performed using the SPSS Statistics 17.0 software (Chicago, IL, USA).

Results

General information and differences in baseline characteristics

Both groups consisted of the same number of 466 patients. All patients' LVEF were documented less than 40% before enrollment. Differences in baseline characteristics among the two groups are shown in Table 1. Generally, age, gender, vital signs, and past medical histories were similar between Groups A and B patients.

HF medication prescription rates and implantation rates of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) of both groups are shown in Table 1. In Group A patients before the initiation of sacubitril/valsartan therapy, the prescription rates of ACEI/ARB, beta-blocker, MRA were 73.8%, 83.7%, and 71.0%, respectively. The prescription rates of these medications in Group B patients were 69.6%, 77.4%, and 63.2%, respectively. The prescription rates of ivabradine were both

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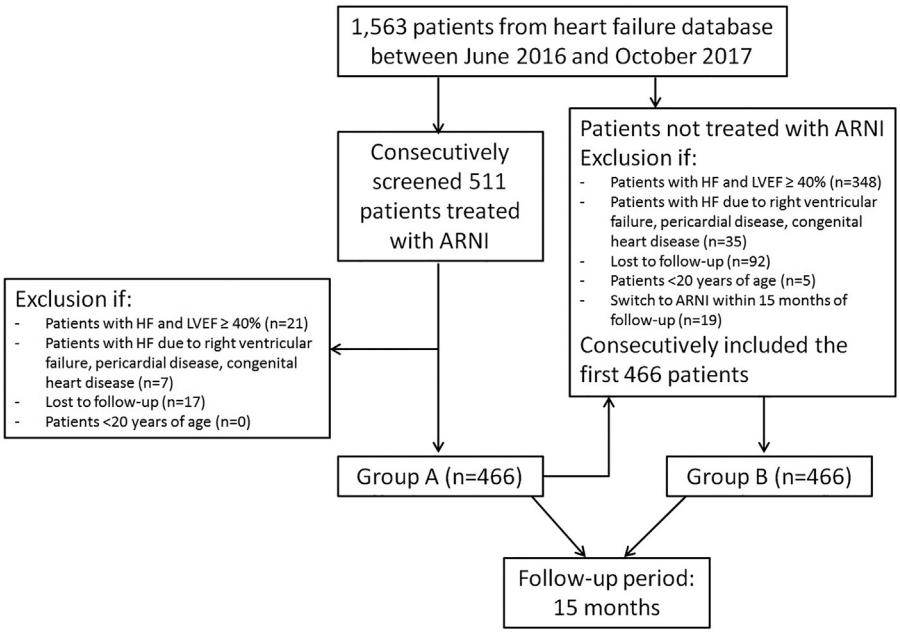

Fig. 1. The flowchart of the current study.

Table 1
Baseline characteristics between different study groups.

	Group A ($N=466$)	Group B ($N=466$)	p-Value
Age (years)	61.3 ± 14.5	62.2 ± 15.3	0.359
Male gender, *n* (%)	351 (75.3)	342 (73.4)	0.500
LVEF (%)	27.0 ± 6.8	27.4 ± 7.1	0.382
NYHA Fc, *n* (%)			
II	367 (78.8)	374 (80.3)	0.570
III/IV	99 (21.2)	92 (19.7)	
Body mass index (kg/m^2)	26.0 ± 4.7	25.8 ± 5.0	0.656
Systolic BP (mmHg)	121.8 ± 19.2	121.9 ± 19.5	0.926
Systolic BP ≥140 mHg, *n* (%)	79 (17)	82 (17.6)	0.944
Systolic BP 130–140 mmHg, *n* (%)	73 (15.7)	72 (15.5)	
Systolic BP 120–130 mmHg, *n* (%)	91 (19.5)	94 (20.2)	
Systolic BP 110–120 mmHg, *n* (%)	100 (21.5)	97 (20.8)	
Systolic BP 100–110 mmHg, *n* (%)	75 (16.1)	66 (14.2)	
Systolic BP <100 mmHg, *n* (%)	48 (10.3)	55 (11.8)	
Heart rate (bpm)	81.0 ± 14.9	82.5 ± 15.5	0.165
Medical history, *n* (%)			
Ischemic cardiomyopathy	190 (40.8)	185 (39.7)	0.738
Diabetes mellitus	172 (36.9)	165 (35.4)	0.633
Hypertension	207 (44.4)	236 (50.6)	0.057
Old myocardial infarction	136 (29.2)	141 (30.3)	0.720
Stroke/TIA	50 (10.7)	54 (11.6)	0.677
Atrial fibrillation	172 (36.9)	151 (32.4)	0.148
Previous HF Hospitalization	304 (65.2)	315 (67.6)	0.446
Previous valvular surgery	53 (11.4)	42 (9.0)	0.234
Hyperlipidemia	240 (51.6)	225 (48.3)	0.310
COPD/asthma	37 (7.9)	52 (11.2)	0.095
Chronic kidney disease	116 (24.9)	133 (28.5)	0.208
GFR (ml/min/1.73 m^2)	67.6 ± 26.0	66.7 ± 31.6	0.622
GFR ≥60 ml/min/1.73 m^2, *n* (%)	291 (62.4)	277 (59.4)	0.006
GFR 30–60 ml/min/1.73 m^2, *n* (%)	139 (29.8)	123 (26.4)	
GFR <30 ml/min/1.73 m^2, *n* (%)	36 (7.7)	66 (14.2)	
Heart failure management, *n* (%)			
Prescription of ACEI/ARB	344 (73.8)	325 (69.7)	0.167
Prescription of beta-blocker	390 (83.7)	360 (77.3)	0.013
Prescription of MRA	331 (71.0)	295 (63.3)	0.012
Prescription of ivabradine	46 (9.9)	46 (9.9)	1.000
ICD or CRT implantation	50 (10.7)	44 (9.4)	0.514

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA Fc, New York Heart Association functional classification; TIA, transient ischemic attack.

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Table 2
Comparison between patients in current study and the PARADIGM-HF trial.

	Current study (N = 932)	PARADIGM-HF (N = 8399)	p-Value
Age (years)	61.8 ± 14.9	63.8 ± 11.5	<0.001
Male gender, n (%)	693 (74.4)	6567 (78.2)	0.008
Region: Asia-Pacific, n (%)	932 (100)	1487 (17.7)	<0.001
LVEF (%)	27.2 ± 6.9	29.6 ± 6.1	<0.001
NYHA Fc, n (%)			
I/II	741 (79.5)	6308 (75.2)	0.004
III/IV	191 (20.5)	2078 (24.8)	
Body mass index (kg/m^2)	25.9 ± 4.9	28.1 ± 5.5	<0.001
Systolic BP (mmHg)	121.8 ± 19.3	122 ± 15	0.708
Systolic BP ≥140 mHg, n (%)	161 (17.3)	1185 (14.1)	<0.001
Systolic BP 130–140 mmHg, n (%)	145 (15.6)	1477 (17.6)	
Systolic BP 120–130 mmHg, n (%)	185 (19.8)	2059 (24.5)	
Systolic BP 110–120 mmHg, n (%)	197 (21.1)	1931 (23.0)	
Systolic BP 100–110 mmHg, n (%)	141 (15.1)	1747 (20.8)	
Systolic BP <100 mmHg, n (%)	103 (11.1)	0 (0)	
Heart rate (bpm)	81.7 ± 15.2	72 ± 12	<0.001
Medical history, n (%)			
Ischemic cardiomyopathy	375 (40.2)	5036 (60.0)	<0.001
Diabetes mellitus	337 (36.2)	2907 (34.7)	0.347
Hypertension	443 (47.5)	5940 (70.7)	<0.001
Old myocardial infarction	277 (29.7)	3634 (43.3)	<0.001
Stroke/TIA	104 (11.2)	725 (8.7)	0.010
Atrial fibrillation	323 (34.7)	3091 (36.8)	0.197
Previous HF hospitalization	619 (66.4)	5274 (62.8)	0.030
GFR (ml/min/1.73 m^2)	67.2 ± 28.9	68	[a]
GFR ≥60 ml/min/1.73 m^2, n (%)	568 (60.9)	5338 (63.6)	<0.001
GFR 30–60 ml/min/1.73 m^2, n (%)	262 (28.1)	3061 (36.4)	
GFR <30 ml/min/1.73 m^2, n (%)	102 (10.9)	0 (0)	

BP, blood pressure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA Fc, New York Heart Association functional classification; TIA, transient ischemic attack.
[a] Standard deviation is missing.

9.9% in Groups A and B. The utilization rates of ICD/CRT were 10.7% in Group A and 9.4% in Group B patients, respectively.

Comparisons of the baseline characteristics between current study and the PARADIGM-HF trial are shown in Table 2. Patients in the PARADIGM-HF trial were older, heavier, more likely to be male, and being diagnosed with ischemic cardiomyopathy than patients in current study. Regarding past medical history, patients in the PARADIGM-HF trial were more likely to have a history of hypertension and myocardial infarction but less likely to have history of stroke, transient ischemic attack, and HF hospitalization than patients in current study. The mean systolic blood pressure (SBP) and glomerular filtration rates (GFR) were similar in the PARADIGM-HF study and the current study. Patients with SBP less than 100 mmHg or GFR less than 30 ml/min/1.73 m^2 were excluded from the PARADIGM-HF trial. In contrast, 11.1% patients in the current study had baseline SBP less than 100 mmHg, and 10.9% patients were in chronic kidney disease stage IV or V.

Outcomes

During a follow-up period of 15 months, death from cardiovascular causes or first unplanned hospitalization for HF occurred in 100 patients in Group A (21.5%) and 144 in Group B [30.9%, hazard ratio in the Group A, 0.66; 95% confidence interval (CI), 0.51–0.85; p = 0.001; Fig. 2A).

A total of 31 deaths (6.7%) in Group A and 59 (12.7%) in Group B were due to cardiovascular causes (hazard ratio, 0.50; 95% CI, 0.33–0.78; p = 0.002; Fig. 2B). Overall, a total of 43 patients (9.2%) in the Group A and 78 patients (16.7%) in the Group B died (hazard ratio for death from any cause, 0.53; 95% CI, 0.36–0.77; p = 0.001; Fig. 2D). A total of 16 deaths (3.4%) in the Group A and 30 (6.4%) in the Group B happened suddenly and unexpectedly (hazard ratio, 0.51; 95% CI, 0.28–0.94; p = 0.027; Fig. 2E). Of the patients receiving sacubitril/valsartan treatment, 87 (18.7%) were hospitalized for heart failure, as compared with 132 patients (28.3%) receiving standard HF without ARNI (hazard ratio, 0.62; 95% CI, 0.48–0.82; $p < 0.001$; Fig. 2C). The effect of sacubitril/valsartan was consistent in preventing the occurrence of first unplanned HF re-hospitalization and decreasing the frequency of HF re-hospitalization (Fig. 2C and F).

Characteristics, management, and outcomes in patients with hypotension

Table 3 shows the characteristics of patients with baseline SBP less than 100 mmHg between the two groups. Although age, gender, vital signs, renal function, and prescription rates of HF medications were similar between the two groups, Group A patients with baseline SBP less than 100 mmHg were more likely to have history of valvular surgery (20.8% vs. 7.3%, p = 0.045), history of CRT and/or ICD implantation (20.8% vs. 5.5%, p = 0.019), and have higher incidence of NYHA Fc III/IV (58.3% vs. 30.9%, p = 0.005) compared with Group B patients with baseline SBP <100 mmHg.

Initial daily dosage of sacubitril/valsartan in patients with baseline SBP less than 100 mmHg was 69.8 ± 33.0 mg. The mean daily dosage of sacubitril/valsartan was up-titrated to 99.4 ± 52.7 mg at 6 months and 112.5 ± 58.7 mg at 12 months. Systolic BP increased from 92.7 ± 6.7 mmHg at baseline to 102.9 ± 18.6 mmHg during follow-up in Group A patients (p = 0.001) and from 92.3 ± 5.1 mmHg to 108.2 ± 16.5 mmHg in Group B patients ($p < 0.001$), respectively.

Fig. 3 shows Kaplan–Meier survival curves of death from cardiovascular causes or first unplanned hospitalization for HF, stratified according to SBP (Fig. 3A and B) and GFR (Fig. 3C and D). Death from cardiovascular causes or first unplanned hospitalization for HF occurred in 18.4% patients in Group A with SBP more than 100 mmHg, 29.7% patients in Group B with SBP more than 100 mmHg, 47.9% patients in Group A with SBP less than

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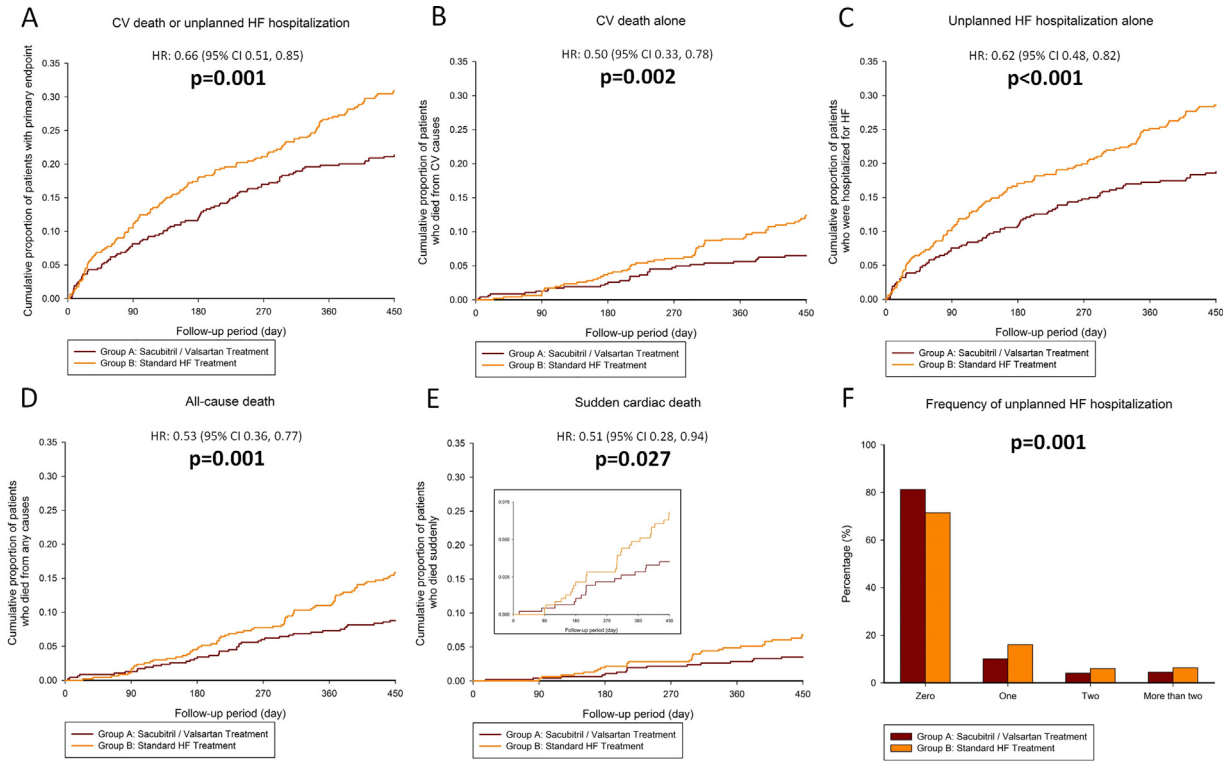

Fig. 2. Kaplan–Meier curves of different clinical outcomes and frequencies of unplanned hospitalization for heart failure in the two groups. CV, cardiovascular; HF, heart failure.

Table 3
Baseline characteristics in patients with baseline SBP <100 mmHg.

	Group A ($N=48$)	Group B ($N=55$)	p-Value
Age (years)	60.6 ± 13.8	62.6 ± 13.9	0.482
Male gender, *n* (%)	36 (75.0)	37 (67.3)	0.389
LVEF (%)	23.1 ± 5.5	24.6 ± 6.8	0.224
NYHA Fc, *n* (%)			
II	20 (41.7)	38 (69.1)	0.005
III/IV	28 (58.3)	17 (30.9)	
Body mass index (kg/m^2)	24.2 ± 4.5	24.1 ± 4.2	0.979
Baseline systolic BP (mmHg)	92.7 ± 6.7	92.3 ± 5.1	0.774
Baseline heart rate (bpm)	80.0 ± 14.8	82.6 ± 14.7	0.411
Medical history, *n* (%)			
Ischemic cardiomyopathy	16 (33.3)	15 (27.3)	0.504
Diabetes mellitus	19 (39.6)	18 (32.7)	0.469
Hypertension	10 (20.8)	14 (25.5)	0.580
Old myocardial infarction	13 (27.1)	14 (25.5)	0.851
Stroke/TIA	6 (12.5)	4 (7.3)	0.508
Atrial fibrillation	22 (45.8)	21 (38.2)	0.432
Previous HF Hospitalization	42 (87.5)	42 (76.4)	0.146
Previous valvular surgery	10 (20.8)	4 (7.3)	0.045
Hyperlipidemia	17 (35.4)	19 (34.5)	0.926
COPD/asthma	8 (16.7)	4 (7.3)	0.138
Chronic kidney disease	12 (25.0)	15 (27.3)	0.794
GFR (ml/min/1.73 m^2)	67.1 ± 23.3	69.7 ± 32.5	0.643
Heart failure management, *n* (%)			
Prescription of ACEI/ARB	26 (54.2)	39 (70.9)	0.079
Prescription of beta-blocker	31 (64.6)	44 (80.0)	0.079
Prescription of MRA	39 (81.3)	46 (83.6)	0.092
Prescription of ivabradine	6 (12.5)	5 (9.1)	0.576
ICD or CRT implantation	10 (20.8)	3 (5.5)	0.019

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA Fc, New York Heart Association functional classification; TIA, transient ischemic attack.

100 mmHg, and 40.0% patients in Group B with SBP less than 100 mmHg ($p < 0.001$). Of the patients with baseline SBP who fulfilled the inclusion criteria of PARADIGM-HF trial, those treated with sacubitril/valsartan had 24% fewer cardiovascular deaths or hospitalizations for HF than those treated with standard HF treatment (hazard ratio, 0.76, 95% CI, 0.66–0.88; $p < 0.001$). Of the patients with severe hypotension and baseline SBP less than 100 mmHg, both groups had similar event rates of cardiovascular deaths or unplanned hospitalizations for HF ($p = 0.331$).

Outcomes in patients with severe kidney disease

Death from cardiovascular causes or first unplanned hospitalization for HF occurred in 20.5% patients in Group A with GFR more than 30 ml/min/1.73 m^2, 26.5% patients in Group B with GFR more than 30 ml/min/1.73 m^2, 33.4% patients in Group A with GFR less than 30 ml/min/1.73 m^2, and 56.6% patients in Group B with GFR less than 30 ml/min/1.73 m^2 ($p < 0.001$). Of the patients with chronic kidney disease stage I to III, Group A patients had 14% fewer cardiovascular deaths or hospitalizations for HF than Group B patients (hazard ratio, 0.86, 95% CI, 0.75–0.99; $p = 0.039$). Of the patients with chronic kidney disease stage IV or V, those treated with sacubitril/valsartan had 28% fewer cardiovascular deaths or hospitalizations for HF than those treated with standard HF treatment (hazard ratio, 0.72, 95% CI, 0.52–0.99; $p = 0.041$).

Factors associated with cardiovascular death or unplanned hospitalization for HF

Multivariate Cox regression analysis was performed to assess the predictability of factors on the death from cardiovascular causes or unplanned hospitalization for HF, and the results are shown in Table 4. Poor baseline heart failure functional class (NYHA Fc III/IV versus II, hazard ratio, 3.37, 95% CI, 2.57–4.42;

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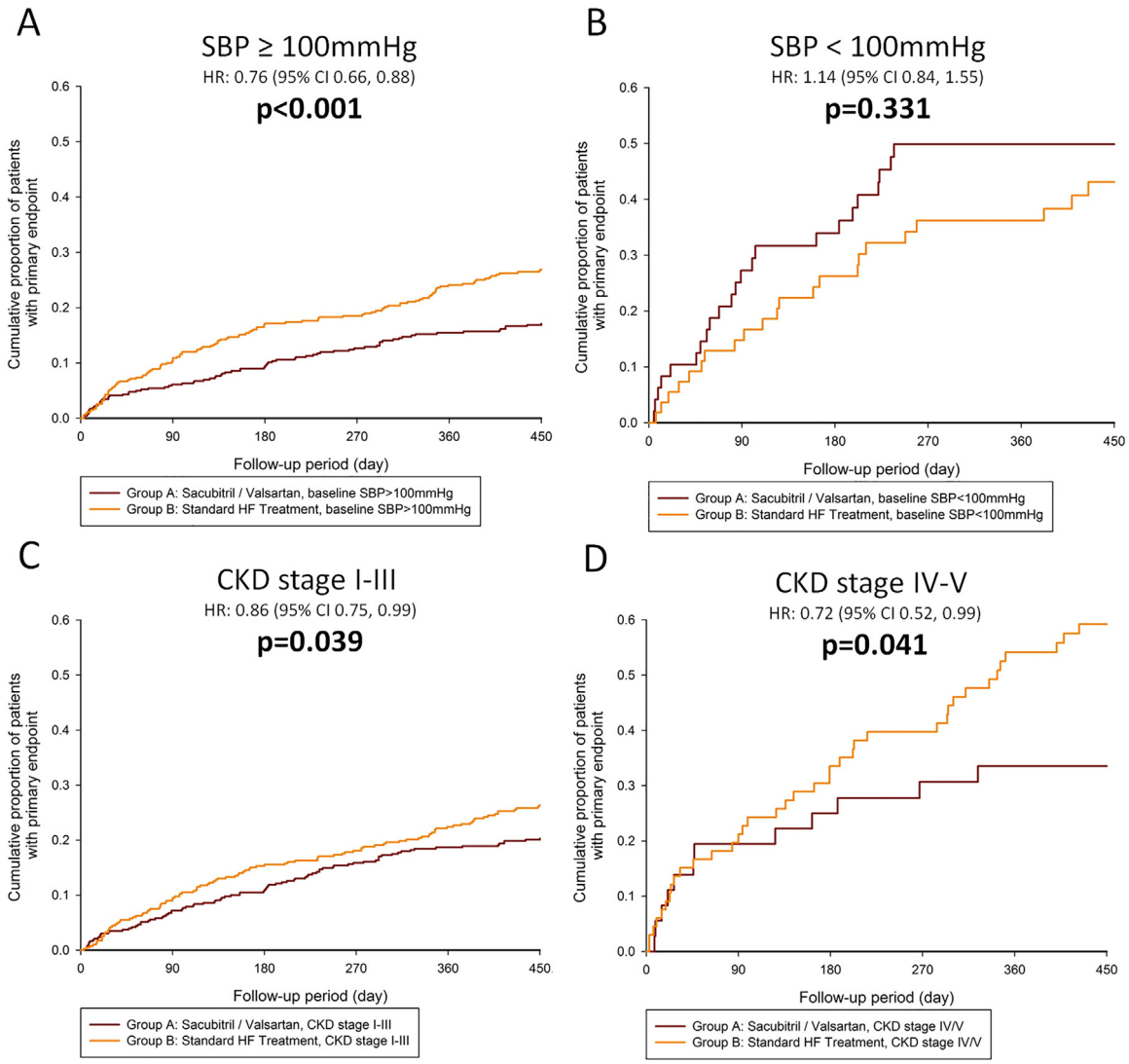

Fig. 3. Kaplan–Meier curves of death from cardiovascular causes or first unplanned hospitalization for heart failure (HF) in the two groups, stratified according to baseline systolic blood pressure (SBP) and chronic kidney disease (CKD) stage.

$p < 0.001$), baseline GFR <30 ml/min/1.73 m^2 (hazard ratio, 2.23, 95% CI, 1.62–3.06; $p < 0.001$), previous HF hospitalization (hazard ratio, 1.44, 95% CI, 1.03–2.00; $p = 0.033$), and past medical history of chronic obstructive pulmonary disease or asthma (hazard ratio, 1.54, 95% CI, 1.08–2.18; $p = 0.017$) were associated with higher incidences of cardiovascular death or unplanned hospitalization for HF. Echocardiographic parameters including lower LVEF and larger left atrial diameter were also associated with higher incidences of cardiovascular death or unplanned hospitalization for HF. Prescription of ARNI (hazard ratio, 0.67, 95% CI, 0.52–0.87; $p = 0.003$) and beta-blocker (hazard ratio, 0.65, 95% CI, 0.49–0.88; $p = 0.004$) could both independently decrease the incidences of cardiovascular death or unplanned hospitalization for HF.

Drug titration pattern and its effect on outcomes

During follow-up, physicians escalated the dosages of sacubitril/valsartan to at least 100 mg twice daily in 194 (41.6%) of Group A patients. A total of 201 (43.1%) Group A patients continued to receive sacubitril/valsartan but the dosage was less than 100 mg twice daily, and 71 (15.2%) Group A patients received dose de-escalation of sacubitril/valsartan treatment.

Fig. 4 shows Kaplan–Meier survival curves of death from cardiovascular causes or first unplanned hospitalization for HF, stratified according to description pattern of sacubitril/valsartan. There are significant differences among the 3 description patterns. Escalation of sacubitril/valsartan was associated with the best clinical outcomes compared with dose de-escalation of sacubitril/valsartan or stationary usage of sacubitril/valsartan.

Discussion

Comparison between PARADIGM-HF trial and current real-world study

Several differences were observed between the PARADIGM-HF trial and the current study. All patients in the current study came from the Asia-Pacific region. Many large-scale HF registry databases showed that compared to Asian patients, Western patients were older, taller, heavier, more likely to be male, and have a history of coronary artery disease and myocardial infarction [15–17]. These features were also noted in the current study. Moreover, in this study we enrolled 10.9% patients with chronic kidney disease stage IV or V and 11.1% patients with baseline SBP less than

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Table 4
Multivariate analysis for factors associated with cardiovascular death or first unplanned hospitalization for heart failure.

	Univariate analysis			Multivariate analysis	
	Event (+)	Event (−)	*p*-Value	HR (95% CI)	*p*-Value
Prescription of ARNI	41.0%	53.2%	0.001	0.67 (0.52–0.87)	0.003
Baseline characteristics					
Age (y/o)	63.8 ± 16.1	61.4 ± 14.4	0.035	–	NS
Baseline NYHA Fc III/IV	45.9%	11.5%	<0.001	3.37 (2.57–4.42)	<0.001
Baseline systolic BP < 100 mmHg	18.0%	8.3%	<0.001	–	NS
Baseline GFR ≤ 30 ml/min/1.73 m^2	21.7%	7.1%	<0.001	2.23 (1.62–3.06)	<0.001
Echocardiographic parameters					
LVEF (%)	25.4 ± 6.9	27.8 ± 6.8	<0.001	0.97 (0.95–0.99)	0.003
LA dimension (mm)	52.5 ± 10.1	48.9 ± 7.3	<0.001	1.03 (1.01–1.04)	<0.001
LVEDD (mm)	59.9 ± 10.3	57.6 ± 8.6	0.018	–	NS
LVESD (mm)	50.5 ± 11.3	47.2 ± 10.3	<0.001	–	NS
PASP (mmHg)	45.5 ± 16.9	38.5 ± 14.8	<0.001	–	NS
Past medical history					
Diabetes mellitus	41.0%	34.0%	0.051	–	NS
Stroke/TIA	14.3%	10.0%	0.066	–	NS
Atrial fibrillation	41.4%	32.3%	0.010	–	NS
Previous HF hospitalization	79.5%	61.8%	<0.001	1.44 (1.03–2.00)	0.033
Hyperlipidemia	43.0%	52.4%	0.012	–	NS
COPD/asthma	16.8%	7.0%	<0.001	1.54 (1.08–2.18)	0.017
Baseline medication					
Prescription of ACEI/ARB	63.0%	74.8%	<0.001	–	NS
Prescription of beta-blocker	72.0%	83.6%	<0.001	0.65 (0.49–0.88)	0.004

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin-receptor and neprilysin inhibition; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LA, left atrial; NYHA Fc, New York Heart Association functional classification; PASP, pulmonary artery systolic pressure; TIA, transient ischemic attack.

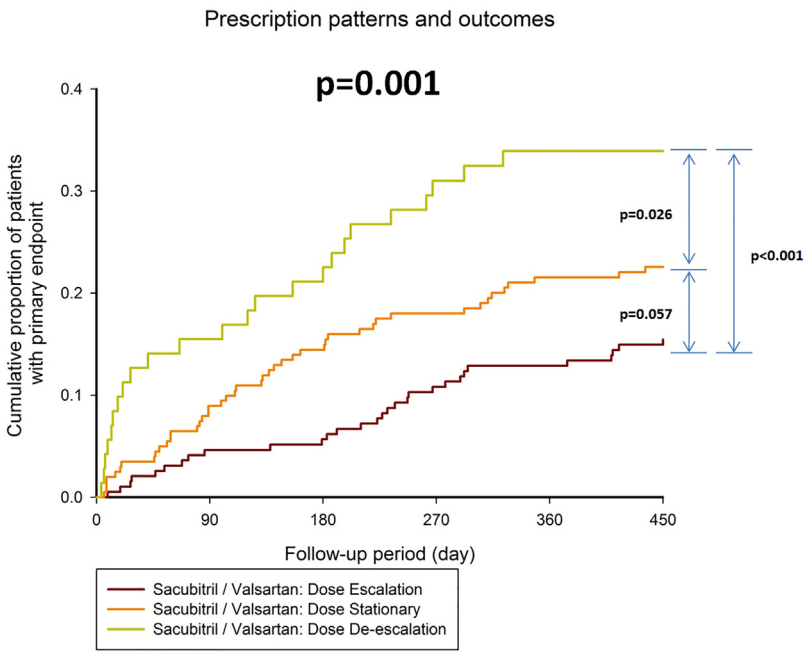

Fig. 4. Kaplan–Meier curves of death from cardiovascular causes or first unplanned hospitalization for heart failure in the two groups, stratified according to prescription pattern of sacubitril/valsartan.

100 mmHg. These patients were generally excluded from the PARADIGM-HF trial and therefore the effectiveness of sacubitril/valsartan was not reported in severely renal impaired and hypotensive patients.

In the PARADIGM-HF trial, death from cardiovascular causes or hospitalization for HF was 20% lower in patients treated with sacubitril/valsartan than enalapril [12]. Our study showed that in real-world practice, Group A patients who were treated with sacubitril/valsartan had 34% lower incidence of death from cardiovascular causes or hospitalization for HF than Group B patients who were treated with standard HF medication without ARNI. Multivariate analysis was performed to show that the prescription of ARNI could independently reduce death from cardiovascular causes or hospitalization for HF by 33%. This result confirmed the effectiveness of sacubitril/valsartan on HFrEF patients in real-world practice.

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Effectiveness of sacubitril/valsartan in patients with advanced kidney disease

In the PARADIGM-HF trial, ARNI showed a favorable renal outcome, as the decrease in GFR during follow-up was less with sacubitril/valsartan compared with enalapril [18]. In clinical practice, concern about renal function deterioration often prohibits the prescription of ACEI/ARB in HF patients, and sacubitril/valsartan has potential benefits on renal function even in chronic kidney disease patients with GFR between 30 and 60 ml/min/1.73 m^2. Regarding cardiovascular outcomes, the relative risk reduction of primary endpoint with sacubitril/valsartan, compared with enalapril, was 0.79 in patients with GFR 30 to 60 ml/min/1.73 m^2 and 0.81 in patients with GFR $\geq$60 ml/min/1.73 m^2 [18].

In the current study, we enrolled patients with all stages of kidney disease. Low baseline GFR $<$30 ml/min/1.73 m^2 was identified as an independent predictor for death from cardiovascular causes or hospitalization for HF by multivariate analysis. Patients with GFR $\geq$30 ml/min/1.73 m^2 who received treatment with sacubitril/valsartan had 14% fewer cardiovascular deaths or hospitalizations for HF than those who received standard therapy. Of the patients with severe renal impairment, GFR $<$30 ml/min/1.73 m^2, treatment with sacubitril/valsartan lowered cardiovascular deaths or hospitalizations for HF by 28%. This was a significant novel finding based of our controlled study. The underlying mechanism of sacubitril/valsartan on further risk reduction in patients with severe chronic kidney disease stage IV or V merits further investigation. Our study emphasized the benefits of sacubitril/valsartan in various kidney disease stages and included patients with significant renal insufficiency which had not been reported in the PARADIGM-HF trial.

Effectiveness of sacubitril/valsartan in patients with low blood pressure

The current study showed that patients with baseline blood pressure more than 100 mmHg, and treated with sacubitril/valsartan had 24% fewer cardiovascular deaths or hospitalizations for HF than those treated with standard HF treatment. However, in the patients with baseline SBP less than 100 mmHg, the prescription of sacubitril/valsartan failed to reduce the rate of cardiovascular deaths or unplanned hospitalizations for HF.

Patients with HF often present with low SBP. Several randomized controlled trials have shown that patients with low blood pressure had worse outcomes than those with higher blood pressure [19,20]. The OPTIMIZE-HF registry showed the poorest prognosis in patients with low SBP of less than 120 mmHg at admission despite medical therapy [21]. On the contrary, a meta-analysis demonstrated a favorable outcome associated with higher SBP [22].

HF patients with significant low SBP might imply the advanced stage of disease due to severe pump failure, and thus treatment strategy should include not only oral guideline-recommended medical therapy, but also ventricular-assisted device and heart transplant. The PARADIGM-HF trial generally excluded advanced HF patients, as baseline SBP needed to be more than 100 mmHg and the entire trial only enrolled 0.7% of patients in NYHA functional class IV. In our current study, sacubitril/valsartan was prescribed to some patients with baseline SBP less than 100 mmHg, but cardiovascular deaths or hospitalizations for HF soon occurred after the initiation of sacubitril/valsartan, particularly during the first 90 days (Fig. 3B). Moreover, Group A patients with baseline SBP less than 100 mmHg were more likely to have history of CRT and/or ICD implantation and had higher incidence of NYHA Fc III/IV compared with the Group B counterpart patients with baseline SBP less than 100 mmHg. It is speculated that those HF patients were too sick and too late to gain further benefit from ARNI.

It is difficult to conclude that ARNI should be avoided in every patient with low SBP, as the hypotensive patient numbers are small in the current study, and therefore the result has to be interpreted with caution. A post hoc analysis of the PARADIGM-HF trial showed the benefit of sacubitril/valsartan over enalapril was consistent across all baseline SBP groups for all outcomes [23]. Moreover, after 4 months of ARNI treatment, SBP would increase in patients with the lowest baseline SBP, indicating the improvement of cardiac output. In patients with low baseline SBP, conservative up-titration regimens and the use of down-titration in patients not initially tolerating sacubitril/valsartan could help to achieve the target dose, as shown in the TITRATION study [24].

Drug titration pattern and its effect on outcomes

Current HF guidelines recommend that disease-modifying medications should be up-titrated to the maximum tolerated dose in order to achieve adequate neuro-hormonal inhibition. Unfortunately, in real-world practice only 30% of HF patients received the target dosage of these drugs [25]. Because a run-in period was designed in the PARADIGM-HF trial, patients would be directly assigned to treatment with either enalapril 10 mg or sacubitril/valsartan 200 mg twice daily after randomization. In real-world practice, sacubitril/valsartan was usually initiated at a low dose to prevent the occurrence of symptomatic hypotension.

However, after initiation of sacubitril/valsartan, different prescription and drug titration patterns existed. Merely 40% patients received dose escalation of sacubitril/valsartan during follow-up, this prescription pattern was associated with a more favorable outcome. A recent HF registry in Taiwan also showed that only a few patients received guideline-recommended medications with $\geq$50% of the target dose, and these patients had better prognosis than those who did not receive adequate escalation [26].

Several barriers for the guideline adherence have been proposed [27,28]. Patient factors including old age, frailty, and comorbidities, could directly lead to intolerance of higher doses of evidence-based drug treatment. Physician factors, such as lack of awareness of treatment goals, focusing on symptom relief rather than reduction of mortality, or fear of adverse effects, might also lead to the inertia to escalate the guideline-recommended dosage. Given the evidence that drug escalation prescription pattern was associated with better prognosis in the current study, establishing scheduled drug-escalation programs for physicians might be helpful to improve clinical outcomes.

Study limitations

There are several limitations in the present study that have to be acknowledged. First, the design was an observational, retrospective survey. Despite covariate adjustment, several factors such as dementia, frailty, or economic status, were not measured in the current study but these factors might affect clinical outcomes. However, either sacubitril/valsartan or other HF management were generally covered by National Health Insurance, the impact of patients' financial status on treatment decision should be minimal. Second, in Group B patients, the reasons for not initiating ARNI or not switching from ACEI/ARB to ARNI therapy had not been recorded, therefore, we could not provide detailed explanations for not prescribing sacubitril/valsartan.

Conclusion

Our study confirmed the effectiveness of sacubitril/valsartan on HFrEF patients in real-world practice for all outcomes, including

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patients with severe chronic kidney disease stage IV or V. Dose of sacubitril/valsartan should be escalated to target in order to achieve the best outcome.

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Conflicts of interest

All the authors declare no conflict of interest.

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