Original Article

Kidney Res Clin Pract 2024;43(5):614-625
pISSN: 2211-9132 • eISSN: 2211-9140
https://doi.org/10.23876/j.krcp.24.021

KIDNEY RESEARCH AND CLINICAL PRACTICE

Cardiac and kidney outcomes after sacubitril-valsartan therapy: recovery of cardiac function relative to kidney function decline

Hyo Jeong Kim[1,*], Eunji Yang[1,*], Hee Byung Koh[2,*], Jong Hyun Jhee[1], Hyeong Cheon Park[1,3], Hoon Young Choi[1,3]

[1]*Division of Nephrology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea*
[2]*Division of Nephrology, Department of Internal Medicine, Catholic Kwandong University International Saint Mary's Hospital, Incheon, Republic of Korea*
[3]*Severance Institute for Vascular and Metabolic Research, Yonsei University College of Medicine, Seoul, Republic of Korea*

Background: Sacubitril-valsartan reduces the risk of cardiovascular mortality among patients with heart failure with reduced ejection fraction (HFrEF). However, its long-term protective effects on cardiac function with concurrent acute kidney injury (AKI) remain unclear. This study investigated the recovery of cardiac function relative to kidney function decline.

Methods: A total of 512 patients with HFrEF who started sacubitril-valsartan or valsartan treatment were enrolled in cohort 1. Additionally, patients who experienced AKI and underwent follow-up transthoracic echocardiography were enrolled in cohort 2. In cohort 1, short- and long-term kidney outcomes were analyzed. For cohort 2, changes in cardiac function in relation to changes in kidney function after drug initiation were analyzed.

Results: The mean age of the patients was 68.3 ± 15.1 years, and 57.4% of the patients were male. AKI occurred in 15.9% of the sacubitril-valsartan group and 12.5% of the valsartan group. After AKI, 78.4% of patients in the sacubitril-valsartan group and 71.4% of those in the valsartan group underwent recovery. Furthermore, cardiovascular outcomes in patients who developed AKI after drug initiation were analyzed in cohort 2. The sacubitril-valsartan group showed a greater improvement in cardiac function compared with the valsartan group (12.4% ± 15.4% vs. 1.4% ± 5.7%, p = 0.046). The ratio of deltas of cardiac and kidney function in the sacubitril-valsartan and valsartan groups were −1.76 ± 2.58 and −0.20 ± 0.58, respectively (p = 0.03).

Conclusion: Patients with HFrEF treated with sacubitril-valsartan exhibited significant improvements in cardiovascular outcomes despite AKI.

Keywords: Acute kidney injury, Heart failure, Sacubitril, Valsartan

Introduction

Heart failure (HF) is a growing public health burden, affecting 1% to 2% of adults, which represents approximately 64.3 million people worldwide [1,2]. HF has a poor prognosis, with a 5-year mortality rate reaching 50% to 75%, and a

Received: January 17, 2024; **Revised:** July 24, 2024; **Accepted:** August 13, 2024
Correspondence: Hoon Young Choi
Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Republic of Korea. E-mail: hychoidr@yuhs.ac
ORCID: https://orcid.org/0000-0002-4245-0339

*Hyo Jeong Kim, Eunji Yang, and Hee Byung Koh contributed equally to this study as co-first authors.

high rate of hospitalization [1]. Cardiac and kidney diseases are closely related, and HF usually develops concurrently with acute kidney injury (AKI). Several mechanisms are involved in worsening cardiac and kidney functions. Hemodynamic changes due to reduced cardiac output affect kidney blood flow, and the activation of neurohormonal systems, such as the renin-angiotensin-aldosterone system (RAAS), leads to sodium and water retention [3–5]. Furthermore, chronic inflammation triggers cellular damage, creating a cycle of worsening kidney dysfunction [4,5].

According to recent guidelines, treatments for HF with reduced ejection fraction (HFrEF) include beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, mineralocorticoid-receptor antagonists, and diuretics [6,7]. In the PARADIGM-HF study, the importance of the first-in-class angiotensin receptor-neprilysin inhibitor, sacubitril-valsartan, was emphasized because of its ability to reduce cardiovascular events and mortality [8–10]. Sacubitril-valsartan is a combination of an angiotensin receptor blocker (ARB) and neprilysin inhibitor that increases the levels of natriuretic peptides, which ultimately suppress angiotensin II through angiotensin blockade. Through these mechanisms, sacubitril-valsartan reduces sodium and water retention, lowers blood pressure (BP), prevents cardiovascular remodeling, and reduces cardiac hypertrophy and fibrosis [11].

Despite its survival benefits in patients with HFrEF, there is limited research on the effectiveness of sacubitril-valsartan in patients with HFrEF with concurrent AKI. Prior studies showing the beneficial effects of sacubitril-valsartan were conducted after excluding patients with poor kidney function [8,12]. Additionally, many studies discontinued sacubitril-valsartan whenever AKI developed [13,14]. Consequently, there is a lack of research on the cardiovascular effects of sacubitril-valsartan in patients with concurrent HF and AKI. Owing to insufficient evidence, adherence to guideline-directed medical therapy is relatively low. Therefore, this study was conducted to investigate the cardiovascular effects and long-term outcomes of patients with HF and AKI after sacubitril-valsartan administration.

Methods

This study was conducted in adherence to the Helsinki Declaration, and the research protocol was approved by the Institutional Review Board of Yonsei University Health System (No. 3-2023-0314). The need for informed consent was waived due to the retrospective study design.

Study patients

Data were retrieved from the Severance Clinical Research Analysis Portal (SCRAP). Clinical data at Severance Hospital are de-identified and loaded on a clinical data warehouse (CDW). The CDW data were accessed and customized through the institution's proprietary software, known as SCRAP. A total of 8,604 patients with HFrEF who first took sacubitril-valsartan or valsartan were retrospectively enrolled from May 2015 to June 2022 using diagnostic codes recorded in the International Classification of Diseases, 10th revision (ICD-10) clinical modification (I50.00 or I50.04). Patients who did not meet the medication usage criteria were excluded from the study cohort (n = 4,075). In addition, patients with end-stage kidney disease (n = 144), no available baseline estimated glomerular filtration rate (eGFR) (n = 1,453), no eGFR follow-up data within 7 days, 8–89 days, and 90 days to 1 year of drug initiation (n = 1,957), and those diagnosed with sepsis, pneumonia, or urinary tract infection within 30 days of drug initiation (n = 71) were further excluded. A total of 512 patients were included in the cohort 1. From this cohort, patients were divided into two groups, AKI and non-AKI groups, based on whether they experienced AKI. The definition of AKI, which is an increase in the serum creatinine level of ≥0.3 mg/dL within 48 hours or >1.5 times than the baseline value within 7 days, followed the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines [15]. Furthermore, we excluded 41 patients without transthoracic echocardiography (TTE) follow-up and one patient who underwent dialysis from the AKI group, creating cohort 2 (n = 42). Each cohort was then categorized into two groups: one group receiving sacubitril-valsartan and the other group receiving valsartan (Fig. 1).

Data collection and measurements

Baseline demographic data and medical history, including age, history of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, and chronic kidney disease (CKD), were collected at drug initiation. Medical

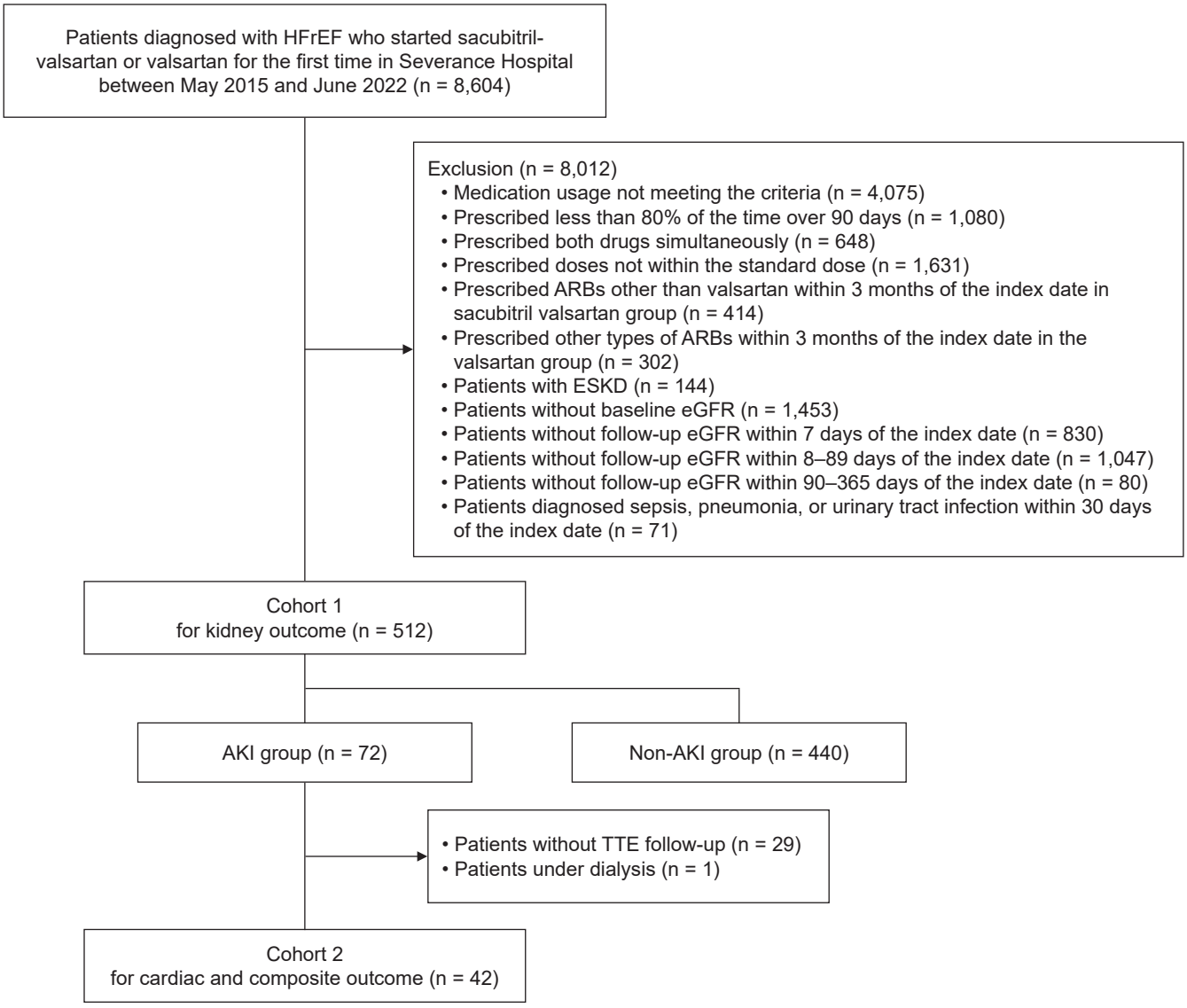

Figure 1. Flow diagram of the study cohort.
AKI, acute kidney injury; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HFrEF, heart failure with reduced ejection fraction; TTE, transthoracic echocardiography.

conditions regarding comorbidities were collected based on ICD-10 codes. Hypertension and diabetes mellitus histories were further collected if they had received any medication. Anthropometric data, including height, weight, and BP measurements, were also collected. Data on blood samples, including hemoglobin, albumin, creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and electrolytes, were obtained prior to drug initiation. Serum creatinine levels were measured using an isotope-dilution mass spectrometry-traceable method, and the eGFR was calculated using the CKD Epidemiology Collaboration equation. The data for eGFR were collected at baseline and within 7 days of drug initiation for AKI evaluation, 8 to 89 days for AKI recovery evaluation, and 90 days to 1 year for long-term kidney outcome evaluation. Additionally, data on TTE measurements were obtained for assessing cardiac function, and ejection fraction (EF) was collected at baseline and during follow-up. Follow-up TTE results were collected between 1 month and 1 year after the initiation of either sacubitril-valsartan

or valsartan treatment.

Exposure and study outcome assessment

The exposure was a start of sacubitril-valsartan or valsartan for the first time. A 3-month washout period was established to exclude prior use of other ARBs before starting the study medication. During this washout period, participants were excluded if they had taken any ARBs other than valsartan in the sacubitril-valsartan group. For the valsartan group, participants were excluded if they had taken any other form of ARBs during the washout period. The index date was defined as the date of first drug initiation (Fig. 2). We further excluded cases where both drugs were prescribed simultanvvzvv eously, and where they were prescribed in doses not within the standard range: 50–400 mg for sacubitril-valsartan and 80–320 mg for valsartan. Moreover, to ensure medication adherence, patients were included in the study if they had medication adherence of 80% or more during the 90-day period starting from the index date.

According to each cohort, various outcomes were analyzed. For cohort 1, short- and long-term kidney changes were analyzed compared to baseline. For short-term kidney outcomes, we assessed the occurrence of AKI within 7 days of drug initiation and further evaluated its recovery within 8 to 89 days after drug initiation in each drug group. AKI recovery was defined as a return of serum creatinine to ≤150% of baseline without dialysis, and non-recovery was defined as the need for dialysis or no return of serum creatinine to ≤150% of baseline. Additionally, long-term kidney outcomes, specifically declines in eGFR to 30%, 40%, or 50% beyond 90 days to 1 year from the index date, were analyzed within each drug group. Lastly, for cohort 2, we analyzed the changes in cardiac function and the composite outcome. Composite outcome was defined as changes in cardiac function in relation to changes in kidney function using the following calculation.

$$\frac{\Delta EF}{\Delta eGFR} = \frac{\frac{\{(EF\ after\ medication)-(EF\ before\ medication\ start)\}}{EF\ before\ medication\ start}}{\frac{\{(eGFR\ within\ 7\ days\ of\ medication)-(eGFR\ before\ medication\ start)\}}{eGFR\ before\ medication\ start}}$$

Statistical analysis

Baseline characteristics and clinical outcomes were presented according to sacubitril-valsartan and valsartan use. Continuous variables are presented as mean ± standard deviation and categorical variables are presented as number and percentage. Two-sample t test was used to evaluate the difference in eGFR and EF between the two groups. Additionally, a paired t test was employed to analyze the chang-

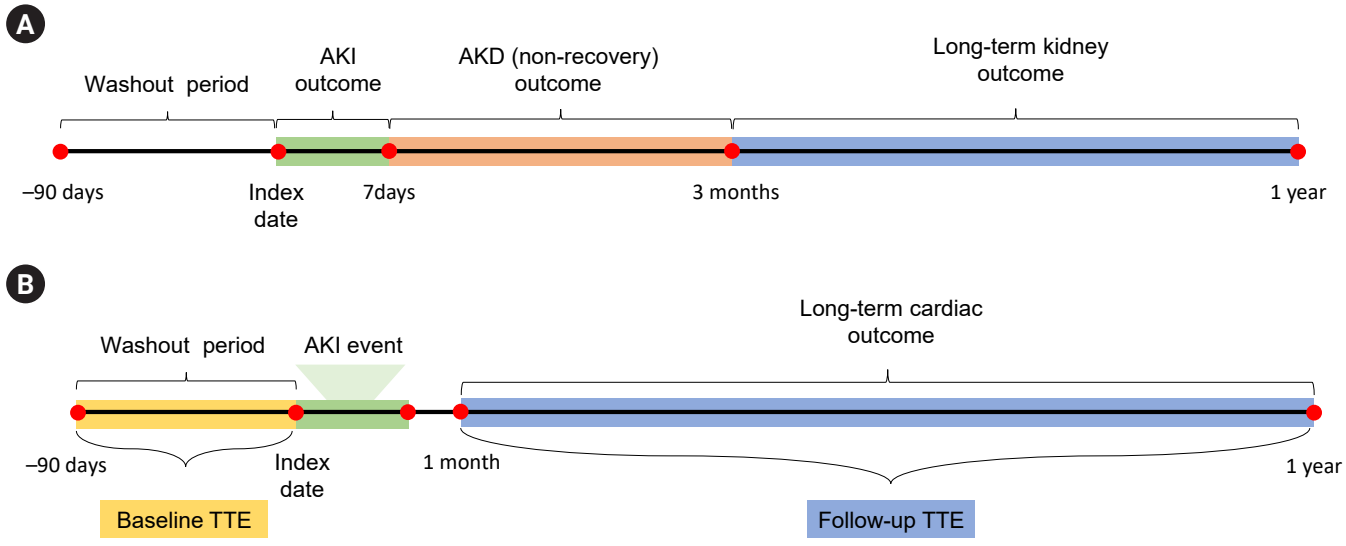

Figure 2. Study flow and outcomes over time. (A) Cohort 1, for kidney outcome. (B) Cohort 2, for cardiac and composite outcomes. AKD, acute kidney disease; AKI, acute kidney injury; TTE, transthoracic echocardiography.

es in eGFR and EF between baseline and follow-up. The ΔEF/ΔeGFR ratio between the two groups was compared using both the two-sample t test and the Mann-Whitney U test for parametric and nonparametric methods, respectively. Moreover, multivariable linear regression was conducted to examine the association between two drugs and ΔEF/ΔeGFR. Adjustments were performed with covariates having a significance level of 0.1 in the univariate analysis, including systolic BP, history of coronary artery disease, hemoglobin, serum calcium, sodium, and the use of spironolactone. All statistical analyses were performed using Stata version 18 (Stata Corp.), with statistical significance determined at p-value of <0.05.

Results

Baseline characteristics

The baseline characteristics of the 512 patients are presented in Table 1. A total of 233 and 279 patients were included in the sacubitril-valsartan and valsartan groups, respectively. The mean age of the patients was 68.3 ± 15.1 years, and 294 of them (57.4%) were male . Patients in the valsartan group were older and had a higher BP. Patients in the sacubitril-valsartan group had a higher prevalence of diabetes mellitus but showed no significant difference in other comorbidities. Baseline laboratory data showed that the mean eGFR of total patients was 76.5 ± 28.7 mL/min/1.73 m^2, and no significant difference between drug groups. Levels of N-terminal pro–B-type natriuretic peptide (NT-proBNP), which is an indicator of the degree of HF, were significantly higher in the sacubitril-valsartan group (7,038.0 ± 9,098.8 vs. 5,067.4 ± 7,954.7, p = 0.03). In addition, anti-hypertensive drugs such as beta-blockers, furosemide, and spironolactone were more frequently used in the sacubitril-valsartan group along with high use of sodium-glucose cotransporter-2 inhibitors.

Cohort 1: short-term kidney outcome after drug initiation

From cohort 1, AKI occurred in 72 patients, with one patient requiring dialysis due to AKI. Patients who experienced AKI were older and had a higher prevalence of CKD compared to the non-AKI group. In laboratory parameters, the AKI group had lower albumin and eGFR levels as well as higher levels of NT-proBNP than the non-AKI group. Additionally, there was no significant difference in medication use between the two groups (Supplementary Table 1, available online). Among AKI patients, 37 (15.9%) were in the sacubitril-valsartan group, and 35 (12.5%) were in the valsartan group, with no significant difference between these two groups (p = 0.28). Furthermore, 29 (78.4%) in the sacubitril-valsartan group, and 25 (17.4%) in the valsartan group recovered from AKI but showed no significant difference between the two groups (Table 2).

Cohort 1: long-term kidney outcome after drug initiation

Long-term changes in kidney function after drug initiation are presented in Table 2. For long-term kidney outcomes, a decline in eGFR from baseline between 90 days and 1 year after the index date across both groups was compared. A decrease in eGFR by 30%, 40%, and 50% occurred in 173 (33.8%), 110 (21.5%), and 63 patients (12.3%), respectively, with a higher rate in the sacubitril-valsartan group compared to the valsartan group. However, no statistically significant difference was observed between the two drug groups. When comparing long-term kidney outcomes separately in the AKI and non-AKI groups, the decline in eGFR was higher in the sacubitril-valsartan group compared to the valsartan group within the AKI cohort; however, these differences did not reach statistical significance (Supplementary Table 2, available online). Similarly, there was no significant difference between the two drugs in the non-AKI cohort.

Kidney function, the eGFR values, over time and the difference compared to baseline are presented in Supplementary Table 3 (available online). In sacubitril-valsartan and valsartan groups, the eGFR decreased by 16.4% and 15.4% from baseline, respectively, 1 month after starting the medication. Compared to the change in eGFR 1 month after medication use, the declines in eGFR at 3, 6, and 12 months were minimal. Throughout all follow-up periods, including baseline, there were no statistically significant differences in eGFR values between the two medication groups. Although a decline in eGFR was observed after medication use, the dosage of the medication for the patients did not decrease; instead, the dose increased in both drug groups. While a decrease in eGFR was observed following the use of the two drugs, the drug concentration

Table 1. Baseline characteristics of cohort 1 according to sacubitril-valsartan and valsartan groups

Characteristic	Total (n = 512)	Sacubitril-valsartan (n = 233)	Valsartan (n = 279)	p-value
Demographic data				
Age (yr)	68.3 ± 15.1	66.4 ± 16.4	69.8 ± 13.8	0.009
Male sex	294 (57.4)	151 (64.8)	143 (51.3)	0.002
Body mass index (kg/m^2)	25.9 ± 15.8	25.3 ± 15.2	26.5 ± 16.3	0.40
Systolic BP (mmHg)	126.3 ± 17.5	118.7 ± 15.6	132.9 ± 16.3	<0.001
Diastolic BP (mmHg)	74.1 ± 10.7	71.6 ± 10.0	76.2 ± 10.8	<0.001
Comorbidities				
Diabetes mellitus	269 (52.5)	151 (64.8)	118 (42.3)	<0.001
Dyslipidemia	201 (39.3)	92 (39.5)	109 (39.1)	0.92
Coronary artery disease	242 (47.3)	118 (50.6)	124 (44.4)	0.16
Chronic kidney disease	140 (27.3)	72 (30.9)	68 (24.4)	0.099
Laboratory parameters				
Hemoglobin (g/dL)	12.1 ± 2.3	12.1 ± 2.3	12.1 ± 2.3	0.99
White blood cells (×10^3/μL)	7.4 ± 3.0	7.1 ± 3.1	7.6 ± 2.9	0.04
Platelet (×10^3/μL)	213.3 ± 96.7	204.7 ± 102.5	220.4 ± 91.2	0.07
Calcium (mg/L)	8.7 ± 0.6	8.7 ± 0.5	8.8 ± 0.6	0.05
Phosphorous (mg/L)	3.7 ± 0.8	3.8 ± 0.8	3.6 ± 0.7	0.003
Albumin (g/dL)	3.8 ± 0.9	3.8 ± 0.5	3.8 ± 1.2	0.48
Uric acid (mg/L)	6.0 ± 2.3	6.4 ± 2.5	5.7 ± 2.2	0.002
Glucose (mg/L)	129.6 ± 54.6	122.6 ± 48.9	135.3 ± 58.3	0.009
eGFR (mL/min/1.73 m^2)	76.5 ± 28.7	76.1 ± 33.1	76.8 ± 24.6	0.79
Total cholesterol (mg/dL)	151.3 ± 44.7	144.8 ± 42.0	156.8 ± 46.3	0.005
LDL-C (mg/dL)	87.5 ± 36.4	80.3 ± 33.7	94.5 ± 37.7	<0.001
HDL-C (mg/dL)	42.6 ± 13.9	41.1 ± 14.1	43.9 ± 13.7	0.07
Na (mmol/L)	138.8 ± 3.6	138.5 ± 3.3	139.1 ± 3.7	0.065
K (mmol/L)	4.07 ± 0.55	4.03 ± 0.52	4.12 ± 0.59	0.40
tCO_2 (mmol/L)	24.4 ± 3.8	25.1 ± 3.8	23.8 ± 3.6	0.002
HbA1c (%)	7.0 ± 1.6	7.0 ± 1.7	7.0 ± 1.5	0.87
C-reactive protein (mg/L)	22.7 ± 40.2	16.8 ± 27.9	28.3 ± 48.5	0.004
NT-proBNP (pg/mL)	6,137.1 ± 8,639.9	7,038.0 ± 9,098.8	5,067.4 ± 7,954.7	0.03
Dipstick				0.02
Negative	213 (45.8)	91 (41.9)	122 (49.2)	
Trace	70 (15.1)	33 (15.2)	37 (14.9)	
1+	90 (19.4)	37 (17.1)	53 (21.4)	
2+	57 (12.3)	32 (14.7)	25 (10.1)	
≥3+	35 (7.5)	24 (11.1)	11 (4.4)	
uACR	983.6 ± 1,774.4	988.7 ± 1,924.3	978.2 ± 1,618.9	0.98
Medications				
Anti-hypertensive agents				
Beta-blockers	387 (75.6)	203 (87.1)	184 (65.9)	<0.001
Calcium channel blockers	245 (47.9)	85 (36.5)	160 (57.3)	<0.001
Furosemide	406 (79.3)	211 (90.6)	195 (69.9)	<0.001
Spironolactone	212 (41.4)	158 (67.8)	54 (19.4)	<0.001
Anti-diabetic agents				
SGLT2 inhibitor	111 (21.7)	97 (41.6)	14 (5.0)	<0.001
Insulin	123 (24.0)	55 (23.6)	68 (24.4)	0.84
Others	164 (32.0)	74 (31.8)	90 (32.3)	0.90

Data are expressed as mean ± standard deviation or number (%).

BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; K, potassium; LDL-C, low-density lipoprotein cholesterol; Na, sodium; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SGLT2, sodium-glucose cotransporter-2; tCO_2, total carbon dioxide; uACR, urinary albumin to creatinine ratio.

Table 2. Short and long-term kidney outcomes after drug initiation in cohort 1

Variable	Total (n = 512)	Sacubitril-valsartan (n = 233)	Valsartan (n = 279)	p-value
Short-term outcome				
AKI[a]	72 (14.1)	37 (15.9)	35 (12.5)	0.28
Non-recovery	18 (25.0)	8 (21.6)	10 (28.6)	0.50
Recovery[b]	54 (75.0)	29 (78.4)	25 (71.4)	
AKI-dialysis	1 (0.2)	1 (0.4)	0 (0)	0.27
Long-term outcome[c], decline eGFR (%)				
>30	173 (33.8)	85 (36.5)	88 (31.5)	0.24
>40	110 (21.5)	54 (23.2)	56 (20.1)	0.39
>50	63 (12.3)	30 (12.9)	33 (11.8)	0.72

Data are expressed as number (%).
AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.
[a]AKI was defined as an increase in the serum creatinine level of ≥0.3 mg/dL within 48 hours or >1.5 times than the baseline value within 7 days. [b]Kidney recovery was evaluated within 8 to 89 days from drug initiation and was defined as a return of serum creatinine to ≤150% of baseline without dialysis. Non-recovery was defined as a need for dialysis or no return of serum creatinine to ≤150% of baseline. [c]Long-term outcome was defined as a period beyond 90 days to 1 year from the index date and assessed the decline in eGFR compared to baseline eGFR.

tended to increase. Additionally, potassium levels showed a slight increase in both drug groups after drug initiation, but there was no significant difference between the groups (Supplementary Table 4, available online).

Cohort 2: changes in kidney and cardiac function in patients with acute kidney injury

The baseline characteristics of patients in cohort 2 are presented in Table 3. The mean age of the patients was 71.9 ± 14.3 years, and 25 of them (59.5%) were male . Patients in the sacubitril-valsartan group had lower systolic BP and had higher use of spironolactone. The differences in cardiac and kidney function between drug initiation and follow-up in each group are shown in Table 4. There was a significant EF improvement in the sacubitril-valsartan group after follow-up (31.3 ± 10.2 vs. 43.2 ± 12.4, p for paired t test < 0.001), while no improvement in the valsartan group (46.6 ± 17.2 vs. 48.6 ± 15.6, p for paired t test = 0.32). Moreover, the difference in EF and ratio between before and after drug initiation showed a significant difference between the two drug groups, showing greater improvement in the sacubitril-valsartan group compared to the valsartan group. This trend was similarly found in both CKD and non-CKD groups. In addition, a decline in eGFR was prominent in both drug groups, with a similar pattern in both the CKD and non-CKD subgroups.

To further analyze the degree of improvement in cardiac function compared to the degree of decrease in kidney function, the ΔEF/ΔeGFR ratio was used. The parametric method showed that the mean ΔEF/ΔeGFR ratio was –1.76 ± 2.58 in the sacubitril-valsartan group and –0.20 ± 0.58 in the valsartan group, indicating that sacubitril-valsartan had a positive effect on improving cardiac function compared to kidney function decline after drug initiation (p = 0.03). The nonparametric method also showed an advantage in long-term cardiac function protection against temporary kidney failure decline, with a ΔEF/ΔeGFR ratio of –0.76 (–1.61 to –0.09) in the sacubitril-valsartan group (p = 0.006) (Table 5). Similar results were found in CKD subgroups; however, there was no statistical significance in non-CKD subgroups. Due to several factors that can influence kidney and cardiac function, we conducted a linear regression analysis. In the multiple regression analysis, after adjusting for all significant variables, the ΔEF/ΔeGFR ratio was significantly 1.27 lower with sacubitril-valsartan compared to valsartan (Supplementary Table 5, available online). This suggests that sacubitril-valsartan leads to a greater improvement in cardiac function relative to kidney function compared to valsartan.

Discussion

In this study, AKI occurred in 14.1% of patients following the use of sacubitril-valsartan and valsartan, but no statistically significant difference was observed between the

Table 3. Characteristics of cohort 2 in the sacubitril-valsartan and valsartan groups

Characteristic	Total (n = 42)	Sacubitril-valsartan (n = 27)	Valsartan (n = 15)	p-value
Demographic data				
Age (yr)	71.9 ± 14.3	70.8 ± 13.6	73.9 ± 15.9	0.51
Male sex	25 (59.5)	16 (59.3)	9 (60.0)	0.96
Body mass index (kg/m^2)	24.5 ± 7.0	25.1 ± 8.2	23.6 ± 4.0	0.52
Systolic BP (mmHg)	124.7 ± 16.1	120.3 ± 14.9	132.6 ± 15.4	0.02
Diastolic BP (mmHg)	72.6 ± 7.8	73.3 ± 8.4	71.4 ± 6.8	0.45
Comorbidities				
Diabetes mellitus	23 (54.8)	16 (59.3)	7 (46.7)	0.43
Dyslipidemia	18 (42.9)	12 (44.4)	6 (40.0)	0.78
Coronary artery disease	20 (47.6)	14 (51.9)	6 (40.0)	0.46
Chronic kidney disease	22 (52.4)	12 (44.4)	10 (66.7)	0.17
Laboratory parameters				
Hemoglobin (g/dL)	11.2 ± 2.2	11.1 ± 2.2	11.4 ± 2.0	0.63
White blood cells (×10^3/μL)	7.3 ± 3.6	7.5 ± 4.0	7.0 ± 2.8	0.65
Platelet (×10^3/μL)	210.3 ± 86.9	213.8 ± 94.0	204.0 ± 75.1	0.73
Calcium (mg/L)	8.5 ± 0.6	8.5 ± 0.7	8.6 ± 0.5	0.81
Phosphorous (mg/L)	3.8 ± 0.8	3.8 ± 0.8	3.7 ± 0.9	0.78
Albumin (g/dL)	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.4	0.96
Uric acid (mg/L)	6.3 ± 2.6	6.3 ± 2.9	6.4 ± 2.0	0.90
Glucose (mg/L)	138.1 ± 72.6	134.1 ± 73.1	146.0 ± 73.9	0.62
eGFR (mL/min/1.73 m^2)	63.4 ± 31.0	67.0 ± 31.5	57.1 ± 30.2	0.33
Total cholesterol (mg/dL)	139.7 ± 46.0	144.8 ± 50.4	130.7 ± 37.0	0.37
LDL-C (mg/dL)	79.9 ± 38.9	74.8 ± 31.0	86.9 ± 48.3	0.44
HDL-C (mg/dL)	40.6 ± 11.9	40.1 ± 10.5	41.2 ± 13.9	0.82
Na (mmol/L)	138.0 ± 4.1	137.4 ± 3.9	138.9 ± 4.4	0.29
K (mmol/L)	3.9 ± 0.7	3.7 ± 0.7	4.1 ± 0.9	0.45
tCO_2 (mmol/L)	24.6 ± 3.0	24.8 ± 3.1	24.2 ± 2.6	0.54
HbA1c (%)	6.8 ± 1.5	7.2 ± 1.7	6.0 ± 0.4	0.04
C-reactive protein (mg/L)	23.5 ± 28.2	20.9 ± 25.5	29.1 ± 33.9	0.41
NT-proBNP (pg/mL)	9,607.1 ± 13,255.5	9,215.3 ± 9,262.8	10,532.9 ± 20,413.5	0.79
Dipstick				0.10
Neg	11 (26.8)	8 (29.6)	3 (21.4)	
Trace	7 (17.1)	6 (22.2)	1 (7.1)	
1+	10 (24.4)	3 (11.1)	7 (50.0)	
2+	8 (19.5)	6 (22.2)	2 (14.3)	
≥3+	5 (12.2)	4 (14.8)	1 (7.1)	
uACR	1,342.5 ± 2,220.9	1,880.3 ± 2,687.8	497.2 ± 755.2	0.21
Medications				
Anti-hypertensive agents				
Beta-blockers	34 (81.0)	24 (88.9)	10 (66.7)	0.08
Calcium channel blockers	17 (40.5)	9 (33.3)	8 (53.3)	0.21
Furosemide	40 (95.2)	26 (96.3)	14 (93.3)	0.67
Spironolactone	23 (54.8)	18 (66.7)	5 (33.3)	0.04
Anti-diabetic agents				
SGLT2 inhibitor	14 (33.3)	11 (40.7)	3 (20.0)	0.17
Insulin	13 (31.0)	8 (29.6)	5 (33.3)	0.80
Others	18 (42.9)	12 (44.4)	6 (40.0)	0.78

Data are expressed as mean ± standard deviation or number (%).

BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; K, potassium; LDL-C, low-density lipoprotein cholesterol; Na, sodium; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SGLT2, sodium-glucose cotransporter-2; tCO_2, total carbon dioxide; uACR, urinary albumin to creatinine ratio.

Table 4. Effects of sacubitril-valsartan and valsartan in patients with acute kidney injury in cohort 2

Variable	Ejection fraction (%)			eGFR (mL/min/1.73 m^2)		
	Sacubitril-valsartan	Valsartan	p-value[d]	Sacubitril-valsartan	Valsartan	p-value
All patients	(n = 27)	(n = 15)		(n = 27)	(n = 15)	
Baseline	31.3 ± 10.2	46.6 ± 17.2	<0.001	67.0 ± 31.5	57.1 ± 30.2	0.33
Follow-up	43.2 ± 12.4	48.6 ± 15.6	0.22	45.2 ± 25.3	37.0 ± 19.5	0.28
Difference[a]	11.9 ± 14.1	2.0 ± 7.5	0.02	−21.7 ± 11.0	−20.1 ± 12.0	0.67
Ratio, mean[b]	0.53 ± 0.70	0.08 ± 0.23	0.02	−0.33 ± 0.11	−0.34 ± 0.10	0.83
p for paired t test[c]	<0.001	0.316		<0.001	<0.001	
CKD patients	(n = 12)	(n = 10)		(n = 12)	(n = 10)	
Baseline	29.2 ± 8.7	50.2 ± 14.8	<0.001	38.1 ± 10.9	39.7 ± 12.3	0.74
Follow-up	41.6 ± 13.9	51.6 ± 14.9	0.12	25.0 ± 7.7	25.2 ± 6.8	0.95
Difference	12.4 ± 15.4	1.4 ± 5.7	0.046	−13.1 ± 5.1	−14.5 ± 7.3	0.59
Ratio, mean	0.53 ± 0.65	0.04 ± 0.11	0.03	−0.34 ± 0.10	−0.34 ± 0.11	0.86
p for paired t test	0.018	0.457		<0.001	0.004	
Non-CKD patients	(n = 15)	(n = 5)		(n = 15)	(n = 5)	
Baseline	33.1 ± 11.3	39.4 ± 21.0	0.39	90.0 ± 21.5	91.9 ± 24.4	0.87
Follow-up	44.5 ± 11.4	42.6 ± 17.0	0.78	61.4 ± 22.5	60.5 ± 14.1	0.93
Difference	11.4 ± 13.4	3.2 ± 10.9	0.23	−28.6 ± 9.4	−31.4 ± 12.1	0.60
Ratio, mean	0.53 ± 0.76	0.16 ± 0.39	0.32	−0.33 ± 0.12	−0.33 ± 0.07	0.97
p for paired t test	0.005	0.55		<0.001	<0.001	

Data are expresses as mean ± standard deviation.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
[a]Difference between baseline and follow-up. [b]The mean value of the ratios of each baseline and follow-up value. [c]p-value between baseline and follow-up. [d]p-value between sacubitril-valsartan and valsartan.

Table 5. Analysis of ΔEF compared to ΔeGFR between each group stratified by parametric and nonparametric methods

Variable	Sacubitril-valsartan	Valsartan	p-value
All patients	(n = 27)	(n = 15)	
Mean	−1.76 ± 2.58	−0.20 ± 0.58	0.03
Median	−0.76 (−1.61 to −0.09)	−0.14 (−0.37 to 0.11)	0.006
CKD patients	(n = 12)	(n = 10)	
Mean	−1.49 ± 1.83	−0.11 ± 0.37	0.03
Median	−1.01 (−1.86 to −0.10)	−0.15 (−0.37 to 0.00)	0.03
Non-CKD patients	(n = 15)	(n = 5)	
Mean	−1.97 ± 3.10	−0.37 ± 0.91	0.28
Median	−0.76 (−1.61 to −0.09)	−0.12 (−0.17 to 0.11)	0.15

Data are expresses as mean ± standard deviation or median (interquartile range).
To compare the ΔEF/ΔeGFR ratio between groups, the two-sample t test and Mann-Whitney U test are employed as parametric and nonparametric methods, respectively. CKD, chronic kidney disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate.

two groups. The majority of patients who developed AKI experienced recovery and their kidney function was stabilized 1 month after drug initiation. Meanwhile, compared with valsartan use, sacubitril-valsartan use resulted in a significant improvement in cardiac function despite kidney function decline.

Sacubitril-valsartan has become a cornerstone therapy for HFrEF as it improves cardiovascular outcomes and mortality [6,8,16,17]. Sacubitril-valsartan acts through a unique dual mechanism that targets the RAAS and natriuretic peptide system [18,19]. First, antagonizing the angiotensin II receptors helps dilate blood vessels, thereby

reducing arterial pressure. Second, the drug acts as an inhibitor of neprilysin, which is an enzyme responsible for breaking down beneficial natriuretic peptides that play a crucial role in promoting diuresis, natriuresis, and vasodilation. By inhibiting neprilysin, sacubitril increases the levels of natriuretic peptides, leading to enhanced diuretic and vasodilatory effects, which reduce preload and afterload on the heart and improve overall cardiac function. This unique dual mechanism improves cardiac remodeling, reduces symptoms of HF, and lowers cardiovascular mortality and morbidity [9,10].

Despite the benefits of sacubitril-valsartan on the heart, many patients experience worsening kidney function. Although several studies have reported that sacubitril-valsartan use results in comparable kidney outcomes to that following ARB and ACE inhibitor use [20–22], AKI after drug initiation has led to an inability to adhere to guideline-directed medical therapy, which poses a significant challenge in the management of patients with HFrEF. However, few studies have examined the beneficial effects, or potential trade-offs, of sacubitril-valsartan on the heart despite the development of kidney failure with sacubitril-valsartan therapy. Preliminary studies suggest that in certain subgroups of patients, particularly those with CKD, sacubitril-valsartan may still confer cardiovascular benefits even in the presence of kidney impairment [23,24]. Regardless, there is a lack of evidence to support the benefits of sacubitril-valsartan on reducing cardiovascular risk that outweighs its tendency to decrease kidney function during the early stages of treatment [25]. Therefore, more studies are needed to establish a solid foundation for maintaining sacubitril-valsartan therapy despite the potential decline in kidney function.

The present study showed an improvement in cardiac function following sacubitril-valsartan initiation despite the development of AKI. The mechanism behind sacubitril-valsartan's positive impact on cardiovascular outcomes despite reduced kidney function remains unclear, but recent studies suggest promising clues. The fact that poor kidney function is associated with increased mortality risk in patients with HF has been consistently revealed through numerous studies [26,27]. However, contrary to this trend, the worsening of kidney function occurring shortly after the use of ARBs reduced the risk of mortality [28–30]. This contrasting outcome can likely be attributed to the fact that kidney function decline owing to HF and RAAS blocker use may involve different mechanisms, with each mechanism potentially exerting distinct effects on cardiac function. Moreover, other studies have even suggested that the more severe the worsening of kidney function, the better the prognosis of patients with HF. This result implies that in the group with severe worsening of kidney function, there might have been an intensified stimulation of the RAAS due to HF before drug administration, leading to a more favorable prognostic effect of using RAAS blockers.

Nevertheless, our study has several limitations. First, as this was a retrospective study, there were differences in baseline characteristics between the groups, and potential confounding factors may not have been completely controlled. Markers that are associated with the prognosis of HF, such as uric acid and NT-proBNP levels were higher in the sacubitril-valsartan group. However, improvement in cardiac function relative to kidney function was greater in the sacubitril-valsartan group compared to the valsartan group, despite having poorer cardiac function, is a noteworthy result. In addition, we further conducted a multivariate regression analysis to adjust for the potential confounding factors. The results of the analysis remained consistent despite these adjustments. Second, the study had a short follow-up duration after drug administration, a small sample size, and limited laboratory data to assess the association between sacubitril-valsartan and clinical outcomes. Despite these limitations, we made efforts to accurately define the medication use and outcomes in order to minimize bias. Lastly, the definition of AKI was based on changes in creatinine levels within 7 days. It is noteworthy that most patients rarely visit outpatient clinics for regular check-ups and undergo laboratory testing within the first 7 days after starting medication. Therefore, if a patient has laboratory tests done within this 7-day period, there is a higher likelihood that they experienced a significant change in their condition or were classified under the high-risk group. Further research and larger studies are warranted to fully elucidate the impact of sacubitril-valsartan on kidney and cardiac outcomes.

In conclusion, this study showed that sacubitril-valsartan use resulted in a similar degree of kidney function decline compared to that observed with valsartan use. In patients who developed AKI, sacubitril-valsartan showed a greater cardiovascular improvement compared to valsartan. Our

findings provide new insights for patients with HFrEF and highlight the complexities in managing both heart failure and kidney function.

Conflicts of interest

Jong Hyun Jhee is the Deputy Editor of *Kidney Research and Clinical Practice* and was not involved in the review process of this article. All authors have no other conflicts of interest to declare.

Funding

This study was supported by a faculty research grant from Yonsei University College of Medicine for 2012 (6-2012-0036) and by a research grant from Gangnam Severance Hospital, Yonsei University College of Medicine.

Data sharing statement

The data are not publicly available since the ownership belongs to Severance Hospital and Gangnam Severance Hospital. However, the data will be shared on reasonable request to the corresponding author.

Authors' contributions

Conceptualization, Data curation, Funding acquisition: HJK, EY, HBK, HYC
Methodology: HJK, HBK, HYC
Formal analysis: HJK, HBK
Supervision: JHJ, HCP, HYC
Writing–original draft: HJK
Writing–review & editing: All authors
All authors read and approved the final manuscript.

ORCID

Hyo Jeong Kim, https://orcid.org/0000-0002-7654-8473
Eunji Yang, https://orcid.org/0000-0001-7039-5093
Hee Byung Koh, https://orcid.org/0000-0002-4510-2823
Jong Hyun Jhee, https://orcid.org/0000-0002-1255-1323
Hyeong Cheon Park, https://orcid.org/0000-0002-1550-0812
Hoon Young Choi, https://orcid.org/0000-0002-4245-0339

References

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GM, Coats AJ. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res* 2023;118:3272–3287.
2. Yan T, Zhu S, Yin X, et al. Burden, trends, and inequalities of heart failure globally, 1990 to 2019: a secondary analysis based on the Global Burden of Disease 2019 Study. *J Am Heart Assoc* 2023;12:e027852.
3. Jentzer JC, Bihorac A, Brusca SB, et al. Contemporary management of severe acute kidney injury and refractory cardiorenal syndrome: JACC Council perspectives. *J Am Coll Cardiol* 2020;76:1084–1101.
4. Rangaswami J, Bhalla V, Blair JE, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2019;139:e840–e878.
5. Kumar U, Wettersten N, Garimella PS. Cardiorenal syndrome: pathophysiology. *Cardiol Clin* 2019;37:251–265.
6. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145:e895–e1032.
7. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599–3726.
8. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993–1004.
9. Lee WC, Liao TW, Chen TY, et al. Sacubitril/valsartan improves all-cause mortality in heart failure patients with reduced ejection fraction and chronic kidney disease. *Cardiovasc Drugs Ther* 2024;38:505–515.
10. Greene SJ, Choi S, Lippmann SJ, et al. Clinical effectiveness of sacubitril/valsartan among patients hospitalized for heart failure with reduced ejection fraction. *J Am Heart Assoc* 2021;10:e021459.
11. Kario K. The sacubitril/valsartan, a first-in-class, angiotensin receptor neprilysin inhibitor (ARNI): potential uses in hypertension, heart failure, and beyond. *Curr Cardiol Rep* 2018;20:5.
12. Solomon SD, McMurray JJ, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019;381:1609–1620.
13. Desai AS, Solomon S, Claggett B, et al. Factors associated with

noncompletion during the run-in period before randomization and influence on the estimated benefit of LCZ696 in the PARADIGM-HF trial. *Circ Heart Fail* 2016;9:e002735.
14. Suzuki K, Claggett B, Minamisawa M, et al. Influence of study discontinuation during the run-in period on the estimated efficacy of sacubitril/valsartan in the PARAGON-HF trial. *Eur J Heart Fail* 2021;23:2085–2090.
15. Ostermann M, Bellomo R, Burdmann EA, et al. Controversies in acute kidney injury: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. *Kidney Int* 2020;98:294–309.
16. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. *Can J Cardiol* 2017;33:1342–1433.
17. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019;380:539–548.
18. Bozkurt B, Nair AP, Misra A, Scott CZ, Mahar JH, Fedson S. Neprilysin inhibitors in heart failure: the science, mechanism of action, clinical studies, and unanswered questions. *JACC Basic Transl Sci* 2023;8:88–105.
19. Zhang R, Sun X, Li Y, et al. The efficacy and safety of sacubitril/valsartan in heart failure patients: a review. *J Cardiovasc Pharmacol Ther* 2022;27:10742484211058681.
20. Tan NY, Deng Y, Yao X, et al. Renal outcomes in patients with systolic heart failure treated with sacubitril-valsartan or angiotensin converting enzyme inhibitor/angiotensin receptor blocker. *Mayo Clin Proc Innov Qual Outcomes* 2021;5:286–297.
21. Bhatt AS, Vaduganathan M, Zhuo M, Fu EL, Solomon SD, Desai RJ. Risk of acute kidney injury among older adults with heart failure and with reduced ejection fraction treated with angiotensin-neprilysin inhibitor vs renin-angiotensin system inhibitor in routine clinical care. *J Card Fail* 2023;29:138–146.
22. Haynes R, Judge PK, Staplin N, et al. Effects of sacubitril/valsartan versus irbesartan in patients with chronic kidney disease. *Circulation* 2018;138:1505–1514.
23. Xu Y, Chen Y, Zhao JW, Li C, Wang AY. Effect of angiotensin-neprilysin versus renin-angiotensin system inhibition on renal outcomes: a systematic review and meta-analysis. *Front Pharmacol* 2021;12:604017.
24. Damman K, Gori M, Claggett B, et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *JACC Heart Fail* 2018;6:489–498.
25. Coca SG. Learning to embrace the decline in eGFR after initiation of therapies for heart failure. *J Am Coll Cardiol* 2023;81:1456–1458.
26. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2000;35:681–689.
27. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 2000;102:203–210.
28. Clark H, Krum H, Hopper I. Worsening renal function during renin-angiotensin-aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction. *Eur J Heart Fail* 2014;16:41–48.
29. Lesogor A, Cohn JN, Latini R, et al. Interaction between baseline and early worsening of renal function and efficacy of renin-angiotensin-aldosterone system blockade in patients with heart failure: insights from the Val-HeFT study. *Eur J Heart Fail* 2013;15:1236–1244.
30. Vardeny O, Wu DH, Desai A, et al. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). *J Am Coll Cardiol* 2012;60:2082–2089.