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Risk stratification by renal function and NYHA class in patients with hypotension initiated on sacubitril/valsartan: a retrospective cohort study from 17 centres in Japan

Koshiro Kanaoka ,[1,2] Takahito Nasu,[3] Atsushi Kikuchi,[4] Takeshi Ijichi,[5] Tatsuhiro Shibata,[6] Keisuke Kida,[7] Nobuyuki Kagiyama,[8,9] Wataru Fujimoto,[10,11] Syunsuke Ishii,[12] Yoshitaka Iwanaga,[1] Yoshihiro Miyamoto,[1] Shingo Matsumoto [13]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/openhrt-2024-002764).

To cite: Kanaoka K, Nasu T, Kikuchi A, *et al*. Risk stratification by renal function and NYHA class in patients with hypotension initiated on sacubitril/valsartan: a retrospective cohort study from 17 centres in Japan. *Open Heart* 2024;**11**:e002764. doi:10.1136/openhrt-2024-002764

Received 25 May 2024
Accepted 6 October 2024

For numbered affiliations see end of article.

Correspondence to
Dr Koshiro Kanaoka; kanaokak@ncvc.go.jp

ABSTRACT

Background Patients with heart failure exhibiting low systolic blood pressure (SBP) have a poor prognosis. Sacubitril/valsartan reduces cardiovascular events; however, its use in patients with low SBP has not been fully examined. Therefore, in this study, we aimed to investigate the association between baseline SBP and adverse events (AEs) in patients starting sacubitril/valsartan therapy using data from a real-world registry in Japan.

Methods We analysed data from a multicentre retrospective study, including patients who initiated sacubitril/valsartan between August 2020 and August 2021. The patients were categorised into five groups based on their baseline SBP (<100, 100–109, 110–119, 120–129 and ≥130 mm Hg). The composite of AEs occurring within 3 months according to baseline SBP and the patient characteristics associated with AEs in a baseline SBP <110 mm Hg were analysed.

Results Among the 964 patients newly prescribed sacubitril/valsartan, the median (IQR) age was 73 (61–80) years, and 388 (40.2%) patients had a baseline SBP <110 mm Hg. AEs occurred in 24% (n=232) of patients. The adjusted ORs for all AEs were 1.91 (95% CI (CI) 1.13–3.23; p=0.02) for the SBP <100 mm Hg group and 3.33 (95% CI 1.98 to 5.59; p<0.001) for the SBP 100–109 mm Hg group, compared with the SBP 110–119 mm Hg group. In patients with a baseline SBP <110 mm Hg, factors associated with an increased risk of AEs included a higher New York Heart Association class (II, III or IV) and a lower estimated glomerular filtration rate <30 mL/min/1.73 m^2.

Conclusions Caution is needed when initiating sacubitril/valsartan in patients with lower baseline SBP. The severity of heart failure and kidney function may be useful for risk stratification in these high-risk patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sacubitril/valsartan has demonstrated benefits in patients with heart failure and reduced ejection fraction.

⇒ Sacubitril/valsartan consistently shows benefits across the baseline systolic blood pressure (SBP), but its use in patients with low SBP is controversial, as such patients were excluded from clinical trials.

WHAT THIS STUDY ADDS

⇒ Among all included patients who started sacubitril/valsartan, 20.7% had a baseline SBP <100 mm Hg, and 19.5% had a baseline SBP of 100–109 mm Hg.

⇒ While patients with a lower baseline SBP (<110 mm Hg) were at higher risk for adverse events, those with New York Heart Association (NYHA) class I and an estimated glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2 had a lower incidence of adverse events, even in the lower baseline SBP group.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Initiating sacubitril/valsartan in patients with lower baseline SBP requires careful consideration, and assessing the baseline NYHA class and estimated GFR may help guide the safer use of sacubitril/valsartan in these patients.

INTRODUCTION

Low blood pressure (BP) is relatively common in patients with heart failure (HF), particularly in those with a reduced ejection fraction.[1 2] Various factors contribute to low BP in such patients, including reduced cardiac function, treatment-induced vasodilation and hypovolaemia. Previous studies have consistently demonstrated that patients with low BP tend to have poor outcomes.[3 4] Achieving the target doses of HF medications in patients with low BP can improve outcomes but remains challenging owing to the risk of

potential BP reduction associated with higher doses of HF medications. Moreover, there is insufficient evidence regarding the optimal dosing for patients with HF and low BP, leading to hesitancy among physicians when initiating or adjusting medications that might further lower BP.

Sacubitril/valsartan has demonstrated benefits in patients with HF and reduced ejection fraction,[5 6] but its use in patients with lower systolic BP (SBP) needs further debate. Clinical trials have reported a higher incidence of symptomatic hypotension in the sacubitril/valsartan group than in the control group.[5 7] The use of sacubitril/valsartan has consistent benefits across the baseline SBP; however, hypotension frequently occurs in patients with lower SBP.[8 9] Furthermore, some patients withdrew from the trials owing to hypotension before randomisation, and patients with a baseline SBP <100 mm Hg were excluded. These findings suggest a potential risk of adverse events (AEs) when initiating sacubitril/valsartan in patients with low BP. However, real-world practice patterns on the use of studies on sacubitril/valsartan in relation to BP and studies demonstrating the safety of sacubitril/valsartan focusing on low BP are limited.

Therefore, this study aimed to investigate sacubitril/valsartan use in real-world settings according to the baseline SBP. We analysed the relationship between baseline SBP and the risk of AEs, especially in patients with a lower baseline SBP.

METHODS

Study design and patients

We used data from the Real-World Evidence of Angiotensin Receptor-Neprilysin Inhibitor in Patients with Heart Failure (REVIEW-HF), a multicentre retrospective cohort study conducted during the post-marketing period in Japan.[10] The study protocol was prospectively registered with UMIN-CTR (UMIN000047636). This study included patients aged ≥20 years with HF who were newly prescribed sacubitril/valsartan at 17 facilities in Japan between August 2020 and August 2021. Patients who had received sacubitril/valsartan before the post-marketing period, such as those who participated in clinical trials, were excluded from this registry. In Japan, sacubitril/valsartan is approved for patients with HF regardless of left ventricular ejection fraction (LVEF) or baseline SBP. Cardiologists at each facility reviewed patients' charts and recorded data using an electronic data capture system. Patients with missing variables were excluded from the analysis. Patients were categorised into five groups based on their baseline SBP (<100, 100–109, 110–119, 120–129 or ≥130 mm Hg), and subsequent analyses were conducted.

Outcomes and other variables

The primary outcome of this study was a composite of AEs, including hypotension, hyperkalaemia, renal events and angioedema, occurring within 3 months of initiating sacubitril/valsartan. The definitions for these AEs were as follows: (1) hypotension was defined as a reduction in SBP to <90 mm Hg if the baseline SBP was ≥100 mm Hg, or an SBP reduction of >10% if the baseline SBP was <100 mm Hg; (2) hyperkalaemia was defined as a potassium level ≥5.6 mEq/L; (3) renal events were defined as a reduction in estimated glomerular filtration rate (eGFR) of ≥50% of the baseline value, an absolute reduction in eGFR of >30 mL/min/1.73 m^2, an eGFR of<20 mL/min/1.73 m^2 or the initiation of haemodialysis.

We extracted the following data: age, sex, BP, sacubitril/valsartan dose, body mass index, New York Heart Association (NYHA) class, HF history and aetiology, comorbidities, baseline medications, laboratory data and LVEF. Furthermore, we analysed data on the up-titration of sacubitril/valsartan, the maximum dose achieved and the discontinuation of the medication within 1 year.

Statistical analysis

Patient baseline clinical characteristics and outcomes are presented as means±SD or medians (IQR) for continuous variables and as frequencies and percentages for categorical variables. Trends in categorical variables were assessed using the Cochran–Armitage trend or Cuzick's test, while the Jonckheere–Terpstra trend test was used for continuous variables.

First, the association between baseline SBP and outcomes was analysed in all included patients. Multivariable logistic analysis was conducted, adjusting for age, sex, initiation setting (inpatient or outpatient), NYHA category, hypertension, diabetes mellitus, atrial fibrillation, eGFR and LVEF based on prior studies.[11–13] Restricted cubic spline analysis with four knots placed at 5%, 35%, 65% and 95% was used to explore potential non-linear relationships between baseline SBP and the primary outcome.[14] Second, patients with lower SBP (<110 mm Hg) had higher rates of cardiovascular events and AEs in the prior study.[8] We focused on patients with a baseline SBP <110 mm Hg in our cohort. We divided these patients into two groups based on the adverse events experienced within 3 months, and the patient characteristics associated with these events were described. Outcomes associated with AEs were analysed using multivariable logistic analysis if patient characteristics were significant in univariate analysis (p<0.05). Finally, we analysed changes in SBP, N-terminal-pro brain natriuretic peptide (NT-proBNP) and LVEF at follow-up time points. All analyses were conducted using Stata V.17 (Stata Corp., College Station, Texas, USA), and a two-sided p value <0.05 was considered statistically significant.

Ethical approval and informed consent

Informed consent was obtained through an opt-out process at each facility owing to the retrospective nature of this study.

Table 1 Baseline characteristics according to systolic blood pressure category

	Available N	<100 mm Hg	100–109 mm Hg	110–119 mm Hg	120–129 mm Hg	≥130 mm Hg	P for trend
N		200	188	171	160	245	
Age (years)	964	70 (58–77)	71 (60–79)	74 (63–82)	74 (63–81)	75 (64–82)	<0.001
Female	964	59 (29.5)	51 (27.1)	54 (31.6)	44 (27.5)	75 (30.6)	0.75
Systolic blood pressure (mm Hg)	964	90.9±6.1	104.1±2.8	114.4±3.0	123.4±3.0	143.7±12.6	<0.001
Diastolic blood pressure (mm Hg)	955	57.4±8.0	63.8±9.5	66.6±11.0	72.1±12.5	79.2±14.5	<0.001
Heart rate (bpm)	932	75.4±14.1	74.8±15.8	73.5±14.1	73.7±13.9	74.5±14.2	0.45
Initiation of sacubitril/valsartan during hospitalisation	964	108 (54.0)	96 (51.1)	92 (53.8)	79 (49.4)	110 (44.9)	0.06
Initial daily dose	964						<0.001
≤50 mg		60 (30.0)	23 (12.2)	17 (9.9)	9 (5.6)	10 (4.1)	
100 or 150 mg		135 (67.5)	156 (83.0)	146 (85.4)	142 (88.8)	215 (87.8)	
200 or 250 mg		5 (2.5)	7 (3.7)	7 (4.1)	6 (3.8)	18 (7.3)	
300 or 400 mg		0 (0.0)	2 (1.1)	1 (0.6)	3 (1.9)	2 (0.8)	
Body mass index (kg/m^2)	923	22.1 (20.1–25.0)	22.3 (19.8–25.9)	22.9 (20.5–25.3)	23.6 (20.5–25.9)	22.8 (20.5–26.2)	0.02
NYHA class	953						0.002
I		20 (10.0)	27 (14.6)	21 (12.5)	31 (19.4)	39 (16.2)	
II		86 (43.0)	92 (49.7)	90 (53.6)	78 (48.8)	118 (49.2)	
III		69 (34.5)	55 (29.7)	47 (28.0)	44 (27.5)	65 (27.1)	
IV		25 (12.5)	11 (5.9)	10 (6.0)	7 (4.4)	18 (7.5)	
History of HF hospitalisation	963	153 (76.9)	124 (66.0)	107 (62.6)	107 (66.9)	131 (53.5)	<0.001
Time since HF diagnosis	960						<0.001
<1.5 years		76 (38.0)	91 (48.7)	85 (50.0)	73 (46.2)	143 (58.4)	
1.5–4 years		12 (6.0)	15 (8.0)	24 (14.1)	22 (13.9)	37 (15.1)	
5–9 years		46 (23.0)	36 (19.3)	27 (15.9)	30 (19.0)	31 (12.7)	
≥10 years		66 (33.0)	45 (24.1)	34 (20.0)	33 (20.9)	34 (13.9)	
Aetiology of HF	964						
Ischaemic cardiomyopathy		56 (28.0)	76 (40.4)	62 (36.3)	61 (38.1)	92 (37.6)	0.12
Valvular heart disease		28 (14.0)	42 (22.3)	41 (24.0)	39 (24.4)	49 (20.0)	0.16
Dilated cardiomyopathy		76 (38.0)	52 (27.7)	49 (28.7)	37 (23.1)	40 (16.3)	<0.001
Comorbidities							
Hypertension	962	78 (39.0)	107 (56.9)	110 (65.1)	117 (73.1)	210 (85.7)	<0.001
Diabetes mellitus	964	57 (28.5)	68 (36.2)	71 (41.5)	60 (37.5)	79 (32.2)	0.51
Atrial fibrillation	964						0.12
None		111 (55.5)	100 (53.2)	89 (52.0)	87 (54.4)	149 (60.8)	
Paroxysmal		35 (17.5)	44 (23.4)	39 (22.8)	37 (23.1)	47 (19.2)	
Persistent		54 (27.0)	44 (23.4)	43 (25.1)	36 (22.5)	49 (20.0)	
Medications	964						
ACE inhibitors		102 (51.0)	74 (39.4)	59 (34.5)	52 (32.5)	66 (26.9)	<0.001
ARBs		91 (45.5)	101 (53.7)	105 (61.4)	106 (66.2)	176 (71.8)	<0.001
Beta blockers		179 (89.5)	155 (82.4)	145 (84.8)	135 (84.4)	183 (74.7)	0.001
Loop diuretics		165 (82.5)	151 (80.3)	133 (77.8)	128 (80.0)	177 (72.2)	0.01
MRAs		159 (79.5)	133 (70.7)	123 (71.9)	98 (61.3)	143 (58.4)	<0.001
SGLT2 inhibitors		83 (41.5)	68 (36.2)	76 (44.4)	48 (30.0)	60 (24.5)	<0.001

Continued

Table 1 Continued

	Available N	<100 mm Hg	100–109 mm Hg	110–119 mm Hg	120–129 mm Hg	≥130 mm Hg	P for trend
Haemoglobin (g/L)	964	125 (111–141)	130 (114–144)	127 (109–143)	124 (107–144)	127 (107–145)	0.59
Potassium (mEq/L)	963	4.3 (4.0–4.6)	4.3 (4.0–4.6)	4.2 (3.9–4.6)	4.2 (3.9–4.5)	4.2 (3.8–4.6)	0.06
Estimated GFR (mL/min/1.73 m^2)	964	45 (32–62)	46 (31–60)	46 (33–62)	45 (33–58)	47 (35–60)	0.66
BNP (pg/mL)	449	441.4 (222.0–809.4)	369.4 (193.0–649.0)	330.8 (155.0–681.6)	291.8 (87.8–770.5)	347.8 (159.6–668.8)	0.05
NT-pro BNP (pg/mL)	737	2753 (1,408–5,642)	2305 (1,126–3,904)	2050 (731–3,994)	2349 (837–4,334)	1978 (1,054–4,779)	<0.001
LVEF (%)	962	30 (24–40)	34 (25–46)	36 (29–48)	37 (29–48)	44 (35–59)	<0.001
LVEF category	962						<0.001
HFrEF (EF <40%)		147 (73.5)	116 (61.7)	101 (59.1)	88 (55.0)	86 (35.4)	
HFmrEF (EF: 40–49%)		29 (14.5)	40 (21.3)	32 (18.7)	39 (24.4)	67 (27.6)	
HFpEF (EF ≥50%)		24 (12.0)	32 (17.0)	38 (22.2)	33 (20.6)	90 (37.0)	

Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.
ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro brain natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose transporter 2.

RESULTS

Patient characteristics

Among the 995 patients aged ≥20 years with HF, 31 with missing baseline SBP were excluded, and 964 were analysed. Table 1 presents the baseline characteristics of patients in each baseline SBP category. The median (IQR) age was 73 (61–80) years, and 289 (29.4%) patients were women. The mean±SD SBP was 116±20 mm Hg. Among all included patients, 200 (20.7%) had a baseline SBP <100 m Hg and 188 (19.5%) had a baseline SBP of 100–109 mm Hg. Patients with lower SBP were younger and had a higher prevalence of NYHA class III or IV, a history of hospitalisation owing to HF, dilated cardiomyopathy and HF with reduced ejection fraction (LVEF of <40%) than those with higher baseline SBP. Furthermore, patients with lower SBP were more likely to be treated with ACE inhibitors, beta blockers, mineralocorticoid receptor antagonists, loop diuretics and sodium-glucose transporter 2 inhibitors. No difference in baseline eGFR and potassium levels between SBP categories was observed.

Baseline SBP and safety events

Table 2 provides an overview of the relationship between the baseline SBP category and AEs occurring within 3 months of initiating sacubitril/valsartan. AEs were observed in 24% (n=232) of the patients, with hypotension being the most frequent event (n=193). The median (IQR) length from sacubitril/valsartan initiation to any AE within 90 days was 14 (5–29) days. The proportion of AEs was higher in the lower SBP group than in the higher SBP group. Adjusted ORs for all AEs were 1.91 (95% CI 1.13 to 3.23, p=0.02) for the SBP <100 mm Hg group and 3.33 (95% CI 1.98 to 5.59, p<0.001) for the SBP 100–109 mm Hg group, compared with the SBP 110–119 mm Hg group (figure 1). The cubic spline curve indicated that the adjusted OR for the primary outcome increased with lower SBP, while it remained stable for higher SBP (online supplemental figure 1). Hypotension was more prevalent in the lower SBP groups (31% in the SBP <100 mm Hg group and 39% in the SBP 100–109 mm Hg group). Symptomatic hypotension was predominantly observed in the SBP <100 mm Hg group (P for trend <0.001). Furthermore, renal events frequently occurred in the SBP<110 mm Hg group (P for trend<0.007). Among all renal events, the proportion of an eGFR absolute reduction of >30 mL/min/1.73 m^2 or an eGFR of <20 mL/min/1.73 m^2 was higher in the lower SBP groups (P for trend=0.002).

Online supplemental table 1 details the sacubitril/valsartan dosing and discontinuation by baseline SBP category. Up-titration of sacubitril/valsartan was less frequent in the lower SBP group (n=103, 51.5% in the SBP <100 mm Hg group) than in the higher SBP group (n=186, 75.9% in the SBP ≥130 mm Hg) group. After adjusting for covariates, the ORs for up-titration of sacubitril/valsartan were 0.52 (95% CI 0.34 to 0.79, p=0.002) for the SBP <100 mm Hg group and 0.62 (95% CI 0.40 to 0.95, p=0.03) for the SBP 100–109 mm Hg group, relative to the SBP 110–119 mm Hg group (online supplemental table 2). In the SBP <100 mm Hg group, >50% of patients were prescribed a maximum daily dose of sacubitril/valsartan of <200 mg. The adjusted ORs for discontinuation of sacubitril/valsartan were 1.97 (95% CI 1.20 to 3.23, p=0.008) for the SBP <100 mm Hg group and 1.89 (95%

Table 2 Adverse events within 3 months according to baseline systolic blood pressure category

	<100 mm Hg	100–109 mm Hg	110–119 mm Hg	120–129 mm Hg	≥130 mm Hg	P for trend
N	200	188	171	160	245	
Any adverse events	71 (35.5)	79 (42.0)	34 (19.9)	27 (16.9)	21 (8.6)	<0.001
Hypotension*	62 (31.0)	74 (39.4)	30 (17.5)	17 (10.6)	10 (4.1)	<0.001
Symptomatic hypotension	32 (16.0)	23 (12.2)	9 (5.3)	5 (3.1)	3 (1.2)	<0.001
Hyperkalaemia	9 (4.5)	8 (4.3)	1 (0.6)	5 (3.1)	9 (3.7)	0.24
Potassium ≥5.6 mEq/L	6 (3.0)	6 (3.2)	1 (0.6)	3 (1.9)	8 (3.3)	0.94
Potassium ≥6.0 mEq/L	3 (1.5)	2 (1.1)	0 (0.0)	2 (1.2)	1 (0.4)	0.28
Renal events	13 (6.5)	13 (6.9)	6 (3.5)	6 (3.8)	5 (2.0)	0.007
eGFR reduction ≥50%	2 (1.0)	3 (1.6)	1 (0.6)	2 (1.2)	2 (0.8)	0.73
eGFR absolute reduction >30 mL/min/1.73 m^2 or eGFR <20 mL/min/1.73 m^2	11 (5.5)	9 (4.8)	5 (2.9)	2 (1.2)	3 (1.2)	0.002
Dialysis	0 (0.0)	1 (0.5)	0 (0.0)	2 (1.2)	0 (0.0)	0.75
Angioedema	1 (0.5)	2 (1.1)	0 (0.0)	1 (0.6)	0 (0.0)	0.27

Data are presented as n (%) for categorical measures.
*SBP reduction of <90 mm Hg if the baseline SBP is ≥100 mm Hg or SBP reduction of >10% if the baseline SBP <100 mm Hg.
eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

CI 1.14 to 3.14, p=0.013) for the SBP 110–119 mm Hg group, compared with the SBP 110–119 mm Hg group. Hypotension was the primary reason for discontinuation in the lower SBP groups.

Patients with low baseline SBP and factors associated with AEs

Patients with lower SBP (<110 mm Hg) comprised 40.2% of the cohort and had a higher incidence of AEs (38.7%). We focused on this subgroup to analyse patient characteristics associated with AEs. Patients without AEs were younger, had a higher body mass index, higher eGFR, a lower proportion of in-hospital initiation and NYHA class III or IV, and a higher baseline use of beta blockers (table 3). Table 4 shows baseline clinical factors associated with AEs within 3 months based on multivariable logistic regression. Higher NYHA class (II, III or IV) and lower eGFR (<30 mL/min/1.73 m^2) were associated with AEs. Specifically, AEs occurred in 40 out of 147 (27.2%) patients with NYHA class I and an eGFR of ≥30 mL/min/1.73 m^2 but occurred in 27 out of 46 (58.7%)

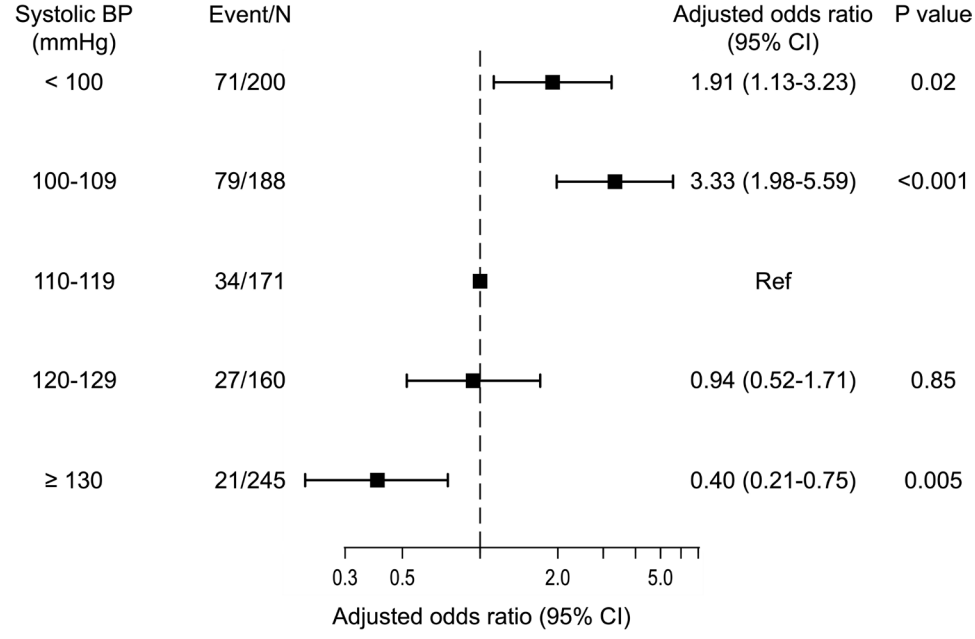

Figure 1 The adjusted OR for AEs within 3 months according to the baseline systolic blood pressure category. The OR for AEs increased in patients with SBP <110 mm Hg. AE, adverse event; BP, blood pressure.

Table 3 Baseline characteristics according to adverse events in patients with baseline systolic blood pressure <110 mm Hg

	Any adverse events (–)	Any adverse events (+)	P value
N	238	150	
Age (years)	70 (58–77)	72 (62–80)	0.045
Female	68 (28.6)	42 (28.0)	0.90
Systolic blood pressure (mm Hg)	96.9±8.3	98.0±7.8	0.18
Diastolic blood pressure (mm Hg)	60.4±9.1	60.6±9.6	0.88
Heart rate (bpm)	74.5±13.3	76.0±17.1	0.33
Initiation of sacubitril/valsartan during hospitalisation	111 (46.6)	93 (62.0)	0.003
Body mass index (kg/m^2)	22.5 (20.4–25.2)	21.4 (19.5–25.0)	0.03
NYHA class			<0.001
I	39 (16.5)	8 (5.4)	
II	120 (50.8)	58 (38.9)	
III	63 (26.7)	61 (40.9)	
IV	14 (5.9)	22 (14.8)	
History of HF hospitalisation	167 (70.2)	110 (73.8)	0.44
Aetiology of HF			
Ischaemic cardiomyopathy	77 (32.4)	55 (36.7)	0.38
Valvular heart disease	41 (17.2)	29 (19.3)	0.60
Dilated cardiomyopathy	86 (36.1)	42 (28.0)	0.10
Comorbidities			
Hypertension	117 (49.2)	68 (45.3)	0.46
Diabetes mellitus	83 (34.9)	42 (28.0)	0.16
Atrial fibrillation			0.28
None	137 (57.6)	74 (49.3)	
Paroxysmal	45 (18.9)	34 (22.7)	
Persistent	56 (23.5)	42 (28.0)	
Medications			
ACE inhibitors	105 (44.1)	71 (47.3)	0.54
ARBs	125 (52.5)	67 (44.7)	0.13
Beta blockers	213 (89.5)	121 (80.7)	0.014
Loop diuretics	192 (80.7)	124 (82.7)	0.62
MRAs	176 (73.9)	116 (77.3)	0.45
SGLT2 inhibitors	91 (38.2)	60 (40.0)	0.73
Estimated GFR (mL/min/1.73 m^2)			0.007
<30	38 (16.0)	46 (30.7)	
30–44.9	67 (28.2)	38 (25.3)	
45–59.9	65 (27.3)	34 (22.7)	
≥60	68 (28.6)	32 (21.3)	
LVEF (%)	31 (24–42)	34 (24–46)	0.20
LVEF category			0.22
HFrEF (EF <40%)	169 (71.0)	94 (62.7)	
HFmrEF (EF: 40–49%)	39 (16.4)	30 (20.0)	
HFpEF (EF ≥50%)	30 (12.6)	26 (17.3)	

Data are presented as mean±SD or median (IQR) for continuous measures and n (%) for categorical measures.
ARB, angiotensin receptor blocker; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2, sodium-glucose transporter 2.

Table 4 Baseline clinical factors associated with AE within 3 months in patients with SBP <110 mm Hg

	OR (95% CI)	P value
Age, per 1 year	1.00 (0.98 to 1.02)	0.94
Initiation of sacubitril/valsartan during hospitalisation	1.46 (0.9 to 2.36)	0.12
Body mass index, per 1 kg/m^2	0.96 (0.9 to 1.01)	0.11
NYHA class		
I	Ref	
II	3.04 (1.18 to 7.78)	0.02
III	4.95 (1.9 to 12.91)	0.001
IV	7.57 (2.4 to 23.93)	0.001
Beta blockers	0.55 (0.29 to 1.03)	0.06
Estimated GFR (mL/min/1.73 m^2)		
<30	2.30 (1.07 to 4.95)	0.03
30–44.9	1.30 (0.63 to 2.69)	0.48
45–59.9	1.16 (0.58 to 2.31)	0.67
≥60	Ref	

AE, adverse event; SBP, systolic blood pressure.

patients with NYHA class II, III or IV, and an eGFR of ≥30 mL/min/1.73 m^2.

Follow-up data

Online supplemental figure 2 illustrates follow-up outcomes based on baseline SBP and AEs within 3 months of therapeutic intervention. The cumulative incidences of all-cause mortality and rehospitalisation owing to HF were higher in patients who had AEs (both log-rank p<0.001). In contrast, among patients without AEs, all-cause mortality rates were similar between the SBP <110 and ≥110 mm Hg groups.

Online supplemental figure 3 shows the changes in SBP based on the baseline BP category in patients who continued sacubitril/valsartan for 12 months. Patients with a baseline SBP <100 mmHg showed an increase in median SBP at 12 months, while those with a baseline SBP ≥120 mm Hg demonstrated a decrease. In patients with follow-up data and a prescription for sacubitril/valsartan at 12 months, improvements in median LVEF and NT-pro BNP levels were observed across all SBP groups (online supplemental figure 4).

DISCUSSION

Main findings

The key findings of this study were as follows: (1) a significant proportion of patients newly prescribed sacubitril/valsartan had a low baseline SBP; (2) patients with lower baseline SBP were at a higher risk of AEs; and (3) higher NYHA class (II, III or IV) and lower estimated GFR (<30 mL/min/1.73 m^2) were independently associated with AEs in patients with lower SBP (online supplemental file 2). This large cohort study, which encompassed

patients ineligible for prior randomised controlled trials (RCTs), offers important insights into the safety and eligibility of sacubitril/valsartan in current clinical practice.[5 7] These findings provide valuable insights to guide clinicians in the appropriate use of sacubitril/valsartan in real-world settings.

Sacubitril/valsartan use in patients with lower SBP

This study demonstrated that AEs were common in patients with a lower baseline SBP, and that hypotension and renal events were increased in these patients. While the baseline SBP did not modify the efficacy of sacubitril/valsartan, similar findings were reported in the PARADIGM-HF trial, which demonstrated a higher incidence of symptomatic hypotension in the sacubitril/valsartan group, especially among patients with an SBP of <110 mmHg.[8] This association between lower baseline SBP and hypotensive events has also been observed in previous RCTs investigating ACE inhibitors and angiotensin II receptor blockers.[15 16]

The proportion of AEs in our study was higher than that reported in other RCTs for sacubitril/valsartan.[5 7] The mean SBP in the PARADIGM-HF and PARAGON-HF trials was higher than the baseline SBP in our study (122 and 131 mm Hg, respectively). These RCTs excluded patients with HF who did not tolerate the full-dose sacubitril/valsartan during an active run-in period. In our study, approximately 20% of patients had an SBP <100 mm Hg, with most already receiving baseline treatment of ACE inhibitors or angiotensin II receptor blockers before the initiation of sacubitril/valsartan. This could result in a higher rate of AEs among patients with a lower SBP. Prior studies demonstrated that a low dose of sacubitril/valsartan may be more effective than a low dose of ACE inhibitors and that gradual up-titration is effective in reaching the target dose of sacubitril/valsartan.[17 18] Given the higher prevalence of patients with low SBP in current clinical settings, cautious initiation of sacubitril/valsartan, particularly in patients with lower baseline SBP, and starting with a lower dose may be a practical approach in real-world clinical practice.

Suitable strategy for initiating sacubitril/valsartan in patients with lower baseline SBP

Lower baseline SBP was associated with an increased risk of AEs, highlighting the need for careful risk stratification when initiating sacubitril/valsartan in patients with a lower SBP. In our study, patients with a baseline SBP <110 mm Hg accounted for approximately 40% of all included patients who initiated sacubitril/valsartan. These patients exhibited higher proportions of severe HF, which was a notable finding in our study compared with previous RCTs.[8 9] Considering the elevated risk of AEs in these high-risk patients, extra caution is warranted when initiating sacubitril/valsartan in patients with low SBP and severe HF. We also demonstrated that initiating sacubitril/valsartan in patients with NYHA class I and an eGFR ≥30 mL/min/1.73 m^2 is associated with a lower incidence of AEs. Such patients accounted for 38% (147/388) of those with a baseline SBP <110 mm Hg, and risk stratification using these variables may be useful in our clinical practice.

Continuation of sacubitril/valsartan and outcomes

This study revealed that patients who discontinued sacubitril/valsartan were at a higher risk of all-cause mortality and rehospitalisation for HF in the SBP <110 and ≥110 mm Hg groups. These results are consistent with a substudy of the PARADIGM-HF trial, which demonstrated that hypotension following medication initiation is linked to an increased risk of adverse outcomes.[8] Our findings suggest that discontinuing sacubitril/valsartan can lead to worse clinical outcomes. Conversely, patients who continued sacubitril/valsartan had a lower risk of AEs across the baseline SBP categories. Previous research has revealed that continuation of sacubitril/valsartan reduces the risk of unfavourable outcomes.[19 20] While our study was observational, the NT-pro BNP level and LVEF improved from baseline to the 1-year follow-up across all SBP groups, supporting the efficacy of sacubitril/valsartan across all baseline SBPs.[9 11 21]

Limitations

This study has some limitations. First, its retrospective characteristic, relying on available medical records, introduced the possibility of missing variables. Moreover, unmeasured confounders could exist, potentially introducing selection bias. Second, our study included patients who were prescribed sacubitril/valsartan during the post-marketing period beginning in August 2020, but long-term follow-up data were unavailable. However, most AEs occurred within the early period following sacubitril/valsartan initiation. Hence, we focused on the AEs within 3 months of the first prescription. Lastly, as this was a single-arm registry that included patients treated with sacubitril/valsartan without a control group receiving alternative medications, we could not determine the efficacy of sacubitril/valsartan compared with other medications.

CONCLUSION

Among patients prescribed sacubitril/valsartan following its introduction in Japan, approximately 40% had a baseline SBP <110 mm Hg in real-world settings. Initiating sacubitril/valsartan in patients with lower SBP was associated with a higher incidence of AEs. However, the baseline NYHA classification and eGFR may be useful for risk stratification in these high-risk groups. These findings provide valuable insights for clinicians when determining the appropriate utilisation of sacubitril/valsartan in real-world practice.

Author affiliations
[1]Department of Medical and Health Information Management, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

[2]Department of Cardiovascular Medicine, Nara Medical University, Kashihara, Nara, Japan
[3]Department of Internal Medicine, Iwate Medical University, Shiwa-gun, Iwate, Japan
[4]Osaka General Medical Center, Osaka, Japan
[5]Department of Cardiology, Tokai University School of Medicine, Isehara, Kanagawa, Japan
[6]Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan
[7]Cardiology, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan
[8]Department of Cardiovascular Biology and Medicine, Juntendo University Faculty of Medicine, Tokyo, Japan
[9]Department of Digital Health and Telemedicine R&D, Juntendo University, Bunkyo-ku, Japan
[10]Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
[11]Department of Cardiology, Hyogo Prefectural Awaji Medical Center, Sumoto, Japan
[12]Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, none, Japan
[13]Cardiovascular Medicine, Toho University Graduate School of Medicine, Ota-ku, Japan

Contributors K Kanaoka is the guarantor and takes full responsibility for the content of the manuscript. TN, K Kida, NK, WF, SI, AK, TI and TS contributed to data entry. YI and YM contributed to the review and editing of the manuscript. SM contributed to the conceptualisation and project administration.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests K Kanaoka received speaker honoraria from Eli Lilly Japan and Otsuka Pharmaceutical Co., Ltd. K Kida received honorariums from AstraZeneca, Ono Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Otsuka Pharmaceutical Co., Ltd. and Novartis Pharmaceuticals Co., Ltd. SM received research grants and personal fees from Abbott, Bayer Pharma, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Novartis, Ono Pharma, Orbus Neich, Otsuka Pharma and the Uehara Memorial Foundation.

Patient consent for publication Not applicable.

Ethics approval The ethics committees of Toho Omori Hospital approved this study protocol (registration number M21257). Informed consent was obtained in the form of an opt-out in each facility because of the retrospective characteristics of this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The data underlying this article cannot be shared publicly due to protect the privacy of individuals that participated in the study.

ORCID iDs
Koshiro Kanaoka http://orcid.org/0000-0001-7900-7835
Shingo Matsumoto http://orcid.org/0000-0002-2000-1954

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