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ORIGINAL ARTICLE

Effect of carperitide on the 1 year prognosis of patients with acute decompensated heart failure

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Abstract

Aims Acute heart failure (AHF) is a clinical syndrome with a poor prognosis and a major public health concern worldwide. The aim of this study was to investigate whether carperitide administration improves the 1 year prognosis of patients with AHF and to check whether there is an optimal dose of the drug.

Methods and results We analysed the data of COOPERATE-HF-J (the Consortium for Pooled Data Analysis regarding Hospitalized Patients with Heart Failure in Japan), combining two cohorts (NARA-HF and REALITY-AHF), which included 2435 patients with acute decompensated heart failure. The patients were divided into no carperitide (NO-ANP, n = 1098); very low-dose carperitide (VLD-ANP, $<$0.02 μg/kg/min, n = 593); and low-dose carperitide groups (LD-ANP, $\geq$0.02 μg/kg/min, n = 744). The primary endpoint was cardiovascular mortality within 1 year after admission. The secondary endpoints were all-cause mortality and rehospitalization due to worsening heart failure within 1 year after admission. The median carperitide doses in the VLD-ANP and LD-ANP groups were 0.013 and 0.025 μg/kg/min, respectively. Kaplan–Meier analysis showed that cardiovascular mortality and all-cause mortality were significantly lower in the LD-ANP group than in the NO-ANP and VLD-ANP groups ($P < 0.001$ and $P = 0.002$, respectively). Multivariable Cox regression analysis for cardiovascular and all-cause mortality revealed that LD-ANP was significantly associated with lower cardiovascular and all-cause mortality within 1 year after admission, even after adjusting other covariates (hazard ratio: 0.696 and 0.791, 95% confidence interval: 0.513–0.944 and 0.628–0.997, $P = 0.020$ and 0.047, respectively).

Conclusions Low-dose carperitide was significantly associated with lower cardiovascular and all-cause mortality within 1 year after admission. Our results suggest the necessity for well-designed randomized controlled trials to determine the doses of carperitide that could improve clinical outcomes in patients with AHF.

Keywords Acute heart failure; Atrial natriuretic peptide; Carperitide; Dosing

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Introduction

Heart failure (HF) is a clinical syndrome with a poor prognosis in the terminal stage of any heart disease. It is a major public health concern worldwide, because the number of patients with HF is expected to increase in the super-aging society.[1,2] However, till date, no therapy for acute HF (AHF) has resulted in improvements in the long-term mortality outcomes.

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are cardiac hormones that affect natriuresis, vasodilation, and renin-angiotensin-aldosterone system (RAAS) suppression.[3–6] These peptides exert their effects via natriuretic receptor A (NPR-A) and are cleared from the circulation both by receptor-mediated cell uptake and neutral endopeptidase (NEP)-mediated degradation.[7] ANP has a higher affinity for clearance receptors and NEPs than BNP. Therefore, it is unlikely that ANP and BNP have the same behaviour as a therapeutic agent.

The latest Japanese Circulation Society (JCS) guidelines for the diagnosis and treatment of AHF and chronic HF recommend intravenous carperitide (an intravenous formulation of human ANP; class of recommendation IIa, level of evidence B) as a therapeutic drug for AHF, based on a small randomized controlled trial and large observational studies on the safety and efficacy of carperitide.[8–10] Therefore, carperitide has been widely used to treat patients with AHF in Japan.[11] However, several retrospective studies have revealed that carperitide did not improve survival rates and that it was rather associated with increased in-hospital mortality and higher total hospitalization costs.[12–14] Furthermore, carperitide may cause hypotension at the beginning of treatment, which is possibly associated with worse outcomes. One of the plausible reasons for hypotension is the vasodilatory property of carperitide. In fact, the JCS guidelines recommend that carperitide should be administered by continuous intravenous infusion at a low dose (0.025–0.050 μg/kg/min, and 0.0125 μg/kg/min for some cases).[8] However, till date, the clinical outcomes of patients with AHF on different doses of carperitide have been evaluated in very few studies.

Recently, sacubitril/valsartan, which has both neprilysin-inhibiting and angiotensin receptor blocking activities, has been proposed to be beneficial in the treatment of acute decompensated HF (ADHF) and chronic HF.[15] The treatment with sacubitril/valsartan elevates circulating natriuretic peptides more potently in ANP than in BNP.[16] The information on the effect of the intravenous infusion of ANP on AHF would help better understand the role of sacubitril/valsartan in the treatment of AHF. Thus, in this study, we aimed to investigate whether carperitide administration improves the 1 year prognosis of patients with AHF and to check whether there is an optimal dose of the drug.

Methods

Study design and patients

The Consortium for Pooled Data Analysis regarding Hospitalized Patients with Heart Failure in Japan (COOPERATE-HF-J) was a patient-level meta-analysis combining two cohorts of patients with ADHF: the Nara Registry and Analyses for Heart Failure (NARA-HF) and Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure (REALITY-AHF). Representative investigators for each registry (K. N. and Y. M.) performed preassigned analyses for the present study. Briefly, 100% of patients admitted to each participating institution and fulfilled the inclusion criteria were registered. The inclusion and exclusion criteria of each registry have been described elsewhere.[17,18] Both registries did not include patients whose condition was complicated with acute coronary syndrome and acute myocarditis. In our study, patients receiving maintenance dialysis with BNP level $<$ 100 pg/mL or N-terminal pro-brain natriuretic peptide (NT-proBNP) level $<$ 300 pg/mL at baseline or treated with both carperitide and nitrates were also excluded. Study information, including objectives, inclusion and exclusion criteria, and the names of participating hospitals, has been published in the publicly available University Hospital Information Network (unique identifier: UMIN 000039975).

The patients were divided into three groups according to the initial dose of carperitide within 48 h after their arrival at the emergency department (ED): no carperitide (NO-ANP) group (n = 1098), very low-dose carperitide (VLD-ANP) group ($<$0.02 μg/kg/min, n = 593), and low-dose carperitide (LD-ANP) group ($\geq$0.02 μg/kg/min, n = 744). The study protocols were approved by the institutional review boards of each of the participating institutions, and all research was conducted according to the tenets of the Declaration of Helsinki. Written or verbal informed consent was obtained from each participant before the study.

Participating registries

NARA-HF

NARA-HF was a single-centre cohort registry designed to collect data on clinical backgrounds and outcomes of patients following an emergency admission. The registry included retrospectively enrolled consecutive patients with ADHF admitted to Nara Medical University Hospital from January 2007 to March 2011 and prospectively enrolled patients from April 2011 to December 2018.

REALITY-AHF

REALITY-AHF was a prospective multicentre study (involving 20 hospitals in all regions of Japan) that was designed to evaluate the association between time to treatment and clinical outcomes in patients with AHF who presented at the ED.[18] From August 2014 to December 2015, consecutive patients with AHF admitted to the ED of the participating hospitals were included in the registry at the initial hospital admission and followed up.

Data collection and definitions

The following laboratory parameters were measured in all patients: haemoglobin (Hb), albumin, blood urea nitrogen (BUN), serum creatinine (Cr), estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease method, serum electrolytes (sodium and potassium), and BNP at admission, and delta-BNP ([admission − discharge] BNP/admission BNP × 100). The plasma level of ANP within 24 h after carperitide infusion was measured in the patients enrolled in NARA-HF. Vital signs, including the heart rate and blood pressure (BP) at admission, were recorded.

Clinical outcomes

The primary endpoint was cardiovascular mortality within 1 year after admission. The secondary endpoints were all-cause mortality and rehospitalization due to the worsening of HF within 1 year after admission, in-hospital mortality, 1 year mortality, and the incidence of minimum systolic blood pressure (SBP) $<$ 90 mmHg within 48 h after arrival at the ED. The status of all patients was surveyed, and information on outcomes was obtained from patient medical records and the participating cardiologists. When this information was unavailable in the medical records, the clinicians sent letters to the residence of patients or telephoned the patients or their families to collect these data.

Statistical analysis

Data are expressed as mean and standard deviation for normally distributed variables and median with interquartile range for non-normally distributed data. Kolmogorov–Smirnov test was performed for normality. Categorical data were expressed as number and percentage. The difference among the three groups was tested for significance with Kruskal–Wallis test for distributed variables. Chi-squared test was used to compare categorical variables.

Cumulative event-free survival estimates were calculated using the Kaplan–Meier method. The log-rank test was used to compare the curves. Associations between the initial dose of carperitide and outcome were determined using Cox proportional hazards analysis (both univariate and multivariate models). To identify the independent effect of the initial dose of carperitide on the outcomes, multivariate Cox regression models were constructed with adjustments for well-established risk markers evaluated at the time of admission.[19] The following variables were selected as pre-existing and known prognostic factors for HF: age; sex; a history of HF, diabetes mellitus (DM), and coronary artery disease (CAD); left ventricular ejection fraction (LVEF); prescription for a beta-blocker, an angiotensin-converting enzyme (ACE) inhibitor, or angiotensin II receptor blocker (ARB); New York Heart Association (NYHA) functional class; SBP; Hb; serum sodium; BUN; Cr; and BNP at admission. The homogeneity of treatment effects across subgroups defined by age, sex, SBP, DM, atrial fibrillation, CAD, LVEF, and eGFR was evaluated using *P*-values for interactions in the Cox regression models. Furthermore, a sensitivity analysis was performed in patients who were not treated with intravenous nitrates to evaluate the robustness of the results. Results with $P < 0.05$ were considered significant for individual comparisons. All statistical analyses were performed using R software Version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

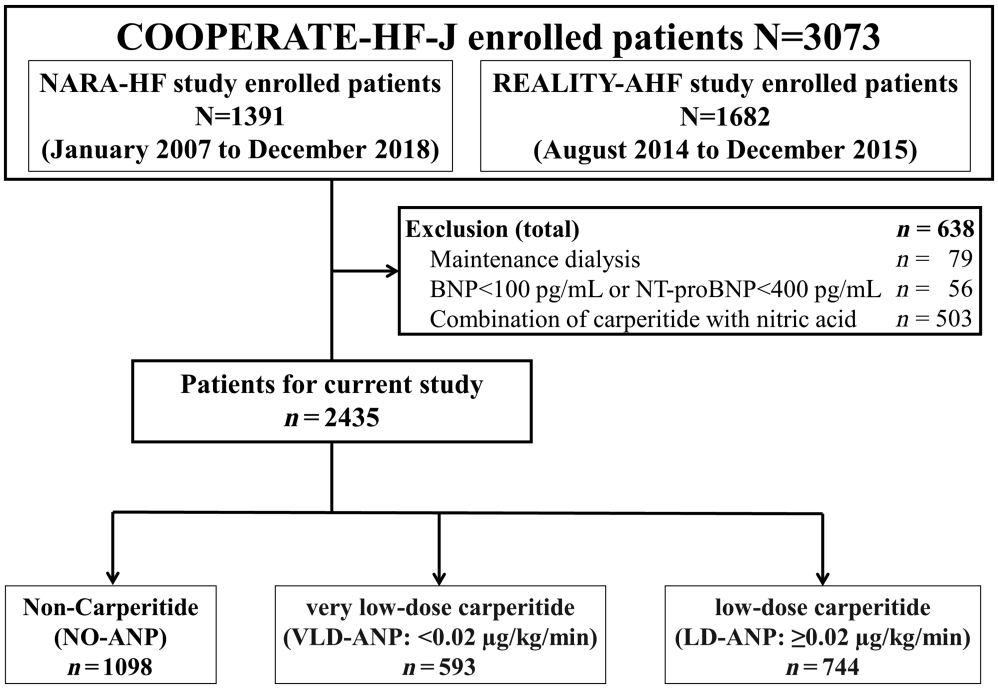
Among 3073 patients, we excluded 79 who were receiving maintenance dialysis, 56 with BNP level $<$ 100 pg/mL or NT-proBNP level $<$ 300 pg/mL at baseline, and 503 who were treated with both carperitide and nitrates. Thus, 2435 patients were included in the study (*Figure 1*). The median patient age was 79 (69–85) years, and 55.3% were males. The median carperitide doses in the VLD-ANP and LD-ANP groups were 0.013 and 0.025 μg/kg/min, respectively. The associations of baseline characteristics across the initial dose of carperitide within 48 h after ED arrival are shown in *Table 1*.

The initial doses of carperitide within 48 h after ED arrival were not associated with any significant trends in sex, heart rate, dyslipidaemia, DM, CAD, atrial fibrillation, and medication use at admission. However, LVEF $<$ 35%, NYHA class III or IV, and smoking were more prevalent in the VLD-ANP group. Hypertension was more prevalent in the LD-ANP group, and new-onset HF was less prevalent in the NO-ANP group. The VLD-ANP group was also associated with lower age and SBP. In terms of the laboratory parameters, although the NO-ANP group was associated with lower Alb and BNP levels and the LD-ANP group was associated with higher serum sodium, lower serum potassium, and higher delta-BNP levels, there were no significant differences in Hb, BUN, Cr, and eGFR levels among the three groups.

Carperitide dose and clinical outcome

In-hospital, 30 day, and 1 year all-cause mortality were significantly lower in the LD-ANP group than in the VLD-ANP group (χ^2 test, $P < 0.05$ with Bonferroni correction) (*Table 2*). The Kaplan–Meier analysis showed that cardiovascular and all-cause mortality within 1 year after admission were significantly lower in the LD-ANP group than in the NO-ANP and VLD-ANP groups ($P < 0.001$ and $P = 0.002$,

Figure 1 Flow chart of the study cohort. BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide.



respectively) (*Figure 2*). However, there was no significant difference in rehospitalization due to the worsening of HF within 1 year after admission among the groups (*Figure 2*). The multivariable Cox regression analysis revealed that LD-ANP, but not VLD-ANP, was significantly associated with lower rates of cardiovascular and all-cause mortality within 1 year after admission, even after adjusting other covariates (hazard ratio: 0.696, 95% confidence interval: 0.513–0.944, P = 0.020; hazard ratio: 0.791, 95% confidence interval: 0.628–0.997, P = 0.047) (*Table 3*). The sensitivity analysis in patients who were not treated with intravenous nitrates also showed that LD-ANP was significantly associated with cardiovascular and all-cause mortality within 1 year after admission, even after adjusting other covariates (hazard ratio: 0.695, 95% confidence interval: 0.506–0.955, P = 0.025; hazard ratio: 0.778, 95% confidence interval: 0.611–0.990, P = 0.041) (Supporting Information, *Table S1*). The plasma level of ANP within 24 h after carperitide infusion was higher in the LD-ANP group [999 (648–1504) pg/mL] than in the NO-ANP [185 (94–289) pg/mL] and VLD-ANP [595 (341–879) pg/mL] groups ($P < 0.001$ and $P < 0.001$, respectively) (*Figure 3*). The incidence of minimum SBP $<$ 90 mmHg within 48 h after ED arrival was significantly higher in the VLD-ANP group than in the NO-ANP and LD-ANP groups ($P < 0.001$ and $P < 0.001$, respectively) (*Figure 4*). The cardiovascular mortality within 1 year after admission was consistent among all subgroups in the LD-ANP, NO-ANP, and VLD-ANP groups (Supporting Information, *Figures S1–S3*).

Discussion

In this study, we examined the association between the initial carperitide dose within 48 h after ED arrival of patients and prognosis within 1 year after admission in patients with ADHF. The main finding of the present study was that the administration of LD-ANP within 48 h after ED arrival was independently associated with lower cardiovascular and all-cause mortality within 1 year after admission among patients with ADHF (based on the multivariate analysis). To the best of our knowledge, this is the first study to reveal the clinical and prognostic implications of the initial carperitide dose in patients with ADHF.

The latest JCS guidelines recommend carperitide (class of recommendation IIa and level of evidence B) for treating AHF. This recommendation is based on only a small randomized clinical trial in 49 patients with AHF, in which carperitide significantly reduced the incidence of the composite outcomes of all-cause mortality and HF-related rehospitalization during an 18 month follow-up period.[9] However, among the 11 events reported in the previous study, there was only one death, and the study did not describe how the sample size was determined. In contrast, recent retrospective studies have revealed that carperitide was associated with increased in-hospital mortality.[12,13] A three-centre retrospective cohort study involving a propensity score matching analysis and a retrospective study using data from the Japanese nationwide administrative claim database, Diagnosis Procedure Combination, involving propensity score matching analysis revealed

Table 1 Baseline characteristics of the study patients

	NO-ANP n = 1098	VLD-ANP n = 593	LD-ANP n = 744	P-value
Age, years	80 (70–86)	77 (67–84)	79 (70–85)	<0.001
Male sex, no. (%)	587 (53.5)	349 (58.9)	411 (55.2)	0.104
Body mass index	22.5 (19.7–25.3)	23.1 (20.7–26.2)	22.7 (20.3–25.2)	0.001
Systolic blood pressure, mmHg	140 (115–170)	133 (115–153)	143 (124–162)	<0.001
Diastolic blood pressure, mmHg	78 (64–95)	79 (65–92)	80 (68–96)	0.012
Heart rate, b.p.m.	94 (76–114)	93 (76–112)	90 (74–111)	0.158
Left ventricular ejection fraction, no. (%)				0.011
<35%	374 (34.7)	247 (42.1)	248 (33.4)	
35–50%	316 (29.3)	156 (26.6)	212 (28.6)	
>50%	389 (36.0)	184 (31.3)	282 (38.0)	
NYHA functional class III/IV, no. (%)	886 (83.9)	506 (91.3)	635 (87.3)	<0.001
Medical history, no. (%)				
Hypertension	719 (65.5%)	387 (65.3%)	549 (74.0%)	<0.001
Dyslipidaemia	398 (36.2%)	226 (38.2%)	283 (38.1%)	0.626
Diabetes mellitus	394 (35.9%)	238 (40.2%)	267 (36.0%)	0.172
Smoking	442 (40.4%)	274 (46.2%)	308 (41.4%)	<0.001
New-onset heart failure	566 (51.6%)	379 (63.9%)	496 (66.9%)	<0.001
Coronary artery disease	289 (26.3%)	169 (28.5%)	208 (28.0%)	0.553
Atrial fibrillation	447 (40.7%)	252 (42.5%)	306 (41.1%)	0.780
Medication, no. (%)				
Loop diuretic	575 (52.7%)	311 (52.4%)	356 (48.1%)	0.127
ACE inhibitor or ARB	519 (47.4%)	305 (51.4%)	378 (51.0%)	0.167
Beta-blocker	443 (40.5%)	253 (42.7%)	275 (37.2%)	0.113
MRA	263 (24.0%)	122 (20.6%)	147 (19.8%)	0.068
Carperitide, dose (μg/kg/min)	0 (0–0)	0.013 (0.013–0.014)	0.025 (0.025–0.029)	<0.001
Nitrate, i.v. (%)	207 (22.5)	0 (0)	0 (0)	<0.001
Laboratory data				
Haemoglobin, g/dL	11.5 (10.2–13.1)	11.7 (10.0–13.3)	11.5 (9.8–13.1)	0.149
Alb, g/dL	3.5 (3.2–3.9)	3.6 (3.2–3.9)	3.6 (3.3–3.9)	0.049
BUN, mg/dL	25.0 (17.9–36.5)	25.0 (18.1–36.0)	24.3 (18.0–35.9)	0.691
Serum creatinine, mg/dL	1.10 (0.81–1.65)	1.16 (0.86–1.69)	1.12 (0.85–1.60)	0.366
eGFR, mL/min/1.73 m^2	35.7 (22.1–50.5)	33.8 (22.0–48.2)	35.2 (23.4–49.1)	0.537
Serum sodium, mEq/L	139 (136–142)	139 (136–142)	140 (137–142)	0.012
Serum potassium, mEq/L	4.2 (3.8–4.7)	4.2 (3.9–4.6)	4.1 (3.8–4.6)	0.005
BNP, pg/mL	721 (432–1260)	868 (489–1659)	820 (447–1427)	<0.001
Delta BNP, (%)[a]	60.8 (33.0–77.6)	60.8 (36.3–79.1)	65.4 (39.3–82.0)	0.019

ACE, angiotensin-converting enzyme; Alb, albumin; ANP, atrial natriuretic peptide; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; LD, low dose; MRA, mineralocorticoid receptor antagonist; NO, no carperitide; NYHA, New York Heart Association; VLD, very low dose.
Values are n (%) or median [interquartile range]. The body mass index is the weight in kilograms divided by the square of the height in metres.
[a]Delta BNP = [admission − discharge] BNP/admission BNP × 100.

Table 2 In-hospital mortality, and mortality at 30 days, 1 year, and readmission due to heart failure at 1 year according to the dose of carperitide

	NO-ANP n = 1098	VLD-ANP n = 593	LD-ANP n = 744	P-value
In-hospital death	60 (5.5)	42 (7.1)	29 (3.9)	0.037
Sudden cardiac death	2 (0.2)	8 (1.3)	3 (0.4)	0.006
Heart failure death	37 (3.4)	22 (3.7)	12 (1.6)	0.037
Other death	21 (1.9)	12 (2.0)	14 (1.9)	0.981
30 day death	52 (4.7)	38 (6.4)	24 (3.2)	0.024
Sudden cardiac death	0 (0)	3 (0.5)	2 (0.3)	0.081
Other cardiovascular death	37 (3.4)	26 (4.4)	15 (2.0)	0.046
Non-cardiovascular death	12 (1.1)	8 (1.3)	6 (0.8)	0.628
Unknown death	3 (0.3)	0 (0)	1 (0.1)	0.404
1 year death	251 (22.9)	132 (22.3)	123 (16.5)	0.003
Sudden cardiac death	18 (1.6)	12 (2.0)	11 (1.5)	0.735
Other cardiovascular death	123 (11.2)	66 (11.1)	49 (6.6)	0.002
Non-cardiovascular death	84 (7.7)	42 (7.1)	55 (7.4)	0.913
Unknown death	26 (2.4)	12 (2.0)	8 (1.1)	0.130
1 year heart failure readmission	239 (21.8)	129 (21.8)	156 (21.0)	0.908

ANP, atrial natriuretic peptide; LD, low dose; NO, no carperitide; VLD, very low dose.

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Figure 2 Kaplan–Meier analyses of the initial dose of carperitide with regard to cardiovascular death, all-cause death, and hospitalization for heart failure. Kaplan–Meier survival curves show the time to CV death (A), all-cause death (B), and hospitalization for HF (C) among the three groups. The log-rank test demonstrated that CV and all-cause mortality within 1 year after admission were significantly lower in the LD-ANP group than in the NO-ANP and VLD-ANP groups ($P < 0.001$ and $P = 0.002$, respectively). However, there was no significant difference in rehospitalization due to the worsening of HF within 1 year after admission among the three groups. CV, cardiovascular; HF, heart failure; LD-ANP, low-dose carperitide; NO-ANP, no carperitide; VLD-ANP, very low-dose carperitide.

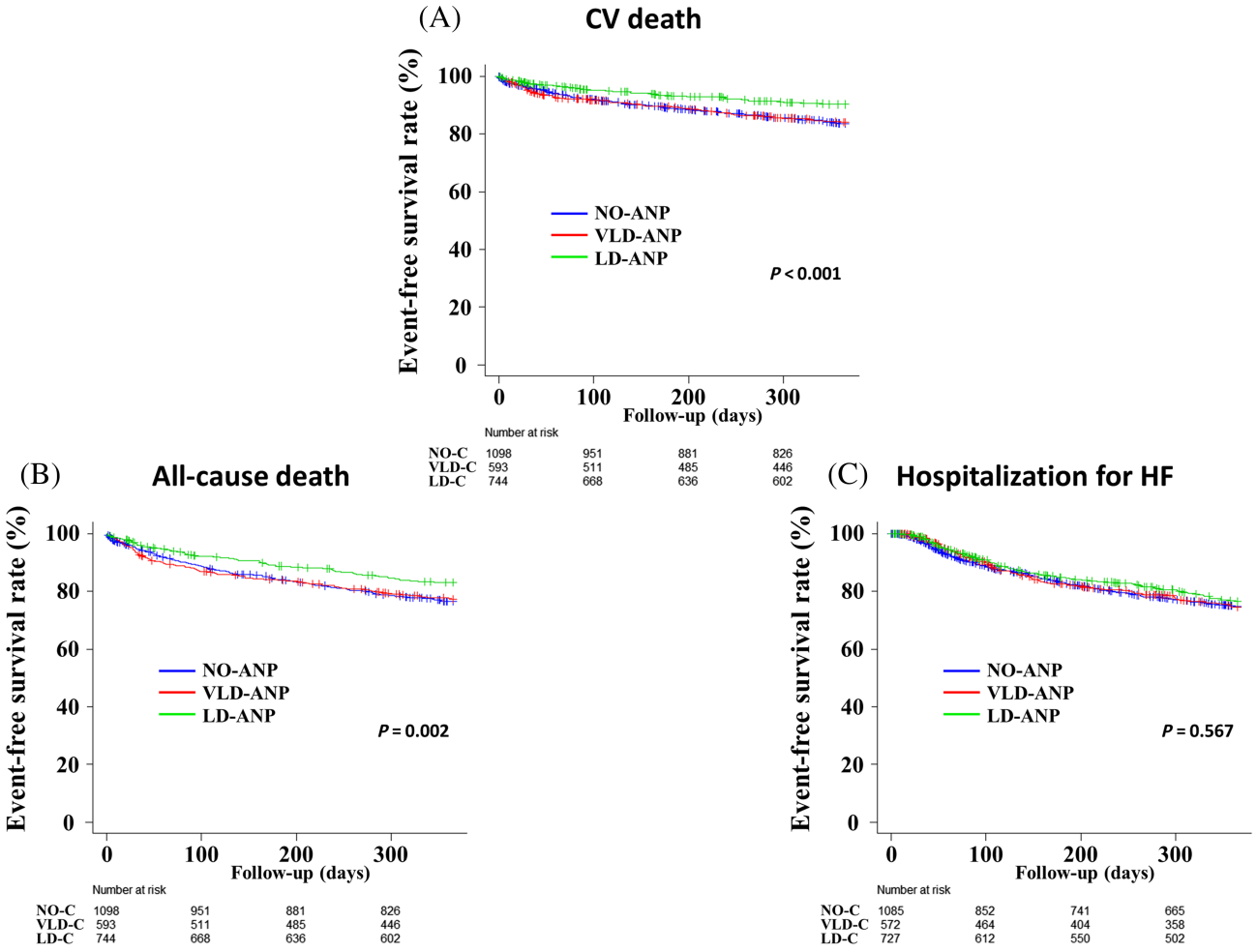


Table 3 Independent predictors of all-cause death, cardiovascular death, and hospitalization for heart failure at the 1 year follow-up

	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
CV death				
No carperitide	Reference		Reference	
Carperitide < 0.02γ	1.192 (0.934–1.521)	0.159	1.026 (0.768–1.370)	0.864
Carperitide ≥ 0.02γ	0.579 (0.443–0.757)	<0.001	0.696 (0.513–0.944)	0.020
All-cause death				
No carperitide	Reference		Reference	
Carperitide < 0.02γ	1.111 (0.911–1.355)	0.298	0.999 (0.792–1.260)	0.994
Carperitide ≥ 0.02γ	0.700 (0.571–0.857)	<0.001	0.791 (0.628–0.997)	0.047
Hospitalization for HF				
No carperitide	Reference		Reference	
Carperitide < 0.02γ	1.041 (0.853–1.269)	0.695	1.003 (0.789–1.278)	0.980
Carperitide ≥ 0.02γ	0.903 (0.749–1.089)	0.287	1.115 (0.899–1.383)	0.324

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio.

Figure 3 Comparison of plasma level of ANP within 24 h after carperitide infusion in patients registered in the NARA-HF. The plasma level of ANP within 24 h after carperitide infusion was higher in the LD-ANP group than in the NO-ANP and VLD-ANP groups ($P < 0.001$ and $P < 0.001$, respectively). ANP, atrial natriuretic peptide; LD-ANP, low-dose carperitide; NO-ANP, no carperitide; VLD-ANP, very low-dose carperitide.

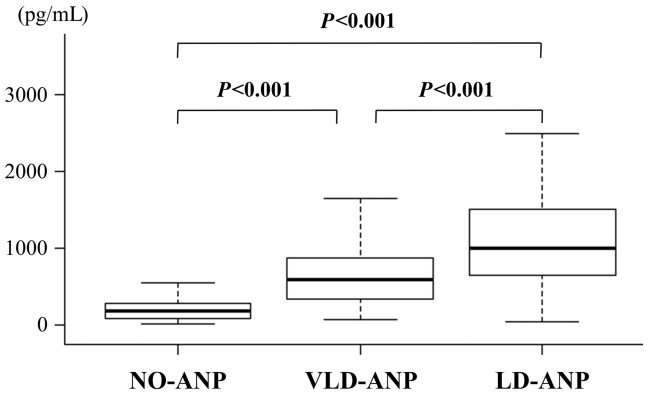
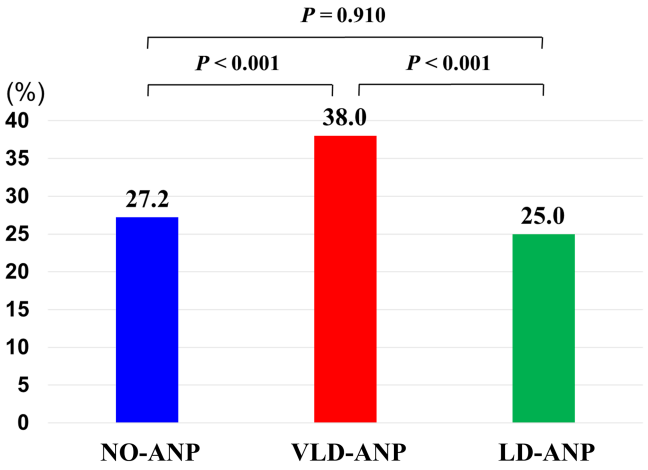


Figure 4 Incidence of minimum systolic blood pressure (SBP) < 90 mmHg within 48 h after arrival at the emergency department (ED). The incidence of minimum SBP < 90 mmHg within 48 h after ED arrival was significantly higher in the VLD-ANP group than in the NO-ANP and LD-ANP groups ($P < 0.001$ and $P < 0.001$, respectively). LD-ANP, low-dose carperitide; NO-ANP, no carperitide; VLD-ANP, very low-dose carperitide.



that carperitide use was significantly associated with higher in-hospital mortality in patients with AHF. However, the study had major limitations because information regarding the dose and duration of carperitide treatment was not available, which might have affected the results.[12,13] Consequently, the researchers conducting the study might have failed to adjust the odds of mortality by unmeasured important prognostic variables regardless of the propensity score matching analysis. Furthermore, in these two studies, the follow-up was not long-term but limited to the hospital stay. The strength of our study was the use of 1 year outcomes as the endpoint and the inclusion of a higher number of patients.

The present study showed that the plasma level of ANP within 24 h after carperitide infusion was higher in the LD-ANP group than in the NO-ANP and VLD-ANP groups. Previous studies have shown a favourable effect of ANP on ventricular remodelling and neurohormonal systems, including the sympathetic nervous system, RAAS, oxidative stress, and endothelin-1 (ET-1) level in patients with HF.[9,20–24] Furthermore, the inhibitory effect of ANP on RAAS and ET-1 was dose dependent.[25] Therefore, the prevention of left ventricular remodelling in the acute phase by carperitide may lead to a better long-term outcome. In addition, the plasma ANP level in patients treated with ANP was approximately three-fold to five-fold higher than that in patients not treated with ANP, similar to the value achieved with sacubitril/valsartan.[26]

On the other hand, our study showed that the incidence of minimum SBP < 90 mmHg within 48 h after ED arrival was significantly higher in the VLD-ANP group than in the NO-ANP and LD-ANP groups. Previous studies have suggested that the BP reduction in the acute-phase treatment of AHF was associated with a poor prognosis.[27,28] In our study, SBP

at admission was significantly lower in the VLD-ANP group than in the NO-ANP and LD-ANP groups. Therefore, the infusion of carperitide in the VLD-ANP group may have led to BP reduction and a worse outcome despite carperitide infusion.

Furthermore, in the present study, the delta-BNP level was significantly higher in the LD-ANP group. Previous studies have shown that decongestion in patients with AHF was independently associated with lower post-discharge all-cause mortality even if renal function worsened.[29,30] Therefore, the NO-ANP and VLD-ANP groups may have had residual congestion at discharge, resulting in a worse 1 year prognosis. These findings suggest that decongestion without BP reduction by the highest possible dose of carperitide may improve prognosis. Further research is necessary to confirm our findings and elucidate why LD-ANP use in patients with ADHF is associated with a better 1 year prognosis.

This study had some limitations that should be acknowledged. First, the present analysis was performed based on data combined from two registries. Each registry consists of different participating hospitals, suggesting that some important variables and comorbidities may have been defined and recorded in the medical records differently. Second, although we performed a multivariate Cox proportional hazard regression analysis, there was no adjustment for unmeasured or unknown confounding factors. Third, we retrospectively analysed the initial dose of carperitide within 48 h after ED arrival of patients and did not consider the late-phase dose and administration period of carperitide. Fourth, the dose of carperitide was determined at the discretion of each attending physician and may be biased. Finally, although we excluded patients treated with nitrates in the VLD-ANP and LD-ANP groups, we included patients treated with nitrates in the NO-ANP group, which may have affected the outcomes. However, we performed a sensitivity analysis of patients who were not treated with intravenous nitrates and obtained comparable results.

Low-dose carperitide was significantly associated with lower cardiovascular and all-cause mortality of patients within 1 year after admission. High-quality and well-powered randomized controlled trials are necessary to determine the doses of carperitide that could improve clinical outcomes in patients with ADHF.

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None.

Conflict of interest

Saito Y. has received research funds from Otsuka Pharmaceutical Co., Ltd, OnoPharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd, Mitsubishi Tanabe Pharma Corporation, Bristol-Myers Squibb Company, Actelion Pharmaceuticals Japan Ltd, Kyowa Kirin Co., Ltd, Kowa Pharmaceutical Co., Ltd, Shionogi & Co., Ltd, Dainippon Sumitomo Pharma Co., Ltd, Teijin Pharma Ltd, Chugai Pharmaceutical Co., Ltd, Eli Lilly Japan K.K., Nihon Medi-Physics Co., Ltd, Novartis Pharma K.K., Pfizer Japan Inc., and Fuji Yakuhin Co., Ltd; research expenses from Novartis Pharma K.K., Roche Diagnostics K.K., Amgen Inc., Bayer Yakuhin, Ltd, Astellas Pharma Inc., and Actelion Pharmaceuticals Japan Ltd; speakers' bureau/honorarium from Alnylam Japan K.K., AstraZeneca K.K., Otsuka Pharmaceutical Co., Ltd, Kowa Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd, Mitsubishi Tanabe Pharma Corporation, Tsumura & Co., Teijin Pharma Ltd, Toa Eiyo Ltd, Nippon Shinyaku Co., Ltd, Nippon Boehringer Ingelheim Co., Ltd, Novartis Pharma K.K., Bayer Yakuhin Ltd, Pfizer Japan Inc., Bristol-Myers Squibb Company, and Mochida Pharmaceutical Co., Ltd; and consultation fees from Ono Pharmatical Co., Ltd and Novartis Pharma K.K.

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Supporting information

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

Table S1. Independent predictors of all-cause death, cardiovascular death, and hospitalization for heart failure at the 1-year follow-up (patients treated without nitrates).

Figure S1. Subgroup analyses of CV death by baseline characteristics (LD-ANP vs NO-ANP).
The effect of LD-ANP group compared to NO-ANP group in cardiovascular mortality within 1-year after admission was consistent across all subgroups.
Hazard ratios for 8 predefined subgroups. Horizontal bars represent 95% confidence interval. *P* values are for the tests of subgroup heterogeneity (tests of interactions).
AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; LVEF, left ventricle ejection; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Figure S2. Subgroup analyses of CV death by baseline characteristics (NO-ANP vs VLD-ANP).
The effect of VLD-ANP group compared to NO-ANP group in cardiovascular mortality within 1-year after admission was consistent across all subgroups.
Hazard ratios for 8 predefined subgroups. Horizontal bars represent 95% confidence interval. *P* values are for the tests of subgroup heterogeneity (tests of interactions).
AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; LVEF, left ventricle ejection; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Figure S3. Subgroup analyses of CV death by baseline characteristics (LD-ANP vs VLD-ANP).
The effect of LD-ANP group compared to VLD-ANP group in cardiovascular mortality within 1-year after admission was consistent across all subgroups.
Hazard ratios for 8 predefined subgroups. Horizontal bars represent 95% confidence interval. *P* values are for the tests of subgroup heterogeneity (tests of interactions).
AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; LVEF, left ventricle ejection; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

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