Effect of intravenous carperitide versus nitrates as first-line vasodilators on in-hospital outcomes in hospitalized patients with acute heart failure: Insight from a nationwide claim-based database

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ABSTRACT

Backgrounds: Carperitide is a recombinantly produced intravenous formulation of human atrial natriuretic peptide. Despite of negative impacts of nesiritide on clinical outcomes for acute heart failure (AHF), carperitide has been used for around a half of Japanese AHF patients as a vasodilator based on limited evidences. We sought to determine the effect of carperitide compared to nitrates in the early care for AHF patients treated with vasodilators.
Methods and results: We conducted a cohort study of patients admitted with AHF to 808 hospitals from April 2012 to March 2014. Patients were extracted from 1,422,703 hospitalizations according to ICD-10 heart failure codes. Patients who had sepsis or mechanical supports during hospitalization were excluded. Outcomes were in-hospital death, length of hospitalization and cost of hospitalization. Among 76,924 patients, 45,595 were in patients treated with either carperitide or nitrates during the first 2 days (carperitide; 33,386, nitrates; 12,209). After application of inverse probability of treatment weighting with variables including demographics, comorbidities and treatments, there was perfect balance in both groups. Patients who were treated with carperitide had substantially higher covariate adjusted in-hospital mortality (HR 1.49 95%CI 1.35–1.64), longer length of hospitalization (Coefficients 0.062 95%CI 0.048 to 0.076) and greater cost of hospitalization (Coefficients 0.024 95%CI 0.010 to 0.037) compared to those treated with nitrates.
Conclusions: In Japanese AHF patients during their early inpatient care, carperitide use was significantly associated with worse outcomes when compared to nitrates use, suggesting the routine use of carperitide might not be recommended as a first-line vasodilator for AHF.

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1. Introduction

Despite optimal medical therapies substantially improving clinical outcomes of ambulatory patients with chronic heart failure (HF), treatment for patients hospitalized with acute HF (AHF) has changed little in recent decades, with few treatments showing safe improvements in outcomes [1,2]. Among the initial medical treatments for patients with AHF, intravenous vasodilators are the second-most predominantly used agents for symptomatic relief [1,2]. However, there is insufficient evidence confirming their effects, especially on subsequent death or worsening HF [3–6].

Carperitide is a recombinantly produced, intravenous formulation of human atrial natriuretic peptide, a circulating peptide of cardiac origin consisting of 28 amino acids [7,8]. A multicenter, open-label, randomized clinical trial with an insufficient sample size (n = 49) indicated significant additional positive effects of carperitide compared to those of standard therapy on long-term cardiovascular mortality and HF hospitalization for patients with AHF [9], and there have been several recent conflicting reports from studies of real-world AHF cohorts [10,11]. Negative effects of nesiritide on clinical outcomes in AHF have been reported [6]; however, carperitide is currently used in more than half of

Japanese AHF cases receiving vasodilator treatment (e.g., carperitide, 58.2%; nitrates, 35.3%; nicorandil, 9.6%; and calcium antagonists, 7.8%) based on this limited evidence [12]. Japanese HF guidelines recommend carperitide or nitrate use as initial vasodilators without stating which should be selected [13], and the selection of initial vasodilators for AHF is based on each physician's preference. Thus, the effects of carperitide compared to nitrates on clinical outcomes in patients with AHF are still under debate.

Accordingly, the aim of our study was to compare the effects of intravenous carperitide on outcomes, including in-hospital death, length of hospitalization, and cost of hospitalization, with those of intravenous nitrates administered as vasodilators in the early care of patients with AHF in a Japanese nationwide claim-based database.

2. Methods

2.1. Data source

All data were extracted from the Japanese Registry Of All cardiac and vascular Diseases-Diagnosis Procedure Combination (JROAD-DPC), a project that involves the collection of administrative data from nearly all teaching hospitals with cardiovascular beds. Teaching hospitals participate in this project to meet the Japanese Circulation Society (JCS) cardiology training requirement for physicians who wish to be JCS board-certified cardiologists and take the JCS board test, as described previously [14].

2.2. Study population

We included patients aged 20 years or older that were hospitalized between April 1, 2012 and March 31, 2014 with a principal discharge diagnosis of HF as defined by International Classification of Diseases 10th Revision (ICD-10) codes I50.0, I50.1, I50.9, I11.0, I42.0, I25.5, and I42.9. Exclusion criteria were as follows (Fig. 1): 1) non-emergency admission, 2) age < 20 years, 3) New York Heart Association (NYHA) class I or no NYHA data on admission, 4) no intravenous HF medication (diuretics, vasodilators, inotropes or vasopressors) on day 1 or 2, 5) length of hospital stay ≤ 2 days, 6) sepsis, 7) major cardiovascular procedures during hospitalization (which might influence the current study outcomes), 8) renal replacement therapy on day 1 or 2, 9) mechanical support on day 1 or 2, 10) no additional acute HF exacerbation codes, 11) use of both intravenous carperitide and nitrates on day 1 or 2, and 12) subject duplication. ICD-10, procedure and operation codes related to these exclusion criteria are shown in Supplementary Appendix.

This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (M28-099).

2.3. Outcome measures

Outcomes were in-hospital death, length of hospitalization, and cost of hospitalization, which included costs related to drugs, medical materials, food, and personnel. All costs and charges were converted into US dollars according to the current exchange rate (1 US dollar = 110.0 yen).

2.4. Statistical analysis

Continuous variables are presented as means ± standard deviations when normally distributed, and as medians and interquartile (IQR) ranges when not normally distributed. Comparisons of differences among groups were made using the unpaired Student's *t*-test or Mann-Whitney *U* test for continuous variables and the chi-squared test for dichotomous variables as appropriate. Inverse probability weighting (IPTW) propensity score analysis was used to evaluate the association between carperitide use and outcomes (in-hospital death, survival time; length of hospitalization, days; cost of hospitalization, Japanese Yen and US dollars) compared to the association between nitrates use and outcomes by estimating average treatment effects (ATEs) and ATEs on the treated (ATET) as described previously [15]. ATEs represent the absolute difference in survival time and length of hospitalization (days) and total cost of hospitalization (US dollars) between carperitide treatment versus nitrate treatment across the weighted cohort. ATETs represent the absolute difference in survival time, length of hospitalization and total cost of hospitalization between carperitide treatment versus nitrate treatment estimated only among those who were treated. Thirteen case-mix variables, including those validated as important predictors of in-hospital death in patients with AHF from a Japanese DPC claim cohort (c-index: 0.80 [95% confidential interval 0.78–0.82]) [16], and the use of other intravenous treatments (diuretics, calcium antagonists, nicorandil, inotropes and vasopressors) were used for adjustments. Balance between the weighted groups was evaluated using the standardized differences approach and kernel density plots. Furthermore, we performed multivariable Cox regression analyses, IPTW with Cox regression (doubly-robust IPTW), to compare the risk of in-hospital death in the carperitide-treated and nitrates-treated groups. The same analyses were also applied for comparing the effects between carperitide use and no carperitide/nitrate use, and between nitrate use and no carperitide/nitrate use. All analyses were performed with STATA MP64 version 15 (StataCorp, College Station, TX, USA).

3. Results

3.1. Baseline characteristics

From the database, we identified 195,024 unplanned hospitalizations for HF between April 2012 and March 2014 in which the patients were aged 20 years or older. After applying the exclusion criteria, there were 76,924 patients in the study population (Fig. 1). Of these, 33,386 (43.4%) received carperitide during the first 2 days of hospitalization. There were significant differences in the baseline characteristics of patients treated with carperitide and nitrates, carperitide and no carperitide/nitrates, and no nitrates and no carperitide/nitrates (Table 1, Supplementary Tables S1 and S2, respectively).

Patients who received carperitide were older, more frequently admitted by ambulance, and less frequently classified as NYHA class IV than were those who received nitrates. Compared with patients who received nitrates, those who received carperitide more frequently exhibited comorbidities, such as atrial fibrillation and chronic renal failure, but the frequencies of life-threatening arrhythmias and shock were comparable between the patient groups. Patients who received nitrates more frequently required respiratory support (invasive or non-invasive positive-pressure ventilations) and received other intravenous vasodilators (calcium antagonists or nicorandil).

3.2. Inverse probability weighting (IPTW) propensity score analysis

For the balanced IPTW propensity score analysis, 902 observations at the tails (i.e., outside the bounds of 0.1 to 0.9) of the estimated propensity score distribution were removed, leaving 44,683 patients (32,552 with carperitide; 12,131 with nitrates) for analysis. After application of IPTW with all variables presented in Table 1, there was good balance in baseline characteristics between patients treated with carperitide and nitrates (Table 1). Finally, weighted and doubly-robust weighted analyses showed higher in-hospital mortality rates, longer length of hospitalizations, and greater costs of hospitalization in patients treated with carperitide than in those treated with nitrates (Tables 2 and 3). As presented in Table 3, coefficients of ATE and ATET represent the absolute difference in survival time (2.5%, 2.4%, respectively), length of hospitalization (days) (6.2%, 5.8%, respectively) and total cost of hospitalization (US dollars) (2.4%, 1.8%, respectively) in the carperitide versus nitrate treatment groups (positive value means worse outcome with carperitide than with nitrate use).

When comparing carperitide and no carperitide/nitrate use, and nitrate and no carperitide/nitrate use, after application of IPTW with all variables presented in Supplementary Tables S1 and S2, baseline characteristics showed good balance between patients treated with carperitide and no carperitide/nitrates, and between patients treated with nitrates and no carperitide/nitrates (Supplementary Tables S1 and S2). Weighted and doubly-robust weighted analyses demonstrated lower in-hospital mortality rates, longer length of hospitalization, and greater cost of hospitalization in patients treated with carperitide/nitrates than in those not treated with carperitide/nitrates (Supplementary Tables S3–S6). In subgroup analyses, a worse effect of carperitide on adjusted in-hospital mortality was observed in patients who had lower NYHA class and were admitted without an ambulance compared to that of patients receiving nitrates (Supplementary Fig. S1). Worse adjusted in-hospital mortality in patients who had higher age, and were treated with intravenous diuretics, nicorandil and inotropes/vasopressors was also observed in the carperitide group compared to the no carperitides/nitrate group (Supplementary Fig. S2).

4. Discussion

Our present findings suggest that the use of intravenous carperitide as an initial vasodilator in AHF during the first 2 days of hospitalization is associated with a higher risk of in-hospital death, longer length of
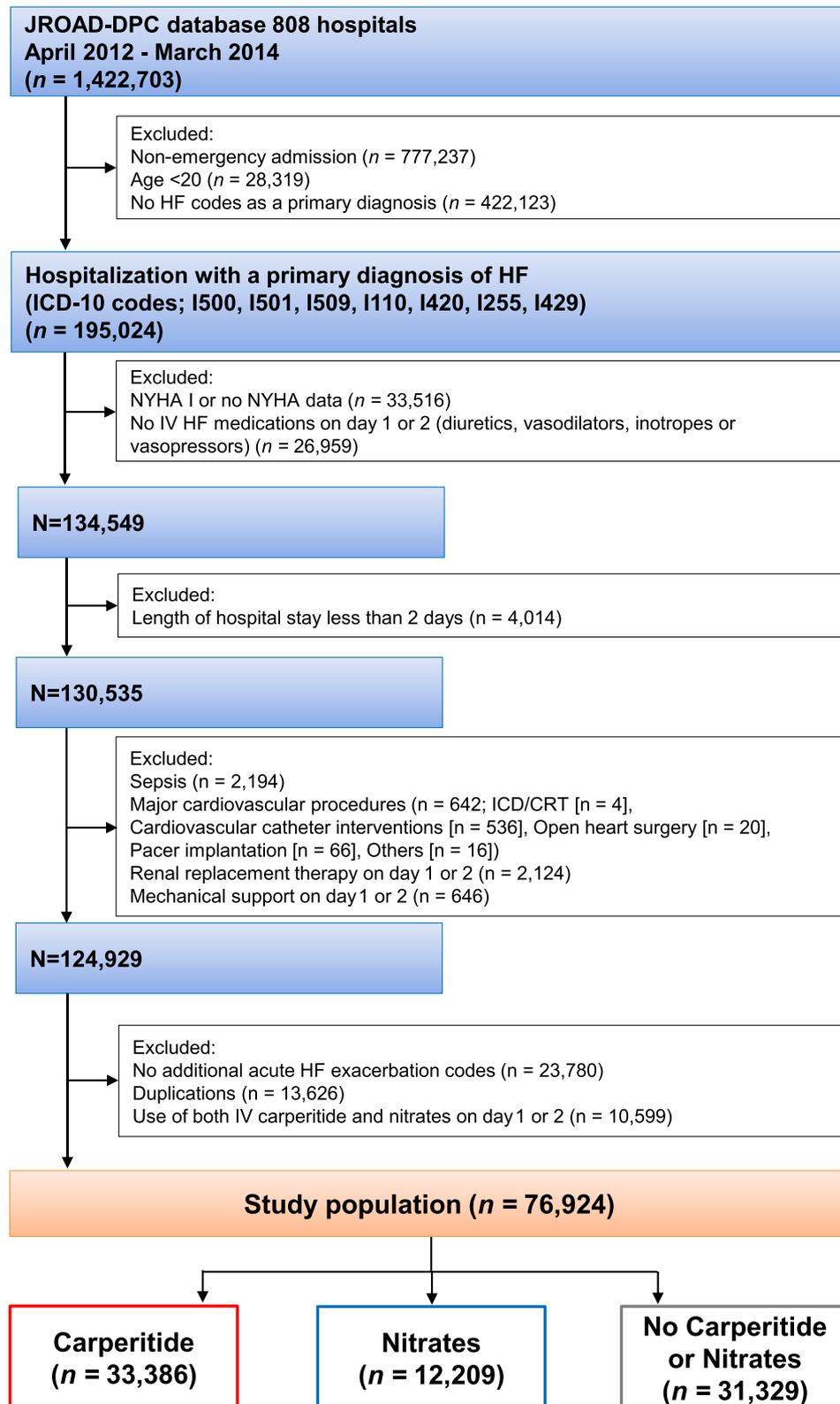
Fig. 1. Flow diagram of this study. HF, heart failure; IV, intravenous; JROAD-DPC, the Japanese Registry Of All cardiac and vascular Diseases-Diagnosis Procedure Combination; NYHA, New York Heart Association.

hospitalization, and greater hospitalization cost than the use of intravenous nitrates. The Japanese HF guidelines recommend that patients with pulmonary congestion should be treated with vasodilators and those with systemic congestion should be treated mainly with diuretics [13]. Thus, these indications and starting/stopping criteria would depend on the physician's initial assessment. In Japan, >80% of first-line vasodilators are carperitide or nitrates for AHF, without any further recommendation for selection in the Japanese HF guidelines [12,13]; however, recent studies from real world data just compared carperitide and no carperitide use [10,11]. Accordingly, our findings in a large

Table 1
Baseline characteristics in study population between carperitide and nitrates use.

Variable	Unweighted study population			Weighted study population		
	Carperitide (n = 33,386)	Nitrates (n = 12,209)	P value	Carperitide (n = 32,552)	Nitrates (n = 12,131)	Standardized difference
Age, years	78.5 ± 12.0	78.0 ± 12.2	<0.001	–	–	–
Age group, years						
20–59	2514 (7.5)	977 (8.0)	<0.001	7.9%	7.9%	0.003
60–69	3961 (11.9)	1691 (13.9)		13.1%	13.1%	0.006
70–79	8315 (24.9)	3003 (24.6)		24.5%	24.5%	0.002
80–89	13,746 (41.2)	4744 (38.9)		39.6%	39.6%	−0.003
≥90	4850 (14.5)	1794 (14.7)		14.9%	14.9%	−0.005
Male sex	15,884 (47.6)	5787 (47.4)	0.74	47.8%	47.8%	−0.009
Admission route						
Scheduled	4241 (12.7)	1110 (9.1)	<0.001	10.1%	10.1%	0.001
Emergency with ambulance	17,265 (51.7)	4338 (35.5)		39.8%	39.8%	0.008
Emergency without ambulance	11,880 (35.6)	6761 (55.4)		50.1%	50.1%	−0.009
NYHA class						
II	8993 (26.9)	2865 (23.5)	<0.001	24.4%	24.4%	0.004
III	12,869 (38.5)	3949 (32.3)		34.0%	34.0%	0.002
IV	11,524 (34.5)	5395 (44.2)		41.6%	41.6%	−0.006
Comorbidities						
Ischemic heart disease	8887 (26.6)	3657 (30.0)	<0.001	29.0%	29.0%	−0.004
Hypertension	18,582 (55.7)	7842 (64.2)	<0.001	62.3%	62.3%	0.007
Atrial fibrillation	10,538 (31.6)	2768 (22.7)	<0.001	24.4%	24.4%	0.001
Life threatening arrhythmias	481 (1.4)	174 (1.4)	0.90	1.4%	1.4%	−0.001
Chronic renal failure	3496 (10.5)	1050 (8.6)	<0.001	9.0%	9.0%	0.004
Shock	246 (0.7)	111 (0.9)	0.065	0.9%	0.9%	−0.003
Treatments						
Respiratory support	4401 (13.2)	2887 (23.6)	<0.001	22.0%	22.0%	−0.004
IV diuretics	24,797 (74.3)	10,325 (84.6)	<0.001	83.4%	83.4%	−0.03
IV calcium antagonists	2067 (6.2)	957 (7.8)	<0.001	7.3%	7.3%	−0.001
IV nicorandil	2557 (7.7)	1051 (8.6)	<0.001	7.4%	7.4%	−0.01
IV inotropes	3006 (9.2)	1070 (8.8)	0.170	8.8%	8.8%	−0.002
IV vasopressors	2143 (6.4)	927 (7.6)	<0.001	7.3%	7.3%	−0.01

Continuous variables are presented as mean ± SD. Categorical variables are presented as number of patients (%). IV = intravenous; NYHA = New York Heart Association.

nationwide cohort could provide some additional information when selecting first-line vasodilators (carperitide versus nitrates) for AHF.

Carperitide reportedly promotes vasodilation and salt and water excretion while improving diastolic filling properties, which results in reduced cardiac filling pressures without serious adverse effects [17,18]. However, American and European clinical guidelines do not strongly recommend the use of any natriuretic peptides, such as nesiritide and carperitide, as first-line therapy for patients with AHF according to the results of large-scale randomized controlled trials and real-world registries [1,2,6,19]. In contrast, carperitide is well recommended in the latest Japanese guidelines for the treatment of AHF as class IIa and level B based on favorable results in a randomized controlled trial and large cohort studies examining its safety and efficacy, which reported improved subjective symptoms and hemodynamics in over 80% of patients [9,13,20,21]. Nevertheless, this randomized controlled trial had only 49 patients, and only one death out of 11 total adverse events was observed despite the open-label design of the trial, which may have influenced the decision to admit HF cases. Therefore, the randomized controlled trials performed thus far have not adequately assessed the efficacy of

carperitide added to standard therapy compared with that of standard therapy alone in patients with AHF.

Notably, our current findings demonstrate the negative therapeutic impact of intravenous carperitide used as an initial vasodilator on in-hospital death, length of hospitalization, and cost of hospitalization for patients with AHF. These results are consistent with recent reports from two real-world AHF cohorts. First, carperitide use was significantly associated with higher in-hospital mortality of patients with AHF from a three-center retrospective cohort by propensity score-matched analyses [10]. Second, it had unfavorable effects on in-hospital survival outcomes as well as cost-effectiveness when used during the index hospitalizations of patients with AHF from a Japanese DPC dataset [11]. Generally, Japanese DPC datasets have insufficient baseline data for variables strongly related to HF severity and survival outcomes in patients with AHF (e.g., systolic blood pressure, serum sodium level, and renal function), including the DPC used in a previous report [11] and our own JROAD-DPC. Consequently, studies using such datasets might fail to adjust the odds of mortality by important prognostic variables regardless of propensity score-matched analyses. In the present

Table 2
In-hospital death, and length and cost of hospitalization between carperitide and nitrates use.

Carperitide vs. nitrates	Unweighted study population			Weighted study population		
	Carperitide (n = 33,386)	Nitrates (n = 12,209)	P value	Carperitide (n = 32,552)	Nitrates (n = 12,131)	P value
In-hospital death	2268 (6.8)	529 (4.3)	<0.001	7.0%	4.4%	<0.001
Length of hospitalization, median [IQR], days	19 [13–28]	18 [12–26]	<0.001	19 [13–28]	18 [12–26]	<0.001
Cost of hospitalization, median [IQR], Japanese yen	830,801 [583,522–1,247,556]	844,835 [597,074–1,253,732]	0.018	860,096 [602,432–1,239,236]	835,881 [591,988–1,239,994]	<0.001
Cost of hospitalization, median [IQR], US dollars	7553 [5305–11,341]	7680 [5428–11,398]		7819 [5477–11,809]	7599 [5382–11,273]	

Continuous variables are presented as median [IQR]. Categorical variables are presented as number of patients (%). US = United States.

Table 3
Effect of carperitide compared to nitrates: in-hospital death, and duration and cost of hospitalization.

	Weighted					Weighted (doubly robust)	
	ATE			ATET only			
	Coefficients (95% CI)	P value		Coefficients (95% CI)	P value	Hazard ratio (95% CI)	P value
In-hospital death	0.025 (0.020 to 0.029)	<0.001		0.024 (0.020 to 0.029)	<0.001	1.49 (1.35–1.64)	<0.001
Length of hospitalization	0.062 (0.048 to 0.076)	<0.001		0.058 (0.043 to 0.072)	<0.001	–	–
Cost of hospitalization	0.024 (0.010 to 0.037)	0.001		0.018 (0.004 to 0.033)	0.011	–	–

ATEs = average treatment effects, ATET = average treatment effects on the treated.

study, we limited the population to patients with AHF who received either intravenous carperitide or nitrates in the first 2 days of hospitalization to reduce selection bias for vasodilator use and minimize this important limitation. Moreover, we adjusted the models for outcomes with 13 variables validated as important predictors of in-hospital death of patients with AHF from a Japanese DPC claim cohort [16].

It is difficult to determine from our present findings why patients treated with carperitide had worse in-hospital outcomes than did those treated with nitrates. However, in our current investigation, a worse effect of carperitide on adjusted in-hospital mortality was observed in patients who had less severe HF (lower NYHA class) compared to that of nitrates, but the use of intravenous diuretics showed no significant interaction. Carperitide but not nitrates promotes natriuresis; therefore, excessive natriuresis by carperitide use might be associated with worse outcomes compared to nitrate use. Another hypothesis could be considered based on the concept of acute vasodilation for AHF. Recent sub-analyses of clinical trials of vasodilators indicated that serelaxin had no benefit in patients with AHF with less than minor peripheral edema, but had greater absolute benefit in patients with more than moderate peripheral edema, and nesiritide had no beneficial effect on subsequent mortality regardless of the presence of systemic congestion [22,23]. These results suggest beneficial effects of pure vasodilators (e.g. serelaxin, nitrates) for AHF compared to natriuretic peptides. To further examine this hypothesis, well-designed prospective studies are warranted. The ongoing LASCAR-AHF trial is examining whether low-dose intravenous carperitide reduces the risk of mortality and rehospitalization for HF for up to 2 years in patients hospitalized with AHF [24]. This trial might shed light on the role of carperitide in the initial management for AHF.

4.1. Study limitations

First, our study was limited by the lack of access to biomarkers related to kidney function, B-type natriuretic peptide level, echocardiographic parameters of left ventricular function, and hemodynamics, including blood pressure and heart rate, because JROAD-DPC did not collect these data initially. Availability of these data would have improved mechanistic evaluations and prognostication, and improve understanding of the mechanisms of differences among the groups. Second, we were unable to distinguish between HF phenotypes (i.e., HF with preserved versus reduced ejection fraction). Third, there were no adjustments for unmeasurable or unknown confounders in this study, although we performed IPTW propensity score analysis with a mortality prediction model for AHF previously validated in a Japanese DPC dataset with c-index at 0.80 [16]. Fourth, patients treated with carperitide or nitrates were younger, had more comorbid conditions, and had less treatment with other intravenous medication (diuretics, inotropes and vasopressors) compared to those not treated with carperitide/nitrates (Supplementary Tables S1 and S2). Consequently, our study population for comparing between carperitide and nitrate use could be a highly selected AHF population. Finally, there were no data regarding dose and duration of vasodilator treatment during hospitalization, which may have affected in-hospital death and costs.

In summary, in patients with AHF, the use of carperitide during the first 2 days of hospitalization was significantly associated with worse outcomes when compared to nitrates use. These findings suggest that the routine use of carperitide should not be recommended as a first-line vasodilator for AHF.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.049.

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