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Effects of Carperitide on the Long-Term Prognosis of Patients With Acute Decompensated Chronic Heart Failure

— The PROTECT Multicenter Randomized Controlled Study —

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Background Carperitide is used to treat acute decompensated heart failure (ADHF), but its effects on long-term prognosis have not been studied.

Methods and Results A multicenter randomized controlled study of 49 patients with ADHF was performed to clarify the drug's effects on long-term prognosis. Low-dose carperitide (0.01–0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused for 72h as the initial treatment (n=26), whereas in the control group (n=23), standard medical treatment other than carperitide was given without limitation. Anti-aldosterone drugs were prohibited in both groups. During carperitide infusion, significant increases of the atrial natriuretic peptide and cyclic GMP levels and a significant decrease in the heart-type fatty acid-binding protein/serum creatinine ratio were observed, suggesting inhibition of myocyte cell membrane damage. On the other hand, no significant differences in the plasma brain natriuretic peptide, troponin T, and creatinine levels were noted in either group. During 18-month follow-up, significant reductions of death and rehospitalization occurred in the carperitide vs control group (11.5% vs 34.8%; p=0.0359). Cox regression analysis revealed that randomization to carperitide (p=0.020), pretreatment systolic blood pressure ≥140 mmHg (p=0.043), and β-blocker therapy (p=0.016) were independent predictors for freedom from cardiac events.

Conclusions Acute-phase low-dose carperitide infusion improved the long-term prognosis of patients with ADHF. (*Circ J* 2008; **72:** 1787 – 1793)

Key Words: Carperitide; Heart failure; Prognosis

Atrial natriuretic peptide (ANP) was identified in 1984 as a circulating peptide consisting of 28 amino acids of cardiac origin[1,2] and carperitide is a commercially developed recombinant form of ANP that has been used clinically for the management of acute decompensated heart failure (ADHF). The main cardiovascular effects of carperitide are vasodilation to reduce both cardiac preload and afterload, natriuretic action, and inhibition of the renin – angiotensin – aldosterone system (RAAS).[2,3] Shono et al found that carperitide infusion has a direct antioxidant effect on the failing heart;[4] but although the clinical effectiveness of carperitide has been reported in patients with ADHF[5–9] or acute myocardial infarction (MI) complicated with heart failure,[10–13] its effects on cardiorenal protection and long-term prognosis remain unknown.

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Methods

Study Population

Between January 1, 2002 and December 31, 2004, 49 patients with ADHF from 8 institutes were enrolled. Inclusion criteria were: (1) New York Heart Association (NYHA) class Ⅲ–Ⅳ; (2) left ventricular ejection fraction (LVEF) ≤45%; (3) presence of dyspnea; and (4) able to be treated within 24 h of hospitalization. Exclusion criteria were: (1) systolic blood pressure (BP) <90 mmHg or cardiogenic shock; (2) ongoing ventilator therapy; (3) dehydration; (4) MI in the previous 3 months; (5) severe organ failure; (6) ongoing participation in a clinical trial; (7) severe infection; (8) pregnancy, possibility of pregnancy, or lactating; (9) lack of informed consent; and (10) any other condition

Table 1 Study Design

	Before treatment	After treatment			One day after last carperitide infusion*	Before discharge	After discharge
		6 h	24 h	4 days			
Background	○						
Physical findings	○	○	○	○	○	○	
UCG	○			○	○	○	
ECG monitor	←	—	—	—	→		
Blood sampling	○	○	○	○	○	○	
Clinical events	←	—	—	—	—	—	→

UCG, ultrasound cardiography.
**Evaluations and examinations performed during carperitide infusion period (duration, 4 days).*

Table 2 Patients' Backgrounds

	Carperitide group	Control group	p value
Sex (M/F)	14/12	18/5	NS
Age (years)	67.4±10.9	68.9±9.0	NS
Body weight (kg)	61.2±12.3	61.2±10.5	NS
Etiology			
MI	12	8	NS
CM	7	7	
Valve	10	10	
HHD	5	5	
Other	4	4	
NYHA			
III	21	13	0.07
IV	5	10	
Killip			
I	6	2	NS
II	12	10	
III	7	11	
IV	1	0	
Forrester			
I	2	0	NS
II	2	0	
III	0	0	
IV	1	2	
Unknown	21	21	
LVEF (%)	31.8±8.6	31.5±8.5	NS
Dyspnea			
Mild	14	5	0.07
Moderate	9	12	
Severe	3	6	
History of HF			
No	23	17	NS
Yes	3	6	
Comorbidity			
Kidney	10	7	NS
Liver	2	4	
Lung	0	3	
HL	8	4	
DM	7	9	

MI, myocardial infarction; CM, cardiomyopathy; Valve, valvular heart disease; HHD, hypertensive heart disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HF, heart failure; HL, hyperlipidemia; DM, diabetes mellitus.

Table 3 Additional Drugs Administered Intravenously During Study Period

	Carperitide group	Control group	p value
Diuretics			
Furosemide (IV infusion)	16	20	NS
Furosemide (continuous infusion)	1	1	
Vasodilator			
Nitroglycerin	4	11	0.0165
Isosorbide dinitrate	2	2	
Inotropics			
Dopamine	3	4	NS
Dobutamine	1	2	
Olprinone	0	1	
Amrinone	1	1	
Others	9	5	NS

rendering the patient unsuitable for inclusion.

Study Design and Protocol

We designed a multicenter, prospective, randomized, open-labeled, controlled study (Table 1). Subjects were randomly assigned to receive standard therapy plus carperitide (carperitide group) or standard therapy without carperitide (control group). Carperitide was administered continuously by intravenous infusion for 48–72 h, initially at $0.01\,\mu g \cdot kg^{-1} \cdot min^{-1}$ and increased to $\leq 0.05\,\mu g \cdot kg^{-1} \cdot min^{-1}$ based on each patient's physical condition. There were no limitations on the standard therapies for heart failure in either group, except for the use of aldosterone blockers such as spironolactone and potassium canrenoate.

Clinical Evaluation

Echocardiography was performed to assess LVEF before and 4 days after treatment, 1 day after termination of carperitide infusion, and before discharge from hospital. ECG monitoring was continued throughout the treatment period. Blood sampling was performed before, 6 and 24 h, and 4 days after starting the treatments, 1 day after termination of carperitide infusion, and before discharge. After informed consent was given, blood was collected by direct venipuncture of an antecubital vein while the patient was supine. Blood samples were collected into tubes containing EDTA and centrifuged within 30 min of collection. Serum concentrations of brain natriuretic peptide (BNP; radioimmunoassay, Shionoria, Shionogi, Osaka, Japan), heart-type fatty-acid-binding protein (H-FABP; 2-step direct sandwich-ELISA quantitative measures; Market-M, Dainippon Pharmaceutical Co, Osaka, Japan), troponin T (ELISA, Elecsys, Roche Diagnostics, Basel, Switzerland; detection limit: 0.01 ng/ml), creatinine, and β-2-microglobulin were measured to evaluate left ventricular (LV) wall stress, membrane damage or myofibril damage of cardiomyocyte as the initial process of ongoing myocardial damage[4] and glomerular filtration function, respectively.

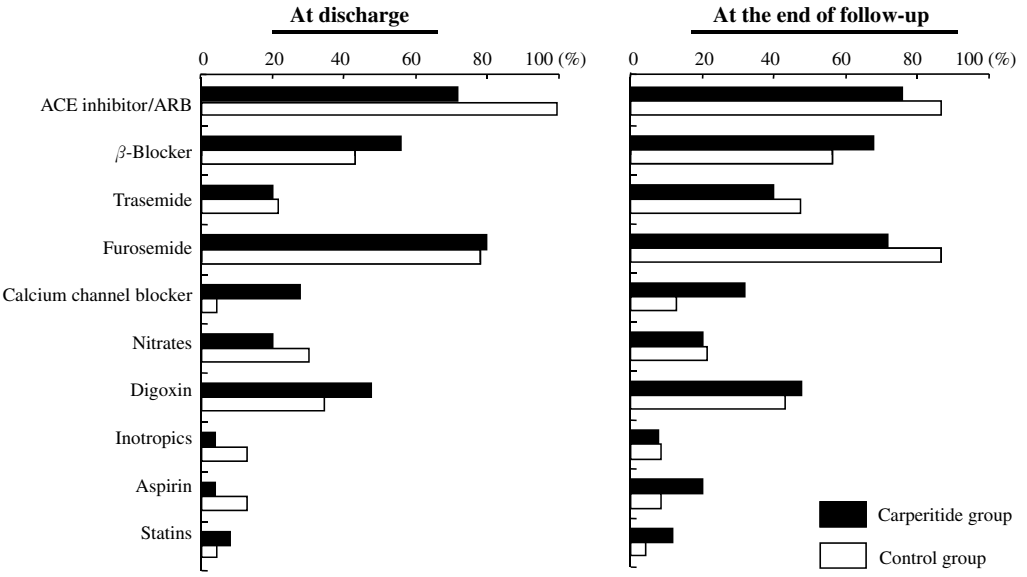
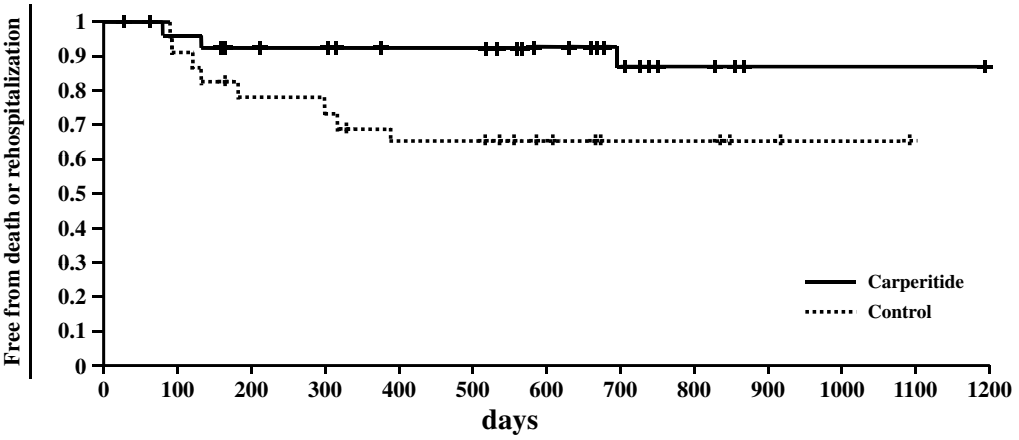


Fig 1. Medications at discharge (Left) and at the end of follow-up (Right). ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker.



	Patients	Patients with cardiac event	Log-rank test	
Carperitide	26	3	χ^2=4.4024	p=0.0359
Control	23	8		

Fig 2. Outcome of patients: 3 of 26 carperitide group patients and 8 of 23 control group patients had cardiac events during the follow-up period. Clinical outcomes of the discharged patients with acute decompensated heart failure in the carperitide group were better than those of patients in the control group.

Etiology and past history of heart failure, as well as concurrent diseases (diabetes mellitus, hypertension, hyperlipidemia, renal diseases, hepatic diseases, and respiratory diseases) were recorded. Medications and clinical outcome were investigated for an average of 500 days. The evaluation of outcome after discharge included all deaths and rehospitalization for progressive heart failure, or severe arrhythmia. Written informed consent was given by all participants, and the study was approved by the institutional review board/independent ethics committee of each participating institution.

Statistical Analysis

All numerical data are expressed as mean ± SD. An error probability of $p<0.05$ was regarded as significant. Time-related comparison of hemodynamic and biochemical parameters was analyzed by 1-way analysis of variance (ANOVA). Improvement of clinical signs and comparison of medications were analyzed by Whitney-Mann U-test and chi-square test. Among the patients' characteristics and clinical parameters, selected variables used in the Cox proportional hazard model for multivariate analysis with stepwise method were used to predict heart failure outcome.

Table 4 Changes in the Clinical Parameters

	Before treatment	After treatment			Before discharge
		6 h	24 h	4 days	
SBP (mmHg)					
CAR	141.6±27.0	122.4±29.0	122.6±21.4	124.8±23.6	117±17.0
CON	150.3±25.5	129.1±16.8	123.9±19.5	117.3±16.6	117±14.6
DBP (mmHg)					
CAR	80.4±20.6	71.8±18.0	64.6±14.8	72.8±16.6	67.2±13.8
CON	85.3±15.7	73.0±16.3	68.7±8.5	67.3±10.2	65.4±10.7
HR (beats/min)					
CAR	97.0±21.6	85.3±22.2	80.7±20.0	71.5±12.7	68.0±9.8
CON	97.7±20.9	83.4±17.6	81.1±12.6	74.5±13.9	71.0±10.7
LVDd (mm)					
CAR	62.9±10.5	–	–	–	58.5±12.0
CON	60.0±8.2	–	–	–	59.7±8.9
LVDs (mm)					
CAR	54.3±10.7	–	–	–	47.5±11.6
CON	51.7±9.0	–	–	–	46.3±11.4
LVEF (%)					
CAR	30.7±10.1	–	–	–	42.4±13.5
CON	31.7±8.6	–	–	–	44.8±14.3
ANP (pg/ml)					
CAR	234.0±160.8	–	904.4±1,029.5†	476.2±705	120±91.3
CON	207.9±133.1	–	185.7±101.0	151.6±111.0	121.0±112
cGMP (pmol/ml)					
CAR	13.7±9.9	–	15.4±6.4†	10.1±4.9	8.0±4.3
CON	12.3±4.9	–	11.3±5.5	10.2±4.2	9.4±7.9
BNP (pg/ml)					
CAR	1,110.9±1,001	–	612.4±580.6	532.2±562	393±385
CON	841.7±521.8	–	489.2±453.9	377.3±305	313±306
Troponin-T (>0.02 mg/ml)					
CAR	11/26	–	10/26	13/26	4/26
CON	11/23	–	10/23	8/23	5/26
H-FABP (ng/ml)					
CAR	8.68±6.85	–	6.19±3.19	6.89±4.79	5.57±4.17
CON	9.76±6.81	–	9.04±5.64	7.46±4.82	7.07±5.31
H-FABP/Cr					
CAR	7.79±8.29	–	5.33±2.24†	6.01±4.30	4.66±1.99
CON	8.01±4.28	–	7.33±3.05	6.20±3.21	5.13±2.13
Cr (mg/dl)					
CAR	1.16±0.52	–	1.18±0.46	1.18±0.57	1.21±0.60
CON	1.20±0.56	–	1.22±0.54	1.22±0.54	1.31±0.64
β2MG (mg/L)					
CAR	3.0±1.8	–	2.9±1.6	3.2±1.8	2.9±1.6
CON	3.3±2.00	–	3.3±2.0	3.7±2.5	4.0±2.8

†p<0.05 vs control group.
CAR, carperitide group; CON, control group; S(D)BP, systolic (diastolic) blood pressure; HR, heart rate; LVDd(s), diastolic (systolic) left ventricular diameter; ANP, atrial natriuretic peptide; cGMP, cyclic guanosine monophosphate; BNP, brain natriuretic peptide; H-FABP, heart-type fatty-acid-binding protein; Cr, creatinine; β2MG, β-2 microglobulin. Other abbreviation see in Table 2.

Results

Patients' Backgrounds

Etiology of heart failure was prior MI in 12 cases in the carperitide group and in 8 in the control group; NYHA classification was IV in 5 of the carperitide group and 10 of the control group; and the degree of dyspnea was judged as mild in 14 of the carperitide group and in 5 of the control group. There was no significant difference between the carperitide and control groups in the pretreatment background (Table 2).

Treatment of Heart Failure

The initial dose of carperitide was 0.024±0.023 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (median, 0.01), with a treatment duration 102.43±86.87 h (median, 71.98). Table 3 lists additional drug treatments administered intravenously during the study period. Intravenous vasodilators (nitroglycerin, isosorbide dinitrate, and nicardipine) were used significantly (p=0.0165) more frequently in the control group than in the carperitide group. There was no significant difference between the 2 groups in the use of other drugs (diuretics, inotropic agents). Medications used following discharge from hospital and at the end of follow-up are shown in Fig 1, with no significant difference noted between the 2 groups.

Duration of Hospitalization and Follow-up

The duration of hospitalization was 54.8±44.9 days in the carperitide group and 35.9±21.4 days in the control group. The follow-up period was 507±226 days in the carperitide group and 517±230 days in the control group. There was no significant difference between the 2 groups for either of these time periods.

Effects of Carperitide Treatment on ADHF Inpatients

At 24 h after starting treatment, serum ANP and cGMP levels were elevated significantly higher in the carperitide group (904.4±1,029.5 pg/ml and 15.4±6.4 pmol/ml, respec-

Table 5 Predictive Variables of Cardiac Events

	Category	HR (95% CI)	p value
Medication	*Control/carperitide*	*5.945 (1.290–23.41)*	*0.021*
SBP before treatment	*≥/<140 mmHg*	*0.264 (0.072–0.949)*	*0.041*
β-blocker use at the end of follow-up period	*Present/absent*	*0.151 (0.031–0.727)*	*0.018*

CI, confidence interval. Other abbreviations see in Table 4.

tively) than in the control group (185.7±101.0 pg/ml and 11.3±5.5 pmol/ml, respectively). During this period, the H-FABP/creatinine ratio in the carperitide group (5.33±2.24) was significantly lower than that in the control group (7.33±3.05; p=0.0219, respectively). However, there were no significant differences in the changes in the other biomarkers analyzed.

Effects of Carperitide on Long-Term Prognosis

Outcomes of the all patients were able to be evaluated throughout the study period; 3 of 26 carperitide group patients (1 cardiac death and 2 re-hospitalizations) and 8 of 23 control group patients (re-hospitalizations in all) had cardiac events during the follow-up period. Fig 2 shows the Kaplan-Meier curves of death or rehospitalization in the carperitide and control groups. There was a significant difference between the 2 groups (11.5% vs 34.8%; p=0.0359). Cox proportional hazard model for multivariate analysis with stepwise method was performed to select variables predicting outcome of ADHF. The first model, including medication and patients' characteristics (Table 2) and clinical parameters (Table 4) as covariates, was developed using a stepwise method for variable selection. Medication with carperitide infusion and systolic BP on admission were selected. Subsequently, serum levels of biomarkers (H-FABP, creatinine, H-FABP/creatinine and β-2 microglobulin), and β-blocker therapy at the end of the study period were examined using the same manner. In the final model, carperitide infusion, systolic BP on admission ≥140 mmHg, and β-blocker therapy at the end of the study period were judged as independent predictors of freedom from cardiac events in the ADHF population (Table 5).

Discussion

Effects of Carperitide in ADHF Patients

In a previous study, Munzel et al reported the clinical efficacy of a short infusion of low-dose carperitide ($0.075\mu g \cdot kg^{-1} \cdot min^{-1}$; 20 h) in patients with chronic heart failure, and they concluded that the main responses that contributed to the improvement of heart failure symptoms were reduction of both central filling pressure and the plasma aldosterone level, and increased cardiac output, diuresis, glomerular filtration rate, and plasma cGMP level[6] Saito et al also reported the clinical efficacy of a short infusion of carperitide ($0.1\mu g \cdot kg^{-1} \cdot min^{-1}$) in the treatment of chronic heart failure and attributed the clinical improvements to the drug's vasodilating property[5] Shono et al found that carperitide infusion has a direct antioxidant effect on the failing heart[4] Kitashiro et al reported good efficacy of carperitide infused over an average of 7 days for the treatment of heart failure[7] and Suwa et al investigated real-world registry data and found that improvement of heart failure symptoms occurred in 82% of patients without significant adverse effects, other than transient lowering of BP, during 3 days of intravenous carperitide administration ($0.05–0.1\mu g \cdot kg^{-1} \cdot min^{-1}$)[8]

In the present study, low-dose carperitide was infused as the initial treatment (average initial dose, $0.024\mu g \cdot kg^{-1} \cdot min^{-1}$) for 3–4 days (average, 102 h). Although the initial dose was lower than those used in previous investigations, almost equivalent clinical effects were obtained with no significant adverse events.

In accordance with the cardiovascular effects of carperitide, the H-FABP/creatinine ratio decreased only in the carperitide group, suggesting possible inhibition of myocyte cell membrane damage in acute heart failure.

Colucci et al[15] and the Committee for Vasodilatation in the Management of Acute CHF (VMAC) Investigators[16] reported that the mechanism and effects of synthesized BNP (nesiritide) in heart failure were similar to those of carperitide. Fifer et al found the same effect of another vasodilating natriuretic peptide, anaritide![17]

Decrease in H-FABP/Creatinine Ratio

We have previously shown that the presence of ongoing myocardial damage can be detected by increased levels of cardiac troponin T, a myofibril damage marker, and H-FABP, a membrane damage marker, in patients with chronic heart failure, which identifies increased risk for future cardiac events![14] There is a difference in the release kinetics of troponin T and H-FABP following myocardial damage. Serum levels of H-FABP, a low-molecular-weight protein abundantly contained in the cytosol of cardiomyocytes and a useful marker of early-phase acute MI, are increased in patients with CHF![14] and H-FABP measurement compensates for the limitations of troponin T in the early phase of acute MI. Thus it is reasonable to infer that analyzing the combination of markers might be clinically useful for pathophysiological assessment of ongoing myocardial damage in patients with CHF. We assessed the H-FABP/creatinine ratio rather than the H-FABP concentration per se because of renal clearance of H-FABP. In the present study, changes in the troponin T level were not significantly different between the carperitide and control groups. However, the H-FABP/creatinine ratio displayed significant decreases in the carperitide group compared with the control group, suggesting possible protection from cardiomyocyte membrane damage and resultant decreased H-FABP release. Although troponin T is an established sensitive marker of myocardial damage, elevated levels are relatively small, even in severe CHF, because most troponin T exists as a contractile apparatus in cardiac myocytes. In contrast, H-FABP concentrations elevate more readily when accompanying ongoing myocardial damage in CHF, as we previously reported![14] Thus, measurement of H-FABP will detect ongoing myocardial damage and reflect the severity of CHF more definitely. In the present study, we measured serum H-FABP and troponin T levels simultaneously as part of our investigation into the possibility of cardioprotection by carperitide infusion therapy in the acute stage of heart failure. Thus the difference between the release kinetics of troponin T and H-FABP suggested the cardioprotective effect of carperitide

infusion therapy could be detected by H-FABP, which should be a more sensitive marker and have faster release kinetics than troponin T.

Improvement of Long-Term Prognosis in ADHF Patients

Chang et al[18] and Lenz et al[19] reported that nesiritide infusion shortened the period of hospitalization for the treatment of heart failure. Abraham et al also reported improvements in the outcome of heart failure patients receiving nesiritide that were similar to those observed in patients receiving intravenously infused nitroglycerin and superior to those seen with milrinone and dobutamine.[20] Additionally, Hammermeister et al[12] and Hayashi et al[13] reported that infused ANP suppressed remodeling of the left ventricle in patients with acute MI, resulting in prognostic improvement. Experimental studies have revealed that LV remodeling is closely related to activation of the angiotensin II and endothelin-1 systems.[21–23] Thus, infused ANP may improve the outcome of heart failure by inhibiting RAAS and endothelin-1 activation. Sezai et al[24] reported that carperitide infusion during emergency coronary artery bypass grafting could lower the incidence of postoperative cardiac events, as well as the peak levels of creatine kinase-MB and BNP.[24] On the other hand, there are no reports of the effects of ANP infusion on improvement of the long-term prognosis in ADHF. Therefore, we consider the results of this study to have new and important significance for the treatment of acute heart failure.

Cox regression analysis revealed that patients with systolic BP ≥140 mmHg before treatment and those starting β-blocking agents during the follow-up period had better outcomes after discharge from hospital. We had assumed that drug treatment including diuretics and carperitide would be more problematic in heart failure patients with low BP than in patients with normal or high BP, as few reports have addressed systolic BP before treatment.[25–28]

Study Limitations

First, the number of cases was not large. Second, vasodilating drugs were more frequently used in the control group than in the carperitide group, probably because of the open-label study design. Third, we could not clarify the cardiorenal protective effects of carperitide and the mechanism of improvement of heart failure in the present study, based on our analysis of cardiac markers, except for possible inhibition of myocyte membrane damage. In future research, a controlled large-scale double blind study would be useful to resolve the issues raised by our study.

Conclusions

Acute-phase low-dose carperitide infusion did improve the long-term prognosis of patients with ADHF.

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References

1. Kangawa K, Fukuda A, Matsuo H. Structural identification of beta- and gamma-human atrial natriuretic polypeptides. *Nature* 1985; **313:** 397–400.
2. Kangawa K, Matsuo H. Purification and complete amino acid sequence of alpha-human atrial natriuretic polypeptide (alpha-hANP). *Biochem Biophys Res Commun* 1984; **118:** 131–139.
3. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* 1981; **28:** 89–94.
4. Shono M, Yoshimura M, Nakayama M, Yamamuro M, Abe K, Suzuki S, et al. Predominant effect of A-type natriuretic peptide on reduction of oxidative stress during the treatment of patients with heart failure. *Circ J* 2007; **71:** 1040–1046.
5. Saito Y, Nakao K, Nishimura K, Sugawara A, Okumura K, Obata K, et al. Clinical application of atrial natriuretic polypeptide in patients with congestive heart failure: Beneficial effects on left ventricular function. *Circulation* 1987; **76:** 115–124.
6. Munzel T, Drexler H, Holtz J, Kurtz S, Just H. Mechanisms involved in the response to prolonged infusion of atrial natriuretic factor in patients with chronic heart failure. *Circulation* 1991; **83:** 191–201.
7. Kitashiro S, Sugiura T, Takayama Y, Tsuka Y, Izuoka T, Tokunaga S, et al. Long-term administration of atrial natriuretic peptide in patients with acute heart failure. *J Cardiovasc Pharmacol* 1999; **33:** 948–952.
8. Suwa M, Seino Y, Nomachi Y, Matsuki S, Funahashi K. Multicenter prospective investigation on efficacy and safety of carperitide for acute heart failure in the 'real world' of therapy. *Circ J* 2005; **69:** 283–290.
9. Ishikawa C, Tsutamoto T, Wada A, Fujii M, Ohno K, Sakai H, et al. Inhibition of aldosterone and endothelin-1 by carperitide was attenuated with more than 1 week of infusion in patients with congestive heart failure. *J Cardiovasc Pharmacol* 2005; **46:** 513–518.
10. Serizawa T, Kohmoto O, Iizuka M, Hirata Y, Matsuoka H, Ohya T, et al. Effects of alpha human atrial natriuretic polypeptide on the systemic hemodynamics and coronary circulation in patients with ischemic heart disease. *Jpn Circ J* 1988; **52:** 1107–1113.
11. Kikuchi M, Nakamura M, Suzuki T, Sato M, Takino T, Hiramori K. Usefulness of carperitide for the treatment of refractory heart failure due to severe acute myocardial infarction. *Jpn Heart J* 2001; **42:** 271–280.
12. Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary disease: Selection by univariate and multivariate analyses from the clinical, electrocardiographic, exercise, arteriographic, and quantitative angiographic evaluations. *Circulation* 1979; **59:** 421–430.
13. Hayashi M, Tsutamoto T, Wada A, Maeda K, Mabuchi N, Tsutsui T, et al. Intravenous atrial natriuretic peptide prevents left ventricular remodeling in patients with first anterior acute myocardial infarction. *J Am Coll Cardiol* 2001; **37:** 1820–1826.
14. Setsuta K, Seino Y, Ogawa T, Arao M, Miyatake Y, Takano T. Use of cytosolic and myofibril markers in the detection of ongoing myocardial damage in patients with chronic heart failure. *Am J Med* 2002; **113:** 717–722.
15. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure: Nesiritide Study Group. *N Engl J Med* 2000; **343:** 246–253.
16. Publication Committee for the VMAC INvestigators (Vasodilation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: A randomized controlled trial. *JAMA* 2002; **287:** 1531–1540.
17. Fifer MA, Molina CR, Quiroz AC, Giles TD, Herrmann HC, De Scheerder IR, et al. Hemodynamic and renal effects of atrial natriuretic peptide in congestive heart failure. *Am J Cardiol* 1990; **65:** 211–216.
18. Chang R, Elatre WA, Heywood JT. Effect of nesiritide on length of hospital stay in patients with decompensated heart failure. *J Cardiovasc Pharmacol Ther* 2004; **9:** 173–177.
19. Lenz TL, Foral PA, Malesker MA, Hunter CB, Hilleman DE. Impact of nesiritide on health care resource utilization and complications in patients with decompensated heart failure. *Pharmacotherapy* 2004; **24:** 1137–1146.
20. Abraham WT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: An analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; **46:** 57–64.
21. Brilla CG, Zhou G, Matsubara L, Weber KT. Collagen metabolism in cultured adult rat cardiac fibroblasts: Response to angiotensin II and aldosterone. *J Mol Cell Cardiol* 1994; **26:** 809–820.
22. Ito H, Hirata Y, Adachi S, Tanaka M, Tsujino M, Koike A, et al. Endothelin-1 is an autocrine/paracrine factor in the mechanism of angiotensin II-induced hypertrophy in cultured rat cardiomyocytes. *J Clin Invest* 1993; **92:** 398–403.
23. Harada K, Sugaya T, Murakami K, Yazaki Y, Komuro I. Angiotensin

II type 1A receptor knockout mice display less left ventricular remodeling and improved survival after myocardial infarction. *Circulation* 1999; **100:** 2093–2099.
24. Sezai A, Hata M, Wakui S, Niino T, Takayama T, Hirayama A, et al. Efficacy of continuous low-dose hANP administration in patients undergoing emergent coronary artery bypass grafting for acute coronary syndrome. *Circ J* 2007; **71:** 1401–1407.
25. Pulignano G, Del Sindaco D, Tavazzi L, Lucci D, Gorini M, Leggio F, et al. Clinical features and outcomes of elderly outpatients with heart failure followed up in hospital cardiology units: Data from a large nationwide cardiology database (IN-CHF Registry). *Am Heart J* 2002; **143:** 45–55.
26. Siirila-Waris K, Lassus J, Melin J, Peuhkurinen K, Nieminen MS, Harjola VP. Characteristics, outcomes, and predictors of 1-year mortality in patients hospitalized for acute heart failure. *Eur Heart J* 2006; **27:** 3011–3017.
27. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: A report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006; **47:** 76–84.
28. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006; **296:** 2217–2226.