Results of Low-Dose Carperitide Infusion in High-Risk Patients Undergoing Coronary Artery Bypass Grafting

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Background. This study investigated the efficacy of human atrial natriuretic peptide (hANP, carperitide) for high-risk patients undergoing coronary artery bypass grafting (CABG).

Methods. This was a randomized controlled trial of 367 high-risk patients (European System for Cardiac Operative Risk Evaluation above 6) undergoing CABG. The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE). Secondary endpoints were (1) postoperative death, (2) MACCE + hemodialysis, and (3) serum creatinine and brain natriuretic peptide (BNP) levels. Logistic regression analysis was conducted to identify preoperative and perioperative factors related to early death and MACCE.

Results. There was no significant difference of survival between the hANP and placebo groups (p = 0.1651), but the MACCE-free rate was significantly higher in the hANP group than in the placebo group (p < 0.0001). No patient from the hANP group started hemodialysis after operation, but 7 patients did in the placebo group, and the dialysis rate was significantly lower in the hANP group (p = 0.0147). Serum creatinine and BNP were also significantly lower in the hANP group at 1 year postoperatively. MACCE were strongly associated with age 75 years or older, chronic kidney disease, hemodialysis, left ventricular dysfunction, and nonuse of carperitide.

Conclusions. In the early postoperative period, carperitide has a cardiorenal protective effect that prevents postoperative MACCE and hemodialysis. Perioperative low-dose carperitide infusion may be useful in high-risk patients undergoing on-pump CABG.

Owing to the aging of society and technical advances, coronary artery bypass grafting (CABG) is increasingly being done in high-risk patients with coronary heart disease [1]. For such high-risk patients, a detailed strategy encompassing both the surgical procedure and perioperative management is needed. Although many studies have investigated the clinical outcome in the acute postoperative period or over the long term for high-risk patients, few studies have examined therapies that can reduce their level of risk.

We evaluated the effectiveness of human atrial natriuretic peptide (hANP, carperitide) (Daiichi-Sankyo Pharmaceutical, Inc, Tokyo, Japan, and Asubio Pharmaceuticals, Inc, Kobe, Japan) for patients with acute coronary syndrome, left ventricular dysfunction, and with or without chronic kidney disease (CKD). These investigations revealed that carperitide inhibits the renin-angiotensin-aldosterone system (RAAS) and has a potent natriuretic effect, allowing it to compensate for the adverse effects of cardiopulmonary bypass (CPB), inhibit left ventricular remodeling, and prevent renal dysfunction.

Thus, carperitide has shown cardioprotective and renoprotective effects in patients receiving on-pump CABG [2–6]. Although there are many scoring systems for assessment of severity, this study used the additive EuroSCORE: 0 to 2 is low risk, 3 to 5 is medium risk, and 6 and above is high risk [1, 7].

In the present study, the Nihon University Working Group Study of low-dose hANP infusion therapy during cardiac surgery (NU-HIT) for high-risk patients), the efficacy of carperitide in patients with multiple comorbidities was investigated. The additive European System for Cardiac Operative Risk Evaluation (EuroSCORE) was judged to be the most appropriate objective indicator of risk, and we enrolled patients registered in the NU-HIT trial for CABG with an additive EuroSCORE of 6 or higher. Both early postoperative results and the long-term outcome were examined.

Patients and Methods

Study Protocol

The subjects were patients registered in the NU-HIT trial for CABG with an additive EuroSCORE of 6 points or higher who underwent isolated CABG with CPB. Exclusion criteria were refusal to provide informed consent, off-pump CABG, and concomitant operations. The 925...
patients enrolled in the NU-HIT trial were randomized by the lottery method to two groups: a hANP group that received infusion of carperitide from the initiation of CPB, and a placebo group. A total of 384 patients (EuroSCORE > 6) were evaluated in the present NU-HIT trial for high-risk patients. Because carperitide is approved for treatment of acute cardiac failure in Japan, but not for administration during cardiac surgical procedures, approval for this study was obtained from the Ethics Committee of Nihon University Itabashi Hospital, the details of the study were explained to subjects, and informed consent was obtained from each patient. This study was registered with the University Hospital Medical Information Network (study ID: UMIN000004537). Treatment was provided in a double-blind manner. Administration of carperitide was initiated at the start of CPB. The infusion rate was decreased to 0.01 μg/kg/min at the commencement of oral medication, and then infusion was discontinued after another 12 hours. CPB was performed with nonpulsatile low-temperature perfusion.

Study Endpoints
The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE). The secondary endpoints were (1) postoperative death, (2) MACCE + hemodialysis (HD), and (3) serum creatinine (sCr) and brain natriuretic peptide (BNP) levels at 1 week and 1 year postoperatively.

Risk Analysis
Logistic regression analysis was conducted to assess the relation of preoperative factors (age ≥ 80 years or ≥ 75 years, male sex, coronary risk factors, cerebrovascular disease, chronic obstructive pulmonary disease [COPD], CKD [estimated glomerular filtration rate < 60 mL/min/1.73 m²], hemodialysis, acute myocardial infarction, emergency operation, left main trunk disease, shock, preoperative intraaortic balloon pumping, and left ventricular dysfunction [EF < 40%]) and perioperative factors (ACT > 90 min, ECCT > 180 min, and hANP therapy) to the early outcome and MACCE.

MACCE were defined as all-cause death, postoperative cardiac failure, myocardial infarction, repeat revascularization, hospitalization for heart failure, and cerebrovascular accidents.

Statistical Analysis
Data are expressed as the mean ± standard deviation (SD). Statistical significance of differences was determined by using Student’s t test for continuous variables and Fisher’s exact test for categoric variables. Because of the skewed distribution of the data, BNP and sCr were assessed by the Mann-Whitney test. The overall survival rate, MACCE-free rate, and MACCE + HD—free rate were determined by the Kaplan-Meier method, and the significance of differences was assessed by the log-rank test. Independent predictors of early death and MACCE were examined by multivariate analysis using the parameters with p < 0.05 in univariate analysis. In all analyses, p < 0.05 was taken to indicate statistical significance.

Results
Patient Disposition
Initially, 384 patients were enrolled in this trial, but 5 patients were switched to off-pump CABG and 12 patients underwent concomitant operations in addition to CABG. After they were excluded from the trial, 367 patients remained. Among these 367 patients, 183 were assigned to the hANP group and 184 to the placebo group (Fig 1). The high-risk patients assessed in this study accounted for 41.5% of patients registered in the NU-HIT trial (Fig 2).

Baseline Characteristics
Preoperative patient characteristics showed no significant differences between the two groups (Table 1).

Surgical Procedures and Postoperative Management
Table 2 shows the aortic cross-clamping time, CPB time, number of bypasses performed, and mechanical and inotropic support. There were no significant differences of these parameters between the hANP group and the placebo group. The length of hospital stay was significantly shorter in the hANP group (p = 0.0492).

Primary Endpoint
The primary endpoint was MACCE (Table 3), which occurred in 17 patients from the hANP group and in 46 patients from the placebo group (p < 0.0001). The MACCE-free rate was 94.0% ± 1.8% in the hANP group and 90.7% ± 2.1% in the placebo group at 6 months.
postoperatively, and it was, respectively, 91.8% ± 2.0% versus 77.7% ± 3.1% at 1 year postoperatively and 90.7% ± 2.1% versus 75.0% ± 3.2% at 2 years postoperatively. The rates in the hANP group were significantly higher ($p < 0.0001$) (Fig 3).

Secondary Endpoints

Postoperative death. Death occurred in 14 patients from the hANP group and 22 patients from the placebo group (Table 3). There was no significant difference between the two groups ($p = 0.2189$). In the hANP group, the cause of death was heart failure in 6 patients (including 2 with low output syndrome); infection in 5; and acute myocardial infarction, arrhythmia, and malignancy in 1 patient each. In the placebo group, 8 patients died of heart failure (including 3 with low output syndrome), 4 patients each died of infection and cerebral infarction, 2 died of acute renal failure, and 1 patient each died of cardiac rupture, liver dysfunction, arrhythmia, and malignancy. The overall survival rate was 95.1% ± 1.6% in the hANP group and 90.8% ± 2.1% in the placebo group at 6 months postoperatively, 93.4% ± 1.8% versus 90.2% ± 2.2% at 1 year postoperatively, and 92.3% ± 2.0% versus 88.0% ± 2.4% at 2 years postoperatively. No significant differences were observed between the two groups ($p = 0.1651$) (Fig 4).

Cardiac-related death occurred in 7 patients from the hANP group and 10 patients from the placebo group. There was no significant difference between the two groups (Table 3). Six patients underwent emergency operations in the hANP group (86%) and 8 in the placebo group (80%), whereas 5 patients received postoperative IABP in the hANP group (71%) and 8 in the placebo group (80%). Also, there were 3 patients with decreased cardiac function before operation in the hANP group (43%) and 3 in the placebo group (30%), 2 AMI patients in the hANP group (29%) and 3 in the placebo group (30%), 5 CKD patients in the hANP group (71%) and 7 in the placebo group (70%), 2 patients who had HD in the hANP group (29%) and 3 in the placebo group (30%), and the rates are high. Furthermore, the rates of patients who showed EuroSCORE above 12 were also high in both hANP and placebo groups, with 3 patients (43%) and 6 patients (60%), respectively. The cardiac-related death—free rate was 97.8% ± 1.0% in the hANP group and 94.4% ± 1.7% in the placebo group at 6 months postoperatively, 96.7% ± 1.3% versus 94.4% ± 1.7% at 1 year postoperatively, and 96.1% ± 1.4% versus 94.4% ± 1.7% at 2 years postoperatively. No significant differences were observed between the two groups ($p = 0.442$) (Fig 4).

MACCE + Hemodialysis. Although no patients from the hANP group started dialysis after operation, 7 patients started dialysis in the placebo group (including 2 who died). The hANP group had a significantly lower dialysis rate ($p = 0.0147$). The HD-free rate was 100% in the hANP group and 96.8% ± 3.2% in the placebo group at 6 months postoperatively, 100% versus 96.8% ± 3.2% at 1 year postoperatively, and 100% versus 95.4% ± 4.6% at 2 years.
postoperatively. These rates were all significantly higher in the hANP group \( (p = 0.02) \). The MACCE + HD—free rate was 94.0% \( \pm 1.8\% \) in the hANP group and 78.8% \( \pm 3.0\% \) in the placebo group at 6 months postoperatively, 91.8% \( \pm 2.0\% \) versus 76.1% \( \pm 3.1\% \) at 1 year postoperatively, and 90.7% \( \pm 2.1\% \) versus 72.3% \( \pm 3.3\% \) at 2 years postoperatively. These rates were significantly higher in the hANP group \( (p < 0.0001) \) (Fig 3).

### Risk Analysis

Analysis of the risk factors for early death showed the factors given in Table 4. Univariate analysis indicated that age 75 years or older, HD, and COPD were risk factors, and multivariate analysis confirmed that age 75 years or older and HD were risk factors.

Analysis of the risk factors for MACCE showed the factors given in Table 5. Univariate analysis indicated that age 75 years or older, CKD, hemodialysis, left ventricular dysfunction, and nonuse of hANP were risk factors. Multivariate analysis confirmed that age 75 years or older, hemodialysis, left ventricular dysfunction, and nonuse of hANP were risk factors.

### Comment

This study of patients with an additive EuroSCORE of 6 or higher undergoing CABG showed that perioperative infusion of carperitide could reduce MACCE immediately after operation and up to 2 years postoperatively. In addition, it was found that age 75 years or older and the need for HD were strongly associated with the risk of death after operation, and MACCE was closely associated with age 75 years or older, CKD, HD, left ventricular dysfunction, and nonuse of hANP. The participants in the present study were patients with a EuroSCORE of 6 points or higher; therefore, some patients registered in the NU-HIT trial for CKD or NU-HIT trial for LVD are also included. Because not all subjects of these trials had a EuroSCORE of 6 points or higher, we analyzed 131 of 285 patients (46%) from the NU-HIT trial for CKD (6) and 63 of 133 patients (47%) from the NU-HIT trial for LVD [5] who had a EuroSCORE of 6 points or higher. As a result of the present study, the efficacy of carperitide was indicated in high-risk patients with multiple complications such as CKD or left ventricular dysfunction.

With regard to the safety of carperitide, it was reported that adverse drug reactions were observed in 4.6% of 1832 participants in the COMPASS study of patients with acute cardiac failure, and most of the adverse reactions were hypotension [8]. The incidence of severe adverse drug reactions was reported to be very low (ie, 14 episodes, or 0.71%). In this study, administration was not
discontinued in any patient because of adverse drug reactions that might have been caused by carperitide. Perioperative low-dose carperitide (0.02 μg/kg/min) was used safely and showed efficacy even at this dose.

To improve the long-term prognosis after CABG, it is important to prevent heart failure and renal failure. The sCr and BNP data obtained at 1 year in the present study suggest that initiation of carperitide infusion during operation prevents heart failure and renal failure over the long term after discharge from hospital. Our previous research has shown significantly stronger RAAS inhibition in patients receiving carperitide than in those treated with placebo [2, 4, 5]. Aldosterone promotes sodium retention, myocardial hypertrophy and fibrosis, endothelial cell damage, and renal dysfunction, which are important risk factors for cardiovascular events [9]. In studies of heart failure and myocardial infarction, a positive correlation has been identified between plasma aldosterone concentration and mortality [10, 11]. Although we are unaware of any reports of a correlation between plasma aldosterone levels and mortality after cardiac operation, rapid suppression of the early postoperative increase in aldosterone could prevent sodium retention, myocardial hypertrophy, myocardial fibrosis, and endothelial cell damage, leading to better long-term results. Even short-term treatment with carperitide can have a long-term effect (legacy effect).

At present, carperitide is available only in Japan. Although BNP (nesiritide) has not been approved in Japan, it is a natriuretic peptide product similar to carperitide that is available in Western countries. There have been a few reports about the use of carperitide in the field of cardiology [12], but the only large-scale studies of carperitide

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**Fig 3.** MACCE and MACCE+HD free rates. (hANP = human atrial natriuretic peptide; HD = hemodialysis; MACCE = major adverse cardiovascular and cerebrovascular events.)

**Fig 4.** Overall survival rate and cardiac-related death free rate. (hANP = human atrial natriuretic peptide.)

**Fig 5.** Changes in serum creatinine and brain natriuretic peptide (BNP). (hANP = human atrial natriuretic peptide.)
Table 4. Intraoperative and Postoperative Factors and Early Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>p Value</td>
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<tr>
<td>Preoperative factors</td>
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<td></td>
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<tr>
<td>Age ≥80 years</td>
<td>1.62 (0.45–5.85)</td>
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<tr>
<td>Age ≥75 years</td>
<td>2.92 (1.08–7.87)</td>
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<td>Sex; m</td>
<td>0.89 (0.31–2.61)</td>
<td>0.8375</td>
</tr>
<tr>
<td>AMI</td>
<td>1.86 (0.67–5.20)</td>
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<td>Diabetes mellitus</td>
<td>0.92 (0.35–2.44)</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Dyslipidemia</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Smoking</td>
<td>0.96 (0.35–2.65)</td>
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<td>Cerebrovascular disease</td>
<td>2.29 (0.62–8.40)</td>
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<td>CKD</td>
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<tr>
<td>Hemodialysis</td>
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<td>COPD</td>
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<tr>
<td>Left main tract lesion</td>
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<tr>
<td>Emergent</td>
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<tr>
<td>Shock</td>
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<tr>
<td>Pre-IABP</td>
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<tr>
<td>EF &lt;40%</td>
<td>0.38 (0.09–1.69)</td>
<td>0.2039</td>
</tr>
<tr>
<td>ACCT ≥90 min</td>
<td>1.10 (0.45–2.31)</td>
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<tr>
<td>CPBT ≥180 min</td>
<td>1.62 (0.20–13.2)</td>
<td>0.6515</td>
</tr>
<tr>
<td>hANP therapy</td>
<td>0.40 (0.14–1.17)</td>
<td>0.0938</td>
</tr>
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</table>

ACCT = aortic cross-clamping time; AMI = acute myocardial infarction; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CPBT = cardiopulmonary bypass time; EF = ejection fraction; hANP = human atrial natriuretic peptide; IABP = intraaortic balloon pumping.

Conducted so far are a multicenter study of its administration after reperfusion therapy in patients with acute myocardial infarction (J-WIND study) and our study on its use in patients undergoing cardiac surgical procedures (NU-HIT trial). In the J-WIND study, the hANP group had a significantly smaller infarct size, more marked improvement of cardiac function, and significantly lower rates of cardiac death and heart failure than the placebo group [13]. A metaanalysis of studies on nesiritide showed an increased risk of death and exacerbation of renal dysfunction [14]. Because this metaanalysis raised some safety concerns, a large-scale trial (ASCEND-HF) was conducted [15]. The results were presented at the American Heart Association meeting in 2010, with no increase of the death rate being reported. However, total deaths and rehospitilizations resulting from heart failure were comparable with those in the placebo group (standard therapy) [16]. Although the efficacy of nesiritide for heart failure is thus unproven, its efficacy for cardiac and renal protection has been reported in patients undergoing cardiac operations. Mentzer and colleagues [17] conducted the NAPA trial in CABG in patients with cardiac dysfunction and reported that the early postoperative peak of sCr was lower and the eGFR was higher in the BNP group, indicating that BNP improved postoperative renal function. They also found that the survival rate up to 180 days postoperatively was significantly higher in the BNP group than in the placebo group. Our study differed in using hANP rather than BNP, and the study participants did not have cardiac dysfunction, but the effects on renal function (sCr and eGFR) during the acute postoperative period were similar to those seen in the NAPA trial. Chen and colleagues [18] reported that administration of nesiritide to patients with preoperative renal dysfunction improved the postoperative cystatin level, aldosterone level, and estimated creatinine clearance. In previous studies of patients with heart failure, both bolus administration and continuous infusion of nesiritide were assessed, whereas low-dose continuous infusion was used in our study and in previous studies of cardiac operations. Although the hemodynamics of heart failure patients and changes of the RAAS may differ from those seen with cardiac operations, it is still considered that the risk of inducing hypotension is reduced by low-dose continuous infusion compared with bolus injection. From the viewpoint of safety and to maintain blood pressure and renal blood flow, the former method of administration is probably more effective. In conclusion, low-dose carperitide infusion during and after CABG may reduce cardiac and renal events in both the early postoperative period and over the long term. To our knowledge, there have been no studies comparing carperitide and nesiritide, so a head-to-head comparison may be worthwhile in the future.

We found that the efficacy of carperitide was evident in patients undergoing on-pump CABG, which is
a high-risk procedure. We concluded that carperitide is beneficial not only in patients with risk factors such as CKD or LV dysfunction but also in patients with a EuroSCORE of 6 or higher. This finding is clinically significant and could contribute to improving the long-term outcome in CABG patients. We think that further studies including low-risk patients are necessary to identify patients who do not require hANP and to define the appropriate use of hANP.

Limitations

The study participants in this research were limited to patients undergoing isolated CABG with a cardiopulmonary bypass. In the future, it will be necessary to report on the necessity of carperitide based on research on off-pump CABG and on operative procedures other than isolated CABG.

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References


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