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EXPEDITED REVIEWS

Effects of Perioperative Nesiritide in Patients With Left Ventricular Dysfunction Undergoing Cardiac Surgery

The NAPA Trial

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Objectives The purpose of this study was to determine the role nesiritide might play in patients with left ventricular dysfunction undergoing coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB).

Background Given the hemodynamic, neurohormonal, and renal effects of natriuretic peptides, nesiritide might be useful in the management of patients undergoing cardiac surgery.

Methods This prospective, double-blind, exploratory evaluation randomly assigned patients with ejection fraction ≤40% who were undergoing CABG with anticipated use of CPB to receive either nesiritide or placebo, in addition to usual care, for 24 to 96 h after induction of anesthesia. Postoperative renal function, hemodynamics, and drug use (primary end points) were assessed in patients who underwent CABG using CPB; mortality and safety (secondary end points) were assessed in all patients who received the study drug.

Results Of 303 randomized patients, 279 received the study drug and 272 underwent CABG using CPB. Compared with placebo, nesiritide was associated with a significantly attenuated peak increase in serum creatinine (0.15 ± 0.29 mg/dl vs. 0.34 ± 0.48 mg/dl; $p < 0.001$) and a smaller fall in glomerular filtration rate (−10.8 ± 19.3 ml/min/1.73 m^2 vs. −17.2 ± 21.9 ml/min/1.73 m^2; $p = 0.001$) during hospital stay or by study day 14, and a greater urine output (2,926 ± 1,179 ml vs. 2,350 ± 1,066 ml; $p < 0.001$) during the initial 24 h after surgery. In addition, nesiritide-treated patients had a shorter hospital stay ($p = 0.043$) and lower 180-day mortality ($p = 0.046$).

Conclusions Nesiritide in the setting of CABG with CPB is associated with improved postoperative renal function and possibly enhanced survival. (The NAPA Trial; http://www.clinicaltrials.gov/ct/show; NCT00090792) (J Am Coll Cardiol 2007;49:716–26) © 2007 by the American College of Cardiology Foundation

Nesiritide is recombinant human B-type natriuretic peptide (1). Physiologically, the natriuretic peptides have important effects on salt and water balance and vascular tone (2).

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When administered to patients with heart failure, nesiritide decreases preload, afterload, and pulmonary vascular resistance and increases cardiac output without inducing tachyarrhythmias (2–4). In some studies, nesiritide has been associated with increased urine output; reduced diuretic requirements; and suppression of aldosterone, endothelin, and norepinephrine (5,6). Nesiritide therapy effectively reduces pulmonary capillary wedge pressure and relieves dyspnea in patients hospitalized with acute decompensated heart failure (2–4). Several small, retrospective, and/or uncontrolled evaluations have suggested beneficial effects in patients undergoing cardiac surgery (7–9). However, the

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role of nesiritide in the management of patients undergoing coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB) has not been definitively established.

Coronary artery bypass grafting using CPB induces neurohormonal and renal responses that are similar to those seen in acute decompensated heart failure (10). Postoperative renal dysfunction and acute renal failure are frequent and serious complications of cardiac surgery (10–13). Several observational reports have demonstrated that postoperative renal dysfunction significantly increases morbidity and mortality and prolongs both intensive care unit (ICU) and total hospital length of stay (LOS) (10,12,13). Preoperative renal dysfunction is also common in CABG patients. In 1 study, 78% of CABG patients had at least mild renal dysfunction, as defined by the National Kidney Foundation, preoperatively (14). Furthermore, morbidity, mortality, and LOS were all significantly and inversely related to baseline renal function, even after adjusting for other clinical risk factors (14). Similarly, renal dysfunction occurs frequently in association with chronic heart failure (15) and, as in CABG surgery, adversely impacts prognosis (16).

Consequently, effective strategies for preserving renal function postoperatively and improving outcomes in patients with left ventricular (LV) dysfunction undergoing CABG might have a substantial clinical impact. Several pharmacologic agents, including *N*-acetylcysteine, "renal-dose" dopamine, and fenoldopam, have been assessed and found to be ineffective for prevention of postoperative renal dysfunction (11,17,18). Thus, a major unmet need in the management of these patients persists. The objective of the NAPA (Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery) trial was to explore the effects of nesiritide on postoperative renal function, hemodynamics, clinical outcomes, and safety in patients with LV dysfunction undergoing CABG using CPB.

Methods

The NAPA trial was a prospective, multicenter, randomized, double-blind, placebo-controlled, exploratory study in patients with chronic LV dysfunction undergoing CABG, with or without mitral valve replacement/repair, using CPB. Patients were enrolled at 54 centers throughout the U.S. over a 15-month period from March 2004 through May 2005 and were followed for 6 months after enrollment. Eligibility requirements included age ≥18 years, New York Heart Association functional class II to IV heart failure, and documented LV ejection fraction ≤40% within 90 days before surgery. Subjects with planned mitral valve repair or replacement at the time of surgery were eligible. However, subjects with planned aortic valve repair or replacement were excluded. Additional exclusion criteria were: a requirement for ongoing or chronic dialysis; presence of restrictive or obstructive cardiomyopathy, pericarditis, or pericardial tamponade; documented low cardiac filling pressures; known congenital heart disease; evidence of ongoing infection; and pulmonary disease, including chronic obstructive pulmonary disease or asthma, requiring hospital stay within 60 days. All patients provided written, informed consent before study participation.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CI = confidence interval
CPB = cardiopulmonary bypass
GFR = glomerular filtration rate
HR = hazard ratio
ICU = intensive care unit
LOS = length of stay
LV = left ventricular
SCr = serum creatinine

Study protocol. Patients were randomized to receive either a fixed dose of intravenous nesiritide (0.01 μg/kg/min without bolus) or placebo for a minimum of 24 h in addition to usual perioperative and postoperative care. Study drug infusion was started after induction of anesthesia but before chest incision and was continued for a minimum of 24 h up to a maximum of 96 h at the discretion of the attending physician. Right heart pressures were assessed with a Swan-Ganz catheter placed immediately before the start of study drug infusion. Patients with mean pulmonary pressures consistently <15 mm Hg, central venous pressure consistently <6 mm Hg, or systolic blood pressure consistently <90 mm Hg were excluded from further study participation. Blood samples for serum creatinine (SCr) determination were obtained preoperatively ("baseline"); at postoperative hours 0, 6, 12, and 18; and then at ICU and hospital discharge. Hemodynamic assessments were obtained at baseline and at postoperative hours 0, 6, 12, 18, and 24.

End points. This exploratory study included 5 end points of interest: 1) change from baseline to peak SCr by the end of hospital stay or by study day 14 (whichever came first); 2) change from baseline glomerular filtration rate (GFR) to the lowest GFR measured during hospital stay or by study day 14 (whichever came first), with GFR calculated using the Modification of Diet in Renal Disease equation (19); 3) intravenous inotropic agent/vasopressor and vasodilator use; 4) change from baseline in mean pulmonary artery pressure for 24 h after the start of study drug or until removal of the Swan-Ganz catheter (whichever came first); and 5) urine output during the initial 24 h after admission to the ICU or until ICU discharge (whichever came first). Secondary end points included: 1) duration of intubation; 2) duration of stay in the ICU; 3) total hospital LOS; 4) change from baseline in mean pulmonary capillary wedge pressure, central venous pressure, cardiac index, and systemic vascular resistance; and 5) 30- and 180-day mortality and drug safety.

Statistical analysis. The change from baseline to postoperative peak SCr was compared using an analysis of covariance model, with treatment group as qualitative factor and baseline SCr value as covariate, as well as using a nonparametric Wilcoxon rank-sum test. The change in GFR was analyzed similarly. Urine outputs were compared using a 1-way analysis of variance model. Analyses of change in

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pulmonary and systemic hemodynamic parameters were performed using a 1-way analysis of covariance model, with the baseline value as covariate. Temporal changes in SCr and hemodynamic parameters were analyzed using longitudinal repeated measures analysis of variance model. Use of concomitant medications was compared using analysis of variance for continuous variables and chi-square or Fisher exact test for categorical variables. The ICU LOS and hospital LOS were analyzed using the Wilcoxon rank-sum test, owing to the non-normality of the data. Kaplan-Meier estimates and log-rank tests were performed for the mortality rates comparison. Hazard ratios (HRs) were computed at day 30 and day 180 using the Cox proportional hazard model. All tests were 2-sided with p values <0.05 considered significant. Because this was a pilot study, formal adjustment for multiplicity was not made. Unless otherwise noted, all summary statistics for continuous variables are presented as mean ± SD.

Results

Patient enrollment. Initially, 303 patients were randomized; perioperative hemodynamics (n = 10) and other factors (rescheduled surgery: n = 4; decision not to use CPB before administration of study drug: n = 3; withdrawn consent: n = 3; and failure to meet other entry criteria: n = 4) precluded study drug administration in 24 of these patients, and 7 patients who received study drug ultimately underwent surgery without CPB (Fig. 1). The remaining 272 patients (nesiritide: n = 137; placebo: n = 135) constitute the "efficacy population," which was used for all outcome evaluations except mortality and safety. Mortality (at 30 and 180 days) and safety (within 30 days) were assessed in all 279 patients (nesiritide: n = 141; placebo: n = 138) who received study drug regardless of CPB use.

Baseline characteristics and surgical procedures. Mean age of the study population was 64 ± 11 years; 219 (78%) were men and 232 (83%) were white. There were no significant differences between the 2 study groups with respect to baseline demographic and clinical characteristics (Table 1). Mean LV ejection fraction at baseline was 29.9%, and mean baseline blood B-type natriuretic peptide level was 418 pg/ml. Concomitant oral medications for heart failure (medications prescribed at any time from informed consent through the end of the study) were similar between the groups and included angiotensin-converting enzyme inhibitors (76%), angiotensin II receptor blockers (8%), beta-blockers (96%), and loop diuretics (68%). Surgical procedures were similar between the 2 study groups (Table 2).

Study drug administration. The mean duration of study drug infusion was 39.4 ± 21.6 h in the nesiritide group and 40.6 ± 23.4 h in the placebo group (p = 0.67 with analysis of variance); the median infusion durations were 29.1 and 30.1 h, respectively. Total infusion duration was <24 h in 13% of nesiritide and 11% of placebo patients, ≥ 24 but ≤ 48 h in 60% of nesiritide and 61% of placebo patients, >48 but ≤ 72 h in 16% of nesiritide and 15% of placebo patients, and >72 h in 11% of nesiritide and 13% of placebo patients. During the infusion period, 13 (9.2%) nesiritide and 11 (8.0%) placebo patients (p = 0.83) had a reduction in study drug dose, primarily for hypotension. None of these reductions were due to changes in SCr or GFR.

Efficacy. Although mean SCr increased postoperatively in both groups, the increase was attenuated in patients receiv-

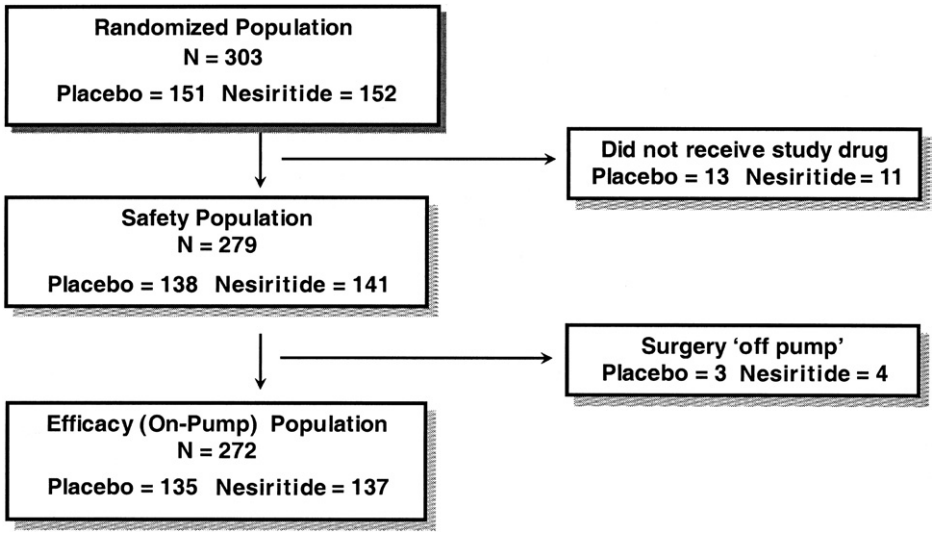

Figure 1 Analysis Populations

Consort diagram depicting the progress of the randomized patients over the course of the trial and their contribution to the various analysis groups.

Table 1 Demographic and Clinical Characteristics at Baseline

Characteristic	Placebo (n = 138)	Nesiritide* (n = 141)
Age, yrs	64.1 ± 11.3	63.6 ± 10.5
Male gender, n (%)	108 (78)	111 (79)
Race/ethnicity, n (%)		
White	117 (85)	115 (82)
Black	9 (7)	10 (7)
Hispanic	10 (7)	11 (8)
Other	2 (1)	5 (4)
Weight, kg	89.2 ± 21.7	86.9 ± 19.6
New York Heart Association functional class, n (%)		
I	1 (1)	0 (0)
II	71 (51)	64 (45)
III	52 (38)	62 (44)
IV	13 (9)	14 (10)
Left ventricular ejection fraction, %	30.1 ± 7.3	29.7 ± 7.5
BNP, pg/ml	406 ± 511	431 ± 615
N-terminal pro-BNP, pg/ml	3026 ± 4224	2877 ± 4802
Medical history, n (%)†		
Non–insulin-dependent diabetes mellitus	43 (31)	45 (32)
Insulin-dependent diabetes mellitus	26 (19)	23 (16)
Chronic obstructive pulmonary disease	25 (18)	25 (18)
Other pulmonary disease	17 (12)	21 (15)
Reactive precapillary pulmonary hypertension	7 (5)	5 (4)
Mild liver disease	5 (4)	5 (4)
Anemia	24 (17)	27 (19)
Peripheral vascular disease	30 (22)	29 (21)
Diabetic nephropathy	8 (6)	6 (4)
Other chronic renal disease	33 (25)	28 (21)
Renal function		
Serum creatinine, mg/dl	1.11 ± 0.44	1.07 ± 0.40
Blood urea nitrogen, mg/dl	22.4 ± 8.8	22.5 ± 11.3
Glomerular filtration rate, ml/min/1.73 m^2	77.6 ± 28.1	82.0 ± 30.3
Hemodynamics		
Mean systolic blood pressure, mm Hg	120 ± 21	122 ± 21
Mean pulmonary artery pressure, mm Hg	25.4 ± 8.8	25.6 ± 8.7

*Differences between placebo and nesiritide groups are all non-significant (analysis of variance continuous variables and chi-square for categorical variables). †As reported by the attending physician.
BNP = B-type natriuretic peptide.

ing nesiritide. In the nesiritide patients, mean SCr returned to baseline by 12 h after ICU admission and remained there throughout the remainder of the hospital stay. In placebo patients, however, mean SCr was elevated significantly relative to baseline within 12 h of ICU admission, and this elevation persisted through the hospital stay (Fig. 2). The maximum absolute increase in SCr and absolute decline in GFR during hospital stay or by study day 14 (whichever came first) were significantly less in nesiritide patients compared with placebo patients with either parametric (Fig. 3) or non-parametric analyses (data not shown). Relative to baseline, SCr increased 17 ± 29% in nesiritide and 33 ± 46% in placebo patients, and GFR decreased 11 ± 22% in nesiritide and 20 ± 24% in placebo patients. The effects of nesiritide on postoperative renal dysfunction were especially pronounced in patients with renal dysfunction at baseline (defined as baseline SCr >1.2 mg/dl) (Fig. 3). In these

Table 2 Surgical Procedures

	Placebo (n = 138)	Nesiritide (n = 141)
Coronary artery bypass grafting alone, n (%)	92 (67)	96 (68)
Concomitant procedures, n (%)*		
Mitral valve repair	24 (17)	21 (15)
Mitral valve replacement	4 (3)	4 (3)
Maze procedure	5 (4)	7 (5)
Dor procedure	4 (3)	7 (5)
Transmyocardial laser revascularization	2 (1)	0 (0)
Intra-aortic balloon pump	10 (7)	12 (9)
Other	14 (10)	12 (9)
Re-operations (prior CABG)	11 (8)	8 (6)

*Subjects may have undergone more than one procedure.
CABG = coronary artery bypass graft.

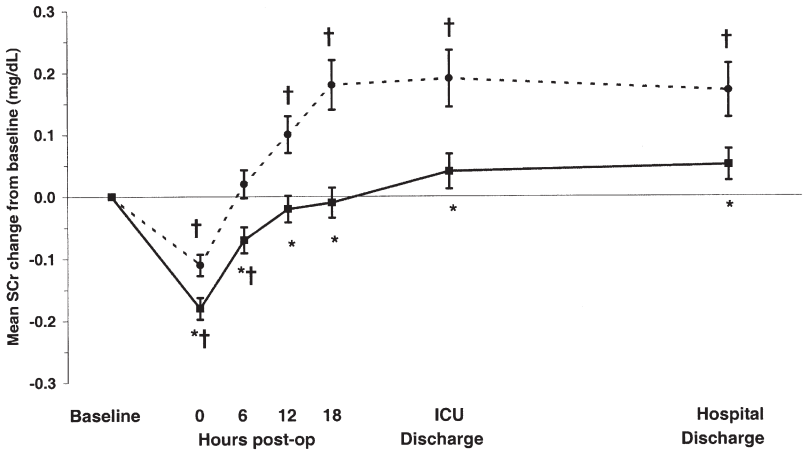

Figure 2 Time Course of SCr Response

Mean change from baseline in postoperative (post-op) serum creatinine (SCr) values over the course of the hospital stay in nesiritide **(solid line)** and placebo **(dotted line)** patients. **Vertical lines** signify 1 SEM. *p < 0.05 nesiritide versus placebo on the basis of longitudinal repeated measures analysis of variance model; †p < 0.05 change from baseline on the basis of paired *t* test. ICU = intensive care unit.

patients, SCr increased 3 ± 20% in nesiritide and 29 ± 36% in placebo patients and GFR increased 1 ± 22% in nesiritide and decreased 19 ± 23% in placebo patients relative to baseline.

Urine output during the initial 24 h after surgery was significantly greater in nesiritide than in placebo patients (2,926 ± 1,179 ml vs. 2,350 ± 1,066 ml; p < 0.001). Although the subset of patients who had renal dysfunction at baseline is small, there was a significant improvement in urine output with nesiritide compared with placebo in this subset (2,838 ± 1,106 ml vs. 2,251 ± 897 ml; p = 0.025). After surgery, 80% of nesiritide and 77% of placebo patients received a diuretic, predominantly furosemide (Table 3).

Use of inotropic agents, vasopressors, inodilators, and vasodilators was similar between the groups (Tables 3 and 4). During hospital stay, 96% of nesiritide patients and 95% of

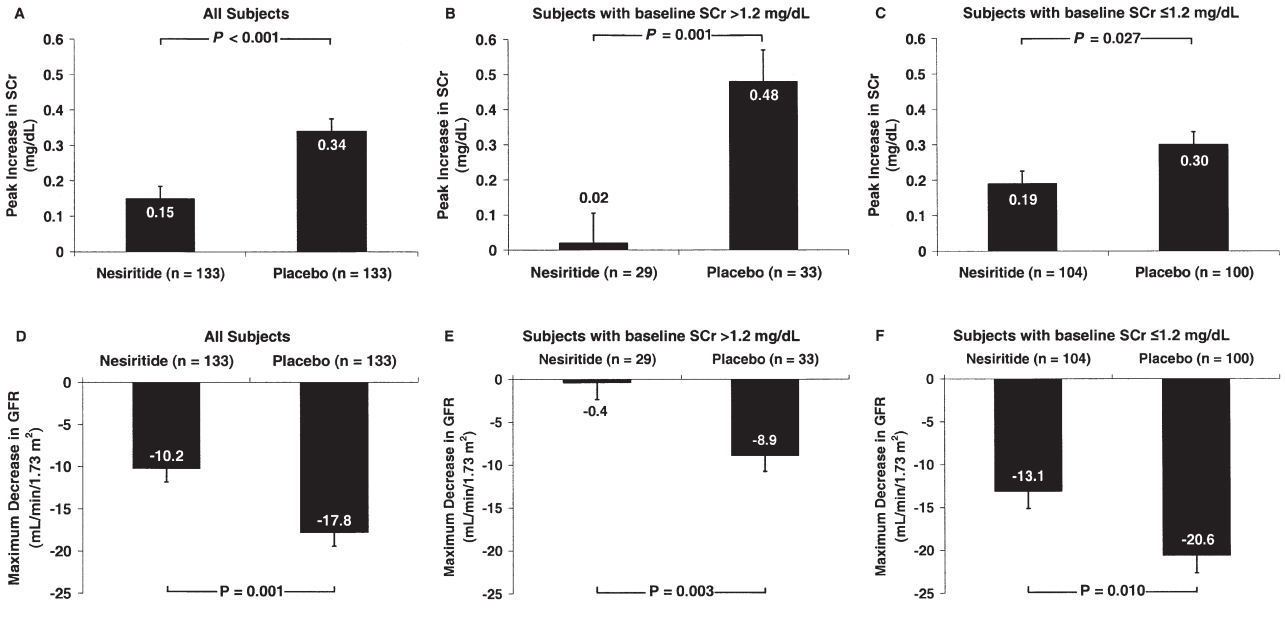

Figure 3 Maximal Change in SCr and GFR by Baseline Renal Function

Adjusted mean maximum increase in serum creatinine (SCr) **(A, B, and C)** and decrease in glomerular filtration rate (GFR) **(D, E, and F)** from baseline through hospital discharge or by study day 14, whichever came first, using an analysis of covariance model. **Lines above the bars** represent 1 SEM.

Table 3 Number of Patients Receiving Selected Concomitant Postoperative Cardiovascular Medications

	Placebo (n = 135)	Nesiritide* (n = 137)
Any, n (%)	135 (100)	137 (100)
Intravenous loop diuretics, n (%)	104 (77)	109 (80)
Furosemide	102 (76)	107 (78)
Bumetanide	18 (13)	14 (10)
Torsemide	2 (1)	0 (0)
Ethacrynic acid	1 (1)	0 (0)
Inotropic agents/vasopressors, n (%)	128 (95)	131 (96)
Norepinephrine	76 (56)	79 (58)
Phenylephrine	70 (52)	67 (49)
Epinephrine	49 (36)	44 (32)
Dobutamine	50 (37)	39 (28)
Dopamine	45 (33)	41 (30)
Vasopressin	32 (24)	28 (20)
Ephedrine	15 (11)	16 (12)
Inodilator	64 (47)	60 (44)
Milrinone	63 (47)	60 (44)
Amrinone	2 (1)	0 (0)
Vasodilators	104 (77)	102 (74)
Glyceryl trinitrate	89 (66)	86 (63)
Nitroprusside	22 (16)	22 (16)
Nicardipine	17 (13)	11 (8)
Hydralazine	16 (12)	10 (7)
Nesiritide†	6 (4)	7 (5)
Nitric oxide	0 (0)	1 (1)
Other		
Aprotinin	61 (45%)	64 (47%)

*Differences between placebo and nesiritide groups are all non-significant (Fisher exact test).
†Reflects protocol-deviation, open-label use of nesiritide.

placebo patients received an inotropic agent/vasopressor, predominantly norepinephrine and/or phenylephrine. Almost one-half of the patients (nesiritide: 44%; placebo: 47%) received an inodilator, predominantly milrinone. A median of 3 different inotropic agents/vasopressors/inodilators were used in both nesiritide and placebo patients (Table 4).

Changes in hemodynamic parameters over time were similar between the treatment groups (Fig. 4). During the initial 24 h of study drug administration, mean pulmonary artery pressure decreased: −2.8 ± 7.9 mm Hg in nesiritide and −1.9 ± 7.8 mm Hg in placebo patients (p = 0.297). Likewise, mean arterial pressure decreased: −5.5 ± 19.5 mm Hg in nesiritide and −5.3 ± 19.3 mm Hg in placebo patients (p = 0.958). Cardiac index increased 0.6 ± 0.9 l/min/m^2 in nesiritide and 0.7 ± 0.7 l/min/m^2 in placebo patients (p = 0.429).

Mean ventilation times were 21.8 ± 22.2 h and 29.3 ± 72.9 h in the nesiritide and placebo groups, respectively (p = 0.498). Nesiritide patients had a mean total ICU LOS of 78.8 ± 92.2 h compared with 103.2 ± 156.6 h for placebo patients (p = 0.370) and a total hospital LOS of 9.1 ± 6.1 days compared with 11.5 ± 9.8 days for placebo patients (p = 0.043).

Safety. MORTALITY. Thirty-day mortality data were available for 132 patients in the nesiritide group and 127 in the placebo group; 180-day mortality data were available for 94 and 95 patients, respectively. Survival at 180 days was significantly greater in patients receiving nesiritide (Fig. 5). Thirty days after initiation of the study drug, 4 (2.8%) nesiritide and 8 (5.9%; p = 0.219) placebo patients had died; all but 1 of these deaths, a placebo patient, occurred in the hospital. Causes of death in the 4 nesiritide patients, as determined by the attending physician, included: 1) cardiac arrest, 2) multisystem organ failure, 3) aortic rupture, and 4) fulminant clostridium difficile colitis. Causes of death in the 8 placebo patients were: 1) cardiac arrest, 2) ventricular tachycardia arrest, 3) ventricular fibrillation, 4) probable cardiac arrhythmia, 5) multisystem organ failure (2 patients), 6) stroke, and 7) dead bowel. By 180 days, 8 (6.6%) nesiritide and 17 (14.7%; p = 0.046) placebo patients had died. The additional causes of death included multisystem organ failure (3 patients) and bacterial meningitis (1 patient) in nesiritide patients and cardiac arrest, heart attack, heart failure, anoxic encephalopathy, sepsis, cholangitis, "coma," and unknown (2 patients) in placebo patients. The mortality HR for nesiritide relative to placebo was 0.48 (95% confidence interval [CI] 0.14 to 1.59) at 30 days and 0.44 (95% CI 0.19 to 1.01) at 180 days.

ADVERSE EVENTS. Adverse events were common, with similar rates of overall adverse events in each group (Table 5). Serious adverse events occurred in 43 (30.5%) nesiritide and 51 (37.0%) placebo patients; only 8 patients (2 [1.4%] nesiritide and 6 [4.3%] placebo) had an event thought to be potentially related to the study drug. These potentially related adverse events were hypotension and ventricular tachycardia in the 2

Table 4 Degree of Postoperative Inotropic and Vasoactive Pharmacotherapy

	Placebo (n = 135)	Nesiritide* (n = 137)
Inotropic agents/vasopressors/inodilators		
Number of different agents used per patient		
Mean ± SD	3.1 ± 1.5	2.8 ± 1.3
Median	3.0	3.0
Patients receiving, n (%)		
0	5 (4)	3 (2)
1 to 3	84 (62)	95 (69)
>3	45 (33)	37 (27)
Vasodilators		
Number of different agents used per patient		
Mean ± SD	1.4 ± 0.7	1.3 ± 0.6
Median	1.0	1.0
Patients receiving, n (%)		
0	30 (22)	33 (24)
1 to 2	95 (70)	95 (69)
>2	9 (7)	7 (5)

*Differences between placebo and nesiritide groups are all non-significant (analysis of variance for continuous variables and chi-square for categorical variables).

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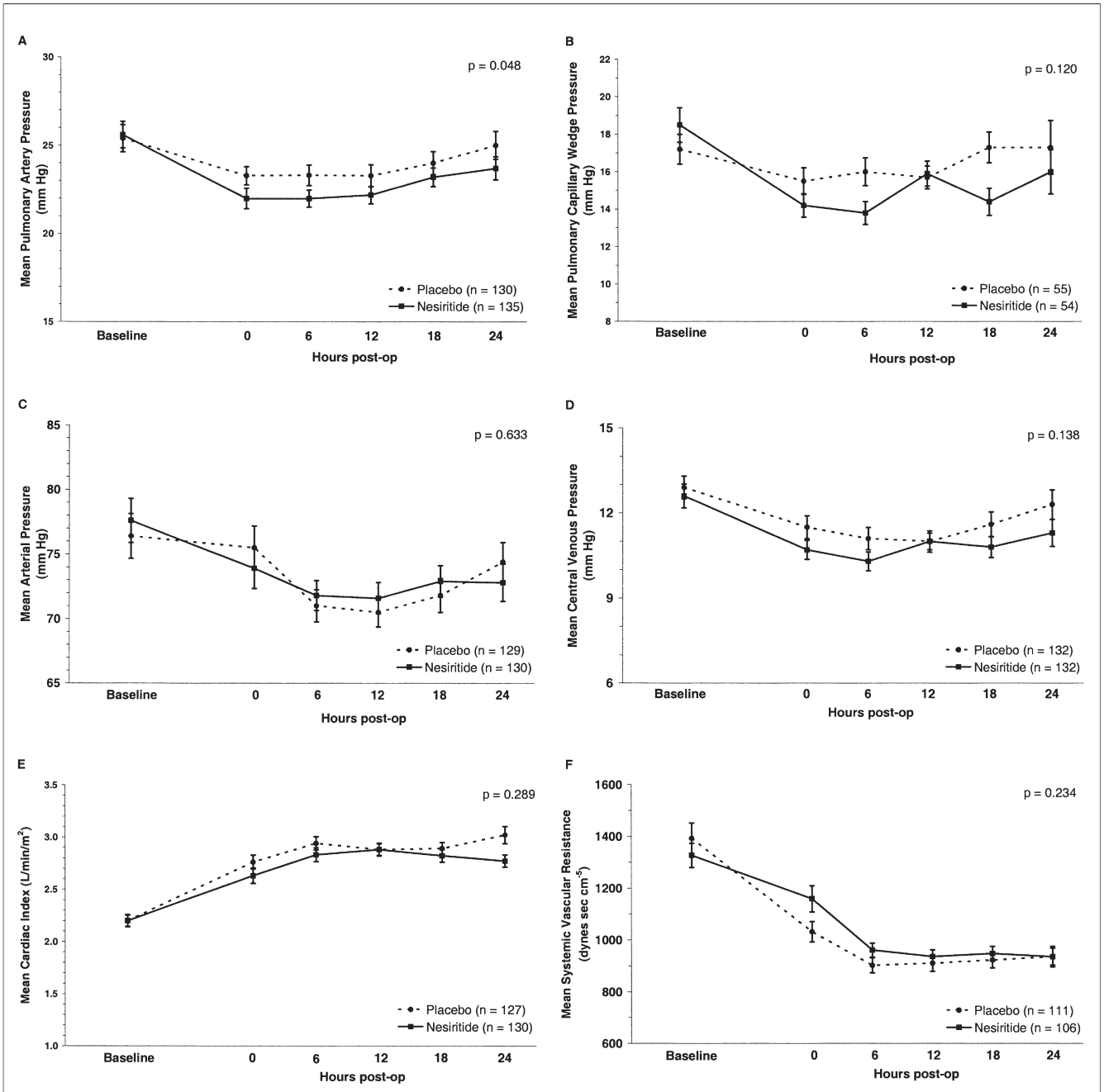

Figure 4 **Time Course of Hemodynamic Parameters During the Initial 24 Postoperative Hours**

Mean pulmonary artery pressure **(A)**, pulmonary capillary wedge pressure **(B)**, mean arterial pressure **(C)**, central venous pressure **(D)**, cardiac index **(E)**, and systemic vascular resistance **(F)** at baseline and over the initial 24 postoperative hours in nesiritide **(solid lines)** and placebo **(dotted lines)** patients. **Points** represent mean values and **vertical lines** represent 1 SEM. The p values are for nesiritide versus placebo comparison using a longitudinal repeated measures analysis of variance model.

nesiritide patients and hypotension, hypotension with renal failure, renal failure, worsening heart failure with cardiac arrest, atrial fibrillation, and confusion in the 6 placebo patients.

Discussion

The results of this exploratory trial suggest that perioperative infusion of nesiritide might have favorable effects in patients with LV dysfunction undergoing CABG using CPB. Patients receiving nesiritide had better overall preservation of GFR, lower peak increase in SCr levels, and greater urine output in the immediate postoperative period compared with patients receiving placebo. These beneficial effects were preserved, if not enhanced, in high-risk patients with preexisting renal dysfunction.

Short- and medium-term outcomes after surgical myocardial revascularization are affected adversely by both

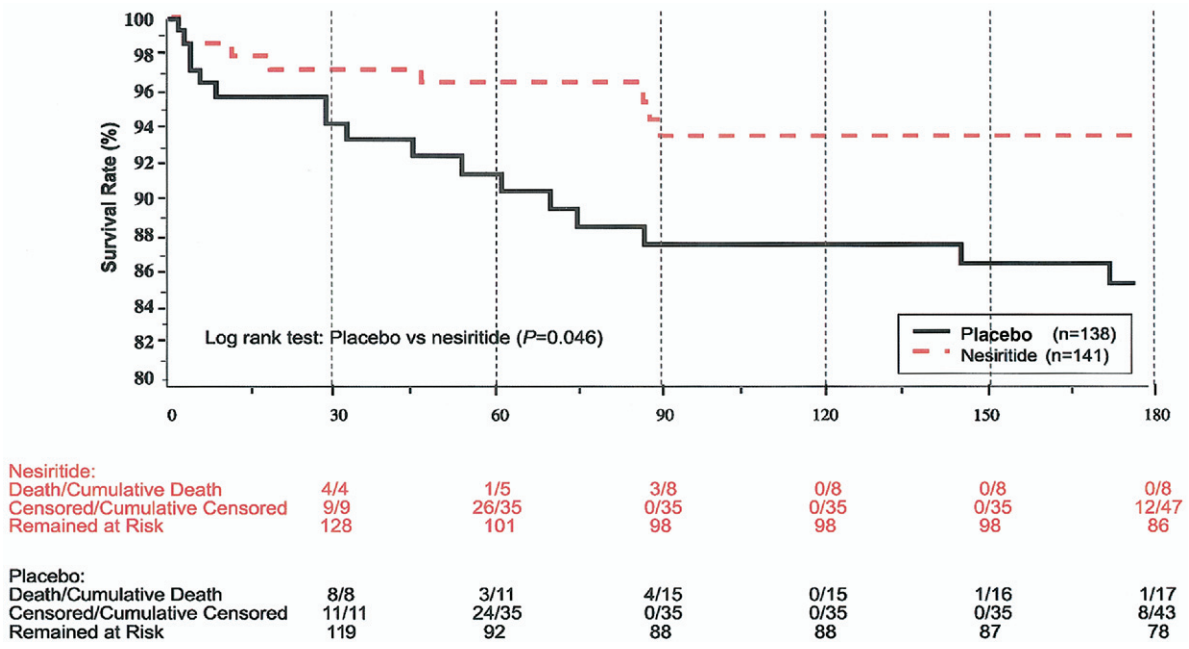

Figure 5 Kaplan-Meier Survival Curve to Day 180 by Treatment Group in the Safety Population

chronic and acute renal insufficiency. More than 75% of patients undergoing CABG in the U.S. have abnormal renal function at baseline; this is associated with an increased risk-adjusted mortality odds ratio that ranges from 1.55 (95% CI 1.45 to 1.65) for patients with moderate dysfunction to 3.82 (95% CI 3.45 to 4.25) for patients who are dialysis dependent (14). In addition, depending on definitions used, 25% to 30% of patients undergoing CABG develop acute renal failure or dysfunction after surgery, and postoperative mortality in these patients is approximately 15% to 30% (10,12,13). In 843 consecutive patients undergoing cardiac surgery with CPB, acute postoperative renal dysfunction significantly increased mortality risk both in-hospital (HR 12.6; 95% CI 5.7 to 27.0) and long-term (HR 1.83; 95% CI 1.38 to 3.20) (13). Similarly, in 2,672 consecutive patients undergoing CABG, in-hospital mor-

Table 5 Adverse Events

	Placebo (n = 138) n (%)	Nesiritide (n = 141) n (%)	p Value
Overall summary			
Any event	123 (89.1)	132 (93.6)	0.205
Any event classified as related to study drug	27 (19.6)	32 (22.7)	0.560
Any serious event	51 (37.0)	43 (30.5)	0.258
Any serious event classified as related to study drug	6 (4.3)	2 (1.4)	0.170
Any event causing withdrawal from the study	5 (3.6)	5 (3.5)	1.000
Cardiac, renal, and pulmonary adverse events occurring in ≥5% of patients			
Hypotension	43 (31.2)	36 (25.5)	0.352
Atrial fibrillation	44 (31.9)	30 (21.3)	0.057
Pleural effusion	31 (22.5)	30 (21.3)	0.885
Atelectasis	28 (20.3)	24 (17.0)	0.540
Peripheral edema	15 (10.9)	13 (9.2)	0.694
Acute renal failure*	17 (12.3)	10 (7.1)	0.160
Ventricular tachycardia	11 (8.0)	14 (9.9)	0.676
Respiratory failure	16 (11.6)	3 (2.1)	0.002
Sinus tachycardia	11 (8.0)	7 (5.0)	0.339
Dyspnea	7 (5.1)	9 (6.4)	0.798

*Based on investigator classification without a predetermined requirement for dialysis.

tality was 28% in patients with acute renal failure and 12% in patients with acute renal dysfunction, compared with 1% in patients with neither (12). Furthermore, the mortality risk associated with an acute decrease in renal function increases with declining baseline renal function. In 2,067 consecutive patients undergoing CABG, an additional acute 10 ml/min/1.73 m^2 decrease in GFR increased mortality risk by 67%, 40%, and 17% in patients with baseline GFR of 20, 40, and 60 ml/min/1.73 m^2, respectively (20).

Pre- and postoperative renal dysfunction also prolongs hospital LOS (10,14,21). Preoperative renal failure was 1 of 6 significant multivariate predictors of prolonged LOS in an evaluation of 194 patients undergoing CABG (21), and postoperative acute renal failure and renal dysfunction significantly prolonged both ICU LOS (acute renal failure: 14.9 days; postoperative renal dysfunction: 6.5 days; neither: 3.1 days) and total hospital LOS (acute renal failure: 28.8 days; postoperative renal dysfunction: 18.2 days; neither: 10.6 days) in 2,222 patients undergoing myocardial revascularization (10). Consequently, preserving renal function pre- and postoperatively is an important component of improving clinical outcomes in patients undergoing cardiac surgery.

Several therapeutic strategies for preserving renal function after cardiac surgery have been investigated, but to date none have been proven effective. In separate evaluations, intravenous administration of *N*-acetylcysteine (11) and "renal-dose" dopamine (18) were found no more effective than placebo, and intravenous fenoldopam was no more effective than "renal-dose" dopamine (17).

The observation in this study that no significant differences were detected in either pulmonary or systemic hemodynamic parameters or in use of concomitant medications might be explained by the fact that nesiritide or placebo was added to usual care, as determined by the patient's attending physician. The use of intravenous fluids and multiple vasoactive drugs, with adjustments made in response to hemodynamic monitoring in the immediate postoperative period, could also explain the similarity of postoperative hemodynamic findings in the 2 treatment groups. Although the number and class of drugs initially used were similar between treatment groups, intensity of drug exposure, as indicated by dose and duration, was not assessed. Differences in exposure intensity might account for some of the observed differences between treatment groups in this study.

Several physiologic mechanisms might account for the observed beneficial effects of nesiritide on renal function. In a randomized, placebo-controlled evaluation of patients undergoing CABG, infusion of human atrial natriuretic peptide (ANP), initiated at the start of CPB and continued for 24 h, significantly blunted bypass-associated neurohormonal activation, maintained GFR, improved urine output, and reduced the prevalence of postoperative renal insufficiency (22). Nesiritide has neurohormonal effects that are similar to those of ANP. It inhibits sympathetic overactivity, decreasing circulating as well as local cardiac and renal norepinephrine levels (5,23). It inhibits both the renin-angiotensin-aldosterone system, reducing both renin and aldosterone levels (2,5,24–29), and endothelin-1, a potent stimulant of both vasoconstriction and sodium retention (6,27).

In healthy volunteers, nesiritide increases GFR and produces dose-dependent diuresis and natriuresis (24–26). In patients with heart failure, it maintains renal blood flow and/or GFR (5,26,30,31) and either maintains (5,31) or increases urinary sodium and/or water excretion (2,26,30).

The beneficial renal effects of nesiritide observed in this study differ from those reported previously in medical patients with acute decompensated heart failure. In a randomized, controlled clinical trial of 489 patients with acute decompensated heart failure, nesiritide improved hemodynamic and clinical status but had no effect on SCr levels in patients with or without renal insufficiency at baseline (1). Similarly, nesiritide had no effect (positive or negative) on GFR or urine output in a crossover study of 15 patients with heart failure and worsening SCr levels (31). In addition, a meta-analysis of data from 5 trials suggests that nesiritide therapy might be associated with an increased risk of acute SCr elevation >0.5 mg/dl in patients with heart failure (32). The reasons for these differences are unknown and might be related to several factors, including differences in baseline renal dysfunction, differences in nesiritide dose administered, and differing disease states in the various trials. Although all patients in the current evaluation had LV dysfunction and serum B-type natriuretic peptide levels consistent with advanced heart failure, the patients were not acutely decompensated at the time of surgery. In addition, factors such as heightened catecholamine release during and after surgery, differences in nesiritide dosing regimen (e.g., lack of bolus and no increase in dose in response to systemic or pulmonary hypertension), and extensive concomitant perioperative use of vasoactive drugs (especially norepinephrine and vasopressin to support blood pressure) that would not be routinely employed in medical patients with acute decompensated heart failure might have influenced the renal effects of nesiritide in the current evaluation.

Alternatively, the effects of nesiritide in the present study might reflect the sequence of drug administration. In a previous study, Sica et al. (33) showed that initiation of a nesiritide infusion before administration of intravenous furosemide effectively blocked aldosterone release, whereas furosemide alone elicited marked increases in plasma aldosterone. It is also possible that nesiritide has more specific renal or neurohormonal effects in patients undergoing CABG using CPB than in medical patients with acute decompensated heart failure. Finally, because intensity of exposure to concomitant medications is unknown, subjects who received nesiritide might simply have had less exposure to concomitant medications with possible adverse renal effects.

Study limitations. The limitations of this study include the relatively small sample size and the fact that usual-care

medications and other treatment interventions were not specified in the protocol. Concomitant medications varied greatly, depending on the attending physician's assessment of the patient's clinical status, and there might have been undetected differences between treatment groups in addition to the study drug. Patients enrolled in this study represent only a subset of patients undergoing CABG at participating institutions, and it is impossible to determine how closely this subset reflects the overall patient population at these institutions. Finally, the 180-day mortality end point was added late in the study as an additional safety end point, after the investigators became aware of concerns that nesiritide might be associated with an increased mortality risk in patients with acutely decompensated heart failure. As a result, some subjects were lost to follow-up or declined consent for this later evaluation, leading to censored data. The degree of censoring was similar in both study groups, and the mortality HR was relatively preserved over the 180-day study period. However, the possibility that the significant reduction in 180-day mortality observed in patients who received nesiritide represents a type I error cannot be excluded. Finally, this was an exploratory study, and formal adjustment for multiplicity was not made; any conclusions recognize the limitations due to multiple hypotheses being tested.

Conclusions. Administration of nesiritide to patients with LV dysfunction undergoing CABG using CPB improved postoperative renal function, as indicated by a smaller maximal increase in peak SCr, better preservation of GFR, and greater urine output in the immediate postoperative period. These beneficial effects were enhanced in patients with preoperative renal dysfunction and were observed despite the absence of significant hemodynamic changes. In addition, nesiritide treatment was associated with reduced hospital LOS and decreased mortality at 180 days. Although the most likely explanation for the salutary effects of nesiritide administration on patient outcomes in the NAPA trial seems to be prevention or attenuation of postoperative renal dysfunction, additional studies are needed to confirm these findings.

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APPENDIX

For a list of NAPA Investigators, please see the online version of this article.