

Effect of Nesiritide Versus Dobutamine on Short-Term Outcomes in the Treatment of Patients With Acutely Decompensated Heart Failure

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OBJECTIVES	This study was designed to determine whether nesiritide, administered for acute decompensated congestive heart failure (CHF), affects healthcare costs by hospital length of stay (LOS), readmissions and short-term mortality, compared to dobutamine.
BACKGROUND	Dobutamine is a commonly used inotropic treatment for CHF. Although dobutamine may have favorable hemodynamic and symptomatic effects, its use may be associated with side effects such as tachycardia, cardiac arrhythmias and myocardial ischemia. Nesiritide (B-type natriuretic peptide) is a new intravenous (IV) drug that produces hemodynamic and symptomatic improvement through balanced vasodilatory effects, neurohormonal suppression and enhanced natriuresis and diuresis.
METHODS	From an open-label randomized study of nesiritide versus standard care (SC) in patients with CHF requiring hospitalization, we compared short-term outcome data from patients given nesiritide (0.015 or 0.03 $\mu\text{g}/\text{kg}$ per min) with a subgroup of SC patients given dobutamine. A total of 261 patients are included in this analysis.
RESULTS	Compared to dobutamine, both nesiritide doses were administered for a shorter total duration ($p < 0.001$), and the total duration of all IV vasoactive therapy (including study drug) was also shorter ($p \leq 0.012$). Although there was no difference in LOS, there was a trend toward decreased readmissions in the two nesiritide groups (8% and 11%, respectively, vs. 20% in the dobutamine group). Six-month mortality was lower in the nesiritide groups.
CONCLUSIONS	Treatment of decompensated CHF with nesiritide may lead to lower healthcare costs and reduced mortality compared to treatment with dobutamine. (J Am Coll Cardiol 2002;39:798–803) © 2002 by the American College of Cardiology Foundation

Heart failure is a healthcare problem of enormous proportion. It has recently been reported to be the primary diagnosis in 872,000 hospital admissions in the U.S. and the secondary diagnosis in an additional 1.8 million admissions (1,2). Dobutamine is a widely used inotropic therapy for decompensated heart failure. Although dobutamine can cause early hemodynamic and symptomatic benefits, its use is limited by potentially serious side effects such as tachycardia, hypotension, myocardial ischemia and cardiac arrhythmias. Furthermore, increased mortality associated with chronic administration of oral inotropic agents has raised concern over the safety of these agents, even when used short term (3–6).

Nesiritide, an intravenous (IV) form of human B-type natriuretic peptide (marketed as Natrecor, Scios, Inc., Sunnyvale, California), is the first in a new pharmacologic class of drug for treatment of decompensated congestive heart failure (CHF). Given parenterally, nesiritide causes cyclic guanosine monophosphate-mediated balanced arterial and venous dilation and may lead to neurohormonal suppression, natriuresis and diuresis (7–9). Recent evaluation of nesiritide in the treatment of acute decompensated CHF

has demonstrated significant symptom improvement, in association with decreased preload and afterload and increased cardiac output, without a proarrhythmic effect (7,8).

To determine if treatment with nesiritide in hospitalized patients with decompensated CHF affected healthcare utilization or longer term outcomes compared to dobutamine, we examined length of stay (LOS), readmissions and six-month mortality data from a subgroup analysis prospective, randomized active-control trial.

METHODS

Eligible patients were at least 18 years of age with a history of chronic heart failure and were admitted to an acute care hospital for symptomatic, decompensated heart failure requiring inpatient IV vasoactive treatment. Patients were excluded if they had prior treatment for >4 h with an IV vasoactive agent for this episode of heart failure, a myocardial infarction within 48 h before entry into study, valvular stenosis, hypertrophic obstructive cardiomyopathy, constrictive pericarditis, primary pulmonary hypertension, acute myocarditis, complex congenital heart disease, shock, systolic blood pressure (BP) <90 mm Hg or significant hemodynamic instability requiring immediate inotropic or pressor support. All patients gave informed consent, and each institution's local board for the protection of human subjects approved the study protocol. Prospectively defined end points included duration of IV vasoactive therapy, hospital LOS, hospital readmissions (both all-cause and due

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Abbreviations and Acronyms

BP	=	blood pressure
CHF	=	congestive heart failure
IV	=	intravenous
LOS	=	length of stay
MI	=	myocardial infarction
NYHA	=	New York Heart Association
SC	=	standard care
VT	=	ventricular tachycardia

to CHF) through day 21 and the need for additional vasoactive agents. Six-month mortality data were collected retrospectively.

In this multicenter open-label (double-blind to nesiritide dose) study, patients were randomized to three treatment groups in a 1:1:1 ratio: 1) standard care (SC), an investigator-chosen single IV vasoactive agent; 2) nesiritide 0.015 $\mu\text{g}/\text{kg}$ per min infusion, preceded by a 0.3 $\mu\text{g}/\text{kg}$ IV bolus; or 3) nesiritide 0.030 $\mu\text{g}/\text{kg}$ per min infusion, preceded by a 0.6 $\mu\text{g}/\text{kg}$ IV bolus (Fig. 1). Standard care vasoactive agents included dobutamine, milrinone, nitroglycerin or nitroprusside. Investigators could add a second IV vasoactive agent (or substitute a new agent for the first choice) at their discretion, but nesiritide could not be given as the second agent to SC patients. The addition of a second IV vasodilator to nesiritide therapy was not permitted, but the former could be substituted for the latter. In all groups, dose changes and total duration of therapy were left to investigator's discretion.

Statistical methods. This paper summarizes the comparisons of a subgroup of patients randomized to SC who received dobutamine with patients randomized to two doses of nesiritide. Descriptive statistics were provided for gender, age, ethnicity, New York Heart Association (NYHA) classification, primary etiology of CHF and cardiac history. Summaries of concomitant medication usage, treatment information and healthcare utilization were provided for each treatment group. Generally, continuous data were analyzed by the omnibus F test followed by pairwise contrasts, ordinal data by the Kruskal-Wallis test followed by pairwise two-sample Wilcoxon tests and categorical data by the generalized Fisher Exact test followed by pairwise Fisher Exact test. Kaplan-Meier estimates of the six-month mortality rate were also provided for each group. Log-rank

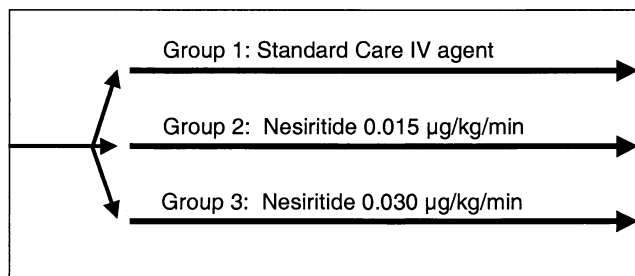


Figure 1. Study schema. IV = intravenous.

test was used to assess the differences of six-month mortality between the dobutamine subgroup and each nesiritide dose group. Data are expressed as mean \pm standard deviation unless otherwise noted. A p value <0.05 was considered statistically significant. No pairwise multiple comparison adjustments are included.

RESULTS

Between January 1997 and July 1997, 305 patients were enrolled into the study from 46 U.S. study sites. One hundred two patients were randomized to SC. Of these, 58 (57%) patients received dobutamine as the first-choice SC agent. One hundred three patients received nesiritide 0.015 $\mu\text{g}/\text{kg}$ per min and 100 patients received nesiritide 0.030 $\mu\text{g}/\text{kg}$ per min. Baseline demographics and medical history information is summarized in Table 1. The study population was elderly (mean age 65 ± 13 years), 32% were women and 31% were minorities. As intended, 92% of patients had a chronic history of NYHA class III or IV CHF before admission. Fifty-four percent had a history of a previous myocardial infarction (MI), 40% had a history of atrial fibrillation and 24% had a history of ventricular tachycardia (VT) (21% nonsustained and 8% sustained). In general, baseline characteristics (Table 1) and baseline hemodynamics (Table 2) among the groups were well balanced, with the following exceptions: more dobutamine patients had a history of previous MI and ischemia as the primary etiology of CHF, fewer nesiritide 0.015 $\mu\text{g}/\text{kg}$ per min patients were white or had a history of sudden death, and more nesiritide 0.030 $\mu\text{g}/\text{kg}$ per min patients had a history of sustained VT. Before study drug administration, there were no significant differences in the chronic use of diuretics (83%), digoxin (59%), angiotensin-converting enzyme inhibitors (60%) or beta-blockers (10%).

Median duration of study drug was significantly shorter in the nesiritide dose groups than in the dobutamine group by 25 h (nesiritide 0.015 $\mu\text{g}/\text{kg}$ per min) and 39 h (nesiritide 0.030 $\mu\text{g}/\text{kg}$ per min) (Table 3). In addition, compared to the dobutamine group, patients randomized to nesiritide received one less day of treatment with *all* IV vasoactive drug therapies combined (overall p = 0.016, pairwise p < 0.05) (Table 3). Dobutamine-treated patients were more likely to undergo both dose increases and dose decreases, whereas nesiritide was more likely to be administered as a fixed-dose infusion (Table 3). The use of combination therapy with other IV vasoactive agents during nesiritide therapy was similar to that observed with dobutamine (overall p = 0.589) (Table 3). A small number of patients (9 in the low-dose and 12 in the high-dose nesiritide groups) were placed on a second IV agent after discontinuing nesiritide. Compared with nesiritide-treated patients, significantly greater numbers of patients treated with dobutamine received a phosphodiesterase inhibitor, dopamine, non-dopamine vasopressors, diuretics or digoxin during treatment with study drug (Table 4). In nesiritide-treated

Table 1. Demographics and Baseline Medical History

Characteristics	All Subjects (n = 261)	Dobutamine Subgroup (n = 58)	Nesiritide ($\mu\text{g}/\text{kg}$ per min)		Overall p Value
			0.015 (n = 103)	0.030 (n = 100)	
Age*	65 \pm 13	64 \pm 14	63 \pm 14	65 \pm 12	0.520†
Race					
White	179 (69%)	47 (81%)	61 (59%)	71 (71%)	0.132‡
Black	57 (22%)	9 (16%)	28 (27%)	20 (20%)	
Hispanic	21 (8%)	2 (3%)	11 (11%)	8 (8%)	
Other	4 (2%)	0 (0%)	3 (3%)	1 (1%)	
Gender: Male	178 (68%)	44 (76%)	67 (65%)	67 (67%)	0.361‡
NYHA					
I, II	22 (8%)	4 (7%)	6 (6%)	12 (12%)	0.548§
III	139 (53%)	30 (52%)	57 (55%)	52 (52%)	
IV	100 (38%)	24 (41%)	40 (39%)	36 (36%)	
CHF etiology					
Ischemia	146 (56%)	39 (67%)	53 (51%)	54 (54%)	0.029‡
IDC	56 (21%)	11 (19%)	27 (26%)	18 (18%)	
Hypertensive	21 (8%)	0 (0%)	12 (12%)	9 (9%)	
Other	38 (15%)	8 (14%)	11 (11%)	19 (19%)	
Previous MI	140 (54%)	40 (69%)	51 (50%)	49 (49%)	0.030‡
Sudden death	23 (9%)	7 (12%)	2 (2%)	14 (14%)	0.002‡
Atrial fibrillation	105 (40%)	28 (48%)	40 (39%)	37 (37%)	0.357‡
Nonsustained VT	55 (21%)	15 (26%)	17 (17%)	23 (23%)	0.304‡
Sustained VT/VF	22 (8%)	4 (7%)	3 (3%)	15 (15%)	0.008‡

*Mean \pm standard deviation; †Omnibus F test; ‡Fisher Exact test, two-tailed; §Kruskal-Wallis test.

IDC = idiopathic dilated cardiomyopathy; MI = myocardial infarction; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

patients who required concomitant IV vasoactive therapy, dobutamine was the most common agent used (Table 4).

Overall hospital LOS was no different among the groups (Table 5). The percentage of nesiritide-treated patients (both doses) readmitted for CHF within 21 days was approximately 69% lower than observed in patients receiving dobutamine ($p < 0.06$ for each nesiritide dose group vs. dobutamine). All-cause readmissions were 60% lower in patients treated with nesiritide 0.015 $\mu\text{g}/\text{kg}$ per min ($p < 0.05$ vs. dobutamine) and 45% lower in the 0.030 $\mu\text{g}/\text{kg}$ per min group ($p > 0.1$ vs. dobutamine, Table 5). Systolic BP at 24 h was significantly reduced in the nesiritide-treated groups compared with the dobutamine-treated group (Table 2). Heart rate for all three groups remained essentially the same after 24 h of treatment. Diastolic BP was signifi-

cantly reduced from baseline in each nesiritide group, but the changes were not significantly different from dobutamine.

Six-month mortality was lower in the 0.015 $\mu\text{g}/\text{kg}$ per min nesiritide group compared with the dobutamine-treated group. Six-month mortality in the 0.030 $\mu\text{g}/\text{kg}$ per min nesiritide group was also lower than that observed with dobutamine (Table 5, Fig. 2).

Adverse events. The incidence of select cardiovascular events reported during the first 24 h of dosing is summarized in Table 6. During the first 24 h, the incidence of symptomatic and asymptomatic hypotension was higher in the nesiritide treatment groups compared to dobutamine. The events were easily managed with either dose reduction or discontinuation. Bradycardia tended to be more common

Table 2. Baseline Blood Pressure and Heart Rate, and Change From Baseline at 24 h (Mean \pm SD)

Parameter	Dobutamine Subgroup (n = 58)	Nesiritide ($\mu\text{g}/\text{kg}$ per min)		Overall p Value*
		0.015 (n = 103)	0.030 (n = 100)	
Systolic BP				
Baseline	118.9 \pm 19.84	126.8 \pm 24.95	123.9 \pm 25.86	0.154
Change from baseline	-3.5 \pm 17.23	-14.1 \pm 18.96†	-14.8 \pm 21.30†	0.002
Diastolic BP				
Baseline	69.9 \pm 13.91	70.8 \pm 14.77	68.4 \pm 15.14	0.507
Change from baseline	-5.2 \pm 14.25	-8.1 \pm 12.50	-8.2 \pm 13.09	0.353
Heart rate				
Baseline	85.6 \pm 16.38	83.2 \pm 18.21	83.8 \pm 14.78	0.687
Change from baseline	0.1 \pm 11.89	0.3 \pm 13.55	1.0 \pm 12.24	0.906

*Fisher Exact test, two-tailed; † $p < 0.05$, relative to dobutamine, analysis of variance.
BP = blood pressure.

Table 3. Treatment Information

Characteristics	Dobutamine Subgroup (n = 58)	Nesiritide ($\mu\text{g}/\text{kg}$ per min)		Overall p Value
		0.015 (n = 103)	0.030 (n = 100)	
Duration of therapy (h)*				
Study drug	65	40†	26†	< 0.001‡
All IV vasoactive therapies	65	42†	41†	0.016‡
Dose modification				
No change	23 (40%)	73 (71%)	57 (57%)	0.001§
Increase above initial dose	16 (28%)	11 (11%)	10 (10%)	0.008§
Other dose increases	12 (21%)	13 (13%)	29 (29%)	0.015§
Decrease	29 (50%)	17 (17%)	18 (18%)	< 0.001§
Study drug as sole IV agent	53 (91%)	86 (83%)	76 (76%)	0.049§
Combination IV therapy	5 (9%)	8 (8%)	12 (12%)	0.589§

*Median; †p < 0.05, relative to dobutamine, Wilcoxon test; ‡Kruskal-Wallis test among all three groups; §Fisher Exact test, two-tailed.

IV = intravenous.

in the nesiritide-treated groups compared with the dobutamine-treated group, although the difference was not statistically significant (overall p = 0.258).

DISCUSSION

Use of nesiritide in the treatment of CHF. The results of this large multicenter trial demonstrate that, in comparison to dobutamine, the use of nesiritide for the initial management of acute decompensated CHF was associated with a shorter treatment course with IV vasoactive therapy, the use of fewer additional parenteral agents and reduced hospital readmission rates. In patients receiving nesiritide 0.015 $\mu\text{g}/\text{kg}$ per min, there was a significantly lower six-month mortality rate compared with patients receiving dobutamine.

Nesiritide versus dobutamine. Readmission for decompensated CHF is a common event for patients with advanced heart failure and can be affected by the adequacy of initial hospital care (10). The present study suggests that nesiritide may be more effective than dobutamine (shorter treatment course, fewer additional agents) and that these short-term benefits may have longer lived effects (reduced

CHF rehospitalization and reduction in mortality). Although the exact mechanisms for the differential effects of nesiritide in this study are not entirely clear, they may include favorable neurohormonal changes and enhanced diuretic effect with nesiritide and/or unfavorable effects of dobutamine such as increased myocardial oxygen consumption, direct myocardial toxicity or arrhythmogenesis.

Pharmacoeconomic considerations. Decompensated CHF is a major cause of hospital admissions in the U.S. and is the leading cause of acute care hospital admissions for patients over the age of 65 years (1,2). Early improvement of symptoms due to hemodynamic compensation, diuresis and natriuresis is often achieved with parenteral therapy, followed by the transition to an appropriate outpatient regimen. Achieving these goals rapidly and economically is essential for improvement of patient care and control of the financial burden from this condition. Overall cost of care is a complex variable that is based not only on the cost of therapeutic agents and procedures, but also on resource utilization (level of care, treatment of serious complications, LOS, readmission rates), which in turn is affected by the efficacy and safety profiles of the therapeutics used.

Table 4. Concomitant Medications During Initial Study Drug Therapy (Number and Percent of Subjects)

Medication	Dobutamine Subgroup (n = 58)	Nesiritide ($\mu\text{g}/\text{kg}$ per min)		Overall p Value*
		0.015 (n = 103)	0.030 (n = 100)	
IV vasoactive				
Dobutamine	—	5 (5%)	11 (11%)	—
PDE inhibitor	4 (7%)	1 (1%)	0 (0%)	0.009
Nitroglycerin	1 (2%)	1 (1%)	1 (1%)	1.000
Nitroprusside	2 (3%)	2 (2%)	0 (0%)	0.169
Dopamine	6 (10%)	1 (1%)	2 (2%)	0.009
Pressors	2 (3%)	0 (0%)	0 (0%)	0.049
Diuretics	58 (100%)	84 (82%)	74 (74%)	< 0.001
Digoxin	49 (84%)	69 (67%)	63 (63%)	0.012
ACE inhibitors	39 (67%)	70 (68%)	54 (54%)	0.089
Beta-blockers	6 (10%)	9 (9%)	7 (7%)	0.745

*Fisher Exact test, two-tailed.

ACE = angiotensin-converting enzyme; IV = intravenous; PDE = phosphodiesterase.

Table 5. Healthcare Utilization and Mortality

Outcomes	Dobutamine Subgroup (n = 58)	Nesiritide ($\mu\text{g}/\text{kg}$ per min)		Overall p Value
		0.015 (n = 103)	0.030 (n = 100)	
Median length of stay (days)	4.5	5	5	0.411‡
Still hospitalized on day 21	4 (7%)	2 (2%)	4 (4%)	0.259§
All-cause readmission (by day 21)	11 (20%)	8 (8%)*	11 (11%)	0.085§
CHF readmission	7 (13%)	4 (4%)†	4 (4%)†	0.081§
Six-month mortality rate	18 (31%)	18 (18%)*	24 (24%)	0.123
Lost to follow-up at six months	0 (0%)	0 (0%)	2 (2%)	—

*p < 0.05 compared to dobutamine, pairwise contrast; †p < 0.06 compared to dobutamine, pairwise contrast; ‡Kruskal-Wallis test; §Fisher Exact test, two-tailed; ||Log-rank test.

CHF = congestive heart failure.

Study limitations. The results of the study are limited by its open-label design, nonrandomized selection of therapies used in the SC group by the investigators and the relatively small number of patients in each subgroup. The dobutamine-treated patients had a higher incidence of ischemia and previous MI compared with the nesiritide-treated patients. Therefore, the choice of dobutamine as the SC agent by the investigator may have selected a sicker patient population for this subgroup. More information from a larger blinded study will be required to confirm the results of this study. In addition, the lack of a placebo group does not allow for the determination of whether the different outcomes observed between the treatment groups were due to a beneficial effect of nesiritide or a detrimental

effect of dobutamine. Finally, although the current recommended dose of nesiritide is an infusion of 0.010 $\mu\text{g}/\text{kg}$ per min (preceded by a 2 $\mu\text{g}/\text{kg}$ bolus), in this study nesiritide was administered at doses one-and-a-half to three times higher.

Conclusions. This study demonstrated that the use of nesiritide was associated with a shorter treatment course, the use of fewer additional parenteral agents, reduced rehospitalization rate and a significantly lower mortality rate at six months (in the 0.015 $\mu\text{g}/\text{kg}$ per min dose group) when compared to dobutamine. Thus, this study suggests that the short-term clinical benefits of nesiritide, the first in the new class of B-type natriuretic peptides for treatment of CHF, may be associated with decreased healthcare utilization costs

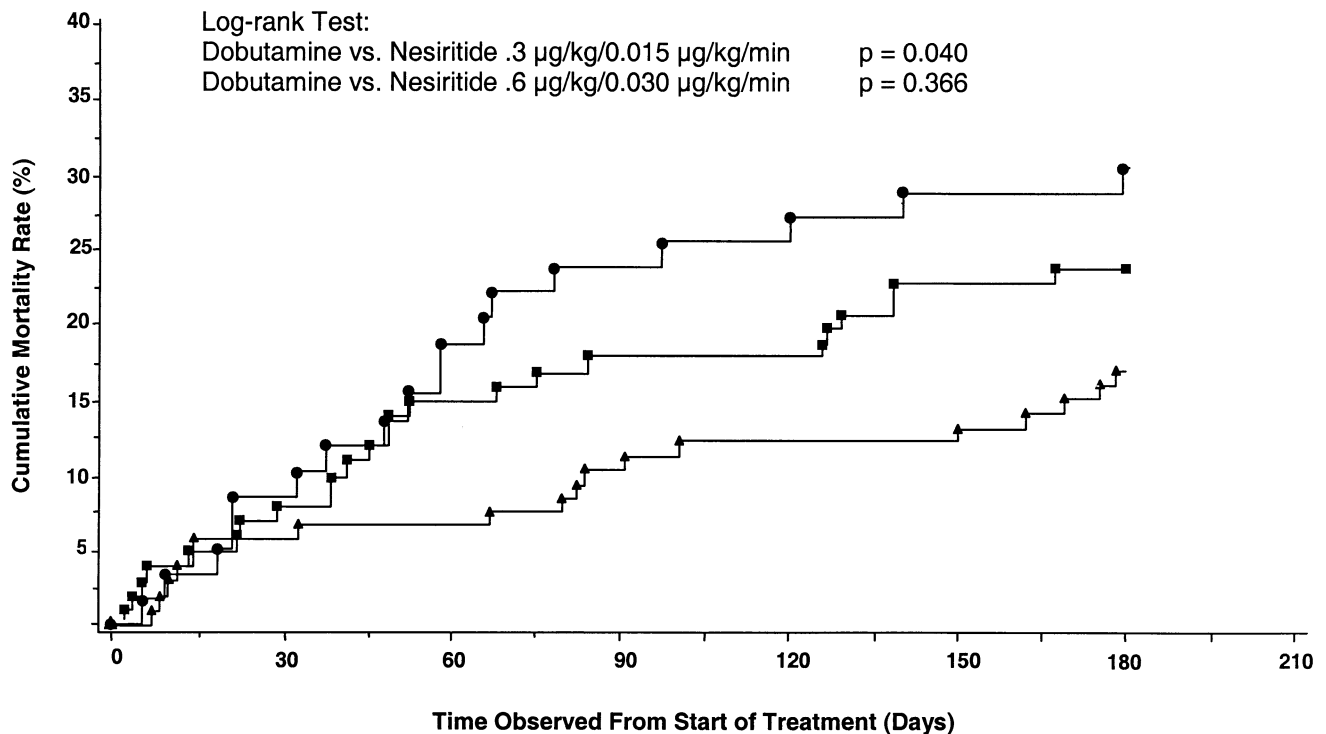


Figure 2. Kaplan-Meier estimate of mortality. Circles = dobutamine (n = 58); squares = nesiritide 0.6 $\mu\text{g}/\text{kg}/0.030$ $\mu\text{g}/\text{kg}$ per min (n = 100); triangles = nesiritide 0.3 $\mu\text{g}/\text{kg}/0.015$ $\mu\text{g}/\text{kg}$ per min (n = 103).

Table 6. Selected Cardiovascular Adverse Events During the First 24 h of Dosing (Number and Percent of Subjects)

Adverse Event	Dobutamine Subgroup (n = 58)	Nesiritide ($\mu\text{g}/\text{kg}$ per min)		Overall p Value*
		0.015 (n = 103)	0.030 (n = 100)	
Symptomatic hypotension	3 (5%)	11 (11%)	17 (17%)	0.085
Asymptomatic hypotension	3 (5%)	15 (15%)	26 (26%)	0.002
Sustained VT	1 (2%)	0 (0%)	0 (0%)	0.222
Nonsustained VT	3 (5%)	10 (10%)	1 (1%)	0.015
Bradycardia	0 (0%)	5 (5%)	4 (4%)	0.258
Heart arrest	1 (2%)	0 (0%)	0 (0%)	0.222

*Fisher Exact test, two-tailed.
 VT = ventricular tachycardia.

and improved long-term survival, compared to the commonly used inotropic agent, dobutamine.

PARTICIPATING INVESTIGATORS

The Nesiritide Study Group—Comparative Trial Investigators has been previously described (7).

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