

INTRAVENOUS NESIRITIDE, A NATRIURETIC PEPTIDE, IN THE TREATMENT OF DECOMPENSATED CONGESTIVE HEART FAILURE

WILSON S. COLUCCI, M.D., URI ELKAYAM, M.D., DARLENE P. HORTON, M.D., WILLIAM T. ABRAHAM, M.D.,
ROBERT C. BOURGE, M.D., ALLEN D. JOHNSON, M.D., LYNNE E. WAGONER, M.D., MICHAEL M. GIVERTZ, M.D.,
CHANG-SENG LIANG, M.D., PH.D., MATTHEW NEIBAUR, M.D., W. HERBERT HAUGHT, M.D.,
AND THIERRY H. LEJEMTEL, M.D., FOR THE NESIRITIDE STUDY GROUP*

ABSTRACT

Background Intravenous infusion of nesiritide, a brain (B-type) natriuretic peptide, has beneficial hemodynamic effects in patients with decompensated congestive heart failure. We investigated the clinical use of nesiritide in such patients.

Methods Patients hospitalized because of symptomatic congestive heart failure were enrolled in either an efficacy trial or a comparative trial. In the efficacy trial, which required the placement of a Swan–Ganz catheter, 127 patients with a pulmonary-capillary wedge pressure of 18 mm Hg or higher and a cardiac index of 2.7 liters per minute per square meter of body-surface area or less were randomly assigned to double-blind treatment with placebo or nesiritide (infused at a rate of 0.015 or 0.030 μg per kilogram of body weight per minute) for six hours. In the comparative trial, which did not require hemodynamic monitoring, 305 patients were randomly assigned to open-label therapy with standard agents or nesiritide for up to seven days.

Results In the efficacy trial, at six hours, nesiritide infusion at rates of 0.015 and 0.030 μg per kilogram per minute decreased pulmonary-capillary wedge pressure by 6.0 and 9.6 mm Hg, respectively (as compared with an increase of 2.0 mm Hg with placebo, $P < 0.001$), resulted in improvements in global clinical status in 60 percent and 67 percent of the patients (as compared with 14 percent of those receiving placebo, $P < 0.001$), reduced dyspnea in 57 percent and 53 percent of the patients (as compared with 12 percent of those receiving placebo, $P < 0.001$), and reduced fatigue in 32 percent and 38 percent of the patients (as compared with 5 percent of those receiving placebo, $P < 0.001$). In the comparative trial, the improvements in global clinical status, dyspnea, and fatigue were sustained with nesiritide therapy for up to seven days and were similar to those observed with standard intravenous therapy for heart failure. The most common side effect was dose-related hypotension, which was usually asymptomatic.

Conclusions In patients hospitalized with decompensated congestive heart failure, nesiritide improves hemodynamic function and clinical status. Intravenous nesiritide is useful for the short-term treatment of decompensated congestive heart failure. (N Engl J Med 2000;343:246-53.)

©2000, Massachusetts Medical Society.

SYMPTOMATIC decompensation is the most common reason for the hospitalization of patients with congestive heart failure due to left ventricular systolic dysfunction. In such patients, the predominant symptoms — dyspnea and fatigue — are associated with pulmonary venous congestion and low cardiac output.¹ Accordingly, the primary goal of therapy, which is the rapid relief of symptoms, is usually approached with the use of intravenous diuretics, vasodilators, and positive inotropic agents to decrease cardiac filling pressures and increase cardiac output.² Although it has generally been assumed that improved hemodynamic function will result in the resolution of symptoms in patients with decompensated congestive heart failure, most studies of new drugs for this purpose have focused on hemodynamic, rather than symptomatic, end points.

Brain (B-type) natriuretic peptide is synthesized in the ventricular myocardium, where its levels increase in patients with congestive heart failure.³ Systemic infusion of nesiritide, a recombinant human brain natriuretic peptide, in patients with congestive heart failure results in beneficial hemodynamic actions, including arterial and venous dilatation, enhanced sodium excretion, and suppression of the renin–angiotensin–aldosterone and sympathetic nervous systems.⁴⁻⁷ To determine the clinical value of nesiritide, we undertook two randomized trials involving a total of 432 patients who were hospitalized because of decompensated congestive heart failure. In one trial (an efficacy trial), we used a double-blind, placebo-controlled design to determine the short-term efficacy of nesiritide with regard to hemodynamic measures and symptoms. In the other trial (a comparative trial), we compared nesiritide with standard intravenous agents, which served as active controls, in terms of clinical efficacy and adverse events.

From Boston University Medical Center, Boston (W.S.C., M.M.G.); the University of Southern California School of Medicine, Los Angeles (U.E.); the Clinical Research Department, Scios, Sunnyvale, Calif. (D.P.H.); University of Cincinnati Medical Center, Cincinnati (W.T.A., L.E.W.); the University of Alabama at Birmingham, Birmingham (R.C.B.); Scripps Clinic and Research Foundation, La Jolla, Calif. (A.D.J.); University of Rochester Medical Center, Rochester, N.Y. (C.L.); Jacksonville Heart Center, Jacksonville, Fla. (M.N.); Jacksonville Center for Research, Jacksonville, Fla. (W.H.H.); and Albert Einstein College of Medicine, Bronx, N.Y. (T.H.L.). Address reprint requests to Dr. Colucci at the Section of Cardiovascular Medicine, Boston University Medical Center, 88 E. Newton St., Boston, MA 02118.

*Other members of the Nesiritide Study Group are listed in the Appendix.

METHODS

Study Population

Between October 1996 and July 1997, 432 patients who required hospitalization and intravenous therapy for decompensated congestive heart failure were recruited at a total of 66 medical centers in the United States (23 centers participated in the efficacy trial and 46 centers in the comparative trial; 3 centers participated in both trials). In both trials, the administration of dobutamine, dopamine, and intravenous vasodilators was discontinued at least 30 minutes before the beginning of the study, and the administration of milrinone was discontinued at least 2 hours before the beginning of the study. Patients were excluded from the comparative trial if they had already received an intravenous vasoactive agent for more than four hours. In both trials, entry criteria required patients to have symptomatic congestive heart failure that, in the opinion of the attending physician, warranted admission to the hospital for therapy with one or more intravenous drugs in addition to diuretics. In the efficacy trial, patients were also required to have a Swan-Ganz pulmonary-artery catheter in place and to meet hemodynamic criteria consisting of a pulmonary-capillary wedge pressure of 18 mm Hg or higher, a cardiac index of 2.7 liters per minute per square meter of body-surface area or less, and a systolic blood pressure of 90 mm Hg or higher. The left ventricular ejection fraction was determined by echocardiography or contrast ventriculography. In the comparative trial, a Swan-Ganz catheter was not required but could be used at the discretion of the attending physician. Patients with recent myocardial infarction or unstable angina (within the preceding 48 hours), clinically important valvular stenosis, hypertrophic or restrictive cardiomyopathy, constrictive pericarditis, primary pulmonary hypertension, or active myocarditis were excluded from both trials.

Study End Points

In the efficacy trial, the prespecified primary end point was the change from base line in the pulmonary-capillary wedge pressure six hours after the start of therapy. Secondary end points were the global clinical status, clinical symptoms, and other hemodynamic measurements. In the comparative trial, the prespecified end points were the global clinical status and clinical symptoms.

Randomization and Study-Drug Administration

In each trial, patients were randomly assigned to a treatment group in blocks of 12 by a randomization center that was independent of both the sponsor and the investigators. Nesiritide (Natrecor, Scios, Sunnyvale, Calif.), supplied as 5 mg of lyophilized powder in a 10-ml glass vial, was reconstituted and further diluted with a solution of 5 percent dextrose in water to the appropriate concentration for each dose group.

In the efficacy trial, the patients were randomly assigned to the three treatment groups in a 1:1:1 ratio. The treatments were as follows: placebo consisting of 5 percent dextrose in water, first given as an intravenous bolus and then as an infusion; nesiritide given as a 0.3- μ g intravenous bolus followed by an infusion of 0.015 μ g per kilogram of body weight per minute; or nesiritide given as a 0.6- μ g intravenous bolus followed by an infusion of 0.030 μ g per kilogram per minute. The study drugs (nesiritide and placebo) were prepared in identical infusion bags and were infused in a double-blind manner. Each subject received a continuous intravenous infusion of study drug for at least six hours. After the assessments at six hours, the treatment-group assignment was revealed to the investigator by the randomization center. If symptomatic hypotension occurred or the systolic blood pressure decreased to less than 85 mm Hg, the infusion was stopped and then restarted at half the initial infusion rate once the systolic blood pressure had stabilized at more than 90 mm Hg. The infusion rate could not be increased over the initial rate or after a dose reduction. Intravenous agents other than the study drug were withheld during the six-hour double-blind period. Oral vasoactive medications and intravenous diuretics were withheld for four hours before the measurement of base-line hemodynamic variables, and

their administration was not resumed until after the six-hour double-blind period.

In the comparative trial, the patients were randomly assigned to the three treatment groups in a 1:1:1 ratio. The treatments were as follows: "standard therapy," consisting of a single intravenous vasoactive agent routinely used for the short-term management of decompensated congestive heart failure (e.g., dobutamine, milrinone, nitroglycerin, or sodium nitroprusside), according to the judgment of the attending physician; nesiritide given as a 0.3- μ g intravenous bolus followed by an infusion of 0.015 μ g per kilogram per minute; or nesiritide given as a 0.6- μ g intravenous bolus followed by an infusion of 0.030 μ g per kilogram per minute. Treatment was given on an open-label basis for standard care but was given in a double-blind manner with respect to the dose of nesiritide. At the discretion of the investigator, the doses of all medications could be increased and a second intravenous vasoactive agent could be added to or substituted for the initial drug. Intravenous diuretics and oral medications could be added at any time. Nesiritide could be discontinued if the patient had symptomatic hypotension or a drop in systolic blood pressure to less than 85 mm Hg, with the option to reinstitute the drug at half the previous infusion rate. Patients randomly assigned to nesiritide could continue to receive nesiritide for up to seven days at the discretion of the investigator.

Assessment of Symptoms

In each trial, global clinical status and specific symptoms of congestive heart failure (dyspnea and fatigue) were assessed at base line and six hours after the treatment with the study drug began. In the efficacy trial, the treatment assignment was revealed after the assessment at six hours. In the comparative trial, the global clinical status and symptoms were also evaluated at 24 hours and at the end of therapy (lasting up to 7 days). Global clinical status was rated independently by both the patient and the investigator on a five-category scale (markedly better, better, no change, worse, or markedly worse) that has been used previously in trials of long-term therapy for congestive heart failure.⁸ Dyspnea and fatigue each were rated jointly by the patient and the investigator on a three-category scale (improved, no change, or worse).

Hemodynamic Assessment in the Efficacy Trial

At base line, repeated measurements of the pulmonary-capillary wedge pressure and of the cardiac index that agreed to within 15 percent were required before administration of the study drug. Pulmonary-capillary wedge pressure, cardiac index, mean right atrial pressure, pulmonary arterial pressures, systolic blood pressure, and heart rate were recorded 1½, 3, 4½, and 6 hours after the start of study-drug administration. In the efficacy trial, plasma levels of aldosterone (measured by radioimmunoassay) and norepinephrine (measured by radioenzymatic assay) were assessed at base line and at six hours.

Statistical Analysis

Data are presented as means \pm SD. In the efficacy trial, the effect of the treatment assignment on hemodynamic variables was analyzed by one-way analysis of variance. In both trials, overall comparisons among the treatment groups were performed with the omnibus F test. Pairwise comparisons were made between each dosage of nesiritide and placebo (in the efficacy trial) or standard therapy (in the comparative trial). Outcomes with respect to global clinical status, symptoms of congestive heart failure, and levels of neurohormones were analyzed by nonparametric methods. All reported P values are two-sided, and P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Base-Line Characteristics

Base-line demographic and clinical characteristics were similar among the patients in the two trials and

were similar among the treatment groups within each trial, with the exception of systolic blood pressure, which was lower in the group assigned to nesiritide at 0.015 μg per kilogram per minute than in the group assigned to nesiritide at 0.030 μg per kilogram per minute or the placebo group ($P < 0.05$) (Table 1). Among the 127 patients enrolled in the efficacy trial, there was marked hemodynamic dysfunction, reflected by a mean pulmonary-capillary wedge pressure of 28 mm Hg, a mean cardiac index of 1.9 liters per minute per square meter, and a mean left ventricular ejection fraction of 0.22. Likewise, plasma levels of norepinephrine and brain natriuretic peptide were markedly elevated among the patients in the efficacy trial.

Efficacy Trial

Five patients discontinued treatment with the study drug before completing the six-hour study period. The reasons for premature termination were sustained ventricular tachycardia in one patient in the placebo

group, worsening congestive heart failure in one patient in the group assigned to nesiritide at 0.015 μg per kilogram per minute, and symptomatic hypotension and nausea, an excessive decrease in pulmonary-capillary wedge pressure, and oliguria in one patient each in the group assigned to nesiritide at 0.030 μg per kilogram per minute. Nesiritide caused dose-dependent decreases in pulmonary-capillary wedge pressure, right atrial pressure, systemic vascular resistance, and systolic blood pressure; a moderate increase in cardiac index; and no substantial change in heart rate (Table 2).

Global clinical status as judged by the patient was better or markedly better than at base line in 60 percent and 67 percent of the patients in the groups assigned to nesiritide at 0.015 and 0.030 μg per kilogram per minute, respectively, as compared with 14 percent of the patients assigned to placebo ($P < 0.001$ for both comparisons) (Fig. 1). There was no change in global status in 25 percent, 23 percent, and 74 percent of patients in the groups assigned to nesir-

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT BASE LINE.*

CHARACTERISTIC	EFFICACY TRIAL			COMPARATIVE TRIAL		
	PLACEBO (N=42)	NESIRITIDE 0.015 $\mu\text{g}/\text{kg}/\text{min}$ (N=43)	NESIRITIDE 0.030 $\mu\text{g}/\text{kg}/\text{min}$ (N=42)	STANDARD CARE (N=102)	NESIRITIDE 0.015 $\mu\text{g}/\text{kg}/\text{min}$ (N=103)	NESIRITIDE 0.030 $\mu\text{g}/\text{kg}/\text{min}$ (N=100)
Age (yr)	59±14	57±14	61±12	63±14	63±14	65±12
Male sex (%)	79	81	60	72	65	67
Race (%)						
White	60	70	52	68	59	71
Black	31	26	33	19	27	20
Other	10	5	14	14	14	9
NYHA functional class†						
I or II	5	0	2	6	6	12
III	60	56	43	60	55	52
IV	36	44	55	34	39	36
Left ventricular ejection fraction	0.22±0.07	0.22±0.08	0.22±0.07	—	—	—
Cause of congestive heart failure (%)						
Ischemic cardiomyopathy	36	56	45	56	51	54
Idiopathic dilated cardiomyopathy	38	16	29	19	26	18
Other	26	28	26	25	22	28
Hemodynamic variables						
Pulmonary-capillary wedge pressure (mm Hg)	29±7	28±7	28±6	—	—	—
Cardiac index (liters/min/m ²)	2.0±0.4	1.8±0.5	1.9±0.5	—	—	—
Systemic systolic blood pressure (mm Hg)	118±17	111±16‡	120±19	—	—	—
Systemic vascular resistance (dyn·sec·cm ⁻⁵)	1524±493	1598±582	1687±589	—	—	—
Plasma brain natriuretic peptide (pg/ml)§	1153±1398	1008±726	1331±670	—	—	—
Plasma norepinephrine (pg/ml)¶	791±426	793±346	633±382	—	—	—

*Plus-minus values are means ±SD. Because of rounding, percentages do not always total 100.

†The New York Heart Association (NYHA) functional class was determined before the episode of acute decompensation.

‡P<0.05 for the comparison with nesiritide at 0.030 μg per kilogram per minute and with placebo.

§The normal value is less than 100 pg per milliliter.

¶To convert the values for plasma norepinephrine to nanomoles per liter, multiply by 0.0059. The normal range is 125 to 310 ng per milliliter.

itide at 0.015 and 0.030 μg per kilogram per minute and in the placebo group, respectively. Likewise, in the physician's judgment, global status was better or markedly better in 55 percent and 77 percent of patients in the groups assigned to nesiritide at 0.015 and 0.030 μg per kilogram per minute, respectively, but in only 5 percent of patients in the placebo group ($P < 0.001$ for both comparisons).

At base line, 93 percent of patients reported dysp-

nea and 96 percent reported fatigue. Dyspnea was rated as improved in 56 percent and 50 percent of the patients receiving nesiritide at 0.015 and 0.030 μg per kilogram per minute, respectively, but in only 12 percent of those receiving placebo ($P < 0.001$ for both comparisons) (Fig. 2). Similarly, fatigue was rated as improved by 32 percent and 38 percent of patients receiving nesiritide at 0.015 and 0.030 μg per kilogram per minute, respectively, but in only 5 per-

TABLE 2. CHANGES IN BASE-LINE HEMODYNAMIC VALUES AT SIX HOURS IN THE EFFICACY TRIAL.*

VARIABLE	PLACEBO (N=42)	NESIRITIDE		P VALUE†
		0.015 $\mu\text{g}/\text{kg}/\text{min}$ (N=43)	0.030 $\mu\text{g}/\text{kg}/\text{min}$ (N=42)	
Pulmonary-capillary wedge pressure (mm Hg)	+2.0±7.2	-6.0±7.2‡	-9.6±6.2‡	<0.001
Right atrial pressure (mm Hg)	+0.4±4.6	-2.6±4.4‡	-5.1±4.7‡	<0.001
Systemic vascular resistance (dyn·sec·cm ⁻⁵)	+161±481	-247±492‡	-347±499‡	<0.001
Cardiac index (liters/min/m ²)	-0.1±0.47	+0.2±0.49§	+0.4±0.69‡	<0.001
Systolic blood pressure (mm Hg)	+0.3±11	-4.4±10.2	-9.3±12.6‡	0.001
Systolic pulmonary-artery pressure (mm Hg)	+1.7±8.2	-9.4±10.3‡	-12.9±12.5‡	<0.001
Mean pulmonary-artery pressure (mm Hg)	+2.0±5.9	-7.0±6.9‡	-7.7±7.6‡	<0.001
Pulmonary vascular resistance (dyn·sec·cm ⁻⁵)	+26±197	-62±100	-2±142	0.03
Heart rate (beats/min)	+1.4±7.5	-1.6±7.1	+0.0±8.8	0.22

*Plus-minus values are means ±SD. Plus signs denote an increase, and minus signs a decrease.

†P values are for the comparison among all three groups and were calculated with the omnibus F test.

‡P < 0.001 for the pairwise comparison with placebo, by the F test.

§P < 0.05 for the pairwise comparison with placebo, by the F test.

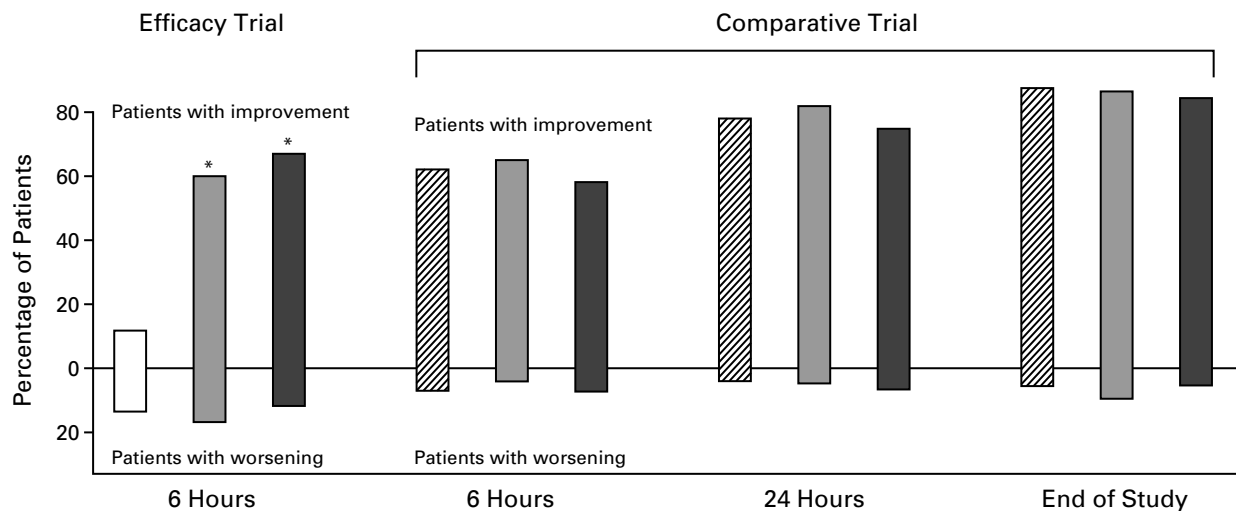


Figure 1. Effects of Nesiritide and Placebo or Standard Therapy on Global Clinical Status as Judged by the Patient.

Open bars represent patients who received placebo (in the efficacy trial), hatched bars patients who received standard therapy (in the comparative trial), and shaded bars and solid bars patients who received nesiritide at 0.015 and 0.030 μg per kilogram per minute, respectively. Bars above the horizontal line at zero indicate the percentage of patients who had improvement or marked improvement, and bars below the line indicate the percentage of patients who had worsening or marked worsening; patients with no change are not shown. The asterisks indicate $P < 0.001$ for the comparison with placebo.

cent of those receiving placebo ($P < 0.001$ for both comparisons) (Fig. 2).

Plasma aldosterone levels decreased by 2.5 ng per deciliter (69.4 pmol per liter) and 1.6 ng per deciliter (44.4 pmol per liter), respectively, in the groups assigned to nesiritide at 0.015 and 0.030 μg per kilogram per minute but increased by 0.6 ng per deciliter (16.6 pmol per liter) in the placebo group ($P = 0.03$). Plasma norepinephrine levels did not change significantly in any group (a decrease of 75 pg per milliliter in the group assigned to nesiritide at 0.015 μg per kilogram per minute, an increase of 8 pg per milliliter in the group assigned to nesiritide at 0.030 μg per kilogram per minute, and an increase of 36 pg

per milliliter in the placebo group). The mean urine output over six hours (380 ml in the placebo group) was 560 ml and 659 ml in the groups assigned to nesiritide at 0.015 and 0.030 μg per kilogram per minute, respectively ($P = 0.004$).

Comparative Trial

The duration of therapy was similar among the three treatment groups, with 68 to 73 percent of the patients in each group treated for one or two days, 14 to 21 percent treated for three to five days, and 9 to 14 percent treated for more than five days ($P = 0.42$). Among the 102 patients assigned to standard therapy, dobutamine was the most common choice

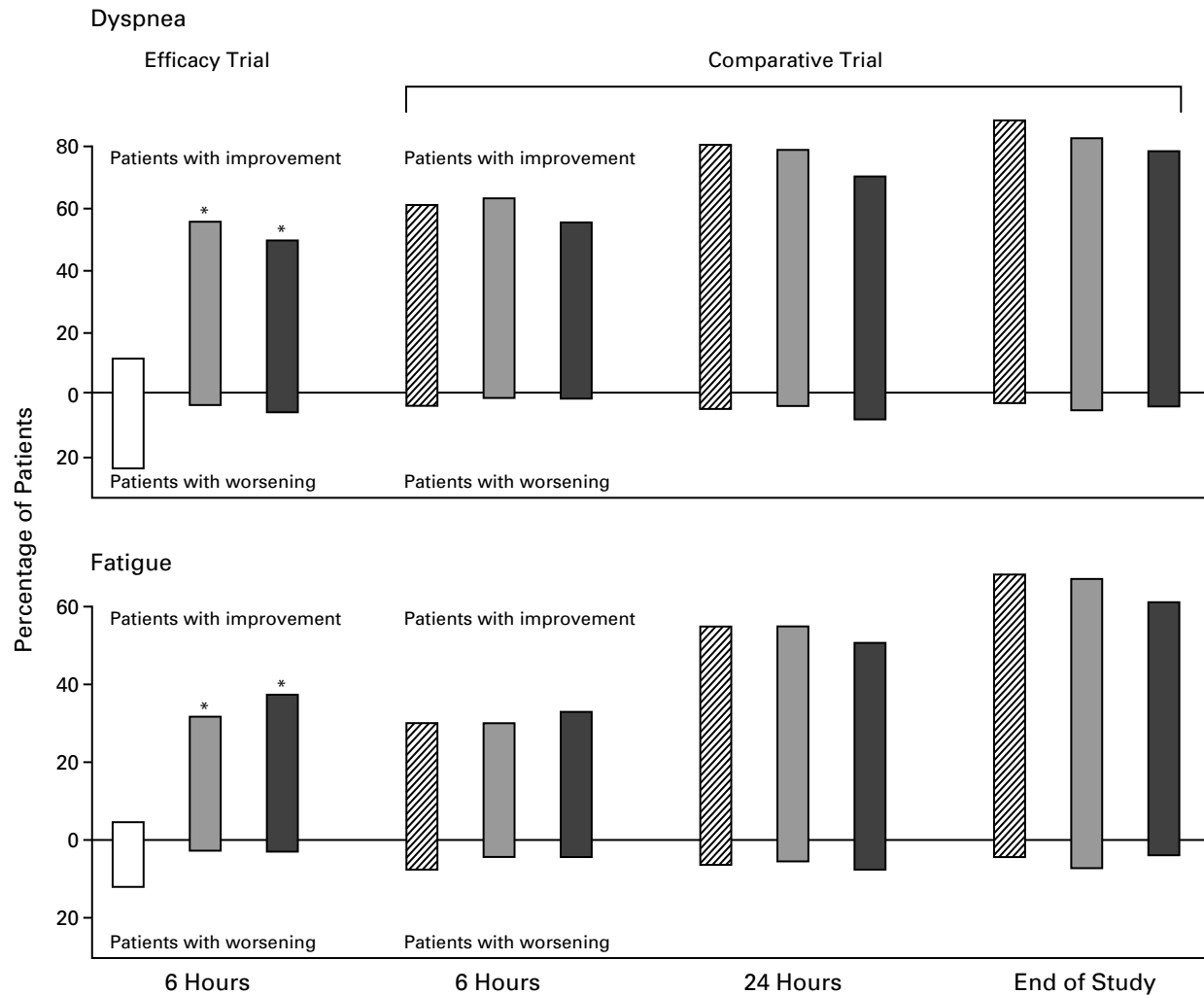


Figure 2. Effect of Nesiritide and Placebo or Standard Therapy on Dyspnea and Fatigue. Open bars represent patients who received placebo (in the efficacy trial), hatched bars patients who received standard therapy (in the comparative trial), and shaded bars and solid bars patients who received nesiritide at 0.015 and 0.030 μg per kilogram per minute, respectively. Bars above the horizontal line at zero indicate the percentage of patients who had improvement, and bars below the line indicate the percentage of patients who had worsening; patients with no change are not shown. The asterisks indicate $P < 0.001$ for the comparison with placebo.

of medication (in 57 percent of patients), followed by milrinone (19 percent), nitroglycerin (18 percent), dopamine (6 percent), and amrinone (1 percent). A Swan–Ganz catheter was used in 19 percent of the patients receiving standard therapy and 18 percent of the patients receiving either dose of nesiritide.

In all three groups, the patients' global clinical status was improved at 6 hours, at 24 hours, and at the end of therapy (Fig. 1). Likewise, dyspnea and fatigue improved in the three groups at all three time points (Fig. 2). There were no significant differences in global status, dyspnea, or fatigue among the three groups at any time. Although the patients in the three groups lost similar amounts of weight during the first two days of treatment (between 0.7 and 1.1 kg), intravenous diuretics were given to fewer patients in the groups assigned to nesiritide at 0.015 and 0.030 μg per kilogram per minute (84 percent and 74 percent of patients, respectively) than in the standard-therapy group (96 percent, $P < 0.001$ for both comparisons).

Adverse Events

In both trials, the most common adverse event in the patients treated with nesiritide was dose-related hypotension, which was usually asymptomatic or mild (Table 3). During the six-hour study period in the efficacy trial, symptomatic hypotension occurred in 2 percent and 5 percent of the patients assigned to nesiritide at 0.015 and 0.030 μg per kilogram per minute, respectively, but in none of the patients in the placebo group. Over the longer time course of the comparative trial, symptomatic hypotension occurred in 4 percent of the standard-therapy group, as compared with 11 percent and 17 percent of the nesiritide groups. Symptomatic hypotension led to discontinuation of nesiritide in 1 patient (receiving

0.030 μg per kilogram per minute) in the efficacy trial and in 15 patients (5 receiving 0.015 μg per kilogram per minute and 10 receiving 0.030 μg per kilogram per minute) in the comparative trial.

In the comparative trial, bradycardia tended to be more common in the two nesiritide groups (Table 3). The rates of other adverse events were similar among the treatment groups in both trials. The rate of death from all causes through day 21 was 6 percent overall and was similar in the three treatment groups; none of the deaths were attributed to the study drug by the investigators. Concomitant use of angiotensin-converting–enzyme inhibitors, digoxin, or beta-blockers did not appear to alter the incidence or distribution of adverse effects observed in patients assigned to nesiritide.

DISCUSSION

The infusion of nesiritide in patients admitted to the hospital for treatment of decompensated congestive heart failure resulted in improvements in hemodynamic function and rapid and sustained improvements in clinical status. Two aspects of this study represent a departure from the usual way that vasoactive agents for congestive heart failure are evaluated. First, the effect of therapy on the chief symptoms of decompensated congestive heart failure was measured prospectively. Second, the study population comprised patients admitted specifically for management of decompensated congestive heart failure.

The evaluation of drugs for the management of decompensated congestive heart failure has generally focused on measures of hemodynamic function in patients with a relatively stable clinical course. This approach is based on the reasonable assumption that hemodynamic improvements in such patients will translate into relief of symptoms. However, there are

TABLE 3. ADVERSE CARDIOVASCULAR EVENTS.*

EVENT	EFFICACY TRIAL				COMPARATIVE TRIAL			
	PLACEBO (N=42)	NESIRITIDE 0.015 $\mu\text{g}/\text{kg}/\text{min}$ (N=43)	NESIRITIDE 0.030 $\mu\text{g}/\text{kg}/\text{min}$ (N=42)	P VALUE	STANDARD THERAPY (N=102)	NESIRITIDE 0.015 $\mu\text{g}/\text{kg}/\text{min}$ (N=103)	NESIRITIDE 0.030 $\mu\text{g}/\text{kg}/\text{min}$ (N=100)	P VALUE
	% of patients				% of patients			
Hypotension								
Symptomatic	0	2	5	0.55	4	11	17	0.008
Asymptomatic	0	9	2	0.13	7	12	24	0.002
Ventricular extrasystole	2	2	0	1.00	4	3	2	0.85
Ventricular tachycardia								
Sustained	2	0	0	0.66	1	0	0	0.66
Nonsustained	5	2	2	0.85	8	10	1	<0.02
Cardiac arrest	0	0	0	—	1	0	0	0.66
Bradycardia	0	0	0	—	0	5	4	0.07

*P values are for the comparisons among all three groups and were calculated with Fisher's exact test.

at least theoretical reasons why such an assumption might not apply, and it has been suggested that the evaluation of new drugs for decompensated congestive heart failure should measure their effects on symptoms directly.⁸ Our study demonstrates that nesiritide relieves the symptoms of decompensated congestive heart failure. When compared with standard therapy consisting primarily of dobutamine or milrinone, nesiritide was found to result in similar improvements in global clinical status and in the symptoms of decompensated congestive heart failure. We cannot exclude the possibility of bias on the part of the physicians or patients as a result of knowledge of the changes in hemodynamic function (in the efficacy trial) or the open-label design (in the comparative trial).

The study population was specifically selected to represent patients in whom rapid symptomatic and hemodynamic effects are desired. All the patients had been admitted to a hospital for treatment of decompensated congestive heart failure. All had dyspnea or fatigue, and most had both symptoms. Measurement of hemodynamic variables at base line confirmed that severe hemodynamic compromise was present. In addition, plasma levels of norepinephrine and brain natriuretic peptide, which are indicators of the severity of disease, were markedly elevated.

Nesiritide caused a dose-related decrease in pulmonary-capillary wedge pressure. This effect was associated with a decrease in systemic vascular resistance and an increase in the cardiac index. Since nesiritide exerts no direct, positive inotropic action on the myocardium, the increase in cardiac output presumably reflects a reduction in left ventricular afterload. At six hours, the decrease in systemic vascular resistance was associated with mean decreases in systolic blood pressure of 4 and 9 mm Hg in the patients receiving nesiritide at infusion rates of 0.015 and 0.030 μg per kilogram per minute, respectively. The decrease in blood pressure was not associated with reflex tachycardia or an increase in plasma norepinephrine levels in either of these groups.

In the efficacy trial, diuretic therapy was discontinued four hours before the study and not resumed until after measurements at six hours had been made. It is therefore noteworthy that urine output increased in a dose-dependent manner with the infusion of nesiritide. Likewise, in the comparative trial, in which intravenous diuretics could be used as needed, nesiritide was associated with decreased use of intravenous diuretics. These observations are consistent with the direct renal effects of natriuretic peptides.^{4,6} In addition, the decrease in aldosterone levels in the nesiritide groups may have contributed to sodium excretion. These observations suggest that nesiritide may be helpful in the clinical management of fluid overload in patients with congestive heart failure.

The most common adverse effect of nesiritide was dose-dependent hypotension, which was usually

asymptomatic or associated with only mild symptoms. By design, half the patients assigned to nesiritide initially received the drug at a dose of 0.030 μg per kilogram per minute. In clinical practice, nesiritide would be started at a dose of 0.015 μg per kilogram per minute or less, and increases in the dose would be guided by the blood pressure. Therefore, the incidence of hypotension in this study is probably greater than it would be in clinical practice.

Standard therapy for decompensated congestive heart failure relies on the use of intravenous diuretics, dobutamine, milrinone, nitroglycerin, and sodium nitroprusside.² The use of dobutamine and milrinone can be limited by the dose-dependent effects of these drugs on heart rate and arrhythmias.^{9,10} Patients taking nitroglycerin are susceptible to the development of tolerance to the drug.¹¹ Although sodium nitroprusside is a potent vasodilator, its use is often limited by the need for close monitoring and by concern about the toxic effects of cyanide or thiocyanide, which are metabolites of sodium nitroprusside. The salutary clinical and hemodynamic profile of nesiritide and the relative absence of adverse effects associated with it circumvent several of these limitations. We therefore suggest that nesiritide would be a valuable addition to the initial treatment of patients admitted to the hospital for decompensated congestive heart failure.

APPENDIX

The other members of the Nesiritide Study Group were as follows: **Efficacy trial** — R. Bies, D. Ferguson, and L. Woodworth (University of Colorado Health Sciences Center, Denver Veterans Affairs Medical Center, and Denver Health Medical Center, Denver); R. Bijou (Montefiore Medical Center, Bronx, N.Y.); R. Benza, M. Smith, and A. Trimble (University of Alabama at Birmingham, Birmingham); K. Chatterjee, T. DeMarco, and D. Lau (University of California, San Francisco, San Francisco); G. Denish III, C. Harrington, and S. Larsen (Scripps Memorial Hospital and San Diego Cardiovascular Associates, San Diego, Calif.); T. Donohue and B. Merkle (St. Louis University Medical Center, St. Louis); M. Slawsky, D. Gauthier, and L. Keane (Boston Medical Center and Boston Veterans Affairs Medical Center, Boston); J.M. Hare and M. Talbot (Johns Hopkins Hospital, Baltimore); R. Hershberger and T. Walker (Oregon Health Sciences Center, Portland); W.B. Hood, Jr., and J. Armstrong (University of Rochester Medical Center—Strong Memorial Hospital, Rochester, N.Y.); M. Ellis (Green Hospital of Scripps Clinic, La Jolla, Calif.); W. Kao and J. O'Sullivan (Rush—Presbyterian—St. Luke's Medical Center, Chicago); M. Kukin, C. Buchholz, and O. O'Campo (Mount Sinai Medical Center, New York); R. Lang and C. Griffiths (University of Chicago Hospital, Chicago); M. Galvao (Jack D. Weiler Hospital of Albert Einstein College of Medicine, Bronx, N.Y.); C. Lui and R. Alves (University of Arizona, Tucson); C. Pepine and D. Leach (Shands Medical Center, University of Florida, Gainesville); J. Plehn and C. Carlson (Dartmouth—Hitchcock Medical Center, Lebanon, N.H.); K. Roush and H. Cole (Toledo Hospital, Toledo, Ohio); V.N. Udhoji and J. Dorman (West Los Angeles Veterans Affairs Medical Center, Los Angeles); P.J. Varghese and A. Nys (George Washington University Medical Center, Washington, D.C.); H.O. Ventura, M.R. Mehra, and B. Robichaux (Ochsner Clinic, New Orleans); and B. Gervers (University of Cincinnati Medical Center, Cincinnati). **Comparative trial** — M. Arendt and E. Springer (Madigan Army Medical Center, Tacoma, Wash.); D.E. Bolster and K. Price (Columbia—Summerville Medical Center, Summerville, S.C.); A. Trimble (University of Alabama at Birmingham, Birmingham); M. Bowles and P. Patterson-Midgley (Columbia Wesley Medical Center, Wichita, Kans.); A. Burger and M. Burger (Beth Israel Deaconess Medical Center, Boston); J. Carley and D. Tracy (Memorial Hospital, Ormond Beach, Fla.); P. Carson and D. Lee (Veterans Affairs Medical Center, Washington, D.C.); P.S. Coleman and S. Campbell (Santa Rosa Memorial, Santa Rosa, Calif.); L. Czer and L. Defensor (Cedars—Sinai Medical Center, Los Angeles); S. El Hafi and R. Keister (Spring

Branch Medical Center, Houston); M. El Shahawy and B. Collentine-Smith (Doctors Hospital of Sarasota, Sarasota, Fla.); J. Johnson and P. Tummala (Los Angeles County–University of Southern California Medical Center, Los Angeles); M. Ellestad and F. Swiger (Long Beach Memorial Medical Center, Long Beach, Calif.); R.D. Ensley and M. Thompson (Saint Francis Hospital, Tulsa, Okla.); R. Feldman and T. Saine (Munroe Regional Medical Center, Ocala, Fla.); D. Fishbein and R. Letterer (University of Washington Medical Center, Seattle); L. Ford and J.M. Birt (Roudebush Veterans Affairs Medical Center, Indianapolis); W. Gandy and J. Miller (St. Joseph's Hospital of Atlanta, Atlanta); J. Ghali and L. Sims (Louisiana State University Medical Center, Shreveport); E.M. Gilbert and K. Volkmann (University of Utah Health Sciences Center, Salt Lake City); M. Greenspan and K. Morgan (Grand View Hospital, Sellersville, Pa.); E. Harlamert and L. Tully (Community Hospital East, Indianapolis); C. Buda (Columbia Memorial Hospital, Jacksonville, Fla.); P. Hoagland and S. Harte (Sharp Memorial Hospital and Sharp Cabrillo Hospital, San Diego, Calif.); K. Cease (Green Hospital of Scripps Clinic, La Jolla, Calif.); R. Karlsberg and T. Gerez (Brotman Medical Center and Midway Hospital Medical Center, Beverly Hills, Calif.); S.N. Lanza and P. Walker (Florida Hospital, Orlando); M. Galvao and J. Varela (Jack D. Weiler Hospital of Albert Einstein College of Medicine, Bronx, N.Y.); T.B. Levine and J. Bolenbaugh (Henry Ford Hospital, Detroit); W. Lewis and B. Pierce (University of California, Davis, Medical Center, Sacramento); C. Edgett (University of Rochester Medical Center, Rochester, N.Y.); S. Mallon and S. Gerity (Jackson Memorial Medical Center, University of Miami, Miami); P. McLaughlin and B. Lee (University Hospital, Columbia, Mo.); D. Hartley and K. Miller (Baptist Medical Center and Baptist Medical Center–Beaches, Jacksonville, Fla.); R. Oren and L. Panther (University of Iowa Hospitals and Clinics, Iowa City); S. Promisloff and D. Jones (Tuality Community Hospital, Hillsboro, Oreg.); D.R. Schwartz and D. Marshall (Columbia Regional Medical Center and Lee Memorial Health System, Fort Myers, Fla.); M.A. Silver and U. Bindingnavle (Christ Hospital and Medical Center, Oak Lawn, Ill.); A. Tenaglia and M. Cash (Tulane University Hospital and Clinics and New Orleans Veterans Affairs Medical Center, New Orleans); G. Torre-Amione and J. Higginbotham (Methodist Hospital, Baylor College of Medicine, Houston); K. Vaska and C. Ageton (Sioux Valley Hospital, Sioux Falls, S.D.); R.C. Johnson (Sioux Falls Veterans Affairs Medical Center, Sioux Falls, S.D.); J. Everett (Christ Hospital, Cincinnati); M.N. Walsh and S. Miller (St. Vincent Hospital and Health Care Center, Indianapolis); D. Wilson and D. DeVore (University of Kansas

Medical Center, Kansas City); and J.R. Wilson and A. Delmotte (Vanderbilt University Medical Center, Nashville).

REFERENCES

1. Braunwald E, Colucci WS, Grossman W. Clinical aspects of heart failure. In: Braunwald E, ed. Heart disease: a textbook of cardiovascular medicine. 5th ed. Vol. 1. Philadelphia: W.B. Saunders, 1997:445-70.
2. Stevenson LW, Colucci WS. Management of patients hospitalized with heart failure. In: Smith TW, ed. Cardiovascular therapeutics. Philadelphia: W.B. Saunders, 1996:199-209.
3. Wei CM, Heublein DM, Perrella MA, et al. Natriuretic peptide system in human heart failure. *Circulation* 1993;88:1004-9.
4. Holmes SJ, Espiner EA, Richards AM, Yandle TG, Frampton C. Renal, endocrine, and hemodynamic effects of human brain natriuretic peptide in normal man. *J Clin Endocrinol Metab* 1993;76:91-6.
5. Marcus LS, Hart D, Packer M, et al. Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure: a double-blind, placebo-controlled, randomized crossover trial. *Circulation* 1996;94:3184-9.
6. Abraham WT, Lowes BD, Ferguson DA, et al. Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. *J Card Fail* 1998;4:37-44.
7. Mills RM, LeJemtel TH, Horton DP, et al. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure: a randomized, double-blind, placebo-controlled clinical trial. *J Am Coll Cardiol* 1999;34:155-62.
8. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. *Circulation* 1996;94:2800-6.
9. Tisdale JE, Patel R, Webb CR, Borzak S, Zarowitz BJ. Electrophysiologic and proarrhythmic effects of intravenous inotropic agents. *Prog Cardiovasc Dis* 1995;38:167-80.
10. Anderson JL, Askins JC, Gilbert EM, Menlove RL, Lutz JR. Occurrence of ventricular arrhythmias in patients receiving acute and chronic infusions of milrinone. *Am Heart J* 1986;111:466-74.
11. Packer M, Lee WH, Kessler PD, Gottlieb SS, Medina N, Yushak M. Prevention and reversal of nitrate tolerance in patients with congestive heart failure. *N Engl J Med* 1987;317:799-804.

CORRECTION

Intravenous Nesiritide, a Natriuretic Peptide, in the Treatment of Decompensated Congestive Heart Failure

Intravenous Nesiritide, a Natriuretic Peptide, in the Treatment of Decompensated Congestive Heart Failure . It should have been stated that the trials were supported by a grant from Scios.

CORRECTION

Intravenous Nesiritide, a Natriuretic Peptide, in the Treatment of Decompensated Congestive Heart Failure

Intravenous Nesiritide, a Natriuretic Peptide, in the Treatment of Decompensated Congestive Heart Failure . On page 247, in the last paragraph of the left-hand column and the first paragraph of the right-hand column, the intravenous bolus doses of nesiritide should have been “0.3 µg per kilogram of body weight” and “0.6 µg per kilogram,” not “0.3 µg” and “0.6 µg,” as printed.