Intravenous Nesiritide vs Nitroglycerin for Treatment of Decompensated Congestive Heart Failure

A Randomized Controlled Trial

Publication Committee for the VMAC Investigators

Context Decompensated congestive heart failure (CHF) is the leading hospital discharge diagnosis in patients older than 65 years.

Objective To compare the efficacy and safety of intravenous nesiritide, intravenous nitroglycerin, and placebo.

Design, Setting, and Patients Randomized, double-blind trial of 489 inpatients with dyspnea at rest from decompensated CHF, including 246 who received pulmonary artery catheterization, that was conducted at 55 community and academic hospitals between October 1999 and July 2000.

Interventions Intravenous nesiritide (n=204), intravenous nitroglycerin (n=143), or placebo (n=142) added to standard medications for 3 hours, followed by nesiritide (n=278) or nitroglycerin (n=216) added to standard medication for 24 hours.

Main Outcome Measures Change in pulmonary capillary wedge pressure (PCWP) among catheterized patients and patient self-evaluation of dyspnea at 3 hours after initiation of study drug among all patients. Secondary outcomes included comparisons of hemodynamic and clinical effects between nesiritide and nitroglycerin at 24 hours.

Results At 3 hours, the mean (SD) decrease in PCWP from baseline was –5.8 (6.5) mm Hg for nesiritide (vs placebo, $P<.001$; vs nitroglycerin, $P=.03$), –3.8 (5.3) mm Hg for nitroglycerin (vs placebo, $P=.09$), and –2 (4.2) mm Hg for placebo. At 3 hours, nesiritide resulted in improvement in dyspnea compared with placebo ($P=.03$), but there was no significant difference in dyspnea or global clinical status with nesiritide compared with nitroglycerin. At 24 hours, the reduction in PCWP was greater in the nesiritide group (–8.2 mm Hg) than the nitroglycerin group (–6.3 mm Hg), but patients reported no significant differences in dyspnea and only modest improvement in global clinical status.

Conclusion When added to standard care in patients hospitalized with acutely decompensated CHF, nesiritide improves hemodynamic function and some self-reported symptoms more effectively than intravenous nitroglycerin or placebo.

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HEART FAILURE OCCURS IN 4.7 million persons living in the United States,[1] and is the discharge diagnosis in approximately 3.5 million hospitalizations annually.[2] Hospitalizations account for 60% of health care expenditures for heart failure.[1-5] Despite its enormous human and economic burden, no new intravenous agents for acutely decompensated congestive heart failure (CHF) have been approved for use in the United States in more than a decade. Furthermore, the rapid relief of symptoms without significant complications or adverse effects of drug therapy have not been addressed previously in patients hospitalized with heart failure.

There is increasing recognition that agents with positive inotropic activity can increase mortality despite acute hemodynamic improvement.[6-14] Current guidelines from the American College of Cardiology and the American Heart Association for management of acutely decompensated CHF and decompensation of chronic CHF without cardiogenic shock advocate use of inotropic agents (dobutamine and dopamine) only if administration of morphine, loop diuretics, sublingual and intravenous nitroglycerin, and nitroprusside provide insufficient improvement.[1] Yet, intravenous inotropic agents continue to be used commonly for this syndrome.

Nesiritide is a recombinant human brain, or B-type, natriuretic peptide that is identical to the endogenous hormone produced by the ventricle in response to increased wall stress, hypertrophy, and volume overload. Nesiritide has venous, arterial, and coronary vasodilatory properties that reduce preload and afterload, increase cardiac out-

See also pp 1541 and 1578.

A list of the Vasodilation in the Management of Acute CHF (VMAC) Investigators and Financial Disclosures are listed at the end of this article.
Corresponding Author and Reprints: James B. Young, MD, Department of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave/F25, Cleveland, OH 44195 (e-mail: youngj@ccf.org).

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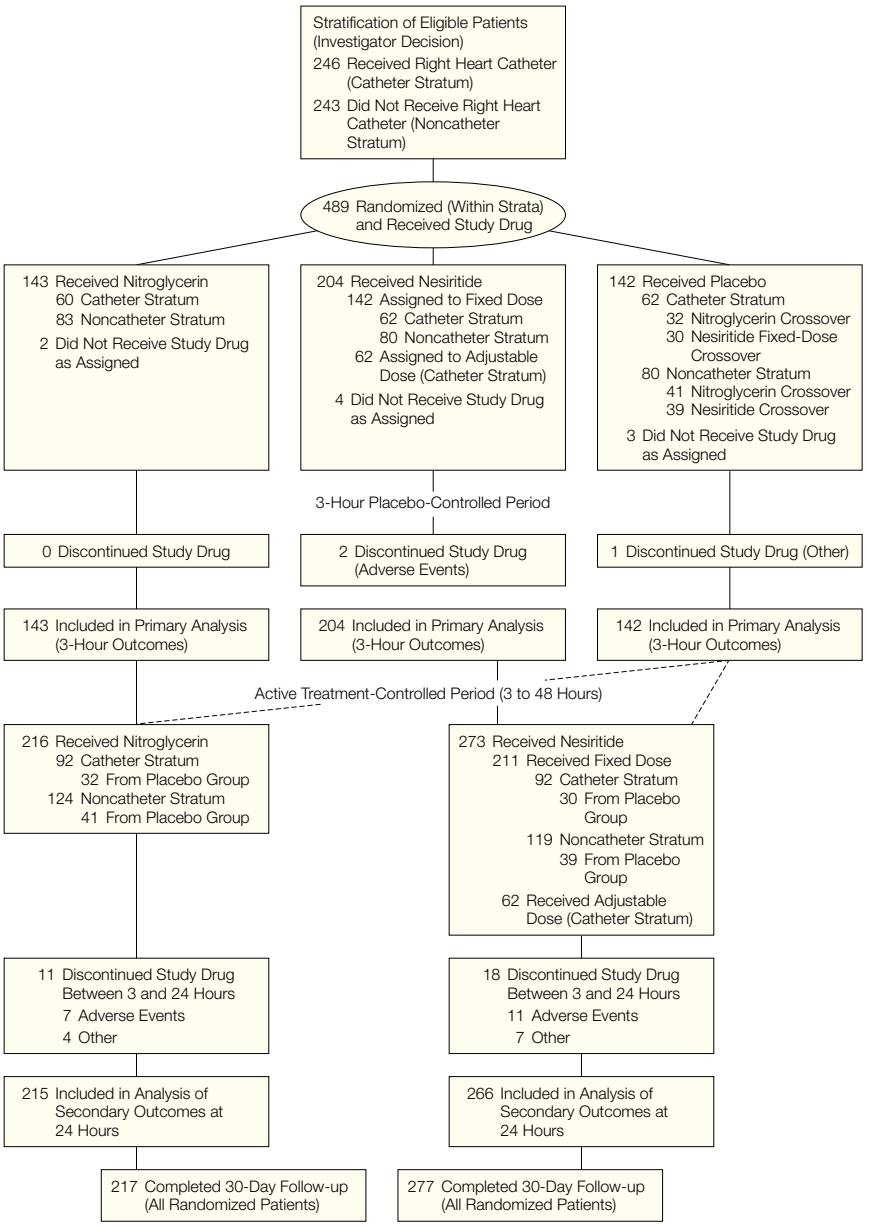
put without direct inotropic effects, improve echocardiographic indices of diastolic function,[15-17] and improve symptoms in patients with acutely decompensated CHF,[18] without increasing heart rate or proarrhythmia.[18,19] In addition, nesiritide has been observed to increase glomerular filtration rate and filtration fraction, suppress the renin-angiotensin-aldosterone axis, and cause natriuresis in patients with decompensated CHF.[20,21]

The Vasodilation in the Management of Acute CHF (VMAC) study is, to our knowledge, the first large multicenter, randomized, double-blind trial to evaluate the hemodynamic and clinical effects of a natriuretic peptide added to standard care, compared with an intravenous vasodilating agent added to standard care, for management of decompensated CHF in hospitalized patients with dyspnea at rest.

Figure 1. Patient Follow-up Throughout the Vasodilation in Management of Acute CHF Trial



CHF indicates congestive heart failure.

METHODS

Study Organization and Design

The VMAC trial was a prospective, multicenter trial in which the randomization was stratified based on the investigator's clinical decision, prior to randomization, to use a right heart catheter to manage decompensated CHF ("catheterized" or "noncatheterized"). Randomization occurred after patients were confirmed to meet all inclusion and exclusion criteria and informed consent was obtained. Randomization was performed using random permuted blocks within strata (catheterized or noncatheterized), with a block size of 8 for the catheterized strata and of 6 for the noncatheterized strata. Noncatheterized patients were randomly assigned to receive either placebo, nitroglycerin that could be titrated, or fixed-dose nesiritide for the first 3 hours. Catheterized patients were randomly assigned to these same 3 treatment groups or to the adjustable-dose nesiritide group. For placebo patients in both strata, the randomization included a crossover to double-blind treatment with either titratable-dose nitroglycerin or to fixed-dose nesiritide at 3 hours after the primary end points were obtained (FIGURE 1). Total duration of the treatment was determined by the investigator, but the minimum duration of dosing was specified as 24 hours.

The study used a double-blind, double-dummy study drug administration design in which each patient received simultaneous infusions of nitroglycerin/placebo and nesiritide/placebo. Study drug concentrations were adjusted so that the total fluid volume administered would be appropriately low for a patient with decompensated CHF, but so that the treatment groups would receive similar fluid volumes. Nesiritide (Natrecor, Scios Inc, Sunnyvale, Calif) was prepared at a concentration of 10 µg/mL and administered as a 2-µg/kg bolus followed by a fixed-dose infusion of 0.01 µg/kg per minute for 3

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hours. Following the first 3 hours, the dose remained the same in the fixed-dose nesiritide group, while for the group assigned to the adjustable-dose nesiritide, investigators could incrementally increase the dose every 3 hours to a maximum of 0.03 µg/kg per minute if the pulmonary capillary wedge pressure (PCWP) was 20 mm Hg or higher and systolic blood pressure was 100 mm Hg or higher (using a 1-µg/kg bolus followed by an increase of 0.005 µg/kg per minute over the previous infusion rate). Downtitration of the nesiritide/placebo infusion flow rate by 30% was permitted according to the investigators' discretion.

Because there is no standard dose of nitroglycerin for heart failure, nitroglycerin (Tridil, DuPont Pharma, Wilmington, Del) was prepared at a concentration of 400 µg/mL, and administration was determined per investigator discretion. The nitroglycerin/placebo infusion could be uptitrated or downtitrated throughout the study to achieve the desired clinical or hemodynamic effect. If study drug was to be decreased or discontinued for any reason, both infusions were to be decreased or stopped simultaneously. Infusion flow rates of both study drugs could be increased or restarted if the patient had a stable blood pressure. In the fixed-dose nesiritide group, doses with infusions greater than 0.01 µg/kg per minute were not permitted at any time.

Study Population

Patients were included if they had dyspnea at rest due to decompensated CHF that was severe enough to require hospitalization and intravenous therapy. A cardiac etiology for dyspnea was established by estimated or measured elevation of cardiac filling pressures (PCWP ≥20 mm Hg in catheterized patients) and at least 2 of the following: (1) jugular venous distention, (2) paroxysmal nocturnal dyspnea or 2-pillow orthopnea within 72 hours before study entry, (3) abdominal discomfort due to mesenteric congestion, or (4) a chest x-ray film consistent with decompensated CHF. Patients may have had acute decompensation of chronic heart failure, gradual worsening of chronic heart failure, or new onset of acutely decompensated CHF. Patients who were receiving dobutamine or dopamine but who otherwise met entry criteria were also permitted into the study. Exclusion criteria were: systolic blood pressure lower than 90 mm Hg, cardiogenic shock or volume depletion, any condition that would contraindicate an intravenous vasodilator, acutely unstable clinical status that would not permit a 3-hour placebo period, use of intravenous nitroglycerin that could not be withheld, mechanical ventilation, and anticipated survival of less than 30 to 35 days. Patients with decompensated CHF in the setting of acute coronary syndromes, preserved systolic function, renal failure, or atrial or ventricular arrhythmias were not excluded based on these conditions alone. The use of intravenous vasodilators or inodilators with study drug was not permitted. The study was approved by all participating centers' institutional review boards for clinical investigation, and written informed consent was obtained from each study participant prior to study entry and randomization.

End Points and Measurements

The protocol-specified primary analysis was a comparison of the hemodynamic and clinical effects of nesiritide vs placebo when both were added to standard care. The primary end points were the absolute changes in PCWP (catheterized patients only) and the patient's self-evaluation of dyspnea (all patients) from baseline to 3 hours after the start of study drug. Secondary end points included comparisons between nesiritide and nitroglycerin of the following hemodynamic and clinical effects: onset of effect on PCWP, the effect on PCWP 24 hours after the start of study drug, self-assessed dyspnea and global clinical status, and the overall safety profile. Additional outcomes included comparison of the use of other intravenous vasoactive agents or diuretics, and the effects on other hemodynamic variables. Dyspnea and global clinical status were assessed using a nonvalidated symptom scale that is similar to the symptom scale used in a prior nesiritide trial.[17]

To avoid potential bias, neither the study staff nor the health care team was allowed to discuss or assist the patient in completing the symptom evaluation form (dyspnea and global clinical status). In the catheterized stratum, symptom evaluation forms were completed before hemodynamic measurements had been obtained at the same time points, and hemodynamic results were not discussed within hearing range of the patient.

During the 3-hour placebo-controlled period, PCWP and pulmonary artery pressures were measured at 15 and 30 minutes, and at 1, 2, and 3 hours in catheterized patients only. In these patients, cardiac output and mean right atrial pressure were measured at 1 and 3 hours. In all patients, vital signs and symptoms (dyspnea and global clinical evaluations) were assessed at 15 and 30 minutes, and at 1, 2, and 3 hours after the start of study drug. After 3 hours, PCWP and pulmonary artery pressure were obtained in catheterized patients at 6, 9, 12, 24, 36, and 48 hours, and when study drug was discontinued (if <48 hours). In all patients, vital signs were assessed every 3 hours for the duration of study drug infusion and at 15-minute intervals for the first hour and 30-minute intervals for the second hour after any dose change, discontinuation, or restarting of the infusion. Dyspnea and global clinical evaluations were repeated at 6 and 24 hours. Serum creatinine level was obtained at baseline, daily through 2 days after discontinuation of study drug, and at study days 14 and 30. General adverse events were assessed through study day 14. Serious adverse events other than death (hospital admissions and nonfatal, life-threatening events) were monitored through study day 30. Mortality was assessed through 6 months.

All patients who received study drug were included in the safety analysis. Symptomatic hypotension was defined prospectively as a significant decrease in blood pressure (in excess of what would

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be intended with an intravenous vasodilator) and was associated with 1 or more of the following symptoms: lightheadedness, dizziness, feeling faint, or having blurred vision.

Statistical Analyses

Efficacy was analyzed in all treated patients, as randomized, except for 9 patients who were randomized but not treated. These patients were excluded from the analysis because hemodynamic and symptom assessments were not performed. As no dose increases of nesiritide were permitted before 3 hours, the prespecified primary analysis evaluated during the placebo-controlled period was a comparison of the pooled nesiritide dose groups (fixed and adjustable dose) with the placebo group when added to standard care. After 3 hours, placebo patients (who crossover to double-blind, active treatment) were included in the subsequent active treatment comparisons.

For the dyspnea and global clinical status evaluations, 2 groups (nesiritide and nitroglycerin) were compared using a stratified 2-sample Wilcoxon procedure (Van Elteren test) for right heart catheter use to evaluate the following 7-point categorical responses of the patient: markedly, moderately, or minimally improved; no change; or minimally, moderately, or markedly worsened. This nonparametric analysis was prespecified as a supplemental analysis to test the robustness of the primary parametric analysis. However, because the protocol allowed for the use of standard care agents before use of the study drug and during the first 3 hours, a heightened placebo effect and a skewed distribution toward more subjects being improved was anticipated. Furthermore, post-hoc testing showing the lack of normality of the dyspnea data justifies the use of the Van Elteran test for this analysis. A parametric analysis using a 2-way analysis of variance (treatment and right heart catheter use) was also used.

A 1-way analysis of variance model was used for the analysis of mean change from baseline for PCWP and other hemodynamic measurements for catheterized patients. Means are presented with SDs, and medians are provided with interquartile ranges for hemodynamic data, unless otherwise noted.

This study was powered to demonstrate significant differences between nesiritide and placebo for PCWP evaluation among all catheterized patients and for dyspnea evaluation among all patients. Based on a 2-sample Wilcoxon procedure, a sample size of 140 in the placebo and 200 in the nesiritide treatment group had approximately 86% power to detect a treatment difference if the proportion of patients' symptoms were markedly (0% vs 5%), moderately (15% vs 20%), or minimally improved (20% vs 25%); no change (50% vs 40%); or minimally (both 5%), moderately (both 5%) or markedly worsened (5% vs 0%). The assumption of this proportion of responses reflects the anticipation that regardless of therapy, most patients' dyspnea will be improved or unchanged at 3 hours, rather than worsened; and active therapy (plus standard care) will be more effective than placebo (plus standard care). Based on the large-sample z statistic, with the assumption of a population mean (SD) decrease in PCWP of 2 (6) mm Hg in the placebo group and 5 (6) mm Hg in the nesiritide group, a pairwise contrast had 88% power with sample sizes of 60 in the placebo group and 120 in the nesiritide treatment group.

RESULTS

Patient Enrollment

Between October 1999 and July 2000, 498 patients were randomized, of which 489 were treated with study drug (143 nitroglycerin, 204 nesiritide, and 142 placebo) at 55 US study centers. Of the total 489 randomized and treated patients, 246 were in the catheterized stratum and 243 were in the noncatheterized stratum. Approximately 240 patients in each of the catheterized and noncatheterized strata were specified prior to the study (Figure 1).

Baseline Characteristics

Baseline clinical characteristics were similar among patients in the study groups (TABLE 1) except that more patients in the nesiritide group were men. All patients had dyspnea at rest (or New York Heart Association class IV symptoms) at study entry, 84% had chronic decompensated CHF that was classified as class III or class IV prior to decompensation, and most had clinical evidence of fluid overload (jugular venous distention in 89%, rales in 73%, and pedal edema in 73%). Other important baseline clinical findings included an acute coronary syndrome in 12%, preserved systolic function (ejection fraction >40%) in 15%, renal insufficiency (serum creatinine ≥2.0 mg/dL [≥176.8 µmol/L]) in 21%, and diabetes in 47%. Many patients had a history of significant arrhythmias including atrial fibrillation or fib/flutter (35%), nonsustained ventricular tachycardia (22%), sudden death (8%), ventricular fibrillation (6%), and sustained ventricular tachycardia (13%). The mean (SD) left ventricular ejection fraction was 27% (14%). Mean (SD) systolic blood pressure at trial entry was 121 (22) mm Hg. Ninety patients (18%) had a baseline systolic blood pressure of 100 mm Hg or lower and 107 patients (22%) had a baseline systolic blood pressure of 140 mm Hg or higher. In catheterized patients, mean PCWP was 27.8 (6.3) mm Hg and mean (SD) cardiac index was 2.2 (0.73) L/min per m^2.

The long-term use of cardiac medications also was well balanced between the nesiritide and nitroglycerin groups, with the exception that more nesiritide patients were receiving a class III antiarrhythmic at baseline (P=.02; TABLE 2), were given an intravenous vasoactive medication within 24 hours before study drug, and had study drug added to ongoing therapy with dobutamine or dopamine (Table 1 and Table 2).

Dosing and Administration

The median time of study drug exposure was the same in both the nesiritide and nitroglycerin groups (24-25 hours). The percentage of nesiritide and nitroglycerin patients who received study drug for 24 to 72 hours (69% vs 71%, respec-

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tively) and more than 72 hours (6% and 5%, respectively) was also similar. During both the placebo-controlled and active-controlled periods, the nitroglycerin infusion was titrated to higher doses in catheterized patients than in noncatheterized patients. At the 3-hour time point, when the primary end points were measured, a mean (SD [median {25th, 75th percentile}]) dose of 42 (61 [13 {10, 40}]) µg/min of nitroglycerin was administered to catheterized patients, whereas a dose of 29 (38 [13 {10, 20}]) µg/min of nitroglycerin was administered to noncatheterized patients. Additional nitroglycerin uptitration from 3 to 24 hours occurred in catheterized patients (to a mean [SD {median; 25th, 75th percentile}] dose of 56 [64 {20; 13, 80}] µg/min) but not in noncatheterized patients (dose of 27 [31 {13; 7, 27}] µg/min). The titrated doses of nitroglycerin lowered blood pressure to a comparable or greater degree than nesiritide (TABLE 3). Nesiritide was administered as a fixed dose in most patients. Of the 62 patients randomized to the adjustable-dose group, only 23 patients had an increase in the nesiritide dose; some dose adjustments (10/23) were up to a maximum of 0.015 µg/kg per minute.

Efficacy

The reduction in PCWP was significantly greater in the nesiritide group than in the nitroglycerin or placebo group, starting with the first measurement at 15 minutes (FIGURE 2A and Table 3). Mean changes in PCWP from baseline at 3 hours were −5.8 (6.5) mm Hg for nesiritide (vs placebo, $P<.001$; vs nitroglycerin, $P=.03$), −3.8 (5.3) mm Hg for nitroglycerin (vs placebo, $P=.09$), and −2 (4.2) mm Hg for placebo. Nesiritide and nitroglycerin were also associated with significantly greater mean reductions in pulmonary vascular resistance than placebo at 1 hour. Nesiritide significantly reduced pulmonary vascular resistance at 3 hours (Table 3). Nesiritide was associated with greater mean reductions in mean right atrial pressure compared with placebo at 1 and 3 hours. Nitroglycerin significantly lowered mean right atrial pressure compared with placebo at 3 hours, but not at the earlier time points (Table 3). Nesiritide, but not nitroglycerin, significantly increased cardiac index and lowered systemic vascular resistance at 1 hour compared with placebo. There were no differences in change in cardiac index among nesiritide, nitroglycerin, or placebo groups at 3 hours (Table 3). Effects on systolic blood pressure through 3 hours were similar with nesiritide and nitroglycerin (Table 3). Nesiritide also was associated with greater mean reductions in systolic and mean pulmonary artery pressure than both nitroglycerin and placebo at every time point through 3 hours (data not shown). There were no significant differences between nitroglycerin and placebo in

Table 1. Baseline Characteristics

Characteristics	No. (%) of Patients			*P* Value
	Nitroglycerin (n = 143)	Nesiritide (n = 204)	Placebo (n = 142)	
Demographics				
Age, mean (SD), y	60 (14)	62 (13)	62 (15)	.41*
Men	86 (60)	148 (73)	103 (73)	.03†
Race				
White	85 (59)	18 (58)	83 (58)	>.99†
Black	35 (24)	50 (25)	34 (24)	
Other	4 (4)	7 (3)	4 (3)	
Medical History				
New York Heart Association Classification for congestive heart failure				
II	18 (13)	13 (6)	7 (5)	.30‡
III	15 (38)	89 (44)	59 (42)	
IV	55 (38)	85 (42)	64 (45)	
Hypertension	94 (66)	143 (70)	105 (74)	.33†
Coronary artery disease	90 (63)	134 (66)	95 (67)	.78†
Previous myocardial infarction	59 (41)	96 (47)	70 (49)	.37†
Atrial fibrillation or fib/flutter	46 (32)	75 (37)	48 (34)	.67†
Diabetes	68 (48)	88 (43)	75 (53)	.21†
Sustained ventricular tachycardia	9 (6)	31 (15)	22 (15)	.02†
Frequent premature ventricular contractions	41 (29)	68 (33)	57 (40)	.12†
Ejection fraction >40%	19 (15)	26 (14)	20 (16)	.89†
Implantable cardiac defibrillator or pacemaker	31 (22)	55 (27)	36 (25)	.52†
Primary etiology of chronic cardiomyopathy				
Ischemic	59 (45)	102 (53)	78 (59)	.42§
Idiopathic, dilated cardiomyopathy	39 (30)	45 (24)	29 (22)	
Hypertensive	15 (11)	18 (9)	12 (9)	
Other	12 (9)	14 (8)	7 (5)	
Acute coronary syndrome within 7 days before start of study drug	20 (14)	20 (10)	21 (15)	.03†
Clinical Presentation‖				
Baseline systolic blood pressure <100 mm Hg	20 (14)	48 (24)	22 (15)	.07†
Intravenous vasoactive drug given within 24 hours of study drug¶	22 (25)	60 (29)	35 (25)	.009†
Baseline dobutamine	11 (8)	33 (16)	25 (18)	.02†
Baseline dopamine	2 (1)	15 (7)	5 (4)	.02†

*Calculated using the *t* test.
†Calculated using the Fisher exact test.
‡Calculated using the Wilcoxon test.
§Calculated using the χ^2 test.
‖No other significant differences were noted at baseline.
¶Includes dobutamine, dopamine, intravenous nitroglycerin and nitroprusside, and phosphodiesterase inhibitors.

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reductions in systolic or mean pulmonary artery pressure at any time point through 3 hours.

At 24 hours, the mean (SD) reduction in PCWP was significantly greater with nesiritide (–8.2 mm Hg) than nitroglycerin (–6.3 mm Hg) ($P=.04$), with no evidence of attenuation of effect (Figure 2B). At 36 and 48 hours, there were no significant differences in PCWP reduction in the nesiritide and nitroglycerin groups, but PCWP was obtained in only about 50% of catheterized patients at 36 hours and in only a third of patients at 48 hours. At 24 hours, the mean decreases in systolic blood pressure were not significantly different in the nesiritide and nitroglycerin groups (–8.7 and –8.1 mm Hg, respectively, $P=.54$).

The differences between nesiritide and placebo or nitroglycerin in the effect on PCWP are not explained by the higher percentage of nesiritide patients who had study drug added to ongoing therapy with dobutamine or dopamine. Among patients who were not receiving ongoing dobutamine or dopamine therapy, the 3-hour mean (SD) change in PCWP was –3.4 (5.4) mm Hg for nitroglycerin (n=51; nitroglycerin vs placebo, $P=.15$); –6.5 (6.8) mm Hg for nesiritide (n=99; nesiritide vs nitroglycerin, $P=.004$); and –1.7 (4.4) mm Hg for placebo (n=48; nesiritide vs placebo, $P<.001$).

The second primary end point (FIGURE 3A), the patient's self-assessment of dyspnea at 3 hours, was significantly improved in the nesiritide group compared with the placebo group ($P=.03$), although improvement in dyspnea scores in the nesiritide and nitroglycerin groups were not significantly different ($P=.56$). At 3 hours (Figure 3B), there were no significant differences in improvement in global clinical status in the nesiritide group compared with the nitroglycerin group ($P=.55$) or the placebo group ($P=.07$).

During the first 24 hours of treatment, there was evidence of progressive improvement in dyspnea and global clinical status over time with both active infusions. No significant differences were found between the nesiritide and nitroglycerin group for dyspnea at 24 hours ($P=.13$; Figure 3C). For the global clinical status in all patients, using a parametric analysis, nesiritide, when compared with nitroglycerin, was associated with significant improvement at 24 hours (2-way analysis of variance, $P=.04$), but showed a nonsignificant trend toward improvement when nonparametric analysis was used (Van-Elteren test, $P=.08$; Figure 3D).

Safety

During the placebo-controlled period, any adverse event occurred in 39 (27%) nitroglycerin, 36 (18%) nesiritide, and 20 (14%) placebo patients (Fisher exact test, $P=.02$); headache in 17 (12%) nitroglycerin, 11 (5%) nesiritide, and 3 (2%) placebo patients ($P=.003$); and abdominal pain in 4 (3%) nitroglycerin patients only ($P=.01$) (TABLE 4). There were significantly fewer adverse events in nesiritide patients than nitroglycerin patients during the placebo-controlled period (Fisher exact test; $P=.04$).

During the first 24 hours after the start of nitroglycerin, headache (20%) was the most common adverse event reported. During the first 24 hours of treatment with nesiritide, headache (8%) occurred significantly less frequently than with nitroglycerin (Fisher exact test, $P<.001$; Table 4). There were no significant differences in the frequency or severity of ischemic events, asymptomatic or symptomatic hypotension or arrhythmias between nitroglycerin and nesiritide groups in the first 24 hours. Symptomatic hypotension occurred in

Table 2. Baseline and Concomitant Cardiac Medication Use*

Drug	Prehospitalization Regimen, No. (%)			Medications Continued During Study, No. (%)		
	Nitroglycerin (n = 216)	Nesiritide (n = 273)	*P* Value	Nitroglycerin (n = 216)	Nesiritide (n = 273)	*P* Value
Diuretics	185 (86)	237 (87)	.79	204 (94)	232 (85)	.001
Digoxin	131 (61)	165 (60)	>.99	129 (60)	161 (59)	.93
Angiotensin-converting enzyme inhibitors	121 (56)	173 (63)	.11	128 (59)	157 (58)	.71
Aspirin	93 (43)	125 (46)	.58	100 (46)	122 (45)	.78
Nitrates (nonintravenous)	72 (33)	101 (37)	.45	78 (36)	88 (32)	.39
β-Blockers	66 (31)	95 (35)	.33	61 (28)	70 (26)	.54
Warfarin	67 (31)	93 (34)	.50	35 (16)	40 (15)	.70
Statins	50 (23)	72 (26)	.46	56 (26)	73 (27)	.92
Class III antiarrhythmics	25 (12)	52 (19)	.02	21 (10)	57 (21)	.001
Calcium-channel blockers	25 (12)	41 (15)	.29	18 (8)	38 (14)	.06
Angiotensin II receptor blockers	27 (13)	24 (9)	.23	21 (10)	18 (7)	.24
Dobutamine						
Continued at baseline	NA	NA	NA	21 (10)	48 (18)	.01
New administration	NA	NA	NA	17 (8)	26 (10)	.63
Dopamine						
Continued at baseline	NA	NA	NA	3 (1)	19 (7)	.003
New administration	NA	NA	NA	4 (2)	1 (0)	.18

*NA indicates categories not applicable. *P* values were calculated using the Fisher exact test.

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5% of nitroglycerin patients and in 4% of nesiritide patients. Angina occurred in 2% of patients in each of the nitroglycerin and nesiritide groups. Most hypotension events were mild or moderate; 1 patient in each treatment group experienced an event that was classified as severe. Most events resolved either spontaneously or with an intravenous volume challenge of 250 mL (or less). Duration of hypotension events was significantly longer with nesiritide, as expected due to its longer half-life than that of nitroglycerin (18-minute half-life for nesiritide[22] and 2.5-minute half-life for nitroglycerin[23]). The mean duration of symptomatic hypotension was 2.2 hours for nesiritide and 0.7 hours for nitroglycerin (2-sample Wilcoxon test; $P=.002$). No event of symptomatic hypotension led to adverse sequelae in either treatment group.

Through 30 days, there were 3 myocardial infarctions reported in nitroglycerin patients and 2 in nesiritide patients. Through 30 days, there were no significant differences in the frequency of serious adverse events or pattern of changes in serum creatinine that occurred in nitroglycerin or nesiritide patients. Through 30 days, 48 (23%) nitroglycerin and 50 (20%) nesiritide patients were readmitted to the hospital for any cause (Fisher exact test, $P=.36$). Readmission for acutely decompensated CHF occurred in 27 (13%) nitroglycerin and 20 (7%) nesiritide patients. Through 7 days, deaths occurred in 1 (0.5%) nitroglycerin and 4 (1.5%) nesiritide patients. None of these deaths was believed to be due to either study drug. There was no significant difference in 6-month mortality for nitroglycerin 20.8% (95% confidence interval, 15.5%-26.5%) vs nesiritide patients 25.1% (95% confidence interval, 20.0%-30.5%; $P=.32$).

COMMENT

The VMAC trial is, to our knowledge, the first trial in patients with acutely decompensated CHF to demonstrate efficacy of a new drug class (nesiritide, B-type natriuretic peptide) when added to standard care in comparison with both placebo and nitroglycerin. This randomized, double-blind trial enrolled severely ill patients with acutely decompensated CHF and dyspnea at rest and many clinically important co-

Table 3. Hemodynamic Variables: Baseline Value and Change With Treatment*

	Nitroglycerin		Nesiritide		Placebo	
	Mean (SD)	Median (Interquartile Range)	Mean (SD)	Median (Interquartile Range)	Mean (SD)	Median (Interquartile Range)
Pulmonary capillary wedge pressure, mm Hg						
Baseline	28 (5.7)	26 (24 to 31.5)	27.8 (7.1)	25.5 (22 to 32.5)	27.7 (5.4)	26 (24 to 30)
15 minutes	−1.2 (3.8)	−1 (−4 to 0)	−3.5 (5.3)†‡	−2 (−6 to 0)	−1.2 (3.6)	−1 (−2 to 0)
1 hour	−2.8 (4.1)	−2 (−6 to 0)	−5.5 (6.3)†‡	−5.5 (−10 to −2)	−1.5 (4.8)	−1 (−5 to 1)
3 hours	−3.8 (5.3)	−3 (−8 to 0)	−5.8 (6.5)†‡	−5 (−10 to −1)	−2 (4.2)	−2 (−5 to 0)
Right atrial pressure, mm Hg						
Baseline	16 (7)	15 (11 to 20)	15 (7)	14 (10 to 18)	14 (7)	14 (10 to 17.5)
1 hour	−1 (3.3)	−1 (−3 to 0)	−2.6 (4.9)†‡	−2 (−5 to 0)	−0.2 (3.3)	0 (−1 to 1)
3 hours	−2.6 (3.5)†	−2 (−5 to 0)	−3.1 (4.6)†	−3 (−5 to 0)	0 (4.4)	0 (−2 to 2)
Systolic blood pressure, mm Hg						
Baseline	124 (23)	118 (105 to 140)	120 (23)	117 (102 to 134)	121 (21)	117 (104 to 134)
15 minutes	−3.1 (11.1)	−1 (−10 to 4)	−4.0 (11.4)†	−3 (−10 to 3)	−1.2 (11.2)	−0.5 (−9 to 5)
1 hour	−6.3 (13.9)†	−4 (−12 to 2)	−3.2 (12.7)	−3 (−11 to 5)	−1.5 (12.6)	−1.5 (−9 to 5)
3 hours	−5.7 (14.9)†	−4 (−13 to 4)	−5.6 (12.9)†	−5.5 (−13.5 to 3)	−2.5 ± 11.2	−4 (−9 to 3)
Pulmonary vascular resistance, dynes/s per cm^{-5}						
Baseline	271 (178)	232 (133 to 376)	250 (168)	203 (141 to 329)	236 (174)	187 (128 to 269)
1 hour	−38 (124)†	−5 (−117 to 47)	−27 (104)†	−27 (−85 to 35)	28 (122)	31 (−31 to 78)
3 hours	−18 (115)	−7.8 (−58 to 48)	−21 (115.7)†	20.4 (−73 to 49)	21 (105)	29 (−36 to 73)
Systemic vascular resistance, dynes/s per cm^{-5}						
Baseline	1509 (697)	1445 (984 to 1884)	1441 (589)	1343 (1084 to 1672)	1384 (563)	1289 (994 to 1767)
1 hour	−136 (458)	−72 (−340 to 157)	−236 (507)†	−151 (−422 to 16)	−8 (394)	21 (−147 to 200)
3 hours	−105 (520)	−122 (−345 to 123)	−144 (447)	−102 (−350 to 84)	−44 (421)	−40 (−175 to 151)
Cardiac index, L/min per m^2						
Baseline	2.1 (0.8)	2 (1.6 to 2.5)	2.2 (0.7)	2.1 (1.7 to 2.6)	2.2 (0.7)	2.1 (1.7 to 2.6)
1 hour	0.1 (0.5)	0.1 (−0.1 to 0.4)	0.3 (0.5)†‡	0.3 (0 to 0.6)	−0.1 (0.5)	0 (−0.4 to 0.2)
3 hours	0.2 (0.5)	0.2 (−0.1 to 0.4)	0.1 (0.5)	0.1 (−0.1 to 0.4)	0 (0.6)	0 (−0.3 to 0.2)

*There were no significant differences between groups for hemodynamics at baseline.
†$P<.05$ for comparison of active therapy with placebo.
‡$P<.05$ for comparison of nesiritide with nitroglycerin.

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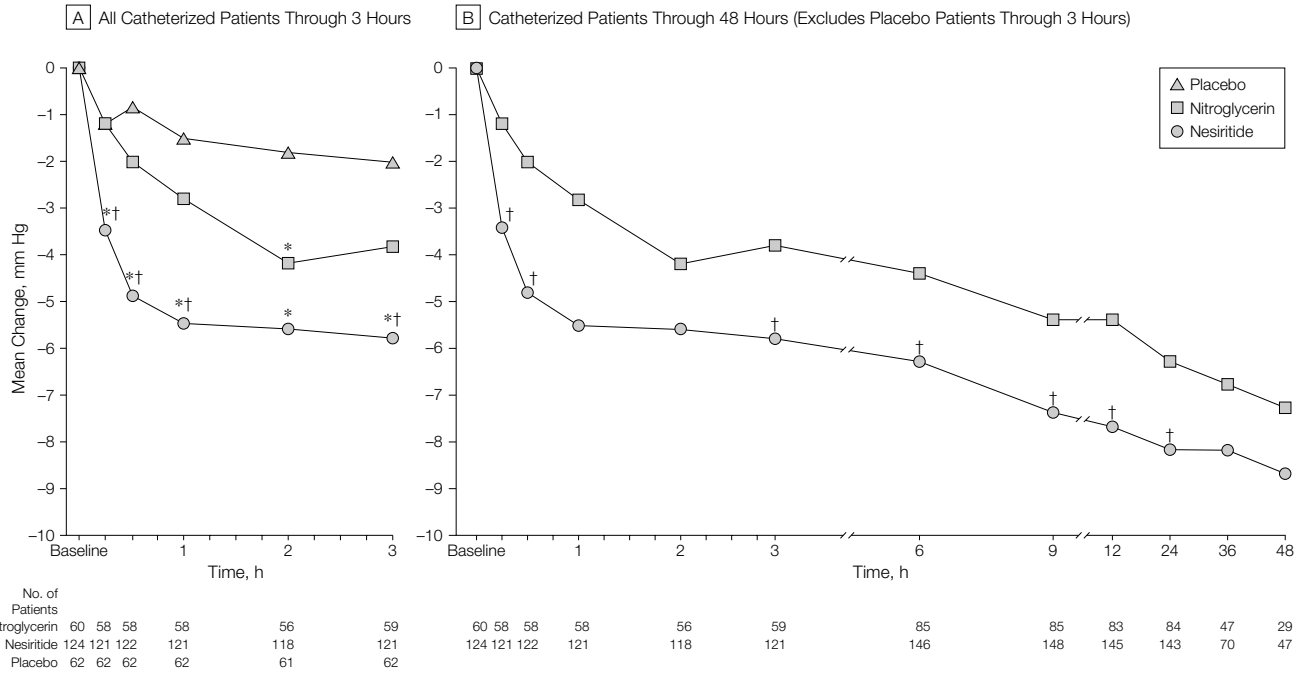
morbidities including acute coronary syndromes, atrial and ventricular arrhythmias, preserved systolic function, and renal insufficiency.

The VMAC trial design reflects the balance between the need to obtain efficacy data pertaining to both hemodynamic and clinical benefit and to do so in a heterogeneous, critically ill patient population that is already receiving standard care medications. Three hours was chosen as the primary end point to allow enough time for an additive symptom effect to occur between an active agent (plus standard care) and the anticipated high rate of early symptom improvement in patients who received placebo (plus standard care). Due to the severity of illness in the intended patient population, it was deemed unethical by the investigator to treat patients with placebo for more than 3 hours or to insist on discontinuation of baseline standard therapies, including intravenous diuretics and inotropic agents. To compare a fixed-dose regimen of nesiritide with a standard dosing regimen of nitroglycerin (ie, titrated regimen) in a double-blinded fashion, a double-dummy study drug administration design was used. Because there is no standard dose or dosing range for nitroglycerin for decompensated heart failure, all dosing of nitroglycerin was left to the investigators' discretion. As the first large decompensated CHF study in which clinical symptoms (rather than hemodynamics alone) were a primary end point, we created a customized categorical dyspnea scale in which patients were required to have dyspnea at rest at baseline.

This trial demonstrated that nesiritide significantly reduced PCWP more than standard care plus nitroglycerin or placebo, and these effects were sustained for at least 24 hours. At 3 hours, nesiritide (when added to standard care) also led to a significant improvement in dyspnea compared with placebo (a prespecified primary end point), but not a significant improvement compared with nitroglycerin. Because patients were concomitantly receiving other drugs (such as intravenous diuretics) to ameliorate their symptoms, improvement was generally expected in all treatment groups. The adverse effect profile of nesiritide was similar to that of nitroglycerin, except for headache and abdominal pain, which occurred more commonly with nitroglycerin.

In comparison with prior trials of nesiritide in decompensated CHF, the dose of nesiritide used in VMAC (2-µg/kg bolus followed by a 0.01-µg/kg per minute infusion) used a larger bolus dose and a lower infusion dose than previously studied doses. The dosing regimen of nesiritide in VMAC was selected from other candidate dosing regimens using a pharmacokinetic/pharmacodynamic model that predicted the following effects compared with a previously studied dosing regimen: a more rapid onset of effect on PCWP and systolic blood pressure, a sustained effect on PCWP over at least 24 hours, and less effect on systolic blood pressure than higher infusion doses.[24] In this study, this dose was effective at improving hemodynamics and symptoms and was associated with less hypotension than has been observed at higher doses.[18] When investigators had the opportunity to increase the nesiritide dose,

Figure 2. Changes From Baseline in Pulmonary Capillary Wedge Pressure



Asterisk indicates $P<.05$ for nesiritide or nitroglycerin compared with placebo; dagger, $P<.05$ for nesiritide compared with nitroglycerin.

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only 23 of 62 adjustable-dose nesiritide patients underwent an increase in the dose, suggesting that the initial dosing regimen was effective in most patients.

The VMAC trial is the largest and most comprehensive evaluation of intravenous nitroglycerin in decompensated CHF. Nitroglycerin is a commonly used intravenous agent for decompensated CHF because it leads to beneficial hemodynamic actions, is well tolerated without proarrhythmic effects, and prevents worsening of ischemic events. In VMAC, the hemodynamic effects of intravenous nitroglycerin were significantly less, and symptomatic effects were similar, but less pronounced, than those observed with nesiritide during the first 24 hours. It is possible that better and more rapid amelioration of hemodynamic abnormalities could have occurred if higher doses of intravenous nitroglycerin were used. However, the investigator-chosen doses used in this trial were within the dose ranges described in other clinical heart failure studies,[25-31] as well as those recommended by the current American College of Cardiology/American Heart Association guidelines for management of acutely decompensated CHF.[1] Nitroglycerin was pharmacologically active at the doses studied in VMAC as evidenced by the rate of headache (20%) and the effect of nitroglycerin on blood pressure.

Results of the VMAC trial also are useful in distinguishing the role of natriuretic peptides, vasodilators, and inotropes as therapy for acutely decompensated CHF. As VMAC characterized the relative efficacy and safety profiles of nitroglycerin and nesiritide, both of which have vasodilating properties, VMAC also confirmed that these agents do not lead to life-threatening arrhythmias or ischemic events. The hemodynamic and symptom improvement with nesiritide, coupled with a safety profile similar to that of nitroglycerin, suggests that the use of nesiritide may decrease the role of inotropes in the treatment for acutely decompensated CHF.

In this study of patients with acutely decompensated CHF, nesiritide resulted in improvement in hemodynam-

Figure 3. Outcomes at 3 and 24 Hours for All Treated Patients by Randomization Group

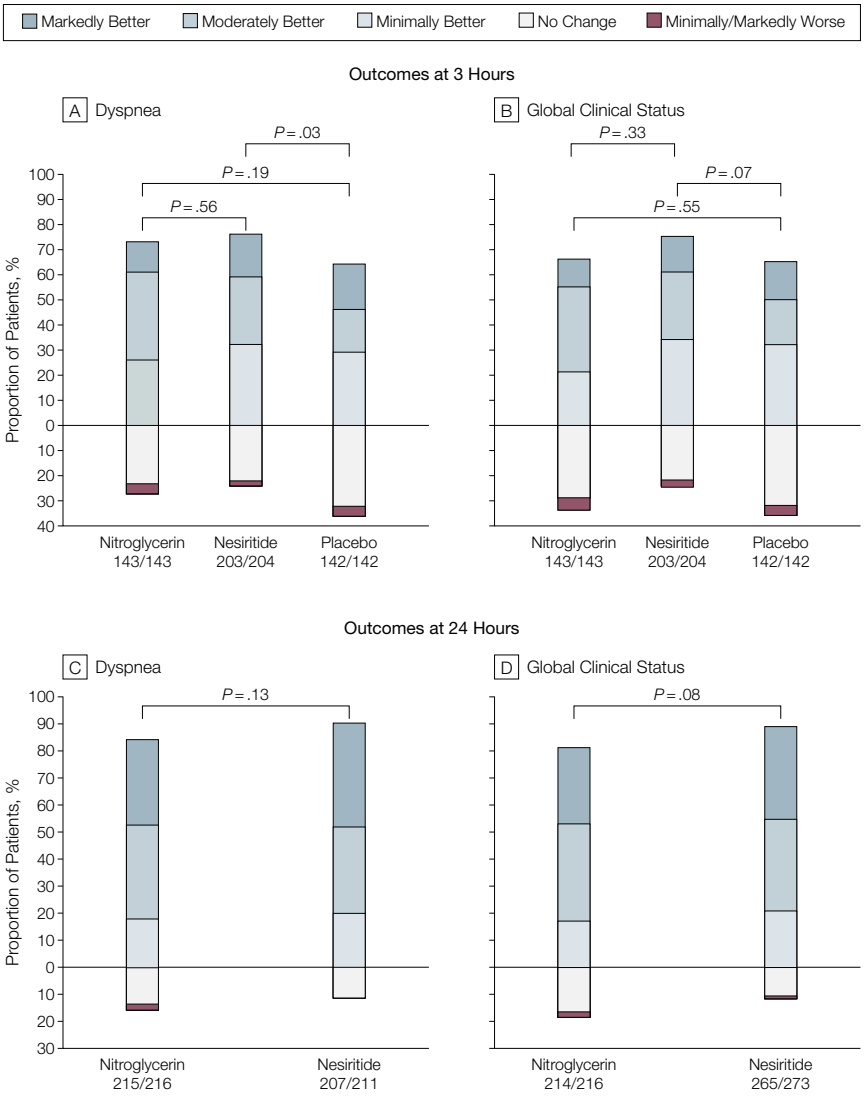

Table 4. Adverse Events During First 24 Hours After Start of Study Drug

Adverse Event	Nitroglycerin (n = 216)	Nesiritide (n = 273)	*P* Value*
Any adverse event	146 (68)	140 (51)	<.001
General headache	44 (20)	21 (8)	<.001
Pain			
General	11 (5)	11 (4)	.66
Abdominal	11 (5)	4 (1)	.03
Catheter	11 (5)	4 (1)	.03
Nausea	13 (6)	10 (4)	.28
Cardiovascular			
Hypotension			
Asymptomatic	17 (8)	23 (8)	.87
Symptomatic	10 (5)	12 (4)	>.99
Nonsustained tidal volume	11 (5)	9 (3)	.36
Angina pectoris	5 (2)	5 (2)	.76

*Calculated using the Fisher exact test.

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ics and some self-reported symptoms more effectively and with fewer adverse effects than intravenous nitroglycerin. This trial suggests that nesiritide, in addition to diuretics (intravenous and/or oral), is a useful addition to initial therapy of patients hospitalized with acutely decompensated CHF.

Author Contributions: Dr Young, as principal investigator, had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Young, Abraham, Warner Stevenson, Horton, Elkayam, Bourge.
Acquisition of data: Young, Abraham, Warner Stevenson, Horton, Elkayam, Bourge.
Analysis and interpretation of data: Young, Abraham, Warner Stevenson, Horton, Elkayam.
Drafting of the manuscript: Young, Abraham, Horton.
Critical revision of the manuscript for important intellectual content: Young, Abraham, Warner Stevenson, Horton, Elkayam, Bourge.
Statistical expertise: Horton.
Obtained funding: Horton.
Administrative, technical, or material support: Young, Horton.
Study supervision: Young, Abraham, Warner Stevenson, Horton, Elkayam, Bourge.
Funding/Support: This trial was funded by a grant from Scios Inc, Sunnyvale, Calif.
Role of the Sponsor: The study sponsor used a steering committee of academic advisors, with Dr Young as chairman of the committee, who were intimately involved in the preparation and design of the trial. The sponsor was involved in monitoring the study in accordance with federal regulations and good clinical research practices. The sponsor analyzed the database with input from the steering committee. Dr Young was involved in all aspects of the analysis and interpretation of data as well as preparation, review, and approval of the manuscript. Dr Young had complete control of the contents of the manuscript.
Financial Disclosures: Drs Warner Stevenson, Elkayam, and Young are consultants for Scios Inc.
VMAC Committees, Investigators, and Centers: *Publication Committee:* James B. Young, Cleveland Clinic Foundation; William T. Abraham, University of Kentucky, Lexington; Lynne Warner Stevenson, Brigham and Women's Hospital; Darlene P. Horton, Scios Inc; Uri Elkayam, Los Angeles County-USC Medical Center; Robert C. Bourge, University of Alabama, Birmingham. *Steering Committee:* James B. Young (chairperson), Cleveland Clinic Foundation; William T. Abraham, University of Kentucky, Lexington; Lynne Warner Stevenson, Brigham and Women's Hospital; Charles L. Emerman, MetroHealth Medical Center; Darlene P. Horton (sponsor representative). *Statistical Analysis*: Mei L. Cheng, Scios Inc. *Nesiritide Pharmacokinetic/Pharmacodynamic Modeling:* Nancy Sambol, University of California, San Francisco. *Investigators and Centers* (in alphabetical order by center): Albert Einstein Hospital (Thierry LeJemtel); Baylor College of Medicine (Guillermo Torre); Beth Israel Deaconess Medical Center (Andrew Burger); Buxmont Cardiology Associates, Lifemark Medical Center (Mitchell Greenspan); Cardiac Centers of LA at Willis Knighton Heart Institute (Jalal Ghali); Cardiology Associates of Gainesville (Steven F. Roark); Cardiovascular Medicine of Virginia at Pratt Medical Center Ltd (Robert Vranian); Cardiovascular Research Institute of Dallas (Martin Berk); Cardiovascular Research Institute of Southern California (Ronald Karlsberg); Care Group (Mary N. Walsh); Christ Hospital and Medical Center (Marc A. Silver); Community Hospital East (Edward Harlamert); Dartmouth Hitchcock Medical Center (Bruce D. Hettleman); Dorn Research Institute (Constantine Hassapoyannes); Durham VA Medical Center (Frederick R. Cobb); George Washington University Medical Center (Jacob Varghese); HeartCare Midwest (Alan Chu); Heart Center, Huntsville Hospital (W. Herbert Haught); Heart Institute of St Petersburg (Michael E. McIvor, Gregg Schuyler); Hennepin County Medical Center (Steven R. Goldsmith); Hillsboro Cardiology (Steven Promisloff); Jacksonville Center for Clinical Research (Michael Koren); Jacksonville Heart Center (Jay Dinerman); Johns Hopkins Hospital (Joshua Hare); Los Angeles County-USC Medical Center (Uri Elkayam); Med-Tech Research Inc (Salah El Hafi); Medical Research Consortium at Winona Memorial Hospital (Jack Hall); MediQuest Research Group Inc (Robert Feldman); Montefiore Medical Center (Robert Moskowitz); Mount Sinai Medical Center (Marrick Kukin, Gervasio Lamas); Northwestern Memorial Hospital (William Cotts); Oregon Health Sciences University (Ray Hershberger); Roudebush VA Medical Center (Lincoln E. Ford); Rush-Presbyterian-St Luke's Medical Center (Walter Kao); St Paul Heart Clinic (Alan J. Bank); San Diego Cardiac Center (Peter M. Hoagland); San Diego Cardiovascular Research Associates (George Dennish); Scripps Clinic, Heart, Lung, Vascular Center (Allen D. Johnson); Stern Cardiovascular Center (Frank A. McGrew); University of Alabama at Birmingham (Mark F. Aaron, Robert C. Bourge); University of Arizona Health Sciences Center (Charles Y. Lui); University of California, San Francisco Medical Center (Teresa DeMarco); James A. Haley Veterans Hospital, Tampa, Fla (Doug Schocken); University of Cincinnati Medical Center (Lynne Wagoner); University of Florida Medical Center, Jacksonville (Alan B. Miller); University of Florida Health Sciences Center, Gainesville (James A. Hill); University of Iowa Hospitals and Clinics (Ron M. Oren); University of Kansas Medical Center (David Wilson); University of Louisville Research Foundation (Geetha Bhat); University of Maryland Medical System (Stephen S. Gottlieb); University of Miami/Jackson Memorial Medical Center (Stephen M. Mallon); University of Missouri Health Sciences Center (Hanumanth Reddy); University of Rochester Medical Center (Chang-seng Liang); University of South Dakota School of Medicine (Kevin Vaska); University of Washington Medical Center (Daniel Fishbein); Vanderbilt University Medical Center (John R. Wilson); VA Medical Center IIIB (A. Maziar Zafari); Watson Clinic (Kevin Browne).

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patients would have influenced our findings. Furthermore, we feel that comprehensiveness of the ODB database counterbalances many of these limitations, as it reflects the experiences of the entire population of Ontarians aged 65 years or older.

Peter C. Austin, PhD
Institute for Clinical Evaluative Sciences
Department of Public Health Sciences
University of Toronto
Toronto, Ontario

Muhammad M. Mamdani, PharmD, MA, MPH
Institute for Clinical Evaluative Sciences
Faculty of Pharmacy
University of Toronto

Liisa Jaakkimainen, MD, MSc, CCFP
Institute for Clinical Evaluative Sciences
Department of Family and Community Medicine
University of Toronto

Janet E. Hux, MD, SM, FRCPC
Institute for Clinical Evaluative Sciences
Department of Medicine
University of Toronto
Clinical Epidemiology and Health Care Research Program
Sunnybrook & Women's College Health Sciences Centre
Toronto

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CORRECTION

Incorrect *P* Value: In the Original Contribution entitled "Intravenous Nesiritide vs Nitroglycerin for Treatment of Decompensated Congestive Heart Failure: A Randomized Controlled Trial" published in the March 27, 2002, issue of THE JOURNAL (2002;287:1531-1540), there was an incorrect *P* value in Table 1. On page 1535, the *P* value should have been .30 for "acute coronary syndrome within 7 days before start of study drug," which is the last entry under the heading "medical history."

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