Intravenous Nesiritide vs Nitroglycerin for Treatment of Decompensated Congestive Heart Failure: A Randomized Controlled Trial

H EART 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.1,3 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.
put without direct inotropic effects, improve echocardiographic indices of diastolic function, and improve symptoms in patients with acutely decompensated CHF, without increasing heart rate or proarrhythmia. 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.

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.

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 (Nattercor, 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

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

CHF indicates congestive heart failure.
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 (Trildil, 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. 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 vaso-
dilator) and was associated with 1 or
more of the following symptoms: light-
headedness, dizziness, feeling faint, or
having blurred vision.

Statistical Analyses
Efficacy was analyzed in all treated pa-
tients, as randomized, except for 9 pa-
tients who were randomized but not
treated. These patients were excluded
from the analysis because hemody-
amic and symptom assessments were
not performed. As no dose increases of
nesiritide were permitted before 3
hours, the prespecified primary analy-
sis 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. Af-
fter 3 hours, placebo patients (who
crossover to double-blind, active treat-
ment) were included in the subse-
quent active treatment comparisons.

For the dyspnea and global clinical sta-
tus evaluations, 2 groups (nesiritide
and nitroglycerin) were compared using a
stratified 2-sample Wilcoxon pro-
dure (Van Elteran test) for right heart
catheter use to evaluate the following
7-point categorical responses of the
patient: markedly, moderately, or mini-
ually improved; no change; or minim-
ally, moderately, or markedly wors-
ened. This nonparametric analysis was
prespecified as a supplemental analysis
to test the robustness of the primary para-
metric analysis. However, because the
protocol allowed for the use of stan-
dard 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 nor-
mality of the dyspnea data justi-
fies 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 he-
modynamic measurements for catheter-
ized patients. Means are presented with
SDs, and medians are provided with in-
terquartile ranges for hemodynamic
data, unless otherwise noted.

This study was powered to demon-
strate significant differences between ne-
siritide and placebo for PCWP evalua-
tion among all catheterized patients and
for dyspnea evaluation among all pa-
tients. Based on a 2-sample Wilcoxon
procedure, a sample size of 140 in the
placebo and 200 in the nesiritide treat-
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 propor-
tion of responses reflects the anticipa-
tion that regardless of therapy, most pa-
tients’ dyspnea will be improved or
unchanged at 3 hours, rather than wors-
ened; and active therapy (plus standard
care) will be more effective than pla-
cebo (plus standard care). Based on the
large-sample z statistic, with the assump-
tion of a population mean (SD) de-
crease 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 pa-
tients, 246 were in the catheterized stra-
tum and 243 were in the noncatheter-
ized 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 pa-
tients in the nesiritide group were men.
All patients had dyspnea at rest (or New
York Heart Association class IV symp-
toms) at study entry, 84% had chronic
decompensated CHF that was classi-
cified as class III or class IV prior to de-
compensation, and most had clinical
evidence of fluid overload (jugular ve-
nous distention in 89%, rales in 73%,
and pedal edema in 73%). Other im-
portant baseline clinical findings in-
cluded an acute coronary syndrome in
12%, preserved systolic function (eject-
ion fraction >40%) in 15%, renal insuf-
iciency (serum creatinine ≥2.0
mg/dL [≥176.8 µmol/L]) in 21%, and
diabetes in 47%. Many patients had a
history of significant arrhythmias in-
cluding atrial fibrillation or fib/flutter
(35%), nonsustained ventricular tachy-
cardia (22%), sudden death (8%), ven-
tricular fibrillation (6%), and sus-
tained ventricular tachycardia (13%).
The mean (SD) left ventricular ejec-
tion fraction was 27% (14%). Mean
(SD) systolic blood pressure at trial en-
try was 121 (22) mm Hg. Ninety pa-
tients (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 m².

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

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nitroglycerin (n = 143)</th>
<th>Nesiritide (n = 204)</th>
<th>Placebo (n = 142)</th>
<th>P Value</th>
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<tr>
<td><strong>Demographics</strong></td>
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<td>Age, mean (SD), y</td>
<td>60 (14)</td>
<td>62 (13)</td>
<td>62 (15)</td>
<td>.41*</td>
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<td>Men</td>
<td>86 (60)</td>
<td>148 (73)</td>
<td>103 (73)</td>
<td>.03†</td>
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<td>Race</td>
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<td>&gt;.99†</td>
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<td>85 (59)</td>
<td>18 (58)</td>
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<td>Black</td>
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<td>34 (24)</td>
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<td>Other</td>
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<td>7 (3)</td>
<td>4 (3)</td>
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<td><strong>Medical History</strong></td>
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<td>New York Heart Association Classification for congestive heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>18 (13)</td>
<td>13 (6)</td>
<td>7 (5)</td>
<td>.30‡</td>
</tr>
<tr>
<td>III</td>
<td>15 (38)</td>
<td>89 (44)</td>
<td>59 (42)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>55 (38)</td>
<td>85 (42)</td>
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<tr>
<td>Hypertension</td>
<td>94 (66)</td>
<td>143 (70)</td>
<td>105 (74)</td>
<td>.33†</td>
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<td>Coronary artery disease</td>
<td>90 (63)</td>
<td>134 (66)</td>
<td>95 (67)</td>
<td>.79†</td>
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<td>Previous myocardial infarction</td>
<td>59 (41)</td>
<td>96 (47)</td>
<td>70 (49)</td>
<td>.37†</td>
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<tr>
<td>Atrial fibrillation or fibr/flutter</td>
<td>46 (32)</td>
<td>75 (37)</td>
<td>48 (34)</td>
<td>.67†</td>
</tr>
<tr>
<td>Diabetes</td>
<td>68 (48)</td>
<td>88 (43)</td>
<td>75 (53)</td>
<td>.21†</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>9 (6)</td>
<td>31 (15)</td>
<td>22 (15)</td>
<td>.02†</td>
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<tr>
<td>Frequent premature ventricular contractions</td>
<td>41 (29)</td>
<td>68 (33)</td>
<td>57 (40)</td>
<td>.12†</td>
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<td>Ejection fraction &gt;40%</td>
<td>19 (15)</td>
<td>26 (14)</td>
<td>20 (16)</td>
<td>.89†</td>
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<td>Implantable cardiac defibrillator or pacemaker</td>
<td>31 (22)</td>
<td>55 (27)</td>
<td>36 (25)</td>
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<td>Primary etiology of chronic cardiomyopathy</td>
<td>59 (45)</td>
<td>102 (53)</td>
<td>78 (59)</td>
<td>.42§</td>
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<td>Ischemic</td>
<td>59 (45)</td>
<td>102 (53)</td>
<td>78 (59)</td>
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<tr>
<td>Idiopathic, dilated cardiomyopathy</td>
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<td>45 (24)</td>
<td>29 (22)</td>
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<td>Hypertensive</td>
<td>15 (11)</td>
<td>18 (9)</td>
<td>12 (8)</td>
<td></td>
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<tr>
<td>Other</td>
<td>12 (9)</td>
<td>14 (8)</td>
<td>7 (5)</td>
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<td>Acute coronary syndrome within 7 days before start of study drug</td>
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<td></td>
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<tr>
<td>Baseline systolic blood pressure &lt;100 mm Hg</td>
<td>20 (14)</td>
<td>48 (24)</td>
<td>22 (15)</td>
<td>.07†</td>
</tr>
<tr>
<td>Intravenous vasoactive drug given within 24 hours of study drug</td>
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<tr>
<td>Baseline dobutamine</td>
<td>11 (8)</td>
<td>33 (16)</td>
<td>25 (18)</td>
<td>.02†</td>
</tr>
<tr>
<td>Baseline dopamine</td>
<td>2 (1)</td>
<td>15 (7)</td>
<td>5 (4)</td>
<td>.02†</td>
</tr>
</tbody>
</table>

*Calculated using the t test.
†Calculated using the Fisher exact test.
‡Calculated using the Wilcoxon test.
§Calculated using the χ² test.

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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 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*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prehospitalization Regimen, No. (%)</th>
<th>Medications Continued During Study, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nitroglycerin (n = 216)</td>
<td>Nesiiritide (n = 273)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>165 (86)</td>
<td>237 (87)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>131 (61)</td>
<td>165 (60)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>121 (56)</td>
<td>173 (63)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>93 (43)</td>
<td>125 (46)</td>
</tr>
<tr>
<td>Nitrates (noninvasive)</td>
<td>72 (33)</td>
<td>101 (37)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>66 (31)</td>
<td>95 (35)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>67 (31)</td>
<td>93 (34)</td>
</tr>
<tr>
<td>Statins</td>
<td>50 (23)</td>
<td>72 (26)</td>
</tr>
<tr>
<td>Class III antiarrhythmics</td>
<td>25 (12)</td>
<td>52 (19)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>25 (12)</td>
<td>41 (15)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>27 (13)</td>
<td>24 (9)</td>
</tr>
</tbody>
</table>

| 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 and 2.5-minute half-life for nitroglycerin). 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, \( P = .36 \)). No event of symptomatic hypotension led to adverse sequelae in either treatment group.

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

<table>
<thead>
<tr>
<th></th>
<th>Nitroglycerin</th>
<th></th>
<th>Nesiritide</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (Interquartile Range)</td>
<td>Mean (SD)</td>
<td>Median (Interquartile Range)</td>
<td>Mean (SD)</td>
<td>Median (Interquartile Range)</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>28 (5.7)</td>
<td>26 (24 to 31.5)</td>
<td>27.8 (7.1)</td>
<td>25.5 (22 to 32.5)</td>
<td>27.7 (5.4)</td>
<td>26 (24 to 30)</td>
</tr>
<tr>
<td>Baseline</td>
<td>-1.2 (3.8)</td>
<td>-1 (-4 to 0)</td>
<td>-3.5 (5.3)†‡</td>
<td>-2 (-6 to 0)</td>
<td>-1.3 (3.6)</td>
<td>-1 (-2 to 0)</td>
</tr>
<tr>
<td>15 minutes</td>
<td>-2.8 (4.1)</td>
<td>-2 (-6 to 0)</td>
<td>-5.5 (6.3)†‡</td>
<td>-5.5 (-10 to -2)</td>
<td>-1.5 (4.8)</td>
<td>-1 (-5 to 1)</td>
</tr>
<tr>
<td>3 hours</td>
<td>-3.8 (5.3)</td>
<td>-3 (-8 to 0)</td>
<td>-5.8 (6.5)†‡</td>
<td>-5 (-10 to -1)</td>
<td>-2 (4.2)</td>
<td>-2 (-5 to 0)</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>16 (7)</td>
<td>15 (11 to 20)</td>
<td>15 (7)</td>
<td>14 (10 to 18)</td>
<td>14 (7)</td>
<td>14 (10 to 17.5)</td>
</tr>
<tr>
<td>Baseline</td>
<td>-1 (-3.3)</td>
<td>-1 (-3 to 0)</td>
<td>-2.6 (4.9)†‡</td>
<td>-2 (-5 to 0)</td>
<td>-0.2 (3.3)</td>
<td>0 (-1 to 1)</td>
</tr>
<tr>
<td>1 hour</td>
<td>-2.6 (3.5)†</td>
<td>-2 (-5 to 0)</td>
<td>-3.1 (4.6)†</td>
<td>-3 (-5 to 0)</td>
<td>0 (4.4)</td>
<td>0 (-2 to 2)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>124 (23)</td>
<td>118 (105 to 140)</td>
<td>120 (23)</td>
<td>117 (102 to 134)</td>
<td>121 (21)</td>
<td>117 (104 to 134)</td>
</tr>
<tr>
<td>Baseline</td>
<td>-3.1 (11.1)</td>
<td>-1 (-10 to 4)</td>
<td>-4.0 (11.4)†</td>
<td>-3 (-10 to 3)</td>
<td>-1.1 (11.2)</td>
<td>-0.5 (-9 to 5)</td>
</tr>
<tr>
<td>15 minutes</td>
<td>-6.3 (13.9)†</td>
<td>-4 (-12 to 2)</td>
<td>-3.2 (12.7)</td>
<td>-3 (-11 to 5)</td>
<td>-1.5 (12.6)</td>
<td>-1.5 (-9 to 5)</td>
</tr>
<tr>
<td>3 hours</td>
<td>-5.7 (14.9)†</td>
<td>-4 (-13 to 4)</td>
<td>-5.6 (12.9)†</td>
<td>-5 (-13.5 to 3)</td>
<td>-2.5 ± 11.2</td>
<td>-4 (-9 to 3)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dynes/s per cm⁻⁵</td>
<td>271 (178)</td>
<td>232 (133 to 376)</td>
<td>250 (168)</td>
<td>203 (141 to 329)</td>
<td>236 (174)</td>
<td>187 (128 to 269)</td>
</tr>
<tr>
<td>Baseline</td>
<td>-38 (124)†</td>
<td>-5 (-117 to 47)</td>
<td>-27 (104)‡</td>
<td>-27 (-85 to 35)</td>
<td>28 (122)</td>
<td>31 (-31 to 78)</td>
</tr>
<tr>
<td>1 hour</td>
<td>-18 (115)†</td>
<td>-7.8 (-58 to 48)</td>
<td>-21 (115.7)†</td>
<td>20.4 (-73 to 49)</td>
<td>21 (105)</td>
<td>29 (-36 to 73)</td>
</tr>
<tr>
<td>Systemic vascular resistance, dynes/s per cm⁻⁵</td>
<td>1509 (697)</td>
<td>1445 (984 to 1884)</td>
<td>1441 (589)</td>
<td>1343 (1084 to 1672)</td>
<td>1384 (563)</td>
<td>1289 (994 to 1767)</td>
</tr>
<tr>
<td>Baseline</td>
<td>-136 (458)‡</td>
<td>-72 (-340 to 157)</td>
<td>-236 (507)†</td>
<td>-151 (-422 to 16)</td>
<td>-8 (394)</td>
<td>21 (-147 to 200)</td>
</tr>
<tr>
<td>1 hour</td>
<td>-105 (520)‡</td>
<td>-122 (-345 to 123)</td>
<td>-144 (447)</td>
<td>-102 (-350 to 84)</td>
<td>-44 (421)</td>
<td>-40 (-175 to 151)</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.1 (0.8)</td>
<td>2 (1.6 to 2.5)</td>
<td>2.2 (0.7)</td>
<td>2.1 (1.7 to 2.6)</td>
<td>2.2 (0.7)</td>
<td>2.1 (1.7 to 2.6)</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.1 (0.5)</td>
<td>0.1 (-0.1 to 0.4)</td>
<td>0.3 (0.5)†‡</td>
<td>0.3 (0.0 to 0.6)</td>
<td>-0.1 (0.5)</td>
<td>0 (-0.4 to 0.2)</td>
</tr>
<tr>
<td>1 hour</td>
<td>0.2 (0.5)</td>
<td>0.2 (-0.1 to 0.4)</td>
<td>0.1 (0.5)</td>
<td>0.1 (-0.1 to 0.4)</td>
<td>0 (0.6)</td>
<td>0 (-0.3 to 0.2)</td>
</tr>
</tbody>
</table>

*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.

**DECOMPENSATED CONGESTIVE HEART FAILURE**

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-
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. 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. When investigators had the opportunity to increase the nesiritide dose,
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, as well as those recommended by the current American College of Cardiology/American Heart Association guidelines for management of acutely decompensated CHF. 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 hemodynamic...

![Figure 3. Outcomes at 3 and 24 Hours for All Treated Patients by Randomization Group](image)

<table>
<thead>
<tr>
<th>Outcomes at 3 Hours</th>
<th>Nitroglycerin</th>
<th>Nesiritide</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>P = .56</td>
<td>P = .19</td>
<td>P = .64</td>
<td></td>
</tr>
<tr>
<td>Global Clinical Status</td>
<td>P = .55</td>
<td>P = .55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes at 24 Hours</th>
<th>Nitroglycerin</th>
<th>Nesiritide</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>P = .13</td>
<td>P = .08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Clinical Status</td>
<td>P = .08</td>
<td>P = .50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

*Calculated using the Fisher exact test.
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 in accordance with federal regulations and good clinical research practices. The sponsor analyzed the database in accordance with federal regulations and good clinical research practices.

Analysis practices. The sponsor analyzed the database in accordance with federal regulations and good clinical research practices.

REFERENCES