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

Publication Committee for the VMAC Investigators

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.¹³ 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, hyper trophy, 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 (Natreco, 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
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 nesirit-
ide, investigators could incrementally in-
crease the dose every 3 hours to a maxi-
mum 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 fol-
lowed by an increase of 0.005 µg/kg per
minute over the previous infusion rate).
Down titration of the nesiritide/placebo
infusion flow rate by 30% was permit-
ted according to the investigators’ dis-
cretion.

Because there is no standard dose of
nitroglycerin for heart failure, nitroglyc-
erin (Tridil, DuPont Pharma, Wilming-
ton, Del) was prepared at a concentra-
tion of 400 µg/mL, and administration
d was determined per investigator discre-
tion. The nitroglycerin/placebo infu-
sion could be uptitrated or downti-
trated throughout the study to achieve
the desired clinical or hemodynamic
effect. If study drug was to be de-
creased or discontinued for any rea-
son, both infusions were to be de-
creased or stopped simultaneously.
Infusion flow rates of both study drugs
could be increased or restarted if the pa-
tient 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 dys-
pnea at rest due to decompensated CHF
that was severe enough to require hos-
pitalization and intravenous therapy. A
cardiac etiology for dyspnea was estab-
lished by estimated or measured eleva-
tion of cardiac filling pressures (PCWP
≥20 mm Hg in catheterized patients) and
at least 2 of the following: (1) jugu-
lar venous distention, (2) paroxysmal
nocturnal dyspnea or 2-pillow orthop-
nea within 72 hours before study en-
try, (3) abdominal discomfort due to
mesenteric congestion, or (4) a chest
x-ray film consistent with decompen-
sated CHF. Patients may have had acute
decompensation of chronic heart fail-
ure, gradual worsening of chronic heart
failure, or new onset of acutely decomp-
ensated CHF. Patients who were re-
ceiving dobutamine or dopamine but
who otherwise met entry criteria were
also permitted into the study. Exclusion
criteria were: systolic blood pres-
sure lower than 90 mm Hg, cardiogenic
shock or volume depletion, any condi-
tion that would contraindicate an
intravenous vasodilator, acutely un-
stable clinical status that would not per-
mit a 3-hour placebo period, use of in-
travenous nitroglycerin that could not
be withheld, mechanical ventilation,
and anticipated survival of less than 30
to 35 days. Patients with decompens-
ated CHF in the setting of acute coro-
nary syndromes, preserved systolic
function, renal failure, or atrial or ven-
tricular arrhythmias were not ex-
cluded based on these conditions alone.
The use of intravenous vasodilators or
inodilators with study drug was not per-
mitted. The study was approved by all
participating centers’ institutional re-
view boards for clinical investigation,
and written informed consent was ob-
tained from each study participant prior
to study entry and randomization.

End Points and Measurements
The protocol-specified primary analy-
sis was a comparison of the hemody-
namic and clinical effects of nesiritide vs
placebo when both were added to stan-
dard care. The primary end points were
the absolute changes in PCWP (cath-
eterized 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 in-
cluded comparisons between nesiritide
and nitroglycerin of the following he-
emodynamic 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 sta-
tus, and the overall safety profile. Ad-
ditional outcomes included comparison of
the use of other intravenous vasoactive
agents or diuretics, and the effects on
other hemodynamic variables. Dys-
pnea and global clinical status were as-
sessed 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 evalua-
tion form (dyspnea and global clinical
status). In the catheterized stratum,
symptom evaluation forms were com-
pleted before hemodynamic measure-
ments had been obtained at the same
time points, and hemodynamic re-
results were not discussed within hear-
ing range of the patient.

During the 3-hour placebo-con-
trolled 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 clini-
cal evaluations) were assessed at 15
and 30 minutes, and at 1, 2, and 3 hours af-
fter 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 du-
ration 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, discontinua-
tion, or restarting of the infusion. Dys-
pnea and global clinical evaluations
were repeated at 6 and 24 hours. Se-
rum creatinine level was obtained at
baseline, daily through 2 days after dis-
continuation of study drug, and at study
days 14 and 30. General adverse events
were assessed through study day 14. Se-
rious adverse events other than death
(hospital admissions and nonfatal, life-
threatening events) were monitored
through study day 30. Mortality was as-
sessed 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
be intended with an intravenous vasodilator) 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 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 Elteren 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 fibrillation (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 m².

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-
glycercin 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>Characteristic</th>
<th>Nitroglycerin (n = 143)</th>
<th>Nesiritide (n = 204)</th>
<th>Placebo (n = 142)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Age, mean (SD), y</td>
<td>60 (14)</td>
<td>62 (13)</td>
<td>62 (15)</td>
<td>.41*</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>85 (59)</td>
<td>18 (58)</td>
<td>83 (58)</td>
<td>&gt;.99†</td>
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<td>Black</td>
<td>35 (24)</td>
<td>50 (25)</td>
<td>34 (24)</td>
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<tr>
<td>Other</td>
<td>4 (4)</td>
<td>7 (3)</td>
<td>4 (3)</td>
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<tr>
<td><strong>Medical History</strong></td>
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<td></td>
</tr>
<tr>
<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>
<td>64 (45)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>94 (66)</td>
<td>143 (70)</td>
<td>105 (74)</td>
<td>.33†</td>
</tr>
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<td>Coronary artery disease</td>
<td>90 (63)</td>
<td>134 (66)</td>
<td>95 (67)</td>
<td>.79†</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>59 (41)</td>
<td>96 (47)</td>
<td>70 (49)</td>
<td>.37†</td>
</tr>
<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>
</tr>
<tr>
<td>Frequent premature ventricular contractions</td>
<td>41 (29)</td>
<td>68 (33)</td>
<td>57 (40)</td>
<td>.12†</td>
</tr>
<tr>
<td>Ejection fraction &gt;40%</td>
<td>19 (15)</td>
<td>26 (14)</td>
<td>20 (16)</td>
<td>.89†</td>
</tr>
<tr>
<td>Implantable cardiac defibrillator or pacemaker</td>
<td>31 (22)</td>
<td>55 (27)</td>
<td>36 (25)</td>
<td>.52†</td>
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<tr>
<td>Primary etiology of chronic cardiomyopathy</td>
<td>59 (45)</td>
<td>102 (53)</td>
<td>78 (59)</td>
<td>.42§</td>
</tr>
<tr>
<td>Ischemic</td>
<td>39 (30)</td>
<td>45 (24)</td>
<td>29 (22)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>15 (11)</td>
<td>18 (9)</td>
<td>12 (8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12 (9)</td>
<td>14 (8)</td>
<td>7 (5)</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome within 7 days before start of study drug</td>
<td>20 (14)</td>
<td>20 (10)</td>
<td>21 (15)</td>
<td>.03†</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<td>22 (25)</td>
<td>60 (29)</td>
<td>35 (25)</td>
<td>.009†</td>
</tr>
<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. †Calculated using the Fisher’s exact test. \( P \leq .05 \) was considered statistically significant.

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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**

<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>Nitroglycerin (n = 216)</td>
</tr>
<tr>
<td></td>
<td>Nesiritide (n = 273)</td>
<td>Nesiritide (n = 273)</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>Diuretics</td>
<td>165 (86)</td>
<td>237 (87)</td>
</tr>
<tr>
<td></td>
<td>237 (87)</td>
<td>204 (94)</td>
</tr>
<tr>
<td></td>
<td>.79</td>
<td>.001</td>
</tr>
<tr>
<td>Digoxin</td>
<td>131 (61)</td>
<td>165 (60)</td>
</tr>
<tr>
<td></td>
<td>.99</td>
<td>161 (59)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>121 (56)</td>
<td>173 (63)</td>
</tr>
<tr>
<td></td>
<td>.11</td>
<td>157 (58)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>93 (43)</td>
<td>125 (46)</td>
</tr>
<tr>
<td></td>
<td>.58</td>
<td>122 (45)</td>
</tr>
<tr>
<td>Nitrates (noninvasive)</td>
<td>72 (33)</td>
<td>101 (37)</td>
</tr>
<tr>
<td></td>
<td>.45</td>
<td>88 (32)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>66 (31)</td>
<td>95 (35)</td>
</tr>
<tr>
<td></td>
<td>.33</td>
<td>70 (26)</td>
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<tr>
<td>Warfarin</td>
<td>67 (31)</td>
<td>93 (34)</td>
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<tr>
<td></td>
<td>.50</td>
<td>40 (15)</td>
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<td>Statins</td>
<td>50 (23)</td>
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<td>Class III antiarrhythmics</td>
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<td>.02</td>
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<td>Calcium-channel blockers</td>
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<td></td>
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<td>38 (14)</td>
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<tr>
<td>Angiotensin II receptor blockers</td>
<td>27 (13)</td>
<td>24 (9)</td>
</tr>
<tr>
<td></td>
<td>.23</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Continued at baseline</td>
<td>Continued at baseline</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>21 (10)</td>
<td>48 (18)</td>
</tr>
<tr>
<td>New administration</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>17 (8)</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Continued at baseline</td>
<td>Continued at baseline</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>3 (1)</td>
<td>19 (7)</td>
</tr>
<tr>
<td>New administration</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>4 (2)</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

*NA indicates categories not applicable. P values were calculated using the Fisher exact test.
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 sequela in either treatment group.

Through 30 days, there were 3 myocardial infarctions reported in nitroglycerin patients and 2 in nesiritide patients. Through 30 days, 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, \( P = .36 \)).

**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*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nitroglycerin</th>
<th>Nesiritide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median</td>
<td>Mean (SD)</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>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 minutes</td>
<td>-1.2 (3.8)</td>
<td>-1 (-4 to 0)</td>
<td>-3.5 (5.3)†‡</td>
</tr>
<tr>
<td>1 hour</td>
<td>-2.8 (4.1)</td>
<td>-2 (-6 to 0)</td>
<td>-5.5 (6.3)†‡</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>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>16 (7)</td>
<td>15 (11 to 20)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>-1 (3.3)</td>
<td>-1 (-3 to 0)</td>
<td>-2.6 (4.9)†‡</td>
</tr>
<tr>
<td>3 hours</td>
<td>-2.6 (3.5)†</td>
<td>-2 (-5 to 0)</td>
<td>-3.1 (4.6)†‡</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>124 (23)</td>
<td>118 (105 to 140)</td>
<td>120 (23)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 minutes</td>
<td>-3.1 (11.1)†</td>
<td>-1 (-10 to 4)</td>
<td>-4.0 (11.4)†</td>
</tr>
<tr>
<td>1 hour</td>
<td>-6.3 (13.9)†</td>
<td>-4 (-12 to 2)</td>
<td>-3.2 (12.7)†</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>
</tr>
<tr>
<td>Pulmonary vascular resistance, dynes/s per cm²</td>
<td>271 (178)</td>
<td>232 (133 to 376)</td>
<td>250 (168)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>-38 (124)†</td>
<td>-5 (-117 to 47)</td>
<td>-27 (104)†</td>
</tr>
<tr>
<td>3 hours</td>
<td>-18 (115)</td>
<td>-7.8 (-58 to 48)</td>
<td>-21 (115.7)†</td>
</tr>
<tr>
<td>Systemic vascular resistance, dynes/s per cm²</td>
<td>1509 (697)</td>
<td>1445 (984 to 1884)</td>
<td>1441 (589)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>-136 (458)</td>
<td>-72 (-340 to 157)</td>
<td>-236 (507)†</td>
</tr>
<tr>
<td>3 hours</td>
<td>-105 (520)</td>
<td>-122 (-345 to 123)</td>
<td>-144 (447)</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>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>0.1 (0.5)</td>
<td>0.1 (-0.1 to 0.4)</td>
<td>0.3 (0.5)†‡</td>
</tr>
<tr>
<td>3 hours</td>
<td>0.2 (0.5)</td>
<td>0.2 (-0.1 to 0.4)</td>
<td>0.1 (0.5)</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.
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 hemodynam-
DECOMPENSATED CONGESTIVE HEART FAILURE

Sics 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, Bourge. 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.

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REFERENCES


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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.

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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.”

CME ANNOUNCEMENT
CME Hiatus: July Through December 2002

CME from JAMA/Archives Journals will be suspended between July and December 2002. Beginning in early 2003, we will offer a new online CME program that will provide many enhancements:

- Article-specific questions
- Hypertext links from questions to the relevant content
- Online CME questionnaire
- Printable CME certificates and ability to access total CME credits

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