Risk of Worsening Renal Function With Nesiritide in Patients With Acutely Decompensated Heart Failure

Jonathan D. Sackner-Bernstein, MD; Hal A. Skopicki, MD, PhD; Keith D. Aaronson, MD, MS

Background—Renal function is an important prognostic factor for patients with acutely decompensated heart failure (ADHF). We investigated the renal effects of nesiritide as treatment for ADHF.

Methods and Results—Randomized clinical trials comparing nesiritide with either placebo or active control for ADHF were identified by electronic and manual searches and thorough review of US Food and Drug Administration files available via the website. Worsening renal function was defined as an increase in serum creatinine >0.5 mg/dL. Relative risk across all studies was determined by meta-analysis with Mantel-Haenszel fixed-effects models (RRMH). Risk of dialysis and medical intervention for worsening renal function were compared between therapies. Frequency of worsening renal function was determined from 5 randomized studies that included 1269 patients. Use of Food and Drug Administration–approved doses of nesiritide (≤0.03 μg · kg⁻¹ · min⁻¹) significantly increased the risk of worsening renal function compared with non–inotrope-based control (RRMH, 1.52; 95% CI, 1.16 to 2.00; P=0.003) or any control therapy, including non–inotrope- and inotrope-based therapies (RRMH, 1.54; 95% CI, 1.19 to 1.98; P=0.001). Even low-dose nesiritide (≤0.015 μg · kg⁻¹ · min⁻¹) significantly increased risk (P=0.012 and P=0.006 compared with non–inotrope- and inotrope-based controls, respectively), as did nesiritide administered at any dose up to 0.06 μg · kg⁻¹ · min⁻¹ (P=0.002 and P=0.001, respectively). There was no difference in the need for dialysis between therapies.

Conclusions—Nesiritide significantly increases the risk of worsening renal function in patients with ADHF. Whether worsening renal function reflects hemodynamic effect or renal injury is unknown, but the prognostic importance of worsening renal function suggests the need for further investigation in appropriately powered clinical trials.

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Key Words: heart failure • kidney • meta-analysis • natriuretic peptides • pharmacology

Nesiritide is a potent vasodilator proven to rapidly reduce cardiac filling pressures and to improve dyspnea in patients with acutely decompensated heart failure.1–4 Several moderately sized controlled trials suggest that it is safe,5–8 as do large prospective registries.9 Nonetheless, no adequately powered randomized clinical trial has defined the long-term safety of nesiritide.

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Renal dysfunction is a strong correlate of long-term risk in cardiovascular medicine. The level of renal dysfunction, measured by serum creatinine,10–12 glomerular filtration rate,13,14 or calculated creatinine clearance,15–17 predicts outcome in patients with heart failure13–17 and in those after infarction.10,18,19 In parallel with the prognostic importance of the presence of renal dysfunction, worsening renal function immediately after coronary bypass portends a worse prognosis,20,21 as is the case for worsening renal function in patients hospitalized for acutely decompensated heart failure,22–25 with an increase in serum creatinine of just 0.1 mg/dL predictive of worsened outcome independently of baseline creatinine.23 Moreover, the relationship between even transient increases in creatinine and worse outcome has been demonstrated at levels of 0.3 to 0.5 mg/dL.22–25 Therefore, to determine whether there is potential risk with nesiritide, we performed a meta-analysis of randomized, double-blind, controlled trials of nesiritide in patients with acutely decompensated heart failure to assess the risk of worsening renal function.

Methods

Searching

The primary sources used to identify trials were (1) US Food and Drug Administration (FDA) documents released by the Cardiovascular and Renal Drug Advisory Committee for meetings in 1999 and 2001, which included the New Drug Application submission prepared by Scios (http://www.fda.gov/ohrms/dockets/ac/01/briefing/3749b2.htm); (2) the sponsor of the drug (Scios Inc, Medical Affairs Department); (3) a literature search using PubMed (using the search criteria “nesiritide” limited to clinical trials on humans published in English through July 2004); and (4) a manual search of

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annual meetings of the American Heart Association, American College of Cardiology, and Heart Failure Society of America. From these sources, 7 unique randomized trials were identified.

Selection
Trials were selected for this meta-analysis when they fulfilled each of the following characteristics: randomized, double-blind, parallel-group study on patients with acutely decompensated chronic heart failure and effect on serum creatinine reported.

Risk of Worsening Renal Function
Although several definitions of worsening renal function were recorded in the study reports, the one used consistently in each of these trials was an increase in serum creatinine (SCr) >0.5 mg/dL recorded at any time during the inpatient portion of the trial. The clinical trials performed to date with nesiritide do not permit formal determination of dose-related effects of the drug. To address the concerns that any differences detected could be due to use of inappropriately high doses or conversely that higher doses might minimize potential adverse effects by achieving maximal hemodynamic benefit, 6 separate comparisons were performed: (1) the FDA-approved doses for nesiritide infusion (≤0.03 μg · kg⁻¹ · min⁻¹) and non-inotrope-based control therapy (defined as control therapy that did not mandate use of positive inotropic agents), (2) FDA-approved doses of nesiritide and all control therapies (including trials that did and did not mandate use of positive inotropic agents in the control group), (3) low doses of nesiritide (≤0.015 μg · kg⁻¹ · min⁻¹) and non-inotrope-based controls, (4) low doses of nesiritide (≤0.015 μg · kg⁻¹ · min⁻¹) and all control therapies (including trials that did and did not mandate use of positive inotropic agents in the control group), (5) all nesiritide doses (up to 0.06 μg · kg⁻¹ · min⁻¹) and all control therapies, and (6) all nesiritide doses (up to 0.06 μg · kg⁻¹ · min⁻¹) and all control therapies.

Studies were reviewed for the incidence of worsening renal function; the data were extracted by 2 authors (J.S.B. and H.A.S.) into spreadsheet format.

Intervention for Worsening Renal Function
The occurrence of renal failure requiring dialysis was reported in 3 studies, and the occurrence of renal failure requiring a medical intervention but not dialysis was reported in 2 studies (Table 1). The frequency of each was tabulated separately.

Statistical Analyses
Meta-analyses were performed to determine the risk ratios (RRs) for worsening renal function (for each of the previously defined data sets), dialysis, and medical intervention without dialysis for nesiritide versus control therapy. For each analysis, data were assessed for interstudy heterogeneity by the Breslow-Day test. Because there was no evidence of heterogeneity, fixed-effects models were obtained with the Mantel-Haenszel technique (PROC FREQ, SAS for Macintosh, version 6.12, SAS Inc), with results expressed as adjusted RRs (RRadj) with 95% CIs. Two-tailed values of P<0.05 were considered significant without adjustments for multiple hypothesis testing.

Results

Seven multicenter randomized controlled trials were identified that assessed nesiritide infusions for the treatment of acutely decompensated heart failure (Table 1). Of those studies, the effects on creatinine were not available for 2 studies, PROACTION and FUSION. Five randomized studies (1288 patients were enrolled and randomized, 1269 underwent assessment of renal function) reported the effects of nesiritide on renal function as measured by the frequency of increased Scr (≥0.5 mg/dL), forming the basis of these analyses (Table 2). Because there was no evidence of heterogeneity across trials (Breslow-Day test probability value ranged from 0.43 to 0.70; rejecting the null hypothesis of homogeneity would conservatively require P=0.1), all meta-analyses were performed with fixed-effects models.

The incidence of worsening renal function requiring medical intervention was reported in 2 of the phase II infusion trials (studies 325 and 326), as was the need for dialysis, which was also reported in VMAC (Table 3).

Risk of Worsening Renal Function
Compared with non—inotrope-based control therapy (ie, diuretics and other vasodilators), use of FDA-approved doses of nesiritide (≤0.03 μg · kg⁻¹ · min⁻¹) in patients with acutely decompensated heart failure significantly increased the risk of worsening renal function (22% versus 15%; RRadj: 1.52; 95% CI, 1.16 to 2.00; P=0.003), as did low-dose nesiritide (≤0.015 μg · kg⁻¹ · min⁻¹; 23% versus 15%; RRadj: 1.46; 95% CI, 1.09 to 1.95; P=0.012) and nesiritide administered

### TABLE 1. Characteristics of the Randomized, Controlled, Double-Blind Trials Assessing the Clinical Impact of Nesiritide in Decompensated Heart Failure That Reported the Effect on Worsening Renal Function

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Men/Women, n</th>
<th>Doses of Nesiritide, μg bolus · μg/kg · min⁻¹ infusion</th>
<th>Duration of Infusion</th>
<th>Control Therapy</th>
<th>Increase in Scr &gt;0.5 mg/dL</th>
<th>Frequency of Dialysis</th>
<th>Frequency of Medical Intervention for Worsening Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>311</td>
<td>103</td>
<td>83/20</td>
<td>0.25 ± 0.015, 0.5 ± 0.03, 1.0 ± 0.06</td>
<td>24 h</td>
<td>Non-inotrope-based control</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>325</td>
<td>127</td>
<td>93/34</td>
<td>0.3 ± 0.015, 0.6 ± 0.03</td>
<td>Up to 5 d</td>
<td>Non-inotrope-based control</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>326</td>
<td>305</td>
<td>207/98</td>
<td>0.3 ± 0.015, 0.6 ± 0.03</td>
<td>Up to 12 d</td>
<td>Non-inotrope-based control</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>VMAC</td>
<td>498</td>
<td>333/152</td>
<td>0.2 ± 0.01, 2.0 ± 0.03</td>
<td>≥24 hours</td>
<td>Nitroprusside</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PRECEDENT</td>
<td>255</td>
<td>170/85</td>
<td>0.015, 0.03 (no bolus)</td>
<td>≥24 h to 14 d</td>
<td>Dobutamine</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Worsening renal function is defined as increased Scr (≥0.5 mg/dL). n indicates number with worsening renal function; N, total number of patients.

### TABLE 2. Frequency of Worsening Renal Function During Infusion Studies of Nesiritide in Acutely Decompensated Heart Failure From the Individual Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Control, n/N (%)</th>
<th>Nesiritide, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>311</td>
<td>4/29 (14)</td>
<td>15/74 (20)</td>
</tr>
<tr>
<td>325</td>
<td>2/42 (5)</td>
<td>15/85 (18)</td>
</tr>
<tr>
<td>326</td>
<td>9/102 (9)</td>
<td>36/203 (18)</td>
</tr>
<tr>
<td>VMAC</td>
<td>45/216 (21)</td>
<td>74/273 (27)</td>
</tr>
<tr>
<td>Precedent</td>
<td>9/83 (11)</td>
<td>29/162 (18)</td>
</tr>
<tr>
<td>Totals</td>
<td>69/472 (15)</td>
<td>169/797 (21)</td>
</tr>
</tbody>
</table>
TABLE 3. Incidence of Worsening Renal Function Requiring Medical Intervention or Dialysis During Infusion Studies of Nesiritide for Acutely Decompensated Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Control, n/N (%)</th>
<th>Nesiritide, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical intervention required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>325</td>
<td>0/42 (0)</td>
<td>13/85 (15)</td>
</tr>
<tr>
<td>326</td>
<td>6/102 (6)</td>
<td>19/203 (9)</td>
</tr>
<tr>
<td>Totals</td>
<td>6/144 (4)</td>
<td>32/288 (11)</td>
</tr>
<tr>
<td>Dialysis required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>325</td>
<td>1/42 (2)</td>
<td>2/85 (2)</td>
</tr>
<tr>
<td>326</td>
<td>2/102 (2)</td>
<td>3/203 (1)</td>
</tr>
<tr>
<td>VMAC</td>
<td>5/216 (2)</td>
<td>9/273 (3)</td>
</tr>
<tr>
<td>Totals</td>
<td>8/360 (2)</td>
<td>14/561 (2)</td>
</tr>
</tbody>
</table>

n indicates number with worsening renal function; N, total number of patients.

at any dose (≥0.06 μg·kg⁻¹·min⁻¹; 22% versus 15%; RR_{MHI}, 1.53; 95% CI, 1.16 to 2.00; P=0.002).

Compared with any control therapy, both non–inotrope- and inotrope-based, nesiritide administered at FDA-approved doses, at low doses, or at any dose increased the risk of worsening renal function (21% versus 15% for each; RR_{MHI}, 1.54; 95% CI, 1.19 to 1.98; P=0.001; RR_{MHI}, 1.47; 95% CI, 1.12 to 1.93; P=0.006; and RR_{MHI}, 1.54; 95% CI, 1.20 to 1.99; P=0.001, respectively; Table 4 and the Figure).

Intervention for Worsening Renal Function

The frequency of worsening renal function requiring medical intervention short of dialysis was increased in nesiritide-treated patients. As determined by the investigators, 32 of 288 nesiritide patients (11.1%) compared with 6 of 144 (4.2%) required medical intervention. This represented a statistically significant excess risk of 129% for the nesiritide group (RR_{MHI}, 2.29; 95% CI, 1.07 to 4.89; P=0.03).

There was, however, no difference between nesiritide and control groups in the need for dialysis, which was instituted in 14 of 561 nesiritide patients (2.5%) and 8 of 360 control patients (2.2%). The adjusted RR_{MHI} for nesiritide compared with control patients was 1.18 (95% CI, 0.50 to 2.76; P=0.71).

Discussion

Nesiritide is a potent vasodilator that promptly and consistently lowers cardiac filling pressures.1–4 Along with the marked reduction in pulmonary capillary wedge pressure, nesiritide significantly reduces dyspnea.1–4 In contrast to positive inotrope agents, nesiritide poses no arrhythmic risk.6 Together, these effects make nesiritide an attractive treatment for patients with acutely decompensated heart failure. However, the data from randomized, double-blind, controlled trials of nesiritide for the treatment of acutely decompensated heart failure show significant risk of worsening renal function compared with control therapy.

During treatment of patients with acutely decompensated heart failure, serum creatinine levels can be quite dynamic. Krumholz et al22 reported that 28% (469 of 1681) of patients developed worsening renal function during heart failure hospitalization, which they defined as an increase in serum creatinine of ≥0.3 mg/dL. Patients with worsening renal function were at increased risk of death while hospitalized

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TABLE 4. Effect of Nesiritide on Development of Worsening Renal Function in Patients With Acutely Decompensated Heart Failure

<table>
<thead>
<tr>
<th>Events, n/N (%)</th>
<th>Nesiritide</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesiritide ≤ 0.03 vs non–inotrope based controls</td>
<td>134/610 (22)</td>
<td>60/389 (15)</td>
</tr>
<tr>
<td>Nesiritide ≤ 0.03 vs all control therapies, including inotropes</td>
<td>163/772 (21)</td>
<td>69/472 (15)</td>
</tr>
<tr>
<td>Nesiritide ≤ 0.015 vs non–inotrope based controls</td>
<td>100/442 (23)</td>
<td>60/389 (15)</td>
</tr>
<tr>
<td>Nesiritide ≤ 0.015 vs all control therapies, including inotropes</td>
<td>99/464 (21)</td>
<td>69/472 (15)</td>
</tr>
<tr>
<td>Nesiritide ≤ 0.06 vs non–inotrope based controls</td>
<td>140/635 (22)</td>
<td>60/389 (15)</td>
</tr>
<tr>
<td>Nesiritide ≤ 0.06 vs all control therapies, including inotropes</td>
<td>169/797 (21)</td>
<td>69/472 (15)</td>
</tr>
</tbody>
</table>

Nesiritide doses refer to infusion rates (μg·kg⁻¹·min⁻¹) that followed bolus administration.
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and within 30 days and 6 months of discharge [odds ratio (OR), 2.72; 95% CI, 1.62 to 4.58; OR, 1.87; 95% CI, 1.25 to 2.80; and OR, 1.56; 95% CI, 1.19 to 2.05, respectively]. Using similar definitions, Forman et al.\(^2\) reported similar risks during the index hospitalization (RRM, 7.5; 95% CI, 2.9 to 19.3). Although no threshold has been defined below which risk does not appear to be affected, as the magnitude of the change increases, so does the magnitude of the risk and the statistical robustness of the association.\(^2\) Larger increases in creatinine (≥0.5 mg/dL) portend a worse prognosis, with a significantly increased risk of death (hazard ratio, 2.86; 95% CI, 1.55 to 5.26)\(^2\) predicted with high specificity (82%).\(^2\) In each of these studies, the changes in creatinine were assessed as peak levels, not the level that was eventually reached.

An acknowledged limitation to meta-analyses is the inability to adjust statistically for differences in other factors beyond treatment group assignment that could have influenced the development of renal dysfunction. Access to raw data might permit further risk adjustment by meta-regression techniques. Appropriately powered prospective studies could delineate whether the risk of worsening renal function is caused by nesiritide or is related to baseline characteristics in a subset of patients and could identify predictors of this phenomenon.

Despite the strength of the observation that worsening renal function is associated with worse clinical outcomes, no data in these or other studies demonstrate that this relationship is true for nesiritide as it is for some other therapies. The physiology of antagonizing the renin-angiotensin system appears to be an exception in which the relationship does not hold between transient worsening renal function and adverse outcome. Antagonizing angiotensin II–induced efferent arteriolar vasoconstriction reduces glomerular filtration rate and generally leads to increases in creatinine levels.\(^3\) In fact, increased creatinine is a barometer that reflects adequacy of renin-angiotensin system blockade. Although it is possible that nesiritide could lead to worsening renal function without adversely affecting outcomes, this can be determined only by a prospective mortality trial. Furthermore, even if the basis for elevated creatinine levels were hemodynamic, it would not obviate the need for further investigation because both calcium channel blockers and nonsteroidal antiinflammatory drugs can worsen renal function in patients with acutely decompensated heart failure, in part by hemodynamic effects.\(^2\)

Nesiritide is widely used, largely because of its prompt improvement of pulmonary capillary wedge pressure and symptoms.\(^1\)\(^-\)\(^4\) However, this should be balanced against the possibility of worsening renal function, especially in the absence of a long-term outcomes trial. The strong association between elevations in serum creatinine levels and risk reported by several studies,\(^2\)\(^-\)\(^5\) coupled with the statistically significant risk of worsening renal function and the need for medical intervention with nesiritide therapy, suggests that nesiritide could be associated with clinically relevant risk. The presence of such an association suggests that the short-term effects of nesiritide may not be sufficient to ensure long-term safety. A prospective mortality trial is necessary to determine the proper use of nesiritide for patients with acutely decompensated heart failure.

Acknowledgment

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In the article by Sackner-Bernstein et al, “Risk of Worsening Renal Function With Nesiritide in Patients With Acutely Decompensated Heart Failure,” which appeared in the March 29, 2005, issue of the journal (Circulation. 2005;111:1487–1491), there was a typographical error in the figure legend on page 1489. The legend currently reads “Relative risk of worsening heart failure with nesiritide...” but should read “Relative risk of worsening renal function with nesiritide.”