Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure
A Pooled Analysis of Randomized Controlled Trials

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I MPROVING QUALITY OF LIFE AND SUR-vival are the 2 primary goals of heart failure treatment. Typically, thera-pies are tested for short-term ef-fects on clinical end points or disease surrogates before establishing their ef-fects on long-term clinical status. This was the case for nesiritide, approved by the US Food and Drug Administration (FDA) for the treatment of acutely de-compensated heart failure based on its ability to reduce symptoms of dyspnea and left ventricular filling pressure rela-tive to placebo within 3 hours of admin-istration.[1-4] There is concern, however, that patients treated with nesiritide are at heightened risk of worsening renal function.[5] Several studies have shown that an increase in serum creatinine lev-els, such as that observed with nesiri-tide, predicts a higher risk of death even when that increase is transient.[6-9]

Prior studies suggest that nesiritide should be safer than positive inotropic agents, particularly dobutamine.[10,11] However, in light of the mortality risk associated with positive inotropic agents,[12-17] such comparisons may over-estimate the safety of nesiritide. A com-parison to alternative vasodilators or di-uretics has not been performed.

To determine whether the worsen-ing renal function that is associated with

nesiritide[5] reflects an increased risk of death, we pooled available individual patient-level data from completed ran-domized controlled trials to deter-mine the safety of nesiritide relative to noninotrope-based control therapies, primarily consisting of diuretics or vasodilators.

Context Nesiritide improves symptoms in patients with acutely decompensated heart failure compared with placebo and appears to be safer than dobutamine. Its short-term safety relative to standard diuretic and vasodilator therapies is less clear.

Objective To investigate the safety of nesiritide relative to noninotrope-based con-trol therapies, primarily consisting of diuretics or vasodilators.

Data Sources Primary reports of completed clinical trials as of December 2004 were obtained from the US Food and Drug Administration (FDA), the study sponsor (Scios Inc), a PubMed literature search using the terms *nesiritide*, *clinical trials*, and *hu-mans*, and a manual search of annual meetings of 3 heart associations.

Study Selection Of 12 randomized controlled trials evaluating nesiritide, 3 met all inclusion criteria: randomized double-blind study of patients with acutely decompen-sated heart failure, therapy administered as single infusion (≥6 hours), inotrope not mandated as control, and reported 30-day mortality.

Data Extraction Data were extracted from FDA and sponsor documents and cor-roborated with published articles when available. Thirty-day survival was assessed by meta-analysis using a fixed-effects model and time-dependent risk by Kaplan-Meier analysis with Cox proportional hazards regression modeling. Where deaths were described within a range of days after treatment, an extreme assumption was made favoring nesiritide over control therapy, an approach relevant to the time-dependent analyses.

Data Synthesis In the 3 trials, 485 patients were randomized to nesiritide and 377 to control therapy. Death within 30 days tended to occur more often among patients randomized to nesiritide therapy (35 [7.2%] of 485 vs 15 [4.0%] of 377 patients; risk ratio from meta-analysis, 1.74; 95% confidence interval [CI], 0.97-3.12; $P = .059$; and hazard ratio after adjusting for study, 1.80; 95% CI, 0.98-3.31; $P = .057$).

Conclusions Compared with noninotrope-based control therapy, nesiritide may be associated with an increased risk of death after treatment for acutely decompensated heart failure. The possibility of an increased risk of death should be investigated in a large-scale, adequately powered, controlled trial before routine use of nesiritide for acutely decompensated heart failure.

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METHODS
Searching

The primary sources used for the identification of trials were the FDA via 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 Inc (http://www.fda.gov/ohrms/dockets/ac/01/briefing/3749b2.htm)[1,2,18-20]; the sponsor of the drug (Scios Inc, Medical Affairs Department, Fremont, Calif)[21]; a literature search using PubMed (using the search criteria terms *nesiritide* limited to *clinical trials* on *humans* and published in English)[22-26]; and a manual search of annual meetings of the American Heart Association, American College of Cardiology,[27] and Heart Failure Society of America, all through December 2004. From these sources, 12 unique randomized controlled trials were identified.

Selection

Trials were selected when they fulfilled all of the following characteristics: randomized, double-blind, parallel-group study of patients with acutely decompensated chronic heart failure; nesiritide therapy administered as a single infusion for at least 6 hours; control therapy that did not mandate use of positive inotropic agent; and mortality reported during 30 days of follow-up.

Validity Assessment

The summaries of the FDA and the sponsor disclose pertinent trial design, aggregate population characteristics, and clinical outcomes. Studies described in multiple sources were compared to ensure completeness without duplication.

Study Characteristics

Three randomized controlled trials used noninotrope-based control therapies and provided at least 30-day follow-up of vital status—the Nesiritide Study Group Efficacy Trial (NSGET),[22] Vasodilation in the Management of Acute Congestive heart failure (VMAC),[4] and the

Figure 1. Process of Identification, Selection, and Inclusion/Exclusion Criteria of RCTs
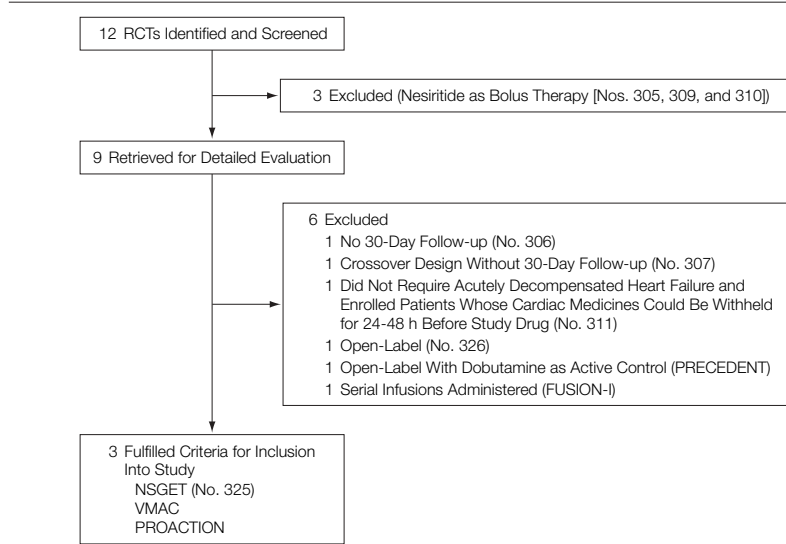
RCTs indicate randomized controlled trials; NSGET, Nesiritide Study Group Efficacy Trial; VMAC, Vasodilation in the Management of Acute Congestive heart failure; PROACTION, Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor. The numbers 305, 306, 307, 309, 310, 311, 325, and 326 refer to the sponsor's protocol designation.

Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor (PROACTION)[21,27]—and met inclusion criteria. Nine trials of nesiritide were excluded (**FIGURE 1**) for at least 1 of the following reasons: administered nesiritide as a bolus, did not report 30-day mortality, enrolled patients who did not have acutely decompensated heart failure, designed as open-label trial, used obligatory positive inotropic therapy as a comparator, or mandated therapy with intermittent infusions.[1,2,10,11,19,20,23-26]

Data Abstraction

In NSGET, dates of death were reported in the FDA review document.[28] For VMAC, the FDA review provided clinical summaries of deaths within 30 days that specified date of death, randomized treatment group, and whether a pulmonary artery catheter or an inotrope (dobutamine) was used.[19] A study report of PROACTION provided by the trial sponsor provided dates of deaths.[21] The principal investigator (J.D.S.-B.) performed the data abstraction.

Quantitative Data Synthesis

Death within 30 days was the common principal outcome measure for all analyses. The NSGET protocol prespecified follow-up for a minimum of 21 days, and the sponsor reported separately all deaths after day 21 as well.[18,28] Although vital status was provided for all control patients, 2 patients randomized to nesiritide therapy were lost to follow-up prior to day 30.[18] We made an assumption that favored nesiritide by assuming these 2 patients were alive at day 30.

In VMAC, 9 patients were excluded from the safety analysis published in the VMAC trial because they were randomized but not treated.[19] In accordance with the intention-to-treat principle, these patients were included in our analyses. The FDA documents indicate that 2 of these 9 patients randomized to fixed-dose nesiritide therapy died on the first day after randomization and 1 patient randomized to control therapy died on the second day, none of whom received study medication. The survival of the remaining 6 patients (1 control and 5 nesiritide) was not specified and their survival was censored at day 1. For 2 pa-

tients who were randomized but not treated, pulmonary artery catheter and dobutamine use were not listed in the clinical summary but information within the FDA documents allowed assignment of missing data. Use of a pulmonary artery catheter was not listed explicitly for 4 patients randomized to fixed-dose nesiritide therapy and 1 control patient, but study identification numbers could be used to determine the use of pulmonary artery catheter for each of these 5 patients. Four patients were lost to follow-up after treatment (1 control and 3 nesiritide, each censored at day 5, chosen to represent the minimum in-hospital follow-up based on national average length of stay data[29]). For those patients who survived to 30 days, randomized treatment group, use of pulmonary artery catheter, and dobutamine were determined based on summary tables within these documents.

In PROACTION, several of the deaths were noted to occur between days 15 and 30. Survival times were assigned to favor nesiritide therapy (deaths between days 15 and 30 in patients treated with nesiritide designated to be on day 30 and control therapy deaths designated to be on day 15).

Statistical Analyses

Crude risk of death at 30 days was compared by calculating a risk ratio with 95% confidence limits. Meta-analysis was performed to determine the risk of death after evaluating for interstudy heterogeneity by the Breslow-Day test.[30] As there was no evidence of heterogeneity (P=.58), fixed-effects models were obtained using the Mantel-Haenszel technique, with results expressed as adjusted risk ratios (RRs) with 95% confidence intervals (CIs). SAS version 8.2 (SAS Inc, Cary, NC) was used for all analyses.

Kaplan-Meier curves were compared by log-rank tests. Analyses were performed both unadjusted and adjusted, using multivariable Cox proportional hazards regression modeling. A backward elimination method was used with $P < .10$ for elimination. To account for the possibility of a dif-

ferential effect of therapy in the individual studies (NSGET vs VMAC vs PROACTION), a model including studies, treatment, and study × treatment interactions (using appropriate "dummy" variables to account for the 3 studies and study × treatment interactions in each) was evaluated. To investigate the potential impact of use of pulmonary artery catheter and dobutamine on survival, multivariable analyses evaluating treatment, pulmonary artery catheter and dobutamine use, and all first-order statistical interactions (ie, treatment × pulmonary artery catheter, treatment × dobutamine, pulmonary artery catheter × dobutamine) were performed for the VMAC study group. Although dobutamine was more frequently used in patients randomized to nesiritide therapy in the VMAC study, there was no significant interaction between survival and use of dobutamine (P=.20). Neither pulmonary artery catheter use (P=.32) nor the first-order interaction terms were significantly related to survival; therefore, these variables were not introduced in the final survival model, which included only treatment and study as dependent variables.

RESULTS
Study Characteristics

In NSGET,[22] patients admitted with acutely decompensated heart failure with an indwelling pulmonary artery catheter and documented pulmonary capillary wedge pressure of at least 18 mm Hg, cardiac index of less than 2.8 L/min/m², and systolic blood pressure of at least 90 mm Hg were randomized to a 6-hour infusion of nesiritide or placebo therapy. Patient eligibility required clinical stability without ongoing positive inotropic or intravenous vasodilator therapies during the 6-hour blinded treatment period. Although the primary end points were hemodynamic, survival was assessed prospectively for a minimum of 21 days with additional deaths reported on days 22, 30, and 31, each in patients treated with nesiritide.[28] The death at day 31 was not included in any of the analyses.

In VMAC,[4] patients were enrolled with acutely decompensated heart failure experiencing dyspnea at rest with signs and symptoms of congestion. Positive inotropic agents were permitted before, during, and after study drug administration at the discretion of the treating physicians. Patients were randomized for 3 hours to nesiritide, nitroglycerin-based control therapy, or placebo; the placebo group was rerandomized after 3 hours to either nitroglycerin or nesiritide. Patients with an indwelling pulmonary artery catheter were randomized in a stratified manner to adjustable-dose nesiritide in addition to these other groups. The nitroglycerin and adjustable-dose nesiritide groups had doses adjusted as deemed necessary by the treating physicians. The primary end points were the clinical and hemodynamic effects of nesiritide compared with placebo therapy after 3 hours, with similar comparisons between nesiritide and nitroglycerin defined as secondary end points. A blinded monitoring board reviewed major adverse clinical events including deaths for the first 30 days.[1]

In PROACTION,[21,27] patients with acutely decompensated heart failure presenting to the emergency department or observation unit were treated with nesiritide (bolus followed by infusion at 0.01 µg/kg per minute) or placebo for a minimum of 12 hours, in addition to nitrates and diuretics. Positive inotropic agents were not allowed. The study was designed to determine whether this strategy could reduce hospitalizations, and survival was assessed prospectively for 30 days. Trends were observed for less frequent hospitalizations and less days spent in the hospital during the 30-day follow-up period for patients randomized to nesiritide therapy.[21,27]

The study population included 127 patients from NSGET, 498 from VMAC, and 237 patients from PROACTION. The baseline characteristics available for qualitative comparison between trials include differences in blood pressure and degree of functional limitation before decompensa-

tion (% New York Heart Association class III-IV) that are consistent with differences in acuity expected based on the intensity of medical care required for patients enrolled into the individual trials (**TABLE 1**).[1,2,4,19-22,27]

Overall, 377 patients (43.7%) were randomized to control therapy and 485 patients were randomized to nesiritide therapy (337 [39.1%], 43 [5.0%], and 42 [4.9%] to fixed-dose nesiritide at 0.01, 0.015, or 0.03 μg/kg, respectively; and 63 [7.3%] adjustable-dose nesiritide, starting at 0.01 μg/kg per minute). Dobutamine, used at each investigator's discretion in VMAC only, was more frequently used in patients randomized to nesiritide therapy (71 [25.4%] of 280 patients treated with nesiritide vs 33 [15.1%] of 218 patients treated with control therapy, P=.006).

Quantitative Data Synthesis

The crude risk of dying within the first 30 days after randomization was significantly higher for patients in VMAC than for patients in PROACTION (36 [7.2%] of 498 vs 6 [2.5%] of 237 patients; RR, 2.86; 95% CI, 1.22-6.67; P=.01) with the risk intermediate in NSGET (8 [6.3%] of 127 patients; RR, 2.49; 95% CI, 0.88-7.01; P=.09 vs PROACTION).

The crude 30-day mortality was higher for nesiritide than for control therapy (35 [7.2%] of 485 vs 15 [4.0%] of 377; RR, 1.81; 95% CI, 1.01-3.27; P=.04). Meta-analysis using a fixed-effects model (Mantel-Haenszel technique) revealed a trend suggesting higher risk with nesiritide therapy (RR, 1.74; 95% CI, 0.97-3.12; P=.059) (**TABLE 2**).

Unadjusted Kaplan-Meier 30-day survival curves showed worse survival in the nesiritide treatment group (mean [SD], 93.5 [1.1%] vs 96.0 [1.0%] for the nesiritide and control groups, respectively; P=.04); the associated hazard ratio (HR) was 1.86 (95% CI, 1.02-3.41) (**FIGURE 2**). Survival adjusted for study revealed a similar trend toward worse outcome with nesiritide, with an 80% greater probability of death by 30 days (HR, 1.80; 95% CI, 0.98-3.31; P=.057).

Table 1. Baseline Characteristics of Component Trials

Characteristic	NSGET	VMAC	PROACTION
No. of patients	127	498	237
Age, mean, y	59	61	66
Men, %	73	69	56
Clinical setting	ADHF requiring invasive monitoring	ADHF requiring hospitalization	ADHF presenting to emergency department or observation unit
NYHA class III-IV, %*	98	83	60
Systolic blood pressure <100 mm Hg, %	NA†	19	6

Abbreviations: ADHF, acutely decompensated heart failure; NA, not available; NSGET, Nesiritide Study Group Efficacy Trial; NYHA, New York Heart Association; PROACTION, Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor; VMAC, Vasodilation in the Management of Acute Congestive heart failure.
*Refers to severity of symptoms prior to acute decompensation.
†The percentage of patients with systolic blood pressure of less than 100 mm Hg was not reported but mean systolic blood pressure was 116 mm Hg in NSGET.[1,2,4,19-22,27]

Table 2. Mortality Within 30 Days of Treatment Associated With Nesiritide or Control Therapy With Overall Risk Ratio Calculated by Mantel-Haenszel Test Using a Fixed-Effects Model

	No. of Deaths/Total No. (%) of Patients		Risk Ratio (95% CI)	P Value
Study	Nesiritide Therapy	Control Therapy		
NSGET	6/85 (7.1)	2/42 (4.8)	1.48 (0.31-7.03)	ND
VMAC	24/280 (8.6)	12/218 (5.5)	1.56 (0.80-3.04)	ND
PROACTION	5/120 (4.2)	1/117 (0.9)	4.88 (0.58-41.1)	ND
Total	35/485 (7.2)	15/377 (4.0)	1.74 (0.97-3.12)	.059

Abbreviations: CI, confidence interval; ND, not determined; NSGET, Nesiritide Study Group Efficacy Trial; PROACTION, Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor; VMAC, Vasodilation in the Management of Acute Congestive heart failure.

COMMENT

In the absence of large-scale morbidity and mortality trials, meta-analyses and pooled analyses provide insight into the risks associated with particular therapies.[31] The sequence of events leading to the withdrawal of rofecoxib from the market underscores the importance of rigorous evaluation of safety from all data sources.[32,33] We analyzed data from the only 3 studies with at least 30-day follow-up that evaluated the effects of an infusion of nesiritide compared with a control therapy that did not mandate positive inotropic agents. Coincidentally, the 3 trials in this analysis are the only double-blind studies to evaluate the 30-day outcomes associated with nesiritide therapy for patients with acutely decompensated heart failure. The 30-day outcomes of nesiritide relative to positive inotropic agents have not been tested in a randomized, double-blind trial. Our analysis suggests that despite appearing safer than dobutamine in open-label trials,[10,11] nesiritide

Figure 2. Kaplan-Meier Curves of 30-Day Mortality Associated With Control and Nesiritide Therapies Based on NSGET, VMAC, and PROACTION Studies
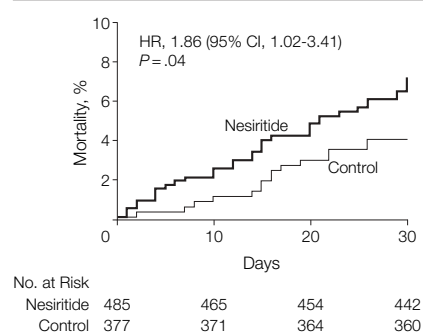
NSGET indicates Nesiritide Study Group Efficacy Trial; VMAC, Vasodilation in the Management of Acute Congestive heart failure; PROACTION, Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor; CI, confidence interval; HR, hazard ratio.

therapy may be associated with meaningful mortality risk. This finding is consistent with the recently noted obser-

vation that nesiritide is associated with worsening renal function during its administration for acutely decompensated heart failure,[5] a surrogate for increased mortality risk.[6-9] Because of this possibility of risk, nesiritide may not be an optimal choice as first-line therapy for acutely decompensated heart failure.

Previous reports suggested increased risk associated with nesiritide treatment when compared with regimens that did not include inotropes.[1,2,4,27] During the regulatory review process, the FDA estimated a magnitude of risk possibly associated with nesiritide treatment that is similar to those calculated in this analysis.[19] At that time, the FDA advisory panel and the sponsor cited data that showed that VMAC had not ruled out up to a 50% increase in the risk of death associated with nesiritide relative to nitroglycerin.[2,19,20] Viewed in comparison with criteria for noninferiority used in other cardiovascular clinical trials,[34-38] these data indicate that despite being better than placebo at improving hemodynamics and symptoms of dyspnea in VMAC[4] and appearing likely to be safer than dobutamine,[10,11] nesiritide has not clearly been shown to be noninferior to noninotrope-based diuretic and conventional vasodilator regimens. This lack of noninferiority reinforces the need for large-scale prospective trials to more precisely define the safety of nesiritide relative to noninotrope-based therapies of acutely decompensated heart failure.

Although it may appear difficult to perform a mortality analysis without access to the study databases, the FDA provides the necessary data on its Web site (http://www.fda.gov/ohrms/dockets/ac /01/briefing/3749b2.htm). The FDA files contain the actual data on survival times, and in VMAC, for use of inotropic agents and pulmonary artery catheter for each patient who died. In addition, these files provide information about patients randomized but not treated, which permits an intention-to-treat analysis that was not reported in the primary study publication.[4] Our analysis from documents readily available from the FDA

and the manufacturer of nesiritide represent the first comprehensive report of the effects on death within 30 days of follow-up, which was not reported explicitly in any of the trials. The NSGET trial described mortality (over 21 days as it prespecified) as being similar between groups but this similarity was evident only after combining the results of this trial with a larger open-label study comparing nesiritide with dobutamine.[22] The VMAC trial reported mortality only at 7 days and 180 days (0.5% vs 1.5% and 20.8% vs 25.1% for control and nesiritide groups, respectively, and reported $P=.32$ for the difference at 180 days), yet 30-day follow-up was the primary safety outcome monitored by an independent data and safety monitoring board.[4] The PROACTION trial has not yet been published as a manuscript.

The baseline differences between treatment groups in VMAC underscore the importance of risk adjustments in our analyses. We were able to adjust our analyses for pulmonary artery catheter and dobutamine use, for each of which we had patient-specific information from VMAC. However, we were not able to more completely adjust our analyses for other characteristics and exposures that differed between groups but for which we did not have information for individual patients. Nevertheless, we can be confident that this information would not have affected our results or conclusions. The FDA analyzed the mortality risk after adjusting for these additional baseline differences and stated that the "Cox regression analysis containing these variables did not appear to change the hazard ratio greatly."[20]

There are 3 important limitations to this analysis. First, the NSGET, VMAC, and PROACTION studies were not designed to definitively determine whether nesiritide is associated with risk of death, although each prospectively monitored for deaths following therapy. Second, none of the 3 studies collected complete information on the use of additional medications or procedures through the 30-day follow-up

period. It is possible that these unmeasured confounders contributed to the differences between nesiritide and control therapies. Third, it is possible that these results are due to chance. However, safety cannot be presumed until a prospective clinical outcomes trial demonstrates it to be so.[13-16,39-41]

In conclusion, nesiritide may be associated with an increased risk of death within the first month after its use for the treatment of decompensated heart failure when compared with noninotrope-based control therapies. As this is not an analysis based on an adequately powered prospective trial but rather an analysis pooling data from existing trials, our finding should be viewed as hypothesis generating rather than as conclusive evidence of harm. However, given the high mortality rate associated with heart failure, excluding an increased risk with nesiritide is imperative. An adequately powered, controlled randomized mortality trial comparing nesiritide with traditional diuretic and vasodilator drug therapy must be performed. Until then, it may be prudent to reserve use of this agent to situations in which a combination of diuretics and nitroglycerin has proven inadequate.

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