Nesiritide in Acute Decompensated Heart Failure: A Pooled Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Previous randomized controlled trials (RCTs) evaluating nesiritide for the treatment of acute decompensated heart failure (ADHF) have reported wide variances in mortality hazard ratios for nesiritide vs controls, but these individual trials were neither designed nor powered to evaluate mortality. This study used relevant data from all RCTs of nesiritide in ADHF completed as of June 2006 to independently estimate the effect of nesiritide on 30- and 180-day mortality.

Hypothesis: Administration of nesiritide to treat patients with ADHF does not significantly increase mortality at 30 or 180 days.

Methods: Six trials met prespecified criteria for inclusion in this analysis. Primary data from these trials were obtained from Scios Inc. (Fremont, CA). Statistical models were fitted to estimate 4 effects: dose response, differing control groups, vulnerable subgroup interactions, and time of death relative to nesiritide administration. All models included 4 baseline covariates that were significantly and independently associated with mortality.

Results: Complete covariate data were available in 1472 of 1538 subjects (96%). The risk-adjusted hazard ratio for mortality was 1.05 (95% confidence interval [CI]: 0.85–1.30) at 30 and 1.00 (95% CI: 0.88–1.14) at 180 days with no clear relationship to nesiritide dose. In addition to consistent results across 2 time points, no significant evidence of sensitivity to control group or baseline risk factors was found.

Conclusions: Currently available data suggest nesiritide does not significantly increase mortality at 30 or 180 days.

Introduction

Randomized controlled trials (RCTs) have shown that nesiritide provides significant symptomatic and hemodynamic improvement in acute decompensated heart failure (ADHF) patients. However, these trials were neither designed nor powered to evaluate mortality. Wide variances in mortality hazard ratios (HRs) for nesiritide vs controls were reported, ranging from 0.38 to 4.99 at 30 days. HR ranges were narrower at 180 days (0.74–1.25), reflecting greater statistical stability with 180-day mortality.¹ A pooled analysis of

selected data from 3 of these trials suggested that nesiritide might be associated with an increased mortality risk.²

Mortality risk factors in ADHF include age, male gender, diabetes, New York Heart Association (NYHA) class, systolic hypotension, hyponatremia, renal insufficiency, and use of inotropic agents.^{3–8} In clinical trials designed before recognition of these risk factors, baseline differences could have influenced unadjusted mortality risk assessments and may explain the wide variability in mortality ratios. We attempted to determine whether there is any significant evidence of increased mortality with nesiritide. Pooling data across trials generated narrower confidence intervals (CIs) for nesiritide mortality ratios than had been reported previously. This study used all relevant data from RCTs of nesiritide in ADHF completed as of June 2006.

Methods

Data Sources

The sources used to identify RCTs of nesiritide in ADHF included (1) Scios Inc. (Fremont, CA), the drug's sponsor, (2) PubMed literature search using relevant search terms,

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and (3) search of abstracts from annual meetings of the American College of Cardiology, American Heart Association, and Heart Failure Society of America. Twelve unique trials were identified. All were sponsored by Scios Inc., which provided unrestricted independent access to all trial data for this analysis. The analysis was performed independently in the Center for Biostatistics at The Ohio State University (Columbus, Ohio).

Study Selection

We included randomized, placebo- or active-controlled nesiritide trials in ADHF patients with planned study drug infusion for ≥ 4 hours in a hospital setting and follow-up ≥ 30 days.

Data Extraction and Validity Assessment

Scios Inc. provided complete study databases, which were validated against data in the primary study publications whenever possible. Scios staff also validated tables of patient and study characteristics.

Study Characteristics

Twelve RCTs of nesiritide were evaluated (Figure 1). Four studies were excluded because they assessed nesiritide either as bolus therapy (studies 305, 309, 310) or as serial outpatient infusions (study 348). Studies 306 and 307 lacked 30-day data and were excluded. Six trials, studies 311, 325, 326, 329 (Prospective, Randomized Evaluation of Cardiac Ectopy With Dobutamine or Natreco Therapy [PRECEDENT] trial), 339 (Vasodilation in the Management of Acute Congestive Heart Failure [VMAC] trial), and 341 (Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients With Natreco [Nesiritide] [PROACTION]

trial) met inclusion criteria,^{9–13} and 4 trials (325, 326, 329, and 339) also had 180-day follow-up data.

Four trials studied nesiritide at doses higher than currently recommended (Table 1). Control groups varied across trials, including “standard care”, placebo, dobutamine infusion, nitroglycerin infusion, or placebo followed by standard care or nitroglycerin infusion. Not all protocols excluded inotrope-treated subjects.

Analytical Strategy

We analyzed the complete study databases. To enhance the probability of detecting an increased mortality risk associated with nesiritide, we developed 4 different statistical models based on rational pharmacologic hypotheses. Our many significance tests must be considered exploratory. We applied no corrections, increasing the probability of declaring a significant increase in mortality due to nesiritide when there was no true increase. We have emphasized a single CI for the mortality ratio associated with our most reasonable model, and then reported CIs for other models in our sensitivity analysis.

Statistical Models

To account for different doses used across the 6 trials, each treatment group within each trial was assigned the median total dose delivered to patients within that treatment group (Table 1). This median across all patients was based on each patient’s bolus dose and total infusion over time in $\mu\text{g}/\text{kg}$. Thus each treatment group was indexed with an empirical total dose level. In our main model, we assessed mortality as a function of median total nesiritide dose using a Cox proportional hazards model with surviving patients censored at 30 days. In sensitivity analyses, we evaluated this relationship after eliminating control subjects from the modeling, and also evaluated the relationship between the assigned infusion rate and mortality. We also ignored dose and estimated a model based on the dichotomous variable of treatment or control group assignment. Under dose-mortality modeling, the mortality HRs were calculated by multiplying the slope coefficient for nesiritide by the median total dose for the protocol corresponding to the current recommended bolus dose and infusion rate. This included the dose used in one of the VMAC arms (a median total dose of $17 \mu\text{g}/\text{kg}$). For the model with infusion rate, the HR was based on the current recommendation of $0.01 \mu\text{g}/\text{kg}/\text{minute}$.

The VMAC trial data had been previously used to identify important mortality risk predictors.¹⁴ Multivariate Cox regression models identified four covariates obtained at baseline before randomization in the 6 trials: NYHA class IV heart failure, systolic blood pressure ≤ 100 mm Hg, creatinine clearance ≤ 60 mL/minute/1.73m², and intravenous inotrope administration prior to randomization. These 4 variables were adopted to add precision to the study; all were clinically meaningful and highly correlated with mortality.

Figure 1. Trial selection flow diagram. The study numbers in the boxes refer to the sponsor’s protocol designation.

Table 1. Randomized Controlled Natreacor Trials With 30-day Mortality Data

Study	Setting	Dosing Duration	Nesiritide Dose Groups	N ^a	Median Dose (μg/kg)	Control Group(s)	N ^a
311 (Mills et al ⁹)	Inpatient	24 hr	1. 0.25 μg/kg bolus + 0.015 μg/kg/min infusion 2. 0.5 μg/kg bolus + 0.030 μg/kg/min infusion 3. 1.0 μg/kg bolus + 0.060 μg/kg/min infusion	21 25 26	22 44 70	Placebo	27
325 (Efficacy trial ¹⁰)	Inpatient	At least 6 hr	1. 0.3 μg/kg bolus + 0.015 μg/kg/min infusion 2. 0.6 μg/kg bolus + 0.03 μg/kg/min infusion	41 42	22 44	Placebo for 6 hr, then standard care	42
326 (Comparative trial ¹⁰)	Inpatient	Up to 7 d	1. 0.3 μg/kg bolus + 0.015 μg/kg/min infusion 2. 0.6 μg/kg bolus + 0.03 μg/kg/min infusion	97 94	29 46	Standard care	100
329 (PRECEDENT ¹¹)	Inpatient	At least 24 hr	1. 0.015 μg/kg/min infusion 2. 0.030 μg/kg/min infusion	83 78	22 43	Dobutamine infusion	82
339 (VMAC ¹²)	Inpatient	At least 24 hr	1. Placebo for 3 hr then 0.01 μg/kg/min infusion 2. 0.01 μg/kg/min infusion 3. Adjustable dose	68 141 60	15 17 25	1. Placebo for 3 hr then nitroglycerin infusion 2. Nitroglycerin infusion	72 140
341 (PROACTION ¹³)	ED	At least 12 hr for discharged patients; at least 24 hr for admitted patients	1. 2 μg/kg bolus + 0.01 μg/kg/min infusion added to standard care. Increase in dose permitted at 3-hr intervals to maximum of 0.03 μg/kg/min	119	12	Placebo added to standard care	114

Abbreviations: ED, emergency department; n, number of patients; PRECEDENT, Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natreacor Therapy trial; PROACTION, Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially as Outpatients with Nesiritide trial; VMAC, Vasodilation in the Management of Acute Congestive Heart Failure trial.

^a Ns cited are number of patients per protocol group with baseline covariates available.

Cox proportional hazard models, including interaction effects, were used to assess potential control group interactions and “vulnerable” subgroup interactions. Models provided estimated HRs for the dobutamine and nitroglycerin control groups separately from the other control groups, for emergency department patients separately from admitted patients, and for patients with a high mortality risk at baseline. In this latter analysis, each of the 4 previously determined baseline mortality risk predictors was evaluated separately. Temporal association between nesiritide administration and mortality was assessed using Cox proportional hazard models to determine 10-day and 180-day mortality HRs for nesiritide, relative to control, in addition to the 30-day mortality HR. Departure from assumptions about proportional hazards or functional form for covariates was tested for each model based on methods developed by Lin et al.^{15,16} Analyses were performed using Version 9.1 of SAS software (SAS Institute, Inc., Cary, NC).

Results

Study Characteristics

In the 6 trials, 1538 patients were randomized (Table 1); 66 patients (4%) were missing data on at least 1 of the baseline covariates and were not included in most of the analyses. Seven (nesiritide: n = 5; control: n = 2) of these 66 patients died before receiving their assigned treatment. The remaining 1472 patients were used for most of the models. However, in models that excluded baseline covariates, all 1538 patients were included. One patient randomized to nesiritide did not receive the assigned treatment and was classified based on intention-to-treat.

Baseline Risk Factors for Mortality

Surprisingly, 3 baseline mortality risk factors tended to be more prevalent in nesiritide patients than in controls across the 6 trials (Table 2): NYHA class IV, systolic blood pressure ≤100 mm Hg, and prior administration of inotropes.

Table 2. Independent Mortality Risk Factors at Baseline

	Treatment Group Prevalence		Difference (%) [95% CI]
	Nesiritide (%)	Control (%)	
NYHA class IV	33.5	31.5	2.0 [−3, 7]
SBP ≤100 mm Hg	18.3	14.7	3.6 [−0.3, 8]
CrCl <60 mL/min/1.73m ²	49.5	49.7	−0.2 [−6, 5]
Inotrope use prior to study drug	12.1	8.7	3.4 [0.2, 7]

Abbreviations: CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; NYHA, New York Heart Association; SBP, systolic blood pressure.

HR >1 indicates increased risk due to nesiritide; <1 indicates protective effect of nesiritide.

Dose-Response Relationship for 30-day Mortality

Of the 1472 patients, 79 (5.4%) died within the 30-day follow-up. In the model that included total nesiritide dose and the 4 baseline covariates, the χ^2 goodness-of-fit test, evaluating the departure from linearity of the dose/hazard relationship ($P = 0.89$), and the test of the proportional hazards assumptions for dose and for the 4 covariates were not significant (all $P < 0.77$), eliminating concerns about model fit. In this model, there was no significant association between median nesiritide dose and mortality ($P = 0.63$). Based on the dose-mortality (slope) coefficient, the HR at the currently recommended dose was estimated as 1.05 (95% CI: 0.85–1.30). We consider this our primary CI.

In contrast, each of the 4 baseline covariates was associated with a significantly increased mortality risk, with HRs of 1.83 ($P = 0.008$) for NYHA class IV, 2.01 ($P = 0.01$) for prior inotrope use, 2.22 ($P = 0.001$) for systolic blood pressure ≤100 mm Hg, and 2.95 ($P = 0.001$) for creatinine clearance ≤60 mL/minute/1.73m². The mortality HR rises slightly from 1.05 to 1.11 (95% CI: 0.90–1.36) when these covariates are not included in the model. However, even in this case, there was no significant association between total nesiritide dose and mortality (based on all 1538 patients). Likewise, there was no significant association between nesiritide dose and mortality when the analysis was repeated, either excluding control patients or using assigned infusion rate instead of total nesiritide dose. Based on the infusion rate–mortality coefficient, the HR at the currently recommended infusion rate was estimated as 0.93 (95% CI: 0.77–1.13). In a final sensitivity analysis, we ignored dose and simply categorized patients as nesiritide or control. The HR for this model was also not significant (HR: 1.24, 95% CI: 0.77–2.01, $P = 0.37$).

Control Groups and 30-day Mortality

Thirty-day mortality as a function of differing controls in the second set of models did not show any significant differences when data from PRECEDENT (dobutamine control), VMAC (nitroglycerin control), or PROACTION (emergency department initiation) were considered separately. Although the HR for PROACTION was large, the CI was wide. As with the primary model, the χ^2 goodness-of-fit and proportional hazards tests were statistically nonsignificant (all fit P values were >0.46).

“Vulnerable” Subgroup Interactions

Most patients (71%) had at least 1 of the 4 baseline covariates associated with increased mortality. However, nesiritide administration in these “vulnerable” patients was not associated with greater mortality risk compared with “nonvulnerable” patients (Table 3). All interaction tests were nonsignificant (Table 3), as were all tests of departure from linearity and proportional hazards (all fit P values were >0.87).

Ten- and 180-day Mortality and Nesiritide Administration

There was no significant association between nesiritide dose and mortality at 10 days. The HR at the recommended dose was 1.20 (95% CI: 0.85–1.70, $P = 0.29$). However, only 26 patients (1.8%) had died; the resultant wide CI precludes any conclusions about 10-day mortality risk (Figure 2).

There were 1140 evaluable patients in the 4 trials with 180-day follow-up data; 244 (21%) died within that time. Mortality HR for nesiritide at the recommended dose at 180 days was similar to that at 30 days, but the CI is narrower due to the increased number of deaths (HR: 1.00; 95% CI: 0.88–1.14, $P = 0.95$) (Figure 2).

Table 3. Impact of Nesiritide on Mortality Risk in Vulnerable Patients

	30-day Mortality HRs Due to Nesiritide (95% CI)		Test of Interaction
	Risk Factor Present	Risk Factor Absent	P Value
NYHA class IV	1.00 (0.74–1.35)	1.11 (0.83–1.48)	0.62
SBP ≤100 mm Hg	0.95 (0.66–1.39)	1.10 (0.86–1.42)	0.52
CrCl ≤60 mL/min/1.73m ²	1.03 (0.81–1.32)	1.11 (0.73–1.67)	0.77
Inotrope use prior to study drug	0.92 (0.55–1.54)	1.08 (0.86–1.36)	0.56

Abbreviations: CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; NYHA, New York Heart Association; SBP, systolic blood pressure.

HR >1 indicates increased risk due to nesiritide; HR <1 indicates protective effect of nesiritide.

Figure 2. Comparative mortality hazard ratios for nesiritide relative to control at 10, 30, and 180 days.

Discussion

Nesiritide was not associated with significant increases in the risk of death at 10, 30, or 180 days after modeling many potential effects, including baseline differences in mortality risk factors. The 10-day mortality HR was greater than the 30- or 180-day HRs; however, the low 10-day mortality produced large CIs, making any conclusion impossible. We found no significant departure from the proportional hazards assumption through 180 days (test of constant HR through time). In addition, CIs around the 30- and 180-day HRs are sufficiently narrow to eliminate concern about a substantial increase in mortality due to nesiritide at these times.

The neutral effect of nesiritide on mortality cannot be explained by the differing control therapies or sites of nesiritide initiation in this pooled analysis. Although the mortality HR appears to be lower in PRECEDENT and greater in VMAC and PROACTION than in the remaining trials, the small absolute number of deaths in these trials makes the HRs less reliable, as indicated by large 95% CIs. The nonsignificant test of interaction between each of these trials and the remaining trials demonstrates that mortality risk in these trials does not differ significantly from that of the other trials, justifying their inclusion in the overall analysis. As indicated by the 30-day mortality HRs when these trials were individually excluded from the analysis (range: 1.03–1.08 vs 1.05 for all 6 trials), inclusion of these trials did not influence overall results. Most importantly, this neutral effect was seen in high-risk patients. In vulnerable subgroups of patients, as defined by baseline risk factors, mortality HR for nesiritide, relative to control, ranged from 0.92 to 1.03 and was not significantly different from subgroups without these risk factors.

Evidence for therapeutic decisions in ADHF management from RCTs is limited. Consequently, assessing the mortality impact of ADHF therapy requires either observational data from registries or analysis of pooled data from existing RCTs to obtain statistical power.

The confounding effects of covariates and the need for adjusted analyses are well recognized in analyses of registry

data.^{17,18} Although similar imbalances in covariates usually occur by chance in RCTs, it is still valuable to use covariates to add precision to pooled analyses. When pooled trial data include subgroup covariates, interaction effects between treatment and subgroups can be tested, which is usually impossible in a single trial. (This study demonstrates the importance of using complete trial datasets to adjust for covariates and test for interactions).

Several factors may account for the difference between our findings and those of a previous analysis suggesting increased mortality with nesiritide at 30 days (HR: 1.80; 95% CI: 0.98–3.31).² First, the earlier analysis was based on data extracted from US Food and Drug Administration Web sites and sponsor documents for only 3 nesiritide trials (325, 339, and 341). We addressed this by estimating the 30-day HR based on all 6 relevant trials. In addition, without complete data, authors of the previous study could not adjust for differences in mortality risk between treatment groups and could not model the effects of varying dosages. Although the earlier analysis considered the potential confounding effect of dobutamine administration in 1 of the 3 trials, that analysis ignored the potential effects of dobutamine or other positive inotropes in the other trials. As a result, dobutamine alone did not appear to confer significant mortality risk; mortality HR was not adjusted for use of this or any other inotropic agent. We demonstrated that inotropic therapy significantly increased mortality risk. By chance, inotrope use at baseline was more prevalent in patients randomized to nesiritide. Failure to consider this or other baseline risk factors more common in the nesiritide group resulted in erroneously increasing the estimated HR for nesiritide in the earlier limited pooled analysis.

Second, only 77 patients died within 30 days in all 6 trials. Consequently, any data exclusion substantially decreases the reliability of the estimated HR. Exclusion should be considered only if there is a unique mortality effect in the excluded trial. We specifically tested for unique mortality effects and found none. Because the earlier analysis excluded data from 3 of the 6 trials, the 95% CI for the mortality HR is too wide to permit meaningful interpretation. In the current evaluation, the CI was reduced by more than 86% when data from all 6 trials were considered. Finally, the earlier analysis, unlike the current evaluation, did not consider confounding effects from the different dosing regimens in the trials, some of which exceeded the present recommendations by 3-fold.

It is important to consider the limitations of the current evaluation. None of the 6 trials was designed or powered to assess mortality. Although pooling data increases statistical power, heterogeneity of the combined data limits conclusions based on pooled analyses. Nesiritide dose, control group therapy, and treatment setting varied from one trial to the next. However, we specifically addressed these differences using dose-response relationships and

interaction tests; none contradict the finding that nesiritide does not substantially increase mortality at 30 or 180 days.

Finally, looking at so many possible ways to find an increase in mortality due to nesiritide increased the chance of finding at least 1 significant result. We did not adjust *P* values for the many looks, which made the lack of any small *P* values more convincing. Most importantly, we designated a primary analysis ahead of time, which was the nesiritide HR estimate for 30-day mortality. Based on a model with 4 baseline covariates and dose effects, the primary HR was 1.05, and its 95% CI (0.85–1.3) was much narrower than any previously reported mortality HRs for nesiritide.

Conclusion

There are insufficient data (ie, too few deaths) to determine whether nesiritide infusion is associated with increased mortality risk at 10 days. However, our analysis using multiple models and more than 1000 patients demonstrates that nesiritide infusion was not significantly associated with substantially increased mortality risk at either 30 or 180 days.

Author Contributions

Drs. Abraham and Jarjoura had unrestricted access to all the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors were individually responsible for the following: study concept and design: Abraham, Trupp, Jarjoura; acquisition of data: Abraham, Jarjoura; analysis and interpretation of data: Abraham, Jarjoura; drafting of manuscript: Abraham, Trupp, Jarjoura; critical revision of the manuscript for important intellectual content: Jarjoura, Abraham, Trupp; statistical analysis: Jarjoura; administrative, technical, or material support: biostatistical programming by Keding Hua, MS, of the Center for Biostatistics; study supervision: Abraham.

Role of Sponsor

The sponsor provided the authors with full access to all data from the completed, randomized, controlled nesiritide trials. Dr. Jarjoura independently analyzed these data. All of the authors participated in the interpretation of the data, and, along with Dr. Abraham, had complete control over the contents of the manuscript and the decision to submit the manuscript for publication.

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