Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials

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CRD summary
This review assessed the safety of nesiritide compared with noninotrope-based therapies for acutely decompensated heart failure. The authors concluded that nesiritide may be associated with increased deaths compared with control, but further research is required before definitive conclusions can be drawn. The methods of the review methods were not described in full. The authors' cautious conclusions correctly reflect the evidence presented.

Authors' objectives
To assess the safety of nesiritide in comparison with noninotrope-based therapies in the treatment of acutely decompensated heart failure.

Searching
The primary sources of trials were the Food and Drug Administration (FDA), PubMed (restricted to reports published in English; search terms reported) and contents of annual meetings of the American Heart Association, American College of Cardiology and Heart Failure Society (through December 2004). The FDA held documents released by the Cardiovascular and Renal Drug Advisory Committee for meetings in 1999 and 2000 and included new drug application submissions prepared by Scios Inc., the sponsor of the drug.

Study selection
Study designs of evaluations included in the review
Double-blind, parallel-group, randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared a single infusion of nesiritide for at least 6 hours with a control treatment that did not mandate the use of a positive inotropic drug were eligible for inclusion. The included studies compared a 6-hour infusion of nesiritide versus placebo; 3 hours of nesiritide (fixed dose 0.01 to 0.03 microg/kg or adjustable dose 0.1 microg/kg per minute) versus a nitroglycerine-based control or placebo (with re-allocation of the placebo group after 3 hours to the active therapies); and a bolus of nesiritide (0.01 microg/kg per minute) for at least 12 hours versus placebo. Cointerventions included nitrates and diuretics and no positive inotropic agents in one study, while another study allowed the use of positive inotropic agents before, during and after the study drug.

Participants included in the review
Studies of patients with acutely decompensated heart failure were eligible for inclusion. In the included studies the proportion of patients in New York Heart Association category III to IV ranged from 60 to 98%.

Outcomes assessed in the review
Studies that assessed mortality within 30 days were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity. Multiple reports of studies were compared to ensure complete data were obtained without duplication.
Data extraction
One reviewer extracted the data. The reviewers made the following assumptions about patients with missing data: for one RCT they assumed that 2 patients randomised to nesiritide and lost to follow-up were alive at 30 days; in a second RCT they analysed 9 patients who were randomised but not treated according to allocated treatment, and they censored 4 patients lost to follow-up (1 control and 3 nesiritide) at day 5; and in the third RCT they assumed deaths reported between 15 and 30 days occurred at day 30 in patients assigned to nesiritide and at 15 days for patients assigned to control. The reviewers also determined in which patients pulmonary artery catheters and dobutamine were used in one RCT with missing data (details were reported). For each study, the number of deaths within 30 days and the risk ratio (RR) with 95% confidence interval (CI) were calculated.

Methods of synthesis
How were the studies combined?
The adjusted pooled RR of mortality was calculated, along with the 95% CI, using the Mantel-Haenszel fixed-effect model. Kaplan-Meier survival curves were compared using log rank tests. Adjusted and unadjusted multivariate Cox proportional hazard regression models were used.

How were differences between studies investigated?
Crude RRs and 95% CIs were compared among studies and statistical heterogeneity was assessed using the Breslow-Day test. The adjusted Cox proportion hazard model took account of study, treatment and study treatment interactions.

The influence on survival of the use of pulmonary catheter and dobutamine in the one study using these interventions was explored using models with terms for these variables and all first-order interactions between these variables and treatment. Neither pulmonary catheter use nor dobutamine use were significantly associated with survival, so these terms were omitted from the final survival model.

Results of the review
Three RCTs (n=862) were included.

The meta-analysis showed a trend towards higher risk of death with nesiritide compared with the control (RR 1.74, 95% CI: 0.97, 3.12, P=0.059). No statistically significant heterogeneity was found (P=0.58).

Unadjusted 30-day survival curves showed poorer survival with nesiritide than with the control. The hazard ratio (HR) was 1.86 (95% CI: 1.02, 3.41, P=0.059).

The results were similar after adjusting for study (HR 1.80, 95% CI: 0.98, 3.31, P=0.057).

Authors’ conclusions
Nesiritide may be associated with increased deaths in comparison with a control, but further research is required before definitive conclusions can be drawn.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched and attempts were made to minimise publication bias. However, only one bibliographic database was searched, and this search was restricted to English language publications. The methods used to select the studies were not described, so it is not known whether any efforts were made to reduce errors and bias. One reviewer extracted the data, which raises the possibility of bias and errors. Only double-blind RCTs were included, but validity was not assessed.

Adequate information on the individual studies was reported and the methods used to deal with missing data were described. Differences between the studies were described, and the effect of some factors on survival within studies was explored. The studies were appropriately combined in a meta-analysis and statistical heterogeneity was assessed.
The adjusted analysis took account of the effect of many different variables. In two of the three included studies only a small number of deaths were reported in each treatment arm (range: 1 to 6). The authors' cautious conclusions correctly reflect the evidence presented.

Two of the authors received support, honoraria and consulting fees from GlaxoSmithKline. One author owned shares in Johnson and Johnson.

**Implications of the review for practice and research**

**Practice:** The authors stated that until further research is undertaken, it may be prudent to only use nesiritide in patients with acutely decompensated heart failure who fail to respond to combinations of diuretics plus nitroglycerin.

**Research:** The authors stated that a large adequately powered RCT is required to assess the safety of nesiritide compared with noninotrope-based (diuretic plus vasodilator drugs) treatments for acutely decompensated heart failure.

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