



## Evidence-Based Medicine Journal Club

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### Journal club critique

## Nesiritide – Run and hide?

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### Expanded Abstract

#### Citation

Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K: Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005, 293:1900-1905 [1].

#### Background

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.

#### Methods

**Design:** Pooled analysis of randomized controlled trials.

**Objective:** To investigate the safety of nesiritide relative to noninotrope-based control 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 humans, 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 decompensated heart failure, therapy administered as single infusion (> or =6 hours), inotrope not mandated as control, and reported 30-day mortality.

**Data extraction:** Data were extracted from FDA and sponsor documents and corroborated 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.

#### Results

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;  $P = .057$ ).

#### Conclusion

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.

#### Commentary

In 2004, there were more than one million hospitalizations in the United States for congestive heart failure (CHF), and inpatient treatment for this condition accounts for as much as \$35 billion in health care expenditures annually [2]. Standard treatments, such as diuretics, angiotensin converting enzyme (ACE) inhibitors, and digitalis, are not always successful in improving symptoms and may not improve survival. Accordingly, scientists and clinical investigators have been searching for improved agents for the treatment of acutely decompensated CHF.

Nesiritide is a recombinant human B-type natriuretic peptide that increases intracellular cyclic-GMP in vascular smooth muscle cells, leading to smooth muscle relaxation, preload

and afterload reduction, and increased cardiac index in patients with CHF [2]. It is US FDA approved for the treatment of acutely decompensated CHF based on its ability to rapidly reduce the surrogate endpoints of dyspnea and left ventricular filling pressure. Two recent meta-analyses raised concern that nesiritide might lead to worsening renal function [3] and increased mortality [1]. It is this latter study that we review in this journal club critique.

Sackner-Bernstein and colleagues conducted a pooled analysis of short-term risk of death in three large randomized controlled trials of nesiritide in patients with acutely decompensated CHF. They found that treatment with nesiritide was associated with a 74% increased risk of death within 30 days, though this increase was marginally significant ( $p=0.059$ ). The importance of the study in raising the awareness of the potential risks associated with nesiritide cannot be overstated. However, there are a few limitations to this study that deserve consideration.

Because the authors wished to focus on nesiritide's FDA approved indication (treatment of acutely decompensated CHF), this meta-analysis only considered the results of three of the twelve randomized controlled trials of nesiritide. The authors clearly establish their criteria for study selection, including complete 30-day follow-up, noninotrope-based control therapies, and closed-label trial design. However, it would have been useful for the authors to have presented estimates of risk with and without the nine excluded studies, especially if these additional studies also highlight the potential for harm with the drug. While the three studies they examined were randomized trials, there were important differences among the treatment groups. The authors adjusted for these differences, but others have raised concerns about the adequacy of this adjustment [4,5]. Many of the subjects in the three trials received infusions of nesiritide that were on the high end of the approved range, raising the possibility that these higher infusion rates may have been responsible for the trend toward increased mortality.

These limitations notwithstanding, this meta-analysis raises serious concern about the use of nesiritide and highlights the potential risks of drugs that receive FDA approval based on surrogate endpoints as opposed to mortality. The controversy that this and other analyses have generated has been impressive [4-9], prompting an advisory panel review and a "Dear Healthcare Provider" letter in July 2005 from the manufacturer, Scios. This letter stressed that the use of nesiritide should be strictly limited to patients presenting to the hospital with acutely decompensated CHF who have dyspnea at rest and that physicians should carefully consider the potential risk and benefits and the availability of alternative therapies. It goes on to state that the drug should not be used for intermittent outpatient "tune-up" infusions, a common and expensive practice of unproven benefit [6].

To clear up the confusion, Scios is initiating a European registration trial: Evaluating Treatment with Nesiritide in Acute Decompensated Heart Failure (ETNA). The ETNA study will enroll at least 1,900 patients with acutely decompensated CHF in approximately 400 sites in Europe and Latin America. The first patient is expected to be enrolled sometime in 2006. The study will randomize patients to either nesiritide or placebo through a 24-72 hour infusion added to standard care. Importantly, ETNA will prospectively evaluate mortality (through 30 and 180 days) and re-hospitalizations and will also include a pharmacoeconomic analysis.

### Recommendation

Until the results of ETNA are available, we cannot recommend the use of nesiritide for the treatment of acutely decompensated CHF outside the setting of clinical trials.

### Competing interests

The authors declare no competing interests.

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