Reviewer's report

**Title:** Treatment with Nesiritide is Not Associated with Positive Outcomes in Patients Hospitalized for Acute Decompensated Heart Failure

**Version:** 1  **Date:** 9 August 2007

**Reviewer:** John Rumsfeld

**Reviewer's report:**

General
The topic of this study is of high interest, and the study is generally well-conducted. Specific limitations include the single-center setting, and primarily that therapeutic evaluations using observational data can yield associations but cannot determine causality. The authors over-state the findings, and the manuscript should be re-written to be much more circumspect in this regard, as there is high potential for both selection bias and unmeasured confounding.

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**Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)**

1. The principal limitations of this study (as with all observational evaluations of therapeutic efficacy) are selection bias/confounding by indication (the nesiritide patients were much sicker, shown clearly by the patient characteristics/severity of disease measurements provided), and potential for unmeasured confounding (almost certainly the patients who did and didn’t receive nesiritide differed by measures not available in this study). This does not invalidate the observational associations found, and there can still be some value in reporting such observational data as a reflection of ‘real-world’ practice. However, strongly recommend that the authors go through the paper and a) remove all language that implies causality (e.g. ‘significantly increased the odds’, ‘nesiritide remained a significant risk factor’, ‘increase in the odds’, ‘were linked to nesiritide treatment’; b) substitute language that reports associations only (e.g. ‘was associated with higher odds’, etc.); c) consider a propensity matched analysis utilizing all available baseline data on patient demographics, clinical history and comorbidities, and severity of disease – note that this will not obviate the potential for selection bias/unmeasured confounding, but would be more robust than the current risk adjustment; and d) be much more circumspect with regard to implications/discussion....in particular, the Discussion should be toned down – sicker patients will have longer length of stay, cost more, and have worse outcomes....since these patients were also more likely to receive nesiritide the deck was stacked; this must be acknowledged, and the Discussion should note that nesiritide is being used in sicker patients, who have longer LOS, cost more, and have worse outcomes – then, as already is in the final paragraph – make the
call for additional randomized trials evaluating the efficacy and cost effectiveness of nesiritide.

2. Methods: How much missing data was there….and thus, how many patients were excluded from analyses on this basis? If a substantial number and missing data rates relatively low, why was multiple imputation not utilized?

3. Strongly recommend a secondary analysis (or switch this to the primary analysis) utilizing unique patients (18298 instead of 25,330) as the use of repeat admissions likely reflects a clustering of sicker patients (wish associated bias toward more nesiritide use).

4. Why was PROC GENMOD used instead of PROC LOGISTIC for the multivariable analyses, which appear to have been multiple logistic regression?

5. Given the significant baseline differences between the nesiritide and no-nesiritide patients, there is no reason to present (and then reiterate in the Discussion) the unadjusted results. Somewhat related, any additional clinical characteristics (demographic, clinical history and comorbidities, and hospital course in addition to what is provided in the manuscript) available to the authors should be added to Table 1 to better show the ways in which the 2 cohorts differ (and these variables should be utilized in adjustment as noted in earlier comment), with statistical comparison.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

'I declare that I have no competing interests'