Reviewer’s report

Title: Outcomes of Patients Hospitalized for Acute Decompensated Heart Failure: Does Nesiritide Make a Difference?

Version: 2 Date: 21 September 2007

Reviewer: John Rumsfeld

Reviewer’s report:

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

This is a revised manuscript of an observational study of nesiritide use in a real-world setting. The reviewer appreciates the clarifications provided by the authors in their response to initial review (number of centers, low proportion of missing data, etc.). Unfortunately, however, the authors have not fully addressed the primary concern raised about the study – namely that they make causal conclusions about nesiritide and outcomes, which is not possible in an observational study due to the possibility of unmeasured confounding and selection bias in use of the medication in sicker patients. Stratifying by one measure of disease severity does not overcome the selection bias of use of nesiritide in sicker patients. And accounting for repeat admissions using GEE does not overcome any bias of use of nesiritide in sicker patients with multiple admissions (GEE cannot overcome selection bias). And while it is true that a propensity-matched analysis will only deal with measured confounders, it would be more robust – by matching patients on all measured characteristics - than the current risk-adjustment approach, and the authors discussion of the number of covariates was not the reason for suggesting that approach, and the assertion regarding ‘another layer of complexity’ is not a reason to not pursue more robust analytic methods. Nonetheless, propensity models also have limitations and this reviewer will not further suggest that approach, since the authors are not interested in pursuing it. However, the authors should address the repeat patients in the analytic cohort, and should be more circumspect in their language in the manuscript with regard to causality and be open about the limitation of unmeasured confounding and selection bias in observational studies of therapeutic efficacy, such that studies like this are ultimately hypothesis generating.

Therefore, these specific suggestions still remain:

1. Strongly recommend additional analysis (it can be secondary) utilizing unique patients (18298 instead of 25330) to ensure that this supports the primary analysis findings, by eliminating ‘repeat’ patients in the analytic cohort (use their first hospitalization only) which are undoubtedly sicker and may be more likely to receive nesiritide.
2. The following language (or similar) should be added to the limitations section of the Discussion: The principal limitation of this study is the observational design and the fact that it is known/clear that sicker patients receive nesiritide. The study design cannot overcome unmeasured confounding nor selection bias in the therapy, and therefore the results are ultimately hypothesis generating. However, the results of this study provide clear impetus for randomized controlled trials to define the role of nesiritide in the treatment of heart failure.

3. Similarly, while minor and semantic, strongly recommend changing wording in a few places to eliminate causal language. Most important, the Abstract conclusion should be re-worded to avoid causal language to something like: “In this observational study, nesiritide therapy was associated with increased length of stay and pharmacy cost, but not hospital mortality or readmission. Randomized trials are urgently needed to better define the efficacy, if any, of nesiritide in the treatment of decompensated heart failure.” Other specific recommendations include: in the Abstract, the language ‘significantly increase’ is used twice, and ‘increases the risk’ is used once. These should to be changed to ‘are associated with’ (or similar), because causality cannot be determined with this study design. Another example on p. 7, ‘59% increase in the odds’ should be ‘59% higher odds’, and p. 8, change ‘significantly increased the odds’ to ‘was associated with higher odds’.

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'