Author's response to reviews

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

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Response to Reviewer

Dear Editorial Staff: All of the recommended changes have been made. Our paper adheres to the format guidelines of BMC Cardiovascular Disorders. Thank you for your attention. (Total length of response: 2 pages)

Reviewer comment 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.

Authors’ response

We agree. We have conducted a secondary analysis only using unique patients. If a patient was readmitted during the study period for CHF then only their first record was retained. These new results are found in a new table on page 23 (Table 5). The following text was added to the Methods section (underlined for easy identification) on pages 7 and 8:

Secondary Statistical Analysis

To ensure a more homogenous study sample only unique patients were included in a secondary analysis. To clarify, the primary analysis included a group of patients who were admitted multiple times for CHF during the study period. It is likely that these individuals were sicker than CHF patients who were only admitted once during the three-years of observation and therefore more likely to receive nesiritide. To minimize the risk of confounding by disease severity a secondary analysis was performed in which only the record of the initial episode of care was retained if the patient had two or more admissions for CHF. There were 18,195 patients who fell into this category after deleting records with missing values.

Crude and adjusted ORs associated with inpatient nesiritide treatment were calculated using PROC LOGISTIC in SAS. The following four outcomes were studied: hospital mortality, prolonged length of stay (defined below), elevated pharmacy cost (defined below), and readmission to an AHS hospital within 31 days for a cardiac/circulatory system disorder other than CHF. Prolonged length of stay was defined as a length of stay greater than the 75th percentile, > 6 days in our study. Elevated pharmacy cost was defined as a pharmacy cost greater than the 75th percentile, > $928 in our study.

The following text was added to the Results section on page 9:

In a secondary analysis the sample was restricted to only one record per patient. If the patient was admitted more than once for CHF during the three-year study period then only the initial episode of care was retained. Unadjusted and adjusted ORs for the four outcomes of interest are shown in Table 5 for these 18,195 unique patients. The unadjusted hospital mortality OR (Table 5) was slightly attenuated compared to its counterpart in Table 2 but was still statistically significant. The four ORs for readmission within 31 days for a cardiac condition/disorder of the
circulatory system other than CHF (Table 5) were higher than the readmission ORs in Table 2 and were significant at the 0.05-level unlike the readmission ORs in Table 2.

Reviewer comment 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.

Authors’ response

We have now added essentially the same sentence. The following was added per the reviewer’s request to page 12 of our Discussion section:

The principal limitation of this study is the observational design and the fact that it is known that sicker patients receive nesiritide. The study design cannot overcome unmeasured confounding or a bias from the inclusion of a select group of severe patients who were no doubt channeled to the therapy under investigation. 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.

Reviewer comment 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 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’.

Authors’ response

We agree. All of the changes recommended above were made (Abstract p. 2, and Results p. 8). We deleted the text that the reviewer recommended deleting (indicated with the strike through feature) and replaced these words with the suggested text using underlined font. We also deleted the words “if any” from the last sentence of the paper (p. 12) to maintain a neutral, circumspect tone as the reviewer suggested.