

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Efficacy and safety of nesiritide in patients with decompensated heart failure: a meta-analysis of randomized trials
<b>AUTHORS</b>	GONG, Bojun; Wu, Zhineng; Li, Zicheng

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Kawther Alquadan, MD and A. Ahsan Ejaz, MD University of Florida, Gainesville, Florida, USA
<b>REVIEW RETURNED</b>	09-Jun-2015

<b>GENERAL COMMENTS</b>	<p>This is a meta-analysis of 25 clinical trials involving the the use of nesiritide as initial treatment in decompensated heart failure incomparison to placebo, NTG or dobutamine.</p> <p>Major Concerns:</p> <ol style="list-style-type: none"><li>1. One of the main criteria for the inclusion into analysis was that the trial had to be conducted in patients with heart failure. However, the authors have included Study # 25, 26 and 30 for analysis and these studies were not performed in heart failure patients, but in stable patients undergoing cardiac surgery with mostly preserved EF. Therefore, the analysis and consequent results and conclusions may not reflect the aims of the study.</li><li>2. A second issue is the time frame chosen (?) to assess the effect of nesiritide on renal indices (SCreat). Changes in SCreat, i.e., surrogate for AKI, is defined as 0.3mg/dL increase within 48 hours. Were the SCreat values within 48hours or any time during study duration?</li><li>3. A surprising finding is the increased risk for hypertension associated with significant decrease in SVR and increased adverse cardiovascular events with nesiritide. The adverse cardiovascular events associated with nesiritide have mostly been associated with nesiritide-induced hypotension in most trials.</li></ol> <p>Other issues</p> <p>Spelling and grammar errors:</p> <ol style="list-style-type: none"><li>1. Under objective in abstract: Current evidence “ suggests”</li><li>2. In the abstract under methods: Paragraph that states “ Nesiritide was performed a comparison with dobutamine m placebo or nitroglycerin” – sentence dose not make sense.</li><li>3. In abstract under Results section, we should add “and” before – long term mortality- sentence.</li><li>4. In the introduction paragraph: in the sentence – CHF is one of the more frequent reasons for –before( should be” for” ) hospital admission in patient over 65 , and ( should be “with “ instead of and)</li></ol>
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	<p>more than one million people are( delete are ) hospitalized in the Untied States each year</p> <p>5. Under introcuction paragraph also – the sentence of – connected with increased local and systemic release of oxygen free radicals that myocardial dysfunction in patient with syndrome - does not make sense.</p> <p>6. Under introduction section, line 20- it should say – It also increases- instead of increased.</p> <p>7. Under introduction section, line 22- it should say – It also improves- instead of improved.</p> <p>8. Under efficacy outcomes section ,line 9, the sentence “ combing ( I think he meant combining ) data from studies comparing high dose Nesiritide with placebo, the result( should be without “ the” and “results “instead of result “</p> <p>9. Under Cardiovascaular advese events Paragraph: should be hypotension instead of hypertension, and should say symptomatic hypotension instead of hypotension symptomatic, or place a comma after hypotension “ hypotension, symptomatic” and the same thing applies for asymptomatic hypotension.</p> <p>10. Under NON cardiovascular adevse events- can substitute dialysis with “ the need for dialysis or initiation of dialysis”, which applies for all paragraphs throughout the paper.</p> <p>11. Under discussion paragraph , line 3, “ demonstrated no significant increases ( should be increase).</p> <p>12. Under discussion paragraph , line 6 , need to change to hypotension instead of hypertension.</p> <p>13. Under discussion paragraph , line 17 – in what concerns short and long term outcomes.however a meta-anaylsis of 7 randomized controlled trials updated – sentence “ the word however is not needed??</p> <p>14. Under discussion paragraph , line 20- our meta- analysis include a large number – should be larger number-</p> <p>15. Under discussion paragraph , line 48, next page – typo “ renal plasma flow- and not folw.</p> <p>16. Under discussion paragraph , line 51- may be it should say – Nesiritide has instead of had</p> <p>17. Under discussion paragraph , line 60 - sentence – mild symptoms- should say with mild symptoms???</p> <p>18. Under discussion paragraph , line 70 , should say hypotension , instead of hypotensive.</p> <p>19. Under discussion paragraph , line 73, should say “One study documented” – instead of study had been documented.</p> <p>20. Under limitation paragraph – “ Finally this analysis have not” should say has not.</p>
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<b>REVIEWER</b>	Gang Wang Department of Emergency Medicine, the Second Affiliated Hospital, Xi'an Jiaotong University, Xi'an, China
<b>REVIEW RETURNED</b>	07-Jul-2015

<b>GENERAL COMMENTS</b>	<p>The authors investigated the efficacy and safety of nesiritide on patients with decompensated heart failure using meta-analysis. This study involved 25 RCTs and revealed that nesiritide was not associated with a worsening of renal function and risk of mortality.</p> <p>Major comments:</p> <p>1. There are a few meta-analyses published before in the same topic and showed similar results. Especially, Yan et al had showed that neither mortality nor readmission was reduced or increased for any</p>
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	<p>length of follow-up after treatment with Nesiritide in addition to conventional treatment in adult patients with ADHF (Int J Cardiol. 2014 Dec 15; 177(2):505-9).</p> <p>2. The current study demonstrated that nesiritide was not associated with a worsening of renal function in the abstract, but the results in page 8 did not support the conclusion. Moreover, a current meta-analysis also found that nesiritide may have a dose-dependent effect on renal function in patients with acute decompensated heart failure (PLoS One. 2015 Jun 24; 10(6):e0131326).</p> <p>Papers mentioned above should be cited in the manuscript. More data mining is needed to improve the novelty and academic significance.</p> <p>Other comments: The paper needs extensive language improvement.</p>
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<b>REVIEWER</b>	Dr Victoria Allgar University of York
<b>REVIEW RETURNED</b>	21-Oct-2015

<b>GENERAL COMMENTS</b>	<p>This states that it is a meta-analysis of all randomized trials to obtain the best estimates of efficacy and safety of nesiritide for the initial treatment of decompensated heart failure.</p> <p>One aspect is the choice of control group (control therapy), which includes nesiritide versus placebo, nitroglycerin, or dobutamine (grouped as control therapy). Table 2 does provide some split and demonstrates differences depending on the comparator, yet Figure 2 combines these. I would like to see a separate figure for each comparison, and the objective changed to reflect the 'control therapy' rationale and a discussion in the background regarding these other comparators.</p> <p>The approach to analysis is appropriate for the analysis.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Kawther Alquadan, MD and A. Ahsan Ejaz, MD

Institution and Country: University of Florida, Gainesville, Florida, USA

Please leave your comments for the authors below

This is a meta-analysis of 25 clinical trials involving the the use of nesiritide as initial treatment in decompensated heart failure incomparison to placebo, NTG or dobutamine.

Major Concerns:

1. One of the main criteria for the inclusion into analysis was that the trial had to be conducted in patients with heart failure. However, the authors have included Study # 25, 26 and 30 for analysis and these studies were not performed in heart failure patients, but in stable patients undergoing cardiac surgery with mostly preserved EF. Therefore, the analysis and consequent results and conclusions

may not reflect the aims of the study.

→**Thank you very much to mention this. Considering that study 25, 26, and 30 were not performed in heart failure patients, we had deleted these studies.**

2. A second issue is the time frame chosen (?) to assess the effect of nesiritide on renal indices (SCreat). Changes in SCreat, i.e., surrogate for AKI, is defined as 0.3mg/dL increase within 48 hours. Were the SCreat values within 48 hours or any time during study duration?

→Study # **21, 28, and 36** have mentioned the definition of Scr.

**In study 21**, it has mentioned that most studies defined WRF as a rise in serum creatinine of  $\geq 0.3$  mg/dl from baseline, with final creatinine levels  $> 1.5$  mg/dl. In this study, they chose a final creatinine level  $> 1.5$  mg/dl to exclude those patients who developed an increase in serum creatinine of  $\geq 0.3$  mg/dl from baseline, but with final levels still being within normal range. It seems unreasonable to categorize these patients as 'WRF' in the presence of normal renal function. They also analysed the incidence of WRF using a less strict definition of increase in serum creatinine levels ( $\geq 0.5$  mg/dl), as done in some previous studies. We valued serum creatinine concentrations at day 3.

**In study 28**, serum creatinine concentrations with NTG infusion at 48 hours when compared with baseline. We valued serum creatinine concentrations at 48 Hours.

**In study 36**, serum creatinine concentrations is  $> 2.5$  mg/dL at admission.

We valued serum creatinine concentrations at discharge.

3. A surprising finding is the increased risk for hypertension associated with significant decrease in SVR and increased adverse cardiovascular events with nesiritide. The adverse cardiovascular events associated with nesiritide have mostly been associated with nesiritide-induced hypotension in most trials.

→There is spelling error in the abstract. We have changed "hypertension" into "hypotension".

Other issues

Spelling and grammar errors:

1. Under objective in abstract: Current evidence "suggests".
2. In the abstract under methods: Paragraph that states "Nesiritide was performed a comparison with dobutamine m placebo or nitroglycerin" – sentence dose not make sense.
3. In abstract under Results section, we should add "and" before – long term mortality- sentence.
4. In the introduction paragraph: in the sentence – CHF is one of the more frequent reasons for –

- before( should be” for” ) hospital admission in patient over 65 , and ( should be “with “ instead of and) more than one million people are( delete are ) hospitalized in the Untied States each year
5. Under introduction paragraph also – the sentence of – connected with increased local and systemic release of oxygen free radicals that myocardial dysfunction in patient with syndrome - does not make sense.
  6. Under introduction section, line 20- it should say – It also increases- instead of increased.
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  9. Under Cardiovascaular advese events Paragraph: should be hypotension instead of hypertension, and should say symptomatic hypotension instead of hypotension symptomatic, or place a comma after hypotension “ hypotension, symptomatic” and the same thing applies for asymptomatic hypotension.
  10. Under NON cardiovascular adevse events- can substitute dialysis with “the need for dialysis or initiation of dialysis”, which applies for all paragraphs throughout the paper.
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  18. Under discussion paragraph, line 70, should say hypotension , instead of hypotensive.
  19. Under discussion paragraph , line 73, should say “One study documented” – instead of study had been documented.
  20. Under limitation paragraph – “Finally this analysis have not” should say has not.
- We have done.**

Reviewer: 2

Reviewer Name: Gang Wang

Institution and Country: Xi’an Jiaotong University, Xi’an, China.

Please leave your comments for the authors below

The authors investigated the efficacy and safety of nesiritide on patients with decompensated heart failure using meta-analysis. This study involved 25 RCTs and revealed that nesiritide was not associated with a worsening of renal function and risk of mortality.

Major comments:

1. There are a few meta-analyses published before in the same topic and showed similar results. Especially, Yan et al had showed that neither mortality nor readmission was reduced or increased for any length of follow-up after treatment with Nesiritide in addition to conventional treatment in adult patients with ADHF (Int J Cardiol. 2014 Dec 15; 177(2):505-9).

2. The current study demonstrated that nesiritide was not associated with a worsening of renal function in the abstract, but the results in page 8 did not support the conclusion. Moreover, a current meta-analysis also found that nesiritide may have a dose-dependent effect on renal function in patients with acute decompensated heart failure (PLoS One. 2015 Jun 24; 10(6):e0131326).

Papers mentioned above should be cited in the manuscript. More data mining is needed to improve the novelty and academic significance.

→**We have added the two studies mentioned above.**

Other comments:

The paper needs extensive language improvement.

Reviewer: 3

Reviewer Name: Dr Victoria Allgar

Institution and Country: University of York, UK.

Please leave your comments for the authors below

This states that it is a meta-analysis of all randomized trials to obtain the best estimates of efficacy and safety of nesiritide for the initial treatment of decompensated heart failure.

One aspect is the choice of control group (control therapy), which includes nesiritide versus placebo, nitroglycerin, or dobutamine (grouped as control therapy). Table 2 does provide some split and demonstrates differences depending on the comparator, yet Figure 2 combines these. I would like to see a separate figure for each comparison, and the objective changed to reflect the 'control therapy' rationale and a discussion in the background regarding these other comparators.

→**We have provided some split depending on the comparator in figure 2 and have changed the discussion in the background about other comparators.**

The approach to analysis is appropriate for the analysis.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Gang Wang Xi'an Jiaotong University
<b>REVIEW RETURNED</b>	05-Dec-2015

<b>GENERAL COMMENTS</b>	The reviewer completed the checklist but made no further comments.
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<b>REVIEWER</b>	Dr Victoria Allgar University of York, England
<b>REVIEW RETURNED</b>	07-Dec-2015

<b>GENERAL COMMENTS</b>	<p>This is a meta-analysis of all randomized trials to obtain the best estimates of efficacy and safety of nesiritide for the initial treatment of decompensated heart failure.</p> <p>The meta analysis is appropriately undertaken, with appropriate assumptions. The data tables are clear and the figures stand alone from the text.</p> <p>Overall a well written paper.</p>
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