Author's response to reviews

Title: A Randomised Controlled Trial of Ivabradine and Atorvastatin in Emergent Orthopaedic Lower Limb Surgery: A Mechanistic Study of Peri-Operative Myocardial Injury and Its Prevention Using Computed Tomography Coronary Plaque Imaging and Novel Biomarkers of Cardiovascular Stress and Lipid Metabolism: Study Protocol For a Randomized Controlled Trial.

Authors:

Nima Rudd (nima.rudd@nh.org.au)
Ivan Subiakto (ivansubiakto@gmail.com)
Muhammad Asrar ul Haq (hissper@me.com)
Vivek Mutha (vivekm@me.com)
William van Gaal (w.vangaal@nh.org.au)

Version: 4  Date: 4 August 2014

Author's response to reviews: see over
August 4, 14

Editor in Chief


Dear editors,

Thank you for the opportunity to address the reviewer’s feedback and provide a revised version of this manuscript. In the revised document we have reformatted the manuscript as suggested. We have:

1. Added the email addresses for all the authors
2. Moved the trial status
3. Reformatted the table as per guidelines

Furthermore, as per the reviewer’s suggestions, we have:

1. Revised the background section, amended the sections 1-3, discussed role of ivabradine in section 1, role of atorvastatin in section 2, and biomarkers in section 3.
2. Have critically revised the section on biomarkers and omitted the non relevant details to make it concise and relevant.
3. We have reviewed the spelling and grammer to minimize the language errors.
4. In the “methods” section, we have clustered all clinical outcomes first and corrected the sequence of biomarkers.
Overall the manuscript looks much improved and we thank the reviewer for taking time and providing valuable suggestions. A further point-by-point discussion in detail follows. Please do not hesitate to contact me if any further queries.

Yours Sincerely

Dr M Asrar ul Haq
Reviewer Comments:

Major corrections:
Background:
- Still, it lacks a clear and to the point structure. The section “1. Myocardial stress and role of Ivabradine” flows nicely up to the discussion on BNP and biomarkers. I would finish section 1 at “No randomised studies with Ivabradine in patients undergoing cardiac or non-cardiac surgery has been performed to date.” I would then have a second section clearly discussing the role of Atorvastatin (kind of a mirror image of section 1 on Ivabradine). I would finally cluster all the discussion around cardiac biomarkers together at the end of the background section under the same subtitle (e.g. Current and novel cardiac biomarkers and imaging modalities reflecting myocardial stress and plaque burden). And I still think that it would be possible to cut a bit of information about the biomarker to make it about the same length as the other sections.

Thank you once again for your valuable input. We have amended the structure accordingly:

Section 1. Myocardial stress (Myocardial oxygen supply-demand imbalance) and role of Ivabradine

Section 2. Acute Coronary Syndromes and role of Atorvastatin

Section 3. Novel Cardiac Biomarkers.

Furthermore, we have revised all 3 sections to make all the information relevant to the section as well as to the manuscript scope. Particularly the section 3 on biomarkers have been concised as per above.

Minor revisions:
Abstract:
- Enroll (spelling)
Corrected.

- In background, I would add: “study Ivabradine and Atorvastatin as protective pharmacotherapies against PMI in the context of orthopedic surgery”.

Updated:
“We investigate the presence of elevated novel cardiac markers and pre-operative coronary artery plaque through contemporary laboratory technique to determine the correlation with PMI, and study Ivabradine and Atorvastatin as protective pharmacotherapies against PMI in the context of orthopedic surgery.”
- “The benefit from reduction in the incidence and magnitude of PMI by IVabradine and Atorvastatin is derived primarily in patients with greater atherosclerotic burden as measured by higher CT coronary calcium scores.” I would again mention that this is a hypothesis, not a confirmed statement.

Amended:
“We sought to see if the benefit from reduction in the incidence and magnitude of PMI by IVabradine and Atorvastatin is derived primarily in patients with greater atherosclerotic burden as measured by higher CT coronary calcium scores.”

**Article (Methods):**
- “Currently the recruitment and patient enrollment is continuing.” It should be removed as it is repeated just below in trial status.

Removed.

- *In secondary outcomes measures, I would cluster all clinical outcomes first (1-3) and make the following corrections:*

  4) **Markers of myocardial stress:** NT-proBNP (pmol/L), MR-proANP (pmol/L), MR-proADM (nmol/L) and CT-proET-1 (pmol/L)

  5) **Markers of plaque burden:** sPLA2 and Lp-PLA2 mass (%) and activity (%)

- *In safety outcomes, I would add “2. Liver enzyme elevation > 3 times the upper limits of normal (ALP, GGT,AST and ALT measured in U/L ) requiring cessation of Atorvastatin.”*

In Methods, we agreed with the suggestion to cluster all clinical outcomes first. After amendment:

1) Myocardial infarction according to the universal definition

2) Death in-hospital, at 30 days and 12 months

3) Stroke in-hospital, at 30 days and 12 months

4) **Markers of myocardial stress:** NT-proBNP (pmol/L), MR-proANP (pmol/L), MR-proADM (nmol/L) and CT-proET-1 (pmol/L)  (Markers of myocardial stress )

5) **Markers of plaque burden:** sPLA2 and Lp-PLA2 mass (%) and activity (%).

**Safety outcomes:**

1) Symptomatic bradycardia or heart block requiring cessation of Ivabradine

2) Liver enzyme elevation > 3 times the upper limits of normal (ALP, GGT,AST and ALT measured in U/L ) requiring cessation of Atorvastatin.
Furthermore, we have reviewed the spelling and grammar of the manuscript extensively to minimize the language errors. The title has been reformatted as per the comments. We once again thank the reviewer for the valuable feedback and helping us improve the article.

**Editorial Comments:**

1. *Please include all author emails on your title page.*
   We have provided the emails in our resubmitted manuscript now.

2. *Please remove the tables from the main body of your manuscript. For more information on where to include the tables please see the following link:*
   [http://www.trialsjournal.com/authors/instructions/studyprotocol#preparing-tables](http://www.trialsjournal.com/authors/instructions/studyprotocol#preparing-tables).

   Table 1 has been labelled as “Table 1. Calcium Score Interpretation” and moved down to the end of manuscript as per the guidelines.

3. *Move your Trial Status below your Discussion.*
   The trial status has been moved below the discussion in our manuscript.