Reviewer's report

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.

Version: 3 Date: 24 July 2014

Reviewer: Stacy O’Blenes

Reviewer's report:

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 (1 and 2).

Minor corrections:

Title:
- Needs uniform and proper capitalization

Abstract:
- Enroll (spelling)
- In background, I would add: “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.

Article (Background):
- “In our study of patients undergoing urgent orthopaedic surgery, PMI [...]”. I would say “In a previous study of patients undergoing urgent orthopaedic
surgery, PMI, as defined
- by troponin I elevation, occurred in 52.9% of our population” to clarify that this isn’t part of the results of your current trial that is brought up.
- “We subsequently performed an intervention study of patients with troponin elevation following emergent surgery for fractured neck of femur (NOF), and randomised patients to standard care or referral to the cardiology unit.” We need a reference at the end of that paragraph.

Article (Methods):
- “Currently the recruitment and patient enrollment is continuing.” It should be removed as it is repeated just below in trial status.
- In secondary outcomes measures, I would cluster all clinical outcomes first (1-3) and make the following corrections:
  4) Markers of myocardiac 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 protocols, I would replace the subtitle “Lipidomics, sPLA2 Mass and Activity” by “Markers of Plaque Burden”

There are still many spelling mistakes and inconsistencies in capitalization. Please get an external proof reader.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.