

## 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>	Performance of high sensitive cardiac troponin T assay to detect ischemia at PET-CT in low-risk patients with acute coronary syndrome: a prospective observational study.
<b>AUTHORS</b>	Morawiec, Beata; Fournier, Stephane; Tapponnier, Maxime; Prior, John; Monney, Pierre; Dunet, Vincent; Lauriers, Nathalie; Recordon, Frederique; Trana, Catalina; Iglesias, Juan-Fernando; Kawecki, Damian; Boulat, Olivier; Bardy, Daniel; Lamsidri, Sabine; Eeckhout, Eric; Hugli, Olivier; Muller, Olivier

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Prof P O Collinson St George's Hospital and Medical School University of London UK
<b>REVIEW RETURNED</b>	18-Jan-2017

<b>GENERAL COMMENTS</b>	<p>The authors have performed a prospective observational study to define a level of high sensitivity cardiac troponin which could be used to exclude ischaemia detected by PET CT. The authors find that they value around the limit of detection has a high negative predictive value in this regard.</p> <p>The authors acknowledge the problems of the study in that it was a small number of participants and has a potential verification bias. However, the authors do not mention in the discussion, which really rather strengthens their case, that there have been a number of studies that have looked at very low levels of troponin to exclude subsequent cardiac events and it has been suggested that sensitive troponin measurements (both cTnT and cTnI) at the limit of detection can be used for this purpose. Their study is in fact one of the first that has combined stress induced ischaemia with troponin measurement and they really should discuss their findings in the context of these other studies. Their study in fact provides supportive evidence that this strategy is safe.</p> <p>Body R, Carley S, McDowell G, Jaffe AS, France M, Cruickshank K et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. <i>J Am Coll Cardiol</i> 2011;58:1332-9.</p> <p>Zhelev Z, Hyde C, Youngman E, Rogers M, Fleming S, Slade T et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-</p>
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	analysis. BMJ 2015;350:h15.  Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015.
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<b>REVIEWER</b>	Christian Müller University Hospital Basel, Switzerland
<b>REVIEW RETURNED</b>	18-Jan-2017

<b>GENERAL COMMENTS</b>	The paper is well written and addresses an important topic. Some suggestions: 1) Please put your findings in context with previous studies examining hs-cTnT and hs-cTnI in the detection of exercise-induced myocardial ischemia. Unfortunately, the current manuscript lacks a discussion of previous studies on this topic. 2) Methods: Please add 95% CI to all your point estimates of NPV, sensitivity , etc. This will help the reader to understand the important implications of the small sample size and the low number of events. 3) Results: Table 1: Please add two columns for patients with and those without ischemia
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### VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1:

We would like to thank reviewer 1 for his suggestions that we included in the present version of the manuscript.

The authors have performed a prospective observational study to define a level of high sensitivity cardiac troponin which could be used to exclude ischemia detected by PET CT. The authors find that they value around the limit of detection has a high negative predictive value in this regard.

The authors acknowledge the problems of the study in that it was a small number of participants and has a potential verification bias. However, the authors do not mention in the discussion, which really rather strengthens their case, that there have been a number of studies that have looked at very low levels of troponin to exclude subsequent cardiac events and it has been suggested that sensitive troponin measurements (both cTnT and cTnI) at the limit of detection can be used for this purpose. Their study is in fact one of the first that has combined stress induced ischemia with troponin measurement and they really should discuss their findings in the context of these other studies. Their study in fact provides supportive evidence that this strategy is safe.

Body R, Carley S, McDowell G, Jaffe AS, France M, Cruickshank K et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. J Am Coll Cardiol 2011;58:1332-9.

Zhelev Z, Hyde C, Youngman E, Rogers M, Fleming S, Slade T et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-analysis. BMJ 2015;350:h15.

Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015.

These 3 references have been added in the discussion and we described our results by comparing them to these studies. All changes have been marked in yellow in the manuscript file.

Reviewer: 2

We would like to thank reviewer 1 for his suggestions that we included in the present version of the manuscript. The changes have been marked in yellow in the manuscript file.

1) Please put your findings in context with previous studies examining hs-cTnT and hs-cTnI in the detection of exercise-induced myocardial ischemia. Unfortunately, the current manuscript lacks a discussion of previous studies on this topic.

We added 6 references in the discussion section and discuss our results in context of these studies.

1. Hoeller R, Rubini Giménez M, Reichlin T, et al. Normal presenting levels of high-sensitivity troponin and myocardial infarction. Heart 2013;99(21):1567-72.
2. Rubini Giménez M, Hoeller R, Reichlin T, et al. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. Int J Cardiol 2013;168(4):3896-901.
3. Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. J Am Coll Cardiol 2011;58:1332-9.
4. Shah AS, Anand A, Sandoval Y, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015; 386: 2481–88.
5. Zhelev Z, Hyde C, Youngman E, et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-analysis. BMJ 2015;350:h15.
6. Boeddinghaus J, Reichlin T, Cullen L, et al. Two-Hour Algorithm for Triage toward Rule-Out and Rule-In of Acute Myocardial Infarction by Use of High-Sensitivity Cardiac Troponin I. Clin Chem 2016;62(3):494-504.

2) Methods: Please add 95% CI to all your point estimates of NPV, sensitivity , etc. This will help the reader to understand the important implications of the small sample size and the low number of events.

Thank you for this suggestion, it has been done.

3) Results: Table 1: Please add two columns for patients with and those without ischemia.

Thank you for this suggestion, it has been done.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Professor Paul Collinson St Georges University of London
<b>REVIEW RETURNED</b>	16-Mar-2017

<b>GENERAL COMMENTS</b>	No further comments
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