

## 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>	Outcome of revascularization in stable coronary artery disease without ischaemia: a Danish registry-based follow-up study
<b>AUTHORS</b>	Simonsen, Jane; Mickley, Hans; Johansen, Allan; Hess, Søren; Thomassen, Anders; Gerke, Oke; Jensen, Lisette; Hallas, Jesper; Vach, Werner; Hoiland-Carlsen, Poul

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Giuseppe Biondi-Zoccai Sapienza University of Rome, Latina, Italy
<b>REVIEW RETURNED</b>	09-May-2017

<b>GENERAL COMMENTS</b>	<p>The authors report an interesting observational study comparing revascularization vs medical therapy in patients without ischemia at MPI.</p> <p>Despite the work strengths, I recommend addressing the following comments:</p> <ol style="list-style-type: none"><li>1. Methods and Results: The very small sample (26 pts revascularized) requires a core analysis with propensity score matching or inverse probability of treatment weighting, which can be easily done in Stata.</li><li>2. Methods and Results: An analysis exploiting a scoring system for necrosis (eg the MNS, Nudi et al, J Nucl Cardiol 2017) could be useful as exploratory analysis.</li><li>3. Methods, Results and Discussion: Pooling together PCI vs CABG could be seen as inappropriate as CABG also protects from atherothrombosis progression. In addition, PCI with DES is altogether different from PCI with BMS, and could also have protective effects on atherosclerotic plaque with moderate severity.</li><li>4. Discussion: Even in the absence of ischemia, patients with CCS scores 3 or 4 or unprotected left main disease are considered appropriate revascularization candidates by many.</li><li>5. Discussion: What is your take on balanced ischemia? While many nuclear cardiologists don't believe in its clinical importance, it may have caused some false negative MPI tests.</li></ol>
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<b>REVIEWER</b>	Carlos Iribarren Kaiser Permanente Division of Research
<b>REVIEW RETURNED</b>	25-May-2017

<b>GENERAL COMMENTS</b>	<p>The title could actually state what they found: "exceptional revascularization not a good choice", rather than a question. From the source population of 2,157, 1,327 had normal myocardial perfusion scans, 278 had fixed perfusion defects. How about the remaining 552? Did they have reversible perfusion defects? It would</p>
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	<p>have been interesting to see what their outcomes were (Revasc vs. Med).</p> <p>Explain the CCS (coronary calcium score?) of 1,2,3</p> <p>The main problem with this study is the very small number of events in the revascularization groups: 7 MI/cardiac deaths in the normal MPS group and 4 MI/cardiac deaths in the fixed defects group. Any statistical modeling will have questionable power, and the efficiency of the multivariate adjustment is also less than ideal. The matching approach is a good alternative, but not enough detail is given (i.e., matching variables). At a minimum, the authors should provide reassurance that comparison groups are balanced with respect to sex, known CAD and number of stenotic vessels.</p>
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### VERSION 1 – AUTHOR RESPONSE

#### Reviewer #1:

1. As stated in the second paragraph of the Strengths and Limitations section in the Discussion, the inequality of the Med and the Revasc groups made it unreasonable to estimate a propensity score. We argue from the literature that a Cox model adjusted for individual covariates is comparable to results from a propensity score-adjusted Cox model. The supplementary analysis of matched subgroups supports the findings. We now composed a Supplementary Material demonstrating equilibrium between covariates after matching.
2. At our institution we have a tradition for using a 20-segment model of the left myocardium. Since Summed Stress Score has, however, been reported differently over the years, in the present study we categorized defects as small, moderate, or large from their extent and severity, and stratification according to these can be seen from Table 1 b) and Table 4 b).
3. Pooling together PCI vs. CABG: We agree with the reviewer. We added this to the Strengths and Limitations paragraph of the Discussion section.  
PCI with DES vs. PCI with BMS: This is true. One of the authors did another work on this subject (JACC 2007;50:463-70) which is included in the Reference List. Unfortunately, from the present material we do not have detailed information on the myocardial infarctions (whether they were stent thromboses or not). However, we felt that inclusion of this in our discussion would be too extensive.
4. This is exactly what makes our results interesting, since adjustment for angiographic variables did not change the Revasc/Med HR significantly. As can be seen from Table 2, none of the revascularized patients had stenosis of the left main. It is true that angina is a major cause of subsequent revascularization as stated in the paragraph on The Use of MPS in the Discussion section. We agree that the chance of amelioration of symptoms may be higher in case of more severe angina. Our work deals with objective clinical events only according to previous considerations (EuroIntervention 2016;11:1118-24).
5. We agree that there is a potential risk of false negative MPI tests in case of 3-VD which occurred in some of the patients, cf. Table 2. However, as stated in the MPS paragraph of the Materials and Methods section our criterion for normal MPI included normalcy with respect to non-perfusion markers like wall thickening/motion and LVEF/dilation. This renders diffuse ischaemia unlikely, which has now been added to the the paragraph on The Use of MPS in the Discussion section.

#### Reviewer #2:

1. In 25 cases, the MPS was categorized as inconclusive, e.g., in the case of normal perfusion but abnormal LVEF. 527 patients had reversible perfusion defects, and the outcome of these is described in EuroIntervention 2016;11:1118-24.
2. The angina score from the Canadian Cardiovascular Society is mentioned in the Follow-up paragraph of the Materials and Methods section.
3. We omitted this in the first place in order not to confuse the picture. We now composed a Supplementary Material yielding details on the matching approach.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Giuseppe Biondi-Zoccai Sapienza University of Rome  I have consulted for Abbott Vascular
<b>REVIEW RETURNED</b>	27-Jun-2017

The reviewer completed the checklist but made no further comments.

<b>REVIEWER</b>	Carlos Iribarren Kaiser Permanente Division of Research
<b>REVIEW RETURNED</b>	27-Jun-2017

<b>GENERAL COMMENTS</b>	My only lingering concern is clarifying (rephrasing) the fourth point in strengths & limitations:  "The major limitation was the small material with small subsets of patients revascularized"  should say "the small number of patients undergoing revascularization" and including the number in parenthesis.
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