Author’s response to reviews

Title: Oxygen Therapy in Patients with ST Elevation Myocardial Infarction based on the culprit vessel: Results from the Randomized Controlled SOCCER Trial

Authors:

Arash Mokhtari (arash.mokhtari.0561@med.lu.se)
Mahin Akbarzadeh (mahin.a.akbarzadeh@skane.se)
David Sparv (david.sparv@med.lu.se)
Pallonji Bhiladvala (pallonji.bhiladvala@med.lu.se)
Håkan Arheden (hakan.arheden@med.lu.se)
David Erlinge (david.erlinge@med.lu.se)
Ardavan Khoshnood (ardavan.khoshnood@med.lu.se)

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Author’s response to reviews:

Dear Editor,

We would hereby like to submit a revised version of our manuscript “Oxygen Therapy in Patients with ST Elevation Myocardial Infarction based on the culprit vessel: Results from the Randomized Controlled SOCCER Trial”.

We are grateful for the thoughtful comments of the Editor and the Reviewers. We have made all the changes and believe our manuscript has been significantly improved. Our replies to the comments are presented following this statement.

It is our hope that the manuscript can now be accepted for publication in BMC Emergency Medicine.

Yours sincerely,

Ardavan Khoshnood

W Szczeklik (Reviewer 2): Thank you for answering the comments.
Please see some additional suggestions.

1. The authors should explain in the abstract the high drop-out rate. Otherwise it reads as unreliable data, as they recruited 160 patients and analysed only 95.

ANSWER: Thank you for this suggestion. We have in abstract now added that because of primarily technical issues with the CMRI, only 95 patients were included.

2. Please be more clear what you mean by modified intention to treat analysis.

ANSWER: This a very good point. We added “modified” after the comments of the previous reviewer, Dr. Young. We have, however, decided to remove the term “modified” as well as “intention-to-treat” altogether in accordance with recommendations in the literature (Abraha et al. BMJ 2010;340:c2697; Gupta et al. Perspectives in clinical research, 2(3), 109–112) since the number of excluded patients is large, and instead explain the exclusion of patients.

3. In table 2. I would not give P values for chi-squared comparisons of treatment (ex. 0 vs 1 for inotropes) due to small numbers and no possibility to perform reliable statistical tests.

ANSWER: We have removed the P-value column from Table 2.

J Grensemann (Reviewer 3): In this manuscript, Khoshnood et al. report a sub-group analysis of the already published SOCCER trial evaluating the effect of supplemental oxygen on myocardial salvage index (MSI) in patients with ST elevation myocardial infarction. In this sub-group analysis, patients were grouped according to the culprit vessel, i.e. LAD vs. non-LAD. This is an interesting and novel idea and the rationale is now sufficiently outlined in the manuscript. The manuscript is well written, and the authors have adequately addressed the remarks of the previous reviewers. However, in my opinion, one remaining issue needs further clarification:

As Prof Young and Prof Szczeklik have commented, the group sizes were rather small and it is not clear if the study may be underpowered. Khoshnood et al. have calculated a sample size of 100 patients for the detection of an MSI difference of 15% between the O2 and air group with a SD=20 for a power of 0.96 and alpha of 0.05. This yields an effect size of 0.75 and the authors have apparently used a two-tailed approach to obtain a sample size of 100 patients. Unfortunately, CMRI results and thus MSI values were only available for 95 patients overall and for only 46 patients in the studied sub-group with a culprit lesion in the LAD. Therefore, the analysis does not fulfil the calculated sample size. Because the presented sample size calculation is identical to the calculation in the original SOCCER publication, I assume that the authors may have included the wrong sample size calculation for this sub-group analysis by mistake.

Lowering the power to 0.8 reduces the sample size to 58 for a two-tailed approach and to 46 for a one-tailed approach. Since Khoshnood et al. hypothesize that O2 in LAD lesions would not
provide benefits, a two-tailed approach seems reasonable. The available 2x 23 = 46 patients would be sufficient to reject the null-hypothesis above a difference of 17%, at a SD 20 (effect size 0.85), power 0.8, alpha 0.05, two-tails. The last calculation could make sense for a secondary sub-group analysis, albeit the power is lower increasing the risk for type II error, which is already addressed in the limitations section.

ANSWER: We are grateful for these comments and agree on the limitation which we have pointed out in the limitation section, as you also have pointed out.

Based on your comments we had several meetings with our statistical staff and have made some changes. We have added additional comments to the statistical analysis section of the manuscript, and we have changed Tables 5 and 6 also. The changes do not in any way change our results, discussion or conclusion. We believe, however, that the changes have been necessary based on your comments.

The CONSORT-statement recommends against post hoc power calculations, and state confidence intervals should be enough to indicate the power (http://www.consort-statement.org/checklists/view/32--consort-2010/83-sample-size). We have based on our discussions with the statistics team as well as the CONSORT-statement recommending against a post hoc power calculation, decided to not include a power calculation.

Minor points: (page numbers referring to PDF-file)

- The primary outcome measure was the MSI. I suggest reporting the primary outcome measure before other values in the abstract and the tables.

- P14 L17: should read "previously"

- P15 L17 dropout instead of fallout

ANSWER: We have made all of the suggested changes.

Thank you very much for your time.