Reviewer’s report

Title: Effect of intracoronary agents on the no-reflow phenomenon during primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction: a network meta-analysis

Version: 1 Date: 19 Sep 2017

Reviewer: Islam Elgendy

Reviewer's report:

In this revised manuscript, Niu et al performed a network meta-analysis to compare the effect of 7 different intra-agents on no-reflow in patients undergoing primary PCI. The authors identified 41 trials with 4,069 patients which met their inclusion criteria. On network meta-analysis, anisodamine ranked as the highest agent in terms of improvement of surrogate markers as (myocardial infarction flow grade and ST segment resolution), as well as LV ejection fraction and reduction in major adverse cardiac events (MACE), and nitroprusside ranked second. The authors concluded that intracoronary administration of anisodamine improved myocardial reperfusion, cardiac function, and clinical outcomes in patients with STEMI undergoing PPCI and suggested that more rigorous randomized trials to verify this effect.

The meta-analysis is well conducted and the manuscript is well written.

I have some few remarks and suggestions for the authors' consideration:

- Although anisodamine ranked as the highest in terms in efficacy for all the outcomes on the network meta-analysis, it is important to note that this observation is based on a small number of patients (208). This is evident by the fairly wide confidence intervals for most of the analyses. Thus I believe that the authors need to consider that these findings are rather hypothesis generating than to conclude that "anisodamine improved myocardial reperfusion, cardiac function, and clinical outcomes". I agree with the authors' second part of the conclusion regarding that future larger trials are needed to confirm the findings.

- The definition of "control" or "standard care" is rather vague (i.e., could be other therapy or placebo) and is likely to be different across the trials. Since the authors are performing a network meta-analysis to compare the different therapies, it might of interest to clarify how "control" or "standard care" was defined across the trials. Further, the authors might consider performing a sensitivity analysis for the trials with a rather more uniform definition such as placebo.
Along this line, the definition of MACE is not uniform across the trials, thus it might be important to the readers if the authors could provide the definition of MACE across the trials. Also, performing a sensitivity or secondary analysis with a rather uniform definition for MACE might be of interest. In addition, as the authors identified the range for follow up for MACE was variable, did the authors consider performing a secondary analysis to compare short term MACE (e.g. < 1 month) versus longer MACE?

In page 21, the authors make note of the importance of complete revascularization for multivessel disease during primary PCI and the impact on mortality, and make reference to the observational study by Quadri et al. I agree with the authors that complete revascularization might be of benefit, however it is important to highlight that randomized trials have shown that complete revascularization for multivessel disease reduces the risk of MACE due to a reduction in the risk of revascularization with no impact on mortality, thus I would suggest that the authors refer to the randomized trials rather than an observational study.

Another important point to consider in the discussion, that the improvement in surrogate markers does not always translate to an improvement in clinical outcomes such as the case with aspiration thrombectomy (Circulation: Cardiovascular Interventions. 2015:8:e002258).

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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