Author's response to reviews

Title: Improved clinical outcome after invasive management of patients with recent myocardial infarction and proven myocardial viability: Primary results of a randomized controlled trial (VIAMI-trial)

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Author's response to reviews: see over
Dear Dr. Altman, Furberg, Grimshaw, and Rothwell,

I would like to re-submit our manuscript, also on behalf of my co-authors, entitled "Improved clinical outcome after invasive management of patients with recent myocardial infarction and proven myocardial viability. Primary results of the Viability-guided Angioplasty after acute Myocardial Infarction (VIAMI) trial." for publication in Trials.

In this cover letter we provide our point-by-point response to the comments made by the peer reviewers.

Reviewer 1: Michel Hoenig
We would like to thank dr. Hoenig for his valuable review and comments. I hope our reply complies with his comments.

1. I am just a bit confused in the abstract where it states:
Revascularization procedures were performed in 6.6% (7/106) in the invasive group and 31.8% (35/110) in the conservative group (Hazard ratio 0.18; 95% CI 0.13-0.43; p<0.0001).
but in the text the rates of revasc (PCI or CABG) are much higher in the invasive strategy (as they would be expected to be in patients with positive DSE and at-risk myocardium). Please revise this part of the abstract so that the figures match those in the text.

In our abstract we report the repeat revascularizations carried out in the invasive group during follow-up. These procedures are the secondary end points occurring after the initial invasive therapy dictated by the study design (see table 1 for details). 84% received a revascularization after randomization as dictated by the study-protocol. In this group, only 6.6% received a new procedure within 12 months (page 14).

Minor:

1. A minor comment that the authors might consider would be to have an imaging sub study looking at remodeling. In this instance, the patients with evidence of myocardium at risk who are not revascularized will 'lose' the myocardium. MRI with contrast would be ideal but it might be feasible with echo despite the poorer reproducibility of the sample size were large enough.
An imaging sub study looking at remodelling with echocardiography is under construction.

Reviewer 2: Marieke Fokkema
We would like to thank dr. Fokkema for her valuable review and comments. Please find our response to her comments below.

Major comments:

1. Describe the clinical relevance of this trial. In a time period of 5 years, 216 patients were included in a total of 11 hospitals. In what kind of patients the evaluation of myocardial viability should play a role in clinical decision making?

   The results of our study are relevant in the treatment of patients presenting with an AMI in hospitals without PCI-facilities and without the possibility of a direct referral to a PCI-center. In these centers thrombolysis is first choice treatment. Worldwide this applies to a significant amount of the AMI population, estimated up to 50%. Furthermore, the study is also relevant to patients who did not receive reperfusion therapy at all, comprising up to 30% of all AMI-patients. We have adjusted the discussion on page 18.

2. Please explain why the patients in this study were not treated with primary PCI in the first hours after symptom onset. Did they all present late? In current guidelines primary PCI is the preferred treatment strategy.

   At the time this study started, about 50% of the AMI population in the Netherlands was treated with thrombolysis. During the study the fast introduction of primary PCI in the Netherlands slowed down the inclusion rate. About 50% of our study population received thrombolysis because of early presentation (<6 hours). The other half presented too late and was treated conservatively, with intravenous heparin or Low Molecular Weight Heparin (LMWH). In the Methods section we explained this on page 6, with extra addition in the results section (page 11).

3. It may be better to remove the per protocol analysis. It is statistically not acceptable that events are excluded in the invasive group, but not in the conservative group, as described on page 12.

   We agree that results of a randomized controlled trial should be presented according to the intention-to-treat principle, just like we describe in our paper. The results of the per protocol analysis was added to the manuscript to show the real effect of PCI on the reduction of risk of spontaneous cardiac events. The way we described the per-protocol analysis was indeed prone for misinterpretation, so we have rewritten this part to make it more clear. We also moved this section to the methods part (statistical analysis, page 11), because this seems more appropriate. The removal of events in the invasive group was adjusted by also removing events in the conservative group during the average waiting time of 2 days to the actual PCI-procedure. We think that this adjustment made in the per-protocol analysis shows the "true" influence of the PCI in patients with proven viability after AMI.
4. Half of the randomized patients were treated with thrombolysis. What kind of medical therapy did the other patients receive?

The other patients were treated conservatively with intravenous heparin or Low Molecular Weight Heparin (LMWH). On top off this treatment, all patients were treated with aspirin, beta blockers, angiotensin-converting-enzyme inhibitors, statins as accepted by international guidelines. This information is stated on page 6 and 8.

5. In how many invasively and conservatively treated patients a total occluded coronary artery was present during coronary angiography? Do you have data about the presence of collaterals?

Only the invasive group underwent early coronary angiography by protocol. These data were added in table 1 on page 29. In the conservative groups 30% of patients underwent angiography after an average of 93 days after AMI. Of the latter group no data are available on the percentage of totally occluded vessels and on the amount of collaterals.

Minor:
1. What is the definition of stable during the first 48 hours? Does this mean they had no chest pain?

We added the definition of “stable” to page 6. (Stable patients revealed no signs of ongoing ischemia based on electrocardiographic characteristics or persistent chest discomfort. Patients who were admitted within 6 hours after symptom onset, received thrombolysis combined with heparin. Patients admitted more than 6 hours after symptom onset, received only heparin or low weight molecular heparin (LWMH)).

2. Clearly describe how the viability testing was performed, at what time after symptom onset and what dose dobutamine was used?

We added in more detail the requested information on page 7.

3. How many patients in the invasive group underwent revascularization and for what reason? Please add the invasive group to table 5.

The number of revascularized patients as secondary end point in the invasive group, is added on page 14. The reason for creating table 5 was the high rate of revascularization procedures in the non-viable patient group. We expected a low rate, because of the lack of viability. In our search for an explanation, we compared the conservative and the non-viable group in table 5. The similarity of these two groups is resembled by the fact that patients in both groups were initially not revascularized by protocol. We hope that only adding the reasons for revascularization in the text will comply with this comment.

4. On page 13 it is described that 27.3% of conservative patients underwent revascularization. In table 5 the total number of revascularizations is 35 (31.8%).
We corrected this well remarked inconsistency in reporting the data on page 14.

This paper is not under consideration elsewhere and none of the paper's contents have been previously published. All authors have read and approved the manuscript. We sincerely hope the manuscript meets the requirements for publication in the journal and we look forward hearing from you.

Sincerely yours,

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