**Peer Review File**

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**Reviewer A:**

The RECOVER II trial is a multicenter, randomized, double-blind, parallel-group clinical trial of low-dose adjunctive intracoronary reteplase during primary PCI in patients with large anterior myocardial infarction and definite angiographic evidence of thrombus. The trial will enroll 306 patients presenting within 12 hours of STEMI due to proximal or mid left anterior descending artery occlusion undergoing primary PCI. The patients will be randomized to bolus intracoronary reteplase 9mg or reteplase 18mg vs normal saline. The drug will be delivered over 2 minutes proximal to the culprit lesion using an intracoronary catheter early after wire-crossing and before thrombus aspiration or balloon dilation. The primary outcome is the amount of infarct size (% of left ventricular mass) demonstrated by late gadolinium-enhanced MRI at days 7 after enrollment. The secondary outcomes included the amount of microvascular obstruction, myocardial hemorrhage, and myocardial salvage index at days 7, the angiographic measures of reperfusion (TIMI coronary flow grade, TIMI frame count and myocardial blush grade), the incidence of complete ST-segment resolution at 2 hours after reperfusion, troponin T area under the curve, and the incidence of major adverse cardiovascular event at 30 days.

My comments are as follows:

1. The major issue is to how to define the cardiac insult before randomization among the 3 groups. This is essential to get solid results and be sure the observed infarct size changes are induced by testing drug, and not by cofounders, or the differences at baseline, it is possible that patients with less cardiac injury to assigned to bolus intracoronary reteplase 9mg or reteplase 18mg groups, the reported results just reflect the selection bias. Is it possible to perform MRI at baseline?

Response 1: Thanks for your kind comments. The three groups have the same inclusion criteria, which are defined as the acute anterior myocardial infarction with proximal or mid left anterior descending artery occlusion. The patients were randomized to receive the testing treatment to reduce the selection bias. Primary percutaneous coronary intervention to emergently reopen the occluded coronary artery is the standard reperfusion strategy in STEMI patients within 12 h of symptom onset. The target first-medical-contact-to-balloon time should be within the 120min in STEMI guidelines. To shorten time to treatment, MRI at baseline is not realistic because the cardiac MRI is time-consuming about 1 hour and unavailable in most emergency rooms.

2. The title could be modified: as

Impact of Intracoronary Reteplase During Primary Percutaneous Coronary Intervention on Infarct Size in Patients with Large Anterior Myocardial Infarction: rationale and design of the RECOVER II trial

Response 2: Thanks for your careful reviewing and constructive suggestion. We have modified the title as advised (see Page 1, line 1).

**Reviewer B:**

This is a great proposal in order to get a deeper insight into the pathophysiology of coronary thrombus formation and microembolisation.

The reader would like to know why the authors call the study RECOVER II, as RECOVER I is not

mentioned or cited in the introduction or trial design.
The study protocol, particularly the inclusion and exclusion criteria are very good and an excellent step into a study which will definetly show convincing results.
The approach to tacle the occluded vessel is an important part dealing with the effect of recanalization with or without using a balloon. The first trial, which pointed to the effect of recanalization with and without using a ballon was published previously (Erbel R et al JACC 1986 with a three-year follow-up in JACC 1989.
Thus the chosen approach ist supported.
The statistical analysis, proposed, is prefect
In the abstract the authors should use only "presence". Please do not shift to "past".
Response: Thanks for your careful reviewing and constructive suggestions.
RECOVER trial is a prospective, randomized trial to compare the effect of 3 different vasodilators on coronary no-reflow, which is published in *American Heart trial* in 2012. We cited the RECOVER trial in reference 13 and added the description of the trial in *Discussion* part as advised (see Page 15, line 19-21). We also cited the trial to compare the effect of recanalization with and without using a balloon by Erbel R et al in reference 11 as advised (see Page 15, line 13,14). We have modified the verb tenses in the abstract from "past" to "presence" as advised (see Page 2, line 14, 16, 19 and 21).

**Reviewer C:**
The followings should be considered.
In the Discussion section,
1. please discuss more how authors select the current dose of reteplase.
Response 1: Thanks for your kind comments. The dose of reteplase (9mg, 18mg) used in our trial, which was around 25%~50% of the usual total dose given for intravenous fibrinolytic therapy, was selected based on the results of previous trials. We added the discussion in Page 16, line 6 to 21.

2. It is important to state why authors focus on anterior MI according to published data.
Response 2: Thanks for your kind comments. The strongest baseline determinants of infarct size in patients undergoing primary PCI are anterior infarct location (LAD infarct artery), pre-PCI TIMI 0/1 flow, and symptom onset-to-first device time. It is more likely to prove the benefit from a novel cardioprotective therapy for reducing infarct size by careful patient selection to include those high-risk patients. We added the discussion in Page 17, line 2 to 14.