Author's response to reviews

**Title:** Thrombelastographic haemostatic status and antiplatelet therapy after coronary artery bypass surgery (TEG-CABG trial): Rationale and design of a randomized clinical trial assessing and monitoring the antithrombotic effect of clopidogrel and aspirin versus aspirin alone in hypercoagulable patients.

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**Author's response to reviews:** see over
Dear editor and Dr. Gurbel,
We are first of all very thankful, that Dr. Gurbel, took time to review our manuscript. He is a capacity and pioneer in this research field, and his insights could only approve our manuscript and study design. And it does warm our research hearts, to read that our project will have importance in it’s field 😊
We have revised the manuscript according to Dr.Gurbels comments. We hope it will be satisfactory.

On behalf of the authors
Sincerely yours
Sulman Rafiq

Point-by-point revision answers:

1. Background
1st sentence- I suggest revise sentence. CABG is conducted in approximately 1 million patients a year worldwide.

Answer(A): Sentence has been revised.

2. Hypercoagulability and Thromboembolic risk
1st sentence- I suggest using the term thrombin-induced platelet-fibrin clot strength as it is more accurate.

A: this has been done

3. Antiplatelet therapy after CABG
page 6, 2nd para, line 9: incorrectly spelled antiplatelet
page 7, 2nd line. Add a hypen after 3

A: these corrections have been made.

4. Drug Efficacy and Resistance
Multiple studies have now demonstrated a clear association between high on-treatment platelet reactivity (HPR) to ADP measured by multiple methods and adverse clinical event occurrence. There are now cutpoints associated with clinical outcomes and are more predictive and accurate than the term resistance. Suggest using term HPR instead of resistance when referring to clopidogrel. See reference (Bonello L, Working Group on High On-Treatment Platelet Reactivity. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol. 2010 Sep 14;56(12):919-33)

A: this has been done. The whole section has been revised, and a reference referring to HPR to aspirin and SVG graft patency has been added.

Page 8- 2nd sentence, replace activation with aggregation
5. Methods and Design
Add space between Study and population
3rd sentence-Correct acronym CABG.
4th sentence- Suggest omitting sentence
5th sentence-Patients were enrolled between the date of…. 

A: these corrections have been made.

Design and Randomization
4th sentence-suggest using the term MAKH throughout as this more accurate than MA

A: we prefer the term MA, as this is consistent with our other publications.

Should mention how drug compliance was assessed?

A: this has now been mentioned under “description of medical intervention”.

Are you collecting in-hospital events. If so, please describe
(Major compulsory revision) mentioning additional measures to be collected
(characteristics of saphenous veins, demographics, interoperative and inhospital events, blood loss). Refer to reference ( Sarzaeem MR, Scoring system for predicting saphenous vein graft patency in coronary artery bypass grafting. Tex Heart Inst J. 2010;37(5):525-30)

A: This has now been described in the “data collection” section

Last sentence can be omitted and put (figure 1) at the end of 1st sentence

A: correction made

Why did you decide to use Multiplate method over Platelet Mapping with TEG to determine antiplatelet response since you were already assessing hypercoagulability?

A: In our hands platelet mapping did not produce reliable and consistent results, therefore we chose Multiplate.

6. Description and Medical Intervention
Suggest modifying 2nd sentence- In patients randomized to DAPT, Clopidogrel…..

A: sentence modified.

Why was 300mg chosen over 600mg for clopidogrel dosing given that the 600mg is proven to provide greater platelet inhibition?
A: this has now been explained in the text. We are the first trial to utilize 300mg bolus after CABG, therefore we lack information on how patientes would react to greater doses- and even to this dose. Of special concern is ofcourse gastric ulcer which holds a great risk for mortality.

The last 2 sentences are confusing. Suggest omitting or adding a limitation Section

A: limitations section added. We feel it must be explained why a double blinded design was not chosen.

Suggest describing that uniform anticoagulation procedures and techniques (on-pump vs off pump, ect..) were used during CABG? Did you limit the amount of surgeons, as this could be a potential confounding variable for graft occlusion?

A: this has now been described in “surgical procedures”. And no the number of surgeons is not limited.

7. Outcome Measures
I suggest including secondary endpoint to assess the effect of CABG on hypercoagulability post procedure and also assess the difference in platelet reactivity between in hospital measures and 3-months . It has been demonstrated that surgery induces hypercoagulability.

A: We agree, and our group has demonstrated this as well ( Bochsen et al., Platelet hyperreactivity in response to on- and off-pump coronary artery bypass grafting. J Extra Corpor Technol. 2009 Mar;41(1):15-9). We have added this as a secondary endpoint, and added a little section under “hypercoagulability and thromboembolic risk” to support this.

The reason we did not initially mention it is, that we actually have another study, that will explore the degree and impact of postop hypercoagulability even better.

8. Data and statistical Analysis (Major compulsory revision)
Must include a multivariate analysis including multiple confounding factors related to demographics and procedural variables.

A: you are right, and this has been added.

9. Conclusion
2nd sentence- would combine first and second sentence. Thromboembolic is misspelled.

A: the two sentences have been merged.

3rd sentence- Suggest only mentioning patients undergoing CABG not patients undergoing any surgery as you are not studying non-cardiac patients.

A: has been corrected.