Author's response to reviews

Title: Dual antiplatelet therapy in patients with aspirin resistance following coronary artery bypass grafting: Study protocol for a prospective randomized study [NCT01159639]

Authors:

Hrvoje Gasparovic (hgasparovic@gmail.com)
Mate Petricevic (petricevic.mate@gmail.com)
Tomislav Kopjar (tkopjar@gmail.com)
Zeljko Djuric (zeljko.djurich@gmail.com)
Lucija Svetina (lucijasv@gmail.com)
Bojan Biocina (bbiocina@gmail.com)

Version: 4 Date: 14 July 2012

Author's response to reviews:

Zagreb, July 13, 2012

Editors-in-Chief: Doug Altman, Curt Furberg, Jeremy Grimshaw and Peter Rothwell
Trials

Dear Sirs:

I would hereby like to submit the revision of our manuscript titled “Dual antiplatelet therapy in patients with aspirin resistance following coronary artery bypass grafting: Study protocol for a prospective randomized study [NCT01159639]” for evaluation for publication as a study protocol in Trials. I do so, on behalf of all the authors.

I state that there has been no duplicate publication of this manuscript, nor is it being evaluated for publication elsewhere. None of the authors have encountered any conflicts of interest in preparing this article.

We greatly appreciate the comments made by the Editors as well as the reviewers and will respond to them in a point-by-point fashion.

Editorial remarks:

Remark 1: As your research involves humans please include a statement of ethical approval in the Methods section of the manuscript, including the name if the body which gave approval, with a reference number where appropriate. Any experimental research on humans must be in compliance with the Helsinki Declaration.
Response 1: A paragraph concerning the ethical standards employed in the study has been added to the Methods section. A statement of ethical approval has already been implemented in the original manuscript. In the revised manuscript, however, we have expanded upon this to provide the name of the body that gave the approval and the date it was issued. In addition, a statement confirming that the study is in compliance to the Helsinki Declaration has also been included (please see page 7).

Remark 2: Please include a statement confirming that you received written informed consent from the subjects.

Response 2: A statement confirming that written informed consent will be obtained from all study subjects is included within the revised text (please see page 7).

Remark 3: If applicable, please include an acknowledgement section at the end of the manuscript before the reference list. Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for all authors. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements.

Response 3: The authors would like to acknowledge Milan Milosevic for providing expert statistical advice. Mr. Milosevic issued a permission to be acknowledged which is enclosed to the re-submitted manuscript.

No specific external funding for the study has been received. The entire cost of the study is being covered by our Institutional budget (Department of Cardiac surgery, University Hospital Center Zagreb, University of Zagreb, Kispaticeva 12, 10 000 Zagreb, Croatia). None of the authors have received any payments for their involvement in this study.

Remark 4: Please do not include a conclusion section, a summary may be given at the end of the discussion section.

Response 4: The conclusion section has been deleted from the revised manuscript.

Remarks of reviewer 1:

Remark 1. This reviewer can not judge the validity of multiple electrode aggregometry as put forward in reference 17.

Response 1. Toth and coauthors discuss the value of Multiplate Electrode Aggregometry (MEA) in their paper Toth O, Calatzis A, Penz S, Losonczy H, Siess W. Multiple electrode aggregometry: a new device to measure platelet aggregation in whole blood. Thromb Haemost. 2006; 96: 781-8. This paper was referred to as reference 17 in our original manuscript. It is, however, referred to as reference 18 in the revised manuscript. “Multiplate #” is derived from “multiple platelet function analyzer”. Toth et al discuss the methodology behind MEA and
evaluate it by comparing it to single platelet counting (SPC). A direct quote from that paper, which is available for purchase online, is: "MEA is a fast, convenient platelet-function testing method which enables to measure aggregation in whole diluted blood, with very convergent results to those obtained by SPC". The authors go on to summarize that: "In conclusion, MEA is an easy, reproducible and sensitive method for measuring spontaneous and stimulated platelet aggregation, and evaluating anti-platelet drugs in diluted whole blood." We believe that the aforementioned reference 17 (now 18) is important in providing validity to MEA as the method used for evaluating platelet function in our study.

Remark 2. A power calculation has not been given, so the number of patients to be included in this study is unclear
Response 2. A power calculation is now incorporated into the revised version of the manuscript (please see page 8 in the revised manuscript).

Remark 3. The authors fail to refer to 2 randomized controlled studies on this topic (J Am Coll Cardiol 2010; 56:1639-1643 and Circulation 2010;122:2680-2687)
Response 3. We find the reviewer’s suggestion to include the above-mentioned papers into our reference list very helpful and have therefore complied with it (please see pages 15 and 16 in the revised manuscript).

Remark 4. In the Abstract it says that platelets are involved in atherogenesis. This should be atherothrombosis
Response 4. The word “atherogenesis” has been replaced by “atherothrombosis” as suggested by the reviewer.

Remark 5. The abbreviations in figure 1 should be given in the Legends
Response 5. A legend has been added to Figure 1, which explains all the abbreviations in the corresponding Figure.

Remarks of reviewer 2:

Remark 1. The authors need to discuss in detail their power calculations for this trial; how many patients do they anticipate recruiting? How will they deal with cross-over and loss to follow-up? Will the analysis be intention to treat or per-protocol?
Response 1. A power analysis is included in the revised manuscript (please see page 8 in the revised manuscript). The analysis will be conducted in an intention to treat fashion. The number of patients enrolled in the study will be 10% greater than that predicted by the power analysis accounting for a maximum estimated 10% loss to follow up (please see page 8).

Remark 2. Why is this trial not placebo controlled?
Response 2. The main purpose of using placebo would be, of course, to account for the possible placebo effect. It is unlikely, however, that a placebo effect would
significantly impact aggregation. Placebo effects are much more pronounced in clinical outcomes that are difficult to objectively quantify (such as pain control, nausea or anxiety). According to some previously published data, placebo interventions do not seem to produce important clinical effects, except in the afore mentioned patient reported outcomes such as pain and nausea (Cochrane Database of Systematic Reviews. 2010, Issue 1. Art. No.: CD003974. DOI: 10.1002/14651858.CD003974.pub3.; J Intern Med 2004; 256:91–100.) We, therefore, believed that a placebo effect on the process of platelet aggregation is likely negligible. The present study is designed as an open label study. The benefits of using an open label study are enhanced participant recruitment and retention (Clin Trials. 2004;1(6):490-8). In summary to the reviewer’s comment, we believe that the potential benefits of using a placebo controlled study are not likely to be evident in the present study.

Remark 3. The authors need to describe in more detail clinical event adjudication. How will the bleeding events be adjudicated? Will the authors use standard definitions (TIMI, GUSTO etc.)? We would recommend the BARC bleeding scale (Bleeding Academic Research Consortium)

Response 3. We appreciate the reviewer’s suggestion on altering the definition of bleeding events. As suggested, the BARC bleeding scale will be utilized as an instrument for stratifying the documented bleeding events. This change is now incorporated in the revised manuscript (please see page 13 in the revised manuscript).

Remark 4. The introduction is too long; please divide into 3 paragraphs, and please include the clinical guidelines on antiplatelet therapy after CABG.

Response 4. The introduction has been shortened and divided into 3 paragraphs. The clinical guidelines on antiplatelet therapy following CABG have been included.

Remark 5. Please define ASPI

Response 5. ASPI has been defined in the updated version of our paper. The ASPI test evaluates cyclo-oxygenase dependent platelet aggregation (using arachidonic acid) that is sensitive to ASPIrin. The name is not an acronym.

We have made every effort to respond to all the comments and closely followed the suggestions made by both the Editors and the reviewers. We hope that you will find that our revised manuscript now meets the criteria for publication in the Trials.

Allow me to say that it would be a privilege to have our paper published in your esteemed Journal.

Yours faithfully,

Hrvoje Gasparovic, MD, PhD, FETCS

Department of Cardiac Surgery