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To World Journal of Cardiology,

Editors-in-Chief:

Ramdas G Pai, FACC, FRCP (Hon), MD, Doctor, Professor,
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Dimitrios Tousoulis, FACC, MD, PhD, Full Professor,
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Vercelli, May 9th, 2020

Dear professors Ramdas G Pai, Marco Matteo Ciccone, Dimitrios Tousoulis and “World
Journal of Cardiology” Editorial Board,

We would like to submit our revised version of the paper entitled: ***“Effectiveness and safety of antithrombotic strategies in elderly with acute myocardial infarction”*** which we hope you will consider for publication after the major revisions required. A point-to-point response to each issue raised is reported below and changes in the manuscript are reported. We also modified the key revision points suggested by the Editorial Office as well as the figures, tables and bibliography according to the special requirements of the journal.

Thank you for the consideration of our manuscript and for reviewer’s suggestions to improve our work. We look forward to hearing from you.

Sincerely yours,

Alessandro Galluzzo MD, corresponding author, on behalf of all authors.

STRUTTURA: S.C. Cardiologia

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Peer-review report(s)

The authors must resolve all issues in the manuscript based on peer-review report(s) and make a point-to point response to the issues raised in the peer-review report(s) which listed below:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The Authors propose the hospital-based study to evaluate the effectiveness and safety of antithrombotic strategies in elderly with acute myocardial infarction. There are several areas from methodological viewpoint where the manuscript needs to be strengthened.

1. Please describe more details to calculate the power of this study.

We thank the reviewer for his/her comment.

Being a retrospective and descriptive paper, we do not report any superiority analysis, that wouldn't apply to our study. However, in the hypothesis of calculating the sample size needed in order to achieve a significant (>90%) statistical power in comparing NSTEMI and STEMI patients, the following formulas could be used: for the "binary outcomes", $n = f(\alpha/2, \beta) \times [p1 \times (100 - p1) + p2 \times (100 - p2)] / (p2 - p1)^2$, where $p1$ and $p2$ are the percent 'success' in the control and experimental group respectively, and $f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$, where Φ^{-1} is the cumulative distribution function of a standardized normal deviate; and for the "continuous outcomes": $n = f(\alpha/2, \beta) \times 2 \times \sigma^2 / (\mu1 - \mu2)^2$ where $\mu1$ and $\mu2$ are the mean outcome in the control and experimental group respectively, σ is the standard deviation, and $f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$, where Φ^{-1} is the cumulative distribution function of a standardized normal deviate.

Using these formulas, an adequate statistical power with our sample size is reached only concerning the differences in the acute invasive or conservative management between NSTEMI and STEMI patients. However, post-hoc power analyses have been largely criticized, since they may just reflect the p-value [Levine M, Ensom MH. Post hoc power analysis: an idea whose time has passed? Pharmacotherapy. 2001;21(4):405-9. PMID 11310512].

Consequently, these are just to be considered speculative calculations in an observational study.

We therefore added this sentence in limitations:

“Our study is flawed by some limitations. First of all, due to the limited sample size studied, our comparison between STEMI and NSTEMI patients does not hold an adequate statistical power (90%) for all the results reported (though keeping in mind the limits of a post-hoc power analysis), which therefore need to be interpreted with caution”

2.Flow chart of selection of the study sample and procedure is suggested.

We thank the reviewer for his/her comment. We added the asked flowchart in new figure 1.

3.Statement of Ethics: Authors should state the approval of Institutional Review Board

We thank the reviewer for his/her comment. We added this statement in the title page along with the signed document of approval.

4.The authors should point and clarify the feature and novel findings of this study.

5. Describe any efforts to address potential sources of bias, if applicable.

6. How physicians or policy makers could deliberate with patients or people based on the key findings of this manuscript?

7.More discussion regarding the clinical practice of their findings would be important for the specific journal.

Concerning points 4, 5, 6 and 7, we thank the reviewer for his/her comments. Being retrospective and observational, our study may have several biases. However, we present a “real-world” cohort, whose mean age is higher than in previous studies: selection biases were avoided by including all consecutive elderly patients with ACS, independently from comorbidities. In this point of view, the retrospective nature of the paper is somehow a strength point.

We aim to stress out the fact that, for the management of these “frail” patients, even if a thorough knowledge of the scientific evidence is essential, physicians need to draw on experience and common sense.

We added this part in Discussion:

“the authors of this article acknowledge that specific guidelines on the management of elderly patients with ACS are lacking, yet these patients tend to present with various comorbidities, often associated, and exploring every specific scenario in order to standardize clinical management would be impractical.

Trials necessarily restrict enrollment criteria and tend to exclude extreme ages or patients with comorbidities due to the heterogeneity of their clinical presentation.

We therefore present a small cohort of patients showing what is likely to be a common scenario in a cardiology ward. We do believe that, in such a complex context, the approach to treatment should be tailored to the patient: even if a thorough knowledge of the scientific evidence is essential, physicians need to draw on experience and common sense”

And in Highlights:

“In this point of view, the main limitation of this study, namely its retrospective nature, is somehow a strength point, since it allows to overtake selection biases which characterize previous studies.

In the light of these considerations, we advise that future studies on the elderly population should be based on a registry design. Larger cohorts with a higher number of patients enrolled are mandatory”

8. Please consider the comparison with the other epidemiological studies in other areas using table so make clear the significance of this study.

We thank the reviewer for his/her comment. We added the suggested table as table 4.

Totally, I would like to congratulate the authors for the enthusiasm invested in this study. However, the manuscript does not reach the level of quality required for publication as original article without major revision in World Journal of Cardiology.

Editorial Office's comments

The author must revise the manuscript according to the Editorial Office's comments and suggestions, which listed below:

(1) Science Editor:

1 Scientific quality: The manuscript is a retrospective study of effectiveness and safety of antithrombotic strategies in elderly with acute myocardial infarction. The topic is in the scope of WJC. (1) Classification: Grade C. (2) Summary of the peer-review report: Totally, I would like to congratulate the authors for the enthusiasm invested in this study. However, the manuscript does not reach the level of quality required for publication as original article without major revision in World Journal of Cardiology. (3) Format: 3 tables and 2 figures. 38 references were cited, including 11 references published in the last three years. No self-citation.

2 Language evaluation: Grade B. Language editing certificate was not properly provided.

We thank the Editor for his/her comment. We added the language certificate of the corresponding author, who personally revised the manuscript and guarantees for the language level of the paper. We underline that the authors have experience in publishing English papers in many international Journals. Moreover, the reviewer did not specify any peculiar language mistake.

3 Academic norms and rules: The Biostatistics Review Certificate was provided. The conflict-of-interest disclosure form was not properly provided and Copyright License Agreement was provided. The Signed Informed Consent document was not proper, please upload. No academic misconduct was found in the CrossCheck search and the Bing search.

We thank the Editor for his/her comment. We added the conflict of interest disclosure form and the Signed Informed Consent document which we were not able to upload at the first submission for an informatic issue.

4 Supplementary comments: (1) Unsolicited manuscript. (2) Without financial support. (3) Corresponding author has not published articles in BPG.

5 Issues raised:

(1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

We thank the Editor for his/her comment. Original pictures in .ppt format were provided.

(2) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

We thank the Editor for his/her comment. The “Article Highlights” section was added.

(3) The “Author Contributions” section is missing. Please provide the author contributions.

We thank the Editor for his/her comment. We added the “Author Contributions” section.

6 Re-Review: Required.

7 Recommendation: Conditional acceptance. (Xiao-Quan Yu)

(2) Editorial Office Director: I have checked the comments written by the science editor.

(3) Company Editor-in-Chief: I have reviewed the Peer-Review Report and the full text of the manuscript, of which have met the basic publishing requirements, and the manuscript is conditionally accepted with major revision. Before final acceptance, the authors need to meet ethics requirement by submitting correct documents. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report and the Criteria for Manuscript Revision by Authors. Please send the revised manuscript to the reviewer for a second round of peer review.

We thank the Editor for his/her comments. We uploaded the documents required.