Author's response to reviews

Title: Chronic kidney disease is associated with adverse outcomes among elderly patients taking clopidogrel after hospitalization for acute coronary syndrome

Authors:

Michael J Fischer (fischerm@uic.edu)
P M Ho (michael.ho@coloradooutcomes.org)
Kelly McDermott (kellyalanna@gmail.com)
Elliott Lowy (elliott.lowy@va.gov)
Chirag R Parikh (chirag.parikh@yale.edu)

Version: 3 Date: 28 March 2013

Author's response to reviews: see over
March 28, 2013

Editor-in-Chief
BMC Nephrology

Dear Editor,

We appreciate the opportunity to address the additional comments and concerns of the referees of our recent submission to BMC Nephrology, ‘Chronic kidney disease is associated with adverse outcomes among elderly patients taking clopidogrel after hospitalization for acute coronary syndrome’ (MS: 9515053598319553). We believe that the manuscript has been considerably strengthened after incorporating their suggestions.

In an effort to adequately reply to the feedback from the initial review, we have provided point-by-point responses to the Editor and referee remarks as detailed below. We have also revised the manuscript in accordance with the format/style requests from the Editor. We have highlighted all of the corresponding changes in the manuscript as requested for resubmission.

ITEMIZED RESPONSES TO REVIEWER REMARKS

Editor

1. As you will see from the referees’ reports, further concerns have been raised that we would like you to address in a revised manuscript. Please ensure that you respond to each of their concerns as thoroughly as possible, as your revised manuscript will be returned to the referees for further consideration.

We have provided detailed replies to the referees’ concerns below and made accompanying changes in the manuscript as indicated.

2. Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

We made additional minor corrections on the title page (removing authors’ qualifications) and changed ‘Introduction’ to ‘Background’ on line 70.

Referee #1

1. I continue to have the lingering concern that findings of this study can be easily misinterpreted and I feel the authors should help safeguard against this by toning down language in the introduction and discussion. The question that is being addressed is not what is the risk/benefit of clopidogrel in CKD patients (which is the more clinically relevant question), it is what is the “risk/benefit” of CKD in clopidogrel-treated patients. The authors affirm this in their cover letter, “we can’t make any conclusions regarding the benefits or hazards of clopidogrel in the CKD population”, yet in a few places the manuscript is written to imply that their data do tell us something about the risks and benefit of clopidogrel. These sections
should be edited or removed (as detailed below).

We appreciate the referee's concern. As the referee suggests, we have toned down the language in the introduction and discussion as detailed in points #2-5 below.

2. Throughout the manuscript, the authors state that their data represents an advance compared to prior studies. References #24-25 were secondary analyses of randomized trials—while these studies certainly have limitations, they did examine a control group of patients not treated with clopidogrel, and therefore they asked a fundamentally different then this study. Any direct comparison of this study with those previous studies should be removed, or at least it should be made clear that the current study did not address the same question and thus they cannot be directly compared. (page 4, line 79; page 12, line 253-258)

We agree with the referee's point. We revised the introduction (lines 73-83) and discussion (lines 246-256) to avoid inappropriate comparisons with these secondary analyses of randomized trials. We also revised the final paragraph of the introduction (lines 88-92) to clarify the objective of this study.

Specifically, we removed the following from the revised manuscript (discussion paragraph, lines 246-256):

Moreover, they found either a smaller or no beneficial effect of clopidogrel on outcomes in patients with eGFR < 60 compared to placebo.\textsuperscript{[1-2]} However, these two studies were post-hoc subgroup analyses, and the associated methodologic limitations were deemed to produce low quality evidence.\textsuperscript{[1-3]}

3. Page 12, line 270-- Speculation on platelet response to clopidogrel. Again, this line of speculation seems to be brought on by the notion that this study provides data supporting a reduced benefit of clopidogrel among CKD patients (perhaps due to decreased platelet response.). Isn't it quite possible that CKD patients with ACS not treated with clopidogrel could have fared even worse? Therefore there is no data from this study that supports this line of speculation.

We agree with the referee's point. Please see revised paragraph (lines 256-266) where we have removed these lines of speculation in the text:

Furthermore, patients with low platelet response to clopidogrel have higher rates of acute cardiovascular events and death.\textsuperscript{[4]} Some have contended that there is a significantly decreased platelet response to agents like clopidogrel in the setting of low eGFR;\textsuperscript{[4-6]} however, others have not observed an association between antiplatelet responsiveness to clopidogrel and eGFR.\textsuperscript{[7-8]}

4. Page 14, line 301—Limitations. I believe due to the issues raised by both myself and shared by Reviewer #2 regarding the clinical relevance of this study and the lack of a control group should be stated plainly and as the first limitation in this paragraph. I would suggest stating that the lack of a comparison group does not allow for any conclusions regarding the benefits or hazards of clopidogrel in the CKD population as a main limitation of this data.
We agree with the referee’s point. We have revised and reordered to limitations to emphasize this main limitation (lines 293-299).

5. Page 15, line 322.—Conclusion. “These findings stress to clinicians the importance of being mindful of increased risks and reduced benefits in clopidogrel-treated patients.” Discussion of risks and benefits is usually reserved for assessment of treatment effect, but what the authors mean to convey is something about the risks and benefits of having CKD (or not). Since CKD is not a treatment nor is it really a modifiable factor, I think it is improper or at least awkward to discuss CKD in terms of risks and benefits and it is more likely to misguide clinicians into viewing this data as negative data about therapeutic ratio of clopidogrel. As reviewer #2 also states, I’m not certain what the pragmatic message for clinicians should be.

We agree with the referee’s point. We have revised the conclusion to appropriately underscore the main pragmatic message for clinicians, namely that they should have increased vigilance for adverse outcomes in their patients with low kidney function following ACS treated with clopidogrel (lines 316-318). Please also see referee #2, query #1.

Referee #2

1. The authors have done a good job of answering the queries raised. I still feel the article is of limited clinical importance but its limitations are much better described now, and it adds some new information in quantifying the added risk of clopidogrel in chronic kidney disease.

We appreciate the feedback of the referee regarding the detail and completeness of our responses to prior queries, including a more full description of the limitations of our study. We also agree that this manuscript adds new information to the knowledge base. In particular, this manuscript improves the characterization and understanding of the relationship between CKD and a range of outcomes in a cohort of elderly patients treated with clopidogrel following an acute cardiovascular event.

Please do not hesitate to contact me with any concerns. Thank you in advance for your time and consideration. I look forward to hearing your response.

Sincerely,

Michael J. Fischer, MD, MSPH
References


