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)

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Author's response to reviews: see over
Dear Editor,

We appreciate the opportunity to address the comments and concerns of the reviewers 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 reviewer 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. Please upload Figure 1 separately (do not include it in the main manuscript), and include it as either a composite figure or re-labeled as Fig 1, Fig 2, Fig 3 etc.

We have re-labeled the figures as suggested by the Editor and uploaded separately without inclusion in the manuscript.

2. Please include line numbers in the revised version of your manuscript to facilitate re-review.

We have included line numbers in the revised manuscript (from title page until the numbered references).

Reviewer #1

1. Can the authors clarify how patients were identified? The first paragraph seems to indicate that all patients with ACS (determined by a number of factors) were included, and the second paragraph indicates that patients with “AMI and a random sample of all patients with UA” were included. Please unify the inclusion and exclusion criteria.

We apologize for the confusion. We have revised this section of the manuscript to clarify how the patients for the final analytic study cohort were identified (lines 101-119) and below.

Using a retrospective cohort study design, data for this study were collected as part of the Department of Veterans Affairs (VA) Veterans Health Administration Cardiac Care Follow-up Clinical Study, which has been described in detail elsewhere. Briefly, the records of all patients with ACS, as defined by acute myocardial infarction (AMI) and a random sample of all patients with unstable angina (UA), discharged from a VA hospital were abstracted as part of a
national VA cardiac care initiative. All patients with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9CM) diagnosis codes 410.xx (acute myocardial infarction) and 411.xx (other acute and subacute forms of ischemic heart disease) were identified from the VA Patient Treatment File, and their records were manually abstracted by trained abstractors using standard reporting forms. Additional details of the study methods have been published.\[3\]

Based on the above criteria, the study cohort included 22,948 patients who presented to a VA facility between October 1, 2005, and January 10, 2010 with an ACS. We included all patients who were admitted and hospitalized, survived to hospital discharge, and were prescribed clopidogrel at time of discharge. We excluded 8,757 patients who received palliative care, had decisions not to treat, or received same day discharge or non-routine discharges (i.e., transfers), 4,952 were excluded who did not receive clopidogrel at discharge, and an additional 1826 were excluded who lacked an eGFR value. Hence, our final analytic study cohort was 7,413.

2. Decimal places are missing in the ICD9 codes for major bleeding, and the authors should define in text what diagnosis ICD codes are associated with.

We appreciate the reviewer’s comment on this detail and have now added appropriate decimal points for all of the ICD-9 codes and have parenthetically indicated each ICD-9 codes definition in the text (lines 142-150) and below.

Major bleeding events were defined by either i) a hospitalization with a primary ICD-9 CM code for bleeding [430.xx (subarachnoid hemorrhage), 431.xx (intracerebral hemorrhage), 432.xx (other and unspecified intracranial hemorrhage), 578.xx (gastrointestinal hemorrhage) 719.1x (hemarthrosis), 423.0x (hemopericardium), 599.7x (hematuria), 626.2x (excessive or frequent menstruation), 626.6x (metrorrhagia), 627.0x (premenopausal menorrhagia), 627.1x (postmenopausal bleeding), 786.3x (hemoptysis), 784.7x (epistaxis), 459.0x (hemorrhage NOS)] or ii) a secondary ICD-9 CM code for bleeding and blood transfusion (99.0x).

3. The relevance of the chosen primary diagnoses to major bleeding events that might be attributed to clopidogrel is questionable. For example, the ICD codes include hematuria (599.7), post menopausal bleeding and menstrual bleeding (626 and 627), hemoptysis (786.3) and “other disorders of the circulatory system” (459.xx). I would like to see the contribution of these diagnoses codes to their composite outcome of major bleeding. It may be more credible to include these primary diagnoses if there was also evidence that bleeding was severe enough to require a transfusion, but otherwise, the authors should justify why these diagnoses should be considered major bleeding events.

We appreciate the reviewer’s feedback. We agree that there are a variety of bleeding events included in this outcome of the manuscript. As discussed on lines 142-150, we would like to emphasize that the mere presence of one of these bleeding ICD-9 codes was not sufficient to be considered a major bleeding event. Rather, in order to constitute a major bleeding event for our analyses, one of these bleeding ICD-9 codes must have been present as either the primary reason for a hospitalization or along with a blood transfusion. We considered this operational definition (i.e., bleeding requiring hospitalization or transfusion) to constitute a clinically meaningful and major bleeding event. Moreover, we adopted this methodology from existing
published literature characterizing major bleeding events in the setting of coronary artery stent placement and clopidogrel-related bleeding.[4-5]

4. I am concerned that there will be significant confounding involved in including “hematuria” or blood transfusion alone to define medication-related bleeding events in a population with known kidney disease, who are more likely to have hematuria by virtue of their underlying disease and require transfusions due to CKD-related anemia.

We agree with the reviewer that a bleeding ICD-9 code or a blood transfusion ICD-9 code alone is not sufficient to define a clinically significant bleeding event. Please see our response above to query #3. While our stricter definition of a major bleeding event to require a bleeding ICD-9 code along with a hospitalization or transfusion likely reduces confounding by underlying disease, it does not eliminate it. As in all observational studies we can’t conclude causality between severity of CKD and major bleeding events in the setting of clopidogrel usage. Nonetheless, observational studies are appropriate to robustly assess epidemiologic relationships. In this case, we noted a strong graduated signal for an increased risk of a major bleeding event with lower levels of eGFR. We have added the potential for confounding as a limitation to the discussion on lines 314-317.

5. Could the shorter duration of clopidogrel usage among CKD subgroups be attributed to increased mortality or increased non-compliance with refills, instead of purposeful discontinuation?

The reviewer is correct that additional reasons for the observed shorter duration of clopidogrel usage among participants with more severe CKD in this study could also include increased mortality or increased non-adherence with clopidogrel prescription refills. We have added these potential reasons to the ones already discussed based on the existing literature in lines 284-288. This substantial difference in duration of clopidogrel usage by severity of CKD also points to another strength of our analyses, namely that we accounted for length of clopidogrel use in the multivariable Cox models examining the association between eGFR strata and outcomes.

6. The authors should try to clarify how we should understand their findings. The authors should more explicitly state that this study design does not really allow for any conclusions to be made on the potential benefits or hazards of clopidogrel in the CKD population, since there is no comparison group.

We appreciate the reviewer’s feedback. As the reviewer states, we can’t make any conclusions regarding the benefits or hazards of clopidogrel in the CKD population. Rather, we have been careful throughout the manuscript to focus on the impact of severity of CKD (i.e., level of eGFR) on outcomes in a clopidogrel-treated population following ACS. Our objective is to examine outcomes across these different CKD groups, which form the basis of all comparisons in our analyses. We have substantially revised the introduction (lines 69-97) and conclusion (lines 320-326) to underscore the objective of this manuscript and appropriately frame the context for its findings.

7. Discussion on limitations should be expanded to include the limitations of using administrative data (ICD codes) to define comorbidities, the possibility of residual confounding.
We agree with the reviewer and have added these limitations to the discussion (lines 301-317). Please also see query #4 above.

8. Axes are not labeled in figures and abbreviations are used in figure titles.

We have re-labeled the figures, their axes, and avoided abbreviations as suggested. Please also see Editor query #1 above.

Reviewer #2

1. The relevance of the research question is not made very clear.

We appreciate the reviewer’s comment. We have revised the entire introduction (lines 69-97) to clarify our research objective and to underscore its importance. Please also see Reviewer #1 query #6 above.

2. It is currently unclear how much of the observed trend in poorer outcomes with worsening renal function can be explained by ageing mechanisms other than decreasing glomerular filtration rate. It would be better if these analyses were corrected for age.

We agree with the reviewer and have already adjusted the Cox proportional hazards regression models in this manuscript for age. Please see Table 3 footnote in the text.

3. If it were possible to identify a matched group who were never prescribed clopidogrel, then this would be a much more revealing analysis. As it stands the paper lacks any pragmatic clinical relevance or message for clinicians as the conclusions are already well established.

We appreciate the reviewer’s thoughtful comment. We have revised the introduction and conclusion to better clarify the importance of the study objective (lines 69-97) and its message for clinicians (lines 320-326). Please also see Reviewer #1 query #6 above. While examining the impact of clopidogrel on outcomes in a matched cohort analysis is an intriguing question, it is not feasible because current observational techniques are limited in their ability to robustly answer this question. Please also see Reviewer #1 query #4 above and our added comments on limitations of observational study designs (lines 301-317). In order to definitively and properly answer questions regarding the effect of clopidogrel on outcomes in a population with CKD, a randomized clinical trial would need to be conducted, which is beyond the scope of this study.

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


