Reviewer’s report

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

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Reviewer: Patrick Pun

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Dr. Fischer and colleagues present a secondary analysis of a larger VA study, with the purpose of examining the impact of CKD in adults treated with clopidogrel after ACS hospitalization. Essentially, their results suggest that CKD status predicts poor outcomes including mortality, rehospitalization, and bleeding events in this population, just as it does in virtually every other cardiac disease population that has been examined. Since they do not examine patients who were not treated with clopidogrel, this study cannot really address any questions of therapeutic efficacy or harm of clopidogrel among CKD patients. However, they do report a greater risk of significant bleeding risk among those with advanced CKD. Unfortunately, these results are obscured by methodologic flaws in ascertainment of bleeding events that are outlined below.

Major Revisions:

1. Methods: “Study sample” and Design. Can the authors clarify how patients were identified? The first paragraph seems to indicate that all pts 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.

2. Methods: Outcomes and data sources. Major bleeding events were determined by primary ICD codes for diagnoses associated with bleeding OR a secondary diagnosis for transfusion. First, 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. Secondly, 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. Finally, 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.

3. Results: 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?

4. Discussion. The authors should try to clarify how we should understand their findings. As they state in the second paragraph, it is well known that CKD confers increases mortality risk and post ACS adverse outcomes, and one would expect no different in a population of ACS patients who receive clopidogrel. 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. Also discussion on limitations should be expanded to include the limitations of using administrative data (ICD codes) to define comorbidities, the possibility of residual confounding, and address the concerns listed above.

MINOR Revisions:

1. Results: Axes are not labeled in figures and abbreviations are used in figure titles.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests