Reviewer's report

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

**Version:** 2 Date: 6 February 2013

**Reviewer:** Patrick Pun

**Reviewer's report:**

I appreciate the thorough response of the authors to the queries I posed in my prior review and I believe they have adequately addressed all the methodologic concerns. The resulting manuscript is improved overall.

**Major Revisions:**

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 an 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. Specific examples follow:

1. 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)

2. 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.

3. 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.

4. 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.

**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.