Reviewer’s report

**Title:** Renoprotective RAAS inhibition does not affect the association between worse renal function and higher plasma aldosterone levels.

**Version:** 0  **Date:** 13 Apr 2017

**Reviewer:** David Geller

**Reviewer's report:**

This article, by Gant et al, is an interesting investigation into the functioning of the renin angiotensin in CKD. As the authors state, this is a surprisingly sparsely studied topic, and so this article is timely. The authors review components of the renin angiotensin system in the setting of different proscribed sodium intakes and show an association between worse renal function and higher plasma aldosterone ratios as well as elevated aldosterone-renin ratios during renin-angiotensin system inhibition. While elevated aldosterone levels have long been known to be associated with CKD, this study expands that finding in consideration of altered sodium intake and RAAS inhibition. Their conclusions are relevant in that they suggest that sodium restriction coupled with renin-angiotensin system inhibition may be effective in lowering blood pressure in this group, and suggest that mineralocorticoid blockade may be helpful as well. It should be noted that these recommendations are already standard of care, but these data provide a bit of mechanistic support for those recommendations.

Unfortunately, the manuscript as written has some notable issues in need of correction. First of all, the article mentions a primary study and a "confirmation" study. It took me a while to distinguish these in the manuscript - the methods are written in a confusing way, which made it difficult to distinguish the studies to me. Furthermore, the studies have different protocols, so calling the second a "confirmatory" study is misleading. The only "confirmation" I can find in the manuscript is the sentence "study, creatinine clearance was significantly and negatively correlated with PAC during single RAASi, albeit with lisinopril (β=-0.646, P<0.003), with ARR it did not quite reach statistical significance (β=-1.019, P=0.07)." That this "confirmation" came with lisinopril instead of valsartan suggests it is not confirmatory of the first study at all, but actually a new and separate piece of data. I think it is incorrect to assume that Ace inhibition is equivalent to angiotensin-receptor blocking, as alternate pathways, (e.g. angiotensin type 2 receptors and bradykinin pathways) are clearly different in their response to these classes of drugs. Thus, the manuscript should be rewritten to reflect this. This change will expand the reach of the manuscript but at the expense of its "validity" as with the change, there are a limited number of patients in either post-hoc study, limiting the statistical strength.

Both of these studies are post-hoc analyses of previous studies, so this limits the power of their conclusions somewhat. I am not a statistician, so I am hesitant to overstate this, but it would
It seems to me that the statistical bar for a post-hoc (non-prespecified) analysis should be higher, to account for the possibility of multiple hypothesis testing inherent to post-hoc analyses.

Minor point

"These data suggest that treatment with MRA is efficacious to treat hypertension in CKD." -- Poorly worded - "is" should be replaced with "might be" as this is speculative from their data.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
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Yes

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I am able to assess the statistics

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