Reviewer's report

Title: The value of maintaining normokalaemia and enabling RAASi therapy in chronic kidney disease

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Reviewer: Elaine Ku

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Evans and colleagues present in this manuscript a simulation model of the effect of maintaining normokalemia in order to continue RAASi therapy on outcomes such as ESRD onset, life expectancy, QALYs, and cost effectiveness. Overall, the authors found that maintaining normal potassium levels to allow for RAASi continuation would prolong life, delay ESRD onset, and provide cost-savings.

The manuscript is well-written, and this is an important issue. The strengths of this study include the provision of internal and external validation, and the cost-effectiveness analysis is novel. I have the following suggestions:

1. The benefits of RAAS inhibition are likely to differ in terms of ESRD outcomes at least, by baseline level of proteinuria. How did the authors handle modeling of proteinuria? Furthermore, the presence of proteinuria is likely to accelerate progression to ESRD, and hence it would be helpful and of interest to report the results by presence or absence of proteinuria (>1 g versus less). I think there is some debate regarding whether RAAS inhibition should be first-line therapy for CKD patients in the absence of proteinuria.

2. Can the authors provide estimates of how much benefit there would be in advanced CKD (where hyperkalemia is much more common) in sensitivity analysis? It seems that to estimate the benefit from stage 3a when hyperkalemia is rare is less relevant to everyday clinical practice.

3. Related with this, did the models account for time and laboratory costs of more frequent monitoring in order to maintain normokalemia? This is one of the reasons that RAAS inhibition may be frequently discontinued due to the monitoring on the part of the patient and provider that this may take, especially in more advanced CKD.

4. The trajectory of progression to ESRD is frequently not linear; how the authors account for these non-linearities (AKI episodes, etc) in their modeling?

5. A lot of times, low-dose RAAS inhibition can be maintained more reasonably. Could the authors provide a sensitivity analysis looking at the effect of RAAS inhibition using
suboptimal dosing? Also, the assumptions of the benefit of RAAS inhibition are derived from a meta-analysis by Xie et al if I am not mistaken- but wouldn't this meta-analysis be based on a variety of different dosing of RAAS inhibition depending on the trial of interest?

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