Author’s response to reviews

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

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Author’s response to reviews:

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Dear Editors,

Thank you for considering our original research article for publication in BMC Nephrology. We greatly appreciate the valuable feedback provided by the reviewers, and the invitation to resubmit our manuscript after revising it accordingly.

Since our last submission to BMC Nephrology, we have updated our manuscript to address the comments raised by the reviewers. Please accept our revised manuscript, with the revisions outlined in our responses to each reviewer comment, listed below.

Please do not hesitate to contact us if you require any further details regarding our revised submission. Once again, thank you very much for reconsidering our study for publication in BMC Nephrology.

Yours sincerely,

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Editor

Two of three reviewers mentioned the lack of examination of reduced vs. optimal dosing. I believe this is addressed by the sensitivity analyses in Fig. S2. If so, please clarify the wording and perhaps emphasize these results a bit more in the discussion. If I am mistaken, please either address reduced dosing in further sensitivity analyses or note this specifically as a limitation in the manuscript.

Author response

The editor is correct in that dosing is addressed in Fig. S2. As stated in the methods: ‘Additional scenario analyses were conducted to investigate the impact of RAASi dosing on predicted outcomes.’
As suggested, the discussion has been expanded for clarity: 'Scenario analyses highlighted the detrimental impact of suboptimal RAASi dosing on clinical and economic outcomes. Though maintenance of lower doses of RAASi are expected to provide some benefit, reduced efficacy relative to optimal dosing was associated with modelled increases in incidence of ESRD and RRT, and associated costs, and decreases in discounted QALYs, life-years and NMB.'

Reviewer #1.

1. Were the patients diabetic or not? More hyperkalemia in patients with DM.

Author response

The model uses clinical evidence from studies of a general CKD population so will represent a mix of patients with and without diabetes. In the presented application of the model, different incidence rates of hyperkalaemia among different patient populations were not considered. However, the model can simulate different rates for which the prevalence of diabetes and other comorbidities is very relevant.

A statement has been added to the introduction to highlight that there is more hyperkalaemia in patients with DM: ‘As renal secretion is the main route of potassium elimination, patients with renal and metabolic comorbidities such as CKD or diabetes are at increased risk of hyperkalaemia.’

2. What would the data look like with a serum K stabilized at 5.0?

Author response

At a serum potassium level of 5 mmol/L a patient could be considered ‘normokalaemic’ and would be expected to experience outcomes very similar to the ‘reference’ category of our model. However, literature has confirmed the increased risk of developing hyperkalaemia among patients on RAASi and as such this is a group that could potentially benefit from frequent/rigorous monitoring for hyperkalaemia to ensure timely intervention should potassium
levels rise above 5 mmol/L. A sentence has been added to the discussion: ‘However, as RAASi treatment is a known cause of hyperkalaemia careful monitoring for hyperkalaemia may be required to ensure a timely intervention should potassium levels rise’.

3. I presume that RAASi is full dose. No data showing benefit with reduced dose.

Author response

As the reviewer notes, the efficacy of RAASi has been studied at full dose in the RCTs and the literature on efficacy/effectiveness of RAASi therapy on outcomes is focussed on full dose RAASi. The uniqueness of our study is that it allows for sensitivity analyses to simulate both a scenario of full RAASi dose and reduced dose.

As stated in the methods: ‘Additional scenario analyses were conducted to investigate the impact of RAASi dosing on predicted outcomes’. Figure 2 presents the results of this analysis. The discussion has been expanded for clarity: ‘Scenario analyses highlighted the detrimental impact of suboptimal RAASi dosing on clinical and economic outcomes. Though maintenance of lower doses of RAASi are expected to provide some benefit, reduced efficacy relative to optimal dosing was associated with modelled increases in incidence of ESRD and RRT, and associated costs, and decreases in discounted QALYs, life-years and NMB.’

4. Could you do this analysis for CHF; addition of MRA or not?

Author response


This study is referenced in the discussion: ‘Findings from applications of the model are consistent with those recently reported by Bakhai et al, which demonstrated the value of potassium management to avoid hyperkalaemia, enable RAASi therapy and improve long-term health economic outcomes in patients with heart failure [60].’
Our analysis focused on the efficacy of RAASi therapy due to its use as first line therapy, while MRAs are typically used later in the treatment pathway. However, since hyperkalaemia is also a barrier to optimal prescription of MRA this is an important consideration, particularly for patients with heart failure.

The introduction section includes the following regarding the addition of MRAs: ‘Significant benefits have also been observed in patients requiring adjunctive treatment with mineralocorticoid receptor antagonists (MRAs) - an established treatment option for patients with persistent proteinuria, an important surrogate marker of ESRD [6]. However, despite their benefits, these drugs can compound the risk for hyperkalaemia among CKD patients [7-10]. Hyperkalaemia is often a major barrier for the optimal use of RAASi and/or MRAs in an already high-risk CKD population contributing to significant discrepancies between guideline recommendations and real-world practice in the use of RAASi and/or MRAs [8-11].’

The limitations section of the discussion section has been expanded to include: ‘This study focused on RAASi treatment due to its use as first line therapy, and the use of MRAs was not included in analyses. Consequently, the increased risk of hyperkalaemia associated with adjunctive MRA treatment and value of maintaining normokalaemia to enable appropriate prescription of MRAs has not been captured.’

Reviewer #2.

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.

Author response

Since data on proteinuria was not available, proteinuria was not considered in the model. This has been added as a limitation in the discussion. Regarding the degree of proteinuria and whether
RAASi should be prescribed as first-line therapy; we agree that this treatment is debateable in the absence of proteinuria. Therefore, we have added information at what level of proteinuria RAASi is recommended. The following has been added to the discussion: ‘Presence or absence of proteinuria was not modelled, however is also relevant considering guideline recommendations for prescription of RAASi therapy in CKD with urine albumin excretion >30 mg/24 hours (diabetics) and >300 mg/24 hours (non-diabetics) [2].’

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.

Author response

Our sensitivity analysis considers CKD stage: CKD stage 3a (eGFR 52.5 mL/min/1.73m²), 3b (eGFR 37.5 mL/min/1.73m²) or 4 (eGFR 22.5 mL/min/1.73m²). See Fig. S1 (panels a-c): Model-estimated cumulative events over five years, according to CKD stage. In the discussion it has been noted that sensitivity analyses demonstrated that greater value was expected among patients with earlier CKD stage, at the patient level. However, as the reviewer notes the number of patients for whom hyperkalaemia is a real concern is expected to increase in later, more severe CKD stages.

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.

Author response

The models did not quantify costs of any pharmacological or other types of hyperkalaemia management strategies and as such time and laboratory costs of more frequent monitoring in order to maintain normokalaemia, were not accounted for. The methods section has been amended slightly to state: ‘Model analyses were conducted independent of pharmacological potassium management and/or monitoring costs; therefore, incremental NMB represented the amount that could be spent to maintain normokalaemia whilst remaining cost-effective at conventional WTP thresholds.’ A sentence has been added to the discussion: ‘This requirement
to monitor potassium may add to the burden to healthcare providers and patients and could hinder RAASi use in clinical practice.’

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?

Author response

Non-linear eGFR trajectories are not accounted for in the presented analysis. Published evidence characterising eGFR progression typically report eGFR slopes or average rates of change and linear models have commonly been fitted/applied to eGFR progression. Applying these average changes in eGFR via a linear trajectory does represent a simplification of reality as noted by the reviewer, which has now been added to the limitations section of discussion: ‘Furthermore, an average linear decline was applied to model progression of eGFR. Factors such as age, sex, hypertension, acute kidney injury, diabetes or proteinuria may influence rates of renal function decline and associated non-linear trajectories of eGFR are an area for further research and expansion of the model scope.’

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?

Author response

The meta-analysis by Xie et al included more than 100 randomised controlled trial (RCTs) of CKD patients treated with RAASi. As noted by the reviewer there would have been variation in doses evaluated within these trials; however, RCTs (particularly larger, late phase trials) are conducted based on optimal RAASi doses that will be used in product labels and recommended for prescription. In the real world, recommended RAASi doses are often not maintained – due in part to the risk of hyperkalaemia. There is limited evidence quantifying the impact of sub-optimal dosing of RAASi on outcomes, hence the uniqueness of our study is that it allows for different scenarios to be explored and here we present result for a range of efficacy levels associated with RAASi.
Figure 2 presents the results of sensitivity analysis performed to investigate the impact of reduced efficacy associated with sub-optimal dosing. The discussion has been expanded for clarity: ‘Scenario analyses highlighted the detrimental impact of suboptimal RAASi dosing on clinical and economic outcomes. Though maintenance of lower doses of RAASi are expected to provide some benefit, reduced efficacy relative to optimal dosing was associated with modelled increases in incidence of ESRD and RRT, and associated costs, and decreases in discounted QALYs, life-years and NMB.’

Reviewer #3.

A useful clinical model should demonstrate predictive ability and validity in evaluating meaningful outcomes where assumptions are reflective of actual practice. The base case analysis assumed optimal dosing of RAAsi to achieve the full benefit of therapy observed in clinical trials, with scaled efficacy assessment to account for a range of suboptimal dosing that may be common in clinical practice. The findings support the notion that normokalemia with RAAsi optimization results in improved outcomes, but the intervention to achievement of normokalemia is open-ended and leaves many unanswered questions. Consequently, the clinical utility and relevance of such a model may be limited and largely hypothetical. Implications of the findings should be interpreted with caution. For example, certain practices may fall outside the standard of care (like combination therapy with ACEi and ARB) that may be interpreted to be permissible if normokalemia is achieved. Authors should further elaborate on these limitations and the generalizability of results.

Author response

Rather than limiting the generalizability of our results, we believe that conducting analyses independent of intervention costs is a strength of our study, as the analysis may be considered relevant to any intervention, thus supporting healthcare decision making (relating to hyperkalaemia) in its entirety. Reported estimates of NMB reflect the money that could be spent on any intervention or combination of interventions, be that increased monitoring and/or pharmacological treatment, aimed at the maintenance of normokalaemia.

The management of hyperkalaemia is complex, and clinical decisions regarding the most appropriate course of action may vary based on patient characteristics, setting and best available evidence at the time of decision. As cost can be an important consideration, our findings can be informative to a broader range of decisions than if we had evaluated one specific intervention.
The discussion has been expanded to include the following: 'The model developed in this study has the potential to inform broad decision making on interventions for hyperkalaemia, as cost can be an important consideration. To be generalisable across a range of clinical scenarios, the presented model application did not focus on a single intervention and estimates of NMB from this study may be compared against the cost of any intervention to maintain normokalaemia and enable optimal RAASi therapy.'

Previous publications have reviewed the current and future options for intervention. We have added reference to these in the discussion: ‘Currently available approaches to restore potassium homeostasis in patients treated with RAASi are limited to dietary potassium restriction, correction of metabolic acidosis with use of bicarbonate solutions and increasing doses of loop diuretics to enhance renal potassium secretion, whilst recent advances include potassium-exchanging resins to bind potassium in the gut [61-63]. Potassium-binding agents can improve hyperkalaemia management whilst providing the opportunity for patients with CKD to benefit from the full cardio- and renoprotective effects of RAASi [64].’

Based on advice from the reviewer that following the conclusions of our study some practices that may fall outside the standard of care may be interpreted to be permissible if normokalaemia is achieved, we have amended the conclusion: ‘support the notion that maintaining normokalaemia (using guideline-recommended treatments, based on best available evidence) is a valuable strategy to enable optimal RAASi therapy and improve long-term health economic outcomes in CKD patients.’