Author's response to reviews

Title: Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease: Systematic review and meta-analysis

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Version: 3
Date: 28 February 2015

Author's response to reviews: see over
To the editors,

Many thanks for your thoughtful review of the manuscript. We have responded to each of the concerns raised below (in blue).

Associate Editor:

The manuscript is potentially acceptable but please respond to the concerns brought up by the reviewers before we can make a final decision.

The discussion section needs to be longer including a discussion of the biological plausibility of your hypothesis.

We have revised the discussion in keeping with this suggestion, and have moved discussion about biological plausibility from the introduction to the discussion section.

Lines 274-311

Reviewer 1:

This meta-analysis explores the role of urate lowering therapy in renal and cardiovascular outcomes in patients with chronic kidney disease. The topic is interesting, but there are some concerns, which must be addressed by the authors. Minor Essential Revisions

The section of the discussion is too short. The authors should discuss in more details their findings regarding the effect of allopurinol in proteinuria, e-GFR, blood pressure; etc. More notion is needed regarding the nephroprotective effect of allopurinol (as for instance the underlying mechanism). In addition, the authors should report their opinion and/or suggestions regarding the potential effect of urate lowering therapy in renal and cardiovascular outcomes.

Thank you for the suggestion. We have made the appropriate changes to the manuscript.

Lines 274-311, 321-324

Minor Essential Revisions: The section of the discussion is too short.

As above, thank you and changed in the manuscript.

The authors should discuss in more details their findings regarding the effect of allopurinol in proteinuria, e-GFR, blood pressure, etc.

Done, thank you.

Lines 279-311
More notion is needed regarding the nephroprotective effect of allopurinol (as for instance the underlying mechanism).

Done, thank you

Lines 274-311

In addition, the authors should report their opinion and/or suggestions regarding the potential effect of urate lowering therapy in renal and cardiovascular outcomes.

We have expressed an opinion, but given the heterogeneity of the analysis and the absence of data on hard outcomes, we cannot recommend treatment based on these data. We have made that clear in the manuscript.

Lines 321-324

**Level of interest:** An article of importance in its field

Thank you!

Reviewer 2:

**Reviewer's report:**

Minor Essential Revisions

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

Thank you.

Reviewer 3:

The authors did an excellent job summarizing current literature on urate lowering therapy and renal outcomes. They made an effort to include non-English literatures. The major limitation of study is the lack of large, well-conducted RCTs.

Thank you, we agree.

Discretionary Revisions:

Under BACKGROUND, consider combining paragraph 5 & 6 and moving 1st sentence on paragraph 5 to the 2nd paragraph “CKD is often accompanied by hyperuricemia as a result of reduced renal clearance.”

Thank you for the suggestion, we agree that this flows better.

Lines 111-119
The 2nd paragraph under “Study Results”, the authors said “we used serum creatinine and demographic information from the studies, to estimate mean eGFR using ethnically-appropriate formulas.” What formulas did you use?

We used MDRD using Chinese coefficients where appropriate. We have included this in the manuscript.

Lines 191-194

In RESULTS, consider separate the results under “systemic review” and “meta-analysis”

We thought about this, but we were worried that more subheadings might interfere with the flow of ideas, so we have left it without at present. Thank you for the suggestion.

Please add a funnel plot to assess publication bias.

We should have included this before but thank you for the reminder. We have added it. There is mild asymmetry, and we acknowledge this in the text. (We did this only for serum creatinine, because we judged the number of trials too low for the other outcomes for the funnel plot to be informative).

Lines 221-222

Minor: □ Please spell out ACE in ACE inhibitors under Background, 4th paragraph

This paragraph has been removed.

Under METHODS, please also provide Cr values in mg/dL

Done, thank you.

Lines 137

Please rephrase the sentence under “Finding relevant studies”, “Agreement for the second phase of screening, using full-text manuscripts was lower at 0.41.” Please specify that 0.41 is kappa.

Done, thank you

Lines 165

Reference Figure 1 to the first paragraph under RESULTS

Done, thank you

Lines 199

Third paragraph under “study results”, “p=0.000” should be changed to “p<0.001”
Done, thank you

Lines 218

Major Compulsory Revisions: □ Was the protocol for systemic review/meta-analysis registered somewhere?

No, I am sorry, we did not register the protocol. We did however describe in writing a prespecified protocol and followed it throughout. We have made this clear in the text.

Lines 148

The authors listed the search strategies in detail in the Appendix. I think it will be helpful to list the key search terms and describe the search strategies under METHODS.

Done, thank you.

Lines 154-161

There were disagreements for the second phase of screening using full-text manuscripts. How were they resolved?

We resolved disagreements by consensus and have added it to the text.

Lines 165-166

Two paragraphs under “RESULTS-Study results” seem to belong to METHODS.

Thanks, we changed this.

Lines 186-194

Under “Study Results”, it states “The results pertaining to serum creatinine also favoured allopurinol with a mean difference of 0.63 ml/min/1.73m2...” That is confusing. There seems to be an error in units.

Thank you, we have corrected this to mg/dL and clarified.

Lines 215-216

For meta-analyses, there was statistical heterogeneity in serum creatinine, sBP and serum uric acid level. Could authors explain why they still decided to pool these data together?

Having a final pooled result helps people to summarize and describe the results of our study, though this should never be done without commenting also on the size, quality and heterogeneity of the studies that we pooled. We mention this in the abstract to highlight it for readers and users of this information.

The discussion of the results is not sufficient. Please consider the followings: strength and
limitation should be included under DISCUSSION. Authors can consider moving the 3rd and 4th paragraph under BACKGROUND to DISCUSSION. Please also comment on Goicoechea et al.’s most recent publication in the discussion. It was a post hoc analysis of a long-term follow up after completion of a 2-year trial on Allopurinol. “Allopurinol and Progression of CKD and Cardiovascular Events: Long-term Follow-up of a Randomized Clinical Trial” in AJKD, Jan 2015.

Thanks very much for the suggestion; we did move the paragraphs that you mention and agree that the flow is better this way. Thank you for bringing the 5-y Goicoechea data to our attention. The 2-y data are included in our meta-analysis. Because the 5-y data were published outside our date range, without repeating a large part of our methodology and redoing the search, we are unable to include it in our formal review. This is always a problem during the process of bringing a SR to publication. However, we do discuss the paper in detail in the discussion.

Lines 255-264, 274-311, 312-319

In addition, it is also interesting to see that there was no statistical significant difference in dBP in each individual study, but the difference was significant in the meta-analysis.

This is the result of the greater power of the pooled analysis and one of the strengths of this type of work.

Could you please clarify how your study differs from Wang et al study and how it adds to current literature? Based on your discussion, Wang et al also included non-English RCTs. They did literature search up to December 2011. In your study, there was only 1 study beyond 2011, which only had 40 subjects.

Our search date is to June 2013, which though it didn’t identify many more studies, is considerably more recent. The addition of the single study is important for completeness. We also analyzed blood pressure effects, which they did not. We converted serum creatinine data to eGFR in order to pool additional studies. And thanks to you, we have a funnel plot and a discussion of publication bias! The truth is, theirs is actually a nicely done meta-analysis, but ours is an update and methodologically rigorous in its execution, so we feel it deserves publication; though of course it will be replaced by other work in a year or two!

For the studies that eGFR were not available, authors converted serum creatinine into eGFR values using MEAN demographic variables. I am not sure this is a REASONABLE assumption. Can you repeat the meta-analysis without including these calculated eGFR (aka. a sensitivity analysis)?

Thank you for the suggestion. The result became statistically non-significant, which was to be expected given that there are now fewer studies included; but the tendency is in the same direction.

Lines 212-215
Cardiovascular outcomes were not really assessed. There was only one sentence discussion the cardiovascular events in the article. Therefore, I think the article TITLE should reflect that, i.e. take out “cardiovascular outcomes”.

Thank you for this, we have made sure that cardiovascular outcomes are mentioned consistently in methods and results; and have augmented the discussion by including the Goicoechea paper that you referenced. We did take it out of the title given the paucity of data actually identified.

Lines 1-2

Level of interest: An article of limited interest