Reviewer's report

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

Version: 2 Date: 21 January 2015

Reviewer: Wei Chen

Reviewer's report:

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.

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.”
- 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?
- In RESULTS, consider separate the results under “systemic review” and “meta-analysis”
- Please add a funnel plot to assess publication bias.

Minor:
- please spell out ACE in ACE inhibitors under Background, 4th paragraph
- Under METHODS, please also provide Cr values in mg/dL
- 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.
- Reference Figure 1 to the first paragraph under RESULTS
- Third paragraph under “study results”, “p=0.000” should be changed to “p<0.001”

Major Compulsory Revisions:
- Was the protocol for systemic review/meta-analysis registered somewhere?
- 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.
- There were disagreements for the second phase of screening using full-text manuscripts. How were they resolved?
-Two paragraphs under “RESULTS-Study results” seem to belong to METHODS.

-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.

-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?

-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. 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.

-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.

-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)?

-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”.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests