Author's response to reviews

Title: Sodium bicarbonate-based hydration prevents contrast-induced nephropathy: A meta-analysis

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Manuscript title: Title: Sodium bicarbonate-based hydration prevents contrast-induced nephropathy: A meta-analysis

Reply to reviewer comments

Reviewer: Richard Solomon

Meta-analyses of bicarbonate therapy for prevention of CIN The manuscript by Meier et al is a superb example of meta-analyses and its ability to explore reasons for divergent results among clinical trials. The authors have used an appropriate search and selection strategy and include unpublished data from abstracts and major national specialty meetings. Their initial analysis found bicarbonate therapy to be efficacious for prevention of contrast-induced nephropathy (CIN) compared to sodium chloride. These results were not confounded by use of additional prophylaxis with N-acetylcysteine. The authors then explored in a variety of additional analyses the consistency of the odds ratio by deleting each study and repeating the analyses, looking at the impact of type of contrast agent and type of procedure (elective versus urgent), and the average volume of contrast media used in the studies.

1. Is the question posed by the authors new and well defined? Other meta-analysis have been published but none have explored potential confounders with the diligence of this paper.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work? The methods are appropriate. Some further explanations (see below) would be welcome.

3. Are the data sound and well controlled? Not relevant.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Not relevant.

5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes.

6. Do the title and abstract accurately convey what has been found? Yes.

7. Is the writing acceptable? Yes.

Discretionary revisions: A table listing each study with the number of patients, baseline creatinine and eGFR, specific contrast agent used, definition of CIN used and the crude CIN incidence for each arm would enhance the value of the paper as an excellent resource on this issue (your Table 1).

We have included the eGFR data where available in Table 1, we have added a Table 2 with the per arm CIN incidence of each study.

The importance of study size is not clear from the analysis. See comments below. As a reference, the authors might review the N-acetylcysteine meta-analyses by Gonzales et al in BMC Med 2008 and consider a figure to demonstrate the impact of study size.

We would like to thank you for this valuable suggestion. Gonzales et al. have presented a Funnel plot showing effect versus precision (as a proxy for study size) whereas we have plotted the study effect versus the standard error. We had chosen this approach because it may illustrate systematic deviation/ bias somewhat better; we have now exchanged our Figure 9 with the one chosen by Gonzales et al. because it more clearly illustrates the effect of study size on effect estimates as the values on the precision scale are more closely related to the study size. We now
have also integrated a Funnel plot directly showing the influence of study size on estimated effect as a supplementary figure 1.

We have also added two additional plots, the L’Abbé plot (supplementary Figure 2) and the “adapted Modified Galbraith plot” (supplementary Figure 3) to demonstrate the same point. We have not included the figures in the main manuscript to avoid redundancy but will be happy to include them if the reviewers and the editors feel otherwise.

The weakness of study level data is that there is a loss of power to explore confounders and explain heterogeneity. Patient level data is available for most of these trials by contacting the investigators. I would encourage the authors to follow-up this analysis with one done using patient level data.

We completely agree with the reviewer that individual level data would be very valuable to assess impact of confounders. We have contacted most authors and have received a mixed response to sharing of the data. Further, there has been a relative imbalance in this “willingness” from authors of studies with negative and positive outcome as well as those who have not published their data yet. Therefore, we have decided to use study level data instead. We hope that publication of our work would perhaps persuade these authors to reconsider their initial decision.

Minor Revisions:
Page 8, 2nd paragraph: delete ‘benefit’ after the word NAHCO3.

We apologise for the different errors, these have been rectified.

Page 9, 2nd paragraph: Please provide an explanation for how the specific tests suggesting heterogeneity based upon study size should be interpreted (for the non-statistician).

We have revised this paragraph to explain these tests more clearly for the reader (currently highlighted in blue).

A figure, similar to that in the Gonzales meta-analysis, may be helpful.

We have adapted our Funnel plot (Figure 9) according to Gonzales’ meta-analysis, using precision instead of standard error.

Figures: Throughout the figures, the REMEDIAL study is referred to as REMEDIA.

Our apology, we have now replaced REMEDIA with REMEDIAL.

Page 23, Figure 8 legend: “This Forest plot of odds ratios .” (not “rations”). We have fixed that.
Page 22. Figure 2 legend and Figure 2: For consistency, I would indicate that the studies are stratified by year of presentation/publication.

We have clarified that (changes highlighted in blue).

Figure 4: In the iso-osmolar section, the last study and the summary symbols have been reversed.

We have fixed that.

Figure 5: It looks like the slope is highly influenced by the one study at the far right with the most contrast volume. What is the impact of deleting this study on the slope?

The results of the meta-regression are non-significant and exclusion of the RENO study (as suggested) changes the slope dramatically (figure). The overall results however still remain non-significant. Due to the non-significant results and the lack of a consistent trend, we have excluded the results of the meta-regression from the revised version.

Which journal?: Not appropriate for BMC Medicine: an article whose findings are important to those with closely related interests and more suited to BMC Cardiovascular Disorders

We would like to respectfully disagree with the reviewer. We think that this article is well suited for BMC Medicine. It is in line with the previously mentioned meta-analysis by Gonzales et al. in BMC Medicine about N-Acetylcysteine and CIN. We believe that it is not strictly a Cardiology specific topic. As Reviewer 2 states: “It is the impression of this reviewer as a nephrologist that this systematic review provides the reader with an excellent qualitative and quantitative clinical overview on this topic and should be left as is”. CIN is directly relevant to cardiologists and radiologists but is of equal importance to internists and surgeons since they usually refer their patients for diagnostic and therapeutic procedures and to nephrologists who often end up caring for these patients after the event. We hope that you will kindly change your recommendation to offer publication in BMC Medicine.

What next?: Offer publication in BMC Cardiovascular Disorders after discretionary revisions
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests.
Reviewer: Rainer Birck

This is a thoroughly conducted systematic review and meta-analysis on a clinical relevant topic. A systematic review stands or falls with its search strategy, and in this case a comprehensive and systematic approach (several data bases, several hand searches, author contact) was chosen by the authors leading to the inclusion of 9 yet unpublished trials. Effect sizes from individual trials were pooled using the conservative random-effects model, and several and well-grounded stratified analyses were performed. The discussion is well-balanced, highlighting both pros and cons of the chosen scientific approach. It is the impression of this reviewer as a nephrologist that this systematic review provides the reader with an excellent qualitative and quantitative clinical overview on this topic and should be left as is. If anything, the results could be shortened by the last two charts which do not really add much information.

We thank you very much for appreciating our work. The last two charts have been cancelled; we agree that the additional information is limited.

Which journal?: Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field
What next?: Accept for publication in BMC Medicine after discretionary revisions
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests’ below