Author's response to reviews

Title: Retained Organic Solutes, Patient Characteristics and All-Cause and Cardiovascular Mortality In Hemodialysis: Results from the Retained Organic Solutes and Clinical Outcomes (ROSCO) Investigators

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Author's response to reviews: see over
June 5, 2013

Dear Dr. Henderson and Drs. Neild and Frimat,

We are re-submitting the attached original manuscript entitled “Retained Organic Solutes, Patient Characteristics and All-Cause and Cardiovascular Mortality In Hemodialysis: Results from the Retained Organic Solutes and Clinical Outcomes (ROSCO) Investigators” to be considered for publication in BMC Nephrology.

We would like to thank you for your thorough review of our previous version of this manuscript. We have made changes to the manuscript based on your suggestions and we believe it has improved our manuscript. We include in this letter a point by point response to your comments. This manuscript is not under review at any other journal and all authors have approved the new manuscript. We hope that you will now find our manuscript acceptable for publication.

Thank you,

Michal L. Melamed, MD, MHS
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Reviewer 1:

This is an interesting study and another product of the widely reported CHOICE study.

The authors investigate the possible effect of 4 potential uremic toxins, which are all poorly cleared by conventional dialysis, on long-term clinical outcome. The most obvious feature of the report, is that the results are ‘negative’ but they are just as interesting for being negative since previous smaller studies have given positive results and reported relationships between high concentrations of specific toxins and poor outcome.

The paper is written by experts and is comprehensive and clear.

We thank the reviewer for his kind comments.

Major
1. My only comment is that the single samples that have been analyzed were obtained after 2-6 months of dialysis. I think this should be stated in the Abstract, but more importantly there should be a brief comment on this in the Discussion. Ideally, I assume,
in a prospective study one would obtain a sample before dialysis is commenced and one after a several month period of dialysis. There must be some literature on the short term effect of dialysis on these 4 uraemic toxins. If sampling at 2-6 months after start of dialysis is just as valid as sampling before dialysis starts then please inform us.

**We agree with the reviewer that this is a limitation. We have included the timing of the blood draw in the abstract, which now reads:**

*P*-cresol sulfate, indoxyl sulfate, MMA and DMA levels were measured from frozen plasma samples obtained 2 to 6 months after initiation of dialysis.

**We have added the following to the discussion:**

Our study also used specimens from 2 to 6 months after dialysis initiation. The ideal timing of specimen collection for this type of study is unknown. Collecting samples before the initiation of dialysis may lead to more confounding by residual renal function, whereas samples from later in the course of dialysis may lead to survival bias, as not all the participants who started on dialysis will have survived to specimen collection. The uremic toxins we studied are all poorly cleared by current dialysis therapies and by the dialysis therapies used at the initiation of the CHOICE study, therefore, one would not expect large changes in levels after dialysis initiation, but this has never been studied.

Reviewer 2:

The manuscript BMC-2013 by Melamed ML et al. “Retained Organic Solutes, Patient Characteristics and All-Cause and Cardiovascular Mortality In Hemodialysis: Results from the Retained Organic Solutes and Clinical Outcomes (ROSCO) Investigators” deserves to be published.

Authors’ epidemiological expertise is assured. Rationale of the study is well explained. Study design is irreproachable, i.e. prospective cohort study of incident ESRD patients with strict definitions of variables and low rate of lost to follow-up. Analyses depict in-depth all assumptions. Statistical assumptions are precisely checked. Discussion is well balanced. Limitations are clearly set out. Conclusions issued from this study are valid.

One could observe that patients inclusion in CHOICE study date now for more than 10 years. So the conclusion of the study could be somewhat outdated in 2013.

**We thank the reviewer for his kind comments. We agree that the CHOICE data is now almost 20 years old, but, the mainstay of dialysis treatment remains event today, thrice weekly in-center hemodialysis, which was the same dialysis modality used by CHOICE participants. Thus, we believe this data is still clinically relevant.**

Discretionary revisions:
1. The fact that this is the first study in the US about this field might suggest different pathogenesis, dialysis regimens, medications use... than in Europe or elsewhere.

We agree that this is an important aspect that differentiates our study from the previous studies of retained uremic toxins and have incorporated changes in the manuscript to reflect your comment. We have changed the introduction to now say this:

Due to the smaller nature of previous investigations and varying dialysis practices in Europe, we tested the associations between these retained organic solutes and cardiovascular and all-cause mortality in a relatively large, well-characterized cohort of US hemodialysis patients.

We have changed one of the sentences in the discussion to now say this:

Ours is also the only American study evaluating these associations; the different patient population, different medication and dialysis use patterns and different outcomes (CV mortality versus CV events) compared to previous studies may partially explain the differential results between ours and other studies.


We thank you for pointing out this article. We have added it to our discussion in the following sentence:

Our finding are similar to other studies evaluating associations between potential uremic toxins and mortality which also had null results.25 (added Terrier-Lenglet 2011)

3. The conclusion paragraph of the abstract looks too long and redundant with the results paragraph.

We agree with this comment and have changed the conclusion of the abstract to read:

In this cohort of 521 incident hemodialysis patients, only elevated indoxyl sulfate levels were associated with all-cause mortality. Further research is needed to identify causes of the toxicity of uremia to provide better care for patients with kidney disease.

4. Relevant references:
We thank you for reminding us of these two important references. We have added them as references to the manuscript. We have added the Jourde-Chiche reference in our discussion of possible effects of uremic toxins (new reference 12) and the Duranton reference updating the Vanholder 2008 reference (new reference 5).