Author's response to reviews

Title: Association between routine and standardized blood pressure measurements and left ventricular hypertrophy among patients on hemodialysis

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Author's response to reviews: see over
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Dear Dr Shipley,

Thank you for allowing us to revise this manuscript and for the timely, high quality reviews that you have provided to guide the revision.

We have addressed all comments from the Editors and Reviewers. We believe that the revised manuscript is much stronger and hope that it will be suitable for publication. We enclose clean and marked versions of the manuscript. In the latter, new text is shown in red font. Below we provide detailed responses to the editors and reviewers comments and questions.

We look forward to hearing back from you.

Sincerely,
Brenda Hemmelgarn MD PhD

EDITOR'S ADMINISTRATIVE REQUIREMENTS

1) Manuscript sections should include (in the following order): Abstract; Background; Methods; Results; Discussion; Conclusions; Abbreviations (if any); Competing interests; Authors' contributions; Acknowledgements; References; Figure legends (if any); Tables (if any); Description of Additional files (if any).

Sections have been ordered as requested.

2) Please include an Authors' contributions section before the Acknowledgements and Reference list.

This has been included as requested.

Reviewer 1

1) Main limitation is the lack of novelty of the data, MRI determination of LVH notwithstanding. I am not sure that this paper will add substantially to sway the argument one way or the other.

We agree that the results of this paper are not definitive, but they do add to the limited information available regarding optimal BP measurement methods to use in hemodialysis patients to predict adverse outcomes. Our results are consistent with previous studies demonstrating the poor agreement between methods, and that the pre-dialysis measurements have the weakest predictive power for predicting LVH. We did, however, report that a single standardized BP performs just as well as the more resource intensive cumulative measurements, which should help to guide practice and inform new research. This has been highlighted in the study conclusions, page 12.
For ease of practice, a single standardized measurement performs just as well as the more resource intensive cumulative measurements.

2) Lack of home or ambulatory blood pressure in this paper is a major limitation.

We agree that lack of ambulatory blood pressure monitoring could be considered a limitation. However the purpose of the paper was to evaluate the routine blood pressure measurement methods commonly being used. The practicality of having patients complete 24 hour ambulatory monitoring, or use this as a long-term method for BP assessment is questionable. Evaluation of BP measurement methods that are feasible to undertake increases the generalizability and use of the results of this paper.

3) Finally, the small sample size and cross sectional nature of the data limit the ability to draw firm conclusions.

The limitations of the small sample size and cross-sectional nature of the data have been included in the study limitations section, page 12.

Firstly, our sample size was small, including 39 patients.

The cross-sectional nature of the data for baseline BP measurement and assessment of LH hypertrophy prevents us from drawing firm conclusions, however, the results are further supported by cumulative BP measurements obtained over a 12 month period.

4) The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

We have made the editorial changes as requested by the reviewer.

Reviewer 2

1) Absence of a standardized gold-standard: 24/48 h ambulatory blood pressure measurements should be used.

We agree with the reviewer that 24/48 h ambulatory blood pressure measurements are more predictive of outcomes in HD patients. These measurements were not undertaken in this study. The purpose of this study was to determine the predictive ability of the routine BP measurements that are available for HD patients, increasing the utility and generalizability of the results. See also response #2 to Reviewer #1.

2) Casual BP measurements: Pre-HD and post-HD BP are represented only by one measurement, not standardized. The risk of error is not predictable. Moreover, different number of measurements are not comparable: inter-HD BP measurement and standard BP are numerically superior to pre/post-HD measurement.

We agree with the reviewer that the error is not predictable, but the error is likely to be random, and as such would bias the results to the null. We also agree with the reviewer that the inter-HD measurement and standard BP were superior to the pre-measurements, and thus the conclusions
from our study that the pre-dialysis measurements had the weakest predictive power for LVH. This has been highlighted in the study discussion and conclusions.

3) Standard pre HD measurement are the average of one year monthly BP. In literature Office pre-HD BP measurement is reported as the average of one month pre-HD measurement, that is 12 values (3 BP x 4 weeks).

We have clarified within text that the one-year readings were based on one hemodialysis session each month, for a total of 12 monthly sessions (similar to the 12 values noted by the reviewer). This has been clarified in the Methods, page 6.

*Monthly pre-, intra- and post-dialysis BP measurements were retrospectively collected from hemodialysis records for a single hemodialysis session each month during the 12 month period prior to the cMR examination.*

4) The definition of LVH is wrong: Zoccali used LVM/sqm and LVM/h2.7.

We thank the reviewers for pointing this out. We had in fact used cut-points for defining LVH derived specifically for cMRI. The reference has been changed accordingly.


5) Covariates analysis: It is demonstrated that fluid overload is one of the determinant causes of LVH. This covariate is not analyzed.

This is a complex question and it is difficult to ascertain a clear answer to the question posed within the dataset collected. As you know, measurement of volume status in dialysis patients is challenging. We considered performing bioimpedance analysis in all subjects at baseline and study exit but limited funds prevented us from doing so. Therefore we do not have an assessment of fluid overload within the study. This has been noted as a study limitation on page 11. See also response #1 to Reviewer #3 below.

The cross-sectional nature of the data for baseline BP measurement and assessment of LV hypertrophy without an assessment of volume status prevents us from drawing firm conclusions, however the results are further supported by cumulative BP measurements obtained over a 12 month period.

6) Low number = higher probability of statistical errors.

See response # 3 to Reviewer #1 above.

7) Exclusion criteria. It is not reported if patients with left ventricular insufficiency are excluded from the study.
Subjects with LV insufficiency were not excluded. The implications of this have been noted in the study limitations on page 12.

*Finally, our study included patients with a wide range of ESRD etiologies, including diabetes and heart failure, both of which contribute to LV hypertrophy. The autonomic and CV dysfunction in these disease processes could have confounded the BP-LV hypertrophy correlation. Further studies are necessary to delineate whether these co-morbidities affect the BP-LV hypertrophy relationship.*

**Reviewer 3**

1) The authors used cardiac magnetic resonance (CMR) (which is now considered to be the “gold-standard” technique for the assessment of LV dimensions and mass) to accurately estimate left ventricular mass and should be commended by that. However, the volume changes occurring with dialysis sessions can also lead to inaccuracies. Hence, it is important to clearly state when the exams were performed in relation to dialysis session: pre, post-dialysis, or in a non-dialysis day? Days between or the longest day?

For the most part, MRI measurements were performed post dialysis, but due to logistics in completing them this was not consistent for all subjects. However, it is important to point out that MRI measurements of LV mass are not sensitive to volume status. MRI has been shown to be more accurate and less volume and operator dependent than 2D-echo. Cardiovascular MRI technology allows for measurement of cardiac mass that is independent of volume changes that occur with dialysis (Kramer U et al. TrueFISP MR imaging to determine the influence of hemodialysis on the myocardial functional parameters in patients with terminal renal insufficiency. Rofo. 2004;176(3):350-6)

2) The authors chose to index LV mass to body surface area. Thus, the citation of the article by Zoccali et al from JASN 2001 seems inappropriate. The referred article showed that the indexation by height $2.7$ should be the method of choice in patients undergoing dialysis because it identified a larger number of individuals with LVH and was more powerful than the BSA-method in the prediction of mortality. Furthermore, they did not use CMR but echocardiography instead in their study. For a recent authoritative review of the subject of left ventricular mass and hypertrophy in end-stage renal disease (including cut-off limits for LVH), the authors should be referred to the excellent overview of Glassock et al (Clin J Am Soc Nephrol. 2009 Dec;4 Suppl 1:S79-91).

See response #4 to Reviewer #2 above.

3) In results section, first paragraph, the authors wrote that the prevalence of LVH was 74.4%. Differently, they cited the prevalence of 69.2% of LVH in the discussion section, third paragraph.

We thank the reviewers for pointing this out, and have corrected this error on page 11.

4) The article would be further enhanced by a detailed description of the geometric pattern of the LVH as well as by the profile of systolic function found in the study sample. Confounding
factors, such as systolic dysfunction with or without coronary heart disease, could have affected the blood pressure-LVH link.

The results for the imaging studies obtained do not allow us to explore the LVH in this level of detail. Given the purpose of the paper, such an exploration of the data would be beyond its intended purpose. We have addressed the issue of confounding by comorbidities in response #7 to Reviewer #2 above.

5) Inter and intra-observer variability for the calculation of LV mass should be presented.

As noted in the response above, we do not have the level of detail requested to assess inter- and intra-observer variability. However, given the objective criteria required for this calculation the variability is expected to be minimal.