Author's response to reviews

Title: Left Ventricular Global Longitudinal Strain Is Associated With Cardiovascular Risk Factors And Arterial Stiffness In Chronic Kidney Disease

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Author’s response to reviews: see over
Dear Editor-in-Chief,

We are enclosing the revised manuscript; MS: 8097471431476766 entitled ‘Left Ventricular Global Longitudinal Strain is associated with Cardiovascular Risk Factors and Arterial Stiffness in Chronic Kidney Disease’ to be considered for publication in BMC Nephrology.

We thank you and the reviewers for the helpful comments on this manuscript. We have detailed our responses to these comments below, in addition to highlighting all changes made in the revised manuscript document.

If you require any additional information, or clarification, please do not hesitate to contact me, the corresponding author.

We hope we have appropriately addressed your concerns regarding this manuscript.

Thank you for considering our revised manuscript for publication in BMC Nephrology.

Kind regards,

Dr. Rathika Krishnasamy MD
(on behalf of all co-authors)

Reviewer 1:

The manuscript on “Left Ventricular Global Longitudinal Strain Is Associated with Cardiovascular Risk Factors and Arterial Stiffness in Chronic Kidney Disease” by Dr Krishnswamy et al is well conducted study of echocardiographic abnormalities in patients with CKD. Interestingly obesity was common and was associated with Global Longitudinal Strain as was PWV and uraemic toxins. The longterm
implications of abnormal GLS in CKD are unknown.

There are some essential revisions

Background Line 118: Please include anaemia as possible non-traditional risk factor for cardiac changes.

Response: This has been done.

Background Line 118: Renal-specific disturbances known as ‘non traditional risk factors’, including vascular calcification, abnormal bone mineral metabolism (BMM), anaemia, hemodynamic overload, inflammation and uremic toxins are putative contributors to cardiac remodeling

Method: Was there any patient with fasting blood sugar >7 mmol/L but not known to be diabetic

Response: There were 3 patients with fasting blood sugar of 7.1, 7.4 and 8.7 mmol/L that were not known to be diabetics. Only one fasting blood sample was collected for each participant for this study thus these patients could not be confirmed to have diabetes mellitus. However, additional analysis following inclusion of these 3 patients as diabetics still showed no independent association between diabetes and GLS and did not change the main outcome of this study.

Discussion: Could it be possible that hypertension was not a risk factor because the historical values were not available or the number of patients was few.

Response: This has been included in the study discussion as outlined below:

Discussion Line 310: In addition, historical values of BP readings were not available for comparison and the relatively small sample size could account for the lack of association between GLS and BP seen in this study.
Endothelial dysfunction relates to abnormal cardiac structure in CKD and needs to be discussed.

Response: This has been included in the discussion as outlined below.

Discussion Line 318: Previous work has also demonstrated that hemodynamic and metabolic changes associated with the uremic milieu can result in endothelial dysfunction and a cascade of vascular injury in this cohort[34-36]. Endothelial dysfunction is a major pathogenic mechanism for exaggerated atherosclerosis and arteriosclerosis resulting in reduced vascular and myocardial compliance, increased vascular calcification and stiffening[37].

Reviewer 2:

In this study, the associations of CKD risk factors with GLS which is thought to reflect LV function were assessed. In general, the study was well-written and the design/statistical approach seemed appropriate. However, a few clarifications are needed to better interpret the results.

First, were all LANDMARK trial participants recruited to partake in this study? In other words, what proportion does that study population of the current study comprise the overall study population.

Response: 162 patients participated in LANDMARK 3 trial. One hundred and thirty six patients with available speckle tracking echocardiogram and vascular images were included in the current study. Thus, the current study comprised of 84% of the overall LANDMARK study population. This has been included in the methodology:

Methods; Study Design Line 143: The current study included 136 patients who completed the baseline visit and had cardiovascular imaging prior to the intervention of
exercise and dietary modification and comprised of 84% of the overall LANDMARK 3 study population.

Second, the rationale for the GLS cutoff utilized is unclear.

Response: The following text has been added to the manuscript.

Methods; Exercise Stress Echocardiogram and Vascular Imaging Line 196: Previous studies have demonstrated that healthy individuals have GLS ranging from -16 to -19 % [21, 22]. A cut off at -16% has been shown to provide important risk stratification and prognostic value[23]. Therefore, in our study we defined impaired GLS as >-16%(a less negative value reflects a more impaired GLS).

Sensitivity analysis are needed to determine whether the observed associations are robust when perhaps utilizing a different threshold.

Response: This has been added to the following parts of the manuscript. The observed associations between GLS and BMI, uremic toxins and PWV remained using a different GLS cut-off at median value of -18.4%. Two additional supplemental tables (1A and 2A) have also been included.

Methods; statistical analysis Line 228: A sensitivity analysis was done by dividing patients according to above and below the median values of GLS (-18.4%) to determine whether the observed associations were still robust utilizing a different threshold.

Results: Sensitivity analysis Line 289: The associations between GLS, clinical characteristics and indices of LV structure and function were repeated with a GLS cut-off at median value of -18.4 % (Supplemental 1A and 2A). Participants with lower GLS (> -18.4%) were still found to have higher BMI, uremic toxins (free IS and free PCS) and aortic PWV.
Thirdly, the "coefficient" noted needs clarification (i.e. does this note the per unit change in GLS?).

Response: Yes, the coefficient notes the per unit change in GLS. This has been included as a footnote to table 3 and 4.