Author’s response to reviews

Title: Cardiac valve calcification and risk of cardiovascular or all-cause mortality in dialysis patients: A meta-analysis

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Author’s response to reviews:

Maurizio Alberto Gallieni (Reviewer 3): This manuscript deals with a relevant issue in CKD patients, i.e. the association between cardiovascular calcifications and increased risk of morbidity and mortality.

The manuscript appears to be a revision prepared after peer review from other reviewers. I agree that it is worth publishing. Although it does not add substantial information to the established association between cardiac calcifications and unfavorable outcomes, it has the strength of the study design (a meta-analysis) and of a large patient population.

I only have two minor observations:

Reply: Thank you for your comments. We have revised the manuscript according to your comments.

1. The 2012 article by Bellasi et al is cited twice in the manuscript (ref 4 and 24): please correct

Reply: We have revised accordingly.

2. I respectfully suggest to include in the analysis, if the Authors agree, our prospective study on cardiovascular calcifications in peritoneal dialysis patients: Gallieni M, Caputo, F, Filippini A, et al. Prevalence and progression of cardiovascular calcifications in peritoneal dialysis patients: A prospective study. Bone, 2012; 51(3):332-337. This article included an evaluation of cardiac valves calcifications in 369 patients, which was repeated after 36 months in 145 patients. Mortality data were reported.
Reply: Actually, we have read this article with care during the meta-analysis. In the article, the author mentioned “The study examined the presence and progression of CC in two cardiac valves and five arterial sites. Eleven percent (n=42) of subjects died. The most frequent cause of death was CVD (33%).” This suggested that the article focused on the analysis of prognosis of peritoneal dialysis patients of cardiovascular calcifications (cardiac valve calcification and arterial calcification). However, it did not mention the cardiovascular or all-cause mortality in the patients with or without cardiac valve calcification. Therefore, we can not include this article in the meta-analysis. In fact, the article is a nice work, and we cited in the discussion section as reference 23.

Sagar Nigwekar (Reviewer 4): Authors report a meta-analysis conducted to evaluate the association between the CVC and cardiovascular or all-cause mortality in dialysis patients. Following concerns should be addressed-

Reply: Thank you for your comments and suggestions. Please kindly check the following responses.

1. Dialysis vintage (duration between dialysis initiation to assessment) can be a significant confounder. Per Table 1, only two studies adjusted for this confounder. Provide a sensitivity analysis that includes studies with vintage adjustment.

Reply: For the all-cause mortality analysis, only one study (Wang et al, 2003) including 192 cases corrected the dialysis vintage (HR: 2.5, 95%CI: 1.32-4.76). The other five subsequent studies including 2153 subjects (HR: 1.665, 95%CI: 1.351-2.053; I² = 23.8%; P = 0.255).

For the cardiovascular mortality analysis, Wang et al (2003) and Zhong and Na (2011) corrected the dialysis vintage. After a pooled analysis, the following data were obtained: HR: 3.810; 95% CI: 2.539–5.720; I² = 0.0%; P = 0.407. The other four subsequent studies including 1904 subjects were included in the analysis (HR: 2.265; 95% CI: 1.473–3.481; I² = 35.0%; P = 0.202).

2. Page 6- provide number of studies and patients included in each of the subgroup and sensitivity analyses.

Reply: We have added the subgroup analysis data in Table 2.

Sensitivity analyses by excluding one study at each turn showed that there were no changes in the direction of pooling risk estimate of all-cause mortality (pooled HR: 1.62-1.88) and cardiovascular mortality (pooled HR: 2.41-3.25). We added the “sensitivity analysis that includes studies with vintage adjustment”. The answer to the results is similar with the first question.

3. Although statistical tests for publication bias are not significant, the visual suggests small negative studies were likely not published. This should be discussed as a limitation.

Reply: We have added the information in the limitation section.
4. Discussion section is not rich. Instead of rewriting the results section, highlight the most important findings and discuss underlying pathogenesis and implications for clinical care and research.

Reply: In a previous study, CVC patients showed elevation of left ventricular mass index and pulmonary artery pressure and decrease of ejection fraction. Besides, CVC was associated with the arterial wall stiffness, which then resulted in cardiac afterload elevation and left ventricular hypertrophy that were considered to be markers for the decrease of heart function. Furthermore, CVC was significantly associated with peripheral arterial calcification, alterations of mineral metabolism, coronary artery calcification, arterial calcification, carotid atherosclerosis, arrhythmias, stroke and mortality. Therefore, it is necessary to evaluate the CVC of the patients, which contributed to the risk stratification, modulation of treatment regimen, as well as delaying the calcification.

5. Comment on observations related to Asian vs. non-Asian populations, peritoneal vs. hemodialysis patients.

Reply: In the all-cause mortality analysis, the risk of cardiac valve calcification induced all-cause mortality in the Asian population was higher than that of the other populations, among which in a previous study by Panuccio et al (2004) in the non-Asian population [HR (95%CI): 1.20 (0.75-1.92)] that was significantly lower than the other studies. This may be related to the exclusion of heart failure subjects, which may be an important cause for the mortality.

The heterogeneity was large in the cardiovascular mortality analysis, but the heterogeneity showed significant decrease after excluding the study of Panuccio et al (2004).

The cardiovascular and all-cause mortality in the peritoneal dialysis patient with concurrent cardiac valve calcification was higher than that of the hemodialysis patients. Besides the heterogeneity, further studies are needed to investigate the effects of dialysis mode on the effects of vascular calcification and prognosis.

6. Overall, the prevalence of valvular calcification in Chinese studies is lower than in other populations. Please comment.

Reply: The valve calcification incidence among the Chinese patients was 25.5%-32.78%, which was lower than that of the Japanese, but it was higher than that of the Italian. The incidence of valve calcification may be affected by several factors such as diet, environment, comorbidity, dialysis mode and medication.

7. Recent KDIGO CKD-MBD guidelines 2017 mention caution regarding use of calcium and vitamin D in dialysis patients. Please comment on these in the context of observed associations between valvular calcification and mortality.

Reply: In a meta-analysis, patients assigned to non-calcium-based binders had a 22% reduction in all-cause mortality compared with those assigned to calcium-based phosphate binders, and the reduction in vascular calcification was greater in patients assigned to non-calcium-based
phosphate binders than in those assigned to calcium binders. The KDIGO 2017 clinical practice
guideline update for CKD-mineral and bone disorder (CKD-MBD) suggests restricting the dose
of calcium-based phosphate binders. Besides controlling blood phosphorus and parathyroid
hormone, we need to use calcium-based phosphate binders or non-calcium-based phosphate
binders, calcitriol or vitamin D analogs, and calcimimetics in a reasonable manner, in order to
avoid the increased calcium load and the poor calcium phosphate control, prevent or retard the
progression of calcification in dialysis patients.