Author’s response to reviews

Title: Coronary Calcification as a predictor of Cardiovascular Mortality in advanced Chronic Kidney Disease: a prospective long-term follow-up study.

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Author’s response to reviews:

Dear Editor,

We accept your apologies. The current situation has been a very uncomfortable for us.

Thank you for considering our manuscript, ‘Coronary Calcification as a predictor of Cardiovascular Mortality in advanced Chronic Kidney Disease: a prospective long-term follow-up study’ (BNEP-D-17-00526R1), sent to BMC Nephrology.

We really appreciate the opportunity to review our manuscript in order to fully address your concerns and comments of the referee.

Then, we are going to address point by point the reviewer’s recommendations.

Referee 1 comments:
The study is notable for its long-term follow-up though other sited studies have gone out as far as 7 years.
I am glad to see the avoidance of overfitting the model by taking a maximum of one variable per 10 events.

Thank you for these comments and feedback.

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I am curious about the decision to not consider repeat events for a given patient as additional episodes but instead to lump them together. It would seem that coronary calcification not just leading to an event but leading to repeat events would be clinically significant. What was the rational for this?

Commonly, a composite endpoint (fatal, non-fatal events) is analyzed with standard survival techniques. Thus, it is a common approach to time to first occurring event. We are aware that a relevant effect and acceptable statistical power might requires the observation of larger number of cases over long period of time.

We also considered that a single case (individual) might experience more than one even. It requires a different statistical approach, as Alexander Gill Cox proportional models. So, the collection of the data faced different handicaps. In the electronic file, it was recorded in a single individual recurrent event in the same time (e.g. atrial fibrillation, acute ischemic heart attack)- and also in different times. So, if it is considered:

- For each event type, recurrent or terminal, there exist separate event processes that might be correlated or not.
- The event-specific treatment effects related to the different event types may deviate.
- After occurrence of an event, the instantaneous baseline risk for a subsequent event, fatal or non-fatal, increases.
- The instantaneous risk for a subsequent event depends on the time when the previous event occurred.
- After occurrence of an event, the relative treatment effect for a subsequent event (in terms of the hazard ratio) may change.

Putting all these recommendations on a scale, and considering our study design, we selected the time-to-first event as the most sincere and suitable way to analyze the collected data. We try to clarify this aspect building a clearer sentence in the text and specifically mentioning a time-to-first event.

References


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I understand the need to transform non-parametric continuous variables via log transformation prior to analysis but the approach of using abase-2 log of the sum of the CaCs plus one seems very arbitrary. Could the authors comment on how this approach was arrived at?

We followed the proposed of Detrano et al (reference 18 in manuscrit) in 2008. The choice of this method allows to estimate how a double in calcium score affects the risk of mortality/events- each unit difference in the log-transformed variable stand for a doubling in the score.

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One of the most striking statistical issues with this study (though it would bias away from the null) in terms of general applicability of this data is the median HD vintage of 25 months. The median survival for incident HD patients is about ~24 months, those that live longer than this can live significantly longer but many tenuous patients die quickly and would thus might not be included in this analysis. In essence, many of the patients with the highest likelihood of death (and thus perhaps the most severe calcification) would likely have died before they were enrolled in this study. If anything, this would bias away from the association between calcification and death, but the authors should comment on this.

This issue is really interesting. Previous articles assessing the factors associated to death in incident HD did not include coronary calcification. So, data are really scarce (or just lack). The design of the enrollment did not allow us to detect what’s happen to this group. It’s true that it could be expected a more severe coronary calcification, and hence, a greater mortality. We have added some sentences named this potentially bias.

In recent years, mortality of incident hemodialysis has decreased due to improvement in the quality of the technique. According to the US Renal Data System, the life expectancy of those patients, whose enter a hemodialysis program range from 8 to 4.5 years. So that, an increasing length of time on dialysis is related to higher mortality rates. Mortality on hemodialysis tended to be higher after five years than between two to five years after dialysis initiation. Other identified risk factors related to mortality in these population are: age, cardiovascular diseases, vascular access, residual renal function, infections…

We set a minimum period of 6 months of permanence in the hemodialysis program. Thus, those cases incident in hemodialysis that death in a period inferior to 6 months were excluded. All enrolled cases were previously followed up in the Nephrologist outpatient office, and they started the renal substitution therapy in a programmed manner. In fact, the ANSWER study reports that the most potent predictor of early mortality was inadequate pre-dialysis treatment.


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The authors note that on multivariable analysis, only in HD patients, CaCs seems to have influenced overall mortality. While I do not dispute there is a trend there, the CI crosses 1 and thus is not technically statistically significant, perhaps the authors could note this while still acknowledging the trend.

Thank you for your comment. We’re just aware of this point. Exactly, the CI crosses 1 and is not statistically significant. We edited the test to emphasize it is a trend, but not a clear significative result.

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The authors note this as an unexpected result and postulate some explanations such as this being a one-time lab value but I remain struck by the lack of difference in Ca, PO4 CaxPO4 or PTH between the high and low CaCs groups. Granted everything they note, this flies in the face of all that would be expected as to the association between biochemical parameters and coronary calcification.

We also expected, a priori, difference in those parameters related to mineral and bone metabolism in chronic renal disease. I understand your point of view. We have wanted to give the best explanation as possible to these findings. While it is also true, that disorders in the calcium balance could be modulated by treatment (non-calcium-based phosphate binders, dialysate calcium concentration...) - and heterogenicity of this aspect in the selected cases. Besides, second hyperparathyroidism is the most frequent biochemical abnormality, but there are other important parameters that could not be measure as osteocalcin, 23 -fibroblast growth factor and klotho. Thereby, our sample is focused on advanced renal disease, unlike other previous articles, which included a proportion of cases with less advanced chronic renal disease.

Traditionally, hypercalcemia, hyperphosphatemia and secondary hyperparathyroidism have been linked to vascular calcification in chronic renal disease. However, it has been described, that an excess suppression of the PTH (or relative hypoparathyroidism) – that causes a decline in bone mineral turnover or adynamic bone- is also associated to progression of vascular calcification. Hence, plasma levels of calcium and PTH are not systematically associated/correlated to the net calcium balance nor the severity of the vascular calcification.

References


We hope that these comments and improvements have fulfilled the referees’ recommendations. Such way, your editorial office could consider the current version of the manuscript for its final acceptance.

If there are any further questions or comments after this revision, please do not hesitate to contact us.

Sincerely,

Marta Cano Megías