Reviewer's report

Title: Risk factors of one year increment of heart calcifications and survival in hemodialysis patients

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Reviewer: Rozemarijn Vliegenthart

Reviewer's report:

Is the question posed by the authors well defined? Yes.

Are the methods appropriate and well described? Not all well described.

Are the data sound?
Yes, as far as can be evaluated. However, for example no information is given about determination of valvular calcium score and about the follow-up procedure.

Does the manuscript adhere to the relevant standards for reporting and data deposition?
Not fully.

Are the discussion and conclusions well balanced and adequately supported by the data?
Unclear. At least there seems a discrepancy between the predictors of calcium progression in the multivariate analysis, and the predictive factors stated by the authors in the discussion.

Are limitations of the work clearly stated? No, limitations are not discussed.

Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Two articles by the same first author are referenced, although not extensively discussed.

Do the title and abstract accurately convey what has been found? Yes.

Is the writing acceptable? Yes.

Major compulsory revisions:
Introduction:
There are some more studies on the progression of the calcium score in dialysis patients (and risk factors for progression) than mentioned. These should be added and discussed, f.e. Tamashiro, Am J Kidney Disease 2001 and Ammirati, Peritoneal Dialysis International 2007.
The authors do not make a clear distinction between coronary calcifications and heart calcifications. They seem to have studied both. From the introduction it does not become clear what heart calcifications comprise, and what the idea is behind studying heart calcifications in addition to coronary calcifications. This needs more explanation in the Introduction, and more clear distinction of findings for both types of calcifications in the Results section.

Table 1 shows many data. In case of normally distributed variables, please (only) show mean and standard deviation. In case of non-normally distributed variables (hemodialysis duration and calcium scores), show median and interquartile range.

Since the calcium score has a skewed distribution, it is appropriate to use the natural log as outcome, as you did for some analyses. It is better to use \( \ln(\text{calcium score} + 1) \). By adding the 1 there is no loss of patients with a calcium score of 0. Please change.

Materials and Methods:

For scanning, a 64-MDCT scanner was used. Why was a retrospective gating technique used for calcium scoring? This is associated with a much higher radiation dose than the commonly used prospective triggering method. Since the 64-MDCT has 64 detectors of 0.6 mm, you would expect acquisition of 16 x 2.5 mm slices, if combining detectors. How is it possible that a 4 x 2.5 mm collimation was used? What was the reconstructed slice thickness?

More details are needed on the calcium scoring protocol. What software was used? How were heart calcifications calculated? How was prevented that aortic calcification was included?

Were patients informed about their calcium score?

No information is provided concerning the follow-up period and procedures. These need to be added.

Statistical analysis:

The strong advice is to include a statistician in the study, to assess the used statistical procedures.

In general, the statistical analysis is not detailed enough and unclear.

The specific variables that underwent logarithmic transformation are not mentioned.

The variables used in the multivariate logistic regression model should be defined.

It is not clear whether there was adjustment for baseline calcium score in the analyses with delta calcium score as outcome.

Probably, tertiles were used for independent variables, not dependent variables.

There is mention of tertiles for calcium scores, although it is not clear whether this concerns the baseline score or the difference after 1 year or both.
To investigate the association between calcium score/-progression and mortality, it is necessary to perform Cox regression analyses with adjustment for at least age and gender. A higher calcium score is related to a higher age and thus a higher risk of mortality. Kaplan Meier curves are therefore not very informative (unless age/gender are similar in the three calcium score tertiles).

Results:
The Results section is unclear. A number of different analyses results in different sets of predictors of progression. See tables 2 and 3: different predictors included in the tables.
Furthermore, it is unclear when the heart calcium score is meant, and when the coronary calcium score. Please clarify.

Although PTH is a statistically significant predictor of progression, the highest vs the lowest tertile only shows an increase of 0.3% in calcium score. On the basis of these results, PTH explains close to nothing of the progression. If the interscan variability for calcium scores is already around 10%, an increase of 0.3% is negligible, and one could even argue that PTH is a protective factor. Please discuss in the Discussion section.

Discussion:
Limitations of the study need to be added.
The authors mention a number of significant predictors based on their results, that does not seem to fit with the results in tables 2 and 3. For example, CRP is mentioned as significant predictor, but this is not visible in the logistic regression in table 2. And CRP is not added to the predictors in table 3, either. Please re-evaluate which determinants are predictors of progression based on your combined results. In addition, please compare results to those of other studies on determinants of progression in hemodialysis patients.

And was there difference between predictors for progression of coronary calcium and heart calcification?
The finding of relationship between higher progression and higher risk of mortality should be mitigated. Since a higher calcium score is also related to a higher progression rate (at least in absolute terms), and to increased risk of events, it is not surprising that there is a significant association between increase in calcium score and mortality. This could be mostly due to higher baseline calcium score. And in addition this could be (partly/largely) explained by differences in age and gender.

Minor essentials revisions:
Define abbreviations at first use.
Please explain the basis for the size of the study population: inclusion in certain period, power analysis, ..?
A better word for hemodialysis ‘vintage’ is probably duration.
How many patients were on phosphate binders (one or the other)?
Please use the same number of digits for the values in table 1.
Please include blood pressure values, percentage of patients with blood pressure lowering drugs and percentage with cholesterol lowering drugs in table 1.

Discretionary revisions:
In many articles on the progression of the calcium score, and the determinants for progression, the percentage difference is used, with >15% increase defined as progression, because of the significant interscan variability. See for example Barraclough in Nephrol Dial Transplant 2008 or Block in Kidney Int 2005. The strong suggestion is to add this analysis, divide the study population by yes or no progression, and then add a table on the mean value of the independent variables in both groups, with test for significant differences (see table 2, Ammirati).

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests