Reviewer’s report

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

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Reviewer: charles chazot

Reviewer’s report:

1- The patient cohort is prevalent with a large vintage. There is a high risk of confounding effects including patients on HD treatment for a long period as they appear as “survivors” or “selected”. Moreover only 8 have diabetes. It then appears that this etiology is under-represented in this cohort. The dialysis strategies appear very different from one patient to another (membrane type, convection use,…). All these limitations should be discussed.

The age of the patients is rather wide, as generally in these studies. As far as the diabetes mellitus is concerned, there was no intentional exclusion of patients with this diagnosis. In our dialysis patient cohorts, average dialysis proportion is slightly above 14%, therefore lower than in USA. Therefore diabetic patients in the studied cohort is not far from this percentage.

OK for the diabetes. It could appear in the new version. This answer does not answer the issue of the vintage. Basal Agaston score is associated with vintage. That appears logical. The longer you dialyse, the longer you are exposed to the risk factors for calcifications. However, if a patient on dialysis since 6 or 7 years has few or no calcifications for any reason (optimal therapy, good genes, good protective molecules), it is highly probable that he will not develop significant progression of calcifications in the 7th or 8th year of dialysis. By the way, vintage is not associated with the delta of Agaston score. This is the limitation of the prevalent cohort. The editor has to decide if it is necessary or not to add it in the discussion section (limitations of the study).

2- The normal BMI values are not those recommended by the EBPG for dialysis patients (>or=23 kg/m2). It may affect the relationship between BMI and calcification score and its evolution.

The average BMI of our patients cohort is 24, well in line with the general average of our hemodialysis patients population.

I am sorry but I do not by this answer. The EBPG point out that there is an increased risk of death for dialysis patients with a BMI <23Kg/m². However I realize that the normal values in the Table 1 that are referred to are for the
normal population and not for dialysis patients (the other typical example is for PTH…). It should be specified in the legend.

3- It is necessary to clarify when calcitriol was stopped

The calcitriol/paricalcitol was not necessarily stopped but adjusted to comply with the indications of current guidelines for the mineral metabolic parameters. This is now stated in the text.

OK

4- The presentation of statistics is confusing. It should be presented step by step: relationship between baseline factors and Agatston score, between baseline factors and Agatston score variation, Agatston score tertiles and their relationship with baseline parameters, LN transformations and their influence on the results. I would suggest one table by test.

Thanks for your suggestion. We accepted your advise and present now step by step the statistic procedure. First, in table 2 we showed the relationship between basal factors and basal Agatston score. Then, in table 3 and 4 the relationship between basal factors and delta Agatston scores are shown. In each table, on the left side, the bivariate non parametric association is reported, and, in the right side, the output of logistic regression, considering basal or delta Agatston scores as dependent variable. The regression in table 2 and 3 have been created by tertiles of basal and delta Agatston scores. In table 4, three different categorized delta Agatston scores have been considered.

We found that age and calcium in a progressive manner are the most important risk factors, assuming p-value smaller and gradually increasing values of OR, especially with increasing severity of calcification. It is clear that age and calcium are important risk factors, as shown in tab.3 and 4.

The LN transformations have been carried out, but finally discarded in the final manuscript because of no additional information.

OK. However I do not understand the design of the analysis in Table 4. Figure 1 provides tertiles values for the delta Agatston score (<12, 12-239 and >239) and the score delta in Table 4 is < or > 1000. Is it log transformed (a median?)?

5. Moreover percentage should be abandoned for OR and extreme values provided

In this second draft of the manuscript, we have abandoned percentage of OR. In logistic regression we showed confidence intervals of OR, for the only statistically significant variables in the models.

OK

6. What is the validity of a statistical test if the data transformation has discarded a
number of subjects? Please precise the validity of the transformation.

The LN transformation, as above mentioned, has been carried out even using the following procedure: in order not to lose valid cases, we tried to attribute the value of 1 to basal and delta Agatston score equal to zero. Then we made the LN transformation. However the results using the parametric statistics were identical, and so we decided to report just the non parametric solution.

OK

7. It is difficult to admit strong prediction when p=0.049 (basal Agatston score and higher mortality in the higher score tertile)

We agree with the reviewer that there is no reason to admit strong prediction with p=0.049. Mortality has been now studied through Cox regression. In addition now a graph for delta Agatston score and mortality has been created.

8. Why blood pressure was not added in one model as hypertension was found associated to calcification progression?

Thanks for your comment. The independent variables of the regression logistic models have been selected by the output of the non parametric correlation (Spearman). Indeed, firstly we tested the non parametric correlation to study the association between basal and delta Agatston score with clinical, biochemical data; then, thanks to this output, we computed logistic regression, considering independent variables those that were statistically associated to the Agatston score. Blood pressure was not found in our sample associated to basal or delta Agatston score, so that it wasn’t added in any regression models.

OK

9. The KDIGO does not recommend anymore the use of CaxPh product as a marker of BMD in CKD patients. The authors who use it should comment on that.

In this final manuscript, we have excluded CaxPh.

Typo errors or problems:
Table 1: “SIST” for “SYST”
Table 3: Fetuin: 5,84 E-07 4,6 E-12 – 0,074 ?? Explicit also in the legend (as it is in the text)..