Author's response to reviews

Title: "VITamine D Supplementation in RenAL Transplant Recipients: A Prospective Double Blind Multicentre Randomized Trial of Vitamin D Estimating the Benefit and Safety of a Treatment by Vitamin D3 at the Dose of 100,000 UI Compared With a Treatment at the Dose of 12,000 UI in Renal Transplant Recipients (VITALE): study protocol for a randomized, doubled blind controlled trial"

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Author's response to reviews: see over
Dear Editors,

Please find enclosed the revised version of our manuscript as well as a clean version with accepted changes. The modifications appear in read in the revised manuscript.

Our point-by-point responses to the referees are detailed below.

We appreciate the close reading of our manuscript by the reviewer. We hope the changes we have made have addressed their concerns. We hope the revised manuscript is now acceptable for publication in Trials.

Best regards,

Dr Marie COURBEBAISSE

Reviewer's report:
This is a study protocol on a randomized trial comparing the effects of vitamin D supplementation at high versus low dose for 2 years in renal transplant recipients. Primary outcome is a composite endpoint of diabetes mellitus, major cardiovascular events, de novo cancer, and death. The authors have great experience with conducting such trials and are established experts in the field of vitamin D. The work is definitely worth publishing and I have only some minor comments.

We sincerely thank the reviewer for these encouraging comments.

Minor Essential Revisions
1) The authors should use the CONSORT statement for their work and should revise their work by adhering to this guideline (CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials; Journal of Clinical Epidemiology 63 (2010) e1ee37)

We have followed the usual instructions of Trials to present our protocol and it was not mentioned that we had to follow such guidelines. Moreover, we took care to present our work exactly as an interventional study protocol on vitamin D treatment after renal transplantation previously published in Trials:


However, according to these guidelines, we have changed the title as follow:

“VITamine D Supplementation in RenAL Transplant Recipients: A Prospective Double Blind Multicentre Randomized Trial of Vitamin D Estimating the Benefit and Safety of a Treatment by Vitamin D₃ at the Dose of 100,000 UI Compared With a Treatment at the Dose of 12,000 UI in Renal Transplant Recipients (VITALE): study protocol for a randomized, doubled blind controlled trial”
As requested, we also gave more details regarding:

- The interventions for each group with sufficient details (see below).
- Subgroup analysis (see below).

2) The authors provide a good overview of the existing literature but I would suggest to be more balanced regarding the potential beneficial effects of vitamin D. In detail, they should discuss in more detail that previous observational data may be simply explained by reverse causation or confounding.
I would also suggest to consider revising the title and primary research question because in my opinion it should not only be looked at benefits but also at potential adverse effects. This has to be considered throughout the manuscript. In addition, the introduction needs some updates since some recent original papers or meta-analyses on the association between vitamin D and cardiovascular risk factors have not been referenced (e.g. in the field of diabetes).

As requested, we have carefully followed these instructions throughout the text (in red) and updated the references (see references 48, 49, 52, 54, 62, 73, 76 to 81, 89 and 90 in red in the references section).
We also have modified the title (see above).

3) I would suggest including more references and rationale on the sample size calculation and on e.g. why they estimate the incident risk of a first event of the composite endpoint to be around 40%.

We have added references to justify the incident risk of a first event of the composite endpoint and modified the text as follow: “Over a two-year follow-up period, we estimate, according to previous reports in the literature, that the incidence of a first event of the composite endpoint will be around 22% in our population (6% for de novo diabetes [91,92], 6% for major cardiovascular events [93-95], 7% for de novo cancers [15,96] and 3% for patient death). This 22% global estimated incidence does not take into account the fact that some patients may experience several events of the composite endpoint during the follow-up period. According to the results of the numerous observational studies showing an inverse association between 25OHD concentrations and various clinical events and to the ones of the few interventional trials showing effects of high dose vitamin D supplementation on these events (detailed above), we estimate that the overall decrease in the incidence risk of a first event of the composite endpoint will be around 40% in the high dose group compared to the low dose group (33% decrease for de novo DM, 40% decrease for major cardiovascular events and 50% decrease for de novo cancer).”

In addition, the limitations of using a composite endpoint have to be discussed in more detail.

The limitation of using a composite endpoint was discussed in the discussion section as follow: “In our study, we choose a composite criterion for efficacy. The main advantages supporting this choice are that it increases statistical efficiency because of a higher event rate, which reduces sample size requirement. Besides it helps investigators avoid an arbitrary choice between several important outcomes that refer to the same disease process.
Composite outcomes can be misleading when treatment effects vary across components with very different clinical importance. In our study, the rate of each event but death is of similar magnitude. Moreover, we hypothesize that the rate reduction of each event composing the endpoint will be between 30% and 50% giving a mean of 40% reduction overall. We also hypothesize that the drug will not affect death but this latter was introduced in the composite endpoint because of competing risk with major cardiovascular events. In order to limit misleading interpretation, we will clearly present data for all components and discuss the part of each in the total reduction of the composite event rate if any.”

4) The authors include several secondary endpoints and I wonder whether they all analyze these endpoints with a statistical significance for the p-value of <0.05. This has to be discussed. More details on the assessment of the secondary endpoints would also be welcome.

*Usually, multiplicity is considered when there are multiple primary endpoints, multiple component outcomes, multiple patient populations or multiple dose-placebo comparisons. Our clinical trial has one composite primary outcome and several secondary endpoints. An adjustment using Hochberg procedure will be used for the analysis of the components of the primary criteria. The others secondary analyses are exploratory. Drug efficacy will not be ascertained on them thus no adjustment for multiple testing will be done. The following sentence has been added in the paragraph entitled “Statistical analysis”: “Adjustment for multiple testing will be performed using Hochberg procedure for the components of the primary criteria.”*

5) Using the Diasorin assay instead of a mass spectrometry method is a limitation that has to be discussed.

*We added the following explanation regarding 25OHD measurement in the paragraph entitled “Patients follow-up”: “Vitamin D measurements after randomization will be centralized and performed at the end of the study. Given the absence of standardization and reference method of vitamin D measurement when we submitted the VITALE trial to funders (early 2011), we planned to use the most referenced method (DiaSorin radio-immunoassay, Stillwater, MN, USA) [100]. Things have changed and a reference method is now accepted [101] and used in an international program, the Vitamin D standardization program (VDSP), to harmonize vitamin D results [102]. We thus will use the assay, either immunoassay or commercial LC-MS-MS assay, that, at the end of the VITALE study, will provide results that are at the closest of the reference method [103].”*

Regarding the 25(OH)D values the authors should also show conversion factors for nmol/L.

*“30 ng (or 75 nmol/L)” has been added in the abstract and in the full text.*

Some more detailed data on the study medication and the assessment of compliance would be also welcome.

*We have added the following details regarding the study medication in the “study intervention” paragraph: “Each 2 mL vial will contain either cholecalciferol 100,000 IU or 12,000 IU plus Butylhydroxytoluene 0,2mg, Saccharine 1,2mg, Sorbic Acid*
4.00mg, Lemon Essential Oil 6.0mg and Glycosylated Glycerides Polyoxyethylenes in sufficient quantity to have 2 mL. High dose and low dose vials are produced by Crinex (France).”

*We have added the following sentence regarding the study medication in the paragraph entitled “patients follow-up”: In order to assess compliance, patients will be asked to return their empty vials at each follow-up visit.*

6) I wonder whether the authors plan some additional subgroup analyses?

*Yes, we plan to perform some additional post-hoc subgroup analyses (according to: i.e. baseline 25OHD levels, achieved 25OHD levels, VDR and vitamin D binding protein polymorphisms, corticosteroid treatment…). This has been added at the end of the paragraph entitled “Statistical analysis”*

7) There are some typos in the manuscript e.g. Abstract “include a total 640 renal transplant recipients” instead of include a total 640 of renal transplant recipients”

*We have corrected typographical errors.*