Reviewer's report

Title: VITALE: VITamine D Supplementation in RenAL Transplant Recipients: A Prospective Double Blind Multicentre Randomized Trial of Vitamin D Estimating the Benefit 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.

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Reviewer: Stefan Pilz

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.

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)

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).

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

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.

5) Using the Diasorin assay instead of a mass spectrometry method is a
limitation that has to be discussed. Regarding the 25(OH)D values the authors should also show conversion factors for nmol/L. Some more detailed data on the study medication and the assessment of compliance would be also welcome.

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

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” Please correct.

**Level of interest:** An article of importance in its field

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

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No competing interests.