Author’s response to reviews

Title: Vitamin D versus placebo as adjunctive treatment of heart failure patient quality of life and hormonal indices: A randomized, double-blind, placebo-controlled trial

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Dear Dr. Cottini,

Thank you very much for the opportunity to revise our manuscript. We have made all suggested changes to our manuscript, and hope that the reviewers find our changes now meet their expectations. You will find the changes highlighted or in red font within the text of the manuscript and below. Please do not hesitate to contact me with questions. Thanks again.

Best regards,
Heidi Moretti, MS, RD

Reviewer 1:

Suggestion 1: Commentary In this article, authors report the results of their clinical randomized trial with supplementation of vitamin D in the diet of patients with chronic heart failure (CHF); subsequently they address the issue of the possible relationship between low serum vitamin D levels and increased risk of poor clinical outcomes in CHF. - Authors should point out in the Discussion that although plausible evidences has been accumulated over the years in favor of pharmacologic supplementation with vitamin D (cholecalciferol or ergocalciferol) for CHF patients, no consistent demonstration of systematic benefit has emerged so far with regard to hard clinical endpoints, that is, death from all causes, cardiovascular death, and frequency of
heart failure hospitalizations. This is why the administration of vitamin D supplements is not suggested by the recent (2016) guidelines for CHF treatment released by the ESC. Please highlight this point in the Discussion.

The authors agree with the reviewer’s comments, and have added this to page 16-17. The conclusions from our research support prior findings that vitamin D3 supplementation at pharmacological doses may benefit patients with heart failure (7,10-12). However, clinical trials using vitamin D3 supplementation with hard endpoints such as cardiovascular death, hospitalizations, or all-cause mortality still have not yet been conducted. So far, vitamin D supplementation guidelines have not been included in heart failure guidelines by European Society of Cardiology or American College of Cardiology (26-27). Adequate research of vitamin D measuring sufficient repletion in a large number of patients also has not been performed.

Suggestion 2: Severe hypocalcaemia associated with rickets must always be kept in mind among the causes of dilated cardiomyopathy and impaired cardiac function in infants. If diagnosed and treated in time, dilated cardiomyopathy and severe heart failure related to rickets respond well. However, while vitamin D deficiency has been shown to be a proven cause of HFREF in neonatal and pediatric age, it would be correct to recognize that heart failure caused by hypovitaminosis D (diagnosed by means of hemato-chemical determination of serum 25 (OH) - vitamin D levels) is not a very common condition. Please discuss on this issue in the manuscript.

Thank you for this astute recommendation. We have clarified this on page 4. Vitamin D may help resolve cases of hypocalcemic cardiomyopathy as shown in case reports of pediatric cardiomyopathy and heart failure related to rickets[13-14]. This is a rare condition, therefore, extrapolating these data to the adult heart failure population would be inaccurate so inferences can’t necessarily be made for the adult heart failure population.

Suggestion 3: Background."Vitamin D deficiency is common in heart failure; prevalence ranges between 89-98% [8-9]". In my opinion, this assertion is devoid of the necessary documentation (the cited references are inappropriate or misleading). Please rectify or clarify better.

The authors agree. We have modified the background section to more accurately reflect prior research on page 4. Vitamin D deficiency appears to be prevalent in subsets of patients with heart failure, including elderly patients at high northern latitudes or patients with concomitant kidney disease [8-9].
Suggestion 4: It's well known that for CHF treatment some beta-blockers (carvedilol, bisoprolol, metoprolol, nebivolol) have been validated, for which there has been a class 1A indication. Notably, use of these drugs for HFREF patients is not dependent on the demonstration of a high heart rate or a clinically evident excess of adrenergic tone. Indeed, they have been strongly recommended even in HFREF patients with normal heart rate, namely put between 60 and 85 beats/min. Conversely, if a vitamin D3 treatment has to be started in a patient with HFREF, you could wonder whether such treatment should be carried out in the presence of a proven nutritional deficiency (25 (OH) vitamin D <30 ng/ml) or, like in the case of beta-blockers, vitamin D should be administered to HFREF patients as many as possible. Please address this issue in the Discussion.

Determination of vitamin D serum levels is present in the work-up of patients with chronic kidney disease; on the contrary it is not included in the hematocellular determinations usually performed in CHF patients who have not been diagnosed with a cardiorenal syndrome (i.e., CHF patients with normal serum creatinine).

We have expanded our discussion to include these important points made by reviewer 1 on page 22. See below as well:

A question remains as to whether heart failure patients require vitamin D3 treatment only in the cases of 25(OH)D <20-30 ng/ml, or if all patients with heart failure would benefit from supplementation despite normal circulating 25(OH)D levels. As of yet, evaluation of vitamin D status is not routinely performed in heart failure. However, patients with chronic kidney disease patients do have routine monitoring in their guidelines (56?). The example is made for class 1A indication for beta-blocker use in patients with heart failure with reduced ejection fraction even when the heart rate is not elevated (26-27). In that situation, heart rate is a surrogate and possibly imperfect marker for upregulation of sympathetic nervous system in heart failure. In the case of vitamin D, one flaw of previous research may be lack of identification of highest risk patients by not measuring 25(OH)D levels less than 20-30 ng/ml. With the potential benefit that we found for QOL and neurohormonal indices, monitoring 25(OH)D and subsequent repletion has some scientific merit. Further research is needed to elucidate whether vitamin D should be given with or without monitoring serum levels.

Reviewer 2:

Suggestion 1: Written English in the manuscript needs some language corrections. For example) A total of 17 pts -> A total of 17 patients BNP was improved in treatment compared to placebo -> BNP was improved in treatment group compared to placebo group

The authors agree, and have made multiple changes to language within the text. These are highlighted or in red within the text throughout the manuscript.
All results were adjusted for baseline 25(OH)D. In a total of 17 patients, BNP improved in the treatment group, Δ+30±950pg/ml, compared to the placebo group of 19 patients, Δ+400±1900 pg/ml (p=0.002).

Suggestion 2: In Table 1; Baseline characteristics were similar between both groups for all parameters, the results (such as p values) of t-test between placebo group and treatment group should be shown in Table 1. In Table 2; Results of t-test between placebo group and treatment group should be shown in Table 2. Change of Title of Table 1 would be better; [listed as mean ±standard deviation (SD) or number and percentages] -> below the Table 1 Change of Title of Table 2 would be better; [listed as mean absolute values + standard deviation (SD)] -> below the Table 2 Change of Title of Table 3 would be better; [listed as mean ±SD, 95% CI] -> below the Table 3

All of the recommendations for the table changes have been made. See highlighted areas in the tables for changes.

Suggestion 3: Circulating PTH level (90±96 pg/mL) in baseline of Placebo group was higher than that (58±28 pg/mL) of Treatment group, although serum calcium and 25(OH)D levels were similar between both groups. What do the authors think of the reason?

Thank you for pointing this out. We made changes within the text explaining this on page 19. Also see below:

This is possibly because our enrollment criteria did not include PTH parameters for exclusion or inclusion. However, with no change for PTH in the placebo group after 6 months, our reduction of PTH in the treatment group appears to be related to vitamin D3 repletion. Serum calcium did not vary between the groups, but we did not allow patients with hypercalcemia into the study for safety concerns. This may explain why the baseline calcium levels looked similar between groups. Additionally, prior research demonstrates that vitamin D3 treatment does not cause hypercalcemia until 25(OH)D concentrations exceed >200 ng/ml (22).