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Vitamin D supplementation in heart failure: case closed?

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This editorial refers to ‘Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4000 IU of vitamin D daily’[†], by A. Zittermann *et al.*, on page 2279.

Vitamin D deficiency is one of the most common nutritional deficiencies, affecting hundreds of millions of people in western societies, but also in Africa, the Middle East, and Asia.¹ Although mostly denoted as a vitamin, vitamin D in fact is a pleiotropic hormone that acts as a transcription factor, with global effects on gene transcription; it has been suggested that up to 3% of the entire humane genome is regulated by vitamin D.² Transcriptional activity is regulated by the vitamin D–vitamin D receptor (VDR) complex which, in concert with a complex set of co-repressors and co-activators, switches on or off downstream genes. As a result, vitamin D deficiency has been associated with multiple conditions and diseases, in almost all organ systems.³ More specifically, a low vitamin D concentration appeared to be associated with a poor prognosis in patients with heart failure.^{4,5}

Mechanistic studies have provided potential mechanisms that may explain this relationship: vitamin D directly inhibits renin transcription,^{5–7} and regulates genes and pro-inflammatory cytokines involved in tissue fibrosis.^{4,8} Other, indirect, effects may also define why vitamin D deficiency is associated with increased cardiovascular morbidity and mortality: low vitamin D levels directly increase parathyroid hormone (PTH) levels, inducing deleterious effects on cardiac function and structure.⁹ Additionally, vitamin D deficiency in parents has been associated with hypertension in (vitamin D-sufficient) offspring via epigenetic modifications.¹⁰

The effects of vitamin D on the cardiovascular system are thus multifold and strongly suggest that restoration of vitamin D levels may improve cardiac function and outcome. Associative studies, however, cannot prove causality. In order to prove causality, it is essential to embark on interventional studies.

In the current issue of the journal, Zittermann and colleagues have examined the effects of long-term vitamin D supplementation

on hard cardiovascular outcomes in a moderately large sized randomized placebo controlled trial in patients with heart failure.¹¹ This trial is important since it shows that vitamin D supplementation does not improve such outcomes, and, more importantly, suggests that safety may potentially be an issue.

The study by Zittermann *et al.* is methodologically sound: it has a relatively large sample size and adequate long-term follow up of 3 years. Therefore, in our opinion, these findings should carry substantial weight as they allow evaluation of hard outcomes such as death and hospitalizations. Vitamin D supplementation boosted vitamin D levels quite readily, and patients on supplementation remained vitamin D sufficient for the entire study period. Patient recruitment, however, was an issue: although the study initially was powered to recruit 934 patients, recruitment had to be stopped after 31 months at a total of 400 patients because too many patients were already using vitamin D supplements, vitamin D levels were >75 nmol/L (which was the cut-off point for inclusion), or patients declined to participate in the study.

Besides all-cause mortality, this study also considered mechanical circulatory support (MCS) as an (secondary) outcome parameter, since heart transplantation remains scarce because of lack of donors. Interestingly, it was observed that vitamin D supplementation may be associated with more frequent need for MCS. Although this additional analysis provides potentially important and valuable information, we question the importance of this relatively rare event; EVITA was not powered for this secondary outcome analysis, and the result may very well be a chance finding. The overall numbers of MCS systems were low (28/199 in the vitamin D group vs. 15/201 in the placebo group), with a reported *P*-value of 0.031. Given the number of endpoints evaluated, we would have corrected for multiple testing, resulting in a *P*-value exceeding 0.05. We nevertheless agree with the authors that this finding certainly warrants caution; supplementing vitamin D either chronically or in mega dosages, as done in some countries, has (again) not been proven to be efficacious, while safety issues cannot be accepted in this light. Furthermore, a recent intervention trial in the general population also did not provide any

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Table 1 Overview of studies on functional effects of vitamin D supplementation in patients with HF

Study	No. of patients (vitamin D/ control)	Vitamin D dose	Follow-up	Death	Hospitalization, MCS	LVEF	6MWD	Renin	NT-proBNP
Schleithoff <i>et al.</i> (2006)	123 (61/62)	1000 IU daily	9 months	+/-		+/-			+/-
Schroten <i>et al.</i> (2013)	101 (50/51)	2000 IU daily	6 weeks					+	+/-
Thadhani <i>et al.</i> (2012)	227 (112/115)	2 µg/day paricalcitol	48 weeks		+	+/-			
Witham <i>et al.</i> (2010)	105 (53/52)	100 000 IU at baseline and week 10	20 weeks				+/-	+/-	
Witte <i>et al.</i> (2016)	223 (114/109)	4000 IU daily	1 year			+	+/-		
Zitterman <i>et al.</i> (2017)	400 (199/201)	4000 IU daily	3 years	+/-	-				
Overall effect	1179 (589/590)	1000–4000 IU daily	6 weeks–3 years	+/-	-	+/-	+/-	+/-	+/-

Green (+) = significant improvement vs. control group; orange (+/-) = no improvement, no worsening vs. control group; red (-) = significant worsening vs. control group; grey = no information available.

6MWD, 6 min walking distance; IU, International unit; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; NT-proBNP, N-terminal pro brain natriuretic peptide.

benefits from vitamin D supplementation.¹² Given this lack of proof, we consider it surprising and somewhat concerning that vitamin D supplementation has become such a normal thing in our society, especially in the absence of safety data. More trials are awaited, and we hope these will evaluate efficacy and safety.

How do the results from this study compare with outcomes in previous randomized clinical trials investigating vitamin D supplementation in heart failure? *Table 1* provides an overview of vitamin D intervention studies with >100 patients.^{13–16} Overall, the effect of vitamin D supplementation in patients with heart failure should be considered neutral. In more detail, vitamin D supplementation did not improve clinical outcome parameters such as mortality, hospitalization, left ventricular ejection fraction (LVEF), or 6 min walking distance (6MWD), or pre-clinical biomarker plasma levels such as NT-proBNP and renin. Interestingly, only the VINDICATE study¹⁷ suggested that vitamin D might confer cardioprotection as it met one of the secondary endpoints, i.e. an ~6% improvement in LVEF. Nevertheless, it should be noted that also in VINDICATE vitamin D supplementation (4000 IU, 6 months) did not affect 6MWD (which was the primary endpoint), nor did it lower NT-proBNP levels.

What might be reasons for the apparent disparities between the various studies? First, different studies have had different (surrogate) endpoints. Although there is no doubt that inflammation and renin release are contributory factors in heart failure, we still do not know the meaning of small improvements in these markers with regard to heart failure outcomes. Secondly, dosing, follow-up, as well as primary and secondary endpoints varied substantially between studies, making direct comparisons difficult. The improvement in LVEF in VINDICATE was very substantial—comparable with most beta-blockers,¹⁷ which generally are associated with a reduction in mortality of ~35%. This decline in mortality, however, has not been confirmed in the current study from Zittermann and colleagues. As we have no LVEF data in the current study, the exact reasons for this discrepancy remain unclear.

What should be the current recommendation for patients with heart failure with respect to their vitamin D status? It seems that vitamin D follows the path of several other surrogate endpoints of heart failure. There is undisputedly an association between vitamin D deficiency and poor outcome, yet supplementing this deficiency apparently does not do the trick. Probably, low vitamin D levels may be a consequence of poor overall health status and most probably also advanced heart failure, which itself is associated with renal dysfunction, malabsorption due to congestion, and a sedentary lifestyle. Supplementing vitamin D may normalize vitamin levels but cannot alter these factors, potentially explaining why vitamin D supplementation has not been successful to improve clinical outcomes. Since it is doubtful whether larger heart failure outcome trials will follow, we believe the currently available evidence does not provide solid proof to advocate widespread use of vitamin D supplements for patient with heart failure.

Conflict of interest: none declared.

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