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Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4000 IU vitamin D daily

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Aims Circulating 25-hydroxyvitamin D (25OHD) levels <75 nmol/L are associated with a nonlinear increase in mortality risk. Such 25OHD levels are common in heart failure (HF). We therefore examined whether oral vitamin D supplementation reduces mortality in patients with advanced HF.

Methods and results Four hundred HF patients with 25OHD levels <75 nmol/L were randomized to receive 4000 IU vitamin D daily or matching placebo for 3 years. Primary endpoint was all-cause mortality. Key secondary outcome measures included hospitalization, resuscitation, mechanical circulatory support (MCS) implant, high urgent listing for heart transplantation, heart transplantation, and hypercalcaemia. Initial 25OHD levels were on average <40 nmol/L, remained around 40 nmol/L in patients assigned to placebo and plateaued around 100 nmol/L in patients assigned to vitamin D. Mortality was not different in patients receiving vitamin D (19.6%; $n = 39$) or placebo (17.9%; $n = 36$) with a hazard ratio (HR) of 1.09 [95% confidence interval (CI): 0.69–1.71; $P = 0.726$]. The need for MCS implant was however greater in patients assigned to vitamin D (15.4%, $n = 28$) vs. placebo [9.0%, $n = 15$; HR: 1.96 (95% CI: 1.04–3.66); $P = 0.031$]. Other secondary clinical endpoints were similar between groups. The incidence of hypercalcaemia was 6.2% ($n = 10$) and 3.1% ($n = 5$) in patients receiving vitamin D or placebo ($P = 0.192$).

Conclusion A daily vitamin D dose of 4000 IU did not reduce mortality in patients with advanced HF but was associated with a greater need for MCS implants. Data indicate caution regarding long-term supplementation with moderately high vitamin D doses.

Trial Registration Information clinicaltrials.gov Identifier: NCT01326650.

Keywords Vitamin D • Heart failure • Randomized clinical trial • Mortality • Survival • Calcium • Hypercalcaemia • Mechanical circulatory support

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Introduction

In patients with heart failure (HF), 25-hydroxyvitamin D (25OHD) levels <75 nmol/l are common.[1,2] There is accumulating evidence that 25OHD levels below this threshold are non-linearly associated with increased mortality risk.[3] With respect to HF mortality, an almost threefold greater risk of death has been reported, when comparing patients with 25OHD levels <25 nmol/L to persons with 25OHD levels ≥75 nmol/L.[4] Moreover, vitamin D supplementation was associated with improved left ventricular ejection fraction[5,6] and a 25% and 30% reduction in the risk of HF events and fatal HF events, respectively.[7] In these vitamin D supplementation trials, initial 25OHD levels were on average 37–44 nmol/l.[5,6,8]

While the aforementioned analyses were based on large multivariable-adjusted prospective cohort studies or randomized controlled trials (RCTs), mortality was only a secondary outcome in these investigations. The EVITA (**E**ffect of **Vi**tamin D on All-cause Mor**ta**lity in heart failure patients) trial was conducted to examine whether vitamin D supplementation is able to reduce mortality in patients with end-stage HF.

Methods

Study design

EVITA is an investigator-initiated, single-center, prospective, randomized, placebo-controlled clinical trial which was performed at the Clinic for Thoracic and Cardiovascular Surgery of the Heart and Diabetes Center North Rhine-Westphalia, Germany. The Center for Information Management at the Clinic coordinated the study and managed the database. The investigation was performed according to the CONSORT statement for RCTs (www.consort-statement.org). The study protocol was approved by the ethics committee of the Medical Council of Westfalen-Lippe, Germany (No.:2010-052-f-A), and was registered at clinicaltrials.gov as NCT01326650 and at EudraCT as 2010-020793-42.

Patients

Between November 2010 and July 2013, patients with HF who attended the HF unit of our clinic were enrolled. Patients were eligible if they were 18–79 years of age and if they were classified as having New York Heart Association functional class II or higher. Included patients were either in a long-term program for heart transplantation or were already listed as 'elective' for heart transplantation. Key exclusion criteria were 'high urgent' listing for heart transplantation, hypercalcaemia (plasma calcium >2.75 mmol/L), supplemental vitamin D intake >800 IU/d, and baseline 25-hydroxyvitamin D levels ≥75 nmol/L. All study participants gave written informed consent to the study procedures before study randomization.

Randomization, masking, and treatment allocation

Randomization was computer based in blocks of six and stratified by sex. Patients were allocated to receive either 4000 IU vitamin D_3 daily or a matching placebo in a 1:1 ratio. A daily dose of 4000 IU vitamin D_3 was chosen for efficacy and safety reasons. Given that (i) habitual vitamin D intake of our HF patients is on average 50 IU/day,[9] (ii) a commonly used lower target value for adequate circulating 25OHD levels is 75 nmol/L,[10] (iii) a daily vitamin D dose of 3800–5000 IU is required to attain serum 25OHD concentrations >75 nmol/L,[11] and (iv) classical signs of vitamin D intoxication such as hypercalcaemia have not been reported when 25OHD levels were ≤374 nmol/L,[10,12] we concluded that a supplement of 4000 IU daily may be sufficient to increase 25OHD levels of most study participants to 75 nmol/L but not to toxic concentrations. Of note, in November 2010 the Institute of Medicine (IOM) released a new recommendation on vitamin D intake, where the upper tolerable intake level (UL) of vitamin D for adults was increased from 2000 IU to 4000 IU daily.[13]

Randomization was performed by an external clinical pharmacologist (H.K.B.). The randomization list was sent directly and exclusively to the Center for Information Management at the Clinic for Thoracic and Cardiovascular Surgery, that performed the masking. Participants, their treating physicians, and any individual of the HF unit of our clinic were masked to treatment allocation. In addition, data analysis was performed by a blinded external biostatistician (M.D.).

Patients had to take eight drops of an oily vitamin D preparation (Vigantol oil, Merck, Darmstadt, Germany) or eight drops of a matching vitamin D–free oil daily (Migliol oil; Merck) during a meal. Allocation concealment was achieved by sequentially numbered drug containers. Study duration was 3 years and the last patient terminated the study in July 2016. Blood specimens were collected every 6 months between 8 and 11 AM after an overnight fast. Safety parameters such as plasma calcium, creatinine, and circulating 25OHD were measured immediately after blood collection and patients were excluded from further study participation in case of hypercalcaemia (reference range of our laboratory: 2.1–2.75 mmol/L) or of 25OHD levels >374 nmol/L.[13] Aliquots of blood samples were stored at -80 °C for additional analyses.

Endpoints

Primary endpoint was all-cause mortality. We used four sources of information to identify the primary endpoint: repeated contacts with the participants, contacts with family physicians, a regular review of medical records, and consultation of the respective registration office. Causes of death were assessed from the medical records or by contacting the family physicians. Secondary endpoints were hospitalization, resuscitation, mechanical circulatory support (MCS) implantation, high urgent listing for heart transplantation, heart transplantation, hypercalcaemia, and circulating 25OHD levels >374 nmol/L. In case of hospitalization, the underlying cause was also assessed (routine, cardiac-related, or other cause). Decisions for high urgent listing for heart transplantation or MCS implantation were made in weekly institutional and interdisciplinary expert conferences. The criteria are described elsewhere.[14] Secondary clinical endpoints were assessed by the same sources used to identify the primary endpoint (exception: registration office). Regarding hypercalcaemia and hypervitaminosis D, assessment was exclusively based on plasma levels.

Adherence to study medication

Since prescription refill records and bottle counts often overestimate true adherence rates, and direct questioning at the patient interview might not provide accurate assessments,[15] we used open-ended, non-threatening, and non-judgmental questions to assess adherence and to calculate attrition rates. Moreover, we used in-study levels of circulating 25OHD to assess adherence until patients died, terminated the study as planned, dropped out, or were lost to follow-up.

Biochemical analyses

Calcium, phosphate, creatinine, and brain natriuretic peptide were routinely measured using the Architect auto-analyzer (Abbott, Wiesbaden, Germany). The Liaison auto-analyzer (DiaSorin, Stillwater, MN, USA) was used to measure 25OHD levels.[16] The MDRD formula was used to estimate glomerular filtration rate (eGFR).[17]

Statistics

A total sample size of 934 (467 in each group) was projected for the study to have 80% power to detect a 36% reduction in the primary endpoint

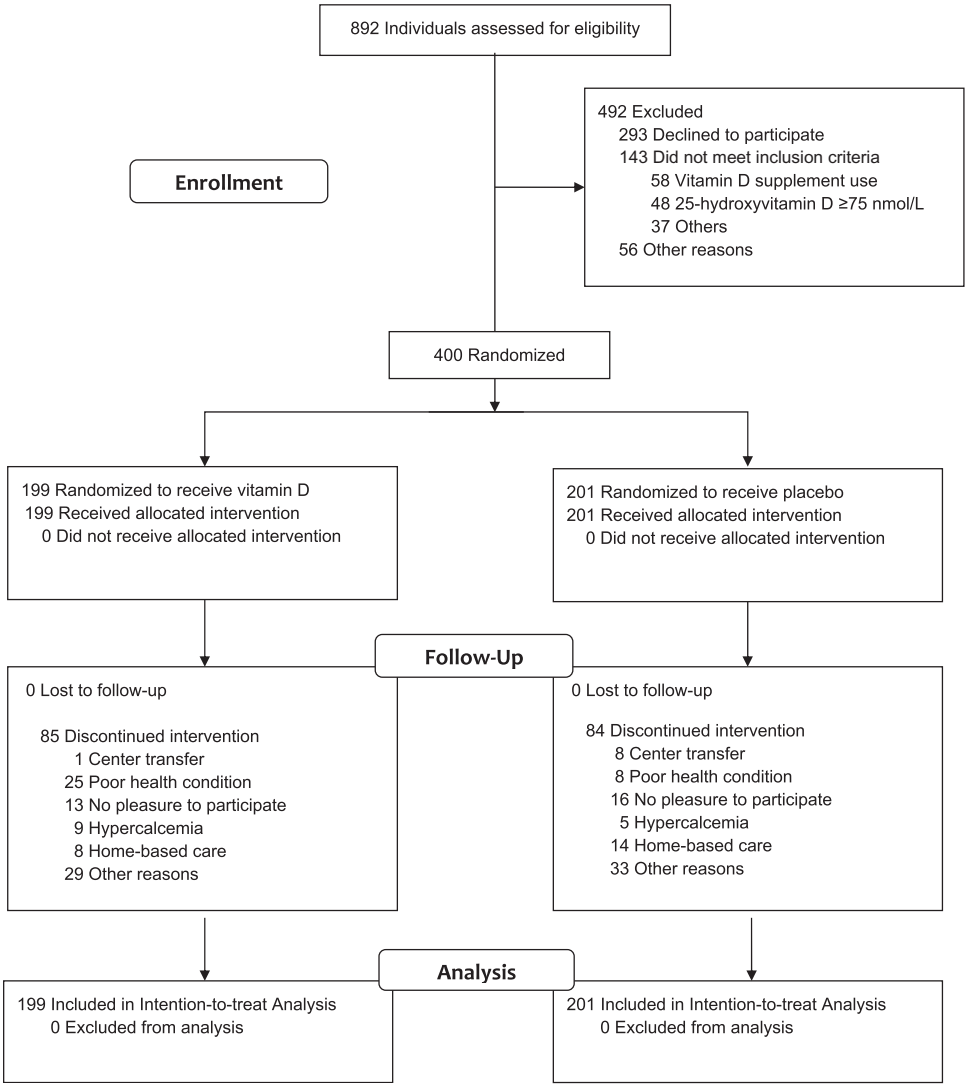

Figure 1 Study flow chart.

with vitamin D compared with placebo, using a 2-sided log-rank test at an α level of 0.05. The sample calculation assumed 18 months of recruitment, 10% mortality per year, and a follow-up of 36 months. However, recruitment was slower than anticipated. Therefore, after screening 892 patients and 31 months of recruitment, enrolment was stopped by the study coordinators (A.Z. and J.B.) at the inclusion of 400 patients, 199 in the vitamin D group and 201 in the placebo group. A large number of patients declined to participate, had 25OHD levels ≥75 nmol/L or were already taking vitamin D supplements (*Figure 1*). Given the aforementioned assumptions, the study now had 80% power to detect a 62% reduction in the primary endpoint with vitamin D compared with placebo.

Cumulative incidence of the primary and secondary endpoints was calculated using the Kaplan–Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. The proportionality of hazard assumption was evaluated by the Schoenfeld test.[18] Proportionality was confirmed for all endpoints. All statistical analyses regarding primary and secondary endpoints were prespecified, unless otherwise stated, and were conducted according to the intention-to-treat principle. Regarding secondary clinical endpoints, patients who were lost to follow-up were censored at their last visit. With respect to biochemical secondary endpoints, patients who dropped out were censored at their last blood sampling. Because recent data indicate a potential interaction between baseline 25OHD levels and mortality,[19] we also performed pre-specified analyses in subgroups with initial 25OHD levels <30 nmol/L and ≥30 nmol/L. Tests for interaction were based on the Wald test for the interaction term (25OHD subgroup x study group), with both the 25OHD subgroup and study group in the model as categorical variables.

To avoid elimination of subjects with missing biochemical data, the influence of time (trend) on plasma calcium, 25OHD, phosphate, and kidney function was analysed using linear mixed models. Fixed effects were treatment, time (month), and the interaction of treatment x time. Categorical variables are summarized as numbers and as a percentage of observations. Continuous parameters are presented as median and

interquartile range or mean and 95% CI, when appropriate. Non-normally distributed data, as checked by quantile–quantile plots and the Kolmogorov–Smirnov test, were normalized by logarithmic transformation before use in parametric statistical analysis. The Mann–Whitney U-test was used for group comparisons. We considered *P*-values <0.05 (two-sided) as statistically significant. Because the pre-specified primary analysis of the mortality rate over time was limited to the single *P*-value for treatment interaction, we did not adjust for multiple testing. However, caution is warranted when interpreting the *P*-values for our secondary and exploratory outcomes. Analyses were performed using SPSS version 21.0 (IBM Corp, Armonk, NY, USA) and R (version 3.2.2) with the routines in the survival and nlme packages.[20]

Results

Baseline characteristics and study adherence

Characteristics of the study groups are given in *Table 1*. The vast majority of patients were male and suffered from either dilated or ischaemic cardiomyopathy. Eighty percent of patients had pacemaker implants, and ~20% were already electively listed for heart transplantation. Forty-one percent of patients had baseline 25OHD levels <30 nmol/L and an additional 38.0% had levels between 30 and 50 nmol/L. Initial 25OHD and eGFR values were slightly lower in patients assigned to vitamin D than in patients assigned to placebo.

Data completeness for the intention-to-treat analysis of the primary endpoint was 100%. One hundred and twenty-nine patients stopped taking study medication before study termination (*Figure 1*). An additional 40 participants ($n = 19$, vitamin D group; $n = 21$, placebo group) were lost to follow-up for secondary clinical endpoint analysis. Attrition rates in the vitamin D and placebo group were 22.8% and 22.7% at year 1, 38.8% and 40.1% at year 2, and 46.0% and 44.8%% at year 3 of the study, respectively.

Biochemical efficacy and safety parameters by treatment group

In the vitamin D group, mean in-study 25OHD levels plateaued around 100 nmol/L, whereas levels remained around 40 nmol/L in the placebo group (*Figure 2*). At baseline, eGFR levels were significantly lower in the vitamin D group than in the placebo group, but the time-dependent decrease in kidney function was similar between groups (*Figure 2*). There were significant time x treatment interactions on plasma calcium, with higher in-study concentrations in the vitamin D group than in the placebo group [+0.036 mmol/L (95% CI: 0.016–0.054 mmol/L); $P = 0.016$]. Regarding plasma phosphate, there were no significant time x treatment interactions on log-transformed values ($P = 0.407$).

Primary endpoint by treatment group

Mortality was 19.6% ($n = 39$) in the vitamin D group and 17.9% ($n = 36$) in the placebo group (*Figure 3*). The HR for the vitamin D group vs. the placebo group was 1.09 (95% CI: 0.69–1.71; $P = 0.726$). Causes of death in the vitamin D group were multiple organ failure ($n = 9$), arrhythmia ($n = 5$), sudden cardiac death ($n = 2$), cardiogenic shock ($n = 2$), other cardiac-related ($n = 3$), sepsis ($n = 2$), other non-cardiac-related ($n = 6$), and unknown ($n = 10$). The corresponding causes of death in the placebo group were multiple organ failure ($n = 6$), arrhythmia ($n = 3$), sudden cardiac death ($n = 3$), cardiogenic shock ($n = 3$), sepsis ($n = 5$), other non-cardiac-related ($n = 5$), and unknown ($n = 11$). Analyses in subgroups with initial 25OHD levels <30 nmol/L and ≥30 nmol/L did not differ substantially from the results of the entire study group [25OHD levels <30 nmol/L: HR = 1.05 (95% CI: 0.53–2.08); 25OHD levels ≥30 nmol/L: HR = 1.07 (95% CI: 0.58–1.97)] and there was no statistical evidence of interaction by initial 25OHD subgroup (*P*-value for interaction = 0.912). *Post hoc* adjustment for age and kidney function did not alter these results considerably [25OHD levels <30 nmol/L: adjusted HR = 0.94 (95% CI: 0.47–1.86); 25OHD levels ≥30 nmol/L: adjusted HR = 0.88 (95%CI: 0.47–1.63)] (*P*-value for interaction = 0.393).

Secondary endpoints by treatment group

Hospitalization rate was 67.4% ($n = 126$) and 60.0% ($n = 112$) in patients assigned to vitamin D and placebo, respectively (*Table 2*; $P = 0.075$). Causes of hospitalization were similar between groups (see Supplementary material online, *Table S1*). The incidence of high urgent listing for heart transplantation, heart transplantation, and resuscitation were similar between groups as well. However, the need for MCS implant was significantly greater in the vitamin D group than in the placebo group (*Table 2*). Subgroup analysis revealed in the vitamin D subgroup with initial 25OHD levels ≥30 nmol/L (reference: placebo group with initial 25OHD levels ≥30 nmol/L) a HR of 3.60 (95% CI: 1.52–8.57) ($n = 19$ vs. 7). No significant treatment effect was observed in the vitamin D subgroup with initial 25OHD levels <30 nmol/L (reference: placebo group with 25OHD levels <30 nmol/L) [HR = 0.81 (95% CI: 0.31–2.11)] ($n = 9$ vs. 8). There was statistical evidence for significant interaction by 25OHD subgroup with study group (*P*-value for interaction = 0.009) and this interaction remained significant after *post hoc* adjustment for age and kidney function [25OHD levels <30 nmol/L: adjusted HR = 0.73 (95% CI: 0.27–1.92); 25OHD levels ≥30 nmol/L: adjusted HR of 3.79 (95% CI: 1.59–9.01)] (*P*-value for interaction = 0.009). On average, 25OHD levels remained <100 nmol/L in the vitamin D subgroup with initial 25OHD levels <30 nmol/L, but increased above 100 nmol/L in the vitamin D subgroup with initial 25OHD levels ≥30 nmol/L (see Supplementary material online, *Table S2*). The sort of device implanted by study group is listed in Supplementary material online, *Table S3*. The incidence of hypercalcaemia was 6.2% in the vitamin D group and 3.1% in the placebo group (*Table 2*). Characteristics of patients with hypercalcaemia are listed in Supplementary material online, *Table S4*. None of the patients in the placebo or vitamin D group had 25OHD levels >374 nmol/L (*Table 2*).

Discussion

The present RCT was unable to demonstrate a significant effect in patients with advanced HF of vitamin D supplementation with 4000 IU daily for 3 years on all-cause mortality. However, vitamin D appears to induce an increase in plasma calcium levels. Moreover, there was a greater need for MCS implants in the vitamin D group, especially in patients with initial circulating 25OHD concentrations ≥30 nmol/L.

With respect to the primary endpoint, enrolment did not achieve the planned number of study participants. Moreover, annual

Table 1 Baseline characteristics of the EVITA subjects

Parameter	Placebo group ($n = 201$)	Vitamin D group ($n = 199$)
Age, median (IQR), years	54 (48–60)	56 (48–62)
Males, number (%)	166 (83)	166 (83)
Body mass index, median (IQR), kg/m^2	27.8 (25.1–30.8)	27.8 (24.5–31.6)
Body weight, median (IQR), kg	88 (75–98)	88 (75–99)
Diagnosis, number (%)		
Dilated cardiomyopathy	100 (50)	92 (46)
Ischaemic cardiomyopathy	86 (43)	93 (47)
Others	15 (7)	14 (7)
New York Heart Association Functional Class, number (%)		
II	145 (72)	147 (74)
III	56 (28)	52 (26)
Left-ventricular ejection fraction, median (IQR), %	27 (24–35)	28 (23–34)
Left-ventricular end-diastolic diameter, median (IQR), mm	67 (61–75)	67 (59–74)
Pulmonary hypertension, number (%)	44 (22)	40 (20)
Arterial hypertension, number (%)	63 (31)	57 (29)
Systolic blood pressure, median (IQR), mmHg	116 (106–130)	115 (103–129)
Diastolic blood pressure, median (IQR), mmHg	74 (66–80)	72 (68–80)
Atrial fibrillation, number (%)	39 (19)	36 (18)
Pacemaker implant, number (%)	166 (83)	158 (79)
Pacemaker plus implantable cardioverter defibrillator, number (%)	158 (79)	152 (76)
Biventricular pacemaker, number (%)	72 (36)	71 (36)
Listed for heart transplantation, number (%)	43 (21)	37 (19)
Diabetes mellitus, number (%)	46 (23)	51 (26)
Estimated GFR, median (IQR), mL/min/1.73 m^2	73 (57–89)	64 (50–85)**
Medications, number (%)		
ACE inhibitors/ARB blockers	191 (95)	193 (97)
Beta-blockers	195 (97)	187 (94)
Aldosterone antagonists	170 (85)	159 (80)
Loop diuretics	166 (83)	173 (87)
Thiazid diuretics	64 (32)	71 (36)
Digitalis	85 (42)	67 (34)
Antiarrhythmics	51 (25)	50 (25)
Calcium antagonists	7 (4)	7 (4)
Lipid-lowering drugs	105 (52)	113 (57)
Vitamin D supplement use	0 (0)	0 (0)
Biochemical parameters		
Brain natriuretic peptide, median (IQR), pg/mL[a]	305 (124–767)	286 (132–615)
Calcium, median (IQR), mmol/L	2.40 (2.32–2.47)	2.39 (2.30–2.47)
25-hydroxyvitamin D, median (IQR), nmol/L	35.2 (25.7–49.2)	31.3 (21.5–44.8)*

GFR, glomerular filtration rate; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; IQR, interquartile range.
[a]Based on 268 routinely measured blood samples (135 samples in patients assigned to placebo and 133 samples in patients assigned to vitamin D).
*$P < 0.05$.
**$P < 0.01$, for comparison between study groups (Mann–Whitney U-test).

mortality was lower than originally suggested. Thus, this investigator-initiated study had low statistical power to assess significant differences between the groups. However, given the estimated HR of 1.09, even the planned enrolment of 1000 participants would not have shown a statistically significant effect on all-cause mortality. Subsequently, our data demonstrate that moderately high daily vitamin D administration is not useful in reducing mortality in advanced HF. A recent Mendelian randomization study reported an association of genetically low 25OHD concentrations with increased all-cause mortality, cancer mortality, and other causes of mortality but not cardiovascular mortality.[21] We can reliably assume that in the vast majority of our patients death was ultimately caused by cardiovascular disease (i.e. HF).

The greater incidence of MCS implants in the vitamin D group is an indication of disease deterioration, since in the era of donor heart shortage MCS implantation is the last option in advanced HF.[22]

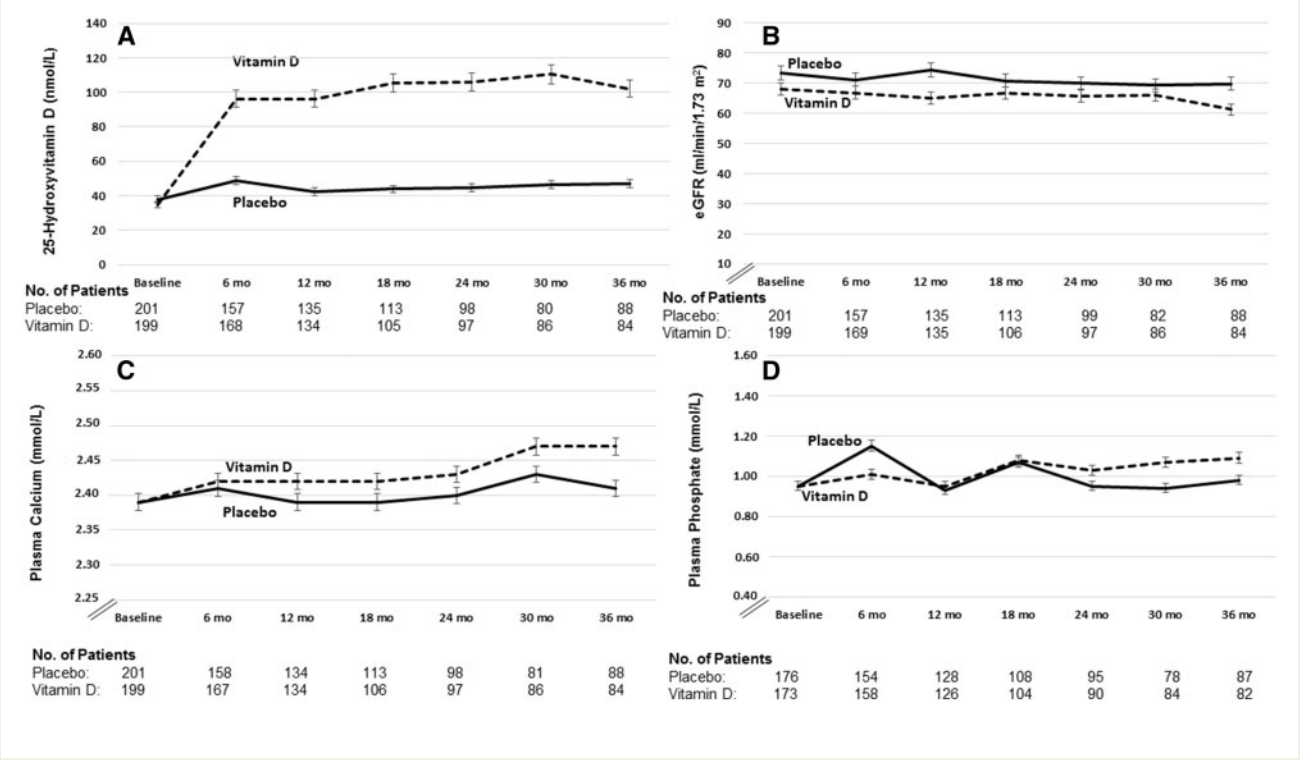

Figure 2 Efficacy and safety data of the EVITA subjects. Trend analysis on circulating 25-hydroxyvitamin D (*A*), kidney function (*B*), plasma calcium concentrations (*C*), and plasma phosphate (*D*) in total sample show: significant group differences in kidney function ($P = 0.009$) and circulating 25-hydroxyvitamin D ($P = 0.042$), but no group differences in plasma calcium ($P = 0.703$) or log-transformed plasma phosphate ($P = 0.749$); significant time effects on circulating 25-hydroxyvitamin D ($P < 0.001$), kidney function ($P < 0.001$), plasma calcium ($P < 0.001$), but no time effects on log-transformed plasma phosphate ($P = 0.126$); significant time x treatment interactions on circulating 25-hydroxyvitamin D ($P < 0.001$), plasma calcium ($P = 0.016$), but no time x treatment interactions on kidney function ($P = 0.320$) and plasma phosphate ($P = 0.407$). Data are presented as mean and 95% confidence interval. To achieve normally distributed phosphate data for statistical analysis, data were log-transformed and extreme phosphate concentrations (>3.23 mmol/L) were eliminated (12 values in the vitamin D group and 11 values in the placebo group).

To our knowledge, no prior RCT has provided evidence for clinically harmful effects of a daily dose of 4000 IU on the adult cardiovascular system. Two smaller RCTs reported a significant increase in left ventricular ejection fraction by vitamin D doses equivalent to 4000 IU daily.[5,6] However, these RCTs did not include patients in their data analysis who dropped out or violated the study protocol. Moreover, they did not assess clinical events. A potential explanation for our finding of adverse vitamin D effects may be the higher in-study plasma calcium concentrations. A meta-analysis of observational data indicates a statistically positive association between plasma calcium and cardiovascular disease.[23] Even more importantly with respect to the present study, the Atherosclerosis Risk in Communities (ARIC) study reported that high-plasma calcium was independently associated with greater risk of incident HF.[24] In that study, HF incidence was lowest at calcium levels of 2.25 mmol/L and increased progressively up to 2.75 mmol/L.

The IOM[13] has set the UL for vitamin D at 4000 IU daily for healthy adults and the Endocrine Society[25] has set the UL at 10 000 IU daily for those adult patients who are at risk of having circulating 25OHD levels <50 nmol/L. Since HF is prevalent, even in the general ageing population,[26] it appears from our data that

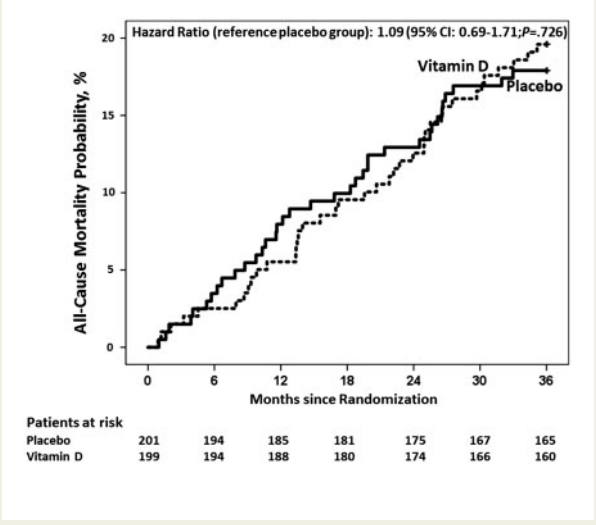

Figure 3 Cumulative incidence of all-cause mortality by study group: vitamin D (dotted line), placebo (solid line).

Table 2 Incidence and hazard ratio of secondary endpoints of the EVITA subjects

Parameter	Placebo group $n = 201$	Vitamin D group $n = 199$	Hazard ratio[a] (95% CI)	*P*-value
Hospitalization, number (%)	112 (60)	126 (67)	1.26 (0.98–1.63)	0.075
Mechanical circulatory support implantation, number (%)	15 (9)	28 (15)	1.96 (1.04–3.66)	0.031
High urgent listing for heart transplantation, number (%)	18 (11)	19 (11)	1.07 (0.56–2.04)	0.835
Heart transplantation, number (%)	19 (12)	21 (13)	1.11 (0.60–2.07)	0.732
Resuscitation, number (%)	3 (2)	2 (1)	0.66 (0.11–4.01)	0.660
Hypercalcaemia, number (%)	5 (3)	10 (6)	2.05 (0.70–5.98)	0.192
Hypervitaminosis D[b], number (%)	0	0	—	—

CI, confidence interval.
[a]Reference: placebo group.
[b]Circulating 25-hydroxyvitamin D level >374 nmol/L.

reconsideration of the ULs may probably be necessary. The concept of vitamin D toxicity is based not only on oral vitamin D dosing but also on circulating 25OHD levels. Target values for adequate 25OHD levels are inconsistent.[10,13] The IOM considers circulating 25OHD levels below 30 nmol/L as deficient, levels between 30 and 49.99 nmol/L as inadequate, and levels between 50 and 125 nmol/L as adequate and, in contrast to others,[10] levels above 125 nmol/L as already potentially harmful.[13] In our study, a greater need for MCS implants was only seen in the vitamin D subgroup with baseline 25OHD ≥30 nmol/L, who also achieved median in-study 25OHD levels >100 nmol/L. Thus, our data are in general agreement with the IOM classification of circulating 25OHD levels. A recent prospective cohort study from our group in cardiac surgical patients,[27] using the same method of measuring 25OHD as the present study, has provided evidence for a U-shaped association between circulating 25OHD and the risk of major adverse cardiac and cerebrovascular events. Risk was highest at both circulating 25OHD levels <30 nmol/L and >100 nmol/L. Collectively, data indicate caution against long-term administration of moderately high-daily vitamin D doses, at least if initial 25OHD levels are above the deficiency threshold of 30 nmol/L.

The present investigation has several strengths, but also some limitations. Strengths include the study design, the homogenous group of patients, the variety of assessed clinical and safety parameters, the study duration of 3 years, and the 100% completeness of follow-up data for the intention-to-treat analysis of the primary endpoint. A major limitation is the aforementioned low-statistical power to detect significant treatment differences in the primary endpoint. Nevertheless, the trial was able to provide significant results in exploratory clinical endpoints/biochemical parameters. While these data analyses should be interpreted with caution since they do not prove causality, they do indicate concern regarding long-term vitamin D supplementation with moderately high-daily doses. However, we cannot definitively rule out the possibility that the vitamin D-related higher risk of MCS implant was just a chance finding. A further limitation is that the study is largely restricted to male patients.

In summary, in patients with advanced HF vitamin D did not improve survival but was associated with increased plasma calcium concentrations and a greater need for MCS implantation, especially in patients with baseline 25OHD levels ≥30 nmol/L. Data indicate caution regarding long-term vitamin D supplementation with 4000 IU daily in the clinical setting.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

Study concept and design: A.Z., J.B. Acquisition, analysis, or interpretation of data: A.Z., J.B.E., S.P., U.F., U.S., J.K., J.D., I.B., C.K., J.F.G., H.K.B., S.P.

Drafting of the manuscript: A.Z. Critical revision for important intellectual content: A.Z., J.B.E., S.P., S.P., I.G-B., H.K.B., M.D., I.B., C.K., J.F.G.

Statistical analysis: M.D. Obtained funding: A.Z. Administrative, technical, or material support: J.K., J.D., I.B., C.K., J.F.G. Study supervision: A.Z., J.B.E., S.P., U.F., J.B.

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Conflict of interest: A.Z. has received speaker honoraria from DiaSorin, Germany.

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