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Vitamin D supplementation of 4000 IU daily and cardiac function in patients with advanced heart failure: The EVITA trial

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ABSTRACT

Background: Data regarding the effects of vitamin D on cardiac function are inconclusive.
Methods: In a post-hoc analysis of the EVITA (Effect of vitamin D on mortality in heart failure) trial, we investigated whether a daily vitamin D_3 supplement of 4000 IU for three years affects echocardiography parameters like left ventricular end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), and LV ejection fraction (LVEF) in patients with advanced heart failure (HF) and 25-hydroxyvitamin D levels <75 nmol/L. Of 400 patients enrolled, 199 were assigned to vitamin D and 201 to placebo. We assessed time × treatment interaction effects using linear mixed models and analyzed in subgroups vitamin D effects at 12 and 36 months post-randomization using analysis of covariance with adjustments for baseline values.
Results: At baseline, values of LVEDD, LVESD, and LVEF were 67.5 ± 10.5 mm, 58.9 ± 12.0 mm, and 30.47 ± 10.2%, respectively. There were no time × treatment interaction effects on LV echocardiographic parameters in the entire study cohort, neither at 12 months nor at 36 months post-randomization (P-values > 0.05). However, in the subgroup of patients aged ≥50 years, vitamin D treatment was associated with an increase in LVEF of 2.73% (95% CI: 0.14 to 5.31%) at 12 months post-randomization (n = 311). The increase was slightly attenuated to 2.60% (95%CI: −2.47 to 7.67%) at 36 months post-randomization (n = 242).
Conclusion: Our data indicate that vitamin D supplementation does not significantly improve cardiac function in all patients with advanced HF. However, vitamin D probably improves LV function in HF patients aged ≥50 years.

1. Introduction

Heart failure (HF) continues to be a medical problem in aging societies with globally almost 23 million people being affected [1]. The illness usually results in cardiac dilatation and decreasing left ventricular ejection fraction (LVEF) [2]. Pharmacologic treatment aims to prevent progressive cardiac hypertrophy and LVEF decline [3], but 5% of patients develop end-stage HF that is refractory to effective medical treatment [4]. Ventricular assist device implants and heart transplantation are the last treatment options for these patients.

Vitamin D may be critical for the heart because vitamin D receptor knockout mice yield elevated production of renin and angiotensin II, hypertension, and cardiac hypertrophy [5–7]. In patients with HF, low circulating 25-hydroxyvitamin D (25OH) levels (i.e. <75 nmol/L) are prevalent [8–11] and some observational studies indicate an inverse association between circulating 25OHD levels and HF [12,13].

With respect to randomized controlled trials (RCTs), a recent meta-analysis [14] indicated that in patients with HF, vitamin D supplementation may suppress biochemical markers of inflammation. Moreover, based on four studies (303 patients) lasting 12 weeks to 9 months and using vitamin D doses equivalent to 1000 IU to 7143 IU daily, this meta-analysis reported a non-significant increase in LVEF by vitamin D supplementation (weighted mean difference: +4.1% [95%CI: −0.91% to +9.12%], P = 0.11). A more recent RCT in 163 patients with HF and mean circulating 25OHD levels of 37 nmol/L [15] reported a significant improvement in LVEF (difference in mean change: +6.07% [95%CI: +3.20% to +8.94%], P < 0.001) and also in left ventricular (LV)

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remodelling by daily vitamin D supplementation with 4000 IU for one year.

Since a beneficial vitamin D effect on LVEF would have important consequences regarding prevention and treatment of HF, we aimed to investigate in a post-hoc analysis of the EVITA (effect of vitamin D on mortality in heart failure) trial [16] whether these reported beneficial effects on cardiac function can be confirmed in patients with advanced HF refractory to optimal medical therapy. Further, we expanded the existing knowledge by investigating the effects of vitamin D supplementation on left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) in this population.

2. Methods

2.1. Study design and participants

EVITA was a single-center, randomized, placebo-controlled, clinical trial, performed at the Clinic for Thoracic and Cardiovascular Surgery of the Heart- and Diabetes Center North Rhine Westphalia, Bad Oeynhausen, Germany. Study design and main study results have already been published elsewhere [16–20]. Briefly, 400 patients of HF with reduced LVEF participated in the trial. Eligible patients were aged ≥18 to 79 years, had New York Heart Association functional class (NYHA) ≥II and circulating 25OHD levels <75 nmol/L. All patients were ambulatory at the time of enrolment and regularly seen at our outpatient clinic. Participants randomly received 4000 IU (100 μg) vitamin D_3 daily as oily drops (Vigantol® Oel, provider: Merck KGaA, Darmstadt, Germany) or a matching placebo (Miglyol Oel, provider: Merck KGaA, Darmstadt, Germany) for three years. During the study, participants remained on guideline-recommended medications. Patient adherence was assessed by measuring in-study levels of circulating 25OHD. The study was registered at http://www.clinicaltrialsregister.eu (EudraCT number 010-020793-42) and at clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT01326650). All study participants provided a written informed consent to the study procedures before randomization. The study protocol was approved by the ethics committee of the Medical Council Westphalia-Lippe, Germany (No. 2010-052-fA). The publications of this trial adhere to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement (www.consort-statement.org).

2.2. Data assessment

The electronic records of the patients were used to assess baseline characteristics such as anthropometric data, clinical parameters, and medication use. Echocardiographic parameters were assessed by transthoracic echocardiography according to recommendations of American and European Echocardiography Societies [21] using the Philips iE33 machine with the X5-1 transducer (Philips GmbH, Hamburg, Germany). The following data were obtained: LVEDD, LVESD, and LVEF. LVEF was calculated using the modified biplane Simpson method. All echocardiographic calculations of LV function were done by two experienced senior echocardiographers (A.G. and L.P.) who were blinded to patient allocation. The inter-observer variability estimated for senior examiners in the echo lab of our institution was 5%. Measurements were performed during regular ambulatory visits of the study participants at baseline, and 12 and 36 months post-randomization. In those patients who still attended our outpatient clinic but dropped out before study termination, echocardiographic data obtained plus/minus 1 month and plus/minus 3 months of the scheduled 12-month and 36-month visit, respectively, were used. LVEF values ≤30% were considered as severely reduced for both females and males. Fasting venous blood samples were collected on study visits between 8 and 11 a.m. under standardized conditions. Blood samples were either measured directly within 4 h of blood collection (calcium, 25OHD, creatinine) or stored at −80 °C until analysis. Circulating 25OHD, renin, and aldosterone levels were measured by the autoanalyzer Liaison (DiaSorin, Stillwater, MN, USA). Brain natriuretic peptide (BNP), calcium, and creatinine values were measured by the Architect Autoanalyzer (Abbott, Wiesbaden, Germany). Circulating 25OHD levels <30 nmol/L were considered as deficient, 30.00–49.90 nmol/L as insufficient, and 50.00–74.99 nmol/L as borderline [22].

2.3. Outcome measures

In the present analysis of the EVITA trial, we assessed the effect of treatment and time × treatment interaction on LVEF, LVEDD, and LVESD. Moreover, we assessed between-group differences of the echocardiography parameters at 12 and 36 months post-randomization, with adjustments for baseline values.

2.4. Statistics

Baseline categorical data are presented as numbers and percentages of observations. Continuous data are shown as mean and standard deviation. Fisher's exact test, the unpaired *t*-test, and the Mann-Whitney *U* test were used for group comparisons at baseline, when appropriate. Box-plots with median and interquartile range (IQR) are used to illustrate values of biochemical parameters and LV echocardiography data at different time points. To avoid elimination of subjects with missing data, we used linear mixed models to analyze the influence of time (trend) on biochemical parameters and echocardiography data. Fixed effects were treatment, time (year), and the interaction effects of treatment × time. Skewed variables, as checked by the Kolmogorov-Smirnov test, were normalized by log(e) transformation before use in parametric statistical analysis, but all results are shown in the original units. Analyses of Covariance (ANCOVA) with adjustments for baseline values was used to assess differences in echocardiography parameters in subgroups by age category, sex, diagnosis, baseline 25OHD category, and transplantation status. All statistical analyses of the outcome measures were conducted according to the intention-to-treat principle. With respect to biochemical parameters, however, patients who dropped out were censored at their last blood sampling. We used Spearman's rank correlation coefficient (rs) to assess the interrelationship between circulating 25OHD and echocardiographic parameters of LV function. P-values <0.05 were considered statistically significant. Given a total number of 400 patients in this two-treatment parallel design study, there is a 90% probability that the study will detect a treatment difference in LVEF at a two-sided 0.05 significance level if the true difference between treatments is 3.6%. This is based on the assumption that the standard deviation of LVEF is 11% [15]. We performed all analyses using IBM SPSS Statistics, version 24 (IBM Corporation, Armonk, NY, USA).

3. Results

Of the 400 study participants, 113 patients dropped out, 75 patients died, and additional 35 patients were lost-to follow-up. At baseline, 12 and 36 months post-randomization LV echocardiographic data were available in 400, 311, and 242 patients for the intention-to-treat analysis, respectively (Fig. 1). Baseline characteristics of the study cohort are presented in Table 1. The vast majority of patients had moderately or severely abnormal LVEF, LVEDD, and LVESD values. Moreover, in both groups mean circulating 25OHD concentrations were close to the deficiency range. Baseline characteristics did not differ substantially between the entire study cohort and those patients with available LV echocardiographic data at the 12-month visit (all P-values > 0.05).

Plasma concentrations of 25OHD, calcium, and creatinine at baseline, and 12 and 36 months post-randomization are shown in Supplemental Fig. 1. There were significant time × treatment interaction effects on circulating 25OHD (P < 0.001), with markedly higher median 25OHD concentrations at study termination in the vitamin D (92.1 nmol/L, IQR: 62.7 nmol/L to 128.0 nmol/L) than in the placebo group (40.2 nmol/L, IQR: 30.5 nmol/L to 57.9 nmol/L). There were also significant time × treatment interaction effects on plasma calcium levels (P = 0.011), with higher concentration at study termination in the vitamin D group (median: 2.45 mmol/L, IQR: 2.38 mmol/L to 2.55 mmol/L) than in the placebo group (median: 2.41 mmol/L, IQR: 2.33 mmol/L to 2.51 mmol/L). There was, however, no significant time × treatment interaction effect on the time-dependent decrease in creatinine concentrations (P = 0.251).

The LVEF, LVEDD, and LVESD values at baseline, 12 months and 36 months post-randomization are shown in Fig. 2. There were no significant time × treatment interactions on LVEF, LVEDD, or LVESD in the entire study cohort (all P-values > 0.05). In detail, the mean LVEF change in the vitamin D versus placebo group was at 12 and 36 months post-randomization 1.47% (95%CI: −0.39 to 3.87%) and −0.22% (95%CI: −4.32 to 3.87%), respectively. The corresponding values for LVEDD and LVESD were −0.41 mm (95%CI: −1.94 to 1.12 mm) and 1.57 mm (95%CI: −1.18 to 4.33 mm), respectively, and −1.27 mm (95%CI: −0.56 to 3.07 mm) and 1.49 mm (95%CI: −1.90 to 4.87 mm), respectively. In Supplemental Fig. 2, subgroup analyses of LVEF values are presented 36 months post-randomization according to age category (≥ and <50 years), sex (male or female), diagnosis (DCM or ICM), baseline 25OHD category (<30 nmol/L, 30–49.99 nmol/L, ≥50 nmol/L), and transplantation status (transplanted/non-transplanted). There was a trend for interaction effects between age category and treatment group, but no interaction effects between other subgroups and treatment group. Therefore, Table 2 presents in more detail the changes in LV echocardiography parameters at 12 (n = 311) and 36 months (n = 242) post-randomization by age category. Briefly, in the subgroup of patients aged ≥50 years vitamin D treatment was associated with an increase in LVEF of 2.73% (95%CI: 0.14 to 5.31%) at 12 months post-randomization. The increase was slightly attenuated to 2.60% (95%CI: −2.47 to 7.67%) at 36 months

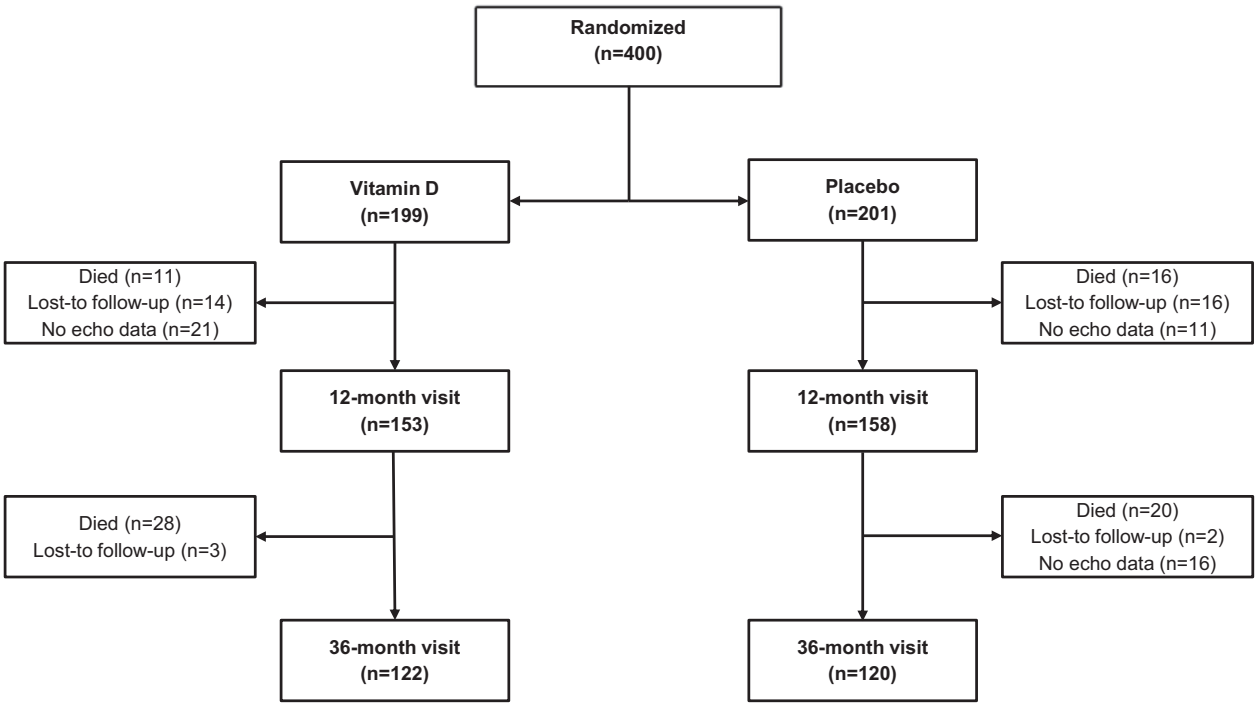

Fig. 1. Study flow chart.

post-randomization. At 12 months and 36 months post-randomization, mean LVEDD and LVESD values were lower in patients aged ≥50 years allocated to vitamin D treated patients than in patients allocated to placebo (Table 2). No consistently beneficial vitamin D effects on LV parameters were seen in patients aged <50 years. Note that Table 2 also includes patients who were transplanted during follow-up and whose LVEF values were substantially higher than in non-transplanted patients (Supplemental Fig. 2). However, exclusion of transplanted

Table 1
Baseline characteristics of those study participants with echocardiographic data at 12 months in comparison to the entire study cohort.

Parameter	Patients with echo data at 12 months (n = 311)	All (n = 400)	Placebo group (n = 201)	Vitamin D group (n = 199)
Age, years	53.2 ± 11.0	53.5 ± 10.6	52.9 ± 10.3	54.0 ± 10.8
Males, number (%)	255 (82)	332 (83)	166 (83)	166 (83)
Heart failure etiology, number (%)				
Dilated cardiomyopathy	154 (49)	192 (48)	100 (50)	92 (46)
Ischemic cardiomyopathy	137 (44)	179 (45)	86 (43)	93 (47)
Others	20 (7)	29 (7)	15 (7)	14 (7)
Diabetes mellitus, number (%)	76 (24)	97 (24)	46 (23)	51 (26)
Body mass index, kg/m^2	28.4 ± 5.1	28.4 ± 5.2	28.4 ± 4.8	28.5 ± 5.5
NYHA functional class, number (%)				
II	222 (71)	292 (73)	145 (72)	147 (74)
III	89 (29)	108 (27)	56 (28)	52 (26)
LVEF, %	30.4 ± 9.9	30.4 ± 10.2	30.7 ± 10.6	30.1 ± 9.8
LVEDD, mm	67.6 ± 10.6	67.5 ± 10.5	67.3 ± 10.3	67.6 ± 10.8
LVESD, mm	59.0 ± 11.9	58.9 ± 12.0	58.6 ± 11.6	59.3 ± 12.4
Systolic blood pressure, mm Hg	118 ± 21	117 ± 22	117 ± 21	117 ± 22
Diastolic blood pressure, mm Hg	73 ± 12	73 ± 12	73 ± 13	74 ± 11
Atrial fibrillation, number (%)	59 (19)	75 (19)	39 (19)	36 (19)
Pacemaker implant, number (%)	258 (83)	324 (81)	166 (83)	158 (79)
25-Hydroxyvitamin D, nmol/L	36.9 ± 16.8	36.4 ± 16.8	38.0 ± 16.7	34.6 ± 16.8
Calcium, mmol/L	2.39 ± 0.12	2.39 ± 0.12	2.39 ± 0.11	2.39 ± 0.13
Creatinine, μmol/L	105 ± 32	107 ± 33	103 ± 32	110 ± 33
BNP (ng/L)[a]	558 ± 731	558 ± 716	533 ± 598	581 ± 813
Renin (mIU/L) [a]	875 ± 1660	885 ± 1697	610 ± 1089	1162 ± 2115
Aldosterone (ng/L) [a]	19.8 ± 12.1	20.3 ± 17.3	23.3 ± 19.6	17.4 ± 14.5
Medications, number (%)				
Aldosterone-antagonists	257 (83)	329 (82)	170 (85)	159 (80)
Loop diuretics	268 (86)	339 (85)	166 (83)	173 (87)
Thiazide diuretics	106 (34)	135 (34)	64 (32)	71 (36)
Beta-blockers	297 (96)	383 (96)	195 (97)	187 (94)
ACE-inhibitors/ARB-blockers	299 (96)	384 (96)	191 (95)	193 (97)
Digoxin	121 (39)	152 (38)	85 (42)	67 (34)

Abbreviations: NYHA, New York Heart Association; LVEF, left ventricular ejection fraction, LVEDD, left ventricular end-diastolic diameter, LVESD, left ventricular end-systolic diameter; BNP, brain natriuretic peptide; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker.
[a] Based on 268 BNP values, 163 renin values, and 163 aldosterone values.

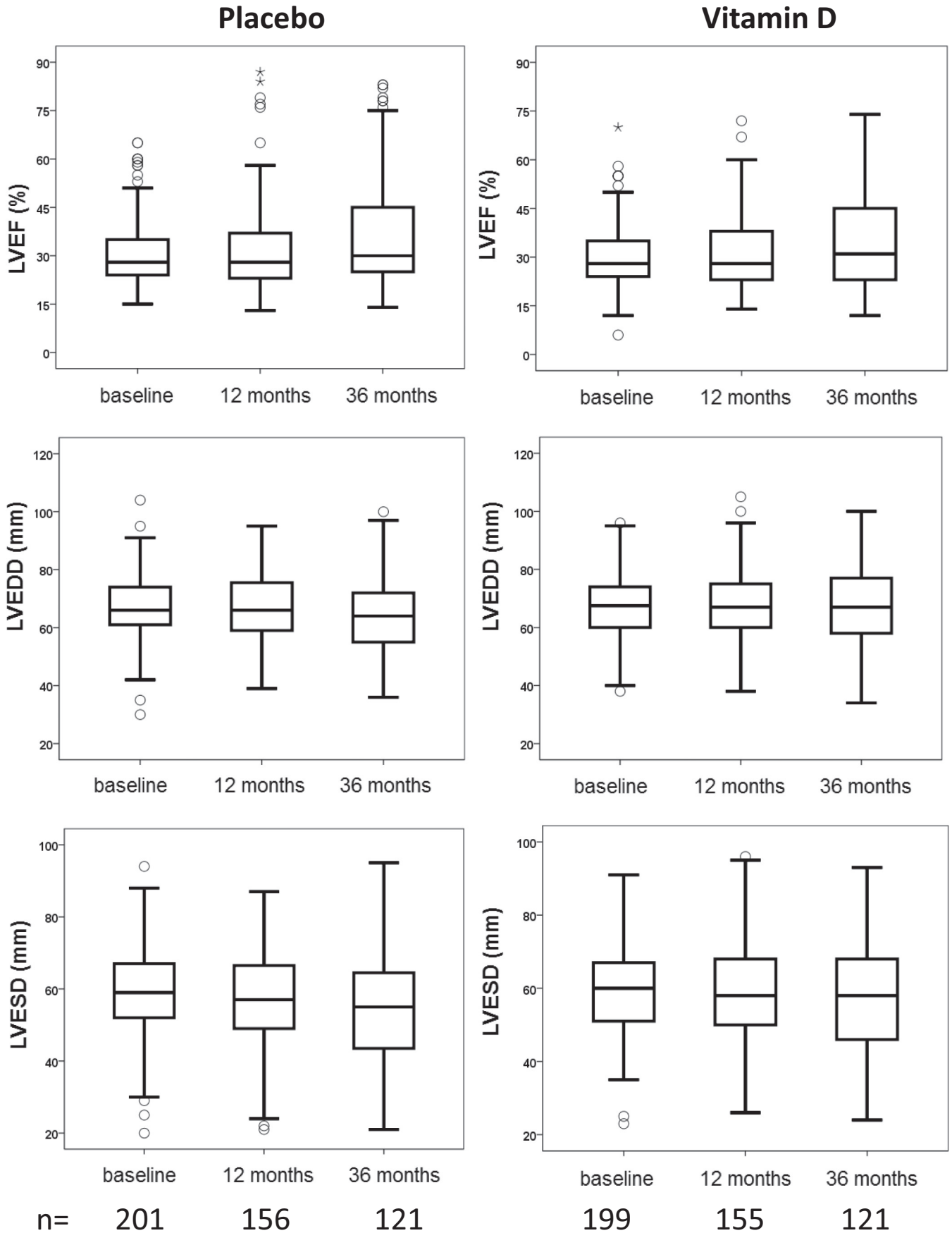
Placebo
Vitamin D
LVEF (%)
LVEDD (mm)
LVESD (mm)
baseline
12 months
36 months
n= 201 156 121 199 155 121

Table 2
Change in echocardiography parameters in participants of the EVITA trial at 12 (n = 311) and 36 months (n = 242) post-randomization by age category; intention-to-treat population.

Endpoint	Mean change after 12 months[a]	Difference in mean change[b]	Mean change after 36 months[a]	Difference in mean change[b]
LVEF, %				
≥50 years		2.73 (0.14 to 5.31)		2.60 (−2.47 to 7.67)
Placebo	−0.54 (−2.35 to 1.27)		3.27 (−0.33 to 6.80)	
Vitamin D	2.37 (0.56 to 4.18)		5.88 (2.49 to 9.27)	
<50 years		0.02 (−3.97 to 4.01)		−5.30 (−12.82 to 2.22)
Placebo	1.89 (−0.77 to 4.55)		7.73 (2.66 to 12.79)	
Vitamin D	1.36 (−1.42 to 4.14)		2.42 (−3.04 to 7.88)	
LVEDD, mm				
≥50 years		−0.57 (−2.23 to 1.18)		−0.67 (−4.11 to 2.78)
Placebo	−0.31 (−1.45 to 0.88)		−2.55 (−4.97 to −0.13)	
Vitamin D	−0.82 (−2.02 to 0.37)		−2.94 (−5.24 to −0.64)	
<50 years		−1.26 (−4.62 to 2.11)		4.27 (−0.94 to 9.48)
Placebo	1.60 (−0.62 to 3.81)		−3.16 (−6.46 to 0.13)	
Vitamin D	0.70 (−1.64 to 3.03)		1.17 (−2.43 to 4.76)	
LVESD, mm				
≥50 years		−2.39 (−6.09 to 1.31)		−0.53 (−4.76 to 3.69)
Placebo	0.61 (−1.83 to 3.05)		−3.10 (−6.07 to −0.13)	
Vitamin D	−1.40 (−3.95 to 1.15)		−3.40 (−6.24 to −0.55)	
<50 years		−1.28 (−3.40 to 0.84)		4.21 (−2.26 to 10.67)
Placebo	−0.31 (−1.79 to 1.17)		−4.28 (−8.41 to −0.16)	
Vitamin D	−1.63 (−3.10 to −0.15)		−0.13 (−4.59 to 4.33)	

Abbreviations: LVEF, left ventricular ejection fraction, LVEDD, left ventricular end-diastolic diameter, LVESD, left ventricular end-systolic diameter.
[a] Change from baseline data is shown as means and 95% confidence interval.
[b] Between-group differences (means and 95% confidence interval) at 12 and 36 months post-randomization, adjusted for baseline values, sex, etiology of heart failure, and baseline 25-hydroxyvitamin D.

patients from data analysis did not change the age-related differences regarding the vitamin D effect on LVEF values materially (data not shown). Moreover, a further subdivision of patients aged ≥50 patients into patients aged <60 years and ≥60 years did not change results fundamentally (data not shown). Notably, age-groups differed regarding heart failure etiology, diabetes mellitus, NYHA functional class, serum creatinine, and diuretics use at baseline (Supplemental Table 1). Age-specific correlations between changes in 25OHD concentrations and echocardiographic data or concentrations of the hormones BNP, renin, and aldosterone are presented in Supplemental Table 2. Only in the group of elderly patients, the Δ 25OHD values at the 36-month visit were positively associated with the respective Δ LVEF values. Notably, the difference in mean change in plasma calcium at the 12-month and 36-month visits was significant in the subgroup of younger patients only (12-month visit: +0.104 mmol/L; 95%CI: 0.044 to 0.164 mmol/L; P = 0.001 and 36-month visit: +0.090 mmol/L; 95%CI: 0.026 to 0.153 mmol/L; P = 0.006), but not in the elderly patients (12-month visit: +0.024 mmol/L; 95%CI: −0.012 to 0.061 mmol/L; P = 0.190 and 36-month visit: +0.039 mmol/L; 95%CI: 0.006 to 0.084 mmol/L; P = 0.087).

4. Discussion

The present investigation indicates that a daily vitamin D_3 supplement of 4000 IU for three years does not significantly influence LV echocardiography data in a cohort of patients with advanced HF, neither 12 months nor 36 months post-randomization. However, our data also indicate that vitamin D probably improves LV function in patients aged ≥50 years.

In our study, the mean difference in LVEF change between study groups at 12 and 36 months was within the 95% confidence interval of the aforementioned meta-analysis by Jiang et al. [14], at least in patients aged ≥50 years. The effect was, however, less pronounced than the vitamin D-related improvement of 6.07% at 12 months post-randomization in the RCT by Witte et al. [15]. Likewise, even in our subgroup of patients aged ≥50 years results on LVEDD and LVESD were less pronounced than their results. Baseline characteristics such as LVEF, NYHA functional class, 25OHD levels, and diabetes prevalence were similar between the two studies. Moreover, the daily vitamin D dose was identical. However, our study cohort was substantially younger and had higher baseline LVEDD and LVESD values than the cohort enrolled by Witte al. [15], indicating more severe HF. In contrast to Witte et al., we used an intention-to-treat approach to analyze the data, which may have attenuated the vitamin D effect on LVEF. Independent of the differences in the results of the two studies, data point to an improved LV function by vitamin D, at least in elderly patients with HF. Notably, the aforementioned meta-analysis also reported a non-significant increase in LVEF by vitamin D supplementation of +4.1% (95%CI: −0.91% to +9.12%). Interestingly, in a small RCT in HF patients with a mean age of 74 years and 25OHD levels <75 nmol/L [23] a vitamin D dose equivalent to 4000 IU/daily increased LVEF significantly in the intervention group (6.71 vs. −4.3%; P < 0.001). In contrast, a daily vitamin D dose of 2000 IU had no significant effect on LVEF in HF patients with a mean age of 56 years [24]. Since heart failure prevalence increases with advanced age [25], a substantial portion of the elderly population potentially benefits from an improvement in vitamin D status, either by vitamin D supplement use or food fortification [26]. Genetic and/or vitamin D-independent lifestyle factors may have prevented beneficial vitamin D effects in our subgroup of younger HF patients with early onset of the disease. Nevertheless, vitamin D deficiency can be an important risk factor in specific groups of younger patients: In a case series of infants with severe vitamin D deficiency and hypocalcemia, combined vitamin D and calcium administration improved cardiac function substantially [27]. These results were supported by a randomized controlled trial in 80 infants with HF [28] and mean 25OHD levels of 35 nmol/L, in which treatment with 1000 IU vitamin D daily suppressed

Fig. 2. Values of left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter are illustrated at baseline, and 12 and 36 months post-randomization. The boxes express the upper and lower quartiles, and the central lines show the median. Whiskers indicate the 5%–95% range, circles designate outliers and stars denote extremes. Trend analysis in total sample show: significant group differences in LVESD (P = 0.029) but not in LVEF (P = 0.129) or LVEDD (P = 0.051), significant time effects on LVEF (P < 0.001) and LVESD (P = 0.025), but not on LVEDD (P = 0.066), and no significant time × treatment interactions on LVEF (P = 0.688), LVEDD (P = 0.280), or LVESD (P = 0.464). Abbreviations: LVEF, left ventricular ejection fraction; LVEDD, left ventricular enddiastoilic diameter; LVESD, left ventricular endsystolic diameter.

PTH levels and increased LVEF significantly. In a female 41-year old adult with osteomalacia, hypocalcemia, HF, and baseline LVEF values of 28% [29], LVEF increased to 35% and cardiac failure improved promptly after correction of hypocalcemia by vitamin D and calcium administration. The earlier case reports have in common that severe vitamin D deficiency was associated with hypocalcemia. In the present study, however, patients were normocalcemic at baseline. As there is evidence for a U-shaped association between plasma calcium and the risk of incident HF [30], the significant increase in plasma calcium in the present study may therefore have blunted beneficial vitamin D effects on cardiac function in the entire study cohort. However, the vitamin D-induced increase in plasma calcium was largely diminished in our subgroup of elderly patients. Therefore, it can be speculated that age-dependent differences of oral vitamin D on cardiac function are at least in part related to different effects on vitamin D and calcium metabolism. Our elderly patients had higher plasma creatinine concentrations than the younger patients, indicating impaired renal function. The age-dependent decline in the concentration of the vitamin D hormone 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) is also well-known [31]. Compared with patients with preserved kidney function, the effect of vitamin D supplementation on incremental $1,25(OH)_2D$ tends to be more pronounced in patients with impaired kidney function [32]. Since $1,25(OH)_2D$ plays a pivotal role in cardiac function [3], beneficial vitamin D effects on $1,25(OH)_2D$ and cardiac function may have outweighed adverse vitamin D effects on calcium metabolism and cardiac function in our subgroup of elderly patients. Future studies should investigate these potential interactions of vitamin D and age on the cardiac system in more detail.

Our study has both strengths and limitations. Strengths are the study design of an RCT, the relatively long study duration, the intention-to-treat analysis, and the high cumulative vitamin D dose. One limitation is that most patients were males and the number of patients ≥60 years of age at baseline was rather small. Another limitation is that many patients presented with early onset of advanced HF and that several patients were transplanted during follow-up. Transplantation had profound effects on echocardiographic data and may have influenced a potential vitamin D effect on study results. Moreover, the inter-observer variability and the patient and disease-related variability in echocardiographic parameters was probably too high to recognize beneficial vitamin D effects. Likewise, it is a limitation that the echocardiographic data were restricted to the three left ventricular parameters LVEF, LVEDD, and LVESD. Finally, it may well be that beside age other yet unknown subgroups would benefit from vitamin D supplementation. Therefore, future studies regarding vitamin D and LV function should focus on clearly defined subgroups of patients with heart failure.

In conclusion, our results do not provide evidence supporting vitamin D supplementation to improve cardiac function in all patients with advanced HF. However, our data do not exclude the possibility of age-related differences in the cardiac response to vitamin D supplementation with potentially beneficial effects in patients aged ≥50 years.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.027.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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