New roles for renin in heart failure and cardio-renal interaction

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Chapter 6

Short-term vitamin D3 supplementation lowers plasma renin activity in patients with stable chronic heart failure: An open-label, blinded end point, randomized prospective trial (VitD-CHF trial)

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Abstract

Background – Many chronic heart failure (CHF) patients have low vitamin D (VitD) and high plasma renin activity (PRA), which are both associated with poor prognosis. VitD may inhibit renin transcription and lower PRA. We investigated whether vitamin D3 (VitD3) supplementation lowers PRA in CHF patients.

Methods and results – We conducted a single-centre, open-label, blinded-endpoint trial in 101 stable CHF patients with reduced left ventricular ejection fraction (LVEF). Patients were randomized to six weeks of 2000 IU oral VitD3 daily or control. At baseline, mean age was 64±10 years, 93% male, LVEF 35±8%, and 56% had vitD deficiency. The geometric mean (95% CI) of 25-hydroxyvitamin D3 increased from 48 nmol/L (43-54) at baseline to 80 nmol/L (75-87) after six weeks in the VitD3 treatment group and decreased from 47 nmol/L (42-53) to 44 nmol/L (39-49) in the control group ($P < 0.001$). The primary outcome PRA decreased from 6.5 ng/mL/h (3.8-11.2) to 5.2 ng/mL/h (2.9-9.5) in the VitD3 treatment group and increased from 4.9 ng/mL/h (2.9-8.5) to 7.3 ng/mL/h (4.5-11.8) in the control group ($P = 0.002$). This was paralleled by a larger decrease in plasma renin concentration (PRC) in the VitD3 treatment group compared to control ($P = 0.020$). No significant changes were observed in secondary outcome parameters, including NT-proBNP and fibrosis markers.

Conclusions – A majority of CHF patients had vitD deficiency and high PRA levels. Six weeks of supplementation with 2000 IU VitD3 increased 25-hydroxyvitamin D3 levels and decreased PRA and PRC.
Clinical Trial Registration: http://www.clinicaltrials.gov (NCT01092130)

Introduction

Vitamin D (VitD) deficiency is very common in patients with chronic heart failure (CHF) and is associated with increased mortality. (1-3) VitD is primarily known for its effect on bone metabolism, but is also correlated with plasma renin activity (PRA). (4) Small studies showed that calcitriol, the hormonally active form of vitD, may reduce PRA, Angiotensin II, blood pressure and myocardial hypertrophy. (5, 6) From experimental studies, it is known that vitD binds to the vitD receptor and inhibits renin transcription through binding to the renin promoter region, thereby reducing PRA. (7-11)

Renin plays a pivotal role in cardiovascular disease. (12) It activates the renin-angiotensin-aldosterone system (RAAS) and is involved in the progression of cardiovascular disease. RAAS blockers are currently the cornerstone of CHF treatment. (13) Although these drugs effectively reduce morbidity and mortality, they increase PRA and plasma renin concentration (PRC). (14) Observational studies paradoxically show that, despite RAAS blockade, high PRA is related to poor survival. (15-17) This may be explained by so-called angiotensin and aldosterone breakthrough, (18) but also by direct effects of renin via the (pro-)renin receptor. (12, 19) Among drugs registered for the treatment of CHF, only beta-blockers decrease renin levels, and part of their beneficial effect may be attributed to the lowering of PRA and PRC. (20) Although direct renin inhibitors lower PRA, there is currently no drug available that specifically reduces PRC. New RAAS blockers are currently being developed and investigated, but vitD may prove to be an effective and already available RAAS blocker.

Summarizing, there is increasing evidence that vitD may have a causal relationship with cardiovascular disease through its effect on renin transcription. If vitD supplementation decreases PRA in CHF patients, this may be a mechanism through which vitD may improve cardiovascular outcome. In this trial we studied the effect of short-term, high-dose cholecalciferol (VitD3), on PRA in CHF patients on optimal CHF medication. We hypothesized that high-dose VitD3 lowers PRA.

Materials and Methods

Study population

We included patients with CHF on optimal medical therapy using the following inclusion criteria: patients ⩾18 years of age with CHF (LVEF < 45%) presenting at the outpatient clinic; treated with an ACE-inhibitor (ACEi) at a stable dose (at least enalapril 10 mg daily or any other ACEi in an equivalent dose or maximum tolerated dose) or, if intolerant to ACEi, with an ARB (candesartan 8 mg daily or any other ARB in an equivalent dose or maximum tolerated dose) for at least four

weeks prior to the baseline visit (i.e. visit 1); treated with a beta-blocker unless contraindicated or not tolerated at a stable dose for at least four weeks prior to visit 1.

For a full list of exclusion criteria, we refer to the (online) supplement. Importantly, patients were excluded from participation in the study when they were using vitD supplements, drugs with a known interaction with vitD homeostasis (e.g. oral corticosteroids, thyroxin, anti-epileptics, tetracyclines or quinolones) or direct renin inhibitors.

The study was conducted according to the Declaration of Helsinki and approved by the ethics committee of the University Medical Centre Groningen. All participants signed written informed consent statements prior to inclusion in the trial. The trial is registered at clinicaltrials.gov (NCT01092130).

Study design

Patients were randomized on visit 2, two weeks after the screening visit and thereafter followed up at the outpatient clinic after three (i.e. visit 3) and six (i.e. visit 4) weeks and by telephone after seven weeks. Patients were randomized by an automated computer system to 2000 IU oral VitD3 once daily or control (i.e. no extra medication) in a 1:1 ratio for a period of six weeks. Blood was collected in a sitting position on visits 2-4 and patients were asked to collect 24h urine samples prior to visits 2 and 4. Blood was collected on ice or room temperature, as appropriate for specific assays (PRC, PRA). CHF medication was maintained unchanged throughout the trial. Changes in diuretic dose were permitted if necessary to treat decompensation or renal dysfunction.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Laboratory measurements

Routine laboratory measurements, including creatinine, NT-proBNP, urinary albumin and PTH were performed on the day of the visit. Additional samples were stored at -80ºC for future analysis including PRC, PRA, 25-hydroxyvitamin D_3 (25 (OH)D), 1,25-dihydroxyvitamin D_3 (1,25 $(OH)_2D$), aldosterone, neutrophil gelatinase-associated lipocalin (NGAL) and fibrosis markers (supplement). Estimated glomerular filtration rate (eGFR) was calculated using the 4-point MDRD formula.

All measurements were performed using commercially available kits according to the manufacturer's instructions. PRA was measured using an indirect radioimmunoassay kit for the quantitative determination of Angiotensin I (Cisbio Inter-

national, France). The detection limit was 0.15 ng/mL. PRA was expressed as ng/mL/h of generated Angiotensin-I. The intra-assay coefficient of variation (CV) at 1.4 and 16 ng/mL/h was 4.3% and 7.2% respectively. The inter-assay CV at 1.4 and 16 ng/mL/h was 9.9% and 8.5% respectively. PRC was measured using a radioimmunometric assay kit for the quantitative determination of active renin (Cisbio International, France) with a functional sensitivity of 5 pg/mL, intra-assay CV at 65 pg/mL of 1.5%, and inter-assay CV at 72 pg/mL of 3.6%. 25 (OH)D was measured by solid-phase extraction followed by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) (Spark-Holland Symbiosis system). The detection limit was 1.2 nmol/L and intra- and inter-assay CV were 5.0%-14.1%. 1,25 $(OH)_2D$ was also measured by LC-MS/MS essentially as described by Casetta et al. (21) with a CV of 5-15% at physiological concentration levels.

Primary and secondary endpoints

The primary endpoint was the difference in PRA between both groups after 6 weeks of treatment corrected for baseline PRA. Secondary endpoints included change in PRC, PTH, NT-proBNP, fibrosis markers and kidney function. Safety assessments included plasma calcium, PTH, hospitalization, and mortality.

Statistical analysis

Statistical analysis was performed using STATA v11SE. All normally distributed variables are represented as means ± SD. Skewed variables are represented as geometric means with 95% confidence intervals and were log-transformed when appropriate for statistical testing. Baseline differences were tested using an independent t-test and chi-square tests as appropriate. Changes between baseline, three and six weeks were tested with ANCOVA including the baseline value and treatment group as covariates. Interactions were tested by adding the product of two terms to the model. Subsequently analyses were repeated with correction for 24h-urinary sodium excretion, loop diuretic dose (1 mg of bumetanide or 40 mg of furosemide were considered one unit), renal function and NT-proBNP. All tests were performed two-tailed and a *P*-value < 0.05 was considered statistically significant. Graphs were drawn in Sigmaplot v10.0.

Sample size

In a large community-based cohort in our centre, the mean log PRA was 1.29± ± 0.65 ng/mL/h. With an alpha of 0.05 and a power of 90%, we calculated a sam-

ple size of 90 patients to demonstrate a 35% reduction in log PRA. We anticipated a dropout of 10% per group; therefore the target was set at 100 subjects. Sample size was calculated conservatively using cross-sectional analysis between-subject variation.

Results

Study population

We included 101 patients from March 2010 until November 2011. Fifty patients were allocated to receive VitD3 and 51 patients to the control group (Figure 1). From both VitD3 treatment and the control group, one patient withdrew consent to participate in the trial shortly after randomization. The primary endpoint was not available for these patients and no adverse events occurred in these patients; therefore they were excluded from further analysis. The mean age of the study cohort was 64±10 years, 93% of the patients were male, mean LVEF was 35±8%, and 90% of the patients were in New York Heart Association (NYHA) class II. All patients were on either an ACEi or ARB, more than 95% of patients were treated with a beta-blocker, and 28% were treated with an aldosterone receptor antagonist. Baseline characteristics were well balanced between the active treatment and control group. In the VitD3 treatment group, 23 patients (46%) used loop diuretics, compared to 26 (51%) in the control group. In the VitD3 treatment group one patient had an increase in diuretic dose and one a decrease. In the control group, 3 patients had an increase and 2 patients a decrease in diuretic dose. Mean diuretic dose in both groups differed by less than 10% on visits 2 and 4.

Table 1: Baseline characteristics

Characteristics	Control (n = 51)		VitD3 (n = 50)		P-value
Age, y	63.5	±11.1	64.0	±9.0	0.79
Male sex, *n* (%)	46	(90)	48	(96)	0.25
Blood pressure systolic, mmHg	118	±19	118	±17	0.96
Blood pressure diastolic, mmHg	74	±12	71	±13	0.31
Heart rate, bpm	67	±10	69	±12	0.39
Heart failure history					
– LVEF, %	33.6	±7.5	35.7	±8.7	0.20
– Duration HF, months*	62	(34-102)	61	(29-133)	0.89
– Ischemic etiology, *n* (%)	36	(72)	35	(71)	0.95
– NYHA II/III/IV, *n* (%)	44/7/0	(86/14/0)	45/5/0	(90/10/0)	0.56
– NT-proBNP, ng/L*	411	(216-704)	357	(200-904)	0.90
Treatment					
– ACEi/ARB, *n* (%)	51	(100)	50	(100)	NA
– Beta-blocker, *n* (%)	49	(96)	49	(98)	0.57
– Aldosterone antagonist, *n* (%)	17	(33)	12	(24)	0.30
– Loop diuretic, *n* (%)	26	(51)	23	(46)	0.62
Laboratory Measurements					
eGFR-MDRD, mL/min/1.73m^2	81	±16	80	±17	0.73
24h Urinary albumin, mg/24h*	5.3	(2.2-15.2)	6.9	(3.2-22.4)	0.41
24h Urinary sodium, mmol/24h	172	±75	159	±75	0.39
HbA1c, %*	5.9	(5.7-6.2)	5.9	(5.7-6.3)	0.47

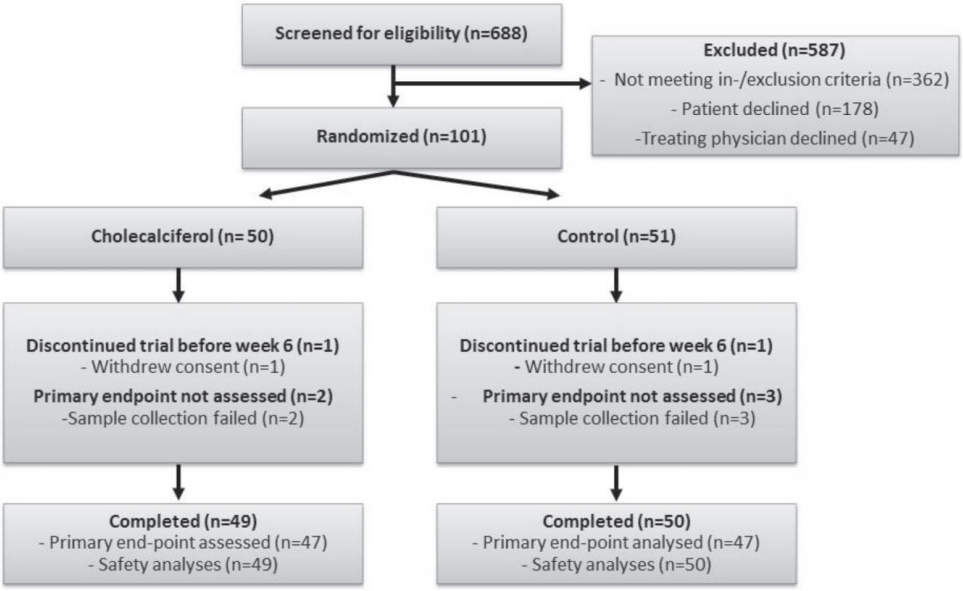
Table 1 (cont)

Characteristics	Control (n = 51)		VitD3 (n = 50)		P-value
Calcium, mmol/L	2.3	±0.1	2.3	±0.1	0.85
PTH, pmol/L*	7.0	(4.4-9.2)	7.8	(4.7-10)	0.45
Plasma Renin Activity, ng/mL/h*	4.5	(1.4-17.5)	5.4	(2.5-28.1)	0.46
Plasma Renin Concentration, ng/L	67	(17-181)	57	(21-193)	0.76
Aldosterone, pmol/L*	0.23	(0.14-0.43)	0.25	(0.14-0.37)	0.91
25 (OH)D, nmol/L*	46	(39-63)	48	(38-61)	0.86
1,25 $(OH)_2D$, pmol/L*	142	(117-170)	133	(107-168)	0.80

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; eGFR--MDRD: Estimated glomerular filtration rate (4-point MDRD formula). LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association Functional Classification; Normally distributed variables are presented as means± SD.

** Non-normally distributed continuous variables are presented as median value (25-75th percentiles).*

Figure 1 – Patient enrollment



VitD before and after randomization

At baseline mean 25 (OH)D level was 51.8±20.9 nmol/L and mean 1,25 $(OH)_2D$ was 144.2±44.8 pmol/L. Ten percent had normal 25 (OH)D levels (> 80 nmol/L), 34% hypovitaminosis (50-80 nmol/L) and 56% was deficient (< 50 nmol/L). There were no significant differences between the groups at baseline. We observed a significant increase in both 25 (OH)D levels and 1,25 $(OH)_2D$ levels in the VitD3 group compared to the control group (Figure 2, Table 2). This increase was already observed after three weeks ($P < 0.001$) and remained present until the end of the trial. At the end of the trial in the VitD3 group 52% had normal 25 (OH)D levels (> 80 nmol/L) compared to 4% in the control group.

There was a significant negative interaction between 25 (OH)D levels and treatment group ($P < 0.001$) consistent with a more pronounced increase in 25 (OH)D levels in patients with low 25 (OH)D levels at baseline after treatment with VitD3 (Figure 3).

Renin before and after randomization

Median PRA was 5.2 ng/mL/h (1.5-19.7) at baseline, and did not differ between the study groups. After three weeks, a non-significant decrease in PRA was observed in the VitD3 group compared to control ($P = 0.236$). After six weeks, PRA was significantly decreased in the VitD3 group compared to control ($P = 0.002$) as was PRC ($P = 0.020$, Figure 4, Table 2). A significant positive interaction was observed between baseline PRA and treatment ($P = 0.020$) for the outcome PRA after six weeks, consistent with a larger decrease of PRA in those of the treatment group with a low PRA at baseline, although numerically this difference was small. Correction for plasma 25 (OH)D, diuretic dose, 24h-urinary sodium excretion, NT-proBNP, and eGFR did not change the correlations.

Table 2: Follow up measurements – geometric mean (95% CI) of VitD, plasma renin activity and concentration

		Baseline (visit 1)	**3 weeks (visit 2)**	**6 weeks (visit 3)**
25 (OH)D, nmol/L	Control	48 (42-53)	46 (41-51)	44 (39-49)
	VitD3	48 (42-54)	71 (67-75)	80 (75-87)
			$P < 0.001$	$P < 0.001$

Table 2 (cont)

		Baseline (visit 1)	3 weeks (visit 2)	6 weeks (visit 3)
1,25 $(OH)_2D$, pmol/L	Control	139 (128-151)	161 (148-174)	132 (121-143)
	VitD3	137 (125-150)	202 (188-218)	194 (179-211)
			P < 0.001	*P* < 0.001
Plasma renin activity, ng/mL/h	Control	5.1 (3.0-8.8)	6.5 (3.9-10.8)	7.3 (4.5-11.8)
	VitD3	6.3 (3.7-10.9)	6.2 (3.7-10.4) *P* = 0.230	5.2 (2.9-9.5) *P* = 0.002
Plasma renin concentration, ng/L	Control	56 (35-89)	65 (41-103)	72 (47-111)
	VitD3	63 (38-104)	60 (37-96) *P* = 0.152	55 (32-93) *P* = 0.020

Data are presented as geometric means with 95% confidence intervals. Differences between groups at each time point were tested using ANCOVA with baseline values as covariate.

Figure 2 – Mean (SE) change in 25 (OH)D from baseline. Data are log2--transformed, therefore an increase of one is equal to a doubling of the value from baseline.

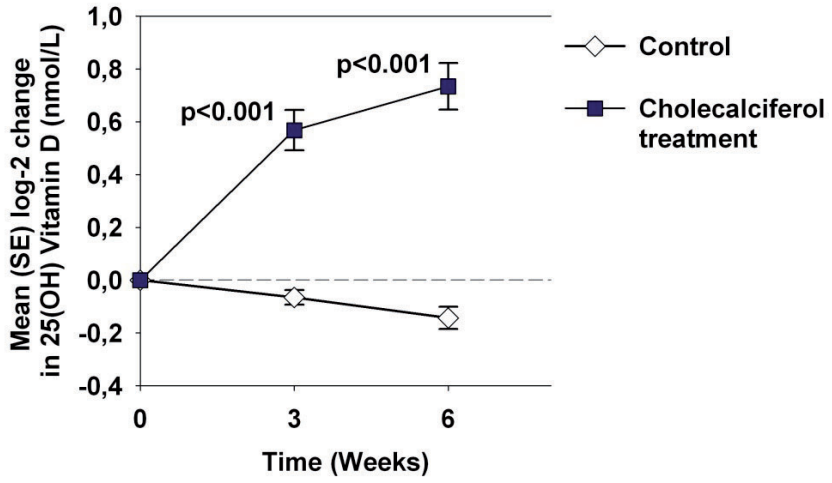


Figure 3 – Correlation of absolute change in 25 (OH)D between baseline and end-of-study with baseline 25 (OH)D. The difference in slope of the regression lines depicts the interaction between baseline 25 (OH)D and change in 25 (OH) D between the treatment groups.

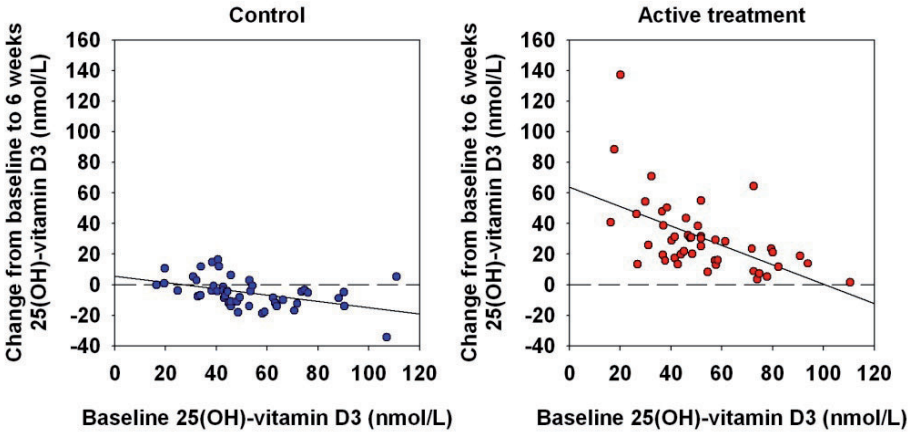
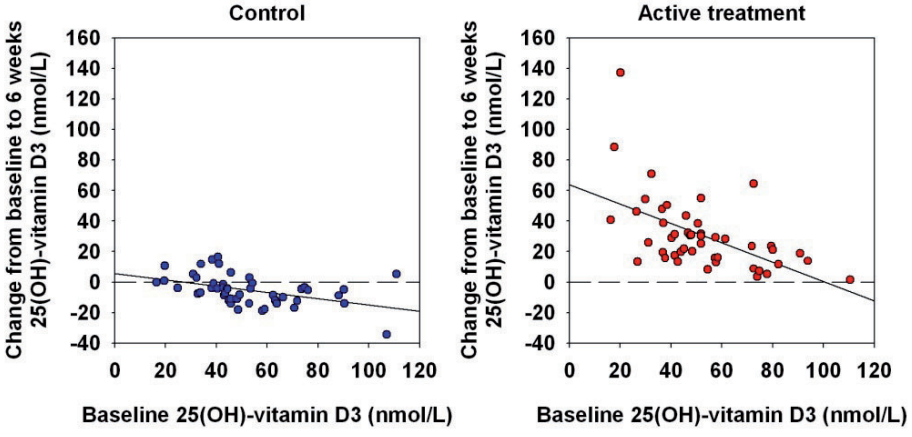


Figure 4 Mean (SE) treatment effect of VitD3 compared to control after three and six weeks of treatment on PRA and PRC, expressed as percentage change from baseline.



Secondary outcomes

Treatment with VitD3 resulted in a decrease in PTH (P = 0.004, Table 3). There were neither differences between both groups in serum calcium levels, nor changes in FGF-23, a novel marker for calcium homeostasis (Table 3). Other laboratory markers, including hs-Troponin T, NT-proBNP, eGFR, urinary albumin excretion, NGAL and fibrosis markers (e.a. PINP, PIIINP), did not differ between groups either (Supplemental Table 1s). Only Galectin-3 was significantly decreased after VitD3 treatment (P = 0.044).

Adverse events

Two severe adverse events occurred. One patient in the VitD3-treated group was diagnosed with a lymphoma and died several weeks after completion of the trial. This was the only subject with hypercalcaemia (corrected calcium 2.77 mmol/L on the final visit). One patient in the control group suffered a traumatic hip fracture, and was admitted for surgery with a quick recovery. The data safety monitoring board (DSMB) reviewed all data of these patients and judged a relationship of these events with the study drug unlikely. Additional measurements in these two patients demonstrated levels of 25 (OH)D, PTH and PTH-related peptide within the reference ranges. None of the subjects reached toxic 25 (OH)D levels.

Discussion

Our study confirms that the majority of CHF patients suffer from VitD deficiency which can be treated effectively and safely with supplementation of dietary vitD3. In our study, treatment with dietary vitD3 was associated with decreases of PRA and PRC.

Although there is no consensus on optimal VitD levels for non-calcaemic benefit, (22) using the definitions of 25 (OH)D above 80 nmol/L as normal, 50-80 nmol/L as hypovitaminosis and below 50 nmol/L as deficient, more than half of the patients was deficient at baseline and only 10% had normal VitD levels. The high prevalence of VitD deficiency in CHF patients is in line with previous studies. (1) Our study showed that oral supplementation of 2000 IU VitD3 once daily for six weeks effectively increased both 25 (OH)D and 1,25 $(OH)_2D$ levels, especially in patients with low vitD levels at baseline, was well tolerated, and did not affect plasma calcium. Indeed, a recent review confirms that adverse effects of VitD3 are very rare. (23)

Studies in CHF patients are scarce and have shown inconsistent results. Schleithoff showed in CHF patients that supplementation of 2000 IU VitD3 for

9 months decreased the level of pro-inflammatory cytokines, without changes in left ventricular function, BNP or blood pressure. (24) Moreover, children with congestive HF achieved marked improvement of both cardiac function measurements and inflammatory markers after 12 weeks of 1000 IU VitD3. (25) Finally, a non-randomized study in HF patients demonstrated that the use of vitD supplements was associated with reduced mortality. (1) There are also trials that report neutral effects. In patients with chronic kidney disease and left ventricular hypertrophy, 48 weeks treatment with the vitD receptor activator paricalcitol did not affect left ventricular mass, nor diastolic function. (26) Moreover, a single injection of 100,000 U vitamin D2 did not show improvement in a 6-minute-walking-distance or NYHA class (27) and another recent study demonstrated that weekly administration of 50,000 U of VitD3 did not improve VO_2 max, NYHA class, or 6-minute walking distance. (28) In contrast to our study, secondary analyses of the Witham study (29) showed a moderate, but significant decrease in BNP, but no significant effects on renin. Possibly, this difference may be attributed to very low vitamin-D levels at baseline (< 25nmol/L) with only a moderate increase of approximately 20 nmol/L after treatment. Collectively, the randomized supplementation studies in patients with CHF have generated inconsistent results with regard to outcome, and larger studies are warranted.

Recent meta-analyses of observational studies suggest a positive effect of vitD supplementation on cardiovascular risk, (29, 30) although not all studies show positive results. A randomized trial with 400-1000 IU vitD3 for one year in healthy postmenopausal women did not show beneficial effects on lipid profile, insulin resistance, inflammatory biomarkers and blood pressure (31) and in diabetic subjects a single dose of 100.000 IU vitD3 significantly decreased systolic blood pressure, despite the absence of significant changes in renin and angiotensin. (32) These varying results may be caused by different dosing and duration of therapy and request for more mechanistic insights. Our study is the first to show that short-term, high-dose vitD3 supplementation may lower PRA and PRC in CHF patients.

From the current study, we cannot conclude whether the reduction in renin would translate into improved outcome. We did not observe effects on fibrosis markers or NT-proBNP; however, sustained elevation in PRA is an independent predictor for adverse outcome in CHF patients (16, 17) despite ACEi and ARB treatment. Moreover, VitD3 supplementation may in fact have additional benefits over direct renin inhibitors, since the latter block PRA at the expense of an increased PRC, whereas VitD may reduce both. The inhibition of renin transcription may explain, in part, the observation that low VitD levels are associated with increased cardiovascular risk.

Strengths and limitations

Both renin levels and VitD levels were measured in a single batch resulting in low intra-assay variation. All patients were optimally treated: more than 95% were on ACEi or ARBs and more than 95% were on beta-blockers. Due to the short follow-up and relatively healthy population, mostly NYHA class II, we could maintain these drugs on a stable dose throughout the trial. Finally, we tested VitD3, which is a cheap and readily available dietary supplement with extensive safety data and excellent tolerability, which could easily be applied on a large scale. However, it cannot be excluded that e.g. calcitriol or VDR activators would have exerted ancillary or stronger effects.

Some limitations need to be acknowledged. First, this is a relatively small trial with a short follow-up, therefore we had no power to study clinical end-points. Likewise, the follow-up may have been too short to observe changes in other biomarkers. Second, this was not a placebo-controlled trial; however, during the trial, investigators were blinded to PRA/PRC results and the outcome analyses were conducted in a blinded fashion. Third, despite significant increases in 25 (OH)D levels in the VitD3 treatment group, almost half of the patients still had suboptimal 25 (OH)D levels after six weeks, suggesting that either the dose or treatment duration could be further increased. Fourth, although cardiovascular drugs were maintained on a stable dose in most patients and correction for loop-diuretic, urinary sodium excretion, renal function and NT-proBNP did not affect the results, we cannot exclude lifestyle changes may have influenced the results. Further, the study population comprised of selected patients that were younger and with fewer less co-morbidities than typical CHF patients and therefore the findings of the current study may not apply to more typical, elderly, CHF patients. Finally, the absolute reduction in PRA and PRC was small and it is difficult to ascertain if these changes will translate into clinical benefit. The control group showed an unexplained increase in PRA and PRC, so that the magnitude of the change between the treatment groups are partially driven by the increase in the control group and not by the reduction in the VitD3-treated group alone. However, to prevent bias, we determined that the pre-specified primary outcome was the changes between groups.

Future research

VitD3 supplementation could benefit CHF patients via various mechanisms. Herein, we explored if dietary VitD3 supplementation could be used to increase VitD levels with the aim to lower renin levels. Published results indicate it is reasonable, safe and efficacious to supplement with dietary VitD3, in a daily dose of 2000 U of even higher. A future trial exploring the potentially beneficial effects

of VitD in HF should desirably target a relevant surrogate endpoint of "hard" CHF outcome – current accepted surrogate endpoints in CHF research include peak oxygen uptake, measures of left ventricular geometry, and biomarker such as NT-proBNP, renin, aldosterone. If such an intermediate sized, rigidly designed, and well-powered trial would have positive results, this would pave the way for a large outcome trial. The results of the current study may help to design the next phase VitD study.

Conclusion

In conclusion, the majority of CHF patients are VitD-deficient. Supplementation with dietary VitD3 (daily intake 2,000 IU) effectively increased VitD levels and lowered both PRA and PRC compared to control. Furthermore, this dose appeared to be safe. These results are encouraging and provide useful data for further, larger trials targeting clinically relevant endpoints.

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Disclosures

Dr. Lambers-Heerspink served as consultant for Abbott, Johnson & Johnson, REATA, VITAE and received payments for lectures from Abbott. Prof. dr. Van Veldhuisen has received Board Membership fees from Amgen, BG Medicine, Pfizer, Sorbent and Vifor. Dr. De Boer received research grants from Abbott and BG Medicine, Inc. and consulted for Abbott, Novartis, and BG Medicine, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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