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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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. Vitamin D 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-center, open-label, blinded end point trial in 101 stable CHF patients with reduced left ventricular ejection fraction. Patients were randomized to 6 weeks of 2,000 IU oral VitD3 daily or control. At baseline, mean age was 64 ± 10 years, 93% male, left ventricular ejection fraction 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 6 weeks in the VitD3 treatment group and decreased from 47 nmol/L (42-53) to 44 nmol/L (39-49) in the control group ($P < .001$). The primary outcome PRA decreased from 6.5 ng/mL per hour (3.8-11.2) to 5.2 ng/mL per hour (2.9-9.5) in the VitD3 treatment group and increased from 4.9 ng/mL per hour (2.9-8.5) to 7.3 ng/mL per hour (4.5-11.8) in the control group ($P = .002$). This was paralleled by a larger decrease in plasma renin concentration in the VitD3 treatment group compared to control ($P = .020$). No significant changes were observed in secondary outcome parameters, including N-terminal pro–B-type natriuretic peptide natriuretic peptide and fibrosis markers.

Conclusions Most CHF patients had VitD deficiency and high PRA levels. Six weeks of supplementation with 2,000 IU VitD3 increased 25-hydroxyvitamin D3 levels and decreased PRA and plasma renin concentration. (Am Heart J 2013;166:357-364.e2.)

Vitamin D (VitD) deficiency is very common in patients with chronic heart failure (CHF) and is associated with increased mortality.[1-3] Vitamin D 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. Renin-angiotensin-aldosterone system 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 β-blockers decrease renin levels, and part of

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Clinical Trial Registration: http://www.clinicaltrials.gov (NCT01092130).

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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 (vitamin D3 [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 (left ventricular ejection fraction [LVEF] <45%) presenting at the outpatient clinic; treated with an angiotensin-converting enzyme 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 angiotensin receptor blocker (ARB) (candesartan 8 mg daily or any other ARB in an equivalent dose or maximum tolerated dose) for at least 4 weeks before the baseline visit (ie, visit 1); and treated with a β-blocker unless contraindicated or not tolerated at a stable dose for at least 4 weeks before visit 1.

For a full list of exclusion criteria, we refer to the online Appendix. Importantly, patients were excluded from participation in the study when they were using VitD supplements, drugs with a known interaction with VitD homeostasis (eg, 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 before 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 3 (ie, visit 3) and 6 (ie, visit 4) weeks and by telephone after 7 weeks. Patients were randomized by an automated computer system to 2,000 IU oral VitD3 once daily or control (ie, no extra medication) in a 1:1 ratio for a period of 6 weeks. Blood was collected in a sitting position on visits 2 to 4, and patients were asked to collect 24-hour urine samples before visits 2 and 4. Blood was collected on ice or room temperature, as appropriate for specific assays (PRC and PRA). Congestive heart failure medication was maintained unchanged throughout the trial. Changes in diuretic dose were permitted if necessary to treat decompensation or renal dysfunction.

Laboratory measurements

Routine laboratory measurements, including creatinine, N-terminal pro–B-type natriuretic peptide (NT-proBNP), urinary albumin, and parathyroid hormone (PTH) were performed on the day of the visit. Additional samples were stored at −80°C 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 Modification of Diet in Renal Disease (MDRD) formula.

All measurements were performed using commercially available kits according to the manufacturer's instructions. Plasma renin activity was measured using an indirect radioimmunoassay kit for the quantitative determination of angiotensin I (Cisbio International, Codolet, France). The detection limit was 0.15 ng/mL. Plasma renin activity was expressed as nanograms per milliliter per hour of generated angiotensin I. The intra-assay coefficient of variation (CV) at 1.4 and 16 ng/mL per hour was 4.3% and 7.2%, respectively. The inter-assay CV at 1.4 and 16 ng/mL per hour was 9.9% and 8.5%, respectively. Plasma renin concentration was measured using a radioimmunometric assay kit for the quantitative determination of active renin (Cisbio International) 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-Hydroxyvitamin D_3 was measured by solid phase extraction followed by liquid chromatography–tandem mass spectrometry (Spark-Holland Symbiosis system, Emmen, The Netherlands). The detection limit was 1.2 nmol/L, and intra-assay and inter-assay CV were 5.0% to 14.1%. 1,25-Dihydroxyvitamin D_3 was also measured by liquid chromatography–tandem mass spectrometry essentially as described by Casetta et al[21] with a CV of 5% to 15% at physiological concentration levels.

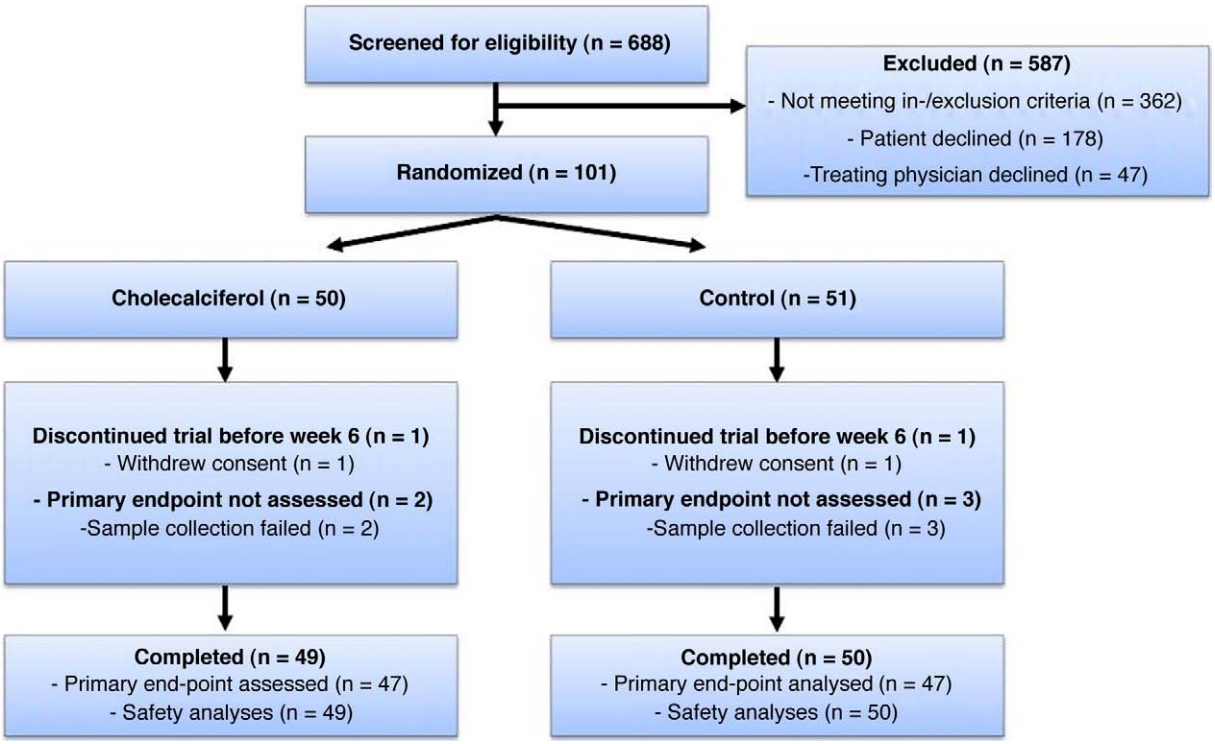
Primary and secondary end points

The primary end point was the difference in PRA between both groups after 6 weeks of treatment corrected for baseline PRA. Secondary end points 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 (College Station, TX). All normally distributed variables are represented as means ± SD. Skewed variables are represented as geometric means with 95% CIs and were log transformed when appropriate for statistical testing. Baseline differences were tested using an independent t test and χ^2 tests as appropriate. Changes between baseline and 3 and 6 weeks were tested with analysis of covariance (ANCOVA) including the baseline value and treatment group as covariates. Interactions were tested by adding the product of 2 terms to the model. Subsequently, analyses were repeated with correction for 24-hour urinary sodium excretion, loop diuretic dose (1 mg of bumetanide or 40 mg of furosemide was considered 1 unit), renal function, and NT-proBNP. All tests were performed 2 tailed, and $P < .05$ was considered statistically significant. Graphs were drawn in Sigmaplot version 10.0 (San Jose, CA).

Figure 1



Patient enrollment.

Sample size

In a large community-based cohort in our center, the mean log PRA was 1.29 ± 0.65 ng/mL per hour. With an α of .05 and a power of 90%, we calculated a sample 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.

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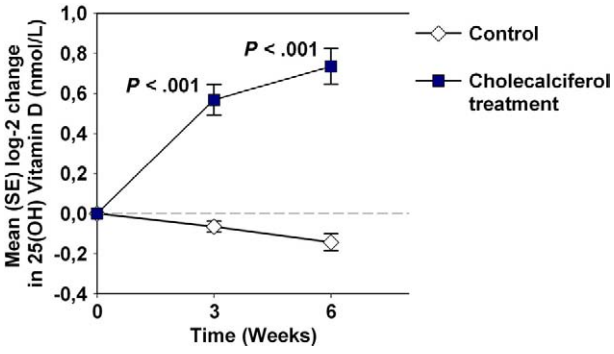
Figure 2



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.

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, 1 patient withdrew consent to participate in the trial shortly after randomization. The primary end point 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)

Table I. Baseline characteristics

Characteristics	Control (n = 51)	VitD3 (n = 50)	*P*
Age, y	63.5 ±11.1	64.0 ±9.0	.79
Male sex, n (%)	46 (90)	48 (96)	.25
Blood pressure systolic, mm Hg	118 ±19	118 ±17	.96
Blood pressure diastolic, mm Hg	74 ±12	71 ±13	.31
Heart rate, beat/min	67 ±10	69 ±12	.39
Heart failure history			
LVEF, %	33.6 ±7.5	35.7 ±8.7	.20
Duration HF, m*	62 (34-102)	61 (29-133)	.89
Ischemic etiology, n (%)	36 (72)	35 (71)	.95
NYHA II/III/IV, n (%)	44/7/0 (86/14/0)	45/5/0 (90/10/0)	.56
NT-proBNP, ng/L*	411 (216-704)	357 (200-904)	.90
Treatment			
ACEi/ARB, n (%)	51 (100)	50 (100)	NA
β-Blocker, n (%)	49 (96)	49 (98)	.57
Aldosterone antagonist, n (%)	17 (33)	12 (24)	.30
Loop diuretic, n (%)	26 (51)	23 (46)	.62
Laboratory measurements			
eGFR-MDRD, mL/min per 1.73 m^2	81 ±16	80 ±17	.73
24-h urinary albumin, mg/24 h*	5.3 (2.2-15.2)	6.9 (3.2-22.4)	.41
24-h urinary sodium, mmol/24 h	172 ±75	159 ±75	.39
HbA1c, %*	5.9 (5.7-6.2)	5.9 (5.7-6.3)	.47
Calcium, mmol/L	2.3 ±0.1	2.3 ±0.1	.85
PTH, pmol/L*	7.0 (4.4-9.2)	7.8 (4.7-10)	.45
PRA, ng/mL per hour*	4.5 (1.4-17.5)	5.4 (2.5-28.1)	.46
PRC, ng/L	67 (17-181)	57 (21-193)	.76
Aldosterone, pmol/L*	0.23 (0.14-0.43)	0.25 (0.14-0.37)	.91
25(OH)D, nmol/L*	46 (39-63)	48 (38-61)	.86
$1,25(OH)_2D$, pmol/L*	142 (117-170)	133 (107-168)	.80

Normally distributed variables are presented as means ± SD. *NA*, Not applicable.
*Non-normally distributed continuous variables are presented as median value (25th-75th percentiles).

class II. All patients were on either an ACEi or ARB, >95% of patients were treated with a β-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 with 26 (51%) in the control group. In the VitD3 treatment group, 1 patient had an increase in diuretic dose, and 1, 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 <10% on visits 2 and 4.

Vitamin D 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 (Table I). We observed a significant increase in both 25(OH)D levels and $1,25(OH)_2D$ levels in the VitD3 group compared with the control group (Figure 2, Table II). This increase was already observed after 3 weeks ($P < .001$) 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 with 4% in the control group.

There was a significant negative interaction between 25(OH)D levels and treatment group ($P < .001$) 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).

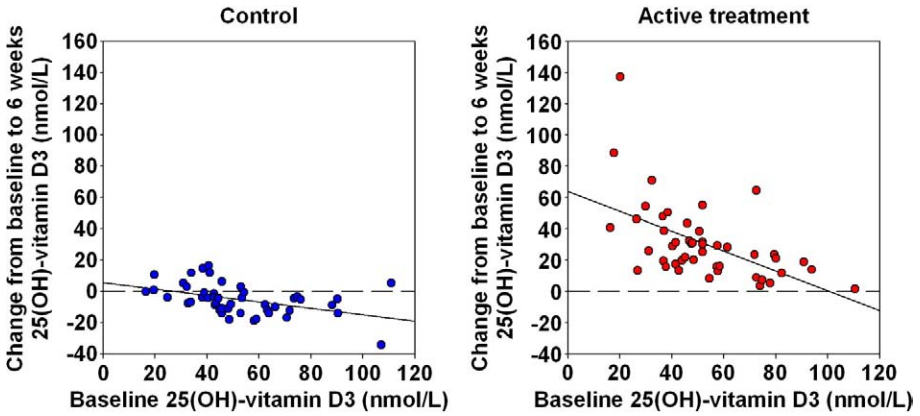
Renin before and after randomization

Median PRA was 5.2 ng/mL per hour (1.5-19.7) at baseline and did not differ between the study groups. After 3 weeks, a nonsignificant decrease in PRA was observed in the VitD3 group compared with control ($P = .236$). After 6 weeks, PRA was significantly decreased in the VitD3 group compared with control ($P = .002$) as was PRC ($P = .020$) (Figure 4, Table II). A significant positive interaction was observed between baseline PRA and treatment ($P = .020$) for the outcome PRA after 6 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, 24-hour urinary sodium excretion, NT-proBNP, and eGFR did not change the correlations.

Secondary outcomes

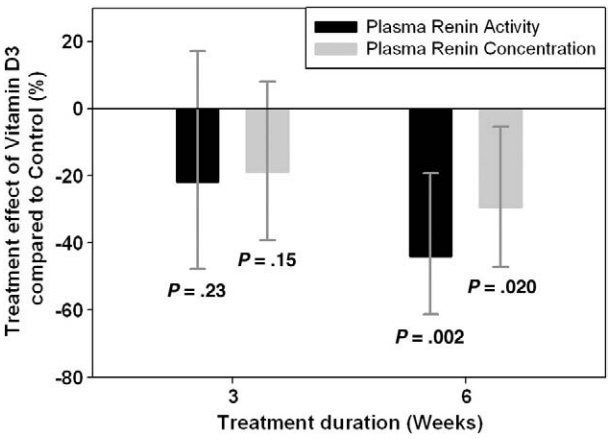
Treatment with VitD3 resulted in a decrease in PTH ($P = .004$) (online Appendix Supplementary Table). There were neither differences between both groups in serum

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 with control after 3 and 6 weeks of treatment on PRA and PRC, expressed as percent change from baseline.

calcium levels nor changes in fibroblast growth factor 23, a novel marker for calcium homeostasis (online Appendix Supplementary Table). Other laboratory markers, including high-sensitivity troponin T, NT-proBNP, eGFR, urinary albumin excretion, NGAL, and fibrosis markers (ie, N-terminal propeptide of type I procollagen and N-terminal propeptide of type III procollagen), did not differ between groups either (online Appendix Supplementary Table). Only galectin 3 was significantly decreased after VitD3 treatment ($P = .044$).

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 hypercalcemia (corrected calcium 2.77 mmol/L on the final visit). One patient in the control group had a traumatic hip fracture and was admitted for surgery with a quick recovery. The data safety monitoring board reviewed all data of these patients and judged a relationship of these events with the study drug unlikely. Additional measurements in these 2 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 most CHF patients with VitD deficiency 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 noncalcemic benefit,[22] using the definitions of 25(OH)D >80 nmol/L as normal, 50 to 80 nmol/L as hypovitaminosis, and <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 2,000 IU VitD3 once daily for 6 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 et al[24] showed in CHF patients that supplementation of 2,000 IU VitD3 for 9 months decreased the level of proinflammatory

Table II. Follow-up measurements—geometric mean (95% CI) of VitD, PRA, and PRC

		Baseline (visit 1)	3 wk (visit 2)	6 wk (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)
			$P < .001$	$P < .001$
1,25(OH)$_2$D, pmol/L	Control	139 (128-151)	161 (148-174)	132 (121-143)
	VitD3	137 (125-150)	202 (188-218)	194 (179-211)
			$P < .001$	$P < .001$
PRA, ng/mL per 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)	5.2 (2.9-9.5)
			$P = .230$	$P = .002$
PRC, ng/L	Control	56 (35-89)	65 (41-103)	72 (47-111)
	VitD3	63 (38-104)	60 (37-96)	55 (32-93)
			$P = .152$	$P = .020$

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

cytokines, without changes in left ventricular function, B-type natriuretic peptide, or blood pressure. Moreover, children with CHF achieved marked improvement of both cardiac function measurements and inflammatory markers after 12 weeks of 1,000 IU VitD3.[25] Finally, a nonrandomized study in heart failure 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-week 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 brain natriuretic peptide but no significant effects on renin. Possibly, this difference may be attributed to very low VitD levels at baseline (<25 nmol/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 to 1,000 IU VitD3 for 1 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 because 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: >95% were on ACEi or ARBs and >95% were on β-blockers. Because of 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, for example, calcitriol or vitD receptor 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 6 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. Furthermore, the study population composed of selected patients who were younger and with fewer comorbidities 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 is 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 prespecified primary outcome was the changes between groups.

Future research

Vitamin D3 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 that it is reasonable, safe, and efficacious to supplement with dietary VitD3, in a daily dose of 2,000 U or even higher. A future trial exploring the potentially beneficial effects of VitD in heart failure should desirably target a relevant surrogate end point of "hard" CHF outcome—current accepted surrogate end points in CHF research include peak oxygen uptake; measures of left ventricular geometry; and biomarker such as NT-proBNP, renin, and 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, most 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 with control. Furthermore, this dose appeared to be safe. These results are encouraging and provide useful data for further larger trials targeting clinically relevant end points.

Disclosures

Dr Lambers-Heerspink served as consultant for Abbott, Johnson & Johnson, REATA, VITAE, and received payments for lectures from Abbott. Prof 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 article to disclose.

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Appendix. Supplementary materials

Study population

Exclusion criteria. Patients with the following criteria were excluded: history of hypersensitivity to the study drug; patients with phenylketonuria or fructose intolerance; current acute decompensated heart failure; hypercalcemia (>2.65 mmol/L, corrected for albumin); hypercalciuria; estimated glomerular filtration rate <60 mL/min per 1.73 m^2 as measured by the Modification of Diet in Renal Disease formula; a history of nephrolithiasis or sarcoidosis; use of oral corticosteroids, thyroxin, antiepileptic drugs, tetracyclines, or quinolones; intake of supplements containing vitamin D and/or calcium; acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or major vascular surgery, percutaneous coronary intervention, or carotid angioplasty (either within the past 3 months or planned); right heart failure due to severe pulmonary disease; diagnosis of peripartum or chemotherapy-induced cardiomyopathy within the last year; patients with a history of heart transplant, on a transplant list, or with left ventricular assistance device; untreated ventricular arrhythmia with syncopal episodes within the past 3 months; documented history of ventricular tachycardia or ventricular fibrillation without internal cardiac defibrillator; symptomatic bradycardia or second- or third-degree heart block without a pacemaker; implantation of a cardiac resynchronization therapy device within 3 months; presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to left ventricular dilatation; presence of hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic stenosis; any surgical or medical condition, which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs; any history of pancreatic injury, pancreatitis, or evidence of impaired pancreatic function/injury; primary liver disease considered to be life threatening; currently active gastritis, duodenal or gastric ulcers, or gastrointestinal/rectal bleeding during the past 3 months; history or presence of any other diseases (ie, malignancies) with a life expectancy of <5 years; current double-blind treatment in heart failure trials; participation in an investigational drug study within the past 30 days or 5 half-lives of enrolment, whichever is longer; any surgical or medical condition that in the opinion of the investigator or medical monitor would jeopardize the evaluation of efficacy or safety; history of noncompliance to medical regimens and patients who are considered potentially unreliable; pregnant or lactating women; and treatment with a direct renin inhibitor or intravenous vasodilator and/or inotropic drugs within the past 4 weeks.

Additional laboratory measurements

Neutrophil gelatinase–associated lipocalin was determined in urine samples by means of enzyme-linked immunosorbent assay (R&D systems, Minneapolis, MN). Urine samples were diluted 100 times in 0.1% BSA-PBS buffer. The median CV of the NGAL enzyme-linked immunosorbent assay was 9.3%. Plasma aldosterone concentration was measured using a solid phase 125I radioimmunoassay (Siemens diagnostics) intra-assay CV <5.4%, inter-assay CV <15.7%. C-terminal telopeptide of type I collagen was measured in serum samples with a quantitative enzyme immunoassay, according to the manufacturer's instructions (UniQ ICTP, cat. no. 05892; Orion Diagnostica, Finland). N-terminal propeptide of type I procollagen and N-terminal propeptide of type III procollagen were measured in serum samples with quantitative radio immunoassays according to the manufacturer's instructions (UniQ PINP, cat. no. 67034, and UniQ PIIINP, cat. no. 68570; Orion Diagnostica).

Supplementary Table. Follow-up measurements of secondary outcomes

		Baseline	End of study	*P*
Parathyroid hormone, pmol/L	Control	6.5 (5.6-7.6)	6.8 (6.0-7.7)	.004
	Active	7.8 (4.7-10)	6.1 (4.4-7.9)	
Calcium, mmol/L	Control	2.28 0.09	2.27 0.08	.10
	Active	2.28 0.08	2.30 0.11	
FGF-23, RU/mL	Control	121 (105-140)	119 (105-136)	.21
	Active	132 (112-155)	134 (114-158)	
hs-Troponin T, pg/mL	Control	6.0 (4.8-7.6)	5.9 (4.7-7.4)	.98
	Active	6.5 (5.1-8.3)	6.4 (5.0-8.2)	
NT-proBNP, ng/L	Control	418 (317-552)	355 (261-485)	.26
	Active	429 (318-580)	446 (333-599)	
Aldosterone, nmol/L	Control	0.23 (0.19-0.29)	0.24 (0.19- 0.29)	.27
	Active	0.24 (0.19-0.31)	0.22 (0.17-0.29)	
eGFR-MDRD, mL/min per 1.73 m^2	Control	81 ±16	81 ±17	.82
	Active	80 ±17	79 ±18	
24-h urinary albumin, mg/24 h	Control	6.9 (4.6-10.2)	6.1 (4.19.0)	.85
	Active	8.8 (5.6-13.8)	8.6 (5.6-13.1)	
Galectin 3, ng/mL	Control	16.7 (15.6-17.8)	17.0 (16.0-18.1)	.044
	Active	16.8 (15.8-17.9)	16.3 (15.2-17.4)	
PINP, μg/L	Control	26 (23-29)	25 (22-28)	.22
	Active	28 (24-32)	28 (25-33)	
PIIINP, μg/L	Control	9 (8-11)	10 (8-12)	.95
	Active	11 (9-13)	11 (9-13)	
ICTP, μg/L	Control	3.3 (2.9-3.7)	3.3 (3.0-3.7)	.44
	Active	3.6 (3.2-4.0)	3.7 (3.3-4.1)	

Data are presented as geometric means with 95% CIs. Changes from baseline were tested using ANCOVA. *FGF-23*, Fibroblast growth factor 23; *hs-Troponin T*, high-sensitivity troponin T; *PINP*, N-terminal propeptide of type I procollagen; *PIIINP*, N-terminal propeptide of type III procollagen; *ICTP*, C-terminal telopeptide of type I collagen.