Nutrition, Metabolism & Cardiovascular Diseases (2017) **27**, 837–849

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

REVIEW

Vitamin D deficiency and clinical outcome in patients with chronic heart failure: A review

C. D'Amore [a], F. Marsico [b], A. Parente [b], S. Paolillo [c], F. De Martino [b], P. Gargiulo [c], F. Ferrazzano [b], A.M. De Roberto [b], L. La Mura [b], C. Marciano [d], S. Dellegrottaglie [e], B. Trimarco [b], P. Perrone Filardi [b,*]

[a] *Clinica Mediterranea, Naples, Italy*
[b] *Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy*
[c] *IRCCS SDN, Naples, Italy*
[d] *Istituto Diagnostico Varelli, Naples, Italy*
[e] *ClinicaVilla dei Fiori, Acerra, Italy*

Received 5 February 2017; received in revised form 17 July 2017; accepted 23 July 2017
Handling Editor: A. Giaccari
Available online 29 July 2017

KEYWORDS
Heart failure;
Vitamin D deficiency;
Vitamin D supplementation;
Cardiovascular outcomes

Abstract *Aim:* The aim of this review was to summarize evidence on the role of Vitamin D deficiency in heart failure (HF), from pathophysiological mechanisms to clinical effects of Vitamin D supplementation.
Data synthesis: Chronic HF secondary to left ventricular (LV) systolic dysfunction is a growing health problem, still associated with poor clinical outcome. In recent years, experimental and epidemiological evidence focused on the role of Vitamin D in HF. Cross sectional studies demonstrated that prevalence of HF is increased in patients with Vitamin D deficiency or parathyroid hormone (PTH) plasma level increase, whereas longitudinal studies showed enhanced risk of developing new HF in patients with Vitamin D deficiency. In addition, in patients with established HF, low plasma levels of Vitamin D are associated with worsening clinical outcome. Yet, clinical studies did not definitively demonstrate a benefit of Vitamin D supplementation for preventing HF or ameliorating clinical outcome in patients with established HF.
Conclusions: Despite convincing experimental and epidemiological data, treatment with Vitamin D supplementation did not show clear evidence of benefit for preventing HF or influencing its clinical course. Ongoing clinical studies will hopefully shed lights on the effects of Vitamin D supplementation on clinical endpoints along the spectrum of HF.

Abbreviations: AF, atrial fibrillation; CV, cardiovascular; EF, ejection fraction; HF, Heart failure; LV, left ventricular; MCS, mechanical circulatory support; MI, myocardial infarction; MMP, metallopreotease; NYHA, New York Heart Association; NT pro-ANP, NT pro-atrial natriuretic peptide; NT pro-BNP, N-terminal pro-brain natriuretic peptide; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; SCD, sudden cardiac death; TRPV6, transient receptor potential channel vanilloid type; TIMPs, tissue inhibitors of metalloproteinases; VDR, Vitamin D receptor; 1,25(OH)2D, 1,25-dihydroxivitamin D; 25(OH)D, 25-hydroxyvitamin D; 6-MWT, 6-min walking test; 6-MWD, 6-min walk distance.

* Corresponding author. Via Pansini, 5, I-80131, Naples, Italy. Fax: +39 081 746 22 24.
E-mail address: fpperron@unina.it (P. Perrone Filardi).

http://dx.doi.org/10.1016/j.numecd.2017.07.009

Introduction

Heart failure (HF) is a complex syndrome secondary to inherited or acquired structural or functional heart abnormalities, and remains a leading cause of mortality and morbidity worldwide [1]. Approximately 10 millions of patients in Europe are affected by chronic HF [1] and, despite substantial advances in therapeutic options over the last years, no substantial changes in prognosis have been observed, with survival rate at 5 years after diagnosis of 35–50% [2,3]. Several mechanisms are involved in the pathogenesis of HF, including haemodynamic abnormalities, neurohormonal activation, enhanced inflammation and micronutrients availability [4], that explains the suboptimal impact of current therapies on clinical outcome.

Vitamin D is an important micronutrient with a significant role in autocrine and paracrine regulation of cellular functions and in growth and differentiation of several organs, including the heart. In fact, Vitamin D deficiency is associated with increased incidence of hypertension, myocardial infarction (MI), HF and stroke [5].

The aim of this review is to summarize evidence regarding Vitamin D deficiency in the pathogenesis and clinical course of HF with reduced systolic function and to report the effects of Vitamin D supplementation in patients with HF.

The search strategy to realize this review article, was a MEDLINE research, made with the following terms: "Vitamin D" or "Vitamin D supplementation" and "heart failure". All initially retrieved articles were subsequently individually analysed and discussed by the Authors group to establish adherence and relevance for the present review.

Vitamin D metabolism (Physiology)

Vitamin D is a secosteroid that exists in two major forms: Vitamin D_2 (or ergocalciferol) and Vitamin D_3 (or cholecalciferol). Vitamin D can be derived from sunlight (UV-B)-induced production in the skin (80%) and from dietary intake [6]. The formation of active Vitamin D_3 metabolite requires two steps, the first in the liver to form 25-hydroxyvitamin D_3 (25(OH)D or calcifediol) and the second in the kidney to convert calcifediol in 1,25-dihydroxivitamin D (1,25(OH)2D or calcitriol) [7]. The 25(OH)D is primarily dependent on Vitamin D supply, with serum levels higher than calcitriol and with longer half-life (~3 weeks) compared to Vitamin D and calcitriol (both with few hours half life). Therefore, 25(OH)D concentrations should be measured to assess Vitamin D status [6,8].

Vitamin D exerts its action binding Vitamin D receptor (VDR), expressed on at least 36 different tissues including cardiac muscle, vascular smooth muscles, endothelium and lymphocytes [9]. VDR forms a heterodimer with the retinoic acid receptor, and this heterodimeric complex acts on gene transcription of Vitamin D response element [10], that consists of a large number of target genes [10]. Recent studies also showed that Vitamin D metabolites might act through non-genomic pathways, using an alternative binding site on VDR [9,10].

From plasma measurement of 25(OH)D, in 2011 the Institute of Medicine classified Vitamin D status as deficiency (values below 12 ng/ml), inadequacy (values from 12 to 19.9 ng/ml), adequacy (values from 20 to 50 ng/ml) and potentially harmful (values above 50 ng/ml). Interestingly, a U-shape relationship emerged between Vitamin D levels and all-cause mortality, cardiovascular (CV) diseases, selected cancer, falls and fracture. This emerging relationship has a remarkable impact in the management of patients with Vitamin D deficiency, since no additional clinical benefit is observed for 25(OH)D concentration above 30 ng/ml, and excess risk has been observed for levels above 50 mg/dl [11].

Vitamin D and the CV system (Mechanisms)

Several potential biological mechanisms link Vitamin D and its metabolites to CV diseases (Fig. 1). Vitamin D acts as a negative regulator of renin-angiotensin-aldosterone system (RAAS) and several studies showed a relationship between low Vitamin D levels and increased RAAS activity [12–14]. Consistently, VDR knockout mice show increased RAAS activity, leading to hypertension, cardiac hypertrophy, increased water intake and sodium retention [12]. In addition, Vitamin D deficiency stimulates renin expression in normal mice, whereas 1,25(OH)2D injection leads to renin suppression [12]. Vitamin D may act directly on growth and differentiation of cardiomyocytes inhibiting their proliferation. This anti-proliferative property may be due to the suppression of proto-oncogene cmic and of natriuretic peptide. VDRs are also expressed on cardiac fibroblasts, and VDR knockout mice show collagen deposition [15].

Vitamin D modulates myocardial extracellular matrix turnovers. In fact, VDR knockout mice show increased metallopreotease (MMP) activity due to a reduced production of tissue inhibitors of metalloproteinases 1 and 3 (TIMP1 and TIMP 3) (MMP inhibitors). Thus, the proteolytic action of MMP promotes the destruction of myocardial tissue leading to ventricular remodelling [16,17].

Calcium deposition in atherosclerotic plaques and vascular calcification are also promoted by Vitamin D [18,19]. This observation is consistent with the inverse correlation between Vitamin D levels and coronary artery calcification [20]. Furthermore, it is documented that endothelial cells express VDR, so that Vitamin D increases nitric oxide synthase activity in vitro [21], enhances vascular endothelial growth factor production [22,23] and reduces endothelial platelet aggregation [24].

By a non-genomic pathway, the functional form of Vitamin D acts on calcium channels in cardiac myocytes inducing a rapid influx of calcium [25]. Experimental animal studies showed that calcitriol, through the phosphorylation of protein kinase C, promotes myocytes relaxation, thus participating in the homoeostasis of diastolic function [26], and enhances myocyte contractility through adenylate cyclase and cyclic adenosine monophosphate (cAMP) pathways [25].

The effects of Vitamin D on CV system are additionally mediated through elevated parathyroid hormone (PTH)

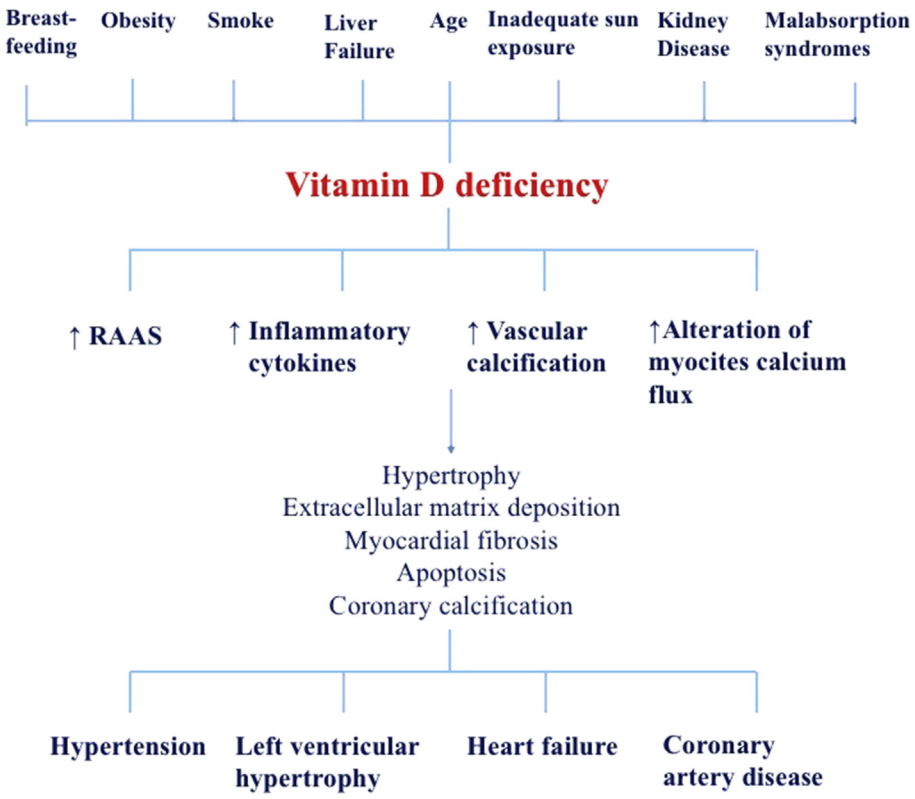

Figure 1 Mechanisms involved in the onset and/or progression of heart failure in patients with Vitamin D deficiency; Abbreviation: RAAS: renin-angiotensine-aldosterone system.

levels. It is well established that Vitamin D is included in the calciotropic hormone system together with PTH [27]. The active Vitamin D form enhances the production and activity of the TRPV6 (Transient Receptor Potential channel Vanilloid type) ion channel and calbindin calcium binding protein in the intestinal epithelium to promote calcium absorption. In addition, 1,25(OH)2D increases renal calcium reabsorption as well as calcium reabsorption from the skeleton together with PTH [28]. Besides, VDRs are present in the parathyroid gland and 1,25(OH) suppresses production of PTH and prevents proliferation of parathyroid glands [29]. Consequently, Vitamin D deficiency is associated with elevated PTH concentration, that exerts a trophic effect on cardiomyocytes with an increase in total cellular mass and arterial stiffness [30], that is associated with development of left ventricular (LV) hypertrophy in patients with elevated PTH levels [31].

In summary, large evidence from experimental data supports a plausible mechanistic association between Vitamin D deficiency and CV damage.

Vitamin D deficiency and HF

Prevalence of vitamin D deficiency in HF (Cross sectional and case–control studies)

It is estimated that 1 billion people worldwide have Vitamin D deficiency or insufficiency, and 40–80% of the elderly population exhibits Vitamin D deficiency [32]. Risk factors for Vitamin D deficiency include sunscreen usage, dark skin, breast fed infants, ageing, inflammatory bowel disease, fat malabsorption disease, obesity and sedentary lifestyle [33].

Several cross-sectional studies showed an association between HF and 25(OH)D levels (Table 1). Shane et al. [34] showed low serum levels of 25(OH)D ($\leq$9 pg/ml) and of 1,25(OH)2D ($\leq$15 pg/ml) in 17% and 26%, respectively, of 101 HF patients being evaluated for heart transplant. Then, Zitterman et al. [35], in a case control study, also reported a statistically significant reduction of 25(OH)D and calcitriol levels in patients with HF compared to a control group.

Similar epidemiological data were obtained from the National Health and Nutrition Examination Survey (NHANES) 2001 to 2004 [28]. In this study in 8351 US adults, who had 25(OH)D levels measured, the prevalence of hypovitaminosis D (using previous definition of Vitamin D deficiency for plasma levels $<$30 ng/ml) was 74%, and a stepwise increase of CV disease was observed from the lowest to the highest serum 25(OH)D tertile (from 3,25%, to 2.4% and 1,5%). Notably, hypovitaminosis D reached 89% prevalence in patients with concomitant coronary heart disease and HF (OR 3.52, 95% CI 1.58–7.84).

Also, the Intermountain Healthcare system study, including 41,504 subjects from a general population with at least one Vitamin D measurement, showed that 36% of the population had Vitamin D levels in the range of normality, 47% had a mild-moderate reduction (16–30 ng/

Table 1 Prevalence of Vitamin D deficiency in heart failure (Cross sectional and case–control studies).

Author	Study design	Publication year	Patients enrolled (n)	Inclusion criteria	Definition of hypovitaminosis	Heart failure and hypovitaminosis D
Shane E [34]	Cross-sectional	1997	101	NYHA class III–IV; Consideration for cardiac transplant	25(OH)D ≤ 9 pg/ml 1,25(OH)2D ≤ 15 ng/ml	17% prevalence of hypovitaminosis D in HF patients with 25(OH)D ≤ 9 pg/ml 26% prevalence of hypovitaminosis D in HF patients with 25(OH)D ≤ 15 ng/ml
Zittermann A [35]	Case control	2003	54	NYHA class ≥II		Not reported. Significant reduction of 25(OH)D and calcitriol serum levels in patients with HF (ANOVA p value < 0.001)
Kim DH [28]	Cross-sectional	2008	8351	Adult subject with measured 25(OH)D levels	25(OH)D < 30 ng/ml	89% of hypovitaminosis D in HF patients with concomitant coronary artery disease
Anderson JL [5]	Prospective cohort	2010	41,504	General healthcare population with measured 25(OH)D levels	25(OH)D ≤ 30 ng/ml	97% of HF in patients with low Vitamin D levels. 1.31 HR for new HF development in patients with low and very low Vitamin d levels.

Abbreviations: HF: Heart failure; NYHA: New York Heart Association; 1,25(OH)2D: 1,25-dihydroxivitamin D; 25(OH)D: 25-hydroxyvitamin D.

ml) and 17% had very low levels (≤15 ng/ml). An increased prevalence of HF (90% relative and 9% absolute) was observed in very low versus normal Vitamin D categories ($p < 0.0001$), and during follow-up (1.3 ± 1.2 years) new onset HF developed in 594 (2,5%) subjects older than 50 years. Vitamin D plasma levels inversely correlated to the risk of developing HF, and adjusted hazards for HF were 2.01 and 1.30 for very low levels and low levels of Vitamin D, respectively [5].

Thus, prevalence of Vitamin D deficiency is increased in patients with HF and a correlation between reduced levels of Vitamin D and HF prevalence has been observed in clinical studies.

Low vitamin D and risk of HF (Observational longitudinal studies)

The association between Vitamin D levels and HF has been also confirmed in longitudinal studies (Table 2).

The prospective Ludwigshafen Risk and Cardiovascular Health (LURIC) [36] study enrolled 3299 patients undergoing coronary angiography and evaluated the association between 25(OH)D levels and HF and sudden cardiac death (SCD) during a mean follow-up of 7.7 years. 25(OH)D and 1,25(OH)2D were independently and inversely correlated with N-terminal pro-brain natriuretic peptide (NT pro-BNP) levels ($r = -0.190$ and -0.255, respectively; $p < 0.001$ for both) and were inversely associated with LV ejection fraction (EF) ($p < 0.001$ for both) and higher New York Heart Association (NYHA) class ($p = 0.05$ for 1,25(OH)2D). Using multivariable adjustment for confounding factors, the inverse correlation of NT pro-BNP and LVEF with 25(OH)D and calcitriol levels was unchanged. In addition, during a median follow-up of 7.7 years, 116 patients died due to HF (110 in low Vitamin D groups and 6 in Vitamin D optimal range group) and 188 due to SCD (182 in low Vitamin D groups and 6 patients with optimal range of Vitamin D). Thus, low levels of 25(OH)D and of 1,25(OH)2D were independent risk factors for mortality due to HF (HR 2.84; 95% CI: 1.20–6.74) and for SCDs (HR 5.05; 95% CI: 2.13–11.97).

The Cardiovascular Health Study [30] measured Vitamin D and PTH levels in 2312 healthy subjects and reported that patients with Vitamin D deficiency and high PTH levels showed higher risk of MI and HF compared to controls, during 14 years follow-up. After adjustment, each 10 ng/ml lower 25(OH)D concentration was associated with a 9% greater (95% CI: 2%–17%; $p = 0.012$) relative hazard of all-cause mortality and a 25% greater (95% CI: 8%–44%; $p = 0.002$) relative hazard of MI. In addition, a serum 25(OH)D concentrations <15 ng/ml was associated with a 29% greater (95% CI: 5%–55%) risk of all-cause mortality. Instead, serum PTH concentration (≥65 pg/ml), that reflects inadequate Vitamin D stores and activity [33,37], was associated with a 30% (95% CI: 6%–61%) greater risk of incident HF.

Consistent with these observations, a recent study [38] prospectively followed up, for a mean of 13 years, 3731 men aged 60–79 years with no prevalent HF or primary hyperpathyroidism and with measured Vitamin D and PTH concentrations. In this study, elevated PTH levels (>55.6 pg/ml) were significantly associated with higher risk of developing HF after adjustment for lifestyle characteristics and comorbidities (HR 1.66; 95% CI: 1.30–2.1;

Table 2 Low Vitamin D and risk of heart failure (Observational longitudinal studies).

Author	Study design	Publication year	Patients enrolled (n)	Inclusion criteria	Mean age	Outcomes	Follow-up	Results
Pilz S [36]	Prospective cohort	2008	3299	Patient referred to coronary angiography	63	Association of 25(OH) with HF measures. Hazard Ratio for death due to HF and SCD according to Vitamin D status.	7.7 years	2.84 HR (95% CI 1.20−6.74) for HF death in patients with hypovitaminosis D. 5.05 HR (95% CI 2.13−11.97) for SCD
Kestenbaum B [30]	Prospective cohort	2011	2312	Healthy subjects aged ≥65 years.	75	Association of 25(OH)D and PTH concentration, separately and in combination, with incident CV events and mortality	14 years	29% greater (95% CI: 5%−55% greater) risk of all-cause mortality in patients with 25(OH)D < 15 ng/ml. 30% (95% CI: 6%−61%) greater risk of incident HF in patients with PTH ≥65 pg/ml.
Wannamethee SG [38]	Prospective cohort	2014	3713	General population aged 60−79 years with and without established CV disease.	68	Association of PTH, 25(OH)D and markers of mineral metabolism with risk of incident HF	13 years	1.66 HR (95% CI: 1.30−2.1) for new HF development in patients with PTH >55.6 pg/ml No association of 25(OH)D or mineral metabolism (calcium or phosphate) with HF risk (HR 1.07; 95% CI: 0.67−1.71)
Bansal N [39]	Prospective cohort	2014	6469	Racial and ethnically different population free of prevalent clinical CV disease.	62	Associations of serum PTH and 25(OH)d with incident HF and LV mass	8.46 years	50% (95% CI: 3%−20%) greater risk of incident HF in patient with PTH > 65 pg/ml No association between 25(OH)D and HF

Abbreviations: CV: cardiovascular; HF: Heart failure; LV: left ventricular; PTH: parathyroid hormone; SCD: sudden cardiac death; 1,25(OH)2D: 1,25-dihydroxivitamin D; 25(OH)D: 25-hydroxyvitamin D.

$p < 0.0001$). Instead, no association was documented between 25(OH)D or mineral metabolism (calcium or phosphate) and HF risk (HR 1.07; 95% CI: 0.67–1.71). Finally, a recent large prospective study [39], including racial and ethnically different populations, also confirmed a significantly increased risk of HF in patient with increased PTH levels (>65 pg/ml) (95% CI: 3%–20%), whereas no association between 25(OH)D and HF was observed in a multivariable model.

The inconsistency in evidence linking Vitamin D deficiency and PTH to HF development might be explained considering that elevated PTH levels usually identify patients with low Vitamin D levels, confounding the relationship between these conditions and HF. In fact, progressive renal function decrease, physical inactivity as well as reduced calcium absorption are either causes or consequences of hypovitaminosis D that are associated with increased PTH levels [40].

In summary, in patients with no evidence of HF, reduced levels of Vitamin D or elevated levels of PTH are independently associated with an increased risk of developing HF.

Impact of vitamin D deficiency on prognosis in HF patients

Several studies (Table 3) have assessed whether, in patients with HF, Vitamin D deficiency is associated with worst prognosis.

In the study of Liu et al. [41] in 548 patients with HF, followed up for 18 months, lower Vitamin D levels were associated with higher HF hospitalization and all-cause mortality, and the combined endpoint of all-cause mortality and HF rehospitalisation increased significantly across decreasing 25(OH)D tertiles. After adjustment in a multivariable Cox regression analysis, low 25(OH)D concentration remained independently associated with increased risk of the combined endpoint (HR 1.09 per 10 nmol/L decrease; 95% CI: 1.00–1.16; $p = 0.040$) and all-cause mortality (HR 1.10 per 10 nmol/L decrease; 95% CI: 1.00–1.22; $p = 0.049$). Gotsman et al. [42] selected adult members from a Health Maintenance Organization with available measurements of Vitamin D and showed that 1,25(OH)2D median levels in HF were lower than in non HF subjects (36.9 nmol/L versus 40.7 nmol/L; $p < 0.00001$) and, at Cox regression analysis, Vitamin D deficiency was a significant independent predictor of mortality in HF patients.

Since calcitriol and PTH are physiologically interrelated, Gruson et al. [43] prospectively analysed the relation between 1,25(OH)2D levels and 1,25(OH)2D to PTH ratio and CV events, including CV mortality and cardiac transplantation in 170 chronic HF patients during a mean follow-up of 4.1 years. In this study, median serum levels of 1,25(OH)2D inversely correlated to HF severity, and the combined endpoint of CV death and cardiac transplantation, occurring in 106 of 170 patients (62%), was independently predicted by 1,25(OH)2D and 1,25(OH)2D to PTH ratio in the Cox proportional hazard modelling.

Table 3 Impact of Vitamin D deficiency on prognosis in heart failure patients.

Author	Study design	Publication year	Patients enrolled (n)	Inclusion criteria	Outcome	Follow-up duration	Results
Liu LC [41]	Prospective	2011	548	Chronic HF; NYHA class II–IV	1°: composite of all-cause mortality + HF rehospitalization. 2°: all-cause of mortality and HF re-hospitalization.	18 month	1.09 HR (95% CI 1.00–1.16) for the primary outcome per 10 nmol/L decrease of 25(OH)D levels. 1.10 HR (95% CI 1.00–1.22) for all-cause mortality per 25(OH)D 10 nmol/L decrease, No association was observed with re-hospitalization due to worsening HF.
Gotsman I [42]		2012	49,834	Age ≥45 years Measured Vitamin D	Effects on mortality of Vitamin D levels and Vitamin D supplementation in HF patients	518 days	1.52 HR (95% CI 1.21–1.92) for mortality in patients with Vitamin D deficiency. 0.68 HR (95% CI 0.54–0.85) for mortality in patients in therapy with Vitamin D supplementation.
Gruson D [43]	Prospective	2015	170	Chronic HF; LVEF ≤35%	Cardiovascular death and heart transplantation	4.1 years	The endpoint occurring in 106 of 170 patients (62%) and was predicted by 1,25(OH)2D and 1,25(OH) 2D to PTH ratio in the Cox proportional hazard modelling.

Abbreviations: HF: Heart failure; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PTH: parathyroid hormone; 1,25(OH)2D: 1,25-dihydroxivitamin D; 25(OH)D: 25-hydroxyvitamin D.

Thus, there is convincing evidence that in patients with established HF low levels of Vitamin D are associated with poorer prognosis.

Vitamin D supplementation and incidence of HF (Primary prevention trials)

There are only 2 studies that investigated whether Vitamin D supplementation prevents new HF [44,45] (Table 4). The first one [44] evaluated whether Vitamin D plus calcium (CaD) supplementation was associated with lower incidence of HF in post-menopausal women enrolled in the Women's Health Initiative without HF. In this study 35,983 post-menopausal women were randomized to receive 1000 mg/day of calcium plus 400 IU/day of Vitamin D_3 or placebo and were followed up for 7.1 years. CaD supplementation was not associated with reduced HF risk compared to placebo in the overall population (HR 0.95, 95% CI 0.82−1.09; p = 0.46). However, stratifying patients by baseline risk of HF, CaD supplementation was associated with a statistically significant 37% lower risk of HF (HR 0.63, CI 95% 0.46 to 0.87; p = 0.005) in the low-risk subgroup.

The second study [45] randomized 5108 adult subjects from a general population to placebo or high monthly dose of Vitamin D supplementation and studied the cumulative incidence of CVDs for a median follow-up of 3.3 years. Baseline 25(OH)D concentration was 25.3 ng/ml and was similar between Vitamin D and placebo groups. The primary outcome of CVD and death occurred in 11.8% in Vitamin D group and 11.5% in the placebo group (HR 1.02 95% CI, 0.87−1.20; p = 0.81) and no significant differences in any of the secondary CV outcomes, including HF, were observed. However, this study reported only the effects of a monthly administration of Vitamin D that might be different from daily or weekly dose administration.

Thus, only scant and not definitive data are available on the prevention of HF in patients with Vitamin D deficiency, yet these limited data support the need for more tailored studies in patients with Vitamin D deficiency at different risk of developing HF.

Vitamin D supplementation and prognosis of HF (Secondary prevention trial)

It remains unclear whether Vitamin D supplementation favourably impacts on CV mortality and morbidity in HF patients, since only one randomized controlled trials on hard clinical endpoints is available (Table 5, Table 1s in supplementary material). Currently, 2 non-randomized [42,46] and 9 randomized (Table 6) [47−53,55,56] studies on surrogate endpoints have been reported.

Non-randomized studies

Gotsman et al. [42] followed up for 518 days 3009 HF patients and 46,825 control subjects. The percentage of patients with Vitamin D deficiency (25(OH)D < 25 ng/ml) was higher in HF patients compared to controls (28% vs 22%, p < 0.00001), and treatment with Vitamin D supplements was independently associated with reduced mortality in patients with Vitamin D deficiency (HR 0.68; 95% CI 0.52−0.85; p < 0.0001). Amin et al. [46] in a prospective study of 100 patients with HF and NYHA class I through III, with insufficient or deficient 25(OH)D serum levels (<30 ng/ml and <20 ng/ml, respectively), reported a significant reduction of BNP levels after 4 months of Vitamin D supplementation, together with improvement in NYHA class and 6-min walking distance (6MWD).

Randomized studies

In a study enrolling 123 patients with HF randomized to Vitamin D supplementation or placebo, followed up for 15 months, Schleithoff et al. [47] reported that Vitamin D reduced the levels of inflammatory cytokines including tumour necrosis factor-α (TNF-α) and interleukin-10 (IL-10). Yet, no changes were observed between treatment arms on functional parameters or survival. In this study, however, evidence of baseline Vitamin D deficiency was not a criterion for enrolment. In a randomized study enrolling 105 patients with HF and Vitamin D deficiency followed up for 20 weeks, Witham et al. [48] did not observe significant differences in the primary endpoint of 6MWD and quality of life, despite a significant decrease of

Table 4 Vitamin D supplementation and incidence of HF (primary prevention trials).

Author	Publication year	Study design	Patients enrolled (n)	Inclusion criteria	Outcomes	Follow-up	Vitamin D levels for enrolment	Dose	Results
Donneyong MM [44]	2015	Randomized, double-blind, placebo-controlled	35 983	Post-menopausal women with cardiovascular risk and without HF	HF cases	7.1 years	Not required	400 IU Vitamin D+400 calcium daily	No difference between groups.
Scragg R [45]	2017	Randomize, double-blind, placebo-controlled	47,905	General population	Number of participants with incident CVD and death	3.3 years	Not required	100,000 IU monthly	No difference between treatment and placebo group in CV events occurrence (303 vs 293)

Abbreviations: CV: cardiovascular; CVD: cardiovascular disease; HF: heart failure.

Table 5 Vitamin D studies in heart failure patients with available results.

ClinicalTrials.gov identifier	Study status	Study design	Aim of the study	Inclusion criteria	Primary endpoint/outcome	Secondary endpoint/ outcome	Results
NCT01326650 (EVITA)	Completed	Randomized, double blind	Investigate whether Vitamin D supplementation reduces mortality and increases event-free survival in end-stage CHF patients	Age 18 to 80 yrs; NYHA class $\geq$ II.	All-cause of mortality.	Hospitalization, resuscitation, MCS implant, high urgent listing for heart transplantation and hypercalcaemia	Vitamin D supplementation not reduce mortality, but increase MCS implants
NCT01092130 (VitD CHF trial)	Completed	Randomized, open label	Investigate the effect of the administration of Vitamin D in patients with CHF	Age $\geq$18 yrs; NYHA class II–IV; Treatment with ACE-I or ARB and BB therapy for at least 4 weeks.	PRA after 6 weeks of treatment.	Safety endpoints, the effect of Vitamin D administration on additional marker of renin-angiotensin system activity, Vitamin D cascade, NT-proBNP, kidney function, extracellular matrix markers	Significant decrease in PRA and plasma renin concentration in treated group. No significant changes in serum concentration of natriuretic peptide, fibrosis markers (exception galectina-3), PTH, PRC and kidney function between the two groups
NCT01230307	Completed	Randomized, double blind	Investigate how rapid Vitamin D supplementation affects biomarkers and submaximal exercise capacity in systolic HF patients with low Vitamin D status	LVEF <40%; 25(OH)D = 10–25 ng/ml; Optimized medical therapy.	How rapid vitamin D supplementation affects biomarkers (CRP, IL-6, TNF-a, PPT I, PP III, MMP-2, MM-9, TIMP-1.	Exercise capacity (6-MWT); Quality of life measured by KCCQ; Vitamin D genomics.	Outcomes were not analysed because enrolment was less than 30% of original goal
NCT01619891 (VINDICATE Study)	Completed	Randomized, double blind	Detect whether Vitamin D has pathophysiologically important effects	CHF; LVEF $\leq$45%; NYHA class II–III; 25(OH)D < 20 ng/ml.	6-MWD.	Changes of LV cardiac function by cardiac magnetic resonance; Peak exercise capacity; Biochemical changes.	No changes in Δ6MWD. Significant variation in cardiac function (LVEF) and reduction in LVEDD, LVESD, LVEDV and LVEDD
NCT01005303	Completed	Randomized, double blind	Investigate if supplementation with micronutrients (including high-dose Vitamin D) will improve the function of the heart in patients with HF	NYHA class II–III; ACE-I and BB therapy; Stable at least 6 month; LVEF $\leq$45%.	LVEF	Cardiac volume; Levels of inflammation; Levels of oxidative stress Biomarker of cardiac function; Quality of life; Physical function.	There was no significant difference in mean LVEF and in any of the secondary endpoints

Abbreviations: CHF: chronic heart failure; CPX: cardiopulmonary exercise test; CRP: C-reactive protein; IL-6: interleukin-6; CV: cardiovascular; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume; MCS: mechanical circulatory support; MI: myocardial infarction; MMP-2: matrix metalloproteinase 2; NYHA: New York Heart Association; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PPT I: propeptide procollagen type I; PP III: plasma procollagen III; PRA: plasma renin activity; TIMP-1: tissue inhibitor of matrix metalloproteinases-1 TNF-a: tumour necrosis factor-a; 6-MWD 6-min walking test; 6-MWD: 6 min walking distance.

Table 6 Randomized study of Vitamin D therapy in heart failure patients.

Author	Year	Study design	Inclusion criteria	Vitamin D/Control patients (n)	Vitamin D Dose	Follow-up Duration	Primary Endpoints	Secondary endpoint	Results
Schleithoff SS [47]	2006	Randomized, double-blind, placebo-controlled	CHF; HYHA class ≥II	61/62	2000 IU/d	9 months 15 months (for survival rate)	Survival rates and biochemical variables	LVEF LVEDD VO_2max Blood Pressure	Significant reduction in serum concentration of TNF-α (−2.0 vs 2.7 pg/ml; p = 0.006) and IL-10 (0.24 vs −0.20 pg/ml; p = 0.042). No significant variation for other parameters.
Witham MD [48]	2010	Randomized, double-blind, placebo-controlled	Age ≥70 y; CHF; NYHA class II–III; LV systolic dysfunction; 25(OH)D < 20 ng/ml.	53/52	100,000 IU at baseline and 10 wk	20 weeks	6MWD	TGUG, daily physical activity levels, quality of life and cardiovascular and inflammatory markers	Significant decrease in BNP level in treatment group in confront of placebo (−22 vs + 78 pg/ml; p = 0.04). No significant variation for other parameters.
Shedeed SA [49]	2012	Randomized, double-blind, placebo-controlled	Infants with CHF; LVEF <40%	42/38	1000 IU/d	12 weeks	Renin-angiotensin system cytokines, clinical, biochemical and echocardiographic parameters		Significant improvement in HF score, LVEDD, LVESD, LVEF, serum IL-10 and a decrease in PTH, IL-6 and TNF-α in Vit D group compared with control group.
Boxer RS [50]	2013	Randomized, double-blind, placebo-controlled	Age ≥50 y; NYHA class II–III; 25(OH)D ≤ 37.5 ng/ml	31/33	50,000 IU/wk	6 months	Peak VO_2	TGUG 6MWD isokinetic muscle testing	No effect
Boxer RS [51]	2014	Randomized, double-blind, placebo-controlled	Age ≥50 y; NYHA class II–III; 25(OH)D ≤ 37.5 ng/ml	31/33	50 000 IU/wk	6 months	Effect on Hormone and Biomarker	Echocardiographic parameters, health status	Significant decrease of serum aldosterone in Vit D group (37% vs 14%; p = 0.02). No significant variation for other parameters.
Schroten NF (VitD-CHF trial) [52]	2013	Randomized, open-label	Age ≥18 y; CHF; LVEF <45%	50/51	2000 IU/d	6 weeks	Plasma renin activity	NT-proBNP, fibrosis markers, PTH, PRC, kidney function	Significant decrease in PRA and plasma renin concentration in treated group. No significant variation for other parameters.

(*continued on next page*)

Table 6 (*continued*)

Author	Year	Study design	Inclusion criteria	Vitamin D/Control patients (n)	Vitamin D Dose	Follow-up Duration	Primary Endpoints	Secondary endpoint	Results
Dalbeni A [53]	2014	Randomized, double-blind, placebo-controlled	Age >40y; CHF; LVEF <55%; NYHA class > II; 25(OH)D < 30 ng/ml	18/18	4000 IU/d	6 months	LVEF	echocardiographic and laboratory parameters	Significant increase in LVEF in Vit D group (6.71% vs −4.3%; $p < 0.001$). Significant increase in PIP serum concentration in control group than placebo (1140. 9 vs −145 mcg/L; $p < 0.05$). No significant variation for other parameters.
Witte KK (VINDICATE Study) [55]	2016	Randomized, double-blind, placebo-controlled	CHF; LVEF ≤45%; NYHA class II–III; 25(OH)D < 20 ng/ml	80/83	4000 IU/d	12 months	6MWD	Change in structure and cardiac function	No changes in Δ6MWD. Significant variation in treated group than placebo in: LVEF (+7.65 vs + 1.36%; $p < 0.0001$) LVEDD (−2.45 vs 0.08 mm; $p = 0.002$), LVESD (−2.72 vs −0.99 mm; $p = 0.043$), LVEDV (−16.47 vs −3.83 ml) and LVESD (−18.77 vs −8.49 ml)
Zitterman A (EVITA) [56]	2017	Randomized, placebo-controlled	Adult patient (18-79ys); NYHA class ≥II; 25(OH) < 75 nmol/L.	201/199	4000 IU/d	3 years	All-cause of mortality	Hospitalization, resuscitation, MCS implantation	Increase MCS implantation in patient that received Vitamin d supplementation (15.4% vs 9%, with HR of 1.96, 95% CI 1.04–3.66; $p = 0.031$). No significant variation for other parameters.

Abbreviations: BNP: B-type natriuretic peptide; CHF: chronic heart failure; CRP: C-reactive protein; IL: interleukin; IU: international units; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume; MCS: mechanical circulatory support; NYHA: New York Heart Association; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PIP: carboxyterminal propeptide of procollagen type I; PTH: parathyroid hormone; 6MWD: 6-min walk distance; TGUG: Timed get Up and Go; TNF-α: tumour necrosis factor-α; Vit D: vitamin D; VO2: oxygen volume; 25(OH)D: 25(OH) vitamin.

natriuretic peptides. However, this study enrolled only elderly (≥70 years) patients for a relatively short follow-up. In contrast, Shedeed et al. [49], in a randomized study in 80 paediatric patients with HF and LVEF <40% randomized to Vitamin D or placebo and followed up for 12 weeks, reported a significant improvement of functional LV parameters (reduced LV volumes and increased EF) together with improved inflammatory profile (reduced IL-6 and TNF alfa-α). In a randomized study involving 64 patients with HF, Boxer et al. [50] did not observe significant differences in the primary outcome of peak oxygen consumption after 6 months of treatment. In this study, however, patients were enrolled independently of LVEF (mean 39 ± 13% in treated patients) and Vitamin D basal levels, that might represent a limitation. The same Author [51] subsequently investigated the effects of Vitamin D supplementation on RAAS activation and functional parameters in a randomized study of 64 patients with HF and Vitamin D deficiency followed up for 6 months. In this study, Vitamin D supplementation significantly reduced aldosterone levels but did not impact LV function or health status. Consistent with the previous study, also Schroten et al. [52], in the VitD-CHF trial, that enrolled 101 patients with HF and EF <45% followed up for 6 weeks in an open label randomized study, observed a significant reduction of renin activity (representing the primary endpoint of the study) in Vitamin D treated patients. However, no changes of natriuretic peptides or functional parameters were reported. In a small study in 36 patients with HF with reduced vitamin D levels (<30 ng/ml) and LVEF <55%, followed up for 6 months, Dalbeni et al. [53] reported a significant increase of LVEF in vitamin D treated patients (6.7% vs −4.3%, $p < 0.001$). A meta-analysis of these 7 randomized studies [54] reported that vitamin D supplementation in HF patients was associated with a significant decrease of TNF-α, C-reactive protein and PTH, but with no significant changes of LVEF, NT pro-BNP and 6MWD. However, as it appears from the description of the 7 included studies, large heterogeneity was present in this analysis, due to large variability in the age of populations, enrolling criteria for Vitamin D and LVEF at baseline, as well as outcome definition and study duration.

More recently the VINDICATE (VitamIN D treatIng patients with Chronic heArT failurE) placebo-controlled randomized trial [55] investigated the effects Vitamin D supplementation on 6MWD (primary endpoint) in 163 patients with systolic HF and low vitamin D levels (25(OH)D < 20 ng/ml), followed up for 1 year. Vitamin D supplementation did not significantly improve 6MWD in HF patients, although the study resulted underpowered to detect a significant difference. However, Vitamin D supplementation was associated with a significant improvement of LVEF (+6.07%, 95% CI: 3.20−8.95; $p < 0.0001$) and of LV end diastolic diameter (−2.49 mm, 95% CI: −4.09 to −0.90; $p = 0.002$) and end systolic diameter (−2.09 mm, 95% CI: −4.11 to −0.06; $p = 0.043$). Thus, although the study did not meet its primary endpoint, the favourable effects on LV remodelling, i.e. on parameters that are associated with clinical outcomes in HF patients, are hypothesis-generating for future clinical studies.

Finally, the EVITA trial (Effect of Vitamin D on all-cause mortality in heart failure) [56], randomized 400 HF patients with 25(OH)D levels <30 ng/ml to receive 4000 IU Vitamin D daily or placebo for 3 years, with primary endpoint of all-cause mortality and secondary endpoint of hospitalization, resuscitation and mechanical circulatory support (MCS) implantation. Although mortality did not significantly differ in treated and placebo group (19.6% vs 17.9% with HR of 1.09, 95% CI 0.68−1.71; $p = 0.726$), there was a significant greater need for MCS implantation in treated patients compared to placebo (15.4% vs 9%, HR 1.96, 95% CI 1.04−3.66; $p = 0.031$).

In summary, there is no definitive evidence supporting a favourable role of Vitamin D supplementation in patients with HF. Yet, completed and published studies so far, appear inadequately powered to provide a clear understanding of the benefit, neutrality or even potential harm of Vitamin D supplementation in HF.

Conclusions

Although an epidemiological association between Vitamin D deficiency and risk of CV events, including HF, is demonstrated pathophysiological mechanisms are still not fully understood. Interventional studies reported inconsistent results on the clinical effects of Vitamin D supplementation in patients with or at risk of HF, and, therefore, additional evidence from ongoing randomized studies is needed to assess whether add-on supplementation therapy with Vitamin D has a role in the prevention and/or management of HF.

Acknowledgements

Dr Fabio Marsico has been supported by a research grant provided by The Cardiovascular Pathophysiology and Therapeutics PhD Program.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2017.07.009.

References

[1] Jessup M, Brozena S. Heart failure. N Engl J Med 2003 May 15; 348:2007−18.
[2] Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure the Rotterdam Study. Eur Heart J 2004;25: 1614−9.
[3] Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347:1397−402.
[4] Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality

in patients with chronic heart failure. Circulation 2000;102:3060–7.
[5] Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, et al., Intermountain Heart Collaborative (IHC) Study Group. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol 2010;106:963–8.
[6] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
[7] Jean G, Terrat JC, Vanel T, Hurot JM, Lorriaux C, Mayor B, et al. Evidence for persistent vitamin D 1-alpha-hydroxylation in hemodialysis patients: evolution of serum 1,25-dihydroxycholecalciferol after 6 months of 25-hydroxycholecalciferol treatment. Nephron Clin Pract 2008;110:c58–65.
[8] Souberbielle JC, Body JJ, Lappe JM, Plebani M, Shoenfeld Y, Wang TJ, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice. Autoimmun Rev 2010;9:709–15.
[9] Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr 2008;88:491S–9S.
[10] Haussler MR, Jurutka PW, Mizwicki M, Norman AW. Vitamin D receptor (VDR)-mediated actions of 1α,25(OH)$_2$ vitamin D$_3$: genomic and non-genomic mechanisms. Best Pract Res Clin Endocrinol Metab 2011;25:543–59.
[11] Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96:53–8.
[12] Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002;110:229–38.
[13] Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C, Boehm BO, et al. Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system: the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study. Clin Chim Acta 2010;411:1354–60.
[14] Forman JP, Williams JS, Fisher ND. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. Hypertension 2010;55:1283–8.
[15] Camici M, Galetta F, Franzoni F, Carpi A, Zangeneh F. Vitamin D and heart. Intern Emerg Med 2013;8:S5–9.
[16] Weber KT, Weglicki WB, Simpson RU. Macro- and micronutrient dyshomeostasis in the adverse structural remodelling of myocardium. Cardiovasc Res 2009;81:500–8.
[17] Agarwal M, Phan A, Willix Jr R, Barber M, Schwarz ER. Is vitamin D deficiency associated with heart failure? A review of current evidence. J Cardiovasc Pharmacol Ther 2011;16:354–63.
[18] Demer LL, Tintut Y. Vascular calcification: pathobiology of a multifaceted disease. Circulation 2008;117:2938–48.
[19] Hruska KA, Mathew S, Saab G. Bone morphogenetic proteins in vascular calcification. Circ Res 2005;97:105–14.
[20] Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, et al. Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation 1997;96:1755–60.
[21] Molinari C, Uberti F, Grossini E, Vacca G, Carda S, Invernizzi M, et al. 1α,25-dihydroxycholecalciferol induces nitric oxide production in cultured endothelial cells. Cell Physiol Biochem 2011;27:661–8.
[22] Cardus A, Panizo S, Encinas M, Dolcet X, Gallego C, Aldea M, et al. 1,25-dihydroxyvitamin D3 regulates VEGF production through a vitamin D response element in the VEGF promoter. Atherosclerosis 2009;204:85–9.
[23] Grundmann M, Haidar M, Placzko S, Niendorf R, Darashchonak N, Hubel CA, et al. Vitamin D improves the angiogenic properties of endothelial progenitor cells. Am J Physiol Cell Physiol 2012;303:C954–62.
[24] Stach K, Kälsch AI, Nguyen XD, Elmas E, Kralev S, Lang S, et al. Kälsch T.1α,25-dihydroxyvitamin D3 attenuates platelet activation and the expression of VCAM-1 and MT1-MMP in human endothelial cells. Cardiology 2011;118:107–15.
[25] Simpson RU, Hershey SH, Nibbelink KA. Characterization of heart size and blood pressure in the vitamin D receptor knockout mouse. J Steroid Biochem Mol Biol 2007;103:521–4.
[26] Green JJ, Robinson DA, Wilson GE, Simpson RU, Westfall MV. Calcitriol modulation of cardiac contractile performance via protein kinase C. J Mol Cell Cardiol 2006;41:350–9.
[27] Zitterman A, Ernst JB. Calciotropic and phosphaturic hormones in heart failure. Nutr Metab Cardiovasc Dis 2016;26:971–9.
[28] Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular disease (from the National Health and Nutrition Examinantion Survey 2001 to 2004). Am J Cardiol 2008;102:1540–4.
[29] DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 2004;80:1689S–96S.
[30] Kestenbaum B, Katz R, de Boer I, Hoofnagle A, Sarnak MJ, Shlipak MG, et al. Vitamin D, parathyroid hormone, and cardiovascular events among older adults. J Am Coll Cardiol 2011;58:1433–41.
[31] Saleh FN, Schirmer H, Sundsfjord J, Jorde R. Parathyroid hormone and left ventricular hypertrophy. Eur Heart J 2003;24:2054–60.
[32] Guillot X, Semerano L, Saidenberg-Kermanac'h N, Falgarone G, Boissier MC. Vitamin D and inflammation. Jt Bone Spine 2010;77:552–7.
[33] Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006;81:353–73.
[34] Shane E, Mancini D, Aaronson K, Silverberg SJ, Seibel MJ, Addesso V, et al. Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. Am J Med 1997;103:197–207.
[35] Zitterman A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? J Am Coll Cardiol 2003;41:105–12.
[36] Pilz S, März W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J Clin Endocrinol Metab 2008;93:3927–35.
[37] Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int 2005;16:713–6.
[38] Wannamethee SG, Welsh P, Papacosta O, Lennon L, Whincup PH, Sattar N. Elevated parathyroid hormone, but not vitamin D deficiency, is associated with increased risk of heart failure in older men with and without cardiovascular disease. Circ Heart Fail 2014;7:732–9.
[39] Bansal N, Zelnick L, Robinson-Cohen C, Hoofnagle AN, Ix JH, Lima JA, et al. Serum parathyroid hormone and 25-hydroxyvitamin D concentration and risk of incident heart failure: th Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc 2014;3:e001278.
[40] Chhokar VS, Sun Y, Bhattacharya SK, Ahokas RA, Myers LK, Xing Z, et al. Hyperparathyroidism and the calcium paradox of aldosteronism. Circulation 2005;111:871–8.
[41] Liu LC, Voors AA, van Veldhuisen DJ, van der Veer E, Belonje AM, Szymanski MK, et al. Vitamin D status and outcomes in heart failure patients. Eur J Heart Fail 2011;13:619–25.
[42] Gotsman I, Shauer A, Zwas DR, Hellman Y, Keren A, Lotan C, et al. Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome. Eur J Heart Fail 2012;14:357–66.
[43] Gruson D, Ferracin B, Ahn SA, Zierold C, Blocki F, Hawkins DM, et al. 1,25-Dihydroxyvitamin D to PTH(1-84) ratios strongly predict cardiovascular death in heart failure. PLoS One 2015;10:e0135427.
[44] Donneyong MM, Hornung CA, Taylor KC, Baumgartner RN, Myers JA, Eaton CB, et al. Risk of heart failure among postmenopausal women: a secondary analysis of the randomized trial of vitamin D plus calcium of the women's health initiative. Circ Heart Fail 2015;8:49–56.
[45] Scragg R, Stewart AW, Waayer D, Lawes CM, Toop L, Sluyter J, et al. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the vitamin D assessment study: a randomized clinical trial. JAMA Cardiol 2017 Apr 5. http://dx.doi.org/10.1001/jamacardio.2017.0175 [Epub ahead of print].
[46] Amin A, Minaee S, Chitsazan M, Naderi N, Taghavi S, Ardeshiri M. Can vitamin D supplementation improve the severity of congestive heart failure? Congest Heart Fail 2013;19:E22–8.
[47] Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind,

randomized, placebo-controlled trial. Am J Clin Nutr 2006;83:754–9.
[48] Witham MD, Crighton LJ, Gillespie ND, Struthers AD, McMurdo ME. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. Circ Heart Fail 2010;3:195–201.
[49] Shedeed SA. Vitamin D supplementation in infants with chronic congestive heart failure. Pediatr Cardiol 2012;33:713–9.
[50] Boxer RS, Kenny AM, Schmotzer BJ, Vest M, Fiutem JJ, Piña IL. A randomized controlled trial of high dose vitamin D3 in patients with heart failure. JACC Heart Fail 2013;1:84–90.
[51] Boxer RS, Hoit BD, Schmotzer BJ, Stefano GT, Gomes A, Negrea L. The effect of vitamin d on aldosterone and health status in patients with heart failure. J Card Fail 2014;20:334–42.
[52] Schroten NF, Ruifrok WP, Kleijn L, Dokter MM, Silljé HH, Lambers Heerspink HJ, et al. 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). Am Heart J 2013;166:357–64.
[53] Dalbeni A, Scaturro G, Degan M, Minuz P, Delva P. Effects of six months of vitamin D supplementation in patients with heart failure: a randomized double-blind controlled trial. Nutr Metab Cardiovasc Dis 2014;24:861–8.
[54] Jiang WL, Gu HB, Zhang YF, Xia QQ, Qi J, Chen JC. Vitamin D supplementation in the treatment of chronic heart failure: a meta-analysis of randomized controlled trials. Clin Cardiol 2016;39:56–61.
[55] Witte KK, Byrom R, Gierula J, Paton MF, Jamil HA, Lowry JE, et al. Effects of vitamin D on cardiac function in patients with chronic HF: the Vindicate study. J Am Coll Cardiol 2016;67:2593–603.
[56] Zittermann A, Ernst JB, Prokop S, Fuchs U, Dreier J, Kuhn J, et al. Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4000 IU vitamin D daily. Eur Heart J 2017 May 12. http://dx.doi.org/10.1093/eurheartj/ehx235 [Epub ahead of print].