Vitamin D Deficiency is a Predictor of Reduced Survival in Patients With Heart Failure

Vitamin D Supplementation Improves Outcome

Israel Gotsman; Ayelet Shauer; Donna R. Zwas; Yaron Hellman; Andre Keren; Chaim Lotan; Dan Admon

Posted: 04/27/2012; Eur J Heart Fail. 2012;14(4):357-366.

Abstract and Introduction

Abstract

Aims Vitamin D deficiency is a highly prevalent, global phenomenon. The prevalence in heart failure (HF) patients and its effect on outcome are less clear. We evaluated vitamin D levels and vitamin D supplementation in patients with HF and its effect on mortality.

Methods and results 25-Hydroxyvitamin D [25(OH)D] levels were evaluated in HF patients from a health maintenance organization (HMO), and compared them with those of the rest of the members of the HMO. Patients with HF (n = 3009) had a lower median 25(OH)D level compared with the control group (n = 46 825): 36.9 nmol/L (interquartile range 23.2–55.9) vs. 40.7 nmol/L (26.7–56.9), respectively, $P < 0.00001$. The percentage of patients with vitamin D deficiency [25(OH)D <25 nmol/L] was higher in patients with HF compared with the control group (28% vs. 22%, $P < 0.00001$). Only 8.8% of the HF patients had optimal 25(OH)D levels (≥75 nmol/L). Median clinical follow-up was 518 days. Cox regression analysis demonstrated that vitamin D deficiency was an independent predictor of increased mortality in patients with HF [hazard ratio (HR) 1.52, 95% confidence interval (CI) 1.21–1.92, $P < 0.001$] and in the control group (HR 1.91, 95% CI 1.48–2.46, $P < 0.00001$). Vitamin D supplementation was independently associated with reduced mortality in HF patients (HR 0.68, 95% CI 0.54–0.85, $P < 0.0001$). Parameters associated with vitamin D deficiency in HF patients were decreased previous solar radiation exposure, body mass index, diabetes, female gender, pulse, and decreased calcium and haemoglobin levels.

Conclusions Vitamin D deficiency is highly prevalent in HF patients and is a significant predictor of reduced survival. Vitamin D supplementation was associated with improved outcome.

Introduction

Heart failure (HF) is a major epidemic and a significant public health burden, and is associated with considerable morbidity and mortality.[1] Numerous factors affect progression and outcome in patients with HF. Vitamin D is emerging as an important factor in the development of cardiovascular diseases,[2–6] and vitamin D deficiency is associated with multiple cardiovascular disease risk factors, including hypertension, diabetes, and obesity.[7, 8] Vitamin D has been shown to be related to cardiovascular death[9] and all-cause mortality in the general population.[10] Severe vitamin D deficiency was shown to be related to an increased incidence of myocardial dysfunction and death due to HF as well as sudden cardiac death in a large population of patients referred for routine angiography.[11]

Vitamin D deficiency is a highly prevalent, global phenomenon.[12–16] The incidence of vitamin D deficiency appears to be on the rise and is related in part to reduced sun exposure due to increased indoor lifestyles and efforts to minimize sun exposure. The global epidemic of obesity is also associated with vitamin D deficiency due to its sequestration in adipose tissue.[17] Israel is a Mediterranean country with high solar radiation during most days of the year. Despite this, there is a high prevalence of vitamin D deficiency in Israel.[18] Limited data exist regarding vitamin D levels in HF patients[19–21] and its association with functional parameters and clinical outcome.[11,20–22]

The purpose of the present study was to evaluate and compare vitamin D levels in patients with and without HF in a large cohort of members belonging to a health maintenance organization (HMO) in Israel. In addition, we evaluated the impact of vitamin D deficiency and vitamin D supplementation on survival in these patients.

Methods

Participants and Study Design

All data associated with members of the largest HMO (Clalit health services) in Jerusalem, Israel are digitally recorded in a

central computerized database. The database includes demographics, comprehensive clinical data, diagnoses, and all laboratory data undertaken in a single centralized laboratory of the HMO. We identified and retrieved electronically from the computerized database all members, 45 years of age or older, with available measurements of vitamin D during the period between January 2006 and June 2010. Clinical data were retrieved and analysed. A total of 49 834 HMO members underwent 25-hydroxyvitamin D [25(OH)D] measurement from a total membership of ~122 700 in this age group (40.6%). These individuals comprised the cohort of this study. Members of the cohort with a diagnosis of HF as coded by the database (3009 patients) were identified and compared with the rest of the members in the HMO. The HF patients in the cohort comprised 45.5% of all patients diagnosed with HF in the HMO (6618 patients). Validation of the diagnosis of HF was performed on a randomly computer-generated 5% of the diagnosed HF patients (*n* = 338). Clinical parameters in this group of patients were statistically comparable with those of the whole HF cohort. We reviewed all available data from medical records and hospital admissions. In this group, 99% fulfilled the European Society of Cardiology (ESC) criteria for the diagnosis of HF.[23] Only 1% (*n* = 4) had equivocal clinical data for HF diagnosis. Retrieval of data regarding prescribed medications was performed only in patients with HF. Data on prescribed vitamin D supplementation during follow-up were retrieved from the database. The mean monthly global daily solar radiation (MJ/m^2) was obtained from the local meteorological service. Data on mortality were retrieved from the National Census Bureau and included mortality up to January 2011. The Institutional Committee for Human Studies of Clalit Health Services approved the study protocol.

Vitamin D Levels

Serum levels of 25(OH)D were measured using a radioimmunoassay kit (DiaSorin, Stillwater, MN, USA) in a single centralized laboratory of the HMO. The intra-assay and interassay coefficients of variation of this assay were 3.8% and 7.9%, respectively. We chose to analyse the first measurement of 25(OH)D done on each individual as this would best represent the baseline 25(OH)D status prior to any intervention that could artificially modify 25(OH)D levels. There is no consensus on a definite cut-off for vitamin D deficiency; however, 25(OH)D levels <25 nmol/L are considered by most clinicians as definite vitamin D deficiency.

Statistical Analyses

SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) was used in all analyses. Comparison of the clinical characteristics between HF patients and the control group, and groups of HF patients according to vitamin D levels, was performed using the Student *t*-test or Mann–Whitney U-test for continuous variables and the $\chi^{[2]}$ test for categorical variables. Multivariate binary logistic regression analysis models were used to identify independent predictors of vitamin D deficiency [serum 25(OH)D levels <25 nmol/L] in both groups. Clinical predictors were transformed where appropriate. Log_{10} was used for logarithmic transformations. Follow-up time was calculated using a Kaplan–Meier estimate of potential follow-up.[24] Kaplan–Meier curves, with the log-rank test, were used to compare survival according to 25(OH)D levels. Multivariate Cox proportional hazards regression analysis was used to evaluate independent variables that determined survival. Parameters included in the multivariate Cox regression analysis incorporated all significant clinical and laboratory parameters on univariate analysis as well as drug treatment. Parathyroid hormone was not included due to the limited number of patients (9%) with this measurement. Proportionality assumptions of the Cox regression models were evaluated by log–log survival curves and with the use of Schoenfeld residuals. Possible interactions were also assessed. A *P*-value of <0.05 was considered statistically significant.

Results

Clinical Parameters

We compared 25(OH)D serum levels of the patients with HF (*n* = 3009) with the levels of the rest of the cohort (*n* = 46 825), the control group for this study. Table 1 presents the demographics and clinical parameters of each group for comparison. Table 2 presents data according to vitamin D levels in each group. Table 3 presents drug therapy in patients with HF. The median 25(OH)D level in the whole cohort was 40.4 [interquartile range (IQR) 26.5–56.9], which is well below optimal 25(OH)D levels (≥75 nmol/L). Patients with HF (*n* = 3009) had a lower median 25(OH)D level compared with the control group (*n* = 46 825): 36.9 nmol/L (IQR 23.2–55.9) vs. 40.7 nmol/L (26.7–56.9), respectively, *P* < 0.00001. The prevalence of vitamin D deficiency [25(OH)D levels <25 nmol/L) was higher in patients with HF compared with the control group (28% vs. 22%, *P* < 0.00001) (*Figure 1*). Only 8.8% of the HF patients and 10.1% of the rest of the study cohort had optimal 25(OH)D levels (≥75 nmol/L) (*Figure 1*).

Table 1. Clinical characteristics of patients with heart failure vs. the control group

Clinical characteristics	HF group (*n* = 3009)	Control group (*n* = 46,825)	*P*-value
Age (years)	75.9 ± 10.7	64.7 ± 11.3	<0.00001
Gender (male)	1459 (49%)	16 270 (35%)	<0.00001
Diabetes mellitus	1506 (50%)	11 343 (24%)	<0.00001
Hypertension	2608 (87%)	22 158 (47%)	<0.00001
Hyperlipidaemia	2637 (88%)	30 893 (66%)	<0.00001
Ischaemic heart disease	2262 (75%)	7388 (16%)	<0.00001
Atrial fibrillation	536 (18%)	947 (2%)	<0.00001
Dementia	240 (8%)	1098 (2%)	<0.00001
Body mass index (kg/m^2)	29 (25–33)	28 (25–31)	<0.00001
Pulse (b.p.m.)	70 (63–79)	72 (66–80)	<0.00001
Systolic BP (mmHg)	127.5 ± 18.2	126.8 ± 15.3	0.03
Diastolic BP (mmHg)	70.1 ± 10.3	74.4 ± 9.1	<0.00001
Creatinine (mg/dL)	1.0 (0.8–1.4)	0.8 (0.7–0.9)	<0.00001
eGFR (mL/min/1.73 m^2)	60 (42–79)	83 (70–96)	<0.00001
Urea (mg/dL)	49 (37–71)	34 (28–41)	<0.00001
Haemoglobin (g/dL)	12.7 ± 1.7	13.6 ± 1.5	<0.00001
Albumin (g/dL)	4.0 (3.8–4.2)	4.2 (4.0–4.4)	<0.00001
Calcium (mg/dL)	9.2 ± 0.5	9.3 ± 0.4	<0.00001
Parathyroid hormone (pg/mL)	146 (86–265)	81 (54–124)	<0.00001
25-Hydroxyvitamin D (nmol/L)	36.9 (23.2–55.9)	40.7 (26.7–56.9)	<0.00001

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables, and counts (percentages) for categorical variables. *P*-value by the Student *t*-test or Mann-Whitney-U test for continuous variables and the χ^2 test for categorical variables.
BP, blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure.

Table 2. Demographics and clinical characteristics of the groups according to vitamin D (Vit D) levels

Clinical characteristics	HF group (*n* = 3009)			Control group (*n* = 46 825)		
	Vit D ≥25 nmol/L (*n* = 2166)	Vit D <25 nmol/L (*n* = 843)	*P*-value	Vit D ≥25 nmol/L (*n* = 36 496)	Vit D <25 nmol/L (*n* = 10 329)	*P*-value
Age (years)	76.1 ± 10.6	75.3 ± 11.0	0.06	65.1 ± 11.1	63.5 ± 11.9	<0.00001
Gender (male)	1123 (52%)	336 (40%)	<0.00001	13 582 (38%)	2688 (26%)	<0.00001
Diabetes mellitus	1004 (46%)	502 (60%)	<0.00001	8076 (22%)	3267 (32%)	<0.00001
Hypertension	1870 (86%)	738 (88%)	0.38	17 100 (47%)	5058 (49%)	0.0001
Hyperlipidaemia	1905 (88%)	732 (87%)	0.40	23 905 (66%)	6988 (68%)	<0.00001
Ischaemic heart	1661 (77%)	601 (71%)	0.002	5878 (16%)	1510 (15%)	0.0003

disease						
Atrial fibrillation	394 (18%)	142 (17%)	0.39	756 (2%)	191 (2%)	0.15
Dementia	163 (8%)	77 (9%)	0.14	782 (2%)	316 (3%)	0.000001
Body mass index (kg/m^2)	28 (25–32)	30 (26–35)	<0.00001	27 (25–31)	29 (26–34)	<0.00001
Pulse (b.p.m.)	70 (63–78)	72 (64–80)	0.15	72 (66–80)	74 (68–82)	<0.00001
Systolic BP (mmHg)	126.9 ± 18.2	129.1 ± 18.3	0.004	126.6 ± 15.1	127.8 ± 15.9	<0.00001
Diastolic BP (mmHg)	70.0 ± 10.2	70.5 ± 10.7	0.23	74.3 ± 9.1	74.6 ± 9.2	0.017
Creatinine (mg/dL)	1.0 (0.8–1.4)	1.0 (0.8–1.5)	0.89	0.8 (0.7–0.9)	0.7 (0.6–0.9)	<0.00001
eGFR ($mL/min/1.73\ m^2$)	60 (43–78)	59 (39–80)	0.49	82 (70–94)	87 (73–102)	<0.00001
Urea (mg/dL)	49 (37–70)	50 (35–74)	0.64	34 (28–41)	32 (26–40)	<0.00001
Haemoglobin (g/dL)	12.8 ± 1.7	12.4 ± 1.7	<0.00001	13.6 ± 1.4	13.3 ± 1.6	<0.00001
Albumin (g/dL)	4.0 (3.9–4.2)	3.9 (3.8–4.2)	0.00009	4.2 (4.0–4.4)	4.1 (3.9–4.3)	<0.00001
Calcium (mg/dL)	9.24 ± 0.52	9.10 ± 0.51	0.10	9.32 ± 0.42	9.26 ± 0.46	<0.00001
Parathyroid hormone (pg/mL)	134 (84–226)	198 (95–344)	0.0002	77 (52–118)	103 (66–166)	<0.00001
25-Hydroxyvitamin D (nmol/L)	46.9 (34.7–63.1)	17.5 (13.7–21.2)	<0.00001	47.2 (35.9–61.4)	18.2 (14.5–21.7)	<0.00001

Data are presented as mean+standard deviation or median (interquartile range) for continuous variables, and counts (percentages) for categorical variables. *P*-value by the Student *t*-test or Mann-Whitney-U test for continuous variables and the χ^2 test for categorical variables.
BP, blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure.

Table 3. Pharmacological treatment of patients with heart failure according to vitamin D (Vit D) levels

Drug therapy	Vit D ≥25 nmol/L (*n* = 2,166)	Vit D <25 nmol/L (*n* = 843)	*P*-value
ACE inhibitor/ARB	1651 (80%)	617 (78%)	0.2
Beta-blockers	1467 (71%)	570 (72%)	0.7
Spironolactone	676 (33%)	236 (30%)	0.1
Furosemide	1371 (67%)	587 (74%)	0.0001
Thiazide	584 (28%)	233 (29%)	0.6
Digoxin	214 (10%)	80 (10%)	0.8
Amiodorone	401 (20%)	132 (17%)	0.1
Aspirin	1419 (69%)	546 (69%)	1.0
Calcium	857 (42%)	240 (30%)	<0.0001
Vitamin D	1325 (64%)	458 (58%)	0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

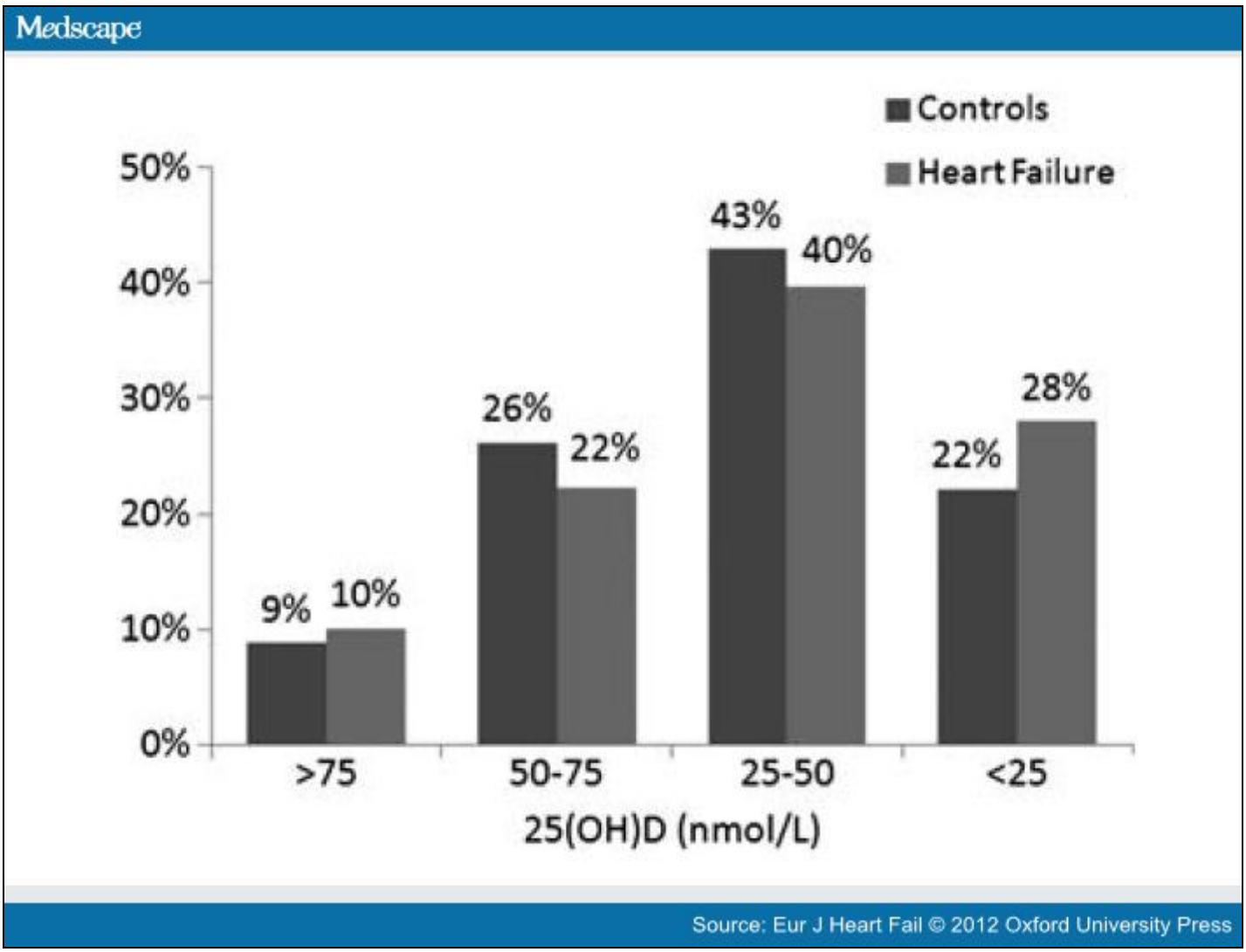


Figure 1. 25-Hydroxyvitamin D [25(OH)D] levels in patients with heart failure compared with the control group. The results are presented as the percentage of patients in each 25(OH)D category level.

Clinical Outcome

The median follow-up was 518 days (IQR 514–521 days). The overall mortality rate during this period was 15.4% (455/3009) in patients with HF and 1.7% (802/46 825) in the control group. Vitamin D deficiency [25(OH)D levels <25 nmol/L] was a predictor of reduced survival in patients with HF as well as in the control group. In the HF group, the estimated cumulative survival rate at the median follow-up time was reduced in patients with vitamin D deficiency [25(OH)D levels <25 nmol/L] (83.3 ± 1.5% vs. 88.6 ± 0.8%, $P < 0.00001$, *Figure 2A*) as well as in the control group (97.5 ± 0.2% vs. 98.6 ± 0.1%, $P < 0.00001$, *Figure 2B*). Cox regression analysis after adjustment for significant predictors demonstrated that vitamin D deficiency was a significant predictor of increased mortality in patients with HF [hazard ratio (HR) 1.52, 95% confidence interval (CI) 1.21–1.92, $P < 0.001$] (Table 4). Analysis with division of the patients into groups based on 25(OH)D levels <25, 25–50, 50–75, and >75 nmol/L demonstrated an increased risk of mortality in patients below 25 nmol/L (Table 5). In addition, analyzing vitamin D levels as a continuous parameter demonstrated that increased 25(OH)D levels were a predictor of reduced mortality in HF patients (Table 5). Inclusion of HF medication in the Cox regression analysis did not influence the result (Table 5). Vitamin D deficiency was also a predictor of increased mortality in the control group (HR 1.91, 95% CI 1.48–2.46, $P < 0.00001$) (Table 4). Analysis based on 25(OH)D levels <25, 25–50, 50–75, and >75 nmol/L demonstrated an increased risk with reduced 25(OH)D (Table 5). In addition, analysis of vitamin D as a continuous parameter demonstrated that increased 25(OH)D levels were a predictor of reduced mortality (Table 5). The prognostic significance of vitamin D deficiency measured in the months with previous exposure to higher solar radiation (June–November) was unchanged when compared with vitamin D deficiency measured in the months with previous exposure to lower solar radiation (December–May). The estimated cumulative survival

rate at the median follow-up time in HF patients with vitamin D deficiency [25(OH)D levels <25 nmol/L] during the months with higher previous solar radiation (*n* = 340) was very similar to the survival in patients with vitamin D deficiency during the months with lower previous solar radiation (*n* = 503): 82.6 ± 2.3% vs. 83.7 ± 2.0%, respectively; log rank *P* = 0.71. Adjustment for significant predictors did not change the result.

Table 4. Predictors of mortality by Cox regression analysis in both groups

	HF group (*n* = 3009)			Control group (*n* = 46825)	
	HR (95% CI)	***P*-value**		**HR (95% CI)**	***P*-value**
Age (years)	1.04 (1.02–1.05)	<0.00001	Age (years)	1.08 (1.07–1.10)	<0.00001
Gender (male)	1.12 (0.89–1.40)	0.34	Gender (male)	2.14 (1.65–2.78)	<0.00001
Diabetes mellitus	1.23 (0.97–1.55)	0.09	Diabetes mellitus	1.53 (1.19–1.97)	0.001
Hyperlipidaemia	0.68 (0.50–0.92)	0.01	Ischaemic heart disease	1.26 (0.96–1.63)	0.09
Ischaemic heart disease	1.32 (1.00–1.75)	0.05	Systolic BP[a] (mmHg)	0.14 (0.01–1.33)	0.09
Atrial fibrillation	1.14 (0.91–1.43)	0.25	Pulse[a] (b.p.m.)	78.0 (14.3–424.6)	<0.00001
Body mass index[a] (kg/m^2)	0.02 (0.00–0.08)	<0.00001	Body mass index[a] (kg/m^2)	0.03 (0.01–0.14)	0.00001
Pulse[a] (b.p.m.)	6.33 (1.38–28.93)	0.02	Urea[a] (mg/dL)	1.83 (0.87–3.82)	0.11
Systolic BP (mmHg)	0.99 (0.99–1.00)	0.003	Haemoglobin (g/dL)	0.90 (0.82–0.98)	0.01
Urea (mg/dL)[a]	5.51 (2.61–11.60)	<0.00001	Albumin ≤3.5g/dL	3.25 (2.12–4.97)	<0.00001
eGFR[b] (mL/min/1.73 m^2)	1.06 (0.97–1.17)	0.17	Calcium (mg/dL)	0.62 (0.48–0.81)	0.0004
Haemoglobin (g/dL)	0.95 (0.88–1.02)	0.14	25(OH)D <25 nmol/L	1.91 (1.48–2.46)	<0.00001
Sodium ≤135 mEq/L	1.56 (1.15–2.12)	0.004			
Albumin ≤3.5 g/dL	2.28 (1.74–2.98)	<0.00001			
Calcium (mg/dL)	0.96 (0.78–1.18)	0.68			
25(OH)D <25 nmol/L	1.52 (1.21–1.92)	0.0003			

BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; 25(OH)D, 25-hydroxyvitamin D.
[a]Log transformed.
[b]Square root transformed.

Table 5. Hazard ratio for mortality according to 25(OH)D levels by Cox regression analysis

	HF group		
	Unadjusted	**Model 1[a]**	**Model 2[b]**
25(OH)D <25 nmol/L	1.51 (1.23–1.85)	1.52 (1.21–1.92)	1.47 (1.17–1.85)
	0.0001	0.0003	0.001
Log-transformed 25(OH)D	0.53 (0.37–0.77)	0.49 (0.33–0.74)	0.53 (0.35–0.80)
	0.0008	0.0007	0.0027
25(OH)D <25 nmol/L	1.54 (1.08–2.19)	1.70 (1.14–2.54)	1.61 (1.08–2.41)
25(OH)D 25–50 nmol/L	0.99 (0.70–1.40)	1.12; (0.75–1.65)	1.08 (0.73–1.60)

25(OH)D 50–75 nmol/L	1.07 (0.74–1.55)	1.17 (0.77–1.77)	1.18 (0.78–1.79)
25(OH)D >75 nmol/L	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
	0.0012	0.0035	0.0097
	Control group		
	Unadjusted	Adjusted[c]	
25(OH)D <25 nmol/L	1.68 (1.44–1.95)	1.91 (1.48–2.46)	
	<0.00001	<0.00001	
Log-transformed 25(OH)D	0.41 (0.31–0.54)	0.29 (0.18–0.46)	
	<0.00001	<0.00001	
25(OH)D <25 nmol/L	1.38 (1.08–1.76)	2.93 (1.78–4.84)	
25(OH)D 25–50 nmol/L	0.88 (0.70–1.12)	1.82 (1.12–2.96)	
25(OH)D 50–75 nmol/L	0.66 (0.50–0.85)	1.35 (0.81–2.27)	
25(OH)D >75 nmol/L	1.0 (Reference)	1.0 (Reference)	
	<0.00001	<0.00001	

Data are presented as hazard ratio (95% confidence interval), *P*-value.
HF, heart failure; 25(OH)D, 25-hydroxyvitamin D.
[a]Parameters that were included in the multivariate analysis were age, gender, ischaemic heart disease, diabetes, hyperlipdaemia, atrial fibrillation, log-transformed body mass index, log-transformed pulse, systolic blood pressure, log-transformed serum urea levels, square root-transformed estimated glomerular filtration rate, haemoglobin, serum sodium, albumin, and calcium levels.
[b]Parameters included in model A with adjustment for HF drug therapies: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blockers, furosemide, thiazides, and spironolactone.
[c]Parameters included were age, gender, ischaemic heart disease, diabetes, log-transformed body mass index, log-transformed pulse, log-transformed systolic blood pressure, log-transformed serum urea levels, haemoglobin, serum albumin, and calcium levels.

Table 5. Hazard ratio for mortality according to 25(OH)D levels by Cox regression analysis

	HF group		
	Unadjusted	**Model 1[a]**	**Model 2[b]**
25(OH)D <25 nmol/L	1.51 (1.23–1.85)	1.52 (1.21–1.92)	1.47 (1.17–1.85)
	0.0001	0.0003	0.001
Log-transformed 25(OH)D	0.53 (0.37–0.77)	0.49 (0.33–0.74)	0.53 (0.35–0.80)
	0.0008	0.0007	0.0027
25(OH)D <25 nmol/L	1.54 (1.08–2.19)	1.70 (1.14–2.54)	1.61 (1.08–2.41)
25(OH)D 25–50 nmol/L	0.99 (0.70–1.40)	1.12; (0.75–1.65)	1.08 (0.73–1.60)
25(OH)D 50–75 nmol/L	1.07 (0.74–1.55)	1.17 (0.77–1.77)	1.18 (0.78–1.79)
25(OH)D >75 nmol/L	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
	0.0012	0.0035	0.0097

	Control group		
	Unadjusted	Adjusted[c]	
25(OH)D <25 nmol/L	1.68 (1.44–1.95)	1.91 (1.48–2.46)	
	<0.00001	<0.00001	
Log-transformed 25(OH)D	0.41 (0.31–0.54)	0.29 (0.18–0.46)	
	<0.00001	<0.00001	
25(OH)D <25 nmol/L	1.38 (1.08–1.76)	2.93 (1.78–4.84)	
25(OH)D 25–50 nmol/L	0.88 (0.70–1.12)	1.82 (1.12–2.96)	
25(OH)D 50–75 nmol/L	0.66 (0.50–0.85)	1.35 (0.81–2.27)	
25(OH)D >75 nmol/L	1.0 (Reference)	1.0 (Reference)	
	<0.00001	<0.00001	

Data are presented as hazard ratio (95% confidence interval), *P*-value.
HF, heart failure; 25(OH)D, 25-hydroxyvitamin D.
[a]Parameters that were included in the multivariate analysis were age, gender, ischaemic heart disease, diabetes, hyperlipdaemia, atrial fibrillation, log-transformed body mass index, log-transformed pulse, systolic blood pressure, log-transformed serum urea levels, square root-transformed estimated glomerular filtration rate, haemoglobin, serum sodium, albumin, and calcium levels.
[b]Parameters included in model A with adjustment for HF drug therapies: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blockers, furosemide, thiazides, and spironolactone.
[c]Parameters included were age, gender, ischaemic heart disease, diabetes, log-transformed body mass index, log-transformed pulse, log-transformed systolic blood pressure, log-transformed serum urea levels, haemoglobin, serum albumin, and calcium levels.

Table 5. Hazard ratio for mortality according to 25(OH)D levels by Cox regression analysis

	HF group		
	Unadjusted	**Model 1[a]**	**Model 2[b]**
25(OH)D <25 nmol/L	1.51 (1.23–1.85)	1.52 (1.21–1.92)	1.47 (1.17–1.85)
	0.0001	0.0003	0.001
Log-transformed 25(OH)D	0.53 (0.37–0.77)	0.49 (0.33–0.74)	0.53 (0.35–0.80)
	0.0008	0.0007	0.0027
25(OH)D <25 nmol/L	1.54 (1.08–2.19)	1.70 (1.14–2.54)	1.61 (1.08–2.41)
25(OH)D 25–50 nmol/L	0.99 (0.70–1.40)	1.12; (0.75–1.65)	1.08 (0.73–1.60)
25(OH)D 50–75 nmol/L	1.07 (0.74–1.55)	1.17 (0.77–1.77)	1.18 (0.78–1.79)
25(OH)D >75 nmol/L	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
	0.0012	0.0035	0.0097
	Control group		
	Unadjusted	Adjusted[c]	
25(OH)D <25 nmol/L	1.68 (1.44–1.95)	1.91 (1.48–2.46)	

	<0.00001	<0.00001	
Log-transformed 25(OH)D	0.41 (0.31–0.54)	0.29 (0.18–0.46)	
	<0.00001	<0.00001	
25(OH)D <25 nmol/L	1.38 (1.08–1.76)	2.93 (1.78–4.84)	
25(OH)D 25–50 nmol/L	0.88 (0.70–1.12)	1.82 (1.12–2.96)	
25(OH)D 50–75 nmol/L	0.66 (0.50–0.85)	1.35 (0.81–2.27)	
25(OH)D >75 nmol/L	1.0 (Reference)	1.0 (Reference)	
	<0.00001	<0.00001	

Data are presented as hazard ratio (95% confidence interval), *P*-value.
HF, heart failure; 25(OH)D, 25-hydroxyvitamin D.
[a]Parameters that were included in the multivariate analysis were age, gender, ischaemic heart disease, diabetes, hyperlipdaemia, atrial fibrillation, log-transformed body mass index, log-transformed pulse, systolic blood pressure, log-transformed serum urea levels, square root-transformed estimated glomerular filtration rate, haemoglobin, serum sodium, albumin, and calcium levels.
[b]Parameters included in model A with adjustment for HF drug therapies: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blockers, furosemide, thiazides, and spironolactone.
[c]Parameters included were age, gender, ischaemic heart disease, diabetes, log-transformed body mass index, log-transformed pulse, log-transformed systolic blood pressure, log-transformed serum urea levels, haemoglobin, serum albumin, and calcium levels.

Table 4. Predictors of mortality by Cox regression analysis in both groups

	HF group (*n* = 3009)			**Control group (*n* = 46825)**	
	HR (95% CI)	***P*-value**		**HR (95% CI)**	***P*-value**
Age (years)	1.04 (1.02–1.05)	<0.00001	Age (years)	1.08 (1.07–1.10)	<0.00001
Gender (male)	1.12 (0.89–1.40)	0.34	Gender (male)	2.14 (1.65–2.78)	<0.00001
Diabetes mellitus	1.23 (0.97–1.55)	0.09	Diabetes mellitus	1.53 (1.19–1.97)	0.001
Hyperlipidaemia	0.68 (0.50–0.92)	0.01	Ischaemic heart disease	1.26 (0.96–1.63)	0.09
Ischaemic heart disease	1.32 (1.00–1.75)	0.05	Systolic BP[a] (mmHg)	0.14 (0.01–1.33)	0.09
Atrial fibrillation	1.14 (0.91–1.43)	0.25	Pulse[a] (b.p.m.)	78.0 (14.3–424.6)	<0.00001
Body mass index[a] (kg/m^2)	0.02 (0.00–0.08)	<0.00001	Body mass index[a] (kg/m^2)	0.03 (0.01–0.14)	0.00001
Pulse[a] (b.p.m.)	6.33 (1.38–28.93)	0.02	Urea[a] (mg/dL)	1.83 (0.87–3.82)	0.11
Systolic BP (mmHg)	0.99 (0.99–1.00)	0.003	Haemoglobin (g/dL)	0.90 (0.82–0.98)	0.01
Urea (mg/dL)[a]	5.51 (2.61–11.60)	<0.00001	Albumin ≤3.5g/dL	3.25 (2.12–4.97)	<0.00001
eGFR[b] (mL/min/1.73 m^2)	1.06 (0.97–1.17)	0.17	Calcium (mg/dL)	0.62 (0.48–0.81)	0.0004
Haemoglobin (g/dL)	0.95 (0.88–1.02)	0.14	25(OH)D <25 nmol/L	1.91 (1.48–2.46)	<0.00001
Sodium ≤135 mEq/L	1.56 (1.15–2.12)	0.004			
Albumin ≤3.5 g/dL	2.28 (1.74–2.98)	<0.00001			
Calcium (mg/dL)	0.96 (0.78–1.18)	0.68			

25(OH)D <25 nmol/L	1.52 (1.21–1.92)	0.0003			

BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; 25(OH)D, 25-hydroxyvitamin D.
[a]Log transformed.
[b]Square root transformed.

Table 5. Hazard ratio for mortality according to 25(OH)D levels by Cox regression analysis

	HF group		
	Unadjusted	**Model 1[a]**	**Model 2[b]**
25(OH)D <25 nmol/L	1.51 (1.23–1.85)	1.52 (1.21–1.92)	1.47 (1.17–1.85)
	0.0001	0.0003	0.001
Log-transformed 25(OH)D	0.53 (0.37–0.77)	0.49 (0.33–0.74)	0.53 (0.35–0.80)
	0.0008	0.0007	0.0027
25(OH)D <25 nmol/L	1.54 (1.08–2.19)	1.70 (1.14–2.54)	1.61 (1.08–2.41)
25(OH)D 25–50 nmol/L	0.99 (0.70–1.40)	1.12; (0.75–1.65)	1.08 (0.73–1.60)
25(OH)D 50–75 nmol/L	1.07 (0.74–1.55)	1.17 (0.77–1.77)	1.18 (0.78–1.79)
25(OH)D >75 nmol/L	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
	0.0012	0.0035	0.0097
	Control group		
	Unadjusted	Adjusted[c]	
25(OH)D <25 nmol/L	1.68 (1.44–1.95)	1.91 (1.48–2.46)	
	<0.00001	<0.00001	
Log-transformed 25(OH)D	0.41 (0.31–0.54)	0.29 (0.18–0.46)	
	<0.00001	<0.00001	
25(OH)D <25 nmol/L	1.38 (1.08–1.76)	2.93 (1.78–4.84)	
25(OH)D 25–50 nmol/L	0.88 (0.70–1.12)	1.82 (1.12–2.96)	
25(OH)D 50–75 nmol/L	0.66 (0.50–0.85)	1.35 (0.81–2.27)	
25(OH)D >75 nmol/L	1.0 (Reference)	1.0 (Reference)	
	<0.00001	<0.00001	

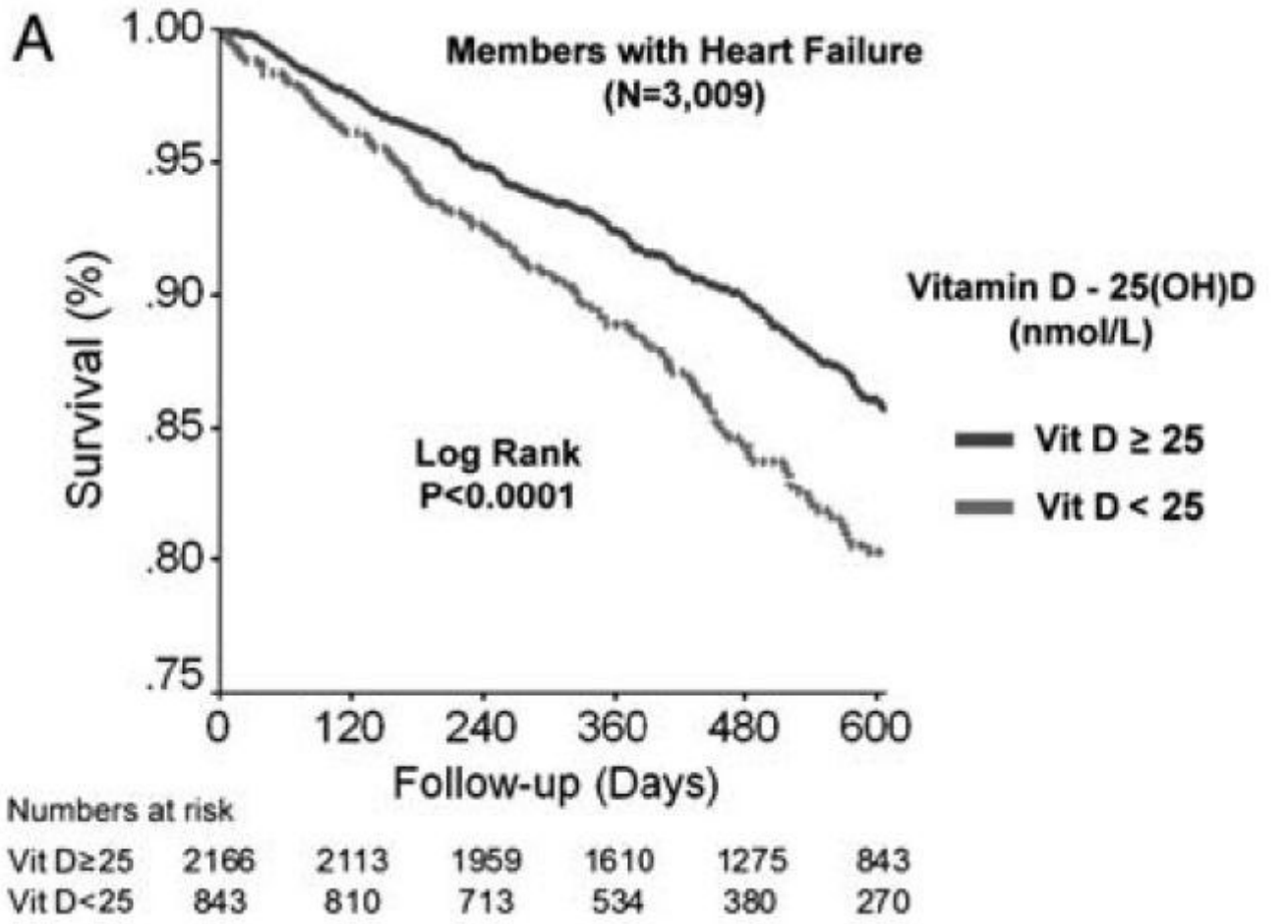
Data are presented as hazard ratio (95% confidence interval), *P*-value.
HF, heart failure; 25(OH)D, 25-hydroxyvitamin D.
[a]Parameters that were included in the multivariate analysis were age, gender, ischaemic heart disease, diabetes, hyperlipdaemia, atrial fibrillation, log-transformed body mass index, log-transformed pulse, systolic blood pressure, log-transformed serum urea levels, square root-transformed estimated glomerular filtration rate, haemoglobin, serum sodium, albumin, and calcium levels.
[b]Parameters included in model A with adjustment for HF drug therapies: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blockers, furosemide, thiazides, and spironolactone.
[c]Parameters included were age, gender, ischaemic heart disease, diabetes, log-transformed body

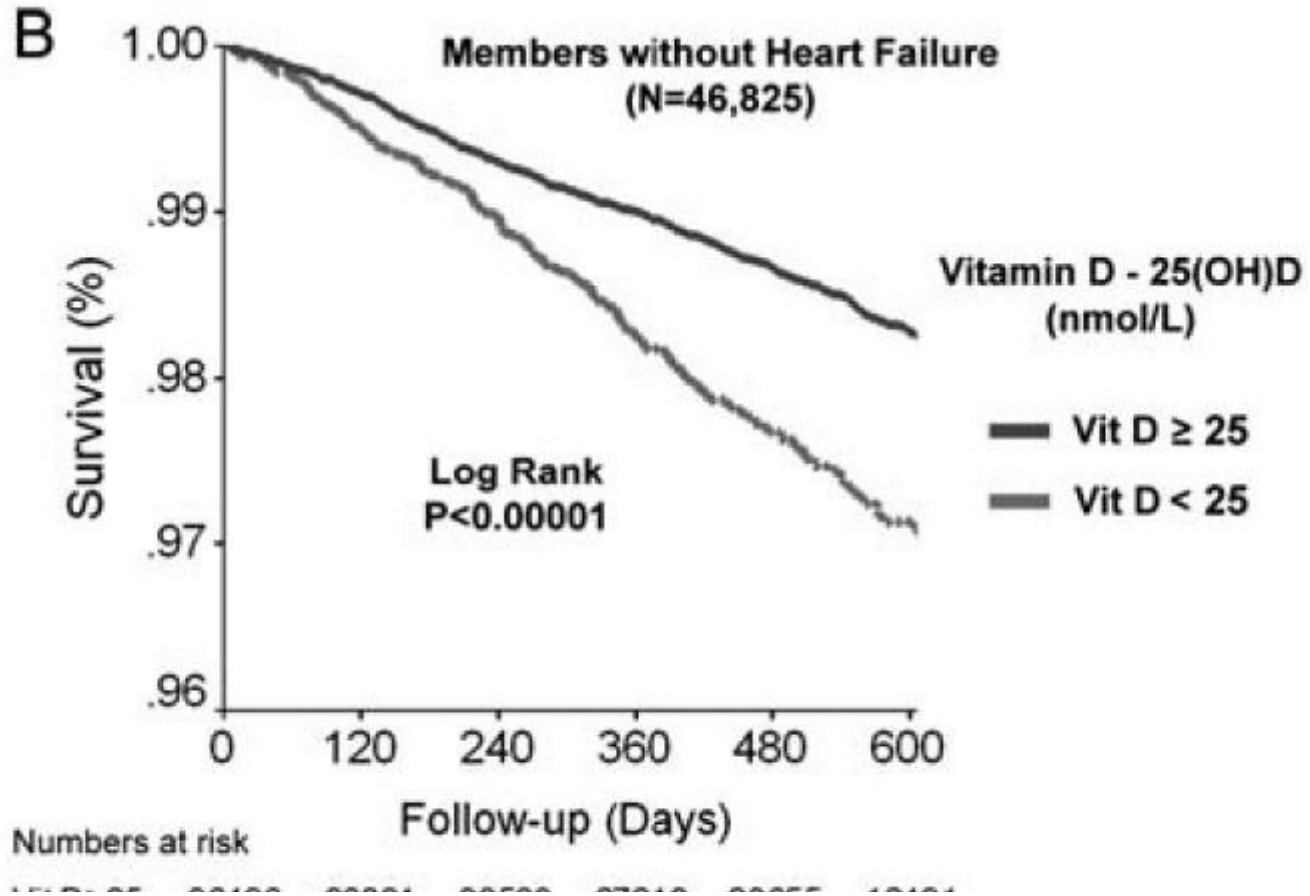
mass index, log-transformed pulse, log-transformed systolic blood pressure, log-transformed serum urea levels, haemoglobin, serum albumin, and calcium levels.

Table 5. Hazard ratio for mortality according to 25(OH)D levels by Cox regression analysis

	HF group		
	Unadjusted	**Model 1[a]**	**Model 2[b]**
25(OH)D <25 nmol/L	1.51 (1.23–1.85)	1.52 (1.21–1.92)	1.47 (1.17–1.85)
	0.0001	0.0003	0.001
Log-transformed 25(OH)D	0.53 (0.37–0.77)	0.49 (0.33–0.74)	0.53 (0.35–0.80)
	0.0008	0.0007	0.0027
25(OH)D <25 nmol/L	1.54 (1.08–2.19)	1.70 (1.14–2.54)	1.61 (1.08–2.41)
25(OH)D 25–50 nmol/L	0.99 (0.70–1.40)	1.12; (0.75–1.65)	1.08 (0.73–1.60)
25(OH)D 50–75 nmol/L	1.07 (0.74–1.55)	1.17 (0.77–1.77)	1.18 (0.78–1.79)
25(OH)D >75 nmol/L	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
	0.0012	0.0035	0.0097
	Control group		
	Unadjusted	Adjusted[c]	
25(OH)D <25 nmol/L	1.68 (1.44–1.95)	1.91 (1.48–2.46)	
	<0.00001	<0.00001	
Log-transformed 25(OH)D	0.41 (0.31–0.54)	0.29 (0.18–0.46)	
	<0.00001	<0.00001	
25(OH)D <25 nmol/L	1.38 (1.08–1.76)	2.93 (1.78–4.84)	
25(OH)D 25–50 nmol/L	0.88 (0.70–1.12)	1.82 (1.12–2.96)	
25(OH)D 50–75 nmol/L	0.66 (0.50–0.85)	1.35 (0.81–2.27)	
25(OH)D >75 nmol/L	1.0 (Reference)	1.0 (Reference)	
	<0.00001	<0.00001	

Data are presented as hazard ratio (95% confidence interval), *P*-value.
HF, heart failure; 25(OH)D, 25-hydroxyvitamin D.
[a]Parameters that were included in the multivariate analysis were age, gender, ischaemic heart disease, diabetes, hyperlipdaemia, atrial fibrillation, log-transformed body mass index, log-transformed pulse, systolic blood pressure, log-transformed serum urea levels, square root-transformed estimated glomerular filtration rate, haemoglobin, serum sodium, albumin, and calcium levels.
[b]Parameters included in model A with adjustment for HF drug therapies: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blockers, furosemide, thiazides, and spironolactone.
[c]Parameters included were age, gender, ischaemic heart disease, diabetes, log-transformed body mass index, log-transformed pulse, log-transformed systolic blood pressure, log-transformed serum urea levels, haemoglobin, serum albumin, and calcium levels.


A
Members with Heart Failure
(N=3,009)
Survival (%)
1.00
.95
.90
.85
.80
.75
Log Rank
P<0.0001
Vitamin D - 25(OH)D
(nmol/L)
Vit D ≥ 25
Vit D < 25
0
120
240
360
480
600
Follow-up (Days)
Numbers at risk
Vit D≥25 2166 2113 1959 1610 1275 843
Vit D<25 843 810 713 534 380 270


B
Members without Heart Failure
(N=46,825)
Survival (%)
1.00
.99
.98
.97
.96
Log Rank
P<0.00001
Vitamin D - 25(OH)D
(nmol/L)
Vit D ≥ 25
Vit D < 25
0
120
240
360
480
600
Follow-up (Days)
Numbers at risk

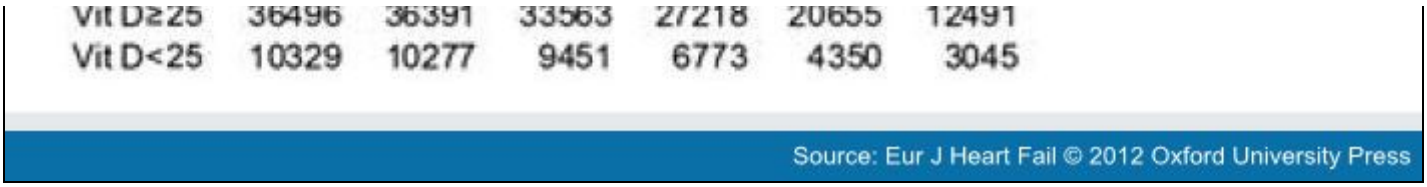


Figure 2. Kaplan–Meier survival analysis according to 25-hydroxyvitamin D [25(OH)D] levels. Vitamin D deficiency [serum 25(OH)D levels <25 nmol/L] was associated with reduced survival in patients with heart failure (log rank $P < 0.0001$) (*A*) and in the control group (log rank $P < 0.00001$) (*B*).

Vitamin D Supplementation and Outcome in Patients With Heart Failure

Data on vitamin D supplementation were evaluated in patients with HF during follow-up. A total of 1783 of the HF patients (63%) were prescribed a vitamin D supplement during follow-up (Table 3). The standard amount prescribed of vitamin D supplement in Israel is between 800 and 1000 units per day. Treatment with vitamin D supplements was associated with reduced mortality in patients with vitamin D deficiency (*Figure 3*). Cox regression analysis after adjustment for significant predictors including drug therapy and vitamin D levels demonstrated that vitamin D supplementation was independently associated with reduced mortality in patients with HF (HR 0.68, 95% CI 0.54–0.85, $P < 0.0001$). Calcium supplementation had no effect on outcome.

Table 3. Pharmacological treatment of patients with heart failure according to vitamin D (Vit D) levels

Drug therapy	Vit D ≥25 nmol/L (*n* = 2,166)	Vit D <25 nmol/L (*n* = 843)	*P*-value
ACE inhibitor/ARB	1651 (80%)	617 (78%)	0.2
Beta-blockers	1467 (71%)	570 (72%)	0.7
Spironolactone	676 (33%)	236 (30%)	0.1
Furosemide	1371 (67%)	587 (74%)	0.0001
Thiazide	584 (28%)	233 (29%)	0.6
Digoxin	214 (10%)	80 (10%)	0.8
Amiodorone	401 (20%)	132 (17%)	0.1
Aspirin	1419 (69%)	546 (69%)	1.0
Calcium	857 (42%)	240 (30%)	<0.0001
Vitamin D	1325 (64%)	458 (58%)	0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

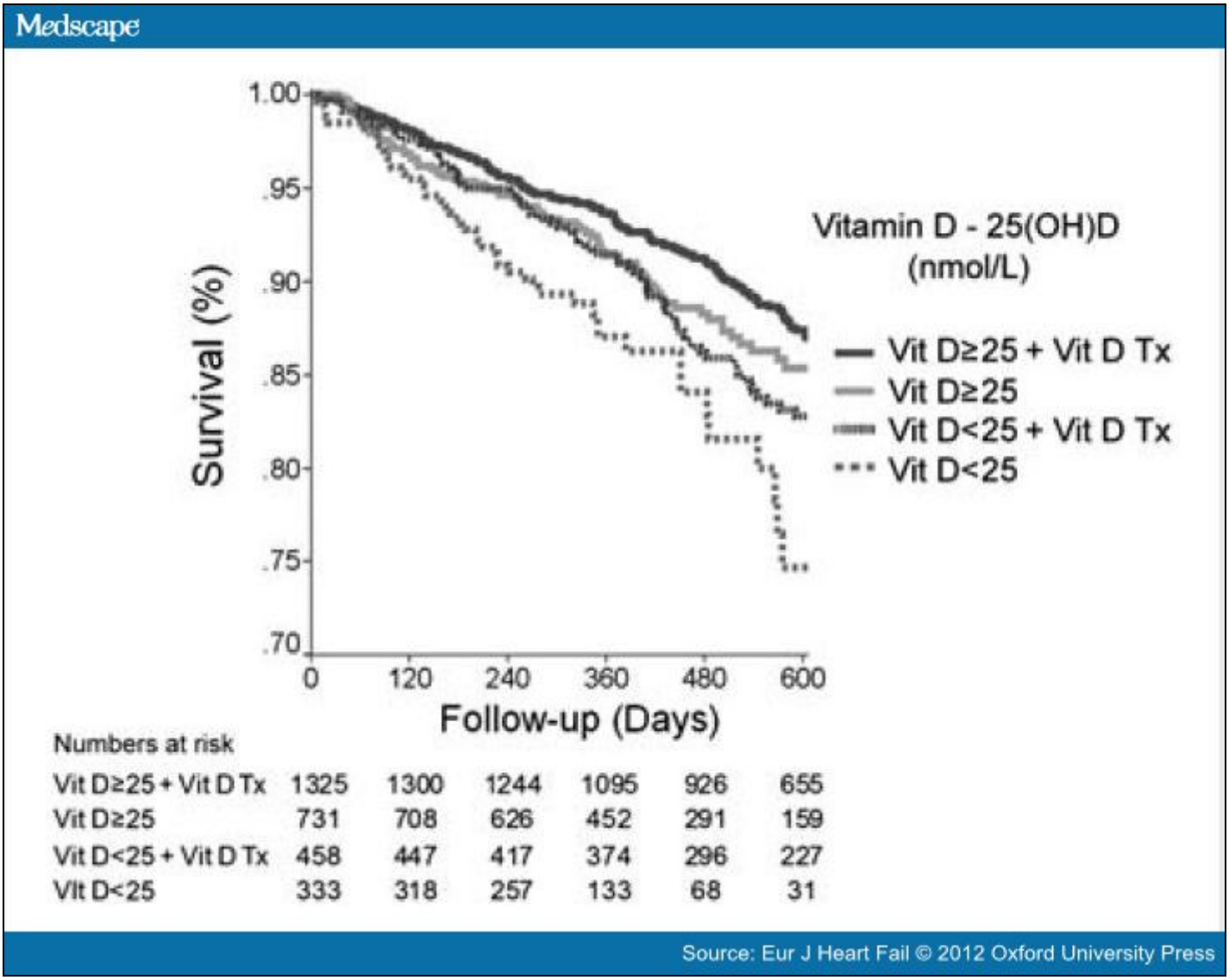


Figure 3. Kaplan–Meier survival analysis of heart failure patients according to vitamin D supplementation and vitamin D levels. Vitamin D supplementation was associated with improved survival in patients with serum 25-hydroxyvitamin D [25(OH)D] levels <25 nmol/L. The estimated cumulative survival rate at median follow-up time (518 days) in patients with serum 25(OH)D levels <25 nmol/L with or without supplementation was 85.6 ± 1.7% (*n* = 458) vs. 81.6 ± 3.1% (*n* = 333), respectively, log rank *P* <0.01).

Seasonal Variation in Vitamin D Levels

We analysed seasonal variation in 25(OH)D in patients with HF compared with the control group. There was a clear seasonal variation in 25(OH)D levels in the control group, with a similar pattern seen in patients with HF, but with lower absolute levels in these patients (*Figure 4A*). Increased levels of 25(OH)D were seen in the summer months (June–August) compared with the winter months (December–February). There was an increase of 14% in 25(OH)D levels in the summer compared with the winter in patients with HF (45.9 nmol/L vs. 40.4 nmol/L, $P < 0.0001$) and a 19% increase in the control group (48.4 nmol/L vs. 40.7 nmol/L, respectively, $P < 0.0001$). As solar ultraviolet B radiation is the main factor determining seasonal variation in 25(OH)D levels and 25(OH)D has a half-life of several weeks, we looked at the correlation between the previous 2 months average daily global solar radiation and mean 25(OH)D levels. When compared with the previous 2 month average daily global solar radiation, there was a strong direct relationship between the mean radiation and mean monthly 25(OH)D levels in both groups. Regression analysis demonstrated a highly significant correlation between mean radiation and mean monthly 25(OH)D levels ($R^{[2]}$ =0.812, $P < 0.0001$) in the control group (*Figure 4B*). A similar correlation was seen in HF patients ($R^{[2]}$ =0.70, $P < 0.001$) (*Figure 4C*).

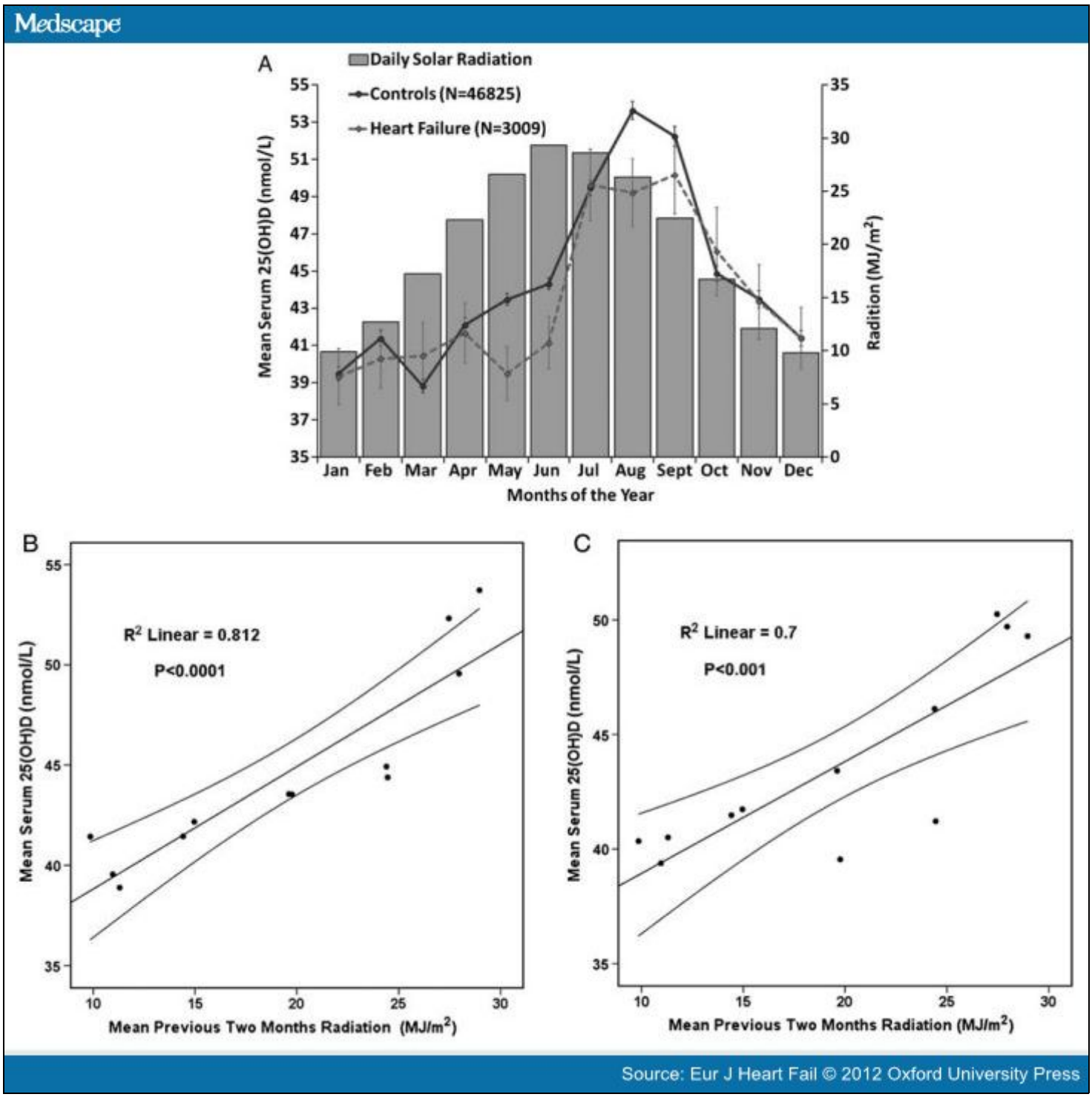


Figure 4. Seasonal variation in vitamin D levels. (*A*) Relationship between mean monthly 25-hydroxyvitamin D [25(OH)D] levels (nmol/L), the month in which 25(OH)D was measured, and mean monthly global daily solar radiation (MJ/m^2) in patients with heart failure (HF) and the control group. A seasonal pattern is seen in both groups. (*B* and *C*) Regression analysis between the previous 2 months average daily global solar radiation and mean 25(OH)D levels: a highly significant correlation between mean radiation and mean monthly 25(OH)D levels in the control group (*B*) and in HF patients (*C*).

Parameters Associated With Vitamin D Levels

Logistic regression analysis demonstrated that parameters associated with 25(OH)D deficiency (<25 nmol/L) were very similar in patients with HF and the control group (Table 6). Parameters associated with 25(OH)D deficiency in both groups were decreased previous solar radiation exposure, increased body mass index, diabetes, female gender, decreased calcium and haemoglobin levels, and an increased pulse. In the control group, 25(OH)D deficiency was also associated with

decreased age and increased systolic blood pressure.

Table 6. Multivariate logistic regression analysis for independent predictors of vitamin D deficiency [serum 25(OH)D levels <25 nmol/L]

	HF group (*n* = 3009)		Control group (*n* = 46 825)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Solar radiation (MJ/m^2)[a]	0.98 (0.96–0.99)	0.0003	0.95 (0.94–0.95)	<0.00001
Age (years)	0.99 (0.99–1.00)	0.22	0.99 (0.99–1.00)	<0.00001
Gender (male)	0.68 (0.55–0.83)	0.0001	0.68 (0.64–0.72)	<0.00001
Diabetes	1.77 (1.46–2.15)	<0.00001	1.60 (1.51–1.70)	<0.00001
Body mass index (kg/m^2)[b]	6.22 (1.92–20.16)	0.002	32.8 (24.1–44.6)	<0.00001
Systolic BP (mmHg)	1.00 (1.00–1.01)	0.08	2.73 (1.66–4.51)	0.0001
Pulse (b.p.m.)[b]	4.41 (1.23–15.86)	0.02	4.13 (2.83–6.03)	<0.00001
Haemoglobin (g/dL)	0.91 (0.85–0.97)	0.003	0.88 (0.86–0.90)	<0.00001
eGFR ($mL/min/1.73\ m^2$)[c]	1.05 (1.00–1.11)	0.06	1.01 (1.01–1.01)	<0.00001
Calcium (mg/dL)	0.60 (0.49–0.72)	<0.00001	0.73 (0.68–0.78)	<0.00001

Included in the multivariate analysis were variables that were significant on univariate analysis.
BP, blood pressure, CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.
[a]Previous 2 months average daily global solar radiation.
[b]Log transformed.
[c]Square root transformed.

Discussion

In the present study, we report the prevalence of vitamin D deficiency in a large cohort of HF patients, and describe the seasonal variation in vitamin D levels and the impact of vitamin D deficiency and supplementation on mortality in this population. The present study demonstrates that vitamin D levels are low in the general population and even lower in HF patients. More importantly, vitamin D deficiency was a significant predictor of reduced survival in patients with HF as well as in the control group. Moreover, vitamin D supplementation in HF patients was associated with improved outcome.

Median 25(OH)D levels among patients with HF in the present study were far below what is generally accepted as optimal levels (>75 nmol/L). Twent-eight per cent of this population had significant vitamin D deficiency (<25 nmol/L) and only 8.8% had optimal levels. HF patients had lower levels of vitamin D compared with the general population, although the differences were small. Mean levels reported in a recent small study in the healthy Israeli population >50 years old were quite similar to the levels in our control group.[25] A larger recent study of vitamin D levels in the general Israeli population also showed a high prevalence of vitamin D deficiency, although the reported prevalence was lower than that reported in our study.[18] Nevertheless, the data from this and previous studies give an indication of the magnitude of vitamin D deficiency in a country with abundant solar radiation.

Vitamin D deficiency in the present study was a significant and independent predictor of reduced survival in the HF and the control group, even when adjusted for significant predictors of vitamin D deficiency. Previous studies have shown this to be the case in the general population.[10,11] However, until recently there was a paucity of data regarding this in patients with HF.[26,27] A recent study[21] demonstrated that vitamin D deficiency was a significant predictor of all-cause mortality and HF re-hospitalization in patients with mild to moderate HF. The present study demonstrates in a large community cohort of HF patients that vitamin D deficiency was a significant independent predictor of mortality.

Is this finding a marker of more severe disease, or is there a possible contribution of vitamin D deficiency to the pathogenesis of HF or to deterioration in function? Several mechanisms may explain this association.[28] Vitamin D is a fat-soluble hormone, formed from 7-dehydrocholesterol in the skin during exposure to solar ultraviolet B radiation or ingested from dietary sources. It is converted to the active metabolite calcitriol (1,25-hydroxyvitamin D_3) in the kidney. Calcitriol binds to a specific nuclear receptor, the vitamin D receptor, which is expressed in most cells, exerting its effects through gene transcription. It primarily regulates calcium homeostasis, but has numerous additional biological effects. Calcitriol is a negative regulator of the renin–angiotensin system[29] and cardiomyocyte proliferation,[30] and suppresses immune and inflammatory responses.[31] All of these processes are important in the development and progression of HF. Calcitriol is also directly involved in calcium-dependent cellular processes, including the synthesis of calcium-binding protein, the activation of adenylate cyclase, the rapid activation of voltage-dependent calcium channels, and the influx, reuptake, and release of calcium from the sarcoplasmic reticulum.[32] This altered intracellular handling of ionized calcium could also contribute to the impaired contractility of the myocardium in HF patients.[33] Strong support for the involvement of vitamin D in the pathogenesis of HF comes from vitamin D receptor knockout mice. These mice develop typical signs of HF including activation of the renin–angiotensin–aldosterone system, cardiac hypertrophy, high blood pressure, and increased levels of atrial natriuretic peptide.[34] In addition, parathyroid hormone is elevated in patients with vitamin D deficiency. Parathyroid hormone has been shown to be an independent predictor of all-cause[35] and cardiovascular mortality in the general population,[36] as well in patients with HF.[27]

Vitamin D deficiency was shown to be a significant predictor of outcome in our study, but vitamin D levels are strongly influenced by the time of the year during which the test is done. Could this influence the outcome? We found that timing of the test in patients with vitamin D deficiency had no influence on outcome, and prognosis was very similar between different seasons. This analysis suggests that vitamin D levels confer prognostic information regardless of the timing of the test.

Although the vitamin D level is an independent predictor of survival in HF patients, insufficient and contradictory data exist regarding the benefit of vitamin D supplementation in this group.[37] In the present study, we found an independent association between vitamin D supplementation and improved outcome in patients with HF. However, this is an association and does not prove a causative effect. A recent meta-analysis[38] demonstrated that vitamin D supplementation in the form of vitamin D(3) decreased mortality in the general population (predominantly elderly women), in agreement with our results. A previous study demonstrated that vitamin D supplementation in HF patients modulated the inflammatory cytokine profile, with a reduction in the pro-inflammatory cytokine tumour necrosis factor-α and an increase in the anti-inflammatory cytokine interleukin-10.[39] However, vitamin D supplementation was not found to improve functional capacity or quality of life in a short-term trial of 105 older patients with HF and vitamin D insufficiency, despite a decrease in brain natriuretic peptide.[40] In addition, vitamin D_3 supplement had no additional beneficial effects on markers of bone metabolism in 102 HF patients with low initial 25(OH)D concentrations if an adequate daily calcium intake was guaranteed.[41] Thus, more evidence is needed to prove a benefit of regular vitamin D supplementation to improve cardiac function, quality of life, or mortality in HF patients. Furthermore, a recent public health report on dietary intake requirements for calcium and vitamin D from the American Institute of Medicine[42] emphasizes that there are insufficient data regarding the benefits of vitamin D supplementation on extraskeletal health outcomes, and randomized trials are urgently needed.

We found a definite seasonal variation in vitamin D levels in both HF patients and the control group, with increased levels of 25(OH)D in the summer months compared with the winter months. There was a strong direct relationship between the solar radiation and vitamin D levels in both groups. In addition, decreased solar radiation exposure was a predictor of vitamin D deficiency. In HF patients, the average level was lower than in the control group during most months of the year, but the difference was more pronounced during the summer. It is possible that the lower levels seen in patients with HF are partially related to a greater reduction in sun exposure due to limited functional capacity and outdoor activities, which is more evident in the summer when there is abundant solar radiation.[43] Direct data regarding actual individual sun exposure were not available in this study. The current data emphasize the importance of sun exposure on vitamin D levels in patients with HF and suggest that sun exposure may significantly increase vitamin D levels in these patients.

There was an association between 25(OH)D deficiency and an increased pulse. This is of interest as a previous randomized study showed that treatment with vitamin D supplementation decreased heart rate.[44]

Limitations of This Study

The present study was an observational study with its known limitations. Vitamin D levels were taken from patients at the

discretion of the treating physician, and, thus, the data may not reflect the actual prevalence of vitamin D deficiency in the whole population. In particular, there were a higher proportion of females in this cohort (HF and control groups). In addition, the prevalence of diseases such as diabetes and ischaemic heart disease was higher in our control group than the rates reported in the general population.

Another limitation is that this study analysed a single measurement of 25(OH)D and this may not adequately reflect the long-term vitamin D status in these patients. We also did not have data on the specific causes of mortality. The decision to administer vitamin D supplementation was also at the discretion of the treating physician.

In conclusion, vitamin D deficiency is highly prevalent in HF patients as well as in the general population, even in a geographic location with exposure to abundant solar radiation. Vitamin D deficiency was a significant predictor of reduced survival in both HF patients and the control groups. In addition, vitamin D supplementation was associated with increased survival in HF patients.

References

1. Gotsman I, Zwas D, Planer D, Azaz-Livshits T, Admon D, Lotan C, Keren A. Clinical outcome of patients with heart failure and preserved left ventricular function. *Am J Med* 2008;121:997–1001.
2. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008;117:503–511.
3. Kilkkinen A, Knekt P, Aro A, Rissanen H, Marniemi J, Heliovaara M, Impivaara O, Reunanen A. Vitamin D status and the risk of cardiovascular disease death. *Am J Epidemiol* 2009;170:1032–1039.
4. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med* 2008;168:1174–1180.
5. Wallis DE, Penckofer S, Sizemore GW. The 'sunshine deficit' and cardiovascular disease. *Circulation* 2008;118:1476–1485.
6. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol* 2008;52:1949–1956.
7. Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, Felsenfeld A, Levine B, Mehrotra R, Norris K. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2007;167:1159–1165.
8. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. *Am J Hypertens* 2007;20:713–719.
9. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, Kinkeldei J, Boehm BO, Weihrauch G, Maerz W. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. *Arch Intern Med* 2008;168:1340–1349.
10. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 2008;168:1629–1637.
11. Pilz S, Marz W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, Boehm BO, Dobnig H. 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;93:3927–3935.
12. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–281.
13. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, Meunier PJ. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int* 1997;7:439–443.
14. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006;81:353–373.
15. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet* 1998;351:805–806.
16. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, Allen C, Doughertly C, Gunter EW, Bowman BA. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr* 2002;76:187–192.
17. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000;72:690–693.
18. Steinvil A, Leshem-Rubinow E, Berliner S, Justo D, Finn T, Ish-shalom M, Birati EY, Shalev V, Sheinberg B, Rogowski O. Vitamin D deficiency prevalence and cardiovascular risk in Israel. *Eur J Clin Invest* 2011;41:263–268.
19. Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases

(from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol* 2008;102:1540–1544.
20. Zittermann 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;41:105–112.
21. Liu LC, Voors AA, van Veldhuisen DJ, van der Veer E, Belonje AM, Szymanski MK, Sillje HH, van Gilst WH, Jaarsma T, de Boer RA. Vitamin D status and outcomes in heart failure patients. *Eur J Heart Fail* 2011;13:619–625.
22. Boxer RS, Kenny AM, Cheruvu VK, Vest M, Fiutem JJ, Pina IL. Serum 25-hydroxyvitamin D concentration is associated with functional capacity in older adults with heart failure. *Am Heart J* 2010;160:893–899.
23. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL; ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;29:2388–2442.
24. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996;17:343–346.
25. Oren Y, Shapira Y, Agmon-Levin N, Kivity S, Zafrir Y, Altman A, Lerner A, Shoenfeld Y. Vitamin D insufficiency in a sunny environment: a demographic and seasonal analysis. *Isr Med Assoc J* 2010;12:751–756.
26. Zittermann A, Schleithoff SS, Gotting C, Dronow O, Fuchs U, Kuhn J, Kleesiek K, Tenderich G, Koerfer R. Poor outcome in end-stage heart failure patients with low circulating calcitriol levels. *Eur J Heart Fail* 2008;10:321–327.
27. Schierbeck LL, Jensen TS, Bang U, Jensen G, Kober L, Jensen JE. Parathyroid hormone and vitamin D—markers for cardiovascular and all cause mortality in heart failure. *Eur J Heart Fail* 2011;13:626–632.
28. Pilz S, Tomaschitz A, Drechsler C, Dekker JM, Marz W. Vitamin D deficiency and myocardial diseases. *Mol Nutr Food Res* 2010;54:1103–1113.
29. 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;110:229–238.
30. O'Connell TD, Berry JE, Jarvis AK, Somerman MJ, Simpson RU. 1,2 5-Dihydroxyvitamin D3 regulation of cardiac myocyte proliferation, hypertrophy. *Am J Physiol* 1997;272:H1751–H1758.
31. Guillot X, Semerano L, Saidenberg-Kermanac'h N, Falgarone G, Boissier MC. Vitamin D and inflammation. *Joint Bone Spine* 2010;77:552–557.
32. Selles J, Bellido T, Boland R. Modulation of calcium uptake in cultured cardiac muscle cells by 1,25-dihydroxyvitamin D3. *J Mol Cell Cardiol* 1994;26:1593–1599.
33. Beuckelmann DJ, Nabauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. *Circulation* 1992;85:1046–1055.
34. Xiang W, Kong J, Chen S, Cao LP, Qiao G, Zheng W, Liu W, Li X, Gardner DG, Li YC. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin–angiotensin systems. *Am J Physiol Endocrinol Metab* 2005;288:E125–E132.
35. Pilz S, Tomaschitz A, Drechsler C, Ritz E, Boehm BO, Grammer TB, Marz W. Parathyroid hormone level is associated with mortality and cardiovascular events in patients undergoing coronary angiography. *Eur Heart J* 2010;31:1591–1598.
36. Hagstrom E, Hellman P, Larsson TE, Ingelsson E, Berglund L, Sundstrom J, Melhus H, Held C, Lind L, Michaelsson K, Arnlov J. Plasma parathyroid hormone and the risk of cardiovascular mortality in the community. *Circulation* 2009;119:2765–2771.
37. Pilz S, Tomaschitz A, Marz W, Drechsler C, Ritz E, Zittermann A, Cavalier E, Pieber TR, Lappe JM, Grant WB, Holick MF, Dekker JM. Vitamin D, cardiovascular disease and mortality. *Clin Endocrinol (Oxf)* 2011;75:575–584.
38. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, Bjelakovic M, Gluud C. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev* 2011.
39. 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;83:754–759.
40. 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.
41. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Combined calcium and vitamin D supplementation is not superior to calcium supplementation alone in improving disturbed bone metabolism in patients

with congestive heart failure. *Eur J Clin Nutr* 2008;62:1388–1394.
42. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. 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;96:53–58.
43. Zittermann A, Fischer J, Schleithoff SS, Tenderich G, Fuchs U, Koerfer R. Patients with congestive heart failure and healthy controls differ in vitamin D-associated lifestyle factors. *Int J Vitam Nutr Res* 2007;77:280–288.
44. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab* 2001;86:1633–1637.

Acknowledgements
We wish to acknowledge the staff of Clalit Health Services for their cooperation in providing data for this study.

Eur J Heart Fail. 2012;14(4):357-366.