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Vitamin D status and the risk of major adverse cardiac and cerebrovascular events in cardiac surgery

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Aims A significant proportion of cardiac surgical patients develop critical post-operative complications. We aimed to investigate the association of pre-operative 25-hydroxyvitamin D (25(OH)D) levels with major cardiac and cerebrovascular events (MACCE) in cardiac surgical patients.

Methods and results From January 2010 to August 2011, we consecutively measured circulating 25(OH)D in 4418 operated patients. Of the study cohort, 38.0% had deficient 25(OH)D values (<30 nmol/L) and additional 32.3% had insufficient values (30–49.9 nmol/L), whereas only 3.1% had values >100 nmol/L. The incidence of MACCE was 11.5%. In multivariable-adjusted logistic regression models, the odds ratio of MACCE at deficient, inadequate, and high 25(OH)D levels was 2.23 [95% confidence interval (CI): 1.31–3.79], 1.73 (95% CI: 1.01–2.96) and 2.34 (95% CI: 1.12–4.89), respectively, compared with 25(OH)D levels of 75–100 nmol/L. A U-shaped association with circulating 25(OH)D was also present for duration of mechanical ventilatory support and intensive care unit stay. Multivariable-adjusted 6- and 12-month mortality were higher in patients with deficient 25(OH)D levels compared with patients with 25(OH)D levels of 75–100 nmol/L.

Conclusion Deficient 25(OH)D levels are prevalent in cardiac surgical patients in Central Europe and are independently associated with the risk of MACCE. Further research should clarify the potential of vitamin D supplements in reducing cardiovascular risk in vitamin D-deficient patients and also the mechanisms leading to adverse effects on the cardiovascular system in the small group of patients with 25(OH)D levels >100 nmol/L.

Trial registration information: Clinicaltrials.gov identifier number: NCT01552382.

Keywords Vitamin D • Cardiac surgery • Kidney function • Major adverse cardiac and cerebrovascular event • Mortality • Survival

Introduction

Low cardiac output syndrome (LOS), myocardial infarction (MI), and in-hospital death are critical post-operative complications in cardiac surgery, affecting 8–12% of operated patients.[1] Approximately 1–3% of patients also develop a potentially devastating post-operative stroke.[2]

Determination of factors that can influence the aforementioned major cardiac and cardiovascular events (MACCEs) is of paramount importance. Recent evidence suggests that vitamin D deficiency [e.g. circulating 25-hydroxyvitamin D levels (25(OH)D) values <30 nmol/L] is independently associated with total and cardiovascular mortality,[3] fatal stroke,[4] sudden cardiac death,[5,6] and death due to heart failure.[5] More importantly, vitamin D-supplemented heart failure patients show improved survival.[7]

EuroSCORE is a key predictor of MACCEs.[8] Some EuroSCORE factors such as age, sex, chronic pulmonary disease, MI, and poor kidney function are also related to vitamin D status.[9–12] Deficient

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circulating 25(OH)D levels are widespread across the world.[13] In Europe, the prevalence of vitamin D deficiency is ~15% in adolescents,[14] 20–40% in general practices,[15,16] and up to 75% and more in nursing home residents.[17]

The effect of pre-operative 25(OH)D status on clinical outcome in cardiac surgery is currently not known. We therefore aimed to investigate in a cohort of cardiac surgical patients the association of pre-operative 25(OH)D levels with MACCE.

Methods

Patients and study design

Since January 2010, we have measured serum 25(OH)D levels as a cardiovascular risk marker at our institution (geographic latitude: 52°N). Measurements were consecutively performed in fasting pre-operative blood samples in all outward patients hospitalized for cardiac surgery. All samples were collected on the last day before cardiac surgery between January 2010 and August 2011. Patients with heart transplants, pacemaker/defibrillator implants and patients under 18 years of age were excluded. In 473 cardiac surgical patients with 25(OH)D measurements data sets were incomplete, e.g. baseline or outcome parameters were missing. Altogether, a total of 4418 patient samples could be included in the present analysis. The vast majority of patients were Caucasians. The investigation was performed according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Statement for cohort studies (www.strobe-statement.org). The study was approved by the local ethics committee and was registered at clinicaltrials.gov as NCT01552382.

Data collection

The database consists of pre-, peri-, and post-operative data that were prospectively collected in all cardiac surgical patients at our institution. Besides 25(OH)D, 38 additional parameters were retrieved for each patient. Among them, 23 patient and surgical characteristics [age, sex, body mass index BMI), height, weight, left ventricular ejection fraction, smoking, concomitant diagnoses such as myocardial infarction, stroke, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), haemofiltration, peripheral arterial occlusive disease (PAOD) stage II or higher, previous thoracic surgery, urgency of surgery, on-pump/off-pump surgery, type of surgery, use of medications such as diuretics, aspirin, ACE-inhibitors, statins, and clopidogrel), six biochemical parameters (calcium, creatinine, glucose, triglycerides, total cholesterol, and C-reactive protein), six major event categories (in-hospital death, post-operative MI, LOS, stroke, 6-, and 12-month mortality), and three other outcome parameters (duration of ventilatory support, intensive care unit stay, and in-hospital stay) were assessed. Data quality was controlled by checking diagnoses with data of the hospitalizing physician. Outcome parameters were checked with the data of the medical controlling of our clinic.

Primary endpoint

The primary endpoint was the rate of MACCEs, defined as in-hospital death, MI, LOS, or stroke. This composite endpoint was a priori chosen because vitamin D deficiency is independently associated with total and cardiovascular mortality,[3] fatal stroke,[4] MI,[9] and sudden cardiac death,[5,6] the latter being particularly influenced by LOS. Myocardial infarction was considered to have occurred in cases of new persistent ST-segment changes. Low cardiac output syndrome was defined as a cardiac index $\leq$2.5 L/min/m^2 or mixed venous oxygen blood saturation (SvO_2) $\leq$50% requiring high-dose inotropic support and/or the need of mechanical circulatory support. A stroke was considered present when a clinically manifest motoric, sensory, or cognitive neurological deficit was recorded due to a cerebrovascular event. All events were assessed until discharge.

Secondary endpoints

Secondary endpoints were the duration of mechanical ventilatory support, intensive care unit (ICU) stay, in-hospital stay, and 6- and 12-month mortality.

Biochemical analyses

Circulating 25(OH)D levels were analysed by the autoanalyzer Liaison (DiaSorin, Stillwater, MN, USA). The Liaison assay reveals very similar 25(OH)D results compared with the liquid chromatography tandem mass spectrometry method,[18] which is considered the gold standard. The measuring range lies between 10 and 375 nmol/L. Values below 10 nmol/L were considered 9.9 nmol/L. Calcium, creatinine, glucose, triglycerides, cholesterol, and C-reactive protein were measured using the Architect Autoanalyzer (Abbott, Wiesbaden, Germany). Glomerular filtration rate (eGFR) was estimated using the creatinine-based modification of diet in renal disease formula.

Statistics

Categorical variables were summarized as frequencies and percentages; continuous variables were summarized as means and SDs. We used the χ^2 test and analysis of variance, respectively, to assess group-specific differences in categorical variables and continuous variables. We tested normal distribution of the data using the Kolmogorov–Smirnov test. Normal distribution was considered if probability values were >0.05. Non-normally distributed data were logarithmically transformed before analysis.

We graphically evaluated the unadjusted association between pre-operative 25(OH)D levels and MACCE using restricted cubic spline function. Multiple logistic regression analysis was carried out to assess the independent relationship between pre-operative 25(OH)D category and MACCE. According to published data,[19–21] we used the following cut-off values for classifying vitamin D status: risk of deficiency (<30 nmol/L), risk of inadequacy (30–49.9 nmol/L), borderline status (50–74.9 nmol/L), adequacy (75–100 nmol/L), and potentially harmful (>100 nmol/L, to convert nanomolar to nanogram per millilitre divide by 2.496). The group with adequate vitamin D status was used as the reference group. We performed unadjusted analyses and estimated age- and sex-adjusted models, as well as multivariable models to examine the association between vitamin D status and the incidence of MACCE. Inclusion in the multivariable models was based on a priori determination of potential confounders of the association between 25(OH)D levels and MACCE. Covariates used for adjustment in multivariable models included concomitant diagnoses (previous cardiac surgery, previous myocardial infarction, diabetes mellitus, COPD, hypertension, previous stroke, haemofiltration, and PAOD), smoking, medications (diuretics, ACE-inhibitors, statins, clopidogrel, and aspirin), type of surgery [coronary artery bypass grafting (CABG), valve surgery, combined CABG and valve surgery, aortic surgery, on-pump/off-pump surgery), urgency of surgery, BMI, left ventricular ejection fraction, the logistic EuroSCORE, kidney function (eGFR in mL/min/1.73 m^2), blood lipids, blood glucose, and inflammatory processes (C-reactive protein in mg/dL). We calculated absolute (incidence) rates and odds ratios (ORs) and corresponding 95% confidence intervals (CIs). In sensitivity analyses, we tested the reliability of our cut-off values by dividing the subgroup of patients with deficient

25(OH)D levels further into patients with severe deficiency (<15 nmol/L) and less severe deficiency (15–29.9 nmol/L).

For evaluating the association of 25(OH)D categories with secondary endpoints (duration of mechanical ventilatory support, ICU stay, and in-hospital stay), we used a two-factor analysis of covariance with the aforementioned patients and surgery characteristics as covariates. We performed multivariable-adjusted Cox regression analysis, including adjustment for season of blood sampling, to assess hazard ratios of 6- and 12-month mortality. Patients with incomplete follow-up were censored. All *P* values are reported two-sided. We considered a *P*-value of <0.05 as statistically significant. Analyses were performed using the statistical software package 'Predictive Analysis SoftWare' (PASW), version 18 (Chicago, IL, USA) and R 2.15.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Figure 1 illustrates the percentages of patients in different pre-operative 25(OH)D categories. Of the study cohort, 38.0% had deficient 25(OH)D values and additional 32.3% had insufficient values, whereas only 3.1% had values >100 nmol/L. Blood drawing in winter was most frequently associated with deficient 25(OH)D levels, whereas blood drawing in spring or summer was more often associated with adequate or high 25(OH)D levels (*Table 1*). Patients with vitamin D deficiency were more likely to be female, had a higher BMI and suffered more often from diabetes compared with patients who had adequate 25(OH)D concentrations. In addition, these patients had a higher prevalence of previous MI, were taking diuretics and ACE-inhibitors more often, and had higher blood lipid, glucose and EuroSCORE values. However, higher EuroSCORE values were also observed in patients with 25(OH)D values >100 nmol/L compared with patients with adequate 25(OH)D values.

In multivariable models, blood drawing between autumn and spring, female sex, higher BMI, diabetes, and a history of MI remained independently associated with deficient 25(OH)D levels (see Supplementary material online, *Table S1*). Season of blood drawing was also significantly associated with high 25(OH)-D levels, the probability being lowest if blood samples were collected in autumn or winter.

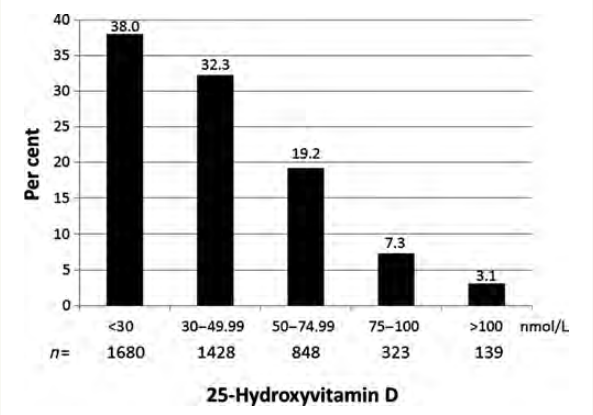

Figure 1 Numbers and percentages of cardiac surgical patients in different 25-hydroxyvitamin D categories.

Primary endpoint

Overall, the risk of MACCE was 11.5%. *Figure 2* illustrates the unadjusted relationship between pre-operative 25(OH)D levels and the composite outcome parameter MACCE. Risk was high in patients with deficient 25(OH)D levels and also in patients with 25(OH)D values >100 nmol/L. In *Table 2*, the OR of MACCE is given by subgroup of 25(OH)D category. Compared with the reference group, in those patients who had 25(OH)D levels in the deficiency range or >100 nmol/L the OR of MACCE was approximately twice as high in the unadjusted model. Results did not change substantially in multivariable-adjusted models. Sensitivity analyses also demonstrate that results did not change substantially when patients with deficient 25(OH)D levels were further divided into subgroups with severe and less severe deficiency in the fully adjusted model of MACCE (OR for severe 25(OH)D deficiency = 2.42 (95% CI: 1.39–4.26) and for less severe 25(OH)D deficiency = 2.14 (95% CI: 1.29–3.57). Incidence rates for the different components of MACCE were all lowest in the subgroup of patients with 25(OH)D levels of 75–100 nmol/L (see Supplementary material online, *Table S2*). Multivariable-adjusted OR for LOS was significantly higher and OR for in-hospital mortality tended to be higher in patients with deficient 25(OH)D levels compared with adequate 25(OH)D levels (see Supplementary material online, *Table S2*). We also imputed data of the 473 patients with missing clinical data in additional statistical analyses. Results did not differ substantially compared with the analysis which was restricted to patients with a complete data set (data not shown).

Secondary endpoints

Data on mechanical ventilatory support, ICU stay, and in-hospital stay are presented in *Table 3*, broken down by 25(OH)D category. Duration of mechanical ventilatory support and ICU stay also showed a U-shaped association with vitamin D status. In detail, patients with deficient 25(OH)D levels and with levels >100 nmol/L had a prolonged duration of mechanical ventilatory support as well as prolonged ICU stay, whereas duration of mechanical ventilatory support and ICU stay was lowest in patients with 25(OH)D levels of 75–100 nmol/L. In-hospital stay was not related to vitamin D status. Multivariable-adjusted 6- and 12-month mortality were higher in patients with deficient pre-operative 25(OH)D levels compared with adequate pre-operative 25(OH)D levels (see Supplementary material online, *Table S2*).

Discussion

This investigation could demonstrate that in cardiac surgical patients circulating 25(OH)D levels below 30 nmol/L were independently associated with poor in-hospital outcome and increased post-operative mortality. Whereas the risk of MACCE was lowest at circulating 25(OH)D levels of 75–100 nmol/L, it rose again at values >100 nmol/L. However, the latter group was very small. Generally, data are in gross agreement with earlier results of a

Table 1 Characteristics of the study cohort[a], broken down by 25-hydroxyvitamin D category

	25(OH)D: <30 nmol/L (*n* = 1680)	25(OH)D: 30–49.9 nmol/L (*n* = 1428)	25(OH)D: 50–74.9 nmol/L (*n* = 848)	25(OH)D: 75–100 nmol/L (*n* = 323)	25(OH)D: >100 nmol/L (*n* = 139)	*P* value
Gender (%, men)	59.1	70.5	76.9	76.2	69.1	<0.001
Age (years)	68.1 ± 11.7	68.5 ± 10.6	67.8 ± 10.7	68.2 ± 10.3	68.0 ± 10.7	0.684
Body mass index (kg/m^2)	27.9 ± 6.4	27.7 ± 6.0	27.2 ± 4.4	26.8 ± 4.3	26.7 ± 4.5	0.001
Smokers (%)	35.9	38.3	38.8	37.7	34.5	0.325
Left ventricular ejection fraction (%)	56 ± 13	56 ± 11	57 ± 12	56 ± 12	56 ± 12	0.114
Glomerular filtration rate (mL/min/1.73 m^2)	73.6 ± 25.3	74.8 ± 22.4	76.0 ± 22.6	72.5 ± 24.0	71.8 ± 25.1	0.051
EuroSCORE (logistic)	9.6 ± 11.6	8.8 ± 10.4	8.2 ± 10.2	7.8 ± 10.4	10.6 ± 10.5	0.002
Season of blood drawing						
Winter (%)	39.1	27.7	20.6	17.3	17.3	<0.001
Spring (%)	32.4	29.7	31.2	41.0	35.8	<0.001
Summer (%)	13.7	25.6	32.6	34.5	35.2	<0.001
Autumn (%)	14.7	16.9	15.5	7.2	11.7	<0.001
Type of surgery						
CABG (%)	41.7	37.9	35.9	43.5	28.8	0.001
Valve surgery (%)	31.9	33.6	34.4	32.1	33.1	0.730
Combined CABG and valve surgery (%)	14.5	16.3	16.3	13.9	18.7	0.382
Aortic surgery (%)	4.6	5.7	7.4	5.2	11.5	0.002
Others (%)	7.3	6.5	6.0	5.3	7.9	0.520
On-pump surgery (%)	77.3	77.4	78.8	76.9	78.4	0.915
Urgency of surgery						
Elective (%)	89.1	90.9	91.9	93.2	89.2	0.067
Urgency (%)	5.7	4.6	4.6	2.5	7.2	0.080
Emergency/ultima ratio (%)	5.2	4.5	3.3	4.3	3.6	0.430
Concomitant diagnoses						
Previous cardiac surgery (%)	8.1	8.0	7.5	9.3	15.8	0.059
Myocardial infarction (%)	18.6	18.1	12.7	13.9	15.8	0.001
Diabetes mellitus (%)	29.5	24.4	18.0	21.3	17.3	<0.001
Chronic obstructive pulmonary disease (%)	11.2	9.8	9.2	6.5	11.5	0.082
Stroke (%)	3.0	2.5	2.4	0.9	1.4	0.210
Renal replacement therapy (%)	2.0	1.5	1.2	2.2	5.0	0.023
Peripheral arterial occlusive disease (%)	9.5	9.7	7.8	9.3	12.2	0.399
Hypertension (%)	76.7	78.6	75.1	73.2	76.4	0.172
Biochemical parameters						
Calcium (mmol/L)	2.39 ± 0.13	2.39 ± 0.12	2.39 ± 0.12	2.39 ± 0.11	2.40 ± 0.11	0.590
C-reactive protein (mg/dL)	1.12 ± 2.63	0.97 ± 2.41	0.80 ± 2.03	1.17 ± 2.92	1.12 ± 2.03	0.019
Glucose (mg/dL)	123 ± 49	118 ± 45	113 ± 35	114 ± 39	114 ± 33	<0.001
Triglycerides (mg/dL)	164 ± 119	149 ± 86	134 ± 70	136 ± 75	124 ± 50	<0.001
Total cholesterol (mg/dL)	197 ± 48	194 ± 45	186 ± 45	184 ± 39	182 ± 40	<0.001
Medications						
Diuretics (%)	51.9	47.2	41.8	46.3	44.6	<0.001
Angiotensin-converting enzyme inhibitors (%)	51.2	51.7	44.9	49.1	40.3	0.002
Clopidogrel (%)	10.7	8.0	7.9	8.3	11.5	0.646
Aspirin (%)	52.7	50.2	52.5	50.3	51.1	0.045
Statins (%)	54.5	54.8	56.9	53.8	55.7	0.802

CABG, coronary artery bypass grafting.
[a]Mean ± SD or percentage of observations when appropriate.

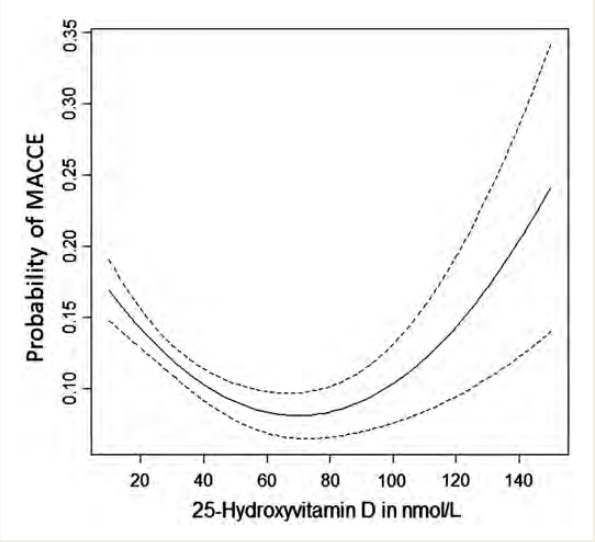

Figure 2 Spline function graph of the unadjusted relationship between pre-operative 25-hydroxyvitamin D concentration and probability of the composite adverse outcome. Top and bottom lines represent the 95% confidence interval of the relationship.

U-shaped or inverse J-shaped association between 25(OH)D and fatal outcome.[10,16,20,22] Nonetheless, to the best of our knowledge this study demonstrates for the first time a significant increase in cardiovascular morbidity and mortality at 25(OH)D levels >100 nmol/L. Our results concur with a recent meta-analysis of prospective cohort studies on circulating 25(OH)D levels and total mortality in the general population,[22] suggesting optimal 25(OH)D levels around 75–87.5 nmol/L.

Several beneficial vitamin D effects on the cardiovascular system have been identified and summarized. [23] Despite these findings the measurement of circulating 25(OH)D in the clinical setting is still hotly debated and has been questioned.[24] However, it is noteworthy that recent studies reported a high prevalence of adverse outcomes, including high mortality rates, in critically ill patients with deficient 25(OH)D levels.[25,26] Our results demonstrate that deficient 25(OH)D levels are very prevalent in cardiac surgical patients in Central Europe and are associated with a two-fold higher risk of MACCE compared with adequate 25(OH)D levels. It should also be noted that vitamin D was already demonstrated to reduce falls and fractures in elderly people[27,28] and that the daily dose for fracture prevention should be 800–2000 international units. Justification for the prevention and treatment of vitamin D deficiency needs only one proven benefit and these are (at least) the beneficial effects on musculoskeletal health.

Table 2 Adjusted odds ratio (OR) for MACCE by subgroup of serum 25-hydroxyvitamin D concentration

	n	MACCE, *n* (%)	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)	Model 4, OR (95% CI)
25-Hydroxyvitamin D						
<30 nmol/L	1680	241 (14.3)	2.29 (1.46–3.61)	2.24 (1.42–3.54)	2.21 (1.31–3.74)	2.23 (1.31–3.79)
30–49.9 nmol/L	1428	147 (10.3)	1.57 (0.99–2.50)	1.55 (0.97–2.47)	1.71 (1,00–2.92)	1.73 (1.01–2.96)
50–74.9 nmol/L	848	78 (9.2)	1.39 (0.85–2.27)	1.41 (0.86–2.31)	1.62 (0.92–2,83)	1.65 (094–2.91)
75–100 nmol/L	323	22 (6.8)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
>100 nmol/L	139	21 (15.1)	2.44 (1.30–4.61)	2.45 (1.30–4.64)	2.31 (1.11–4.79)	2.34 (1.12–4.89)

Model 1: unadjusted data; model 2: adjusted for age and sex; model 3: adjusted for as in model 2 and for all concomitant diagnoses and medications listed in *Table 1*, smoking, type of surgery, on-pump/off-pump surgery, urgency of surgery, BMI, left ventricular ejection fraction, blood glucose and lipids, and the logistic EuroSCORE; model 4: adjusted for as in model 3 and for kidney function (eGFR) and inflammatory processes (C-reactive protein).

Table 3 Ventilatory support, intensive care unit stay, and in-hospital stay by subgroup of 25-hydroxyvitamin D concentration

	<30 nmol/L (*n* = 1680)	30–49.9 nmol/L (*n* = 1428)	50–74.9 nmol/L (*n* = 848)	75–100 nmol/L (*n* = 323)	>100 nmol/L (*n* = 139)	*P* value[a,b]
Ventilatory support (h)	42.1 ± 143.8	33.2 ± 114.5	30.9 ± 114.7	23.9 ± 82.0	54.4 ± 166.7	0.03
ICU stay (h)	94.3 ± 209.3	77.8 ± 192.7	72.2 ± 166.3	71.8 ± 192.5	117.6 ± 259.2	0.016
In-hospital stay (days)	14.9 ± 10.0	14.6 ± 9.3	14.2 ± 8.2	14.8 ± 12.5	16.1 ± 10.6	0.710

[a]Analysis of covariance was used to compare logarithmically transformed dependent variables between the 25(OH)D categories.
[b]Included covariates: all variables listed in *Table 1* except for season of blood drawing.

Likely evidence does also exist for beneficial vitamin D effects on total mortality.[29,30] In line with our data, vitamin D administration is most effective in those patients who have deficient 25(OH)D levels.[11,31] Nevertheless, future research is still needed to clarify causality of the observed association between deficient 25(OH)D concentrations and the risk of MACCE.

The composite endpoint MACCE consists of components that are also important outcome parameters in patients with cardiovascular disease not receiving cardiac surgery.[3–6,9] In a meta-analysis of prospective cohort studies,[32] an inverse association between circulating 25(OH)D ranging from 20 to 60 nmol/L and the risk of cardiovascular disease has been demonstrated. The dose–response association indicates an up to two-fold higher relative risk of cardiovascular disease at circulating 25-OHD levels of 20 nmol/L compared with levels of 60 (to 75) nmol/L. However, this meta-analysis also recognized the need to further clarify the association between 25(OH)D >60 nmol/L and cardiovascular disease risk.

In line with earlier results,[16] only a small percentage of patients had 25(OH)D levels beyond 100 nmol/L. Nevertheless, the increased risk of MACCE in this subgroup needs particular consideration. At present, possible mechanisms of adverse cardiovascular 25(OH)D effects at levels >100 nmol/L, if any, are unclear. In our study, summer blood drawing was an independent predictor of high 25(OH)D levels. Summer blood drawing is also related to enhanced calcium absorption efficiency from the gut.[33] Excess calcium intake—and thus a high amount of absorbed calcium—have been made responsible for an enhanced risk of incident MI,[34] probably induced by a transient rise in serum calcium and subsequent vascular calcification.[35] Interestingly enough, excess vitamin D has also been made responsible for several documented and unforeseeable deaths.[36] However, hypercalcaemia, which is the hallmark of vitamin D intoxication, does not occur unless 25(OH)D levels exceed 375 nmol/L.[37] Note that fasting serum calcium levels did not differ significantly between 25(OH)D categories. Alternative explanations are also possible: high circulating 25(OH)D levels sometimes reflect low availability of the active vitamin D hormone 1,25-dihydroxyvitamin D ($1,25(OH)_2D$),[38] which has important actions on the cellular and subcellular level.[39] Thus, in some cases high 25(OH)D levels may indicate deficient instead of excess vitamin D action. Higher 25(OH)D levels have also been reported in individuals with the APOE ε 4 gene variant.[40] Since this gene variant is associated with an increased cardiovascular disease risk, high 25(OH)D levels may probably only be indicative of an increased risk of MACCE but not causally related to it.

Our study has several strengths. First, we were able to recruit a large number of patients within a relatively small period of time. This substantially reduces the risk of results being biased by progress in cardiac surgical procedures and intensive care medicine. Second, due to the short follow-up, we could reliably assess circulating 25(OH)D levels at the time when an event occurred or the patient was censored. Thus, with respect to the primary endpoint the short follow-up released us from the need to perform adjustments for season of blood drawing. Third, we were able to perform multiple adjustments for various demographically and clinically relevant data, including important surgery-related variables. Finally, the independent and U-shaped association of 25(OH)D with clinically important secondary endpoints such as duration of mechanical ventilatory support and ICU stay further underlines the assumption of a causal relationship between circulating 25(OH)D levels and clinical outcome.

Our study has the limitation that, due to the lack of $1,25(OH)_2D$ measurements, we were unable to completely resolve the question of whether excess vitamin D or deficient vitamin D action is responsible for the excess rate of MACCE in patients with 25(OH)D levels >100 nmol/L. Moreover, the study was largely restricted to Caucasians. However, a U-shaped association between 25(OH)D and total mortality has also been reported in mixed ethnic groups.[10]

In conclusion, deficient circulating 25(OH)D levels are very prevalent in cardiac surgical patients and independently associated with the risk of MACCE. Our data add to the accumulating evidence that vitamin D may have important beneficial effects on the cardiovascular system. Moreover, our data support the assumption that the target range should be 75–100 nmol/L. Nevertheless, randomized controlled trials are needed to assess causality. Clarification of the mechanisms leading to adverse effects on the cardiovascular system in the small group of patients with high 25(OH)D levels is also needed.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contribution

Study concept and design: A.Z.; acquisition of data: A.Z., J.K., J.D.; analysis and interpretation of data: A.Z., J.B.; drafting the manuscript: A.Z.; critical revision of the manuscript for important intellectual content: C.K., J.F.G.

Conflict of interest: A.Z. received speaker honoraria from DiaSorin, Germany and Abbott, Germany.

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