Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of High-Dose Vitamin D_3 on Hospital Length of Stay in Critically Ill Patients With Vitamin D Deficiency
The VITdAL-ICU Randomized Clinical Trial

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IMPORTANCE Low vitamin D status is linked to increased mortality and morbidity in patients who are critically ill. It is unknown if this association is causal.

OBJECTIVE To investigate whether a vitamin D_3 treatment regimen intended to restore and maintain normal vitamin D status over 6 months is of health benefit for patients in ICUs.

DESIGN, SETTING, AND PARTICIPANTS A randomized double-blind, placebo-controlled, single-center trial, conducted from May 2010 through September 2012 at 5 ICUs that included a medical and surgical population of 492 critically ill adult white patients with vitamin D deficiency (≤20 ng/mL) assigned to receive either vitamin D_3 (n = 249) or a placebo (n = 243).

INTERVENTIONS Vitamin D_3 or placebo was given orally or via nasogastric tube once at a dose of 540 000 IU followed by monthly maintenance doses of 90 000 IU for 5 months.

MAIN OUTCOMES AND MEASURES The primary outcome was hospital length of stay. Secondary outcomes included, among others, length of ICU stay, the percentage of patients with 25-hydroxyvitamin D levels higher than 30 ng/mL at day 7, hospital mortality, and 6-month mortality. A predefined severe vitamin D deficiency (≤12 ng/mL) subgroup analysis was specified before data unblinding and analysis.

RESULTS A total of 475 patients were included in the final analysis (237 in the vitamin D_3 group and 238 in the placebo group). The median (IQR) length of hospital stay was not significantly different between groups (20.1 days [IQR, 11.1-33.3] for vitamin D_3 vs 19.3 days [IQR, 11.1-34.9] for placebo; P = .98). Hospital mortality and 6-month mortality were also not significantly different (hospital mortality: 28.3% [95% CI, 22.6%-34.5%] for vitamin D_3 vs 35.3% [95% CI, 29.2%-41.7%] for placebo; hazard ratio [HR], 0.81 [95% CI, 0.58-1.11]; P = .18; 6-month mortality: 35.0% [95% CI, 29.0%-41.5%] for vitamin D_3 vs 42.9% [95% CI, 36.5%-49.4%] for placebo; HR, 0.78 [95% CI, 0.58-1.04]; P = .09). For the severe vitamin D deficiency subgroup analysis (n = 200), length of hospital stay was not significantly different between the 2 study groups: 20.1 days (IQR, 12.9-39.1) for vitamin D_3 vs 19.0 days (IQR, 11.6-33.8) for placebo. Hospital mortality was significantly lower with 28 deaths among 98 patients (28.6% [95% CI, 19.9%-38.6%]) for vitamin D_3 compared with 47 deaths among 102 patients (46.1% [95% CI, 36.2%-56.2%]) for placebo (HR, 0.56 [95% CI, 0.35-0.90], P for interaction = .04), but not 6-month mortality (34.7% [95% CI, 25.4%-45.0%] for vitamin D_3 vs 50.0% [95% CI, 39.9%-60.1%] for placebo; HR, 0.60 [95% CI, 0.39-0.93], P for interaction = .12).

CONCLUSIONS AND RELEVANCE Among critically ill patients with vitamin D deficiency, administration of high-dose vitamin D_3 compared with placebo did not reduce hospital length of stay, hospital mortality, or 6-month mortality. Lower hospital mortality was observed in the severe vitamin D deficiency subgroup, but this finding should be considered hypothesis generating and requires further study.

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Vitamin D deficiency is clearly associated with mortality in noncritically ill populations.[1-3] Recent systematic reviews and meta-analyses came to variable conclusions regarding the role of vitamin D supplementation on different outcomes including mortality.[4-7] However, many of the original trials did not determine baseline 25-hydroxyvitamin D levels or included individuals without deficiency.

Since the first report by Lee et al[8] in 2009, a high prevalence of low vitamin D levels has been confirmed in both adult and pediatric patients who are critically ill.[9] The majority of studies suggest that a low vitamin D status is a significant factor associated with disease severity, mortality, or a shorter survival time in the intensive care unit (ICU).[9] A few studies looked at other clinically relevant outcomes, and some, but not all, reported low vitamin D status to be associated with longer length of ICU or hospital stay[9] and a higher incidence of acute renal failure[10] and sepsis.[11]

In addition to its well-known musculoskeletal effects, vitamin D mediates other "nonclassical" effects on immune, cardiac, and vascular systems.[12] Together with its discussed anti-inflammatory properties and metabolic aspects, the potential pleiotropic effects of vitamin D have received considerable attention among intensivists.[9]

It currently remains unknown whether a low vitamin D status in patients who are critically ill reflects disease severity and a generally poor health status prior to ICU admission, or is an independent contributor to morbidity and mortality.

In our previous single-center, double-blind, randomized, placebo-controlled pilot study in a medical ICU, oral high-dose vitamin D_3 quickly corrected vitamin D deficiency without adverse effects.[13] This study, the Correction of Vitamin D Deficiency in Critically Ill Patients (VITdAL-ICU), was designed to evaluate the efficacy and safety of oral high-dose vitamin D_3 to improve outcomes of critical illness.[14]

Methods

Study Design

The justification, study design, and methods have been reported previously.[14] This trial was approved by the institutional ethical committee of the Medical University of Graz and the Austrian Agency for Health and Food Safety. In accordance with national and European Union requirements and the principles of the Declaration of Helsinki,[15] written informed consent was obtained, if possible, directly from the patient or from a legal surrogate. For patients for whom this was not possible (mechanical ventilation, septic encephalopathy, etc), the institutional ethical committee, similar to other states of the European Union, approved the use of a "surrogate consent." Informed consent was obtained at a later time point when the patient survived and regained mental capacity.

Eligibility Criteria

The study was conducted at the Medical University of Graz, a large tertiary academic center in the southeast of Austria with 1538 beds including 123 ICU beds. Patients were recruited from 5 ICUs: medical, neurological, cardiothoracic surgery, and 2 mixed-surgery units.

Patients who were 18 years or older, expected to stay in the ICU for 48 hours or more, and found to have a 25-hydroxyvitamin D level of 20 ng/mL (to convert to nmol/L, multiply by 2.496) or lower were eligible for study participation.

Exclusion Criteria

Patients who met any of the following criteria were not eligible to participate in the trial: severely impaired gastrointestinal function; other trial participation, including previous participation in the pilot trial; pregnant or lactating women; hypercalcemia (total calcium of >10.6 mg/dL or ionized serum calcium of >5.4 mg/dL [to convert both to mmol/L, multiply by 0.25]); tuberculosis; sarcoidosis; nephrolithiasis within the prior year; and patients not deemed suitable for study participation (ie, psychiatric disease, living remotely from the clinic, or prisoner status).

Randomization and Study Drug Administration

Patients were randomly assigned to either a placebo group or vitamin D_3 group in a 1:1 ratio (**Figure 1**), using the Randomizer for Clinical Trials tool developed at the Medical University of Graz.[16] The randomization block size was 8 for patients stratified according to ICU type and sex.

Because supplementation dosages of vitamin D of 400 IU/d to 4000 IU/d will not restore 25-hydroxyvitamin D levels in a reasonable time frame in ICU patients,[17] a high loading dose regimen was used in this study. This dose was justified based on the safety findings of previous studies using similar oral vitamin D_3 dosing regimens[18,19] and on data from a small, randomized pilot study involving patients in the ICU.[13]

Patients randomized to the vitamin D_3 group received a loading dose of 540 000 IU of vitamin D_3 dissolved in 45 mL of oleum arachidis (Oleovit D_3 [containing 180 000 IU of vitamin D_3 in 15 mL of oleum arachidis per bottle], Fresenius Kabi) either orally or via feeding tube. Patients randomized to the placebo group received 45 mL of oleum arachidis. The study medication was identical in color, consistency, smell, and taste. It was prepared and labeled at our medical university pharmacy.

Starting at 28 days after ingestion of the study medication, patients received 5 monthly maintenance doses of 90 000 IU of oral vitamin D_3 or respective placebo. All trial participants, investigators, and assessors were unaware of the assigned intervention. Patients of both treatment groups were allowed to receive standard vitamin D supplements via enteral nutrition, parenteral nutrition, or both (approximately 200 IU/d) at the discretion of the treating physician. Patients were requested to refrain from taking other vitamin D preparations.

Follow-up and Outcomes

We followed up all patients for vital status for 6 months after enrollment. At the 6-month telephone follow-up, the number of patients with falls, fractures, hospital readmissions, as well as respiratory tract infections, Short Form-12 (SF-12) health survey score, and the Eastern Cooperative Oncology Group

Figure 1. Flow Diagram of the VITdAL-ICU Trial

GI indicates gastrointestinal.
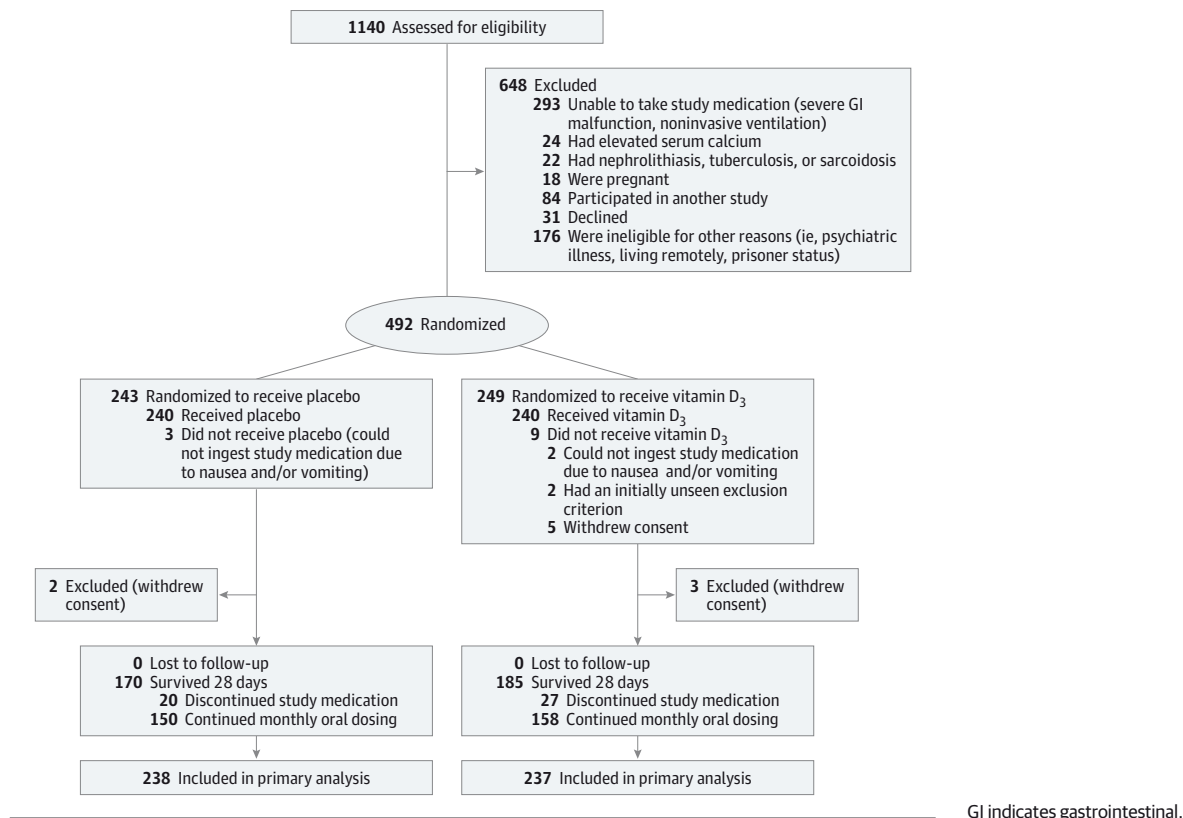
(ECOG) performance status score were recorded. At the voluntary 6-month visits at the clinic, various tests were performed additionally (hand grip strength and Timed Up and Go [TUG] test), and bone mineral density was measured at the lumbar spine and femoral neck using a bone densitometer (Lunar iDXA, GE Healthcare). Blood and urine samples were collected on days 0, 3, 7, and 28 and, where feasible, at month 6. Race/ethnicity was either self-determined or designated by a patient representative. The Charlson comorbidity index was used to predict 10-year mortality from 22 comorbid conditions with each assigned a score of 1, 2, 3, or 6. Scores were summed to provide a total score to predict mortality. The Therapeutic Intervention Scoring System (TISS-28) was used to measure the extent of nursing workload. The maximum TISS-28 score is 78 and a higher score indicates a higher nursing workload.

The primary study outcome was length of hospital stay starting from the application of the study drug to either hospital discharge or death of a patient. Based on the literature precedent whereby 25-hydroxyvitamin D levels of lower than 12 ng/mL hallmark an increased risk for rickets, osteomalacia, and decreased fractional calcium absorption,[20] a predefined subgroup analysis of patients with severe vitamin D deficiency was specified. The decision and justification to expand the analysis of the previously published protocol (online November 7, 2012; study protocol in Supplement 1)[14] to this subgroup was made during the Study Blind Review Meeting on December 20, 2012, and included in the statistical analysis plan (statistical analysis plan in Supplement 1) of February 19, 2013, before any data were analyzed starting with March 2013.

Data Management

Investigators who were blinded to study group assignments collected data. Only potential study drug–related adverse events (hypercalcemia, hypercalciuria, falls, and fractures) were monitored and recorded through the 6-month follow-up. Blinded safety assessments for 28-day mortality were performed after enrollment of 100, 240, and 360 patients and reviewed by the steering committee.

Laboratory Analysis

The 25-hydroxyvitamin D levels and 1,25-dihydroxyvitamin D levels were measured by an assay based on chemiluminescence technology (IDS-iSYS, Immunodiagnostic Systems). For 25-hydroxyvitamin D, the assay coefficients of variation for control material were 13.4% at 13 ng/mL, 10% at 31 ng/mL, and 9.4% at 64 ng/mL.[21] The laboratory routinely participates in the Vitamin D External Quality Assessment Scheme (DEQAS) program. Vitamin D deficiency was defined as a 25-hydroxyvitamin D level of 20 ng/mL or lower.[22] One hundred samples of our study were also analyzed from frozen samples (−70°C) by liquid chromatography tandem mass spectrometry (LC-MS/MS). The overall correlation of 25-hydroxyvitamin D measurements between the assay and LC-MS/MS (after subtraction of the C3-epimer fraction measured by LC-MS/MS) was $R = 0.95$; $P < .001$.

Regarding accuracy, the assay of 25-hydroxyvitamin D measurements were higher by 2.4 ng/mL at the 12 ng/mL cutoff and by 4 ng/mL at the 20 ng/mL cutoff compared with the LC-MS/MS technology.

Statistical Analysis

Sample size calculation was performed using the Mann-Whitney test. It was based on 2008 routine data collected by medical and surgical ICUs participating in our trial from patients who stayed 48 hours or more. A mean length of hospital stay of 14 days with a standard deviation of 7 days was inferred. The effect size of a 2-day shorter hospital stay was set arbitrarily and was delineated as what we decided was the smallest unit of time that would be of benefit to the patient. The number of patients needed for the study was calculated to be 468 at a 2-sided significance level of α = .05 and 80% power. Including a drop-out rate of 5%, 490 patients needed to be randomized.

Analyses were conducted in accordance with the intention-to-treat principle with no imputation for any missing data. There was less than 1% missing data.

For the primary analysis for comparing length of hospital stay between the 2 groups, we used the Mann-Whitney test. Sensitivity analysis considered time to hospital discharge as the survival end point with death as a competing event according to Fine and Gray.[23] For secondary end points, we used a t test or the Mann-Whitney test for continuous variables and the χ^2 or Fisher exact test for categorical variables. Laboratory parameters were analyzed by means of analysis of covariance, taking into account the baseline values.

Kaplan-Meier estimates of survival functions were used and compared with the use of the log-rank test. Hazard ratios (HRs) and corresponding 2-sided 95% CIs were estimated with an unadjusted Cox regression model. The same analysis was performed for the predefined subgroup and extended by a formal test for interaction, including the interaction term between the treatment and the predefined subgroups in the models. Furthermore, Cox regression models were applied adjusting for age, sex, Simplified Acute Physiology Score (SAPS) II, degree of comorbidity, and serum calcium, albumin, procalcitonin, and parathyroid hormone levels at baseline. Colinearity among confounding variables was investigated by correlation analysis and further assessed between these variables using the variance inflation factors (>4) and the tolerance statistic (<0.2). A 2-sided P value of less than .05 was considered significant, and no adjustments were made for multiple comparisons. Analyses were performed with SAS, version 9.2 (SAS institute).

Results

Patients

Enrollment started in May 2010 and was completed in March 2012, after inclusion of 492 patients. Twelve patients did not receive study medication due to various reasons (Figure 1). Follow-up continued through September 2012. The median time

from ICU admission to randomization was 2.1 days; mean (interquartile range [IQR]), 3.0 days (1.1-3.9).

Study enrollment, randomization, and follow-up are shown in Figure 1. Of the 1140 patients who were evaluated for this study, 492 patients were randomized, 480 received the allocated study medication, and 475 were included in the final analyses. Details of baseline demographic and clinical characteristics were comparable in the 2 groups (**Table 1**). The mean age of the patients was 64.6 years (SD, 14.7), and 65% (309 of

Table 1. Baseline Characteristics of the Intention-to-Treat Population

	No. (%)	
	Placebo (n = 238)	Vitamin D$_3$ (n = 237)
Age, mean (SD), y	65.3 (14.0)	63.9 (15.5)
Women[a]	83 (34.9)	83 (35.0)
White race	238 (100)	237 (100)
BMI, mean (SD)	27.1 (5.5)	27.2 (5.0)
Charlson comorbidity index, mean (SD)[b]	3.2 (2.2)	3.0 (2.2)
SAPS II at ICU admission, mean (SD)[c]	34.2 (15.7)	32.4 (15.0)
TISS-28 at study inclusion, mean (SD)[d]	38.0 (8.2)	37.7 (7.6)
Admission diagnosis		
Sepsis	18 (7.6)	19 (8.0)
Cardiovascular	32 (13.4)	28 (11.8)
Neurologic	61 (25.6)	54 (22.8)
Other nonsurgical	36 (15.1)	40 (16.9)
Cardiosurgical	44 (18.5)	45 (19.0)
Trauma	18 (7.6)	23 (9.7)
Other surgical	29 (12.2)	28 (11.8)
Admission ICU[a]		
Cardiosurgical	69 (29.0)	68 (28.7)
Neurological	58 (24.4)	58 (24.5)
Medical	53 (22.3)	52 (21.9)
Mixed surgical, 2 units	58 (24.4)	59 (24.9)
At study inclusion		
eGFR, mean (SD), mL/min/1.73m^2,[e]	65.1 (33.9)	63.7 (34.1)
Chronic kidney disease stage 5[f]	10 (4.2)	9 (3.8)
Mechanical ventilation	154 (64.7)	151 (63.7)
Norepinephrine use	126 (52.9)	131 (55.3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score; TISS-28, Therapeutic Intervention Scoring System.

[a] Criterion for randomization stratification (sex and ICU admission).

[b] The Charlson comorbidity index predicts 10-year mortality from 22 comorbid conditions with each assigned a score of 1, 2, 3, or 6. Scores are summed to provide a total score to predict mortality.

[c] The SAPS II measures the severity of disease for patients admitted to the ICU. The point score is calculated from 12 routine physiological measurements and scores can be 0 to 163 with higher scores indicating higher disease severity.

[d] The TISS-28 measures the extent of nursing workload. The maximum TISS-28 score is 78 and a higher score indicates a higher nursing workload.

[e] The eGFR calculation is based on serum creatinine level, age, sex, and race/ethnicity.

[f] Chronic kidney disease stage 5 refers to severe or end-stage kidney failure with an eGFR of lower than 15.

Table 2. Length of Stay and Mortality Outcomes for the Total and Subgroup Populations

| | Total Study Population (N = 475) | | | Prespecified Subgroup Population | | | | | |
| | | | | Severe Vitamin D Deficiency[a] (n = 200) | | | Less-Severe Vitamin D Deficiency[b] (n = 275) | | |
	Placebo (n = 238)	Vitamin D₃ (n = 237)	P Value	Placebo (n = 102)	Vitamin D₃ (n = 98)	P Value	Placebo (n = 136)	Vitamin D₃ (n = 139)	P Value
Length of stay, median (range)									
Hospital, d[c]	19.3 (0.1-154.1)	20.1 (0.2-181)	.98	19.0 (1.0-154.1)	20.1 (0.2-181)	.40	20.5 (0.1-113.9)	20.1 (0.2-133)	.47
ICU, d	10.7 (0.1-154.1)	9.6 (0.2-181)	.38	9.1 (0.8-154.1)	9.7 (0.2-181)	.98	12.3 (0.1-113.9)	9.0 (0.2-127)	.26
Mortality, No. (%)									
ICU	63 (26.5)	54 (22.8)		34 (33.3)	23 (23.5)		29 (21.3)	31 (22.3)	
HR (95% CI)	0.97 (0.67-1.39)		.86	0.70 (0.41-1.19)		.18[d]	1.32 (0.79-2.20)		.28[d]
28-d	68 (28.6)	52 (21.9)		37 (36.3)	20 (20.4)		31 (22.8)	32 (23.0)	
HR (95% CI)	0.76 (0.53-1.09)		.14	0.52 (0.30-0.89)		.02[d]	1.06 (0.64-1.73)		.83[d]
Hospital	84 (35.3)	67 (28.3)		47 (46.1)	28 (28.6)		37 (27.2)	39 (28.1)	
HR (95% CI)	0.81 (0.58-1.11)		.18	0.56 (0.35-0.90)		.01[d]	1.12 (0.72-1.77)		.61[d]
6-mo	102 (42.9)	83 (35.0)		51 (50.0)	34 (34.7)		51 (37.5)	49 (35.3)	
HR (95% CI)	0.78 (0.58-1.04)		.09	0.60 (0.39-0.93)		.02[d]	0.95 (0.64-1.41)		.81[d]
Causes of death, No. (%)									
Sepsis	30 (29.4)	26 (31.3)		16 (31.4)	12 (25.3)		14 (27.5)	14 (28.6)	
Cardiovascular	30 (29.4)	24 (28.9)	.99	13 (25.5)	9 (26.5)	.95	17 (33.3)	15 (30.6)	.98
Neurologic	19 (18.6)	14 (16.9)		8 (15.7)	4 (11.8)		11 (21.6)	10 (20.4)	
Other	23 (22.5)	19 (22.9)		14 (27.5)	9 (26.5)		9 (17.6)	10 (20.4)	

Abbreviations: HR, hazard ratio; ICU, intensive care unit.

[a] Defined as 25-hydroxyvitamin D level at study inclusion of 12 ng/mL or lower.

[b] Defined as 25-hydroxyvitamin D level at study inclusion higher than 12 ng/mL.

[c] Primary study end point.

[d] P values for interaction between the 2 subgroups: ICU mortality (P = .10), 28-day mortality (P = .06), hospital mortality (P = .04), 6-month mortality (P = .12).

the 475 patients) were men. Baseline mean 25-hydroxyvitamin D levels were 13.0 ng/mL (SD, 4.1); median, 13.1 ng/mL (IQR, 9.7-16.6). Two hundred patients (42%) had severe vitamin D deficiency defined as 25-hydroxyvitamin D levels of 12 ng/mL or lower.

Of the patients surviving 28 days, 88.2% (150 of 170 patients) in the placebo group and 85.4% (158 of 185 patients) in the vitamin D₃ group continued monthly oral doses of the study drug. No patient was lost to follow-up, and all participant data were included in the analysis according to the original study group assignments with the exception of 5 patients who withdrew consent.

Outcomes

The main outcome results are reported in **Table 2**. For the primary study outcome, length of hospital stay, the vitamin D₃ group was not statistically significantly different from the placebo group: 20.1 days (IQR, 11.1-33.3) for the vitamin D₃ group vs 19.3 days (IQR, 11.1-34.9) for the placebo group, P = .98. The same was true for length of ICU stay: 9.6 days (IQR, 4.2-17.8) for the vitamin D₃ group vs 10.7 days (IQR, 4.9-21.9) for the placebo group, P = .38. Treating death as a competing risk did not change our results. Among the patients in the vitamin D₃ group, 28.3% (95% CI, 22.6%-34.5%) died in the hospital compared with 35.3% (95% CI, 29.2%-41.7%) in the placebo group (HR, 0.81 [95% CI, 0.58-1.11], P = .18). After 6 months, 35.0% (95% CI, 29.0%-41.5%)

of the patients had died in the vitamin D₃ group and 42.9% (95% CI, 36.5%-49.4%) in the placebo group (HR, 0.78 [95% CI, 0.58-1.04]; P = .09; **Figure 2**). There were no statistically significant differences between the 2 patient groups with respect to the causes of death, the severity of disease as reflected by the TISS-28, and the percentage of patients with mechanical ventilation or vasopressor treatment (**Table 3**).

Likewise, nutritional status, use of insulin or antibiotics, and percentage of blood culture positivity were not significantly different (Table 3). No differences were noted in total serum calcium, serum ionized calcium, serum phosphate, and urinary calcium excretion levels at all time points with the exception of a 0.16 mg/dL difference seen in ionized serum calcium levels in the vitamin D₃ group at 6 months (P = .04; **Table 4** and **Table 5**). The 1,25-dihydroxyvitamin D levels were significantly higher in the vitamin D₃ group at days 3 and 7 only. Although both groups showed decreases in serum parathyroid hormone levels, this was more pronounced in the vitamin D₃ group. The results on inflammatory markers C-reactive protein (CRP) and procalcitonin, N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP) levels, and selected parameters of the blood count, renal, and liver function as well as blood glucose levels are shown in Table 4. In the vitamin D₃ group at day 28, procalcitonin and CRP levels were lower while serum albumin and hemoglobin levels were higher compared with the placebo group (all P ≤ .05; Table 4 and Table 5).

In the vitamin D_3 group, 52.0% of the patients had increases in absolute 25-hydroxyvitamin D levels higher than 30 ng/mL at day 7, a percentage that remained nearly unchanged until day 28 (Table 4 and Table 5).

Predefined Severe and Less-Severe Vitamin D Deficiency Subgroup Analysis

Baseline characteristics within the 2 subgroups (severe vitamin D deficiency subgroup [25-hydroxyvitamin D levels ≤12 ng/mL] and less-severe vitamin D deficiency subgroup [25-hydroxyvitamin D levels >12 ng/mL]) were not different between vitamin D_3 and placebo groups (eTable 1 and eTable 2 in Supplement 2). In the severe vitamin D deficiency subgroup analysis (n = 200; 42% of the study population), length of hospital or ICU stay was not different between the 2 study groups (median hospital stay: 20.1 days [IQR, 12.9-39.1] for the vitamin D_3 group vs 19.0 days [IQR, 11.6-33.8] for the placebo group, P = .40; and median ICU stay: 9.7 days [IQR, 4.2-17.3] for the vitamin D_3 group vs 9.1 days [IQR, 4.1-20.1] for the placebo group, P = .98). The HR for hospital mortality was 0.56 (95% CI, 0.35-0.90); P for interaction = .04. There were 28 deaths among 98 patients (28.6% [95% CI, 19.9%-38.6%]) in the vitamin D_3 group compared with 47 deaths among 102 patients (46.1% [95% CI, 36.2%-56.2%]) in the placebo group. For 6-month mortality, there were 34 deaths (34.7% [95% CI, 25.4%-45.0%]) in the vitamin D_3 group compared with 51 deaths (50.0% [95% CI, 39.9%-60.1%]) in the placebo group (P for interaction = 0.12; Table 2 and Figure 2). After multivariable adjustment for potential confounders including age, sex, SAPS II, Charlson comorbidity index, serum calcium, albumin, procalcitonin, and parathyroid hormone levels, the HR for hospital mortality in the severe vitamin D deficiency subgroup was 0.51 (95% CI, 0.31-0.84), P = .009; for 6-month mortality, 0.50 (95% CI, 0.31-0.79), P = .003. Although parathyroid hormone baseline level was associated with 6-month mortality, the change in parathyroid hormone levels at day 7 or 28 was not associated with mortality outcome.

In the severe vitamin D deficiency subgroup there were 19 fewer individuals with hospital death among patients treated with vitamin D_3, with a nonsignificantly smaller proportion of deaths related to sepsis and cardiovascular and neurological causes (Table 2). No significant differences were observed in other outcome parameters (Table 3). For the severe vitamin D deficiency subgroup, laboratory parameters relating to vitamin D and mineral metabolism as well as to selected inflammatory, renal, liver, and cardiac parameters were not significantly different between the placebo group and the vitamin D_3 group (eTable 3 in Supplement 2). For the less-severe vitamin D deficiency subgroup, serum and urinary calcium indices were also not significantly different at all time points (eTable 4 in Supplement 2).

6-Month Follow-Up

At the 6-month follow-up, there were no statistically significant differences between both groups. Patients with severe vitamin D deficiency at baseline did not show any significant changes compared with the placebo group, whereas patients with higher baseline 25-hydroxyvitamin D levels showed sig-

nificantly improved grip strength of the right hand as well as a better physical component summary score from the SF-12 questionnaire (eTable 5 in Supplement 2).
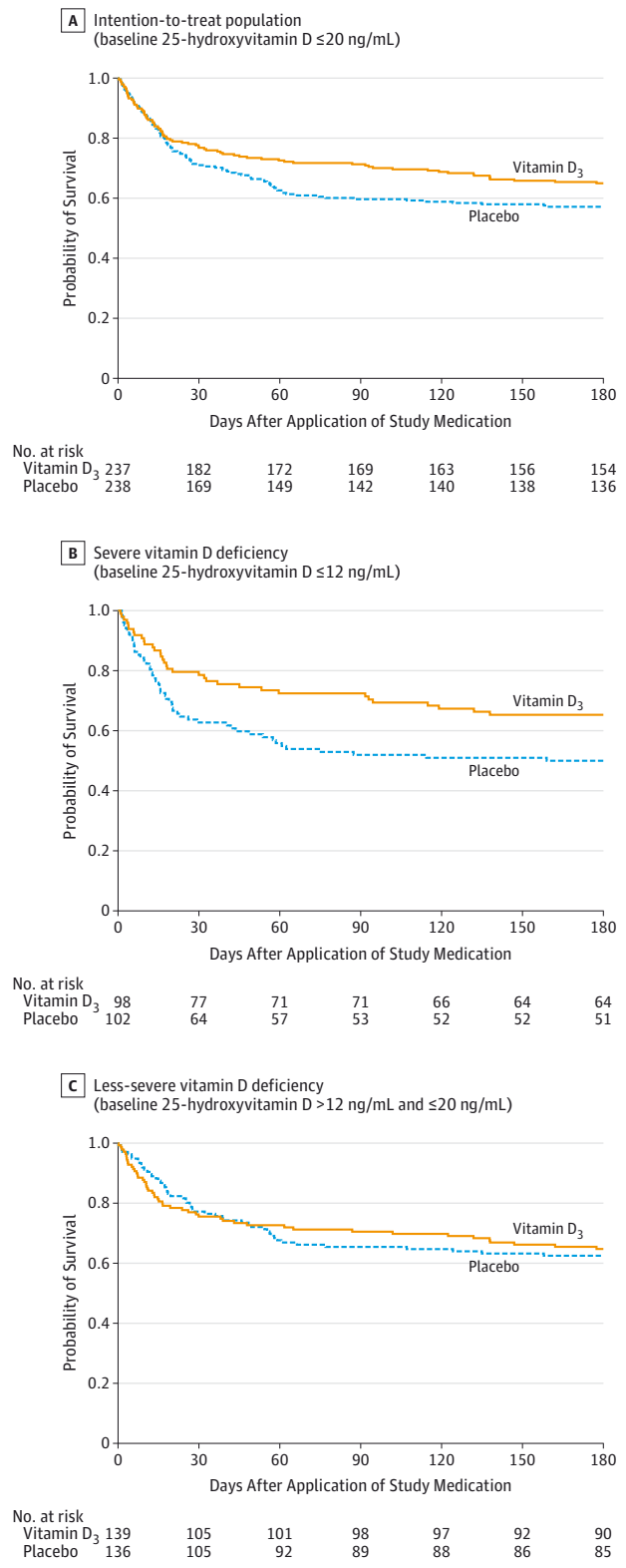
Figure 2. Survival Within 6 Months After Randomization

A Intention-to-treat population
(baseline 25-hydroxyvitamin D ≤20 ng/mL)

No. at risk

Vitamin D_3	237	182	172	169	163	156	154
Placebo	238	169	149	142	140	138	136

B Severe vitamin D deficiency
(baseline 25-hydroxyvitamin D ≤12 ng/mL)

No. at risk

Vitamin D_3	98	77	71	71	66	64	64
Placebo	102	64	57	53	52	52	51

C Less-severe vitamin D deficiency
(baseline 25-hydroxyvitamin D >12 ng/mL and ≤20 ng/mL)

No. at risk

Vitamin D_3	139	105	101	98	97	92	90
Placebo	136	105	92	89	88	86	85

Table 3. Selected Secondary Outcomes for the Intention-to-Treat and Subgroup Populations

| | Intention-to-Treat Population, No. (%) (N = 475) | | | Prespecified Subgroup Populations, No. (%) | | | | | |
| | | | | Severe Vitamin D Deficiency[a] (n = 200) | | | Less-Severe Vitamin D Deficiency[b] (n = 275) | | |
	Placebo (n = 238)	Vitamin D$_3$ (n = 237)	P Value	Placebo (n = 102)	Vitamin D$_3$ (n = 98)	P Value	Placebo (n = 136)	Vitamin D$_3$ (n = 139)	P Value
At day 6									
Insulin use[c]	92 (42.6)	83 (38.3)	.36	39 (43.3)	33 (36.7)	.36	53 (42.1)	50 (39.4)	.66
Daily dose, mean (SD), IU/d	53 (32)	60 (37)	.21	51 (31)	63 (41)	.13	54 (33)	57 (35)	.69
Antibiotics use	166 (78.3)	159 (74.0)	.29	67 (76.1)	68 (77.3)	.86	99 (79.8)	91 (71.7)	.13
At day 7									
TISS-28, mean (SD)[d]	34.9 (8.1)	35.1 (6.9)	.61	34.0 (7.8)	34.3 (8.0)	.94	35.5 (8.4)	35.6 (6.0)	.56
QTc duration, mean (SD), ms[e]	429.7 (43.5)	427.0 (39.4)	.83	434.4 (45.5)	434.9 (39.6)	.92	425.7 (41.8)	422.1 (38.9)	.42
Mechanical ventilation									
Patients	161 (67.7)	159 (67.1)	.90	69 (67.7)	62 (63.3)	.51	92 (67.7)	97 (69.8)	.70
Duration, median (range), h	167 (0.4-2494)	167 (0.5-1898)	.62	147 (0.4-2162)	157 (1.8-1898)	.76	190 (0.5-2494)	167 (0.5-1443)	.31
Tracheotomy	59 (24.8)	44 (18.6)	.10	24 (23.5)	16 (16.3)	.20	35 (25.7)	28 (20.1)	.27
Norepinephrine use	150 (63.0)	148 (62.5)	.90	68 (66.7)	59 (60.2)	.34	82 (60.3)	89 (64.0)	.52
Duration, median (range), h	81 (0.5-940)	79 (1-1368)	.57	75 (2.0-940)	73 (4.0-1368)	.40	84 (0.5-839)	87 (1-1002)	.94
Nutrition									
Enteral	191 (80.3)	188 (79.3)	.80	82 (80.4)	77 (78.6)	.75	109 (80.2)	111 (79.9)	.95
Parenteral	176 (74.0)	180 (76.0)	.62	69 (67.7)	79 (80.6)	.04	107 (78.7)	101 (72.7)	.25
Use of IV vitamin D	139 (58.4)	145 (61.2)	.54	54 (52.9)	61 (62.2)	.18	85 (62.5)	84 (60.4)	.72
Dose, mean (SD), IU/day in the ICU	140 (111)	141 (122)	.84	140 (104)	147 (129)	.91	140 (116)	137 (117)	.84
Blood cultures[f]									
Samples available	85 (35.7)	92 (38.8)	.48	35 (34.3)	39 (39.8)	.42	50 (36.8)	53 (38.1)	.82
Positivity	28 (32.9)	34 (37.0)	.58	7 (20.0)	16 (41.0)	.08	21 (42.0)	18 (34.0)	.40

Abbreviations: ICU, intensive care unit; IV, intravenous; QTc, heart rate corrected by the Bazett formula; TISS-28, Therapeutic Intervention Scoring System.

[a] Defined as 25-hydroxyvitamin D level at study inclusion 12 ng/mL or lower.

[b] Defined as 25-hydroxyvitamin D level at study inclusion higher than 12 ng/mL.

[c] Subcutaneous, intravenous, or both.

[d] The TISS-28 measures the extent of nursing workload. The maximum TISS-28 score is 78 and a higher score indicates a higher nursing workload.

[e] The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarization and repolarization.

[f] Results were thoroughly reviewed for clinical validity by 2 specialized physicians otherwise uninvolved in routine care of the study population. Contaminants such as coagulase-negative staphylococcus were not considered as positive results.

Adverse Events

No serious adverse events were observed. The highest 25-hydroxyvitamin D levels measured were 107 ng/mL on day 7 and 106 ng/mL at month 6. At month 6, 4 of 37 patients (11%) in the vitamin D$_3$ group had total serum calcium levels of higher than 10.6 mg/dL (as opposed to 1 of 43 patients [2%] in the placebo group) and 8 of 37 patients (22%) had 25-hydroxyvitamin D levels higher than 60 ng/mL. Study drug discontinuation rates were similar in the 2 groups (27 of 185 patients [14.6%] for the vitamin D$_3$ group and 20 of 170 patients [11.8%] for the placebo group).

We observed 1 patient in the vitamin D$_3$ group with a total serum calcium level of 12.0 mg/dL and an ionized serum calcium level of 6.0 mg/dL who was found to have primary hyperparathyroidism (normocalcemic at study inclusion). Another patient in the vitamin D$_3$ group inadvertently ingested the whole remaining study medication (450 000 IU) within the first month, but the patient's follow-up 25-hydroxyvitamin D level never exceeded 69 ng/mL and total serum calcium level

never exceeded 10.4 mg/dL during the remainder of the study. The number of patients with falls was similar in the 2 study groups (27 of 153 patients [17.7%] for the vitamin D$_3$ group vs 33 of 136 patients [24.3%] for the placebo group, P = .17). Two fractures occurred in each group until month 6.

Discussion

In this double-blind, randomized trial performed at 5 different ICUs of 1 tertiary hospital, administration of high-dose vitamin D$_3$ compared with placebo did not reduce hospital length of stay, ICU length of stay, hospital mortality, or 6-month mortality among patients with vitamin D deficiency who are critically ill.

Despite adequate power, the results of our primary end point (length of hospital stay) were negative for both the intention-to-treat population as well as the severe vitamin D deficiency subgroup. In the overall cohort, hospital and 6-month

Table 4. Parameters Related to Vitamin D and Mineral Metabolism of the Intention-to-Treat Population, Baseline, Day 3, and Day 7[a]

	Baseline		Day 3		P Value[b]	Day 7		P Value[b]
	Placebo	Vitamin D₃	Placebo	Vitamin D₃		Placebo	Vitamin D₃	
25-Hydroxyvitamin D, mean (SD), ng/mL	13.1 (4.3)	13.0 (4.0)	13.9 (5.0)	33.5 (18.7)	<.001	14.5 (5.1)	35.5 (20.6)	<.001
Patients by 25-hydroxyvitamin D level, No. (%)								
≤12	102 (42.9)	98 (41.4)	88 (39.8)	17 (7.7)		67 (33.2)	14 (6.9)	
13-20	136 (57.1)	139 (58.7)	102 (46.2)	43 (19.6)		109 (54)	36 (17.8)	
21-30	0 (0)	0 (0)	31 (14)	50 (22.7)		23 (11.4)	47 (23.3)	
31-60	0 (0)	0 (0)	0 (0)	87 (39.6)		3 (1.5)	79 (39.1)	
>60	0 (0)	0 (0)	0 (0)	23 (10.5)		0 (0)	26 (12.9)	
Total serum calcium, mean (SD), mg/dL	8.20 (0.80)	8.28 (0.80)	8.44 (0.76)	8.44 (0.72)	.73	8.64 (0.80)	8.68 (0.72)	.69
Maximum level	10.8	11.6	10.8	10.8		10.8	11.2	
Patients with total serum calcium level >10.6, No. (%)	1 (0.4)	3 (1)	1 (0.5)	1 (0.5)		2 (1)	2 (1)	
Serum ionized calcium, mean (SD), mg/dL	4.36 (0.28)	4.40 (0.36)	4.40 (0.32)	4.44 (0.32)	.41	4.44 (0.32)	4.48 (0.28)	.23
Maximum level	4.8	6.0	5.2	5.2		5.6	5.6	
Patients with serum ionized calcium level >5.4, No. (%)	0 (0)	2 (0.8)	0 (0)	0 (0)		1 (0.5)	1 (0.5)	
Serum phosphate, mean (SD), mg/dL	3.60 (1.22)	3.61 (1.32)	3.31 (1.05)	3.41 (1.12)	.26	3.25 (1.14)	3.36 (1.01)	.35
Maximum level	9.7	9.0	8.3	7.9		9.6	7.2	
Patients with serum phosphate level >4.5, No. (%)	45 (19)	47 (20)	28 (13)	25 (12)		17 (9)	23 (11)	
1,25-Dihydroxyvitamin D, median (range), pg/mL	10.01 (1.92-83.46)	11.15 (1.15-88.85)	11.54 (1.92-136.92)	28.08 (2.69-187.69)	<.001	9.42 (0.38-79.62)	22.31 (2.69-150.38)	<.001
PTH, median (range), pg/mL	62.1 (13.7-538.6)	60.2 (8.9-379.8)	58.1 (12.0-456.5)	51.5 (13.6-391.3)	.03	53.0 (8.3-486.7)	44.2 (8.9-297.7)	.02
Urinary calcium:creatinine ratio, median (range), mmol	0.3 (0.0-3.4)	0.2 (0.0-4.3)	0.3 (0.0-3.8)	0.2 (0.0-2.6)	.83	0.4 (0.0-3.1)	0.3 (0.0-6.1)	.31
Maximum ratio	3.4	4.3	3.8	2.6		3.1	6.1	
Patients with urinary calcium:creatinine ratio >0.6, upper limit, No. (%)	58 (27)	50 (24)	43 (24)	35 (20)		44 (30)	36 (24)	
Other biochemical parameters, mean (SD)								
C-reactive protein, median (range), mg/L	105 (0.6-419)	109 (0.8-449)	88 (0.7-475)	89 (0.6-412)	.55	55 (0.6-365)	76 (0.6-356)	.29
Procalcitonin, median (range), ng/mL	0.6 (0.0-363)	0.8 (0.0-318)	0.4 (0.0-114)	0.4 (0.0-97)	.23	0.2 (0.0-95)	0.2 (0.0-36)	.21
Leukocytes, ×10⁹/L	11.2 (5.9)	11.7 (6.2)	10.4 (5.3)	10.7 (5.9)	.94	11.2 (5.1)	11.7 (5.3)	.43
Serum hemoglobin, g/dL	10.2 (1.9)	10.1 (1.7)	10.0 (1.7)	9.9 (1.7)	.94	10.0 (1.8)	10.0 (1.7)	.66
Fibrinogen, mg/dL	465 (186)	470 (195)	551 (175)	537 (191)	.36	556 (171)	549 (177)	.65
Serum creatinine, mg/dL	1.41 (1.04)	1.48 (1.21)	1.29 (1.06)	1.45 (1.29)	.41	1.21 (0.89)	1.28 (1.24)	.71
Serum bilirubin, median (range), mg/dL	0.7 (0.1-11.4)	0.7 (0.2-37)	0.6 (0.2-17.0)	0.6 (0.2-39.3)	.81	0.6 (0.1-30.9)	0.6 (0.2-45.8)	.87
NT-proBNP, median (range), g/mL	1883 (18-35 000)	1715 (27-35 000)	2155 (26-35 000)	1595 (8-35 000)	.22	1744 (11-35 000)	1419 (6-35 000)	.81
Blood glucose, mg/dL	151 (52)	153 (52)	130 (39)	130 (36)	.73	131 (51)	126 (37)	.18
Serum albumin, g/dL	2.89 (0.54)	2.83 (0.56)	2.90 (0.53)	2.81 (0.56)	.36	2.99 (0.57)	2.90 (0.59)	.41

Abbreviations: NT-proBNP, N-terminal fragment of the prohormone brain-type natriuretic peptide; PTH, parathyroid hormone.

SI conversion factors: To convert total and ionized calcium to mmol/L, multiply by 0.25; 25-hydroxyvitamin D to nmol/L, multiply by 2.496; 1,25-dihydroxyvitamin D to pmol/L, multiply by 2.6.

[a] Total blood samples available: at baseline, 428 to 475; at day 3, 356 to 441; at day 7, 299 to 404.

[b] Analysis of covariance for differences between groups at day 3 and day 7, taking into account the baseline values.

mortality rates were numerically lower in the vitamin D₃ group, but these differences were not significant. The absolute difference in the number of survivors at 6 months was 19 for the overall cohort, and of these 17 were in the severe vitamin D deficiency subgroup. However, analysis of the causes of death revealed that the vitamin D₃ group compared with the placebo group had no differences in the proportions of deaths in all categories (sepsis, cardiovascular, neurologic, and other causes).

In the severe vitamin D deficiency subgroup analysis, there was no significant difference in hospital length of stay between the vitamin D₃ group (20.1 days) and the placebo group

Table 5. Parameters Related to Vitamin D and Mineral Metabolism of the Intention-to-Treat Population, Day 28 and Month 6[a]

	Day 28			Month 6		
	Placebo	Vitamin D₃	P Value[b]	Placebo	Vitamin D₃	P Value[b]
25-Hydroxyvitamin D, mean (SD), ng/mL	17.3 (6.9)	32.7 (19.3)	<.001	26.2 (12.8)	46.0 (17.5)	<.001
Patients by 25-hydroxyvitamin D level, No. (%)						
≤12	14 (23.3)	9 (12.5)		5 (11.6)	0 (0)	
13-20	27 (45)	15 (20.8)		9 (20.9)	2 (5.4)	
21-30	17 (28.3)	11 (15.3)		14 (32.6)	2 (5.4)	
31-60	2 (3.3)	31 (43.1)		15 (34.9)	25 (67.6)	
>60	0 (0)	6 (8.3)		0 (0)	8 (21.6)	
Total serum calcium, mean (SD), mg/dL	8.84 (0.68)	9.00 (0.60)	.11	9.56 (0.44)	9.76 (0.68)	.15
Maximum level	10.4	10.4		10.8	12.0	
Patients with total serum calcium level >10.6, No. (%)	0 (0)	0 (0)		1 (2)	4 (11)	
Serum ionized calcium, mean (SD), mg/dL	4.52 (0.28)	4.56 (0.28)	.31	4.60 (0.24)	4.76 (0.28)	.04
Maximum level	5.2	6.0		5.2	6.0	
Patients with serum ionized calcium level >5.4, No. (%)	0 (0)	1 (1.4)		0 (0)	1 (2.7)	
Serum phosphate, mean (SD), mg/dL	3.54 (1.26)	3.55 (0.84)	.85	3.26 (0.52)	3.39 (0.47)	.25
Maximum level	9.1	5.8		4.2	4.2	
Patients with serum phosphate level >4.5, No. (%)	9 (16)	7 (10)		0 (0)	0 (0)	
1,25-Dihydroxyvitamin D, median (range), pg/mL	12.12 (2.69-54.23)	14.81 (2.69-90.00)	.24	35.77 (11.54-88.46)	36.92 (4.23-102.69)	.75
PTH, median (range), pg/mL	38.0 (6.5-450.7)	33.1 (8.7-148.6)	.02	53.6 (15.5-178.5)	40.3 (14.3-161.9)	.09
Urinary calcium: creatinine ratio, median (range), mmol	0.5 (0.0-2.3)	0.7 (0.0-1.9)	.15	0.2 (0.0-0.8)	0.3 (0.0-1.2)	.29
Maximum ratio	2.3	1.9		0.8	1.2	
Patients with urinary calcium:creatinine ratio >0.6, upper limit, No. (%)	18 (40)	25 (51)		2 (5)	4 (11)	
Other biochemical parameters, mean (SD)						
C-reactive protein, median (range), mg/L	51 (0.6-316)	32 (0.6-212)	.04	3.5 (0.6-30)	2.6 (0.6-108)	.32
Procalcitonin, median (range), ng/mL	0.2 (0.0-66)	0.1 (0.0-35)	.05	0.1 (0.0-0.3)	0.1 (0.0-0.5)	.71
Leukocytes, ×10⁹/L	8.2 (3.9)	9.6 (5.2)	.32	6.9 (3.3)	7.1 (2.6)	.95
Serum hemoglobin, g/dL	10.3 (1.9)	10.8 (1.9)	.05	13.2 (1.6)	13.4 (2.0)	.92
Fibrinogen, mg/dL	459 (156)	438 (158)	.23	354 (105)	363 (109)	.65
Serum creatinine, mg/dL	1.21 (1.01)	1.15 (0.90)	.73	1.03 (0.41)	1.10 (0.39)	.72
Serum bilirubin, median (range), mg/dL	0.5 (0.1-30.4)	0.5 (0.1-10)	.17	0.6 (0.3-4.7)	0.6 (0.2-1.7)	.01
NT-proBNP, median (range), g/mL	1730 (12-35 000)	680 (13-35 000)	.38	140 (12-2109)	164 (15-4874)	.73
Blood glucose, mg/dL	131 (59)	121 (40)	.13	105 (39)	100 (28)	.42
Serum albumin, g/dL	3.13 (0.71)	3.25 (0.69)	.04	4.49 (0.48)	4.45 (0.46)	.73

Abbreviations: NT-proBNP, N-terminal fragment of the prohormone brain-type natriuretic peptide; PTH, parathyroid hormone.

SI conversion factors: To convert total and ionized calcium to mmol/L, multiply by 0.25; 25-hydroxyvitamin D to nmol/L, multiply by 2.496; 1,25-dihydroxyvitamin D to pmol/L, multiply by 2.6.

[a] Total blood samples available: at day 28, 94 to 132; at month 6, 69 to 80.

[b] Analysis of covariance for differences between groups at day 28 and month 6, taking into account the baseline values.

(19.0 days), although hospital mortality was significantly lower in the vitamin D₃ group (28.6%) compared with the placebo group (46.1%) (HR, 0.56 [95% CI, 0.35-0.90], P for interaction = .04), and remained significant with adjustment for potential confounders. The 6-month mortality rates were lower in the vitamin D₃ group (34.7%) compared with the placebo group (50.0%), but the test for interaction was not significant (P for interaction = .12).

Reasons to explain the discrepancy between reduced hospital mortality rates and similar length of stay in the severe vitamin D deficiency subgroup include the possibility that vitamin D replacement might decrease the incidence of adverse outcomes in the ICU (eg, nosocomial infections). In such a case, length of stay may remain unchanged and mortality could be expected to be lower in certain disease categories, although there were no significant differences in mortality rates across the death categories examined in our study. In addition, it is possible that in some patients with established diseases, vitamin D₃ treatment may help individuals survive but at the expense of increased length of stay, whereas in other patients, vitamin D₃ treatment might support recovery from disease, potentially leading to a decreased length of stay.

Patients with less-severe vitamin D deficiency did not exhibit a survival benefit with vitamin D_3 treatment. However, the significantly better hand grip strength and physical performance scale after 6 months suggest a potential benefit in the important recovery and rehabilitation phase. This may be a relevant finding as an increasing number of patients in the ICU survive but develop postintensive care syndrome with significant morbidity and limited treatment options.[24]

In this study, we used a high oral loading dose regimen of vitamin D_3 with the intention to restore adequate 25-hydroxyvitamin D levels within days. Previous experiences in small studies[13,18,19] suggest that such single doses of vitamin D_3 are safe. However, only half of patients treated with vitamin D_3 achieved serum 25-hydroxyvitamin D levels higher than 30 ng/mL. This low percentage of vitamin D_3 responders may have been related to critical illness–associated compromised gastrointestinal function and to renal and drug-related compromises of the hepatic cytochrome P450 (CYP450) system that is implicated in 25-hydroxylation of vitamin D_3.[25,26]

Our data suggest that the vitamin D_3 dose used in this study was safe. Mild hypercalcemia was the major adverse effect associated with high-dose vitamin D_3, but no serious adverse events were recorded. Mean calcium and phosphorus levels were similar between the placebo and vitamin D_3 group. Serum ionized calcium levels were somewhat higher in the vitamin D_3 group only at the 6-month follow-up. The 2 highest individual 25-hydroxyvitamin D levels achieved were far from levels considered to be acutely toxic (>150 ng/mL).[12,27] Individual hypercalcemia did occur in some instances in the vitamin D_3 group, but remained asymptomatic and did not require specific treatment. Renal parameters or the degree of hypercalciuria were not different between the groups. Falls and fractures were found to be increased in studies using single, annual high doses of vitamin D_3[28,29] but were not different in our study that in contrast also used a different treatment protocol with monthly maintenance doses of vitamin D_3.

This study has several limitations. First, we opted for length of stay and not mortality as the primary end point. The reason for doing so is that when the study was initiated in early 2010, mortality rates were only reported descriptively in 1 observational study of 42 patients.[8] We presumed that whatever positive effects vitamin D_3 supplementation may have could lead to a general improvement in health status and a shorter length of stay. Second, another limitation is related to external validity, in particular, the single-center design and the lack of nonwhite or pediatric patients. This may limit the generalizability of our findings, even though we treated a mixed population of adult patients who were critically ill without restriction of age, sex, or admission diagnosis. Third, the only positive finding favoring vitamin D administration, the decrease in hospital mortality rate in patients with severe vitamin D deficiency, was based on a subgroup analysis and did not constitute a primary end point. Given this, combined with the null overall effect, this finding should be interpreted as hypothesis-generating only. Fourth, our sample size might not allow for the identification of rare adverse effects of high-dose vitamin D_3; however, this would be of less importance if a clear survival advantage had been confirmed. Fifth, another limitation may have been utilization of an immunoassay for determination of 25-hydroxyvitamin D levels; however this method correlated favorably with the LC-MS/MS method.[30] Sixth, we did not assess hospital infection rates and the analysis was limited to known study drug-specific adverse events.

Conclusions

Among patients with vitamin D deficiency who are critically ill, administration of high-dose vitamin D_3 compared with placebo did not improve hospital length of stay, hospital mortality, or 6-month mortality. Lower hospital mortality was observed in a subgroup of patients with severe vitamin D deficiency, but this finding should be considered hypothesis generating and requires further study.

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