# Effect of High-Dose Vitamin $D_3$ on Hospital Length of Stay in Critically Ill Patients With Vitamin D Deficiency

JAMA. 2014;312(15):1520-1530.
doi:10.1001/jama.2014.13204

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# ABSTRUCT

- IMPORTANCE
- Low VD 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 $VD_3$ treatment regimen intended to restore and maintain normal VD status over 6 months is of health benefit for patients in ICUs.

# ABSTRUCT

- DESIGN, SETTING, AND PARTICIPANTS
- A randomized double-blind, placebo-controlled,single-center trial
- from May 2010 -Sep 2012 at 5 ICUs
- included a medical and surgical population
- 492 critically ill adult white patients with VD deficiency (≦20 ng/mL) assigned to receive either $VD_3$ (n = 249) or a placebo (n = 243).

# ABSTRUCT

- INTERVENTIONS
- $VD_3$ or placebo was given, 540 000 IU, maintenance 90 000 IU/mon, 5 months.

- MAIN OUTCOMES
- Hospital length of stay.

- Secondary outcomes
- length of ICU stay, the percentage of 25(OH)D levels higher than 30 ng/mL at day 7, hospital and 6-month mortality.
- severe VD deficiency (≦12 ng/mL) subgroup analysis

- RESULTS:
- Tn 475 (237 $VD_3$ VS 238 placebo).
- The median (IQR) length of hospital stay($VD_3$ 20.1d [IQR,11.1-33.3] vs placebo 19.3d [IQR, 11.1-34.9]; P=.98).
- Mortality:
- hospital mortality: 28.3%[95%CI, 22.6%-34.5%] for $VD_3$ vs 35.3%[95%CI, 29.2%-41.7%] for placebo; HR, 0.81 [95%CI, 0.58-1.11]; P=.18;
- 6-month mortality: 35.0%[95%CI, 29.0%-41.5%] for $VD_3$ vs 42.9%[95%CI, 36.5%-49.4%] for placebo; HR, 0.78 [95%CI, 0.58-1.04]; P=.09;

- severe VD deficiency (≦12 ng/mL) subgroup analysis
- n = 200
- length of hospital stay: 20.1 d(IQR,12.9-39.1) for $VD_3$ vs 19.0 d(IQR,11.6-33.8) for placebo.
- Hospital mortality:$VD_3$ 28(98), (28.6%[95%CI, 19.9%-38.6%]) VS placebo 47 (102), (46.1% [95%CI,36.2%-56.2%])(HR, 0.56 [95%CI, 0.35-0.90], P=.04);
- 6-month mortality:$VD_3$ 34.7%[95%CI, 25.4%-45.0%] vs placebo 50.0%[95%CI, 39.9%-60.1%];HR, 0.60 [95%CI, 0.39-0.93], P for interaction = .12).

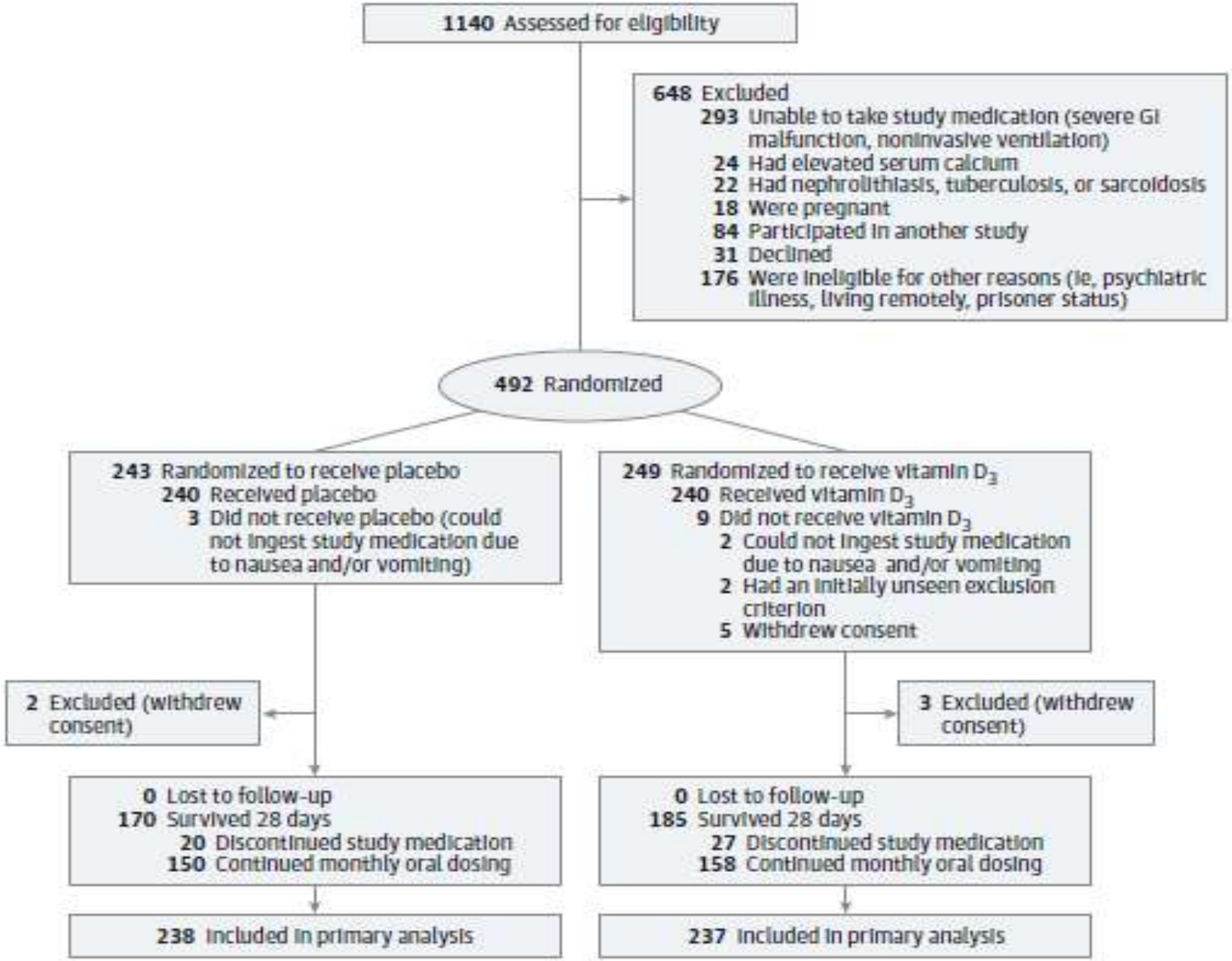
- CONCLUSIONS AND RELEVANCE
- High-dose vitamin $D_3$ compared with placebo did not reduce hospital length of stay, hospital mortality, or 6-month mortality(VD deficience crit ill)
- Lower hospital mortality was observed in these were VD deficiency subgroup, but this finding should be considered hypothesis generating and requires further study.

# Methods

- Eligibility Criteria:
- patients:the Medical University of Graz
- 1538 beds including 123 ICU beds.
- 5 ICUs: medical, neurological, cardiothoracic surgery, and 2 mixed-surgery units.
- ≥18 years, expected to stay in the ICU≥48 hs, and 25(OH)D≤ 20 ng/mL (to convert to nmol/L, multiply by 2.496) .

- Exclusion Criteria:
- 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 serumcalcium of >5.4mg/dL
- 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).

Figure 1. Flow Diagram of the VITdAL-ICU Trial



# Follow-up

- 6 months
- telephone follow-up
- the number of patients with falls, fractures, hospital readmissions,respiratory tract infections, ShortForm-12 (SF-12) health survey score, Eastern Cooperative Oncology Group (ECOG) performance status score.
- Blood and urine samples:days 0, 3, 7, and 28 and, where feasible,at month 6.
- Charlson comorbidity index:predict 10-year mortality
- Therapeutic Intervention Scoring System(TISS-28)

# Outcomes

- The primary study outcome:
- length of hospital stay starting from the application of the study drug to either hospital discharge or death of a patient.

- 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 followup.
- 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(OH)D levels and 1,25-$(OH)_2$D levels were measured by an assay based on chemiluminescence technology

- Statistical Analysis:SAS, version 9.2
- Sample size calculation,length of hospital stay:the Mann-Whitney test.
- Sensitivity analysis:Fine and Gray.
- For secondary end  points:*t* test or the Mann-Whitney test for continuous variables and the $\chi^2$ or Fisher exact test for categorical variables. Laboratory parameters :analysis of covariance,;
- Kaplan-Meier estimates of survival functions were used and compared with the use of the log-rank test.

# Results

- Patients

**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) |

- Outcomes:

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 $D_3$ (n = 237) | *P* Value | Placebo (n = 102) | Vitamin $D_3$ (n = 98) | *P* Value | Placebo (n = 136) | Vitamin $D_3$ (n = 139) | *P* Value |
| 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) | .99 | 16 (31.4) | 12 (25.3) | .95 | 14 (27.5) | 14 (28.6) | .98 |
| Cardiovascular | 30 (29.4) | 24 (28.9) | | 13 (25.5) | 9 (26.5) | | 17 (33.3) | 15 (30.6) | |
| 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) | |

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 |

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

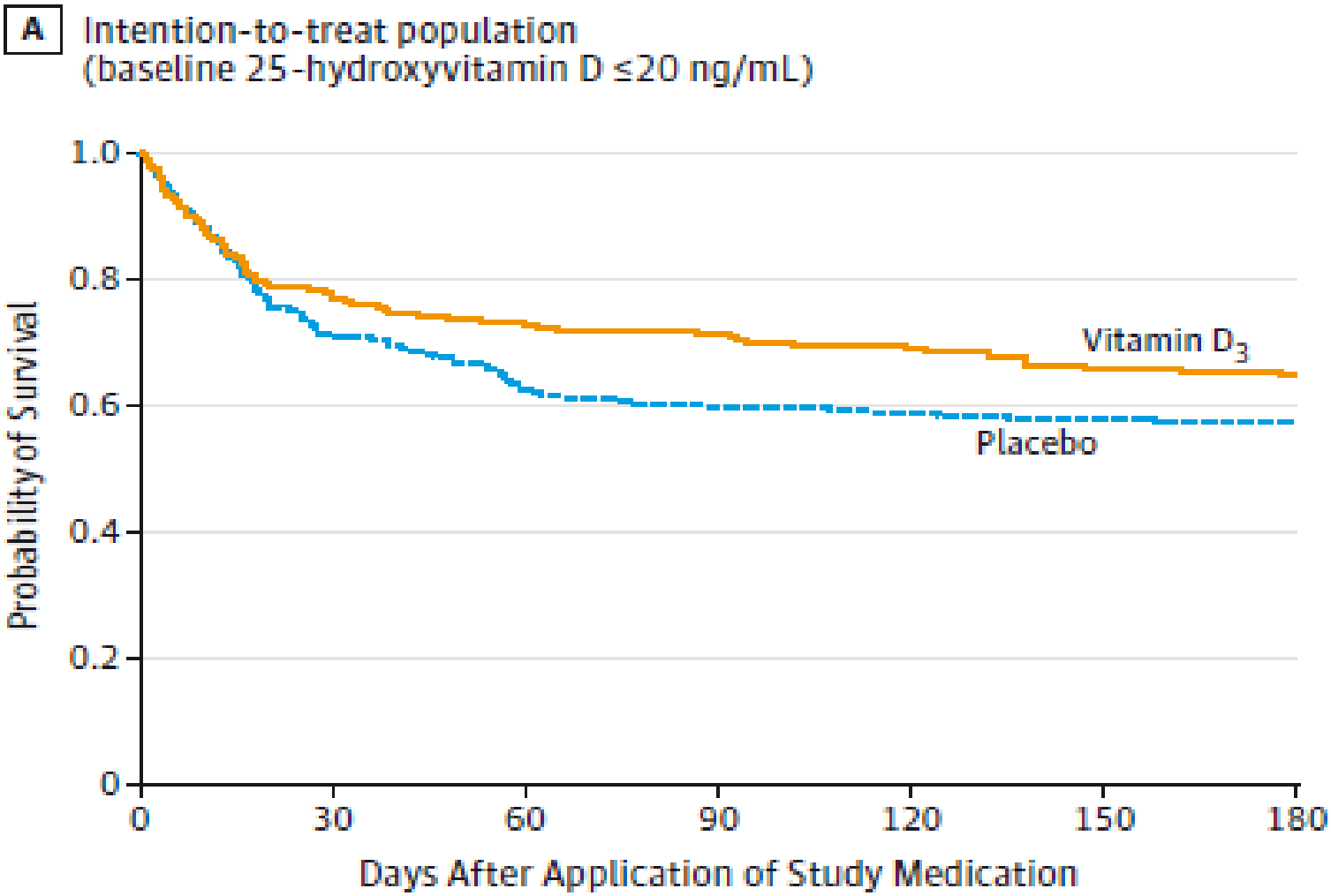
| | Baseline | | Day 3 | | P Value[b] | Day 7 | | P Value[b] |
|---|---|---|---|---|---|---|---|---|
| | Placebo | Vitamin $D_3$ | Placebo | Vitamin $D_3$ | | Placebo | Vitamin $D_3$ | |
| 25-Hydroxyvitamin D, mean (SD), ng/mL | 13.1 (4.3) | 13.0 (4.0) | 13.9 (5.0) | 33.5 (18.7) | <.001 | 14.5 (5.1) | 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, $\times 10^6$/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 |

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

| | Day 28 | | | Month 6 | | |
|---|---|---|---|---|---|---|
| | Placebo | Vitamin $D_3$ | *P* Value† | Placebo | Vitamin $D_3$ | *P* Value† |
| 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, $*10^9$/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 |

- 6-Month Follow-Up:

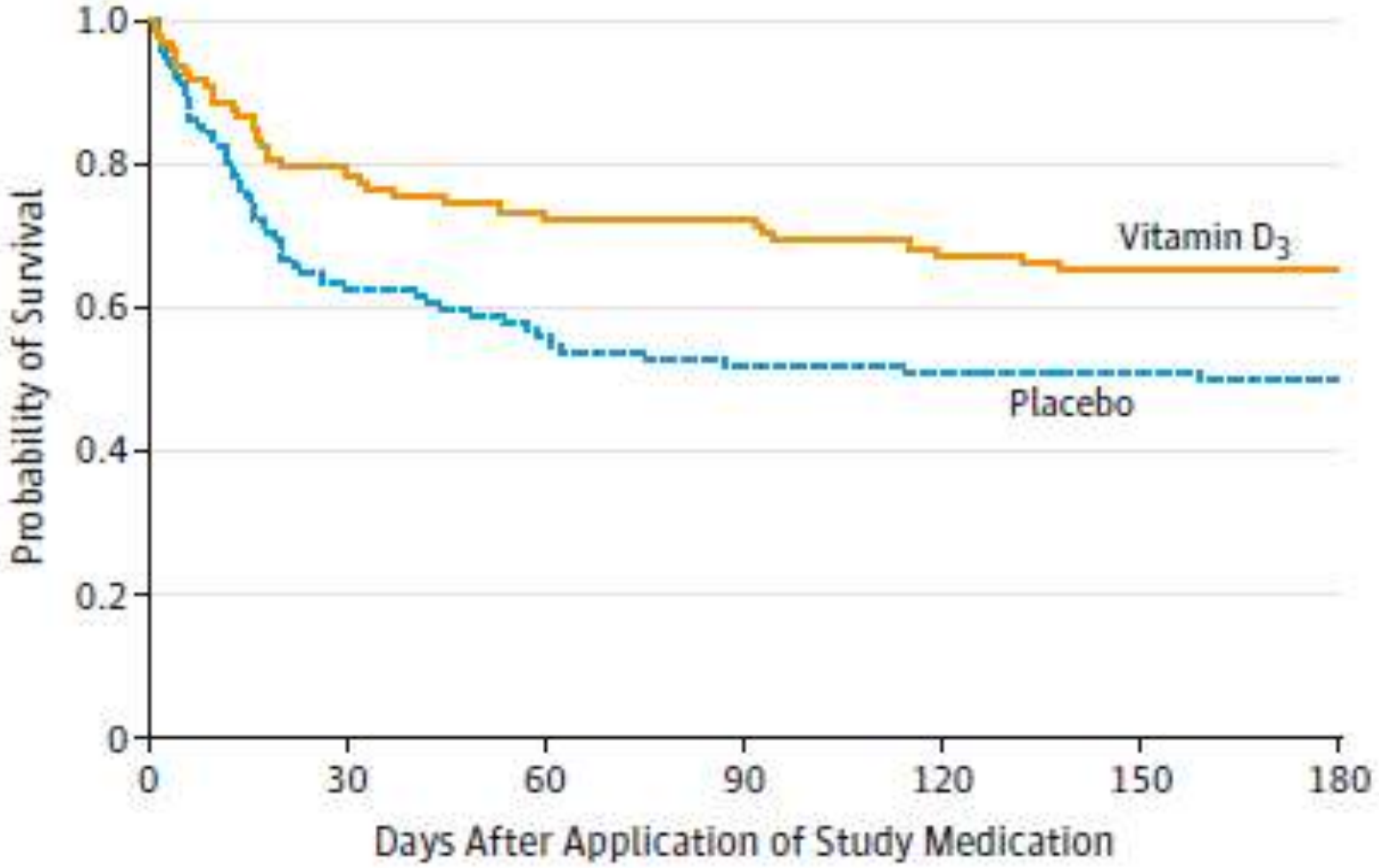
## Figure 2. Survival Within 6 Months After Randomization




No. at risk

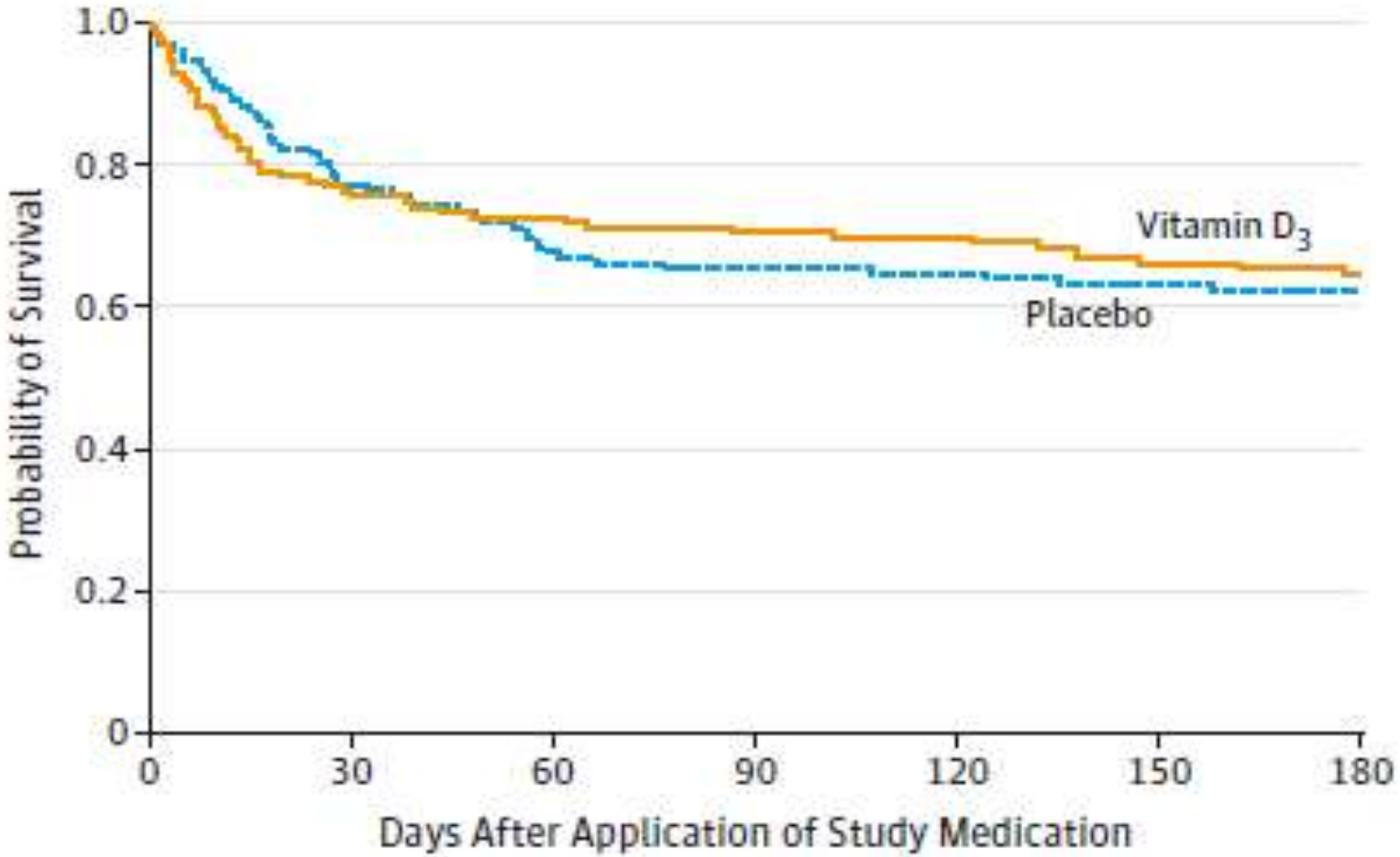
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Vitamin $D_3$ | 237 | 182 | 172 | 169 | 163 | 156 | 154 |
| Placebo | 238 | 169 | 149 | 142 | 140 | 138 | 136 |

**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 |

- Adverse Events:
- No serious adverse events were observed.

# Limitations

- First, we opted for length of stay and not mortality as the primary end point.
- Second, the single-center design and the lack of non-white or pediatric patients.
- Third, the only positive finding favoring VD administration, the decrease in hospital mortality rate in patients with severe VD deficiency, was based on a subgroup analysis
- Fourth, our sample size might not allow for the identification of rare adverse effects of high-dose vitamin D3;
- Fifth,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 vitaminD3 comparedwith 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.