12.0 Vitamin D

Question: Does supplementation with Vitamin D result in better outcomes in critically ill vitamin D deficient adult patients?

Summary of evidence: There were three level 1 studies that compared either the use of a single oral high dose of Vitamin D3 to placebo in critically ill patients that were deficient in Vitamin D (defined as blood values of <20 ng/ml or <50 nmol/L) (Amrein 2011 and 2014) or two different doses of Vitamin D3 for 5 consecutive days in ICU patients (Han 2016). For Han 2016, the results from the two intervention groups were combined for the meta-analyses.

Mortality: In the aggregated analyses, a trend towards a reduction in hospital mortality was seen with supplementation of vitamin D (RR 0.82, 95% CI 0.64, 1.06, p=0.12, heterogeneity I^2=0%; figure 1). Amrein 2014 found a trend in the reduction of 28-day (p=0.14) and 6 month (p=0.09) mortality in the Vitamin D group, but there was no effect on ICU mortality (p=0.86). In a subgroup analysis of severely vitamin D deficient (<12 ng/ml or <30 nmol/L) patients in Amrein 2014, supplementation with vitamin D was associated with a significant reduction in hospital mortality (p=0.01), 28 day mortality (p=0.02) and 6 month mortality (p=0.02) as well as a trend in reduction of ICU mortality (p=0.18).

Infections: In the one study that reported on infectious complications (Han 2016), no effect was seen on hospital acquired infections (p=0.77).

LOS: No differences in ICU length of stay (WMD -2.14, 95% CI -5.59, 1.31, p=0.22, heterogeneity I^2=0%; figure 2) or hospital length of stay (WMD -4.15, 95% CI -13.85, 5.55, p=0.40, heterogeneity I^2=56%; figure 3) was found between the two groups.

Ventilator Days: There was a trend towards a reduction in ventilator days (WMD -2.31, 95% CI -5.40, 0.78, p=0.14, heterogeneity I^2=0%; figure 4) in the groups that received Vitamin D3.

Other: Serum levels of 1,25 (OH)D showed a transient significant increase in the Vitamin D group in all 3 studies. No adverse effects such as hypercalcemia or hypercalciuria were observed in the Amrein 2011 study. Mild hypercalcemia was seen in Amrein 2014 though no serious adverse events were recorded and hypercalciuria was no different between groups. Han et al did not find any significant rise in serum calcium, creatinine and phosphorous in any of the three groups in their study.

Conclusions:

1) Vitamin D3 supplementation in critically ill adult patients may be associated with a reduction in hospital mortality, 28-day mortality and 6-month mortality, particularly in patients with a severe reduction in Vit D levels (<12 ng/ml or <30 nmol/L).
2) Vitamin D3 supplementation in critically ill adult patients may be associated with a reduction in duration of mechanical ventilation.

3) Vitamin D3 supplementation in critically ill adult patients has no effect on infections and ICU and hospital length of stay.

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.
Level 2 study: If any one of the above characteristics are unfulfilled.

Table 1. Randomized studies evaluating vitamin D supplementation in critically ill patients

Study	Population	Methods (score)	Intervention (both interventions started at same time)	Mortality # (%)†		Infections # (%)‡	
1) Amrein 2011	ICU patients with Vit D deficiency Expected LOS > 48 hrs N=25	C.Random: yes ITT: yes Blinding: double (11)	Single dose D3 (540 000 IU) via NG vs placebo	Vit D Hospital 6/12 (50)	Placebo Hospital 6/13 (46)	NR	NR
2) Amrein 2014	Medical and surgical ICU pts with Vit D deficiency. Expected LOS >48 hrs N=492	C.Random: yes ITT: yes Blinding: double (12)	Loading dose of 540 000 IU vitamin D3 in 45 mL of oleum arachidis (Oleovit D3 [containing 180 000 IU of vitaminD3 in 15mLof oleum arachidis per bottle], Fresenius Kabi) PO or NG vs 45 mL of oleum arachidis. Starting 28 days after loading dose, 5 monthly maintenance doses of 90 000 IU of oral vitamin D3 vs placebo.	ICU 54/237 (22.8) Hospital 67/237 (28.5) 28-day 52/238 (21.9)6 month 83/237 (35)	ICU 63/238 (26.5) P=0.86 Hospital 84/238 (35.3) P=0.18 28-day 68/237 (28.6) P=0.14 6 month 102/238 (42.9) P=0.09	NR	NR
3) Han 2016	Mixed ICU pts receiving EN, expected LOS ≥ 96 hrs. N=31	C.Random: yes ITT: yes Blinding: double (8)	2 experimental groups: 1 pill of 50 000 IU vitamin D3 + placebo daily for 5 days (250 000 IU total). Dissolved in sterile water and given through EN tube. 2 pills of 50 000 IU vitamin D3 daily for 5 days (500 000 IU total). Dissolved in sterile water and given through EN tube. 2 placebo pills daily for 5 days. Dissolved in sterile water and given through EN tube.	250 000 IU group Hospital 0/9 84 day 1/9 500 000 IU group Hospital 1/11 84 day 4/11	Hospital 1/10 P=0.76 84 day 2/10 P=0.33	250 000 IU groupHospital Acquired 3/9 500 000 IU group Hospital Acquired 2/11	Hospital Acquired 3/10 P=0.77

Table 1. Randomized studies evaluating vitamin D supplementation in critically ill patients (continued)

Study	LOS days		Ventilator days		Other
1) Amrein 2011	Vit D ICU 13.4 ± 11.7 (12) Hospital 23.7 ± 24.7 (12)	Placebo ICU 14 ± 16.3 (13) Hospital 23.2 ± 21.2 (13)	Vit D 10.57 ± 7.96 (10)	Placebo 13.49 ± 14.23 (11)	Serum 1,25OH-D levels Vit D group: significant increase in 8/10 patients
2) Amrein 2014	ICU 15.7 ± 20.9 (237) Hospital 26.7 ± 25.3 (237)	ICU 17.3 ± 22.3 (238) Hospital 26.7 ± 24.3 (238)	11.58 ± 14.03 (159)	13.3 ± 17.23 (161)	Serum 1,25OH-D levels (ng/ml), Exp vs Control Baseline: 13.0 vs 13.1 Day 3: 33.5 vs 13.9 Day 7: 35.5 vs 14.5 P <0.001
3) Han 2016	250 000 IU group ICU 17 ± 14 (9) Hospital 25 ± 14 (9) 500 000 IU group ICU 15 ± 10 (11) Hospital 18 ± 11 (11) Combined* ICU 15.9 ± 11.944 (20) Hospital 21.15 ± 12.423 (20) *In mean and SD*	ICU 23 ± 14 (10) Hospital 36 ± 19 (10)	250 000 IU group 12 ± 10 (9) 500 000 IU group 14 ± 10 (11) Combined* 13.1 ± 10 (20) *In mean and SD*	20 ± 15 (10)	Mean change in 25(OH)D leavels, baseline to day 7, ng/ml 250 000 IU: 26 ± 13 500 000 IU: 33 ± 16 Control: 0.4 ± 7 P < 0.001

C.Random: concealed randomization
† presumed hospital mortality unless otherwise specified
± ( ) : mean ± Standard deviation (number)
ITT: intent to treat; NA: not available
‡ refers to the # of patients with infections unless specified
*Calculated by combining results from both intervention groups

Table 2. Physical and QOL Outcomes

Study	QOL Outcomes	Physical Outcomes
2) Amrein 2014	Vitamin D / Placebo SF-12 Physical Summary Scale 40.5 ±11.3 (153) / 38.1 ± 10.5 (136) Sf-12 Mental summary scale 48.3 ± 10.2 (153) / 48.4 ± 9.9 (136) Number of readmissions 55/153 (36%) / 59/136 (43.4%) ECOG score 0 26/153 (17%) / 22/136 (16.2%) 1 43/153 (28.1%) / 35/136 (25.7%) 2 43/153 (28.1%) / 34/136 (25%) 3 28/153 (18.3%) / 30/136 (22.1%) 4 13/153 (8.5%) / 15/136 (11%)	Vitamin D / Placebo Fall (# of participants) at 6 months 33/153 (24.3%) / 27/136 (17.7%) Fractures (# of participants) at 6 months 2/153 (1.3%) / 2/136 (1.5%) Hand grip strength, mmHg, left hand 85.5 ± 31.9 (n=36) / 79.8 ± 33.6 (n=40) Hand grip strength, mmHg, right hand 92.4 ± 28.2 (n=36) / 82.8 ± 31.1 (n=40) Timed up and go test, seconds 10 (5-90) (n=35) / 10 (4-17) (n=40) BMD T-score, lumbar spine 0.16 ± 1.49 (n=36) / 0.57 ±1.30 (n=39) BMD T-score, femoral neck 0.86 ± 1.31 (n=37) / 0.88 ± 1.03 (n=39)

Figure 1. Hospital Mortality

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Amrein 2011	6	12	6	13	9.5%	1.08 [0.48, 2.45]	2011
Amrein 2014	67	237	84	238	89.6%	0.80 [0.61, 1.04]	2014
Han	1	20	1	10	0.9%	0.50 [0.03, 7.19]	2016
Total (95% CI)		**269**		**261**	**100.0%**	**0.82 [0.64, 1.06]**	
Total events	74		91				

Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)

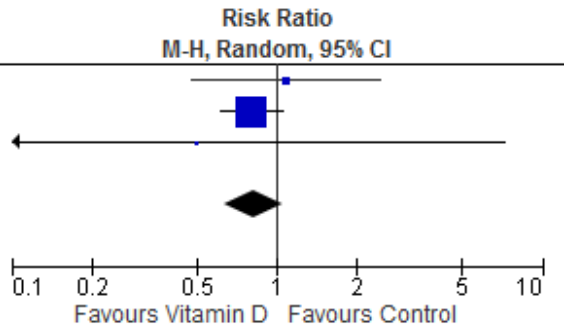

Figure 2. ICU LOS

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Amrein 2011	13.4	11.7	12	14	16.3	13	9.7%	-0.60 [-11.66, 10.46]	2011
Amrein 2014	15.7	20.9	237	17.3	22.3	238	78.7%	-1.60 [-5.49, 2.29]	2014
Han	15.9	11.944	20	23	14	10	11.6%	-7.10 [-17.23, 3.03]	2016
Total (95% CI)			**269**			**261**	**100.0%**	**-2.14 [-5.59, 1.31]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)

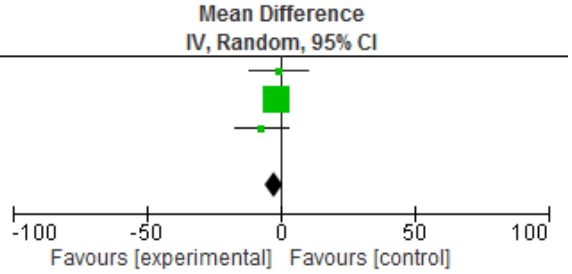

Figure 3. Hospital LOS

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Amrein 2011	23.7	24.7	12	23.2	21.2	13	19.3%	0.50 [-17.61, 18.61]	2011
Amrein 2014	26.7	25.3	237	26.7	24.3	238	52.1%	0.00 [-4.46, 4.46]	2014
Han	21.15	12.423	20	36	19	10	28.6%	-14.85 [-27.82, -1.88]	2016
Total (95% CI)			**269**			**261**	**100.0%**	**-4.15 [-13.85, 5.55]**	

Heterogeneity: Tau² = 41.82; Chi² = 4.55, df = 2 (P = 0.10); I² = 56%
Test for overall effect: Z = 0.84 (P = 0.40)

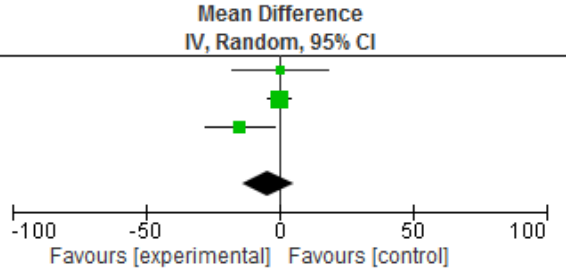

Figure 4. Mechanical Ventilation