VITAMIN D
IN CRITICAL ILLNESS

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5th East Midlands Critical Care
and Peri-Operative Medicine Conference

Crowne Plaza Hotel, Nottingham: 18-19th October 2018


CONFLICTS
FRESENIUS KABI
BBRAUN
SINAPHARM
SIEMENS

OVERVIEW

BASICS

BONE MUSCLE

PICU ICU

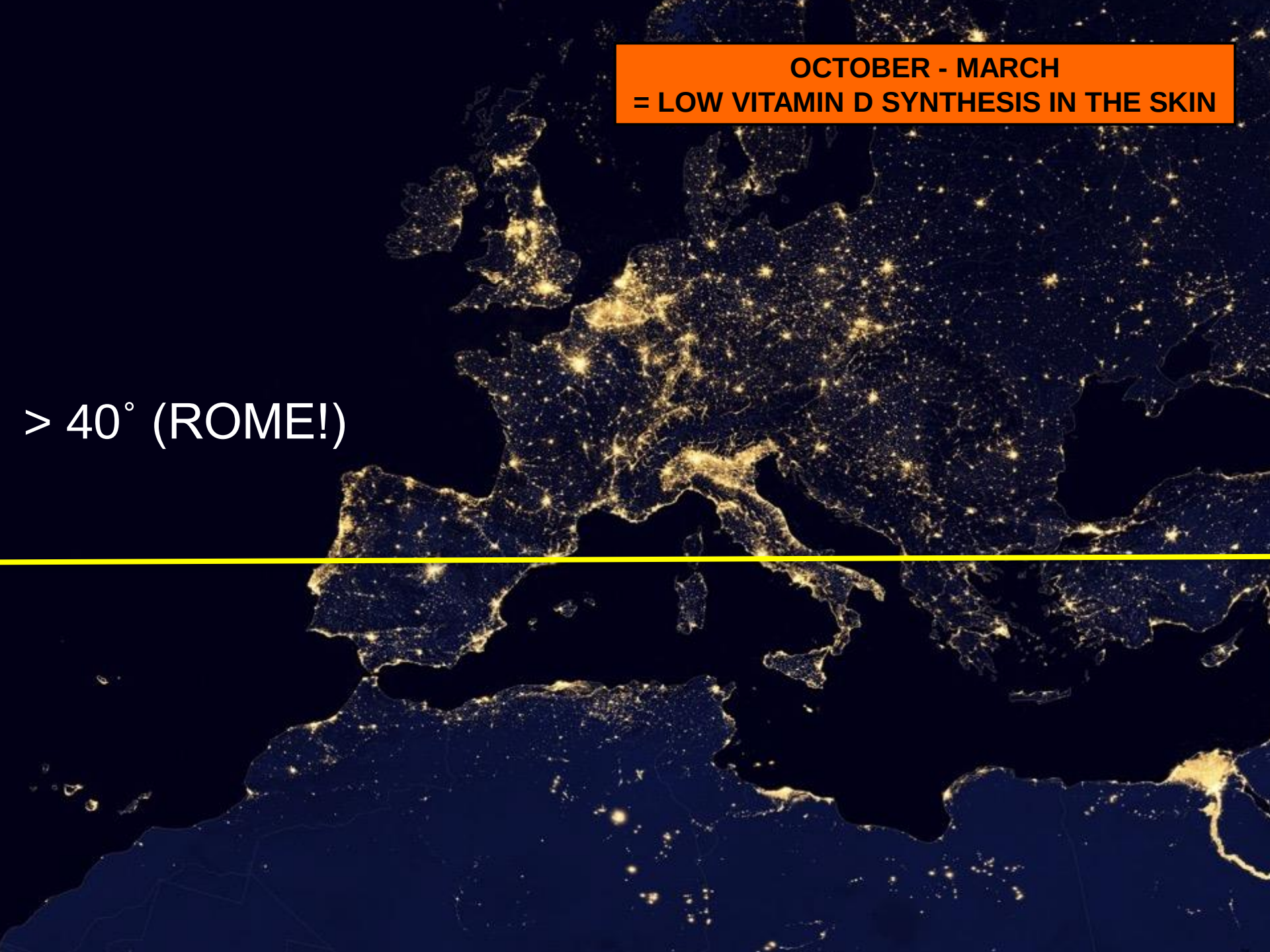
HEART

LUNG

MORTALITY

LIVER

KIDNEY

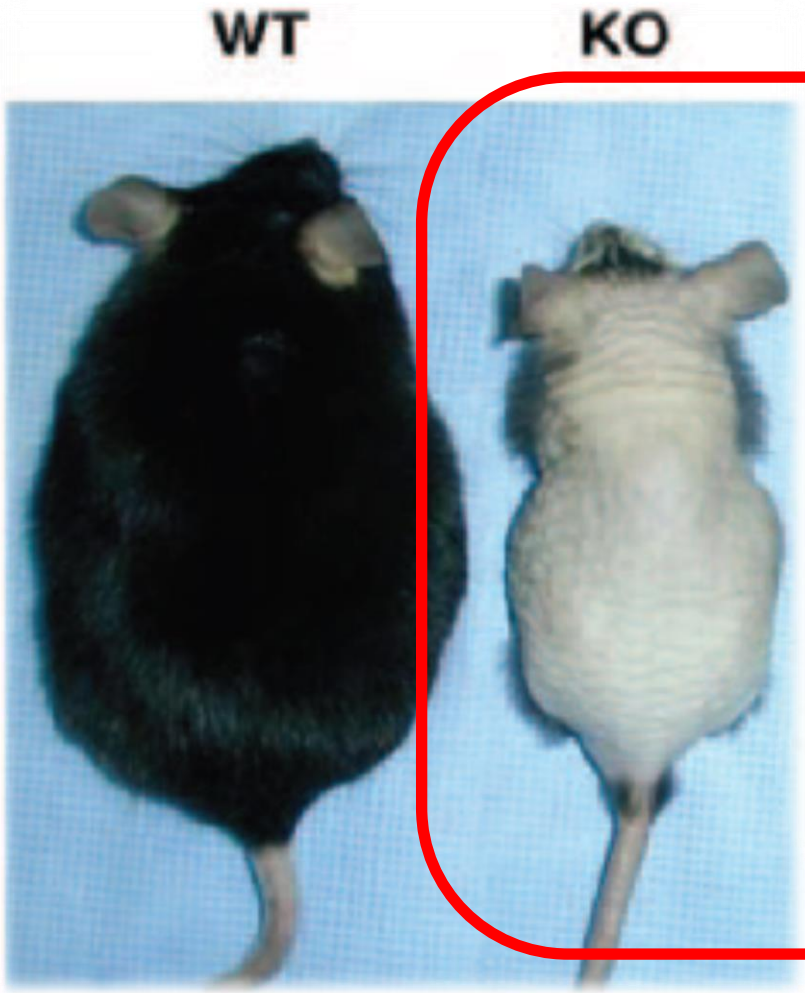

OCTOBER - MARCH
= LOW VITAMIN D SYNTHESIS IN THE SKIN
> 40˚ (ROME!)

VITAMIN D IN EUROPE

- N = 55,844
- 14 POPULATIONS
- **13%: < 30NMOL/L (12 NG/ML)**
- **40% < 50NMOL (20NG/ML)**

Cashman JD Am J Clin Nutr 2016

VDR KNOCKOUT (KO) MOUSE



Bouillon R et al. Endocrine Reviews 2008; 29:726-776

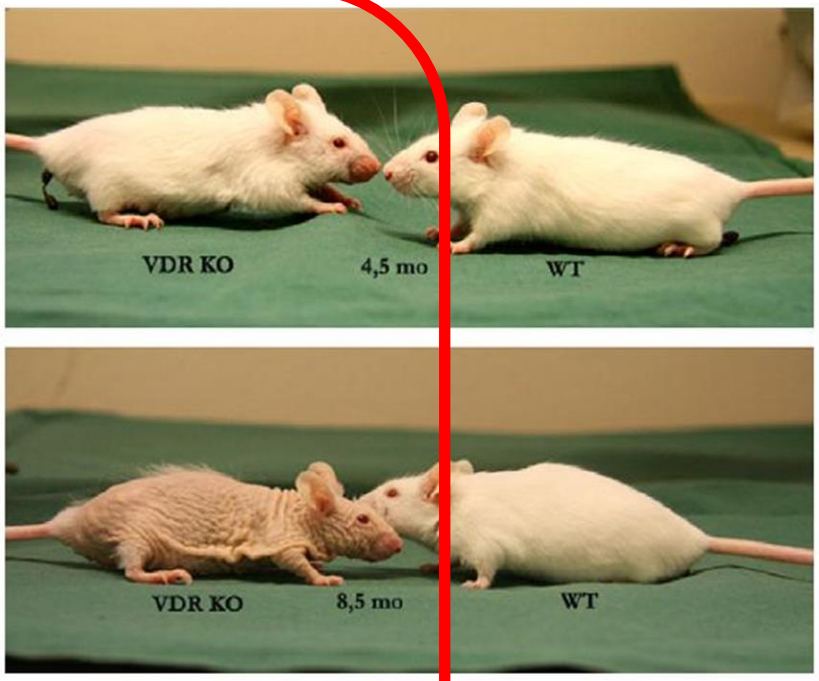
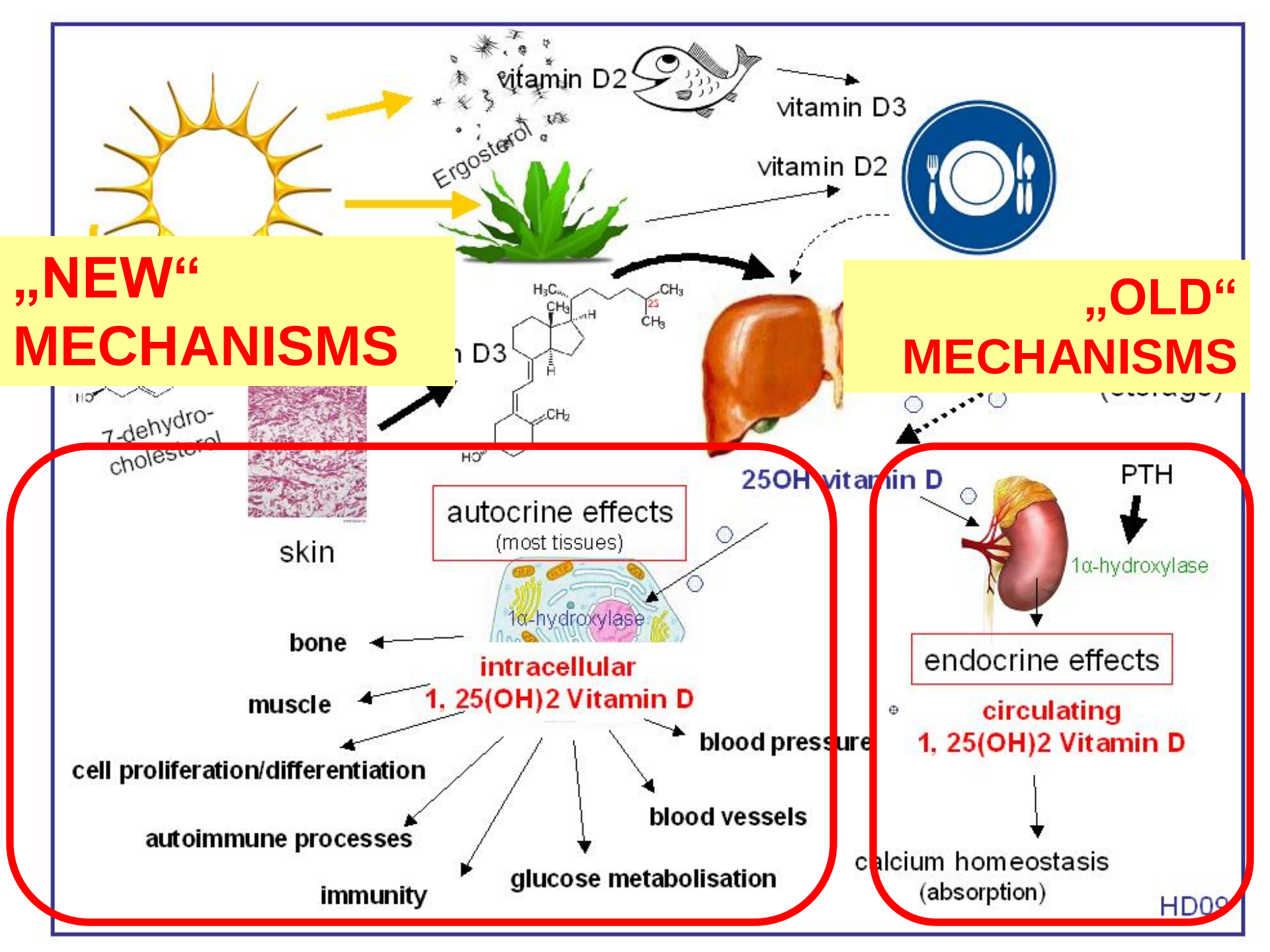


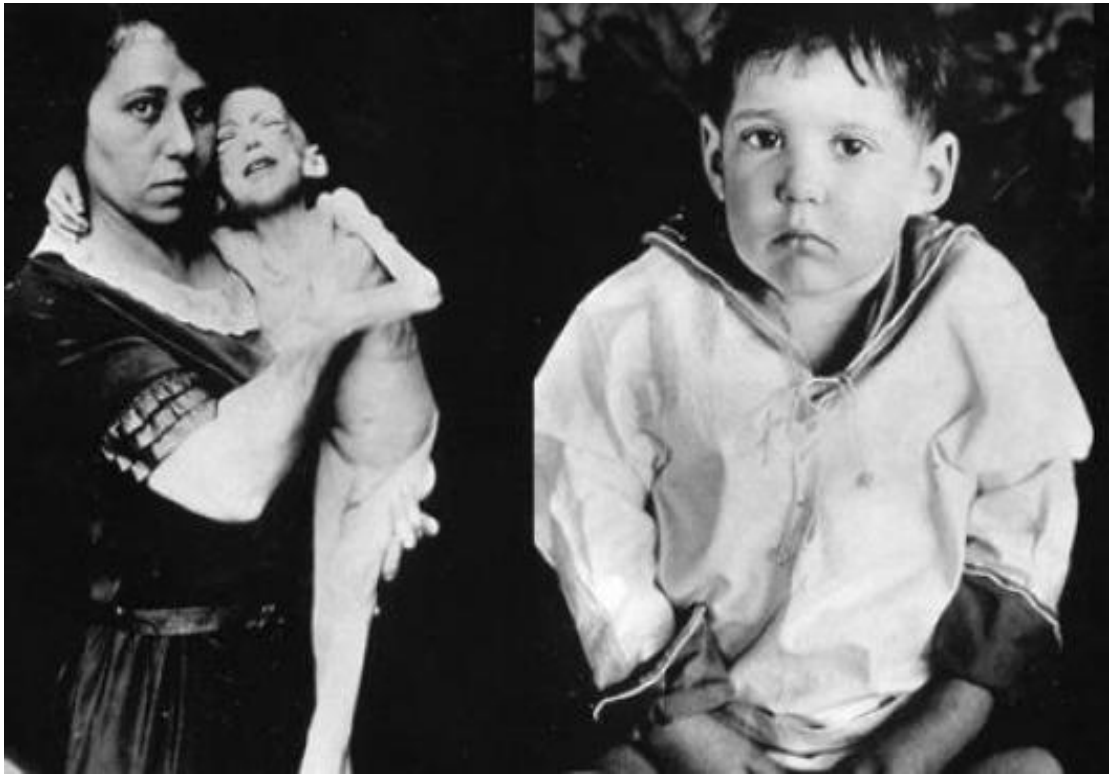
Fig. 2. Phenotype of VDR knockout mouse (KO) compared to wildtype littermate (WT; NMRI background strain) at the age of 4.5 (top) and 8.5 (bottom) months.

Keisala et al. Premature aging in vitamin D receptor mutant mice. J Steroid Biochem Mol Biol. 2009 Jul;115(3-5):91-7


„NEW“ MECHANISMS
„OLD“ MECHANISMS
vitamin D2
vitamin D3
vitamin D2
Ergosterol
7-dehydro-cholesterol
skin
25OH vitamin D
PTH
1α-hydroxylase
autocrine effects
(most tissues)
1α-hydroxylase
bone
muscle
intracellular
1, 25(OH)2 Vitamin D
blood pressure
cell proliferation/differentiation
blood vessels
autoimmune processes
immunity
glucose metabolisation
endocrine effects
circulating
1, 25(OH)2 Vitamin D
calcium homeostasis
(absorption)
HD09

VITAMIN D & MORTALITY

INSULIN ANALOGY!?



trumanlibrary.org

SEVERE DEFICIENCY

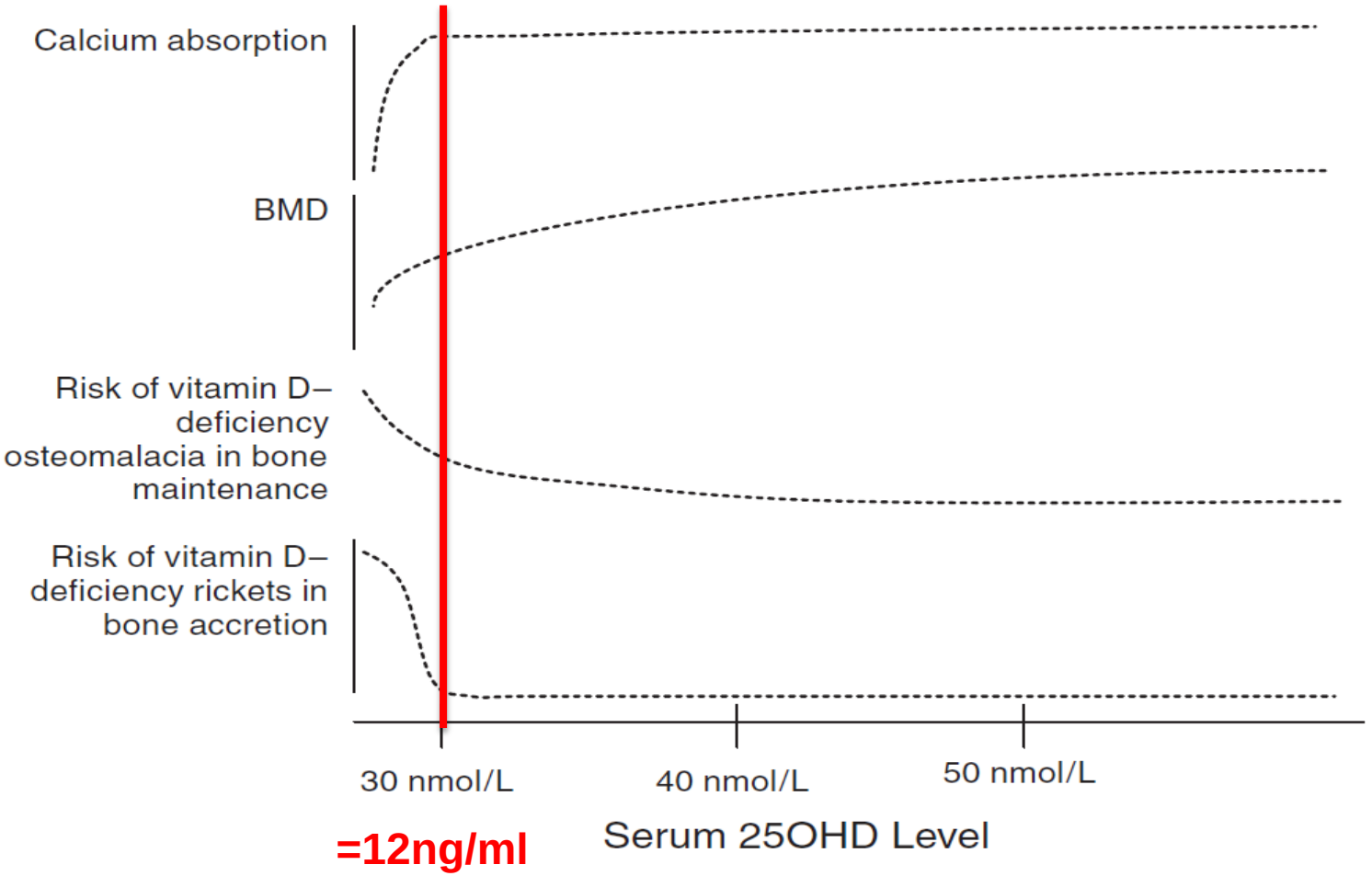


FIGURE 5-1 Conceptualization of integrated bone health outcomes and vitamin D exposure.

IOM report 2011

COCHRANE META-ANALYSIS 2014

Main results

We identified 159 trials, 56 randomised trials **with 95,286 participants** provided usable data on mortality. **Most trials included women older than 70 years**. The mean proportion of **women was 77%**... **35 trials included older people living on their own or in institutional care.** The remaining **eight trials randomly assigned 795 participants with neurological, cardiovascular, respiratory or rheumatoid diseases. Vitamin D was administered for a weighted mean of 4.4 years....**

.... only **vitamin D3** decreased mortality: **RR 0.94** (95% CI 0.91 to 0.98); P = 0.002; I2 = 0%; 75,927 participants; 38 trials). Trial sequential analysis supported our finding regarding vitamin D3, with the cumulative Z-score breaking the trial sequential monitoring boundary for benefit, corresponding to **150 people treated over five years to prevent one additional death.** Vitamin D3 **statistically significantly decreased CANCER mortality (RR 0.88** (95% CI 0.78 to 0.98); P = 0.02; I2 = 0%; 44,492 participants; 4 trials).

Bjelakovic 2014

VITAMIN D &

LUNG

Altmetrics Score > 2000 since 02/2017

Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data

Adrian R Martineau,[1,2] David A Jolliffe,[1] Richard L Hooper,[1] Lauren Greenberg,[1] John F Aloia,[3] Peter Bergman,[4] Gal Dubnov-Raz,[5] Susanna Esposito,[6] Davaasambuu Ganmaa,[7] Adit A Ginde,[8] Emma C Goodall,[9] Cameron C Grant,[10] Christopher J Griffiths,[1,2,11] Wim Janssens,[12] Ilkka Laaksi,[13] Semira Manaseki-Holland,[14] David Mauger,[15] David R Murdoch,[16] Rachel Neale,[17] Judy R Rees,[18] Steve Simpson,Jr[19] Iwona Stelmach,[20] Geeta Trilok Kumar,[21] Mitsuyoshi Urashima,[22] Carlos A Camargo Jr[23]

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Additional material is published online only. To view please visit the journal online.

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http://dx.doi.org/10.1136/bmj.i6583

Accepted: 01 December 2016

ABSTRACT

OBJECTIVES

To assess the overall effect of vitamin D supplementation on risk of acute respiratory tract infection, and to identify factors modifying this effect.

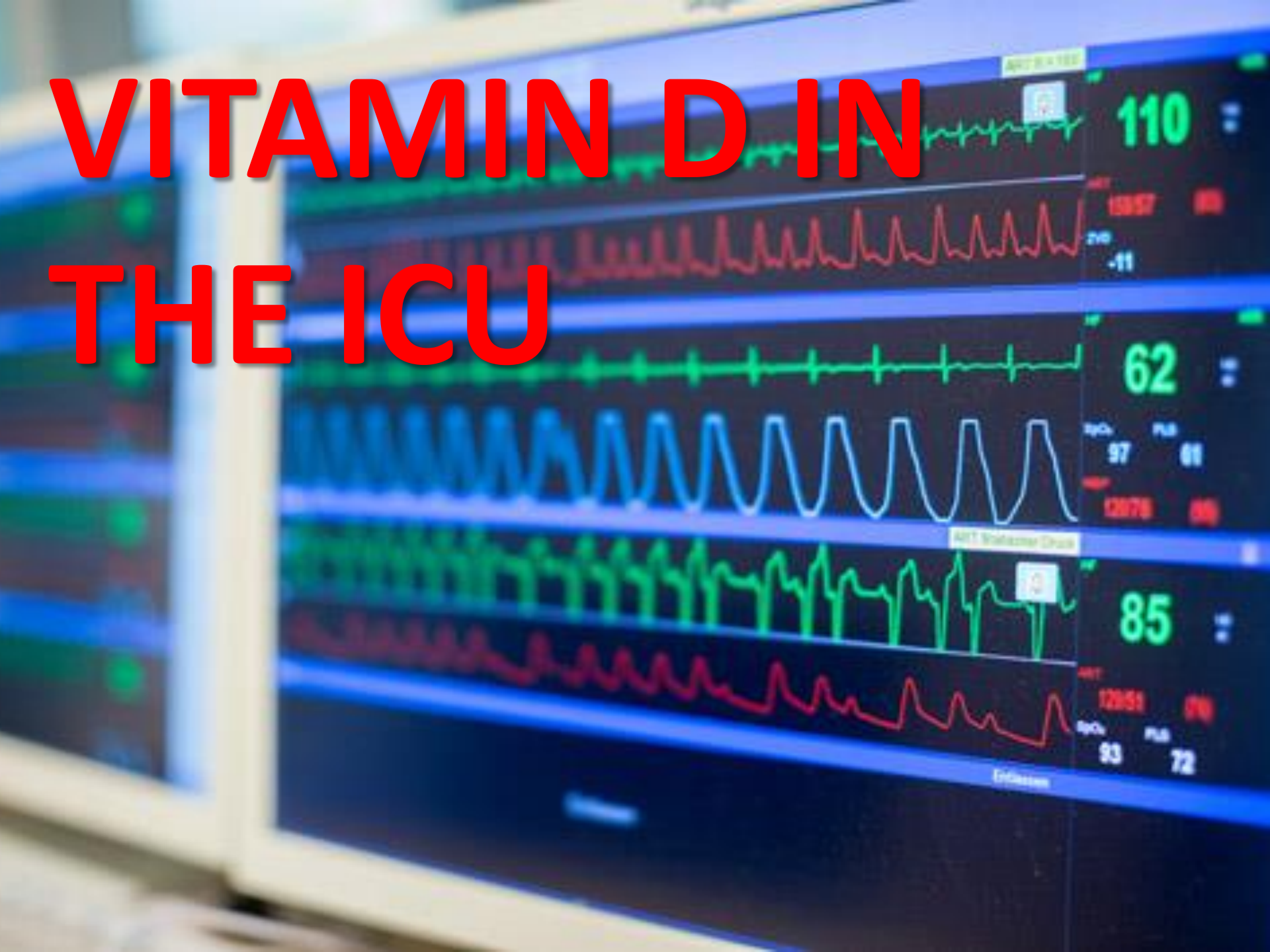
DESIGN

Systematic review and meta-analysis of individual participant data (IPD) from randomised controlled trials.

DATA SOURCES

respiratory tract infection among all participants (adjusted odds ratio 0.88, 95% confidence interval 0.81 to 0.96; P for heterogeneity <0.001). In subgroup analysis, protective effects were seen in those receiving daily or weekly vitamin D without additional bolus doses (adjusted odds ratio 0.81, 0.72 to 0.91) but not in those receiving one or more bolus doses (adjusted odds ratio 0.97, 0.86 to 1.10; P for interaction=0.05). Among those receiving daily or weekly vitamin D, protective effects were stronger in

VITAMIN D IN THE ICU



2009

Vitamin D Deficiency in Critically Ill Patients

THE EDITOR: Vitamin D deficiency is rarely con-
red or treated in critically ill patients. However,
recently reported three cases of life-threaten-
hypocalcemia secondary to vitamin D deficien-
[2] highlighting potential acute complications.
prevalence of vitamin D deficiency and its sig-
cance in the intensive care unit (ICU) are un-
wn.
We performed a prospective study of the vita-
D status in ICU patients (Table 1) referred to
Department of Endocrinology, St. Vincent's
Hospital, Sydney, between January 2007 and Jar
ary 2008. Demographic, physiological, and bi
chemical variables were recorded, including t
Simplified Acute Physiology Score II (SAPS II) (
a scale of 0 to 163, with higher scores indicati
more severe organ dysfunction).[3]

Among approximately 1100 ICU patients p
year, the mean (±SD) serum level of 25-hydroxy
tamin D in 42 referred patients was 41±22 nm
per liter (16±9 ng per milliliter), with a high prev
lence of hypovitaminosis D (Table 1). Moreov

Table 1. Characteristics of 42 Critically Ill Patients Referred for Endocrinologic Evaluation.

Characteristic	No. of Patients (%)
Sex	
Male	20 (48)
Female	22 (52)
Diagnosis	
Cardiac disease	3 (7)
Neurologic disease	3 (7)
Metabolic disease	3 (7)
Trauma	5 (12)
Sepsis	13 (31)
Respiratory disease	15 (36)
Condition identified as reason for referral*	
Hyperglycemia	27 (64)
Abnormal thyroid function	15 (36)
Hyponatremia	12 (29)
Hypocortisolemia	8 (19)
Hypocalcemia	2 (5)†
Medications	
Corticosteroids	28 (67)
Calcium supplement	12 (29)
Vitamin D supplement	10 (24)
Level of 25-hydroxyvitamin D	
Sufficient, >60 nmol/liter	3 (7)
Insufficient, >30 to ≤60 nmol/liter	23 (55)
Deficient, >15 to ≤30 nmol/liter	16 (38)
Undetectable, ≤15 nmol/liter	7 (17)

BASICS
VDD IN THE ICU

- VITAMIN D DEFICIENCY IN ICU IS

  VERY FREQUENT WORLDWIDE

- VITAMIN D STATUS IS ASSOCIATED WITH
  - **EXCESS** MORBIDITY
    - RENAL FAILURE
    - SEPSIS, INFECTIONS, ...
  - **EXCESS** MORTALITY (ADULTS AND CHILDREN)

VDD IN THE ICU - VETERINARY

PLOS ONE

RESEARCH ARTICLE

Vitamin D Metabolites and Their Association with Calcium, Phosphorus, and PTH Concentrations, Severity of Illness, and Mortality in Hospitalized Equine Neonates

Ahmed M. Kamr[1,4], Katarzyna A. Dembek[1], Stephen M. Reed[2], Nathan M. Slovis[3], Ahmed A. Zaghawa[4], Thomas J. Rosol[1], Ramiro E. Toribio[1]*

1 College of Veterinary Medicine, The Ohio State University, Columbus, Ohio, United States of America, **2** Rood and Riddle Equine Hospital, Lexington, Kentucky, United States of America, **3** Hagyard Equine Medical Institute, Lexington, Kentucky, United States of America, **4** Faculty of Veterinary Medicine, University of Sadat City, Sadat City, Egypt

Methods and Results

One hundred newborn foals ≤72 hours old divided into hospitalized (n = 83; 59 septic, 24 sick non-septic [SNS]) and healthy (n = 17) groups were included. Blood samples were collected on admission to measure serum 25-hydroxyvitamin D_3 [25(OH)D_3], 1,25-dihydroxyvitamin D_3 [1,25(OH)$_2D_3$], and PTH concentrations. Data were analyzed by nonparametric methods and univariate logistic regression. The prevalence of hypovitaminosis D [defined as 25(OH)D_3 <9.51 ng/mL] was 63% for hospitalized, 64% for septic, and 63% for SNS foals. Serum 25(OH)D_3 and 1,25(OH)$_2D_3$ concentrations were significantly lower in septic and SNS compared to healthy foals (P<0.0001; P = 0.037). Septic foals had significantly lower calcium and higher phosphorus and PTH concentrations than healthy and SNS foals (P<0.05). In hospitalized and septic foals, low 1,25(OH)$_2D_3$ concentrations were associated with increased PTH but not with calcium or phosphorus concentrations. Septic foals with 25(OH)D_3 <9.51 ng/mL and 1,25(OH)$_2D_3$ <7.09 pmol/L were more likely to die (OR=3.62; 95% CI = 1.1-12.40; OR = 5.41; 95% CI = 1.19-24.52, respectively).

VDD IN THE ICU - VETERINARY

PLOS ONE

RESEARCH ARTICLE

Serum vitamin D concentrations in hospitalized critically ill dogs

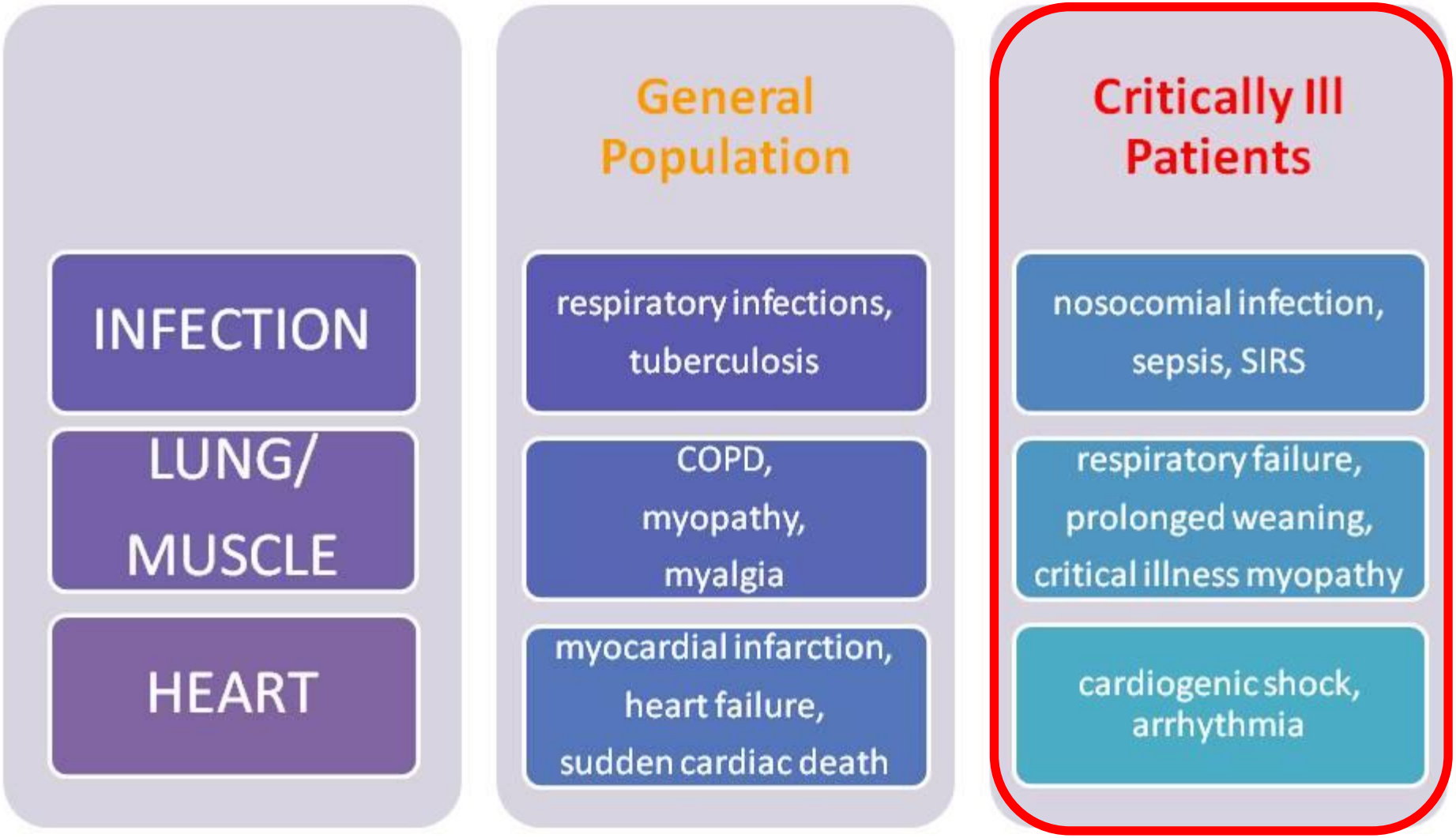
Jared A. Jaffey*, Robert C. Backus, Kaylyn M. McDaniel, Amy E. DeClue

Department of Veterinary Medicine and Surgery, Veterinary Health Center, University of Missouri, Columbia, Missouri, United States of America

* jaffeyj@missouri.edu

intensive care unit or illness severity. Serum concentrations of 25(OH)D together with a range of other clinical, biochemical, and hematological parameters, were measured in 99 dogs within 24 hours of admission to the Intensive Care Unit (ICU). Critically ill dogs (P = 0.001) and dogs with sepsis (P = 0.002) had significantly lower serum 25(OH)D concentrations compared to healthy control dogs. In addition, serum 25(OH)D concentration was an independent predictor of in-hospital and 30 day survival. Using a cut-off of 33 ng/mL, serum 25(OH)D concentrations had excellent sensitivity (0.94; 95% CI, 0.71–1.00), but poor specificity (0.41; 95% CI, 0.31–0.53) for detection of survival. Serum 25(OH)D concentrations were inversely associated with acute patient physiologic and laboratory evaluation (APPLE) fast score but were not associated with ICU length of stay. Hospitalized dogs with critical illness have decreased serum 25(OH)D concentrations compared to healthy dogs and can be used to predict survival in this cohort.

POTENTIAL MECHANISMS OF VITAMIN D



Adapted from: Lee P. et al., Intensive Care Med. 2009 Dec,35(12):2028-32

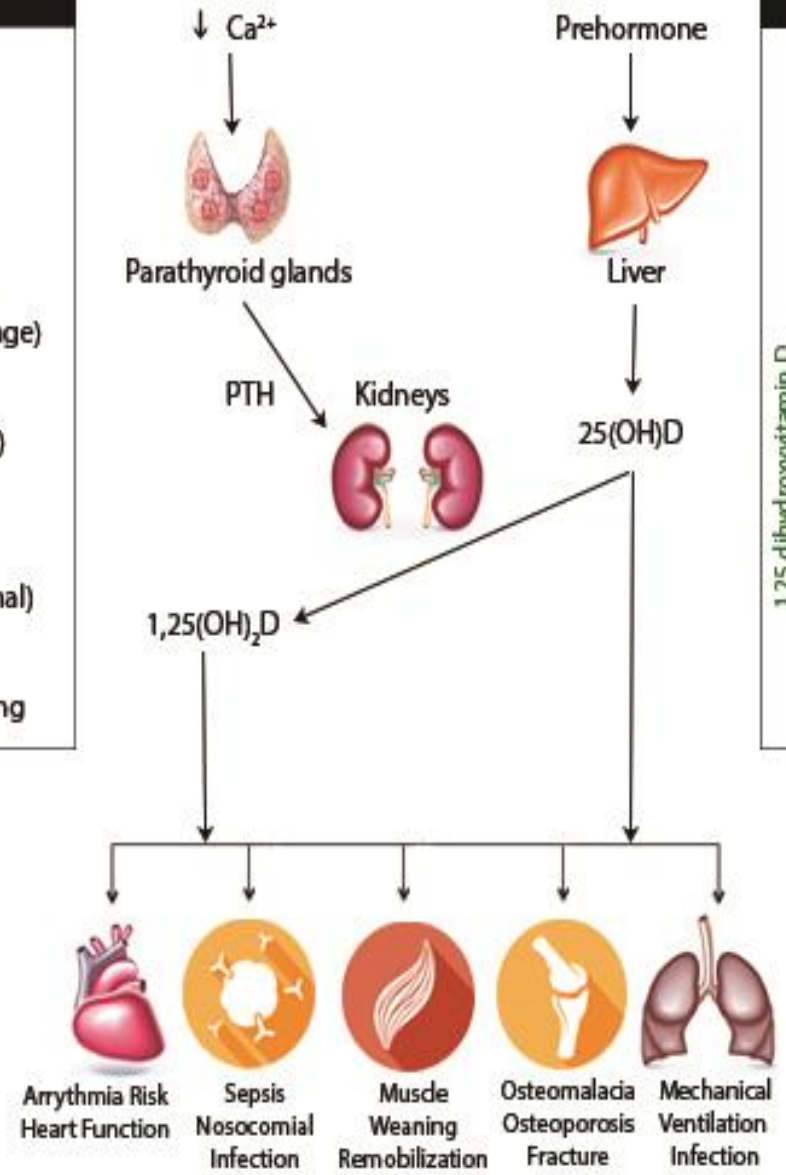
Disruptions to the Axis

Decreased intake
- Poor diet
- Poor adsorption

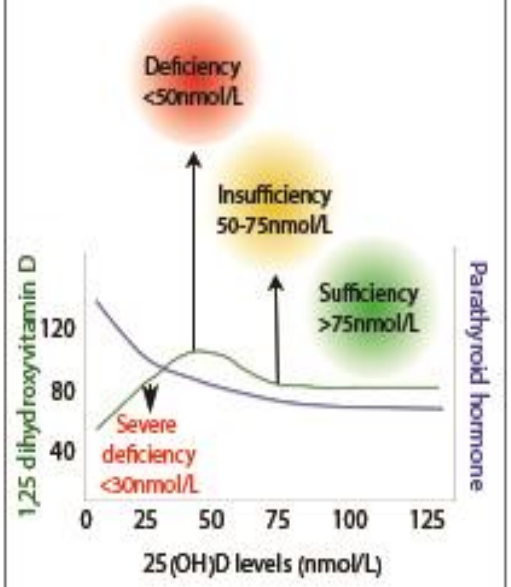
Increased losses
- Bleeding (i.e. trauma, surgery)
- Capillary leak (i.e. inflammation)
- Dilution (i.e. fluids, ECMO, exchange)

Decreased Production
- Reduced UVB (i.e. hospitalization)
- Latitude
- Altered metabolism (e.g. PTH)
- Organ dysfunction
  (e.g. gastrointestinal, hepatic, renal)

End organ resistance
- Heart, immune, muscle, bone, lung



Vitamin D Deficiency Spectrum



Amrein K ICM 2015

VITAMIN D & VENTILATION

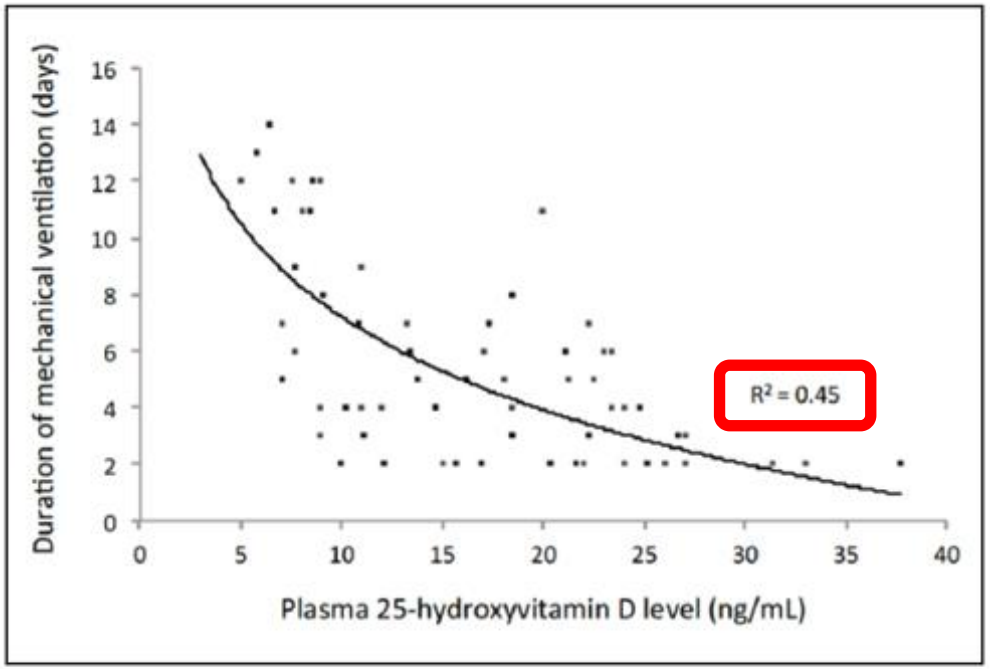
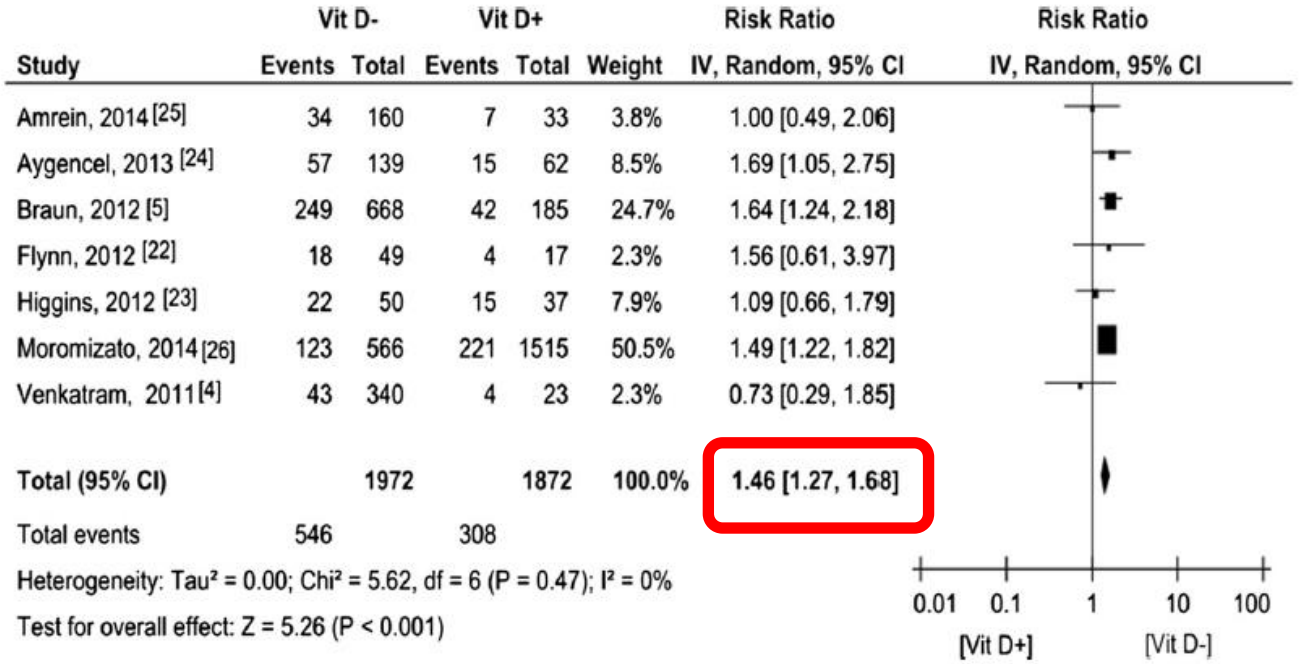


Figure 1. Unadjusted relationship between plasma 25-hydroxyvitamin D levels and duration of mechanical ventilation in surgical intensive care unit patients (n = 94). Logarithmic curve fitting suggests that 45% of the variation in the duration of mechanical ventilation may be explained by vitamin D status at the initiation of critical care.

Quraishi S JPEN 2015

VITAMIN D & SEPSIS



Study	Vit D- Events	Total	Vit D+ Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Amrein, 2014 [25]	34	160	7	33	3.8%	1.00 [0.49, 2.06]
Aygencel, 2013 [24]	57	139	15	62	8.5%	1.69 [1.05, 2.75]
Braun, 2012 [5]	249	668	42	185	24.7%	1.64 [1.24, 2.18]
Flynn, 2012 [22]	18	49	4	17	2.3%	1.56 [0.61, 3.97]
Higgins, 2012 [23]	22	50	15	37	7.9%	1.09 [0.66, 1.79]
Moromizato, 2014 [26]	123	566	221	1515	50.5%	1.49 [1.22, 1.82]
Venkatram, 2011 [4]	43	340	4	23	2.3%	0.73 [0.29, 1.85]
Total (95% CI)		**1972**		**1872**	**100.0%**	**1.46 [1.27, 1.68]**
Total events	546		308			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.62$, df = 6 (P = 0.47); $I^2 = 0\%$

Test for overall effect: Z = 5.26 (P < 0.001)

Figure 2 Forest plot of studies comparing deficient vitamin D levels with sufficient vitamin D levels on sepsis. CI, confidence interval; IV, inverse variance; Vit D-, deficient vitamin D level; Vit D+, sufficient vitamin D level.

de Haan *et al. Critical Care* 2014, **18**:660
http://ccforum.com/content/18/6/660

VITAMIN D & HOSPITAL MORTALITY

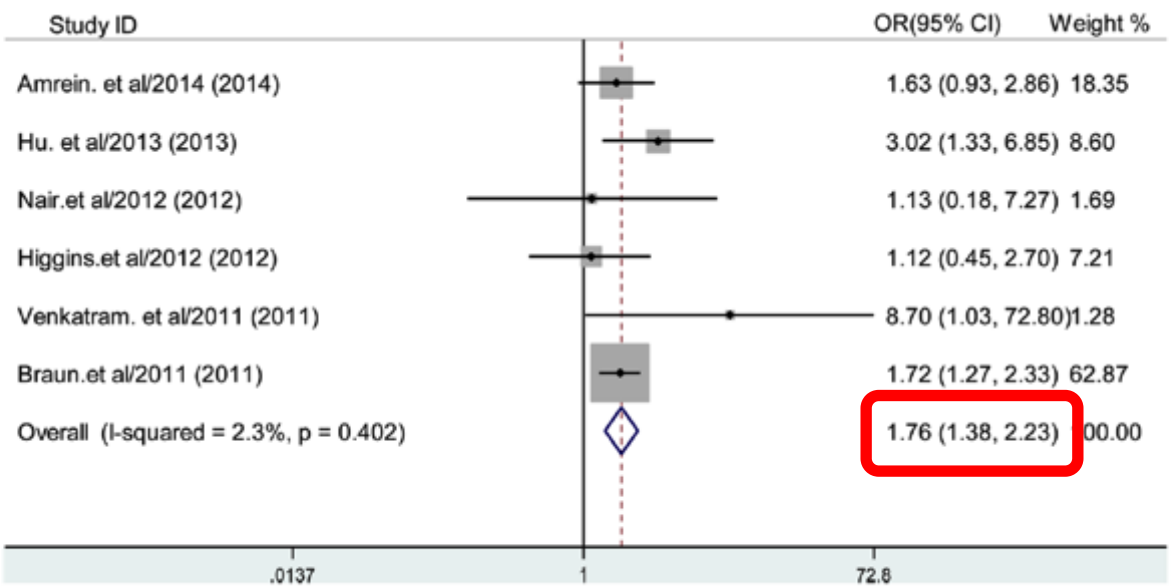


Figure 2 Forest plot showing the effect of vitamin D deficiency on hospital mortality. OR, odds ratio.

Zhang *et al. Critical Care* 2014, **18**:684
http://ccforum.com/content/18/6/684

MEGADOSES?

Pharmacokinetics of a single, large dose of cholecalciferol[1–3]

Marium Ilahi, Laura AG Armas, and Robert P Heaney

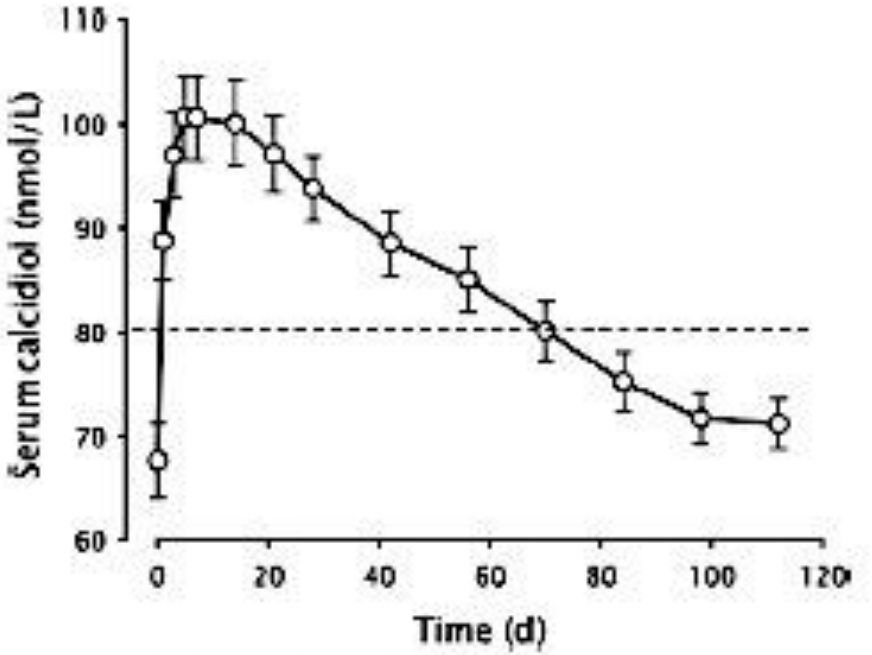


FIGURE 1. Time course of serum calcidiol for 112 d (16 wk) after a single oral dose of 100 000 IU cholecalciferol ($n = 30$). The error bars are 1 SEM. The horizontal dashed line demarcates values above and below 80 nmol/L. To convert nmol/L to ng/mL, divide by 2.496.

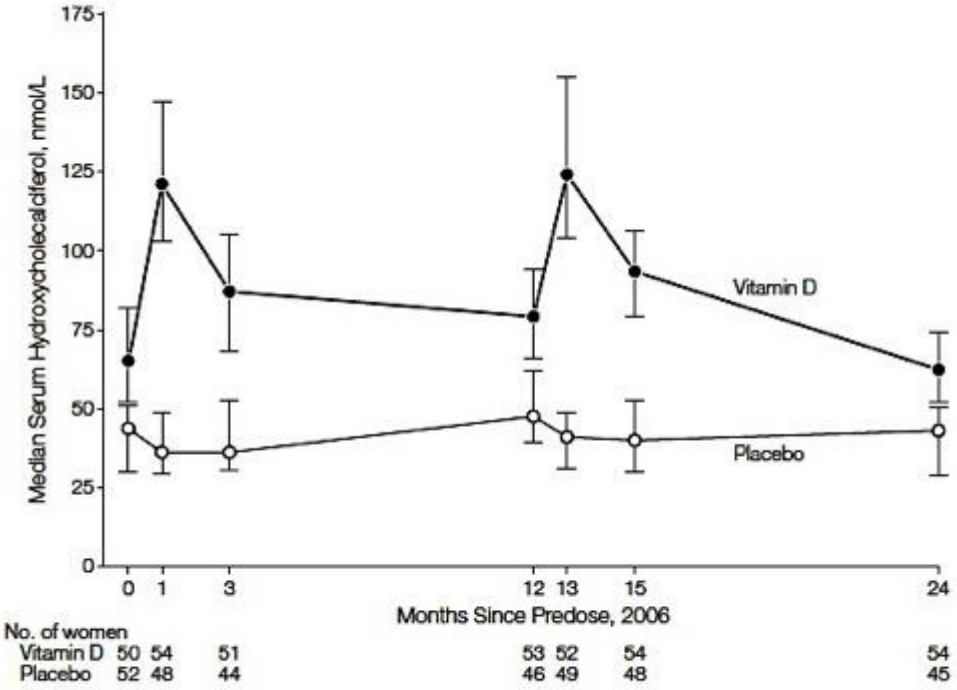
Am J Clin Nutr. 2008 Mar;87(3):688-91.

MEGADOSES ARE OUT!

Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women

A Randomized Controlled Trial

Figure 4. Serum 25-Hydroxycholecalciferol Levels Before Dose, and at 1, 3, and 12 Months After Dose



The points refer to the median level of 25-hydroxycholecalciferol at the time of blood sampling and the error bars represent the interquartile range. These 7 blood sampling time points took place in 2006, 2007, and 2008, and refer to the biochemistry substudy participants.

EXCEPT IN ICU

JAMA. 2010 May 12;303(18):1815-22

Research

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

Karin Amrein, MD, MSc; Christian Schnedl, MD; Alexander Holl, MD; Regina Riedl, MSc; Kenneth B. Christopher, MD; Christoph Pachler, MD; Tadeja Urbanic Purkart, MD; Andreas Waltensdorfer, MD; Andreas Münch, MD; Helga Warnkross, MD; Tatjana Stojakovic, MD; Egbert Biesing, MD; Wolfgang Toller, MD; Karl-Heinz Smolle, MD; Andrea Berghold, PhD; Thomas R. Pieber, MD; Harald Dobnig, MD

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, 0.58-1.13]; $P = .18$. 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]; $P = .091$. 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, 12.9-29.1 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.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01303081

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

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Section Editor: David C. Rogers, MD, MPH, Associate Editor, JAMA (jamajournal@jama.ama-assn.org).

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1520 JAMA October 15, 2014 Volume 312, Number 15 jama.com

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K Amrein and coauthors

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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The JAMA Network

VITDAL-ICU

Correction of Vitamin D Deficiency in Critically Ill Patients
ClinicalTrials: NCT01130181

Setting	• randomized, double blind, placebo controlled • 5 mixed ICUs (medical, surgical, neurologic) • 480 pat. > 48 hours; 25(OH)D ≤ 20 ng/ml
Intervention	• 540,000 IU Vitamin D3 vs. Placebo 1x po/tube • 90,000 IU monthly 5x
Primary Endpoint	**Hospital length of stay (LOS)**
Secondary Endpoints	mortality, ICU-LOS, lab, duration of mech.vent./circulatory support, …

Amrein JAMA 2014

RESULTS
PRIMARY ENDPOINT

Hospital Length of Stay (days)

Vitamin D3: 20.1 [IQR 11.1-33.3]
Placebo: 19.3 [IQR 11.1-34.9]

P=0.981

RESULTS
SECONDARY ENDPOINTS
SUBGROUP ≤ 12NG/ML (n=200 or 42%)

Hospital Mortality

Vitamin D3: 28.6%

Placebo: 46.1%

HR 0.56

[95%CI 0.35-0.90]

NNT=6

P=0.01 (log rank), 0.04 (for interaction)

AE (WITHIN 6 MONTHS)

HYPERCALCEMIA

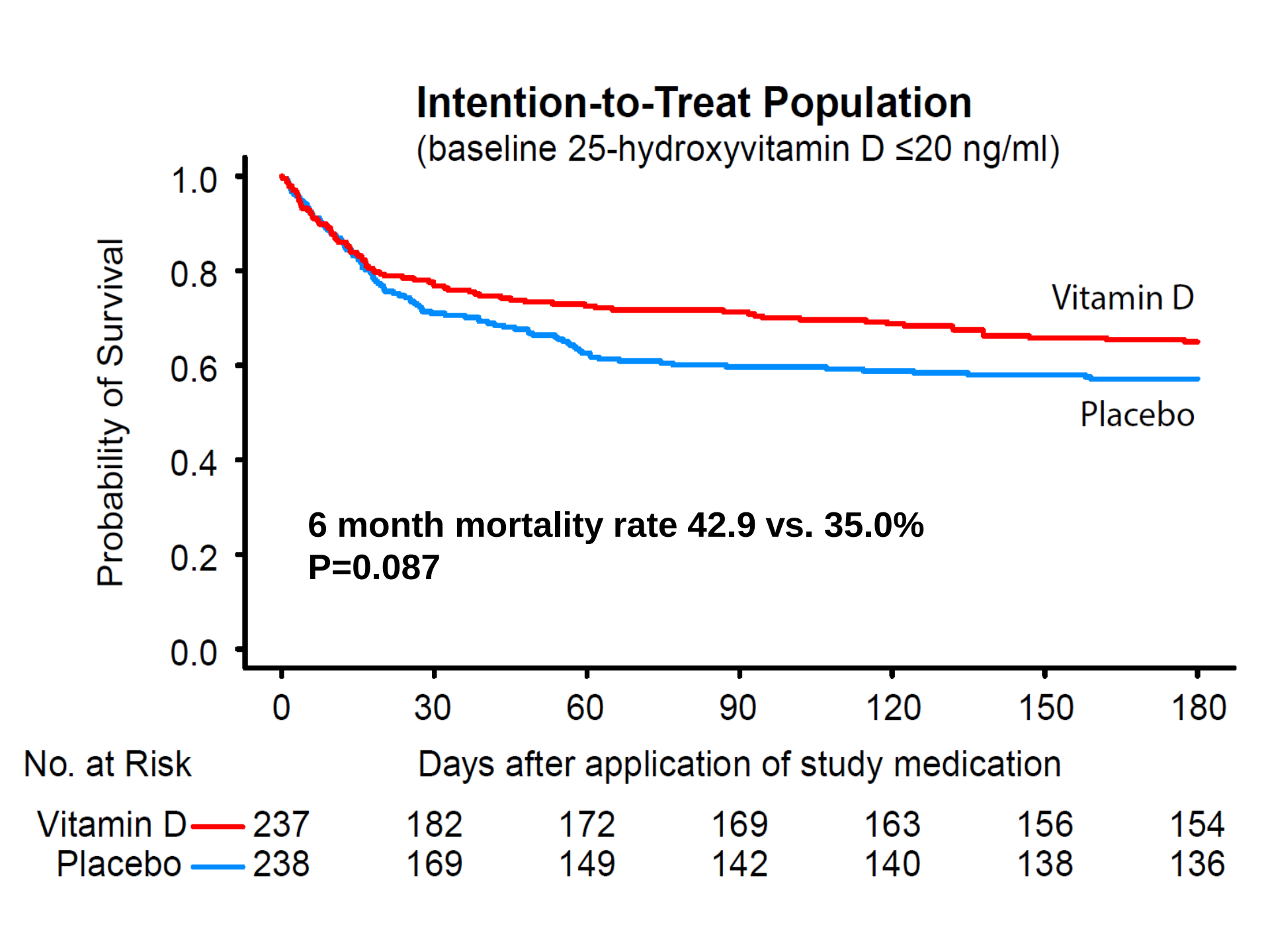
- highest calcium: ***3.0 mmol/l***
- highest ionis. calcium: ***1.5 mmol/l***
- asymptomatic

VITAMIN D INTOXICATION

- Highest 25(OH)D level: ***107 ng/ml***

FALLS & FRACTURES

- falls:
  33 (P) vs. 27 (VIT D)
- fractures: 2 in each arm


Intention-to-Treat Population
(baseline 25-hydroxyvitamin D ≤20 ng/ml)
Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
Vitamin D
Placebo
6 month mortality rate 42.9 vs. 35.0%
P=0.087
0
30
60
90
120
150
180
No. at Risk
Days after application of study medication
Vitamin D 237 182 172 169 163 156 154
Placebo 238 169 149 142 140 138 136

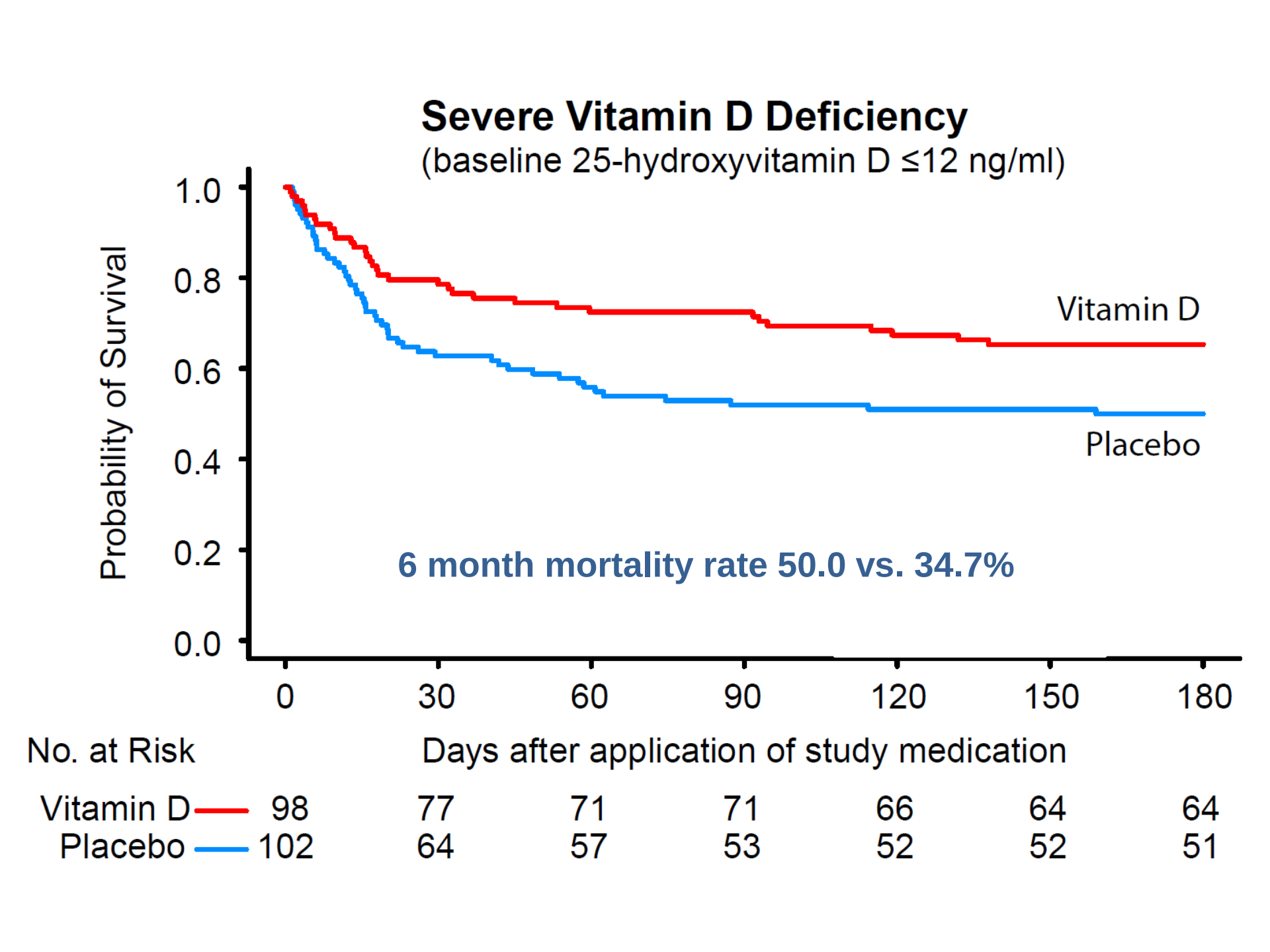

Severe Vitamin D Deficiency
(baseline 25-hydroxyvitamin D ≤12 ng/ml)
Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
Vitamin D
Placebo
6 month mortality rate 50.0 vs. 34.7%
0
30
60
90
120
150
180
No. at Risk
Days after application of study medication
Vitamin D 98 77 71 71 66 64 64
Placebo 102 64 57 53 52 52 51

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)	

THE ANSWER TO EVERYTHING…

THE ANSWER TO EVERYTHING…

…IN EBM IS

META-ANALYSIS

OR NOT?

Intensive Care Med
DOI 10.1007/s00134-016-4391-

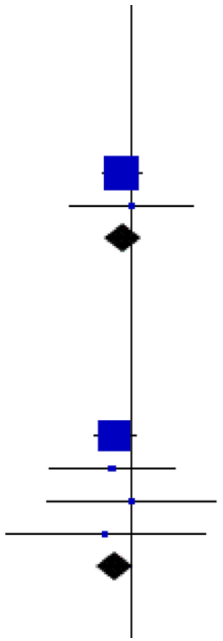
META-ANALYSIS #1

LETTER

Randomised trials of vitamin D_3 for critically ill patients in adults: systematic review and meta-analysis with trial sequential analysis

Hong Weng[1], Jian-Guo Li[2], Zhi Mao[3] and Xian-Tao Zeng[1*]

Total events	76		93			
Heterogeneity: Chi² = 0.45, df = 3 (P = 0.93); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
1.1.2 ICU mortality						
Amrein et al, 2014	54	237	63	238	90.7%	0.86 [0.63, 1.18]
Leaf et al, 2014	7	36	6	31	9.3%	1.00 [0.38, 2.67]
Subtotal (95% CI)		**273**		**269**	**100.0%**	**0.87 [0.65, 1.18]**
Total events	61		69			
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						
1.1.3 28 or 30 days mortality						
Amrein et al, 2014	52	237	68	238	83.4%	0.77 [0.56, 1.05]
Leaf et al, 2014	6	36	7	31	9.2%	0.74 [0.28, 1.96]
Quraishi et al, 2015 a	3	10	3	10	3.7%	1.00 [0.26, 3.81]
Quraishi et al, 2015 b	2	10	3	10	3.7%	0.67 [0.14, 3.17]
Subtotal (95% CI)		**293**		**289**	**100.0%**	**0.77 [0.58, 1.03]**
Total events	63		81			
Heterogeneity: Chi² = 0.19, df = 3 (P = 0.98); I² = 0%						



META-ANALYSIS #2

Journal of Critical Care 38 (2016) 109–114

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Vitamin D and outcomes in adult critically ill patients. A systematic review and meta-analysis of randomized trials☆

Alessandro Putzu [a], Alessandro Belletti [b], Tiziano Cassina [a], Sara Clivio [a], Giacomo Monti [b], Alberto Zangrillo [b,c], Giovanni Landoni [b,c,*]

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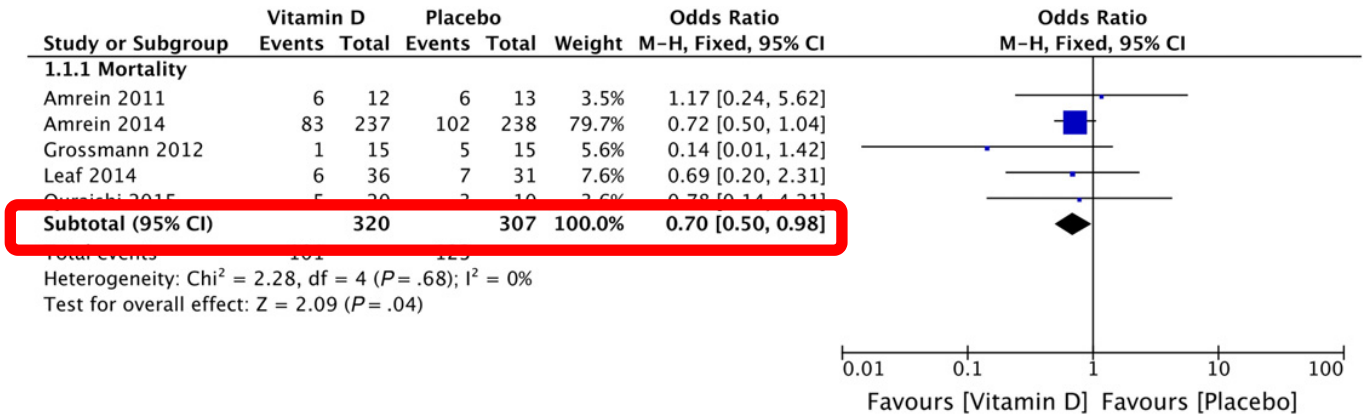

META-ANALYSIS #3

Clinical Nutrition xxx (2017) 1–9

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Vitamin D supplementation in the critically ill: A systematic review and meta-analysis

Pascal L. Langlois [a, 1], Celeste Szwec [b, 1], Frédérick D'Aragon [a], Daren K. Heyland [c, d], William Manzanares [e, *]

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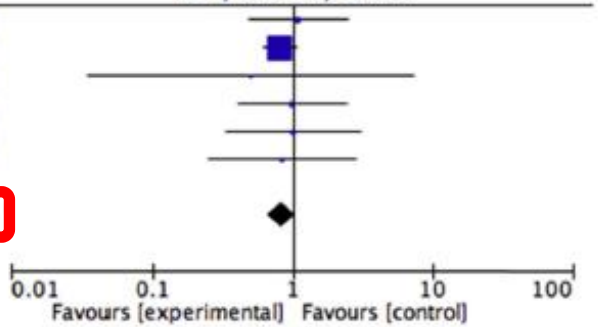
[e] Department of Critical Care, Intensive Care Unit, University Hospital, Faculty of Medicine, UDELAR, Montevideo, Uruguay

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Amrein 2011	6	12	6	13	8.1%	1.08 [0.48, 2.45]
Amrein 2014	67	237	84	238	76.3%	0.80 [0.61, 1.04]
Han 2016	1	20	1	10	0.8%	0.50 [0.03, 7.19]
Leaf 2014	8	36	7	31	6.8%	0.98 [0.40, 2.40]
Nair 2015	5	25	5	25	4.4%	1.00 [0.33, 3.03]
Quraishi 2015	5	20	3	10	3.7%	0.83 [0.25, 2.80]
Total (95% CI)		**350**		**327**	**100.0%**	**0.84 [0.66, 1.06]**
Total events	92		106			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.86$, $df = 5$ ($P = 0.97$); $I^2 = 0\%$
Test for overall effect: $Z = 1.48$ ($P = 0.14$)



Abbreviations: CI: confidence interval; M-H Mantel-Haenszel

Fig. 2. Effect of vitamin D on mortality.

THE ANSWER TO EVERYTHING…

Letter to the Editor

When not to use meta-analysis: Analysing the meta-analyses on vitamin D in critical care

Keywords:
Vitamin D
RCT
Cholecalciferol
Critically ill patients
Meta-analysis

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Dear Editor,

We read with interest the recent article by Langlois and colleagues [1]. We agree that the role of vitamin D deficiency and high dose supplementation represents an important area worthy of further research. However, we have significant concern as to whether the current state of the field is amenable to meta-analyses.

Our primary concern surrounding this publication, and the recent related studies by Weng and by Putzu [2,3], is the lack of a sufficient number and quality of trials to justify meta-analysis that inevitably led to conflicting results and conclusions (Table 1A and 1B). A handful of slightly different intervention studies were identified, the majority being pilot trials (<30 patients per arm), and meta-analyses results were largely driven by the VITDAL-ICU (n = 475) trial. The included trials differ widely in the baseline vitamin D status, the metabolite provided, the route of administration, and the comparator group (Table 1B). As outlined in the Cochrane guidance documents this creates a situation when "a meta-analysis is more of a hindrance than a help" [4]. As two concrete examples, it seems questionable to pool data from a trial giving intravenous calcitriol (active hormone) with those providing cholecalciferol, and merge data from an arm giving 150.000 IU (standard nutrition not defined in the methods) with placebo.

Further, we feel that the authors made some strong statements that warrant discussion and clarification. First, they conclude that "vitamin D administration does not improve clinical outcome". The relatively small amount of trial data produces wide confidence intervals and imprecision in the estimate of the effect size. Consider for example that the RR point estimate for mortality reduction was 0.84 with confidence intervals ranging from 0.66 to 1.06. Given the cost and safety profile of vitamin D, a RR of 0.84 is large, clinically

Table 1
Description of methodological issues in meta-analysis and summary of RCTs of vitamin D supplementation. A: General issues in available meta-analyses. B: Relevant concerns of available meta-analyses. i.m.: intramuscular. C: Intervention arms of published controlled RCTs in the adult critical care setting. D2 = Ergocalciferol; D3 = Cholecalciferol; IM = Intramuscular; IV = Intravenous; IU = International Units; PMID = PubMed ID number. SIRS = Systemic Inflammatory Response Syndrome; VDD = Vitamin D Deficient.

1 A
Population studied
Metabolites used
Administration routes
Comparator

General issues in available meta-analyses
Vitamin D deficiency vs. no vitamin D deficiency vs. unknown
Vitamin D3 with a half-life of weeks vs. calcitriol with a half-life of hours
Oral vs. parenteral
Placebo vs. different dosing strategy

WHICH INTERVENTIONS HAVE EVER IMPROVED MORTALITY IN ICU IN A MULTICENTER DESIGN?

Treatment	Centers	Patients	p	Absolute Risk Reduction	Relativ Risk Reducti n	Number Need to Treat to Save One Life	Follow-Up	Stopped at Interim Analysis	Blinding
lbumin in hepatorenal syndrome (3)	7	126	0.01	0.191	0.668	5	Hospital discharge*; 90 d*	No	Yes
Daily interruption of sedatives (17)	4	336	0.01	0.134	0.232	7	28 d; 1 yr*	No	No
Mild hypothermia (4)	9	275	0.02	0.142	0.258	7	Hospital discharge, 6 mo*	No	No
Noninvasive ventilation (5)	5	85	0.02	0.193	0.675	5	Hospital discharge*	No	No
Noninvasive ventilation (18)	3	50	0.009	0.2	0.714	5	60 d*	No	No
Noninvasive ventilation (19)	14	236	0.05	0.101	0.498	10	Hospital discharge*	No	No
Noninvasive ventilation (20)	3	105	0.028	0.213	0.548	5	ICU discharge*; 90 d*	No	No
Noninvasive ventilation (21)	2	162	0.025	0.142	0.871	8	ICU discharge*; hospital discharge; 90 d*	No	No
Noninvasive ventilation (22)	11	90	0.015	0.12	0.828	7	Hospital discharge*	No	No
Noninvasive ventilation (23)	3	106	0.0244	0.197	0.64	5	ICU discharge; hospital discharge; 90 d*	No	No
Noninvasive ventilation (24)	3	82	0.014	0.122	0.836	8	Hospital discharge*; 6 mo*; 1 yr*	No	No
Prone position (6)	27	474	< 0.001	0.168	0.512	6	28 d; 90 d*	No	No
Protective ventilation (7)	2	53	< 0.001	0.329	0.465	3	ICU discharge*; hospital discharge; 28 d*	Yes	No
Protective ventilation (8)	10	861	0.007	0.088	0.222	11	Hospital discharge*	Yes	No
Protective ventilation (25)	8	103	0.017	0.238	0.441	4	ICU discharge*; hospital discharge*; 28 d*	Yes	No
Tranexamic acid (26)	247	20,211	0.0035	0.015	0.094	68	Hospital discharge*	No	Yes

*Significant.

Mortality in Multicenter Critical Care Trials: An Analysis of Interventions With a Significant Effect*.
Landoni, Giovanni et al. , Critical Care Medicine. 43(8):1559-1568, August 2015.

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Noninvasive ventilation (19)	14	236	0.05	0.101	0.498	10	Hospital discharge*	No	No
Noninvasive ventilation (20)	3	105	0.0	213	0.548	5	ICU [illegible] 90	No	No
Noninvasive ventilation (21)	2	162	[illegible]	142	0.8	8	[illegible] 90 d*		No
Noninvasive ventilation (22)	11	90	0.015	0.12	0.828	7	Hospital discharge*	No	No
Noninvasive ventilation (23)	3	106	[illegible]	0.1		5	ICU [illegible] 90	No	No
Noninvasive ventilation (24)	3	82	014	0.12	0.86	8	Hospital discharge*; 6 [illegible]; 1 y	No	No
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VITAMIN D!?!?!??

Mortality in Multicenter Critical Care Trials: An Analysis of Interventions With a Significant Effect*.
Landoni, Giovanni et al. , Critical Care Medicine. 43(8):1559-1568, August 2015.

VITDALIZE

EFFECT OF HIGH-DOSE VITAMIN D3 ON 28-DAY MORTALITY IN ADULT CRITICALLY ILL PATIENTS WITH SEVERE VITAMIN D DEFICIENCY

Setting	• randomized, double blind, placebo controlled • mixed ICUs (medical, surgical, neurologic) • 2400 ICU patients; **25(OH)D ≤ 12 ng/ml**
Intervention	• 540,000 IU Vitamin D3 vs. Placebo 1x po/tube • 4,000 IU daily for 90 days
Primary Endpoint	**28-DAY MORTALITY**
Secondary Endpoints	morbidity, LOS, lab, duration of mech.vent./circulatory support, readmissions etc.

STARTED OCTOBER 2017, AUSTRIA, n=116

VIOLET

VITAMIN D TO IMPROVE OUTCOMES BY LEVERAGING EARLY TREATMENT

(PETAL GROUP, US)

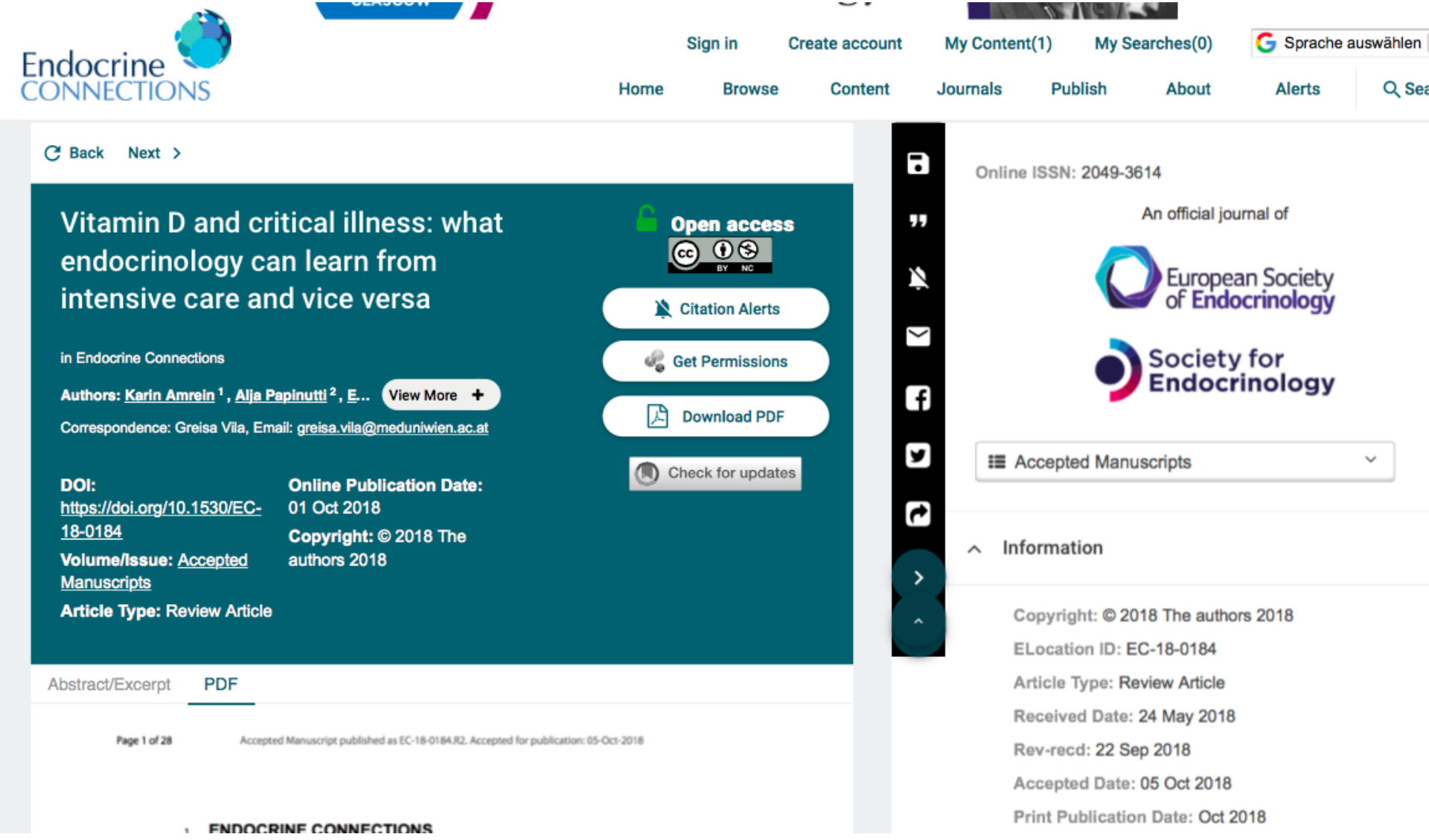
Setting	• randomized, double blind, placebo controlled • mixed ICUs (medical, surgical, neurologic) • 3000 pat @risk for ARDS; **25(OH)D ≤ 20ng/ml**
Intervention	• 540,000 IU Vitamin D3 vs. Placebo 1x po/tube • SINGLE DOSE, no maintenance
Primary Endpoint	**90-DAY MORTALITY**
Secondary Endpoints	ARDS by day 7, hospital LOS, lab etc.

STARTED 04/17, STOPPED 07/17 (ca.1400 PAT)

CONCLUSION

- VITAMIN D LIKELY IS BENEFICIAL IN ICU PATIENTS (WITH (SEVERE?) VITAMIN D DEFICIENCY)
- MA NOT USEFUL IN THIS STAGE
- LARGE INTERVENTION STUDIES NEEDED

REVIEW



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Vitamin D and critical illness: what endocrinology can learn from intensive care and vice versa

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THANK YOU