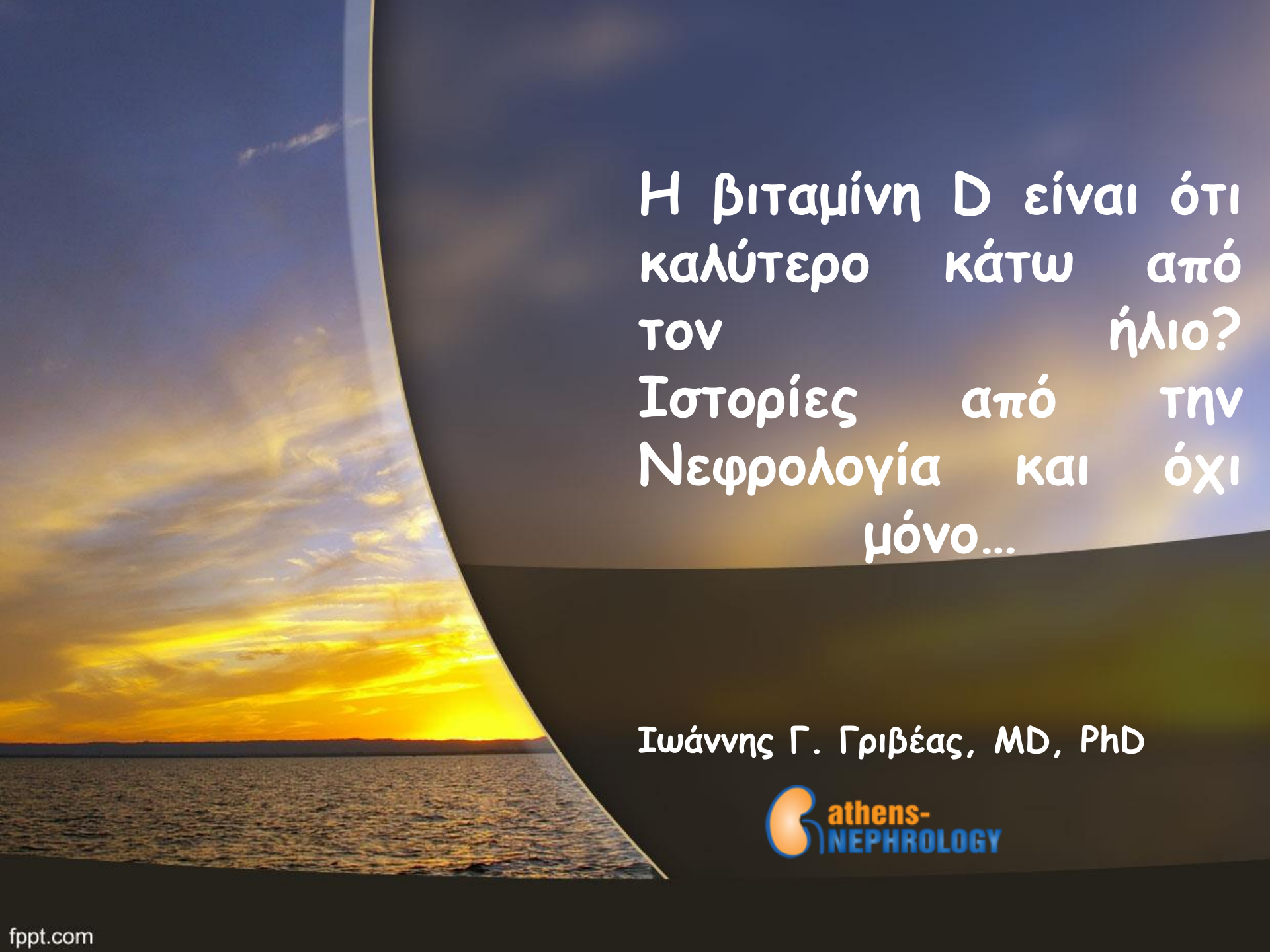
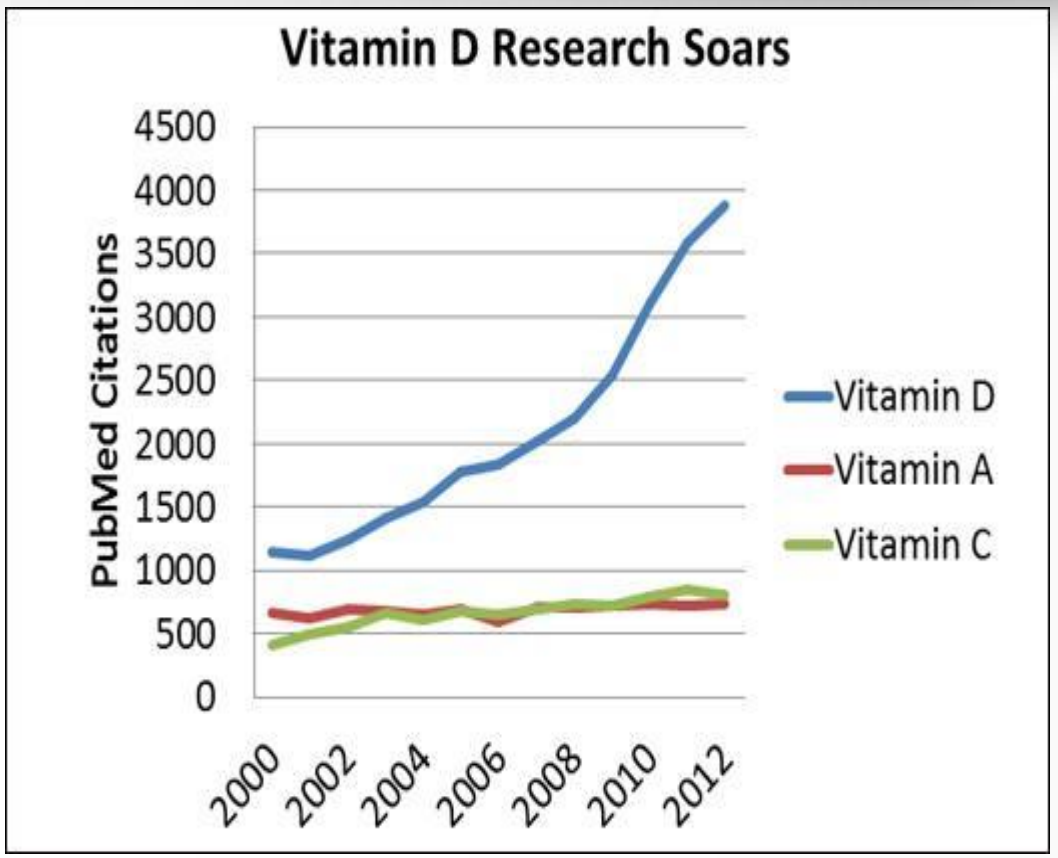


Η βιταμίνη D είναι ότι καλύτερο κάτω από τον ήλιο? Ιστορίες από την Νεφρολογία και όχι μόνο…

Ιωάννης Γ. Γριβέας, MD, PhD

athens-NEPHROLOGY

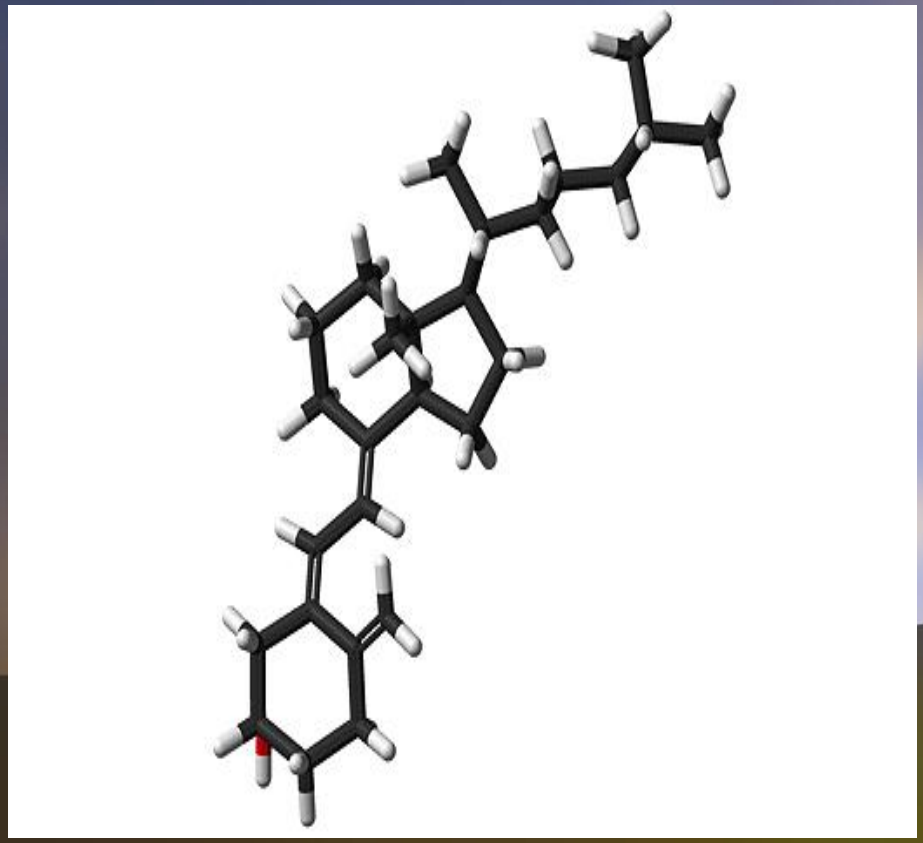


The sun may not be the best way to get vitamin D, but the evidence may yet show that vitamin D is the best thing under the sun.

TOP 10 Medical Breakthroughs 2007

Benefits of Vitamin D

- Bone strength
- Diabetes
- Gum disease
- Multiple sclerosis
- Cancer (in particular colon cancer



Μυοσκελετικό

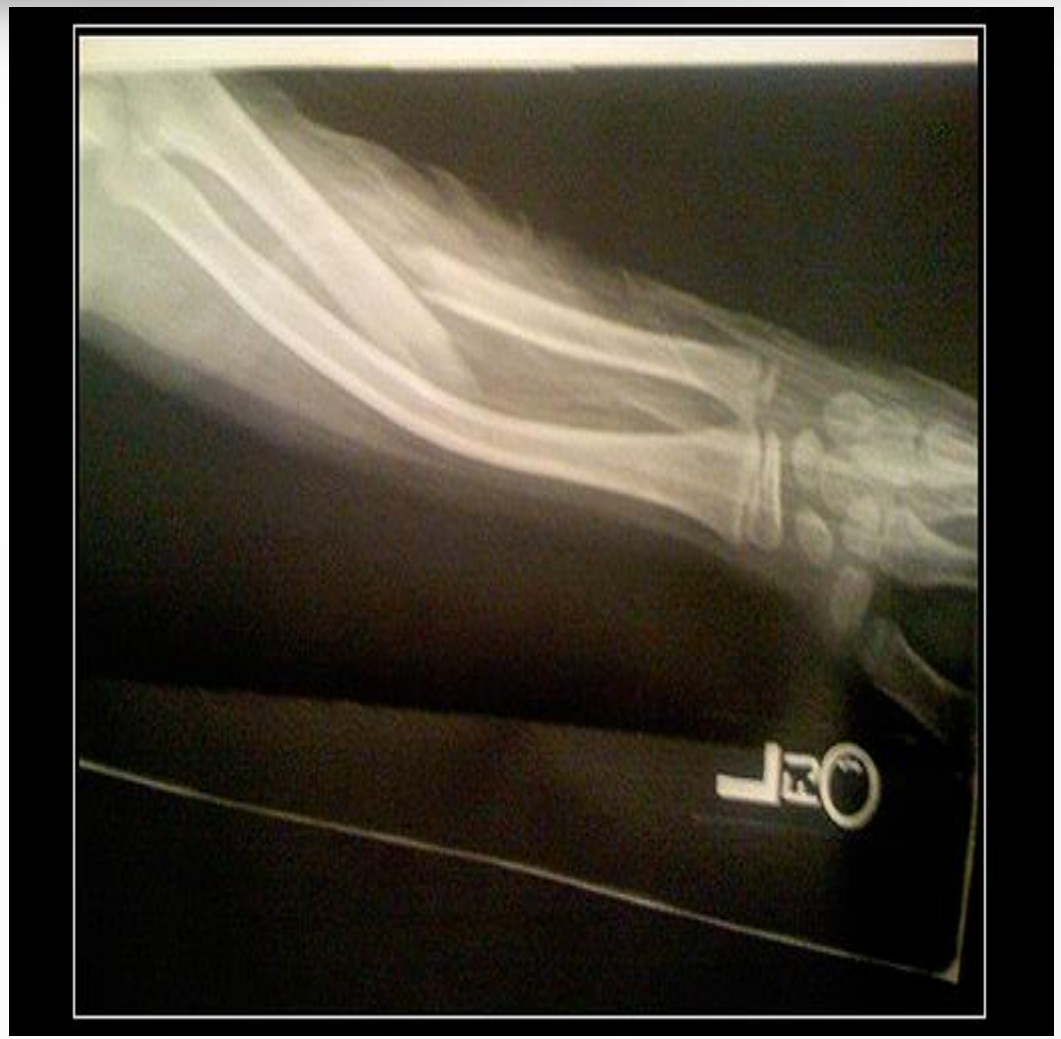
Low levels of vitamin D increase the risk for forearm fracture in children

Girls who consumed the most vitamin D had the lowest risk for stress fractures.

44% of postmenopausal women treated for distal radius fracture were vitamin D deficient or insufficient.

High doses of vitamin D lower the risk for fracture by 14% to 30% in people age 65 years or older

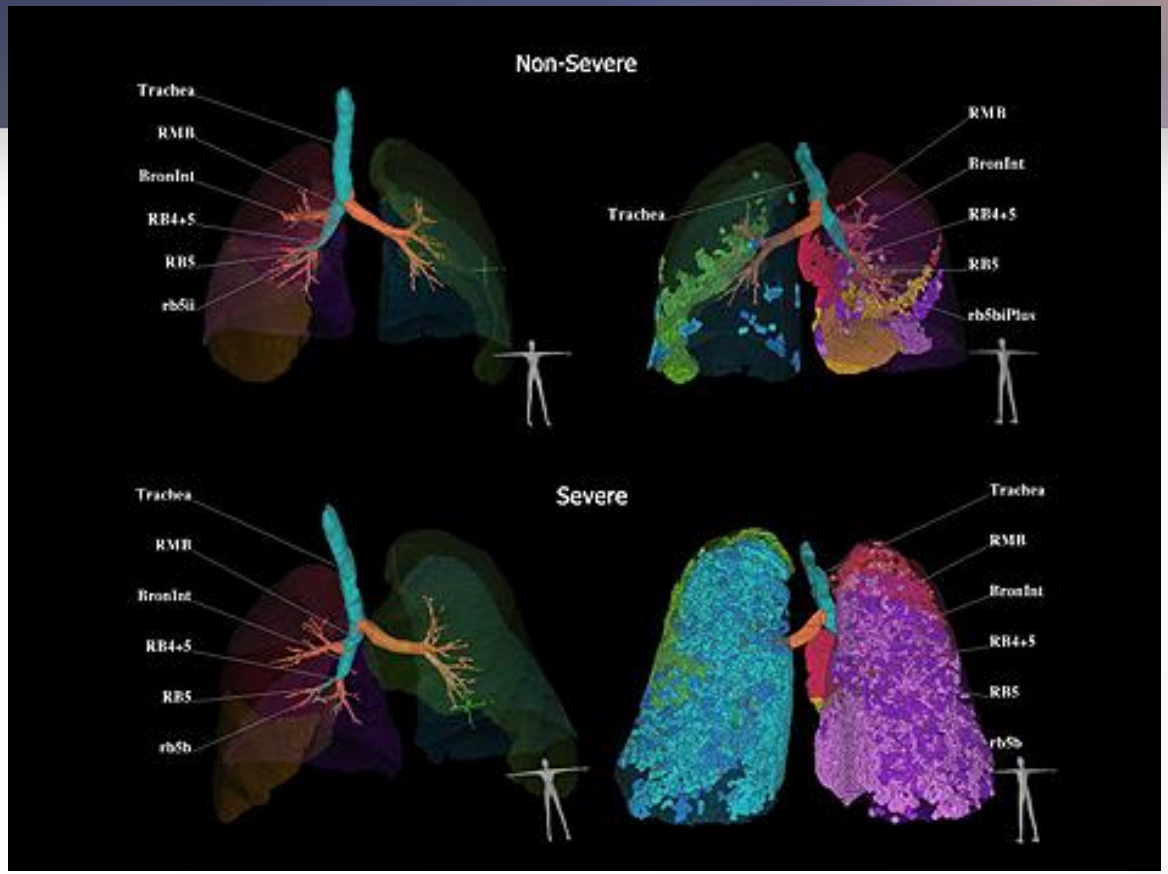
Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med. 2012367:40-49.



Αναπνευστικό

- Camargo CA Jr, Ganmaa D, Frazier AL, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. Pediatrics. 2012;130:e561-567.
- Bergman P, Norlin AC, Hansen S, et al. Vitamin D3 supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study. BMJ Open. 2012, 13;2:e001663.

- Murdoch DR, Slow S, Chambers ST, et al. Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. JAMA. 2012;308:1333-1339.


Non-Severe
Trachea
RMB
BronInt
RB4+5
RB5
rb5ii
Trachea
RMB
BronInt
RB4+5
RB5
rb5biPlus
Severe
Trachea
RMB
BronInt
RB4+5
RB5
rb5b
Trachea
RMB
BronInt
RB4+5
RB5
rb5b

Annals of Internal Medicine | ORIGINAL RESEARCH

High Doses of Vitamin D to Reduce Exacerbations in Chronic Obstructive Pulmonary Disease

A Randomized Trial

An Lehouck, PhD; Chantal Mathieu, MD, PhD; Claudia Carremans, MS; Femke Baeke, PhD; Jan Verhaegen, MD, PhD; Johan Van Eldere, MD, PhD; Brigitte Decallonne, MD, PhD; Roger Bouillon, MD, PhD; Marc Decramer, MD, PhD; and Wim Janssens, MD, PhD

Background: Low serum 25-hydroxyvitamin D (25-[OH]D) levels have been associated with lower FEV_1, impaired immunologic control, and increased airway inflammation. Because many patients with chronic obstructive pulmonary disease (COPD) have vitamin D deficiency, effects of vitamin D supplementation may extend beyond preventing osteoporosis.

Objective: To explore whether supplementation with high doses of vitamin D could reduce the incidence of COPD exacerbations.

Design: Randomized, single-center, double-blind, placebo-controlled trial. (ClinicalTrials.gov registration number: NCT00666367)

Setting: University Hospitals Leuven, Leuven, Belgium.

Patients: 182 patients with moderate to very severe COPD and a history of recent exacerbations.

Intervention: 100 000 IU of vitamin D supplementation or placebo every 4 weeks for 1 year.

Measurements: The primary outcome was time to first exacerbation. Secondary outcomes were exacerbation rate, time to first hospitalization, time to second exacerbation, FEV_1, quality of life, and death.

Results: Mean serum 25-(OH)D levels increased significantly in the vitamin D group compared with the placebo group (mean between-group difference, 30 ng/mL [95% CI, 27 to 33 ng/mL]; $P < 0.001$). The median time to first exacerbation did not significantly differ between the groups (hazard ratio, 1.1 [CI, 0.82 to 1.56]; $P = 0.41$), nor did exacerbation rates, FEV_1, hospitalization, quality of life, and death. However, a post hoc analysis in 30 participants with severe vitamin D deficiency (serum 25-[OH]D levels <10 ng/mL) at baseline showed a significant reduction in exacerbations in the vitamin D group (rate ratio, 0.57 [CI, 0.33 to 0.98]; $P = 0.042$).

Limitation: This was a single-center study with a small sample size.

Conclusion: High-dose vitamin D supplementation in a sample of patients with COPD did not reduce the incidence of exacerbations. In participants with severe vitamin D deficiency at baseline, supplementation may reduce exacerbations.

Primary Funding Source: Applied Biomedical Research Program, Agency for Innovation by Science and Technology (IWT-TBM).

Ann Intern Med. 2012;156:105-114. www.annals.org

For author affiliations, see end of text.

Diabetologia (2012) 55:3224–3227
DOI 10.1007/s00125-012-2709-8

SHORT COMMUNICATION

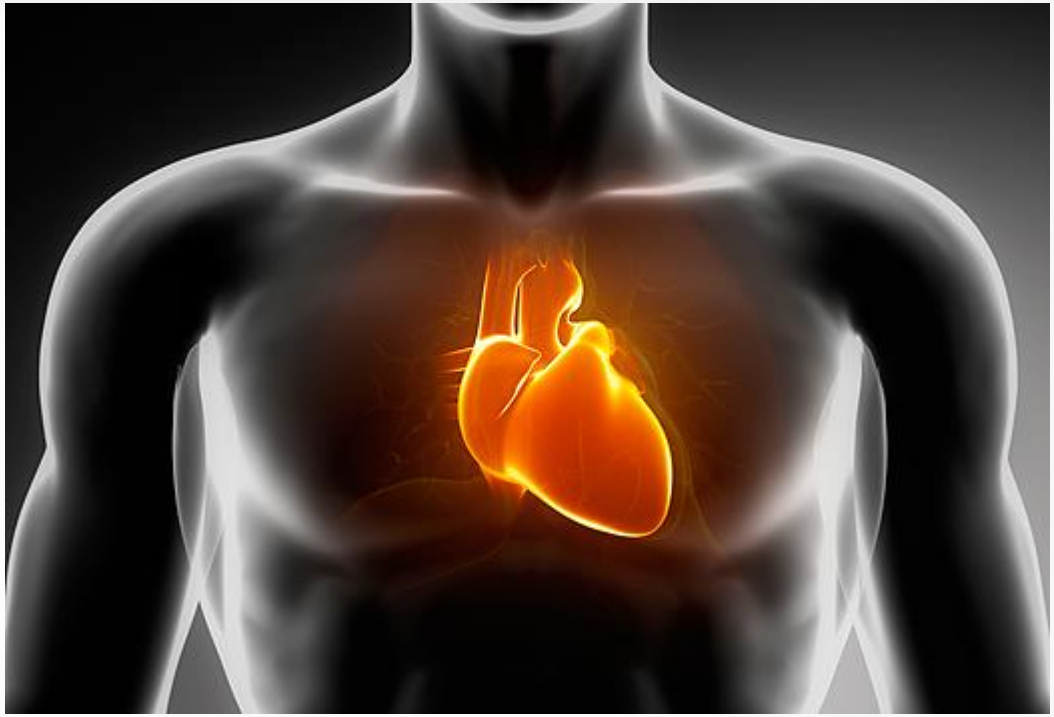
Lower prediagnostic serum 25-hydroxyvitamin D concentration is associated with higher risk of insulin-requiring diabetes: a nested case–control study

E. D. Gorham · C. F. Garland · A. A. Burgi · S. B. Mohr · K. Zeng · H. Hofflich · J. J. Kim · C. Ricordi

Καρδιαγγειακό

Χαμηλά επίπεδα βιταμίνης D αυξάνουν τον κίνδυνο καρδιαγγειακών συμβαμάτων .

Η υγεία της καρδιάς βελτιώνεται καθώς τα επίπεδα της αυξάνονται από 20 σε 60 nmol/L, με κίνδυνο για αύξηση του καρδιαγγειακού κινδύνου σε υψηλότερα επίπεδα βιταμίνης D.



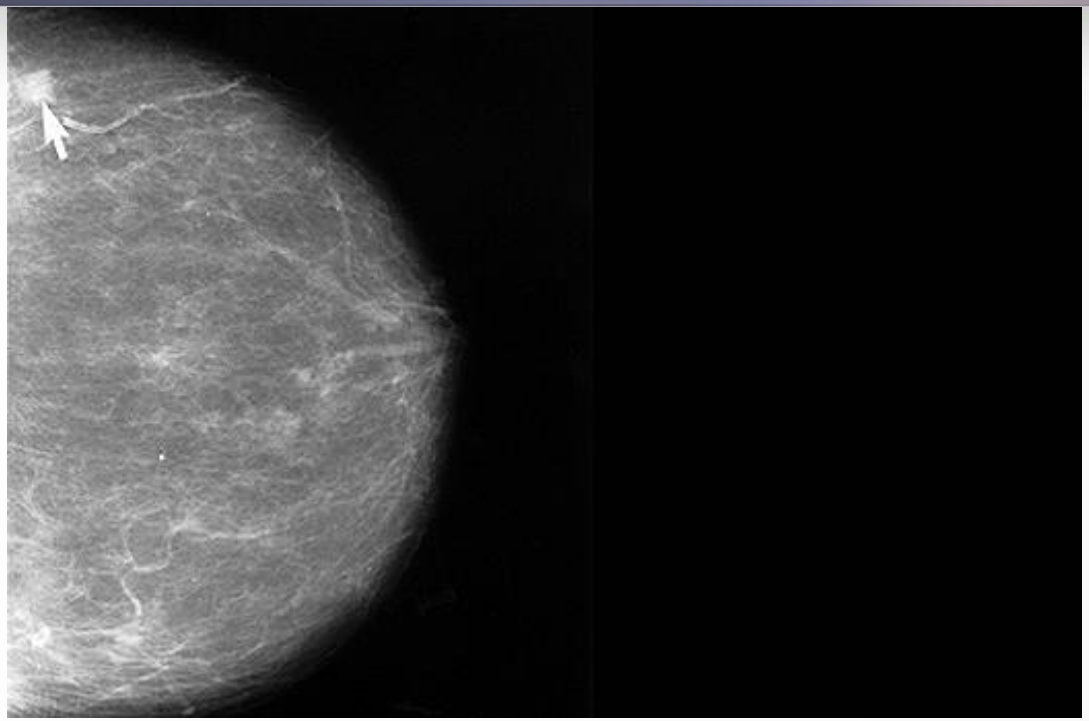
Brøndum-Jacobsen P, Benn M, Jensen GB, et al. 25-hydroxyvitamin D levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. Arterioscler Thromb Vasc Biol. 2012;32:2794-2804.

Wang L, Song Y, Manson JE, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease. A meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes. 2012;5:819-829.

Παχυσαρκία

Turer CB, Lin H, Flores G. Prevalence of vitamin D deficiency among overweight and obese US children. Pediatrics. 2013;131:e152-61.

LeBlanc ES, Rizzo JH, Pedula KL, et al. Associations between 25-hydroxyvitamin D and weight gain in elderly women. J Womens Health (Larchmt). 2012;21:1066-1073.



Καρκίνος του μαστού

Νευρολογικό

Αυτισμός

Grant WB, Cannell JJ. Autism prevalence in the United States with respect to solar UV-B doses: an ecological study. Dermato-Endocrinology. 2013;5:1-6

Νόσος Alzheimer's

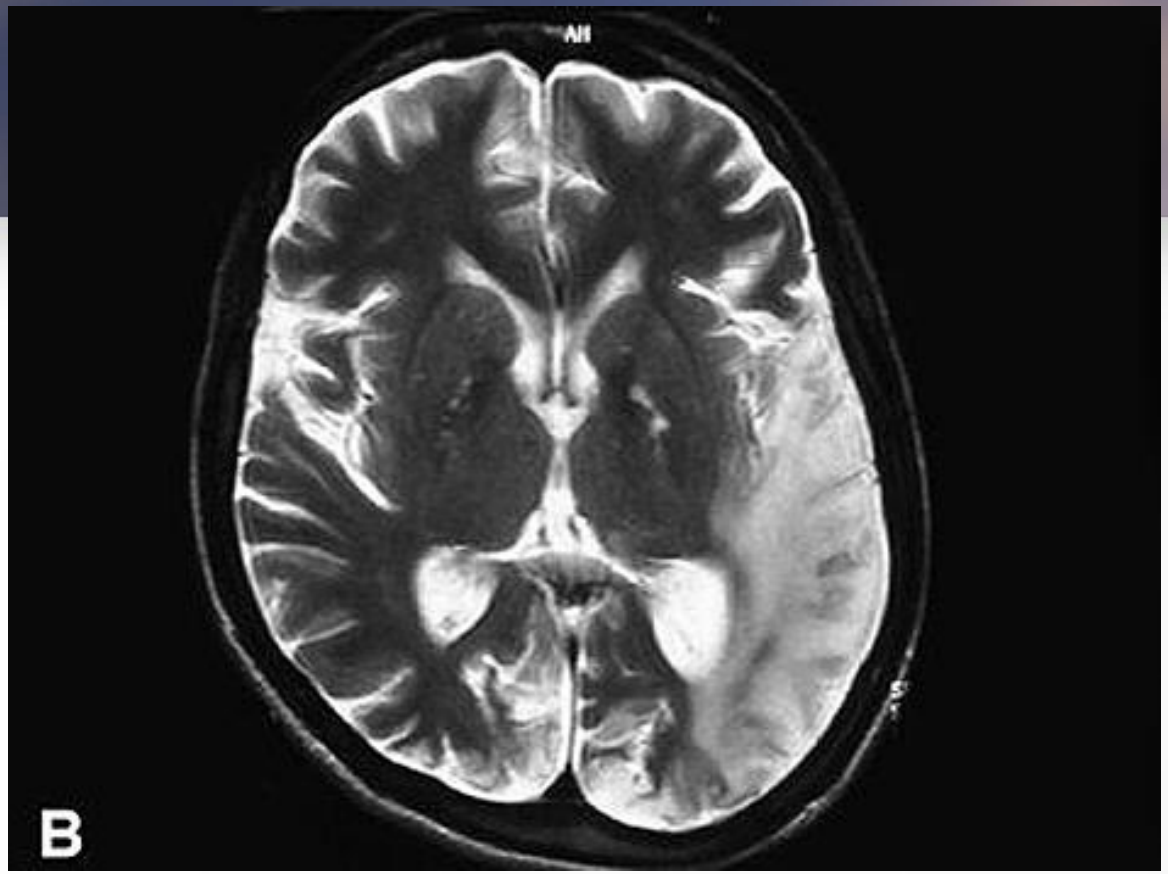
Balion C, Griffith LE, Strifler L, et al. Vitamin D, cognition, and dementia: a systematic review and meta-analysis. Neurology. 2012;79:1397-1405

Αμυλοειδές

Mizwicki MT, Menegaz D, Zhang J, et al. Genomic and nongenomic signaling induced by 1a,25(OH)2-vitamin D3 promotes the recovery of amyloid-β phagocytosis by Alzheimer's disease macrophages. J Alzheimers Dis. 2012;29:51-62

Αναπτυξιακές διαταραχές

Whitehouse AJ, Holt BJ, Serralha M, et al. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. Pediatrics. 2012;129:485-493.



Θρομβοεμβολικά επεισόδια- Σκλήρυνση

Kojima G, Bell C, Abbott RD, et al. Low dietary vitamin D predicts 34-year incident stroke: the Honolulu Heart Program. Stroke. 2012;43:2163-2167.

Décard BF, von Ahsen N, Grunwald T, et al. Low vitamin D and elevated immunoreactivity against Epstein-Barr virus before first clinical manifestation of multiple sclerosis. J Neurol Neurosurg Psychiatry. 2012;83:1170-1173.

Improvement of Primary Dysmenorrhea Caused by a Single Oral Dose of Vitamin D: Results of a Randomized, Double-blind, Placebo-Controlled Study

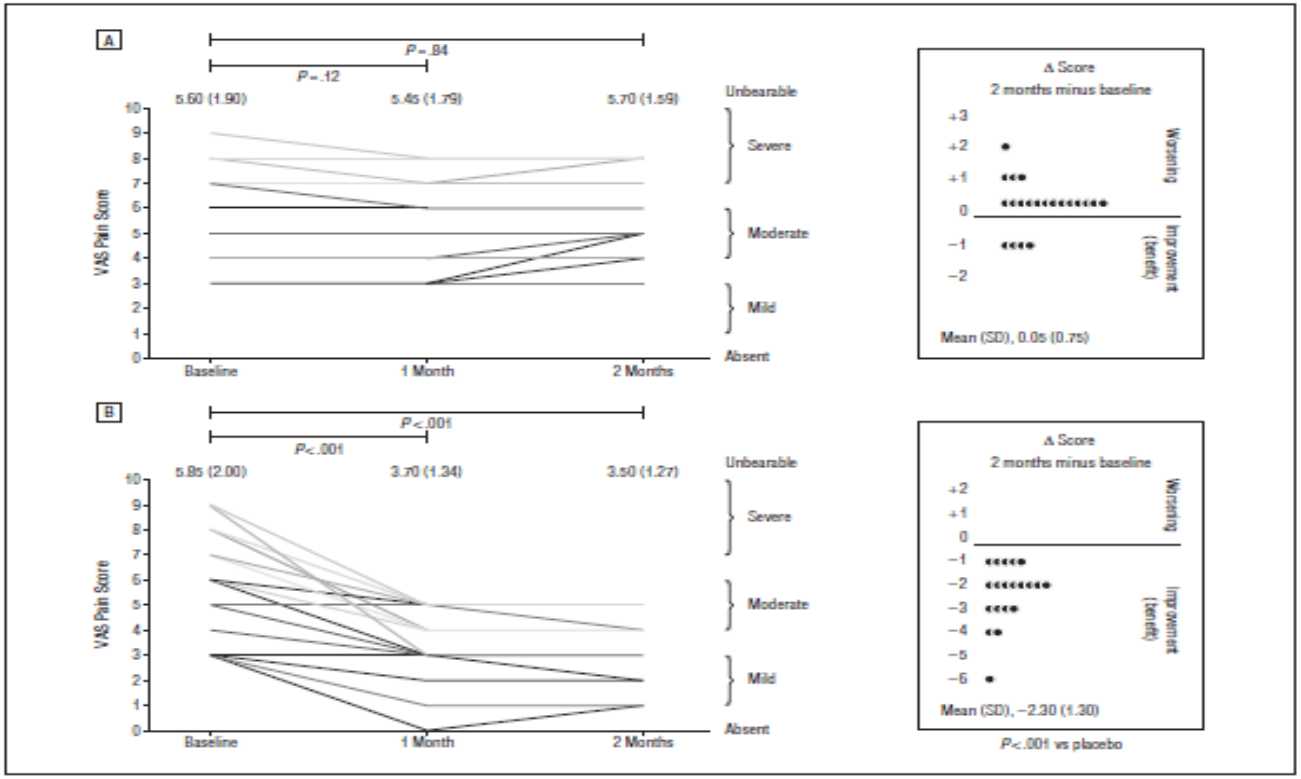


Figure. Changes in mean (SD) pain score in the placebo-treated (A) and vitamin D–treated (B) groups over the 60 days of the study. Eligible women reported intensity of pain on a visual analog scale (VAS) at baseline and then at the end of the first and second month after the dose of placebo or vitamin D. The filled circles in the right panels represent individual changes. Both placebo and vitamin D groups were homogeneous for age (mean [SD], 27 [6.01] y vs 26.3 [6.23] y), body mass index (mean [SD], 21.17 [2.15] vs 21.96 [2.06] [calculated as weight in kilograms divided by height in meters squared]), baseline 25-hydroxyvitamin D_2 levels (mean [SD], 29.97 [7.62] ng/mL vs 27.19 [7.53] ng/mL [to convert to nanomoles per liter, multiply by 2.496]), and baseline VAS pain score (mean [SD], 5.60 [1.90] vs 5.85 [2.00]).

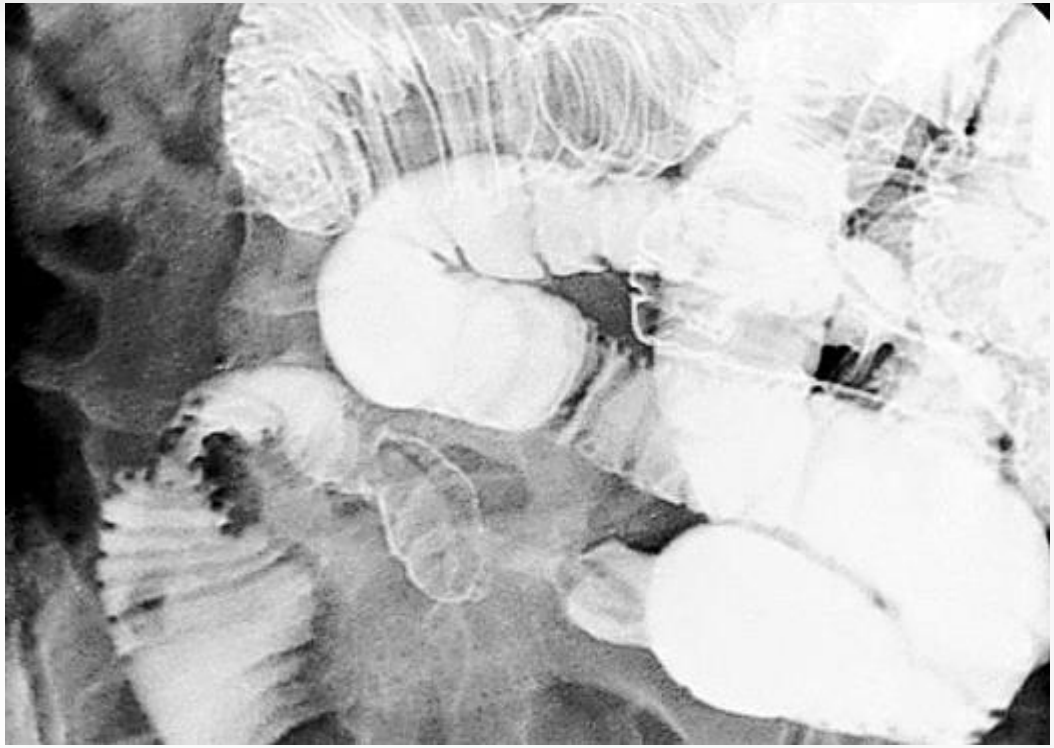
Γαστρεντερικό

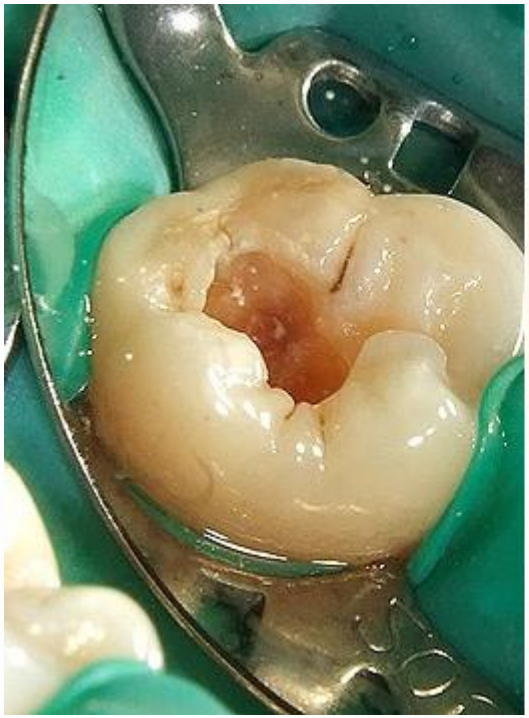
Women with sufficient vitamin D levels at baseline are 62% less likely to develop Crohn's disease over 22 years than those with vitamin D insufficiency.[

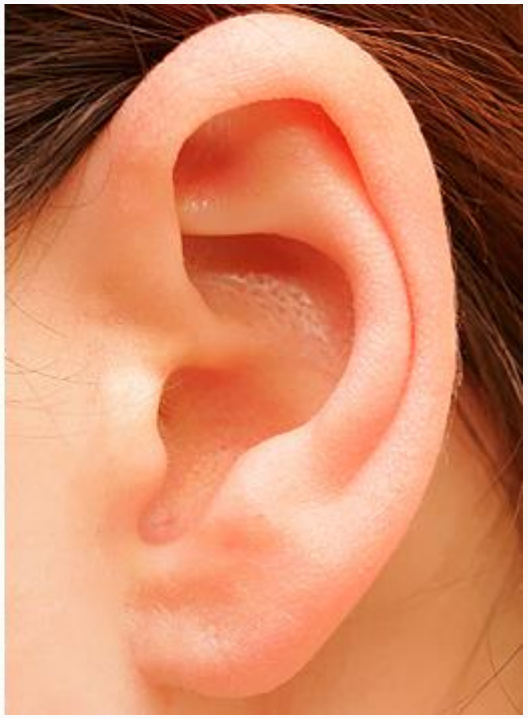
Ananthakrishnan AN, Khalili H, Higuchi LM, et al. Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. Gastroenterology. 2012;142:482-489

Women living at southern latitudes in the United States are 52% less likely to have inflammatory bowel disease than those living in the north.

Khalili H, Huang ES, Ananthakrishnan AN, et al. Geographical variation and incidence of inflammatory bowel disease among US women. Gut. 2012;61:1686-1692.







Πόση βιταμίνη είναι αρκετή?

- The Institute of Medicine says blood levels should be 20 ng/mL, but the Endocrine Society sets the level at 30 ng/mL.
- The US Recommended Dietary Allowance is 600 IU for people ages 1 to 70 years and 800 IU for those who are older.
- Some authorities recommend that people who are deficient should receive supplements of 1000 to 2000 IU daily, but others have recommended single-bolus doses of up to 500,000 IU

Ελιξήριο?

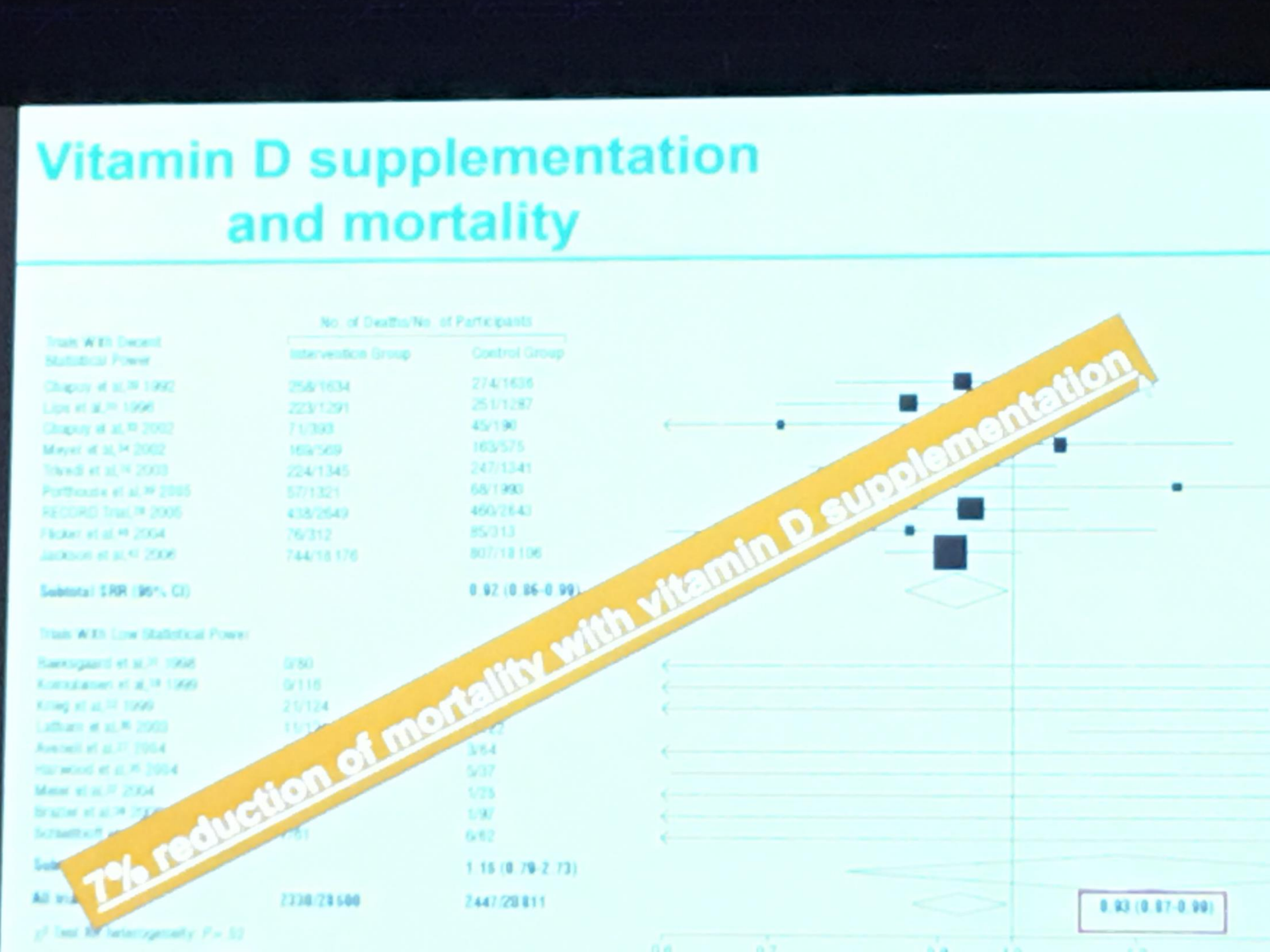
- Vitamin D has also linked to lower mortality in patients with pneumonia.

- Increased intake of vitamin D plus calcium, but not vitamin D alone, is linked to a decrease in all-cause mortality among elderly patients.

Leow L, Simpson T, Cursons R, et al. Vitamin D, innate immunity and outcomes in community acquired pneumonia. Respirology. 2011;16:611-616.

Rejnmark L, Avenell A, Masud T, et al. Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. J Clin Endocrinol Metab. 2012;97:2670-2681.

Vitamin D supplementation and mortality



Levels of 25-hydroxyvitamin D in familial longevity: the Leiden Longevity Study

Raymond Noordam MSc, Anton J.M. de Craen PhD, Pardis Pedram MD MSc, Andrea B. Maier MD PhD, Simon P. Mooijaart MD PhD, Johannes van Pelt PhD, Edith J. Feskens PhD, Martinette T. Streppel PhD, P. Eline Slagboom PhD, Rudi G.J. Westendorp MD PhD, Marian Beekman PhD, Diana van Heemst PhD

Abstract

Background: Low levels of 25(OH) vitamin D are associated with various age-related diseases and mortality, but causality has not been determined. We investigated vitamin D levels in the offspring of nonagenarians who had at least one nonagenarian sibling; these offspring have a lower prevalence of age-related diseases and a higher propensity to reach old age compared with their partners.

Methods: We assessed anthropometric characteristics, 25(OH) vitamin D levels, parathyroid hormone levels, dietary vitamin D intake and single nucleotide polymorphisms (SNPs) associated with vitamin D levels. We included offspring (n = 1038) of nonagenarians who had at least one nonagenarian sibling, and the offsprings' partners (n = 461; controls) from the Leiden Longevity Study. We included age, sex, body mass index, month during which blood sampling was performed, dietary and supplemental vitamin D intake, and creatinine levels as possible confounding factors.

Results: The offspring had significantly lower levels of vitamin D (64.3 nmol/L) compared with controls (68.4 nmol/L; p = 0.002), independent of possible confounding factors. There was no difference in the levels of parathyroid hormone between groups. Compared with controls, the offspring had a lower frequency of a genetic variant in the *CYP2R1* gene (rs2060793) (p = 0.04). The difference in vitamin D levels between offspring and controls persisted over the 2 most prevalent genotypes of this SNP.

Interpretation: Compared with controls, the offspring of nonagenarians who had at least one nonagenarian sibling had a reduced frequency of a common variant in the *CYP2R1* gene, which predisposes people to high vitamin D levels; they also had lower levels of vitamin D that persisted over the 2 most prevalent genotypes. These results cast doubt on the causal nature of previously reported associations between low levels of vitamin D and age-related diseases and mortality.

Competing interests: None declared.

This article has been peer reviewed.

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Diana van Heemst,
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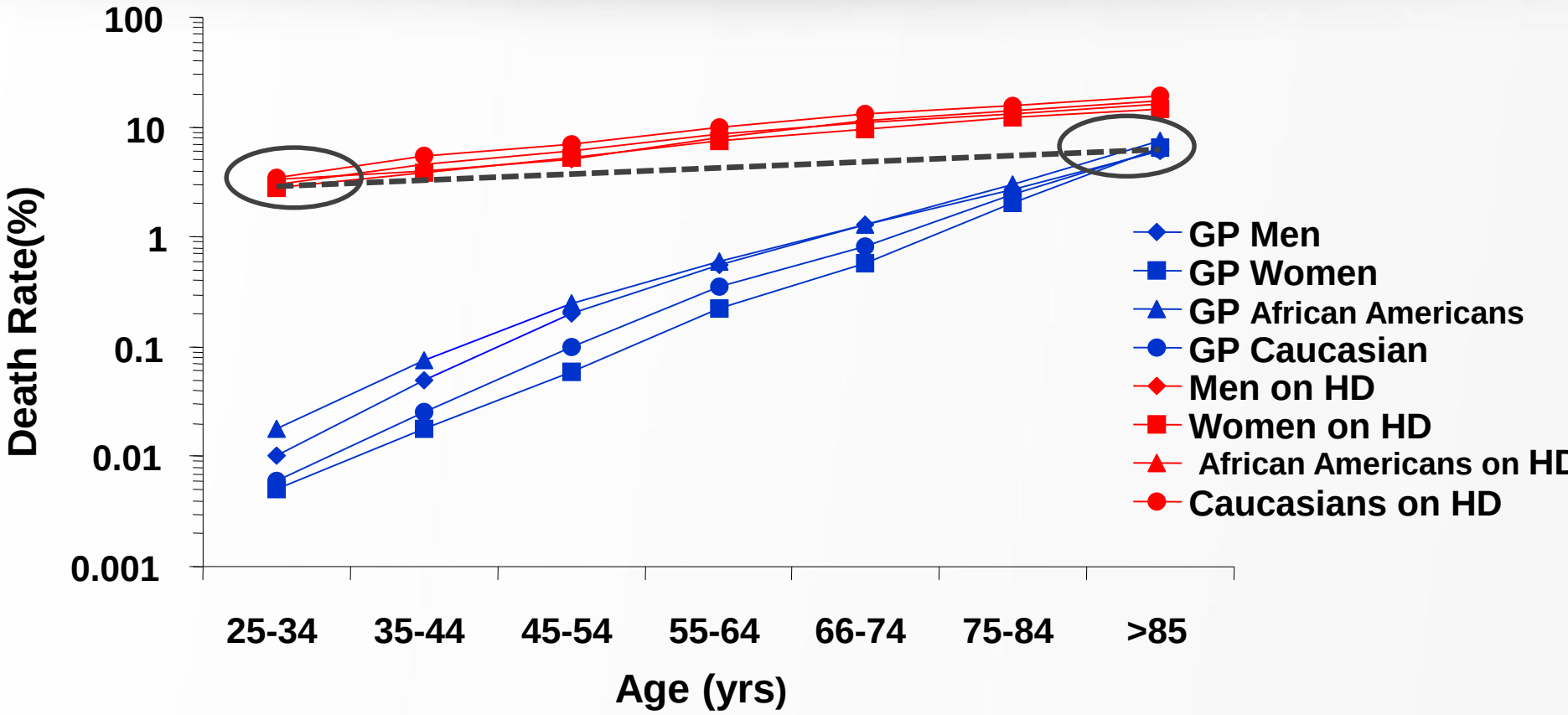
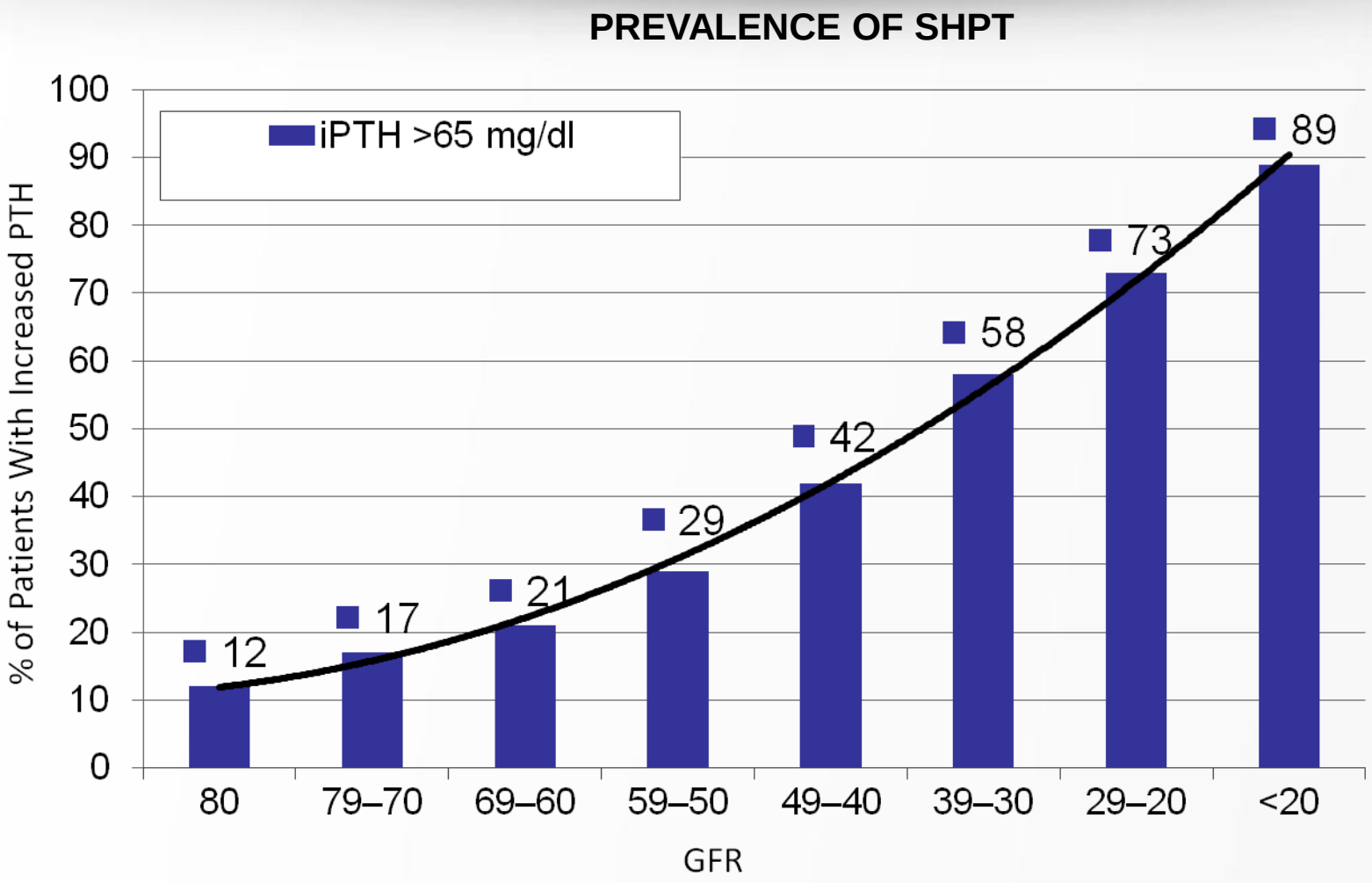
***CMAJ* 2012. DOI:10.1503/cmaj.120233**

Survival in CKD



Foley RN et al. Am J Kidney Dis. 1998; 32(5 suppl 3): S112-9.

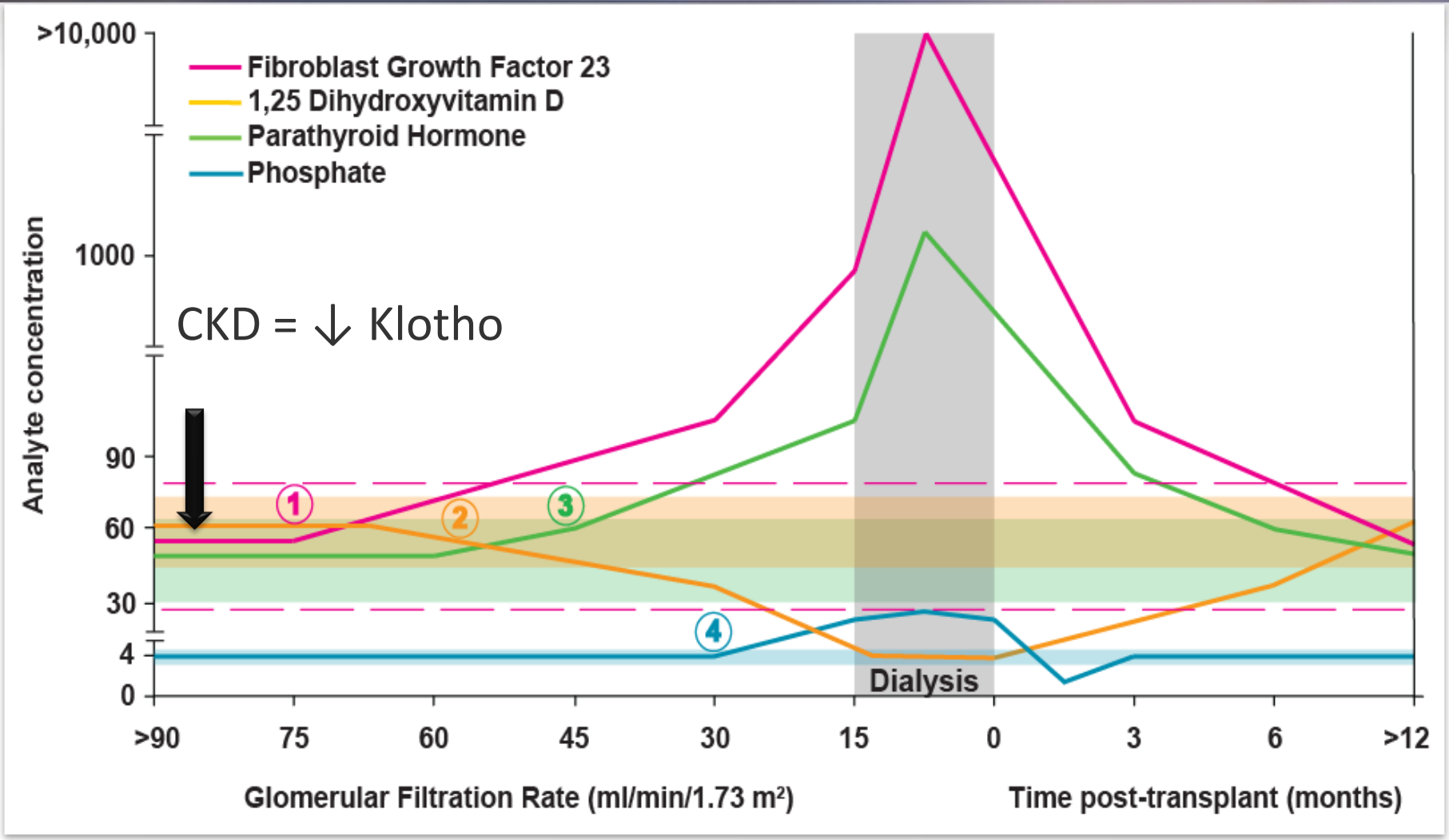
Prevalence of SHPT as GFR Decreases



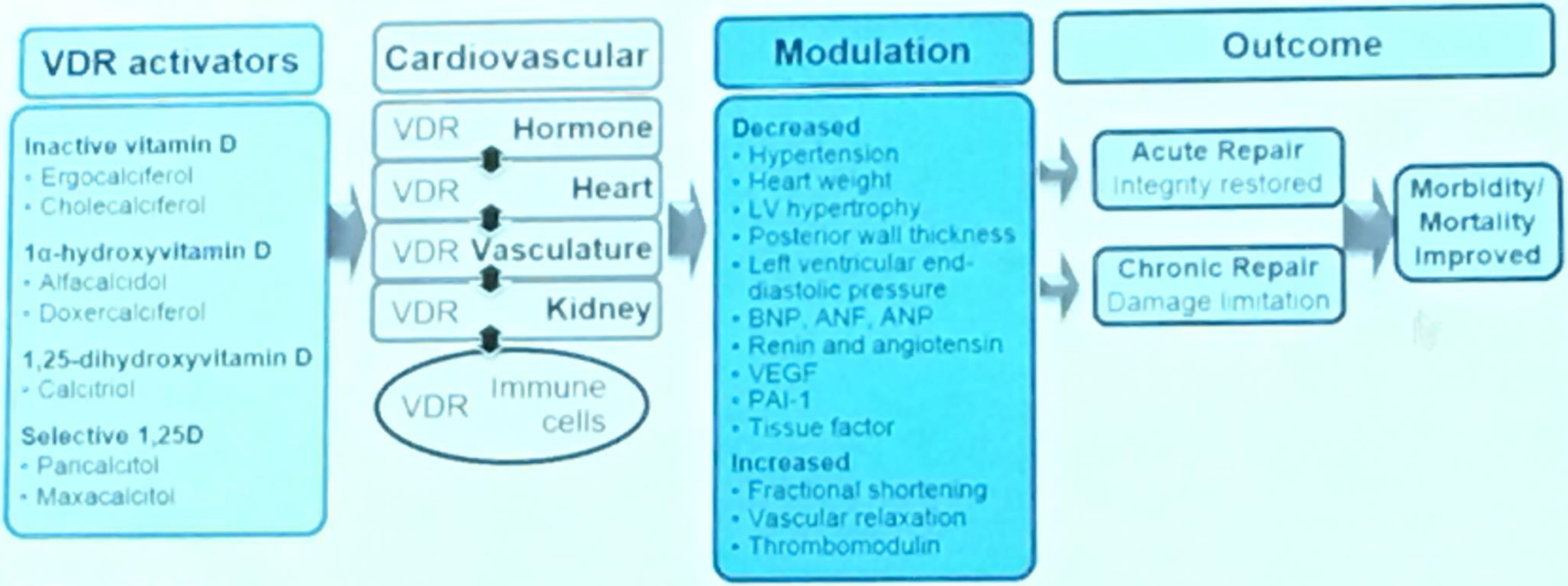
Levin A, et al. *CJAN*. 2009;4:1508-1514.

24

Klotho: Early decrease in CKD



The vitamin D System: a Crosstalk between the Heart and the Kidney



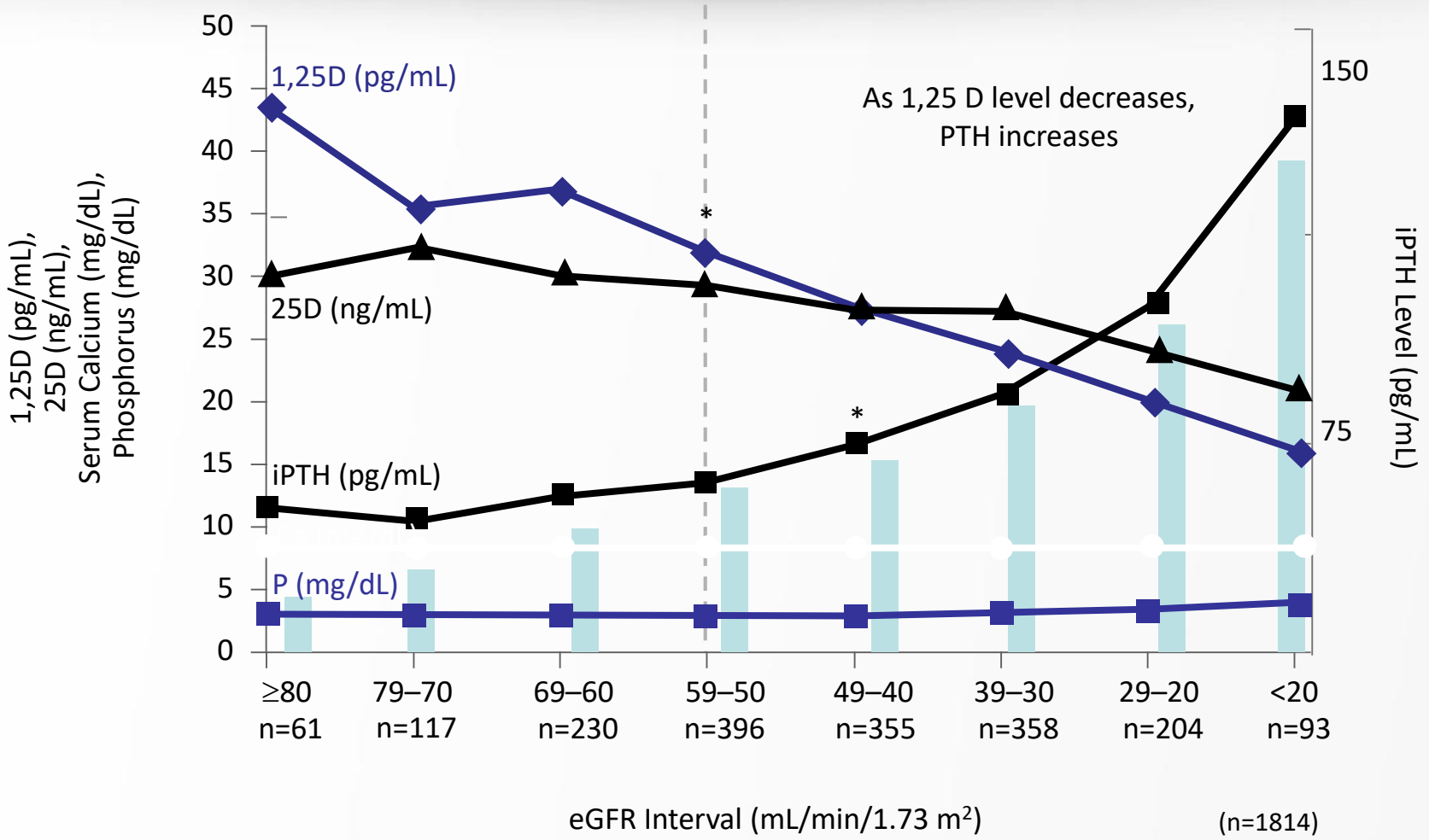
Other effects

Calcification	VDR effect
Inducers	
• BMP-2	↓
• Type 1 collagen	↓
• IL-1β and TNF-α	↓
Inhibitors	
• MGP	↑
• Osteopontin	↑
• Type IV collagen	↑

Kidney fibrosis	VDR effect
• Interstitial volume	↓
• Glomerulosclerosis	↓
• TGF-β1	↓

ANF, atrial natriuretic factor; ANP, atrial natriuretic protein; BMP-2, bone morphogenetic protein-2; BNP, brain natriuretic protein; IL-1β, interleukin-1β; LV, left ventricular; MGP, matrix Gla protein; PAI-1 plasminogen activator inhibitor-1; TGF-β, tumour growth factor-β; TNF-

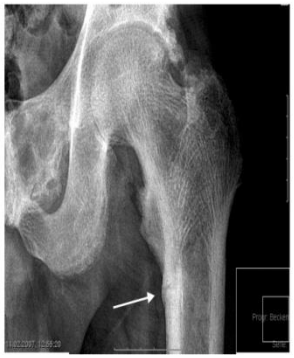
Reduced VDR Activation in SHPT

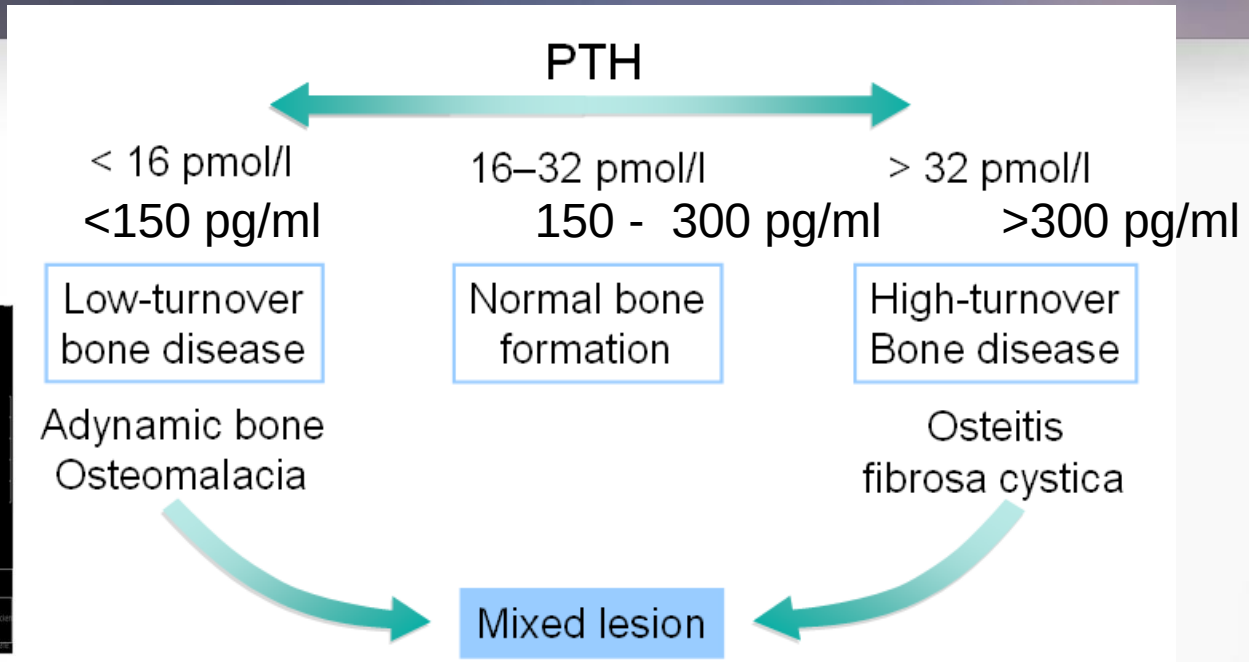


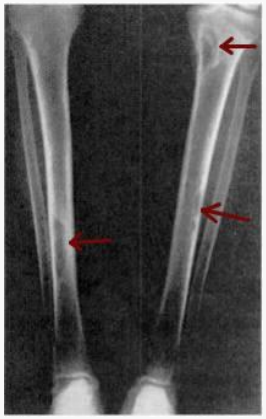
*P<.001.

Levin, et al. *Kidney Int*. 2007;71:31-38.

Renal Bone Disease spectrum







Osteomalacia

- defective mineralization of newly formed osteoid (most often caused by aluminum deposition)
- bone turnover is decreased

Adynamic bone disease (Age, DM, Al)

- abnormally low bone turnover

Osteitis fibrosa (↑PTH)

↑ osteoclast and osteoblast activity

- peritrabecular fibrosis
- increased bone turnover

Kidney International, Vol. 63, Supplement 85 (2003), pp. S83–S87

New vitamin D analogs

EDUARDO SLATOPOLSKY, JANE FINCH, and ALEX BROWN

Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri

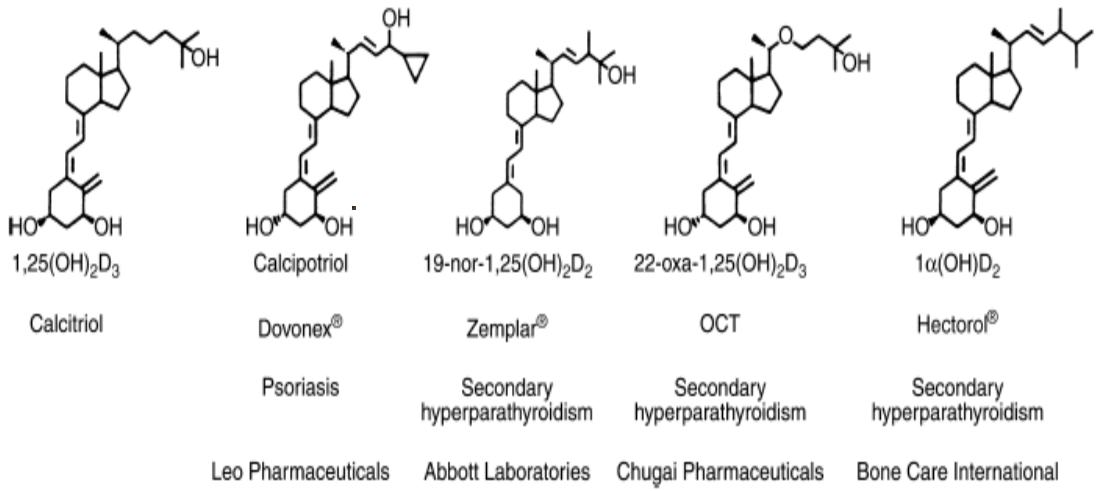
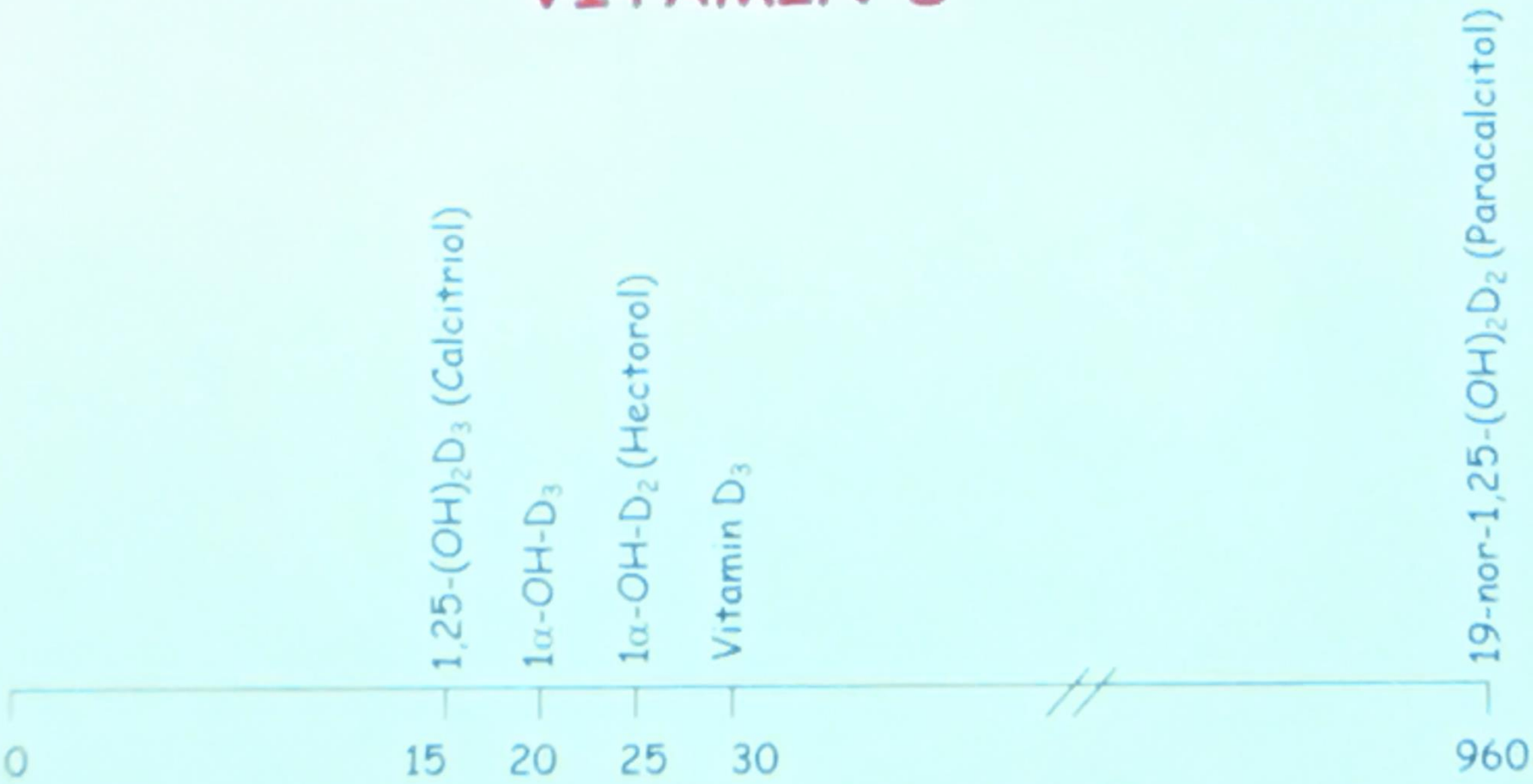


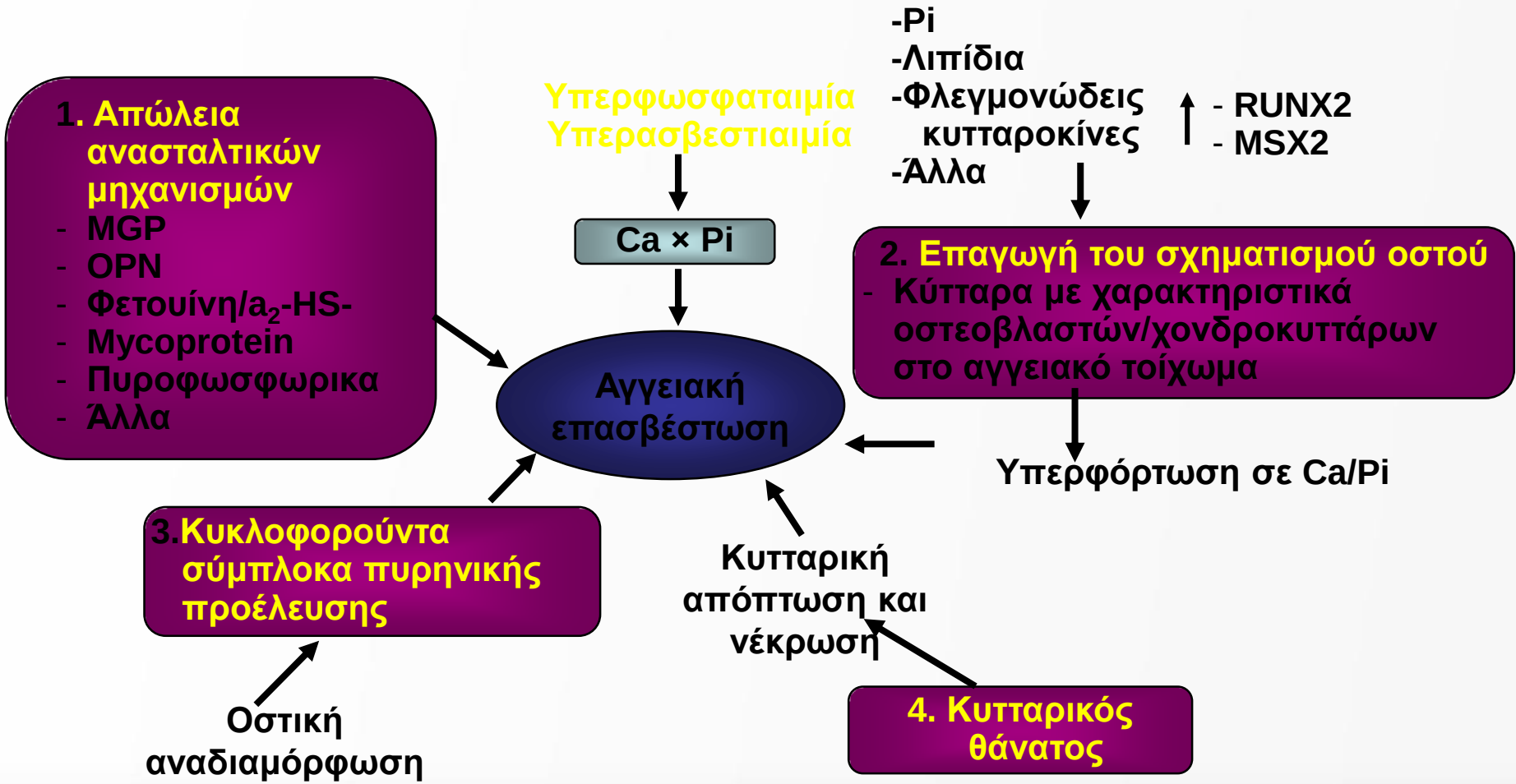
Fig. 1. Chemical structure of $1,25(OH)_2D_3$ and several vitamin D analogs. (Reproduced from reference [29]).

EVOLUTION OF OUR UNDERSTANDING OF VITAMIN D



ng/day required to raise serum calcium 1 mg/100 ml in vitamin D-deficient mice

Αγγειακές επασβεστώσεις: μηχανισμός



Giachelli CM. J Am Soc Nephrol 2004:15:2959–64

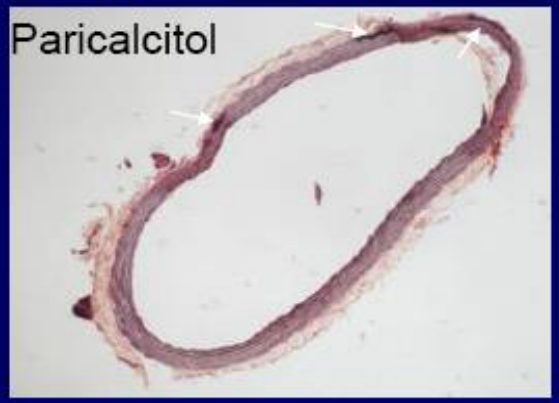
Η επίδραση στις τιμές των Ca, Ph και την εμφάνιση αγγειακών επασβεστώσεων ευνοούν την *paricalcitol*.

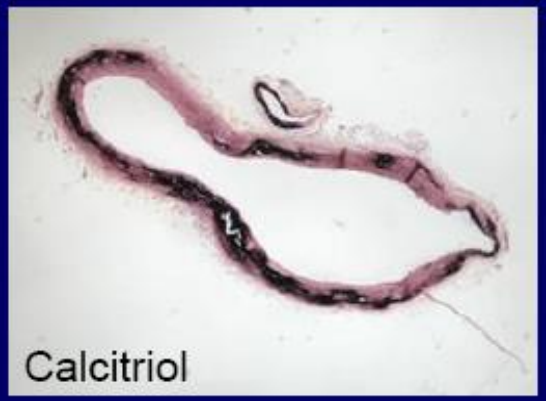
Η αύξηση ινωματώδους ιστού περιαγγειακά ευνοεί την *calcitriol*.

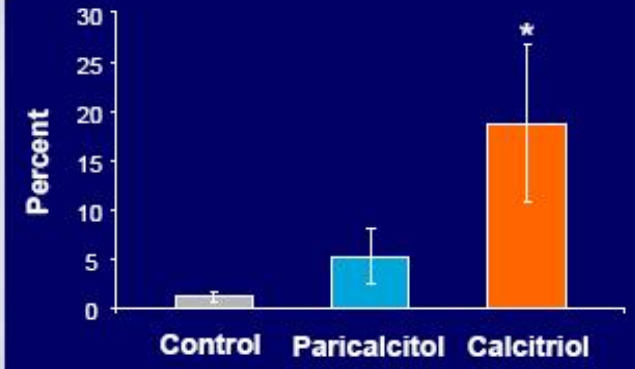
Repo JM, Rantala IS, Honkanen TT, et al.. Paricalcitol aggravates perivascular fibrosis in rats with renal insufficiency and low calcitriol. Kidney Int 2007;72:977-984.

Calcitriol Induces More Calcification Than Paricalcitol

- 5/6 nephrectomized rats with high doses of calcitriol (1 µg/kg) or paricalcitol (3 µg/kg) for 8 weeks



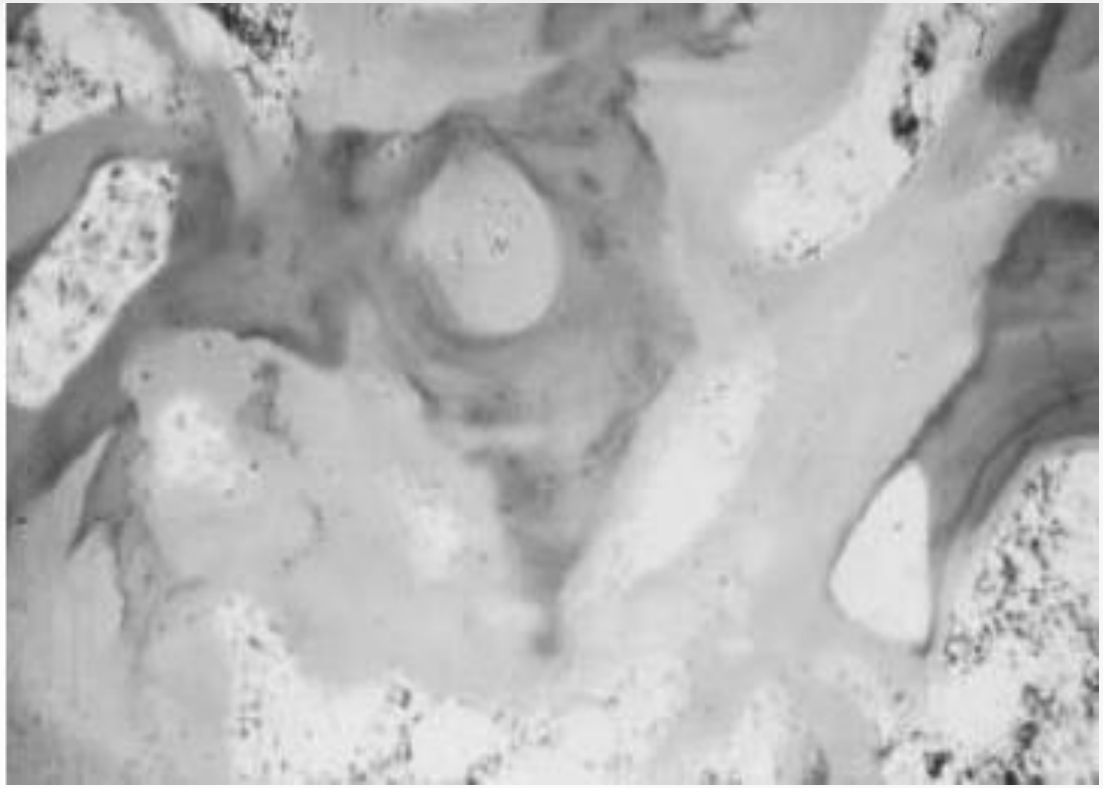




*p<0.01 vs Control

Cardus A, et al. J Bone Miner Res 2007;22:860-6

Αδυναμική Οστική Νόσος



Baker LR, Abrams L, Roe CJ, Faugere MC, Fanti P, Subayti Y, Malluche HH.
1,25(OH)2D3 administration in moderate renal failure: a prospective double-blind.
Kidney Int. 1989 ;35(2

Kidney International, Vol. 63, Supplement 85 (2003), pp. S83–S87

New vitamin D analogs

EDUARDO SLATOPOLSKY, JANE FINCH, and ALEX BROWN

Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri

The vitamin D analogs currently used for the treatment of secondary hyperparathyroidism have less calcemic and phosphatemic activity while still effectively

Επανεξέταση του ρόλου της βιτ-D;

…It is surprising that the uncertainty and ongoing debate over vitamin D use in chronic kidney disease still relies on uncontrolled data and few randomized trials that show efficacy only for correction of bone and serum adnormalities …

S Palmer, G Srippoli. Vitamin D compounds in chronic kidney disease: change may be needed for good! Nephrol Dial Transplant 2008;23:1786-1789

Επανεξέταση του ρόλου της βιτ-D;

Critique of Observational Data Analyses

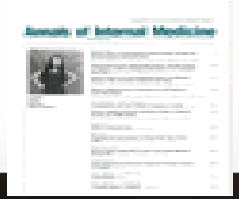
- Differences in baseline characteristics
- Potential misclassification and bias
- Non-random assignment of therapy could have led to unequal susceptibility to the outcome
- Lack of prospective data
- Groups not contemporaneous
- Residual confounding
  - Why people get VDRA therapy in the first place accounts for the benefit even if that factor(s) remains elusive
- Need for supportive biological data

Επανεξέταση του ρόλου της βιτ-D;

- **3500 pts**
- **76 Randomized Controlled Trials**

➢ **Insufficient randomized evidence was available to determine the beneficial effect on mortality and clinical outcomes in chronic kidney disease.**

➢ **Vitamin D compounds have unproven efficacy relative to important clinical end points.**



Palmer SC, McGregor DO, Macaskill P, et al. Vitamin D compounds in chronic kidney disease: a meta analysis. Ann Intern Med 2007;147:840-853

Επανεξέταση του ρόλου της βιτ-D;

…few trials bother to look…large placebo controlled trials with hard clinical end points are justified and must be done…

All you need to read in the other general journals. BMJ 2008;336:16-17

Επανεξέταση του ρόλου της βιτ-D;

Our standards have rightly changed: whereas in the past we celebrated biochemical endpoints, we now insist on improving clinical outcomes. This was certainly the impetus for our own hypothesis-generating studies.[78]

Nevertheless, until we confirm which (if any) measure is a valid surrogate, one biochemical variable cannot be corrected at the expense of worsening another.

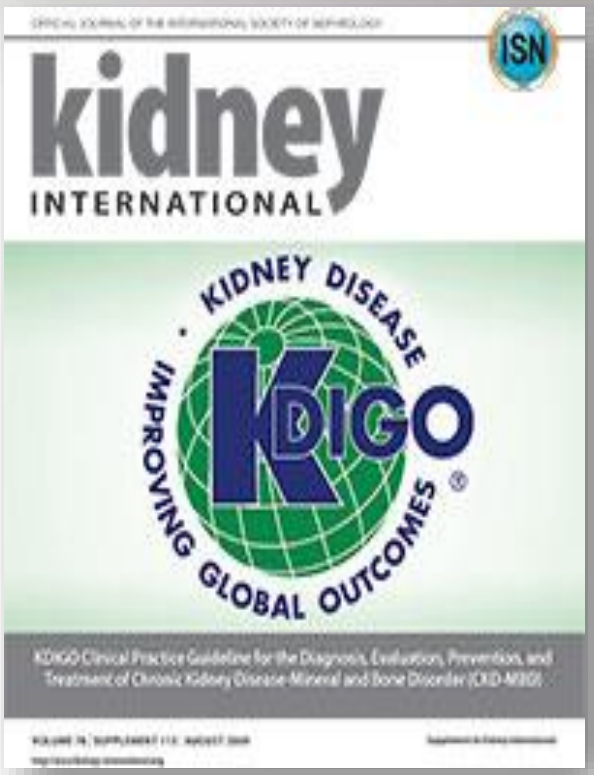
Tradhani R. Activated vitamin D sterols in kidney disease. Lancet 2008;371: 542-544

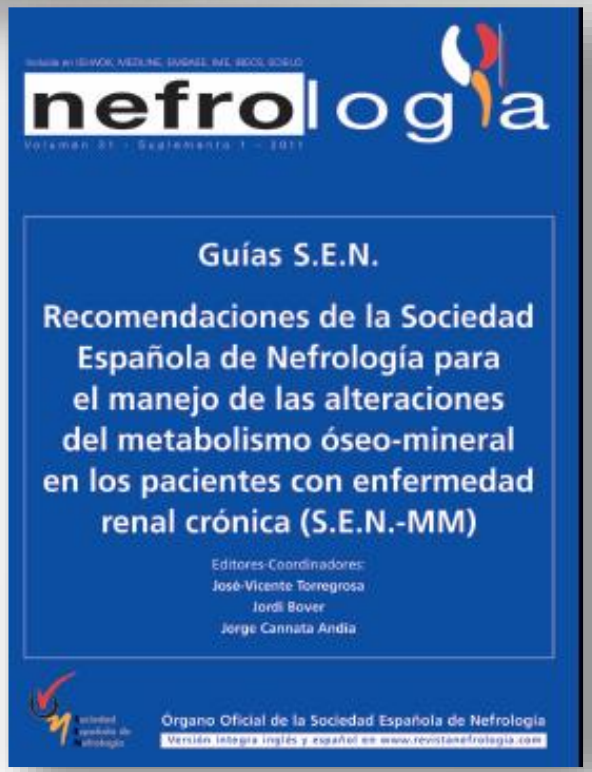
Επανεξέταση του ρόλου της βιτ-D;

…Clinical effects of vitamin D compounds are necessarily pleiotropic and incompletely understood, because of gene transcription by vitamin D in diverse tissues, via activation of vit-D receptors…

Tradhani R. Activated vitamin D sterols in kidney disease. Lancet 2008;371: 542-544

THERE IS NOT AN UNDISPUTABLE "1A" EVIDENCE IN GUIDELINES





" We suggest…

We might…"

KDIGO® CKD-MBD Guidelines: Recommendations for P, Ca and PTH

In patients with CKD stage 5D, we suggest lowering elevated P levels toward the normal range (2C)

In patients with CKD stages 3-5D, we suggest maintaining serum Ca in the normal range (2D)

In patients with CKD stage 5D, we suggest maintaining iPTH levels in the range of approximately 2–9 times the upper normal limit for the assay (2C)

Quality of evidence		
	High	**A**
	Moderate	**B**
	Low	**C**
	Very low	**D**

Strength of recommendation	
	Level 1: Strong "We recommend… should"
	Level 2: Weak "We suggest… might"

KDIGO® treatment recommendations: Rather than specific treatment targets, defines extreme ranges of risk

Laboratory values	KDIGO® recommendation	Grading
iPTH (pg/mL)	Suggested to maintain in the range of 2 to 9 x ULN	2C
Corrected Ca (mg/dL)	Suggested to maintain in the normal range	2D
P (mg/dL)	Suggested to lower toward the normal range	2C
CaxP (mg^2/dL^2)	Not suggested to direct clinical practice	N/A

KDIGO® nomenclature for rating guideline recommendations:
Strength of recommendation: 1: strong ('we recommend'), 2: weak ('we suggest')
Quality of evidence: A: high, B: moderate, C: low, D: very low

KDIGO® Clinical Practice Guideline for CKD-MBD. *Kidney Int* 2009;76(Suppl 113)

KDOQI™ treatment recommendations: Provide treatment target ranges to guide clinical practice

Laboratory values	KDOQI™ recommendation	Grading
iPTH (pg/mL)	150 to 300	Evidence
Corrected Ca (mg/dL)	8.4 to 9.5	Opinion
P (mg/dL)	3.5 to 5.5	Evidence
CaxP (mg^2/dL^2)	<55	Evidence

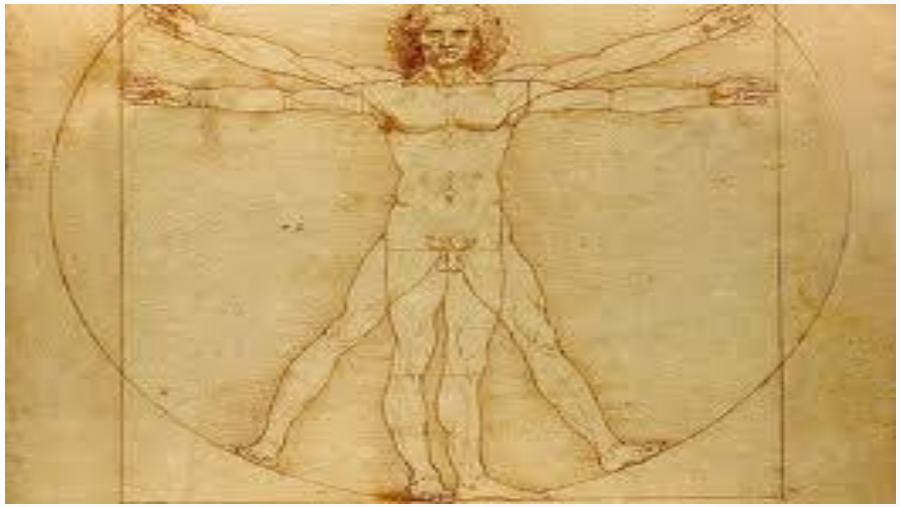
KDOQI™ guideline statements labels:
"Evidence" when all components of the rationale were based on published evidence
"Opinion" when no definite evidence existed or evidence was considered inconclusive

National Kidney Foundation. *Am J Kidney Dis* 2003;42(suppl 3):S1–S201

KDIGO consensus conference on CKD-MBD, held in Madrid in late October 2013
74 attendees /19 countries

Vascular calcification

Ca+Ph



Vit-D-PTH

Bone quality

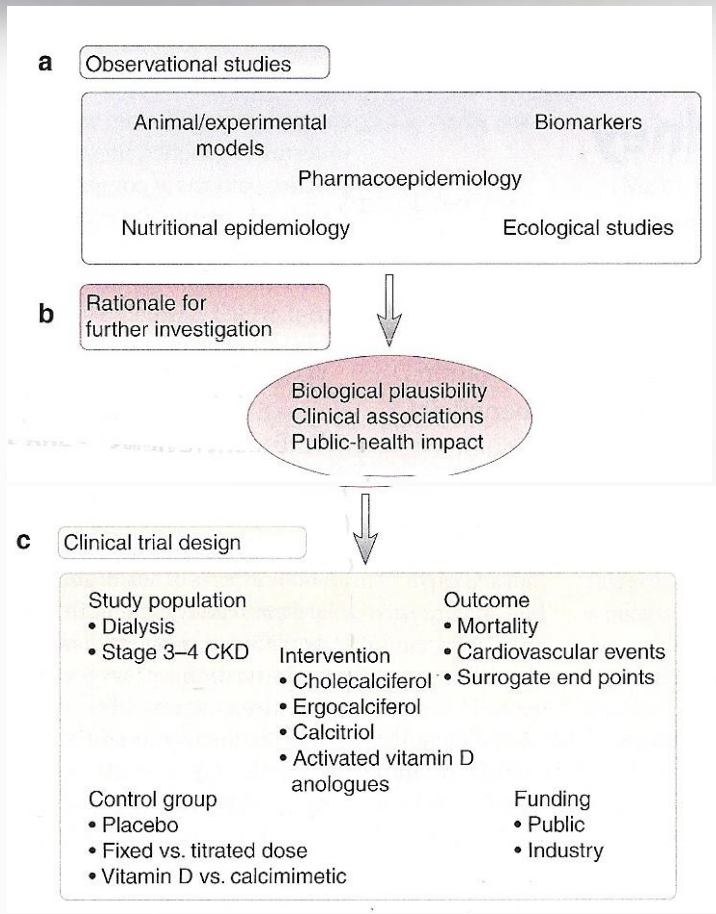
SUMMARY AND COMPARISON OF 2016 UPDATED AND 2009 KDIGO CKD-MBD RECOMMENDATIONS

2016 REVISED KDIGO CKD-MBD Recommendations	2009 KDIGO CKD-MBD Recommendations	Brief rationale for updating
4.2.4. In CKD 5D requiring PTH lowering therapy, we suggest CaMim, calcitriol, or vitamin D analogs, or a combination of CaMim and calcitriol, or vitamin D analogs. (*2B*)	4.2.4. In CKD 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or CaMim, or a combination of CaMim and calcitriol or vitamin D analogs use (*2B*).	Although EVOLVE did not meet its primary endpoint, the majority of the Work Group were reluctant to exclude potential benefits of calcimimetics for Stage 5D patients. CaMim, calcitriol, or vitamin D analogs are all acceptable first-line options in Stage 5D patients.

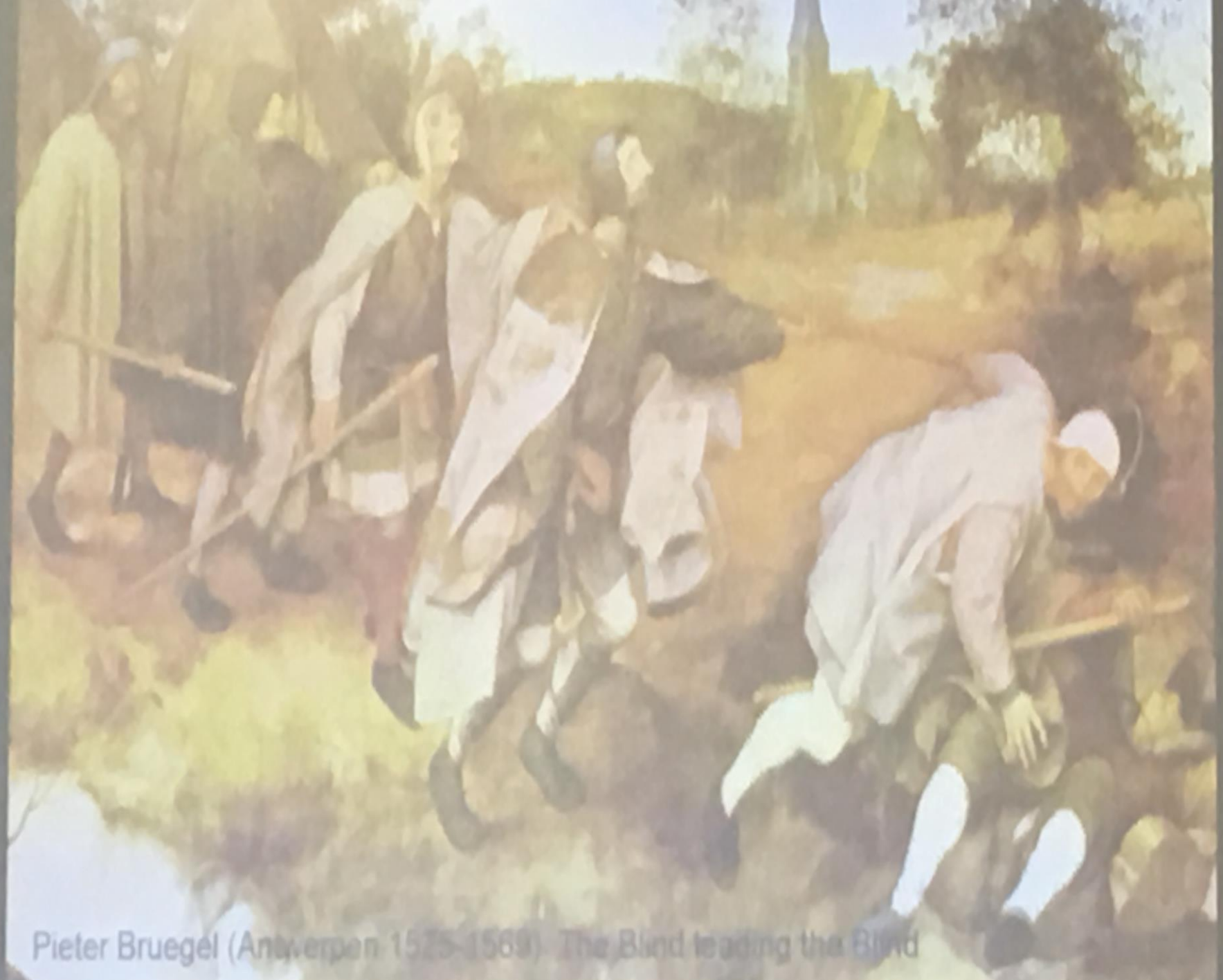
The Work Group was divided as to whether recommend cinacalcet as first-line

Take home messages

- The cardiovascular and renal systems are target tissues for vitamin D and a poor vitamin D status, which is present in the majority of CKD patients, is a risk factor for cardiovascular morbility and mortality, and for renal disease progression
- It is suggested to test for and treat reduced 25(OH)D concentrations with natural vitamin D: this therapy is safe, cheap and simple, reduces PTH levels and might also reduce cardiovascular events and delay CKD progression
- Active vitamin D should be considered to treat SHPT in CKD stage 5D



Repo JM, Rantala IS, Honkanen TT, Kidney Int 2007;72:977-984.



Pieter Bruegel (Antwerpen 1525-1569) The Blind leading the Blind