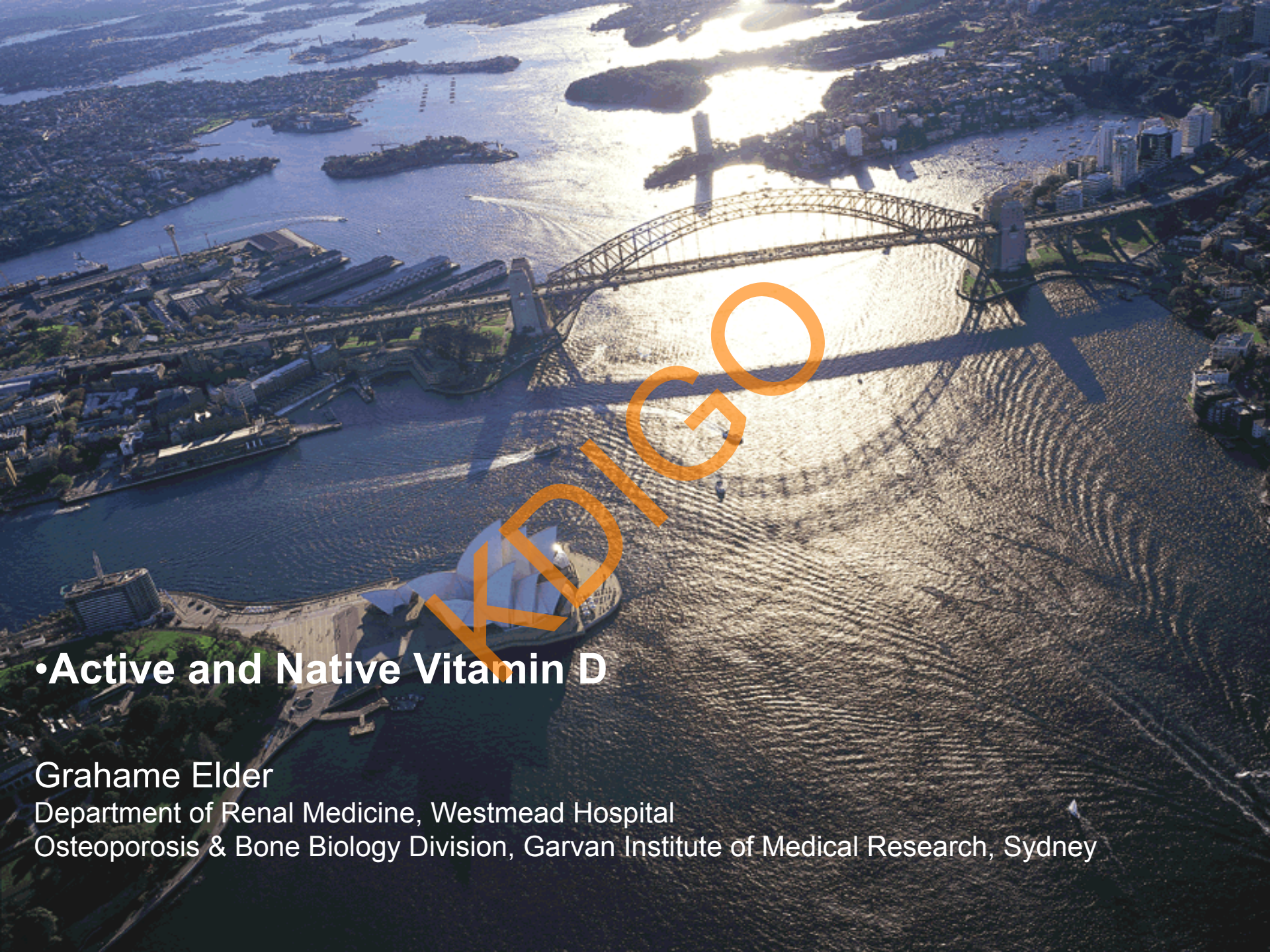


•Active and Native Vitamin D

Grahame Elder
Department of Renal Medicine, Westmead Hospital
Osteoporosis & Bone Biology Division, Garvan Institute of Medical Research, Sydney

Disclosures

- Member of Sanofi, Shire, Amgen and Vifor Australia advisory boards.
- Has received speaker's fees from Amgen and Shire.

Outline

General Population Data

- Bone
- Effects outside bone
- Time to turn out the lights?

25OH-vitamin D Assays

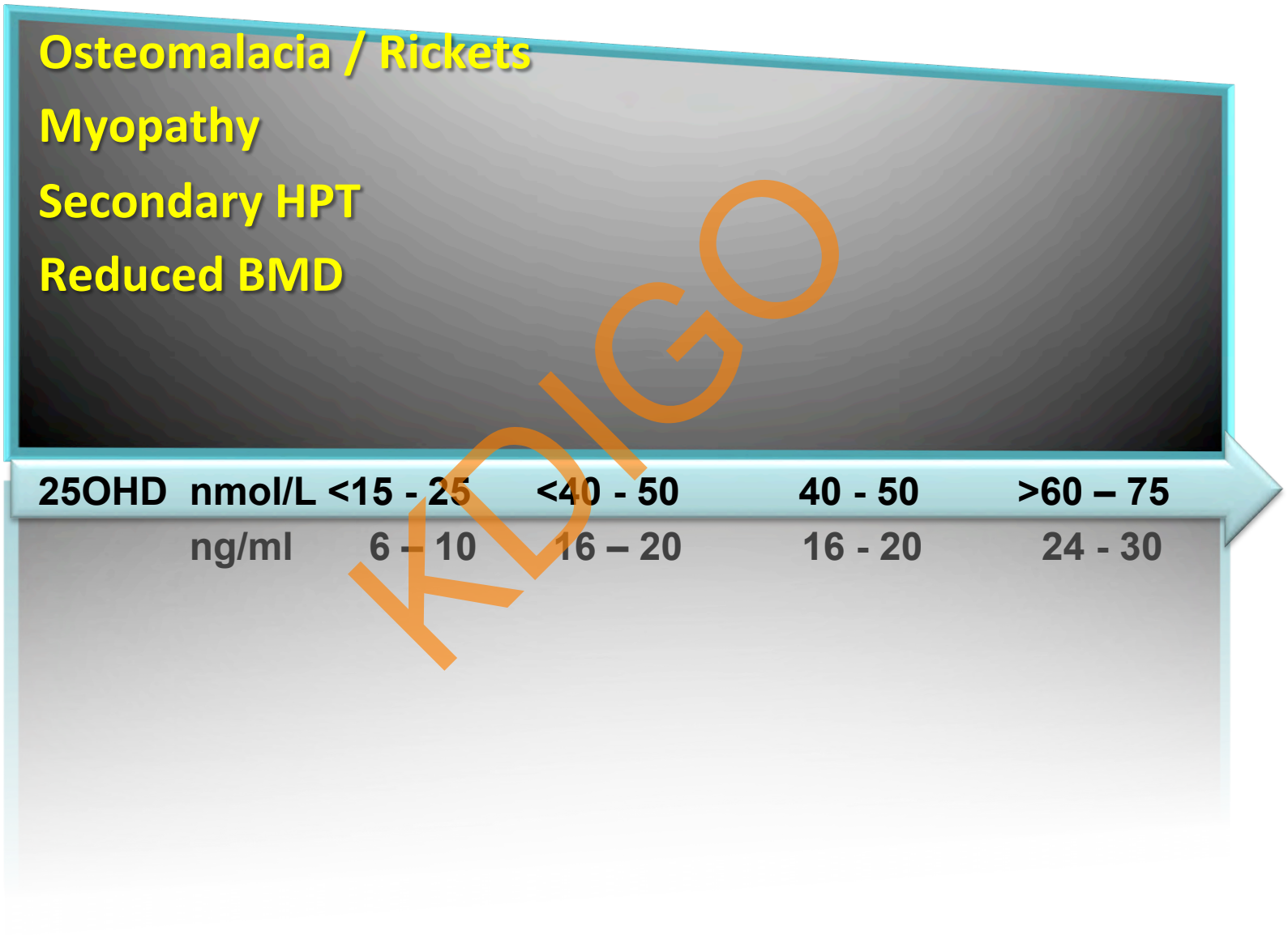
- Seasonal variations
- Specific populations
- What should we be measuring?

Nutritional / 25OHD in CKD 3-5 and 5D

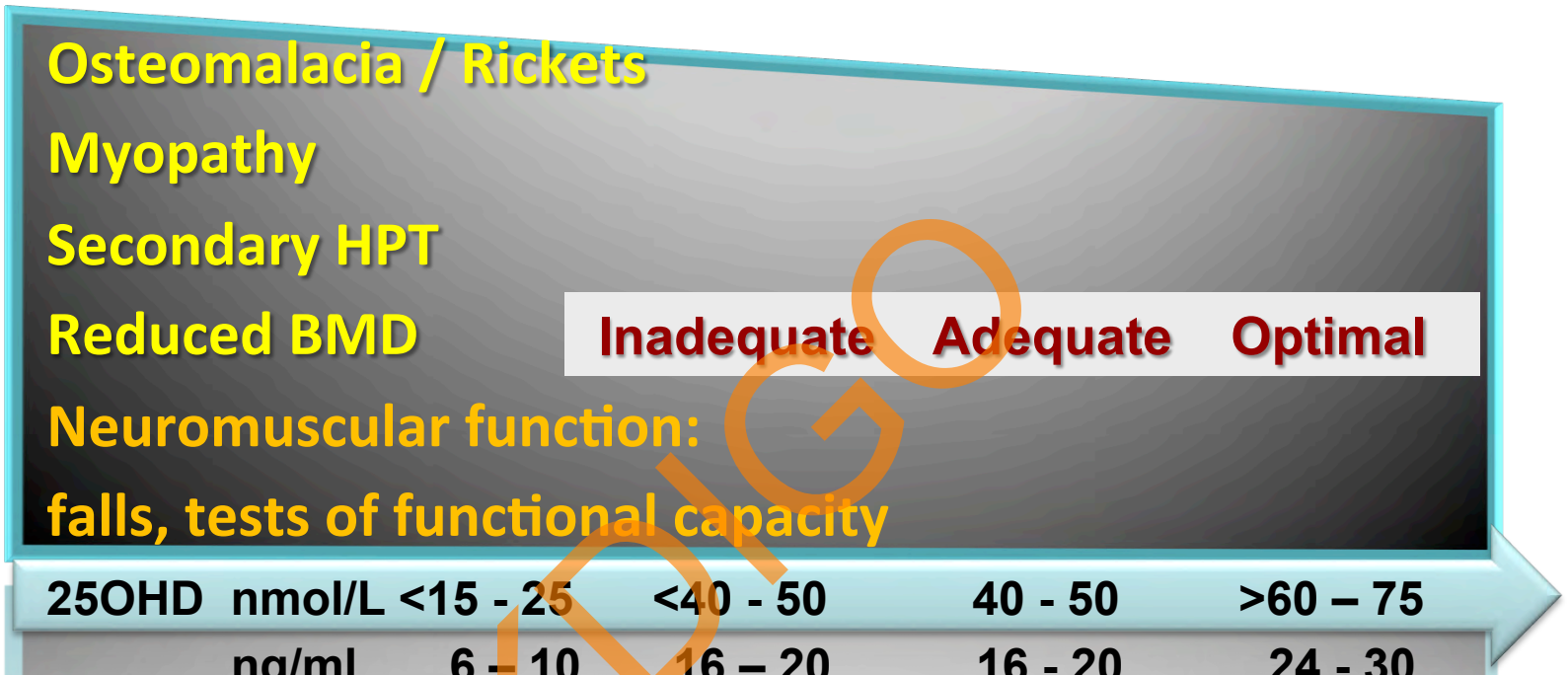
Calcitriol and Analogs in CKD 3-5 and 5D

Conclusions

Skeletal Effects of Vitamin D



Non-Skeletal Effects of Vitamin D



Association Studies

CV Outcomes; RAS regulation; Myocardial cell hypertrophy;

VSMC proliferation; Endothelial cell function;

Diabetes types 1 and 2; Insulin resistance

Infection; Immunomodulation; cancer

Preeclampsia

General Population; Fracture Risk

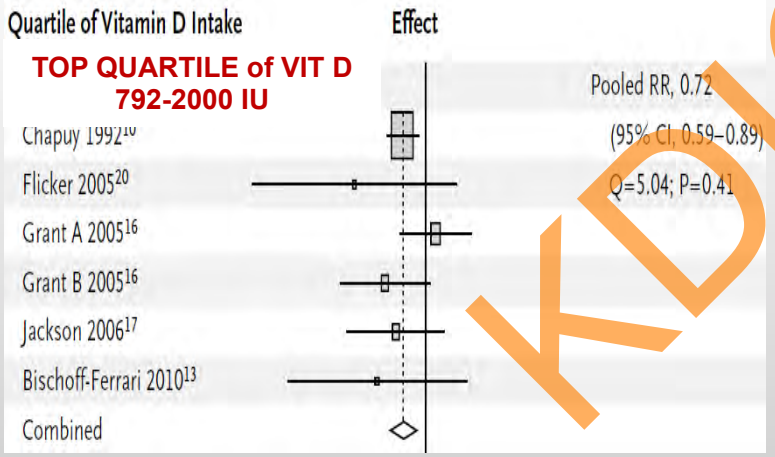
Pooled analysis;12 studies (30011 participants 65 or older; 91% women);

1111 incident hip and 3770 nonvertebral fractures

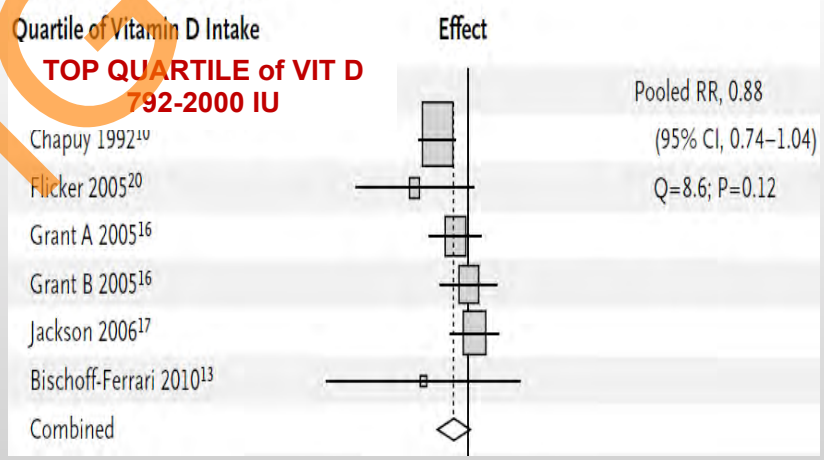
Vitamin D or D plus Ca *vs*. placebo or calcium. Median dose 800 IU (792 - 2000)

Meta-analysis of intervention studies

Risk of hip fracture



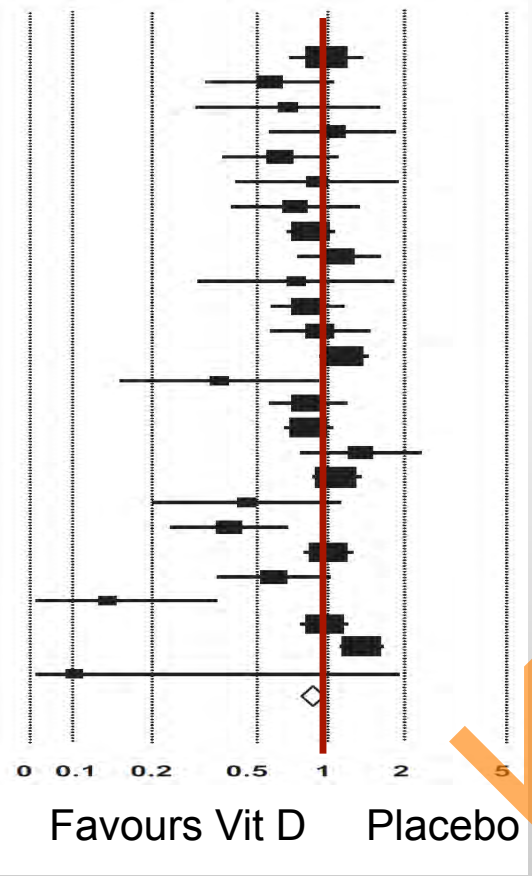
Risk of non vertebral fracture



NOTE: Effect driven by Chapuy 1992; ?prevalence of osteomalacia

Bischoff-Ferrari et al; NEJM 2012;367:40-9

Falls Risk



26 studies; 45782 participants

Is the odds ratio of patients suffering at least 1 fall reduced with calciferol?

- Vit D deficient; Significant;
  OR; 0.53 (0.39 – 0.72)

- Non-deficient; Borderline:
  OR; 0.90 (0.81-0.99)

Similar to earlier analysis of Bischoff-Ferrari; 0.84 *vs.* 0.87 (BMJ 2009)

- Randomised to vitamin D2/D3 (calcitriol and analogs excluded) or control
- Most; elderly women. Dose generally ≥800 IU/day.
- High baseline falls risk (15-69%; median 50%).

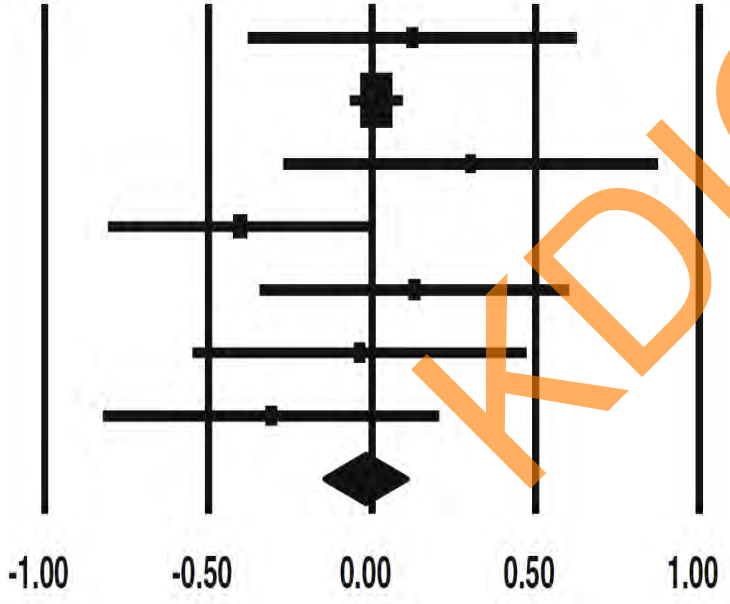
Murad et al. J Clin Endocrinol Metab 2011 96: 2997–3006

Muscle Strength

Grip Strength

7 RCTs, n= 3648

No effect



Favours Vit D **Favours placebo**

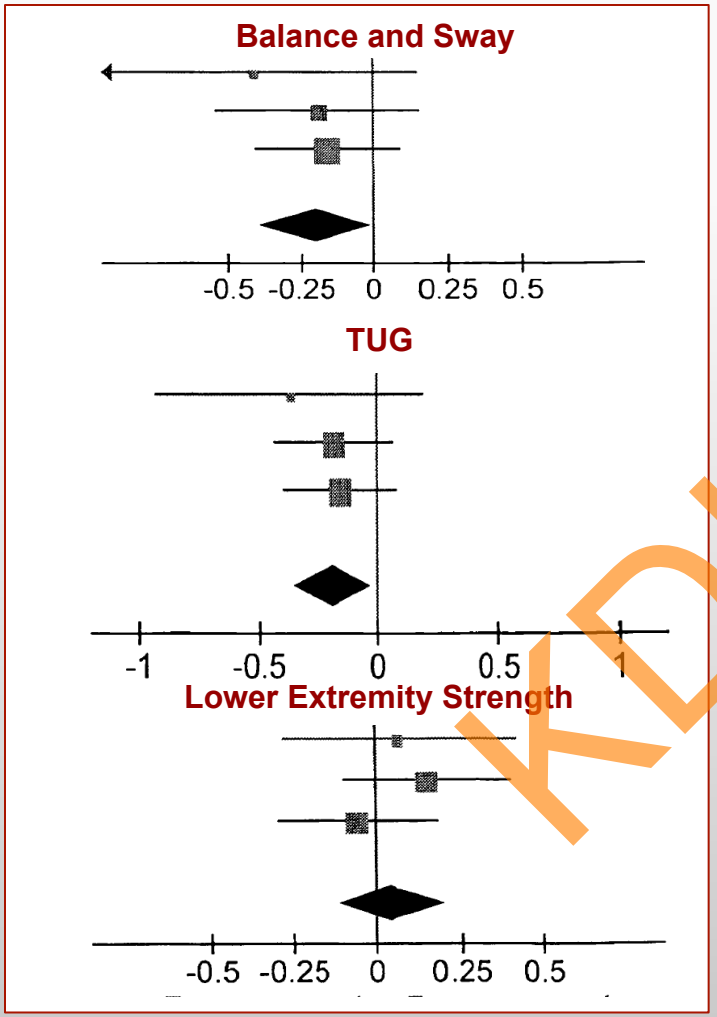
Hip strength

17 RCTs, n = 5072

- No effect in adults with 25OHD >25 nmol/L
- Limited studies report improvement for adults with 25OHD <25 nmol/L

Stockton et al. Osteoporosis Int (2011) 22:859-871

Stability, Gait, Strength



- Balance and Sway (n=207)

  -0.2 (-0.39 to-0.01) P=0.04

  Not robust with removal of one low quality study.

- TUG (n=274)

  -0.19 (-0.35 to -0.02) P=0.03

- Lower Extremity Strength (n=312)

  NS; P=0.55

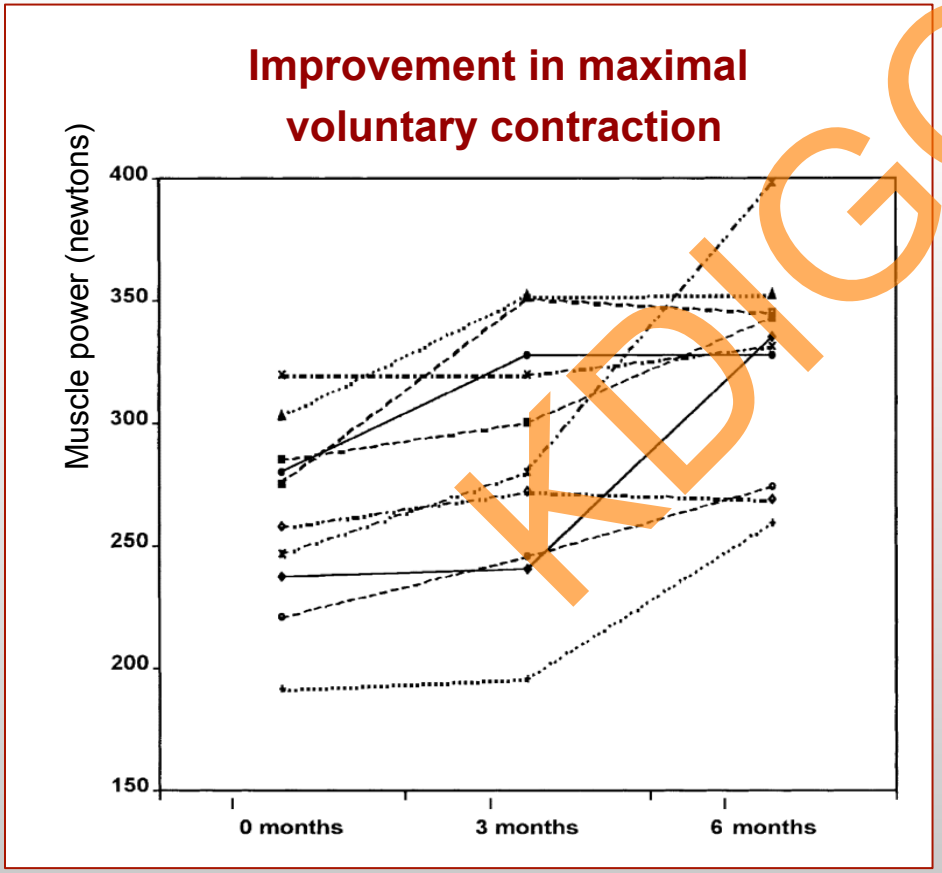
- Effect of Vitamin D Supplementation on Muscle Strength, Gait and Balance in Older Adults: A Systematic Review and Meta-Analysis

Muir et al. J Am Geriatr Soc (2011) 59:2291-2300

Muscle Strength

Veiled Arabic Women living in Denmark with 25OHD levels <20 nmol/L

Hypovitaminosis D myopathy without *biochemical* features of OM



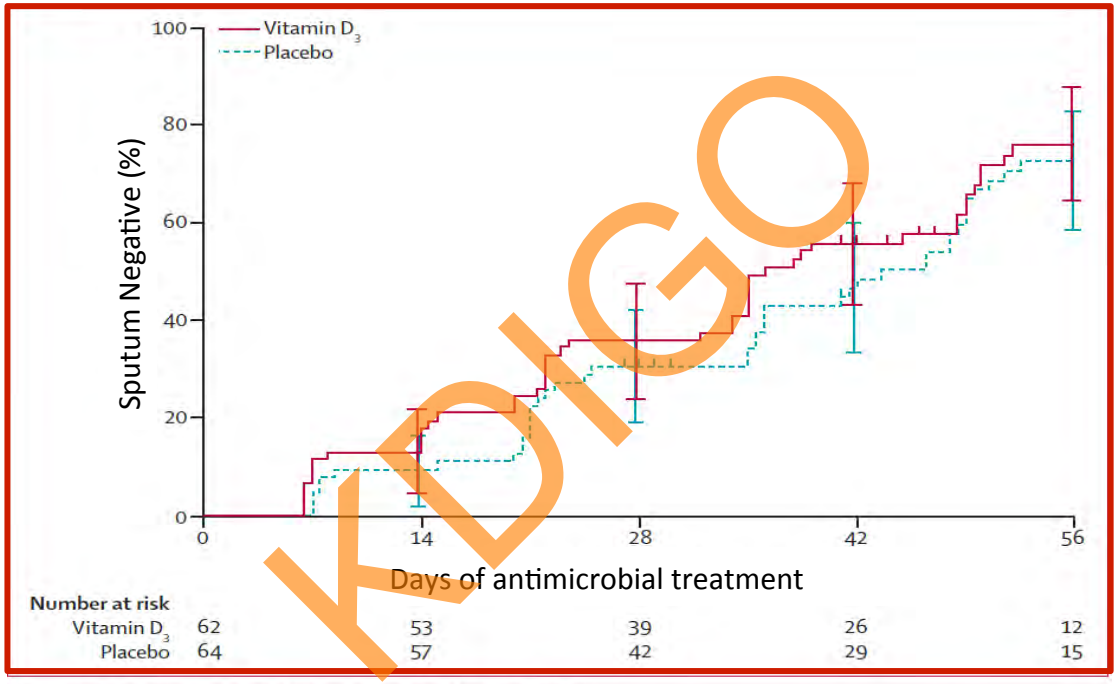
- Improved force by single twitch electrical stimulation
- Improved; Knee extension after 3 and 6 mo. treatment

Gierup et al. Calcif Tissue Int (2000); 66(6):419-24

Effects Outside Bone

- Vitamin D3 or placebo with antituberculous therapy

Time to Negative Sputum Culture



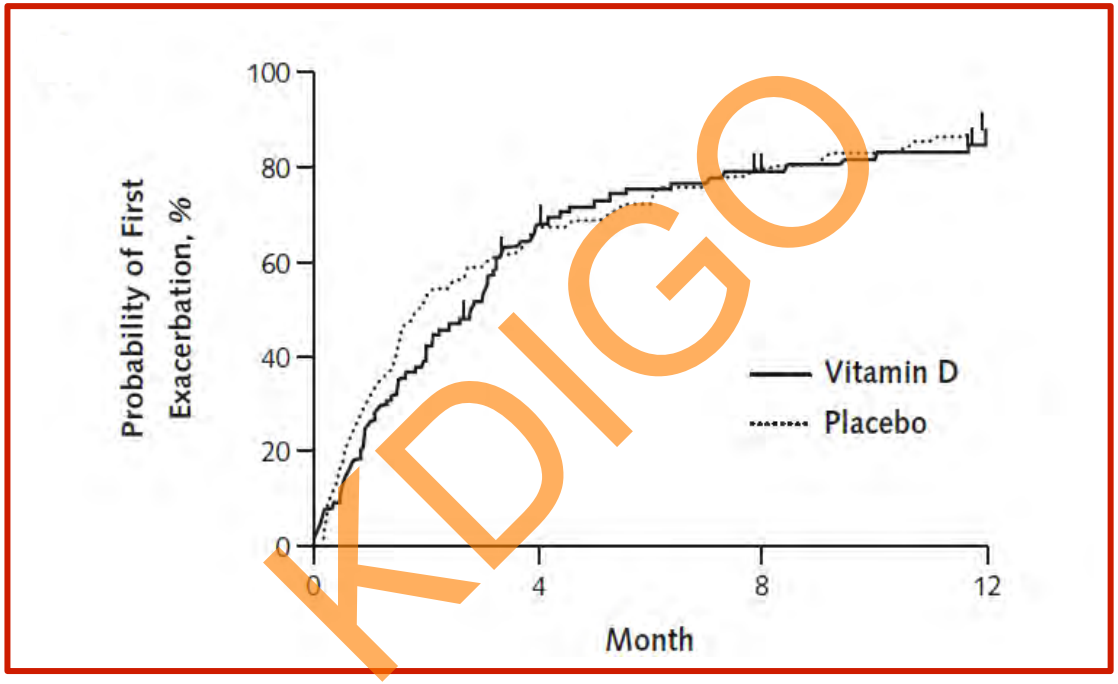
No difference vs. placebo when added to standard therapy

Martineau Lancet 2011 377;242-50

Effects Outside Bone

- Vitamin D and COPD

Probability of 1st exacerbation



No difference vs. placebo over 1 year in 184 patients with moderate to severe deficiency

Lehouck 2012; Annals of Internal Medicine 2012;156(2):105-14.

Effects Outside Bone

- Cardiometabolic Syndrome (MI, Cardiac event or death, stroke)

  The association between vitamin D status and cardiometabolic outcomes is uncertain.
  Trials showed no clinically significant effect of vitamin D supplementation at the dosages given

- Type 1 diabetes with high C-peptide

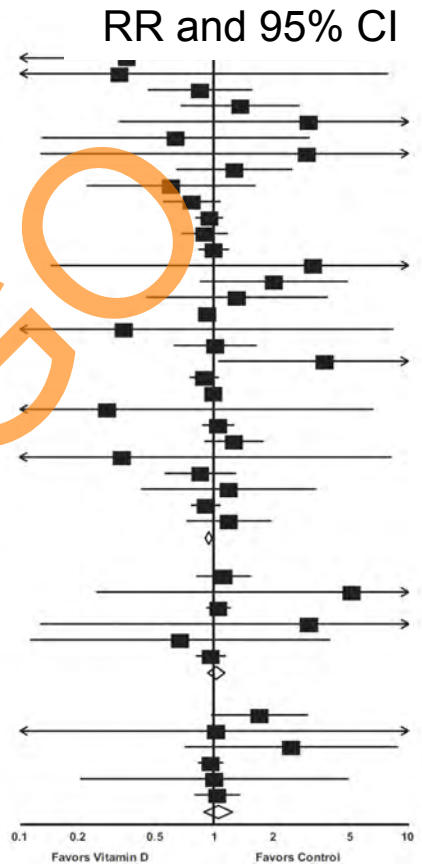
  At doses used, calcitriol is ineffective in protecting beta-cell function in subjects (including children) with recent-onset type 1 diabetes and high C-peptide at diagnosis.

Pittas et al. Annals of Internal Medicine. 152(5):307-314, March 2, 2010
Bizzarri et al.The IMDIAB XIII trial. Diabetes Care, 2010. 33(9):1962-3.

Effects Outside Bone

- Vitamin D and CV outcomes; a systematic review and meta-analysis

Study name	Relative risk	Lower limit	Upper limit	Events / Total Vitamin D	Events / Total Control
Avenell, 2004	0.35	0.02	5.50	1 / 99	1 / 35
Baeksgaard,1998	0.32	0.01	7.79	0 / 65	1 / 63
Berggren, 2008	0.85	0.46	1.56	16 / 102	18 / 97
Björkman, 2008	1.36	0.68	2.73	27 / 150	9 / 68
Brazier, 2005	3.06	0.32	28.93	3 / 95	1 / 97
Broe, 2007	0.63	0.13	3.07	5 / 99	2 / 25
Brohult, 1973	3.00	0.13	70.30	1 / 25	0 / 25
Burleigh, 2007	1.27	0.64	2.50	16 / 101	13 / 104
Campbell, 2005	0.60	0.22	1.61	6 / 196	10 / 195
Chapuy, 2002	0.76	0.55	1.06	71 / 393	45 / 190
Chapuy,1992	0.94	0.81	1.10	258 / 1634	274 / 1636
Flicker, 2005	0.89	0.68	1.16	76 / 313	85 / 312
Grant, 2005	0.99	0.83	1.18	217 / 1343	217 / 1332
Grove, 1981	3.23	0.14	72.46	1 / 12	0 / 13
Harwood, 2004	2.03	0.85	4.84	31 / 113	5 / 37
Inkovaara, 1983	1.31	0.45	3.80	7 / 45	5 / 42
Jackson, 2006	0.92	0.83	1.01	744 / 18176	807 / 18106
Komulainen,1999	0.34	0.01	8.31	0 / 112	1 / 115
Krieg, 1999	1.01	0.62	1.64	21 / 71	26 / 89
Latham, 2003	3.70	1.06	12.92	11 / 121	3 / 122
Lips, 1996	0.89	0.75	1.04	223 / 1291	251 / 1287
Lyons 2007	0.99	0.93	1.05	947 / 1725	953 / 1715
Meier, 2004	0.28	0.01	6.58	0 / 30	1 / 25
Meyer, 2002	1.05	0.87	1.26	169 / 569	163 / 575
Porthouse, 2005	1.26	0.90	1.79	57 / 1321	68 / 1993
Prince, 2008	0.33	0.01	8.12	0 / 151	1 / 151
Sanders, 2010	0.85	0.56	1.28	40 / 1131	47 / 1125
Schleithoff, 2006	1.19	0.42	3.33	7 / 61	6 / 62
Trivedi, 2003	0.90	0.77	1.07	224 / 1345	247 / 1341
Wejse, 2009	1.19	0.72	1.95	30 / 187	24 / 178
Mortality-Pooled estimate	**0.96**	**0.93**	**1.00**	**3209 / 31076**	**3284 / 31155**
Berggren, 2008	1.12	0.81	1.53	47 / 102	40 / 97
Brazier, 2005	5.10	0.25	104.94	2 / 95	0 / 97
Jackson, 2006	1.05	0.92	1.20	411 / 18167	390 / 18106
Komulainen,1999	3.08	0.13	74.81	1 / 112	0 / 115
Prince, 2008	0.67	0.11	3.93	2 / 151	3 / 151
Trivedi, 2003	0.96	0.81	1.13	224 / 1345	233 / 1341
Myocardial Infraction-Pooled estimate	**1.02**	**0.93**	**1.13**	**687 / 19972**	**666 / 19907**
Berggren, 2008	1.71	0.97	3.02	27 / 102	15 / 97
Brazier, 2005	1.02	0.06	16.09	1 / 95	1 / 97
Inkovaara, 1983	2.49	0.71	8.76	8 / 45	3 / 42
Jackson, 2006	0.96	0.83	1.10	362 / 18167	377 / 18106
Prince, 2008	1.00	0.21	4.88	3 / 151	3 / 151
Trivedi, 2003	1.04	0.80	1.35	105 / 1345	101 / 1341
Stroke-Pooled estimate	**1.05**	**0.88**	**1.25**	**506 / 19905**	**500 / 19834**



Favours Vitamin D Favours Control

Forest Plot representing pooled result for mortality, MI and stroke

Elamin et al; JCEM 2011 96: 1931-1942

Effects Outside Bone

Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial).

- 5292 people (85% women) aged at least 70 yr with previous low-trauma fracture
- Randomly allocated to daily vitamin D3 (800 IU), calcium (1000 mg), both, or placebo for 24-62 months
- Follow-up of 3 yr

Conclusions:

- Daily vitamin D or calcium supplementation did not affect mortality, vascular disease, cancer mortality, or cancer incidence

Avenell et al J Clin Endocrinol Metab 2012;97(2):614-22

Summary: Vitamin D in the General Population

For bone and muscle:
Benefits may be limited to

- Older individuals (>60 years)
- Those with levels are <25-50 nmol/L (10-20 ng/ml)

IOM 2011:

With the exception of measures related to bone health, the potential indicators examined are currently not supported by evidence

- Adequate 25OHD 40-50 nmol/L
- UL: 4000 IU/day

*Institute of Medicine 2011. Dietary Reference Intakes for Calcium and Vitamin D. The National Academies Press.

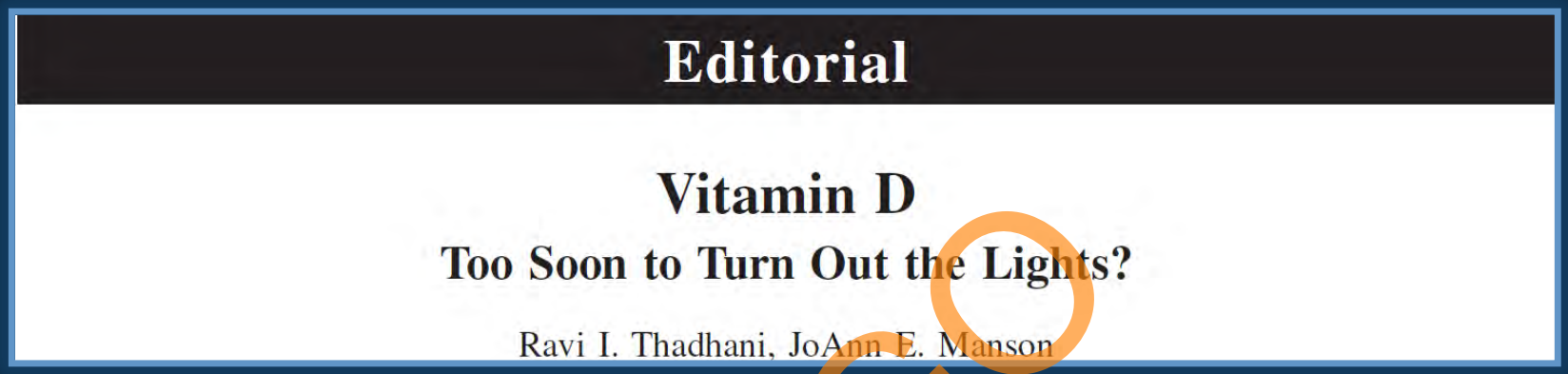
Editorial

Vitamin D

Too Soon to Turn Out the Lights?

Ravi I. Thadhani, JoAnn E. Manson

Arterioscler Thromb Vasc Biol. 2013;33:2467-2469


Editorial

Vitamin D

Too Soon to Turn Out the Lights?

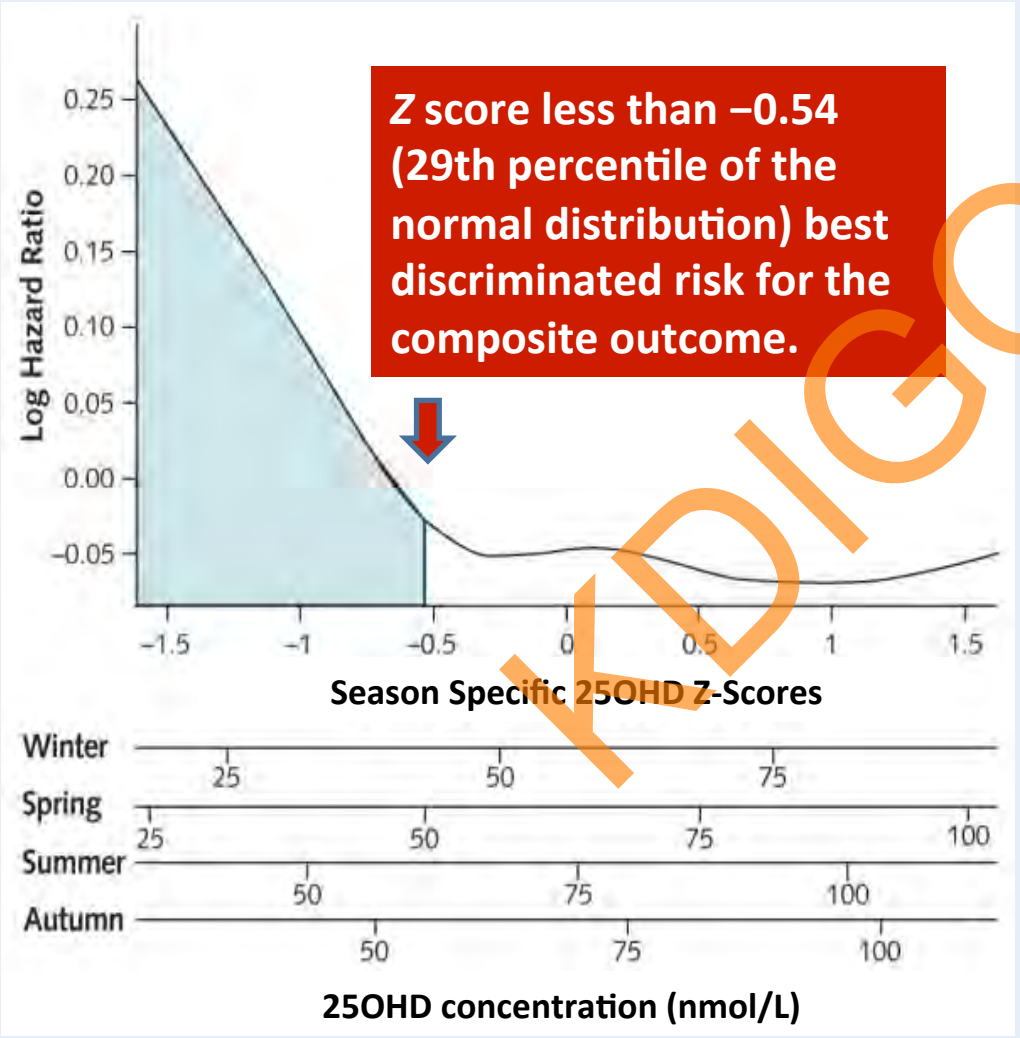
Ravi I. Thadhani, JoAnn E. Manson

Confounding influences:

- What is the cut point for major clinical disease
- Seasonal variation
- Genetic variation and specific populations
- Assays

Arterioscler Thromb Vasc Biol. 2013;33:2467-2469

Cut Points: Serum 25-Hydroxyvitamin D Concentration and Risk for Major Clinical Disease Events in a Community-Based Population .

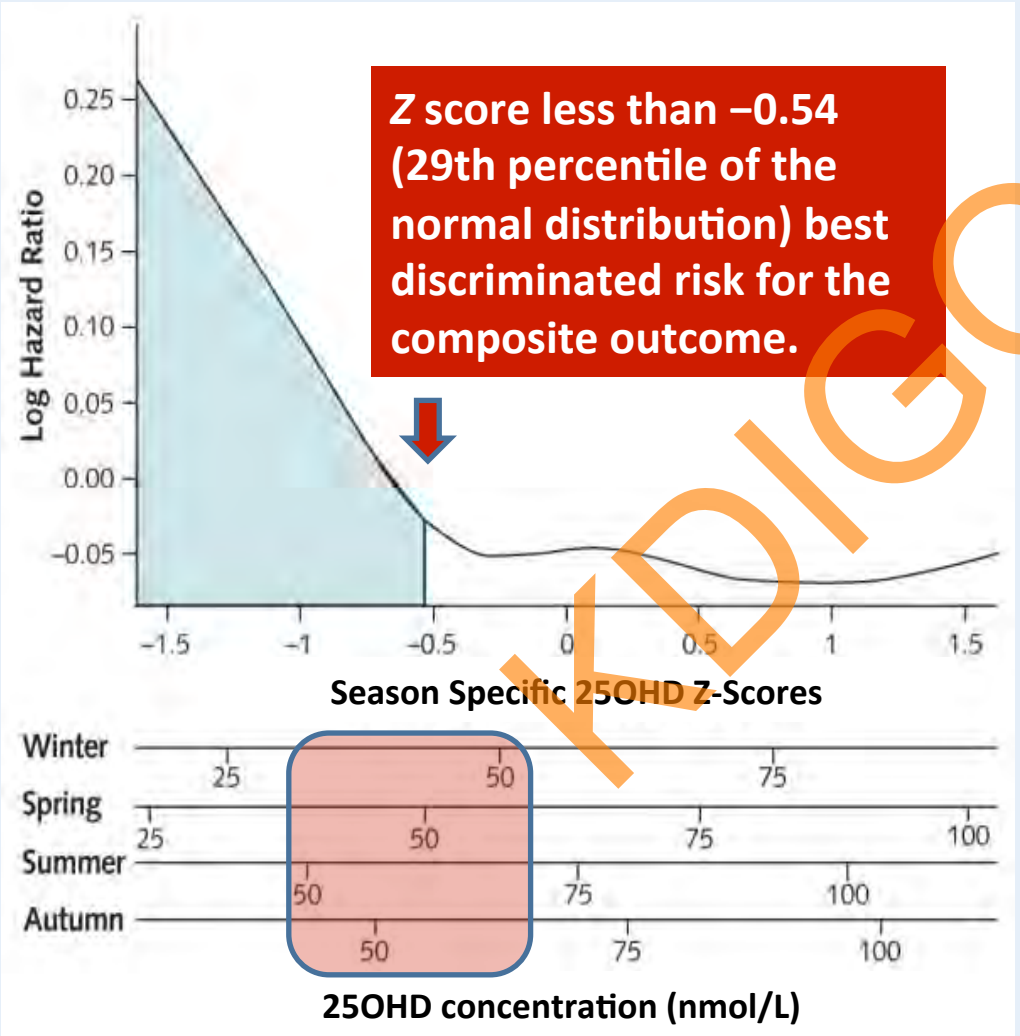


***Z* score less than −0.54 (29th percentile of the normal distribution) best discriminated risk for the composite outcome.**

- **1621 participants ≥ 65 years 4 US communities**
- **Median follow-up 11 years (IQ range 6,13)**
- **Composite clinical outcome 1018 (63%)**
  - **Hip fracture for 137 (8%)**
  - **MI for 186 (11%)**
  - **Cancer for 335 (21%)**
  - **Death for 360 (22%)**

De Boer et al. Ann Intern Med. 2012 May 1; 156(9): 627–634

Seasonal variation: Serum 25-Hydroxyvitamin D Concentration and Risk for Major Clinical Disease Events in a Community-Based Population.



•Based on association with major clinical disease events, optimal 25OHD is ≥ 50 nmol/L (20 ng/ml)

De Boer et al. Ann Intern Med. 2012 May 1; 156(9): 627–634

Genetic Factors

•GWAS studies*

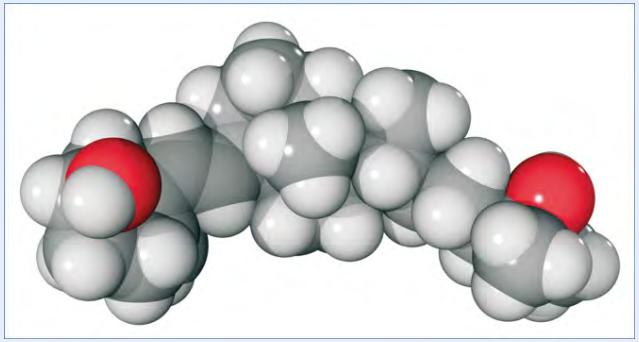
Differences in 25OHD between strongest genetic variants were similar to summer winter seasonal changes.

Variants in 7-DHC reductase

25-hydroxylase (CYP2R1)

CYP24A1

•GC gene polymorphisms, encoding DBP had *greatest* effect on 25OHD values



*Wang et al. The Lancet, 2010:376, (9736), 180 – 188
Genetic and environmental determinants of vitamin D status

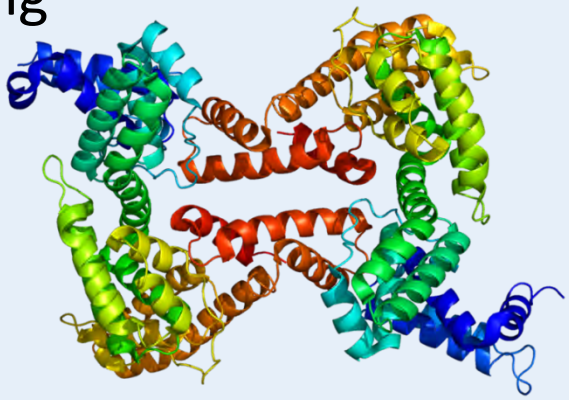
Assays: Vitamin D Binding Protein

- DBP: glycosylated~58kd protein
  t ½ 2-3 days
  Produced in the Liver

- Negative acute phase reactant
  Binds actin in tissue damage
  DBP-actin is rapidly cleared

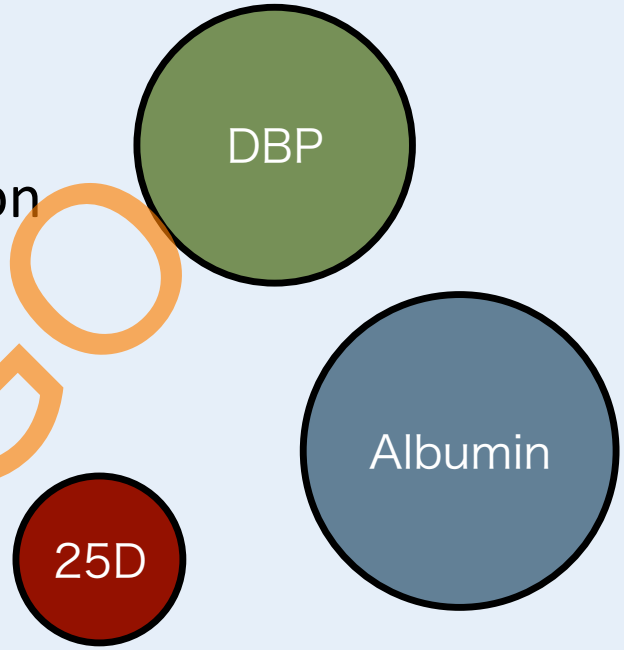
- 25OHD t ½ is 2-3 weeks; ligand recycling

- $1,25(OH)_2D$ t ½ is 4-6 hours



25OHD and Circulating Proteins

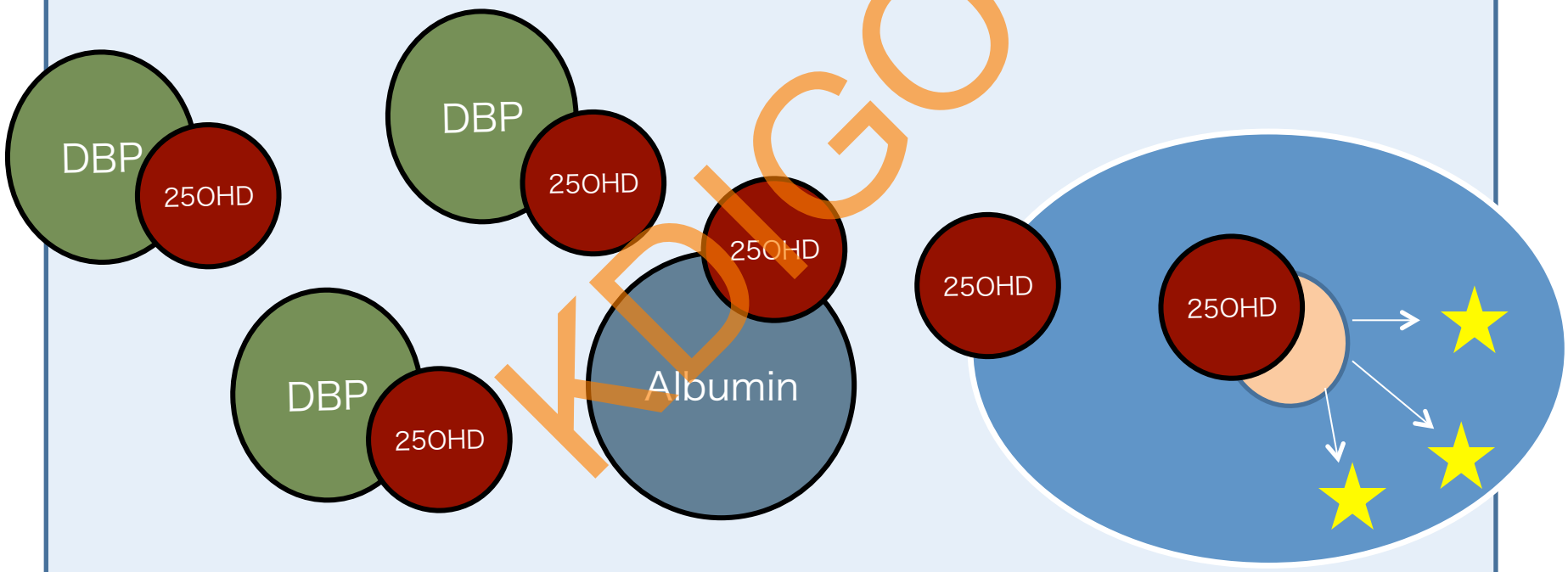
- 25OHD binds to DBP in circulation
- 25OHD binds to Albumin
- 25OHD circulates in a free form
- [Total] = [D] + [DAlb] + [DDBP]



Slide modified from Dr Thadhani

Free Hormone Hypothesis

Only UNBOUND hormones cross cell membranes and have biological action



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Free Hormone Hypothesis

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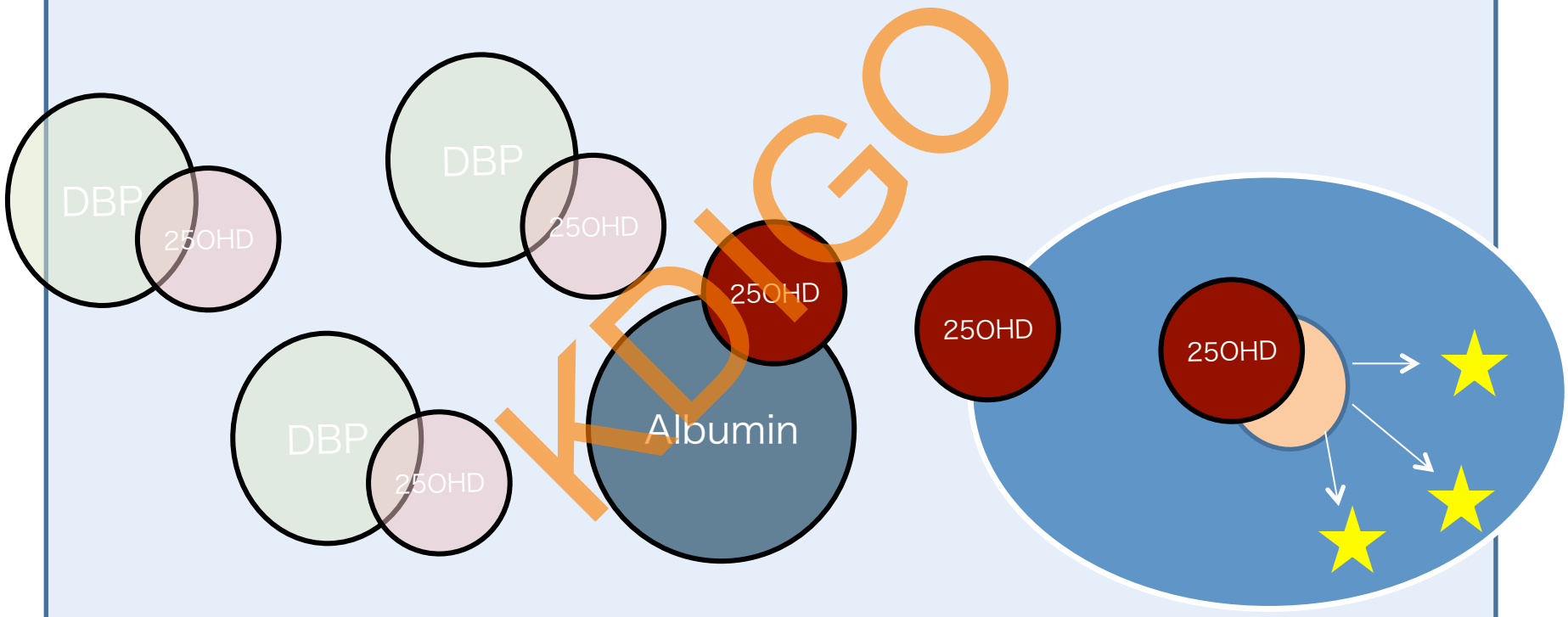
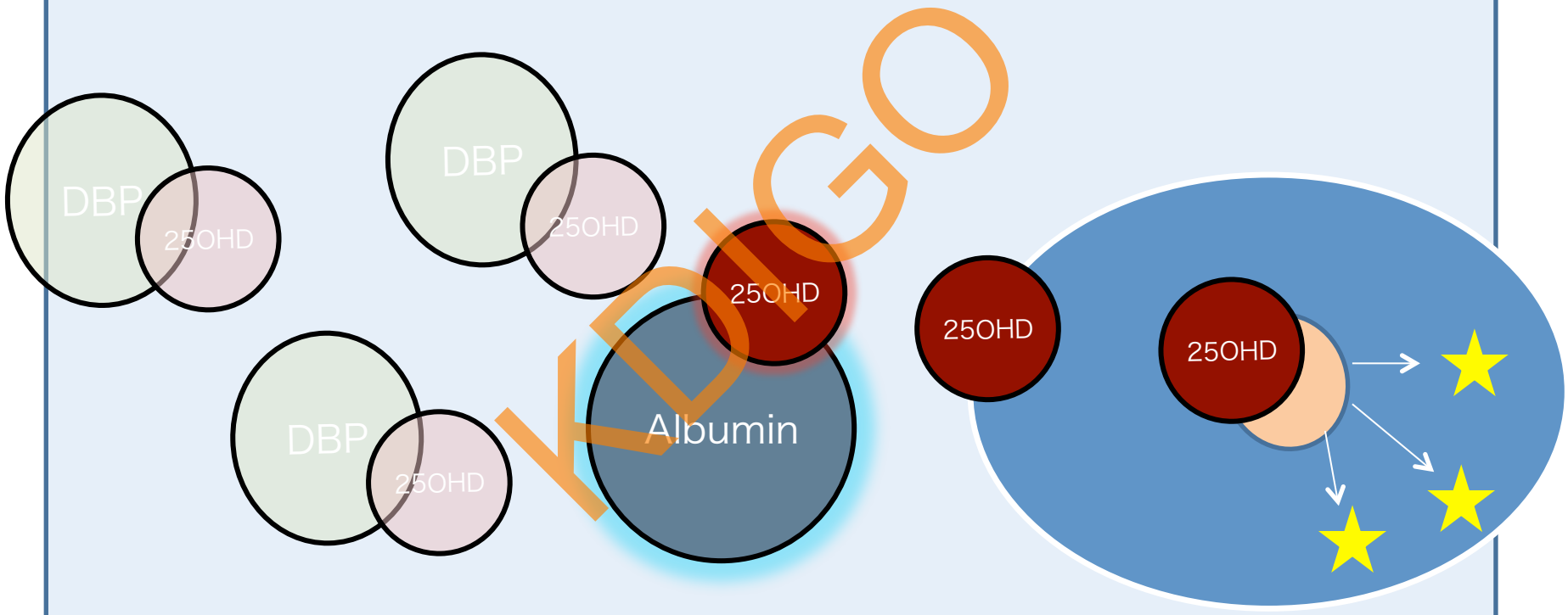


Slide modified from Dr Thadhani

Free Hormone Hypothesis

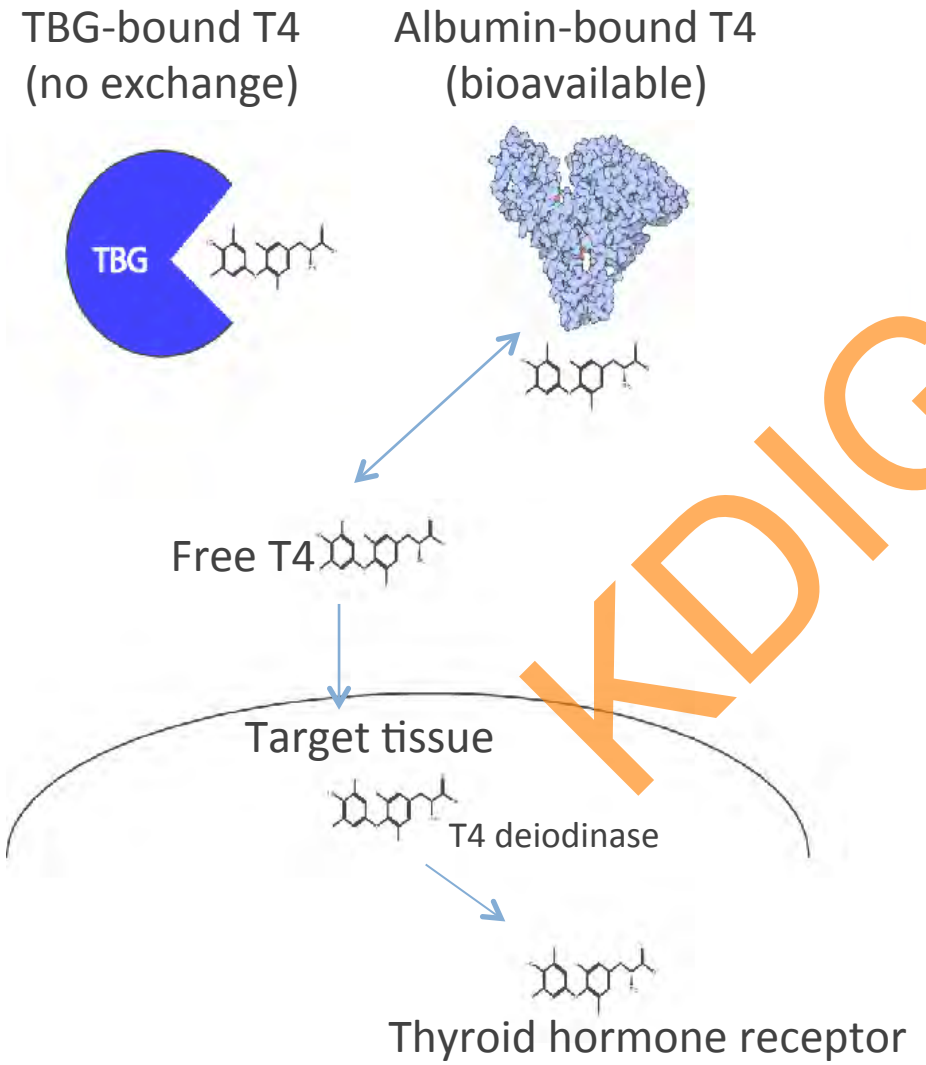
Albumin Bound 25OHD is Bioavailable



Yet, vitamin D deficiency is clinically defined by TOTAL 25(OH)D

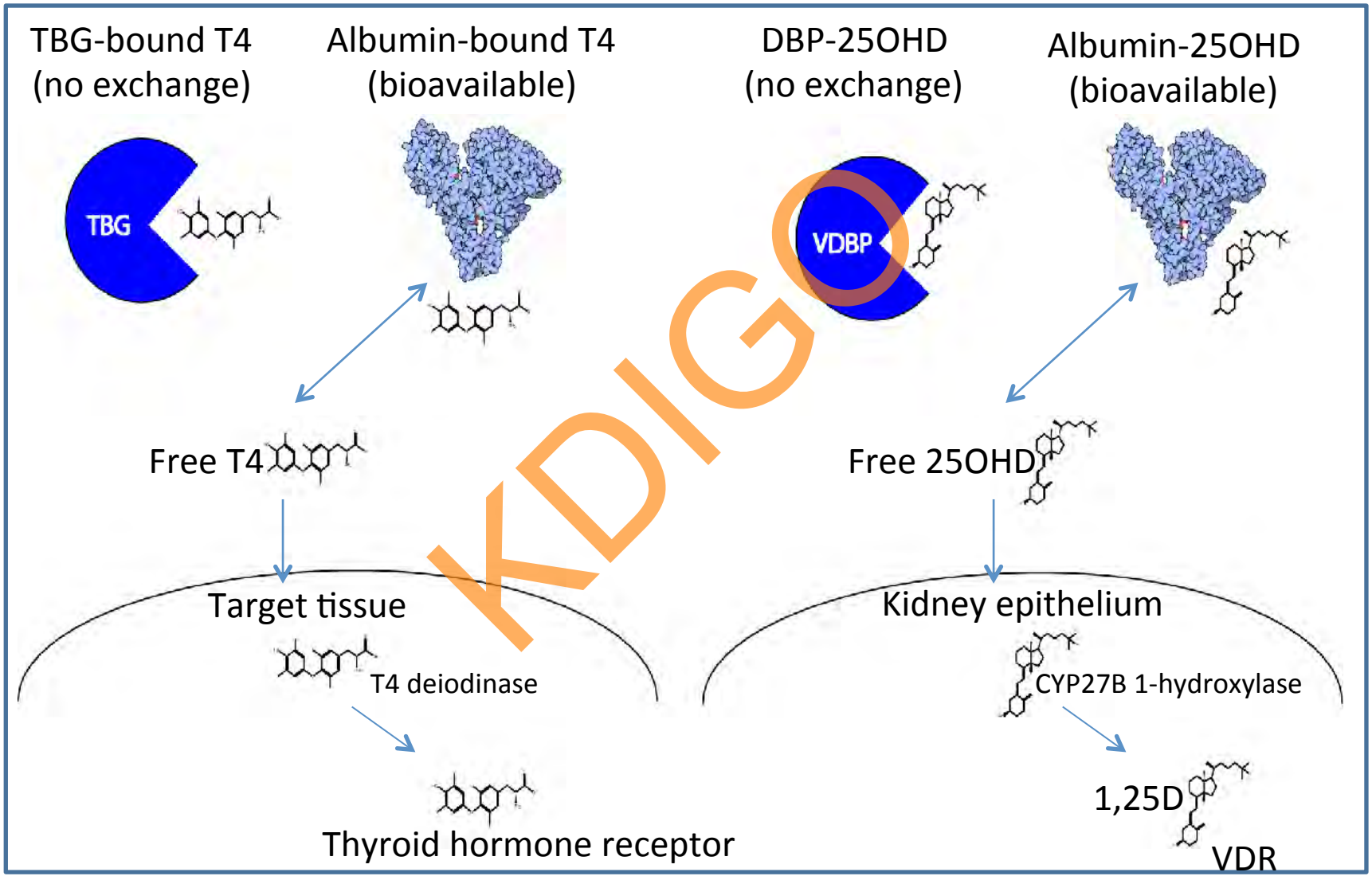
Slide modified from Dr Thadhani

Similar to T4 response



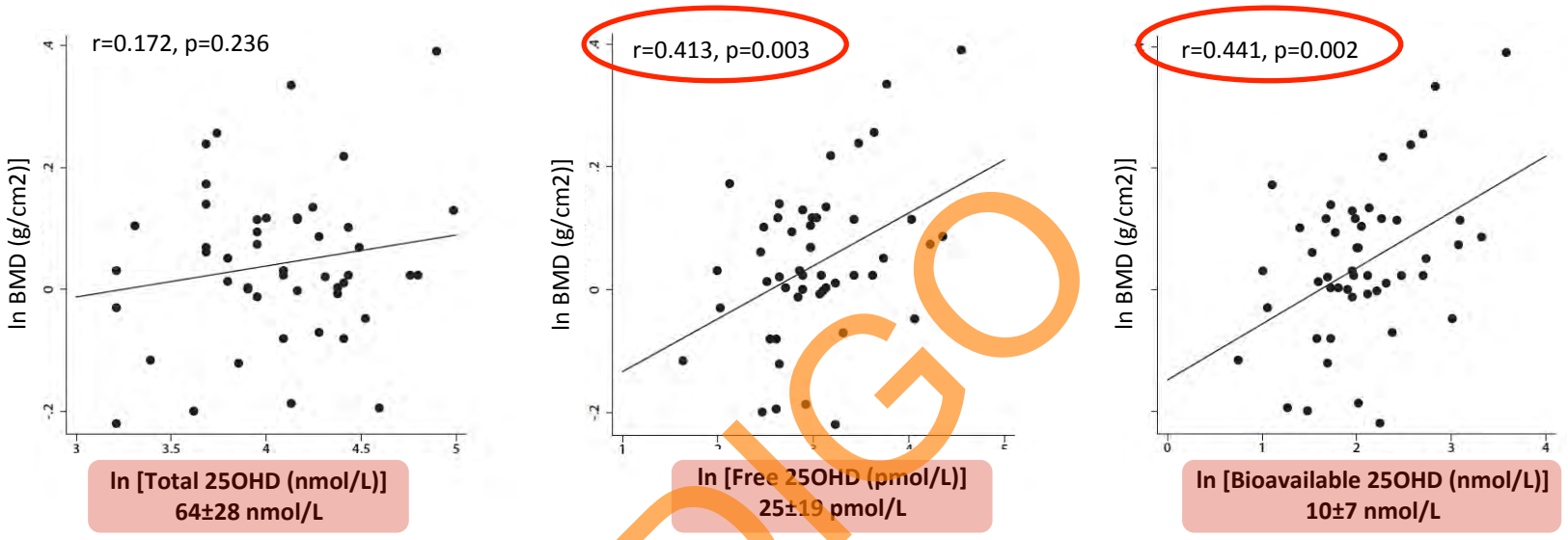
Slide modified from Dr Thadhani

Similar to T4 response



Slide modified from Dr Thadhani

DBP Modifies the Vitamin D - BMD Relationship



- 49 healthy young adults enrolled in the Metabolic Abnormalities in College-Aged Students (MACS) study

- Free and bioavailable 25OHD levels were positively correlated to Lumbar Spine BMD
- No correlation to values of 1,25(OH)2D

Powe, J Bone Miner Res 2011; 2011: 26 (7)1609–1616

DBP Modifies the Vitamin D - BMD Relationship

This may explain the racial paradox

	WHITES	BLACKS
25(OH)D	High	Low
PTH	Low	High
Bone Mineral Density	Low	High
Osteoporosis/Fracture	High	Low

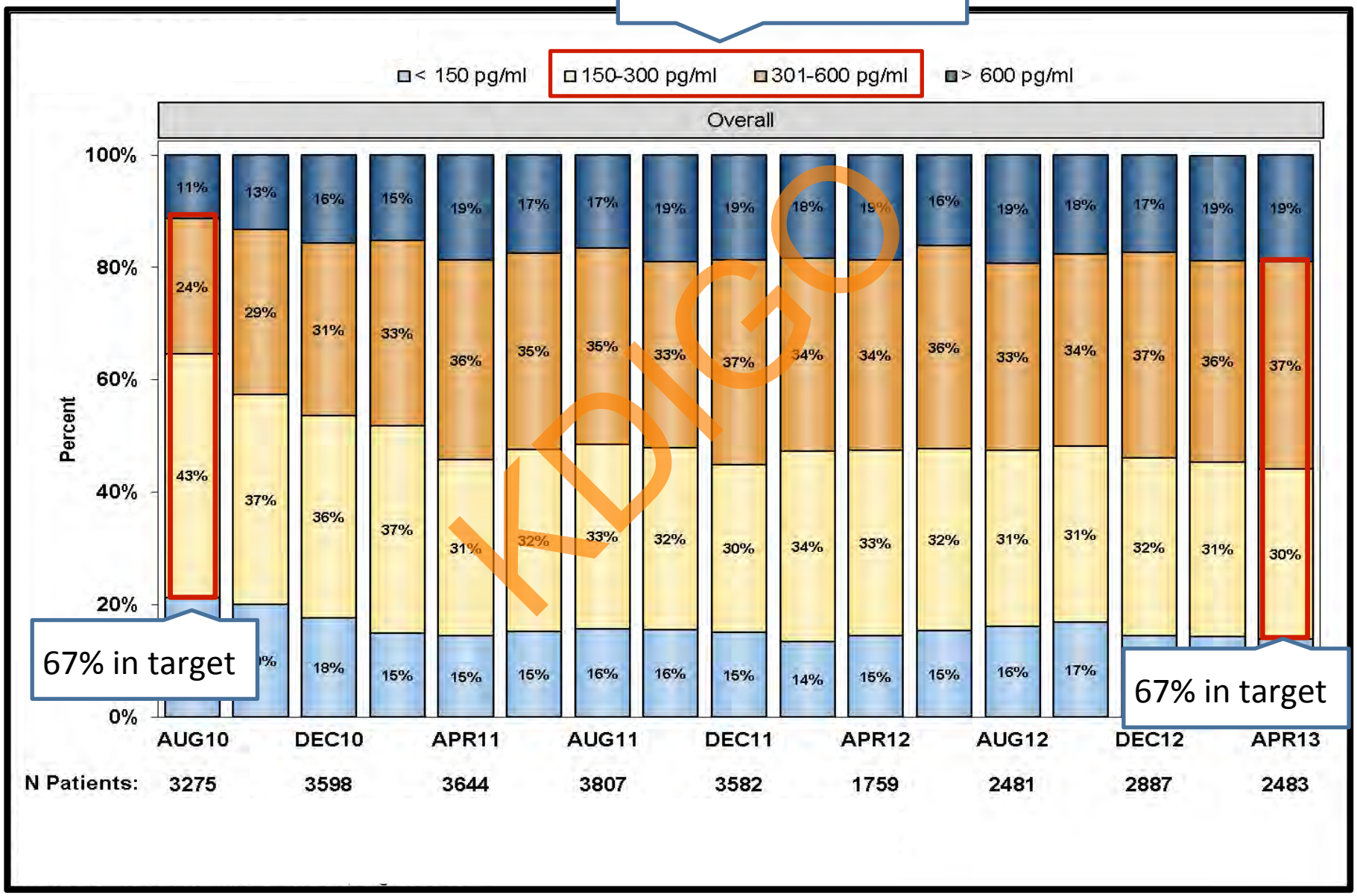
Summary

- Vitamin D deficiency as is currently defined is an epidemic
- Assay quality assurance and standardisation remains a problem
- Seasonal and genetic factors influence 25OHD levels
- Determining bioavailable vitamin D may resolve some paradoxes of association and interventional studies
- Large RCTs may soon provide insight to these Qs

Practise Patterns for Vitamin D in CKD

DOPPS USA Data 2010 - 2013

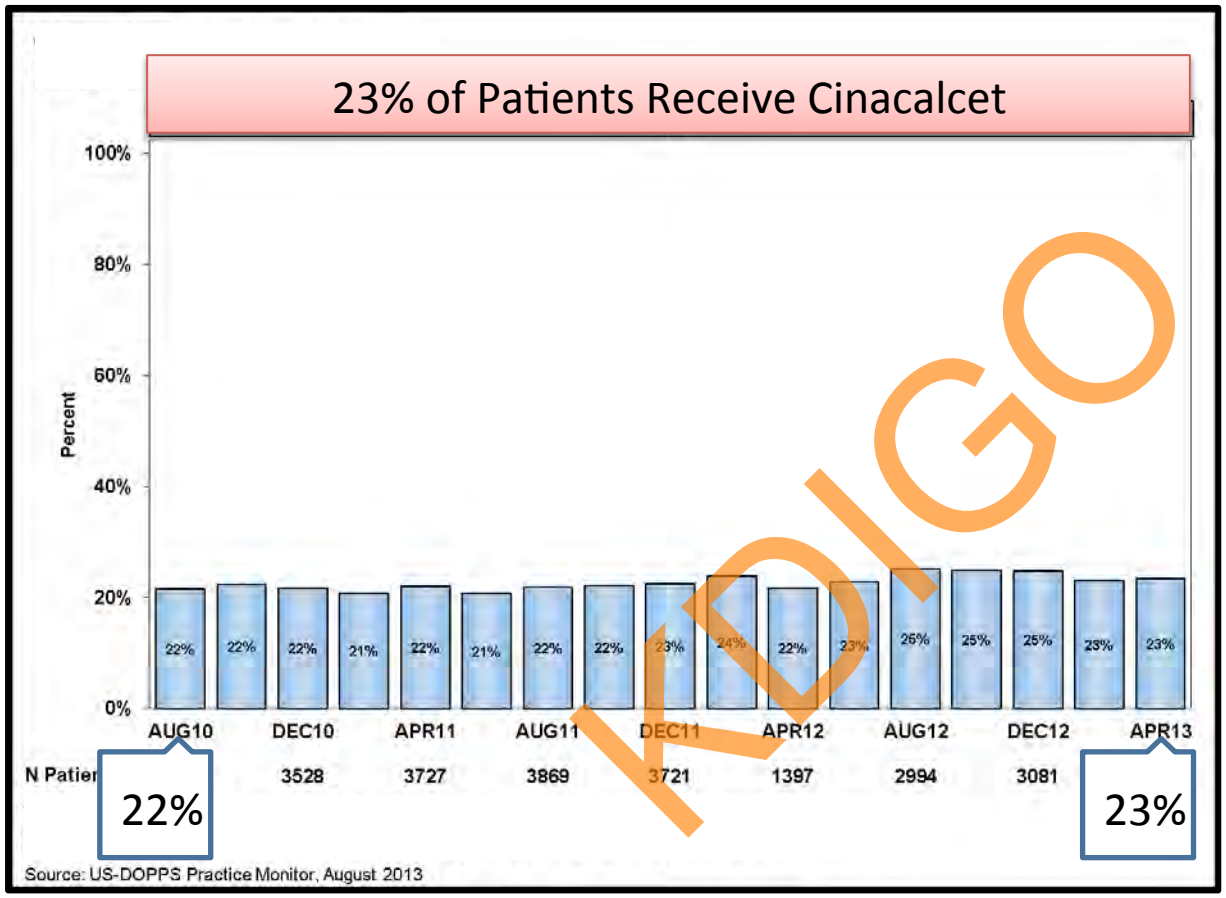
Approximate KDIGO iPTH Range: 2-9X



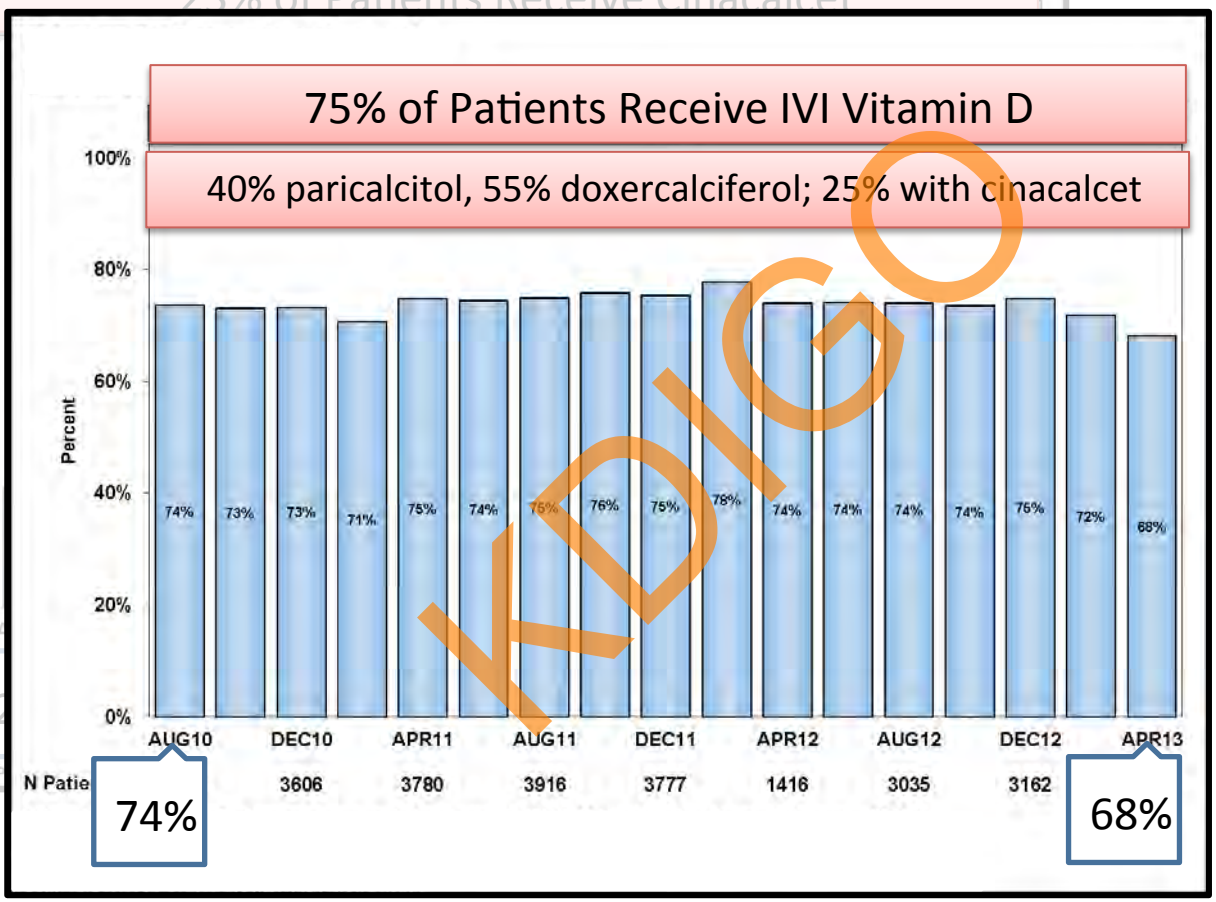
67% in target

67% in target

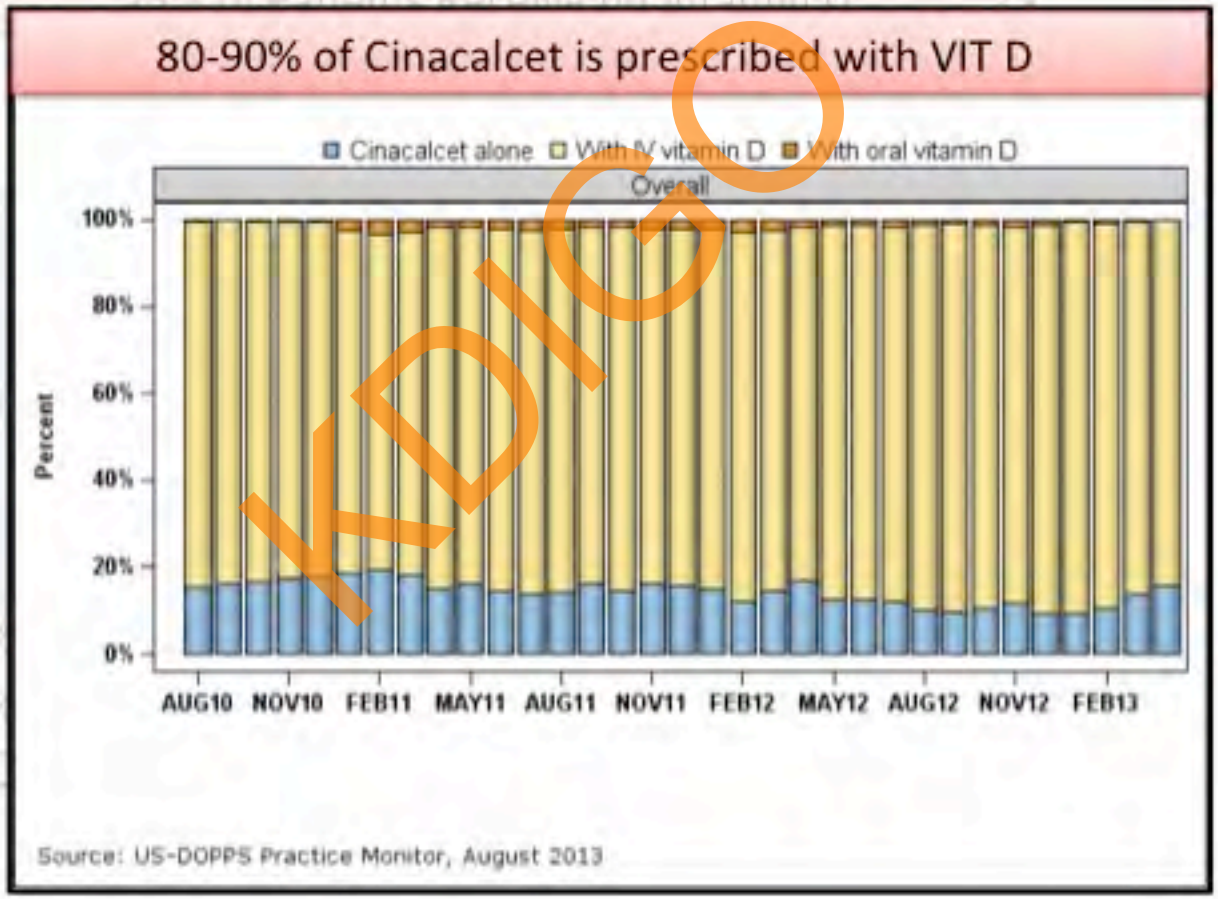
DOPPS USA Data 2010 - 2013



DOPPS USA Data 2010 - 2013



DOPPS USA Data 2010 - 2013

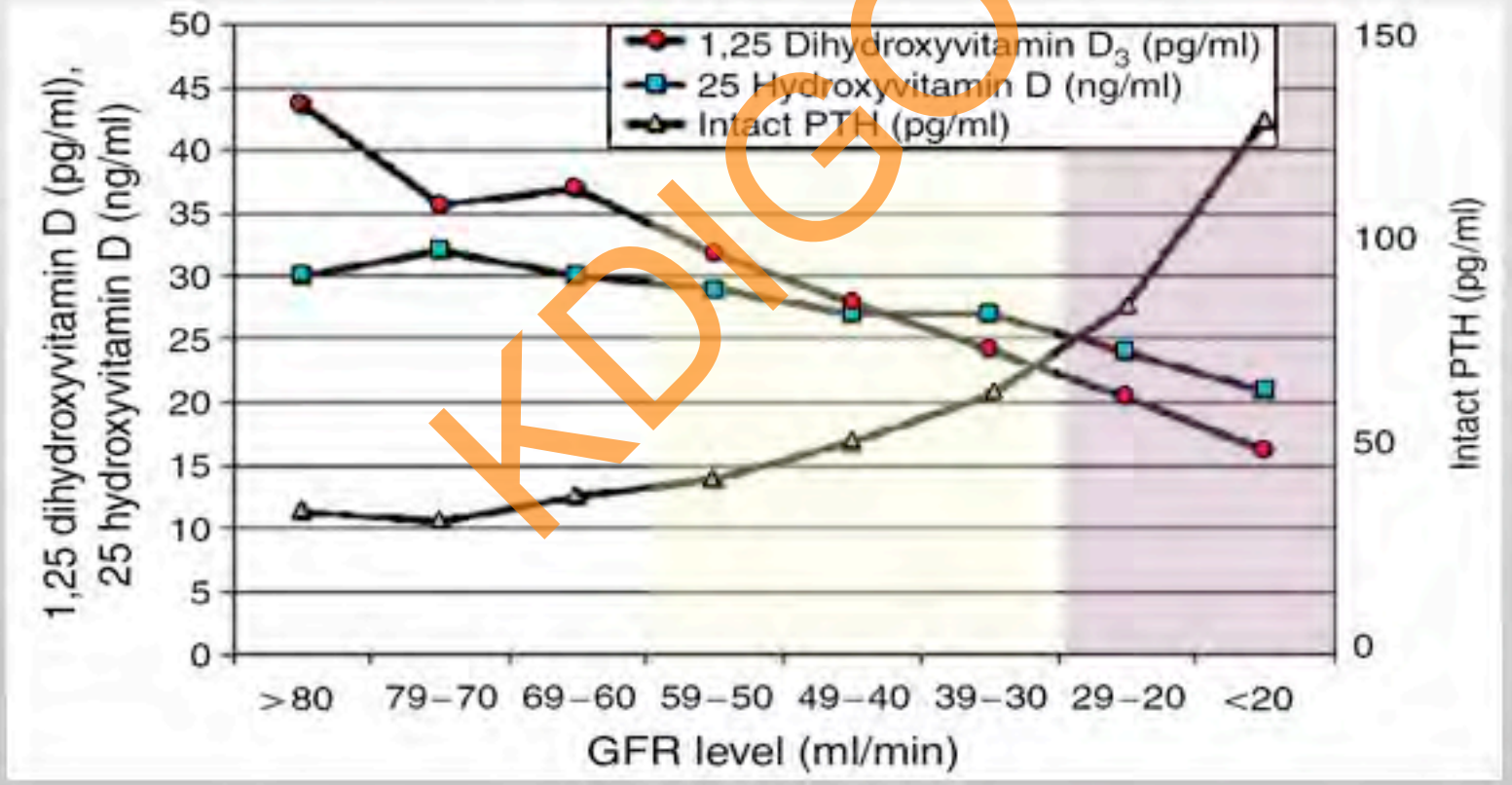


Vitamin D Values in CKD

Study for the Evaluation of Early Kidney disease (SEEK):

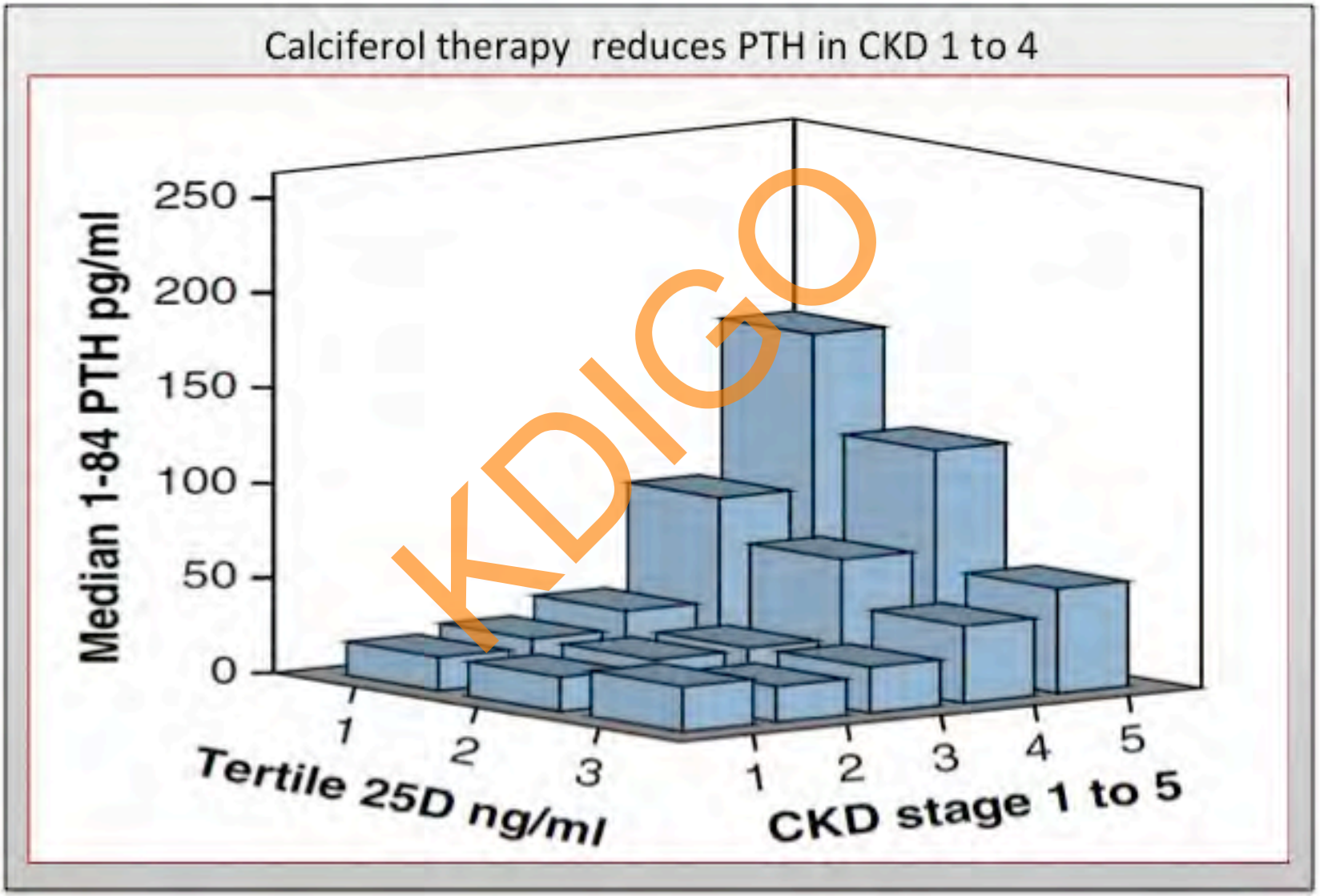
1814 CKD 3-5 patients from USA:

48% male, 47% diabetes, 71% > age 65



Levin, et al. Kidney International (2007) 71, 31–38

Reciprocal Relationship to PTH



Patel et al. J Bone Miner Metab (2011) 29:71–79

Patient-level associations; 25OHDin CKD-5D

Falls, stability and muscle strength in CKD 5D

Clinical Endocrinology (2010) doi: 10.1111/j.1365-2265.2010.03821.x

ORIGINAL ARTICLE

Association between 25-hydroxyvitamin D, somatic muscle weakness and falls risk in end-stage renal failure

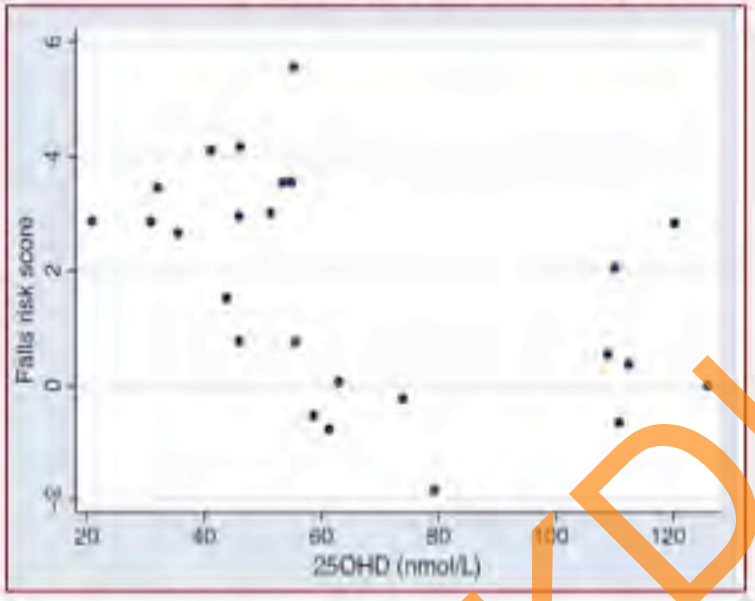
N Boudville*†, C Inderjeeth*‡, GJ Elder§ and P Glendenning*¶

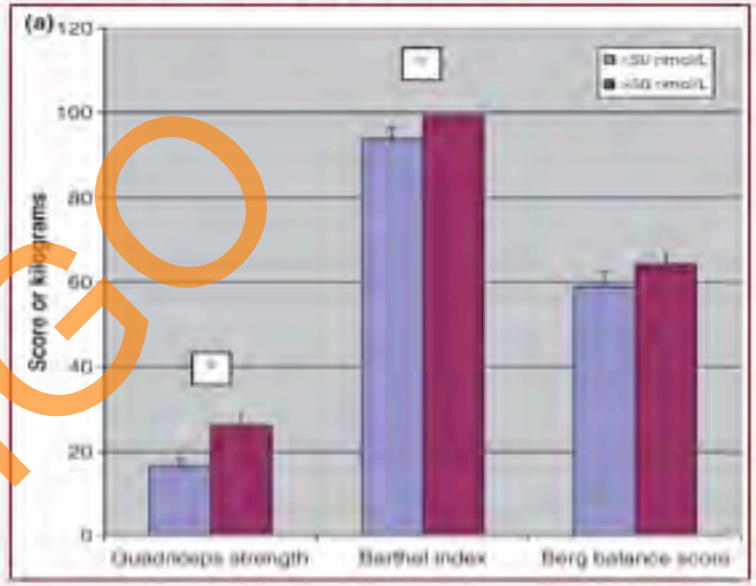
- Cross sectional study of HD patients:

Boudville et al. Clin Endocrinol 2010;73(3):299-304

Patient-level associations; 25OHDin CKD-5D

Falls Risk, stability and muscle strength in CKD 5D





- Significant inverse relationships of 25OHD to falls
- Quadriceps strength
- Function related to falls (Modified Barthel Index)
- No relationship to 1,25(OH)2D

Boudville et al. Clin Endocrinol 2010;73(3):299-304

Patient-level associations; 25OHDin CKD-5D

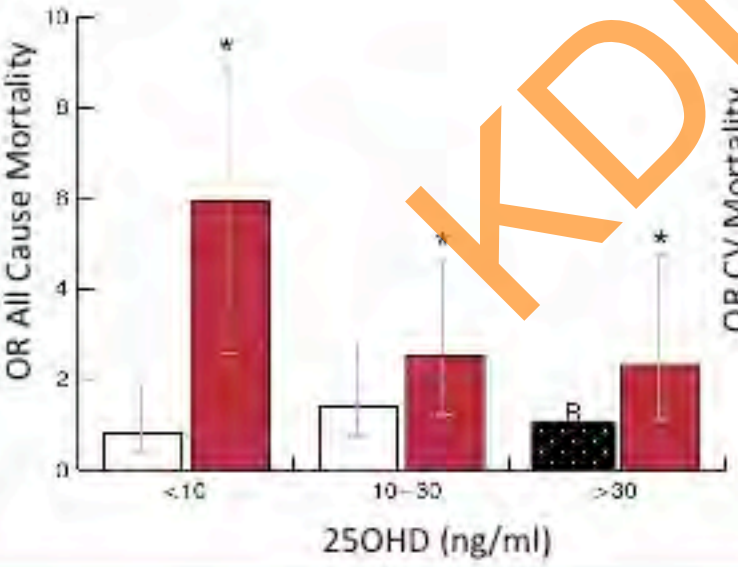
Multivariate adjusted OR of 90-day all-cause and CV mortality

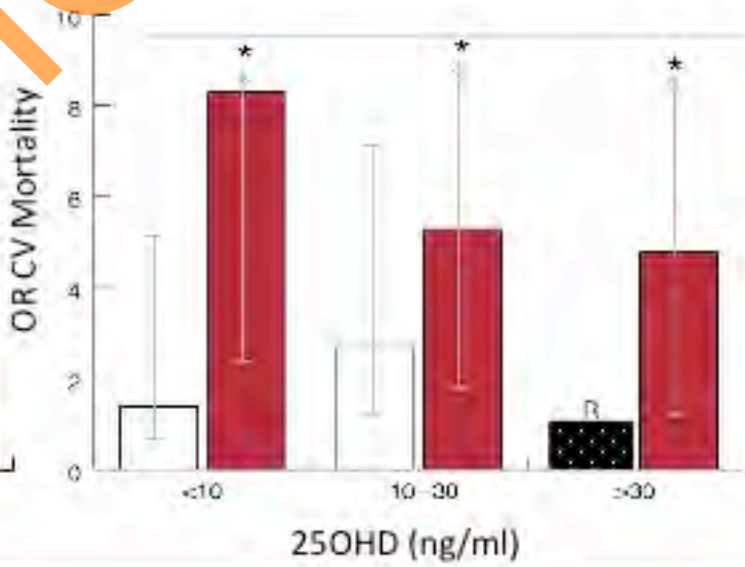
No active vitamin D therapy

Active vitamin D therapy

Reference; *active* vitamin D+25(OH)D >30 ng/ml+calcitriol >13 pg/ml

Lower risk at higher 25OHD values





Wolf et al. Kidney Int (2007) 72, 1004–1013

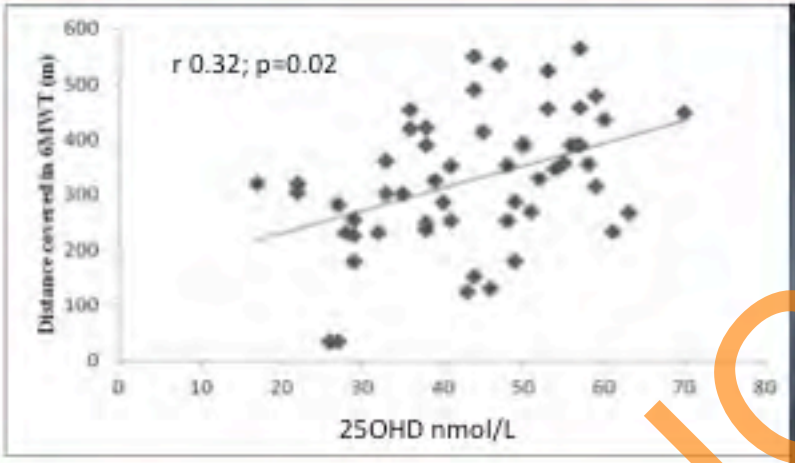
Effects of Cholecalciferol on Biochemical, Vascular, and Quality of Life Outcomes in HD

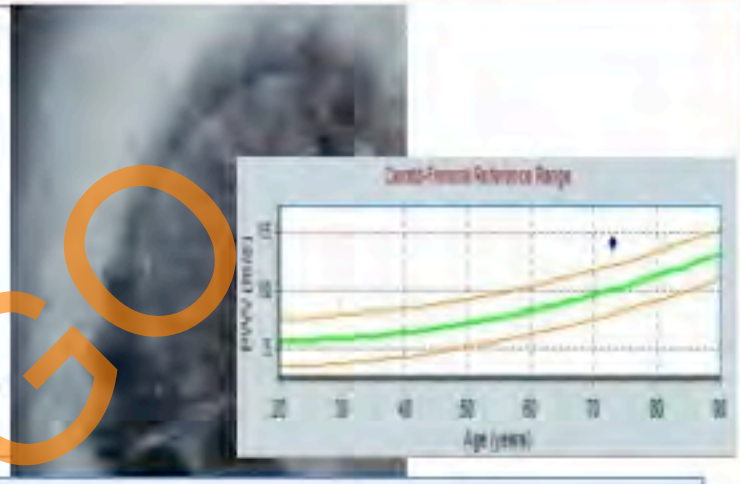
- Double blind RCT over 6 months
- 60 satellite HD patients with 25(OH)D <60 nmol/L
- Oral cholecalciferol 50,000 IU in 10 mls weekly for 8 weeks then monthly for 4 months
- Placebo: medium chain triglyceride

Muscle strength and hand grip
Functional testing and balance
QOL questionnaire (KDQOL-36)
PWV, BP
Ca, P, 25(OH)D, 1,25(OH)$_2$D ,PTH, b-ALP and TRAcP-5b,Hb and ESA
Co-morbidities: ANZDATA
Falls diary, infections, adverse events

Hewitt et al. Clin J Am Soc Nephrol 2013; 8;1143–1149

Effects of Cholecalciferol on Biochemical, Vascular, and Quality of Life Outcomes in HD





Baseline characteristics well matched;
Median age 62 years (20–86), 52% women, 55% diabetes, 25(OH)D 43±13 nmol/L (17±5 ng/ml); BMI (kg/m^2)*31.3 ± 9.5 (placebo) 26.6 ± 6.4 (cholecalciferol)

- 25(OH)D lower with diabetes (39±13 vs. 48±10 nmol/L; p=0.002)
  - Correlated to calcitriol (*r*=0.27; p=0.04)
  - Correlated to distance covered in the 6-min. walk
  - Predicted PWV (adjusted r^2=0.149; p=0.019);
  - Part correlations: Age 0.306, 25(OH)D -0.266).

Hewitt et al. Clin J Am Soc Nephrol 2013; 8;1143–1149

Effects of Cholecalciferol on Biochemical, Vascular, and Quality of Life Outcomes in HD

At 6 months: No effect on primary end point; muscle strength testing

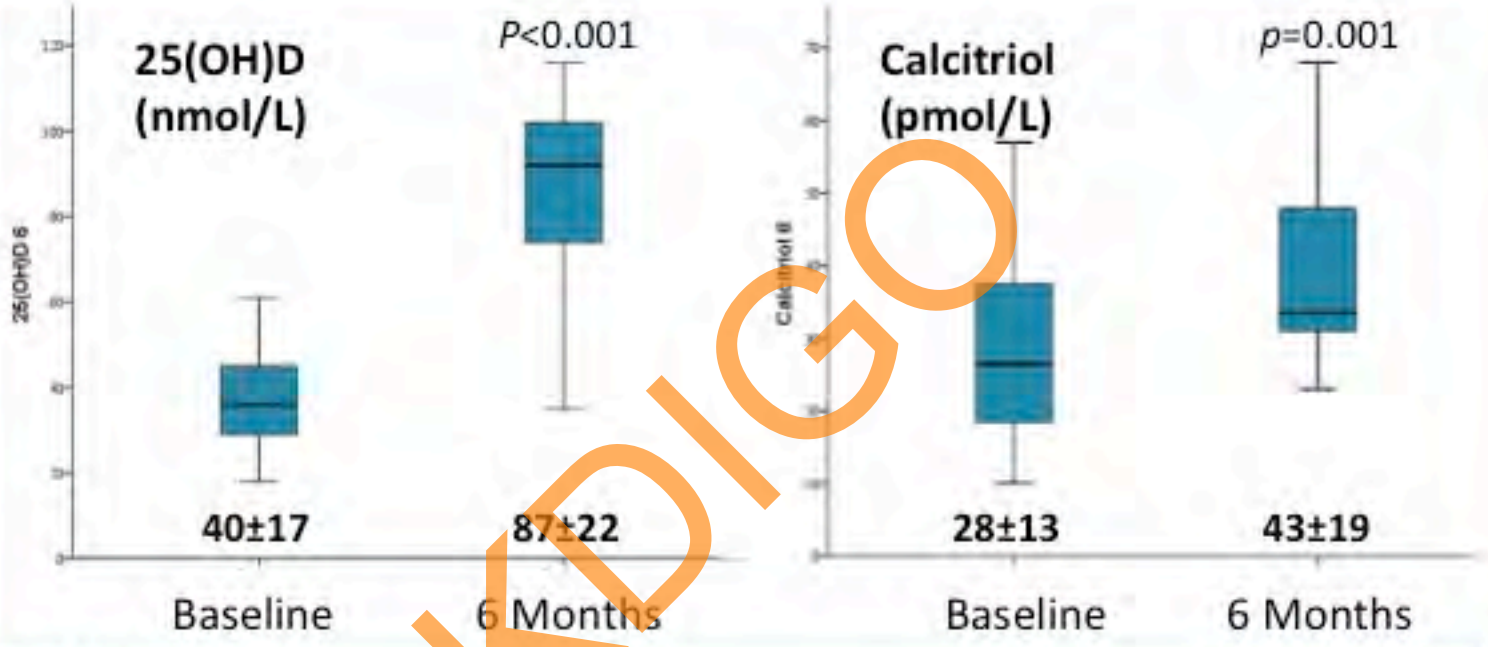
Table 4. Baseline and 6-month muscle group strength

Muscle Group	Time	Placebo	Cholecalciferol	*P* Value
Grip strength	Baseline	21 (17, 25)	23 (19, 28)	
	6 mo	21 (17, 24)	24 (21, 28)	0.28
Shoulder abduction	Baseline	5 (4, 6)	5 (4, 6)	
	6 mo	6 (4, 7)	7 (5, 9)	0.53
Elbow flexion	Baseline	12 (9, 14)	12 (9, 14)	
	6 mo	14 (11, 16)	15 (12, 18)	0.63
Elbow extension	Baseline	10 (8, 11)	10 (9, 12)	
	6 mo	11 (19, 13)	13 (11, 14)	0.41
Hip flexion	Baseline	12 (10, 15)	13 (11, 15)	
	6 mo	16 (14, 17)	16 (15, 18)	0.83
Knee flexion	Baseline	11 (9, 12)	12 (10, 13)	
	6 mo	14 (12, 16)	13 (11, 15)	0.93
Knee extension	Baseline	15 (12, 17)	14 (12, 17)	
	6 mo	19 (16, 21)	19 (16, 22)	0.97

Data are shown in kilograms of force (95% confidence interval). *P* values represent differences in strength between treatment groups over time (repeated-measures ANOVA). There were 30 patients in each group at baseline and 24 patients in the placebo group and 21 patients in the cholecalciferol group at 6 months.

Hewitt et al. Clin J Am Soc Nephrol 2013; 8;1143–1149

Effects of Cholecalciferol on Biochemical, Vascular, and Quality of Life Outcomes in HD



At 6 months

- 25OHD and calcitriol were higher and phosphate lower (p=0.04)
- TRAcP-5b higher; p=0.04
- Reduced Ca-based P binder use
- No between group differences in levels of iPTH, ALP, b-ALP, Ca, functional tests, falls, HRQOL, PWV, ESA dose, Infections, AEs

Hewitt et al. Clin J Am Soc Nephrol 2013; 8;1143–1149

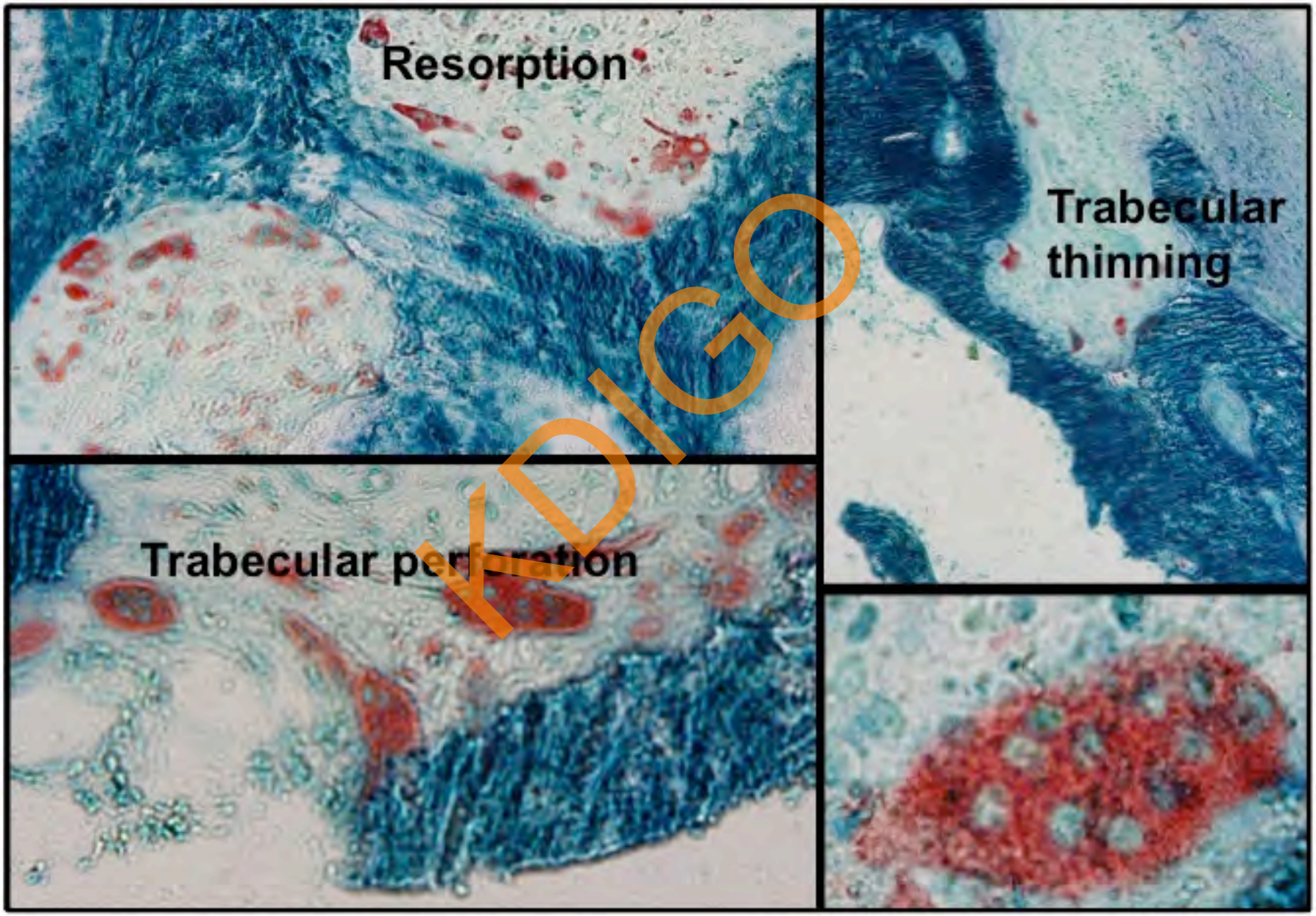
Summary: calciferol

- PTH is inversely related to 25OHD values in CKD 3 - 4 / 5. General population data is applicable to many in this group
- In CKD 5D, association studies suggest relationships of 25OHD to improved mortality, PWV and functional tests but no change was seen after 6 months therapy in patients with vitamin D insufficiency
- Treatment with cholecalciferol effectively increases serum 25(OH)D and levels of calcitriol are higher; possibly supporting the concept of extra-renal conversion
- Cholecalciferol may increase osteoclast markers
- Cholecalciferol does not increase serum Ca or P

Rationale for Treatment with Calcitriol and Analogs

- Control of sHPT and avoidance of PTx
- Control of sHPT effects on bone and mineral metabolism
- Avoidance of related CV events and mortality
- Pleomorphic vitamin D effects; oxidative stress, infection etc
- Physiological Replacement

Control of sHPT



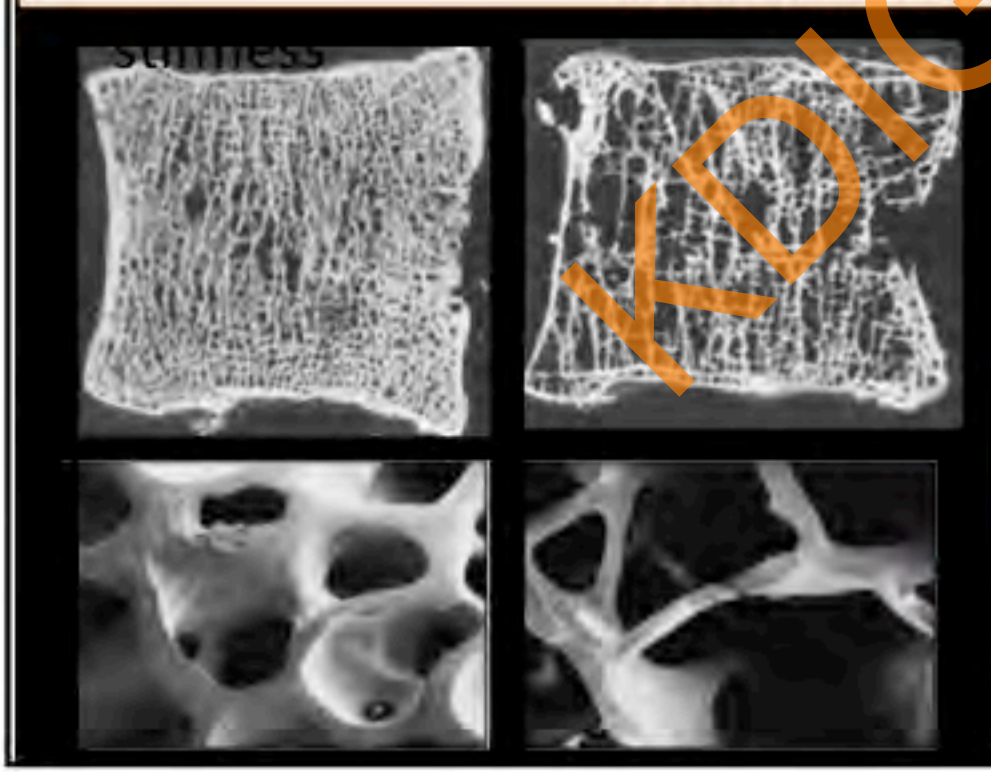
Control of sHPT

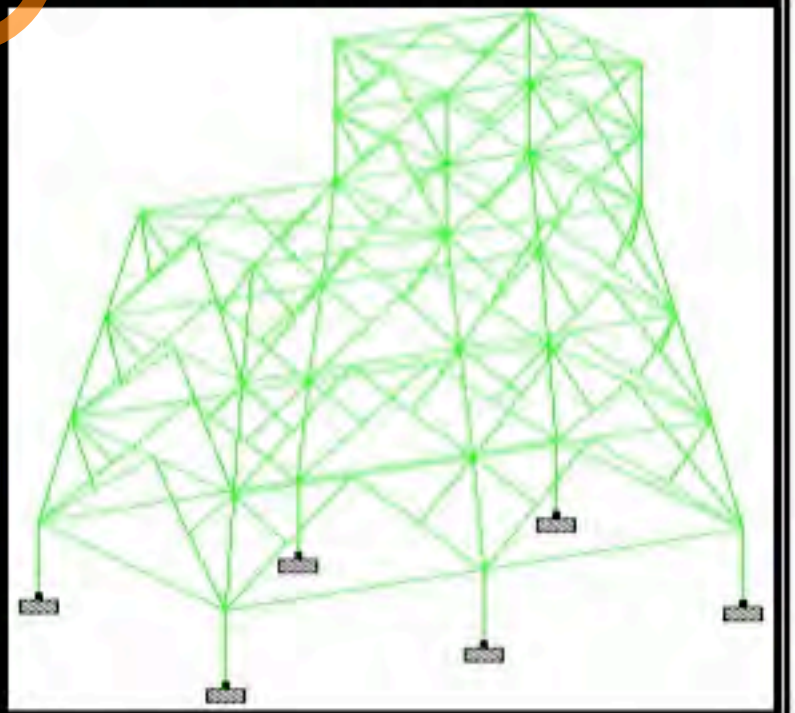
- Reduced bone mass and quality
- Structural properties: micro-architecture;

  loss of plate structures in trabecular bone

  reduced cortical thickness

  increased cortical porosity reduces





Control of sHPT

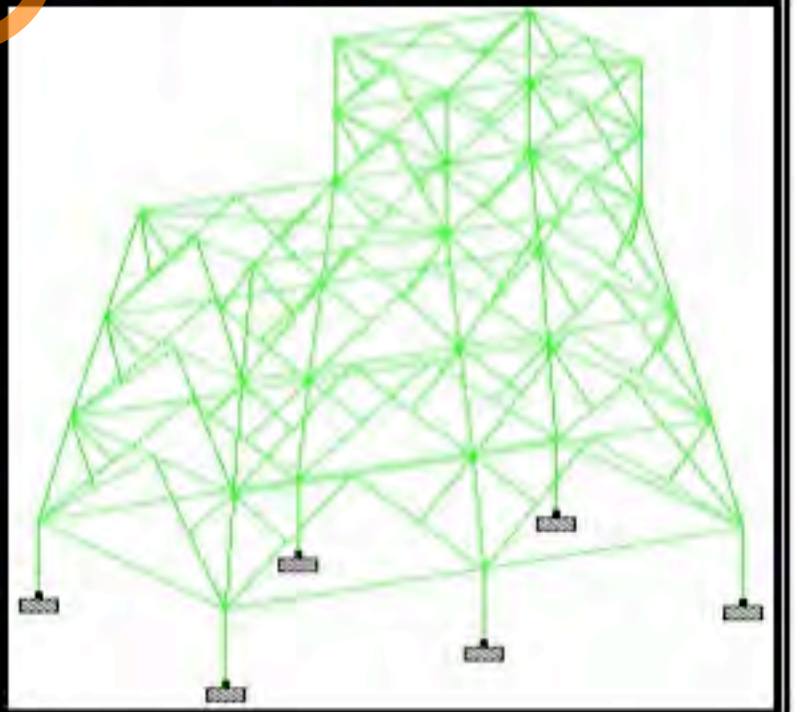
- Reduced bone mass and quality
- Structural properties: micro-architecture;

  loss of plate structures in trabecular bone

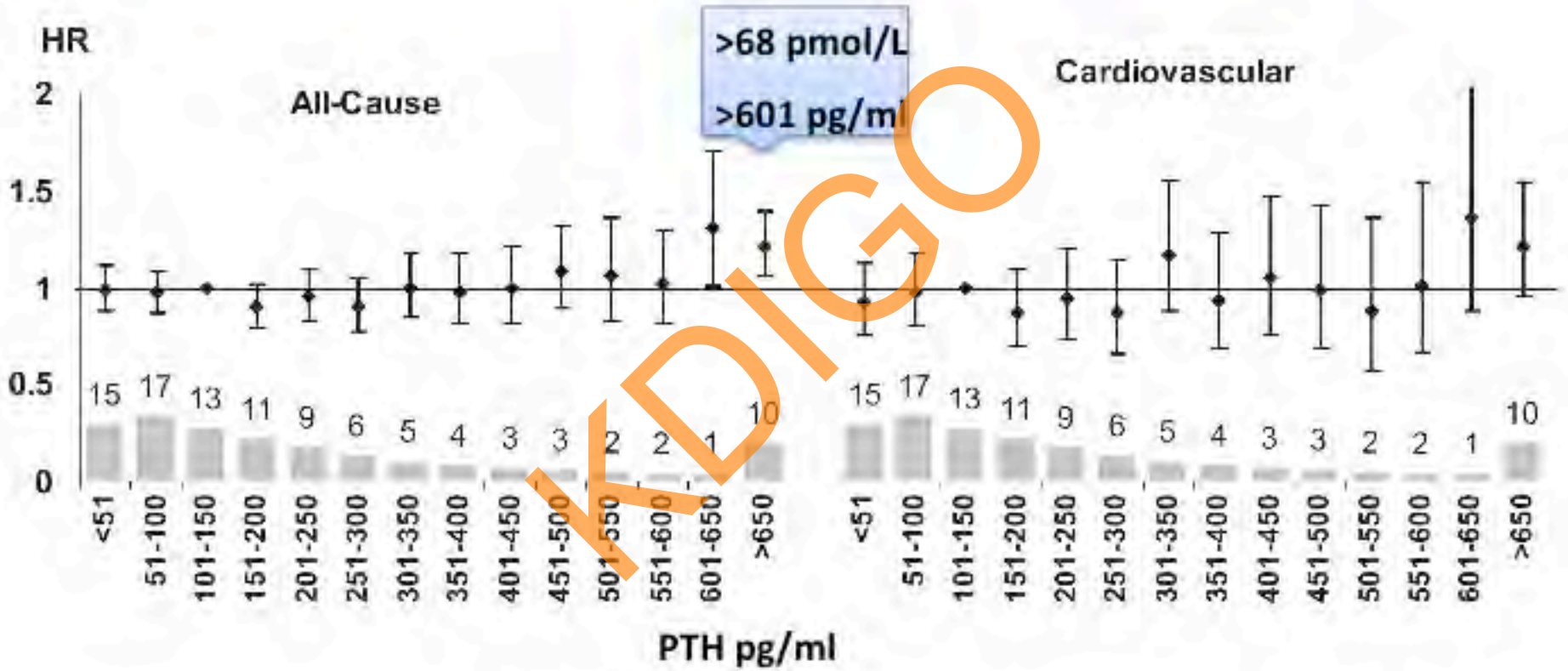
  reduced cortical thickness

  increased cortical porosity reduces

With equal bone volume, resorption cavities cause twice the loss of stiffness as the same amount of loss due to trabecular thinning.



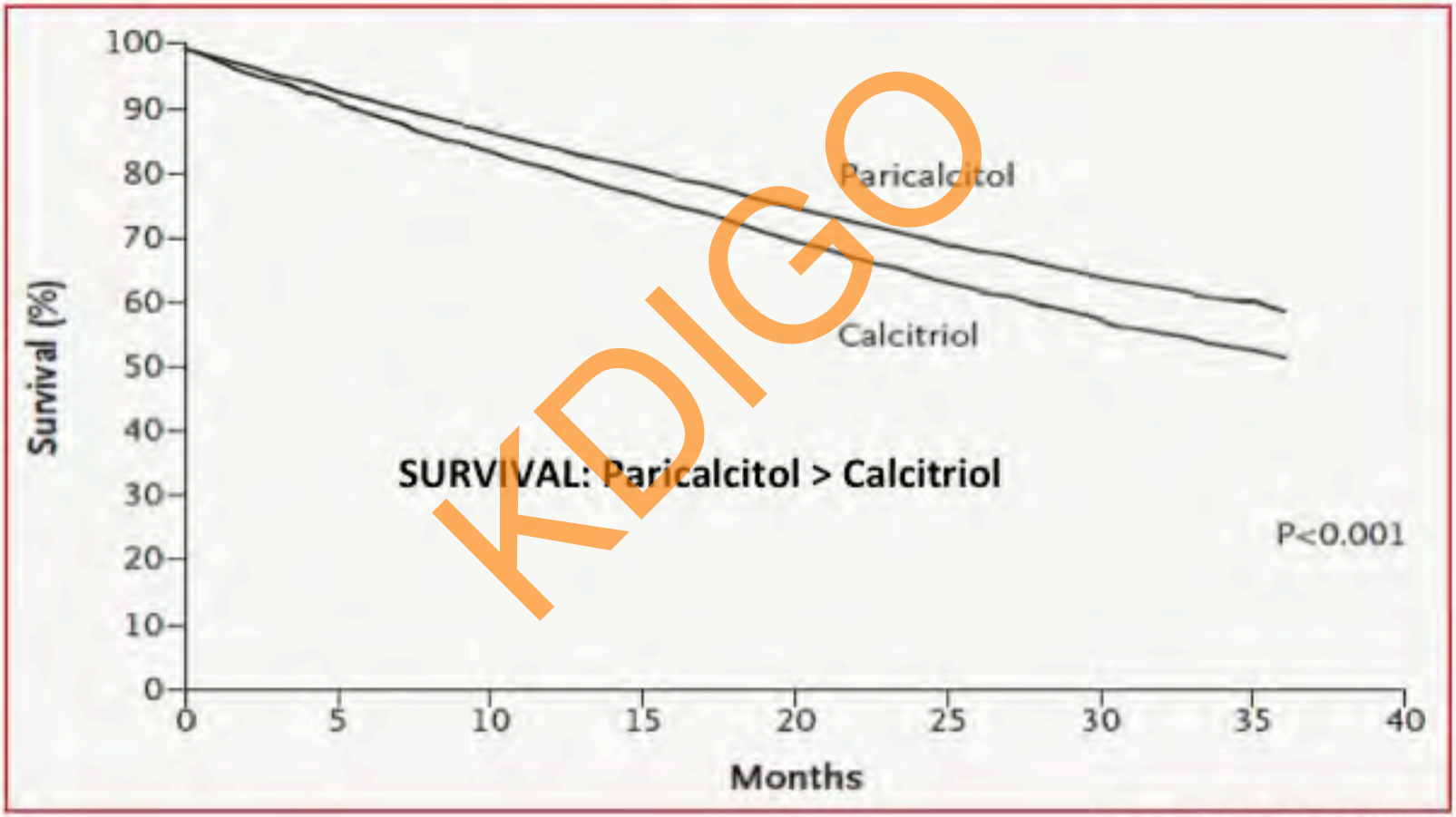
Avoidance of CV events and mortality



Tentori AJKD 2008

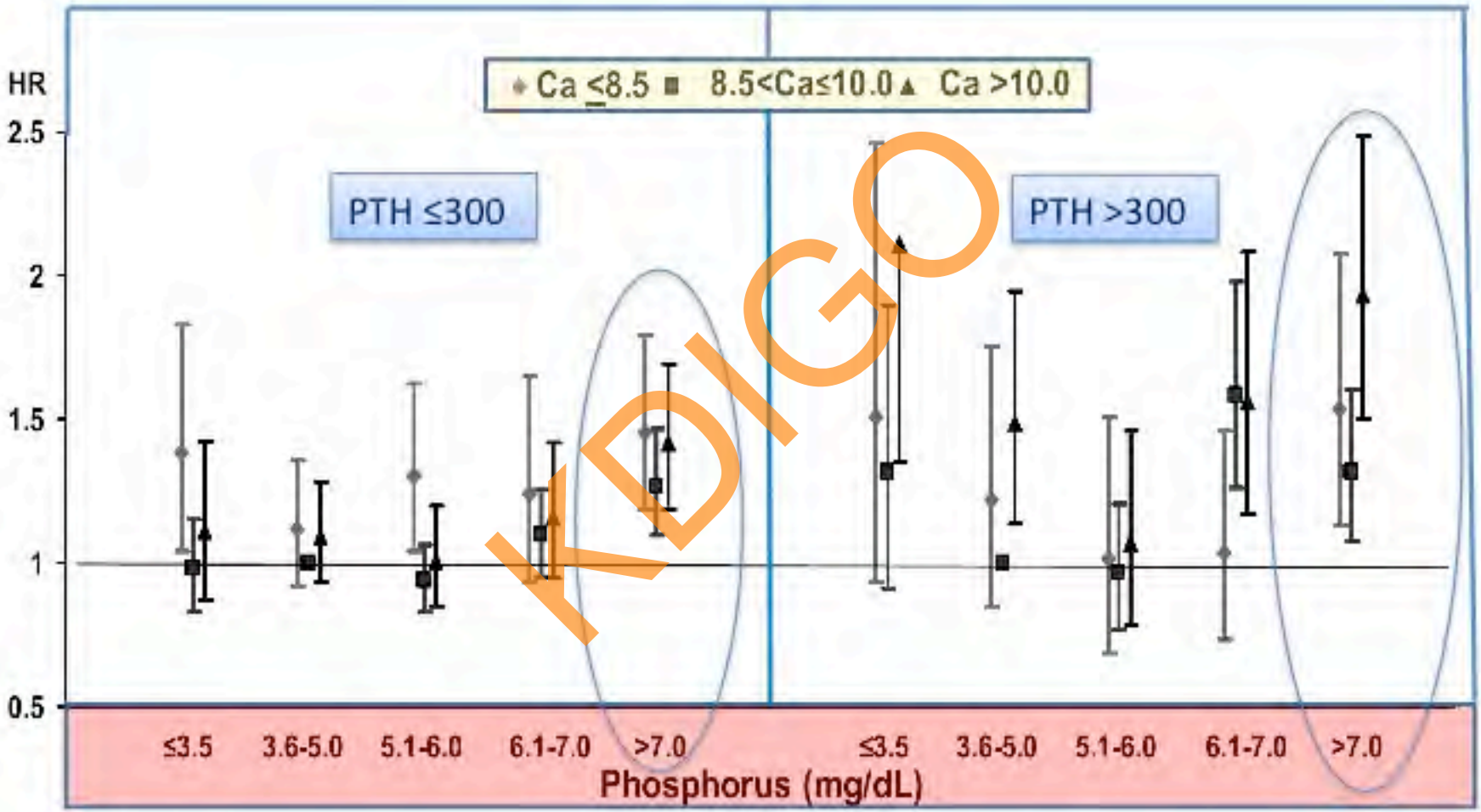
Avoidance of CV events and mortality

FRESENIUS MEDICAL CARE iPTH TARGET <300 pg/ml



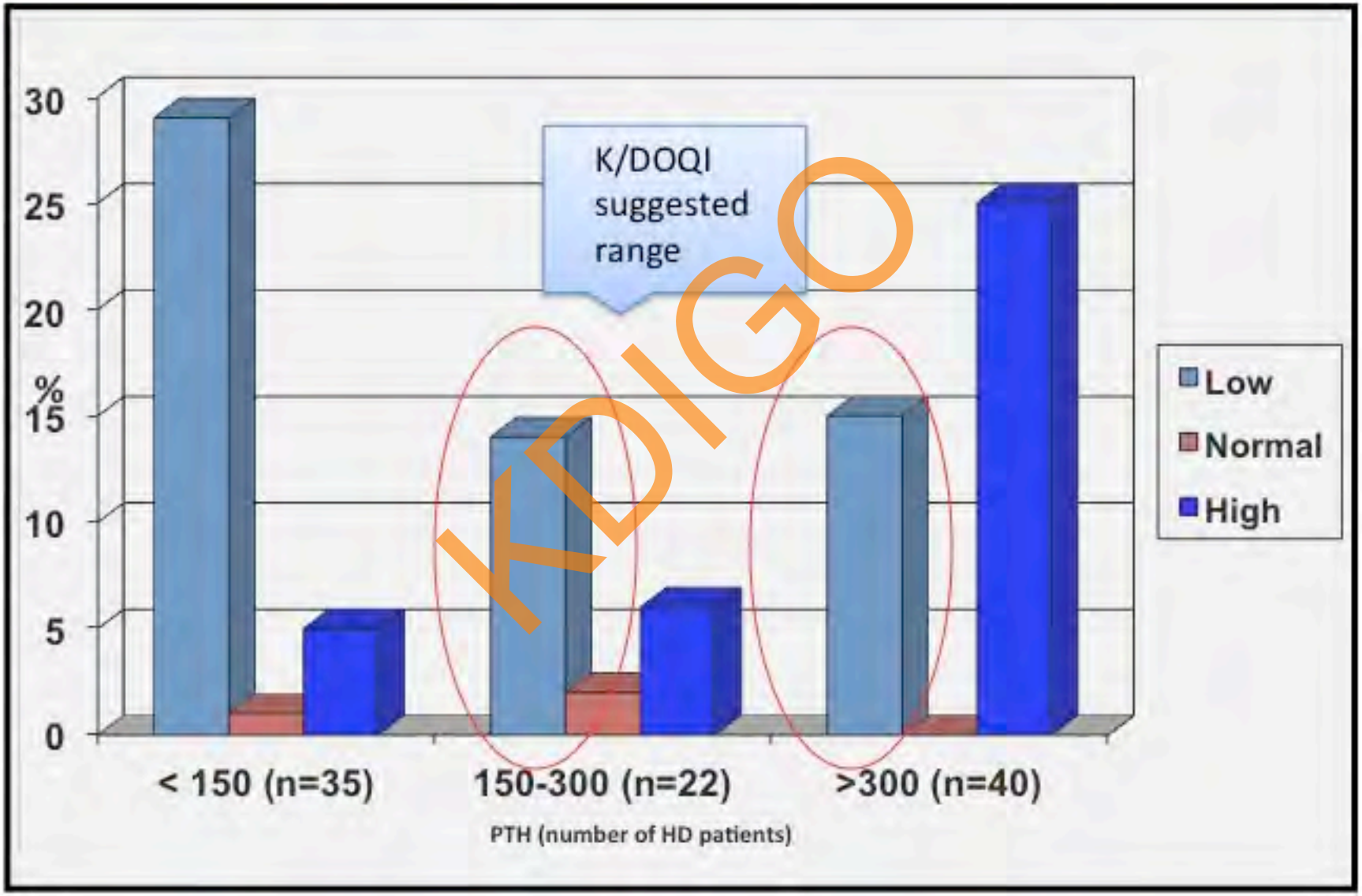
Teng et al N Eng J Med 2003. 349;5

PTH and mortality inconsistently associated



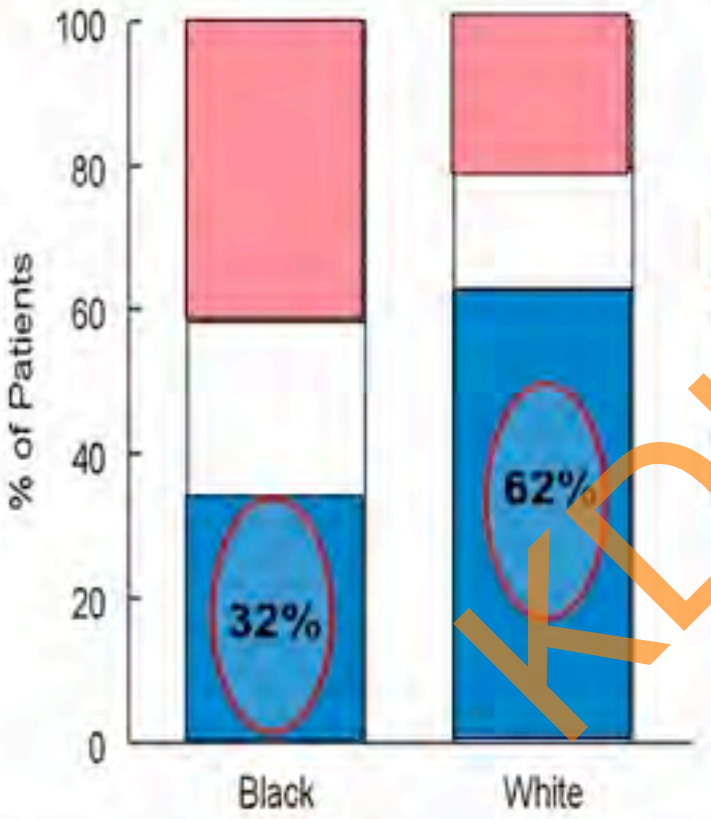
Tentori AJKD 2008

PTH value may not reflect bone turnover



Barreto FC, *et al*. Kidney Int 73:771, 2008

Low bone turnover is common



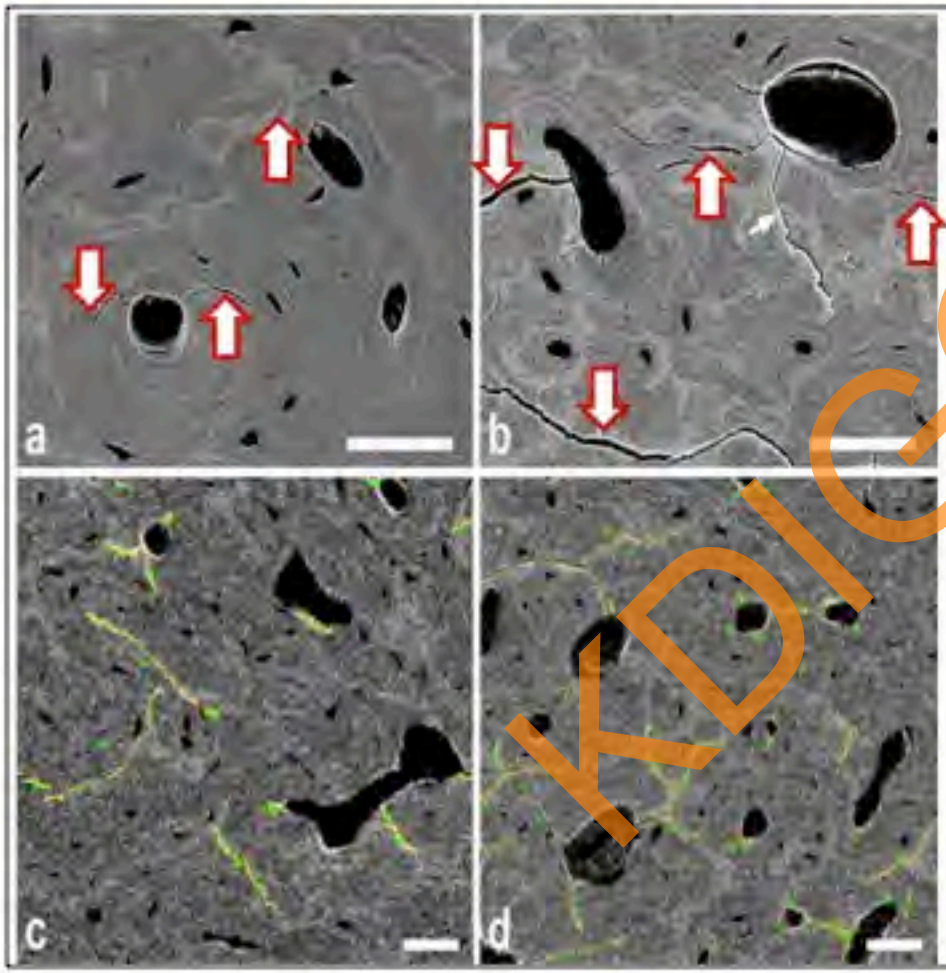
Turnover;

- Afro-Americans
  Low in 32%
- Caucasians
  Low in 62%

630 bone biopsies: 543 Caucasian. Dialysate Ca^{2+} 1.25 mmol/L in 371, 1.75 mmol/L in 259; 429 Ca-based P binders; 4 cinacalcet

Malluche et al. J Bone Miner Res 2011, 26 (6);1368-76

Low turnover may increase bone fragility

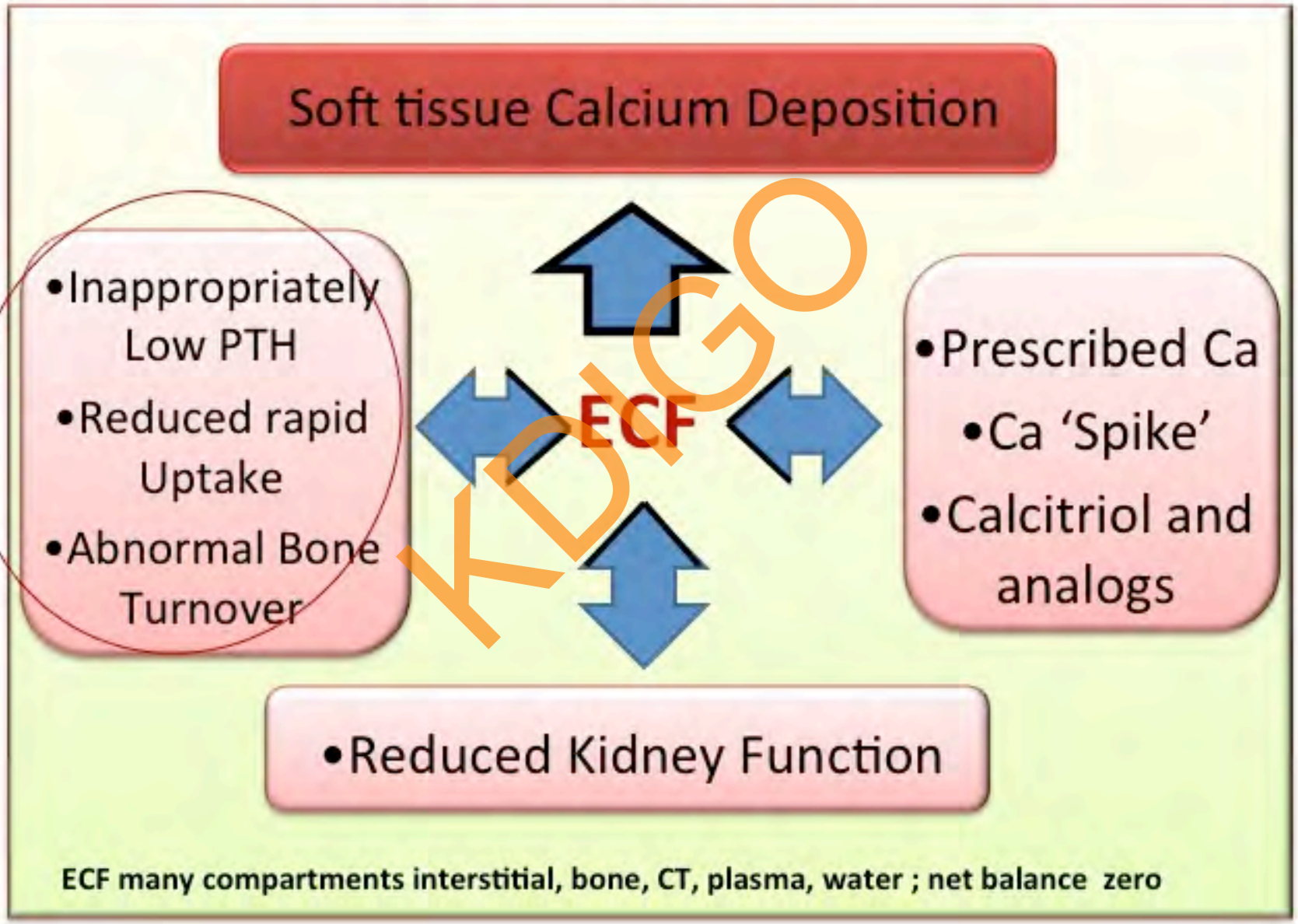


Microcrack frequency and bone remodeling in postmenopausal osteoporotic women on long-term bisphosphonates: a bone biopsy study

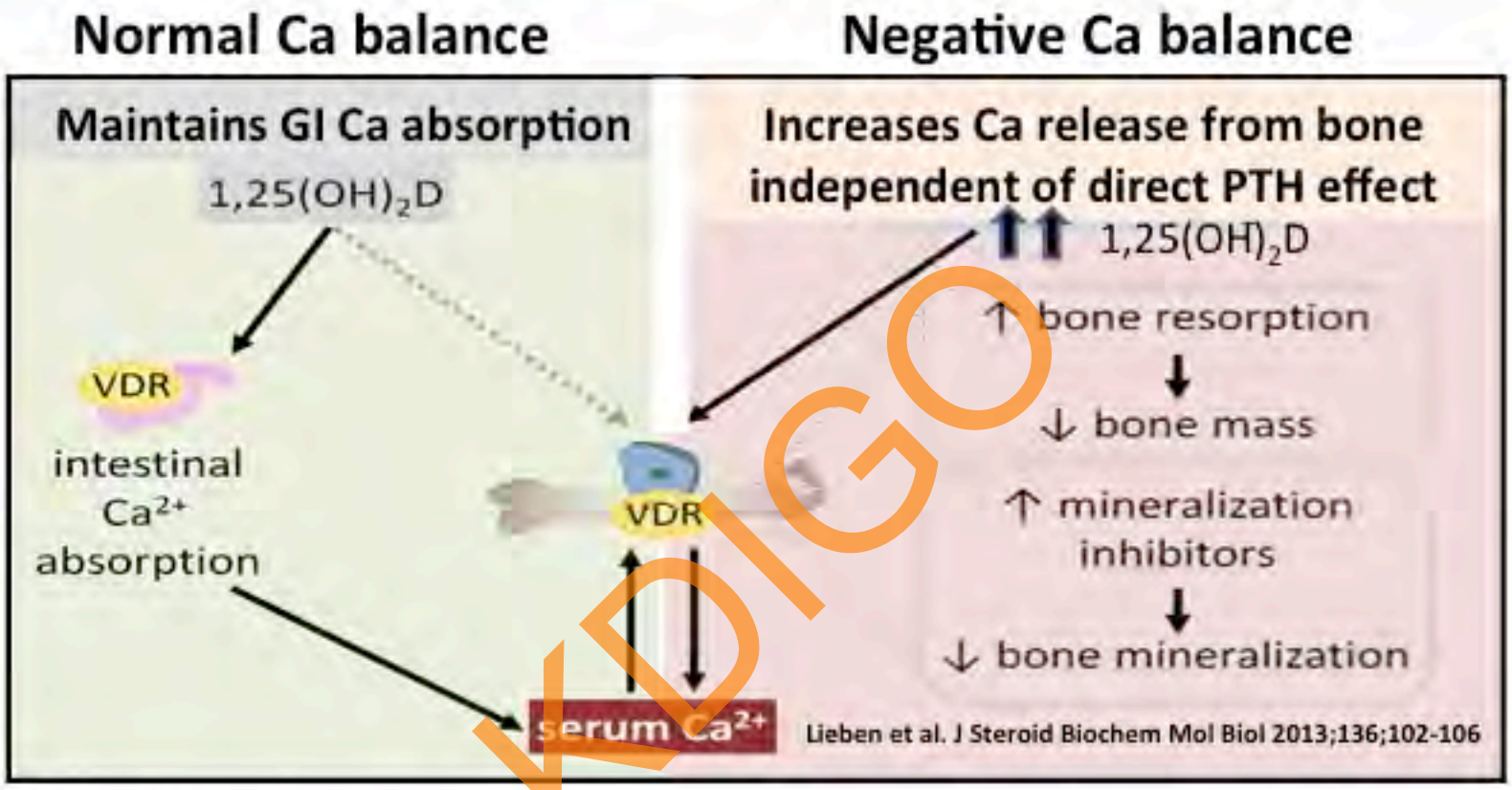
Compared to controls, reduced turnover but no increase in microcrack accumulation

Chapurlat et al J Bine Miner Res2007;22(10):1502-9.

Low and high turnover potentiate VC



$1,25(OH)_2D$ actions vary with calcium balance



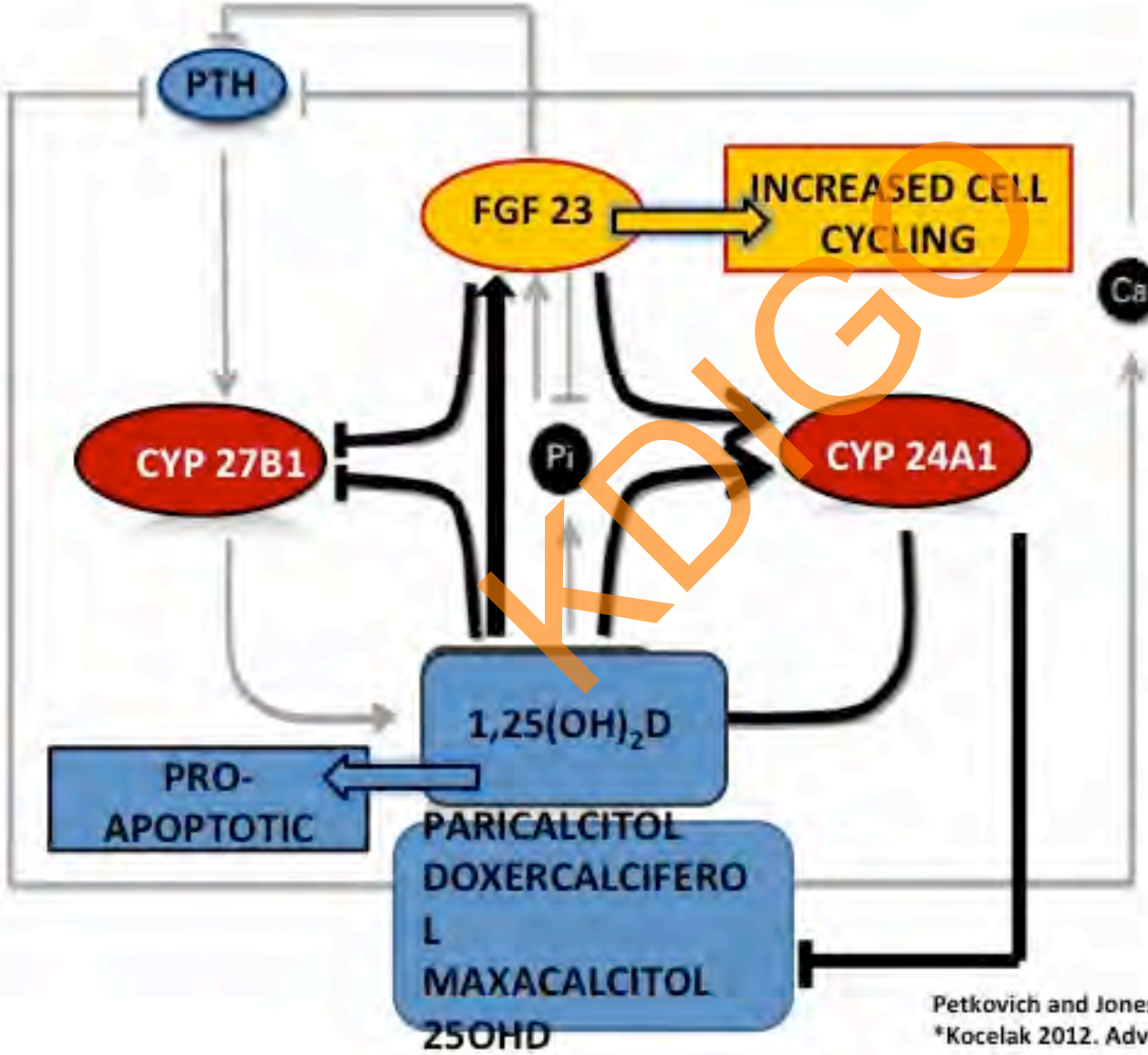
- $1,25(OH)_2D$ suppresses mineralisation by increasing levels of pyrophosphate
- Inhibits osteoblastogenesis and increases osteoclast activity

  Tanaka et al. J Steroid Biochem Mol Biol 2004;89–90;343–345
- BUT: Effects vary with developmental stage

  Anabolic effects on mature osteoblasts also reported

  St Arnaud J Steroid Biochem Mol Biol 2008

$1,25(OH)_2D$ / FGF 23 interactions



Independent effects on P and Ca

$1,25(OH)_2D$ induces FGF 23 release if normocalcaemic; ? reduced in CKD*

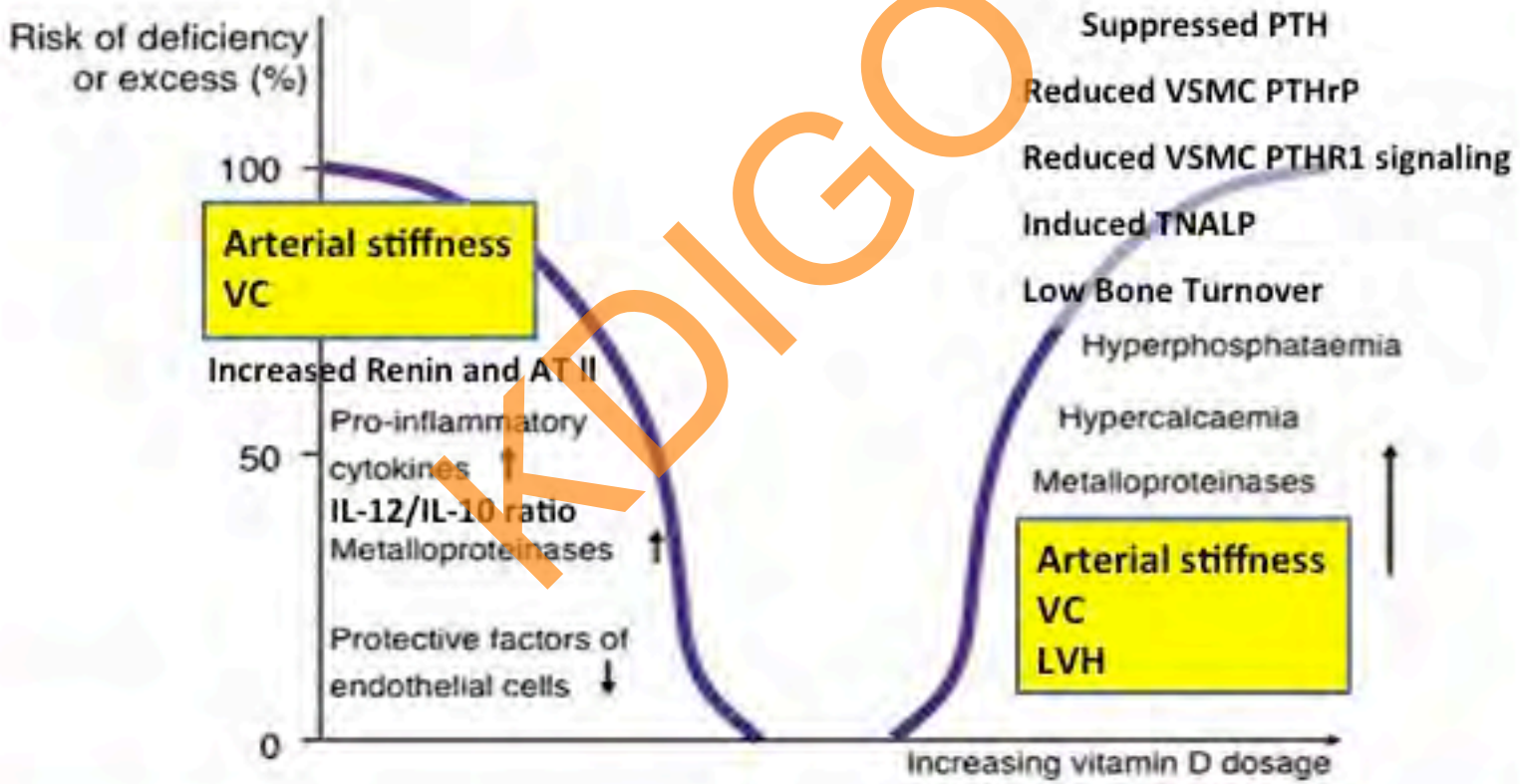
FGF 23 and $1,25(OH)_2D$ induce 24-hydroxylase; clears calcitriol, analogs and 25OHD.

Cell cycling effects

Petkovich and Jones. Current Opin Nephrol Hypertens 2011
*Kocelak 2012. Adv Clin Exp Med 2012, 21, 3, 391–401

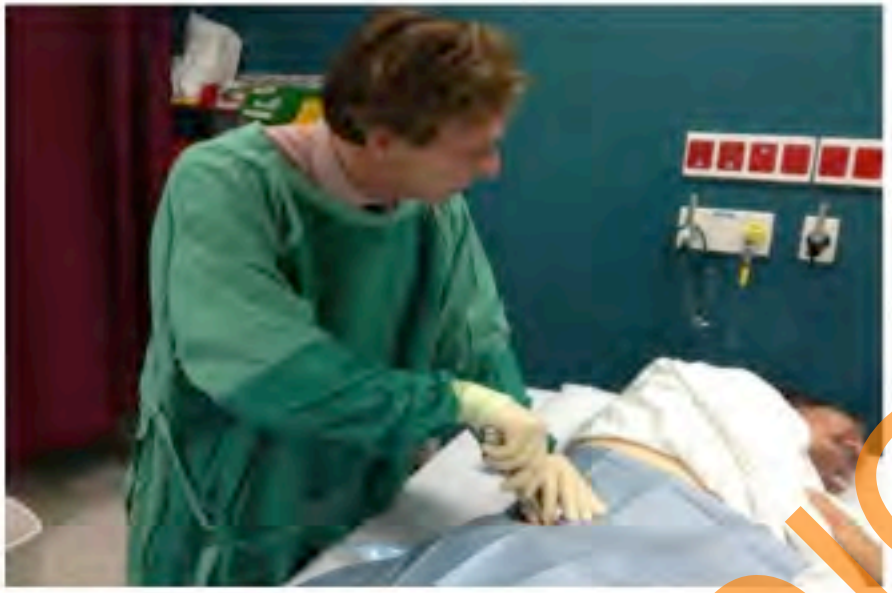
Biphasic Dose-Response Curve for 1,25(OH)2D

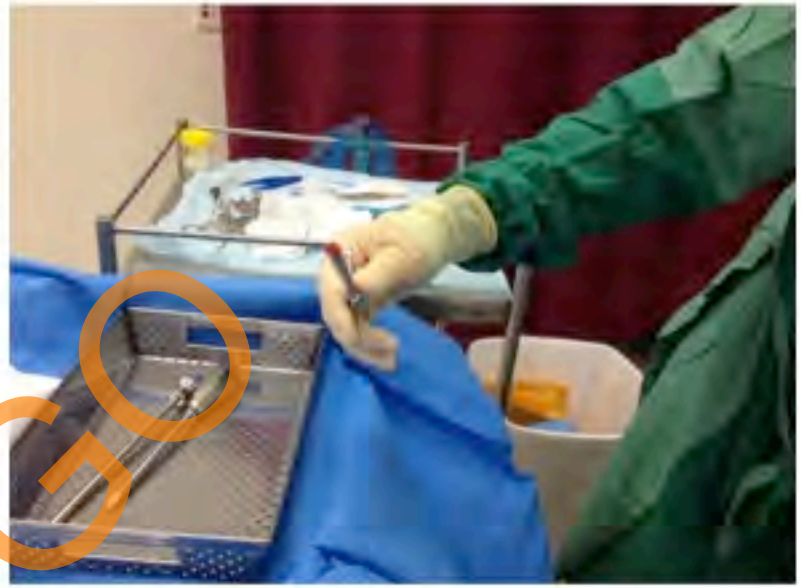
Deleterious Consequences of Deficiency or Excess



Thompson and Towler. Nature Reviews Endocrinology 2012
Cozzolino Clin Nephrol 2009
Zittermann et al, Curr Opin Lipidol 2007; 18: 41–46

Effect of Calcitriol and Analogs on TMV





	Turnover:	Mineralisation:	Volume:
•Calcitriol IV / PO	↓↓	↑	↑
•Alfacalcidol	↓	↑	↑
•Paricalcitol	?	?	?
•Doxercalciferol	?	?	?
•Maxacalcitol	↔	↑	↑

Reduced turnover, woven bone, fibrosis, improved mineralisation

Adapted from Malluche et al. Clin J Am Soc Nephrol 3: S157–S163, 2008

Calcitriol and newer analogs

REVIEW | Annals of Internal Medicine

Meta-analysis: Vitamin D Compounds in Chronic Kidney Disease

Suetonia C. Palmer, MBChB; David O. McGregor, PhD; Petra Macaskill, PhD; Jonathan C. Craig, PhD; Grahame J. Elder, PhD; and Giovanni F.M. Strippoli, MD, MPH(Hons), MM

Purpose: To determine whether vitamin D therapy improves biochemical markers of mineral metabolism and cardiovascular and mortality outcomes in chronic kidney disease.

Data Sources: MEDLINE (January 1966 to July 2007), EMBASE (January 1980 to July 2007), and Cochrane databases were searched without language restriction.

Meta-analysis of 76 trials; 3667 patients; 40 years research!

Palmer et al. Ann Intern Med. 2007;147:840-853.

Calcitriol and newer analogs

- Little data on patient-level outcomes

- Reciprocal relationship of calcitriol / analogs to PTH
  Newer analogs may reduce PTH more effectively

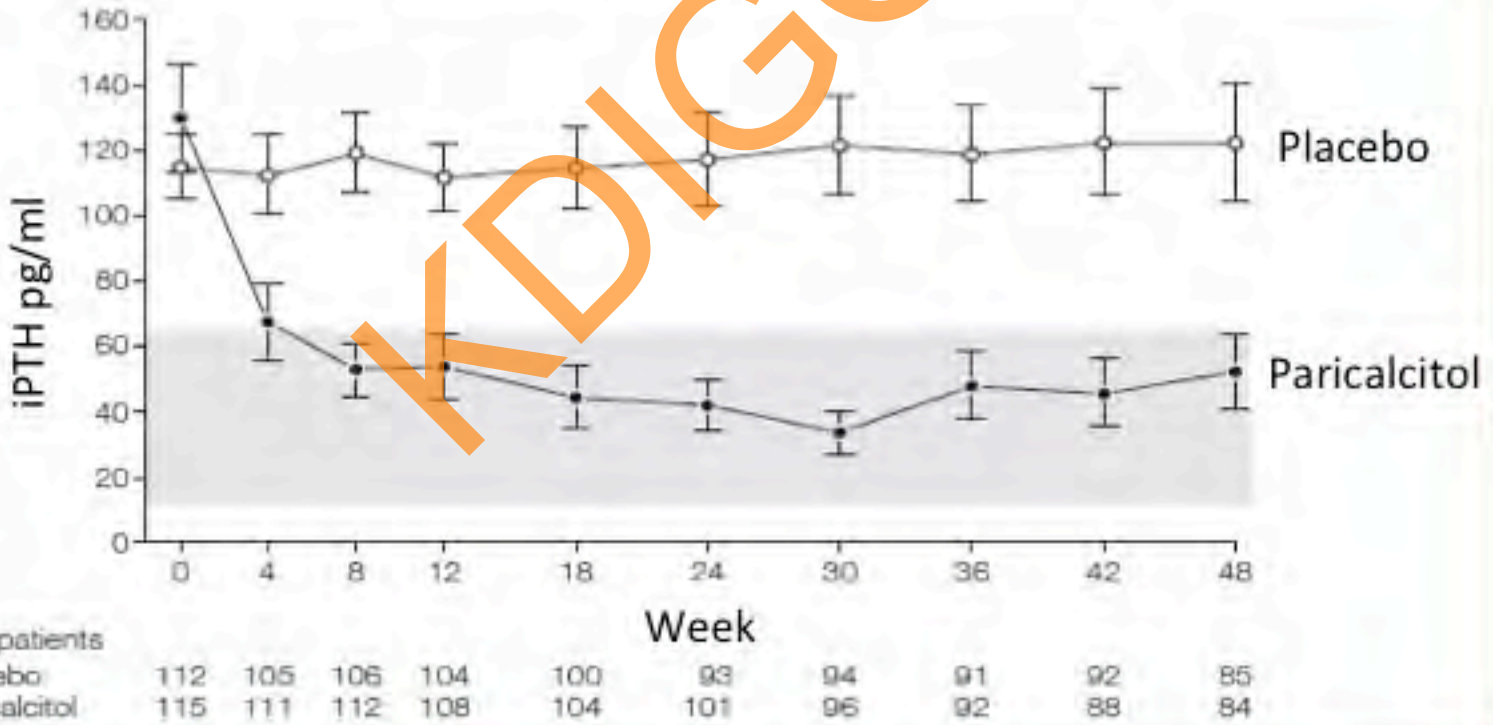
- Established vitamin D therapies were associated with increases in both Ca and P

- Newer analogs were associated with increases in Ca but not P *vs.* placebo

Palmer et al. Ann Intern Med. 2007;147:840-853.

The PRIMO Randomized Controlled Trial

In patients with LVH and CKD, does 48-weeks treatment with paricalcitol reduce LV mass and CVD events and improve diastolic function and cardiac biomarkers?



Thadhani et al. JAMA, 2012 Vol 307, No.7

The PRIMO Randomized Controlled Trial

- NS change in LVMI at 48 weeks (primary endpoint)
- Hospitalizations from any cause NS.
- Between-group differences in BNP NS.
- Paricalcitol reduced left atrial volume index, a measure linked to adverse cardiovascular events, particularly CCF

ADVERSE EVENTS

- Hypercalcemia (paricalcitol, 22.6% vs placebo, 0.9%; P.001)
- Decline in GFR by creatinine and cystatin C-based methods (p=0.001 and 0.06 respectively)

COMMENTS:

- Patients may have been too well controlled: RAS inhibitors, BP, CRP
- BNP and LAVI changes may be adequate surrogates.

Thadhani et al. JAMA, 2012 Vol 307, No.7
Tamez,et al; Am Heart J 2012;164:902-909

Summary: calcitriol and analogs

- Phamacological doses of calcitriol and analogs suppress PTH in CKD 3-5D but increase calcium and/or phosphate levels.
- Calcitriol and analogs improve bone histomorphometry in patients with high bone turnover.
- Patients treated with calcitriol/analogs ± calcimimetics may develop low bone turnover; with increased risks for VC and possibly bone quality.
- Despite observational support for calcitriol/analogs improving CV risk and mortality, the PRIMO study did not show an overall advantage; although surrogate measures suggest subgroups may be benefited.
- Low dose calcitriol/analogs may benefit CV risk and bone