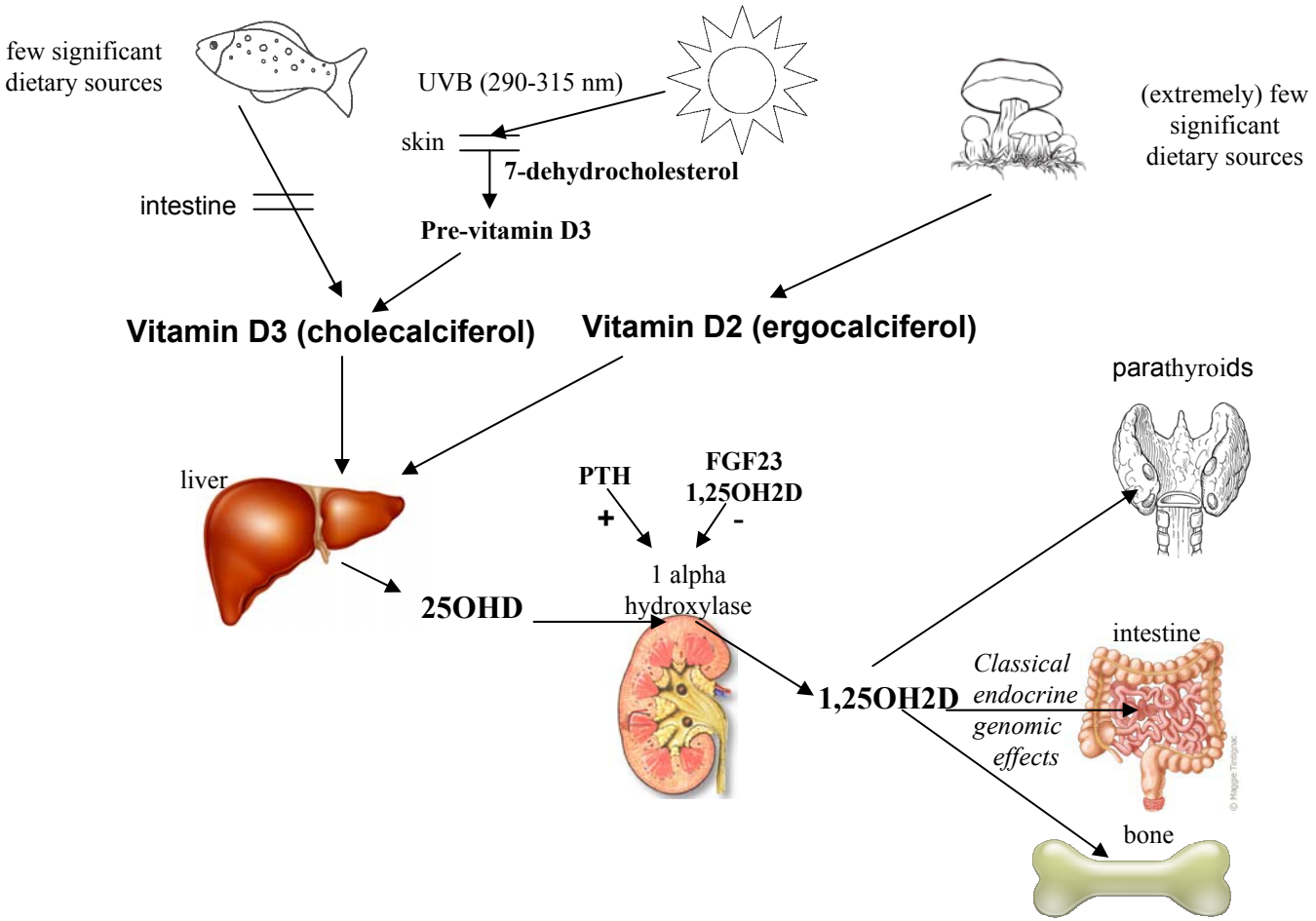
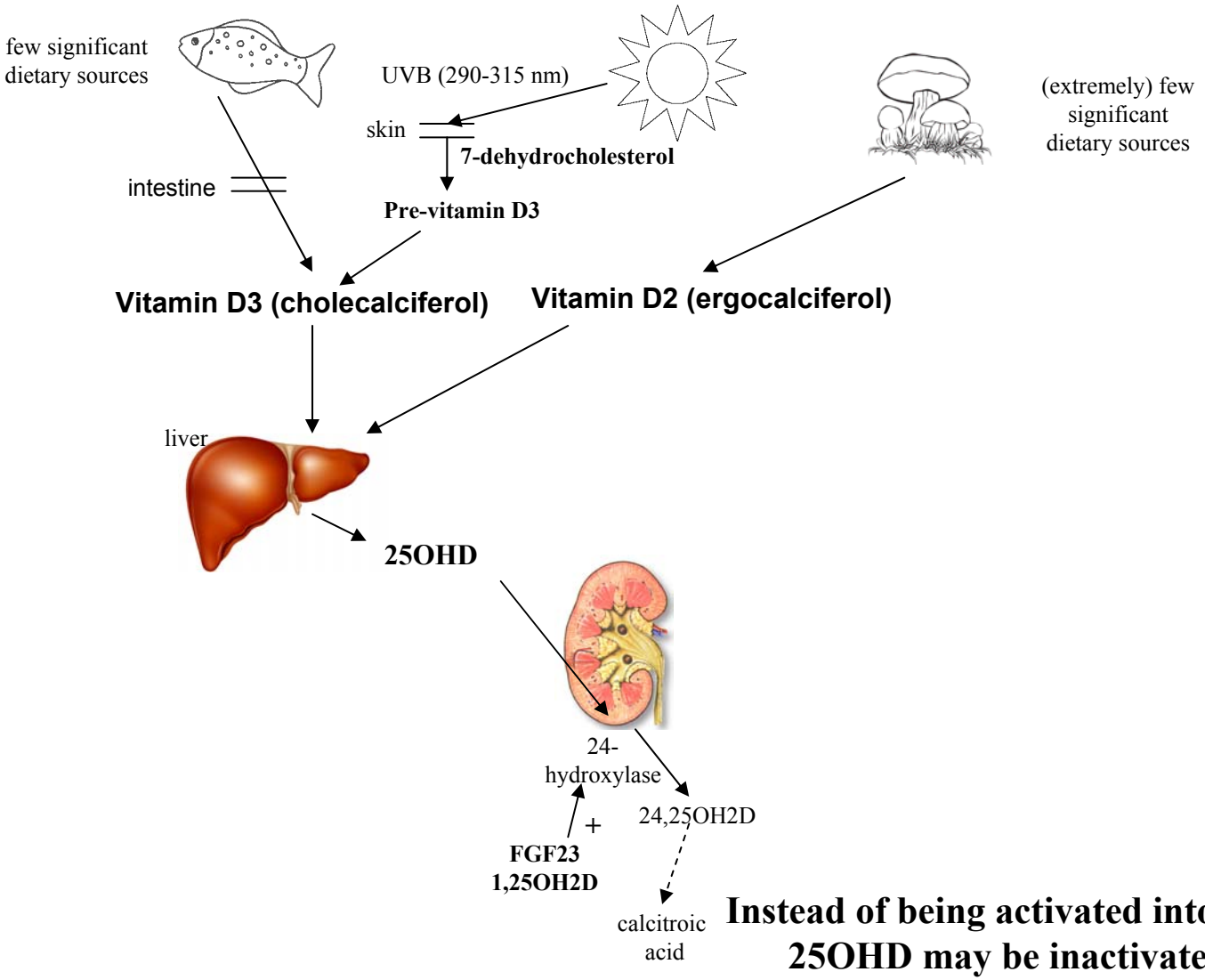
« nutritional » vitamin D
Is it relevant in CKD?

Jean-Claude Souberbielle
Hôpital Necker-Enfants malades



Vitamin D is not a vitamin *stricto sensu* (main source is not from diet).
To become fully active, vitamin D must transformed in the liver to form 25 OH vitamin D, and again in the kidney to form 1,25 dihydroxy vitamin D (also called calcitriol).
Calcitriol is released into the bloodstream and binds to its receptor, the VDR, in target tissues distant from the kidney to exert genomic effects
Calcitriol can thus be considered as a true hormone
25OHD serum level represents vitamin D status (*consensus*)



Instead of being activated into calcitriol, 25OHD may be inactivated by a 24-hydroxylase enzyme.
Several recent reports have highlighted the importance of this inactivating pathway with the demonstration that mutations of CYP24A1 cause severe neonatal hypercalcemia

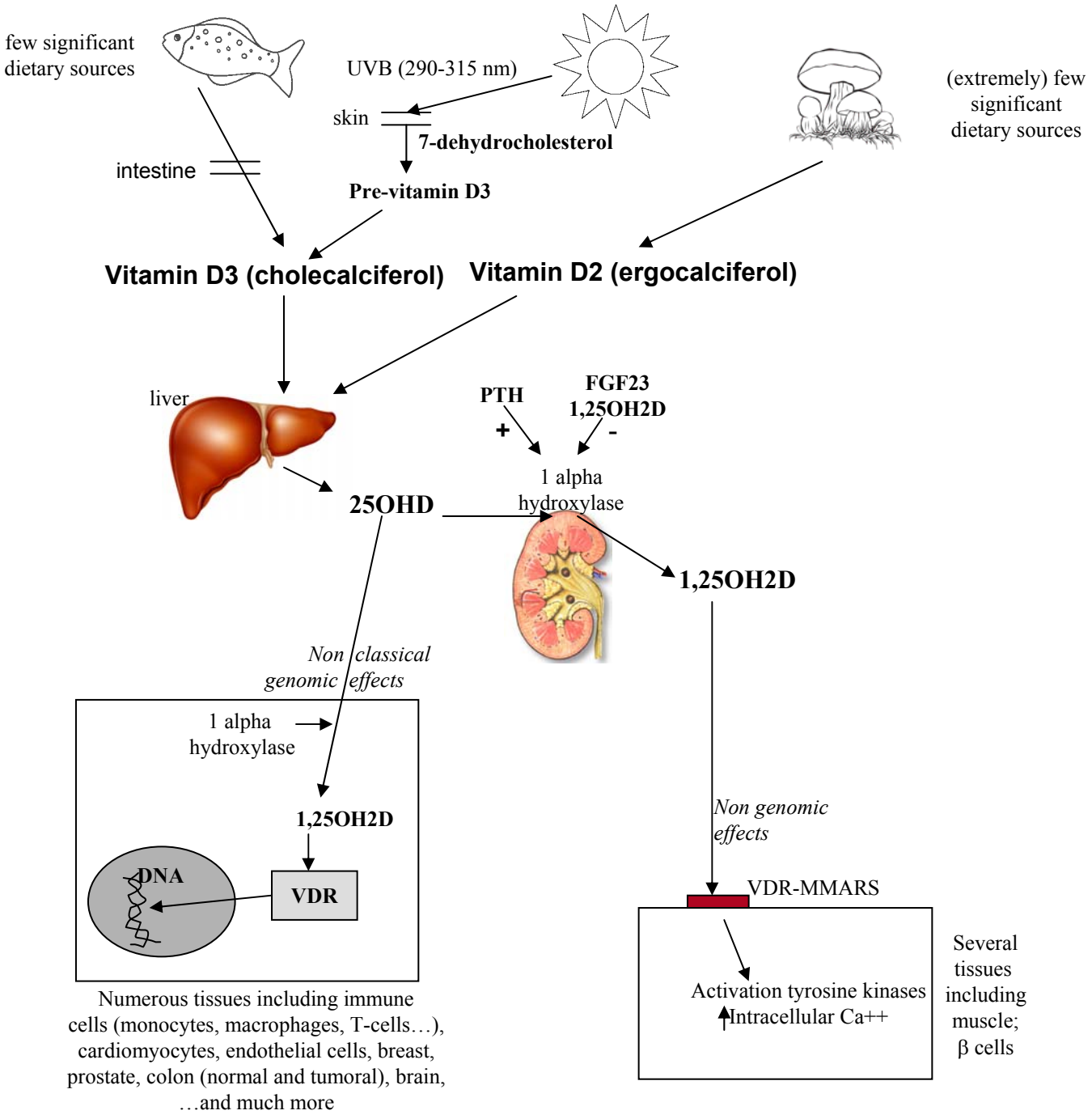
Association between treatment with calcitriol or analogs, and mortality in CKD

Teng M, et al. *N Engl J Med 2003; 349: 446-456.*
Shoji T, et al. *Nephrol Dial Transplant 2004; 19: 1791-84.*
Teng M, et al. *J Am Soc Nephrol 2005; 16:1115-1125.*
Kalantar-Zadeh K, et al.. *Kidney Int 2006; 70: 771-780.*
Tentori F, et al. *Kidney Int 2006; 70: 1858-1865.*
Shoben AB, et al.. *J Am Soc Nephrol 2008; 19: 1613-1619.*
Kovesdy CP, et al. *Kidney Int 2008; 73: 1355-1363.*
Naves-Diaz M, et al. *Kidney Int 2008; 74: 1070-1078.*

« Suggestion » of the KDIGO

3.1.3 In patients with CKD stages 3-5D, we suggest that 25OHD levels might be measured, and repeating testing determined by baseline values and therapeutic intervention (2C).

We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).


few significant dietary sources
UVB (290-315 nm)
skin
7-dehydrocholesterol
intestine
Pre-vitamin D3
(extremely) few significant dietary sources
Vitamin D3 (cholecalciferol)
Vitamin D2 (ergocalciferol)
liver
PTH
+
FGF23
1,25OH2D
-
1 alpha hydroxylase
25OHD
1,25OH2D
Non classical genomic effects
1 alpha hydroxylase
1,25OH2D
DNA
VDR
Numerous tissues including immune cells (monocytes, macrophages, T-cells…), cardiomyocytes, endothelial cells, breast, prostate, colon (normal and tumoral), brain, …and much more
Non genomic effects
VDR-MMARS
Activation tyrosine kinases
Intracellular Ca++
Several tissues including muscle; β cells

Is 25OHD able to bind VDR?

« classical » effects

-<u>stimulates absorption of calcium and phosphorus by the gut</u>

- direct effects on bone

-effects on kidney

-<u>control of PTH secretion</u>

Favours bone mineralisation

700-800UI /day (+calcium)

reduce RR of

« non vertebral » fractures

in the elderly

Importance of « genetic » : SNP of VDR, CYP27B1, CYP24, DBP…

« non classical » effects

Muscle

700-800UI /J (+calcium)

reduce RR of falls in the elderly

Immune System

-stimulation of « innate » immunity

-inhibition of « adaptative » immunity

(favours Th2 and TReg versus Th1, Th17)

Vasculature

-direct effects

-indirect effects

(insulin, inflammation, calcifications, PTH, blood pressure…)

Cancers

Other

(cognition (?) ; renoprotection ; Preeclampsia;…all-cause mortality)

What is the « level of evidence »?

(Evidence-based Medicine)

- « ecologic » studies

- « observation » studies

(retrospective, prospective…)

Importance of statistic « adjustments » for confounders.

Observational nature prevents conclusion on causality !!

- « exprimental » studies

Animal models, cell culture…

May explain mechanisms of action, but (often) use of supra-physiologic doses (application of results to human being?)

- « intervention » studies (RCTs)

(main or secondary endpoints…)

Meta-analyses

“ The panel on calcium and related nutrients quickly reached consensus that serum 25OHD was the correct functional indicator of vitamin D status....
Hence, on this point at least, there is consensus(notably, that was not the case as recently as 5-10 years ago).”

Heaney R. *Editorial*
Vitamin D : how much do we need, and how much is too much.
Osteoporosis Int (2000) 11 : 553-555

“It may be more appropriate to use health-based than population-based
reference values for serum 25OHD i.e., reference limits based on avoidance
of adverse health outcomes for the skeleton”

P Lips Endocrine Reviews
(2001) 22 : 477-501.

How can we do that?

-25OHD level above which there is no clinical/radiological/biological signs of rickets/osteomalacia (15-25 nmoL/L ?)

-25OHD level above which there is no histological signs of mineralization defect (75 nmol/L Priemel et al JBMR 2010; 25: 305-12 - von Domarus et al Clin Orthop Relat Res 2011 - see also Need et al JBMR 2007; 22: 757-61)

-relationship between PTH/25OHD :
25OHD threshold below which PTH may increase (many studies 40 to 110nmol/L)

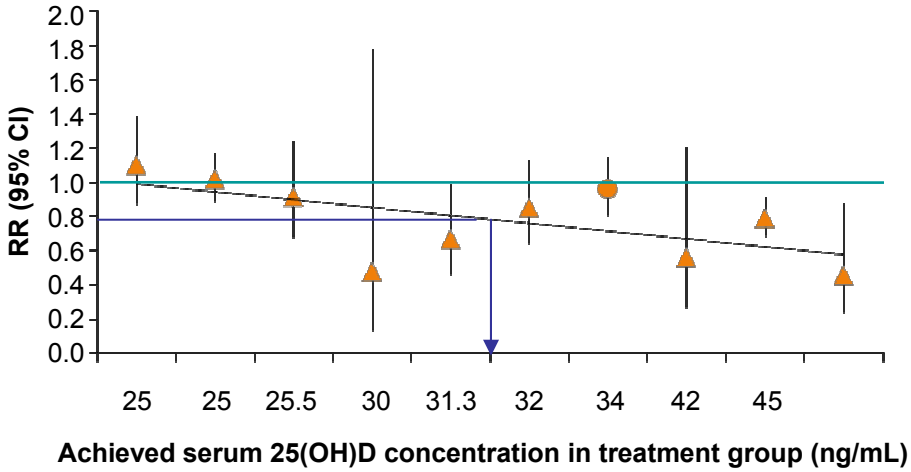
-basal 25OHD levels below which PTH decreases after vitamin D supplementation
Malabanan Lancet 1998 (50 nmol/L); Okazaki JBMM 2011 (70 nmol/L)

-Minimal 25OHD concentration for optimal effect of bisphosphonates
82 nmol/L : Carmel ES et al Osteoporos Int online 12 Jan 2012

-intestinal absorption of calcium = f([25OHD]
80 nmol/L Heaney J Am Coll Nutr 2003 (*but…controversial*)

Variation of fracture prevention by dose and achieved 25(OH)D

- Pooled relative risk (RR):
  0.86 (95% CI, 0.77-0.96) for non-vertebral fractures



Anti-fracture efficacy (non-vertebral) increased significantly with higher received dose and higher achieved 25(OH)D level

Bischoff-Ferrari HA. Arch Intern Med 2009;169:551-61.

For most experts

25OHD <20 ng/mL(that is <50 nmol/L)

= vitamin D deficiency

25OHD 20-<30 ng/mL (that is 50-<75 nmol/L)

= vitamin D insufficiency

These thresholds are based on bone, phospho-calcic and muscle (falls) effects of vitamin D

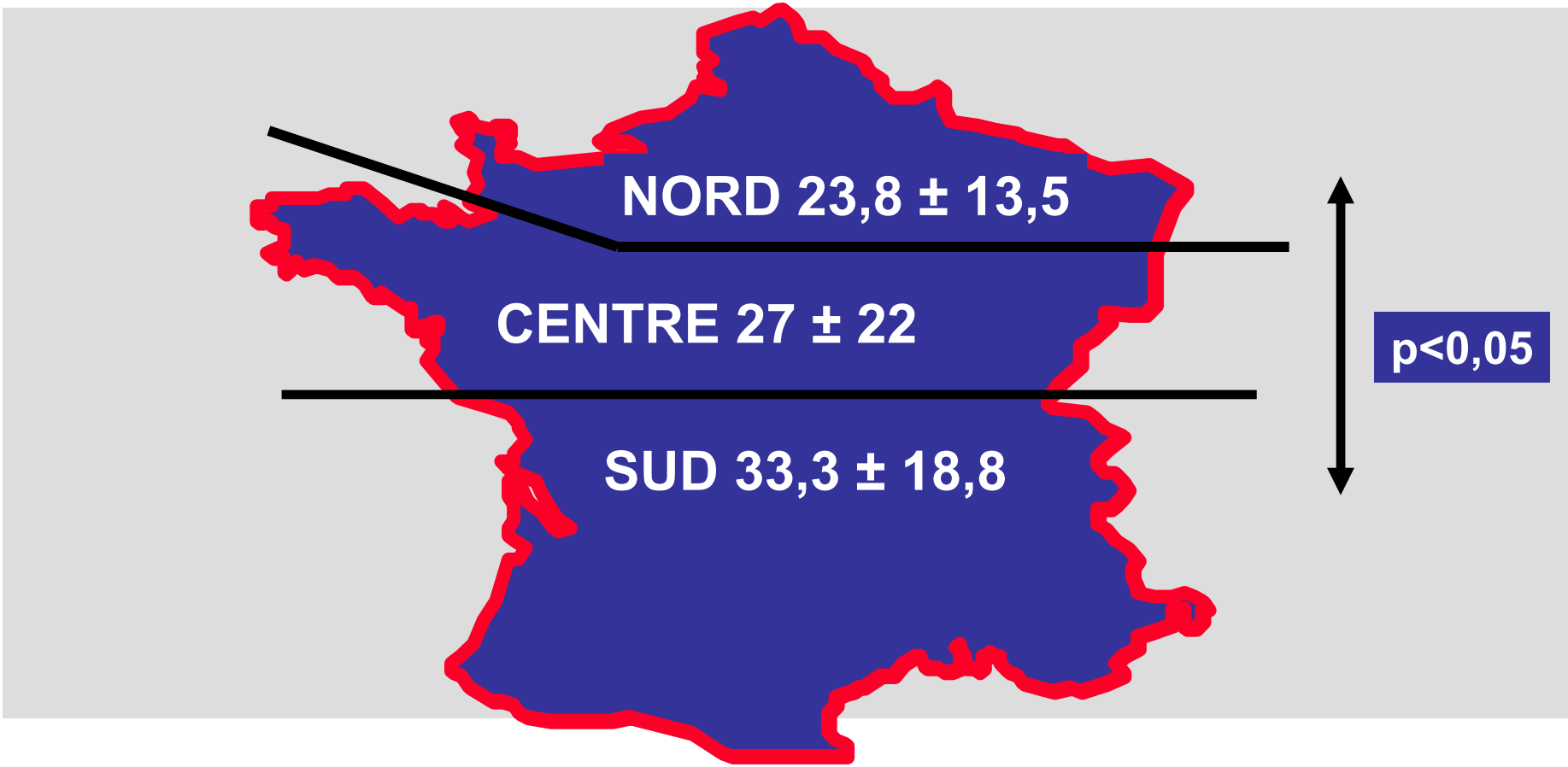
Holick M et al

J Clin Endocrinol Metab 2011

This is not an absolute consensus : some (IOM) consider that 20 ng/mL (50 nmol/L) is largely sufficient while others argue for 40 ng/mL (100 nmol/L) at least .

Whatever the threshold (20, 30 or 40 ng/mL), vitamin D insufficiency is very frequent

Vitamin D insufficiency
Osteoporotic women 65 yrs old



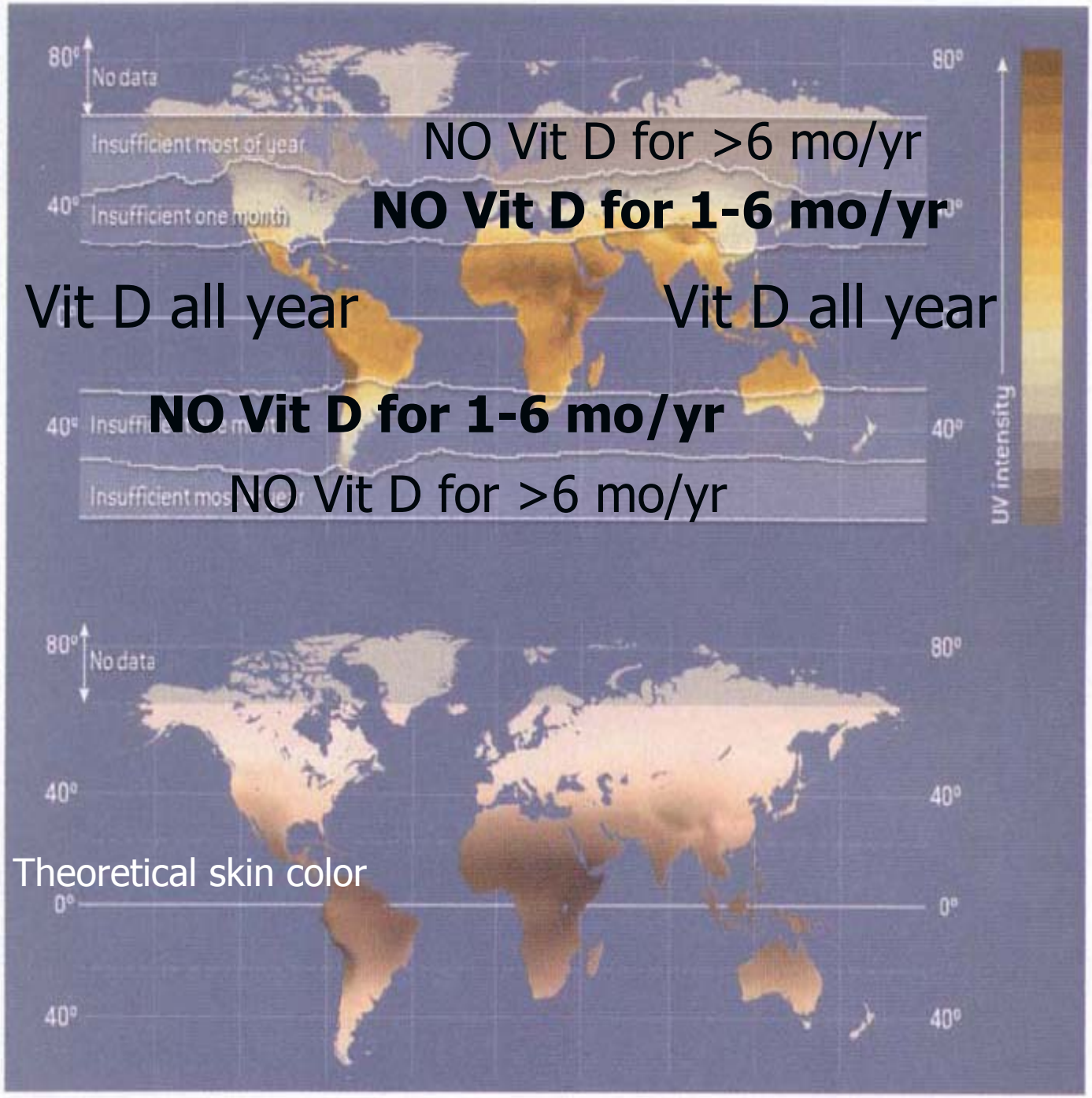
25 (OH)D : nmol/L

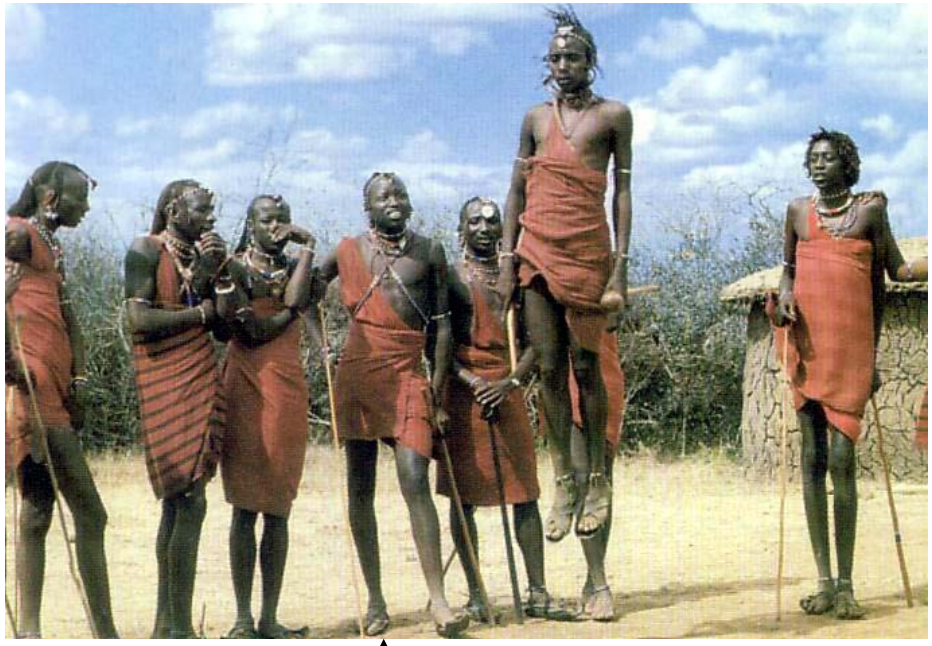
Fardellone P Am J Clin Nutr 1998

Number of Months that UVB from sunshine cannot produce vitamin D_3 in skin

Adapt according to :
-age
-skin colour and/or use of sunscreen
- altitude
-covering clothes
…

sequestration of vitamin D in fat





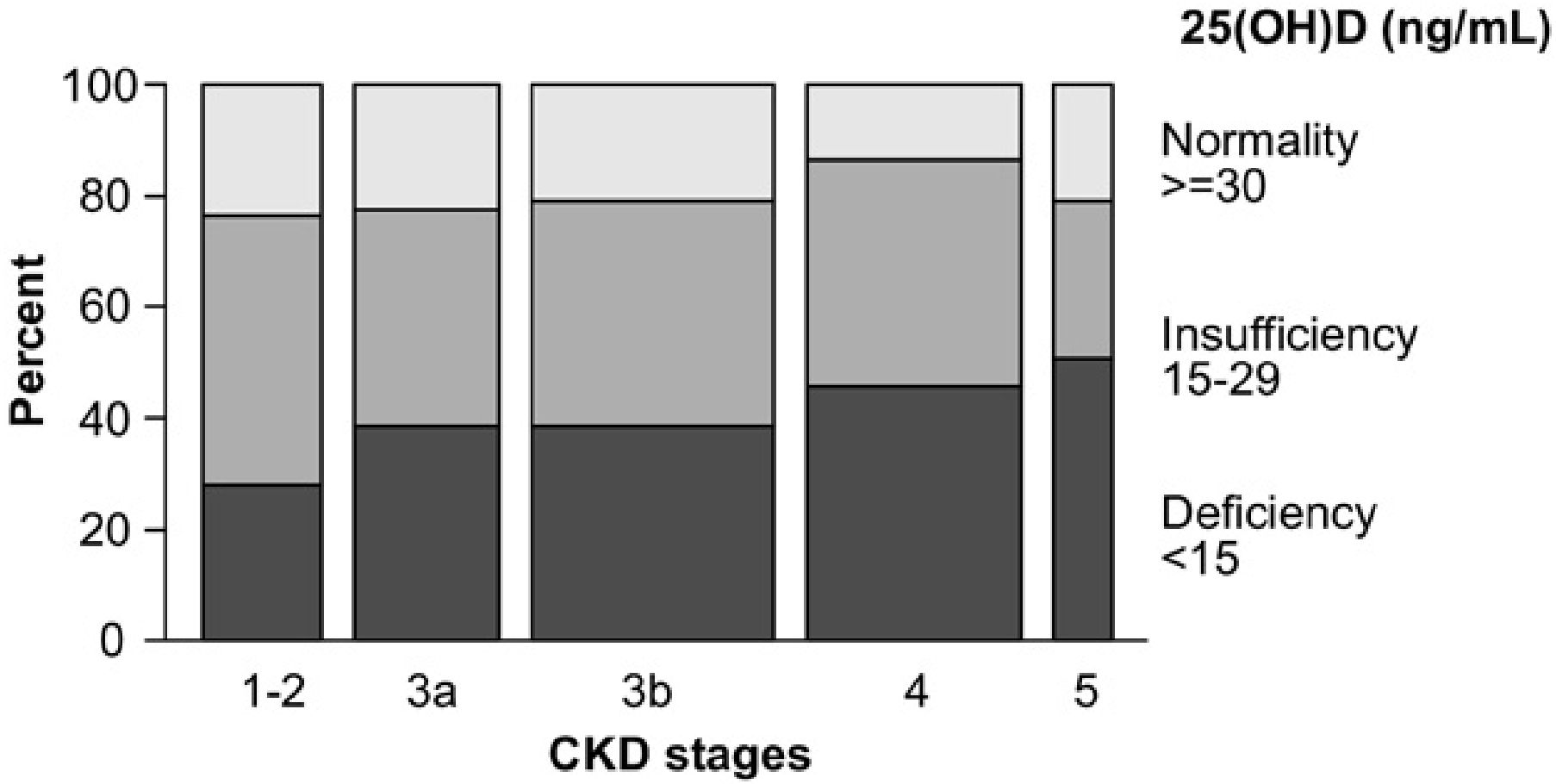
Luxwolda M et al
Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/L.
British Journal of Nutrition 2012; in press

Maasai
Mean 25OHD : 119 nmol/L (range 58-167)

Skin type VI; moderate degree of clothing; spend the major part of the day outdoor, but avoid direct exposure to sunlight when possible.

Hadzabe
Mean 25OHD : 109 nmol/L (range 71-171)

Could these definitions/thresholds be applied to patients with CKD ?



Ureña-Torres P et al. Association of kidney function, vitamin D deficiency, and circulating markers of mineral and bone disorders in CKD
Am J Kidney Dis 2011
Cohorte Nephrotest : 932 patients analysés

%	All	25(OH)D (ng/mL) ≥ 30	15-29	<15	p-value
Hypocalcemia (ionized calcium <2.2 mEq/L)	3.0	1.1	1.9	5.1	0.004
High BAP (>25 ng/mL)	6.3	3.6	5.3	8.7	0.02
Hyperphosphatemia (>4.3 mg/dL)	8.5	7.1	7.2	10.4	0.1
High CTX (>1000 pg/mL)	22.0	17.0	19.1	28.0	0.01
Low $1,25(OH)_2D$ (<16.7 pg/ml)	25.1	14.3	22.4	33.2	<0.001
Hyperparathyroidism (PTH≥60 pg/mL)	53.9	36.4	47.5	68.7	<0.001

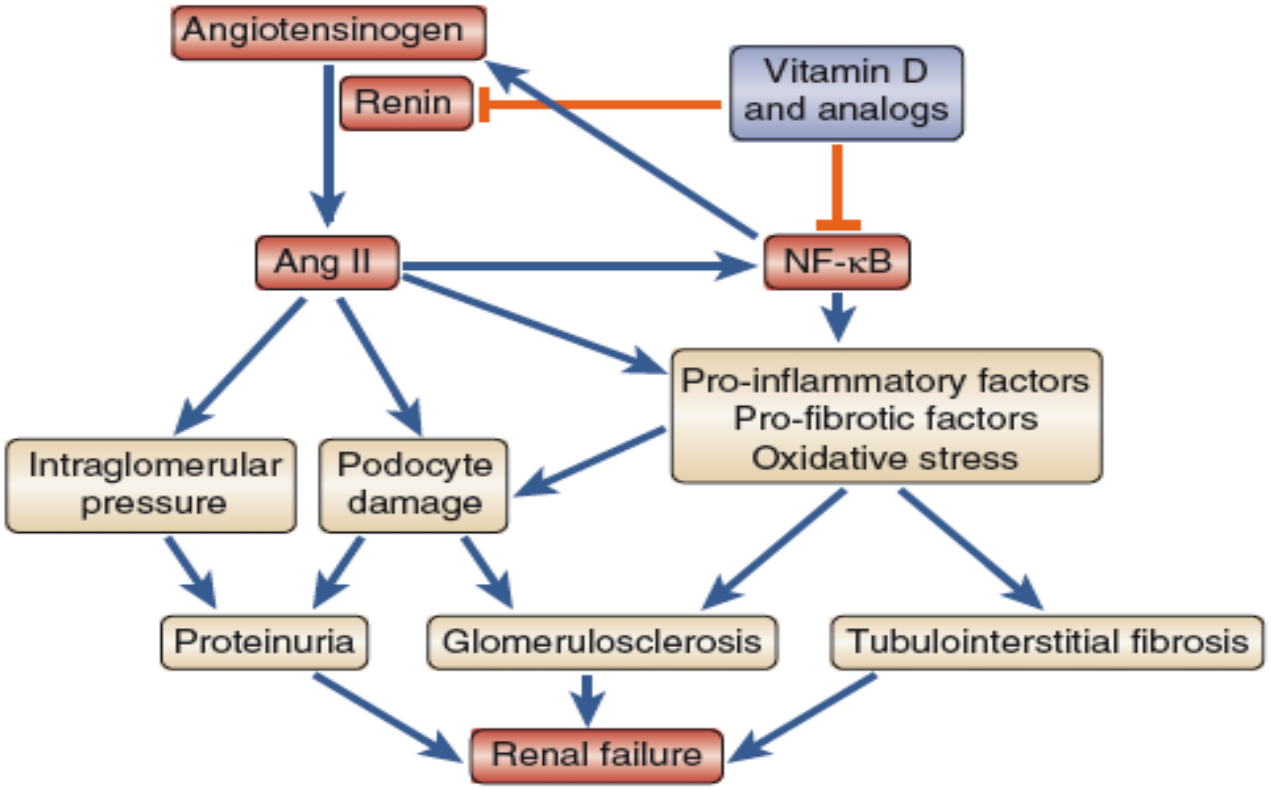
% de patients ayant une anomalie des paramètres « phospho-calciques/osseux »
en fonction du statut vitaminique D

Ureña-Torres P et al. Association of kidney function, vitamin D deficiency, and circulating markers of mineral and bone disorders in CKD
Am J Kidney Dis 2011

1-hydroxylated vitamin D and **renoprotection**

- **Experimental data** *(Review by Li YC, Renoprotective effects of vitamin D analogs, KI, 2010)*

- Inhibition of RA system, NF-Kappa B and TGF-β by calcitriol
- Animal models of CKD : Calcitriol (and analogs) decreases tubulo-interstitial fibrosis and glomerular sclérosis, proteinuria, production of extra cellular matrix
- These effects seem independant of PTH and partially dependant of RA inhibition



Kim MJ et al

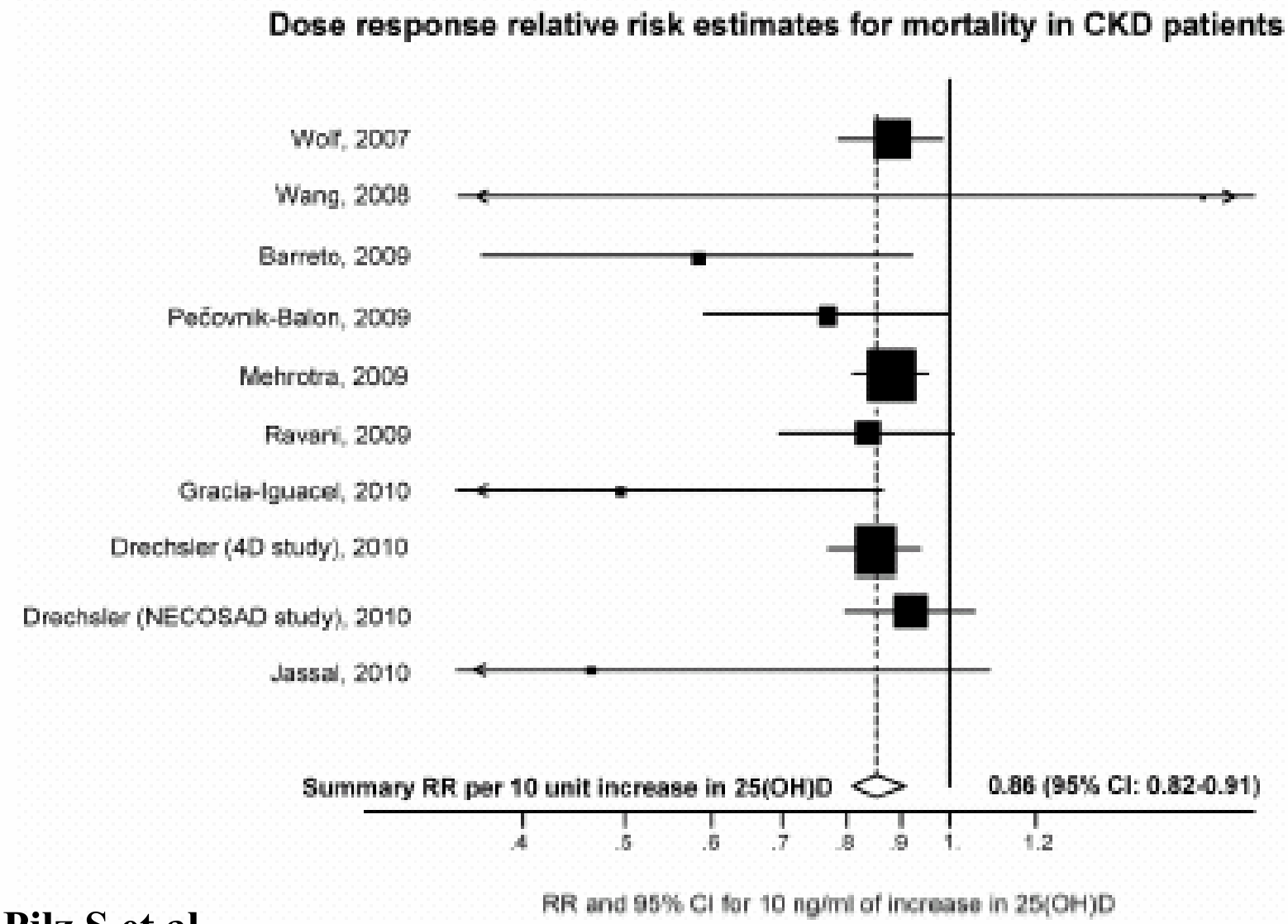
Oral cholecalciferol decreases albuminuria and urinary TGFβ1 in patients with type 2 diabetic nephropathy on established renin-angiotensin-aldosterone system inhibition.

Kidney International 2011; 80: 851-860.

	Baseline	Month 2	Month 4
25OHD (ng/mL)	15.6 +/- 7.0	41.2 +/-11.4*	39.7 +/-12.8*
1,25OH2D (pg/mL)	24.2 +/- 14.4	51.0 +/- 16.0*	42.8 +/- 23.8*
uAlb/Creat (mg/mmol)	16.4 (95%CI : 9.7-27.4)	12.2 (95%CI : 7.1-20.7)*	12.0 (95%CI : 7.0-20.8)*
uTGF β1/Creat (ng/mmol)	26.5 (95%CI : 20.3-34.4)	15.5 (95%CI : 10.7-22.4)*	9.5 (95%CI : 6.0-14.8)*

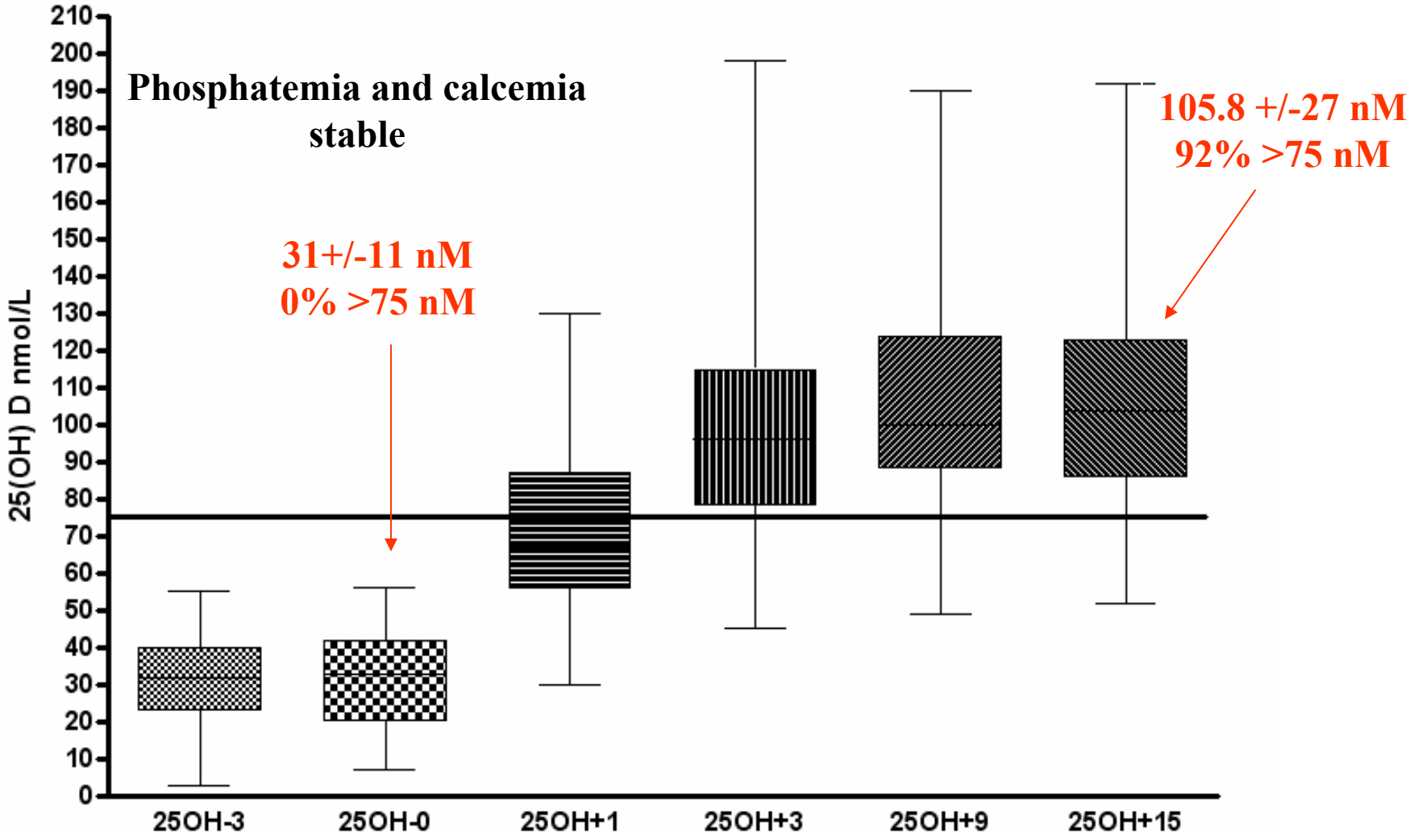
de Boer IH et al.
Serum 25-hydroxyvitamin D and change in estimated glomerular filtration rate. Clin J Am Soc Nephrol 2011; 6: 2141-2149

« 1705 older adults with predominantly normal baseline kidney function participating in the Cardiovascular Health Study… Each 10 ng/mL lower 25OHD was associated with 25% greater risk (CI : 5%-49%, p=0.01) of rapid GFR loss (>12 mL/mn/1.73 m² over 4 years), adjusting for potential confounders. Compared with 25OHD>30 ng/mL, 25OHD concentrations<15 ng/mL were associated with 68% (95%CI :1-177%) greater adjusted risk of rapid GFR loss… »



Pilz S et al
Am J Kidney Dis
2011; 58: 374-382

Jean G et al. Nephrol Dial transplant 2009; 24: 3799-3805



107 HD (66.4 +/-15 ans)
100 000 UI vitamin D3/month
during 15 months

	PTH	bAP	CTX	1,25D
M0:	294 ng/L	21ng/L	2.5µg/L	14 pM
M15:	190*	17.1*	2.07*	45 pM*

* : $p<0.05$

Matias JM et al. Cholecalciferol supplementation in hemodialysis patients : Effects on mineral metabolism, inflammation, and cardiac dimension parameters. Clin J Am Soc Nephrol 2010; 5: 905-911.

158 HD (62.8 +/-14.8 ans)

6 months:

50 000 UI D3/week if 25OHD<15 ng/mL

10 000 UI D3/week if 25OHD 16-30 ng/mL

2700 UI D3 fois/week if 25OHD>30 ng/mL

	before	end of study	P
25OHD (ng/mL)	22.3 +/-12.0	42.0+/-12.1	<0.001
Calcemia (mg/L)	86 +/- 8	84 +/- 7	0.014
Phosphatemia (mg/L)	47 +/- 13	45 +/- 13	0.011
PTH (pg/mL)	233	208	<0.001
Albumin (g/L)	39 +/- 5	42 +/- 4	<0.001
CRP (mg/L)	4	2	0.004
BNP (pg/mL)	338	296	0.008
LVMI (g/m²)	134 +/- 31	121 +/- 32	0.01
Hb (g/dL)	12.1 +/- 1.2	11.9 +/- 1.4	NS

significant decrease of Paricalcitol (p<0.001) EPO (p=0.013) dosages and of the % of patients receiving Paricalcitol ((p<0.001) and Sevelamer (p<0.001)

Vitamin D Supplementation in Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Observational Studies and Randomized Controlled Trials

Praveen Kandula, Mirela Dobre,†‡ Jesse D. Schold,§‖ Martin J. Schreiber, Jr.,§ Rajnish Mehrotra,¶** and Sankar D. Navaneethan§*

Conclusions Available evidence from low-to-moderate quality observational studies and fewer RCTs suggests that vitamin D supplementation improves biochemical endpoints. However, whether such improvements translate into clinically significant outcomes is yet to be determined.

Clin J Am Soc Nephrol 6: 50–62, 2011. doi: 10.2215/CJN.03940510

« Suggestion » of the KDIGO

3.1.3 In patients with CKD stages 3-5D, we suggest that 25OHD levels might be measured, and repeating testing determined by baseline values and therapeutic intervention (2C).

We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).

Thank you for attention