CKD-MBD: Is the Term Still Justified?

Tilman B. Drüeke

Unité 1088 de l'Inserm

UFR de Médecine et de Pharmacie

Jules Verne University of Picardie

Amiens, France

Potential conflicts of interest

Research support: Baxter, Shire

Speaker: Abbott, Amgen, Chugai, FMC, Genzyme, Kirin

Consulting : Abbott, Amgen, FMC, Genzyme, Theraclion

Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO)

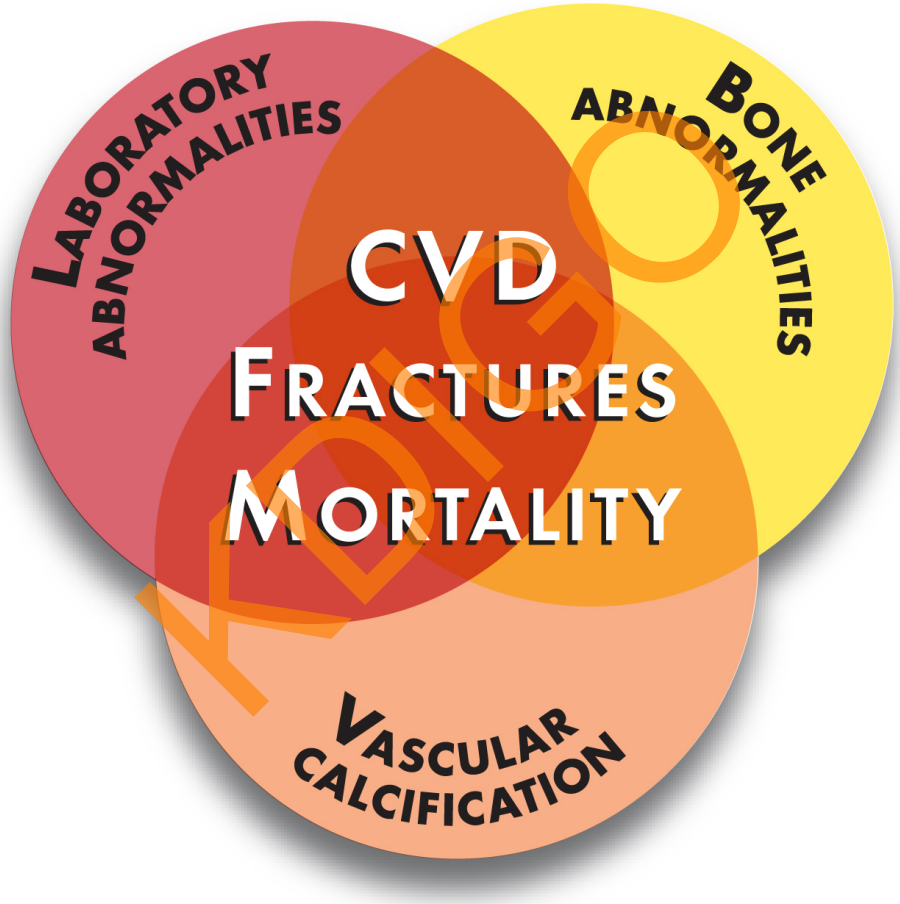
S Moe[1], T Drüeke[2], J Cunningham[3], W Goodman[4], K Martin[5], K Olgaard[6], S Ott[7], S Sprague[8], N Lameire[9] and G Eknoyan[10]

assessment of patients with CKD. It is recommended that (1) the term *renal osteodystrophy* be used exclusively to define alterations in bone morphology associated with CKD, which can be further assessed by histomorphometry, and the results reported based on a unified classification system that includes parameters of turnover, mineralization, and volume, and (2) the term CKD-Mineral and Bone Disorder (CKD-MBD) be used to describe a broader clinical syndrome that develops as a systemic disorder of mineral and bone metabolism due to CKD, which is manifested by abnormalities in bone and mineral metabolism and/or extra-skeletal calcification. The international adoption of these recommendations will greatly enhance communication, facilitate clinical decision-making, and promote the evolution of evidence-based clinical practice guidelines worldwide.

CKD-Mineral and Bone Disorder (CKD-MBD) – Definition –

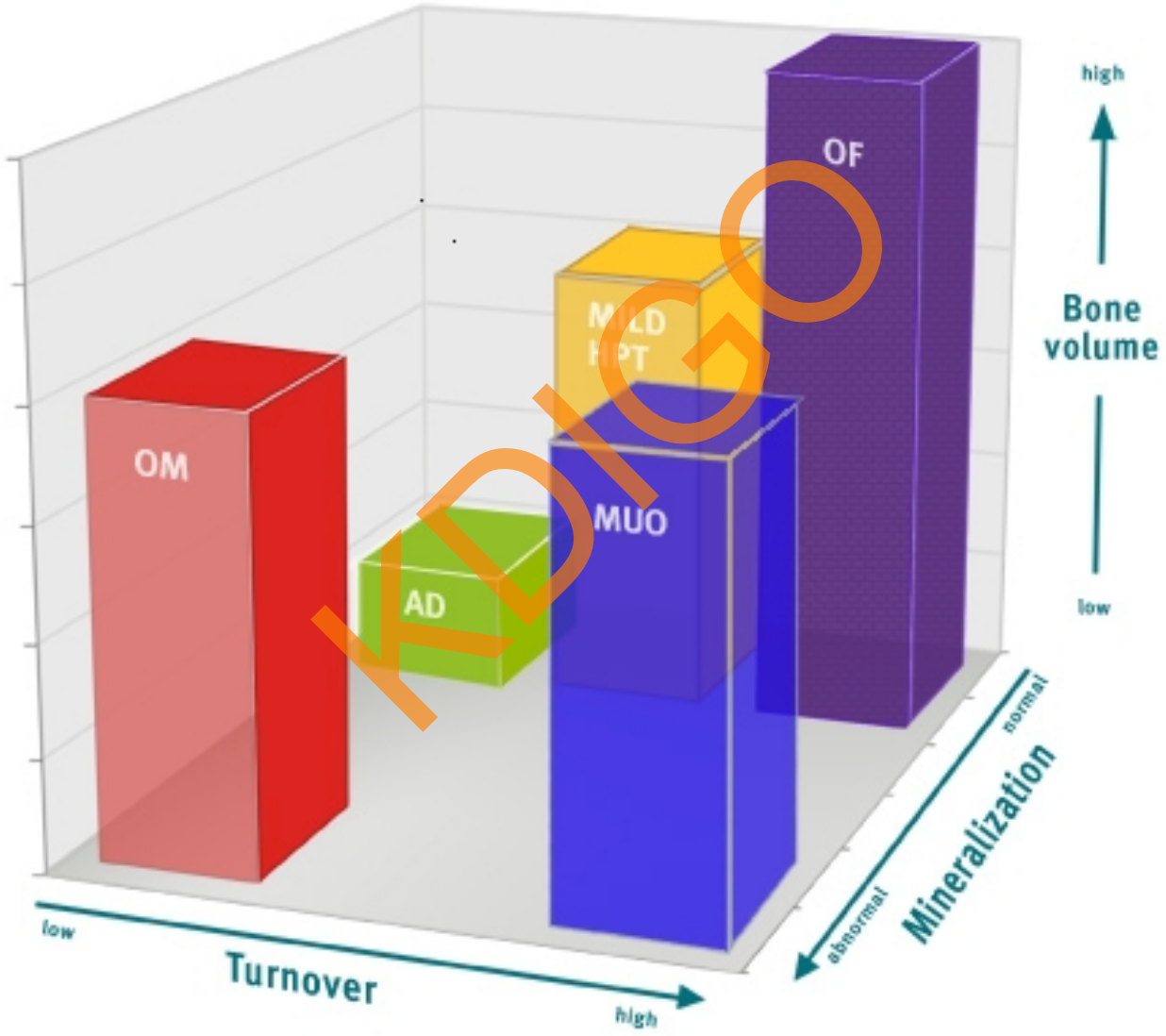
- **CKD-MBD is a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:**
  - Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
  - Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
  - Vascular or other soft tissue calcification

Chronic Kidney Disease–Mineral and Bone Disorder



CKD-MBD

“Renal Osteodystrophy” – term to be reserved for abnormalities in bone structure



*Moe S et al, KI 2006;*69:1945-53

The term CKD-MBD still justified ?
On which basis ?

- Numerical criteria ?
- Pathophysiology – new developments ?
- Treatment & prevention – new data ?

The term CKD-MBD still justified ?
On which basis ?

- **Numerical criteria**
  - usage in clinical/basic science publications
  - introduction into clinical practice

Published reports using the term 'CKD-MBD' since its creation in 2006 *(PubMed)*

- 245 publications *(as of 14 October 2013)*
  - *5 in 2006*
  - *15 in 2007*
  - *10 in 2008*
  - *42 in 2009*
  - *44 in 2010*
  - *39 in 2011*
  - *42 in 2012*
  - *46 in 2013*

Who were the first to use the term 'CKD-MBD' since its creation in 2006 *(PubMed)* ?

- The first 5 all from Japan:
  - Honda H et al, Clin Calcium 2006
  - Fukagawa M & Kazama JJ, Pediatr Nephrol 2006
  - Hamada Y & Fukagawa M, Nihon Rinsho 2006
  - Fukagawa M et al, Clin Exp Nephrol. 2006
  - Fukagawa M et al, J Bone Miner Metab 2006

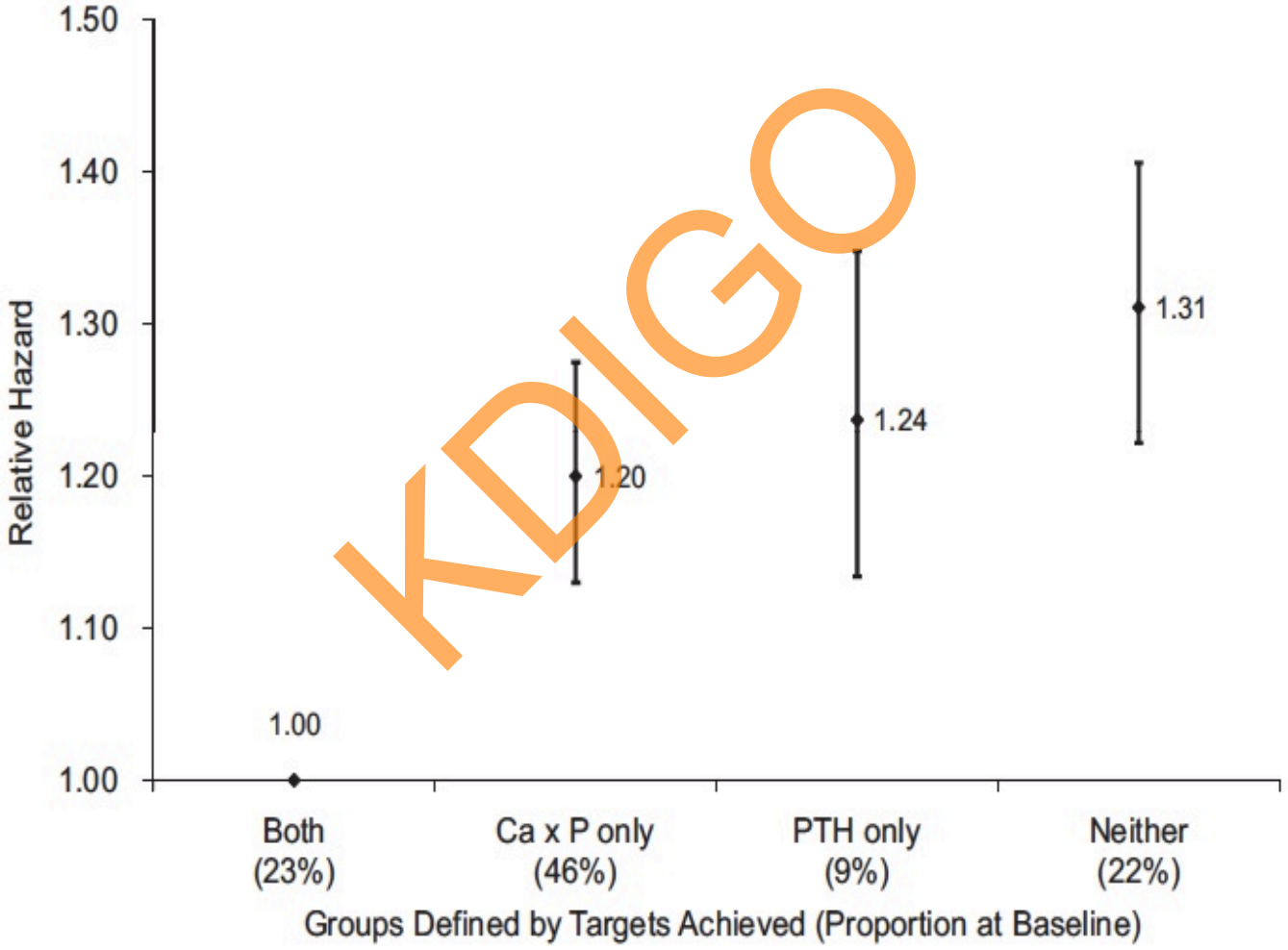
What happened to the term 'Renal Osteodystrophy' *(PubMed) ?*

- 3878 publications *(as of end 2012)*
  - *1 in 1942*
  - *7 in 1952*
  - *11 in 1962*
  - *61 in 1972*
  - *97 in 1982*
  - *75 in 1992*
  - *89 in 2002*
  - *74 in 2012*

How about the utility of 'CKD-MBD' targets and the use of the term in the clinic ?

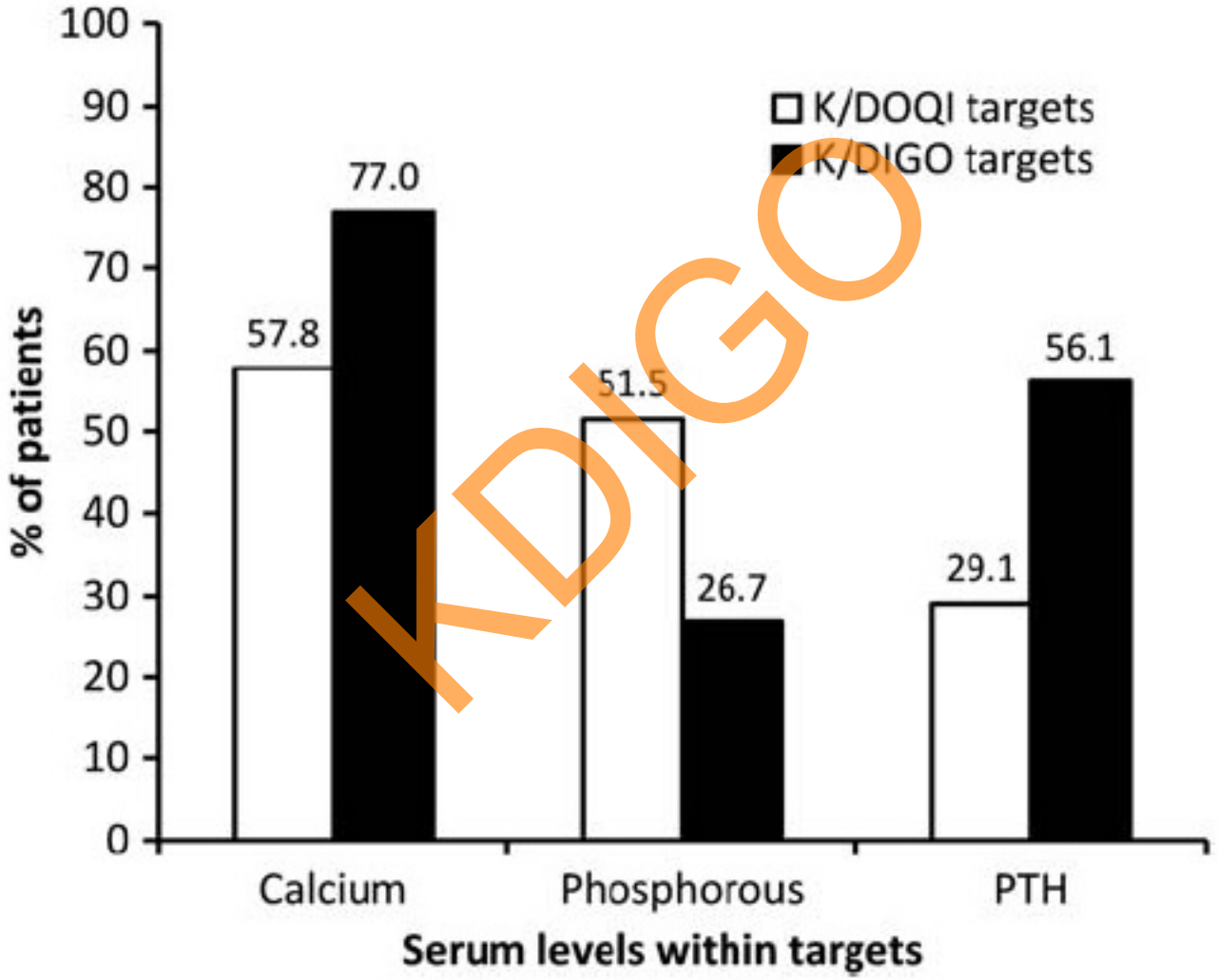
- Evaluation of CKD-MBD targets and outcomes
- Use in day-to-day practice

Relationship between KDOQI biochemical targets achieved and risk for death *(model 2)*



Danese MD et al, CJASN 2008;3:1423-9

Percentage of patients within K/DOQI and KDIGO targets in hemodialsyis patients in Europe *(COSMOS)*



Fernandez-Martin et al, NDT 2013;28:1022-35

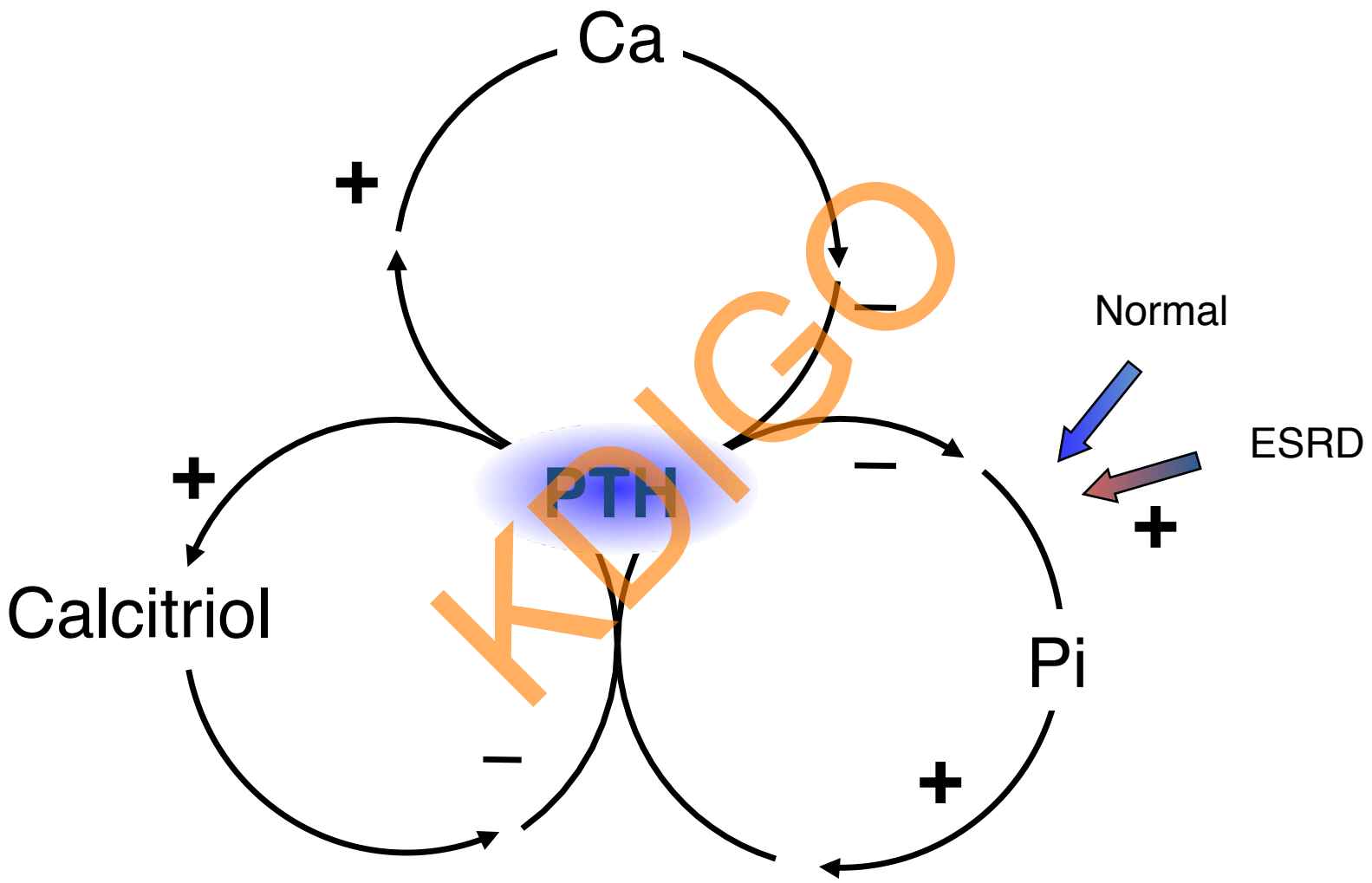
How about the use of the term 'CKD-MBD' in clinical practice ?

- Evaluation of CKD-MBD targets and outcomes
- **Use in day-to-day practice**
  - Translation into local languages
  - Example France : 'TMO-MRC' *(troubles du métabolisme minéral et osseux liés à la maladie rénale chronique)*

The term ‘CKD-MBD’ still justified ?
On which basis ?

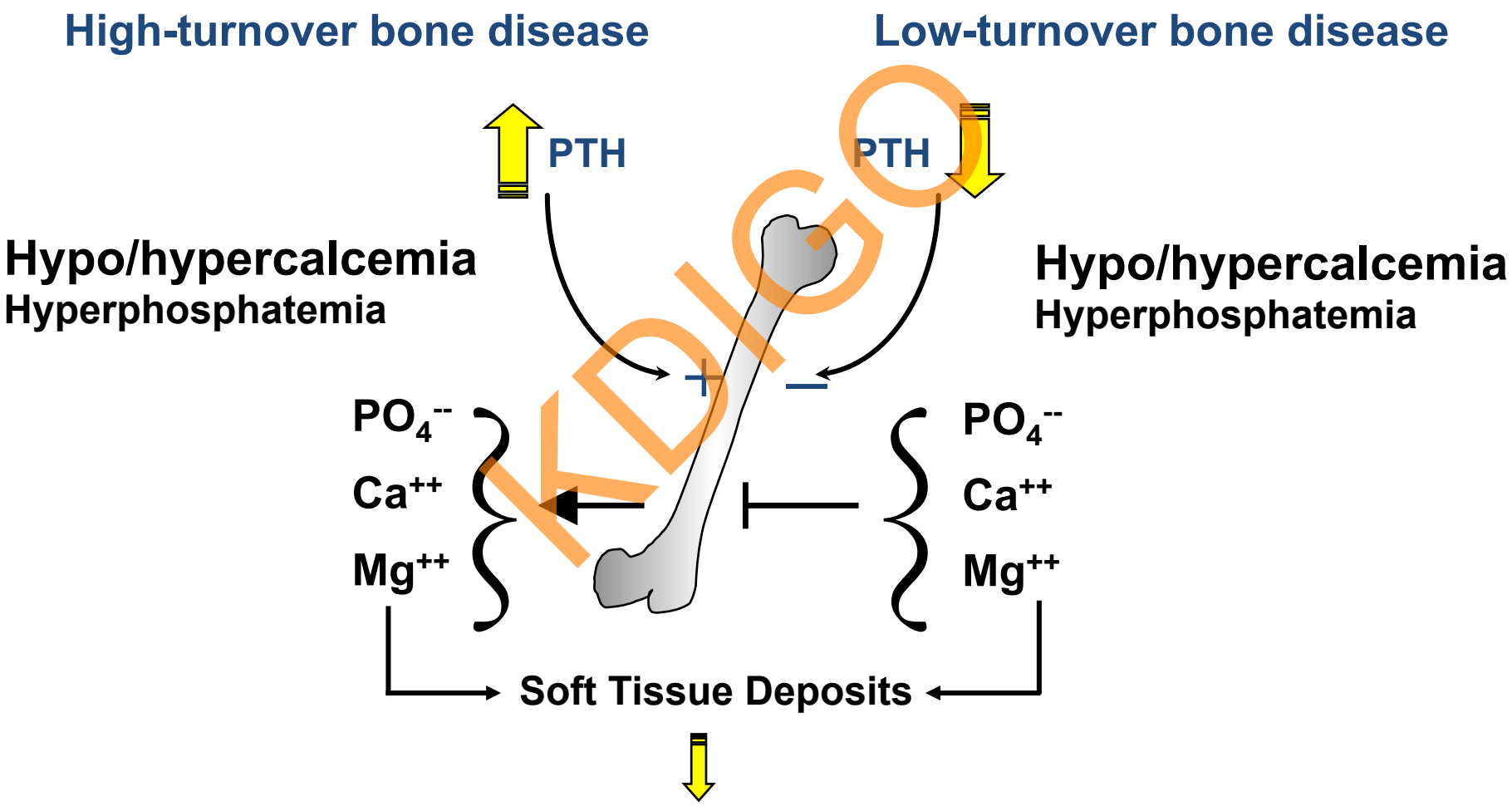
- Numerical criteria ?
- **Pathophysiology – new developments ?**
- Treatment & prevention – new data ?

Pathogenesis of 2° Hyperparathyroidism

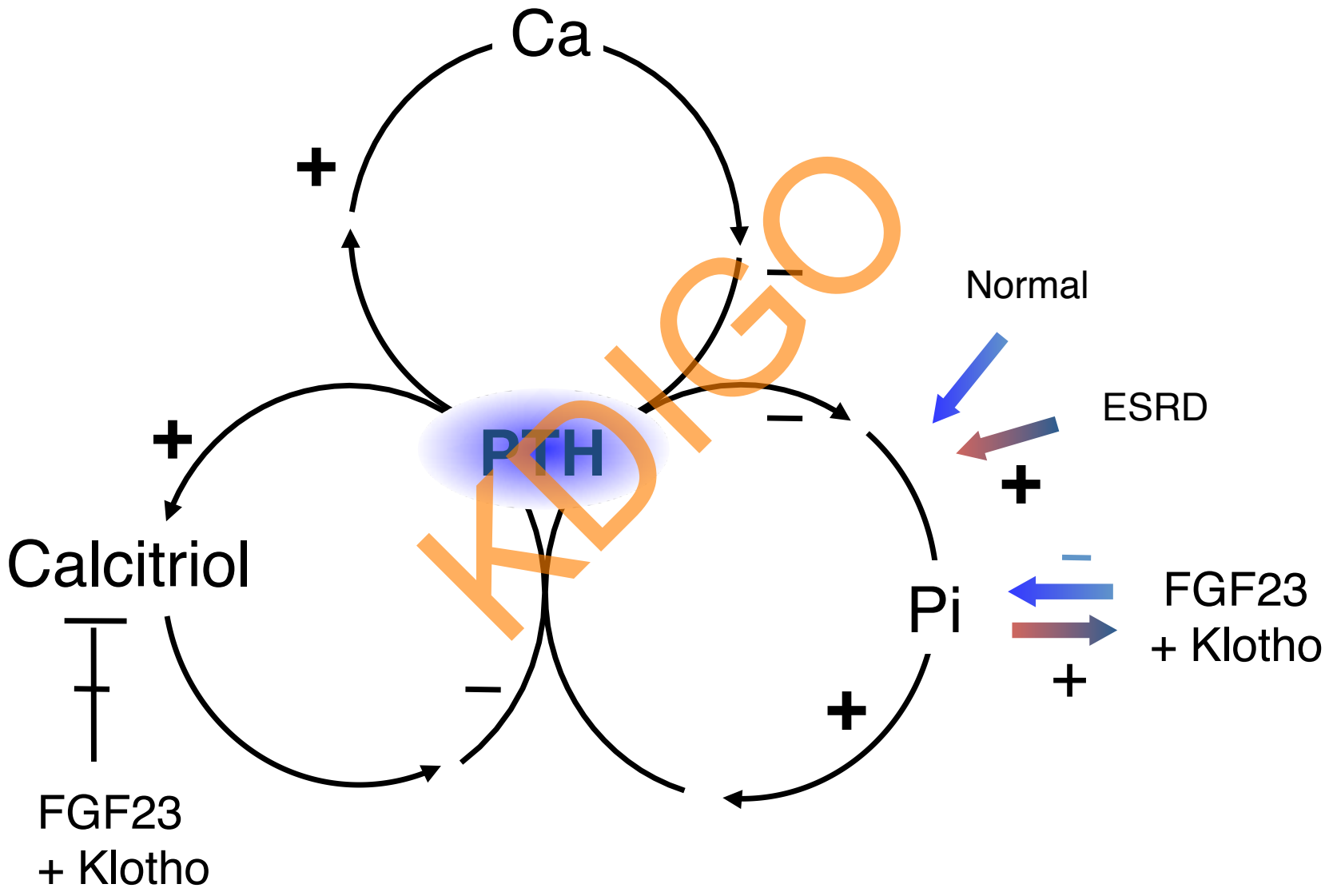


J. Cunningham 1999, modified

Importance of optimal control of mineral and bone disease (MBD) in patients with CKD

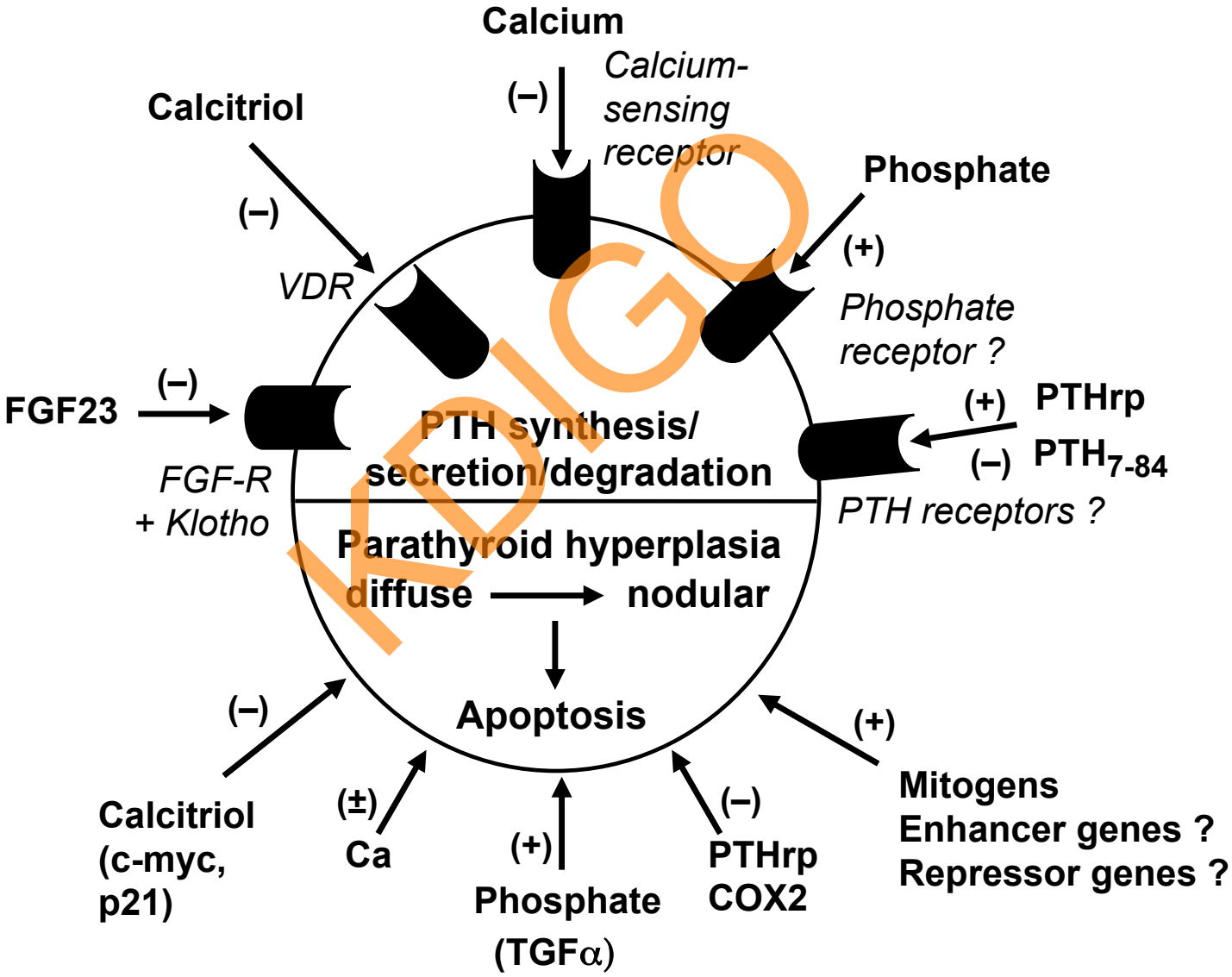


Pathogenesis of 2° Hyperparathyroidism

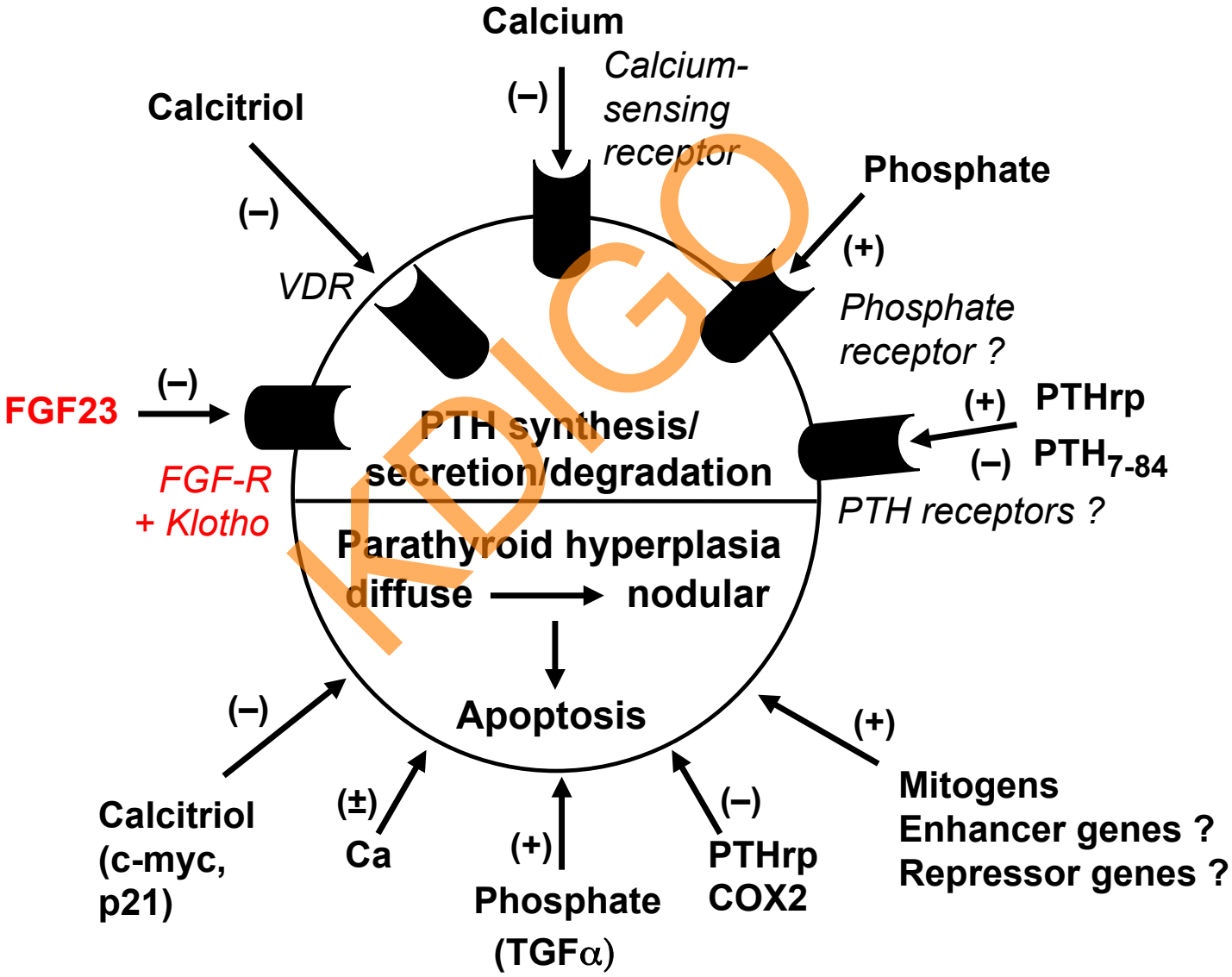


J. Cunningham 1999, modified

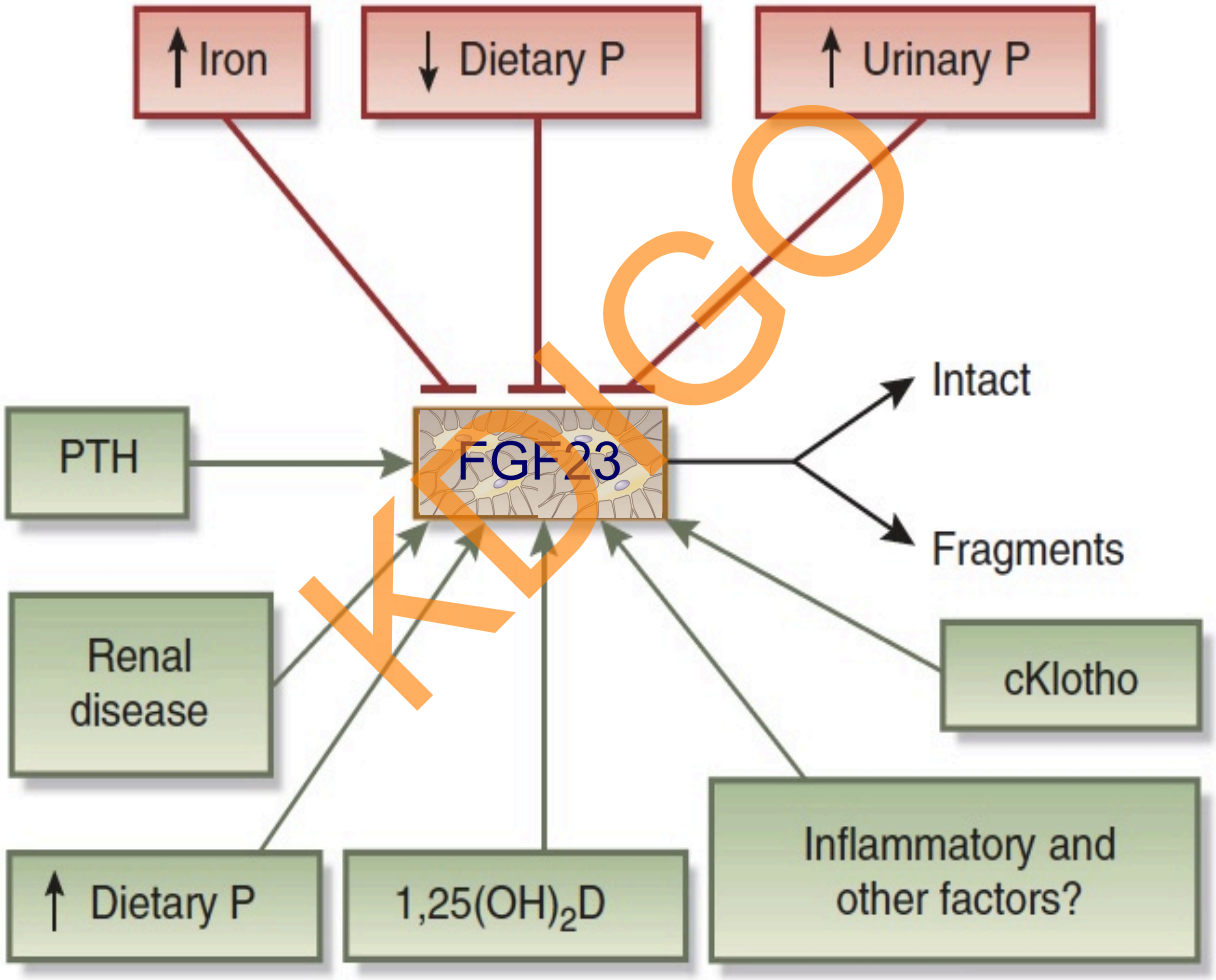
Pathogenesis of 2° Hyperparathyroidism



Pathogenesis of 2° Hyperparathyroidism

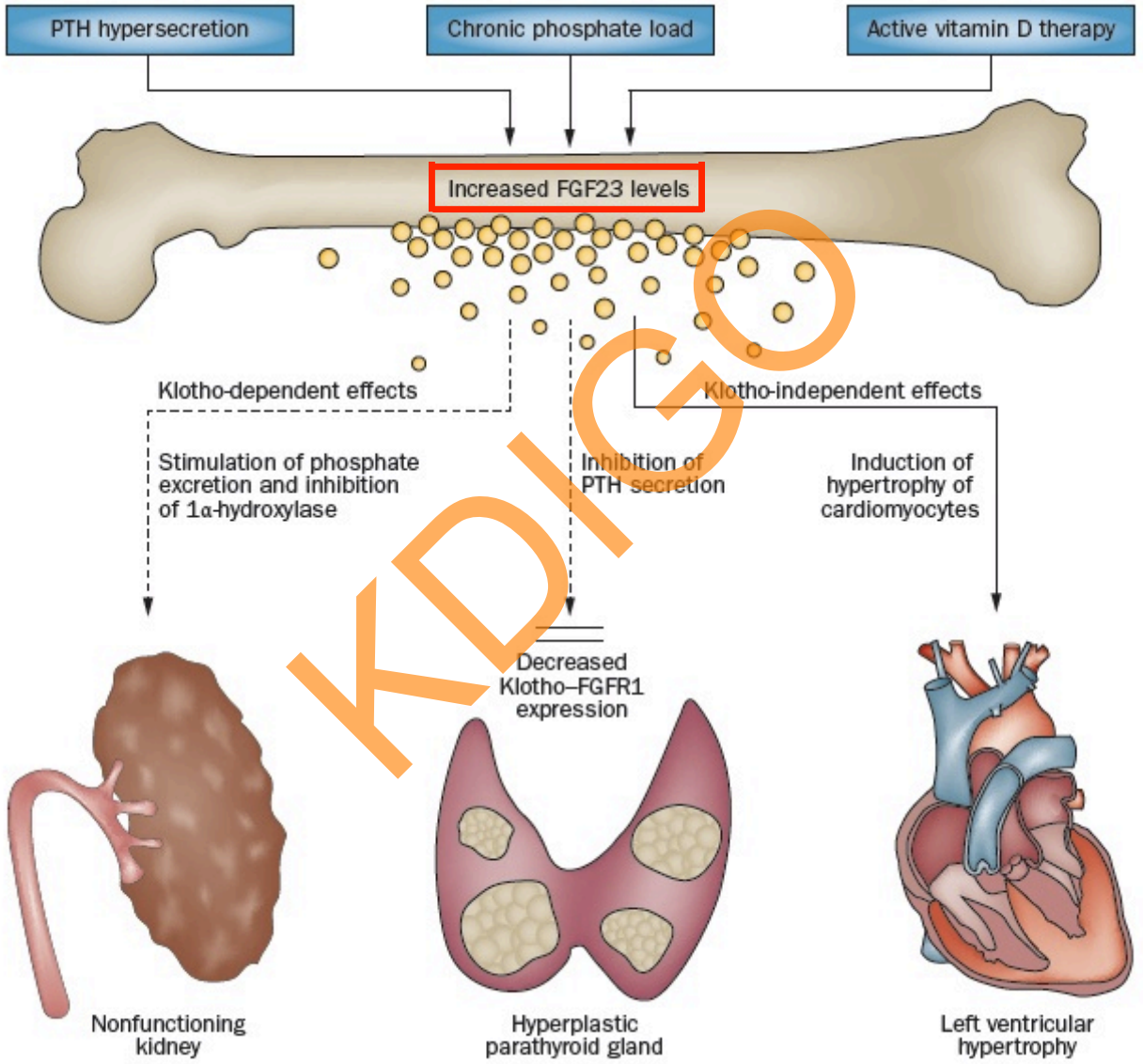


Regulation of FGF23 synthesis/secretion by osteocytes



Christov & Jüppner, Kidney Int 2013;84:639-41

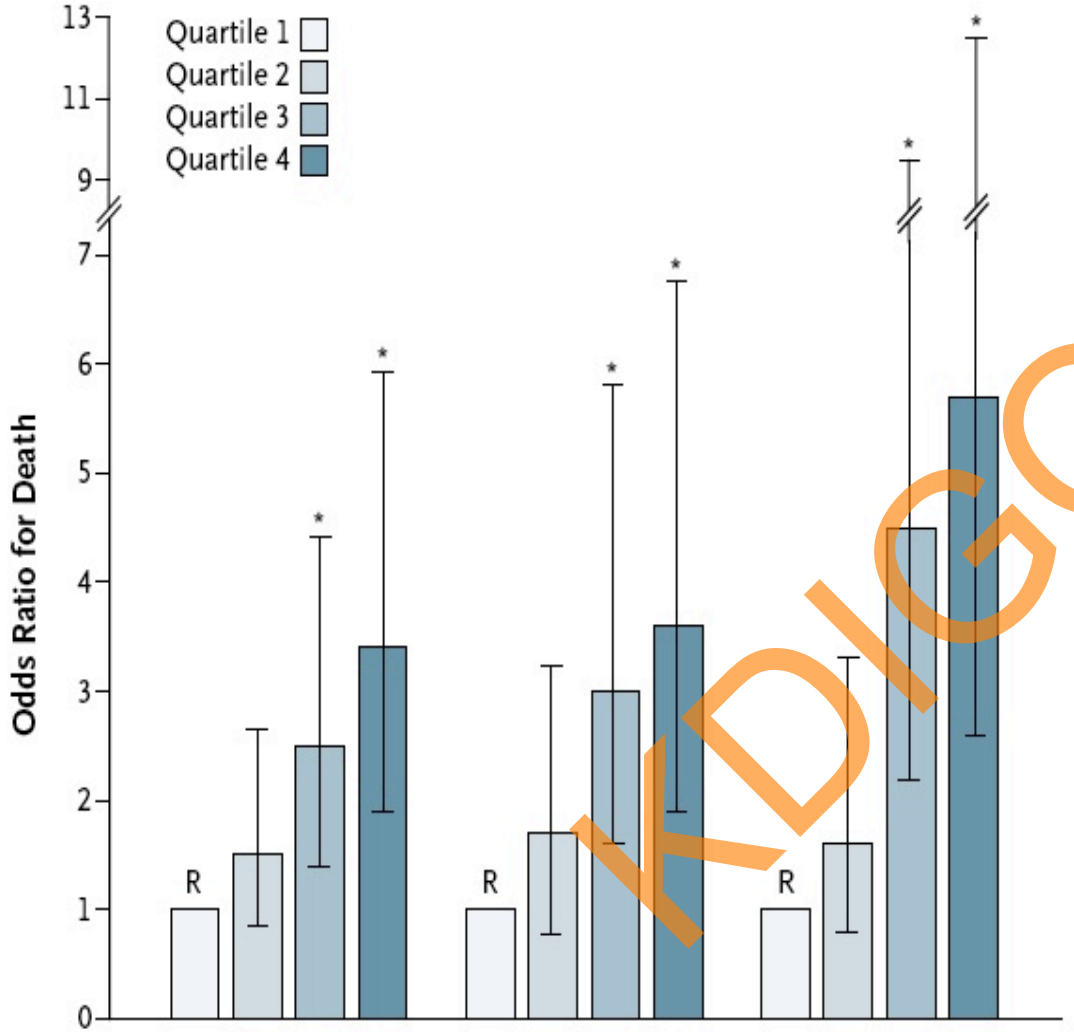
Effects of increased FGF23 secretion



Komaba and Fukagawa, Nat Rev Nephrol 2012;8:484-90

Independent association of high FGF23 with mortality in HD patients

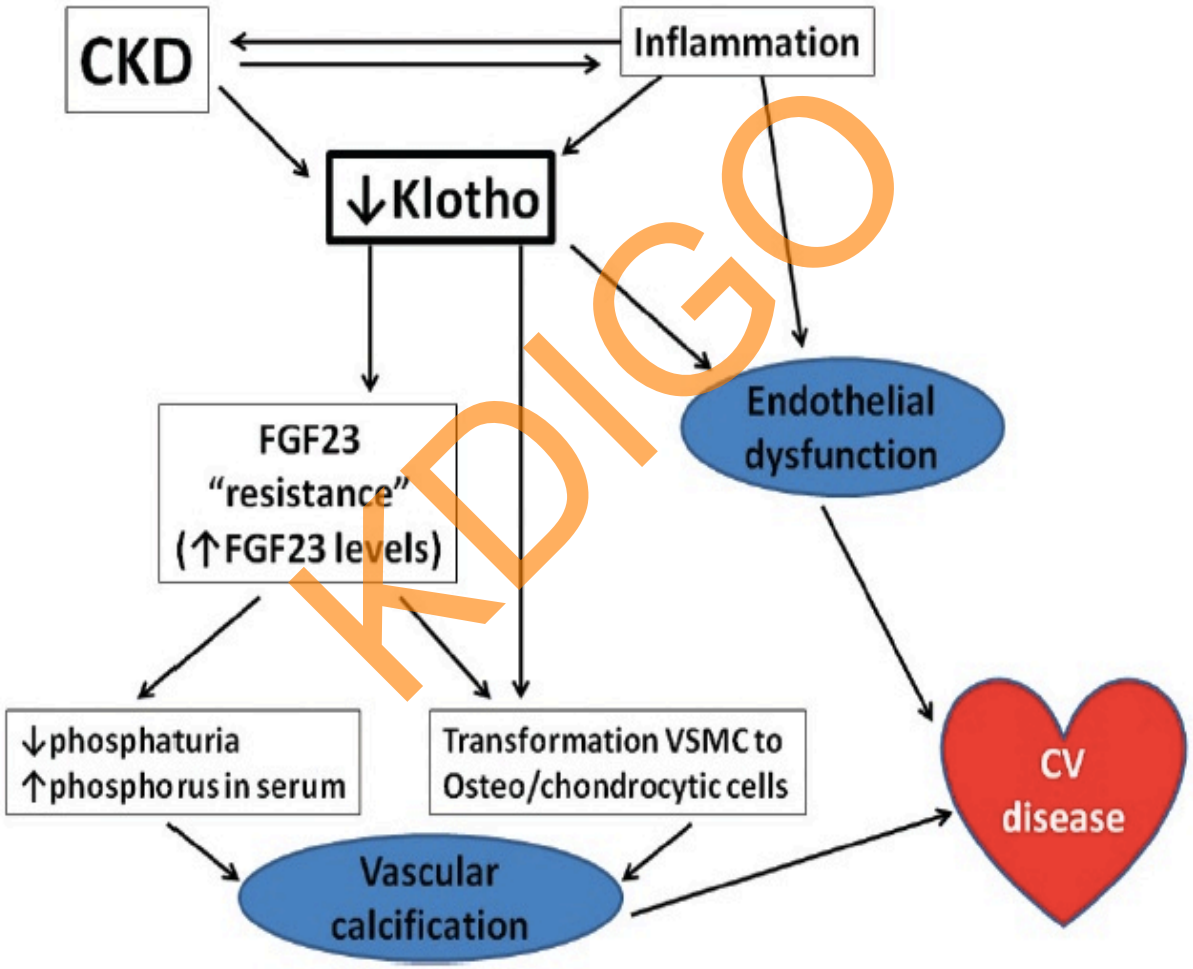
(FGF23 level quartiles)



Quartile 1	Reference	Reference	Reference
Quartile 2	1.5 (0.9–2.7)	1.7 (0.8–3.2)	1.6 (0.8–3.3)
Quartile 3	2.5 (1.4–4.4)	3.0 (1.6–5.8)	4.5 (2.2–9.4)
Quartile 4	3.4 (1.9–5.9)	3.6 (1.9–6.9)	5.7 (2.6–12.6)

Gutierrez OM et al, NEJM 2008; 359: 584-92

Cardiovascular effects of decreased Klotho levels



Moe SM, Circulation 2012 ; 74(3):265-7

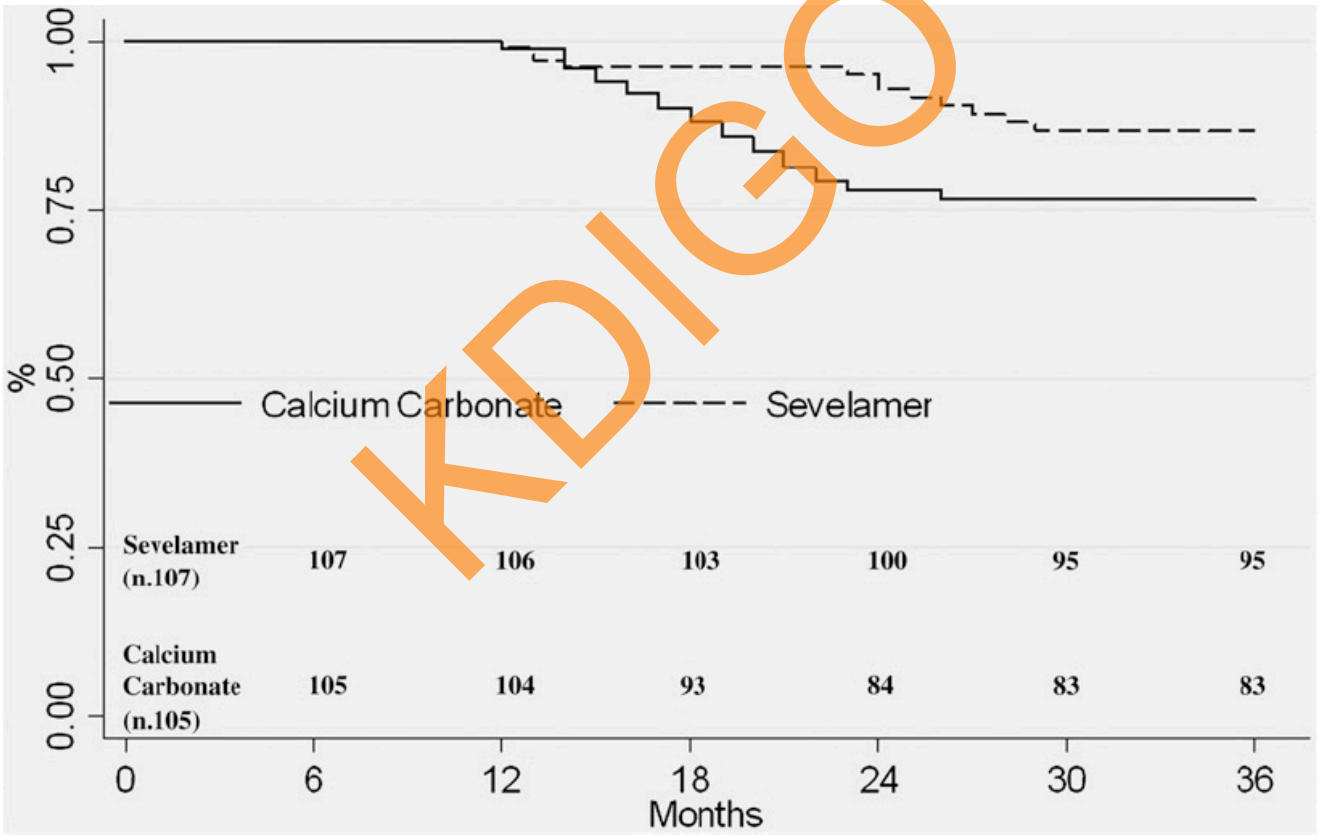
Change the term ‘CKD-MBD’ based on new insight into pathophysiology ?

- “CKD-MB**V**D” ? *(‘V’ for ‘vascular’)*
- “CKD-MB**CV**D” ? *(‘CV’ for ‘cardiovascular’)*

The term ‘CKD-MBD’ still justified ?
On which basis ?

- Numerical criteria ?
- Pathophysiology – new developments ?
- **Treatment & prevention – new data ?**
  - Phosphate binders
  - Vitamin D
  - Calcimimetics

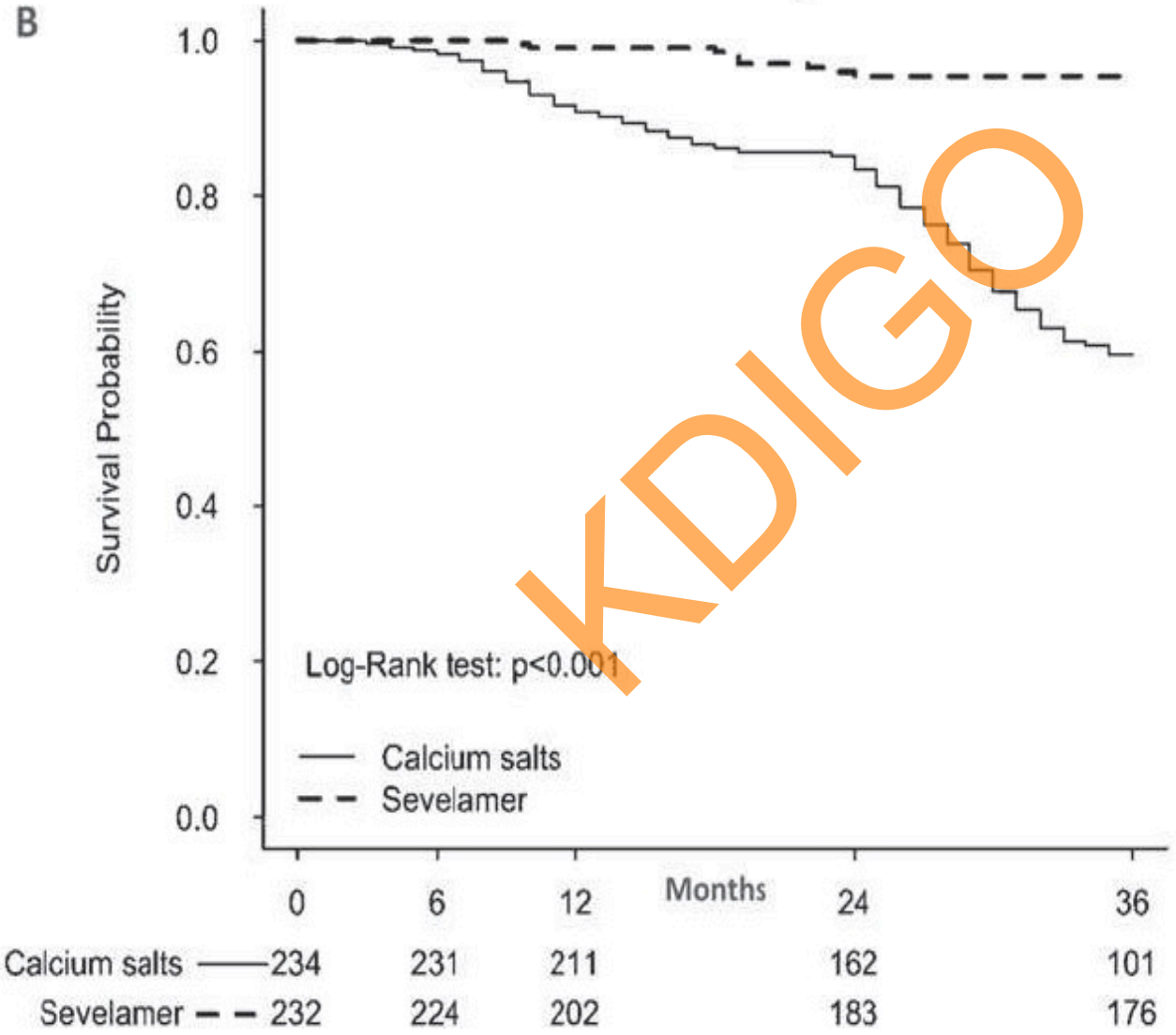
Sevelamer improves all-cause mortality (1° endpoint) in CKD stage 3-4 *(212 patients; pilot RCT)*



P<0.05

Di Iorio B et al, CJASN 2012;7:581-7

Sevelamer improves cardiovascular survival in incident HD patients (*466 patients; open-label RCT)*



P<0.001

Di Iorio B et al,
AJKD 2013;62:771-8

Vitamin D Therapy and Cardiac Structure and Function in Patients With Chronic Kidney Disease

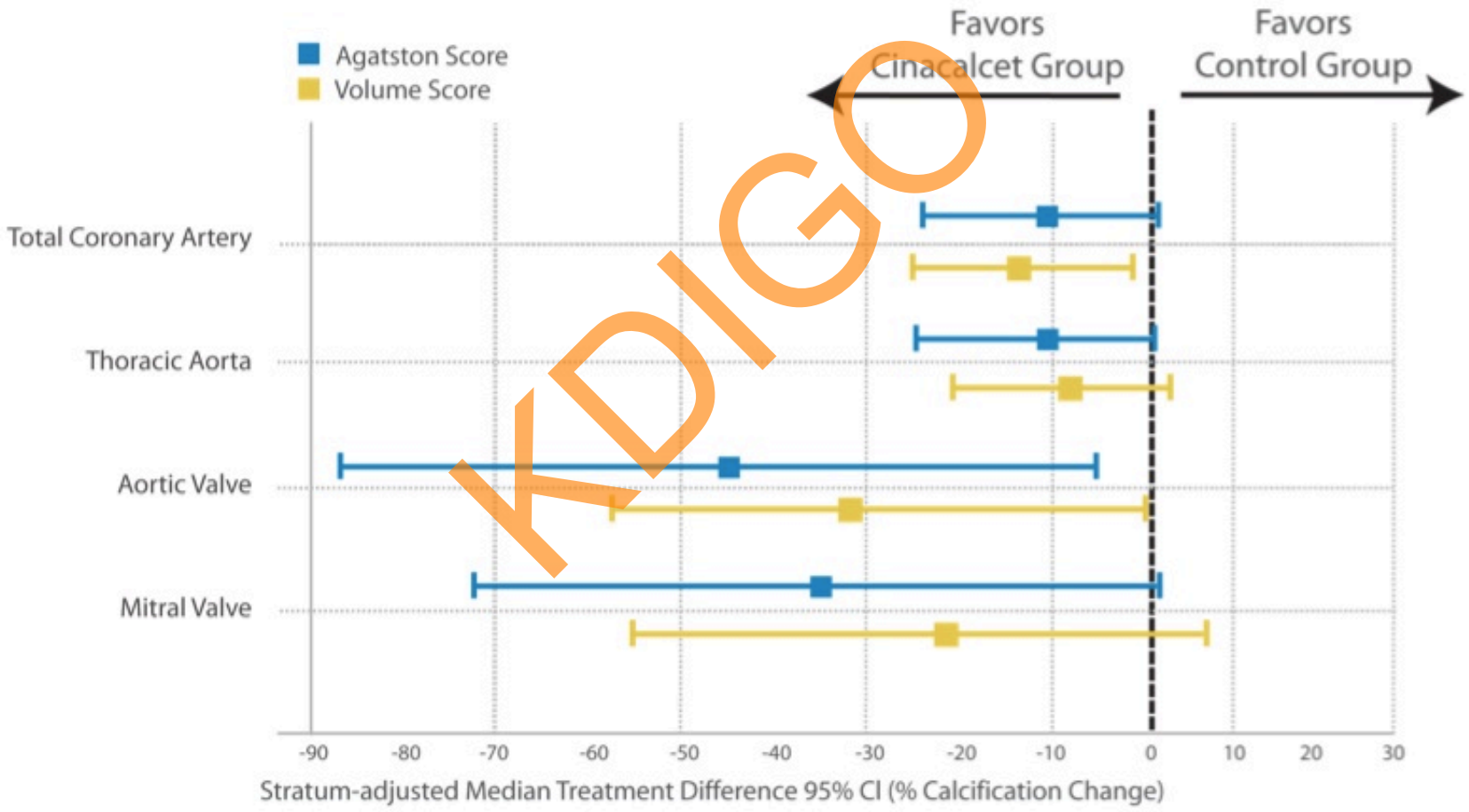
The PRIMO Randomized Controlled Trial

Thadhani R et al, JAMA 2012;307:674-84

Main Outcome Measures Change in left ventricular mass index over 48 weeks by cardiovascular magnetic resonance imaging. Secondary end points included echocardiographic changes in left ventricular diastolic function.

Results Treatment with paricalcitol reduced parathyroid hormone levels within 4 weeks and maintained levels within the normal range throughout the study duration. At 48 weeks, the change in left ventricular mass index did not differ between treatment groups (paricalcitol group, 0.34 g/m$^{2.7}$ [95% CI, –0.14 to 0.83 g/m$^{2.7}$] vs placebo group, –0.07 g/m$^{2.7}$ [95% CI, –0.55 to 0.42 g/m$^{2.7}$]). Doppler measures of diastolic function including peak early diastolic lateral mitral annular tissue velocity (paricalcitol group, –0.01 cm/s [95% CI, –0.63 to 0.60 cm/s] vs placebo group, –0.30 cm/s [95% CI, –0.93 to 0.34 cm/s]) also did not differ. Episodes of hypercalcemia were more frequent in the paricalcitol group compared with the placebo group.

Effect of cinacalcet (+ low dose vitamin D) vs. flexible vit. D doses on coron. artery calcification *(ADVANCE)*

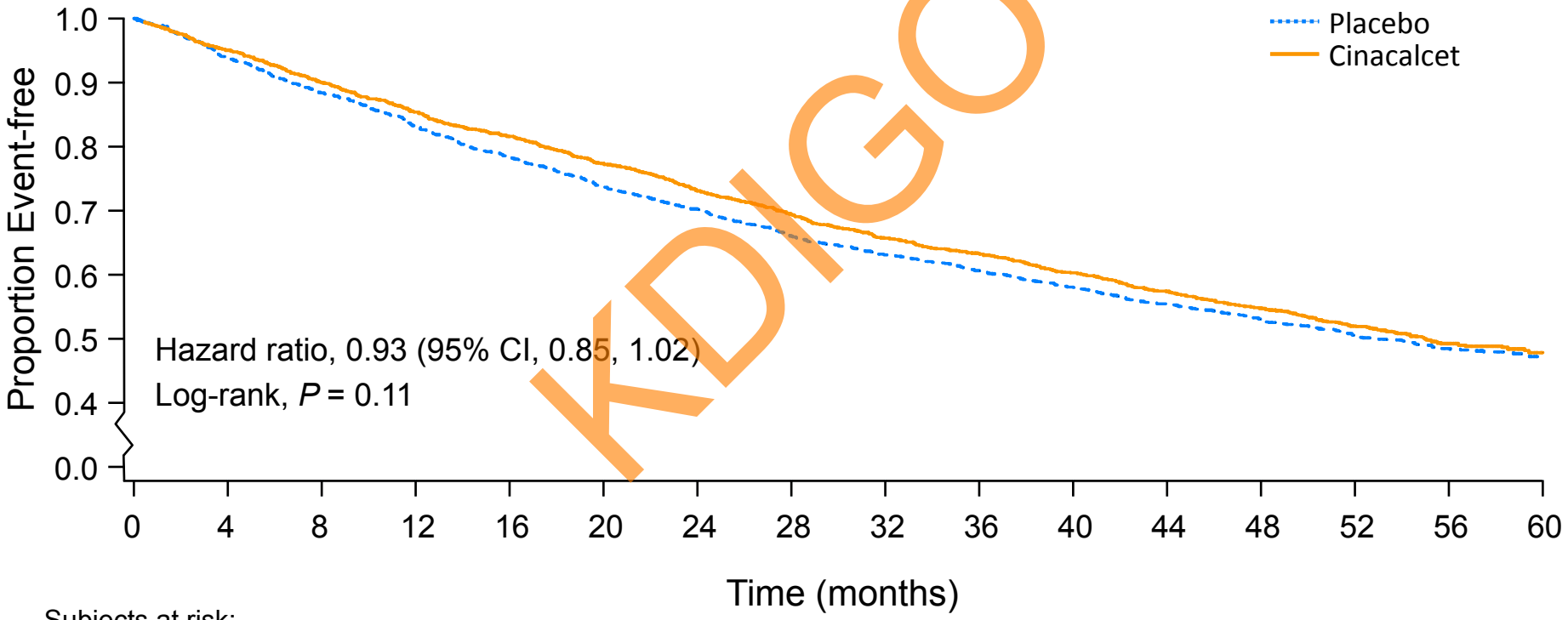


Raggi P et al, NDT 2011;26:1327-39

EVOLVE – Primary Composite Endpoint (ITT) not met:

Non-significant 7% Reduction in the Risk of Death or Cardiovascular Events

Kaplan-Meir plot of the time to the primary composite endpoint (death, myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event) in EVOLVE™.



Subjects at risk:

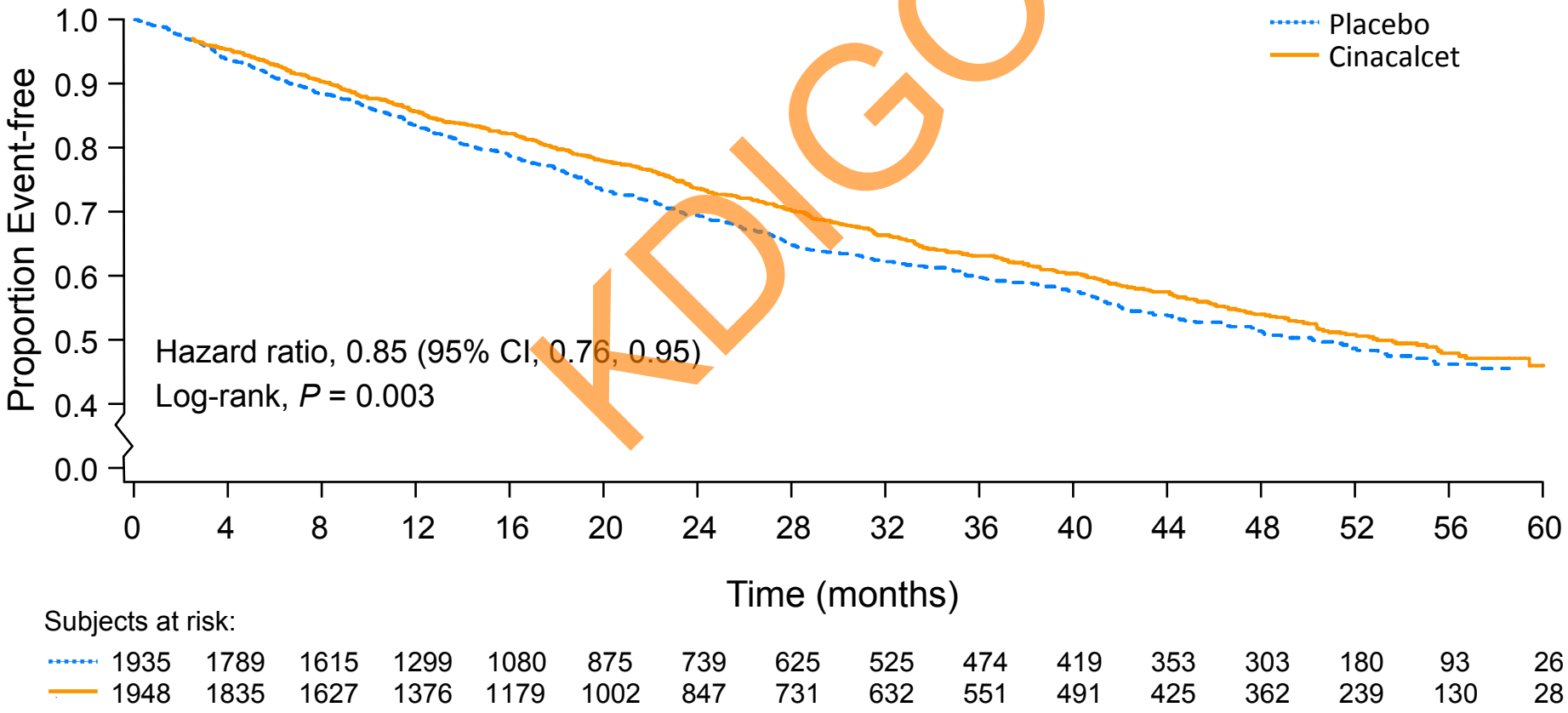
Placebo	1935	1804	1693	1579	1476	1384	1312	1224	1160	1109	1053	996	940	650	404	114
Cinacalcet	1948	1842	1739	1638	1556	1472	1384	1303	1230	1177	1115	1051	989	679	399	113

Chertow GM et al, N Engl J Med 2012; 367: 2482-94

Prespecified 6 Months Lag Censoring Analysis:

Nominally Significant 15% Reduction in Death and Cardiovascular Events

Kaplan-Meir plot of the time to the primary composite endpoint (death, myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event) in EVOLVE™.



Chertow GM et al, N Engl J Med 2012; 367: 2482-94

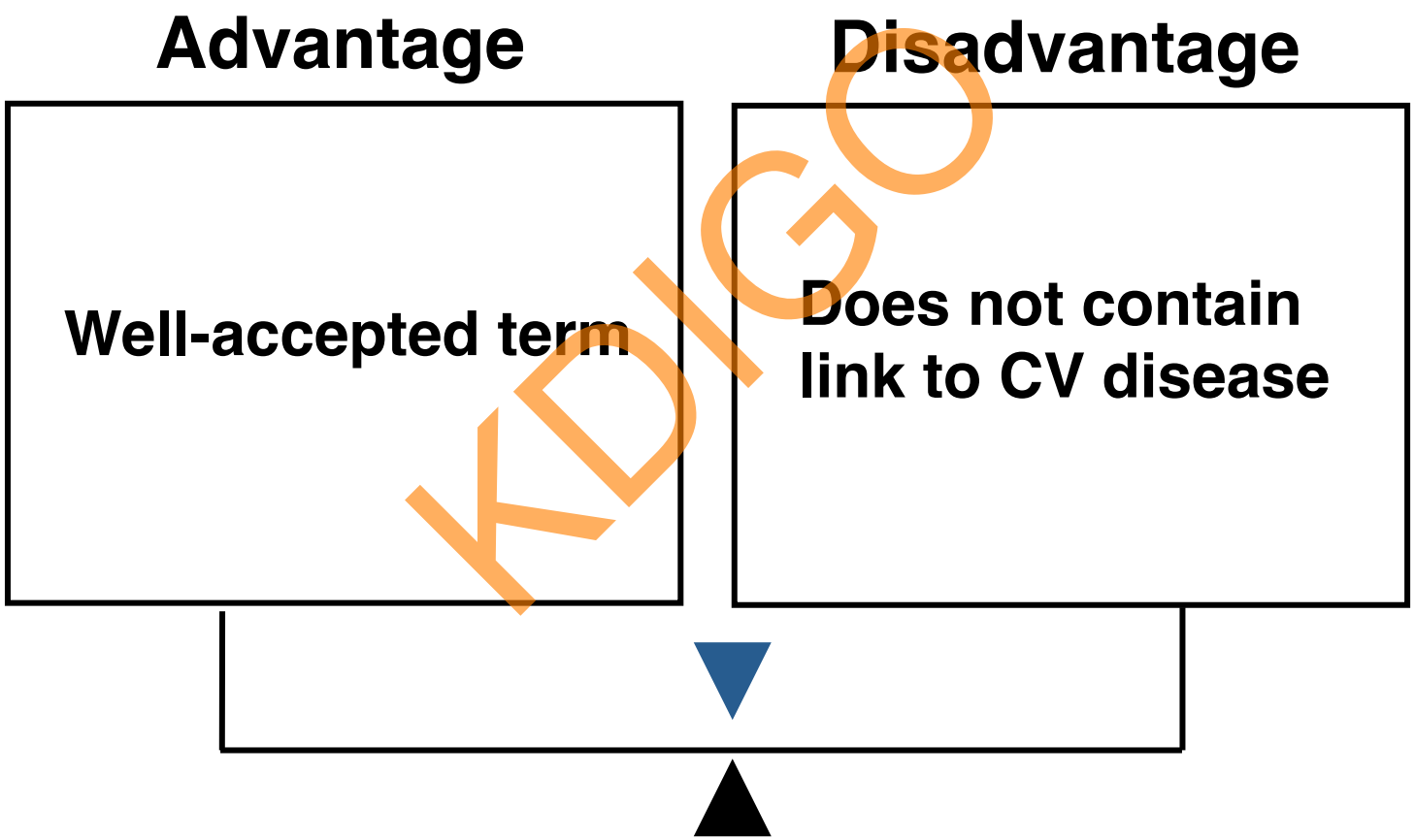
The term ‘CKD-MBD’ still justified ?
On which basis ?

- Numerical criteria ?
- Pathophysiology – new developments ?
- **Treatment & prevention – new data ?**
  - **no RCT aimed at reduction of fractures**

Change the term ‘CKD-MBD’ based on new data from RCTs ?

- Answer probably ‘NO’ *(to be discussed at present meeting)*

‘CKD-MBD’ – to change or not to change ?



The Good and the Bad of a New Disease Term

– The consensus conference will decide –