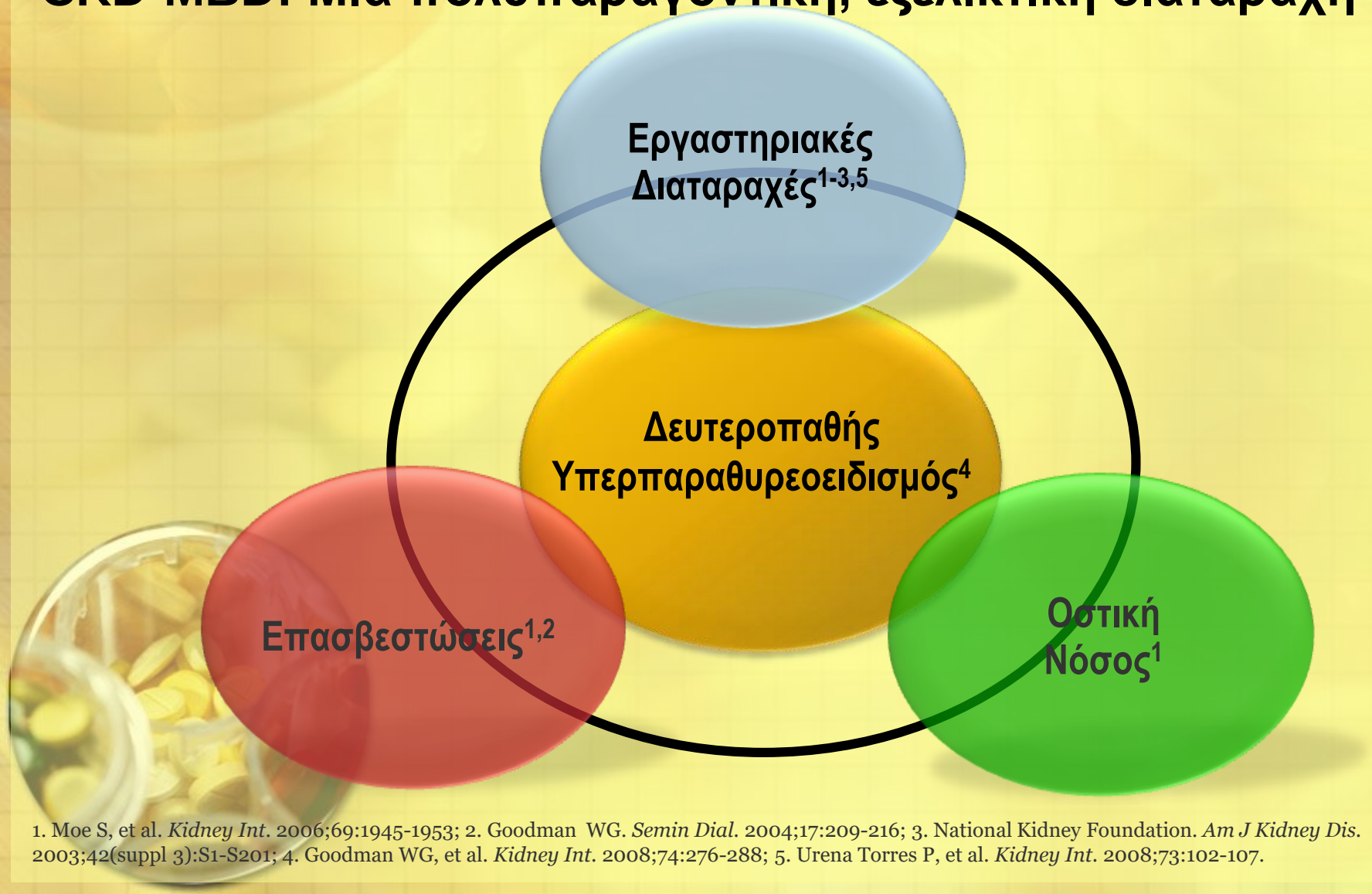
Κατευθυντήριες οδηγίες για την αντιμετώπιση του δευτεροπαθούς υπερπαραθυρεοειδισμού

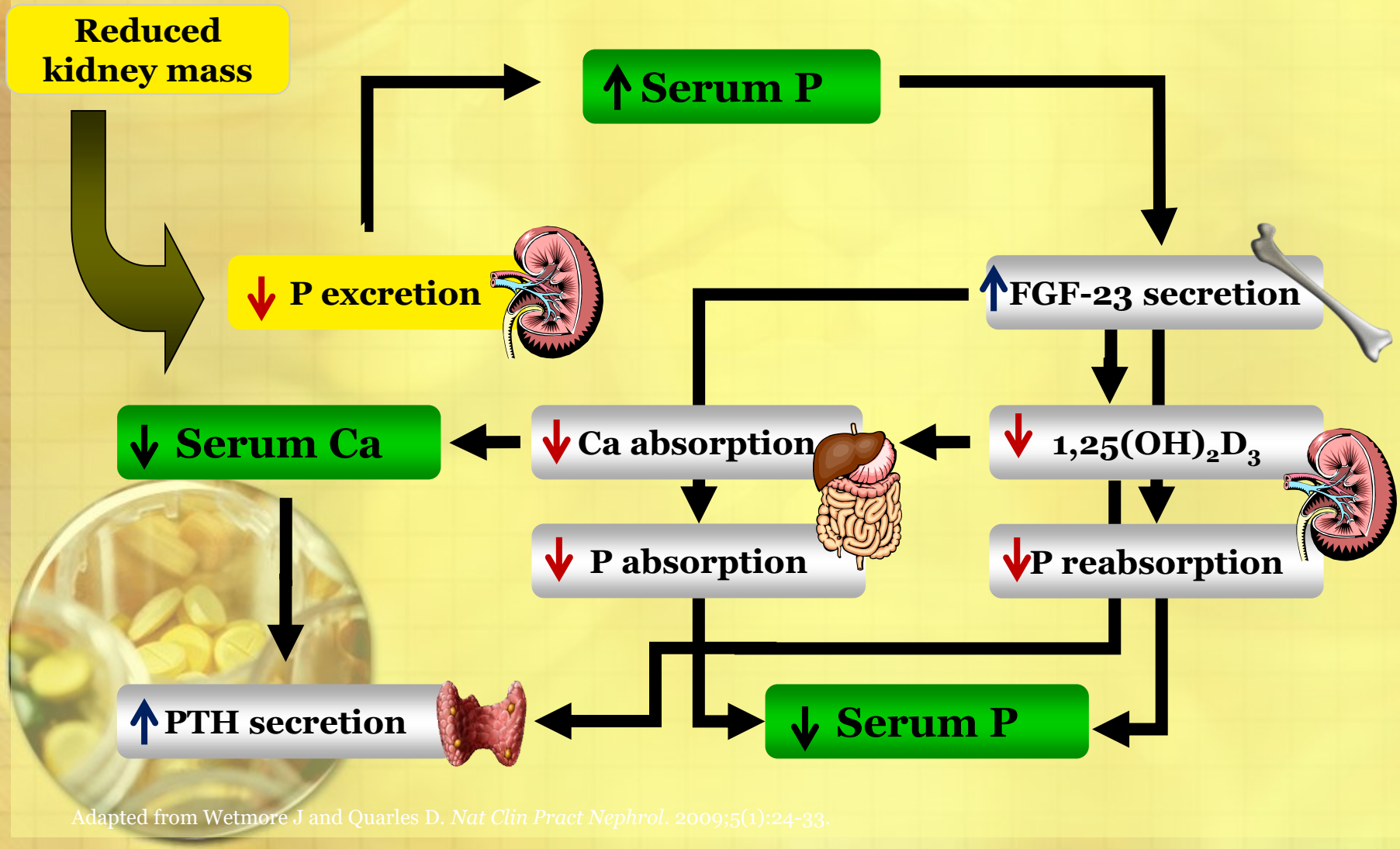
Ιωάννης Γ. Γριβέας
Νεφρολογικό Τμήμα 401 ΓΣΝΑ

CKD-MBD: Μια πολυπαραγοντική, εξελικτική διαταραχή



1. Moe S, et al. *Kidney Int*. 2006;69:1945-1953; 2. Goodman WG. *Semin Dial*. 2004;17:209-216; 3. National Kidney Foundation. *Am J Kidney Dis*. 2003;42(suppl 3):S1-S201; 4. Goodman WG, et al. *Kidney Int*. 2008;74:276-288; 5. Urena Torres P, et al. *Kidney Int*. 2008;73:102-107.

Η παθογένεση του ΔΥ στη ΧΝΝ



Adapted from Wetmore J and Quarles D. *Nat Clin Pract Nephrol*. 2009;5(1):24-33.

http://www.revistanefrologia.com

reviews

The role of Fibroblast Growth Factor 23 in chronic kidney disease-mineral and bone disorder

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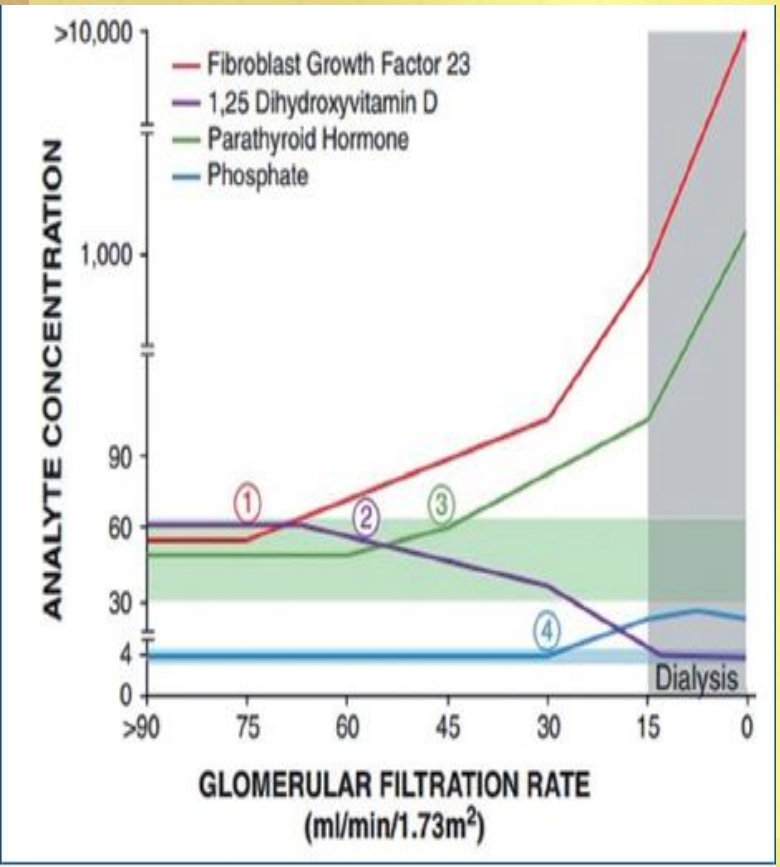
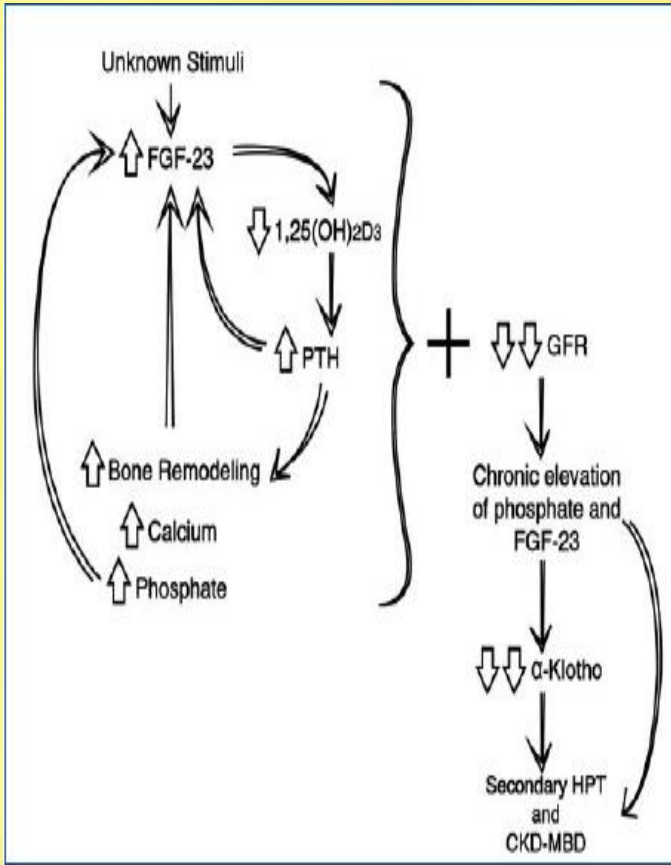
Nefrologia 2013;33(6):835-44





KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of CKD–MBD

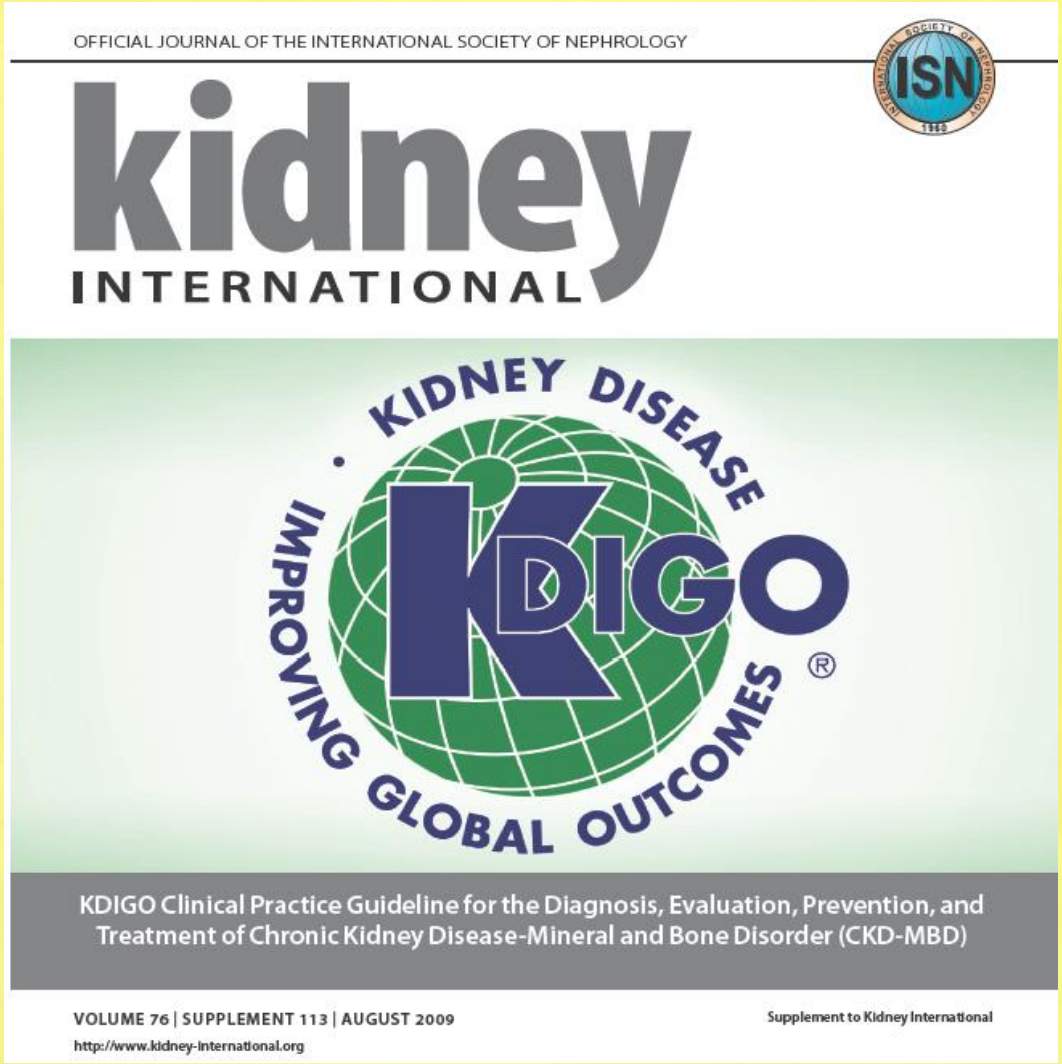


Table 1 Existing CKD cohort studies

Cohort	Population	Year commenced	Number recruited
Chronic Renal Impairment in Birmingham (CRIB) [30]	CKD with Creatinine >1.47 mg/dl (130 mmol/l) pre-dialysis	1997	369 (completed)
Mild to Moderate Kidney Disease study (MMKD) [31]	Patients who had attended secondary care nephrology clinics at least twice	1997	277 (completed)
Longitudinal Chronic Kidney Disease Study (LCKD) [32]	Secondary care, GFR < 50 ml/min on two occasions	2000	820 (completed)
Chronic Renal Insufficiency Standards Implementation Study (CRISIS) [33]	Secondary care stage 3–5 CKD (pre-dialysis)	2002	1325 (completed)
Chronic Renal Insufficiency Cohort (CRIC) [34,35]	Secondary care, all CKD stages	2003	3612 (still recruiting)
Study for the evaluation of early kidney disease (SEEK) [36]	Predominantly primary care (29% from secondary care), inclusion based upon single eGFR ≤60 ml/min	2004	1814 (completed)
Renal Risk In Derby (R^2ID) [37]	Primary care, eGFR 30-59 ml/min on more than two occasions three months apart	2008	1741 (completed)

Stringer *et al. BMC Nephrology* 2013, **14**:95
http://www.biomedcentral.com/1471-2369/14/95

BMC Nephrology

STUDY PROTOCOL Open Access

The natural history of, and risk factors for, progressive Chronic Kidney Disease (CKD): the Renal Impairment in Secondary care (RIISC) study; rationale and protocol

Stephanie Stringer[1,2*], Praveen Sharma[2,3], Mary Dutton[1], Mark Jesky[1,2], Khai Ng[1,2], Okdeep Kaur[1], Iain Chapple[2,3,4], Thomas Dietrich[2,3], Charles Ferro[1,2] and Paul Cockwell[1,2]

Differences in the approaches between KDIGO® and KDOQI™

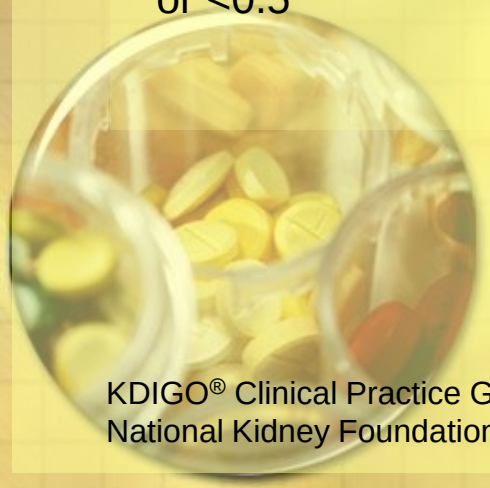
Comparison of KDIGO® and KDOQI™ guidelines: History and aims

KDIGO®	KDOQI™
• **KDIGO®** Clinical Practice Guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD — Established in 2003 as an independently incorporated non-profit foundation governed by an international board — Mission • "Improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines" — Published in 2009	• **KDOQI™** Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease — Developed by a Work Group of experts from North America — Overall aim • "…to develop a set of clinical practice guidelines that would improve diagnoses and treatment of bone disease in CKD and serve as a clinical action plan for the health care practitioner" — Published in 2003

KDIGO® Clinical Practice Guideline for CKD-MBD. *Kidney Int* 2009;76(Suppl 113)
National Kidney Foundation. *Am J Kidney Dis* 2003;42(suppl 3):S1–S201

Comparison of KDIGO® and KDOQI™ guidelines:
KDIGO® used stricter criteria for article selection than KDOQI™

KDIGO®	KDOQI™
• Only included RCTs with prior determined criteria for interventions • Trial duration ≥6 months • n≥50 except n≥20 for studies of bone histomorphometry outcomes • Arbitrary thresholds (as defined by GRADE) to consider only observational studies of treatment effects if RR of >2 or <0.5	• Evaluated all types of studies • n≥10 per arm, except crossover studies where n≥5



KDIGO® Clinical Practice Guideline for CKD-MBD. *Kidney Int* 2009;76(Suppl 113)
National Kidney Foundation. *Am J Kidney Dis* 2003;42(suppl 3):S1–S201

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

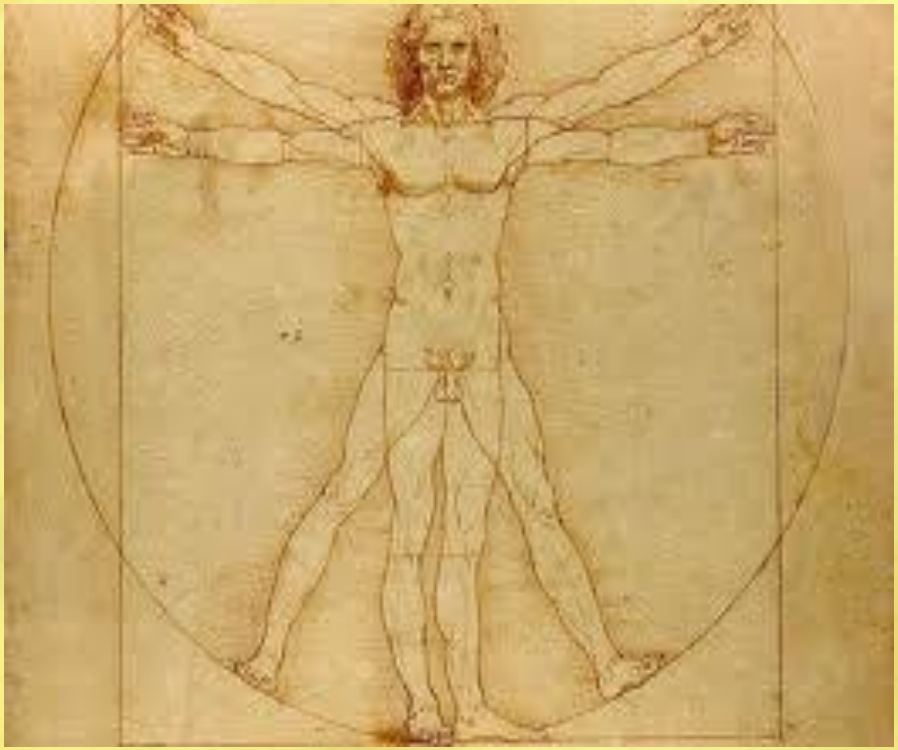
National Kidney Foundation. *Am J Kidney Dis* 2003;42(suppl 3):S1–S201

Recent 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

Treatment strategies to control serum PTH

KDIGO® recommendations:

Treatment of abnormal PTH levels

Lab parameters	• Suggests maintaining iPTH levels in the range of approximately 2–9 x ULN for the assay (2C) • On the basis of observational data, KDIGO® considers that levels of iPTH <2 and >9 x ULN represent extreme ranges of risk • Suggests that changes in PTH levels within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C)
Treatment options	• Calcitriol, vitamin D analogues and calcimimetics • Choice based on serum calcium and phosphorus levels

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

KDIGO® recommendations:

Treatment of abnormal PTH levels

4.2.1 In patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH (iPTH) above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C).

It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (not graded).

4.2.2 In patients with CKD stages 3–5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C).

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

KDIGO® recommendations:

Treatment of abnormal PTH levels

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

We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C)

4.2.4 In patients with CKD stage 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).

It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphorus levels and other aspects of CKD–MBD (not graded).

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

KDIGO® recommendations:

Treatment of abnormal PTH levels

Effect of Paricalcitol on Left Ventricular Mass and Function in CKD--The OPERA Trial- **19 September 2013**

Vitamin D seems to protect against cardiovascular disease, but the reported effects of vitamin D on patient outcomes in CKD are controversial.

52 weeks of treatment with oral paricalcitol (1 µg one time daily) significantly improved secondary hyperparathyroidism but did not alter measures of LV structure and function in patients with severe CKD.

EVOLVE™ (EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events)

EVOLVE™ (EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events)

Secondary Endpoint Result – **Heart Failure**

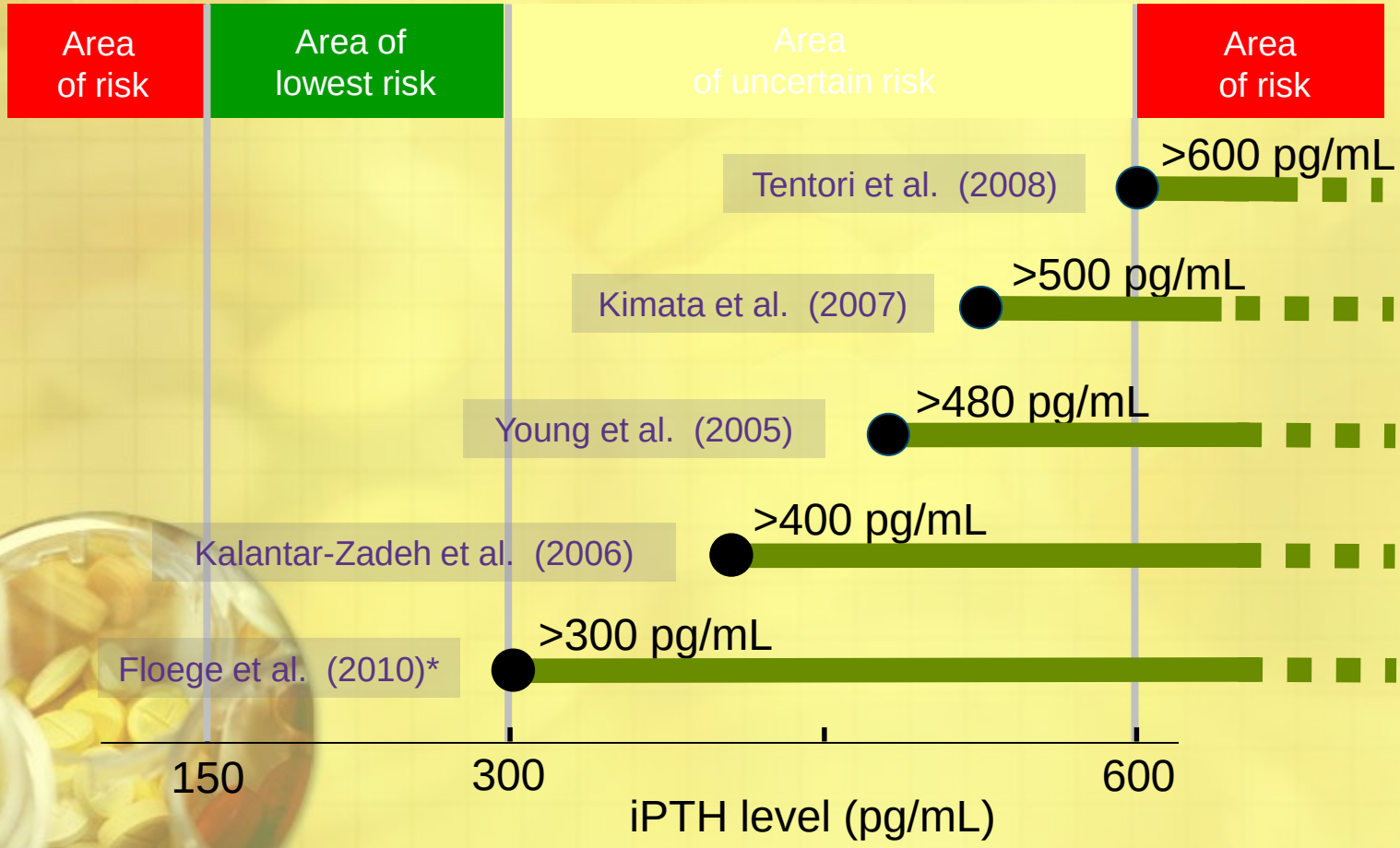
Conclusions

- There was no significant difference in the primary study endpoint of all-cause mortality and CV events when analyzed using an unadjusted ITT analysis.
- After adjustment for baseline characteristics, the relative hazard for the primary composite end point was 0.88 (95% CI, 0.79 to 0.97; P = 0.008)
- In the pre-specified ITT analyses accounting for baseline factors, randomization to cinacalcet resulted in
  - 24% reduction in heart failure (HF) events in patients on HD with sHPT
  - 14% reductions in all-cause (HR = 0.86, 95% CI = 0.78 to 0.96) and CV mortality (HR = 0.86, 95% CI = 0.74 to 0.99).
- Randomization to cinacalcet resulted in a nominally significant* reduction in surgical PTx. Thus cinacalcet allowed better control of sHPT than conventional therapy.
- The results from ARO and EVOLVE were comparable. The findings suggest that well-designed observational studies can show treatment effects which mirror randomised controlled trials.
- Safety data were generally consistent with the previously published safety profile of cinacalcet with nausea, vomiting and hypocalcemia as the most frequently reported adverse events

* Since the primary end point was not significant, reported P values should be considered nominal

Chertow GM, et al. *N Engl J Med*. Epub 2012 Nov 3; DOI: 10.1056/NEJMoa1205624
Floege J. Presentation at *ERA-EDTA*, May 18-21, Istanbul, Turkey.

Definition of extreme ranges of risk on the basis of observational data

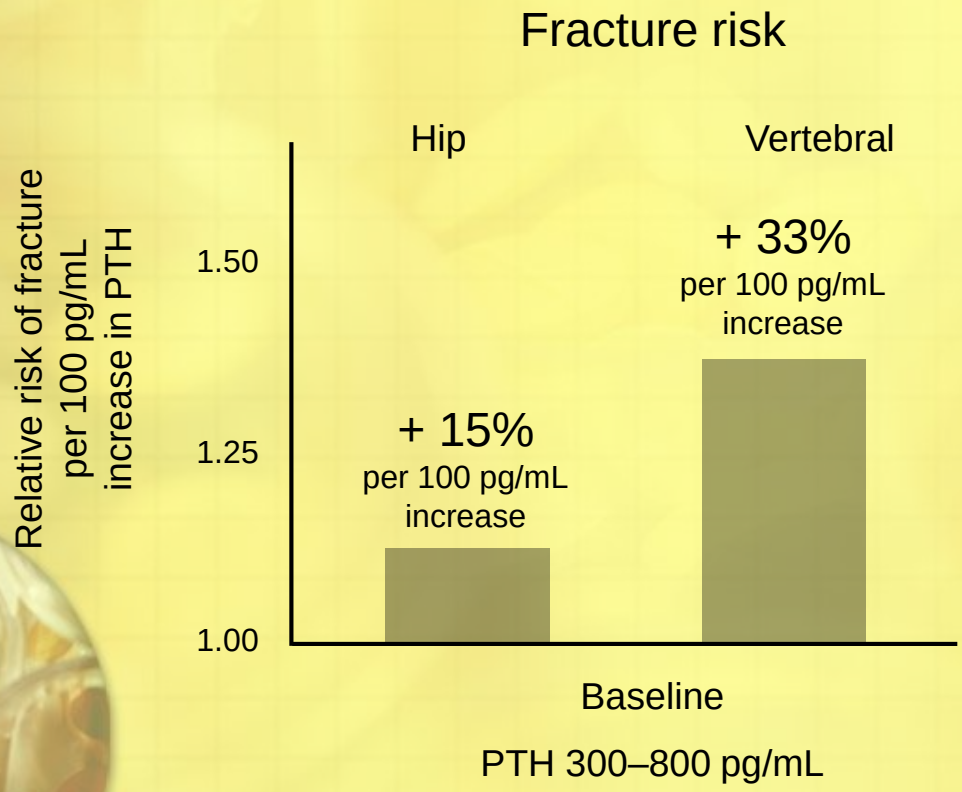


KDIGO® Clinical Practice Guideline for CKD-MBD. *Kidney Int* 2009;76(Suppl 113)

* Has not been reviewed by the KDIGO group as full publication is pending

Evidence from observational research:

Rising PTH levels can increase the risk of fractures



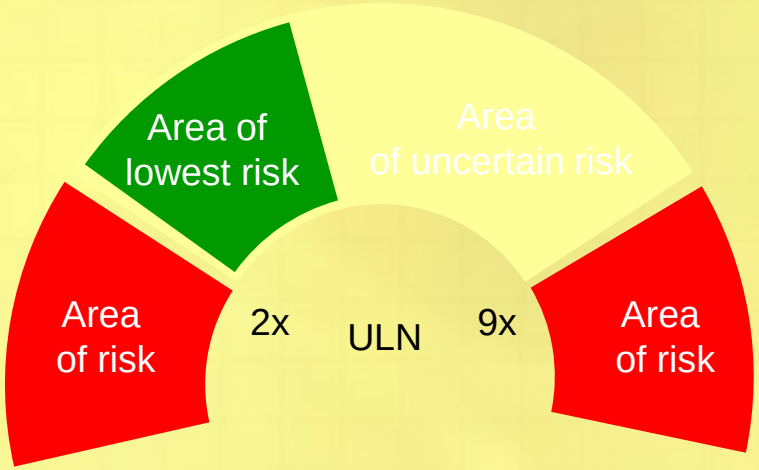
Danese MD et al. *Am J Kidney Dis* 2006;47:149–156

Guidance on managing iPTH in dialysis patients

Due to the paucity of evidence, KDIGO® was only able to define extreme ranges of risk, rather than specific treatment targets

Marked changes in PTH levels should prompt an initiation or change in therapy to avoid progression to the areas of risk

Within the range of KDIGO® a PTH target of 150-300 pg/mL represents the lowest level of risk based on observational data on mortality and fractures[1–3]



1. Danese MD et al. *Am J Kidney Dis* 2006;47:149–156
2. Danese MD et al. *Clin J Am Soc Nephrol* 2008:3:1423–1429
3. Floege J et al. *J Am Soc Nephrol* 2008;11:502A. Abstract and Poster F-PO1746

Treatment strategies to control serum Ca and Ph

KDIGO® recommendations:
Treatment of abnormal Ca levels

Lab parameters	• Suggests maintaining serum Ca in the normal range (2D)
Treatment options	• Choice of PTH-lowering treatment should be based on serum Ca and P levels • Use of calcitriol or vitamin D analogues may increase serum Ca and P • Differences between calcitriol and specific vitamin D analogues not proven • Calcimimetics may lower Ca and P levels

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

KDIGO® recommendations: Treatment of CKD–MBD targeted at lowering high serum phosphorus and maintaining serum calcium

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

4.2.4 It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphorus levels and other aspects of CKD–MBD (not graded)

We recommend that, in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (1B).

We suggest that, in patients with hypocalcemia, calcimimetics be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (2D).

In CKD stages 3–5D, calcitriol and vitamin D analogs may increase serum calcium and phosphorus levels compared with placebo

In studies of patients with CKD stage 5D, calcimimetics may lower serum calcium and phosphorus levels compared with placebo

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

KDIGO® recommendations:
Treatment of abnormal P levels

Lab parameters	• Suggests lowering elevated serum P levels toward the normal range in CKD 5D (2C) • Highlights that laboratory parameters do not move in isolation from one another, but rather change depending on the levels of other parameters
Treatment options	• Limit dietary phosphate intake • Use phosphate binding agents • Increase dialytic phosphate removal

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

KDIGO® recommendations: Treatment of CKD–MBD targeted at lowering high serum phosphorus and maintaining serum calcium

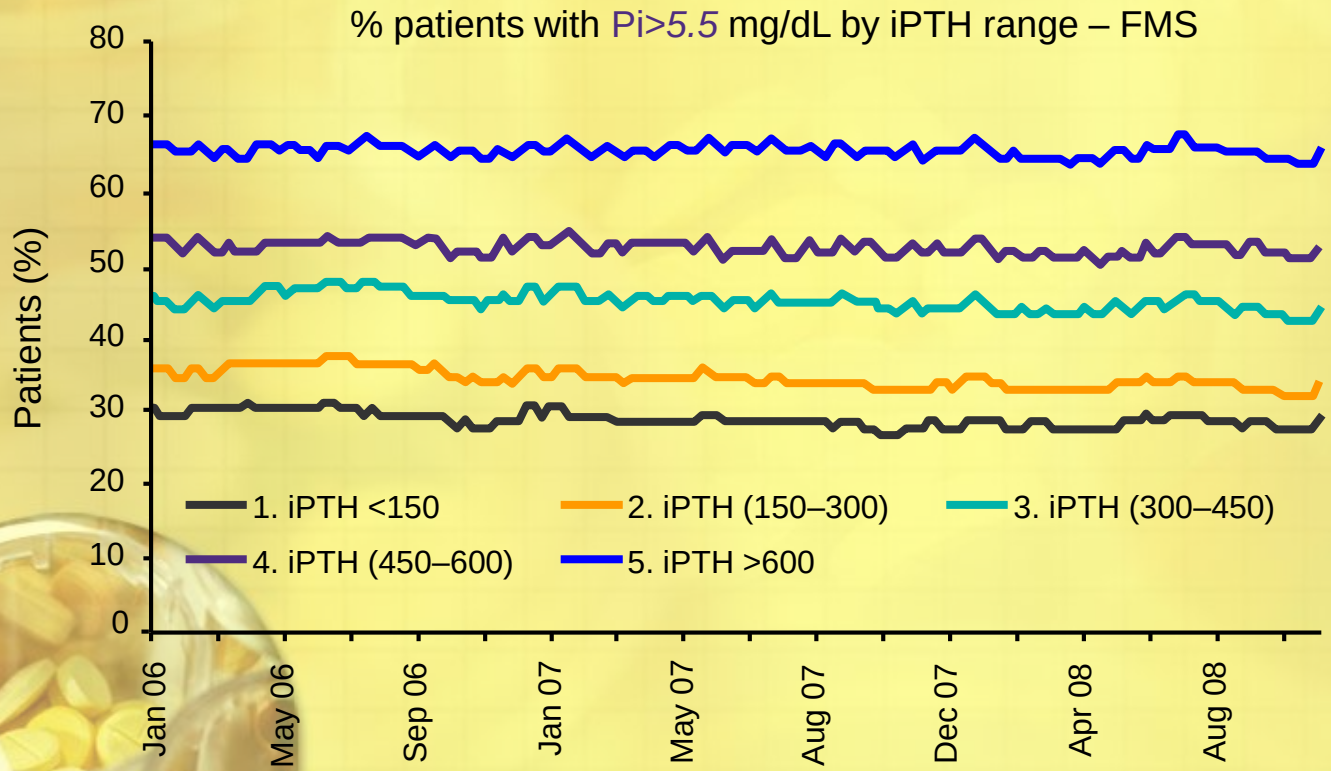
4.1.4 In patients with CKD stages 3–5 (2D) and 5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, presence of other components of CKD–MBD, concomitant therapies, and side-effect profile (not graded).

4.1.7 In patients with CKD stages 3–5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D).

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

Link between phosphate and PTH control:

In patients with high iPTH levels uncontrolled P levels are more common



Data on file Fresenius Medical Care US, data as of Nov 2008, n=221,000

Treatment strategies to control vascular calcification

KDIGO® recommendations:

Diagnosis of CKD-MBD: Vascular Calcification

RECOMMENDATIONS

3.3.1 In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography–based imaging (2C).

3.3.2 We suggest that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide the management of CKD–MBD (not graded).

Diagnosis of CKD–MBD: bone

KDIGO® recommendations:

Diagnosis of CKD–MBD: bone

3.2.1 In patients with CKD stages 3–5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD–MBD (not graded).

3.2.2 In patients with CKD stages 3–5D, with evidence of CKD–MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B).

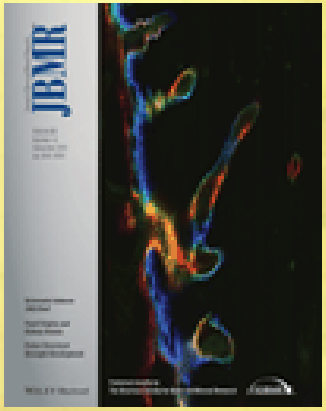
KDIGO® Clinical Practice Guideline for CKD-MBD. *Kidney Int* 2009;76(Suppl 113)

Diagnosis of CKD–MBD: bone

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor kappaB ligand (RANKL), an osteoclast differentiating factor. It inhibits osteoclast formation, decreases bone resorption, increases bone mineral density (BMD), and reduces the risk of fracture.

CLINICAL TRIALS

JBMR



A Single-Dose Study of Denosumab in Patients With Various Degrees of Renal Impairment

Geoffrey A Block,[1] Henry G Bone,[2] Liang Fang,[3*] Edward Lee,[3] and Desmond Padhi[3]

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[2]Michigan Bone and Mineral Clinic, Detroit, MI, USA
[3]Amgen Inc., Thousand Oaks, CA, USA

ABSTRACT

This 16-week study evaluated pharmacokinetics and pharmacodynamics of denosumab in 55 subjects with renal function ranging from normal to dialysis-dependent kidney failure. Participants received a single 60-mg subcutaneous dose of denosumab. Kidney function groups were based on calculations using the Cockcroft-Gault equation and U.S. Food and Drug Administration (FDA) guidance in place when the study was designed. Renal function did not have a significant effect on denosumab pharmacokinetics or pharmacodynamics. These findings suggest denosumab dose adjustment based on glomerular filtration rate is not required. Rapid decreases in serum C-telopeptide in all groups were sustained throughout the study. The most common adverse events were hypocalcemia (15%), pain in extremity (15%), and nausea (11%). Most adverse events were mild to moderate in severity. Calcium and vitamin D supplementation was not initially required by the study protocol, but was added during the trial. No subject who received adequate calcium and vitamin D supplementation became hypocalcemic. Seven subjects had nadir serum calcium concentrations between 7.5 and <8.0 mg/dL (1.9 and <2.0 mmol/L), and 5 subjects (4 with advanced renal disease) had nadir serum calcium <7.5 mg/dL (<1.9 mmol/L). Two subjects (1 symptomatic, 1 asymptomatic) were hospitalized for intravenous calcium gluconate treatment. At the recommended dose, denosumab is a useful therapeutic option for patients with impaired renal function. Supplementation of calcium and vitamin D is strongly recommended when patients initiate denosumab therapy, particularly in patients with reduced renal function.

Received in original form January 31, 2012; revised form March 12, 2012; accepted March 15, 2012. Published online March 28, 2012.

Diagnosis of CKD–MBD: bone

On November 26, 2002, the U.S. Food and Drug Administration (FDA) approved **teriparatide**, a portion of human parathyroid hormone (PTH), was approved for the treatment of osteoporosis in postmenopausal women who are at high risk for having a fracture, and also to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture.

NDT Advance Access published September 12, 2013

Nephrol Dial Transplant (2013) 0: 1–4
doi: 10.1093/ndt/gft222

In Focus

Sclerostin in CKD-MBD: one more paradoxical bone protein?

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Keywords: bone disease, bone marker, kidney disease, sclerostin, survival

Bone disease is frequently observed in chronic kidney disease (CKD) and increases a patient's risk for fracture, cardiovascular (CV) calcification and mortality. The Kidney Disease Improving Global Outcomes foundation defined a new syndrome incorporating the bone, mineral and CV disorders, such as chronic kidney disease–mineral and bone disorders (CKD–MBDs) [1]. The relationship between the bone turnover and CV disease is well documented in patients with CKD [2], as is the relationship between low bone density and aortic calcification in patients without CKD [3]. The quest for a modifiable reliable biomarker of CV and bone disease in CKD–MBD remains the nephrologist's Holy Grail. In recent years, numerous bone proteins have been associated with the outcome in patients with CKD, such as osteoprotegerin (OPG) [4], fibroblast growth factor (FGF)-23 [5], bone-specific alkaline phosphatase (bsALP) [6] and, more recently, sclerostin.

Sclerostin is a glycoprotein (22 kDa) product of the *SOST* gene in osteocytes, which inhibits osteoblast and bone formation. The canonical Wingless-type mouse mammary tumour virus integration site (Wnt) pathway has a bone anabolic and anti-catabolic effect. Sclerostin acts as an inhibitor of the Wnt-coreceptor LRP5/6. In the deep mineralized bone, osteocytes are able to detect mechanical strain, and when bone is subjected to mechanical forces, sclerostin is not secreted and bone formation occurs. Therefore, sclerostin appears to play an important role in the skeletal adaptation to mechanical forces [7]. Wnt signalling inhibits bone resorption and up-regulates OPG, which binds and inhibits the receptor activator of nuclear factor κB-ligand (RANKL) [8]. Patients with sclerosteosis or hyperostosis, who inherited high bone mass, were found to have a mutation of the *SOST* gene that impairs sclerostin activity [9]. Local parathyroid hormone (PTH) [10] and its administration reduces sclerostin expression *in vivo* [11]. Inversely, sclerostin production is increased by calcitonin. Sclerostin acts on osteoblasts in a paracrine manner, but little is known about possible endocrine action. Information on serum sclerostin kinetics with circadian or seasonal variations is lacking. Information on racial differences, factors influencing production and serum levels such as physical activity and nutrition, and the impact of different medications is scarce. However, longitudinal studies showed a relative serum sclerostin level stability.

The factors associated with serum sclerostin levels are shown in Table 1. In the general population, high serum sclerostin levels have been associated with: older age, possibly due to diminished physical activity and clearance; male gender related to bone mass and hormonal effect; type 2 diabetes, particularly in the presence of atherosclerotic disease [12]; low serum PTH levels and low bone turnover; higher fat mass [13] and bone mineral density (BMD) [14]; and mechanical unloading of the skeleton upon bed rest [15] called immobilization-related bone loss. In older men, high serum sclerostin levels were recently reported to be associated with higher BMD, lower bone turnover and lower fracture risk [16]. Whether these unexpected results are related to an adaptation phenomenon or a problem with the assay remains to be assessed. Inversely, in post-menopausal women, a high sclerostin level better predicts the occurrence of osteoporotic fractures than the conventional bone markers [17]. The reason for the positive association between BMD and serum sclerostin level is unknown, but it is hypothesized that a high sclerostin level could indicate a high number of osteocytes. In the field of osteoporosis therapy, sclerostin inhibition by antibodies has been shown to increase bone mass and bone formation in rats [18]. Additionally, serum sclerostin levels decrease after PTH infusion as seen in the case of primary hyperparathyroidism [19]. Risedronate use increases serum sclerostin levels in postmenopausal women [20], whereas raloxifen [21] and oestrogen use decreases its levels.

Serum sclerostin levels increase in patients with CKD and those on dialysis [22]. Whether this is due to decreased

WHO Scientific Group Technical Report

ASSESSMENT OF OSTEOPOROSIS AT THE PRIMARY HEALTH CARE LEVEL

Report of a WHO Scientific Group

Reference
Kanis JA on behalf of the World Health Organization Scientific Group (2007) Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Reference to summary
World Health Organization (2007) Assessment of osteoporosis at the primary health care level. Summary Report of a WHO Scientific Group. WHO, Geneva, www.who.int/chp/topics/rheumatic/en/index.html

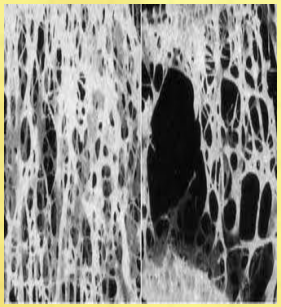
The University Of Sheffield.

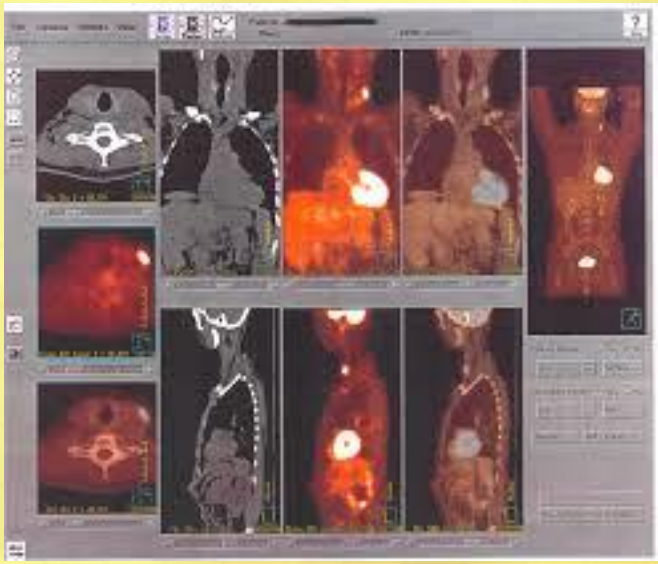
John A Kanis on behalf of the World Health Organization Scientific Group*

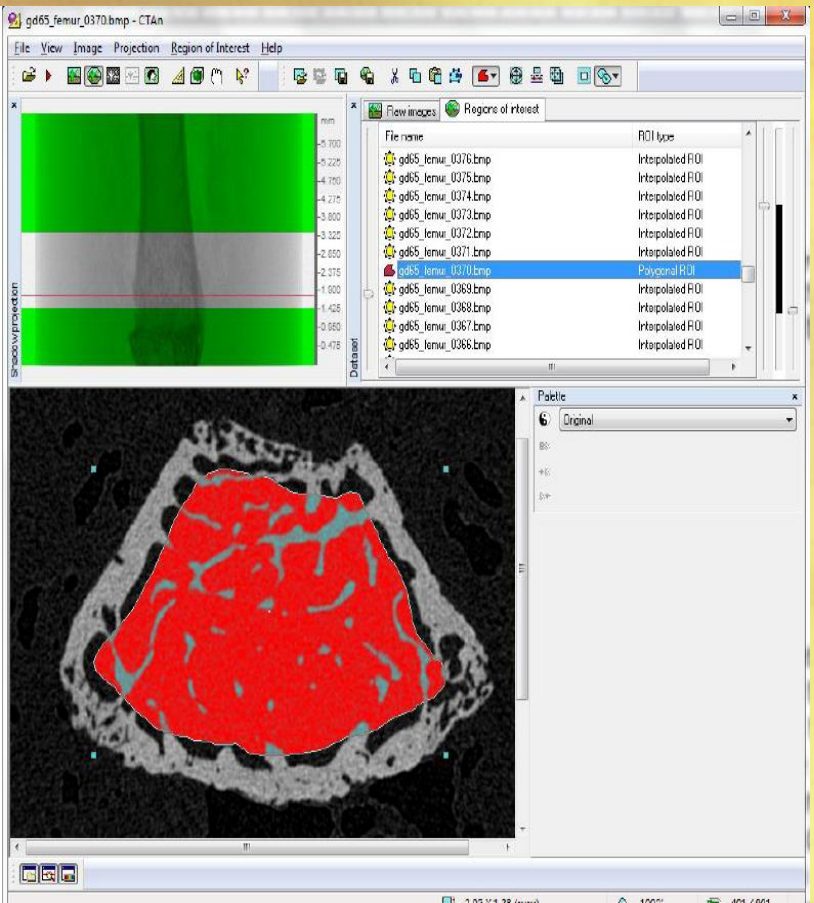
Organized by the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK and the World Health Organization

TBS iNsight®

Easy access to bone microarchitecture





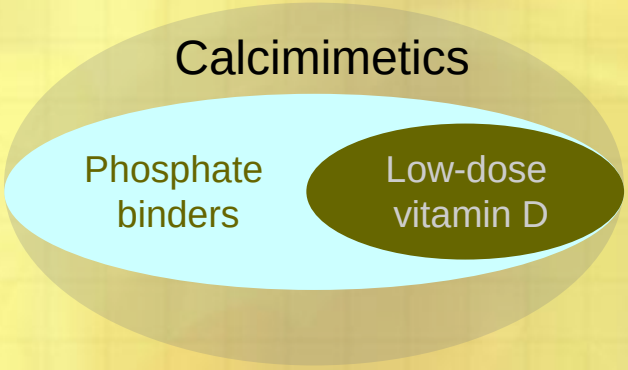


Bone mineral density (BMD) and tissue mineral density (TMD) calibration and measurement by micro-CT using Bruker-MicroCT CT-Analyser

Suggested treatment paradigm in light of the currently available evidence

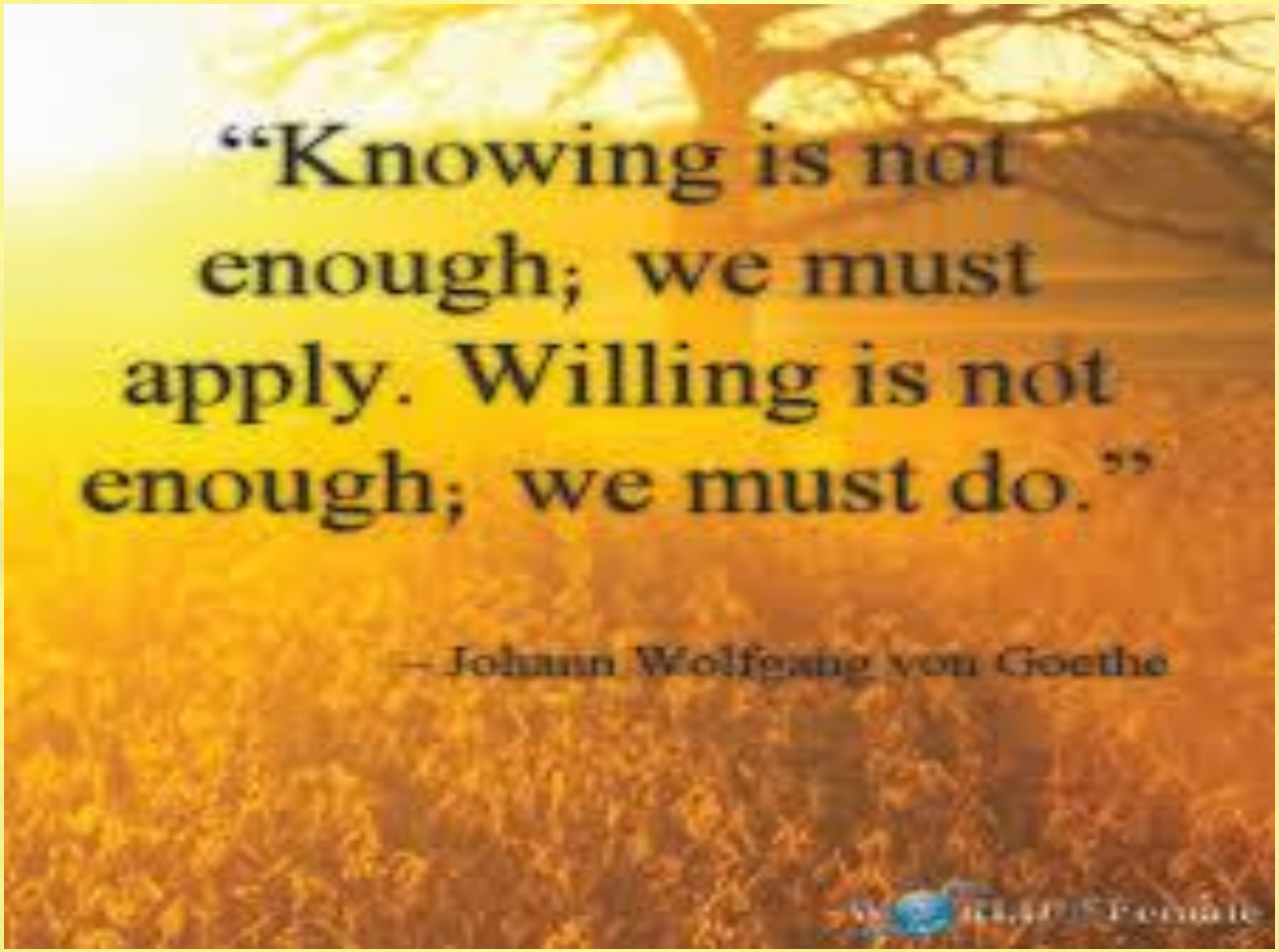
Control P by dietary restriction and oral phosphate binders

Consider low doses of vitamin D analogues
+
Consider calcimimetics as a first-line therapy



Wetmore JB & Quarles LD. *Nat Clin Pract Nephrol* 2009;5:24–33
Messa P et al. *Clin J Am Soc Nephrol* 2008;3:36–45

Illuminati


"Knowing is not enough; we must apply. Willing is not enough; we must do."
– Johann Wolfgang von Goethe

What have we learned about chronic kidney disease-mineral bone disorder from the EVOLVE and PRIMO trials?

Curr Opin Nephrol Hypertens. 2013 Nov;22(6):651-5.

- **PURPOSE OF REVIEW:**
- The treatment of chronic kidney disease-mineral bone disorder (CKD-MBD) has traditionally focused on improvement in biochemical parameters of the disease. However, studies evaluating hard clinical end points or surrogate end points are limited.
- **RECENT FINDINGS:**
- Two randomized controlled trials have recently been published. In the **EVOLVE study (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events),** cinacalcet was compared with placebo in **3883 haemodialysis** patients with secondary hyperparathyroidism. The primary end point (death, myocardial infarction, unstable angina, heart failure or peripheral vascular disease) in an unadjusted intention-to-treat analysis was not significant [hazard ratio 0.93; 95% confidence interval (CI) 0.85-1.02, P=0.11]. However, the pre-specified secondary end points of an adjusted intention-to-treat analysis (hazard ratio 0.88; 95% CI 0.79-0.97, P=0.008) were significant. In the **PRIMO (Paricalcitol Capsule Benefits in Renal Failure Induced Cardiac Morbidity) trial, 227 patients with CKD stage 3-4** and left ventricular hypertrophy by echocardiography were randomized to paricalcitol or placebo. The primary end point of change in left ventricular mass index by MRI after 12 months was not different between the two groups, but the prespecified end point of cardiovascular-related hospitalizations was reduced in the paricalcitol-treated group (P=0.04).
- **SUMMARY:**
- **The results of these two randomized controlled trials have negative primary end points but significant secondary end points and thus require physicians to individualize therapies for the treatment of secondary hyperparathyroidism.**

KDIGO® recommendations:

Treatment of abnormal PTH levels

Effect of Paricalcitol on Left Ventricular Mass and Function in CKD--The OPERA Trial- 19 September 2013

Vitamin D seems to protect against cardiovascular disease, but the reported effects of vitamin D on patient outcomes in CKD are controversial. We conducted a prospective, double blind, randomized, placebo-controlled trial to determine whether oral activated vitamin D reduces left ventricular (LV) mass in patients with stages 3-5 CKD with LV hypertrophy. Subjects with echocardiographic criteria of LV hypertrophy were randomly assigned to receive either oral paricalcitol (1 µg) one time daily (n=30) or matching placebo (n=30) for 52 weeks. The primary end point was change in LV mass index over 52 weeks, which was measured by cardiac magnetic resonance imaging. Secondary end points included changes in LV volume, echocardiographic measures of systolic and diastolic function, biochemical parameters of mineral bone disease, and measures of renal function. Change in LV mass index did not differ significantly between groups (median [interquartile range], -2.59 [-6.13 to 0.32] g/m^2 with paricalcitol versus -4.85 [-9.89 to 1.10] g/m^2 with placebo). Changes in LV volume, ejection fraction, tissue Doppler-derived measures of early diastolic and systolic mitral annular velocities, and ratio of early mitral inflow velocity to early diastolic mitral annular velocity did not differ between the groups. However, paricalcitol treatment significantly reduced intact parathyroid hormone (P<0.001) and alkaline phosphatase (P=0.001) levels as well as the number of cardiovascular-related hospitalizations compared with placebo**. In conclusion, 52 weeks of treatment with oral paricalcitol (1 µg one time daily) significantly improved secondary hyperparathyroidism but did not alter measures of LV structure and function in patients with severe CKD.**

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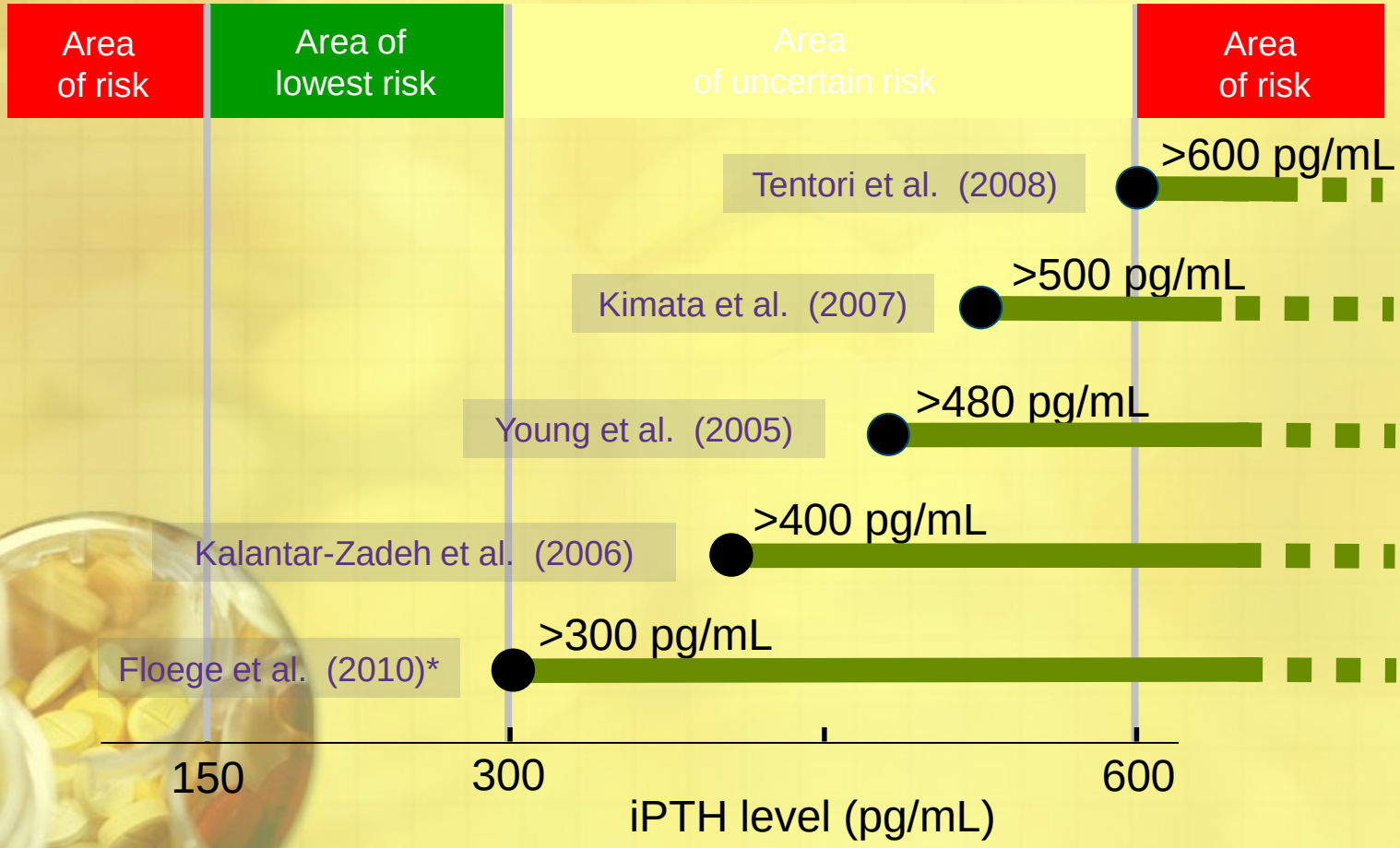
Johann Wolfgang von Goethe

Definition of extreme ranges of risk on the basis of observational data



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

* Has not been reviewed by the KDIGO group as full publication is pending