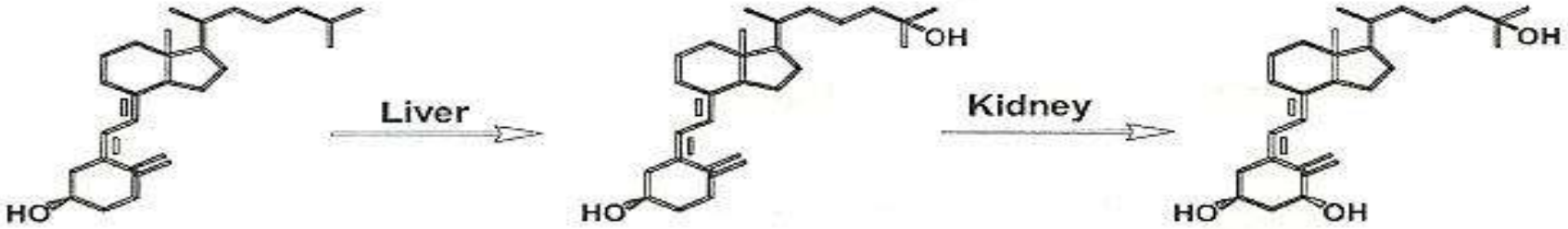
Chronic Kidney Disease- Mineral Bone Disease

KDIGO 2017 , CKD-MBD.

Ioannis Griveas, MD, PhD

athens-NEPHROLOGY

Liver and Kidney Functions Are Essential for Vitamin D Precursor Activation to Calcitriol



Vitamin D_3
Cholecalciferol

25-Hydroxyvitamin D

25(OH)D
(Calcidiol)

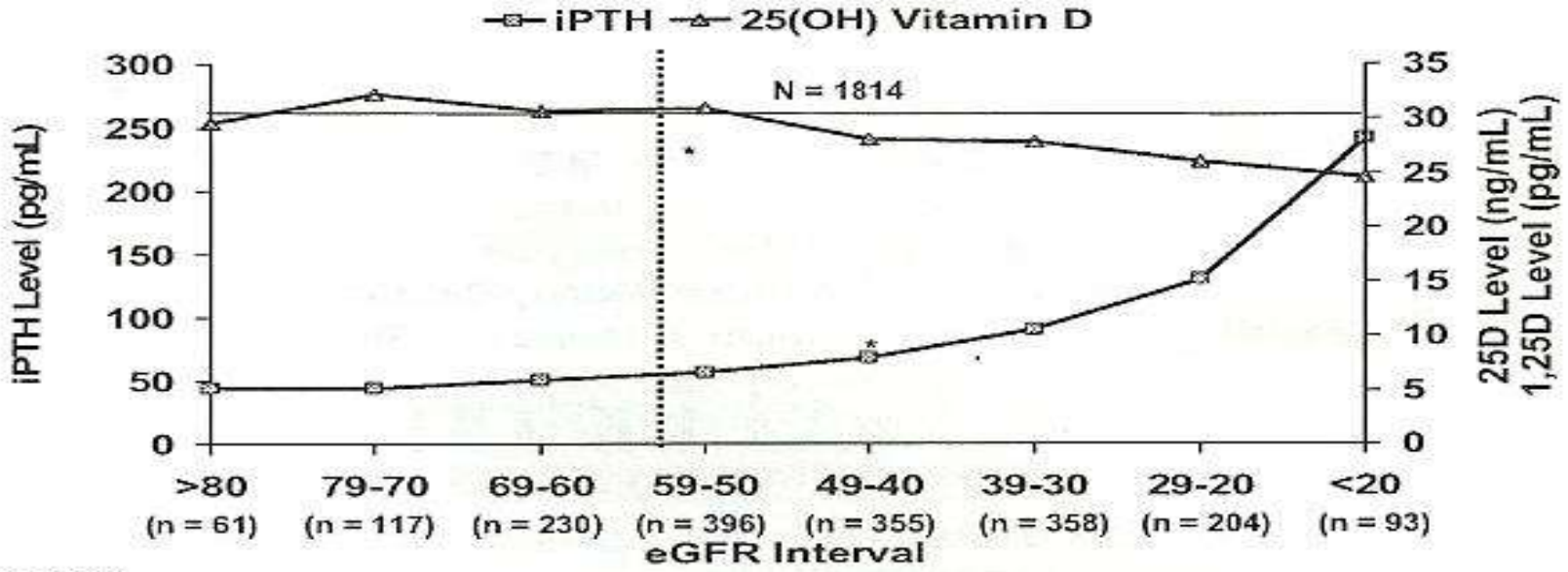
1,25-Dihydroxyvitamin D_3

1,25 $(OH)_2D_3$,
Calcitriol
(Active Vitamin D)

$25(OH)D_{(2+3)}$ < 30 ng/ml is insufficient
< 15 ng/ml is deficient
< 5 ng/ml is severely deficient

Brown et al. *Am J Physiol.* 1999;277:F157-F175.

Mean Values of iPTH, $1,25(OH)_2D_3$, and $25(OH)_2D_3$ by eGFR



*$P<0.001$.

Bakris et al. Poster presented at: American Society of Nephrology Renal Week 2005; November 8-13, 2005; Philadelphia, PA. Abstract F-PO732.

2009 KDIGO

- Work Group acknowledged the lack of high-quality evidence on which to base recommendations.
- Multiple randomized controlled trials (RCTs) and prospective cohort studies.
- KDIGO recognizes the need to reexamine the currency of its guidelines.

Controversies Conference 2013
"CKD-MBD: Back to the Future

A total of
12 recommendations were identified for revision.

2017 Update

- 2017 Update3 followed a rigorous process of evidence review and appraisal, based on systematic reviews of results from clinical trials.
- GRADE

Where appropriate, the Work Group issued "not graded"recommendations, based on general advice, that were not part of a systematic evidence review.

KDIGO 2017 Guideline Update Contributors

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Table 4| GRADE system for grading quality of evidence for an outcome

Step 1: starting grade for quality of evidence based on study design	Step 2: reduce grade	Step 3: raise grade	Final grade for quality of evidence for an outcome[a]
High for randomized controlled trials	Study quality –1 level if serious limitations	Strength of association +1 level is strong,[b] no plausible	High
Moderate for quasi-randomized trial	–2 levels in very serious limitations	confounders, consistent and direct evidence	Moderate
Low for observational study	Consistency –1 level if important inconsistency	+2 levels if very strong,[c] no major threats to validity and direct evidence	Low
Very low for any other evidence	Directness –1 level if some uncertainty –2 levels if major uncertainty	Other +1 level if evidence of a dose-response gradient +1 level if all residual confounders would have reduced the observed effect	Very low
	Other –1 level if sparse or imprecise data –1 level if high probability of reporting bias		

GRADE, grading of recommendations assessment, development, and evaluation; RR, relative risk.
[a]The highest possible grade is "high" and the lowest possible grade is "very low."
[b]Strong evidence of association is defined as "significant RR of > 2 (< 0.5)" based on consistent evidence from two or more observational studies, with no plausible confounders.
[c]Very strong evidence of association is defined as "significant RR of > 5 (< 0.2)" based on direct evidence with no major threats to validity.
Modified with permission from Uhlig K, Macleod A, Craig J, et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2006;70:2058–2065.[171]

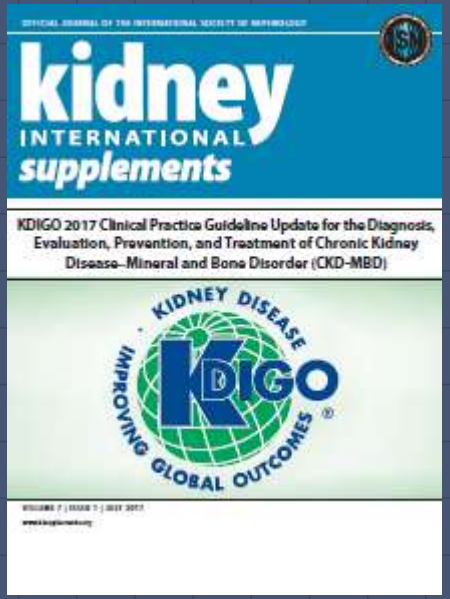


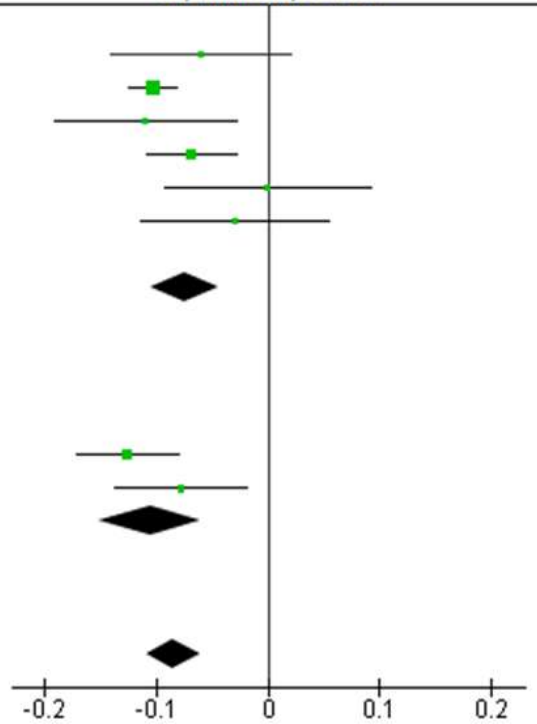
Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
3.2.1. In patients with CKD G3a–G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest BMD testing to assess fracture risk if results will impact treatment decisions (*2B*).	3.2.2. In patients with CKD G3a–G5D 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*).	Multiple new prospective studies have documented that lower DXA BMD predicts incident fractures in patients with CKD G3a–G5D. The order of these first 2 recommendations was changed because a DXA BMD result might impact the decision to perform a bone biopsy.
3.2.2. In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions (*Not Graded*).	3.2.1. In patients with CKD G3a–G5D, 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)*.	The primary motivation for this revision was the growing experience with osteoporosis medications in patients with CKD, low BMD, and a high risk of fracture. The inability to perform a bone biopsy may not justify withholding antiresorptive therapy from patients at high risk of fracture.

Meta-Analysis

DEXA-determined femoral BMD

Study or Subgroup	Fracture Group Mean	SD	Total	Non-Fracture Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Dialysis Patients								
Ambrus 2011	0.66	0.18	21	0.72	0.14	109	7.0%	-0.06 [-0.14, 0.02]
Cejka 2011	0.573	0.048	24	0.6764	0.037	50	28.3%	-0.10 [-0.13, -0.08]
Fontaine 1999	0.62	0.13	11	0.73	0.12	77	7.0%	-0.11 [-0.19, -0.03]
Iimori 2012	0.567	0.133	46	0.636	0.141	416	17.9%	-0.07 [-0.11, -0.03]
Jamal 2002	1.3	0.23	54	1.3	0.25	50	5.7%	0.00 [-0.09, 0.09]
Jamal 2006	0.76	0.17	27	0.79	0.14	25	6.6%	-0.03 [-0.11, 0.05]
Urena 2003	0	0	21	0	0	49		Not estimable
Subtotal (95% CI)			**204**			**776**	**72.5%**	**-0.07 [-0.11, -0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 8.78, df = 5 (P = 0.12); I² = 43%								
Test for overall effect: Z = 4.81 (P < 0.00001)								
1.2.2 Non-dialysis patients								
Nickolas 2010	0.621	0.0718	23	0.747	0.134	59	16.0%	-0.13 [-0.17, -0.08]
Nickolas 2011	0.677	0.127	32	0.755	0.154	59	11.4%	-0.08 [-0.14, -0.02]
Subtotal (95% CI)			**55**			**118**	**27.5%**	**-0.11 [-0.15, -0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 1 (P = 0.21); I² = 38%								
Test for overall effect: Z = 4.47 (P < 0.00001)								
Total (95% CI)			**259**			**894**	**100.**	**[-0.11, -0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 11.33, df = 7 (P = 0.12); I² = 38%								
Test for overall effect: Z = 6.91 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.5%								



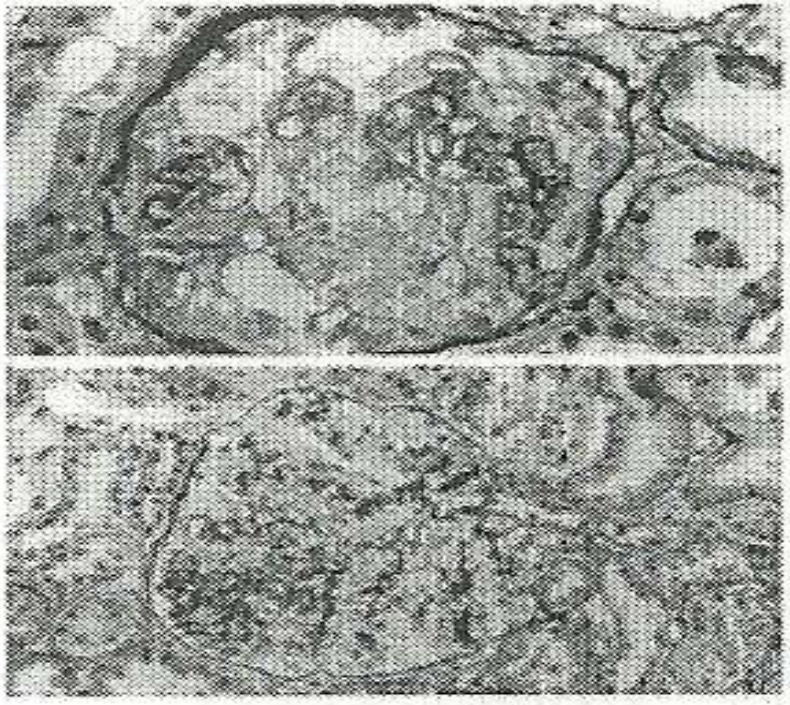
Reduced Bone Density in CKD Stages 2-4

Bone Mineral Density Measurements by DEXA			
Group	Mean GFR (mL/min/1.73 m^2)	Spine (g/cm^2)	Femur (g/cm^2)
1	83	1.00	0.80
2	58	1.00	0.74*
3	39	0.98	0.72*
4	16	0.93*	0.68*

Bone Mass Falls as CKD progresses

Rix et al. *Kidney Int.* 1999;56:1084-1093.

Segmental Sclerosis After Pamidronate



Desikan et al. British Journal of Haematology, 2002, 119, 496–499

Pamidronate Associated Nephrotic Syndrome with Segmental Glomerulosclerosis

- Five patients with Multiple Myeloma
- Prescribed pamidronate to delay osteolytic lesions
- Each received greater than the recommended monthly dose (>90 mg/monthly) (either 180 mg/month or 90 mg/2 weeks)
- All exhibited nephrotic proteinuria (range 3–24 g/day).
- Dose reduction or discontinuation
  - Resolution in NS in 3
  - Reduction in proteinuria to 4 g/day from a peak of 24 g/day in one patient
  - One required haemodialysis
- One patient continued to have elevated creatinine
- Renal biopsies obtained in two patients revealed focal segmental glomerulosclerosis

Desikan British Journal of Haematology, 2002, 119, 496–499

Podocyte Injury May Mediate Pamidronate Nephrotoxicity

- Nitrogen-containing bisphosphonates (pamidronate, ibandronate, zoledronate) differ in the mode of action and toxicities from earlier bisphosphonates, as they cause apoptosis of osteoclasts (van Beek et al, 1999; Bergstrom et al, 2000; Coxon et al, 2000).
- This same process may be responsible for the podocyte abnormalities observed in pamidronate nephrotoxicity (Markowitz et al, 2001).
- The dose effect is critical; increased pamidronate dose has been associated with non-linear excretion, increased accumulation in kidneys and proximal tubular damage in animal models (Cal & Daley-Yates, 1999).

Desikan et al. British Journal of Haematology, 2002, 119, 496–499

Report of Increased Incidence of Renal Failure Following Zoledronic Acid

Renal Failure with the Use of Zoledronic Acid

To the editor: Zoledronic acid (Zometa, Novartis Pharmaceuticals) is a potent bisphosphonate that inhibits bone resorption. In trials of treatment for bone metastases, 9 to 15 percent of the patients who received 4 mg of zoledronic acid over a 15-minute period had renal deterioration, defined by elevations in the serum creatinine level.[1-3] With marketed use of the drug, renal deterioration progressing to renal failure and dialysis has been reported. Although the causes of renal deterioration are multifactorial, acute tubular necrosis has been described as a potential mechanism associated with zoledronic acid.[3]

We identified 73 cases in the Food and Drug Administration (FDA) Adverse Event Reporting System from August 2001 to March 2003 in which physicians reported renal failure associated with zoledronic acid (Table 1). Our case series consisted of a heterogeneous group of patients, including 42 patients with multiple myeloma, 22 with solid tumors, 2 with benign conditions, and 6 with unknown diagnoses. The demographic characteristics and outcomes were similar for patients with and those without multiple myeloma. Treatment details, including hydration status, were not uniform-

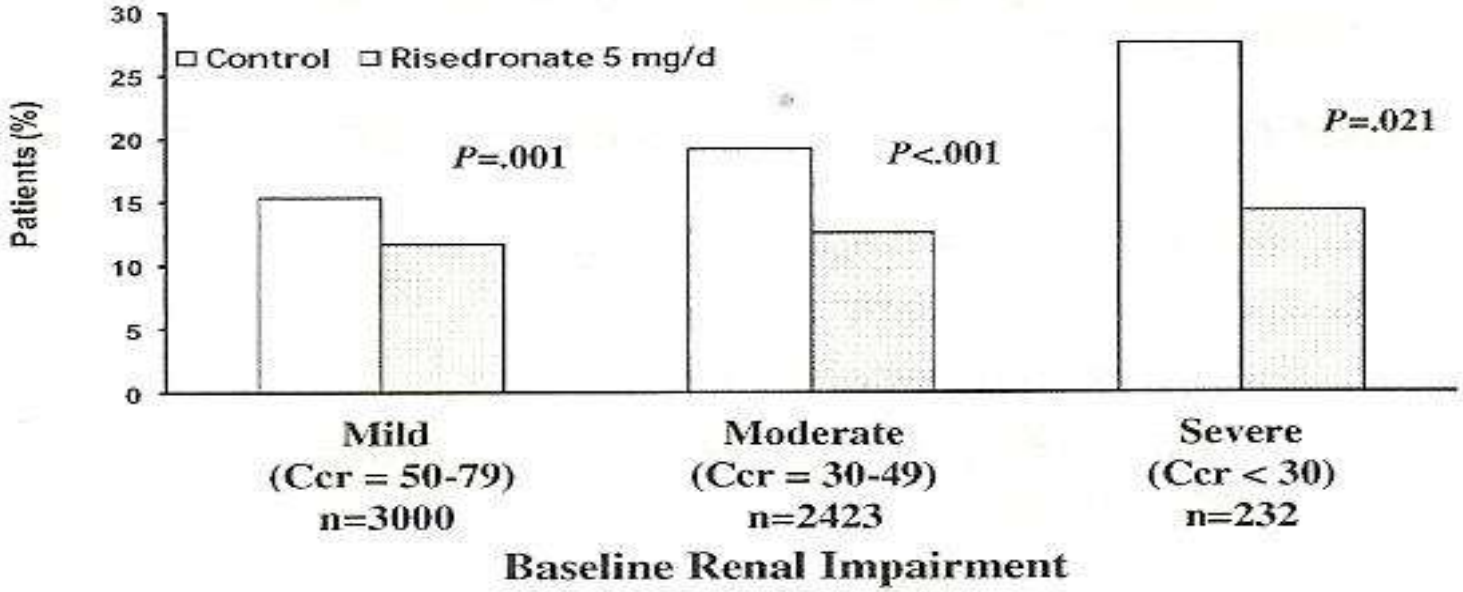
"Because of the serious nature of these events, health care professionals should monitor renal function before each dose of zoledronic acid is administered, provide adequate hydration, and discontinue treatment if renal function deteriorates."

et al. NEJM, 349: 1677, 2003

Summary of Bisophosphonates

- Bisphosphonates appear to cause renal injury, including
  - Nephrotic Syndrome with Focal Segmental Glomerulosclerosis
  - Acute Tubular Necrosis
- The risks appear to be higher with nitrogen containing bisphosphonates (ibandronate, pamidronate, zoledronate)
- The risks appear related to the individual and cumulative dose exposure
- The renal injury usually resolves upon drug cessation

Vertebral Fracture Risk Reduction With Risedronate



n=Patients with evaluable paired spinal radiographs.

Miller et al., J Bone Miner Res 2005;20:2105–2115

Bone Disease in CKD Stage 3 and 4 Bisphosphonates

- Contraindicated when GFR < ~30 ml/min
- May be efficacious in CKD Stage 3/4 patients but long term risks are unclear
- These drugs treat osteoporosis (adynamic - low bone turnover)
- These drugs further reduce bone resorption
- May further reduce the calcium and phosphorus buffering capacity of bone in CKD patients

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
4.1.1. In patients with CKD G3a–G5D, treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together (*Not Graded*).		This new recommendation was provided in order to emphasize the complexity and interaction of CKD-MBD laboratory parameters.
4.1.2. In patients with CKD G3a–G5D, we suggest lowering elevated phosphate levels toward the normal range (*2C*).	4.1.1. In patients with CKD G3a–G5, we suggest maintaining serum phosphate in the normal range (*2C*). In patients with CKD G5D, we suggest lowering elevated phosphate levels toward the normal range (*2C*).	There is an absence of data supporting that efforts to maintain phosphate in the normal range are of benefit to CKD G3a–G4 patients, including some safety concerns. Treatment should be aimed at overt hyperphosphatemia.

Vitamin D in CKD: Stages 3 and 4

- Measure serum 25-hydroxyvitamin D in patients with ↑ PTH

PTH target Stage 3 CKD 35 to 70 pg/ml

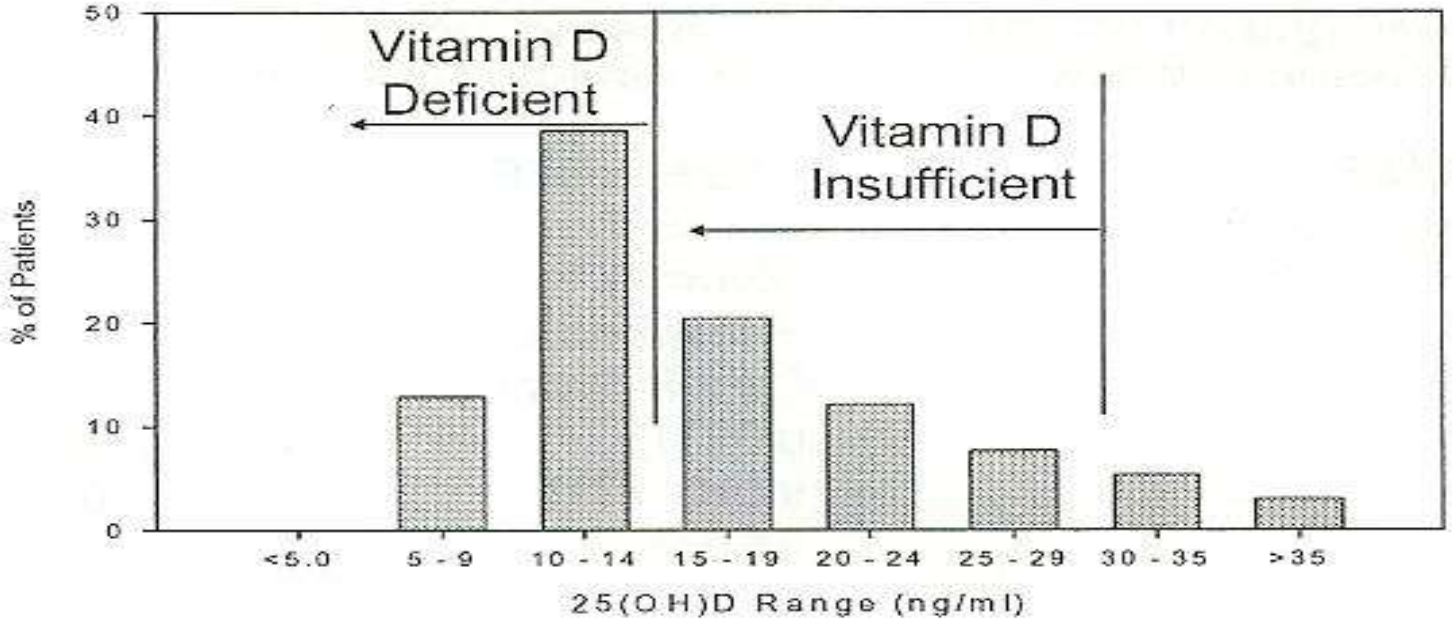
Stage 4 CKD 70 to 110 pg/ml

- If 25(OH)D is normal, repeat annually

Level		Treatment with Vitamin D_2 (Ergocalciferol 50,000 IU)
<5 ng/mL	**Severe Deficiency**	**50,000 IU/wk x 12, then q mo x 6**
5-15 ng/mL	**Deficiency**	**50,000 IU/wk x 4, then q mo x 6**
16-30 ng/mL	**Insufficiency**	**50,000 IU/mo x 6**

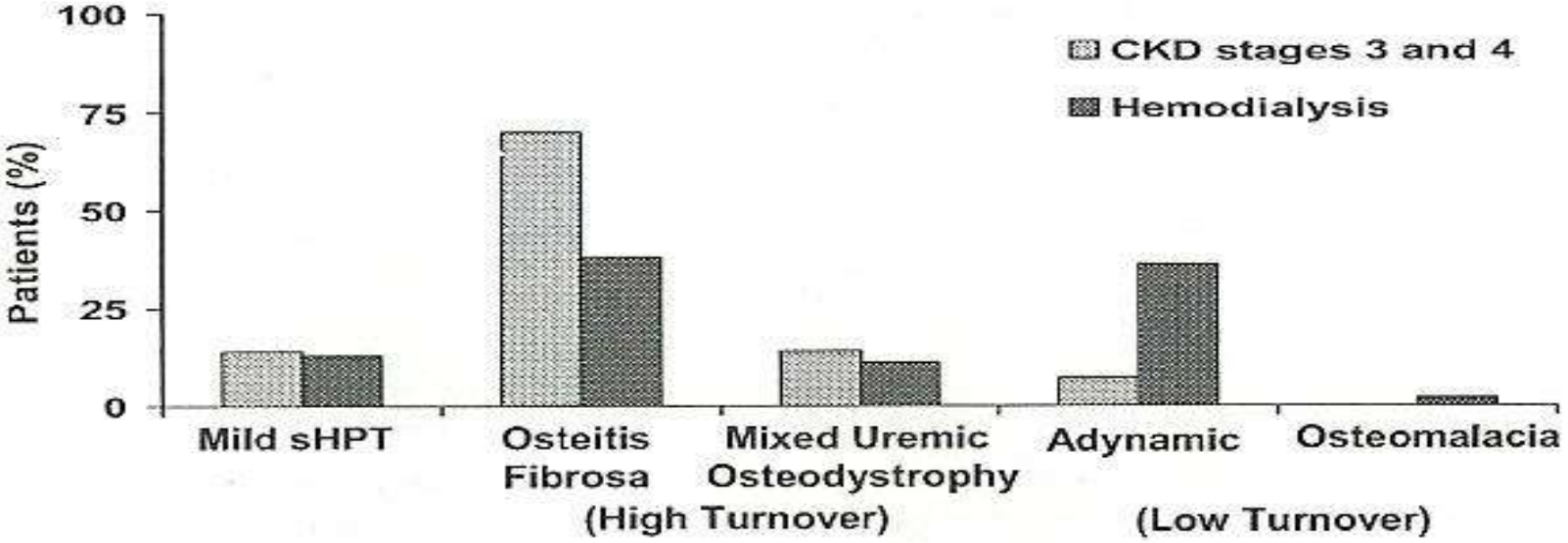
K/DOQI Guidelines for Bone Metabolism and Disease. NKF. *Am J Kidney Dis.* 2003;42(4 suppl 3):1-201.

Vitamin D Levels are Low in Most Dialysis Patients
Distribution of Baseline 25(OH)D Levels
n = 132



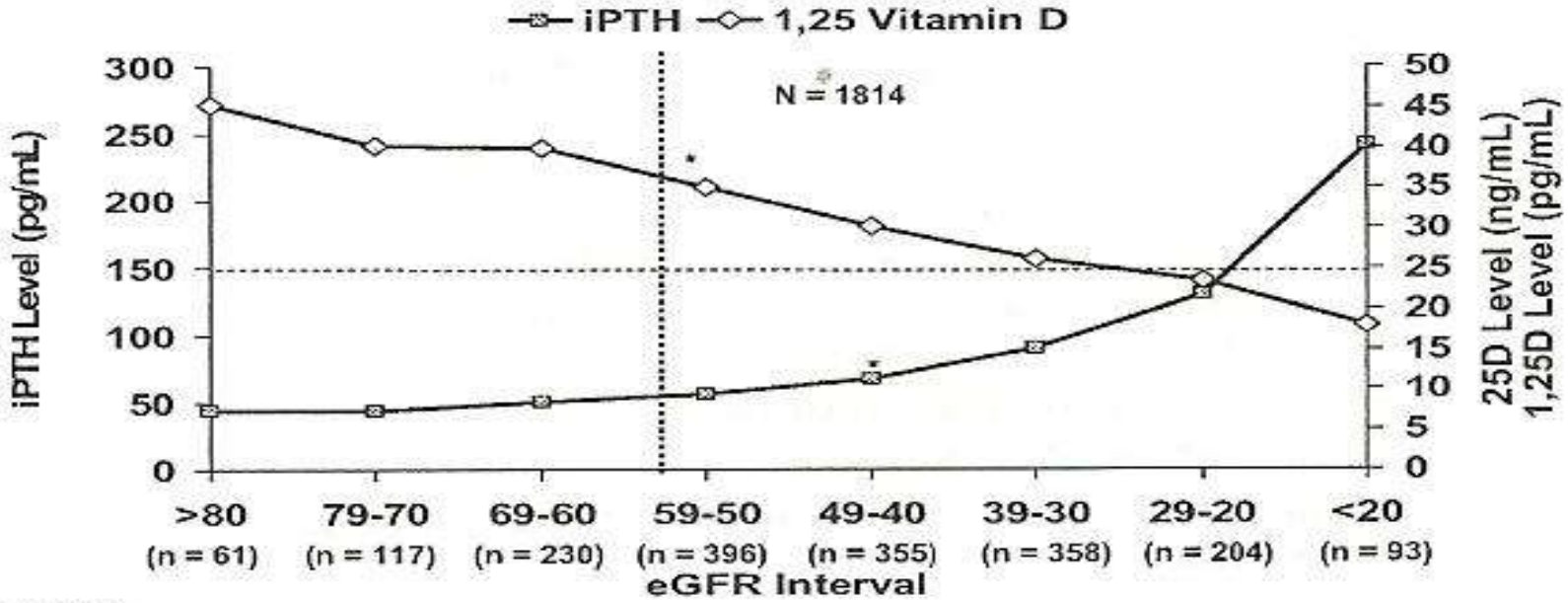
Saab, et al. Nephron Clin Pract 2007

Evidence of High-Turnover Metabolic Bone Disease in CKD



Coen et al. *Nephron.* 2002;91:103-111. (N = 117); Hamdy et al. *BMJ.* 1995;310:358-363;
Ho et al. *Semin Nephrol.* 2002;22:488-493. (N = 27); Wang et al. *Am J Kidney Dis.* 1995;26:836-844. (N = 175).

Mean Values of iPTH, $1,25(OH)_2D_3$, and $25(OH)_2D_3$ by eGFR



*$P<0.001$.

Bakris et al. Poster presented at: American Society of Nephrology Renal Week 2005; November 8-13, 2005; Philadelphia, PA. Abstract F-PO732.

Assessment. The previous Recommendation 4.1.1 from the 2009 KDIGO CKD-MBD Guideline[1] provided guidance regarding treatment based on serum phosphate levels in different glomerular filtration rate (GFR) categories of CKD.

2009

The Work Group considered it reasonable to take the context of therapeutic interventions into account when assessing values of phosphate, calcium, and PTH. Further, it is

2017

biochemical parameters. Based on these assumptions, the Work Group also decided to split the previous 2009 Recommendation 4.1.1 into 2 new Recommendations: 4.1.1 (diagnostic recommendation based on accumulated observational evidence) and 4.1.2 (therapeutic recommendation based mostly on RCTs).

PTH Target and Goals of Therapy

- The real goal of treating SHPT is to maintain relatively normal bone turnover
- Low bone turnover is associated with the greatest risk of hypercalcemia, vascular calcification, and death
- The target PTH range is a general area where many patients have relatively normal bone turnover
  - Individuals may be above or below target and have normal bone turnover
  - Individuals may be below, within, or even above target and have LOW bone turnover
- Other indicators of high bone turnover are high alkaline phosphatase and high bone-specific alkaline phosphatase
- It is generally considered better to have somewhat high bone turnover than low bone turnover

Bone Disease in CKD

- Osteitis Fibrosa
  - PTH mediated high bone turnover
  - TREAT by suppressing PTH
- Adynamic Bone
  - Low bone turnover
  - Pathologically the same as osteoporosis
  - Usually due to low PTH
  - TREAT by:
    - avoid Calcium binders
    - Avoid Active Vitamin D and calcimimetics
    - Use low Calcium bath
- Osteomalacia
  - Low bone turnover with large amounts of unmineralized osteoid
  - Usually due to Vitamin D deficiency
  - In past seen commonly due to Aluminum
  - Suspect in dialysis patients with low bone mass and frequent fractures
  - TREAT with Ergocalciferol or Cholecalciferol with or without Active Vitamin D

Bone Disease in CKD

- Osteomalacia
  - Low bone turnover with large amounts of unmineralized osteoid
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  - TREAT with Ergocalciferol or Cholecalciferol with or without Active Vitamin D

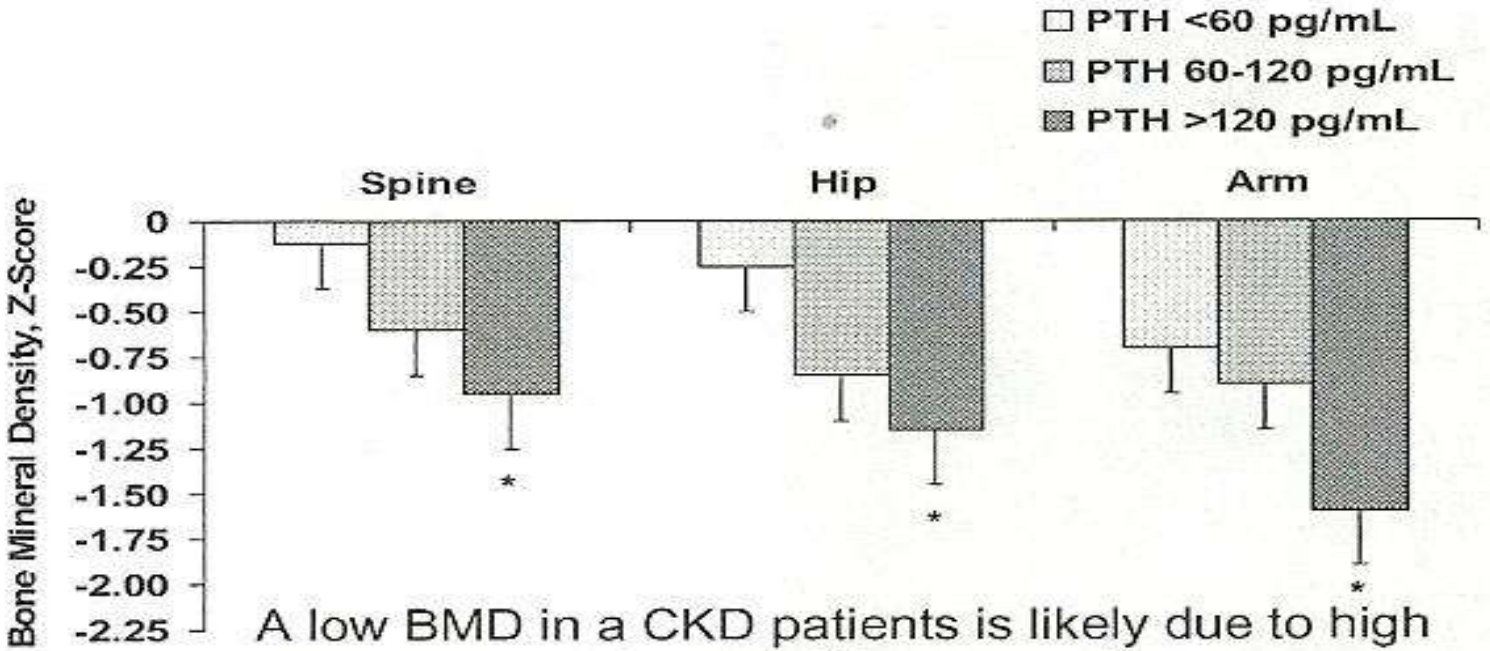
Indications for Bone Biopsy in CKD and other Tests

- BONE BIOPSY INDICATIONS
- Fractures with minimal or no trauma
- iPTH 100 – to 500 pg/ml and unexplained hypercalcemia, severe bone pain or increased bone alkaline phosphatase
- Suspected aluminum bone disease based on symptoms or aluminum exposure

- Bone Mineral Density (DEXA) should be measured in pts. with fractures or risk factors for osteoporosis
- Bone Radiographs are not routinely indicated, but can demonstrate vascular calcification or β2-microglobulin amyloidosis

NKF K/DOQI Bone Guidelines 2003

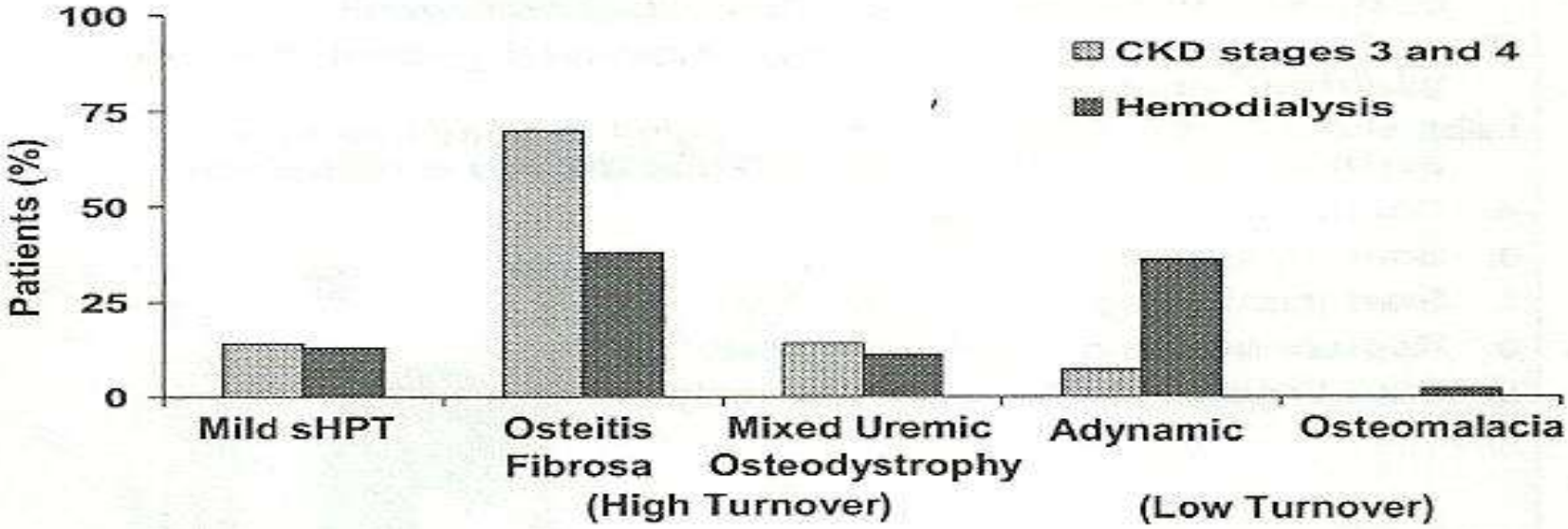
Relationship of PTH to Bone Loss in CKD Stages 2-4



A low BMD in a CKD patients is likely due to high PTH-mediated Osteitis Fibrosa, not Osteoporosis

Rix et al. *Kidney Int.* 1999;56:1084-1093.

Evidence of High-Turnover Metabolic Bone Disease in CKD



Coen et al. *Nephron.* 2002;91:103-111. (N = 117); Hamdy et al. *BMJ.* 1995;310:358-363;
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2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
4.1.2. In patients with CKD G3a–G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).	4.1.1. In patients with CKD G3a–G5, we suggest maintaining serum phosphate in the normal range (2C). In patients with CKD G5D, we suggest lowering elevated phosphate levels toward the normal range (2C).	There is an absence of data supporting that efforts to maintain phosphate in the normal range are of benefit to CKD G3a–G4 patients, including some safety concerns. Treatment should be aimed at overt hyperphosphatemia.

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
4.1.5. In patients with CKD G3a–G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate (*Not Graded*).	4.1.4. In patients with CKD G3a–G5 (*2D*) and G5D (*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*).	Emphasizes the perception that early "preventive" phosphate-lowering treatment is currently not supported by data (see Recommendation 4.1.2). The broader term "phosphate-lowering" treatment is used instead of phosphate-binding agents since all possible approaches (i.e., binders, diet, dialysis) can be effective.
4.1.6. In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binders (*2B*). In children with CKD G3a–G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (*Not Graded*).	4.1.5. In patients with CKD G3a–G5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (*1B*). In patients with CKD G3a–G5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (*2C*) and/or adynamic bone disease (*2C*) and/or if serum PTH levels are persistently low (*2C*).	New evidence from 3 RCTs supports a more general recommendation to restrict calcium-based phosphate binders in hyperphosphatemic patients across all severities of CKD.

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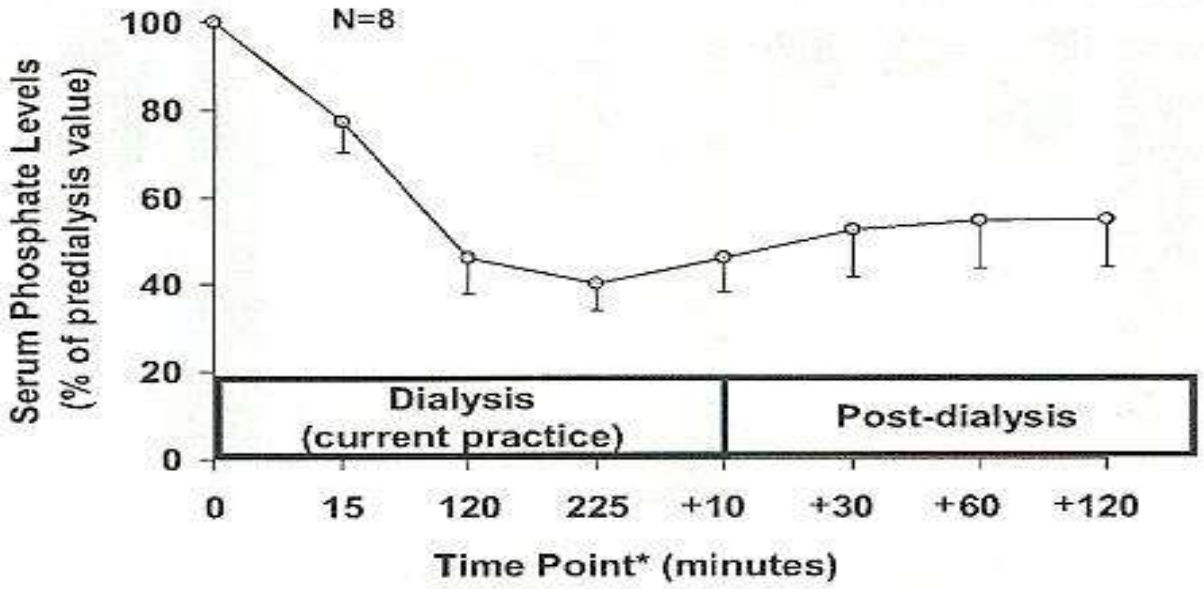
2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
4.1.8. In patients with CKD G3a–G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (*2D*). It is reasonable to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations (*Not Graded*).	4.1.7. In patients with CKD G3a–G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (*2D*).	New data on phosphate sources were deemed important to include as an additional qualifier to the previous recommendation.

the Work Group drew several conclusions: (i) the association between serum phosphate and clinical outcome is not monotonic; (ii) evidence is lacking to demonstrate the efficacy of phosphate binders for lowering serum phosphate in patients with CKD G3a to G4; (iii) the safety of phosphate binders in this population is unproven; and (iv) there is an absence of data showing that dietary phosphate restriction improves clinical outcomes.

Change in Serum Phosphorus during and after a Hemodialysis session



*X axis not drawn to scale.

Musci I et al. *Kidney Int.* 1998;53:1399-1404.
Mucsi I, Hercz G. *Nephrol Dial Transplant.* 1998;13:2457-2460.

Effects of Daily Hemodialysis on Mineral and Bone Metabolism

Review of published data on daily dialysis

- Studies with positive results
  - Serum Phosphorus
    - Decrease of 1.2 mmol/L
  - Phosphorus Binder Use
    - Decrease in P binder use of 38%
- Studies with non-significant trends or No effect
  - Serum Phosphorus
    - 2 trend toward decreased P
    - 4 with no change
  - Phosphorus Binder Use
    - 1 decrease use; 3 no change
- Bone Disease: 1 study with trend of less Adynamic Bone

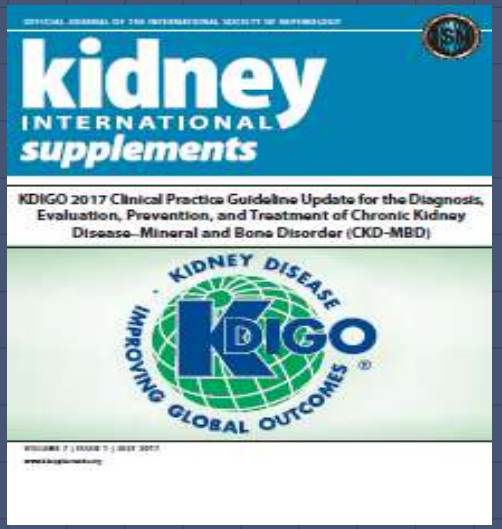
Suri RS et al, Clin J Amer Soc Nephrol 1: 33-42, 2006

Effect of Time and Nocturnal Dialysis on Phosphorus Control

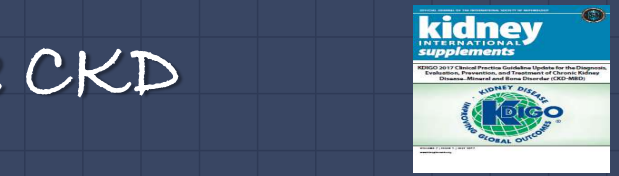
- 9 stable HD patients in random fashion received HD 4h 3x/week or 5h 3x/week (Qb adjusted to keep Kt/V stable)[1]
- Weekly phosphate removal
  - 3,007 +/- 641 mg on 4h TIW
  - 3,400 +/- 647 mg on 5 hr; $P < 0.02$
  - = ~750 mg/hr in 1st 4 hrs, then 400 mg in last hour
- 8 stable HD patients on 5 months 3x/week HD then 5 months of 6x/week Nocturnal HD
  - cumulative weekly phosphate removal was significantly higher with NHD (161.6 +/- 59.0 mumol/week) compared to CHD (75.8 +/- 22.5); $P < 0.01$)

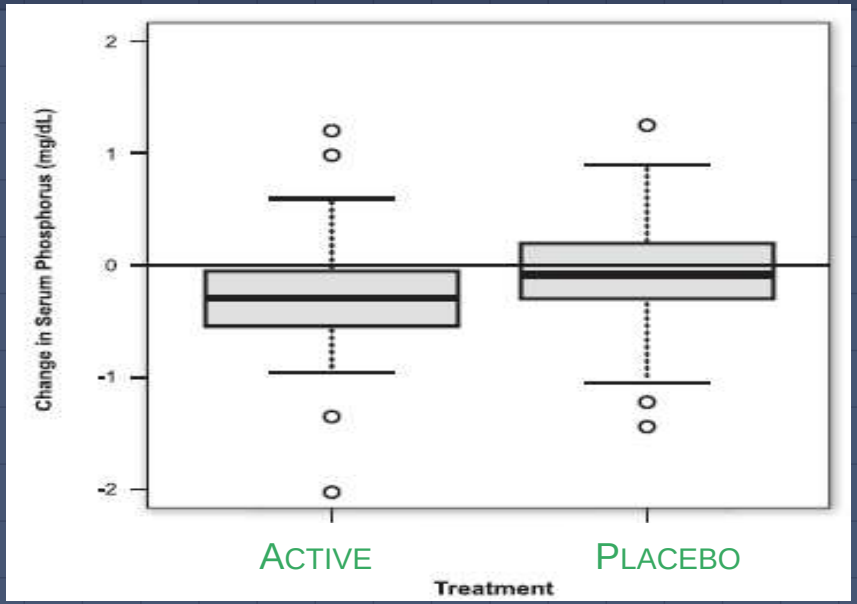
1. Vaithilingam I et al. Am J Kidney Dis 2004 Jan;43(1):85-9.

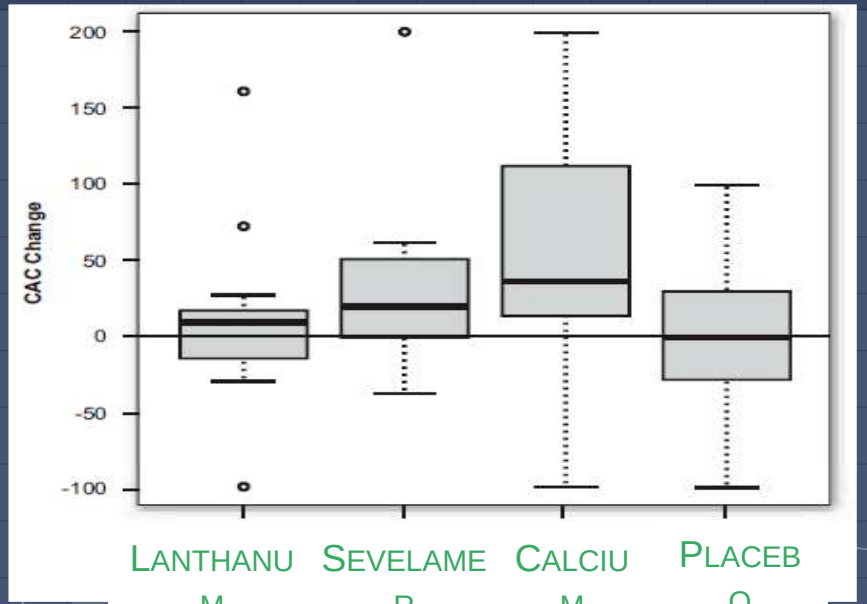
Consequently, the Work Group has abandoned the previous suggestion to maintain phosphate in the normal range, instead suggesting that treatment be focused on patients with hyperphosphatemia. The Work Group recognizes that preventing, rather than treating, hyperphosphatemia may be of value in patients with CKD G3a to G5D, but acknowledges that current data are inadequate to support the safety or efficacy of such an approach.



Phosphate Binders in Moderate CKD





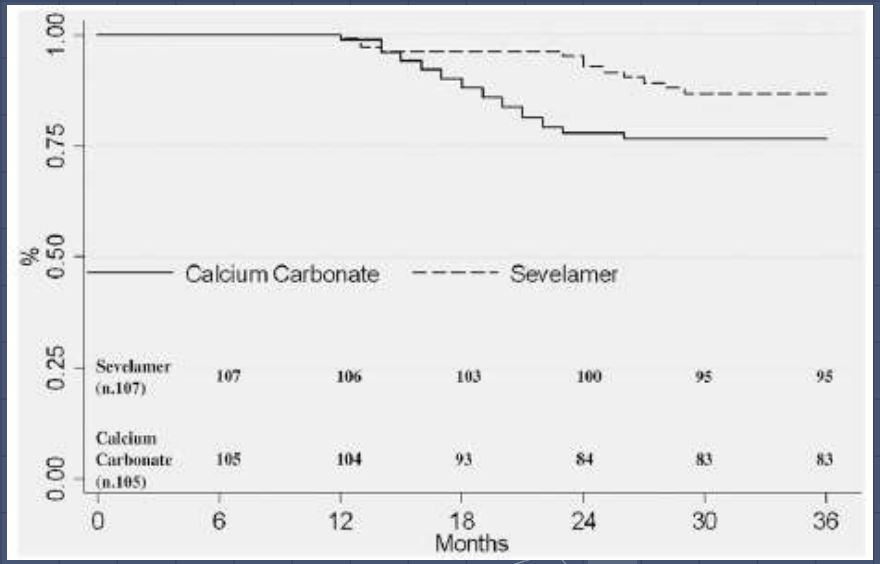


binding of essential nutrients). The Work Group also adopted the term "phosphate-lowering treatment" instead of "phosphate-binding agents," because all possible approaches (i.e., binders, diet, and dialysis) can be effective.

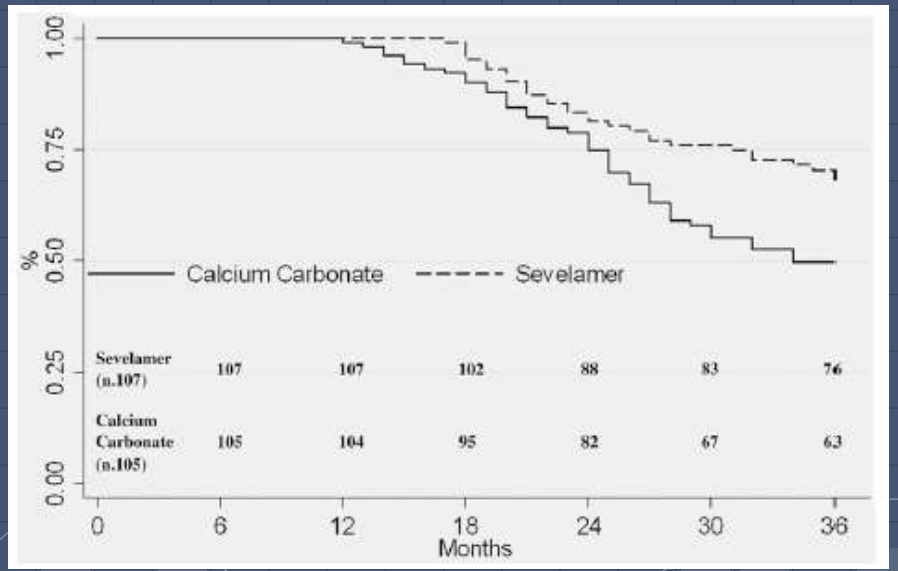
Block G et al. J Am Soc Nephrol. 2012;23:1407-1415

Phosphate Binders and Mortality

All-Cause Mortality



Dialysis Inception

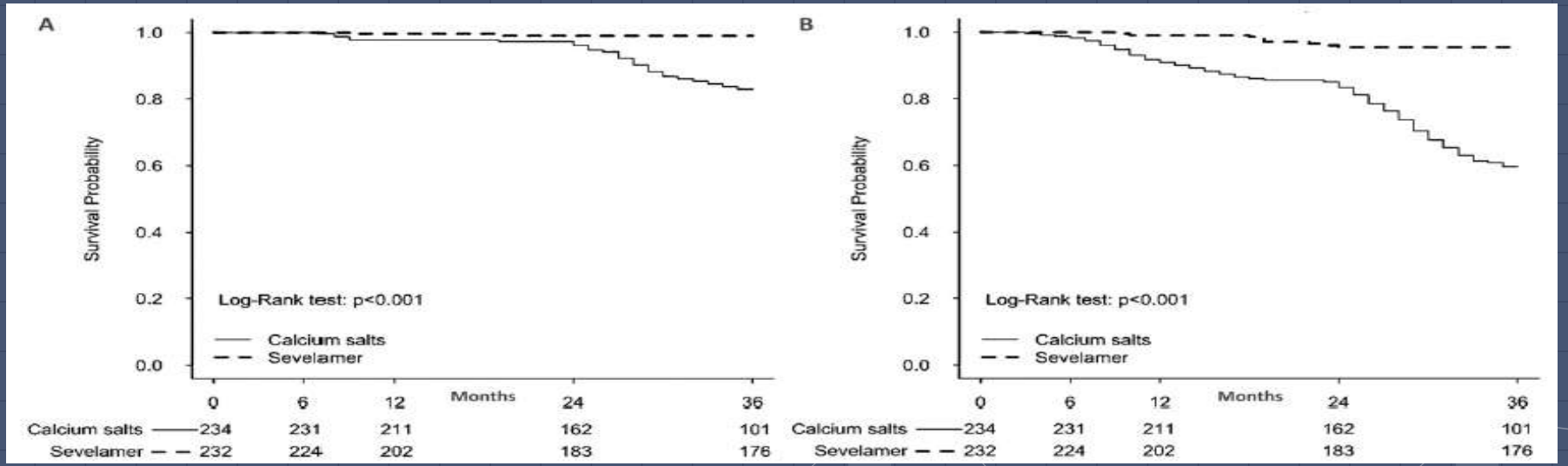


Di Iorio B et al. Clin J Am Soc Nephrol 2012;7:487-493

Sevelamer vs. Calcium

Arrythmias

Cardiovascular Mortality

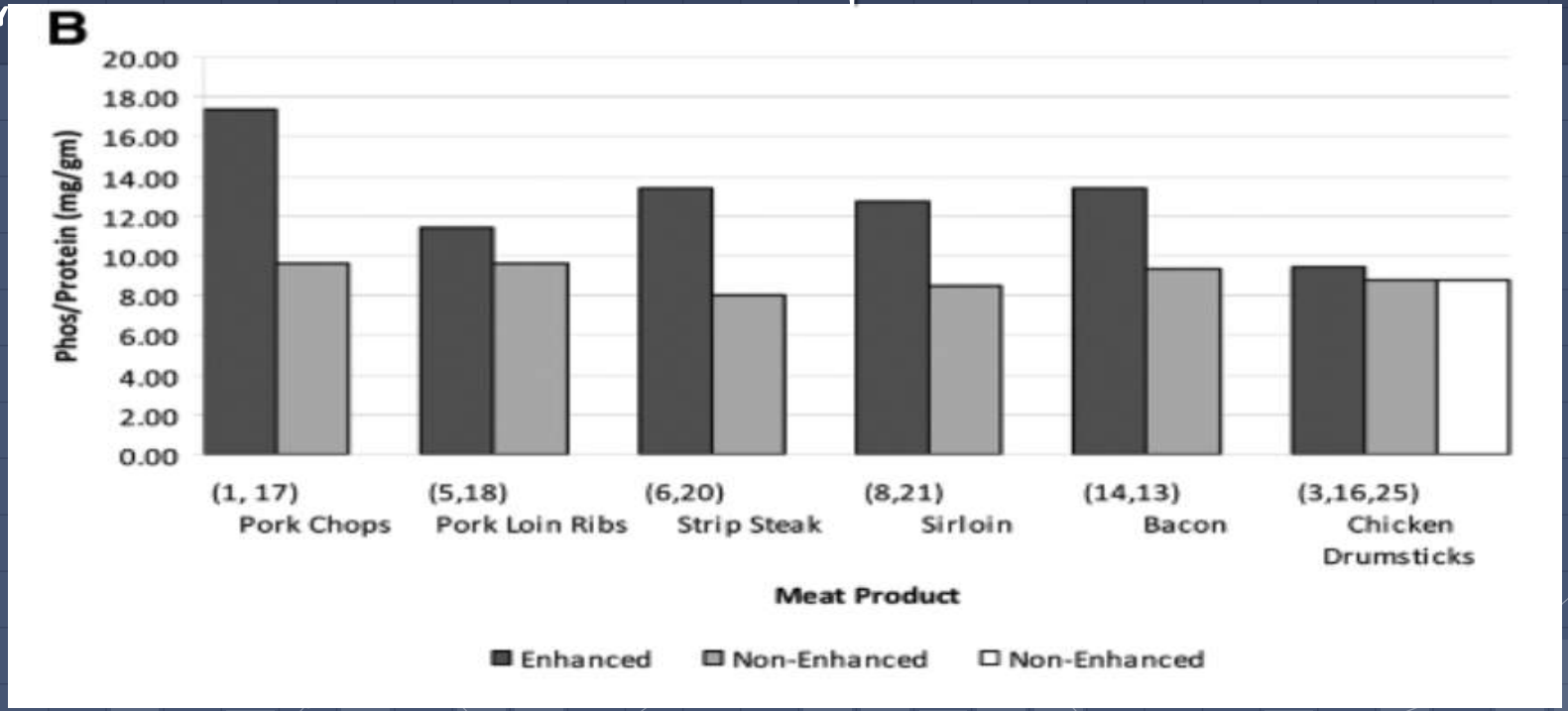


Di Iorio B et al. Am J Kidney Dis. 2013;62:771-778


Foods High in Phospl
Meat
Fast Food
Seeds
Milk
Canned Fish


Processed Food – Health Risks
Food processing removes some of the nutrients, vitamins and fiber present in the food
Processed foods are HIGHLY ADDICTIVE and make you crave them frequently.
Cheap artificial sugars, salt and preservatives in processed foods have less fibre quantity & don't add any nutrition benefits, it slows down digestion
Some processed dairy products, dried
contains Sulphite which causes a range
diseases like headache, skin rashes, im
syndrome etc.
The salts, phosphates and other artificial ingredients in the processed food leads to kidney and other health problems
Processed food kills natural tast
foods. In order to restore the
manufactures add cheap artificial s
colours and preserva
GASTROINTESTINAL problem
Problems, NERVOUS SYST
Frequent consumption of processed foods can lead to hormonal problems like menstrual irregularities, premenstrual syndrome, infertility, thyroid dysfunction etc
Frequent consumption of processe
lead to nervous system problem
depression, irritability and inability
concentrate.
CL

"Hidden" Phosphate



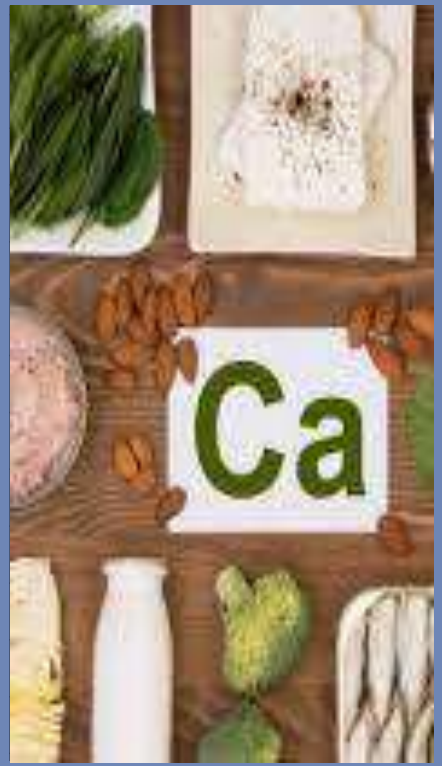
Sherman RA et al. Clin J Am Soc Nephrol. 2009;4:1370-1373

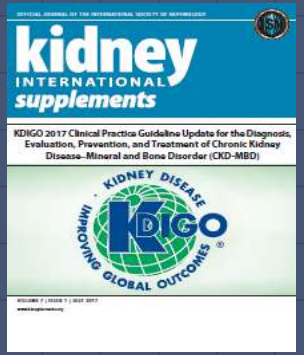
Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
4.1.3. In adult patients with CKD G3a–G5D, we suggest avoiding hypercalcemia (*2C*). In children with CKD G3a–G5D, we suggest maintaining serum calcium in the age-appropriate normal range (*2C*).	4.1.2. In patients with CKD G3a–G5D, we suggest maintaining serum calcium in the normal range (*2D*).	Mild and asymptomatic hypocalcemia (e.g., in the context of calcimimetic treatment) can be tolerated in order to avoid inappropriate calcium loading in adults.
4.1.4. In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (*2C*).	4.1.3. In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (*2D*).	Additional studies of better quality are available; however, these do not allow for discrimination of benefits and harm between calcium dialysate concentrations of 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l). Hence, the wording is unchanged, but the evidence grade is upgraded from 2D to 2C.

Because mild and asymptomatic hypocalcemia may well be harmless, especially in the presence of calcimimetic therapy, the Work Group emphasized an individualized approach to the treatment of hypocalcemia, rather than recommending the correction of hypocalcemia for all patients. However, significant or symptomatic hypocalcemia should still be addressed.

The 2009 Guideline[1] considered that a dialysate calcium concentration of 1.25 mmol/l (2.5 mEq/l) would yield neutral calcium balance. Based on new evidence, the 2017 Work Group felt that this recommendation remains valid as written in 2009. However, because additional studies of better quality are now available, the evidence grade has been changed from 2D to 2C.

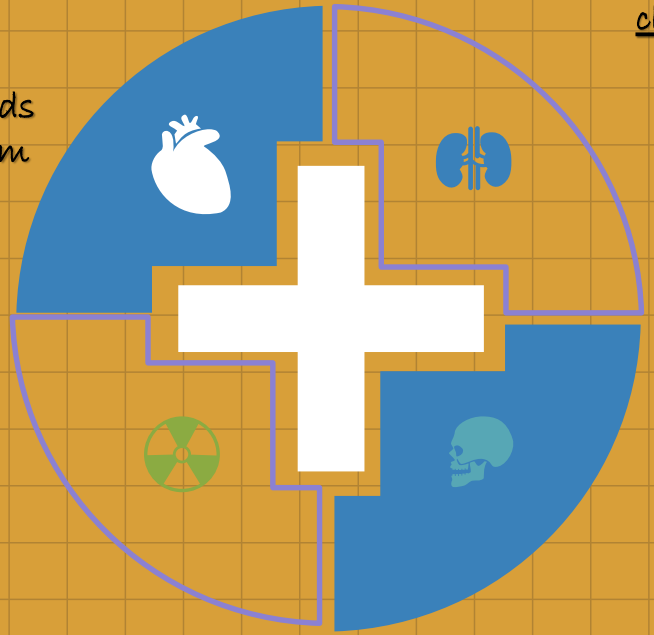




Secondary hyperparathyroidism (sHPT)

Attempt to control the disturbed calcium, phosphorus, and vitamin D metabolism. sHPT causes vascular and soft-tissue calcification and leads to disturbances of mineral metabolism CKD-related mineral and bone disorder (CKD-MBD).

<u>The indication for sHPT treatment results from these clinical consequences</u>

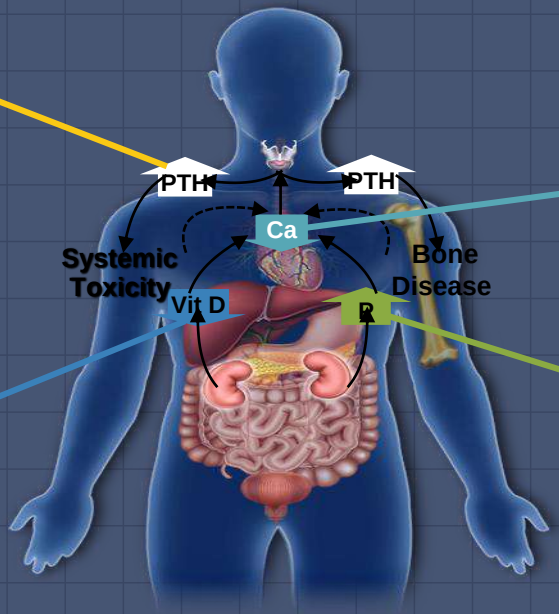


CKD-MBD abnormalities have also been implicated as risk factors for the very rare but devastating calcific and thrombotic arteriolopathy calciphylaxis and lead to reduced health-related quality of life (HRQoL).

sHPT-associated high FGF23 is independently associated with left ventricular hypertrophy, cardiovascular events and premature death.

Abnormalities in Metabolic Parameters Are Consequences of SHPT: Management of PTH, Ca, and P

Involved in homeostasis of bone metabolism
- Maintains correct
- balance of Ca and P
- in the body



Control Ca
- Control intake
- Adjust dialysate Ca
- Use Ca supplements or vitamin D therapy (if Ca low)

Increase Vitamin D Levels
- Administer vitamin D sterols to reduce PTH

Lower Elevated Serum P
- Control dietary intake
- Use phosphate binders

Treatment approaches to the management of SHPT include Ca x P, PTH, and vitamin D.

Use of vitamin D and phosphate binders alone provide no direct way to control PTH levels without the risk of raising Ca and P levels.

Ca = calcium; P = phosphate; PTH = parathyroid hormone; SHPT = secondary hyperparathyroidism.

Tomasello S. Diabetes Spectrum. 2008;21:19-25

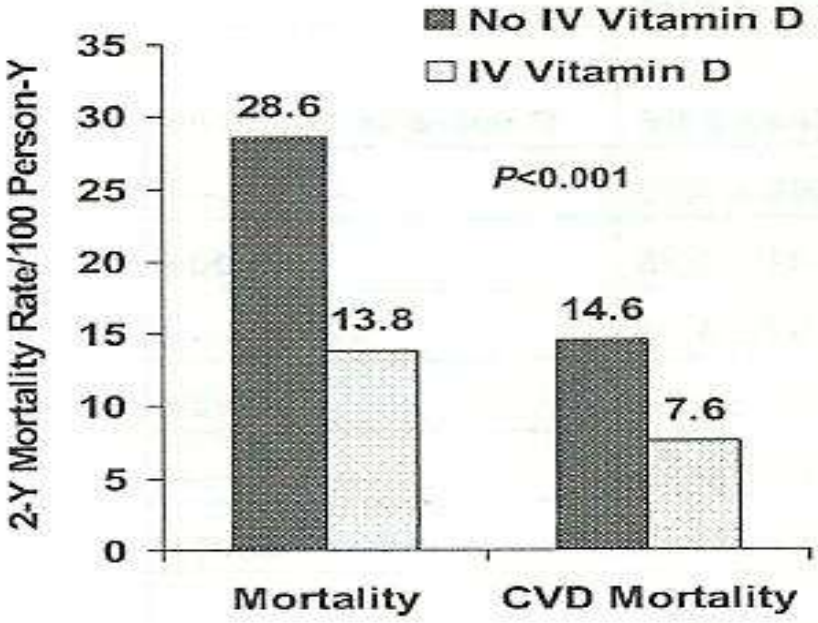
Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
4.2.1. In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (*2C*).	4.2.1. In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH 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*).	The Work Group felt that modest increases in PTH may represent an appropriate adaptive response to declining kidney function and has revised this statement to include "persistently" above the upper normal PTH level as well as "progressively rising" PTH levels, rather than "above the upper normal limit." That is, treatment should not be based on a single elevated value.

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
4.2.2. In adult patients with CKD G3a–G5 not on dialysis, we suggest that calcitriol and vitamin D analogs not be routinely used (*2C*). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (*Not Graded*). In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range (*Not Graded*).	4.2.2. In patients with CKD G3a–G5 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*).	Recent RCTs of vitamin D analogs failed to demonstrate improvements in clinically relevant outcomes but demonstrated increased risk of hypercalcemia.

IV VDRA Therapy and Reduced Mortality for Patients on Dialysis



Design

- Historical cohort study
- N = 37,173 patients who received IV vitamin D sterols
- N = 13,864 patients who received no IV vitamin D sterols

Results

- Adjusted 2-y survival advantage of 20% for IV vitamin D sterol use
- Benefit of IV vitamin D sterol use seen in 35 of 36 strata, even in patients with low iPTH and elevated Ca and P

Teng et al. *J Am Soc Nephrol.* 2005;16:1115-1125.

CLINICAL RESEARCH www.jasn.org

Effect of Paricalcitol on Left Ventricular Mass and Function in CKD—The OPERA Trial

Angela Yee-Moon Wang,* Fang Fang,† John Chan,‡ Yue-Yi Wen,† Shang Qing,† Iris Hiu-Shuen Chan,§ Gladys Lo,‡ Kar-Neng Lai,* Wai-Kei Lo,‖ Christopher Wai-Kei Lam,¶ and Cheuk-Man Yu†

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ABSTRACT

Vitamin D seems to protect against cardiovascular disease, but the reported effects of vitamin D on patie outcomes in CKD are controversial. We conducted a prospective, double blind, randomized, placeb controlled trial to determine whether oral activated vitamin D reduces left ventricular (LV) mass in patier with stages 3–5 CKD with LV hypertrophy. Subjects with echocardiographic criteria of LV hypertrop were randomly assigned to receive either oral paricalcitol (1 μg) one time daily (*n*=30) or matching placel (*n*=30) for 52 weeks. The primary end point was change in LV mass index over 52 weeks, which w measured by cardiac magnetic resonance imaging. Secondary end points included changes in LV volun echocardiographic measures of systolic and diastolic function, biochemical parameters of mineral bo disease, and measures of renal function. Change in LV mass index did not differ significantly betwe groups (median [interquartile range], −2.59 [−6.13 to 0.32] g/m² with paricalcitol versus −4.85 [−9.89 1.10] g/m² with placebo). Changes in LV volume, ejection fraction, tissue Doppler–derived measures early diastolic and systolic mitral annular velocities, and ratio of early mitral inflow velocity to early diasto mitral annular velocity did not differ between the groups. However, paricalcitol treatment significan reduced intact parathyroid hormone (P<0.001) and alkaline phosphatase (P=0.001) levels as well as t number of cardiovascular-related hospitalizations compared with placebo. In conclusion, 52 weeks treatment with oral paricalcitol (1 μg one time daily) significantly improved secondary hyperparathyroi ism but did not alter measures of LV structure and function in patients with severe CKD.

J Am Soc Nephrol 25: 175–184, 2014. doi: 10.1681/ASN.2012101003

Cardiovascular disease is a major cause of mortality in patients with CKD and has been attributed to a very high prevalence of left ventricular (LV) hypertrophy[1] as well as traditional Framingham and kidney disease–related risk factors.[2] Apart from playing a recognized role in suppressing secondary hyperparathyroidism, vitamin D has been suggested to play a protective role against cardiovascular disease and exert its effects on the heart and vascular walls through interaction with the vitamin D receptor.[3,4] Experimental studies showed associations between vitamin D deficiency and impairment of cardiac contractile function,[5] increased myocardial collagen content, and increased cardiac mass.[6,7] Similarly, targeted deletion of the vitam D receptor gene resulted in increased cardiomy cyte size and LV weight.[8] Treatment with activat vitamin D attenuated myocardial hypertrophy experimental models of cardiac hypertrophy[9] a

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ORIGINAL CONTRIBUTION

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

The PRIMO Randomized Controlled Trial

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Scott D. Solomon, MD

Context Vitamin D is associated with decreased cardiovascular-related morbidity and mortality, possibly by modifying cardiac structure and function, yet firm evidence for either remains lacking.

Objective To determine the effects of an active vitamin D compound, paricalcitol, on left ventricular mass over 48 weeks in patients with an estimated glomerular filtration rate of 15 to 60 mL/min/1.73 m².

Design, Setting, and Participants Multinational, double-blind, randomized placebo-controlled trial among 227 patients with chronic kidney disease, mild to moderate left ventricular hypertrophy, and preserved left ventricular ejection fraction, conducted in 11 countries from July 2008 through September 2010.

Intervention Participants were randomly assigned to receive oral paricalcitol, 2 μg/d (n=115), or matching placebo (n=112).

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/m²·⁷ [95% CI, −0.14 to 0.83 g/m²·⁷] vs placebo group, −0.07 g/m²·⁷ [95% CI, −0.55 to 0.42 g/m²·⁷]). 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.

Conclusion Forty-eight–week therapy with paricalcitol did not alter left ventricular mass index or improve certain measures of diastolic dysfunction in patients with chronic kidney disease.

Trial Registration clinicaltrials.gov Identifier: NCT00497146

JAMA. 2012;307(7):674-684 www.jama.com

ALTHOUGH PRIMARILY RECOMMENDED for improving bone health, treatment with vitamin D recently has been suggested for other conditions, including cardiovascular disease (CVD).[1-3] Multiple lines of evidence suggest a link between vitamin D and CVD, including experimental studies identifying vitamin D receptors in vascular smooth muscle, endothelial cells, and possibly cardiac tissue[1,4] and observational studies, small clinical trials, and meta-analyses suggesting that vitamin D therapy reduces cardiovascular events.[2,3] Convincing data demonstrating that vitamin D therapy improves cardiovascular health, however, are lacking.

Patients with chronic kidney disease (CKD) frequently develop deficiency of 1,25-dihydroxyvitamin D_3 (calcitriol) because of a lack of its precursor, 25-

For editorial comment see p 722.

Author Affiliations and a list of the PRIMO Investigators appear at the end of this article.
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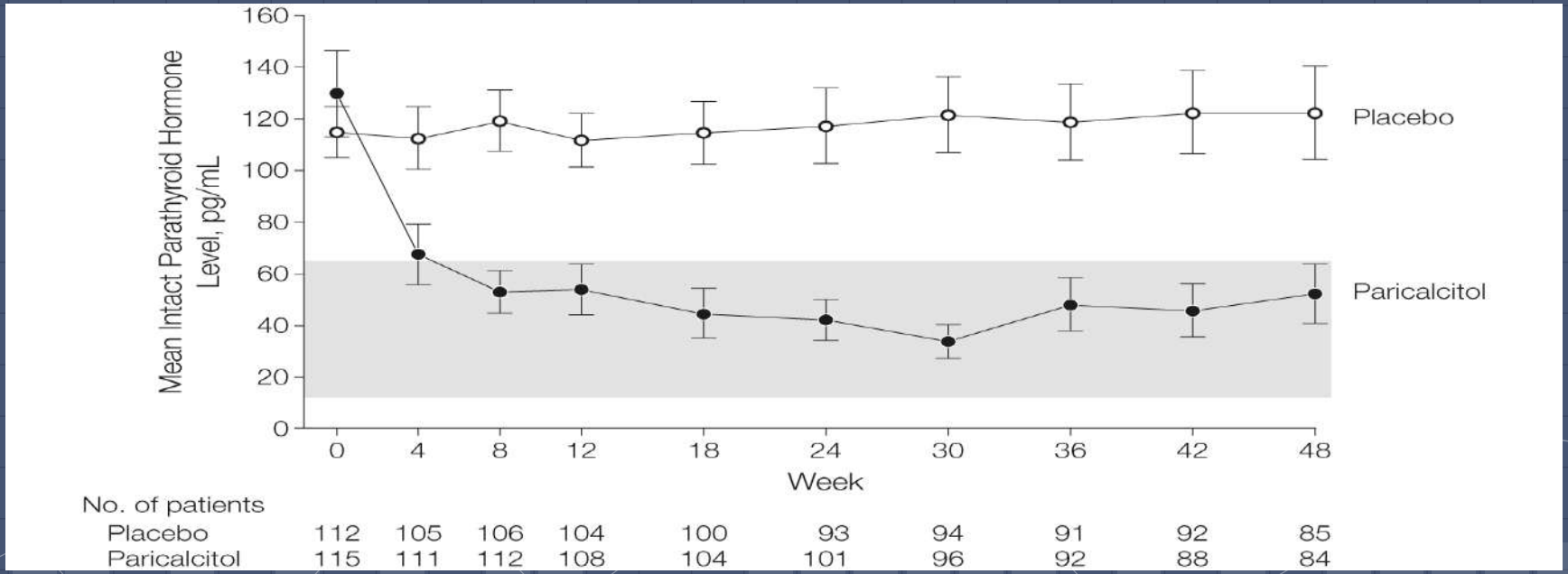
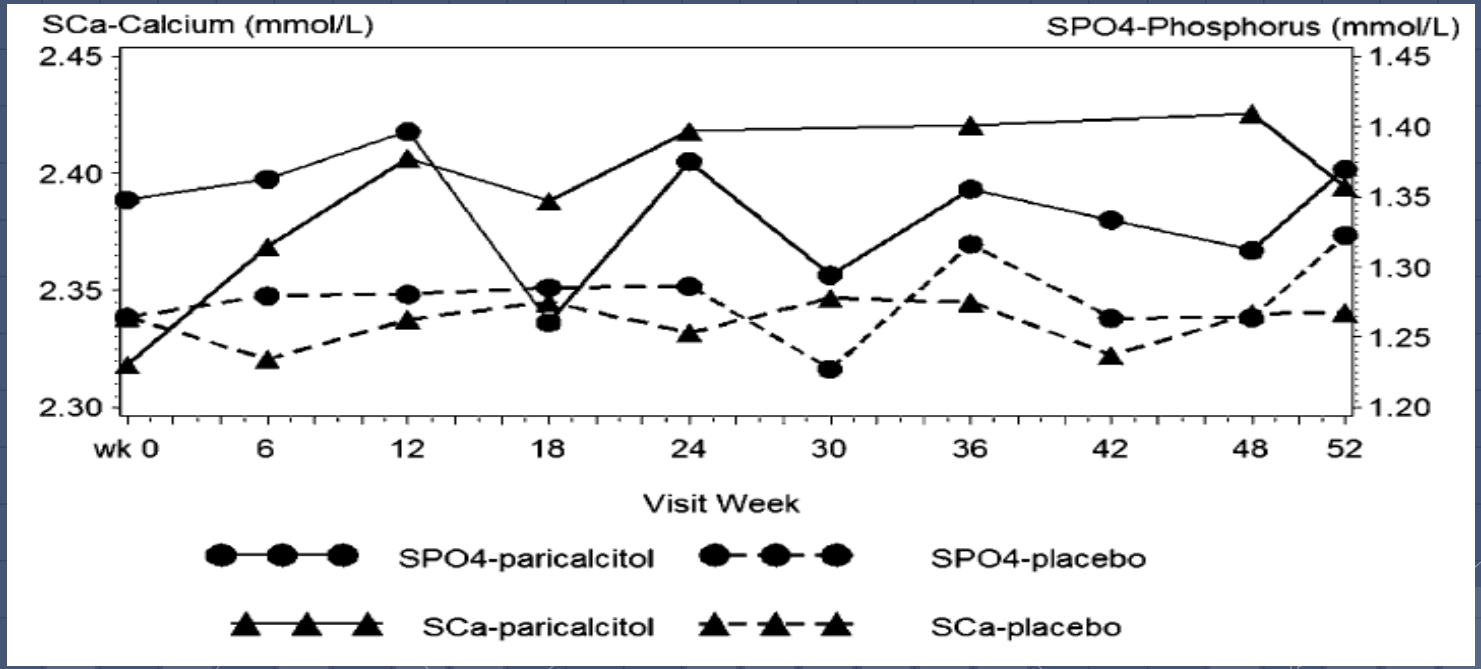
The PRIMO Trial



Thadani R et al. JAMA. 2012;307:674-684

The OPERA Trial



Wang A et al. J Am Soc Nephrol. 2014;25:175-186

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
4.2.4. In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (*2B*).	4.2.4. In patients with CKD G5D 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 phosphate levels and other aspects of CKD-MBD (*Not Graded*). • It is reasonable that calcium or non–calcium-based phosphate binder dosage be adjusted so that treatments to control PTH do not compromise levels of phosphate and calcium (*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 hyperphosphatemia, calcitriol or another vitamin D sterol be reduced or stopped (*2D*). • We suggest that, in patients with hypocalcemia, calcimimetics be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (*2D*). • We suggest that, if the intact PTH levels fall below 2 times the upper limit of normal for the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped (*2C*).	This recommendation originally had not been suggested for updating by the KDIGO Controversies Conference in 2013. However, due to a subsequent series of secondary and *post hoc* publications of the EVOLVE trial, the Work Group decided to reevaluate Recommendation 4.2.4 as well. Although EVOLVE did not meet its primary endpoint, the majority of the Work Group members were reluctant to exclude potential benefits of calcimimetics for G5D patients based on subsequent prespecified analyses. The Work Group, however, decided not to prioritize any PTH-lowering treatment at this time because calcimimetics, calcitriol, or vitamin D analogs are all acceptable first-line options in G5D patients.

Evaluation of Cinacalcet Therapy to Lower Cardiov
Events (EVOLVE): Rationale and Design Overview

Article

The Effect of Cinacalcet on Calc
Arteriolopathy Events in Patients
Hemodialysis: The EVOLVE Trial

CLINICAL RESEARCH www.jacc.org

Effects of Cinacalcet on Fracture Event
Receiving Hemodialysis: The EVOLVE T

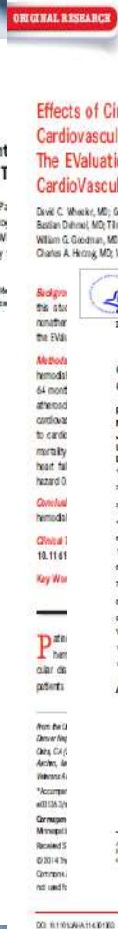
THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Cinacalcet on Cardiovascular
Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*

ABSTRACT



ORIGINAL RESEARCH

Effects of Cinacalcet on Atherosclе
Cardiovascular Events in Patients
The EValuation Of Cinacalcet HCl T
CardioVascular Events (EVOLVE) Tr

The Effects of Cinacalcet in Older and Younger Patients
on Hemodialysis: The Evaluation of Cinacalcet HCl
Therapy to Lower Cardiovascular Events (EVOLVE) Trial

HHS Public Access

Author manuscript

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Cinacalcet, Dialysate Calcium Concentration, and
Cardiovascular Events in the EVOLVE trial

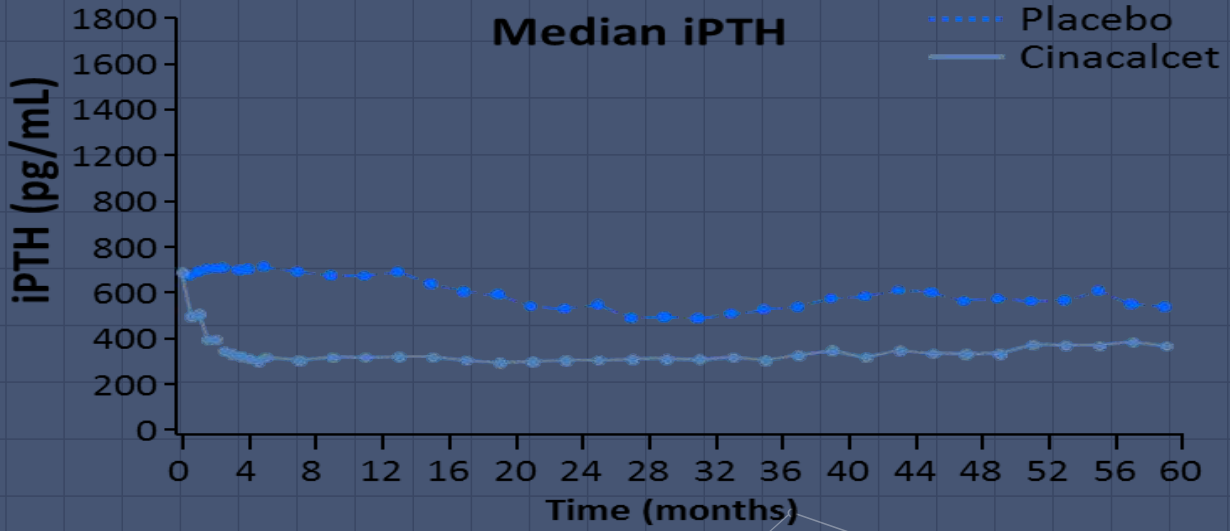
Abstract

Blood Calcification Propensity, Cardiovascular Events,
and Survival in Patients Receiving Hemodialysis in the
EVOLVE Trial

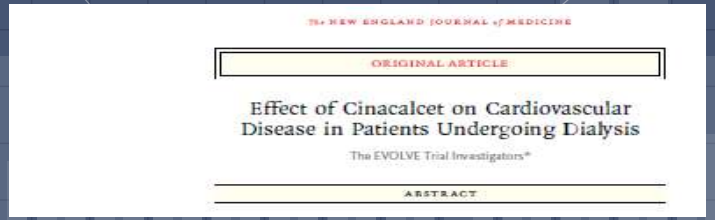
Abstract

Introduction

EVOLVE: Lowering PTH



Chertow GM, et al. N Engl J Med. 2012;367:2482-2494


The NEW ENGLAND JOURNAL of MEDICINE

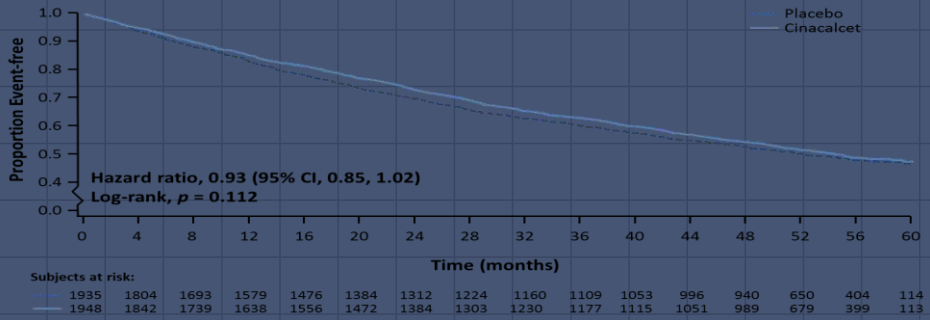
ORIGINAL ARTICLE

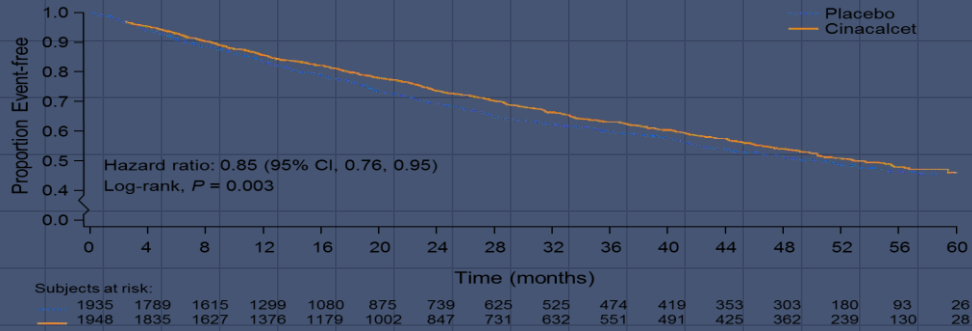
Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*

ABSTRACT

EVOLVE Study: Cinacalcet





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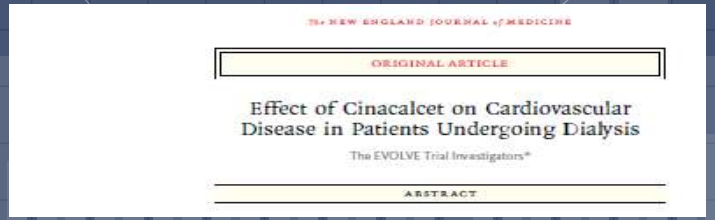

The NEW ENGLAND JOURNAL of MEDICINE

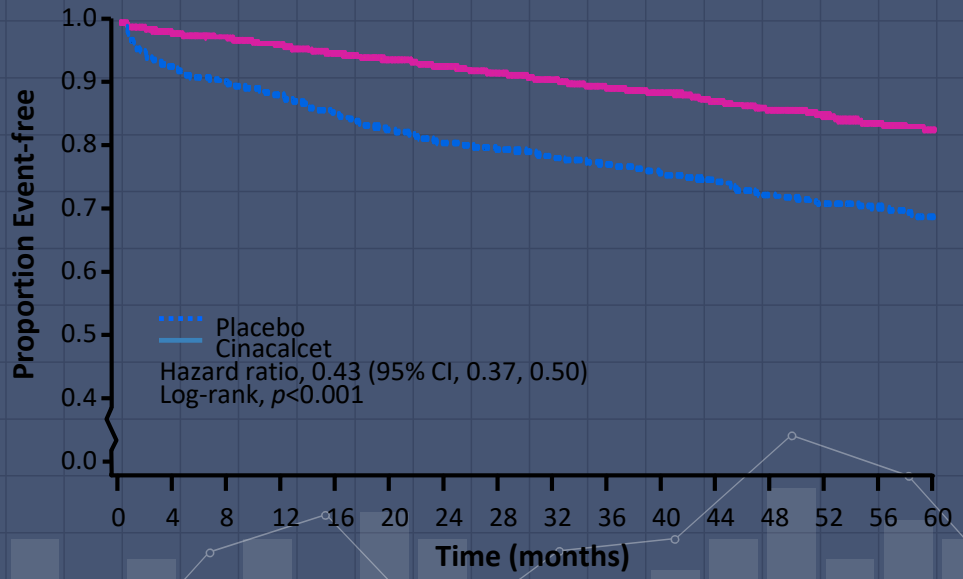
ORIGINAL ARTICLE

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*

ABSTRACT

Time to First Episode of Severe Unremitting HPT (Intent-to-Treat Analysis)



Severe, unremitting HPT

- Prespecified and defined as
  - PTH > 1000 pg/ml (106.0 pmol/l) with serum calcium > 10.5 mg/dl (2.6 mmol/l) on 2 consecutive occasions OR
  - PTH > 1000 pg/ml with serum calcium >10.5 mg/dl on a single occasion and subsequent commercial cinacalcet use within 2 months of the laboratory assessment OR
  - parathyroidectomy

Chertow GM, et al. N Engl J Med. 2012;367:2482-2494

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
4.3.3. In patients with CKD G3a–G5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (*2D*).	4.3.3. In patients with CKD G3a–G3b with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (*2D*). 4.3.4. In patients with CKD G4–G5D having biochemical abnormalities of CKD-MBD, and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy prior to therapy with antiresorptive agents (*2C*).	Recommendation 3.2.2 now addresses the indications for a bone biopsy prior to antiresorptive and other osteoporosis therapies. Therefore, 2009 Recommendation 4.3.4 has been removed and 2017 Recommendation 4.3.3 is broadened from CKD G3a–G3b to CKD G3a–G5D.
5.5. In patients with G1T–G5T with risk factors for osteoporosis, we suggest that BMD testing be used to assess fracture risk if results will alter therapy (*2C*).	5.5. In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min/1.73 m^2, we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (*2D*). 5.7. In patients with CKD G4T–G5T, 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 kidney transplant bone disease (*2B*).	2009 Recommendations 5.5 and 5.7 were combined to yield 2017 Recommendation 5.5.

Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations

2017 revised KDIGO CKD-MBD recommendations[3]	2009 KDIGO CKD-MBD recommendations[1]	Brief rationale for updating
5.6. In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min/1.73 m^2 and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents be considered (*2D*). • We suggest that treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D (*2C*). • It is reasonable to consider a bone biopsy to guide treatment (*Not Graded*). There are insufficient data to guide treatment after the first 12 months.	5.6. In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min/1.73 m^2 and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, or bisphosphonates be considered (*2D*). • We suggest that treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D (*2C*). • It is reasonable to consider a bone biopsy to guide treatment, specifically before the use of bisphosphonates due to the high incidence of adynamic bone disease (*Not Graded*). There are insufficient data to guide treatment after the first 12 months.	The second bullet point is revised, consistent with the new bone biopsy recommendation (i.e., 2017 Recommendation 3.2.2).

Take home messages

- Prospective studies evaluating BMD testing in adults with CKD represent a substantial advance since the original guideline from 2009, making a reasonable case for BMD testing if the results will impact future treatment.
- It is important to emphasize the interdependency of serum calcium, phosphate, and PTH for clinical therapeutic decision-making.

Take home messages

- Phosphate-lowering therapies may only be indicated in the case of "progressive or persistent hyperphosphatemia".

- New evidence suggests that excess exposure to exogenous calcium in adults may be harmful in all severities of CKD, regardless of other risk markers.

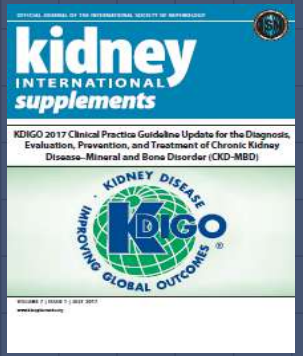
Take home messages

- It is reasonable to limit dietary phosphate intake, when considering all sources of dietary phosphate (including "hidden" sources).

- The PRIMO and OPERA studies failed to demonstrate improvements in clinically relevant outcomes but did demonstrate increased risk of hypercalcemia. Accordingly, routine use of calcitriol or its analogs in CKD G3a-G5 is no longer recommended.

Take home messages

4.2.4. In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (*2B*).



THANKS!

Any questions?