

# Οι ανανεωμένες κατευθυντήριες οδηγίες KDIGO 2017. Τί άλλαξε στη διαχείριση του CKD-MBD.

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Νεφρολόγος





## 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 updates 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.

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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 <sup>a</sup>
High for randomized controlled trials	Study quality -1 level if serious limitations	Strength of association +1 level is strong, <sup>b</sup> no plausible confounders, consistent and direct evidence	High
Moderate for quasi-randomized trial	-2 levels in very serious limitations		Moderate
Low for observational study	Consistency -1 level if important inconsistency	+2 levels if very strong, <sup>c</sup> 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		

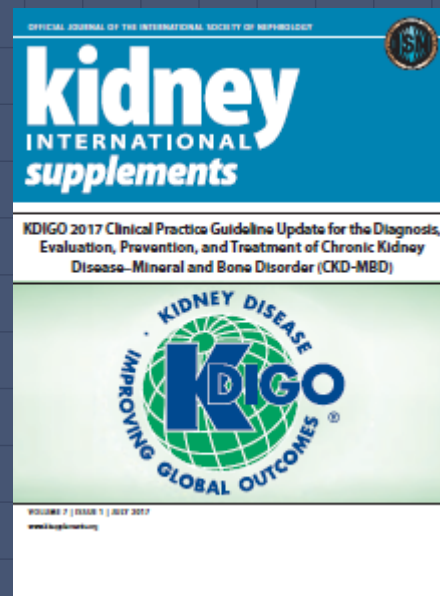
GRADE, grading of recommendations assessment, development, and evaluation; RR, relative risk.

<sup>a</sup>The highest possible grade is "high" and the lowest possible grade is "very low."

<sup>b</sup>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.

<sup>c</sup>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.<sup>171</sup>



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

2017 revised KDIGO CKD-MBD recommendations<sup>3</sup>

2009 KDIGO CKD-MBD recommendations<sup>1</sup>

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.

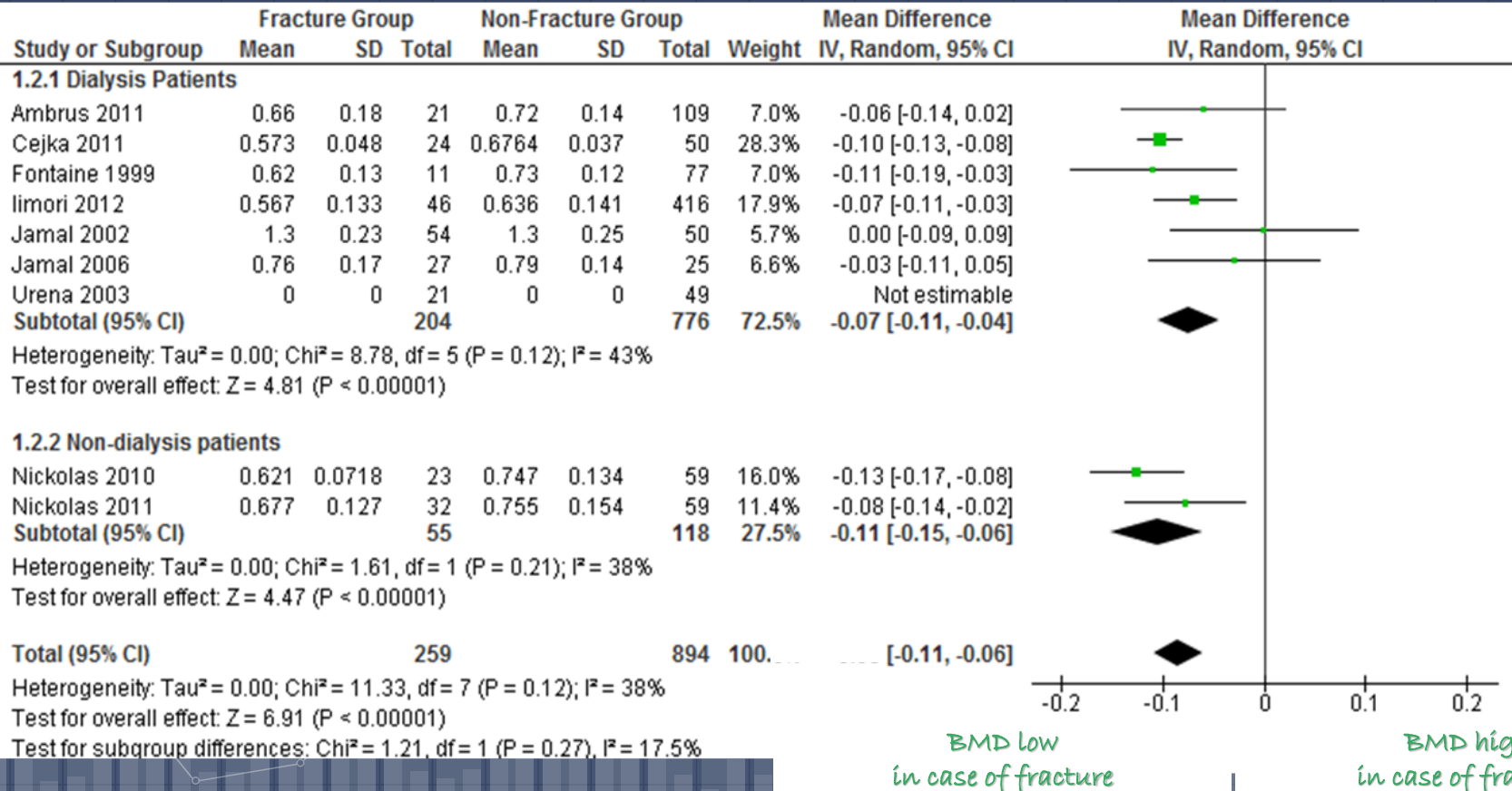
3.2.2. In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions (*Not Graded*).

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



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

2017 revised KDIGO CKD-MBD recommendations<sup>3</sup>

2009 KDIGO CKD-MBD recommendations<sup>1</sup>

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*).

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).

This new recommendation was provided in order to emphasize the complexity and interaction of CKD-MBD laboratory parameters.

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.



*Assessment.* The previous Recommendation 4.1.1 from the 2009 KDIGO CKD-MBD Guideline<sup>1</sup> 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).

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

2017 revised KDIGO CKD-MBD recommendations<sup>3</sup>

2009 KDIGO CKD-MBD recommendations<sup>1</sup>

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<sup>3</sup>**

**2009 KDIGO CKD-MBD recommendations<sup>1</sup>**

**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*).

4.1.6. 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*).

4.1.4. 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*).

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).

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.

New evidence from 3 RCTs supports a more general recommendation to restrict calcium-based phosphate binders in hyperphosphatemic patients across all severities of CKD.

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

2017 revised KDIGO CKD-MBD  
recommendations<sup>3</sup>

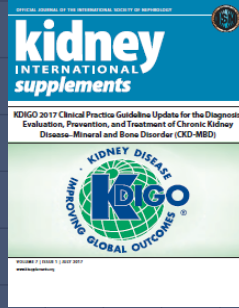
2009 KDIGO CKD-MBD recommendations<sup>1</sup>

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).

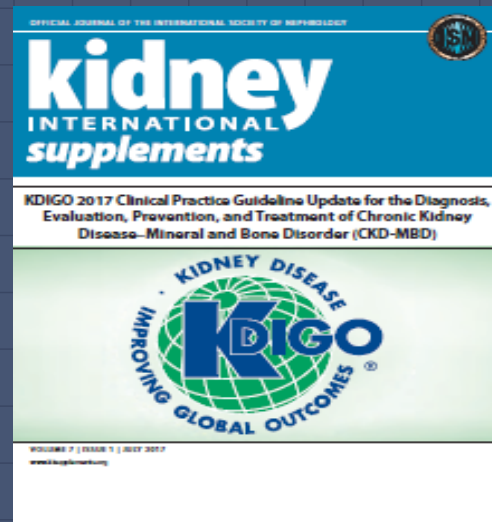
New data on phosphate sources were deemed important to include as an additional qualifier to the previous recommendation.



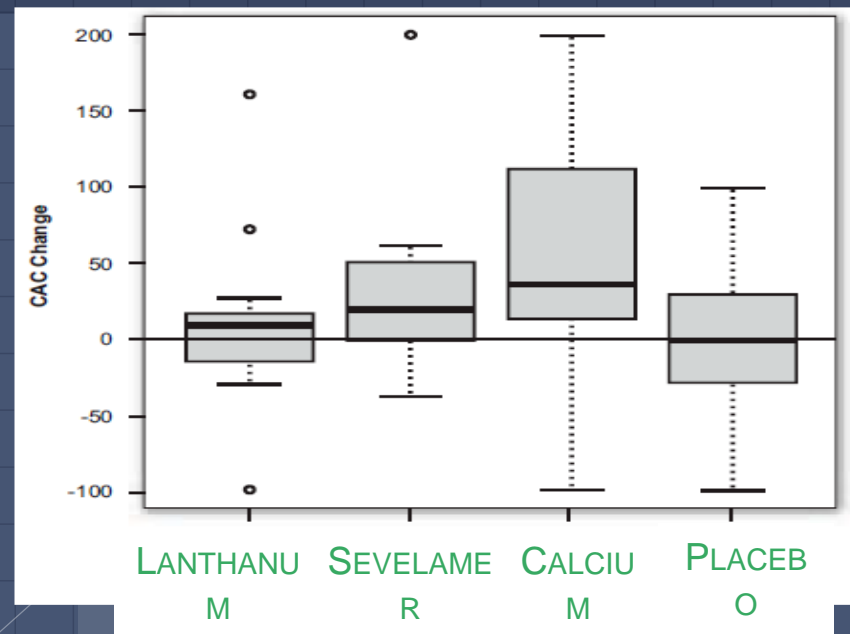
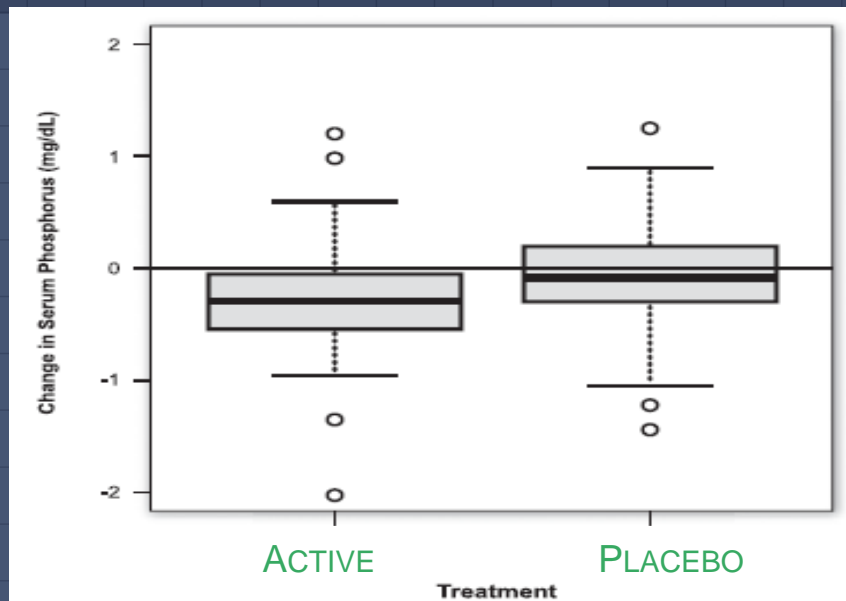
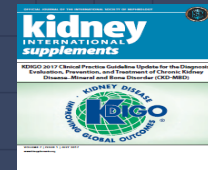
the Work Group drew several conclusions: (i) the association between serum phosphate and clinical outcome is not monotonic; (ii) evidence is lacking to demonstrate the efficacy of phosphate binders for lowering serum phosphate in patients with CKD G3a to G4; (iii) the safety of phosphate binders in this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



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

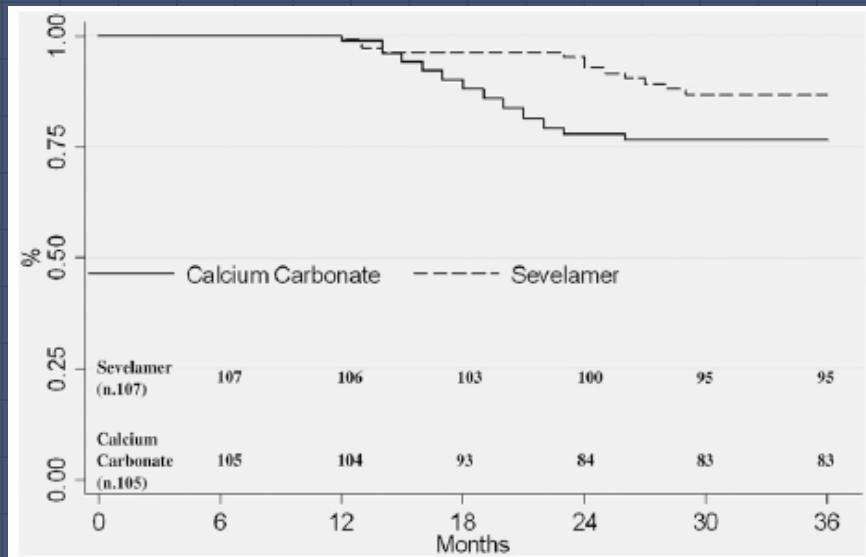


binding of essential nutrients). The Work Group also adopted the term “phosphate-lowering treatment” instead of “phosphate-binding agents,” because all possible approaches (i.e., binders, diet, and dialysis) can be effective.

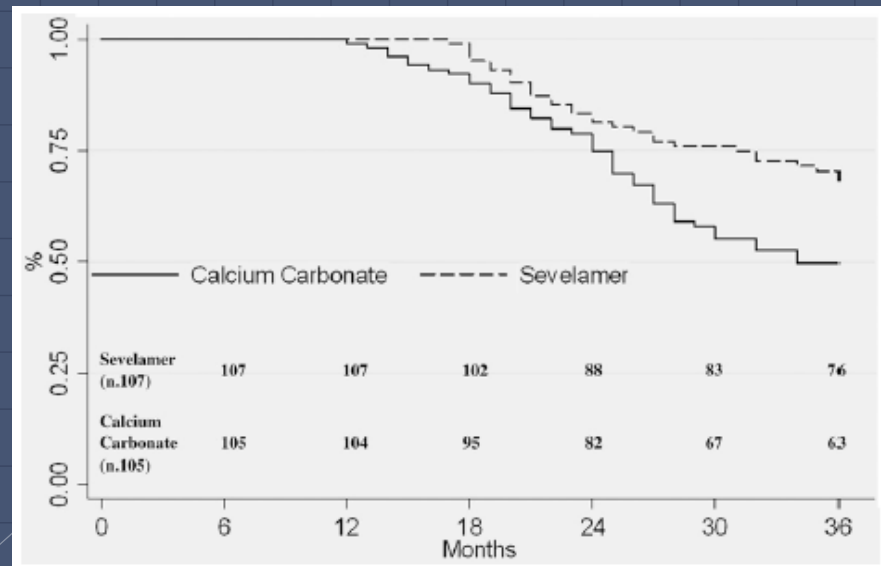
Block G et al. *J Am Soc Nephrol.* 2012;23:1407-1415.

# Phosphate Binders and Mortality

All-cause Mortality



Dialysis Inception



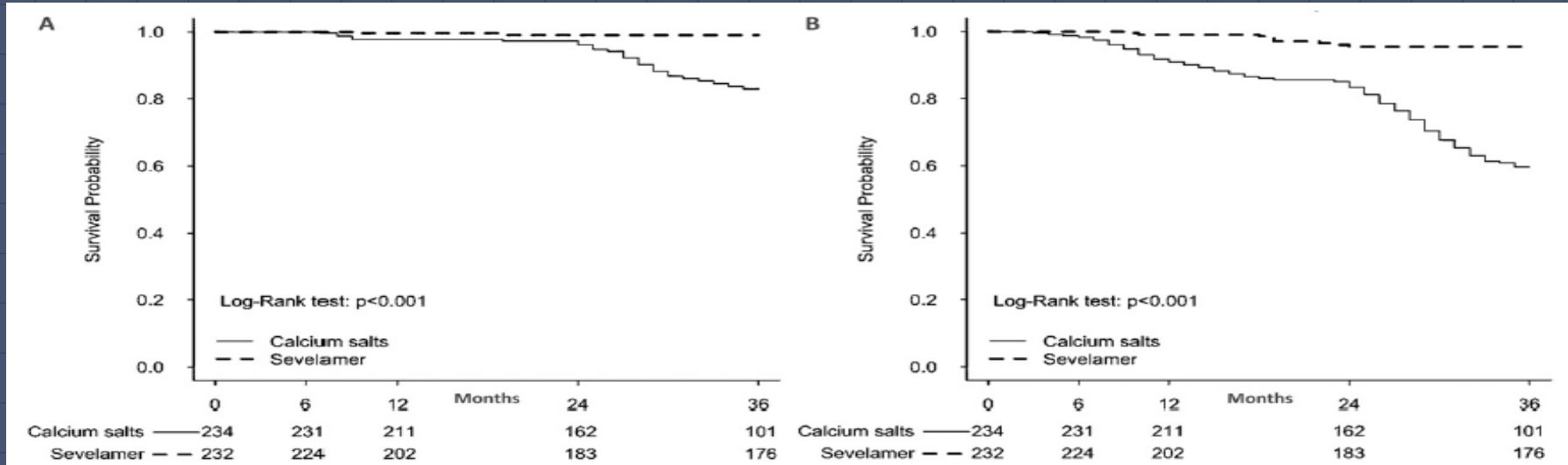
Dí Iorio B et al. *Clin J Am Soc Nephrol* 2012;7:487-493



# Sevelamer vs. Calcium

Arrhythmias

Cardiovascular Mortality



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



# Foods High in Phosph

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

Cheap artificial sugars, salt and preservatives in processed foods have less fibre quantity & don't add any nutrition benefits, it slows down digestion

The salts, phosphates and other artificial ingredients in the processed food leads to kidney and other health problems

Frequent consumption of processed foods can lead to hormonal problems like menstrual irregularities, premenstrual syndrome, infertility, thyroid dysfunction etc



Processed foods are **HIGHLY ADDICTIVE** and make you crave them frequently.



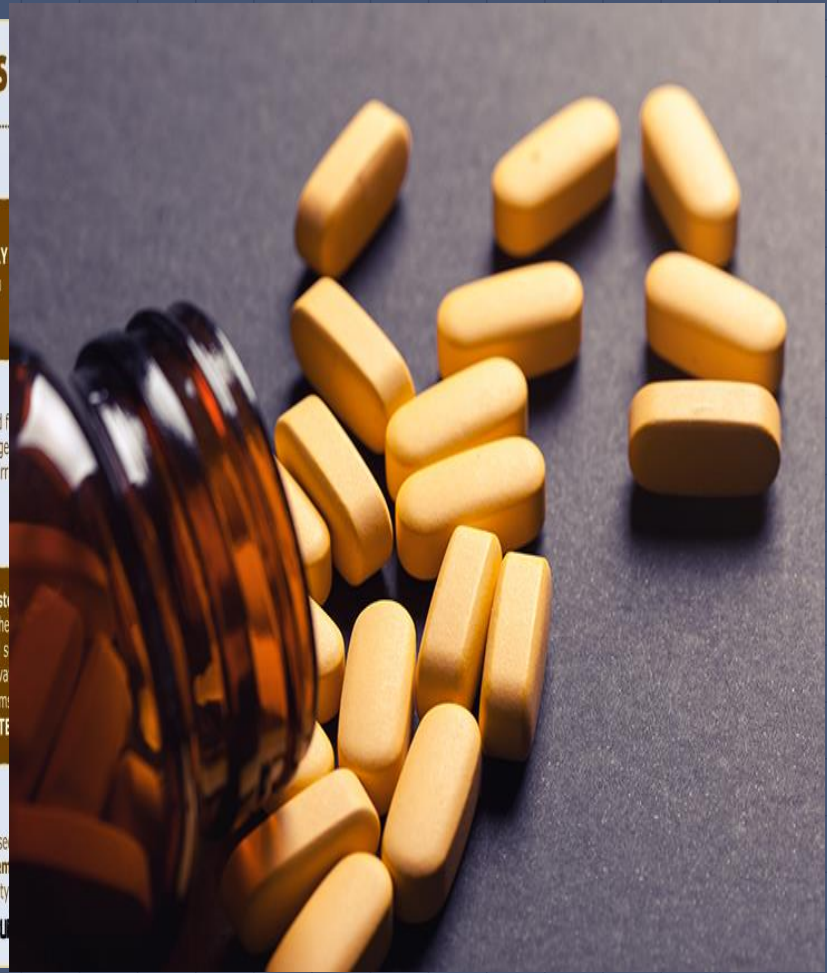
Some processed dairy products, dried fruit contains Sulphite which causes a range of diseases like headache, skin rashes, irritant syndrome etc.



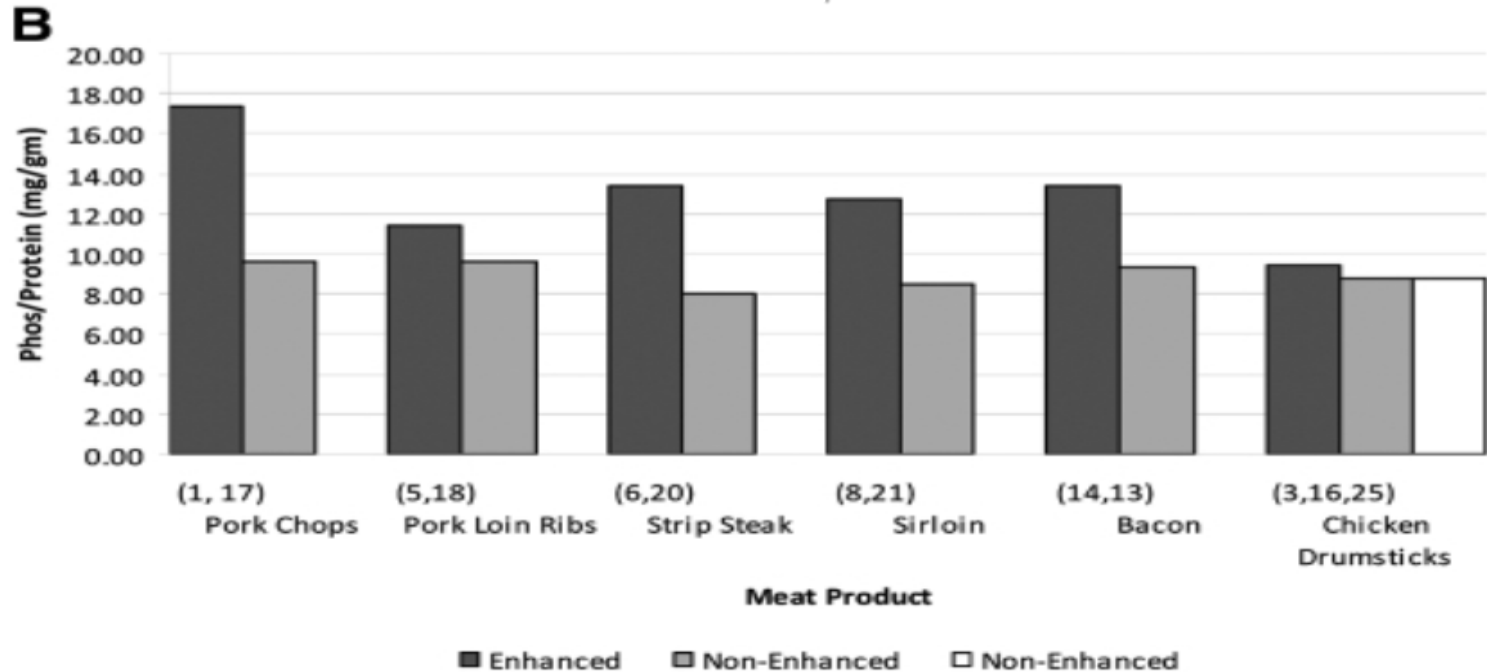
Processed food kills natural taste buds. In order to restore the taste, manufacturers add cheap artificial colours and preservatives. This leads to **GASTROINTESTINAL** problems like indigestion, **NERVOUS SYSTEM** problems, depression etc.



Frequent consumption of processed foods lead to nervous system problems like depression, irritability and inability to concentrate.



# "Hidden" Phosphate



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

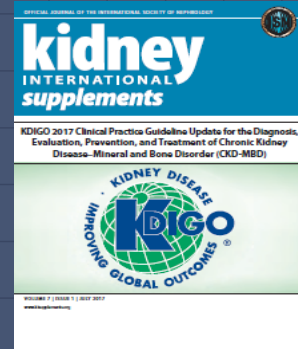


**Table 1 | Comparison of the 2017 and 2009 KDIGO CKD-MBD Guideline recommendations**

2017 revised KDIGO CKD-MBD recommendations <sup>3</sup>	2009 KDIGO CKD-MBD recommendations <sup>1</sup>	Brief rationale for updating
<p>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).</p>	<p>4.1.2. In patients with CKD G3a–G5D, we suggest maintaining serum calcium in the normal range (2D).</p>	<p>Mild and asymptomatic hypocalcemia (e.g., in the context of calcimimetic treatment) can be tolerated in order to avoid inappropriate calcium loading in adults.</p>
<p>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).</p>	<p>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).</p>	<p>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.</p>

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.

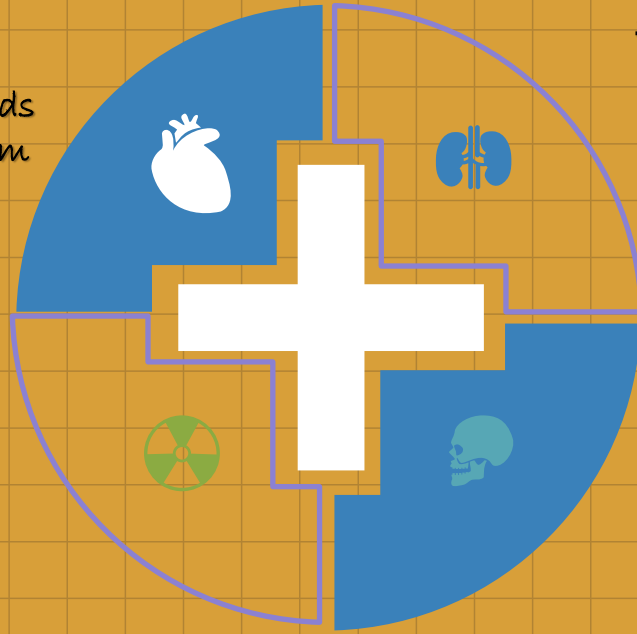
The 2009 Guideline<sup>1</sup> considered that a dialysate calcium concentration of 1.25 mmol/l (2.5 mEq/l) would yield neutral calcium balance. Based on new evidence, the 2017 Work Group felt that this recommendation remains valid as written in 2009. However, because additional studies of better quality 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).

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



The indication for SHPT treatment results from these clinical consequences

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

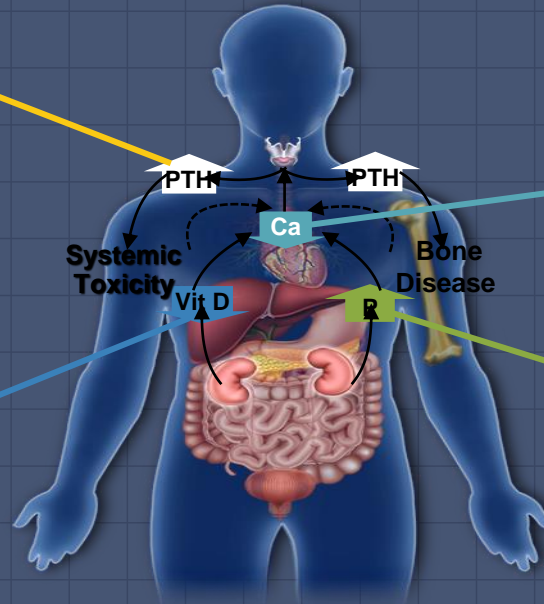
- Control intake
- Adjust dialysate Ca
- Use Ca supplements or vitamin D therapy (if Ca low)

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.

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

**2017 revised KDIGO CKD-MBD recommendations<sup>3</sup>**

**2009 KDIGO CKD-MBD recommendations<sup>1</sup>**

**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<sup>3</sup>

2009 KDIGO CKD-MBD recommendations<sup>1</sup>

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.

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

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### ABSTRACT

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 reduced 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<sup>2</sup> with paricalcitol versus −4.85 [−9.89 to 1.10] g/m<sup>2</sup> with placebo). Change in LV volume, ejection fraction, tissue Doppler-derived measures of early diastolic and systolic mitral annular velocities, and rate 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 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.

*J Am Soc Nephrol* 25: 175–184, 2014. doi: 10.1681/ASN.2013010103

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<sup>1</sup> as well as traditional Framingham and kidney disease-related risk factors.<sup>2</sup> 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 cardiovascular walls through interaction with the vitamin D receptor.<sup>3,4</sup> Experimental studies showed associations between vitamin D deficiency and impairment of cardiac contractile function,<sup>5</sup> increased myocardial collagen content, and increased cardiac

mass.<sup>6,7</sup> Similarly, targeted deletion of the vitamin D receptor gene resulted in increased cardiomyocyte size and LV weight.<sup>8</sup> Treatment with active vitamin D attenuated myocardial hypertrophy in experimental models of cardiac hypertrophy<sup>9</sup> as

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## Vitamin D Therapy and Cardiac Structure and Function in Patients With Chronic Kidney Disease: The PRIMO Randomized Controlled Trial

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**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 m<sup>2</sup>.

**Design, Setting, and Participants** Multirational, 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/m<sup>2</sup> [95% CI, −0.14 to 0.83 g/m<sup>2</sup>] vs placebo group, −0.07 g/m<sup>2</sup> [95% CI, −0.55 to 0.42 g/m<sup>2</sup>]). 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

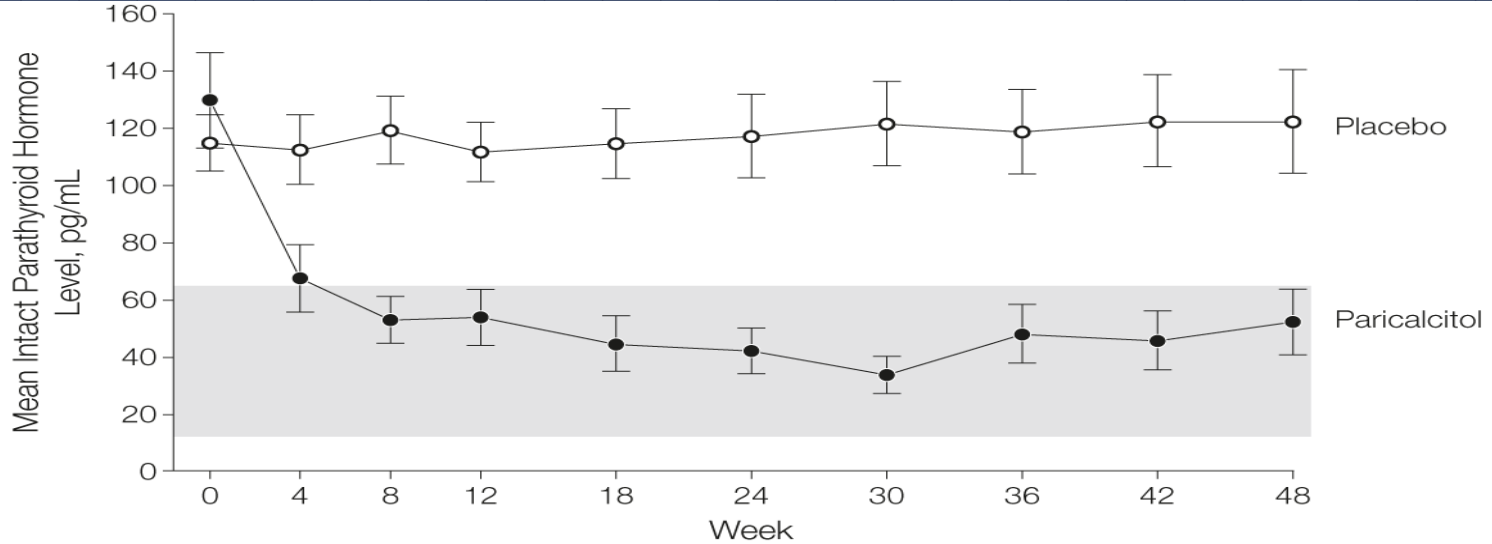
les identifying vitamin D receptors in vascular smooth muscle, endothelial cells, and possibly cardiac tissue<sup>10</sup> and observational studies, small clinical trials, and meta-analyses suggesting that vitamin D therapy reduces cardiovascular events.<sup>11–13</sup> Convincing data demonstrating that vitamin D therapy improves cardiovascular health, however, are lacking.

Patients with chronic kidney disease (CKD) frequently develop deficiency of 1,25-dihydroxyvitamin D<sub>3</sub> (calcitriol) because of a lack of its precursor, 25-

**Author Affiliations and a list of the PRIMO Investigators appear at the end of this article.**  
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For editorial comment see p 722.

# The PRIMO Trial

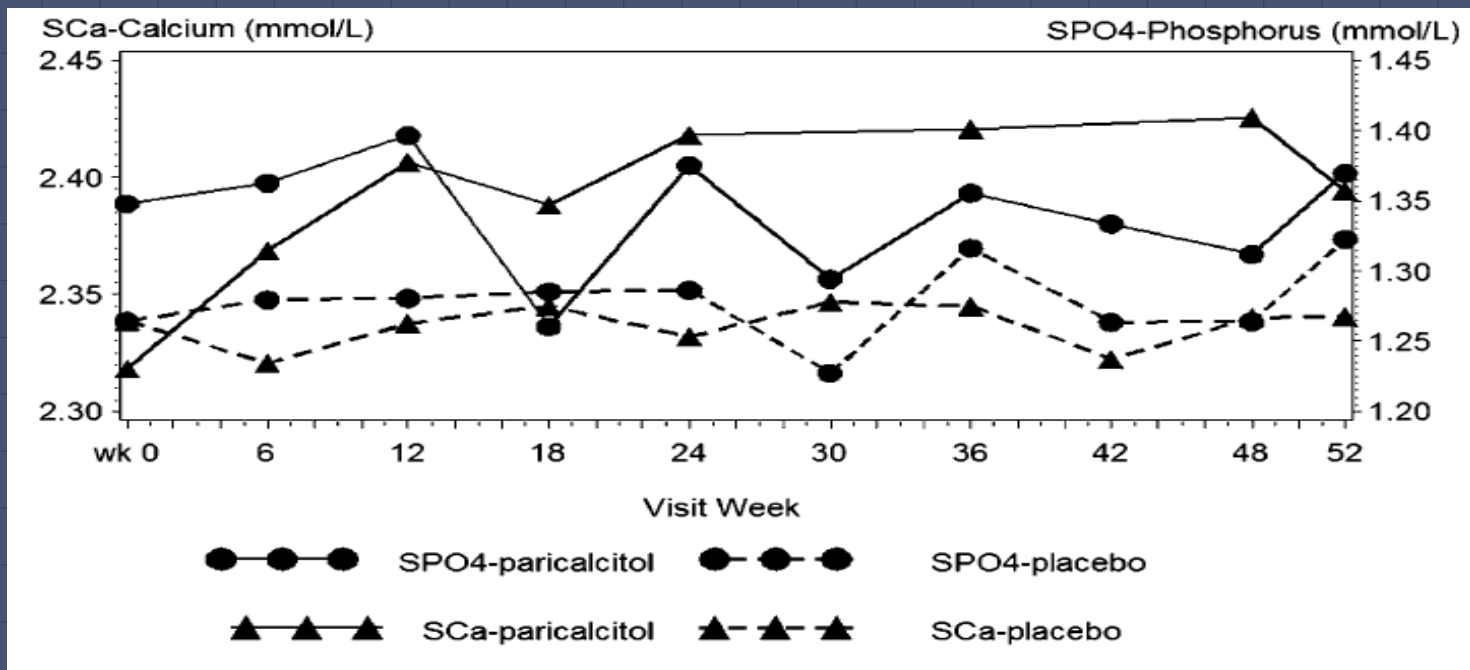


No. of patients

Placebo	112	105	106	104	100	93	94	91	92	85
Paricalcitol	115	111	112	108	104	101	96	92	88	84

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<sup>3</sup>****2009 KDIGO CKD-MBD recommendations<sup>1</sup>****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).

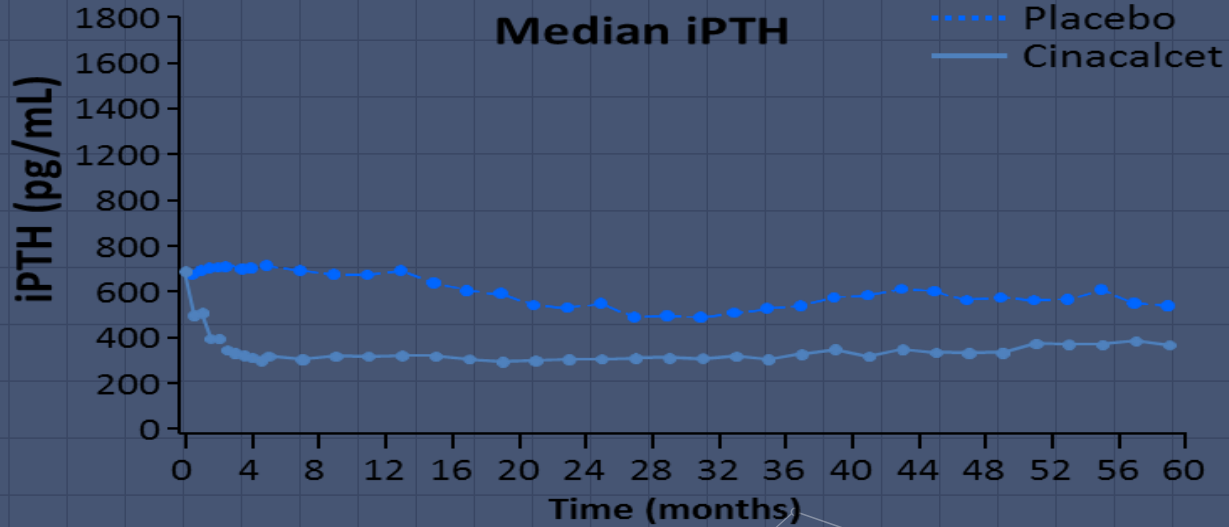
4.2.4. In patients with CKD G5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (2B).

- 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.



# EVOLVE: Lowering PTH



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

THE NEW ENGLAND JOURNAL OF MEDICINE

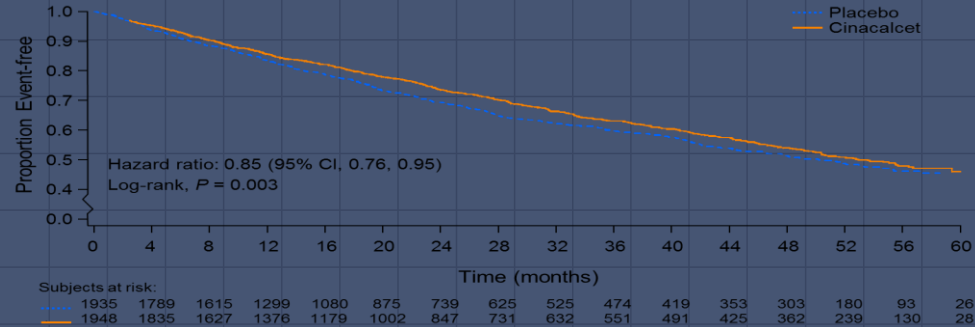
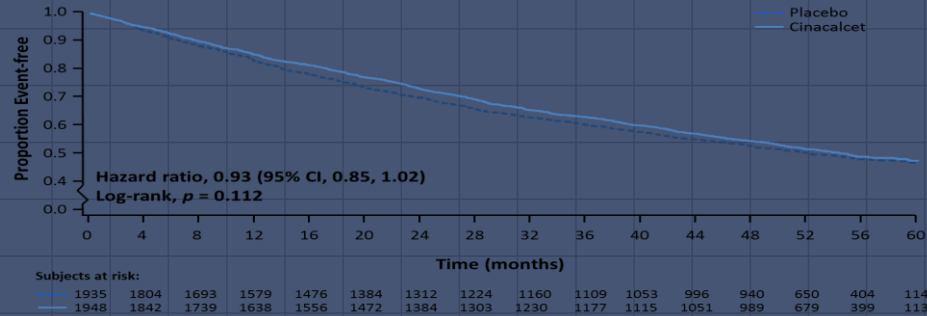
ORIGINAL ARTICLE

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

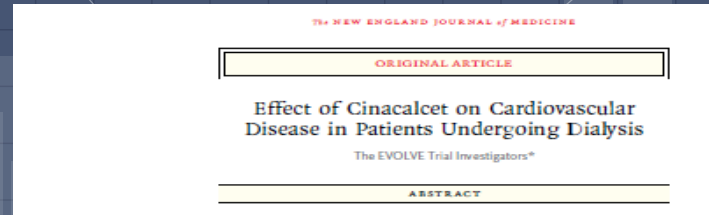
The EVOLVE Trial Investigators\*

ABSTRACT

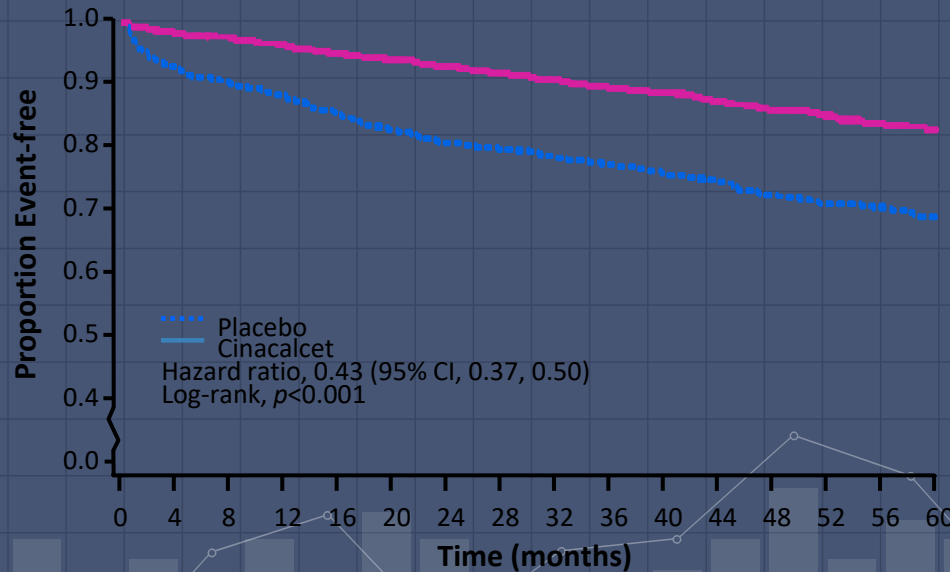
# EVOLVE Study: Cinacalcet



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



# 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<sup>3</sup>**

**2009 KDIGO CKD-MBD recommendations<sup>1</sup>**

**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).

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).

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).

5.5. In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min/1.73 m<sup>2</sup>, 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).

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.

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<sup>3</sup>

2009 KDIGO CKD-MBD recommendations<sup>1</sup>

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<sup>2</sup> 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<sup>2</sup> 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

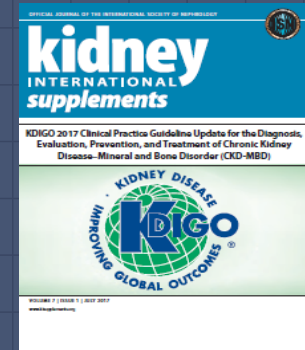
- Phosphate-lowering therapies may only be indicated in the case of “progressive or persistent hyperphosphatemia”.
- New evidence suggests that excess exposure to exogenous calcium in adults may be harmful in all severities of CKD, regardless of other risk markers.

# 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?*

