KDIGO CKD-MBD GUIDELINE UPDATE OVERVIEW

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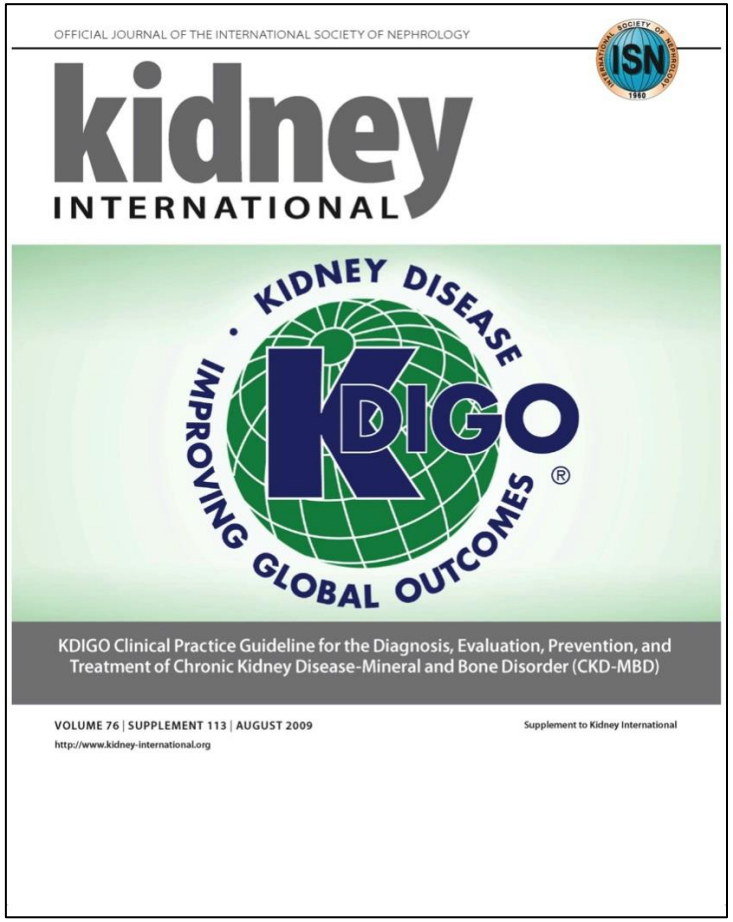
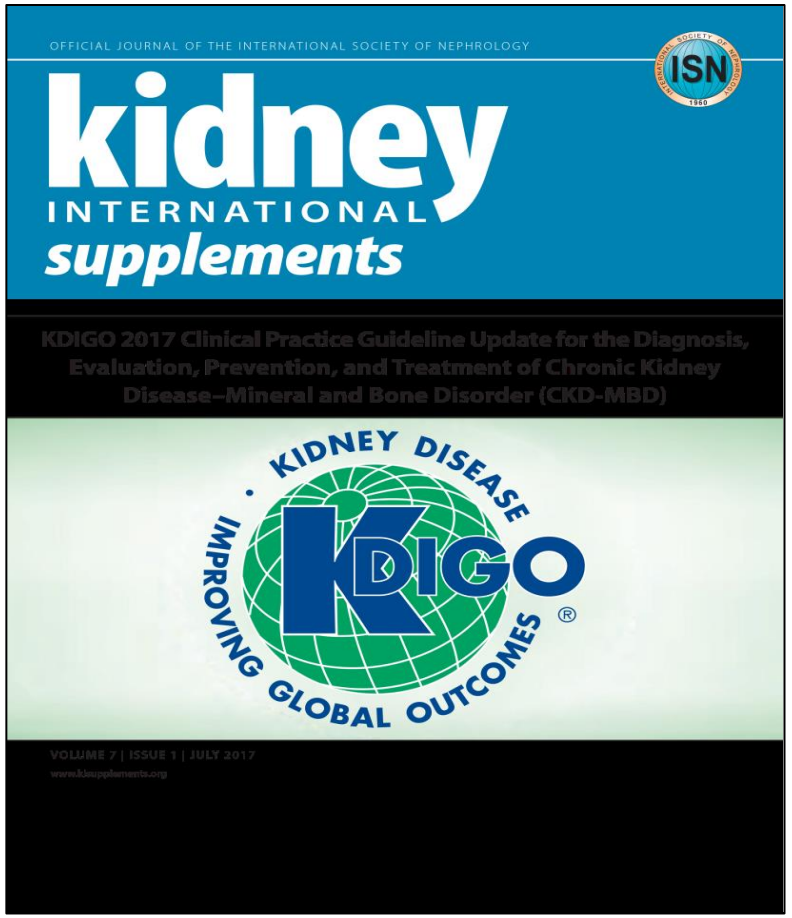
KDIGO CKD-MBD GUIDELINE UPDATE





August 2009

July 2017

GRADING SYSTEM

Descriptor	Recommendation grading	Quality of evidence
Level 1	"We recommend"	
Level 2	"We suggest"	
Not graded	Based on common sense	
A		High
B		Moderate
C		Low
D		Very Low

Chapter 3.1: Diagnosis of CKD-MBD: biochemical abnormalities

- **3.1.1**: We recommend monitoring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity beginning in CKD G3a (1C). In children, we suggest such monitoring beginning in CKD G2 (2D).
- **3.1.2**: In patients with CKD G3a–G5D, it is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (Not Graded).
- **3.1.3**: In patients with CKD G3a–G5D, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (2C). We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).
- **3.1.4**: In patients with CKD G3a–G5D, we recommend that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD-MBD assessments (1C).
- **3.1.5**: In patients with CKD G3a–G5D, we suggest that individual values of serum calcium and phosphate, evaluated together, be used to guide clinical practice rather than the mathematical construct of calcium-phosphate product (Ca * P) (2D).
- **3.1.6**: In reports of laboratory tests for patients with CKD G3a–G5D, we recommend that clinical laboratories inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), or handling specifications to facilitate the appropriate interpretation of biochemistry data (1B).

Chapter 3.2: Diagnosis of CKD-MBD: bone

- 3.2.1,3.2.2 UPDATED
- 3.2.3: In patients with CKD G3a–G5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (2B).
- 3.2.4: In patients with CKD G3a–G5D, we suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) (2C).
- 3.2.5: We recommend that infants with CKD G2–G5D have their length measured at least quarterly, while children with CKD G2–G5D should be assessed for linear growth at least annually (1B).

Chapter 3.3: Diagnosis of CKD-MBD: vascular calcification

- 3.3.1: In patients with CKD G3a–G5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging (2C).
- 3.3.2: We suggest that patients with CKD G3a–G5D with known vascular or valvular calcification be considered at highest cardiovascular risk (2A).
- It is reasonable to use this information to guide the management of CKD-MBD(Not Graded).

Chapter 4.1: Treatment of CKD-MBD targeted at lowering high serum phosphate and maintaining serum calcium

- 4.1.1-6 UPDATED
- 4.1.7: In patients with CKD G3a-G5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD G5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C).
- 4.1.8:updated
- 4.1.9: In patients with CKD G5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (2C)

Chapter 4.2: Treatment of abnormal PTH levels in CKD-MBD

- 4.2.1-2updated
- 4.2.3: In patients with CKD G5D, we suggest maintaining iPTH levels in the range of approximately 2 to 9 times the upper normal limit for the assay (2C).
- We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).
- 4.2.4 UPDATED
- 4.2.5: In patients with CKD G3a–G5D with severe hyperparathyroidism (HPT) who fail to respond to medical or pharmacological therapy, we suggest parathyroidectomy (2B).

Chapter 4.3: Treatment of bone with bisphosphonates, other osteoporosis medications, and growth hormone

- 4.3.1: In patients with CKD G1–G2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we recommend management as for the general population (1A).
- 4.3.2: In patients with CKD G3a–G3b with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we suggest treatment as for the general population (2B).
- 4.3.3: UPDATED
- 4.3.4: In children and adolescents with CKD G2–G5D and related height deficits, we recommend treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD-MBD (1A).

Chapter 5: Evaluation and treatment of kidney transplant bone disease

- 5.1: In patients in the immediate post–kidney transplant period, we recommend measuring serum calcium and phosphateat least weekly, until stable (1B).
- 5.2: In patients after the immediate post–kidney transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (Not Graded).

Reasonable monitoring intervals would be:

- In CKD G1T–G3bT, for serum calcium and phosphate, every 6–12 months; and for PTH, once, with subsequentintervals depending on baseline level and CKD progression.
- In CKD G4T, for serum calcium and phosphate, every 3–6 months; and for PTH, every 6–12 months.
- In CKD G5T, for serum calcium and phosphate, every 1–3 months; and for PTH, every 3–6 months.
- In CKD G3aT–G5T, measurement of alk aline phosphatases annually, or more frequently in the presence of elevated PTH (see Chapter 3.2).
- In CKD patients receiving treatments for CKD-MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for efficacy and side effects (Not Graded).
- It is reasonable to manage these abnormalities as for patients with CKD G3a–G5 (see Chapters 4.1 and 4.2) (Not Graded).

Chapter 5: Evaluation and treatment of kidney transplant bone disease

- 5.3: In patients with CKD G1T–G5T, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions (2C).
- 5.4: In patients with CKD G1T–G5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).
- 5.5and 5.6 UPDATED
- 5.7: In patients with CKD G4T–G5T with known low BMD, we suggest management as for patients with CKD G4–G5 not on dialysis, as detailed in Chapters 4.1 and 4.2 (2C).

CHAPTER 3.2
DIAGNOSIS OF CKD-MBD: BONE

BONE QUALITY

- ***OLD 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).*

NEW 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***).

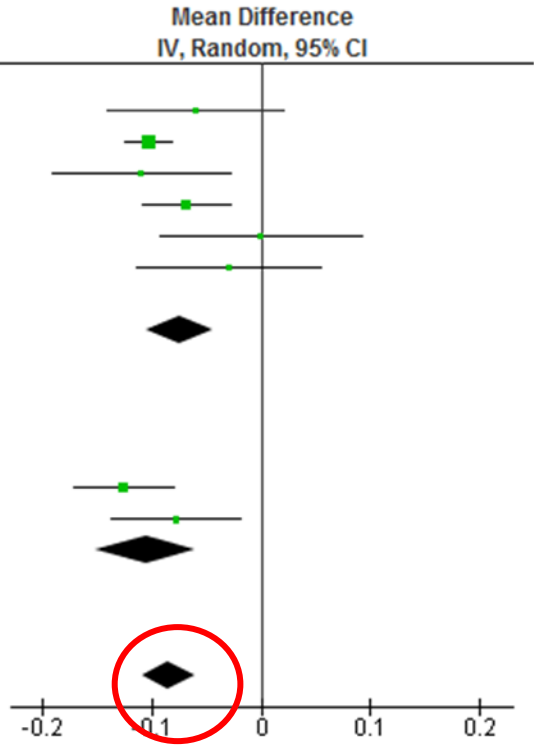
RATIONALE

Multiple new prospective studies have documented that lower DXA BMD does predict incident fractures in patients with CKD Stages 3a-5D.

BONE DENSITY PREDICTS FRACTURE RISK IN CKD

Knochendichte (BMD) Femur mittels DXA

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%**	**-0.08 [-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%								



Bucur RC et al, Osteoporosis 2015;26: 449-458

BONE QUALITY

- ***OLD 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).*

NEW 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***).

RATIONAL FOR UPDATE

- 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 lack of ability to perform a bone biopsy may not justify withholding antiresorptive therapy to patients at high risk of fracture.

- The order of these first two recommendations was changed, since a DXA BMD result might impact the decision to do a bone biopsy.

Case Study:

- 55-y.o. male, 9 months following successful kidney transplantation.
- Routine DEXA demonstrated a T-score of –2.6 at the femoral neck.
- He is on low-dose prednisone, tacrolimus, and MMF. In addition, he uses vitamin D supplements.
- Lab values:
  - PTH: 140 pg/mL (15 pmol/L)
  - Calcium: 8.8 mg/dL (2.2 mmol/L)
  - Phosphate: 3.0 mg/dL (1.0 mmol/L)

CASE STUDY:

- **What would you do next?**
- A. Initiate bisphosphonate therapy
- B.Refer for subtotal parathyroidectomy
- C. Wait and see as appropriate
- D.Lower the dose of prednisone

After kidney transplantation, fracture risk is high especially with low BMD score. In general, treatment can be as for the general population.

Chapter 4.1

Treatment of CKD–MBD: Targeted at Lowering High Serum Phosphate and Maintaining Serum Calcium

SERUM PHOSPHATE

***OLD 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).*

NEW 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***).

NEW 4.1.2: In patients with CKD G3a–G5D, we suggest lowering elevated phosphate levels toward the normal range (***2C***).

RATIONAL

- There is an absence of data that efforts to maintain phosphate in the normal range are of benefit to CKD G3a–G4 patients, including some safety concerns.

- Treatment should aim at overt hyperphosphatemia.

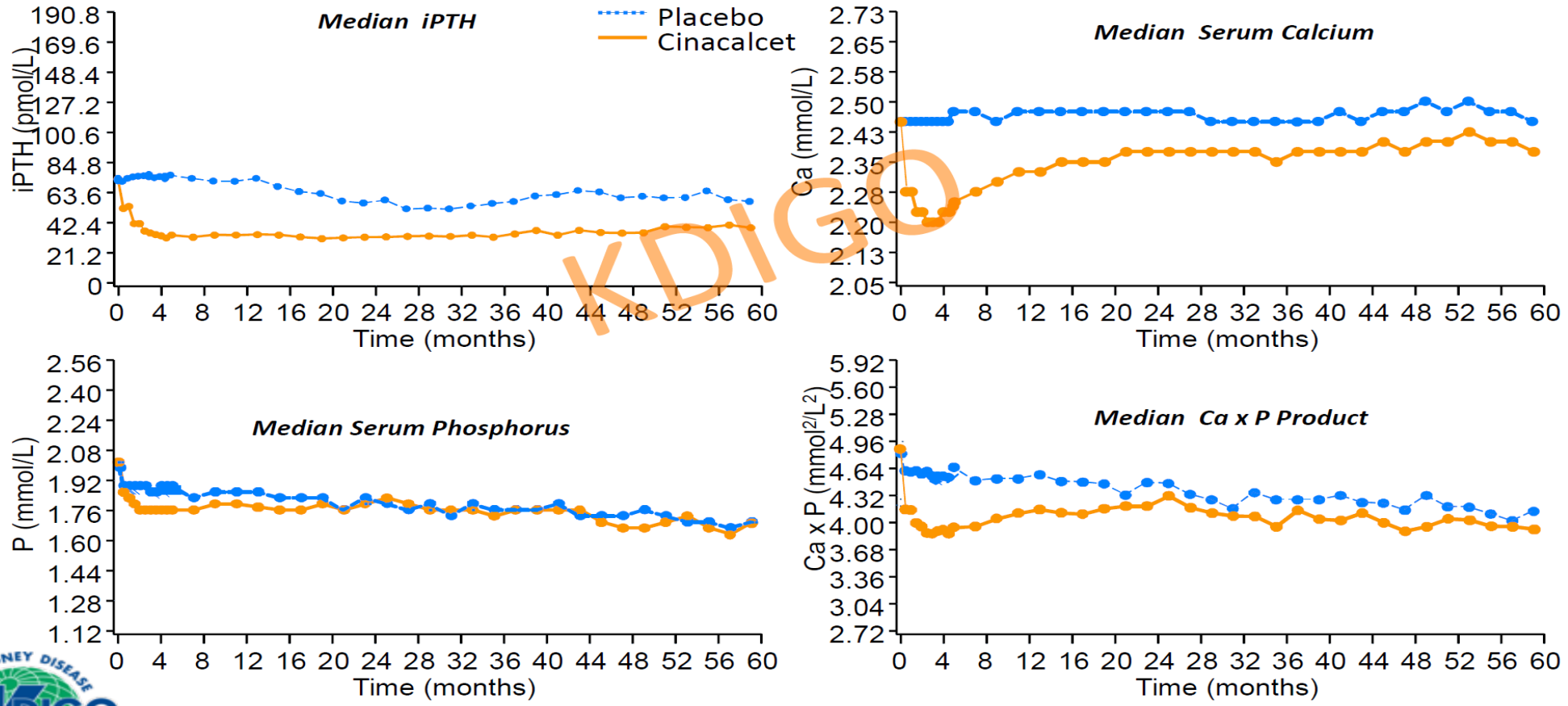
SERUM CALCIUM

- **OLD 4.1.2:** *In patients with CKD G3a–G5D, we suggest maintaining serum calcium in the normal range (2D).*

NEW 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*)**.

EVOLVE TRIAL: LONGITUDINAL LAB VALUES



RATIONAL

Mild and asymptomatic hypocalcemia (e.g., in the context of calcimimetic treatment) can be tolerated in order to avoid inappropriate calcium loading in adults.

DIALYSATE CALCIUM

OLD: 4.1.3 *In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l*

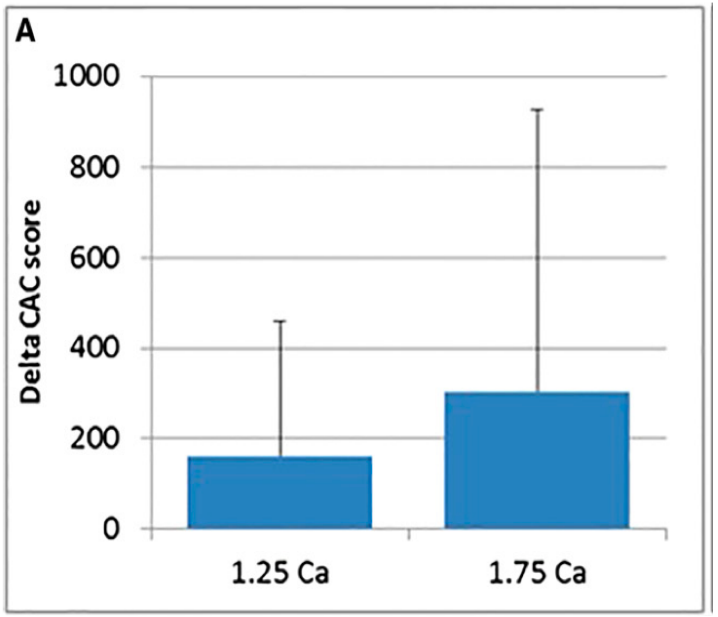
(2.5 and 3.0 mEq/l) ***(2D).***

NEW: 4.1.4: In patients with CKD G5D, we suggest using adialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (***2C***).

CLINICAL RESEARCH www.jasn.org

Reduction of Dialysate Calcium Level Reduces Progression of Coronary Artery Calcification and Improves Low Bone Turnover in Patients on Hemodialysis

Ercan Ok,* Gulay Asci,* Selen Bayraktaroglu,† Huseyin Toz,* Mehmet Ozkahya,* Mumtaz Yilmaz,* Fatih Kircelli,* Ebru Sevinc Ok,* Naim Ceylan,† Soner Duman,* Mustafa Cirit,‡ Marie-Claude Monier-Faugere,§ and Hartmut H. Malluche§



At 24 months, bone formation rate, trabecular thickness, and bone volume were higher in the 1.25 Calcium group than in the 1.75 Calcium group

RATIONAL

- Additional studies of better quality are available; however, they do not allow 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 evidence grade is upgraded from 2D to 2C.

PHOSPHATE BINDERS

- **OLD 4.1.5**: *In patients with CKD G3a–G5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders…..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 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)*

PHOSPHATE BINDERS

- **OLD 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).*

NEW 4.1.5: In patients with CKD G3a-G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphorus. (Not Graded)

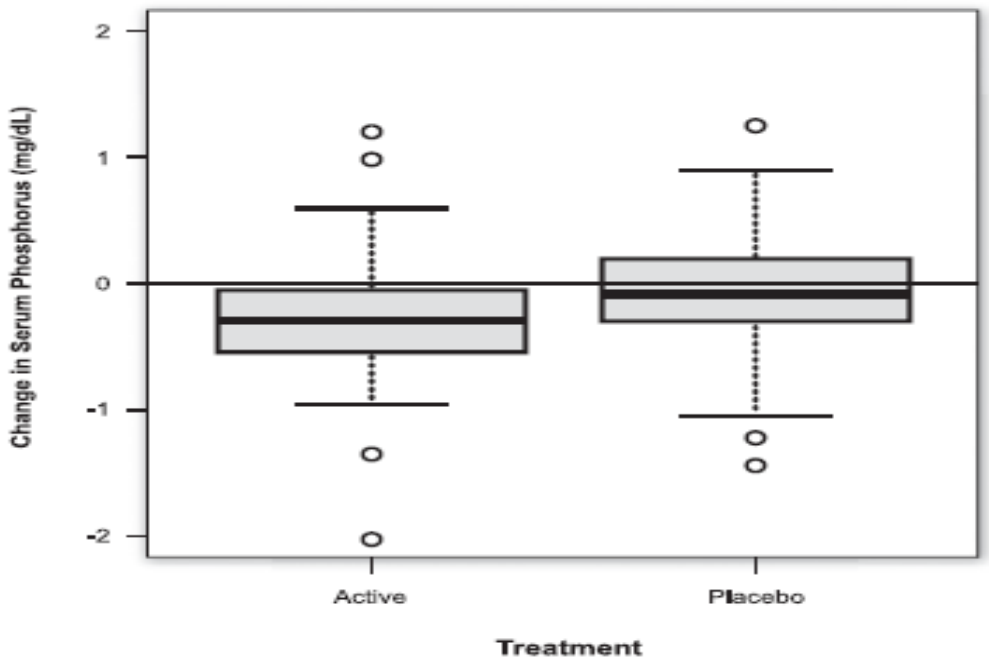
RATIONAL

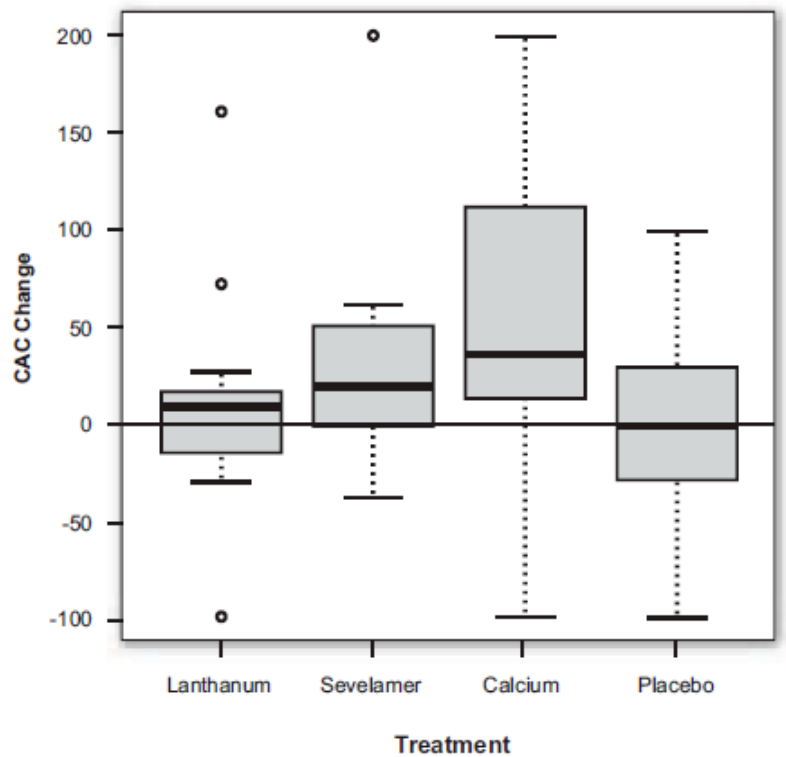
- The update emphasizes the perception that early “preventive” treatment of hyperphosphatemia is currently not supported by data (see Rec. 4.1.2). Recommendation 4.1.2).
- The broader term “phosphate-lowering” treatment is used instead of phosphate binding agents since all possible approaches (i.e., binders, diet, dialysis) can be effective.

CLINICAL RESEARCH www.jasn.org

Effects of Phosphate Binders in Moderate CKD

Geoffrey A. Block,* David C. Wheeler,† Martha S. Persky,* Bryan Kestenbaum,‡ Markus Ketteler,§ David M. Spiegel,‖ Matthew A. Allison,¶ John Asplin,** Gerard Smits,* Andrew N. Hoofnagle,‡ Laura Kooienga,* Ravi Thadhani,†† Michael Mannstadt,†† Myles Wolf,‡‡ and Glenn M. Chertow§§





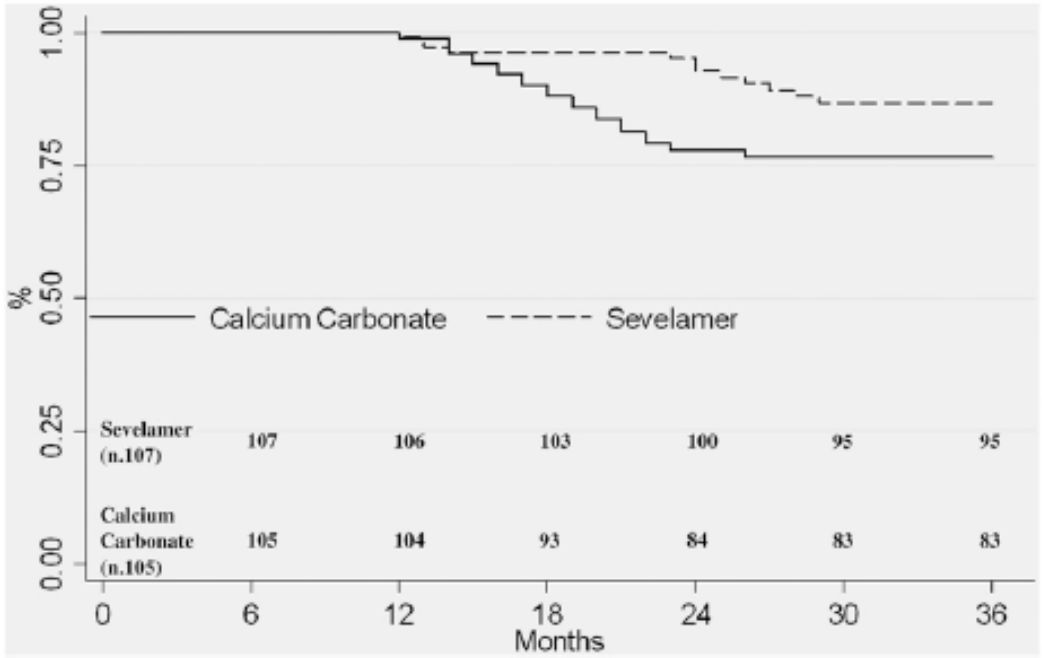
- In conclusion, phosphate binders significantly lower serum and urinary phosphorus and attenuate progression of secondary hyperparathyroidism among patients with CKD who have normal or

near-normal levels of serum phosphorus; however, they also promote the progression of vascular calcification.

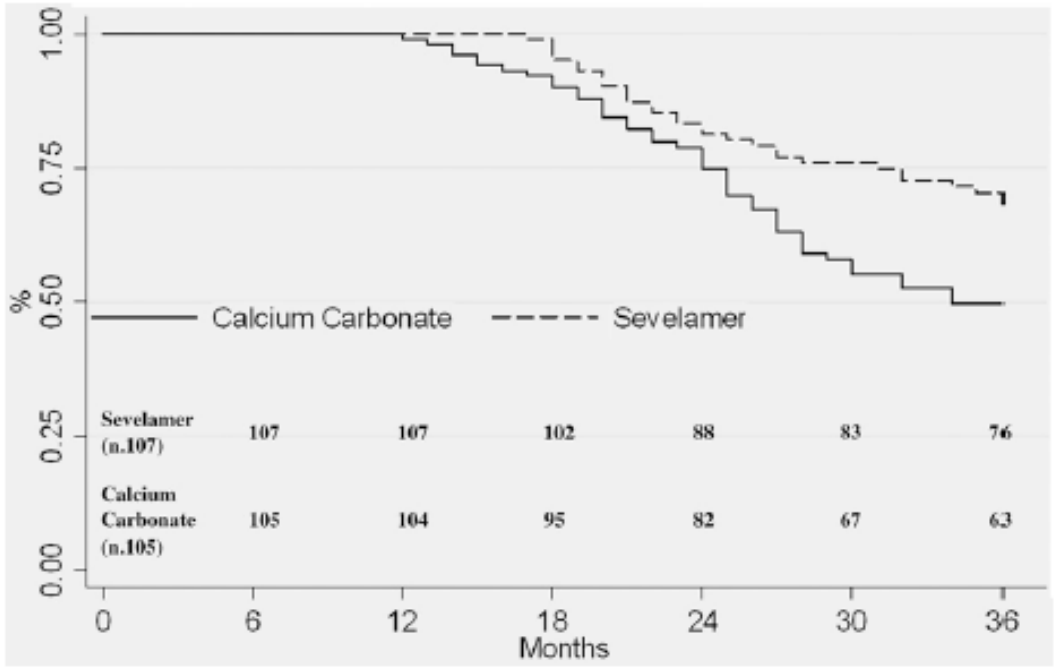
The safety and efficacy of phosphate binders in CKD remain uncertain

Phosphate Binders and Mortality

All-Cause Mortality



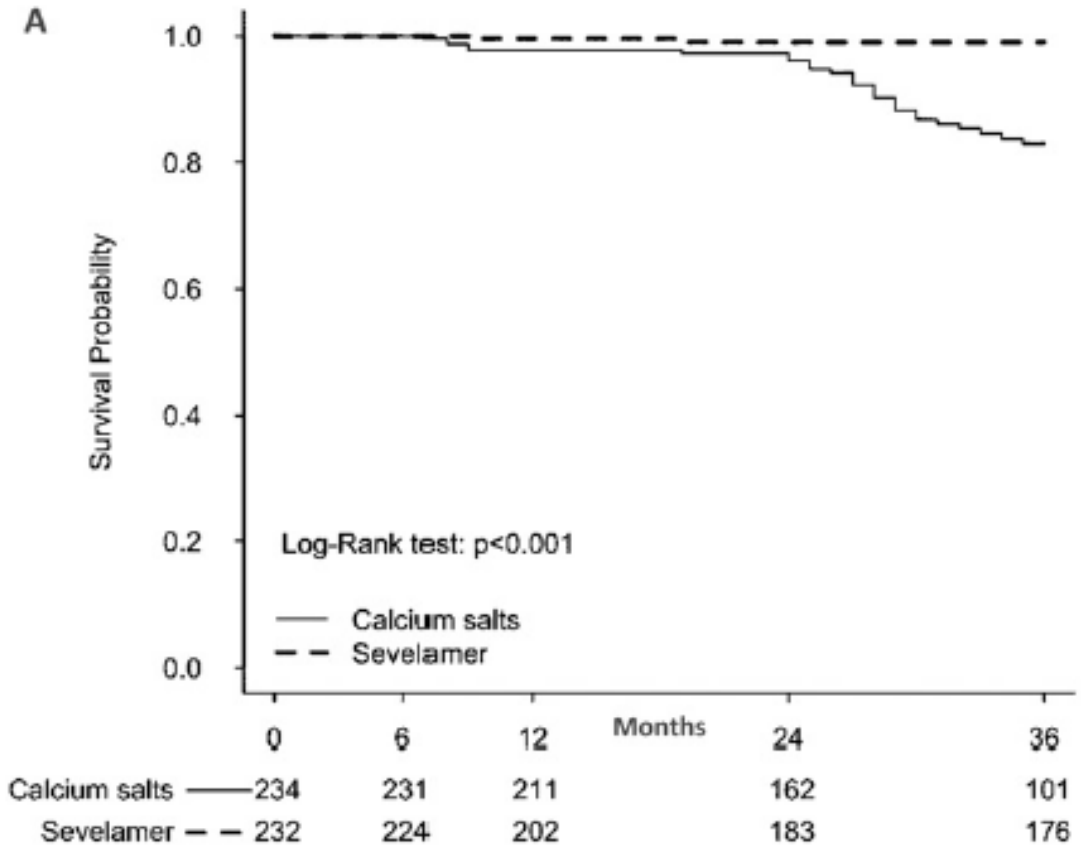
Dialysis Inception



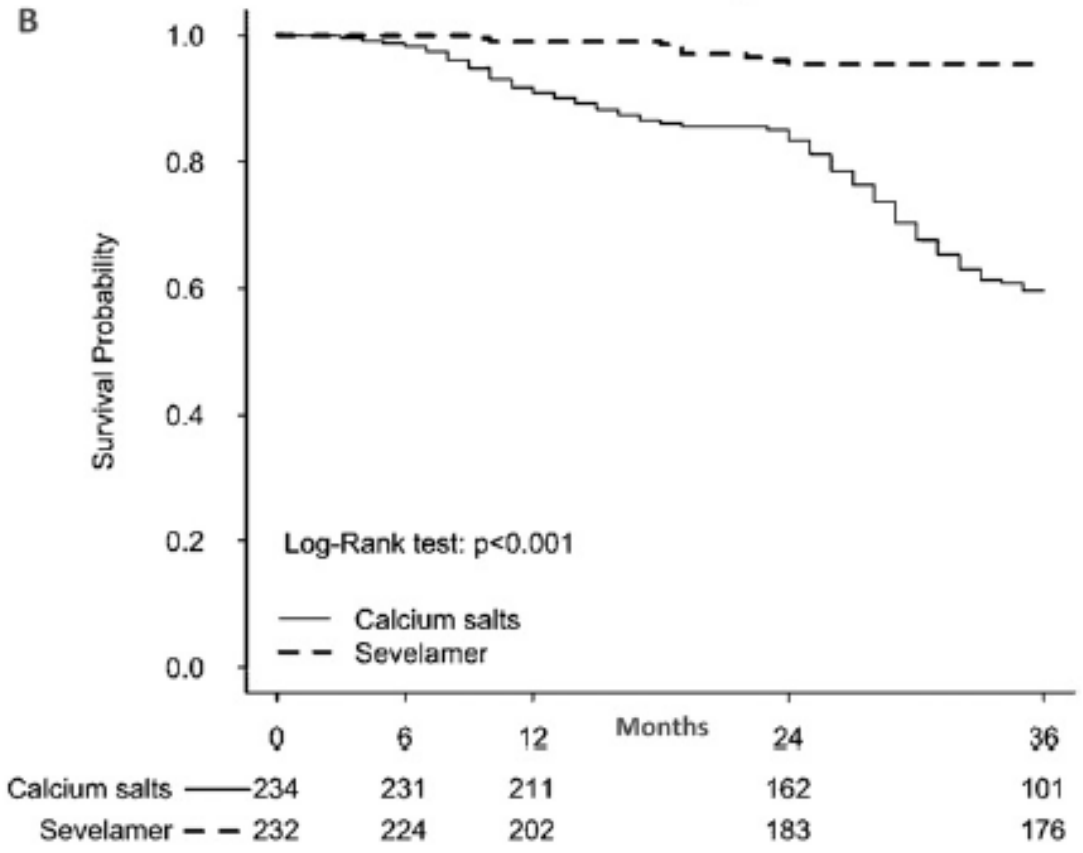
Di Iorio B et al. Clin J Am Soc Nephrol 2012;7:487-493

SEVELAMER VS. CALCIUM

Arrythmias



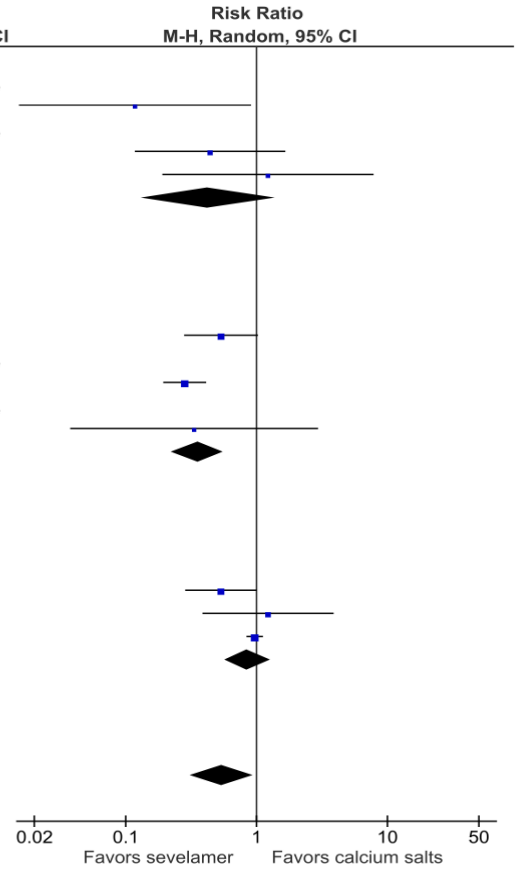
Cardiovascular Mortality



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

META ANALYSIS OF BINDER TRIALS IN CKD

Study or Subgroup	Sevelamer Events	Sevelamer Total	Calcium salts Events	Calcium salts Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Sevelamer versus calcium acetate						
Bleyer 1999	0	40	0	40		Not estimable
BRiC Study 2008	1	52	8	49	5.1%	0.12 [0.02, 0.91]
CARE Study 2004	0	50	0	48		Not estimable
CARE-2 Study 2008	3	100	7	103	8.8%	0.44 [0.12, 1.66]
Hervas 2003	2	18	2	22	5.8%	1.22 [0.19, 7.84]
Subtotal (95% CI)		**260**		**262**	**19.8%**	**0.43 [0.13, 1.38]**
Total events	6		17			
Heterogeneity: Tau² = 0.34; Chi² = 2.87, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 1.42 (P = 0.15)						
1.1.2 Sevelamer versus calcium carbonate						
Di Iorio 2012	12	107	22	105	14.8%	0.54 [0.28, 1.03]
Ferreira 2008 (1)	0	44	0	47		Not estimable
INDEPENDENT-HD Study 2013	28	232	100	234	17.2%	0.28 [0.19, 0.41]
Koiwa 2005	0	16	0	20		Not estimable
Sadek 2003 (2)	1	21	3	21	4.6%	0.33 [0.04, 2.95]
Subtotal (95% CI)		**420**		**427**	**36.6%**	**0.35 [0.22, 0.56]**
Total events	41		125			
Heterogeneity: Tau² = 0.05; Chi² = 2.78, df = 2 (P = 0.25); I² = 28%						
Test for overall effect: Z = 4.42 (P < 0.00001)						
1.1.3 Sevelamer versus calcium salts (calcium acetate and calcium carbonate)						
Block 2005	11	60	23	67	15.0%	0.53 [0.28, 1.00]
Chertow 2002	6	99	5	101	10.1%	1.22 [0.39, 3.88]
DCOR Study 2007	267	1053	275	1050	18.5%	0.97 [0.84, 1.12]
Subtotal (95% CI)		**1212**		**1218**	**43.6%**	**0.85 [0.57, 1.27]**
Total events	284		303			
Heterogeneity: Tau² = 0.06; Chi² = 3.47, df = 2 (P = 0.18); I² = 42%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Total (95% CI)		**1892**		**1907**	**100.0%**	**0.54 [0.32, 0.93]**
Total events	331		445			
Heterogeneity: Tau² = 0.41; Chi² = 45.11, df = 8 (P < 0.00001); I² = 82%						
Test for overall effect: Z = 2.21 (P = 0.03)						
Test for subgroup differences: Chi² = 8.11, df = 2 (P = 0.02), I² = 75.3%						



Footnotes

(1) In Navaneethan et al., 2011, these values are nested under "Sevelamer versus calcium acetate".

(2) These values were found in the publication yet not included in the analysis in Navaneethan et al., 2011.

Patel L et al CJASN 2016;11:232-44

DIETARY PHOSPHATE INTAKE

- **OLD 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 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)***

RATIONAL

- The principal recommendation remains the same as previous

but Work Group added a qualifier statement acknowledging other sources for phosphorus: natural phosphorus (as cellular and protein constituents) contained in raw or unprocessed foods; phosphorus added to foods during processing; and phosphorus in dietary supplements or medications.

PHOSPATE AND DIET

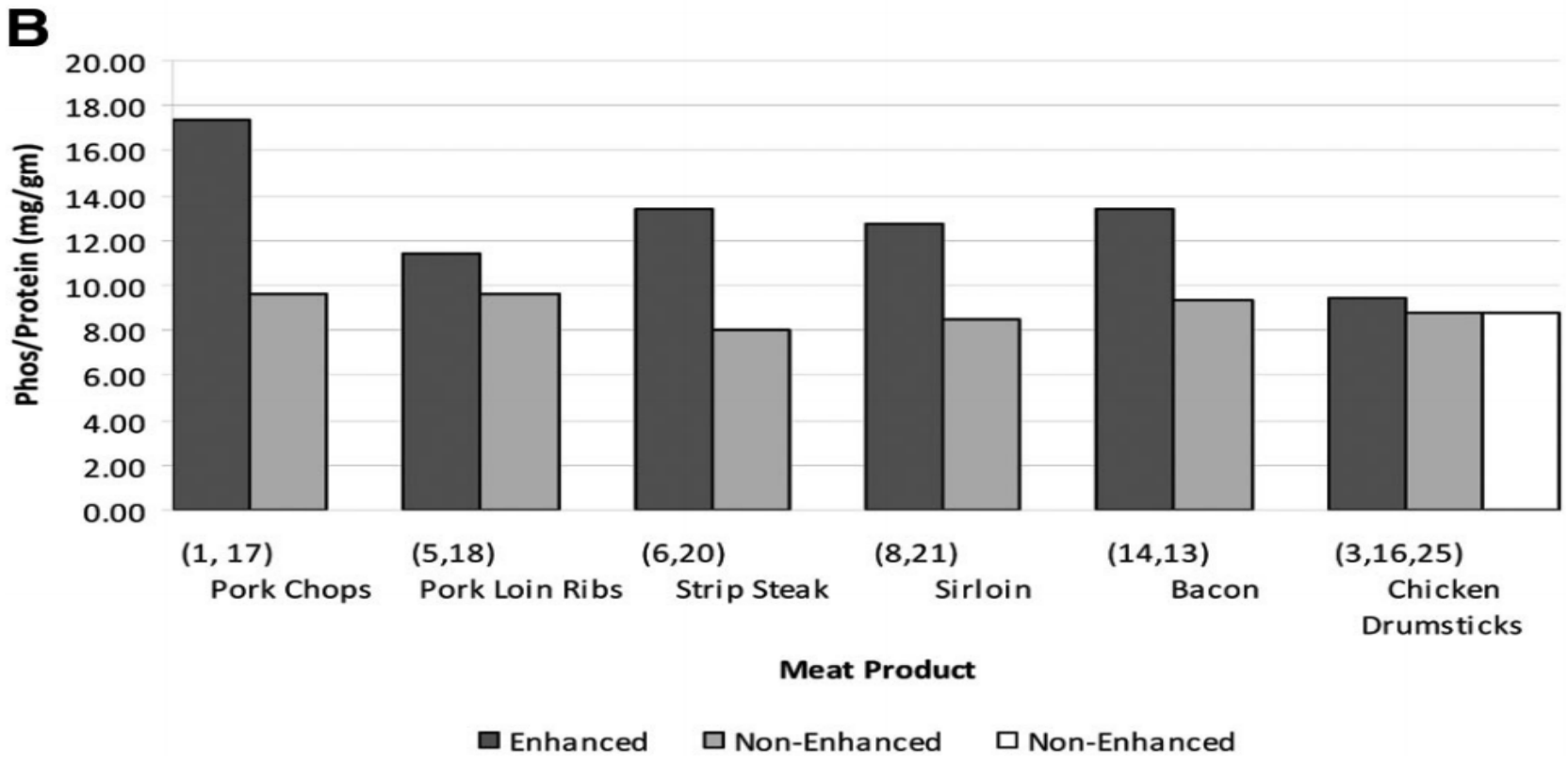
Table 2. Blood and urine measurements after 1 week of diet as outpatient

	Before Meat (casein) Diet	After Meat (casein) Diet	Before Vegetarian (grain) Diet	After Vegetarian (grain) Diet	*P* (paired *t* test)[a]
Average daily phosphorus intake (mg/day)		810 ± 27		795 ± 51	NS
Plasma phosphorus (mg/dl)	3.5 ± 0.6	3.7 ± 0.6	3.5 ± 0.6	3.2 ± 0.5	0.02
Plasma intact PTH (pg/ml)	58 ± 31	46 ± 29	58 ± 39	56 ± 30	0.002
Plasma FGF23 (pg/ml)	72 ± 39	101 ± 83	84 ± 65	61 ± 35	0.008
Plasma calcium (mg/dl)	9.2 ± 0.4	9.4 ± 0.7	9.3 ± 0.4	9.1 ± 0.3	NS
Creatinine clearance (ml/min)	47 ± 16	47 ± 16	43 ± 11	44 ± 16	NS
Urine 24-hour calcium excretion (mg/24 h)	66 ± 69	77 ± 48	60 ± 59	71 ± 43	NS
Urine 24-hour phosphorus excretion (mg/24 h)	836 ± 187	583 ± 216	778 ± 190	416 ± 233	0.07
Urine 24-hour FePhosph (%)	38.0 ± 6.2	23.9 ± 5.1	38.2 ± 11.5	20.9 ± 9.9	NS

[a]By paired *t* test comparing results at end (after) each 7-day controlled diet study period drawn at the same time (8:00 p.m.). Results are mean ± SD. The before values are shown to demonstrate what the patients ate on their own during the before-study and washout periods and to demonstrate no carryover effect.

Moe SM et al. Clin Am J Soc Nephrol. 2011;6:257-264

HIDDEN PHOSPHATE



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

Case Study:

- 67-y.o. female on HD for 2 years.
- Admitted for back pain, due to impression fracture of the tenth thoracic vertebra.
- On daily cholecalciferol (1,000 U), low-dose alfacalcidol, and sevelamer carbonate.
- Lab results:
  - Calcium: 9.0 mg/dL (2.3 mmol/L)
  - Phosphate: 5.7 mg/dL (1.8 mmol/L)
  - PTH: 450 pg/mL (48 pmol/L)
  - Alkaline phosphatase: 140 U/L

CASE STUDY:

- **What would you do next?**
  - A. Perform DEXA to estimate additional fracture risk.
  - B. Increase the dose of sevelamer carbonate.
  - C. Start denosumab.
  - D. Initiate cinacalcet.
  - E. Add calcium-containing phosphate binder.

The combination of low-dose active vitamin D and calcimimetics is effective in controlling hyperparathyroidism. In addition, fracture risk in this patient may be due to SHPT. Finally, phosphate control usually follows PTH control

CHAPTER 4.2

TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

VIT D +PTH

OLD 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).*

NEW 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***).

RATIONALE

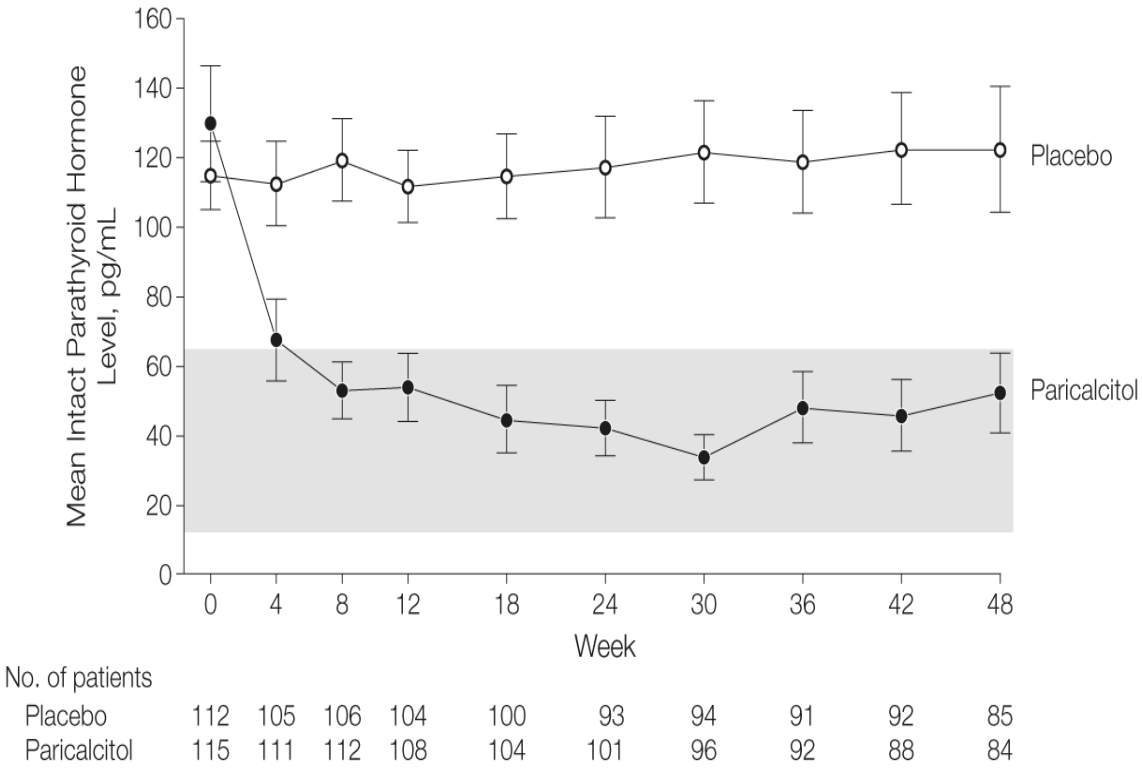
- Suppression of PTH via calcitriol and other vitamin D analogs have been the therapeutic mainstay for the treatment of SHPT.
- Multiple RCTs cited in the 2009 Guideline reported benefits of these agents on improving biochemical endpoints and adverse effects of hypercalcemia were also noted.
- Two trials, PRIMO and OPERA, demonstrated significantly increased risk of hypercalcemia in patients treated with paricalcitol, compared with placebo, in the absence of beneficial effects on surrogate cardiac endpoints.

PRIMO STUDY

At 48 weeks, the change in left ventricular mass index did not differ between treatment groups.

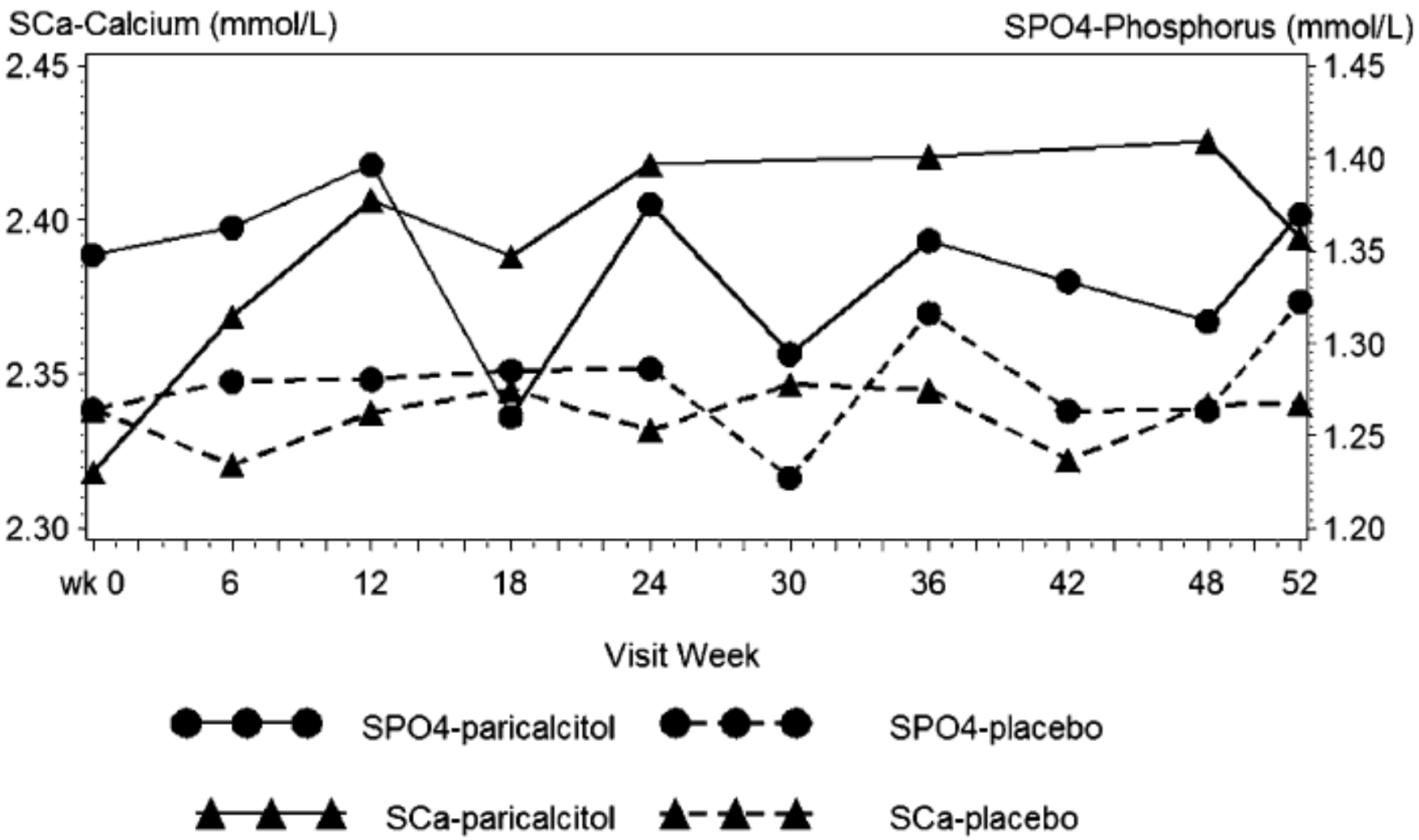
• Episodes of hypercalcaemia were more frequent in the paricalcitol group compared with the placebo group.

Population: 227 CKD patients (LVH)
Intervention: Paricalcitol 2 ug/d
Comparator: Placebo
Outcome: LVMI by echocardiogram
Timeline: 48 weeks



Thadhani et al, JAMA 2012

THE OPERA TRIAL



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

VIT D AND PTH

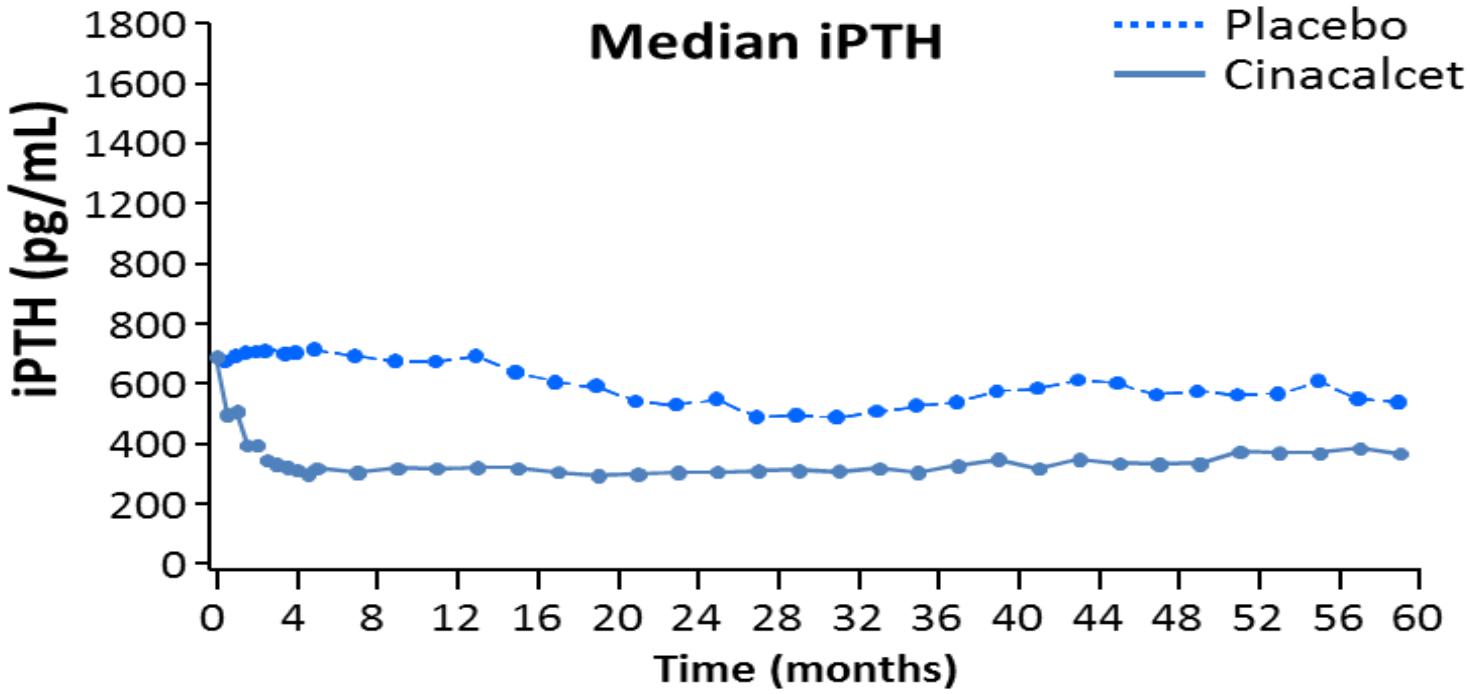
- **OLD 4.2.4:** *In patients with CKD G5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (**2B**).*

NEW 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***).

RATIONALE

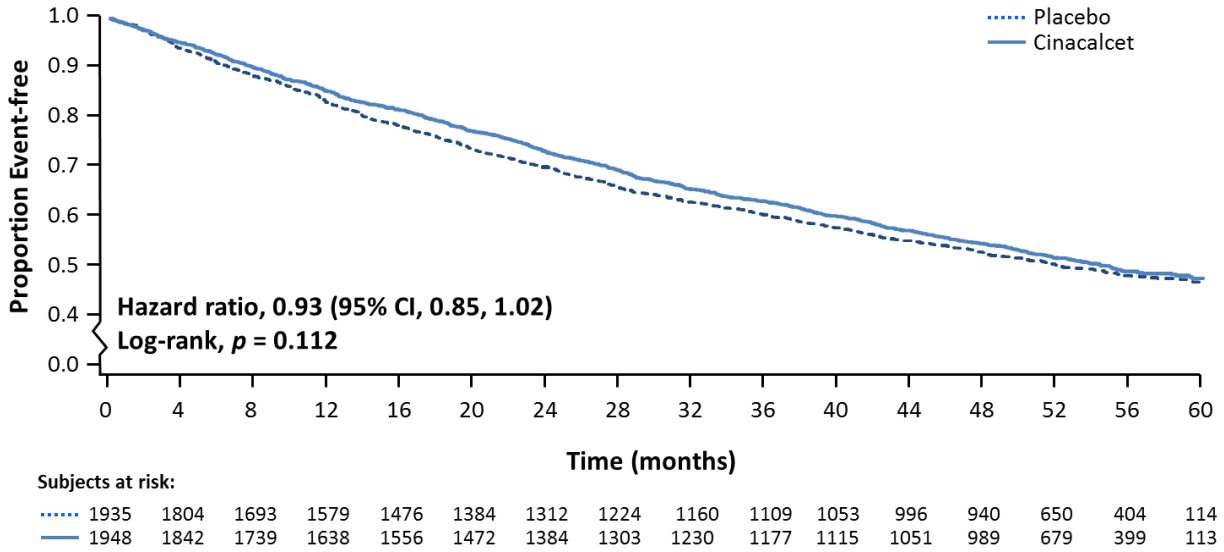
• This recommendation originally had not been identified for an update. However, due to a subsequent series of secondary and *post-hoc* publications of the EVOLVE trial, the Work Group decided to re-evaluate Rec. 4.2.4 as well.

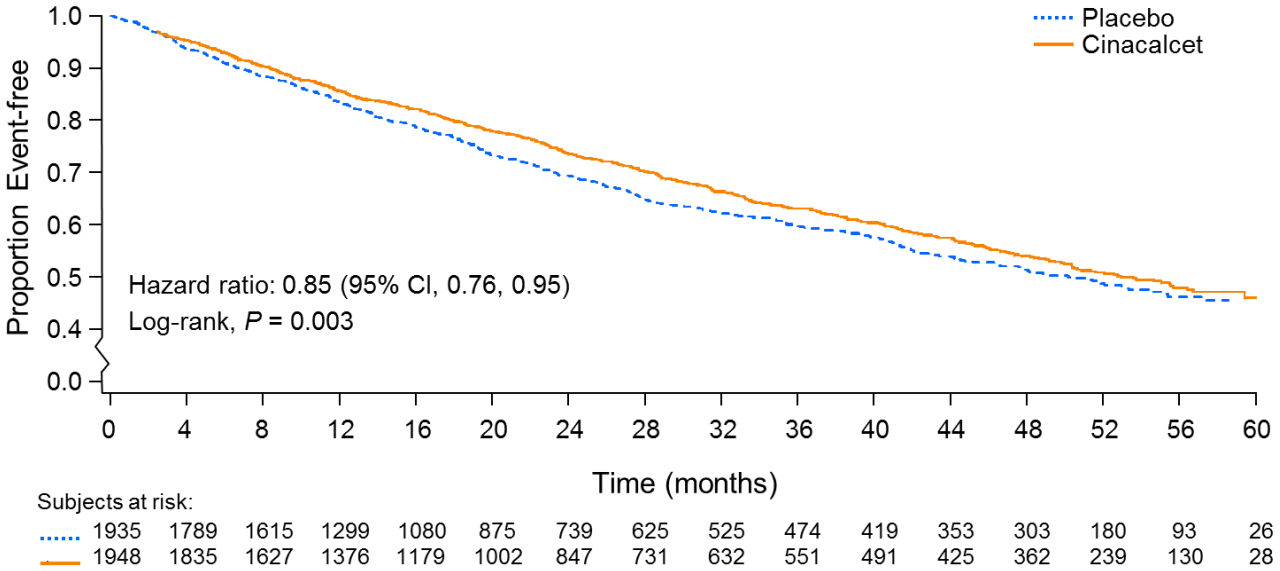
EVOLVE TRIAL



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

EVOLVE STUDY CINACALCATE





Case Study:

- 67-y.o. lean male on with eGFR of 25 ml/min/1.73 m^2, hypertension, ACR (albumin-creatinine ratio) 120 mg/g (1.2 mg/mmol).
- Seen on scheduled outpatient visit.
- Well-controlled blood pressure on lisinopril and metoprolol, besides sodium restriction.
- Lab results:
  - Calcium: 9.6 mg/dL (2.4 mmol/L) [corrected for albumin]
  - PTH: 160 pg/mL (17 pmol/L)
  - Phosphate: 4.2 mg/dL (1.4 mmol/L)

Case Study:

- **What is the best next step?**
  - A. Advise the patient to start a phosphate-restricted diet.
  - B. Measure concentration of 25(OH) vitamin D.
  - C. Initiate active vitamin D.
  - D. Measure FGF23 to estimate phosphate burden.

Although the optimal PTH in predialysis CKD is unknown, elevated concentrations may indicate nutritional vitamin D deficiency.

Chapter 4.3

Treatment of Bone with Bisphosphonates, other Osteoporosis Medications, and Growth Hormone

TREATMENT OPTIONS

New 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).

Old 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).*

TREATMENT OPTIONS

New 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).

Old 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).*

RATIONAL

- Rec. 3.2.2 now addresses the indications for a bone biopsy prior to antiresorptive and other osteoporosis therapies. Therefore, the old Rec. 4.3.4 was removed, and Rec. 4.3.3 was broadened from CKD G3a-G3b to CKD G3a-G5D.

Chapter 5

Evaluation and Treatment of Kidney Transplant Bone Disease

New 5.5: In patients with CKD G1T–G5T with risk factors for osteoporosis, we suggest that BMD testing be used to assess fracture risk if results will alter therapy (2C).

Old 5.5: *In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min per 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).*

New 5.5: In patients with CKD G1T–G5T with risk factors for osteoporosis, we suggest that BMD testing be used to assess fracture risk if results will alter therapy (2C).

Old 5.7: *In patients with CKD G4T–5T, 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)*.

New 5.6: In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 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.

Old 5.6*: In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m2 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, phosphorus, 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.

RATIONAL

- The second bullet is revised, consistent with the new bone biopsy recommendation (i.e., 2017 Rec. 3.2.2).

KEY MESSAGES:

1. 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.
2. It is important to emphasize the interdependency of serum calcium, phosphate, and PTH for clinical therapeutic decision-making.
3. Phosphate-lowering therapies may only be indicated in the case of “progressive or persistent hyperphosphatemia”.
4. New evidence suggests that excess exposure to exogenous calcium in adults may be harmful in all severities of CKD, regardless of other risk markers.

KEY MESSAGES:

5. It is reasonable to limit dietary phosphate intake, when considering all sources of dietary phosphate (including “hidden” sources).

6. 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.

7. No consensus was reached to recommend cinacalcet as first-line therapy for lowering PTH in all patients with SHPT and CKD G5D.


THANK YOU
FOR
ATTENTION