CKD-MBD Guidelines Update from KDIGO

Ali K. Abu-Alfa, MD, FASN, FASH
Professor of Medicine
Head, Division of Nephrology & Hypertension
Director, Human Research Protection Program
Director for Research Affairs
American University of Beirut

Adjunct Faculty
Section of Nephrology
Yale School of Medicine

Novosibirsk | September 23rd, 2017

KDIGO 2017 Clinical Practice Guideline Update

Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD

Summary of KDIGO CKD-MBD Guideline Recommendations

This Speaker's Guide combines the new recommendation statements (noted in green) from the *KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD)* with those that remained unchanged from the *2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD.*

THIS EDUCATIONAL TOOL WAS SUPPORT BY AN INDEPENDENT, EDUCATIONAL GRANT FROM

SANOFI

VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA

CONTENTS

CHAPTER 3.2:

DIAGNOSIS OF CKD-MBD: BONE

TESTING FOR CKD-MBD

New 3.2.1: **In patients with CKD G3a-G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest bone mineral density (BMD) testing to assess fracture risk if results will impact treatment decisions *(2B).***

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*).

Rationale for Update

- Multiple new prospective studies have documented that lower dual-energy X-ray absorptiometry (DXA) BMD predicts incident fractures in patients with CKD G3a–G5D.
- The order of these first two recommendations was changed, since a DXA BMD result might impact the decision to do a bone biopsy.

TESTING FOR CKD-MBD

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).***

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*).

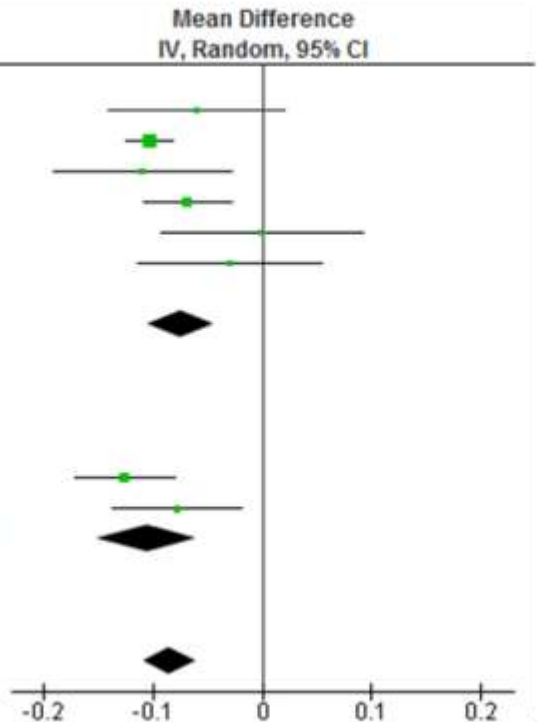
Rationale for Update

- 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.

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%	**-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%								



DXA BMD predicts fracture risk in advanced CKD, but not bone pathology/ROD type

Chapter 4.1:

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

Phosphate and Calcium

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).***

Rationale for Update

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

Phosphate and Calcium

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

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*).

Rationale for Update

- 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.

Phosphate and Calcium

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)*.

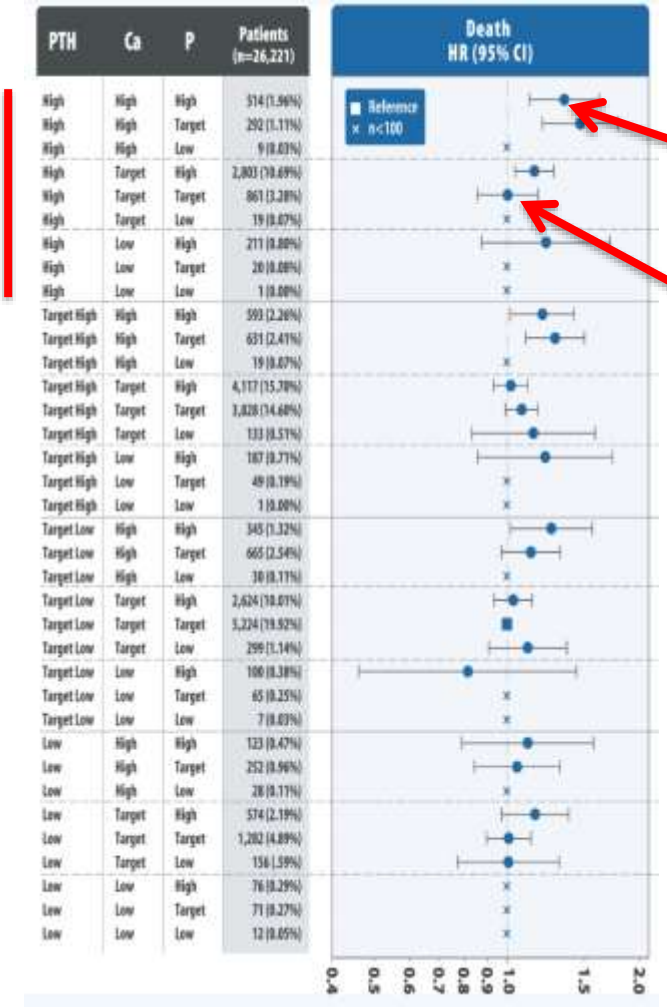
Old 4.1.2: In patients with CKD G3a–G5D, we suggest maintaining serum calcium in the normal range (*2D*).

Rationale for Update

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

CKD-MBD Phenotype and Adjusted Risk of Death or CV Hospitalization

PTH high



Ca, P high

Ca, P target

Block GA et al. Clin J Am Soc Nephrol. 2013;8:2132-2140.

Phosphate and Calcium

New 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).***

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*).

Rationale for Update

- 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 and Calcium

New 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).***

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*).

Rationale for Update

- The update emphasizes the perception that early "preventive" treatment of hyperphosphatemia is currently not supported by data (see Rec. 4.1.2).

Phosphate and Calcium

New 4.1.6:

In adult patients with CKD G3a–5D 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).*

Old 4.1.5:

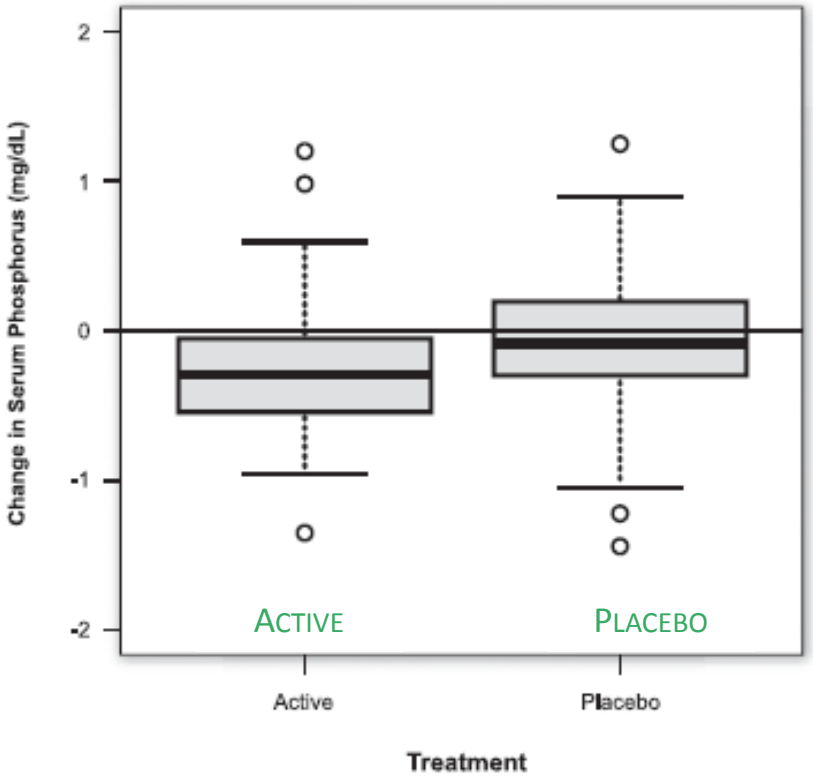
In patients with CKD G3a–G5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (*1B*).

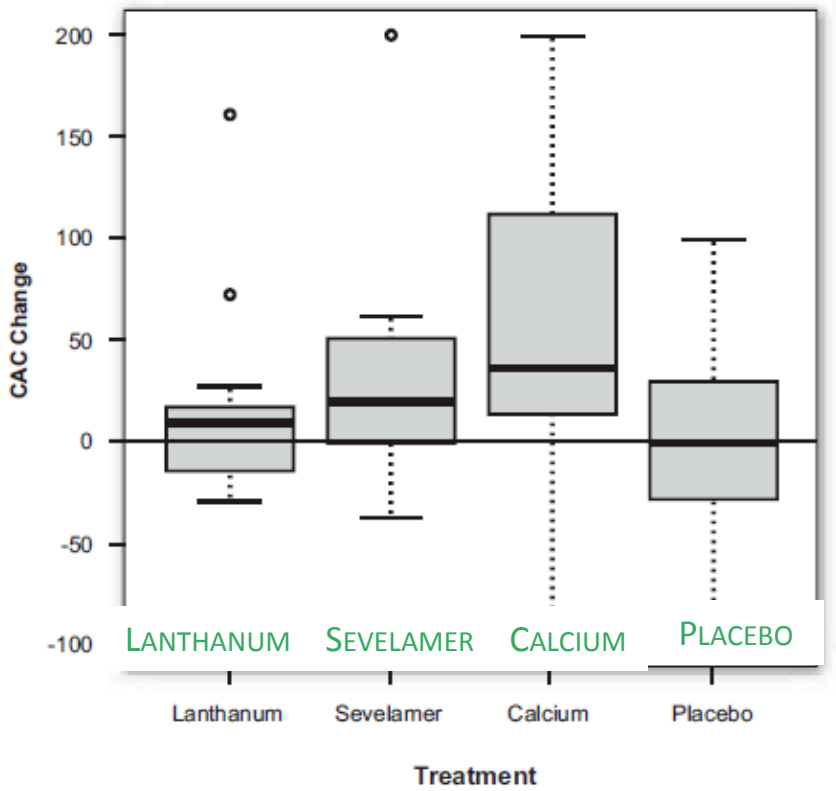
In patients with CKD G3a–G5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (*2C*) and/or adynamic bone disease (*2C*) and/or if serum PTH levels are persistently low (*2C*).

Rationale for Update

- New evidence from three randomized control trials (RCTs) supports a more general recommendation to restrict calcium-based phosphate binders in hyperphosphatemic patients of all severities of CKD.

Phosphate Binders in Moderate CKD

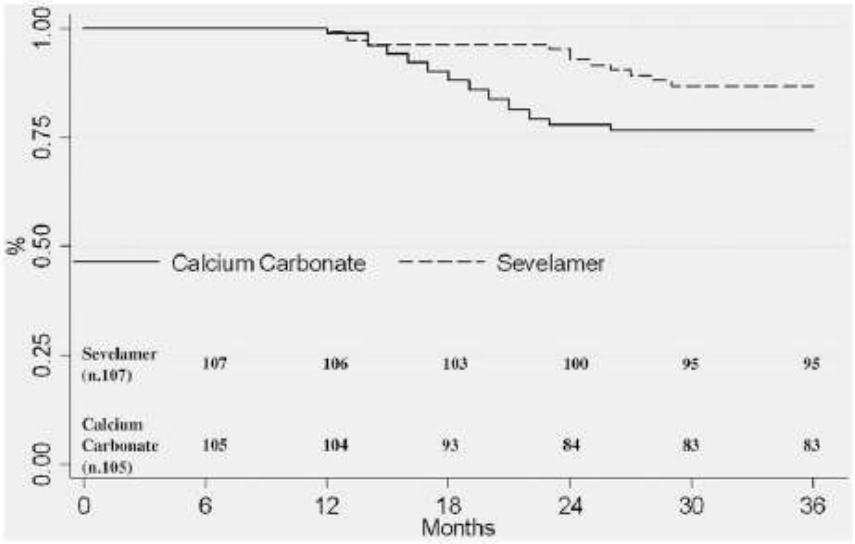




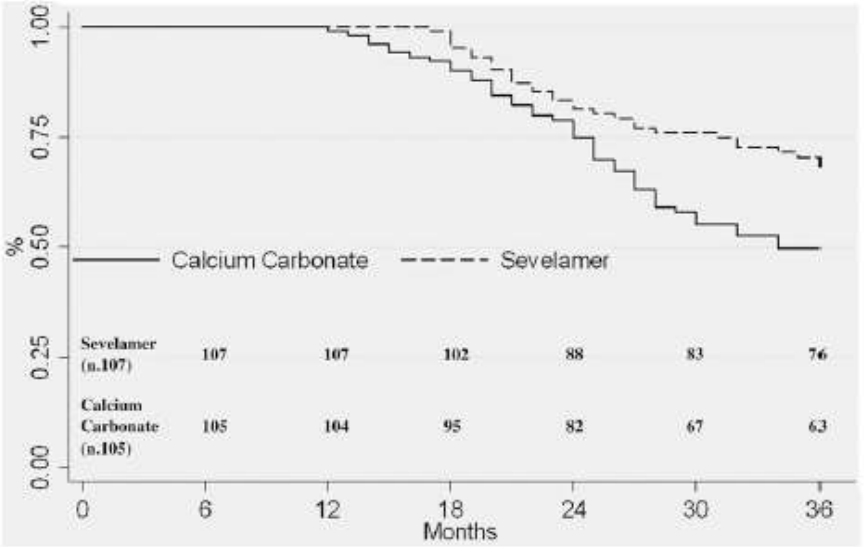
Block G et al. J Am Soc Nephrol. 2012;23:1407-1415.

Phosphate Binders and Mortality

All Cause Mortality (p<0.05)



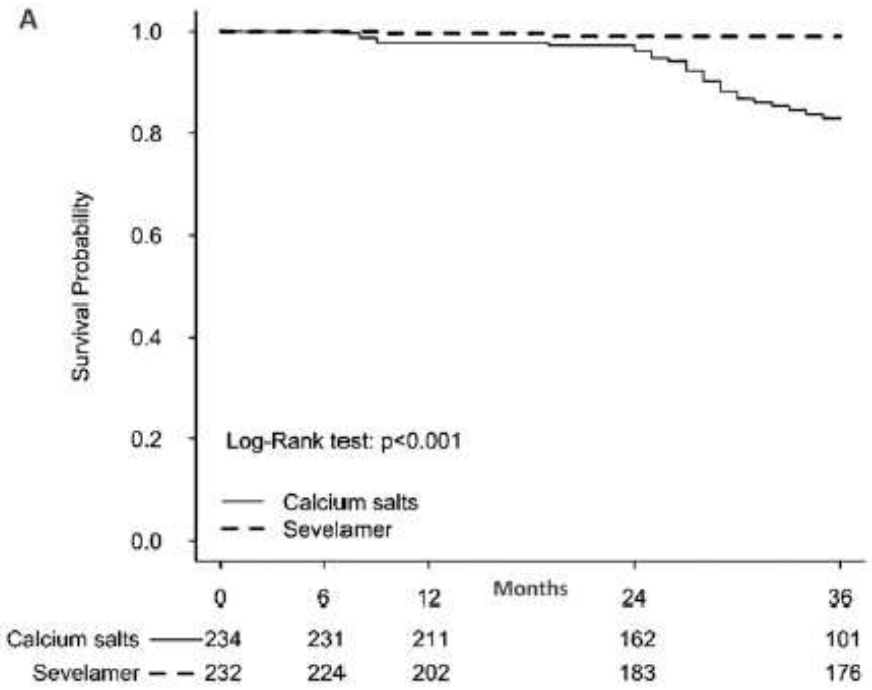
Inception to dialysis (NS)



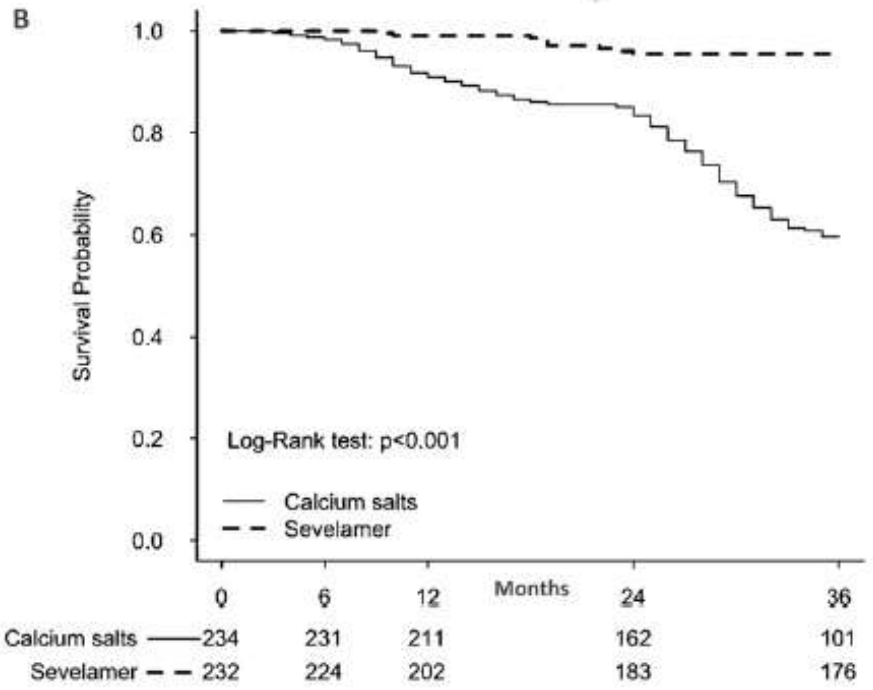
Di Iorio B et al. ***Clin J Am Soc Nephrol*** **2012;7:487-493**

SEVELAMER VS. CALCIUM

Arrythmias (p<0.001)



CV Survival (p<0.001)



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

PHOSPHATE

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).***

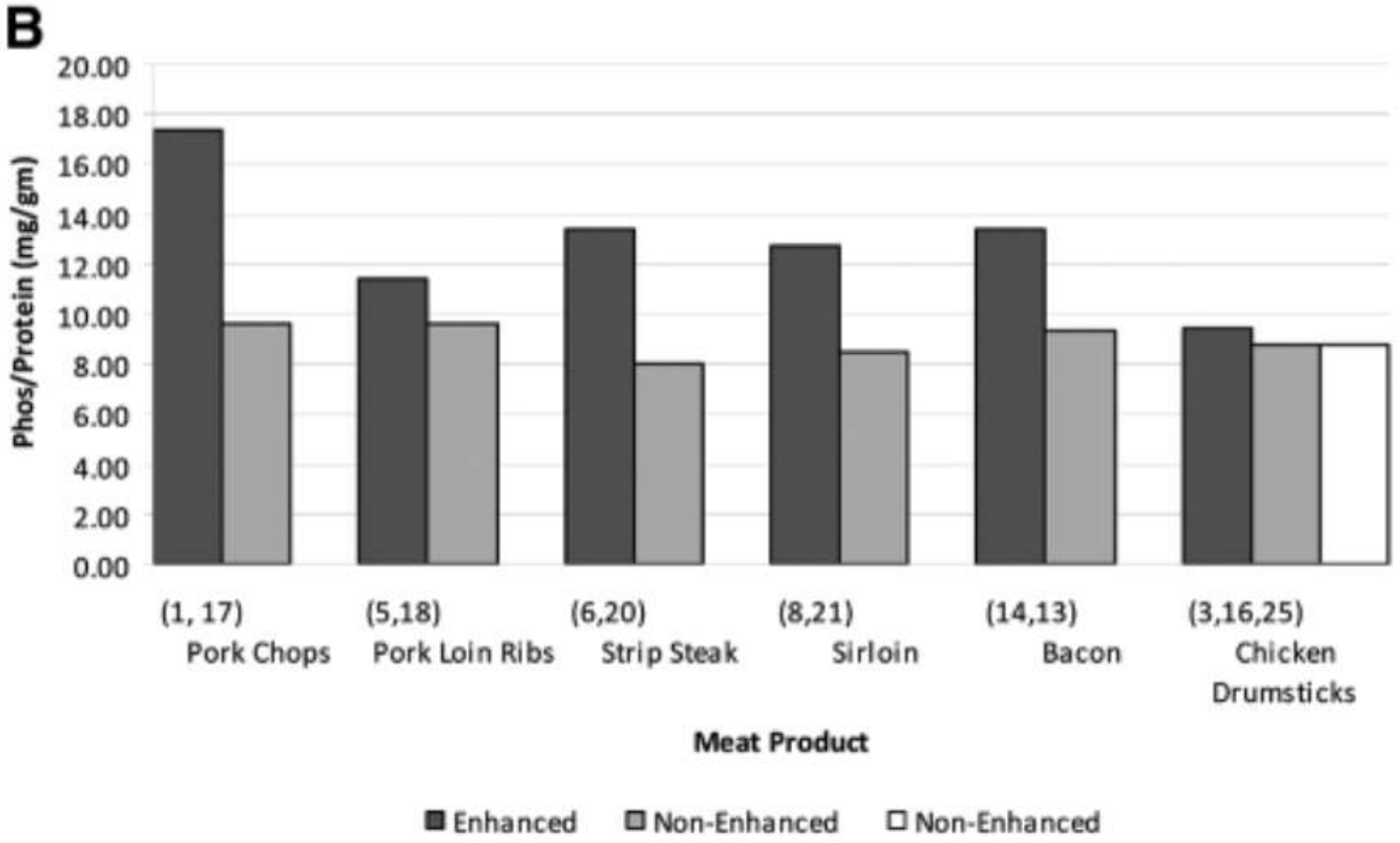
It is reasonable to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations *(Not Graded).*

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*).

Rationale for Update

- New data on phosphate sources were included as an additional qualifier for the previous recommendation.
- These sources included: 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.

"HIDDEN" PHOSPHATE



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

CHAPTER 4.2:

TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

Assessment of PTH

New 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).***

Old 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*).

Rationale for Update

- The Work Group felt that modest increases in PTH may represent an appropriate adaptive response to declining kidney function and have 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.
- Although the optimal PTH is not known, the Work Group felt that rising PTH levels in CKD G3a-G5 warrant examination of modifiable factors:
    - Vitamin D insufficiency/deficiency
    - Hypocalcemia
    - Hyperphosphatemia
    - High phosphate intake

Calcitriol and Vitamin D

New 4.2.2: **In adult patients with CKD G3a–G5 not on dialysis, we suggest 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).***

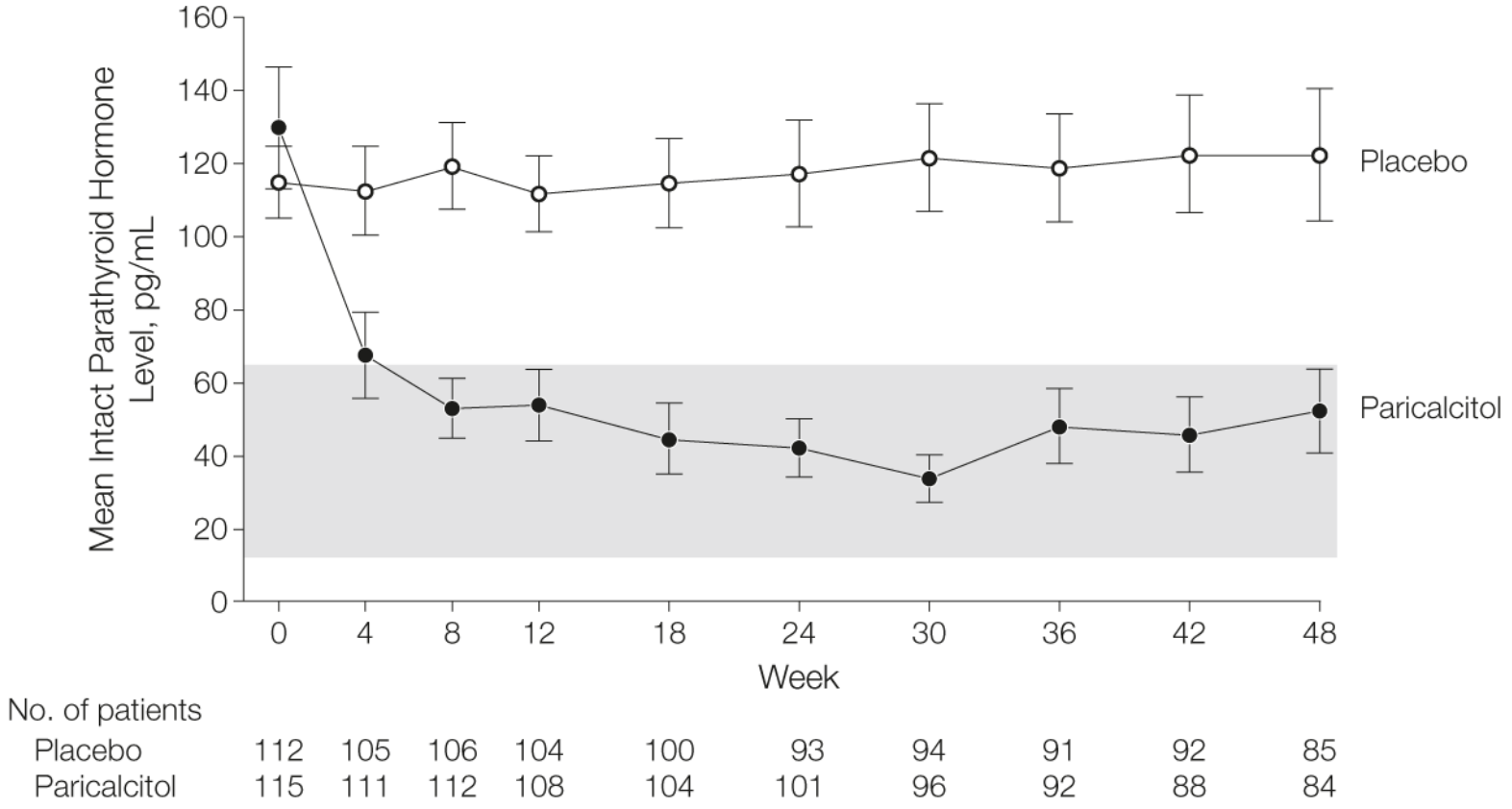
In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range *(Not Graded).*

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*).

Rationale for Update

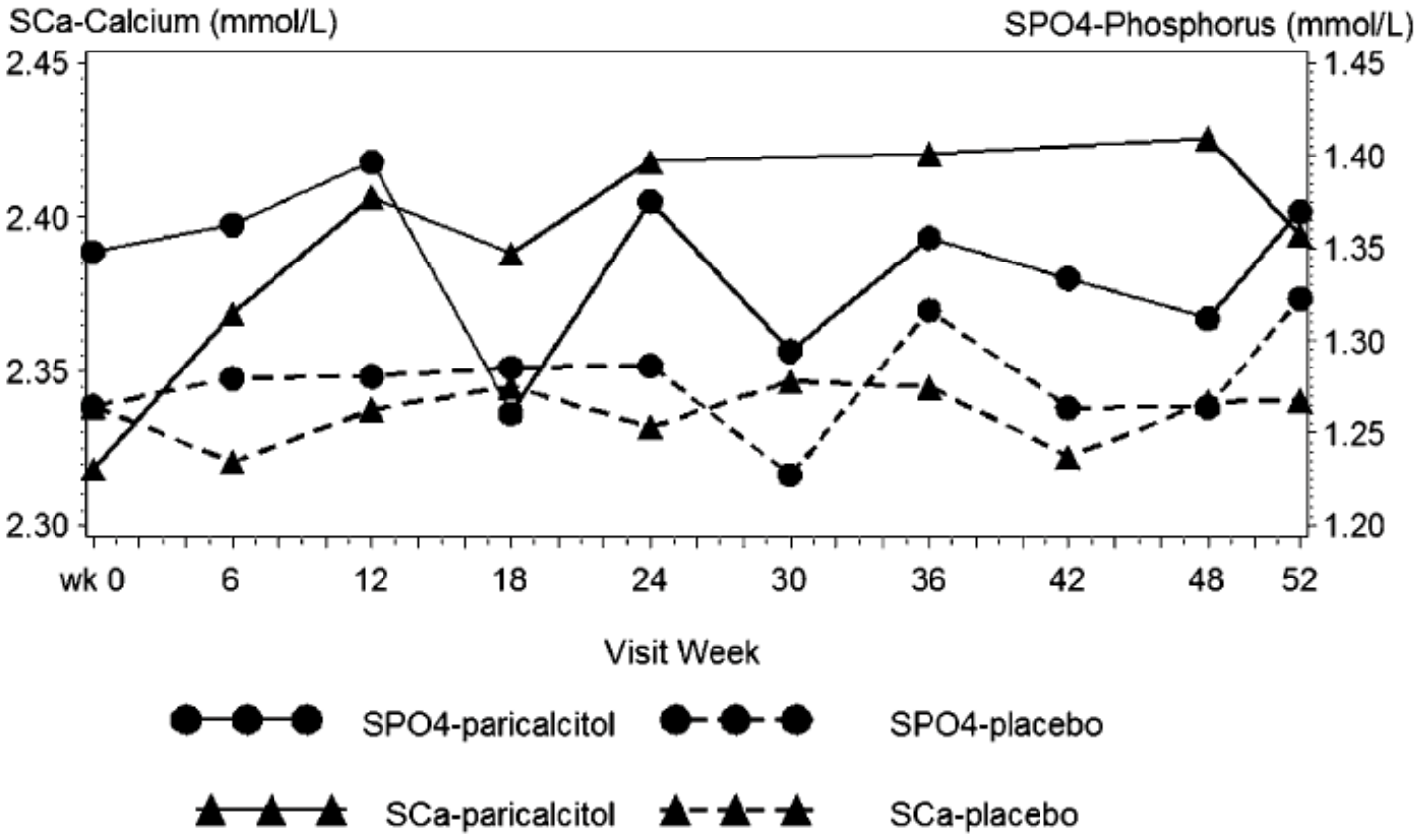
- Suppression of PTH via calcitriol and other vitamin D analogs have been the therapeutic mainstay for the treatment of secondary hyperparathyroidism (SHPT). Multiple RCTs cited in the 2009 Guideline reported benefits of these agents on improving biochemical endpoints, and adverse effects of hypercalcemia 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.

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

MAINTAINING/LOWERING PTH

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)*.**

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)*.

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

MAINTAINING/LOWERING PTH

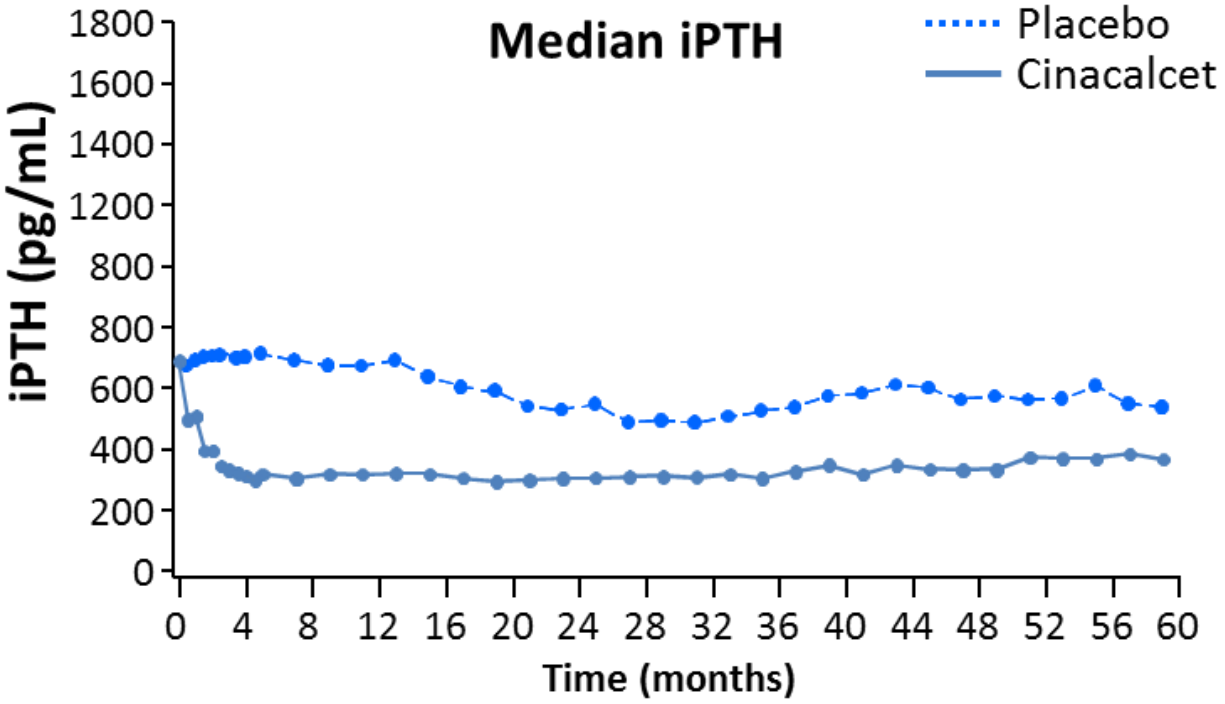
Old 4.2.4 (cont'd.):

- 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 two times the upper limit of normal for the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped *(2C)*.

Rationale for Update

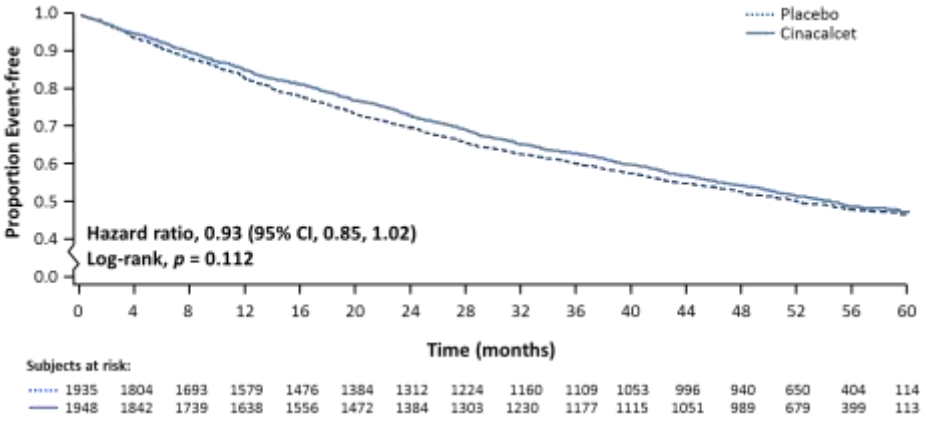
- Recommendation 4.2.4 originally had not been identified for an update. However, due to a subsequent series of secondary and *post-hoc* publications of the EVOLVE trial, the Work Group decided to re-evaluate it.
- Although EVOLVE did not meet its primary endpoint, the majority of the Work Group were reluctant to exclude potential benefits of calcimimetics for CKD G5D patients, based on subsequent prespecified analyses.
- No PTH-lowering treatment was prioritized at this time, since calcimimetics, calcitriol, and vitamin D analogs are all acceptable first-line options in CKD G5D patients.

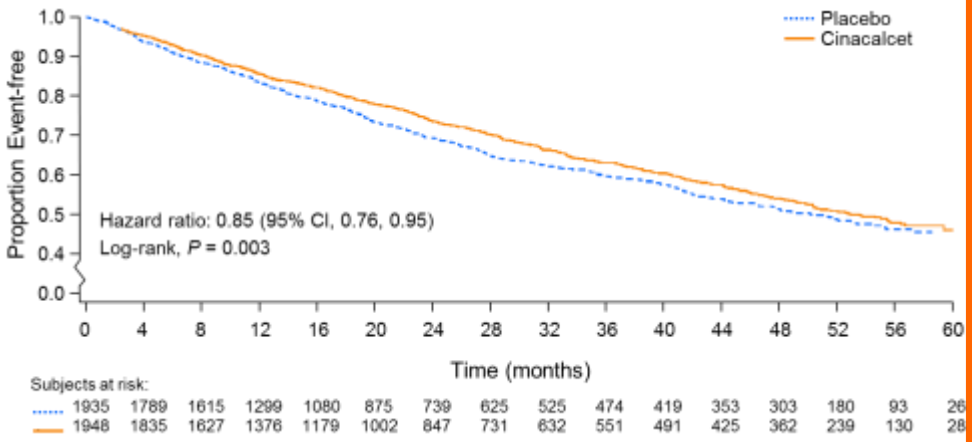
EVOLVE: LOWERING PTH



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

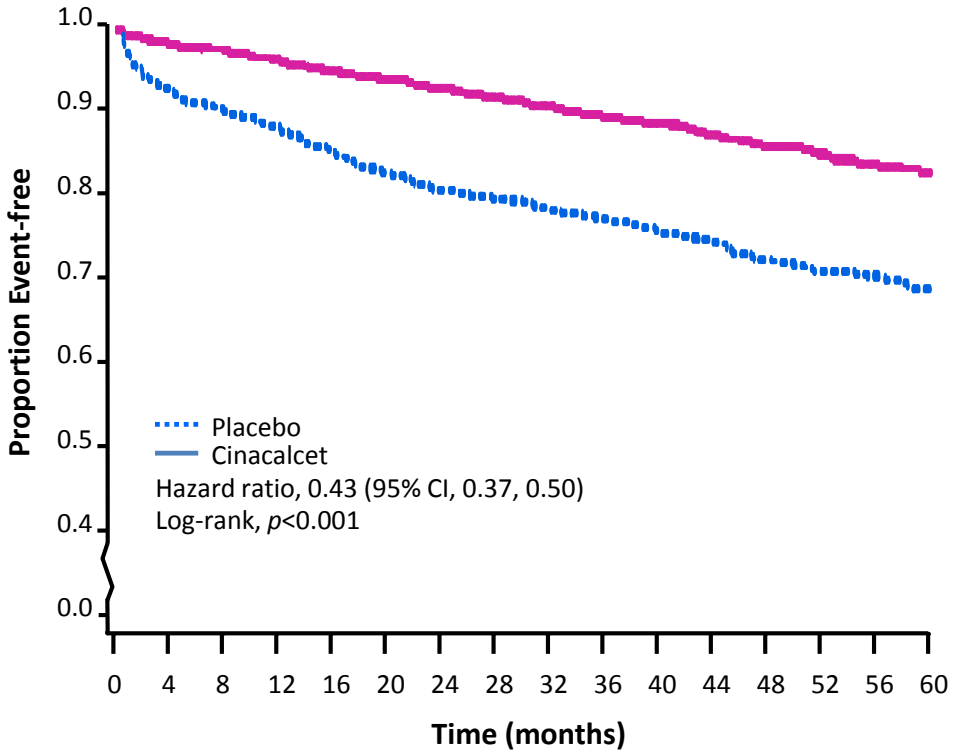
EVOLVE Study: Cinacalcet





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

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*).

Rationale for Update

- 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

Assessment

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*).

ASSESSMENT

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)*.

Rationale for Update

- 2009 Rec. 5.5 (addressing CKD transplant patients with eGFR > 30 ml/min/1.73 m^2) and Rec. 5.7 (addressing CKD G4T-G5T) were combined to yield 2017 Rec. 5.5.
- There is growing evidence that DXA BMD predicts fractures in patients with CKD across the spectrum of CKD data.

TREATMENT

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.

TREATMENT

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 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, 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.

Key Messages I

- 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.
- 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.

Key Messages II

- 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.
- No consensus was reached to recommend cinacalcet as first-line therapy for lowering PTH in all patients with SHPT and CKD G5D. All therapeutic options can be considered.

FOLLOW KDIGO

www.kdigo.org

/goKDIGO

@goKDIGO

@goKDIGO