KDIGO CKD-MBD Guideline Update Overview

David Wheeler, KDIGO Co-Chair

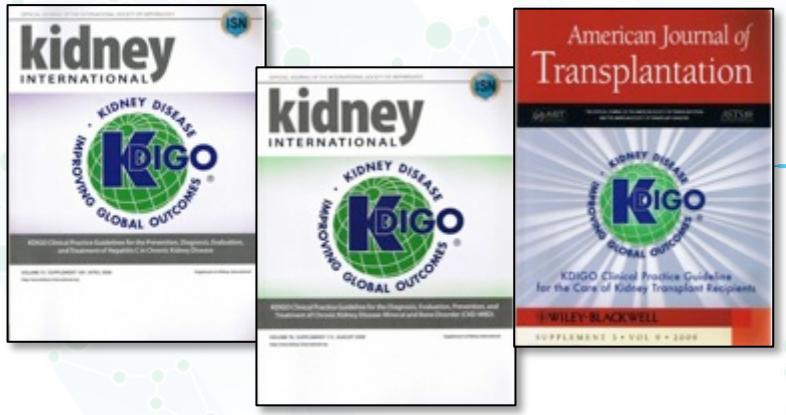
DISCLOSURES:

- Honoraria and/or travel support from: Akebia, Amgen, AstraZeneca, Boehringer Ingelheim, Vifor Fresenius Medical Care, and Janssen.

KDIGO Mission

Improve the care and outcomes of kidney disease patients worldwide through the development and implementation of clinical practice guidelines.

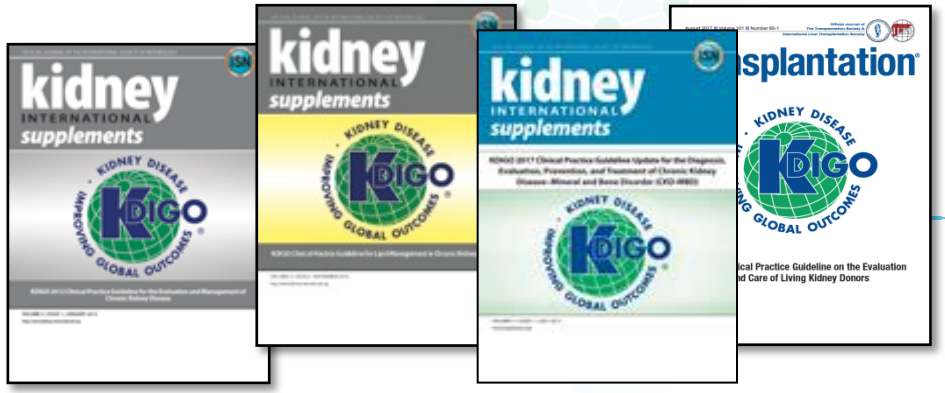
KDIGO GUIDELINES



Acute Kidney Injury March 2012
Glomerulonephritis June 2012
Anemia August 2012
Blood Pressure in CKD November 2012

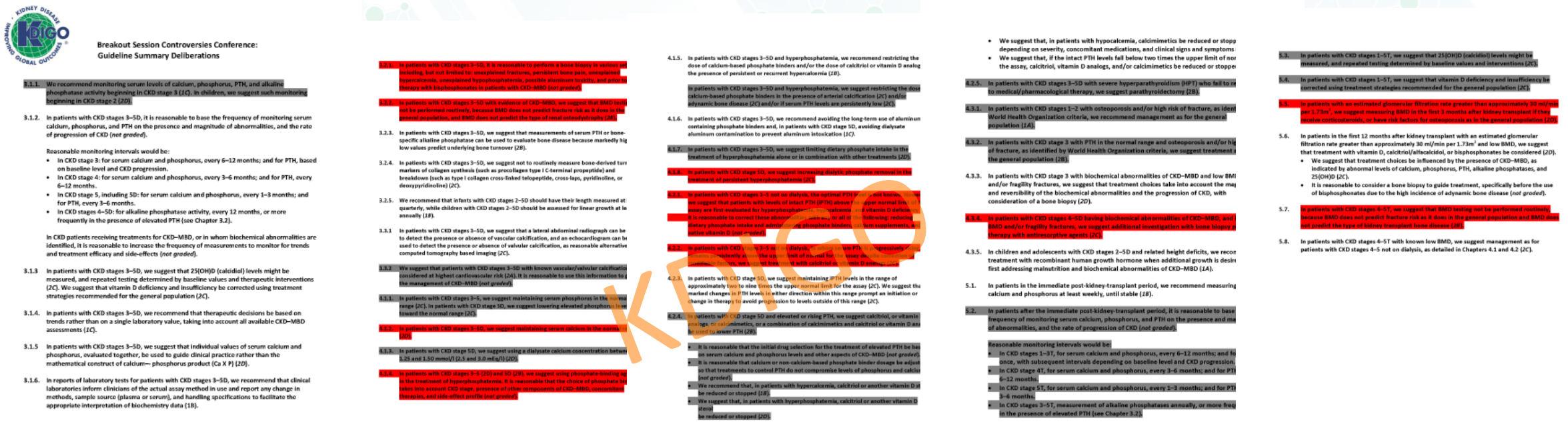
KDIGO

Hepatitis C April 2008
Mineral Bone Disorder July 2009
Transplant Recipient Oct 2009



Diagnosis and Management of CKD January 2013
Lipid Management November 2013
CKD-MBD Update July 2017
Living Kidney Donors August 2017

SELECTIVE GUIDELINE UPDATE:



Breakout Session Controversies Conference:
Guideline Summary Deliberations

3.1.1. We recommend monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity beginning in CKD stage 3 (*1C*). In children, we suggest such monitoring beginning in CKD stage 2 (*2D*).

3.1.2. In patients with CKD stages 3–5D, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, 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 stage 3: for serum calcium and phosphorus, every 6–12 months; and for PTH, based on baseline level and CKD progression.
- In CKD stage 4: for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.
- In CKD stage 5, including 5D: for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.
- In CKD stages 4–5D: for alkaline phosphatase activity, every 12 months, 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 trends and treatment efficacy and side-effects (*not graded*).

3.1.3 In patients with CKD stages 3–5D, 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 stages 3–5D, 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 stages 3–5D, we suggest that individual values of serum calcium and phosphorus, evaluated together, be used to guide clinical practice rather than the mathematical construct of calcium– phosphorus product (Ca X P) (*2D*).

3.1.6. In reports of laboratory tests for patients with CKD stages 3–5D, 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), and handling specifications to facilitate the appropriate interpretation of biochemistry data (*1B*).

4.2.1. In patients with CKD stages 3–5D, it is reasonable to perform a bone biopsy in various se 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*).

4.2.2. In patients with CKD stages 3–5D with evidence of CKD–MBD, we suggest that BMD testi 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*).

3.2.3. In patients with CKD stages 3–5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly hig low values predict underlying bone turnover (*2B*).

3.2.4. In patients with CKD stages 3–5D, we suggest not to routinely measure bone-derived turn 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 stages 2–5D should have their length measured at quarterly, while children with CKD stages 2–5D should be assessed for linear growth at le annually (*1B*).

3.3.1 In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be 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 alternative computed tomography based imaging (*2C*).

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

4.3.1. In patients with CKD stages 3–5, we suggest maintaining serum phosphorus in the norma range (*2C*). In patients with CKD stage 5D, we suggest lowering elevated phosphorus leve toward the normal range (*2C*).

4.3.2. In patients with CKD stages 3–5D, we suggest maintaining serum calcium in the norma (*2D*).

4.3.3. In patients with CKD stage 5D, we suggest using a dialysate calcium concentration betwee 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (*2D*).

4.3.4. In patients with CKD stages 3–5 (2D) and 5D (2B), we suggest using phosphate-binding ag in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate bi 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 stages 3–5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog the presence of persistent or recurrent hypercalcemia (*1B*).

In patients with CKD stages 3–5D and hyperphosphatemia, we suggest restricting the dose 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*).

4.1.6. In patients with CKD stages 3–5D, we recommend avoiding the long-term use of aluminum containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (*1C*).

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

4.1.8. In patients with CKD stage 5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (*2C*).

4.2.1. In patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known. Howe we suggest that patients with levels of intact PTH (iPTH) above the upper normal limit of assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficie It is reasonable to correct these abnormalities, serially, or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, a active vitamin D (*not graded*).

4.2.2. In patients with CKD stages 3–5 not on dialysis, if kidney failure PTH is progressively ri 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*).

4.2.3. In patients with CKD stage 5D, we suggest maintaining iPTH levels in the range of approximately two to nine times the upper normal limit for the assay (*2C*). We suggest tha marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (*2C*).

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

- It is reasonable that the initial drug selection for the treatment of elevated PTH be bas 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 adjust so that treatments to control PTH do not compromise levels of phosphorus and calciu (*not graded*).
- We recommend that, in patients with hypercalcemia, calcitriol or another vitamin D s be reduced or stopped (*1B*).
- We suggest that, in patients with hyperphosphatemia, calcitriol or another vitamin D stero be reduced or stopped (*2D*).

- We suggest that, in patients with hypocalcemia, calcimimetics be reduced or stopp depending on severity, concomitant medications, and clinical signs and symptoms
- We suggest that, if the intact PTH levels fall below two times the upper limit of nor the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stoppe

4.2.5. In patients with CKD stages 3–5D with severe hyperparathyroidism (HPT) who fail to re to medical/pharmacological therapy, we suggest parathyroidectomy (*2B*).

4.3.1. In patients with CKD stages 1–2 with osteoporosis and/or high risk of fracture, as ident World Health Organization criteria, we recommend management as for the general population (*1A*).

4.3.2. In patients with CKD stage 3 with PTH in the normal range and osteoporosis and/or hig of fracture, as identified by World Health Organization criteria, we suggest treatment the general population (*2B*).

4.3.3. In patients with CKD stage 3 with biochemical abnormalities of CKD–MBD and low BM and/or fragility fractures, we suggest that treatment choices take into account the ma 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 stages 4–5D having biochemical abnormalities of CKD–MBD, and l BMD and/or fragility fractures, we suggest additional investigation with bone biopsy p therapy with antiresorptive agents (*2C*).

4.3.5. In children and adolescents with CKD stages 2–5D and related height deficits, we recon treatment with recombinant human growth hormone when additional growth is desir first addressing malnutrition and biochemical abnormalities of CKD–MBD (*1A*).

5.1. In patients in the immediate post-kidney-transplant period, we recommend measuring calcium and phosphorus at least weekly, until stable (*1B*).

5.2. In patients after the immediate post-kidney-transplant period, it is reasonable to base frequency of monitoring serum calcium, phosphorus, and PTH on the presence and ma of abnormalities, and the rate of progression of CKD (*not graded*).

Reasonable monitoring intervals would be:
- In CKD stages 1–3T, for serum calcium and phosphorus, every 6–12 months; and fo once, with subsequent intervals depending on baseline level and CKD progression.
- In CKD stage 4T, for serum calcium and phosphorus, every 3–6 months; and for PT 6–12 months.
- In CKD stage 5T, for serum calcium and phosphorus, every 1–3 months; and for PT 3–6 months.
- In CKD stages 3–5T, measurement of alkaline phosphatases annually, or more freq in the presence of elevated PTH (see Chapter 3.2).

5.3. In patients with CKD stages 1–5T, 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 stages 1–5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (*2C*).

5.5. In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73m^2, we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (*2D*).

5.6. In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73m^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*).

5.7. In patients with CKD stages 4–5T, 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*).

5.8. In patients with CKD stages 4–5T with known low BMD, we suggest management as for patients with CKD stages 4–5 not on dialysis, as detailed in Chapters 4.1 and 4.2 (*2C*).

Overview of proposed changes

- Selective update in **red**
- Minor changes in **dark grey**
- No changes **in black and white**

CKD-MBD Guideline Update 2017

Guideline Chairs

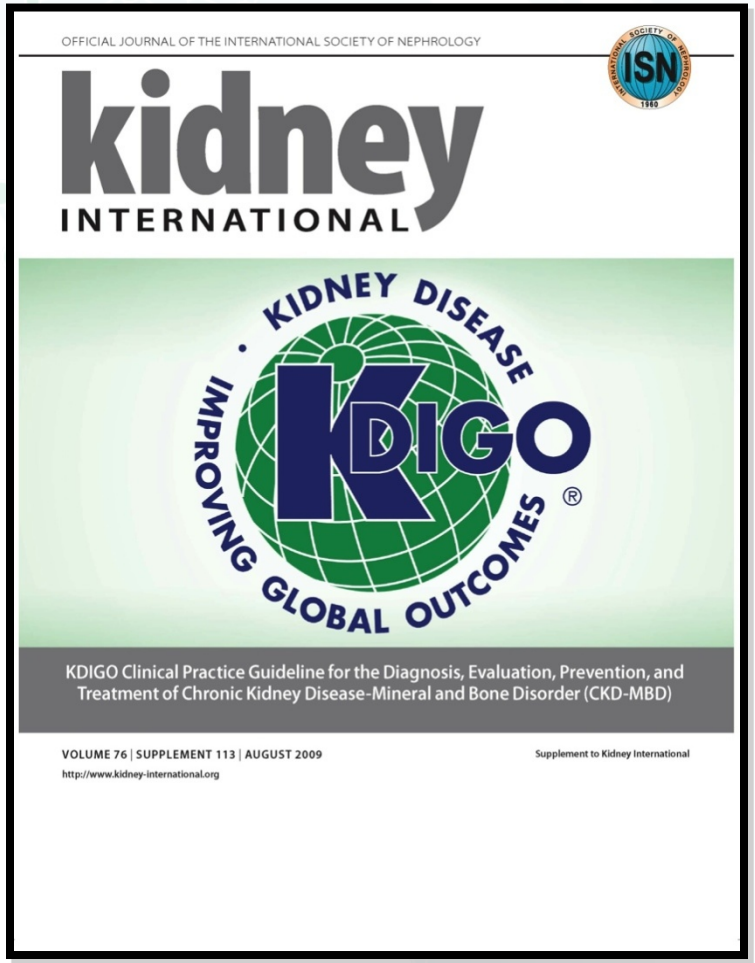
Markus Ketteler (Germany)

Mary B Leonard (USA)

Work Group

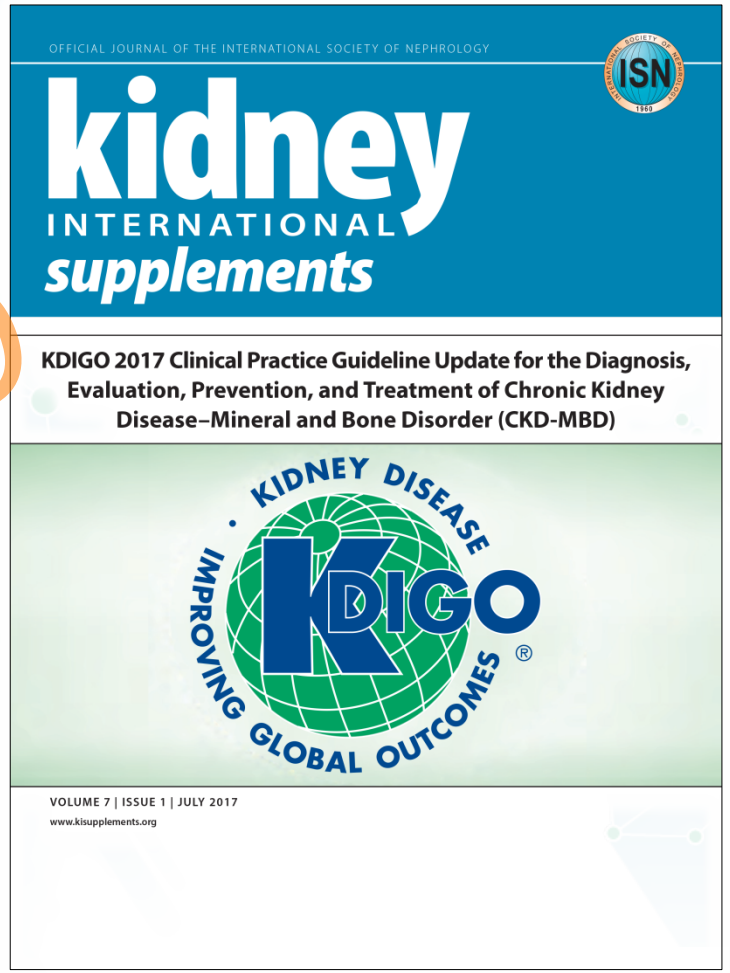
- Geoffrey A. Block (USA)
- Pieter Evenepoel (Belgium)
- Masafumi Fukagawa (Japan)
- Charles A. Herzog (USA)
- Linda McCann (USA)
- Sharon M. Moe (USA)
- Rukshana Shroff (UK)
- Marcello A. Tonelli (Canada)
- Nigel D. Toussaint (Australia)
- Marc G. Vervloet (Netherlands)

KDIGO CKD-MBD GUIDELINE UPDATE



August 2009

KDIGO



July 2017

Summary and comparison of 2017 updated and 2009 KDIGO CKD-MBD recommendations

2017 revised KDIGO CKD-MBD recommendations	2009 KDIGO CKD-MBD recommendations	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.
4.1.1. In patients with CKD G3a–G5D, treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together (*Not Graded*).		This new recommendation was provided in order to emphasize the complexity and interaction of CKD-MBD laboratory parameters.
4.1.2. In patients with CKD G3a–G5D, we suggest lowering elevated phosphate levels toward the normal range (*2C*).	4.1.1. In patients with CKD G3a–G5, we suggest maintaining serum phosphate in the normal range (*2C*). In patients with CKD G5D, we suggest lowering elevated phosphate levels toward the normal range (*2C*).	There is an absence of data supporting that efforts to maintain phosphate in the normal range are of benefit to CKD G3a–G4 patients, including some safety concerns. Treatment should aim at overt hyperphosphatemia.
4.1.3. In adult patients with CKD G3a–G5D, we suggest avoiding hypercalcemia (*2C*). In children with CKD G3a–G5D, we suggest maintaining serum calcium in the age-appropriate normal range (*2C*).	4.1.2. In patients with CKD G3a–G5D, we suggest maintaining serum calcium in the normal range (*2D*).	Mild and asymptomatic hypocalcemia (e.g., in the context of calcimimetic treatment) can be tolerated in order to avoid inappropriate calcium loading in adults.
4.1.4. In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (*2C*).	4.1.3. In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (*2D*).	Additional studies of better quality are available; however, these do not allow for discrimination of benefits and harms 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.
4.1.5. In patients with CKD G3a–G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate (*Not Graded*).	4.1.4. In patients with CKD G3a–G5 (*2D*) and G5D (*2B*), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side effect profile (*Not Graded*).	Emphasizes the perception that early "preventive" phosphate-lowering treatment is currently not supported by data (see Recommendation 4.1.2). The broader term "phosphate-lowering" treatment is used instead of phosphate binding agents since all possible approaches (i.e., binders, diet, dialysis) can be effective.

(*Continued on next page*)

2017 revised KDIGO CKD-MBD recommendations	2009 KDIGO CKD-MBD recommendations	Brief rationale for updating
4.1.6. In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binder (*2B*). In children with CKD G3a–G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (*Not Graded*).	4.1.5. In patients with CKD G3a–G5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (*1B*). In patients with CKD G3a–G5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (*2C*) and/or adynamic bone disease (*2C*) and/or if serum PTH levels are persistently low (*2C*).	New evidence from 3 RCTs supports a more general recommendation to restrict calcium-based phosphate binders in hyperphosphatemic patients across all severities of CKD.
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 to be included as an additional qualifier to the previous recommendation.
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.
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.
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*).	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.

GUIDELINE TOPICS

Topic 1:	Bone Quality
Topic 2:	Serum phosphate
Topic 3:	Serum calcium
Topic 4:	Dialysate calcium
Topic 5:	Phosphate binders
Topic 6:	Dietary phosphate intake
Topic 7:	Vitamin D and PTH
Topic 8:	Vascular calcification
Topic 9:	Parathyroid hormone range

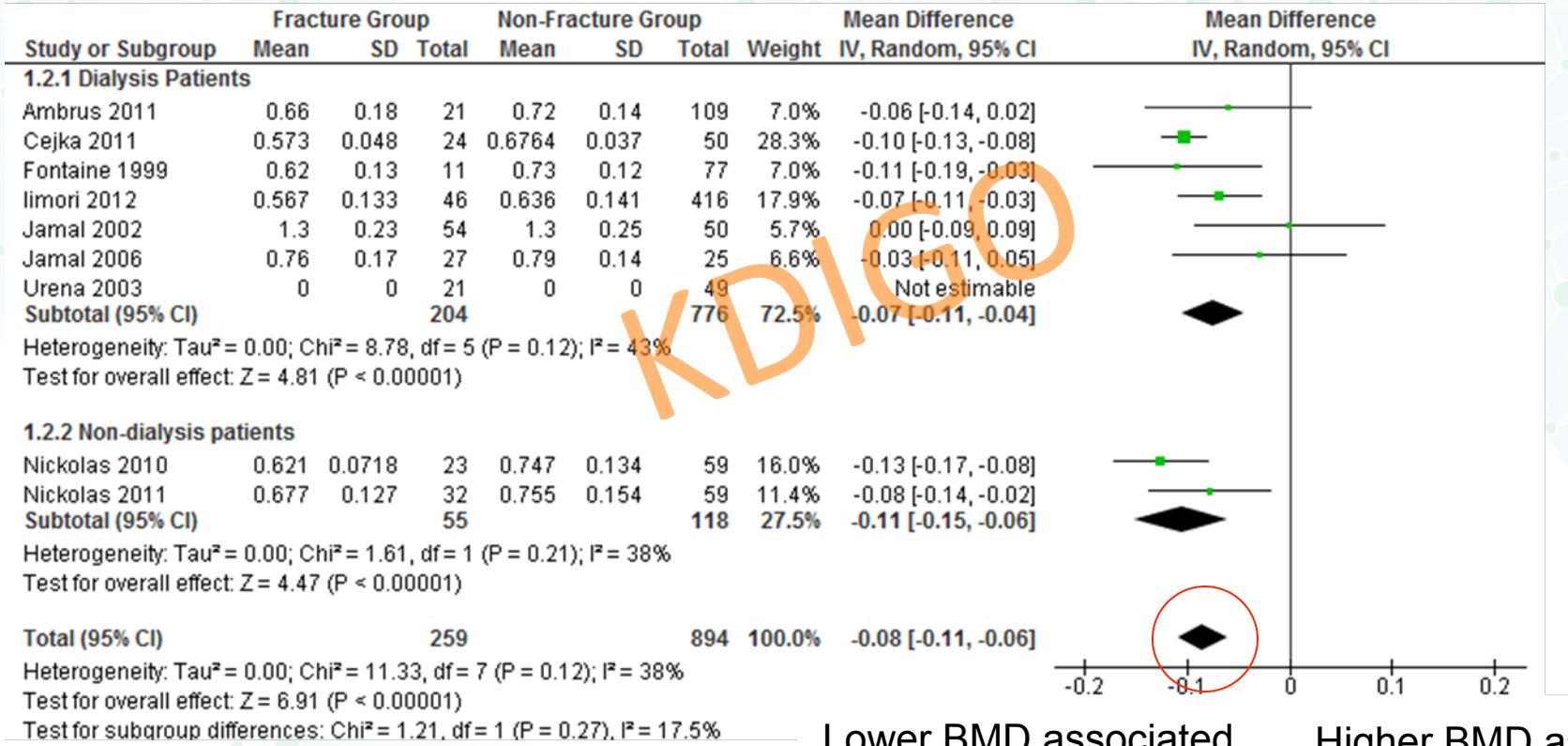
Topic 1: Bone Quality

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***).

Bone Density Predicts Fracture Risk in CKD

Bone mineral density (hip)



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

Topic 1: 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***).

TOPIC 2: 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***).

PHOSPHATE NORMALIZATION TRIAL (PNT)

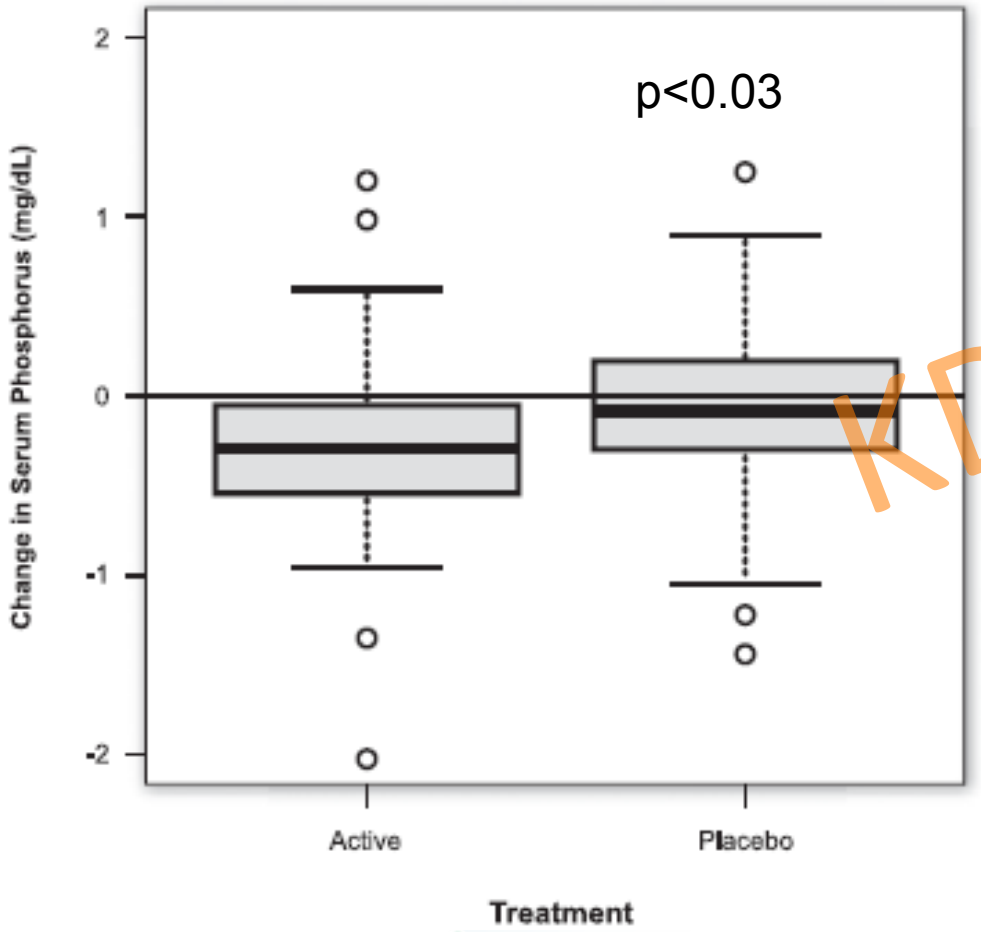
Effects of Phosphate Binders in Moderate CKD

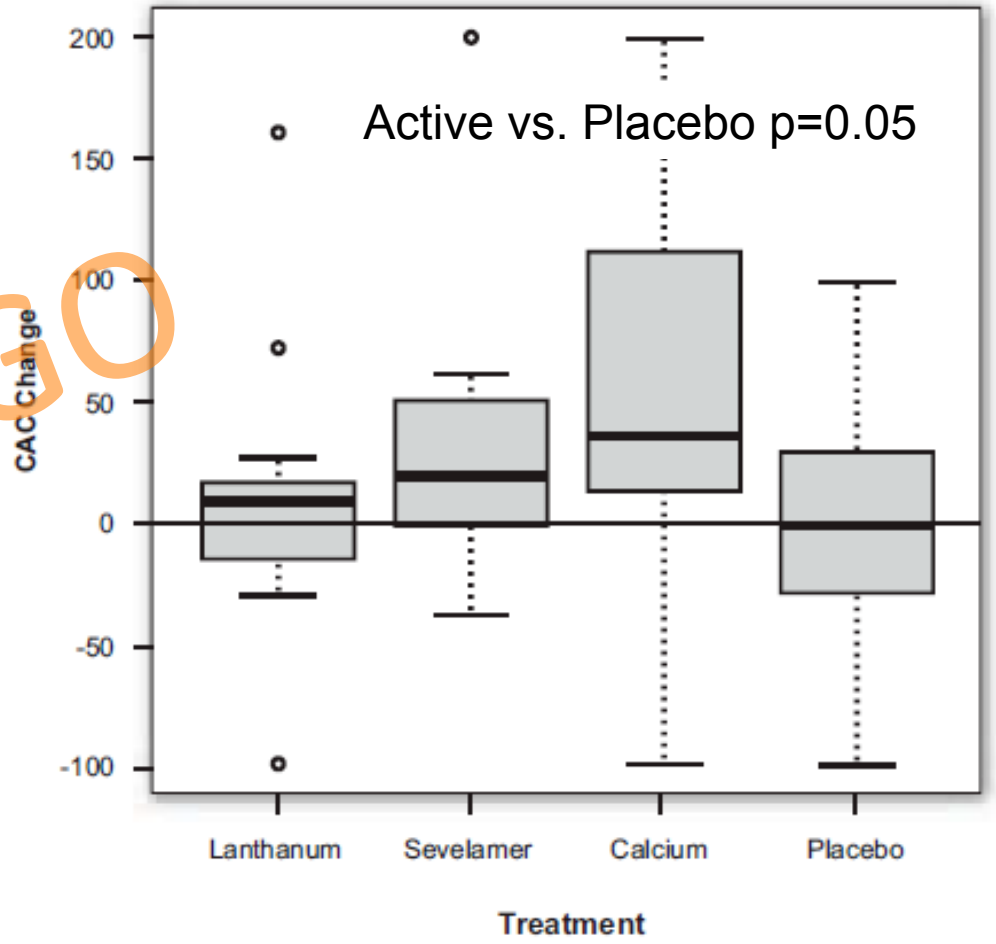
Geoffrey A. Block,* David C. Wheeler,† Martha S. Persky,* Bryan Kestenbaum,‡ Markus Ketteler,§ David M. Spiegel,‖ Matthew A. Allison,¶ John Asplin,** Gerard Smits,* Andrew N. Hoofnagle,‡ Laura Kooienga,* Ravi Thadhani,†† Michael Mannstadt,†† Myles Wolf,‡‡ and Glenn M. Chertow§§

Population: 128 patients with eGFR 20-45 ml/min/1.73 m^2
Intervention: Calcium acetate, lanthanum carbonate, sevelamer carbonate
Comparator: Placebo
Primary endpoint: Change in mean phosphorus from baseline to the average of 3, 6 and 9 months

JASN 2012;23:1407-15

PHOSPHATE NORMALIZATION TRIAL (PNT): RESULTS





Block GA et al, JASN 2012;23:1407-15

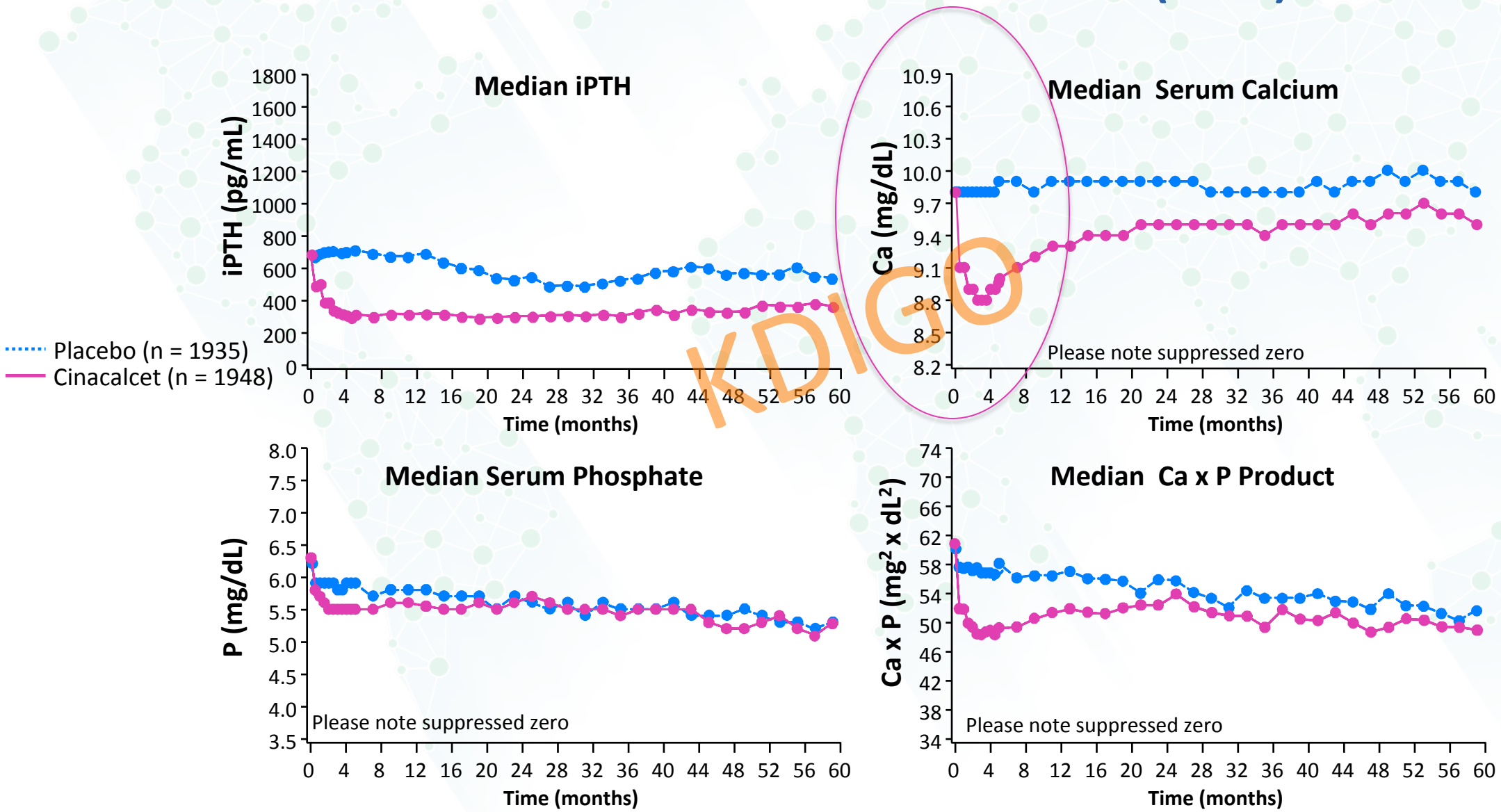
Topic 3: Serum Calcium

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*: BIOCHEMICAL PARAMETERS (ITT)



*EVOLVE did not meet its primary end point

TOPIC 4: 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*).**

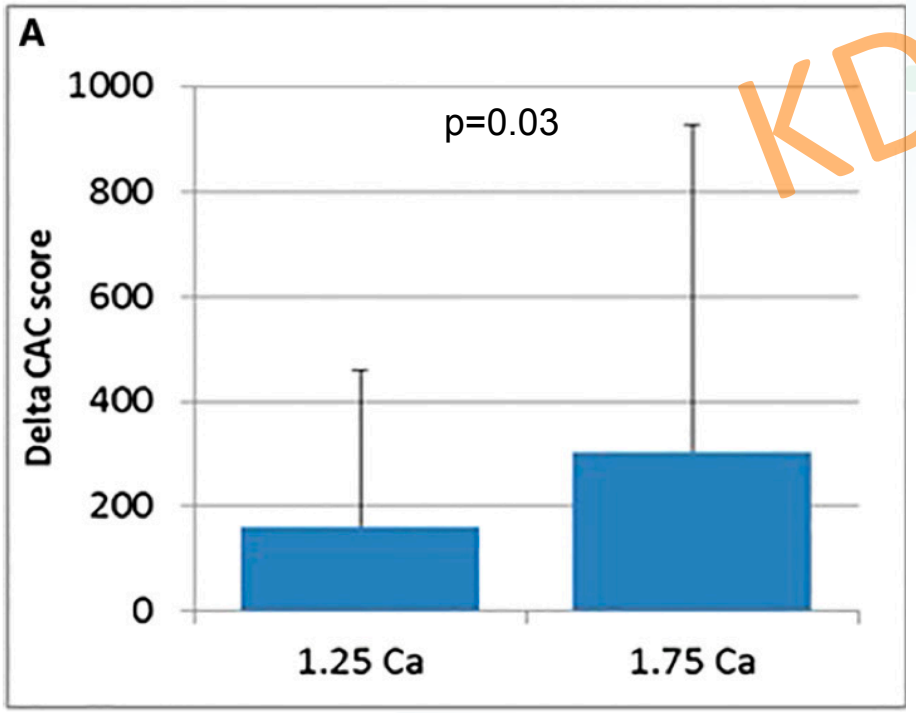
NEW: 4.1.4: In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (***2C***).

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

TRIAL OF 2 DIALYSIS CALCIUM CONCENTRATIONS

Population: 431 HD patients with PTH < 300 pg/ml
Intervention: 1.25 mmol/l calcium bath vs. 1.75 mmol/l calcium bath
Primary Outcome: Coronary calcification (CAC) scores
Secondary Outcome: Bone histomorphometry
Follow-up: 24 months



"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."

Ok et al. J Am Soc Nephrol. 2015

TOPIC 5: 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).

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).~~

TOPIC 5: PHOSPHATE BINDERS

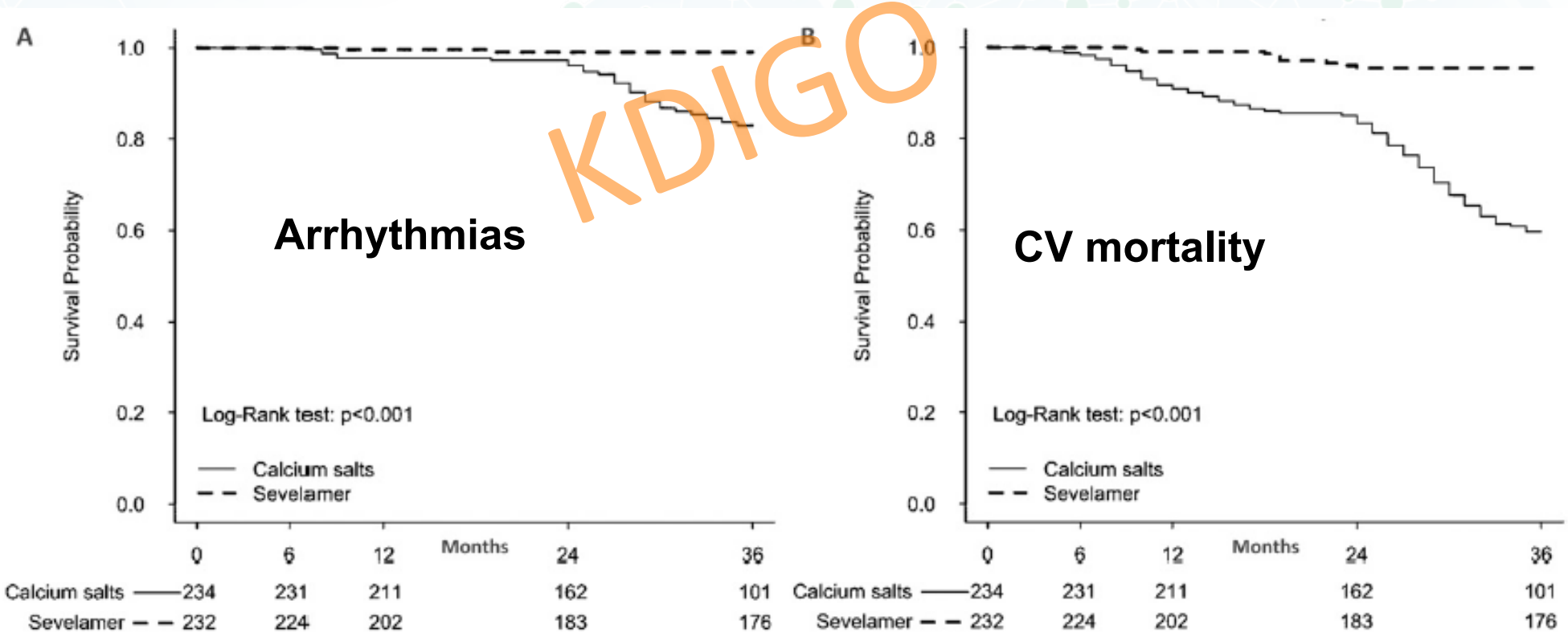
NEW 4.1.5: In patients with CKD G3a-G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphorus. (Not Graded)

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)*

BINDER CHOICE IN HD: INDEPENDENT TRIAL

Population: 466 incident haemodialysis patients
Intervention: Sevelamer
Comparator: Calcium binder
Outcome: CV death due to cardiac arrhythmia
Timeline: 24 months (36 months follow-up)

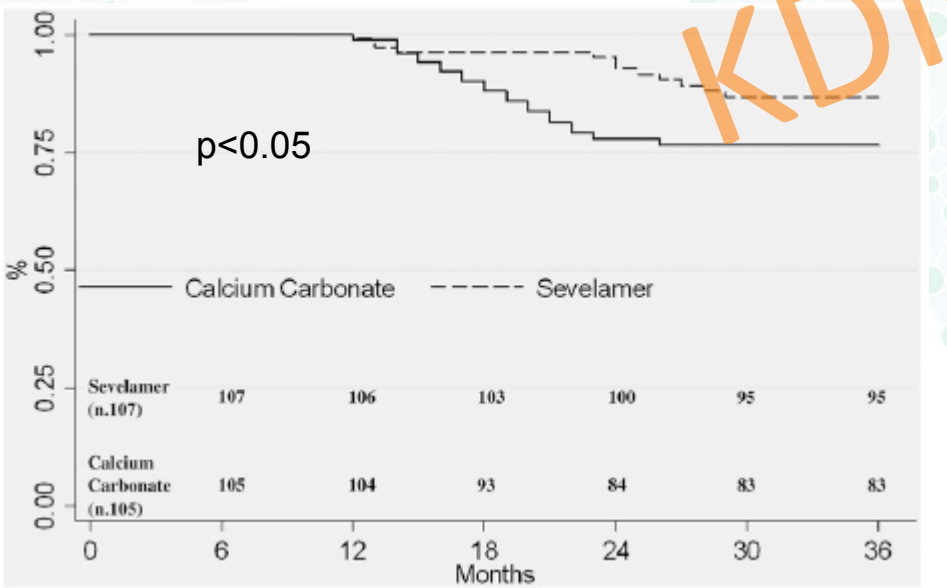


Di Iorio et al., AJKD 2013; 62:771-78

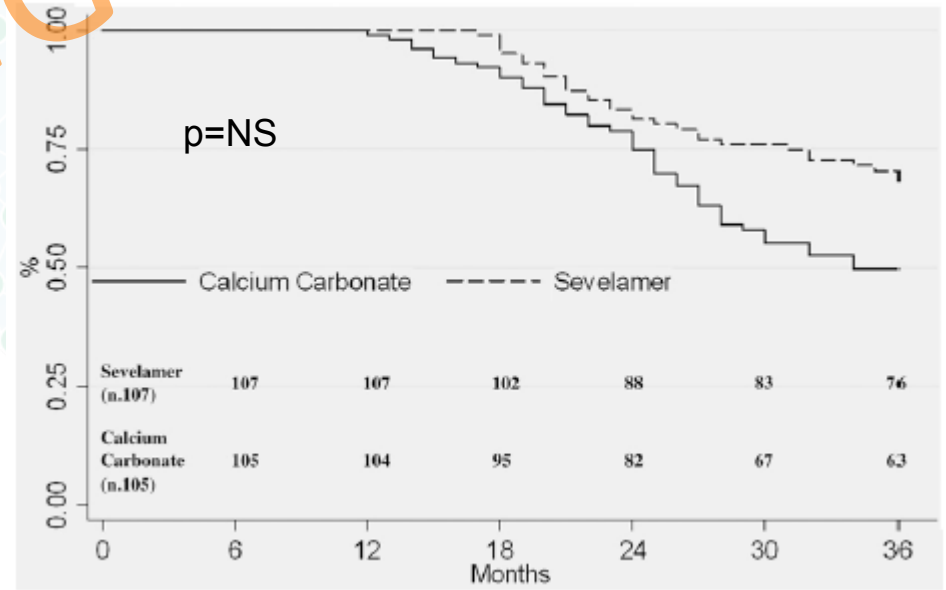
BINDER CHOICE IN NON-DIALYSED PATIENTS

Population: 212 G3a-G4 CKD patients
Intervention: Sevelamer
Comparator: Calcium carbonate
Outcome: All cause mortality
Timeline: 24 months (36 months follow-up)

All-cause mortality



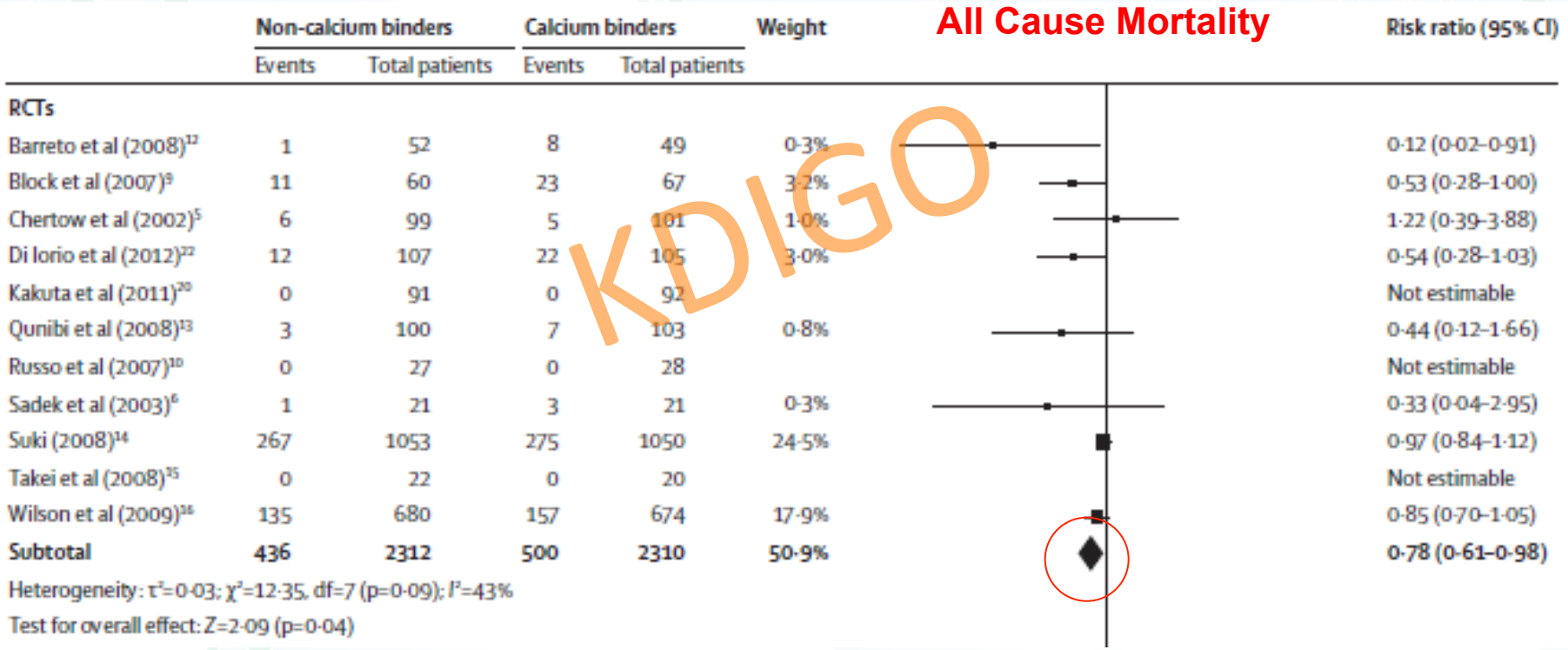
Start of dialysis



Di Iorio et al., CJASN 2012; 7:487-93

META ANALYSIS OF BINDER TRIALS IN CKD

Data from 11 RCTs.
Patients taking Sevelamer had 22% lower mortality RR 0.78 (95% CI 0.61 – 0.98)



	Non-calcium binders		Calcium binders		Weight	Risk ratio (95% CI)
	Events	Total patients	Events	Total patients		
RCTs						
Barreto et al (2008)[12]	1	52	8	49	0·3%	0·12 (0·02–0·91)
Block et al (2007)[9]	11	60	23	67	3·2%	0·53 (0·28–1·00)
Chertow et al (2002)[5]	6	99	5	101	1·0%	1·22 (0·39–3·88)
Di Iorio et al (2012)[22]	12	107	22	105	3·0%	0·54 (0·28–1·03)
Kakuta et al (2011)[20]	0	91	0	92		Not estimable
Qunibi et al (2008)[13]	3	100	7	103	0·8%	0·44 (0·12–1·66)
Russo et al (2007)[10]	0	27	0	28		Not estimable
Sadek et al (2003)[6]	1	21	3	21	0·3%	0·33 (0·04–2·95)
Suki (2008)[14]	267	1053	275	1050	24·5%	0·97 (0·84–1·12)
Takei et al (2008)[15]	0	22	0	20		Not estimable
Wilson et al (2009)[16]	135	680	157	674	17·9%	0·85 (0·70–1·05)
Subtotal	**436**	**2312**	**500**	**2310**	**50·9%**	**0·78 (0·61–0·98)**

Heterogeneity: τ^2=0·03; χ^2=12·35, df=7 (p=0·09); I^2=43%
Test for overall effect: Z=2·09 (p=0·04)

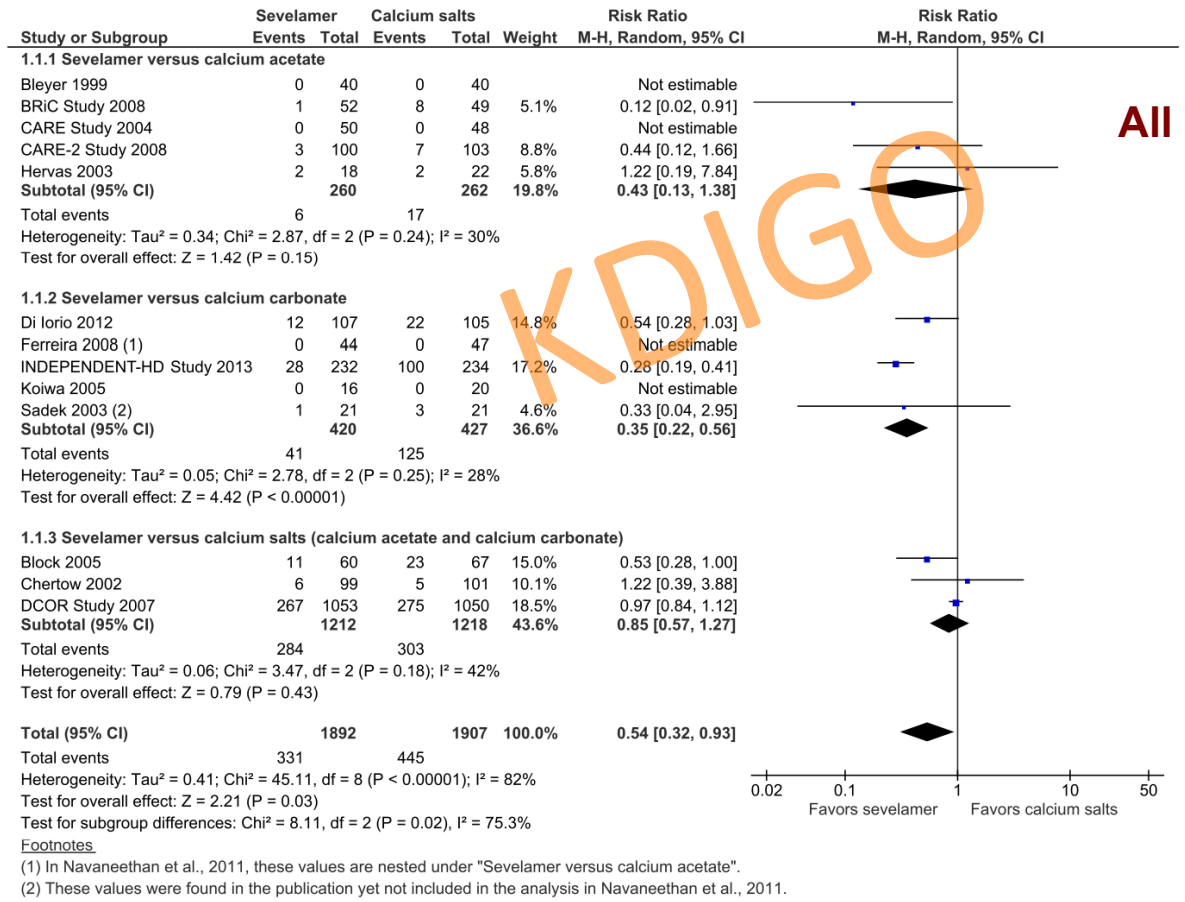
Favors non-calcium ***Favors calcium***

Jamal, et al. Lancet 2013;382:1268-77

META ANALYSIS OF BINDER TRIALS IN CKD

Data from 25 studies

Patients taking Sevelamer had 46% lower mortality RR 0.54 (95% CI 0.32 – 0.93)



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%						

Risk Ratio M-H, Random, 95% CI

0.02 0.1 1 10 50

Favors sevelamer Favors calcium salts

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.

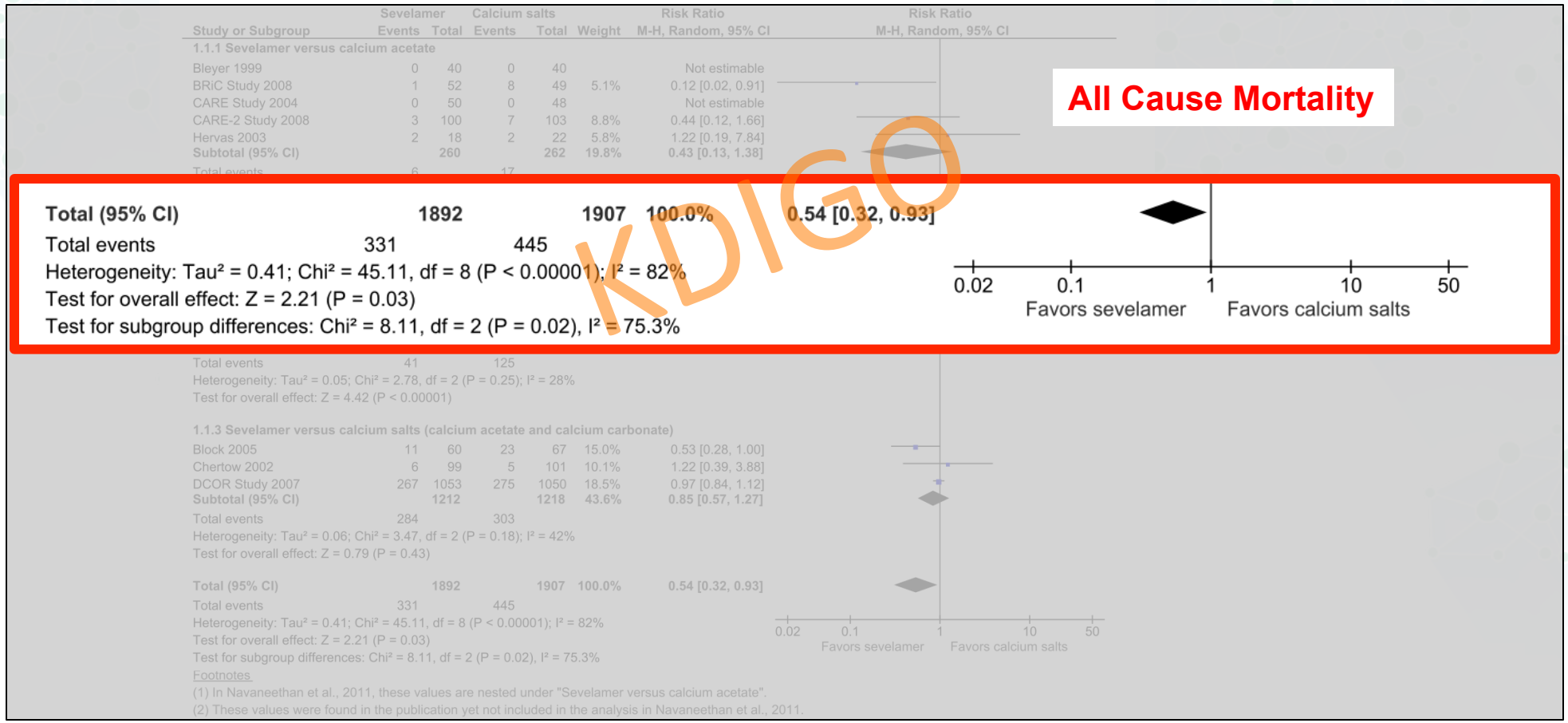
All Cause Mortality

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

META ANALYSIS OF BINDER TRIALS IN CKD

Data from 25 studies

Patients taking Sevelamer had 46% lower mortality RR 0.54 (95% CI 0.32 – 0.93)



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

META-ANALYSIS OF BINDER TRIALS IN CKD

Sevelamer					
0.50 (0.09, 2.65)	**Lanthanum**				
0.39 (0.21, 0.74)	0.78 (0.16, 3.72)	**Calcium**			
1.04 (0.27, 3.97)	2.08 (0.26, 16.5)	2.67 (0.63, 11.4)	**Iron**		
0.71 (0.09, 5.46)	1.42 (0.12, 17.4)	1.82 (0.23, 14.7)	0.68 (0.07, 6.40)	**Colestilan**	
0.47 (0.08, 2.59)	0.93 (0.11, 8.05)	1.20 (0.21, 6.77)	0.45 (0.08, 2.66)	0.66 (0.10, 4.29)	**Placebo**

Network estimated odds ratios of phosphate binders on all-cause mortality

Palmer SC, et al. Am J Kidney Dis 2016;68:691–702

TOPIC 6: 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**).*

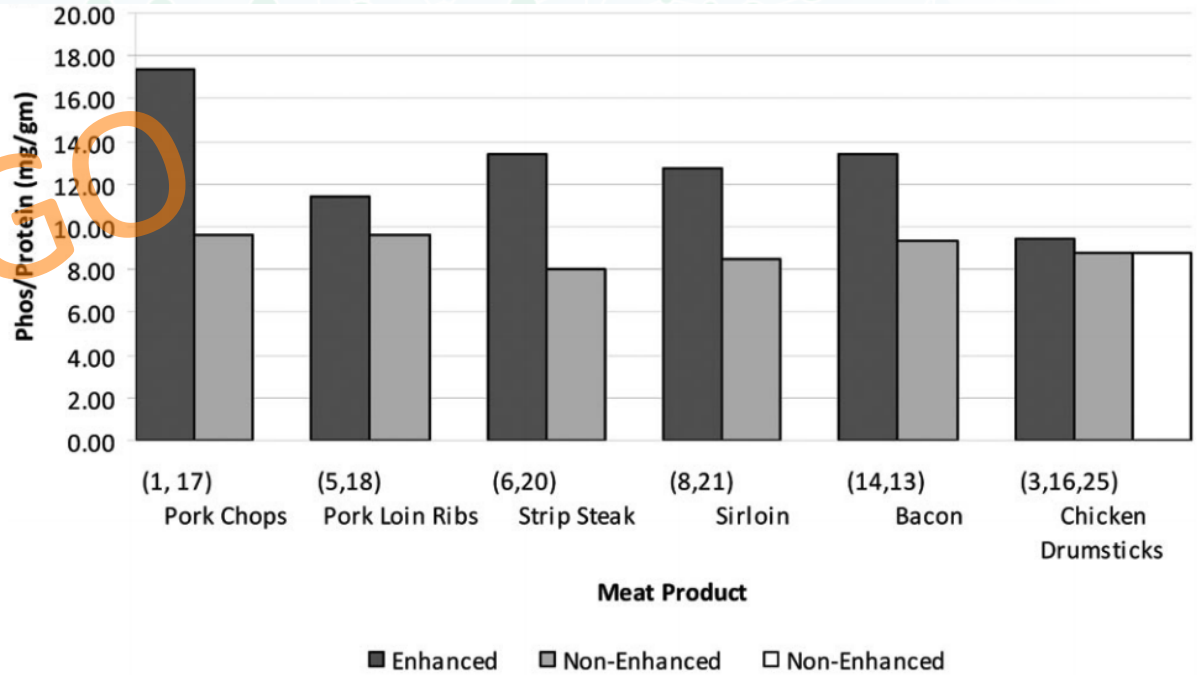
It is reasonable to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations. ***(Not Graded)***

TOPIC 6: DIETARY PHOSPHATE INTAKE

9 patients, eGFR 30 ml/min/1.73 m^2
7-day crossover trial[1]

Measurement	Meat (casein) diet		Vegetarian (grain) diet		P-value
	Before	After	Before	After	
Daily PO_4 (mg/day)		810 ± 27		795 ± 51	NS
Plasma PO_4 (mg/day)	**3.5** ± 0.6	**3.7** ± 0.6	**3.5** ± 0.6	**3.2** ± 0.5	0.02
Plasma iPTH (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 Ca (mg/dl)	9.2 ± 0.4	9.4 ± 0.7	9.3 ± 0.4	9.1 ± 0.3	NS
Urine CA exc. (mg/day)	66 ± 69	77 ± 48	60 ± 59	71 ± 43	NS
Urine PO_4 exc. (mg/day)	836 ± 187	583 ± 216	778 ± 190	416 ± 233	0.07

Phosphate/protein ratio (mg/g) in processed vs unprocessed meat products[2]



1. Moe S, et al. Clin J Am Soc Nephrol 2011;6:257–64;
2. Sherman RA, et al. Clin J Am Soc Nephrol 2009;4:1370–3

TOPIC 7: VITAMIN D + PTH

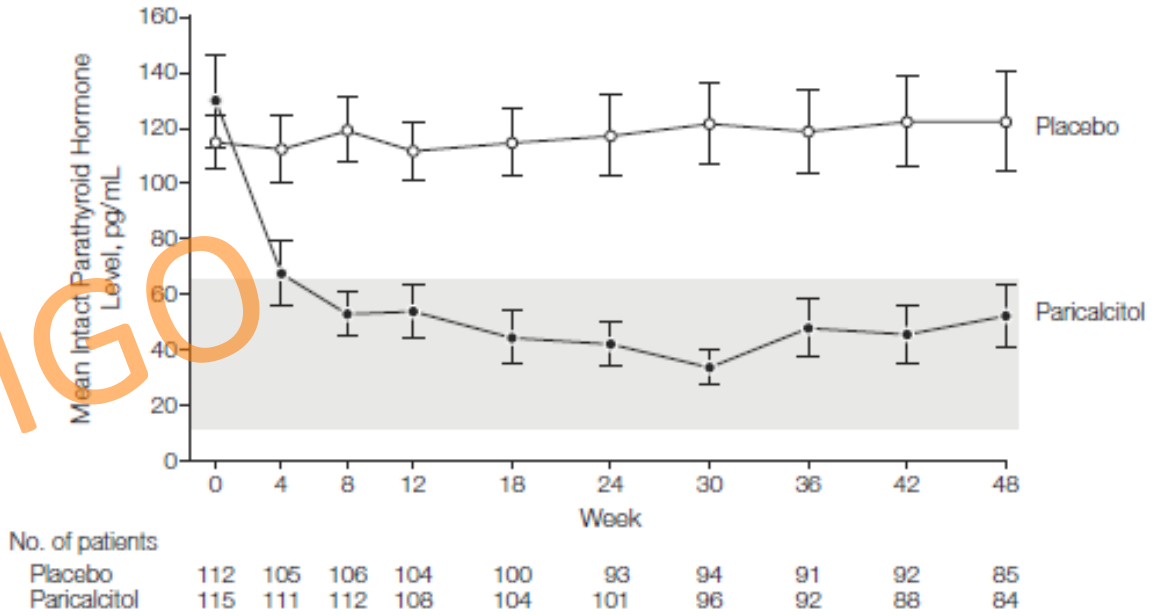
OLD 4.2.2: In patients with CKD G3a–G5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (***2C***).

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***).

PRIMO STUDY: PARICALCITOL VS. PLACEBO

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

Figure 2. Blood Levels of Intact Parathyroid Hormone During the Study by Treatment Group



Error bars indicate 95% CIs. The shaded area corresponds to the normal range of values.

- 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.

Thadhani et al, JAMA 2012

OPERA STUDY: PARICALCITOL VS. PLACEBO

Population: 60 CKD patients (LVH)
Intervention: Paricalcitol 1 µg/day
Comparator: Placebo
Outcome: LVMI by CMR
Timeline: 52 weeks

Table 3. Changes in cardiac MRI and echocardiographic parameters from baseline to 52 weeks

Cardiac Parameters	Paricalcitol (*n*=30)	Placebo (*n*=30)	*P*
LV mass index by body surface area, g/m^2			
Baseline	81.2 (14.8)	79.5 (14.7)	
Week 52	79.0 (15.1)	75.2 (17.7)	
Change from baseline to 52 wk	−2.59 (−6.13 to +0.32)	−4.85 (−9.89 to −1.10)	0.40

- At 52 weeks, the change in left ventricular mass index did not differ between treatment groups.
- PTH levels lower in patients receiving paricalcitol.
- Serum calcium increased in paricalcitol group but not in placebo group.

Wang A et al, JASN 2014; 25:1257

TOPIC 7: VITAMIN 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***).

Topic 8: Vascular calcification
Topic 9: Parathyroid hormone range

No changes

KDIGO CKD-MBD 2017 Guideline: 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 Ca, P, 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 stages of CKD, regardless of other risk markers.

KDIGO CKD-MBD 2017 Guideline: Key Messages

5. It is reasonable to limit dietary P intake, when considering all sources of dietary P (including “hidden” sources).
6. The PRIMO and OPERA trials 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.