Seoul – May 20, 2017

37th Annual Meeting of the Korean Society of Nephrology

KDIGO CKD-MBD Guideline Update 2017: What is new?

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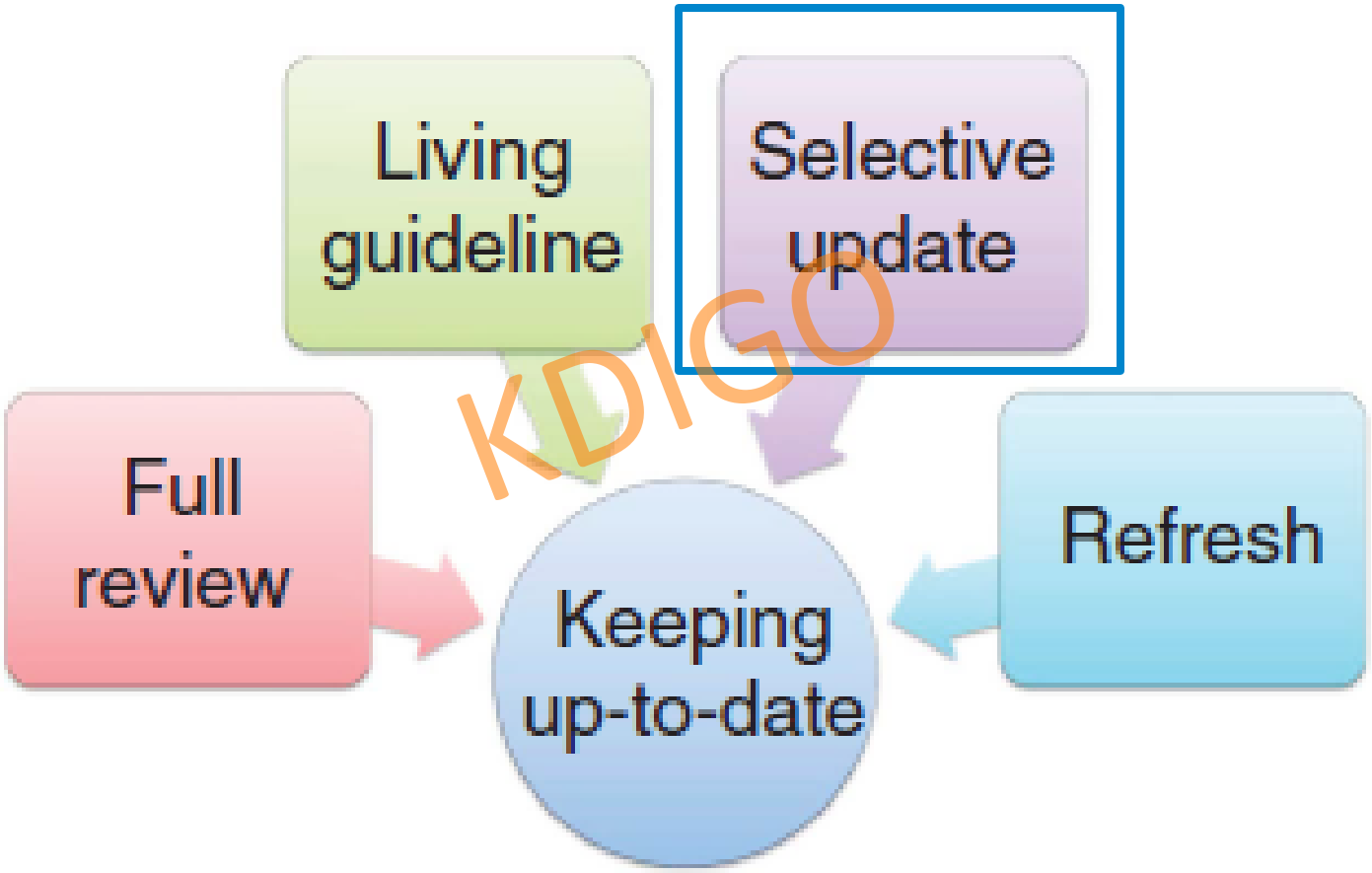
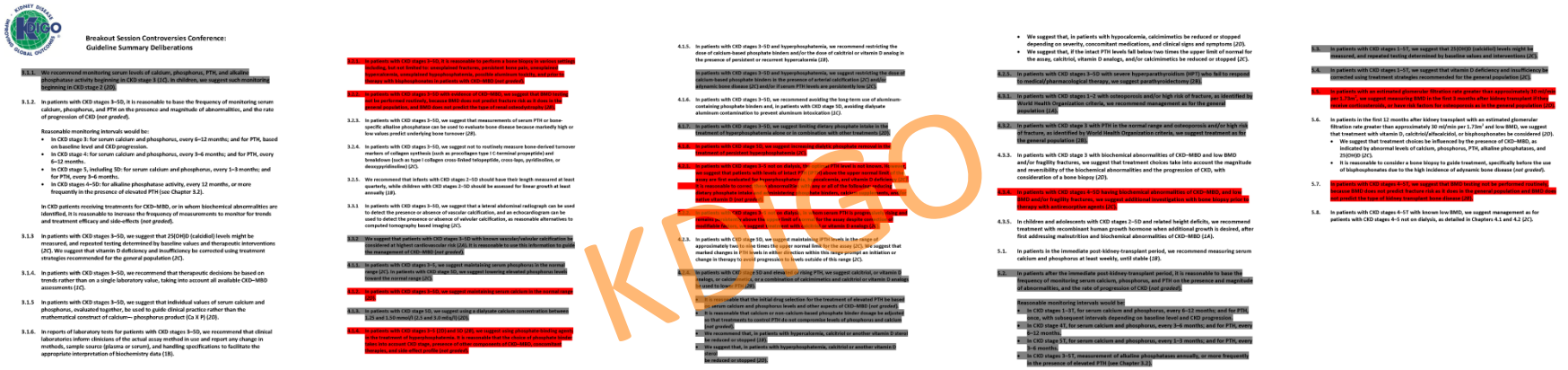
KDIGO Controversies Conference on CKD-MBD (Madrid, October 2013)

- 74 attendees from 5 continents and 19 countries
- Represented experts in adult, pediatric, and transplant nephrology; endocrinology, cardiology, bone histomorphometry, and epidemiology
- Divided into 4 Breakout Groups
  - Vascular Calcification
  - Bone Quality
  - Calcium and Phosphorus
  - Vitamin D and PTH

KDIGO Controversies Conference on CKD-MBD (Madrid, October 2013)



Conference recommendation…



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).

Overview of recommended changes

- Selective Update in **Red**
- Minor Adaptation in **Grey**
- No changes left uncoloured

meeting report

http://www.kidney-international.org

Revisiting KDIGO clinical practice guideline on chronic kidney disease—mineral and bone disorder: a commentary from a Kidney Disease: Improving Global Outcomes controversies conference

Markus Ketteler[1], Grahame J. Elder[2,3], Pieter Evenepoel[4], Joachim H. Ix[5,6,7], Sophie A. Jamal[8], Marie-Hélène Lafage-Proust[9], Rukshana Shroff[10], Ravi I. Thadhani[11], Marcello A. Tonelli[12,13], Bertram L. Kasiske[14], David C. Wheeler[15] and Mary B. Leonard[16]

CKD-MBD Guideline Update 2016

Guideline Chairs

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Mary B Leonard (USA)

Work Group

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

Supported by an Evidence Review Team led by

Karen A. Robinson

Johns Hopkins University, Baltimore (USA)

CHAPTER 3.2:

TREATMENT OF CKD–MBD: BONE

ASSESSMENT OF PHOSPHORUS AND CALCIUM

3.2.1. In patients with CKD Stages 3a-5D 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)

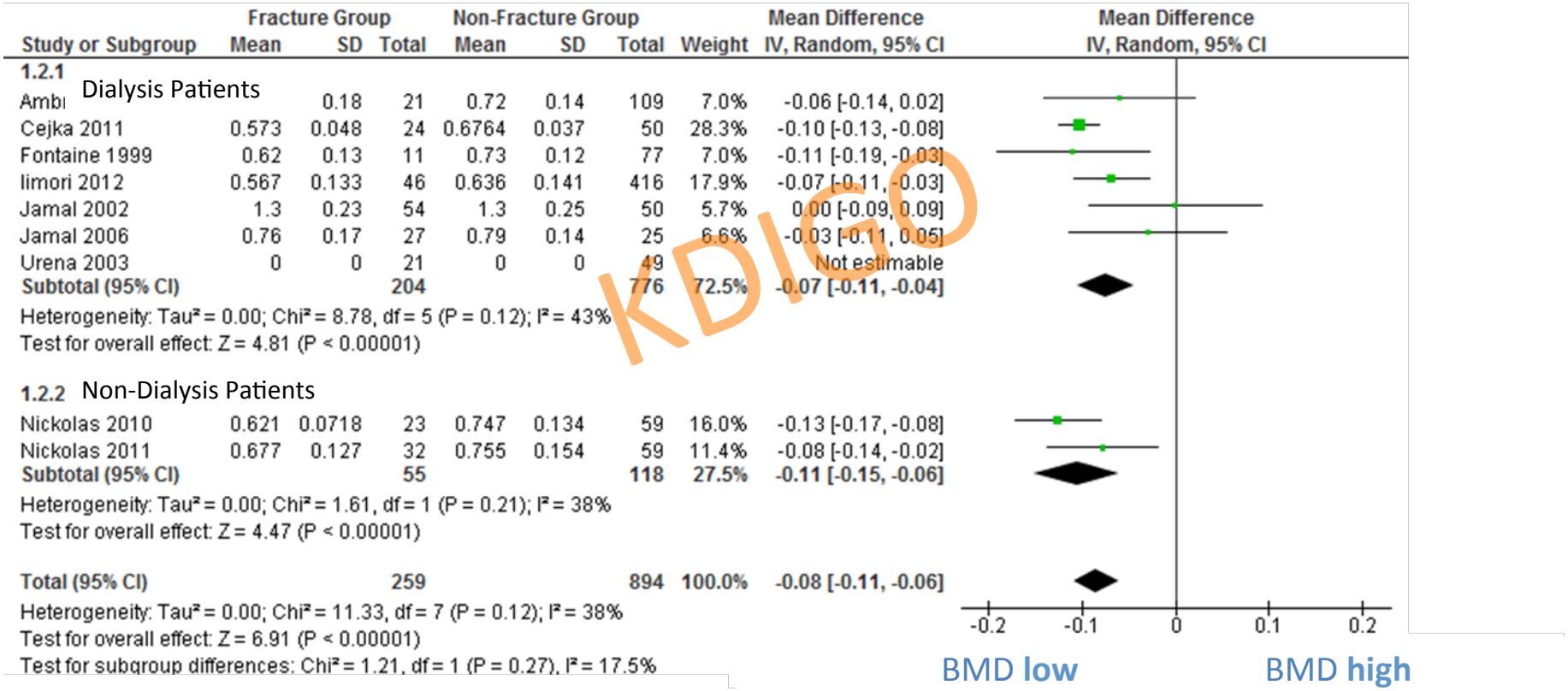
2009:
In patients with CKD stages 3–5D with evidence of CKD–MBD, we suggest that BMD testing ***not*** *be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy*
(2B).

RATIONALE

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

RATIONALE: Meta analysis

DEXA determined femoral BMD



BMD **low** in case of fracture

BMD **high** in case of fracture

Chapter 4.1:

Treatment of CKD–MBD: Lowering High Serum Phosphorus and Maintaining Calcium

Assessment of Phosphorus and Calcium

4.1.1: In patients with CKD Stages 3a-5D, treatments of CKD-MBD should be based on serial assessments of phosphorus, calcium and PTH levels, considered together. (*Not Graded)*

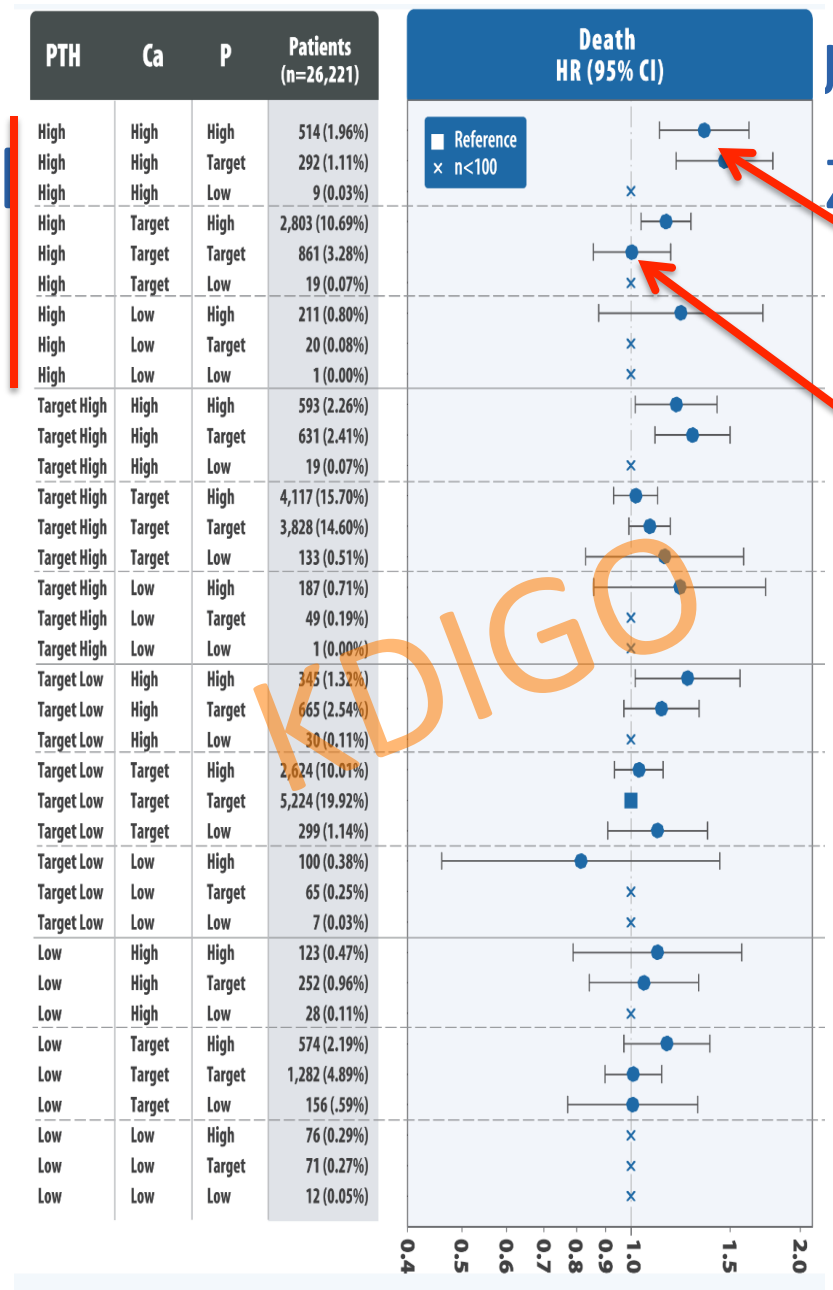
2009:
No comparable statement

RATIONALE

- This new recommendation was provided in order to emphasize the complexity and interaction of CKD-MBD laboratory parameters.
- Serum phosphorus, calcium and PTH concentrations are all routinely measured and clinical decisions are often made based on these values. Clinical decision making should not be based on a single result, but rather on the trends. Recent *post-hoc* analyses of large dialysis cohorts suggest that the prognostic implications of individual biochemical components of CKD-MBD largely depend on their context with regard to constellations of the full array of MBD biomarkers.

CKD-MINERAL AND BONE DISORDER: ADJUSTED RISK OF DEATH

PTH high



Calcium and Phosphate high

Calcium and Phosphate target

Kidney Disease: Improving Global Outcomes

Block, CJASN 2013.

RATIONALE

- Furthermore, therapeutic maneuvers aimed at improving one parameter often have unintentional effects on other parameters. Therefore, the Work Group considered it reasonable to take the context of therapeutic interventions into account when assessing values of phosphorus, calcium and PTH, and felt that it was important to emphasize the interdependency of these biochemical parameters for clinical therapeutic decision making.

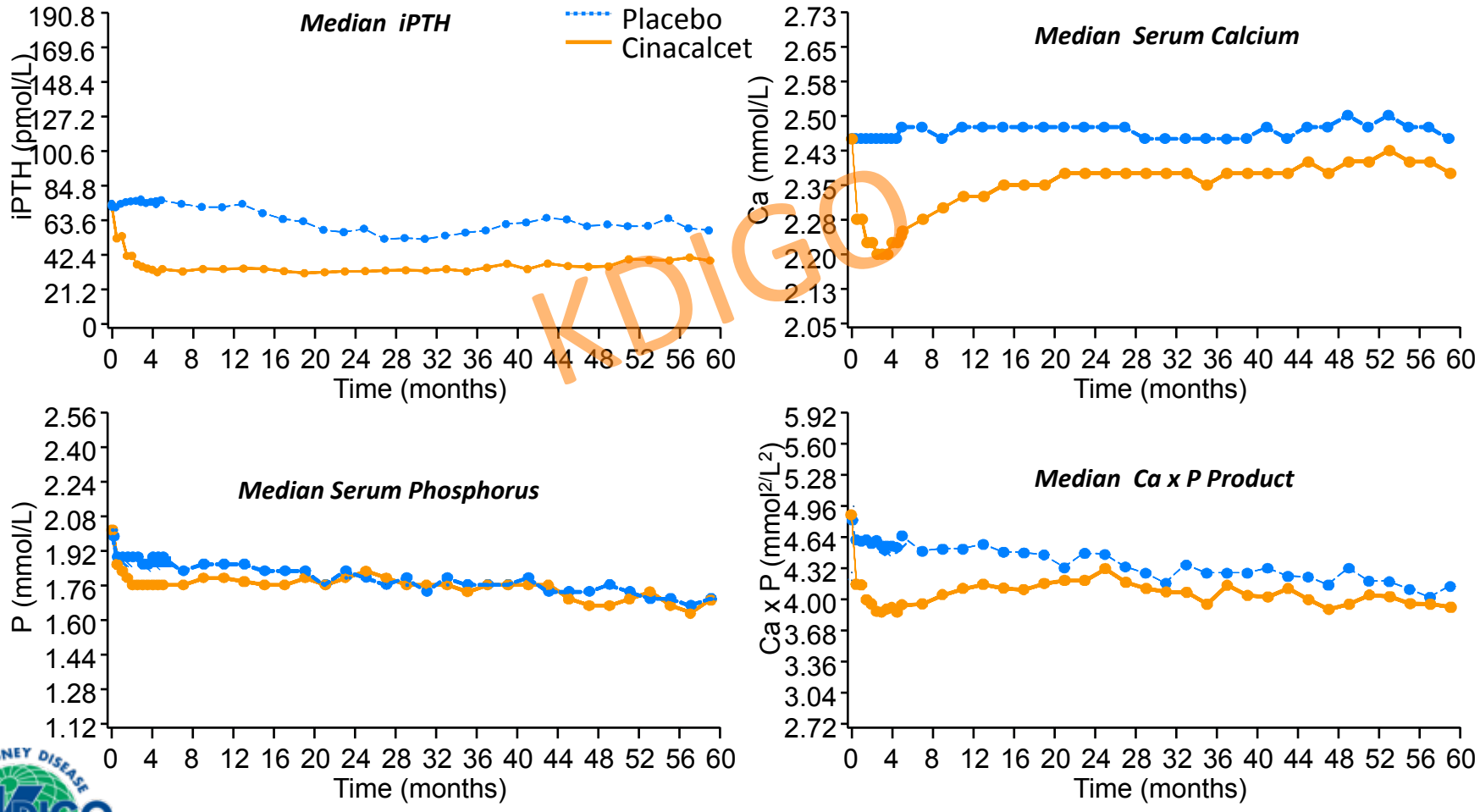
Assessment of Phosphorus and Calcium

4.1.3: In adult patients with CKD Stages 3a-5D, we suggest avoiding hypercalcemia *(2C)*.

In children with CKD Stages 3a-5D, we suggest maintaining serum calcium in the age-appropriate normal range. *(2C)*

2009:
In patients with CKD stages 3–5D, we suggest maintaining serum calcium in the normal range (2D).

EVOLVE TRIAL: LONGITUDINAL LAB VALUES



RATIONALE

- The Work Group emphasizes an individualized approach to the treatment of hypocalcemia rather than recommending the correction of hypocalcemia for all patients.
- Mild and asymptomatic hypocalcemia (e.g., in the context of calcimimetic treatment) can be tolerated in order to avoid inappropriate calcium loading in adults.

TREATMENT

4.1.5: In patients with CKD Stages 3a-5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphorus. *(Not Graded)*

2009:
In patients with CKD stages 3–5 (2D) and 5D (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).

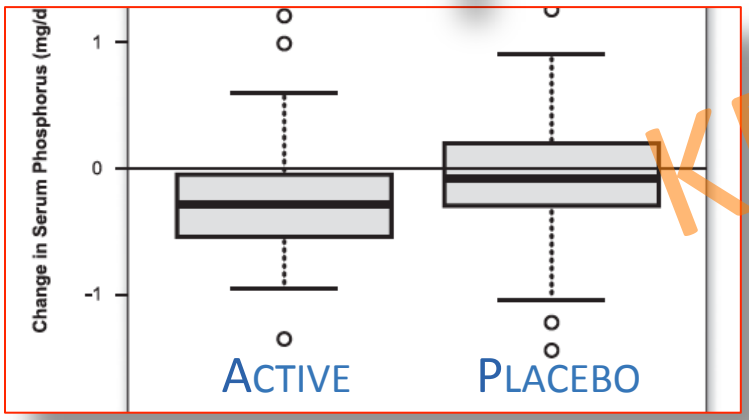
RATIONALE

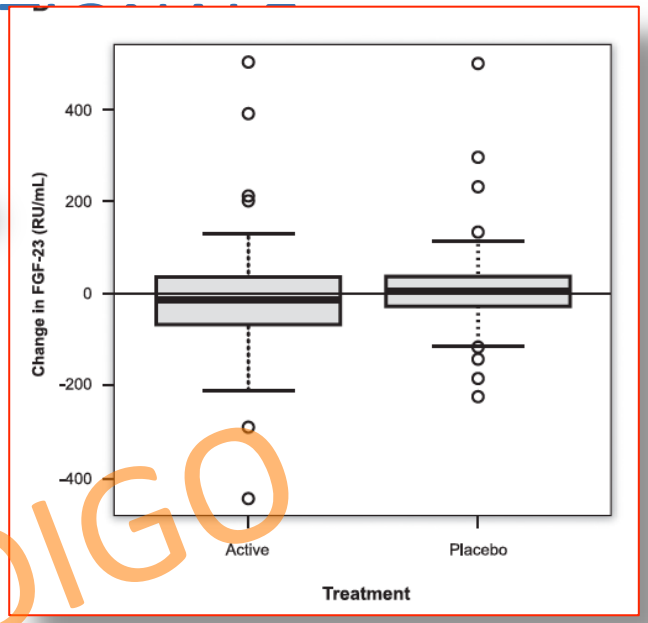
- The 2009 KDIGO Guideline commented that available phosphate binders are all effective in the treatment of hyperphosphatemia, and that there is evidence that calcium-free binders may favor halting progression of vascular calcifications vs. calcium-containing binders
- But concerns about calcium balance, uncertainties about phosphate lowering in CKD patients not on dialysis, additional hard endpoint RCTs and a systematic review (effects on mortality comparing calcium-free vs. calcium containing phosphate binders) prompted in the decision to re-evaluate this recommendation.

- CKD 3b – 4
- Serum phosphate in the upper normal range
- „Active“: Lanthanum – Sevelamer – Ca acetate

RA

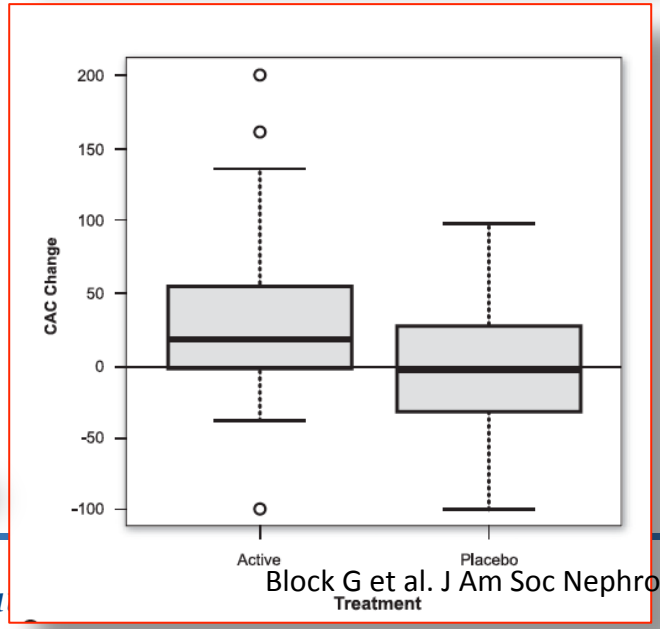
PHOSPHATE





FGF23

KDIGO



CORONARY CALCIFICATION

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

RATIONALE

- Block *et al*. studied subjects with essentially normal phosphorus and as such, normophosphatemia may not be an indication to start phosphate-lowering treatments. This suggests that that early "preventive" treatment of hyperphosphatemia is currently not supported by data (see Rec 4.1.2)

- The Work Group felt that the updated guideline should clarify that phosphate-lowering therapies may only be indicated in case of "progressive or persistent hyperphosphatemia"

RATIONALE

- The broader term “phosphate-lowering therapies” is preferred over the term “phosphate-binding agents” introduced in 2009 Guideline because it appears likely that all possible approaches (i.e., binders, diet, dialysis) can be effective

TREATMENT

4.1.6: In adult patients with CKD Stages 3a-5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binders. *(2B)*

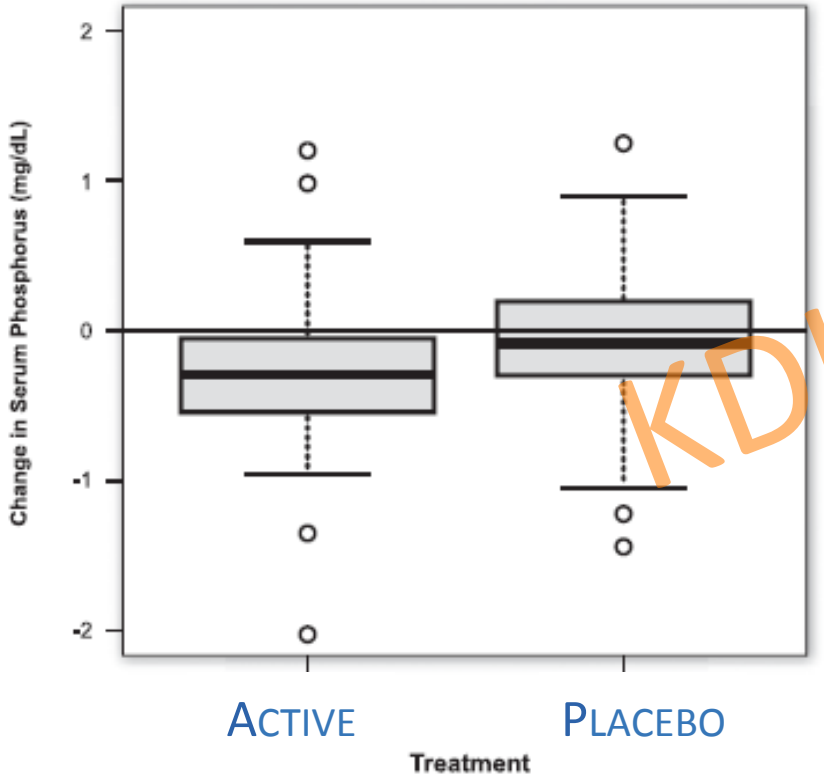
In children with CKD Stages 3a-5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels. *(Not Graded)*

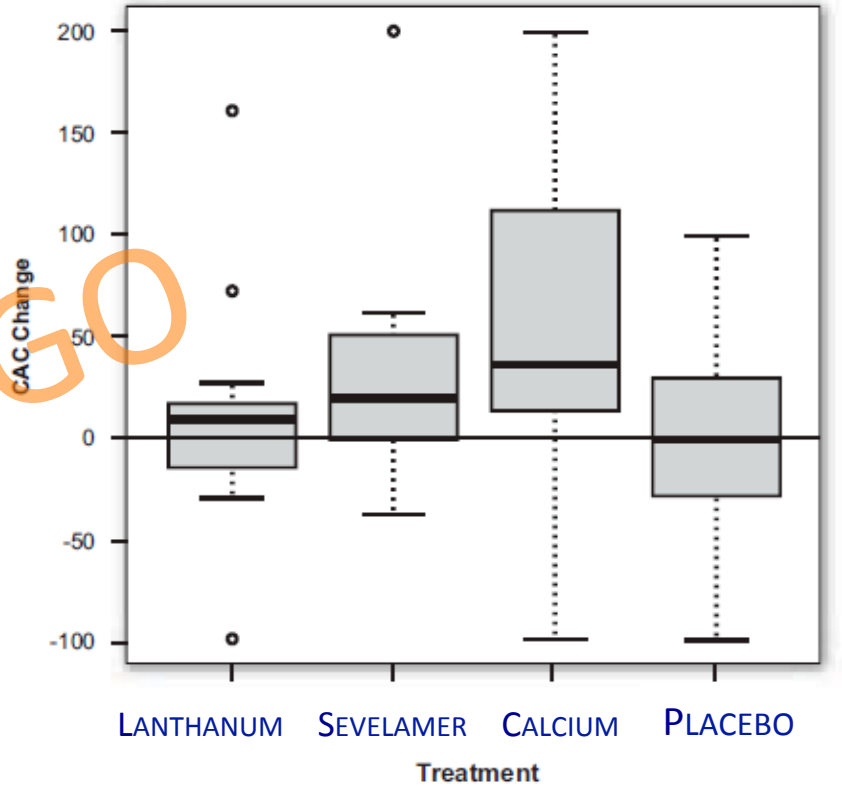
2009:
In patients with CKD stages 3–5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders….in the presence of persistent or recurrent hypercalcemia (1B). In patients with CKD stages 3–5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate 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

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

PHOSPHATE BINDERS IN MODERATE CKD

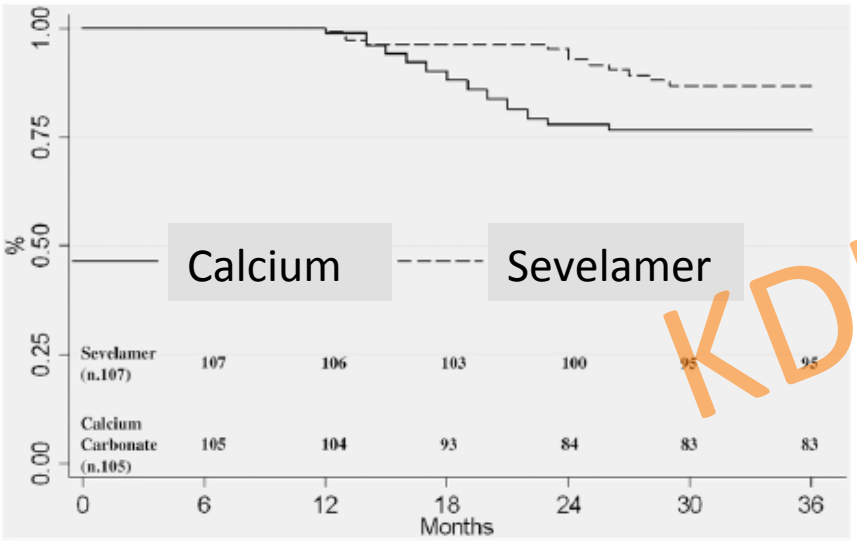




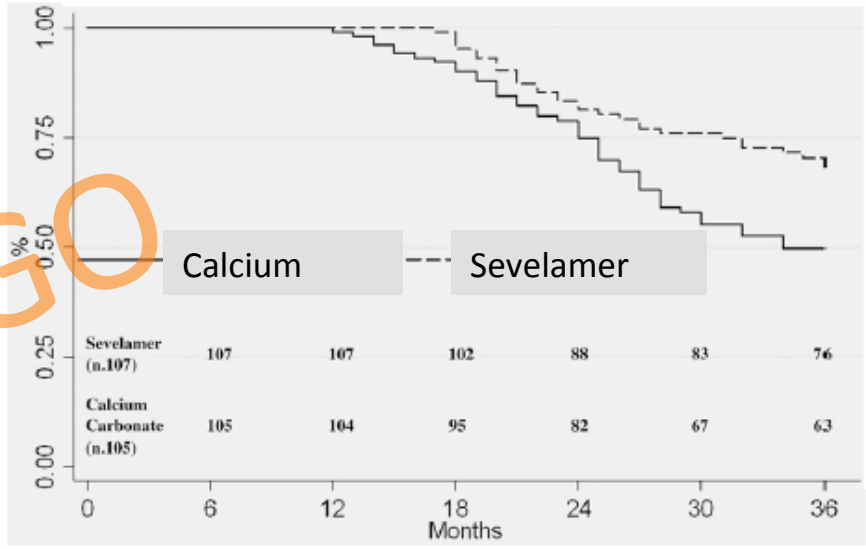
Block G et al. J Am Soc Nephrol. 2012;23:1407-1415.

Phosphate Binders and Mortality (Predialyis)

All-Cause Mortality



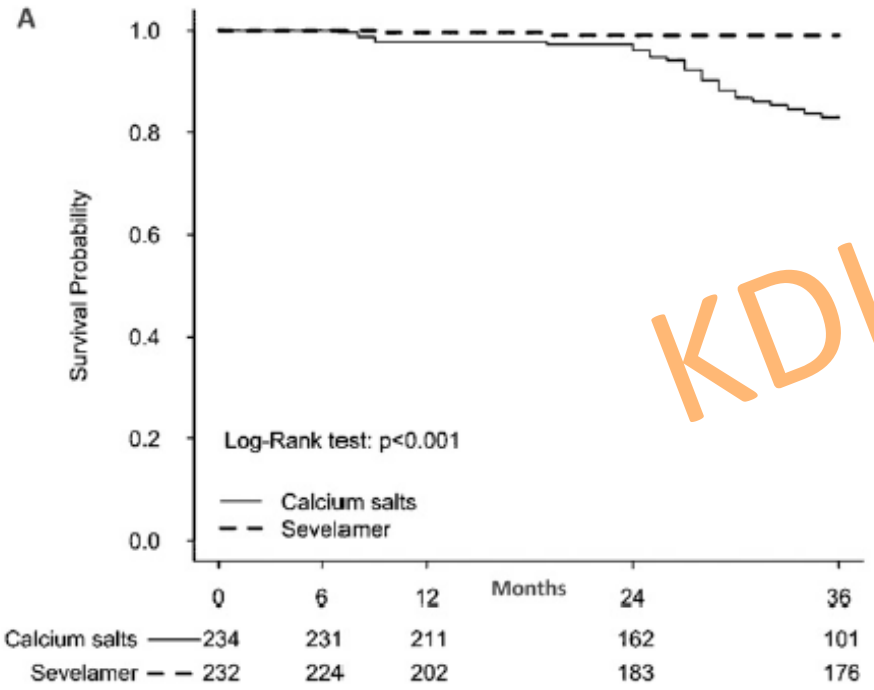
Dialysis Inception



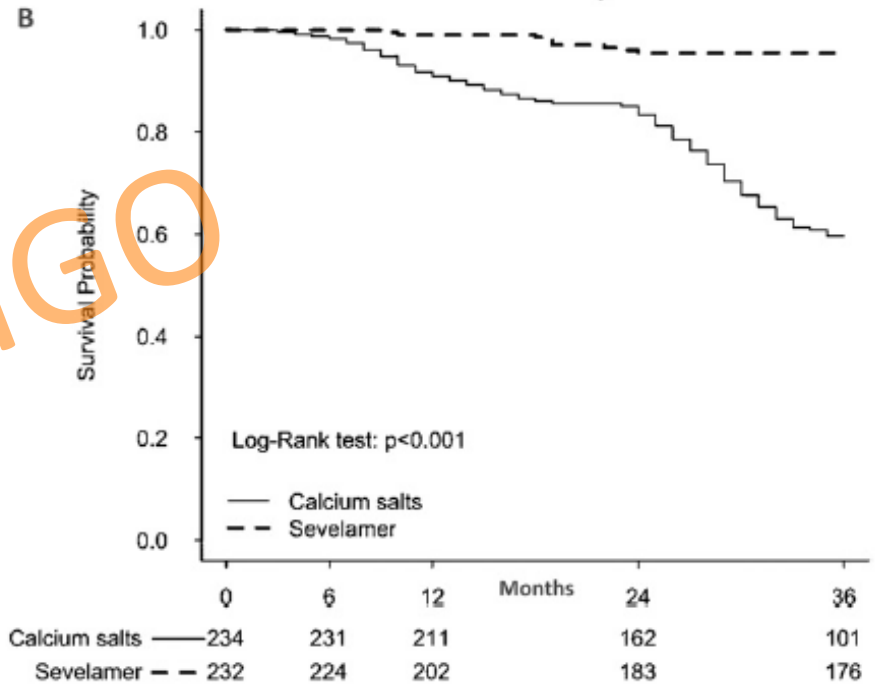
Di Iorio B et al. Clin J Am Soc Nephrol 2012;7:487-493

SEVELAMER VS. CALCIUM (DIALYSIS)

Arrythmias



CV Mortality



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

DIETARY PHOSPHATE

4.1.8: In patients with CKD Stages 3a-5D, 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)*

2009:
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).

RATIONALE

- 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.

PHOSPHATE AND DIET

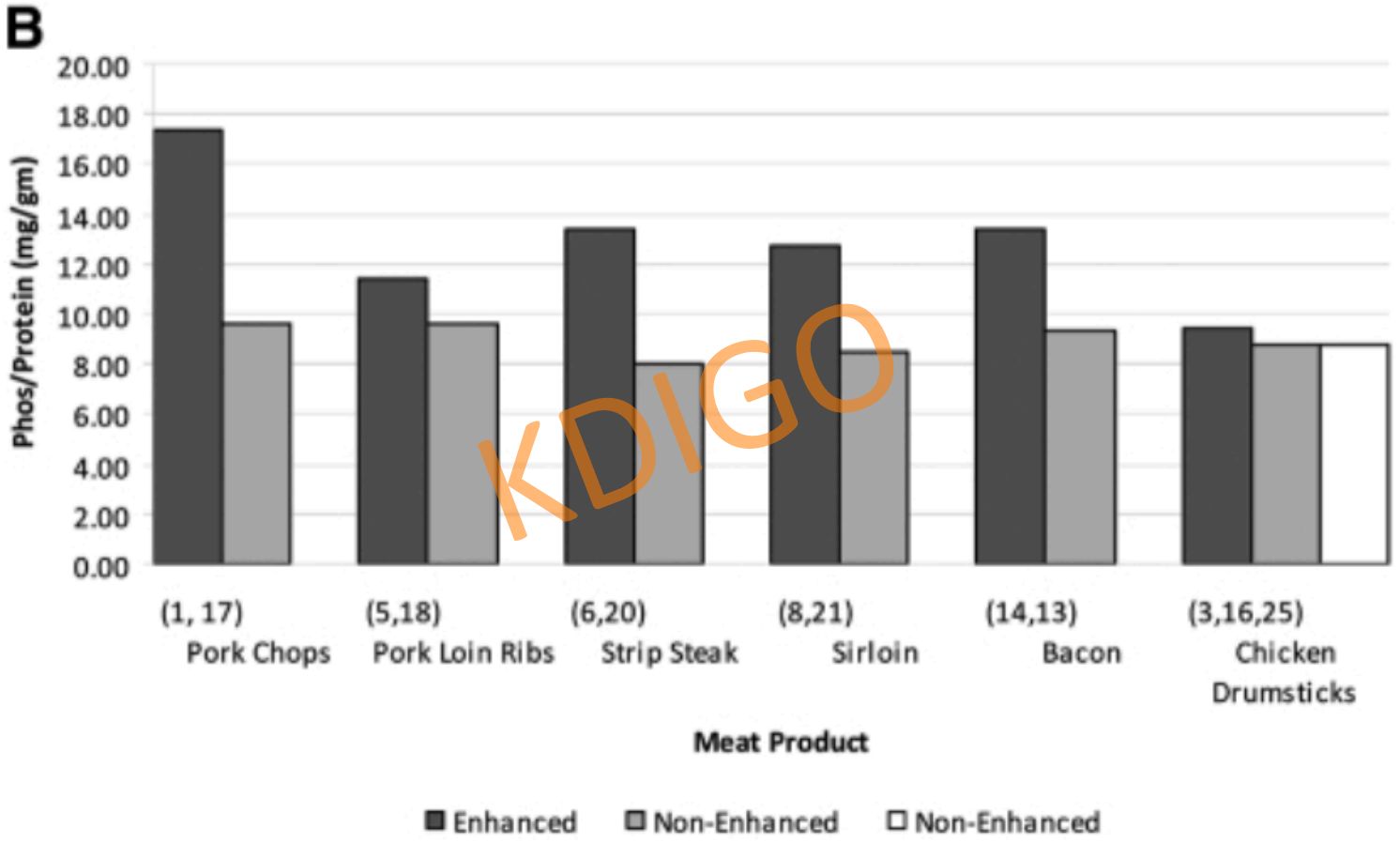
Table 2. Blood and urine measurements after 1 week of diet as outpatient

	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

Clinical Key Messages

- It is important to emphasize the interdependency of serum Ca, P, 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 stages of CKD, regardless of whether other risk markers are present (e.g., hypercalcemia, arterial calcification, adynamic bone disease or low PTH levels).

KEY MESSAGES

- It is reasonable to limit dietary phosphorus intake, when considering all sources of dietary phosphorus (including "hidden" sources).
- In CKD (including post-transplantation) DEXA is as predictive for future fracture risk as in the general population

CHAPTER 4.2:

TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

VITAMIN D

4.2.2: In adult patients with CKD Stages 3a-5 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 Stages 4-5 with severe and progressive hyperparathyroidism. *(Not Graded)*

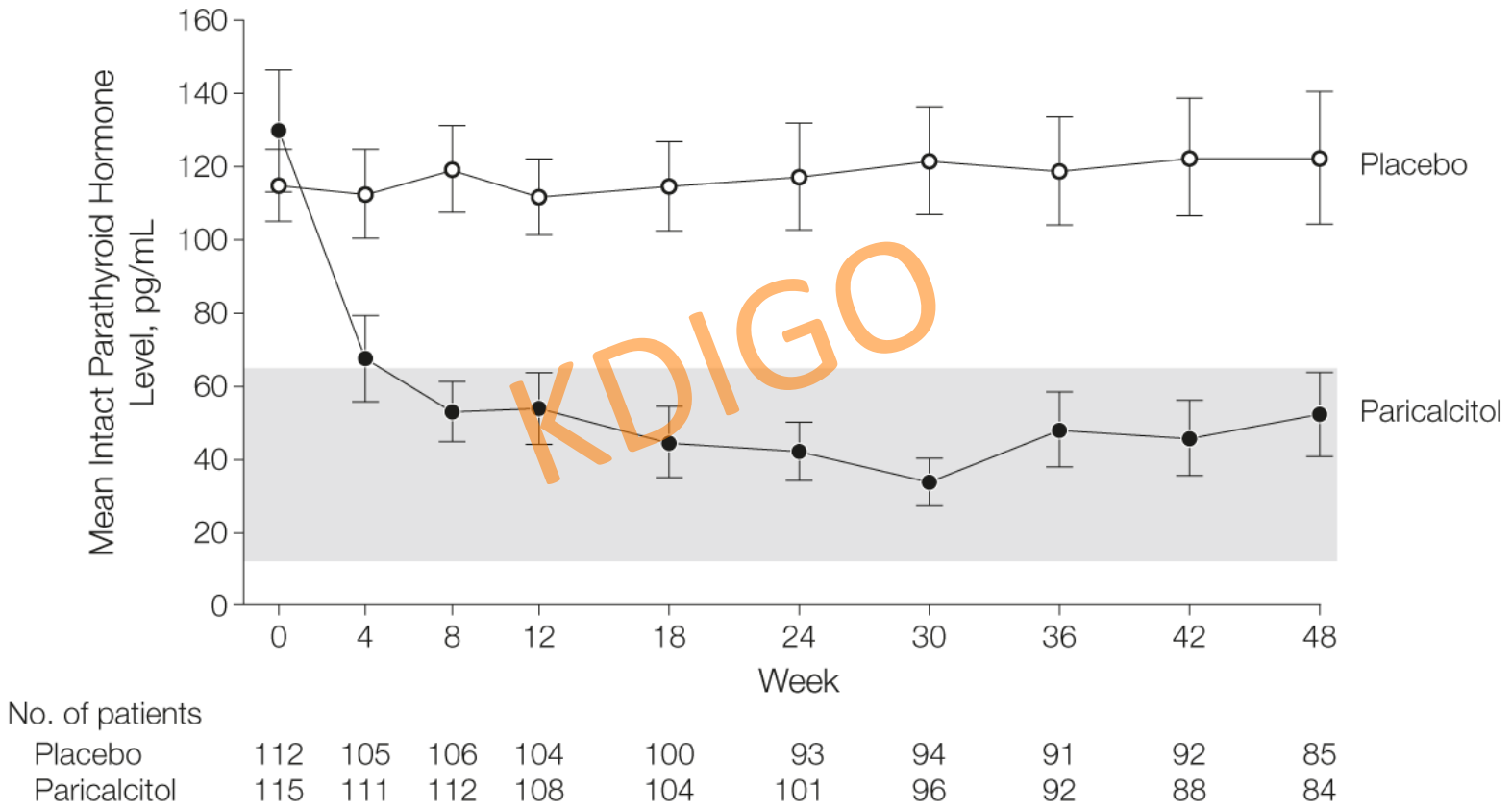
In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range. *(Not Graded)*

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.

THE PRIMO TRIAL



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

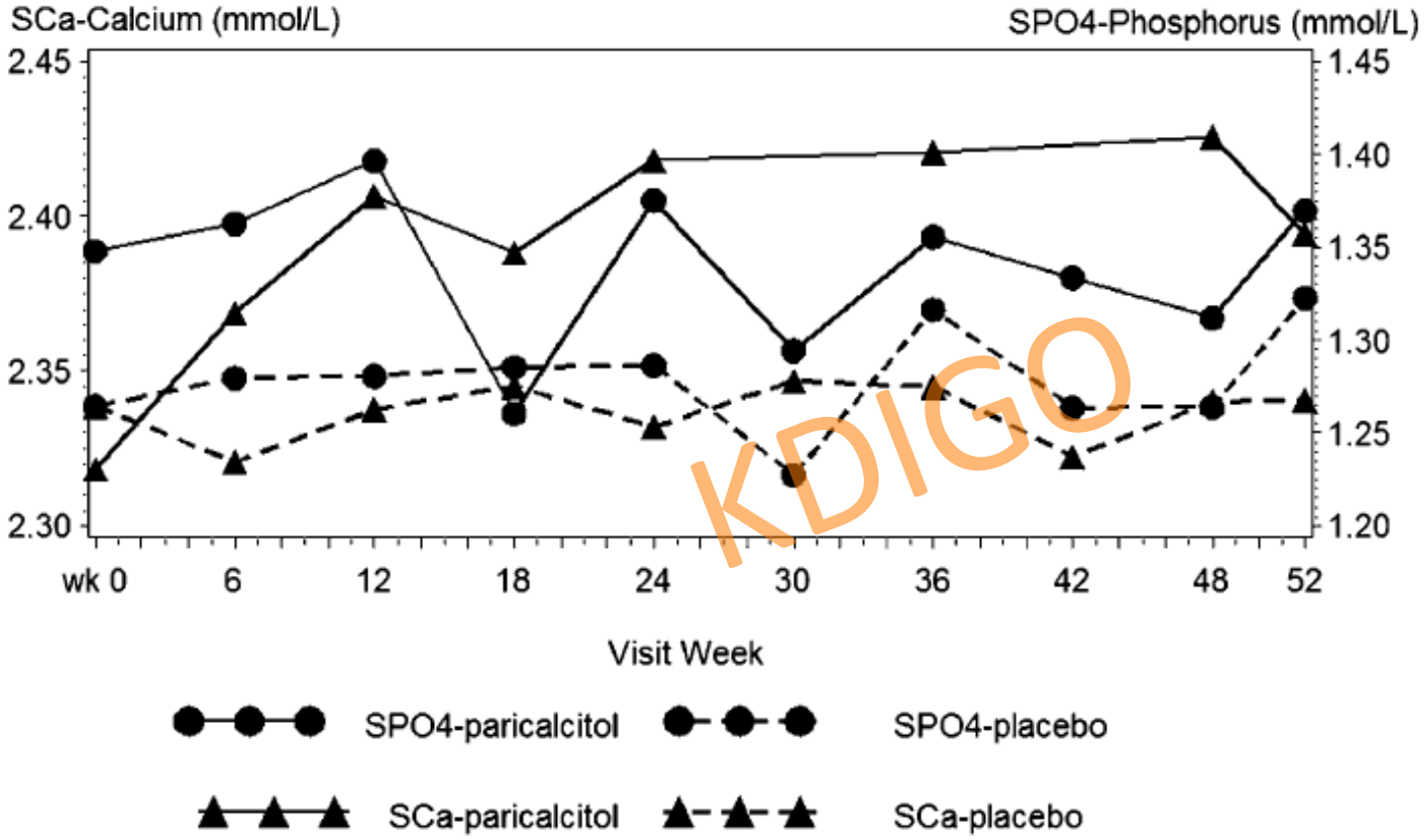
Paricalcitol Effect on Calcium and Phosphate

- Serum calcium levels increased a mean of 0.32 mg/dL (95% CI, 0.19-0.45 mg/dL) in the paricalcitol group and decreased 0.25 mg/dL (95% CI, −0.37 to −0.12 mg/dL) in the placebo group (between-group difference, *P* < .001).

- Serum phosphorus levels increased 0.23 mg/dL (95% CI, 0.07-0.39 mg/dL) in the paricalcitol group and increased 0.04 mg/dL (95% CI, −0.12 to 0.20 mg/dL) in the placebo group (between-group difference, *P* = .05).

- Hypercalcemia-paricalcitol 22.6% versus placebo 0.9%, p<.001
- eGFR decrease (creatinine) paricalcitol -4.1 ml/min versus placebo -0.1 ml/min, p<.001
- No significant effect on measures of LV size or function

THE OPERA TRIAL



Hypercalcemia > 2.55 mmol/L:

Paricalcitol 43.3%

Placebo 3.3%

No significant effect on measures of LV size or function

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

CONCLUSIONS

- Recent RCTs of vitamin D analogs failed to demonstrate improvements in clinically relevant outcomes but did demonstrate increased risk of hypercalcemia. Recent meta-analyses were largely confirmatory and supported the hypercalcemia risk association with calcitriol and vitamin D analogs.
- These results, combined with the opinion that moderate PTH elevations may represent an appropriate adaptive response, led the Work Group to conclude that the risk-benefit ratio of treating moderate PTH elevations was no longer favorable and that the use of calcitriol or vitamin D analogs should be reserved for only severe and progressive SHPT.

CONCLUSIONS

- There are still no RCTs demonstrating beneficial effects of calcitriol or vitamin D analogs on patient-level outcomes, such as cardiac events or mortality, and the optimal level of PTH in CKD stages 3a-5 is not known.
- Therapy with these agents may have additional harmful effects related to increases in serum phosphate and FGF23 levels.
- If initiated for severe and progressive SHPT, calcitriol or vitamin D analogs should be started with low doses, independent of the initial PTH concentration, and then titrated based on the PTH response.
- Hypercalcemia should be avoided.

LOWERING PTH

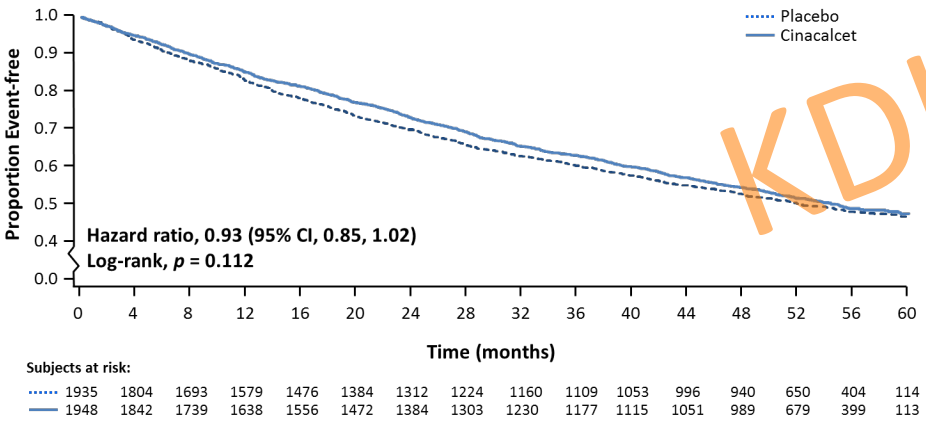
4.2.4: In patients with CKD Stage 5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics and calcitriol, or vitamin D analogs. *(2B)*

RATIONALE

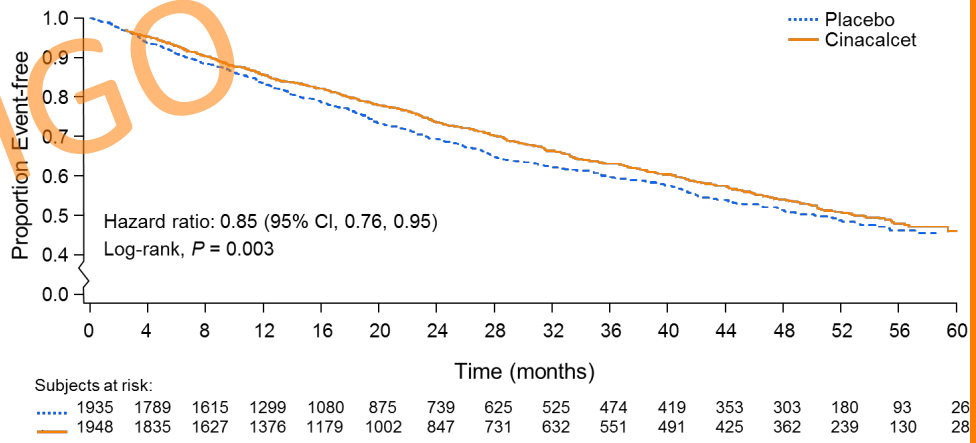
- This recommendation originally had not been identified for an update. However, due to a subsequent series of secondary and *post-hoc* publications of the EVOLVE trial, the Work Group decided to re-evaluate Rec. 4.2.4 as well.

EVOLVE Study: Cinacalcet

Intention-to-treat population

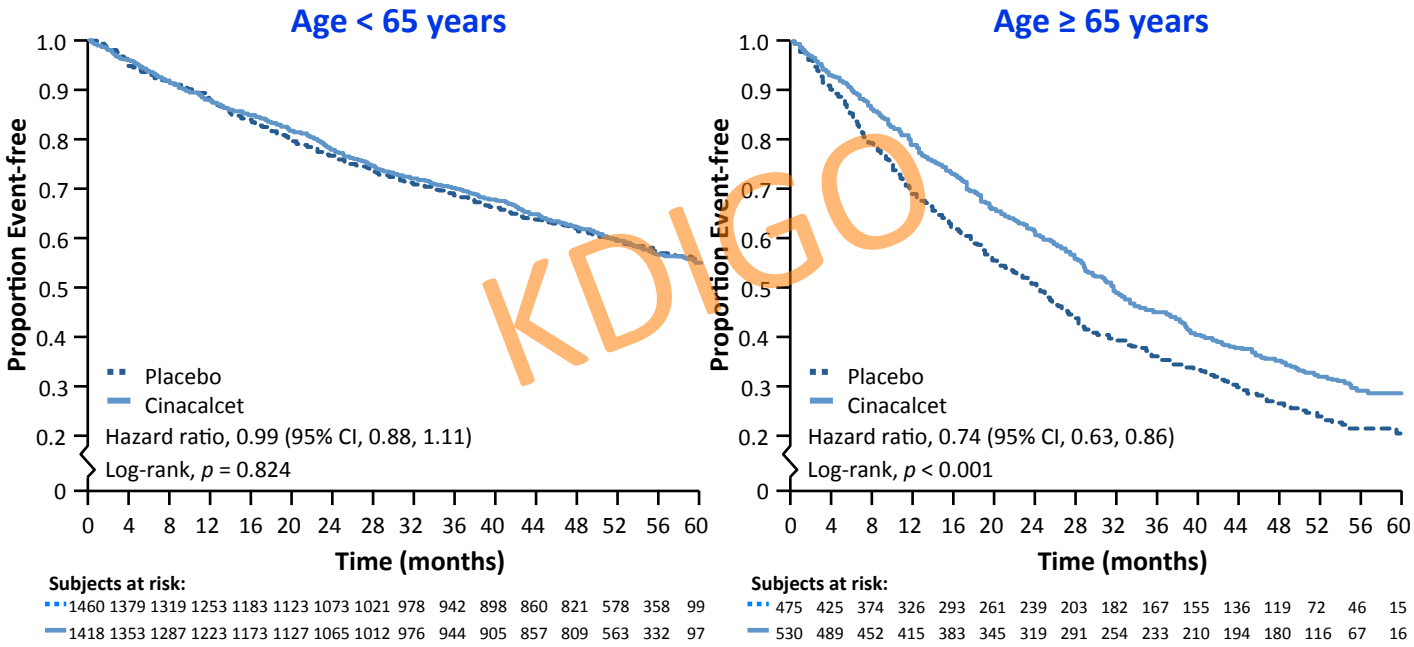


Lag-censoring population



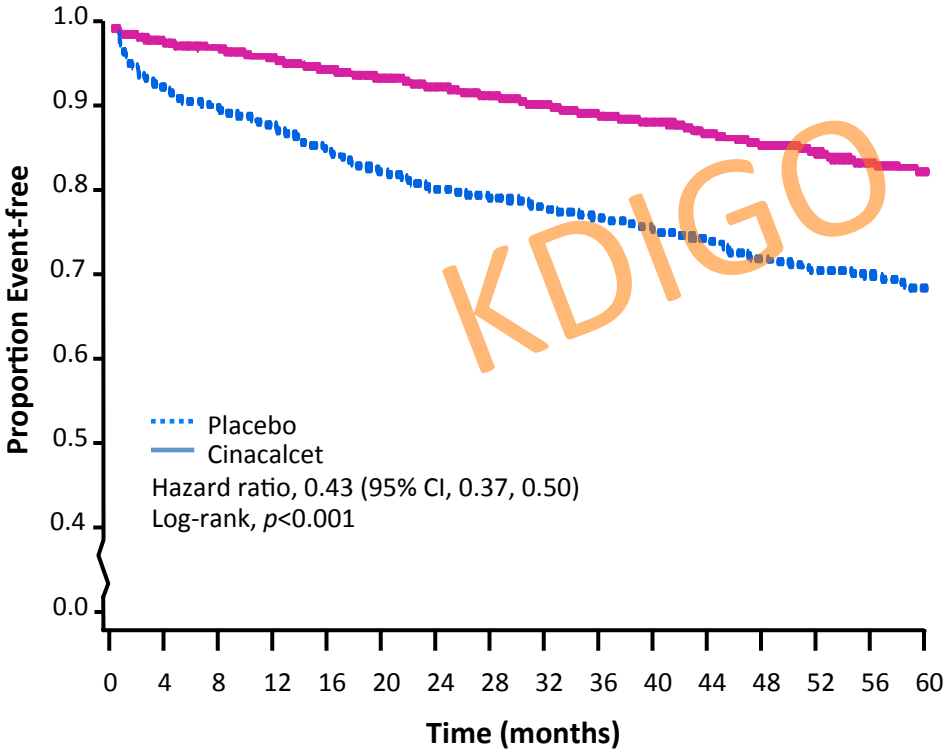
Chertow GM, et al. N Engl J Med. 2012;367:2482-2494

TIME TO PRIMARY COMPOSITE ENDPOINT



Parfrey et al, CJASN, 2015

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



EVOLVE

Severe, unremitting HPT

- Pre-specified 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

RATIONALE

- Although EVOLVE did not meet its primary endpoint, the majority of the Work Group were reluctant to exclude potential benefits of calcimimetics for Stage 5D patients, based on subsequent prespecified analyses.
- No PTH-lowering treatment was prioritized at this time, since calcimimetics, calcitriol, or vitamin D analogs are all acceptable first-line options in CKD Stage 5D patients.
- The Work Group explicitly endorses the presence of clinical equipoise and the need to conduct placebo controlled trials with calcimimetics versus standard therapy for the treatment of SHPT in patients with CKD stage 5D with emphasis on those at greatest risk (e.g., older, presence of cardiovascular disease).

CONCLUSION

- No consensus was reached to recommend cinacalcet as first-line therapy for lowering PTH in all patients with SHPT and CKD Stage 5D. The Work Group decided to modify the 2009 recommendation to list calcimimetic therapy now first, in alphabetical order, among acceptable treatment options while still recognizing the utility and efficacy of active vitamin D compounds.