



Seoul – May 20, 2017

37<sup>th</sup> Annual Meeting of the Korean Society of Nephrology

## KDIGO CKD-MBD GUIDELINE UPDATE 2017:

### WHAT IS NEW?

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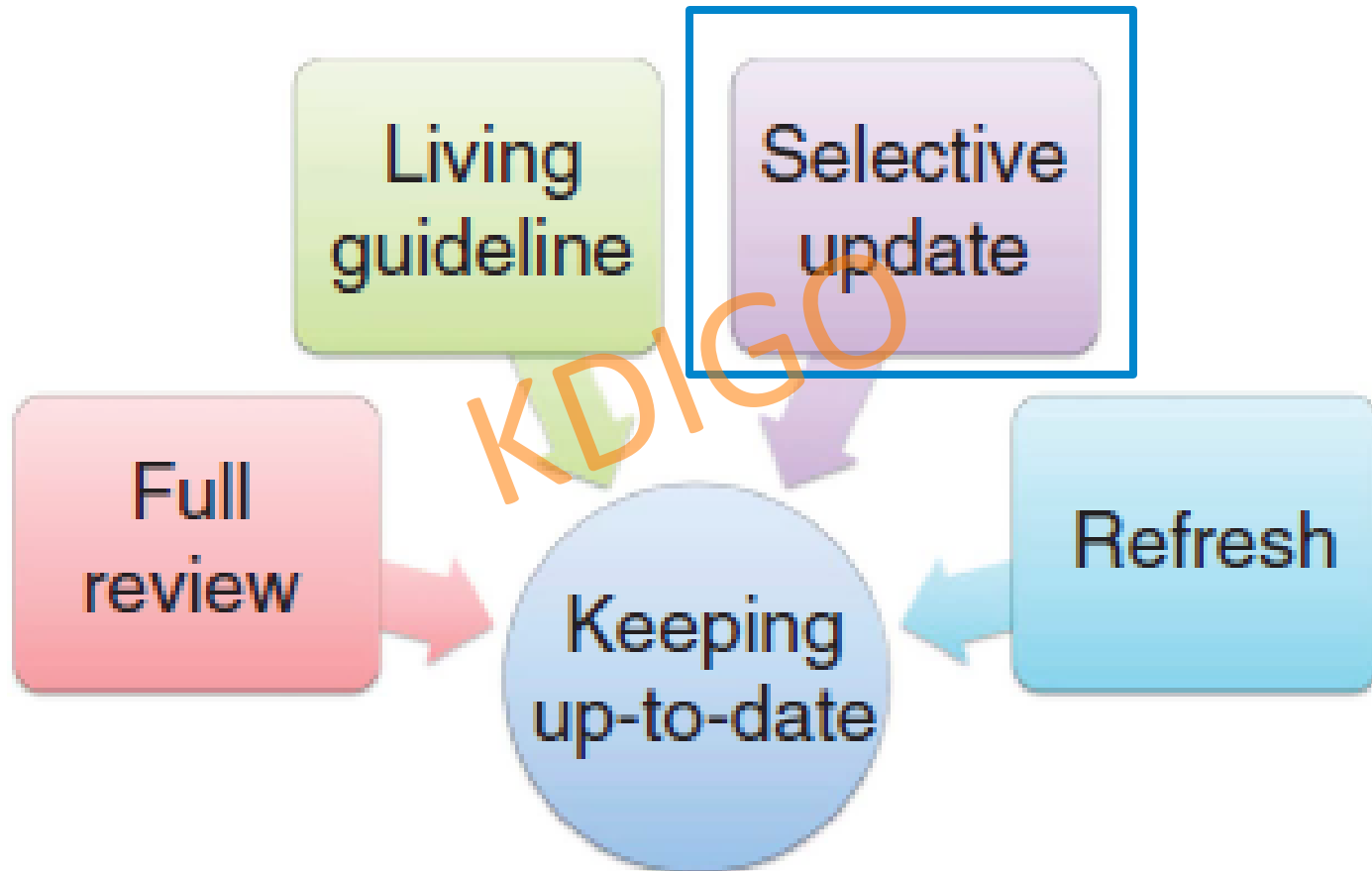
# KDIGO CONTROVERSIES CONFERENCE

## 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

- 4.1.1. **No recommended monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity beyond an eGFR stage 3-5G. In addition, we suggest discontinuing testing in CKD stage 2-5G.**
- 4.1.2. In patients with CKD stages 3-5G, 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 (see table).
- Reasonable monitoring intervals would be:
  - In CKD stages 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 3-6 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 treatment 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 safety (see table).
- 4.1.3. In patients with CKD stages 3-5G, we suggest that  $25(OH)D$  (calcitriol) levels might be measured, and reported 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).
- 4.1.4. In patients with CKD stages 3-5G, 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).
- 4.1.5. In patients with CKD stages 3-5G, we suggest that individual values of serum calcium and phosphorus, measured together, be used to guide clinical practice rather than the mathematical construct of calcium-phosphorus product (Ca X P) (2D).
- 4.1.6. In reports of laboratory tests for patients with CKD stages 3-5G, we recommend that clinical laboratory reports (inclusion of the actual stage method to use and report any change in methods, sample source (plasma or serum), and handling specifications to facilitate the appropriate interpretation of biochemistry data (1B).

4.1.1. **No recommended monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity beyond an eGFR stage 3-5G. In addition, we suggest discontinuing testing in CKD stage 2-5G.**

4.1.2. In patients with CKD stages 3-5G, 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 (see table).

Reasonable monitoring intervals would be:

- In CKD stages 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 3-6 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 treatment 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 safety (see table).

4.1.3. In patients with CKD stages 3-5G, we suggest that  $25(OH)D$  (calcitriol) levels might be measured, and reported 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).

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4.1.6. In reports of laboratory tests for patients with CKD stages 3-5G, we recommend that clinical laboratory reports (inclusion of the actual stage method to use and report any change in methods, sample source (plasma or serum), and handling specifications to facilitate the appropriate interpretation of biochemistry data (1B).

4.1.3. In patients with CKD stages 3-5G and hypocalcaemia, we recommend restricting the dose of calcitonin-based phosphate binders to the dose of calcitonin or vitamin D analog in the presence of parathyroid or reserved hypercalcaemia (2E).

4.1.4. In patients with CKD stages 3-5G and hyperphosphatemia, we suggest restricting the dose of calcitonin-based phosphate binders to the presence of elevated calcitriol (2C) (adding vitamin D analogs (2C) and/or (if serum PTH levels are persistently low (2D)).

4.1.5. In patients with CKD stages 3-5G, we recommend avoiding the long term use of aluminum-containing phosphate binders in patients with CKD stage 5G, avoiding aluminum accumulation to prevent aluminum intoxication (1C).

4.1.6. In patients with CKD stages 3-5G, we suggest testing dietary phosphate levels in the presence of hypercalcaemia, unless it is combined with other treatment (2E).

4.1.7. In patients with CKD stage 3-5G, we suggest restricting the use of oral phosphate binders to patients with CKD stage 4-5G, unless the patient has a history of hypercalcaemia, and unless a dietary phosphate restriction is not possible (2E) (if the patient has a history of hypercalcaemia, we suggest a dietary phosphate restriction (2E)).

4.1.8. In CKD stages 3-5G, or CKD stage 5G patients with CKD-MBD, we suggest that a dietitian be consulted to assist with dietary phosphate restriction (2E).

4.1.9. In patients with CKD stage 3-5G, we suggest electrolyte monitoring at the highest appropriate frequency to detect the presence of hyponatremia, hyperkalemia, and other electrolyte abnormalities (2E).

4.1.10. In patients with CKD stages 3-5G, we suggest monitoring serum phosphorus in the range 1.0 to 1.50 mmol/L (2.4 to 3.6 mg/dL) (2D).

4.1.11. In patients with CKD stages 3-5G, we suggest monitoring serum calcium in the range 2.0 to 2.60 mmol/L (8.0 to 10.4 mg/dL) (2D).

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- We suggest that, in patients with hypercalcaemia, calcitonins be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (2D).
  - We suggest that, in the latest 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).
- 4.2.3. In patients with CKD stages 3-5G with severe hypernatremia (Na<sup>+</sup>) who fail to respond to medical/therapeutic therapy, we suggest sodium restriction (2E).
- 4.3.1. In patients with CKD stage 3-5G with development and/or high risk of PTHrP, as identified by Blood Health Organization criteria, we suggest treatment as follows (see table).
- 4.3.2. In patients with CKD stage 3 with PTH in the normal range and subnormal and/or high risk of fracture, as identified by Blood Health Organization criteria, we suggest treatment as follows for the general population (2E).
- 4.3.3. In patients with CKD stage 3 with biochemical abnormalities of CKD-MBD and low BMD and/or healthy fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (2D).
- 4.3.4. In patients with CKD stage 3-5G having biochemical abnormalities of CKD-MBD, and low BMD and/or healthy fractures, we suggest additional investigation with bone biopsy (see table) in those with antiresorptive therapy (2C).
- 4.3.5. In children and adolescents with CKD stages 3-5G and related height deficits, we recommend treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD-MBD (1A).
- 5.1. In patients in the immediate post kidney transplant period, we recommend measuring serum 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 the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (see table).
- Reasonable monitoring intervals would be:
- CKD stages 1-2E: for serum calcium and phosphorus, every 6-12 months; and for PTH, based on baseline level and CKD progression.
  - CKD stage 3E: for serum calcium and phosphorus, every 3-6 months; and for PTH, every 6-12 months.
  - CKD stage 4: for serum calcium and phosphorus, every 3-6 months; and for PTH, every 6-12 months.
  - CKD stage 5: for serum calcium and phosphorus, every 3-6 months; and for PTH, every 3-6 months.
- In CKD stages 4-5E, measurement of alkaline phosphatase activity, or more frequently in the presence of elevated PTH (see Chapter 3.2).

- In patients with CKD stages 3-5G, we suggest that  $25(OH)D$  (calcitriol) levels might be measured, and reported testing determined by baseline values and interventions (2C).
  - In patients with CKD stages 3-5G, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).
  - In patients with CKD stages 3-5G, we suggest that individual values of serum calcium and phosphorus, measured together, be used to guide clinical practice rather than the mathematical construct of calcium-phosphorus product (Ca X P) (2D).
  - In reports of laboratory tests for patients with CKD stages 3-5G, we recommend that clinical laboratory reports (inclusion of the actual stage method to use and report any change in methods, sample source (plasma or serum), and handling specifications to facilitate the appropriate interpretation of biochemistry data (1B).
- 5.4. 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<sup>2</sup> and low BMD, we suggest that treatment with vitamin D<sub>3</sub>, calcitriol/calcipotriol, 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 phosphatase, 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 atypical bone disease (see table).
- 5.7. In patients with CKD stages 4-5E, we suggest that BMD testing not be performed routinely because BMD may not predict fracture risk in the general population (2D). We suggest that BMD testing be performed in those with low bone mass (see table).
- 5.8. In patients with CKD stages 4-5E with known low BMD, we suggest management as for patients with CKD stages 4-5E on dialysis, as detailed in Chapters 4.1 and 4.2 (2C).

## Overview of recommended changes

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



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



# CKD-MBD GUIDELINE UPDATE 2016

## Guideline Chairs

Markus Ketteler (Germany)

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)
- Rukshana Shroff (UK)
- 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:

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## TREATMENT OF CKD–MBD: BONE

KDIGO



# 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)

KDIGO

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

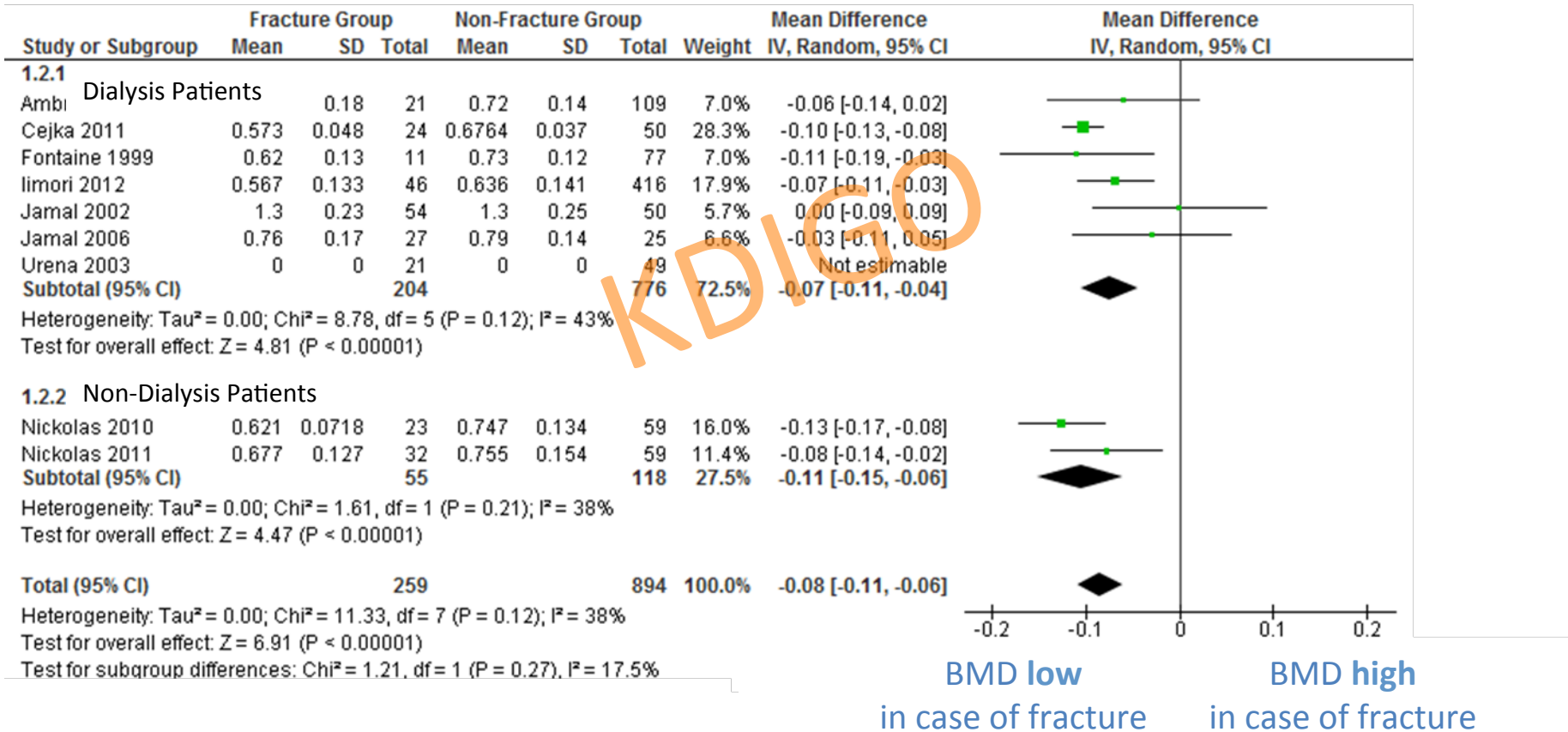
- Multiple new prospective studies have documented that lower DXA BMD does predict incident fractures in patients with CKD Stages 3a-5D.

KDIGO



# RATIONALE: Meta analysis

## DEXA determined femoral BMD



# CHAPTER 4.1:

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## 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*)

KDIGO

2009:

*No comparable statement*



# RATIONALE

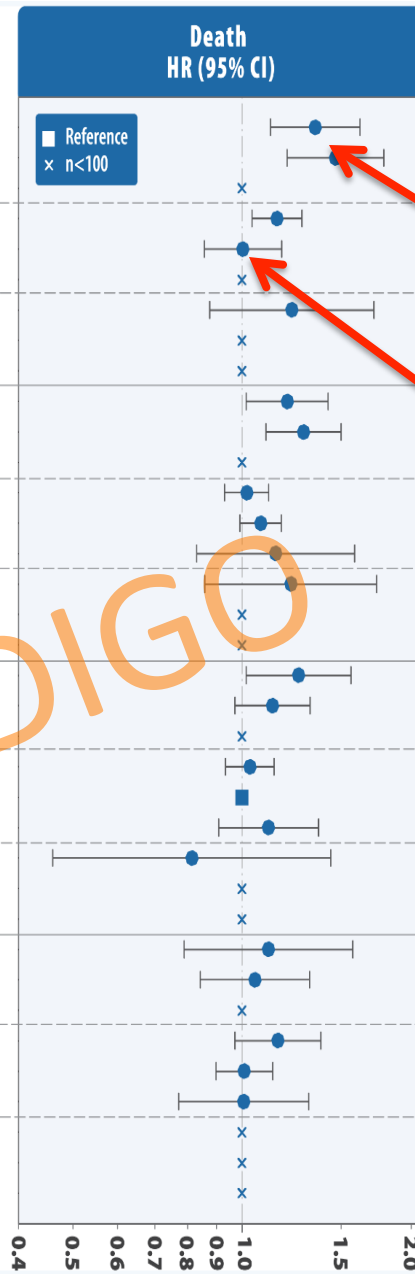
- This new recommendation was provided in order to emphasize the complexity and interaction of CKD-MBD laboratory parameters.
- Serum phosphorus, calcium and PTH concentrations are all routinely measured and clinical decisions are often made based on these values. Clinical decision making should not 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-M

OF PTH high

PTH	Ca	P	Patients (n=26,221)
High	High	High	514 (1.96%)
High	High	Target	292 (1.11%)
High	High	Low	9 (0.03%)
High	Target	High	2,803 (10.69%)
High	Target	Target	861 (3.28%)
High	Target	Low	19 (0.07%)
High	Low	High	211 (0.80%)
High	Low	Target	20 (0.08%)
High	Low	Low	1 (0.00%)
Target High	High	High	593 (2.26%)
Target High	High	Target	631 (2.41%)
Target High	High	Low	19 (0.07%)
Target High	Target	High	4,117 (15.70%)
Target High	Target	Target	3,828 (14.60%)
Target High	Target	Low	133 (0.51%)
Target High	Low	High	187 (0.71%)
Target High	Low	Target	49 (0.19%)
Target High	Low	Low	1 (0.00%)
Target Low	High	High	345 (1.32%)
Target Low	High	Target	665 (2.54%)
Target Low	High	Low	30 (0.11%)
Target Low	Target	High	2,624 (10.01%)
Target Low	Target	Target	5,224 (19.92%)
Target Low	Target	Low	299 (1.14%)
Target Low	Low	High	100 (0.38%)
Target Low	Low	Target	65 (0.25%)
Target Low	Low	Low	7 (0.03%)
Low	High	High	123 (0.47%)
Low	High	Target	252 (0.96%)
Low	High	Low	28 (0.11%)
Low	Target	High	574 (2.19%)
Low	Target	Target	1,282 (4.89%)
Low	Target	Low	156 (.59%)
Low	Low	High	76 (0.29%)
Low	Low	Target	71 (0.27%)
Low	Low	Low	12 (0.05%)



# JUSTED RISK

ZATION

Calcium and Phosphate high

Calcium and Phosphate target



# 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)

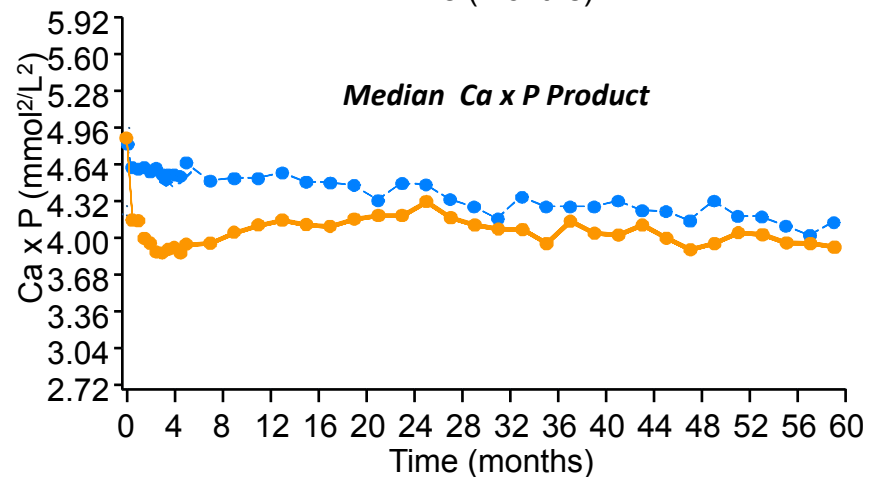
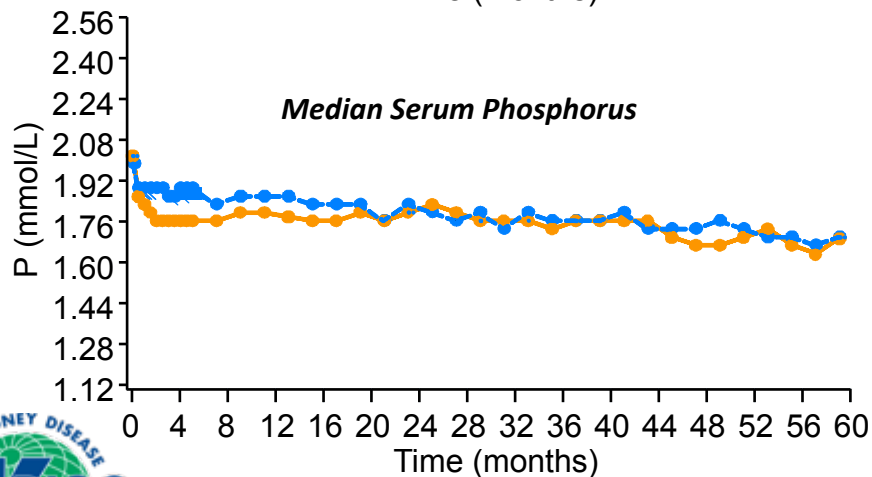
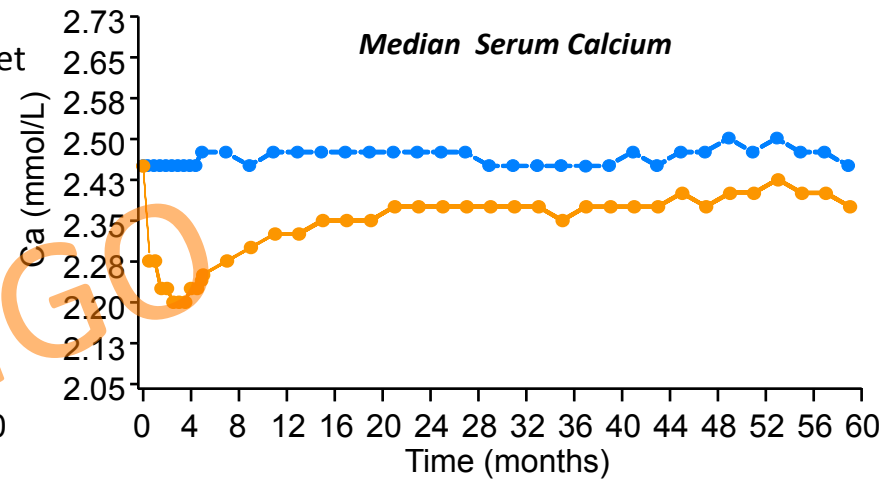
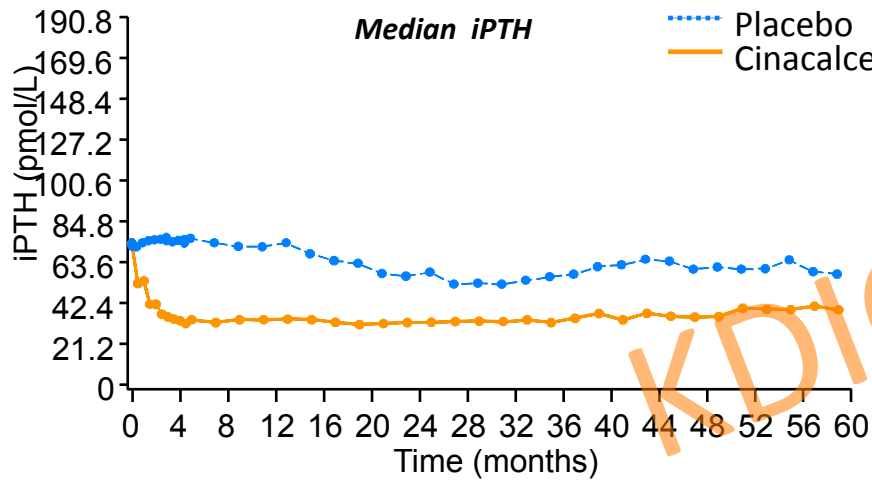
2009:

*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)*

KDIGO

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

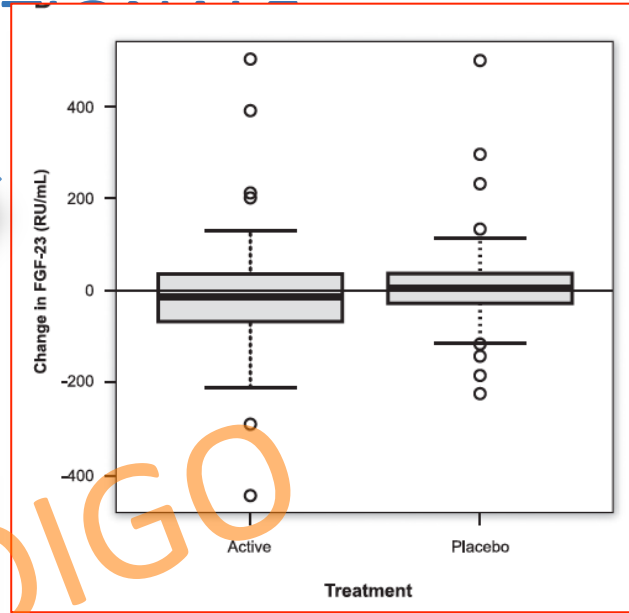
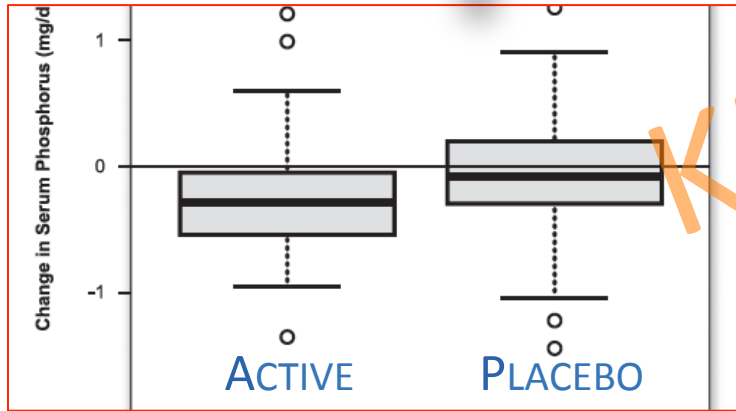
- The 2009 KDIGO Guideline commented that available phosphate binders are all effective in the treatment of hyperphosphatemia, and that there is evidence that calcium-free binders may favor halting progression of vascular calcifications vs. calcium-containing binders
- But concerns about calcium balance, 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.



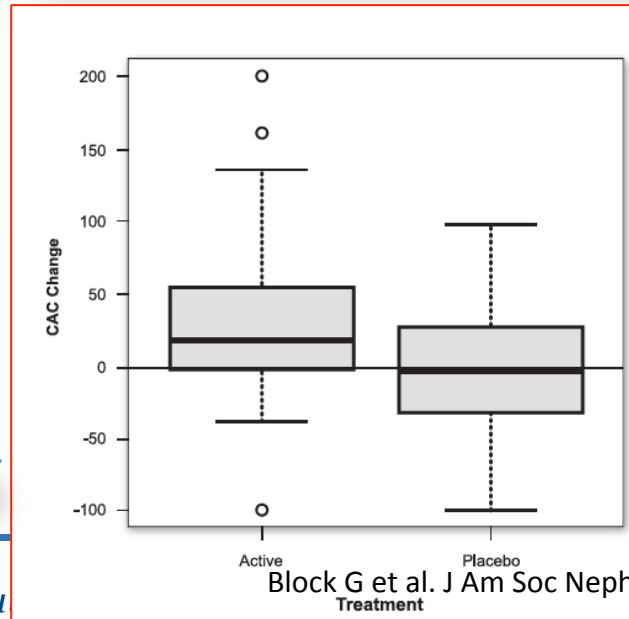
- CKD 3b – 4
- Serum phosphate in the upper normal range
- „Active“: Lanthanum – Sevelamer – Ca acetate

RA

PHOSPHATE



FGF23



CORONARY  
CALCIFICATION



# 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

KDIGO



# 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).~~





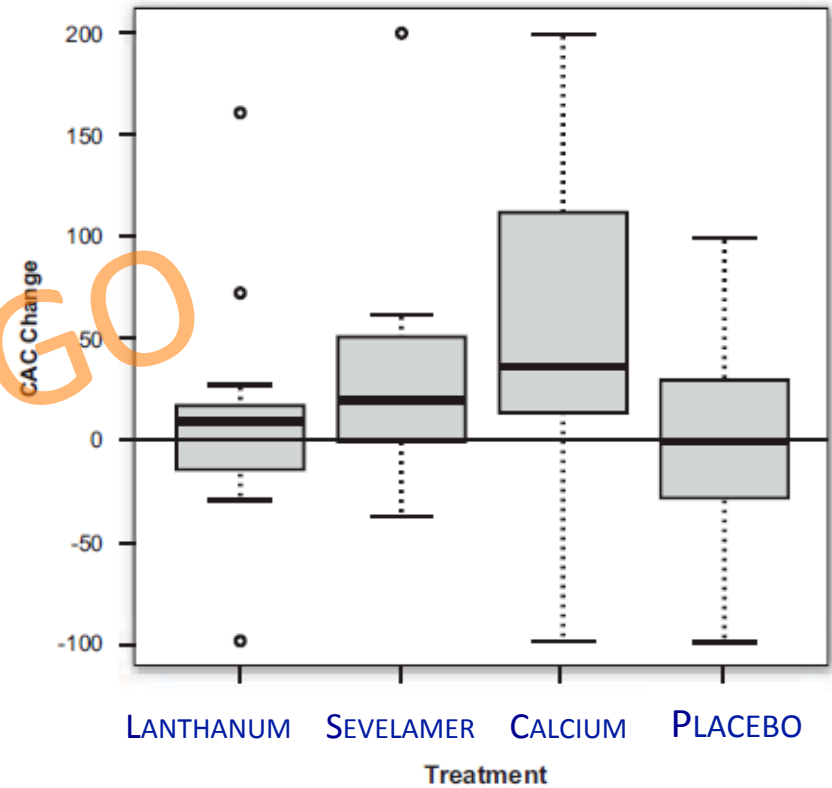
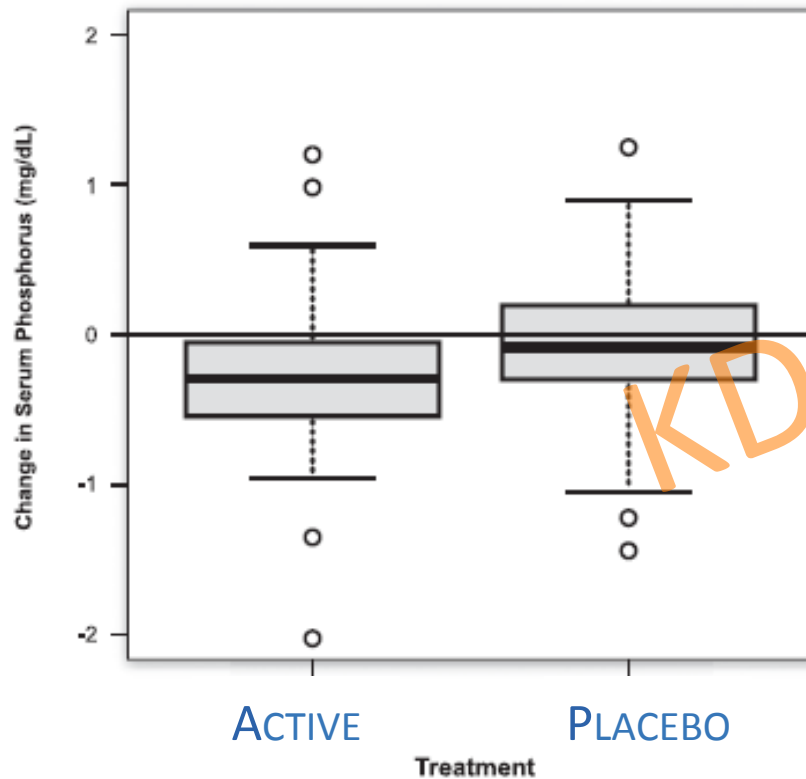
# RATIONALE

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

KDIGO

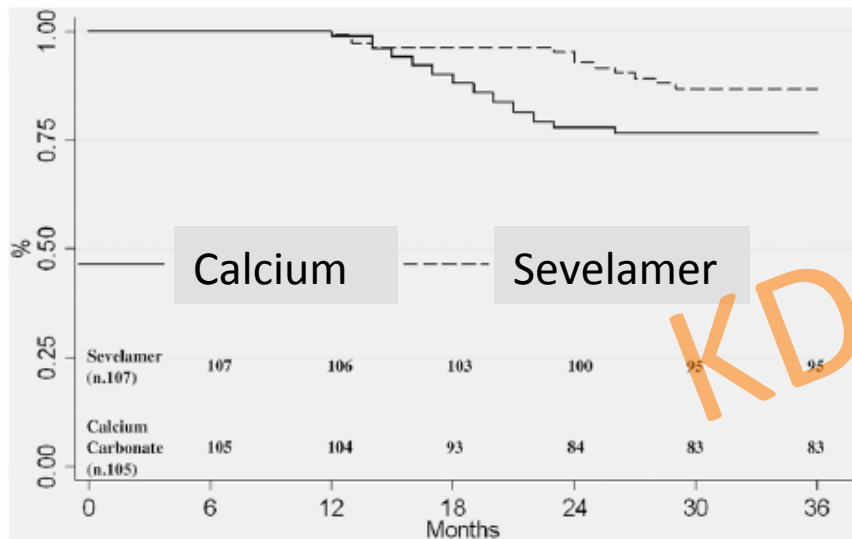


# PHOSPHATE BINDERS IN MODERATE CKD

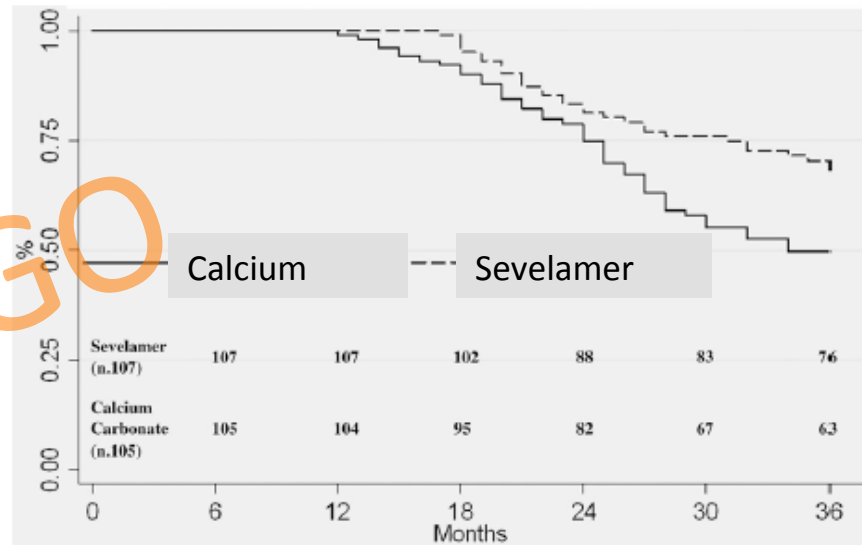


# PHOSPHATE BINDERS AND MORTALITY (PREDIALYSIS)

All-Cause Mortality



Dialysis Inception



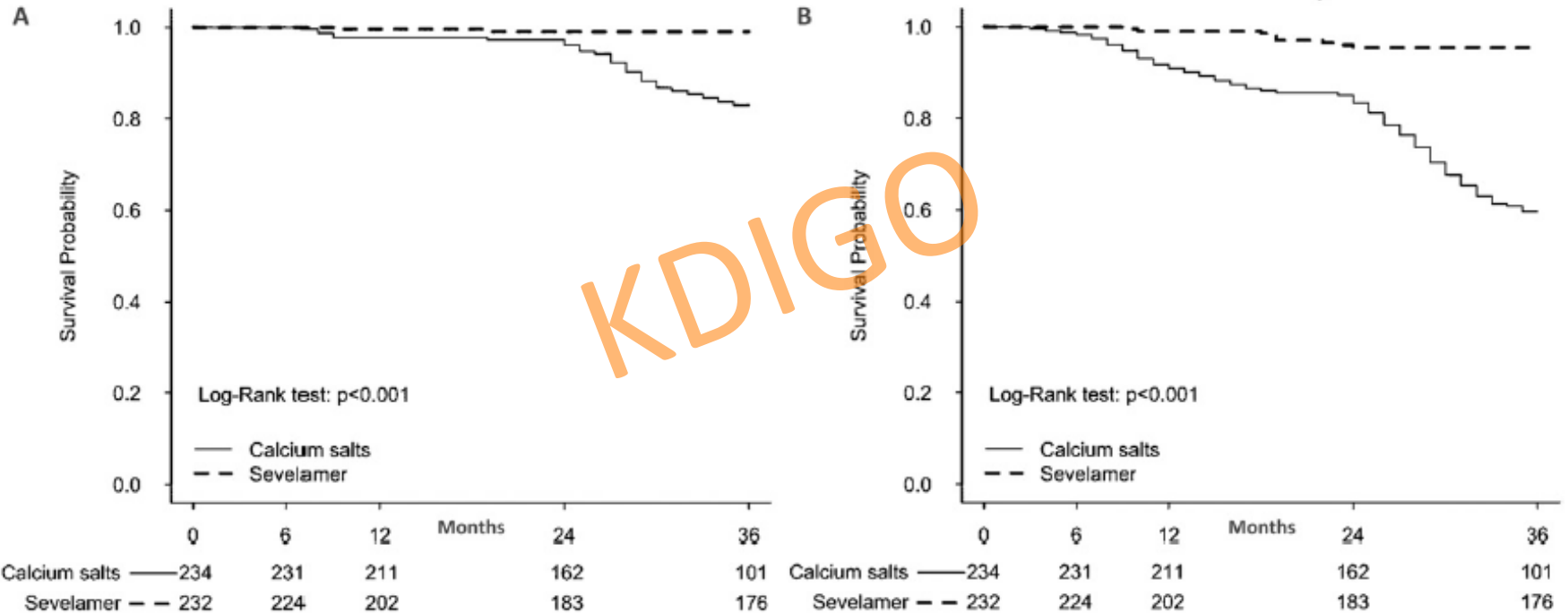
Di Iorio B et al. Clin J Am Soc Nephrol 2012;7:487-493

# SEVELAMER VS. CALCIUM

(DIALYSIS)

Arrhythmias

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

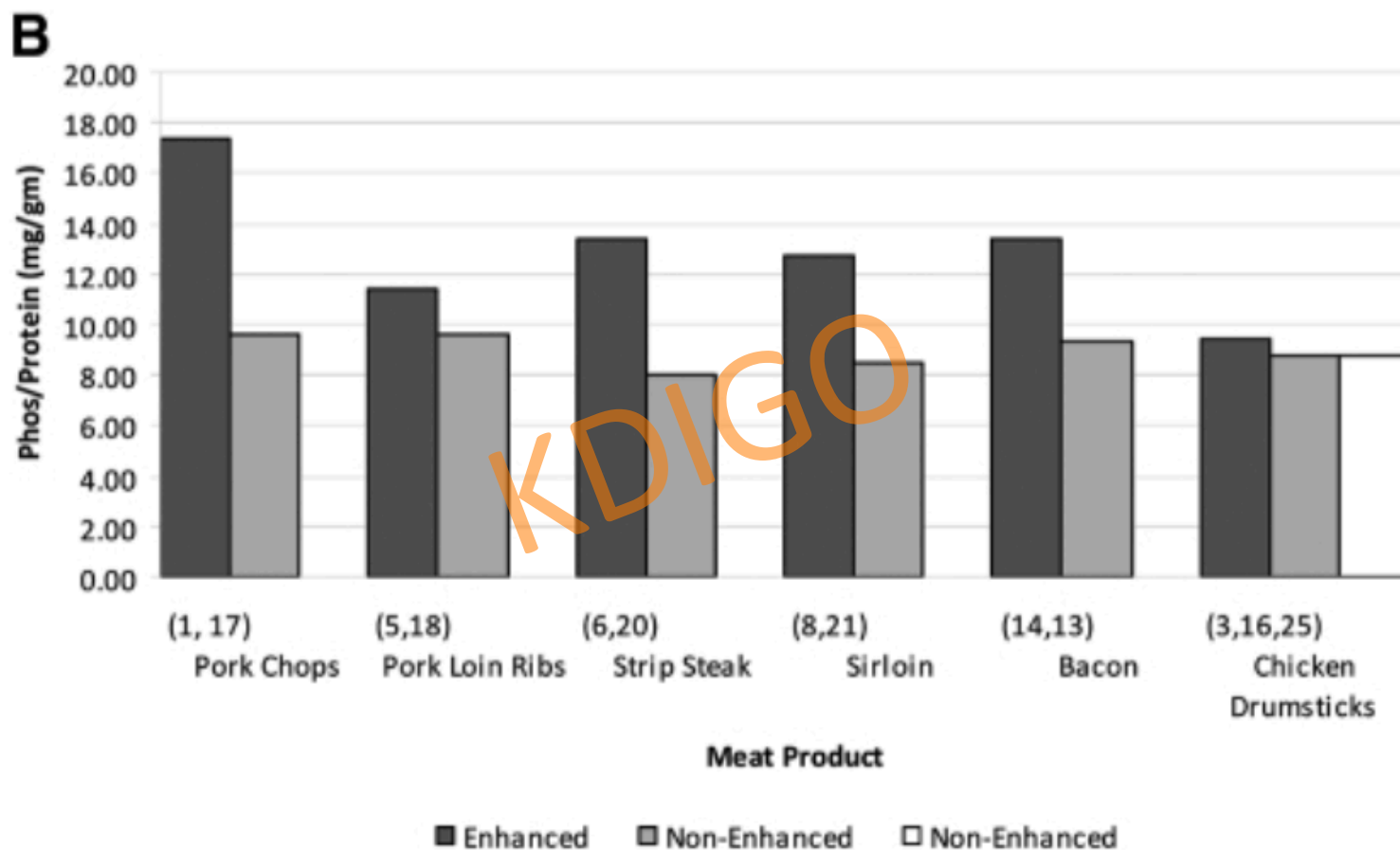
	Before Meat (casein) Diet	After Meat (casein) Diet	Before Vegetarian (grain) Diet	After Vegetarian (grain) Diet	P (paired t test) <sup>a</sup>
Average daily phosphorus intake (mg/day)		810 ± 27		795 ± 51	NS
Plasma phosphorus (mg/dl)	3.5 ± 0.6	3.7 ± 0.6	3.5 ± 0.6	3.2 ± 0.5	0.02
Plasma intact PTH (pg/ml)	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

<sup>a</sup>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:

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## 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*)

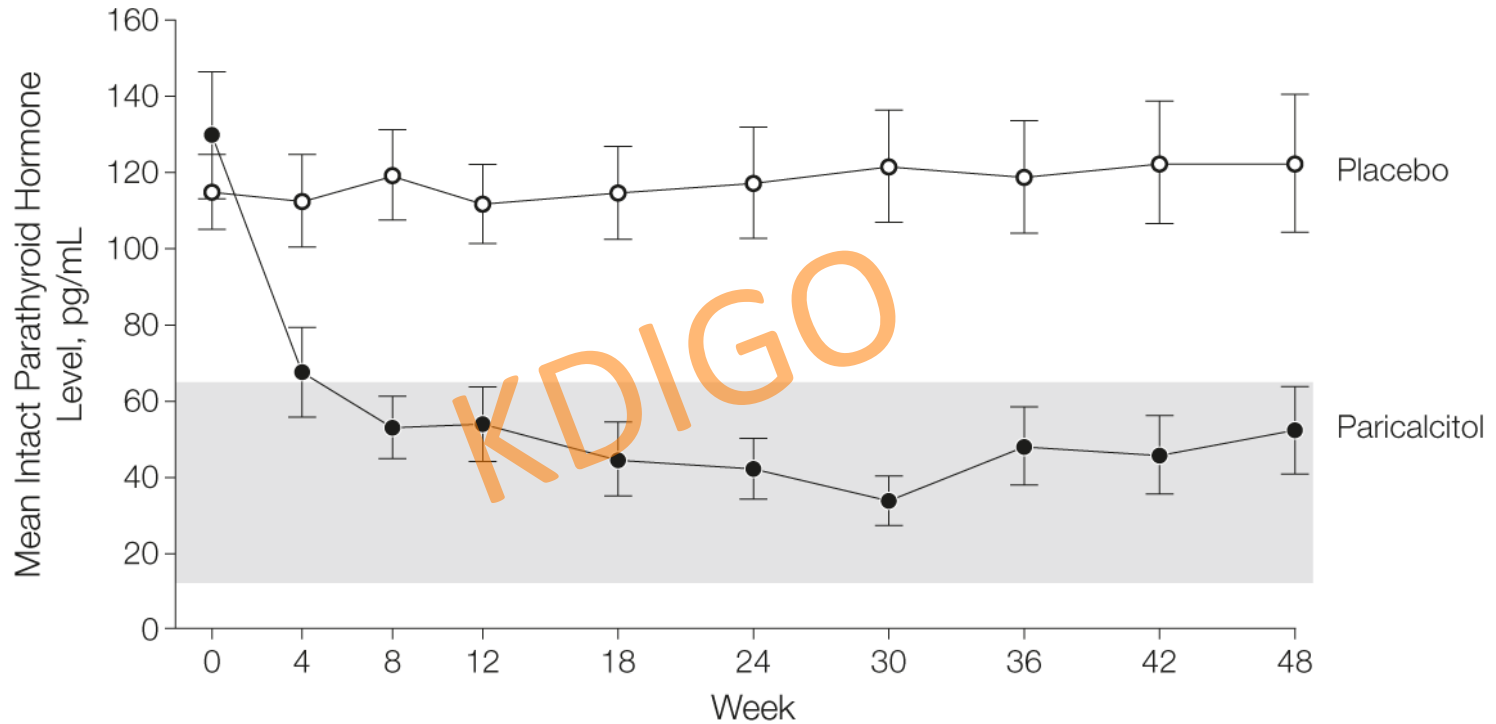


# RATIONALE

- 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



No. of patients

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

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



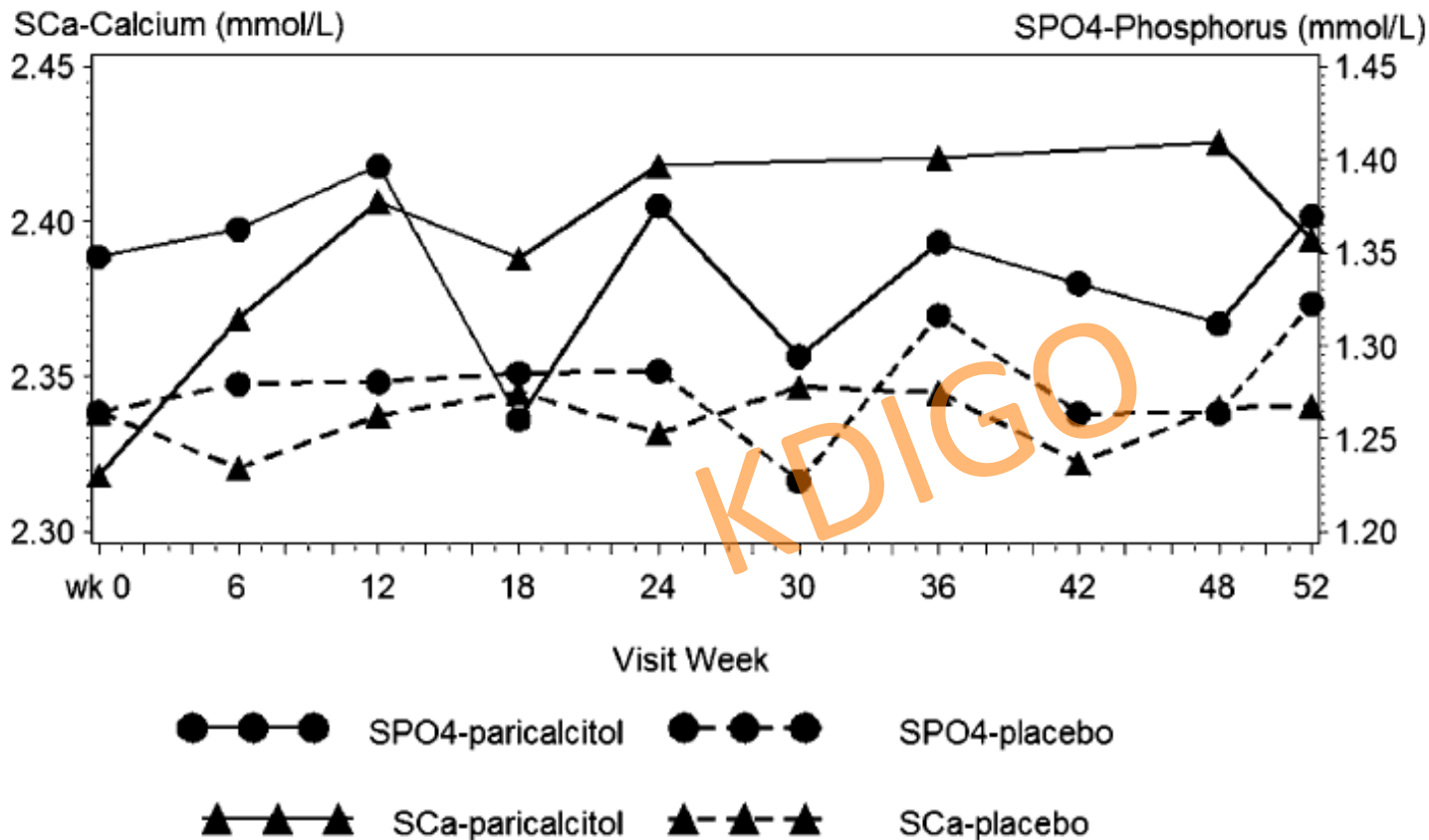
*Kidney Disease: Improving Global Outcomes*

# 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

*Kidney Disease: Improving Global Outcomes*





# 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)

KDIGO



# RATIONALE

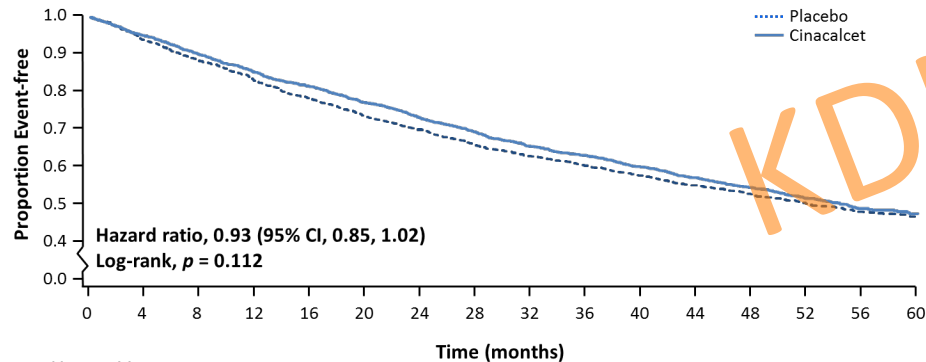
- This recommendation originally had not been identified for an update. However, due to a subsequent series of secondary and *post-hoc* publications of the EVOLVE trial, the Work Group decided to re-evaluate Rec. 4.2.4 as well.

KDIGO



# EVOLVE STUDY: CINACALCET

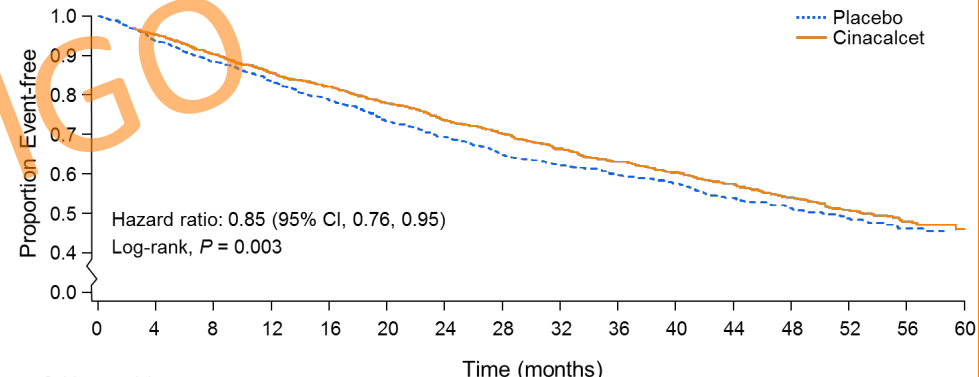
## Intention-to-treat population



Subjects at risk:

1935	1804	1693	1579	1476	1384	1312	1224	1160	1109	1053	996	940	650	404	114
1948	1842	1739	1638	1556	1472	1384	1303	1230	1177	1115	1051	989	679	399	113

## Lag-censoring population



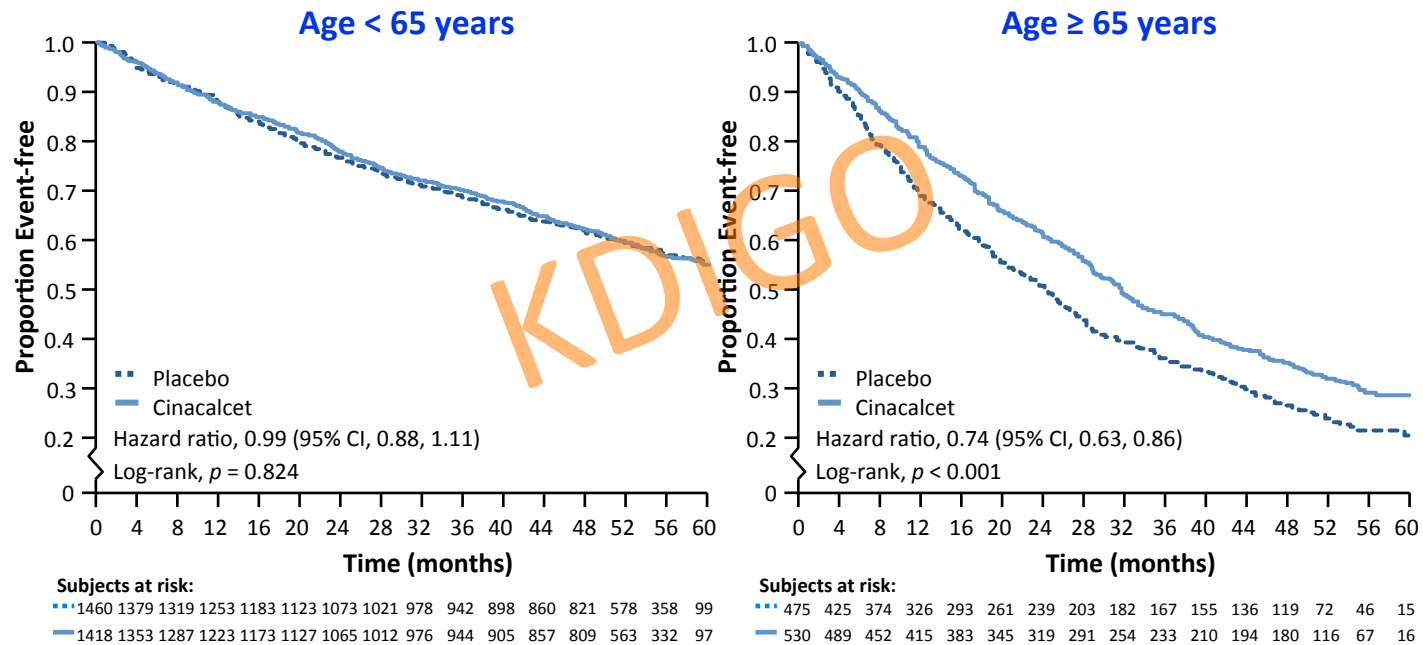
Subjects at risk:

1935	1789	1615	1299	1080	875	739	625	525	474	419	353	303	180	93	26
1948	1835	1627	1376	1179	1002	847	731	632	551	491	425	362	239	130	28

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



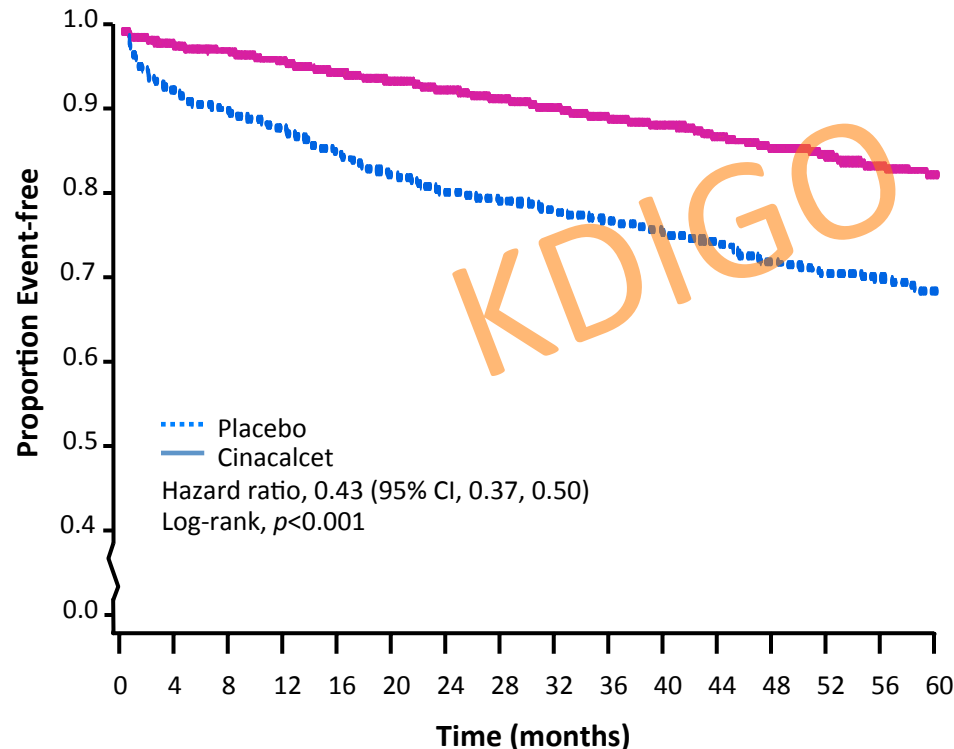
# TIME TO PRIMARY COMPOSITE ENDPOINT



Parfrey et al, CJASN, 2015



# TIME TO FIRST EPISODE OF SEVERE UNREMITTING HPT (INTENT-TO-TREAT ANALYSIS)



## 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.

