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- Marc Vervloet is associate professor at the department of Nephrology of the VU university medical center.
- He is project leader at the Institute of Cardiovascular Research VU (ICaR-VU).
- He co-chaired the national committee developing Dutch guidelines on CKD-MBD, board member of the scientific committee of the Dutch kidney Foundation, and is co-founder and secretary of the ERA-EDTA working group on CKD-MBD.
- He has published several original studies on several topics, mainly focused on CKD-MBD, is member of ERA-EDTA and the ASN.



KDIGO 2016 Clinical Practice Guideline Update

UPDATE ON THE MANAGEMENT OF CALCIUM & PHOSPHATE IN CKD

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Disclosure of Interests

- Employer: VU University Medical Center
- Research funding
 - Dutch Kidney Foundation, European Committee, FMC, Pfizer, Sanofi, Shire, AbbVie, Amgen
- Consultant, lecture fees, other
 - AbbVie, Alexion, Amgen, Astellas, Baxter, FMC
- Membership/Advisor
 - Secretary ERA-EDTA working group on CKD-MBD
 - KDIGO committee working group on CKD-MBD



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)



EVIDENCE REVIEW TEAM

Leader

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Evidence Review Team

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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



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 Ketteler¹, Grahame J. Elder^{2,3}, Pieter Evenepoel⁴, Joachim H. Ix^{5,6,7}, Sophie A. Jamal⁸, Marie-Hélène Lafage-Proust⁹, Rukshana Shroff¹⁰, Ravi I. Thadhani¹¹, Marcello A. Tonelli^{12,13}, Bertram L. Kasiske¹⁴, David C. Wheeler¹⁵ and Mary B. Leonard¹⁶



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*)

KDIGO

2009:

No comparable statement



RATIONALE

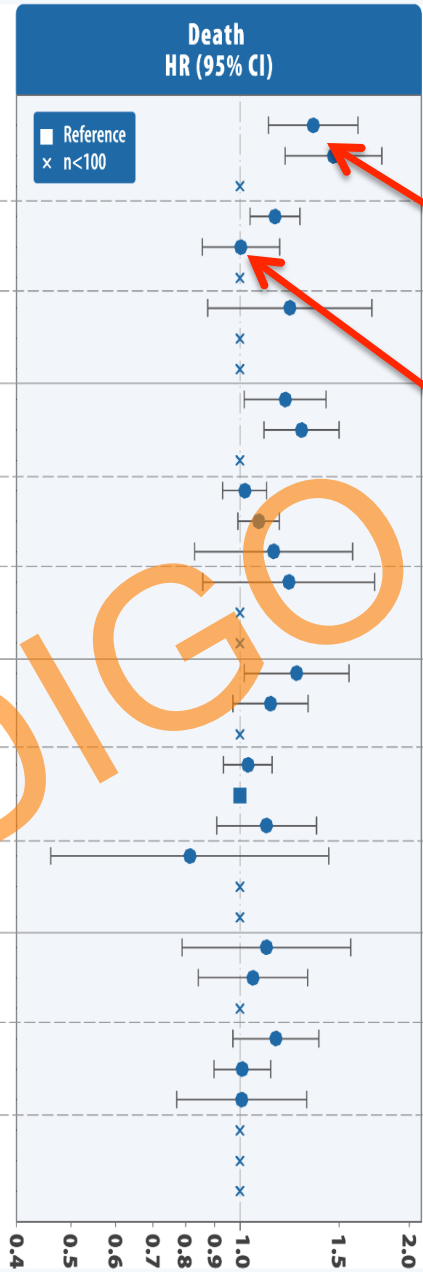
- This new recommendation was provided in order to emphasize the complexity and interaction of CKD-MBD laboratory parameters.
- Serum phosphorus, calcium and PTH concentrations are all routinely measured and clinical decisions are often made based on these values. Clinical decision making should not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

4.1.2: In patients with CKD Stages 3a-5D, we suggest lowering elevated phosphorus levels towards the normal range. (2C)

2009:

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



RATIONALE

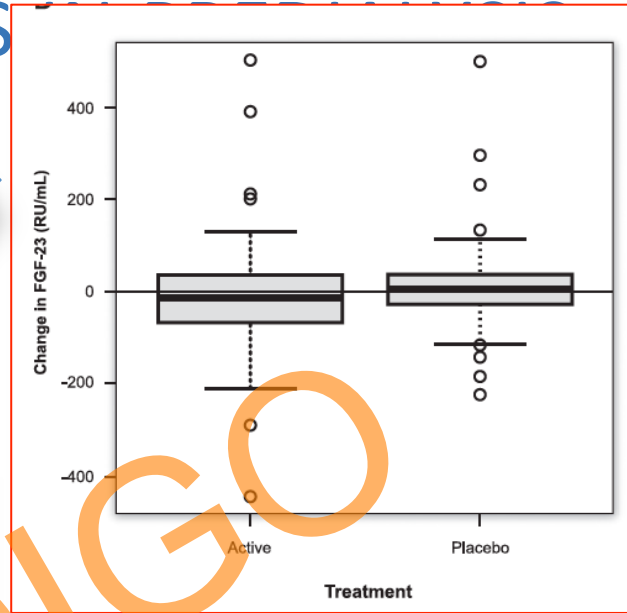
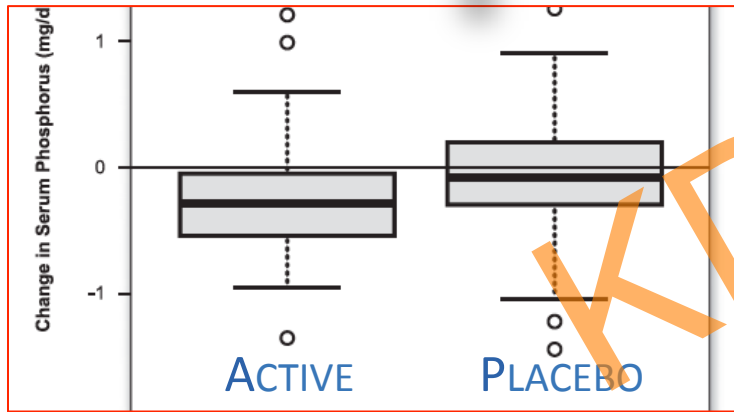
- There is an absence of data that efforts to maintain phosphorus in the normal range are of benefit to CKD Stage 3a-4 patients, including some safety concerns. Therefore, treatment should aim at overt hyperphosphatemia.

KDIGO

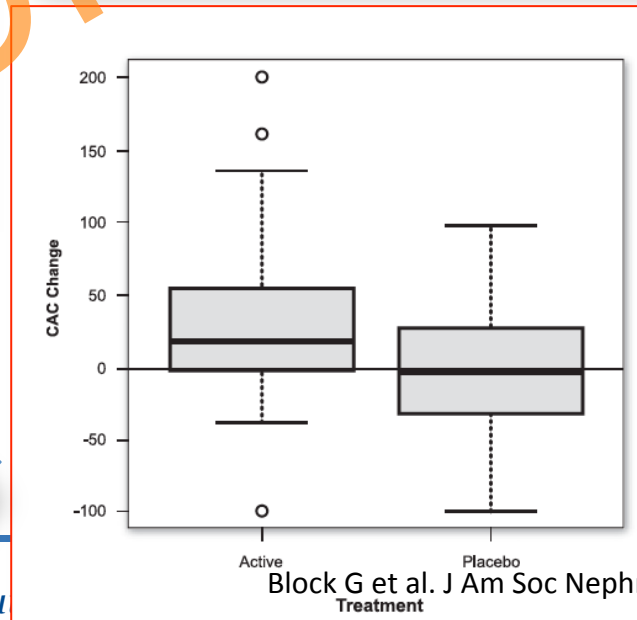


P-BINDERS

PHOSPHATE



FGF23



CORONARY
CALCIFICATION



ASSESSMENT OF PHOSPHORUS AND CALCIUM

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

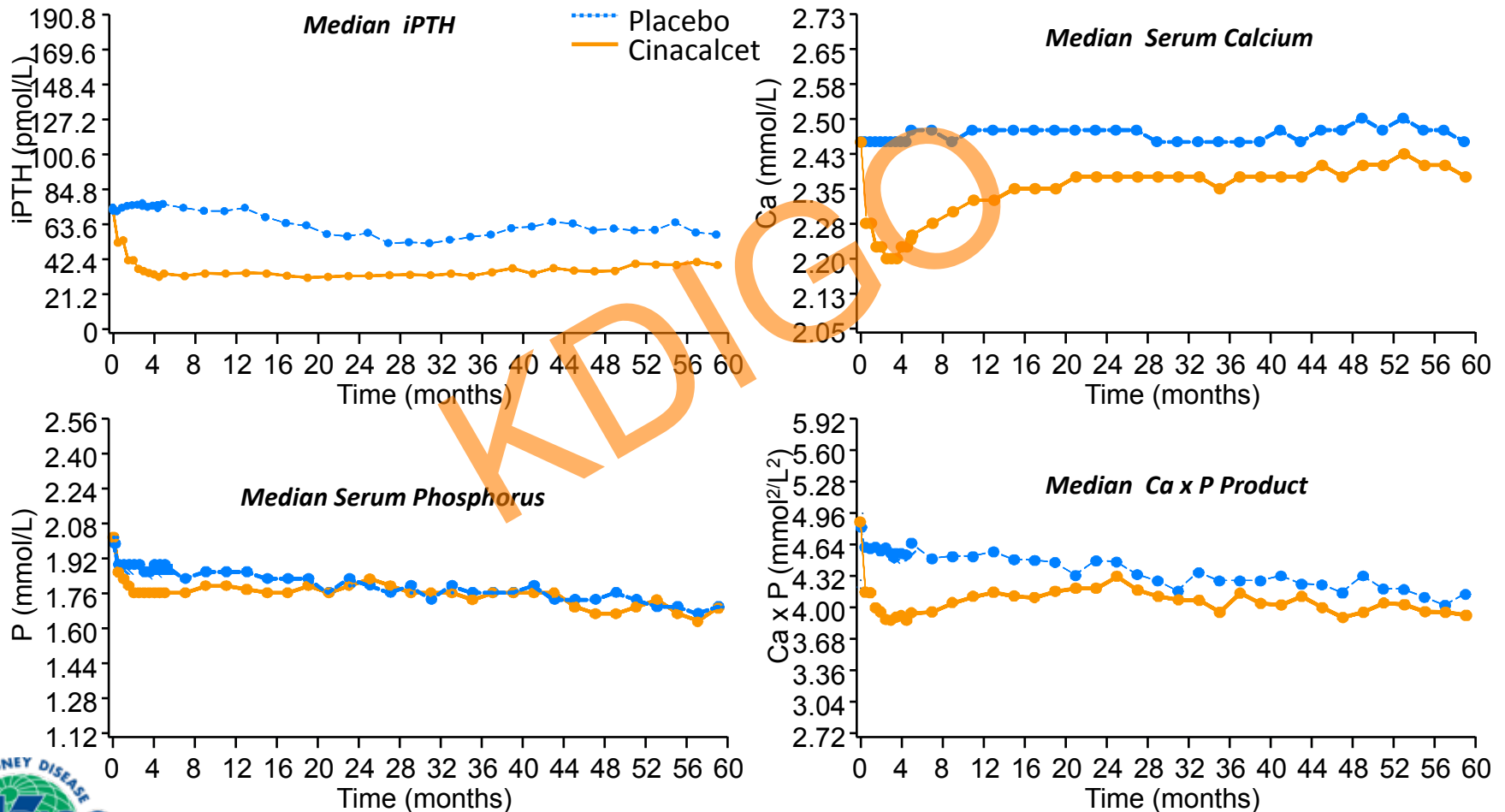
In children with CKD Stages 3a-5D, we suggest maintaining serum calcium in the age-appropriate normal range. (2C)

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.



PEDIATRIC PERSPECTIVE

- Childhood and adolescence are critical periods for bone mass accrual. A prospective pediatric cohort study showed lower serum calcium levels were independently associated with lower cortical volumetric BMD Z-scores, which predicted future fractures. The Work Group recognizes the higher calcium requirements of the growing skeleton and suggests that serum calcium levels are maintained in the age-appropriate normal range.



DIALYSATE CALCIUM

4.1.4: In patients with CKD Stage 5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l). (2C)

2009:

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



RATIONALE

- Two additional studies of better quality are available; however, they do not allow discrimination of benefits and harm between calcium dialysate concentrations of 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l). Hence, the wording is unchanged but evidence grade is upgraded from 2D to 2C.



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).



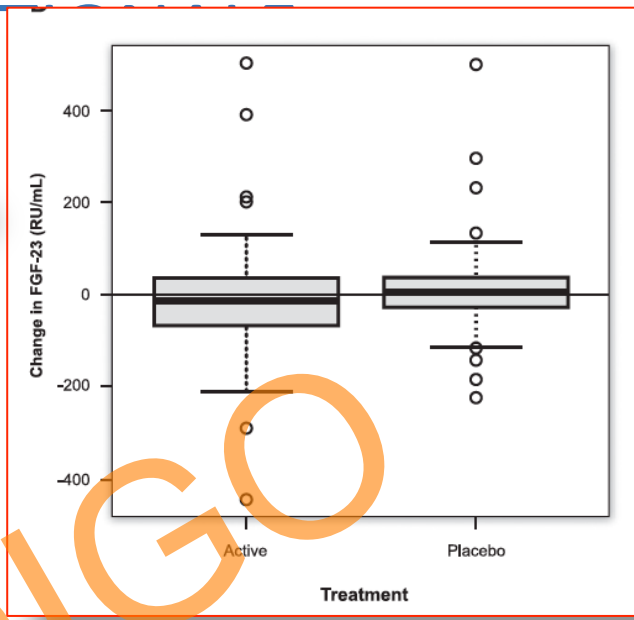
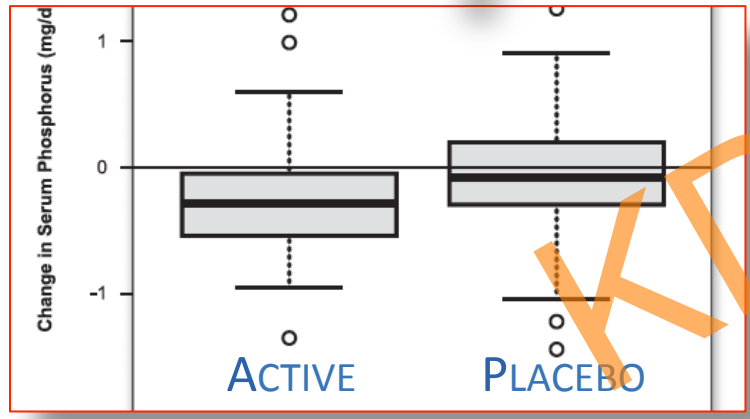
RATIONALE

- 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.

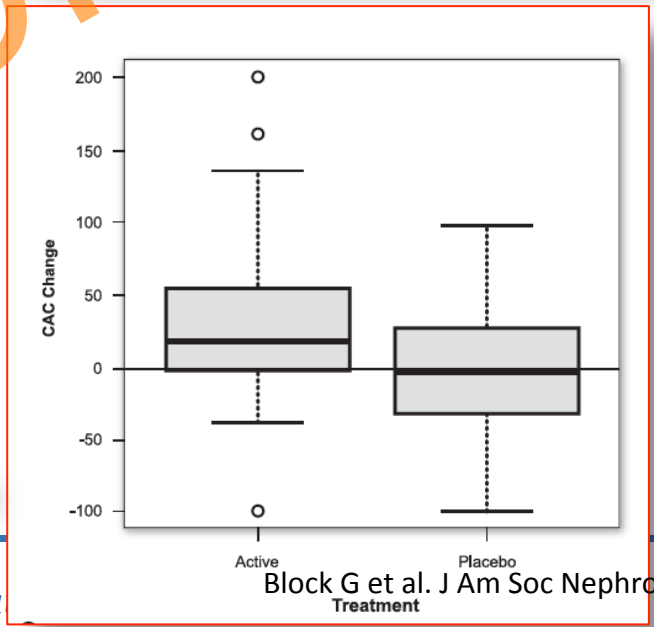


RA

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

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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).~~



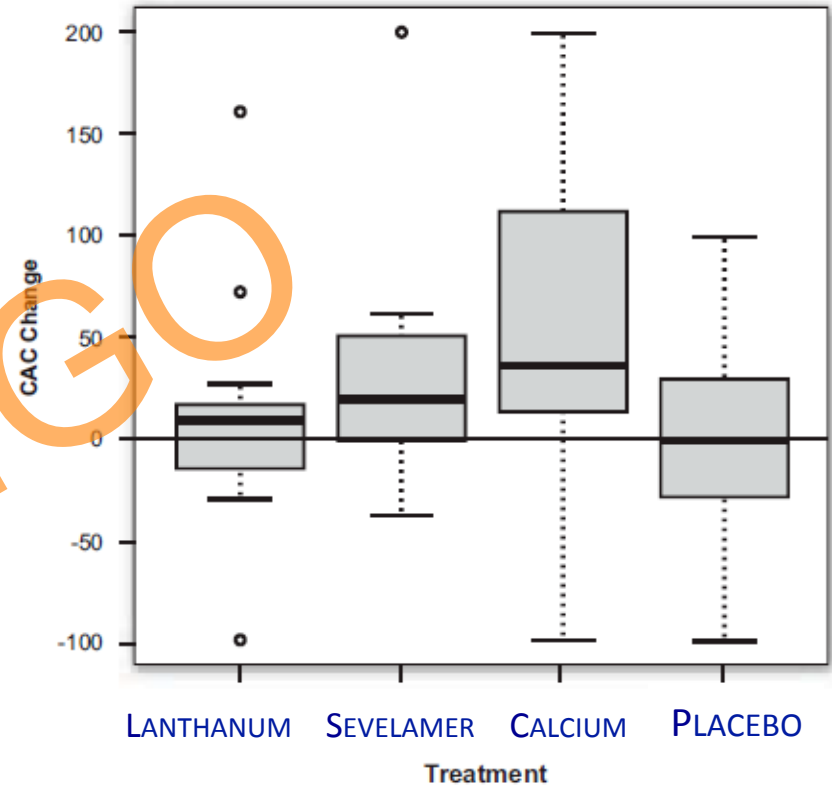
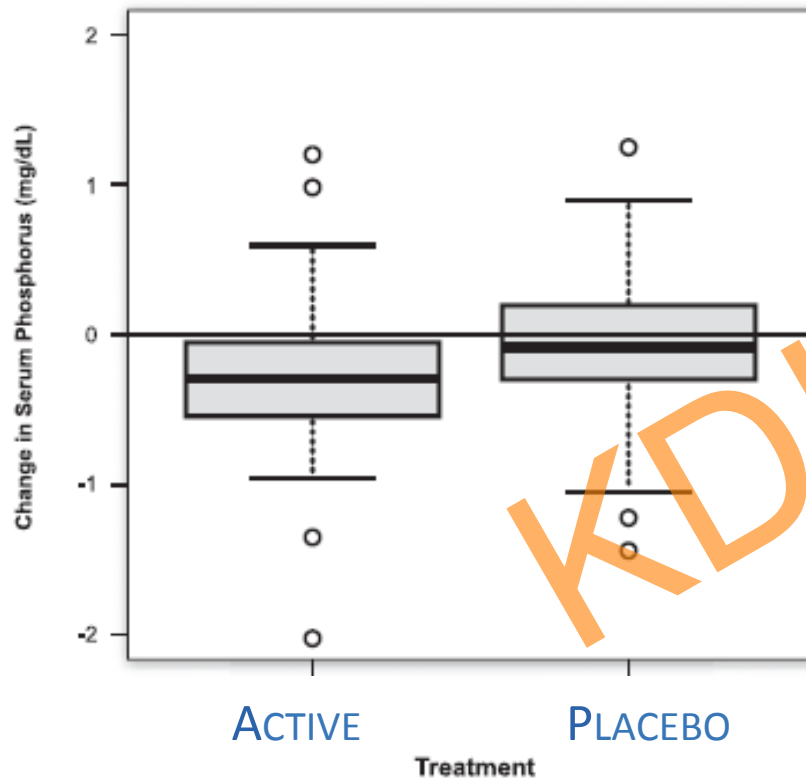
RATIONALE

- 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



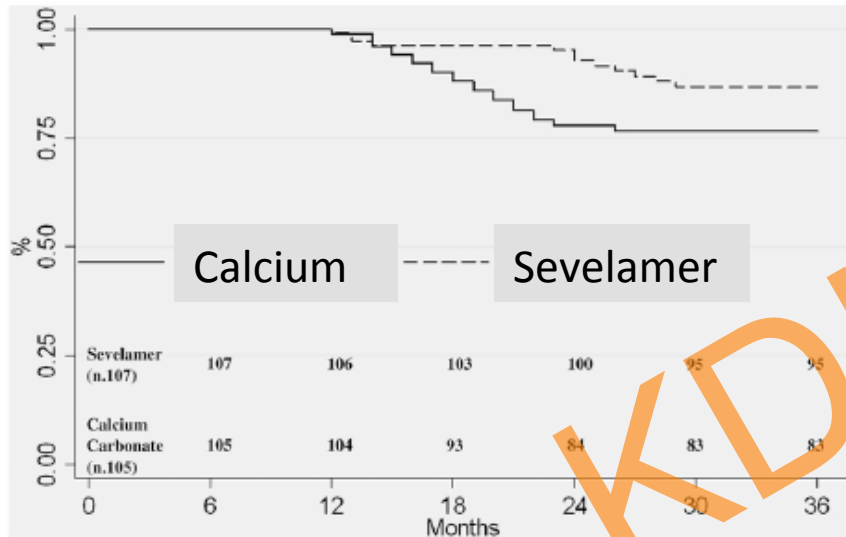
PHOSPHATE BINDERS IN MODERATE CKD



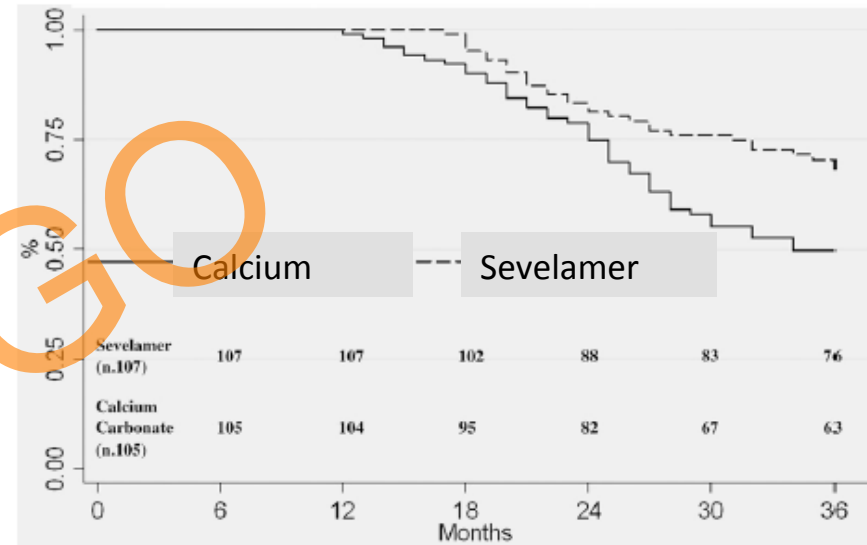
Block G et al. J Am Soc Nephrol. 2012;23:1407-1415.

PHOSPHATE BINDERS AND MORTALITY (PREDIALYSIS)

All-Cause Mortality



Dialysis Inception



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

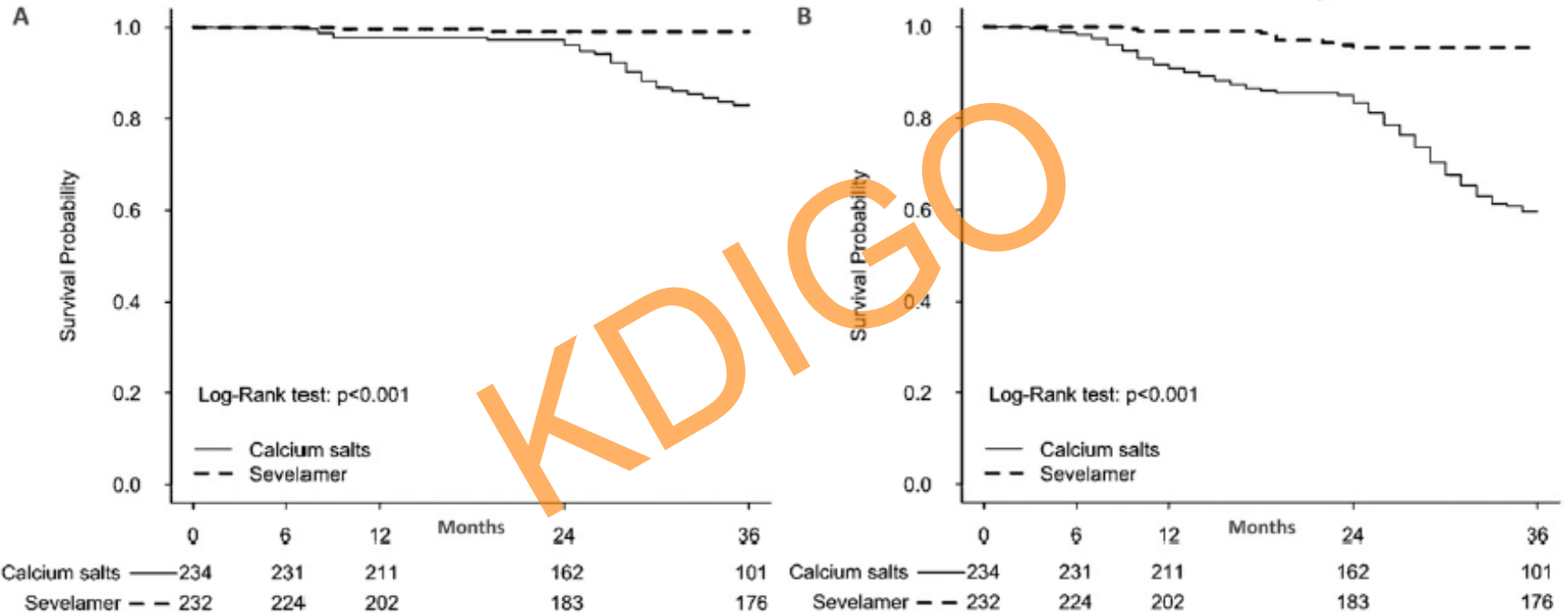


SEVELAMER VS. CALCIUM

(DIALYSIS)

Arrhythmias

CV Mortality



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



PEDIATRIC PERSPECTIVE

- Concerns regarding the adverse effects of exogenous calcium may not be generalizable to children.
- Studies of calcium- and non-calcium-containing binders and other therapies that impact calcium balance should consider the needs of the developing skeleton. The observation that serum calcium levels were positively associated with increases in BMD in children with CKD, and this association was significantly more pronounced with greater linear growth velocity, illustrates the unique needs of the growing skeleton.



PEDIATRIC PERSPECTIVE

- In light of the lack of data suggesting adverse effects of exogenous calcium in children, the Work Group concluded that there was insufficient evidence to change this recommendation in children, who may be uniquely vulnerable to calcium restriction.

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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

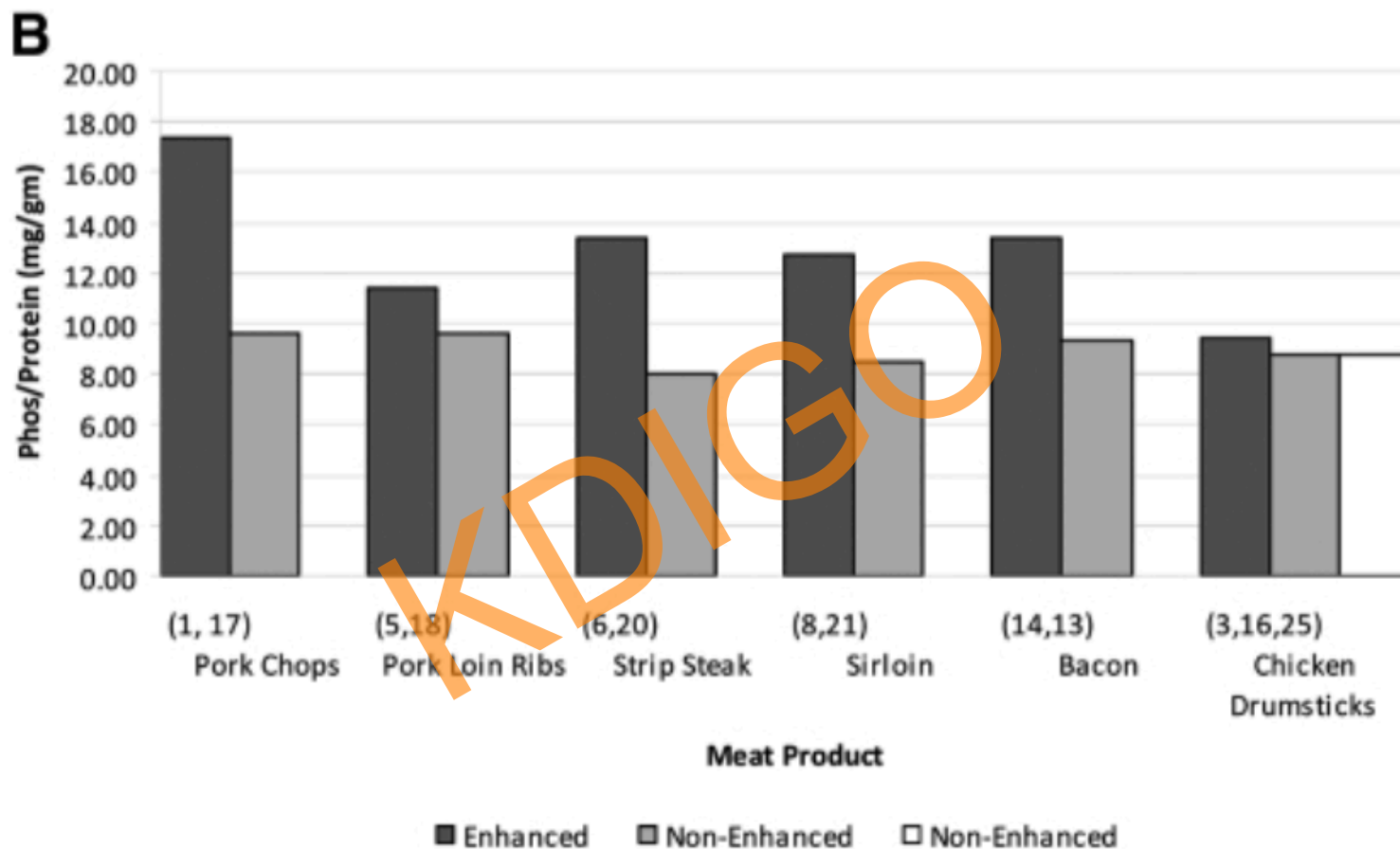
Table 2. Blood and urine measurements after 1 week of diet as outpatient

	Before Meat (casein) Diet	After Meat (casein) Diet	Before Vegetarian (grain) Diet	After Vegetarian (grain) Diet	<i>P</i> (paired <i>t</i> 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

^aBy 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

CHAPTER 3.2:

TREATMENT OF CKD–MBD: BONE

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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

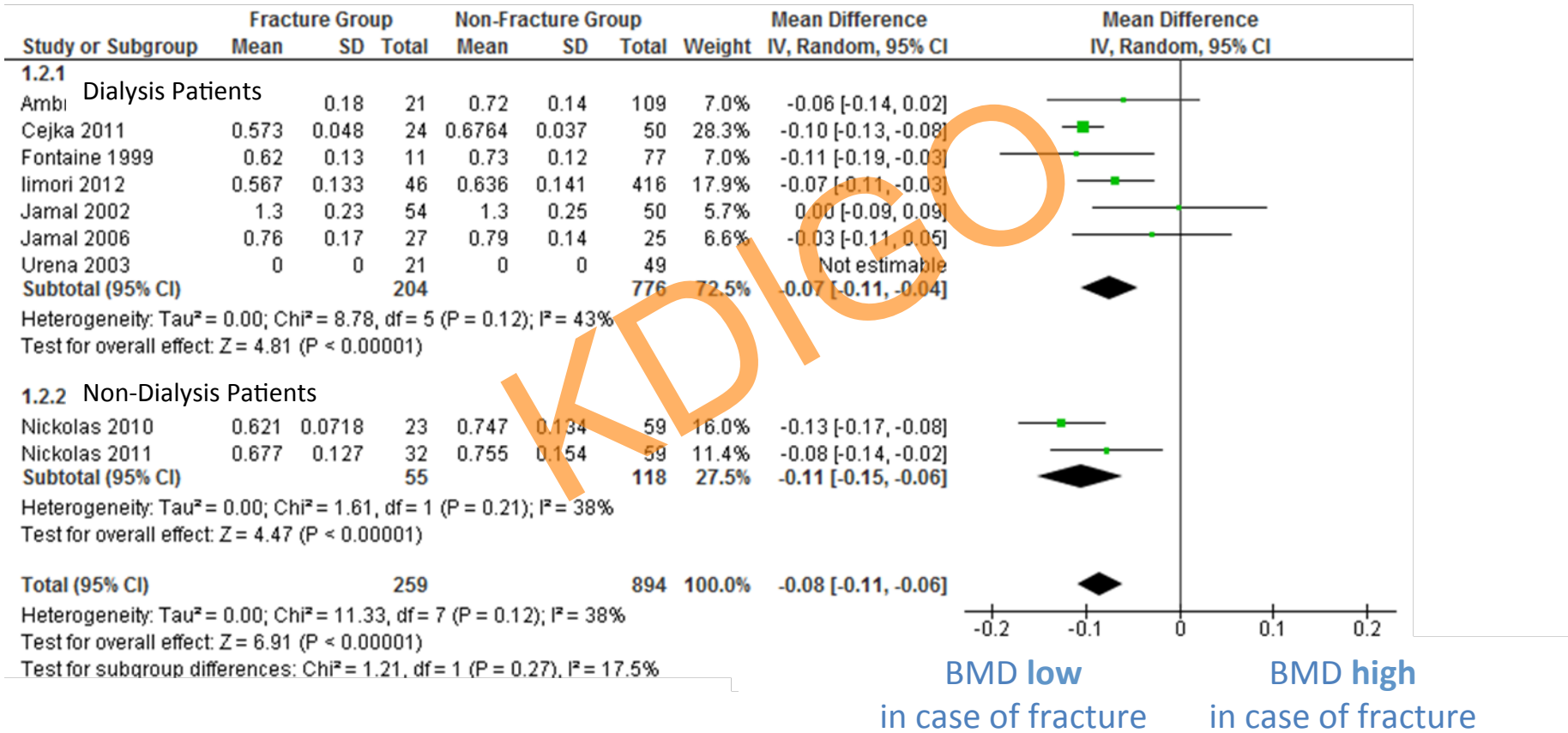
- Multiple new prospective studies have documented that lower DXA BMD does predict incident fractures in patients with CKD Stages 3a-5D.

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RATIONALE: Meta analysis

DEXA determined femoral BMD



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



THANK YOU

To the KDIGO staff for all of the meticulous help they have provided in creating the draft Guidelines and with the dissemination of knowledge

Michael Cheung

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