16th Panhellenic Congress of Nephrology
Kos, June 4, 2010

Recent advances in CKD-MBD treatment

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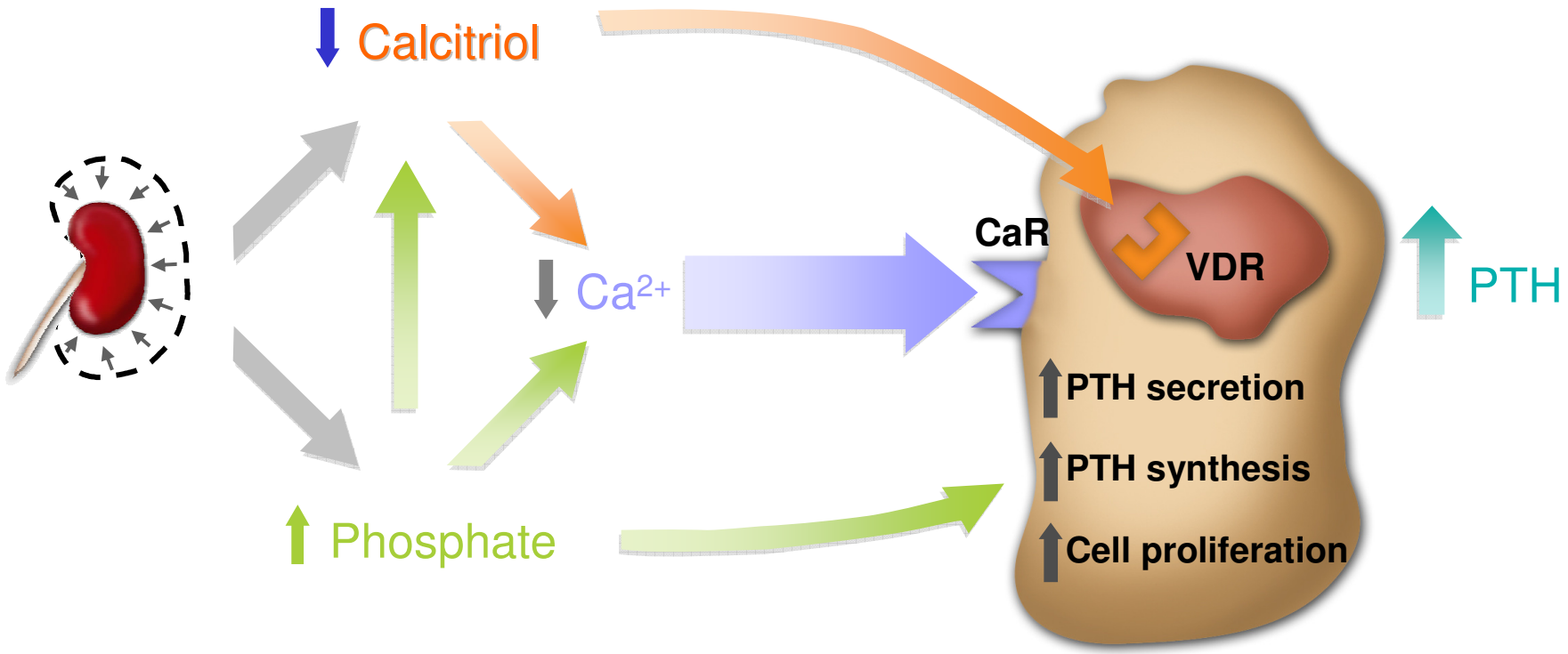
KLINIKUM COBURG

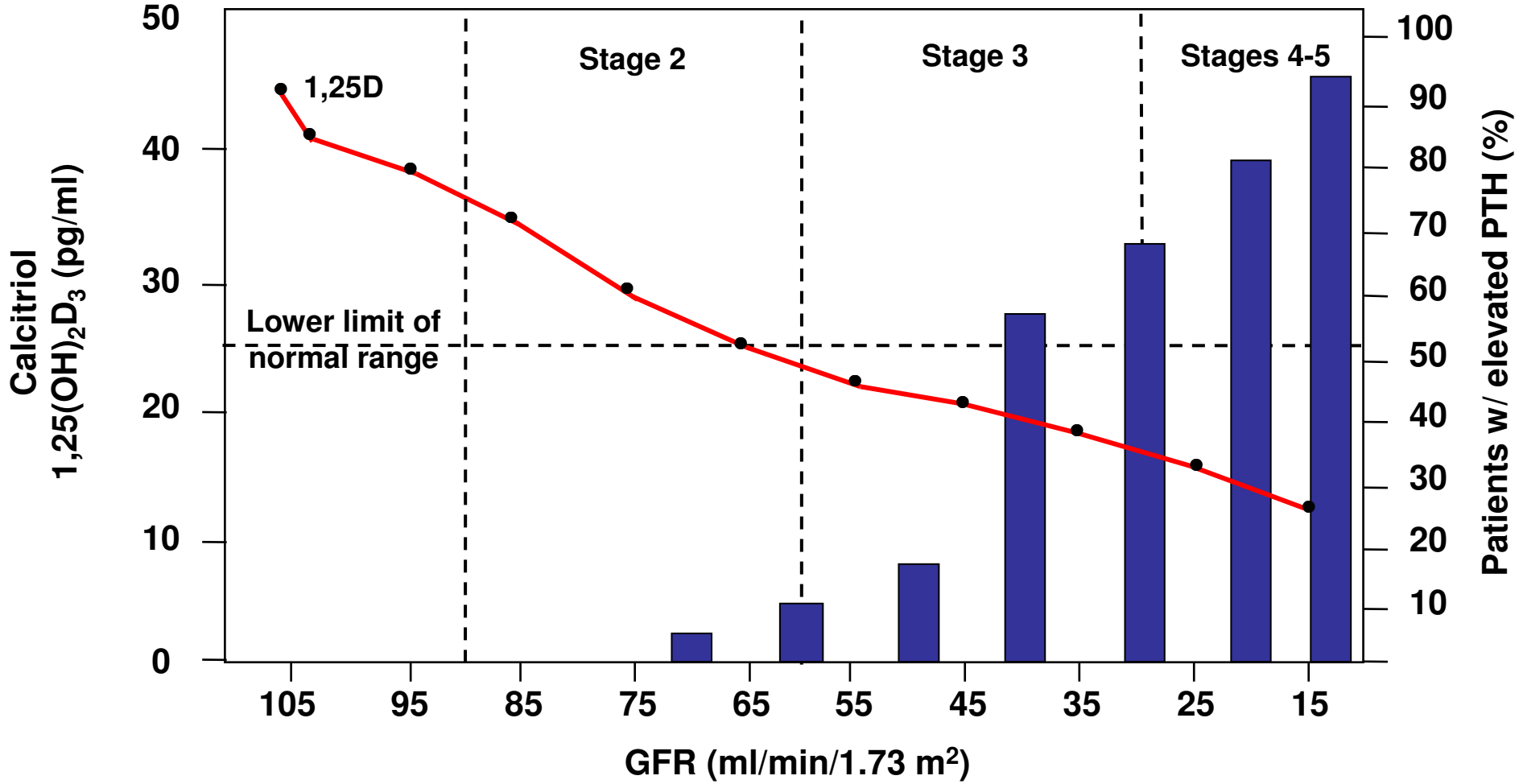
regioMed KLINIKEN

Pathogenesis of secondary hyperparathyroidism



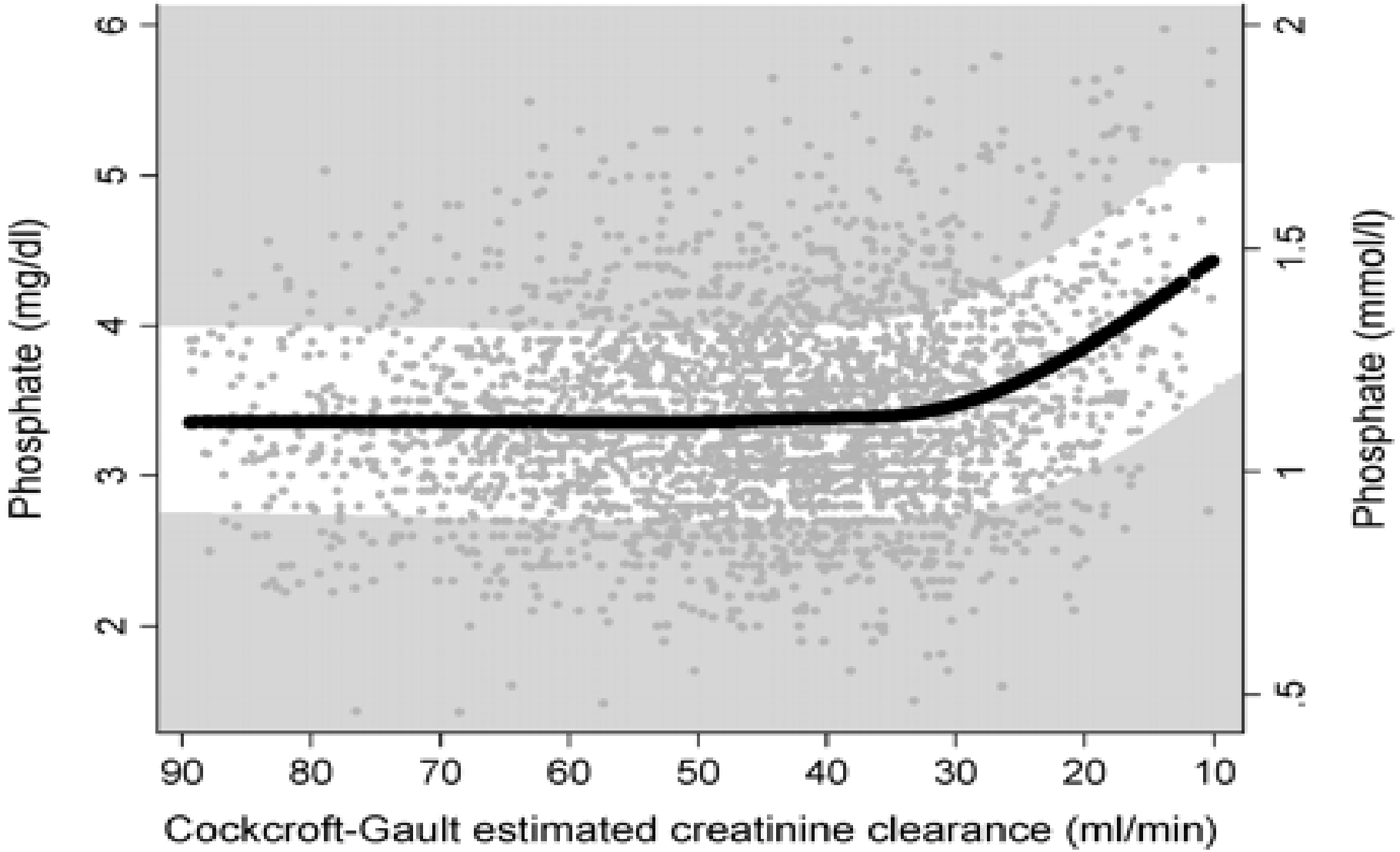
Slatopolsky E *et al. Kidney Int* 1999;73:S14–9

Vitamin D deficiency and sHPT start to manifest in early stages of CKD

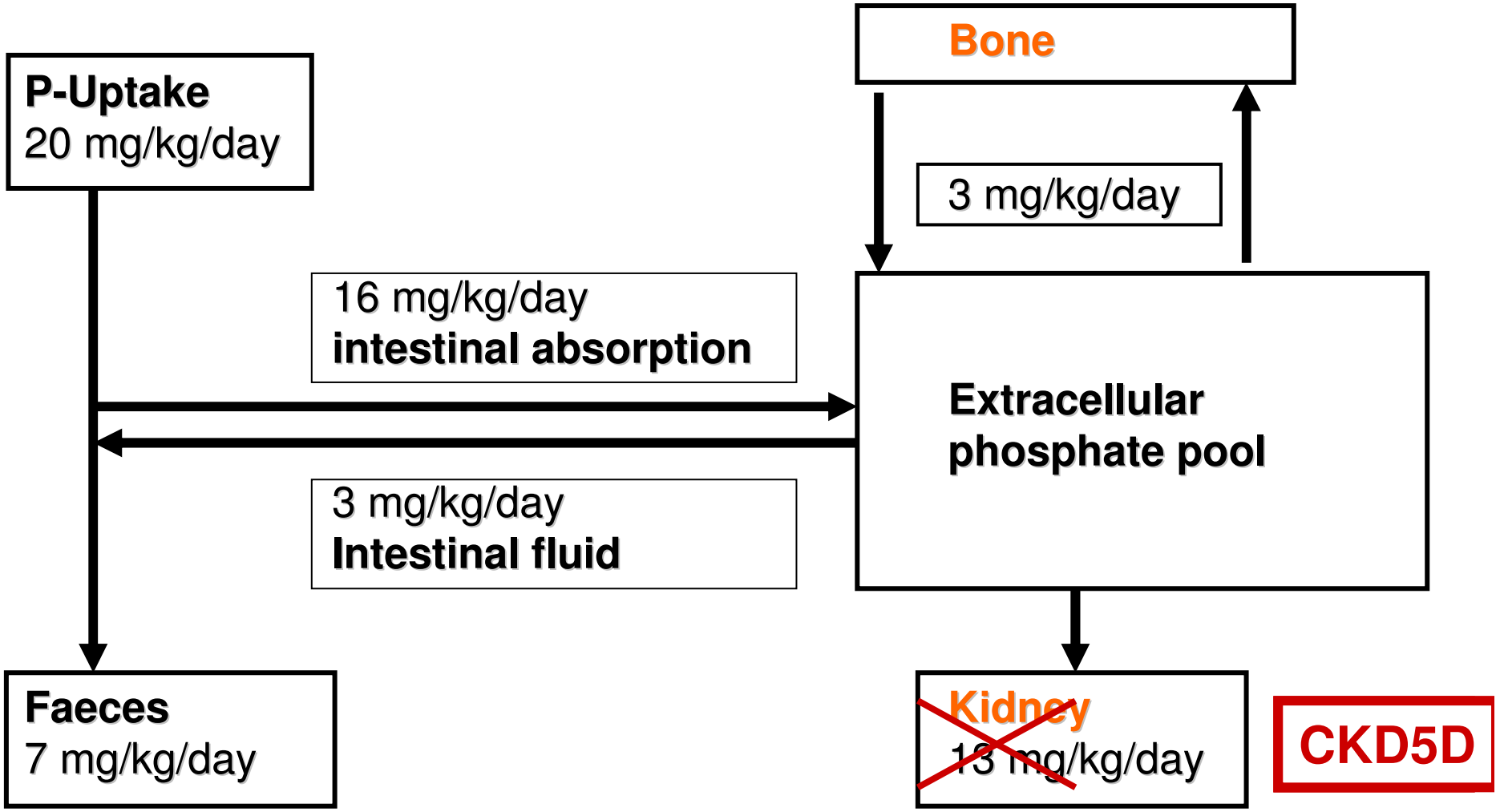


Hyperphosphatemia starts to manifest sich in stages 4-5 in CKD patients

Kestenbaum B et al. J Am Soc Nephrol. 2004;16:520-528



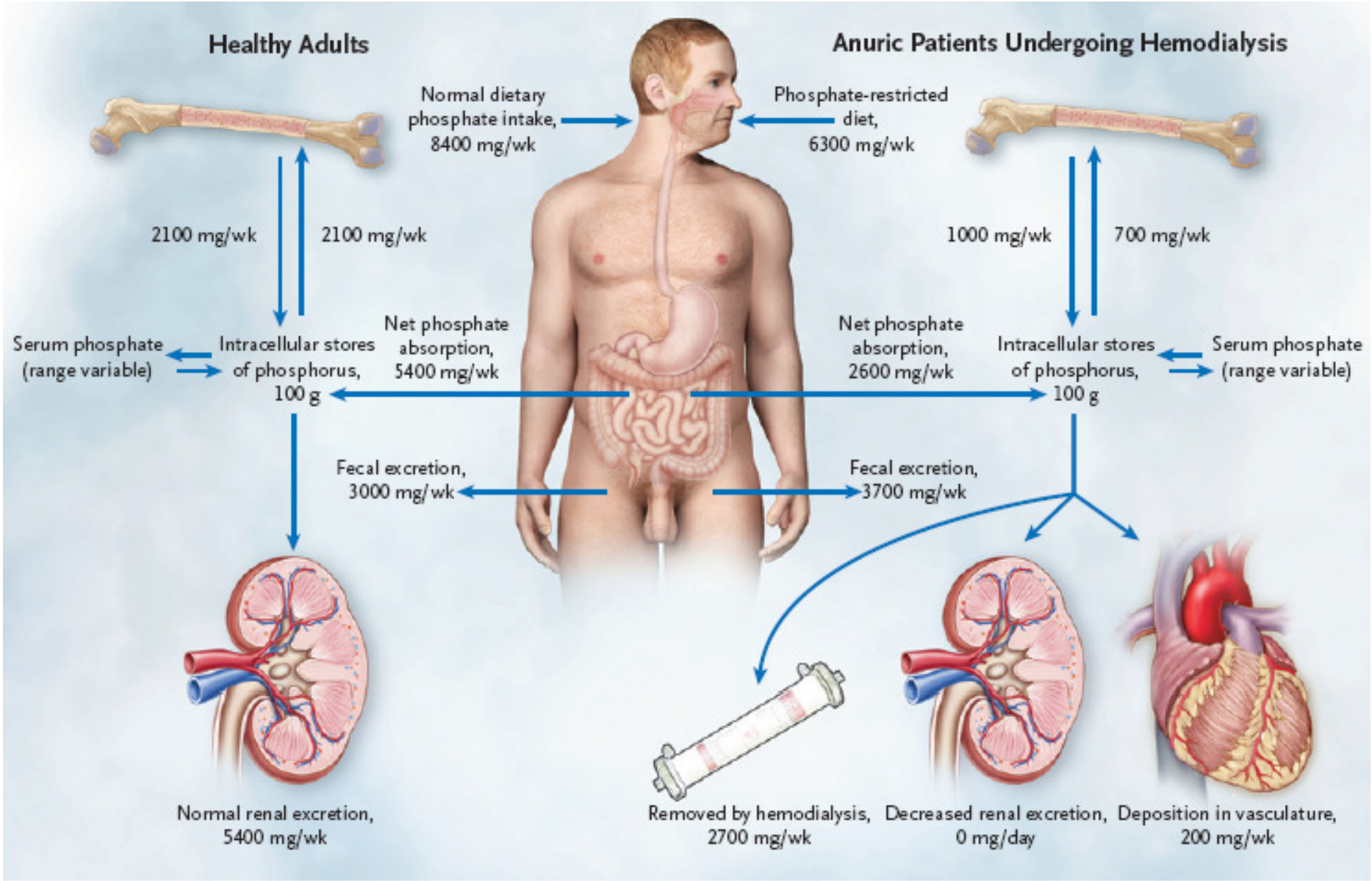
Phosphate Balance



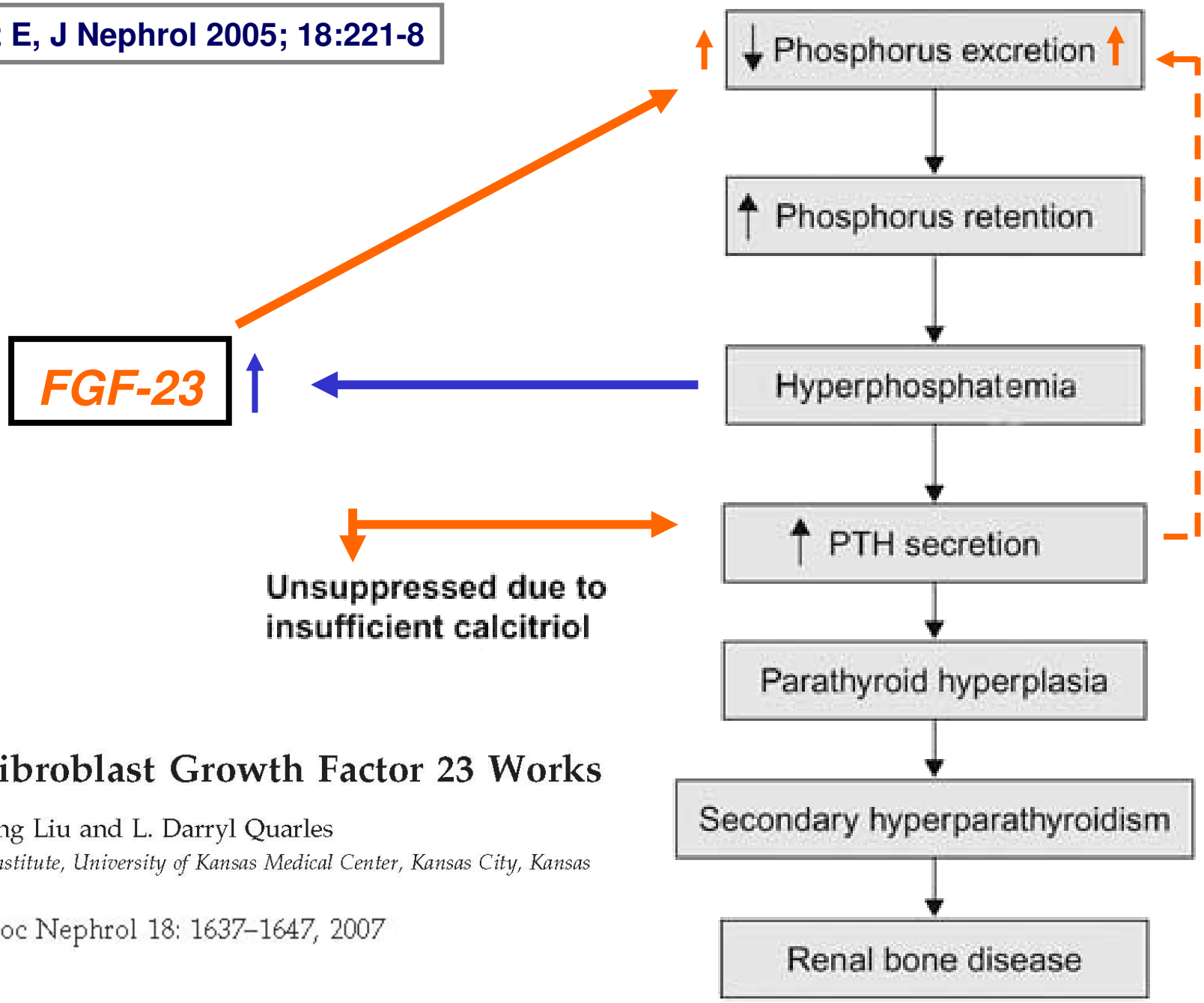
adapted: Schiavi & Kumar, Kidney Int 2004; 65:1-14

Phosphate Balance

Tonelli M et al., N Eng J Med 2010; 362:1312-24



Ritz E, J Nephrol 2005; 18:221-8



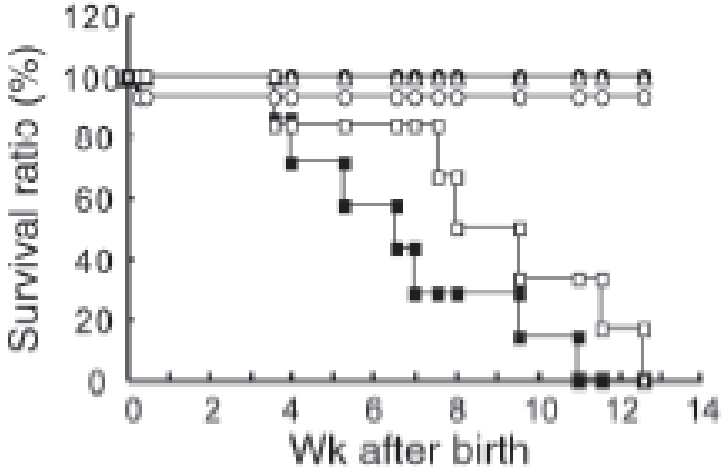
How Fibroblast Growth Factor 23 Works

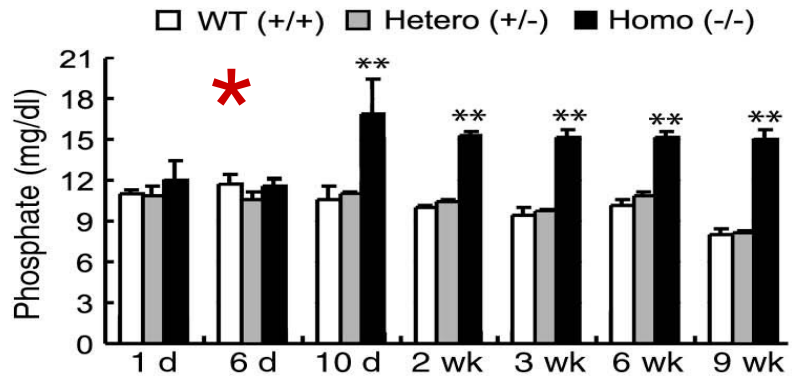
Shiguang Liu and L. Darryl Quarles
Kidney Institute, University of Kansas Medical Center, Kansas City, Kansas

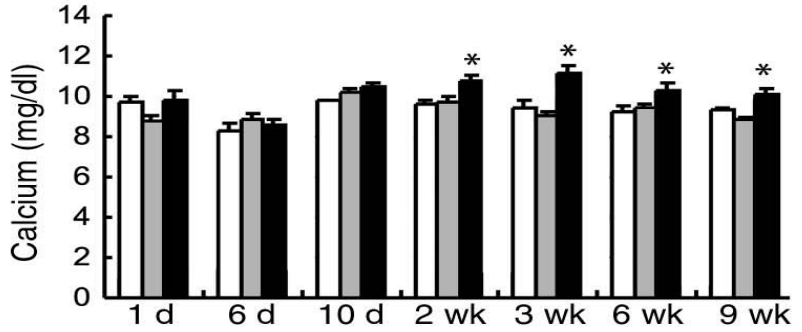
J Am Soc Nephrol 18: 1637–1647, 2007

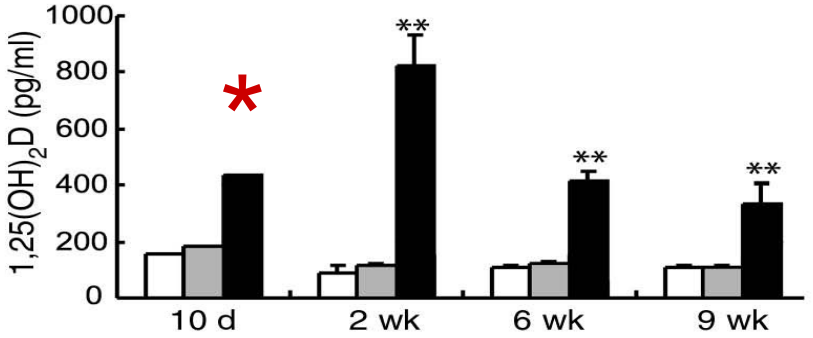
Biochemical parameters in FGF23 knockout mice

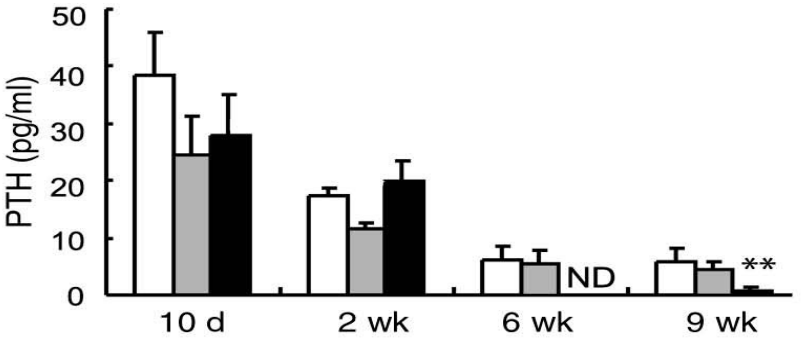
Shimada et al., J Clin Invest 2004; 113:561-8







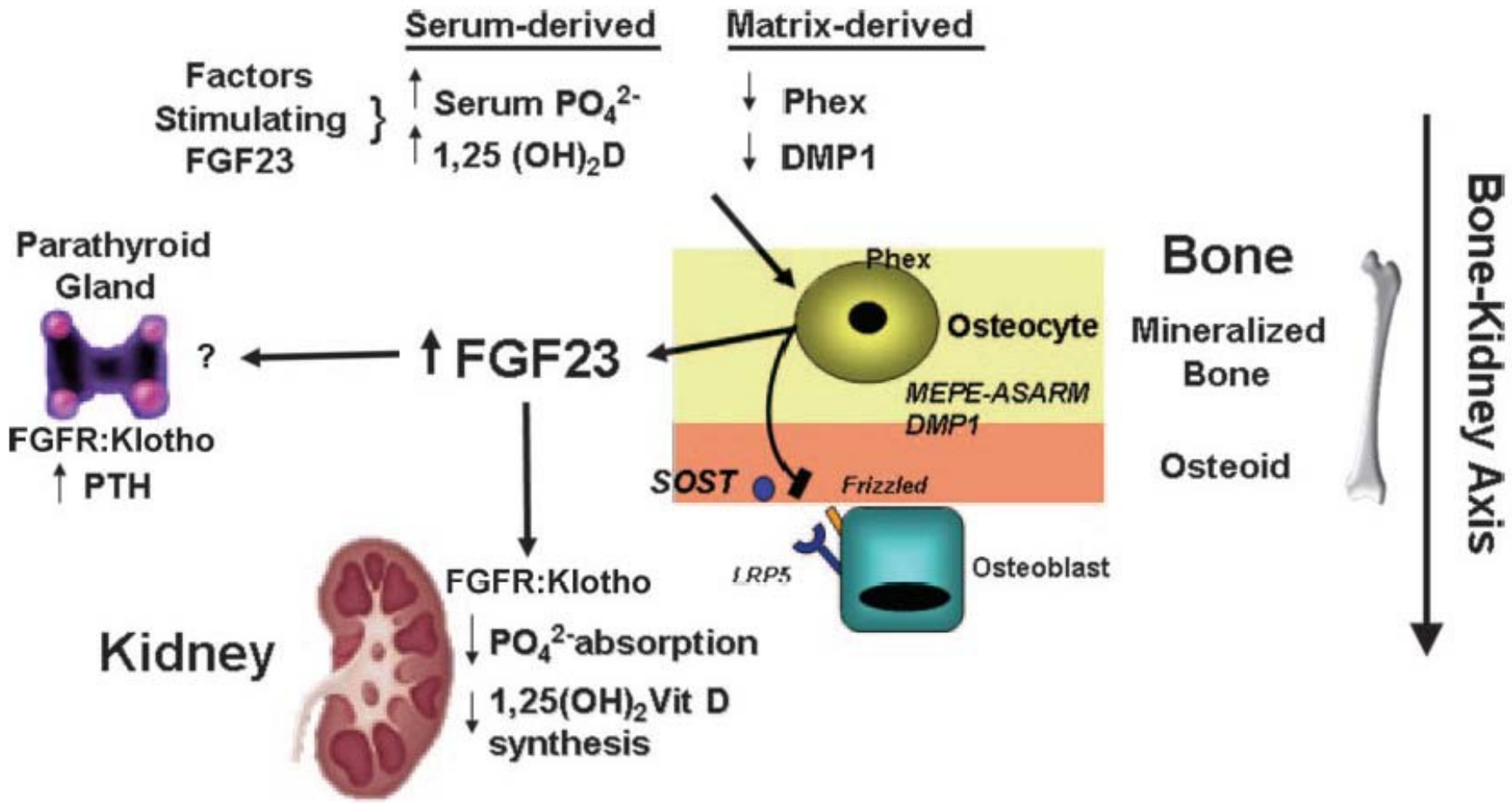




KLOTHO –
the Greek goddess of fate who spins the thread of life

How FGF-23 works !

Liu & Quarles, J Am Soc Nephrol 2007; 18:1637-47



„Loss-of-function“ mutation of the *Klotho* gene causes a phenotype of „AGING“

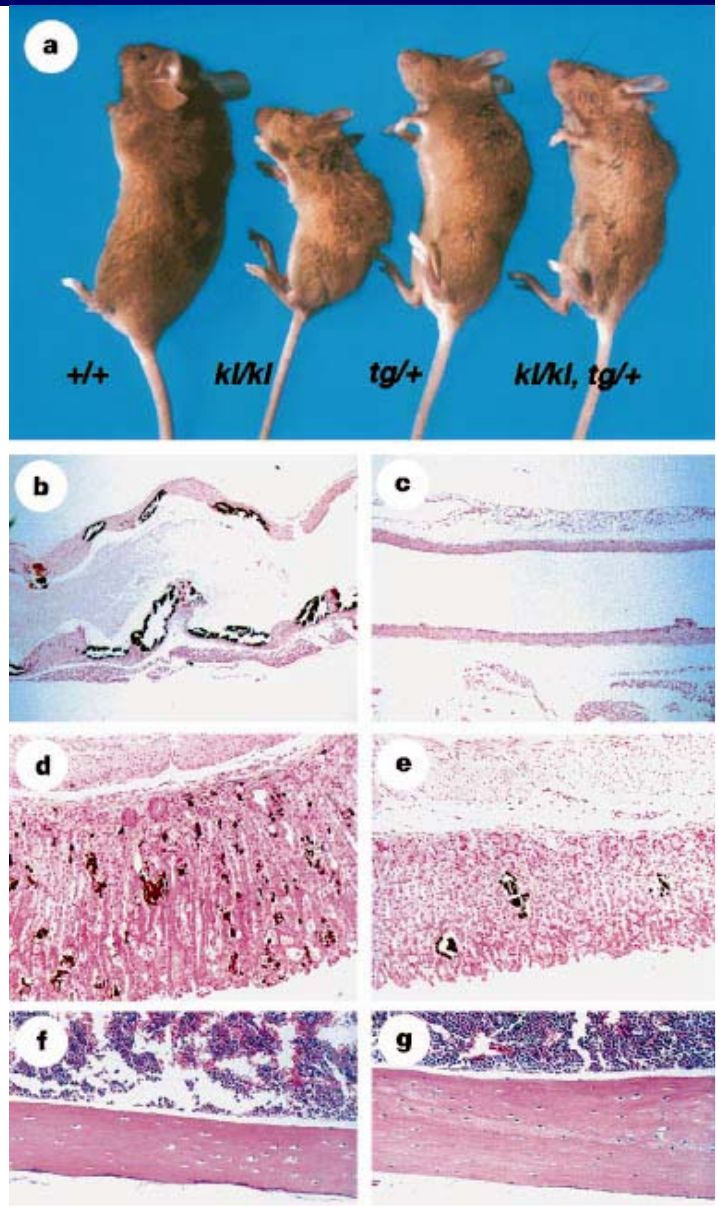
Klotho knockout mice develop...

... Calcifying atherosclerosis
... Osteoporosis
... Skin atrophy
... Emphysema
... Infertility

… and die prematurely.

Transgenic *Klotho* overexpression rescues this phenotype.

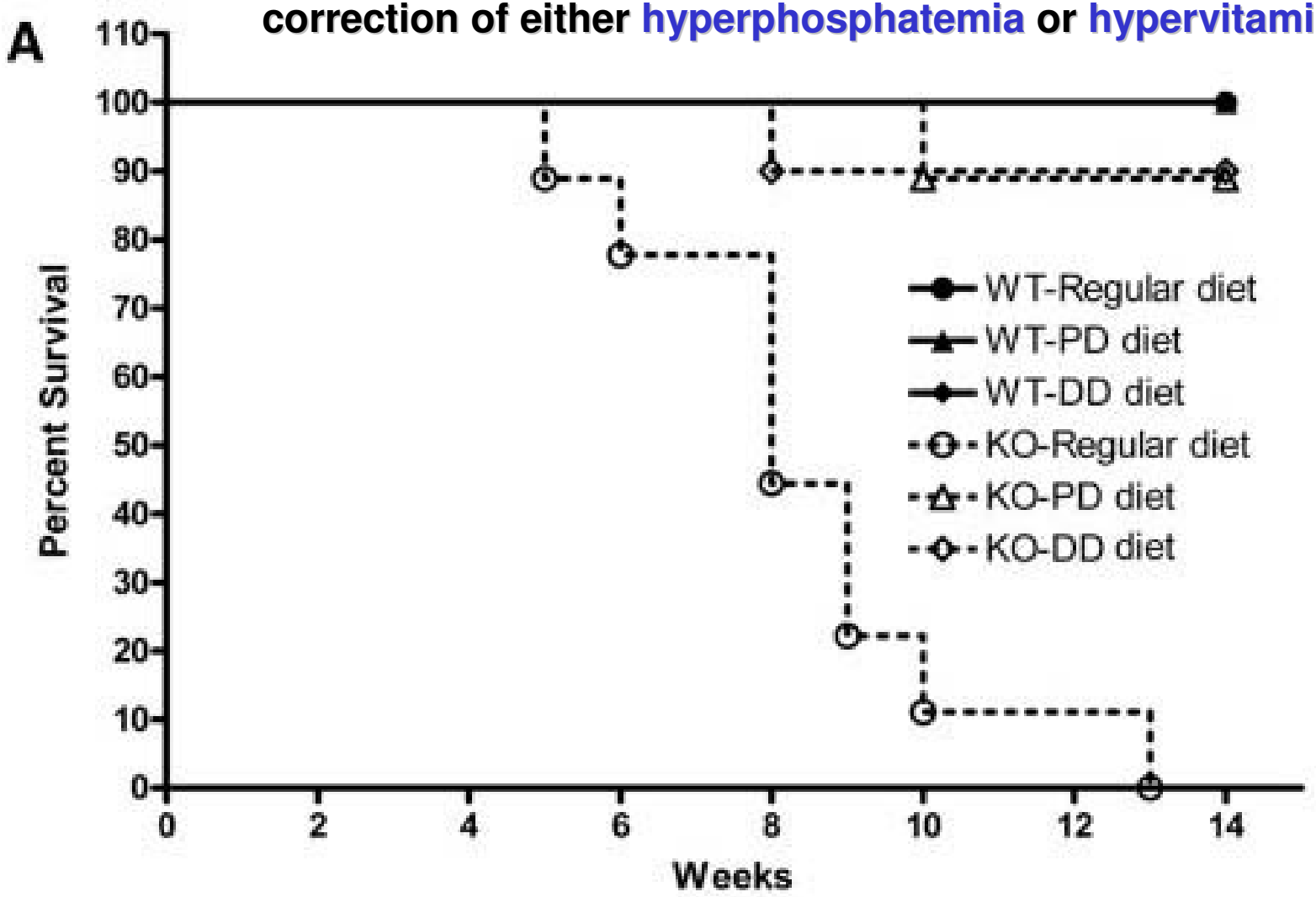
Kuro-o et al., Nature 390:45-51



How FGF-23 works !

Stubbs et al., J Am Soc Nephrol 2007; 18:2116-24

FGF-23 **knockout mice die prematurely, but can be rescued by correction of either hyperphosphatemia or hypervitaminosis D**

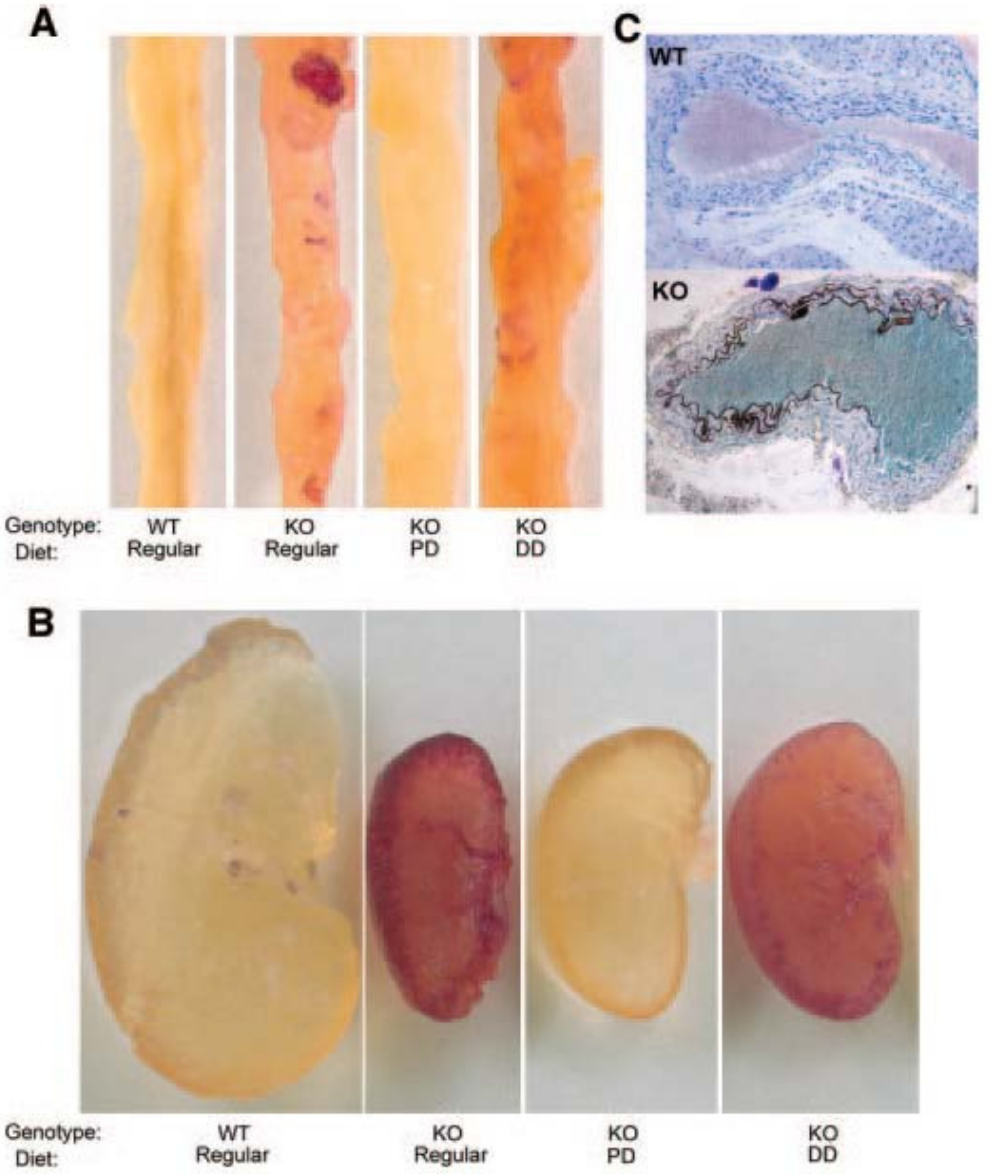


How FGF-23 works !

Stubbs et al., J Am Soc Nephrol 2007; 18:2116-24

Aortic calcifications in *FGF-23*-/- mice fed different diets

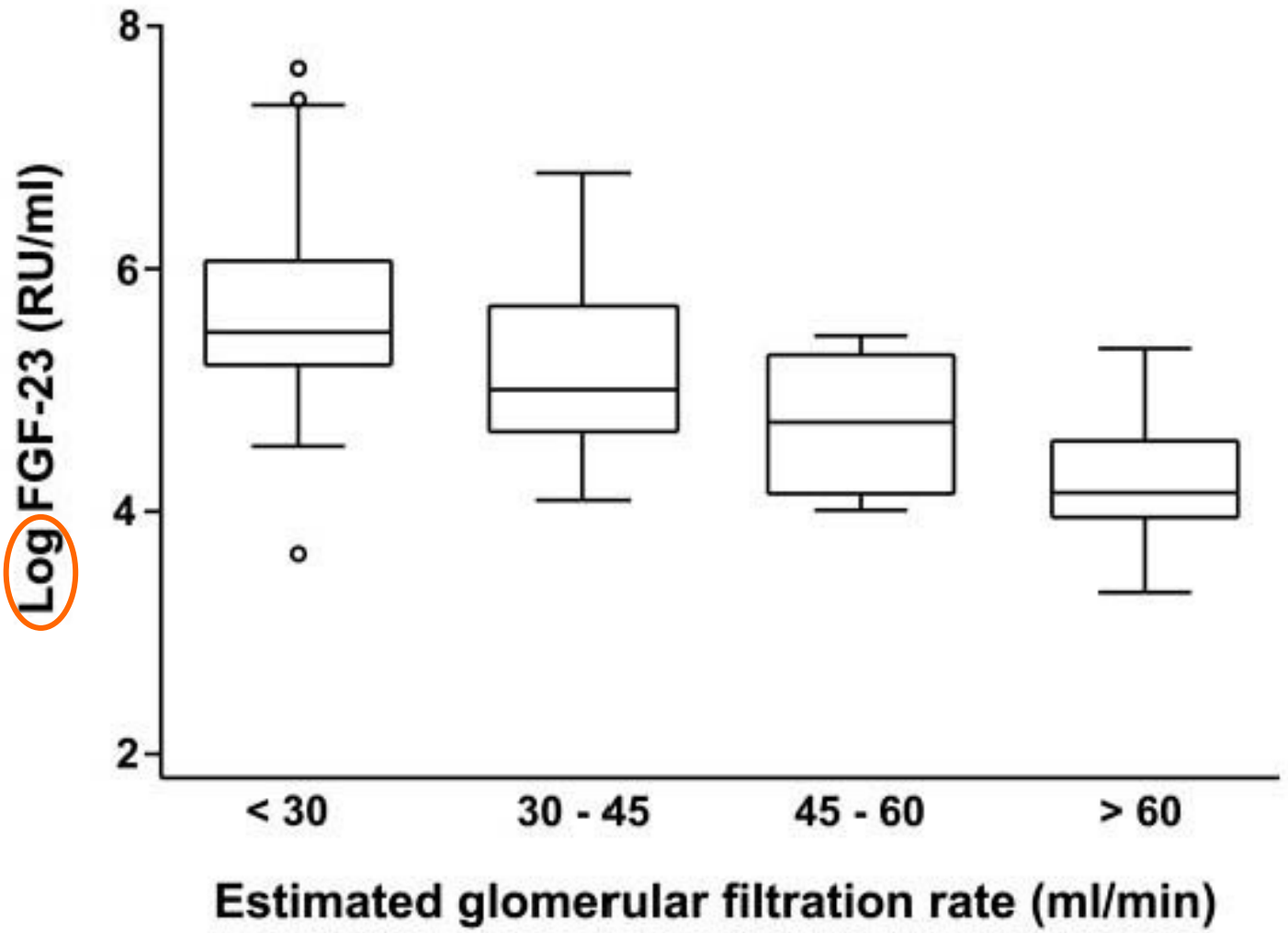
Kidney calcifications in *FGF-23*-/- mice fed different diets



PD = Phosphate-deficient diet
DD = Vitamin D-deficient diet

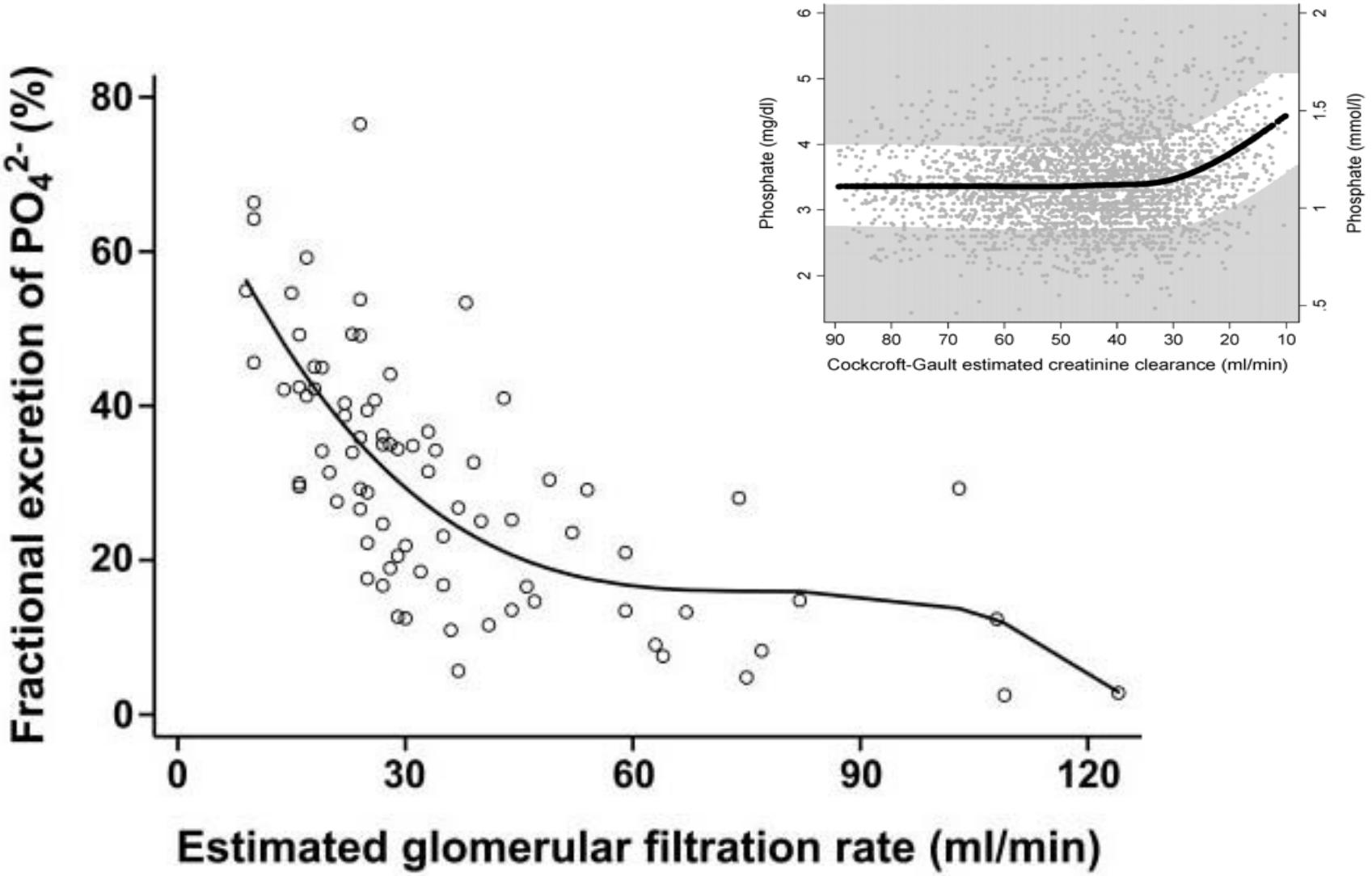
FGF23 and chronic kidney disease (CKD) stage inversely correlate with each other

Guiterrez et al., J Am Soc Nephrol 2005; 16:2205-15



Relative fractional phosphate excretion increases with CKD progression

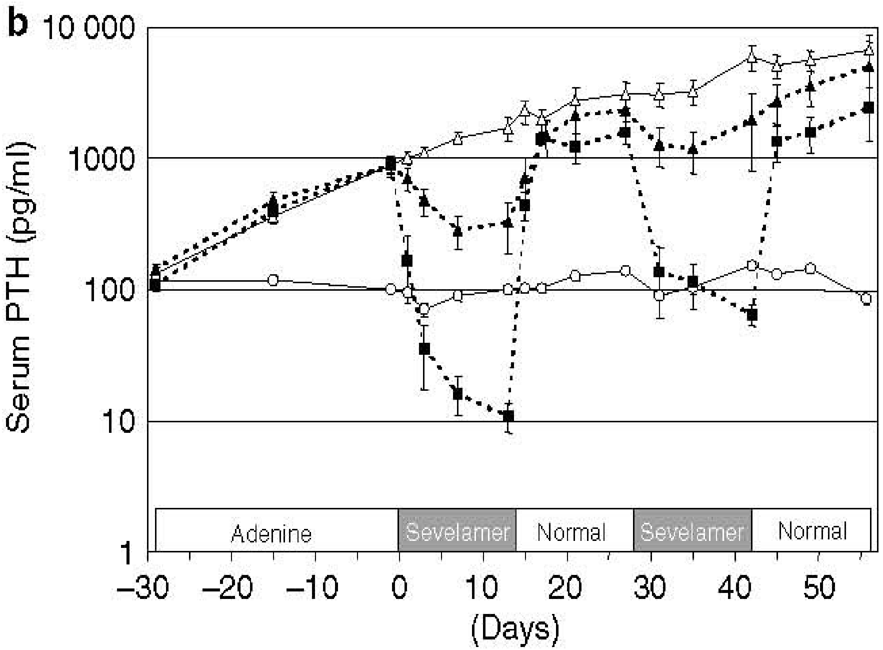
Guiterrez et al., J Am Soc Nephrol 2005; 16:2205-15

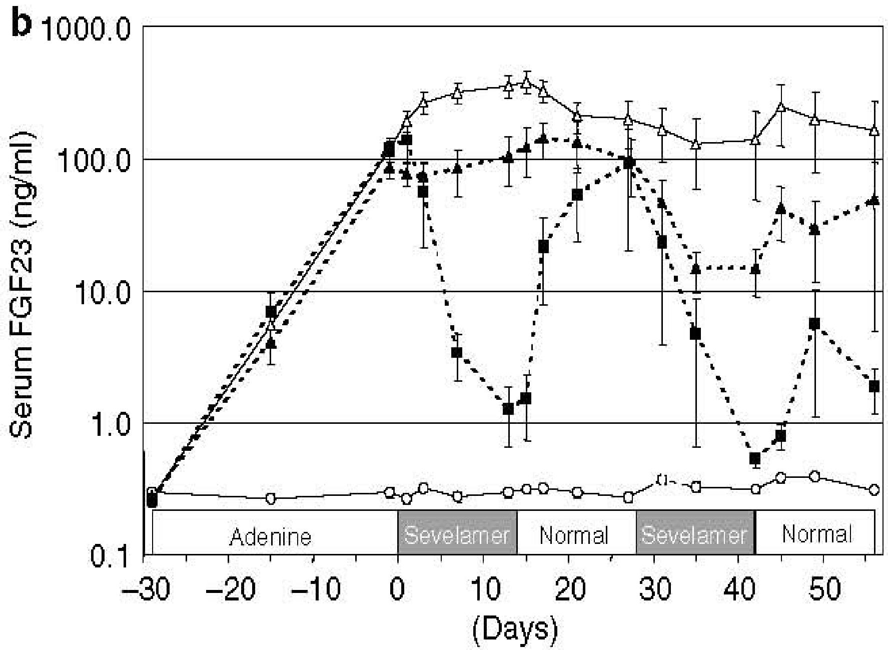


Phosphate binding by sevelamer reproducible lowers FGF23 and PTH levels in hyperphosphatemic uremic rats

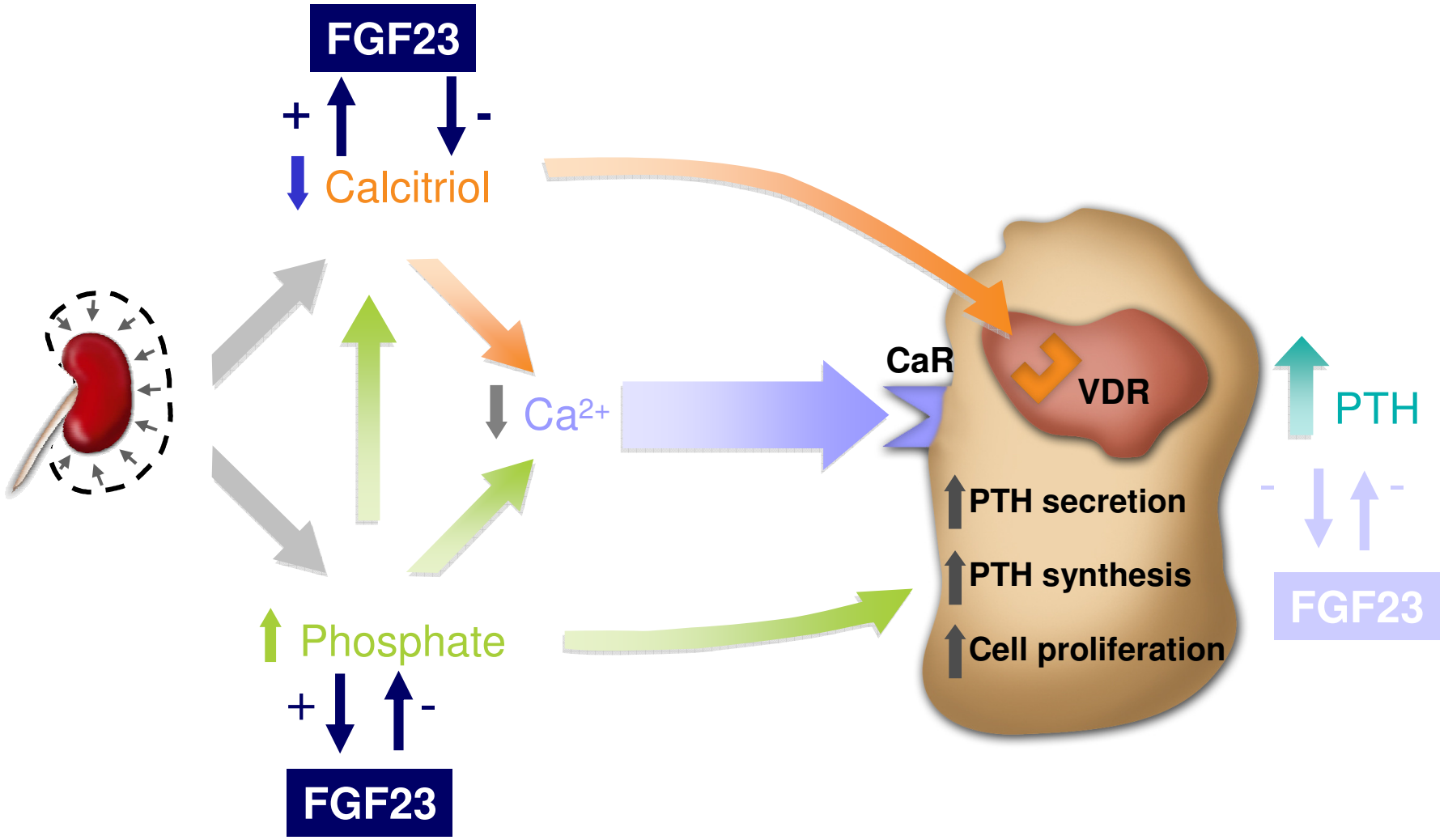
Nagano et al., Kidney Int 2006; 69:531-7

Normal control	Normal diet		Normal diet			
Disease control	0.75% adenine	0.5% adenine	Normal diet			
Continuous treatment	0.75% adenine	0.5% adenine	1% sevelamer			
Continuous treatment	0.75% adenine	0.5% adenine	3% sevelamer			
Intermittent treatment	0.75% adenine	0.5% adenine	1% sevelamer	Normal diet	1% sevelamer	Normal diet
Intermittent treatment	0.75% adenine	0.5% adenine	3% sevelamer	Normal diet	3% sevelamer	Normal diet
	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks
Blood sampling day	−29	−15	−1 1 3 7	13 15 17 21	27 31 35	42 45 49 56
Experimental day	−28	−14	0	14	28	42 56





Pathogenesis of secondary hyperparathyroidism

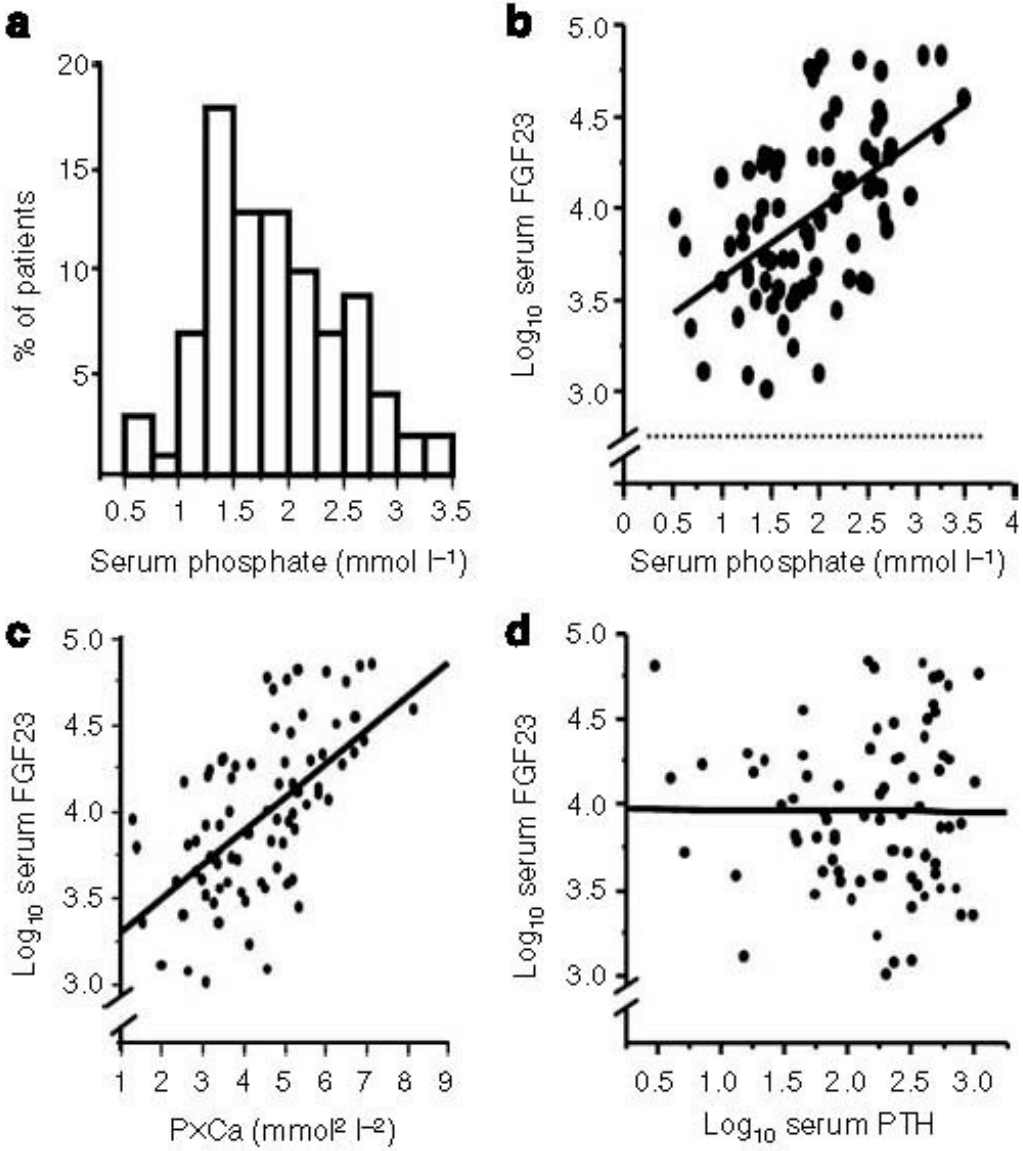


Slatopolsky E *et al. Kidney Int* 1999;73:S14–9

FGF23 and dialysis patients

Torres et al., Kidney Int 2008; 73:102-7

In CKD 5D, FGF23 serum levels correlate as well with phosphate concentrations



FGF23 and mortatlity in CKD 5D: The ArMORR study

Gutiérrez et al., N Engl J Med 2008; 359:584-92

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fibroblast Growth Factor 23 and Mortality among Patients Undergoing Hemodialysis

Orlando M. Gutiérrez, M.D., M.M.Sc., Michael Mannstadt, M.D., Tamara Isakova, M.D., Jose Alejandro Rauh-Hain, M.D., Hector Tamez, M.D., Anand Shah, M.D., Kelsey Smith, B.A., Hang Lee, Ph.D., Ravi Thadhani, M.D., M.P.H., Harald Jüppner, M.D., and Myles Wolf, M.D., M.M.Sc.

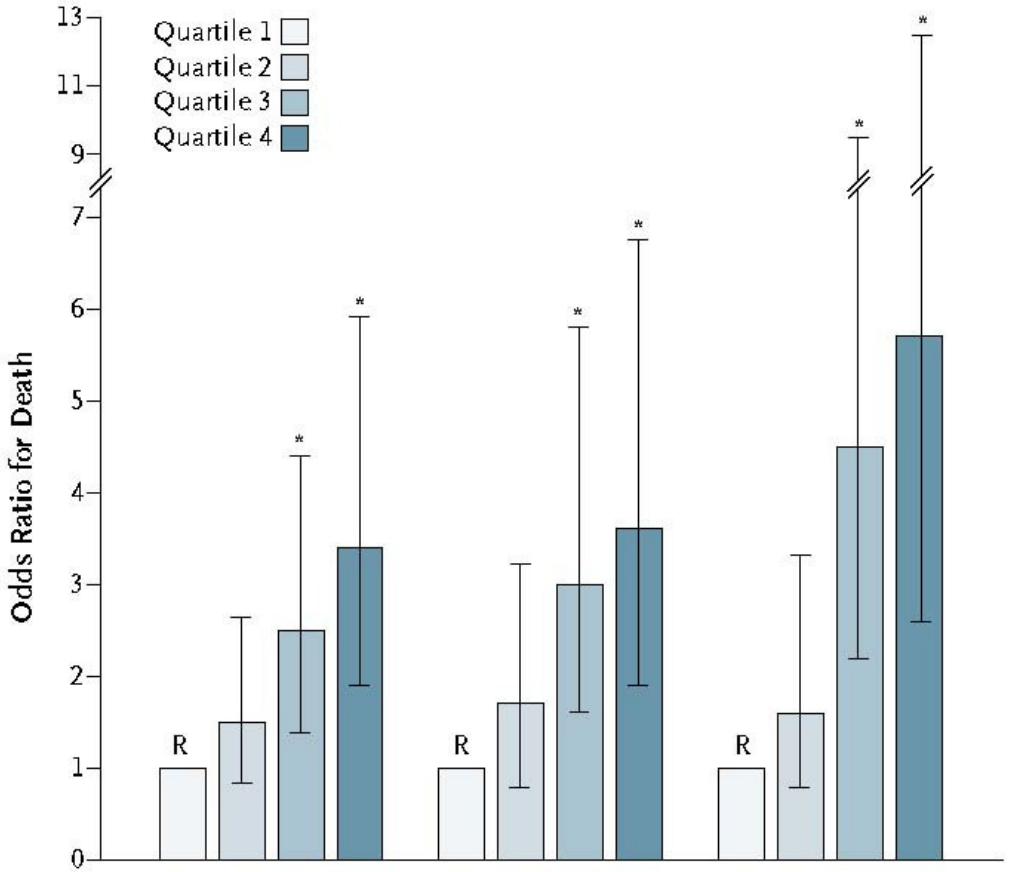
Table 2. Laboratory Results and Use or Nonuse of Phosphorus Binders, According to Quartiles of cFGF-23 Level.*

Variable	cFGF-23 Quartile 1 (<1090 RU/ml)	cFGF-23 Quartile 2 (1090–1750 RU/ml)	cFGF-23 Quartile 3 (1751–4010 RU/ml)	cFGF-23 Quartile 4 (>4010 RU/ml)	P Value
Albumin (g/dl)	3.4±0.5	3.3±0.5	3.3±0.6	3.3±0.5	0.13
Creatinine (mg/dl)	5.3±2.2	5.4±2.2	6.3±2.2	6.6±2.9	<0.001
Phosphate (mg/dl)	3.9±1.2	4.1±1.3	4.5±1.6	5.2±2.1	<0.001
Calcium (mg/dl)	8.8±0.8	8.9±0.7	8.8±0.8	9.0±0.8	0.15
Parathyroid hormone (pg/ml)	180 (99–313)	137 (95–273)	253 (119–377)	234 (145–435)	0.22
Alkaline phosphatase (U/liter)	82 (64–103)	89 (67–114)	91 (69–114)	100 (77–131)	<0.001
1,25-Dihydroxyvitamin D (pg/ml) †	9.1±5.2	6.9±6.0	8.4±5.0	7.5±5.8	0.45
Phosphorus binders (% of patients)	12	8	9	6	0.18

FGF23 and mortatlity in CKD 5D: The ArMORR study

Gutiérrez et al., N Engl J Med 2008; 359:584-92

High FGF23 are mortality risk predictors in incident hemodialysis patients



Quartile 1	Reference	Reference	Reference
Quartile 2	1.5 (0.9–2.7)	1.7 (0.8–3.2)	1.6 (0.8–3.3)
Quartile 3	2.5 (1.4–4.4)	3.0 (1.6–5.8)	4.5 (2.2–9.4)
Quartile 4	3.4 (1.9–5.9)	3.6 (1.9–6.9)	5.7 (2.6–12.6)

FGF23 and mortatlity in CKD 5D: The ArMORR study

Gutiérrez et al., N Engl J Med 2008; 359:584-92

Table 3. Levels of cFGF-23 and Associated Risk of Death within Serum Phosphate Quartiles in the Case–Control Sample.

Phosphate Level	Median cFGF-23 Level (interquartile range)		P Value	Odds Ratio for Death (95% CI)*
	Patients Who Died (N=200)	Patients Who Survived (N=200)		
	reference units per milliliter			
All levels	2260 (1196–5296)	1406 (989–2741)	<0.001	1.5 (1.2–1.8)
<3.5 mg/dl	1790 (1175–3941)	1148 (927–2169)	0.008	1.8 (1.2–2.8)
3.5–4.4 mg/dl	2049 (1109–4865)	1131 (893–1629)	0.003	1.8 (1.2–2.7)
4.5–5.5 mg/dl	2207 (1186–5238)	1499 (1044–2262)	0.02	1.8 (1.1–3.0)
>5.5 mg/dl	3541 (1871–10,491)	2686 (1527–6210)	0.29	1.1 (0.7–1.6)

Significant associations FGF23 and mortality in serum phosphate levels within the KDOQI target range (< 5,5 mg/dl !)

FGF23 and mortatlity in CKD 5D:
Prevalent European patients (Hemodialysis)

Jean G et al., NDT 2009; 24:2792-6

High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients

Guillaume Jean, Jean-Claude Terrat, Thierry Vanel, Jean-Marc Hurot, Christie Lorriaux, Brice Mayor and Charles Chazot

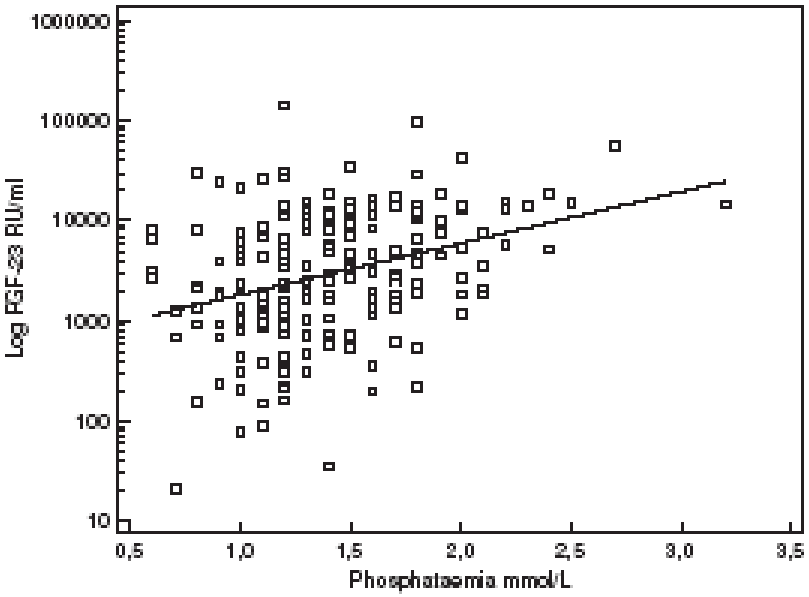
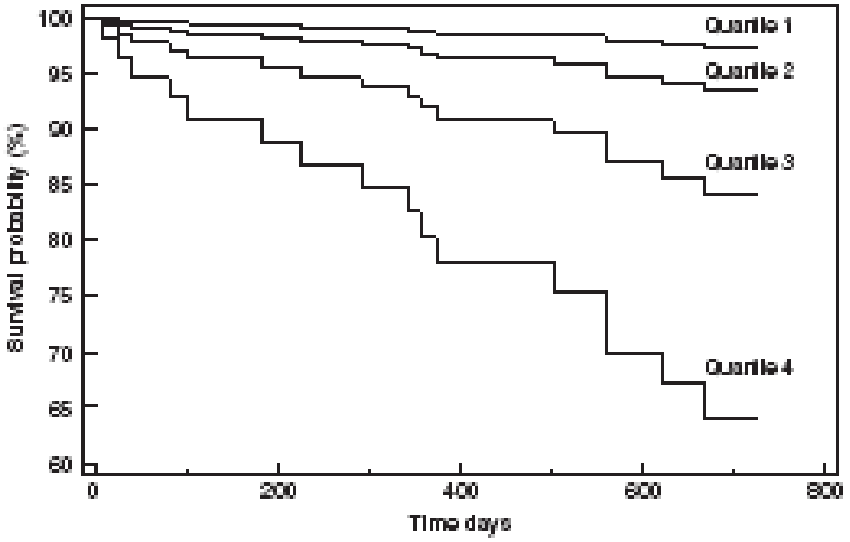


Fig. 1. Regression of phosphataemia against log FGF-23 ($r^2 = 0.11$, $P < 0.001$).



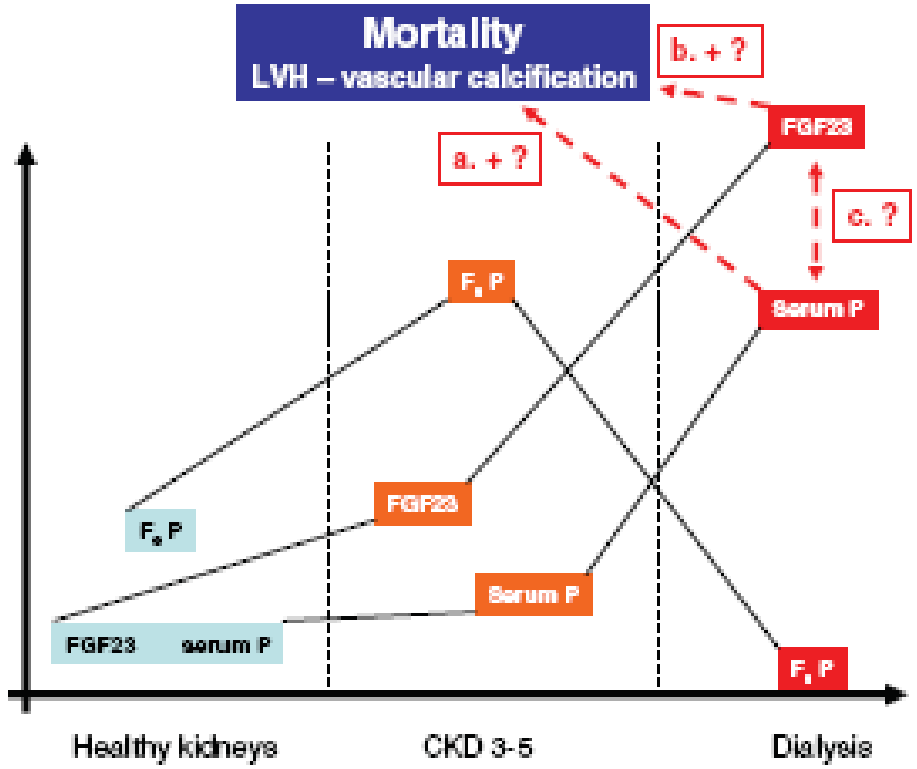
No at risk	219	186	162	137
Quartile 1	54	48	45	41
Quartile 2	55	48	43	39
Quartile 3	55	46	39	32
Quartile 4	55	44	35	25

FGF23 and mortatlity in CKD 5D:
Prevalent European patients (Hemodialysis)

Ketteler M & Biggar P, NDT 2009; 24:2618-20

As nature did not predict dialysis—what we can learn from FGF23 in end-stage renal disease?

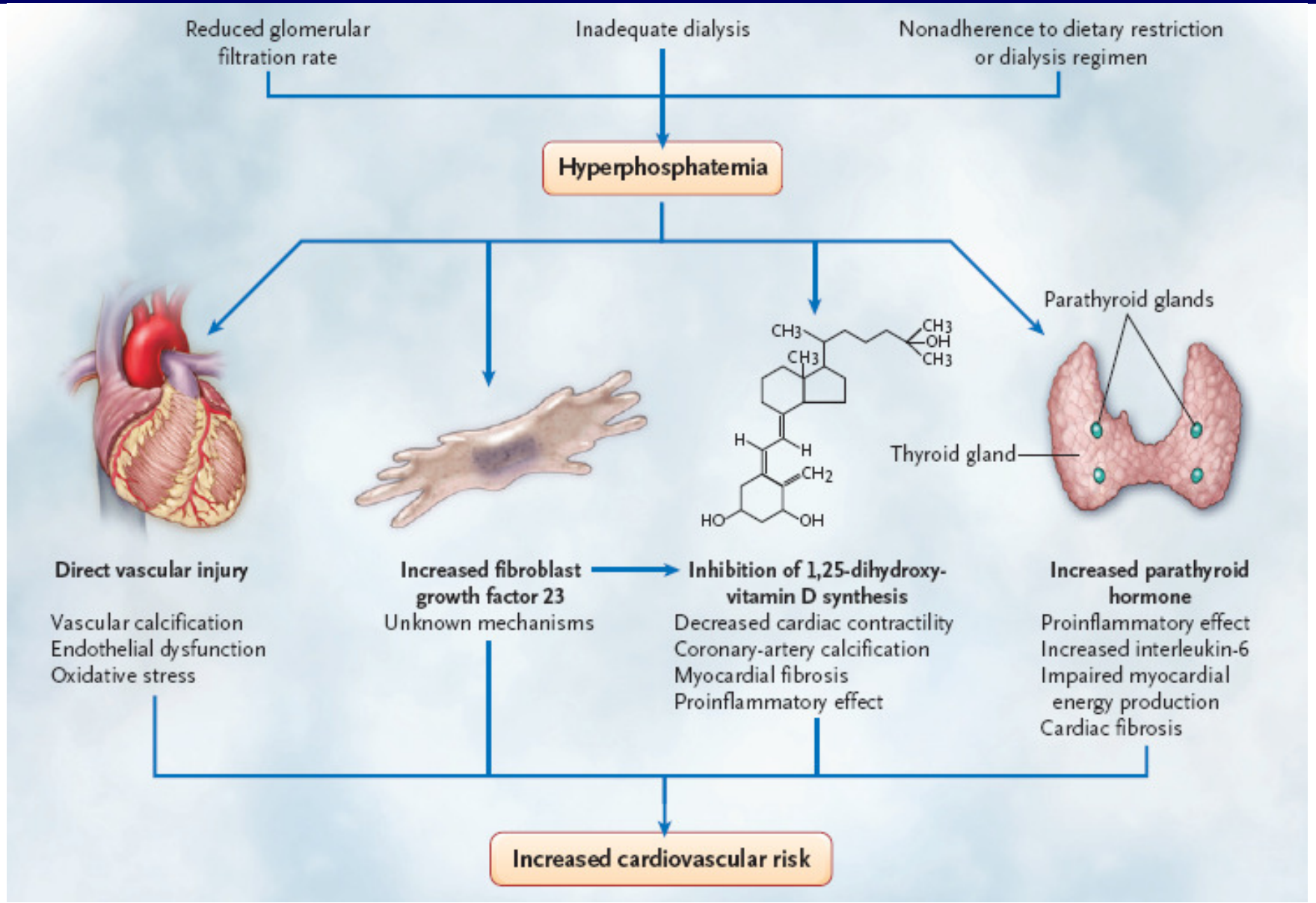
Markus Ketteler and Patrick H. Biggar



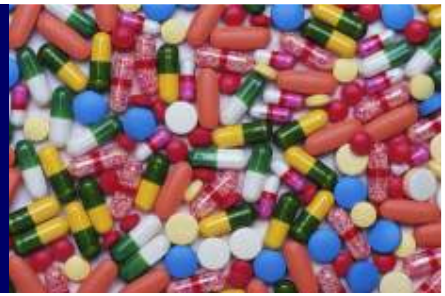
- High FGF23 despite long dialysis sessions – is initial resorption more important than overall balance?
- Warfarin use was associated with high FGF23 – link between vitamin K-dependent pathways (Osteocalcin/MGP), FGF23 regulation and calcification?
- Influence of active vitamin D treatment on FGF23 levels?

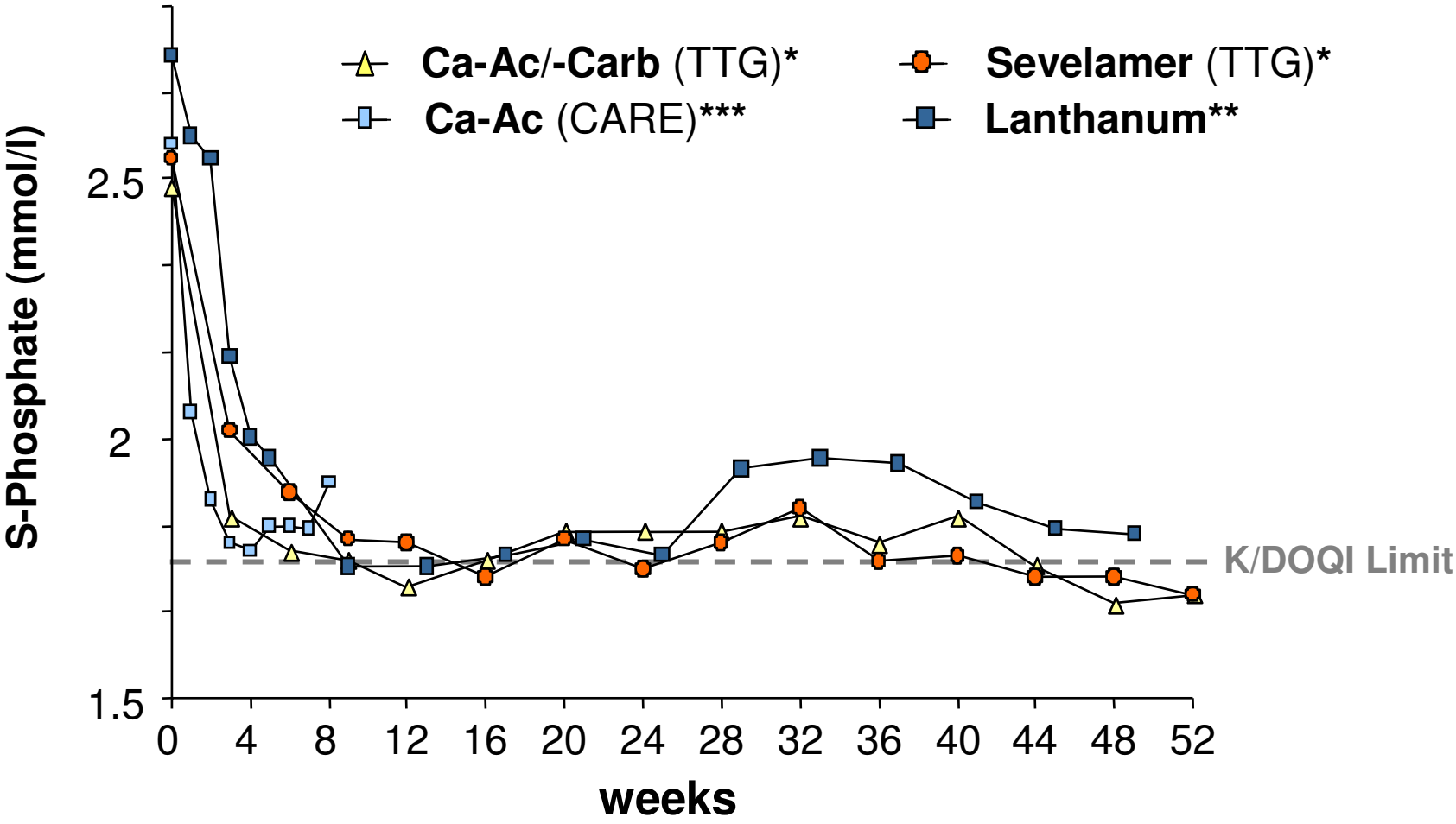
Pathogenesis of secondary hyperparathyroidism

Tonelli M et al., N Eng J Med 2010; 362:1312-24



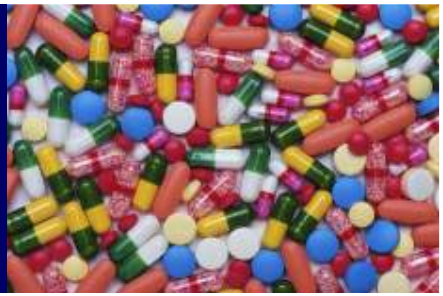
Management of hyperphosphatemia by phosphate binders





* Treat-to-goal Studie: Chertow GM. KI 2002; ** Hutchison WCN 03. Berlin; *** Qunibi W. et al. KI 2004

Available phosphate binders



Calcium-based phosphate binders

- Calciumcarbonate
- Calciumacetate

Calcium-free phosphate binders

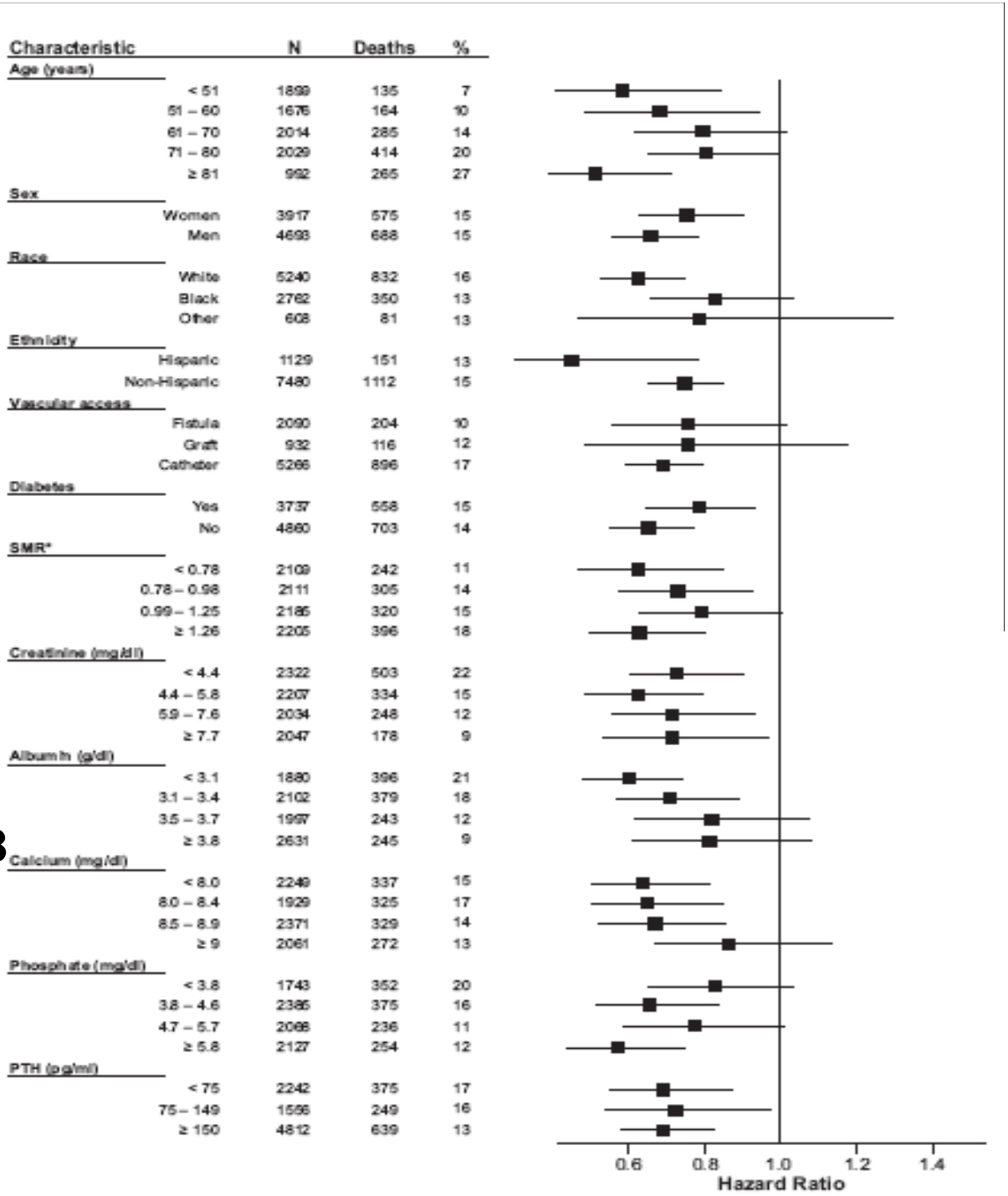
- Aluminium-HCl / Aluminium-OH
- Sevelamer-HCl / Sevelamercarbonate
- Lanthanumcarbonate
- Magnesium-OH / Magnesiumcarbonate

- Niacin / Nicotinamide*
- Fe-Mg-hydroxycarbonate**
- Fe-(III)-oxid-OH**
- Colestilan**
- Salivary binders…

*Phosphate transport inhibitor (no binder)

**in pivotal studies

Phosphate binder therapy is associated with improved survival in incident dialysis patients



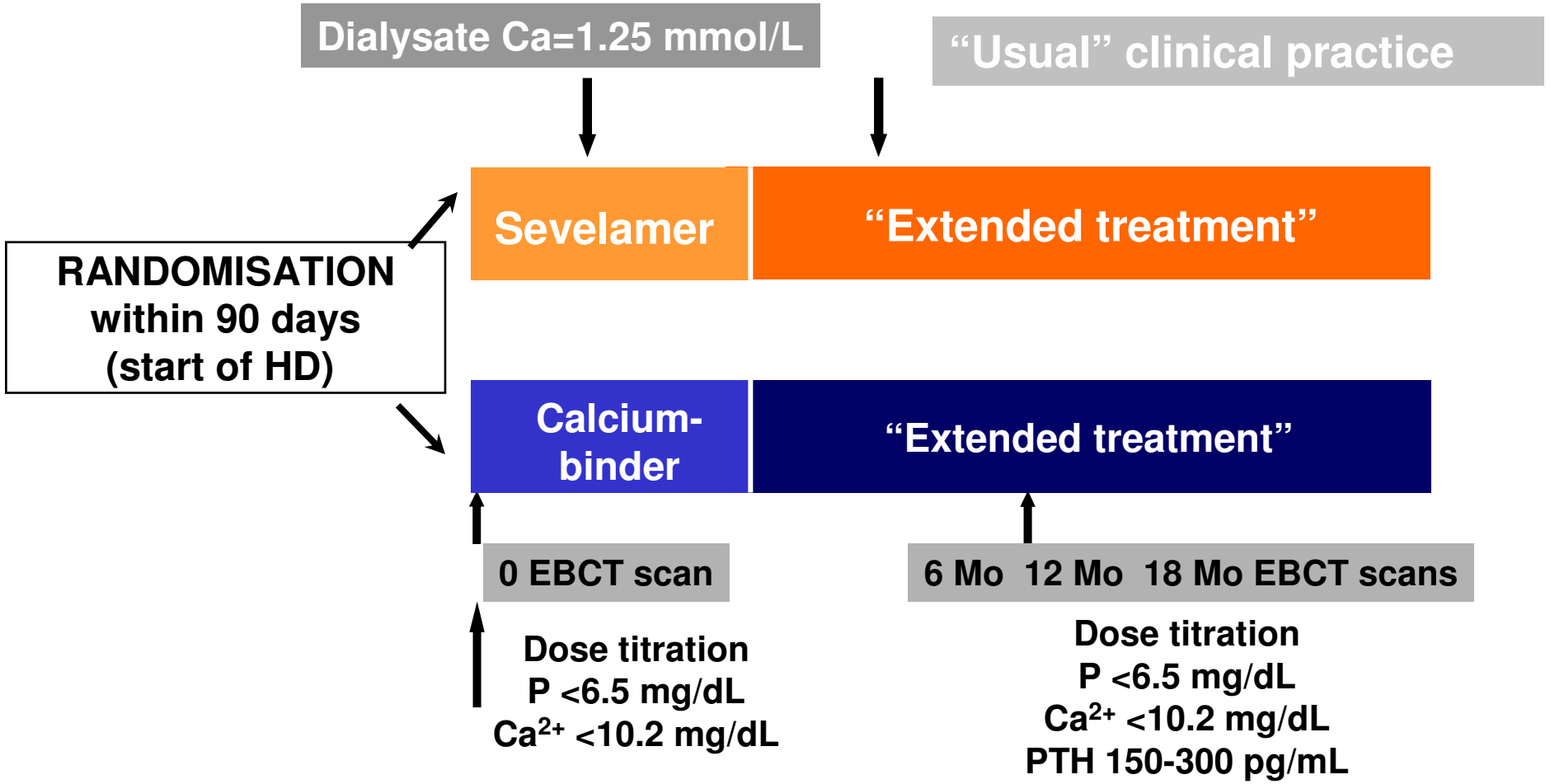
Estimated proportions:

- ✓ ca. 40% Ca-containing PB
- ✓ ca. 40% Sevelamer
- ✓ < 20% Lanthanum
- ✓ many combinations

Isakova T et al., JASN 2009; 20:388

RIND Study: Progression of coronary artery calcifications in incident hemodialysis patients

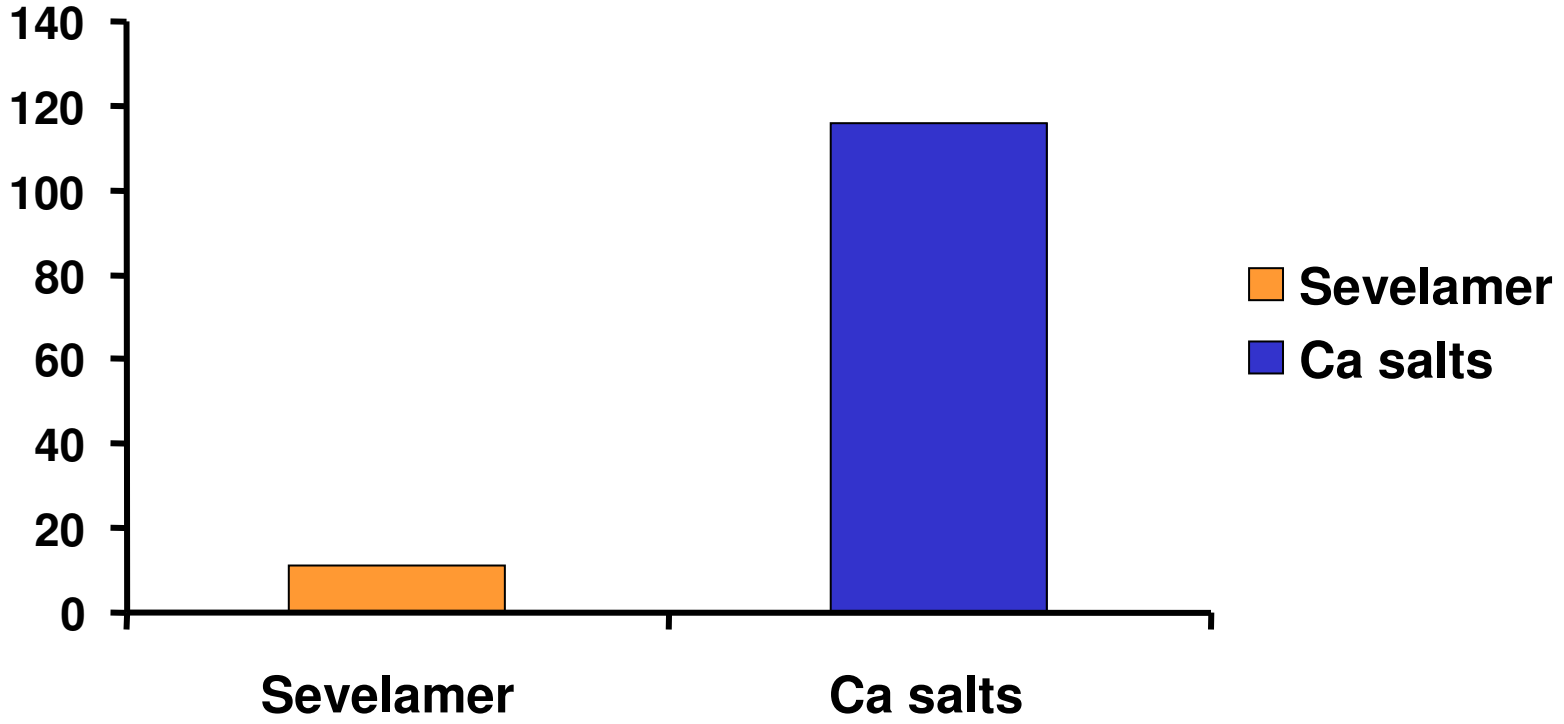
Block GA et al., Kidney Int 2005; 68:1815



•Renagel patients were allowed to receive nightly Ca supplements.

RIND Study: Progression of coronary artery calcifications in incident hemodialysis patients

Block GA et al., Kidney Int 2005; 68:1815



- The absolute rise of CACS (median) after 18 months was 11-fold increased in the Ca salt vs. the sevelamer group!
- „Progressors“ (60%) were already calcified at the start of the study !
- Patients w/out coronary calcifications at the start of the study (40%) remained free of calcification – despite intake of calcium-based binders!

Treatment of CKD-MBD: Phosphorus and Calcium

- **4.1.1. 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 towards the normal range *(2C)*.**

Treatment of CKD-MBD: Phosphorus and Calcium

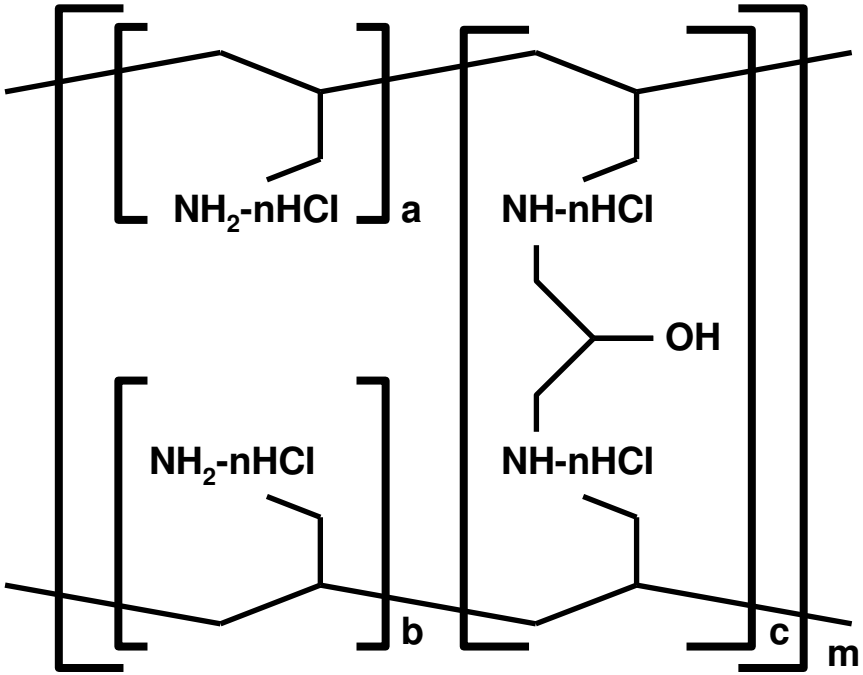
- **4.1.4. In patients with CKD Stages 3-5 *(2D)* and 5D *(2B)*, we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side-effect profile *(not graded)*.**

Treatment of CKD-MBD: Phosphorus and Calcium

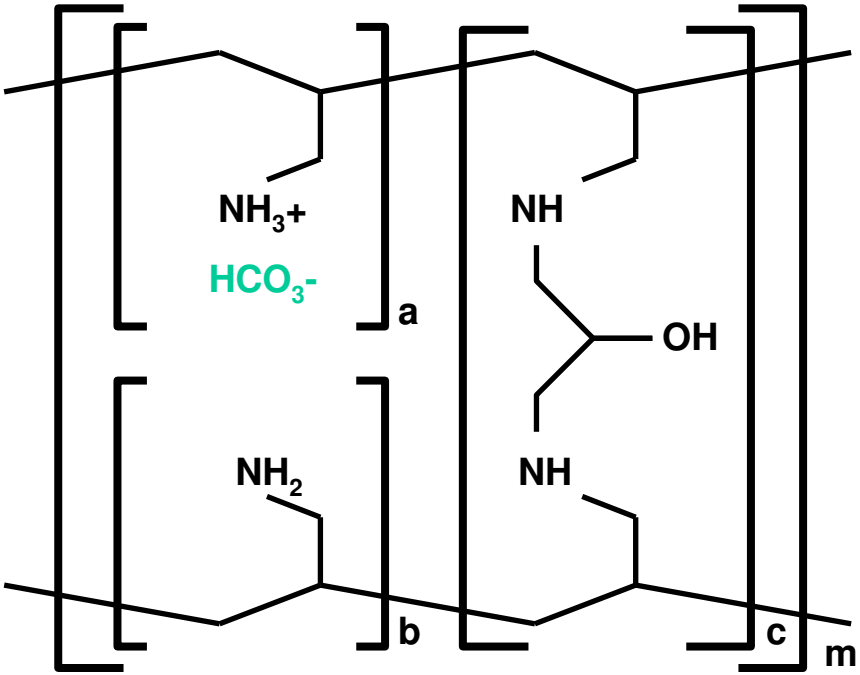
- **4.1.5.** In patients with CKD Stages 3-5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia *(1B)*.
- In patients with CKD Stages 3-5D and hyperphosphatemia, 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)*.

Sevelamer carbonate as a new option for treatment of hyperphosphatemia in CKD stages 3 – 5

Renagel



Renvela



- Same polymer backbone: Retains similar phosphate-binding capacity
- Salt change: Potentially improves buffering capacity
- Available as tablets and powder

Structures adapted from Renagel and Renvela Package Inserts.

KDOQI Clinical Practice Guidelines: Guideline 15 – Metabolic Acidosis

- **15-1 In CKD Stages 3, 4 and 5, the serum level of total CO_2 should be measured.**
- **15-1a The frequency of these measurements should be based on the stage of CKD as shown in Table. (OPINION)**

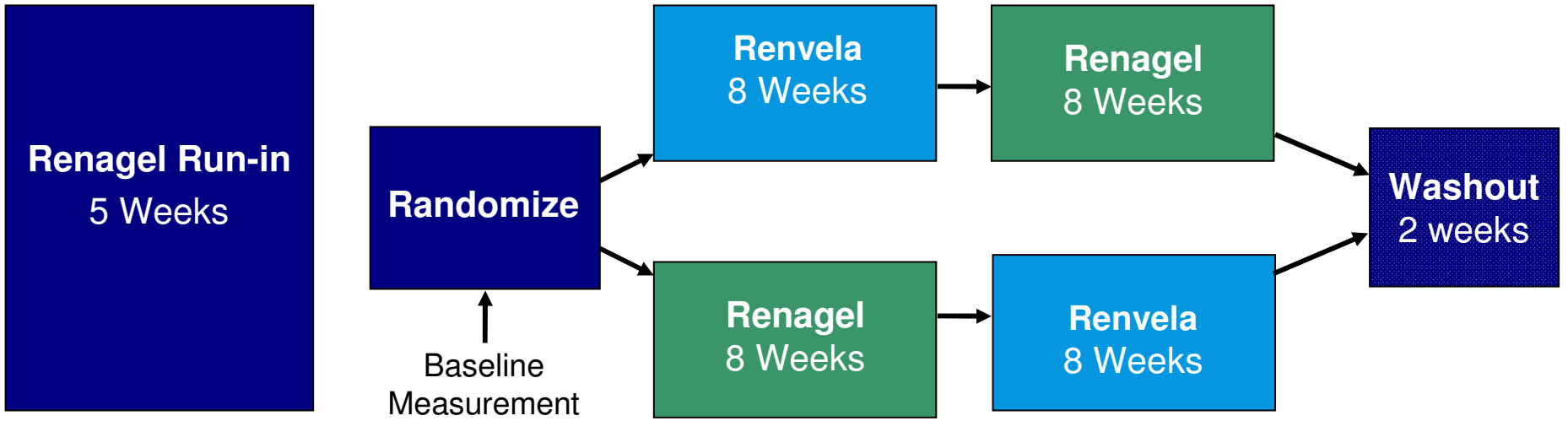
Frequency for Measurement of Serum Levels of Total CO_2		
CKD Stage	GFR Range ($mL/min/1.73m^{2)}$	Frequency of Measurement
3	30-59	At least every 12 months
4	15-29	At least every 3 months
5	<15	At least every 3 months
	Dialysis	At least every month

15-2 In these patients, serum levels of total CO_2 (bicarbonate) should be maintained at ≥22 mEq/L (22 mmol/L). (EVIDENCE) If necessary, supplemental alkali salts should be given to achieve this goal. (OPINION)

KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Available at http://www.kidney.org/professionals/KDOQI/guidelines_bone/Guide15.htm

Renvela Equivalence Study
Study Design

Multicenter, Double-blind, Randomized, Crossover Study



- **Starting dose of Renvela or Renagel was based on most recently prescribed dose of Renagel during run-in period**
- **Stable doses of cinacalcet and vitamin D were maintained throughout the study**

Delmez J, Block G, Robertson J, et al. *Clin Nephrol* 2007; 68:386-391

Renvela Equivalence Study
Baseline Laboratories

	Renvela (N=73)	Renagel (N=78)
Phosphorus (mg/dL)	**4.6 ± 1.09**	**4.6 ± 1.13**
Calcium (mg/dL)	**9.3 ± 0.67**	**9.3 ± 0.66**
Calcium x Phosphorus (mg^2/dL^2)	**42.9 ± 10.19**	**42.4 ± 10.70**
Albumin (g/dL)	**3.8 ± 0.31**	**3.8 ± 0.31**
iPTH (pg/mL)*	**245**	**249**

*iPTH is presented as median.

Delmez J, Block G, Robertson J, et al. Poster presented at the National Kidney Foundation 2007 Spring Clinical Meetings

Renvela Equivalence Study Efficacy Results

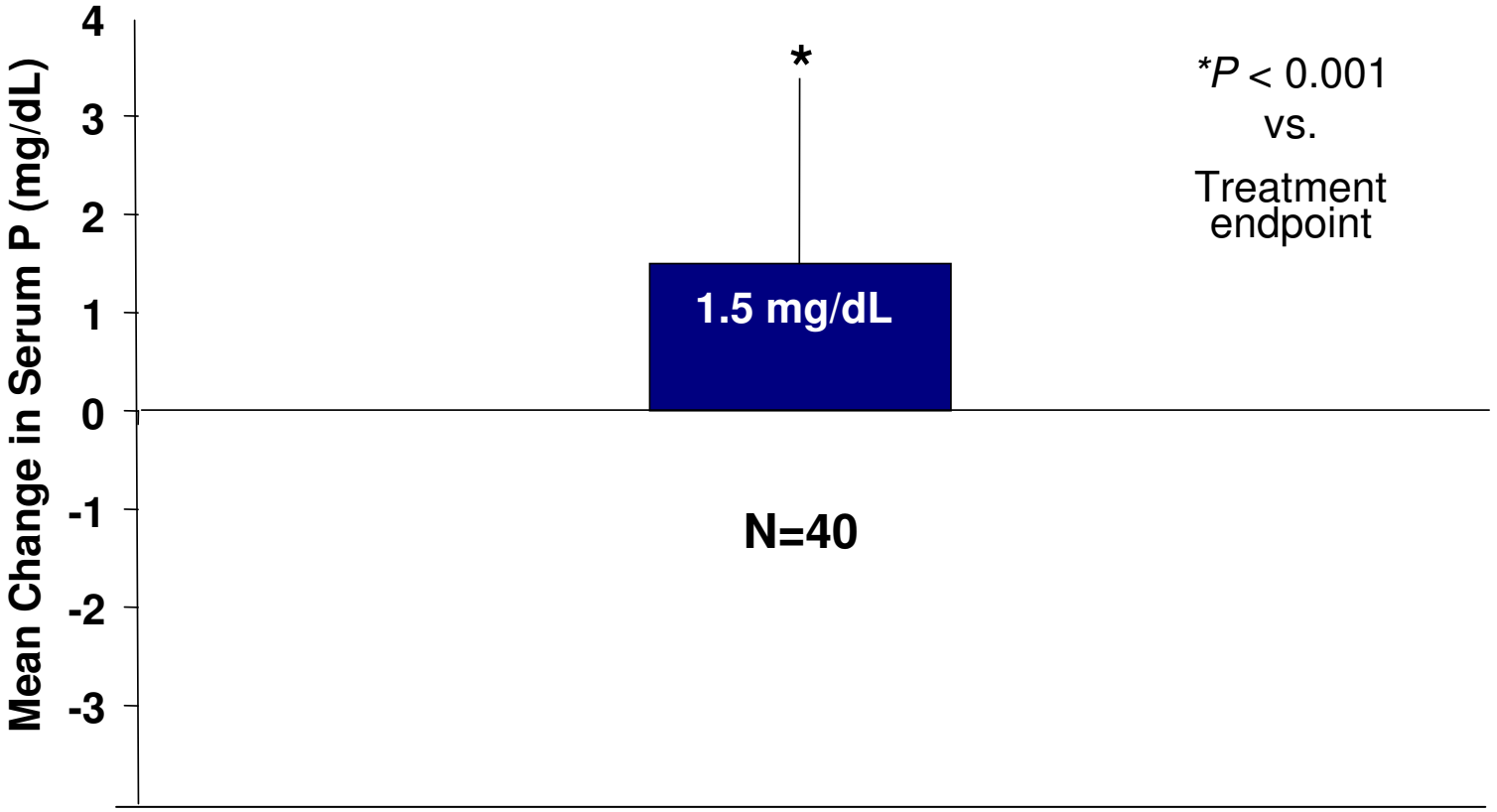
Mean Serum Phosphorus Levels ± SD (mg/dL)

	Renvela (mean ± SD) N=56	Renagel (mean ± SD) N=56	Geometric LS Mean Ratio (CI)
mg/dL	4.6 ± 0.9	4.7 ± 0.9	0.99 (0.95 – 1.03)*

*90% CI for the ratio is within the interval 0.80-1.25
LS=Least Square

Delmez J, Block G, Robertson J, et al. *Clin Nephrol* 2007; 68:386-391

Renvela Equivalence Study
Serum Phosphorus During Washout Period

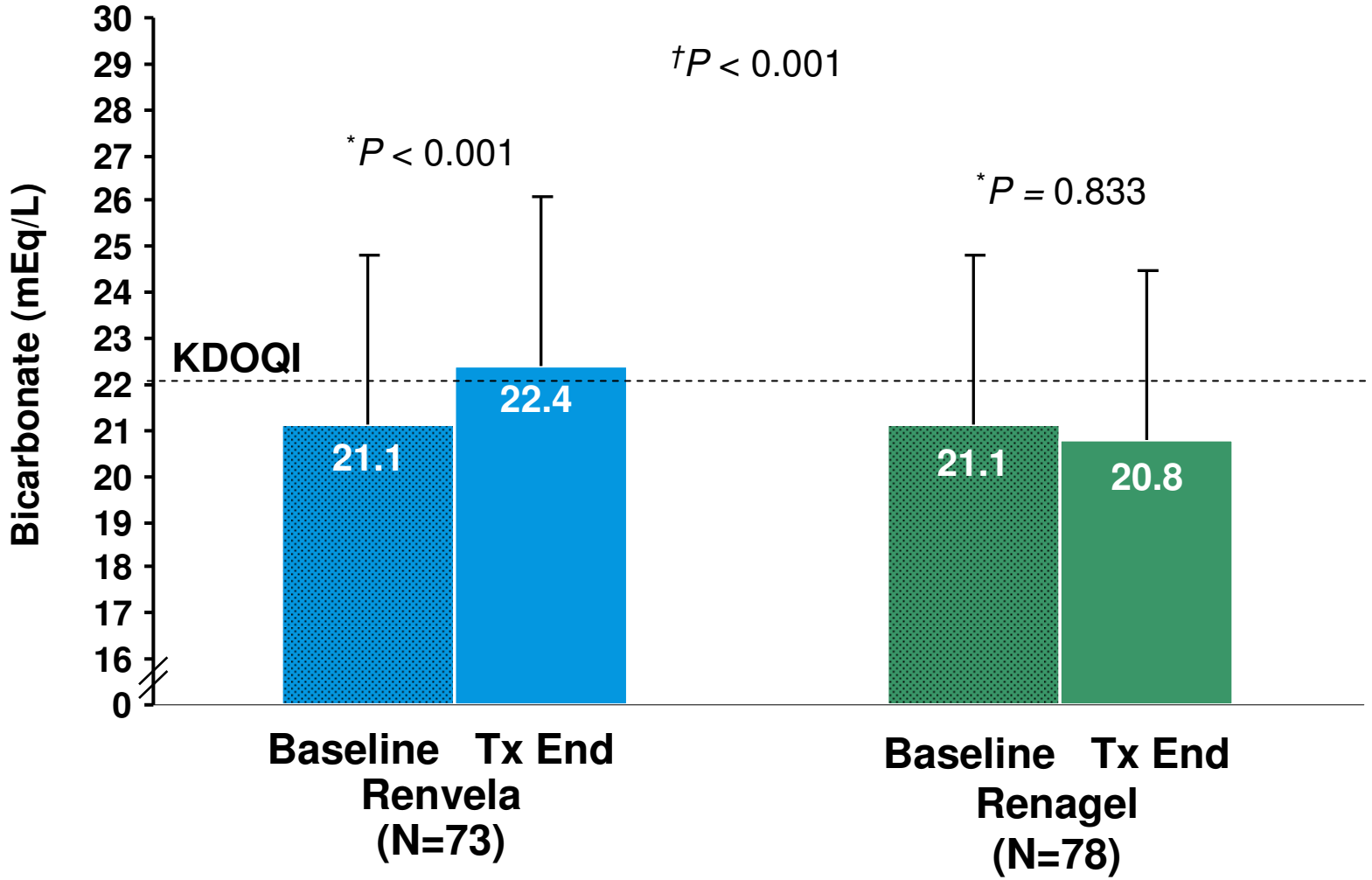


*Wilcoxon signed rank test used to compare change from baseline.

†All patients who completed washout regardless of form of sevelamer prescribed during treatment period.

Delmez J, Block G, Robertson J, et al. *Clin Nephrol* 2007; 68:386-391

Renvela Equivalence Study
Effect of Treatment on Serum Bicarbonate



*Wilcoxon signed rank test used to compare change from baseline within treatment.
†Wilcoxon signed rank test used to compare change from baseline between treatments.
All baseline values are post-5-weeks run-in on Renagel.

Delmez J, Block G, Robertson J, et al. *Clin Nephrol* 2007; 68:386-391
KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, Guideline 15 – Metabolic Acidosis.

Renvela Equivalence Study Adverse Events*

	Renvela N=73		Renagel N=78		
Adverse Event	Patients N (%)	Events N	Patients N (%)	Events N	*P*-value†
Any Gastrointestinal Event	**15 (20.5)**	**25**	**28 (35.9)**	**45**	**0.007**
Nausea	**7 (9.6)**	**9**	**10 (12.8)**	**13**	**0.467**
Vomiting	**6 (8.2)**	**7**	**8 (10.3)**	**8**	**0.527**
Diarrhea	**2 (2.7)**	**3**	**5 (6.4)**	**6**	**0.257**
GERD	**1 (1.4)**	**1**	**4 (5.1)**	**5**	**0.180**
Constipation	**0 (0.0)**	**0**	**3 (3.8)**	**3**	**0.083**
Dyspepsia	**1 (1.4)**	**1**	**3 (3.8)**	**3**	**0.317**
Abdominal pain	**2 (2.7)**	**2**	**1 (1.3)**	**1**	**0.564**

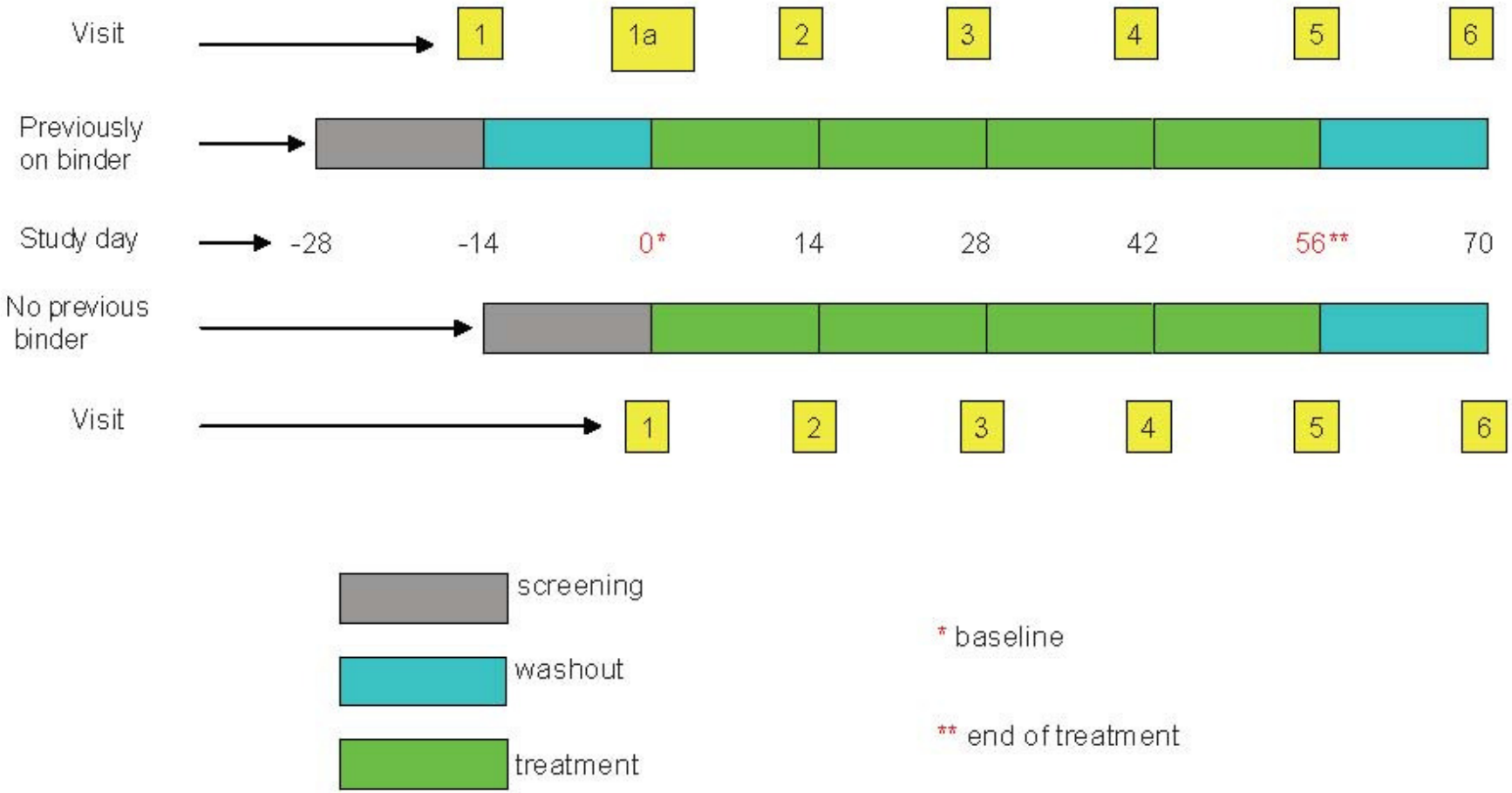
*Occurring in ≥ 2% of patients; †McNemar's Test.

GERD=Gastroesophageal Reflux Disease

Delmez J, Block G, Robertson J, et al. *Clin Nephrol* 2007; 68:386-391

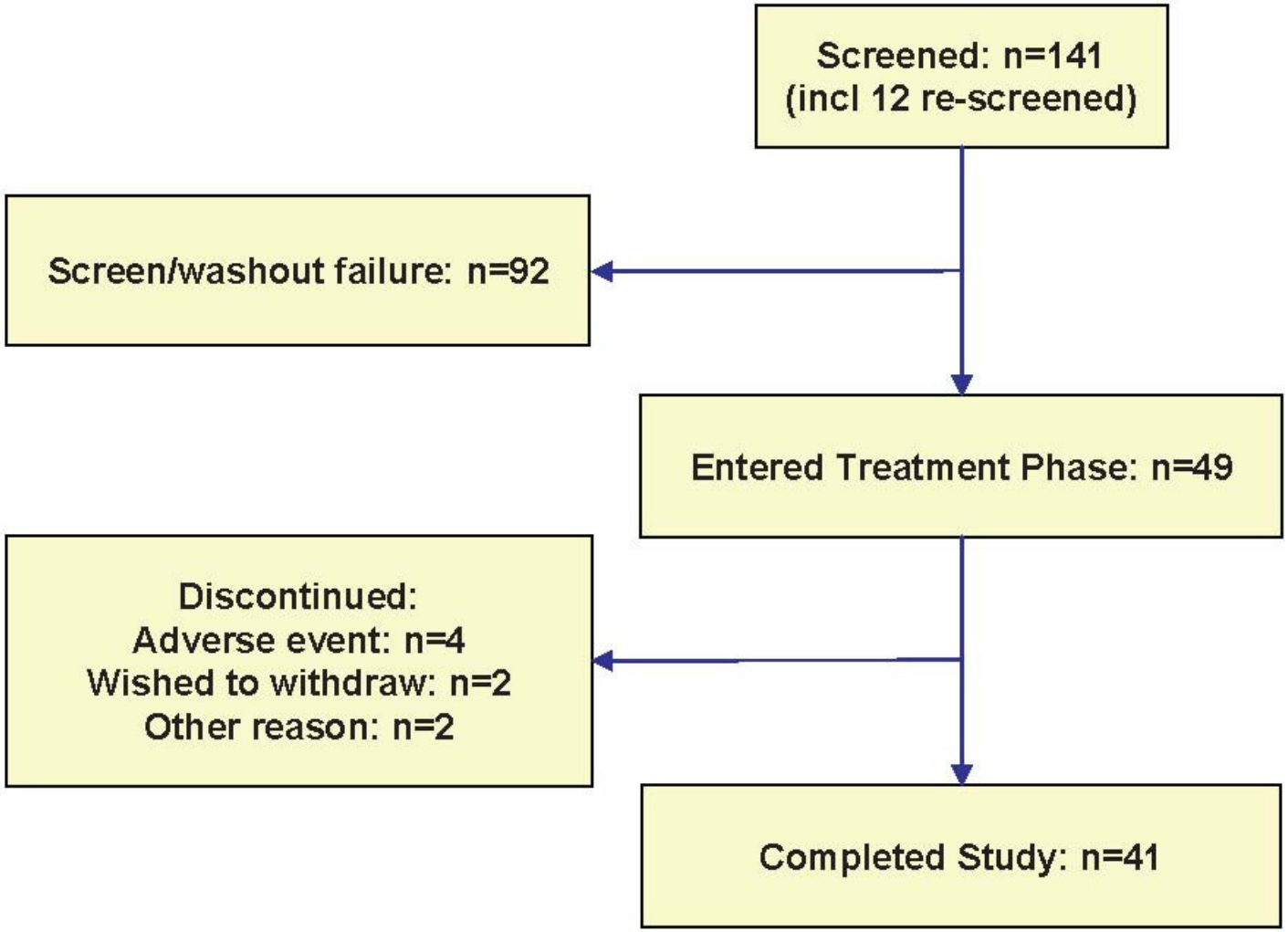
Sevelamer carbonate (Renvela) in patients in CKD stages 4-5

Ketteler M et al., CJASN 2008

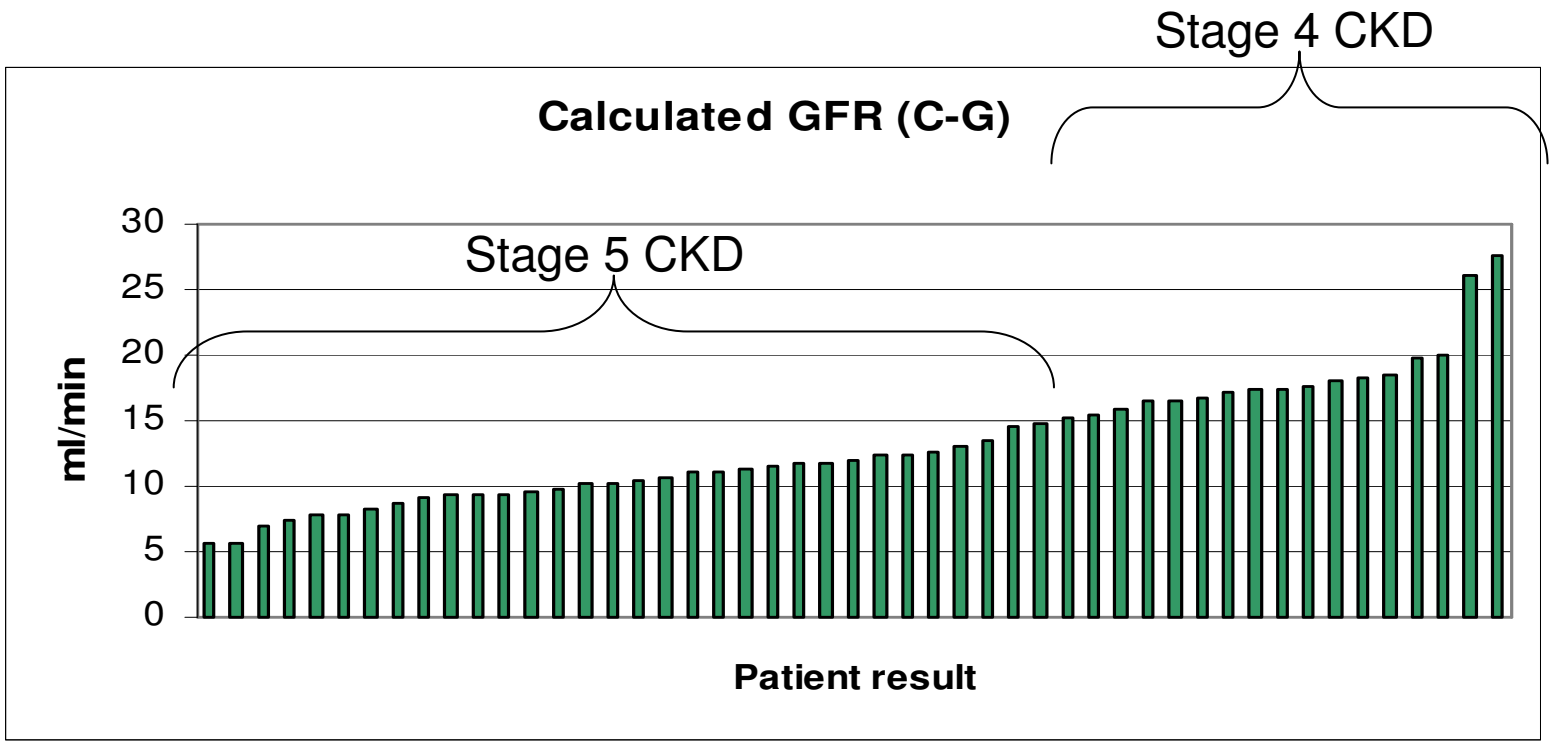


Sevelamer carbonate (Renvela) in patients in CKD stages 4-5

Ketteler M et al., CJASN 2008

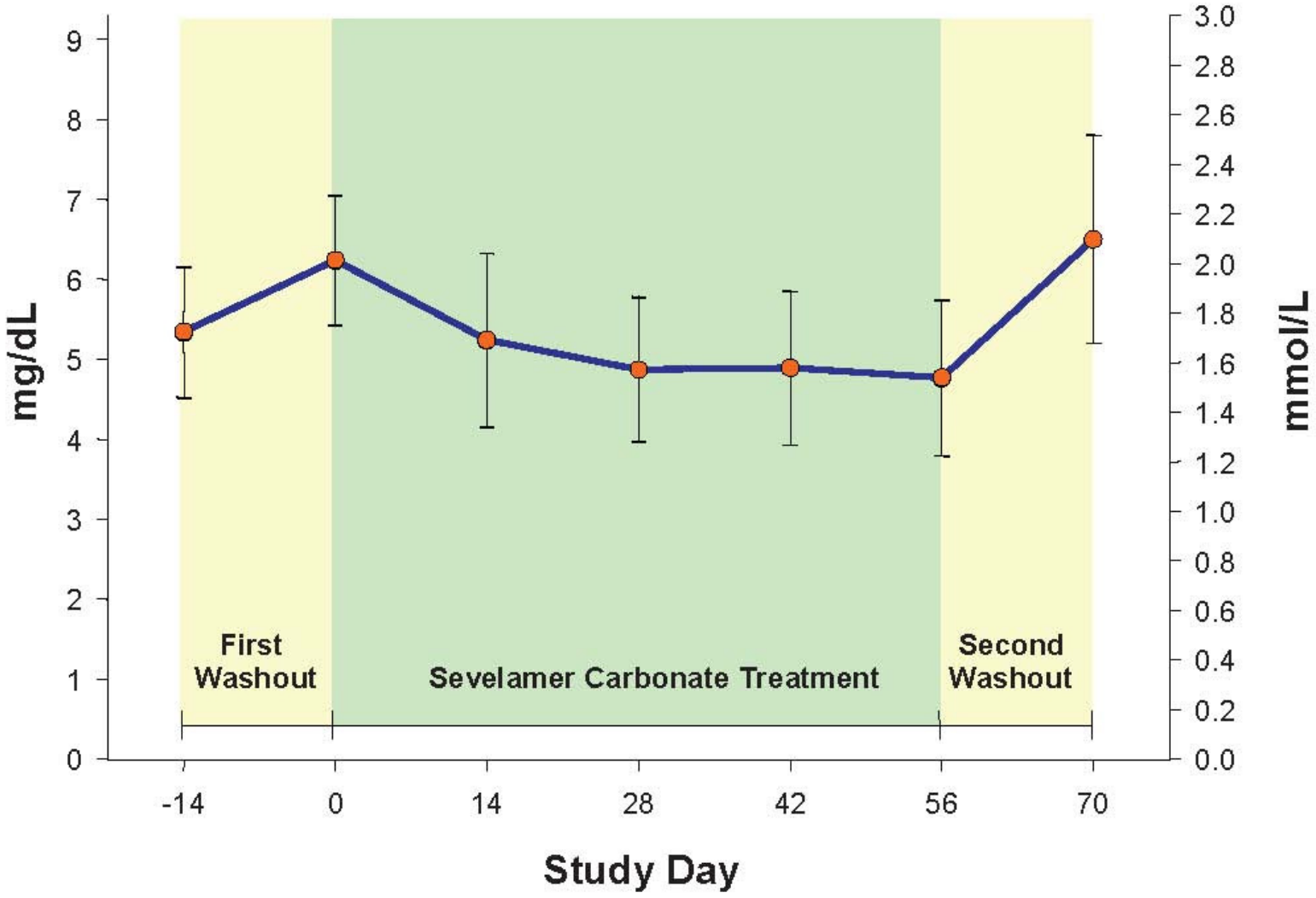


GFR for all patients (PPS – SVCARB00105)



Sevelamer carbonate (Renvela) in patients in CKD stages 4-5

Ketteler M et al., CJASN 2008



Sevelamer carbonate (Renvela) in patients in CKD stages 4-5

Ketteler M et al., CJASN 2008

Laboratory parameter (serum)	Pre-washout †	Baseline	Day 56/ET	Change from Baseline to Day 56/ET	P-value*	Post-washout	Change from Day 56 to Day 70	P-value*
Bicarbonate (mEq/L)	–	16.6 ± 3.6	18.2 ± 3.7	1.3 ± 2.9	0.005	18.0 ± 3.6	-0.5 ± 3.5	0.326
Calcium (mg/dL)	9.1	8.5	8.8	0.3	<0.001	8.6	-0.2	0.007
iPTH (pg/mL) median	208	341	319	-39	0.013	362	63	<0.001
25-OH Vit D (ng/mL)	28.1 ± 18.8	28.9 ± 16.2	31.1 ± 12.9	2.0 ± 10.3	0.080	32.3 ± 13.7	0.2 ± 7.7	0.890
1,25 (OH)2 Vit D (pg/mL)	–	25.4 ± 10.1	31.8 ± 12.1	5.3 ± 14.9	0.026	31.8 ± 11.7	–0.3 ± 14.4	0.942

Acid base changes: sevelamer treated CKD patients

Sevelamer carbonate provides a differential of ~ + 4mmol/L in serum bicarbonate in CKD patients not on dialysis in comparison with sevelamer hydrochloride

Phosphate Binder	**CKD patients not on dialysis** Change from baseline in serum bicarbonate level
Sevelamer carbonate (SVCARB00105)	**+1.3 ± 2.9 mmol/L***
Sevelamer hydrochloride (GTC-45-204)	**–2.6 ± 4.6 mmol/L****

* 8 weeks treatment, ** 12 weeks treatment

Early management of phosphate regulation Conclusions

- ✓ Sevelamer carbonate is a non-absorbable phosphate binder equivalent to sevelamer HCl in controlling serum phosphorus (availability: tablets & powder formulation)
- ✓ Sevelamer carbonate is acid/base-neutral
- ✓ Sevelamer carbonate is well-tolerated and was associated with a significantly lower number of patients with GI adverse events than sevelamer HCl
- ✓ Lipid profiles are favorable with sevelamer carbonate treatment
- ✓ Sevelamer carbonate appears as an safe, effective and feasible first choice for treatment of hyperphosphatemia in both predialysis and dialysis CKD stages

Delmez J, Block G, Robertson J, et al. *Clin Nephrol* 2007; 68:386-391

Hemodialysis International 2009; 13:360–362

Letter to the Editor

A randomized double-blind pilot study of serum phosphorus normalization in chronic kidney disease: A new paradigm for clinical outcomes studies in nephrology

- Do you believe that a randomized clinical trial of target levels of serum phosphorus is necessary in patients with CKD? Is it achievable in patients with stage 5D CKD? Can it be placebo controlled?
- Do you believe that *serum* phosphorus is the most appropriate measure to use as a primary outcome variable for such a randomized clinical trial?
- Do you believe that it is important to compare at least 1 noncalcium phosphate binder and at least 1 calcium-containing phosphate binder in addition to placebo in such a trial?
- What would be the most compelling result from such a trial that would demand that clinical practice change to target lower serum phosphorus values in all patients with CKD?

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