# Treatment of Serum Phosphate in Early CKD

Geoffrey Block

Denver Nephrology Research

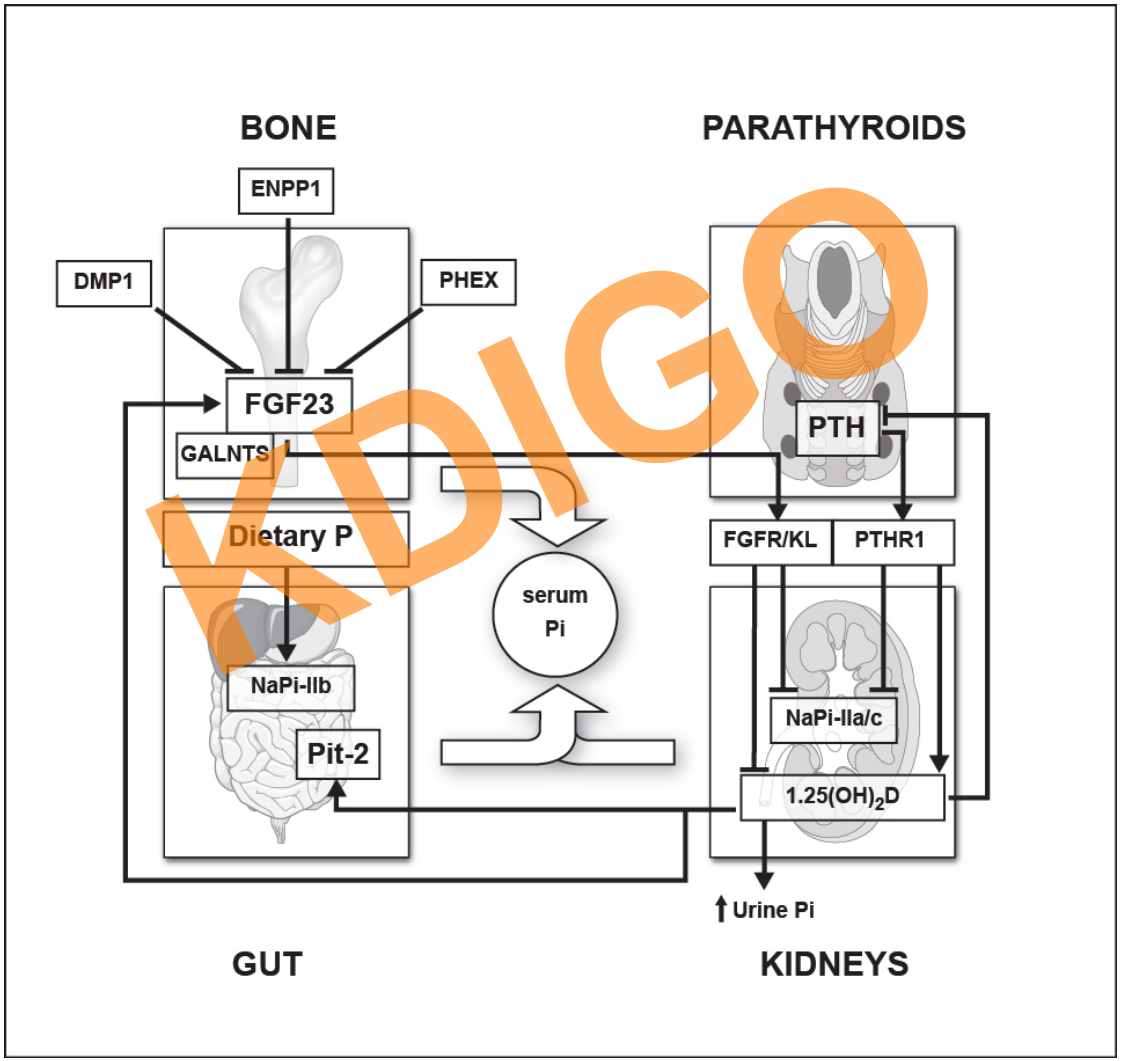
# Disclosure of Interests

- Amgen: Consultancy, research grant
- Keryx: Consultancy, honoraria
- Sanofi: No current relationships, past honoraria, research grant sponsored education grants
- Shire: No current relationship, past research grant
- JTT: Consultancy

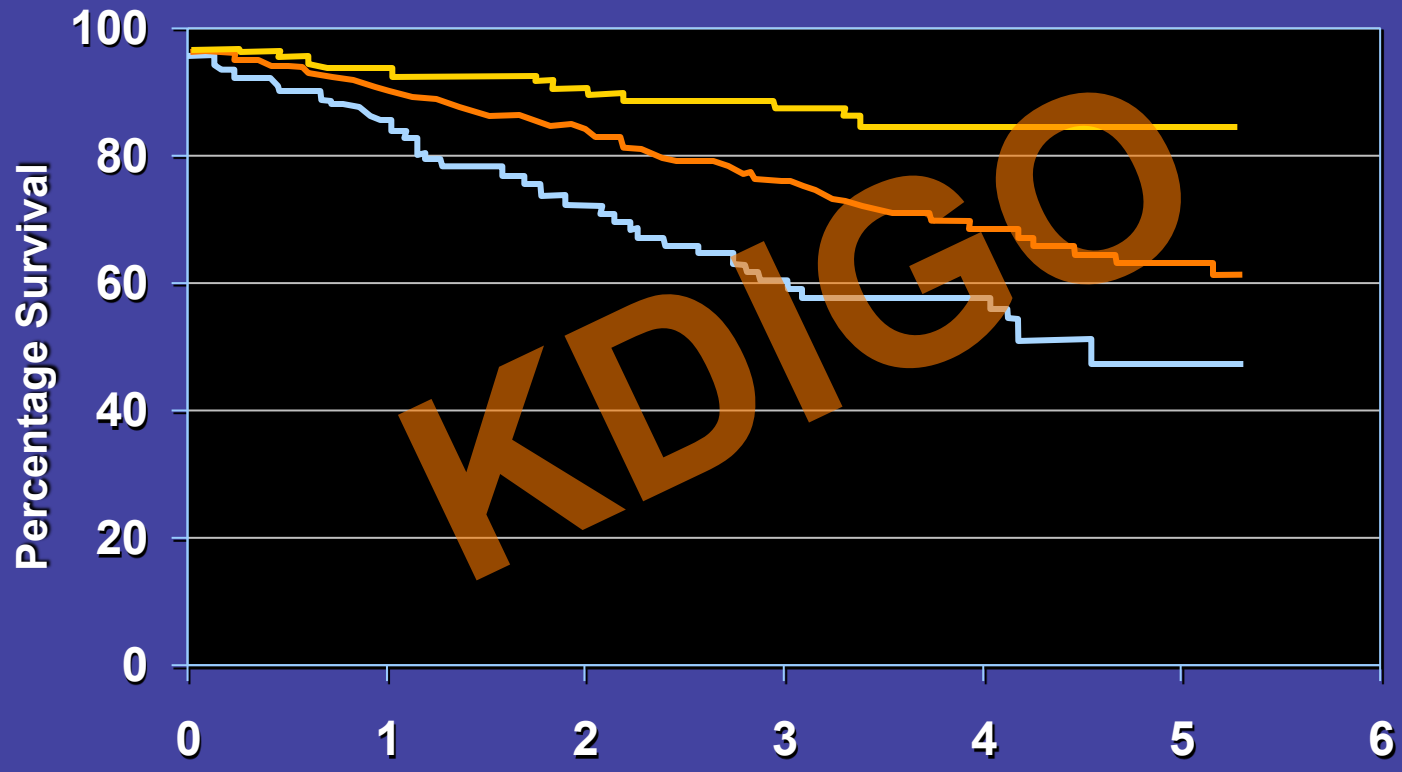
# Treatment of Phosphate in Early Chronic Kidney Disease

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

# Phosphate Homeostasis



# Survival According to Phosphate Levels Relative to KDIGO Guidelines

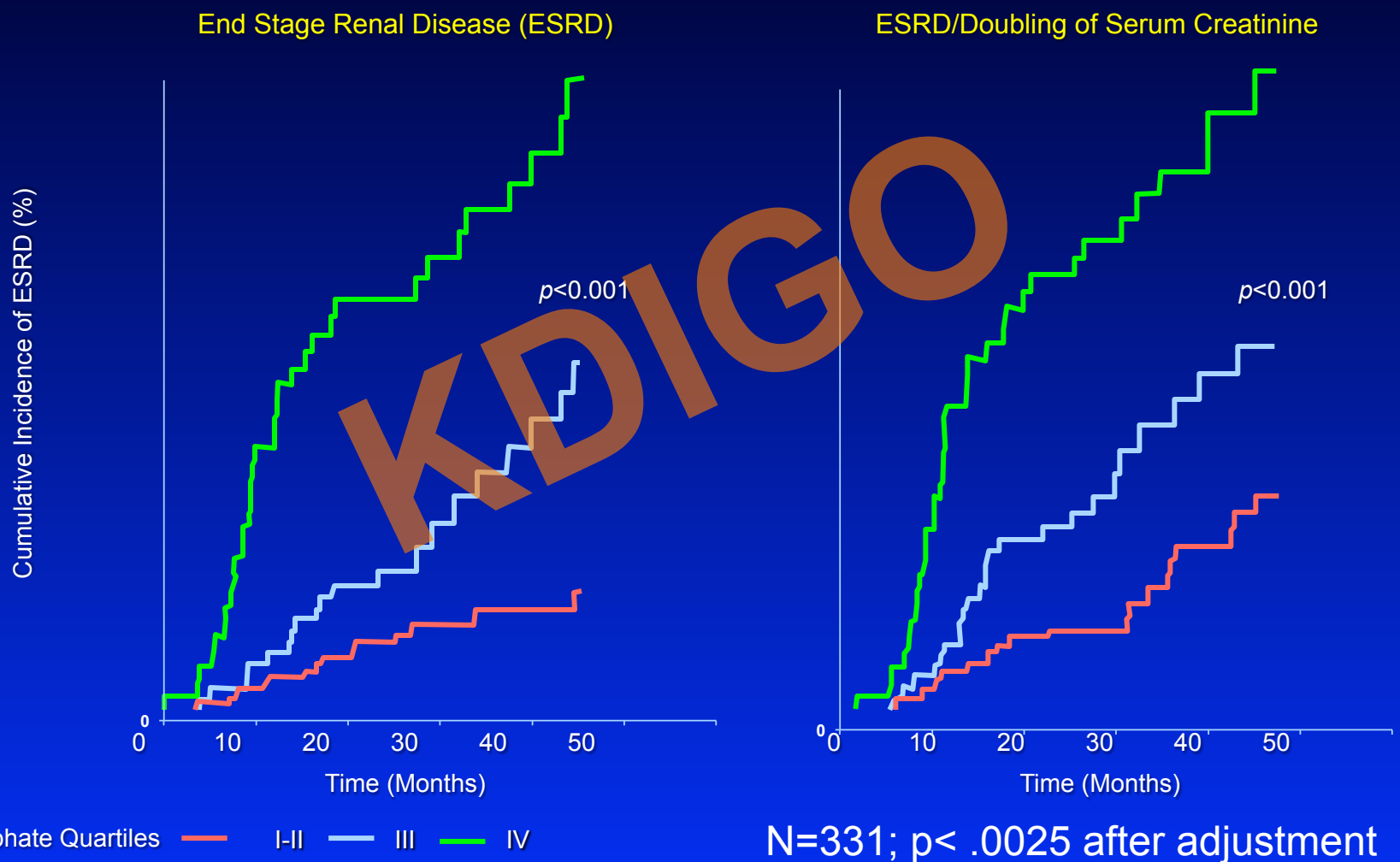



**Hazard Ratio**
**In Target: 1.8 (0.98, 3.8) *p*=0.06**
**Above Target: 2,7 (1.3, 5.7) *p*=0.009**

Analysis adjusted for age, gender, proteinuria, diabetes, hemoglobin, systolic blood pressure, current smoking status, cardiovascular disease, eGFR, and vitamin D analog and phosphate binder use.

Eddington H et al. Clin J Am Soc Nephrol 5: 2251–2257, 2010. doi: 10.2215/CJN.00810110.

# Serum Phosphate Modifies Risk of CKD Progression



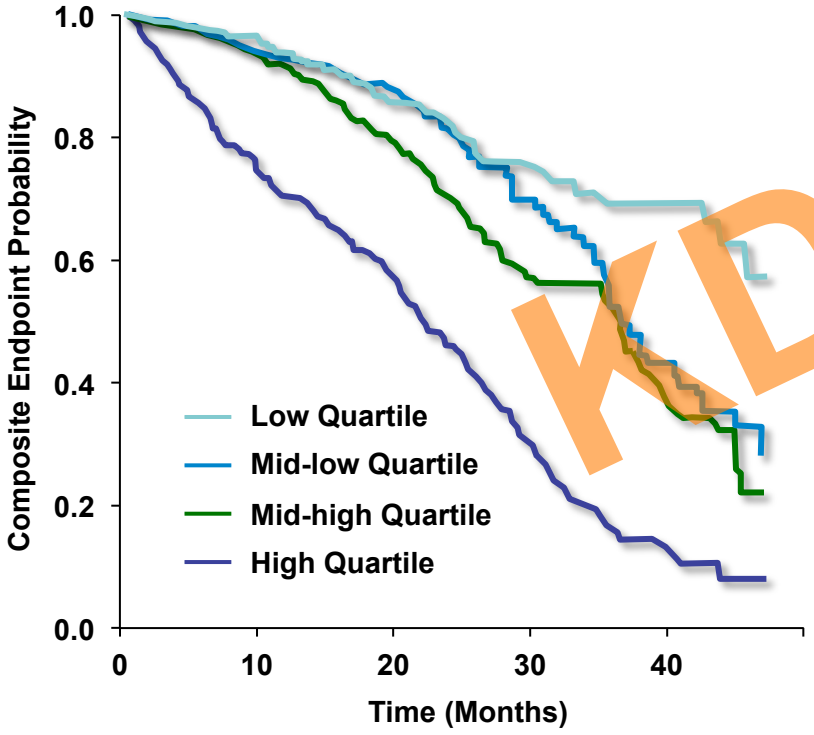



N=331; p< .0025 after adjustment for GFR, proteinuria, ramipril, albumin, gender, systolic BP

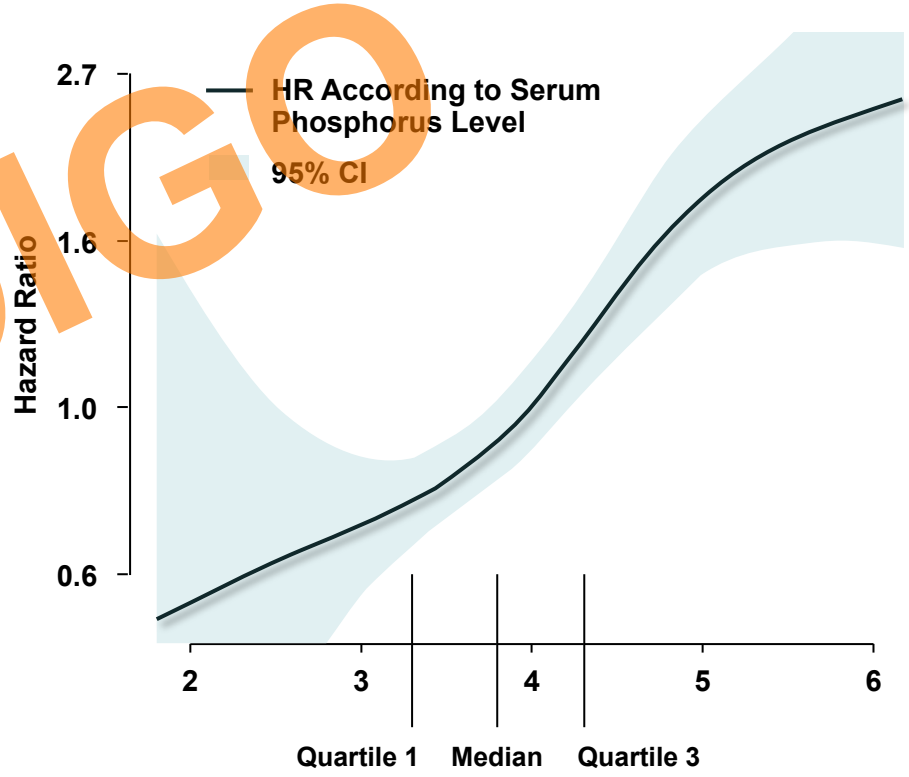
I/II quartile: <3.45 mg/dl. III quartile: 3.45 to 4.00 mg/dl. IV quartile: >4.00 mg/dl.
Zocalli C, et al. *J Am Soc Nephrol.* 2011;22:1923-30.

# Composite End Point of ESRD or Death According to Serum Phosphorous Levels

## Overall Likelihood




## Hazard Ratio*






*Adjusted for age, case mix, hemoglobin, total calcium, uric acid and ACE inhibitors, vitamin D, and calcium salts use

Bellasi A et al. *Clin J Am Soc Nephrol.* 2011;6:883-91.

# Association Between Hyperphosphatemia and the Composite Outcome (Death or Progression to ESRD) In the Study Cohort

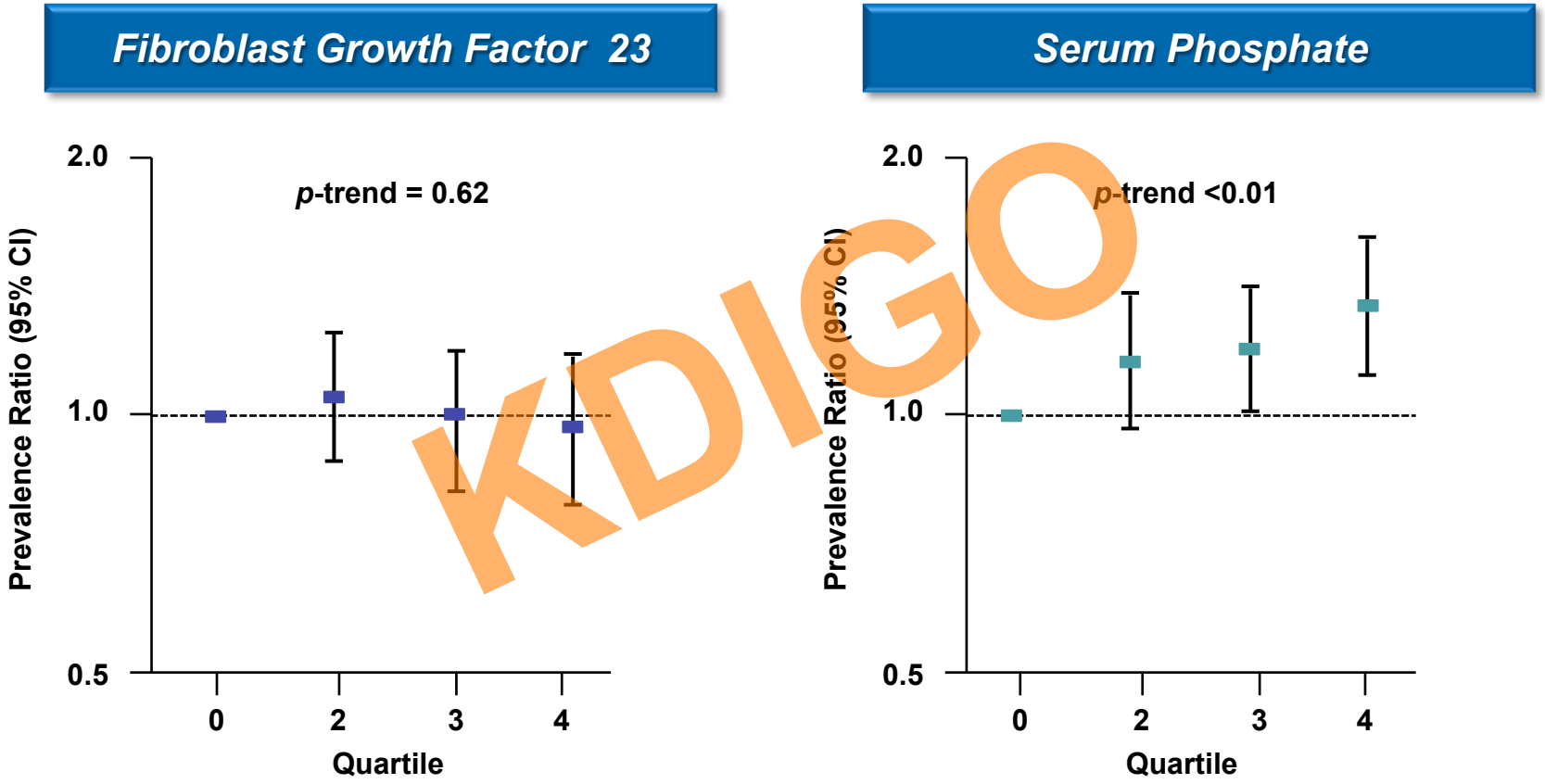
***Overall (n=1716)***

| | *Age-Adjusted* | | | *Case Mix Model** | | | *Cox Full Model†* | | |
|---|---|---|---|---|---|---|---|---|---|
| ***Variable*** | ***HR*** | ***95% CI*** | ***P*** | ***HR*** | ***95% CI*** | ***P*** | ***HR*** | ***95% CI*** | ***P*** |
| ***P<3.3 mg/dl*** | **0.64** | **0.42 to 0.96** | **0.03** | **0.75** | **0.49 to 1.14** | **0.18** | **0.78** | **0.51 to 1.19** | **0.25** |
| ***P≥3.3 and <3.8*** | **Ref** | | | **Ref** | | | **Ref** | | |
| ***P≥3.8 and <4.3*** | **1.29** | **0.91 to 1.81** | **0.14** | **0.98** | **0.69 to 1.39** | **0.94** | **0.93** | **0.66 to 1.33** | **0.72** |
| ***P≥4.3*** | **4.01** | **2.93 to 5.47** | **<0.001** | **2.32** | **1.64 to 3.27** | **<0.001** | **2.04** | **1.44 to 2.90** | **<0.001** |



* Case mix: age + gender, eGFR, history of diabetes mellitus, history of hypertension, and history of COPD and CVD.
† Full model: age + case mix + hemoglobin, total calcium, uric acid and ACE inhibitors, vitamin D, and calcium salts use.
Bellasi A et al. *Clin J Am Soc Nephrol.* 2011;6:883-91.

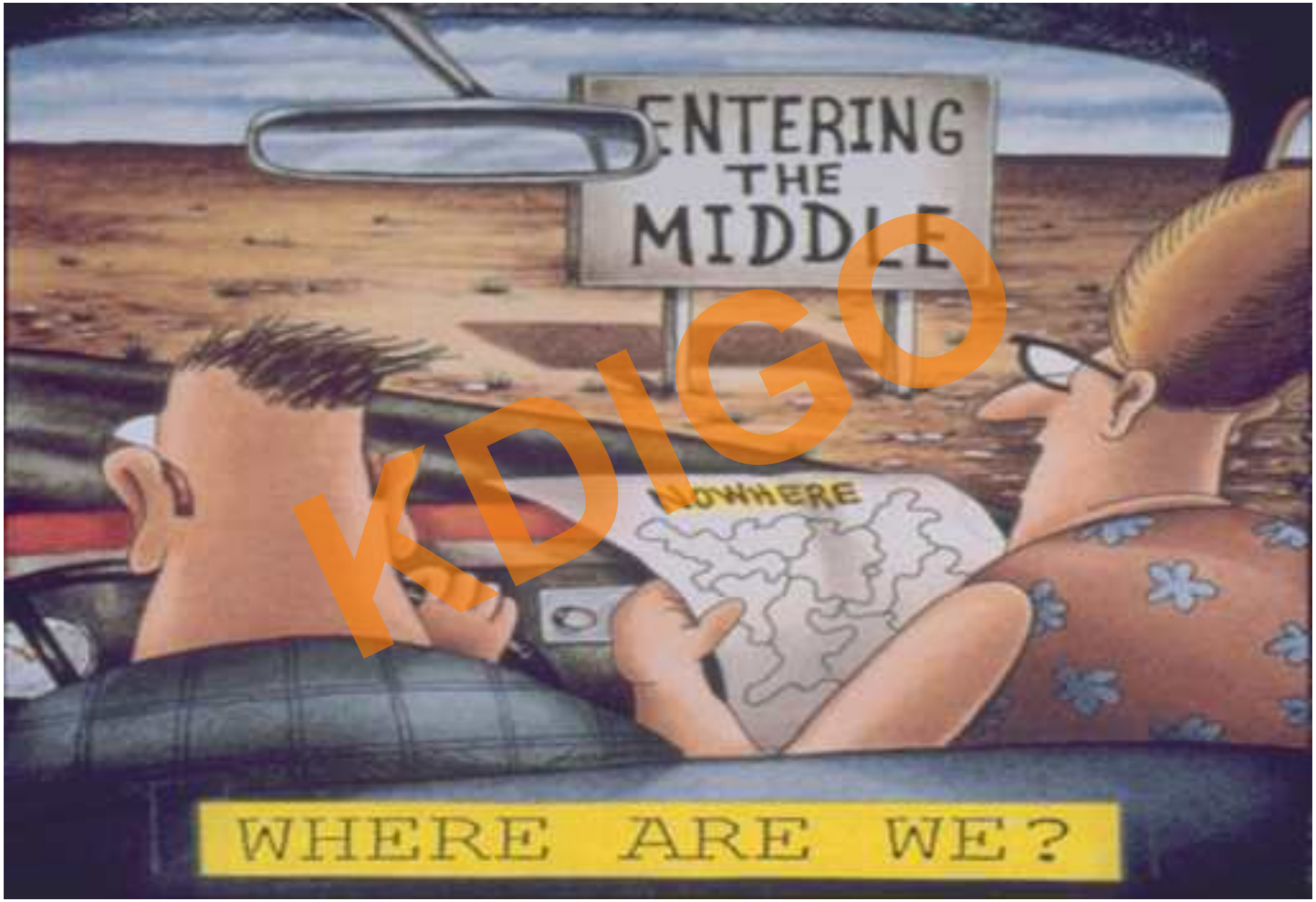
# Prevalence of Coronary Artery Calcium (CAC) Score > 100 in CRIC Cohort



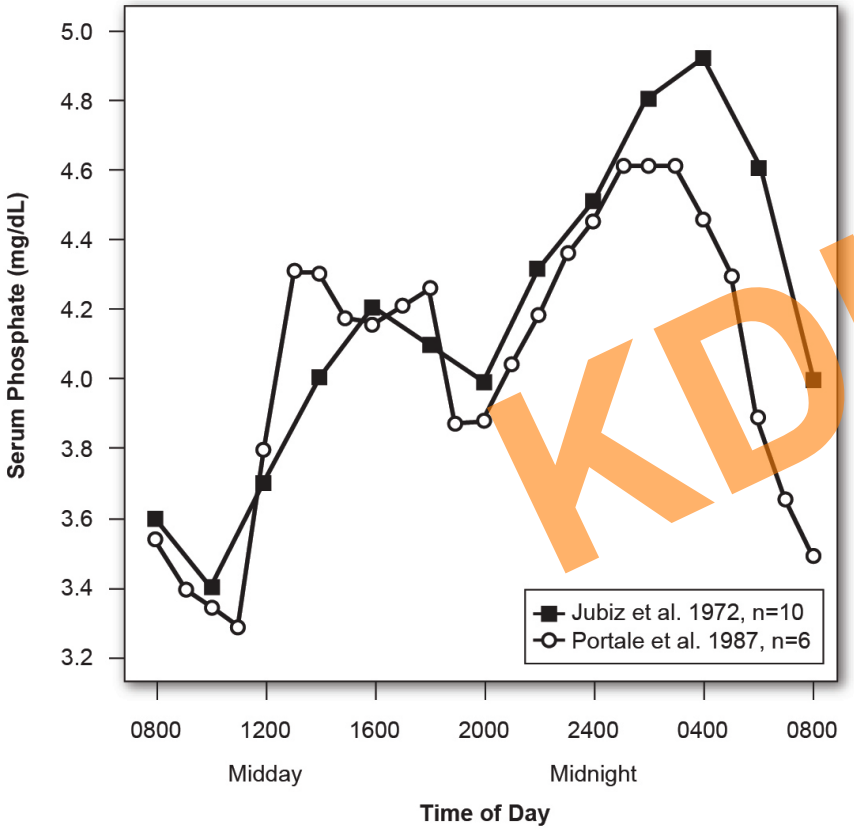


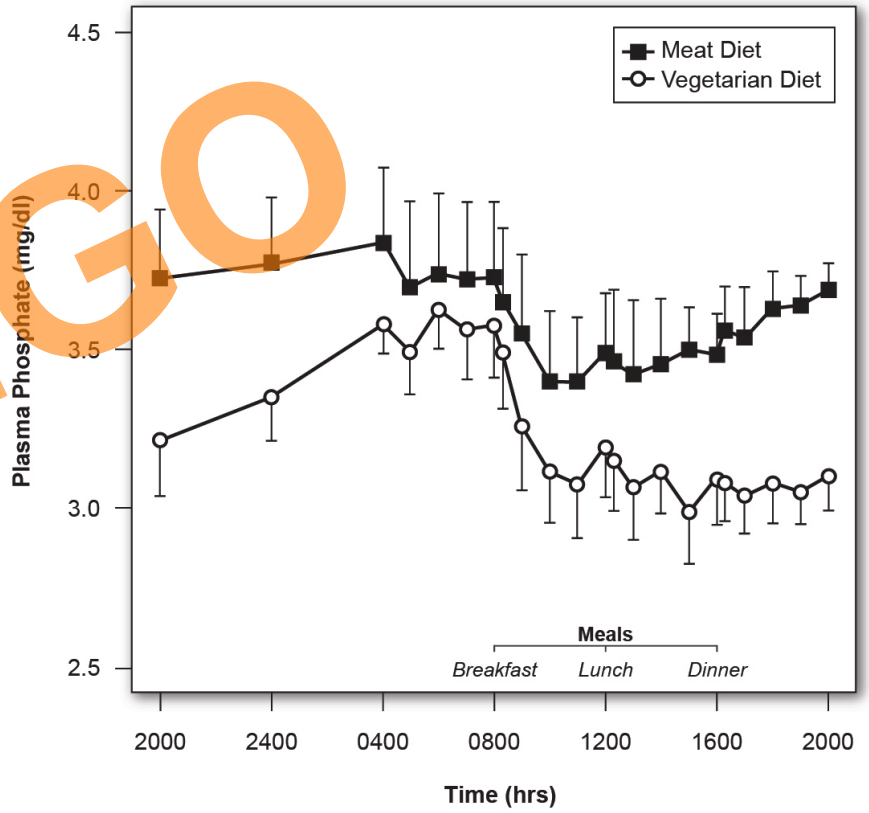

l models adjusted for age, sex, race, ethnicity, eGFR, uACR, CVD, diabetes, smoking, HTN, high cholesterol, BMI, PTH, Ca and center and either FGF23 or P

Scialla JJ, et al. *Kidney International*. 2013. Advance online publication, 6 Feb 2013.

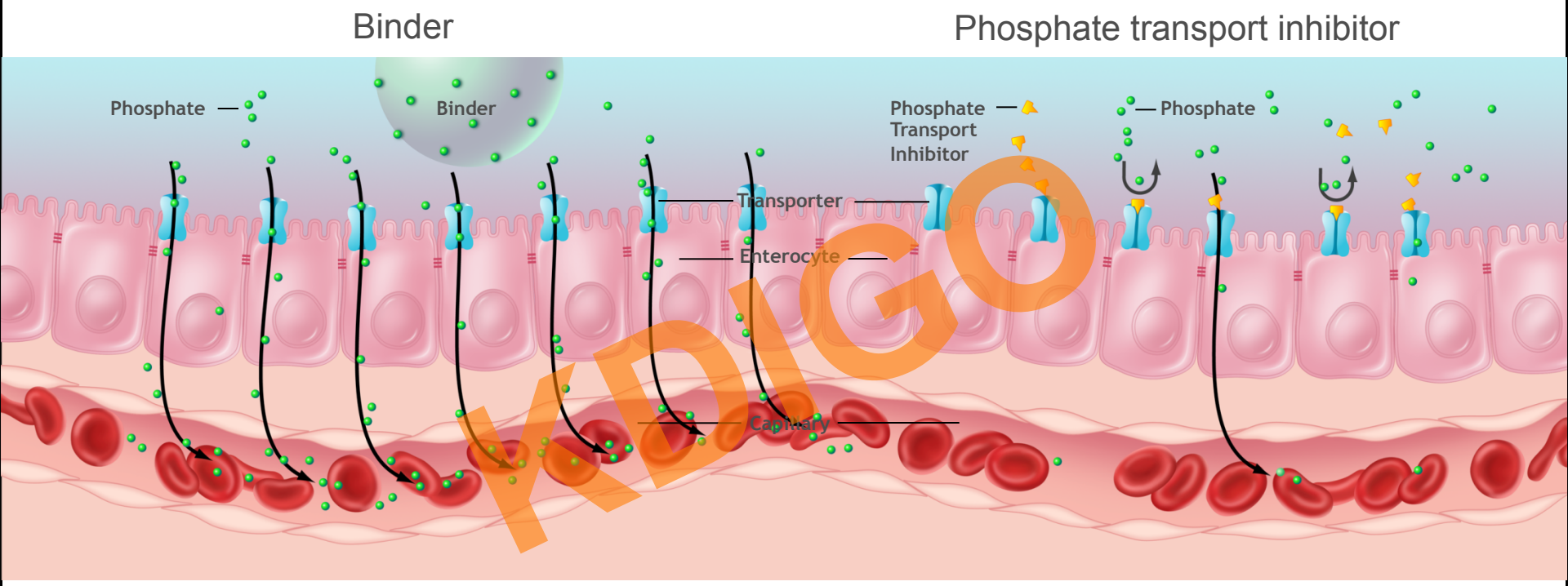

ENTERING
THE
MIDDLE
WHERE ARE WE?

# PROGRESS

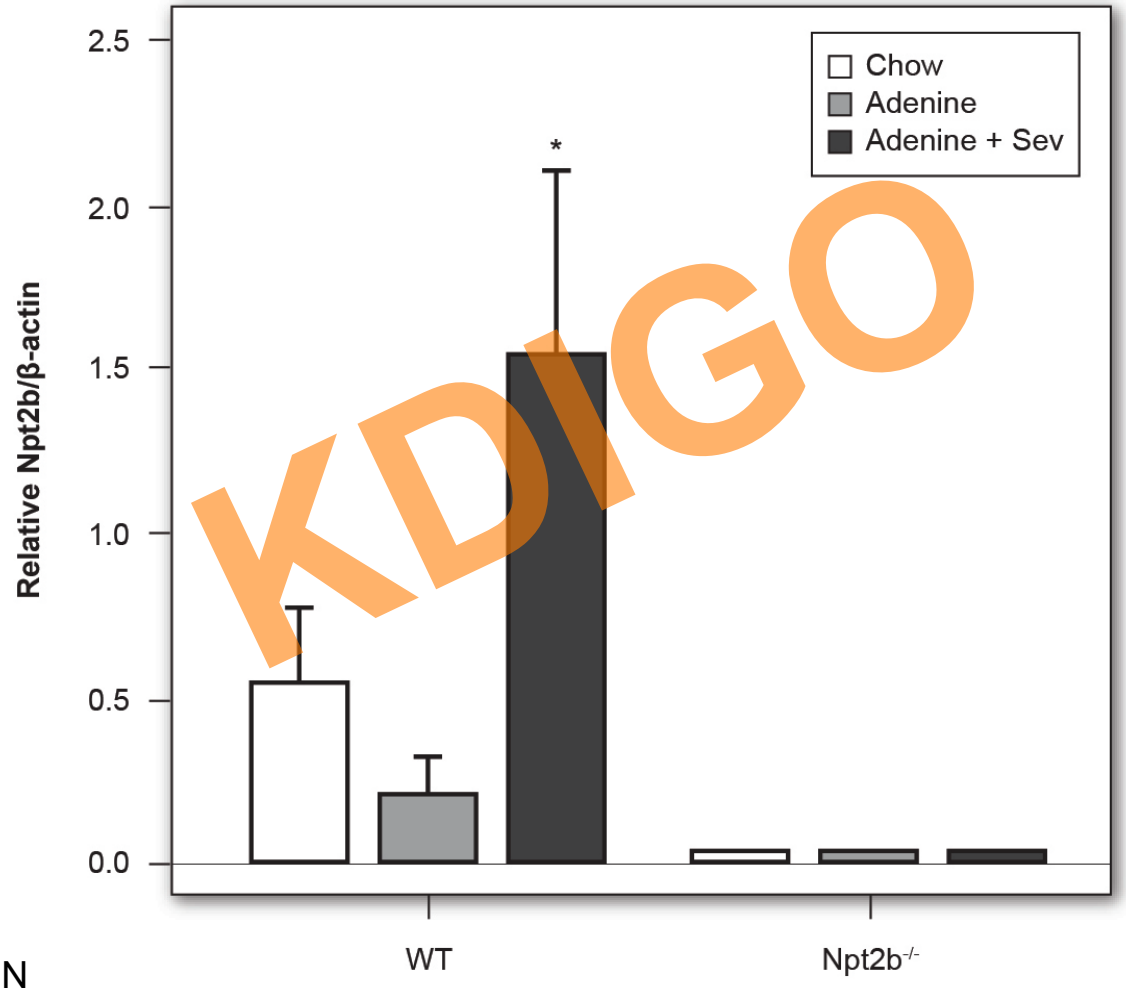

Serum Phosphate (mg/dL)
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
0800
1200
1600
2000
2400
0400
0800
Midday
Midnight
Time of Day
Jubiz et al. 1972, n=10
Portale et al. 1987, n=6


Plasma Phosphate (mg/dl)
4.5
4.0
3.5
3.0
2.5
2000
2400
0400
0800
1200
1600
2000
Time (hrs)
Meat Diet
Vegetarian Diet
Meals
Breakfast
Lunch
Dinner

# Phosphate Absorption: Sodium Dependent, Sodium Independent



# NPT2B Expression in CKD with or without P Binders

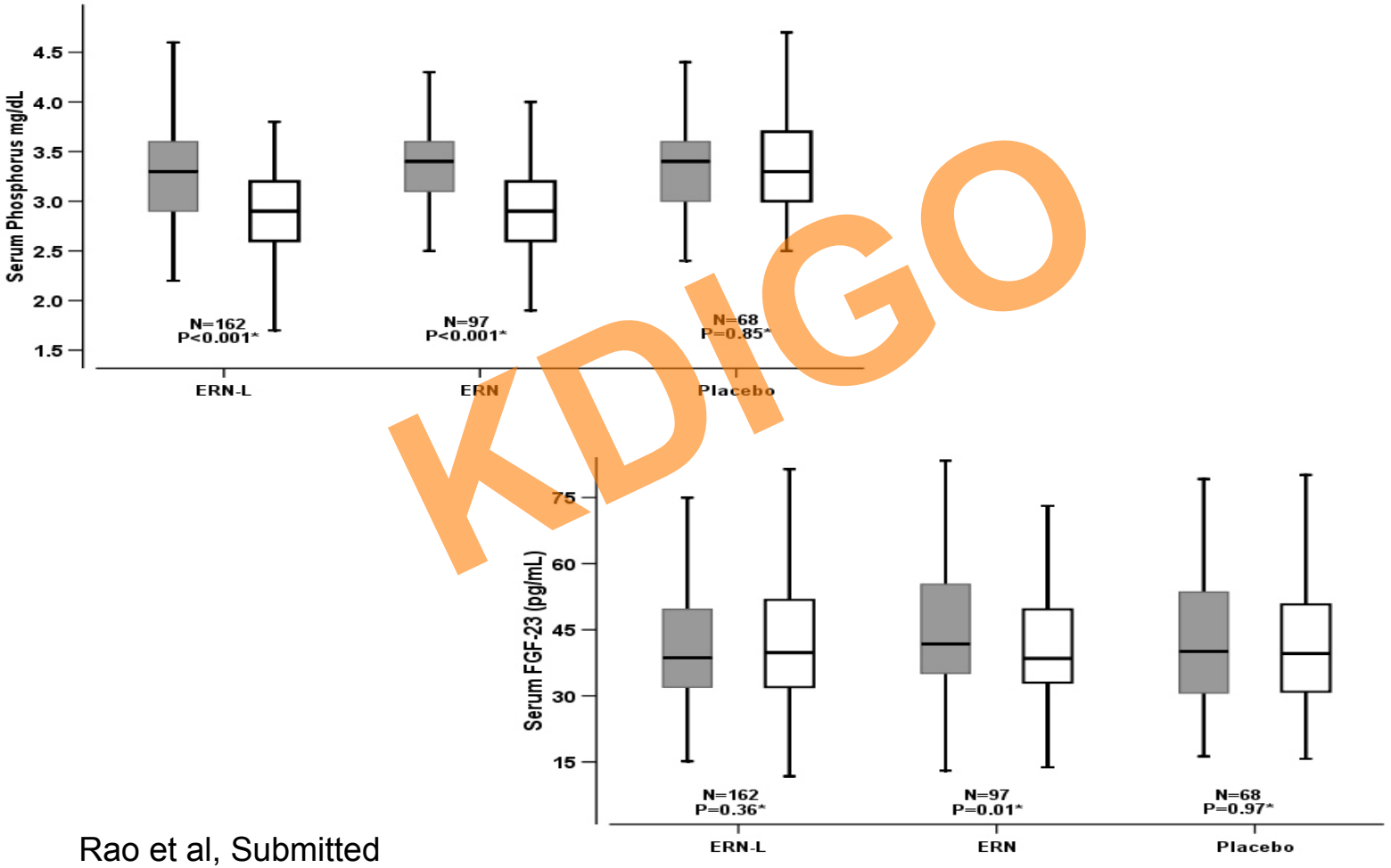





Schiavi, JASN 2012

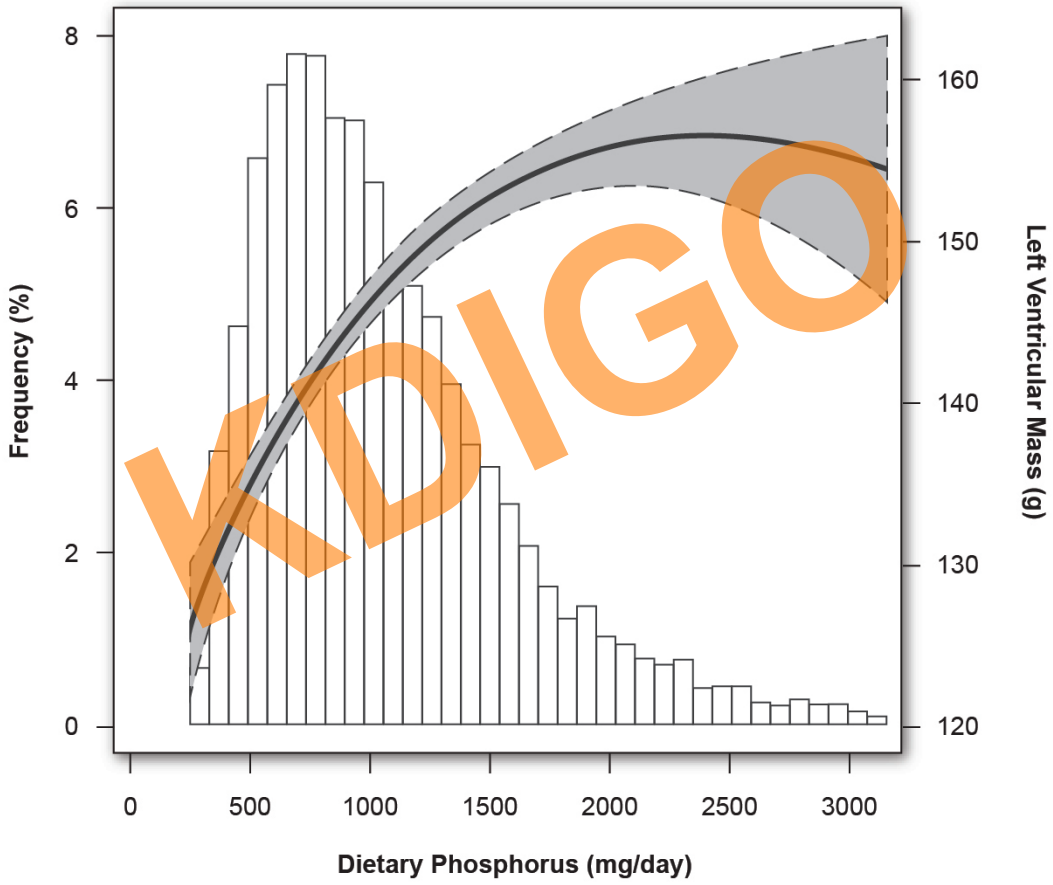
*p.0.05 vs adenine *n*=8-10/group

# Niacin with or without Laropiprant : Differential Effects on Serum P and FGF23



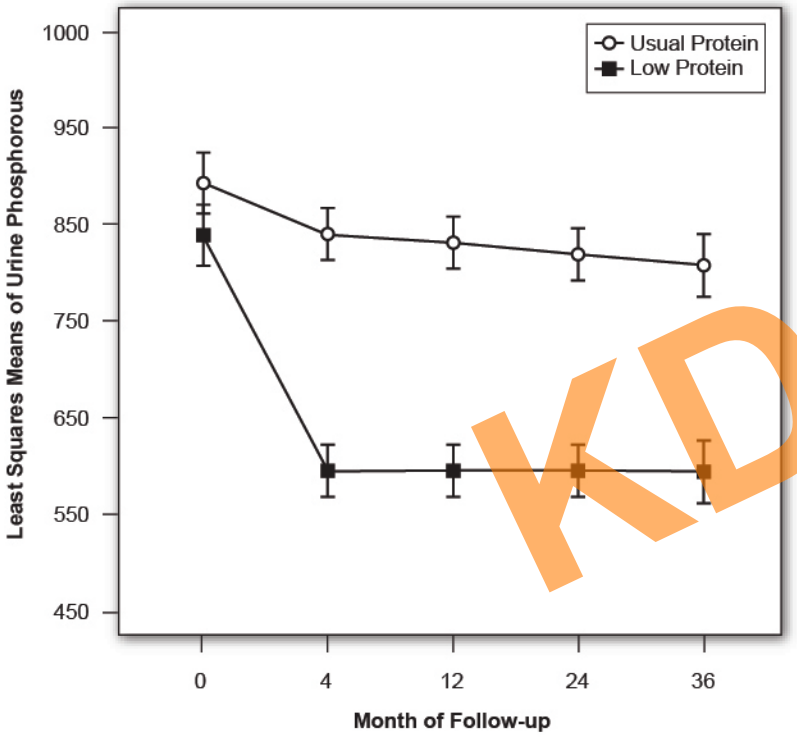


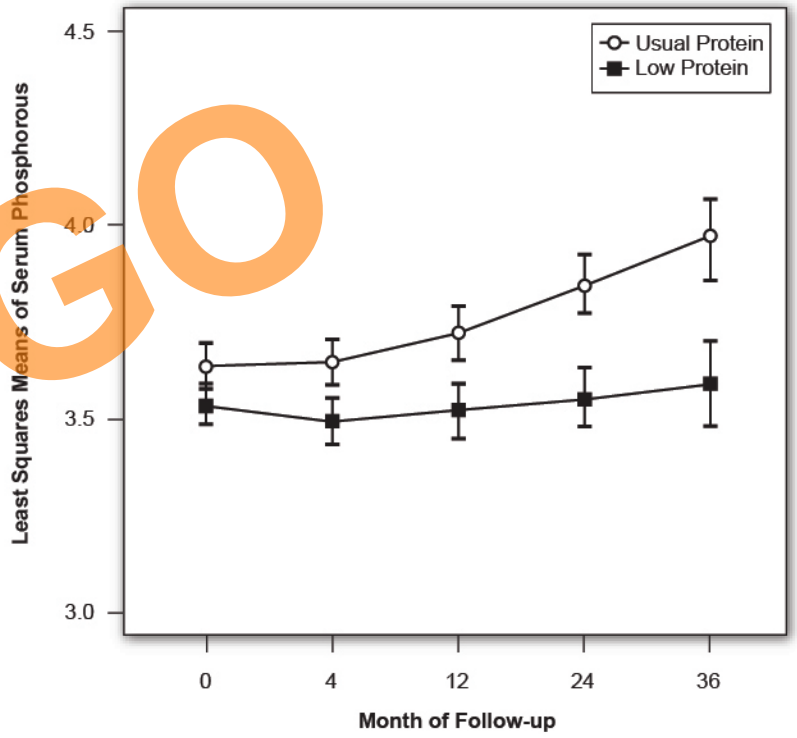

Rao et al, Submitted
NDT 2013




Yamamoto, Kidney Int, 2012, MESA study

MDRD Study A- 585 subjects with eGFR 25-55 ml/min with usual vs. low protein diet

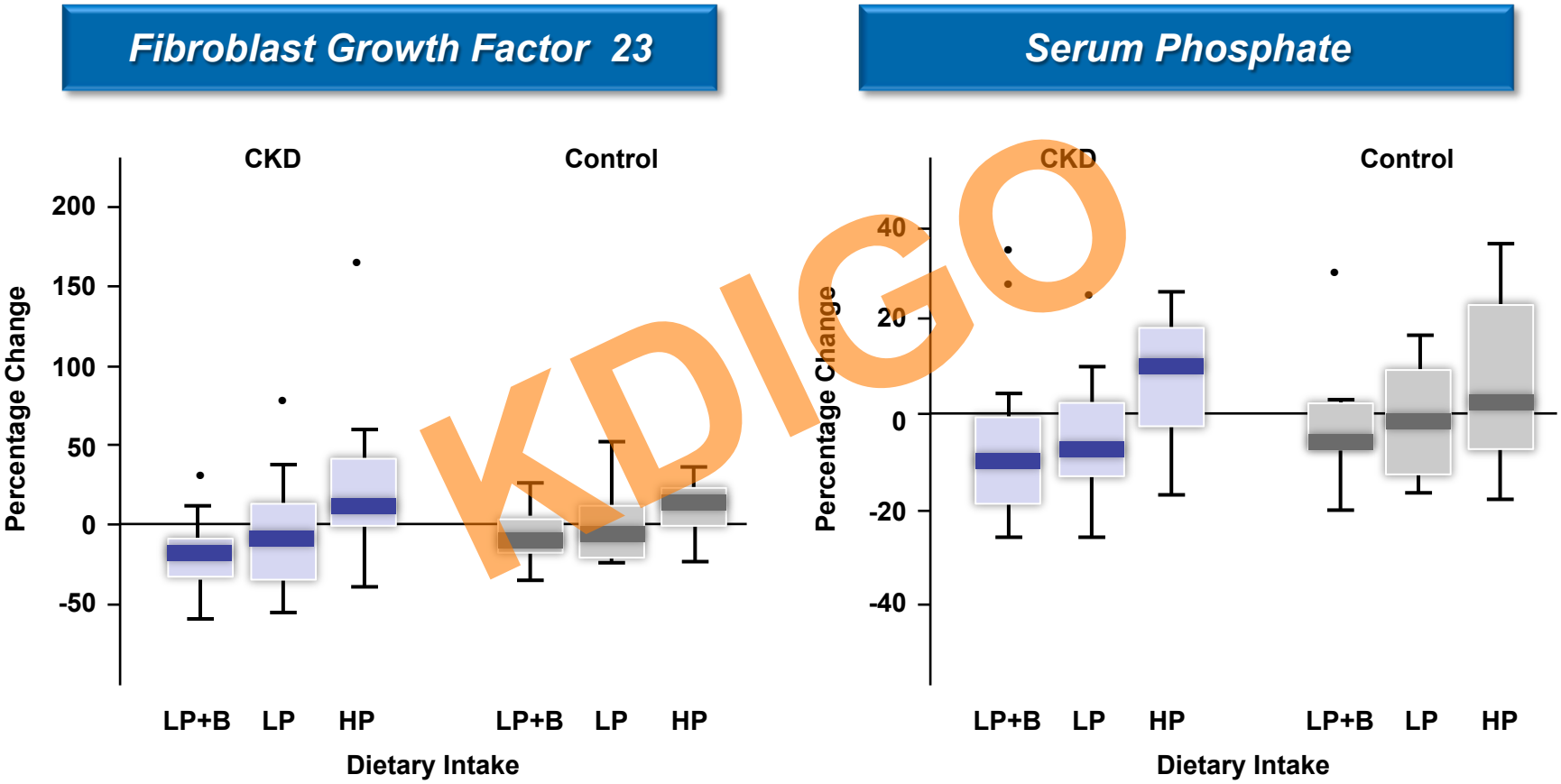





Block, AJKD 2013

# Change in Biochemical Markers

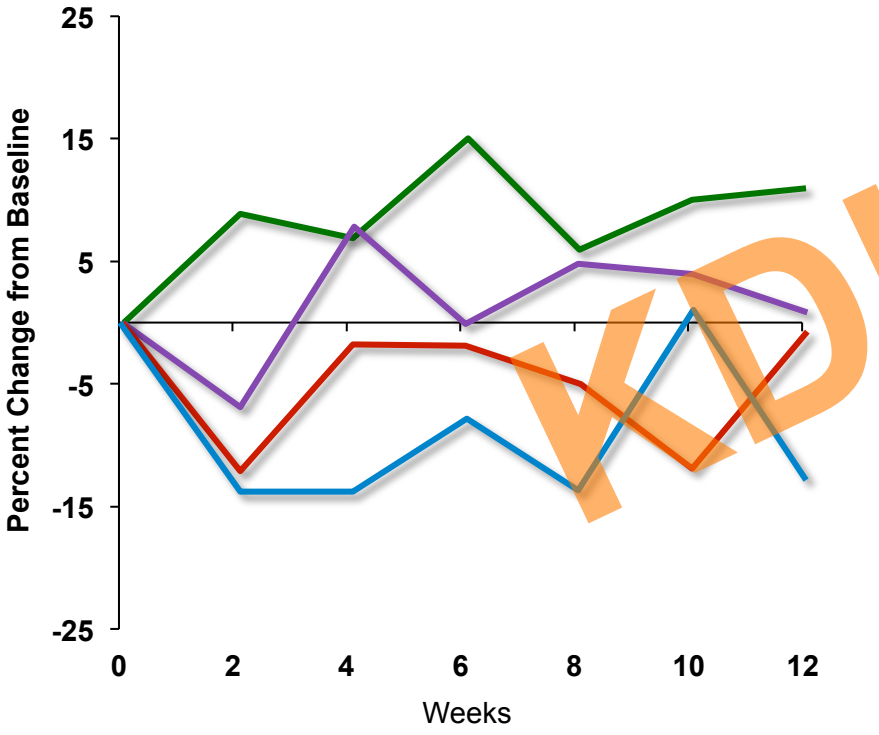




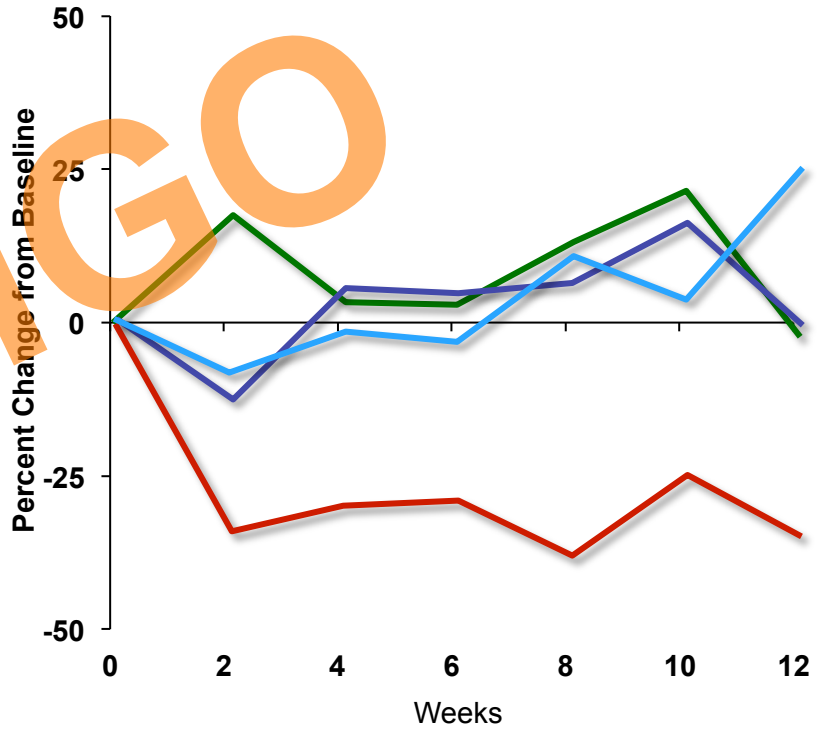

Sigrist M, et al. *Nephrol Dial Transplant.* 2012;0:1–8. Originally published online Sept 28, 2012.

# Combined Effects of Lanthanumcarbonate (LC) and Dietary Intervention on Fibroblast Growth Factor 23 (FGF23)

## Change in Serum Phosphate




## Change in FGF23

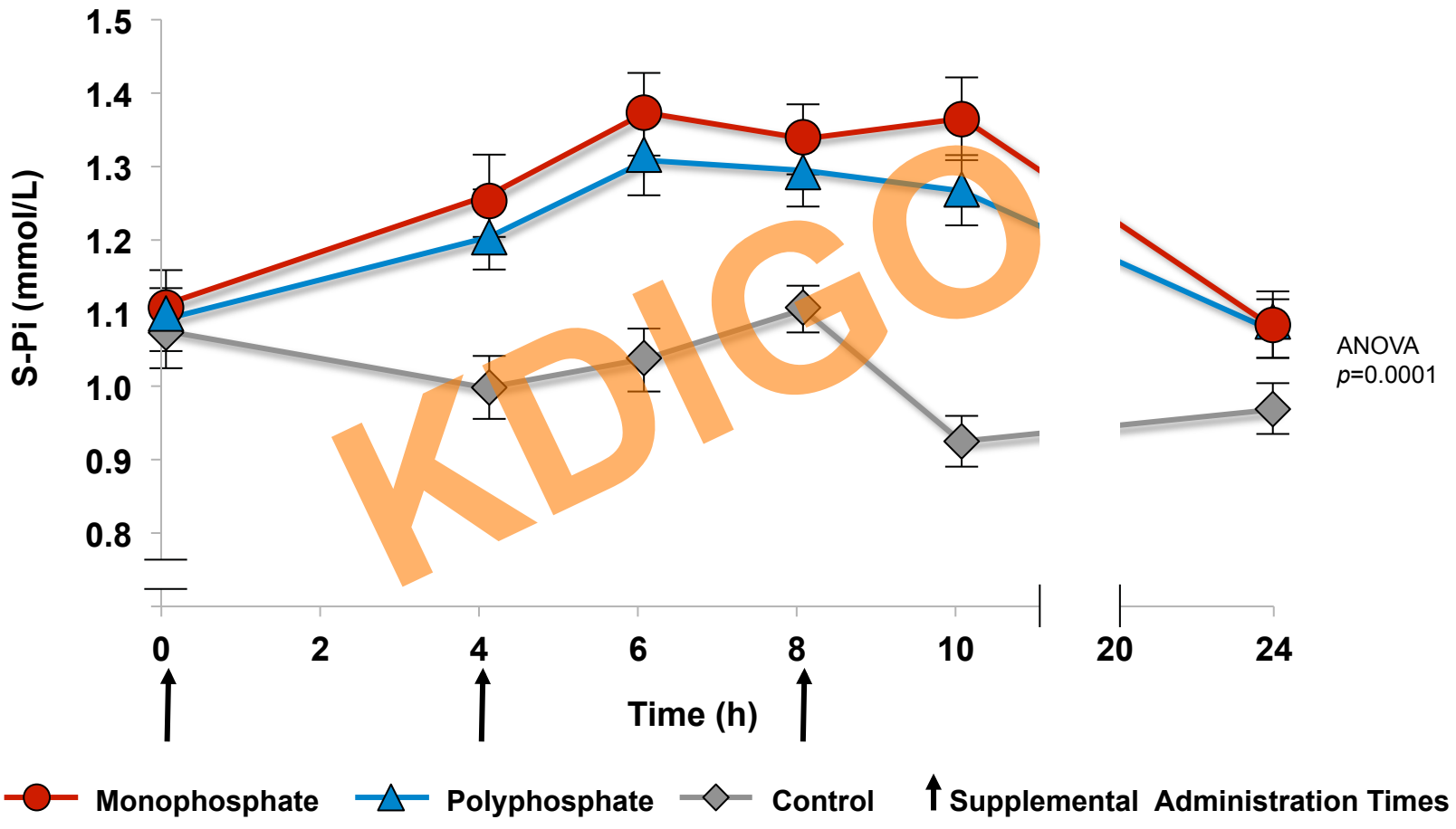



AD Lib Diet + LC Placebo — 900 mg P Diet + LC Placebo — Ad Lib Diet + LC — 900 mg P Diet + LC



Isakova T et al. *Clin J Am Soc Nephrol* 2013;8: doi: 10.2215/CJN.09250912.

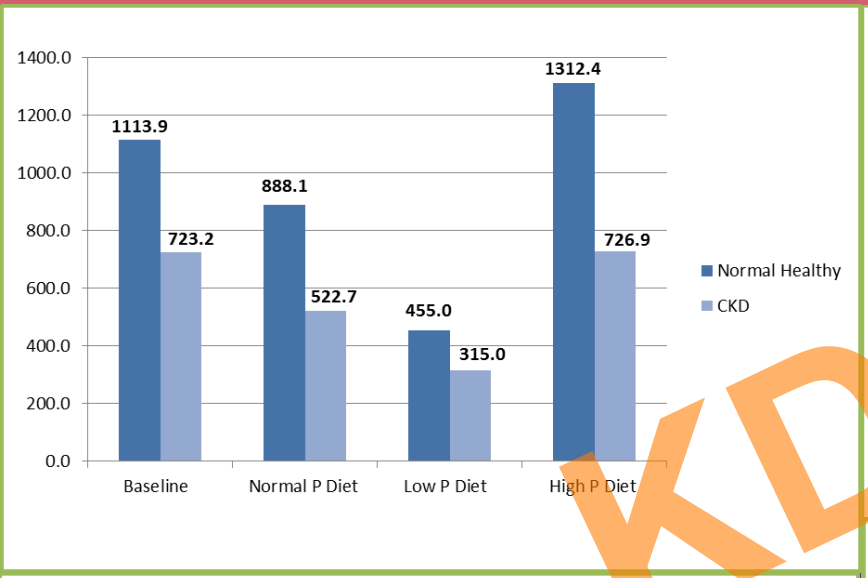
# Changes in Serum Phosphate (S-Pi) Concentration

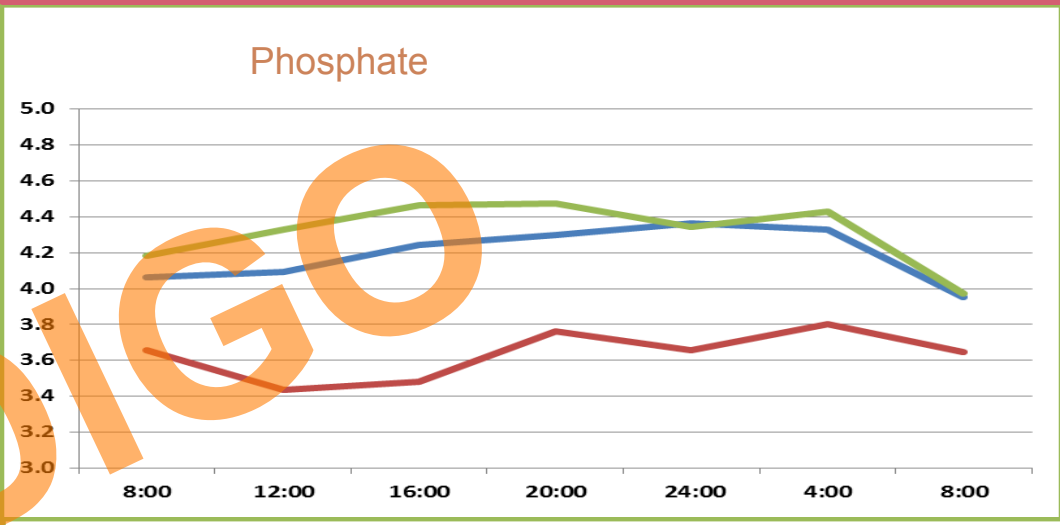


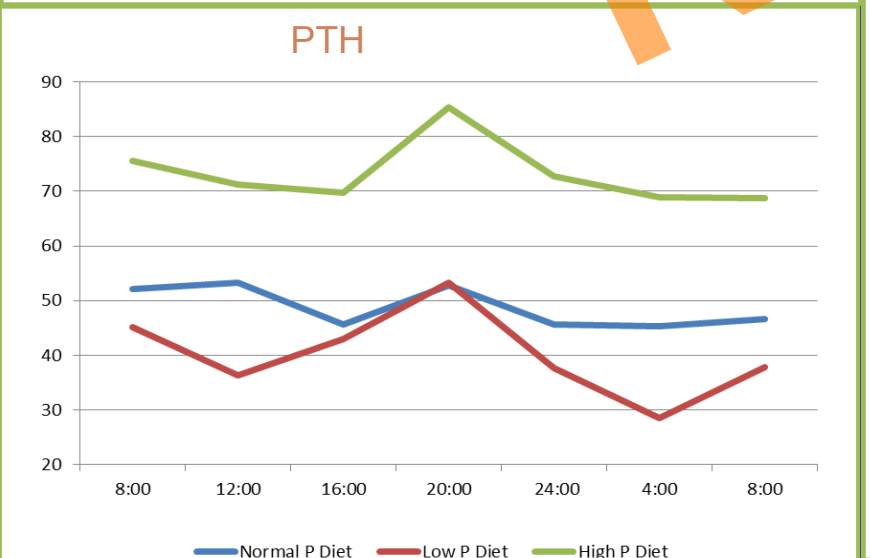

*Significantly different from control session

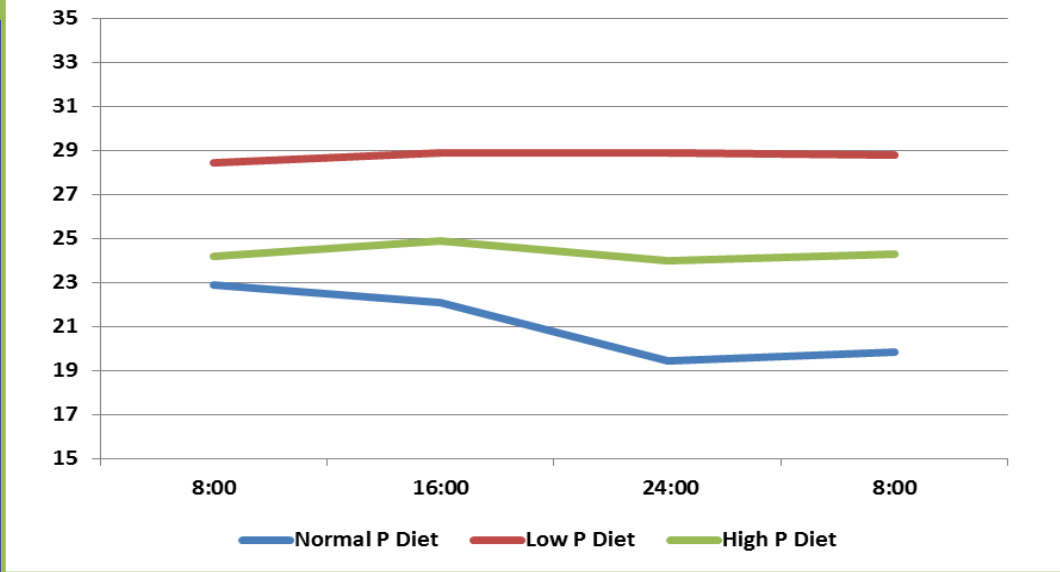
Karp H et al. *Eur J Nutr.* 2013; 52:991–996 DOI 10.1007/s00394-012-0406-5

# Effects of ‘Real’ Food +/- P Binder

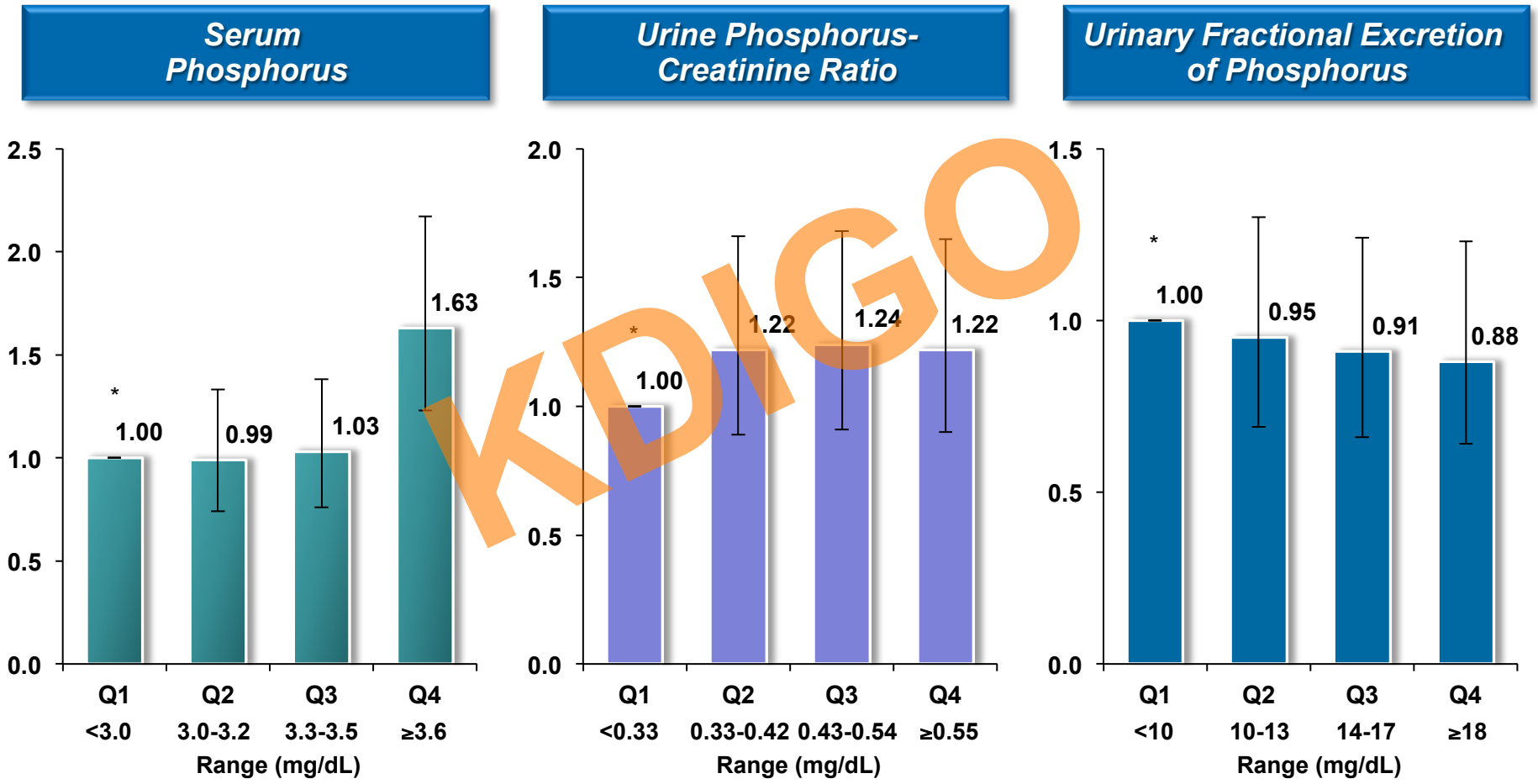


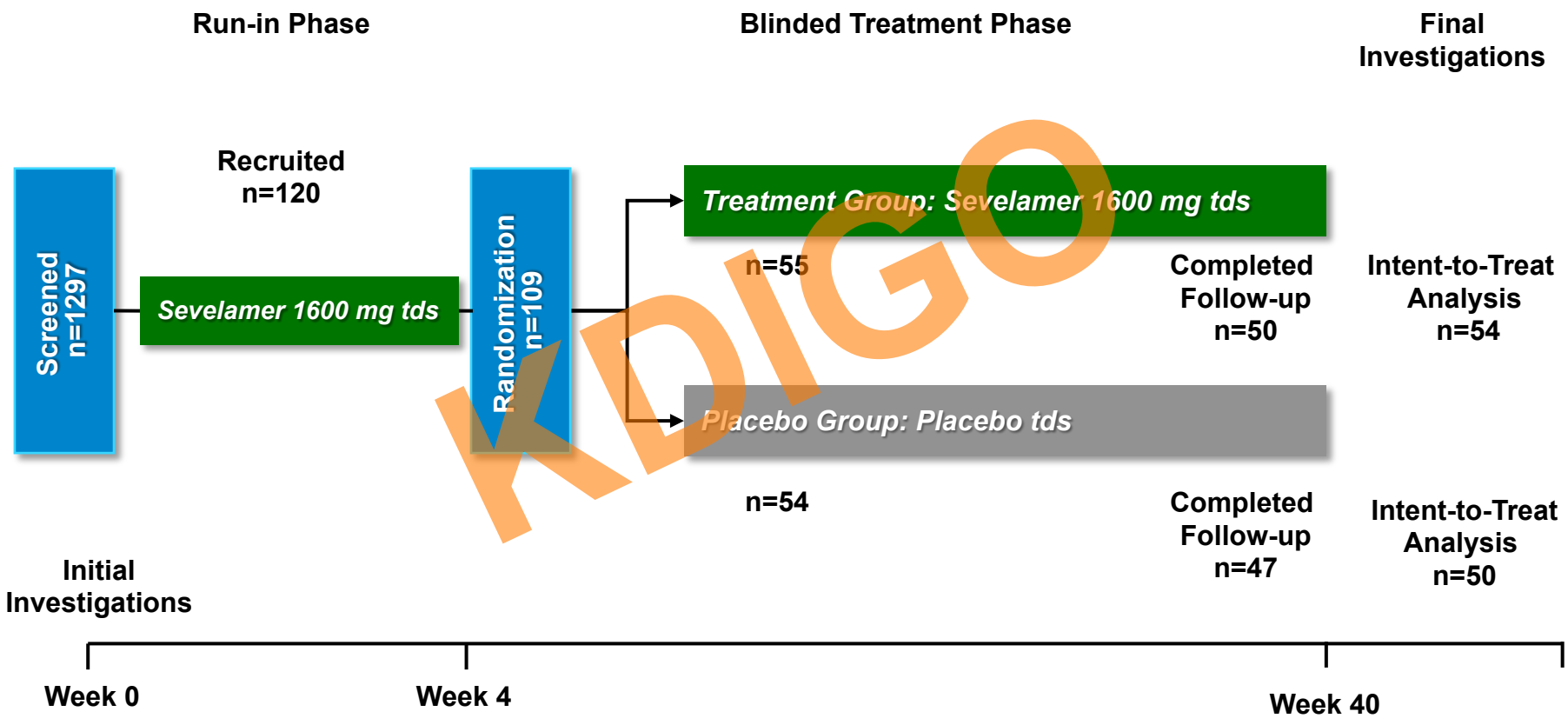
# Association with All-Cause Mortality by Serum P, Urine P:C and Urine FeP






*Reference. Associations given as hazard ratio (95% CI)
Dominguez, JR, et al. *Am J Kidney Dis.* 2012. Article in press.

# Study Design






Chue CD, et al. *J Am Soc Nephrol.* 2013;24: Published online ahead of print.

# Treatment Effects

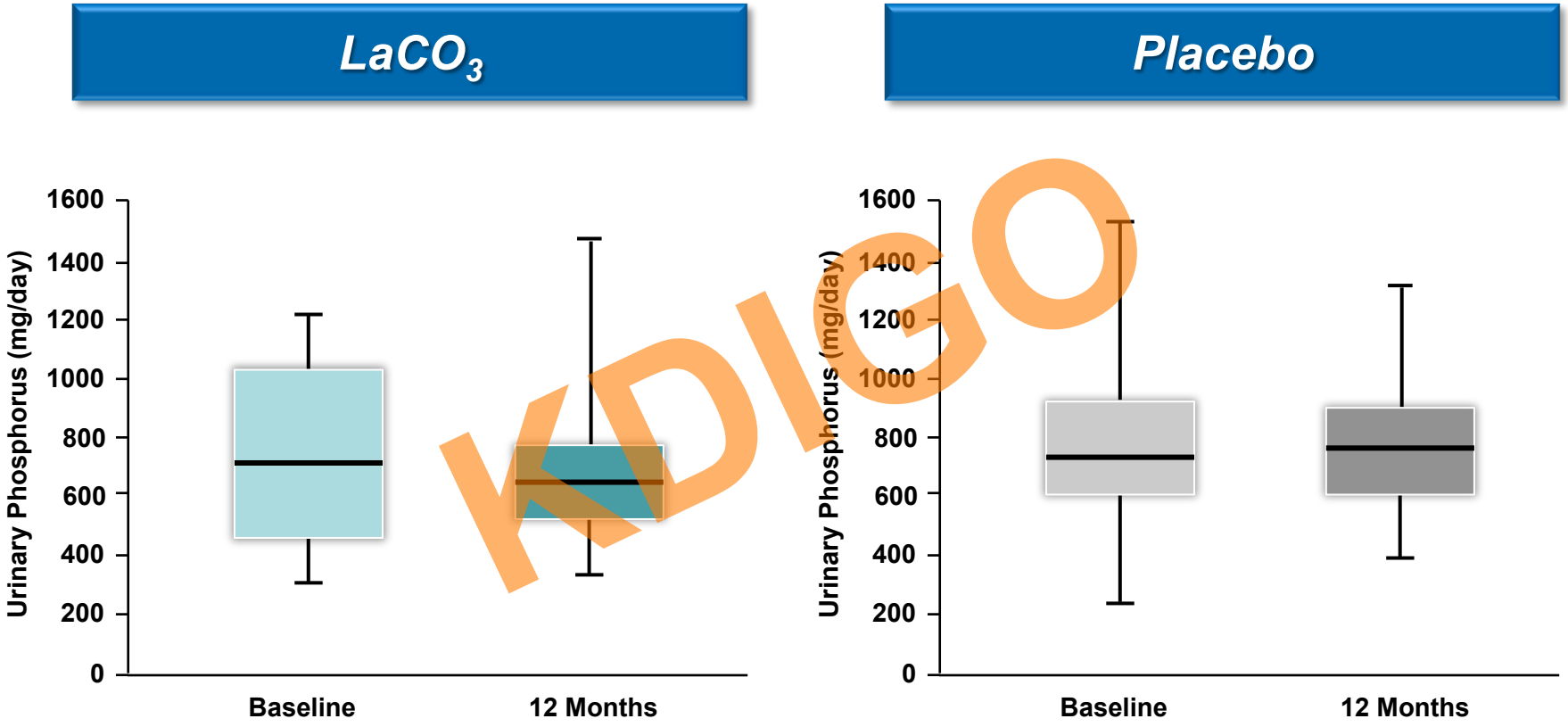
| Biochemical | Placebo (n=50) | | Sevelamer (n=54) | | Mean Difference in Change Between Groups | 95% CI |
|---|---|---|---|---|---|---|
| | Week 0 | Week 40 | Week 0 | Week 40 | | |
| eGFR (ml/min per 1.73 $m^2$) | 49±13 | 50±14 | 49±13 | 48±14 | 1.2 | -1.3–3.6 |
| Bicarbonate (mEq/L) | 26.4±2.8 | 27.2±3.4 | 27.0±2.7 | 27.2±6.2 | 0.6 | -1.3–2.6 |
| Total cholesterol (mg/dl) | 181±42 | 170±46 | 193±50 | 166±54 | 18.7 | -1.9–39.3 |
| LDL cholesterol (mg/dl) | 105±36 | 100±42 | 106±35 | 92±39 | 9.2 | -2.6–21.1 |
| Phosphate (mg/dl) | 3.25±0.53 | 3.31±0.53 | 3.16±0.50 | 3.16±0.71 | 0.06 | -0.18–0.30 |
| Corrected calcium (mg/dl) | 8.80±0.40 | 8.76±0.32 | 8.88±0.36 | 8.84±0.32 | 0.00 | -0.14–0.15 |
| PTH (pg/ml)* | 54 (37–73) | 51 (39–72) | 52 (39–70) | 52 (35–75) | -3.1 | -10.4–4.3 |
| FGF-23 (pg/ml)* | 67.6 (51.1–87.7) | 63.6 (52.0–83.6) | 70.8 (52.5–83.0) | 65.9 (49.2–90.7) | 0.8 | -7.7–9.3 |
| Klotho (pg/ml) | 869±279 | 873±320 | 1001±500 | 980±533 | 40 | -58–139 |
| 1,25-dihydroxyvitamin D (pg/ml) | 28.8±12.7 | 26.1±10.8 | 28.5±10.3 | 27.3±10.4 | -3.6 | -13.8–6.7 |
| 25-hydroxyvitamin D (ng/ml) | 22.2±12.5 | 21.9±12.3 | 23.0±11.2 | 23.4±13.3 | -2.2 | -11.1–6.8 |



*Log-transformed before analysis.

Chue C et al. *J Am Soc Nephrol. 2013;*24.

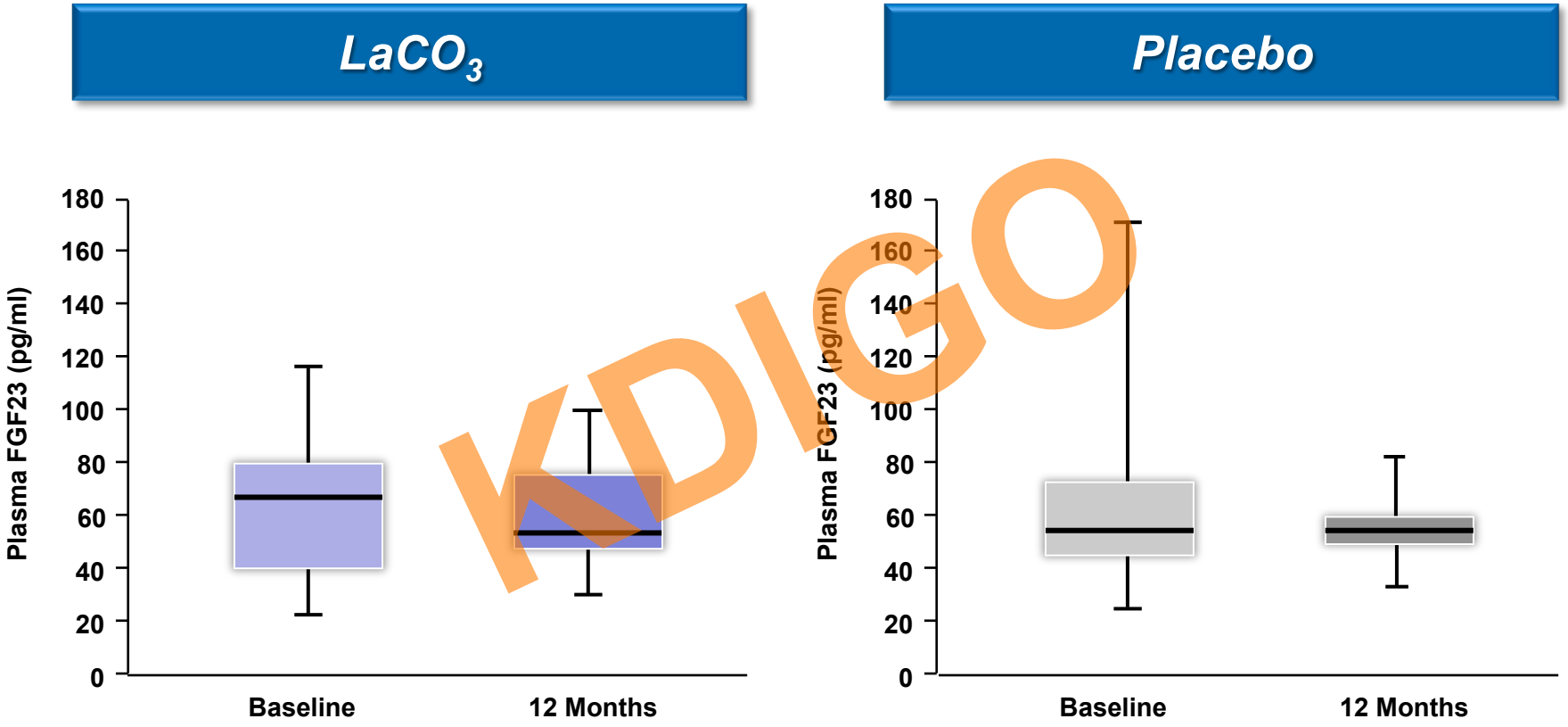
# Lanthanum Carbonate vs. Placebo in Stage 3 CKD




38 subjects- no dietary intervention. La 1000 mg TID

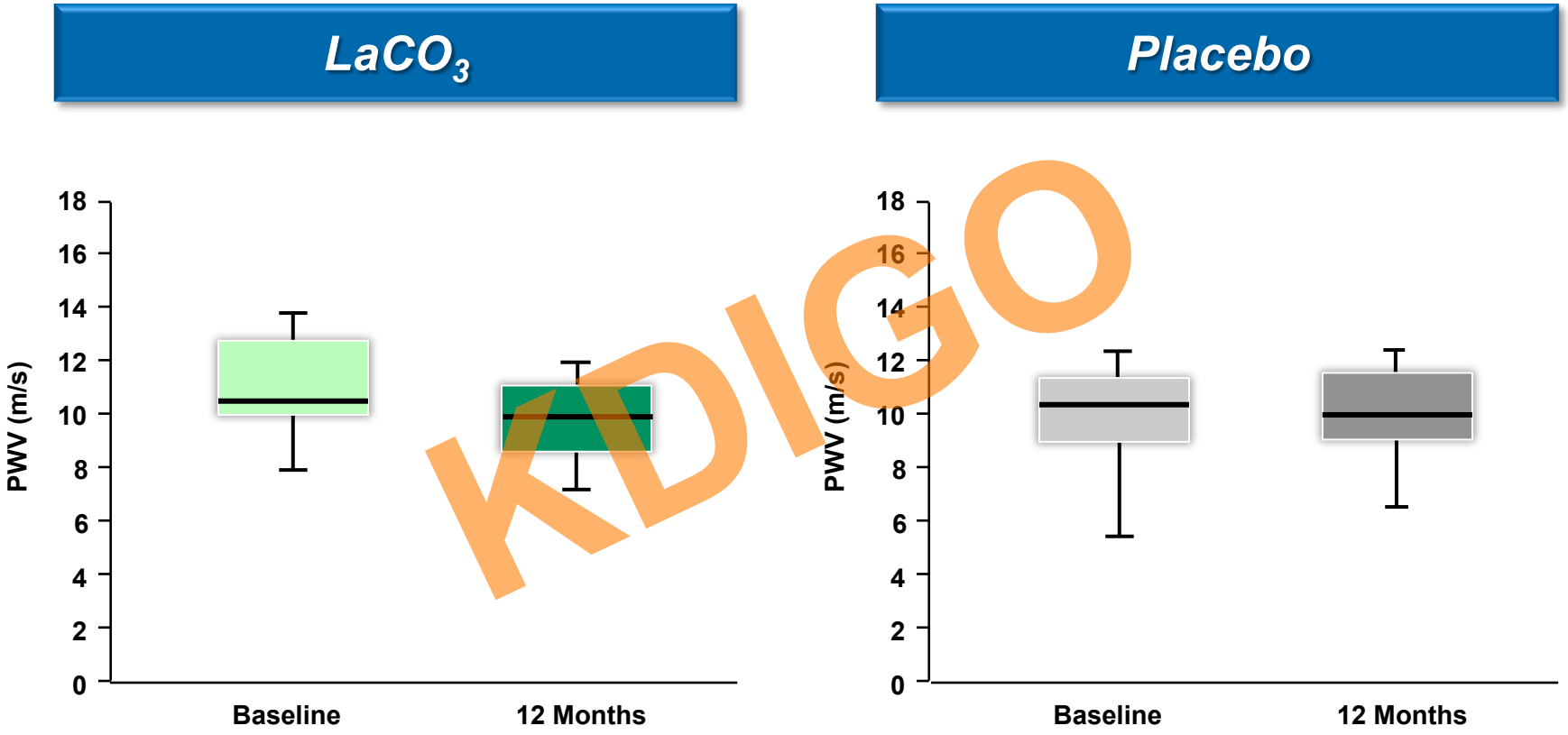
Seifert ME, et al. *Am J Nephrol.* 2013;38:158–167.

# FGF23 Levels




Seifert ME, et al. *Am J Nephrol.* 2013;38:158–167.

# Effect of $LaCO_3$ on PWV






Seifert ME, et al. *Am J Nephrol.* 2013;38:158–167.

# Calcium Acetate vs. Sevelamer in CKD

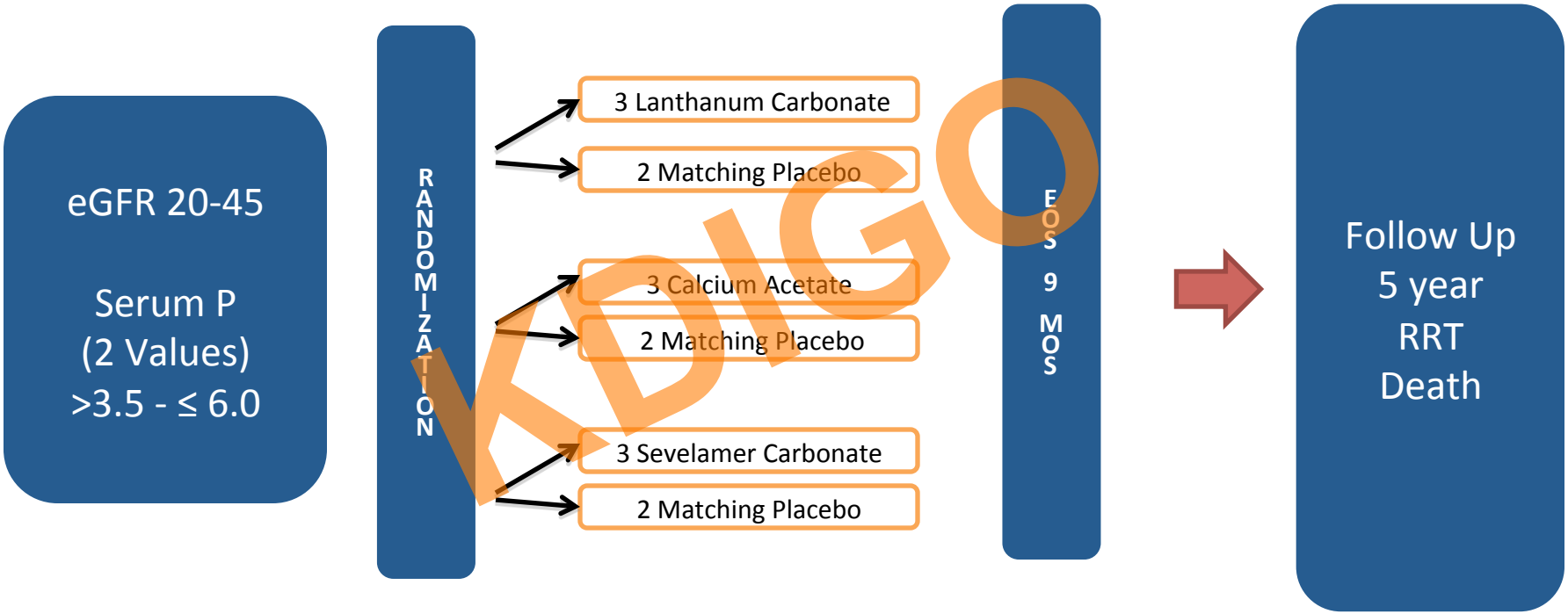
| | Sevelamer | | | Calcium Acetate | | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | 8 Wk | % Change (95% CI) | Baseline | 8 Wk | % Change (95% CI) | Diff Btw % Δ at 8 Wk (95% CI)* | P† |
| Serum phosphate (mg/dl) | 7.7 | 5.3 | -31.1 (-34.9 to -27.1) | 7.7 | 6.5 | -14.9 (-19.1 to -10.9) | -16.2 (-15.8 to -16.5) | <0.001 |
| iPTH (pg/mL) | 159.4 | 166.1 | 4.5 (0.3 to 8.7) | 145.9 | 161.5 | 11.7 (5.6 to 17.8) | -7.2 (-5.3 to -9.1) | 0.1 |
| FGF-23 (pg/mL) | 39.9 | 28.9 | -27.1 (-33.2 to -8.8) | 38.9 | 37.4 | 3.5 (-8.4 to 12.1) | -30.6 (-20.9 to -41.6) | 0.002 |
| eGFR (mL/min/1.73 $m^2$) | 23.8 | 22.4 | -5.3 (-8.9 to -1.6) | 21.9 | 20.7 | -4.7 (-8.3 to -1.1) | -0.6 (-0.7 to 0.6) | 0.8 |



N= 47 Sevelamer; 53 Calcium Acetate
† Statistical analysis comparing changes seen with sevelamer with those seen with calcium acetate.
Yilmaz MI et al. *Am J Kidney Dis.* 2012;59(2):177-185

# PNT Trial

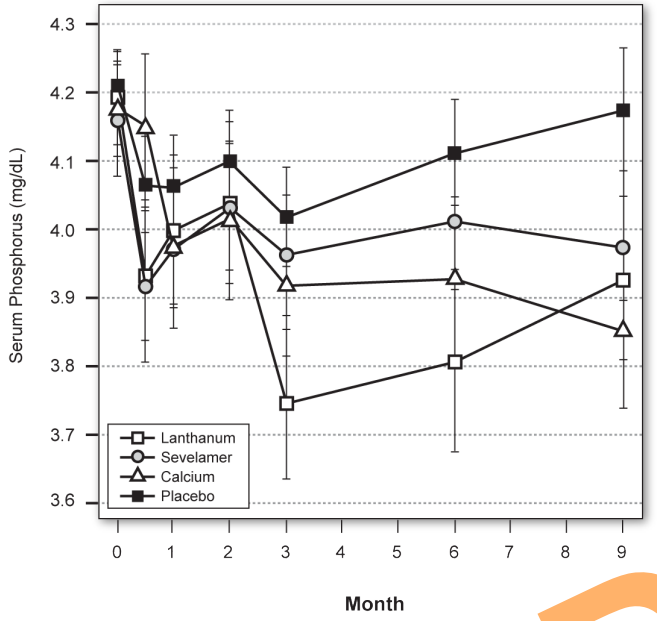
PILOT study with primary goal to inform treatment effect for design of larger outcome based RCT
Does active treatment with P binders lower serum P over 9 months compared to placebo?
Does reduction of serum P OR treatment with P binders affect biochemical, vascular or skeletal outcomes?



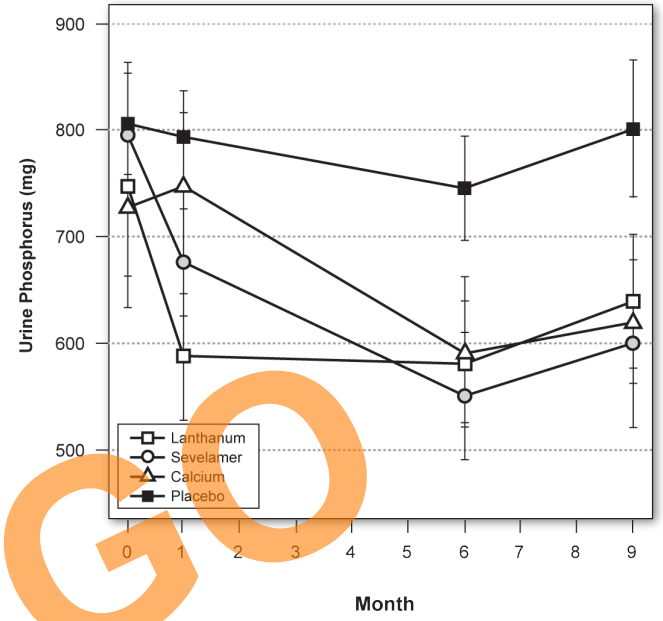



**VISIT SCHEDULE**
Screen , Baseline, Week 2, Month 1, Month 2, Month 3, Month 6, Month 9

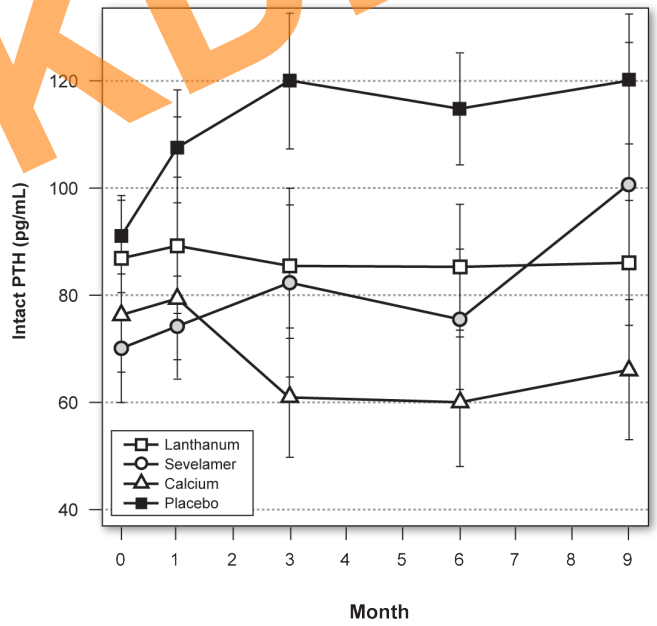
## Serum Phosphorus



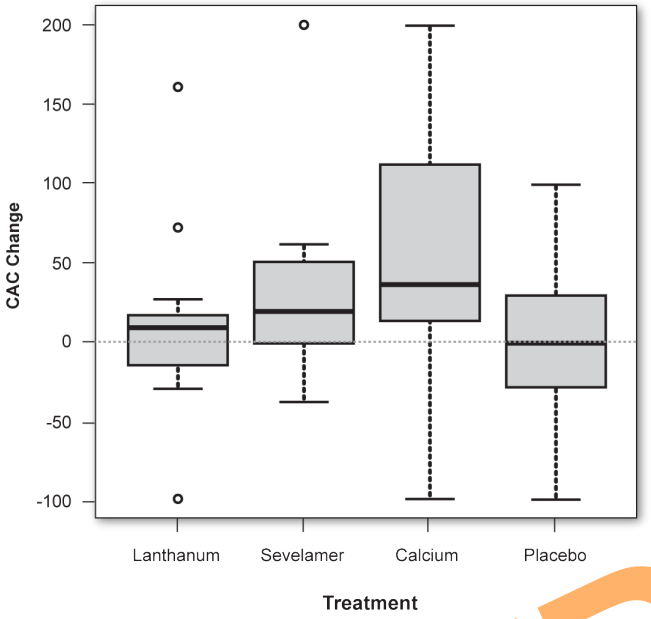

## 24 Hour Urine Phosphorus



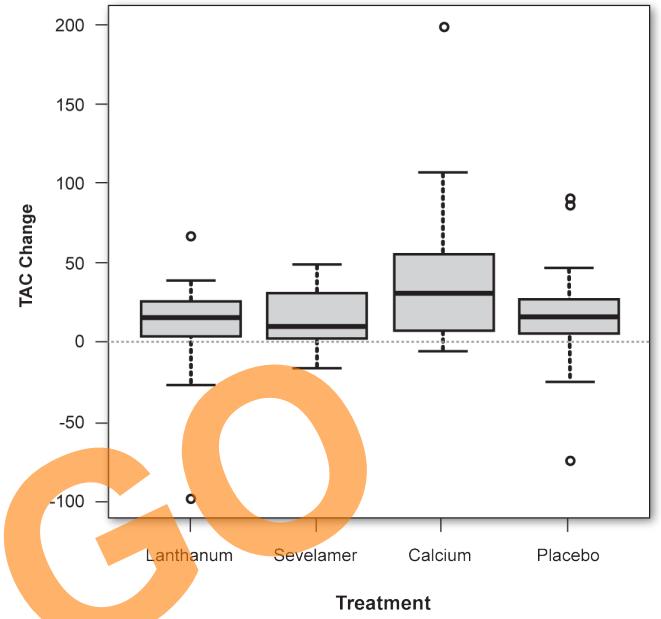

## Intact PTH



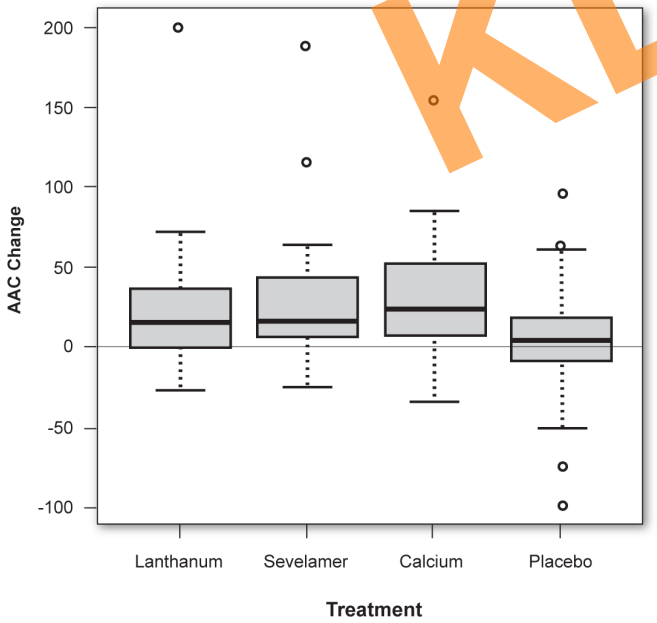
## Change in Coronary Artery Calcium Volume



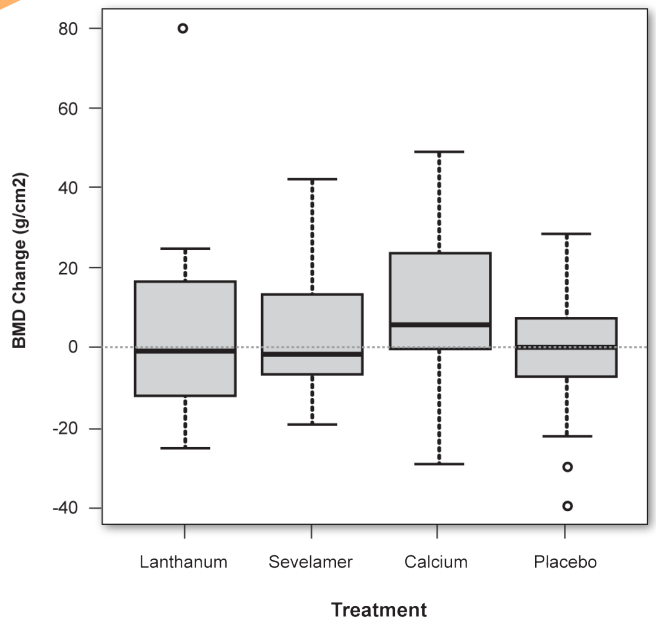

## Change in Thoracic Aorta Calcium Volume

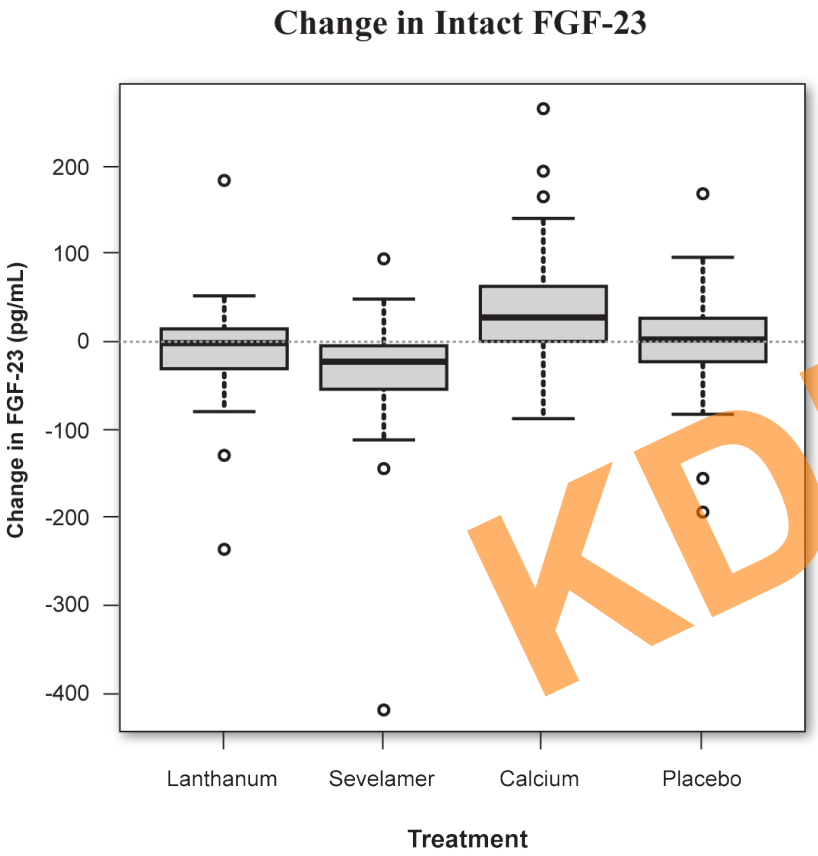


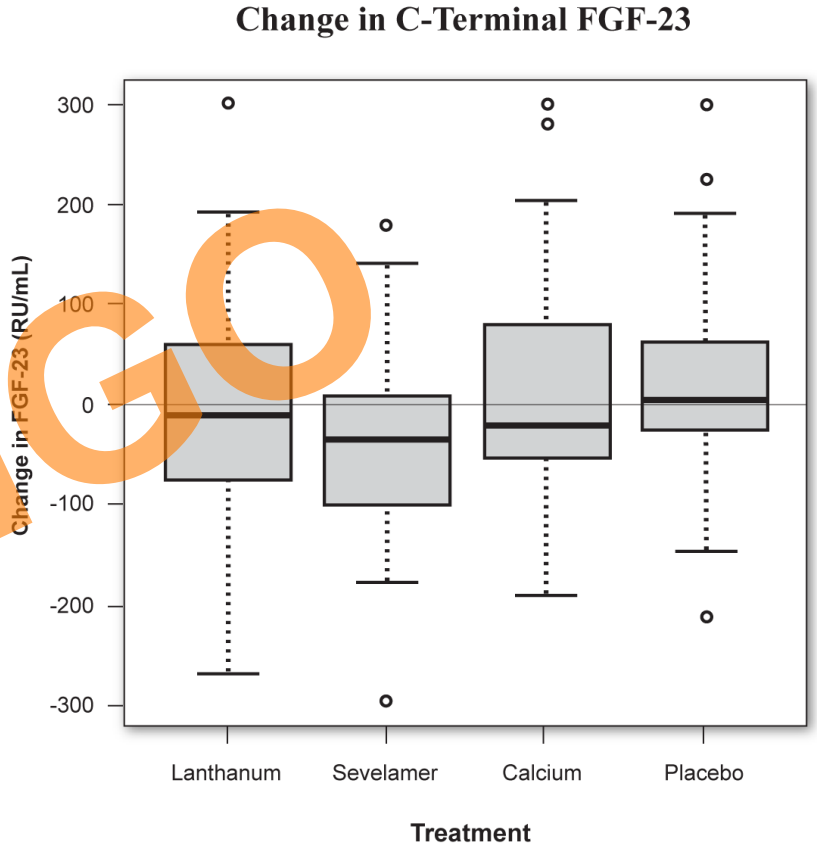

## Change in Abdominal Aorta Calcium Volume




## Change in Bone Mineral Density

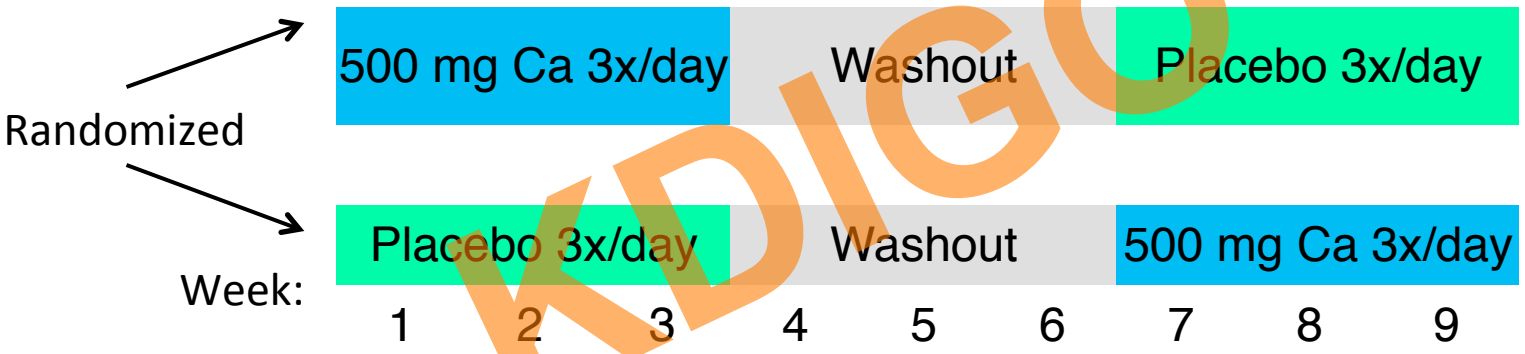



Change in Intact FGF-23
Change in FGF-23 (pg/mL)
200
100
0
-100
-200
-300
-400
Lanthanum
Sevelamer
Calcium
Placebo
Treatment


Change in C-Terminal FGF-23
Change in FGF-23 (RU/mL)
300
200
100
0
-100
-200
-300
Lanthanum
Sevelamer
Calcium
Placebo
Treatment

# Balance and kinetic study design

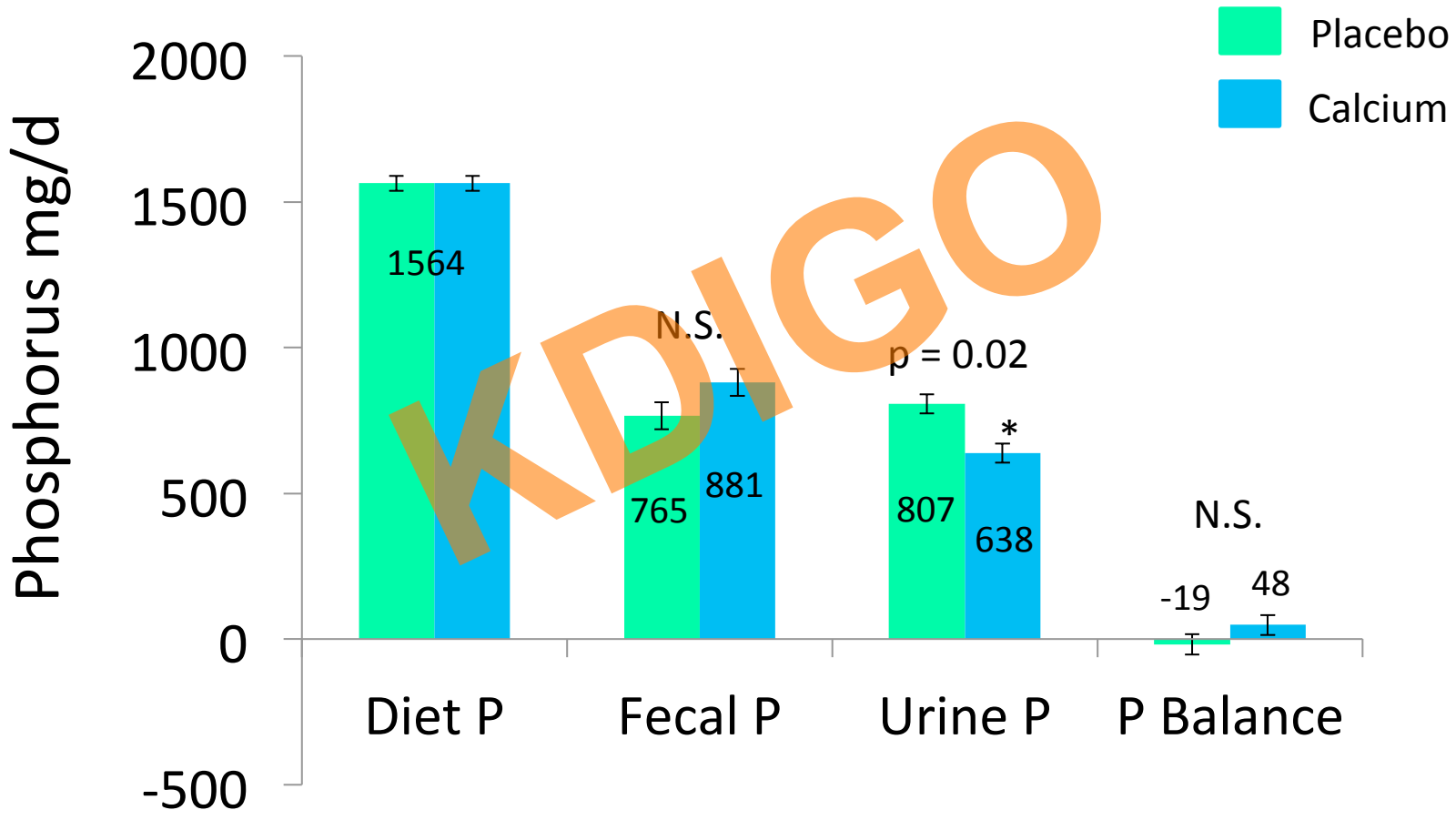
- Randomized placebo-controlled trial with cross-over in 7 patients with CKD stage 3/4






- Week 1 of each 3 week balance period – equilibration period
- Weeks 2 & 3 of each 3 week balance period – urine and fecal collections

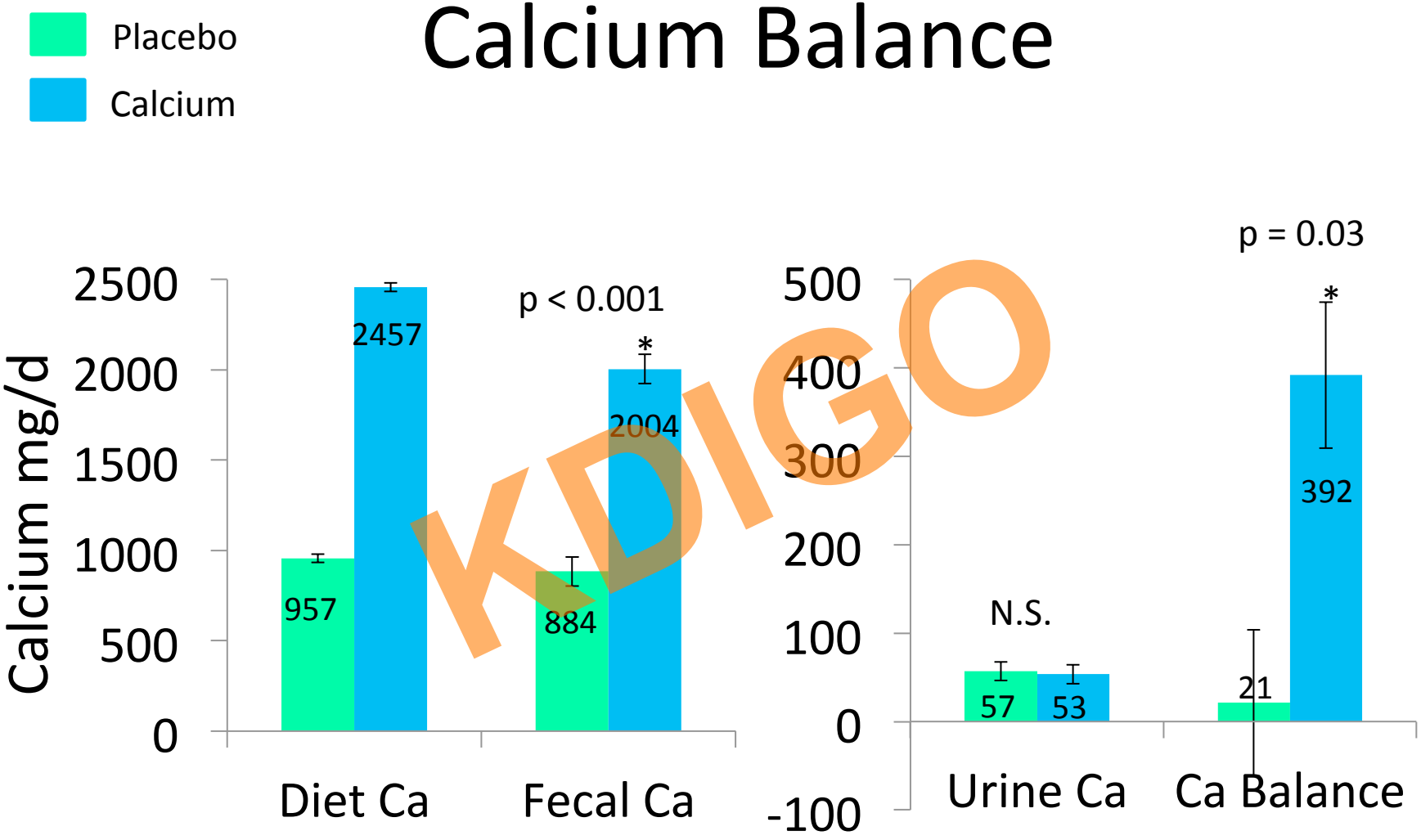
# Challenging the Concept of Phosphate 'Load'






Hill et al, 2012

# Calcium Balance



# Calcium Absorption in CKD

**Table 2. Participants' laboratory results**

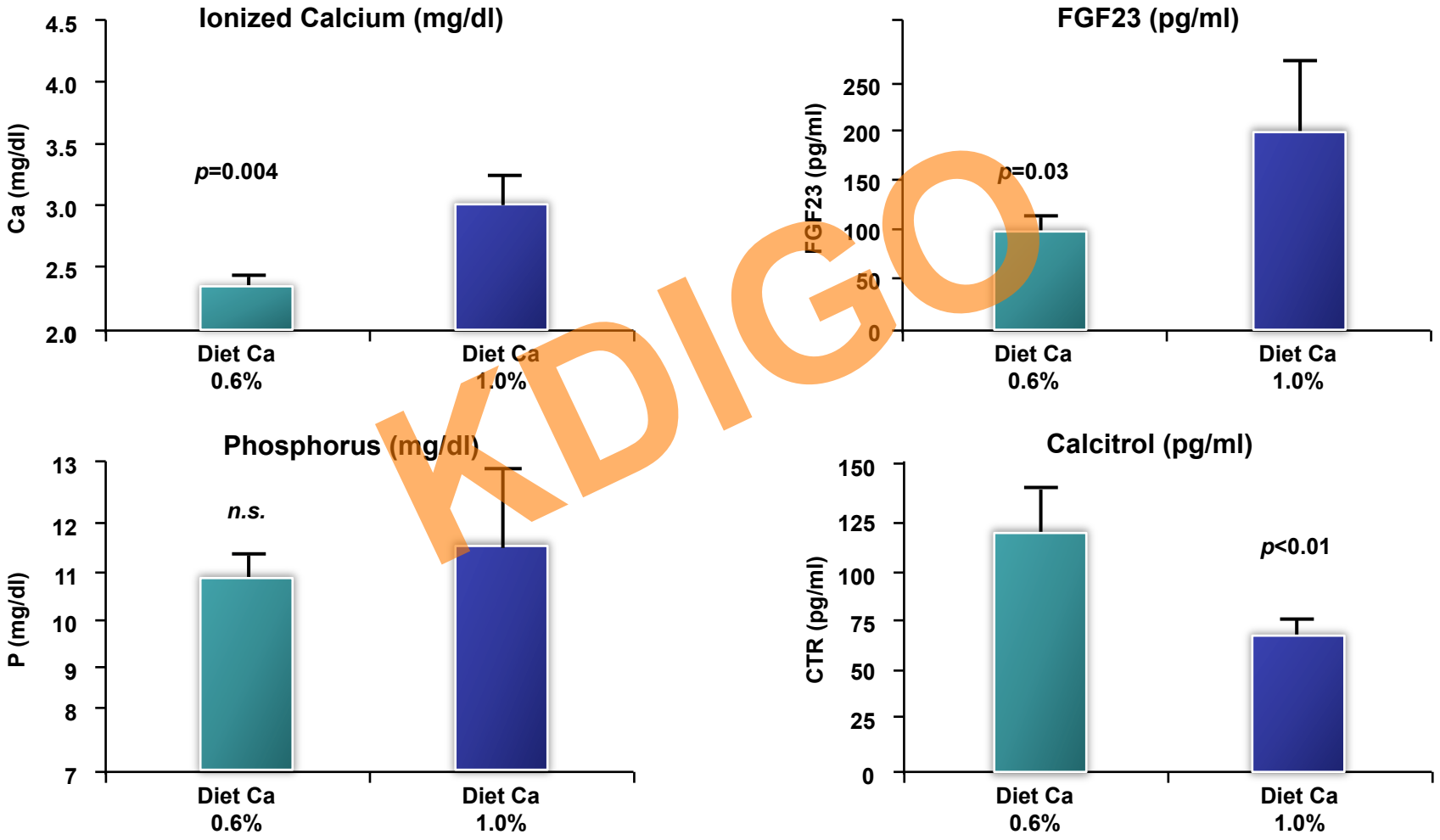
| *N* | 30 | | | |
|---|---|---|---|---|
| | Baseline | Post-treatment | Change | *P*[a] |
| FxAbs (%)[b] | 12 (7–17) | 12 (7–16) | 0.01 (−0.05 to 0.03) | 0.50 |
| 25(OH)D (ng/ml) | 14.2 (11.5–18.5) | 49.3 (42.3–58.1) | 32.0 (27.5–40.6) | <0.001 |
| Calcium (mg/dl) | 9.0 (8.5–9.5) | 9.0 (8.5–9.2) | −0.0 (−0.3 to 0.1) | 0.82 |
| Albumin (g/dl) | 3.6 (3.4–3.8) | 3.6 (3.4–3.9) | 0.1 (−0.0 to 0.2) | 0.48 |
| Corrected calcium[c] | 9.3 (8.7–9.9) | 9.2 (8.8–9.6) | −0.2 (−0.3 to 0.4) | 0.53 |
| Phosphorus (mg/dl) | 5.9 (4.7–7.1) | 5.8 (4.7–6.6) | −0.5 (−1.3 to 0.7) | 0.25 |
| Parathyroid hormone (pg/ml) | 325 (218–552) | 376 (269–611) | 42 (−127 to 218) | 0.28 |
| $1,25(OH)_2D$ (pg/ml) | 15.1 (10.5–18.8) | 20.5 (17.0–24.7) | 5.6 (1.9–11.1) | 0.002 |

Median (interquartile range).
[a]*P* value for individual change from baseline to end of study (paired *t* test).
[b]Calcium absorption fraction.
[c]Corrected calcium=((0.8×(4.0−subject's albumin))+subject's serum calcium).



Armas, CJASN 2013

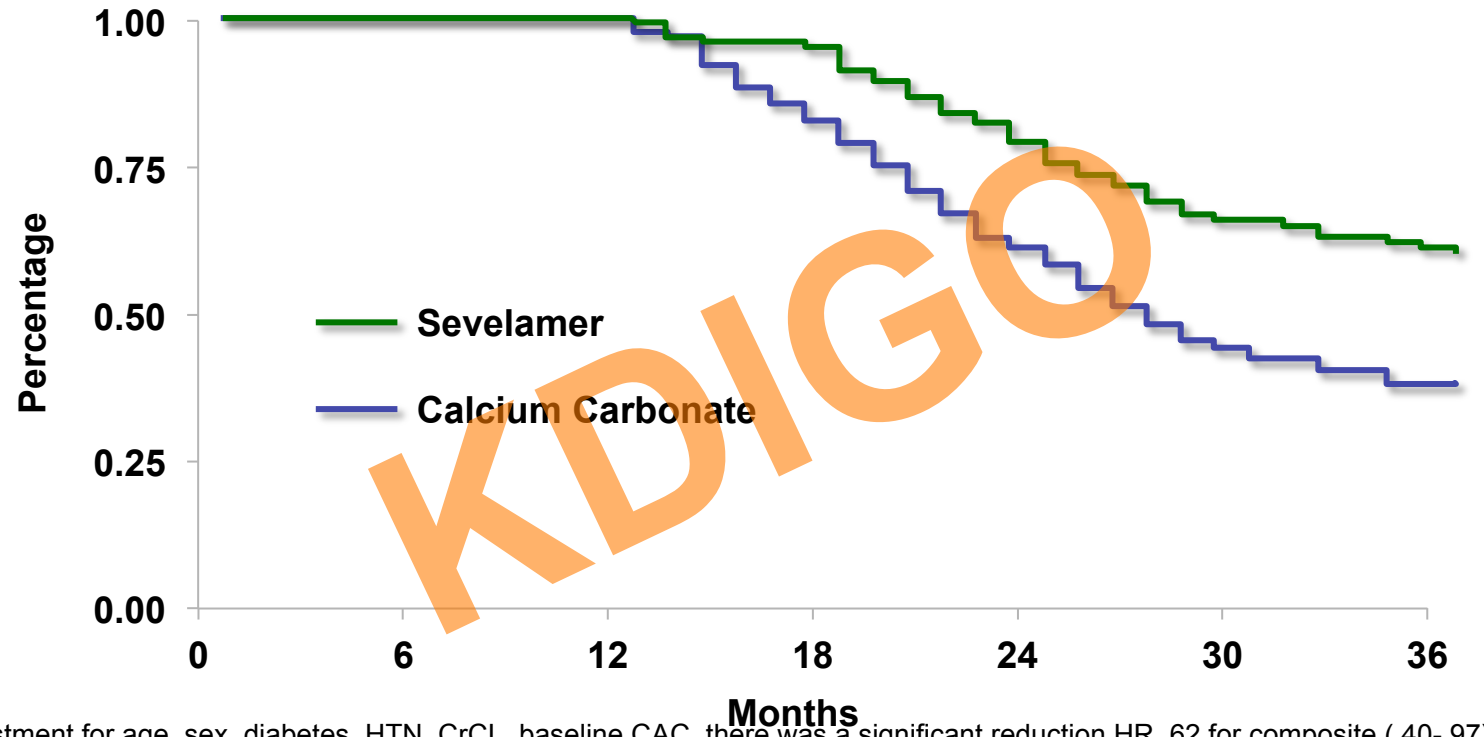
# Effect of High Calcium Diet on FGF23






Rodriquez-Ortiz ME, et al. *J Am Soc Nephrol.* 2012;23:1190–1197.

# Event-Free Survival from the Composite End Point of All-Cause Mortality and Dialysis Inception Among Treated Patients






After adjustment for age, sex, diabetes, HTN, CrCL, baseline CAC there was a significant reduction HR .62 for composite (.40-.97) events

| | | | | | | |
|---|---|---|---|---|---|---|
| ***Sevelamer (n=107)*** | 107 | 106 | 98 | 81 | 71 | 64 |
| ***Calcium Carbonate (n=105)*** | 105 | 103 | 83 | 61 | 45 | 41 |

Di Iorio B et al. *Clin J Am Soc Nephrol* 2012;7:487-93.

# Summary- It's Time for New Guidelines!

- New epidemiologic data convincingly and consistently demonstrate an association of fasting serum P with a variety of adverse clinical outcomes including CKD progression and mortality.
- Data to support current guideline recommendations such as dietary intervention OR phosphate binders ALONE are limited at best although data exist to show effect of combined treatment with both diet + binders.
- Physiology of Na-dependent and Na-Independent P absorption is poorly understood and an immediate need for research to determine if any adverse effect on health
- Current ACTUAL care of patients with CKD most commonly involves dietary P restriction and provision of calcium containing P binders
- NEW guidelines are warranted to address the uncertainty and potential harm associated with current recommendations (diet + binders) in CKD. Many additional questions remain….