

# Calcium and phosphate balance in CKD

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# Disclosures

- **Dr. Moe has current grant support from the NIH, the Veterans Administration, Novartis**
- **The balance study was funded by Genzyme/Sanofi to Dr. Munro Peacock; Dr. Moe was a co-investigator.**
- **Dr. Moe has served as a scientific advisor/consultant/received honoraria for Amgen and Sanofi.**

# Current KDIGO Guidelines

- 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*).
- 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).

# K/DOQI Guidelines

## *In CKD Patients (Stages 3 and 4):*

- **5.2 Calcium-based phosphate binders** are effective in lowering serum phosphorus levels (EVIDENCE) and **may be used as the initial binder therapy. (OPINION)**

## *In CKD Patients With Kidney Failure (Stage 5):*

- **5.3 Both calcium-based phosphate binders and other noncalcium-, nonaluminum-, nonmagnesium-containing phosphate-binding agents (such as sevelamer HCl) are effective in lowering serum phosphorus levels (EVIDENCE) and either may be used as the primary therapy. (OPINION)**
- **5.5 The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500 mg/day (OPINION), and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day. (OPINION)**
- **5.6 Calcium-based phosphate binders should not be used in dialysis patients who are hypercalcemic (corrected serum calcium of  $>10.2$  mg/dL [ $2.54$  mmol/L]), or whose plasma PTH levels are  $<150$  pg/mL ( $16.5$  pmol/L) on 2 consecutive measurements. (EVIDENCE)**

# Break Out Group Questions

4. What is the role of phosphorus binders/NaPi inhibitors in controlling serum phosphorus and calcium (recommendations 4.1.4, 4.1.5, 4.1.6)?

**Factors to consider:**

**calcium- vs non-calcium binders (including magnesium), including safety of aluminum**

**cost/efficacy/safety**

**maximum dose?**

**when to initiate?**

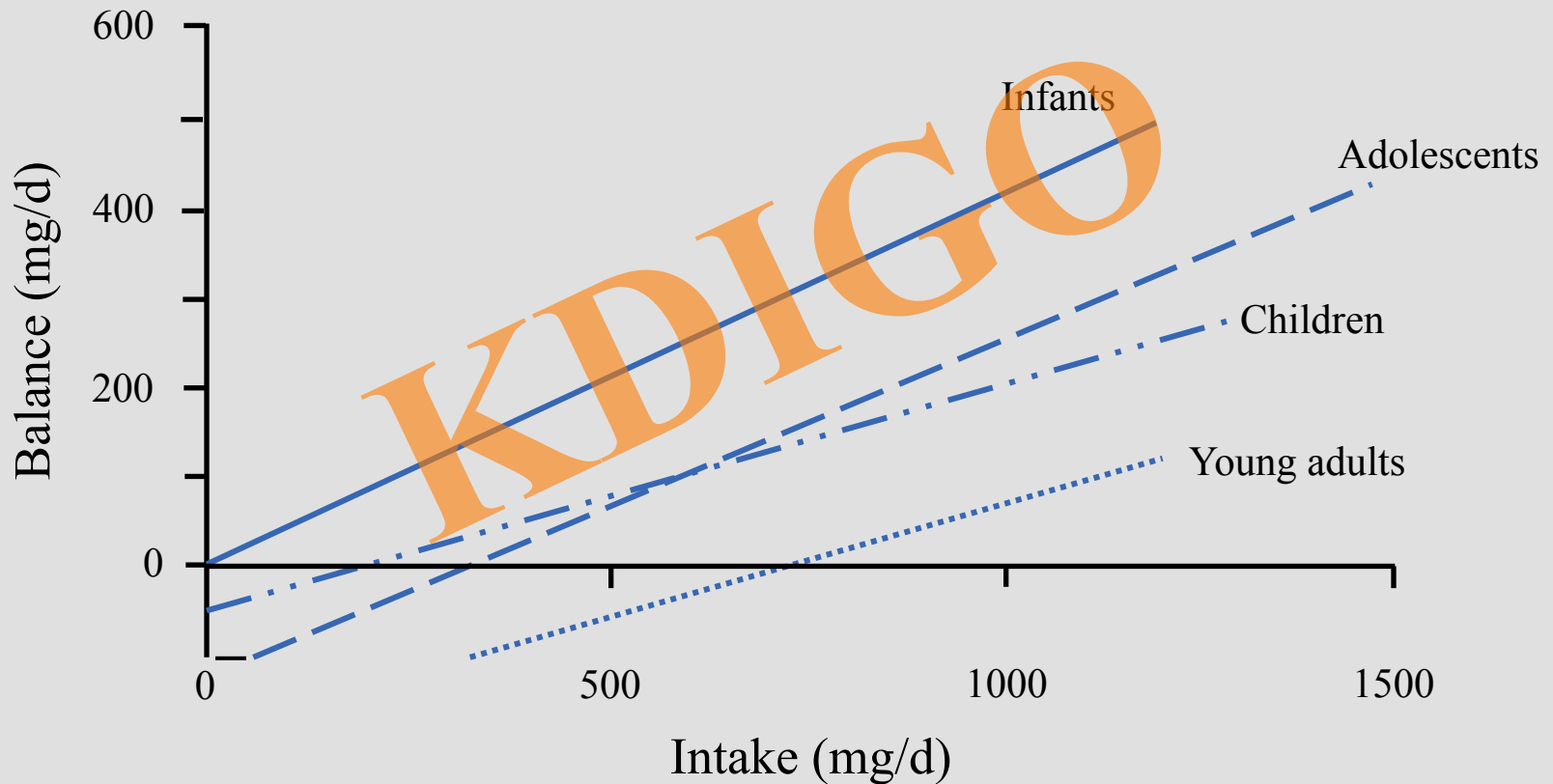
**clinical characteristics that should modify recommendations for treatment selection**

**Understanding calcium and phosphate balance may help in this discussion**

# Balance vs. Homeostasis

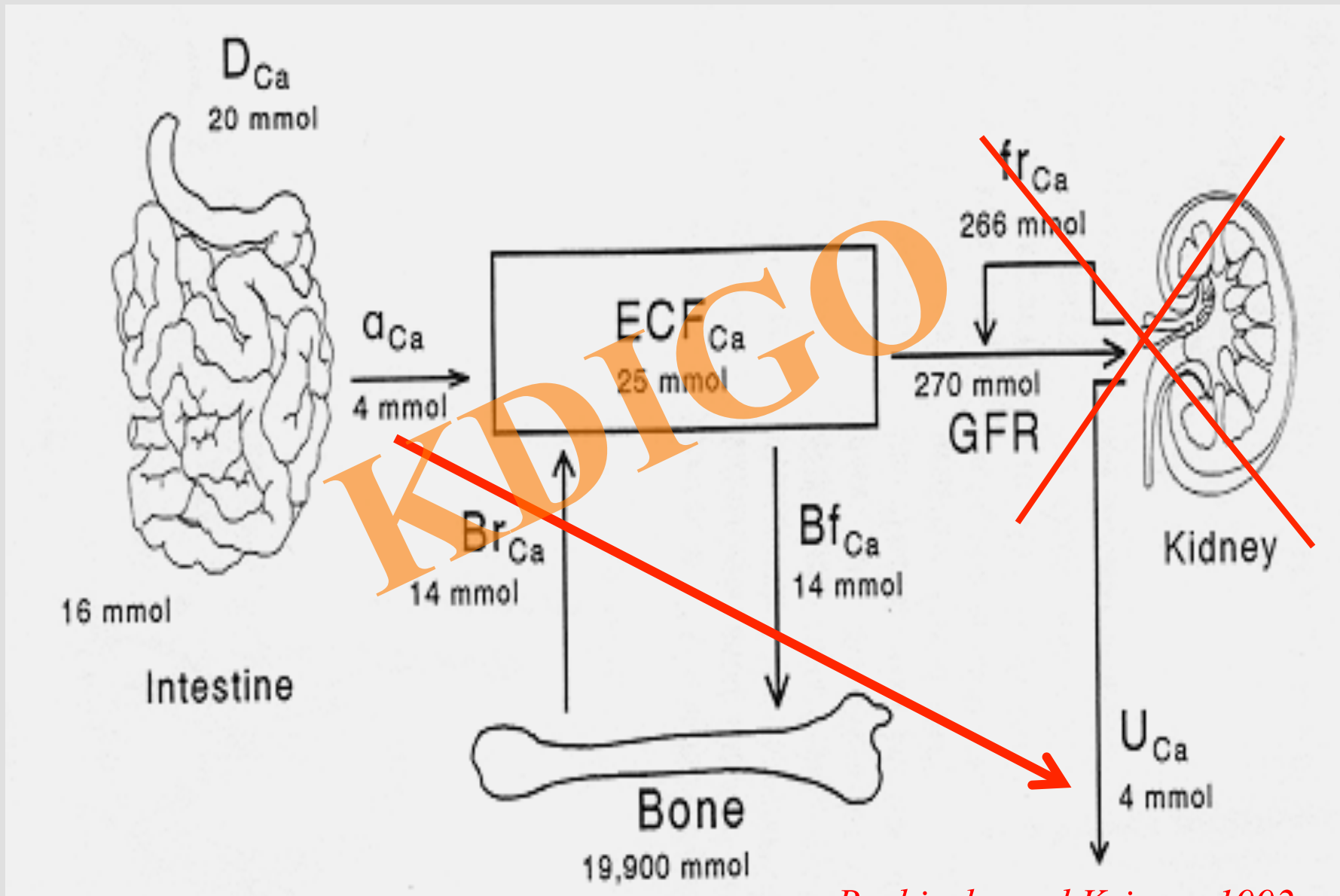
- **BALANCE:** The difference between intake and output
- **HOMEOSTASIS:** Physiological processes responsible for the maintenance of the internal environment (serum and intracellular levels), regardless of balance.
- For calcium and phosphorus these processes are determined by:
  - Target organs: Intestine, Kidney, Bone, Parathyroid gland
  - Regulators: Parathyroid Hormone, Vitamin D, FGF23, Klotho
- Long term goal of homeostasis is to maintain balance.

# Calcium Balance in Non-CKD patients



**Peak bone mass is achieved by age 25-35 y**

# Neutral Calcium Balance

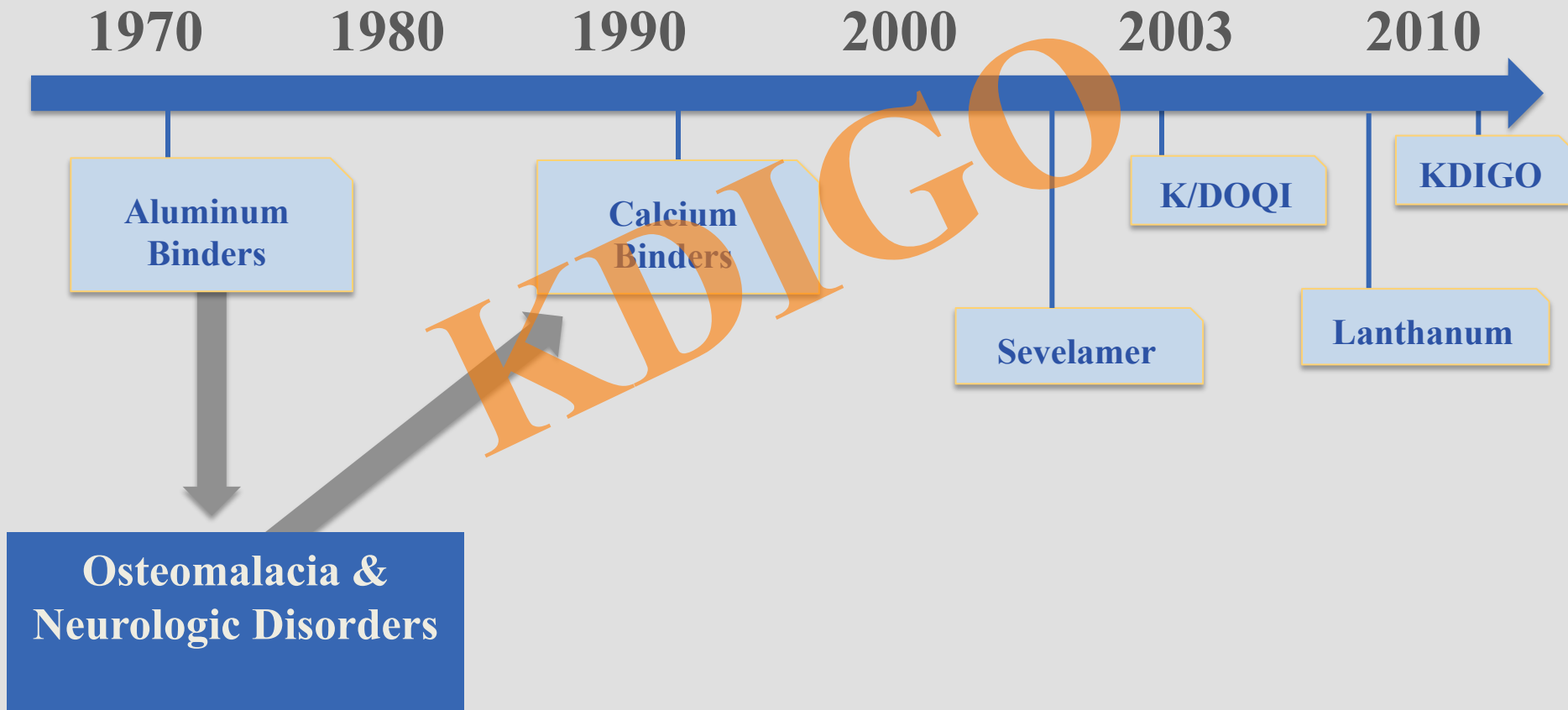




**Why do we care about calcium and phosphorus balance and homeostasis in CKD?**

**We alter it with our therapies.**

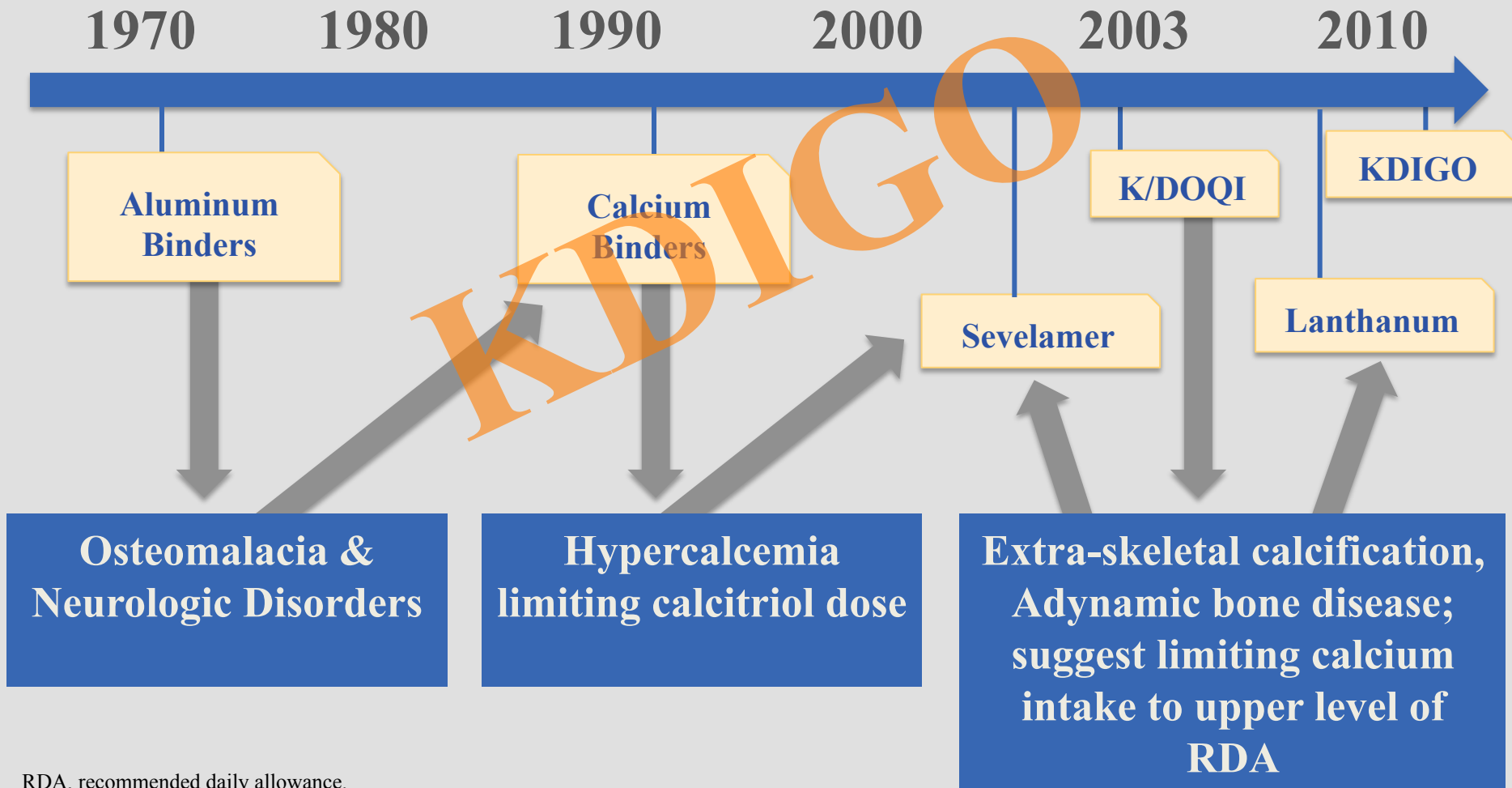
# History of Phosphate Binder Use In CKD



# Historical Perspective: Calcium Is an Ideal Phosphate Binder Because...

- 1. Higher calcium levels will further suppress PTH**
- 2. Patients have decreased intestinal absorption of calcium due to calcitriol deficiency**
- 3. Better alternative than aluminum: cheap and “nontoxic”; safely used in the general population**

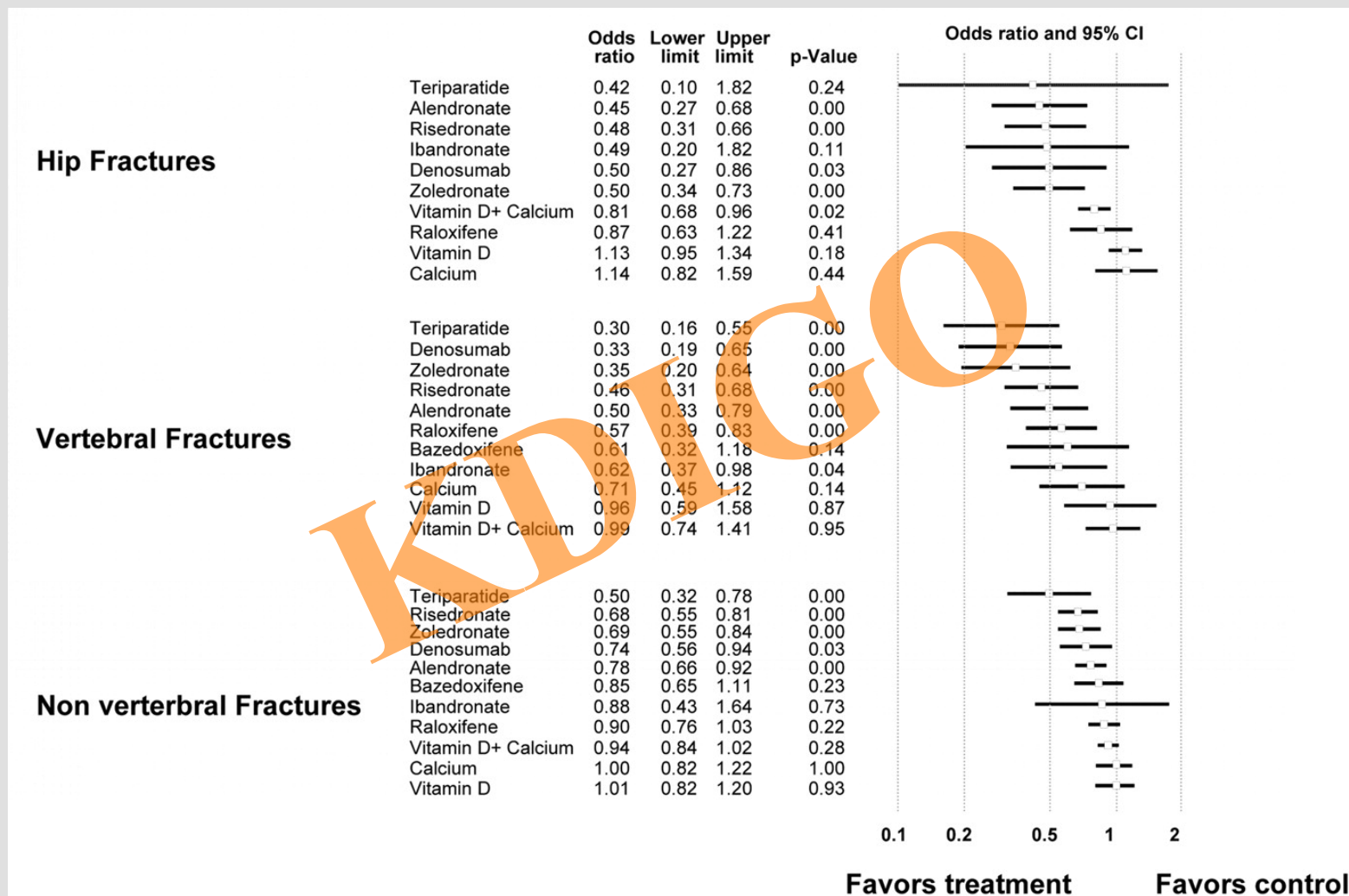
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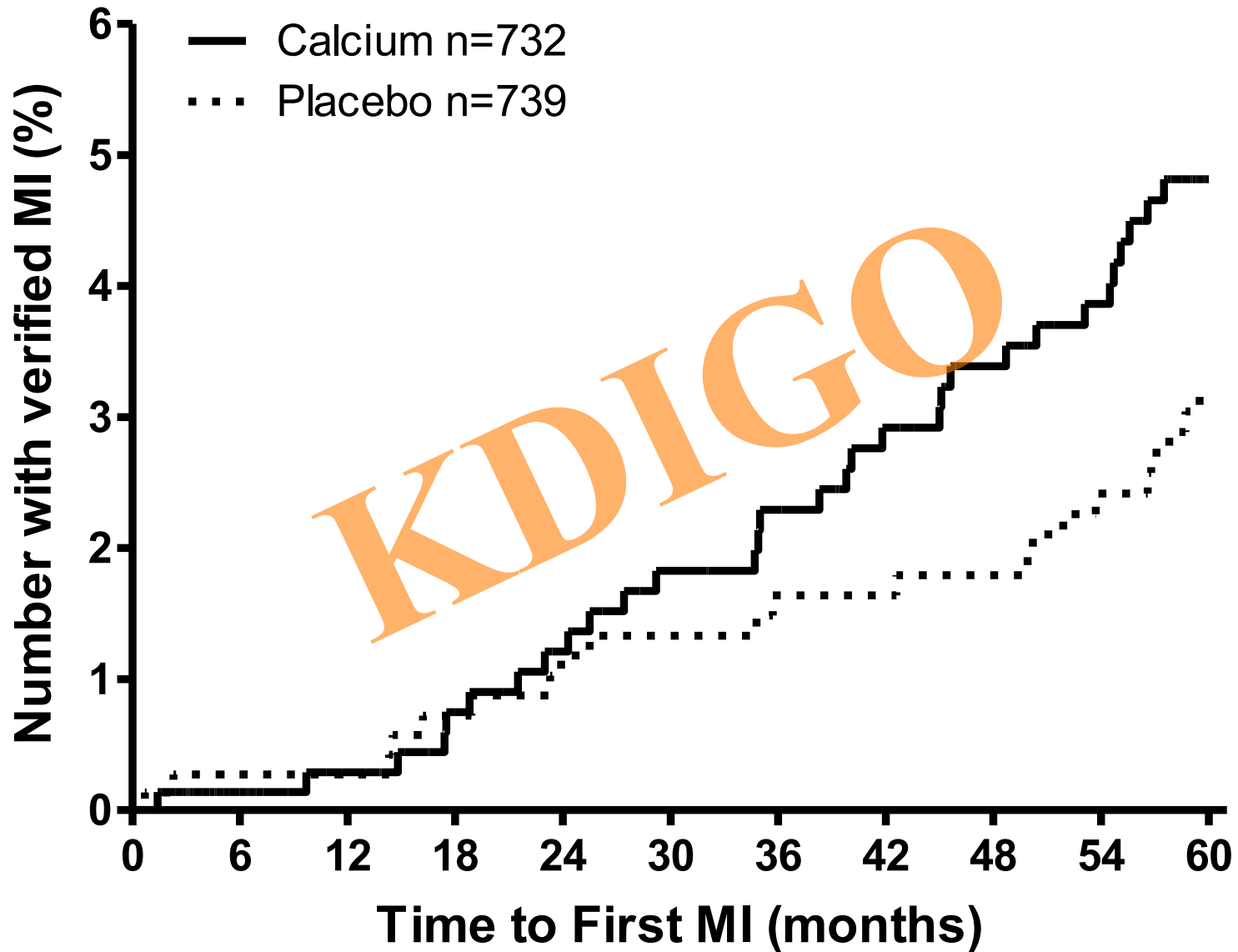
- 1. Higher calcium levels will further suppress PTH**
- 2. Patients have decreased intestinal absorption of calcium due to calcitriol deficiency**
- 3. Better alternative than aluminum: cheap and “nontoxic”; safely used in the general population**
- 4. Excess calcium will go into bone: positive calcium balance is a good thing**

# Agents for the prevention of fragility fractures compared against placebo (combined direct and indirect estimates).

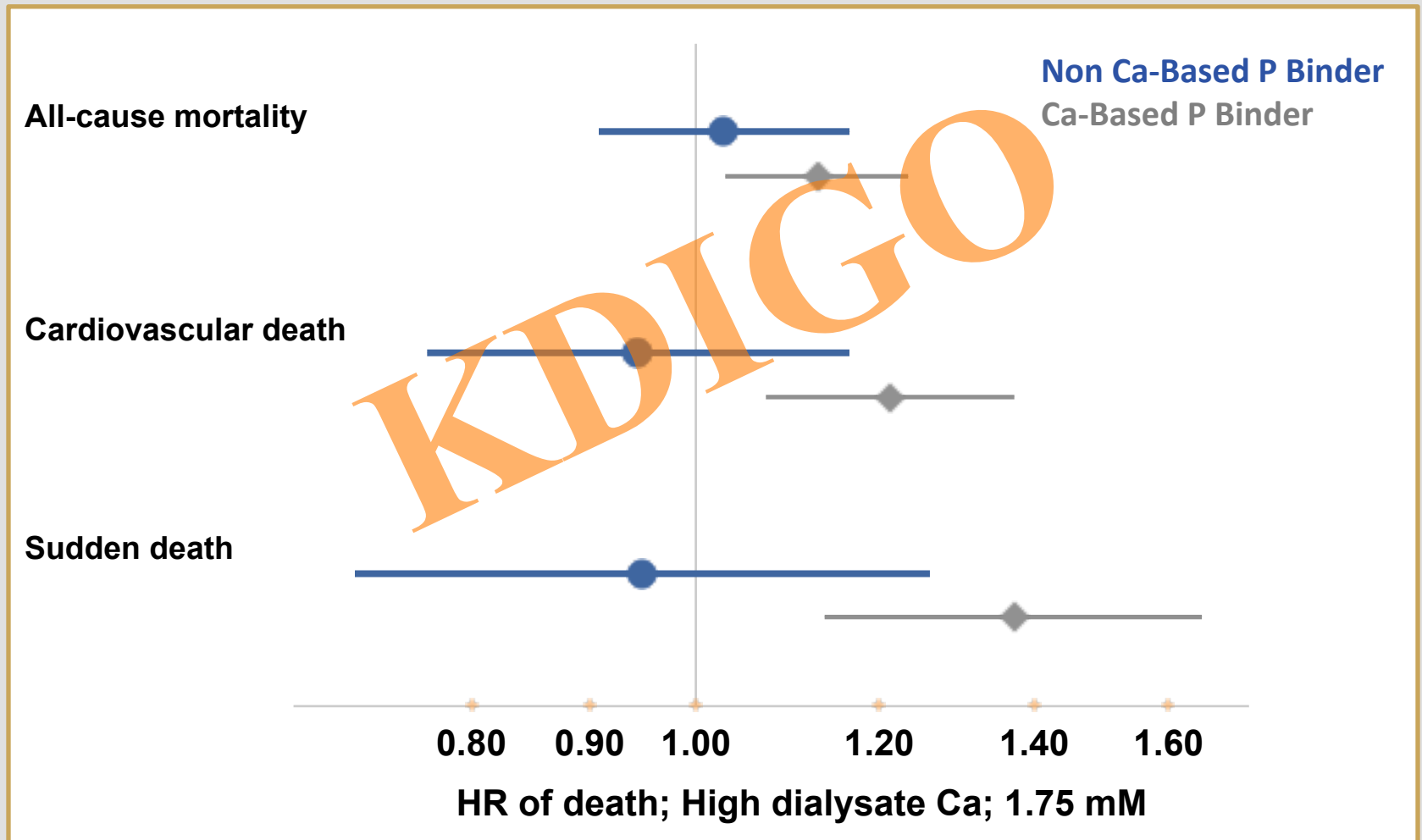


Murad M H et al. JCEM 2012;97:1871-1880

# Effect of Calcium on Myocardial Infarction in General Population



# Phosphate Binders and Cause-Specific Mortality



HR, hazard ratio.  
n=34,575 patients (869 facilities) in DOPPS I-III (1996-2008).



# Current Dilemma

- **No definitive proof that non-calcium-based binders are superior to calcium-based binders in terms of hard clinical end points such as mortality**
- **But, no proof that calcium binders improve clinical end points either**
- **Is there a safe level of calcium intake? Are patients in positive calcium balance with some calcium?**
- **When does the risk outweigh the benefit?**
- **Balance studies are desperately needed**

# Methods for Measuring Calcium Balance and Kinetics

- **Intestinal absorption**



**Plasma appearance after oral radiocalcium**

- **Metabolic balance studies (collection of feces only)**

- **Net balance**



**Fecal and urinary recovery of radiocalcium**

**Body retention after oral  $^{47}\text{Ca}$  (whole body counter)**

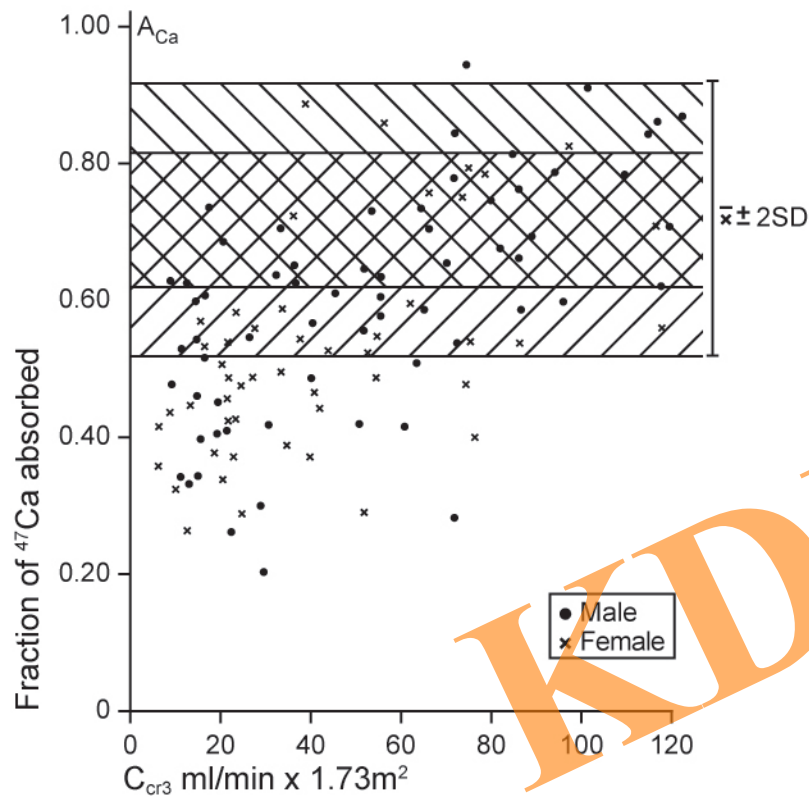
- **Kinetics (distribution)**

- **Double isotope method [one given orally, the other IV ( $^{45}\text{Ca}/^{47}\text{Ca}$ )]**

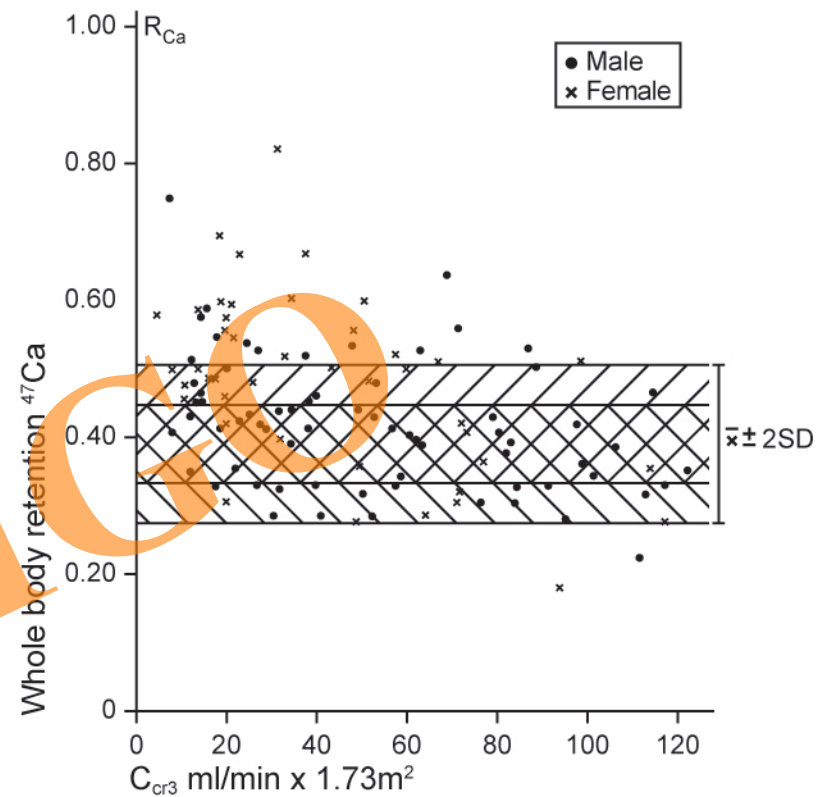
- **Metabolic balance plus kinetics after oral/IV radiocalcium**

An assumption of all balance studies is that patients are in steady state. By definition, cannot do balance studies in patients on dialysis!

# Intestinal absorption and net balance



**Figure 1.** Fractional intestinal absorption of calcium, at various levels of glomerular filtration rate. The absorption was measured by whole body counting and double dose of  $^{47}\text{Ca}$ . Shaded area represents normal range with 1 SD (cross-hatched area) and 2 SD (lined area).



**Figure 2.** Fractional retention of calcium after 28 days of intravenous application (measured by whole body counting) at various levels of glomerular filtration rate. Shaded area represents normal range with 1 SD (cross-hatched area) and 2 SD (lined area).

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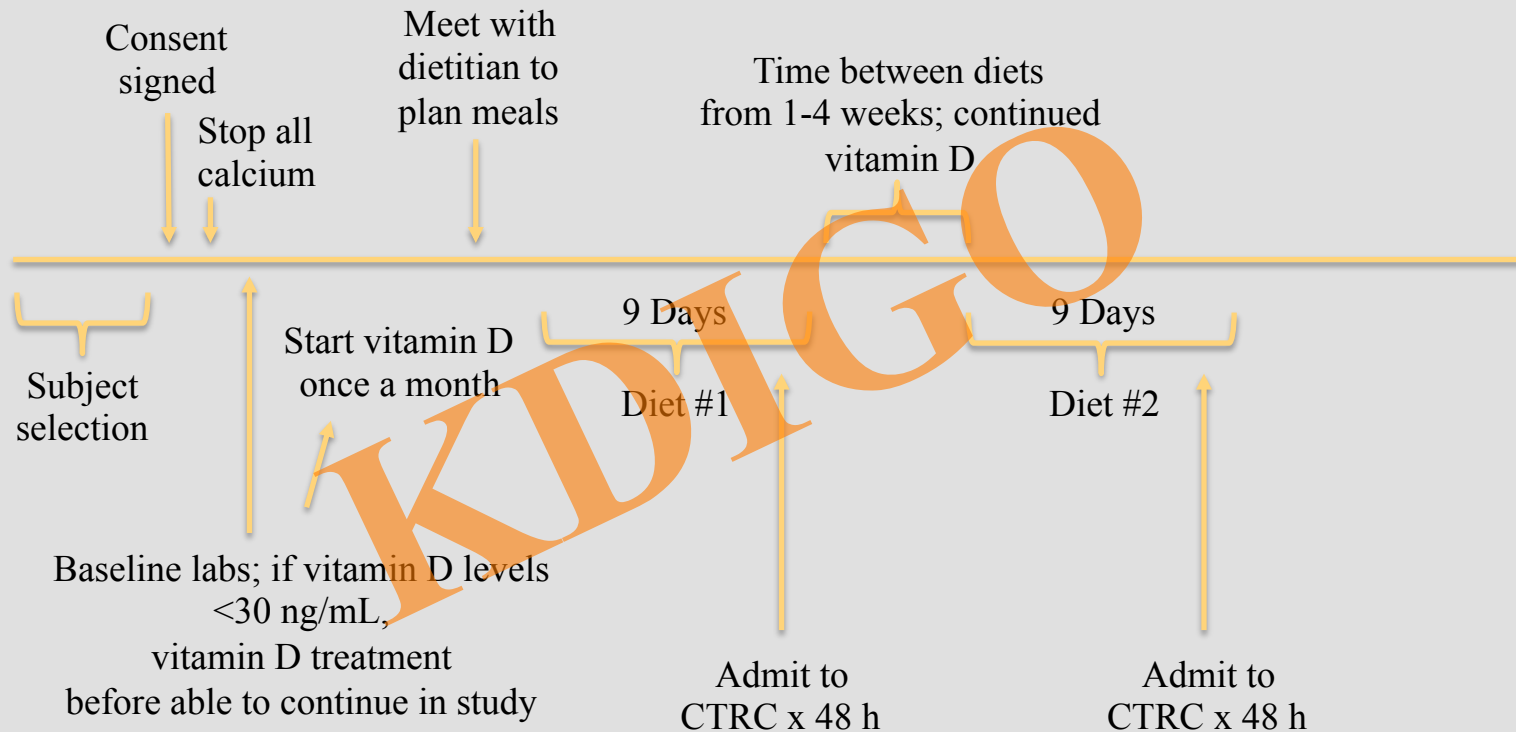
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# Calcium Balance in Normal Individuals and in Patients With CKD (Stage 3b/4) on Low- and High-Calcium Diets



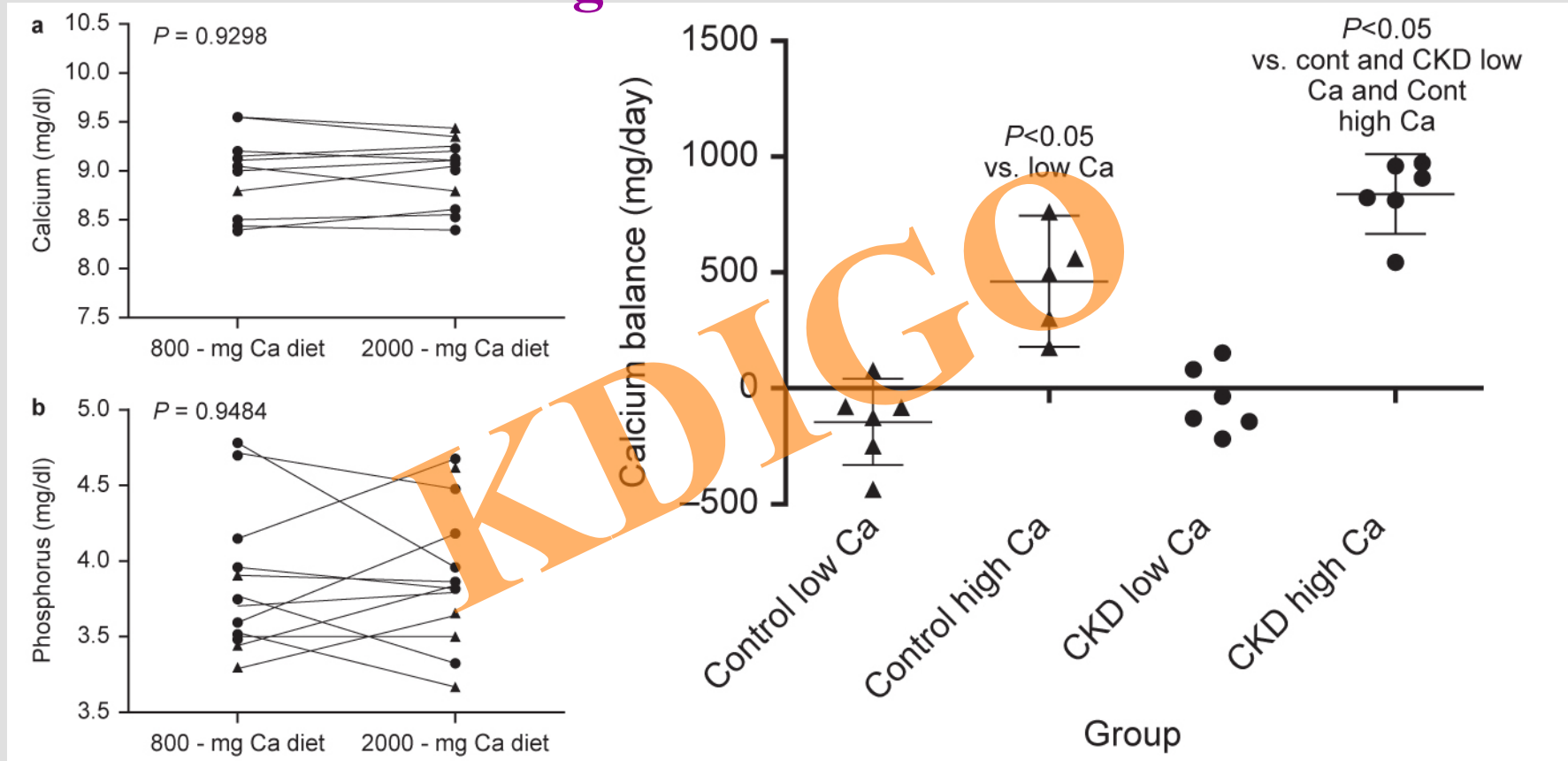
**Diet 1 = 800 mg calcium**  
**Diet 2 = 2000 mg calcium**  
Sequence randomized

*Food prepared for subject by clinical research center*

**Assessments:** 24-hour urine calcium and phosphorus, fecal calcium.

**Balance = Dietary intake – (stool + urine)**

# Calcium Balance in Normal Individuals and in Patients With CKD (Stage 3b/4) on Low- and High-Calcium Diets



**No change in blood calcium or phosphorus levels despite positive calcium balance on the high calcium diet**

# Methods for Measuring Calcium Balance and Kinetics

- **Intestinal absorption**

- Plasma appearance after oral radiocalcium
- Metabolic balance studies (collection of feces only)

- **Net balance**

- Fecal and urinary recovery of radiocalcium
- Body retention after oral  $^{47}\text{Ca}$  (whole body counter)

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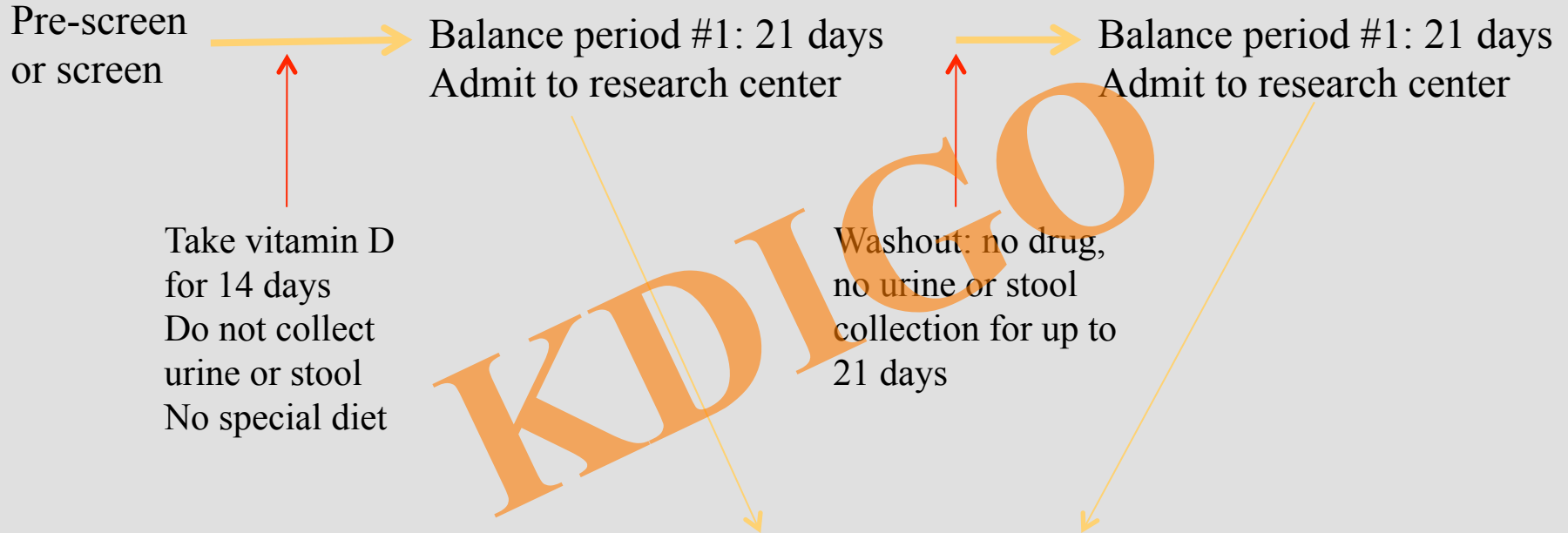
# Indiana University/Purdue University Balance Study

- To determine the effect of a calcium carbonate binder given with meals on calcium and phosphate balance and calcium kinetics in patients with stage 3/4 CKD
- Crossover trial in CKD subjects with GFR < 45 mL/min; PTH in upper end of normal or greater; no malabsorption, no bone drugs
- Placebo vs calcium carbonate 500 mg with each meal on background of 1000 mg dietary calcium

Hill, KM, Martin, BR, Wastney, ME, McCabe, GP, Moe, SM, Weaver, CM, Peacock, M: Oral calcium carbonate affects calcium but not phosphorus balance in stage 3-4 chronic kidney disease. *Kidney international*, 83: 959-966, 2013



# Balance Study Outline



Day 1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18-19-20-21

Take pills

Eat special diet

Collect daily urine and stool

Must stay in hospital

Get blood drawn

X

X

X

X

X

X

X

X

X

X

X

X

X

# Diets

- Prepared by CRC kitchen
- Two versions, 2200 kcal and 2500 kcal, each with 4 different menus that were alternated
- Based on our previous study, the diets were ashed and analyzed for Ca, Phosp, Mg, Na, K (rather than trusting database), but protein, fat, carbs based on food label values

Diet	Phosp (mg)	Ca (mg)	Protein (g)	Fat (g)	Carb (g)	Na (mg)	Mg (mg)	K (mg)
2200 kcal (avg 2177)	1564 ± 52	957 ± 23	87 ± 10 (16%)	59 ± 10 (25%)	324 ± 35 (59%)	2749 ± 541	293 ± 49	1708 ± 272
2500 kcal (avg 2393)	1582 ± 66	956 ± 10	92 ± 10 (15%)	62 ± 9 (24%)	365 ± 42 (61%)	3059 ± 566	326 ± 53	1917 ± 320

# Calcium/Phosphate Balance

- All urine and feces were collected for 2 weeks during each study period
- Calcium/phosphate balance is calculated as
$$Ca (mg/d) - urine Ca (mg/d) - fecal Ca (mg/d)$$
$$Pi (mg/d) - urine Pi (mg/d) - fecal Pi (mg/d)$$
- Diet, urine, and fecal Ca were determined by inductively coupled plasma spectroscopy
- Compliance was assessed by urinary creatinine and stool PEG

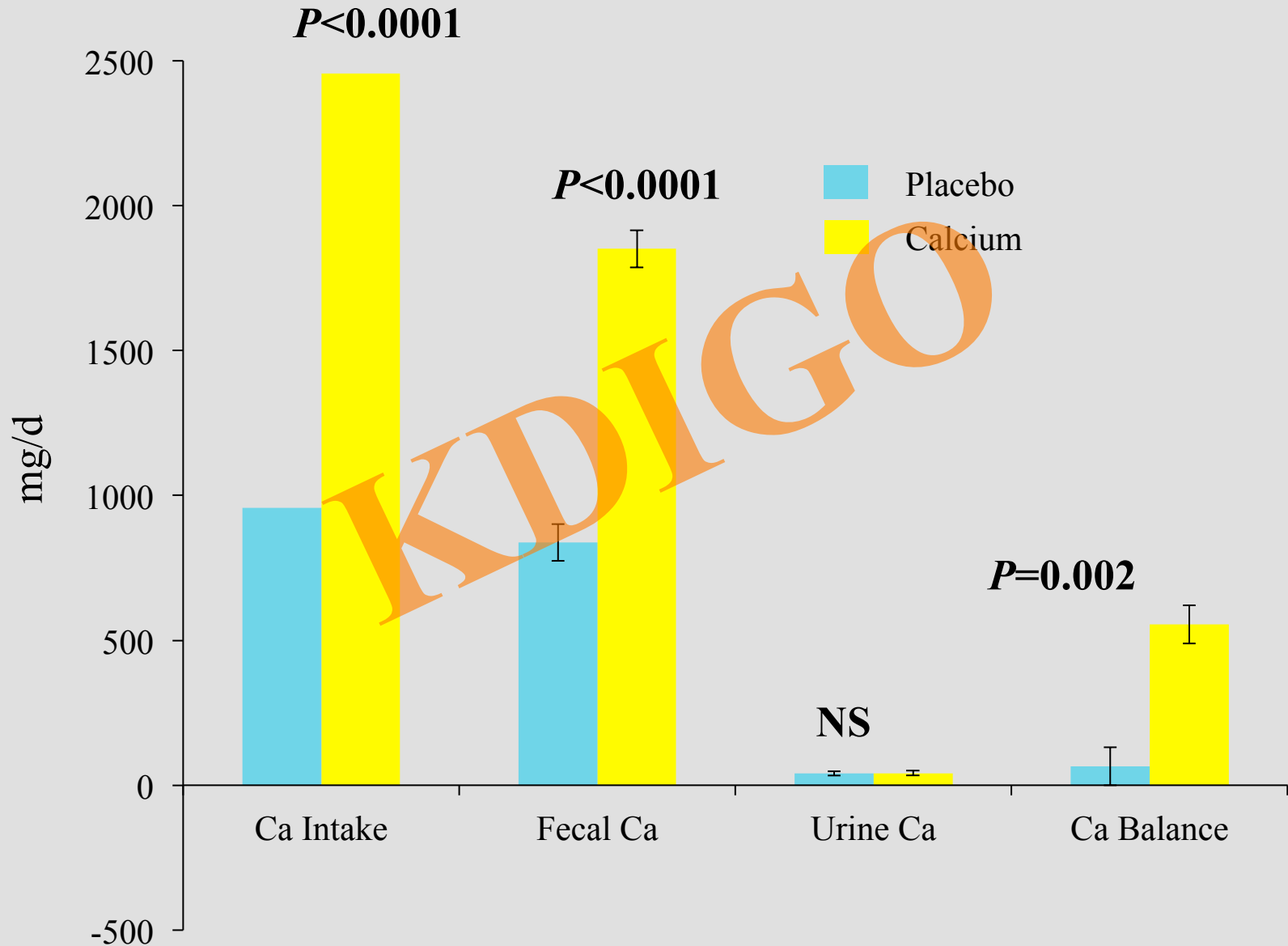
## Statistical Analysis

- Repeated Measures ANOVA for Cross-Over Designs (SAS 9.2 software [Cary, NC]);  $P < 0.05$

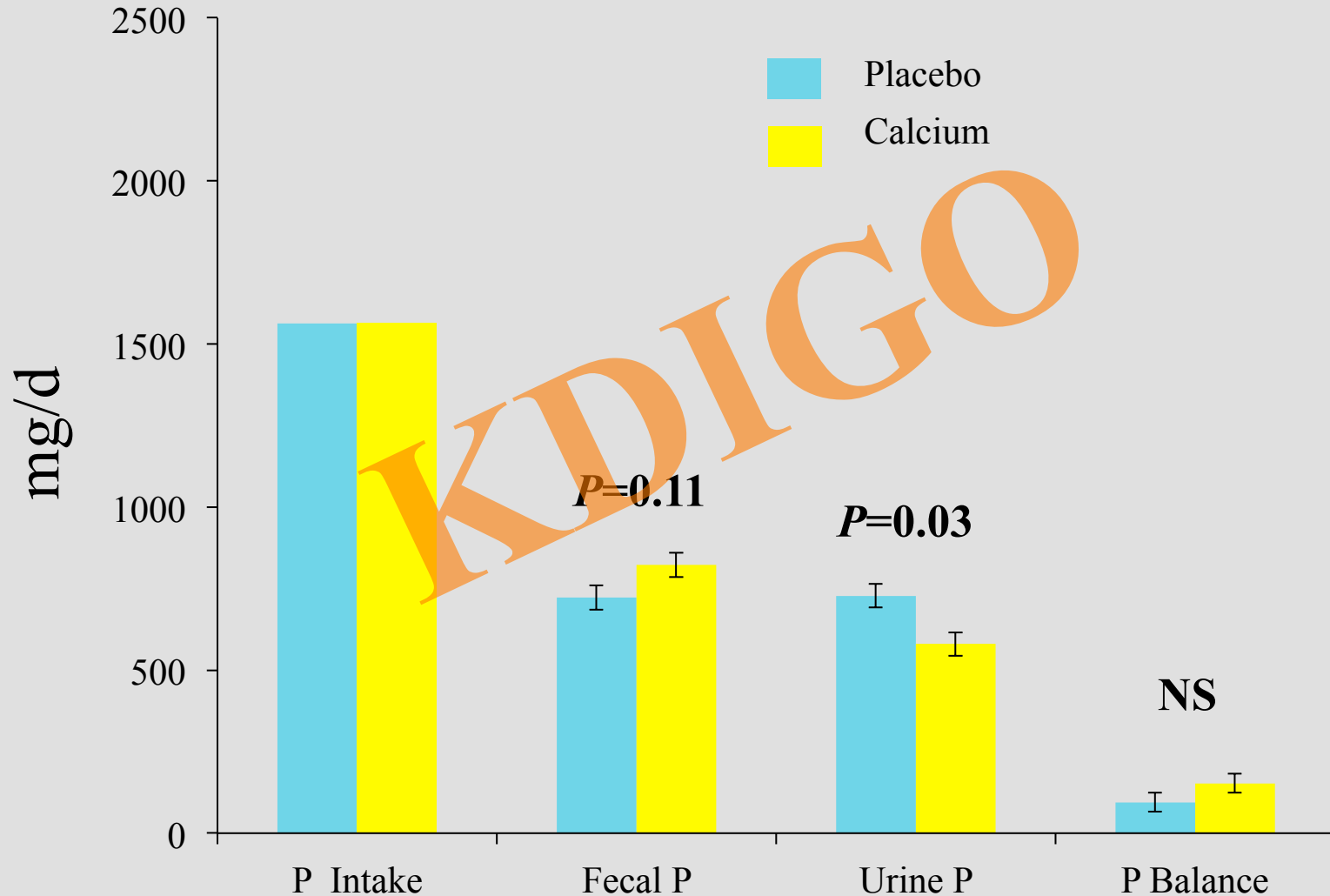
# Baseline Characteristics

Male/female, n	2/6		
Black/white, n	5/3		
Diabetes present, n	6		
Hypertension present, n	8		
Age, y	58.5 ± 6.9		(47.2, 68.7)
Body mass index, kg/m <sup>2</sup>	38.7 ± 8.7		(27.9, 52.2)
<b>Estimated GFR, mL/min/1.73 m<sup>2</sup></b>	<b>36 ± 8.8</b>		<b>(26, 53)</b>
Serum Ca, mg/dL	9.6 ± 0.3		(9.3, 10.3)
Serum Pi, mg/dL	3.8 ± 0.6		(3.2, 4.9)
<b>Serum PTH, pg/mL</b>	<b>84.5 ± 58.7</b>		<b>(36.6, 214.0)</b>
<b>Serum intact FGF-23, pg/mL</b>	<b>79.4 ± 39.7</b>		<b>(33.7, 149.6)</b>
Total body bone mineral density (BMD), g/cm <sup>2</sup>	1.26 ± 0.10		(1.11, 1.38)
Z-score	0.4 ± 1.0		(-0.8, 1.9)
Lumbar spine BMD, g/cm <sup>2</sup>	1.29 ± 0.21		(0.98, 1.51)
Z-score	0.5 ± 1.5		(-1.3, 2.6)
Femoral neck BMD, g/cm <sup>2</sup>	0.98 ± 0.12		(0.80, 1.11)
Z-score	-0.5 ± 0.5		(-1.3, 0.3)

# Calcium Balance Results



# Phosphate Balance Results



# Biochemical Results

	Placebo	Calcium
Calcium (mg/dl)	9.5 ± 0.1	9.7 ± 0.1
Phosphorus (mg/dl)	3.8 ± 0.1	4.0 ± 0.1
25(OH)D (ng/ml)	26.7 ± 0.4	25.1 ± 0.4
1,25(OH)2D (pg/ml)	33.1 ± 3.3	30.6 ± 2.3
PTH (pg/ml)	63.1 ± 3.3	58.9 ± 3.0
FGF23 (pg/ml)	75.6 ± 14.5	89.9 ± 3.0

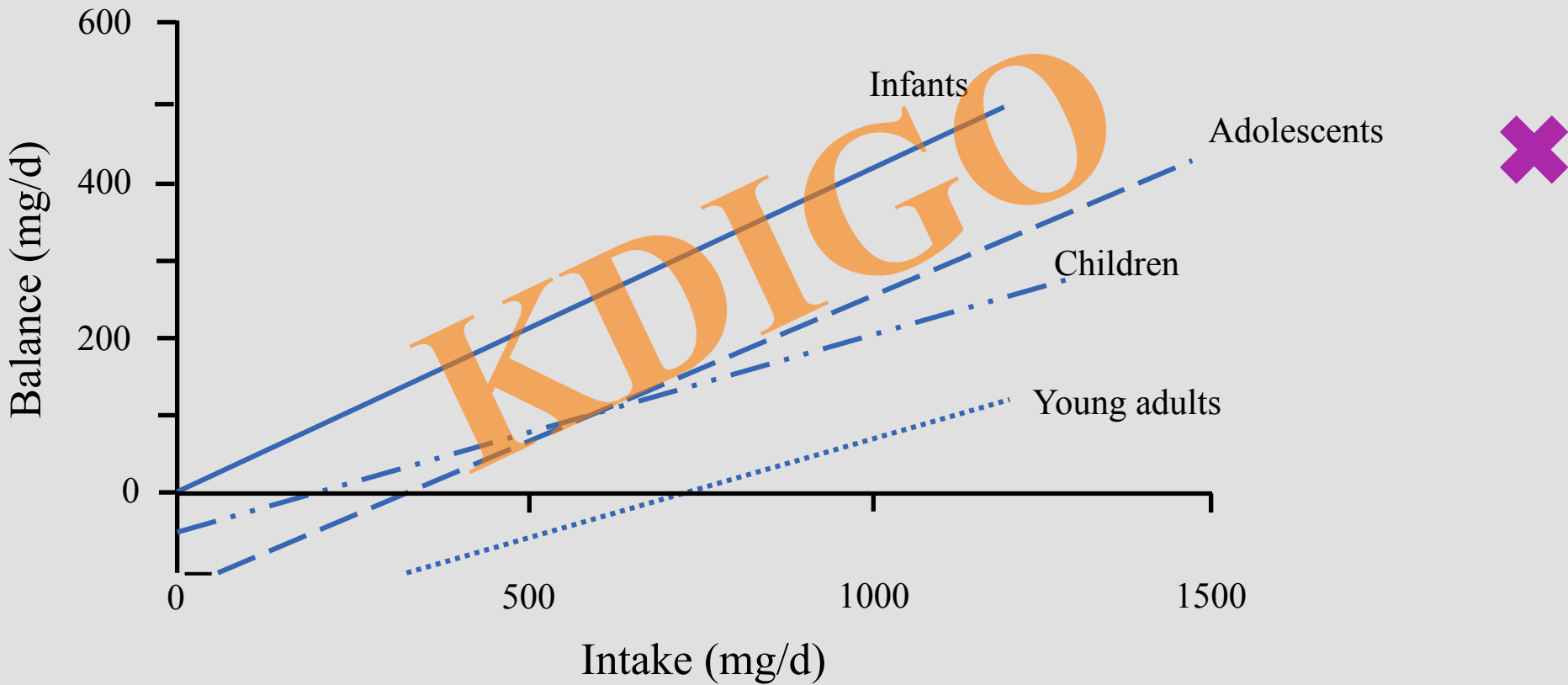
**No significant differences between arms**

# Summary of Balance Studies

- **In patients with CKD stage 3b and 4, patients are in neutral phosphate balance.**
  - This is because of intricate homeostatic mechanisms that work to decrease intestinal phosphate absorption (low 1,25vitamin D), and increase renal phosphate excretion (PTH and FGF23). This preserves phosphate for bone.
- **In patients with CKD stage 3b and 4, patients on a 1000 mg daily calcium diet are in neutral calcium balance.**
  - This is because of intricate homeostatic mechanisms that work to decrease intestinal calcium absorption (low 1,25 vitamin D), and enhance renal reabsorption (elevated PTH and ??). This preserves calcium for bone.
- **In these patients, the administration of calcium carbonate 500 mg with meals as a binder did not decrease blood phosphorus levels significantly, but did increase calcium balance.**

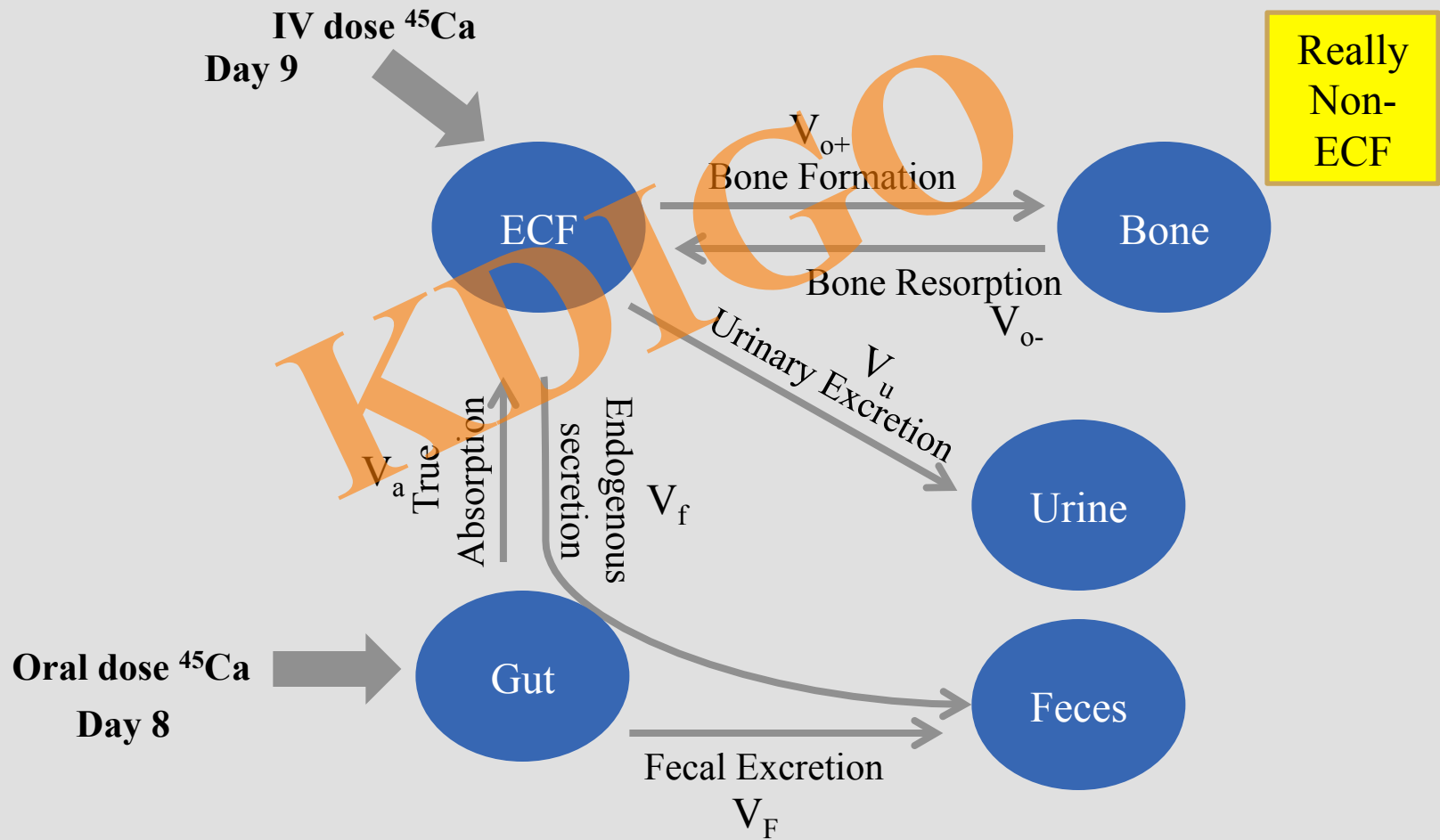


# Calcium Balance

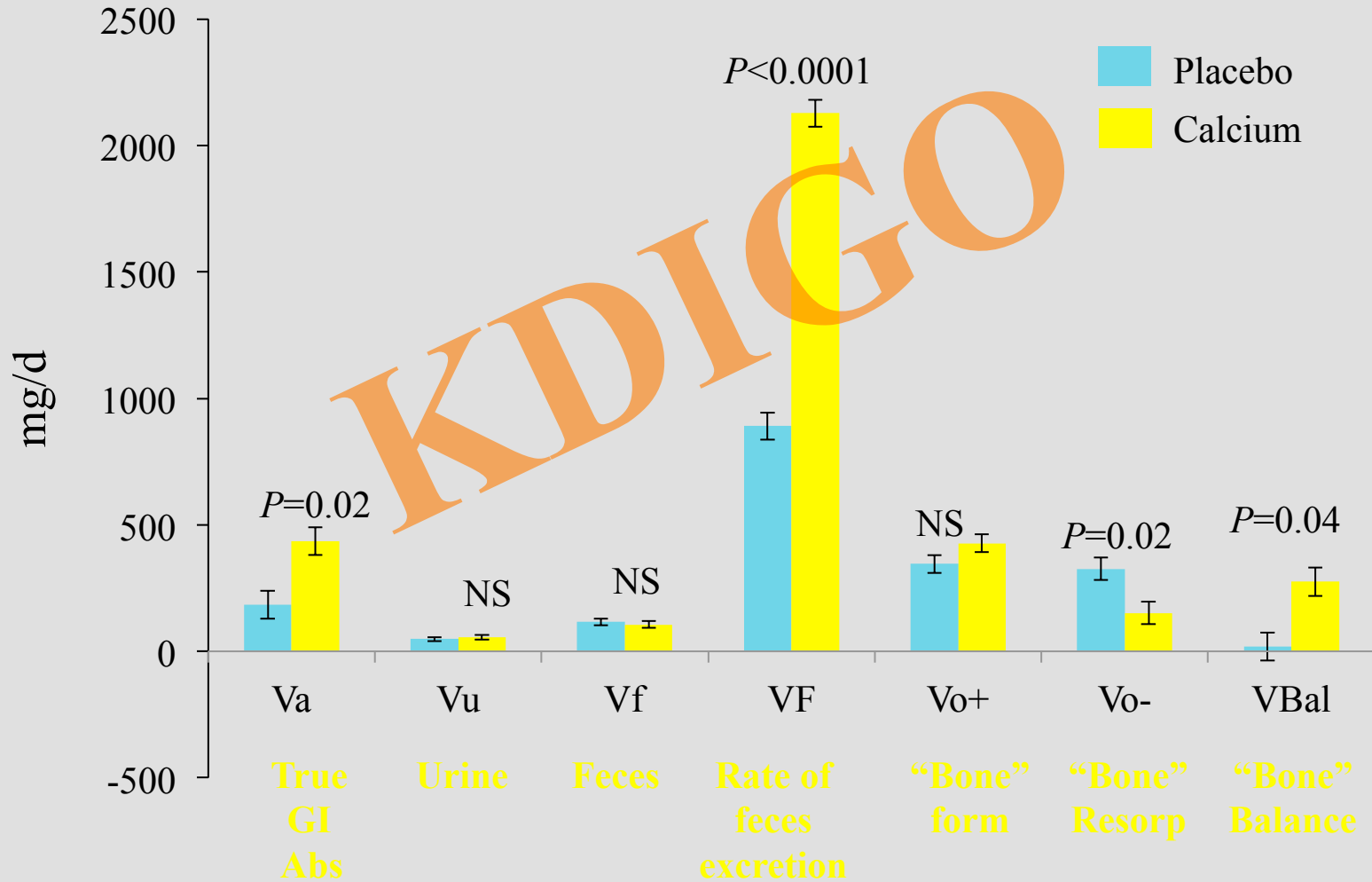


**Peak bone mass is achieved by age 25-35 y**

# Principles of Calcium Kinetic Modeling

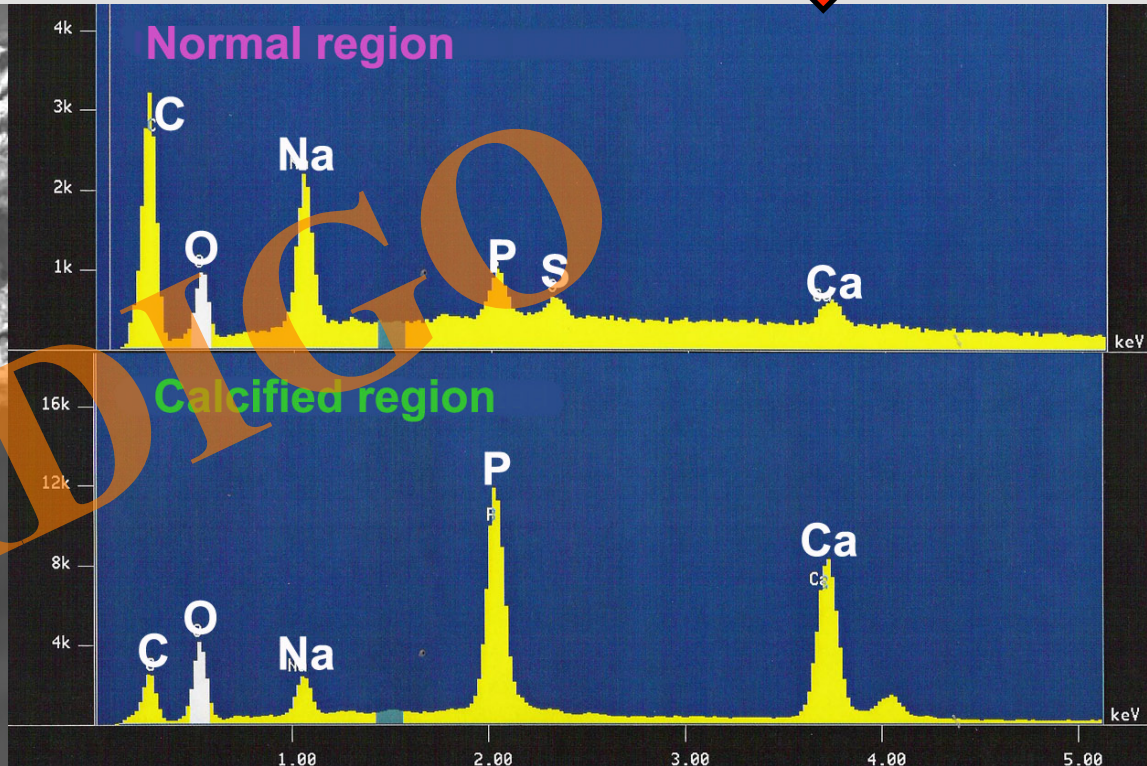
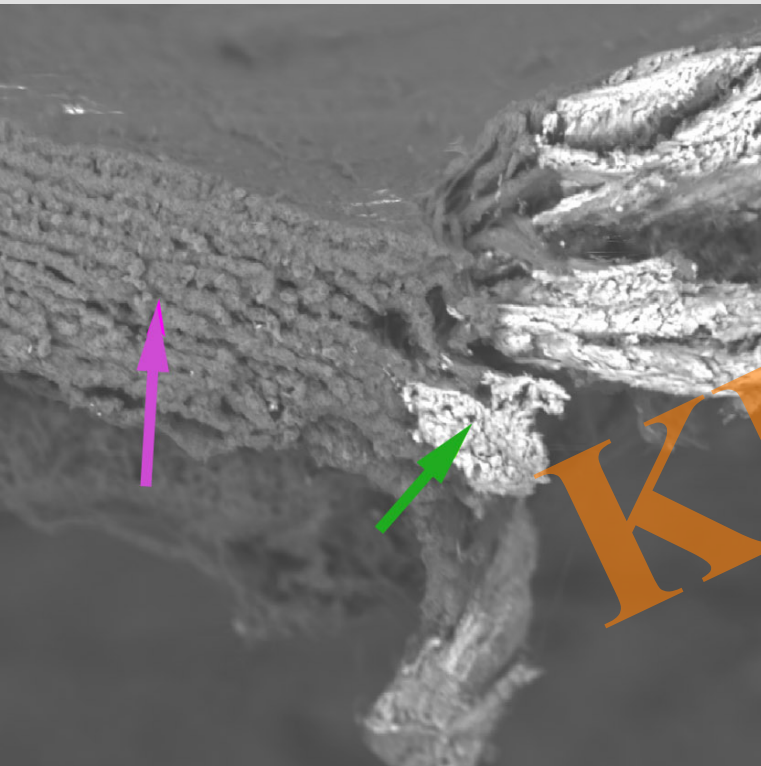
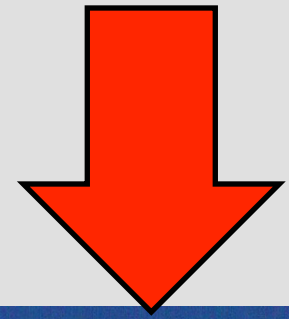


# Calcium Balance Results



# Conclusions

- **Stage 3-4 CKD patients consuming an adequate calcium diet (1000 mg per day)**
  - **Are in neutral calcium balance**
  - **Have low net intestinal calcium absorption**
  - **Have VERY low urinary calcium excretion**
- **A calcium carbonate supplement providing 1500 mg/d of elemental calcium produces positive calcium balance**
- **In many animal studies, positive calcium balance (calcium in water or as binder in food) with or without hypercalcemia leads to vascular calcification.**



# Collaborators

## Lab studies

- Neal Chen
- Kali O'Neill
- Ming Chen
- Vince Gattone
- Matt Allen
- Mark Seifert
- Scott Radcliff
- Alex Carr
- Bob Bacallao
- K. Kiattisunthorn

## Human studies

- Mary Chambers
- Gail Douglas
- Ranjani Moorthi
- Laurie Trevino
- Lisa Jackman
- Munro Peacock
- Katie Hill
- Connie Weaver
- The patients