FGF23 & Other Emerging Diagnostic Markers

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Disclosures: Abbott, Amgen, Keryx, Luitpold, OPKO, Pfizer, Sanofi, Shire

PHYSIOLOGY and EPIDEMIOLOGY

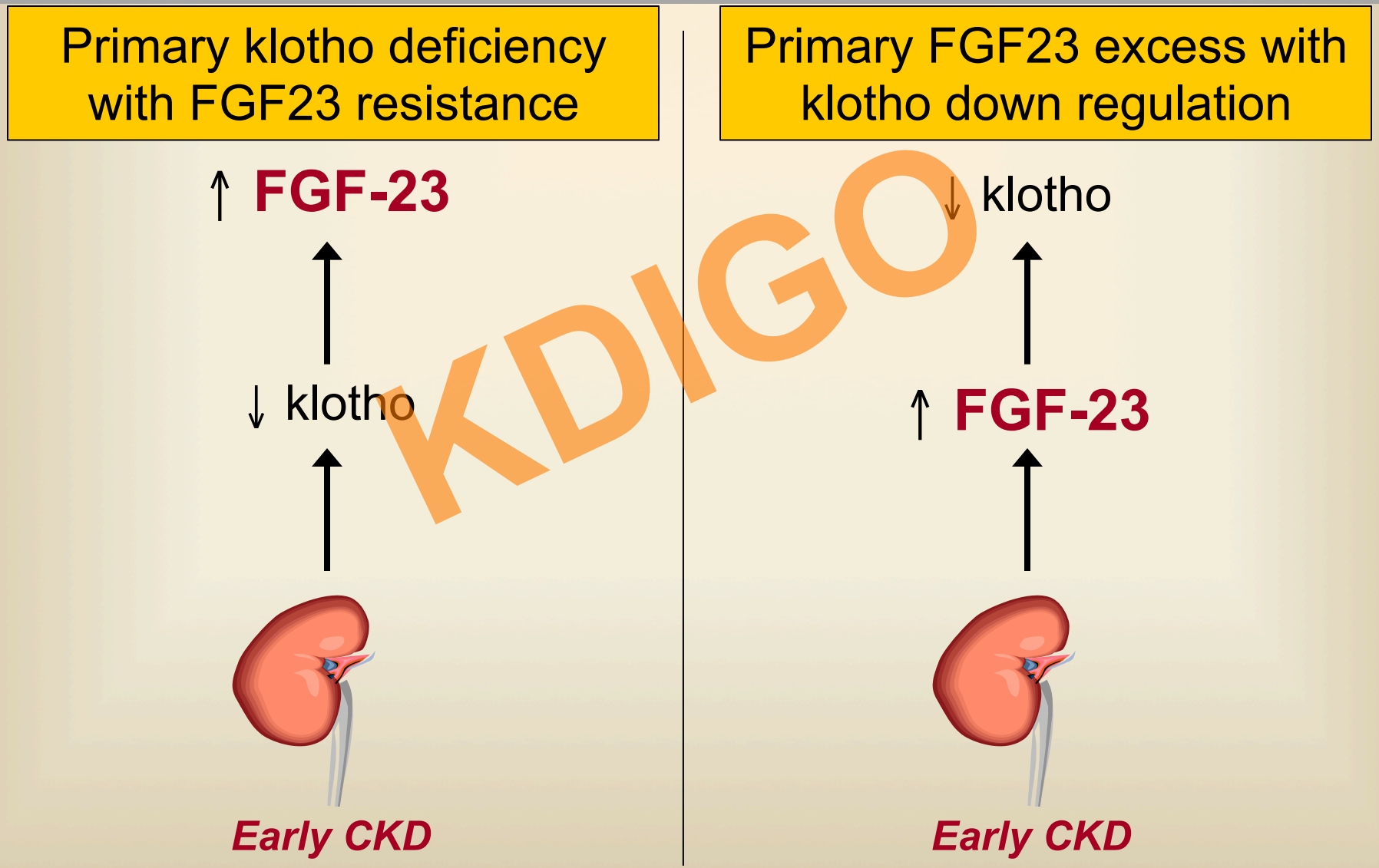
Classic actions and stimuli of FGF23

- Stimulates phosphaturia
- Inhibits CYP27B1
- Stimulates CYP24A1
- Inhibits PTH

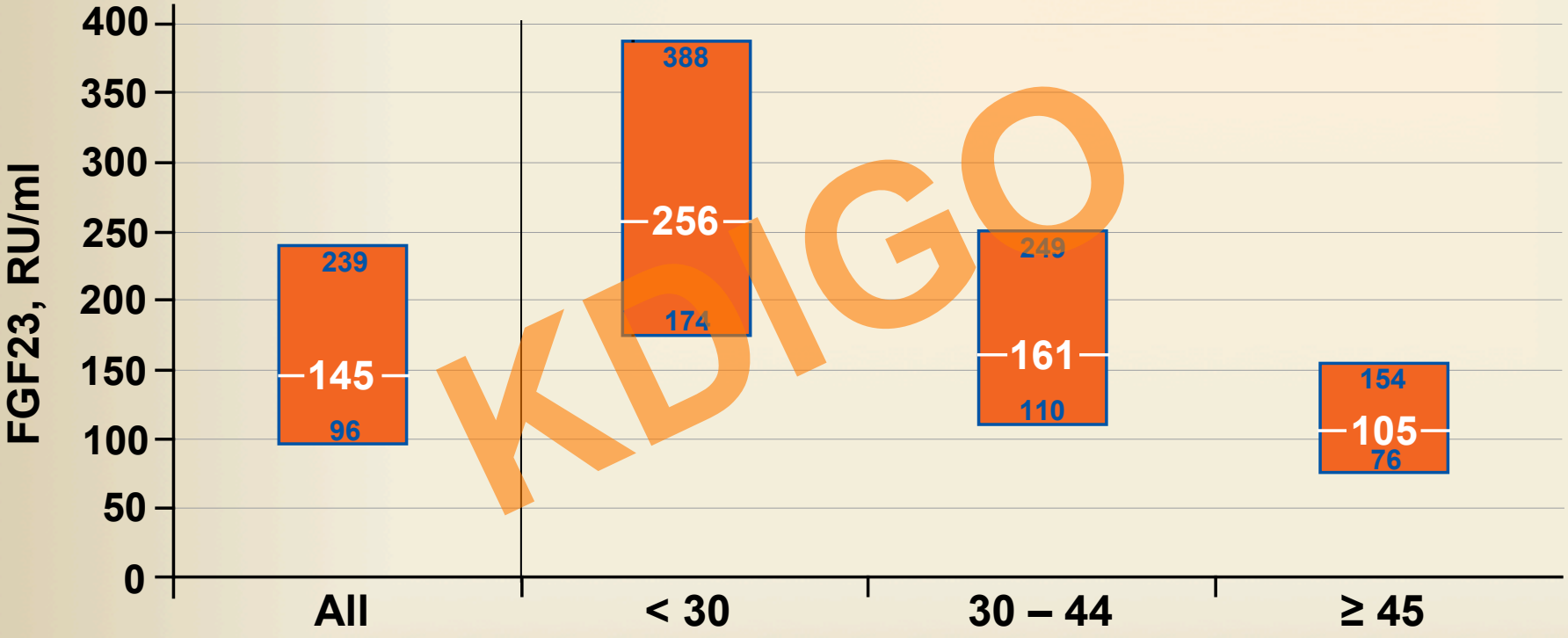
Lower 1,25-dihydroxyvitamin D

- Classic actions require “permissive” serum calcium
- Stimuli:
  - phosphate intake, 1,25-dihydoxyvitamin D, PTH, calcium

CKD Chickens and Eggs



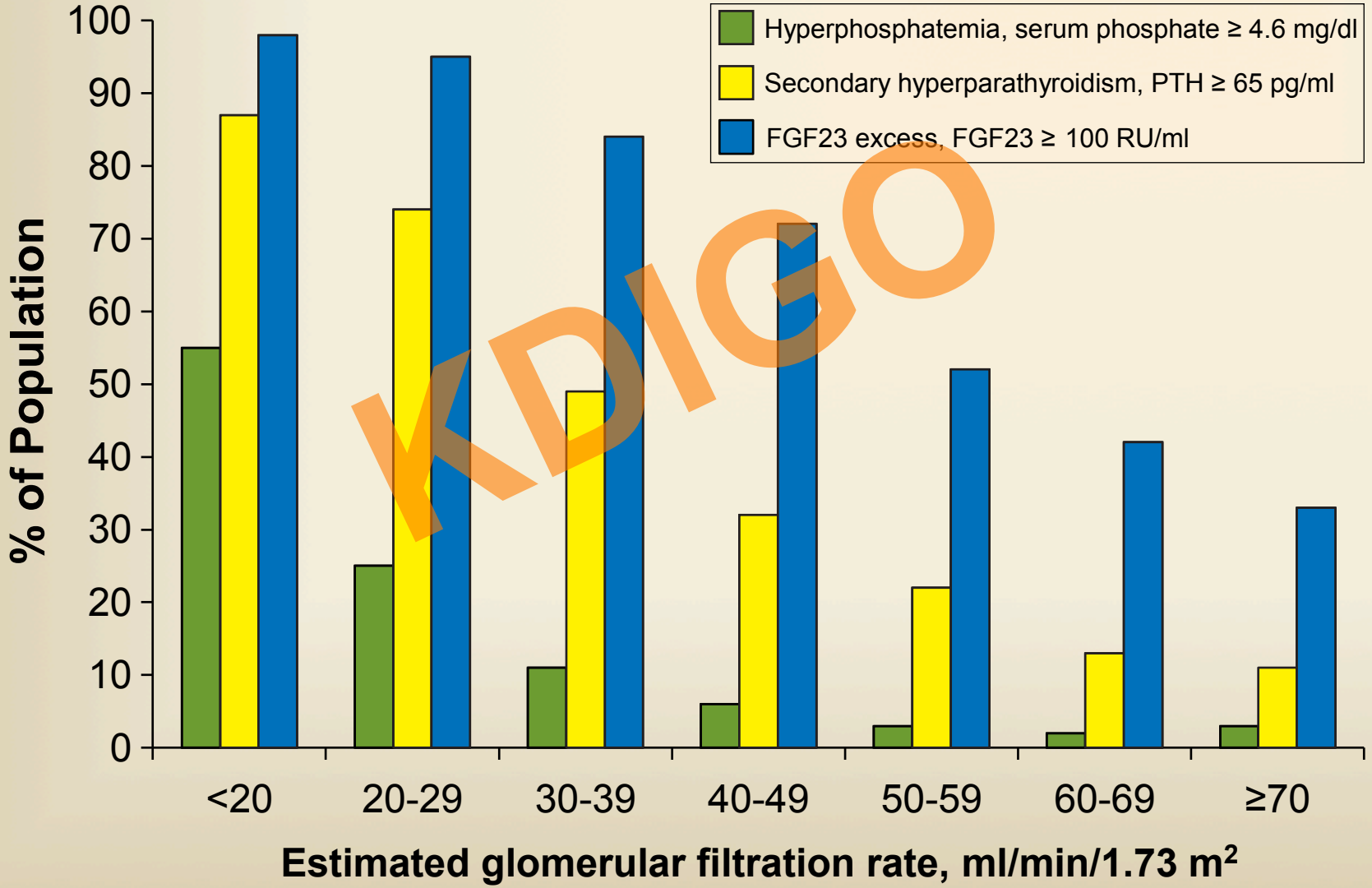
FGF23 by CKD stage in CRIC



All	< 30	30 – 44	≥ 45
N = 3879	N = 752	N = 1472	N = 1649
P = 3.7	P = 4.1	P = 3.7	P = 3.5

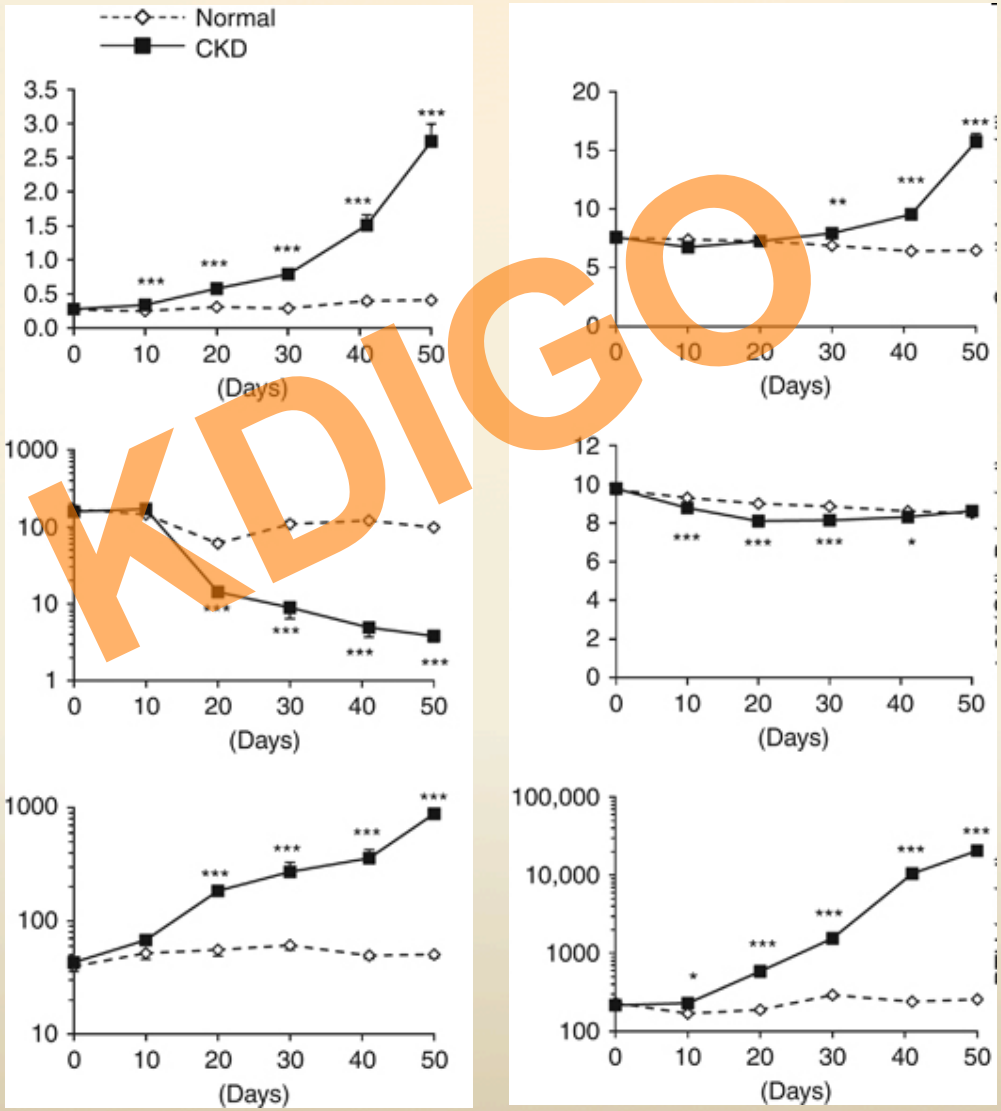
Isakova et al. Kidney Int 2011

FGF23, phosphate and PTH in CRIC



Isakova et al. Kidney Int 2011

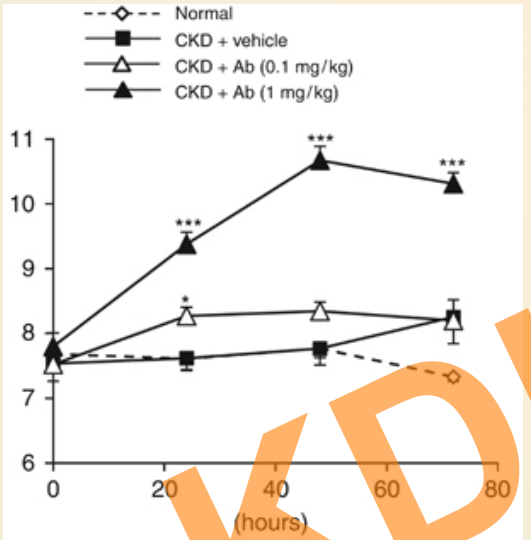
Disordered Mineral Metabolism in Rats with Anti-GBM Nephritis



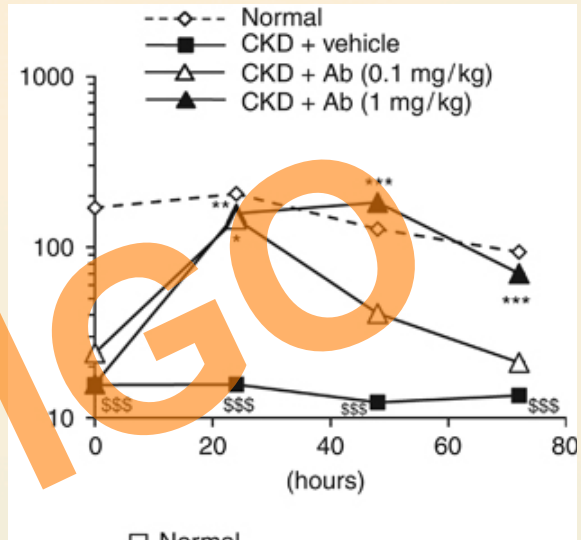
Hasegawa et al. Kidney Int 2010

Effects of Anti-FGF23 Antibodies

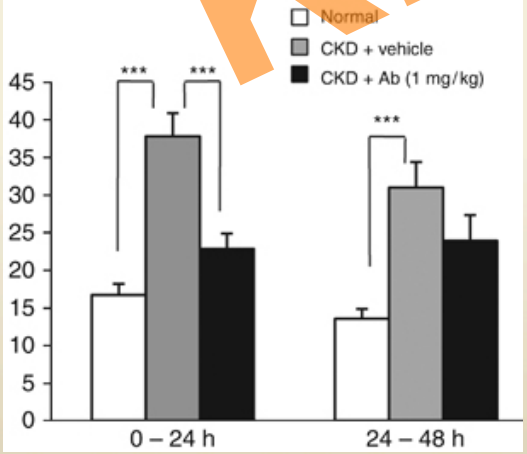
Increase serum P



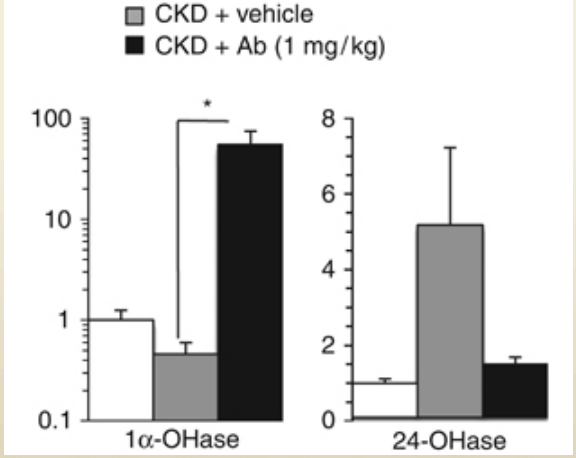
Normalize 1,25D



Decrease phosphaturia: FEPi

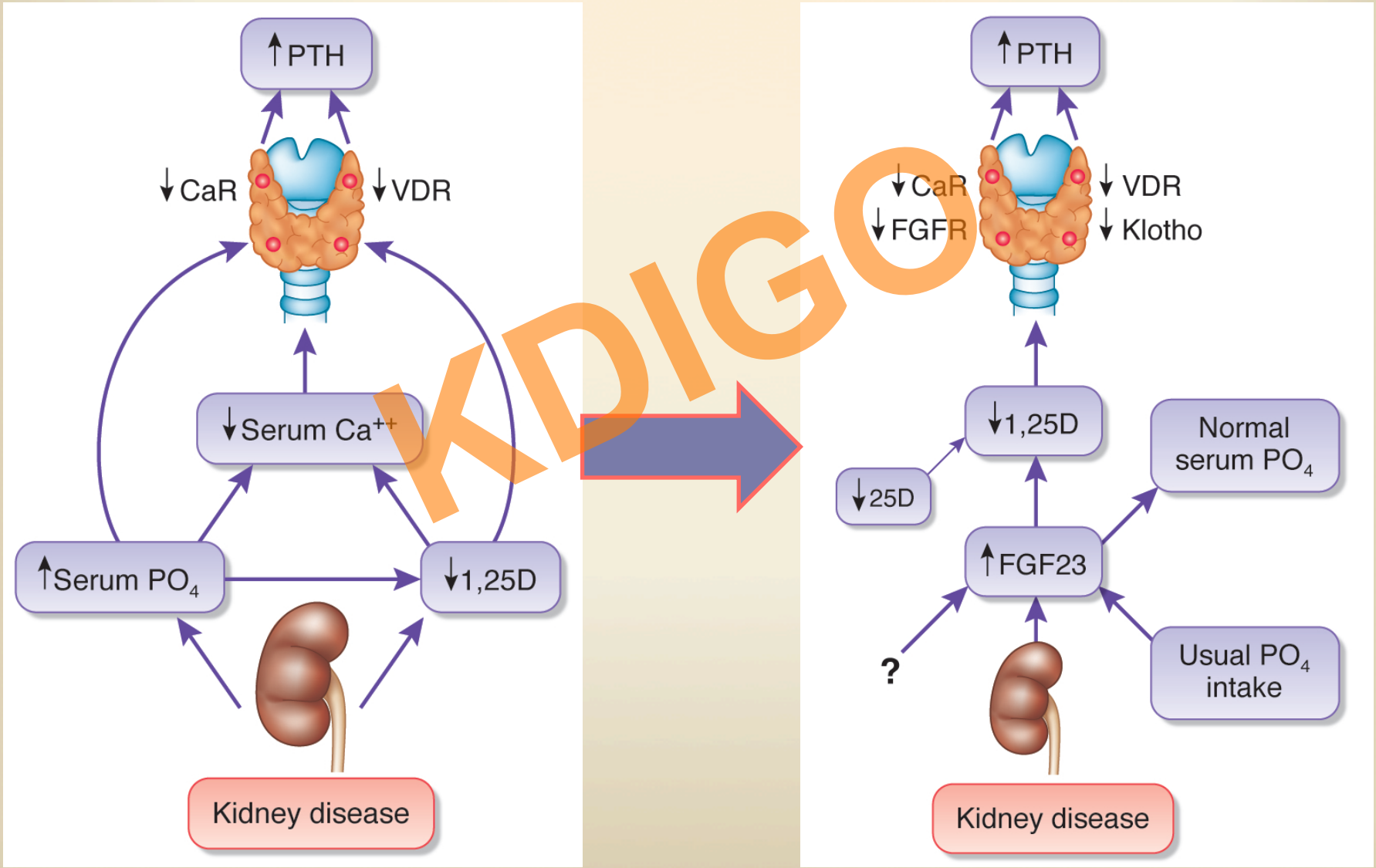


Reverse CYP regulation



Hasegawa et al. Kidney Int 2010

Emerging views on the pathogenesis of disordered mineral metabolism in CKD

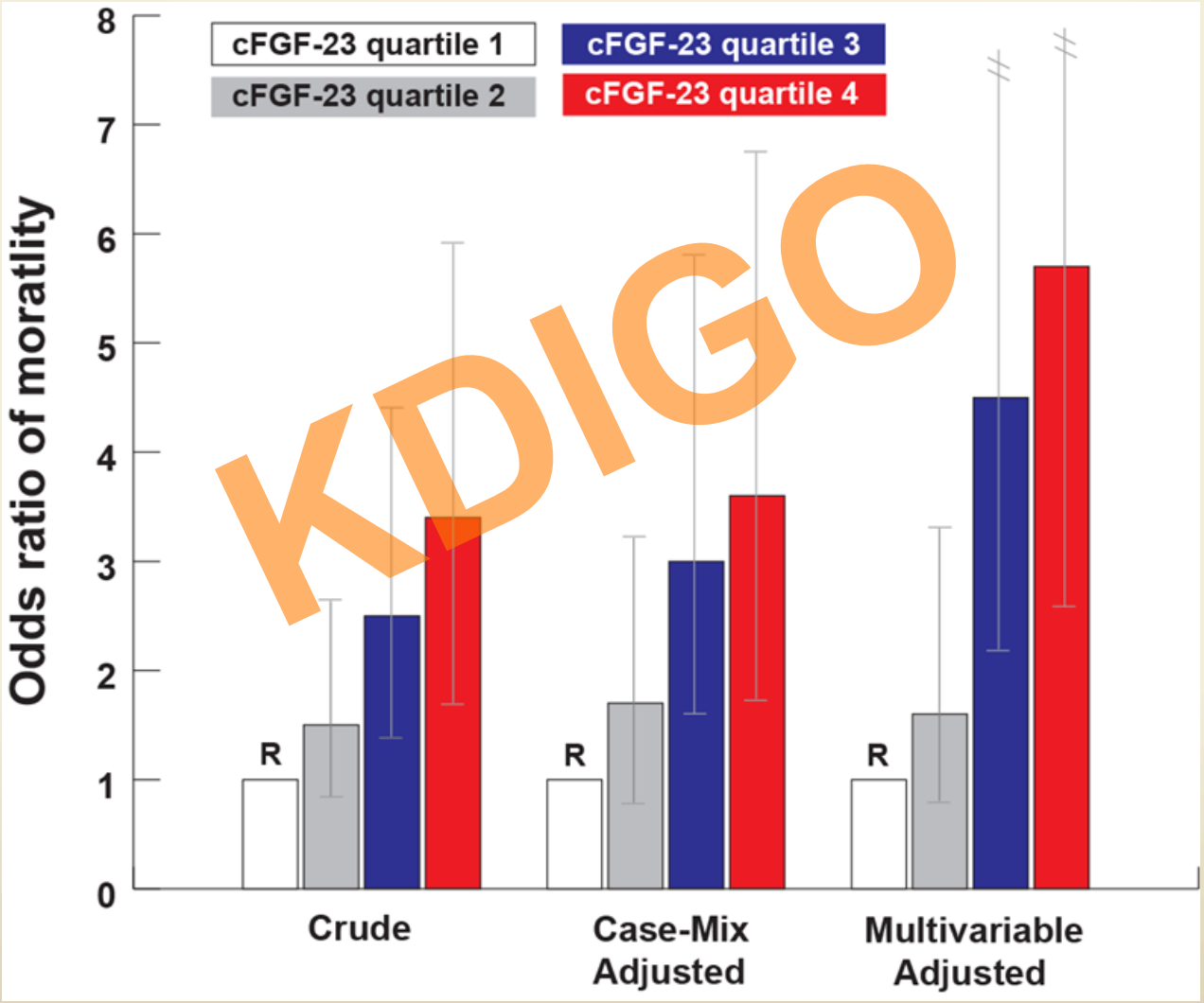


Isakova, Wolf, Kidney Int 2010

OUTCOMES STUDIES

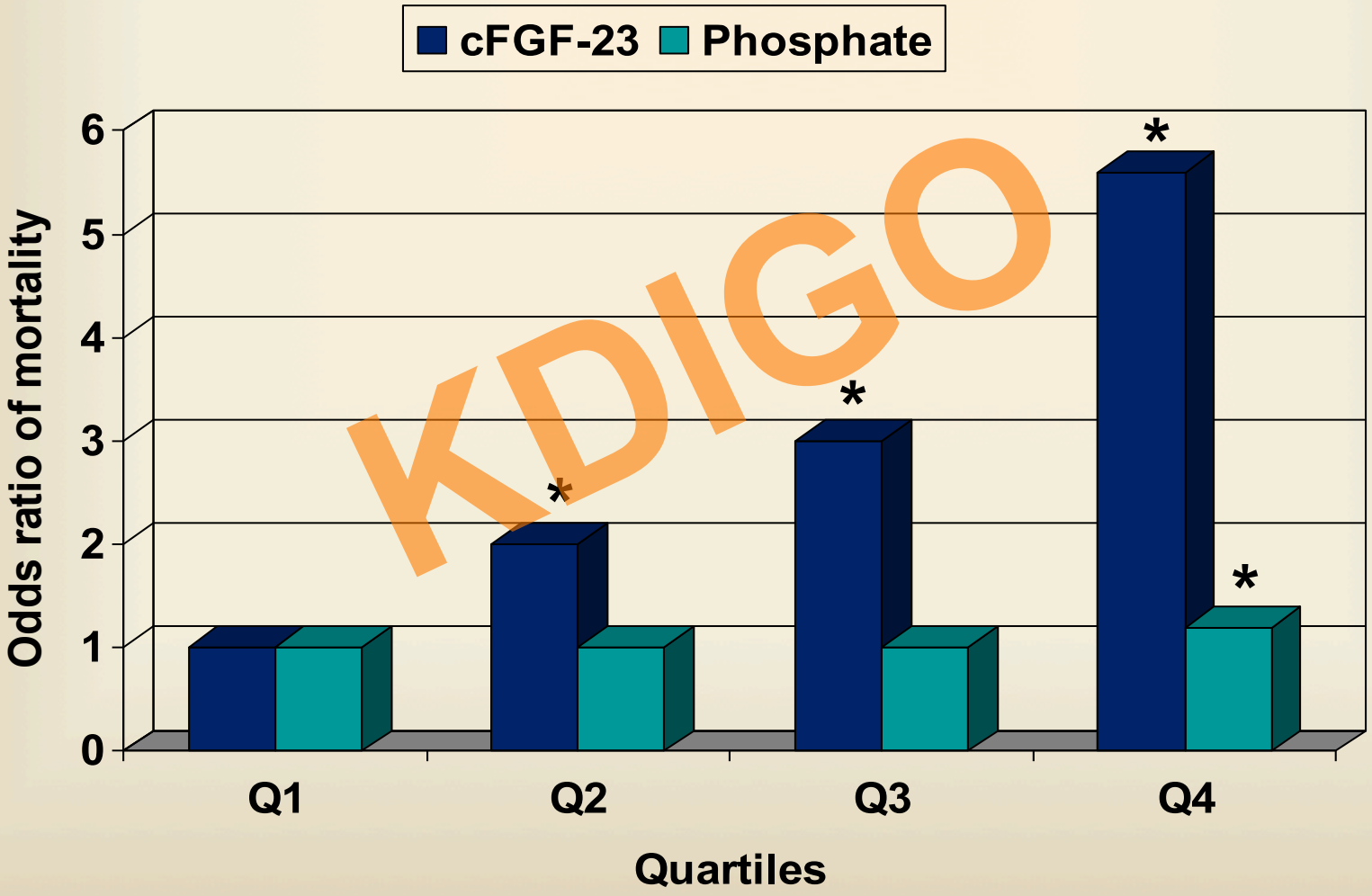
Mortality
CVD Events
CKD Progression

FGF23 and Mortality in Incident ESRD



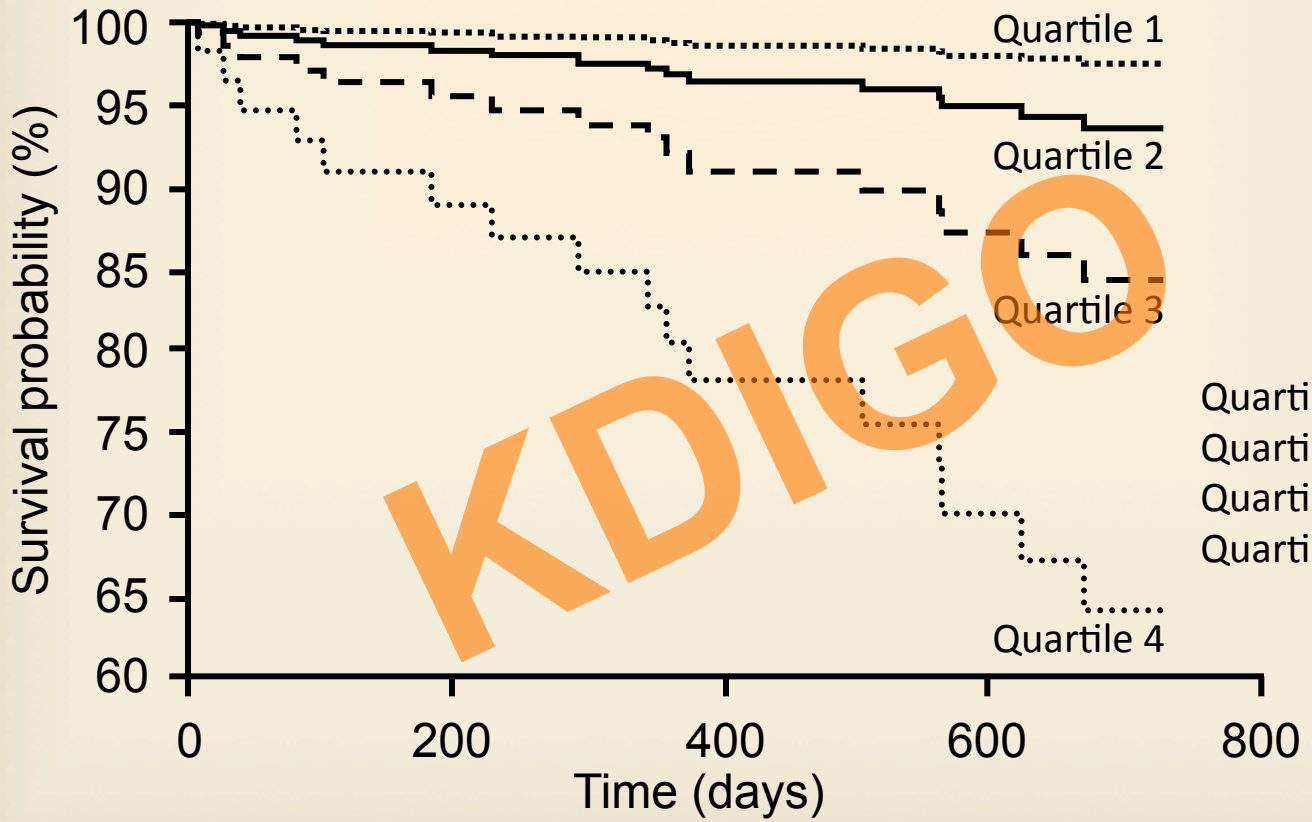
Gutierrez et al N Engl J Med 2008

cFGF-23 vs. Phosphate Quartiles & Mortality



Gutierrez et al N Engl J Med 2008

Two-year survival according to FGF23: Prevalent hemodialysis

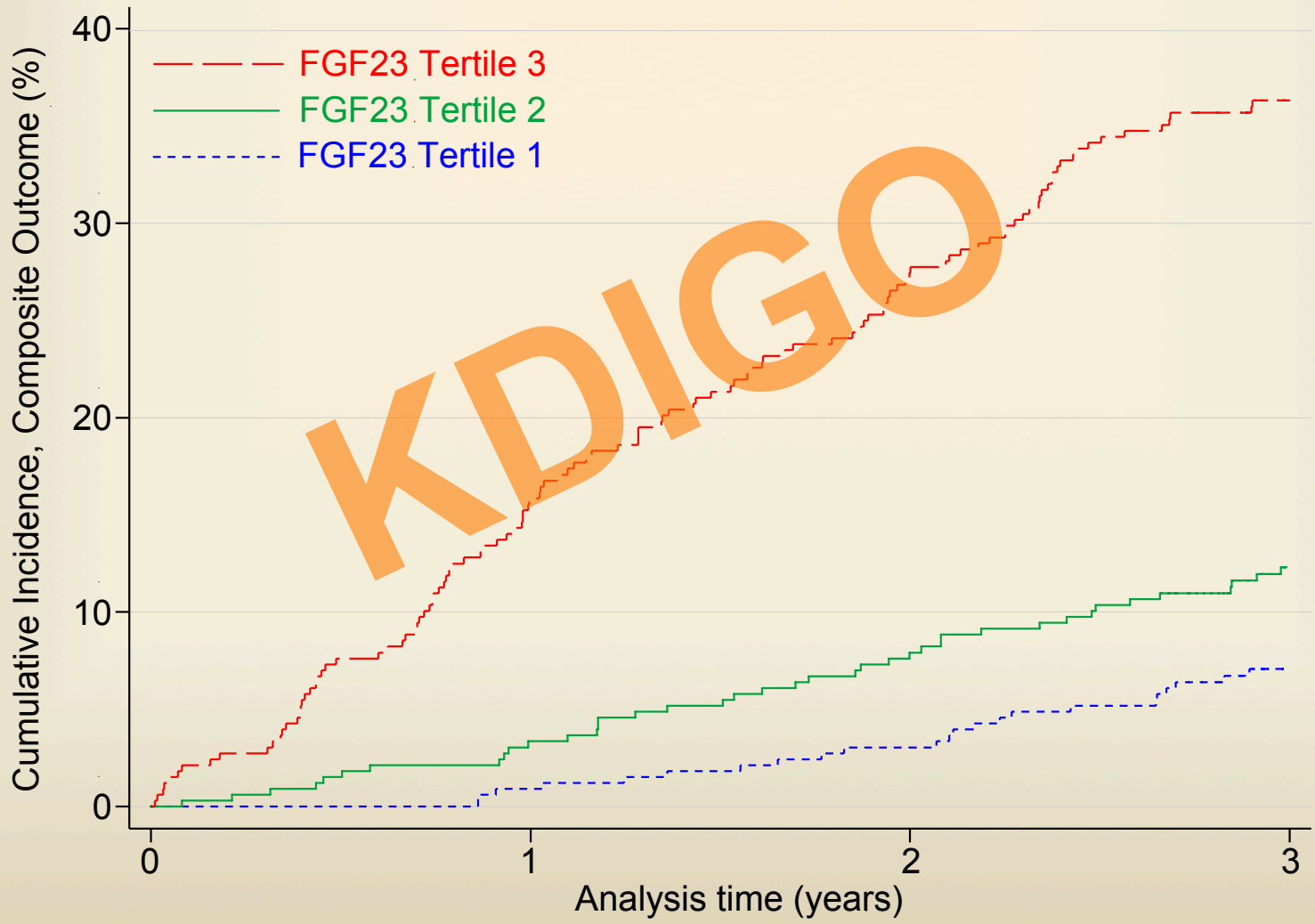


Quartile 1= <1100 RU/mL
Quartile 2= 1100–2700 RU/mL
Quartile 3= 2701–8400 RU/mL
Quartile 4= >8400 RU/mL

Nb 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

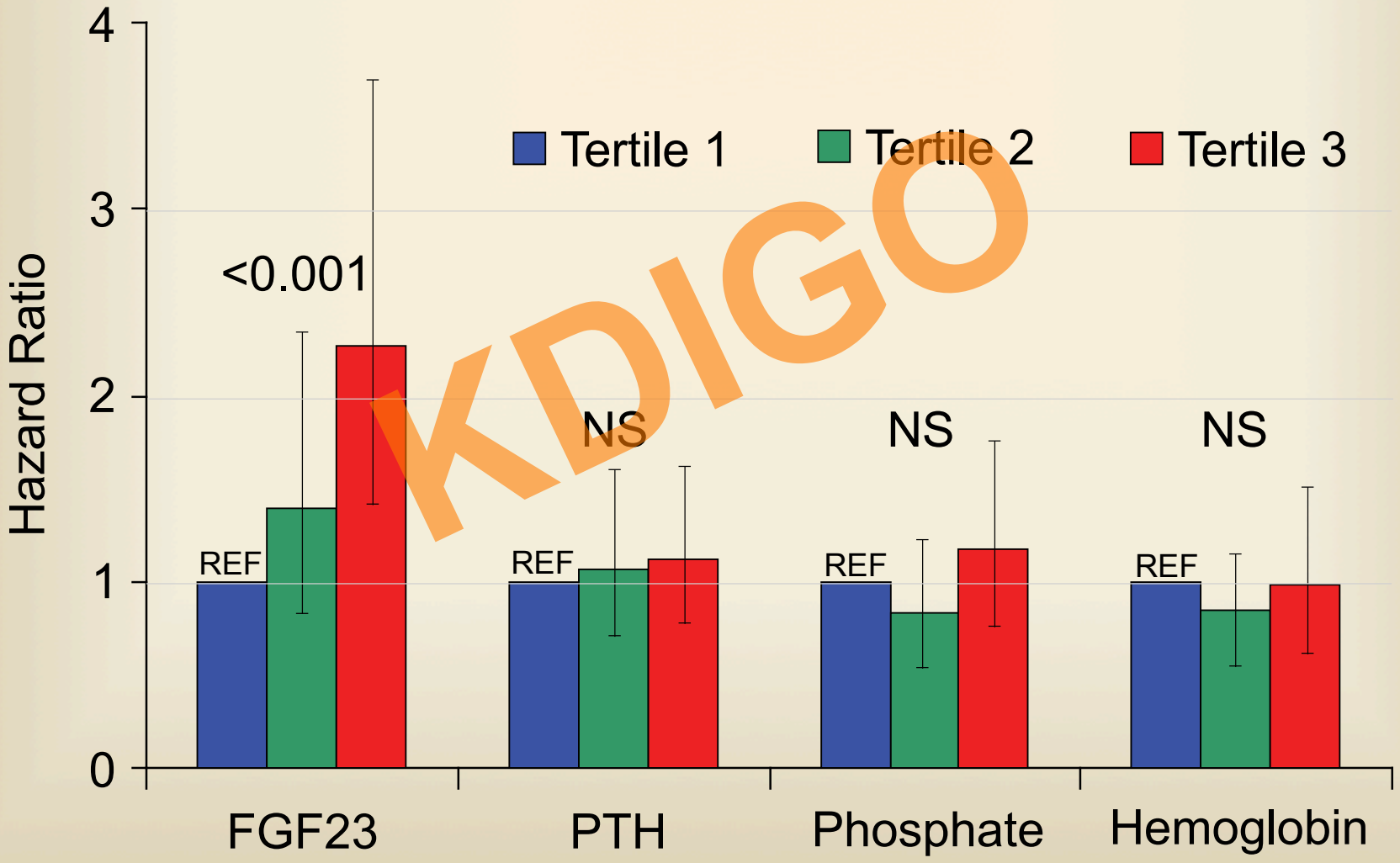
Jean et al. Nephrol Dial Transplant 2009; e-pub ahead of print

FGF23 Tertiles & Composite Risk of Death or Allograft Loss



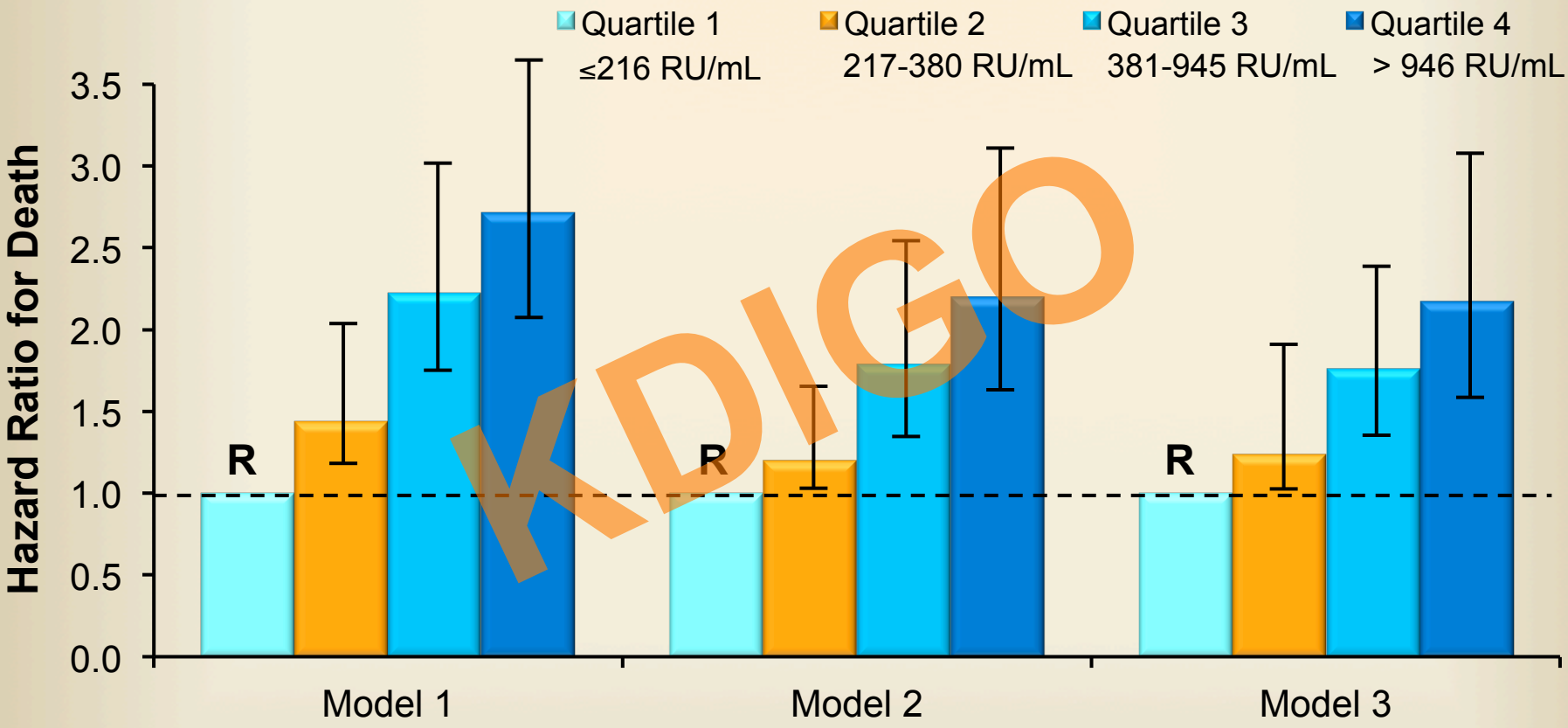
Wolf et al. J Am Soc Nephrol. 2011

FGF23 vs. PTH, Phosphate, Hgb as Risk Factor for Composite Outcome



Wolf et al. J Am Soc Nephrol. 2011

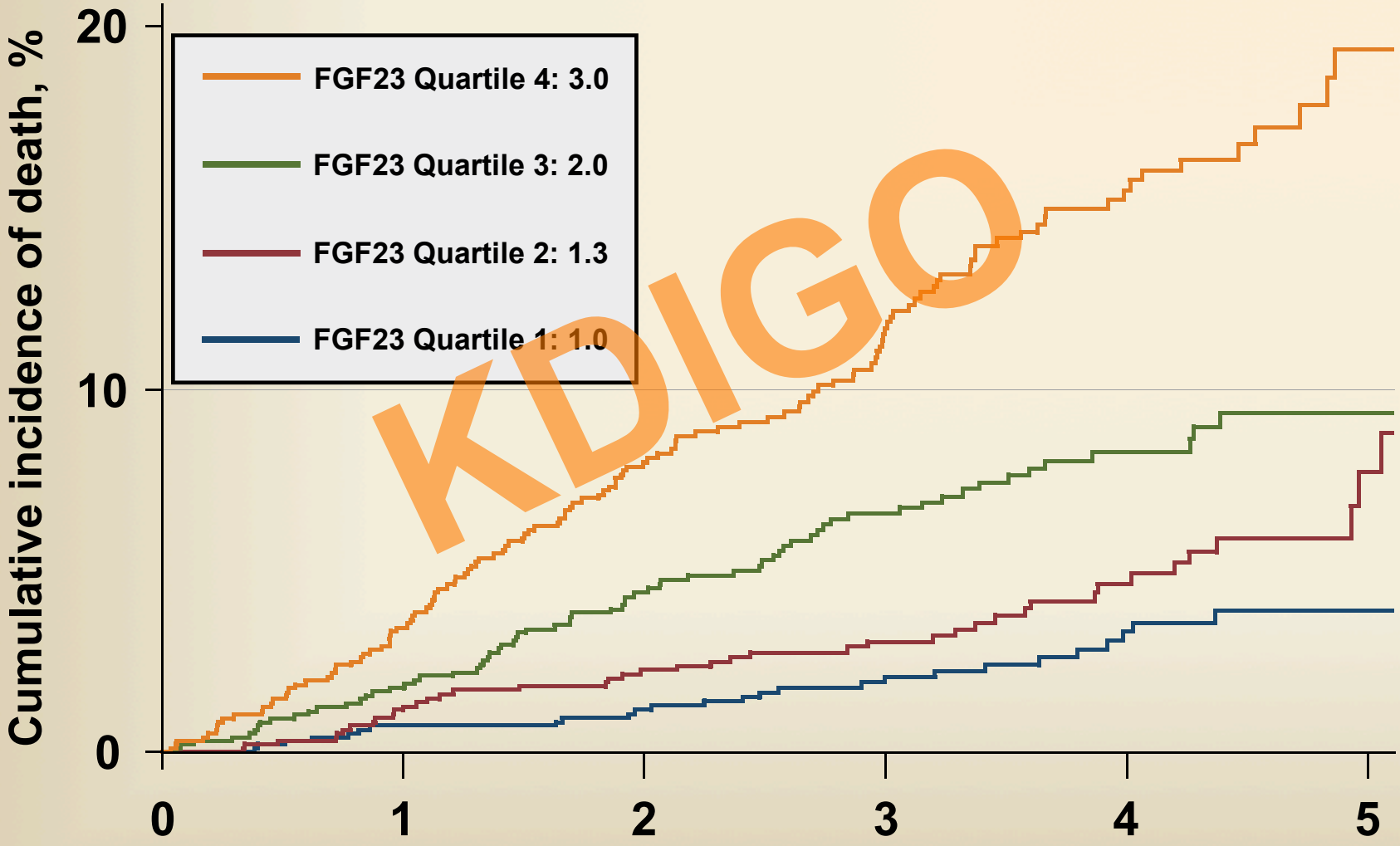
HOST: Higher FGF23 Associated With Greater Risk of All-Cause Mortality in CKD 4



Model 1: age, race, gender.
Model 2: Model 1 + smoking status, alcohol intake, DM, HTN, CVD, BMI, SBP, GFR, treatment assignment, homocysteine, hemoglobin, folate, B12, albumin, calcium, 25(OH)D, $1,25(OH)_2D$, iPTH, phosphorus, HDL, LDL, triglycerides, and total cholesterol.
Model 3: Model 2 + use of medications.

Kendrick JR, et al. *J Am Soc Nephrol*. 2011

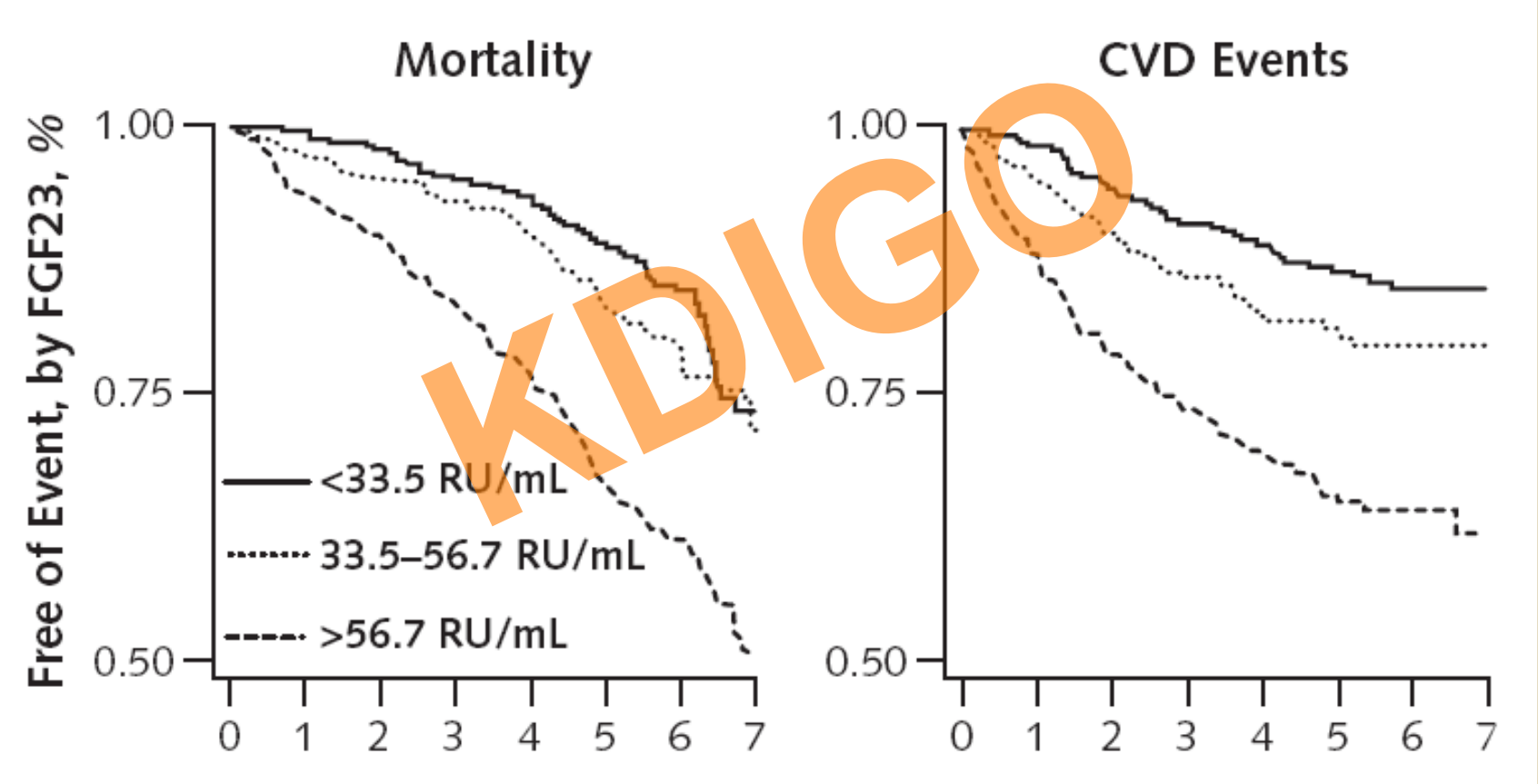
FGF23 and Mortality in CKD 2-4: 266 events, 20.3/1000 person-years



Isakova et al. JAMA 2011.

FGF-23 and CVD in non-CKD: Heart & Soul

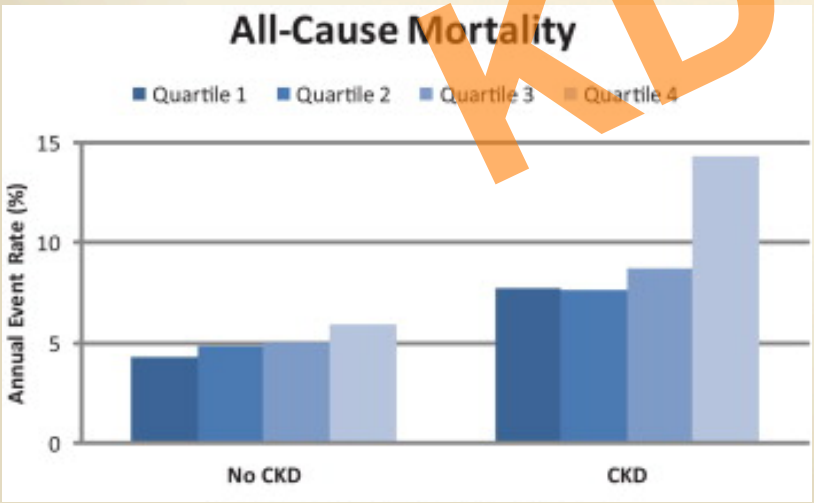
N=833 with history of CAD

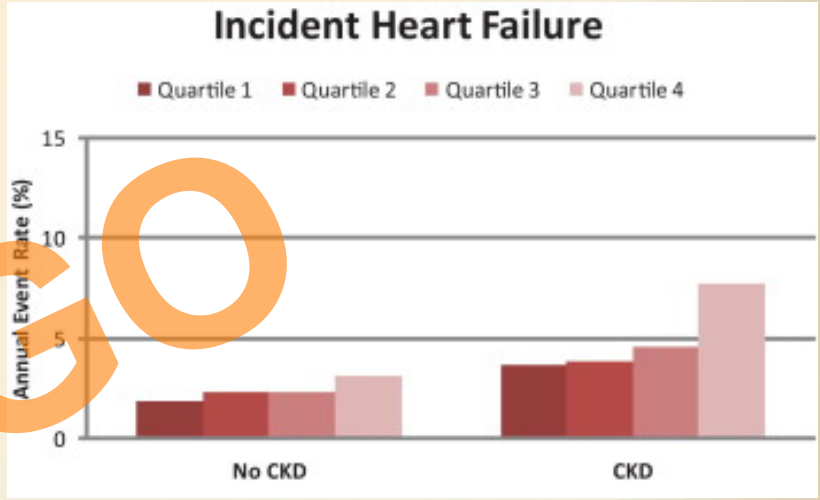


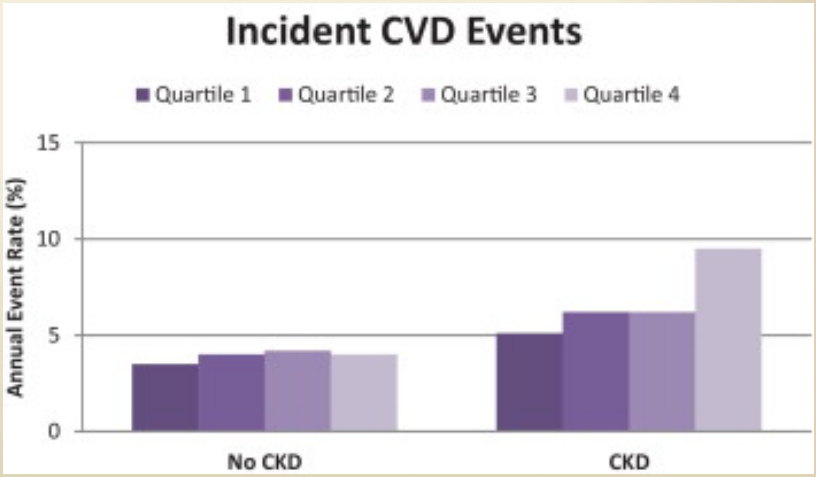
Parker et al. Ann Intern Med 2010

FGF23 and outcomes in CHS

- N=3107; 1128 with CKD (eGFR<60 or ACR>30 mg/g)
- Strongest association: death, CHF
- No association of FGF23 with MI
- Greater risks in CKD vs. non-CKD







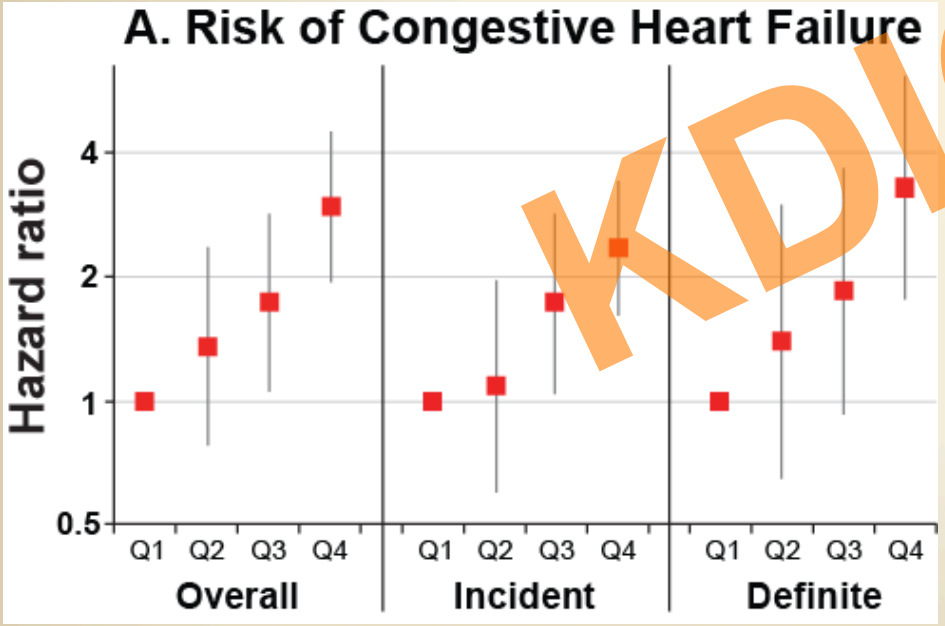
Ix J et al. JACC 2012

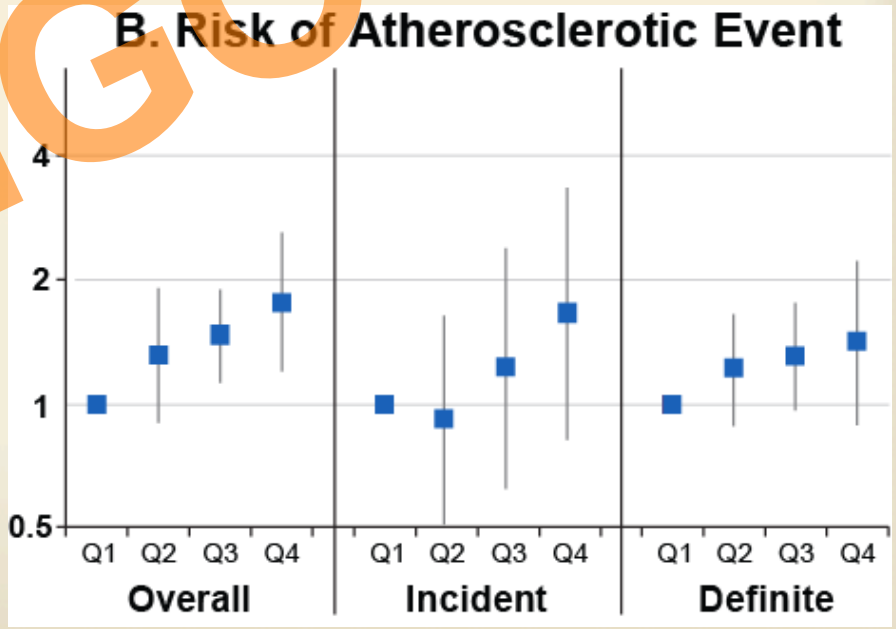
FGF23 and risk of cardiovascular disease events in CKD stages 2 – 4

N=3860; Median follow-up, 3.7 years

Congestive Heart Failure
360 events (27/1000 person-years)

Atherosclerosis
287 events (22/1000 person-years)

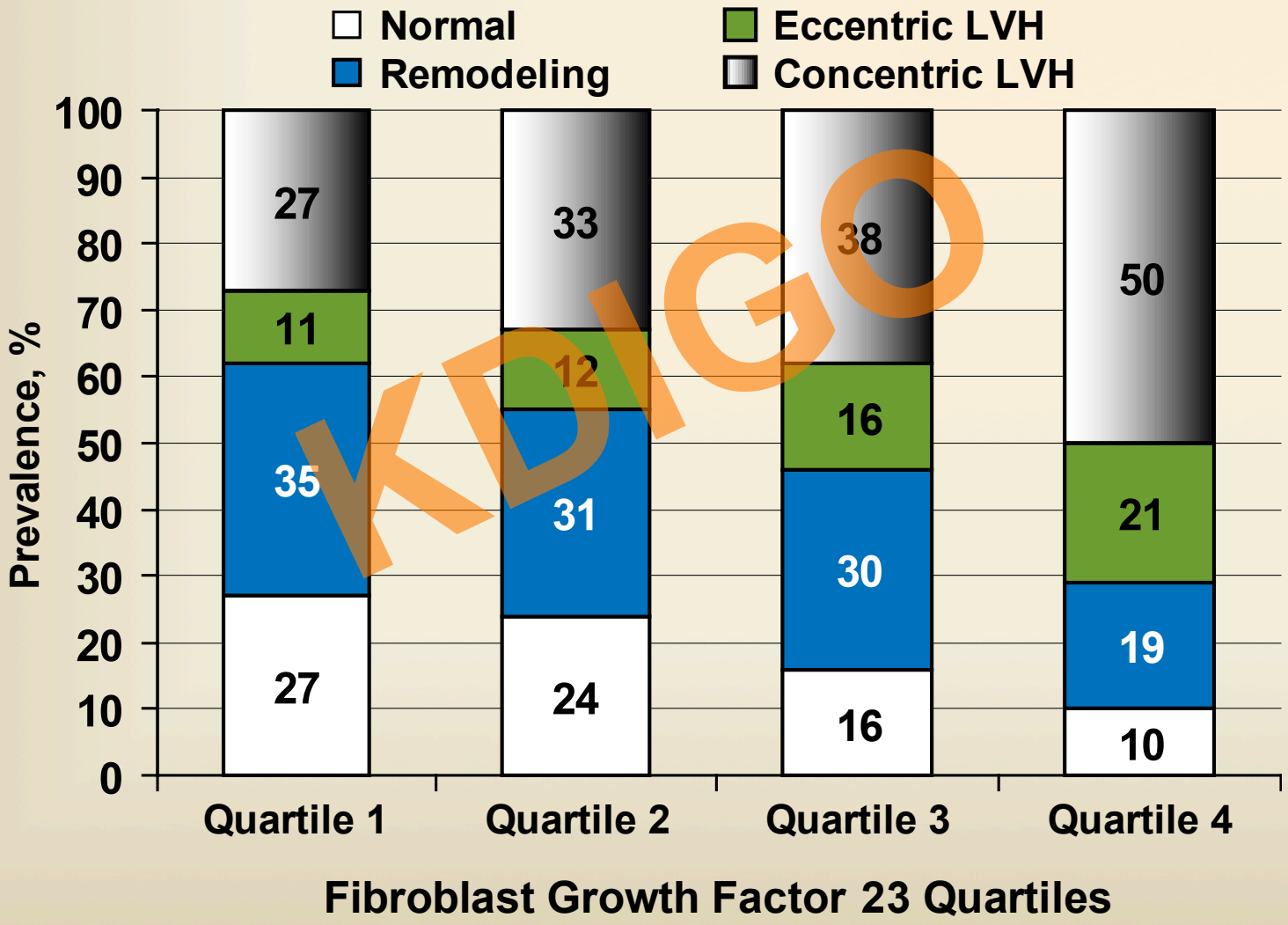




Adjusted for demographics, kidney function, traditional CVD risk factors, medications

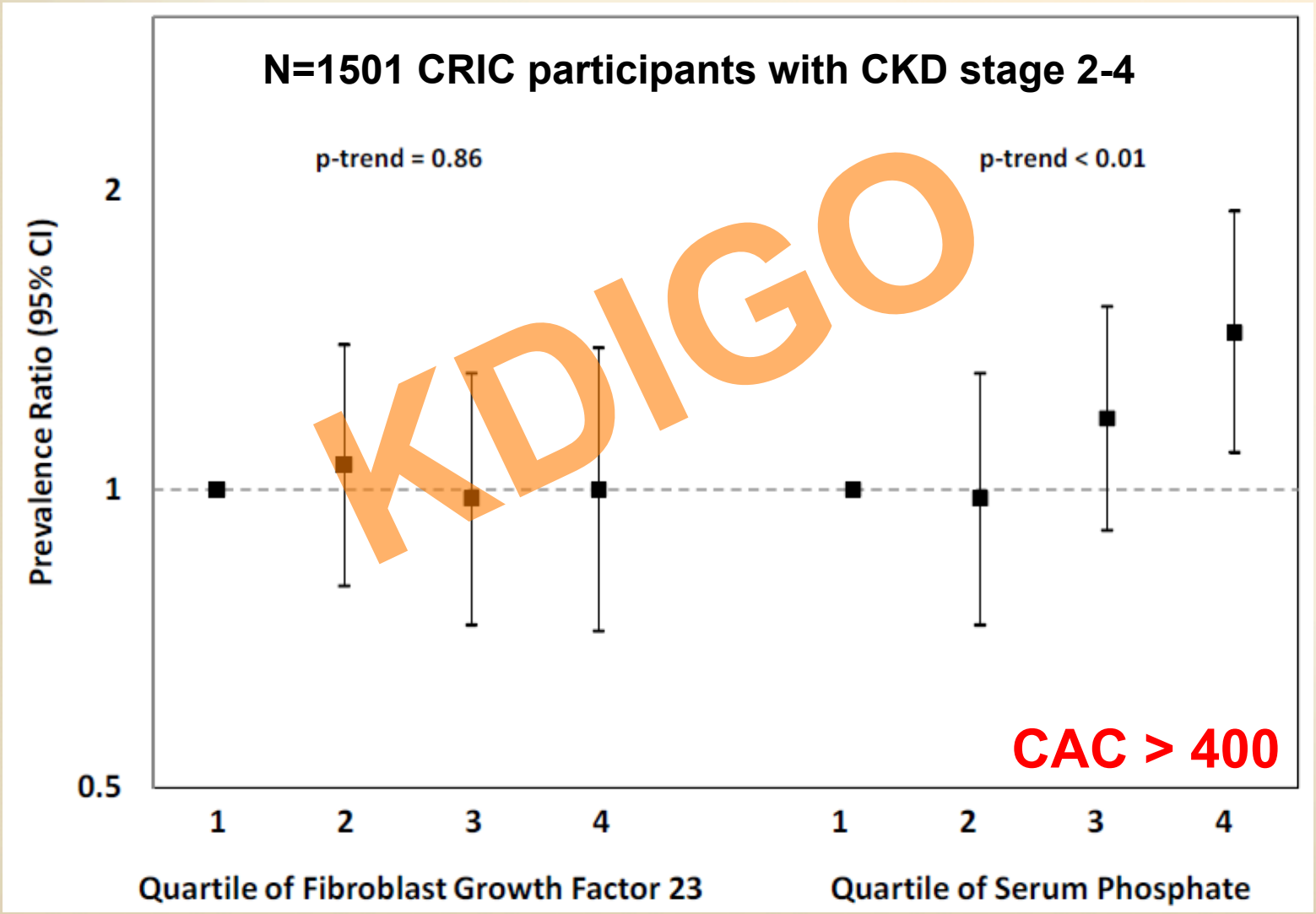
Scialla J et al. J Am Soc Nephrol; In press

LV Geometry According to Ascending Quartiles of FGF23



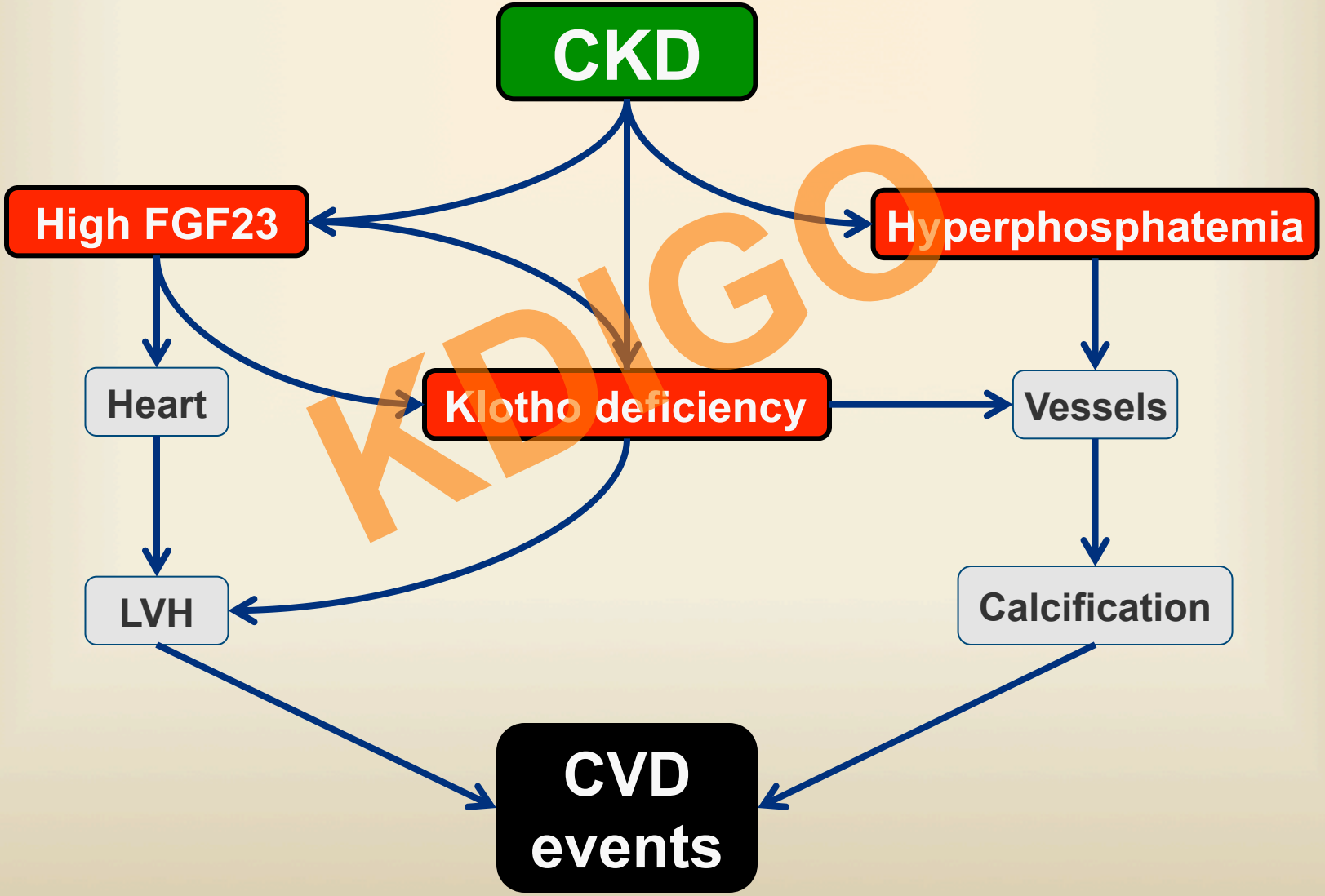
Faul, Amaral, Oskuei et al. J Clin Invest. 2011.

FGF23 vs. phosphate as risk factors for CAC

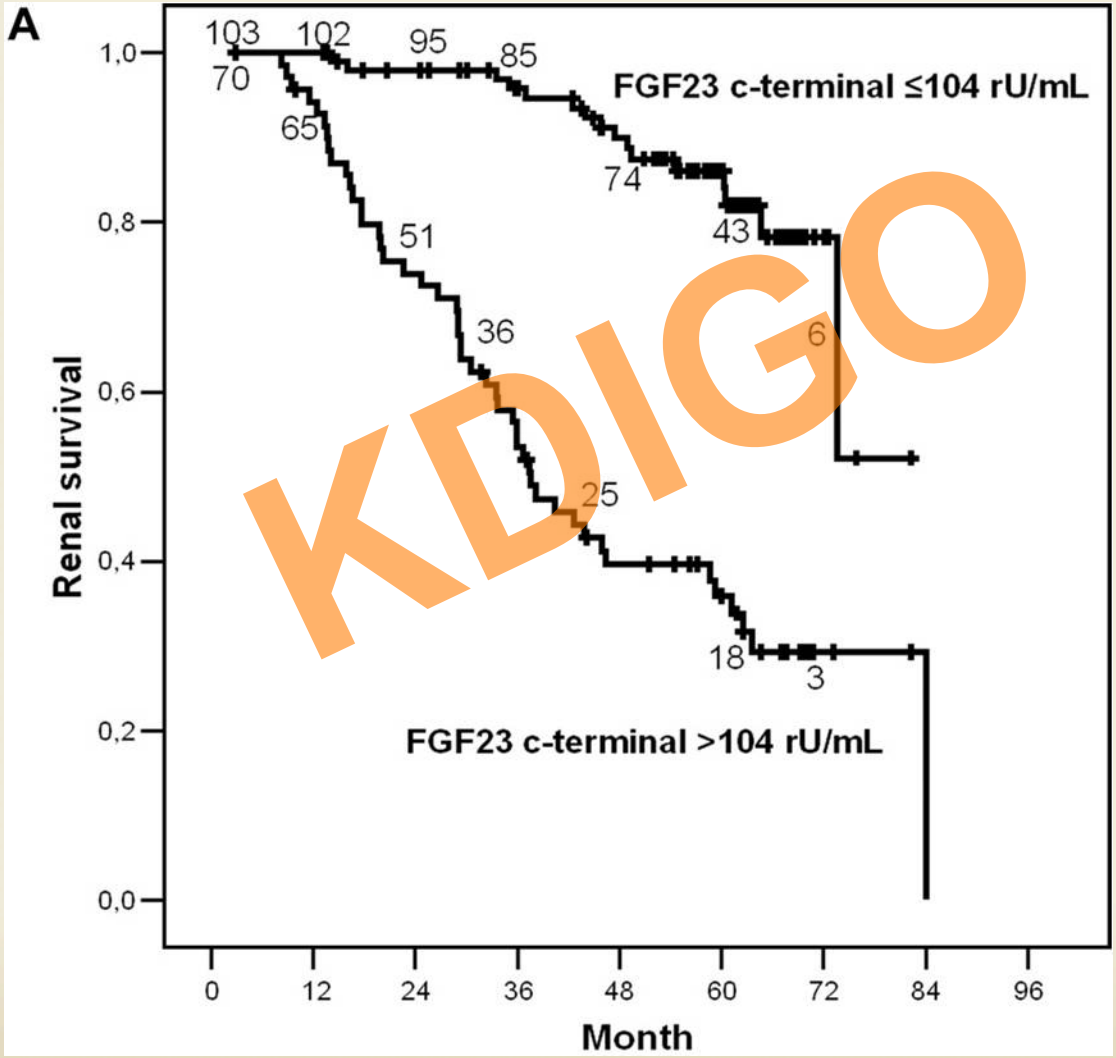


Scialla et al. Kidney Int 2013

Disordered phosphate homeostasis and cardiovascular disease in CKD

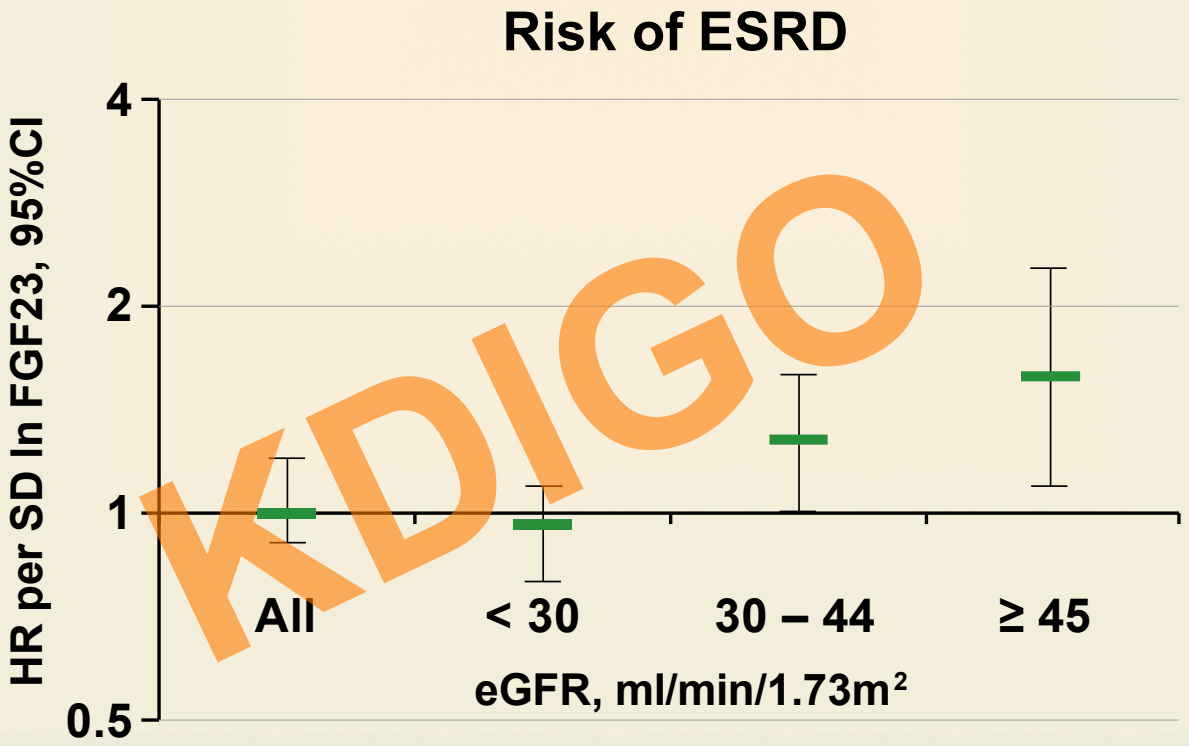


Renal progression according to cFGF-23 levels



Fliser et al. J Am Soc Nephrol 2007

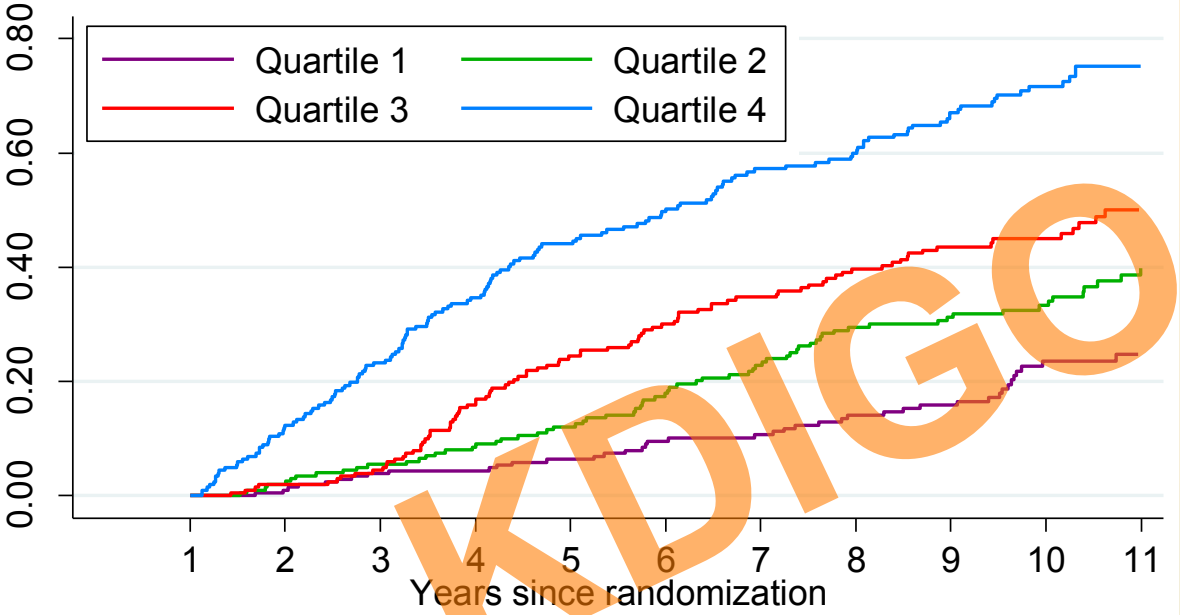
Interaction between FGF23, eGFR and ESRD



N	3879	758	1472	1649
FGF23	145	256	161	105
Events	410	231	143	36
Incidence	33.0	111.2	30.6	6.3

Isakova et al. JAMA 2011.

FGF23 is a risk factor for ESRD in AASK



FGF23	+GFR	MV	+MM	+GFR slope
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	1.40	1.47	1.54	1.44
Quartile 3	1.58	1.67	1.79	1.65
Quartile 4	2.17	2.24	2.29	2.22
p-trend	<0.01	<0.01	<0.01	<0.01

N = 809

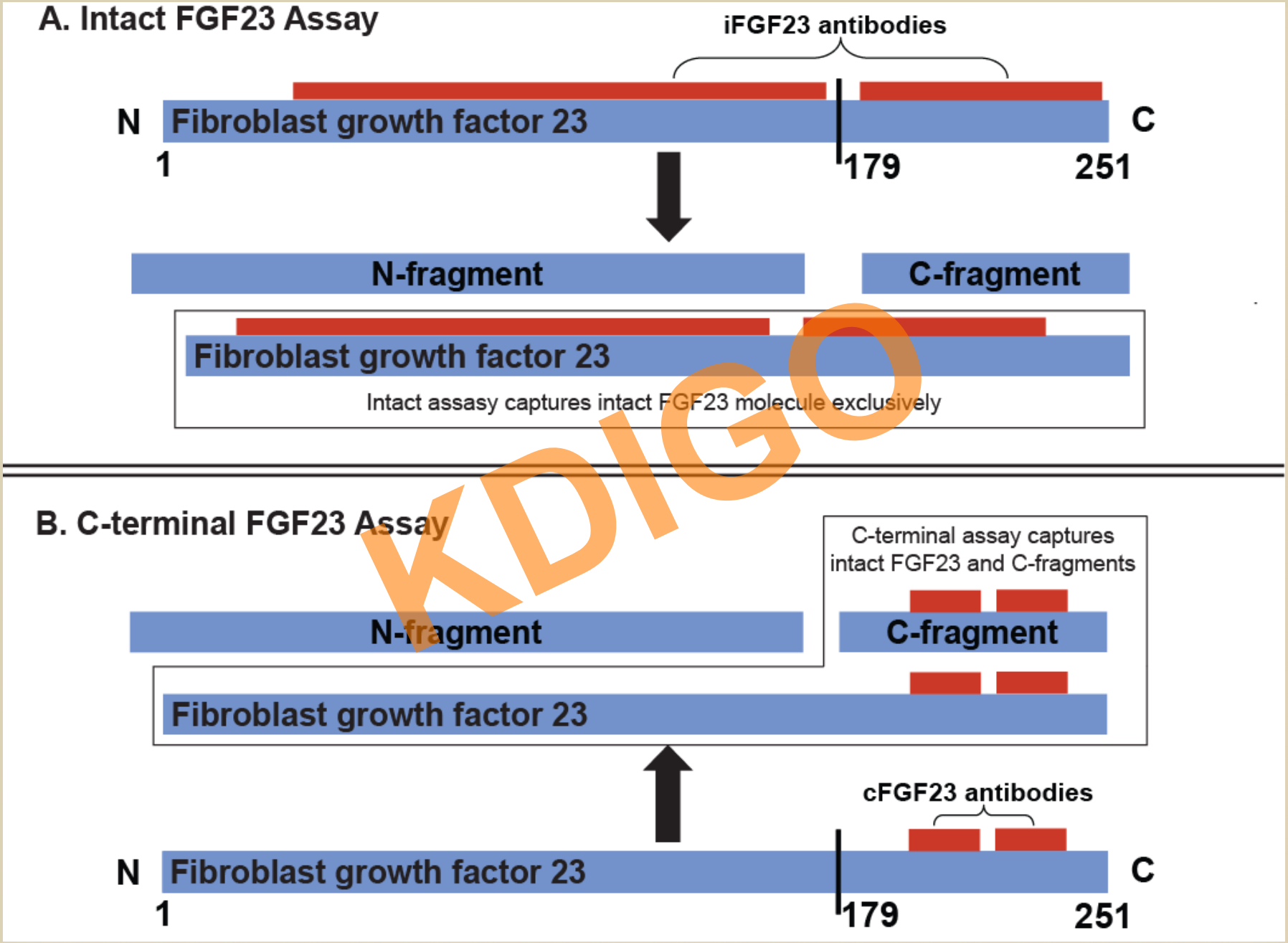
MV: adjusted for: age, sex, Rx group; GFR; UPCR; income, prior heart disease, smoking, albumin, BMI, center

+MM: adjusted for PTH, phosphate, 25-hydroxyvitamin D, calcium

+GFR slope: adjusted for year 1 GFR slope

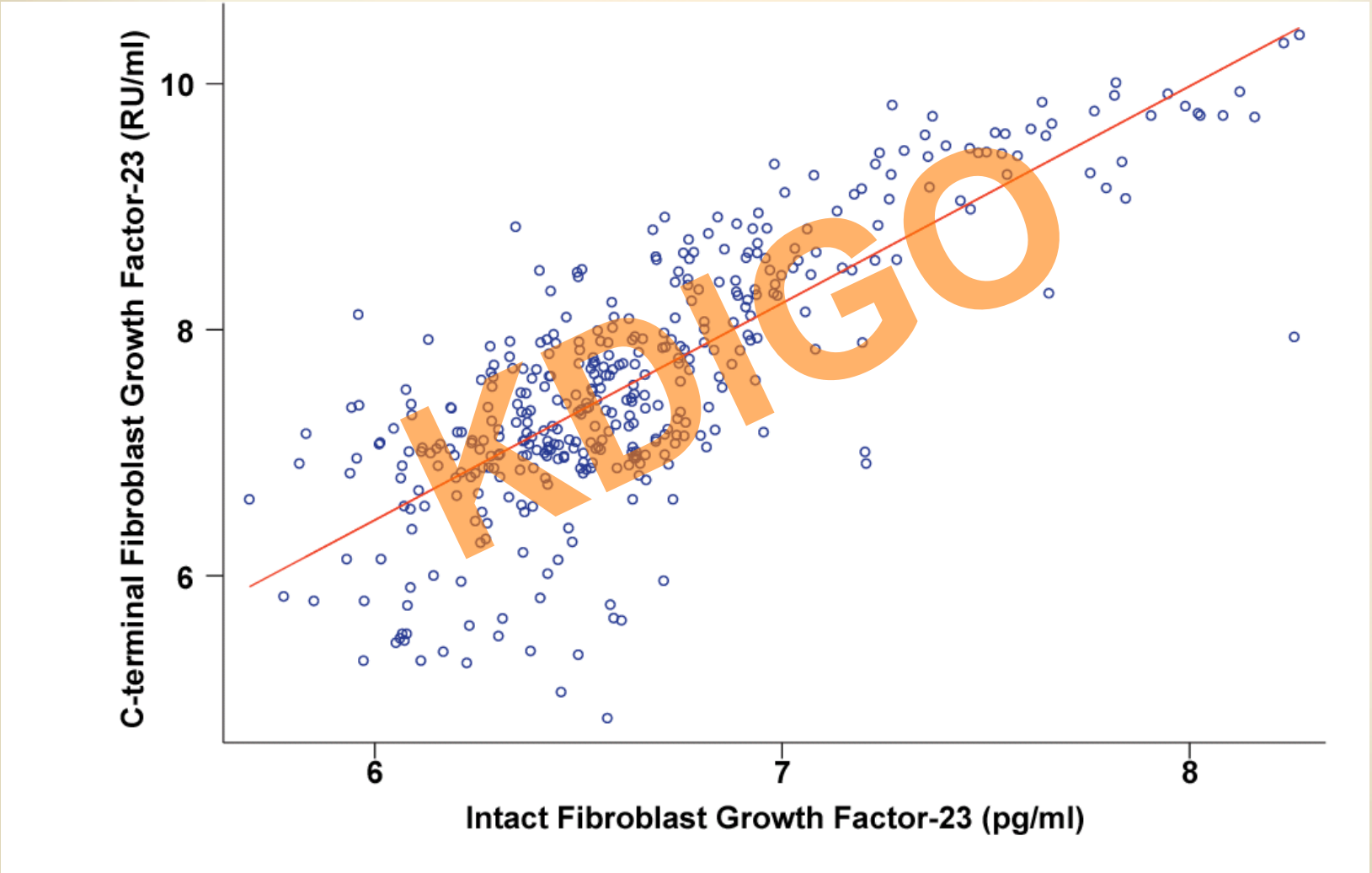
Scialla et al. JASN 2012

ASSAYS and OTHER ODDS AND ENDS



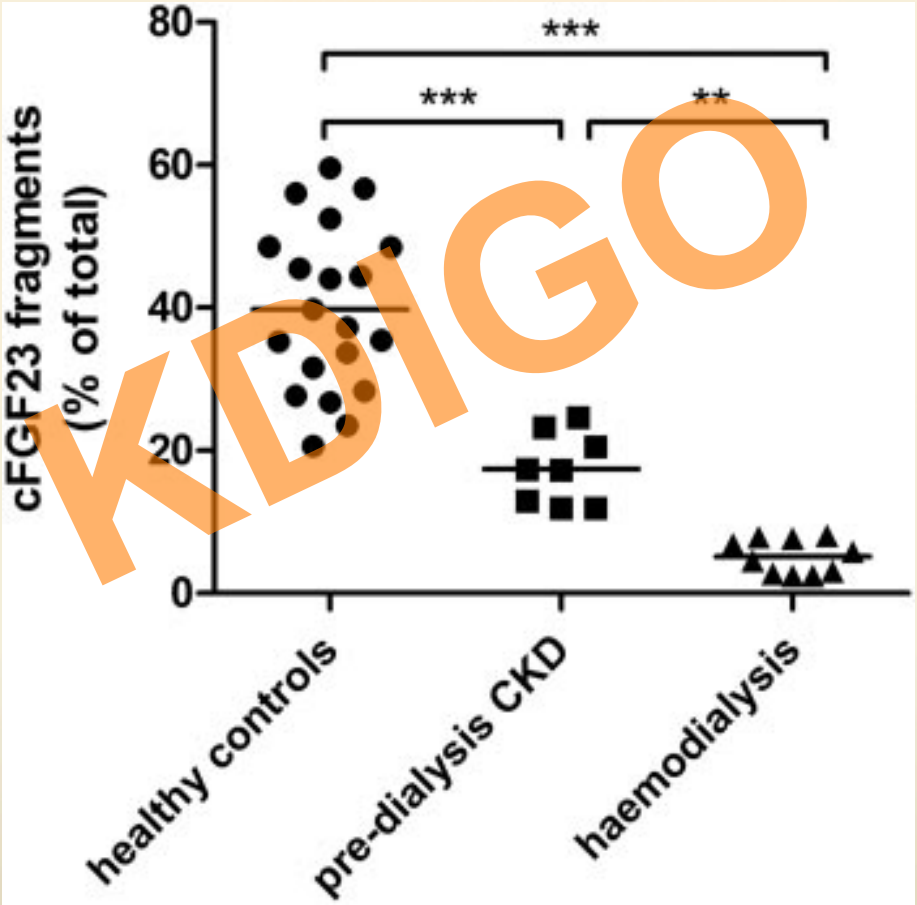
Zisman, Wolf; Curr Opin Nephrol Hypertens 2010

Correlation between cFGF-23 & iFGF-23



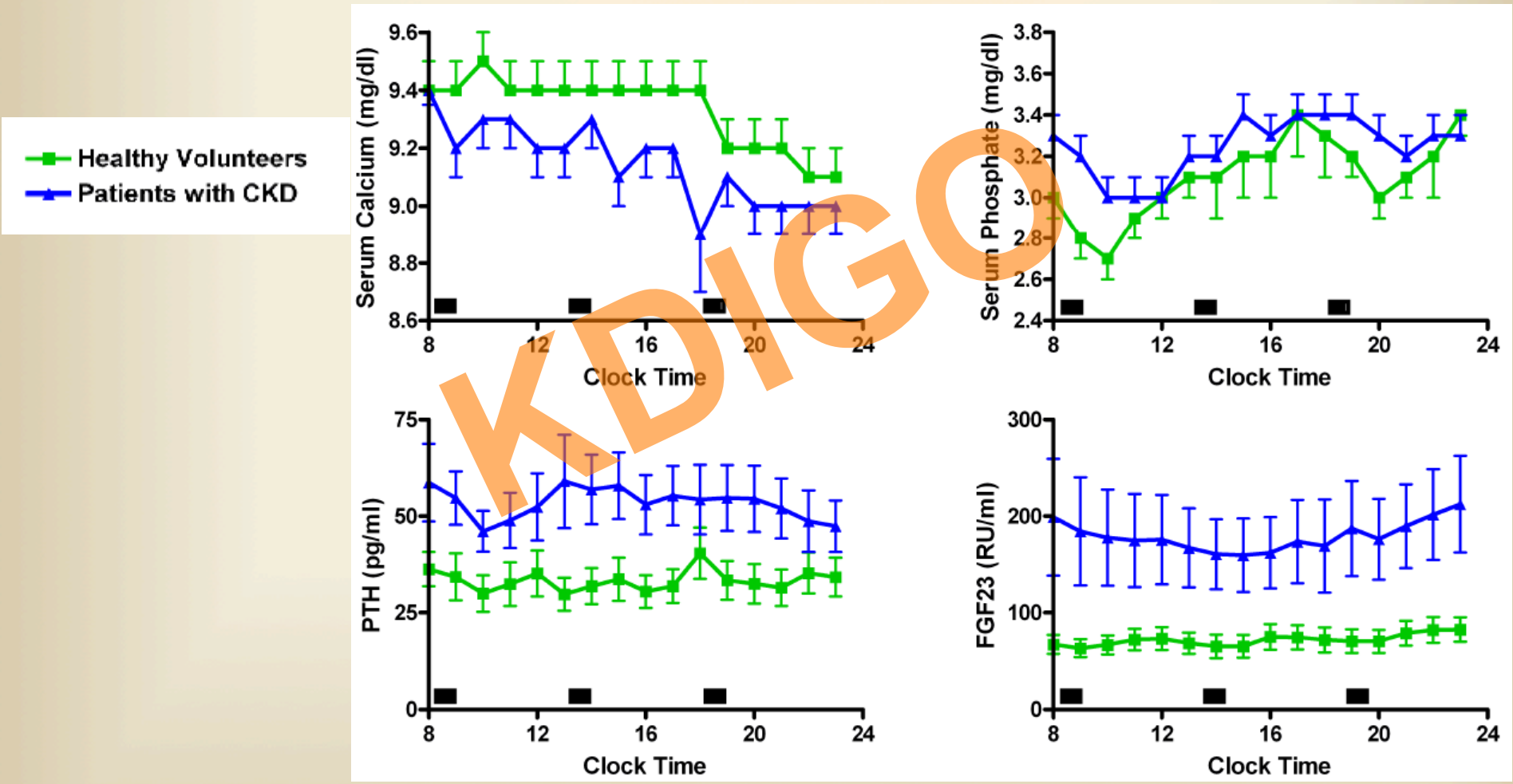
Gutierrez et al N Engl J Med 2008

Differences in the Proportion of FGF23 Present as C-terminal Fragments



Smith et al. JCEM 2012

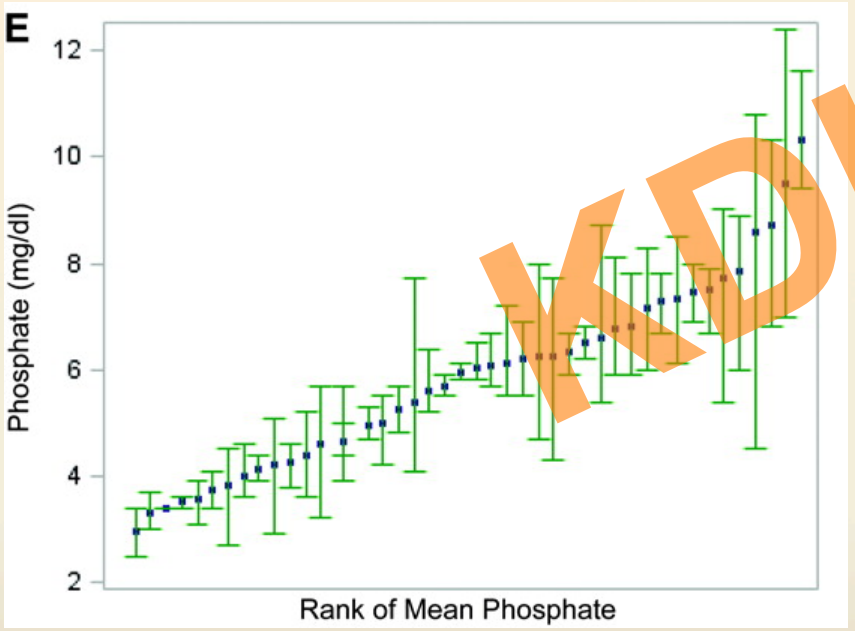
Intact Diurnal Variation in Mineral Metabolism in CKD

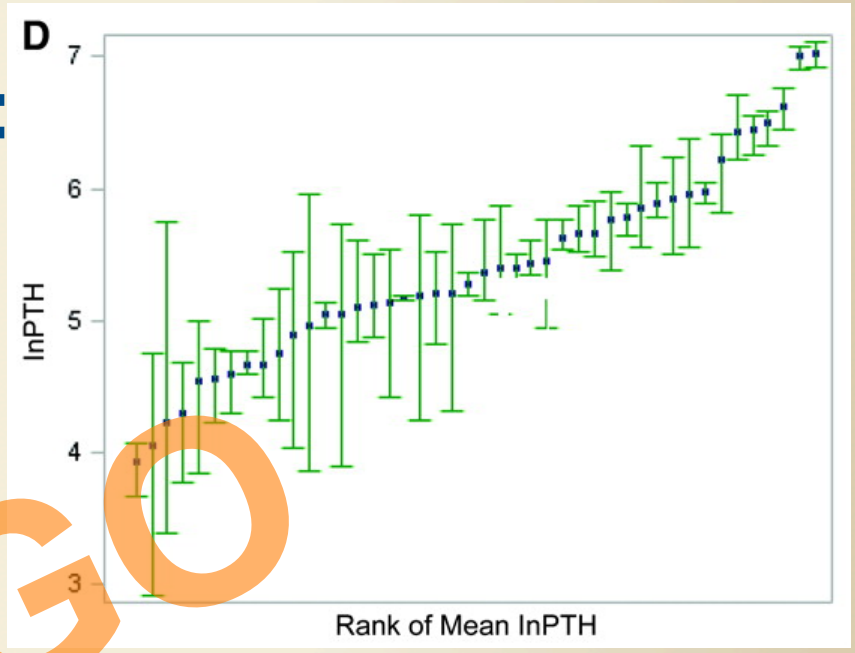


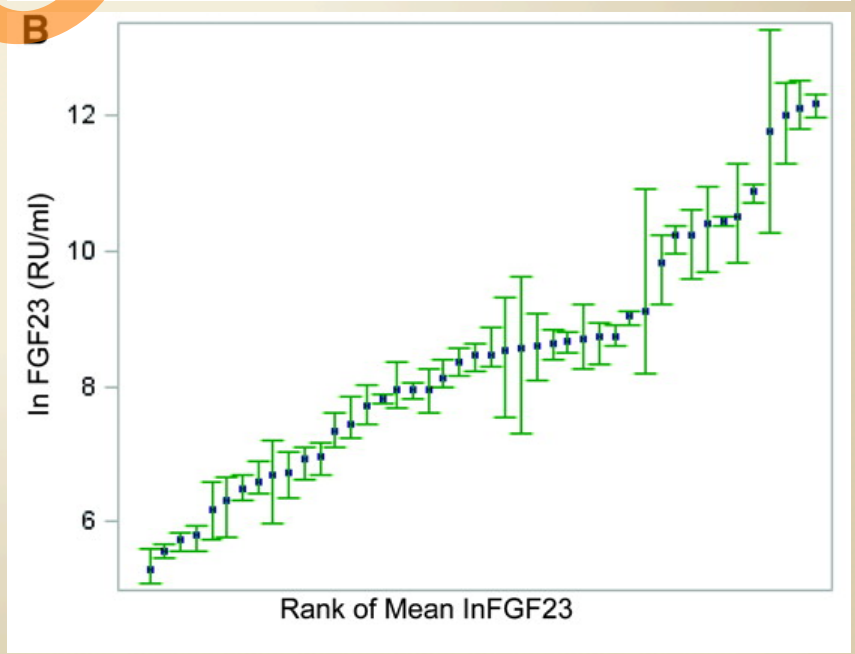
Isakova T et al. CJASN 2012

Within-Subject Variation: FGF23, PTH, Phosphate

3 monthly measurements in 67 PD patients







Isakova T et al. CJASN 2011;6:2688-2695

Factors that Modify FGF23

Raises FGF23	Lowers FGF23
CKD Low GFR AKI	Kidney transplantation
High phosphate diet	Low phosphate diet
Calcium PTH	Hypocalcemia Non-calcium P-binders
1,25D and analogs	Cinacalcet
Certain IV iron formulations	Certain IV iron formulations

Major unanswered questions

- What stimulates FGF23 production in early CKD?
- Does the FGF23 response differ by CKD etiology?
- What is FGF23 actually regulating?
- How and where is phosphate sensed?
- How and where is FGF23 degraded?
- What are other “off-target” effects of FGF23?
- What are the ideal therapeutic approaches to lower (or slow elevation) FGF23?
- If FGF23 can be modified, can we improve clinical outcomes?