KDIGO Clinical Practice Conference
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FGF-23 and vascular calcification: is it set in stone?

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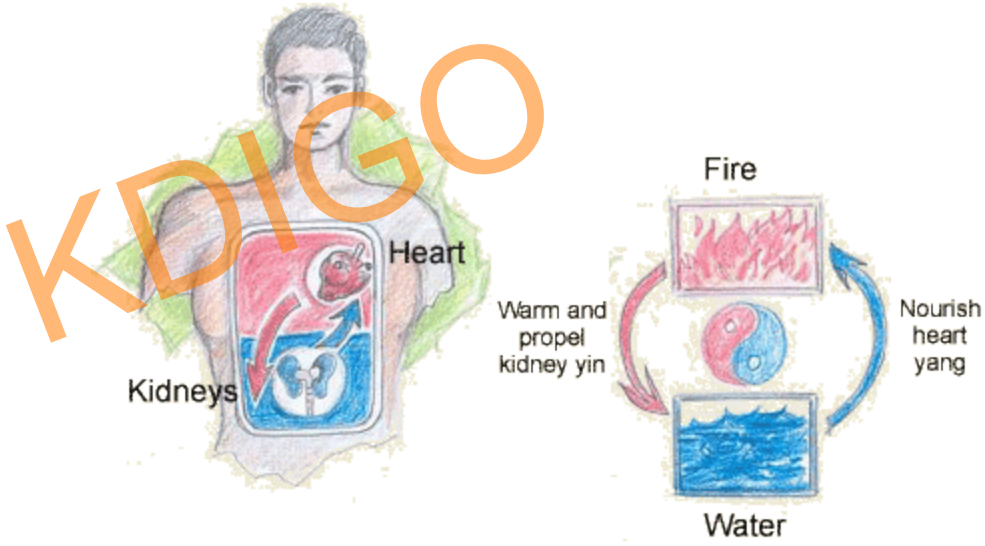
Outline

- The cardiorenal connection
  - Epidemiology
  - Clinical observations
- FGF23 and vascular calcification
  - Mixed data: for and against
- Is FGF23 a useful biomarker afterall?
- The way forward

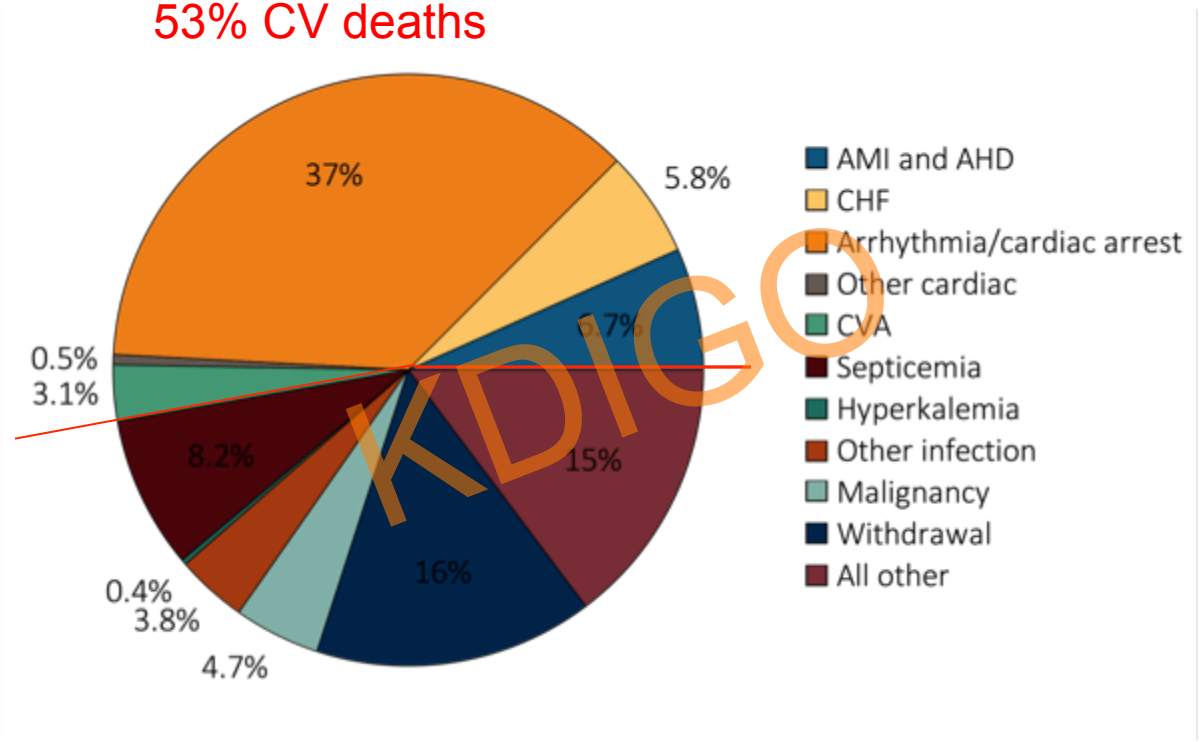
Shennong is thought to have lived between the 27th and 25th centuries BC



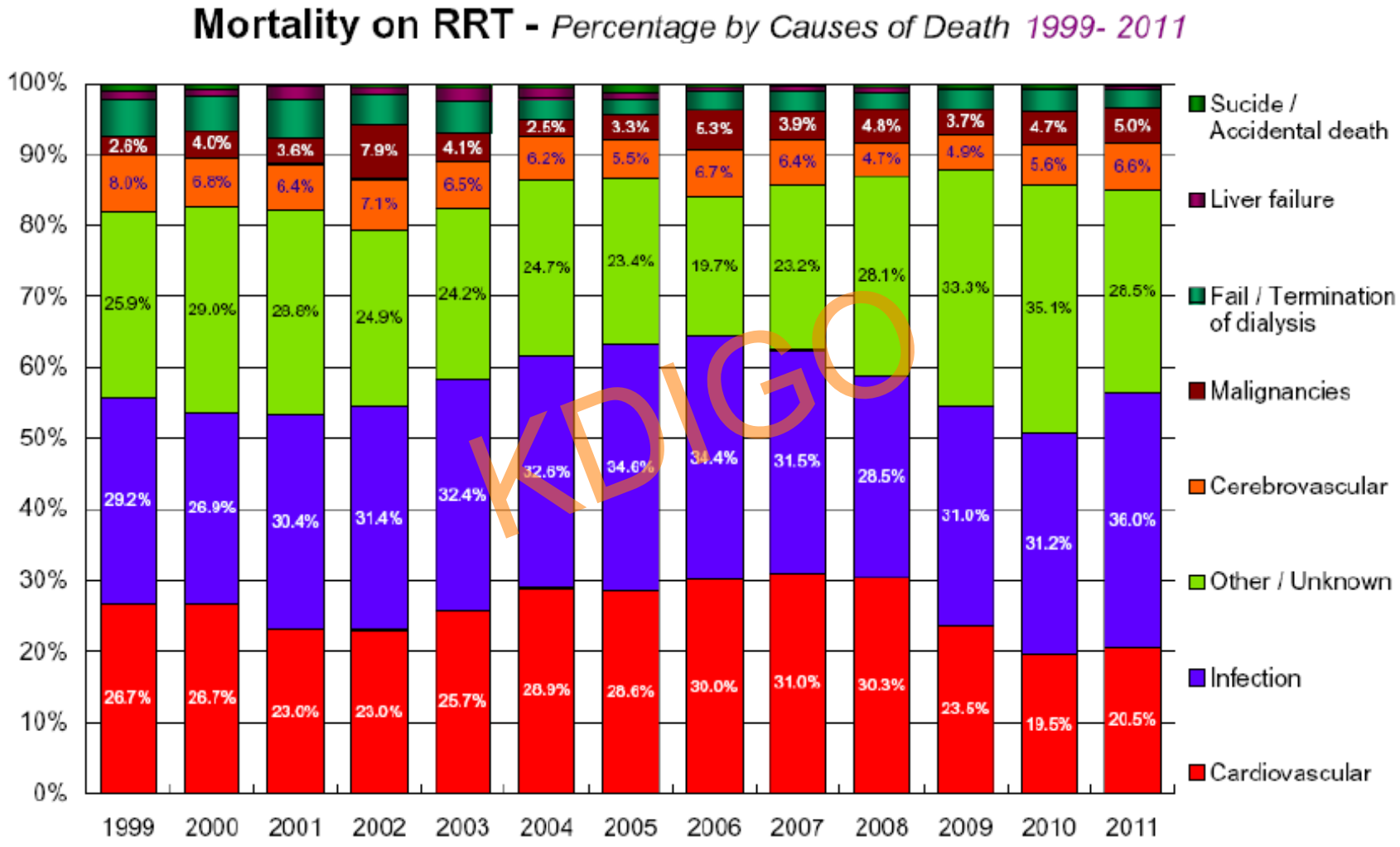
"The heart and the kidneys were closely related"

Ailment: "non-coordination between the heart and the kidney" or "心腎不交"

Causes of death in ESRD patients, 2013

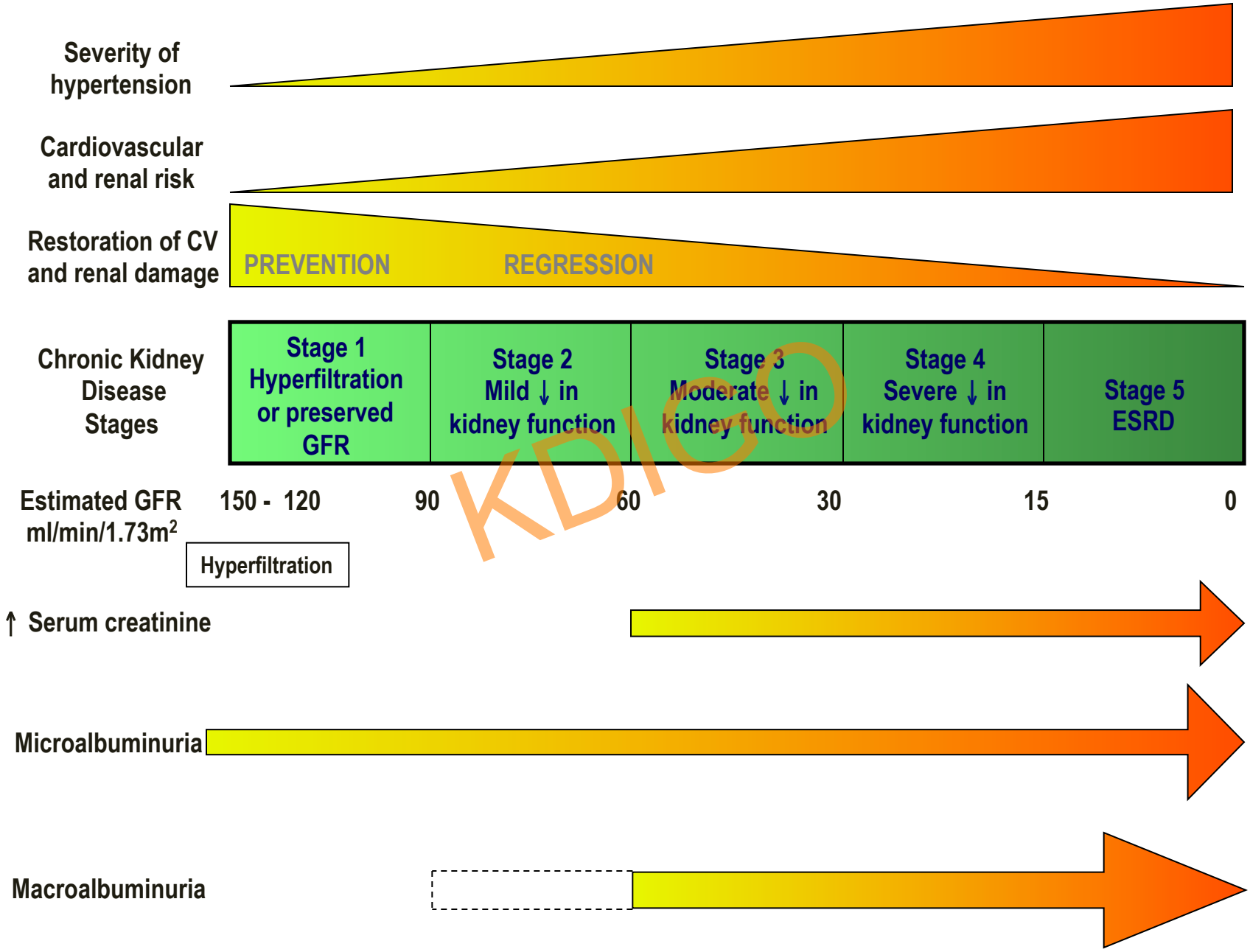


Data Source: Reference Table H12. Abbreviations: AHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA, cerebrovascular accident.



Ho YW, et al. HK J Nephrol 2013

HK Renal Registry, HACRC

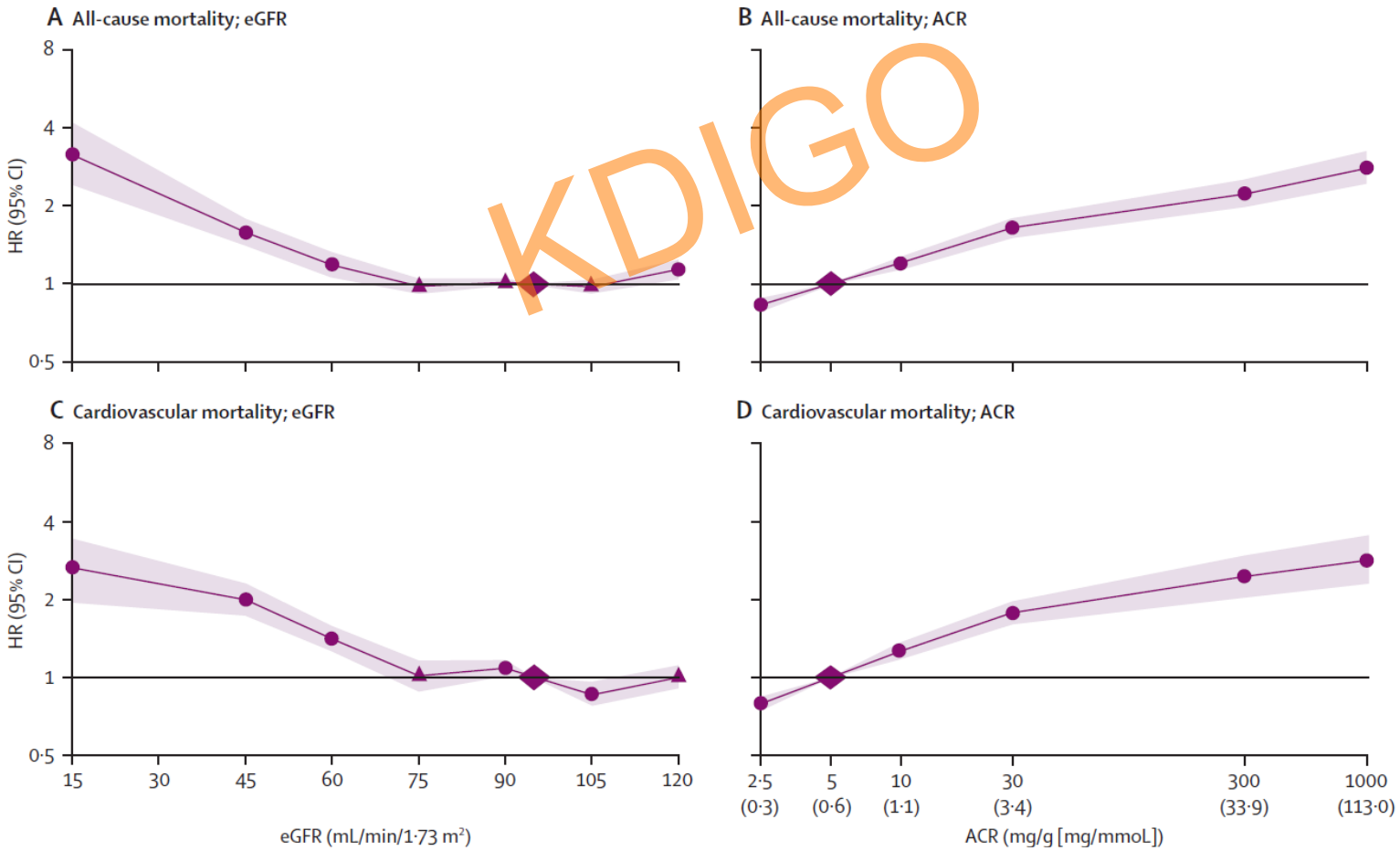

Severity of hypertension
Cardiovascular and renal risk
Restoration of CV and renal damage
PREVENTION
REGRESSION
Chronic Kidney Disease Stages
Stage 1 Hyperfiltration or preserved GFR
Stage 2 Mild ↓ in kidney function
Stage 3 Moderate ↓ in kidney function
Stage 4 Severe ↓ in kidney function
Stage 5 ESRD
Estimated GFR ml/min/1.73m2
150 - 120
90
60
30
15
0
Hyperfiltration
↑ Serum creatinine
Microalbuminuria
Macroalbuminuria

Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis

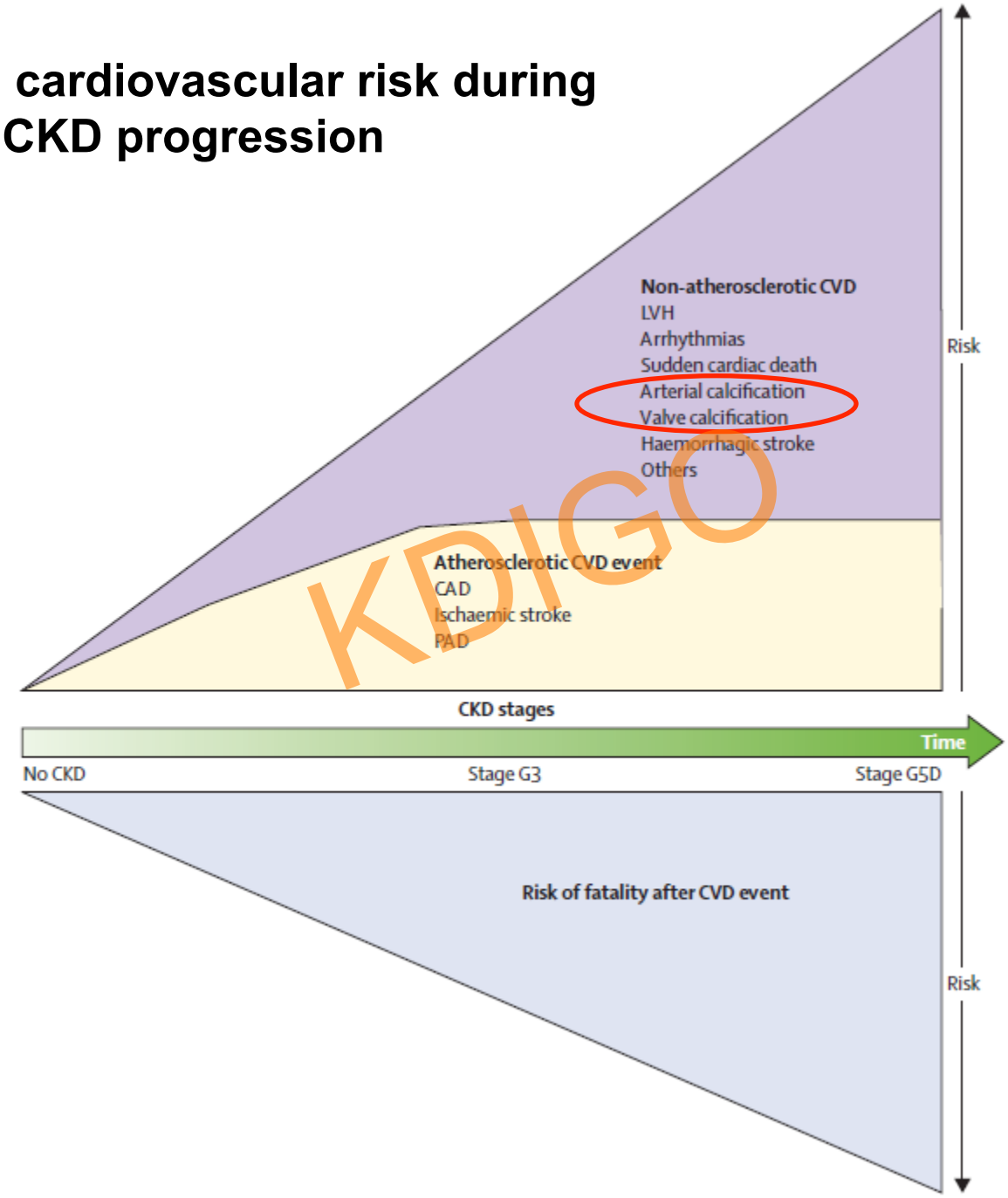
*Chronic Kidney Disease Prognosis Consortium**

Meta-analysis of 1.2 M subjects from 21 studies

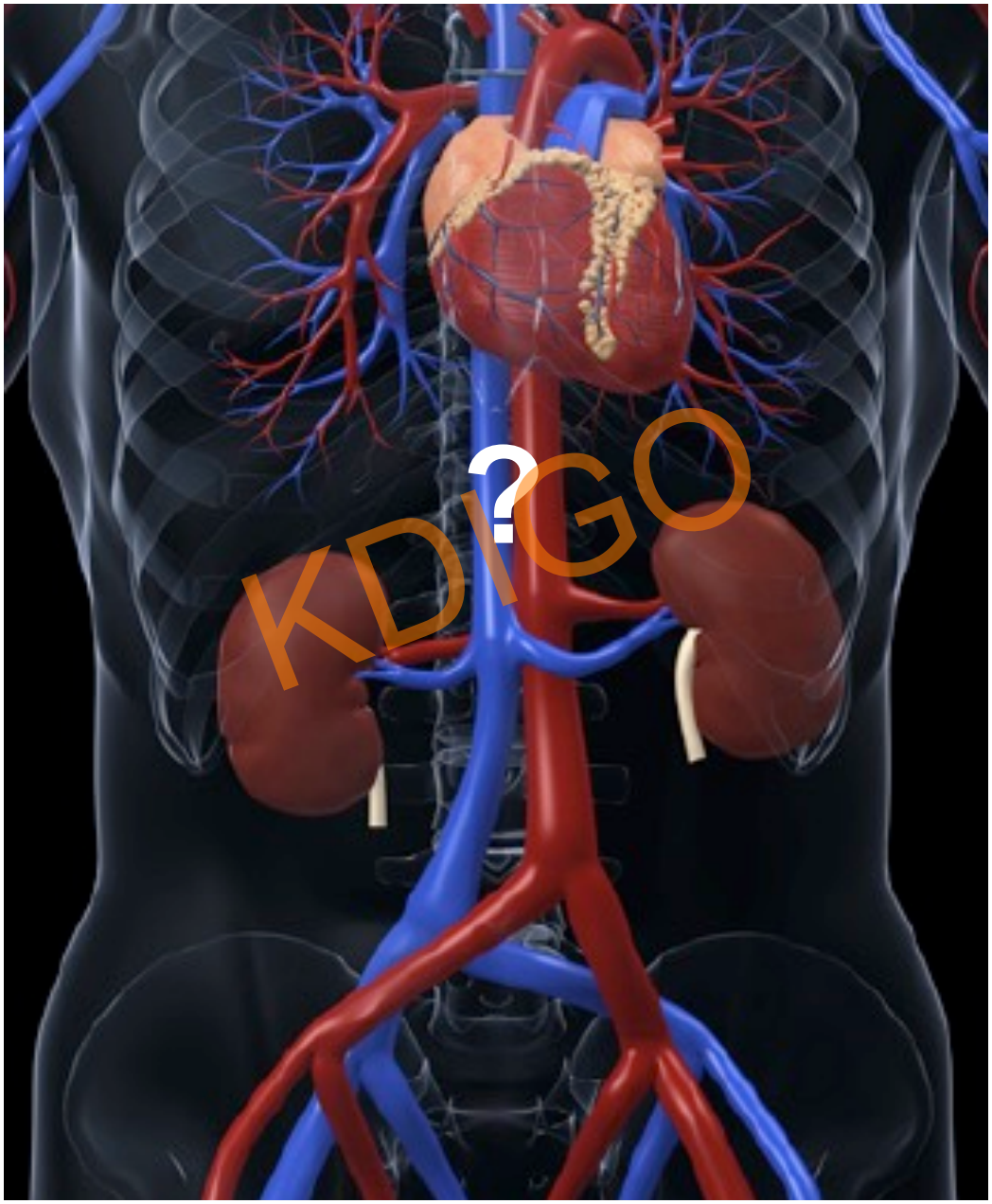
Lancet 2010; 375: 2073–81

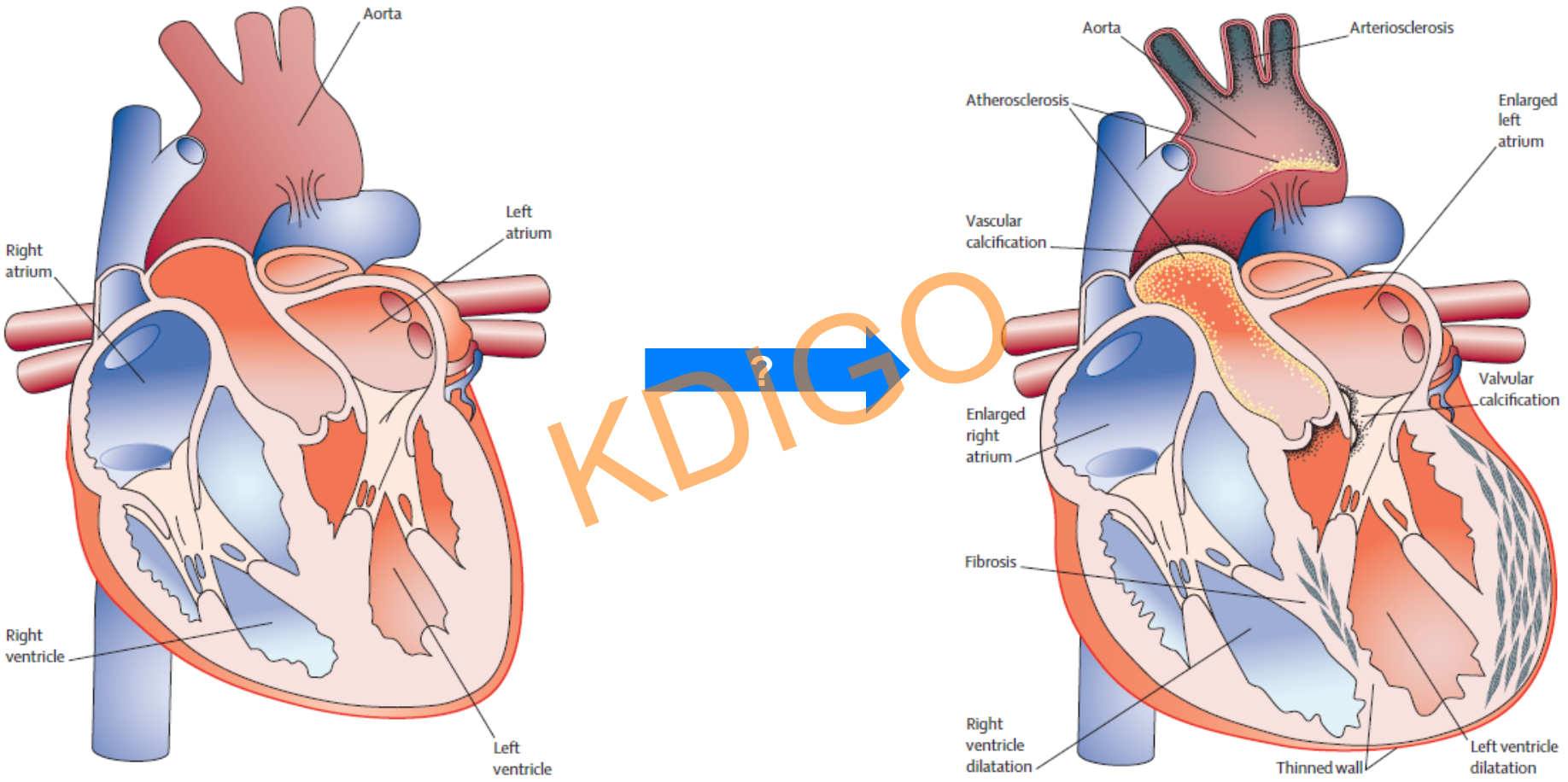


Change in cardiovascular risk during CKD progression

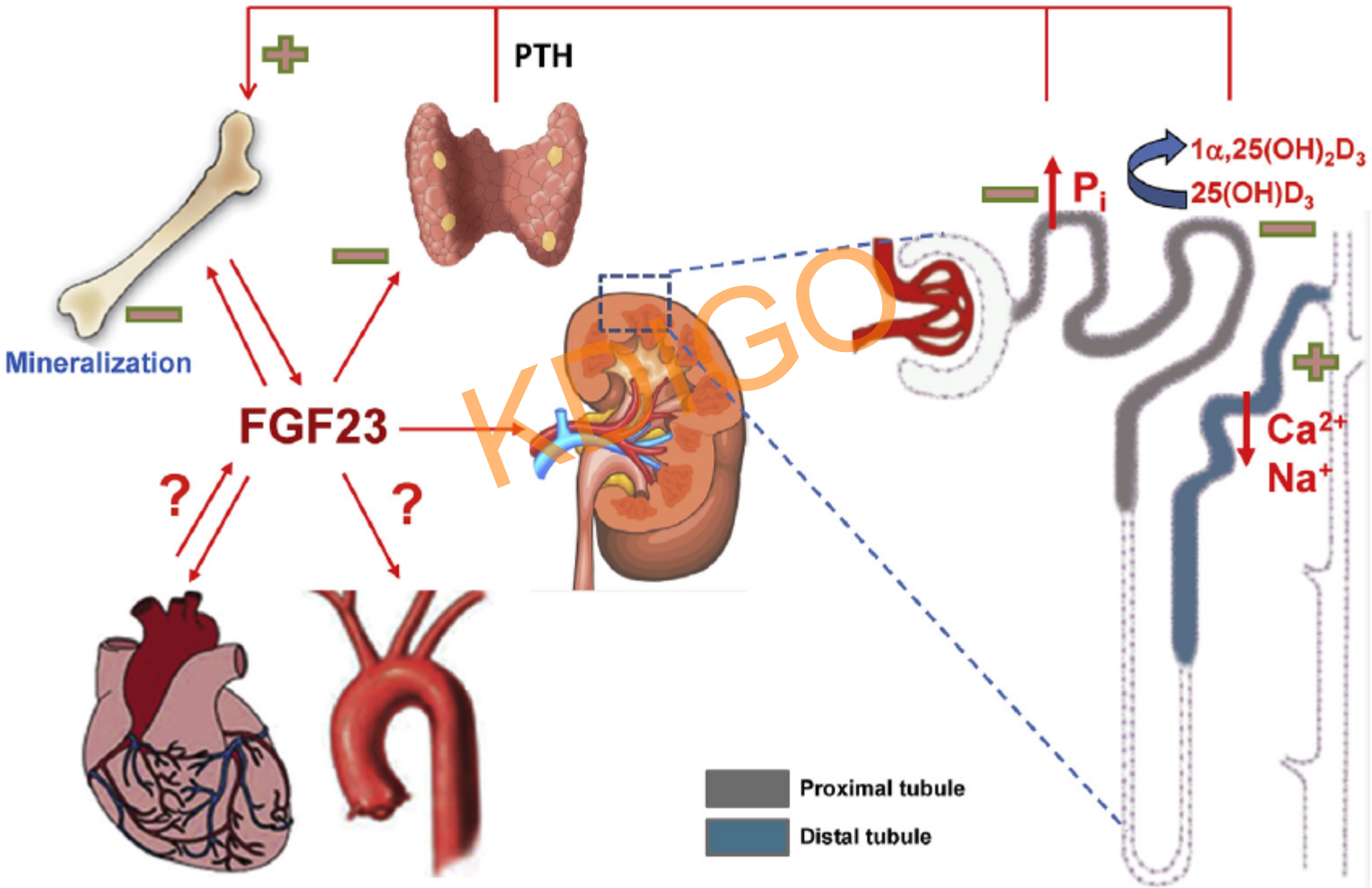


CV-renal connection



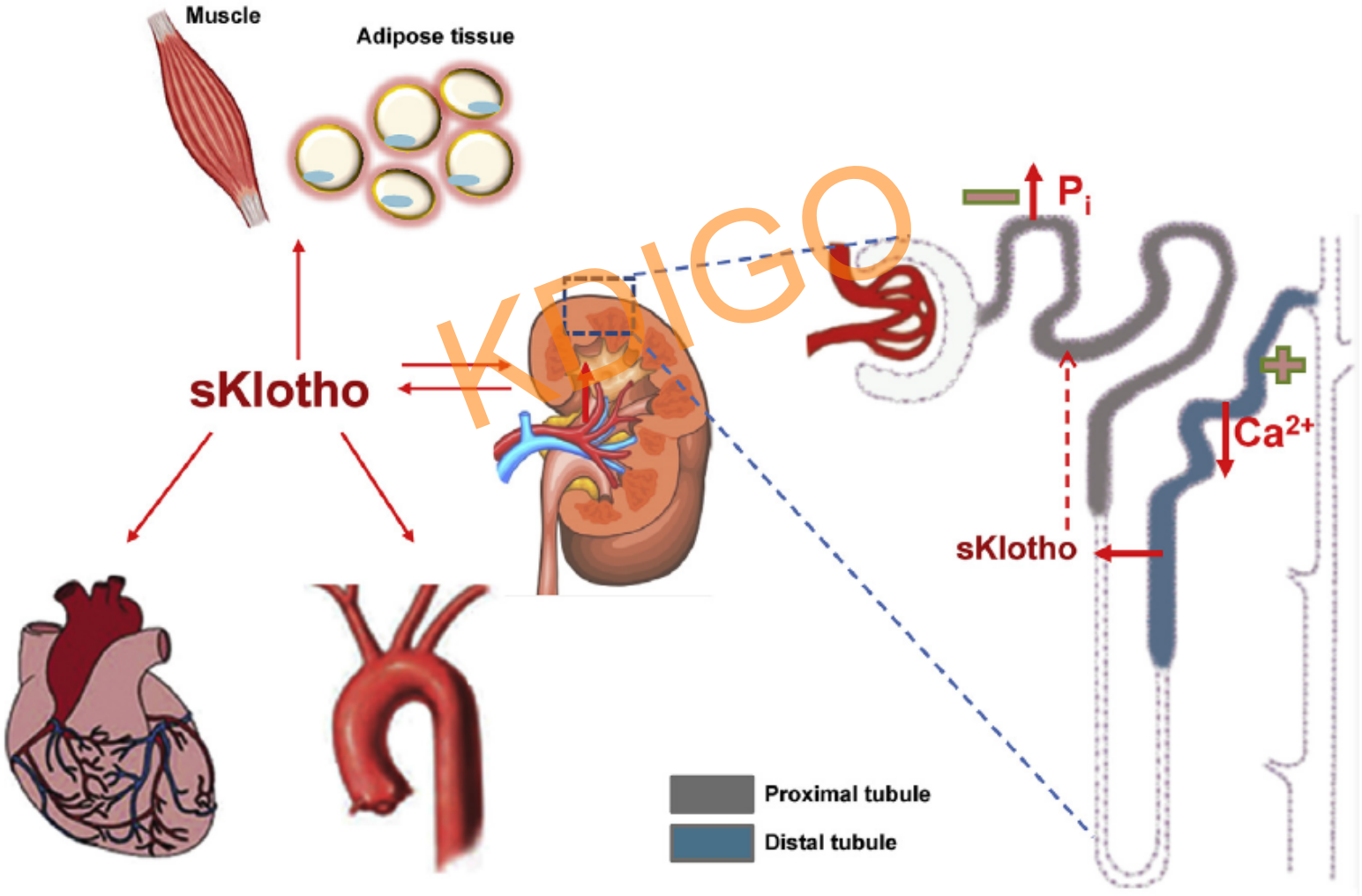

Aorta
Left atrium
Right atrium
Right ventricle
Left ventricle
?
KDIGO
Aorta
Arteriosclerosis
Atherosclerosis
Enlarged left atrium
Vascular calcification
Valvular calcification
Enlarged right atrium
Fibrosis
Right ventricle dilatation
Thinned wall
Left ventricle dilatation

Pleiotropic endocrine and auto-/paracrine functions of FGF23



R.G. Erben / Molecular and Cellular Endocrinology 432 (2016) 56–65

Endocrine and auto-/paracrine functions of soluble Klotho



FGF23 is independently associated with vascular calcification but not bone mineral density in patients at various CKD stages

L. Desjardins · S. Liabeuf · C. Renard · A. Lenglet · H.-D. Lemke · G. Choukroun · T. B. Drueke · Z. A. Massy · on behalf of the European Uremic Toxin (EUTox) Work Group

	Total n=142	Plasma FGF23		p value
		≤33.5 pg/ml (n=71)	>33.5 pg/ml (n=71)	
Age, years	67±12	66±11	68±13	0.358
Male gender, n (%)	86 (60.6)	44 (62)	42 (59)	0.734
CKD stage, n (%)				<0.001
2	12 (8.5)	12 (7)	0 (0)	
3	37 (26.1)	25 (35)	12 (17)	
4	37 (26.1)	26 (37)	11 (15)	
5	10 (7)	3 (4)	7 (10)	
5D	46 (32.4)	5 (7)	41 (58)	
Aortic calcification score (%)	3±3.0 (1.8; 0.7–4.3)	2.3±2.6 (3.1; 1.1–4.5)	3.6±3.2 (1.2; 0.5–2.5)	0.002
Coronary calcification score (AUs)[a]	585±1,224 (4.5; 0.2–10)	406±699 (6.0; 1.0–6.0)	804±1,636 (3.0; 0–8.0)	0.027

FGF23 is independently associated with vascular calcification but not bone mineral density in patients at various CKD stages

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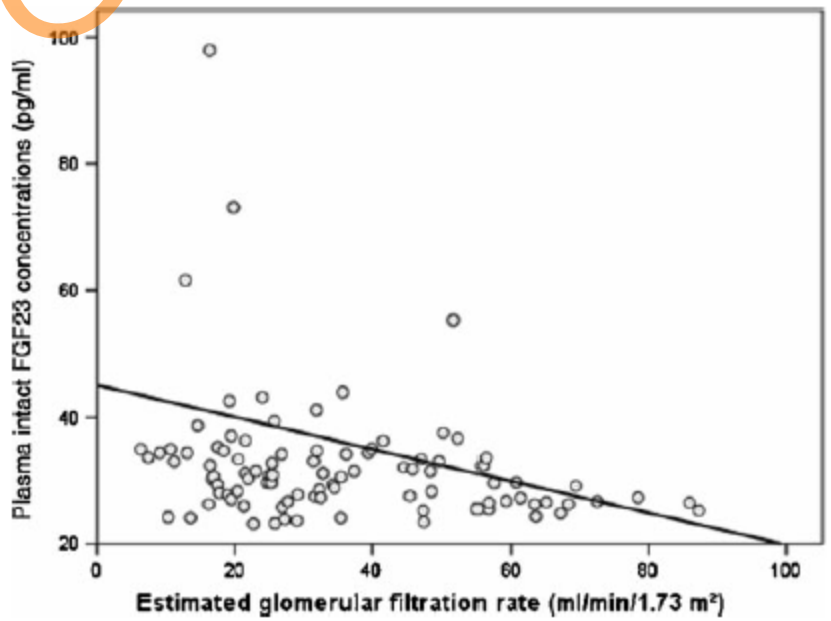
Table 5 Multivariate linear regression: variables independently associated with aortic calcification score (log-normalized) (n=142)

	β (95% CI)	p value
Age	0.057 (0.038–0.076)	<0.001
FGF23	0.525 (0.140–0.909)	0.008

Variables entered in the model: age, FGF23, bone mineral density, and chronic kidney disease stage; R^2 for the model=0.315

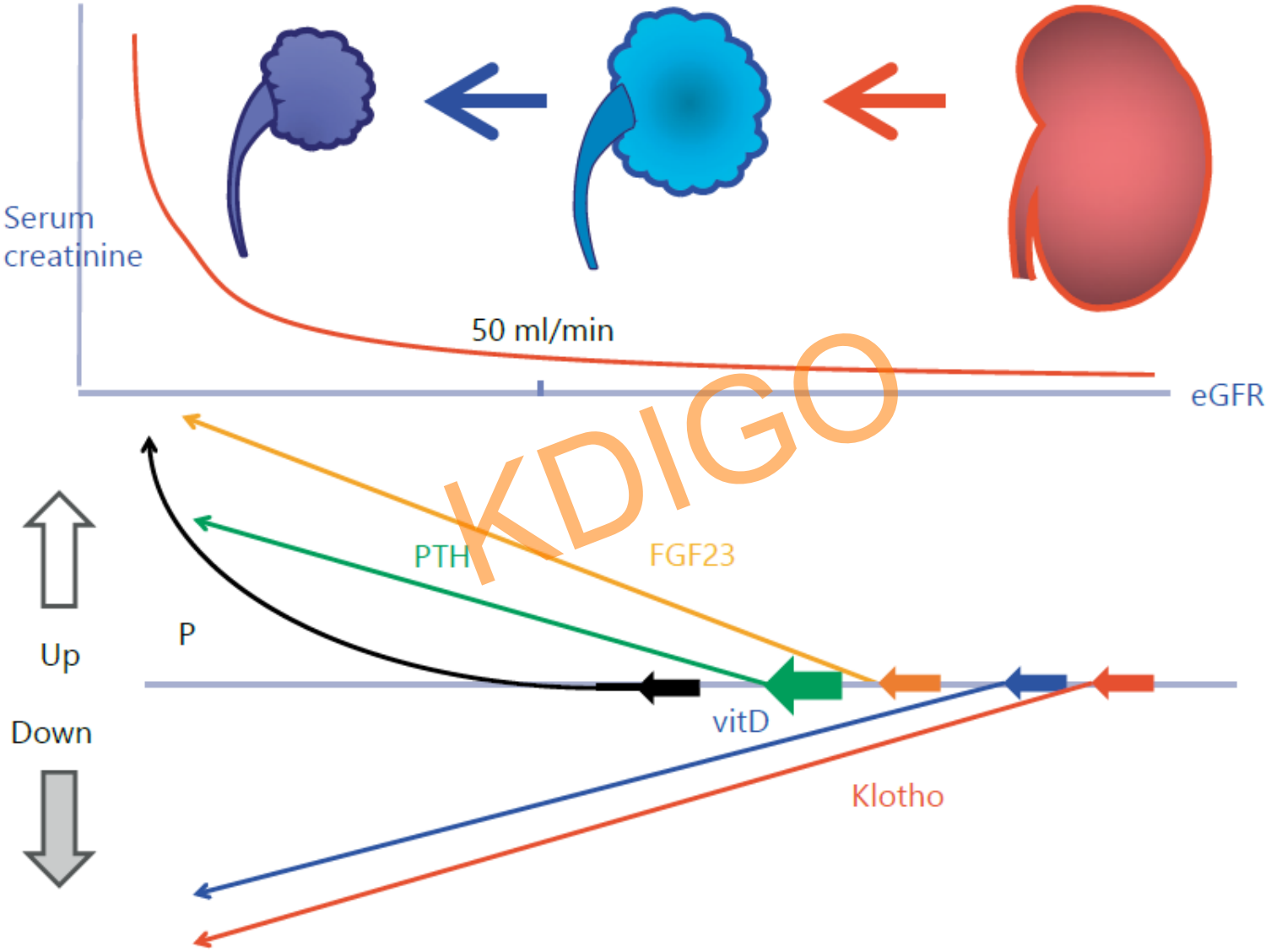
CI confidence interval, *FGF23* fibroblast growth factor 23



Osteoporos Int (2012) 23:2017–2025

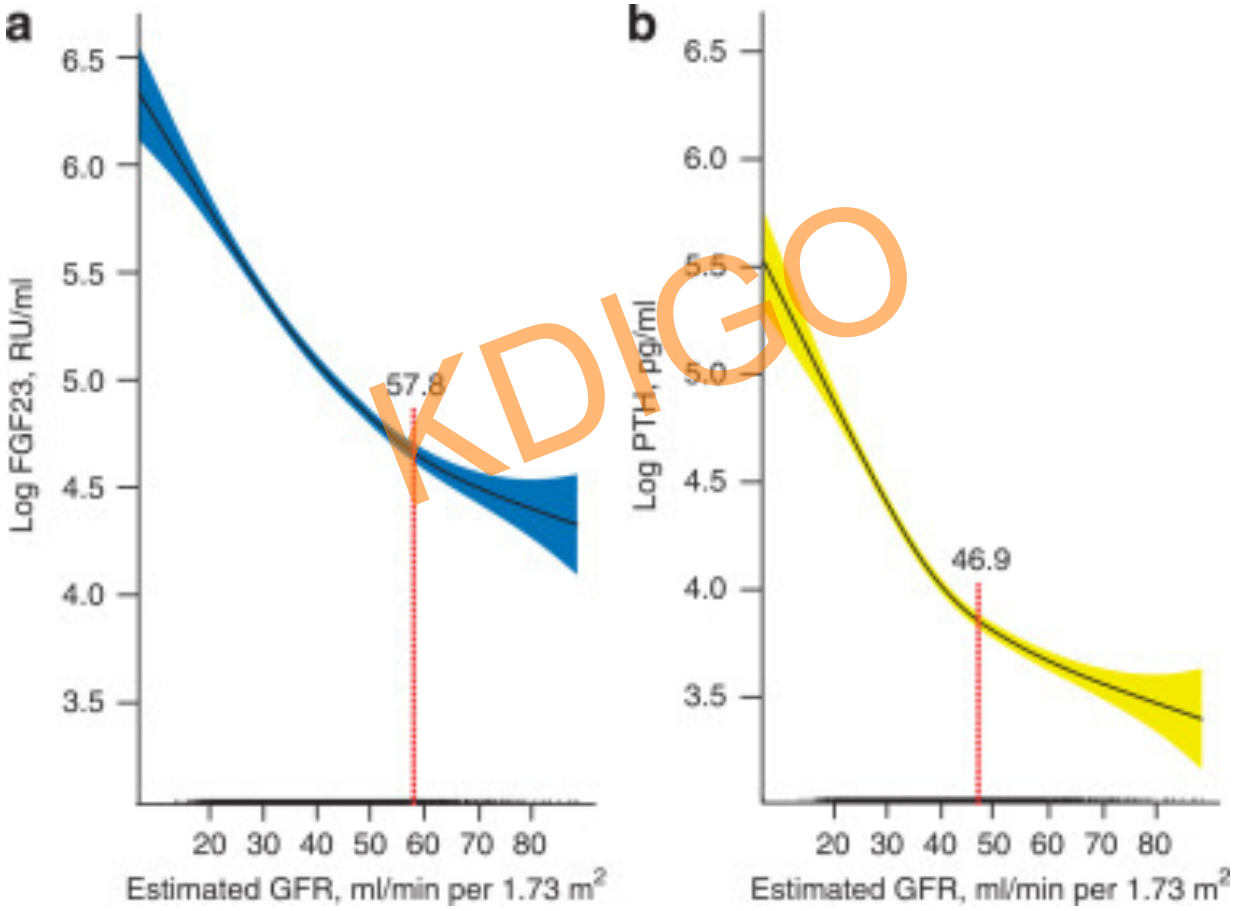
Vascular calcification

- is highly prevalent in CKD / ESRD
- independently predicts future CV events / mortality
- Calcification occurs in both the intimal and medial layers of vessels, but medial calcification is the major form in ESRD patients.
- Medial calcification increases arterial stiffness and pulse pressure, induces LVH, reduces perfusion of the coronary arteries, and ultimately promotes increased CV mortality.



Tsuchiya K, et al. Contrib Nephrol 2015

Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease

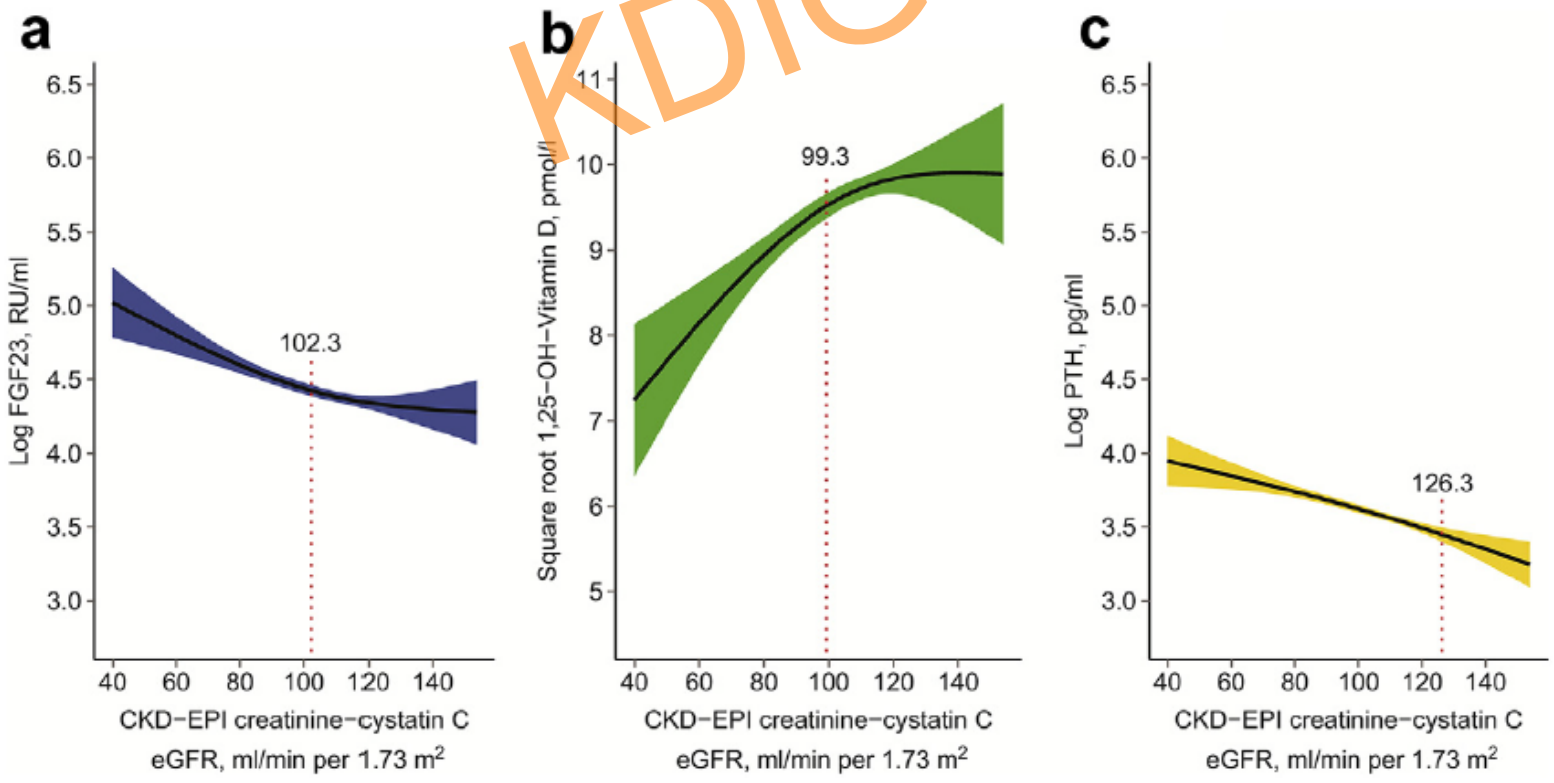


Isakiva T, et al. Kidney International, Volume 79, Issue 12, 2011, 1370–1378

Kidney International (2016) **90,** 648–657

Fibroblast growth factor 23 and markers of mineral metabolism in individuals with preserved renal function

Nasser A. Dhayat[1,10,11], Daniel Ackermann[1,11], Menno Pruijm[2], Belen Ponte[3], Georg Ehret[4], Idris Guessous[5,6], Alexander Benedikt Leichtle[7,11], Fred Paccaud[6], Markus Mohaupt[1], Georg-Martin Fiedler[7,11], Olivier Devuyst[8], Antoinette Pechère-Bertschi[9], Michel Burnier[2,11], Pierre-Yves Martin[3], Murielle Bochud[6], Bruno Vogt[1,11] and Daniel G. Fuster[1,10,11]

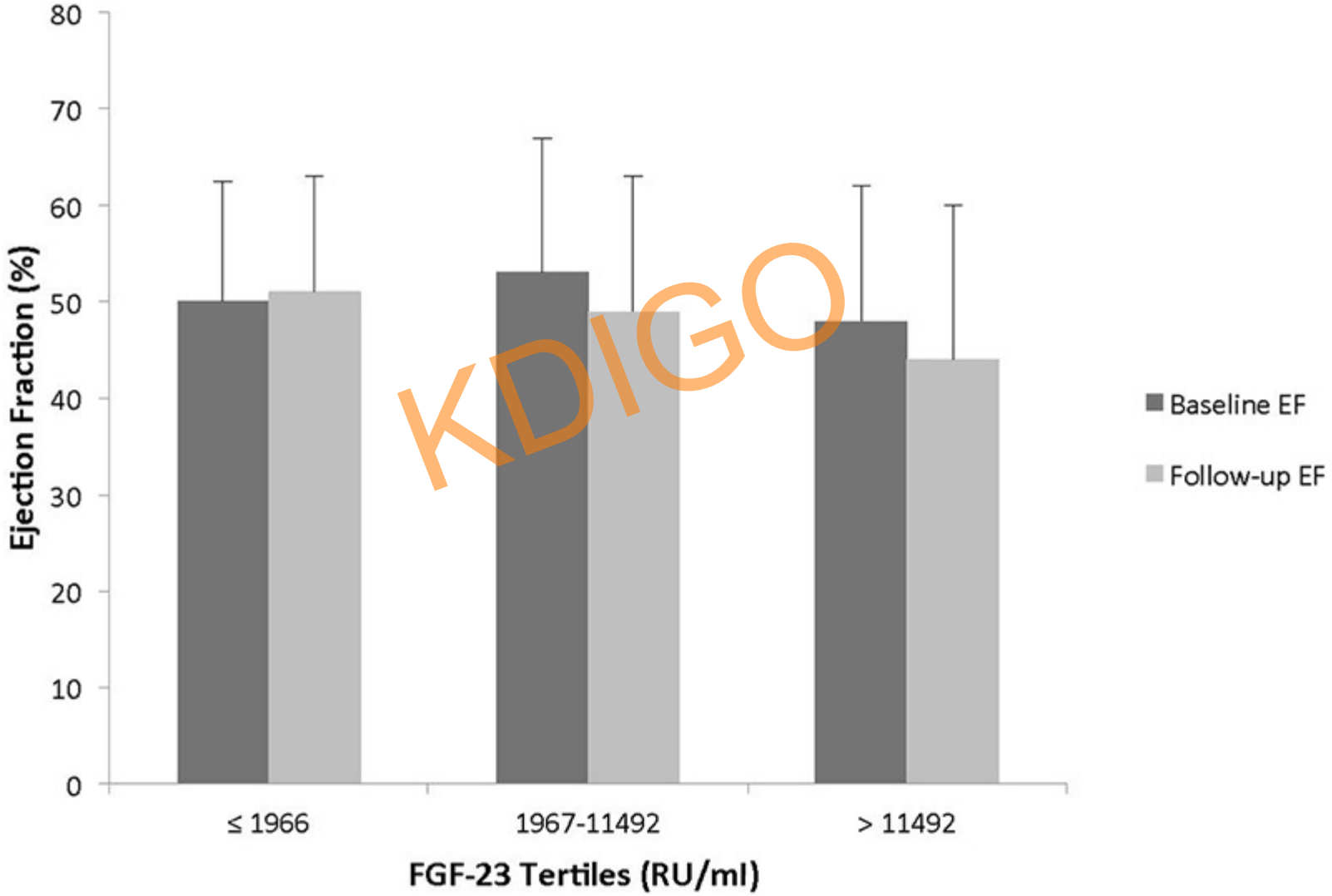


FGF23 was negatively associated with 1,25-dihydroxyvitamin D3 but not urinary absolute or fractional phosphate excretion

		Model 1				Model 2				Model 3				Model 4			
Predictor variable		*N*	β	95% CI	*P* value	*N*	β	95% CI	*P* value	*N*	β	95% CI	*P* value	*N*	β	95% CI	*P* value
Blood values																	
PTH, pg/ml	Linear	1007	0.00277	0.00059–0.00499	<0.05	999	0.00082	−0.00155 to 0.00322	0.50	912	0.00008	−0.00239 to 0.00259	0.95	918	0.00089	−0.00153 to 0.00335	0.47
25-OH-vitamin D_3, nmol/l	Linear	1006	−0.00204	−0.00353 to −0.00052	<0.01	998	−0.00200	−0.00351 to −0.00044	<0.05	911	−0.00148	−0.00288 to −0.00004	<0.05	917	−0.00164	−0.00305 to −0.00018	<0.05
	Quadratic		0.00003		0.084		0.00003	0–0.00007	0.085								
1,25-diOH vitamin D_3, pmol/l	Linear	941	−0.00312	−0.00408 to −0.00218	<0.001	934	−0.00297	−0.00397 to −0.002	<0.001	866	−0.00253	−0.00352 to −0.0016	<0.001	858	−0.00310	−0.00413 to −0.00209	<0.001
	Quadratic		0.00002	0–0.00004	<0.05		0.00002	0–0.00004	<0.05						0.00002	0.00001–0.00004	<0.05
Phosphate, mmol/l	Linear	1001	0.32701	0.15639–0.50727	<0.001	1000	0.33620	0.15815–0.52269	<0.001	914	0.31000	0.12398–0.50134	<0.01	919	0.35740	0.17323–0.55234	<0.001
Calcium corrected, mmol/l	Linear	1002	0.24939	−0.0723–0.60622	0.14	1001	0.18370	−0.1372–0.55068	0.28	914	0.07364	−0.26377–0.45544	0.68	920	0.14470	−0.18285–0.52334	0.40
Urine values																	
Phosphaturia, mmol/24 hr	Linear	976	−0.00218	−0.00518 to 0.00088	0.16	968	0.00165	−0.00178 to 0.00517	0.35	882	0.00269	−0.00087 to 0.00634	0.14	911	0.00406	−0.00034 to 0.00836	0.07
Fractional excretion of phosphate, %	Linear	968	−0.00067	−0.00578 to 0.00407	0.79	967	−0.00235	−0.00798 to 0.003	0.40	882	−0.00357	−0.00939 to 0.00205	0.22	909	−0.00295	−0.00877 to 0.00265	0.31

The main demonstrable effect of FGF23 in the setting of preserved renal function is suppression of 1,25-dihydroxyvitamin D3 rather than stimulation of renal phosphate excretion.

Higher FGF23 concentrations associate with LV systolic dysfunction in dialysis patients



Sharma S et al. Clin Nephrol 2013

Association of Fibroblast Growth Factor 23 With Atrial Fibrillation in Chronic Kidney Disease, From the Chronic Renal Insufficiency Cohort Study

Rupal Mehta, MD; Xuan Cai, MS; Jungwha Lee, PhD; Julia J. Scialla, MD, MHS; Nisha Bansal, MD, MAS; James H. Sondheimer, MD; Jing Chen, MD, MMSc, MSc; L. Lee Hamm, MD; Ana C. Ricardo, MD, MPH, MS; Sankar D. Navaneethan, MD, MPH; Rajat Deo, MD; Mahboob Rahman, MD; Harold I. Feldman, MD, MSCE; Alan S. Go, MD; Tamara Isakova, MD, MMSc; Myles Wolf, MD, MMSc; for the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators

Table 1. Baseline Characteristics According to Atrial Fibrillation Prevalence

Variable	Prevalent Atrial Fibrillation (n = 660)	No Prevalent Atrial Fibrillation (n = 3216)	*P* Value
Age, mean (SD), y	60.9 (9.3)	57.0 (11.2)	<.001
Female sex, No. (%)	306 (46.4)	1430 (44.5)	.37
Heart failure, No. (%)	183 (27.7)	194 (6.0)	<.001
Stroke, No. (%)	98 (14.9)	287 (8.9)	<.001
Cardiovascular disease, No. (%)	388 (58.8)	909 (28.3)	<.001
Ratio (IQR) of urinary albumin to creatinine, mg/g	44.4 (9.3-382.2)	53.3 (8.4-479.7)	.11
Estimated glomerular filtration rate, mean (SD), mL/min/1.73 m^2	42.2 (14.7)	44.7 (15.1)	<.001
Intact parathyroid hormone level, median (IQR), pg/mL	61.5 (38.9-97.0)	52.3 (34.0-88.0)	<.001
FGF23 level, median (IQR), RU/mL	181.2 (113.3-307.6)	138.6 (93.9-227.4)	<.001

JAMA Cardiology Published online July 6, 2016

Table 2. Fibroblast Growth Factor 23 (FGF23) and Prevalent Atrial Fibrillation[a]

Variable	Cases/Total No.	Per 1-U Increase in Natural Log FGF23	FGF23 Quartile, RU/mL				
			Quartile 1 (≤95.9)	Quartile 2 (96.0-145.6)	Quartile 3 (145.7-239.2)	Quartile 4 (>239.2)	*P* for Trend
Prevalence, No./total No. (%)	660	660/3876 (17.0)	117/969 (12.1)	124/969 (12.8)	185/969 (19.1)	234/969 (24.1)	NA
Odds ratio (95% CI)							
Unadjusted	660/3876	1.51 (1.36-1.68)	1 [Reference]	1.07 (0.82-1.40)	1.72 (1.34-2.21)	2.32 (1.82-2.96)	<.001
Plus demographic factors[b]	660/3876	1.53 (1.37-1.71)	1 [Reference]	1.03 (0.78-1.35)	1.66 (1.28-2.14)	2.30 (1.80-2.95)	<.001
Plus cardiovascular risk factors[c]	655/3847	1.36 (1.21-1.54)	1 [Reference]	0.95 (0.71-1.25)	1.44 (1.10-1.88)	1.83 (1.40-2.40)	<.001
Plus CKD-specific factors[d]	655/3847	1.44 (1.27-1.64)	1 [Reference]	1.00 (0.75-1.33)	1.62 (1.22-2.15)	2.18 (1.62-2.93)	<.001
Plus markers of mineral metabolism[e]	633/3729	1.46 (1.27-1.67)	1 [Reference]	1.04 (0.78-1.39)	1.63 (1.22-2.19)	2.30 (1.69-3.13)	<.001

Abbreviations: CKD, chronic kidney disease; NA, not applicable; RU, reference units.

[a] Continuous results are reported as odds ratios per 1-U increase in natural log-transformed FGF23.

[b] Adjusts for age, sex, and race/ethnicity.

[c] Adjusts for factors in model 1 and for cardiovascular disease, systolic blood pressure, diabetes, smoking, and diuretic use.

[d] Adjusts for factors in model 2 and for estimated glomerular filtration rate and ratio of urinary albumin to creatinine.

[e] Full multivariable model adjusts for factors in model 3 and for levels of calcium, phosphate, and parathyroid hormone.

Incidence of AF: Median follow-up of 7.6 years

Table 4. Incidence of Atrial Fibrillation and Its Association With Fibroblast Growth Factor 23 (FGF23)[a]

Variable	Events/Total No.	Per 1-U Increase in Natural Log FGF23	FGF23 Quartile, RU/mL				*P* for Trend
			Quartile 1 (≤93.9)	Quartile 2 (94.0-138.6)	Quartile 3 (138.7-227.4)	Quartile 4 (>227.4)	
Incidence rate (95% CI), events per 1000 person-years	247/3216	11.9 (10.4-13.4)	7.5 (5.4-10.1)	9.6 (7.1-12.5)	14.2 (11.1-17.8)	17.2 (13.7-21.4)	<.001
Hazard ratio (95% CI)							
Unadjusted	247/3216	1.57 (1.35-1.83)	1 [Reference]	1.28 (0.86-1.93)	1.93 (1.32-2.82)	2.40 (1.65-3.49)	<.001
Plus demographic factors[b]	247/3216	1.78 (1.51-2.11)	1 [Reference]	1.19 (0.79-1.79)	1.90 (1.29-2.79)	2.66 (1.81-3.92)	<.001
Plus cardiovascular risk factors[c]	247/3192	1.61 (1.35-1.92)	1 [Reference]	1.07 (0.71-1.62)	1.60 (1.08-2.37)	2.06 (1.38-3.09)	<.001
Plus CKD-specific factors[d]	247/3192	1.48 (1.22-1.81)	1 [Reference]	1.00 (0.66-1.51)	1.37 (0.91-2.07)	1.64 (1.05-2.56)	.01
Plus markers of mineral metabolism[e]	237/3096	1.47 (1.20-1.80)	1 [Reference]	1.00 (0.65-1.54)	1.34 (0.87-2.05)	1.59 (1.00-2.53)	.02

Abbreviations: CKD, chronic kidney disease; RU, reference units.

[a] Continuous results are reported as hazard ratios per 1-U increase in natural log-transformed FGF23.

[b] Adjusts for age, sex, and race/ethnicity.

[c] Adjusts for factors in model 1 and for cardiovascular disease, systolic blood pressure, diabetes, smoking, and diuretic use.

[d] Adjusts for factors in model 2 and for estimated glomerular filtration rate and ratio of urinary albumin to creatinine.

[e] Full multivariable model adjusts for factors in model 3 and for levels of calcium, phosphate, and parathyroid hormone.

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Fibroblast Growth Factor-23 and Cardiovascular Disease in the General Population

The Multi-Ethnic Study of Atherosclerosis

Bryan Kestenbaum, MD, MS; Michael C. Sachs, PhD; Andy N. Hoofnagle, MD, PhD; David S. Siscovick, MD, MPH; Joachim H. Ix, MD, MAS; Cassianne Robinson-Cohen, PhD; Joao A.C. Lima, MD; Joseph F. Polak, MD, MPH; Marc Blondon, MD; John Ruzinski, BS; Denise Rock, BS; Ian H. de Boer, MD, MS

Table 1. Baseline Characteristics by Fibroblast Growth Factor-23 Quartile

	Serum Fibroblast Growth Factor-23 Concentration, pg/mL			
	<30.5	30.5–37.7	37.7–46.4	46.4–223
No. of subjects	1636	1639	1634	1637
Age, y	60.8 (10.2)	61.8 (10.0)	62.3 (10.3)	63.6 (10.3)
Male	678 (41.4)	786 (48.0)	784 (48.0)	812 (49.6)
Race				
White	525 (32.1)	621 (37.9)	656 (40.1)	741 (45.3)
Chinese	191 (11.7)	214 (13.1)	194 (11.9)	195 (11.9)
Black	485 (29.6)	448 (27.3)	429 (26.3)	415 (25.4)
Hispanic	435 (26.6)	356 (21.7)	355 (21.7)	286 (17.5)
Diabetes mellitus	203 (12.4)	202 (12.3)	175 (10.7)	231 (14.1)
Estimated GFR, mL/min per 1.73 m^2†	90.0 (20.2)	90 (22.1)	81.5 (23.3)	73.7 (27.2)
Estimated GFR ≤60 mL/min per 1.73 m^2	160 (9.9)	202 (12.4)	234 (14.4)	421 (25.9)
Urine albumin-to-creatinine ratio, mg/g†	6.7 (6.7)	6.7 (6.8)	6.7 (7.6)	8.2 (10.5)

Associations of FGF-23 With Subclinical Cardiovascular Disease:

LV mass

	Left Ventricular Mass (n=4832)		Mean Differences in Left Ventricular Mass, g	
FGF-23, pg/mL	LVH, %	Mean, g (SD)	Model 1	Model 2
<30.5	10.5	139.5 (37.8)	0 (reference)	0 (reference)
30.5–37.7	8.9	144.6 (38.6)	0.38 (–1.65 to 2.40)	1.02 (–0.90 to 2.93)
37.7–46.4	9.5	146.7 (39.7)	0.87 (–1.21 to 2.95)	1.46 (–0.49 to 3.42)
46.4–223	11.7	149.9 (41.1)	2.74 (0.54 to 4.94)	2.44 (0.37 to 4.51)
P for trend			0.014	0.020

coronary Ca++

	CAC (n=6547)		Odds Ratios for Higher CAC Score	
FGF-23, pg/mL	Prevalence, %	Median Score*	Model 1	Model 2
<30.5	43.1	74.8 (223.4)	1.0 (reference)	1.0 (reference)
30.5–37.7	48.2	77.6 (271.9)	1.09 (0.95–1.25)	1.12 (0.97–1.29)
37.7–46.4	49.9	88.1 (283.7)	1.08 (0.94–1.24)	1.09 (0.94–1.26)
46.4–223	57.3	106.3 (334.8)	1.32 (1.15–1.52)	1.26 (1.09–1.46)
P for trend			<0.001	0.005

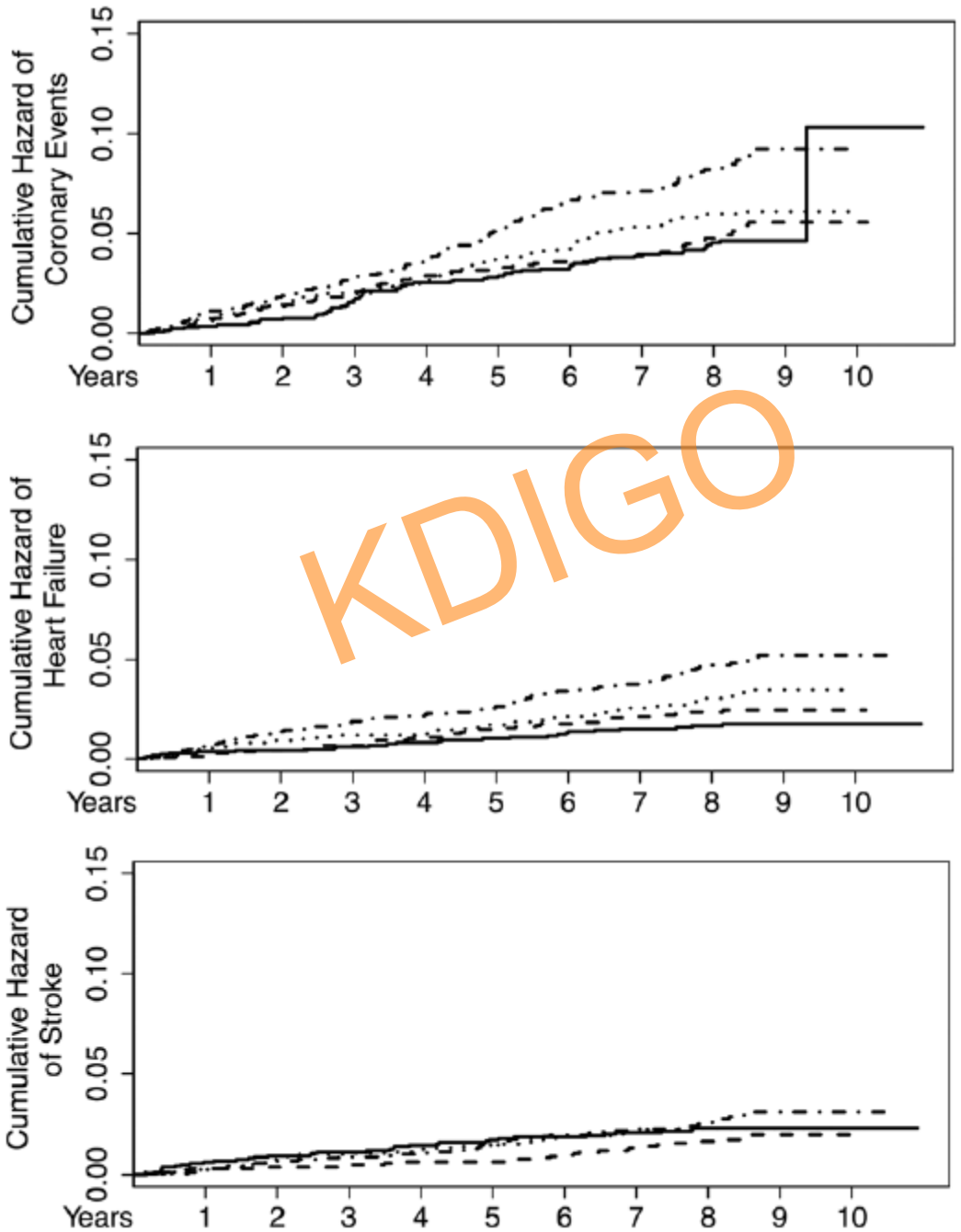
Carotid IMT

	Carotid IMT (n=6470)		Mean Differences in Carotid IMT, μm	
FGF-23, pg/mL	Any Plaque, %*	Mean, μm (SD)	Model 1	Model 2
<30.5	37.6	852.1 (181.1)	0 (reference)	0 (reference)
30.5–37.7	40.3	860.5 (181.7)	–4.06 (–15.21 to 7.09)	0.21 (–10.69 to 11.1)
37.7–46.4	40.9	866.0 (197.7)	–4.28 (–15.68 to 7.12)	–1.79 (–13.04 to 9.46)
46.4–223	46.2	896.7 (210.6)	13.09 (0.89 to 25.28)	11.77 (–0.34 to 23.88)
P for trend			0.045	0.090

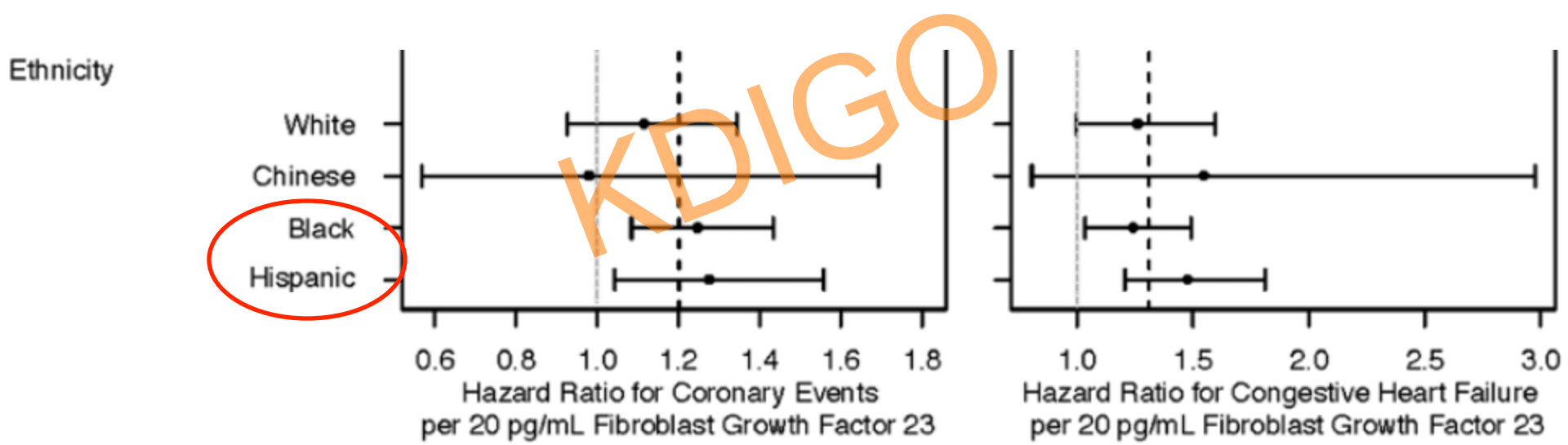
Circ Heart Fail May 2014

Associations of FGF-23 With Incident Cardiovascular Events

During 7.5-year follow-up



Cumulative incidences of CV events by serum FGF-23 concentration



Circ Heart Fail May 2014

American Journal of Nephrology

Plasma FGF23 and Calcified Atherosclerotic Plaque in African Americans with Type 2 Diabetes Mellitus

Barry I. Freedman[a] Jasmin Divers[b] Gregory B. Russell[b] Nicholette D. Palmer[c]
Donald W. Bowden[c] J. Jeffrey Carr[f] Lynne E. Wagenknecht[b]
R. Caresse Hightower[d] Jianzhao Xu[c] Susan Carrie Smith[a] Carl D. Langefeld[b]
Keith A. Hruska[g] Thomas C. Register[e]

Baseline	Male (n = 236)	Female (n = 309)	All (n = 545)	p value
Age, years	56.0 (9.8)	55.4 (9.5)	55.6 (9.6)	0.46
Age at diabetes onset, years	45.5 (10.9)	45.2 (10.2)	45.3 (10.5)	0.70
Diabetes duration, years	10.5 (8.7)	10.2 (7.8)	10.3 (8.2)	0.71
BMI, kg/m^2	32.5 (7.4)	37.4 (8.9)	35.3 (8.6)	<0.0001
SBP, mm Hg	132.0 (18.1)	133.5 (19.9)	132.8 (19.2)	0.36

eGFR 90.9 (22.1) ml/min/1.73 m2
UACR 151 (588) mg/g, median 13 mg/g

Follow-up (mean 5.1 years)	Male (n = 139)	Female (n = 143)	All (n = 282)	p value
Age, years	59.7 (9.3)	60.4 (8.5)	60.1 (8.9)	0.52
Age at diabetes onset, years	44.7 (9.3)	44.8 (9.6)	44.8 (9.5)	0.92
Diabetes duration, years	15.1 (8.1)	15.6 (6.6)	15.3 (7.4)	0.52
BMI, kg/m^2	32.6 (6.8)	37.2 (8.0)	34.9 (7.8)	<0.0001
SBP, mm Hg	129.7 (18.0)	132.6 (17.4)	131.2 (17.7)	0.17

Cross-sectional associations between plasma FGF23 and clinical variables

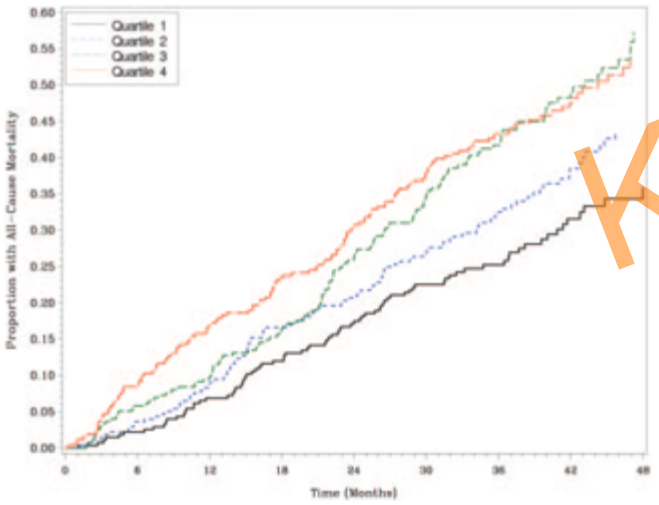
Outcome + sequentially-adjusted models	Estimate	SE	p value
Estimated GFR			
Unadjusted	−8.36	1.34	<0.0001
Age, sex, ancestry, BMI, T2D duration, smoking	−8.27	1.28	<0.0001
Above + HbA1c, SBP, ACEi/ARB medicines	−8.50	1.30	<0.0001
log (UACR + 1)			
Unadjusted	0.38	0.11	0.0007
Age, sex, ancestry, BMI, T2D duration, smoking	0.45	0.11	0.0001
Above + HbA1c, SBP, ACEi/ARB medicines	0.52	0.11	<0.0001
Above + eGFR	0.49	0.11	<0.0001
log (aorta CP + 1)			
Unadjusted	0.49	0.22	0.027
Age, sex, ancestry, BMI, T2D duration, smoking	0.24	0.18	0.17
Above + HbA1c, SBP, statin medicines	0.28	0.18	0.12
Above + calcium supplements, eGFR	0.20	0.19	0.29
log (CAC + 1)			
Unadjusted	0.45	0.19	0.015
Age, sex, ancestry, BMI, T2D duration, smoking	0.42	0.17	0.015
Above + HbA1c, SBP, statin medicines	0.48	0.17	0.006
Above + calcium supplements, eGFR	0.50	0.18	0.005

J Am Soc Nephrol 22: 1913–1922, 2011

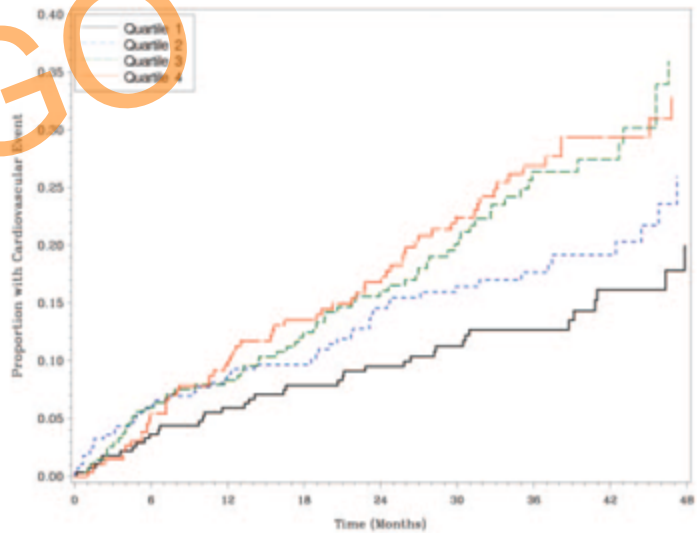
FGF-23 Associates with Death, Cardiovascular Events, and Initiation of Chronic Dialysis

Jessica Kendrick,* Alfred K. Cheung,†‡ James S. Kaufman,§ Tom Greene,‖¶
William L. Roberts,** Gerard Smits,* Michel Chonchol,* and the HOST Investigators

All-cause mortality



CV events



initiation of chronic dialysis re FGF23 quartiles

Models	Q1 ≤ 216 RU/ml	Q2 217–380 RU/ml	Q3 381–945 RU/ml	Q4 >946 RU/ml
Model 1	1.00	1.70 (1.37–2.10)	2.92 (2.36–3.61)	4.43 (3.57–5.49)
Model 2	1.00	1.26 (1.01–1.57)	1.66 (1.31–2.11)	2.32 (1.80–2.98)
Model 3	1.00	1.26 (1.01–1.58)	1.65 (1.30–2.10)	2.30 (1.78–2.96)

Fibroblast growth factor 23 is not associated with and does not induce arterial calcification

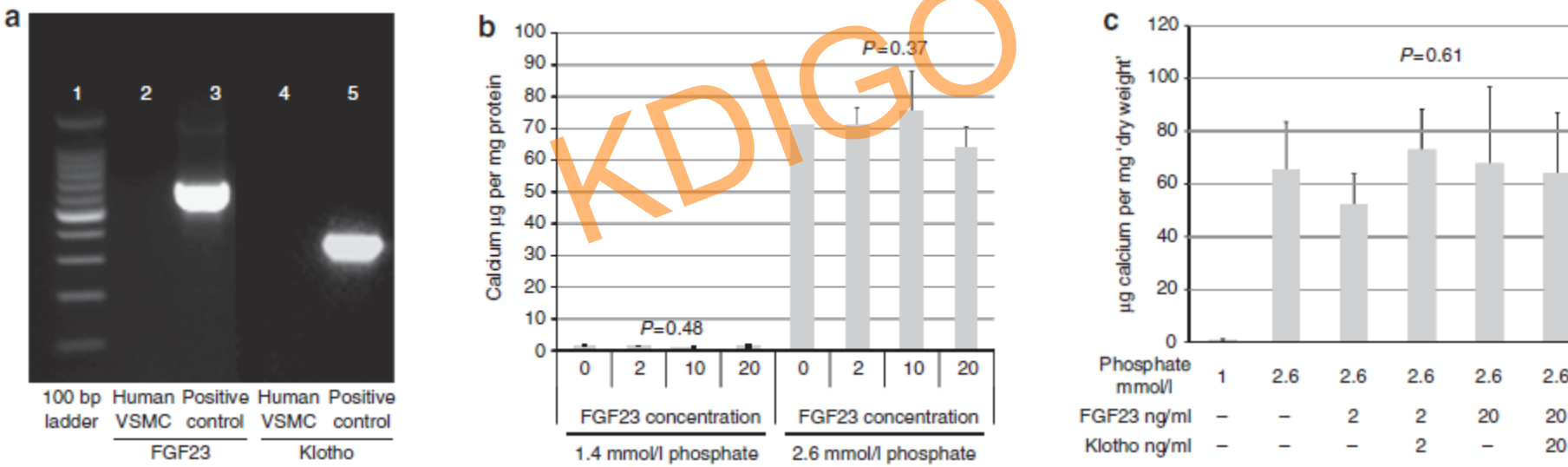
Julia J. Scialla[1,12], Wei Ling Lau[2,12], Muredach P. Reilly[3], Tamara Isakova[1], Hsueh-Ying Yang[4], Matthew H. Crouthamel[4], Nicholas W. Chavkin[4], Mahboob Rahman[5], Patricia Wahl[1], Ansel P. Amaral[1], Takayuki Hamano[6], Stephen R. Master[7], Lisa Nessel[6], Boyang Chai[6], Dawei Xie[6], Radhakrishna R. Kallem[3], Jing Chen[8], James P. Lash[9], John W. Kusek[10], Matthew J. Budoff[11], Cecilia M. Giachelli[4] and Myles Wolf[1] for the Chronic Renal Insufficiency Cohort Study Investigators

Table 3 | Adjusted association of fibroblast growth factor 23 (FGF23) and serum phosphate with categories of coronary artery calcium (CAC) and thoracic aorta calcium (TAC) scores using ordinal logistic regression ($n = 1384$)

Model[a]	Odds ratio for 1-unit increase in CAC category[b]	*P*-value	Odds ratio for 1-unit increase in TAC category[b]	*P*-value
ln FGF23 (per s.d.[c])				
−Phosphate	1.05 (0.93–1.20)	0.43	1.07 (0.94–1.21)	0.33
+Phosphate	1.02 (0.90–1.16)	0.74	1.06 (0.93–1.21)	0.38
Phosphate (per s.d.[c])				
−FGF23	1.29 (1.14–1.46)	<0.01	1.12 (0.98–1.27)	0.10
+FGF23	1.29 (1.13–1.46)	<0.01	1.11 (0.97–1.26)	0.13

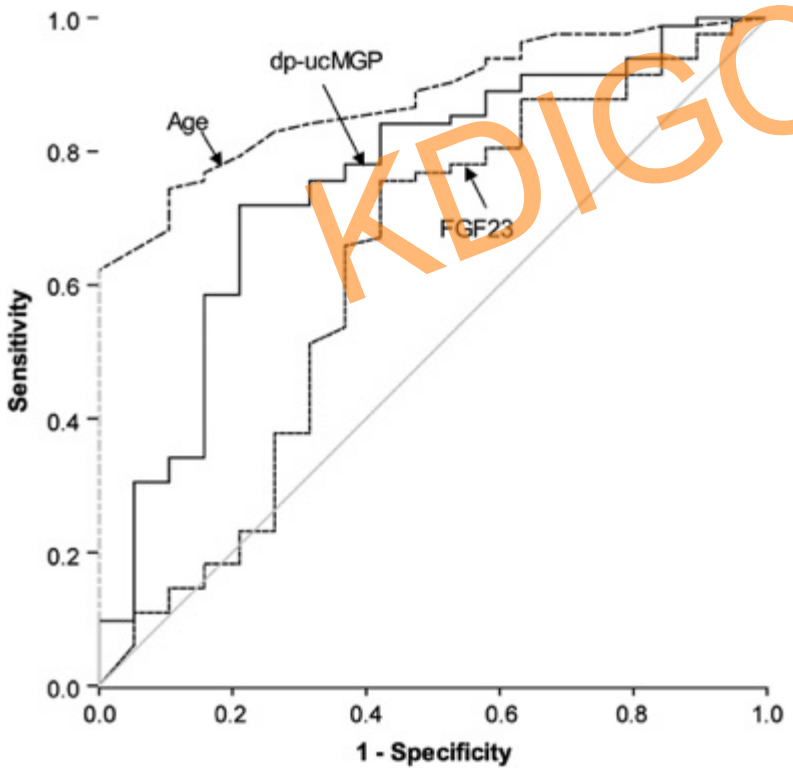
Fibroblast growth factor 23 is not associated with and does not induce arterial calcification

Julia J. Scialla[1,12], Wei Ling Lau[2,12], Muredach P. Reilly[3], Tamara Isakova[1], Hsueh-Ying Yang[4], Matthew H. Crouthamel[4], Nicholas W. Chavkin[4], Mahboob Rahman[5], Patricia Wahl[1], Ansel P. Amaral[1], Takayuki Hamano[6], Stephen R. Master[7], Lisa Nessel[6], Boyang Chai[6], Dawei Xie[6], Radhakrishna R. Kallem[3], Jing Chen[8], James P. Lash[9], John W. Kusek[10], Matthew J. Budoff[11], Cecilia M. Giachelli[4] and Myles Wolf[1] for the Chronic Renal Insufficiency Cohort Study Investigators



Vascular calcification in chronic kidney disease: are biomarkers useful for probing the pathobiology and the health risks of this process in the clinical scenario?

Sophie Liabeuf[1,2], Hirokazu Okazaki[1], Lucie Desjardins[1,2], Danilo Fliser[3], David Goldsmith[4], Adrian Covic[5], Andrzej Wiecek[6], Alberto Ortiz[7], Alberto Martinez-Castelao[8], Bengt Lindholm[9], Gultekin Suleymanlar[10], Francesca Mallamaci[11], Carmine Zoccali[11], Gerard London[12] and Ziad A. Massy[1,13]



no biomarker outperformed age and the classical risk factors as a predictor of VC either in the aorta or in the coronaries.

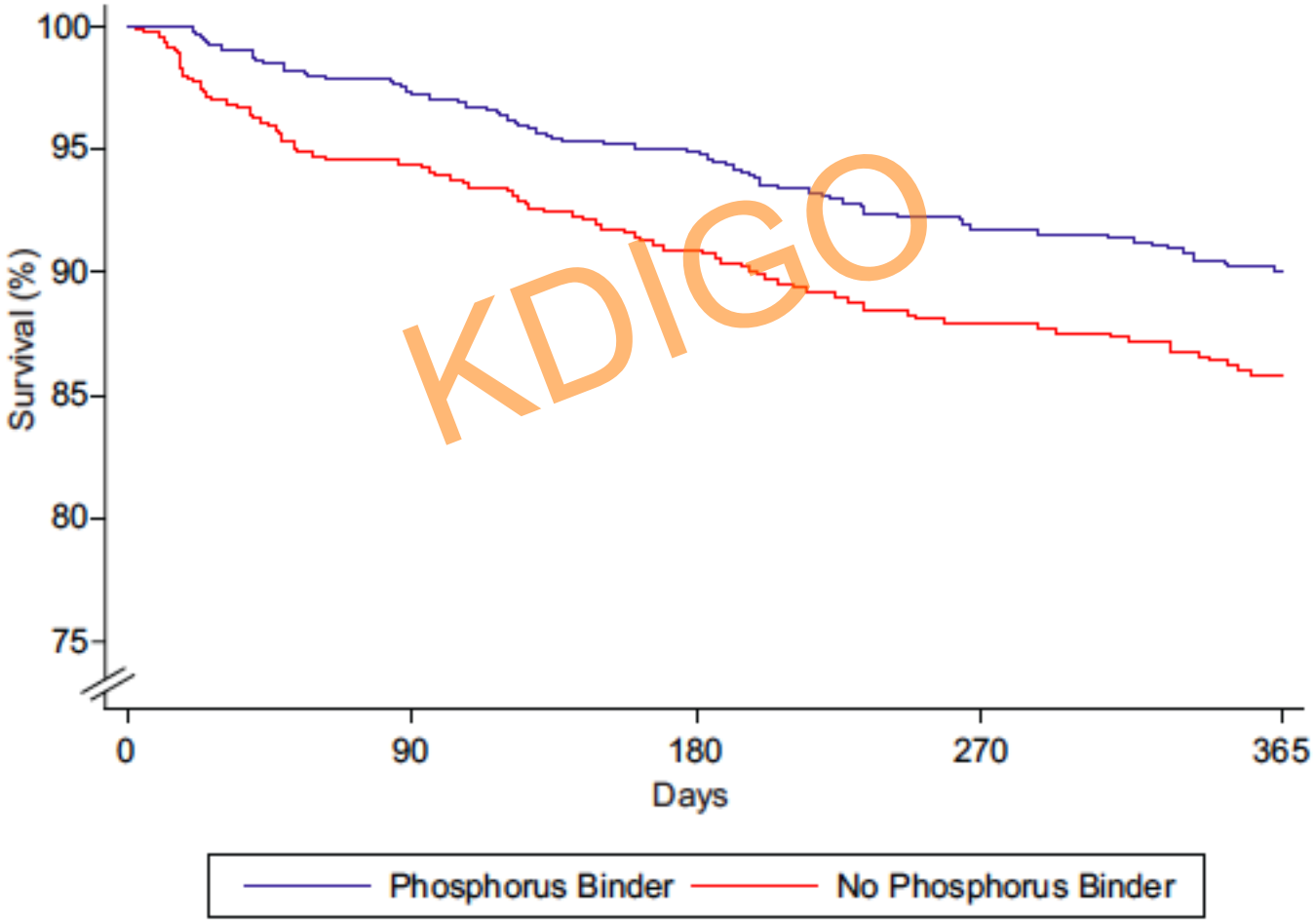
Nephrol Dial Transplant (2014) 29: 1275–1284

Lowering the load of PO4 to control FGF23

- Use of PO4 binders
- Limiting dietary phosphate / protein

Phosphorus Binders and Survival on Hemodialysis

Tamara Isakova,* Orlando M. Gutiérrez,† Yuchiao Chang,‡ Anand Shah,* Hector Tamez,* Kelsey Smith,† Ravi Thadhani,* and Myles Wolf†



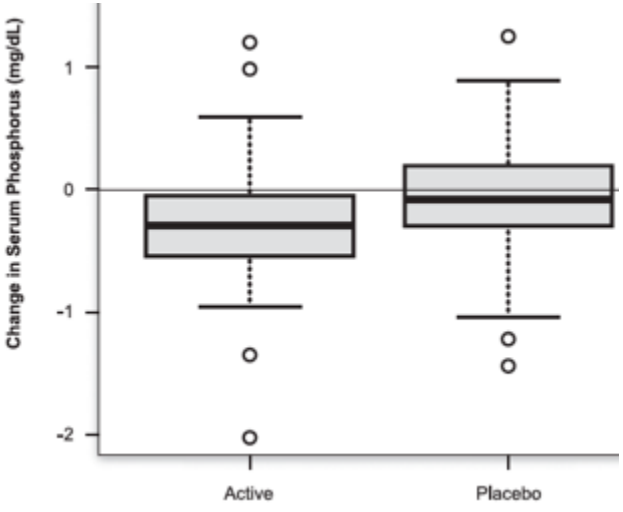
J Am Soc Nephrol 20: 388–396, 2009

J Am Soc Nephrol 23: 1407–1415, 2012.

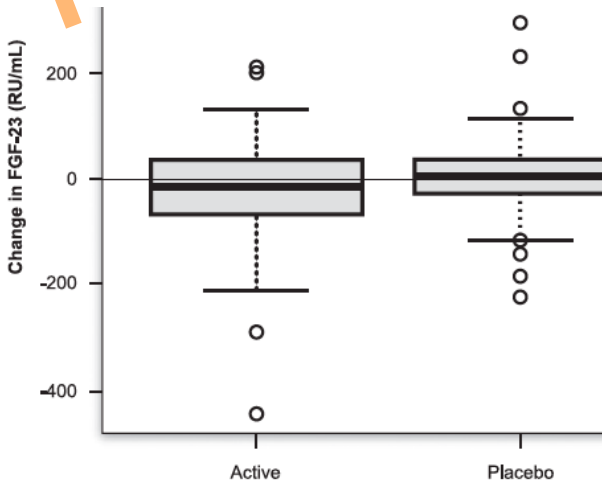
Effects of Phosphate Binders in Moderate CKD

Geoffrey A. Block,* David C. Wheeler,† Martha S. Persky,* Bryan Kestenbaum,‡ Markus Ketteler,§ David M. Spiegel,‖ Matthew A. Allison,¶ John Asplin,** Gerard Smits,* Andrew N. Hoofnagle,‡ Laura Kooienga,* Ravi Thadhani,†† Michael Mannstadt,†† Myles Wolf,‡‡ and Glenn M. Chertow§§

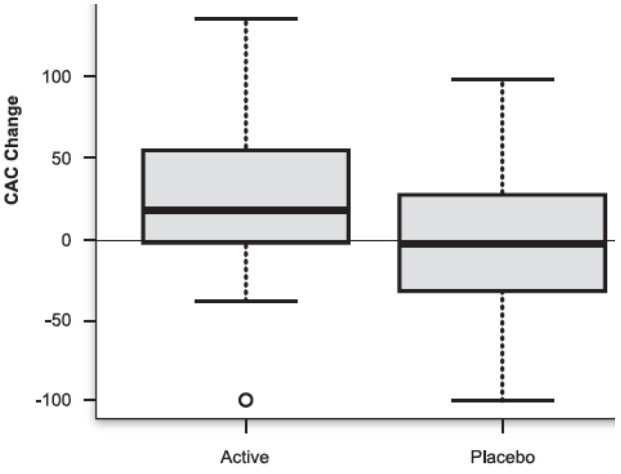
148 patients with eGFR=20–45 randomized to calcium acetate, lanthanum carbonate, sevelamer, or placebo. Primary endpoint was change in mean serum phosphorus from baseline to 9 months



Reduction serum P



No change in FGF23



Increase in CAC

J Am Soc Nephrol 23: 1407–1415, 2012.

Effects of Phosphate Binders in Moderate CKD

Geoffrey A. Block,* David C. Wheeler,† Martha S. Persky,* Bryan Kestenbaum,‡ Markus Ketteler,§ David M. Spiegel,‖ Matthew A. Allison,¶ John Asplin,** Gerard Smits,* Andrew N. Hoofnagle,‡ Laura Kooienga,* Ravi Thadhani,†† Michael Mannstadt,†† Myles Wolf,‡‡ and Glenn M. Chertow§§

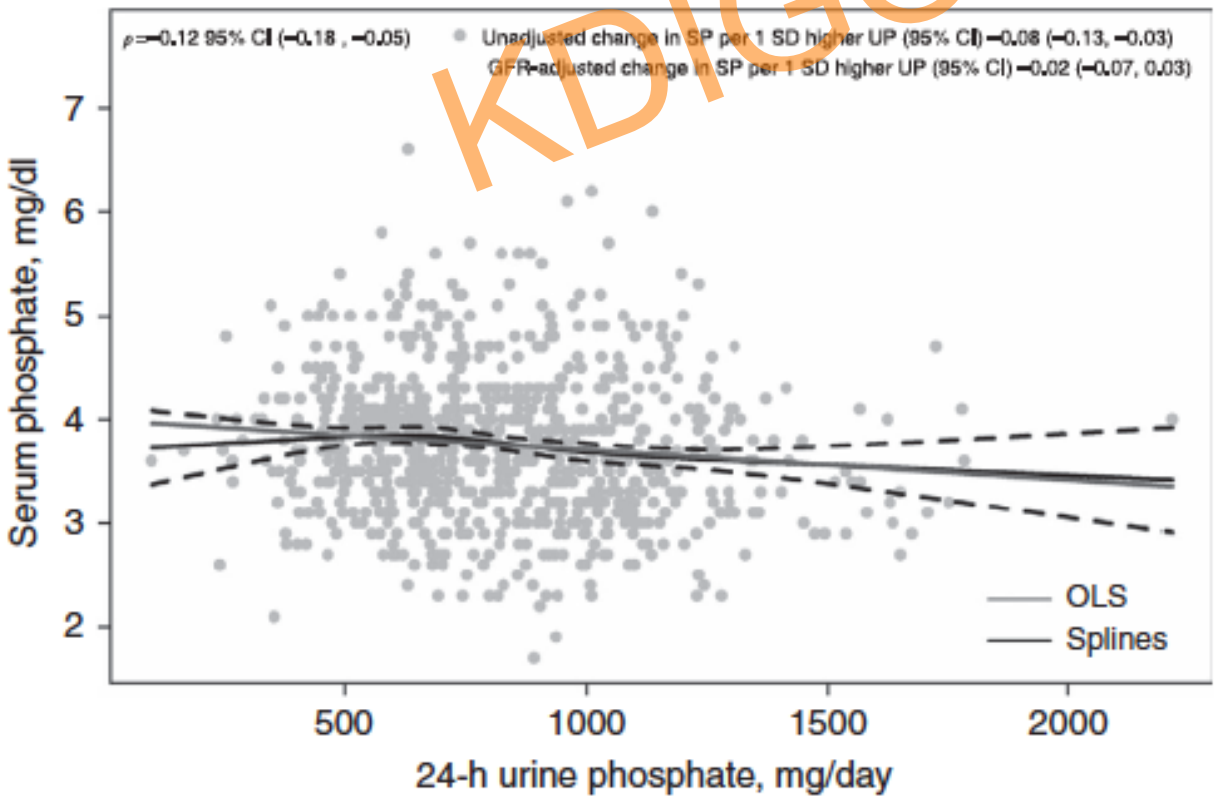
Lowering serum P did not improve medium term outcome in predialysis CKD subjects with near-normal serum P; it increases vascular calcification rates

Kidney International (2016) **89,** 176–184

Relationship of dietary phosphate intake with risk of end-stage renal disease and mortality in chronic kidney disease stages 3–5: The Modification of Diet in Renal Disease Study

see commentary on page 21

Umut Selamet[1], Hocine Tighiouart[2], Mark J. Sarnak[3], Gerald Beck[4], Andrew S. Levey[3], Geoffrey Block[5] and Joachim H. Ix[1,6,7]



795 MDRD study participants randomized to low or high PO4 diet

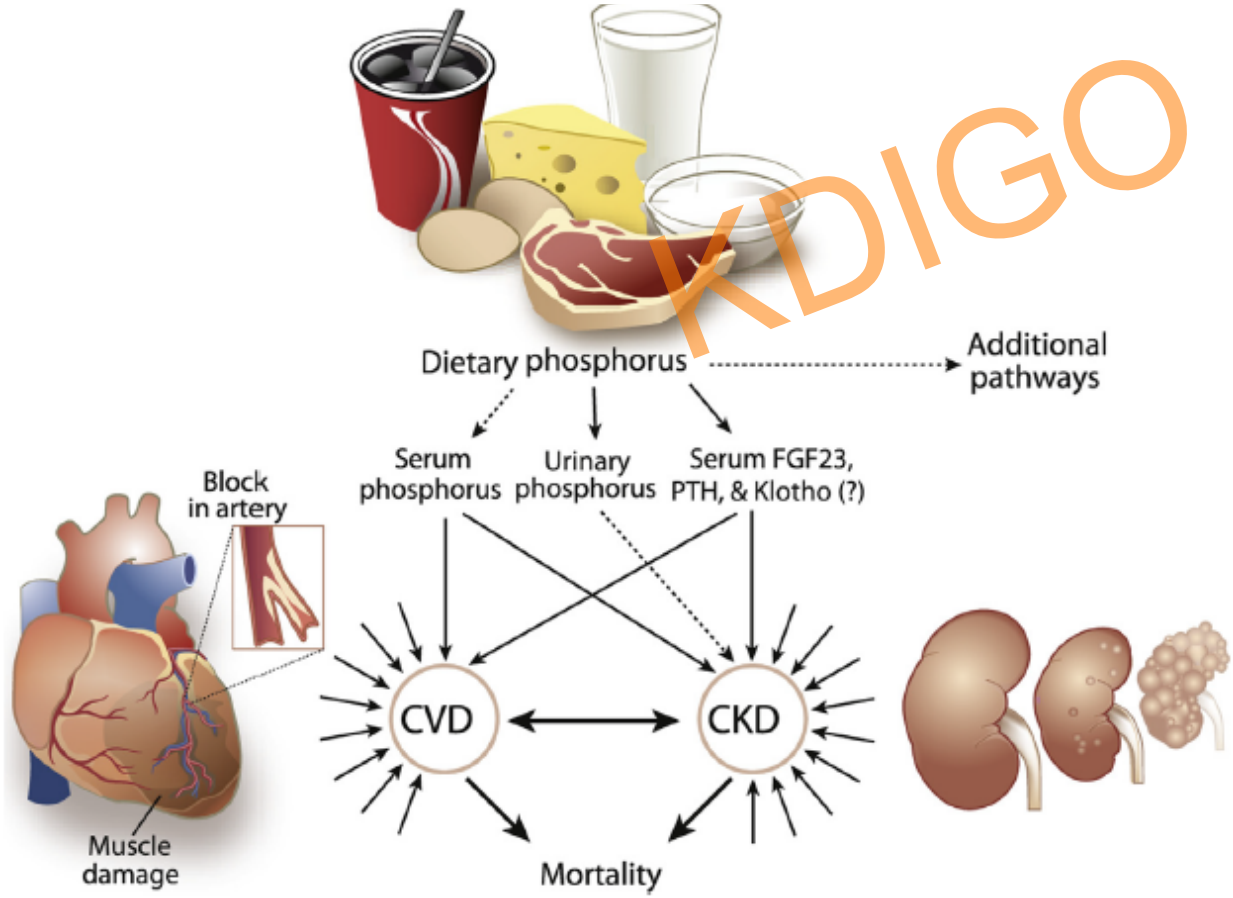
No Association of 24-h urine phosphate excretion with incident ESRD, CVD mortality, non-CVD mortality, and all cause mortality

24-H UPE range of quartiles (mg/day)	Q1 100–608	Q2 609–788	Q3 791–1008	Q4 1010–2211	Continuous (per higher SD)	*P*-value
ESRD						
Number of events/number at risk	145/198	153/200	144/199	147/198	589/795	
Event rate (per 100 PY)	9.62	8.97	9.06	8.58	9.04	
Model 1: HR (95% CI)	1.00 (Reference)	0.93 (0.74, 1.17)	0.91 (0.71, 1.16)	0.85 (0.65, 1.10)	0.93 (0.85, 1.02)	0.13
Model 2: HR (95% CI)	1.00 (Reference)	0.93 (0.73, 1.17)	1.03 (0.81, 1.32)	1.05 (0.80, 1.38)	1.02 (0.93, 1.13)	0.64
Model 3: HR (95% CI)	1.00 (Reference)	0.98 (0.77, 1.24)	1.03 (0.79, 1.33)	1.10 (0.82, 1.46)	1.04 (0.94, 1.15)	0.48
CVD mortality						
Number of events/number at risk	43/198	50/200	54/199	44/198	191/795	
Event rate (per 100 PY)	1.39	1.56	1.84	1.42	1.55	
Model 1: HR (95% CI)	1.00 (Reference)	1.03 (0.68, 1.57)	1.02 (0.67, 1.56)	0.80 (0.50, 1.27)	0.93 (0.79, 1.10)	0.40
Model 2: HR (95% CI)	1.00 (Reference)	1.08 (0.71, 1.65)	1.12 (0.73, 1.72)	0.94 (0.57, 1.53)	1.00 (0.84, 1.20)	0.99
Model 3: HR (95% CI)	1.00 (Reference)	1.12 (0.73, 1.72)	1.08 (0.69, 1.70)	0.93 (0.56, 1,56)	1.00 (0.82, 1.21)	0.97
All-cause mortality						
Number of events/number at risk	100/198	101/200	109/199	109/198	419/795	
Event rate (per 100 PY)	3.23	3.15	3.71	3.52	3.40	
Model 1: HR (95% CI)	1.00 (Reference)	0.97 (0.73, 1.29)	0.98 (0.74, 1.31)	0.98 (0.72, 1.33)	0.99 (0.89, 1.11)	0.90
Model 2: HR (95% CI)	1.00 (Reference)	1.01 (0.76, 1.35)	1.08 (0.81, 1.45)	1.16 (0.84, 1.61)	1.07 (0.95, 1.20)	0.26
Model 3: HR (95% CI)	1.00 (Reference)	1.00 (0.75, 1.33)	0.94 (0.69, 1.27)	1.02 (0.73, 1.44)	1.02 (0.90, 1.16)	0.76

Selamet et al. KI 2016

Dietary phosphorus restriction in predialysis chronic kidney disease: time for a cease-fire?

Pieter Evenepoel[1] and Marc G. Vervloet[2]



Dietary PO4 control may not be effective in improving clinical endpoints

Limitations of the MDRD posthoc analysis ((baseline P, low ACEi penetrance, drastic inc in P intake over time)

Need of further studies

When targeting dietary phosphate restriction, however, the focus should clearly be on phosphate additives and not on protein

Kidney International (2016) **90,** 477–479 commentary

The rise of FGF23: should insights from population-based studies inform future clinical trials?

James B. Wetmore[1]

The practicing clinician might wonder **"**does it matter to patient care whether the FGF23 level rises before PTH or the reverse?**"**

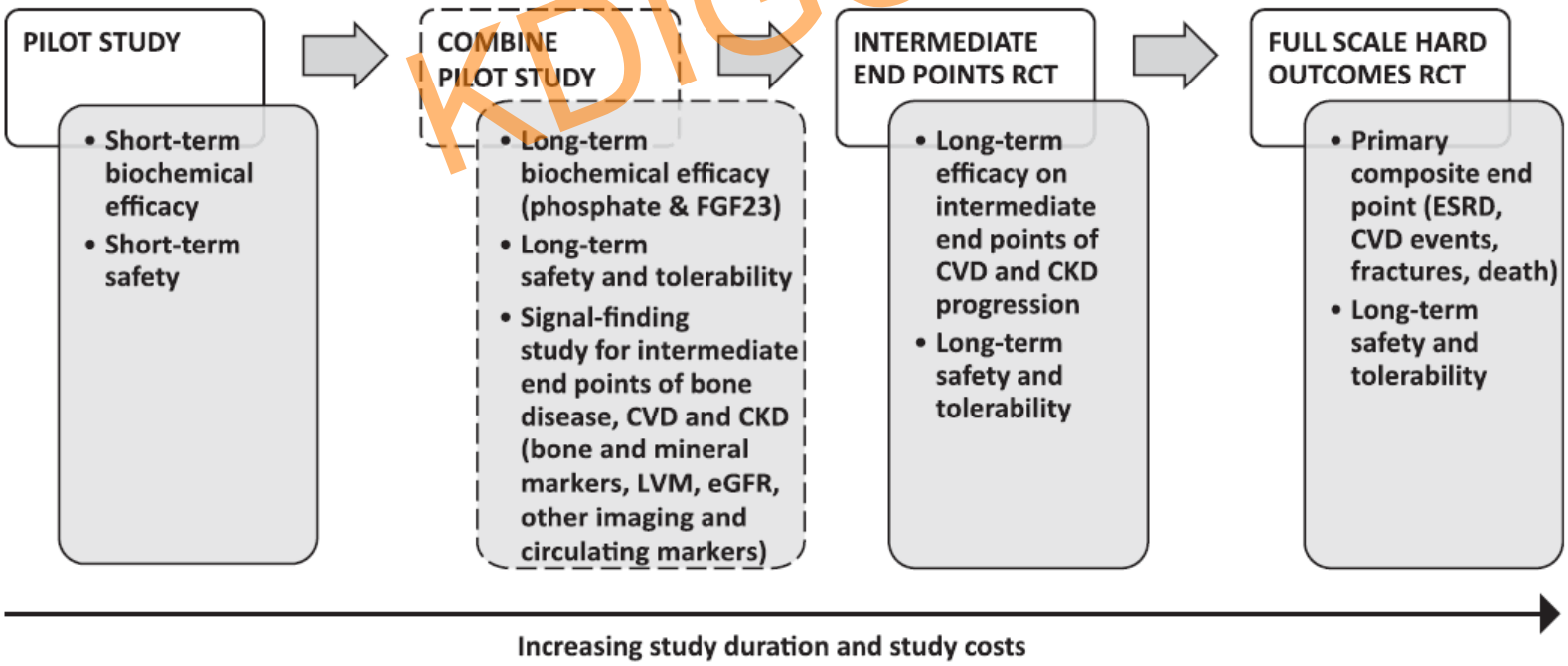
Interventions designed to slow the progression of CKD, such as those targeting FGF23, are unlikely to be undertaken on any widespread basis when the eGFR is well above 60 ml/min per 1.73 m2 .

Practical implications: the earlier that the FGF23 level rises, the more pronounced is its rise, and the greater its demonstrable effects on other biological processes (e.g., on vitamin D metabolism), the stronger the rationale is for undertaking an intervention designed to lower FGF23 levels**—** such as the COMBINE study and large potential follow-up studies. Such studies take time, energy, and resources….

Phosphate Binding Therapy to Lower Serum Fibroblast-Growth-Factor-23 Concentrations in Chronic Kidney Disease: Rationale and Study Design of the Sevelamer on FGF23 Trial (SoFT)

Aaltje Y. Adema[a] Maarten A. de Jong[c] Martin H. de Borst[c] Pieter M. ter Wee[a]
Marc G. Vervloet[a, b] for the NIGRAM Consortium

COMBINE Study: The CKD Optimal Management With BInders and NicotinamidE study



Isakova T, et al J Am Soc Nephrol 26: 2328–2339, 2015

American Journal of Nephrology

Fibroblast Growth Factor 23 and Vascular Calcification: Is It Set in Stone?

Gary C.W. Chan Sydney C.W. Tang

Division of Nephrology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China

- FGF23 is evidently a biomarker for CKD-MBD
- Evidence for and against FGF23 for an early biomarker and relation with CV events
- Hence **the jury is still out!**
- Interventional studies that reduce FGF23 with longitudinal FU may yield a more definitive answer – maybe in 10 yrs (Vervloet M, personal comm, 25 Aug 2016)

Thank you!

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Dickson Wong
Chris Chan
Joseph Leung
Loretta Chan
Kar Neng Lai

Victoria Harbour, HK