

# ***The 20th Budapest Nephrology School***

*August 28, 2013*

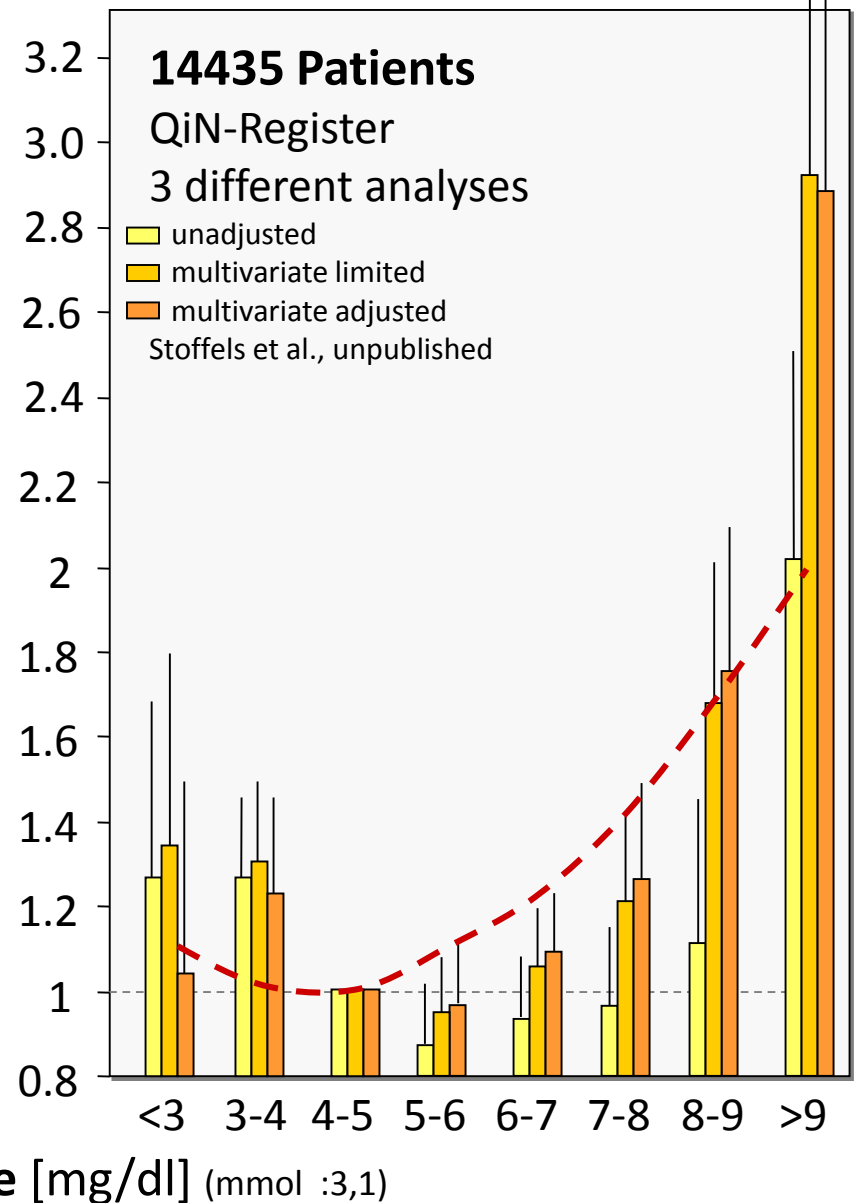
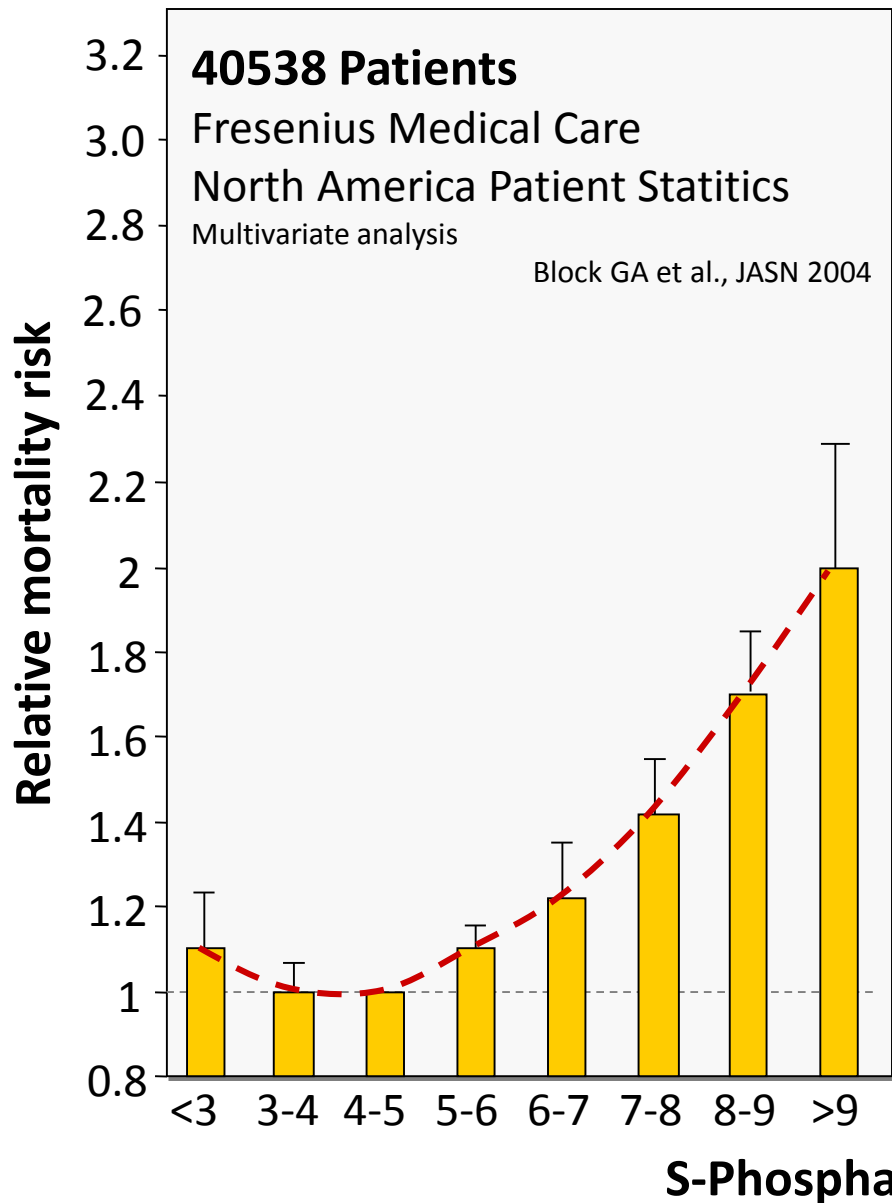
**FGF23 Antagonism: The thin line between adaptation and maladaptation in chronic kidney disease**

**Markus Ketteler**

[markus.ketteler@klinikum-coburg.de](mailto:markus.ketteler@klinikum-coburg.de)

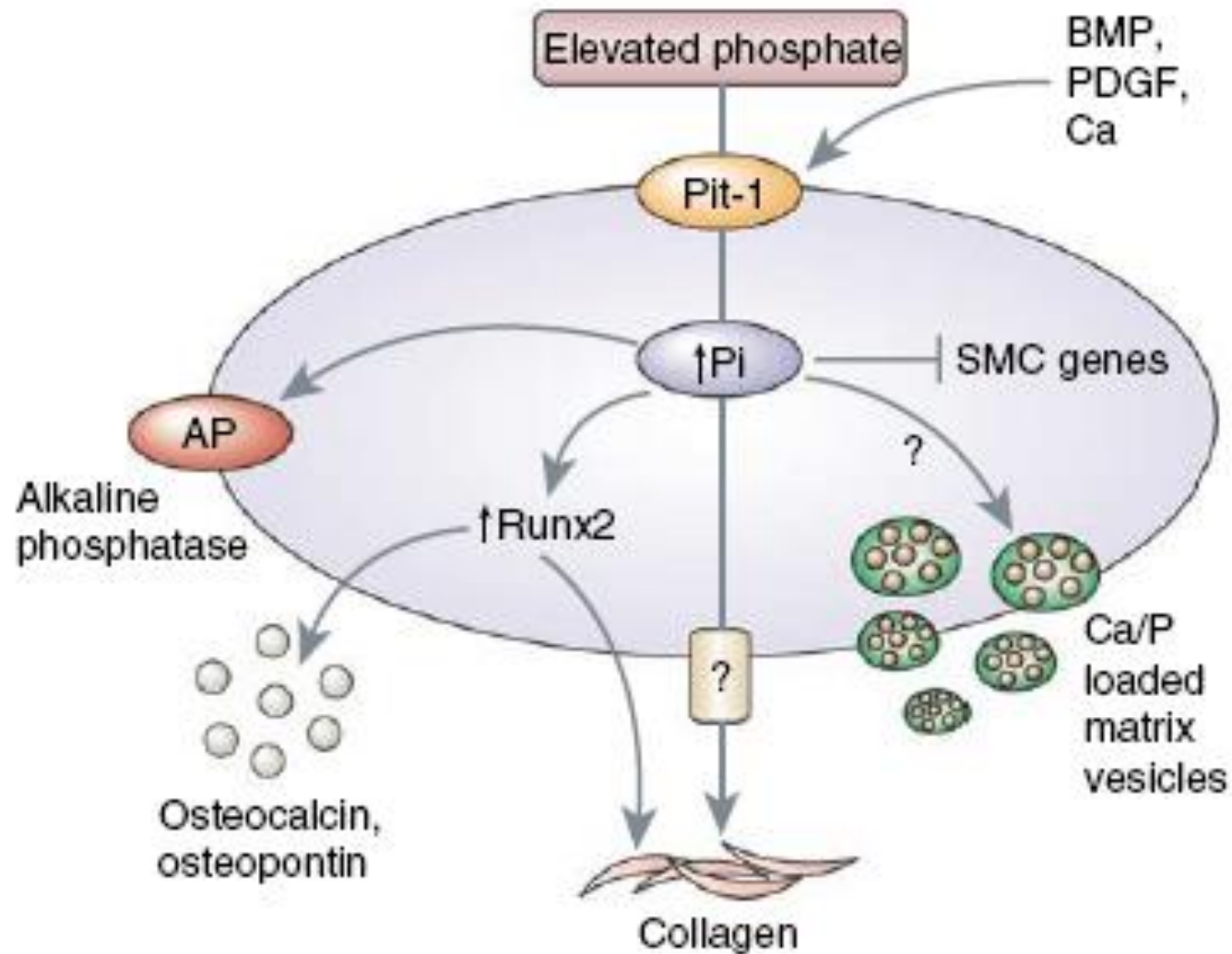


# Serum phosphate vs. mortality risk in hemodialysis patients



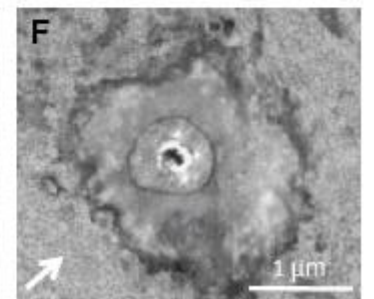
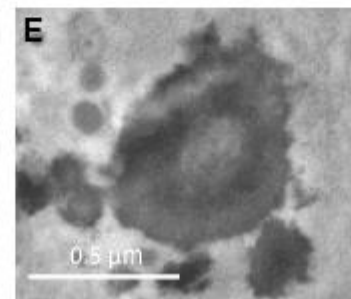
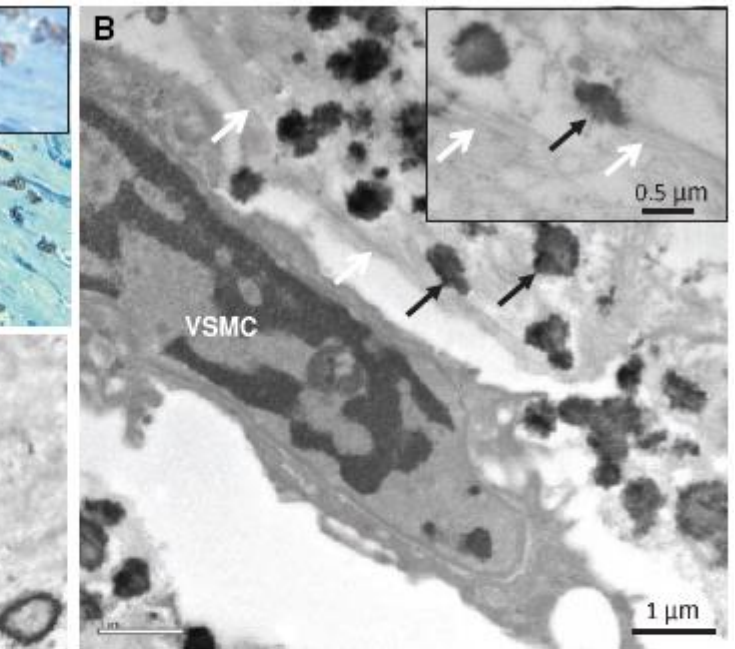
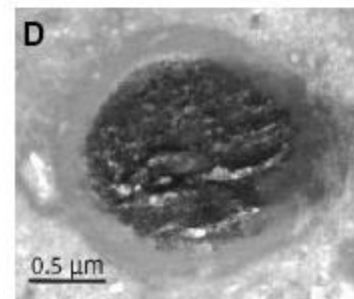
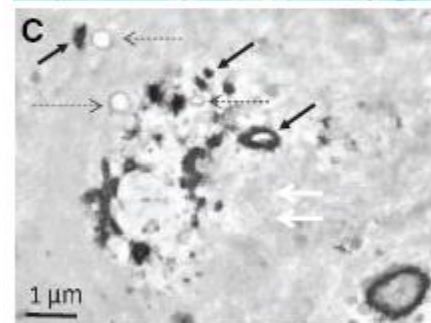
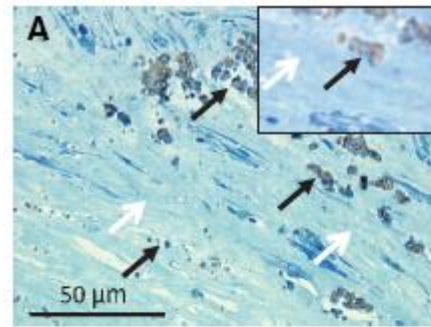
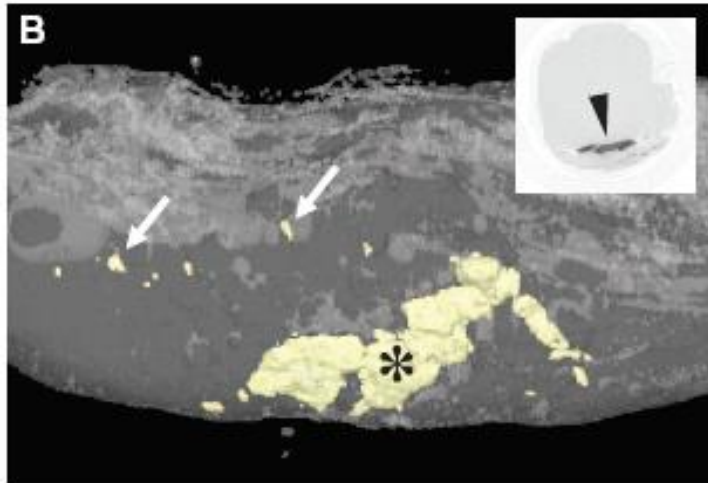
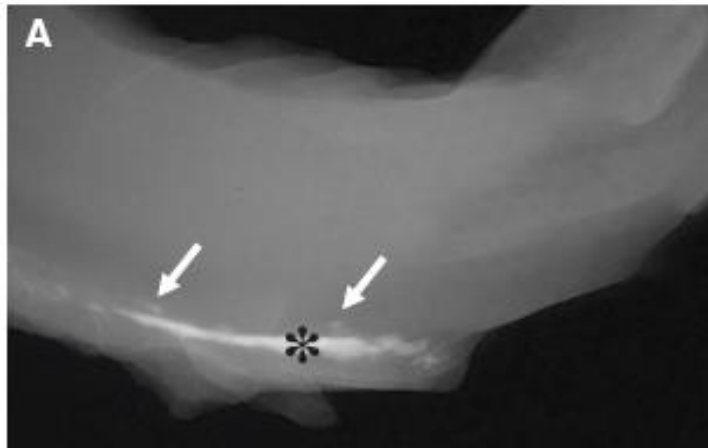
# Pathomechanisms of extraosseous calcification

Giachelli C. Kidney Int 2009



# Ultrastructure of arterial calcifications: Nanocrystals, matrix vesicles, and apoptosis

Schlieper G et al., JASN 2010; 21:689-96

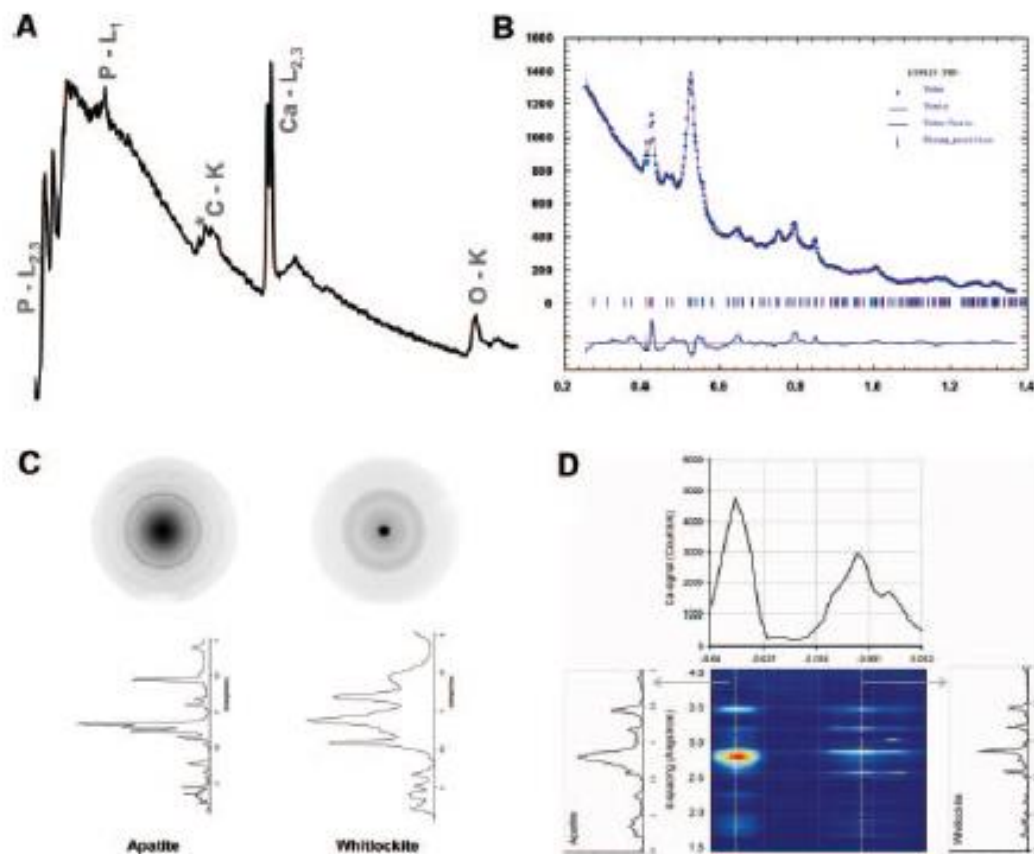
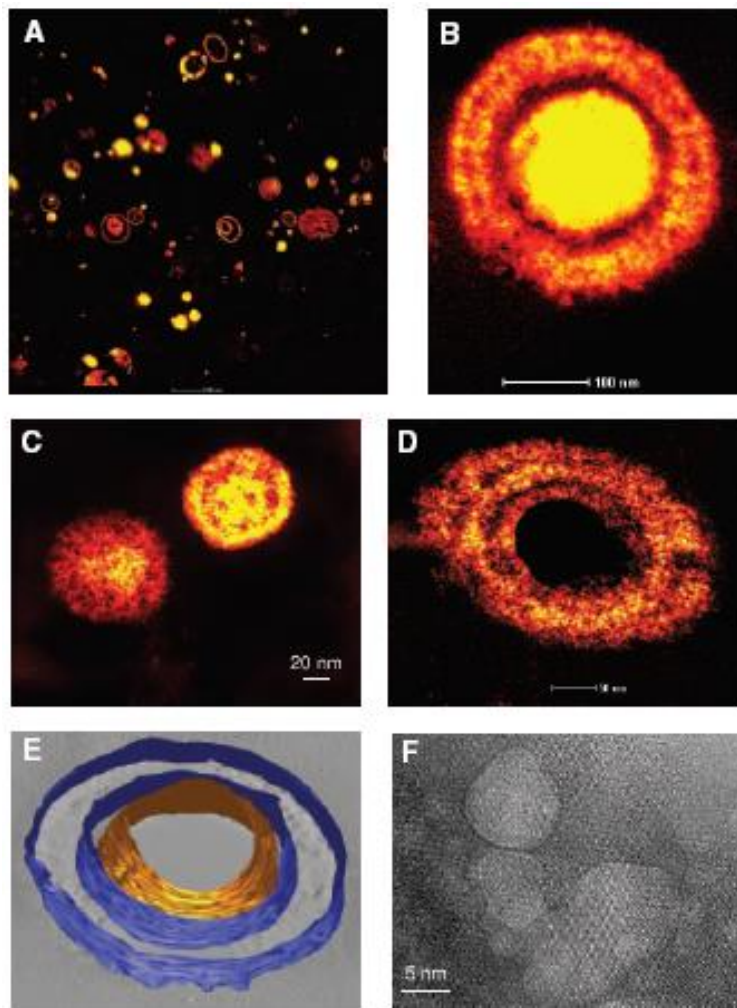


Micro-CT

TEM

# Ultrastructure of arterial calcifications: Nanocrystals, matrix vesicles, and apoptosis

Schlieper G et al., JASN 2010; 21:689-96

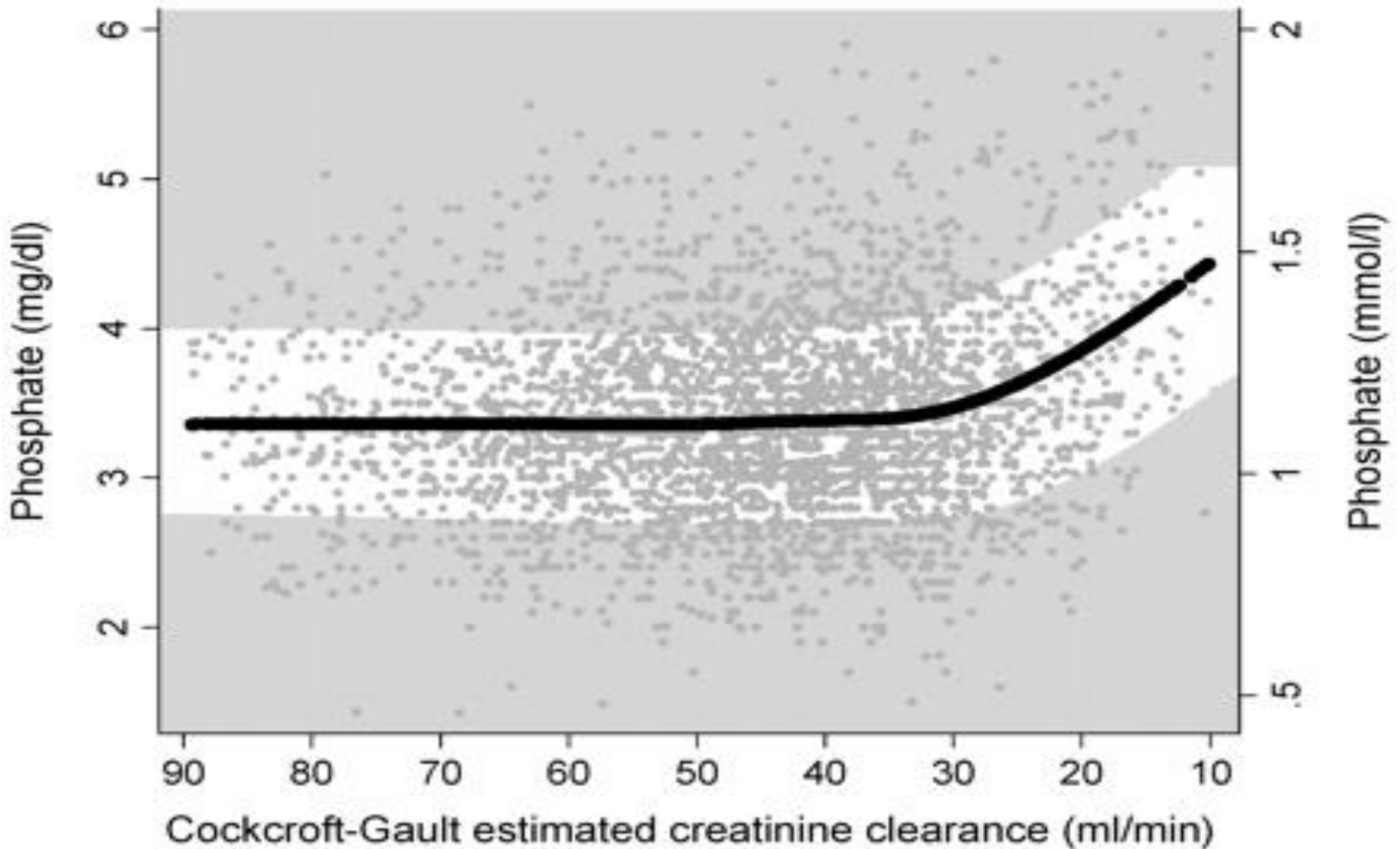


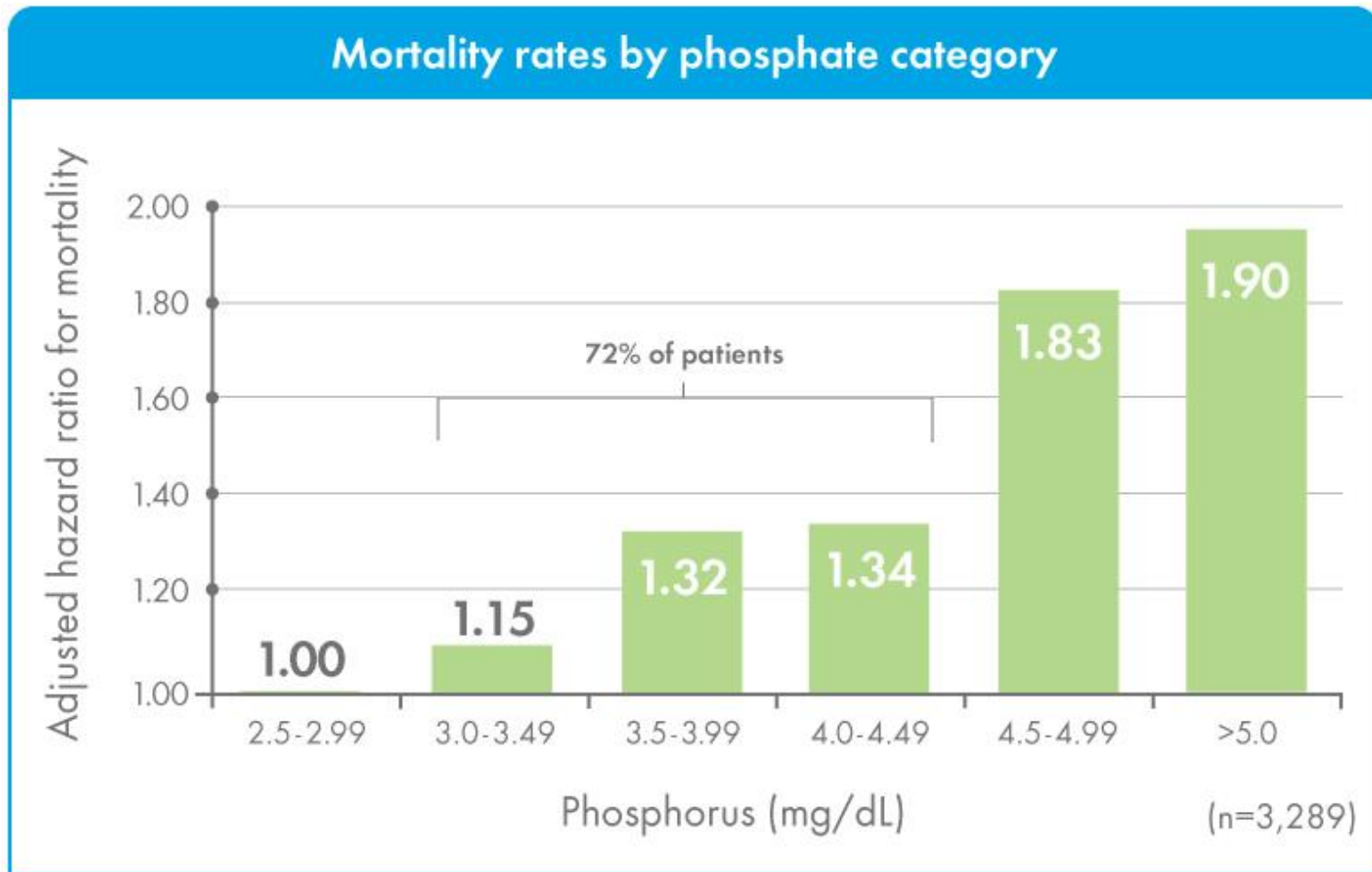
Normal + „high resolution“ TEM /  
„Modelling“

Electron diffraction pattern /  
Synchrotron radiation:  
Hydroxyapatite + Whitlockite (Ca x P)

# Hyperphosphatemia manifests no sooner than in CKD stage 4

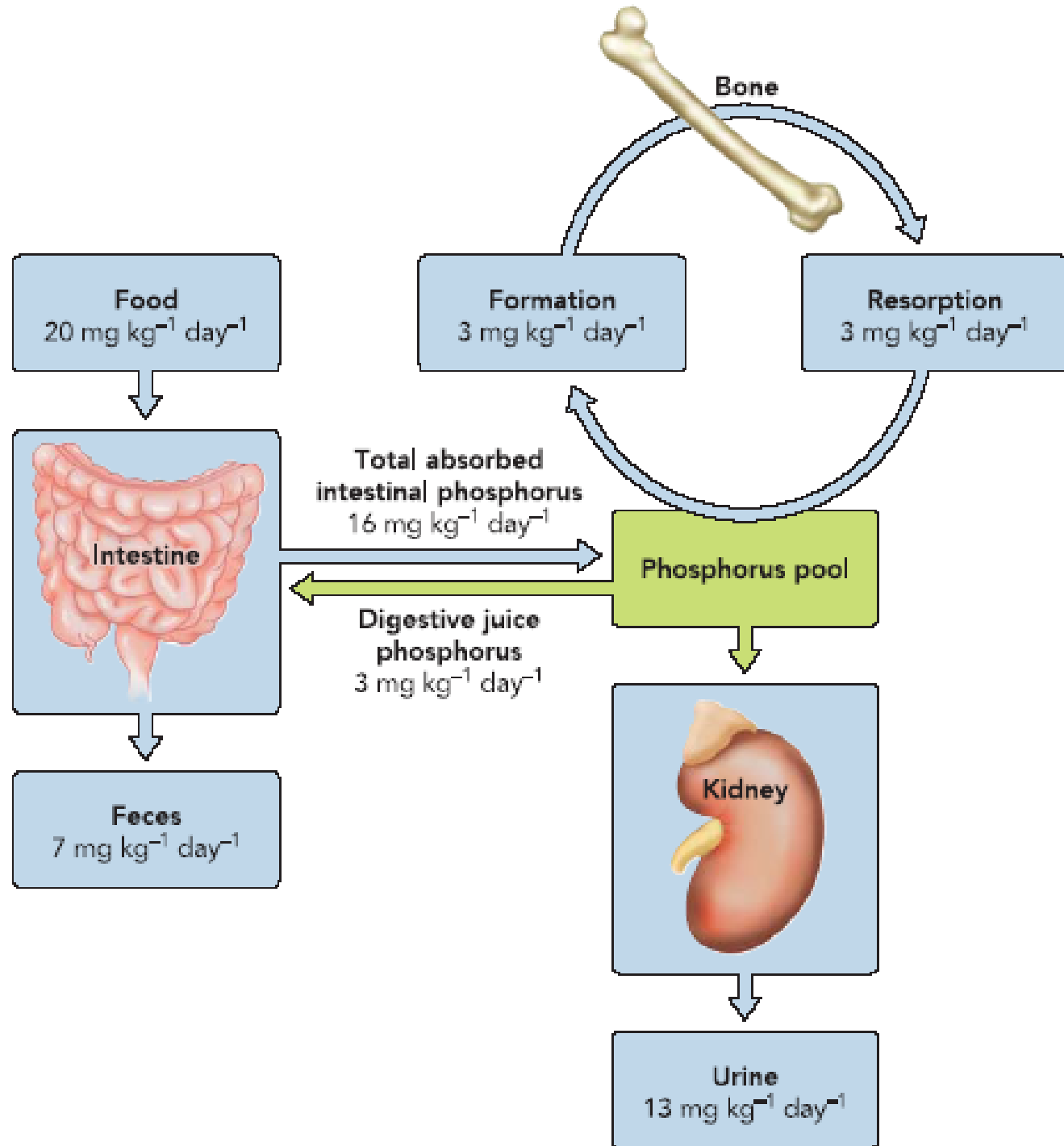
Kestenbaum B et al. J Am Soc Nephrol. 2004;16:520-528





- **Predialysis patients:** Association between phosphate and mortality with high-normal serum levels

# Phosphate balance in normal kidney function

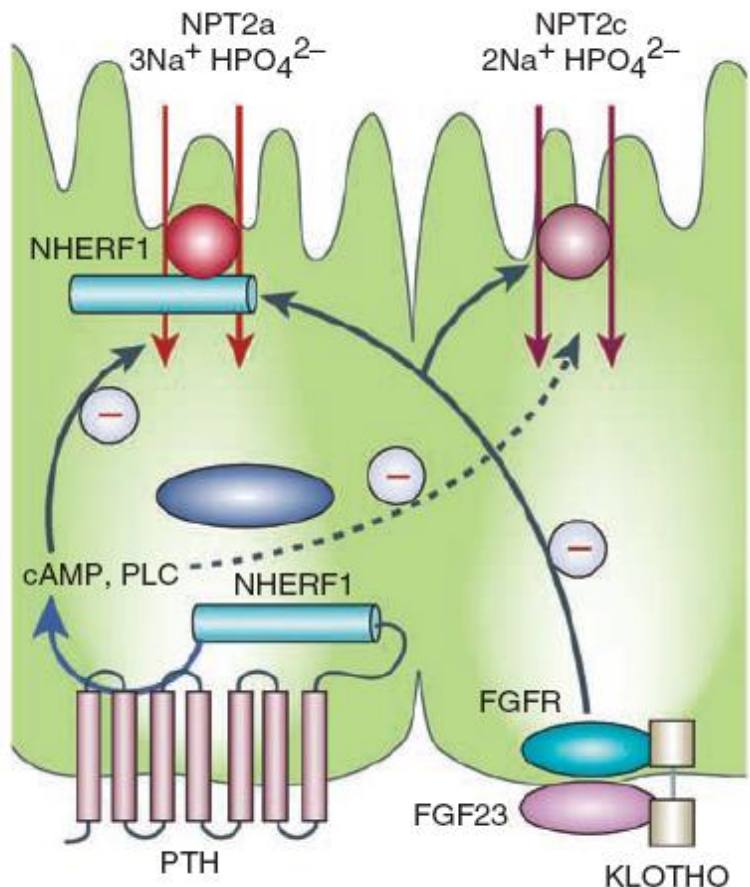
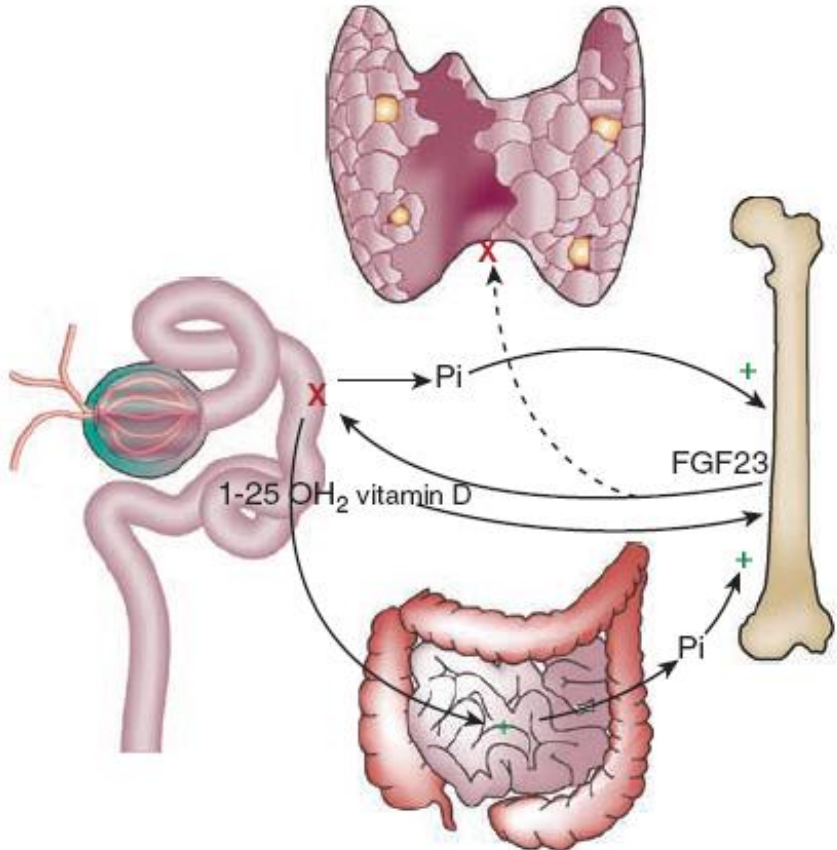


# Latest findings in phosphate homeostasis

Dominique Prié<sup>1,2</sup>, Pablo Ureña Torres<sup>3</sup> and Gérard Friedlander<sup>2,4</sup>

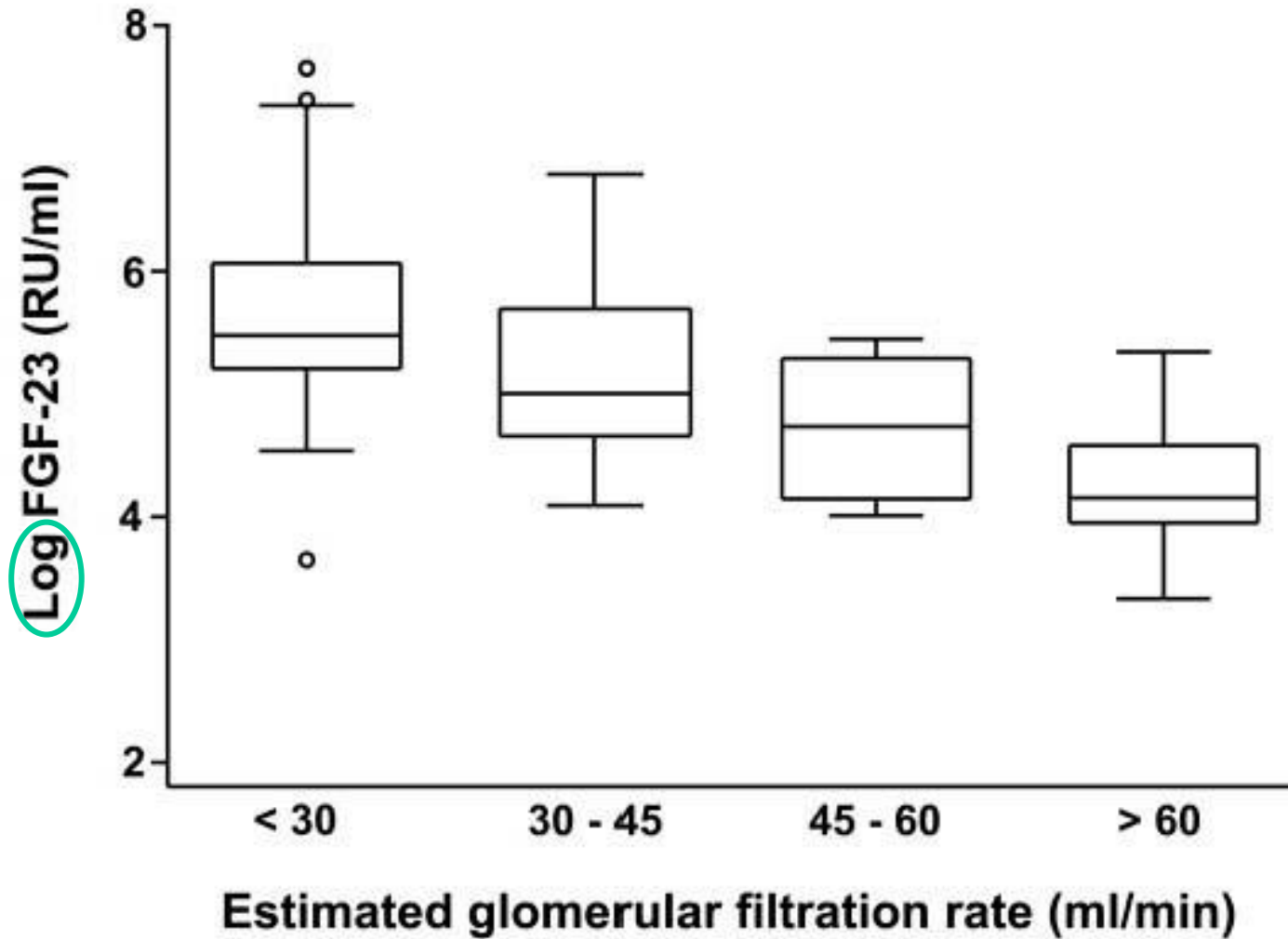
<sup>1</sup>Service d'Explorations Fonctionnelles, Hôpital Necker-Enfants Malades, AP-HP, Paris, France; <sup>2</sup>Centre de Recherche Croissance et Signalisation (Inserm U845), Université Paris Descartes, Faculté de Médecine, Paris, France; <sup>3</sup>Service de Néphrologie et Dialyse, Clinique du Landy, Saint Ouen, France and <sup>4</sup>Service de Physiologie et Radio-isotopes, Hôpital Européen Georges Pompidou, AP-HP, Paris, France

Prié et al., *Kidney Int* 2009; 75:882-9



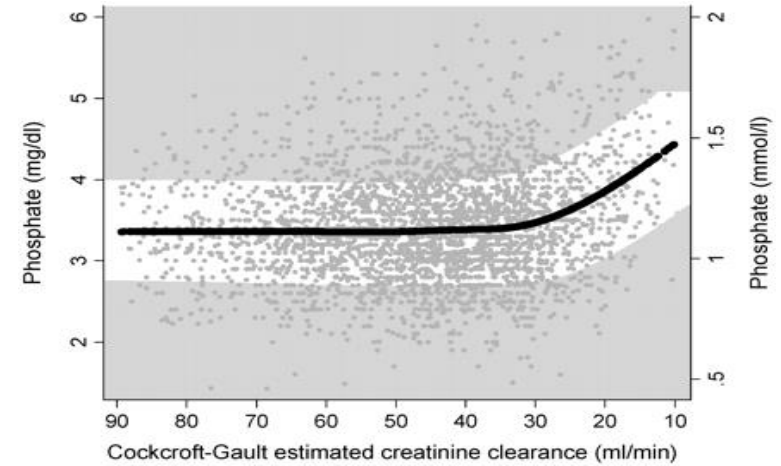
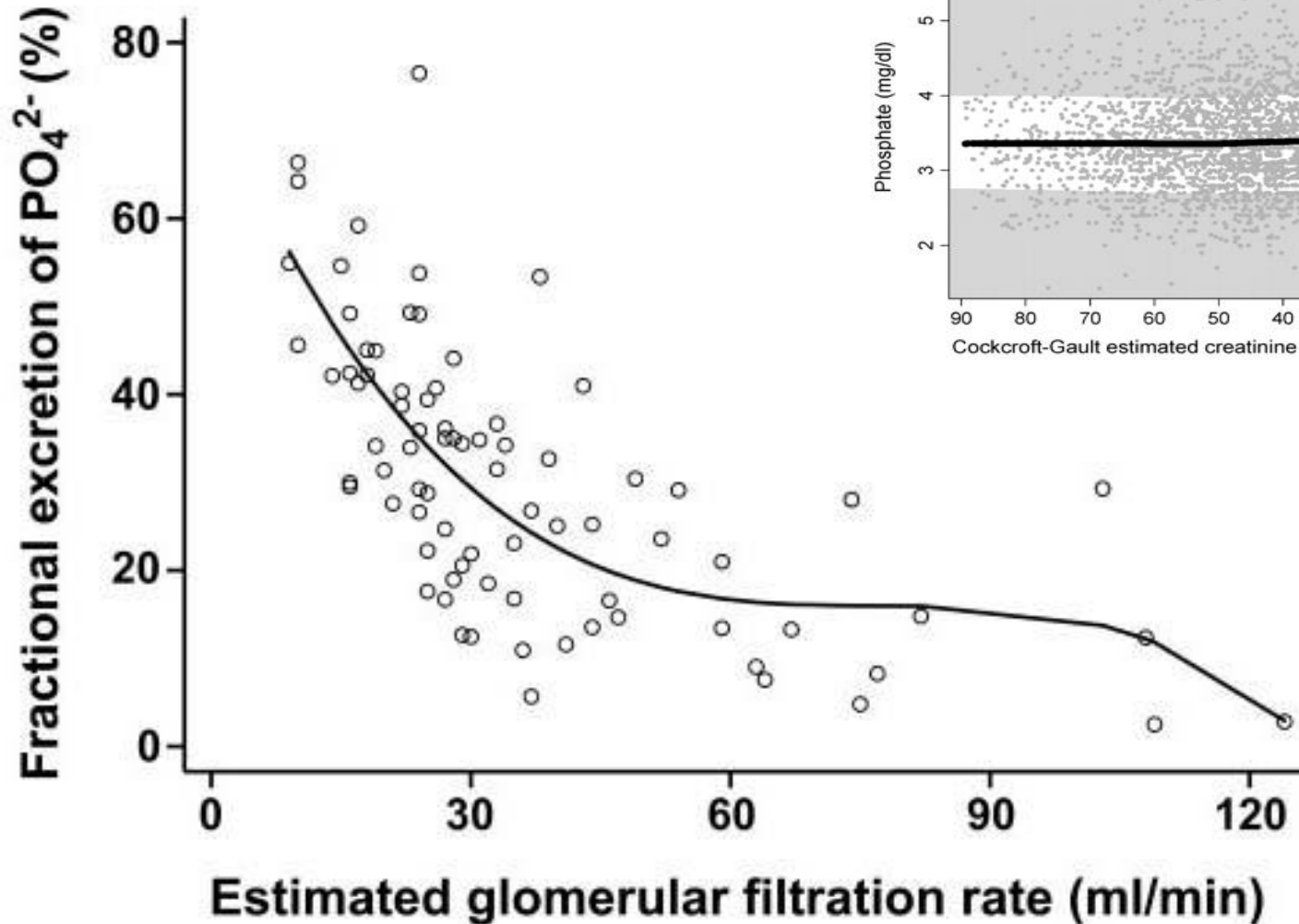
# FGF23 and renal function (GFR) inversely correlate with each other

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



# Fractional phosphate excretion increases with declining renal function

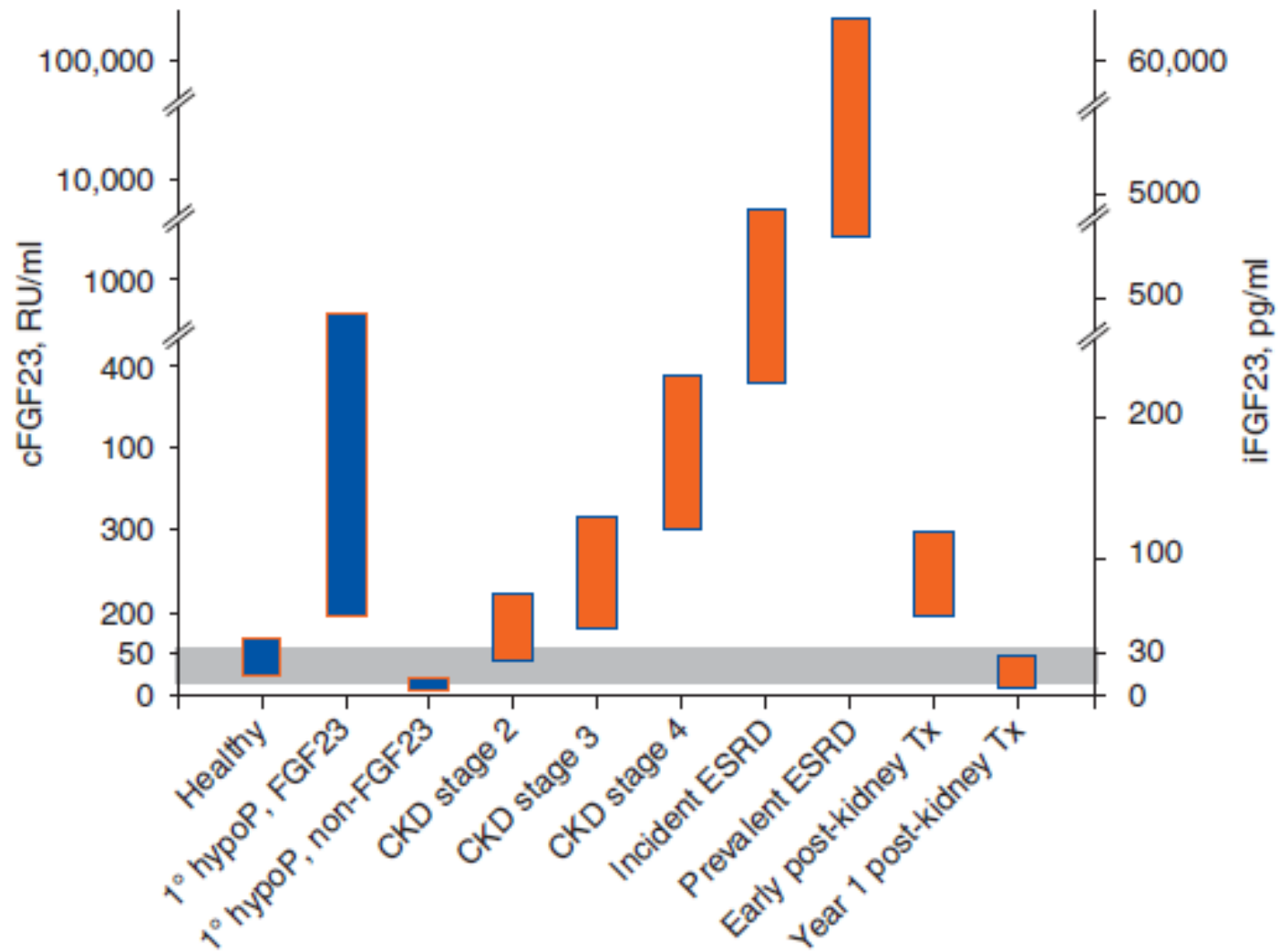
Gutierrez et al., J Am Soc Nephrol 2005; 16:2205-15



# Update on fibroblast growth factor 23 in chronic kidney disease

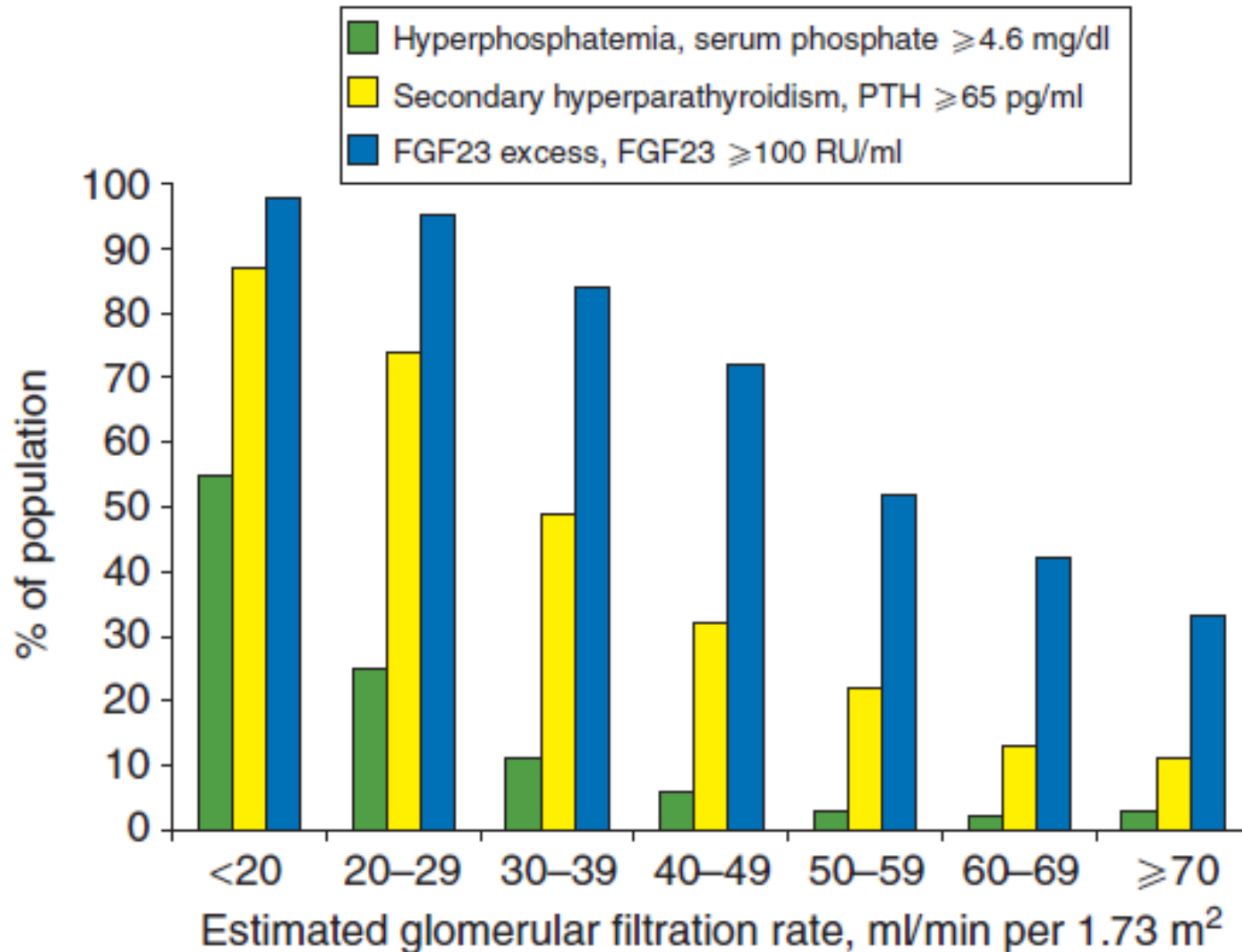
*Kidney International* advance online publication, 23 May 2012;  
doi:10.1038/ki.2012.176

Myles Wolf<sup>1</sup>



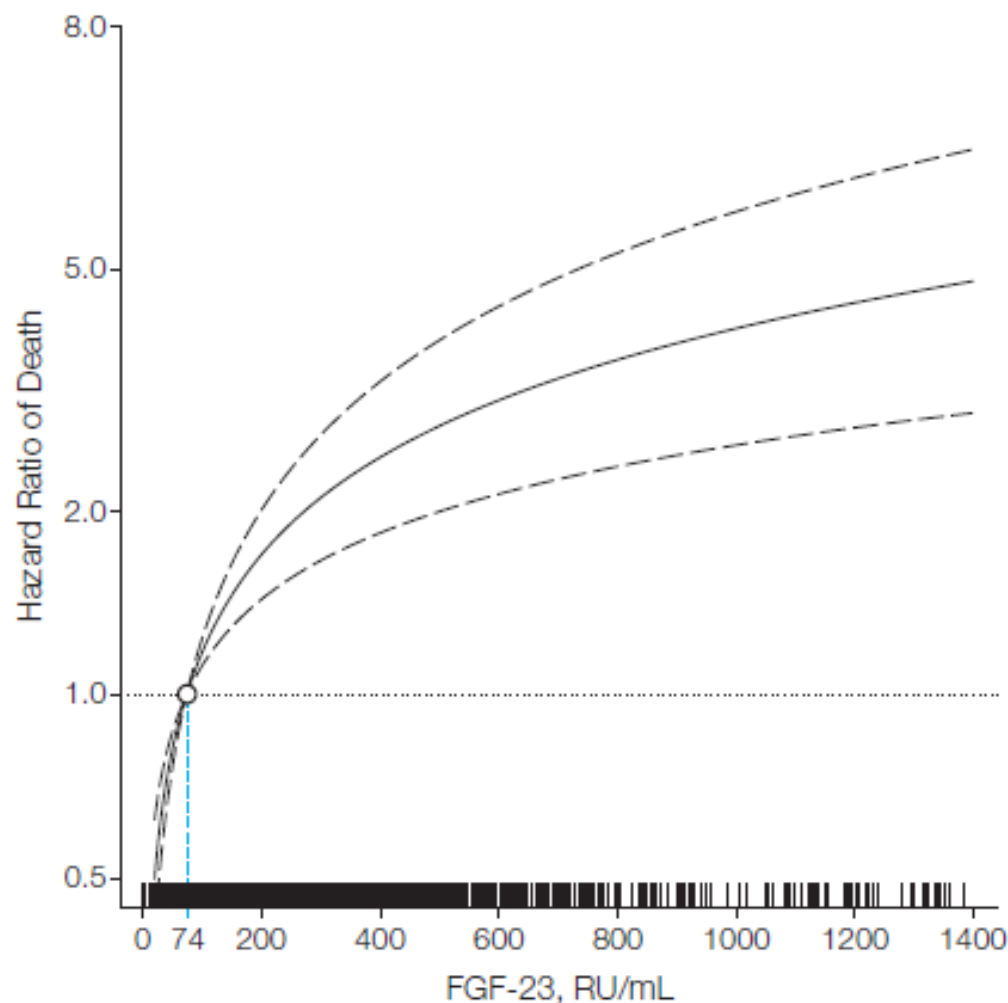
# FGF23, PTH and Phosphate in CKD

Isakova T et al., Kidney Int 2011



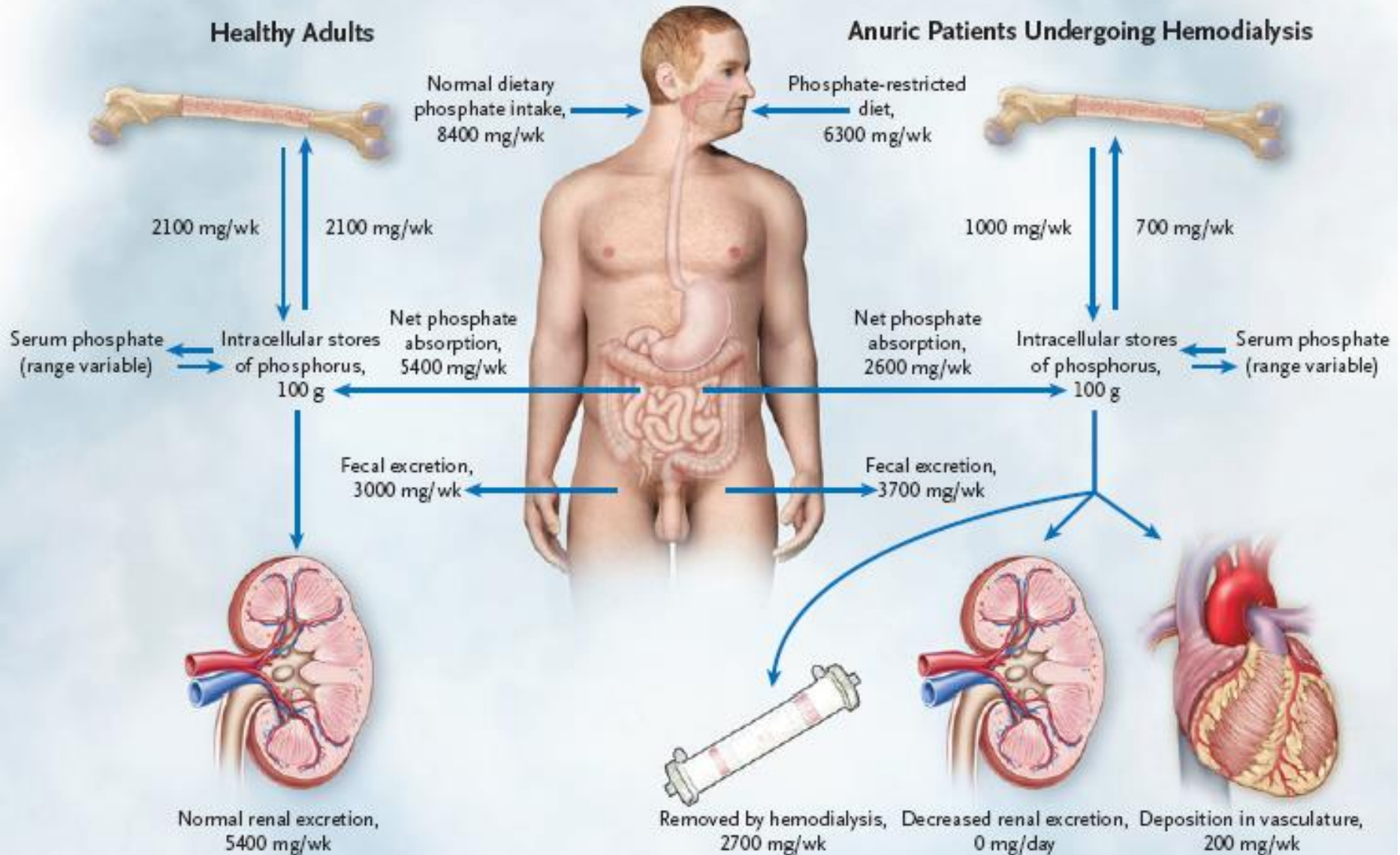
# Fibroblast Growth Factor 23 and Risks of Mortality and End-Stage Renal Disease in Patients With Chronic Kidney Disease

*JAMA. 2011;305(23):2432-2439*



# Phosphate balance in ESRD

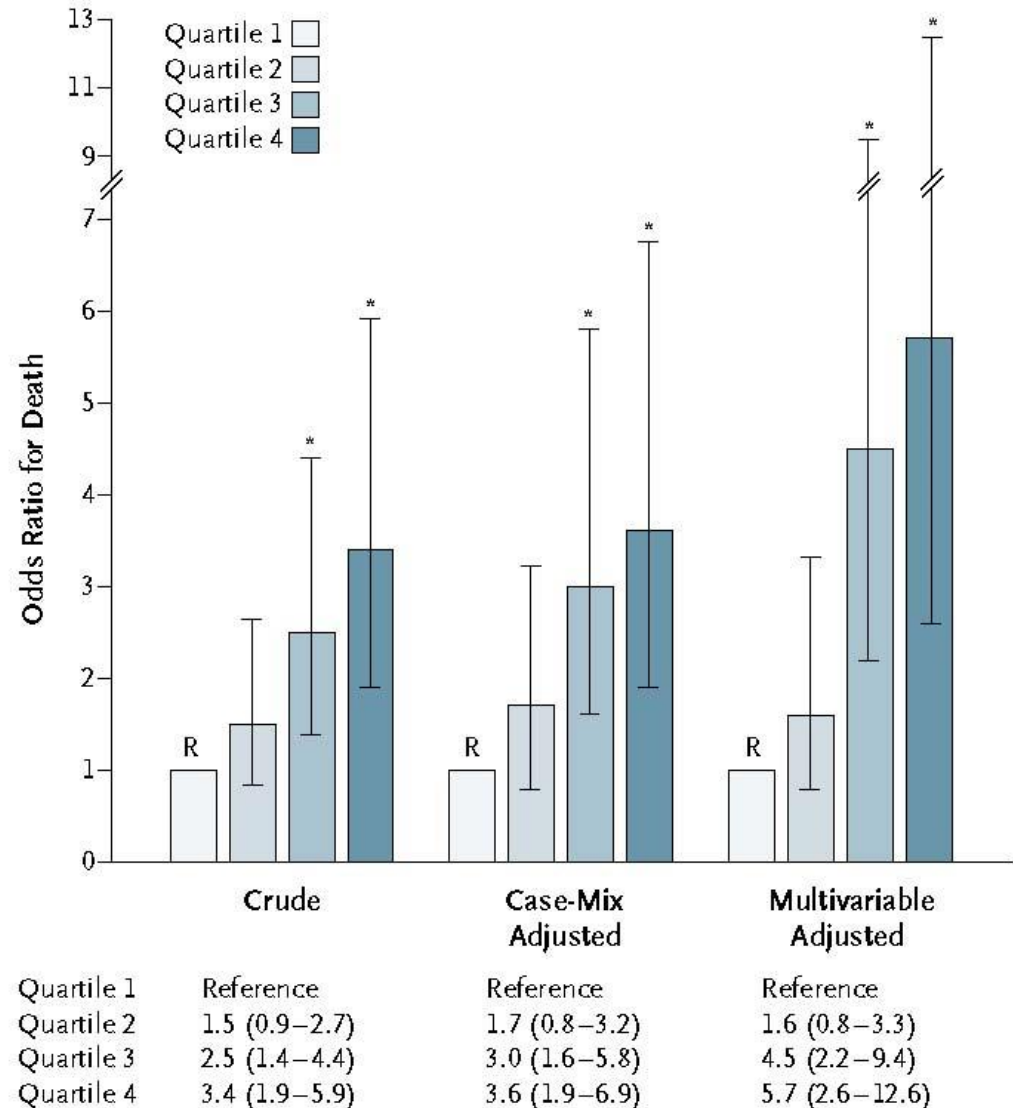
Tonelli M et al., N Eng J Med 2010; 362:1312-24



# FGF23 and mortality in dialysis patients: ArMORR study

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

High **FGF23** levels are risk predictors in incident hemodialysis patients



# FGF23 and mortality in dialysis patients: Prevalent patients in Tassin (F)

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

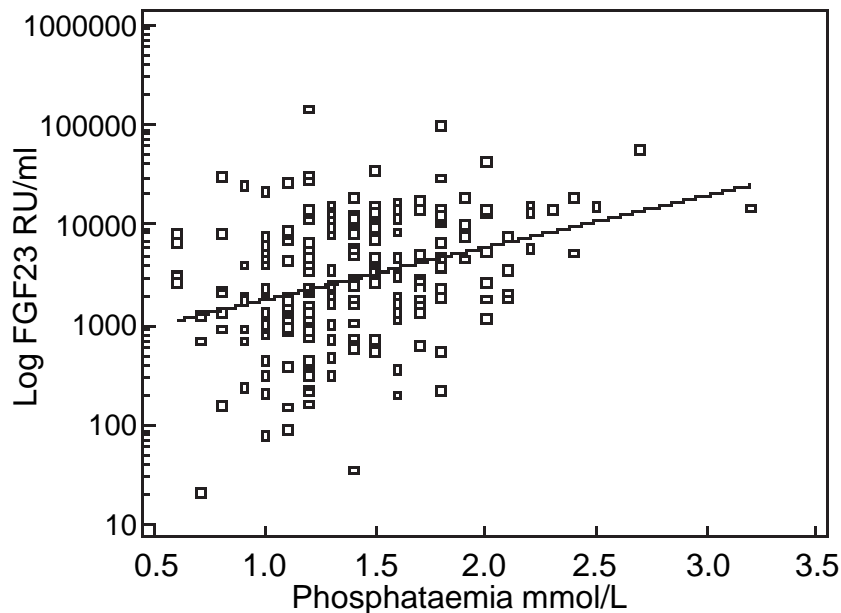
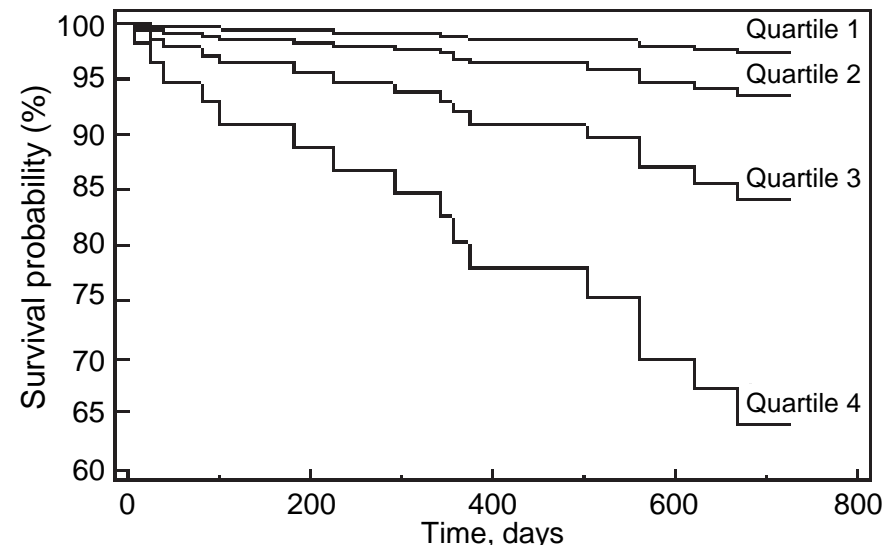


Fig 1. Regression of phosphataemia against log FGF23 ( $r^2 = 0.11$ .  $P < 0.001$ )



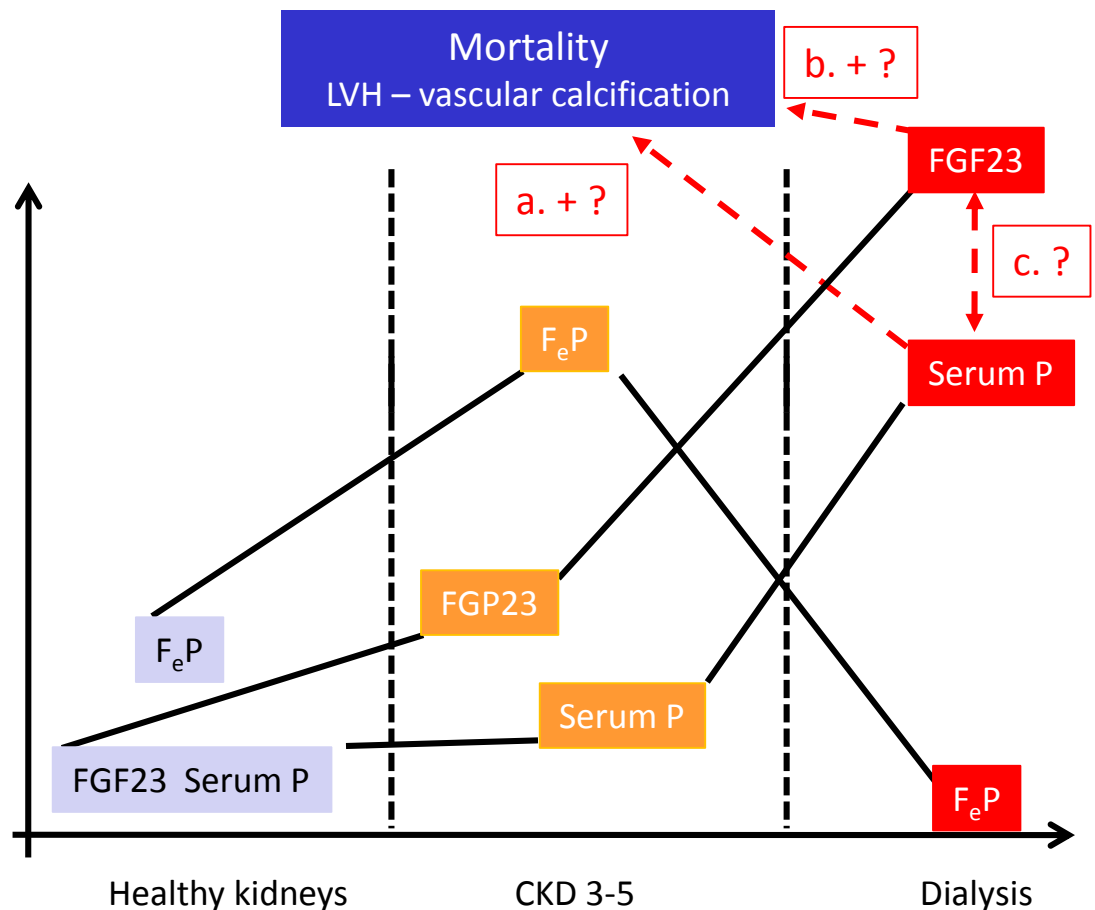
No at risk	219	186	162	137
Quartile 1	54	48	45	41
Quartile 2	55	48	43	39
Quartile 3	55	46	39	32
Quartile 4	55	44	35	25

# FGF23 and mortality in dialysis patients

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

**An invited editorial for Jean G et al. NDT 2009: As nature did not predict dialysis—what we can learn from FGF23 in end-stage renal disease?**

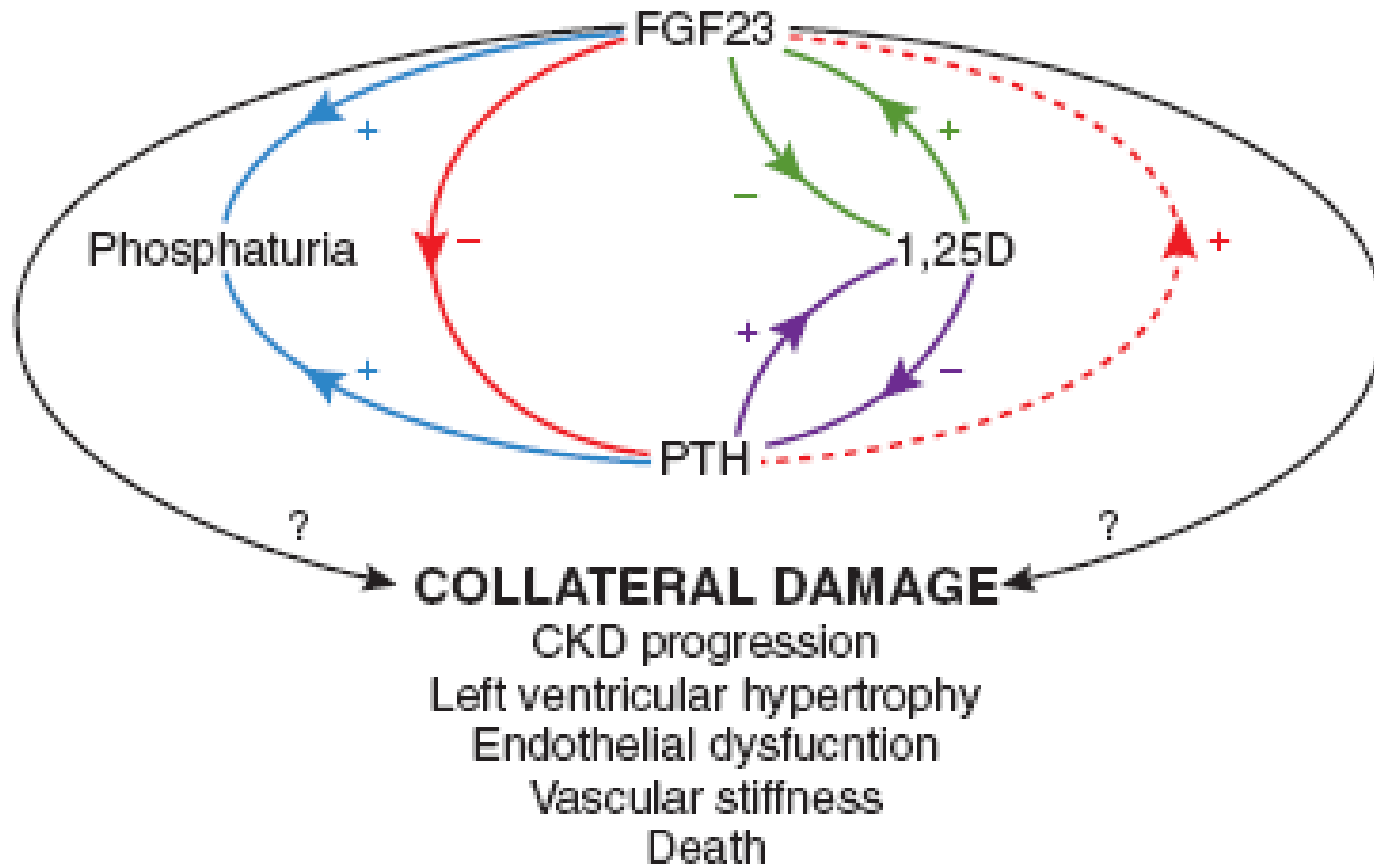
Markus Ketteler and Patrick H. Biggar



# Phosphate balance and FGF23:

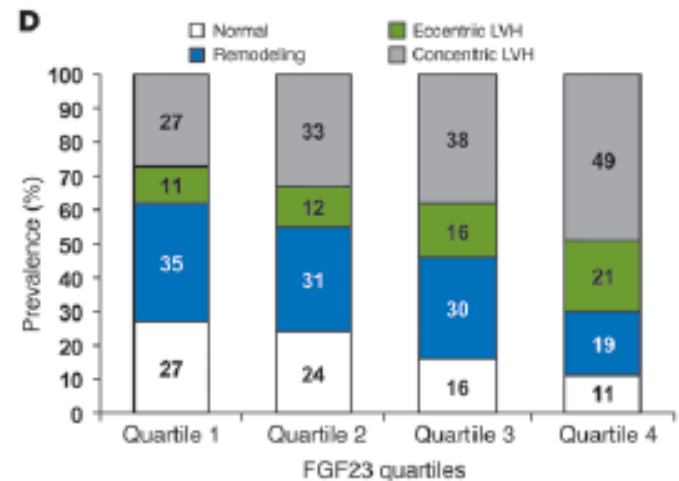
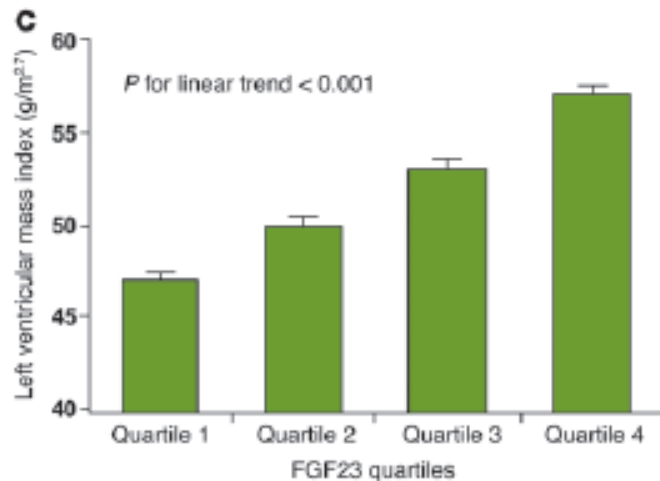
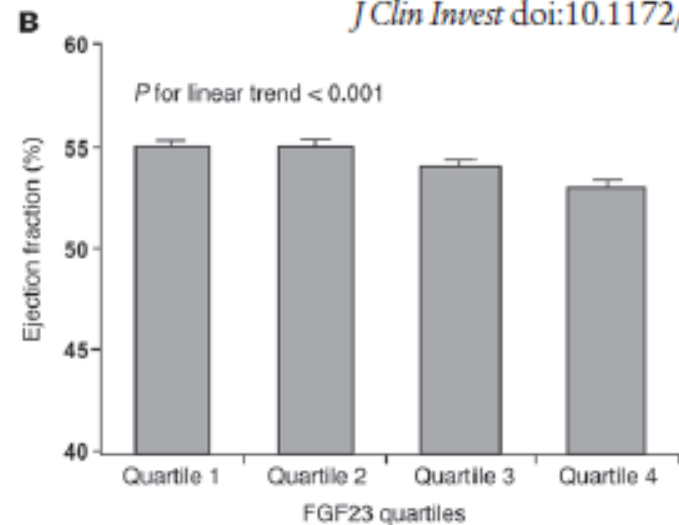
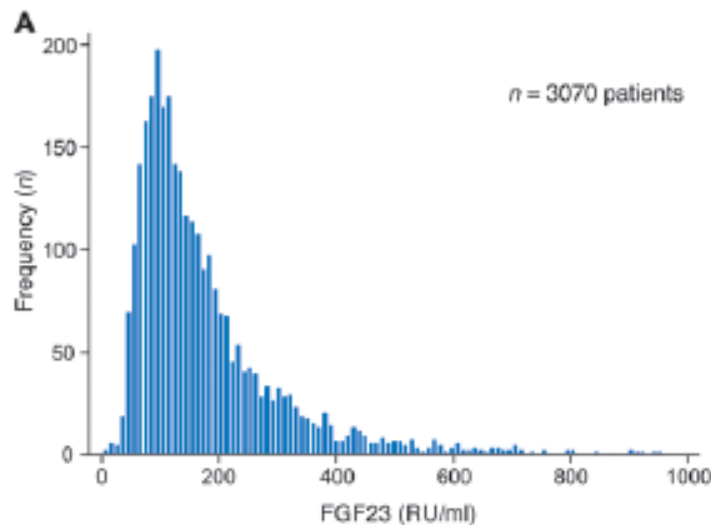
## Surrogate parameter or primary damaging factor?

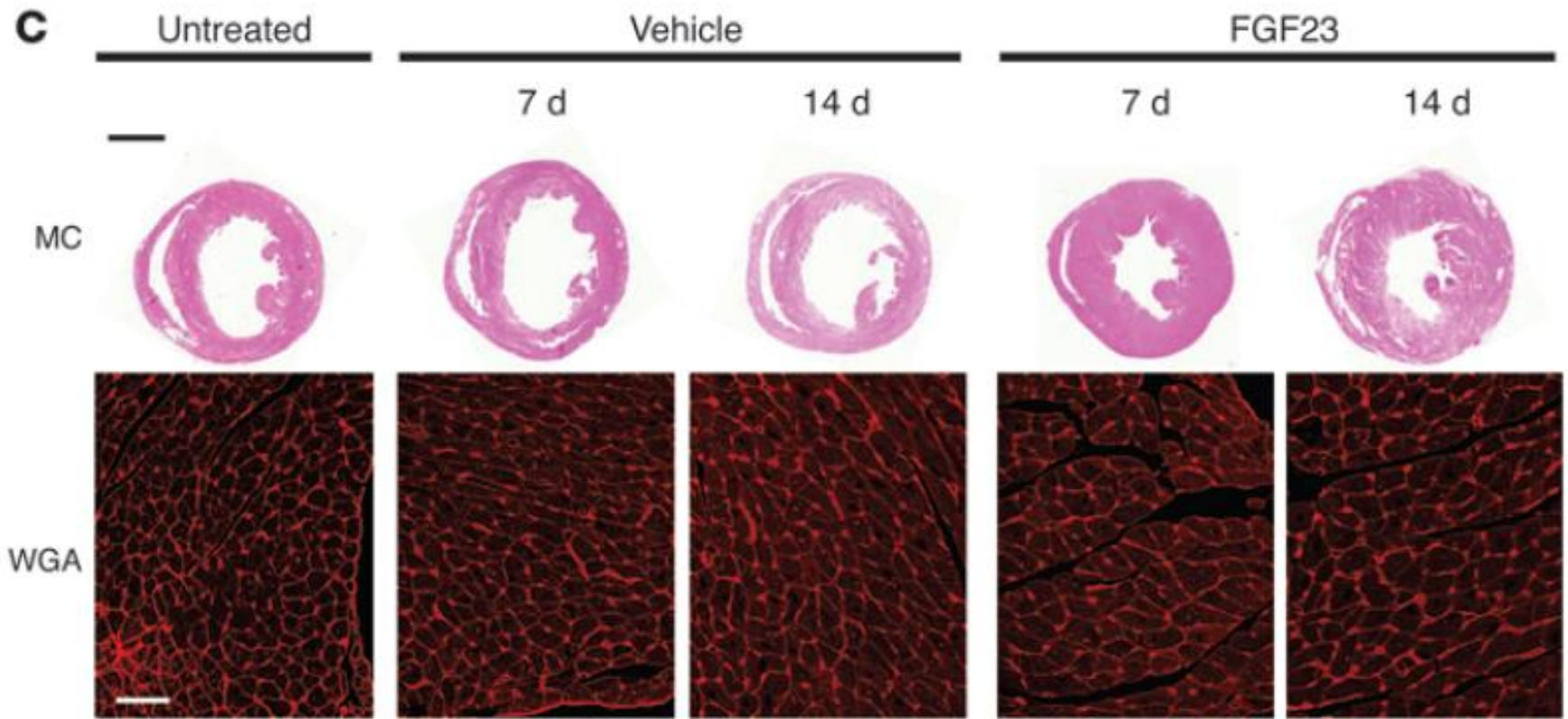
Wolf M. JASN 2010; 21:1427-35



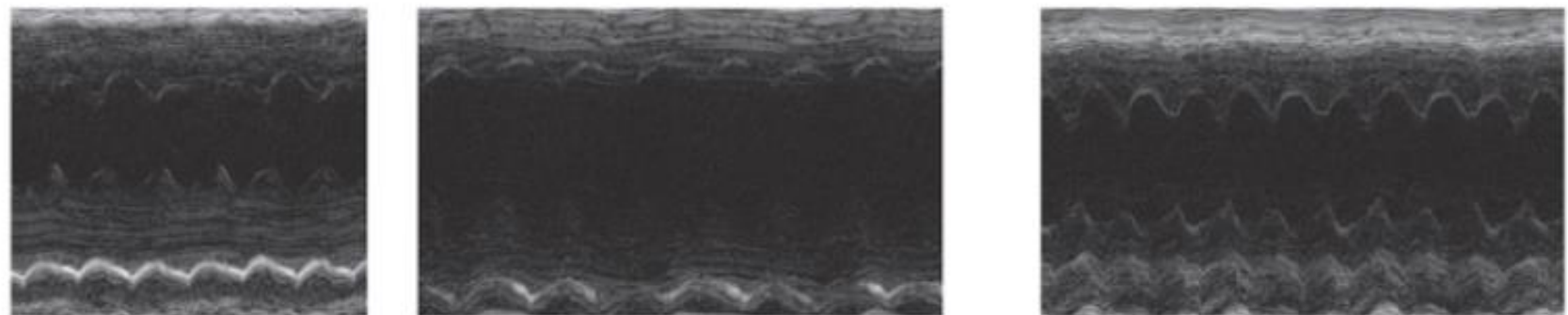
# FGF23 induces left ventricular hypertrophy

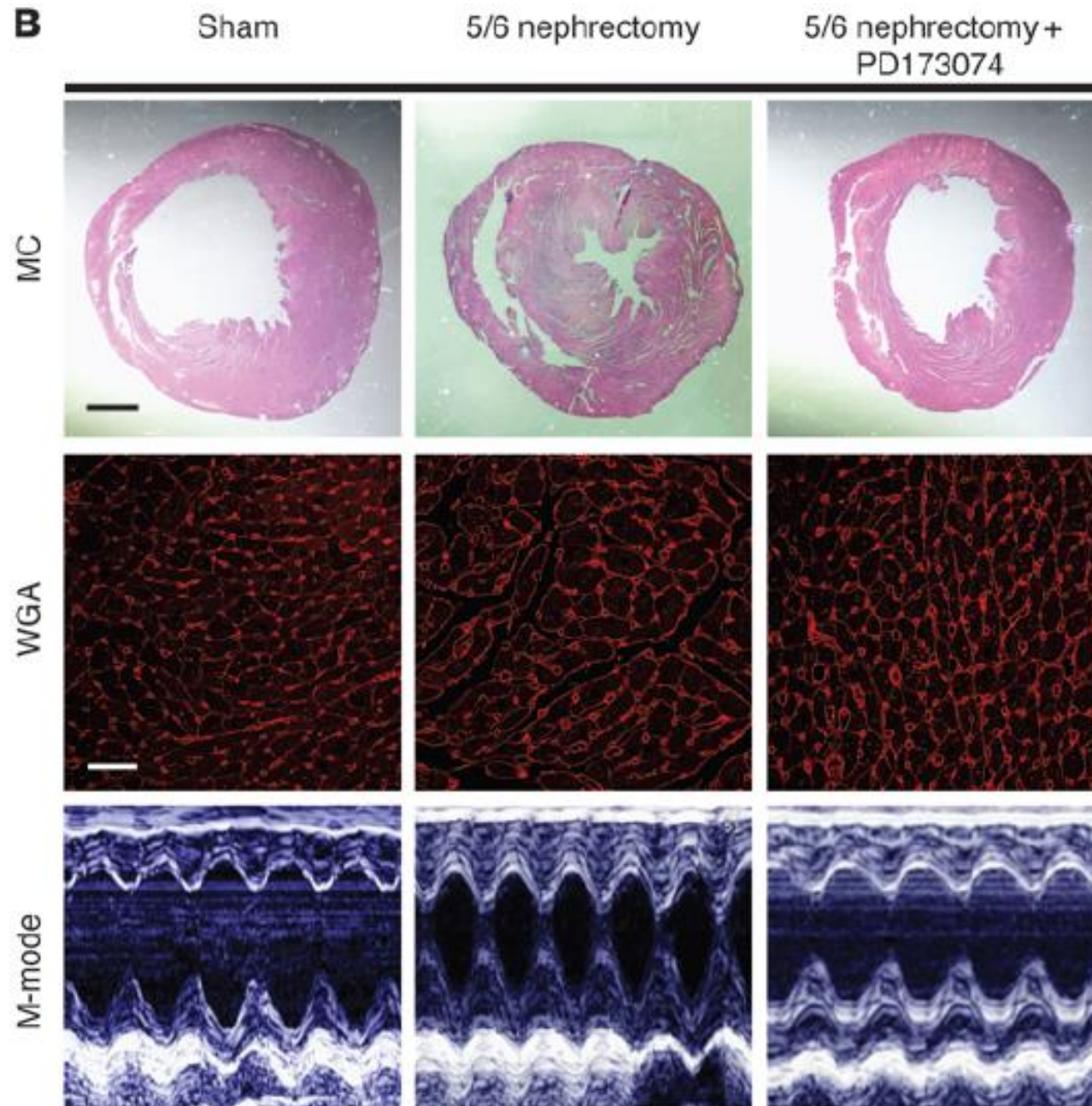
Christian Faul,<sup>1,2</sup> Ansel P. Amaral,<sup>1,2</sup> Behzad Oskoueï,<sup>3</sup> Ming-Chang Hu,<sup>4,5,6</sup> Alexis Sloan,<sup>1,2</sup> Tamara Isakova,<sup>1</sup> Orlando M. Gutiérrez,<sup>7</sup> Robier Aguilon-Prada,<sup>1</sup> Joy Lincoln,<sup>8</sup> Joshua M. Hare,<sup>3</sup> Peter Mundel,<sup>9</sup> Azorides Morales,<sup>10</sup> Julia Scialla,<sup>1</sup> Michael Fischer,<sup>11,12</sup> Elsayed Z. Soliman,<sup>13</sup> Jing Chen,<sup>14</sup> Alan S. Go,<sup>15</sup> Sylvia E. Rosas,<sup>16</sup> Lisa Nessel,<sup>17</sup> Raymond R. Townsend,<sup>16</sup> Harold I. Feldman,<sup>16,17</sup> Martin St. John Sutton,<sup>18</sup> Akinlolu Ojo,<sup>19</sup> Crystal Gadegbeku,<sup>20</sup> Giovana Seno Di Marco,<sup>21</sup> Stefan Reuter,<sup>21</sup> Dominik Kentrup,<sup>21</sup> Klaus Tiemann,<sup>22</sup> Marcus Brand,<sup>21</sup> Joseph A. Hill,<sup>4,23</sup> Orson W. Moe,<sup>4,6,24</sup> Makoto Kuro-o,<sup>6,25</sup> John W. Kusek,<sup>26</sup> Martin G. Keane,<sup>18</sup> and Myles Wolf<sup>1</sup>





M-mode echocardiogram windows at 14 d

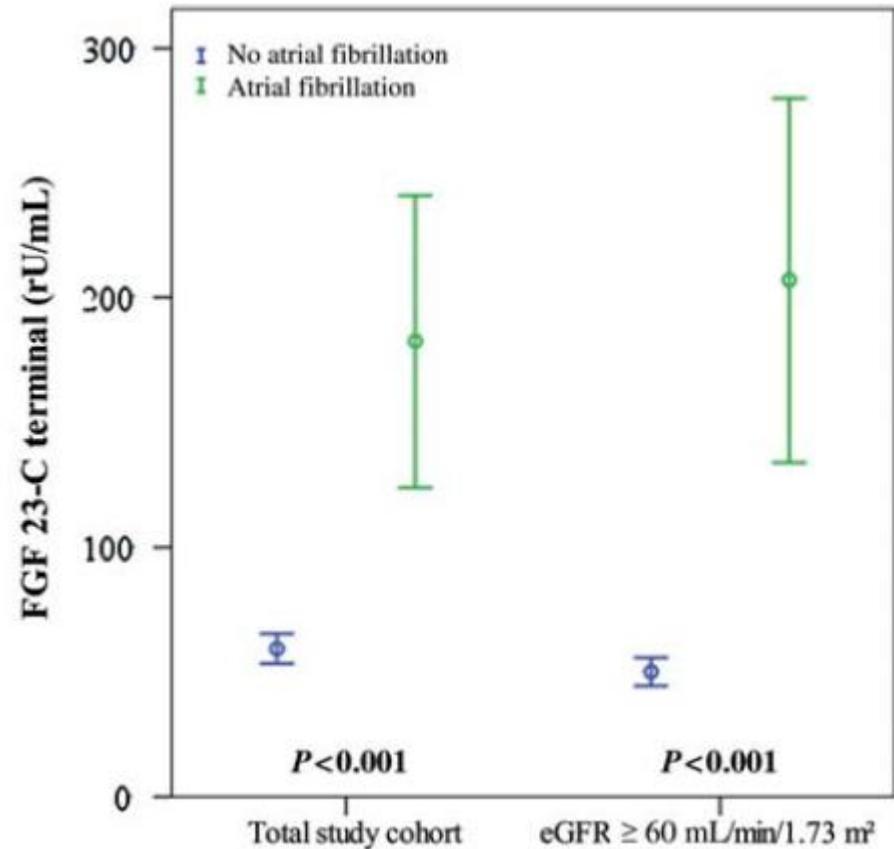
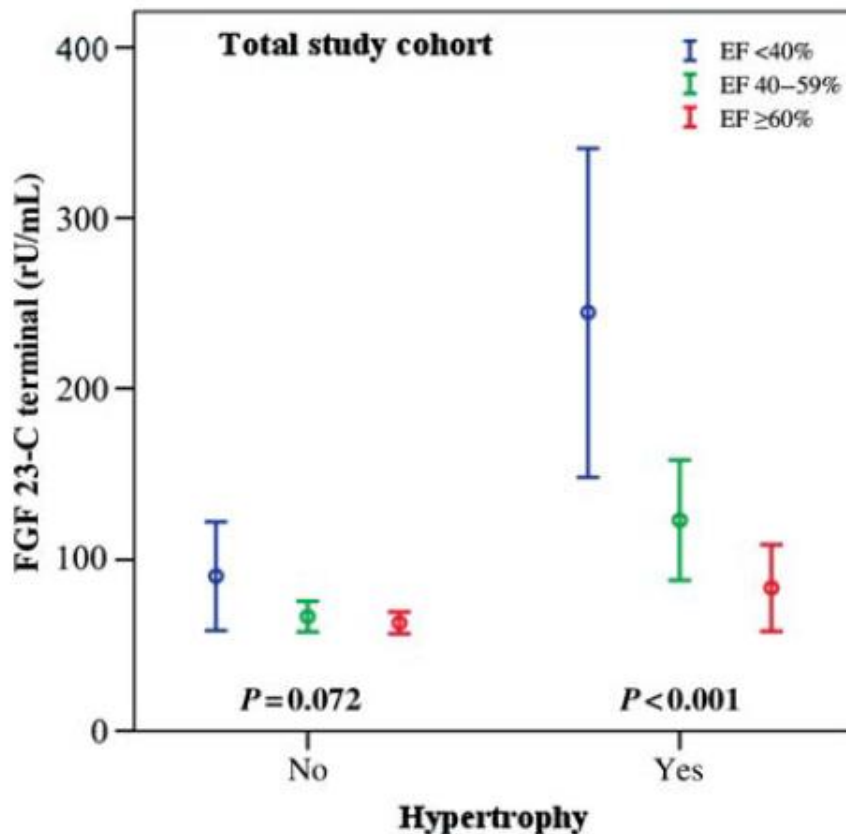




# The phosphatonin fibroblast growth factor 23 links calcium–phosphate metabolism with left-ventricular dysfunction and atrial fibrillation

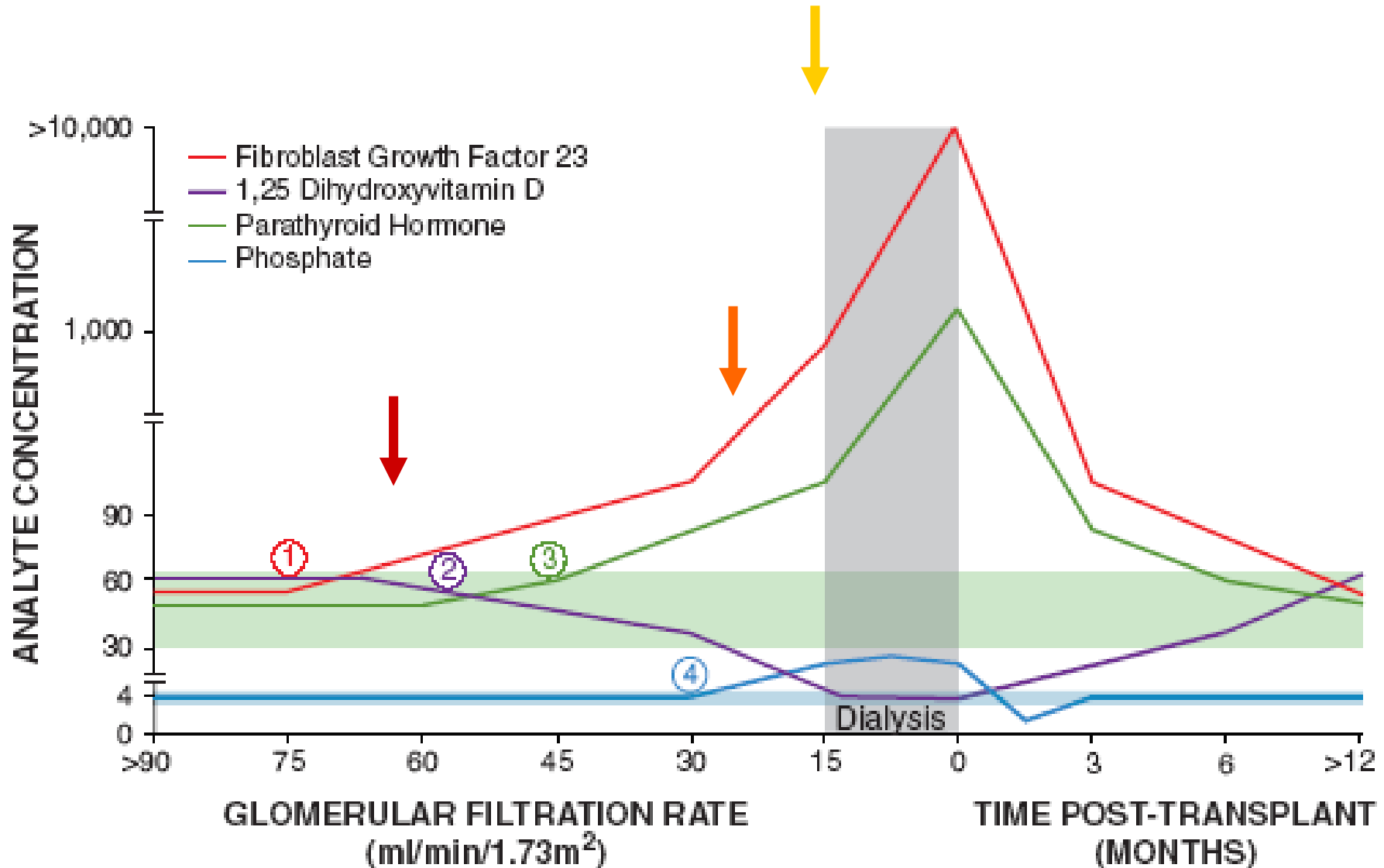
Sarah Seiler<sup>1†</sup>, Bodo Cremers<sup>2†</sup>, Niko M. Rebling<sup>1</sup>, Florian Hornof<sup>1</sup>, Jana Jeken<sup>1</sup>, Sylvie Kersting<sup>1</sup>, Charlotte Steimle<sup>1</sup>, Philipp Ege<sup>1</sup>, Michael Fehrenz<sup>1</sup>, Kyrill S. Rogacev<sup>1</sup>, Bruno Scheller<sup>2</sup>, Michael Böhm<sup>2</sup>, Danilo Fliser<sup>1</sup>, and Gunnar H. Heine<sup>1\*</sup>

European Heart Journal Advance Access published July 6, 2011



# Phosphate balance and FGF23: When and how to treat in CKD-MBD ?

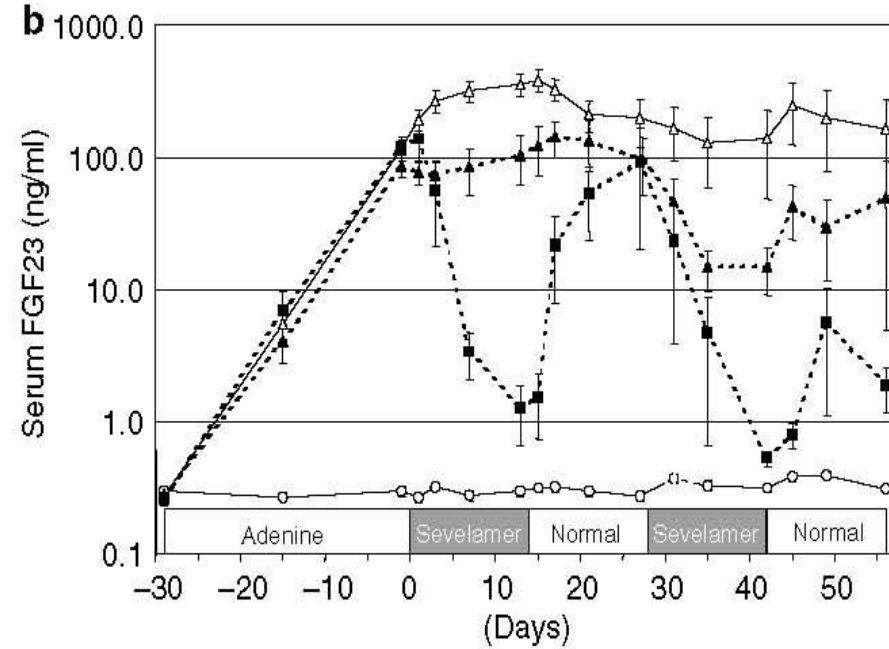
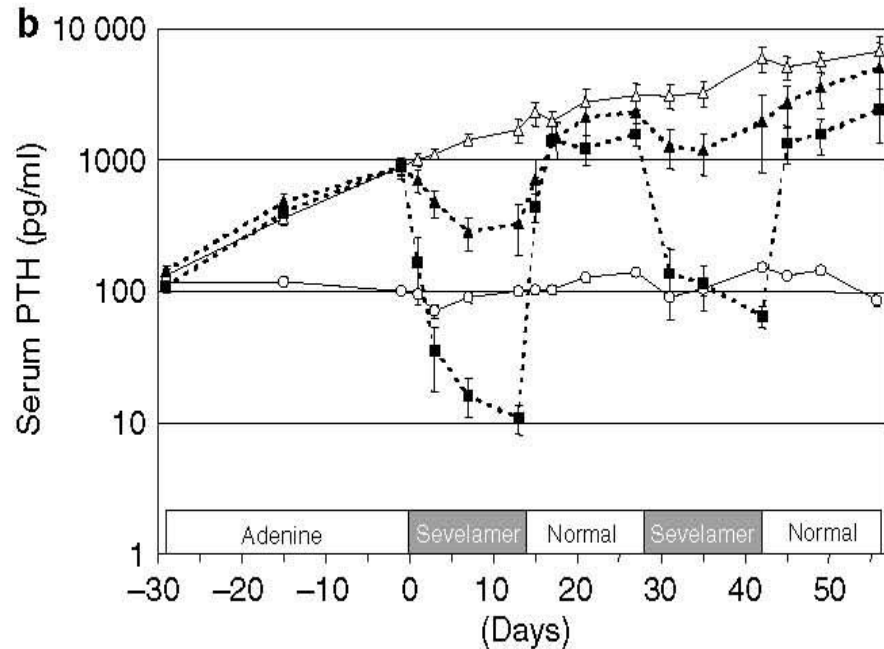
Wolf M. JASN 2010; 21:1427-35



# Sevelamer lowers both PTH- and FGF23 serum levels in uremic rats

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

Normal control Disease control Continuous treatment Continuous treatment Intermittent treatment Intermittent treatment	Normal diet		Normal diet				Normal diet										
	0.75% adenine	0.5% adenine	1% sevelamer		3% sevelamer		Normal diet		Normal diet								
							1% sevelamer		Normal diet								
							3% sevelamer		Normal diet								
							1% sevelamer	Normal diet	1% sevelamer	Normal diet							
							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		



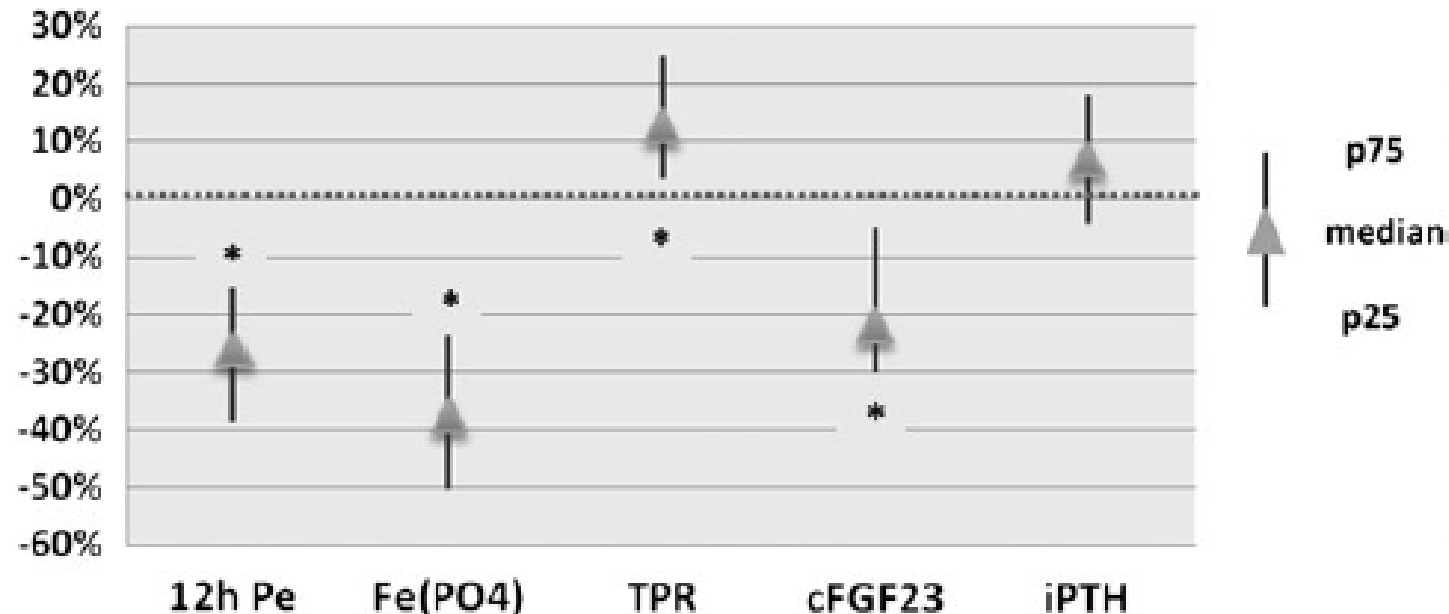
# Phosphate binders lowers FGF23 levels in patients in CKD stage 3

Gonzalez-Parra et al., NDT 2011 [epub]

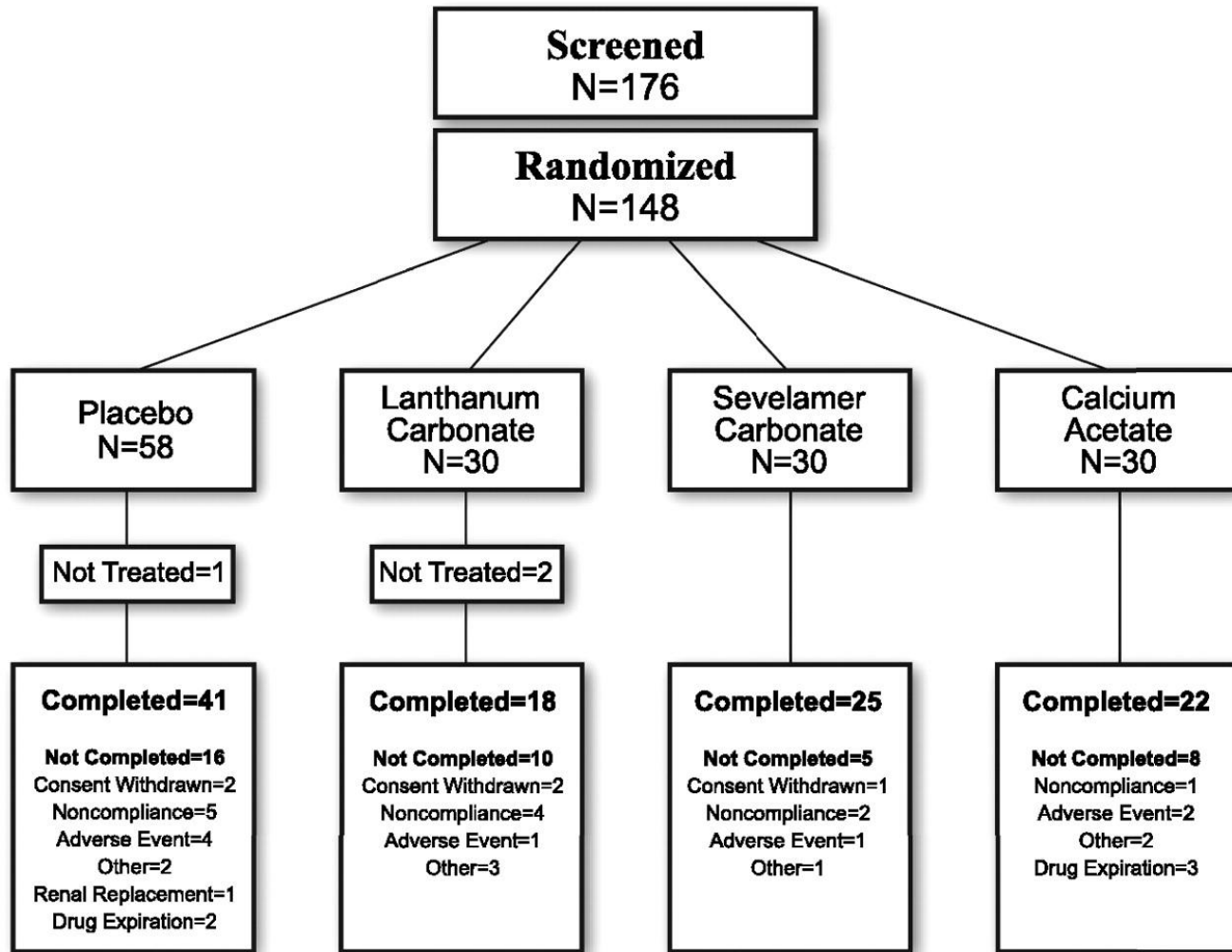
## Lanthanum carbonate reduces FGF23 in chronic kidney disease stage 3 patients

Emilio Gonzalez-Parra<sup>1</sup>, Maria Luisa Gonzalez-Casaus<sup>2</sup>, Antonio Galán<sup>3</sup>, Alberto Martinez-Calero<sup>4</sup>, Victor Navas<sup>5</sup>, Mariano Rodriguez<sup>6</sup> and Alberto Ortiz<sup>1</sup>

### Change from baseline after Lanthanum treatment

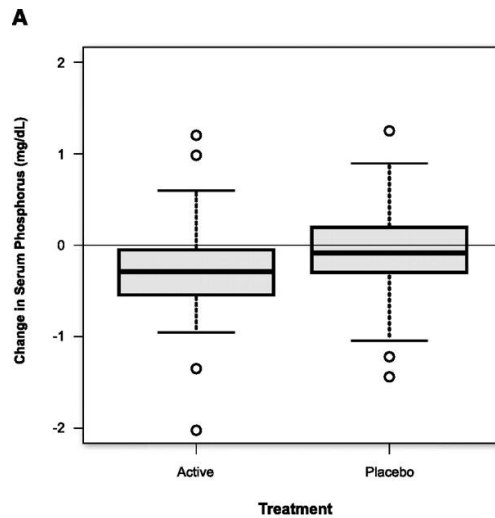


# Early phosphate lowering, FGF23, and calcification

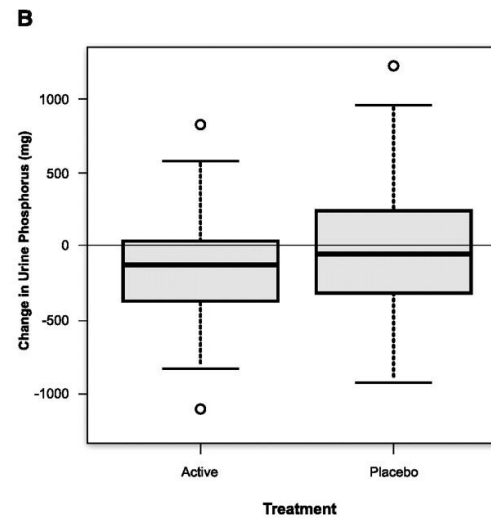


# Early phosphate lowering, FGF23, and calcification

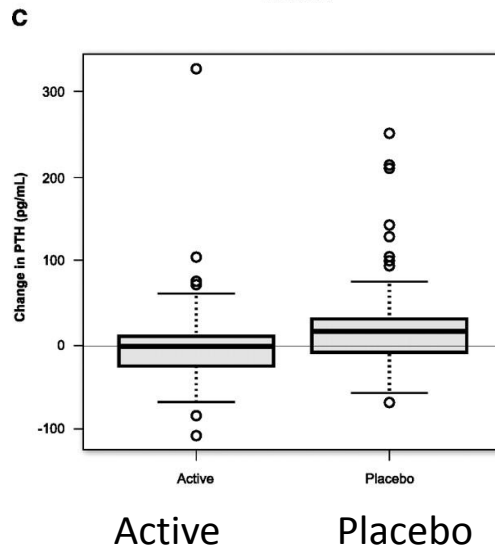
Serum P



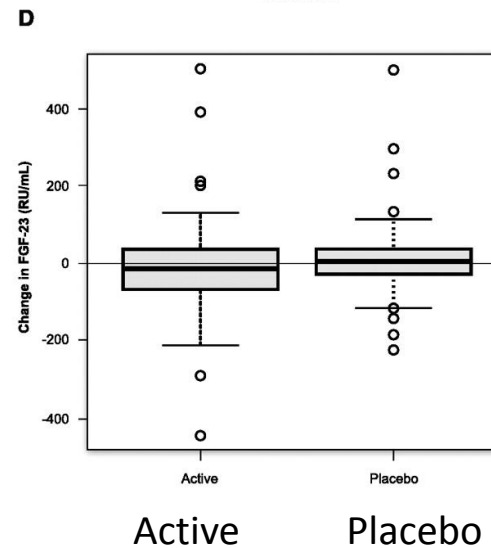
Urinary P



iPTH

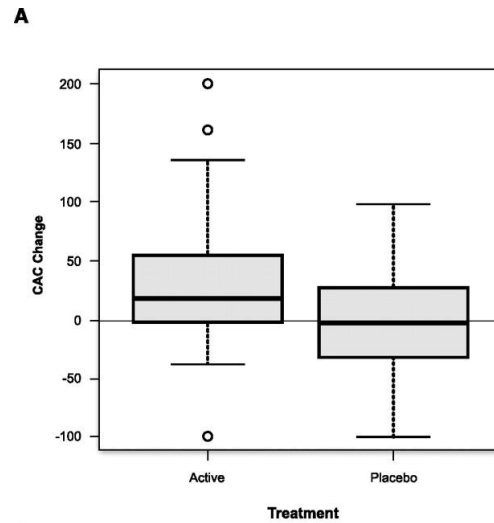


FGF23

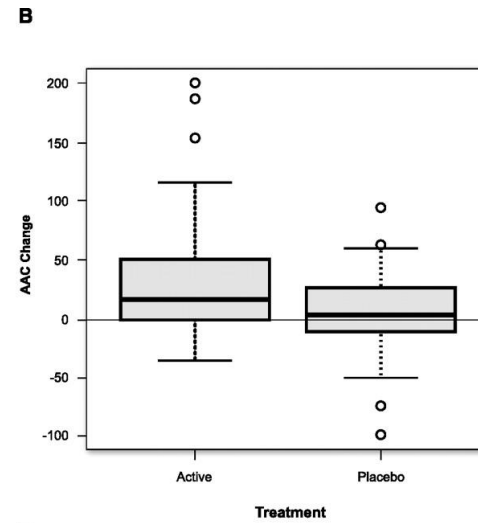


# Early phosphate lowering, FGF23, and calcification

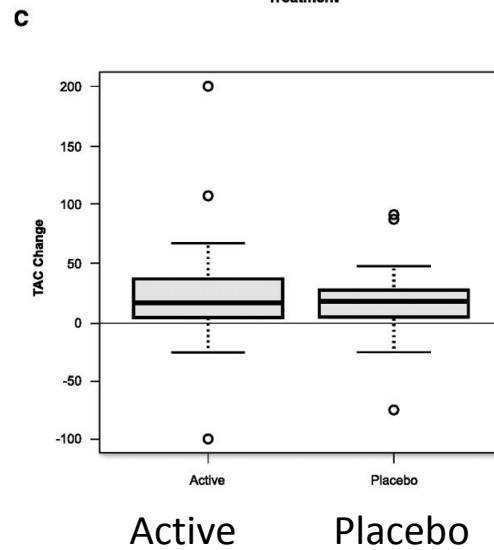
CAC change



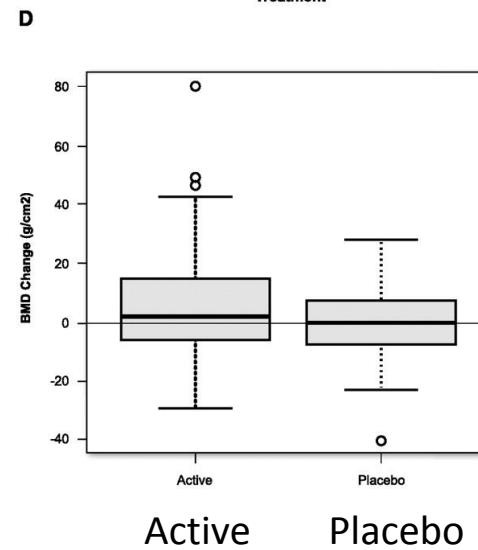
AAC change



TAC change

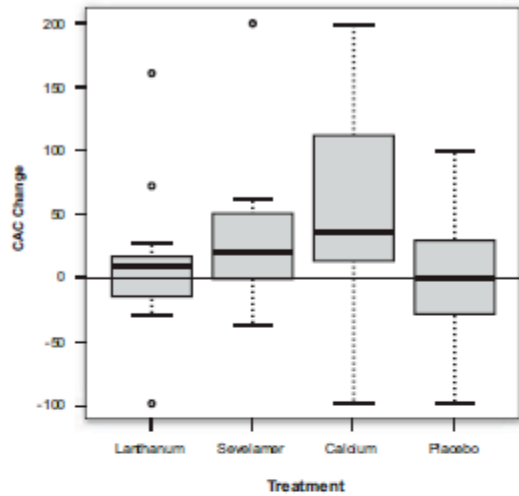


BMD change

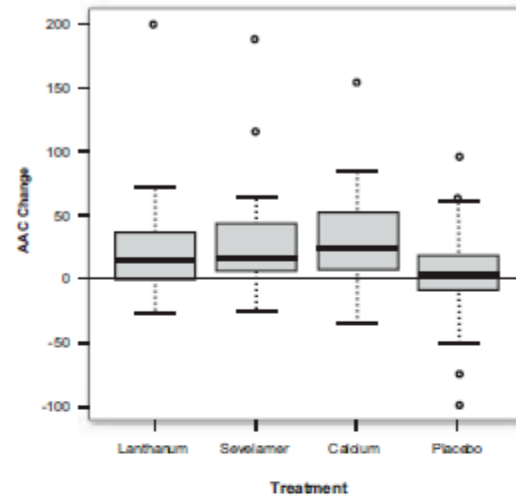


# Early phosphate lowering, FGF23, and calcification

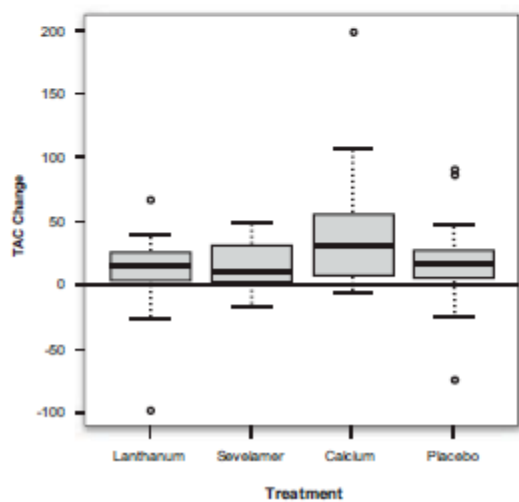
**A** Change in Coronary Artery Calcium Volume



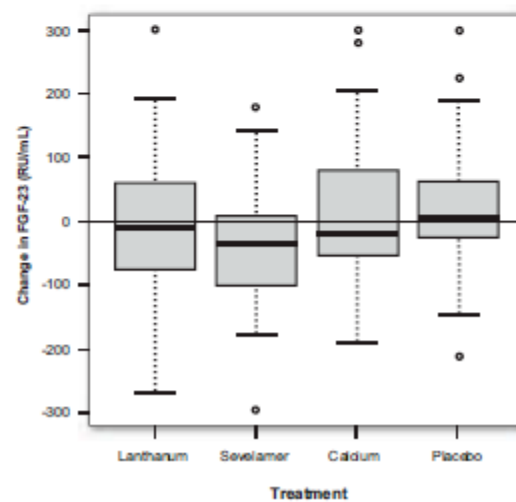
**B** Change in Abdominal Aorta Calcium Volume



**C** Change in Thoracic Aorta Calcium Volume



**D** Change in C-Terminal FGF-23

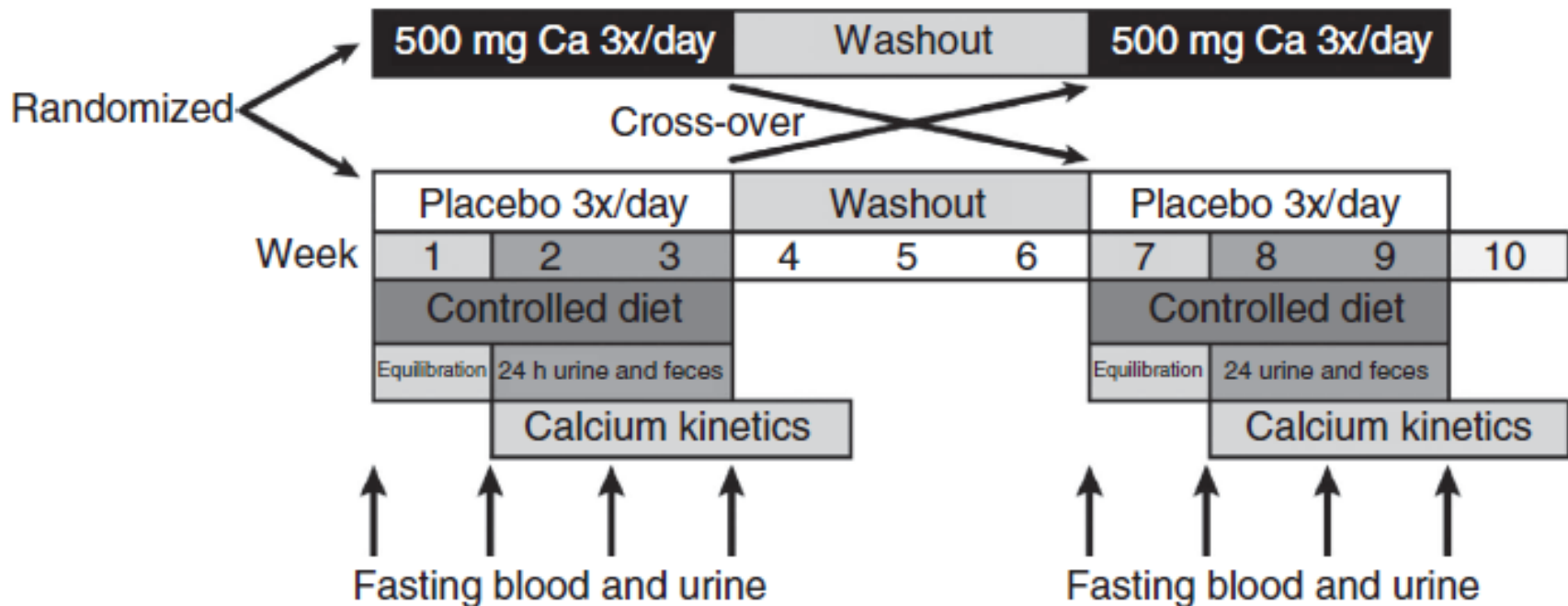


# Calcium balance in CKD stages 3b/4

Hill et al., *Kidney Int* 2013 [epub]

## Oral calcium carbonate affects calcium but not phosphorus balance in stage 3–4 chronic kidney disease

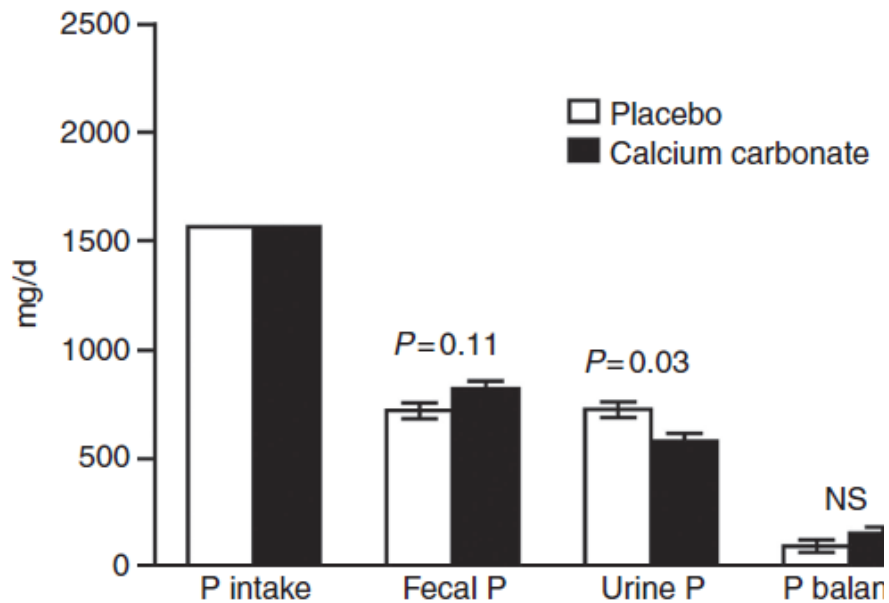
Kathleen M. Hill<sup>1</sup>, Berdine R. Martin<sup>2</sup>, Meryl E. Wastney<sup>2</sup>, George P. McCabe<sup>3</sup>, Sharon M. Moe<sup>4</sup>,  
Connie M. Weaver<sup>2</sup> and Munro Peacock<sup>1</sup>



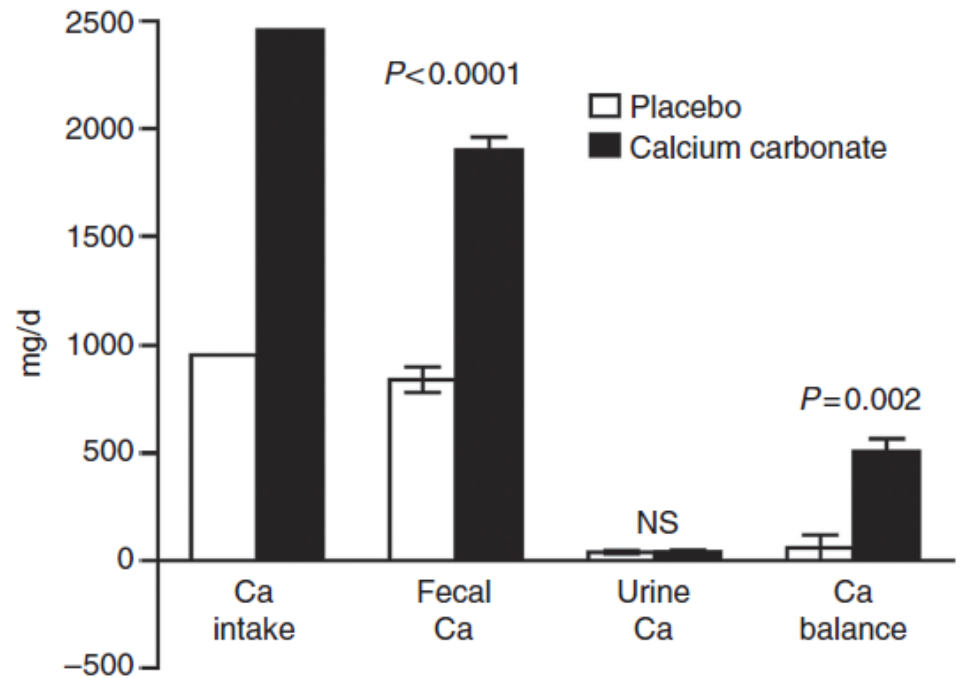
# Calcium balance in CKD stages 3b/4

Hill et al., Kidney Int 2013 [epub]

## Phosphate balance:



## Calcium balance:



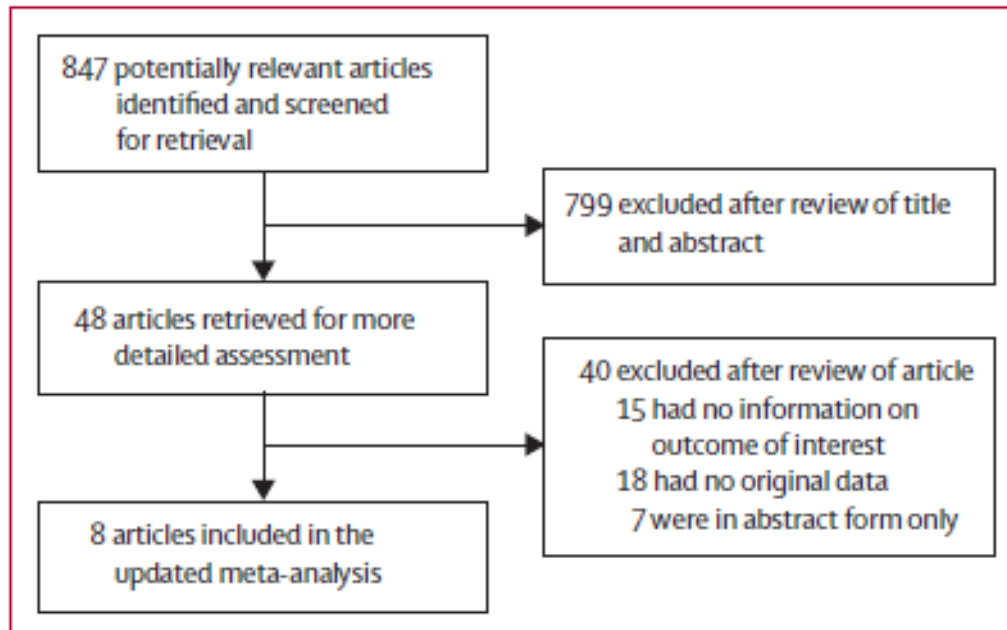
# Phosphate binders and mortality: Calcium-containing vs. Calcium-free

Jamal S et al., Lancet 2013; in press



## Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis

*Sophie A Jamal, Ben Vandermeer, Paolo Raggi, David C Mendelssohn, Trish Chatterley, Marlene Dorgan, Charmaine E Lok, David Fitchett, Ross T Tsuyuki*



# Phosphate binders and mortality: Calcium-containing vs. Calcium-free

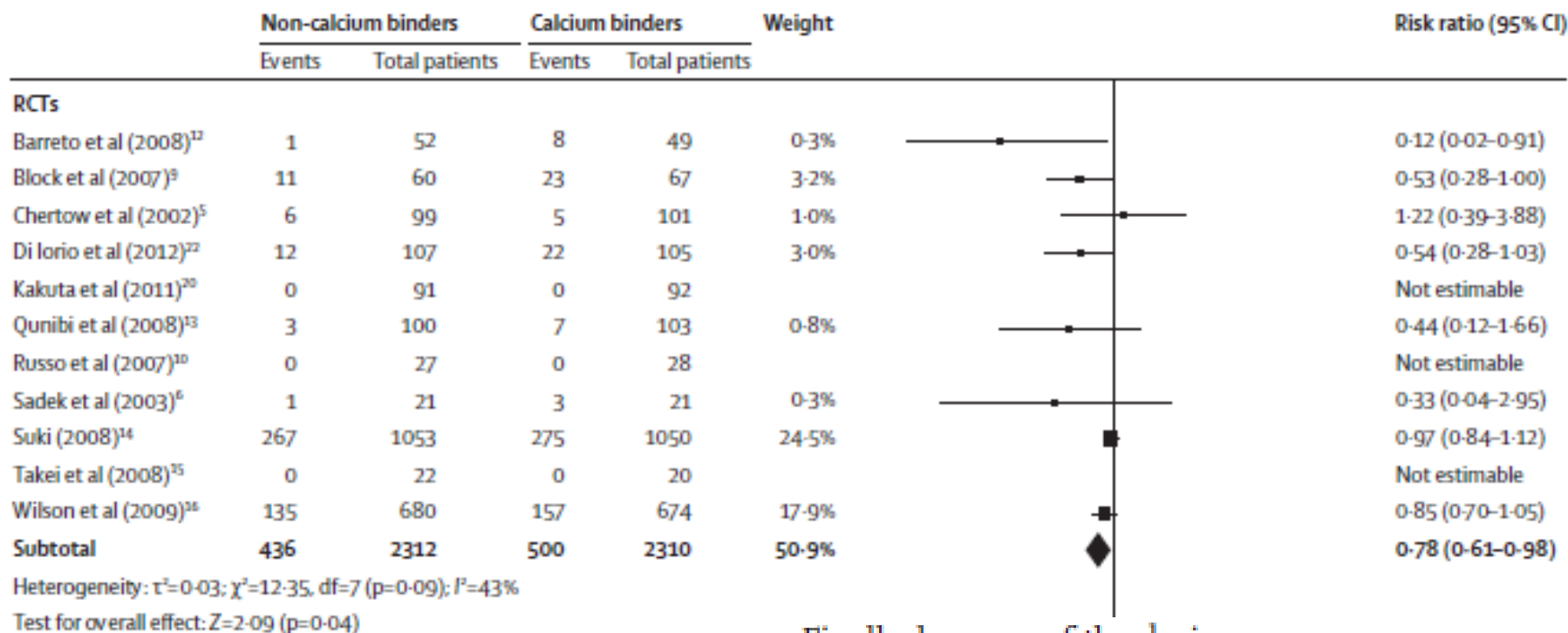
Jamal S et al., Lancet 2013; in press



Original studies										
Chertow et al (2002) <sup>5</sup>	RCT	Haemodialysis	57	35%	32.5%	39.0	Sevelamer (99)	Calcium acetate or calcium carbonate (101)	12	Unclear
Sadek et al (2003) <sup>6</sup>	RCT	Haemodialysis	--	--	--	--	Sevelamer (15)	Calcium carbonate (16)	5	Unclear
Braun et al (2004) <sup>7</sup>	RCT	Haemodialysis	56.5	37.5%	18.8%	63.4	Sevelamer (56)	Calcium carbonate (57)	12	High
Block et al (2005 <sup>8</sup> and 2007 <sup>9</sup> )	RCT	Haemodialysis	58	37%	60.6%	2.9	Sevelamer (54)	Calcium acetate or calcium carbonate (55)	18, 44*	Low
Russo et al (2007) <sup>30</sup>	RCT	Non-dialysis	55	17%	--	--	Sevelamer (27)	Calcium carbonate (28)	24	High
Borzecki et al (2007) <sup>11</sup>	RCS	Haemodialysis	61.5	2.5%	48.6%	--	Sevelamer (608)	Calcium acetate or calcium carbonate (769)	24	NA
Barreto et al (2008) <sup>12</sup>	RCT	Haemodialysis	47	32%	14.1%	--	Sevelamer (52)	Calcium acetate (49)	12	Low
Qunibi et al (2008) <sup>13</sup>	RCT	Haemodialysis	59	49%	57.1%	22.2	Sevelamer (100)	Calcium acetate (103)	12	Low
Suki (2008) <sup>14</sup>	RCT	Haemodialysis	60	46%	50.2%	38.2	Sevelamer (1053)	Calcium acetate or calcium carbonate (1050)	20	High
Takei et al (2008) <sup>15</sup>	RCT	Haemodialysis	54	52%	35.7%	--	Sevelamer (22)	Calcium carbonate (20)	24	High
New studies										
Wilson et al (2009) <sup>16</sup>	RCT	Haemodialysis	54.3	0.7%	34.5%	40.2	Lanthanum (680)	Calcium acetate or calcium carbonate (674)	24	High
Panichi et al (2010) <sup>7</sup>	OS	Haemodialysis	66	36%	22.6%	--	Sevelamer (242)	Calcium acetate or calcium carbonate (310)	24	NA
Shantouf et al (2010) <sup>18</sup>	CS	Haemodialysis	54.6	33.3%	45.8%	--	Sevelamer (57)	Calcium carbonate or Calcium acetate (60)	NA	NA
Jean et al (2011) <sup>19</sup>	OS	Haemodialysis	68.0	43%	33.6%	62.6	Sevelamer (247)	Calcium carbonate (432)	42	NA
Kakuta et al (2011) <sup>20</sup>	RCT	Haemodialysis	58.0	46%	20.8%	118	Sevelamer (91)	Calcium carbonate (92)	12	Unclear
Toussaint et al (2011) <sup>21</sup>	RCT	Haemodialysis	57.4	35.6%	37.8%	--	Lanthanum (22)	Calcium carbonate (23)	18	High
Di Iorio et al (2012) <sup>22</sup>	RCT	Non-dialysis	57.9	39%	28%	--	Sevelamer (107)	Calcium carbonate (105)	36	Low
Block et al (2012) <sup>23</sup>	RCT	Non-dialysis	66.8	50.3%	57%	--	Lanthanum (28); sevelamer (30)	Calcium acetate (30)	9	Low

# Phosphate binders and mortality: Calcium-containing vs. Calcium-free

Jamal S et al., Lancet 2013; in press



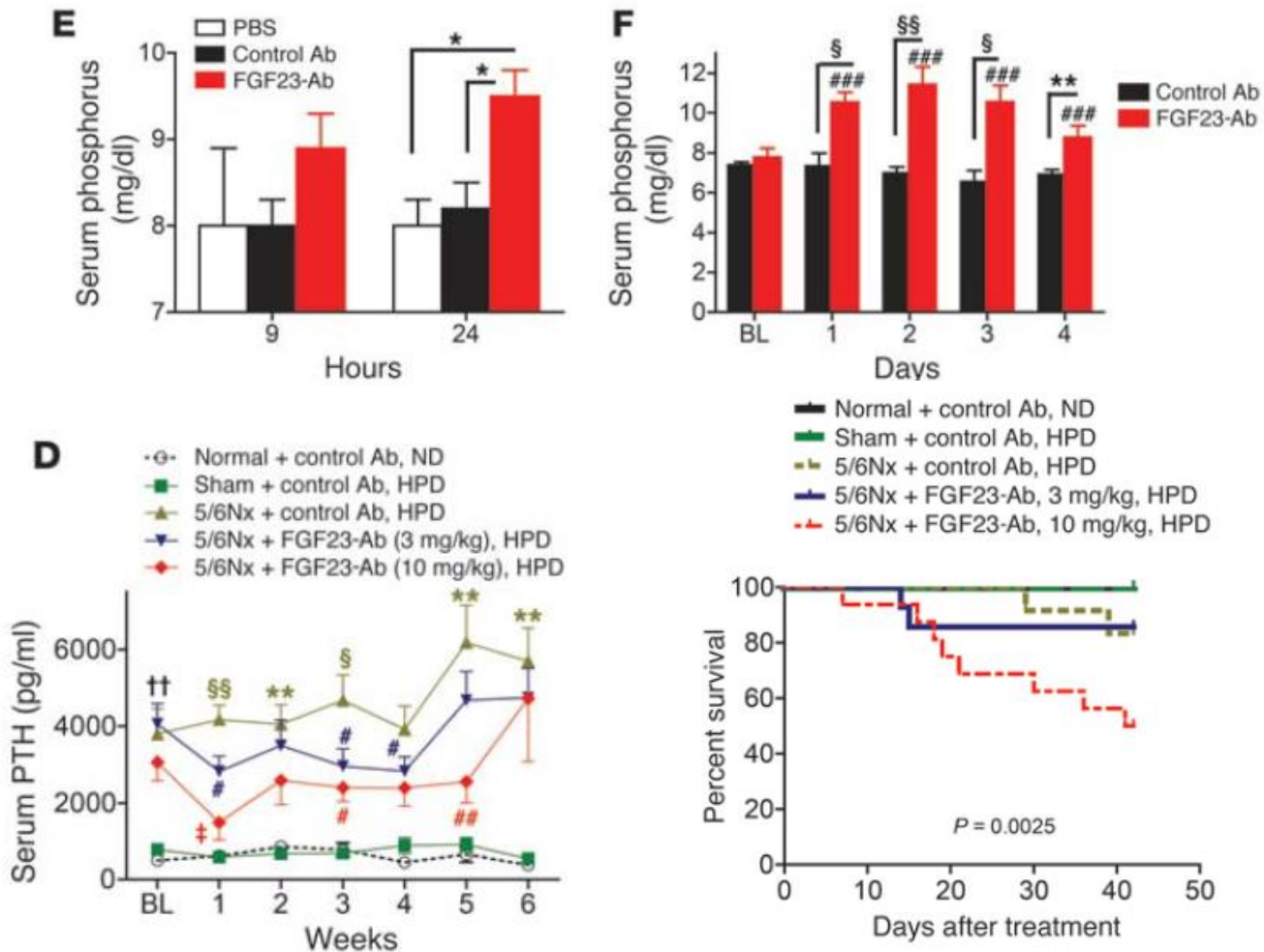
Finally, because of the design of the studies included in this review, we cannot establish whether non-calcium-based phosphate binders are inherently beneficial, or if calcium-based binders are harmful, or a bit of both.

**Interpretation** Non-calcium-based phosphate binders are associated with a decreased risk of all-cause mortality compared with calcium-based phosphate binders in patients with chronic kidney disease. Further studies are needed to identify causes of mortality and to assess whether mortality differs by type of non-calcium-based phosphate binder.

# FGF23 neutralization improves chronic kidney disease–associated hyperparathyroidism yet increases mortality

Victoria Shalhoub,<sup>1</sup> Edward M. Shatzken,<sup>1</sup> Sabrina C. Ward,<sup>1</sup> James Davis,<sup>1</sup> Jennitte Stevens,<sup>2</sup> Vivian Bi,<sup>2</sup> Lisa Renshaw,<sup>2</sup> Nessa Hawkins,<sup>2</sup> Wei Wang,<sup>2</sup> Ching Chen,<sup>2</sup> Mei-Mei Tsai,<sup>2</sup> Russell C. Cattley,<sup>3</sup> Thomas J. Wronski,<sup>4</sup> Xuechen Xia,<sup>4</sup> Xiaodong Li,<sup>1</sup> Charles Henley,<sup>1</sup> Michael Eschenberg,<sup>5</sup> and William G. Richards<sup>1</sup>

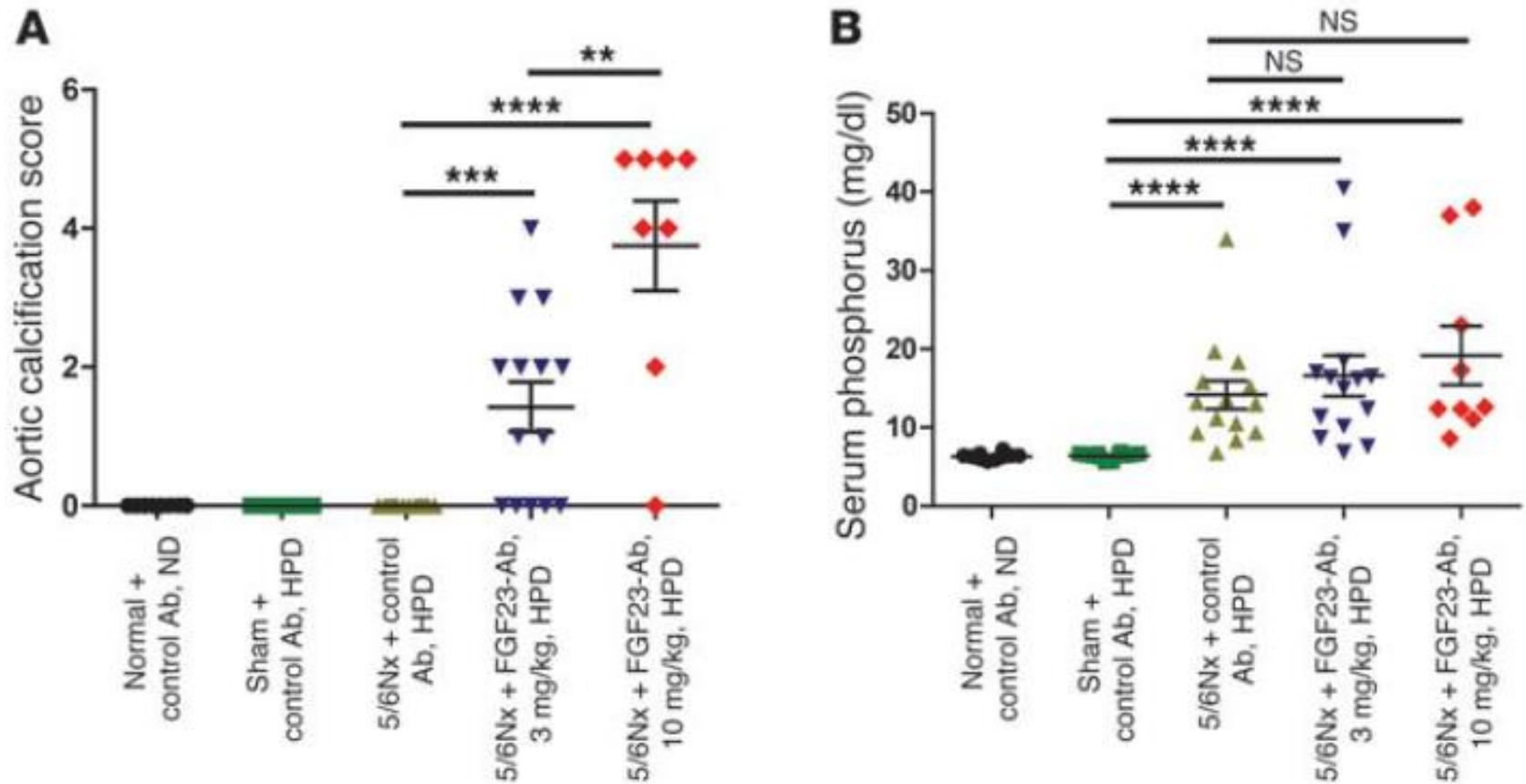
*J Clin Invest.* 2012;122(7):2543–2553. doi:10.1172/JCI61405.



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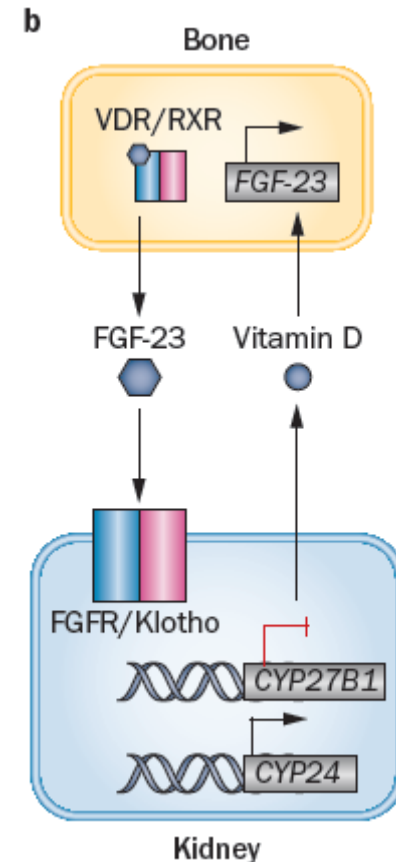
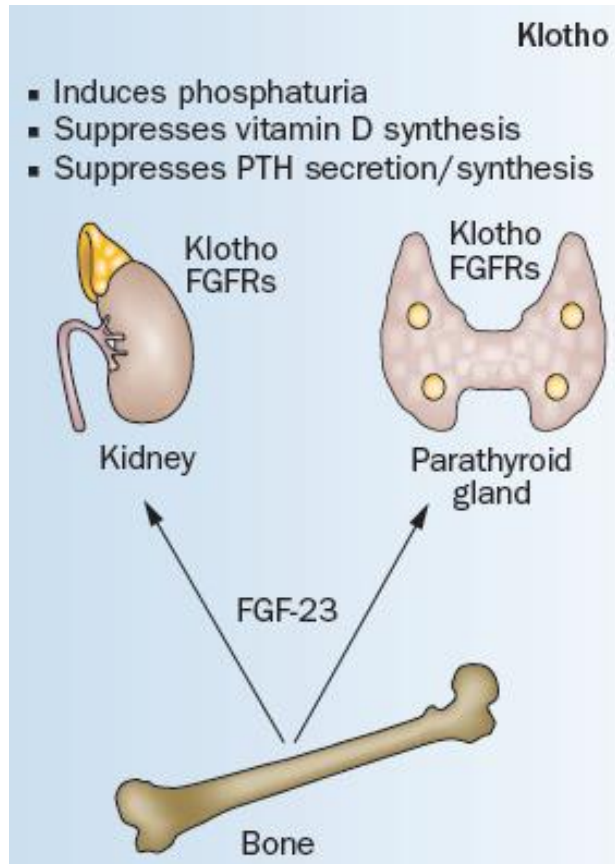
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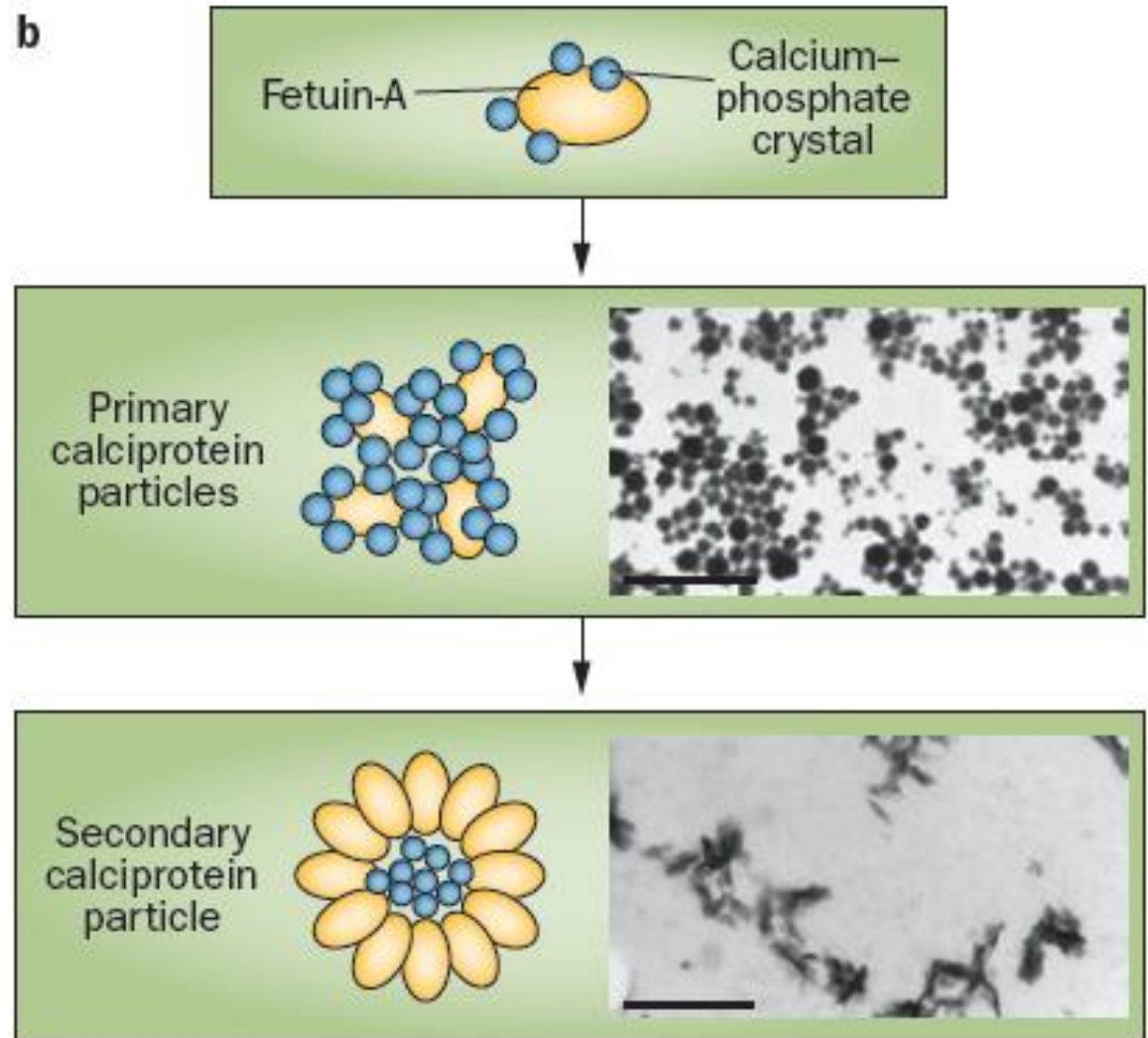
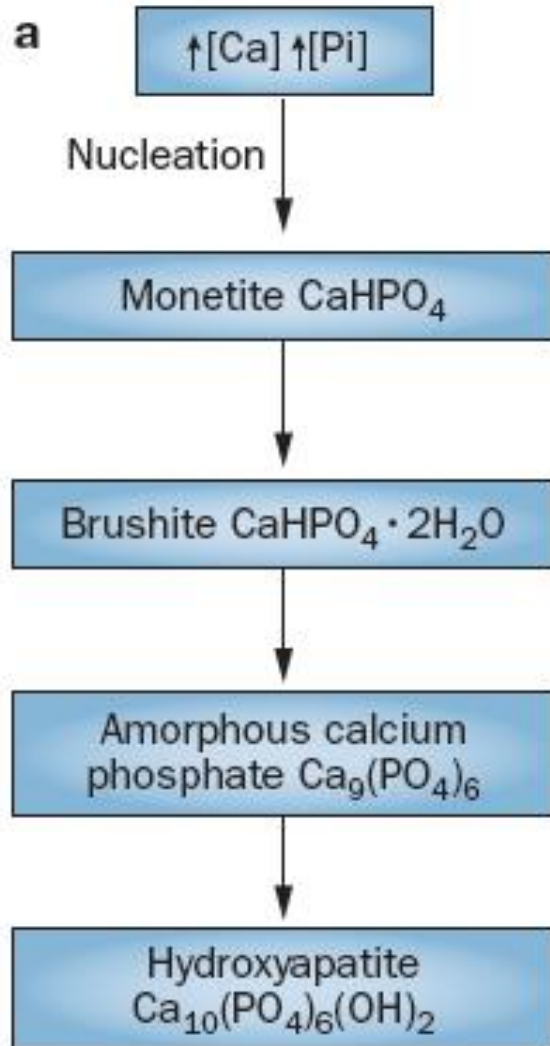
# Phosphate + FGF23: A novel concept

## Klotho, phosphate and FGF-23 in ageing and disturbed mineral metabolism

Makoto Kuro-o



# Phosphate + FGF23: A novel concept



# Phosphate + FGF23: A novel concept

**Table 1** | Current and proposed phosphate restriction paradigms

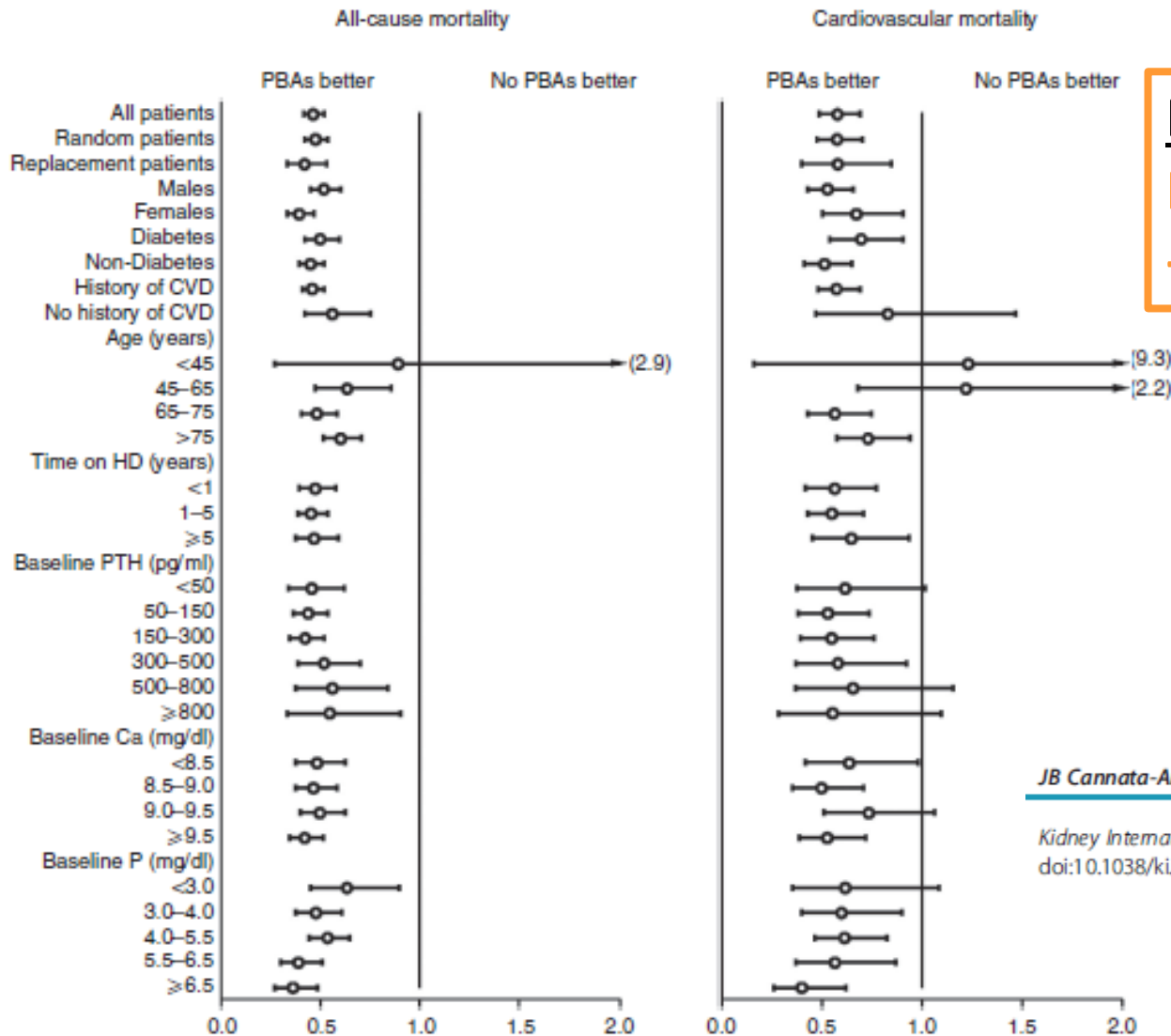
Therapy	Current paradigm	Proposed paradigm
Rationale	High levels of serum phosphate promote vascular calcification and cardiovascular events	High levels of urinary phosphate injure renal tubules and induce renal fibrosis
Goal	To decrease serum phosphate level	To decrease serum FGF-23 level
Indication	End-stage renal disease with hyperphosphataemia (~0.3% of patients with CKD)	Stage 2–5 CKD with high FGF-23 levels (~35% of patients with CKD)

Abbreviations: CKD, chronic kidney disease; FGF-23, fibroblast growth factor 23.

# Phosphate + FGF23: A novel concept

- Raised phosphate intake and/or decreased nephron number increase the rate of phosphate excretion per nephron, potentially causing calciprotein particle formation in the tubular lumen and tubular injury
- Serum fibroblast growth factor 23 (FGF-23) level correlates with phosphate excretion per nephron and, when combined with 24 h urinary phosphate excretion, may be useful for estimating changes in residual nephron number
- A new paradigm for phosphate restriction proposed in this Review argues for phosphate binders to be used in patients with CKD and an abnormally high FGF-23 level, regardless of serum phosphate level
- The therapeutic goal is to reduce serum FGF-23 level but not serum phosphate level, with the primary aim of preventing histological kidney damage and progression of CKD without increasing vascular calcification and cardiovascular events

# Phosphate + FGF23: A novel concept



**But:**  
**No FGF23 orientation**  
**+ CKD 5D**

*JB Cannata-Andía et al.: Phosphate-binding agents and mortality*

*Kidney International* advance online publication, 3 July 2013;  
 doi:10.1038/ki.2013.185

Sausage is so expensive, boy!  
Just be so kind to eat your **phosphate**  
pure today...

