AFECTACION CARDIOVASCULAR CKD-MBD

Mariano Rodriguez

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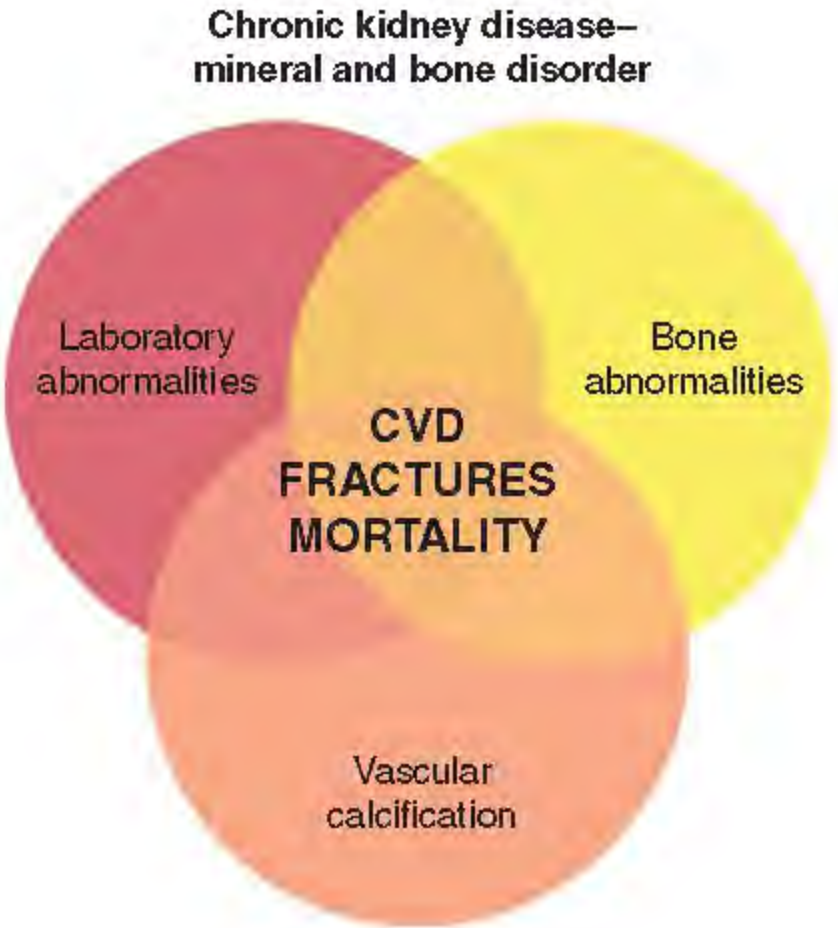
Hospital Univ. Reina Sofia (IMIBIC). Fundación Nefrologica-Red Renal

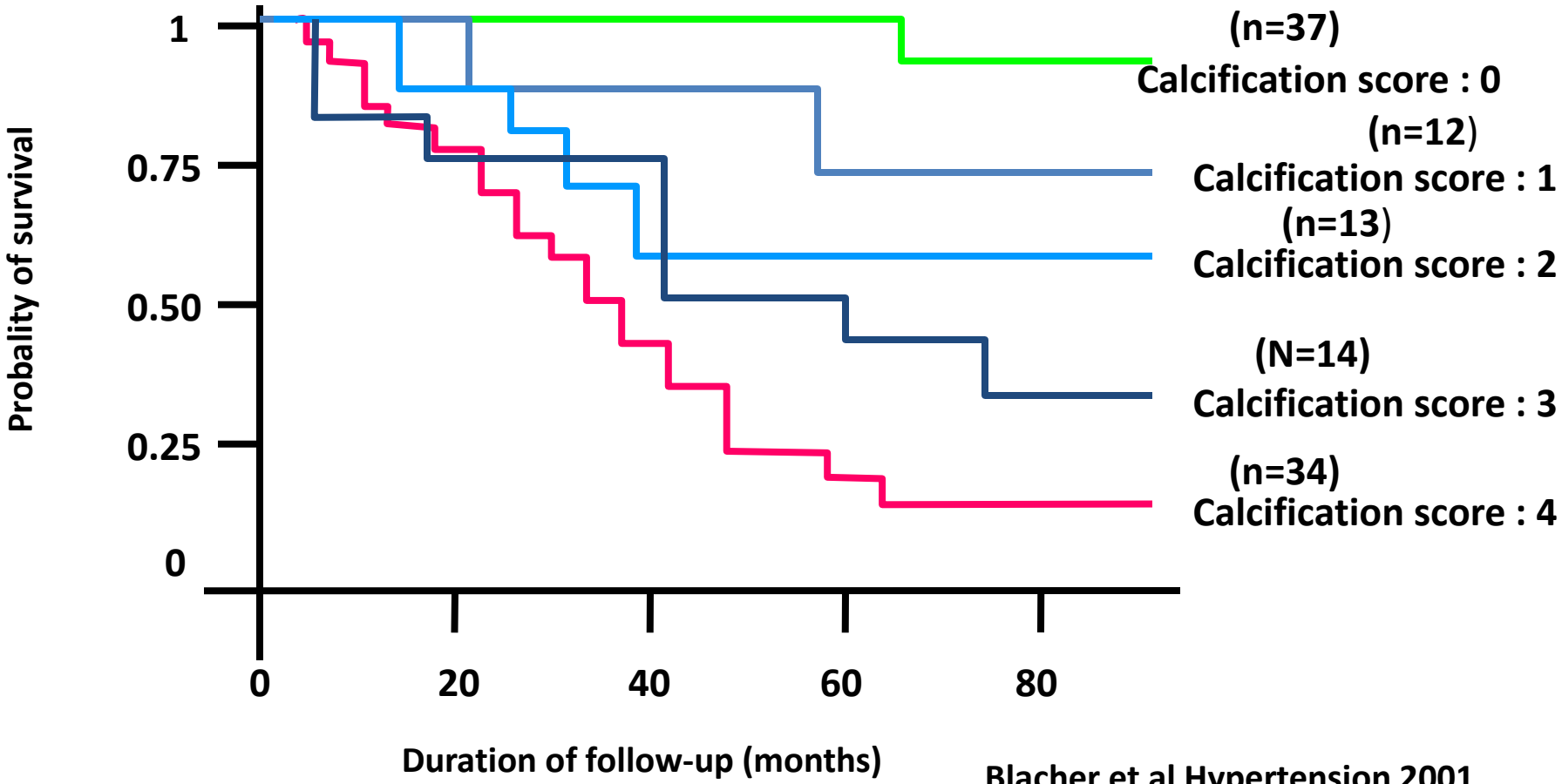
PROYECTO PROMETEO.

Alcalá de Henares, Oct 2011


Chronic kidney disease–
mineral and bone disorder
Laboratory
abnormalities
Bone
abnormalities
CVD
FRACTURES
MORTALITY
Vascular
calcification

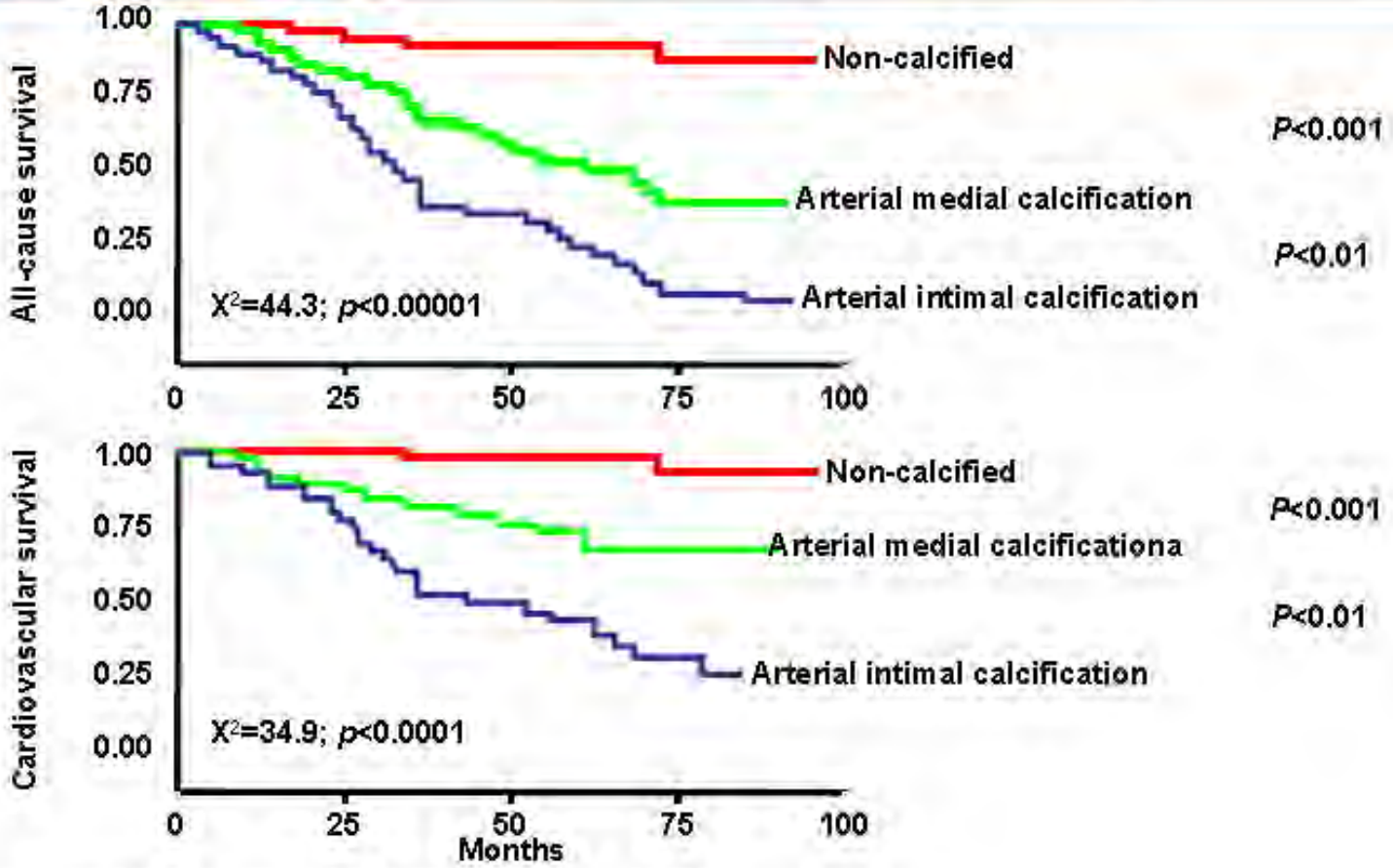
Calcification score-Survival

- **Probality of all-cause survival according to calcification score. Comparison (log-rank test) between curves was highly significant (Chi D =42.66 ; P<0.0001).**



Blacher et al Hypertension 2001

Arterial media calcification in ESRD: impact on all-cause and cardiovascular mortality



London GM, *et al.* Nephrol Dial Transplant 2003;18:1731-40.

Datos clínicos y aproximaciones terapeuticas

- -Ca
- -P
- -PTH
- -Vit D
- -FGF23
- -Klotho

Mecanismos de calcificación

- -P
- -se puede reparar el vaso calcificado?

Mild Hyperphosphatemia and Mortality in Hemodialysis Patients

Alberto Rodriguez-Benot et al ***Am J Kidney Dis*** **46:68-77, 2005.**

Table 4. Multivariated Risk Ratios for Mortality

	RR	5% CI	95% CI	Significance
Phosphate (unadjusted)	1.30	1.14	1.49	0.00
Adjusted Risk Ratios				
Phosphate (1 mg/dL)	1.26	1.09	1.47	0.02

etes, hemoglobin level, albumin level, nPCR, Kt/V, serum calcium, level, andPTHlevel.

JAMA. 2011;305(11):1119-1127

Serum Levels of Phosphorus, Parathyroid Hormone, and Calcium and Risks of Death and Cardiovascular Disease in Individuals With Chronic Kidney Disease

A Systematic Review and Meta-analysis

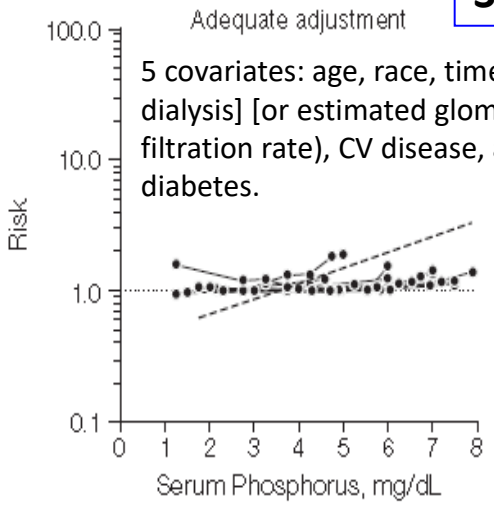
Suetonia C. Palmer, MB ChB, PhD
Andrew Hayen, PhD
Petra Macaskill, PhD
Fabio Pellegrini, MSc
Jonathan C. Craig, MB ChB, PhD
Grahame J. Elder, MB BS, PhD
Giovanni F. M. Strippoli, MD, PhD

Of 8380 citations identified in the original search, 47 cohort studies (N=327 644 patients) met the inclusion criteria.

Figure 2. Risks of All-Cause Mortality Grouped According to Level of Study Adjustment for Confounding Variables

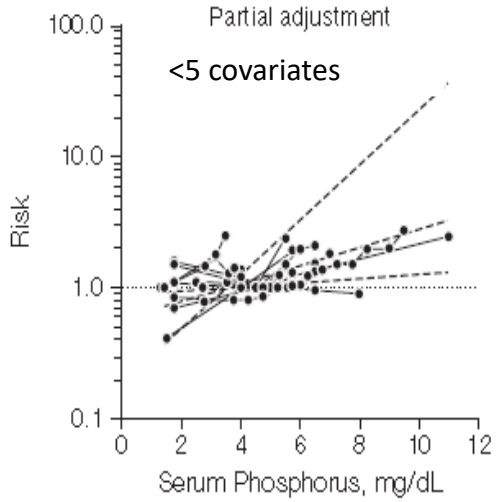
S. Phosphorus

Studies
Block et al,[21] 1998
Saran et al,[29] 2003
Port et al,[27] 2004
Kestenbaum et al,[58] 2005
Slinin et al,[30] 2005
Young et al,[32] 2005
Melamed et al,[49] 2006
Voormolen et al,[65] 2007
Tentori et al,[31] 2008
Wald et al,[44] 2008
Kovesdy et al,[60] 2010



5 covariates: age, race, time on dialysis] [or estimated glomerular filtration rate), CV disease, and diabetes.

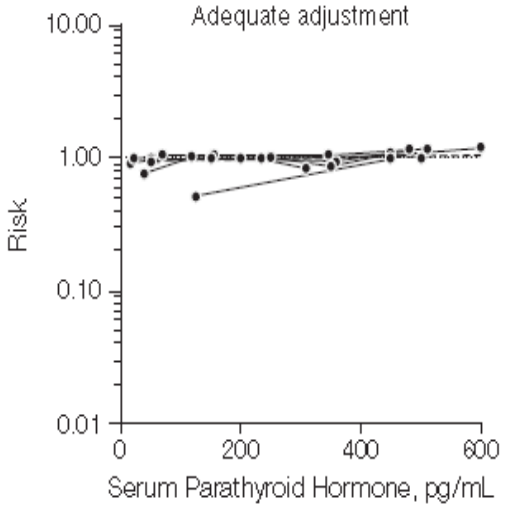
Studies
Jassal et al,[38] 1996
Coco and Rush,[33] 2000
Cueto-Manzano et al,[45] 2001
Block et al,[22] 2004
Stevens et al,[52] 2004
Menon et al,[61] 2005
Noordzij et al,[18] 2005 (HD)
Noordzij et al,[18] 2005 (PD)
Osawa et al,[50] 2005
Rodriguez-Benot et al,[42] 2005
Kimata et al,[25] 2007
Schaeffner et al,[57] 2007
Komaba et al,[39] 2008
Phelan et al,[51] 2008
Connolly et al,[54] 2009
Lacson et al,[26] 2009



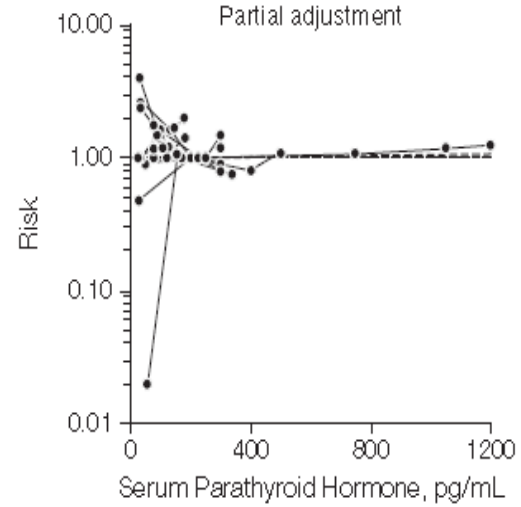
<5 covariates

S. PTH

Studies
Block et al,[21] 1998
Slinin et al,[30] 2005
Young et al,[32] 2005
Melamed et al,[49] 2006
Tentori et al,[31] 2008
Wald et al,[44] 2008
Dukkipati et al,[35] 2010

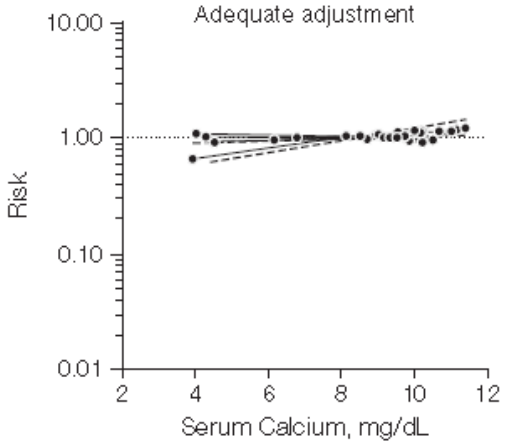


Studies
Coco and Rush,[33] 2000
Avram et al,[17] 2001 (HD)
Avram et al,[17] 2001 (PD)
Dimkovic et al,[46] 2002
Guh et al,[37] 2002
Block et al,[22] 2004
Stevens et al,[52] 2004
Noordzij et al,[18] 2005 (HD)
Noordzij et al,[18] 2005 (PD)
Osawa et al,[50] 2005
Dussol et al,[36] 2007
Kimata et al,[25] 2007
Komaba et al,[39] 2008
Kovesdy et al,[59] 2008
Drechsler et al,[34] 2009
Fellah et al,[53] 2009
Morrone et al,[41] 2009
Smith et al,[64] 2009
Lacson Jr et al,[26] 2009



S. Calcium

Studies
- Block et al,[21] 1998
- Kestenbaum et al,[58] 2005
- Slinin et al,[30] 2005
- Young et al,[32] 2005
- Melamed et al,[49] 2006
- Voormolen et al,[65] 2007
- Tentori et al,[31] 2008
- Wald et al,[44] 2008



Studies
- Stevens et al,[52] 2004
- Noordzij et al,[18] 2005 (HD)
- Noordzij et al,[18] 2005 (PD)
- Osawa et al,[50] 2005
- Rodriquez-Benot et al,[42] 2005
- Egbuna et al,[55] 2007
- Kimata et al,[25] 2007
- Schaeffner et al,[57] 2007
- Komaba et al,[39] 2008
- Lacson Jr et al,[26] 2009

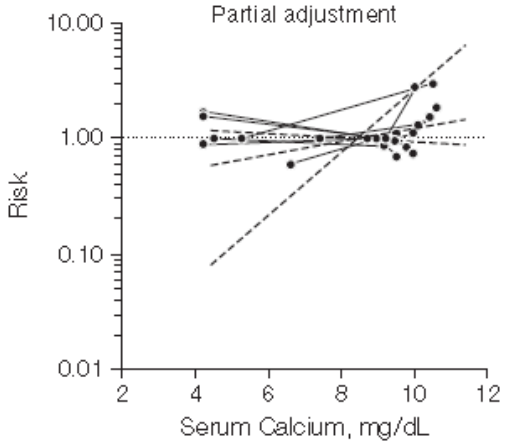
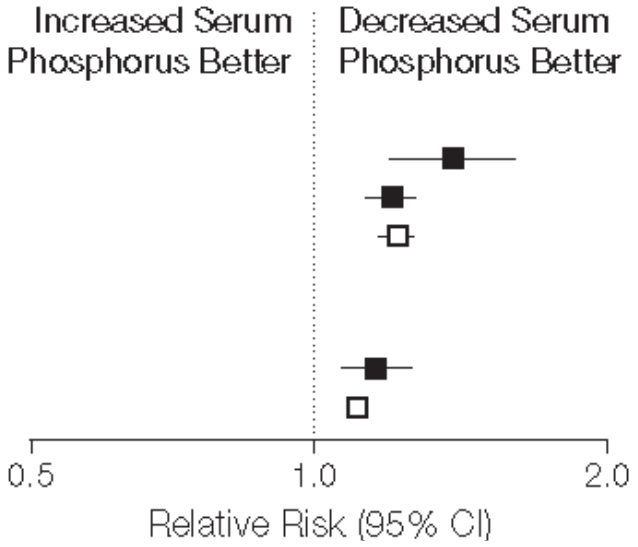


Figure 3. Summary Estimates for Risks of All-Cause Mortality and Cardiovascular Mortality Associated With Levels of Serum Phosphorus, Parathyroid Hormone, and Calcium

S. Phosphorus

	No. of Cohorts	No. of Participants	Relative Risk (95% CI) Per Unit Increase
All-cause mortality			
Adequate adjustment	3	4651	1.35 (1.16-1.57)
Partial adjustment	10	87 694	1.16 (1.09-1.23)
All studies combined	13	92 345	1.18 (1.12-1.25)
Cardiovascular mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	2	5881	1.14 (1.05-1.24)
All studies combined	3	23 207	1.10 (1.06-1.13)



S. PTH

	No. of Cohorts	No. of Participants	Relative Risk (95% CI)
All-cause mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	3	83 732	1.01 (0.99-1.03)
All studies combined	4	101 058	1.01 (1.00-1.02)
Cardiovascular mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	1	5041	Not estimable
All studies combined	2	22 367	1.05 (0.99-1.11)

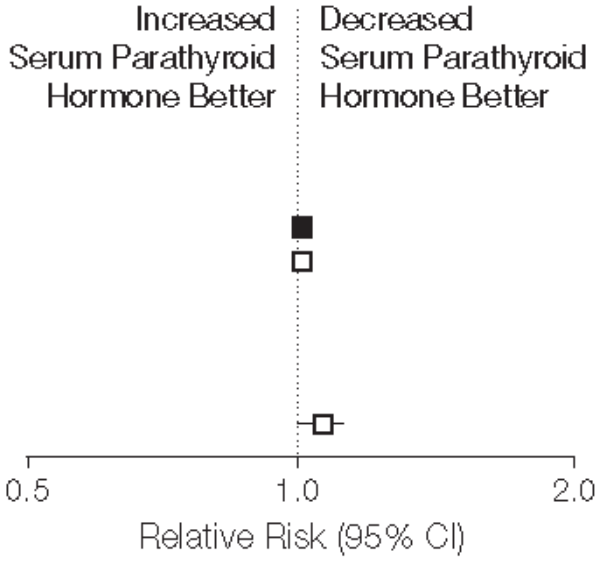
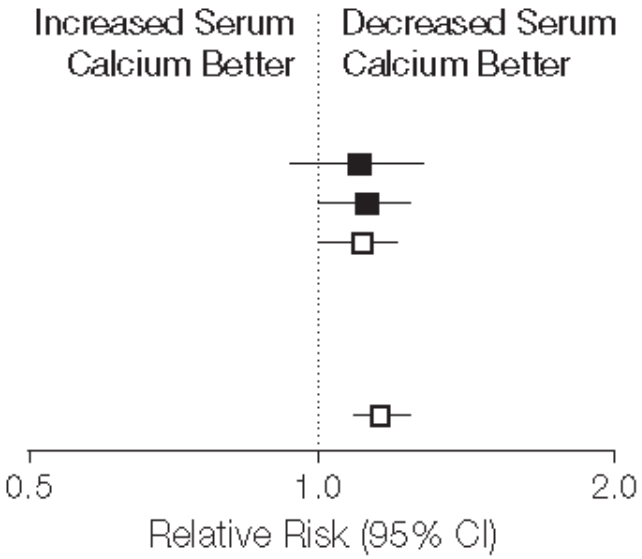


Figure 3. Summary Estimates for Risks of All-Cause Mortality and Cardiovascular Mortality Associated With Levels of Serum Phosphorus, Parathyroid Hormone, and Calcium

S. Calcium

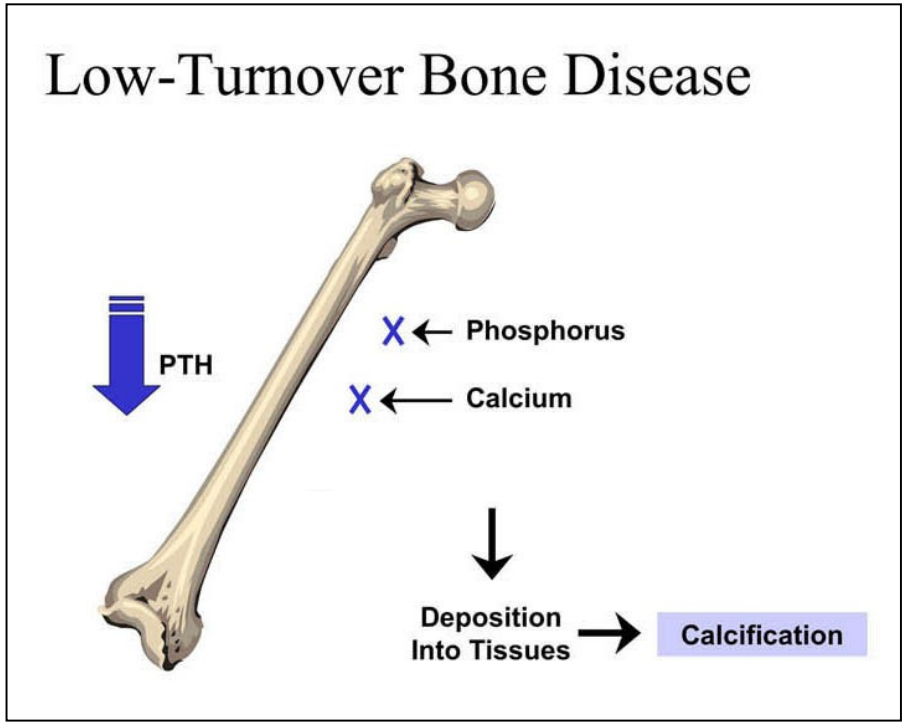
	No. of Cohorts	No. of Participants	Relative Risk (95% CI)
All-cause mortality			
Adequate adjustment	2	22 367	1.07 (0.91-1.24)
Partial adjustment	6	83 789	1.09 (0.99-1.20)
All studies combined	8	106 156	1.08 (1.00-1.16)
Cardiovascular mortality			
Adequate adjustment	1	17 326	Not estimable
Partial adjustment	1	5041	Not estimable
All studies combined	2	22 367	1.15 (1.08-1.23)

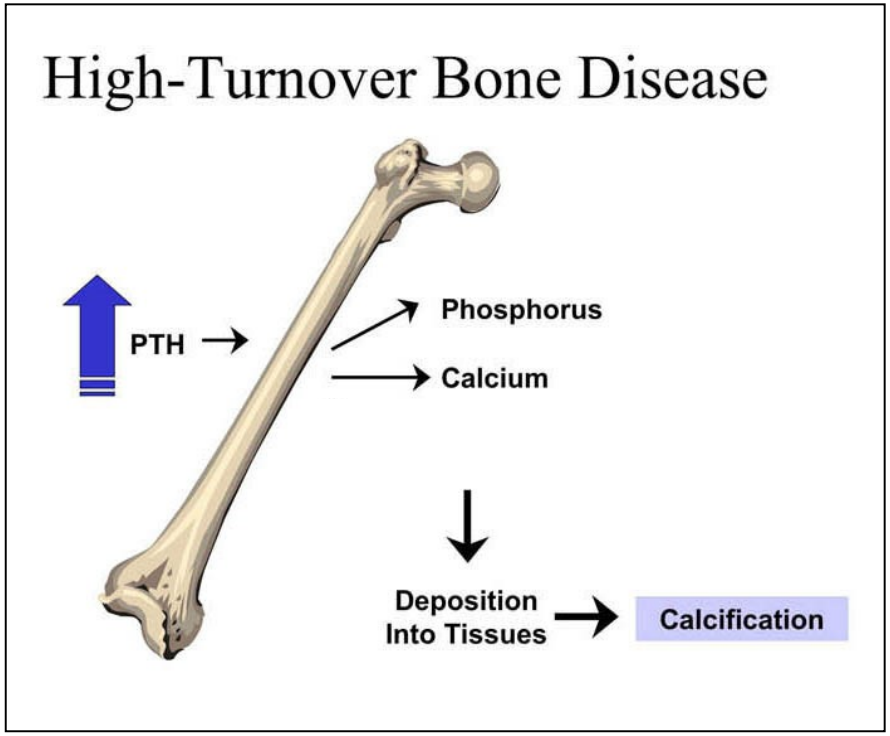


In individuals not yet requiring dialysis, the risk of all cause mortality for each 1-mg/dL increase In P (RR, 1.29) was similar to that observed in individuals requiring Dialysis (RR, 1.17)(*P = .22).*

No evidence of an association between serum calcium and all-cause mortality was found in either individuals with earlier stages of chronic kidney disease (RR, 1.02) or those requiring dialysis (RR, 1.09) *P=.63*

Bone Disease :
Impact on Soft Tissue Calcification





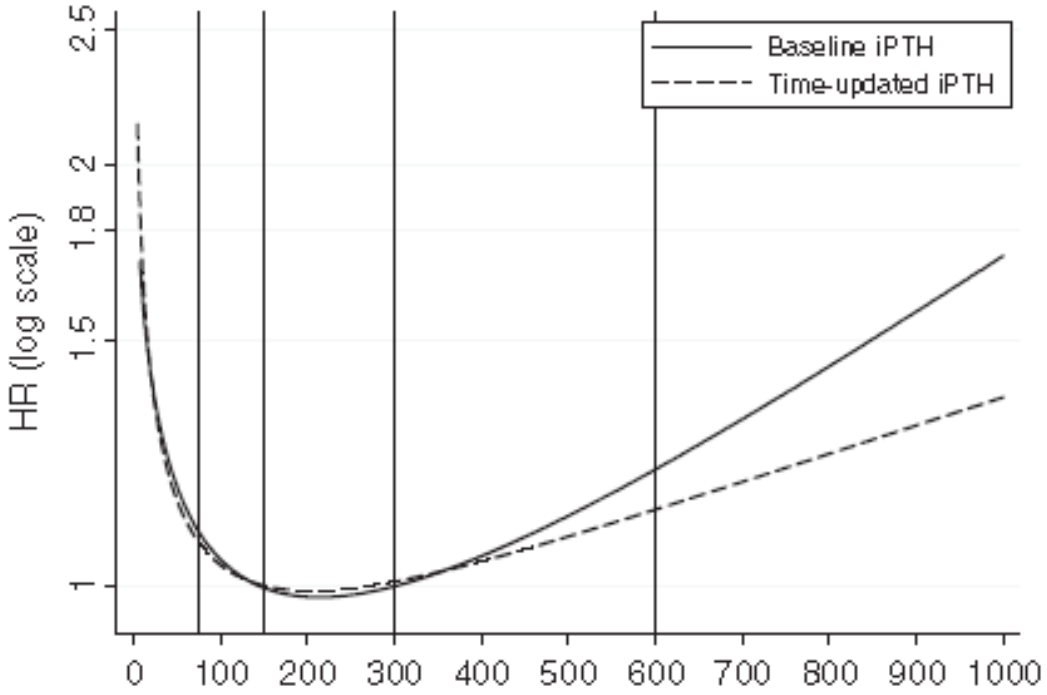
Nephrol Dial Transplant (2010) 1 of 8
doi: 10.1093/ndt/gfq219

NDT
Nephrology Dialysis Transplantation

Original Article

Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population

Jürgen Floege[1], Joseph Kim[2], Elizabeth Ireland[2], Charles Chazot[3], Tilman Drueke[4], Angel de Francisco[5], Florian Kronenberg[6], Daniele Marcelli[7], Jutta Passlick-Deetjen[7], Guntram Schernthaner[8], Bruno Fouqueray[9], David C. Wheeler[10] and on behalf of the ARO Investigators



see commentary on page 931

Chronic kidney disease, hypovitaminosis D, and mortality in the United States

Rajnish Mehrotra[1,2], Dulcie A. Kermah[3], Isidro B. Salusky[2], Myles S. Wolf[4], Ravi I. Thadhani[5], Yi-Wen Chiu[1,6], David Martins[3], Sharon G. Adler[1,2] and Keith C. Norris[2,3]

Table 2 | Adjusted hazards ratios for the relationship between serum 25-hydroxy vitamin D levels and all-cause mortality in participants with chronic kidney disease from the Third National Health and Nutrition Examination Survey cohort

Models adjusted for	Total events	Vitamin D[a] >30 ng/ml	15–30 ng/ml	<15 ng/ml
Demographics[a]	1123	Reference	1.18 (1.01,1.38)	1.52 (1.18,1.96)
Demographics and cardiovascular risk factors[b]	989	Reference	1.21 (1.03,1.43)	1.60 (1.22,2.10)
Demographics, cardiovascular risk factors, and laboratory and socioeconomic variables[c]	848	Reference	1.17 (0.99,1.38)	1.56 (1.12,2.18)

Table 3 | Adjusted hazards ratios for the relationship between serum 25-hydroxy vitamin D levels and cardiovascular and non-cardiovascular mortality in the Third National Health and Nutrition Examination Survey cohort

Models adjusted for	Total events	Vitamin D[a] >30 ng/ml	15–30 ng/ml	<15 ng/ml
Cardiovascular mortality				
Demographics[a]	588	Reference	1.19 (0.94,1.52)	1.51 (1.01,2.28)
Demographics and cardiovascular risk factors[b]	518	Reference	1.21 (0.93,1.58)	1.51 (0.96,2.38)
Demographics, cardiovascular risk factors, and laboratory and socioeconomic variables[c]	444	Reference	1.19 (0.91,1.57)	1.49 (0.94,2.36)
Non-cardiovascular mortality				
Demographics[a]	535	Reference	1.17 (0.93,1.46)	1.52 (1.00,2.29)
Demographics and cardiovascular risk factors[b]	471	Reference	1.22 (0.96,1.55)	1.67 (1.04,2.67)
Demographics, cardiovascular risk factors, and laboratory and socioeconomic variables[c]	404	Reference	1.17 (0.88,1.55)	1.64 (0.94,2.88)

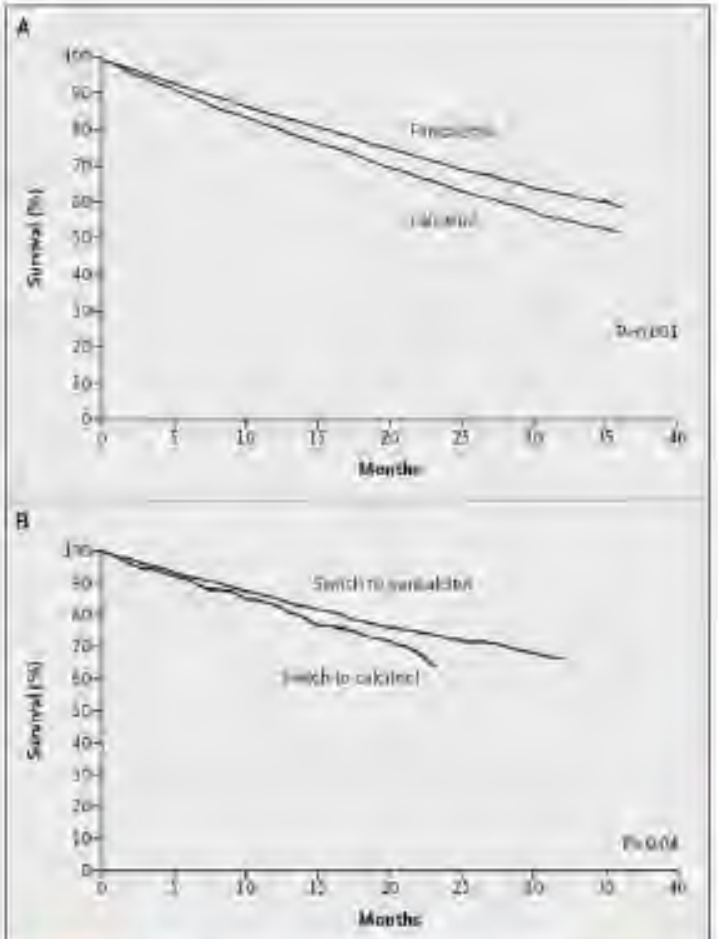


Figure 1. Kaplan–Meier Analysis of Survival According to the Type of Vitamin D Therapy.

Panel A shows the survival of patients treated with either paricalcitol or calcitriol who received the same therapy for the duration of the follow-up. Panel B shows the survival of patients who switched from calcitriol to paricalcitol or from paricalcitol to calcitriol during the follow-up period. The time of switching was approximately 900 days after the initiation of dialysis for both groups. P values were calculated with the use of the log-rank test.

ORIGINAL ARTICLE

Survival of Patients Undergoing Hemodialysis with Paricalcitol or Calcitriol Therapy

Ming Teng, M.D., Myles Wolf, M.D., M.Sc., Edmund Lowrie, M.D., Hanwa Ofsthun, Ph.D., E. Michael Lazarus, M.D., and Ray Thadhani, M.D., M.P.H.

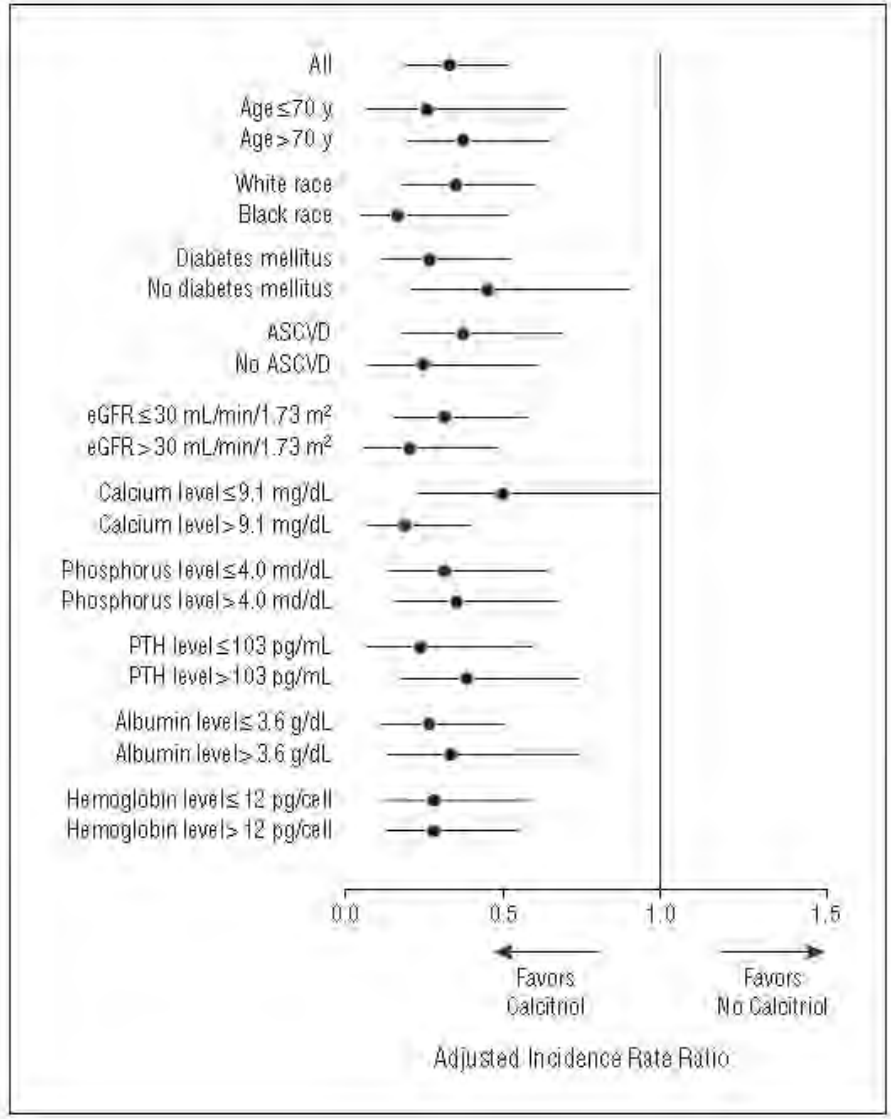
Even after Adjustment of Serum Minerals, VDR Activation was still independently associated with improved survival

N Engl J Med. 2003

Association of Activated Vitamin D Treatment and Mortality in Chronic Kidney Disease

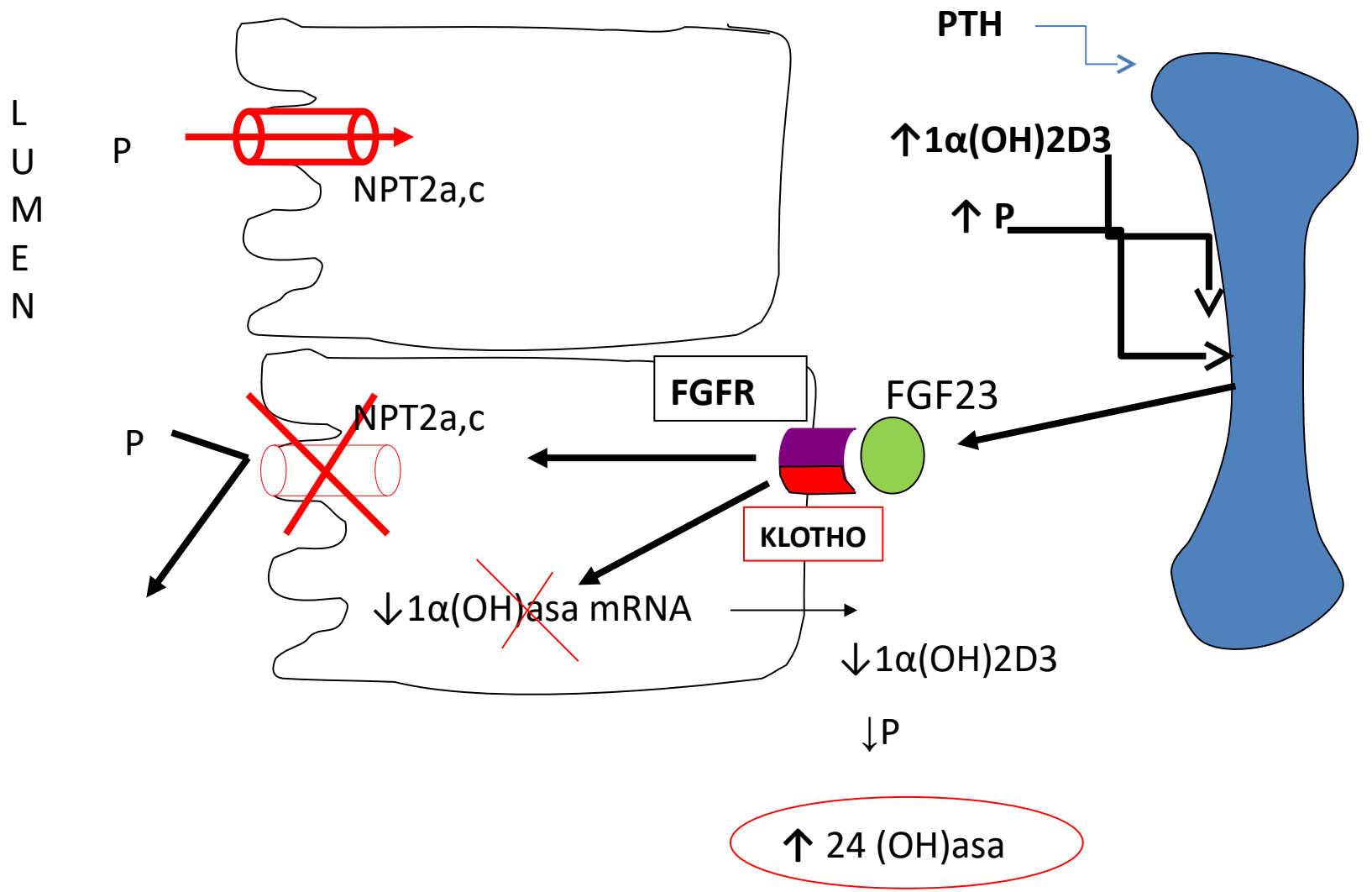
Csaba P. Kovesdy, MD; Shahram Ahmadzadeh, MD; John E. Anderson, MD; Kamyar Kalantar-Zadeh, MD

Arch Intern Med. 2008;168(4):397-403



Klotho converts canonical FGF receptor into a specific receptor for FGF23

Itaru Urakawa[1], Yuji Yamazaki[1], Takashi Shimada[1], Kousuke Iijima[1], Hisashi Hasegawa[1], Katsuya Okawa[1], Toshiro Fujita[2], Seiji Fukumoto[2] & Takeyoshi Yamashita[1]



Hyperphosphatemia

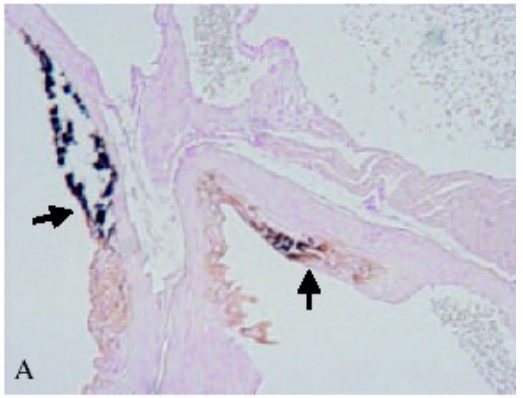
FGF23 null

Calcification

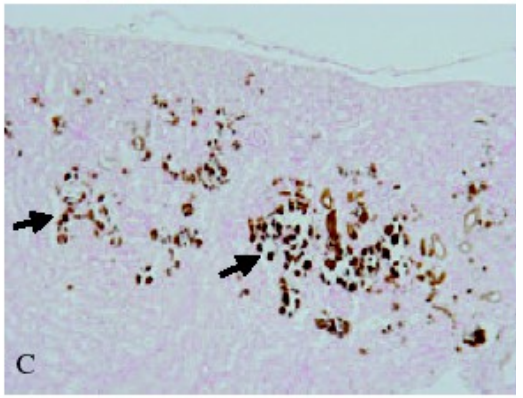
High calcitriol levels

FGF23 null

Heart

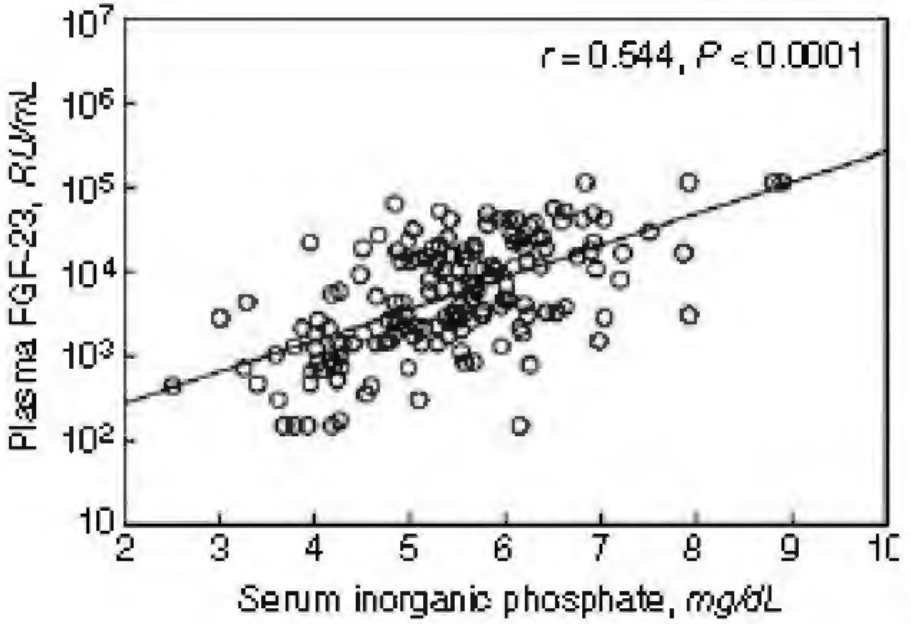


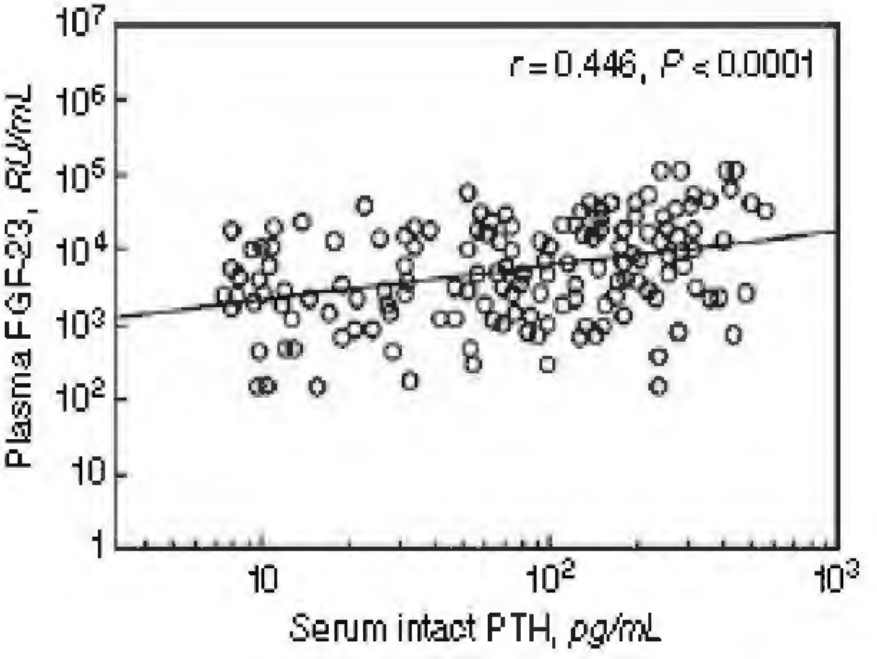
Kidney



FGF-23 in patients with end-stage renal disease on hemodialysis

YASUO IMANISHI, *Kidney International, Vol. 65 (2004), pp. 1943–1946*





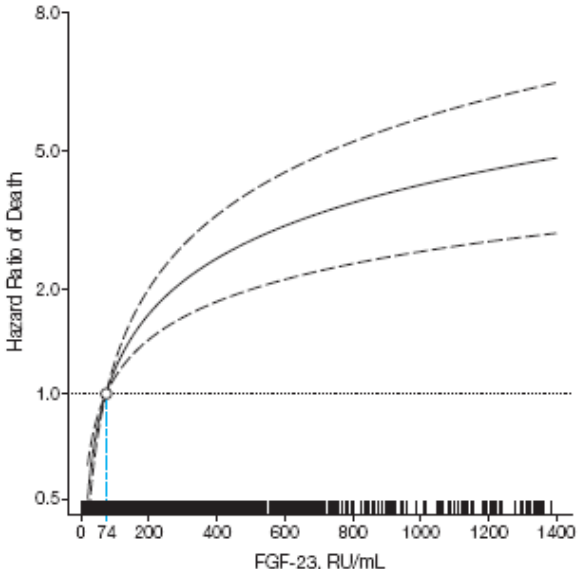
The NEW ENGLAND JOURNAL of MEDICINE

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

Nephrol Dial Transplant (2009) 24: 2792–2796

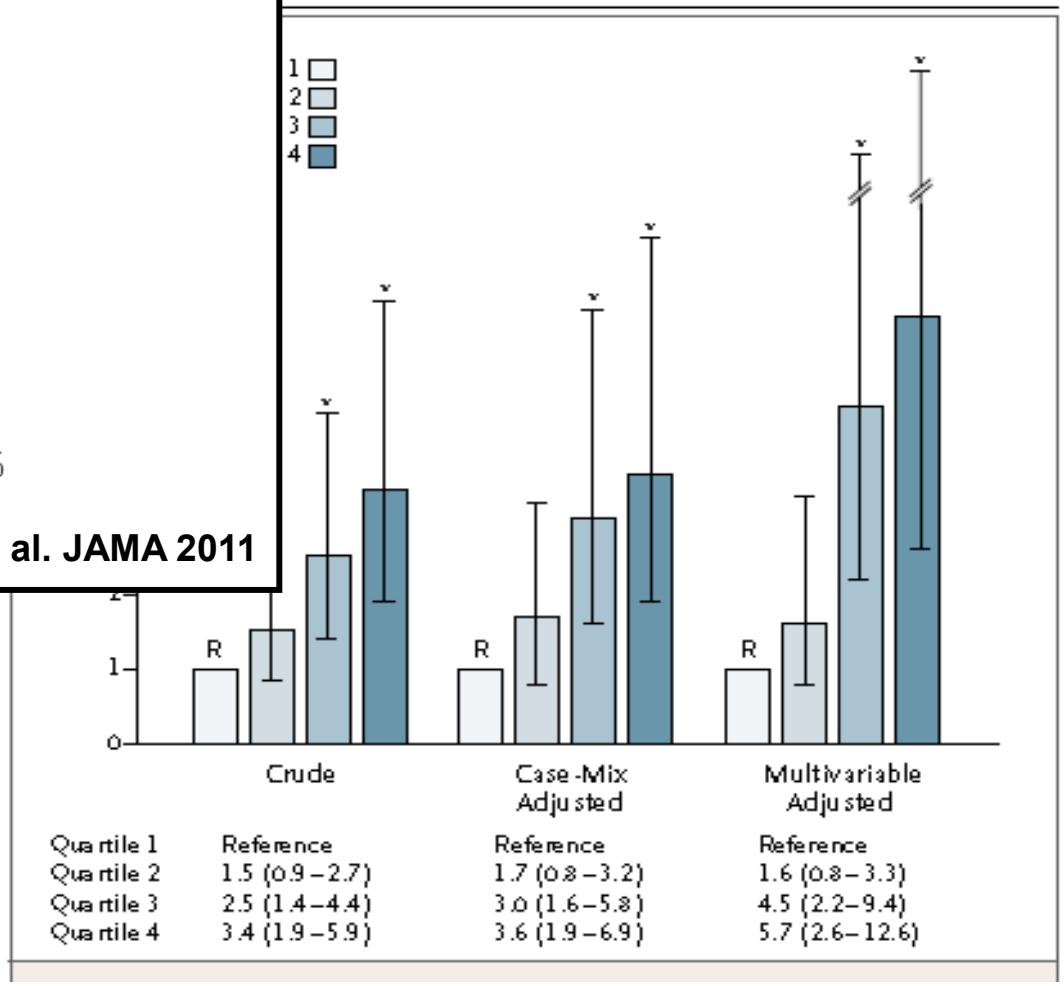
among Patients Undergoing Hemodialysis



FGF-23 and Mortality in CKD. Isakova et al. JAMA 2011

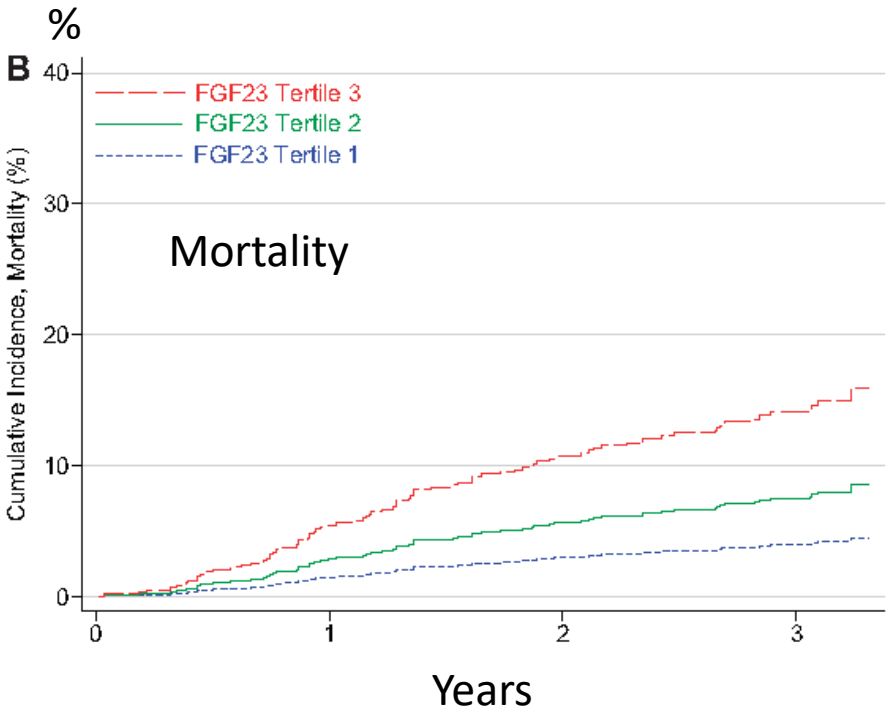
historial de P alto.

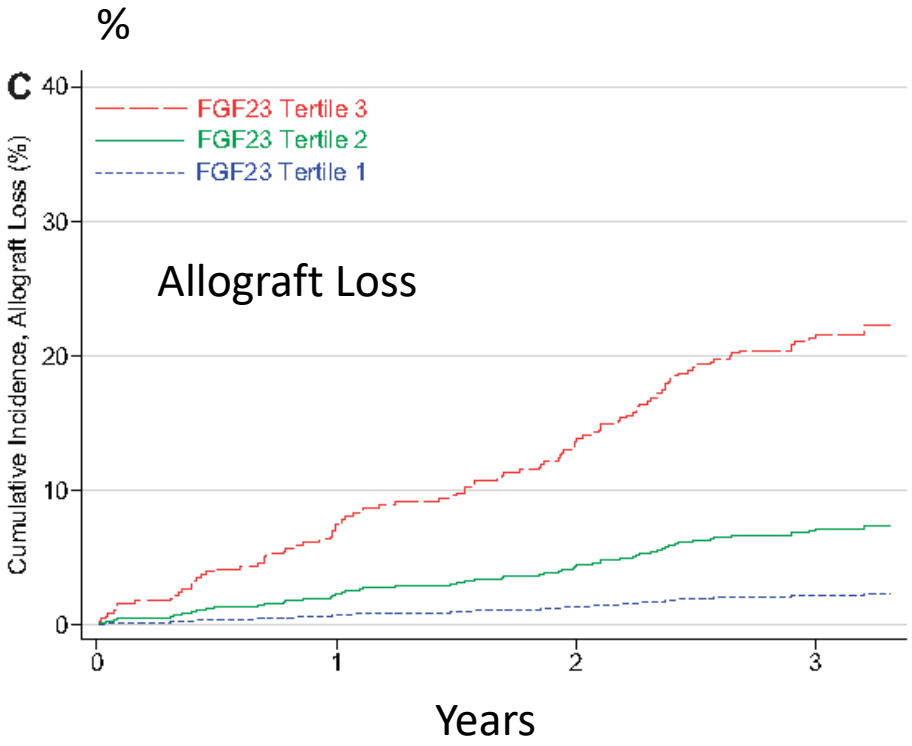
- FGF23 refleja otras alteraciones CKD MBD además del P elevado



Elevated Fibroblast Growth Factor 23 is a Risk Factor for Kidney Transplant Loss and Mortality

Myles Wolf…*J Am Soc Nephrol 22: 956–966, 2011*





Fibroblast Growth Factor 23 and Left Ventricular Hypertrophy in Chronic Kidney Disease

Orlando M. Gutiérrez, MD, MMSc; James L. Januzzi, MD; Tamara Isakova, MD; Karen Laliberte, RN, MS; Kelsey Smith, BA; Gina Collerone, AS; Ammar Sarwar, MD; Udo Hoffmann, MD; Erin Coglianese, MD; Robert Christenson, PhD; Thomas J. Wang, MD, MPH Christopher deFilippi, MD; Myles Wolf, MD, MMSc

(*Circulation*. 2009;119:2545-2552.)

ARTICLE | **Annals of Internal Medicine**

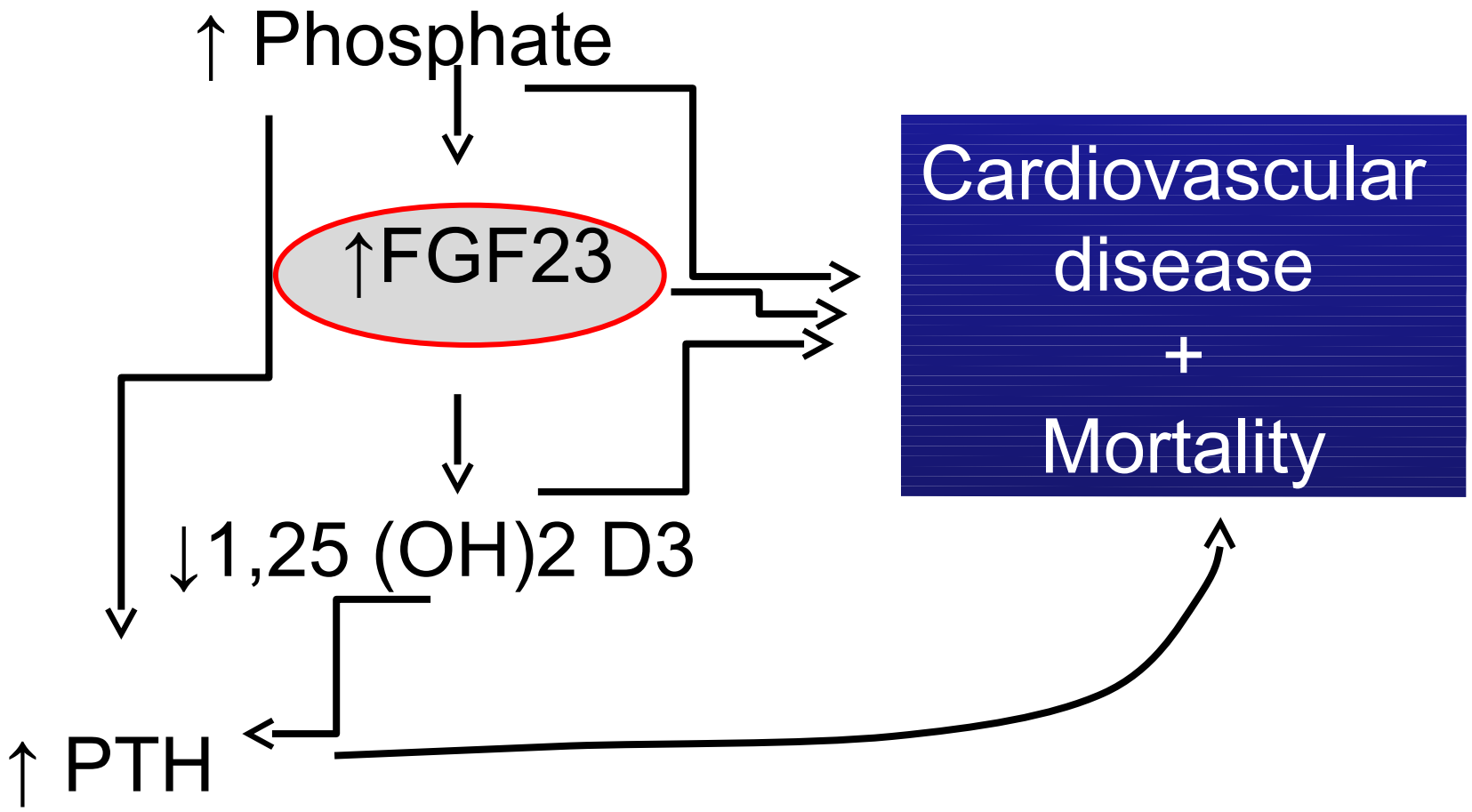
The Associations of Fibroblast Growth Factor 23 and Uncarboxylated Matrix Gla Protein With Mortality in Coronary Artery Disease: The Heart and Soul Study

Benjamin D. Parker, MD; Leon J. Schurgers, PhD; Vincent M. Brandenburg, MD; Robert H. Christenson, PhD; Cees Vermeer, PhD; Markus Ketteler, MD; Michael G. Shlipak, MD, MPH; Mary A. Whooley, MD; and Joachim H. Ix, MD, MAS

Circulating fibroblast growth factor-23 is associated with vascular dysfunction in the community

Majd A.I. Mirza[a], Anders Larsson[a], Lars Lind[a], Tobias E. Larsson[a,b,*]

Atherosclerosis 205 (2009) 385–390


↑ Phosphate
↑FGF23
↓1,25 (OH)2 D3
↑ PTH
Cardiovascular disease + Mortality

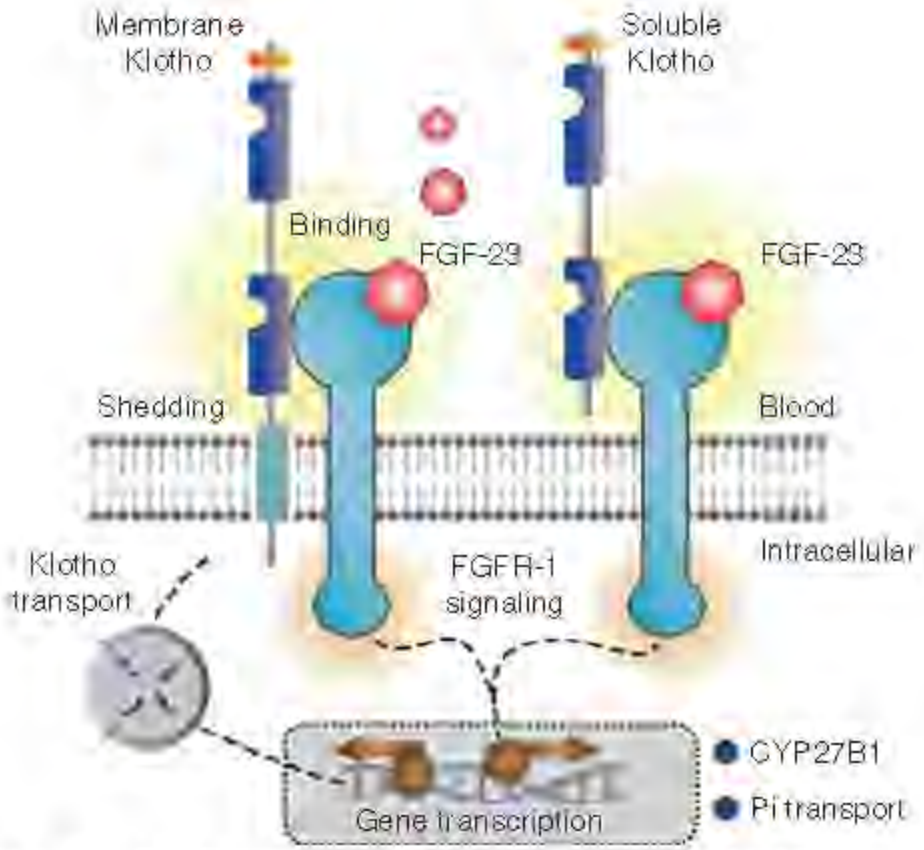


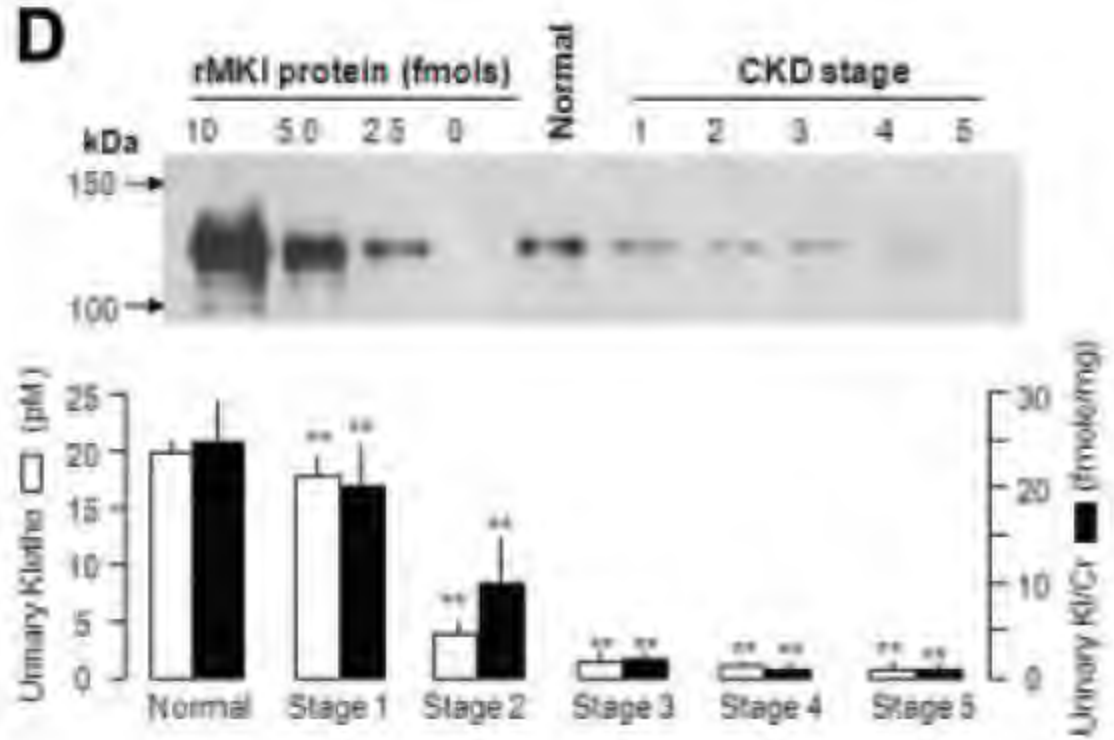
Figure 2 | The fibroblast growth factor (FGF)-23 receptor. In light blue, FGF receptor type-1 (FGFR-1). In dark blue, left-sided membrane-bound Klotho; right-sided soluble, shed Klotho. The red hexagon depicts FGF-23. FGF-23 signal transduction is established when Klotho and FGFR-1 colocalize (left side). It is unknown whether signal transduction can occur by soluble Klotho (right side). In the kidney, signaling leads to down-regulation of CYP27B1 and retrieval of phosphate transporters in the proximal tubule (figure provided by J Hoenderop, Department of Physiology, University Medical Center Nijmegen, The Netherlands).

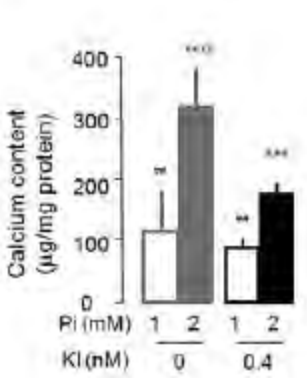
Vervloet MG, Larsson TE. Fibroblast growth factor-23 and Klotho in chronic kidney disease. *Kidney inter., Suppl.* 2011; **1**: 130–135.

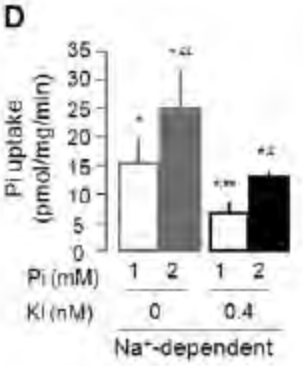
Klotho Deficiency Causes Vascular Calcification in Chronic Kidney Disease

Ming Chang Hu,*†‡ Mingjun Shi,* Jianning Zhang,† Henry Quiñones,† Carolyn Griffith,* Makoto Kuro-o,*§ and Orson W. Moe*†‖

J Am Soc Nephrol 22: 124–136, 2011.







Calcificación Vascular ≈ Mortalidad vascular ??

ESTUDIOS PROSPECTIVOS (progresión de la CV)

1-Estudios clínicos han mostrado que control del P con Sevelamer y también con lantano disminuyen la progresión de la CV.

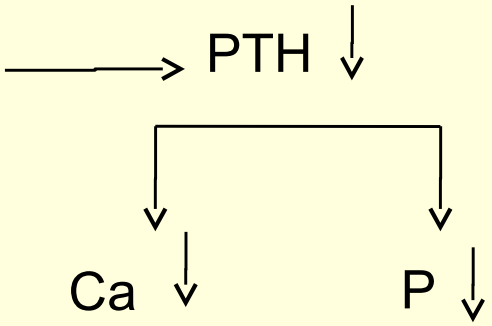
2- ADVANCE sugiere que Calcimimeticos retrasan la progresión de la CV

FRENAR CALCIFICACIÓN:

- Eliminar factores que estimulen la calcificación
- Intervenir sobre los mecanismos celulares
- Favorecer la reparación
  -reabsorción de calcificación
  -restitución (reparación) del tejido

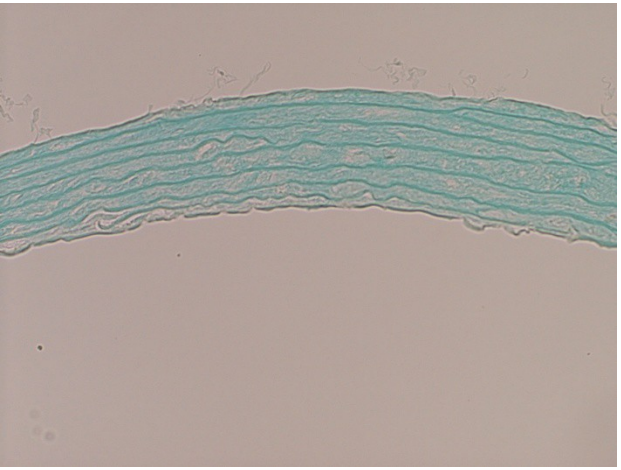
-

Calcimimetico

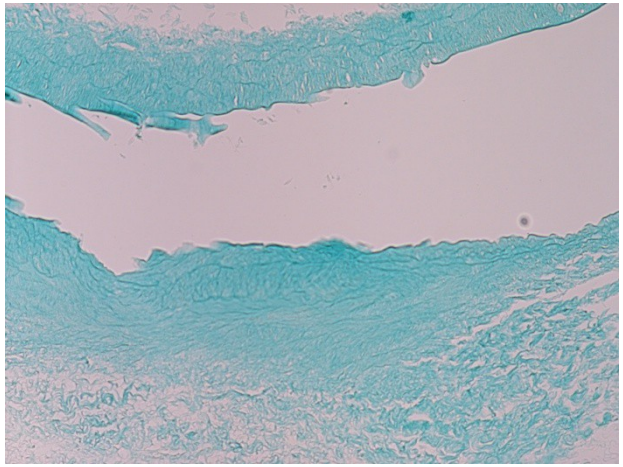


Se puede controlar el hiperperatiroidismo y además disminuir el Ca y el P

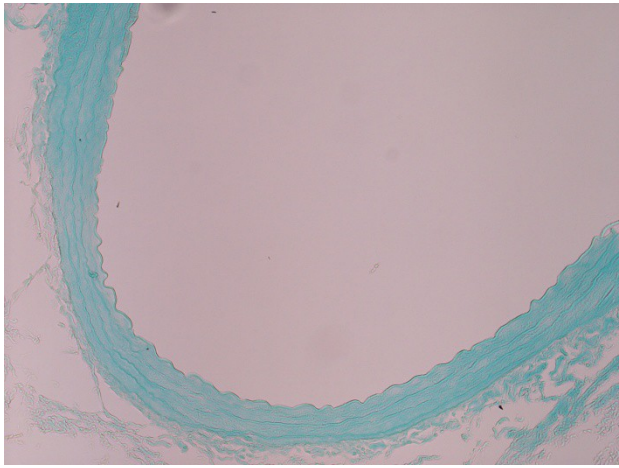
Que pasa con las calcificaciones vasculares??



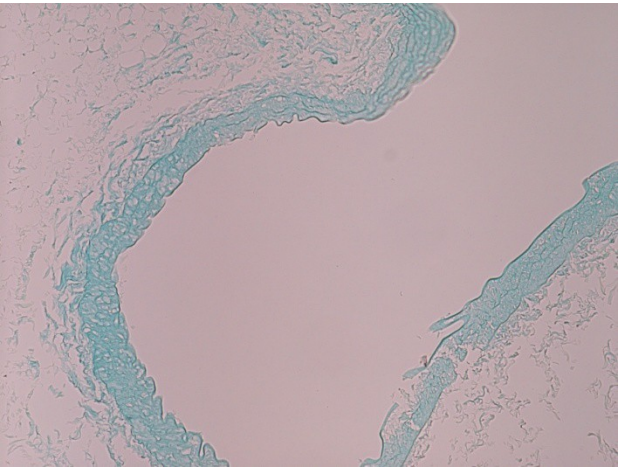
(A) Sham



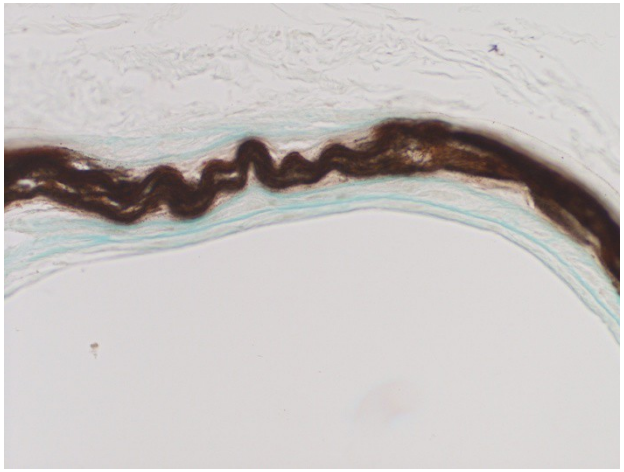
(B) 5/6 Nx + vehicle



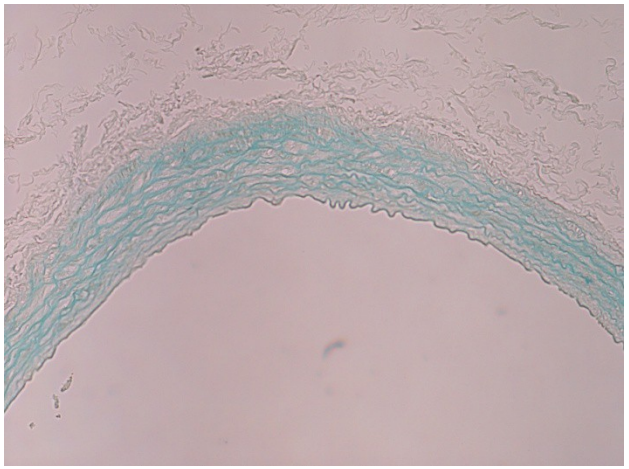
(C) 5/6 Nx + R-568 (1.5mg/kg)



(C) 5/6 Nx + R-568 (3 mg/kg)



(E) 5/6 Nx + Calcitriol

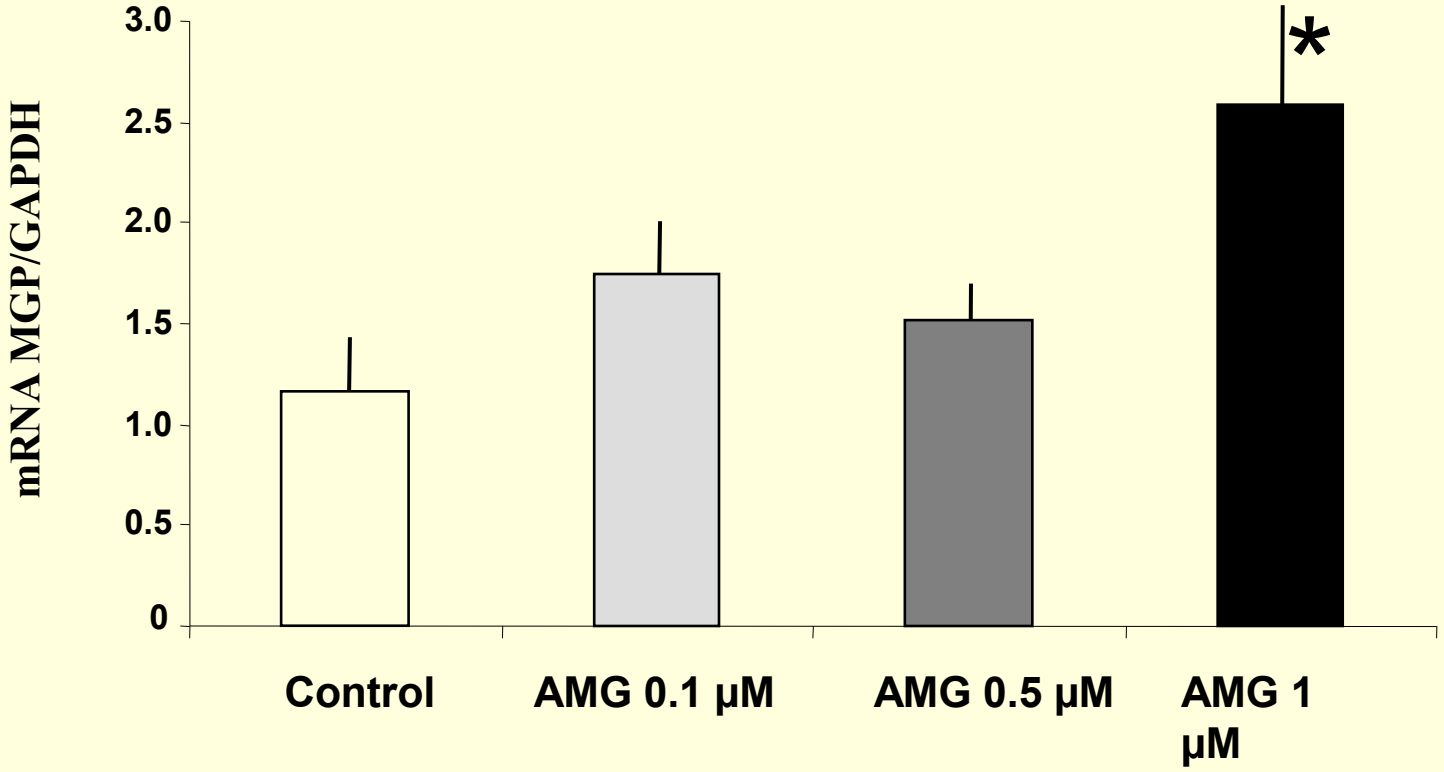


(F) 5/6 Nx + Calcitriol + R-568 (1.5 mg/kg)

FIGURE 5

Lopez I et al
J Am Soc Nephrol 17: 795–804, 2006

Calcimimetico estimula la expresion de MGP



aP<0.05 vs AMG 1 µM

Mendoza et al, Calcified Tissue International (2010)

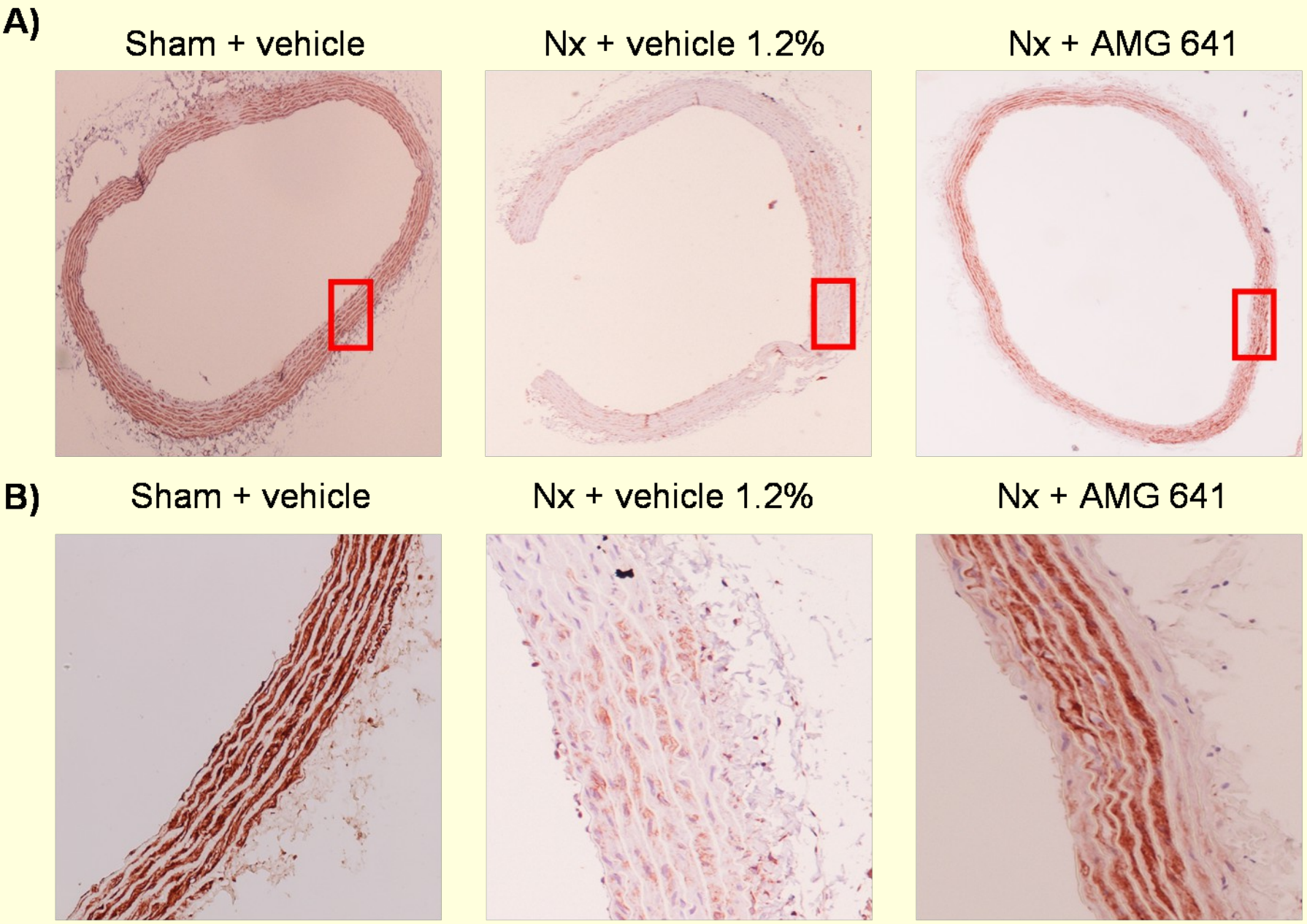
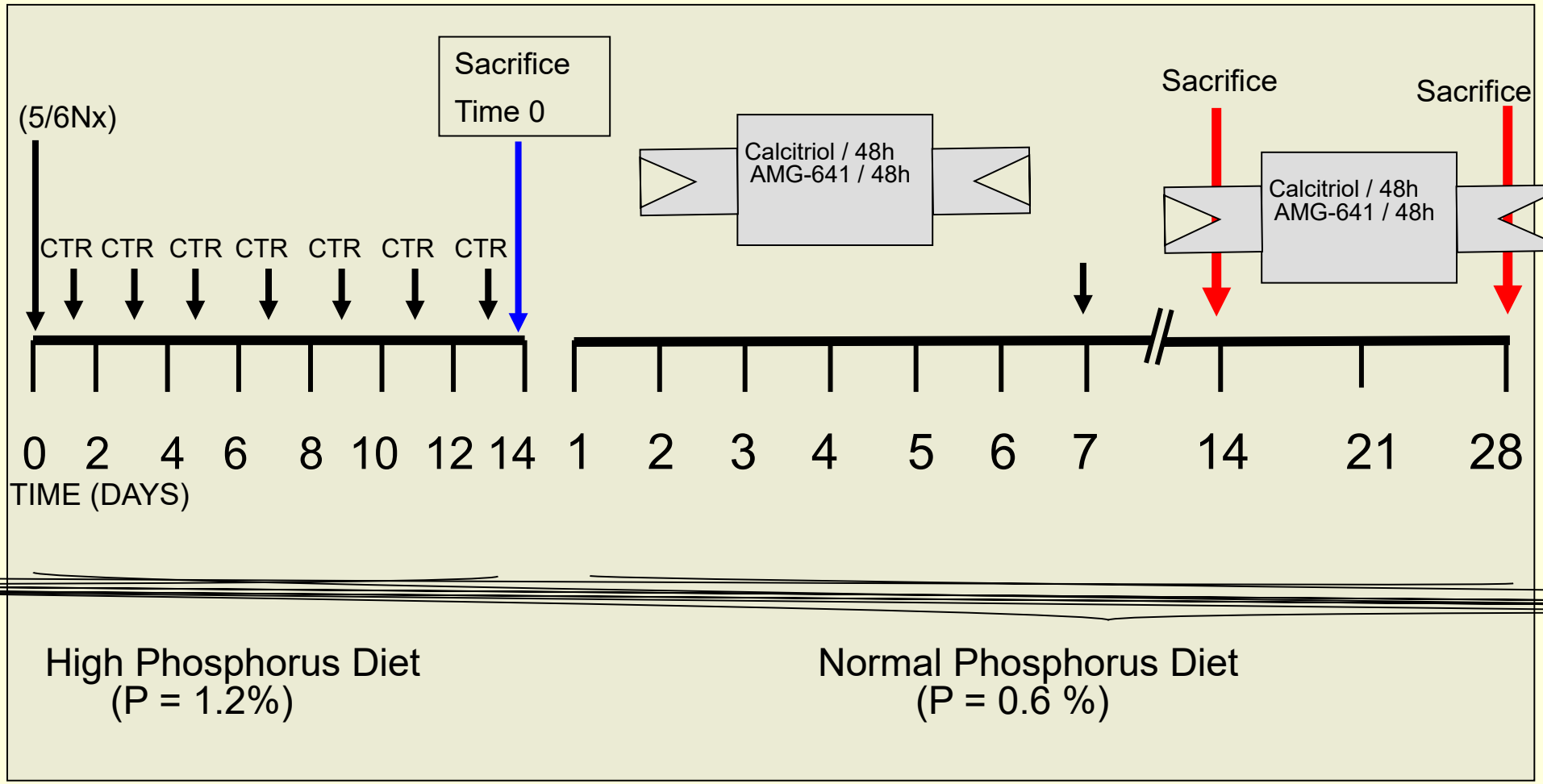


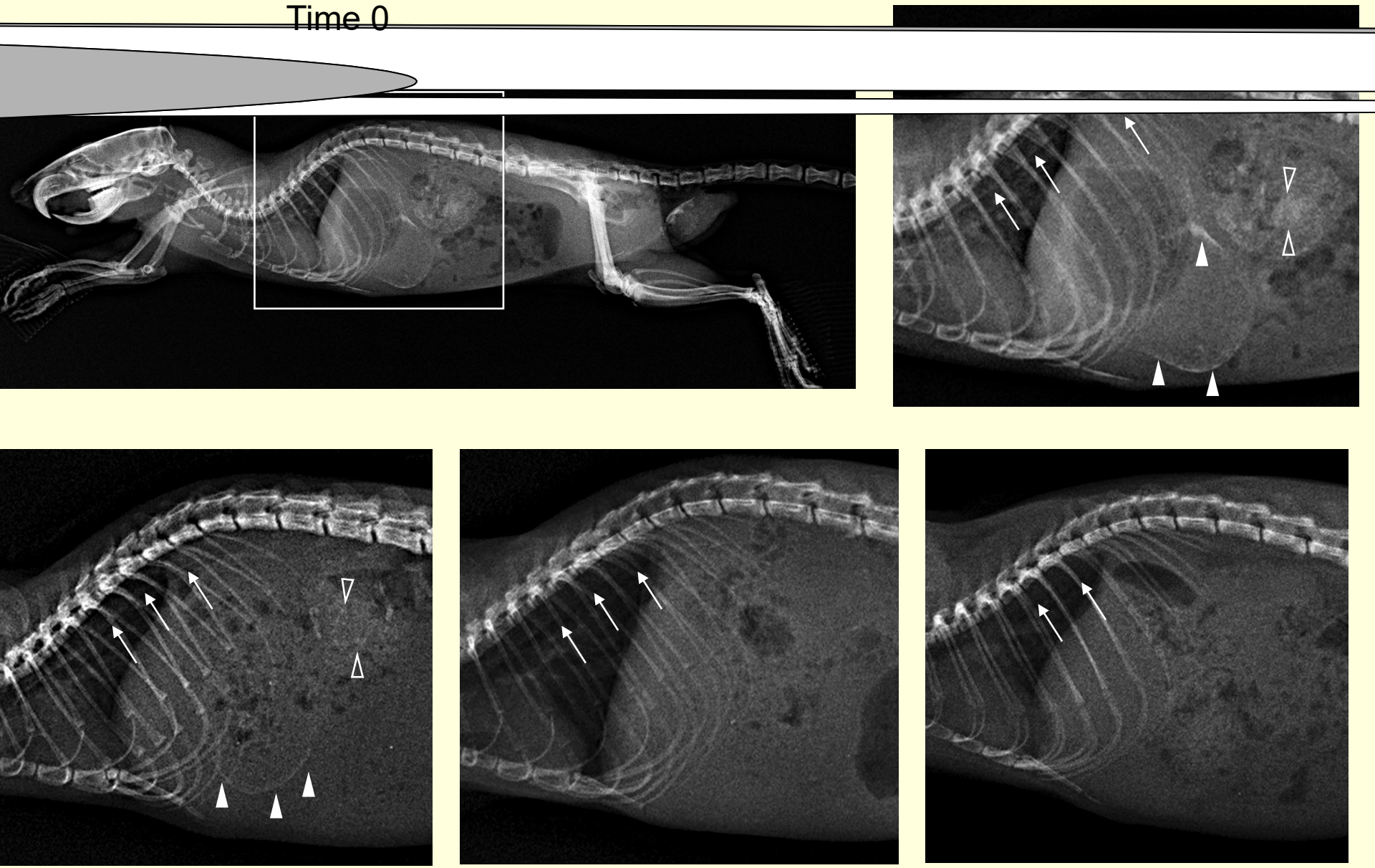
Figure 4 Mendoza et al (en AJP)

Are calcifications reversible?



Lopez I

Am J Physiol Renal Physiol. 2009 Mar 25. [Epub ahead of print] PubMed PMID: 19321594.



Lopez I

Am J Physiol Renal Physiol. 2009

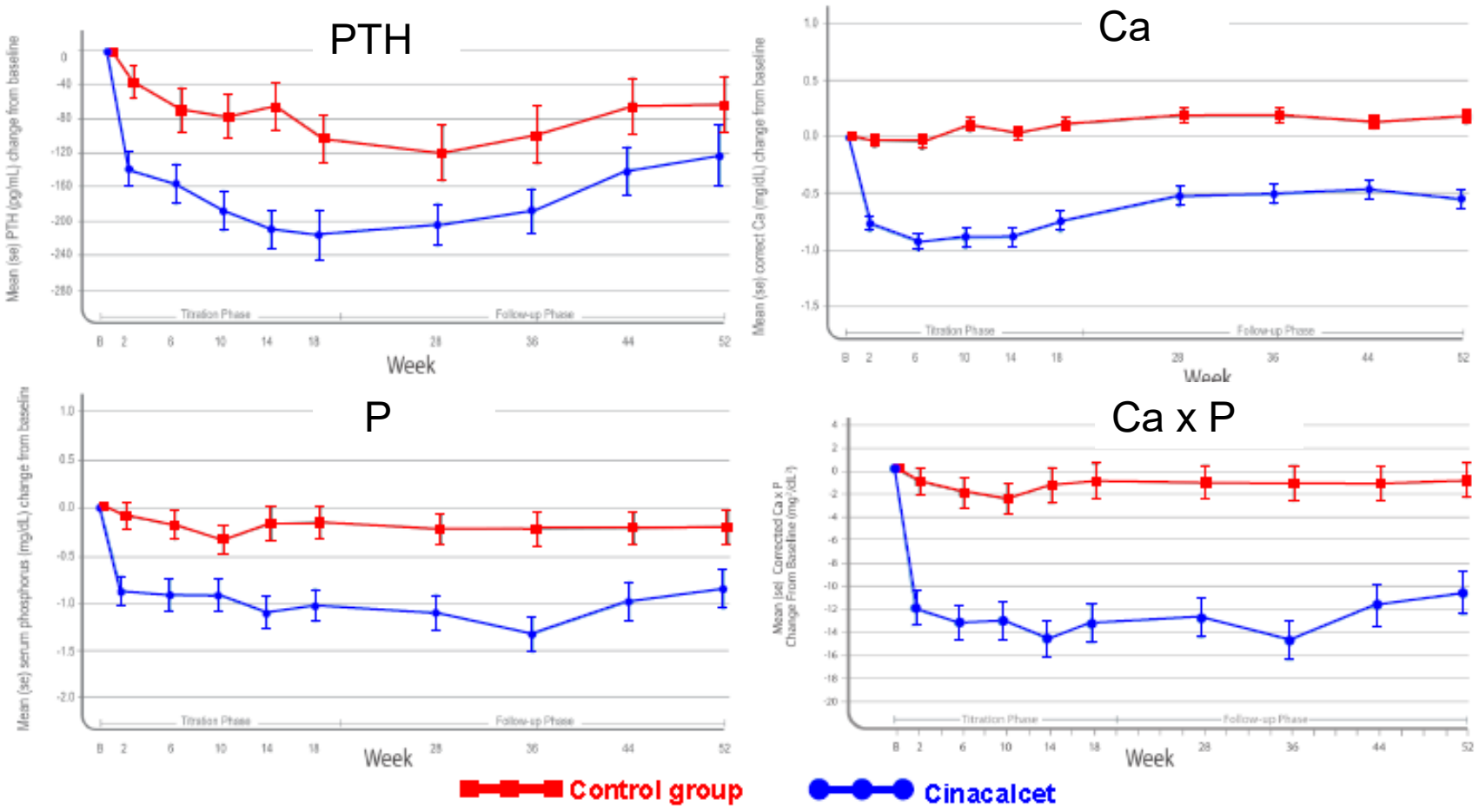
A *randomize****D*** ***VA****scular calcification****N*** *study to evaluate the effects of* ***C****inacalc****E****t*

ADVANCE

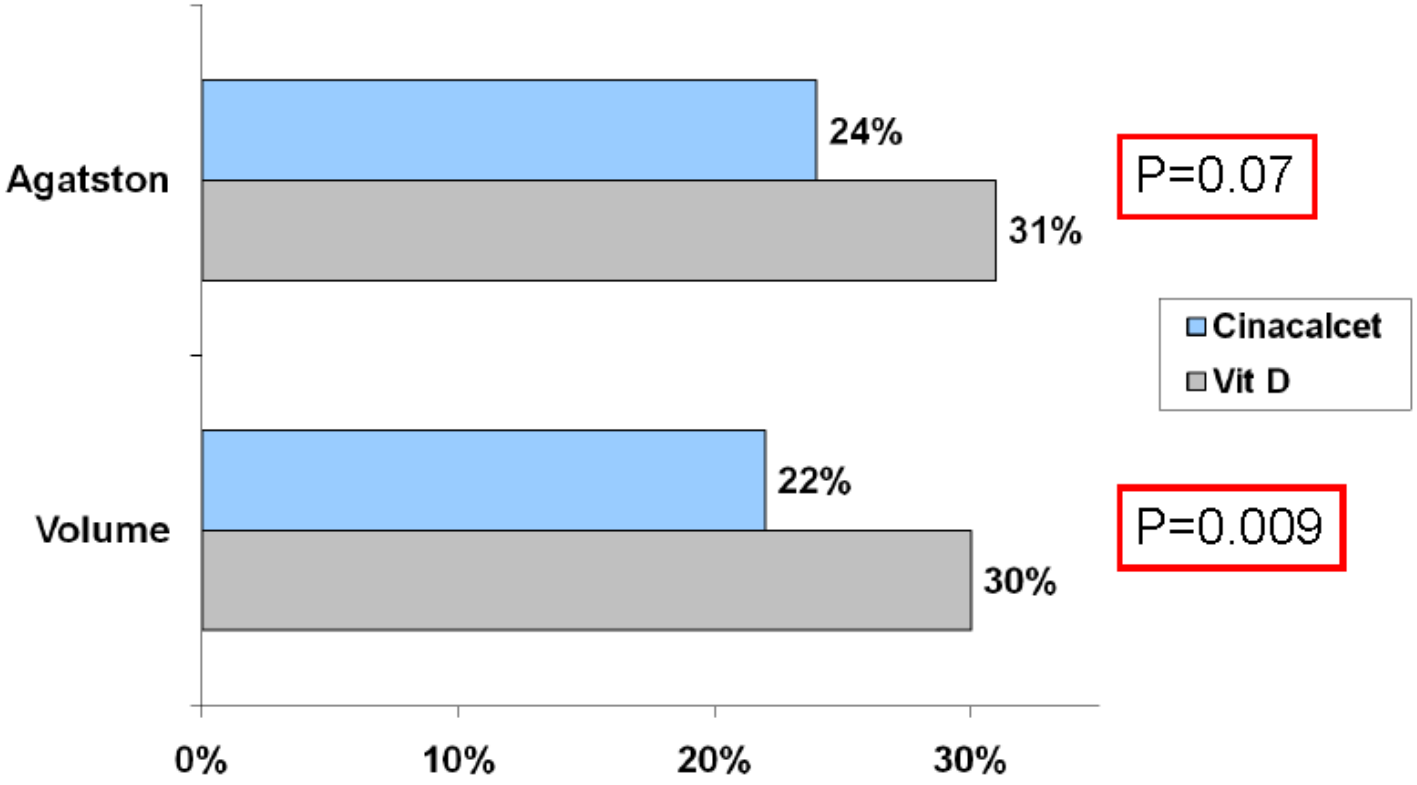
HIPOTESIS

Un régimen de tratamiento que incluya cinacalcet y dosis bajas de análogos de vitamina D atenuará la progresión de la calcificación de la arteria coronaria (CAC) durante un año, en comparación con el tratamiento convencional*, en pacientes sometidos a hemodiálisis tratados con o sin quelantes de fósforo cálcicos.

Resultados

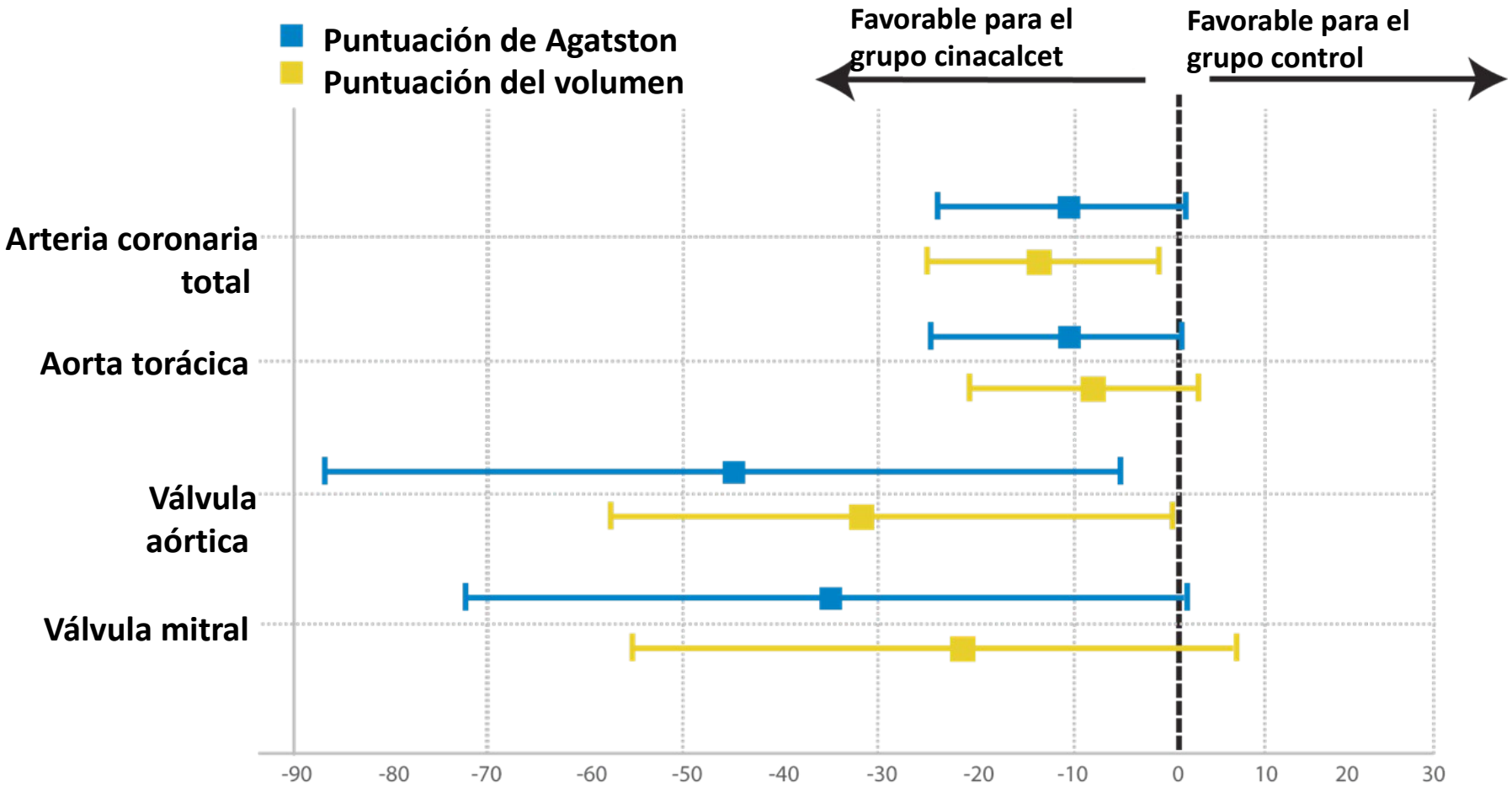

PTH
Mean (se) PTH (pg/mL) change from baseline
Titration Phase
Follow-up Phase
Week
Ca
Mean (se) correct Ca (mg/dL) change from baseline
Titration Phase
Follow-up Phase
Week
P
Mean (se) serum phosphorus (mg/dL) change from baseline
Titration Phase
Follow-up Phase
Week
Ca x P
Mean (se) Corrected Ca x P Change From Baseline (mg²/dL²)
Titration Phase
Follow-up Phase
Week
Control group
Cinacalcet

Cambio porcentual en la puntuación total de la calcificación de la arteria coronaria (CAC)



Análisis primario basado en una prueba generalizada de Cochran-Mantel-Haenszel sobre rangos.
Análisis complementario (según lo establecido en el protocolo) utilizando un modelo lineal generalizado para ajustar según el desequilibrio basal en los niveles de fósforo entre los grupos de tratamiento.

Mediana de las diferencias según tratamiento, todos los puntos



Mediana (IC 95%) de la de la diferencia del tratamiento ajustado por grupos (cambio % en la calcificación)

FRENAR CALCIFICACIÓN:

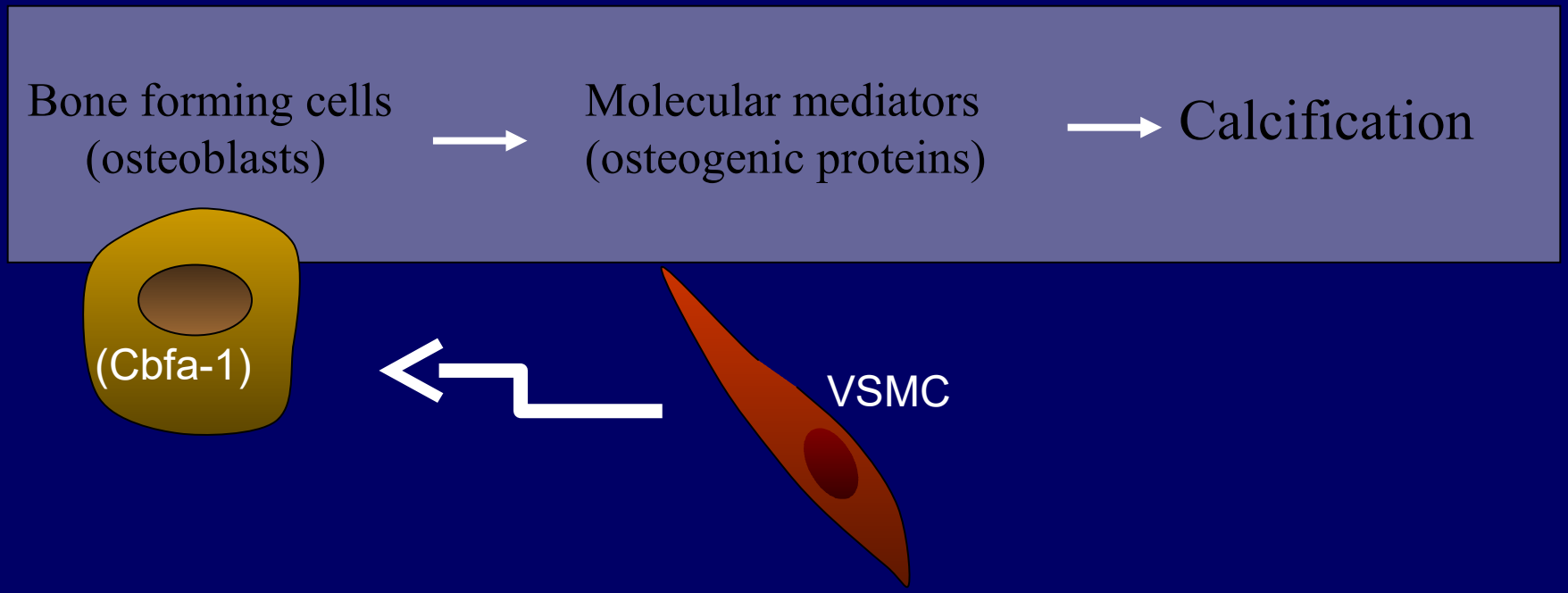
- Eliminar factores que estimulen la calcificación
- Intervenir sobre los mecanismos celulares
- Favorecer la reparación
  -reabsorción de calcificación
  -restitución (reparación) del tejido

-

VASCULAR CALCIFICATION (vascular ossification).
Essential elements:

- Cells (Bone forming cells: osteoblasts)

- Molecular mediators (osteogenic proteins)



<u>Pathogenic factors</u> of Vascular Calcification particularly relevant in uremia:

-Phosphate
-Calcium
-Calcitriol

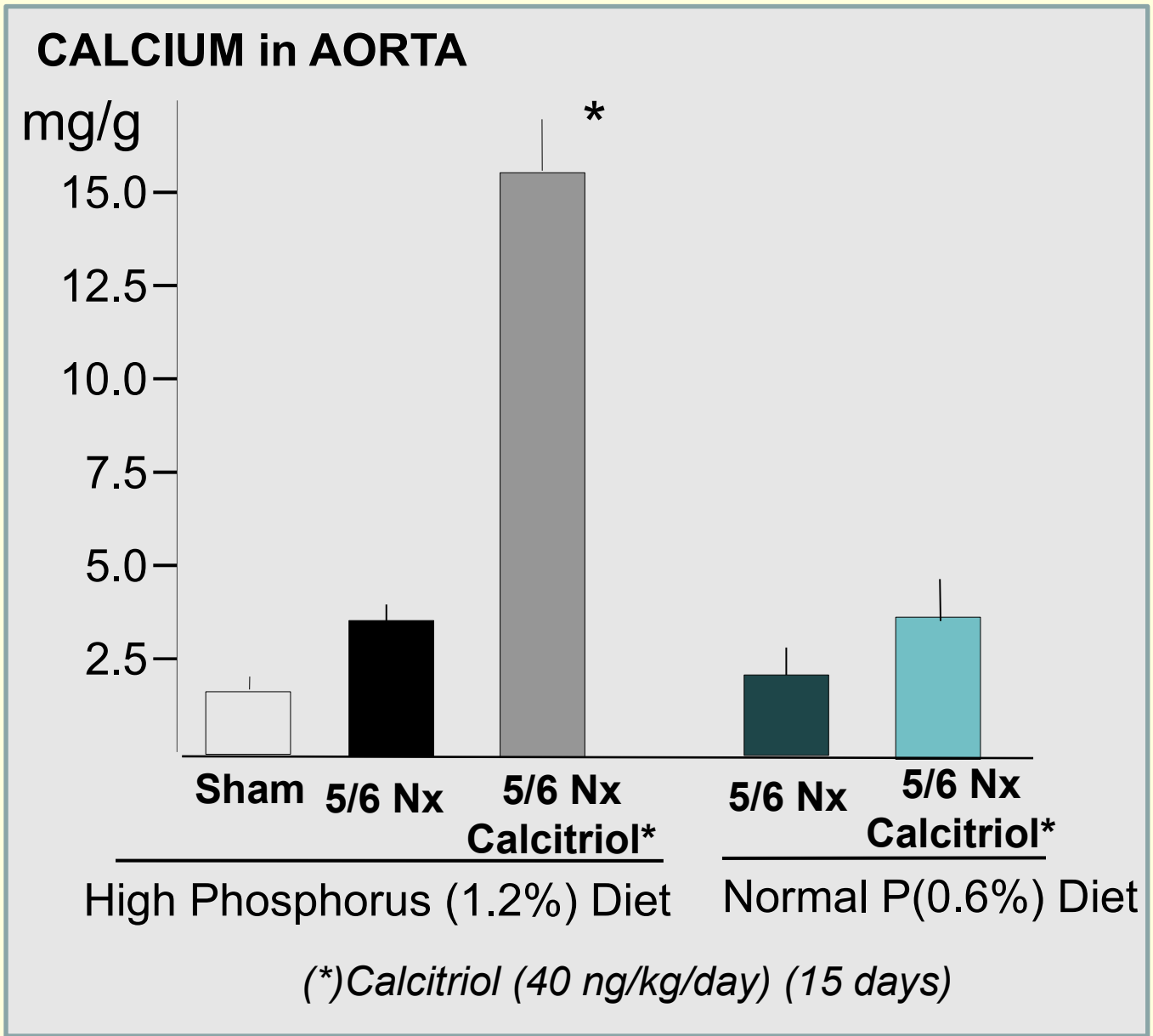
-Inflammation
-Uremic toxins
-Dyslipemia

PTH –Bone remodeling

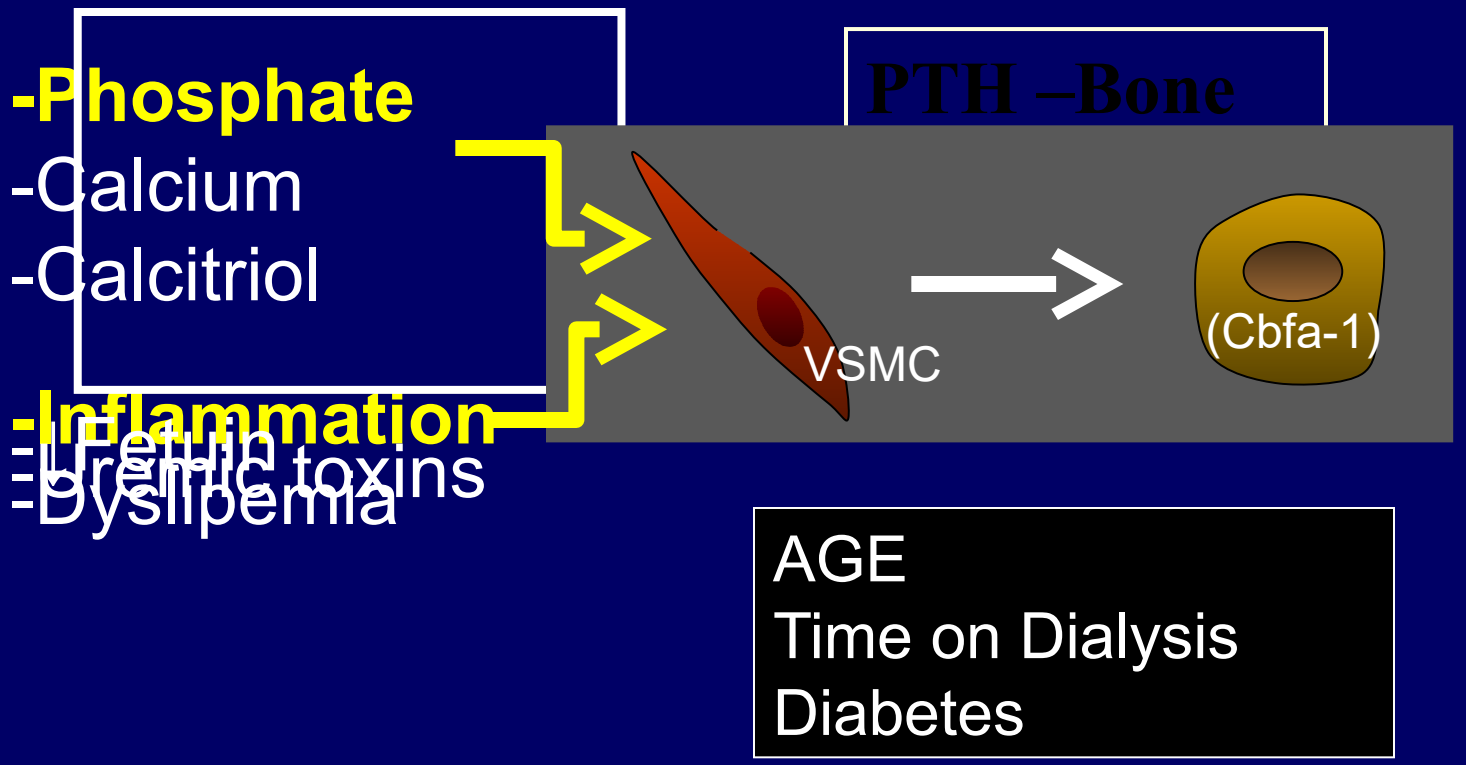
FGF23

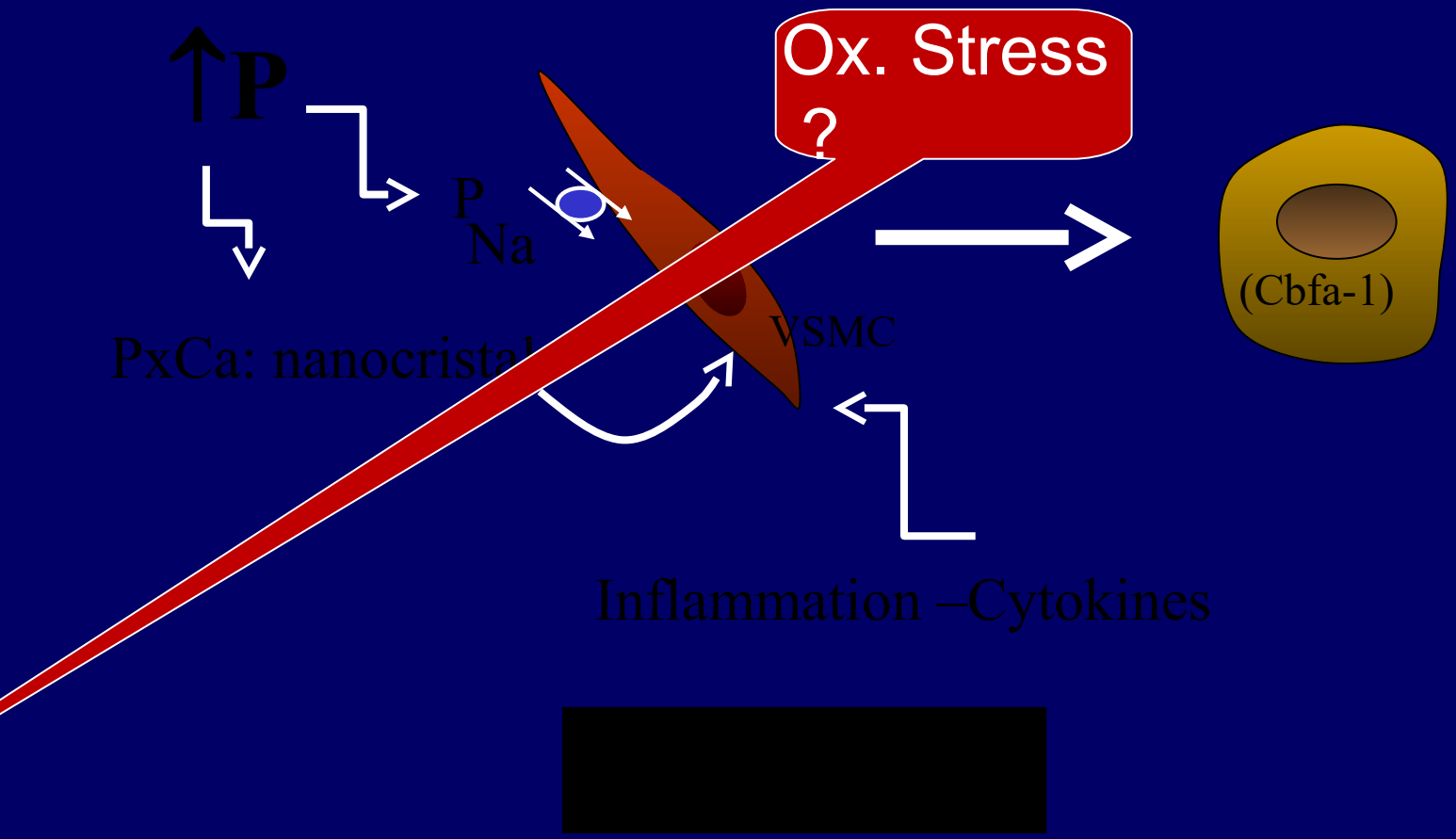
AGE
Time on Dialysis
Diabetes

Phosphate is a key factor in vascular calcification associated to vitamin D administration



Pathogenic factors of Vascular Calcification particularly relevant in uremia:

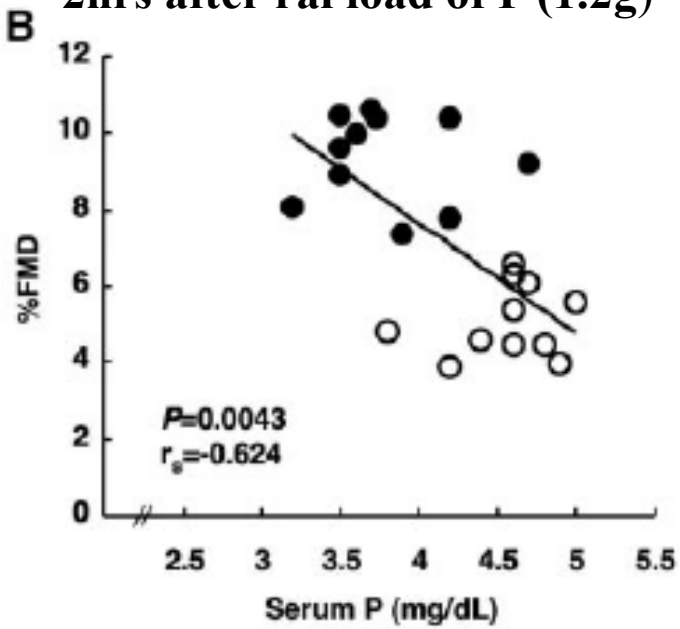



↑P
P
Na
Ox. Stress
?
(Cbfa-1)
VSMC
PxCa: nanocrista
Inflammation –Cytokines

Dietary Phosphorus Acutely Impairs Endothelial Function

Emi Shuto *J Am Soc Nephrol* 20: 1504–1512, 2009.

2hrs after ral load of P (1.2g)



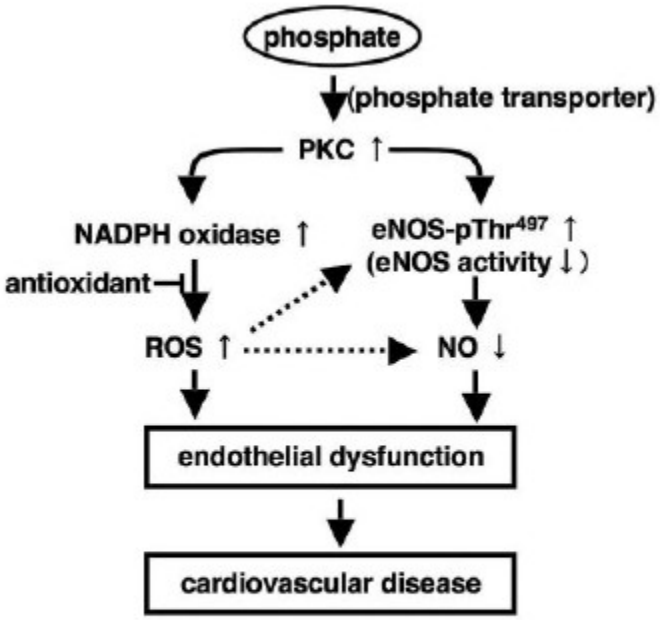


Figure 6. Possible pathway of phosphate-mediated endothelial dysfunction. High P loading increases ROS production through PKC and NAD(P)H oxidase in endothelial cells. In addition, high P loading also decreases NO production through phosphorylation of eNOS. Increased ROS production and decreased NO production may cause endothelial dysfunction and CVD.

Soluble klotho decreases oxidative stress in senescent endothelial cells
(work submitted)

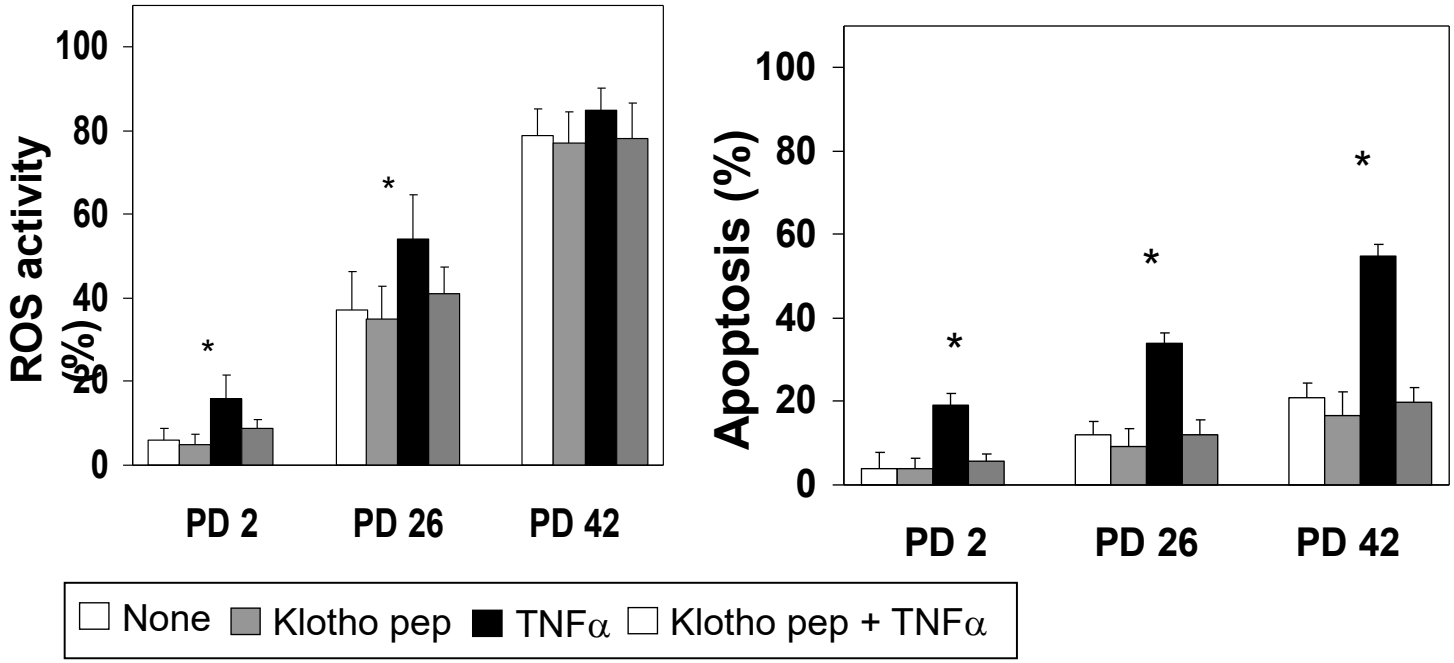
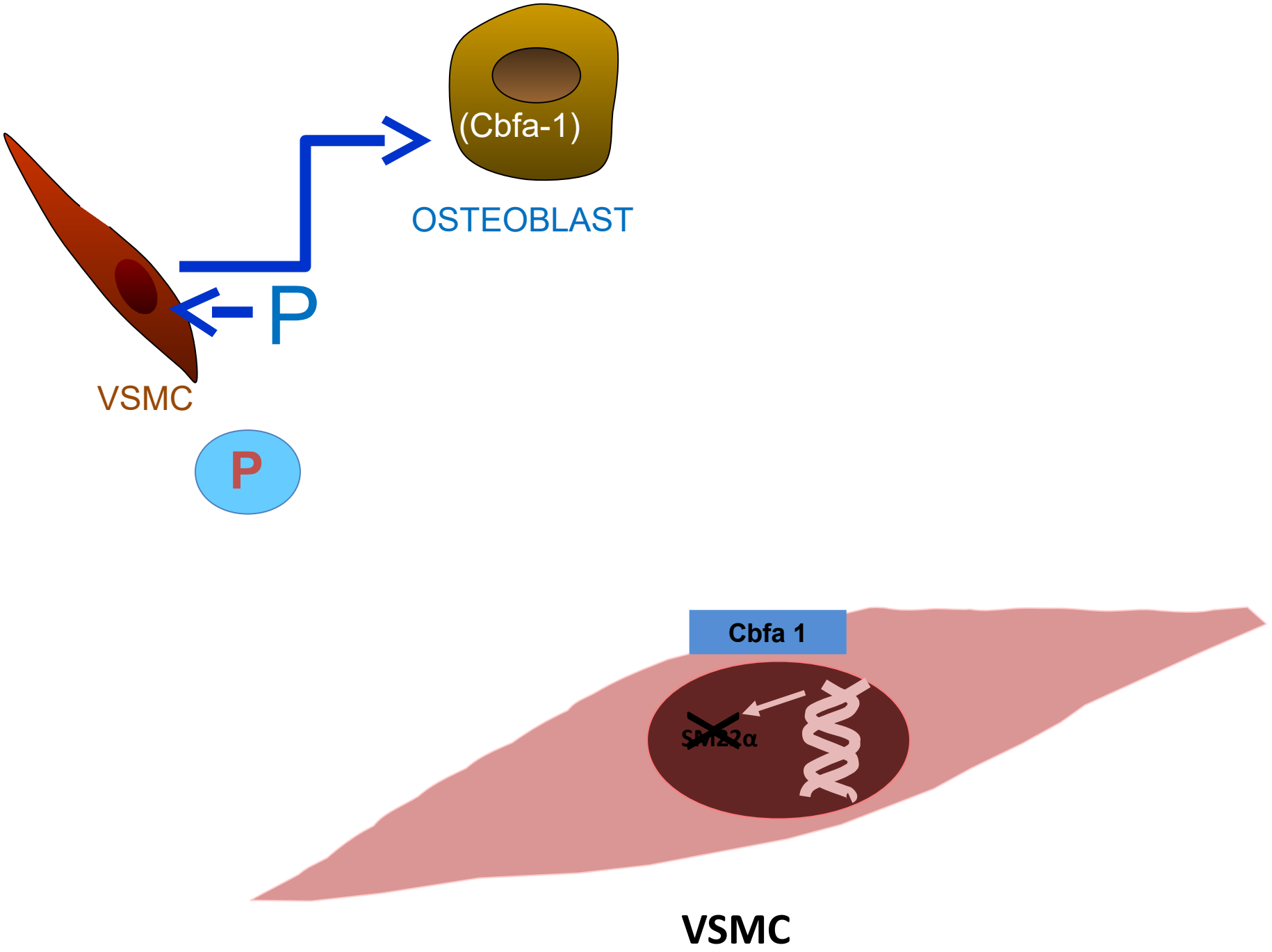
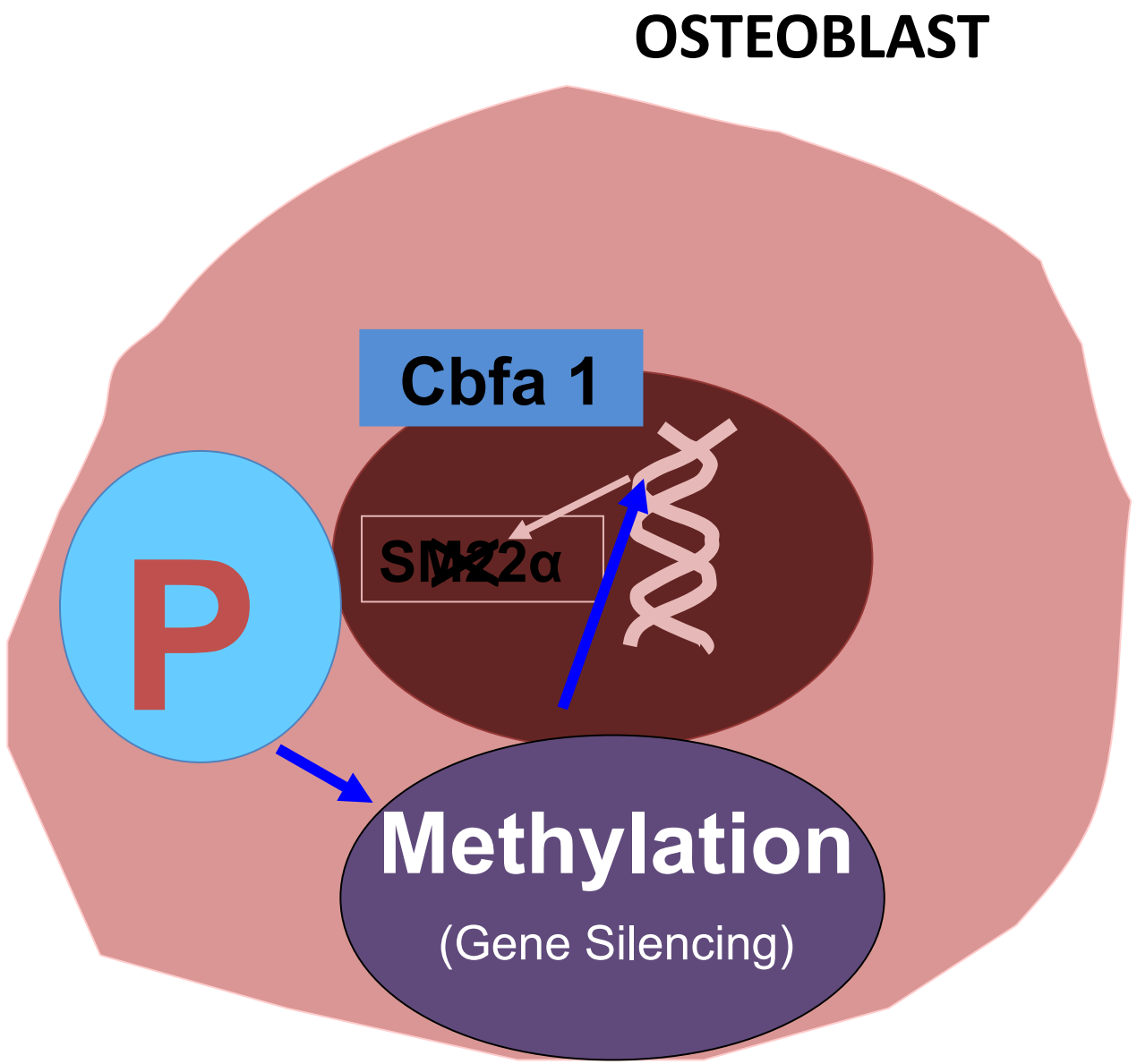


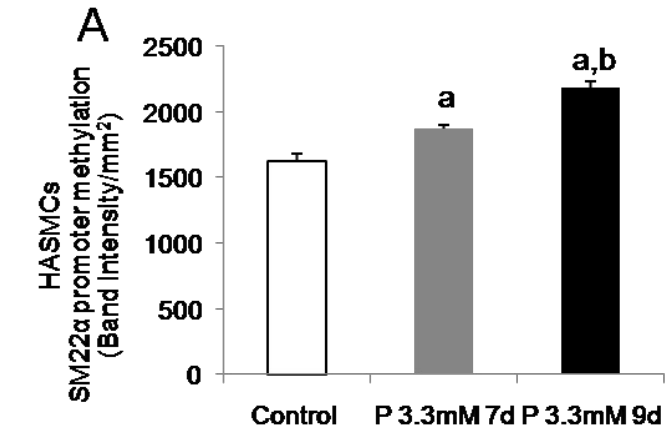
Figure 6


(Cbfa-1)
OSTEOBLAST
P
VSMC
P
Cbfa 1
SM22α
VSMC


OSTEOBLAST
Cbfa 1
SMAD2α
P
Methylation
(Gene Silencing)

High phosphate induces methylation of SM22α promoter

SM22α promoter methylation



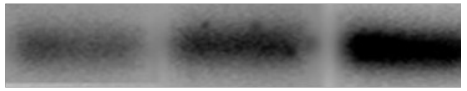
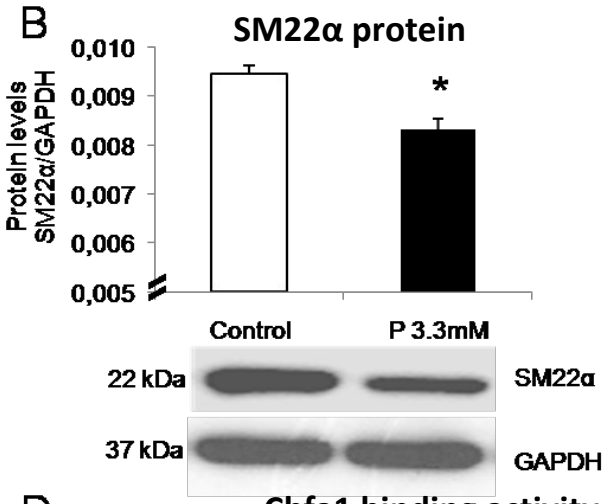
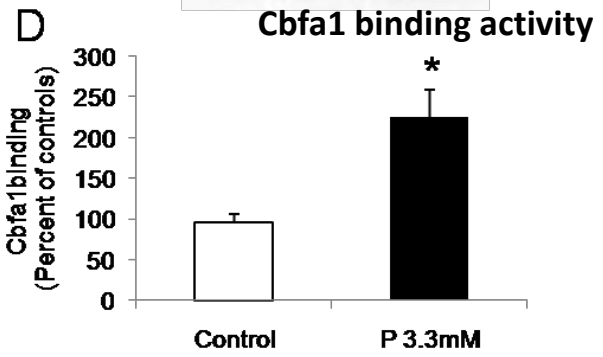
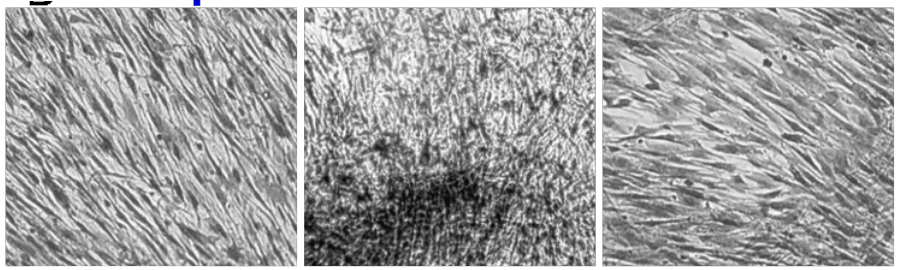


Fig. 2.

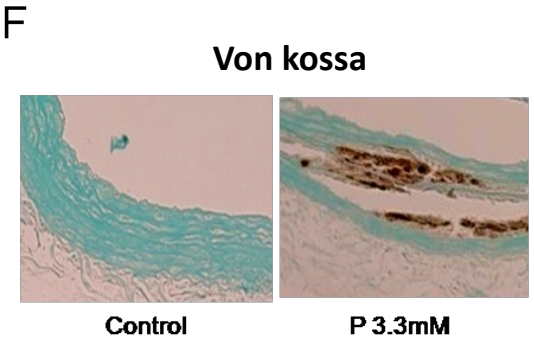




Inhibition of Methylation prevents Calcification



Control P P + Procaine (1mM) (methylation inhibitor)



Montes de Oca
J Bone Miner Res 2010
25(9):1996-2005.

methylation of the SM22α promoter causes calcification (independent of phosphate)

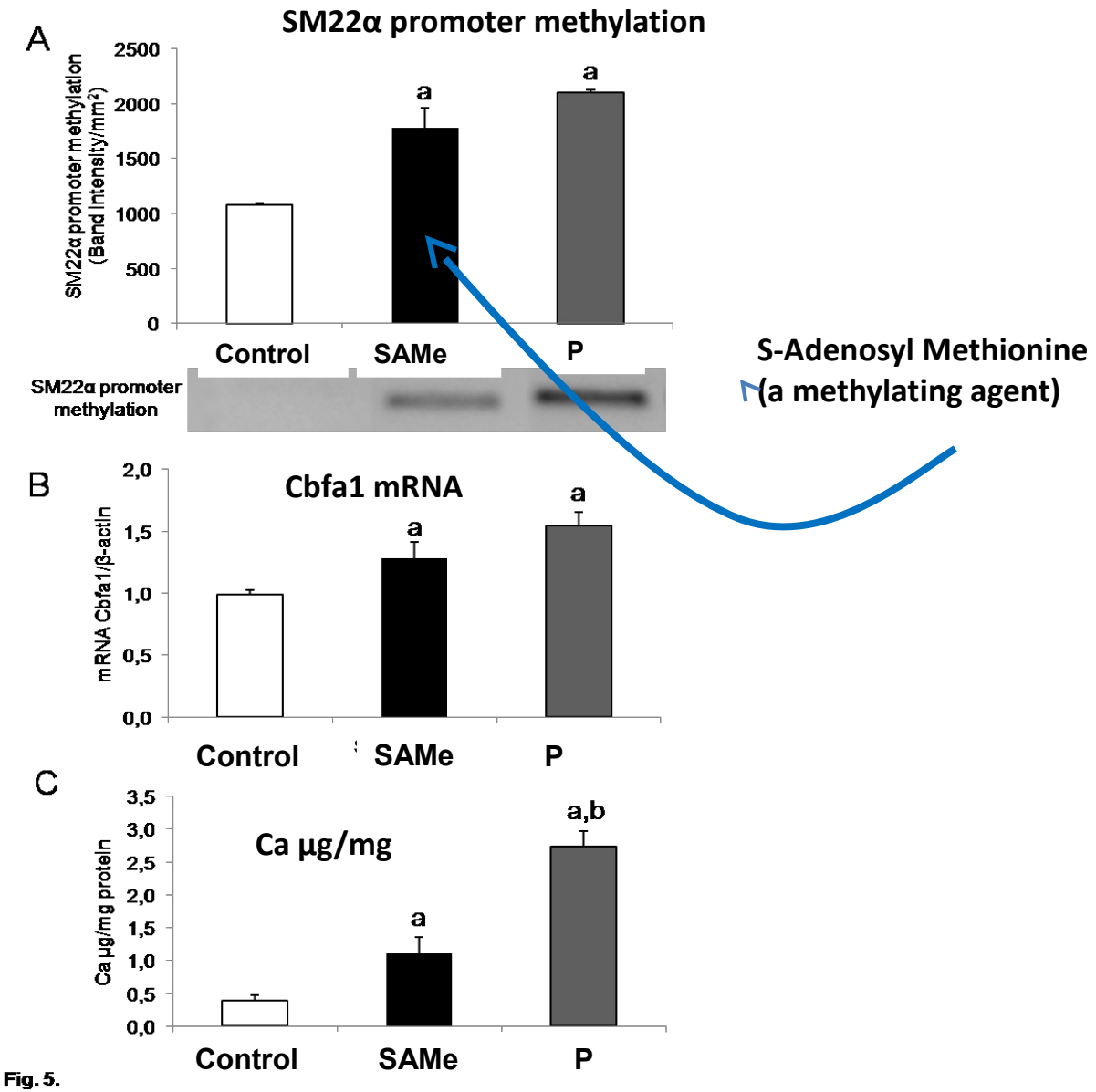


Fig. 5.

Outcomes of SiRNA knockdown of SM22α on Cbfa1 expression in HASMCs

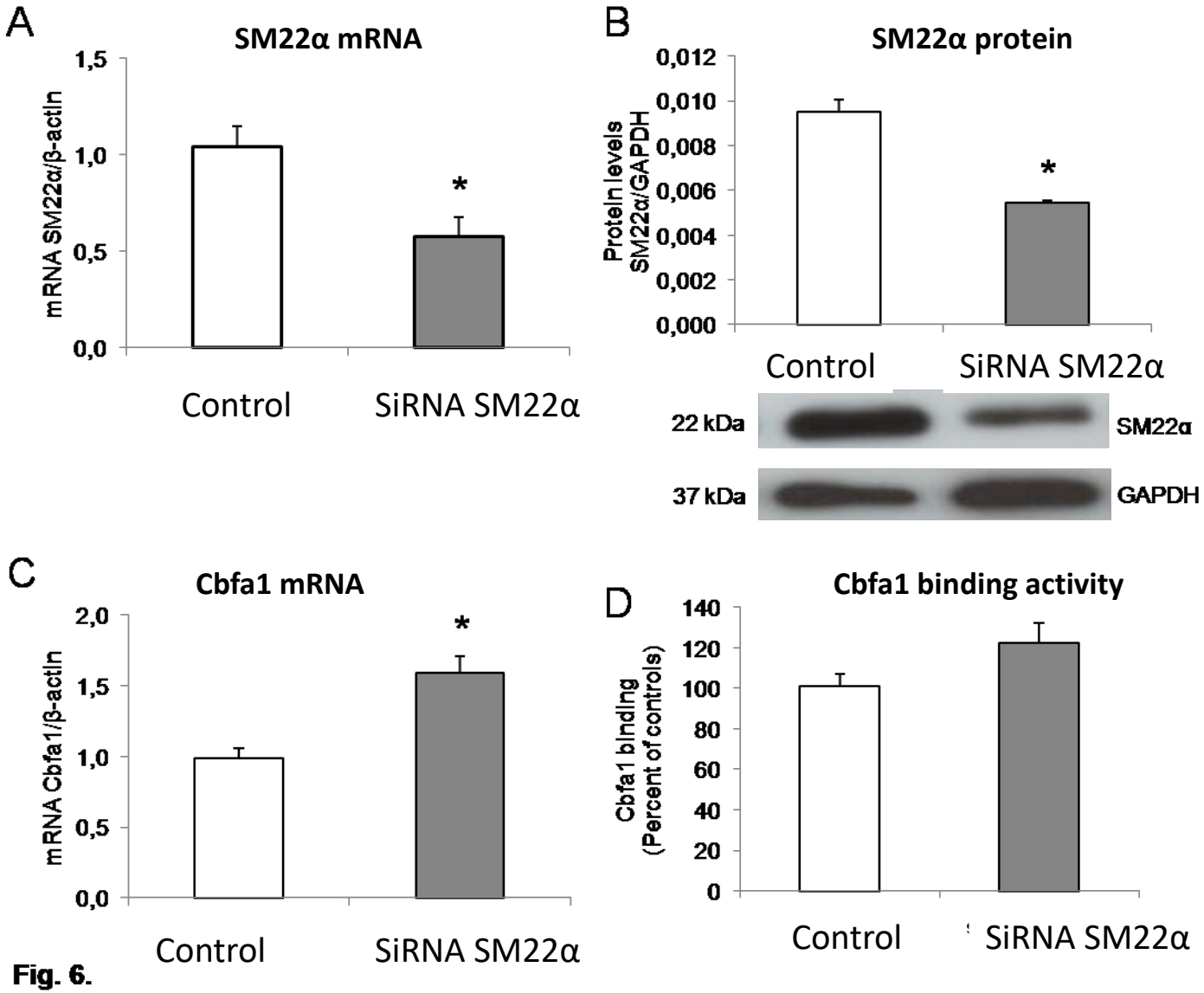


Fig. 6.

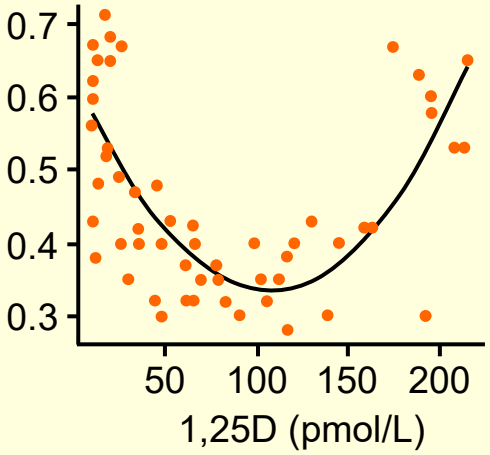
CLINICAL RESEARCH www.jasn.org

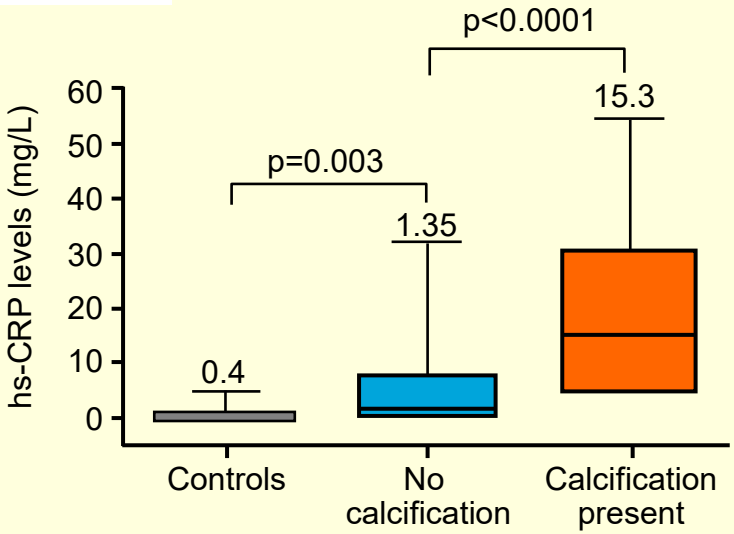
A Bimodal Association of Vitamin D Levels and Vascular Disease in Children on Dialysis

Rukshana Shroff,*† Martyn Egerton,‡ Michala Bridel,‡ Vanita Shah,* Ann E. Donald,† Tim J. Cole,§ Melanie P. Hiorns,‖ John E. Deanfield,† and Lesley Rees*

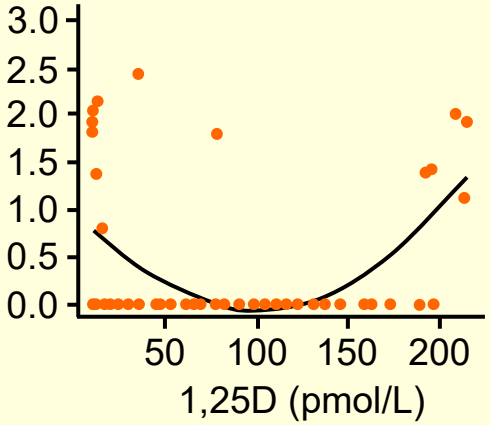
J Am Soc Nephrol 19: 1239–1246, 2008.

Carotid intima media thickness

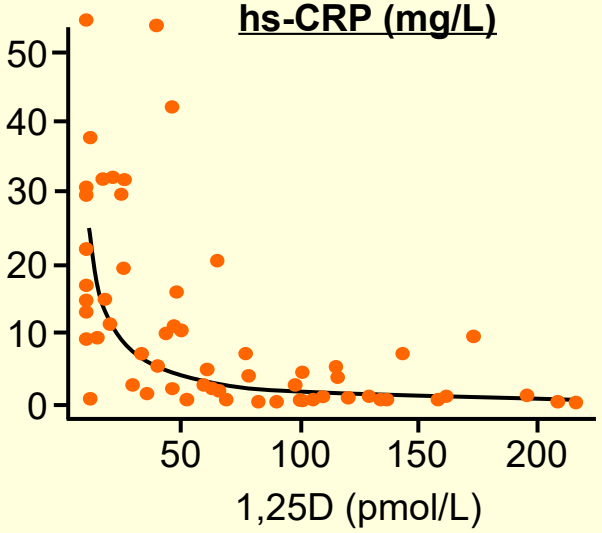




Log calcification score +1



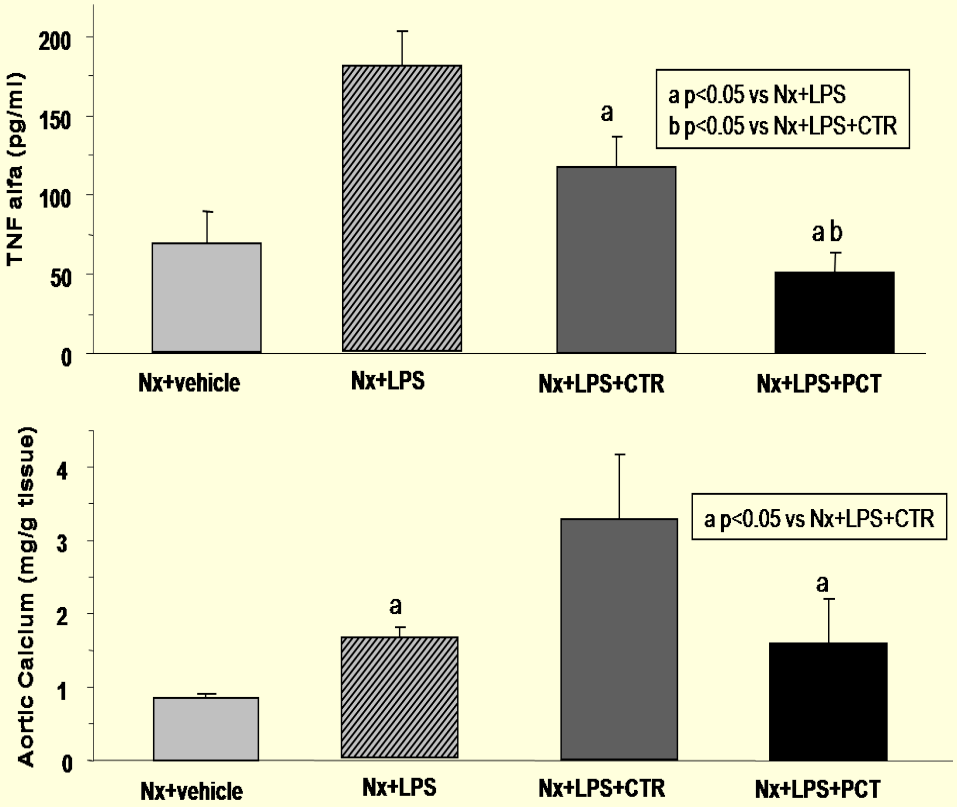
hs-CRP (mg/L)



The effect of vitamin D derivatives on vascular calcification in uremic rats treated with LPS

Guerrero F,1 Montes de Oca A,1 Aguilera-Tejero E,1 Zafra R, 2 Rodríguez M,3 López I1

5/6Nx, High P diet (P:0.9%, Ca:0.8%)
LPS daily
-Calcitriol(1,25D3)= 80ng/kg (3/week)
-Paricalcitol(19-nor) = 240ng/kg (3/week)



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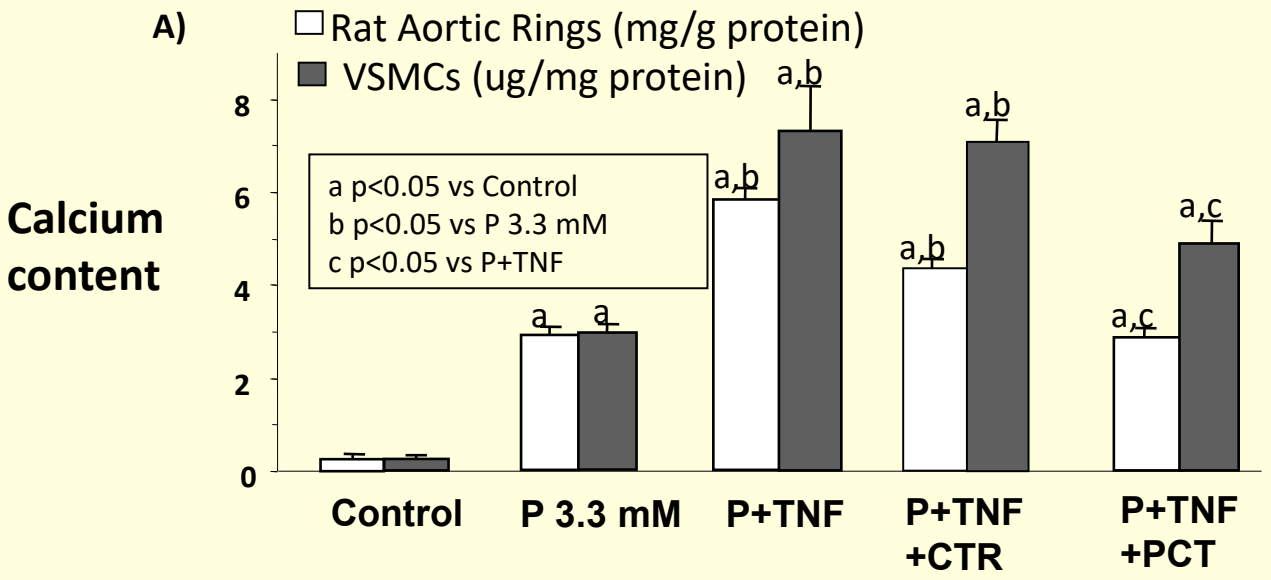
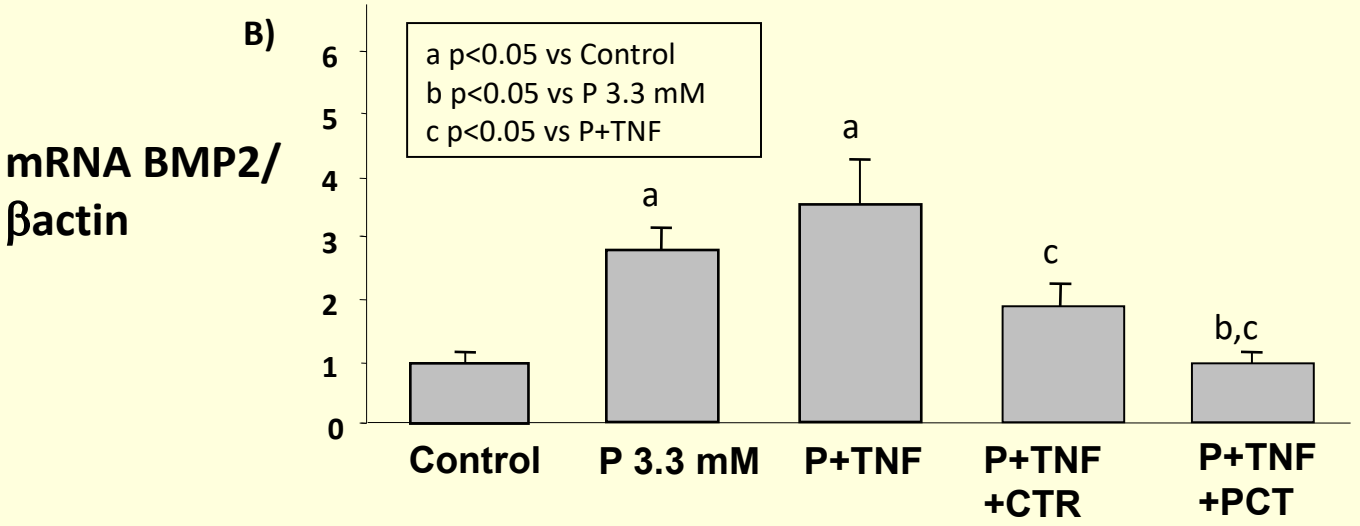
Guerrero F,1 Montes de Oca A,1 Aguilera-Tejero E,1 Zafra R, 2 Rodríguez M,3 López I1





Gracias