Calcificación vascular marcador subrogado
¿El tratamiento es imposible?

¿Debemos valorar las calcificaciones vasculares?
Orense, Octubre 2016

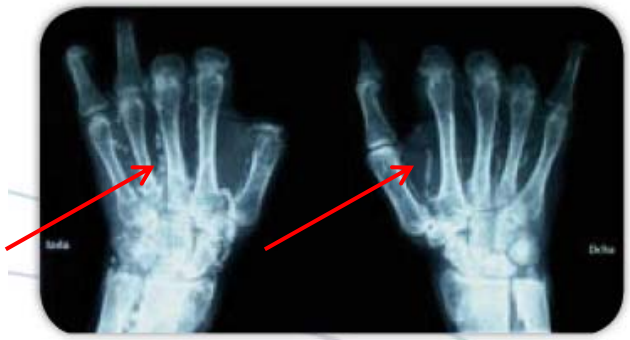
Jordi Bover

Fundació Puigvert

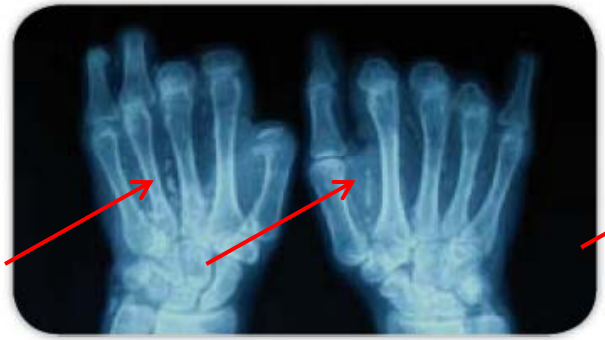
Barcelona

Catalonia, Spain

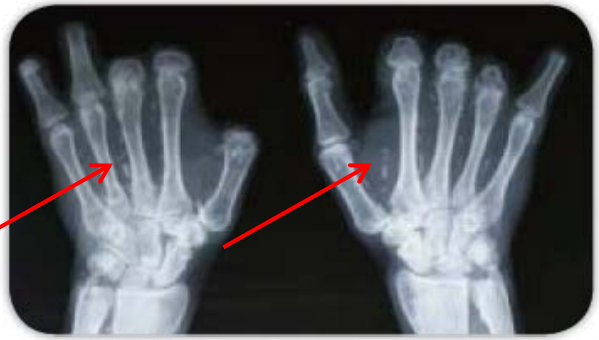
Efecto de cinacalcet sobre las calcificaciones vasculares y de tejidos blandos en pacientes con HPS en diálisis



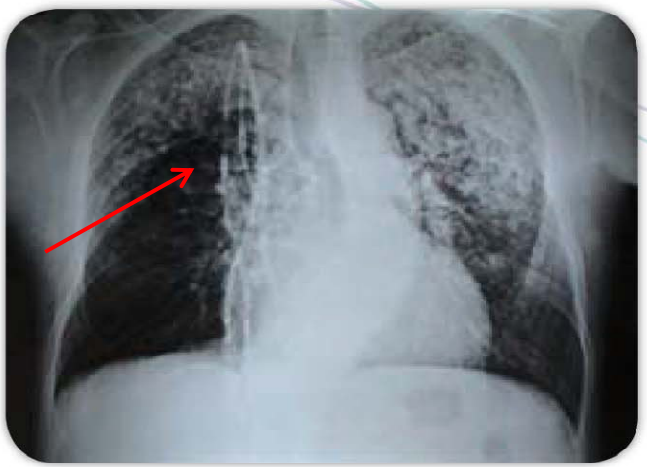
Radiografía de manos basal



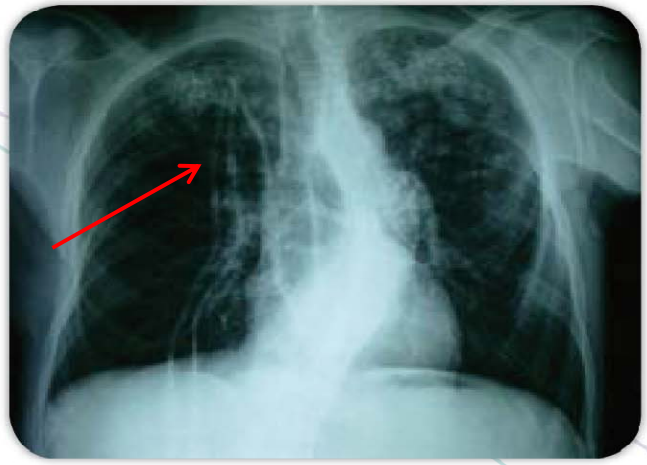
Radiografía de manos 12 meses



Radiografía de manos 24 meses



Radiografía de tórax basal



Radiografía de tórax 24 meses

M.J. Aladrén Regidor Clinical Nephrology 2009;71:207-213

AMGEN

Efecto de cinacalcet sobre la rigidez arterial en pacientes con HPTS

- Tras 12 meses de tratamiento, se redujeron de forma significativa tanto los niveles de PTH como de fosfatasa alcalina, así como se disminuyó la rigidez arterial en el 81% de los pacientes

PARÁMETRO	BASAL	1 AÑO	Valor P
Ca, mmol/l	2,5 (0,1)	2,4 (0,2)	ns
P, mmol/l	2 (1)	1,9 (1,2)	ns
Fosfatasa Alcalina , U/l	168,5 (79,6)	124,8 (72,8)	<0,001
PTH, pg/l	1007,9 (846,7)	341,6(264,7)	<0,001
Presión arterial diástolica periférica, mmHg	83,5 (13,2)	77,3 (14,2)	**<0,051**
Velocidad Onda Pulso (PWV) , m/sc	9,3 (1,8)	8,6 (1,8)m/sc	**<0,03**

AMGEN

ERC es un factor independiente de riesgo CV

Envejecimiento acelerado

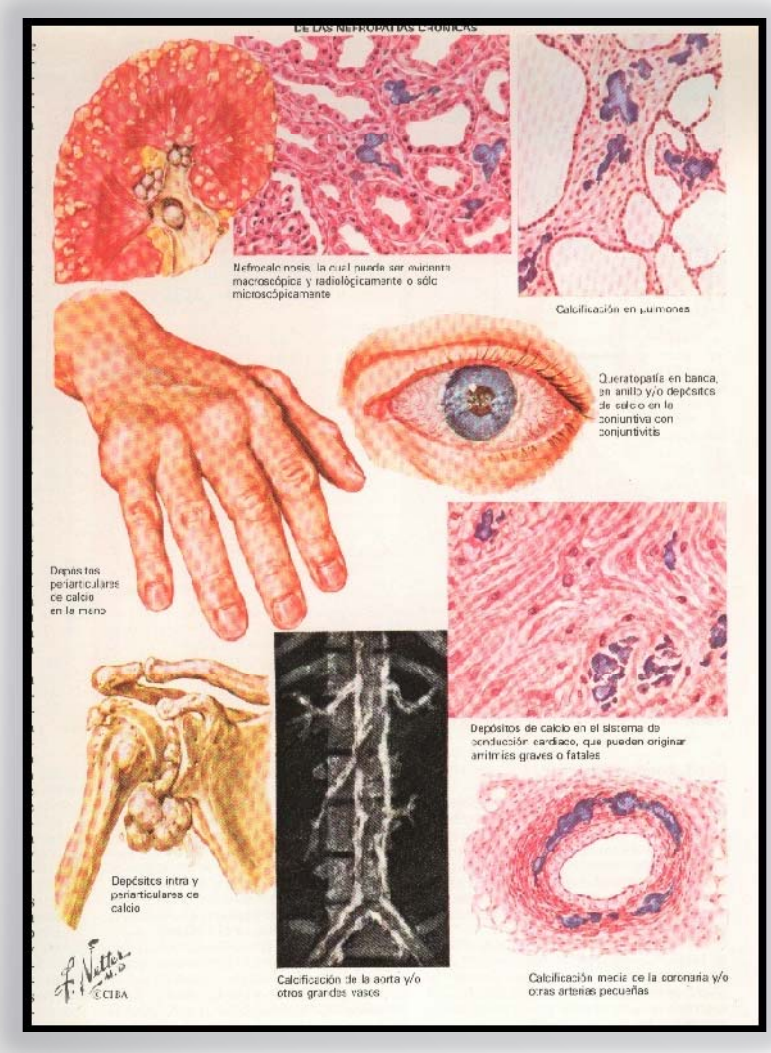
Ateromatosis y Calcificación acelerada

FR tradicionales

No tradicionales

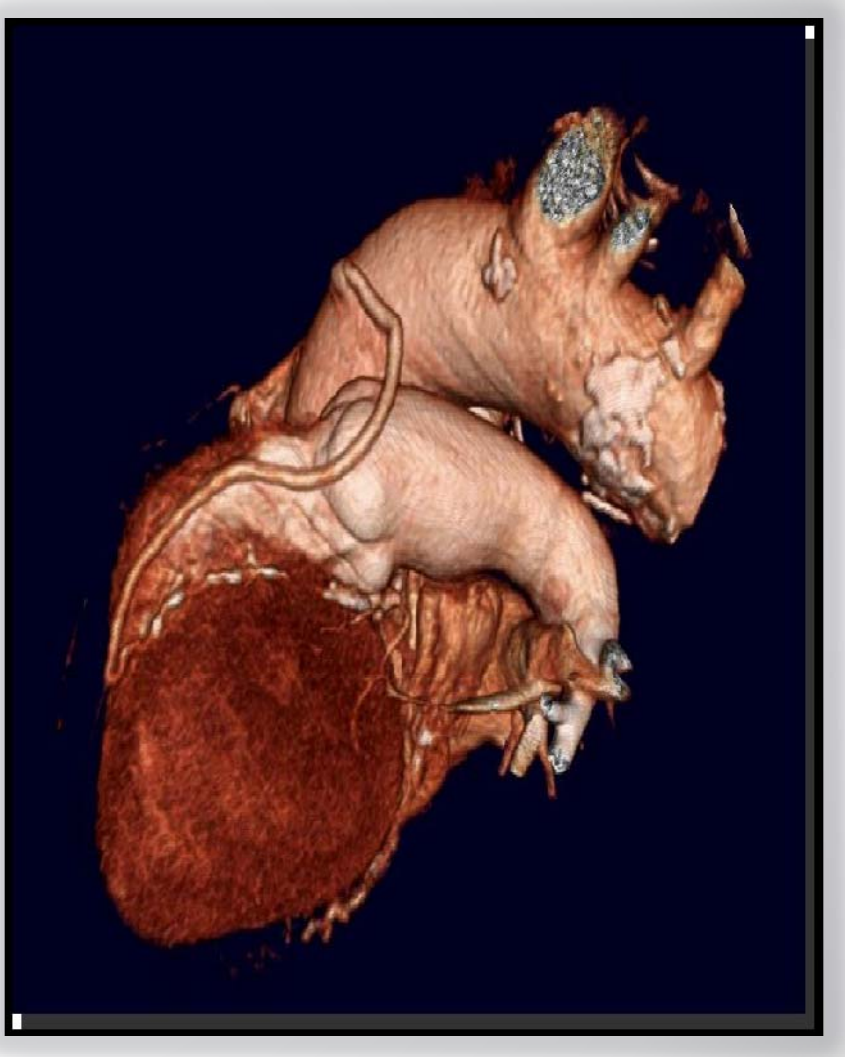
Burden CV disease, mortality, Cancer

ERC: Calcificación sistémica



Netter 70's

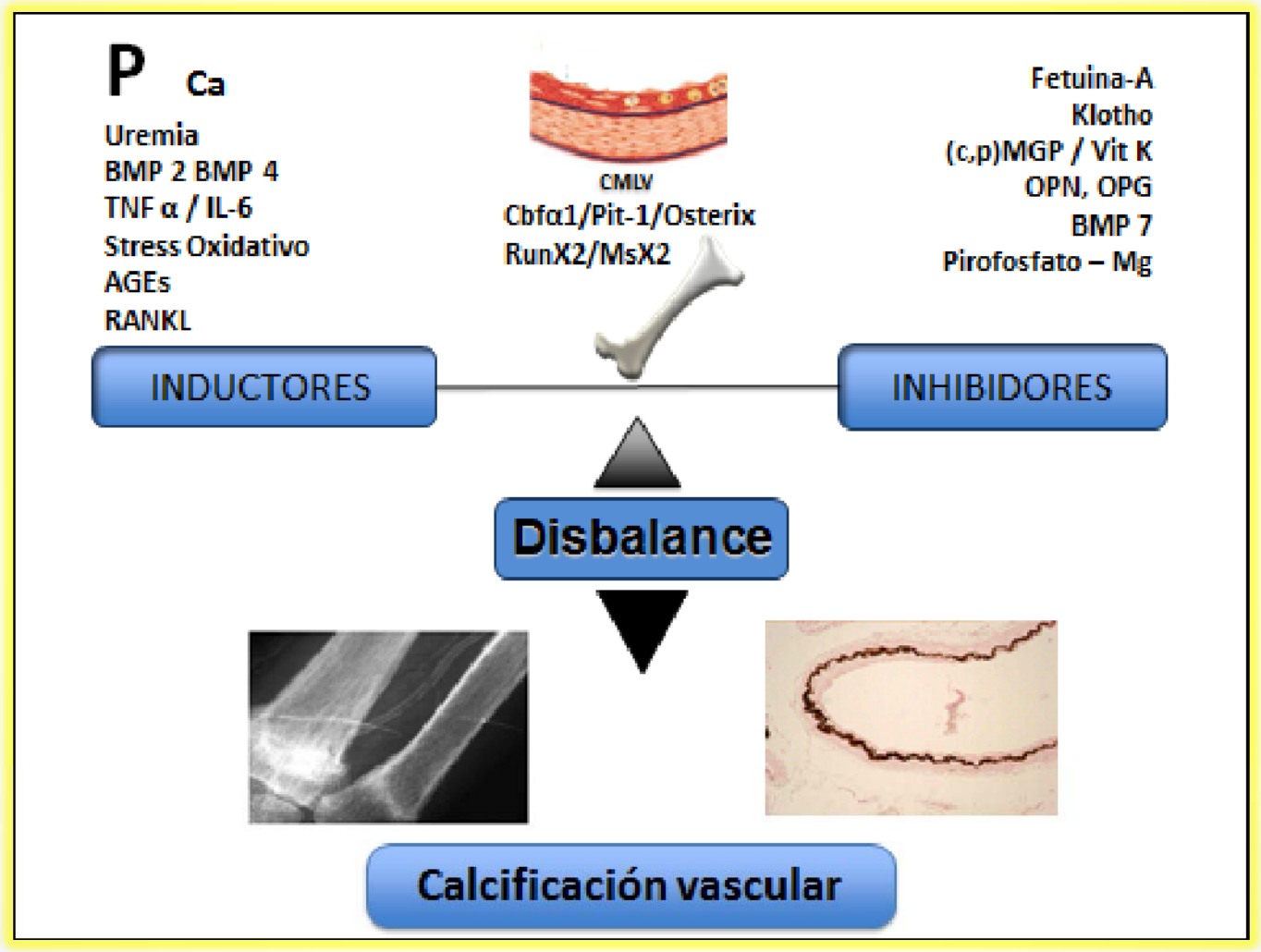
MDCT
EBCT



Cortesía Cardiology Dpt, HSCySP, Barcelona

Osificación de los vasos (activa y pasiva)

CALCIFICACIÓN-OSIFICACION VASCULAR PASIVA Y ACTIVA



Lloret M.J, Bover J. et al. Nefrologia Sup 2013;4(2):2-10

nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

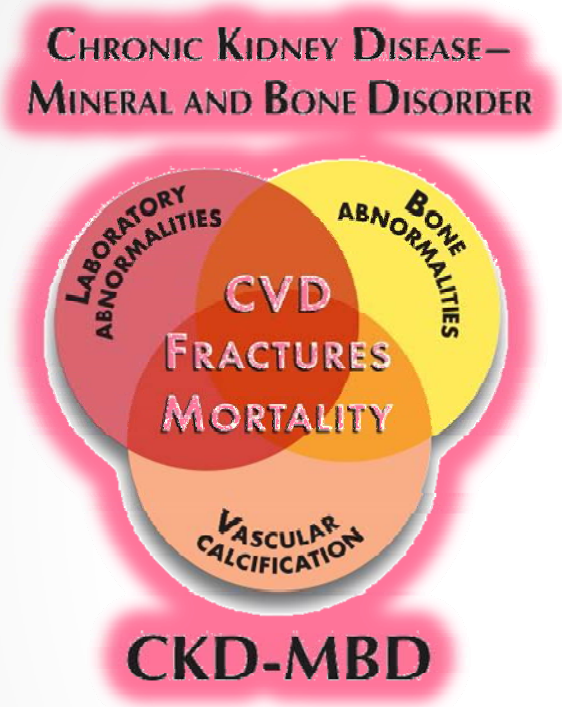
Detección de las calcificaciones cardiovasculares: ¿una herramienta útil para el nefrólogo?

Jordi Bover[a,*], *José Luis Górriz*[b], *Pablo Ureña-Torres*[c], *María Jesús Lloret*[a], *César Ruiz-García*[a], *Iara daSilva*[a], *Pamela Chang*[a], *Mariano Rodríguez*[d] y *José Ballarín*[a]

Calcificaciones cardiovasculares en la enfermedad renal crónica: Potenciales implicaciones terapéuticas

Jordi Bover[a,*], *Pablo Ureña-Torres*[b,c], *José Luis Górriz*[d], *María Jesús Lloret*[a], *Iara da Silva*[a], *César Ruiz-García*[a], *Pamela Chang*[a], *Mariano Rodríguez*[e] y *José Ballarín*[a]

CKD–MBD: Alteración (síndrome?) sistémico



CKD-MBD

Chronic-Kidney Disease-Mineral and Bone Disorder
ERA-EDTA Working Group

- **Eje Riñón–Hueso**
- **Eje Hueso-Vaso**

Bone: a new endocrine organ at the heart of chronic kidney disease and mineral disorders

*Marc G Vervloet, Ziad A Massy, Vincent Brandenburg, Sandro Mazzaferro, Mario Cozzolino, Pablo Ureña-Torres, Jordi Bover, David Goldsmith, on behalf of the CKD-MBD Working Group of ERA-EDTA **

KDIGO GUIDELINES on vascular calcification (2009)

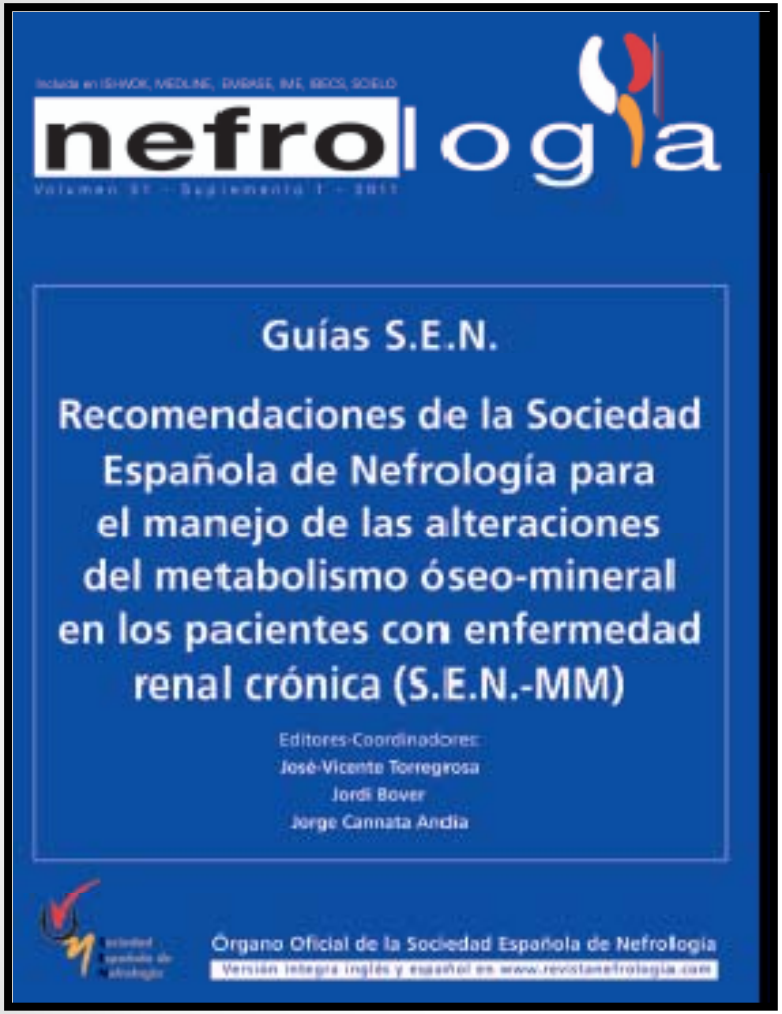
3.3.1 In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging (2C).

3.3.2 We suggest that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide the management of CKD–MBD (not graded).

VC and progression are predictive of outcomes with any imaging Rapid limited value of Framingham scoring

KDIGO Kidney Int 2009;76(Suppl 113):S3-S8

2011 Recomendaciones SEN



Sociedad Española de Nefrología

It is reasonable to screen ALL patients with CKD and it is reasonable to use this Information to guide managemet

- **Lateral Abdominal XR (Kauppila)**
- **Hands and pelvis (Adragao):**
- **Ecocardiography**
- **Ultrasonography**
- **Thorax XR**
- **Breast arterial calcification**
- **PWV, ABI**
- **PP** (CAC correlation?)

- **MDCT-scan**
- **EBCT**

} **Research purposes**

PRO: CARDIOVASCULAR CALCIFICATIONS ARE CLINICALLY RELEVANT

Jordi Bover[1], Pieter Evenepoel[2], Pablo Ureña-Torres[3], Marc G. Vervloet[4], Vincent Brandenburg[5], Sandro Mazzaferro[6], Adrian Covic[7], David Goldsmith[8], Ziad A. Massy[9,10], Mario Cozzolino[11]

NDT pro-con debate

CKD-MBD
Chronic-Kidney Disease-Mineral and Bone Disorder
ERA-EDTA Working Group

Depending on the available resources, screening for CV calcifications should be performed in all CKD patients at first presentation and at regular intervals or only in selected cases (e.g. from incident dialysis patients considered for renal transplantation to any patient in whom the caring physician decides that knowledge of the presence of VC may impact a therapeutic decision).

Screening for VC fits in the paradigm of personalized medicine; at present not ready for prime time but eager to jump in.

Nephrol Dial Transplant 2015

CON: Vascular calcification is a surrogate marker, but not the cause of ongoing vascular disease, and it is not a treatment target in CKD

Carmine Zoccali and Gerard London

NDT pro-con debate

To maximize health benefits, the approach to vascular disease in CKD patients should focus on the prevention of arterial lesions by correcting the several, traditional and non-traditional, pro-atherogenic risk factors responsible for arterial injury, including hyperphosphatemia and CKD-MBD disorders. Interventions aiming at modifying late arterial lesions like calcifications are unlikely to produce tangible health benefits in these patients.

Nephrol Dial Transplant 2015

Inflammation. NO. Microcalcifications.

Moderator's view: Christoph Wanner

Treatment of vascular calcification is a physical impossibility, so far

Prevalence of subclinical atheromatosis and associated risk factors in chronic kidney disease: the NEFRONA study

Angels Betriu[1], Montserrat Martinez-Alonso[2], Maria Vittoria Arcidiacono[1,3], Jorge Cannata-Andia[4,5], Julio Pascual[5,6], José Manuel Valdivielso[1,3,5*] and Elvira Fernández[1,3,5,*], on behalf of the investigators from the NEFRONA study

NEFRONA study.

UDETMA Lleida

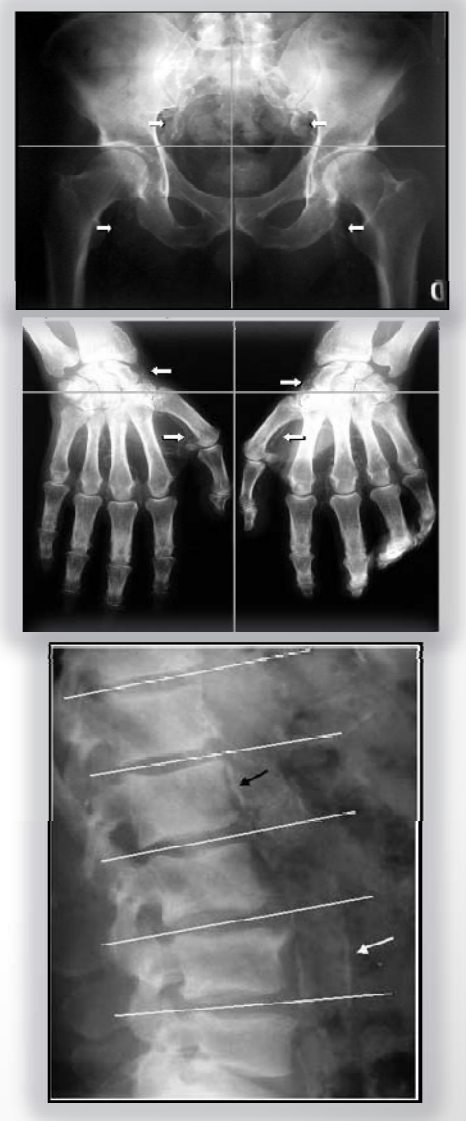
Catalonia, Spain

Nephrol Dial Transplant 2014

Itinerant team Carotid and femoral artery US

OSERCE II: Detection of VC by plain X rays

Centralized 2X



Adragao Score (0-8)

Pelvis:

-cuadrante superior derecho: 0 / 1
cuadrante superior izquierdo: 0 / 1
cuadrante inferior derecho: 0 /1
cuadrante inferior izquierdo: 0 / 1

- Hands:

- Mano der: superior: 0 / 1
- Mano der: inferior: 0 / 1
- Mano izq superior: 0 / 1
- Mano izq inferior: 0 / 1

Kauppila´s index (0-24)

Vertebral bodies L1-L4

-0: No calcificación
-1: Calcificación pequeña
-2 Calcificación moderada
-3 Calcificación grande,
Anterior y posterior

Adragao T, et al. Nephrol Dial Transplant 2004;19:1480–8; Kauppila LI et al. Atherosclerosis 1997; 132: 245-250

Courtesy Dr JL Górriz

Vascular Calcification in Patients with Nondialysis CKD over 3 Years

José L. Górriz, Pablo Molina, M. Jesús Cerverón, Rocío Vila, Jordi Bover, Javier Nieto, Guillermina Barril, Alberto Martínez-Castelao, Elvira Fernández, Verónica Escudero, Celestino Piñera, Teresa Adragao, Juan F. Navarro-Gonzalez, Luis M. Molinero, Cristina Castro-Alonso, Luis M. Pallardó, and Sophie A. Jamal

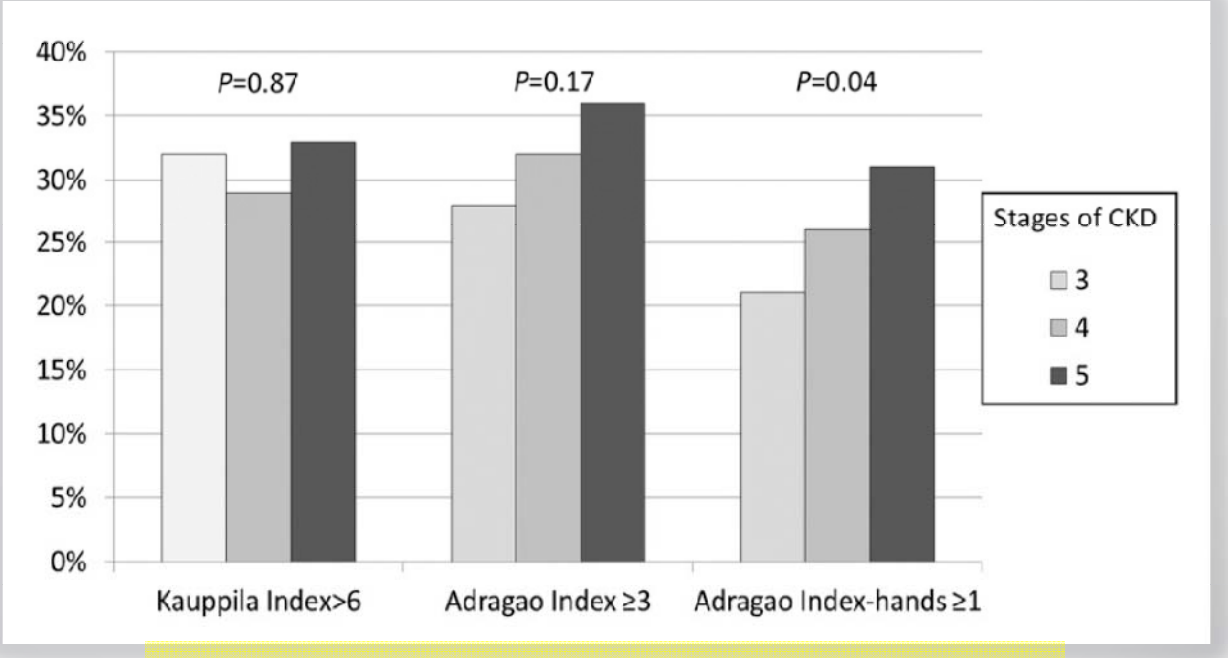
Conclusions VC is highly prevalent in patients with CKD. VC assessment using AS independently predicts death and time to hospitalization. Therefore, it could be a useful index to identify patients with CKD at high risk of death and morbidity as previously reported in patients on dialysis.

Clin J Am Soc Nephrol 10: ●●●–●●●, 2015. doi: 10.2215/CJN.07450714

742 patients
eGFR 27±12
Prevalence 79%

K > 6 or AS ≥ 3 47%

Late phenomenon, early presence



Large-slastic Medium-size muscular arteries; peripheral

HR All-cause; CV mortality, , time to hospitalization

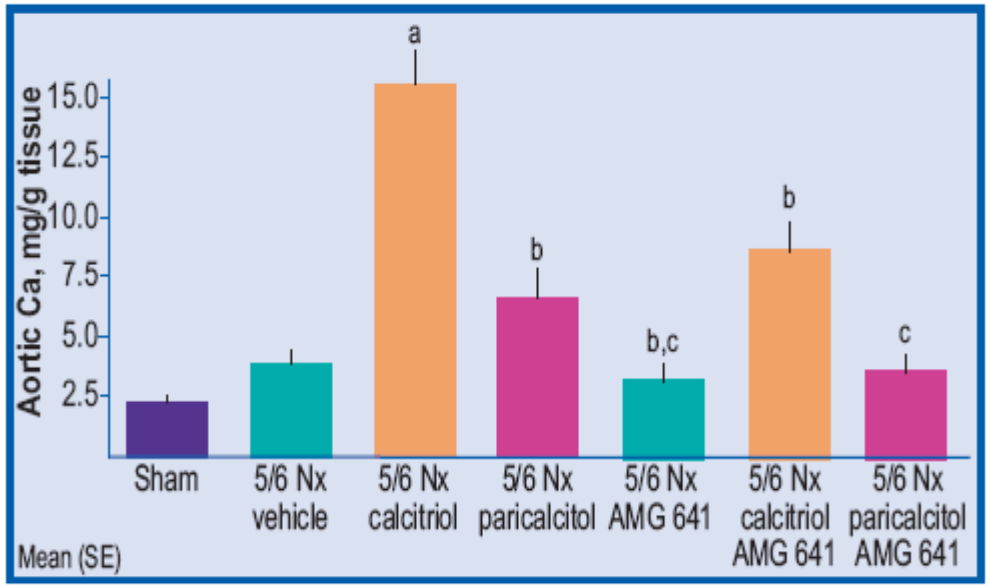
HR 2.07; 3.46;1.14 PTH, CKD st, CV mort, hosp-free

Table 1. Comparison of distinct effects of P binders and anti-parathyroid agents on CKD-MBD laboratory parameters, progression of vascular calcification (VC) and/or survival. Ca = Calcium; P = Phosphate; PTH = Parathyroid hormone; NA = Not available; RCT = Randomized Clinical Trial; Exp = only experimental studies.

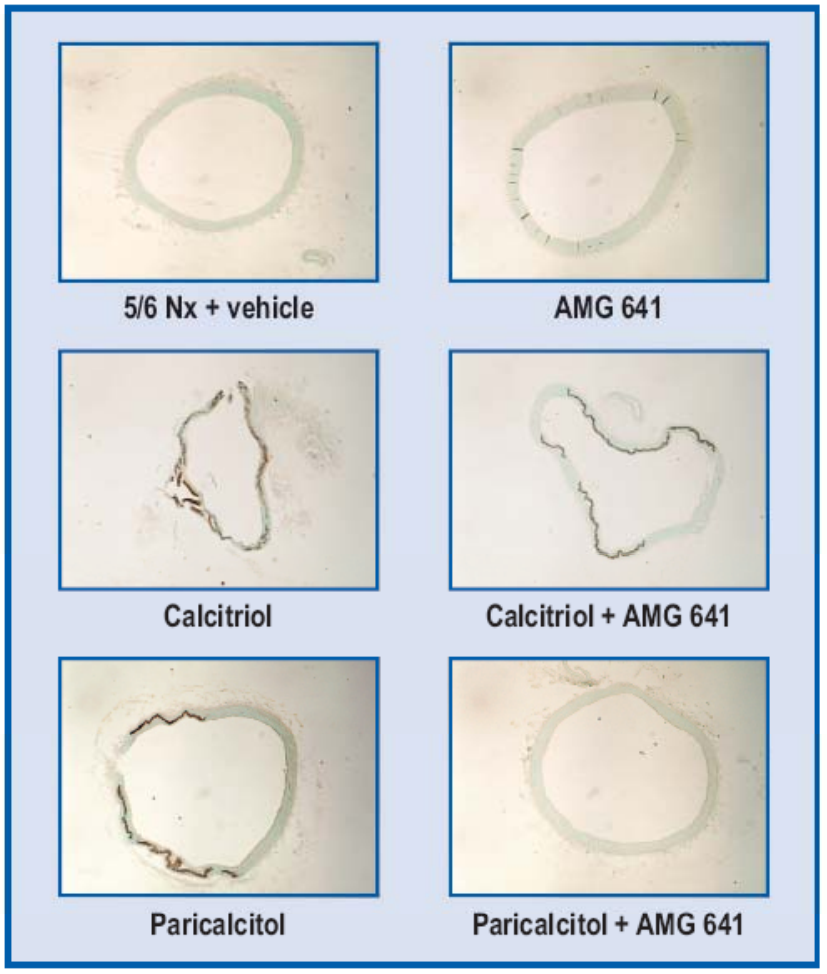
P binders	Ca	P	Ca x P	PTH	VC	Survival
Aluminum	-	↓↓↓	↓↓	-↓	NA	NA
Ca-based	↑-↑↑	↓↓	↓-	↓↓	↑↑- (RCTs)	- (RCT)
Non-Ca-Based	-	↓↓	↓	-↑	↑- (RCTs)	- (RCT) ↑ (2ry analysis RCT) ↑ (metanalysis)
Anti-parathyroid drugs						
Calcitriol (CTR), Alfacalcidol, Doxercalciferol	↑-↑↑	↑	↑	↓↓↓	↓-↑↑↑ (Exp)	- (no RCT) ↑ (metanalysis) ↑ (CTR, retrospective)
Paricalcitol	-↑	-↑	-↑	↓↓↓	↓-↑ (Exp)	- (no RCT) ↑ (metanalysis) ↑ (retrospective vs CTR)
Calcimimetics	↓-↓↓	-↓	↓↓	↓↓↓	-↓ (RCT)	- (RCT) ↑ (2ry adjusted analysis RCT) - (metanalysis) ↑ (retrospective)

Bover J et al NDT 2015

Diferential effects of CTR, paricalcitol and/or CM in experimental vascular calcification



[a]$P < 0.05$ vs 5/6 Nx + vehicle
[b]$P < 0.05$ vs 5/6 Nx + calcitriol
[c]$P < 0.05$ vs 5/6 Nx + paricalcitol



Henley et al. NDT 2005;
Cinacalcet + CTR 250-280 µg/kg

I. López et al, Kidney Int

Breve comparación de guías: ERC 5D

	K/DOQI 2003[1]	KDIGO 2009[2]	SEN 2011[4]	¿ KDIGO 2016[5] ?
P	1.3–1.78 mmol/L (3,5-5,5 mg/dl)	"Towards" normal	Normal Long gap Tolerance up to 1.6 mmol/L (5 mg/dl)	"Towards" normal (including 3a-5D)
Ca	Normal preferably towards the lower end (2.1–2.37 mmol/L)	Normal	Normal	Avoiding hypercalcemia
iPTH	150–300 ng/L	2–9 times the upper normal range of the assay	150–300 pg/mL Avoid <100 >500; PTH converter 2–5 times the upper normal range of the assay	=

DMO y OSTEOPOROSIS EN ERC!!!

- **RX dorso-lumbar!**

1. NKF. K/DOQI. Am J Kidney Dis 2003;42(suppl 3):S1-S202)
2. KDIGO CKD Work Group. Kidney Int. 2013;Suppl 3:1–150
3. Prados-Garrido MD, et al. Dial Traspl 2011;32:108–118
4. Torregrosa J-V, et al. Nefrologia 2011;31(Suppl 1):3–32
5. www.kdigo.org

Revisiting KDIGO clinical practice guideline on CKD-MBD: a commentary from KDIGO controversies conference

The group was unanimous in their assesment of the clinical significance of CV calcification and the conclusion that CV calcification SHOULD BE CONSIDERED for guidance of CKD-MBD management. However, they concluded that there was INSUFFICIENT NEW EVIDENCE to warrant a reasessment of these statements

Specifically, no high-quality data have been published to justify ROUTINE screening and no new data comparing different imaging methods have emerged.

The overall perception of the WG was that the available data may indeed strengthen the existing clinical practice guideline, but updating the evidence rating was outside the scope of the conference since no systematic review was performed a priori on this issue

Ketteler M et al, Kidney Int 2015

INTEGRAL PHARMACOLOGICAL MANAGEMENT OF BONE MINERAL DISORDERS IN CHRONIC KIDNEY DISEASE: From treatment of **phosphate imbalance** (part I) to **control of PTH** and **prevention of progression of cardiovascular calcification** (part II)

J.Bover, P.Ureña, M.J. Lloret, C.Ruiz, I.DaSilva, M.Diaz-Encarnacion, C.Mercado, S.Mateu, E.Fernandez, J.Ballarín

Use knowledge of CVC to guide treatment of CKD-MBD, use drugs in combination, and individualize treatment.

Phosphate (and/or FGF23) control: (P-binders) (see Part I)[1]

- Achieve P levels as close to normality as possible with reasonable measures, including optimization of dialysis*
- Avoid additives by all possible means, prioritize a balanced vegetarian vs animal dietary protein source and limit ↑ P/protein index foods
- Prioritize P-binder prescription over unsupervised non-specific protein diet restriction
- If very high serum PTH and P levels are present, consider the possibility that P may NOT be of intestinal origin.
- Personalize choice of P-binder prescription depending on patient preferences, CKD stage (dialysis vs non-dialysis), presence/absence/degree of VC, concomitant therapies (i.e., VDRA, calcimimetics) and side effect profile (i.e., palatability, constipation, diarrhea)
- Avoid Ca-based P-binders in patients with hypercalcemia, low PTH levels, and/or ABD. Avoid or limit Ca-based P-binders in diabetics, patients with VC, and patients treated with coumadin.
- Combination of P-binders is possible and inhibition of intestinal transporters may

PTH control (specific anti-parathyroid treatment)

- Aim for iPTH levels between 2 and 5 times the upper limit of normality and avoid extremes of risk (<2X or >9X).
- Treat tendencies and do not respond to minor variations in PTH.
- Initial drug selection may be based on CKD stage, Ca and P levels as well as on other aspects of CKD-MBD (e.g., CVC).
- Cinacalcet is not approved for the treatment of secondary hyperparathyroidism in CKD stages 3-5
- In CKD stage 5D, use vitamin D and calcimimetics in combination to improve efficacy with fewer secondary effects, eventually always considering the Ca and P levels
- Selective VDRA (paricalcitol) may provide a wider therapeutic window, especially in those with a trend toward hypercalcemia or hyperphosphatemia, diabetic patients, and those prone to VC (experimental).
- Cinacalcet is considered first-line treatment in hypercalcemic (and perhaps significantly hyperphosphatemic) dialysis patients.
- I.V. etelcalcetide may improve compliance

Expert Opinion on Pharmacotherapy 2016. Published on line

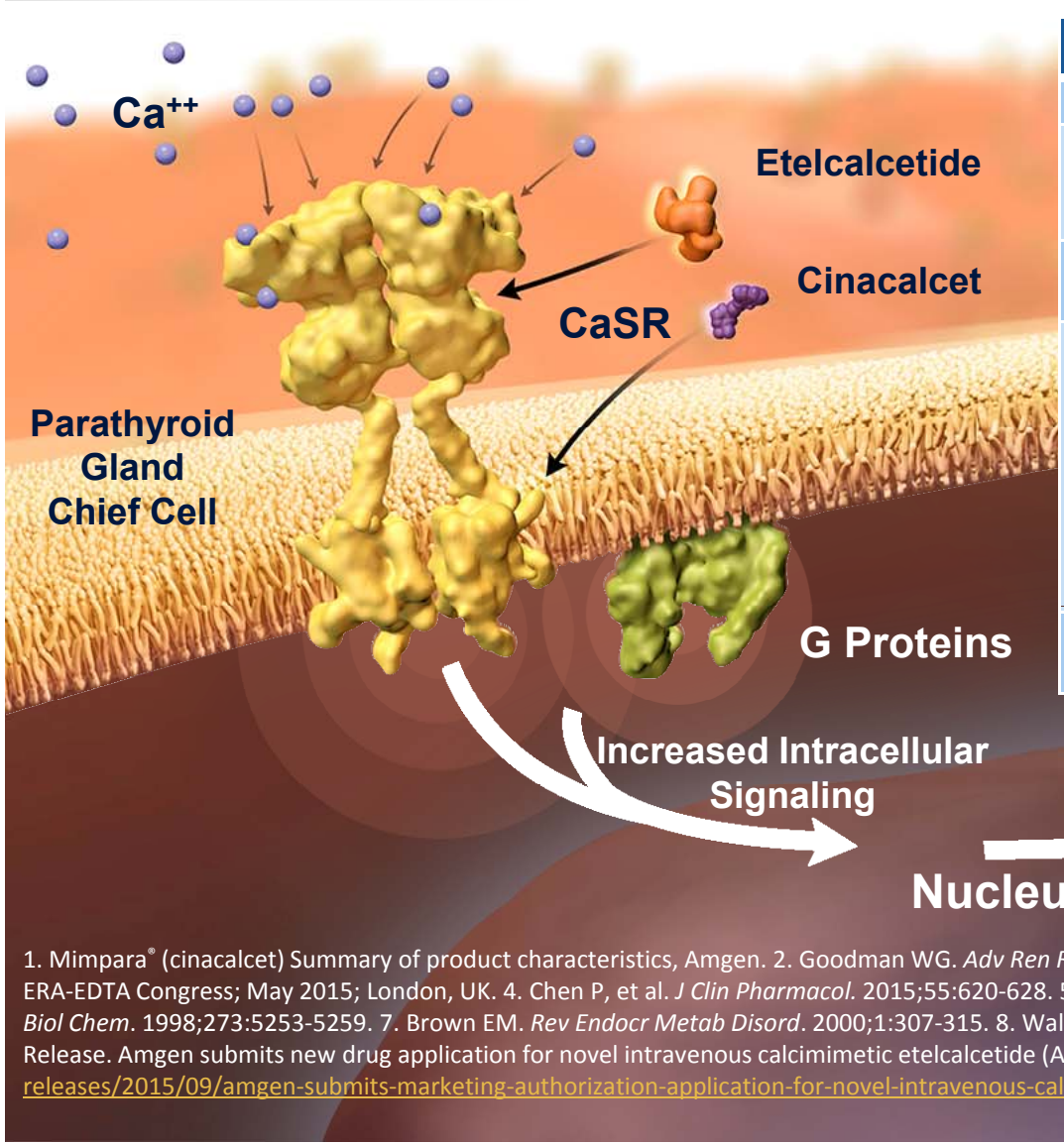
Adynamic Bone Disease

Table 1. Treatment Options in ABD

Avoid
Aluminum or trace metal exposure
Bisphosphonates and other antiresorptive agents
Excessive calcium load: ↓ calcium-based P binders, ↓ active forms of vitamin D
Excessive PTH oversuppression: ↓ vitamin D, ↓ calcimimetics
Consider
Non–calcium-based P binders
Native vitamin D to achieve calcidiol levels > 20-30 ng/mL
Paricalcitol > calcitriol
Active increase in PTH levels
Decrease previous Ca dialysate content
Low Ca dialysate
Others (?)
Recombinant PTH
Parathyroid allotransplantation
Antisclerostin monoclonal antibodies

Bover et al Semin Nephrol 2015

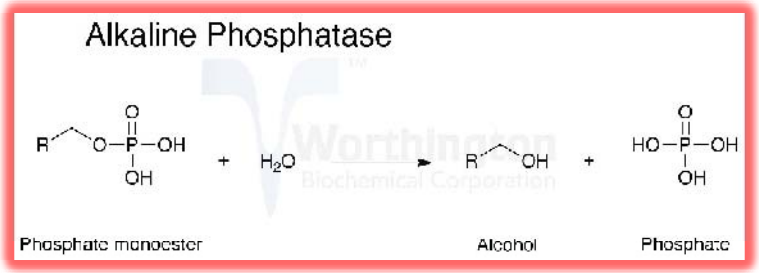
Etelcalcetida: Nuevo calcimimimético EV

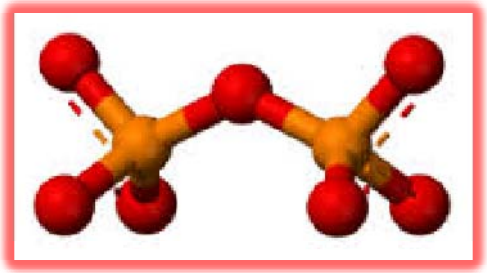


	Cinacalcet[1,2]	Etelcalcetide[3,4,8,9]
Class	Calcimimetic	Calcimimetic
Description	Small organic molecule	Synthetic 7-amino acid peptide agonist linked to L-cysteine
Size	molecular weight = 393.9 g/mol	molecular weight =1048.3 g/mol
MOA	Interacts with membrane-spanning segments of CaSR and enhances signal transduction, thereby reducing PTH secretion	Interacts with and activates the CaSR thereby reducing PTH secretion
Admin.	Daily oral	IV at the end of each HD session

1. Mimpara® (cinacalcet) Summary of product characteristics, Amgen. 2. Goodman WG. *Adv Ren Replace Ther*. 2002;9:200-208. 3. Cunningham J, et al. Presented at the 52nd ERA-EDTA Congress; May 2015; London, UK. 4. Chen P, et al. *J Clin Pharmacol.* 2015;55:620-628. 5. Goodman WG, et al. *Kidney Int*. 2008;74:276-288. 6. Moallem E, et al. *J Biol Chem*. 1998;273:5253-5259. 7. Brown EM. *Rev Endocr Metab Disord*. 2000;1:307-315. 8. Walter S, et al. *J Pharmacol Exp Ther*. 2013;346:229-240. 9. Amgen Media News Release. Amgen submits new drug application for novel intravenous calcimimetic etelcalcetide (AMG 416). http://wwwext.amgen.com/media/news-releases/2015/09/amgen-submits-marketing-authorization-application-for-novel-intravenous-calcimimetic-etelcalcetide-amg-416-to-the-european-medicines-agency

Inhibidores de la fosfatasa alcalina





Alkaline phosphatases (APs) are membrane-bound glycoprotein **hydrolases** responsible for **removing phosphate (P) groups** (dephosphorilation or P ester hydrolysis) from many molecules (nucleotides, proteins, pyrophosphate...), most effectively operating in an alkaline environment. Thus, P becomes available for many processes such as **mineralization**.

Circulating APs may increase **hydrolysis of pyrophosphate**, a natural inhibitor of hydroxyapatite formation in the extracellular fluid and a well-known **potent inhibitor of vascular calcification** by preventing incorporation of inorganic P into hydroxyapatite crystals.

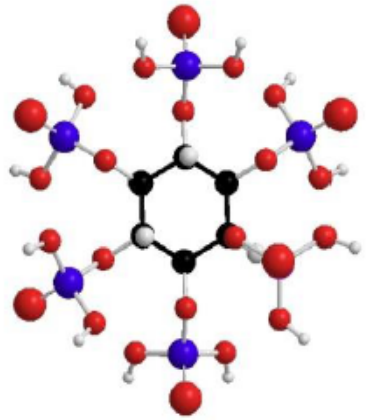
Aryl sulphonamides (Dahl)
Pyrazole derivatives (Sidique)

High-throughput screens

Narisawa JBMR 2007, Dahl J Med CHem 2009, Sidique Bioorg Med Chem Lett 2009, Sergienko J Biomol Screen 2009, Chung TD Molecules 2010, Sergienko Nat Protoc 2010,

Introduction to SNF472 **Natural "phytate"**

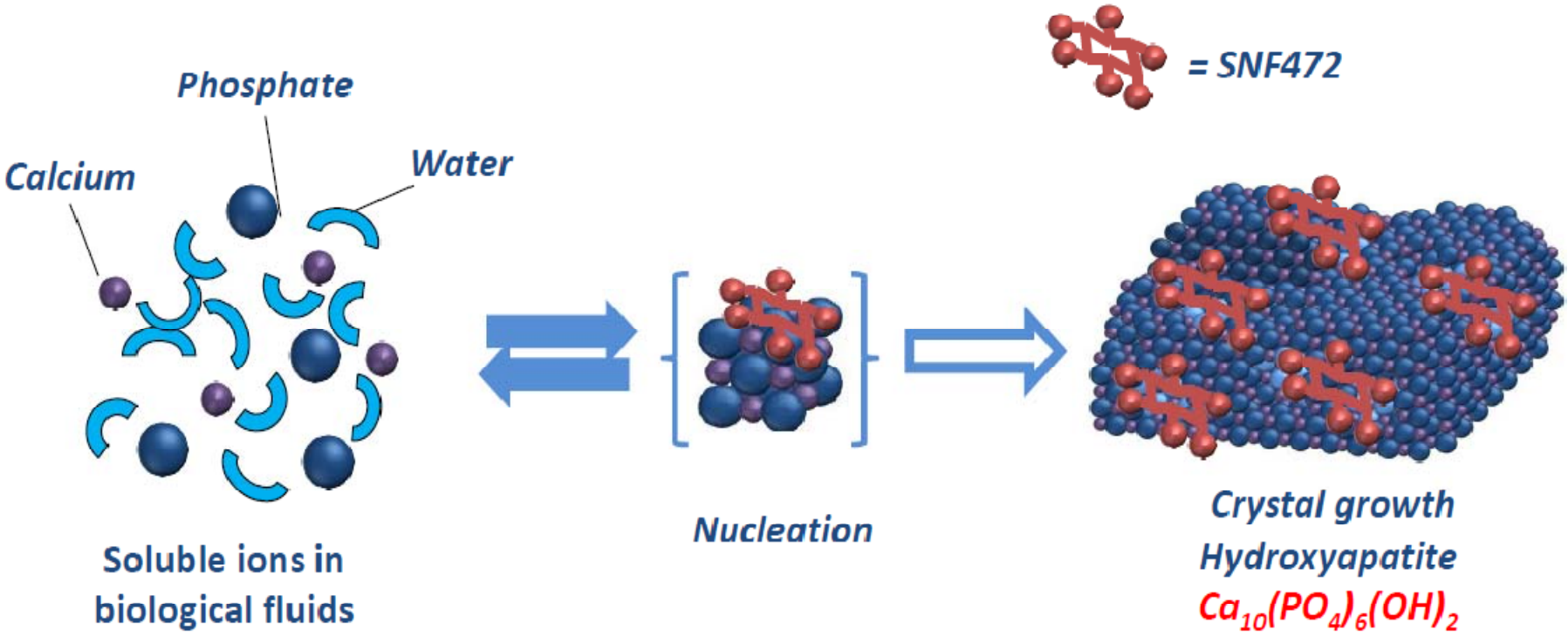
- **IP6:** myo-inositol hexaphosphate (MW = 792 Da)
- **IP6:** potent modulator of calcification
- Natural nutritional ingredient, **GRAS listed**
- **Low oral availability** (highly polar)
- **SNF472:** modified IP6 salt, i.v. formulation
- **IP6** found in blood and intracellular compartment.
- Physiological levels: blood < 0.3 uM / Intracellular 10-100 uM
- **SNF472** impacts on **extracellular** compartment levels
- Expected **therapeutic** concentrations **2-3 uM**
- **SNF472** in clinical development for cardiovascular calcification in ESRD dialysis patients and calciphylaxis



IP6: ácido fítico (o fitato en forma de sal) es la principal forma de almacenamiento de P en plantas, especialmente salvado y semillas (precisa fitasa – rumiantes)

SNF472. Mechanism of Action

Physico-chemical MoA: prevents cardiovascular calcification (CVC) by blocking Ca-crystal formation/growth



A PHASE 1B/2A RANDOMISED, PLACEBO-CONTROLLED CLINICAL TRIAL WITH SNF472 IN HAEMODIALYSIS PATIENTS

C. Salcedo[1], J. Perelló[1,2], R. Ojeda[3], P.H. Joubert[1], M. Arias[3], AZ. Canals[1], M.D. Ferrer[1,] V. Torregrosa[3,] JM Campistol[3], F.Maduell[3]

[1] Laboratoris Sanifit SL, 07121 Palma de Mallorca, Spain

[2] Laboratory of Renal Lithiasis Research, IUNICS, University of the Balearic Islands, 07122 Palma, Spain

[3] Nephrology Department, Hospital Clinic, Barcelona, Spain.

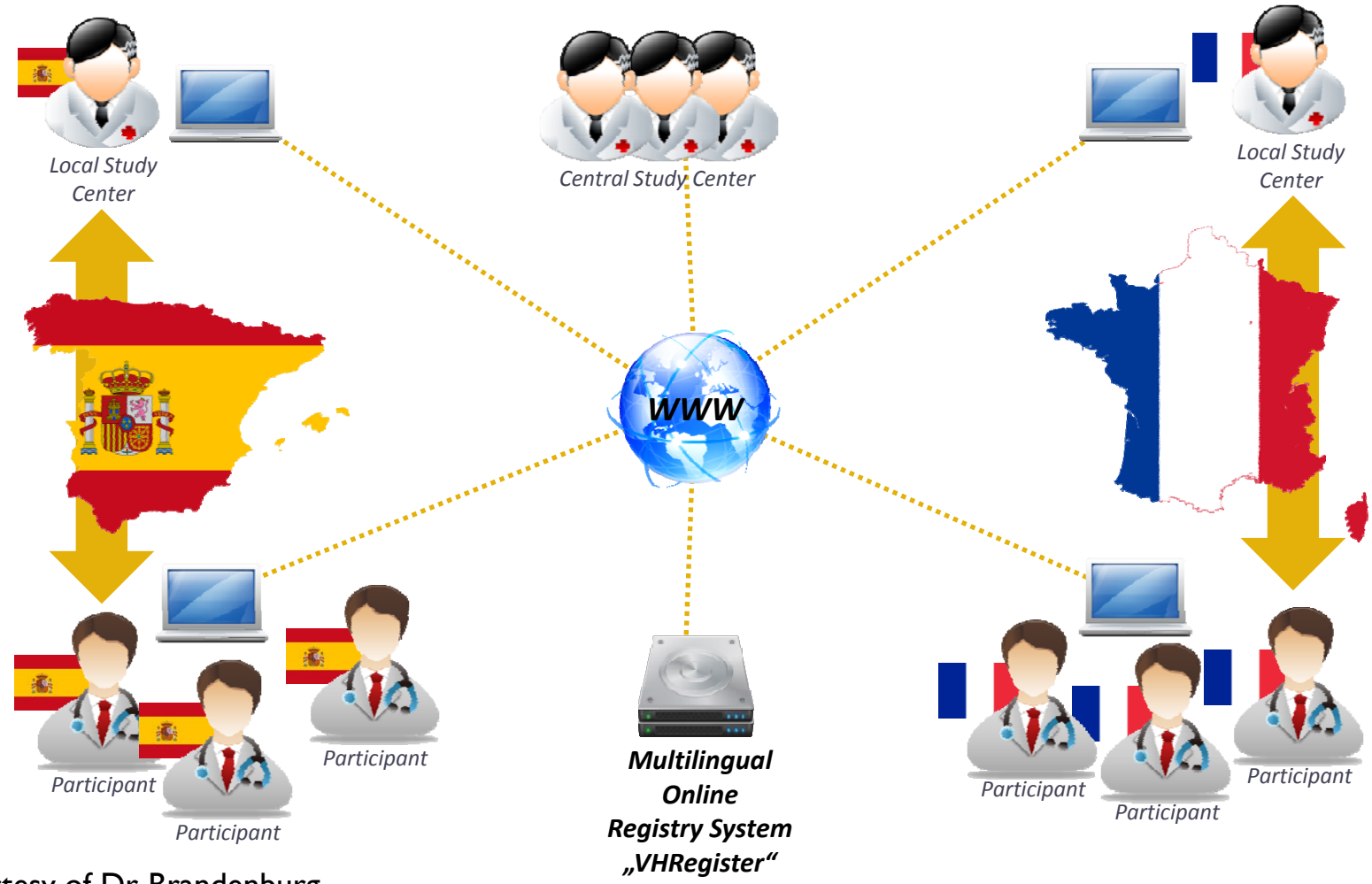
ERA-EDTA 2016, Vienna
May 21st, 2016

- **SNF472 reduces vascular calcification in animal models and calcification propensity in HD patients dose-dependently.**
- **Plateau of calcification propensity inhibition from 3 mg/kg (10000 ng/mL; 15 uM)**
- **Good safety at all tested doses, up to 20 mg/kg (70000ng/mL; 105 uM)**

CKD-MBD
Chronic-Kidney Disease-Mineral and Bone Disorder
ERA-EDTA Working Group

Perspective: www.calciphylaxis.eu

- Local study centers collect and manage cases from their country
- One central study center reviews and consolidates all collected data



Courtesy of Dr. Brandenburg

CONCLUSIONES I

- Los pacientes con calcificación vascular/valvular deberían considerarse en el **grupo de mayor riesgo CV**
- Además del score de Kauppila (KDIGO), otros **(Adragao's…) son más fáciles y potencialmente útiles** para su uso clínico (incluso en ERC no-en-diálisis)
- Las guías sugieren (y sugerirán) que **es razonable** usar esta información para **guiar el manejo del complejo CKD-MBD** a pesar de que no hay evidencia de alta calidad que esta aproximación mejore el pronóstico o eventos duros

CONCLUSIONES II

- Dependiendo de los recursos disponibles, la evaluación de las calcificaciones vasculares puede ser **global** o solo en **pacientes seleccionados** (i.e. cualquier paciente en el que el médico decide que esta **información pueda impactar una decisión terapéutica**)

- La ausencia de evidencias 1A en Nefrología **NO debería ser equivalente a aceptar NIHILISMO TERAPEUTICO como opción** mientras se esperan estudios « definitivos », especialmente teniendo en cuenta que el **TRATAMIENTO puede que sea muchas veces IMPOSIBLE pero…**

…PODEMOS NO MEJORAR LA CALCIFICACION CV.

Sin embargo, ES MODIFICABLE y **PODEMOS EMPEORAR SU PROGRESION**

“PRIMUM NON-NOCERE”

Aforismo hipocrático

WHO , WHEN AND HOW?

WHO?

- Depending on available resources … all patients or those where knowledge of the presence of VC may impact a therapeutic decision
- Hypersensitized patients
- Waiting list for RT: O > B > A > AB
- Age criteria?

WHEN?

- Diagnosis of CKD (before dialysis)

HOW?

- Depending on available resources and objectives:
  - Research: MDCT (EBCT)
  - Clinical: Kaupilla
    - Agragao's Index, Adragao's hands
    - Any indirect form

Nephrology and the Kidney are strategically located in the field of CV risk

- **A** lbuminuria
- **B** lood pressure
- **C** holesterol, Cigarette
- **D** iabetes, Vitamin **D**

- **E** stimated GFR
- **“F”** osphate

Nephrology and the Kidney are strategically located in the field of CV risk

- **A** lbuminuria
- **B** lood pressure
- **C** **ALCIFICATION**
- **D** iabetes, Vitamin **D**

- **E** stimated GFR
- **"F"** osphate

“PRIMUM NON-NOCERE”

“FIRST, DO NOT HARM”

Hypocratic aphorism


Fundació Puigvert

- Although the Framingham cohort identified BP as a "factor risk" in 1961, many of the seminal RCT's showing the benefit of lowering diastolic, then systolic BP, were not completed until 2-3 decades later. Screening for elevated BP and instituting appropriate treatment remains a national priority today.

  - "To screen or not to screen: That is not (yet) the question". Tuot DS and Peralta CA. *CJASN 2015 (editorial)*

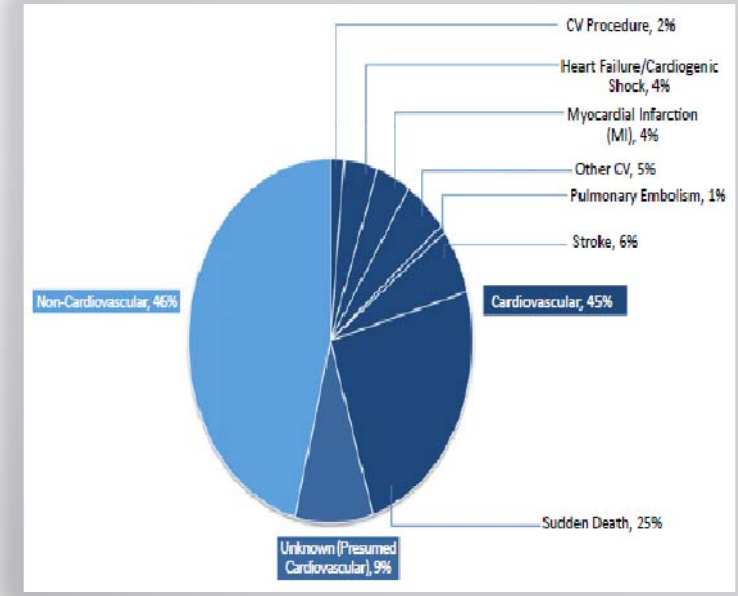
  On CKD and "preventive nephrology" that should be prioritized by the nephrology community

Effects of Cinacalcet on Atherosclerotic and Nonatherosclerotic Cardiovascular Events in Patients Receiving Hemodialysis: The EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events (EVOLVE) Trial

David C. Wheeler, MD; Gerard M. London, MD; Patrick S. Parfrey, MD; Geoffrey A. Block, MD; Ricardo Correa-Rotter, MD; Bastian Dehmel, MD; Tilman B. Drüeke, MD; Jürgen Floege, MD; Yumi Kubo, MS; Kenneth W. Mahaffey, MD; William G. Goodman, MD; Sharon M. Moe, MD; Marie-Louise Trotman, MS; Safa Abdalla, MD; Glenn M. Chertow, MD; Charles A. Herzog, MD; for the EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events (EVOLVE) Trial Investigators*

J Am Heart Asoc 2014

Conclusions—Accepting the limitations of post hoc analysis, any benefits of cinacalcet on cardiovascular disease in the context of hemodialysis may result from attenuation of nonatherosclerotic processes.



- **Greater relative benefit on nonatherosclerotic CV events, including sudden death and heart failure**
- **The potential CV benefit of cinacalcet in HD patients may be mediated by nonatherosclerotic mechanisms:**
  - **slowing arterial calcification or reducing myocardial Ca accumulation**
  - **↓ FGF-23 → ↓ LVH**

Coffee consumption and coronary artery calcium in young and middle-aged asymptomatic adults

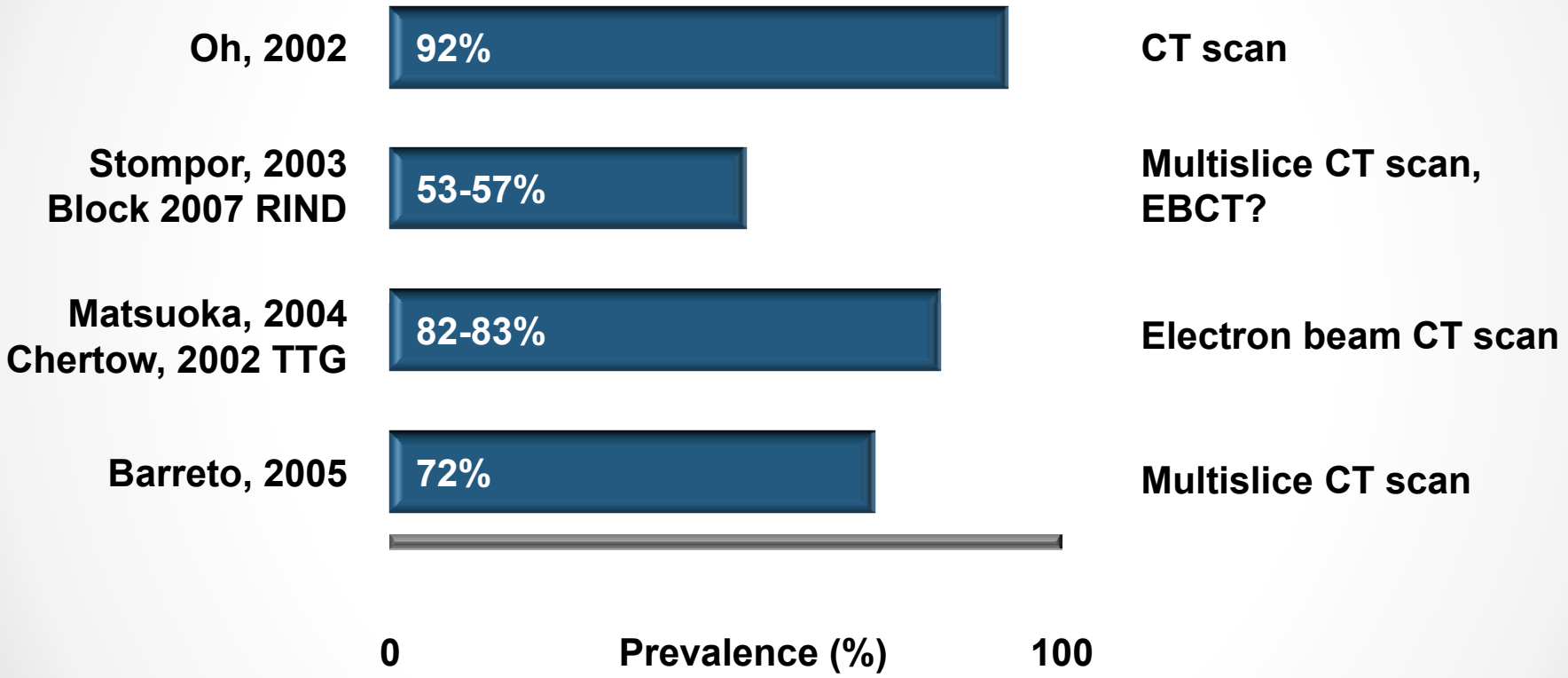
Choi Y et al. Heart 2015

Coffee drinkers were less likely to have calcium in their coronary arteries than nondrinkers. The relationship was U-shaped, with the lowest levels occurring in people who drank 3 or 4 cups daily

Conclusions In this large sample of men and women (25138 South Korean men and women) apparently free of clinically evident cardiovascular disease, moderate coffee consumption was associated with a lower prevalence of subclinical coronary atherosclerosis.

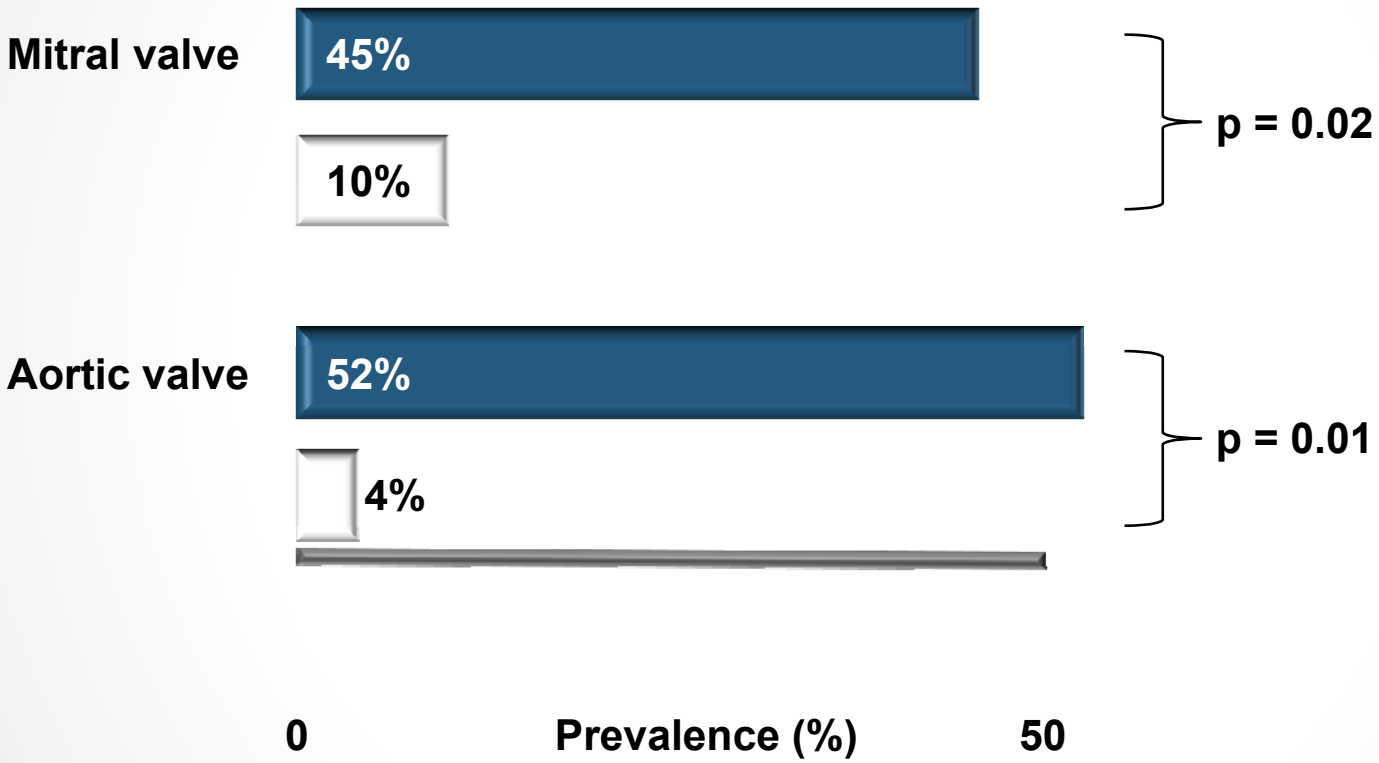
Despite the positive findings, study author Eliseo Gualiar said in an email that he was "concerned that the role of coffee in preventing cardiovascular disease is exaggerated. Our study was an observational association study that by itself cannot prove causation." Moderate coffee drinkers, he said, "should not be concerned that coffee is increasing their risk of cardiovascular disease. On the other hand, we believe that at this point we should still not recommend drinking coffee for preventing cardiovascular disease."

La mayoría de pacientes en diálisis tienen calcificación CORONARIA (CAC)



CT: computerised tomography
Adapted from Kalpakian MR et al. *Semin Dial.* 2007;20:139-143.

Alta prevalencia de calcificación VALVULAR en pacientes en diálisis vs. controles

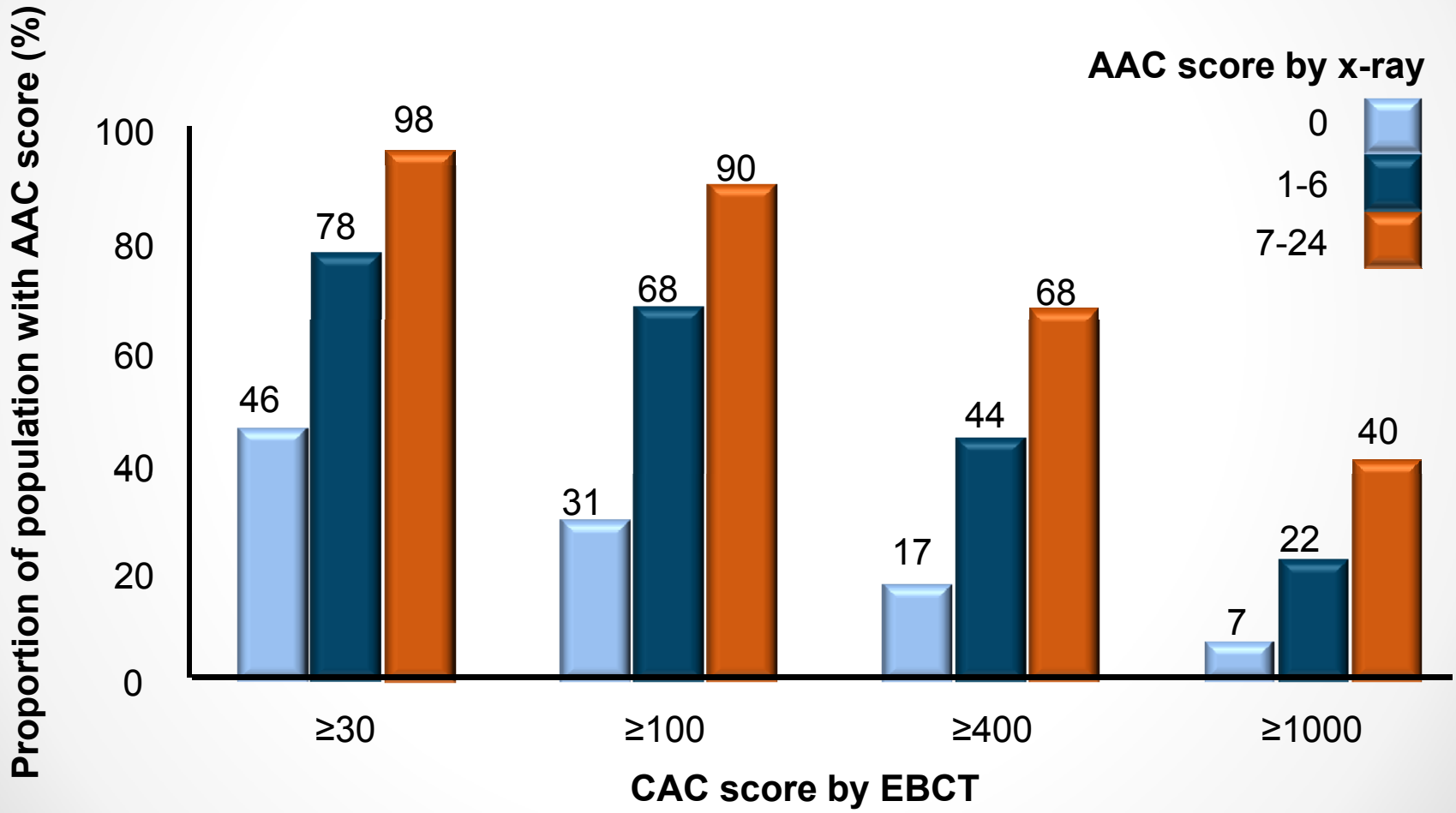


N = 92 patients on dialysis
N = 92 age-matched controls

Ribeiro S et al. NDT 1998;13:2037-2040

Sanchez-Perales et al Nefrologia 2015
50% incidentes; ambas en 69/128 pac; 39/128 mitral, 20/128 aortica y se relaciona con eventos y muerte CV

Los pacientes con mayor calcificación aórtica (RX) tienen consistentemente índices de CAC más elevados (EBCT)

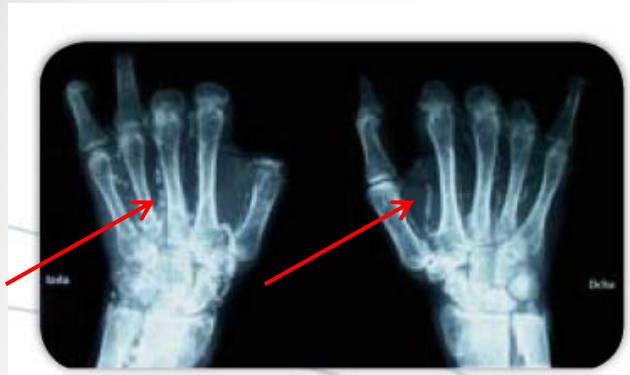


N = 140

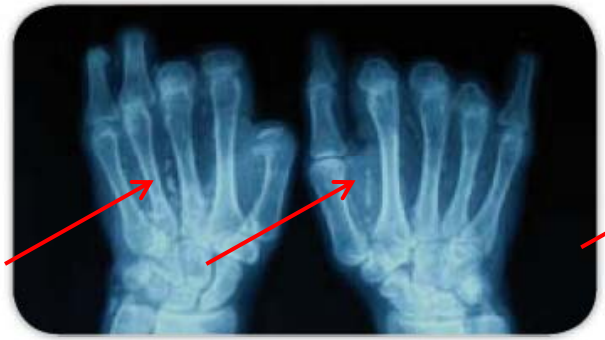
AAC: abdominal aorta calcfication; CAC: coronary artery calcification; EBCT: electron beam computerised tomography

Bellasi A et al. *Kidney Int*. 2006;70:1632-8

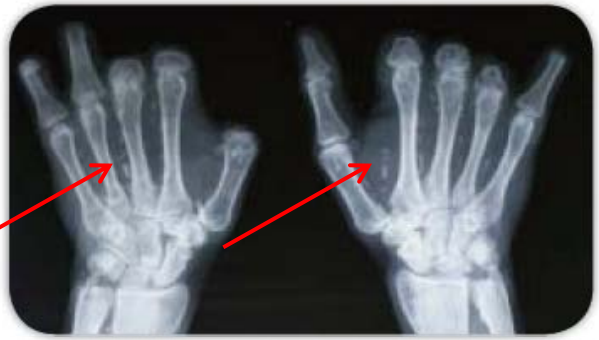
Efecto de cinacalcet sobre las calcificaciones vasculares y de tejidos blandos en pacientes con HPTS en diálisis



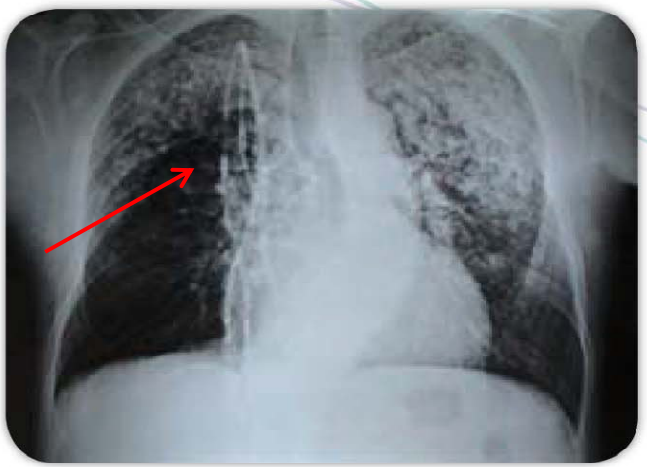
Radiografía de manos basal



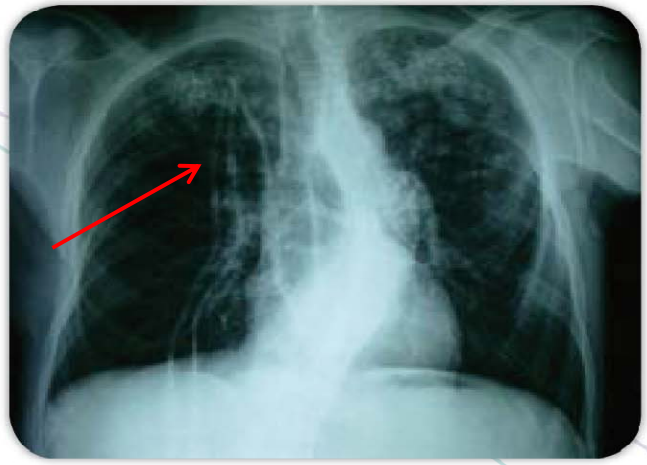
Radiografía de manos 12 meses



Radiografía de manos 24 meses



Radiografía de tórax basal

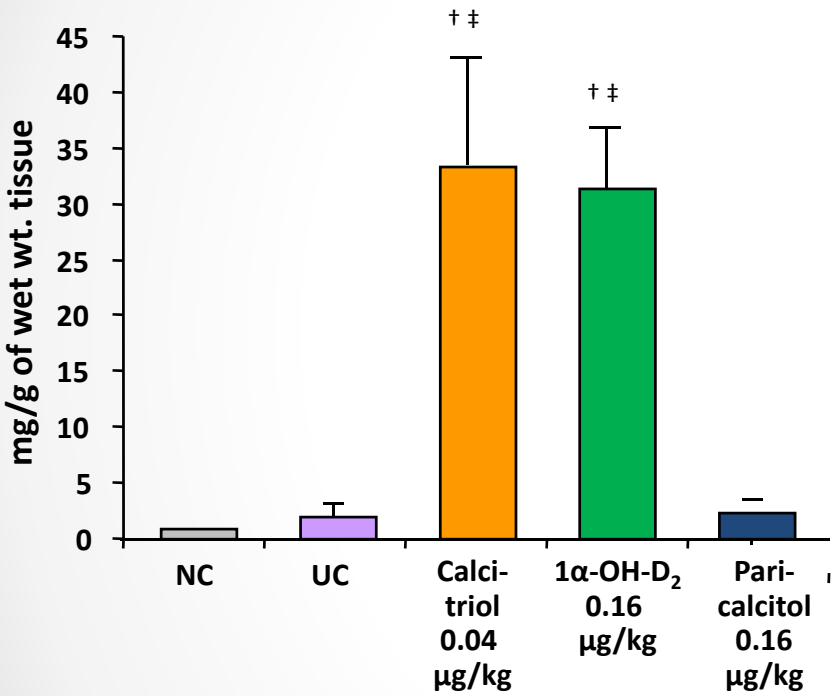


Radiografía de tórax 24 meses

M.J. Aladrén Regidor Clinical Nephrology 2009;71:207-213

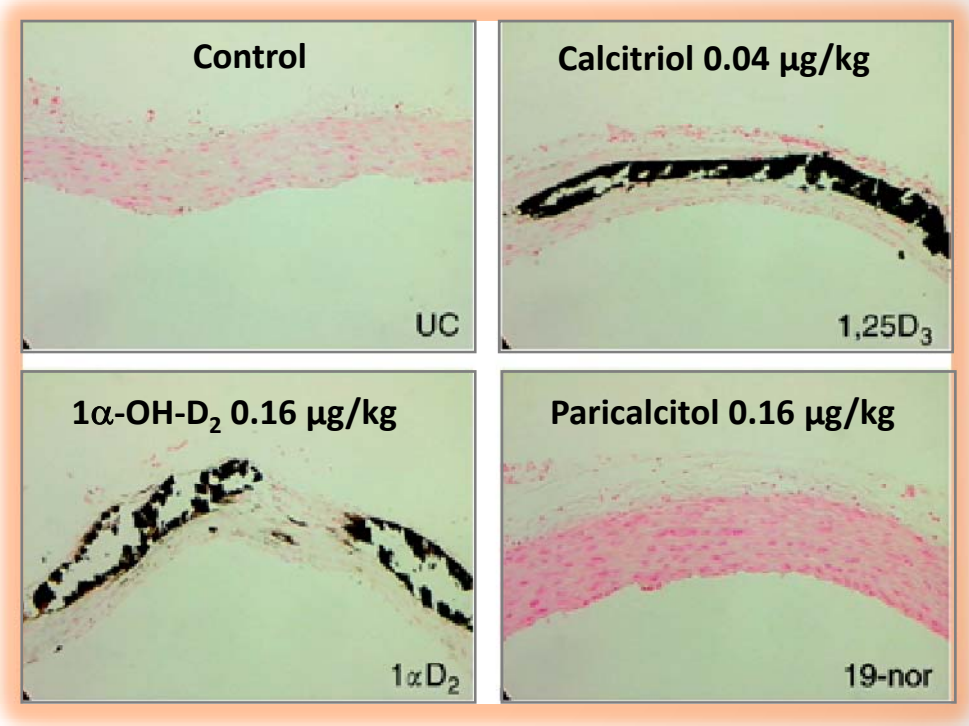
Calcitriol and doxercalciferol, but not paricalcitol, increase vascular calcification in uremic rats*

Aortic Ca content



Aortic calcification

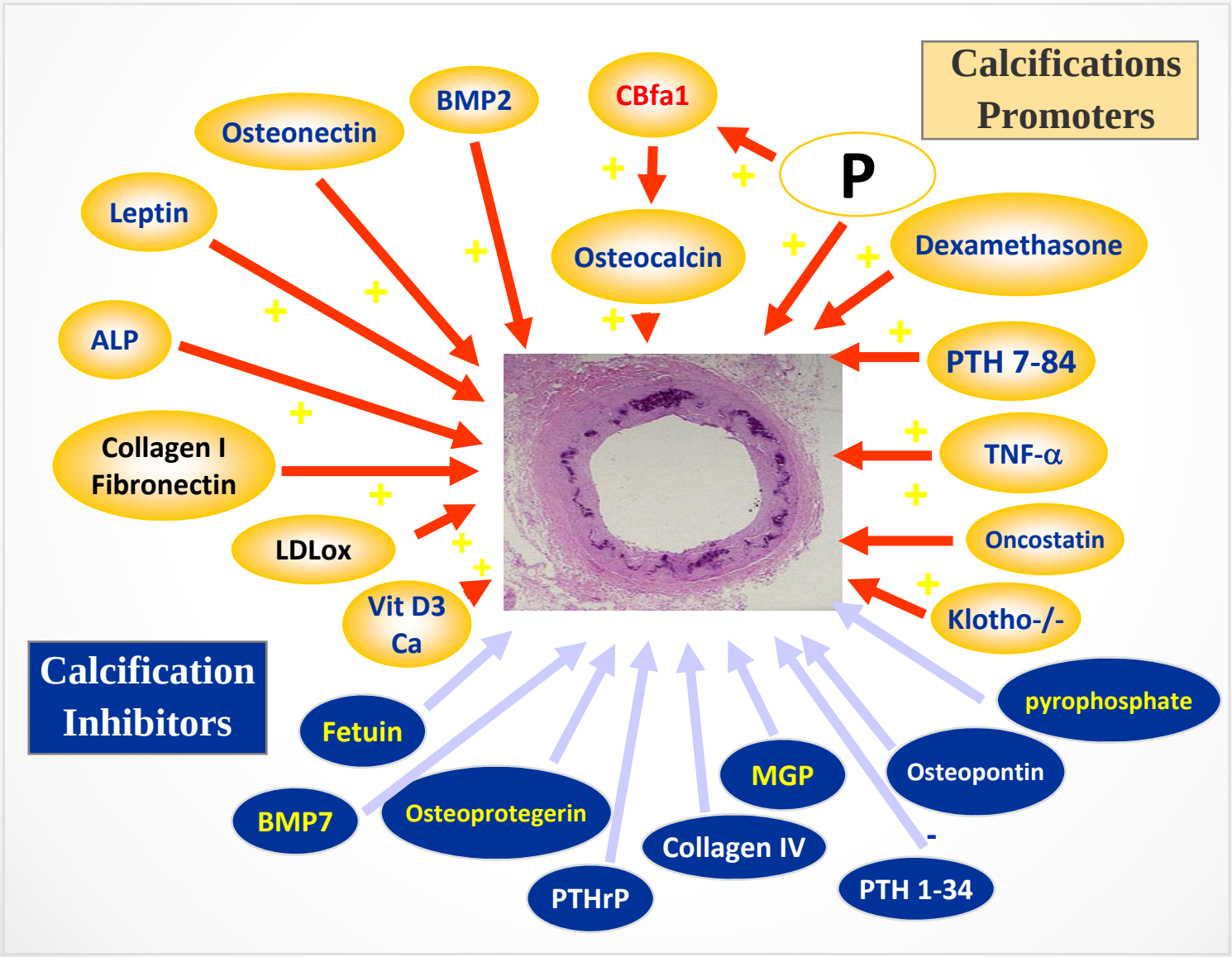
(von Kossa staining; black areas represent calcification)



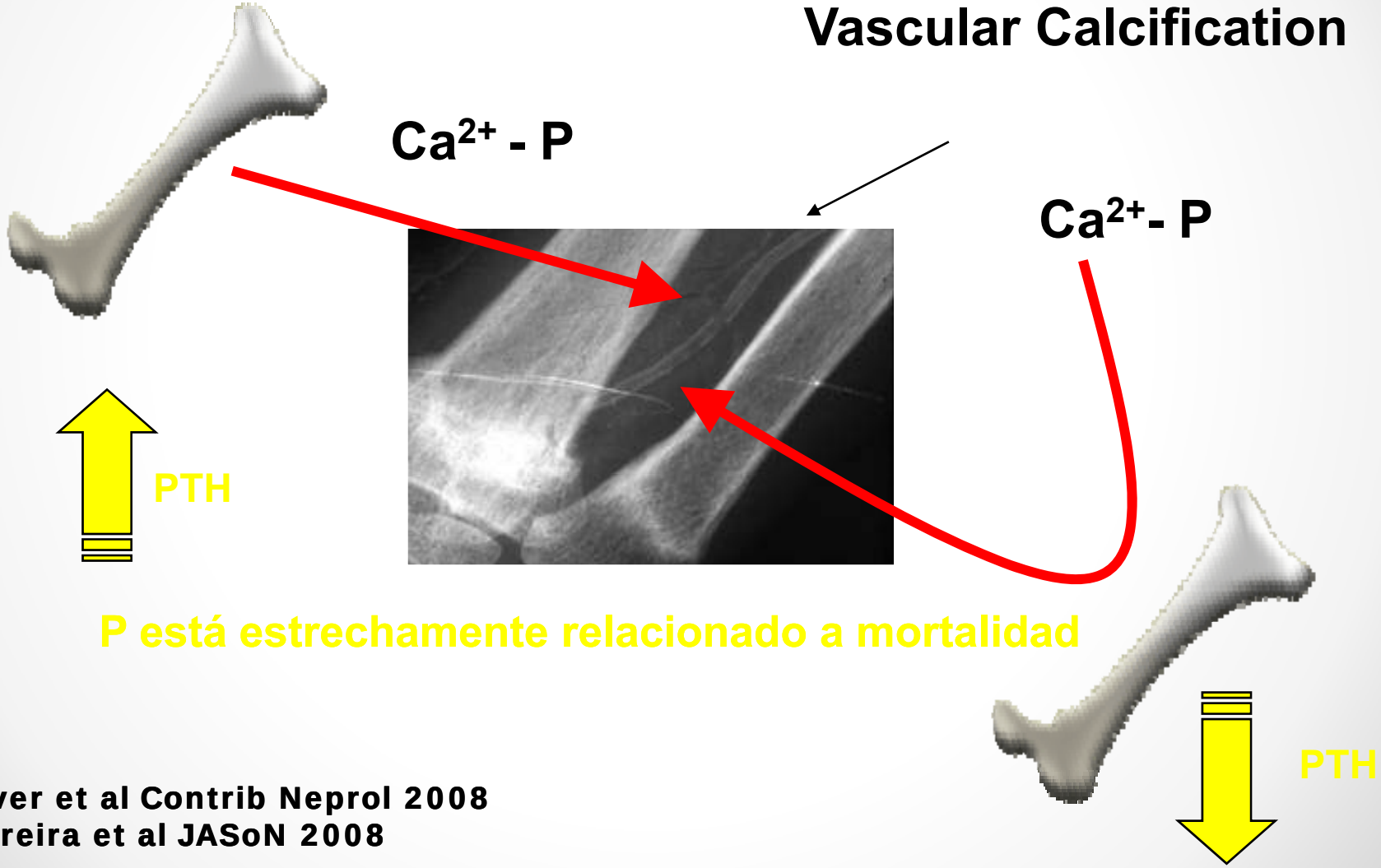
Mizobuchi M et al. Kidney Int 2007;72:709–15

Cardús A, et al. J Bone Miner Res 2007;22:860–6

El sistema vascular está sometido a promotores e inhibidores de la calcificación vascular

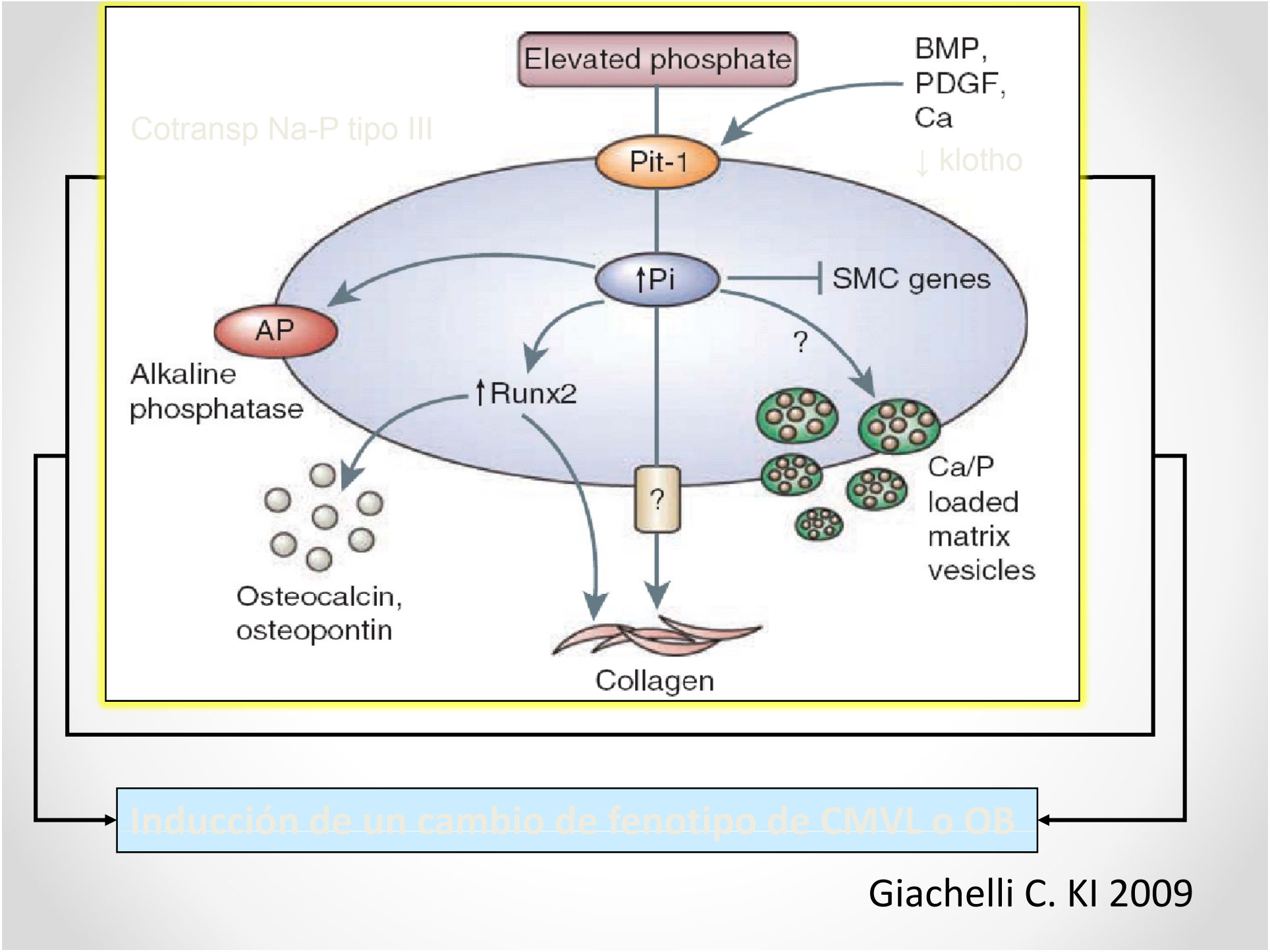


Calcificaciones-Mortalidad P y PTH

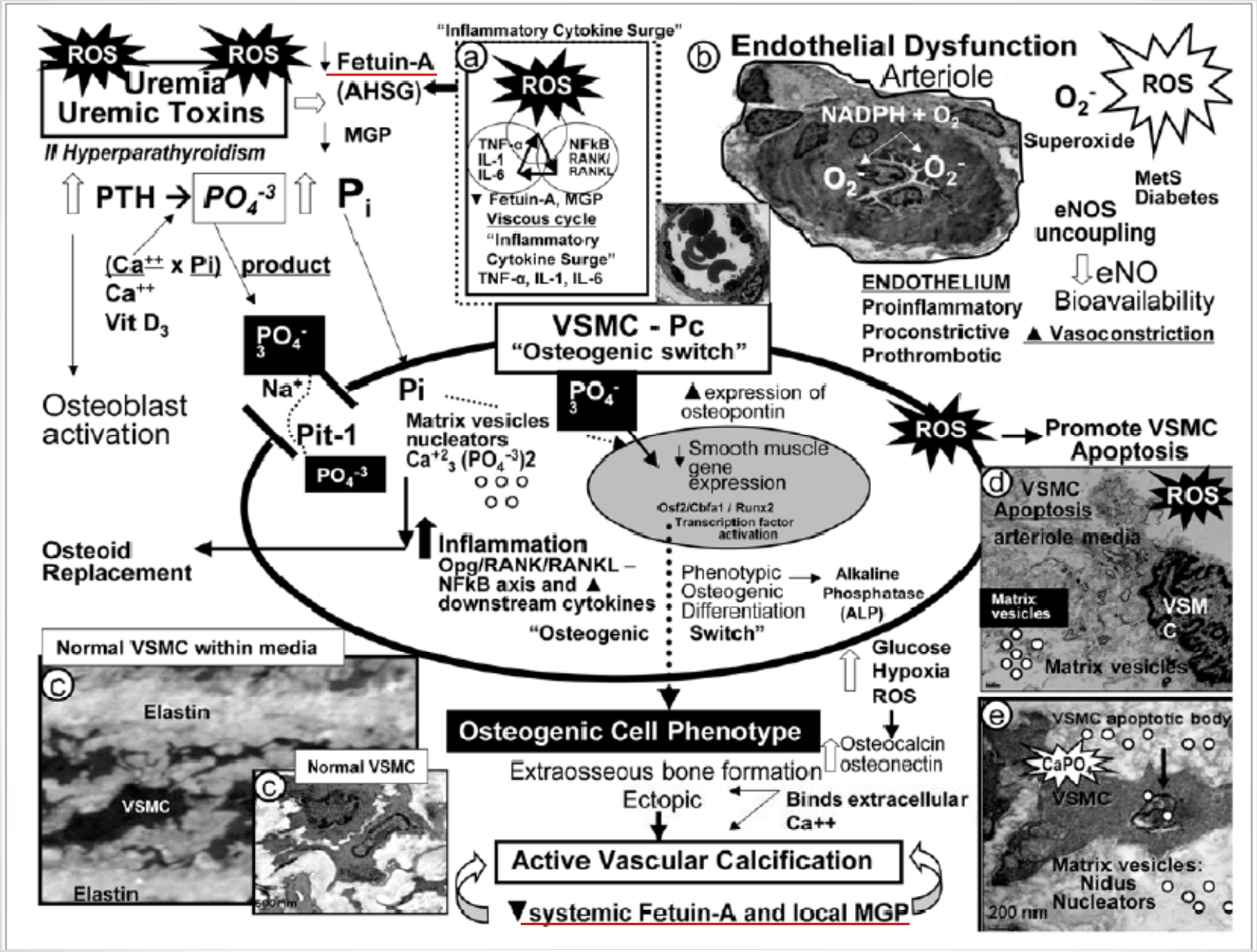


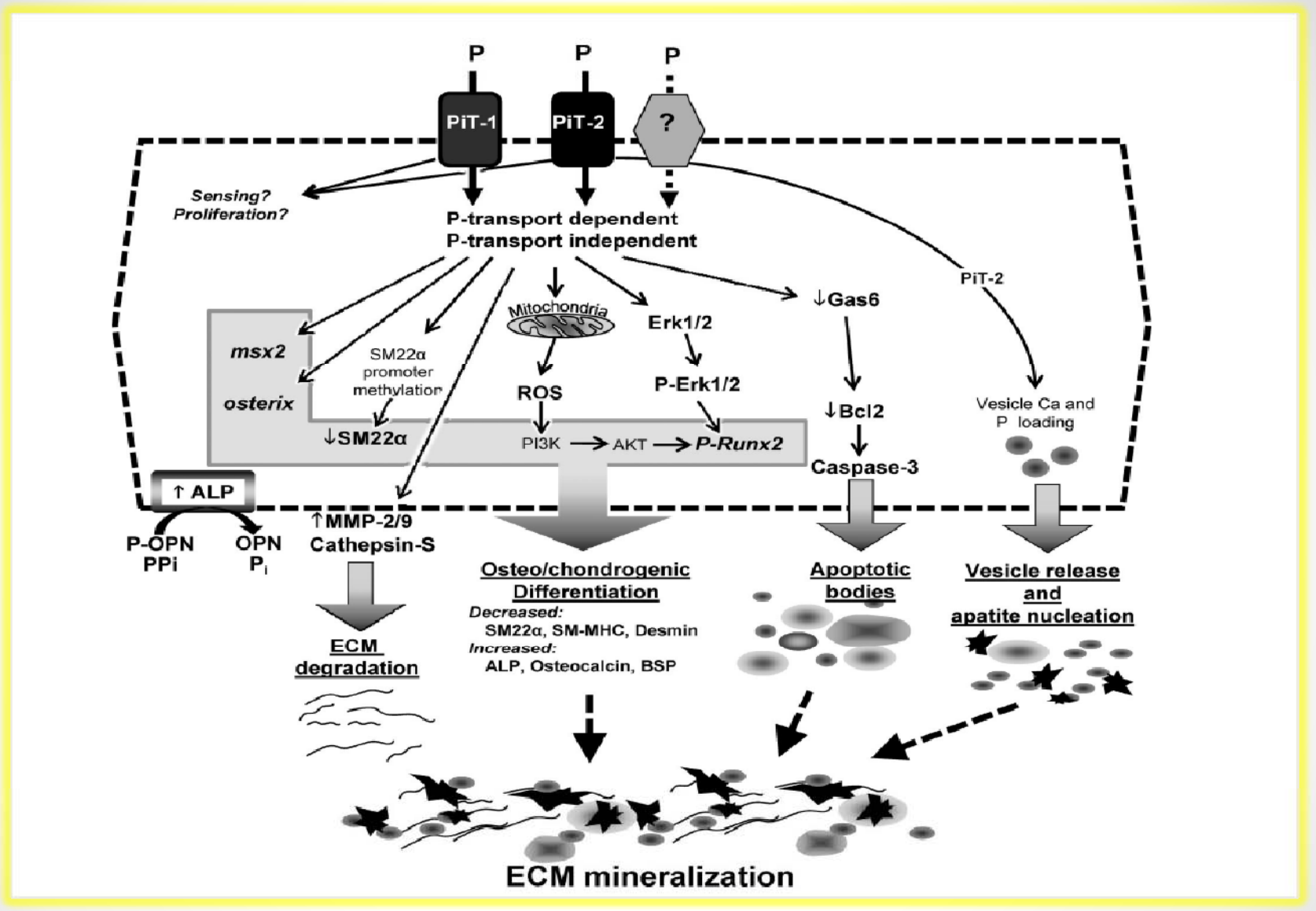
P está estrechamente relacionado a mortalidad

Bover et al Contrib Neprol 2008
Ferreira et al JASoN 2008

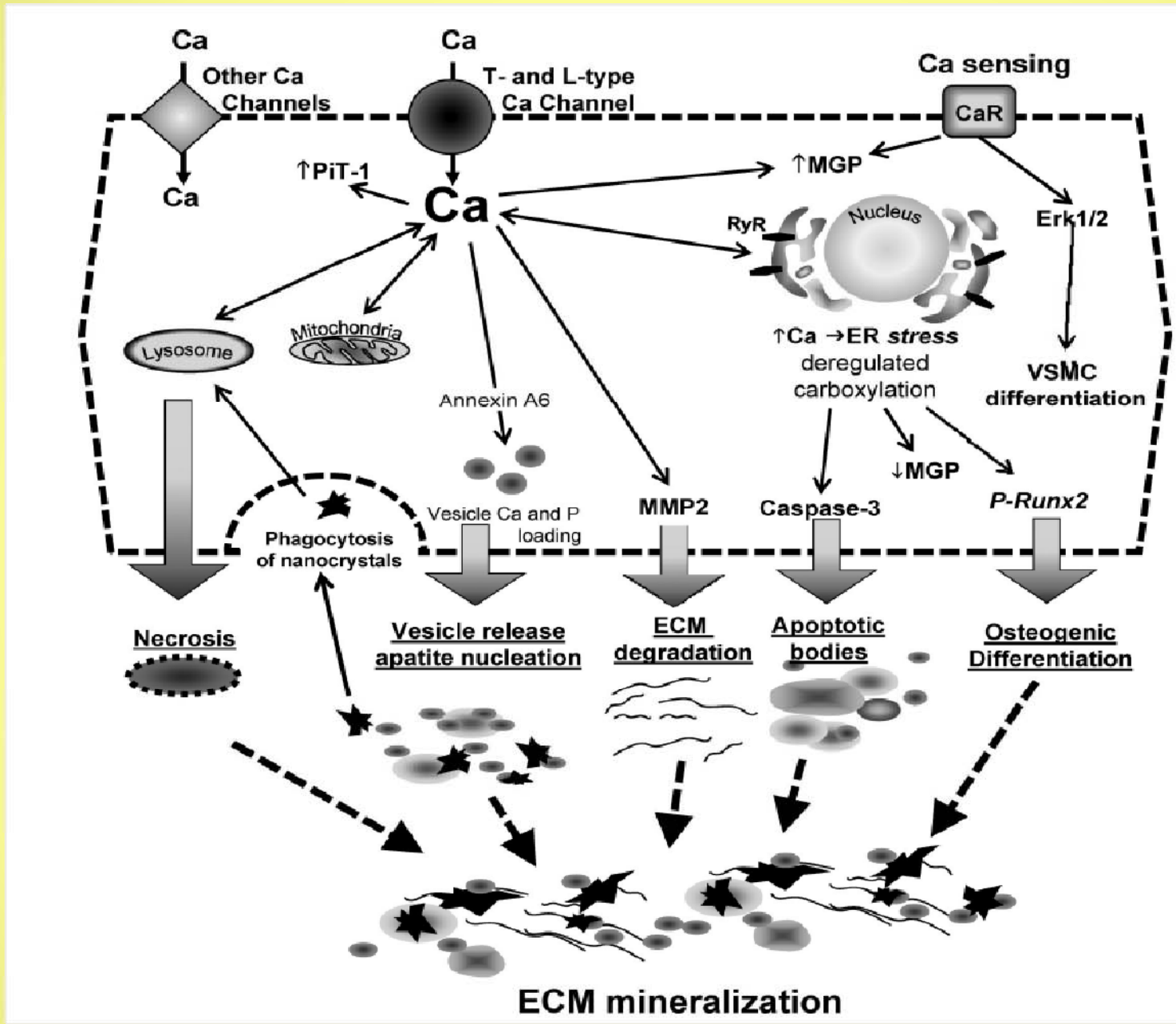


Giachelli C. KI 2009

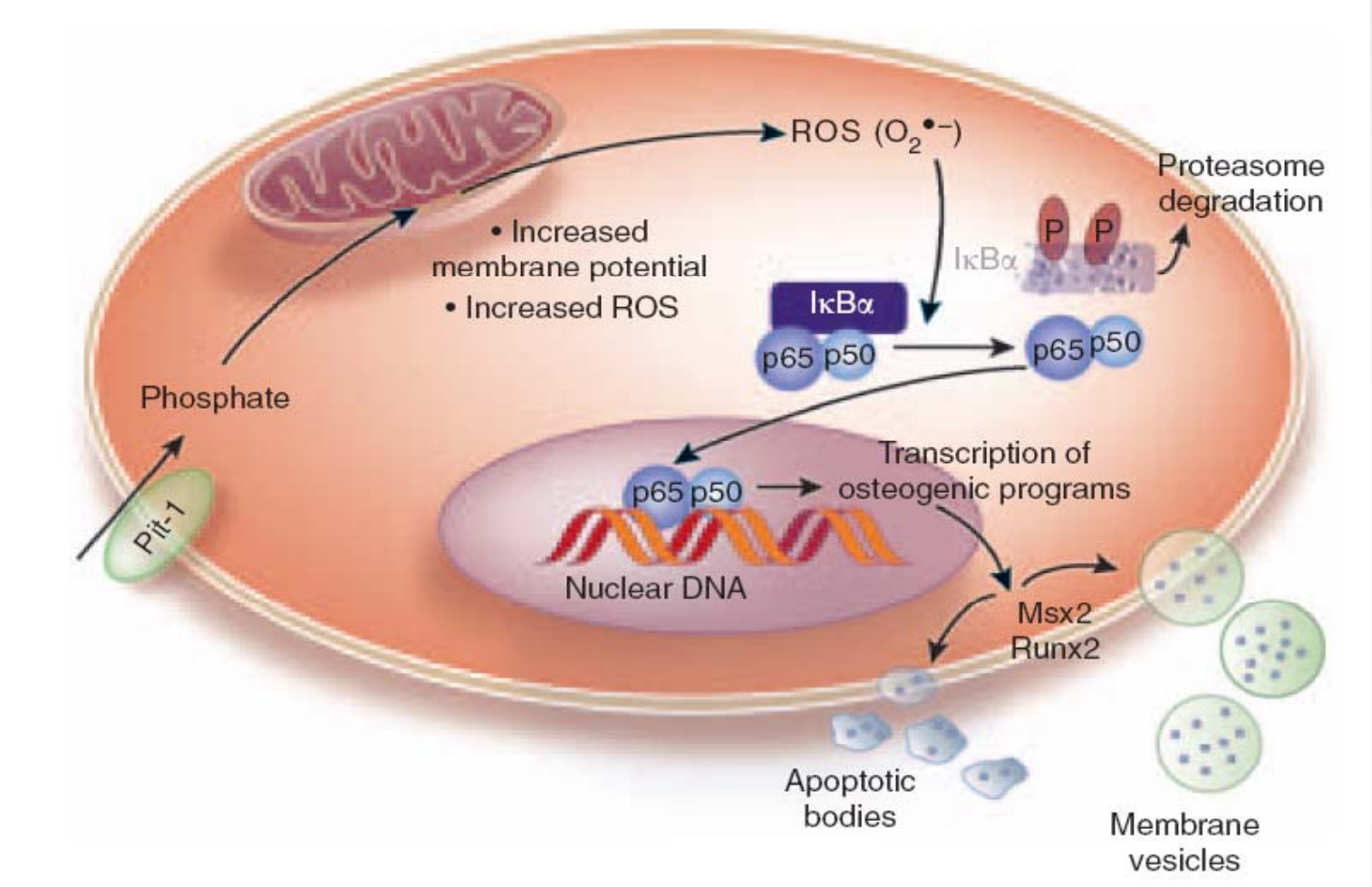

ROS
ROS
Uremia
Uremic Toxins
If Hyperparathyroidism
Fetuin-A
(AHSG)
MGP
PTH → PO4-3
Pi
(Ca++ x Pi) product
Ca++
Vit D3
Osteoblast activation
"Inflammatory Cytokine Surge"
a
ROS
TNF-α
IL-1
IL-6
NFkB
RANK/
RANKL
▼ Fetuin-A, MGP
Viscous cycle
"Inflammatory Cytokine Surge"
TNF-α, IL-1, IL-6
b Endothelial Dysfunction
Arteriole
NADPH + O2
O2-
O2-
O2- ROS
Superoxide
MetS
Diabetes
eNOS uncoupling
⇩eNO Bioavailability
ENDOTHELIUM
Proinflammatory
Proconstrictive
Prothrombotic
▲ Vasoconstriction
VSMC - Pc
"Osteogenic switch"
PO4-3
Na+
Pit-1
PO4-3
Pi
Matrix vesicles nucleators
Ca+2 3 (PO4-3)2
▲expression of osteopontin
PO4-3
Smooth muscle gene expression
Osf2/Cbfa1 / Runx2
Transcription factor activation
ROS
Promote VSMC Apoptosis
d VSMC Apoptosis
arteriole media
ROS
Matrix vesicles
VSMC
Matrix vesicles
Osteoid Replacement
Inflammation
Opg/RANK/RANKL – NFkB axis and ▲ downstream cytokines
Phenotypic Osteogenic Differentiation Switch"
"Osteogenic
Alkaline Phosphatase (ALP)
Glucose
Hypoxia
ROS
Normal VSMC within media
c
Elastin
VSMC
Elastin
Normal VSMC
c
Osteogenic Cell Phenotype
Osteocalcin
osteonectin
Extraosseous bone formation
Ectopic
Binds extracellular Ca++
Active Vascular Calcification
▼systemic Fetuin-A and local MGP
e
VSMC apoptotic body
CaPO4
VSMC
Matrix vesicles:
Nidus
Nucleators
200 nm



Shanahan et al, Circ Res 2011



Shanahan et al, Circ Res 2011



Phosphate-induced vascular calcification is mediated through activation of mitochondrial reactive oxygen species, and p65 nuclear translocation.

P → Inflamación y Stress Oxidativo

Khao et al. KI 2011
Al-Aly Z. KI 2011

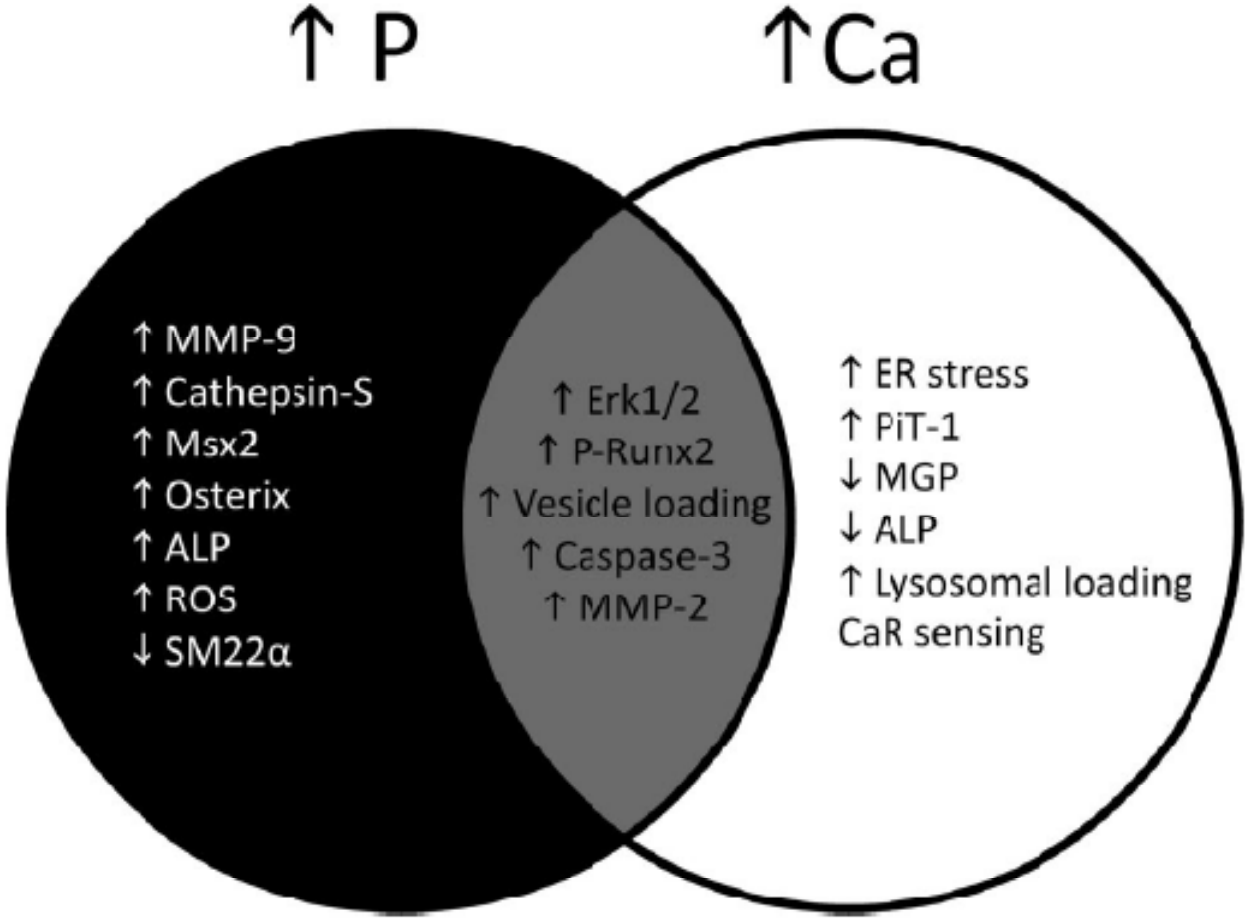
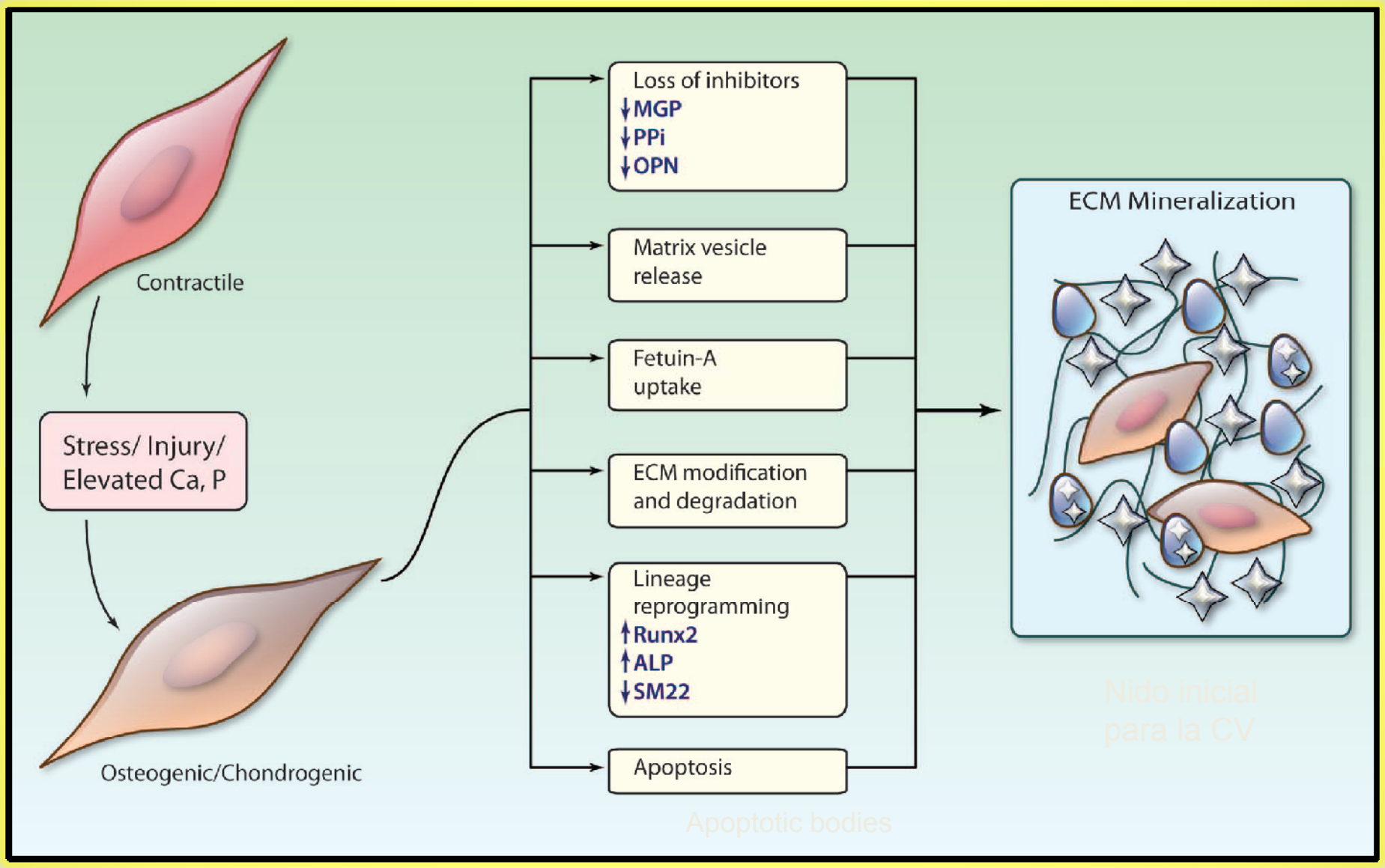
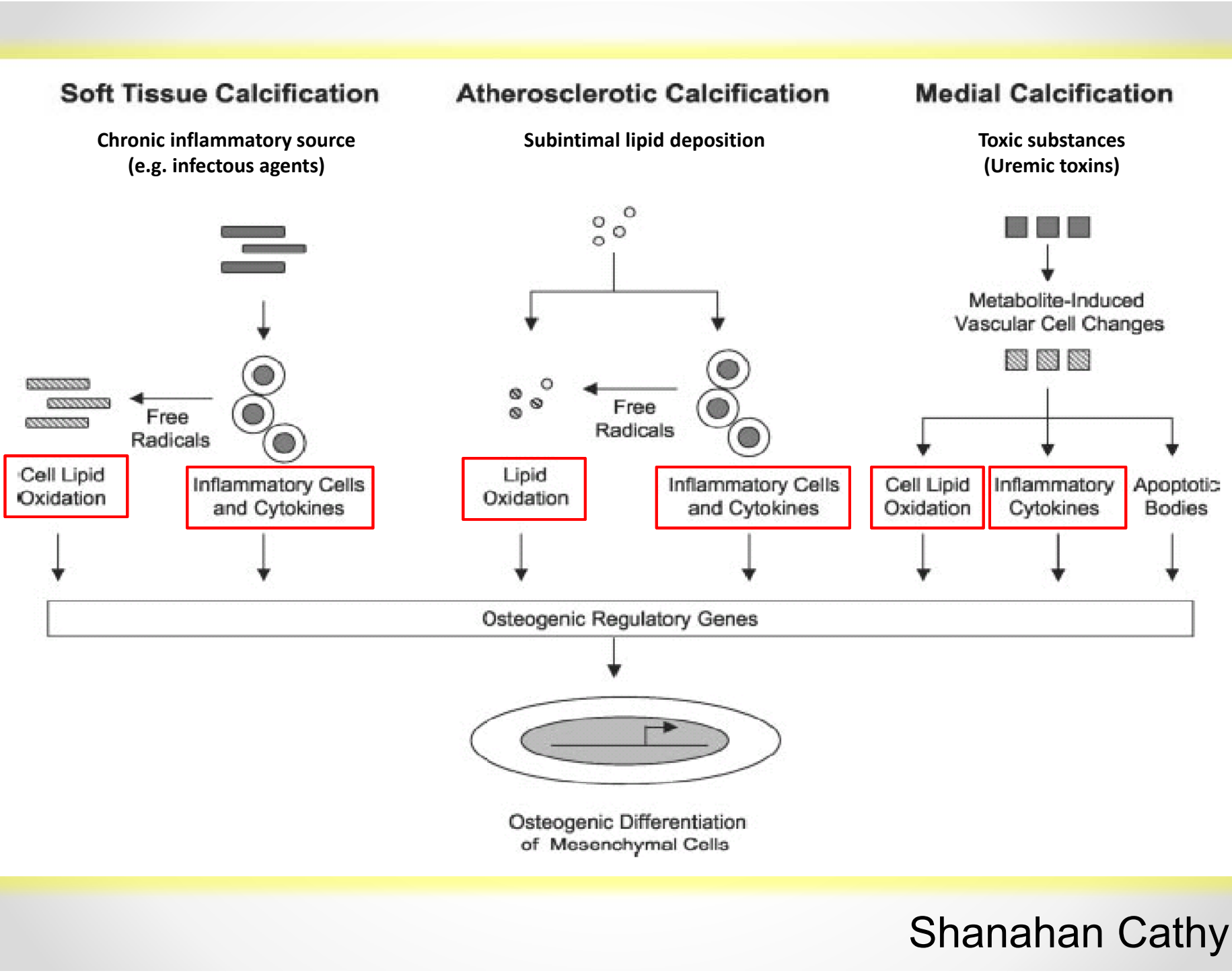


Figure 5. Overview of distinct and overlapping pathways initiated by elevated calcium (Ca) and phosphate (P) in vascular smooth muscle cells (VSMCs). Black background indicates pathways specific to elevated serum inorganic phosphate (Pi), white background indicates pathways specific to elevated serum Ca, and gray area shows common pathways.

Shanahan et al, Circ Res 2011

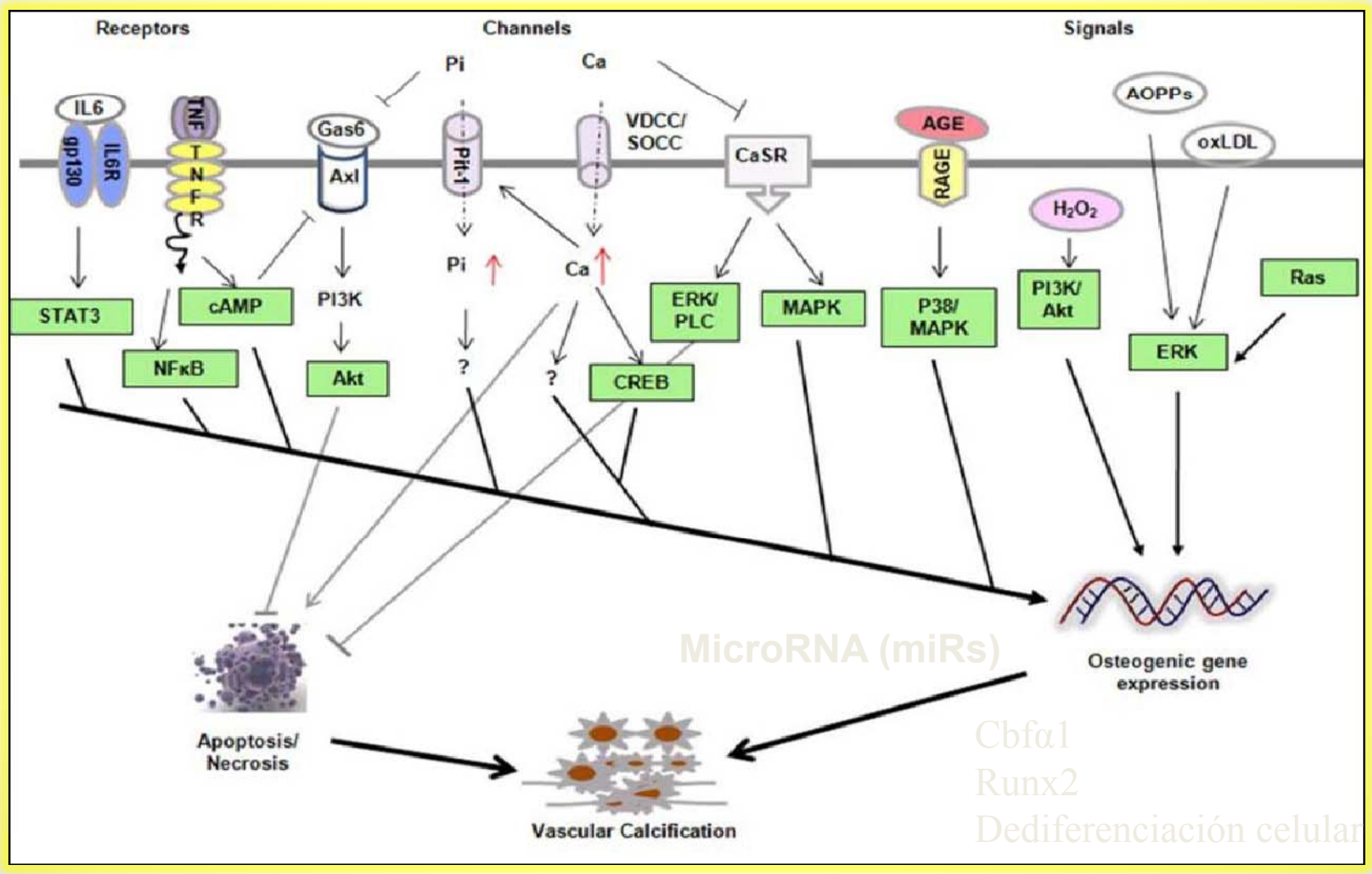


Shanahan et al. Arterial Calcification in CKD:
Key roles for calcium and phosphate. Circ Res 2011

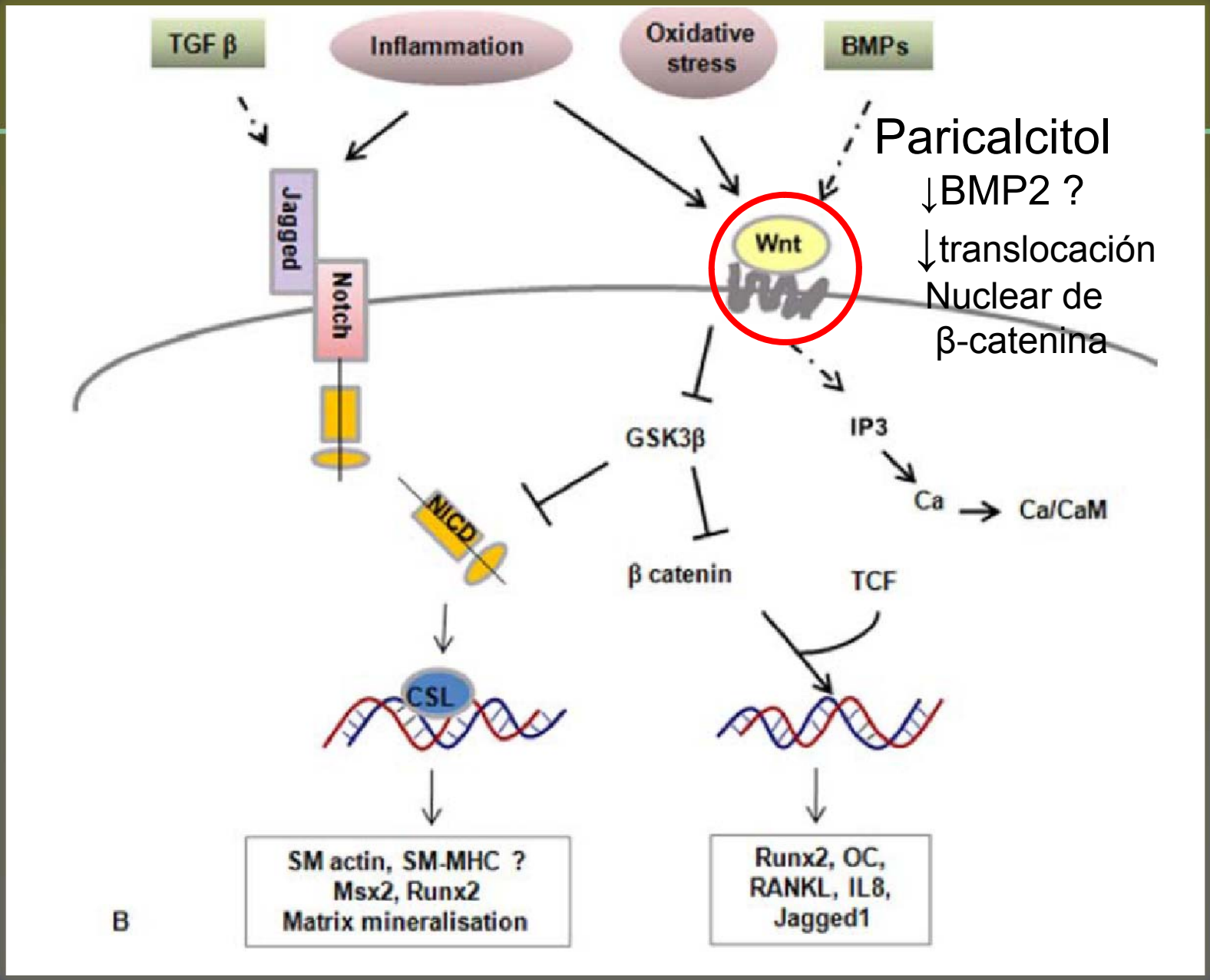


Shanahan Cathy

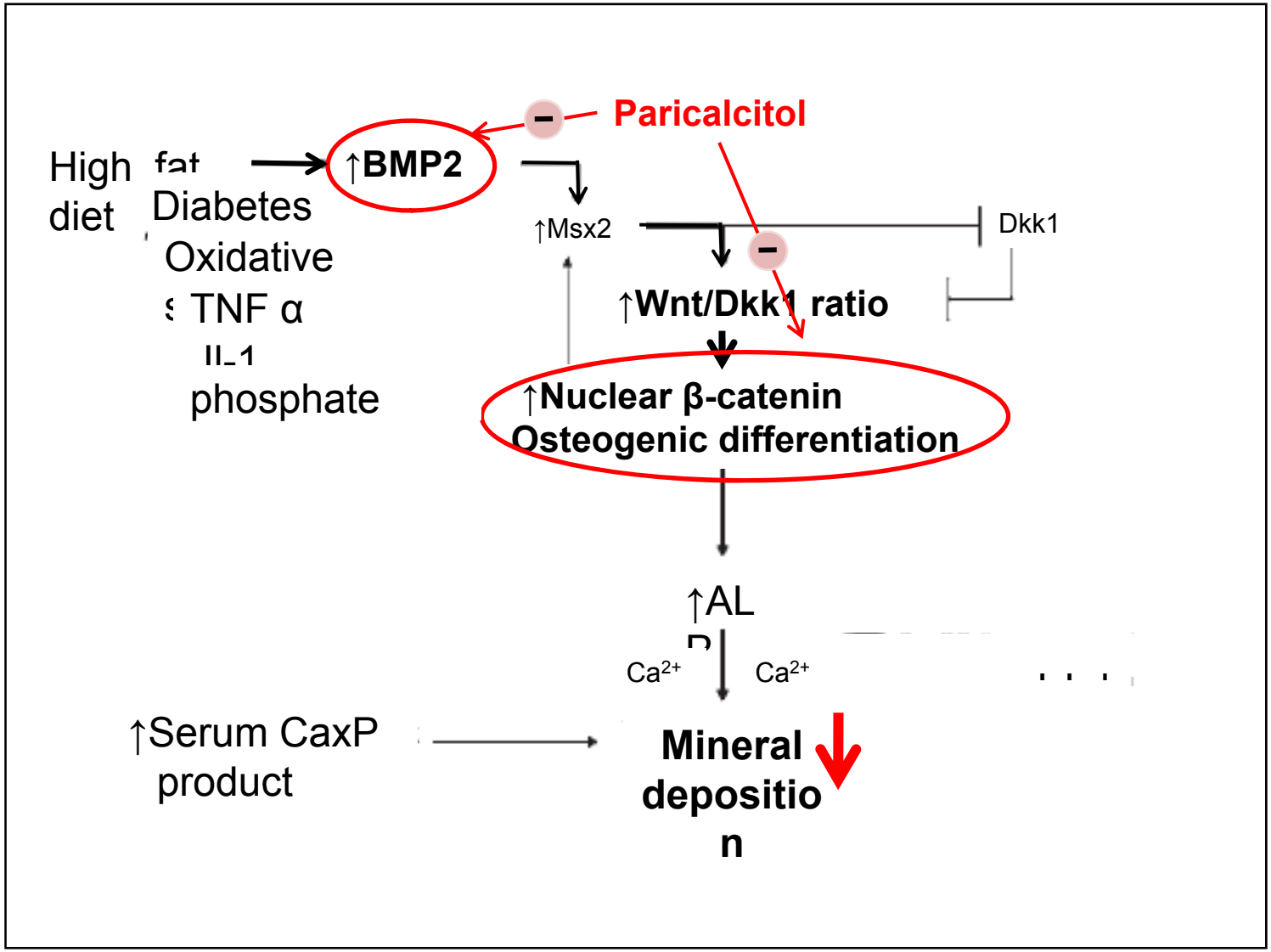
Señalización celular de la CV



Y. Liu & C. Shanahan Front Biosc 2011


TGF β
Inflammation
Oxidative stress
BMPs
Jagged
Notch
Wnt
Paricalcitol
↓BMP2 ?
↓translocación Nuclear de β-catenina
GSK3β
IP3
Ca
Ca/CaM
NICD
β catenin
TCF
CSL
SM actin, SM-MHC ?
Msx2, Runx2
Matrix mineralisation
Runx2, OC,
RANKL, IL8,
Jagged1
B

Working model: osteogenic regulation of vascular calcification



- **ACTUAR CON LA MEJOR DE LAS EVIDENCIAS DISPONIBLES**

en contraposición a

- **ESPERAR A LA MEJOR DE LAS EVIDENCIAS PARA EMPEZAR A ACTUAR**

- NOT A NEW PHENOMENON : MUMMY

  CLASIFICACION ATEROMATOSIS

- NDT VASCULAR CALCIFICATION
- FIRST DO NOT HARM
- P-PTH and renin = Bozic J Hypertnes 2014

- Chirinos Reducing arterial stiffness in CKD editorial CJASN 2015
- To screen or not to screen Tuot CJASN 2015

Table 2. Presence of plaque at any territory [*n*(%)] stratified by age, sex, CKD stage and diabetic condition

	Men					Women				
Age (years)	Non-CKD	CKD 3	CKD 4–5	CKD 5D	P trend	Non-CKD	CKD 3	CKD 4–5	CKD 5D	P trend
Non-diabetics										
≤35	1 (5.0)	1 (3.8)	2 (9.5)	6 (13.0)	0.171	1 (4.0)	0 (0)	1 (5.6)	8 (25.8)	0.008
36–45	10 (27.0)	11 (31.4)	9 (25.0)	37 (51.4)	0.009	4 (11.1)	3 (13.6)	9 (29.0)	13 (31.7)	0.015
46–55	43 (60.6)	30 (65.2)	37 (59.7)	60 (81.1)	0.019	24 (34.3)	18 (45.0)	23 (44.2)	35 (59.3)	0.007
56–65	65 (77.4)	105 (73.4)	94 (89.5)	77 (92.8)	<0.001	28 (42.4)	38 (58.5)	49 (68.1)	36 (75.0)	<0.001
66–75	39 (78.0)	167 (89.8)	91 (89.2)	55 (96.5)	0.009	24 (61.5)	69 (67.6)	60 (82.2)	45 (88.2)	<0.001
Diabetics										
≤35	0 (0)	0 (0)	0 (0)	1 (33.3)	na[a]	0 (0)	0 (0)	0 (0)	1 (50.0)	na[a]
36–45	0 (0)	8 (61.5)	6 (60.0)	8 (80.0)	na[a]	1 (100)	3 (60.0)	1 (11.1)	5 (55.6)	0.704
46–55	2 (33.3)	11 (73.3)	16 (84.2)	10 (100.0)	0.002	6 (100)	5 (62.5)	10 (76.9)	3 (50.0)	0.138
56–65	15 (93.8)	62 (87.3)	35 (81.4)	25 (96.2)	0.827	5 (71.4)	18 (69.2)	14 (77.8)	14 (93.3)	0.141
66–75	11 (78.6)	78 (94.0)	69 (95.8)	27 (100.0)	0.017	6 (54.5)	29 (90.6)	41 (80.4)	15 (93.8)	0.114

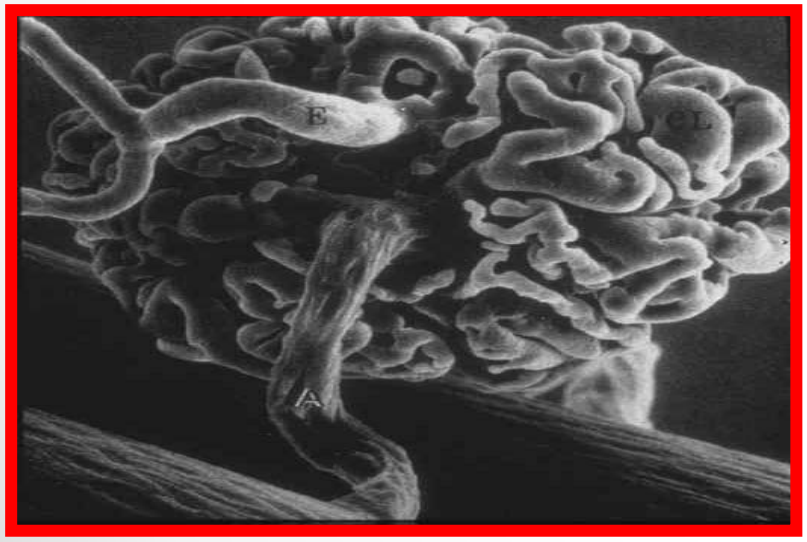
[a]na stands for not applicable groups, i.e. those empty groups (with nobody) for whom any plaque percentages cannot be estimated.

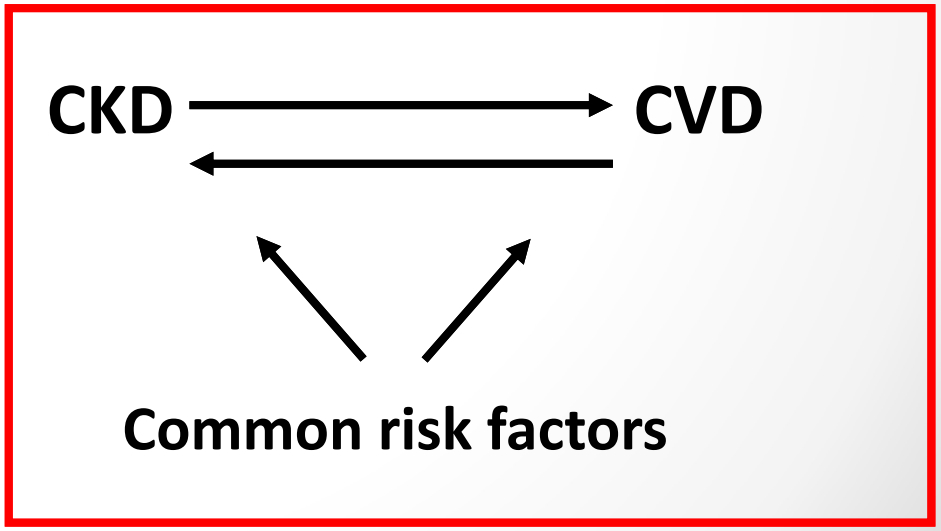
NEFRONA study. UDETMA Lleida

Nephrol Dial Transplant 2014

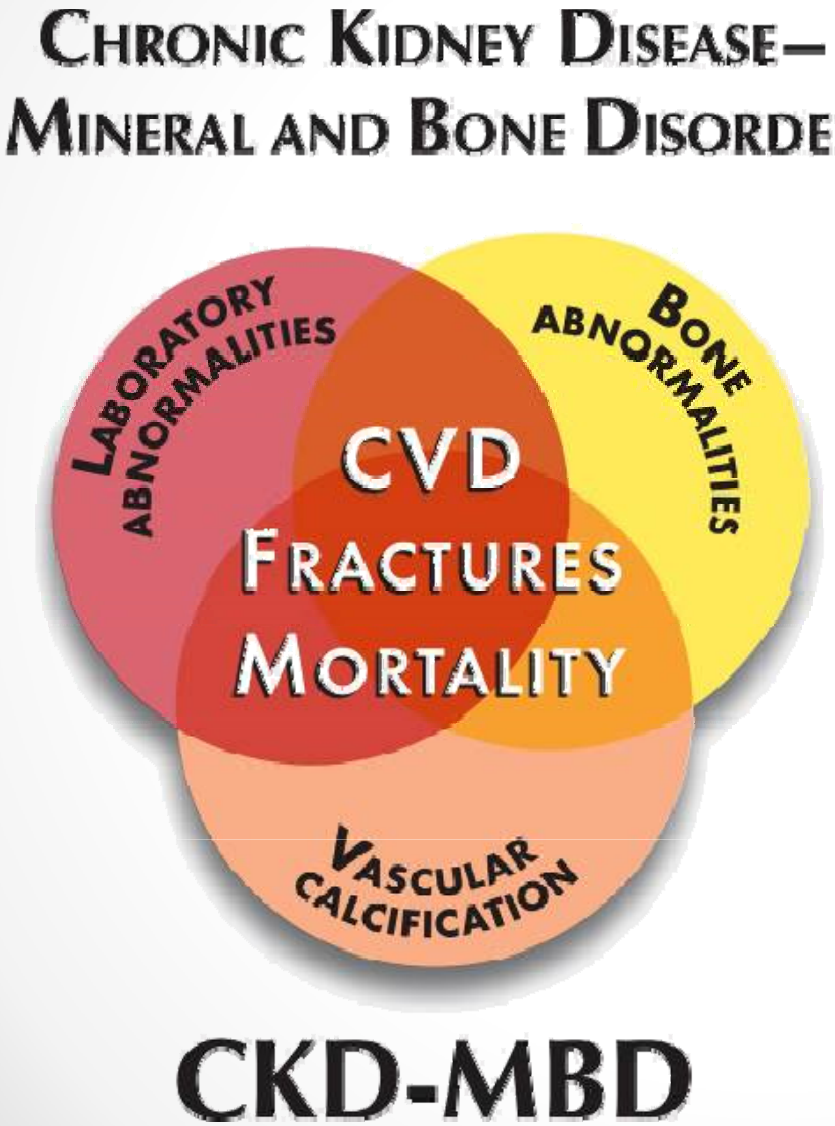
Chronic Kidney Disease (CKD) and Cardiovascular Disease (CVD)

C K D





CKD–MBD: **Systemic** disorder



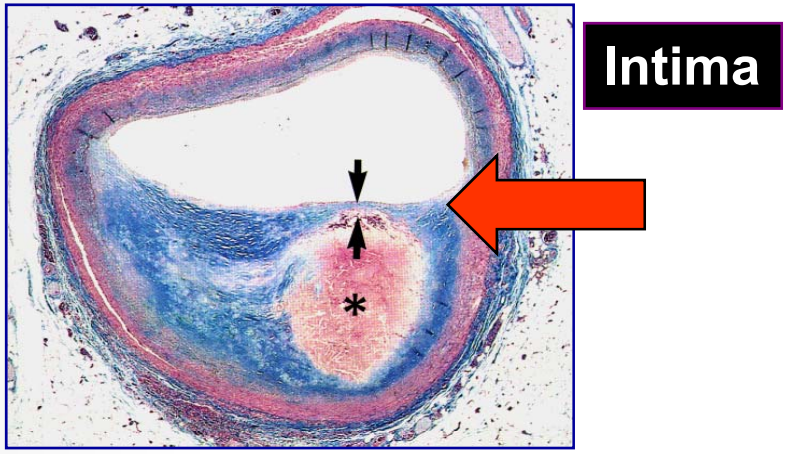
Beyond laboratory abnormalities

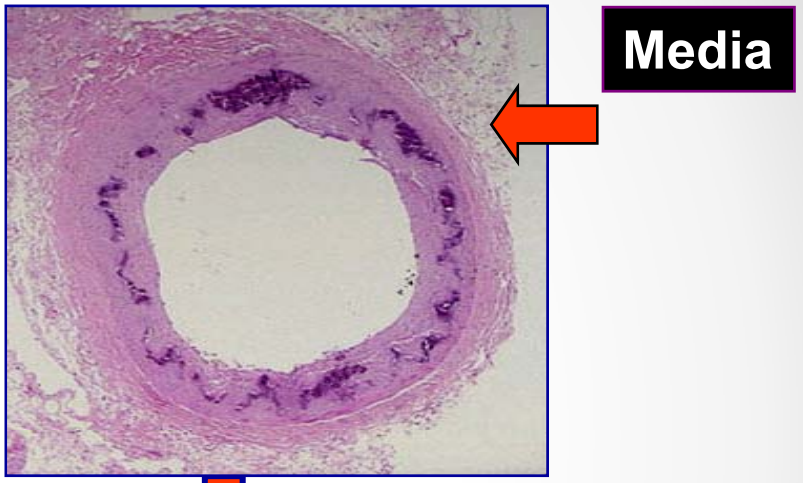
- **Bone–kidney axis**
- **Bone–vascular axis**

Among non-traditional

CVD en ERC: No sólo es ateromatosis

Ateromatosis y envejecimiento acelerados





ATEROMATOSIS

Lesiones isquémicas

Oclusión vascular

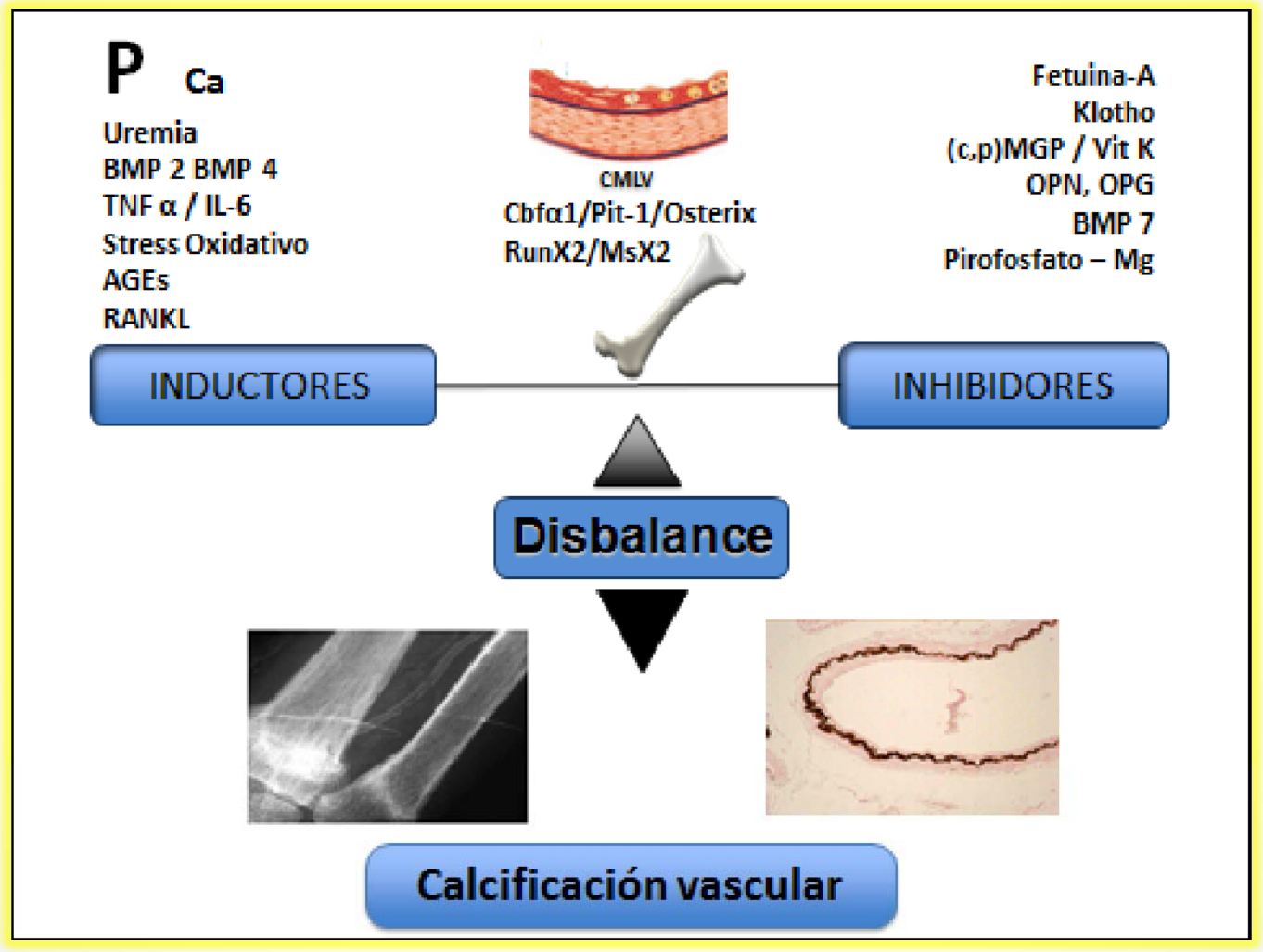
ARTERIOESCLEROSIS

Rigidez Vascular

↓ Amortiguación

↑ VOP (↑PAS↓PAD)

CALCIFICACIÓN VASCULAR PASIVA Y ACTIVA



Lloret M.J, Bover J. et al. Nefrologia Sup 2013;4(2):2-10

OSERCE II: Detección de calcificaciones mediante Radiografías simples

Lectura centralizada por dos radiólogos (748 pacientes x 3 Rx)

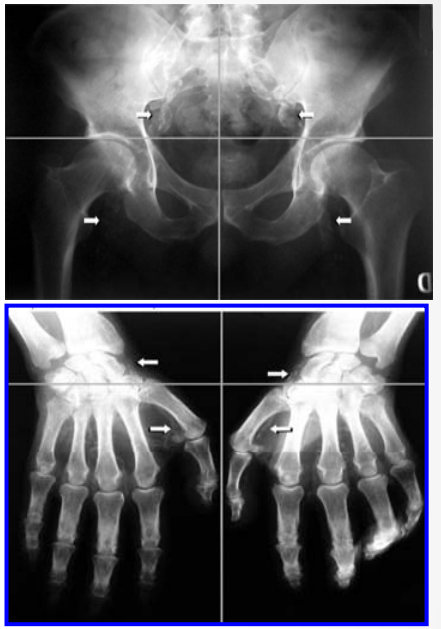
Indice de Adragao (0-8)

Pelvis:

-cuadrante superior derecho: 0 / 1
cuadrante superior izquierdo: 0 / 1
cuadrante inferior derecho: 0 /1
cuadrante inferior izquierdo: 0 / 1

- Manos:

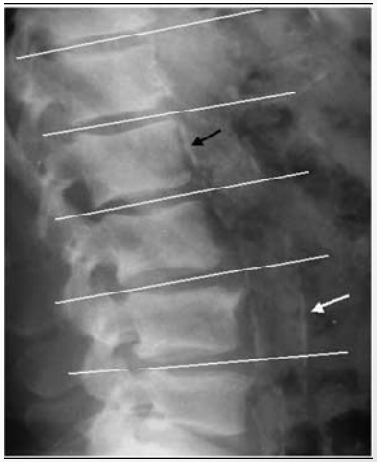
- Mano der: superior: 0 / 1
- Mano der: inferior: 0 / 1
- Mano izq superior: 0 / 1
- Mano izq inferior: 0 / 1



Indice de Kauppila (0-24)

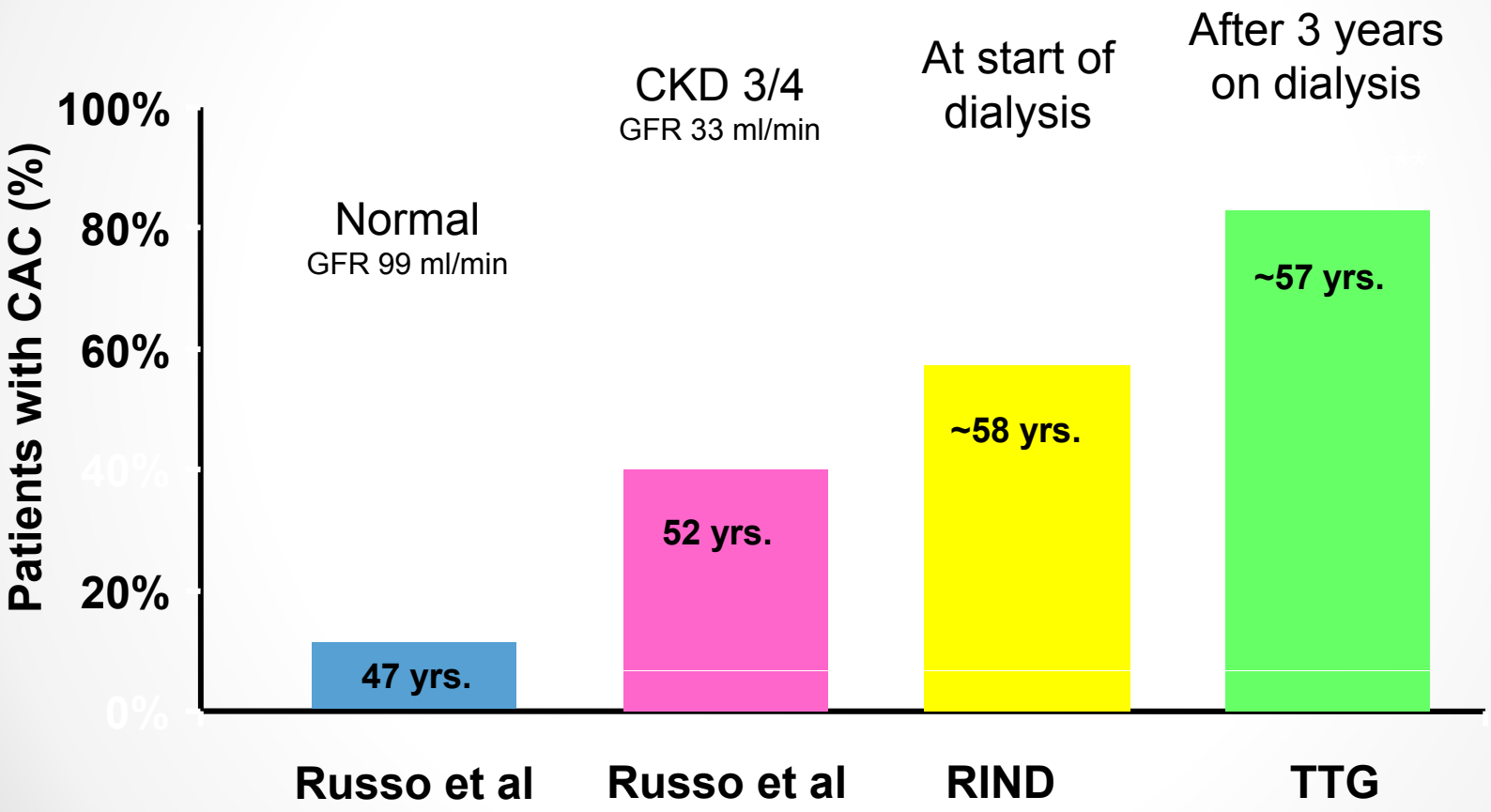
-Análisis vértebras L1-L4

-0: No calcificación
-1: Calcificación pequeña
-2 Calcificación moderada
-3 Calcificación grande,
Anterior y posterior



Adragao T, et al. Nephrol Dial Transplant 2004;19:1480–8; Kauppila LI et al. Atherosclerosis 1997; 132: 245-250

Coronary artery calcification (CAC) is associated with GFR and dialysis vintage



*Russo D et al Am J Kidney Dis 2004;44:1024-1030
**Spiegel D et al. Hemod Internat 2004: 8:265
*** Chertow GM et al. Kidney Int 2002;62:245-252

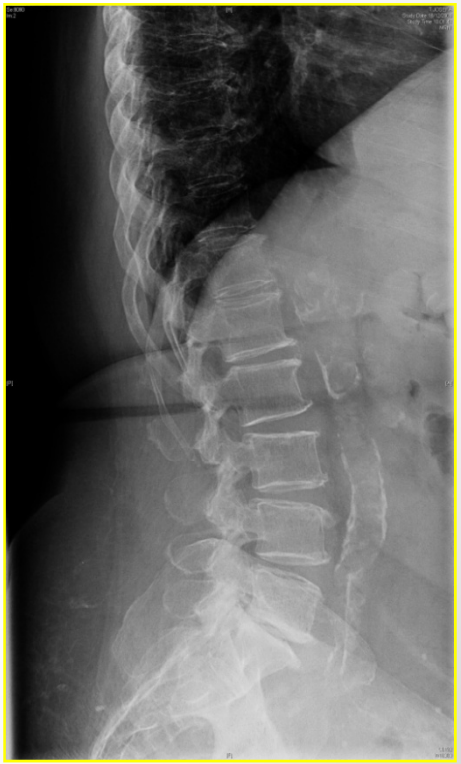
Calcificación vascular (preHD)

(X Ray 695 patients)

79 % some degree of Vascular Calcification

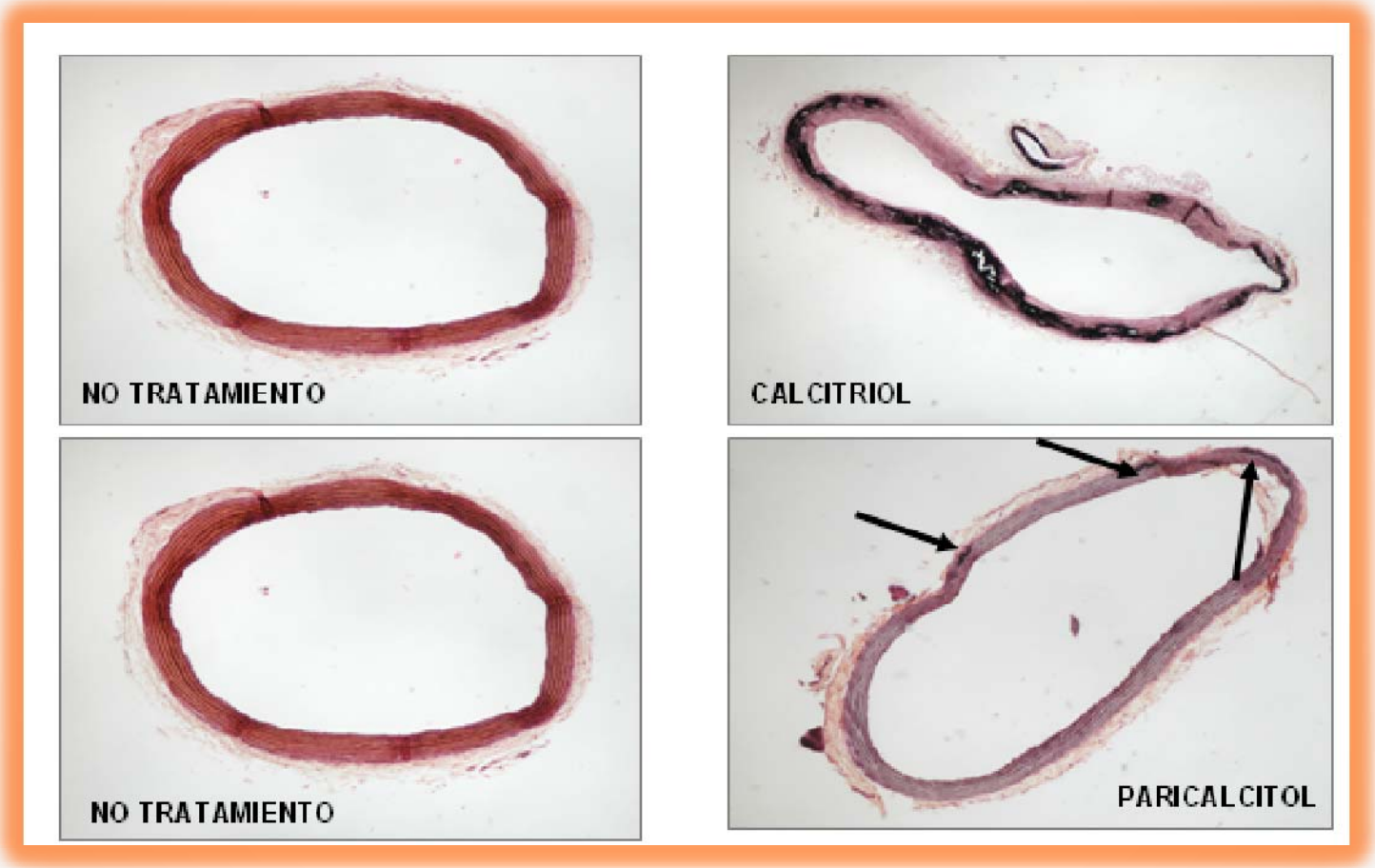
47 % significant calcifications (Adragao ≥3 or Kauppila > 6)

	%
Vascular calcification	79
Vascular calcification by Adragao's score	46
Vascular calcification by Kaupilla's score	72,5



Gómez JL et al. JASN 2010 (abstract)

Differential effect of calcitriol and paricalcitol on aortic calcification



Cardús et al. Effects of 1,25 (OH) 2D3 and 19-nor-1,25-(OH) 2D2 on VSMC proliferation and calcification. JBMR, 2007

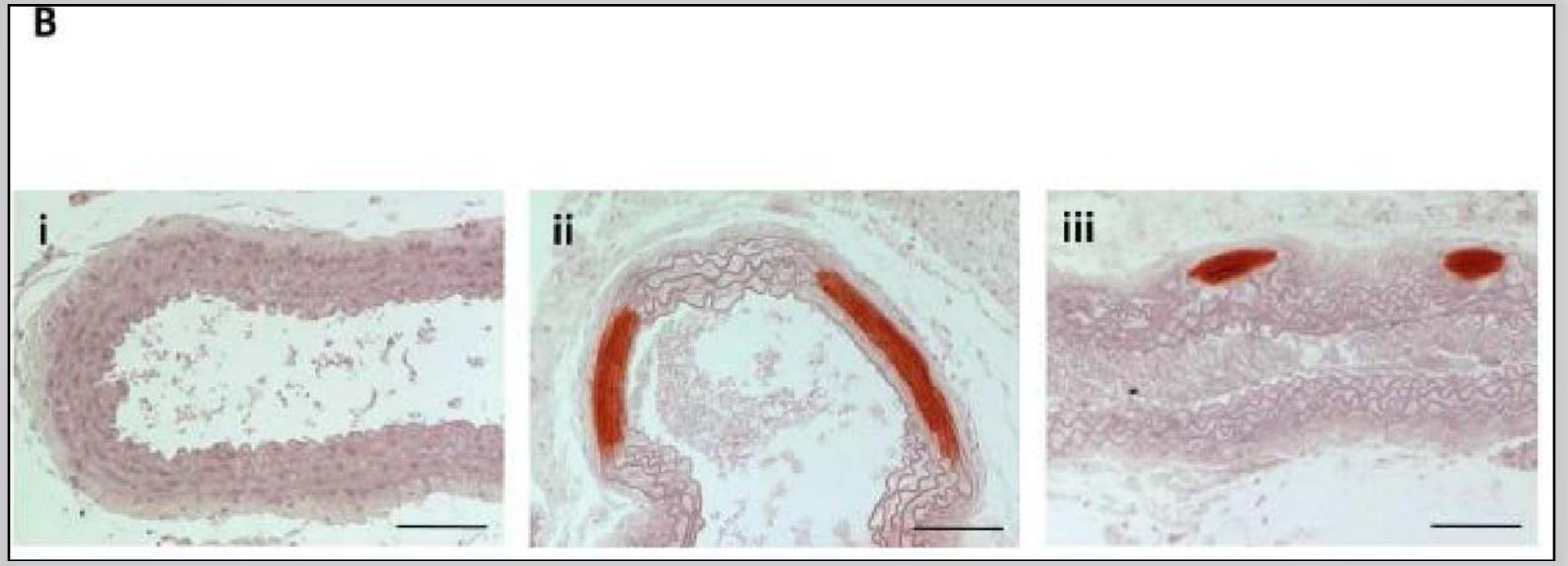
↓BMP2?, ↓translocación nuclear B catenina (Wnt) → RUNX2

Kidney Int. 2012 Dec;82(12):1261-70. doi: 10.1038/ki.2012.322. Epub 2012 Aug 29.

Vitamin D receptor agonists increase klotho and osteopontin while decreasing aortic calcification in mice with chronic kidney disease fed a high phosphate diet.

Lau WL, Leaf EM, Hu MC, Takeno MM, Kuro-o M, Moe OW, Giachelli CM.

Department of Nephrology, University of Washington, Seattle, Washington 98195, USA.



Thoracic aorta with Alizarin Red-S stain showing marked medial calcification in CKD+HP animal (ii) compared to NC+NP animal (i), and significantly less calcification in an animal treated with paricalcitol (CKD+HP+P300, iii).

EVOLVE: NS Primary end-point.
Predefined Adjustment for Baseline Characteristics (ITT)*: Nominally Significant** 12% Reduction in the Risk of Death and Cardiovascular Events in Patients with SHPT#

	HR (95% CI)	P value**
Treatment group (Cinacalcet vs. Placebo)	0.88 (0.79, 0.97)	0.008

* prespecified adjustment for up to 40 characteristics, including age (years) at randomisation, BMI (kg/m^2),history of CV disease

the trial did not meet its primary endpoint in the unadjusted intent-to-treat analysis

** formal statistical significance cannot be claimed. reported P values should be considered nominal

Chertow GM, et al. *N Engl J Med*. 2012;367:2482-94.

CKD-MBD

Chronic–Kidney Disease–Mineral and Bone Disorder
ERA–EDTA Working Group

NDT Perspectives

Is chronic kidney disease-mineral bone disorder (CKD-MBD) really a syndrome?

Nephrol Dial Transplant. 2014 Oct;29(10):1815-20.

Mario Cozzolino[1], Pablo Ureña-Torres[2], Marc G. Vervloet[3], Vincent Brandenburg[4], Jordi Bover[5], David Goldsmith[6], Tobias E. Larsson[7,8], Ziad A. Massy[9,10] and Sandro Mazzaferro[11], on Behalf of the CKD-MBD Working Group of ERA-EDTA

Bone: a new endocrine organ at the heart of chronic kidney disease and mineral disorders

*Marc G Vervloet, Ziad A Massy, Vincent Brandenburg, Sandro Mazzaferro, Mario Cozzolino, Pablo Ureña-Torres, Jordi Bover, David Goldsmith, on behalf of the CKD-MBD Working Group of ERA-EDTA**

Lancet Diabetes Endocrinol. 2014 May;2(5):427-36.

Chronic Kidney Disease (CKD) and Cardiovascular Disease (CVD)

CKD

CKD ⟷ CVD

Common risk factors

Cardio-Renal Sd

CVD - MBD

Jamal et al. Lancet 2013 meta-analysis 3-5D

22% mortality risk reduction associated with non-Ca based P binders, sevelamer and lanthanum. However,

- Binders were titrated to high doses (protocol-driven targets)

- Cautious extrapolation to situations of low-Ca exposure, including combination therapy

Hill et al. ERC 3b-4 Ca^{45} meals 1 g Ca . 1,5 g P

Kidney Int 2013

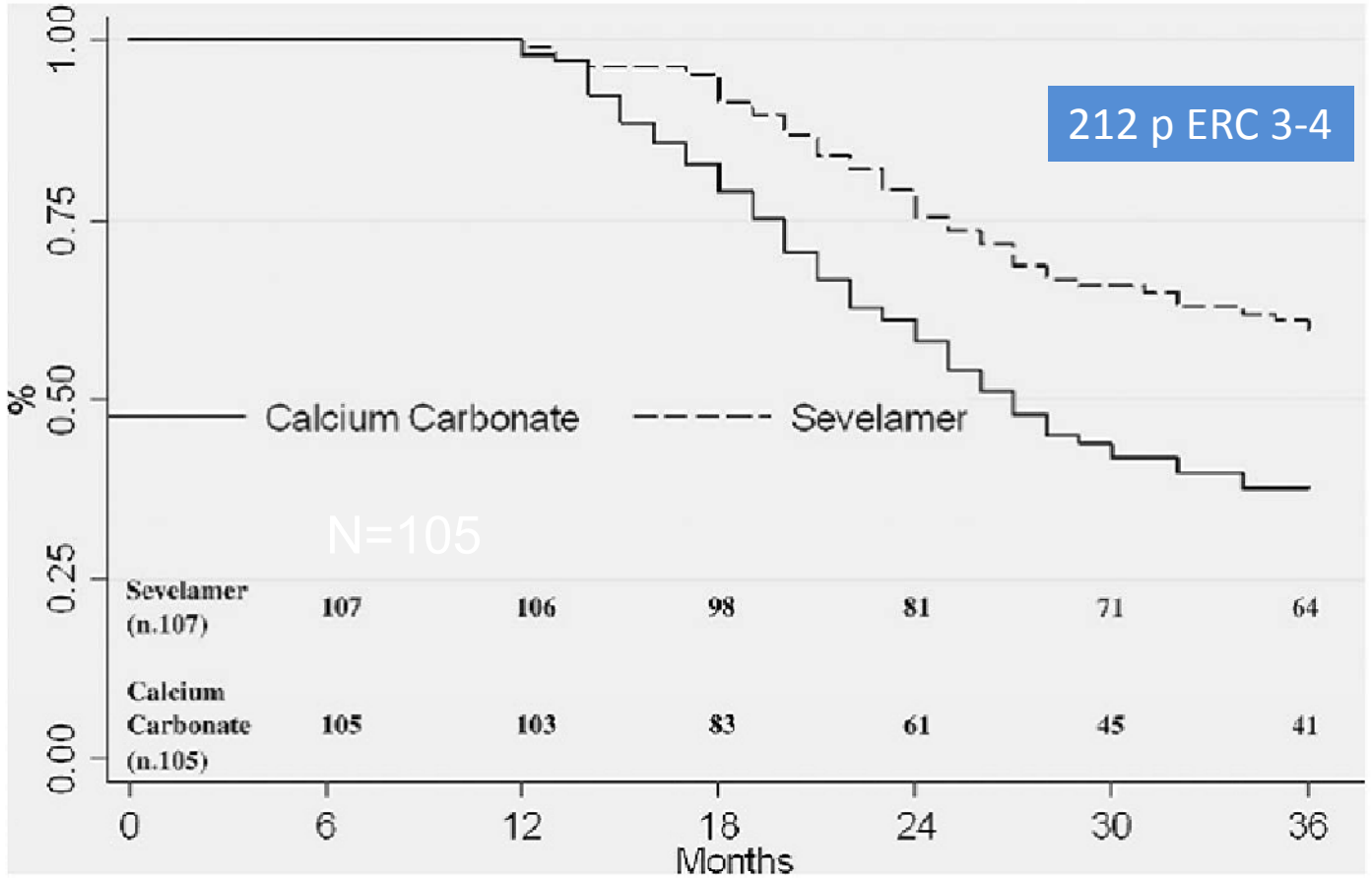
2 experimental weeks

Supplementation of 3 x 500 mg Ca → + Ca balance , Ca carbonate did not have any effect on P balance … transient? Adaptations?

Most recent DI IORIO

Mortality in Kidney Disease Patients Treated with Phosphate Binders: A Randomized Study

Biagio Di Iorio, Antonio Bellasi,† and Domenico Russo,† on behalf of the INDEPENDENT Study Investigators*



All cause-mortality and composite death-dialysis inception

CJASN 7: 487-493, 2012

P binders may not slow VC in moderate CKD: Block et al JASN 2012; Lemos et al Clin Nephrol 2013

Table 1. Comparison of distinct effects of P binders and anti-parathyroid agents on CKD-MBD laboratory parameters, progression of vascular calcification (VC) and/or survival. Ca = Calcium; P = Phosphate; PTH = Parathyroid hormone; NA = Not available; RCT = Randomized Clinical Trial; Exp = only experimental studies.

P binders	Ca	P	Ca x P	PTH	VC	Survival
Aluminum	-	↓↓↓	↓↓	-↓	NA	NA
Ca-based	↑-↑↑	↓↓	↓-	↓↓	↑↑- (RCTs)	- (RCT)
Non-Ca-Based	-	↓↓	↓	-↑	↑- (RCTs)	- (RCT) ↑ (2ry analysis RCT) ↑ (metanalysis)
Anti-parathyroid drugs						
Calcitriol (CTR), Alfacalcidol, Doxercalciferol	↑-↑↑	↑	↑	↓↓↓	↓-↑↑↑ (Exp)	- (no RCT) ↑ (metanalysis) ↑ (CTR, retrospective)
Paricalcitol	-↑	-↑	-↑	↓↓↓	↓-↑ (Exp)	- (no RCT) ↑ (metanalysis) ↑ (retrospective vs CTR)
Calcimimetics	↓-↓↓	-↓	↓↓	↓↓↓	-↓ (RCT)	- (RCT) ↑ (2ry adjusted analysis RCT) - (metanalysis) ↑ (retrospective)

Sev, Lanth, Iron? ↑ P control!!!, Vit K, Bisphosphonates, Thiosulfate, Phytates

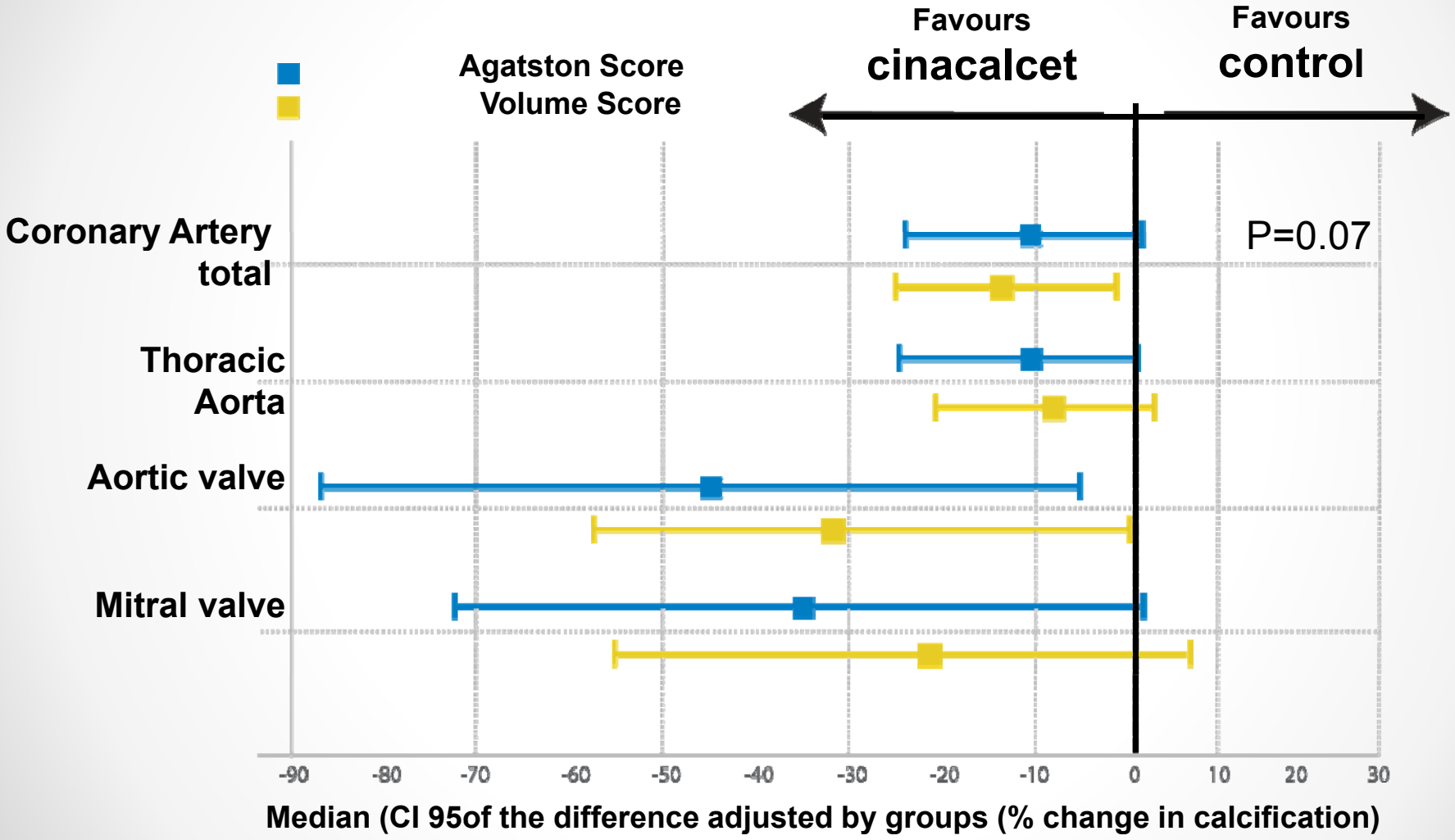
Bover J et al NDT 2015

Anti-parathyroid drugs						
Calcitriol (CTR), Alfacalcidol, Doxercalciferol	↑-↑↑	↑	↑	↓↓↓	↓-↑↑↑ (Exp)	- (no RCT) ↑ (metanalysis) ↑ (CTR, retrospective)
Paricalcitol	-↑	-↑	-↑	↓↓↓	↓-↑ (Exp)	- (no RCT) ↑ (metanalysis) ↑ (retrospective vs CTR)
Calcimimetics	↓-↓↓	-↓	↓↓	↓↓↓	-↓ (RCT)	- (RCT) ↑ (2ºº adjusted analysis RCT) - (metanalysis) ↑ (retrospective)

Sev, Lanth, Iron? ↑ P control!!!, Vit K, Bisphosphonates, Thiosulfate, Phytates

Bover J et al NDT 2015

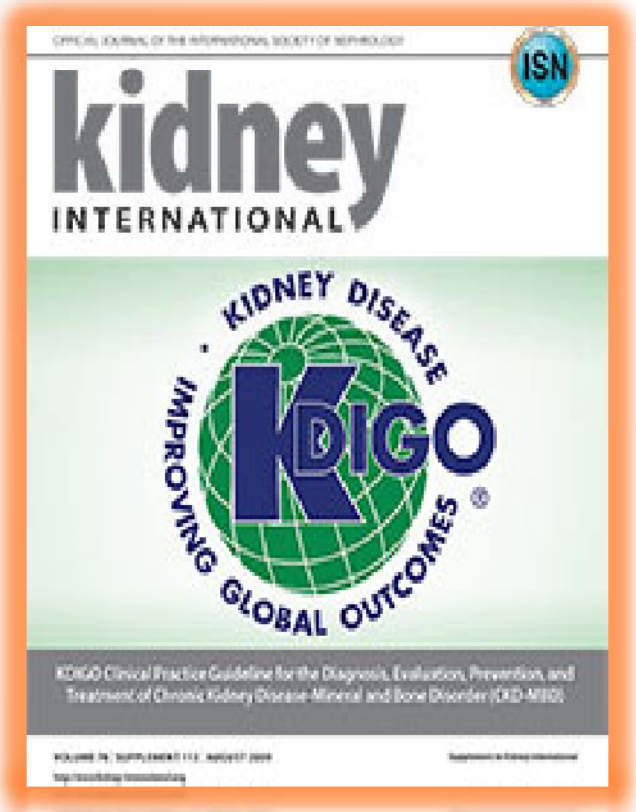
Cinacalcet effect on vascular/valvular calcification: ADVANCE study

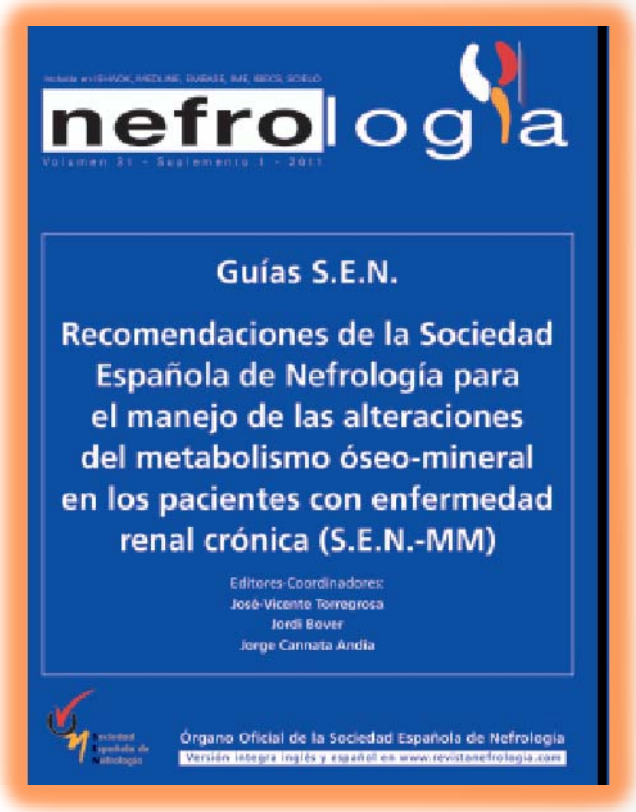


Raggi P et al. Nephrol Dial Transplant 2011;
Ureña P et al Nephrol Dial Transplant 2012 (posthoc, protocol-adherent subjects)

Positive signals pre-defined

THERE IS NOT AN UNDISPUTABLE "1A" LEVEL OF EVIDENCE IN GUIDELINES





" We suggest…We might…"

The absence of evidence is not an evidence of absence

ERC: del MDRD (IDMS) a CKD-EPI

Ver comentario editorial en página 143

Valoración de la nueva ecuación CKD-EPI para la estimación del filtrado glomerular

R. Montañés Bermúdez[1], J. Bover Sanjuán[2], A. Oliver Samper[1], J.A. Ballarín Castán[2], S. Gràcia García[1]

Servicios de [1]Laboratorio y [2]Nefrología. Fundació Puigvert. Universitat Autònoma de Barcelona FP/UAB. Red Nacional de Investigación en Nefrología (REDINREN). Instituto de Investigación Carlos III. Madrid

Nefrologia 2010;30(2):185-94

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                                ente.
BIOQUIMICA SANGRE (suero)
GLUCOSA ..........................      5.6     [  ] mmol/L       (4.2-6.0)
UREA .............................     13.2     [+2] mmol/L       (3.2-7.5)
CREATININA (Método compensado) ....    217     [+2] umol/L        (65-110)
 Filtrado Glomerular (MDRD-IDMS) ..     26          mL/min/1.73m
 Filtrado Glomerular (MDRD-IDMS) .. FG estimado indicador de ERC estadio 4 (
                                si persiste durante más de 3 meses).
 Filtrado Glomerular (CKD-EPI).....     26          mL/min/1.73m
```

Sociedad Española de Nefrología:
10 Sociedades Españolas (Martinez-Castelao A, Górriz JL, Bover J et al Nefrologia 2014)

- **Documneto común para el diagnóstico y tratamiento de la ERC y sus complicaciones**

(HTA, diabetes, dislipemia, anemia, HPS…)

Preoperative eGFR and the risk of MACVE in non-cardiac surgery. Br J Anaesth 2014
MDRD GFR is a better prognostic factor of CV events than classical CV RF in patients with PAD. J Vasc Surg 2012