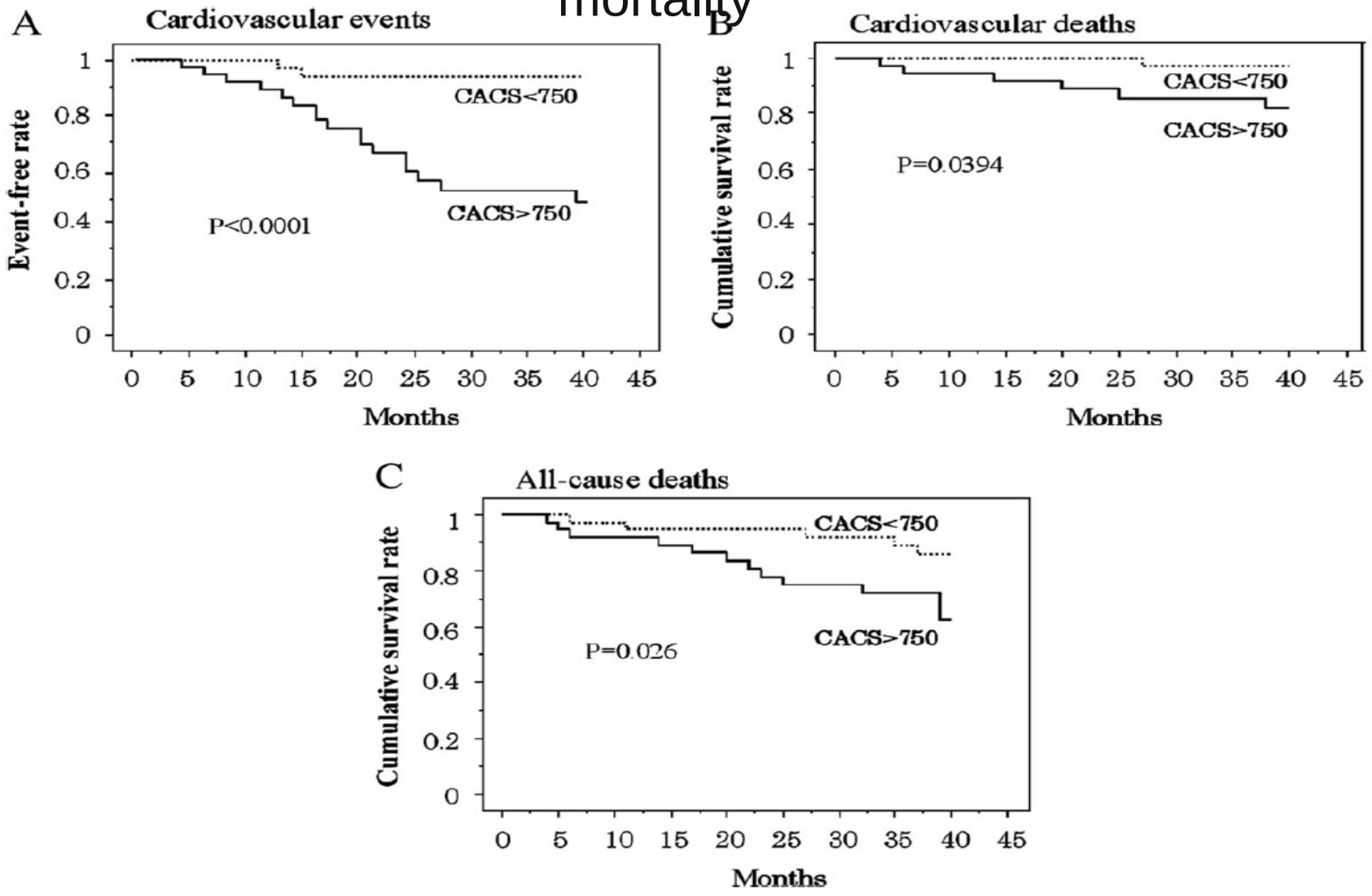
Vascular calcification in chronic kidney disease

Dr tamaddondar

Cardiovascular disease is the most common cause of death in patients with CKD, dialysis and those with a kidney transplant

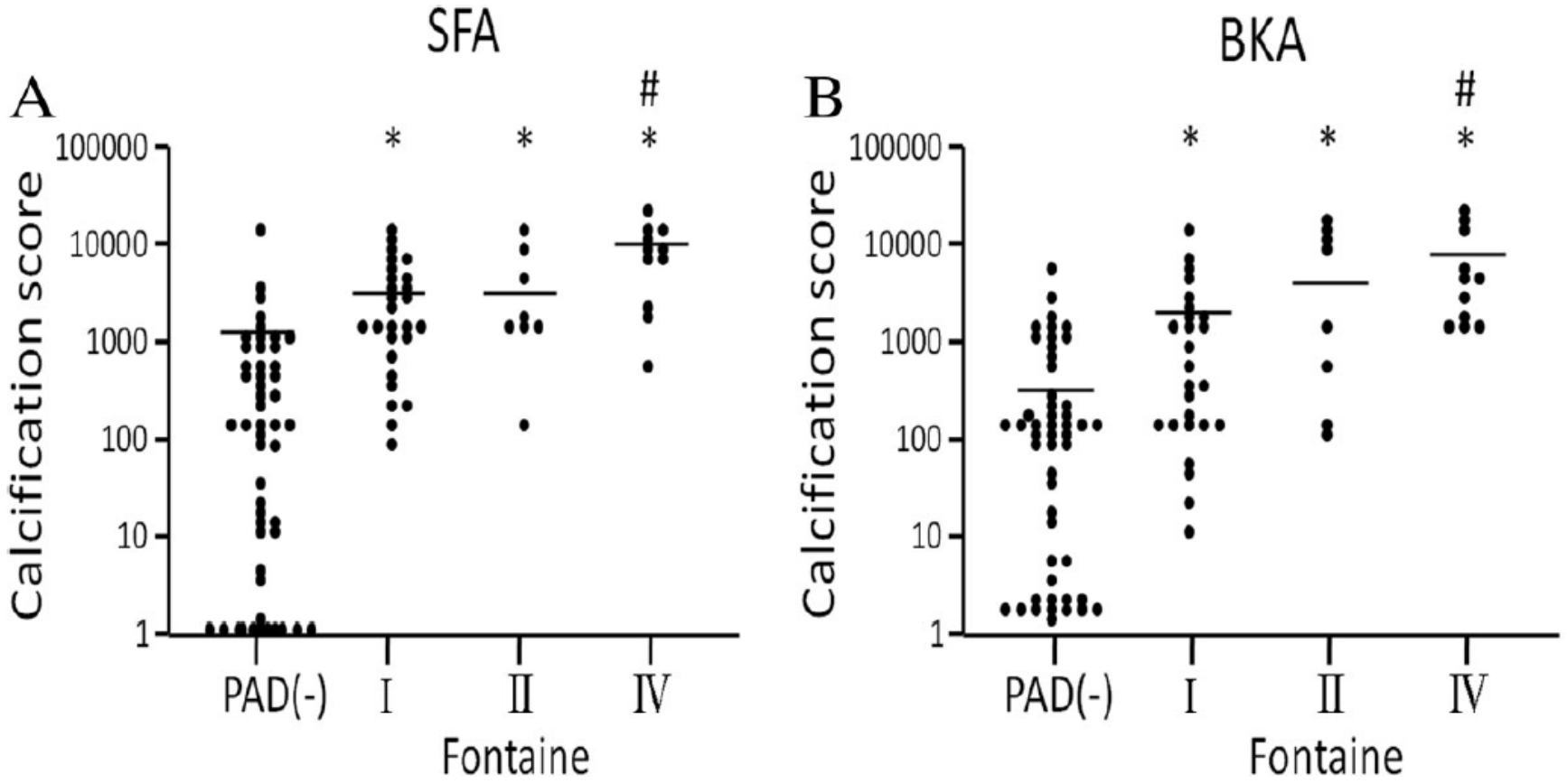
Impact of CACS on cardiovascular events, cardiovascular mortality, and all-cause mortality



Ohtake T, Ishioka K, Honda K, Oka M, Maesato K, Mano T, et al.
Hemodial Int. 2010;14:218–2

Impact of lower limbs' arterial calcification on the prevalence and severity of PAD in patients on hemodialysis

Lower limbs' arterial calcification score and severity of peripheral arterial disease in hemodialysis patients

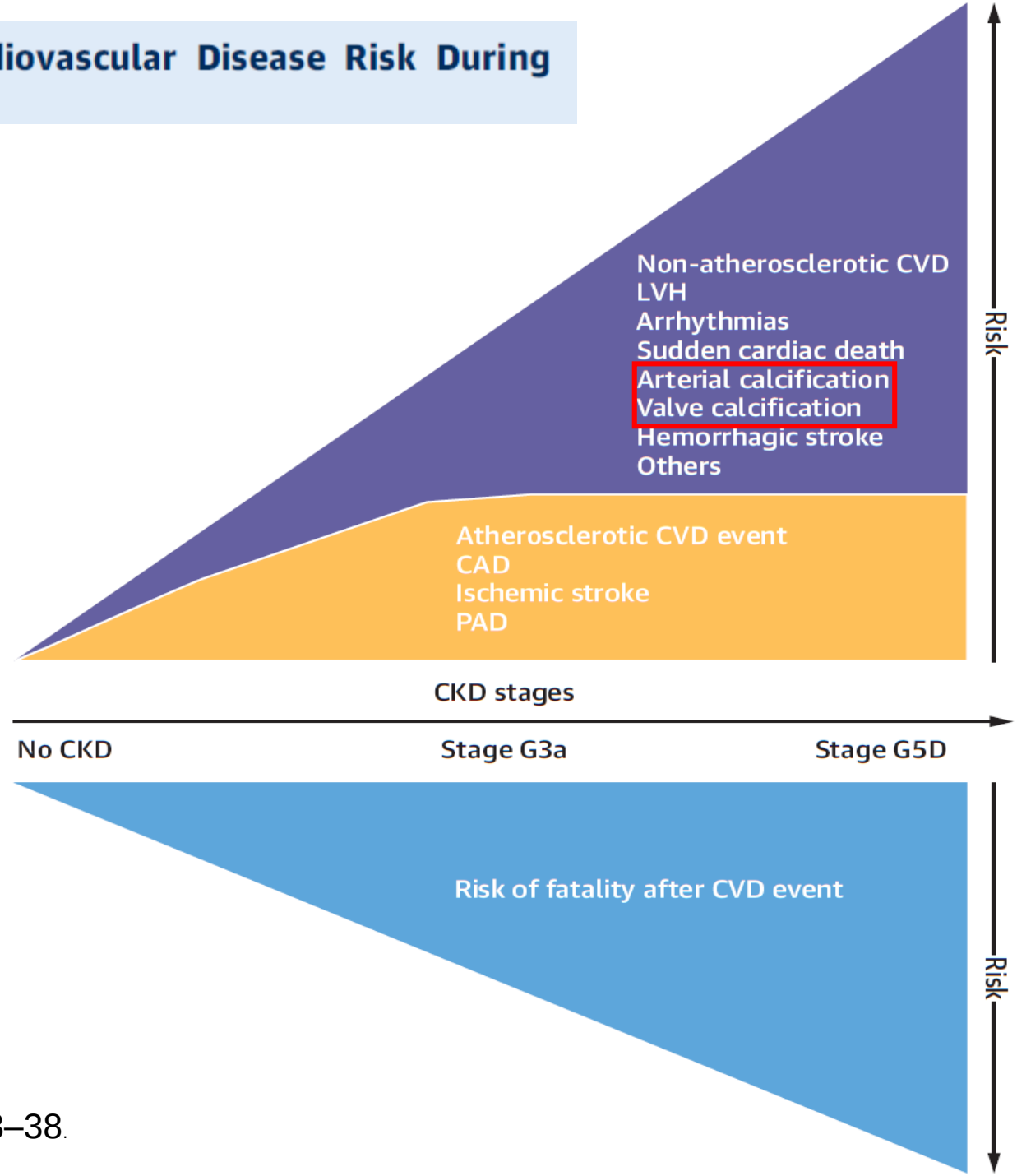


Ohtake T, Oka M, Ikee R, Mochida Y, Ishioka K, Moriya H, et al.
J Vasc Surg. 2011;53:676–83

CENTRAL ILLUSTRATION Changes in Cardiovascular Disease Risk During Chronic Kidney Disease Progression

Cardiovascular disease (CVD) event (upper triangle)

Contributions of atherosclerotic CVD (yellow);
Nonatherosclerotic CVD (purple),
Risk of fatality after CVD event (blue).



Sarnak, M.J. et al. J Am Coll Cardiol. 2019;74(14):1823–38.

All large and medium-sized arteries and arterioles can calcify

veins hardly ever calcify, unless injured or arterialized

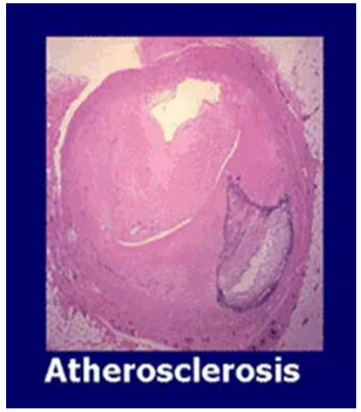
EPIDEMIOLOGY

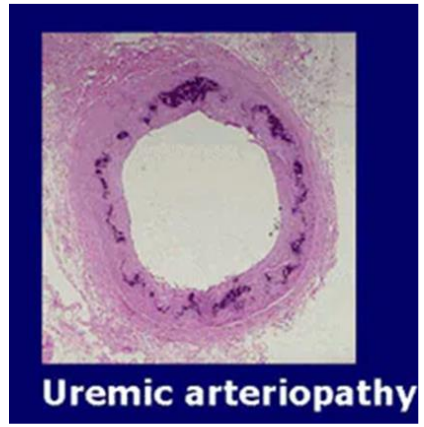
Prevalence of vascular calcification

By CT scan

1. >80 percent among patients on dialysis
2. 47 to 83 percent nondialysis CKD, eGFR<60 mL/min/1.73 m^2 .

studies over a period of 20 years demonstrated that the prevalence of calcification has been consistent over the last several decades





Arterial calcification

Intimal calcification

↓

Atherosclerosis

↓

Stenosis, occlusion

↓

Infarction, ischemia

Medial calcification

↓

Arteriosclerosis

↓

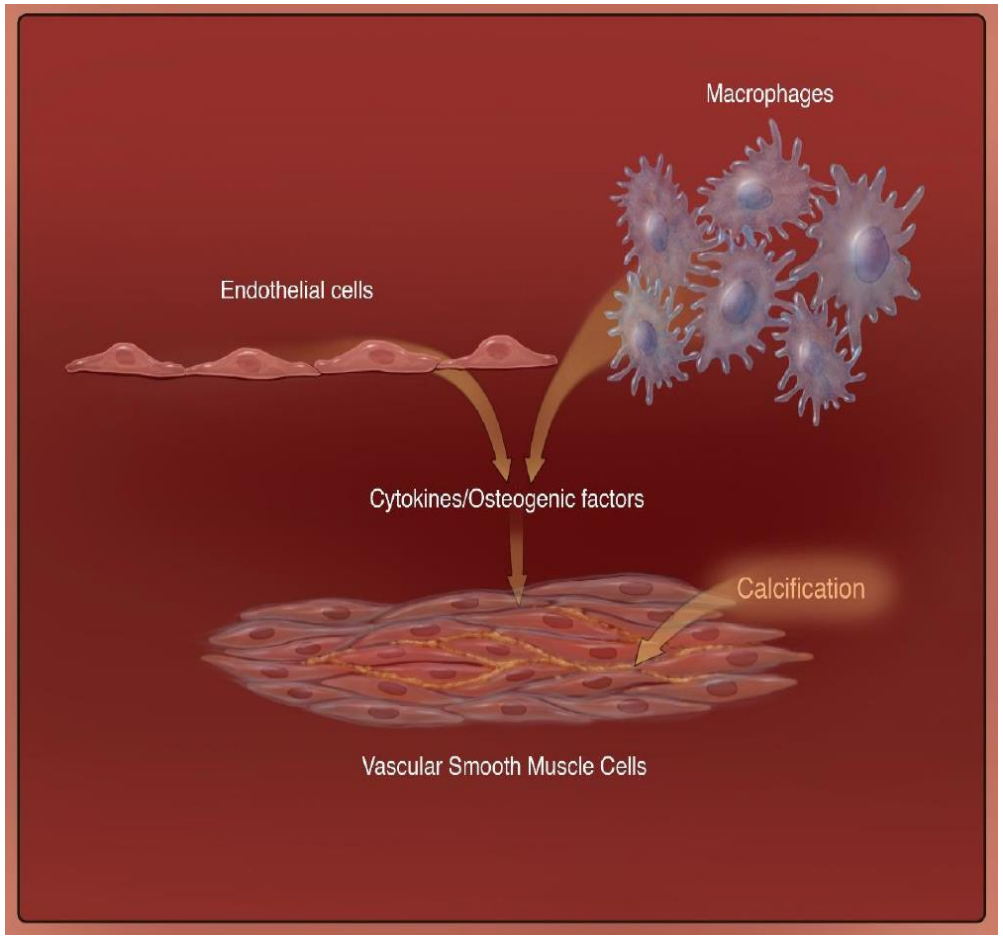
Stiffening

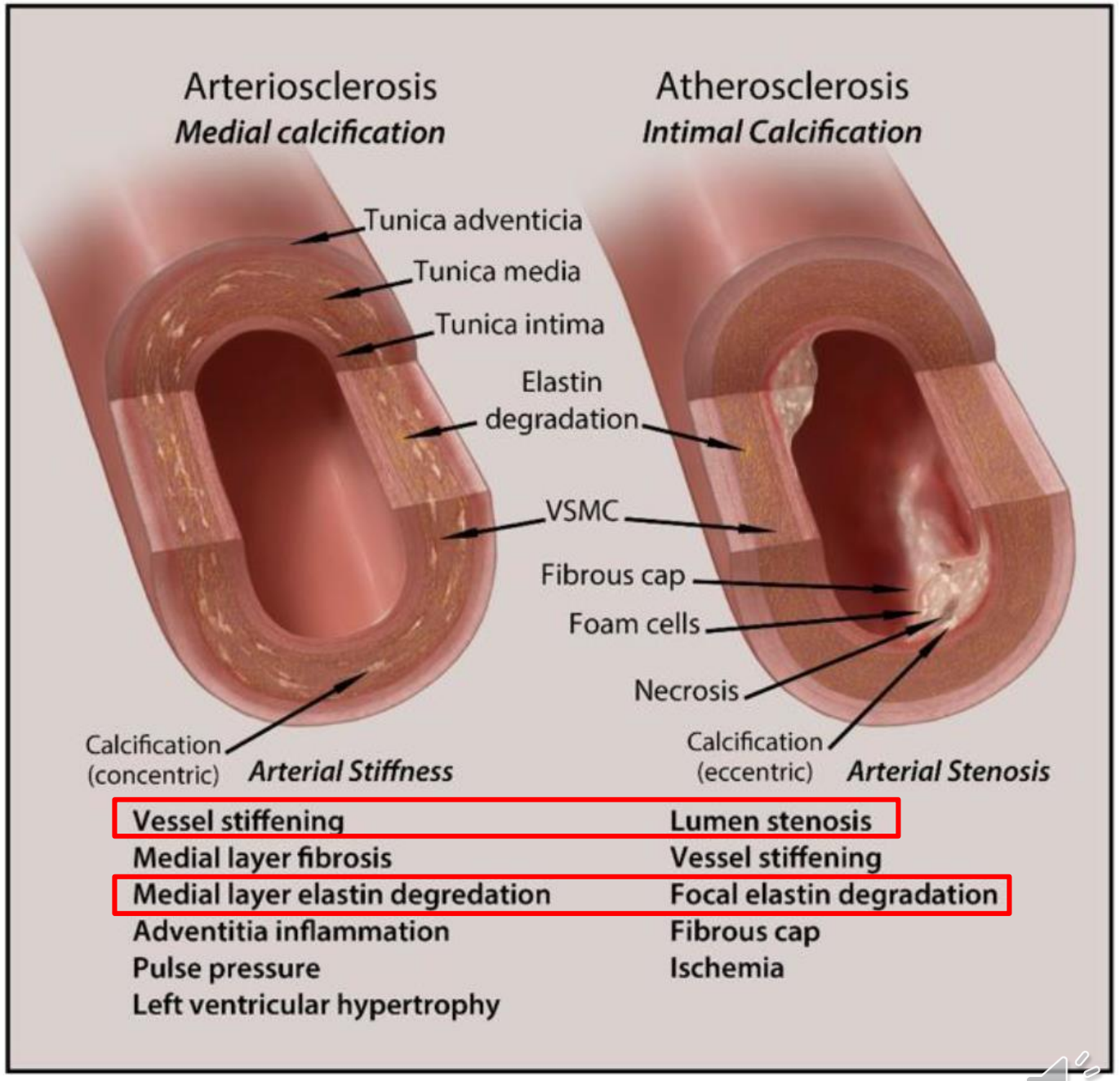
↓

↑Systolic and pulse pressures, early return of wave reflections

↓

Altered coronary perfusion, left-ventricular hypertrophy


Macrophages
Endothelial cells
Cytokines/Osteogenic factors
Calcification
Vascular Smooth Muscle Cells


Arteriosclerosis
Medial calcification
Atherosclerosis
Intimal Calcification
Tunica adventicia
Tunica media
Tunica intima
Elastin degradation
VSMC
Fibrous cap
Foam cells
Necrosis
Calcification (concentric)
Arterial Stiffness
Calcification (eccentric)
Arterial Stenosis
Vessel stiffening
Medial layer fibrosis
Medial layer elastin degredation
Adventitia inflammation
Pulse pressure
Left ventricular hypertrophy
Lumen stenosis
Vessel stiffening
Focal elastin degradation
Fibrous cap
Ischemia

- Mechanisms -

Bone		Vasculature
	Initiation	
Matrix vesicles	↓	Apoptotic and matrix vesicles
		Loss of inhibitors
	Nucleation	
Osteoblasts	↓	Osteoblast-like VSMC
osteoblast matrix		osteoblast matrix
	Crystal growth	
Osteoclasts	↓	Osteoclast-like activity
		macrophages
	Resorption	

Medial calcification

- predominant form among patients with CKD.
- occurs as a result of

1. **phenotype switch** of vascular smooth muscle cells to osteoblast–like.
2. **local inflammation**

The phenotype change is initiated by

1. Hyperphosphatemia,
2. Hypercalcemia,
3. High concentrations of PTH
4. Oxidative stress

- Mechanisms -

Hypercalcemia and hyperphosphatemia→ increase the release of VSMC-derived matrix vesicles→deposition of hydroxyapatite

Vasculature

Apoptotic and matrix vesicles

Loss of inhibitors

Osteoblast-like VSMC

osteoblast matrix

osteoblast matrix

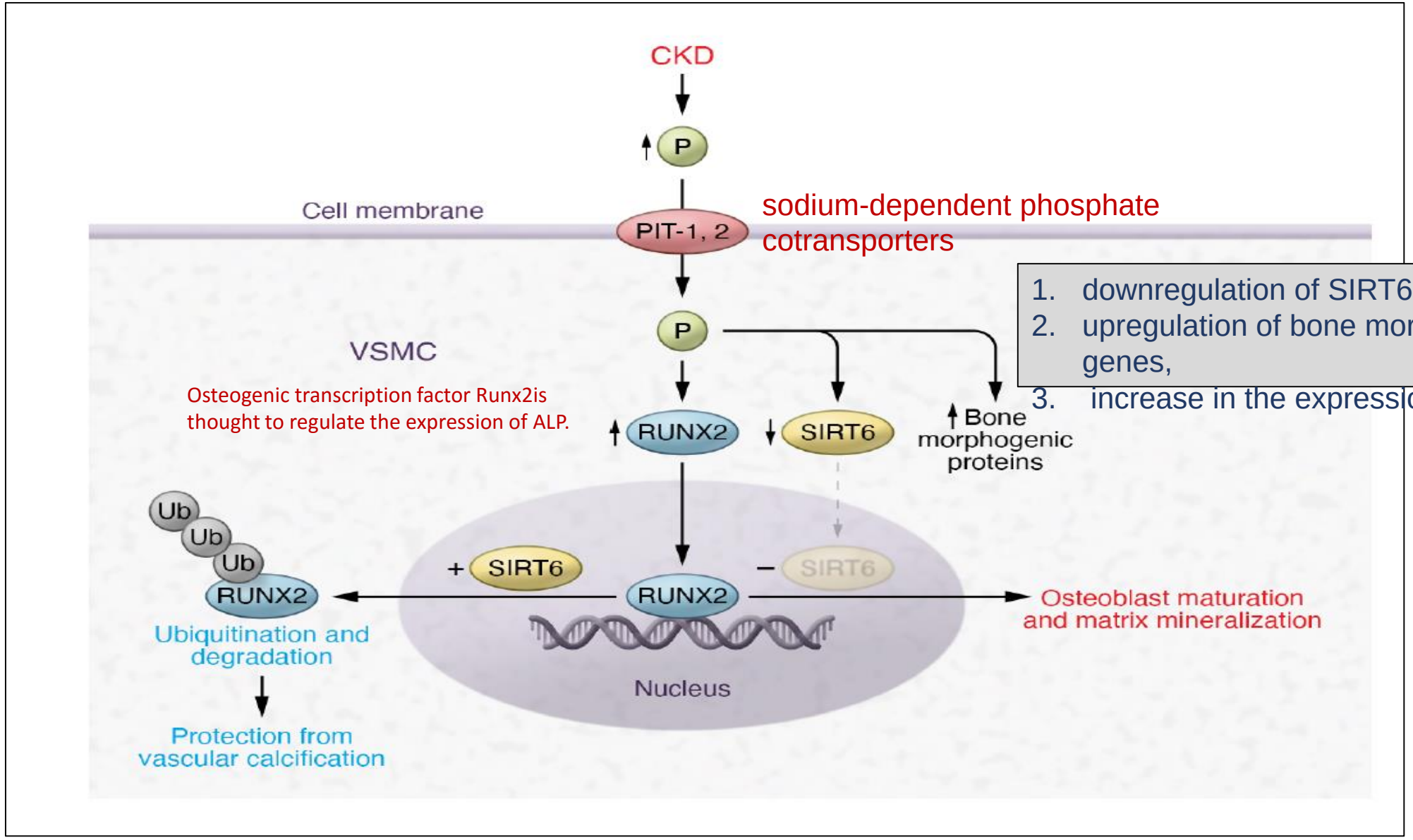
Crystal growth

Osteoclasts

Osteoclast-like activity

macrophages

Resorption



1. downregulation of SIRT6 expression,
2. upregulation of bone morphogenic genes,
3. increase in the expression of Runx2,

Runx2 signals osteoblast maturation and matrix mineralization,
In contrast, overexpression of SIRT6 marks Runx2 protein for ubiquitination and degradation, preventing VSMC calcification.

Intimal calcification

Secondary to established atherosclerosis

mechanisms

1. Shear stress,
2. Local inflammation,

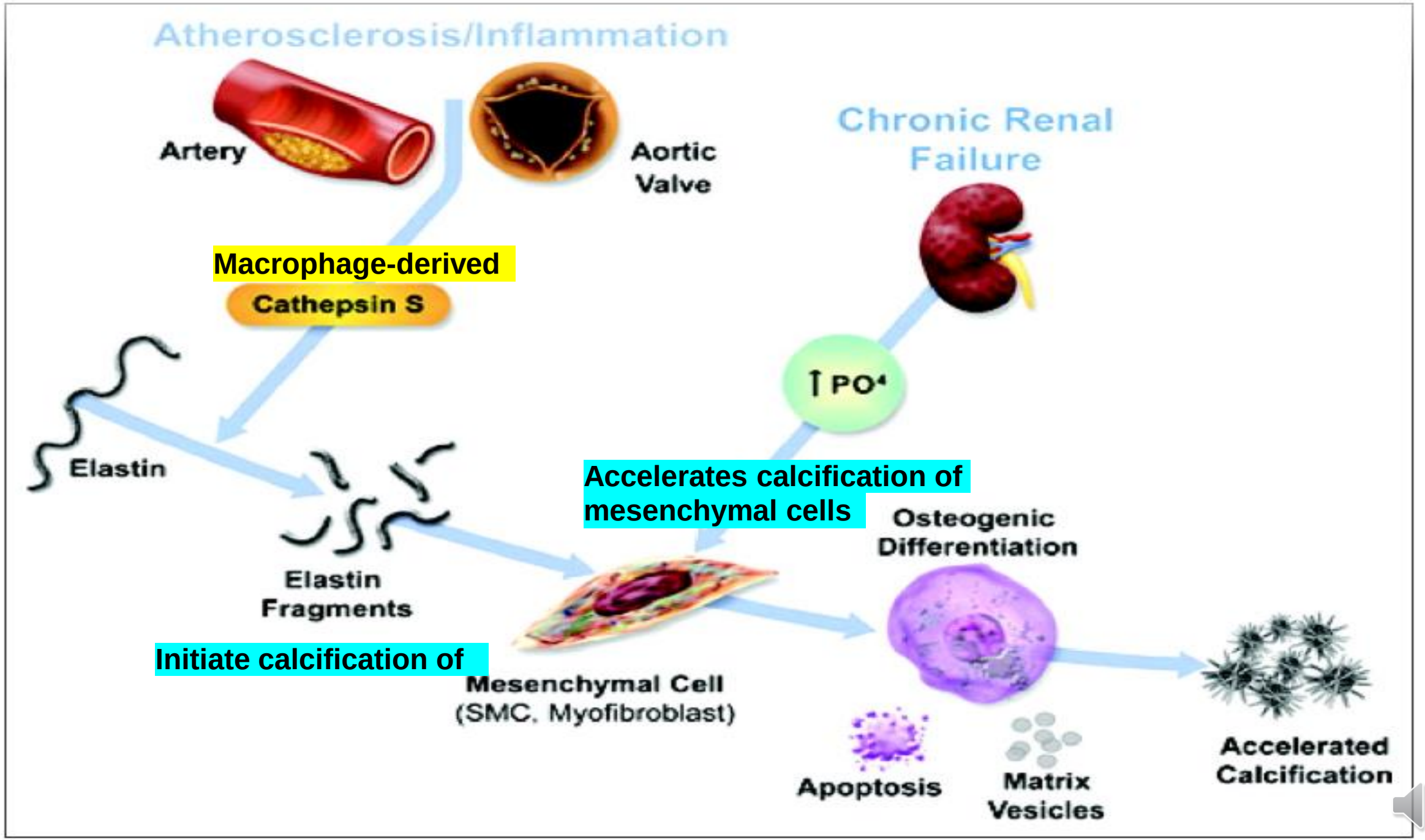
The calcification of macrophage and VSMC-derived microvesicles, are amplified in patients with CKD

- Hyperphosphatemia, hypercalcemia, and hyperparathyroidism ➔worsen intimal calcification of preformed atherosclerotic plaques.
- Arterial stiffness ➔directly contributes to the shear stress, atherosclerosis, and calcification of the intima

Inflammation and oxidative stress

Infiltrating macrophages

- release proinflammatory cytokines →influx of lymphocytes
- cellular microvesicles released from macrophages or apoptotic macrophages → form a nidus for calcification,
- oxidative stress, →vascular calcification


Atherosclerosis/Inflammation
Artery
Aortic Valve
Chronic Renal Failure
Macrophage-derived
Cathepsin S
↑ PO4
Elastin
Elastin Fragments
Accelerates calcification of mesenchymal cells
Osteogenic Differentiation
Initiate calcification of
Mesenchymal Cell (SMC, Myofibroblast)
Apoptosis
Matrix Vesicles
Accelerated Calcification

Inhibitors

Vascular calcification is inhibited by multiple regulatory proteins.

Calciprotein particles

CPPs are circulating nanoparticles composed of calcium-phosphate crystals + chaperone-binding proteins

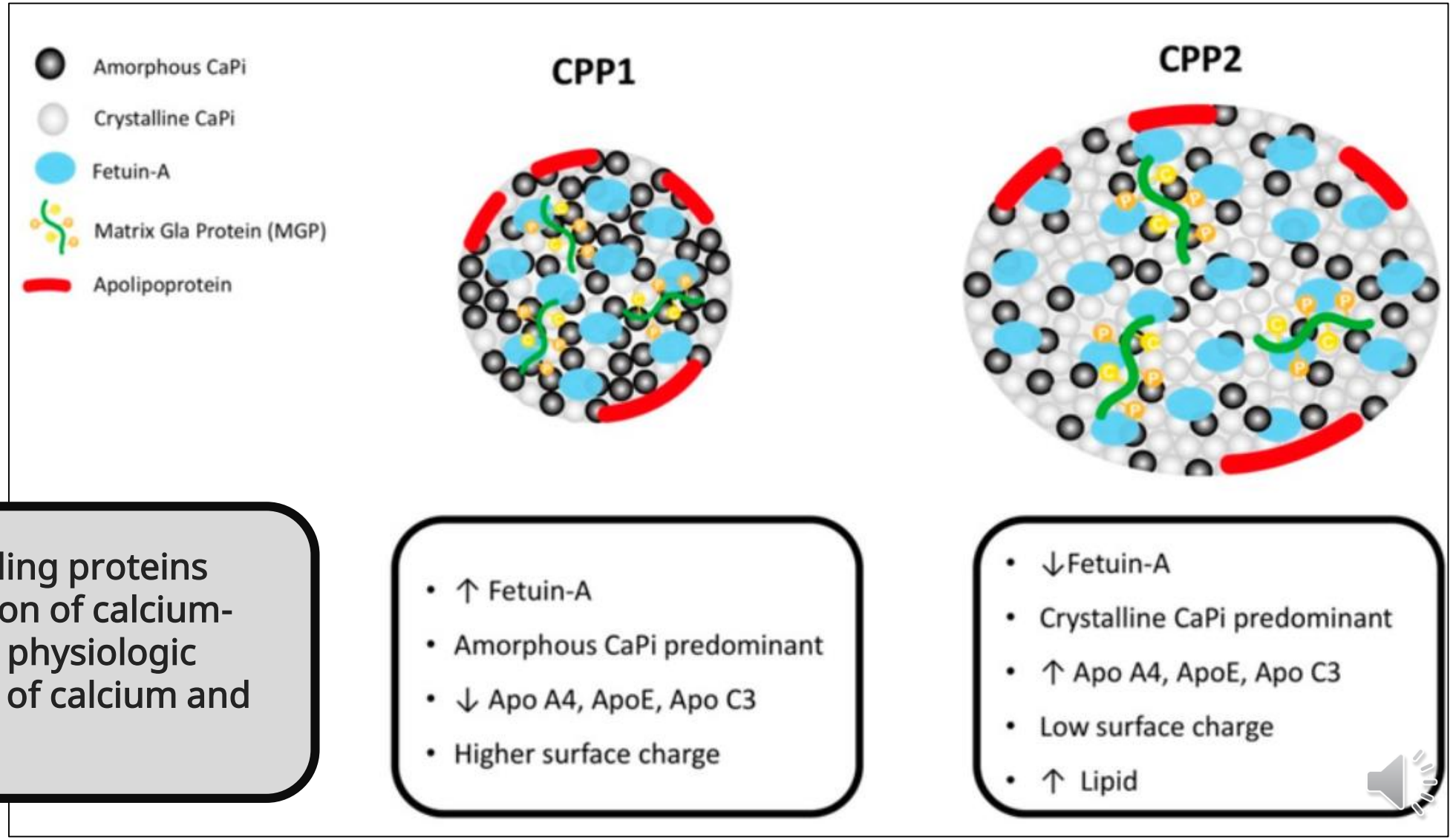
Chaperone-binding proteins

- Fetuin A,
- Albumin and other plasma proteins
- Matrix Gla-protein (MGP) and gamma-carboxylated Gla-rich protein (GRP),

MGP and GRP are dependent upon vitamin K to exert their activity

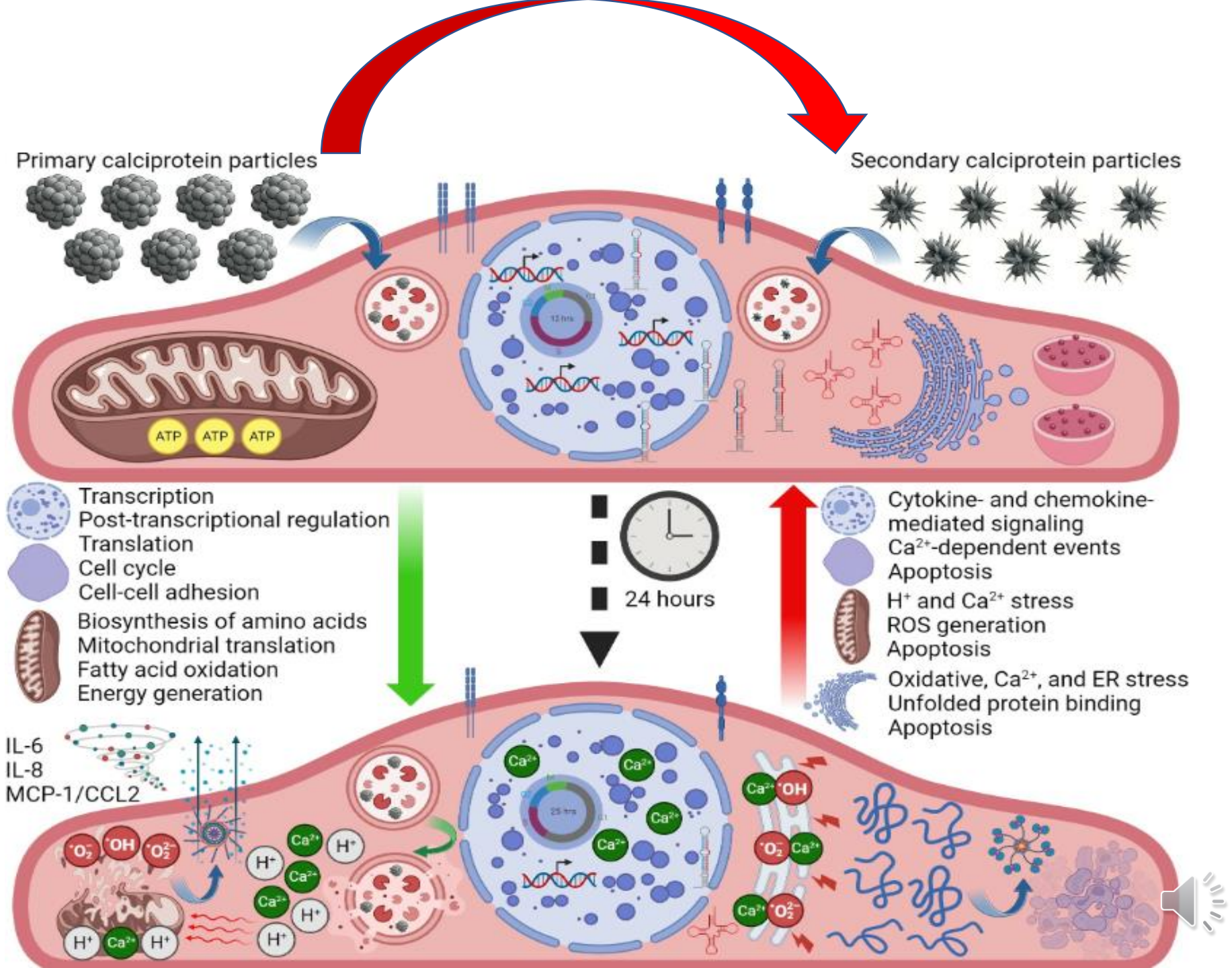
The inhibition of this activation of GRP and MGP may contribute to vascular calcification in patients on warfarin

Calciprotein particles



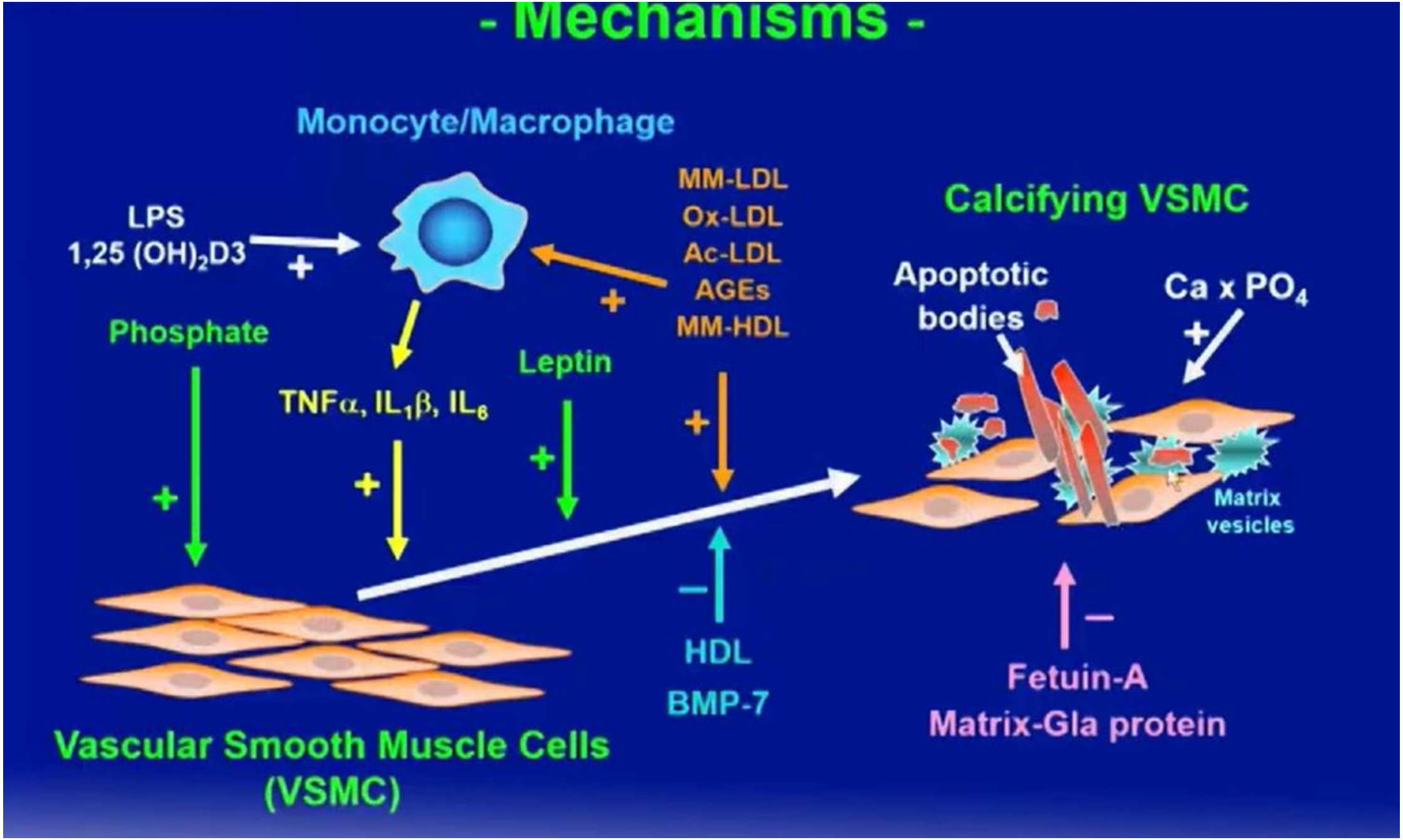
These chaperone-binding proteins inhibit the crystallization of calcium-phosphate in blood at physiologic serum concentrations of calcium and phosphate

The formation rate from primary to secondary CPPs reflects an individual's intrinsic defense against ectopic calcification



Other inhibitors

1. Klotho, membrane protein that is highly expressed in the kidney,
2. Pyrophosphate, produced by vascular smooth muscle cells and inhibits formation of hydroxyapatite
3. Osteoprotegerin, competes with the receptor activator of NF-kB ligand (RANKL) and its receptor, RANK, on osteoclast precursor cell membranes
4. Magnesium, inhibition of calcium-phosphate crystal growth in the circulation, and prevention of the phenotype change of vascular smooth muscle to osteoblasts
5. Iron, ?preventing apoptosis
6. Activin-A, several bone morphogenic proteins, osteopontin, zinc, and PTH-related protein

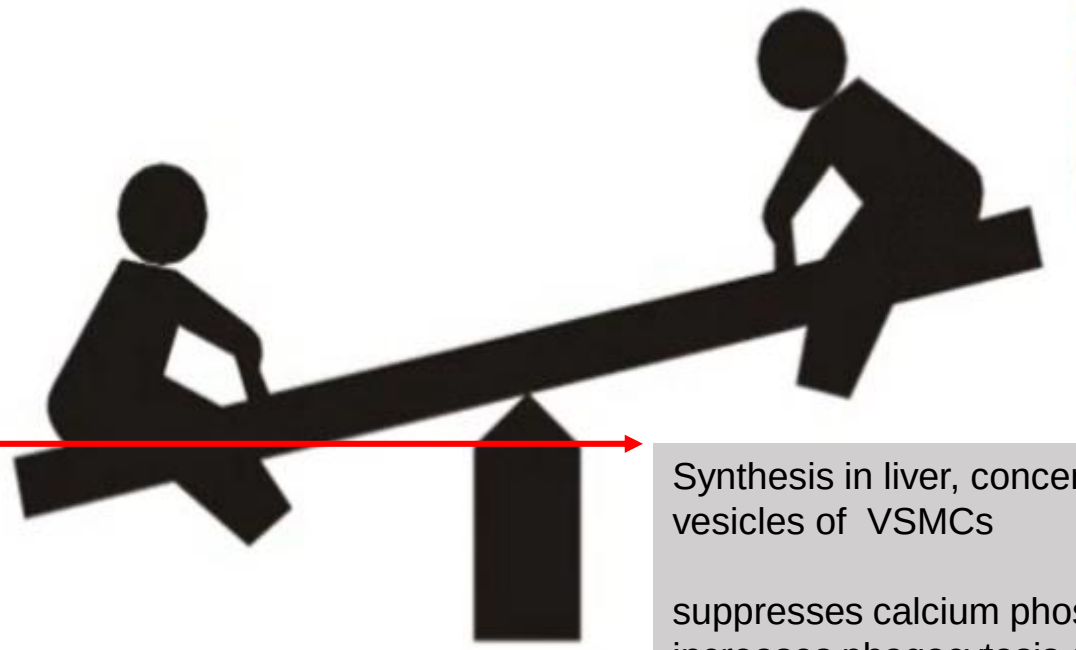

- Mechanisms -
Monocyte/Macrophage
LPS
1,25 (OH)2D3
+
MM-LDL
Ox-LDL
Ac-LDL
AGEs
MM-HDL
+
Calcifying VSMC
Apoptotic bodies
Ca x PO4
+
Phosphate
TNFα, IL1β, IL6
Leptin
+
+
+
+
Matrix vesicles
–
HDL
BMP-7
–
Fetuin-A
Matrix-Gla protein
Vascular Smooth Muscle Cells (VSMC)

* Matrix Gla protein

loaded in matrix vesicles of VSMCs
•MGP binds to calcium and bone morphologic protein 2 (BMP2) and inactivates it

Active Inducers
BMP2
Cbfa1 **Runx**2
Glucose & AGEs
Uremic toxins
Calcium & Phosphate
PTH
Vitamin D

Active Inhibitors
Pyrophosphate
MGP *
Osteopontin &
osteoprotegerin
Fetuin-A
Smad 6
Iron/Magnesium

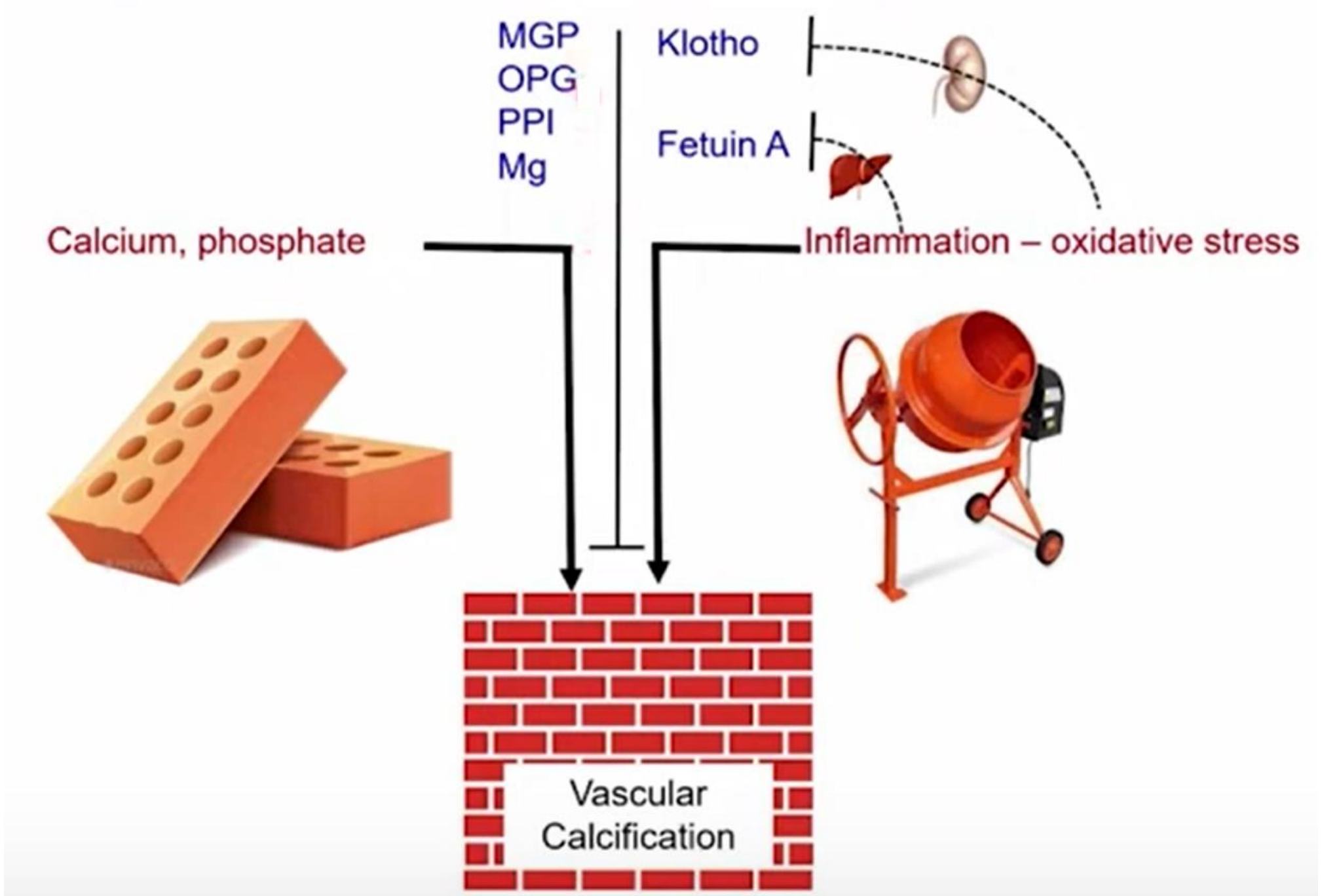


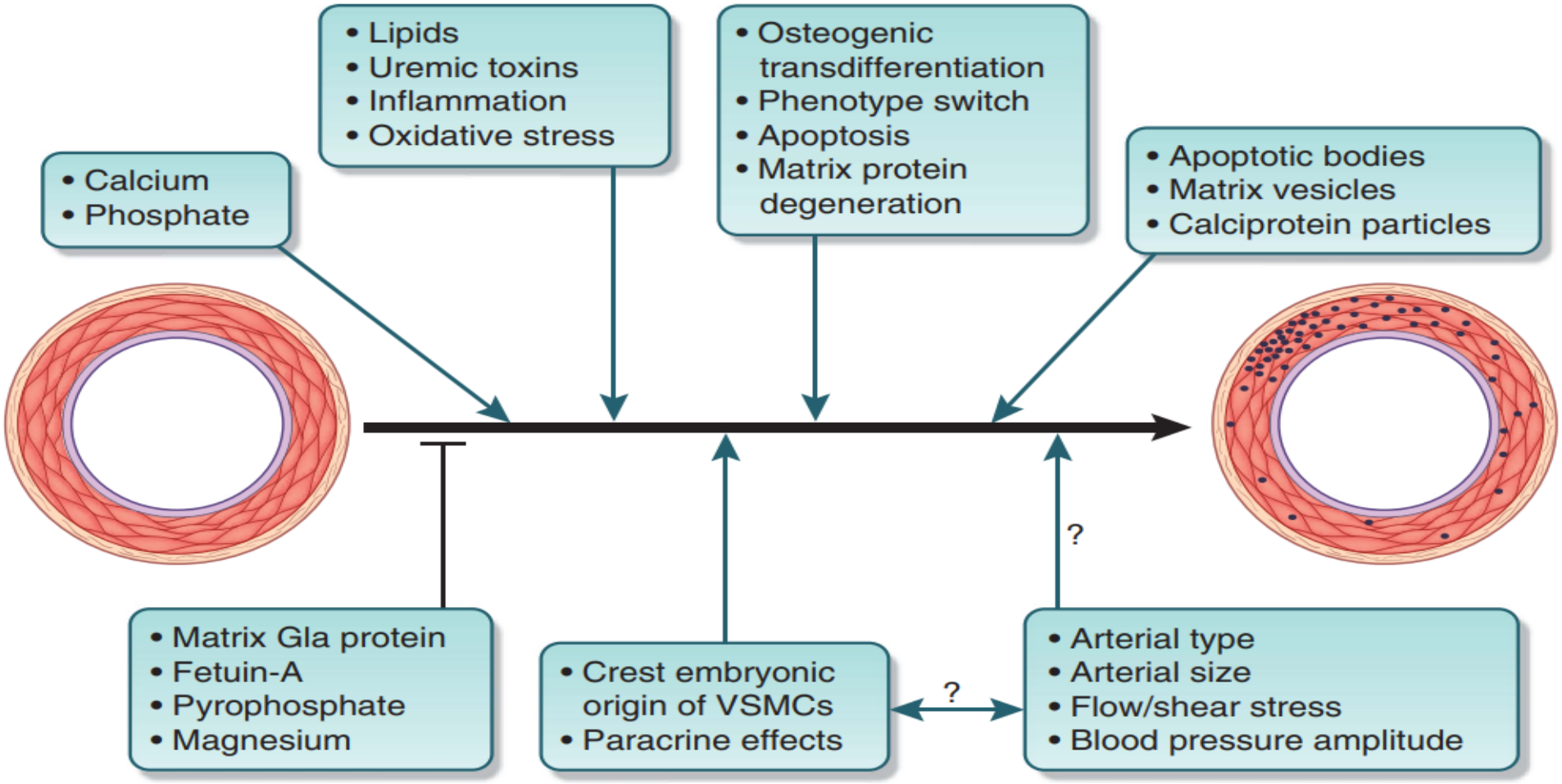
Synthesis in liver, concentrated in intracellular vesicles of VSMCs

suppresses calcium phosphate nucleation, increases phagocytosis of vesicles by VSMCs.

Contractile VSMCs

A Tóth et al. Antioxidants (Basel). 2020 Oct 8;9(10):963.


MGP
OPG
PPI
Mg
Klotho
Fetuin A
Calcium, phosphate
Inflammation – oxidative stress
Vascular
Calcification



Several factors can induce vascular calcification and are likely responsible for variable susceptibility to vascular calcification. Systemic circulating and local factors may enhance or prevent vascular calcification. Some factors, such as arterial type, do play a role but need to be further investigated. Other influencing factors may be added, as the list is not complete. Known and possible interactions between several factors are not depicted. VSMCs, vascular smooth muscle cells.

RISK FACTORS

- Increasing age and dialysis vintage
- Hyperphosphatemia and hypercalcemia
- Oral calcium intake
- Phosphate binders
- Secondary hyperparathyroidism and adynamic bone disease
- Vitamin D deficiency and excess
- Vitamin K antagonists and deficiency
- Dialysate calcium
- Hypomagnesemia
- Diabetes
- Dyslipidemia

Inducers and inhibitors for vascular calcifications If the inhibitory system would fail, serious complication might occur. Treatment target which we can intervene are also listed Abbreviations: AGEs advanced glycation end products, BMP bone morphogenic protein, LDL low-density lipoprotein, MGP matrix Gla protein, PTH; parathyroid hormone

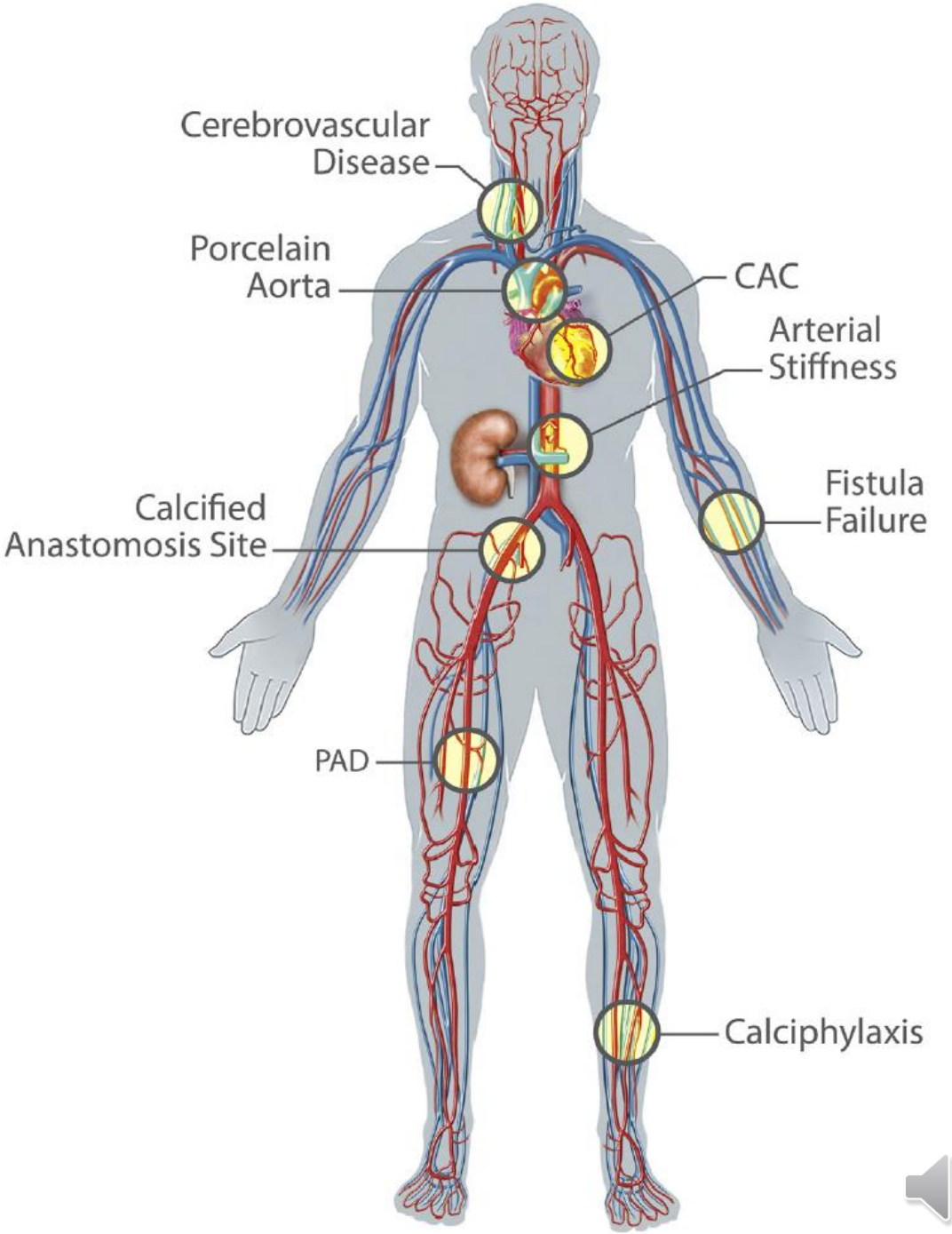
Table 1 Associating factors for vascular calcification in hemodialysis patients

Inducers	Inhibitors	Target for treatment
Aging	Fetuin A	Phosphate
Phosphate/calcium	MGP	Calcium
Inflammation	Pyrophosphate	Intact PTH
Aldosterone	Osteopontin	Vitamin D
Warfarin use	Osteoprotegerin	Vitamin K
AGEs/diabetes	BMP7	Acidosis
BMP2/4	Adiponectin	Inflammation
Leptin	Collagen IV	Dialysate
oxLDL		
Collagen I/fibronectin		
High blood pressure		

CLINICAL SIGNIFICANCE

Depends upon

- Site,
- Histologic location (medial or intimal),
- Type (microcalcification or confluent large, calcified areas).



DETECTION

Most often detected incidentally on imaging obtained for other purposes.

Screen patients with chronic kidney disease for vascular calcification→**not** recommended

- A plain radiography, which demonstrates pipe-stem calcification of the tunica media and more irregular, patchy calcifications of the internal elastic lamina.

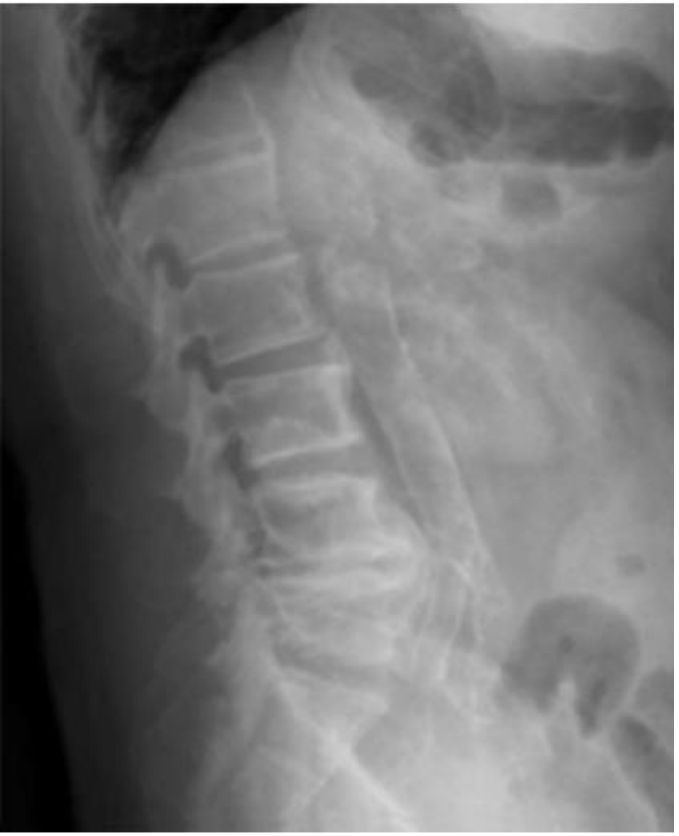
- May differentiate to some degree between intimal and medial calcification, it is an insensitive method and does not quantify the severity of vascular calcification

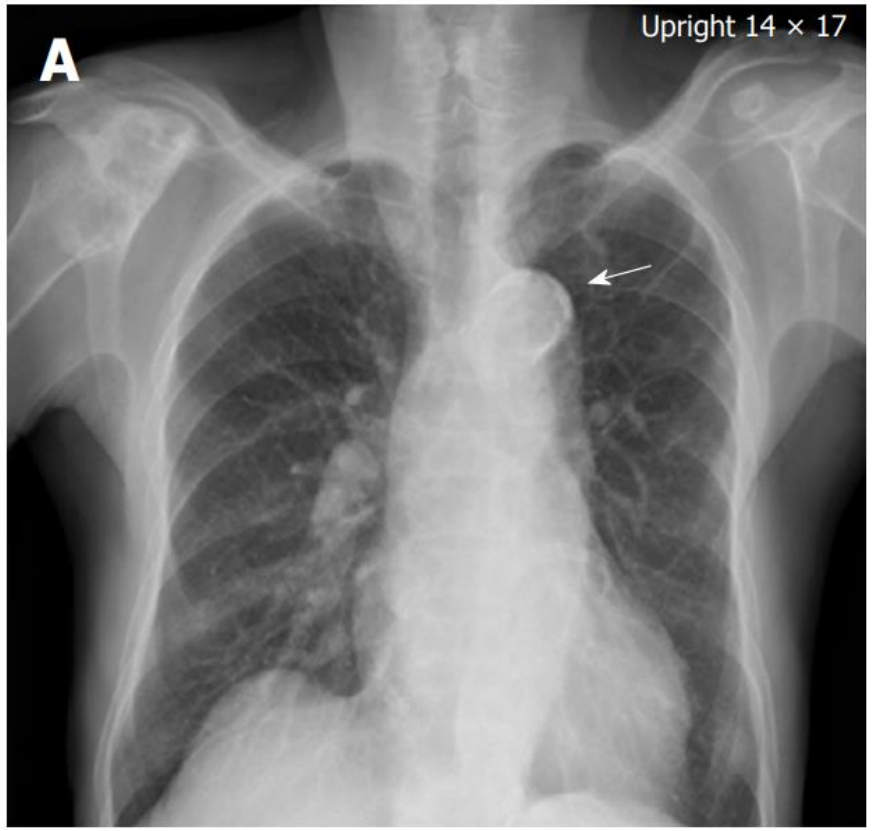
Kauppila score

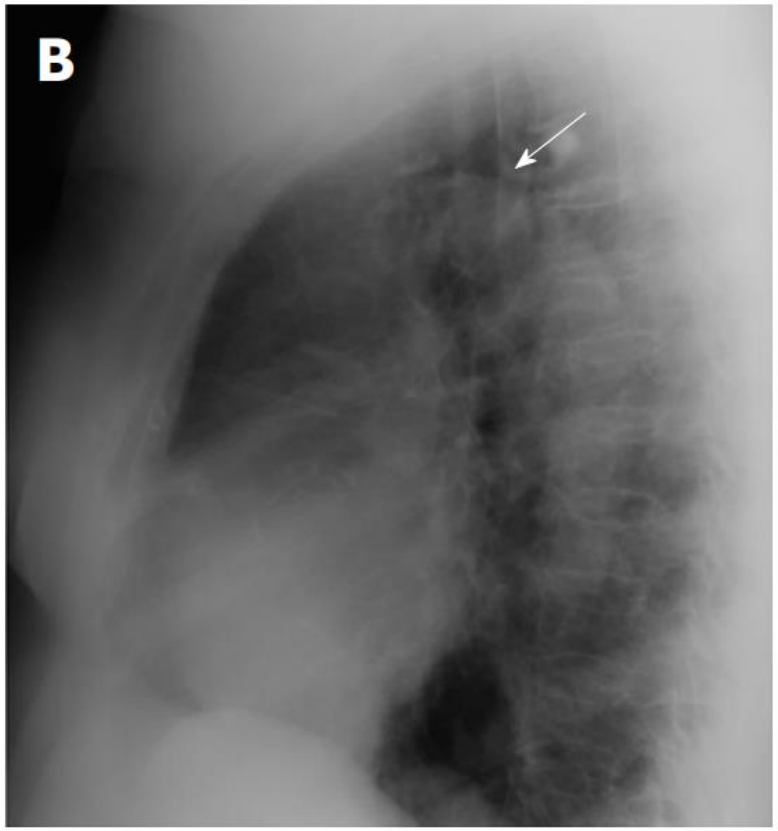
The Kauppila score quantifies the severity of lumbar aortic calcifications observed on a lateral abdominal radiograph that includes from the T10 vertebra-the first two sacral vertebra

A score of 1 to 3 is assigned based on extent of calcification (ie, one-third, two-thirds, or more than two-thirds

Kauppila score

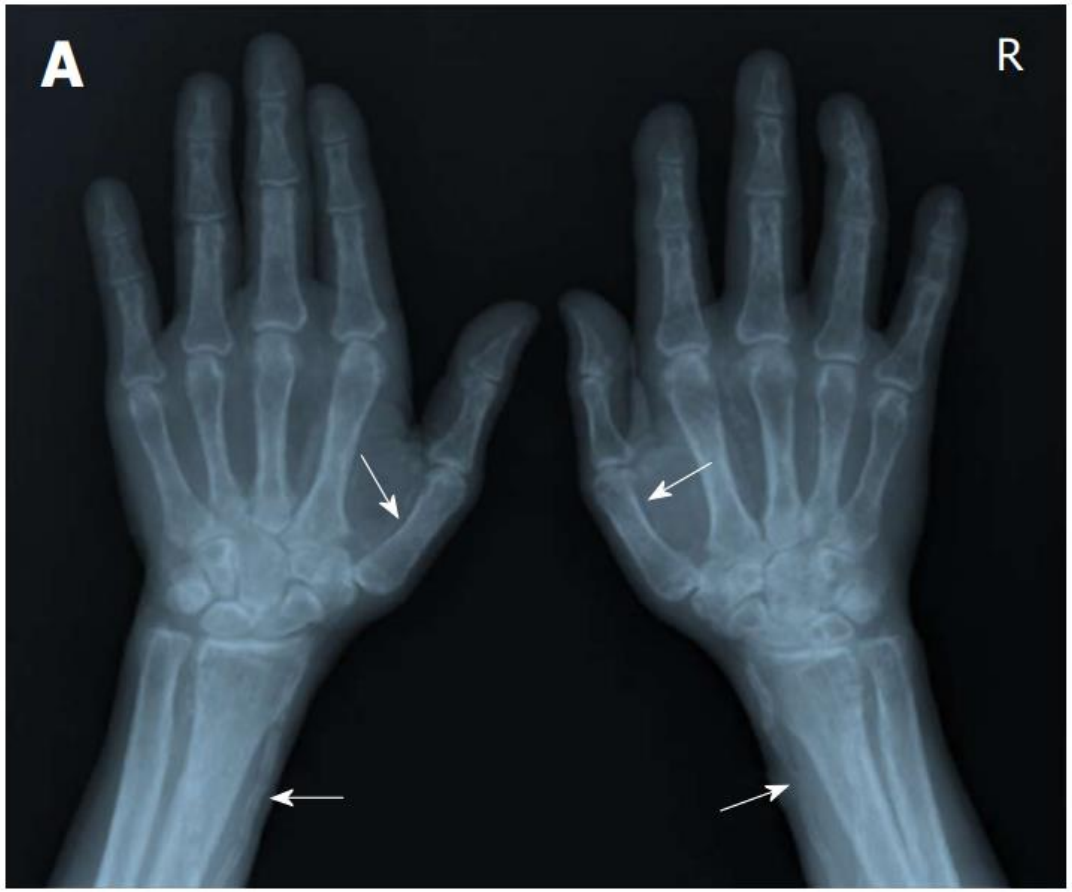


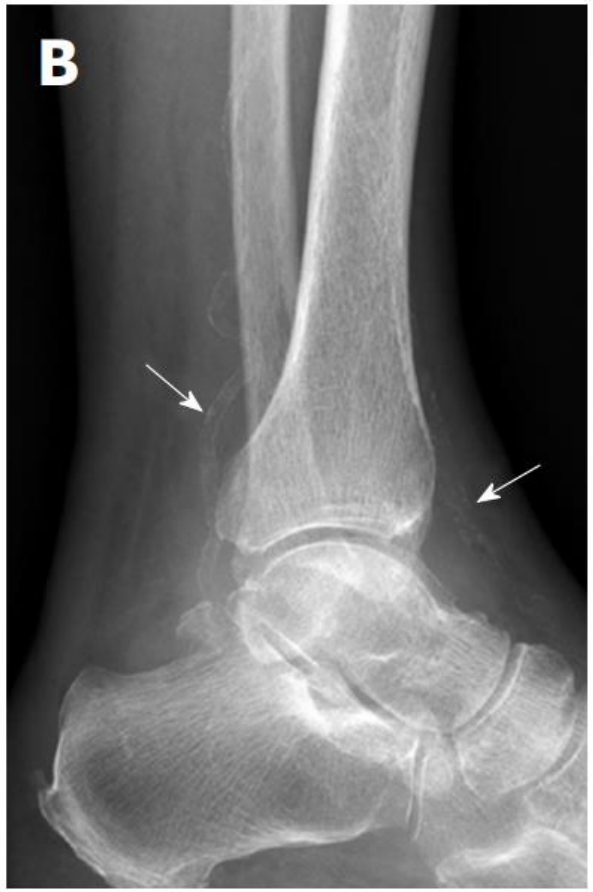


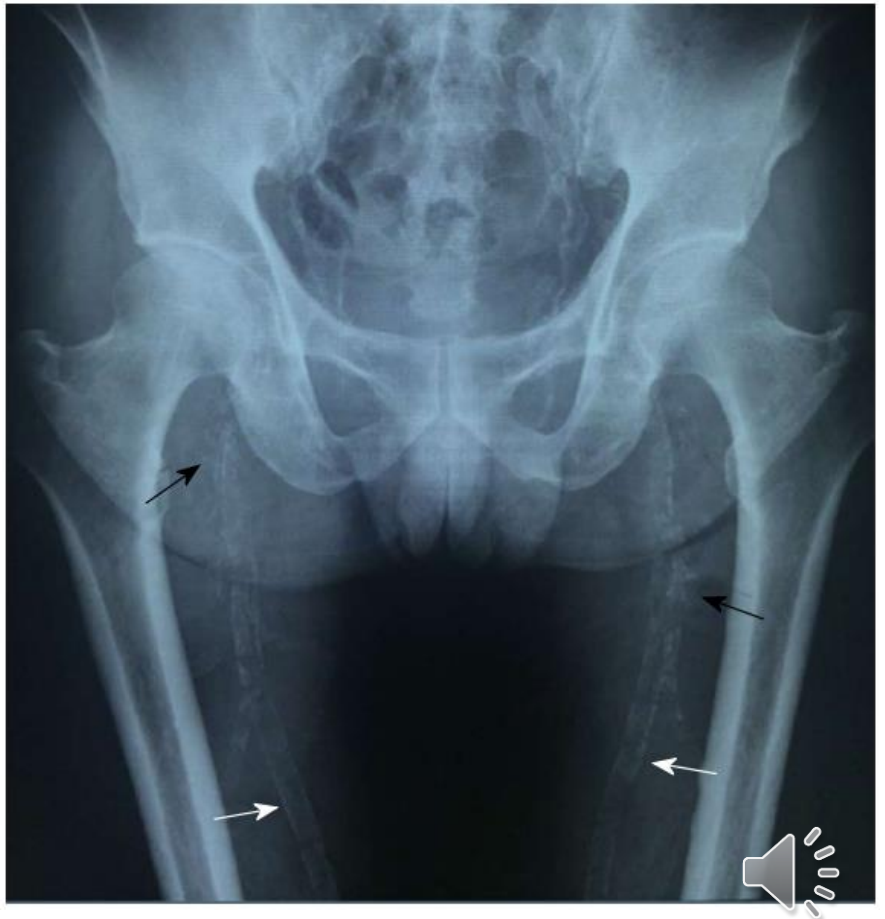


Adragão score

The Adragão score quantifies calcification of the iliac, femoral, radial, and digital arteries observed on plain radiographs of the hands and pelvis.
The final value ranges between 0 and 8 points (0 to 4 in the pelvis and 0 to 4 in the hands).
vascular calcification score ≥3 had an almost fourfold higher risk of cardiovascular mortality

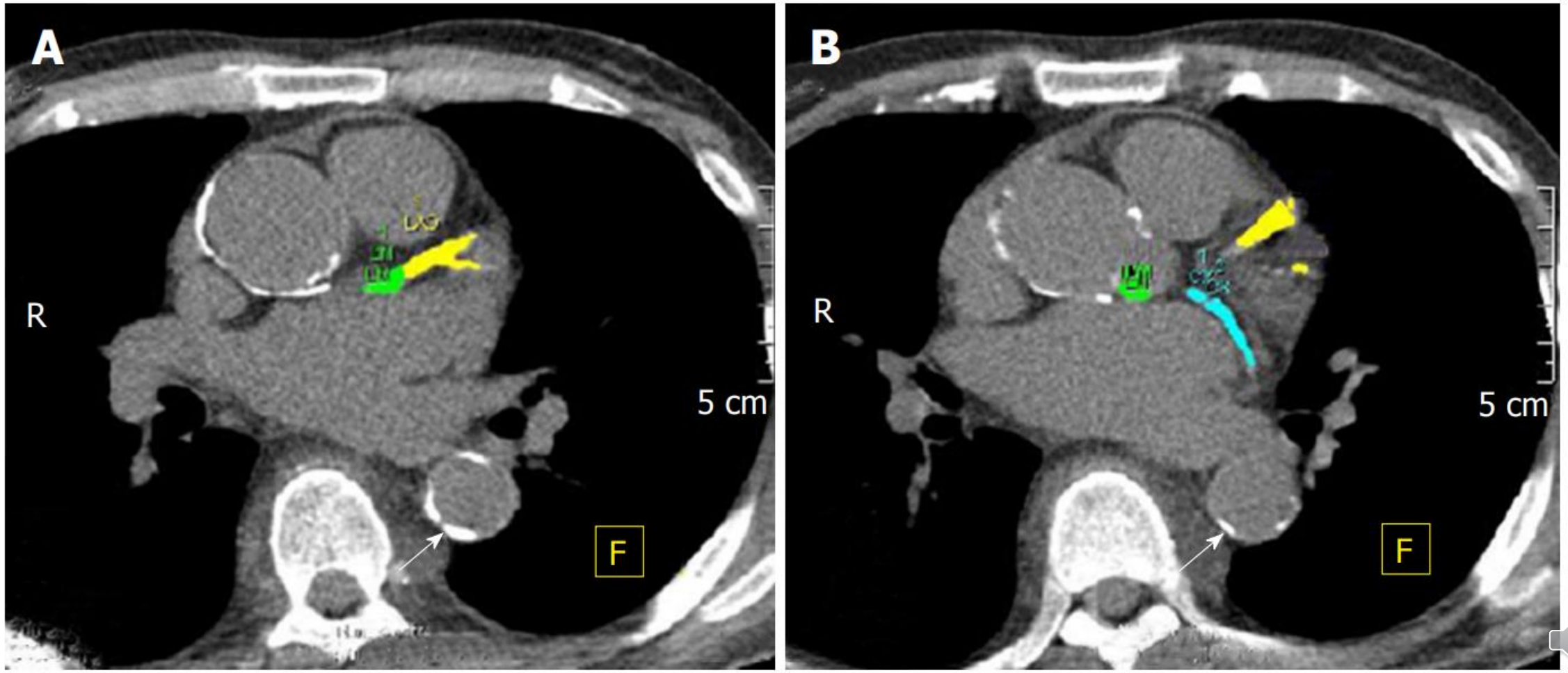




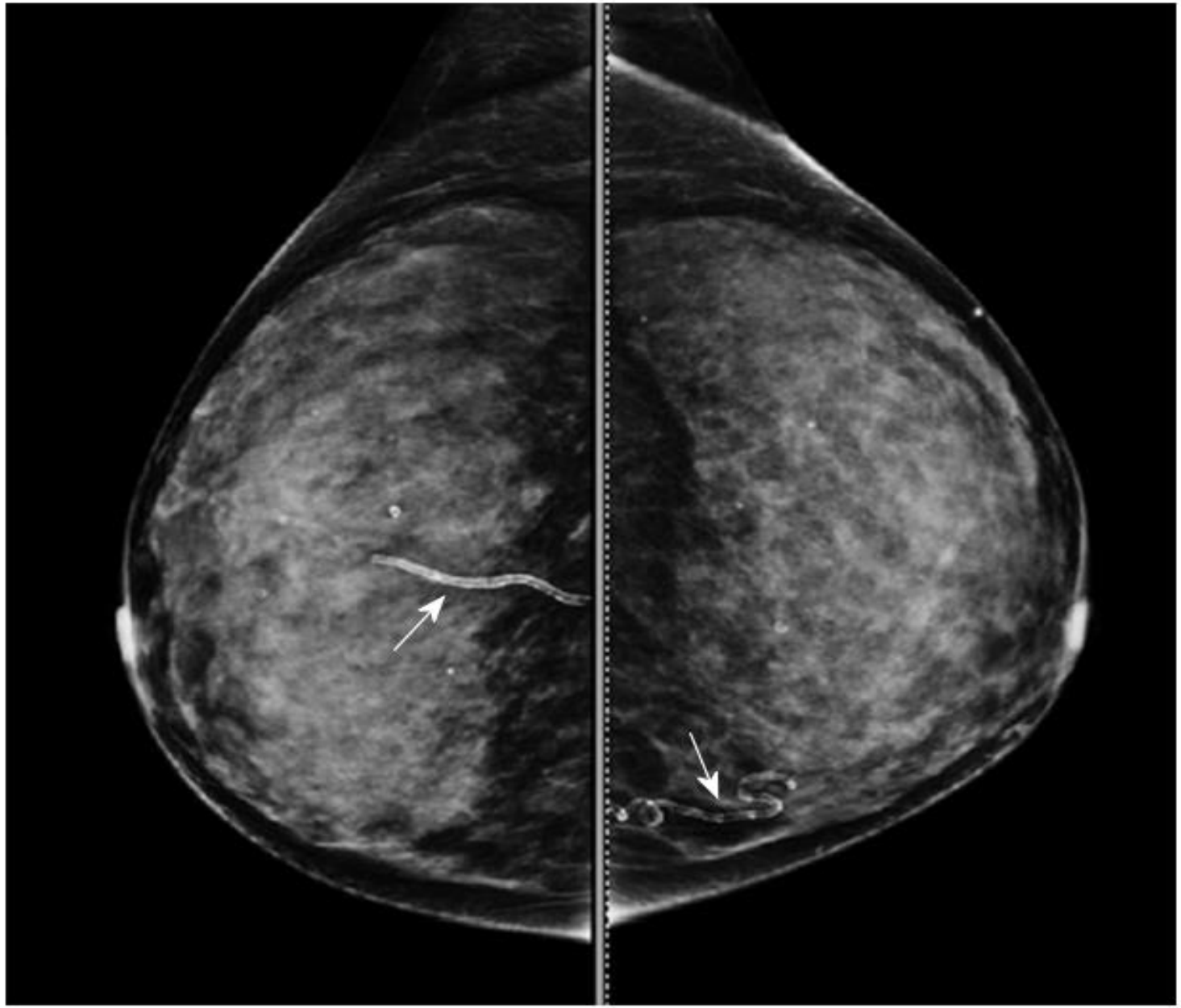


CT scan detects and quantifies vc, does not differentiate between intimal and medial deposition.

Agatston score ,quantifies CAC detected by an unenhanced low-dose cardiac CT scan.
early risk stratification for a major adverse cardiac event



mammograms,
have high spatial resolution
may be able to identify
exclusively medial calcification



Breast arterial calcification with the typical linear tram-track medial-type calcification

vascular ultrasound, intravascular ultrasound, and optical coherence tomography

PREVENTION AND TREATMENT

- **General measures** — There is no specific therapy to prevent progression or to facilitate regression of vascular calcification in patients with CKD.

- It remains uncertain if modifying the natural history of vascular calcification translates into improved patient outcomes.

- The optimal management of vascular calcification in patients with CKD remains unclear.

Preventive measures as treatment of

- Persistent hyperphosphatemia,
- Secondary hyperparathyroidism,
- Regulating oral calcium intake,
- Hypomagnesemia,
- Appropriate use of anticoagulation when indicated

In addition, cardiovascular risk factors should also be managed as appropriate.

Myoinositol hexaphosphate

Circulation

ORIGINAL RESEARCH ARTICLE

Slowing Progression of Cardiovascular Calcification With SNF472 in Patients on Hemodialysis

Results of a Randomized Phase 2b Study

274 patients on hemodialysis randomly assigned to treatment with SNF472 (300 or 600 mg) or placebo three times weekly during hemodialysis,

Circulation. 2020

Myoinositol hexaphosphate

Myoinositol hexaphosphate (SNF472) is an intravenous small molecule inhibitor of hydroxyapatite crystal growth.

patients receiving SNF472 , at 52 weeks compared with those receiving placebo had

- **slower progression of coronary artery and aortic valve calcification,**
- **but not thoracic aorta calcification**

Sodium thiosulfate
STS

Used to treat calciphylaxis among patients on hemodialysis.

Nephrol Dial Transplant (2020) 35: 162–169
doi: 10.1093/ndt/gfz204
Advance Access publication 25 November 2019

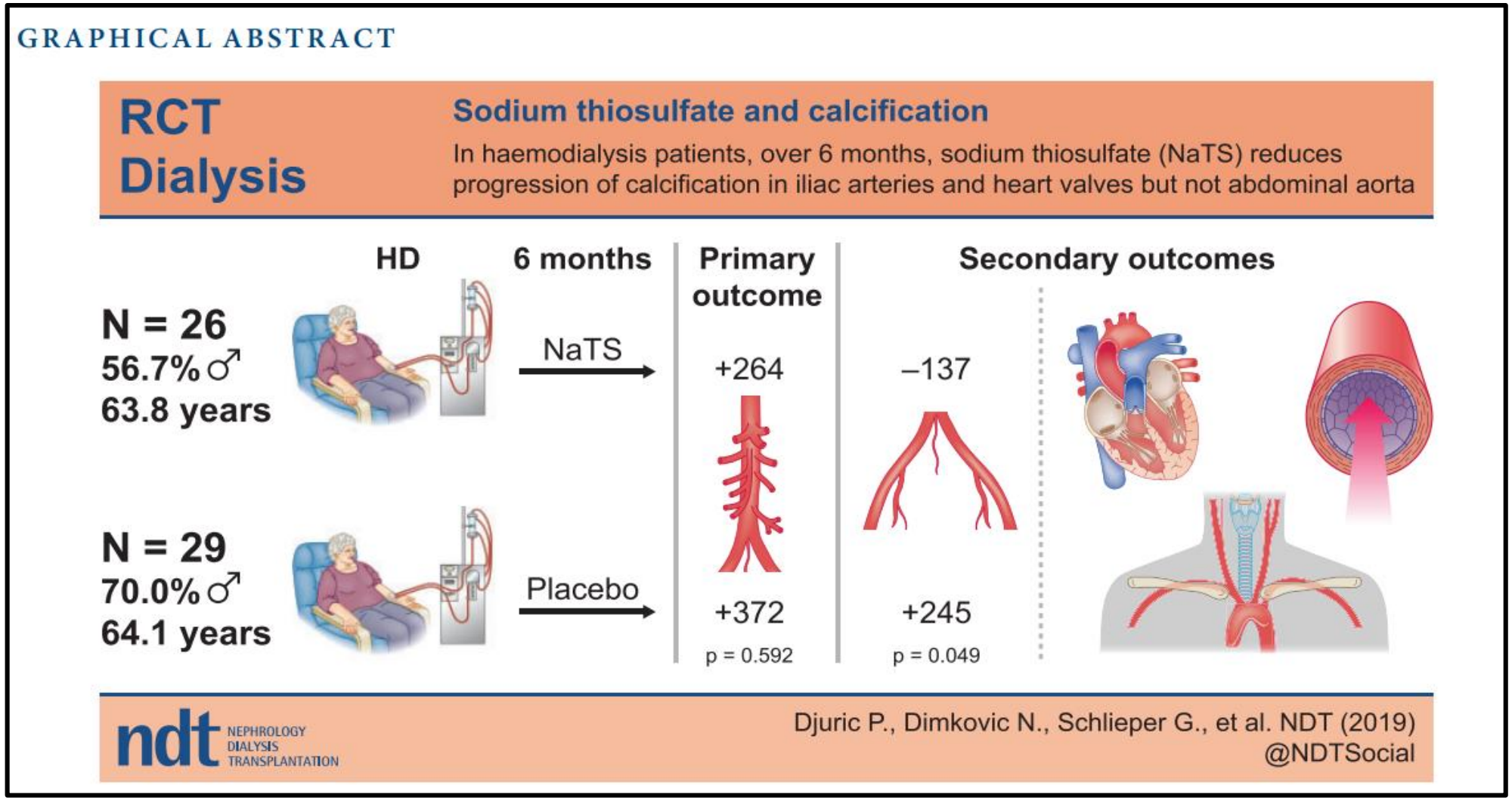
ndt
Nephrology Dialysis Transplantation

Sodium thiosulphate and progression of vascular calcification in end-stage renal disease patients: a double-blind, randomized, placebo-controlled study

Petar Djuric[1], Nada Dimkovic[1,2], Georg Schlieper [3,4], Zivka Djuric[1], Milan Pantelic[5], Milica Mitrovic[6], Aleksandar Jankovic[1], Marko Milanov[7], Jovana Kuzmanovic Pficer[8] and Jürgen Floege[3]

Patients group received NaTS 25 g/1.73 m2 dissolved in 100 mL saline intravenously during the last 15 min of every HD session

Randomly assigned 60 patients on hemodialysis with an abdominal aorta Agatston score ≥100 to receive STS or sodium chloride at the end of each hemodialysis session over six months,



- There was no difference in progression of calcification of the aorta between the groups
- slower progression of calcification of the iliac arteries, reduced pulse wave velocity (indicating less arterial stiffness), and a lower incidence of aortic valve calcification.

Nephrol Dial Transplant (2023) 38: 733–745
https://doi.org/10.1093/ndt/gfac171
Advance Access publication date 6 May 2022

Intravenous sodium thiosulphate for vascular calcification of hemodialysis patients—a systematic review and meta-analysis

Wen Wen[1,2], Ignacio Portales-Castillo[2], Rituvanthikaa Seethapathy[2], Scott Krinsky[2], Daniela Kroshinsky[3], Sahir Kalim[2], Jeremy Goverman[4], Rosalynn M. Nazarian[5], Vipul Chitalia[6], Rajeev Malhotra[7], Rafael Kramann[8,9,10], Cindy K. Malhotra[11] and Sagar U. Nigwekar[2]

[1]Department of Nephrology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China, [2]Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA, [3]Department of Dermatology, Massachusetts General Hospital, Boston, MA, USA, [4]Sumner Redstone Burn Center, Massachusetts General Hospital, Boston, MA, USA, [5]Department of Pathology, Massachusetts General Hospital, Boston, MA, USA, [6]Renal Section, Department of Medicine, Boston University Medical Center, Boston, MA, USA, [7]Cardiovascular Research Center and the Cardiology Division of the Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, [8]Division of Nephrology and Clinical Immunology, Medical Faculty RWTH Aachen University, Aachen, Germany, [9]Institute of Experimental Medicine and Systems Biology, Medical Faculty RWTH Aachen University, Aachen, Germany, [10]Department of Internal Medicine, Nephrology and Transplantation, Erasmus Medical Center, Rotterdam, The Netherlands and [11]Department of Pharmacy, Massachusetts General Hospital, Boston, MA, USA

Intravenous sodium thiosulphate treatment for vascular calcification of hemodialysis patients–a systematic review and meta-analysis

Background

Vascular calcification is common in patients with chronic kidney disease (CKD) and indicative of poor cardiovascular outcomes. Sodium thiosulfate, used in calciphylaxis, may ameliorate vascular calcification. Evaluation and safety profile of sodium thiosulfate (STS) in treating vascular calcification among dialysis patients.

Methods

Electronic databases
PubMed, EMBASE, Web of Science, Cochrane, and ClinicalTrials.gov

August 2021

PRISMA guidelines

6 studies (5 RCTs), **305** patients on hemodialysis

Results

Efficacy

Calcification* score

Coronary artery –241.27
95% CI (–421.50, –61.03)

Iliac artery –382
95% CI (–751.07, – 12.93)

Arterial stiffness
PWV⁺ –1.29 m/s
95% CI (–2.24, –0.34 m/s)

STS group vs. Control

Safety

1 in 4 developed GI side effects

Unchanged CKD–bone disease parameters

Increased anion gap

*mean difference of agatston score; score reflects density of the calcium, ⁺pulse wave velocity

Conclusion

Intravenous STS may attenuate the progression of vascular calcification and arterial stiffness in hemodialysis patients. Large and well-designed randomized controlled trials are warranted.

ERA NDT NEPHROLOGY DIALYSIS TRANSPLANTATION

Wen, W., et al. NDT (2022)
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KI REPORTS
KIReports.org
CLINICAL RESEARCH

Sotatercept Safety and Effects on Hemoglobin, Bone, and Vascular Calcification

Daniel W. Coyne[1], Hem N. Singh[2], William T. Smith[2,9], Ana Carolina Giuseppi[2], Jamie N. Connarn[2], Matthew L. Sherman[3], Frank Dellanna[4], Hartmut H. Malluche[5,8] and Keith A. Hruska[1,6,7,8]

Activin receptor type IIA (ActRIIA)-IgG1 fusion protein trap

Binds with high affinity to activin A and other members of (TGF-b) superfamily, acts on late-stage erythropoiesis to increase production of mature erythrocytes

In a small randomized trial of 43 patients on dialysis, treatment with subcutaneous sotatercept, compared with placebo, showed a dose-dependent trend toward slowing progression of abdominal aortic vascular calcification

Vascular Calcification Slows But Does Not Regress After Kidney Transplantation

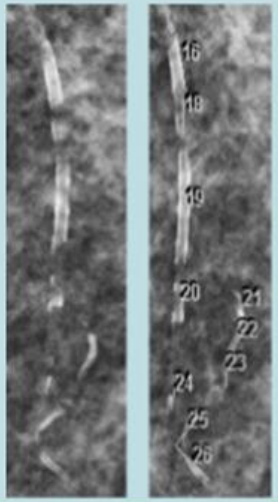
STUDY POPULATION

- Women with prior end stage renal disease (ESRD) and kidney transplants with creatinine <2 (Tx).
- Women with ESRD on transplant waitlist.
- ≥2 mammograms >1 year apart showing arterial calcification.

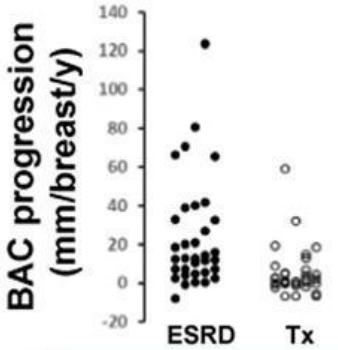
Tx=treatment

METHODS

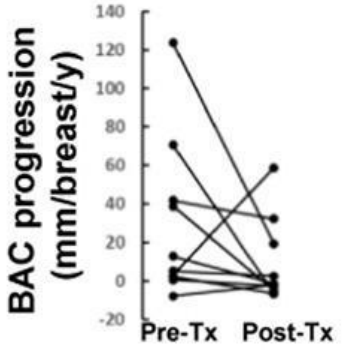
- Lengths of calcified arteries summed to derive total breast arterial calcification (BAC).



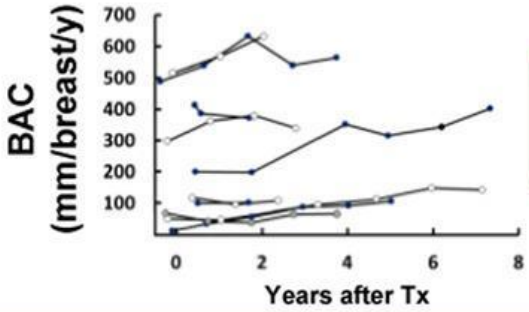
FINDINGS



BAC progression slower in Tx patients



Progression slowed in most patients after Tx



Calcification did not regress after transplantation

CONCLUSION:
Vascular calcification slows after kidney transplantation to rates seen in subjects without CKD but there was no evidence of regression.

KI REPORTS
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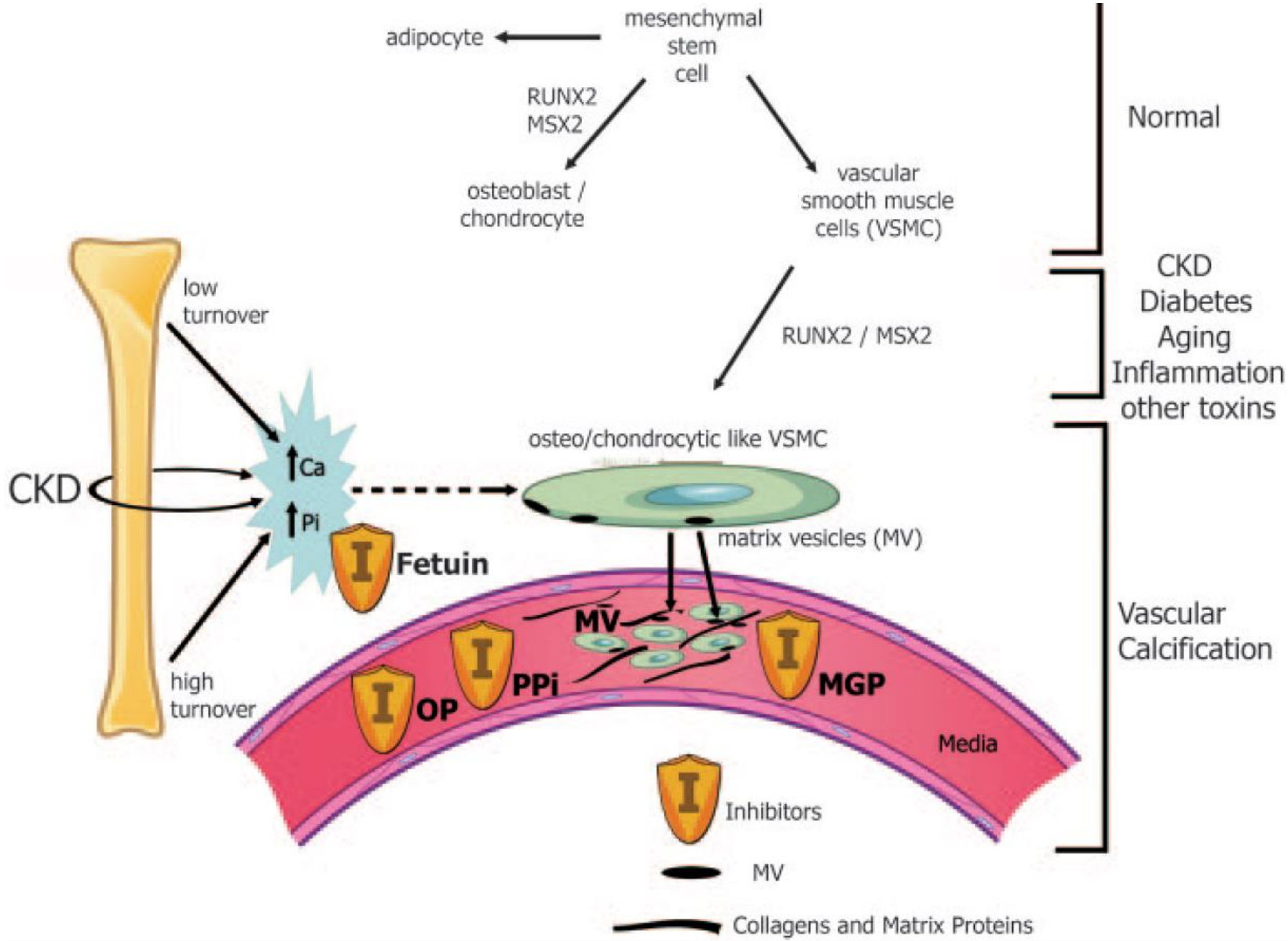
mesenchymal stem cell
adipocyte
RUNX2
MSX2
osteoblast / chondrocyte
vascular smooth muscle cells (VSMC)
RUNX2 / MSX2
osteo/chondrocytic like VSMC
matrix vesicles (MV)
low turnover
high turnover
CKD
Ca
Pi
Fetuin
MV
OP
PPi
MGP
Media
Inhibitors
MV
Collagens and Matrix Proteins
Normal
CKD
Diabetes
Aging
Inflammation
other toxins
Vascular Calcification

Thanks for attention