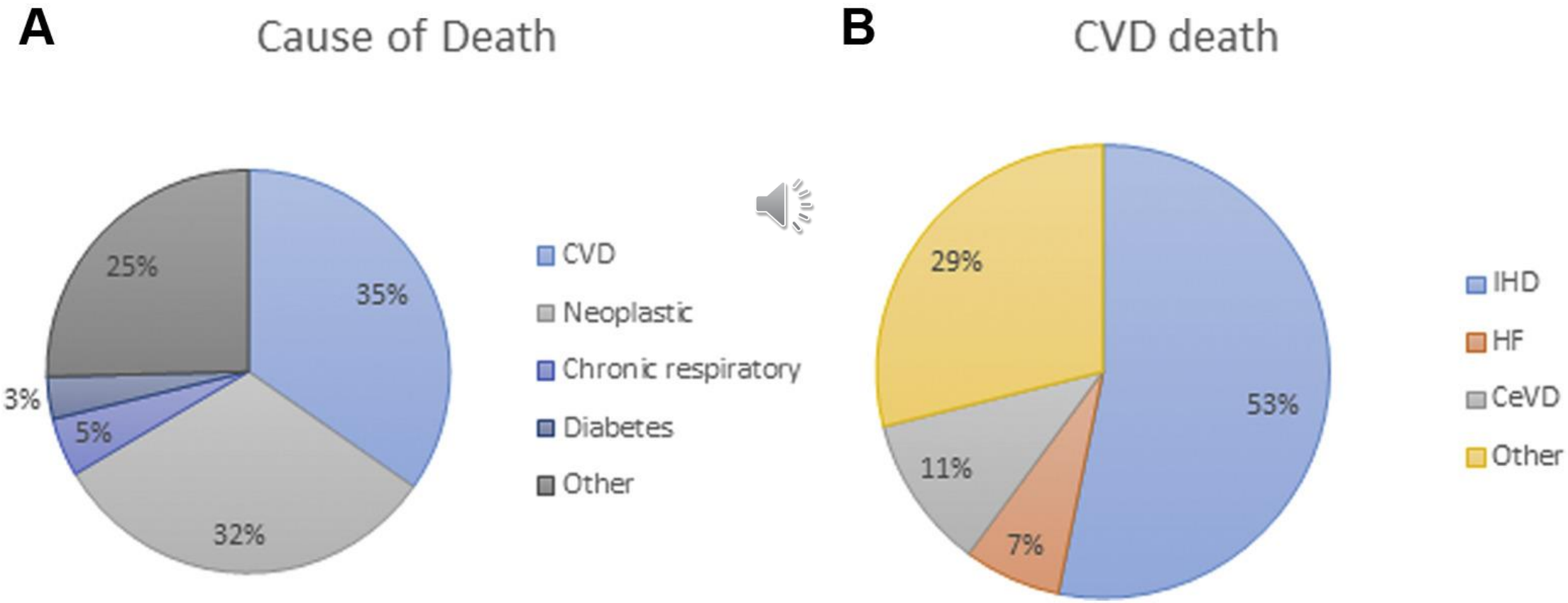
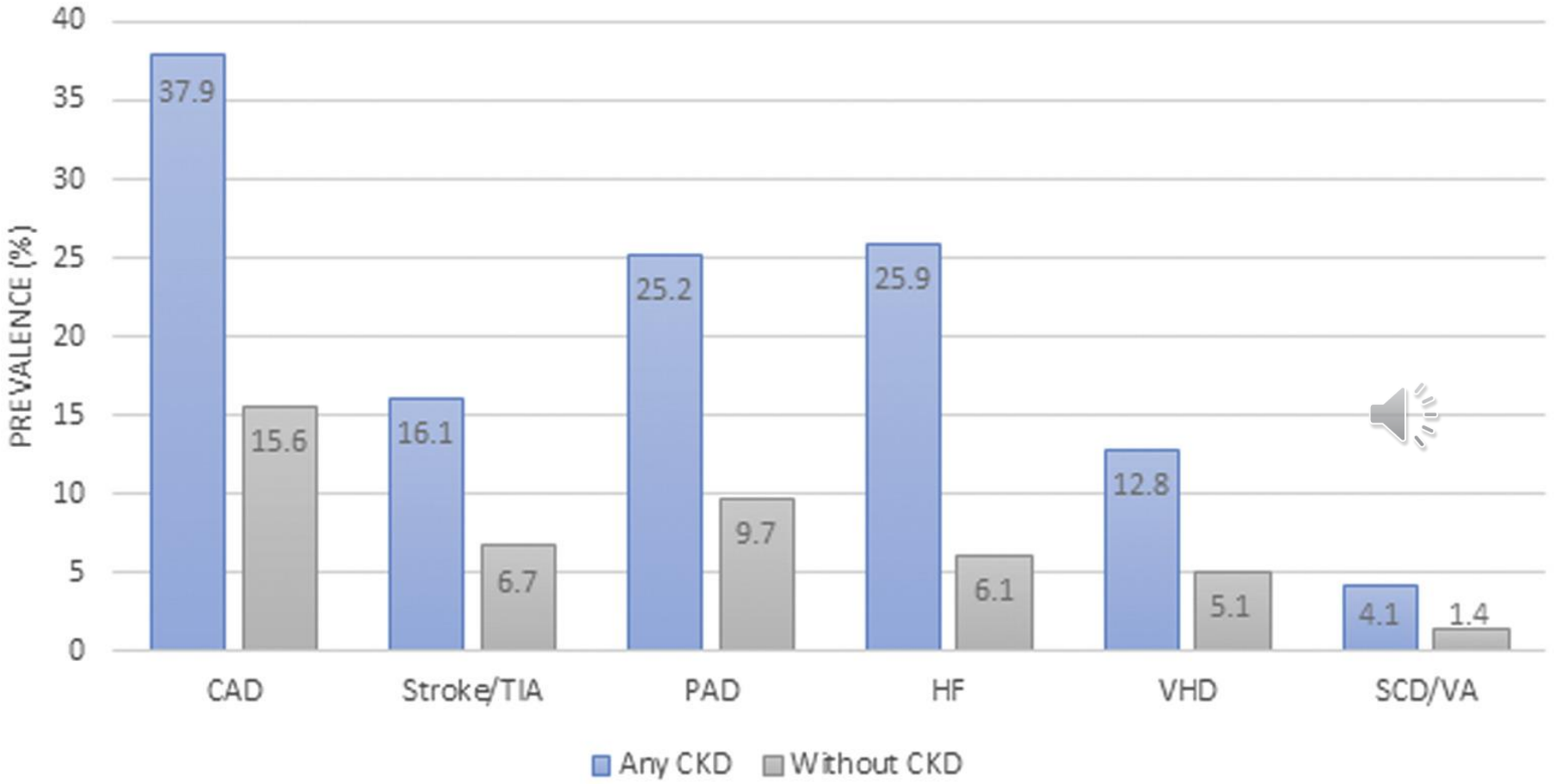
Vascular calcification in ESKD

- Despite improvements in the care of patients with CKD, life expectancy remains significantly reduced across all stages of kidney disease , and the global burden of kidney disease continues to rise .
- Cardiovascular disease (CVD) is a significant contributor to the high morbidity experienced by patients with CKD and CV death is the most common cause of death in this population.

Categorical and Cardiovascular Disease Cause-Specific Mortality



Cardiovascular Disease Burden in a Sample of Medicare



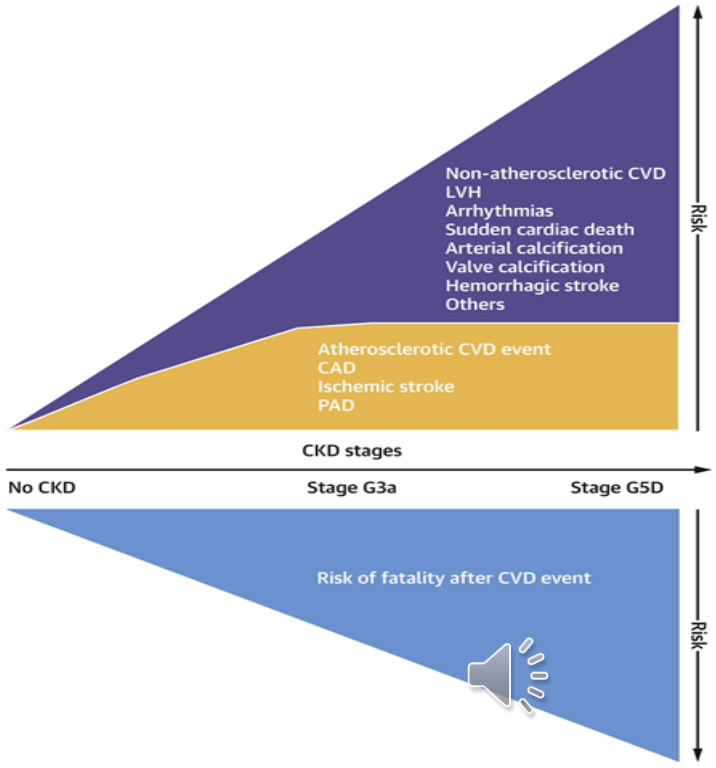
Journal of the American College of Cardiology
Volume 74, Issue 14, 8 October 2019, Pages 1823-1838

The Present and Future
JACC State-of-the-Art Review

Chronic Kidney Disease and Coronary Artery Disease: JACC State-of-the-Art Review

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among patients with CKD. Even after adjustment for known CAD risk factors, including diabetes and hypertension, mortality risk progressively increases with worsening CKD 1, 2. As glomerular filtration rate (GFR) declines below ~60 to 75 ml/min/1.73 m2, the probability of developing CAD increases linearly (Figure 1) 1, 3, and patients with CKD stages G3a to G4 (15-60 ml/min/1.73 m2) have approximately double and triple the CVD mortality risk, respectively, relative to patients without CKD

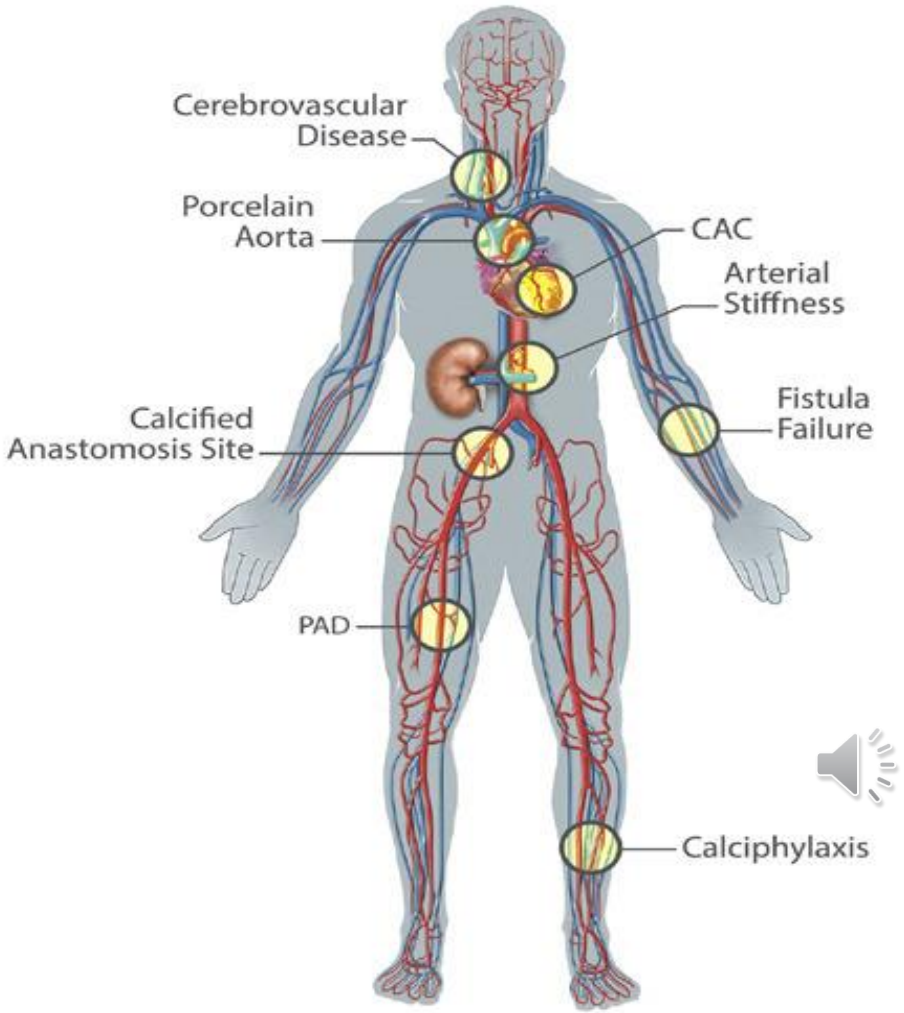
CENTRAL ILLUSTRATION: Changes in Cardiovascular Disease Risk During Chronic Kidney Disease Progression



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

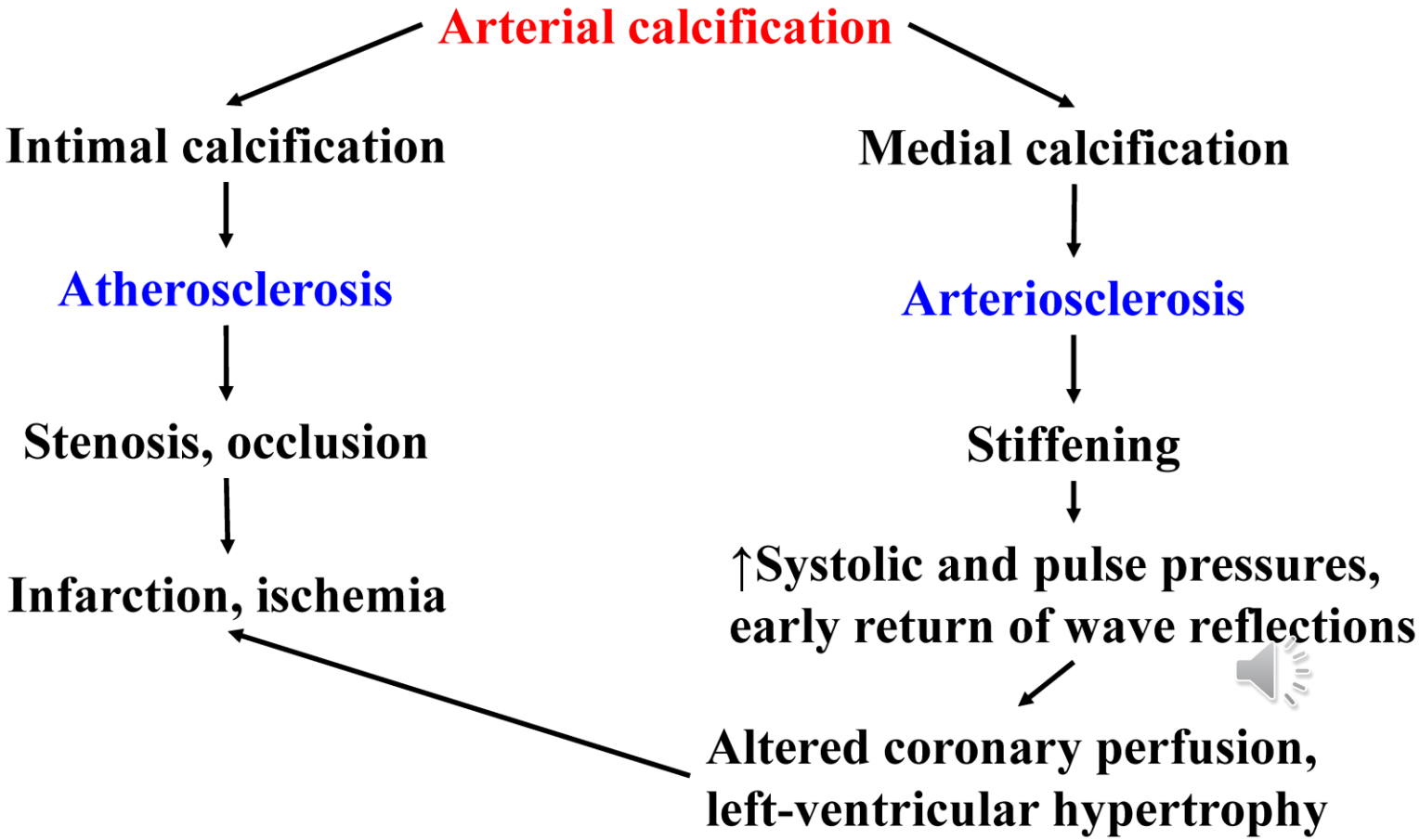
- Vascular calcification, the pathological deposition of calcium salts in the arterial wall, has been observed among patients with CKD at between 2- and 5-fold the rate of age-matched non-CKD patients.
- A large body of evidence has subsequently supported biologically plausible, temporal , and dose−response relations between vascular calcification and CV risk in patients with CKD. However, whether the regression or halting of vascular calcification is possible and subsequently results in improved CV outcomes remains to be determined.

CENTRAL ILLUSTRATION **Distribution of Vascular Calcification With Attendant Clinical Consequences**



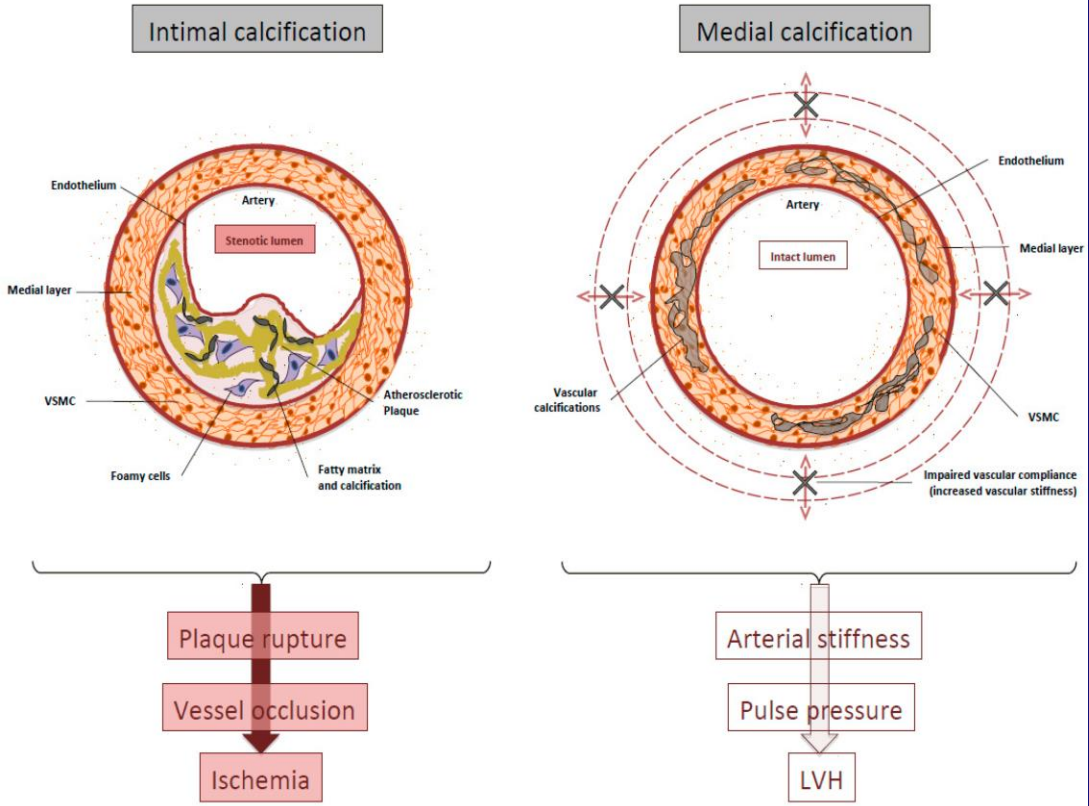
Nelson, A.J. et al. J Am Coll Cardiol Basic Trans Science. 2020;5:398-398.

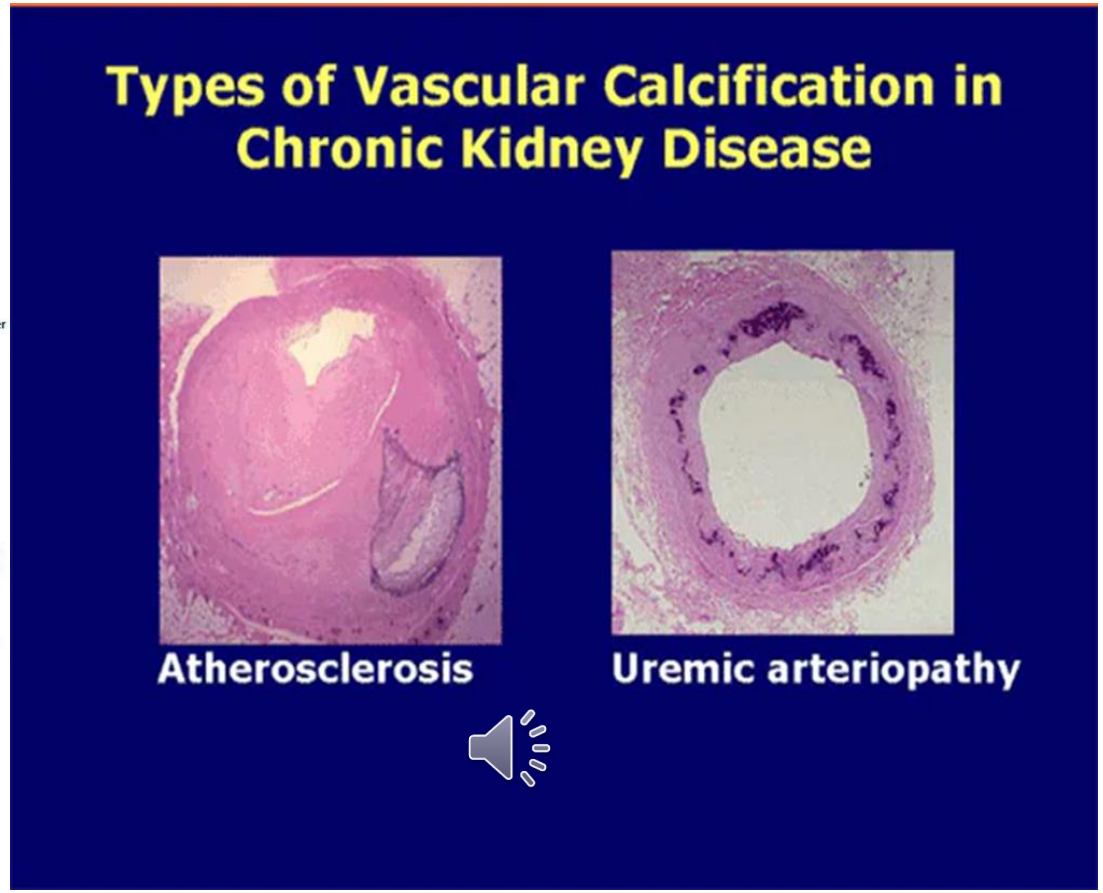
Schematic representation of the clinical effects of arterial intimal and medial calcification.



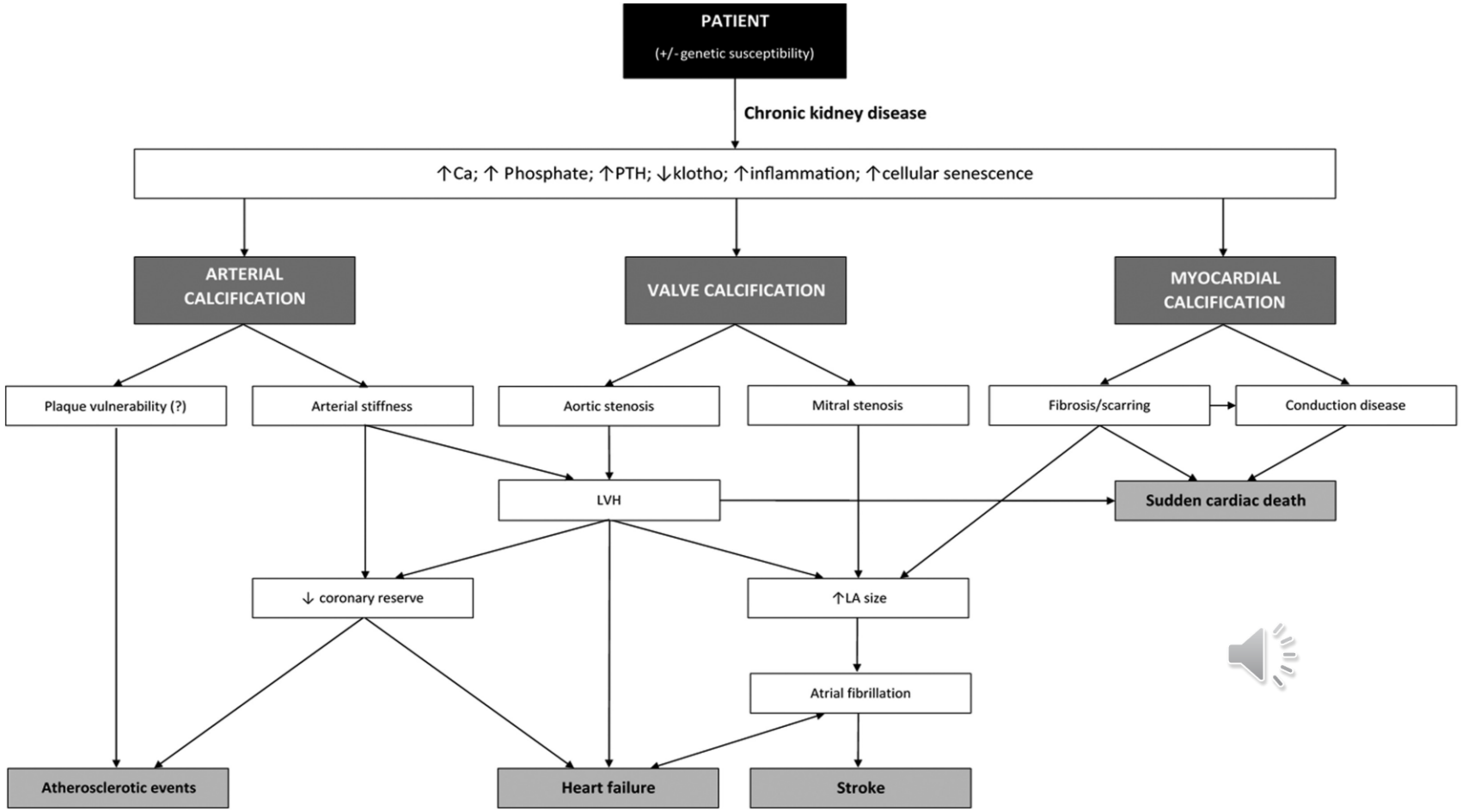
The lumen of the artery with medial calcification is largely patent but the wall is hardened causing poor arterial compliance and decreased blood flow.

Disthabanchong S, Boongird S. Role of different imaging modalities of vascular calcification in predicting outcomes in chronic kidney disease. World J Nephrol 2017; 6(3): 100-110 [PMID: 28540199 DOI: 10.5527/wjn.v6.i3.100





Flowchart Linking Clinicopathological Calcification



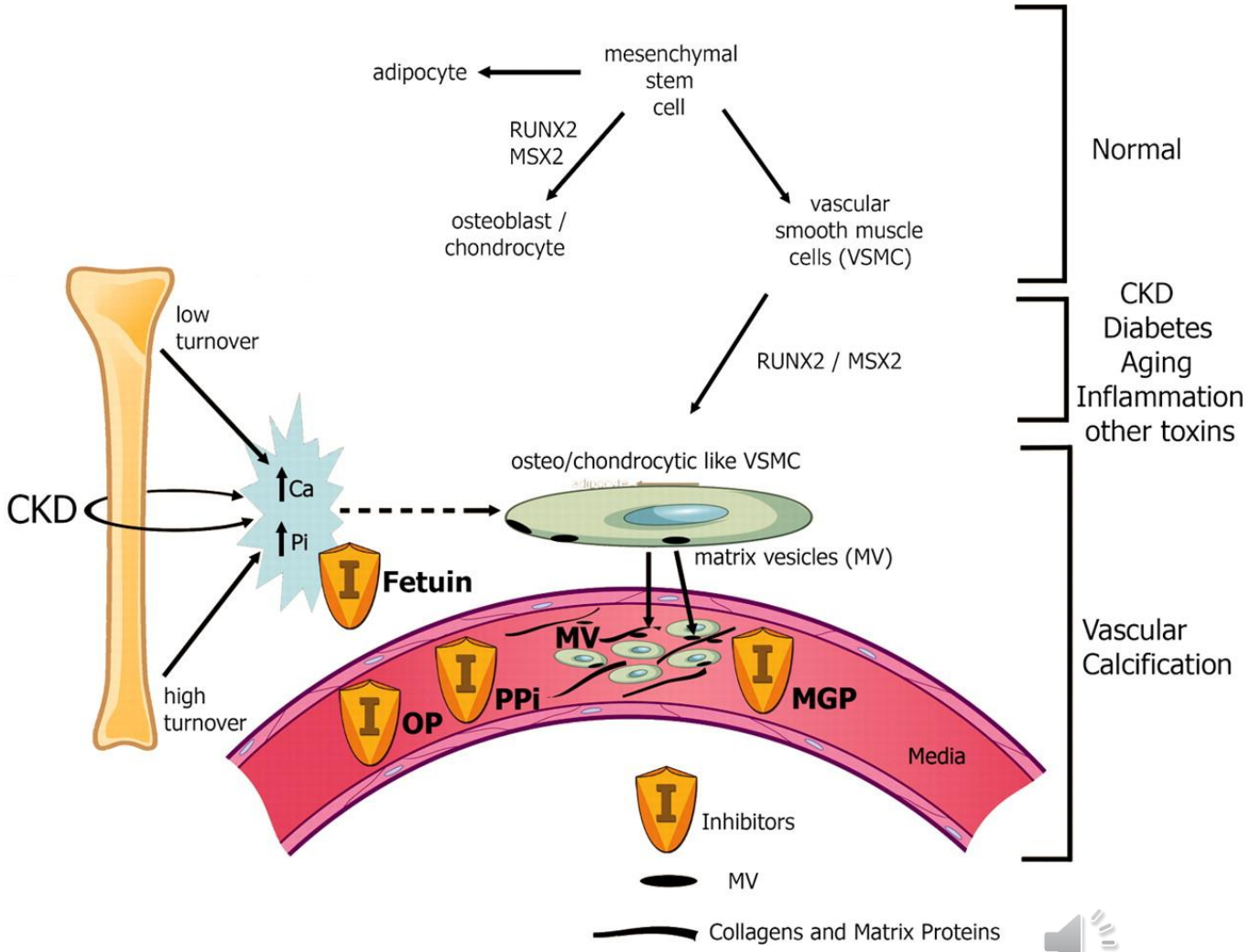
Pathogenesis of vascular calcification in CKD

- The pathogenesis of vascular calcification in CKD is complex, and instead of occurring by a simple process of calcium and phosphate precipitation, it is produced by an active process in which vascular smooth muscle cells (VSMCs) undergo apoptosis and vesicle formation and are transformed into osteoblast-like cells that induce matrix formation and attract local factors that are involved in the mineralization process .

- By Kosaku Nitta

Submitted: June 4th 2014Reviewed: October 2nd 2014Published: September 9th 2015
DOI: 10.5772/59403

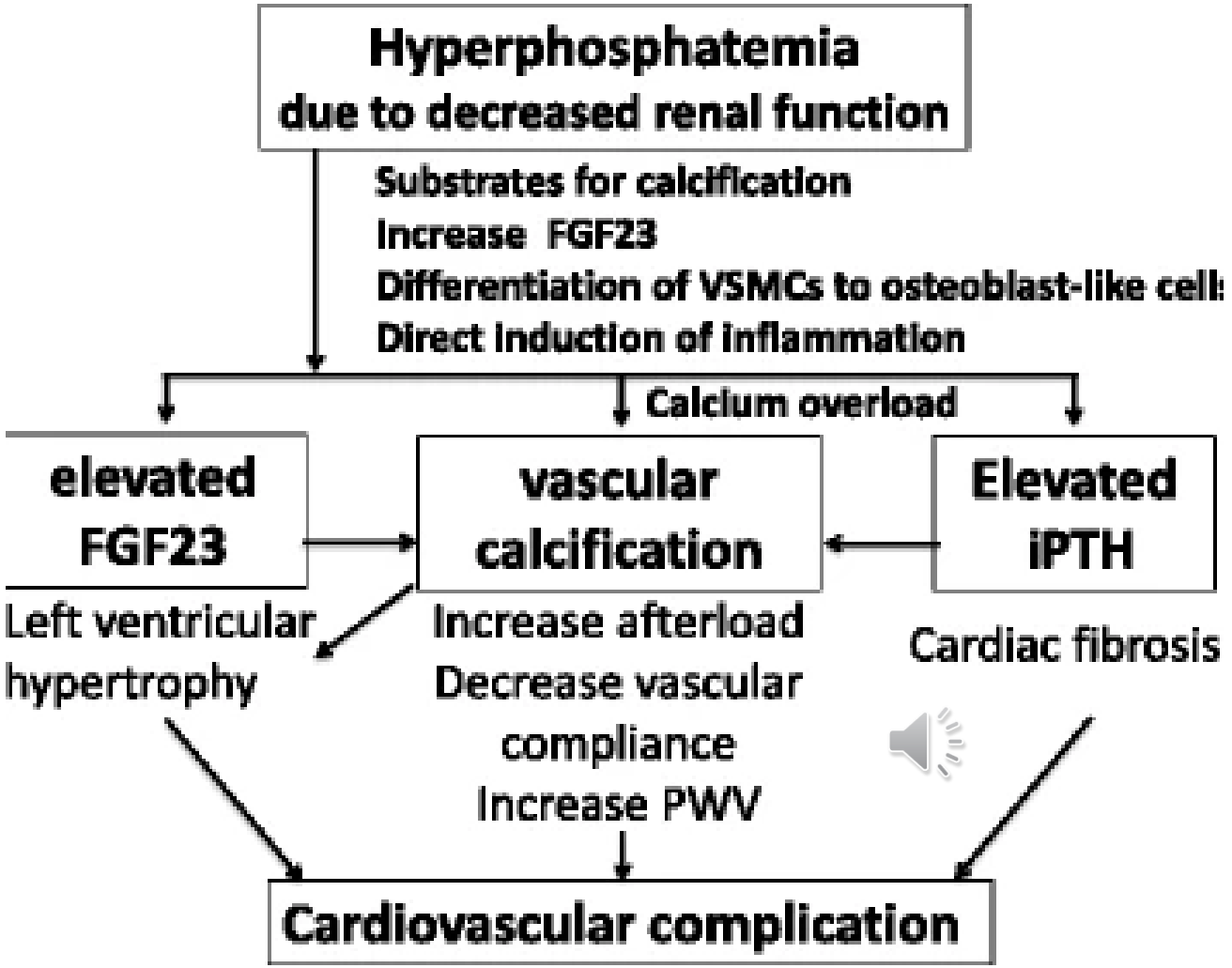
Normally, mesenchymal stem cells differentiate to adipocytes, osteoblasts, chondrocytes, and vascular smooth muscle cells (VSMC).



Sharon M. Moe, and Neal X. Chen JASN 2008;19:213-216

Impact of vascular calcification on cardiovascular mortality in hemodialysis patients: clinical significance, mechanisms and possible strategies for treatment
Takayasu Ohtake &
Shuzo Kobayashi
Renal Replacement Therapy **volume 3**,
Article number: 13 (2017

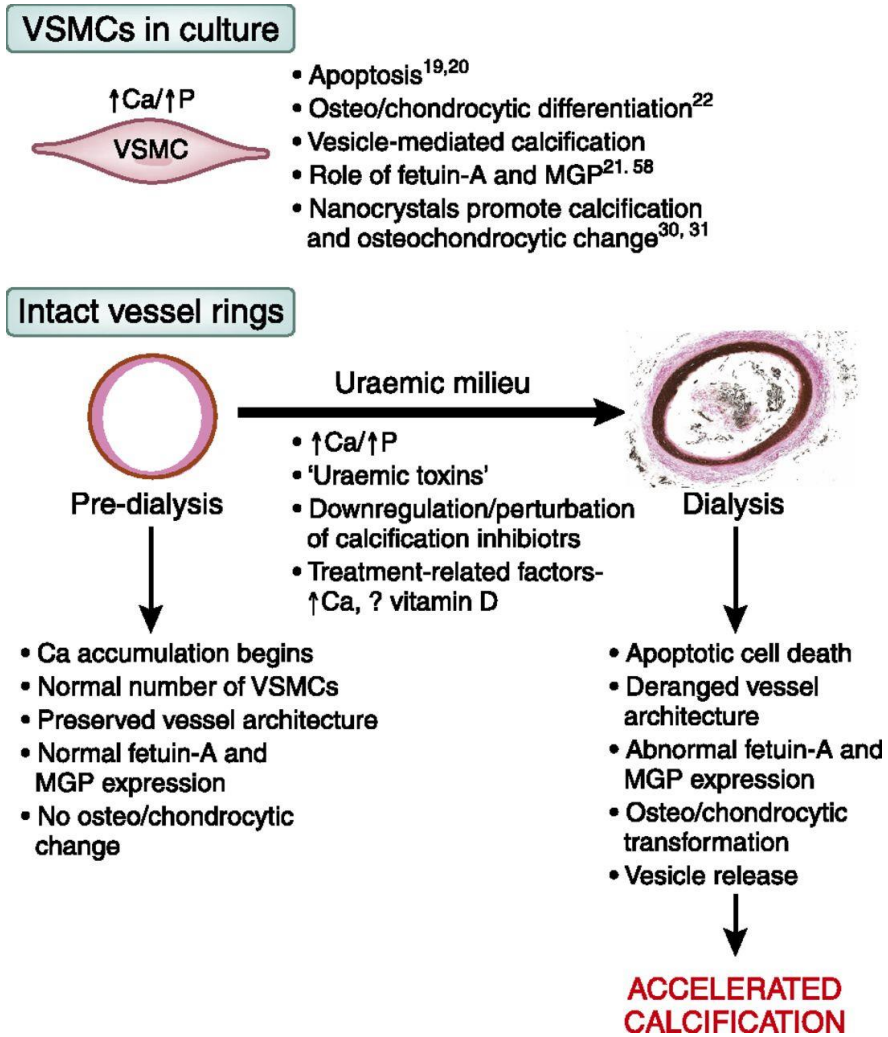
Clinical aspect of vascular calcification leading to cardiovascular complication. The critical key for vascular calcification is hyperphosphatemia due to decreased renal function. Hyperphosphatemia causes vascular calcification through several mechanisms. Vascular calcification, concomitantly with left ventricular hypertrophy and cardiac fibrosis, causes cardiovascular complication. *Abbreviations*: *FGF23* fibr oblast growth factor 23, *VSMC* vascular smooth muscle cell, *iPTH* intact parathyroid hormone, *PWV* pulse wave velocity



Osteoblastic differentiation

- Runx2 upregulation and ALP expression in VSMCs is the most important process in the early phase of osteoblast-like cell differentiation of VSMCs.
- Expression of Runx2 is normally restricted in the bone and cartilage.
- However, VSMCs express Runx2 via the stimulation of several uremia-related factors including phosphate, oxidative stress , and aldosterone
- Among which phosphate is the strongest stimulator of Runx2 upregulation.

Mechanisms of calcification in VSMCs in culture and in intact vessel rings in predialysis and dialysis vessels.



Rukshana Shroff et al. JASN 2013;24:179-189

Inducers and inhibitors for vascular calcifications are listed. As shown in the table, several factors associate the pathophysiology of vascular calcification. Several inhibitor systems exist in the human body, and it might mean the importance to protect from ectopic vascular calcification. If the inhibitory system would fail, serious complication might occur. Treatment target which we can intervene are also listed

Abbreviations :AGEs ,stcudorp dne noitacylg decnavda *BMP* ,nietorp cinegohprom enob *LDL* ,nietorpopil ytisned-wol *MGP* xirtam ,nietorp alG*PTH*enomroh dioryhtarap ;

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		

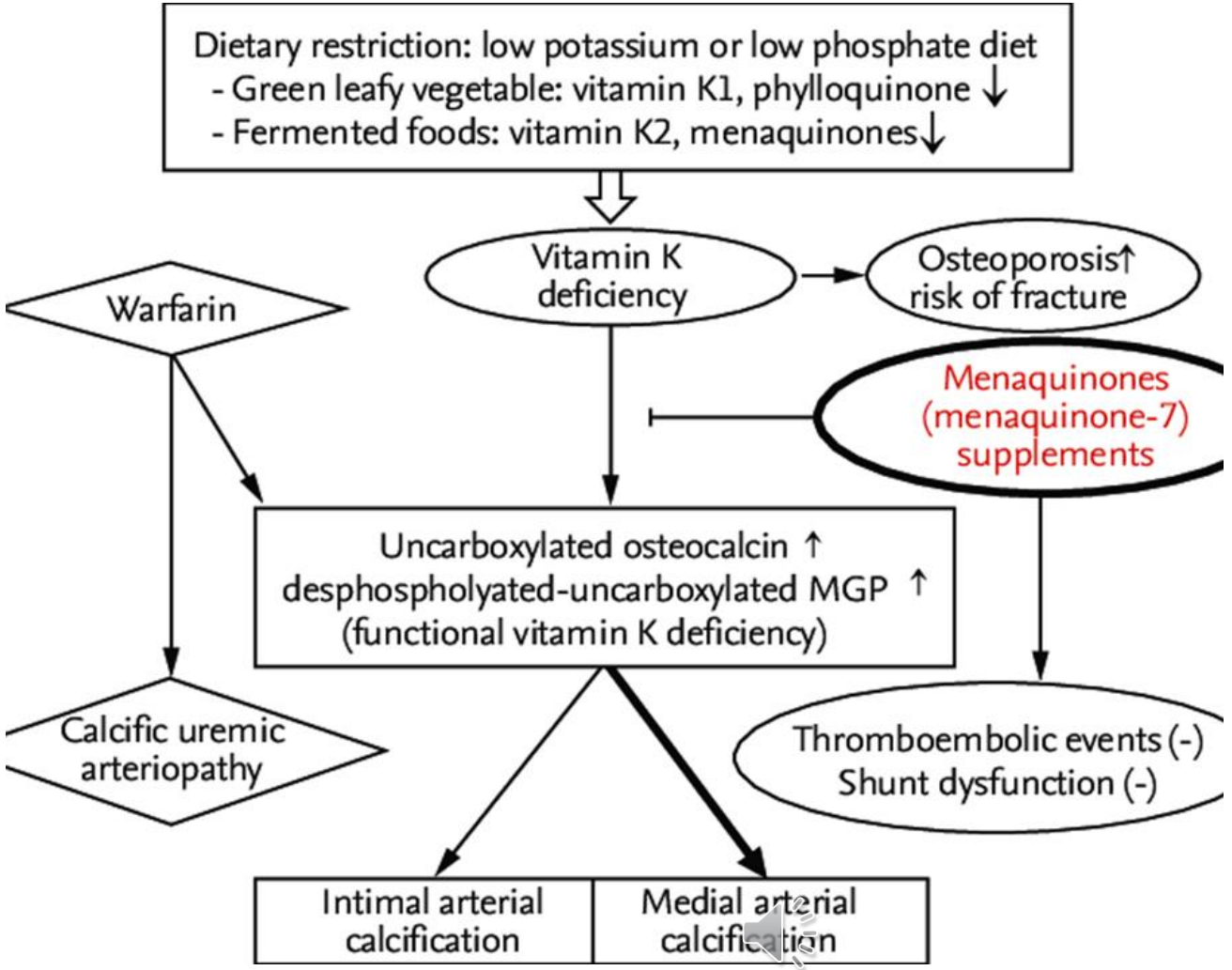
Fetuin-A

- Synthesized in the liver, and circulating fetuin-A concentrations fall during the inflammatory process .
- Extracellular calcium-regulatory factor that functions as a new inhibitor of calcium-phosphate deposition , suppresses calcinosis by binding hydroxyapatite , and protects VSMCs from the harmful effects of calcium overload and subsequent calcification . Fetuin-A suppresses VSMC apoptosis through death-signaling pathways:
- (i) it is internalized by VSMCs, concentrated in intracellular vesicles, and secreted via vesicle release from apoptotic and living VSMCs;
- (ii) fetuin-A in vesicles suppresses their ability to nucleate calcium phosphate; and
- (iii) fetuin-A increases phagocytosis of vesicles by VSMCs.
- These results confirm finding that the internalization of fetuin-A into VSMCs is a key finding in the inhibition of vesicle-mediated VSMC calcification .
- A recent study demonstrated that ESRD patients who had lower serum fetuin-A concentrations showed a lower survival rate from cardiovascular diseases, indicating that fetuin-A is related to the mechanism of the accelerated extraskeletal calcinosis.

MGP

- Is expressed in VSMCs and loaded in matrix vesicles (scaffold of calcification) around VSMCs, consequently inhibiting their calcification.
- MGP binds to calcium and pro-osteogenic factor bone morphologic protein 2 (BMP2) and inactivates it in normal condition .
- However, loading of MGP is decreased in high calcium circumstances, and matrix calcification is promoted .
- Vitamin K is essential for MGP activation. Therefore, deficiency of vitamin K inhibits MGP activity, thus leading to vascular calcification enhancement. Warfarin, an antagonist to vitamin K, is a strong promoter of arterial calcification via blocking the activation of vitamin K-dependent MGP .

Mechanism by which vitamin K modulates arterial intimal and medial calcification in patients with chronic kidney disease. Bold arrow indicates more related with arterial medial vascular calcification than thin arrow. Bold circle, vitamin K for prevention of vascular calcification in patients with chronic kidney disease. MGP, matrix γ-carboxyglutamate protein.



Pyrophosphate

- binds to hydroxyapatite crystals and inhibits their further growth.
- ALP, which is upregulated in VSMCs in the early stages of vascular calcification and a key factor for mineralization, degrades pyrophosphate, thereby promoting calcification .
- Osteogenic transcription factor Runx2 is thought to regulate the expression of ALP.

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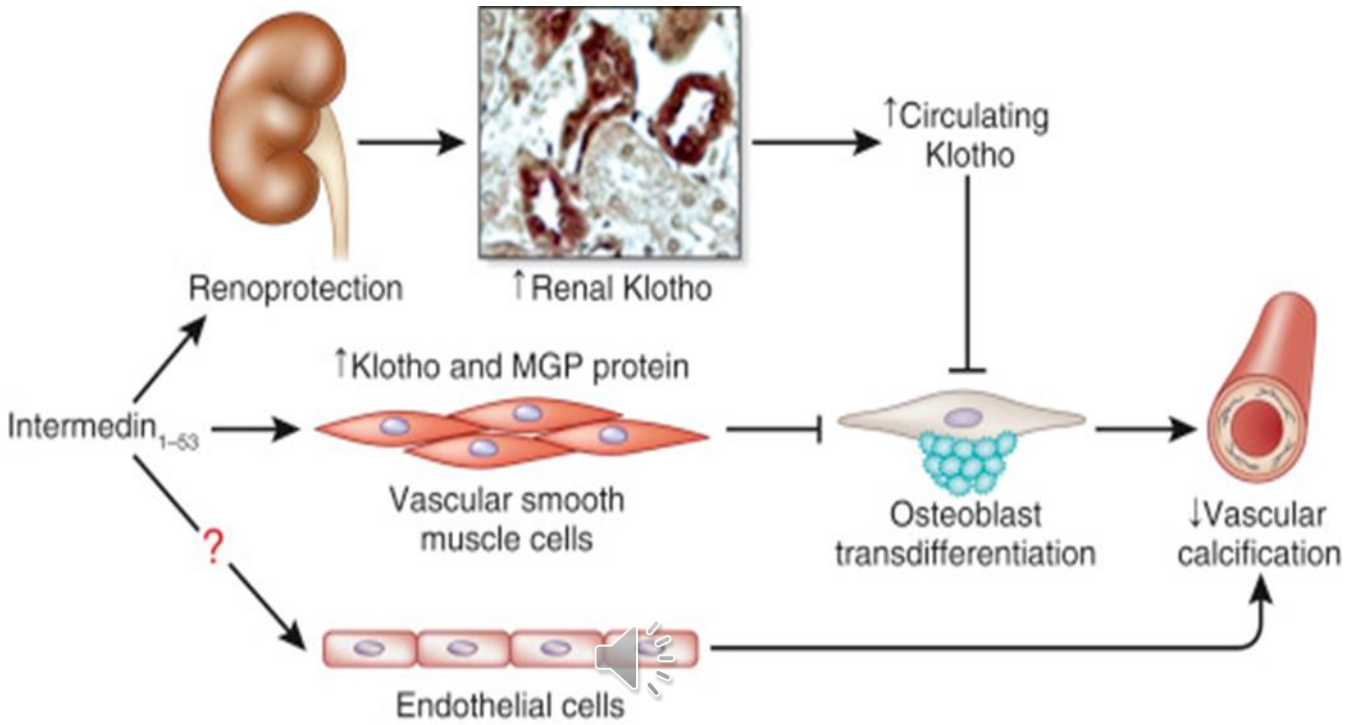
COMMENTARY | VOLUME 89, ISSUE 3, P534-537, MARCH 01, 2016

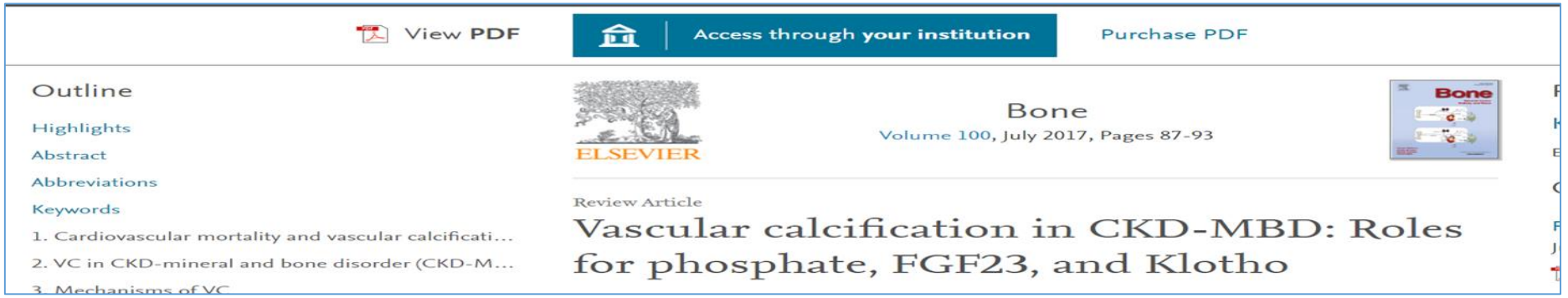
PDF [232 KB] Figures Save Share

Klotho connects intermedin$_{1–53}$ to suppression of vascular calcification in chronic kidney disease

Ming Chang Hu

Schematic model of the effects of intermedin (IMD)1–53 on the suppression of vascular calcification in chronic kidney disease (CKD). IMD1–53 protects the vasculature against calcification in CKD by direct and indirect actions. Indirect prevention of vascular calcification comes from the role of IMD1–53 in slowing down the progression of CKD, better maintaining renal Klotho expression, and consequently increasing the level of plasma Klotho in CKD (top). In addition, IMD1–53 directly upregulates Klotho and matrix γ-carboxyglutamic acid protein (MGP) protein expression in vascular smooth muscle cells (middle). The elevation of Klotho blocks the transdifferentiation of vascular smooth muscle cells into the osteoblast and inhibits vascular calcification. Whether IMD1–53 can directly protect endothelium against uremic toxin, high phosphate, or both, and prevent vascular calcification, are to be explored (bottom).



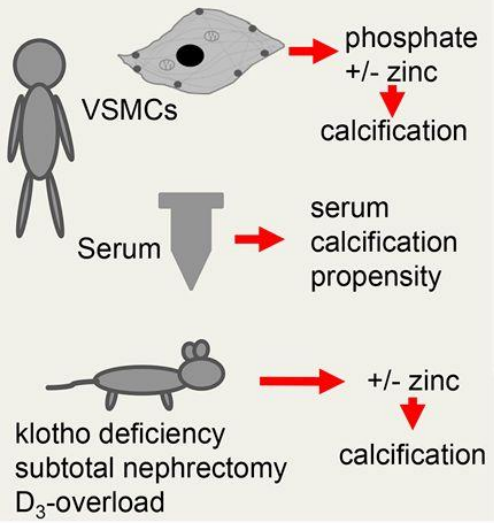


- Highlights
- Elevated serum phosphate in CKD has been shown to accelerate mineral deposition in both the vessel wall and heart valves
- α-Klotho and FGF23 are emerging players in the pathogenesis of uremic vascular calcification
- While the role of FGF23 in vascular calcification is controversial, mounting evidence supports protective roles for α-Klotho

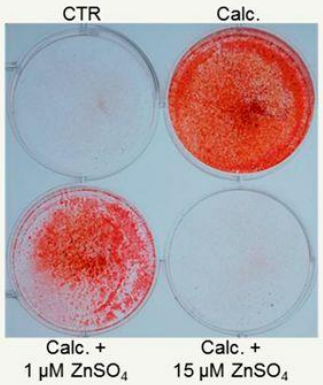
Zinc inhibits phosphate-induced vascular calcification via TNFAIP3-mediated suppression of NF-kB

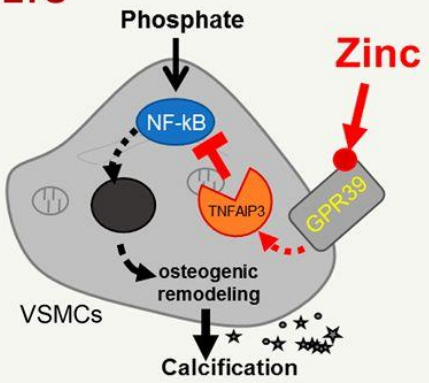
METHODS

Primary human aortic VSMCs, serum samples from CKD patients and mouse calcification models.



RESULTS





Zinc supplementation acts via GPR39 to induce expression of TNFAIP3, subsequently impairing NF-kB activation, osteo-/chondrogenic transdifferentiation and calcification in VSMCs.

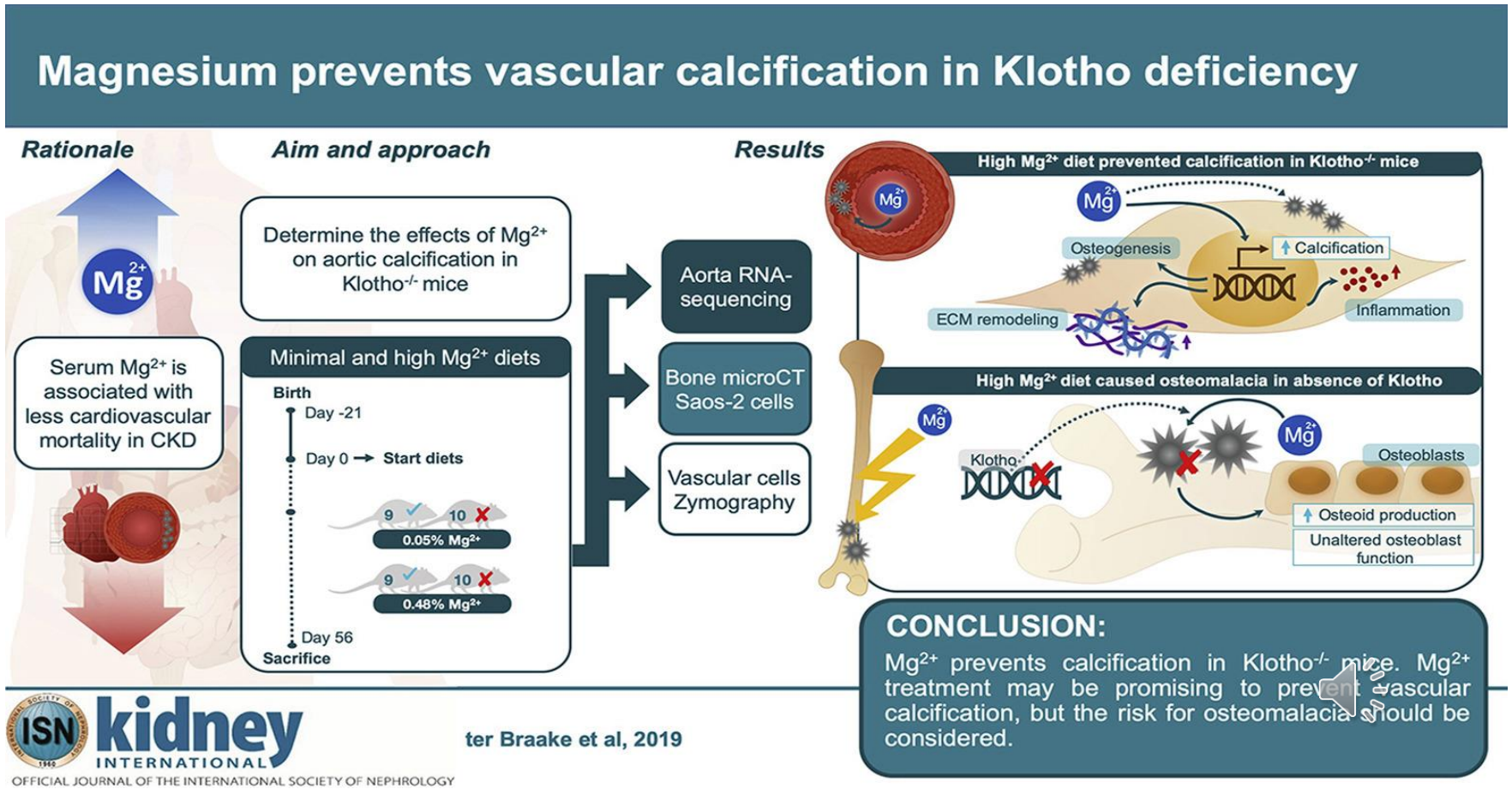
CONCLUSION

Zinc supplementation may potentially ameliorate vascular calcification in chronic kidney disease.

doi: 10.1681/ASN.2017050492

Jakob Voelkl et al. JASN 2018;29:1636-1648

Magnesium prevents vascular calcification in Klotho deficiency



CONCLUSION:

Mg^{2+} prevents calcification in Klotho$^{-/-}$ mice. Mg^{2+} treatment may be promising to prevent vascular calcification, but the risk for osteomalacia should be considered.

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ter Braake et al, 2019

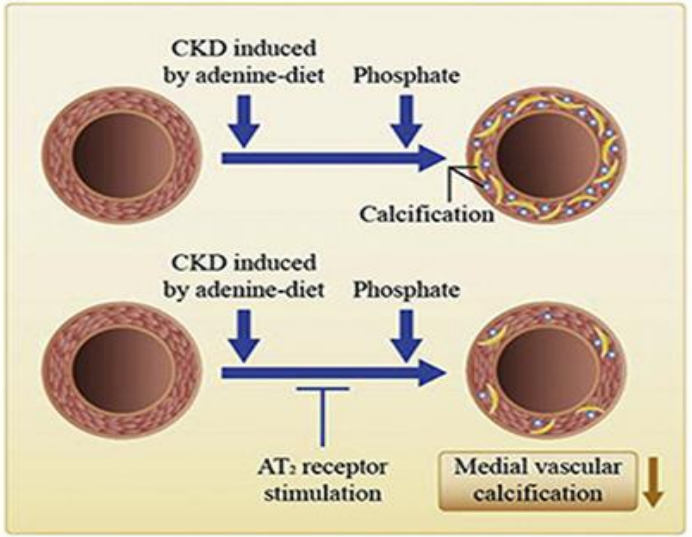
BASIC RESEARCH | VOLUME 95, ISSUE 1, P138-148, JANUARY 01, 2019

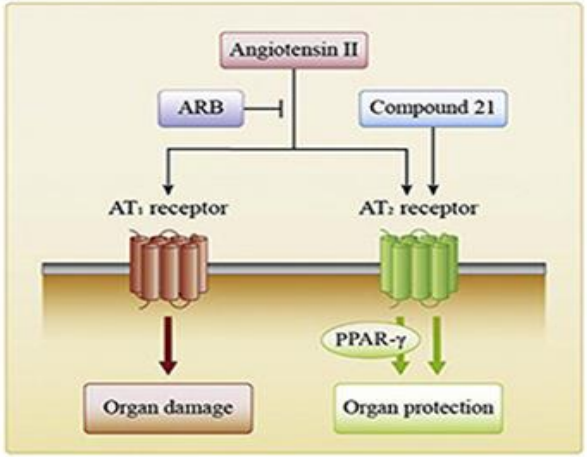
AT2 receptor stimulation inhibits phosphate-induced vascular calcification

Masayoshi Kukida • Masaki Mogi • Harumi Kan-no • ... Takafumi Okura • Jitsuo Higaki • Masatsugu Horiuchi • Show all authors

Published: November 12, 2018 • DOI: https://doi.org/10.1016/j.kint.2018.07.028 •

AT_2 receptor stimulation inhibits phosphate-induced vascular calcification





CONCLUSION:
AT_2 stimulation is an efficient endogenous vasoprotective factor in vascular calcification

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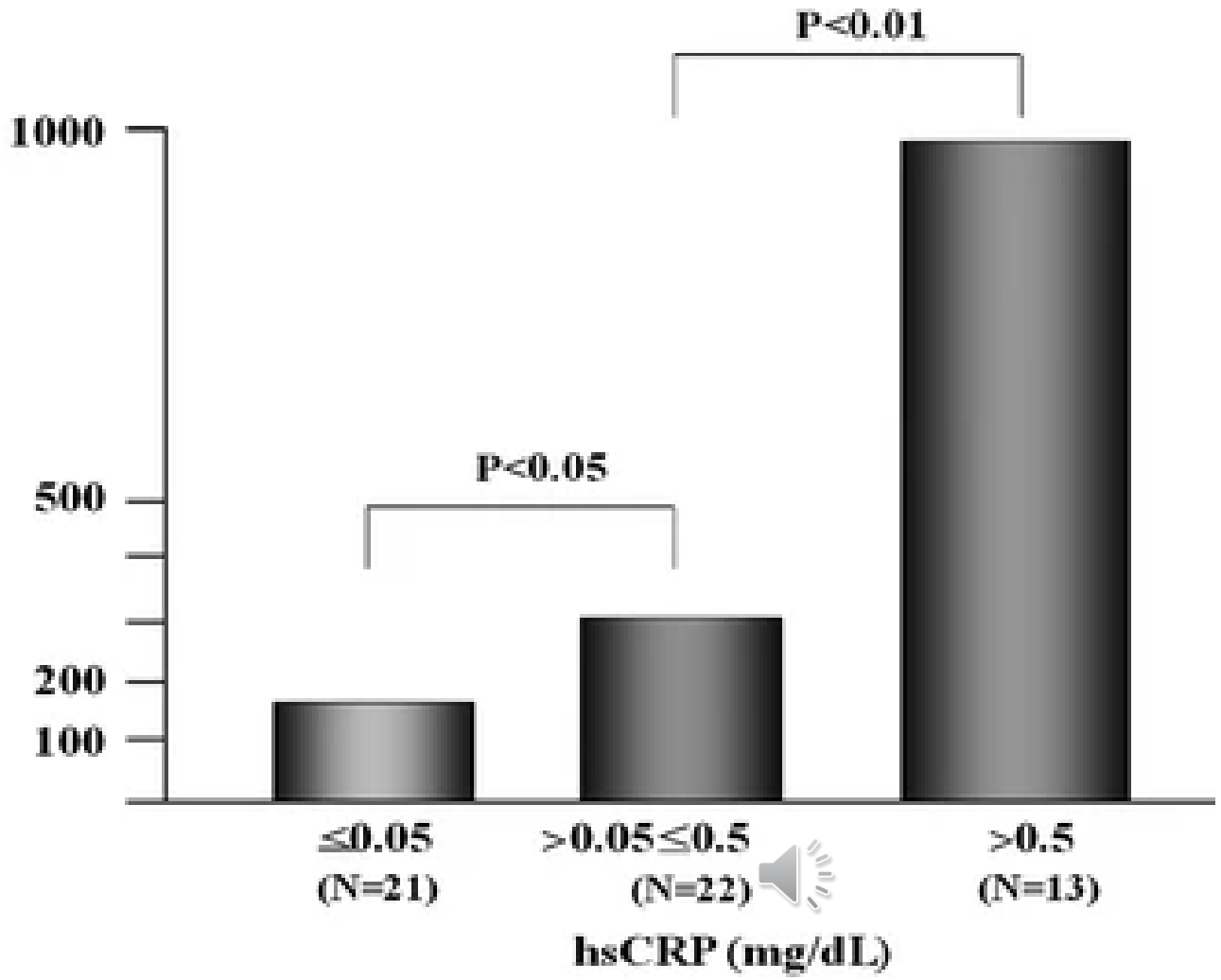
Kukida et al, 2018

Impact of vascular calcification on cardiovascular mortality in hemodialysis patients: clinical significance, mechanisms and possible strategies for treatment
Takayasu Ohtake &
Shuzo Kobayashi
Renal Replacement Therapy **volume 3**,
Article number: 13 (2017

Stratified hsCRP and the progression of CAC . CACS of 56 patients on maintenance hemodialysis were evaluated repeatedly with 15 months interval, and delta CACS (changes of CACS) were shown according to stratified hsCRP. Progression of CACS was significantly correlated with baseline hsCRP values. *Abbreviations*: *hsCRP* high sensitive C-reactive protein, *CACS* coronary artery calcification score



CRP

- Our previous study showed micro-inflammation, represented by elevated highly sensitive C-reactive protein, was another strong and independent predictor for CAC progression .
- Other studies also provided the link between micro-inflammation and progression of CAC .
- It has now been known that hyperphosphatemia itself is an important source of inflammation .
- Inflammatory cytokine TNF-α upregulates Pit-1 expression and Na-Pi co-transporter and increases phosphate uptake into VSMCs .
- Both phosphate overload and accompanying inflammation is thought to concomitantly enhance the vascular calcification.

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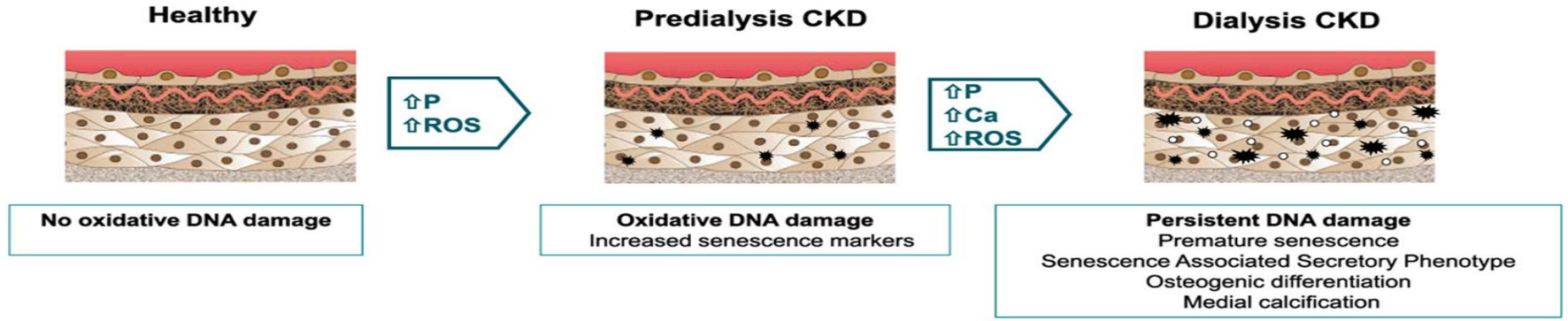
Arterial "inflammaging" drives vascular calcification in children on dialysis

Pilar Sanchis [4, 5] • Chin Yee Ho [4] • Yiwen Liu • ... David A. Long • Rukshana Shroff • Catherine M. Shanahan • Show all authors • Show footnotes

Open Access • Published: March 01, 2019 • DOI: https://doi.org/10.1016/j.kint.2018.12.014 •

Arterial 'Inflammaging' drives vascular calcification in children on dialysis.



CONCLUSION:
Dysregulated mineral metabolism drives oxidative DNA damage and premature senescence to promote inflammation and vascular calcification in CKD.

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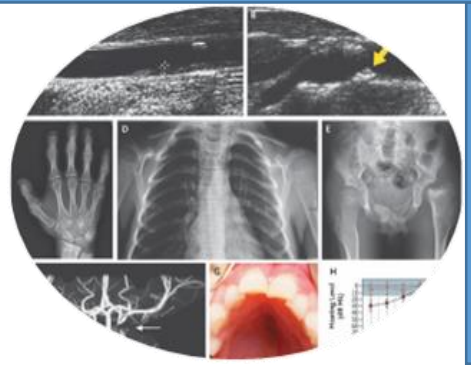
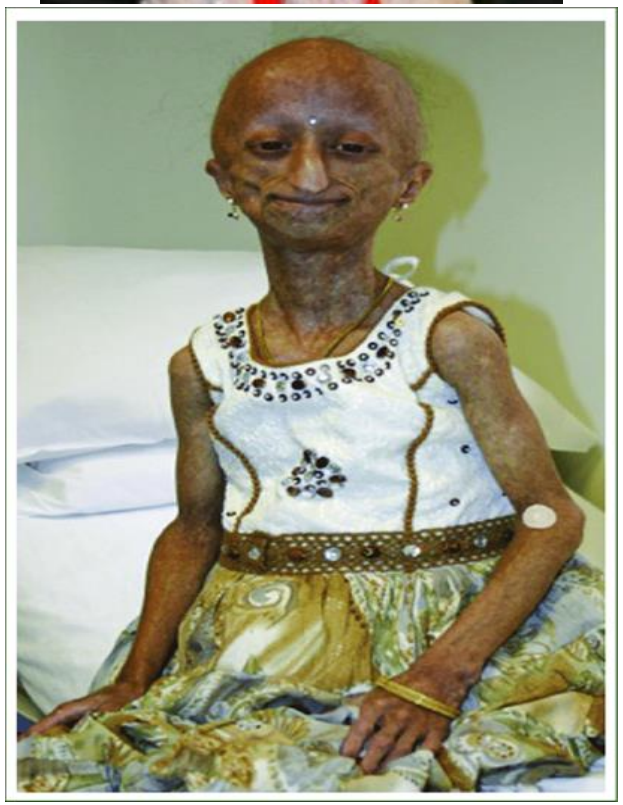
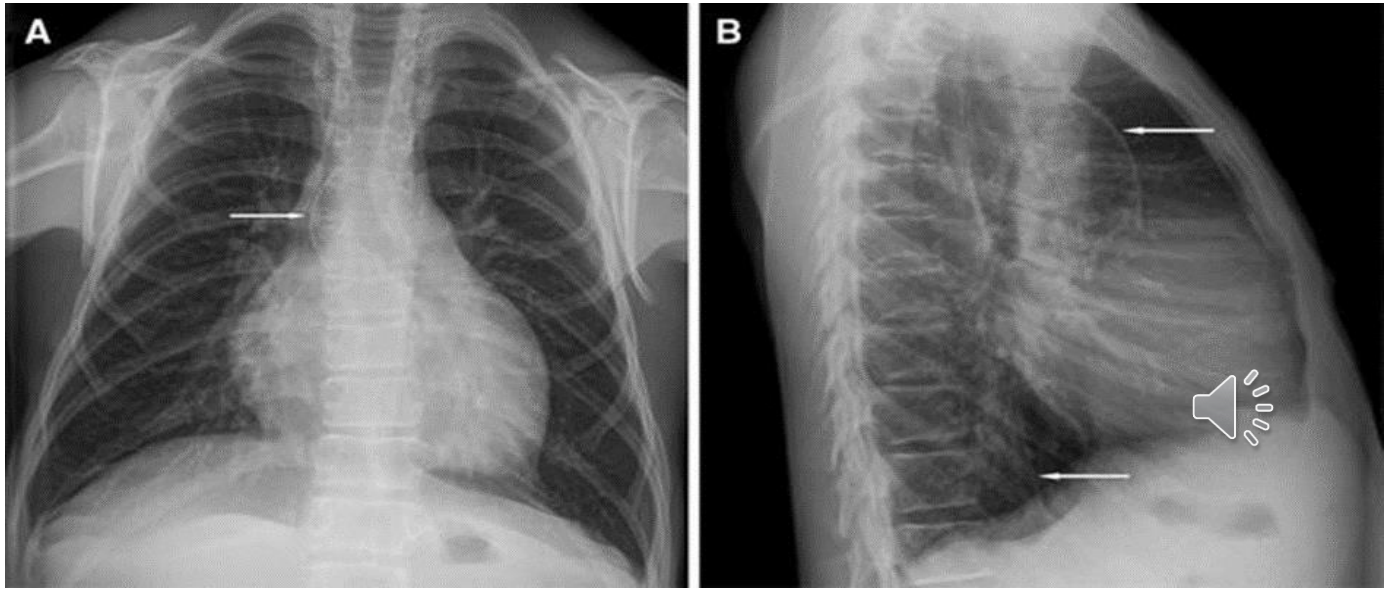
Sanchis, 2018

Photograph of a 17-year-old girl with Hutchinson-Gilford progeria syndrome. Courtesy of The Progeria Research Foundation



Hutchinson-Gilford progeria syndrome is a rare, sporadic, autosomal dominant syndrome that involves premature aging, generally leading to death at approximately 13 years of age due to myocardial infarction or stroke. The genetic basis of most cases of this syndrome is a change from glycine GGC to glycine GGT in codon 608 of the lamin A (LMNA) gene





Detection and Prognosis

- pointing to a positive linear relationship between the amount of vascular calcification as detected by plain radiographic images or computed tomography (CT) scanning, and the risk for clinical outcomes including all-cause and cardiovascular mortality

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Novel Risk Factors for Progression of Diabetic and Nondiabetic CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study

Amanda H. Anderson • Dawei Xie • Xue Wang • ... Myles Wolf • Harold I. Feldman •

on behalf of the CRIC Study Investigators • Show all authors

Open Access • Published: August 28, 2020 • DOI: https://doi.org/10.1053/j.ajkd.2020.07.011 •

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Graphical abstract

Rationale & Objective

Identification of novel risk factors for chronic kidney disease

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Serum Calcification Propensity and Coronary Artery Calcification Among Patients With CKD: The CRIC (Chronic Renal Insufficiency Cohort) Study

Joshua D. Bundy • Xuan Cai • Julia J. Scialla • ... Andreas Pasch • Tamara Isakova •

on behalf of the CRIC Study Investigators • Show all authors

ch 29, 2019 • DOI: https://doi.org/10.1053/j.ajkd.2019.01.024 • Check for updates

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FULL LENGTH ARTICLE | VOLUME 271, P53-60, APRIL 01, 2018

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Risk factors for progression of coronary artery calcification in patients with chronic kidney disease: The CRIC study

Joshua D. Bundy • Jing Chen • Wei Yang • ... Xiaoming Zhang • Jiang He •

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Published: February 10, 2018 • DOI: https://doi.org/10.1016/j.atherosclerosis.2018.02.009 •

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World J Nephrol. May 6, 2017; 6(3): 100-110
Published online May 6, 2017. doi: 10.5527/wjn.v6.i3.100

Role of different imaging modalities of vascular calcification in predicting outcomes in chronic kidney disease

Sinee Disthabanchong, Sarinya Boongird

Sinee Disthabanchong, Sarinya Boongird, Division of Nephrology, Department of Medicine, Faculty

COMMENTARY | VOLUME 74, ISSUE 12, P1505-1507, DECEMBER 02, 2008

Cardiovascular risk in dialysis patients: an X-ray vision on vascular calcifications

Teresa Adragão • João M. Frazão

Open Archive • DOI: https://doi.org/10.1038/ki.2008.503

Introduction

Methods to evaluate vascular calcifications

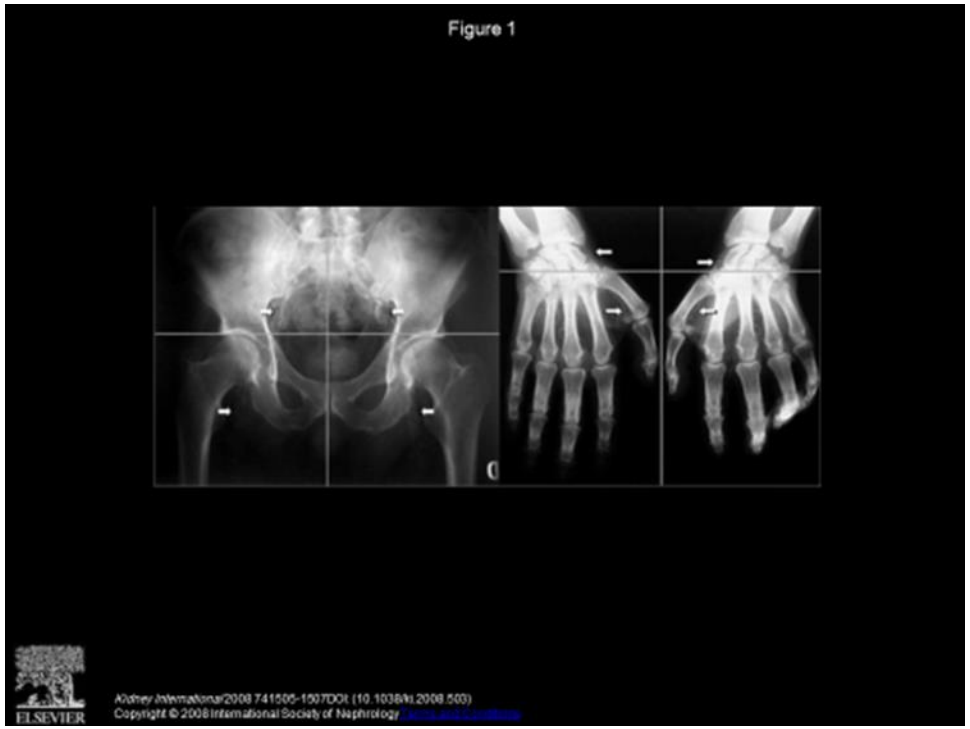
In dialysis patients, there is an association between vascular calcifications and mortality. Hyperphosphatemia and calcium overload are associated with development of vascular calcifications, especially in the presence of low bone turnover. Different plain X-ray methods are now available to evaluate

Detection and Prognosis

- Most vascular calcification is detected incidentally through imaging obtained for other indications. In the research setting, several methods have been developed to quantitate vascular calcification and stratify risk.
- Agatston score (often synonymous with “calcium score”) for coronary artery calcification on CT scans.
- Kauppila index for abdominal aortic calcification and the Adragao score for both lower abdominal aorta and peripheral arteries have also been shown to have a prognostic value.
- noninvasive imaging is unable to discern intimal from medial calcification; a limitation that is amplified in CKD in which there is a greater degree of coexistence of both processes, particularly in the coronary arteries, peripheral arteries, and the aorta. For this reason, there has been enthusiasm for evaluating arterial beds that are generally devoid of atherosclerosis, thereby providing more specific measures of medial calcification.

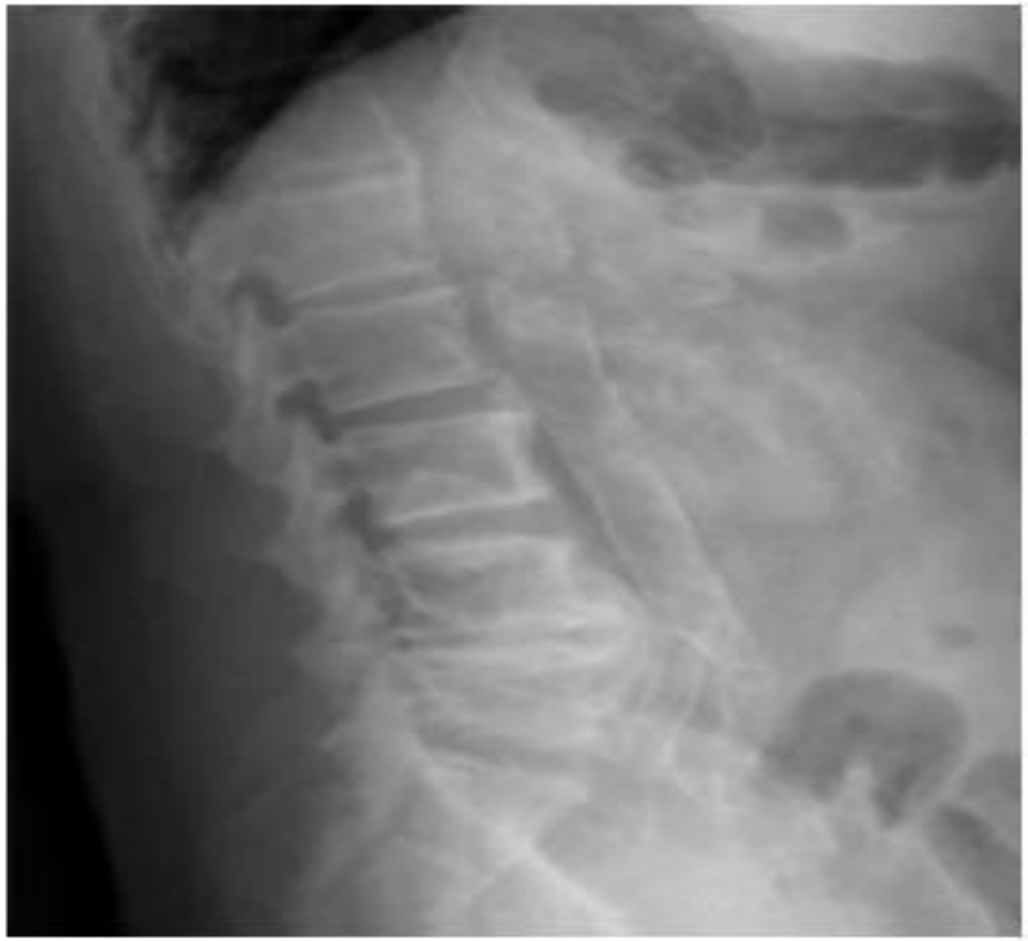
Scoring methods	Calcification area	Details
Kauppila et al	Abdominal aorta between L1-L4 in a lateral lumbar spine radiograph	The length of calcification in the anterior and posterior wall of the aorta in front of each vertebra is scored between 0-3. Total score is the sum of calcification in both walls of the aorta between L1-L4
Agatston et al[63] (CAC score by area)	Coronary arteries in a thoracic CT scan	CT images of 3 mm thickness are acquired from the carina to the diaphragm. The calcified lesion in coronary arteries is the area of at least 0.5 mm2 that has a threshold density ≥ 130 HU. The density score 1 = 130-199 HU, 2 = 200-299 HU, 3 = 300-399 HU and 4 ≥ 400 HU. The calcification area is then multiplied by the density score

Scoring methods	Calcification area	Details
Adragao et al	Iliac and femoral arteries in a pelvic radiograph and arteries of both hands in a bilateral hand radiograph	The pelvic radiograph is divided into four sections by a horizontal line over the top of both femoral heads and a vertical line over the vertebral column. The bilateral hand radiograph is divided by a vertical line which separates each hand and a horizontal line over the top of metacarpal bones. The presence of linear calcifications in each section is counted as 1
Ogawa et al	Aortic knob in a PA chest radiograph	A scale with 16 circumferences is attached to the aortic knob. The number of sections with calcification are counted



calcification score evaluation. Calcification score is the sum of the presence (1) or absence (0) of vascular calcifications in each section. Pelvis score (1+1+1+1) = 4 and hands score (1+1+1+1) = 4. Total score is 8.

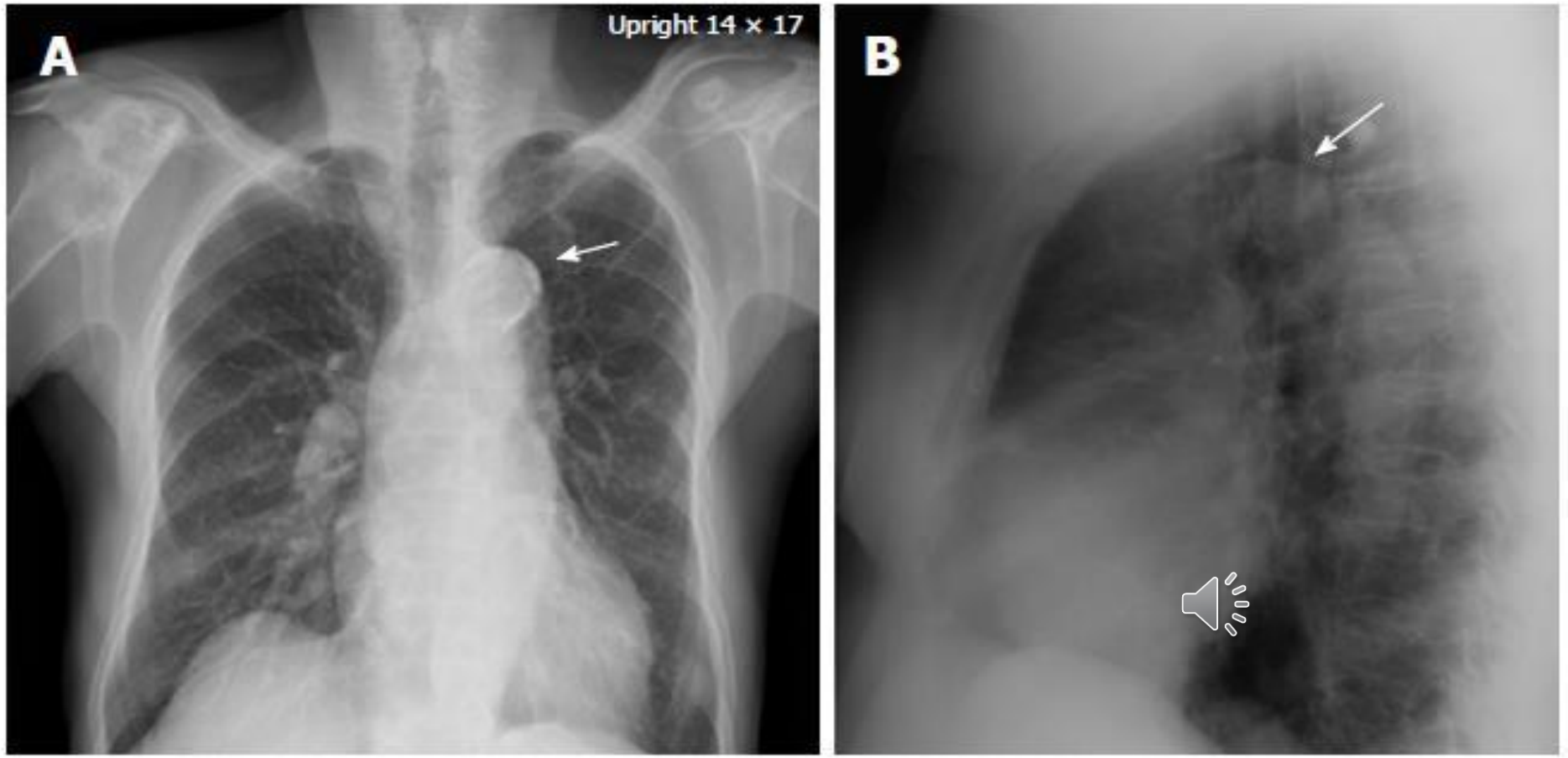
Abdominal aortic calcification seen on lateral lumbar spine radiograph



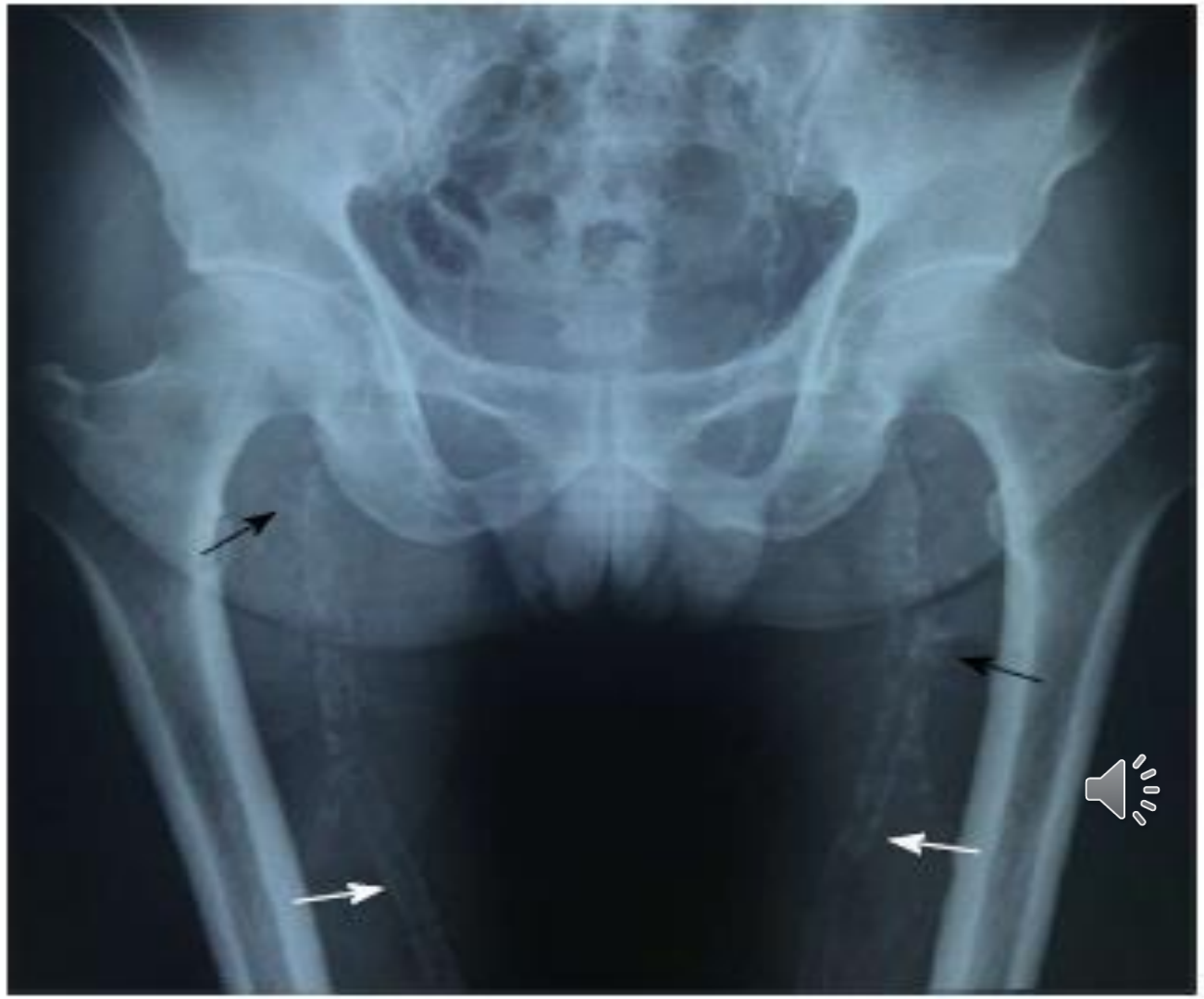
- When applying Kauppila score to hemodialysis patients, the degree of calcification was highly correlated with coronary artery calcification score (CAC score) obtained from the electron beam CT and arterial stiffness analyzed by the pulse wave velocity (PWV). In two large cohorts of maintenance hemodialysis patients, Kauppila score could predict all-cause and CV mortality and non-fatal CV events.
- Due to such evidence, the 2009 Kidney Disease improving Global Outcomes (KDIGO) guidelines recommended lateral lumbar spine X-ray for the assessment of VC burden in dialysis patients. Few studies have also reported the use of lateral abdominal X-ray in non-dialysis CKD population. The calcification score obtained from lateral lumbar spine radiograph was highly correlated to the score obtained by . As kidney function declined, the degree of calcification increased and Kauppila score ≥ 4 predicted future CV events.

Disthabanchong S, Boongird S. Role of different imaging modalities of vascular calcification in predicting outcomes in chronic kidney disease. *World J Nephrol* 2017; 6(3): 100-110 [PMID: 28540199 DOI: 10.5527/wjn.v6.i3.100]

Aortic arch calcification (arrow) seen on postero-anterior chest radiograph (A) and lateral chest radiograph (B).



Plaque-like intimal calcification (black arrow) and uniform linear railroad track-like medial calcification (white arrow).



Medial calcification in small arteries in hands (A) and foot (B)

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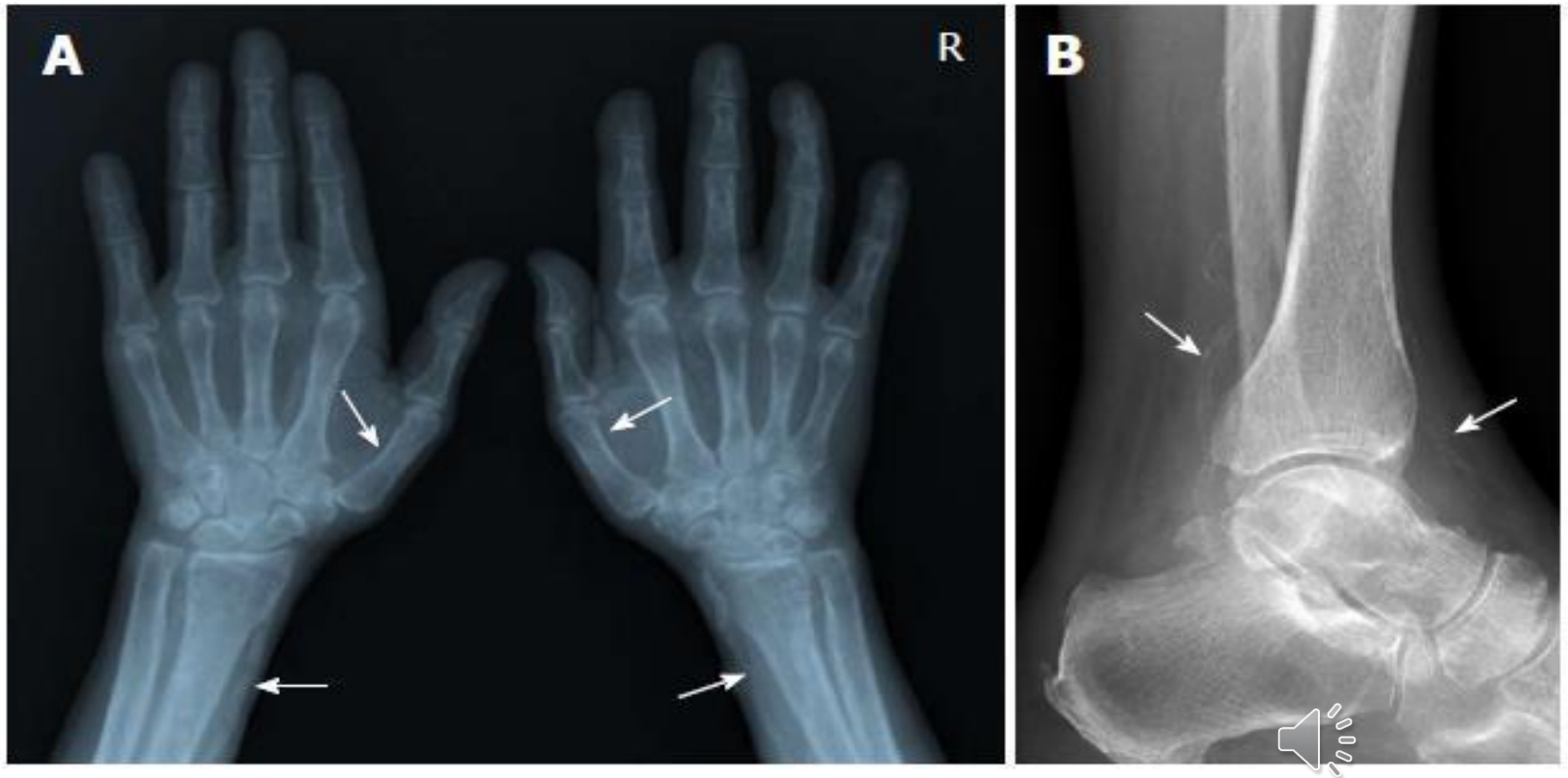
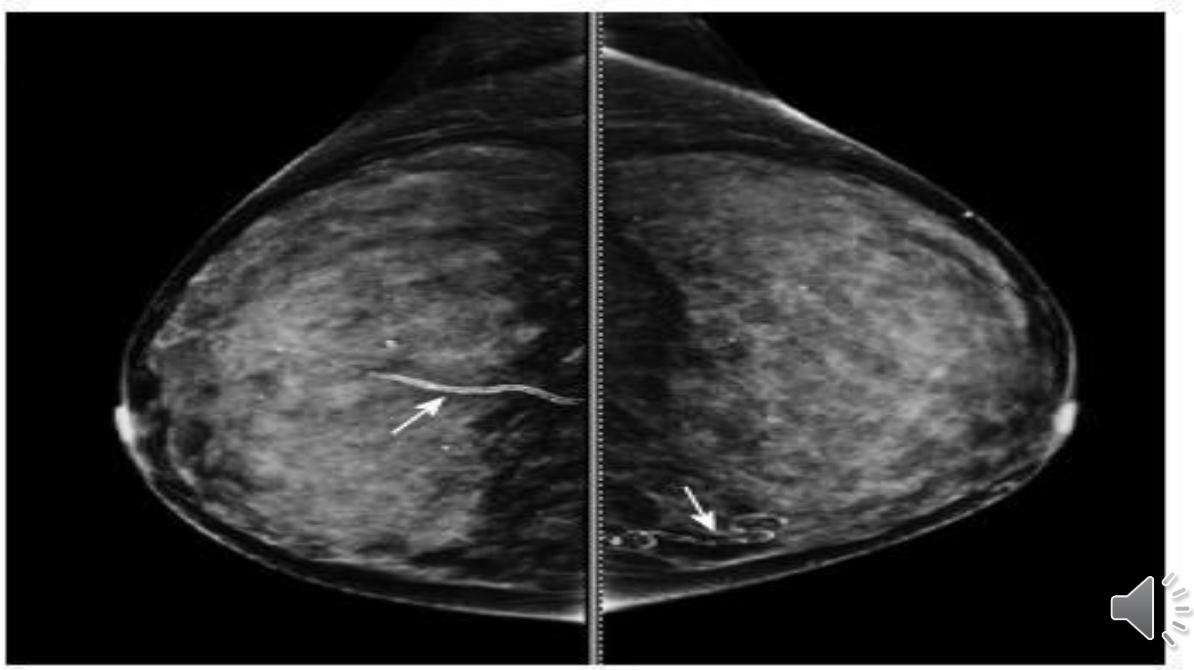


Breast arterial calcification with the typical linear tram-track medial-type calcification (arrows)

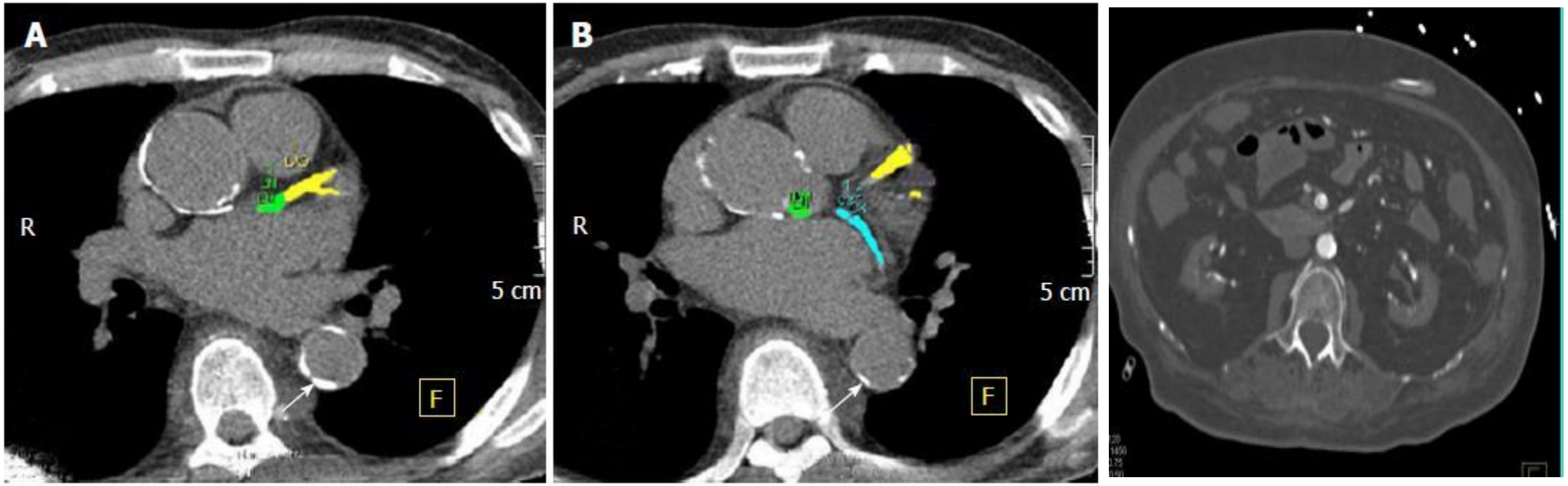


ULTRASONOGRAPHY

- Ultrasonography has the benefit of no radiation exposure and offers a unique mean to evaluate arterial wall thickness and lumen size. The resolution of ultrasound depends on the depth of field, therefore, ultrasound is suitable for imaging of superficial arteries such as carotid, femoral and peripheral arteries. The quantification is largely subjective and operator dependent. Ultrasound assessment of carotid arterial atherosclerotic disease has become the first choice for screening of carotid artery stenosis. Carotid intima-media thickness (IMT) is also an early atherosclerotic risk marker, therefore, most studies focus on carotid IMT rather than calcification, which is a late event.
- In elderly subjects, calcified carotid plaques predicted mortality and CV outcomes independent of traditional CV risk factors[. In ESRD patients, calcified plaques in carotid and femoral arteries were present in 71% compared to 21% in age-matched control. Patients with calcification were significantly older, predominantly male, and had a higher prevalence of previous CV disease. The presence of calcification was associated with increased carotid IMT and higher number of plaques[51]. Another study in hemodialysis patients found the association between carotid calcification with age, duration of dialysis, calcium x phosphate product and prescribed dose of calcium-based phosphate binder Similarly, in peritoneal dialysis patients, the prevalence of carotid calcification was high and was associated with diabetes mellitus, increased left ventricular mass index, and lower survival rate[55]. The calcification score of combined sites evaluated by both ultrasonography and plain X-rays of carotid artery, abdominal aorta, iliofemoral axis, and legs predicted all-cause and CV mortality

  Disthabanchong S, Boongird S. Role of different imaging modalities of vascular calcification in predicting outcomes in chronic kidney disease. *World J Nephrol* 2017; 6(3): 100-110 [PMID: 28540199 DOI: 10.5527/wjn.v6.i3.100]

Coronary artery calcification (marked with colors) and descending thoracic aortic calcification (arrows) seen on non-contrast multislice computed tomography.



CONCLUSION

- In summary, VC can be detected by several imaging techniques. Plain radiographs are simple and readily available and the presence of VC can be examined in a single X-ray film. Plain radiographs also allow differentiation between intimal and medial calcification, which comes in useful in CKD population. Mammography is especially advantageous among women because the severity of medial calcification can be assessed in images acquired during the routine screening mammogram. Ultrasonography offers a mean to evaluate arterial wall thickness and lumen size as well as calcification with the benefit of no radiation exposure. CT scan, the gold standard, is the most sensitive technique that offers an accurate and an objective analysis of the severity of VC. Plain radiographs are appropriate in situations where risk evaluation is the main focus, whereas CT scan is indispensable for accurate analysis of progression or changes after intervention.

Disthabanchong S, Boongird S. Role of different imaging modalities of vascular calcification in predicting outcomes in chronic kidney disease.

- *World J Nephrol* 2017; 6(3): 100-110 [PMID: 28540199 DOI: 10.5527/wjn.v6.i3.100]

Screening

- Proponents of routine screening for vascular calcification among patients with CKD suggest there is significant incremental value in identifying a high-risk CV cohort. Conversely, others have argued that all patients with CKD should be considered at the highest CV risk and, in the absence of specific vascular calcification therapies, screening for vascular calcification does not influence management. Routine vascular calcification screening using either lateral pelvic x-ray or CT imaging received a weak (level 2C) recommendation in the 2017 Kidney Disease Improving Global Outcomes guidelines, reflecting the paucity of outcomes-driven data . The wording used in the 2017 updated guidelines was nearly identical to that used in the 2009 Guidelines, highlighting the lack of progress in the search for specific therapies proven to reverse, arrest, or attenuate vascular calcification

Vascular Calcification Slows But Does Not Regress After Kidney Transplantation

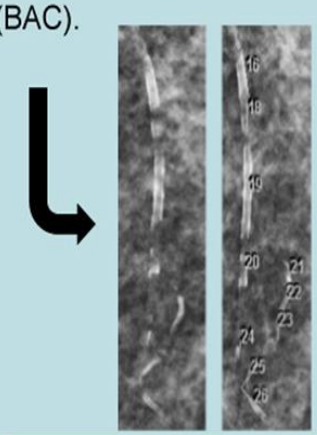
STUDY POPULATION

- 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.

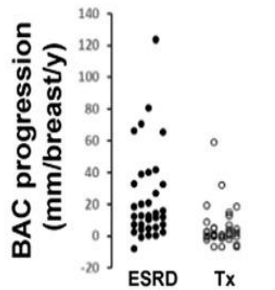
Tx=treatment

METHODS

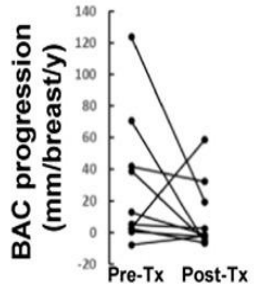
- Lengths of calcified arteries summed to derive total breast arterial calcification (BAC).



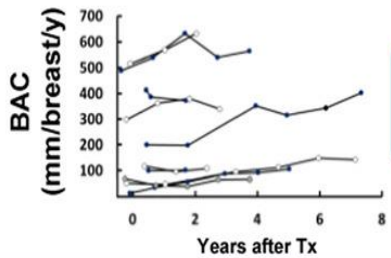
FINDINGS



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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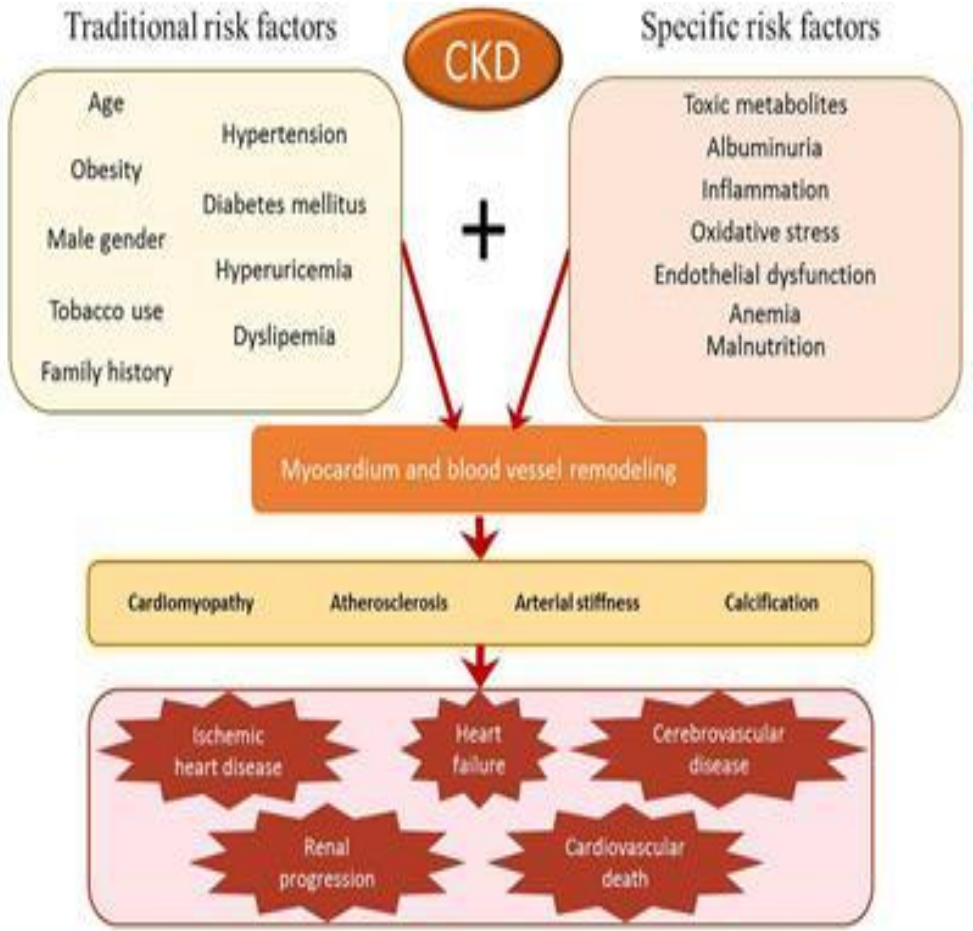
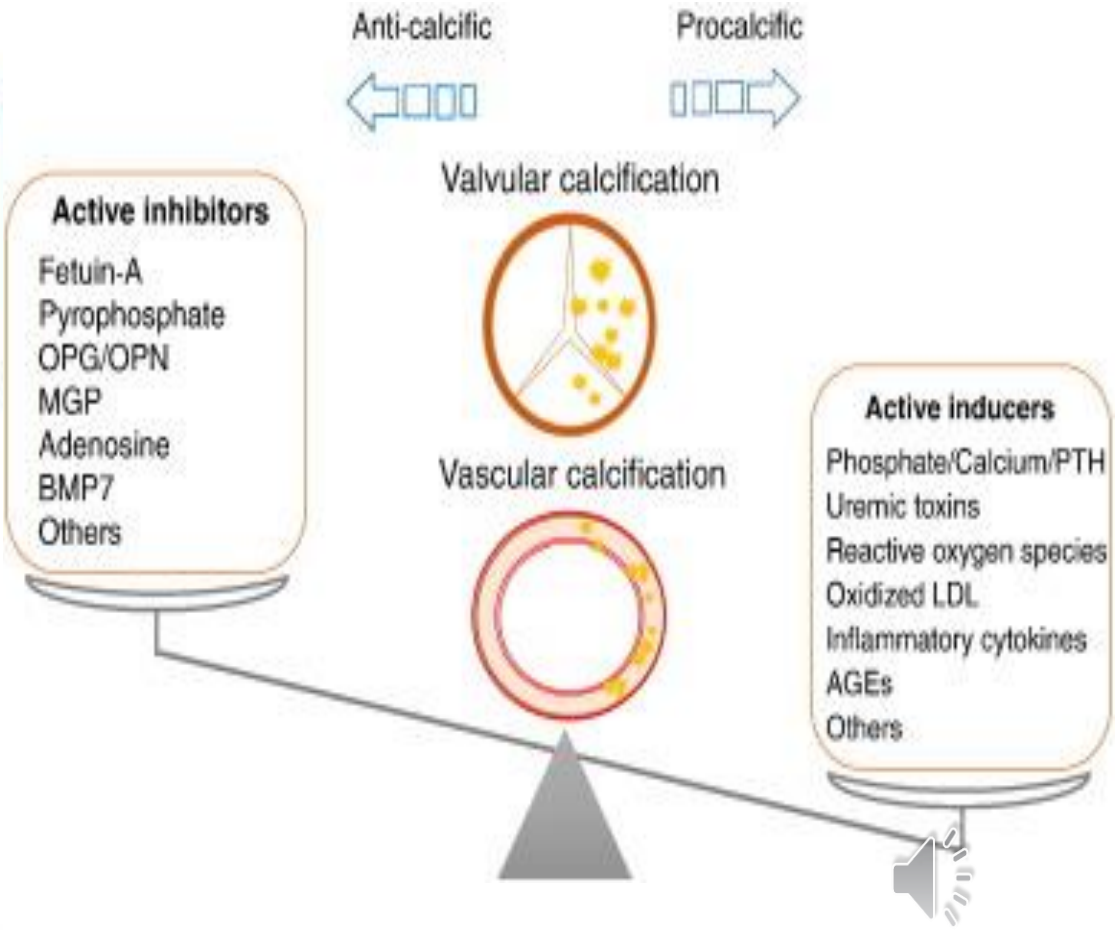
CONCLUSION


Traditional risk factors
CKD
Specific risk factors
Age
Hypertension
Obesity
Diabetes mellitus
Male gender
Hyperuricemia
Tobacco use
Dyslipemia
Family history
+
Toxic metabolites
Albuminuria
Inflammation
Oxidative stress
Endothelial dysfunction
Anemia
Malnutrition
Myocardium and blood vessel remodeling
Cardiomyopathy
Atherosclerosis
Arterial stiffness
Calcification
Ischemic heart disease
Heart failure
Cerebrovascular disease
Renal progression
Cardiovascular death


Anti-calcific
Procalcific
Active inhibitors
Fetuin-A
Pyrophosphate
OPG/OPN
MGP
Adenosine
BMP7
Others
Valvular calcification
Vascular calcification
Active inducers
Phosphate/Calcium/PTH
Uremic toxins
Reactive oxygen species
Oxidized LDL
Inflammatory cytokines
AGEs
Others