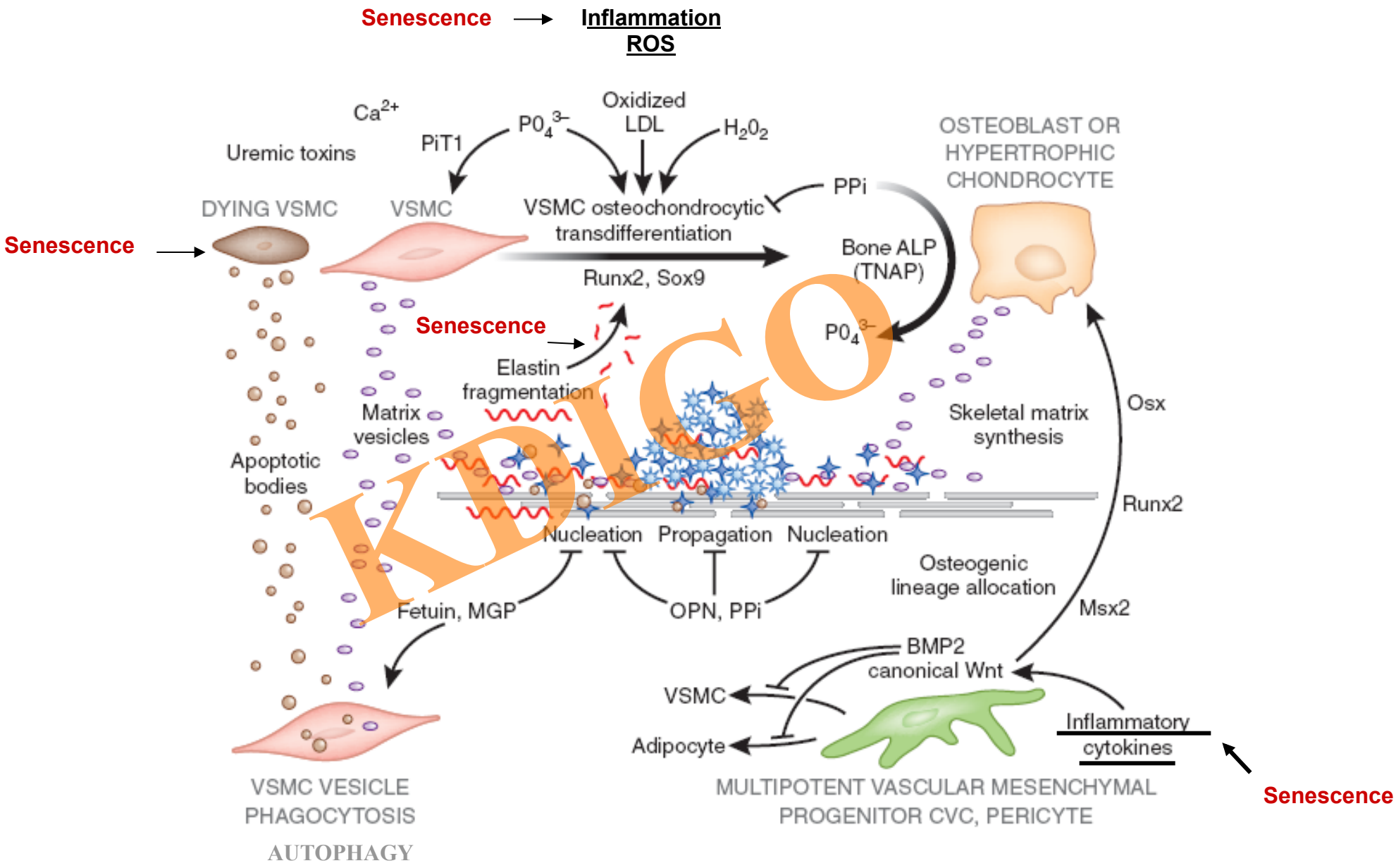
Arterial Calcifications and functions

Dr Gérard London

Manhes Hospital and

INSERM U970 - Paris, France

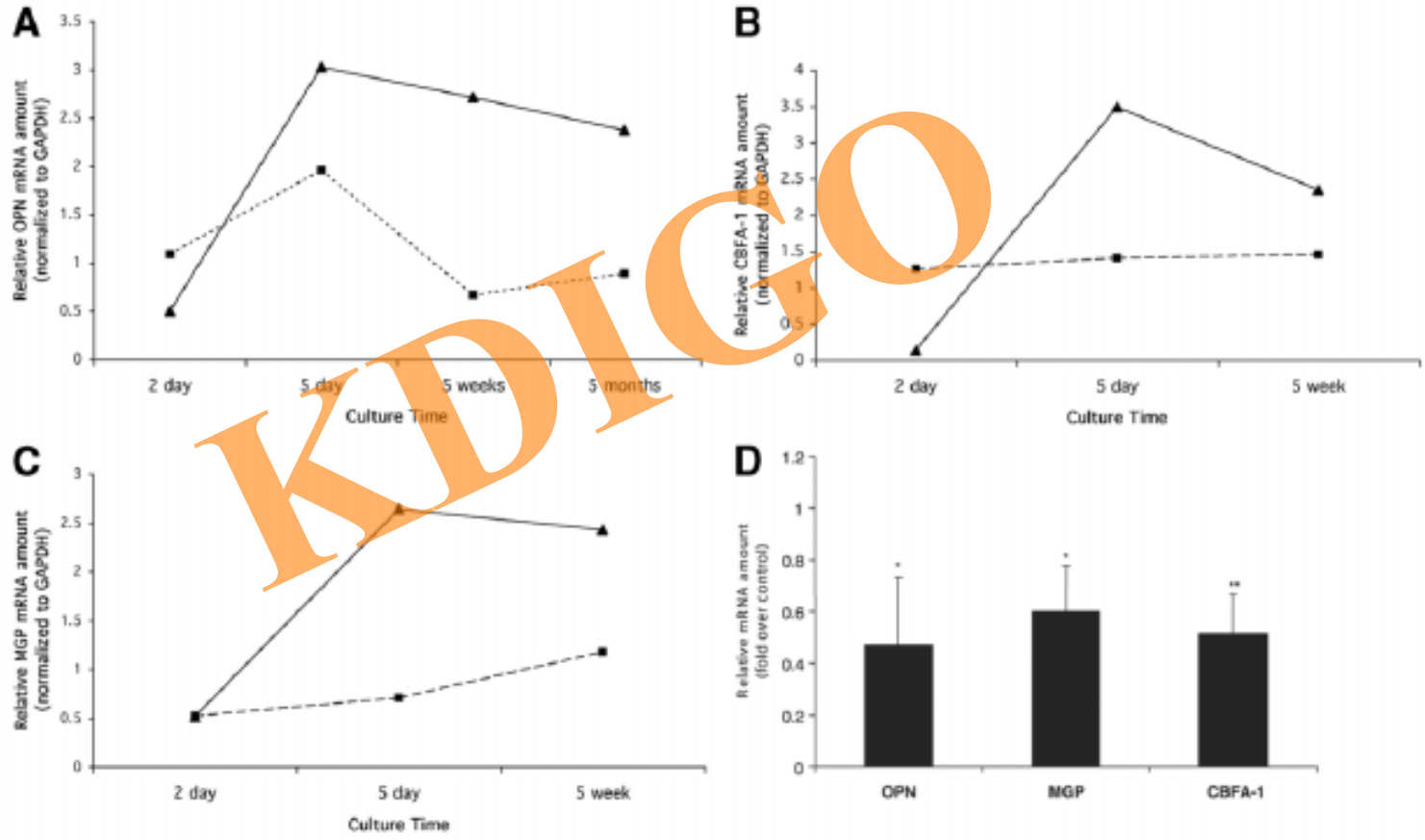


Modified from JASN 2010

The FASEB Journal express article 10.1096/fj.02-0459fje. Published online January 2, 2003.

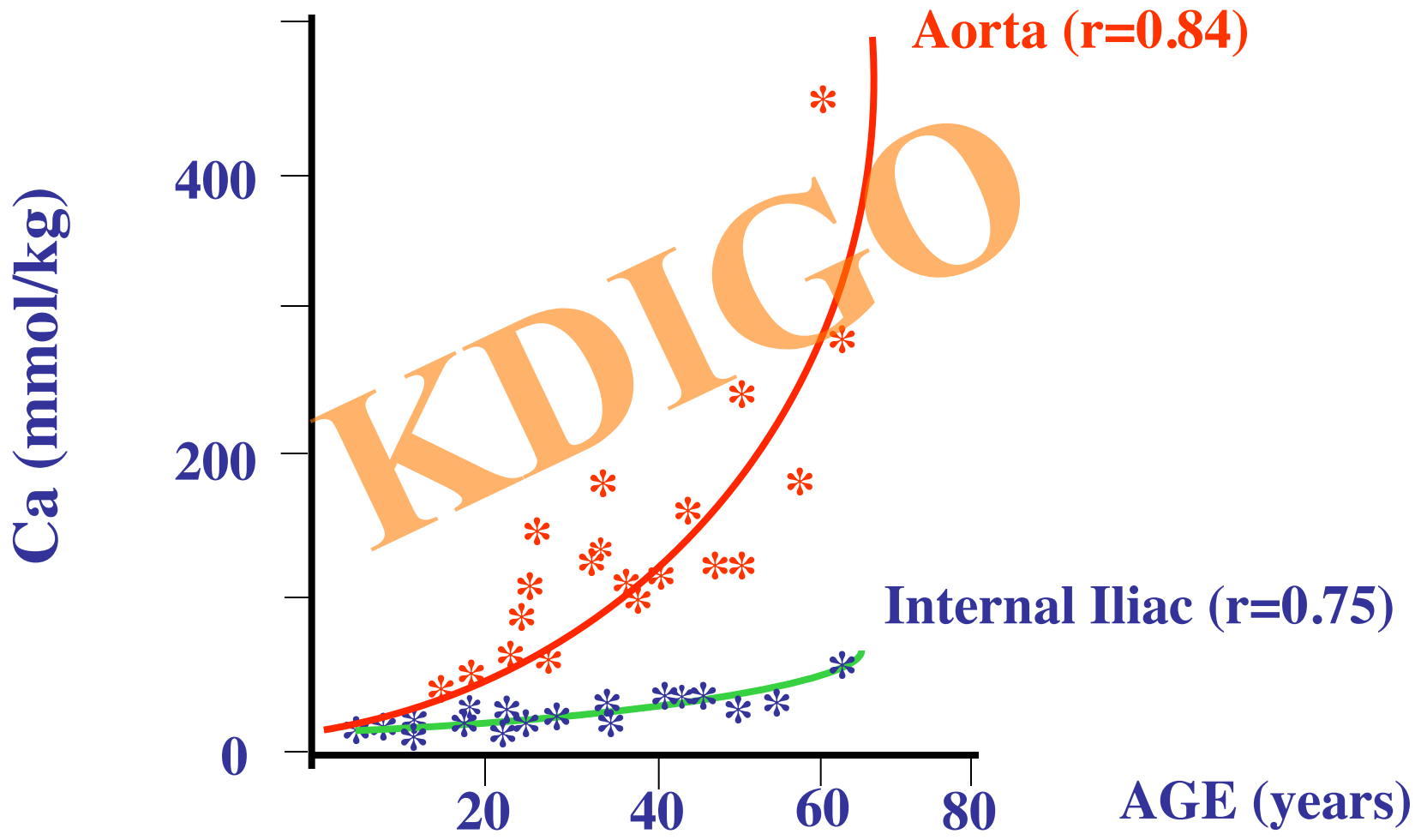
Cyclic strain inhibits switching of smooth muscle cells to an osteoblast-like phenotype

Janeta Nikolovski,* Byung-Soo Kim,[§] and David J. Mooney*[,†,‡]



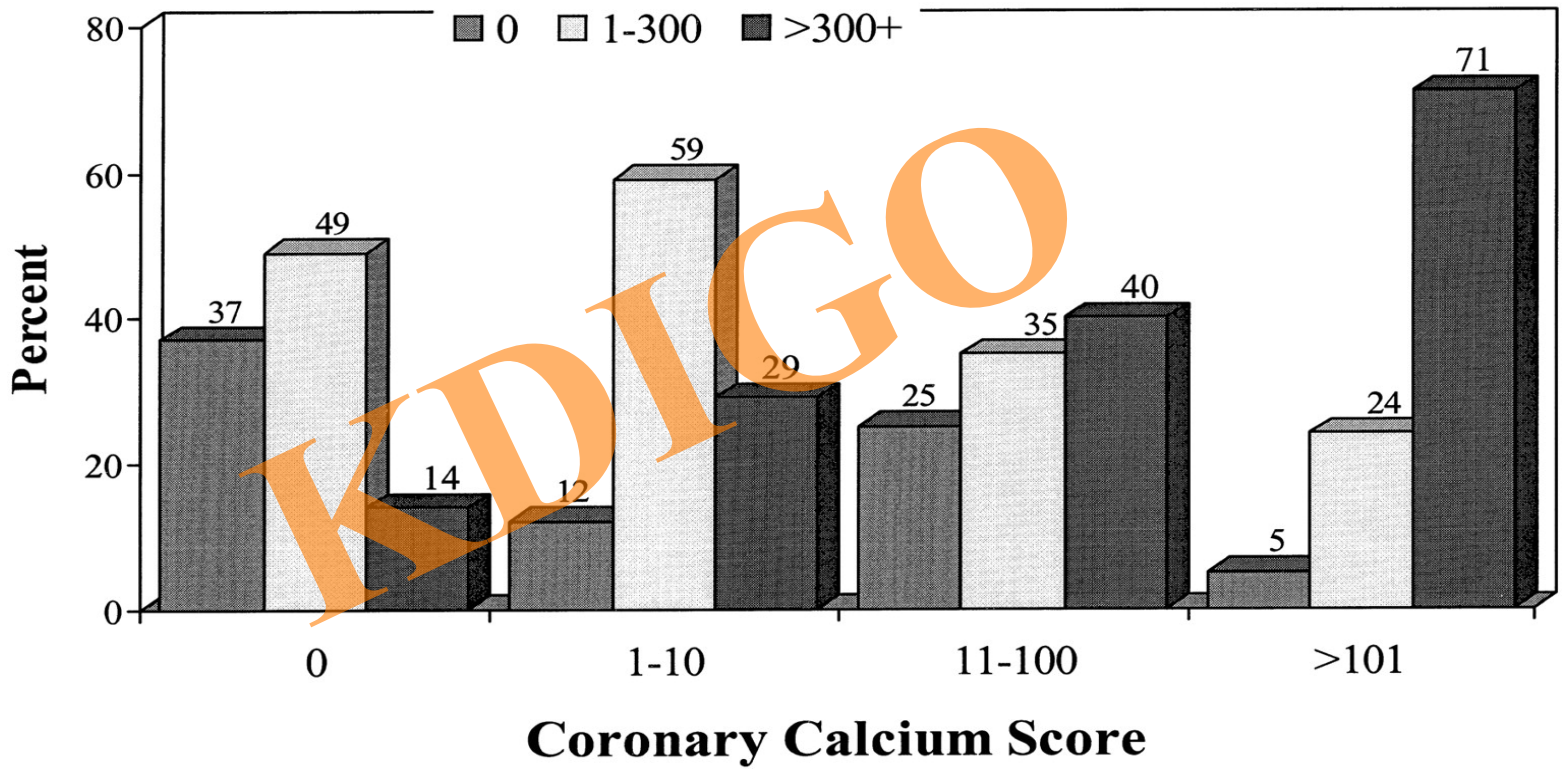
Chronic cyclic strain down-regulates bone-specific genes in smooth muscle tissues.

Correlation between age and arterial calcium (Ca) concentration in the aorta and internal iliac artery in nonuremic control subjects

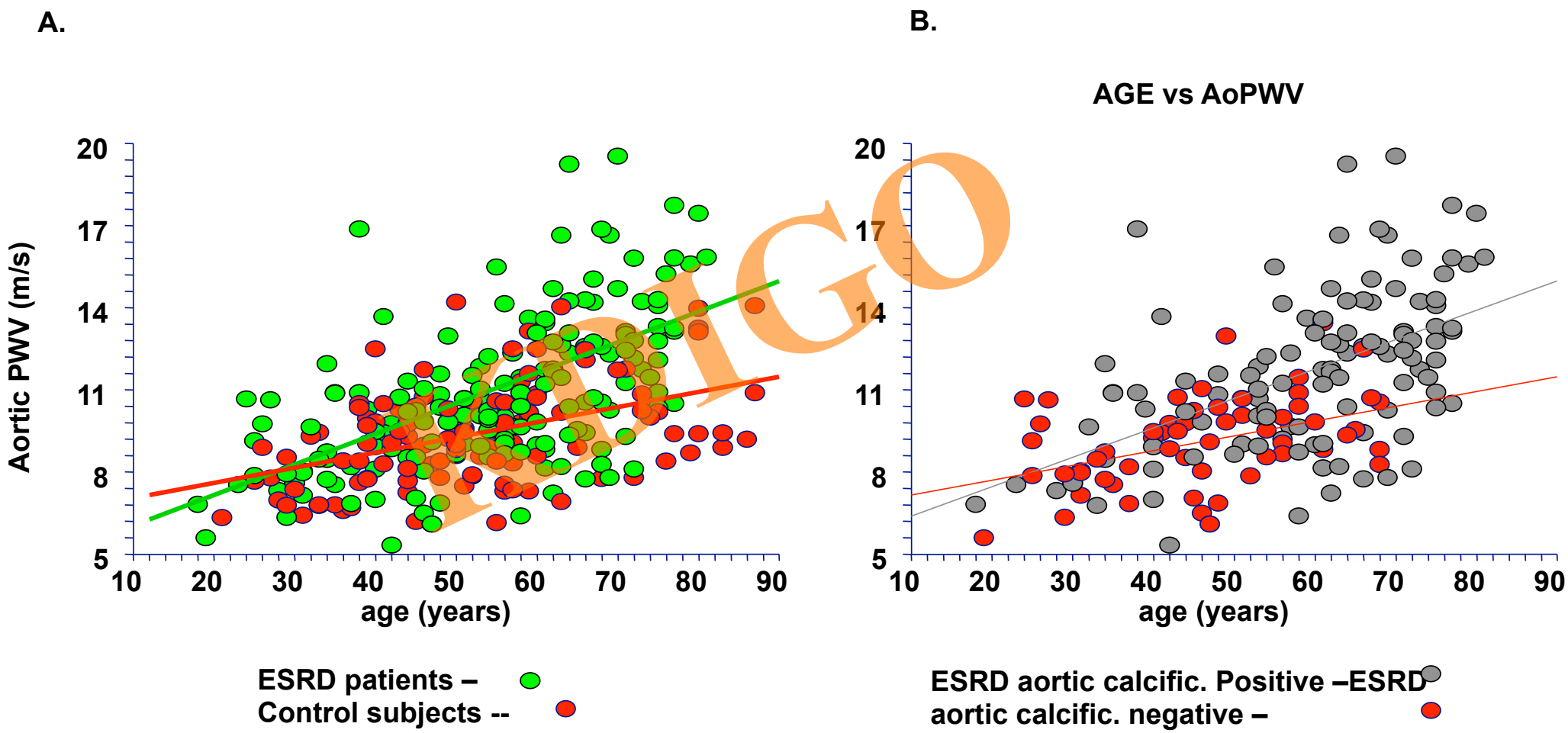


Ibels et al. Am J Med 1979

Comparison of aortic total calcium score with coronary total calcium score

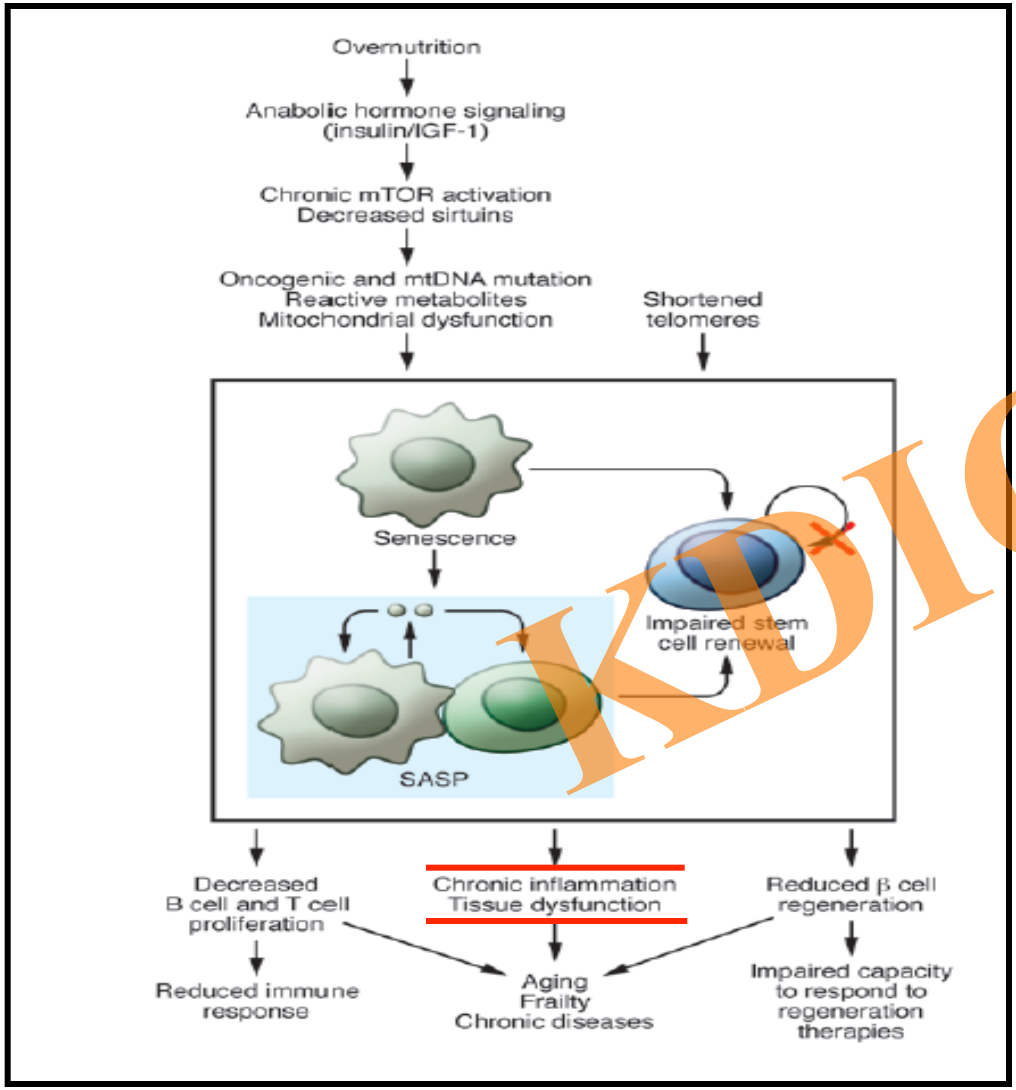


Kuller, L. H. et al. Arterioscler Thromb Vasc Biol 1999;19:2189-2198



London GM et al Blood purification 2013

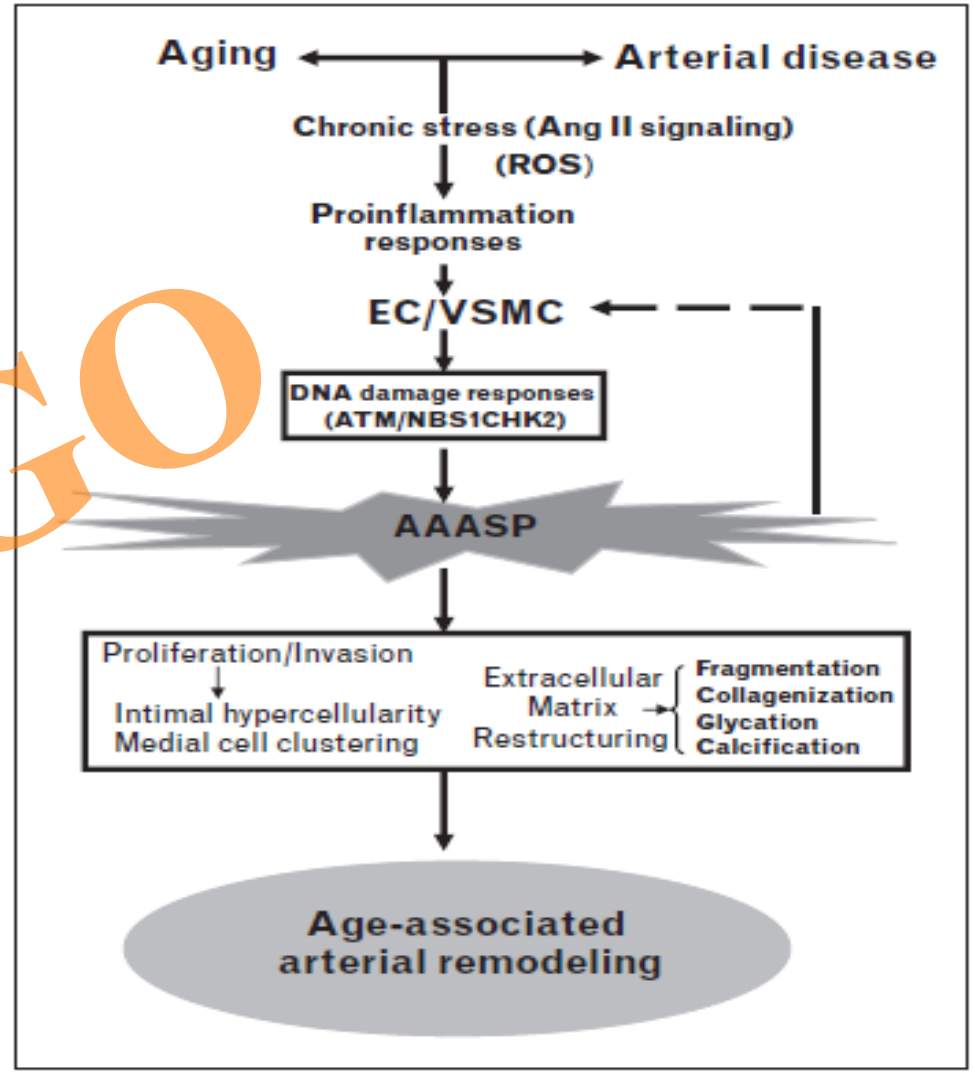
Molecular pathways implicated in aging and Senescence-associated secretory phenotype



SASP - senescence associated secretory phenotype

Newgard CB and Sharpless NE JCI 2013;123

Molecular and cellular mechanisms for arterial remodelling in aging



AAASP – age-associated arterial secretory phenotype

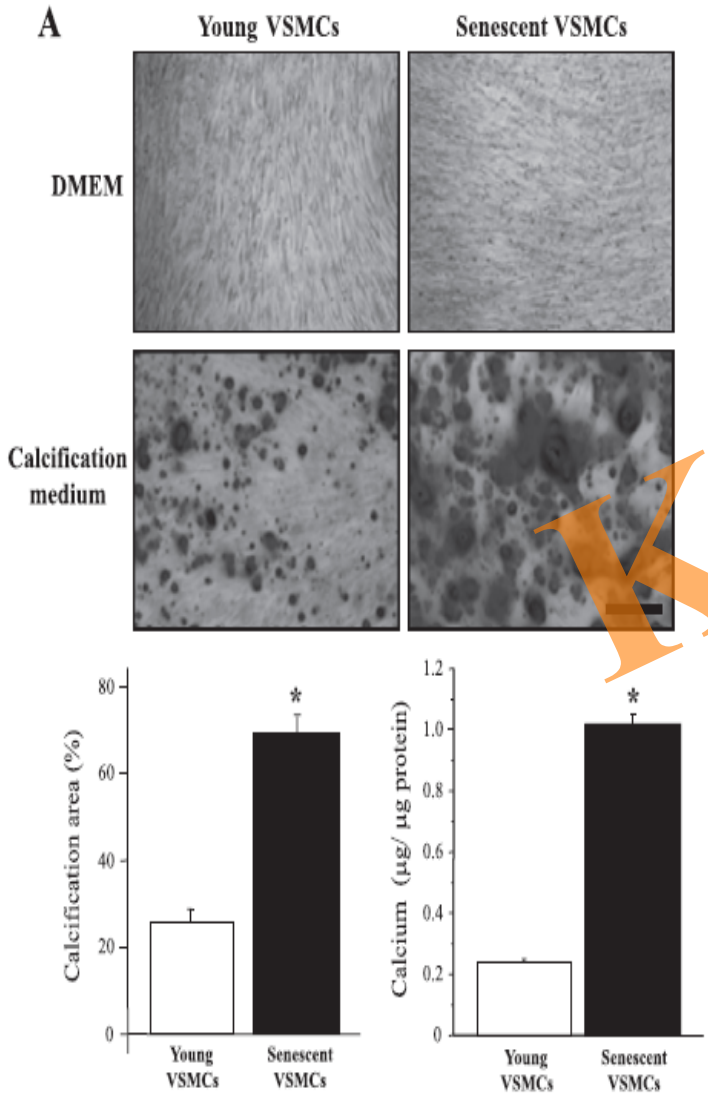
Wang M. et al. Current Opin Nephrol Hypertens 2010

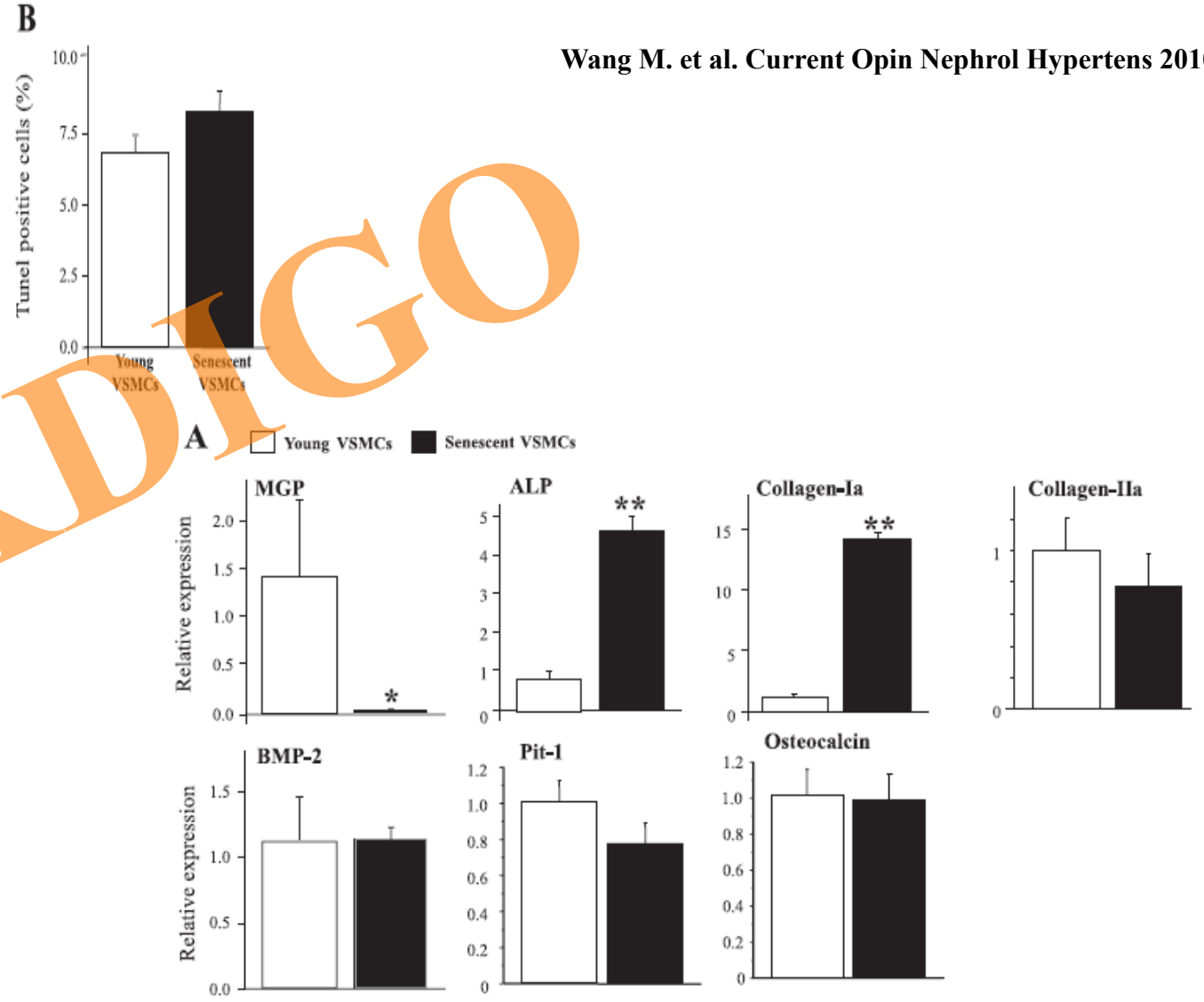
Replicative senescence of vascular smooth muscle cells enhances the calcification through initiating the osteoblastic transition

Ritsuko Nakano-Kurimoto, Koji Ikeda, Maki Uraoka, Yusuke Nakagawa, Kotaro Yutaka, Masahiro Koide, Tomosaburo Takahashi, Satoaki Matoba, Hiroyuki Yamada, Mitsuhiko Okigaki and Hiroaki Matsubara

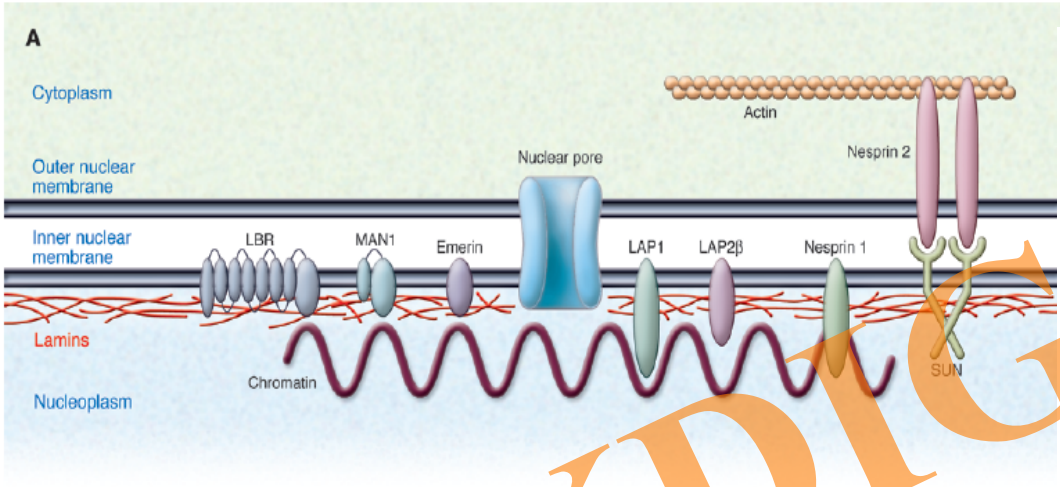
Am J Physiol Heart Circ Physiol 297:H1673-H1684, 2009. First published 11 September 2009; doi:10.1152/ajpheart.00455.2009

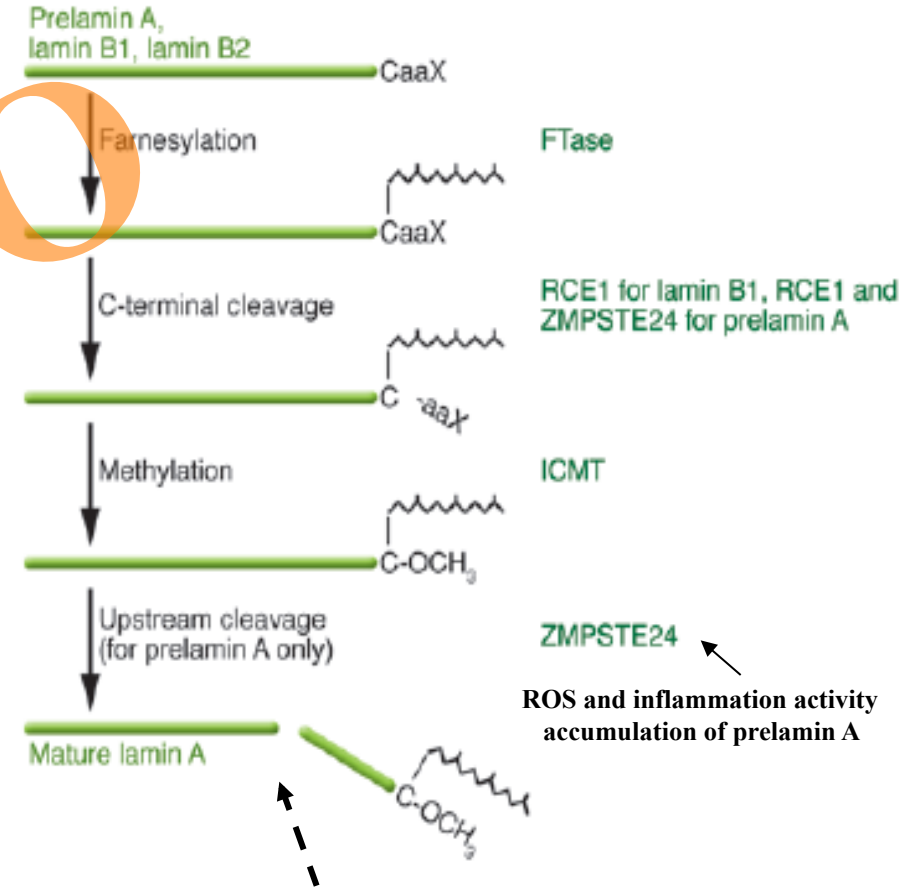
Wang M. et al. Current Opin Nephrol Hypertens 2010





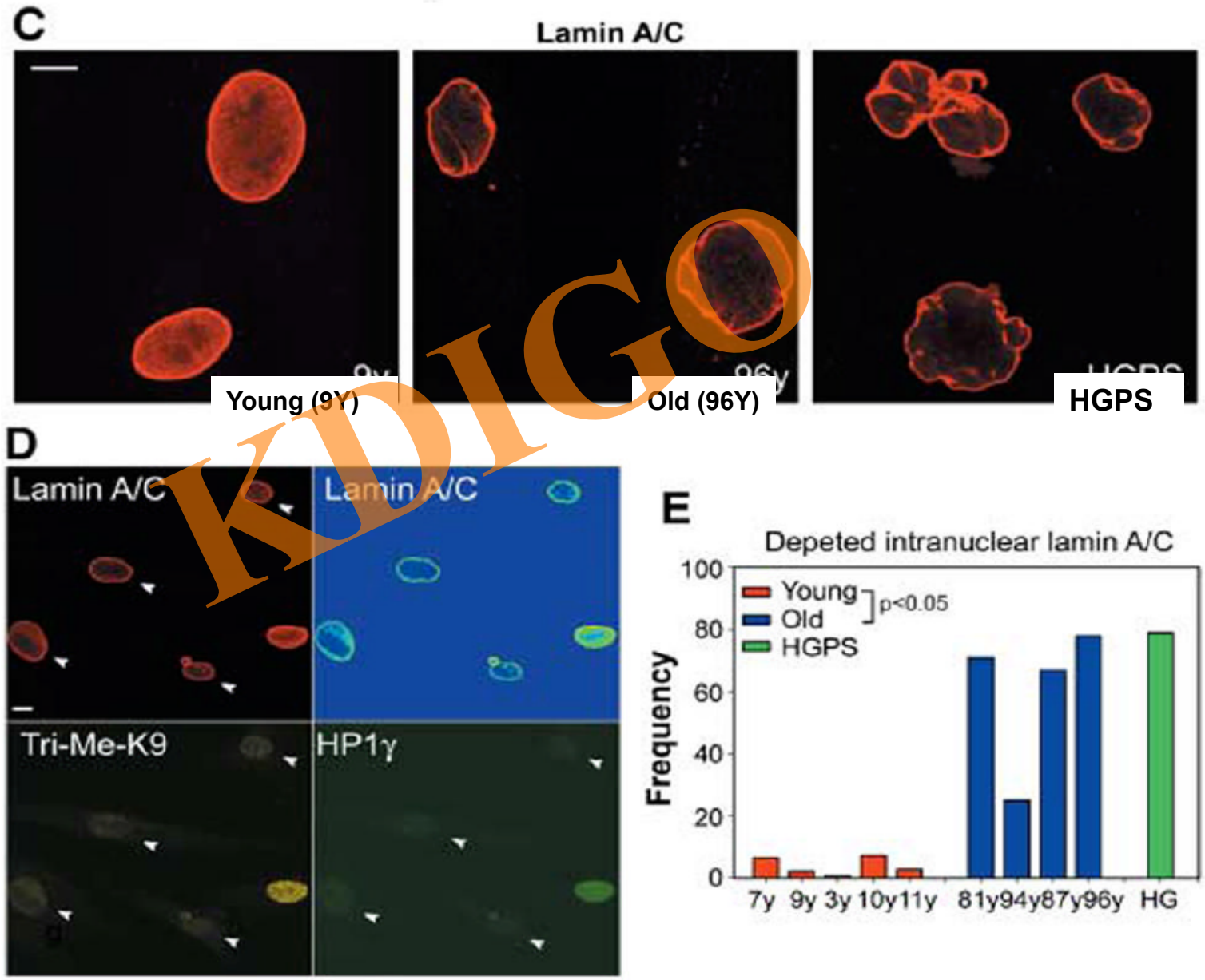
• Nuclear lamina and posttranslational processing





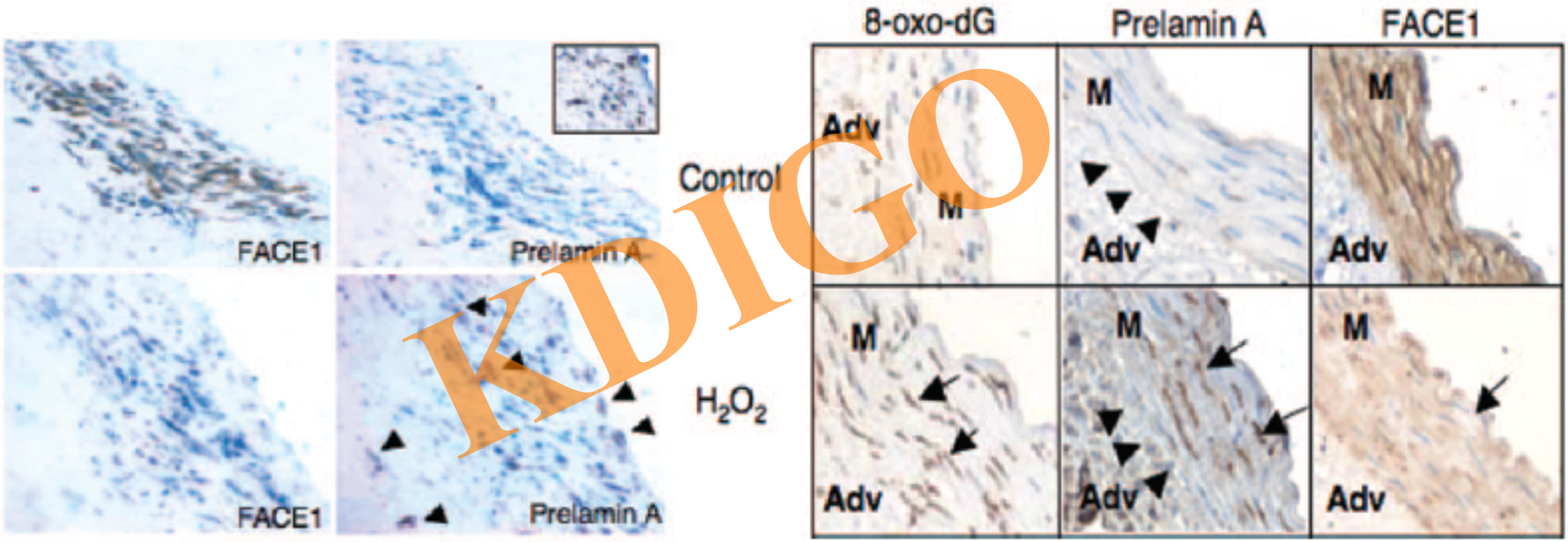
Cleavage impossible in HG for deletion of 50 aminoacids
In the clivage site with accumulation of progerin and decreased lamin A

Lamin A/C in fibroblasts from Young, Old and HGPS patients



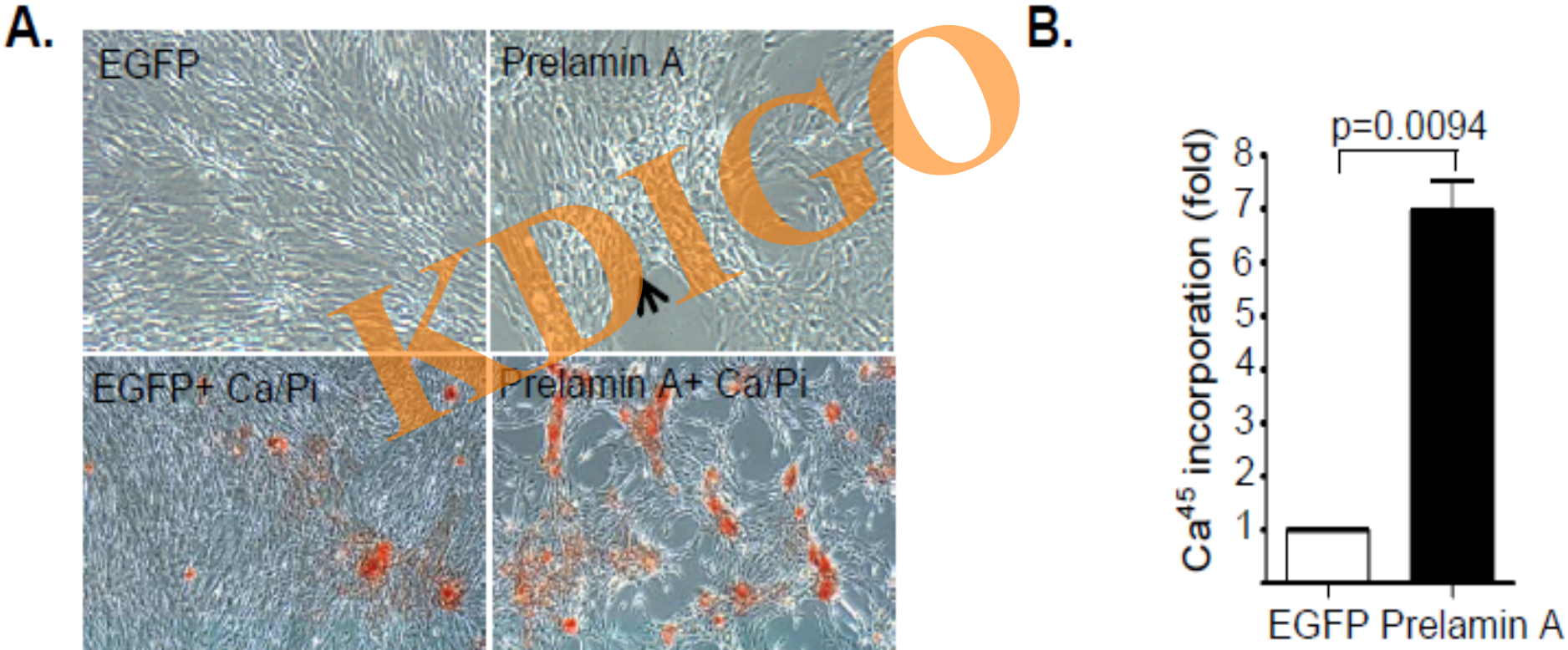
Scafidi Science 2006

Oxidative stress reduces ZMPSTE24/FACE1 activity and accumulates Prelamin A



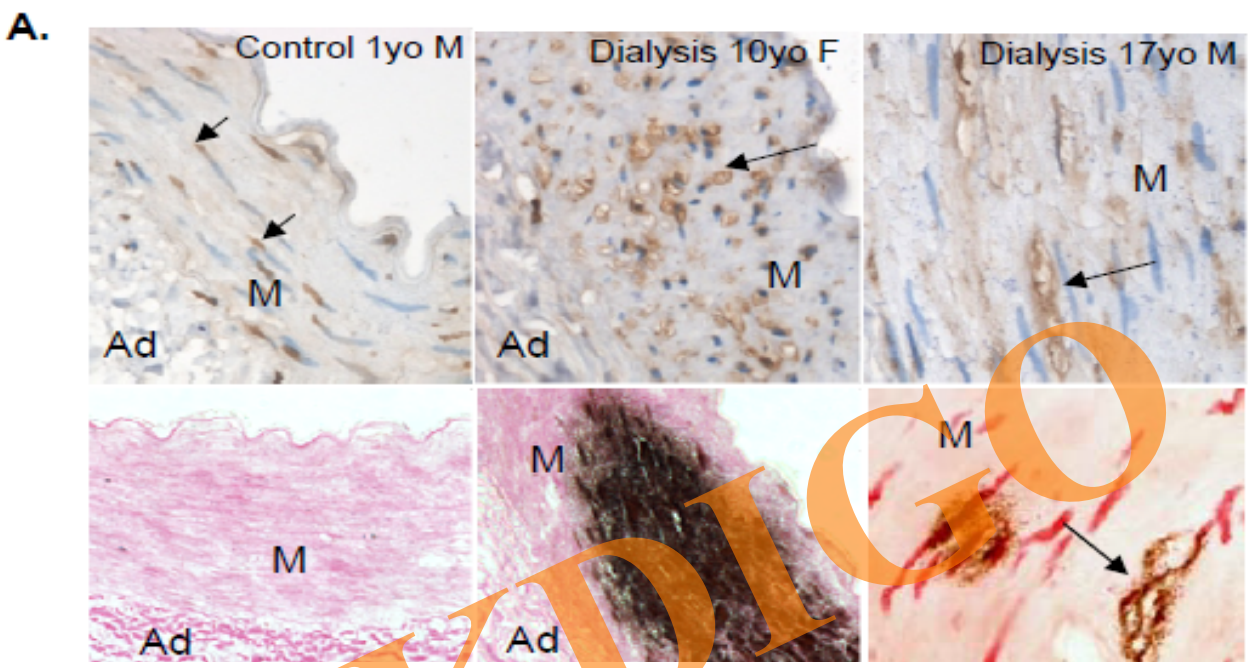
Ragnauth C. et al Circulation 2010;121:2200-10

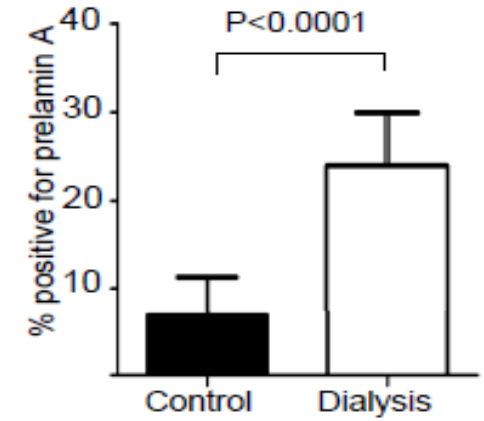
Prelamin A accumulation promotes VSMC calcification

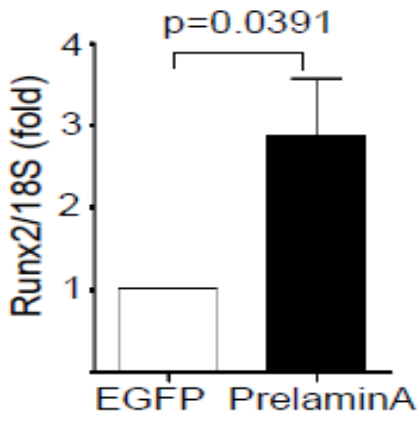


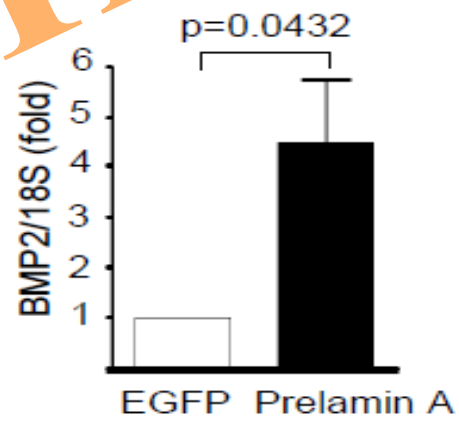
Liu Y et al Circ.Res 2013

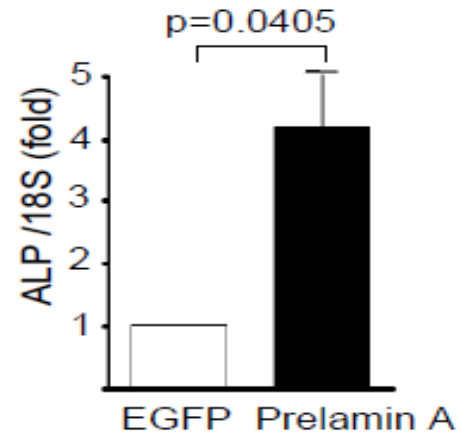
Prelamin A accumulated in calcified VSMCs both in vivo and in vitro.

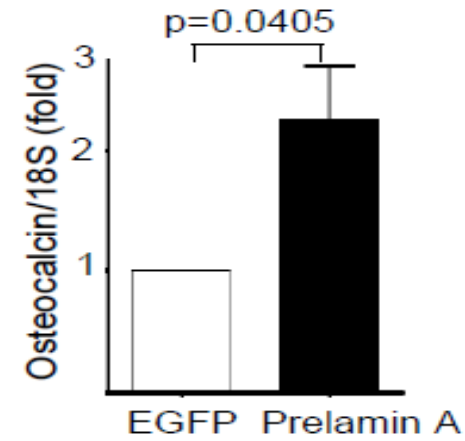






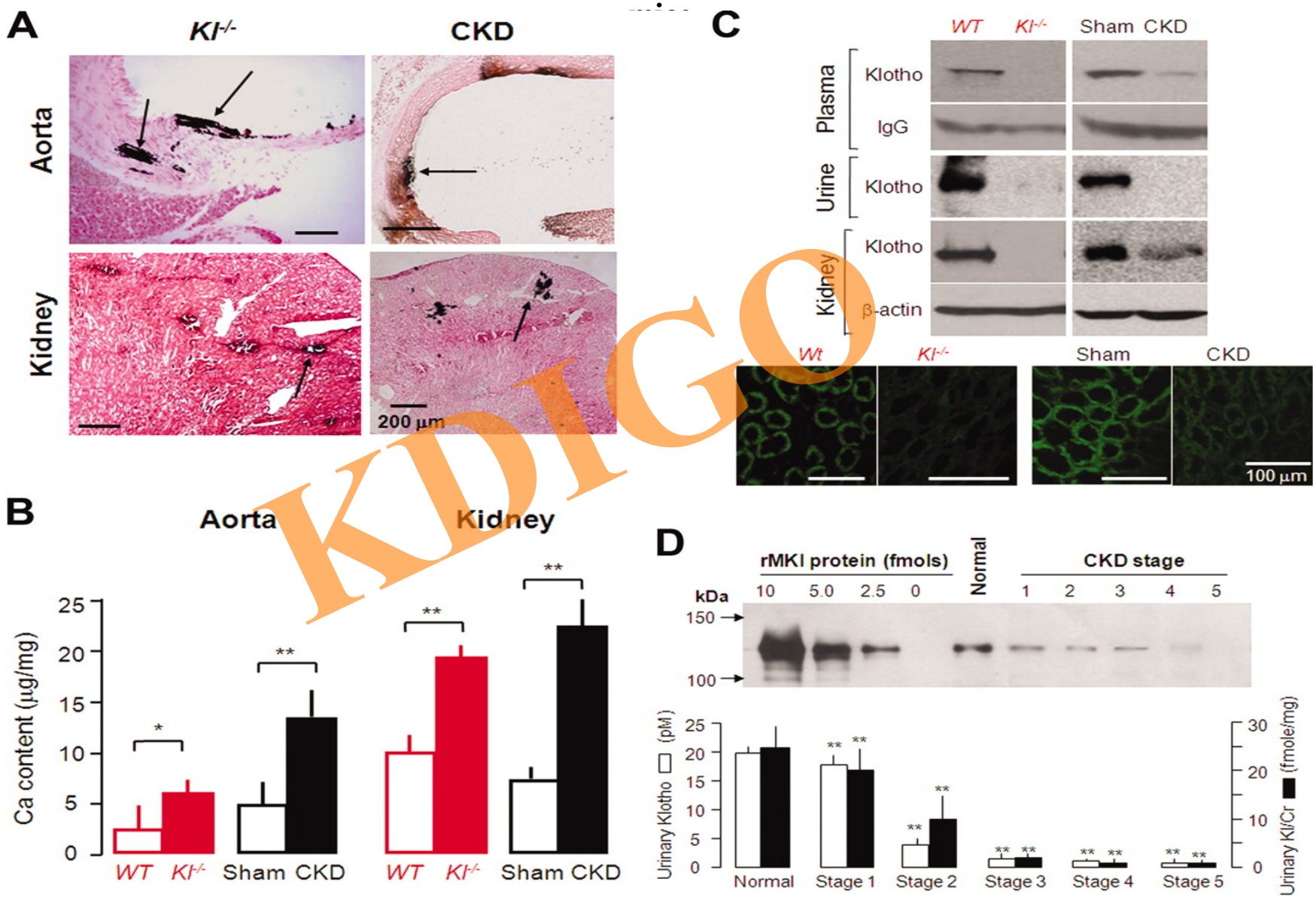




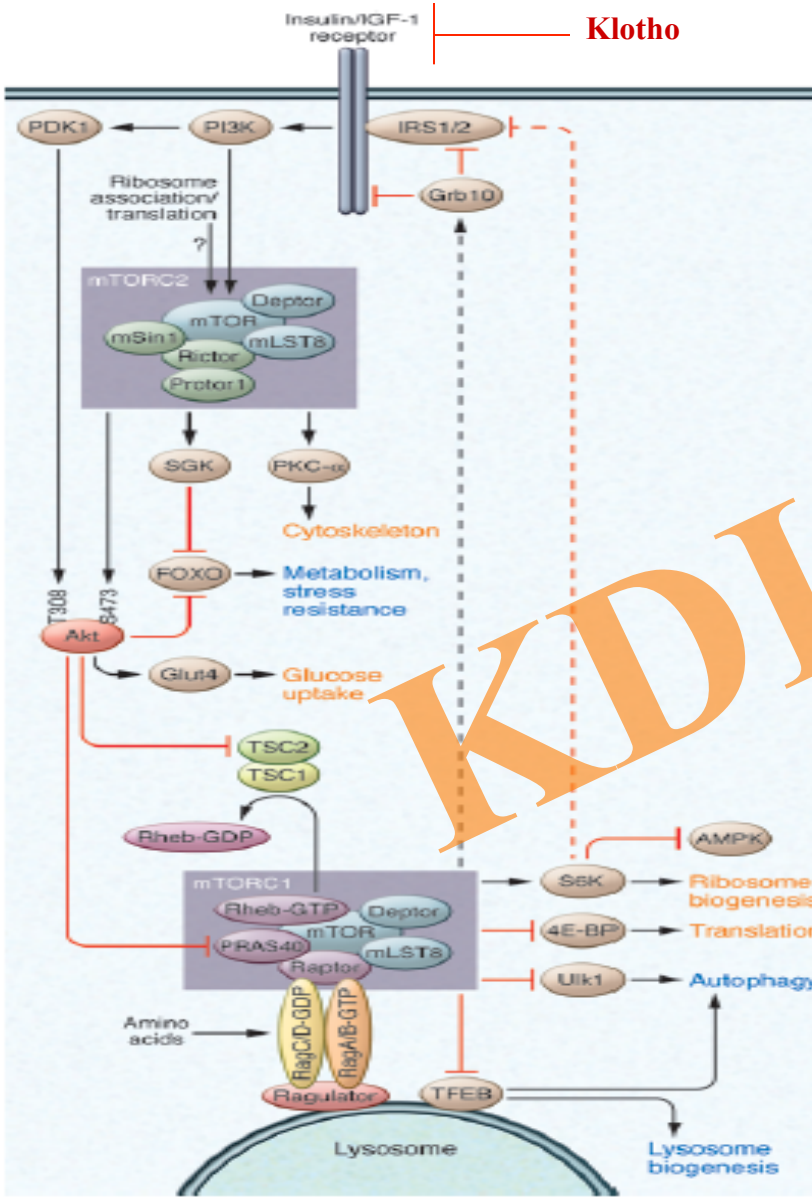


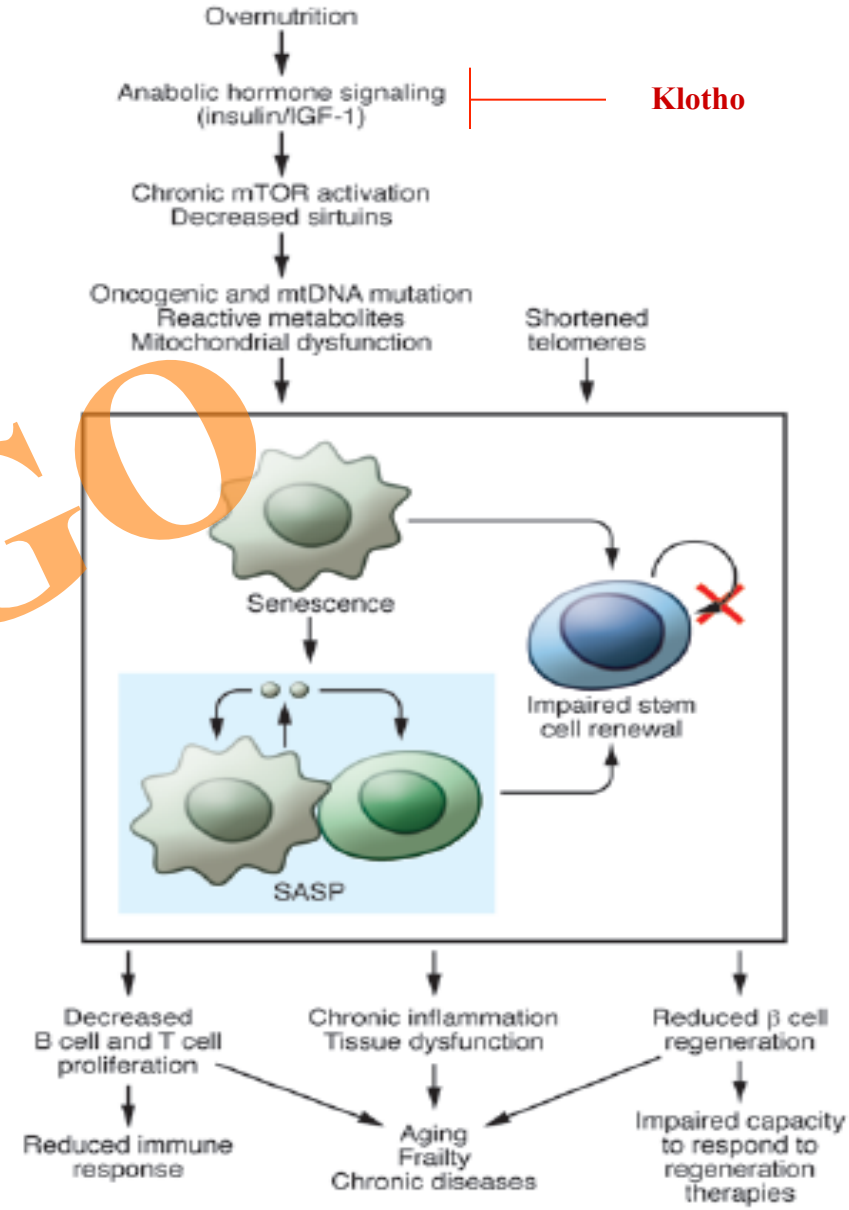
Liu Y et al Circ.Res 2013

Klotho levels are reduced in CKD mice and CKD patients, and soft tissue calcification is observed in CKD

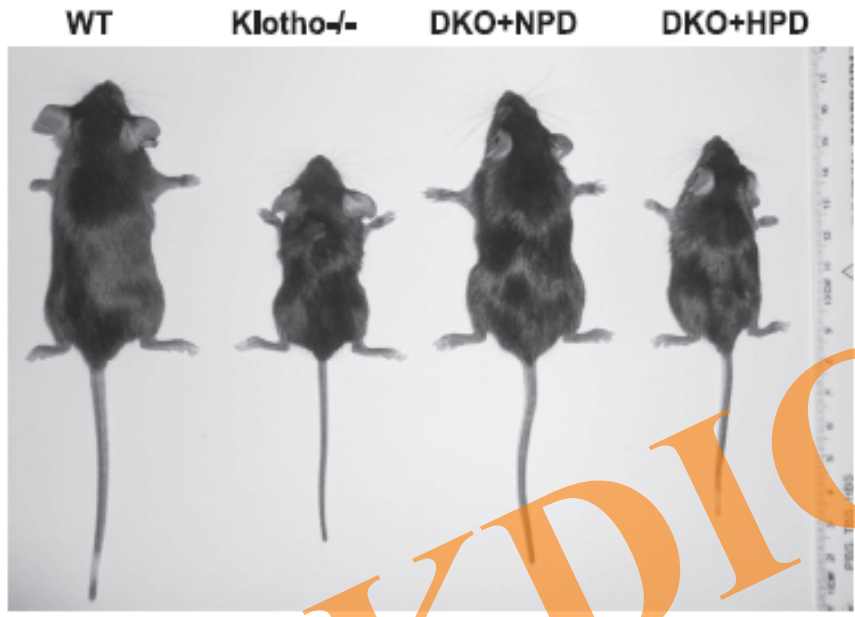


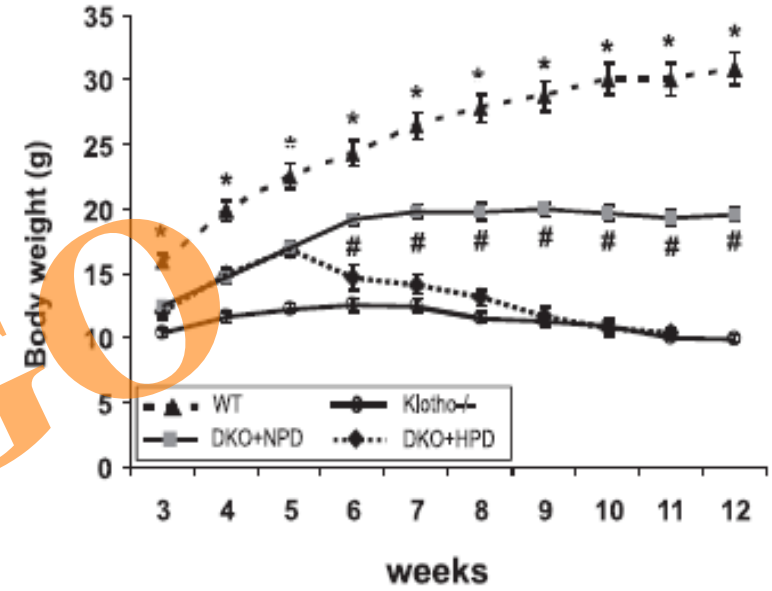
Hu M C et al. JASN 2011;22:124-136

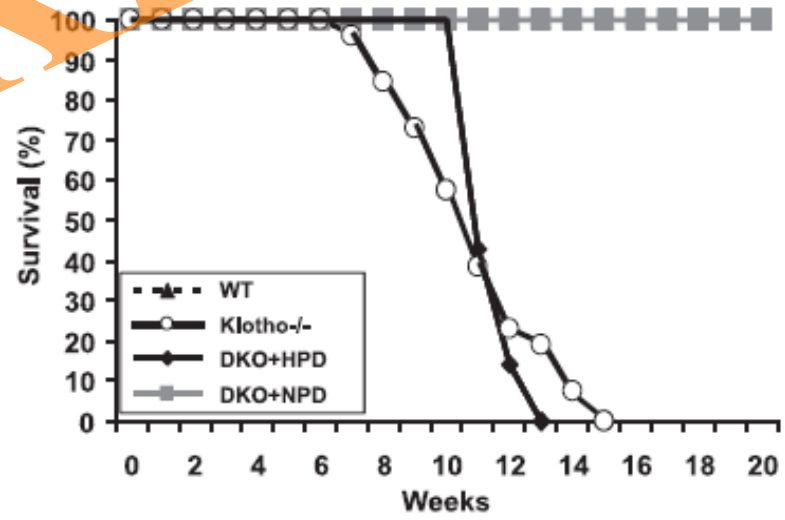

Insulin/IGF-1 receptor
Klotho
PDK1
PI3K
IRS1/2
Grb10
Ribosome association/ translation
?
mTORC2
Deptor
mTOR
mSin1
mLST8
Rictor
Protor1
SGK
PKC-α
Cytoskeleton
FOXO
Metabolism, stress resistance
T308
S473
Akt
Glut4
Glucose uptake
TSC2
TSC1
Rheb-GDP
AMPK
mTORC1
Rheb-GTP
Deptor
mTOR
PRAS40
mLST8
Raptor
S6K
Ribosome biogenesis
4E-BP
Translation
Ulk1
Autophagy
Amino acids
RagC/D-GDP
RagA/B-GTP
Ragulator
TFEB
Lysosome
Lysosome biogenesis


Overnutrition
Anabolic hormone signaling (insulin/IGF-1)
Klotho
Chronic mTOR activation
Decreased sirtuins
Oncogenic and mtDNA mutation
Reactive metabolites
Mitochondrial dysfunction
Shortened telomeres
Senescence
Impaired stem cell renewal
SASP
Decreased B cell and T cell proliferation
Chronic inflammation
Tissue dysfunction
Reduced β cell regeneration
Reduced immune response
Aging
Frailty
Chronic diseases
Impaired capacity to respond to regeneration therapies

Dietary and genetic evidence of phosphate toxicity accelerating mammalian aging. Ohnishi M and Razzaque MS Faseb 2010 24;3562

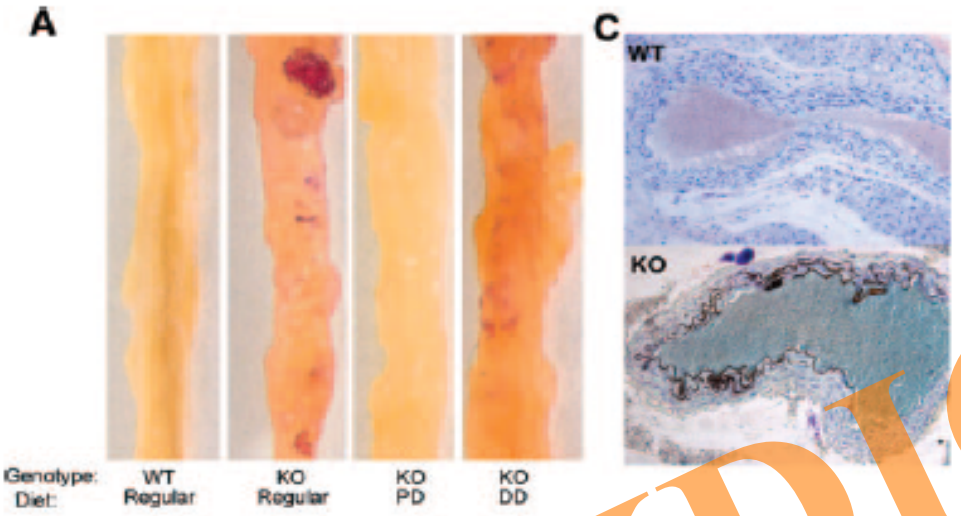


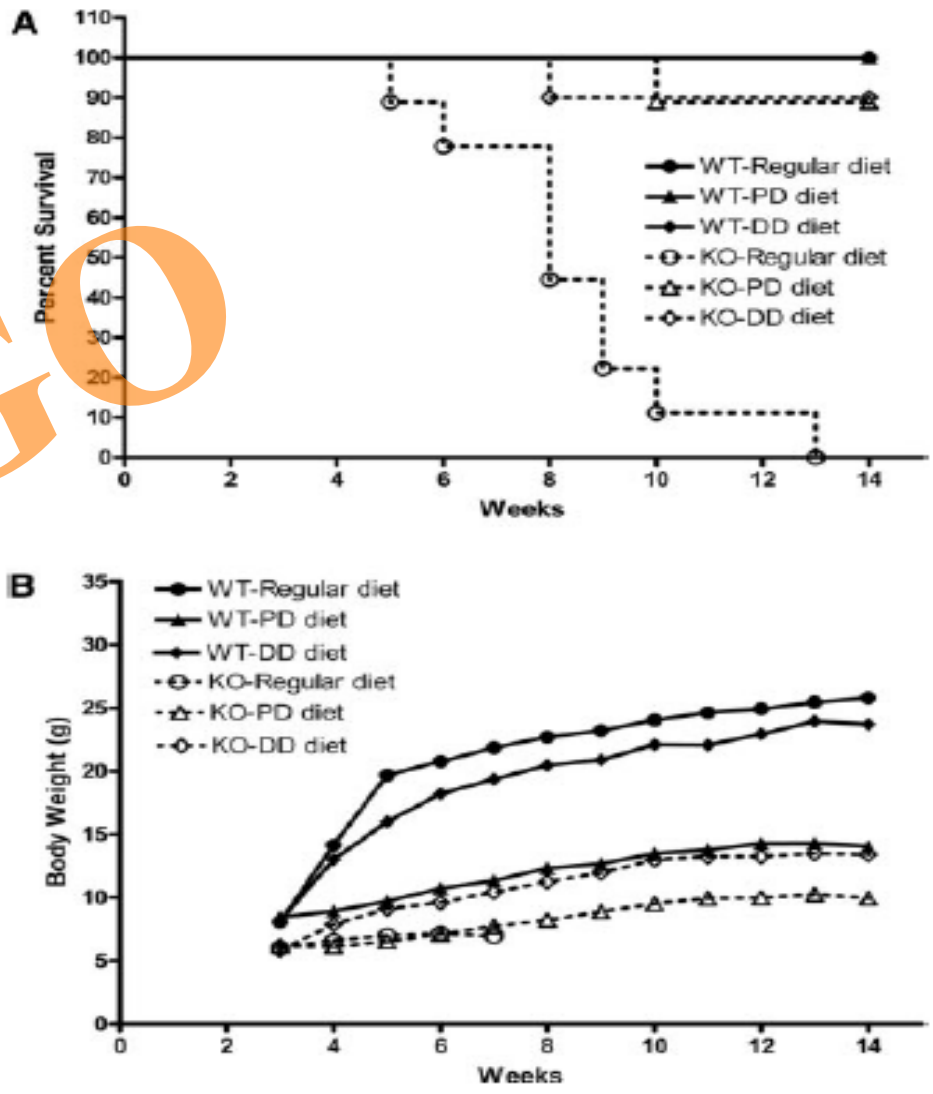




DKO klotho/Napi double knock-out
NPD normal phosphate diet
HPD high phosphate diet

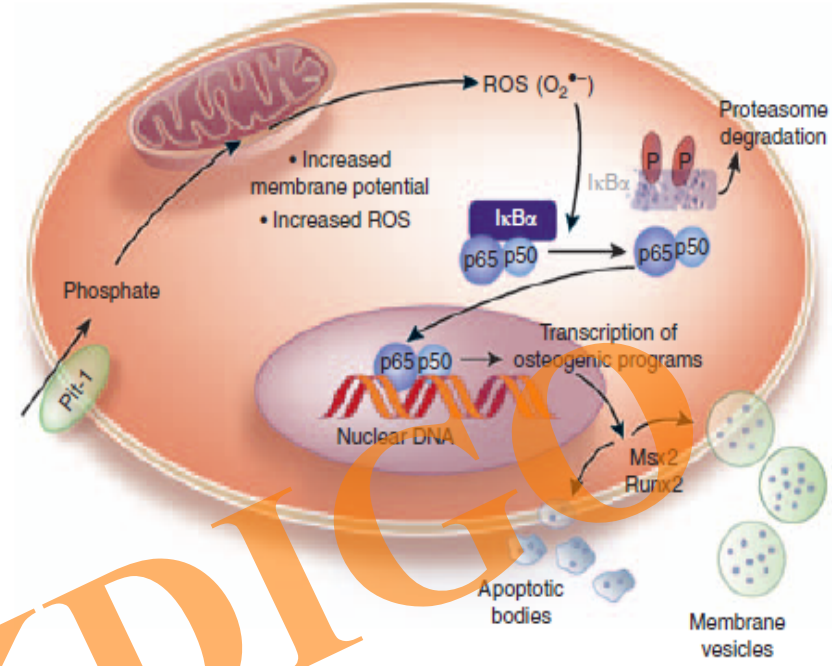
Effects of low phosphate (PD) and low vitamin D diet (DD) On aortic calcifications in FGF23 knock-out (KO) mice



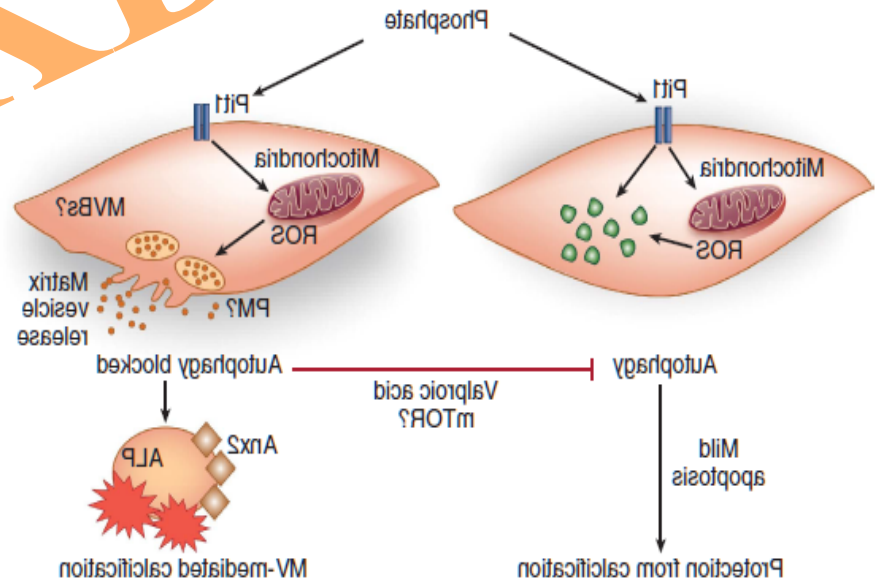


Worman HJ et al. JASN 2007;18:2116

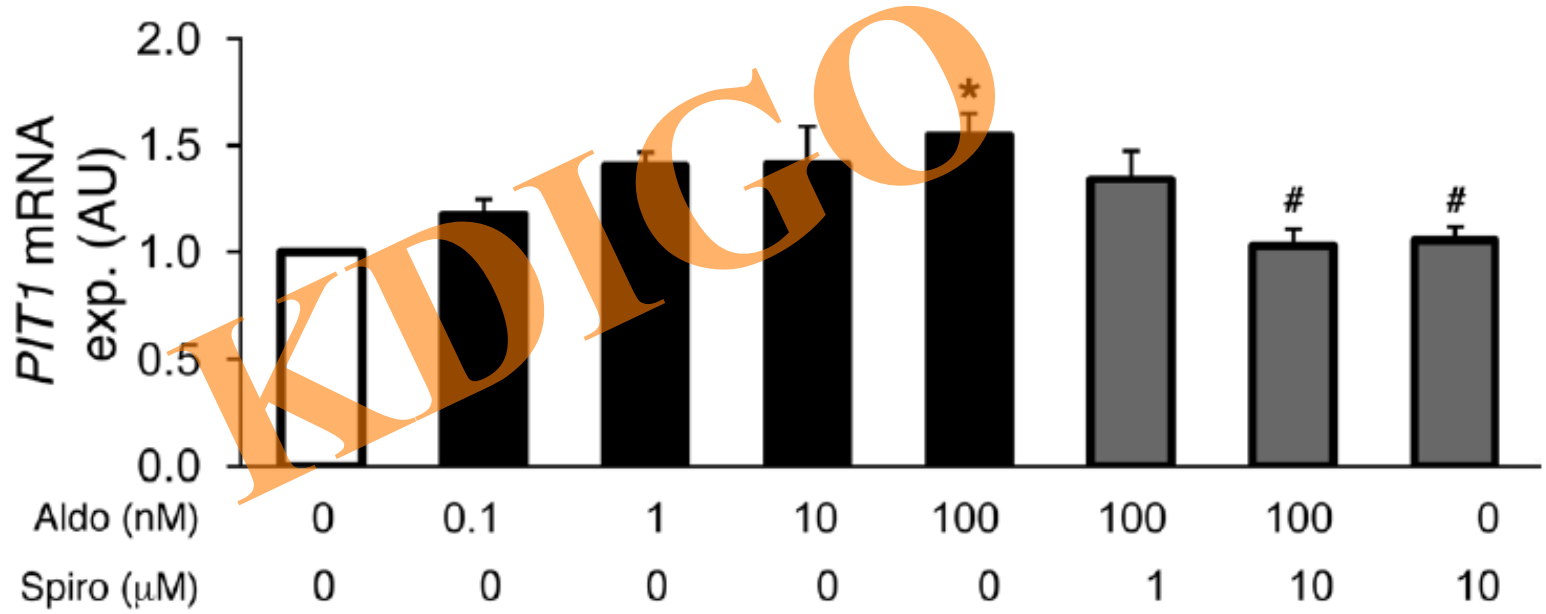
KI 2011;79:1044



KI 2013;83:984

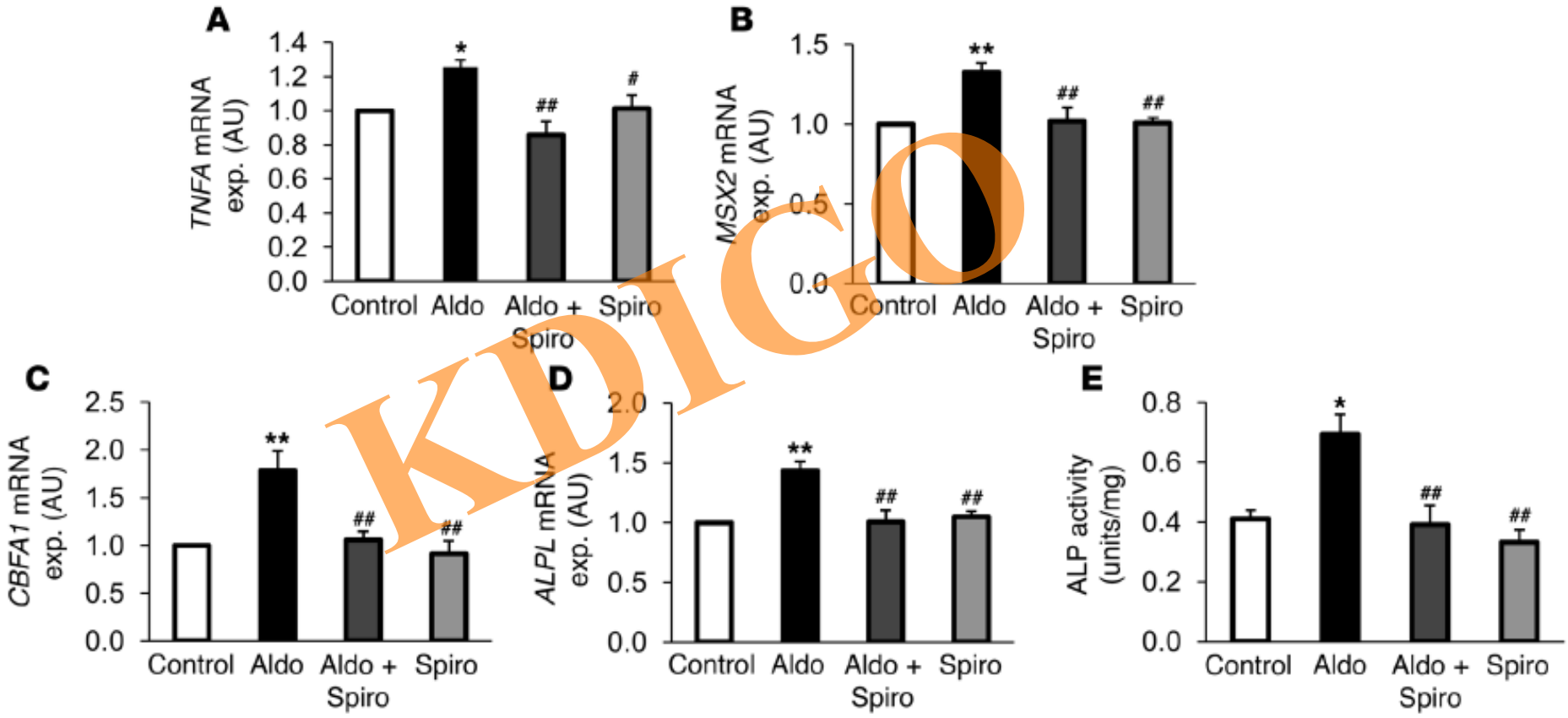


Effects of aldosterone and spirolactones on PIT1 expression



: *J Clin Invest.* 2013;123(2):812–822.

Effects of aldosterone and spirolactones on calcification factors



J Clin Invest. 2013;123(2):812–822.

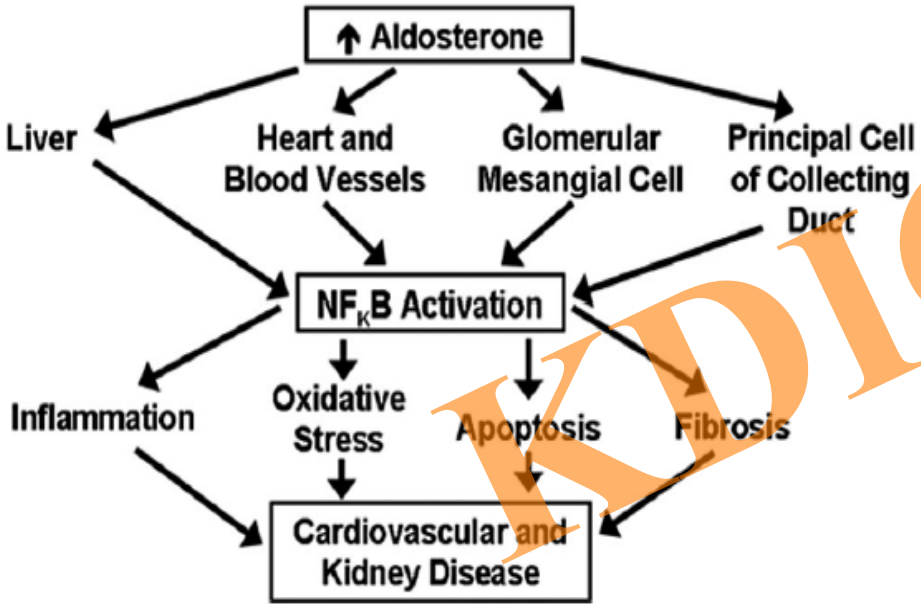
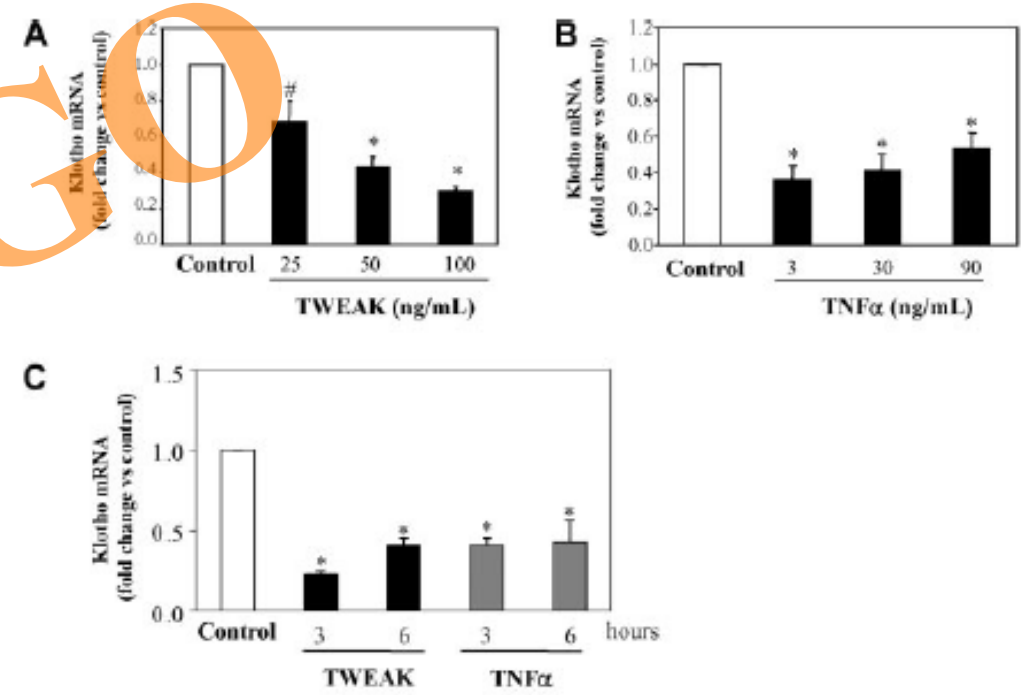


Figure 2. Role of NF-κB in mediating the nongenomic effects of aldosterone in cardiovascular and kidney disease.

Schrier RW et al. Clin J Am Soc Nephrol 2010

Figure 5. Inflammatory cytokines decrease Klotho expression in cultured tubular cells in an NFκB-dependent manner. TWEAK (A) and TNFα (B) decrease Klotho mRNA

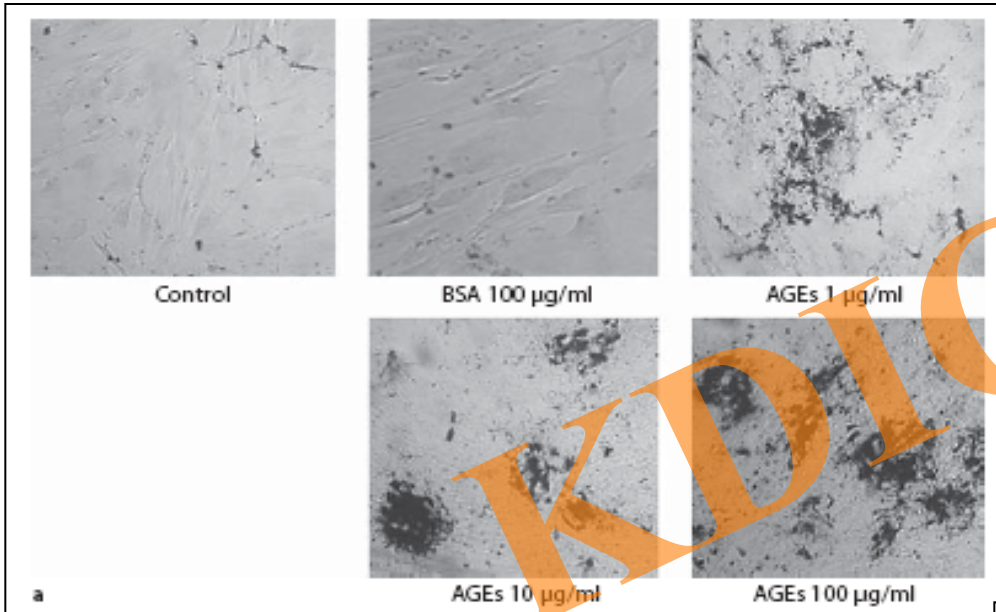


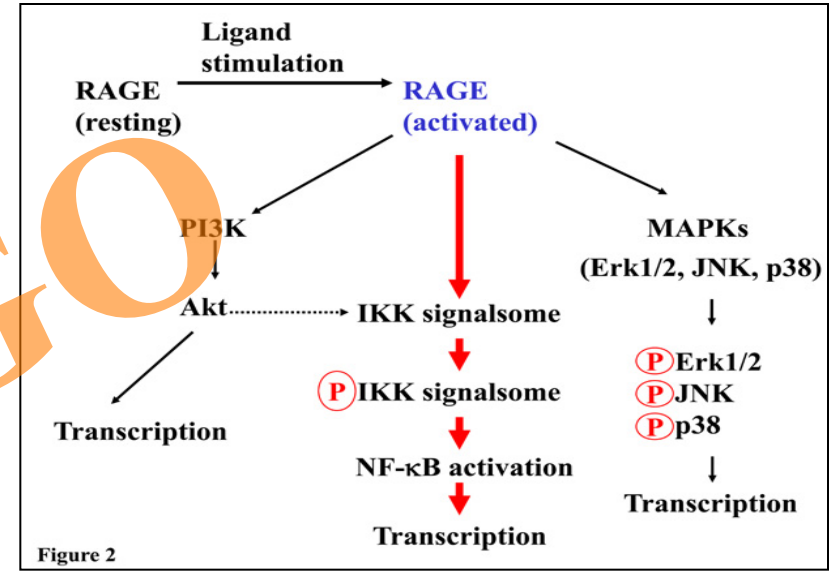
TWEAK: TNF-like weak inducer of apoptosis

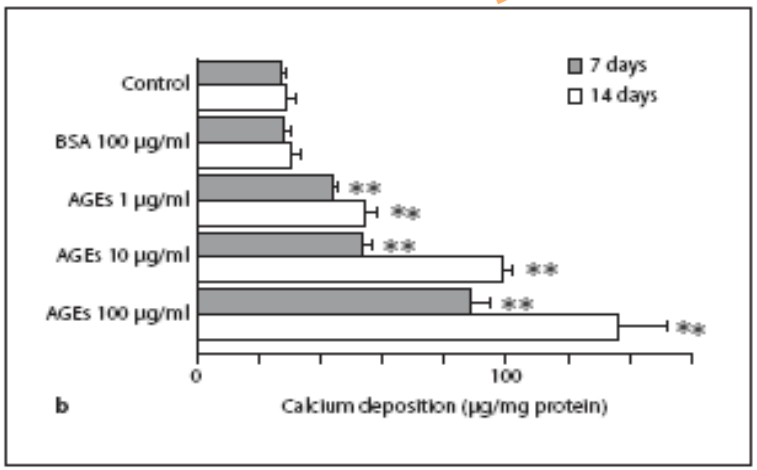
Moreno JA et al JASN 2011;22:1315

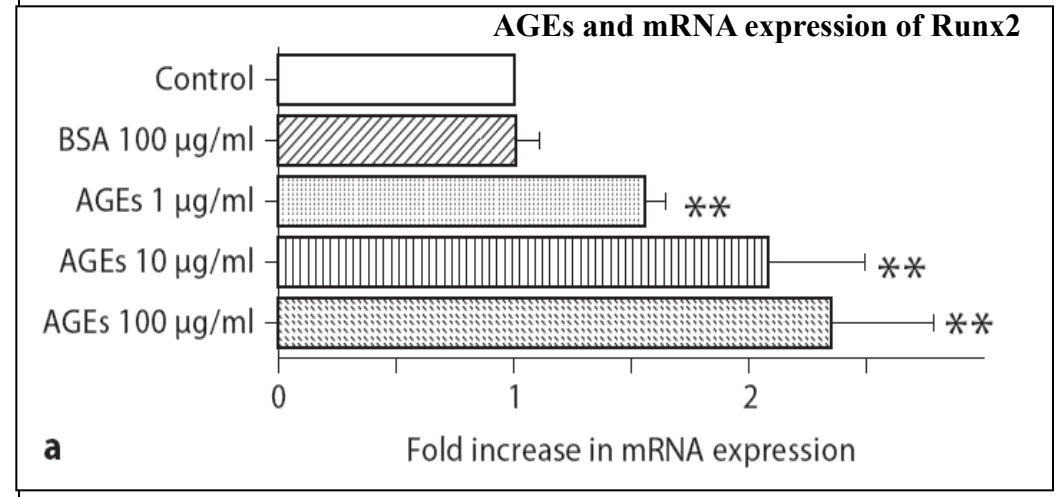
Advanced glycation end products induce calcification of VSMC through RAGE/ p38MAPK and upregulation of Runx2

Tanikawa T et al.J Vasc Res 2009;46:572-580

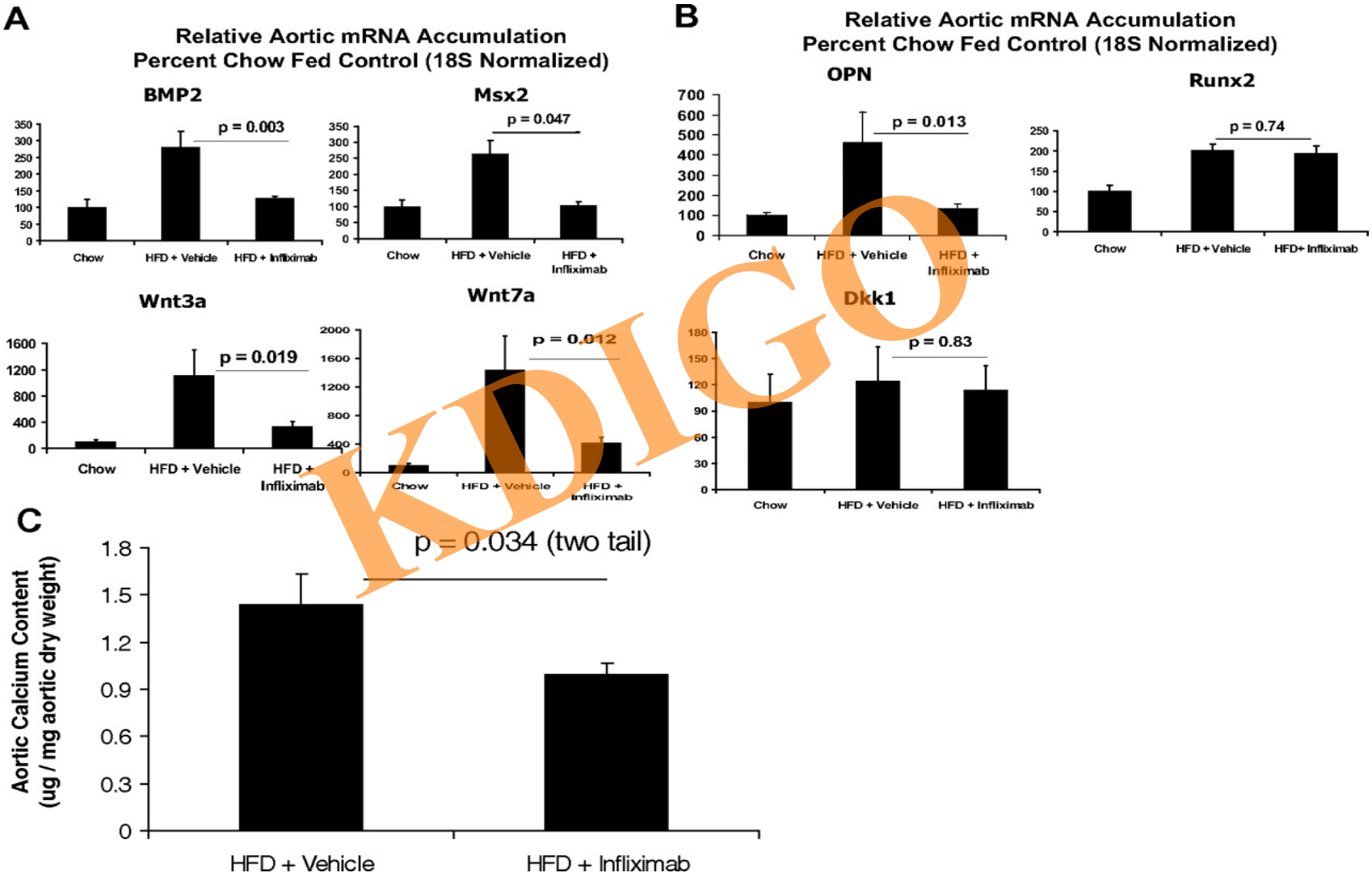






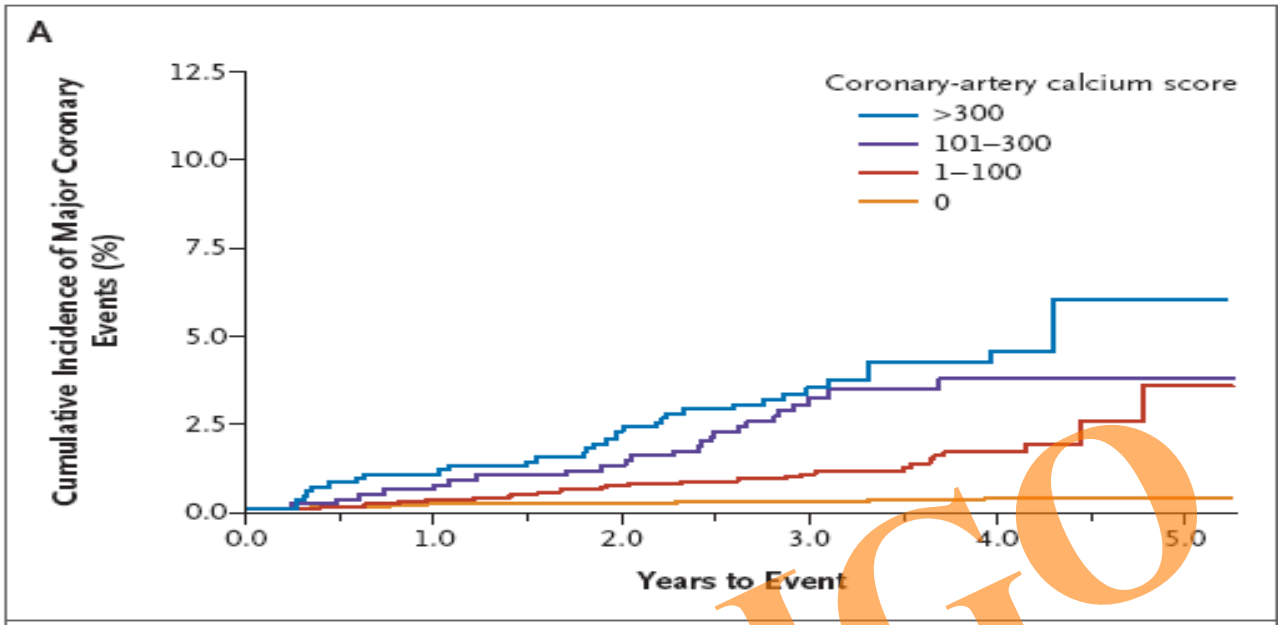


Infliximab downregulates osteogenic BMP2-Msx2-Wnt programs in Ldlr-/- mice fed HFD



Al-Aly, Z. et al. Arterioscler Thromb Vasc Biol 2007;27:2589-2596

HFD-high fat diet



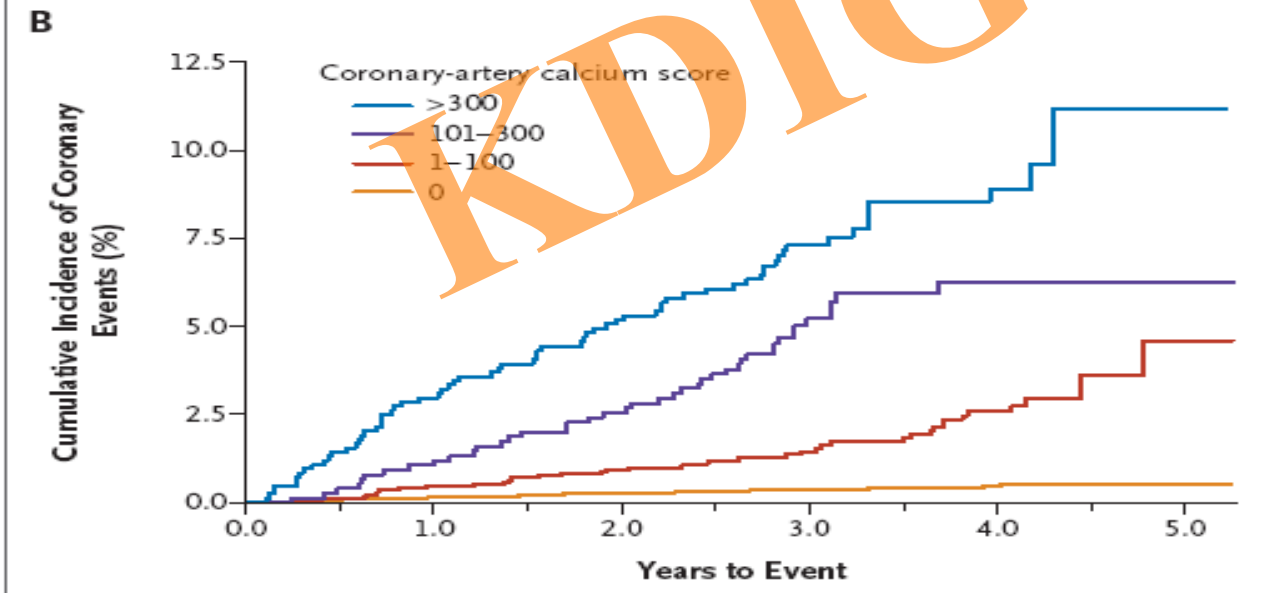
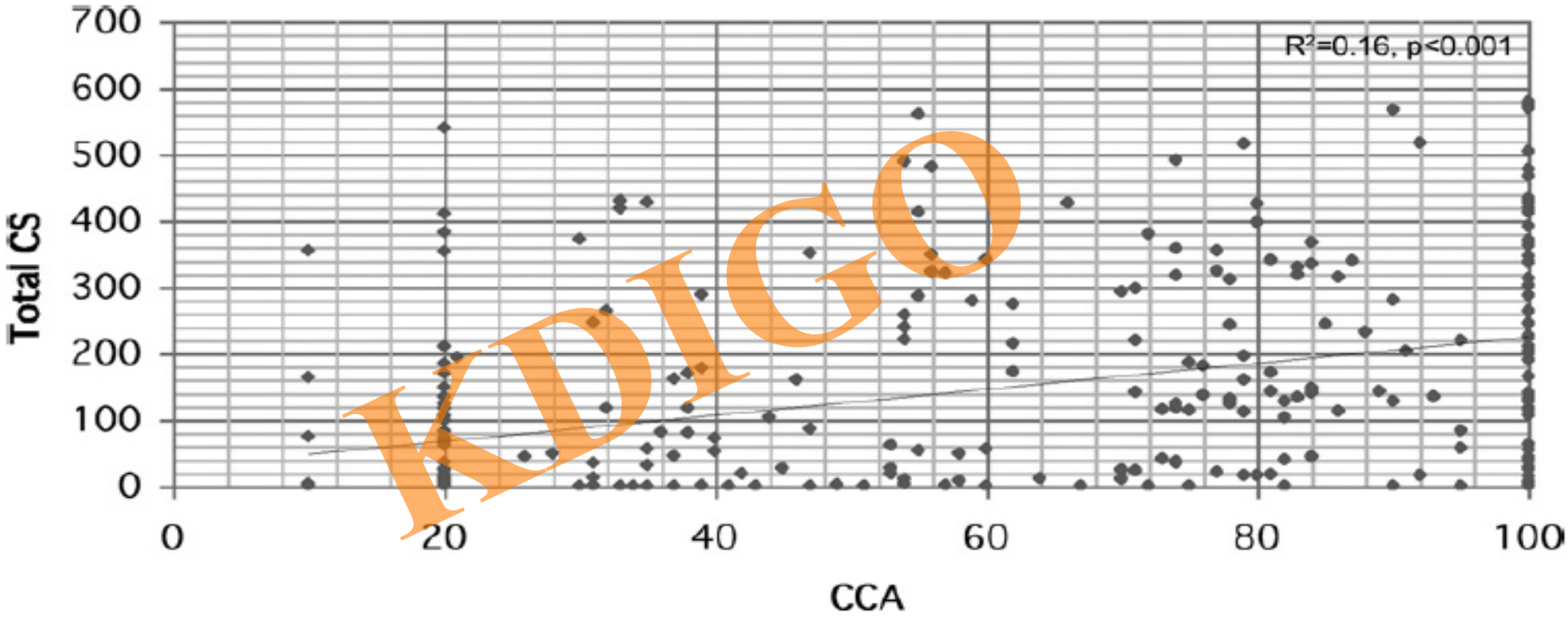


Figure 1. Unadjusted Kaplan–Meier Cumulative-Event Curves for Coronary Events among Participants with Coronary-Artery Calcium Scores of 0, 1 to 100, 101 to 300, and More Than 300.

Detrano et al

N Engl J Med 2008;358:1336-45.

Correlation between calcium score and degree of stenosis is weak

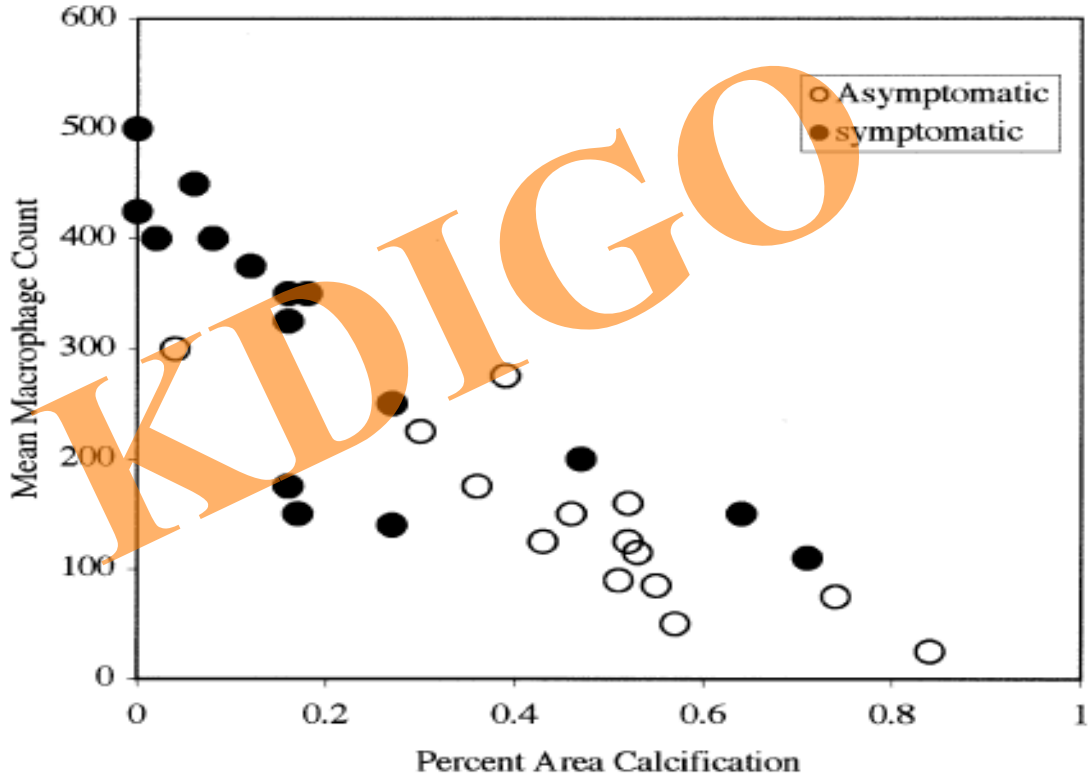


- **Calcification is not equivalent to coronary stenosis**

Gottlieb. JACC 2010

Degree of carotid plaque calcification in relation to symptomatic outcome and plaque inflammation

Wael E. Shaalan, MD,[a] Hongwei Cheng, MD, PhD,[a] Bruce Gewertz, MD,[a] James F. McKinsey, MD,[a] Lewis B. Schwartz, MD,[a] Daniel Katz, MD,[a] Dindcai Cao, PhD,[b] Tina Desai, MD,[a] Seymour Glagov, MD,[a] and Hisham S. Bassiouny, MD,[a] *Chicago, Ill*



Conclusions: Symptomatic plaques are less calcified and more inflamed than asymptomatic plaques. Regardless of clinical outcome, a strong inverse correlation was found between the extent of carotid plaque calcification and the intensity of plaque fibrous cap inflammation as determined by the degree of macrophage infiltration. Carotid plaque calcification is associated with plaque stability, and is a potential spiral CT in vivo quantitative marker for cerebrovascular ischemic event risk. (J Vasc Surg 2004;40:262-9.)

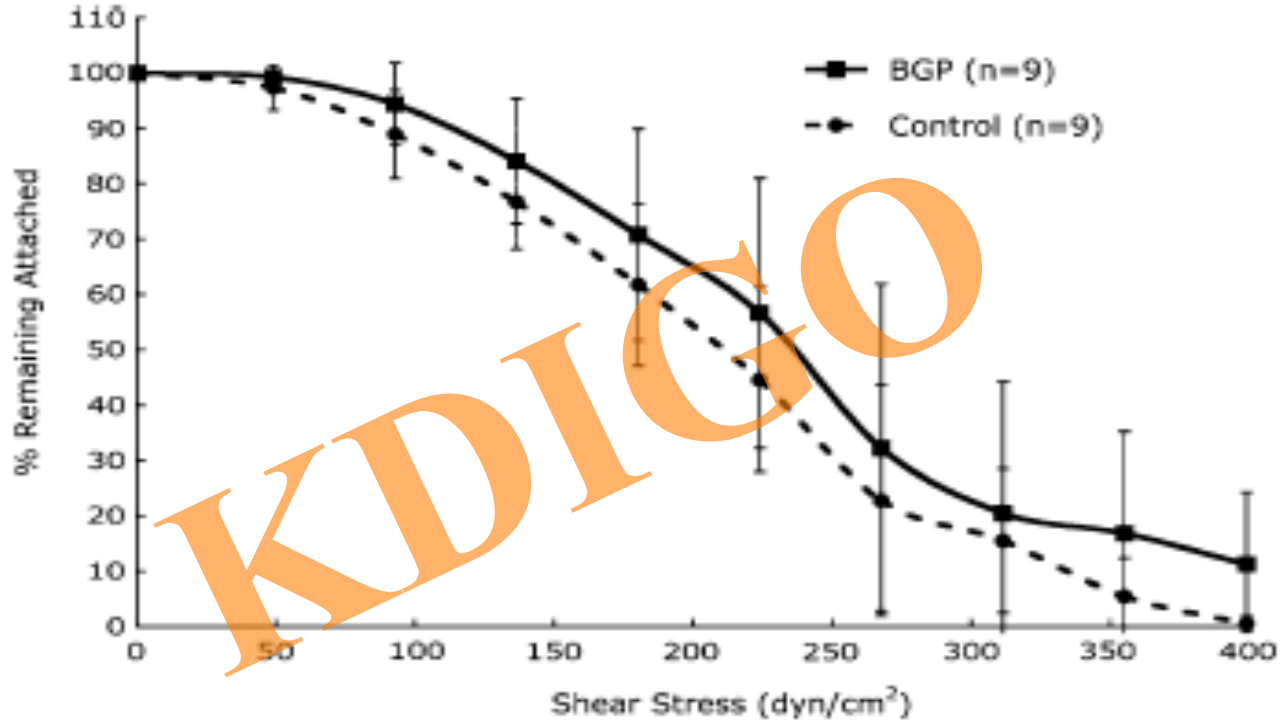


FIGURE 5. Lumped average percentages of nodules remaining attached for both control (triangles) and BGP-treated (squares) cultures (n = 9, p = 0.47) as a function of shear stress (dyn/cm^2).

AHA Recommandations 2010

What is the role of coronary calcium measurement by fast CT scan in asymptomatic patients with high CHD risk ?

The Committee does not advise CAC measurement in this selected patient stratum as they are already judged to be candidates for intensive risk reducing therapies based on current NCEP guidelines.

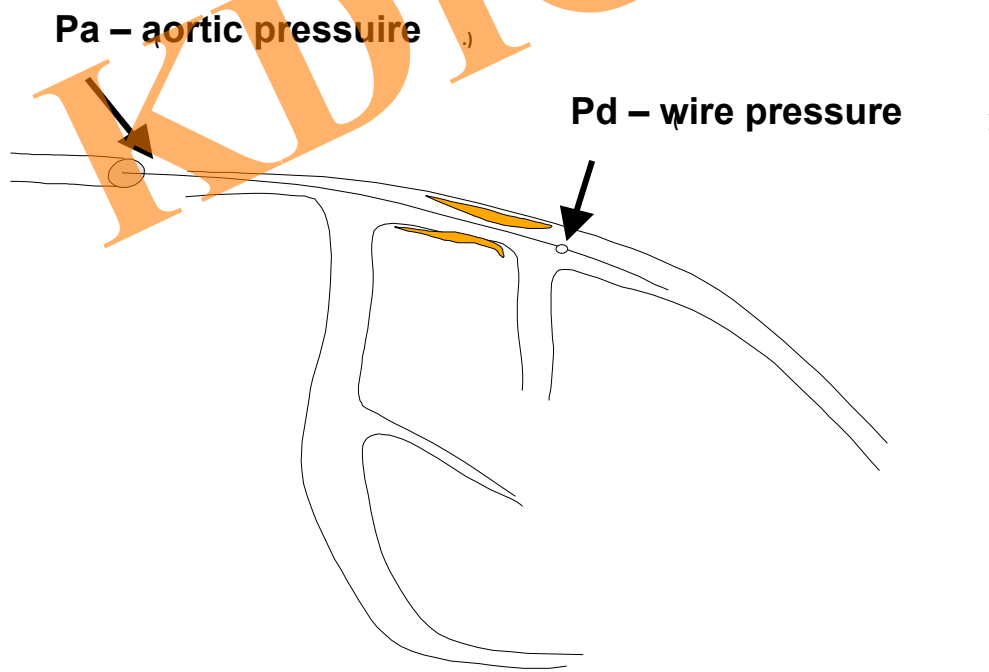
Is there evidence that coronary calcium measurement is better than other potentially competing tests in intermediate risk patients for modifying cardiovascular disease risk estimate?

In general, CAC measurement has not been compared to alternative approaches to risk assessment in head-to-head studies. This question cannot be adequately answered from available data.

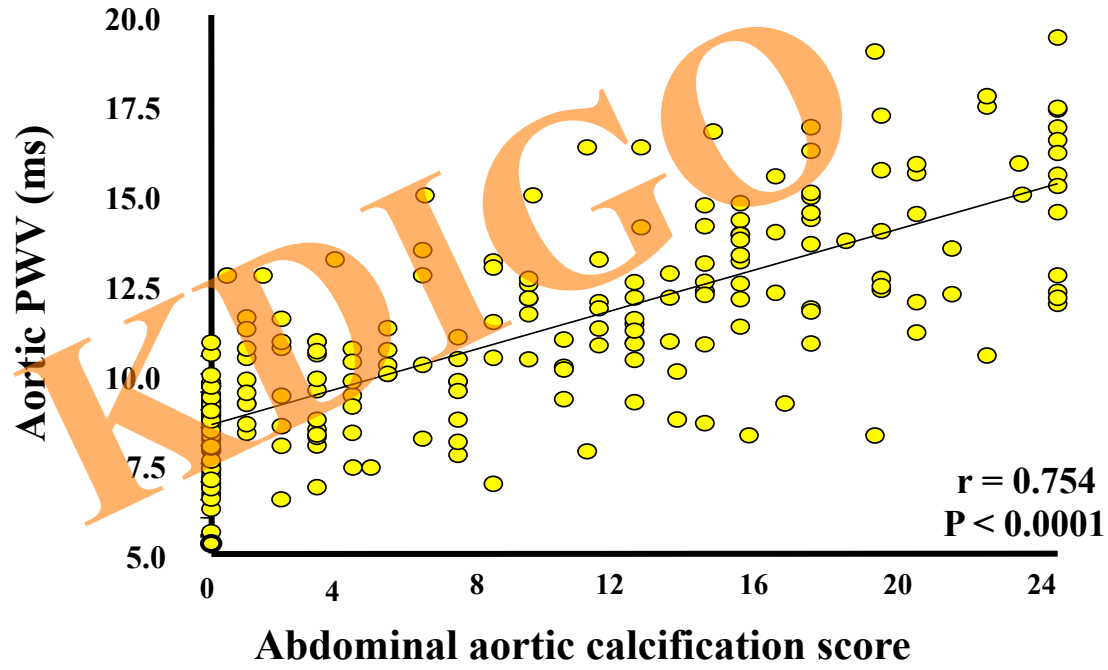
Paradigm change

- **Cardiology switched from anatomy to function**
- **Recommandations 2004: tight stenosis with lumen reduction > 50%**
- **Recommandations 2010: functional evaluation FFR: <0.8 ischemia (functional flow rate)**

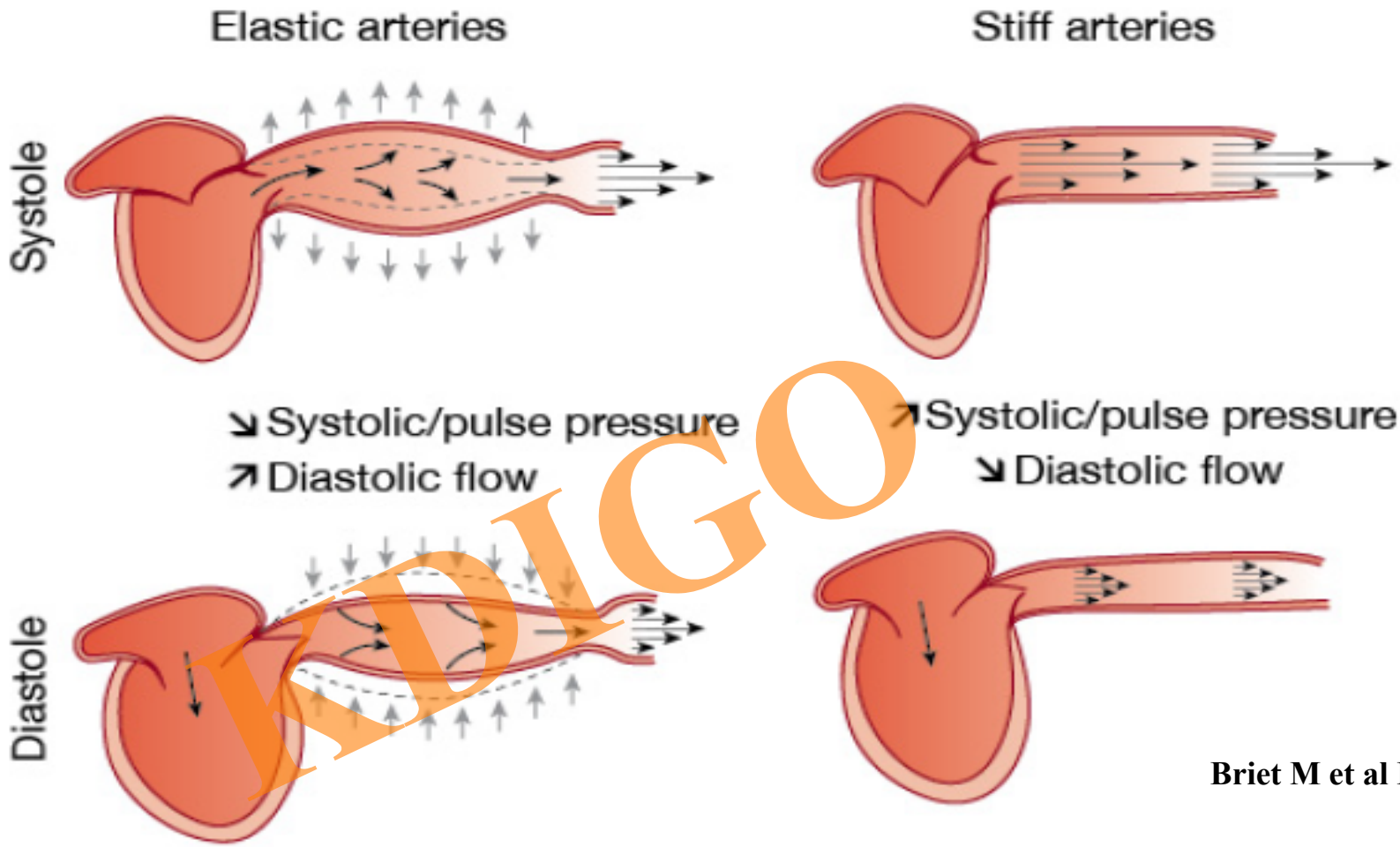
$$FFR = \frac{Q^{S}_{max}}{Q^{N}_{max}} = \frac{(Pd-Pv)/R}{(Pa-Pv)/R} = \frac{P_d}{P_a}$$



Correlation between aortic calcification score and aortic PWV in ESRD patients



Pannier et al. Artery 2007



Briet M et al KI 2012

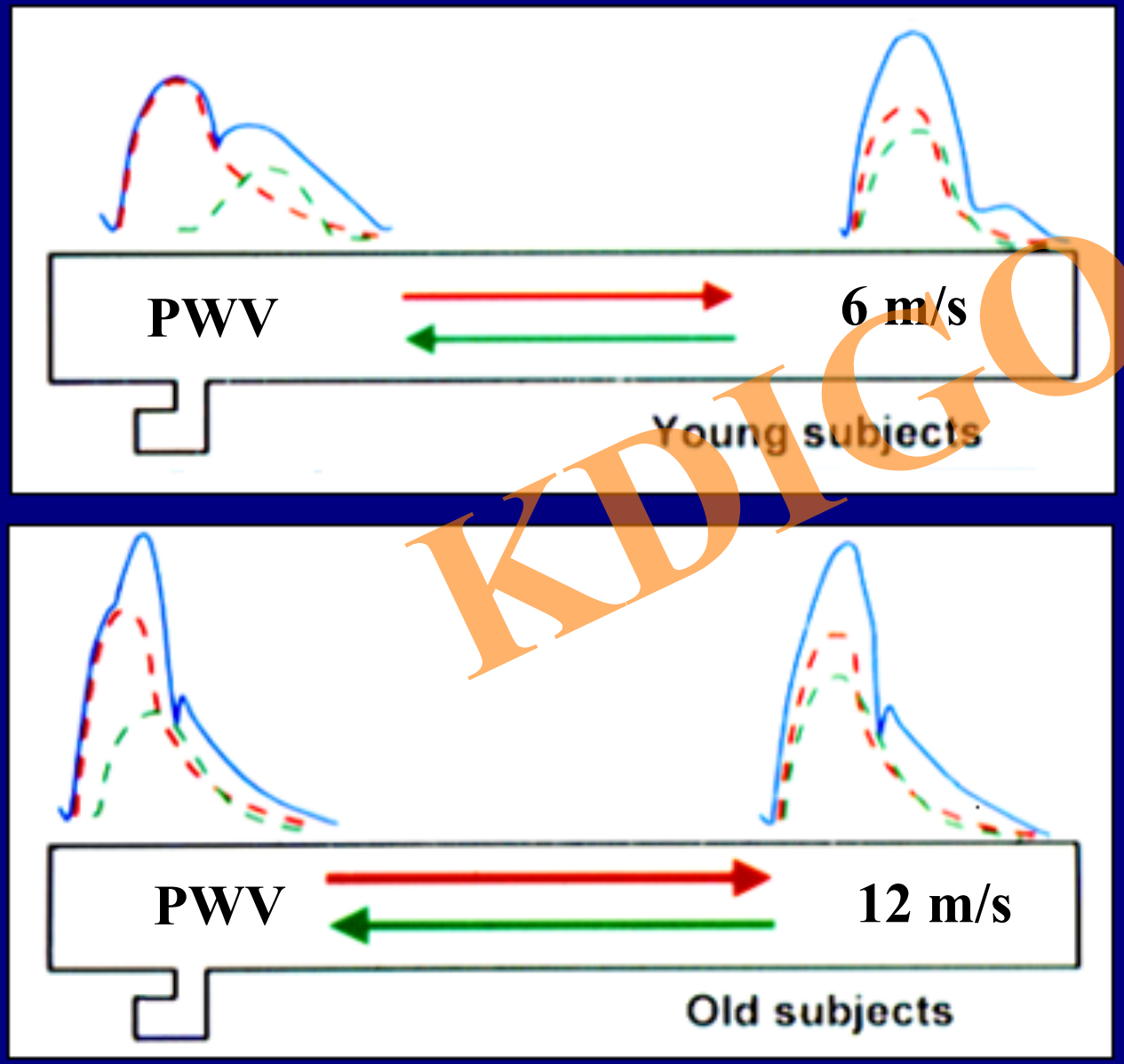
Oxygen Limitation Model

↑ Blood Velocity → **↓ Capillary Transit Time** → **↓ O_2 Extraction** → **Smaller Fraction of O_2 Available for Metabolism**

(NOT capillary recuitment

Normally 2-3 seconds

Pressure wave analysis



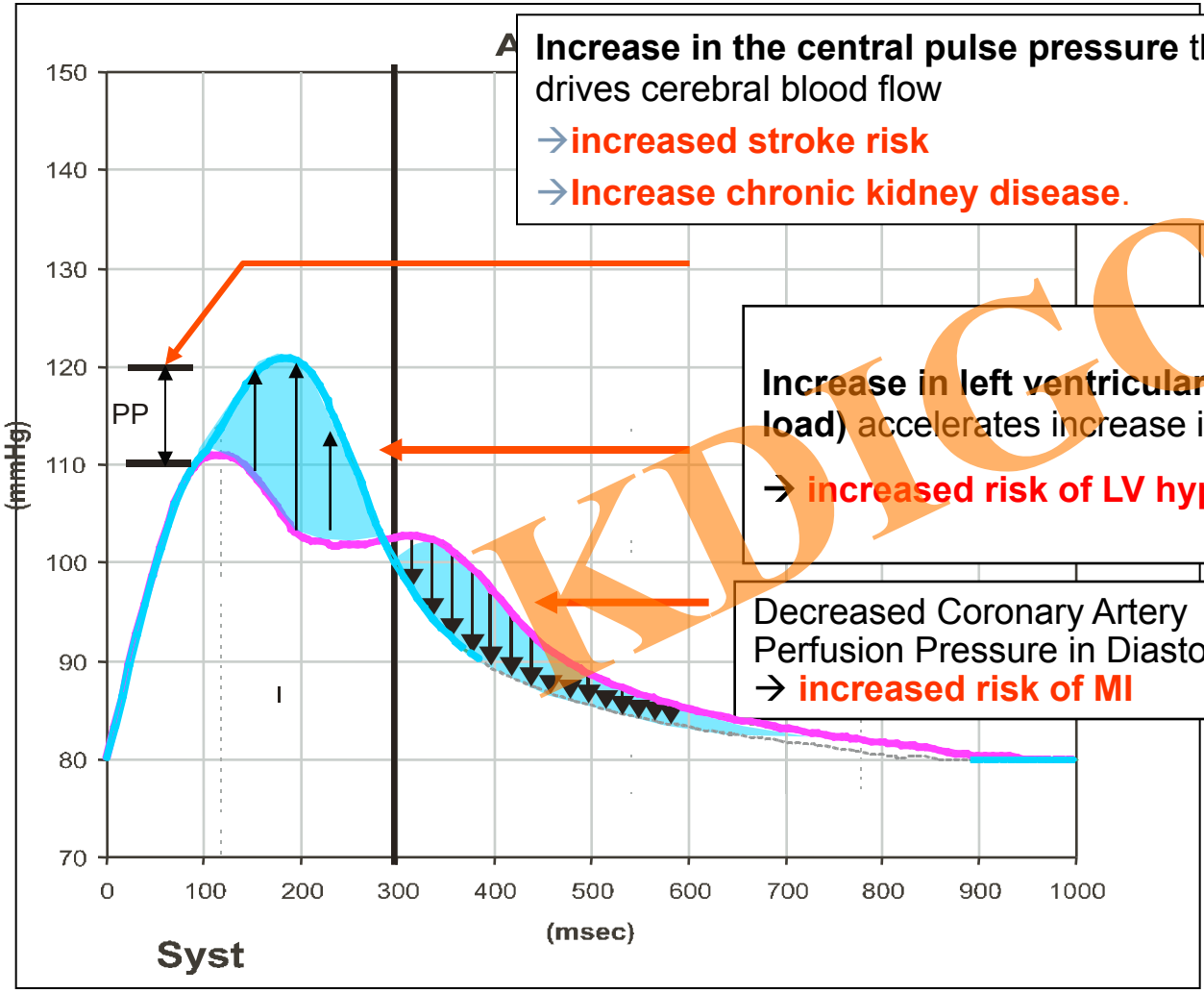
measured pressure wave

forward/incident pressure wave

reflected pressure wave

pulse wave velocity

Role of increased central aortic and pulse pressures in the increase of cardiovascular events



Increase in the central pulse pressure that drives cerebral blood flow

→**increased stroke risk**

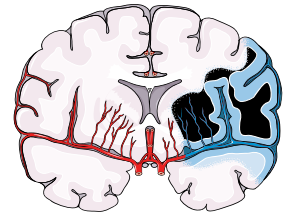
→**Increase chronic kidney disease**.

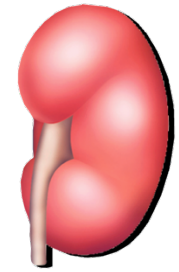
Increase in left ventricular load (LV load) accelerates increase in **LV mass**

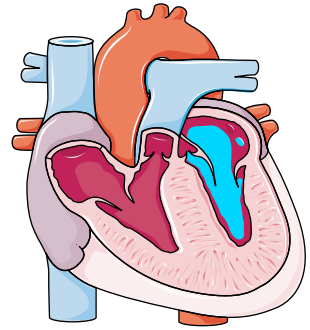
→ **increased risk of LV hypertrophy**

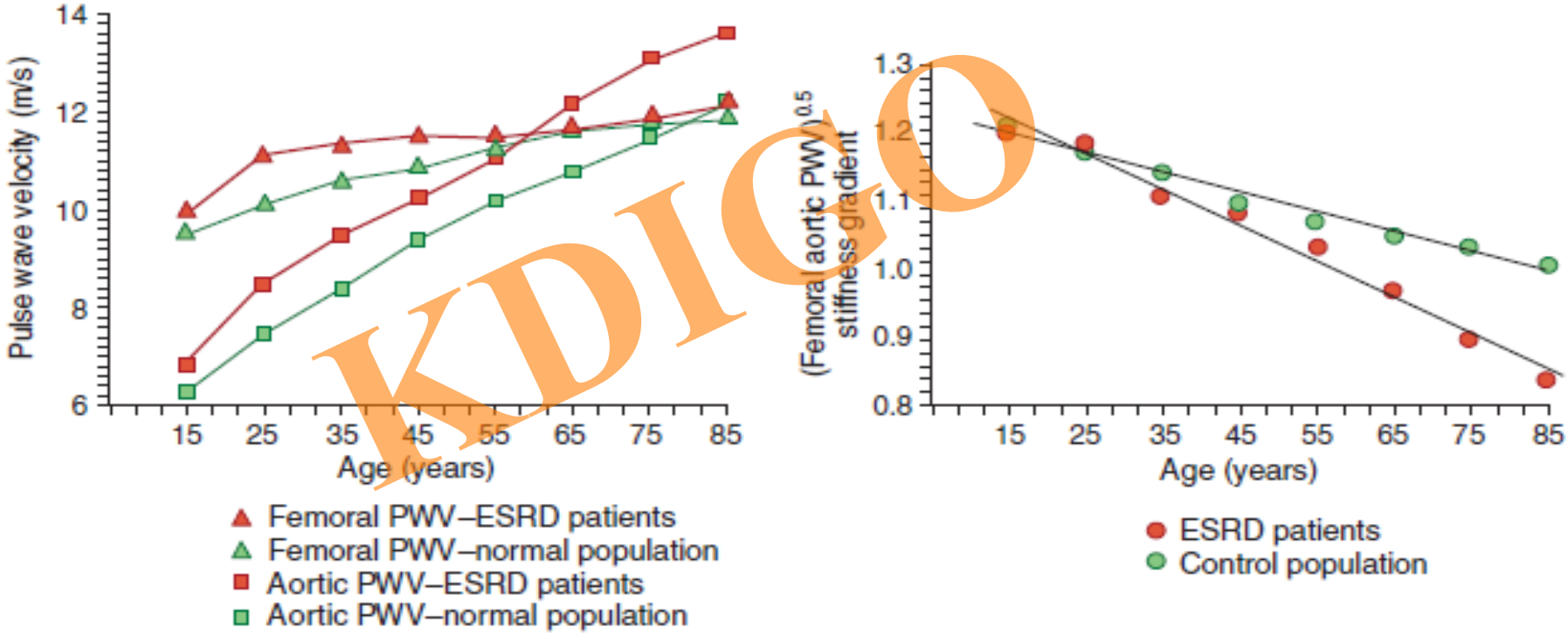
Decreased Coronary Artery Perfusion Pressure in Diastole

→ **increased risk of MI**

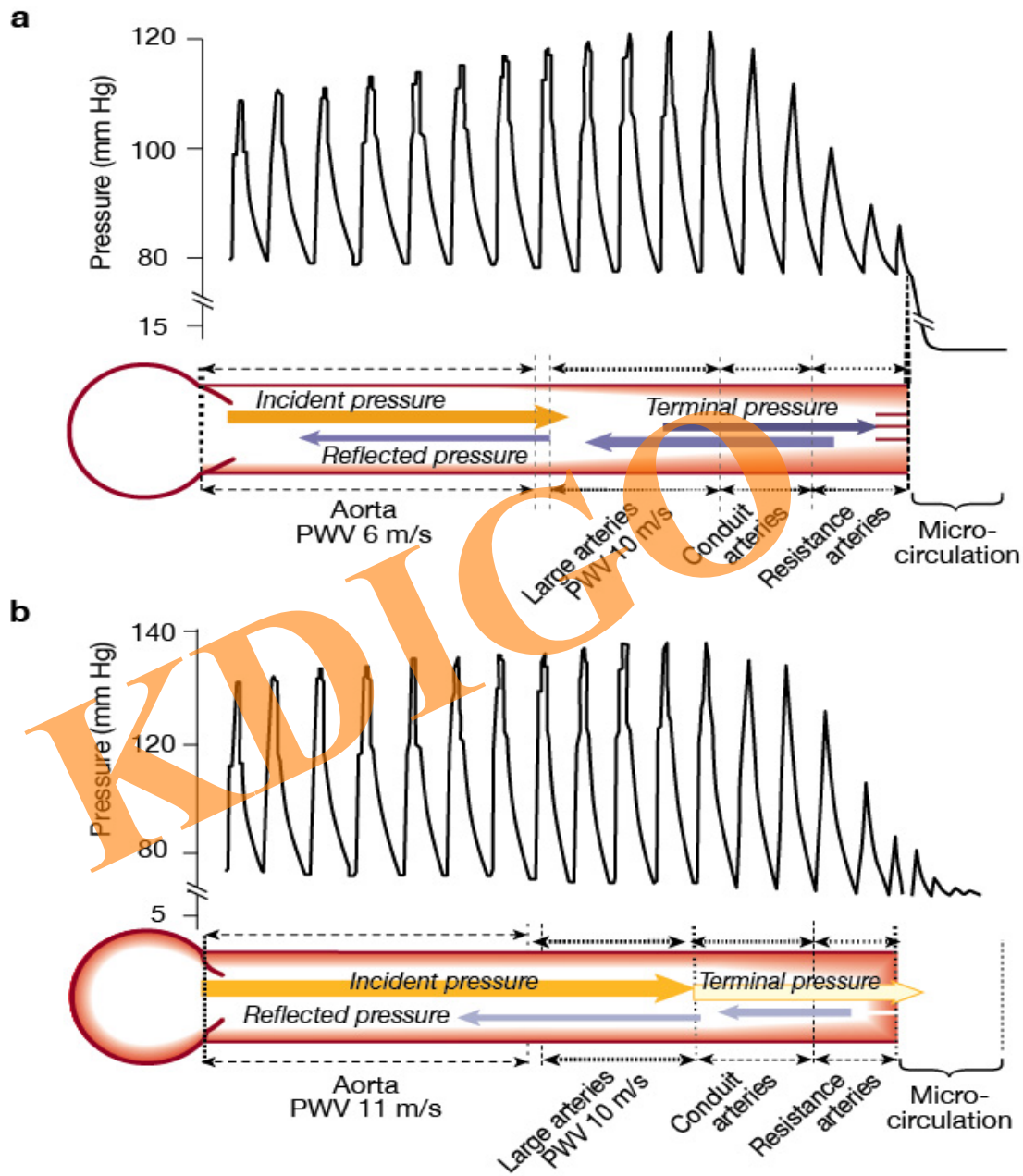






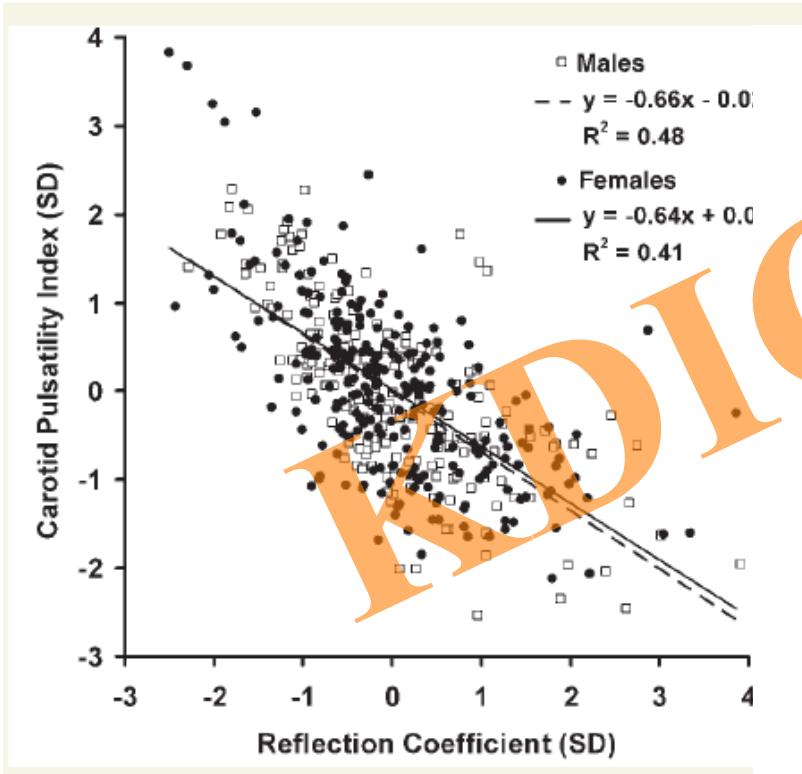


Briet M et al. KI 2012

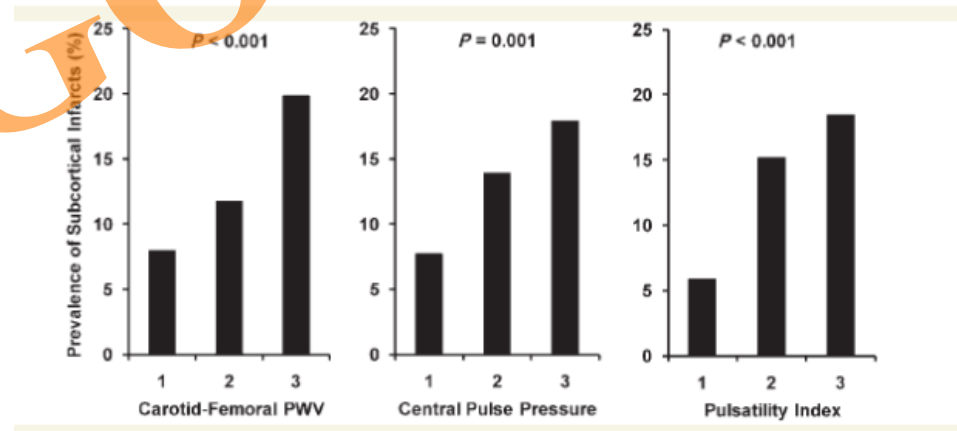


Reflection coefficient=RefP/Forward P

Briet et al KI 2012

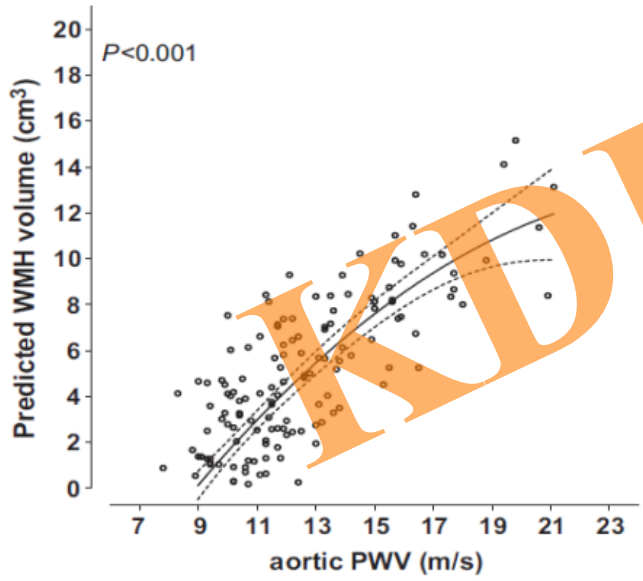


Mitchell GF et al Brain 2011;134:3398



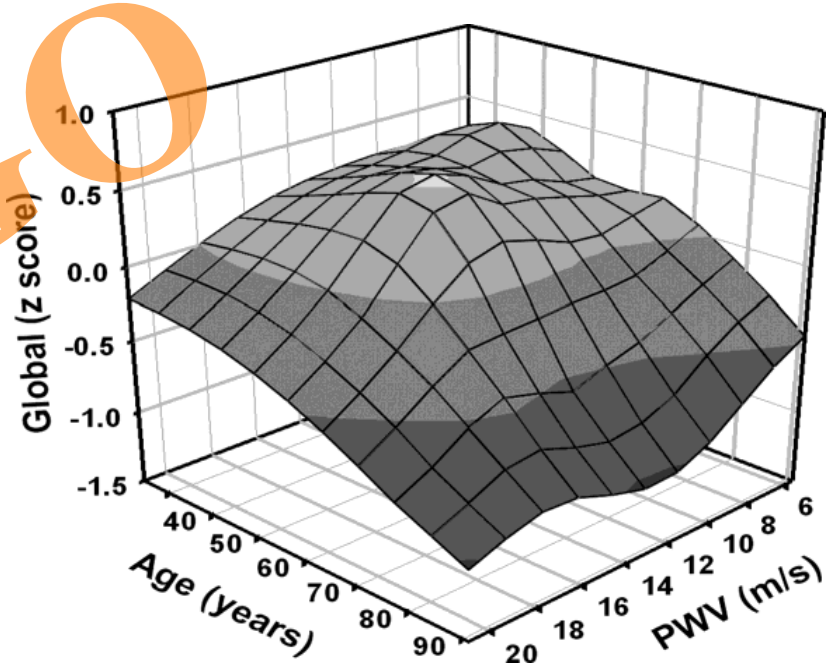
Mitchell GF et al Brain 2011;134:3398

Aortic PWV and White matter Hyperdensities (WMH)



Henskens et al Hypertension 2008;52:1120

The interaction of PWV and age in relation to the global composite cognitive score

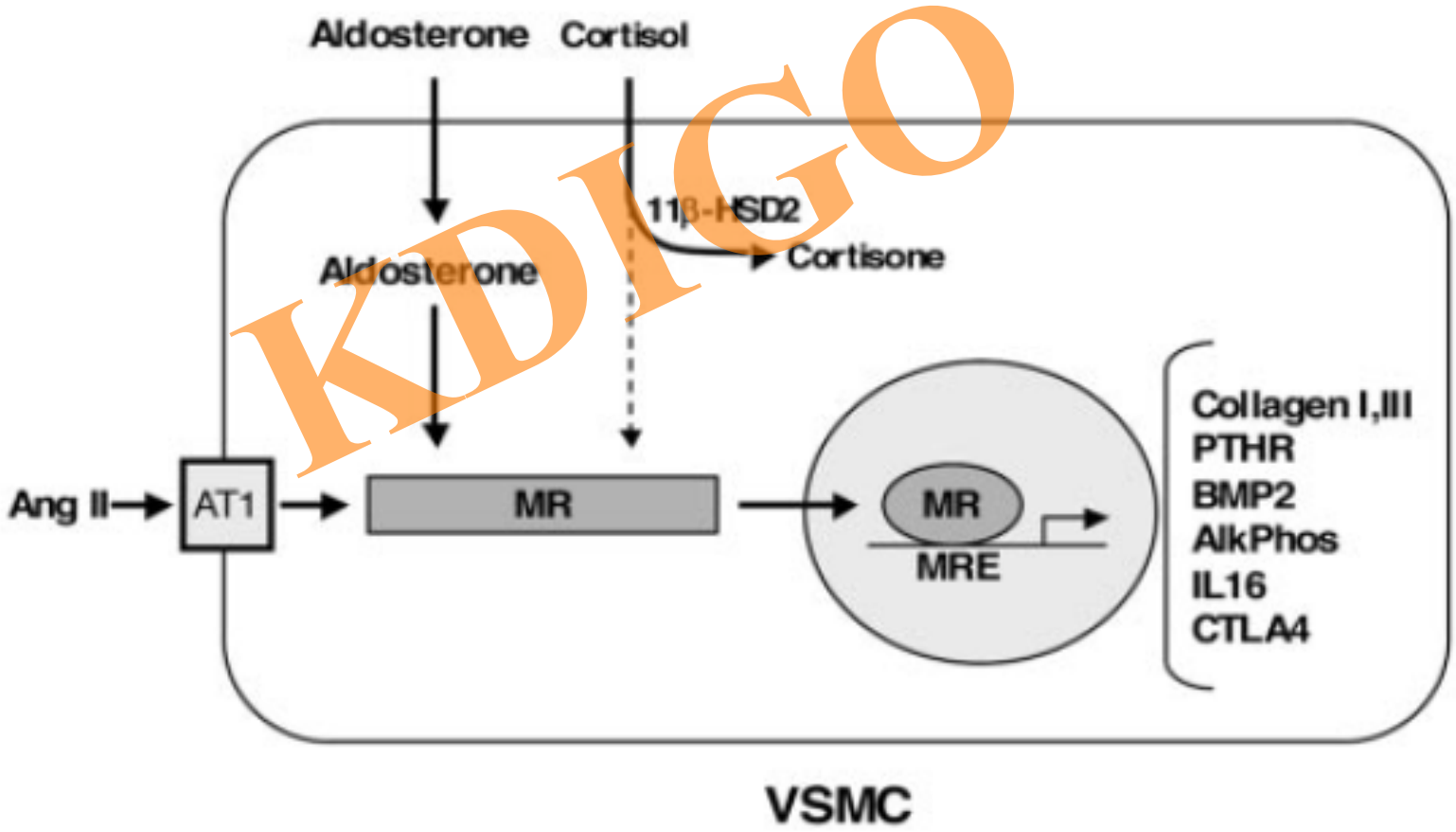


Elias, M. F. et al. Hypertension 2009;53:668-673

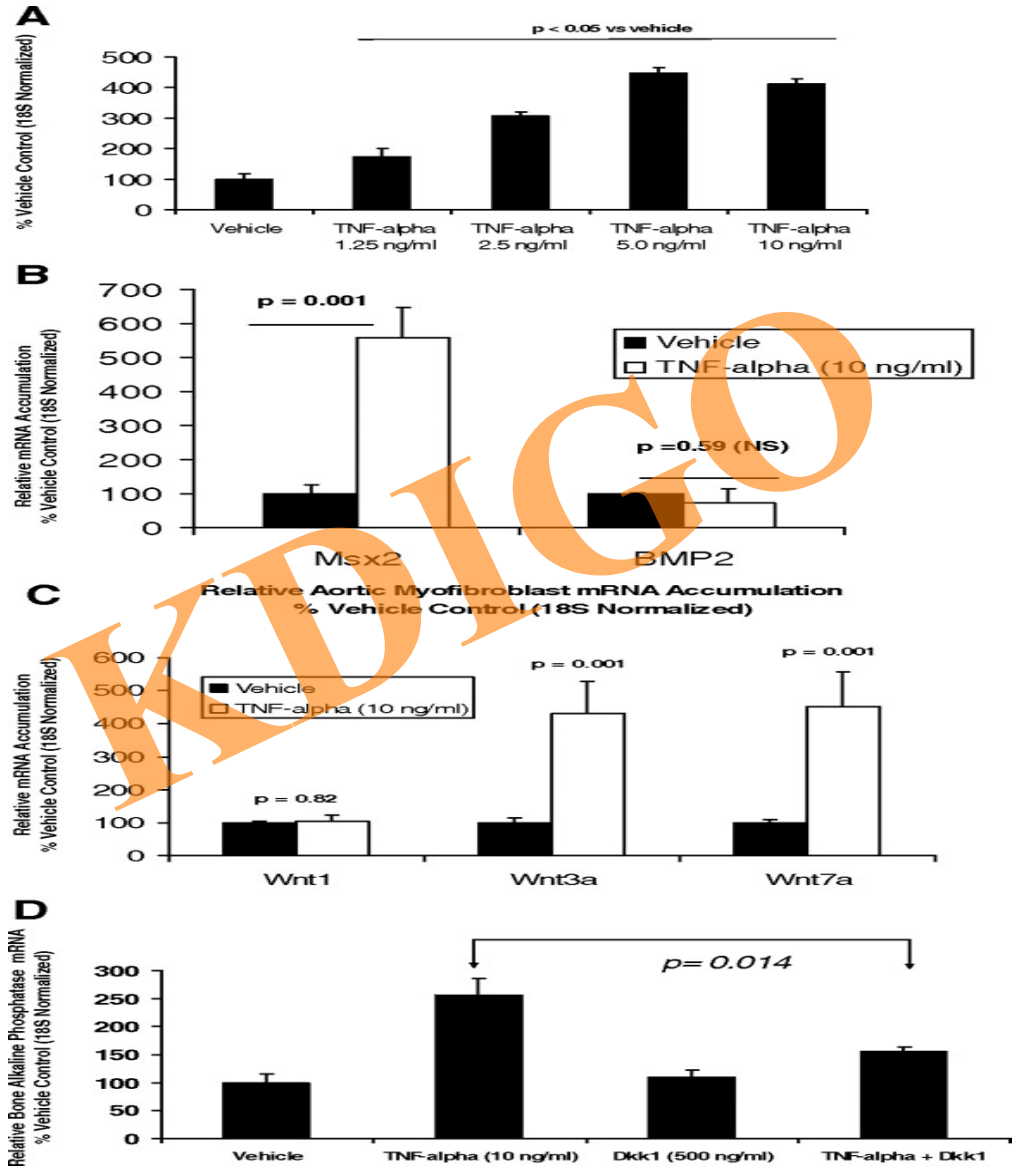
Angiotensin II and Aldosterone Regulate Gene Transcription Via Functional Mineralocortocoid Receptors in Human Coronary Artery Smooth Muscle Cells

Iris Z. Jaffe and Michael E. Mendelsohn

Circ Res. 2005;96:643-650

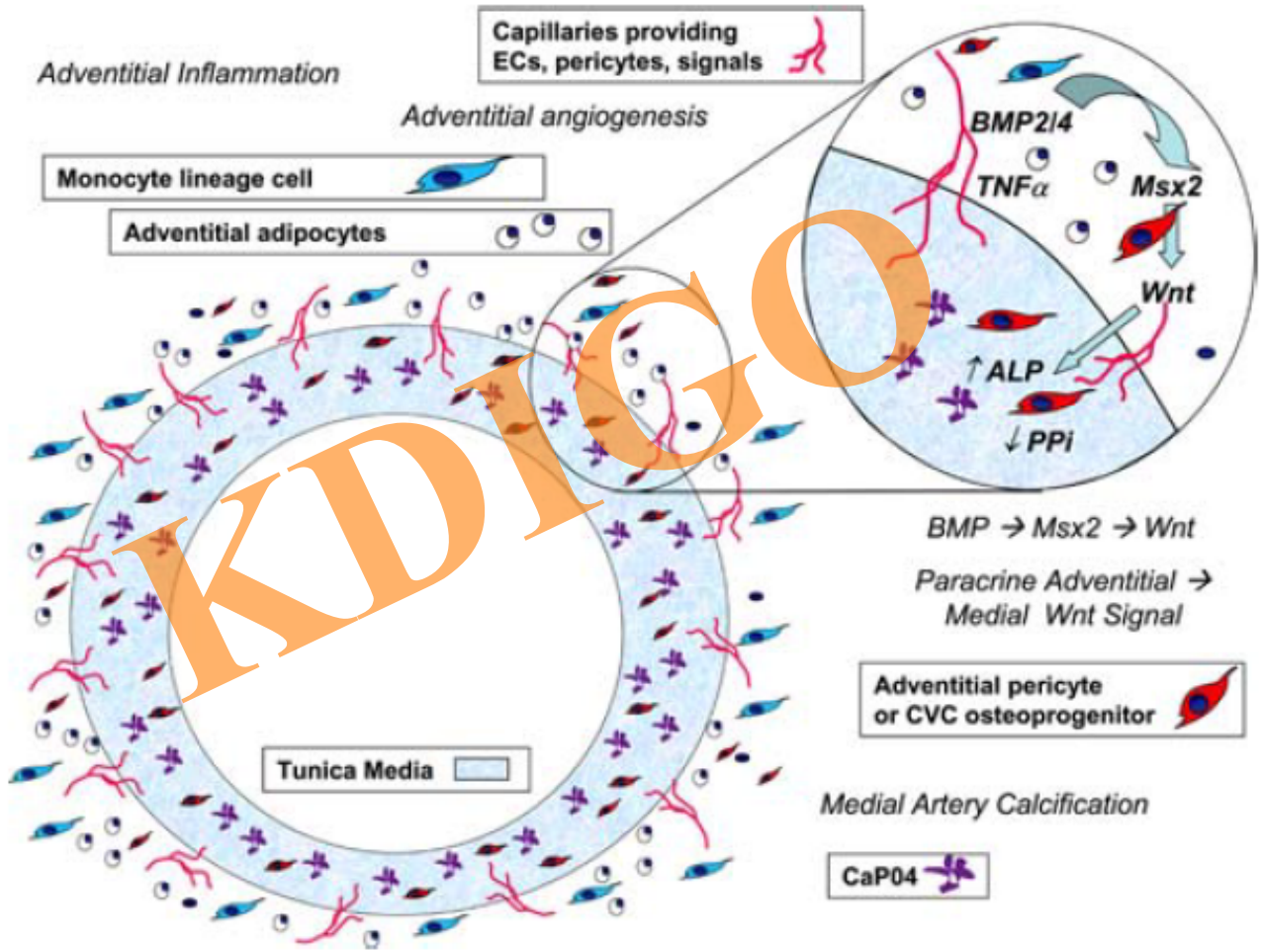


TNF-{alpha} directly activates Msx2-Wnt signaling with subsequent ALP induction

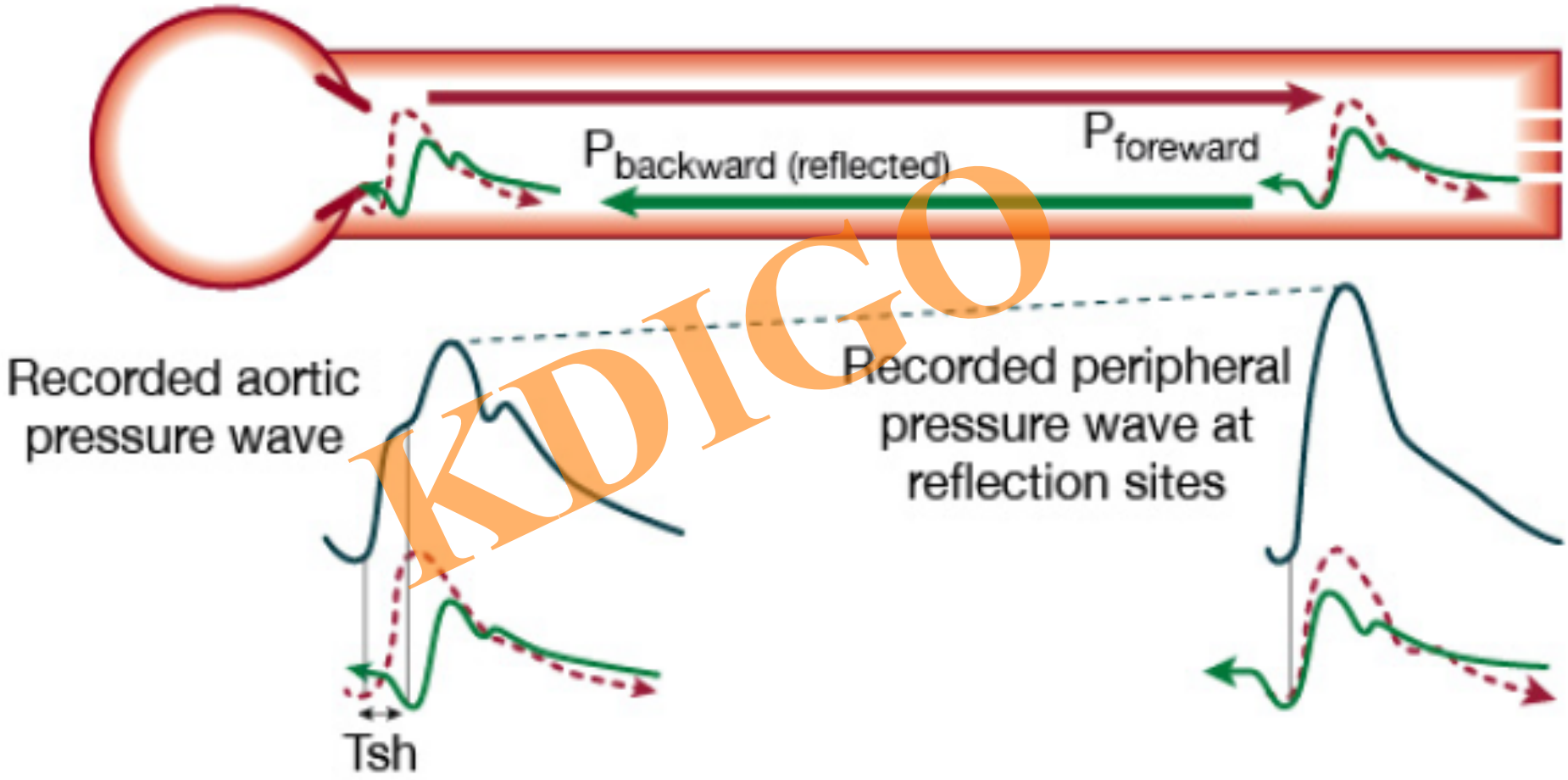


Al-Aly, Z. et al. Arterioscler Thromb Vasc Biol 2007;27:2589-2596

Working model for arterial media calcification



Towler D et al Ann NY Acad Sci 2006;1068:327-33

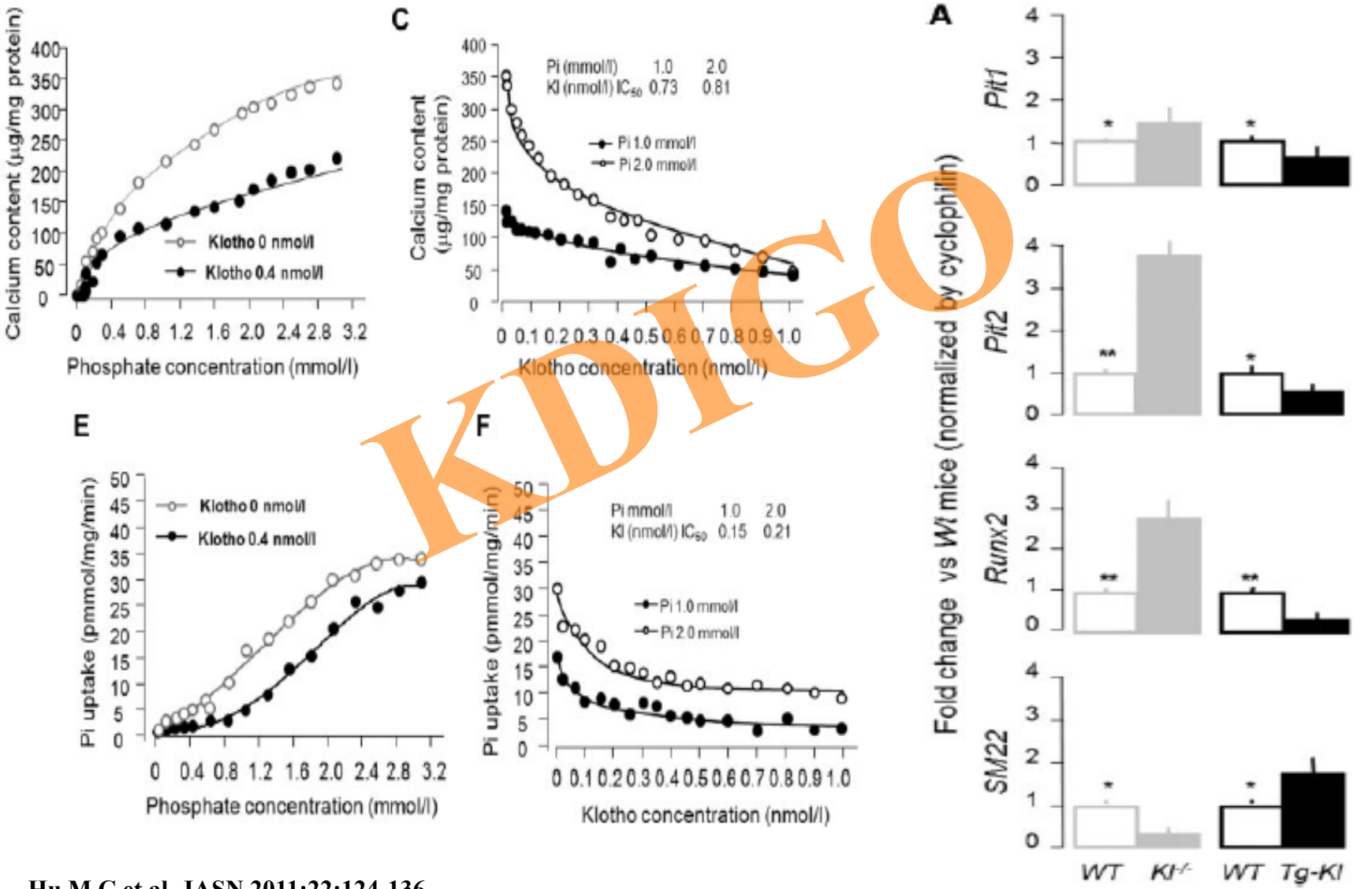


The time interval of pressure wave to and back from reflection sites

Forward and backward pressures are in phase: no time interval

Briet M et al KI 2012

Klotho regulates phosphate uptake and calcium content and VSMC dediferentiation By regulating Pit-1 and 2 and Runx2



Hu M C et al. JASN 2011;22:124-136

Final AHA RECOMMENDATION

Summary and Conclusion

While several serious efforts to understand the cost-effectiveness of CAC measurement have been made, the Committee felt that models were not, and could not be, sufficiently well grounded in data to offer results that could be used for medical decision making or establishing policy at this time.

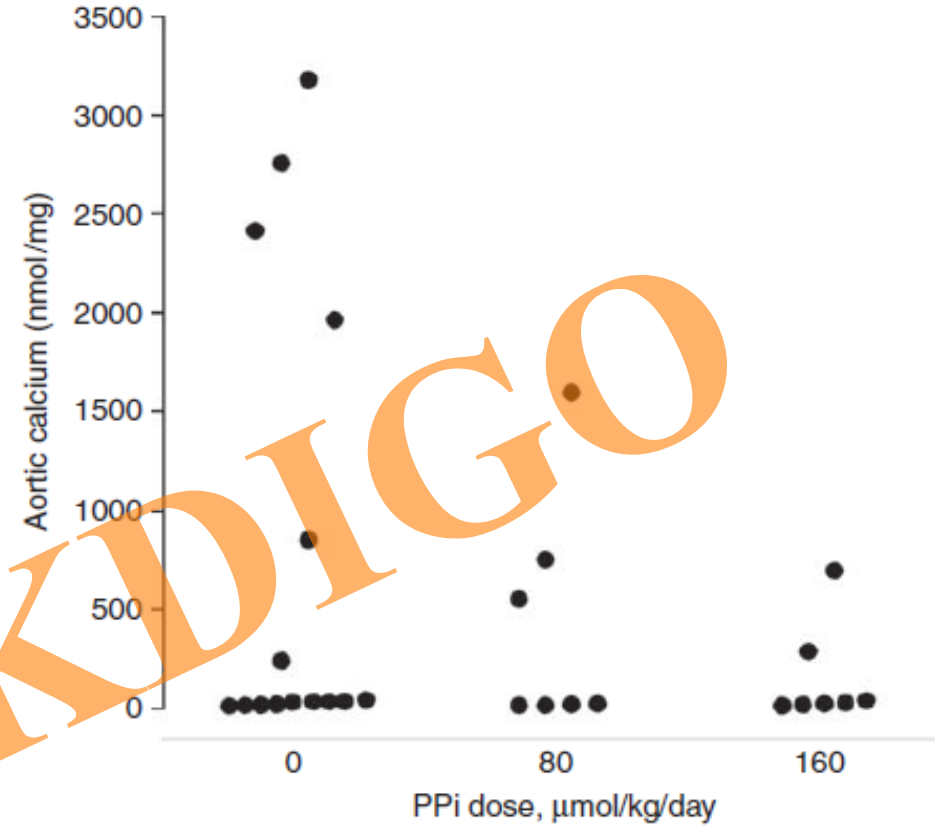
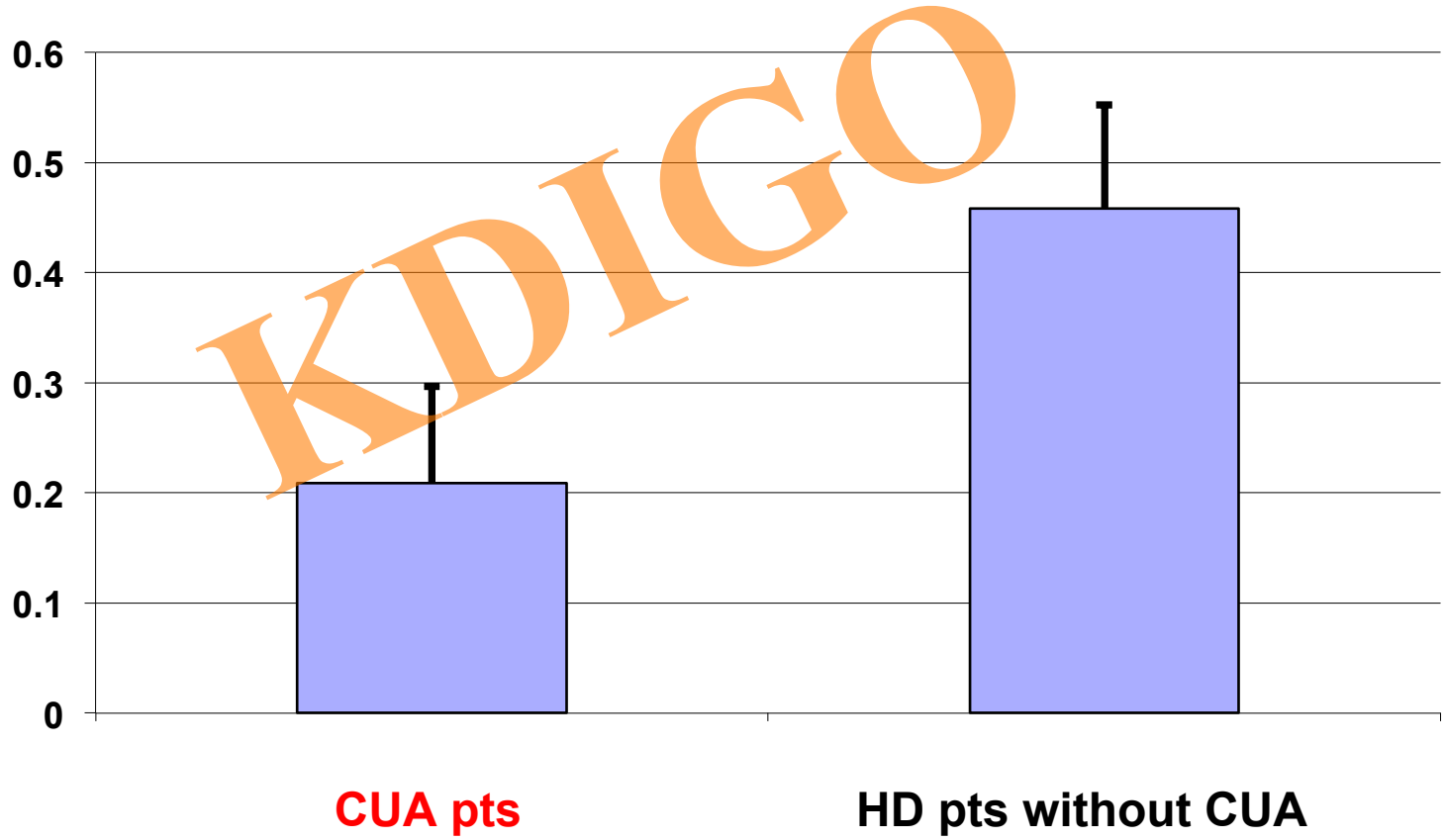


Figure 2 | Effect of pyrophosphate (PPi) on aortic calcium content in uremic rats. Rats were fed a diet consisting of 2.5% protein, 1.06% phosphorus, 0.92% calcium, and 0.75% adenine for 4 weeks and received sodium PPi in Hank's buffered saline or saline alone by daily intraperitoneal injection of 5 ml/kg. Each point represents a single animal.

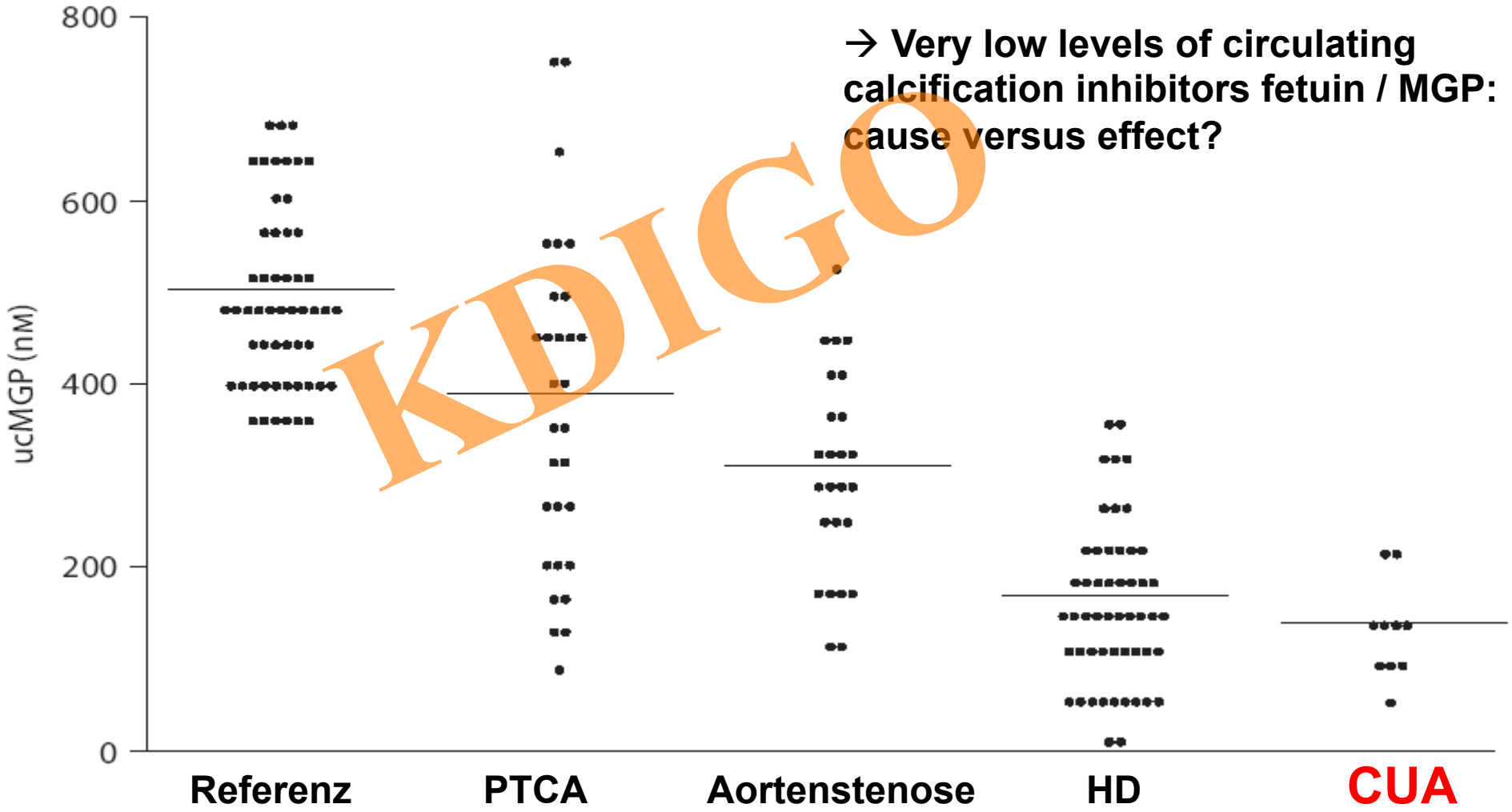
Calciphylaxis Registry:
Role of calcification inhibitors: serum Fetuin-A



Courtesy of Dr. Brandenburg V

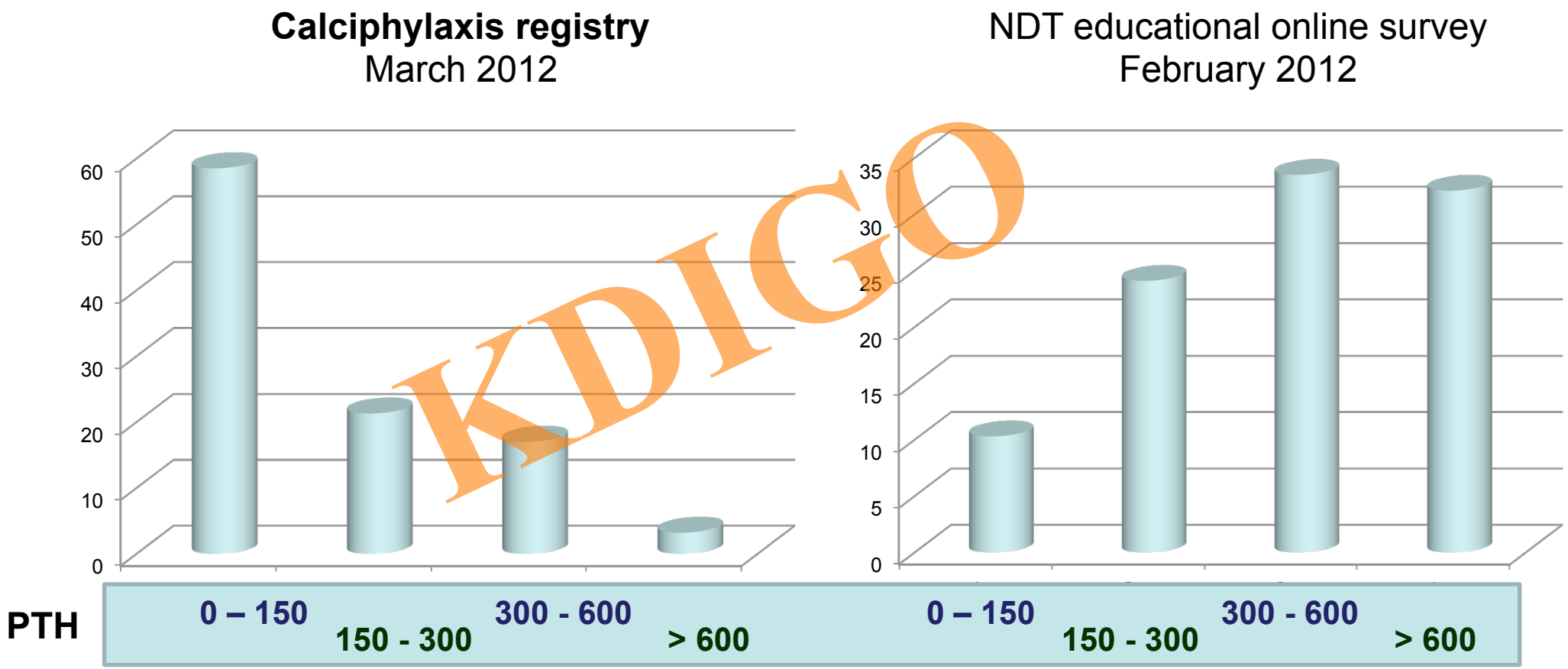
Calciphylaxis
role of calcification inhibitors: serum MGP

Cranenburg / V. Brandenburg et al. J Vasc Res 2008;45:427–436



→ Very low levels of circulating calcification inhibitors fetuin / MGP: cause versus effect?

Calciphylaxis Registry: PTH levels [pg/mL]



→ Relevant differences between perception and registry data regarding PTH levels

Courtesy of Dr. Brandenburg V

Role of vitamin K antagonist usage and CUA

Hayashi M et al; NDT 2012

A case–control study of calciphylaxis in Japanese end-stage renal disease patients

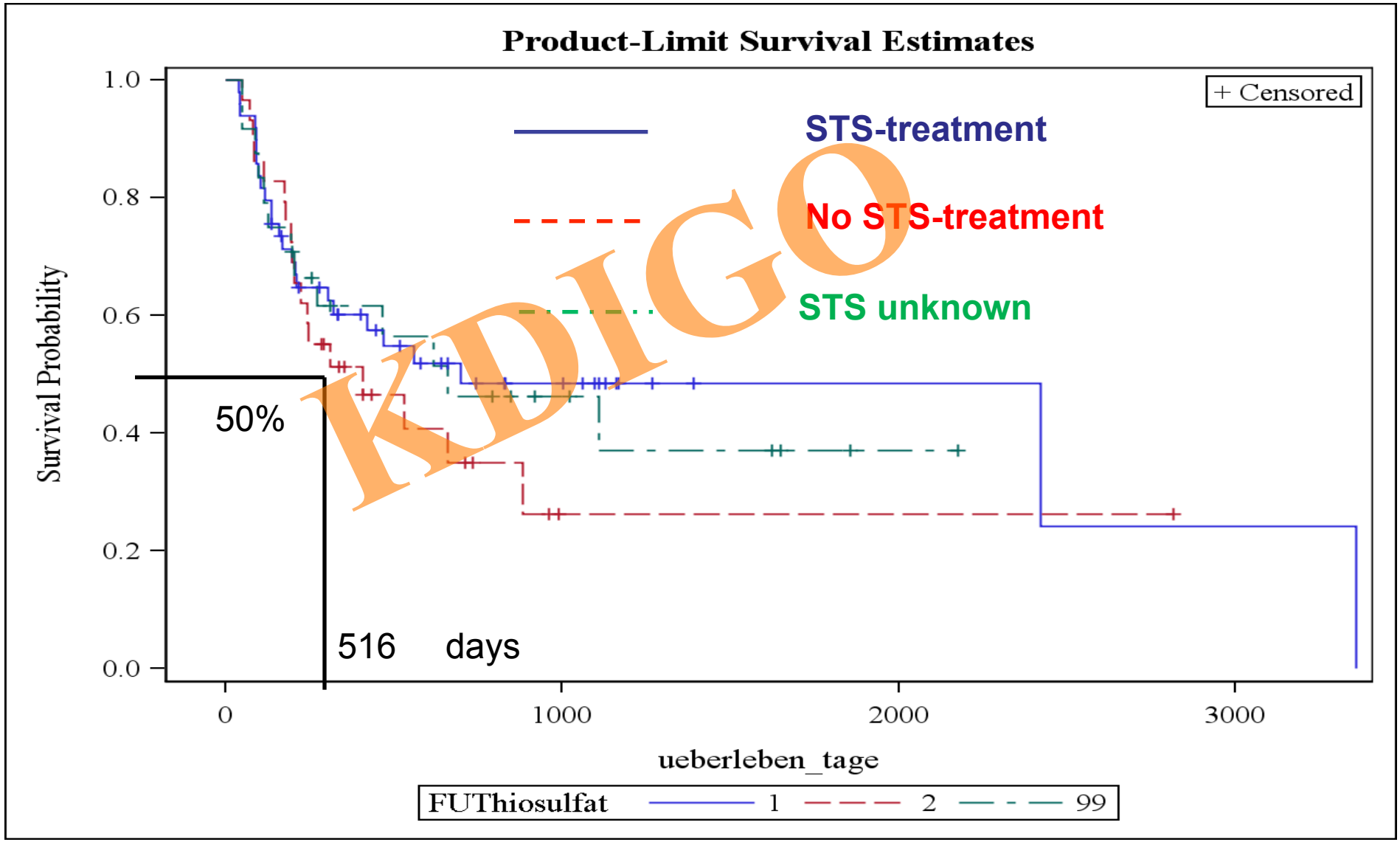
Table 4.
Results of using the multivariate logistic regression model to identify predictors of calciphylaxis at the time the diagnosis of calciphylaxis was made

	P-value	OR (95% CI)
Warfarin therapy	0.013	10.1 (1.63–62.7)
Serum albumin (for each 1 g/dL decline)	0.003	12.7 (2.35–68.6)
Plasma glucose (for each 100 mg/dL increment)	0.309	0.99 (0.97–1.01)

→ Clear association between VKA usage and calciphylaxis: Causality?

Calciphylaxis Registry: outcome

Courtesy of Dr. Brandenburg V



Calciphylaxis Registry:

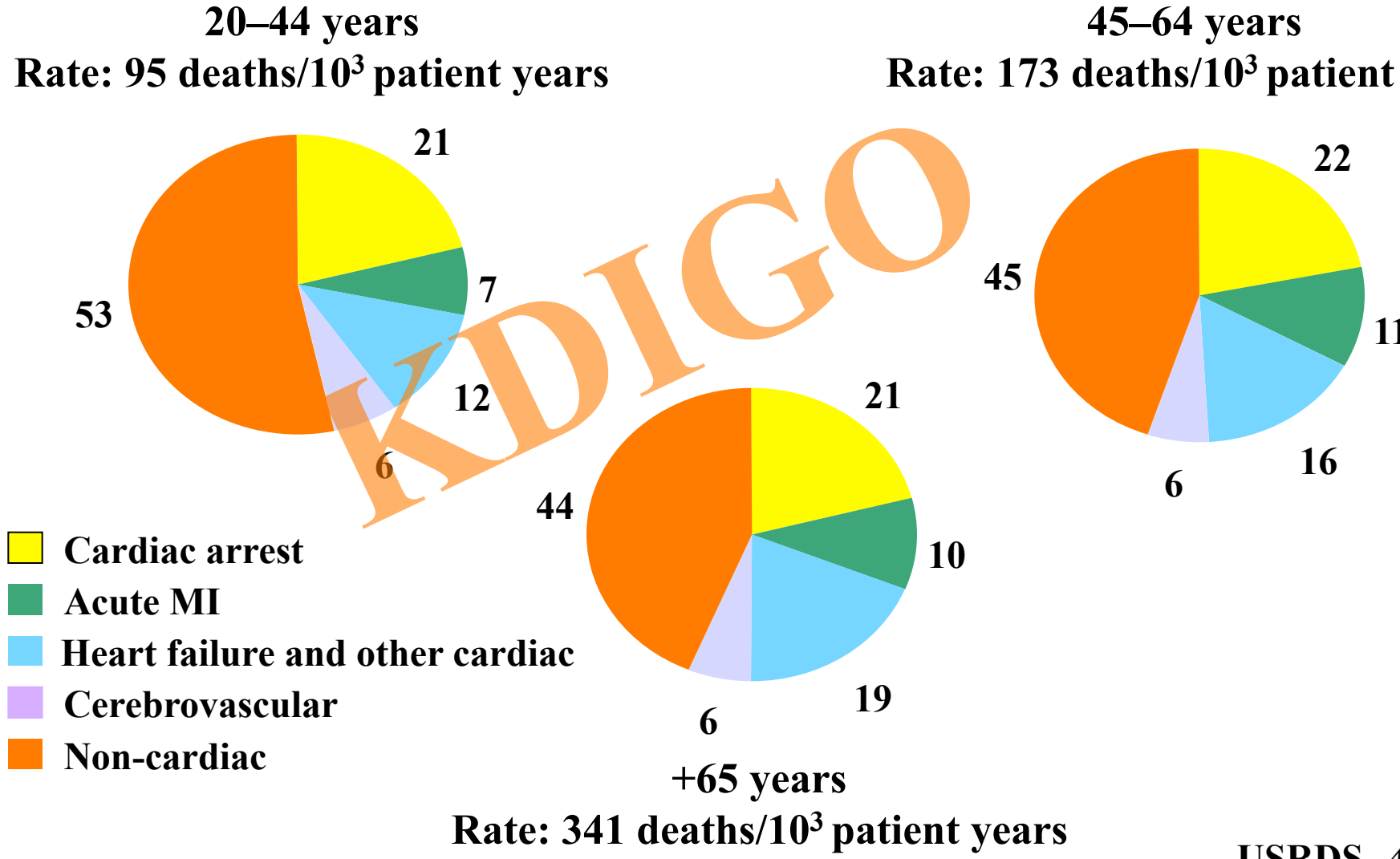
Reported treatment strategies ("state-of-the-art" therapy)

"nephrological"

- Stop calcium containing phosphate-binders
- Use calcium-free phosphate binders
- Intensify dialysis (duration, frequency)
- Lower dialysis bath calcium (e.g. to 1.00 mmol/L)
- Stop active Vitamin D
- Give Sodium thiosulfate (STS) i.v.

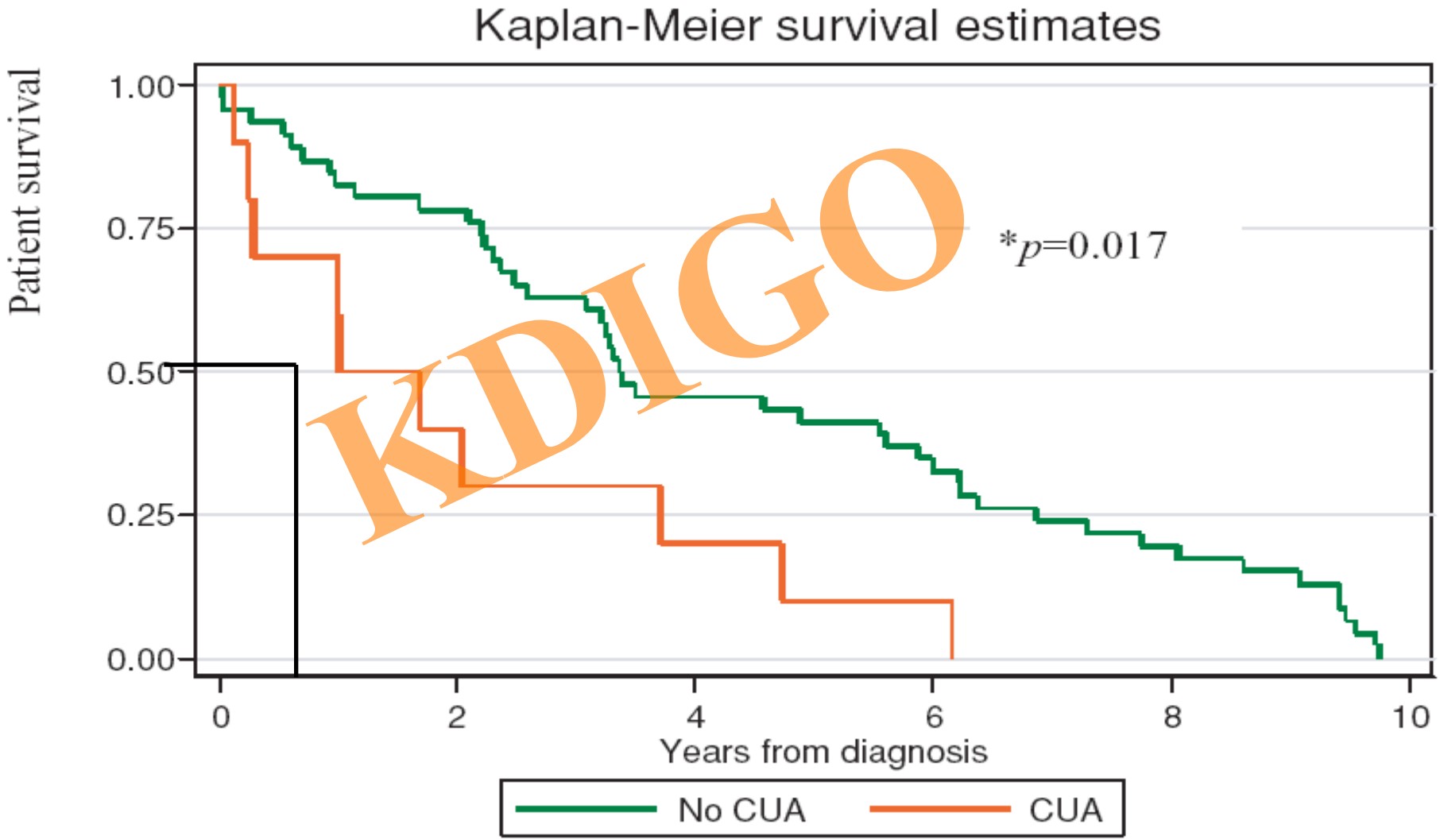
bisphosphonates
parathyroidectomy
cinacalcet
FFP infusion

Causes of death (%) for all dialysis patients by age

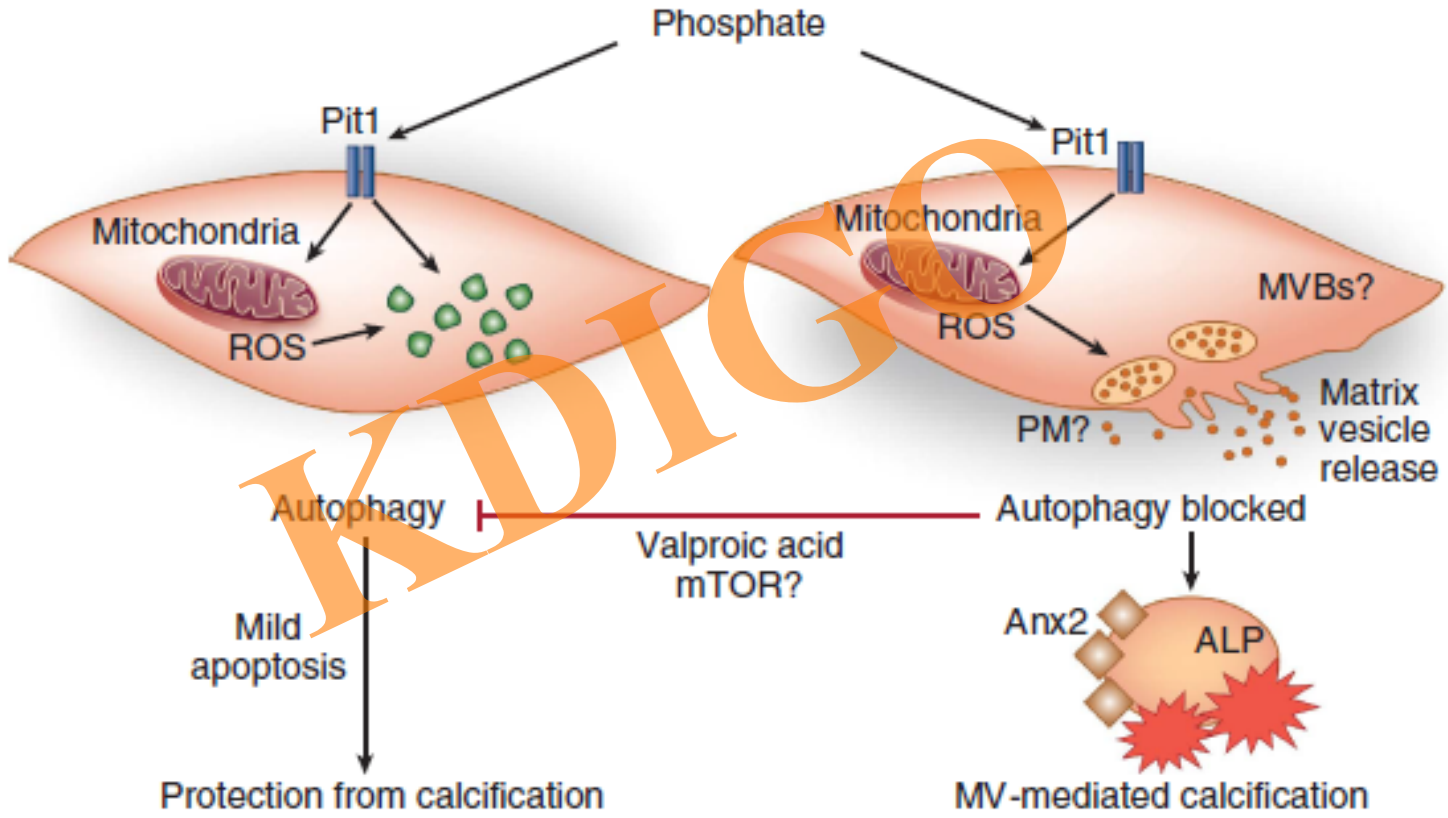


USRDS. *AJKD*, 1998

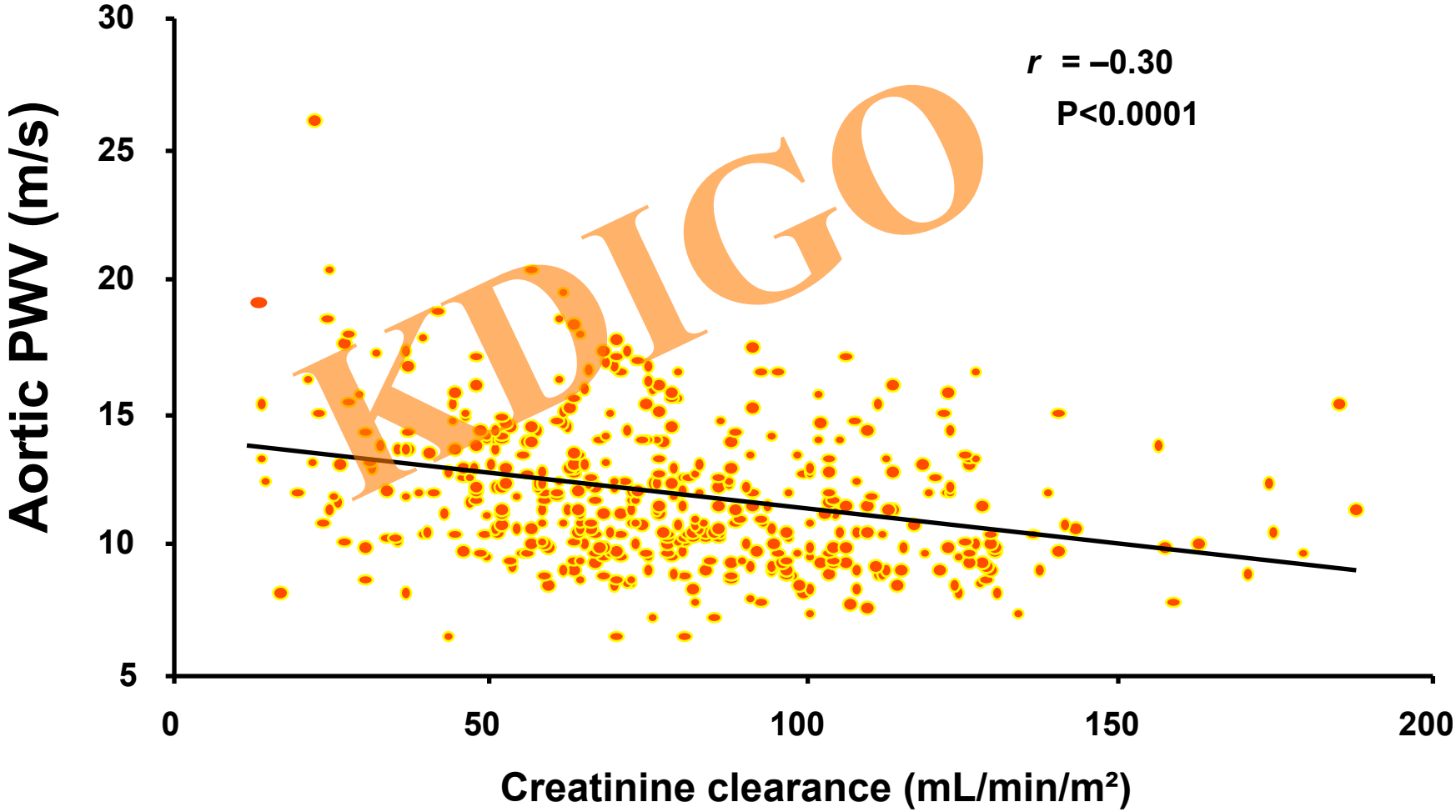
Calciphylaxis outcome literature data



A Kaplan–Meier estimate of patient survival following a diagnosis of CUA compared to control cases matched for age, modality, duration and year of commencing renal replacement therapy. Survival was significantly worse in patients diagnosed with CUA (HR for death 2.9, 95% CI 1.2–6.9, *P* = 0.017).

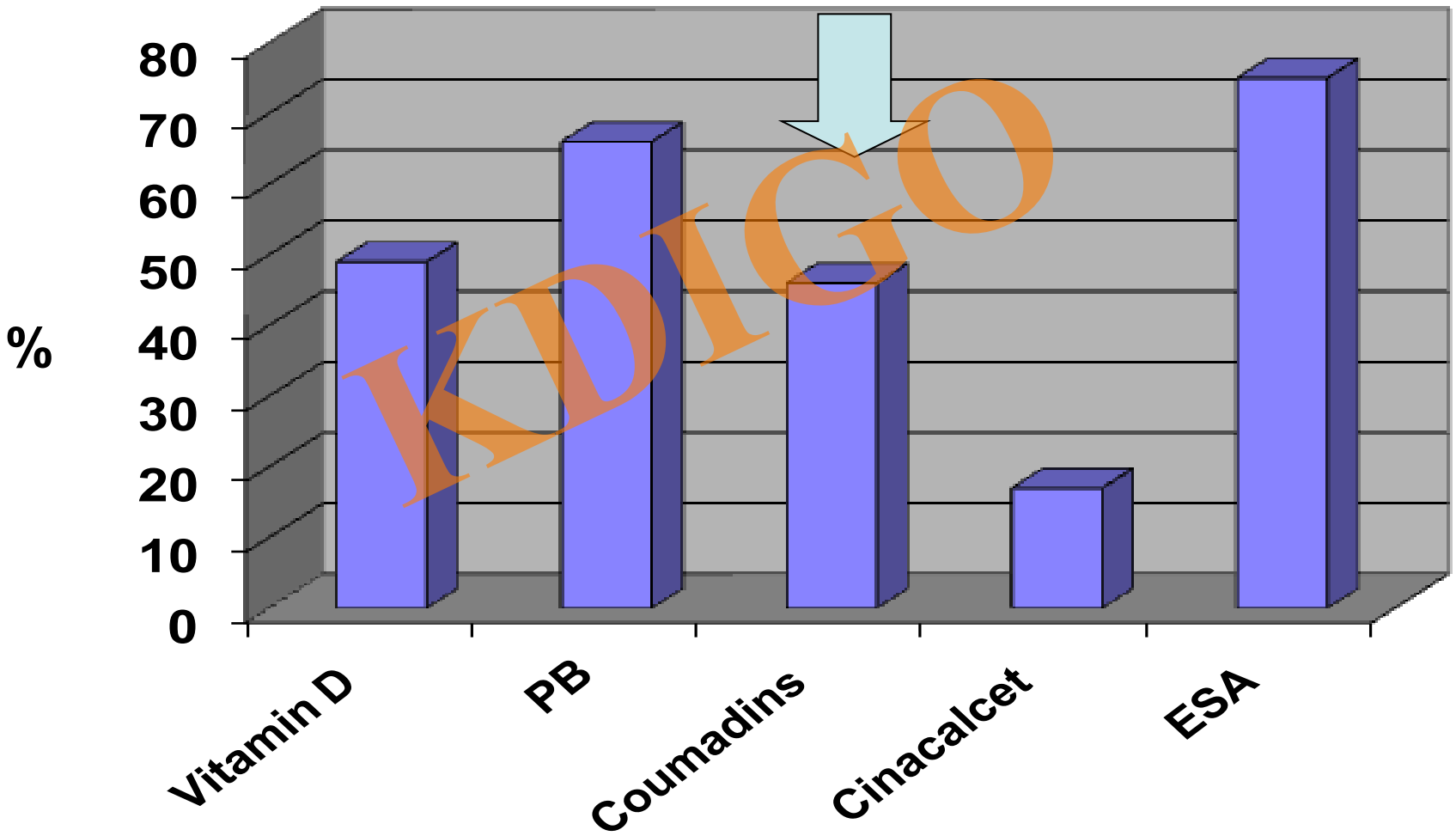

Phosphate
Pit1
Mitochondria
ROS
Pit1
Mitochondria
ROS
MVBs?
PM?
Matrix vesicle release
Autophagy
Valproic acid
mTOR?
Autophagy blocked
Mild apoptosis
Anx2
ALP
Protection from calcification
MV-mediated calcification

Correlation Between CCr (C-G formula) and Aortic PWV



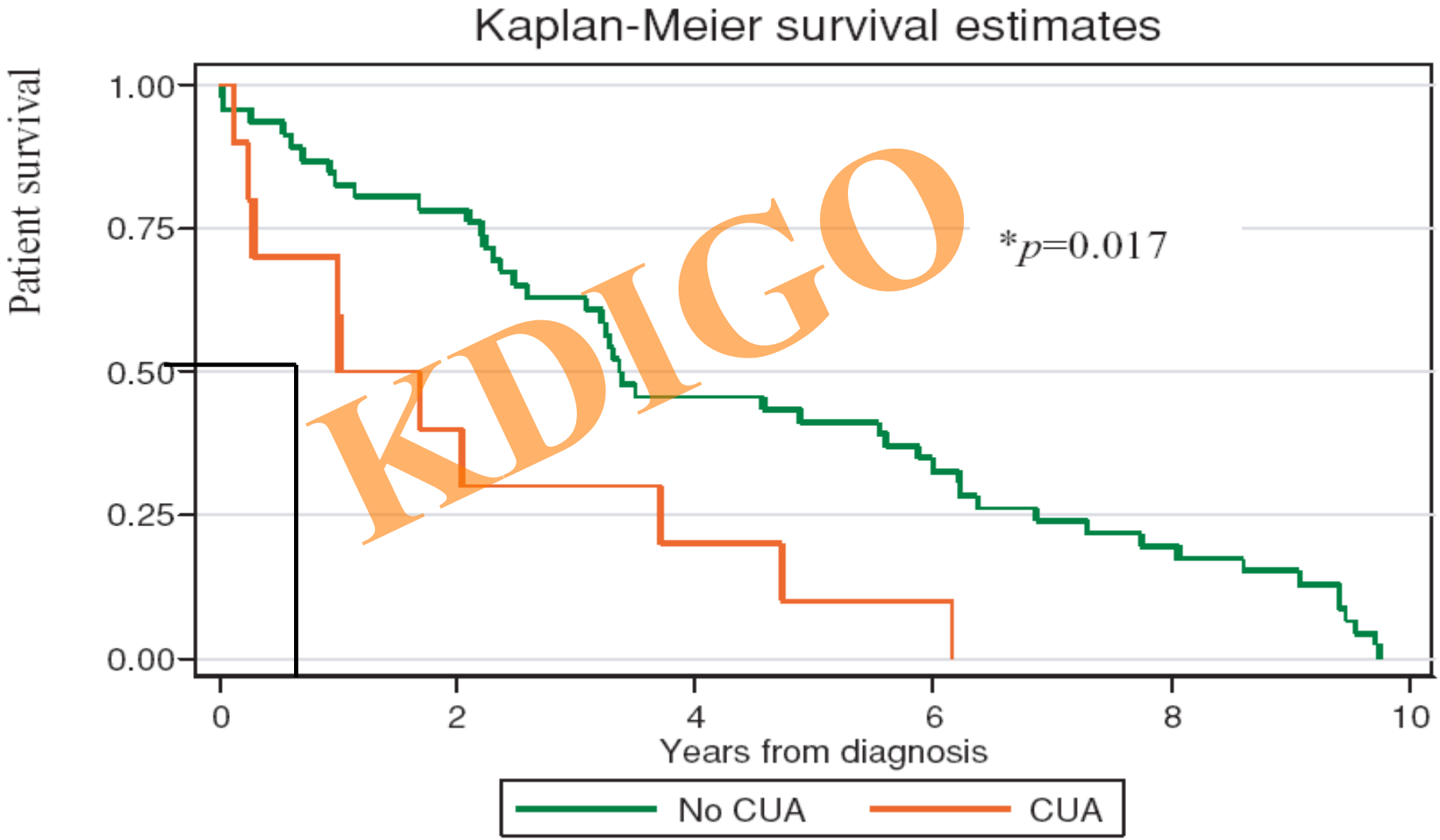
Bortolotto et al KI 2001

Calciphylaxis Registry: Co-medication [%]



Courtesy of Dr. Brandenburg V

Calciphylaxis outcome literature data

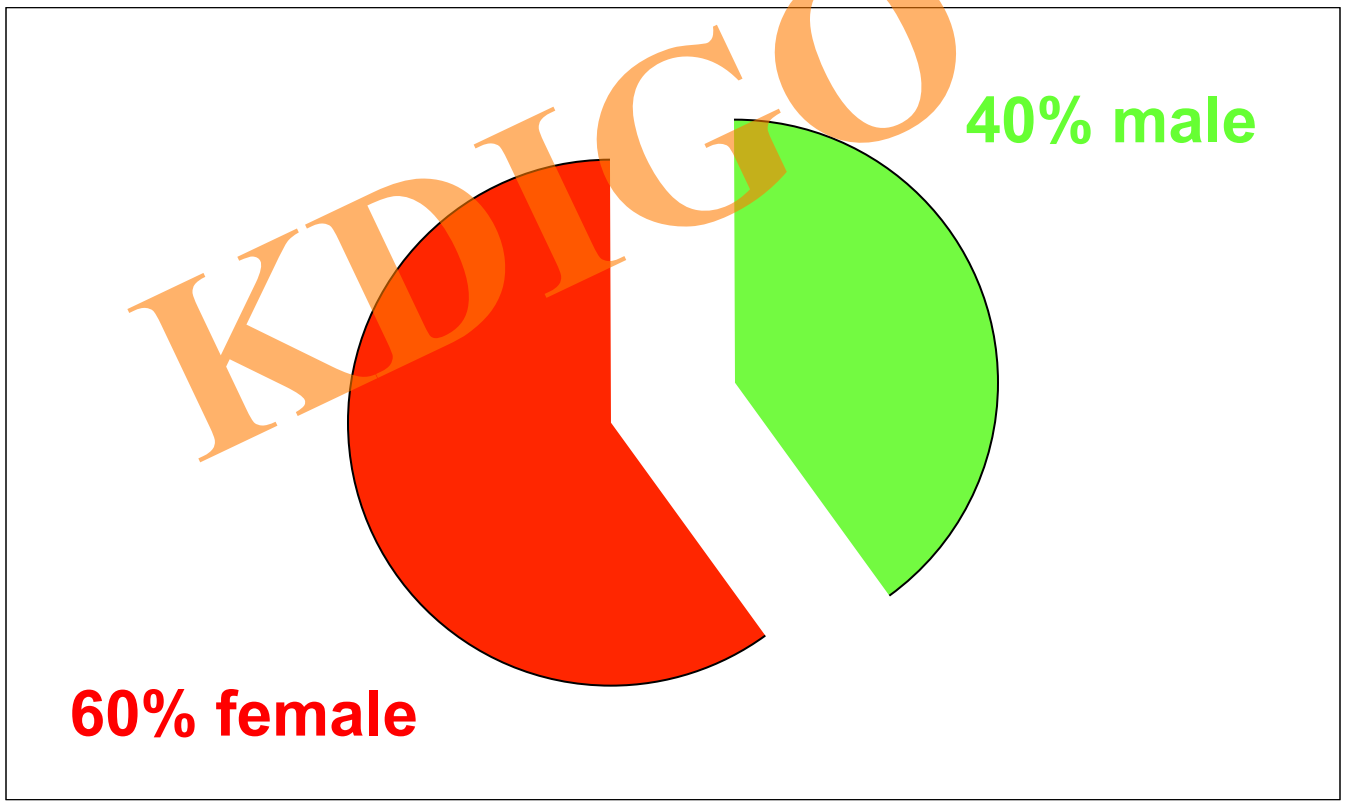


A Kaplan–Meier estimate of patient survival following a diagnosis of CUA compared to control cases matched for age, modality, duration and year of commencing renal replacement therapy. Survival was significantly worse in patients diagnosed with CUA (HR for death 2.9, 95% CI 1.2–6.9, *P* = 0.017).

Calciphylaxis Registry: Patient characteristics April 2012 (5.5

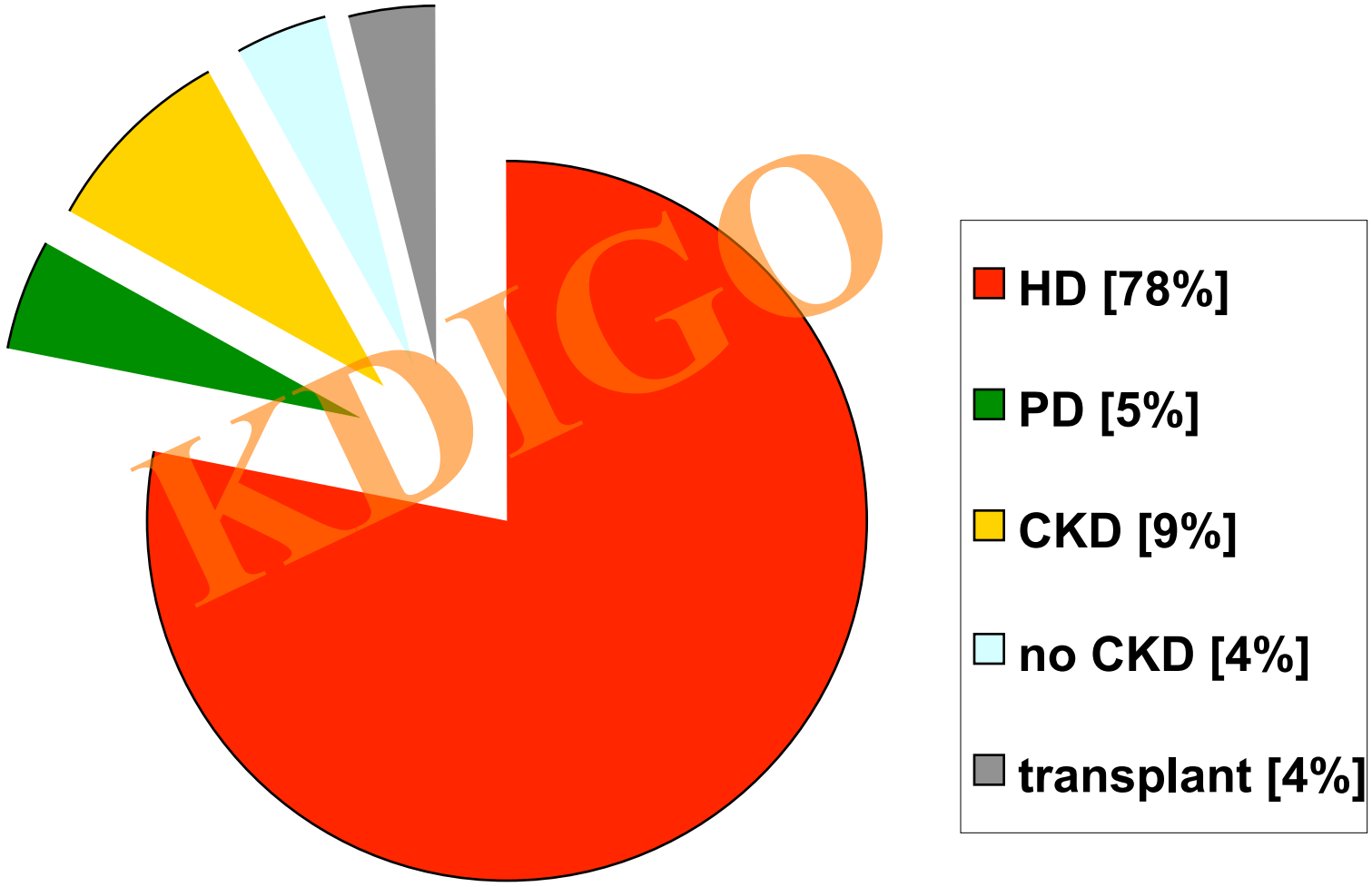
N = 144 pts
N = 27 pts / yr

median age: 69 yrs
age range: 20 – 88 yrs



Courtesy of Dr. Brandenburg V

Calciphylaxis Registry: underlying Renal Disease [%]



→vast majority of registered pts are hemodialysis pts

Courtesy of Dr. Brandenburg V

Activation of Vascular Smooth Muscle Parathyroid Hormone Receptor Inhibits Wnt/β-Catenin Signaling and Aortic Fibrosis in Diabetic Arteriosclerosis

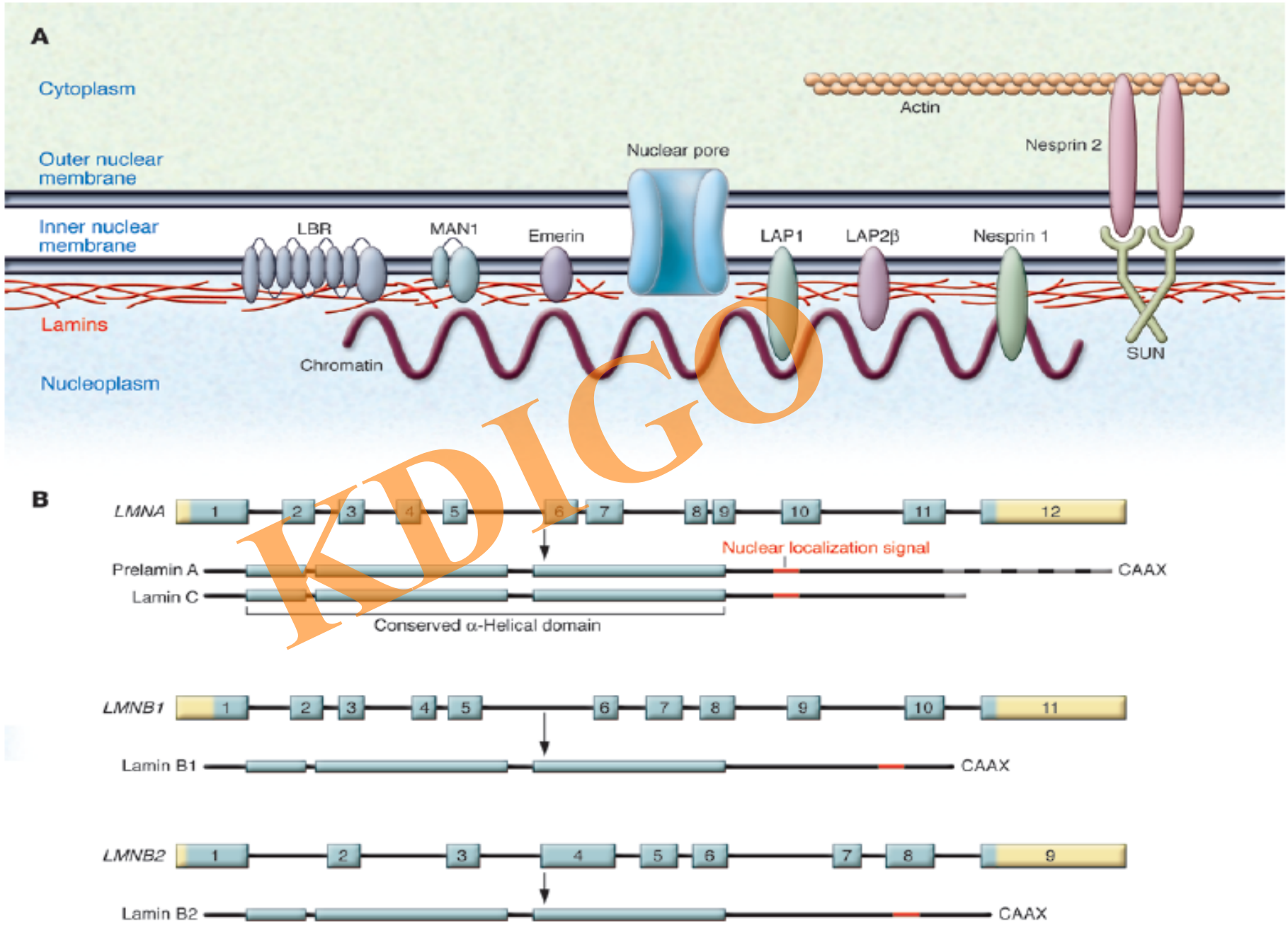
Su-Li Cheng, Jian-Su Shao, Linda R. Halstead, Kathryn Distelhorst, Oscar Sierra, Dwight A. Towler

Rationale: Vascular fibrosis and calcification contribute to diabetic arteriosclerosis, impairing Windkessel physiology necessary for distal tissue perfusion. Wnt family members, upregulated in arteries by the low-grade inflammation of "diabesity," stimulate type I collagen expression and osteogenic mineralization of mesenchymal progenitors via β-catenin. Conversely, parathyroid hormone (PTH) inhibits aortic calcification in low-density lipoprotein receptor (LDLR)-deficient mice fed high fat diabetogenic diets (HFD).

Objective: We sought to determine the impact of vascular PTH receptor (PTH1R) activity on arteriosclerotic Wnt/β-catenin signaling in vitro and in vivo. We generated SM-caPTH1R transgenic mice, a model in which the constitutively active PTH1R variant H223R (caPTH1R) is expressed only in the vasculature.

Methods and Results: The caPTH1R inhibited Wnt/β-catenin signaling, collagen production, and vascular smooth muscle cell proliferation and calcification in vitro. Transgenic SM-caPTH1R;LDLR$^{+/-}$ mice fed HFD develop diabesity, with no improvements in fasting serum glucose, cholesterol, weight, body composition, or bone mass versus LDLR$^{+/-}$ siblings. SM-caPTH1R downregulated aortic *Col1A1*, *Runx2*, and *Nox1* expression without altering *TNF*, *Msx2*, *Wnt7a/b*, or *Nox4*. The SM-caPTH1R transgene decreased aortic β-catenin protein accumulation and signaling in diabetic LDLR$^{+/-}$ mice. Levels of aortic superoxide (a precursor of peroxide that activates pro–matrix metalloproteinase 9 and osteogenic signaling in vascular smooth muscle cells) were suppressed by the SM-caPTH1R transgene. Aortic calcification, collagen accumulation, and wall thickness were concomitantly reduced, enhancing vessel distensibility.

Conclusions: Cell-autonomous vascular smooth muscle cell PTH1R activity inhibits arteriosclerotic Wnt/β-catenin signaling and reduces vascular oxidative stress, thus limiting aortic type I collagen and calcium accrual in diabetic LDLR-deficient mice. (*Circ Res*. 2010;107:271-282.)



Worman AJ et al. JCI 2009;119:1825

Angiotensin II and Aldosterone Regulate Gene Transcription Via Functional Mineralocortocoid Receptors in Human Coronary Artery Smooth Muscle Cells

Iris Z. Jaffe and Michael E. Mendelsohn

Circ Res. 2005;96:643-650

Aldosterone Regulates Endogenous Gene Expression in Human Vascular Smooth Muscle Cells

Gene	Molecular Function	Microarray Fold Change	Q-RT-PCR Fold Change	Q-RT-PCR *P* Value
Collagen type I	Pro-fibrotic, vascular calcification	3.3	2	<0.05
Collagen type III	Pro-fibrotic	1.6	1.9	<0.05
Parathyroid hormone receptor 2 (PTHR2)	Vascular calcification	2.1	3.1	<0.001
Bone morphogenetic protein 2 (BMP2)	Vascular calcification	2.1	3	0.01
Alkaline phosphatase	Vascular calcification	1.5*	2*	0.003
IL-16 (lymphocyte chemoattractant factor)	Immune response/inflammation	1.7	1.8	0.056
Cytotoxic T-lymphocyte–associated protein 4 (CTLA4)	Immune response/inflammation	1.9*	2.1*	0.076
Aldosterone synthase	Aldosterone production	Not detected	Not detected	—
NaK ATPase	Renal ion transport	Unchanged	—	—
Epithelial sodium channel (ENaC)	Renal ion transport	Not detected	—	—

Downregulation of Bone Morphogenetic Protein 4 Expression in Coronary Arterial Endothelial Cells

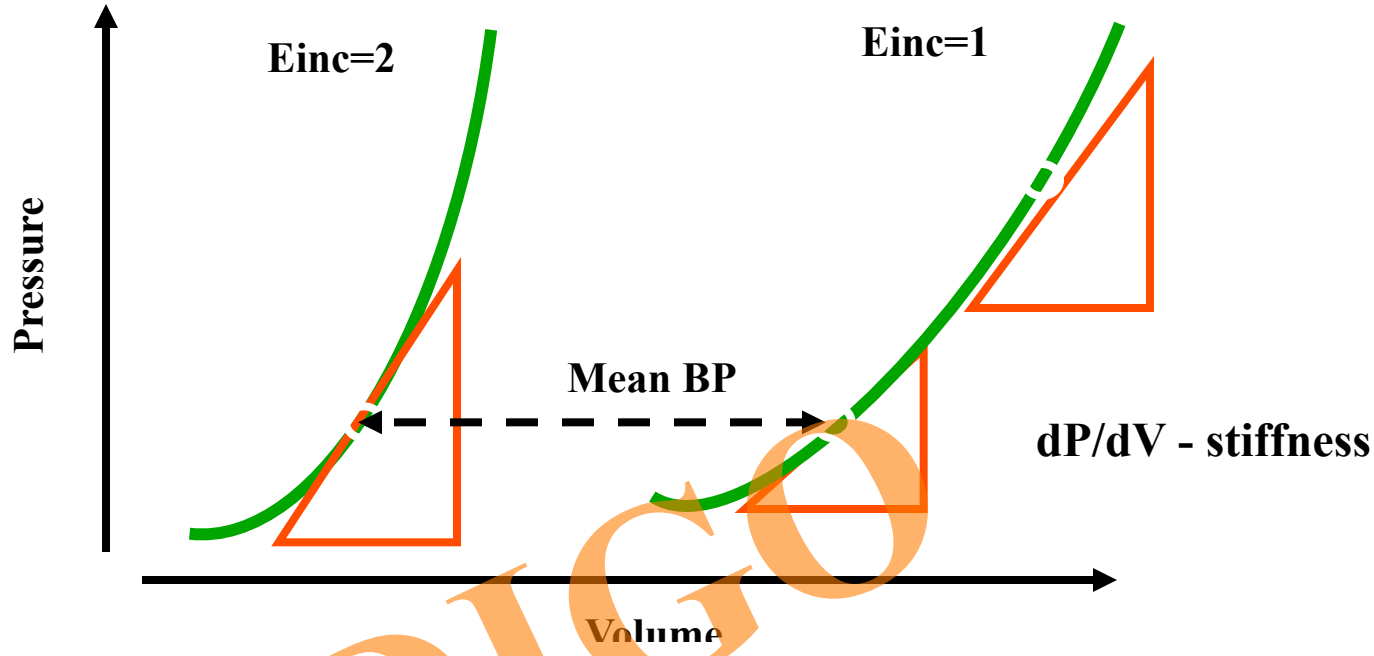
Role of Shear Stress and the cAMP/Protein Kinase A Pathway

Anna Csiszar, Nazar Labinskyy, Kira E. Smith, Aracelie Rivera, Erik N.T.P. Bakker, Hanjoong Jo, Jason Gardner, Zsuzsanna Orosz, Zoltan Ungvari

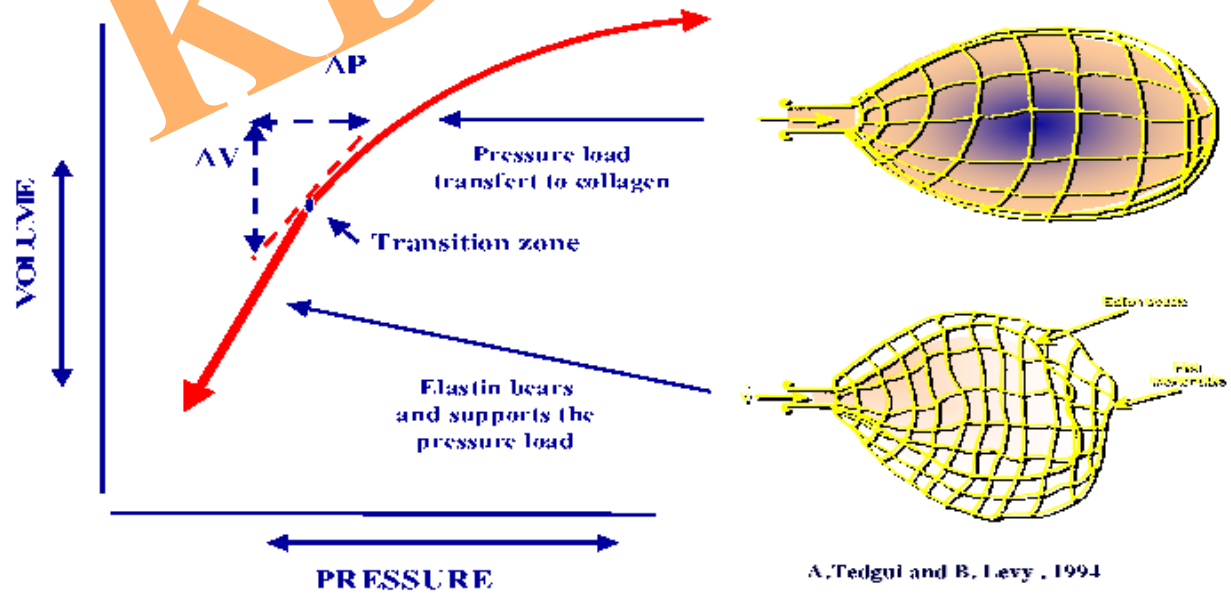
Objective—Bone morphogenetic protein 4 (BMP-4) is a transforming growth factor β family member cytokine that exerts proinflammatory effects on the endothelium and is likely to play a role in atherogenesis. Recent studies suggested that atheroprotective levels of shear stress control endothelial BMP-4 expression; however, the underlying mechanisms remained unknown.

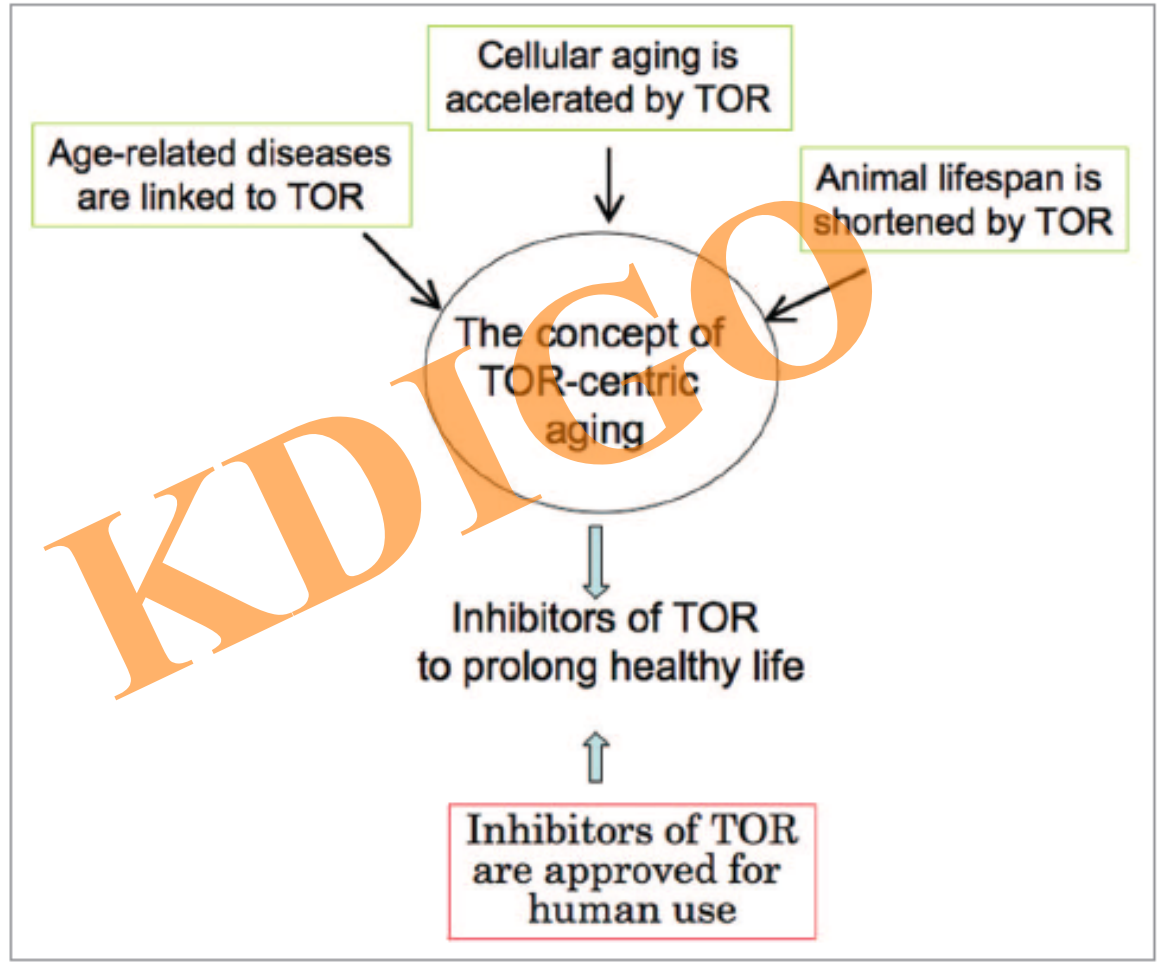
Methods and Results—We found that shear stress downregulated BMP-4 expression in human and rat coronary arterial endothelial cells (CAECs) as well as in cultured mesenteric arterioles, although it had no effect on the expression of BMP-2, a related cytokine. In human coronary arterial endothelial cells, 8-bromo-cAMP, the adenylate cyclase activator forskolin, or a cAMP-dependent protein kinase (PKA) activator effectively decreased BMP-4 expression, mimicking the effects of shear stress. Indeed, shear stress induced the nuclear translocation of PKA-c, and inhibition of PKA attenuated the effects of shear stress and forskolin on BMP-4 expression. RNA decay assay and BMP-4 promoter-driven luciferase reporter gene assay showed that cAMP regulates BMP-4 expression at the transcriptional level.

Conclusions—Laminar shear stress and the cAMP/PKA pathway are important negative regulators of BMP-4 expression in the vascular endothelium. Because BMP-4 elicits endothelial activation and dysfunction, hypertension, and vascular calcification, inhibition of BMP-4 expression by shear stress and the cAMP/PKA pathway is likely to exert antiatherogenic and vasculoprotective effects. (***Arterioscler Thromb Vasc Biol.*** **2007;27:776-782.**)



The arterial wall is a heterogeneous material

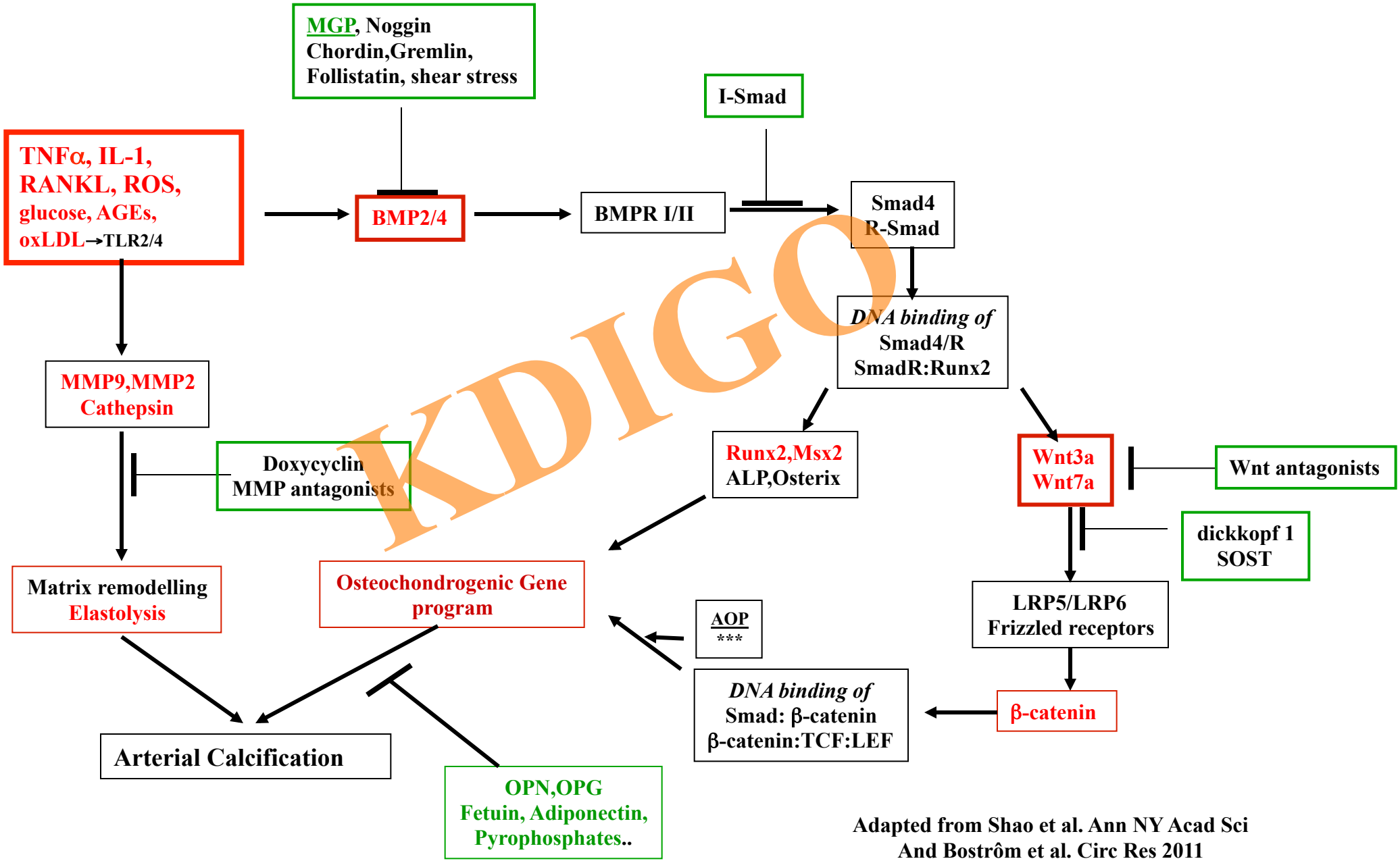




Mikhail V. Blagosklonny Cell Cycle 9:24, 4788-4794; December 15, 2010;

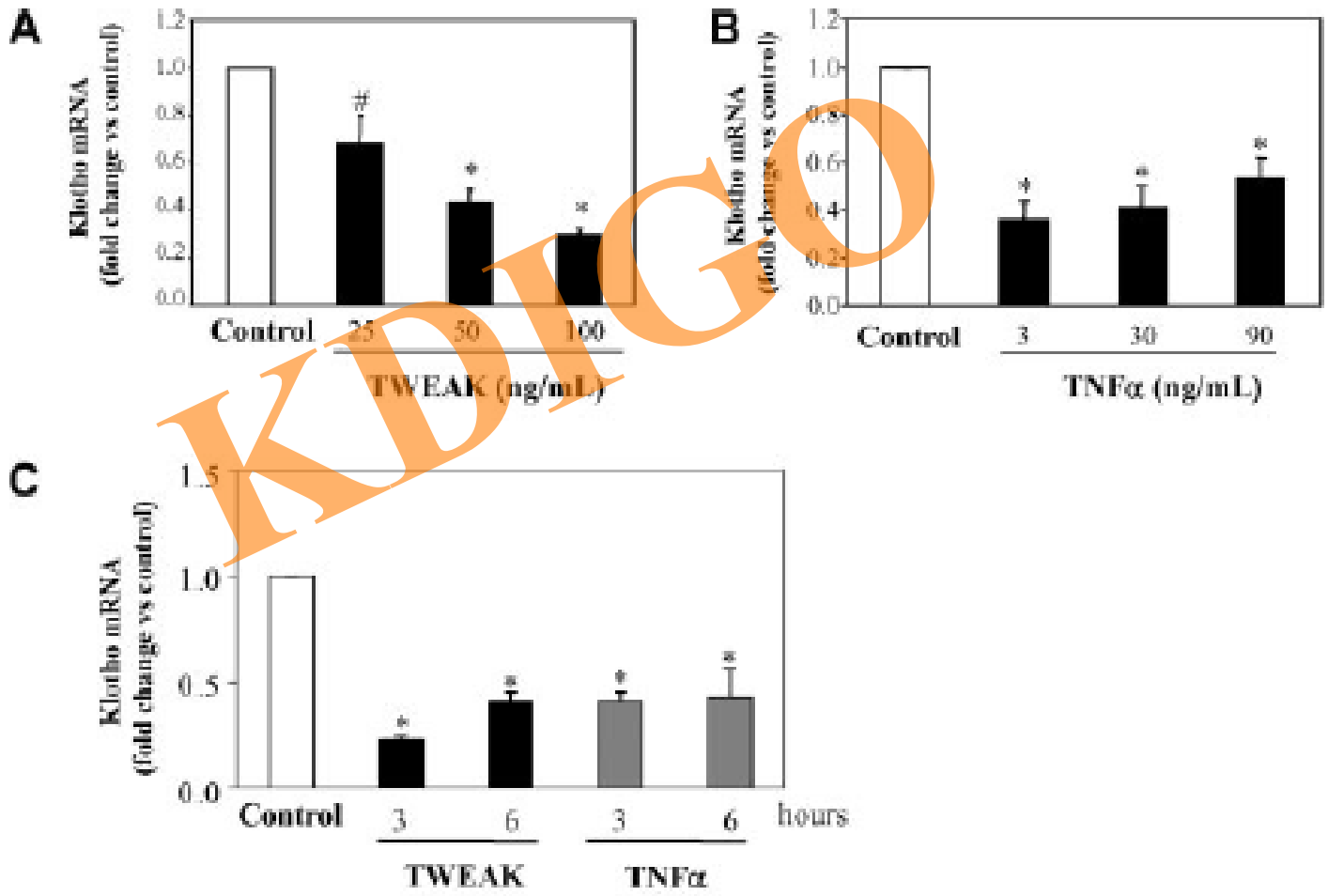
BMP- Msx2-Wnt signaling in arterial calcifications

AOP *** (Accentuated Osteogenic Program)



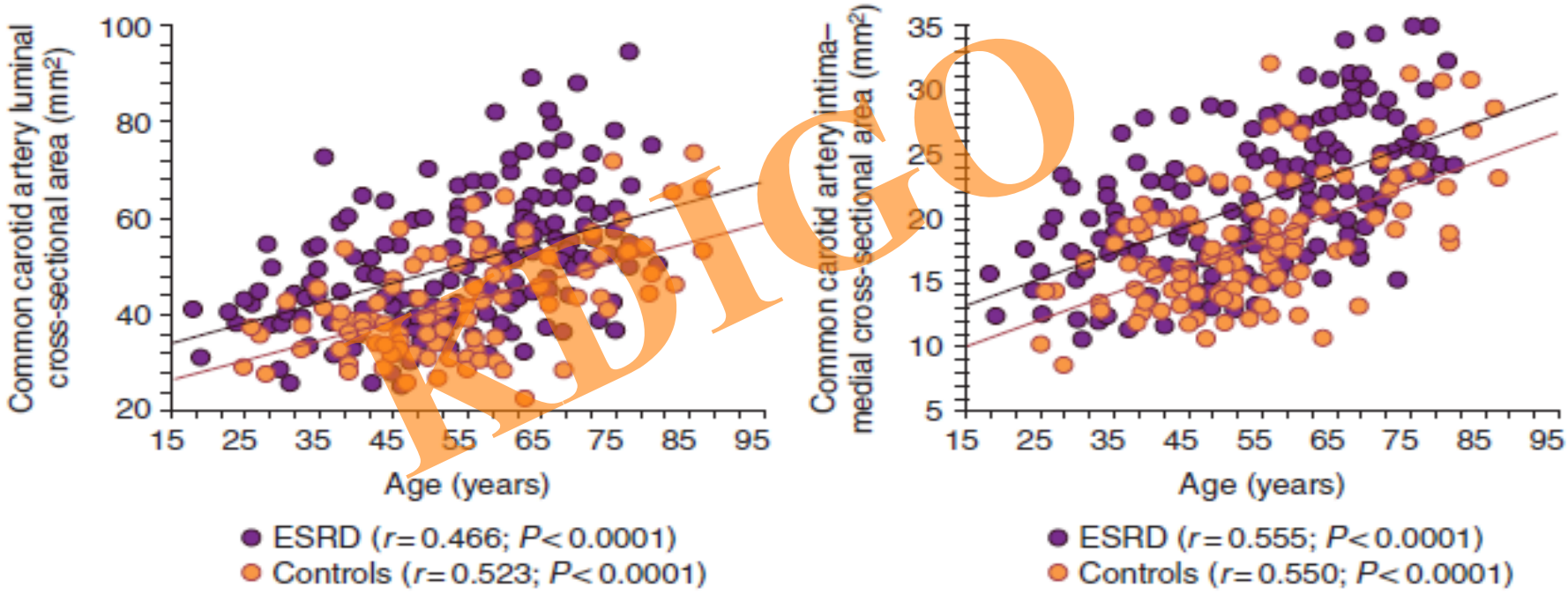
Adapted from Shao et al. Ann NY Acad Sci
And Bostrôm et al. Circ Res 2011

F
ir **Figure 5.** Inflammatory cytokines decrease Klotho expression in cultured tubular cells in an NFκB-dependent manner. TWEAK (A) and TNFα (B) decrease Klotho mRNA

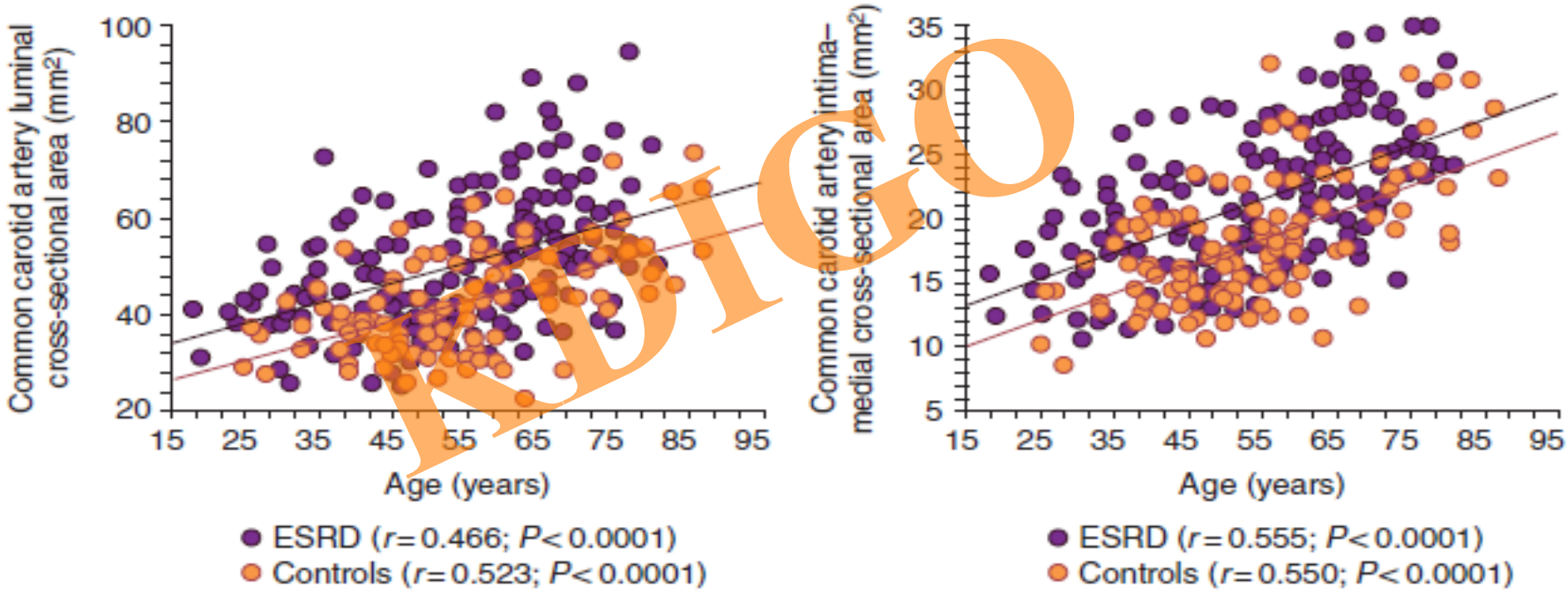


TWEAK: TNF-like weak inducer of apoptosis

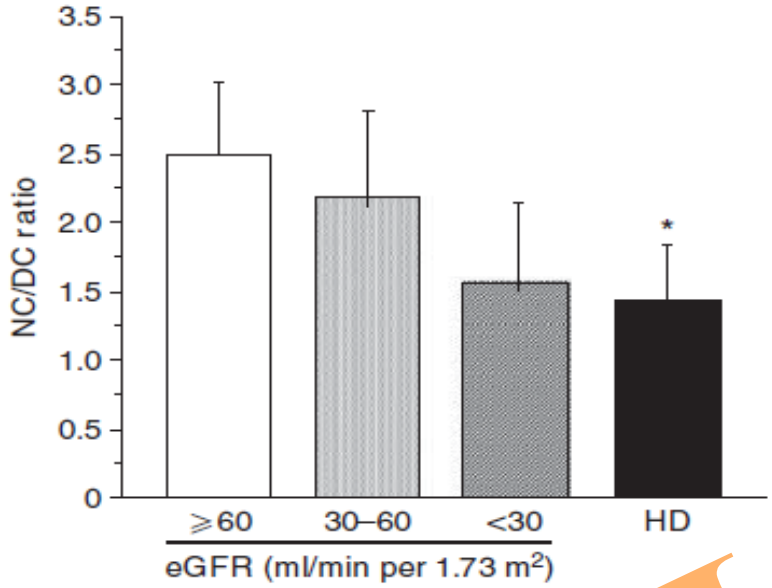
Moreno JA et al JASN 2011;22:1315

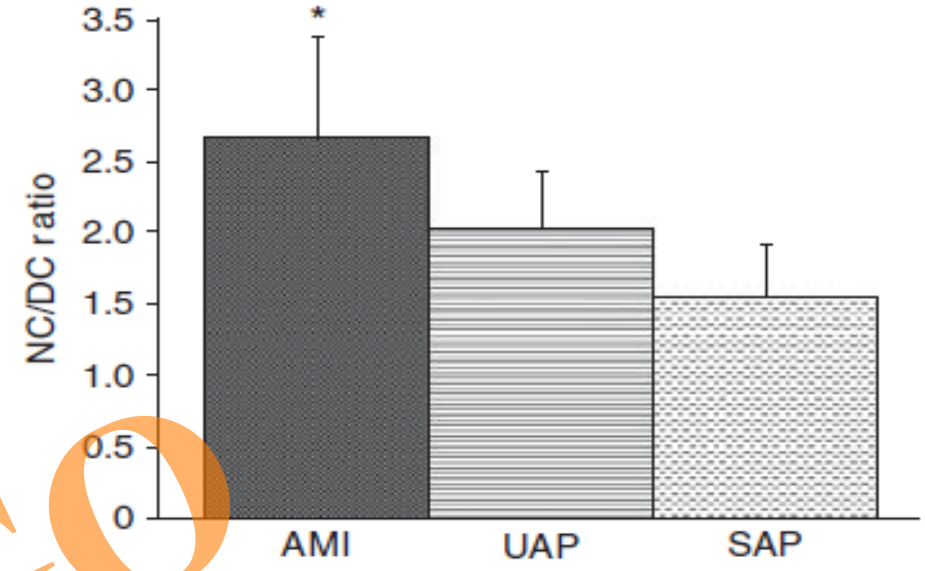


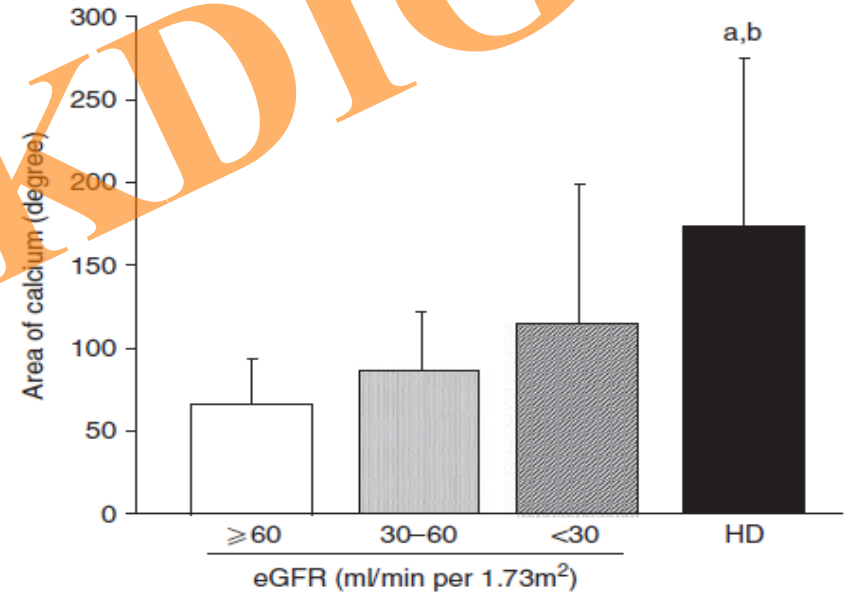
Briet M et al. KI 2011



Briet M et al. KI 2011

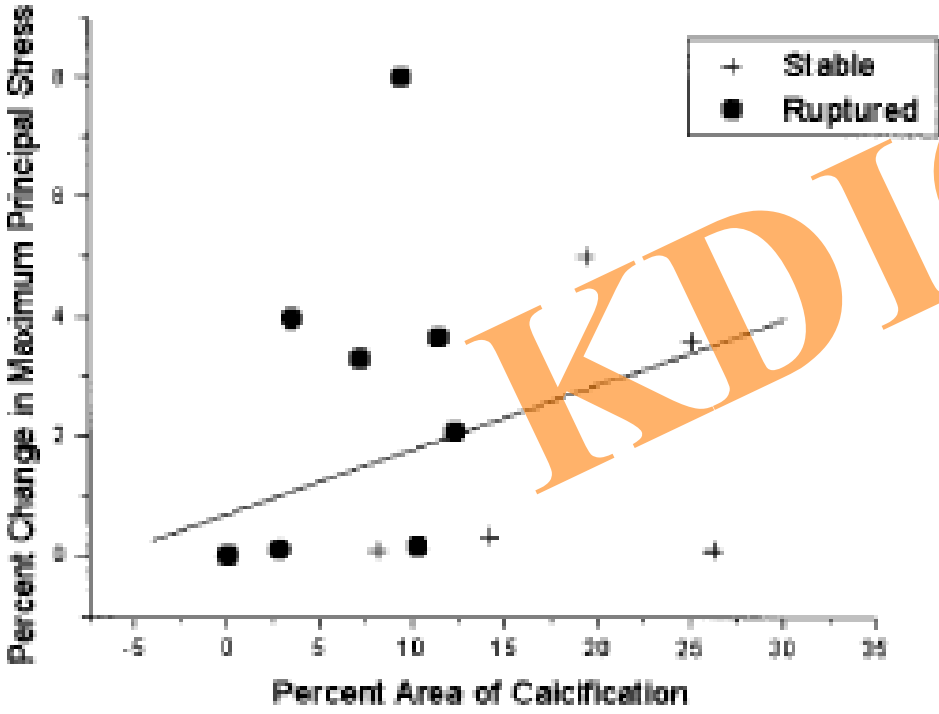


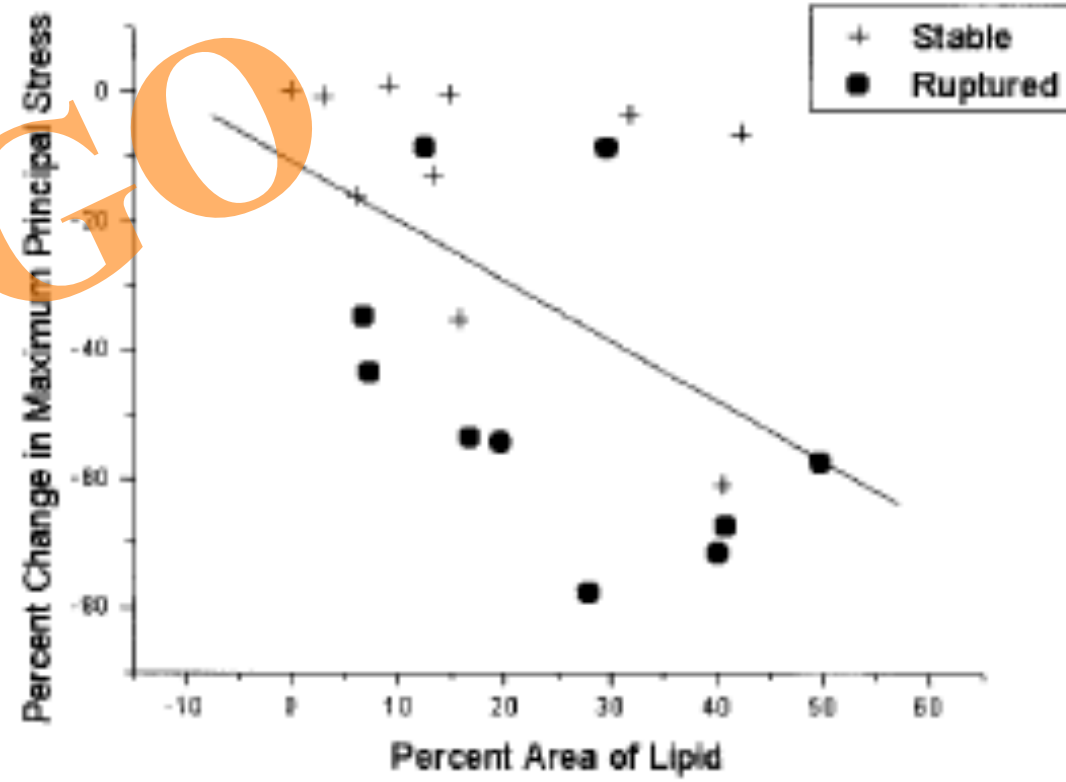




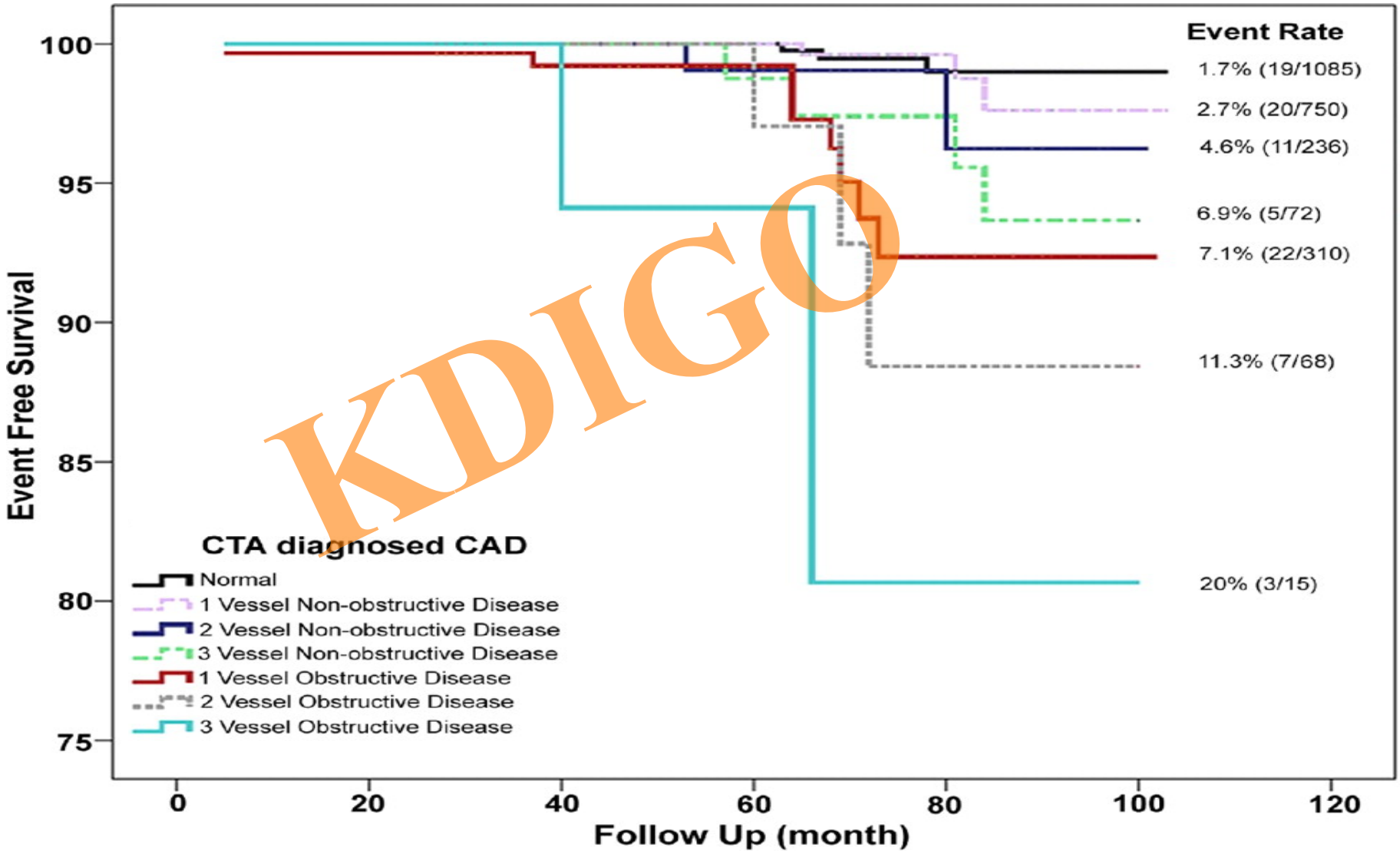
NC/DC –necrotic core/dense calcium
AMI-acute myoc.inf; UAP-unstable ang.pect.
SAP-stable ang.pect

Kono K et al. KI 2012;82:344-51


Stable
Ruptured
Percent Change in Maximum Principal Stress
Percent Area of Calcification
-5
0
5
10
15
20
25
30
35


Stable
Ruptured
Percent Change in Maximum Principal Stress
Percent Area of Lipid
0
-20
-40
-60
-80
-10
0
10
20
30
40
50
60

Prognostic factors for mortality evaluated by coronary scan: Degree of stenosis; Proximal localisation ; Number of vessels



Ostrom . JACC. 2008
Min. JACC 2007

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Should Coronary Calcium Screening Be Used in Cardiovascular Prevention Strategies?

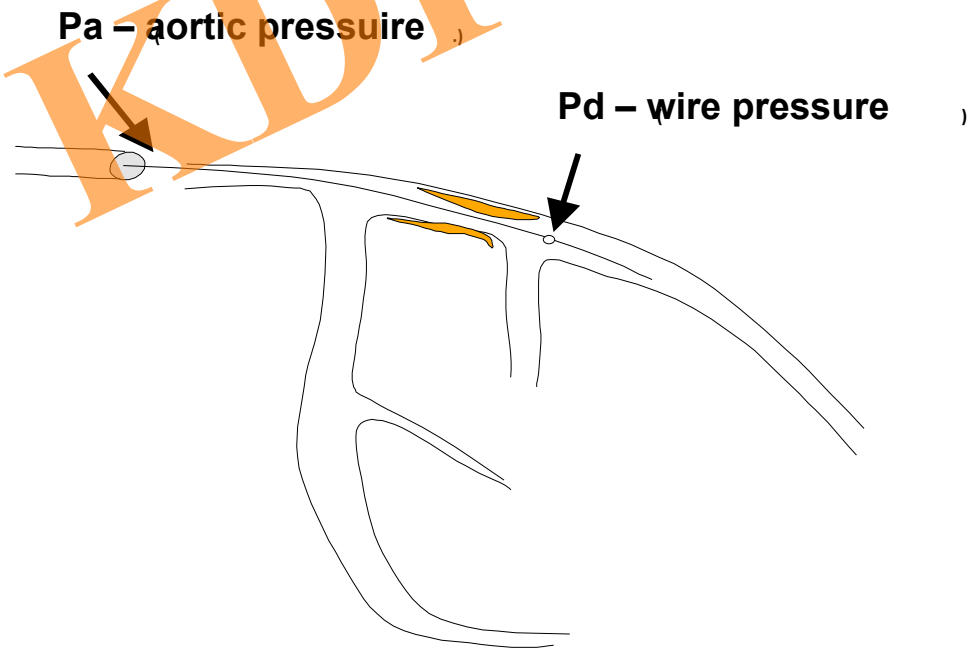
Robert O. Bonow, M.D.

CONCLUSIONS AND RECOMMENDATIONS

A broad population-based strategy of CAC screening does not appear to be warranted. It is not clear whether it is reasonable to consider CAC scanning in persons whose global risk assessment places them in the intermediate-risk category or whether the findings from such testing will lead to a beneficial increase in the intensity of treatment. This issue needs to be addressed in future trials focusing on clinical outcomes and cost-effectiveness.

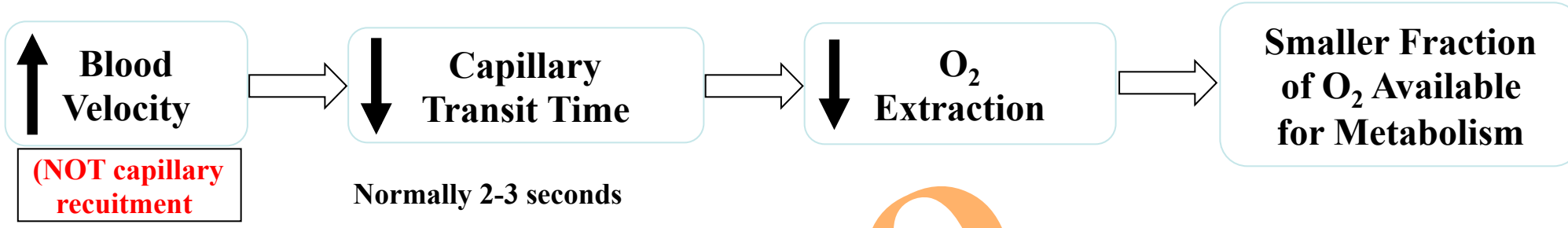
The concept of fractional flow reserve (FFR). $Q^S max$: hyperemic myocardial blood flow in the presence of a stenosis, $Q^N max$: normal hyperemic myocardial blood flow, Pd: distal coronary pressure, Pa: aortic pressure, Pv: venous pressure, R: hyperemic myocardial resistance.

$$FFR = \frac{Q^S_{max}}{Q^N_{max}} = \frac{(Pd-Pv)/R}{(Pa-Pv)/R} = \frac{P_d}{P_a}$$

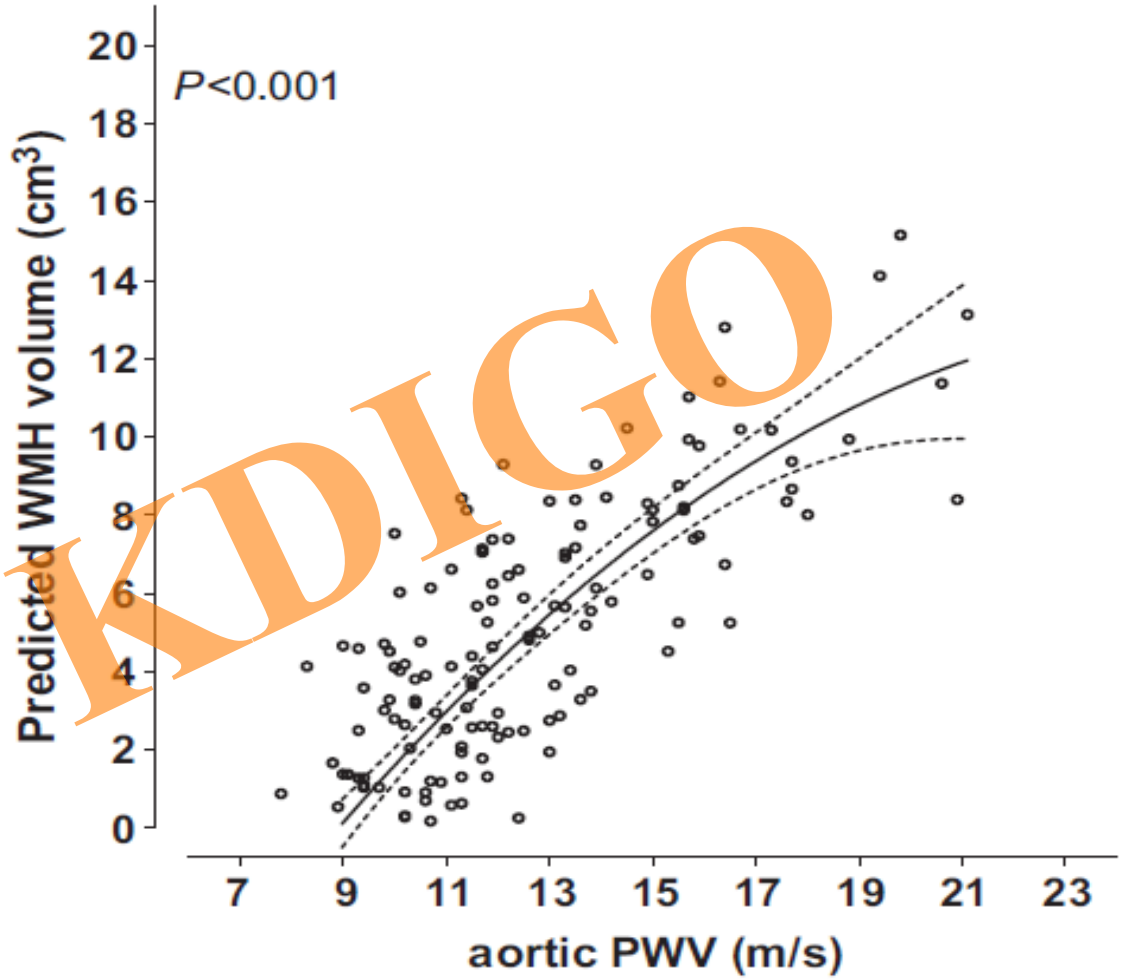


Consequences of stiffening

Oxygen Limitation Model



Aortic PWV and White matter Hyperdensities (WMH)



Henskens et al Hypertension 2008;52:1120