Vascular Calcification: a novel mechanism for aortic stiffness in Hypertension

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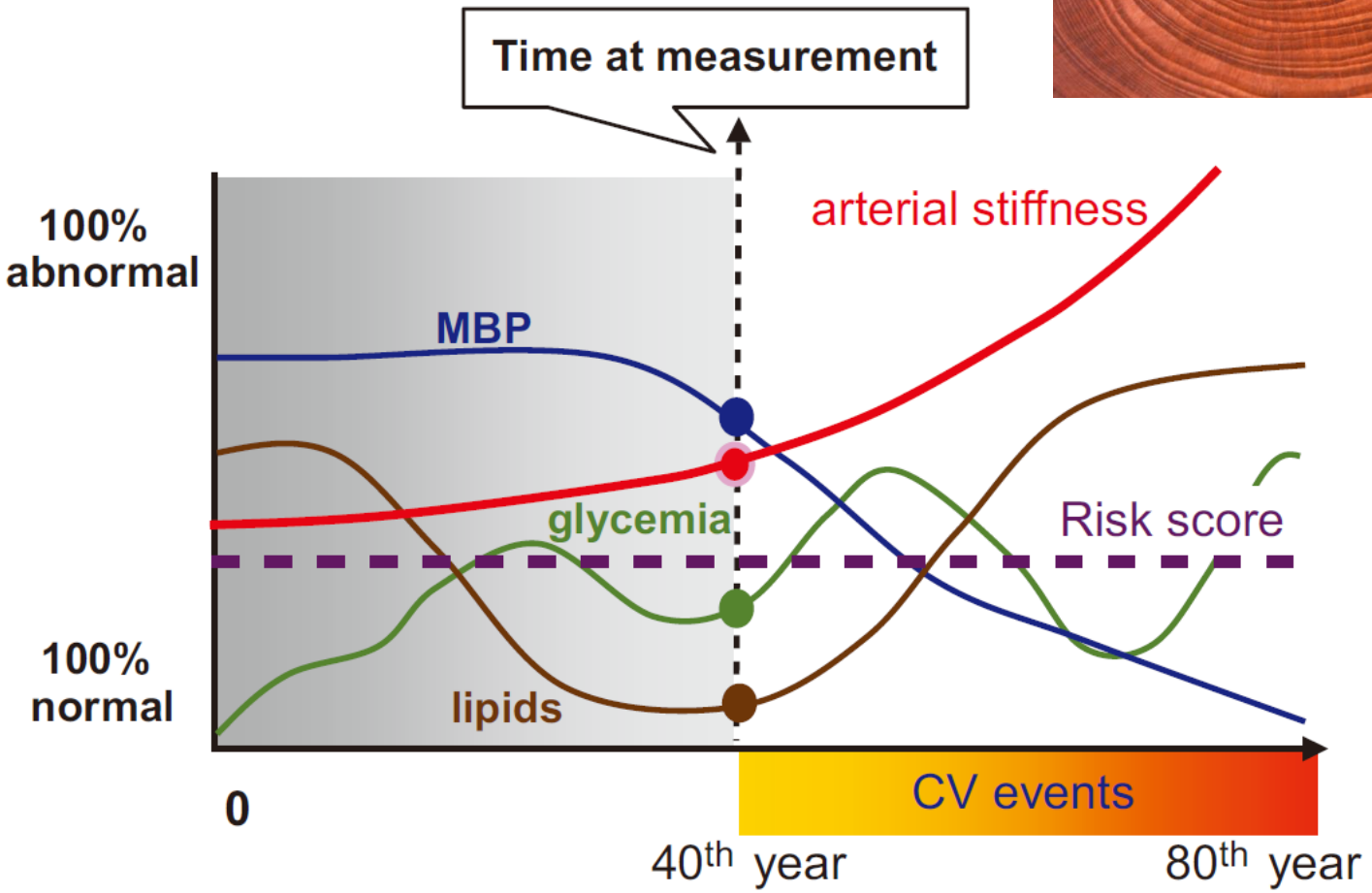
Aortic Stiffness

- An **integrated** marker of the **chronological** damage of the CV risk factors on the arterial wall

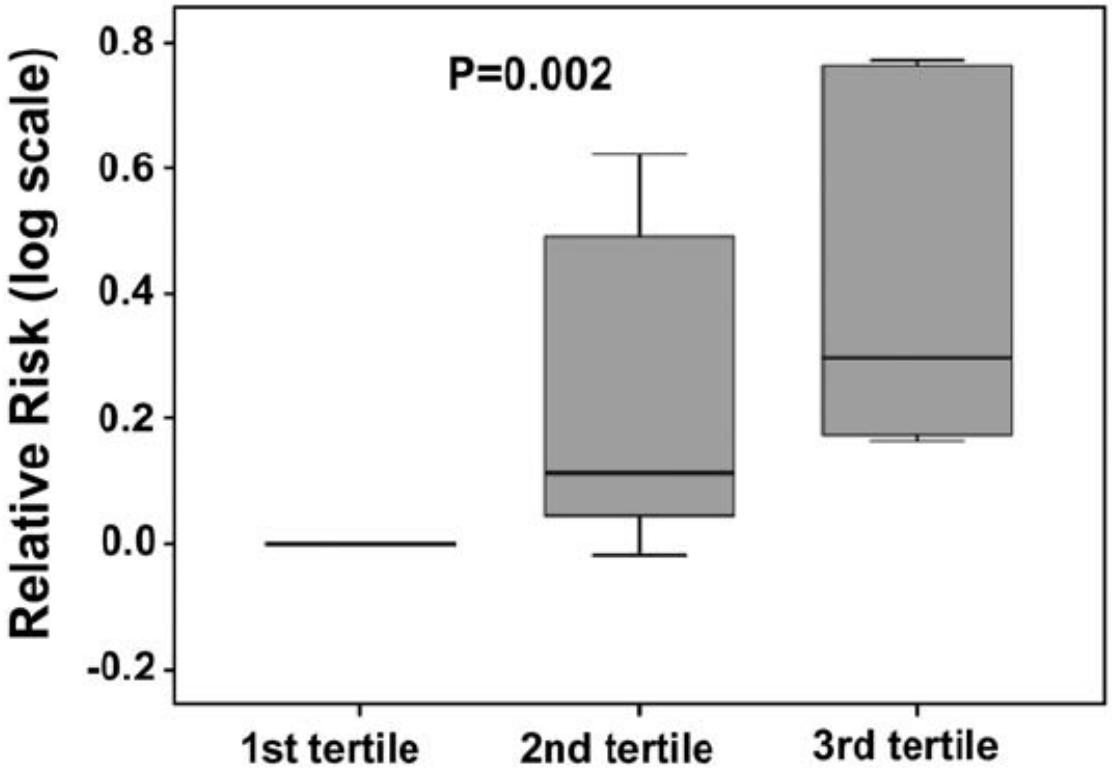
Aortic Stiffness



Nilsson et al, Hypertension 2009:54:3-10

Ao Stiffness-CV outcome

a meta-analysis of 17 longitudinal studies that evaluated aortic PWV and followed up 15,877 subjects for a mean of 7.7 years



JACC 2010:55:1318-27

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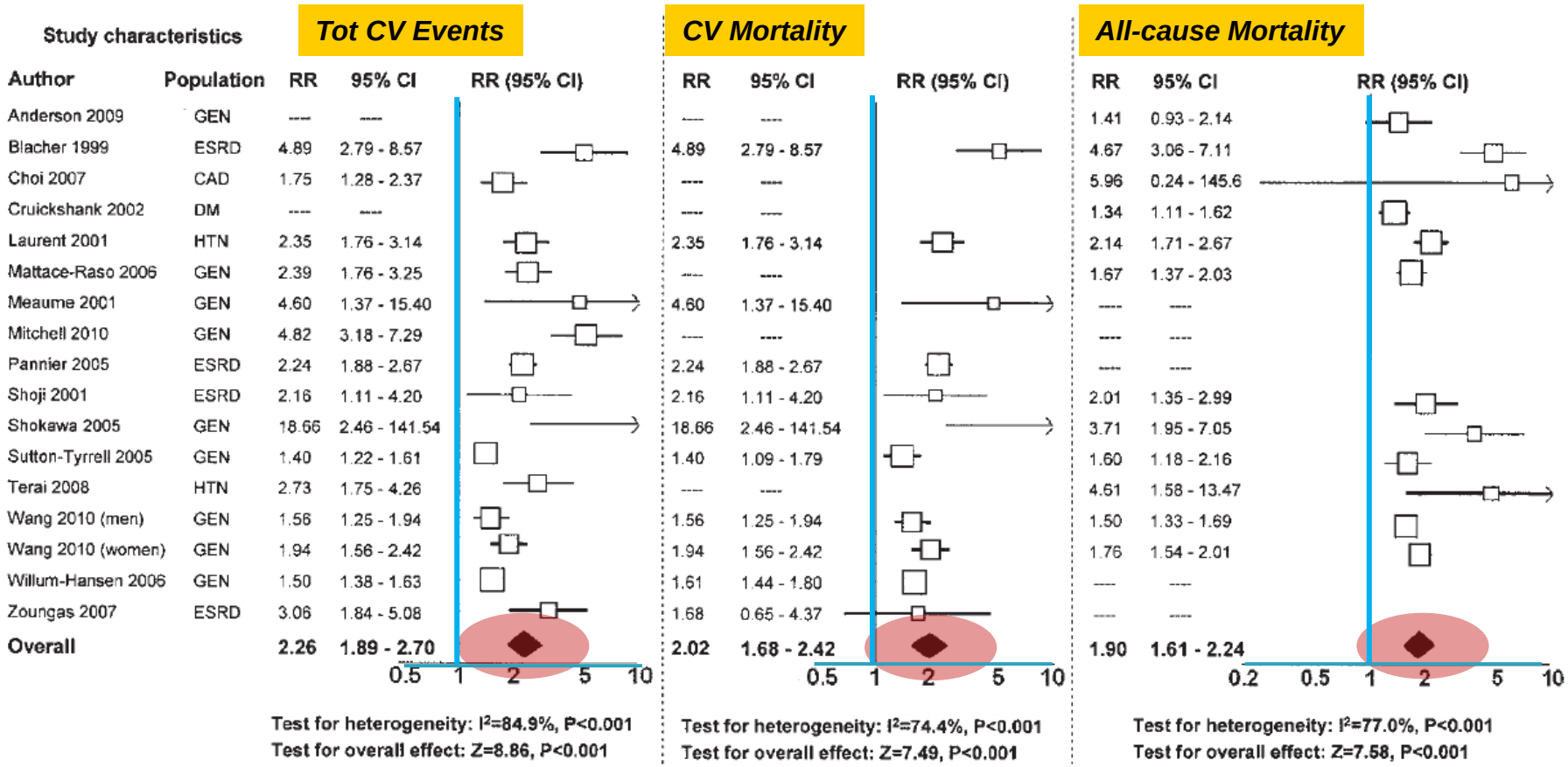
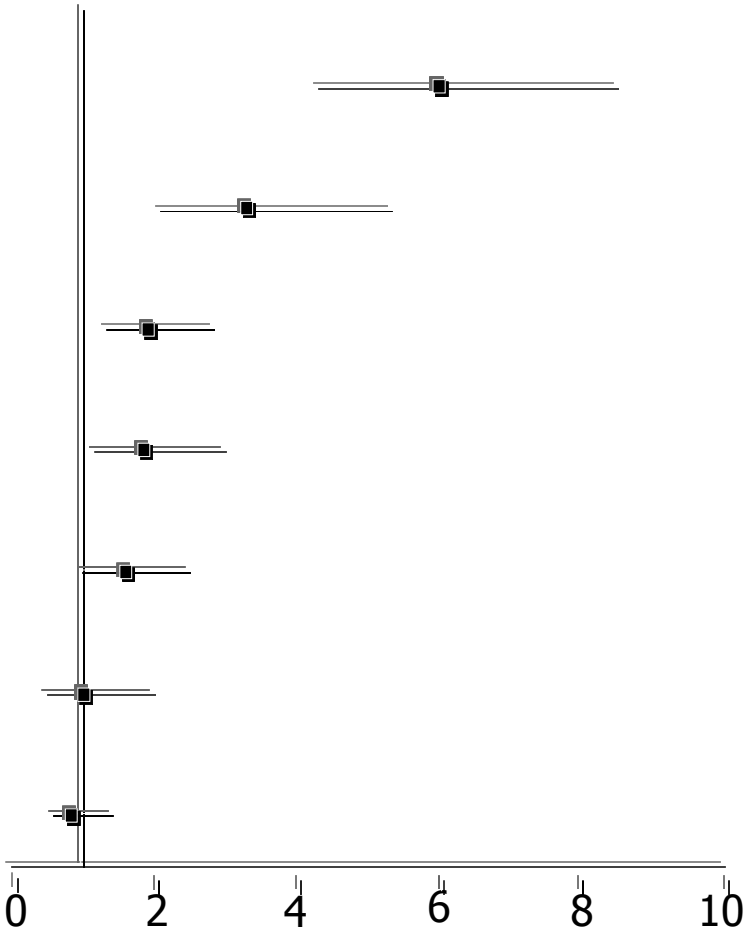


JACC 2010:55:1318-27

Ao Stiffness-Risk Factors

Risk factors	OR (95% CI)	p
Age > 60 yrs	6.2 (4.4-8.7)	<0.001
Hypertension	3.4 (2.1-5.3)	<0.001
Male	1.9 (1.3-2.8)	<0.001
Smoking	1.9 (1.2-3.2)	<0.001
Diabetes	1.6 (1.1-2.4)	0.023
Obesity	1.0 (0.5-2.1)	0.947
Hyperlipid	0.89 (0.5-1.5)	0.672



Kim EJ et al. IJC 2010:139;263–8

Early Vascualr Aging (EVA)

Modifiable risk factors

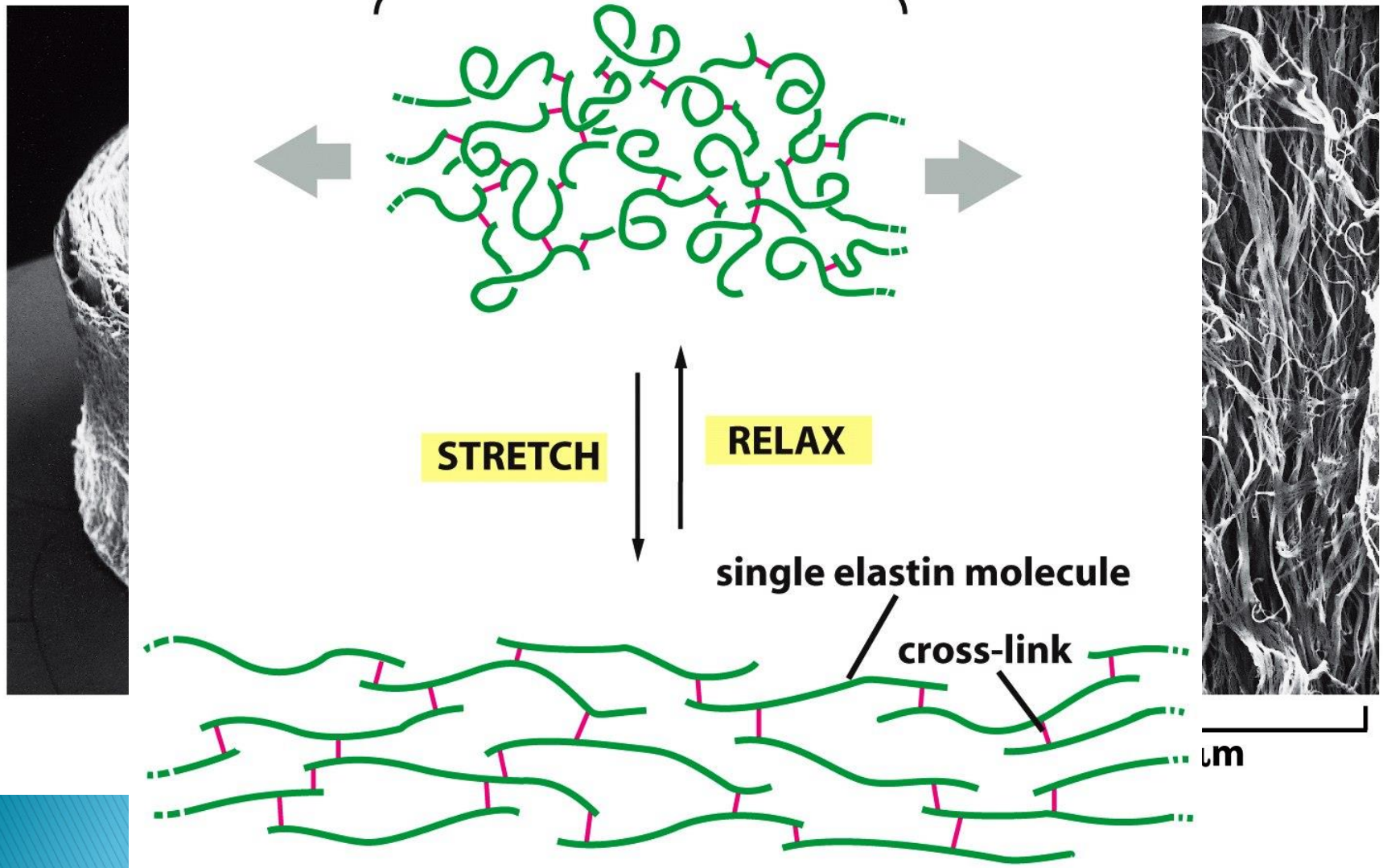
Smoking
Physical inactivity
Excessive alcohol consumption
Dietary factors
Dyslipidemia/Hyperlipidemia
Elevated LDL – cholesterol
Low HDL – cholesterol
Elevated triglycerides
Obesity (abdominal)
Diabetes mellitus/hyperglycemia
High blood pressure
Thrombogenic factors
Psychosocial stress
Poor sleep and relaxation
Adverse fetal growth pattern

Nonmodifiable risk factors

Age (chronological)
Gender
Ethnicity
Medical history of CVD or diabetes
Family history of CVD or diabetes

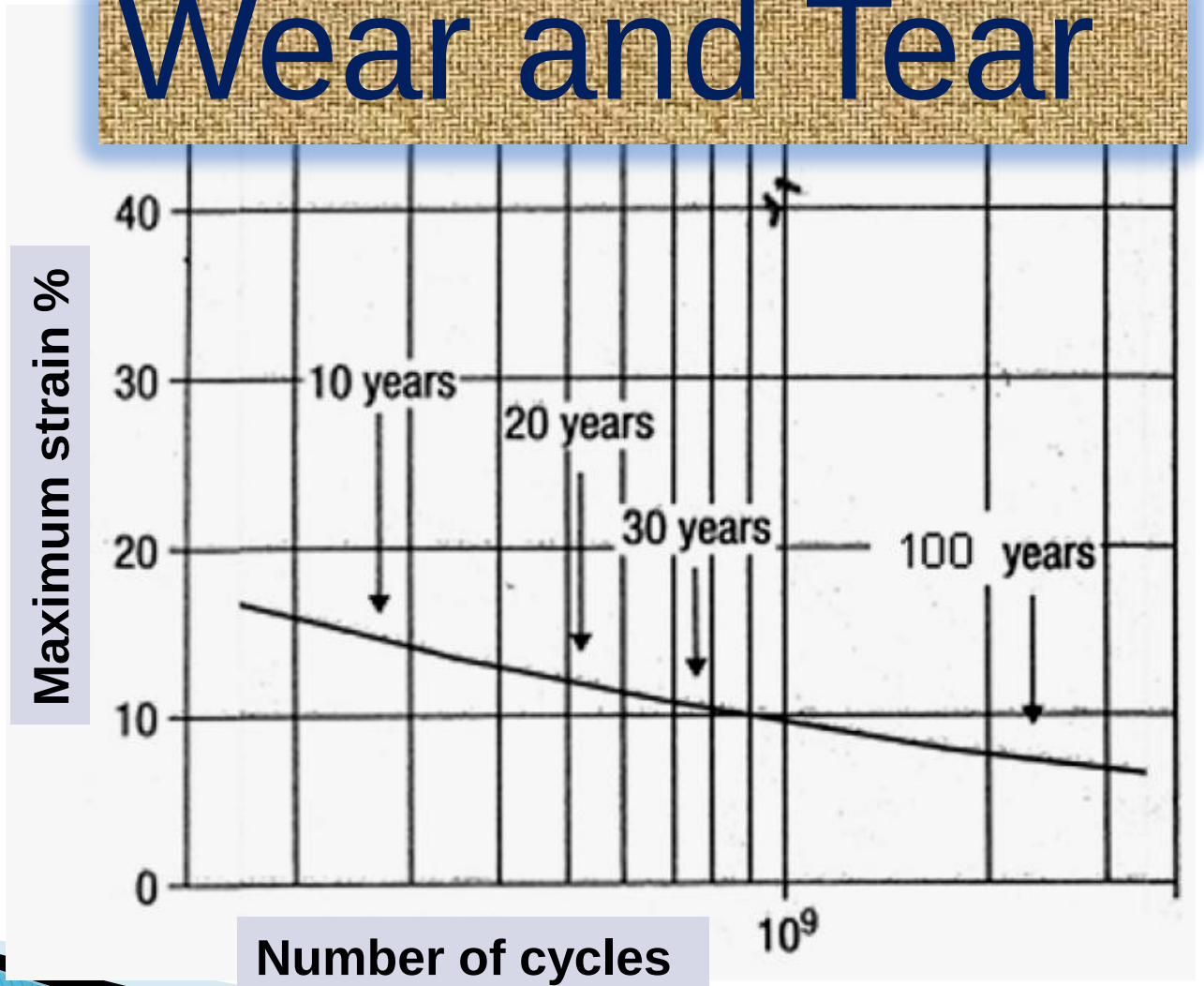
Vascular Health and Risk Management 2008:4;547-52

Ao Stiffness-Mechanisms[1]



Elastin Fibers Fracture with Aging

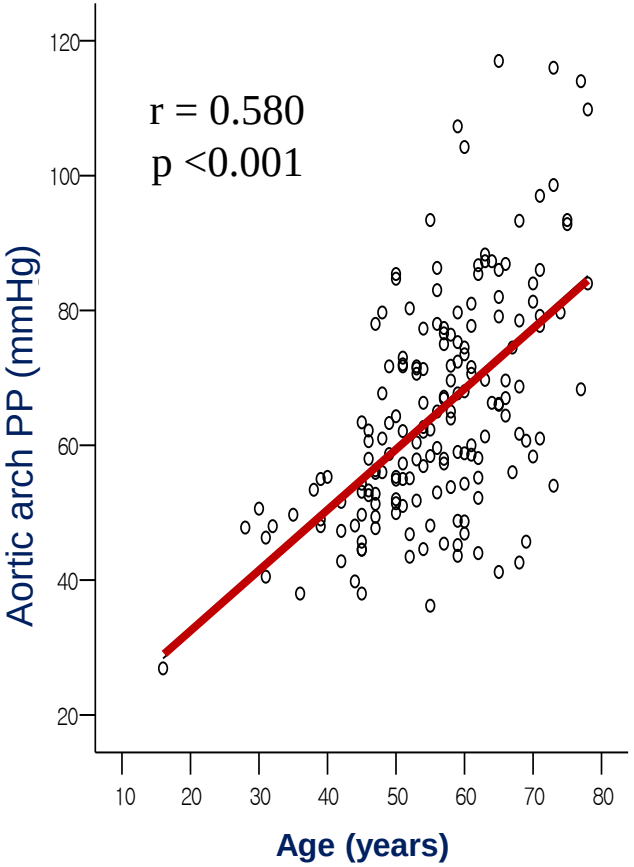
Wear and Tear



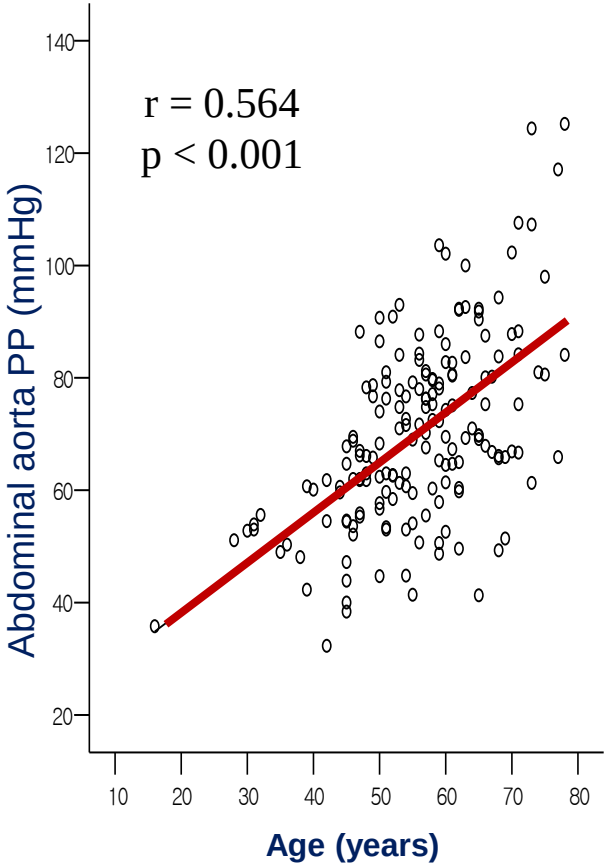
Vas Med 2007:12:329-341

Correlation between Ageing and PP in Elastic vs. Muscular artery

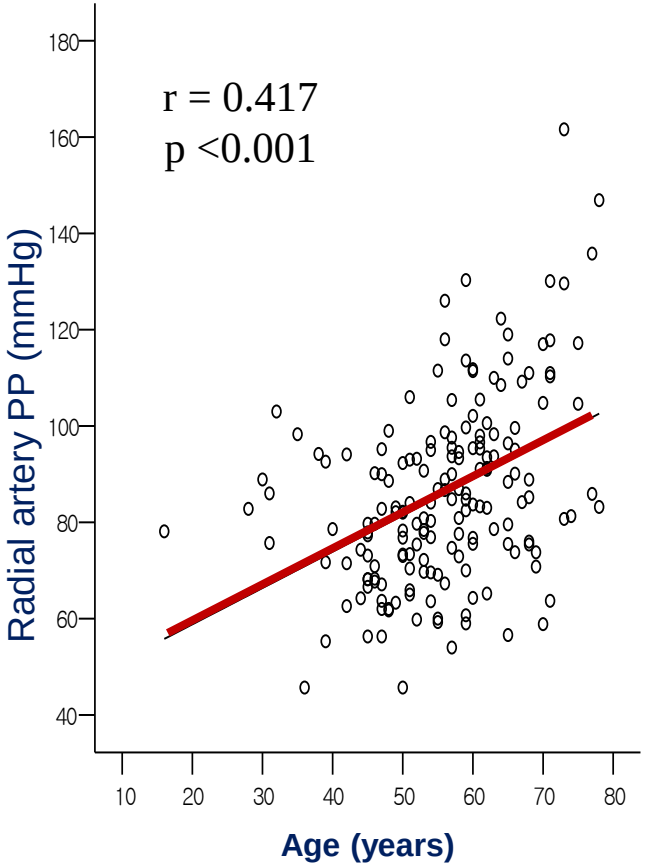
Aortic Arch



Abd Aorta

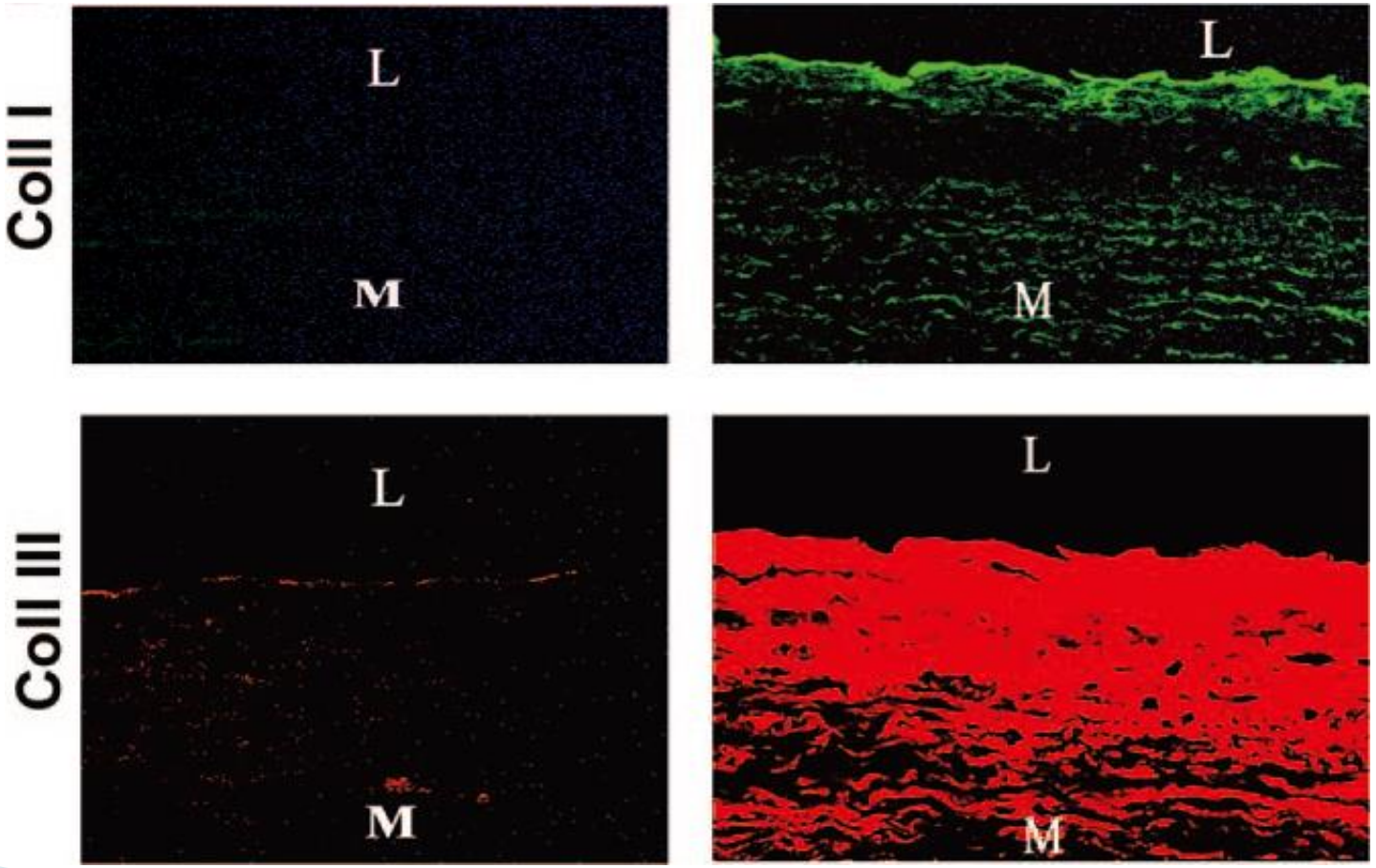


Radial A



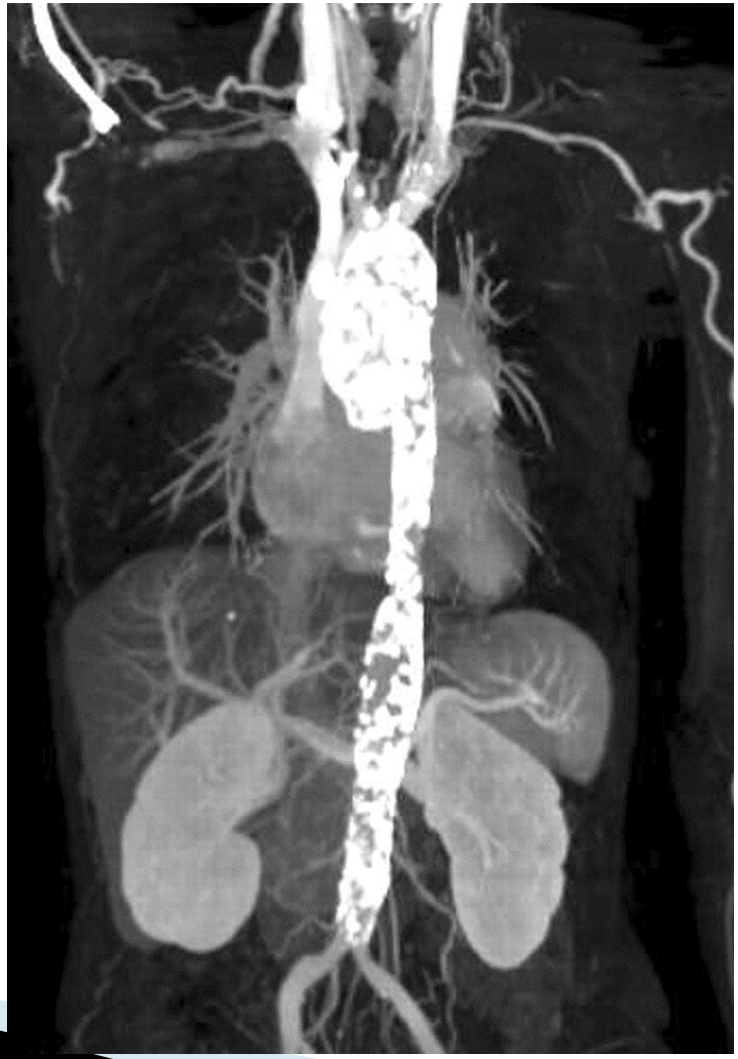
Kim EJ et al J Hypertens 2010;28;1252-60

Ao Stiffness-Mechanisms[2]



Hypertension 2007 ;50:219

Ao Stiffness-Mechanisms[3]



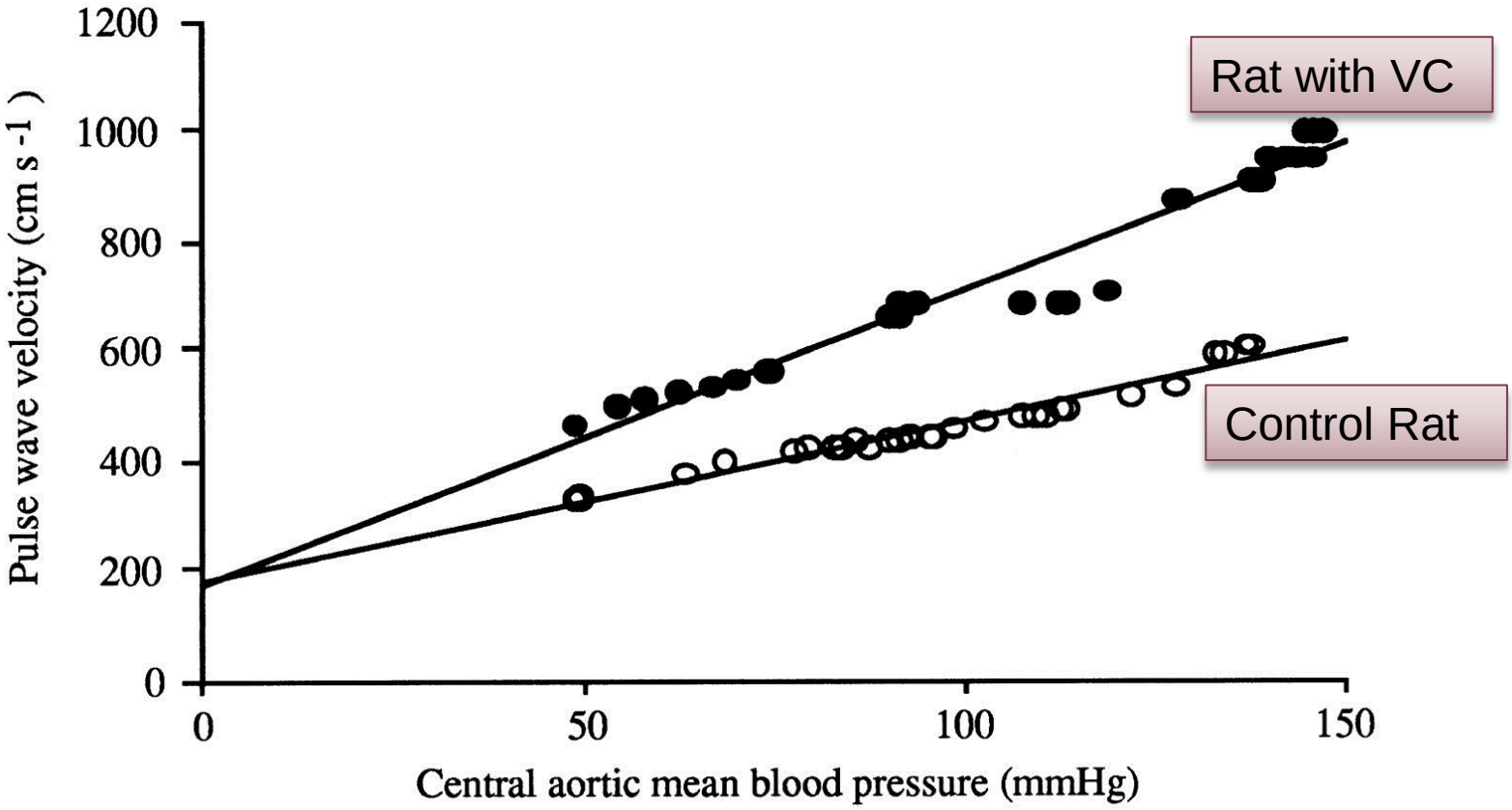
J Rheumatol 2012:39;1291

Ao Stiffness-Mechanisms[4]

- Oxidative stress
- Angiotensin II system
- AGE and RAGE

Vascular Calcification and Aortic Stiffness

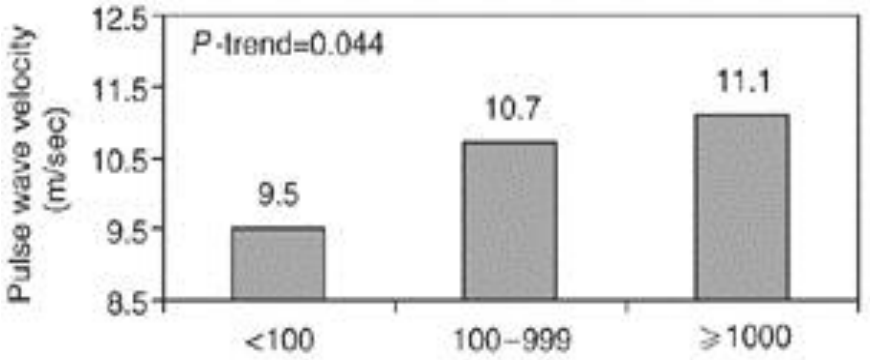
Vascular Calcification & Ao Stiffness (animal)



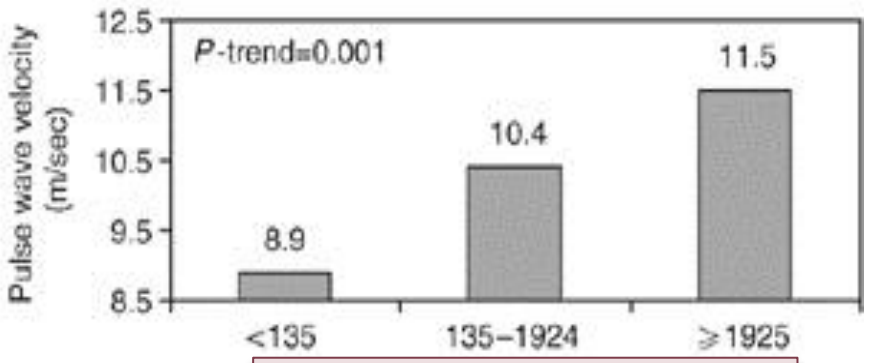
VC by vit D3+nicotine

Hypertension 1997; 29: 999-1006

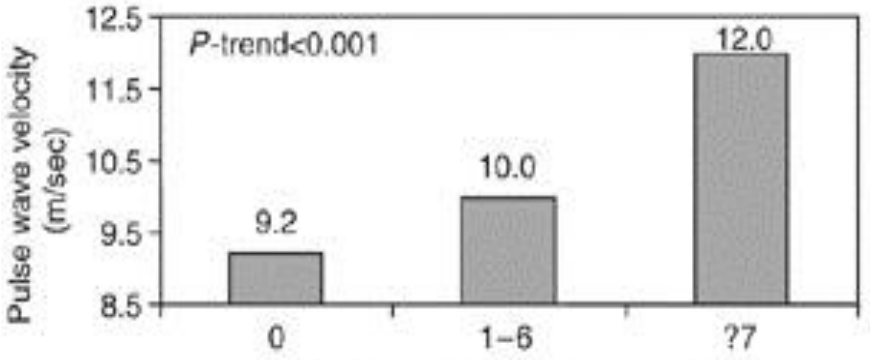
Vascular Calcification & Ao Stiffness (ESRD)



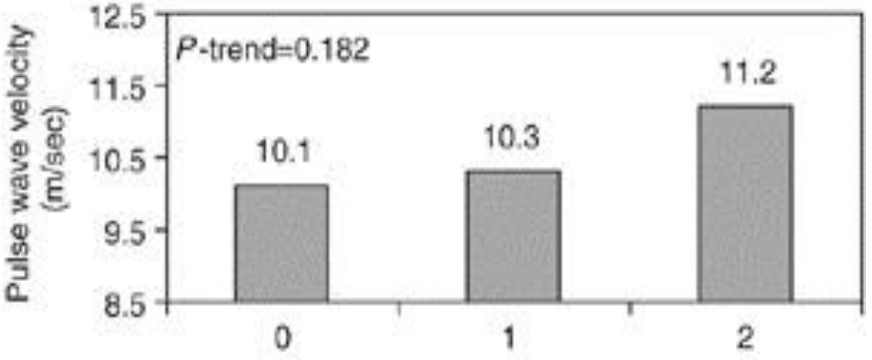
CAC



Thoracic AC



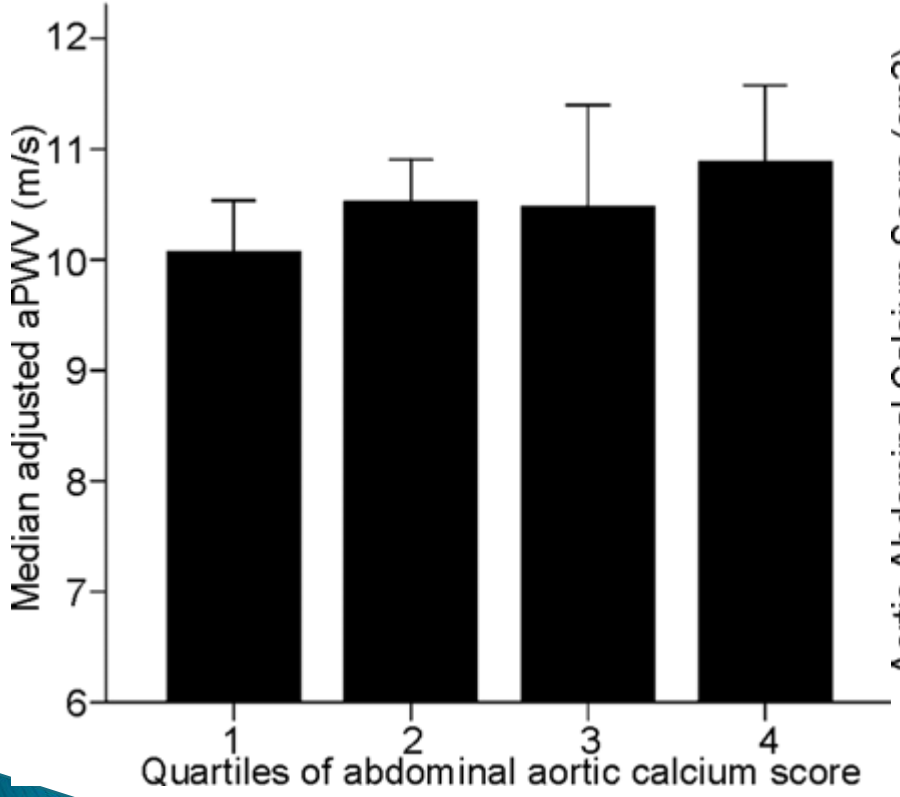
Abdominal AC

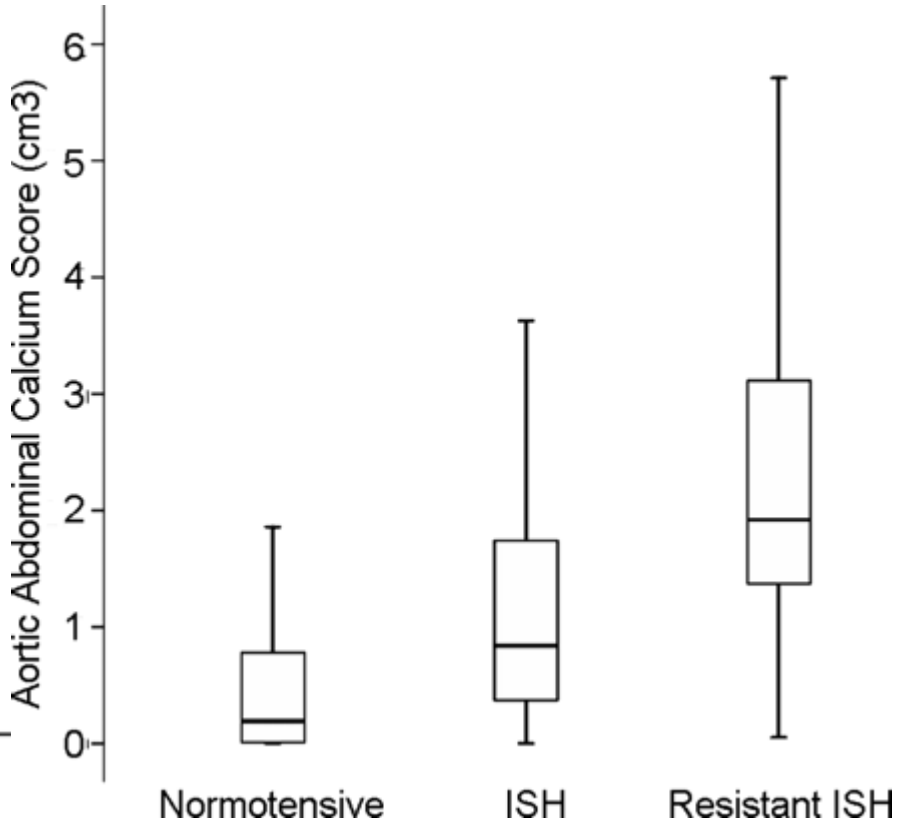


No. of calcified valve

Kidney Int 2007;8: 802-7

Vascular Calcification & Ao Stiffness (healthy elderly)





Hypertension 2009; 53: 524-31

Vascular Calcification & Ao Stiffness (middle-aged men)

	All (n=906)	ACS=0 (n=303)	ACS 1–100 (n=411)	ACS 101–400 (n=110)	ACS 400+ (n=82)	P for trend
Age (years)	45.2 (2.9)	45.0 (2.9)	45.2 (2.9)	45.7 (2.7)	46.0 (2.7)	0.002
Race (%)						
Blacks	8.9	9.9	8.3	9.1	8.5	
JA	30.5	35.3	26.3	29.1	35.4	
Koreans	32.1					
Whites	28.5					0.072
BP sys (mmHg)	123.8 (				2.9)	<0.001
BP dia (mmHg)	75.2 (				0.9)	<0.001
MAP (mmHg)	91.6 (				1.1)	<0.001
Heart rate (/min)	65.8 (				0.5)	0.263
BMI (kg/m^2)	27.0 (				8)	<0.001
Smoking status						
Current (%)	20.6					
Former (%)	25.9					
Never (%)	53.4					<0.001
Pack year	7.3 (				4.5)	<0.001
Drinker (%)	42.2					0.540
LDL-C (mg/dL)	124.3 (34.1)	122.6 (35.4)	126.7 (34.3)	119.1 (29.4)	124.8 (33.1)	0.710
HDL-C (mg/dL)	48.6 (13.0)	51.7 (13.3)	46.5 (11.7)	47.3 (13.0)	51.8 (15.5)	0.582
TG (mg/dL)	161.6 (115.8)	142.4 (104.7)	166.4 (108.3)	177.2 (142.0)	187.8 (141.6)	0.001
Diabetes (%)	8.4	5.6	7.5	17.3	11.0	0.003
Medication						
BP (%)	11.0	7.9	10.7	17.3	15.9	0.005
Lipid (%)	10.8	9.2	9.2	17.3	15.9	0.017

	All (n=906)	ACS=0 (n=303)
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Race (%)		
Blacks	8.9	9.9
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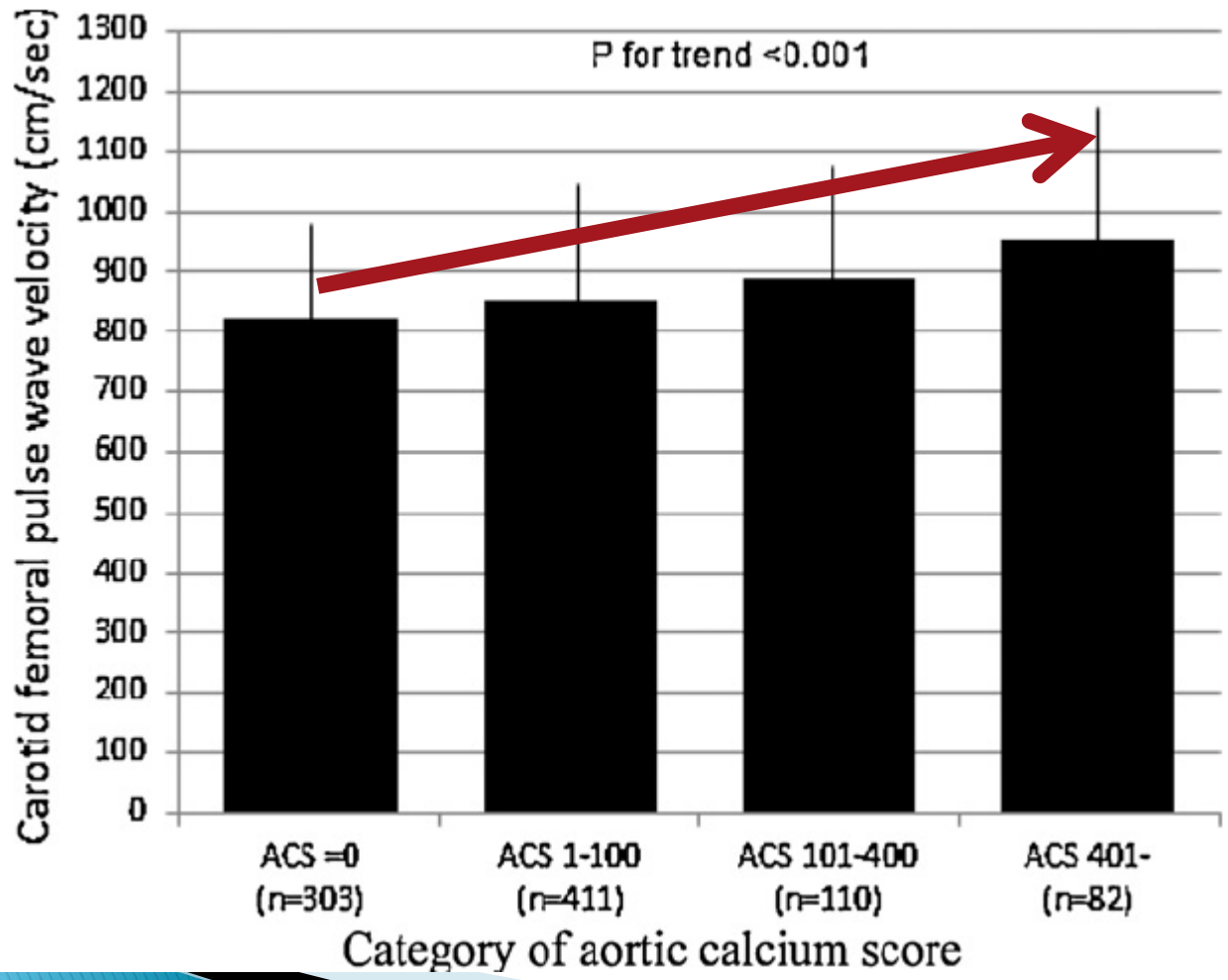
BP sys (mmHg)	123.8 (13.4)	121.4 (12.1)

Atherosclerosis 2012 ; 222: 473-7

Vascular Calcification & Ao Stiffness (middle-aged men)

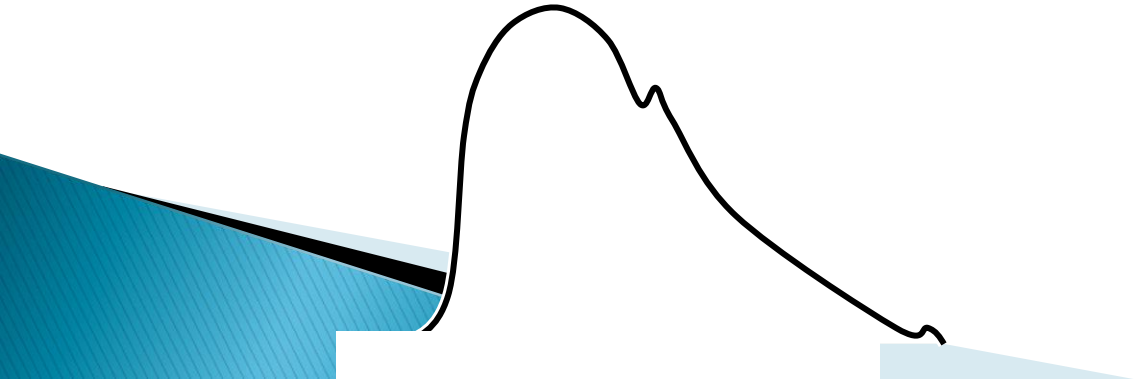


Atherosclerosis 2012 ; 222: 473-7

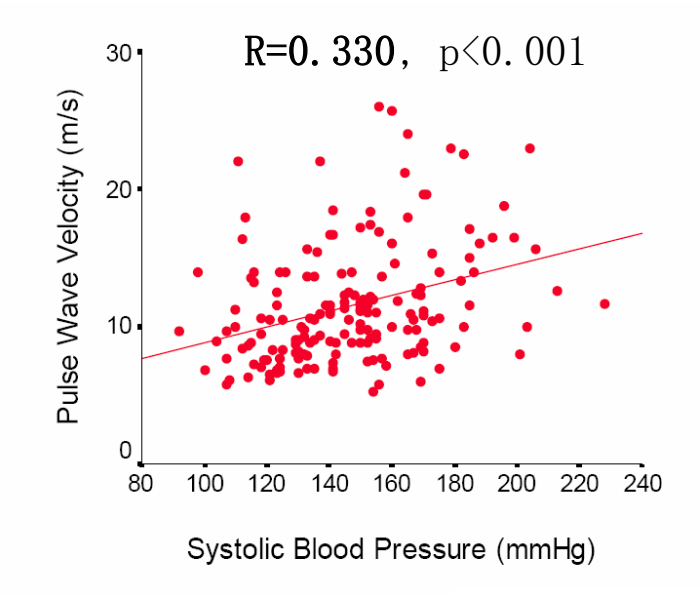
VC, Ao Stiffness & BP

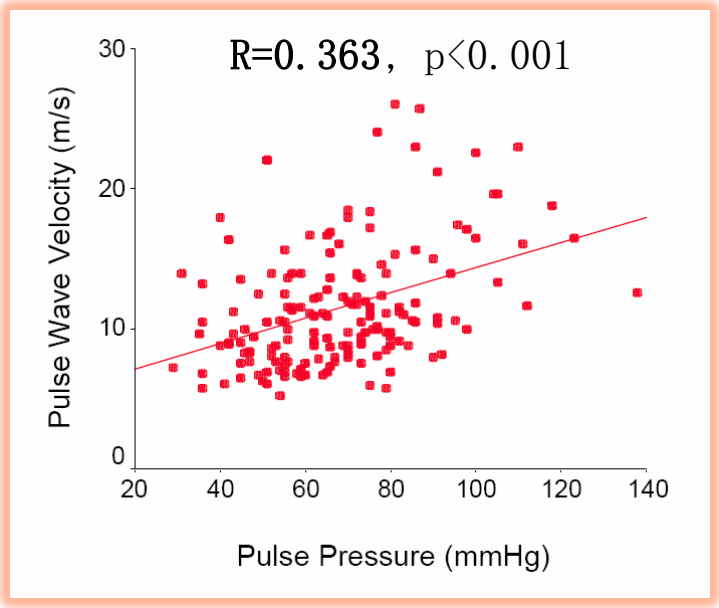
Stiff Aorta

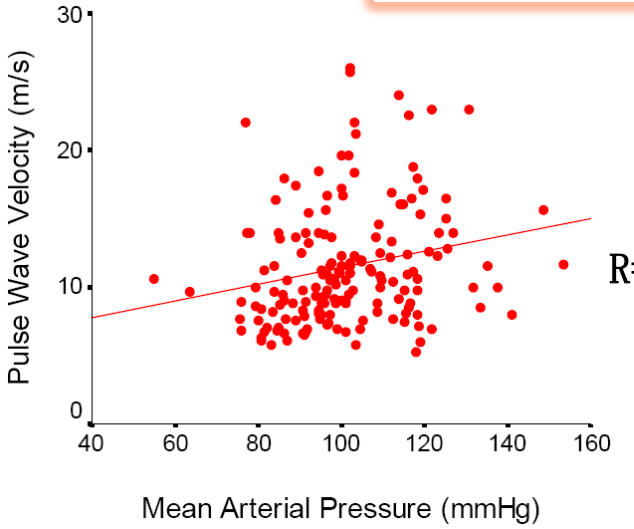
Resistance artery



VC, Ao Stiffness & BP



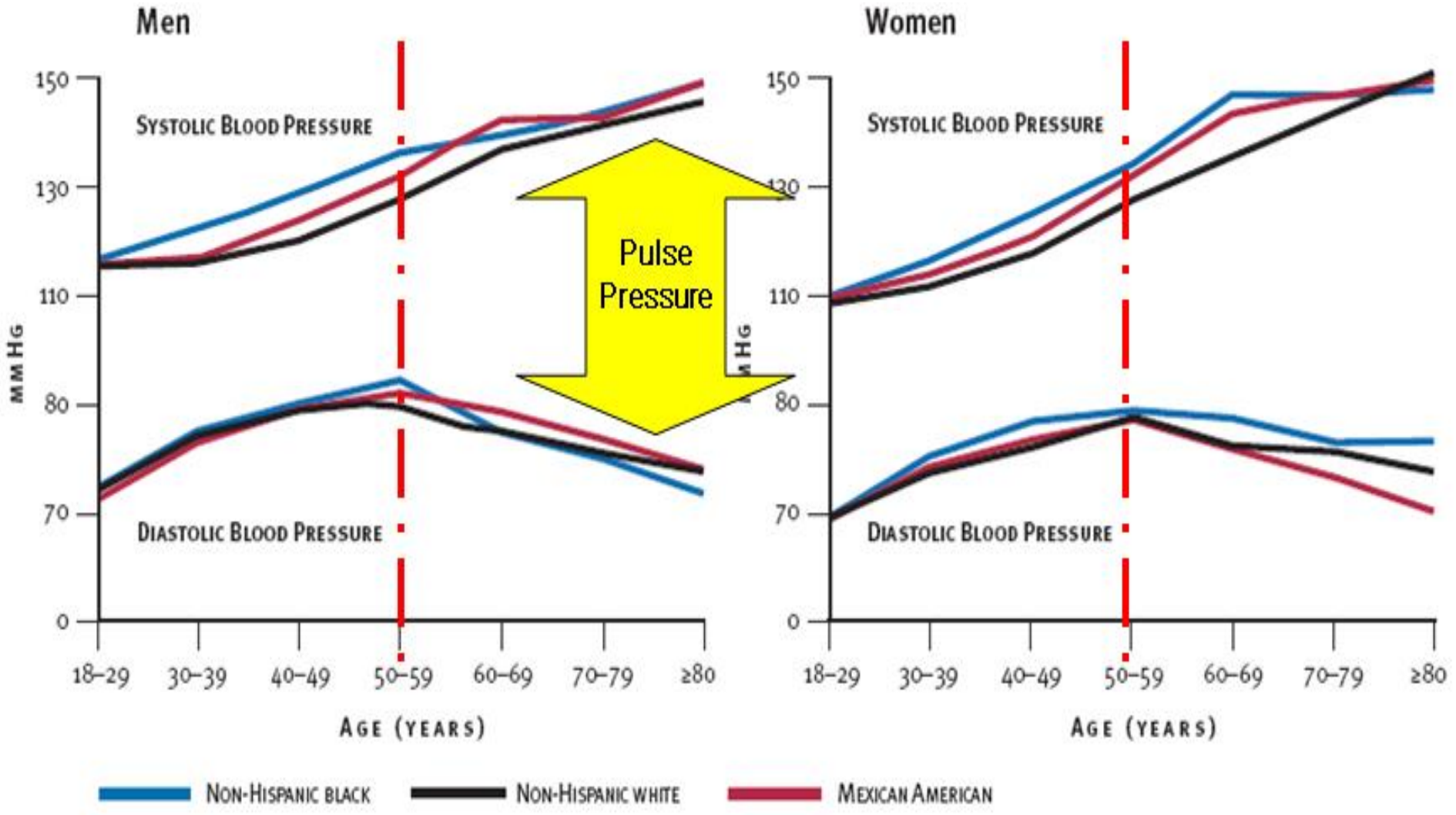




R=0.238, p0.002

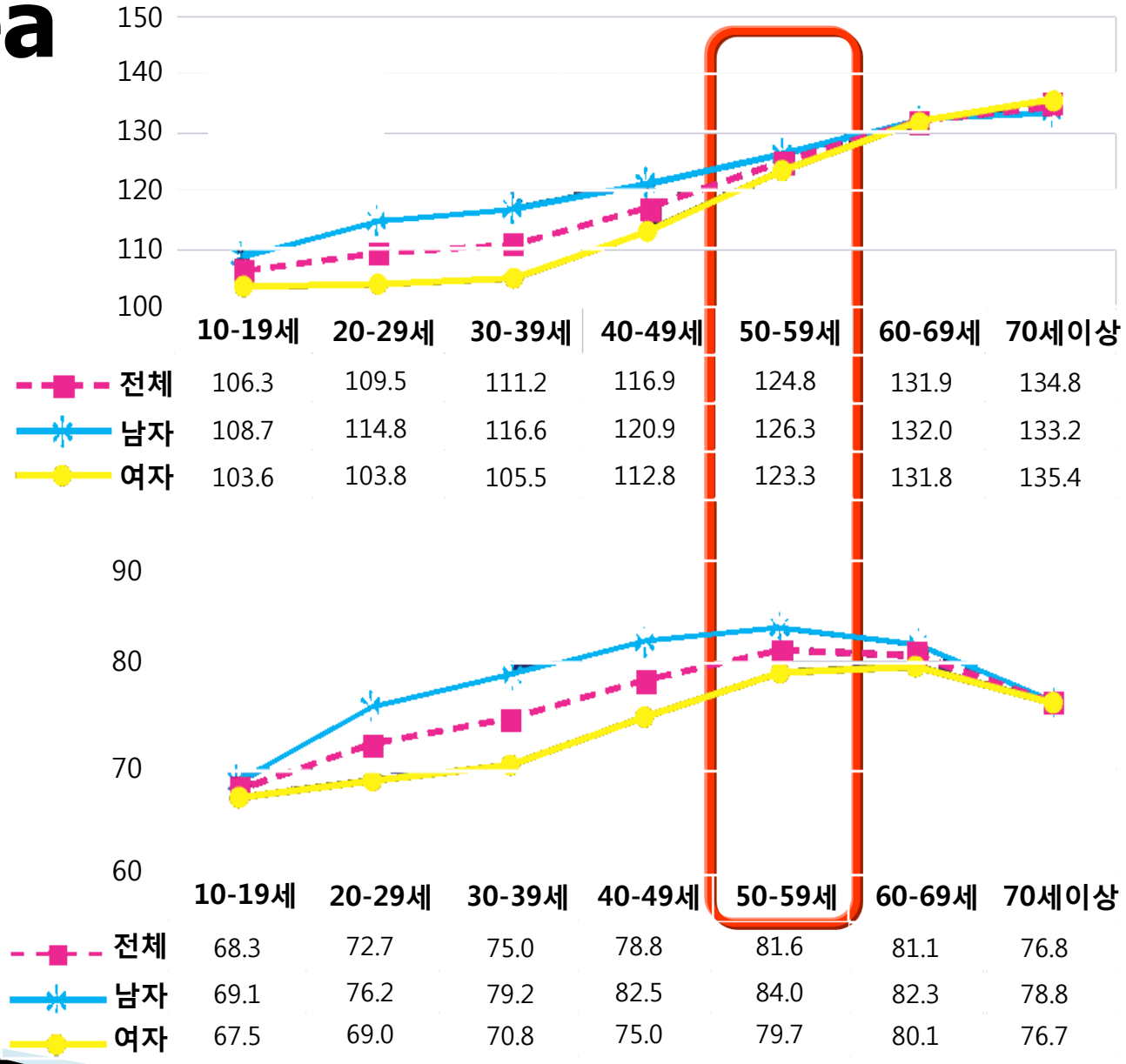
Kim EJ et al. J Hum Hypertens 2007;2:141-8

VC, Ao Stiffness & Hypertension



Hypertension 1995;25:305-13

Korea

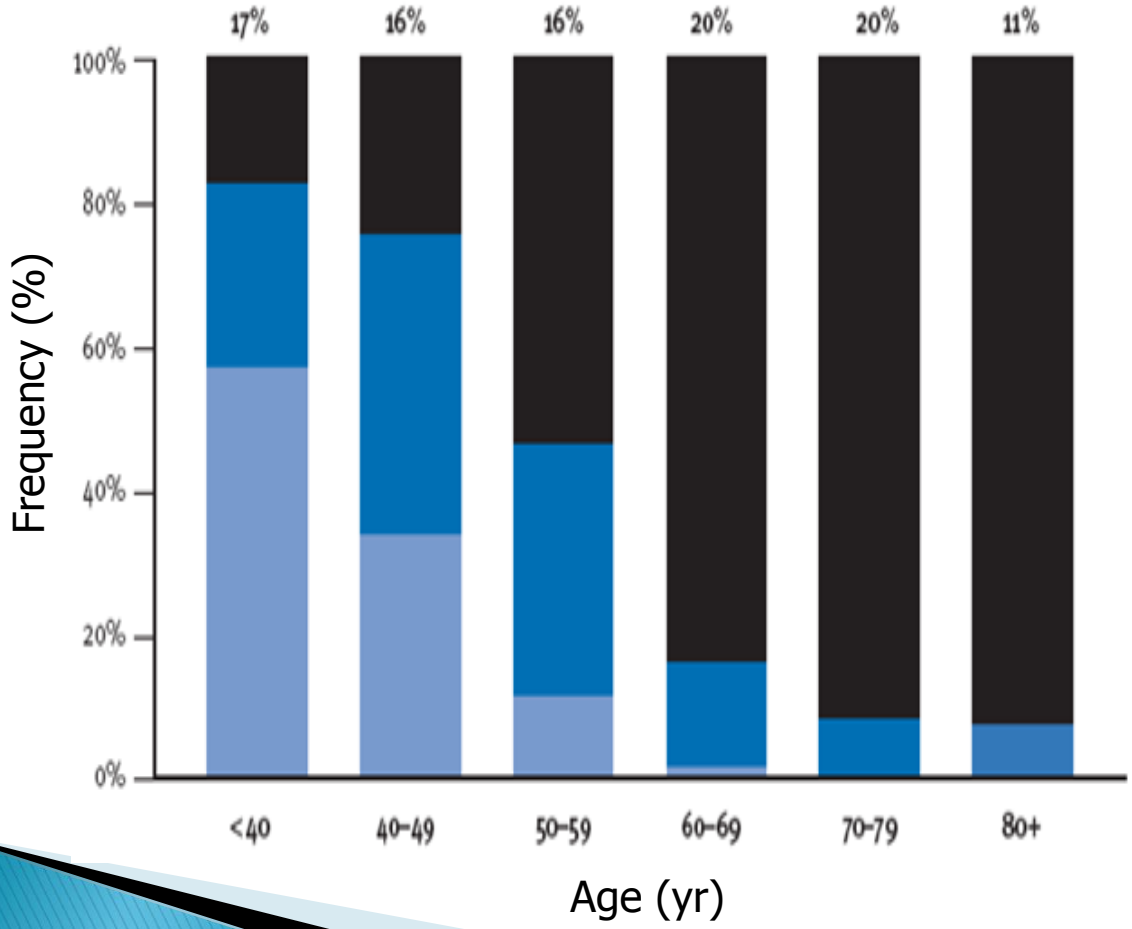


	10-19세	20-29세	30-39세	40-49세	50-59세	60-69세	70세이상
전체	106.3	109.5	111.2	116.9	124.8	131.9	134.8
남자	108.7	114.8	116.6	120.9	126.3	132.0	133.2
여자	103.6	103.8	105.5	112.8	123.3	131.8	135.4

	10-19세	20-29세	30-39세	40-49세	50-59세	60-69세	70세이상
전체	68.3	72.7	75.0	78.8	81.6	81.1	76.8
남자	69.1	76.2	79.2	82.5	84.0	82.3	78.8
여자	67.5	69.0	70.8	75.0	79.7	80.1	76.7

Data from KNHANES 2005

% of Isolated Systolic Hypertension



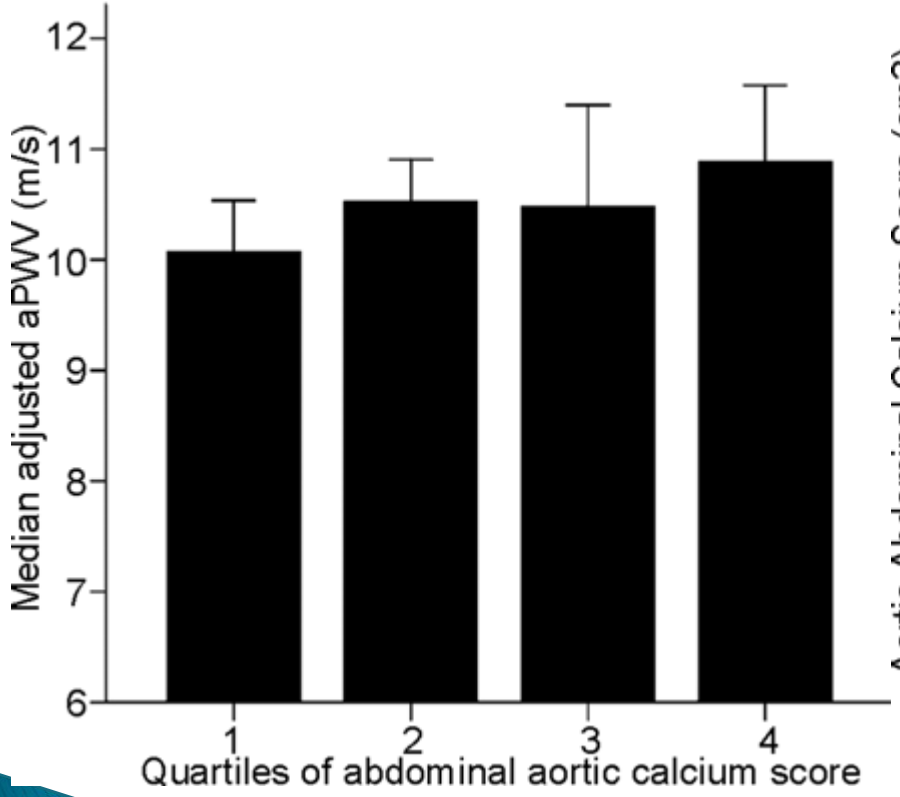
ISH
SBP≥140 & DBP < 90mmHg

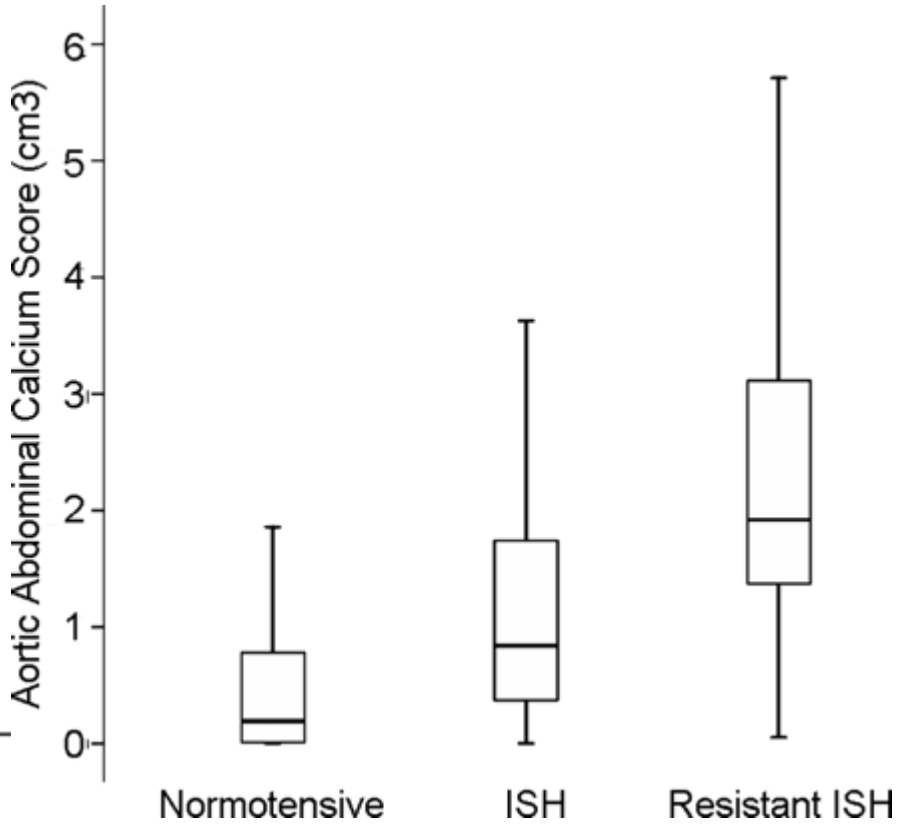
SDH
SBP≥140 & DBP ≥ 90mmHg

IDH
SBP<140 & DBP ≥ 90mmHg

Hypertension 2001;37:869-74

VC, Ao Stiffness & Hypertension

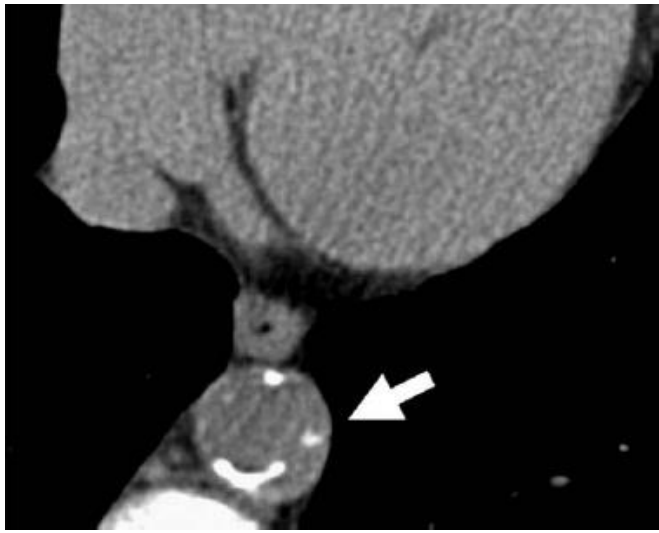




Hypertension 2009; 53: 524-31

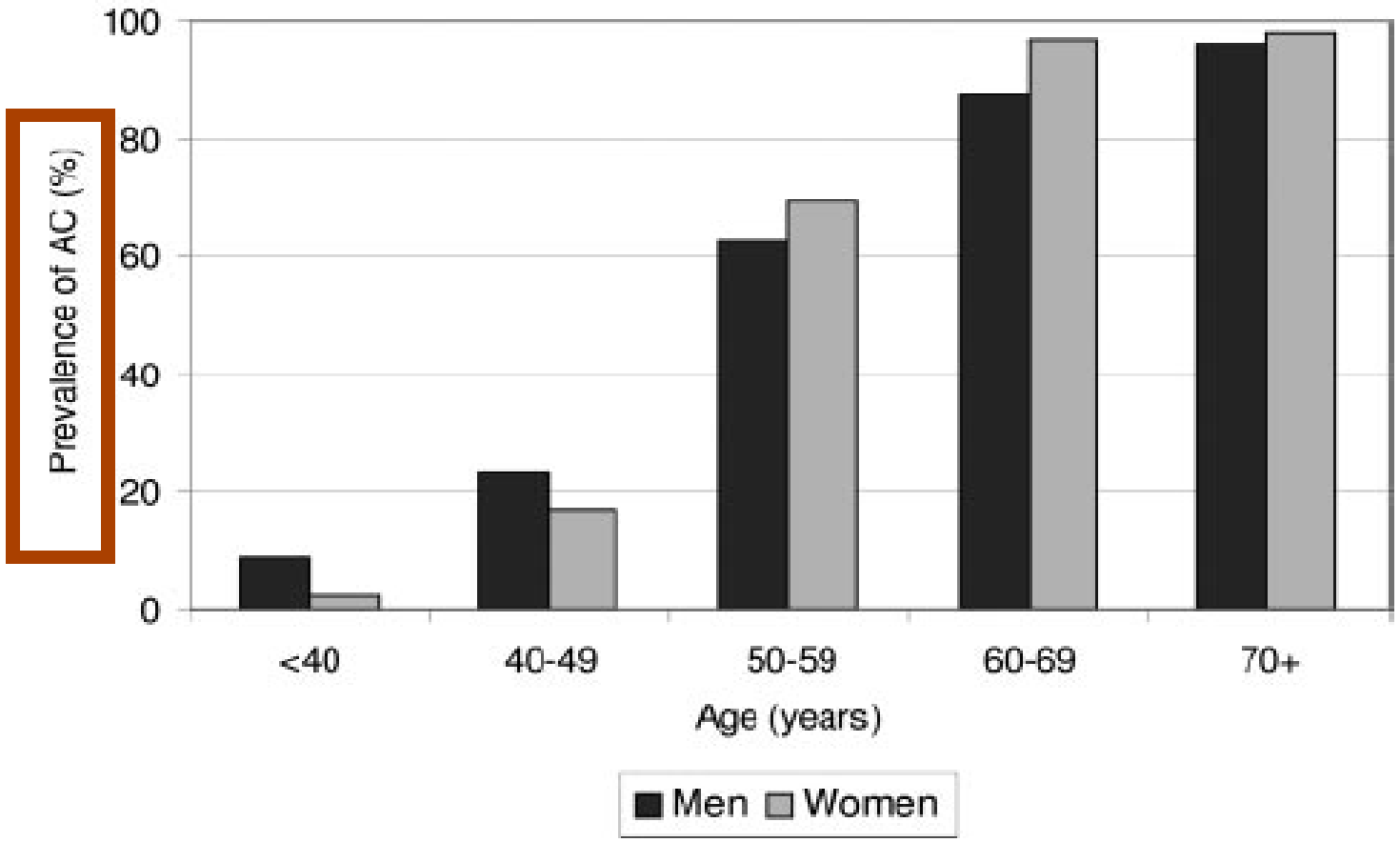
Epidemiology: Thoracic Ao Calc

- MESA (Multi-Ethnic Study of Atherosclerosis)
  - Population-based, 45-84 (mean 63) yrs, n=6814
  - Overall prevalence **28.0%**
    - Chinese & White 32.4%,
    - Hispanic 24.9%, Black 22.4%
    - Female 29.1%, Male 26.8%



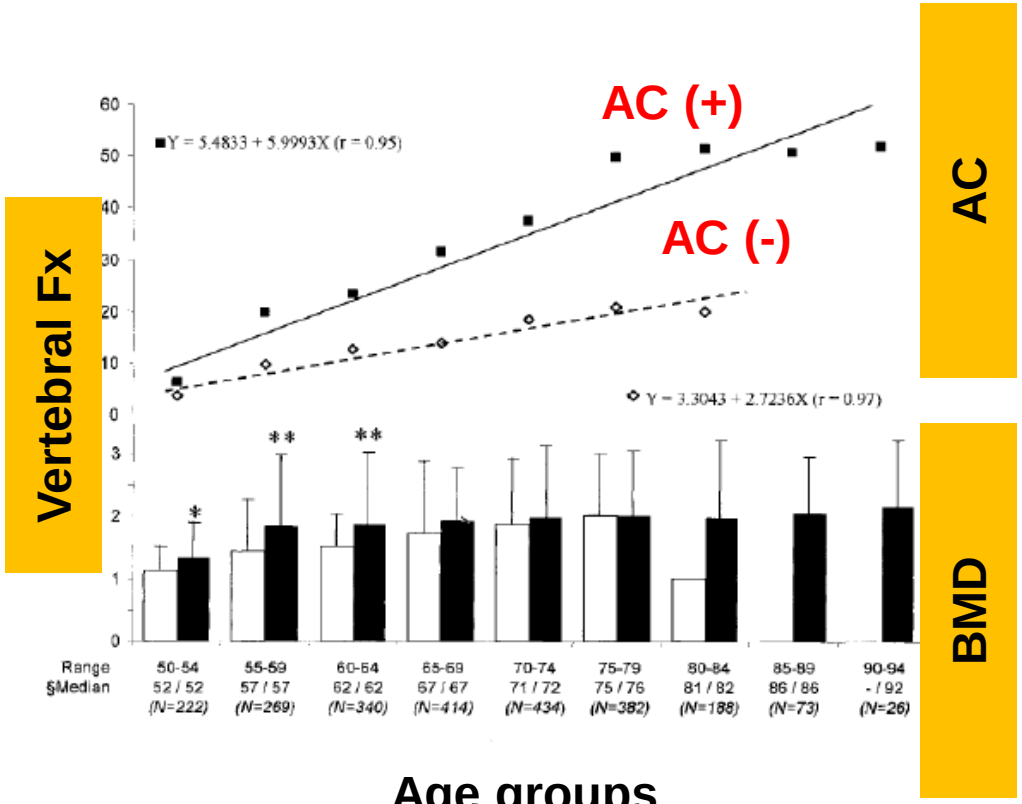
Am Heart J 2008;155:765-71

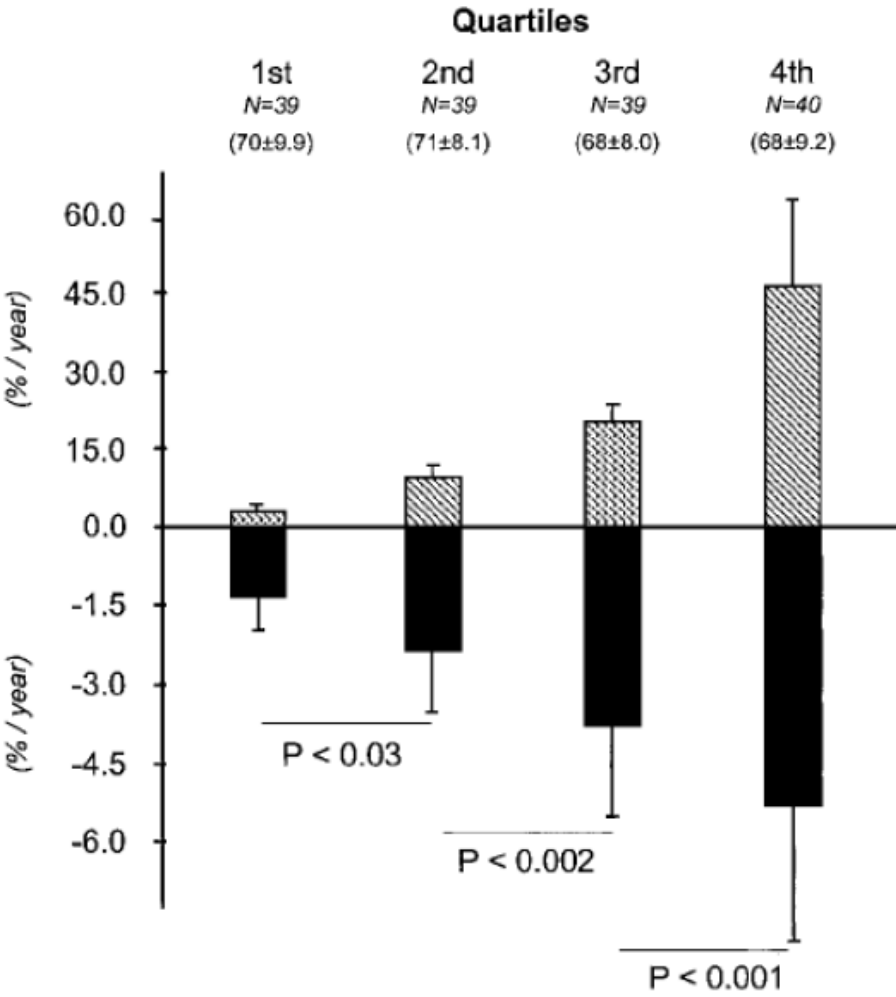
Epidemiology: Thoracic Ao Calc



Circulation 2007;115:717-24

Epidemiology: Correlation between AC & BMD





J Clin Endocrinol Metab 2004;89:4246-53

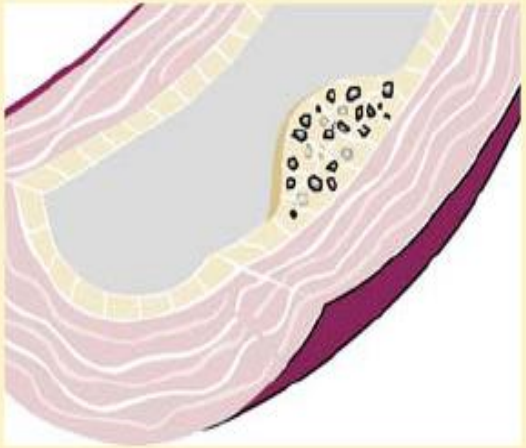
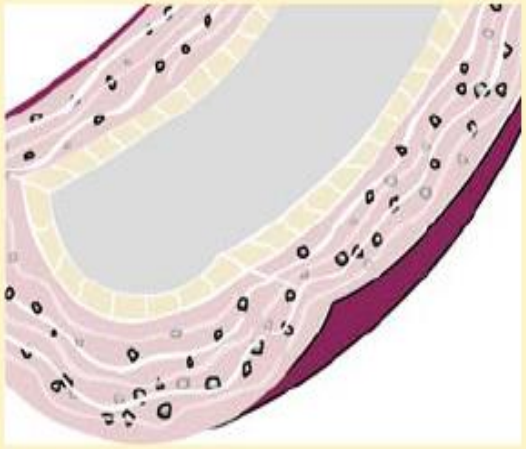
Epidemiology: Correlation between CAC, AC & BMD

		Control		CAD	
		CAC	**AC**	**CAC**	**AC**
BMD	rho	-0.239 †	-0.564‡	-0.184*	-0.563‡
CAC	rho	1	0.338‡	1	0.506‡

*,<0.05; †, <0.01; ‡, <0.001

Kim EJ et al. ISA 2009

Intima vs. Media Calcification

Atherosclerosis	Arteriosclerosis or Mönckeberg's sclerosis
Focal, in plaques	Generalized
	
Dyslipidemia, hypercholesterolemia	Aging, diabetes, renal failure, osteoporosis, hypertension
Lipid accumulation	Transdifferentiation of VSMCs into bone-like cells
Foam cell formation	(osteoblast-chondrocyte and osteoclast-like cells)
Inflammation	Ca, P, vitamin D metabolism
Oxidative stress	Loss of calcification inhibitors (pyrophosphate, MGP, fetuin)
Apoptosis	

Endochondral calcification **Intramembranous ossificaiton**

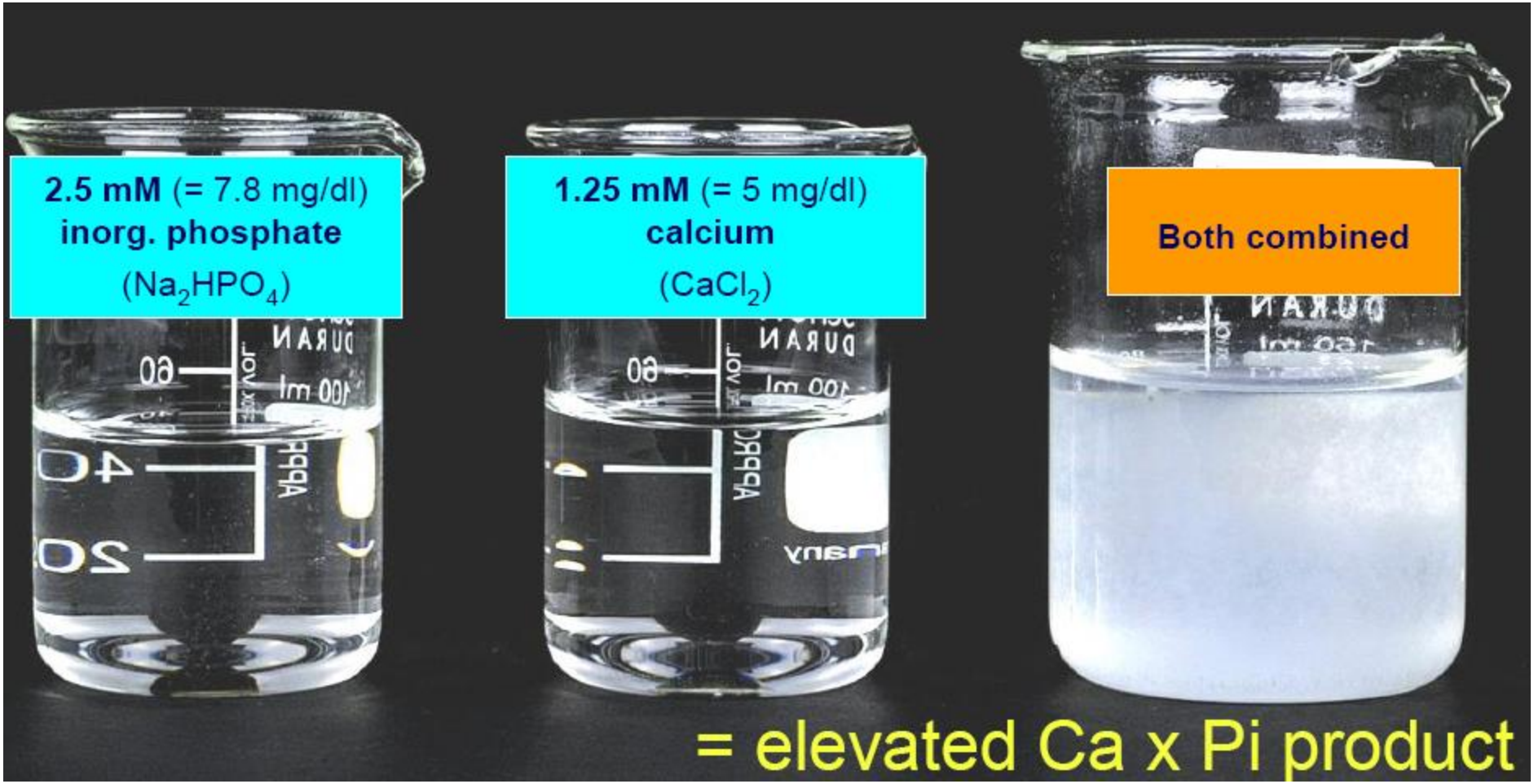
Trends in Molecular Medicine 2009;15:405

Risk Factor	Intimal VC	Medial VC
Advanced age	+	+
Male sex	+	-
Diabetes mellitus	+	+
Dyslipidemia	+	-
Hypertension	+	-
Smoking	+	-
Renal failure (abnormalities of mineral metabolism)	-	+
Inflammation	+	+

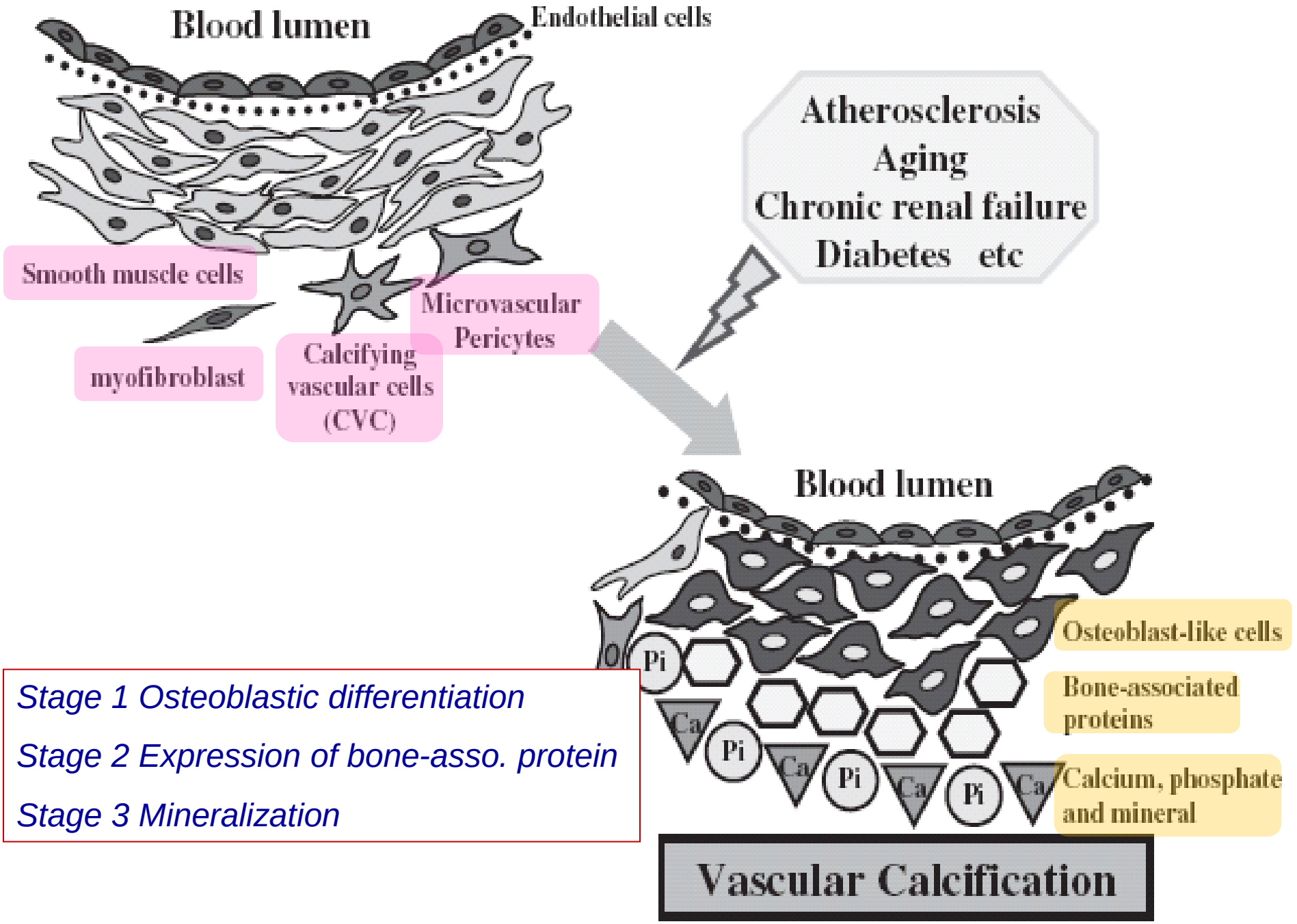
VC : Mechanism

- **Passive process ?**
- **Active process ?**

Process of VC



Passive process ?



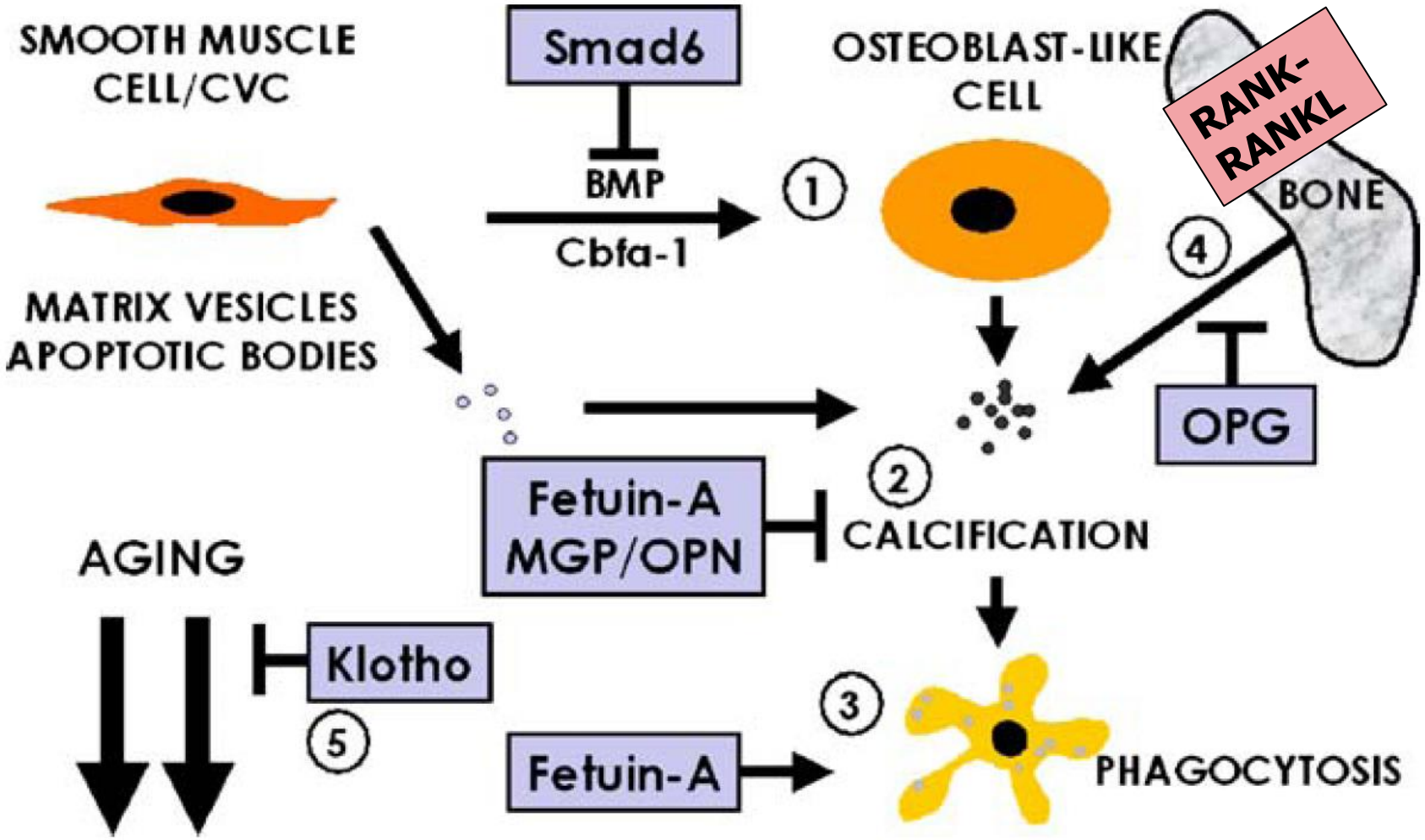
Stage 1 Osteoblastic differentiation

Stage 2 Expression of bone-asso. protein

Stage 3 Mineralization

J Bone Miner Metab, 2006

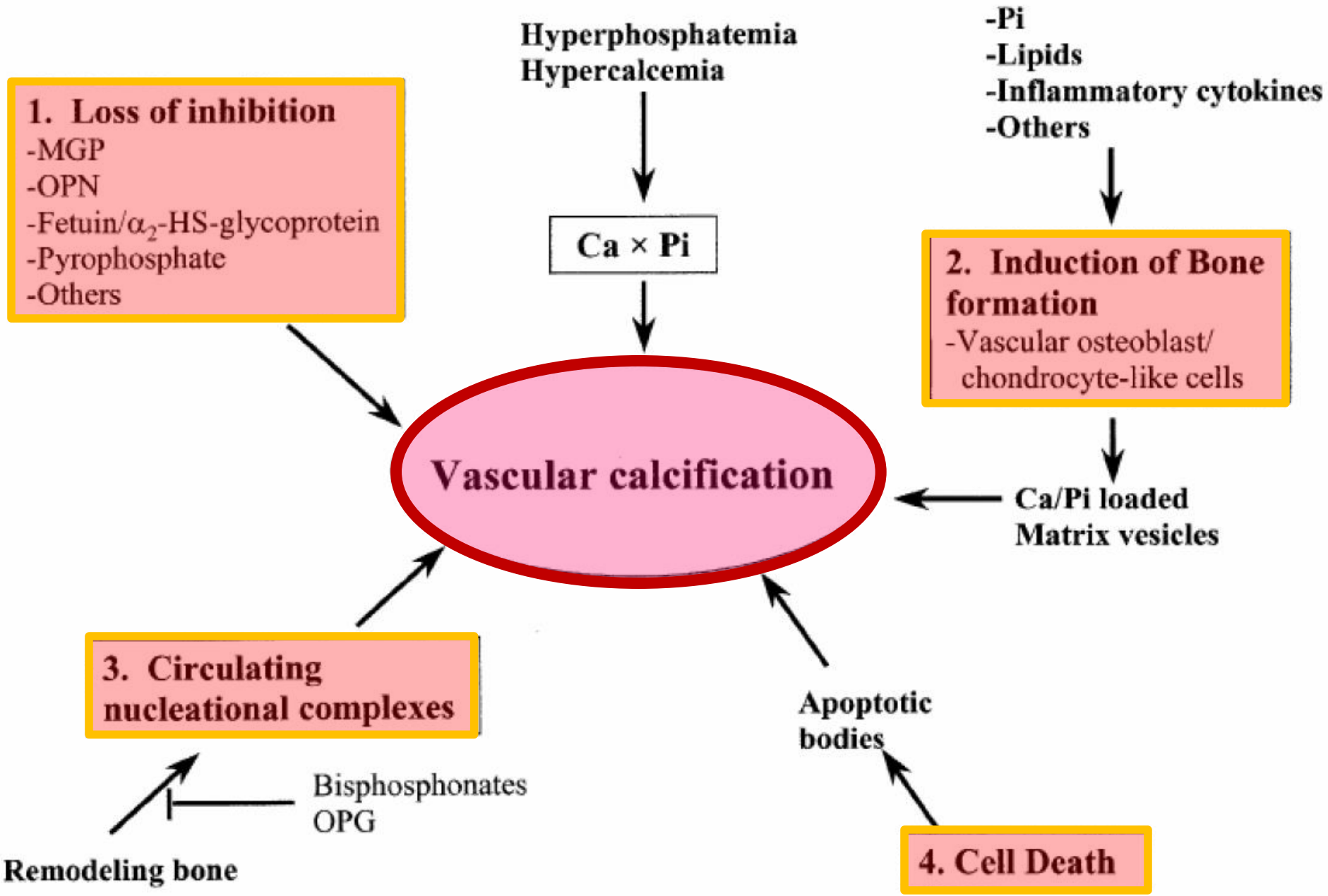
Unifying Hypothesis of AC & Osteoporosis



Osteoporos Int 2007;18:251-259

Vascular Calcification

- A **regulated Active Process**, which parallels many aspects of **calcification in bone** !


Hyperphosphatemia
Hypercalcemia
-Pi
-Lipids
-Inflammatory cytokines
-Others
1. Loss of inhibition
-MGP
-OPN
-Fetuin/α_2-HS-glycoprotein
-Pyrophosphate
-Others
Ca × Pi
2. Induction of Bone formation
-Vascular osteoblast/ chondrocyte-like cells
Vascular calcification
Ca/Pi loaded Matrix vesicles
3. Circulating nucleational complexes
Bisphosphonates
OPG
Remodeling bone
Apoptotic bodies
4. Cell Death

To halt Vascular Calcification

Anti-VC may improve aortic stiffness

- ACEi
- Cross-link breakers
- Bisphophonate
- Calcimimetics
- Phosphate binder
- Recombinant OPG (denosumab) ...

Summary

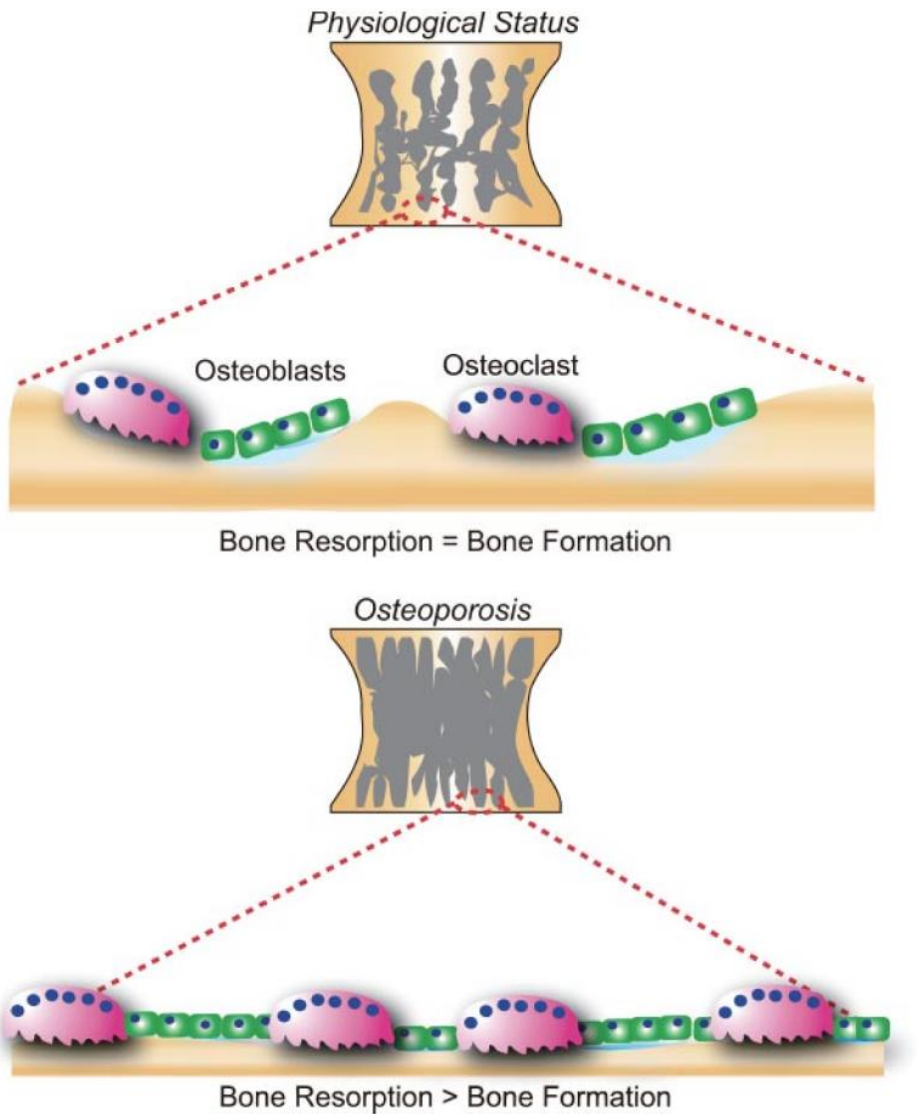
- Ao stiffness is an integrated marker of the chronological damage of the CV risk factors on the arterial wall
- Ao stiffness is better predictive of CV outcomes
- VC is one of the mechanisms of Ao Stiffness
- VC-Ao Stiffness contributes to hypertension
- Targeting VC mechanisms may improve Ao Stiffness


Thank you !

Common Mechanisms in the pathoge nesis of osteoporosis & AC

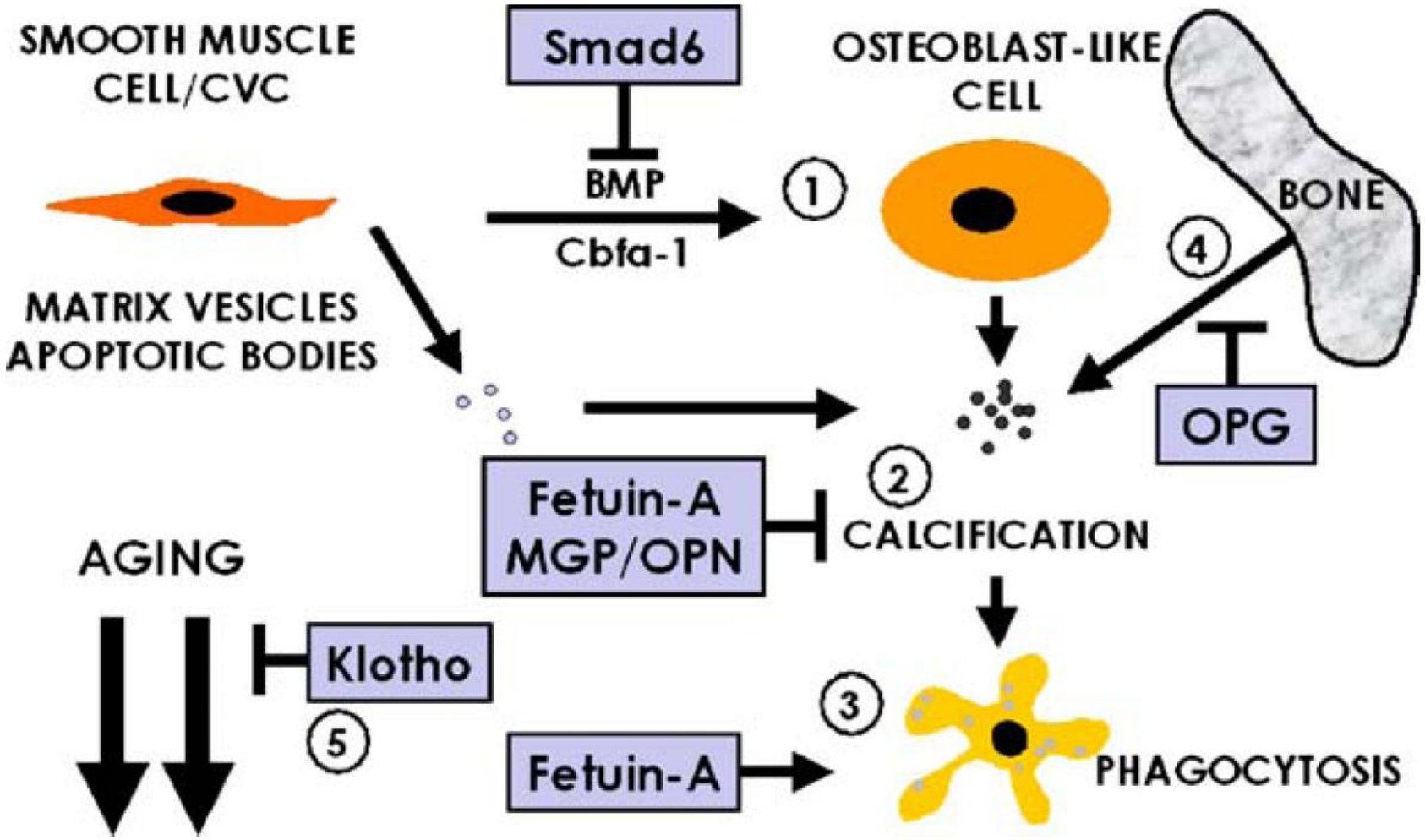
- Age
- Chronic inflammation (e.g. RA)
- Smoking
- DM
- Estrogen deficiency
- Vit C, D & K ↓
- Oxidized lipids & free radicals
- Renal failure

Role of Bone cells in Bone remodeling



Imai Y et al. Mol Endocrinol, 2010

Unifying Hypothesis of AC & Osteroporosis



Osteoporos Int 2007;18:251-259

Vascular Calcification & Osteoporosis

- Epidemiology
- Risk factors and Mechanisms
- **Clinical implication**
- Therapeutic, Preventive challenges
- Summary

Clinical Implication: CAC

AHA Scientific Statement

Assessment of Coronary Artery Disease by Cardiac Computed Tomography

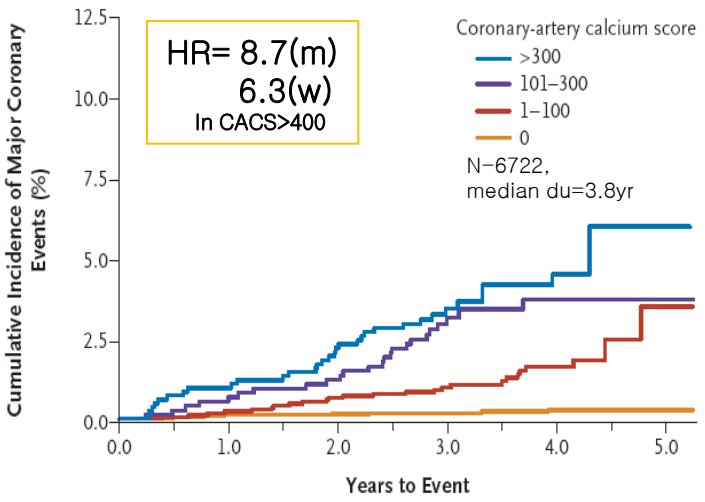
TABLE 5. Sensitivity and Specificity of Diagnostic Tests for Evaluation of CAD

	No. of Patients	Sensitivity, %	Specificity, %
Stress treadmill[85]	2456	52	71
Exercise SPECT[85,86]	4480	87	73
Stress echocardiography[85]	2637	85	77
EBCT calcium[22,23,89]	5730	85	75

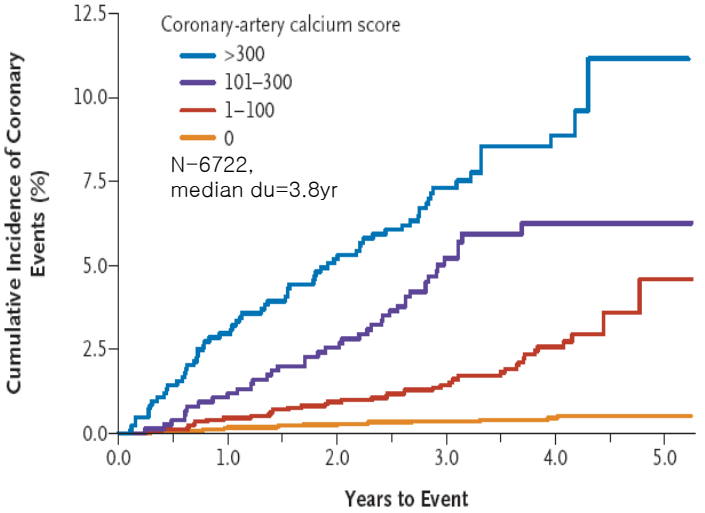
Circulation 2006;114:1761-1791.

CAC as a Predictor of Coronary Events & Survival

MACE (MI & CHD death)

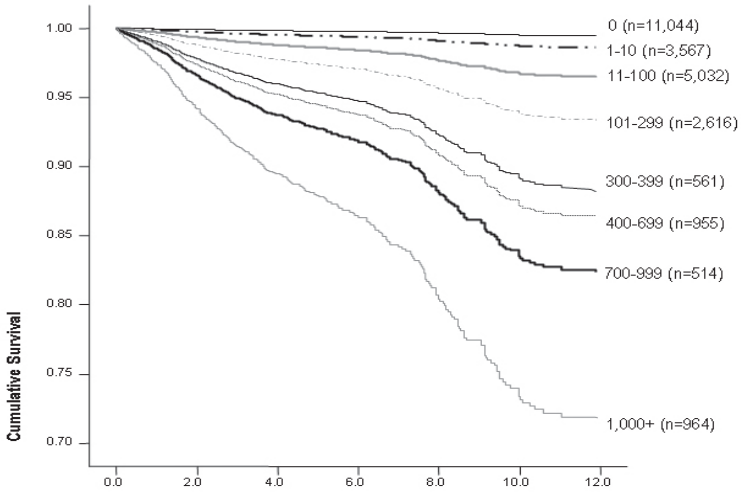


Any coronary events



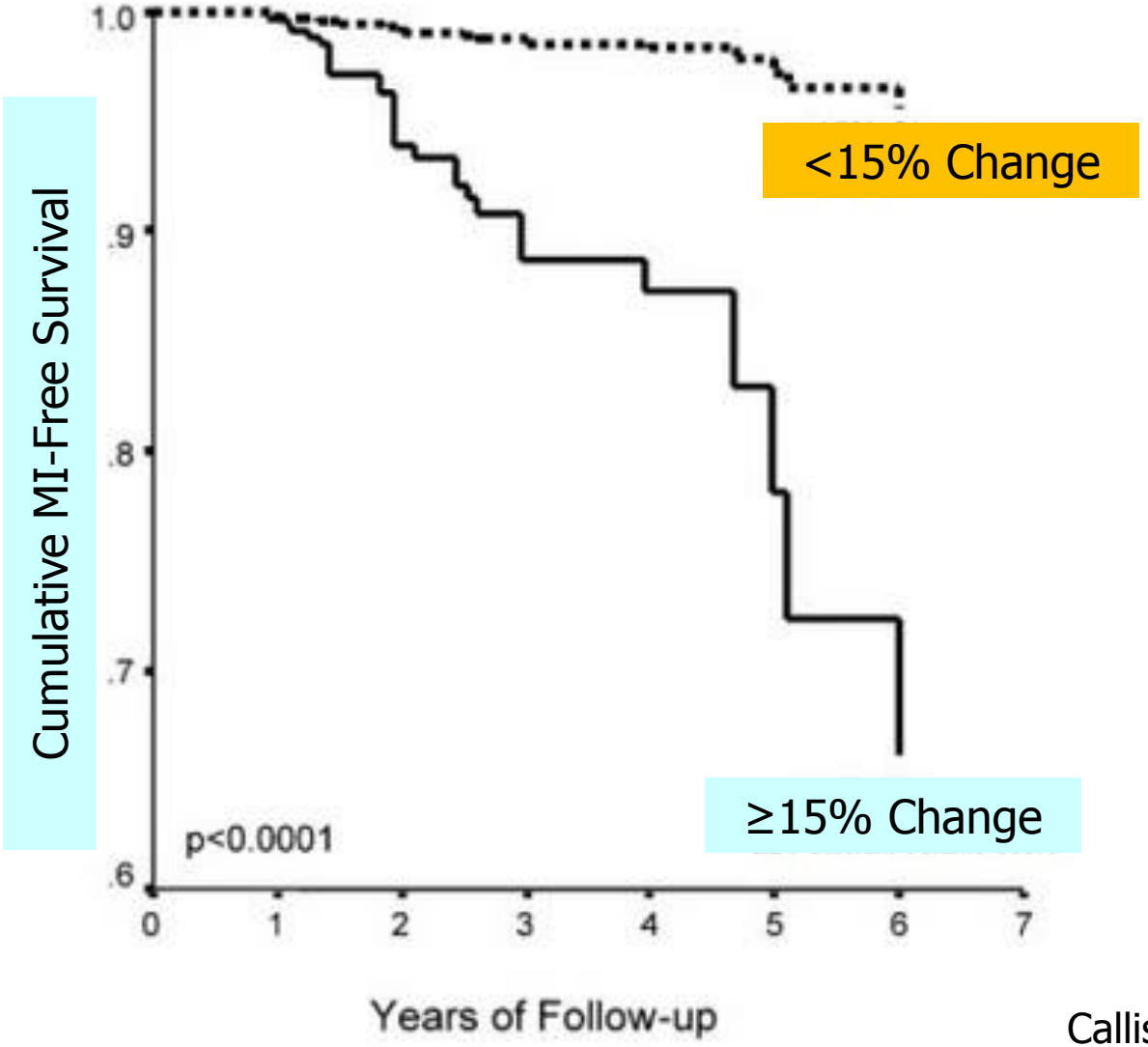
Detrano et al. N Engl J Med 2008;358:1336-45.

Survival



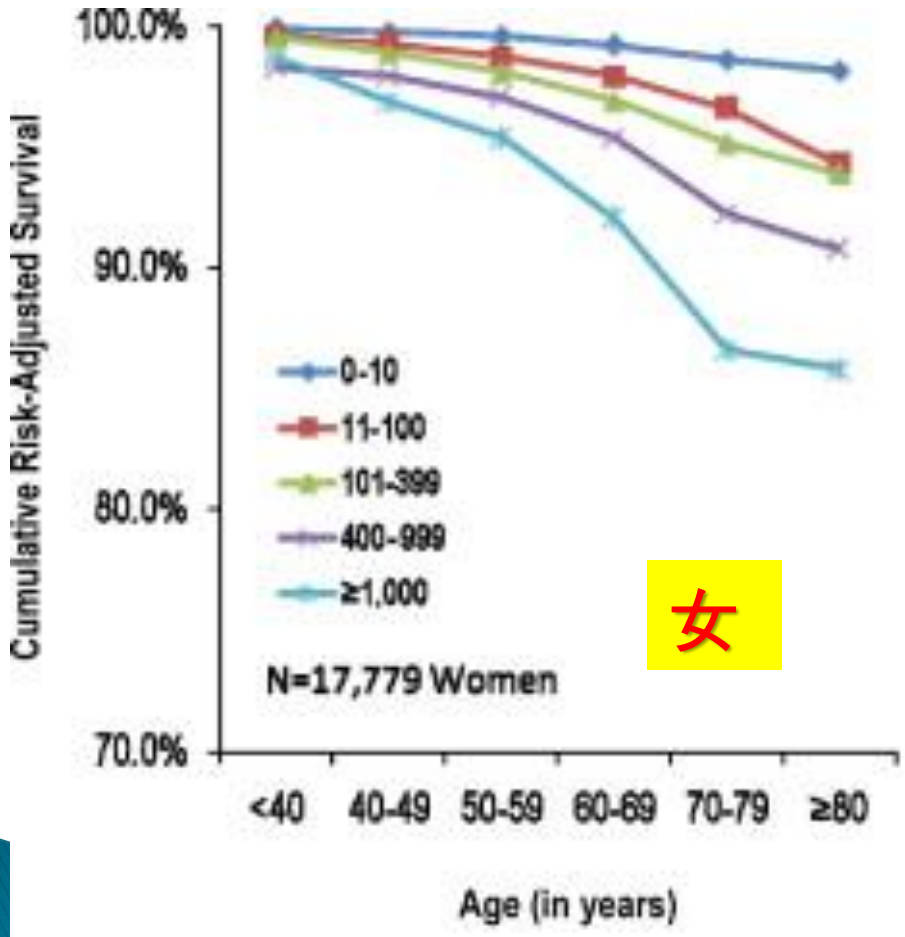
Budoff et al. Vascul Health Risk Manage 2008:4:315-24

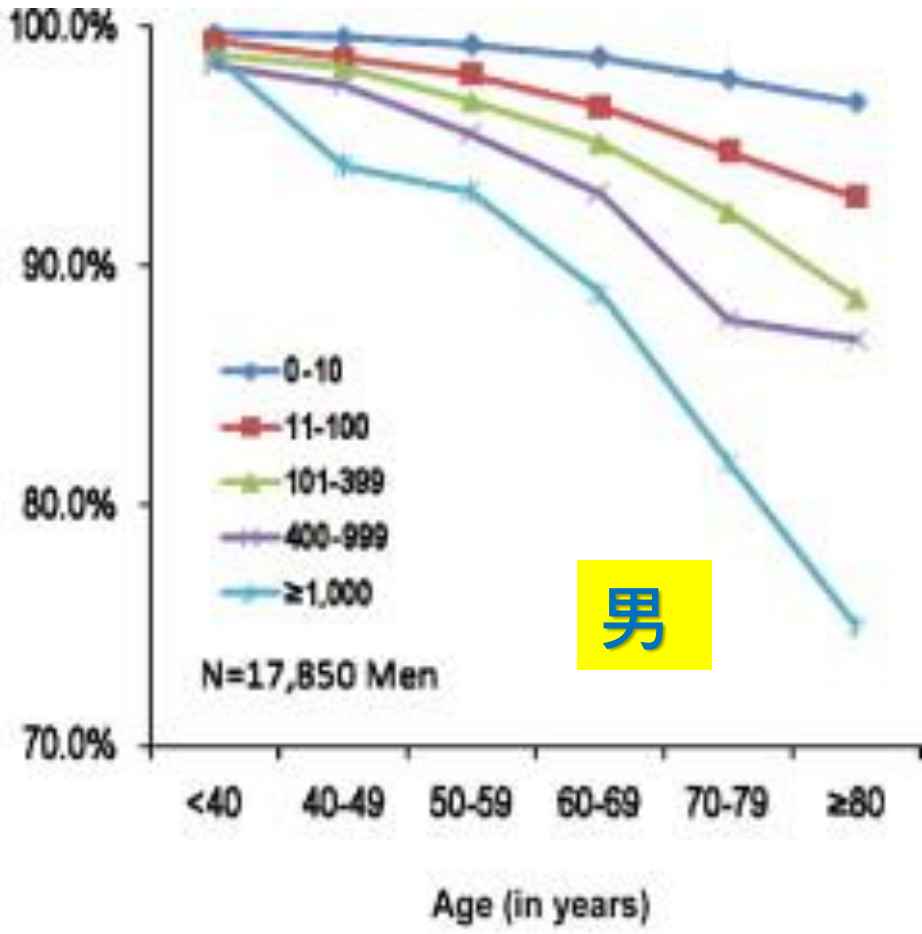
Time to AMI for patients with a yearly calcium volume score change



Callister et al, *ATVB* 2004

Risk-adjusted survival by CAC across age deciles in women and men.





J Am Coll Cardiol 2008;52:17-23

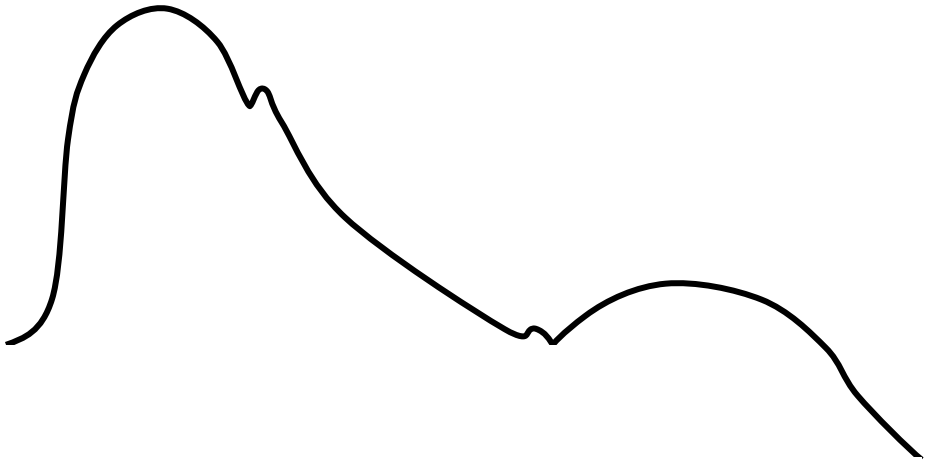
Clinical Implication: AC

Outcome	Aortic Arch Calcification			
	Men (n = 55 916)		Women (n = 60 393)	
	None	Present	None	Present
Coronary heart disease				
No events	7954	242	4901	264
Rate per 1000 person-years	7.6	14.6	4.1	9.6
Relative risk (95% confidence interval)				
Age-adjusted		1.25 (1.09-1.42)		1.22 (1.07-1.39)
Multivariate-adjusted†		1.27 (1.11-1.45)		1.22 (1.07-1.38)
Ischemic stroke				
No events	3089	110	3243	258
Rate per 1000 person-years	2.9	6.6	2.7	9.3
Relative risk (95% confidence interval)				
Age-adjusted		1.17 (0.96-1.42)		1.50 (1.32-1.71)
Multivariate-adjusted†		1.17 (0.97-1.42)		1.46 (1.28-1.67)

JAMA 2000;283:2810-2815.

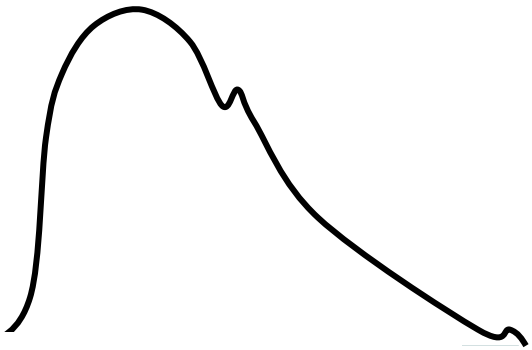
Young normal aorta

Resistance artery

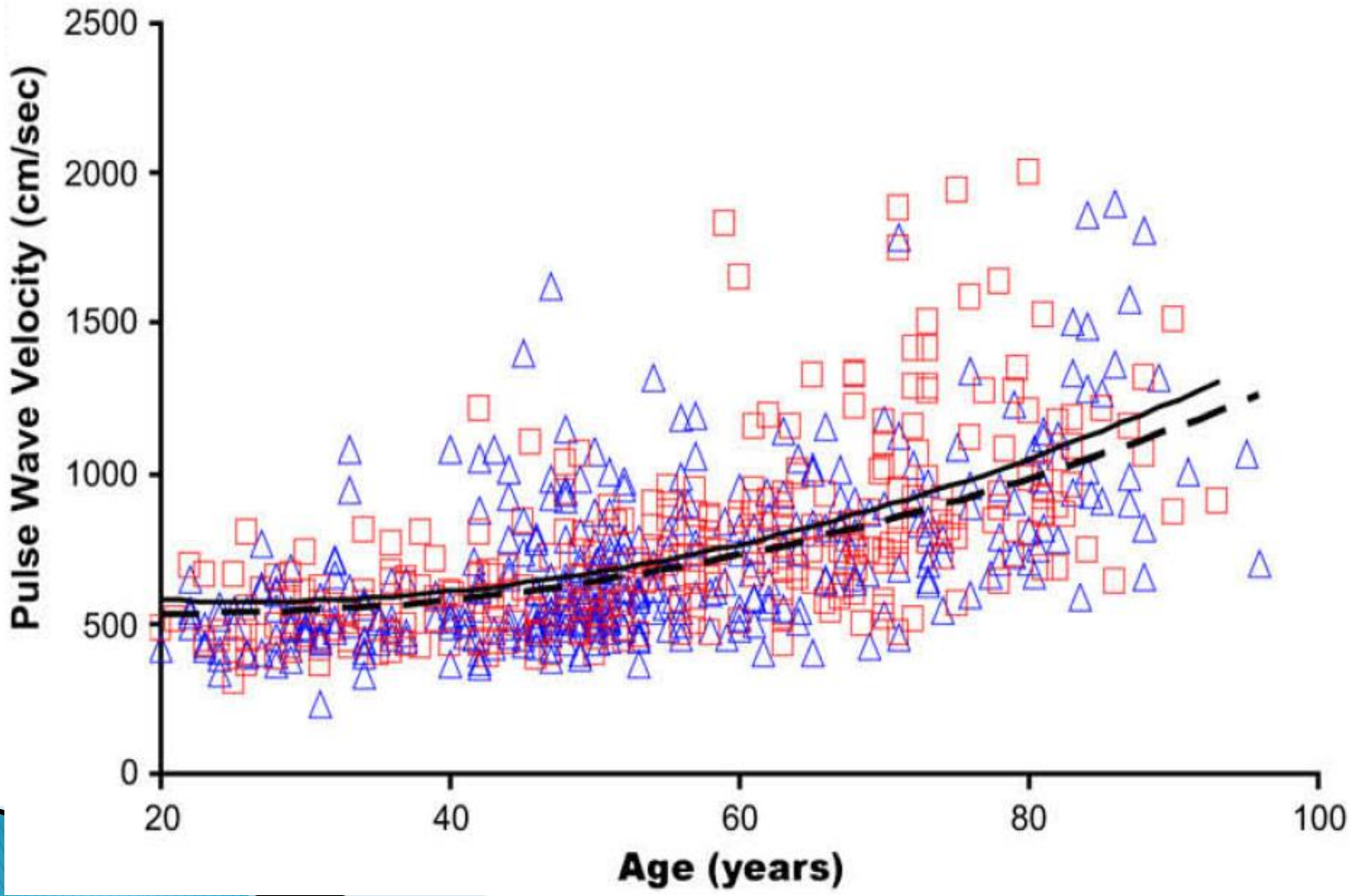


Old stiff aorta

Resistance artery

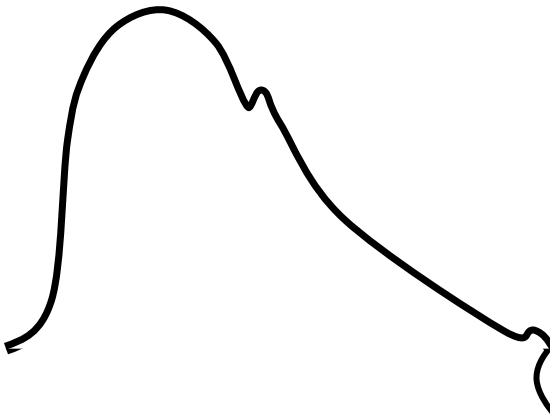


Clinical Implication: A Stiffening (AC) with Aging

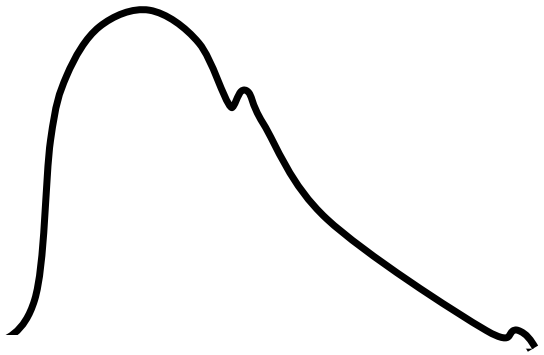


Lakatta et al, Med Clin N Am 2009:93:583–604

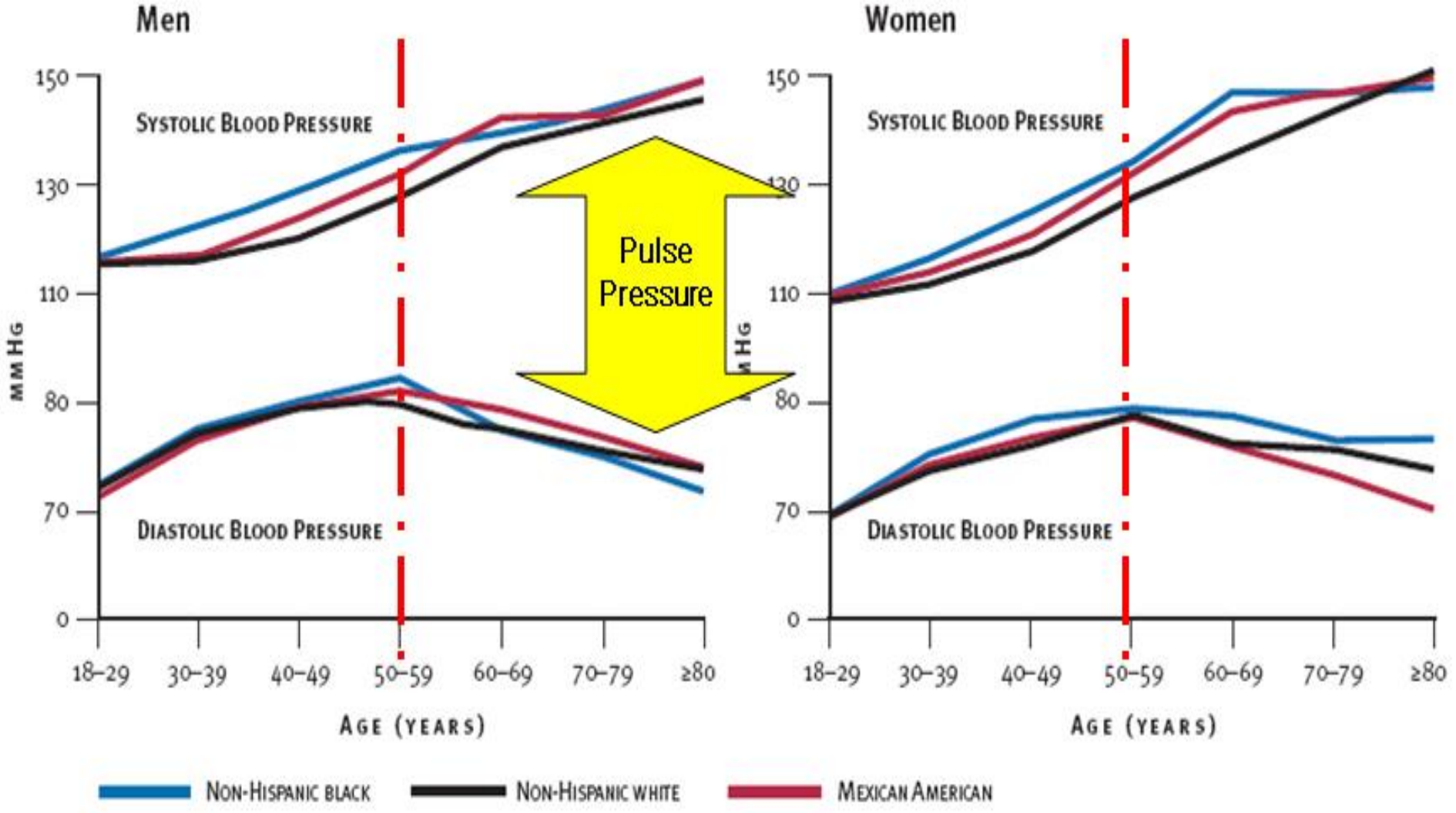
Young normal aorta



Old stiff aorta

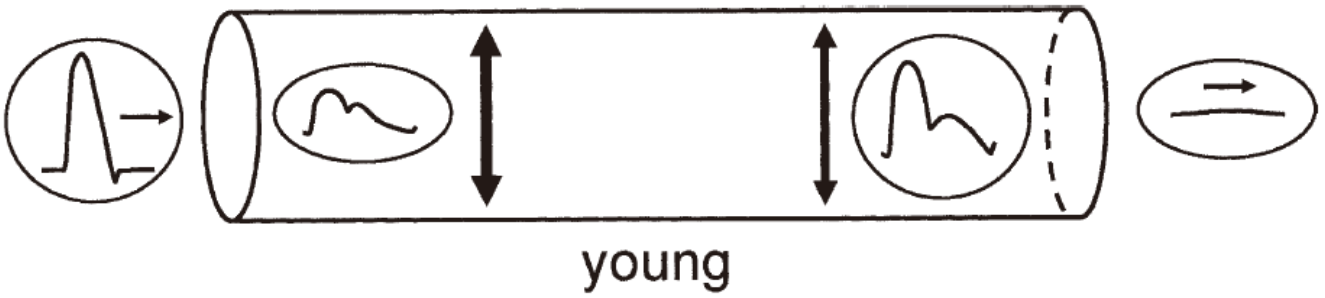


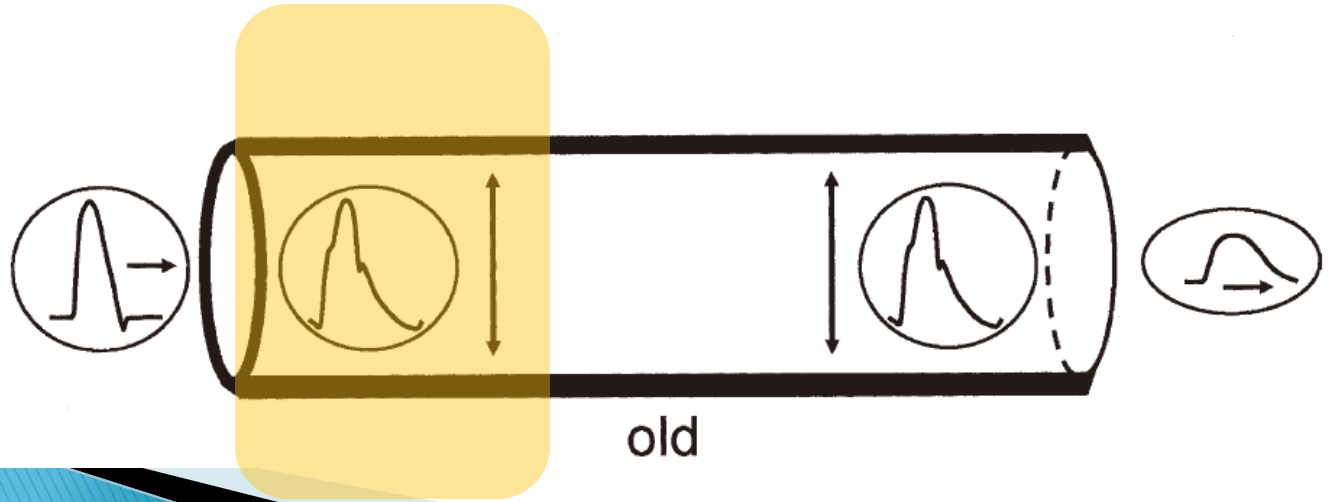
Clinical Implication: A Stiffening (AC) & Blood pressure with Aging



Hypertension 1995;25:305-13

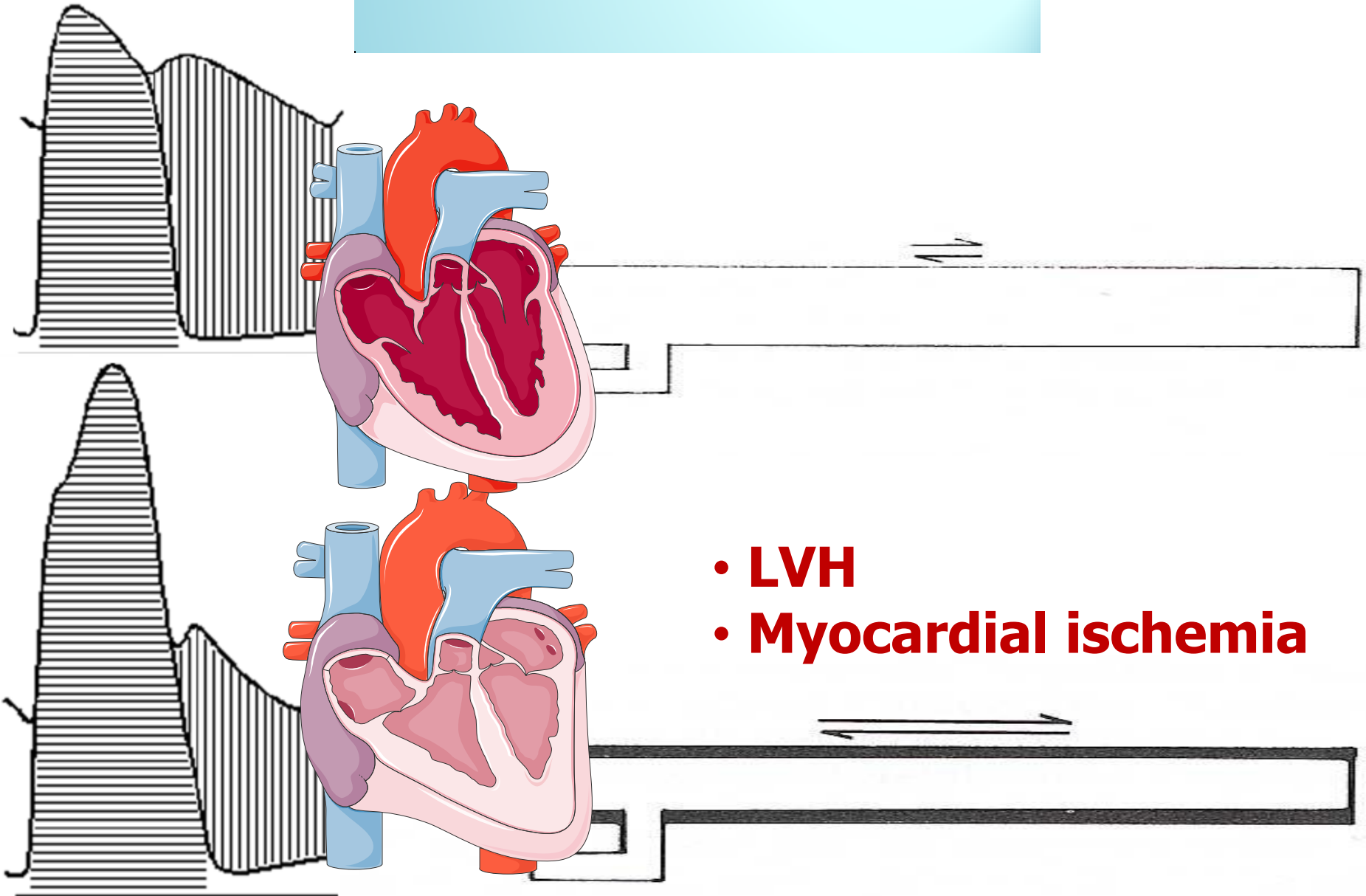
Altered Cushion & Conduit Function





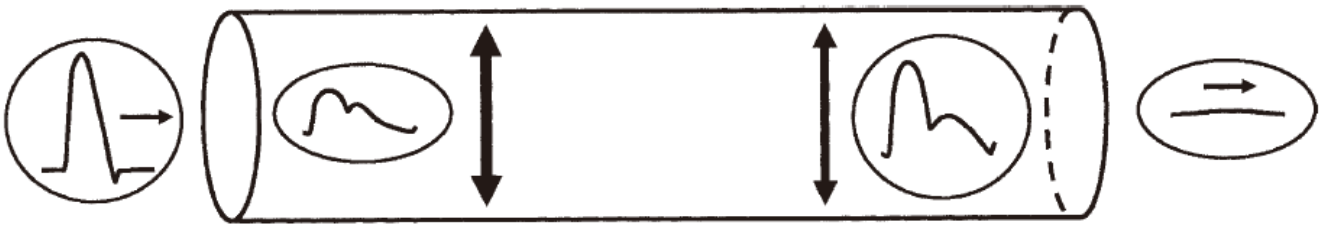
O'Rourke and Hashimoto, *JACC* 2007:50:1-13

On Heart



- **LVH**
- **Myocardial ischemia**

Altered Cushion & Conduit Function



young

old

O'Rourke and Hashimoto, *JACC* 2007:50:1-13

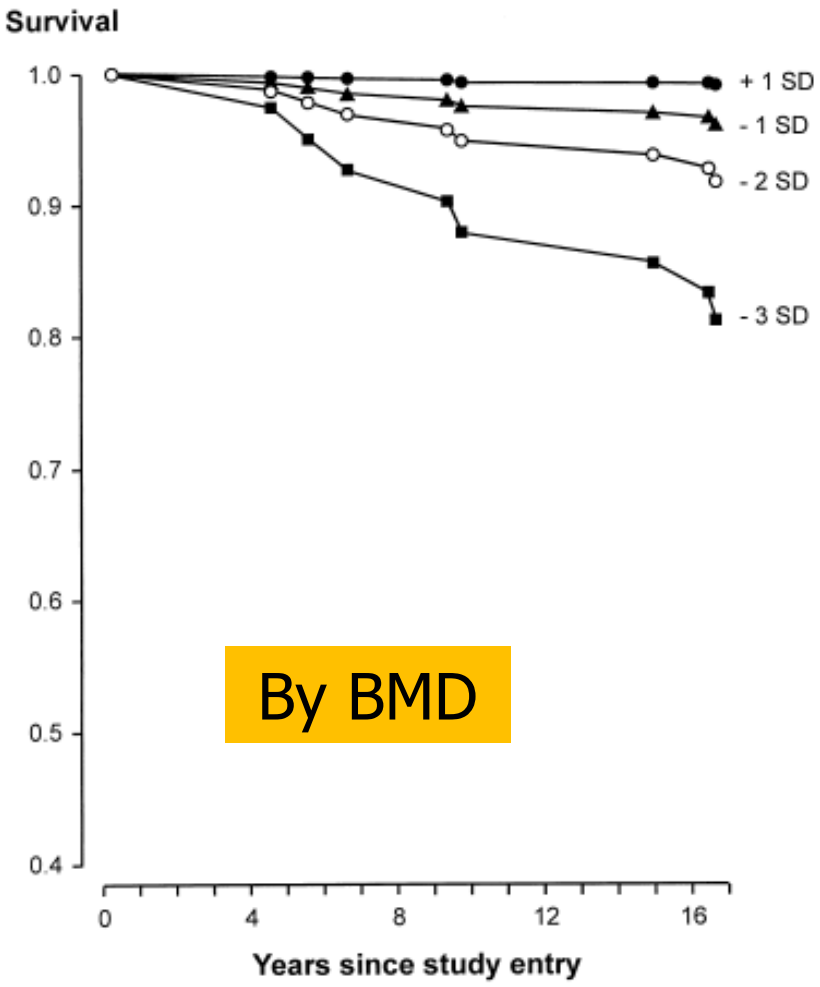
Osteoporosis for CAD

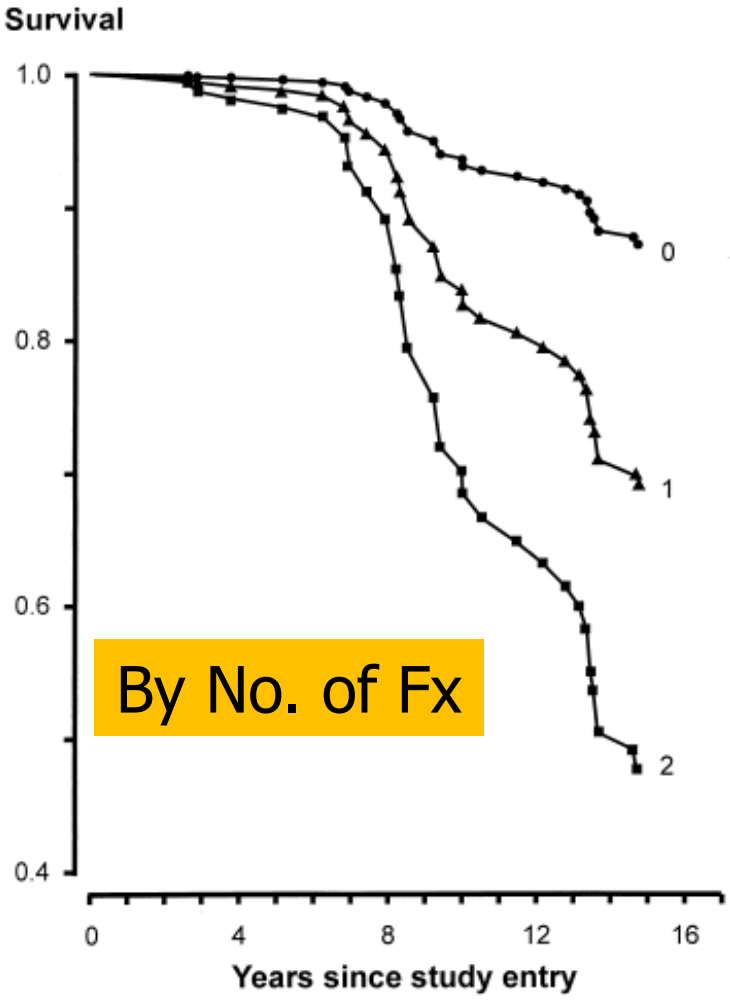
Multivariable model of association between bone density and coronary artery disease

Variables	OR of CAD ≥50%	95% CI	p Value
Osteoporosis	5.58	2.59–12.0	<0.0001
Hypertension	3.92	1.81–8.45	0.0005
Family history of premature CAD	2.99	1.39–6.46	0.0052
Serum glucose level >110 mg/dl	3.28	1.64–6.58	0.0008

Am J Cardiol. 2005;96:1059-63.

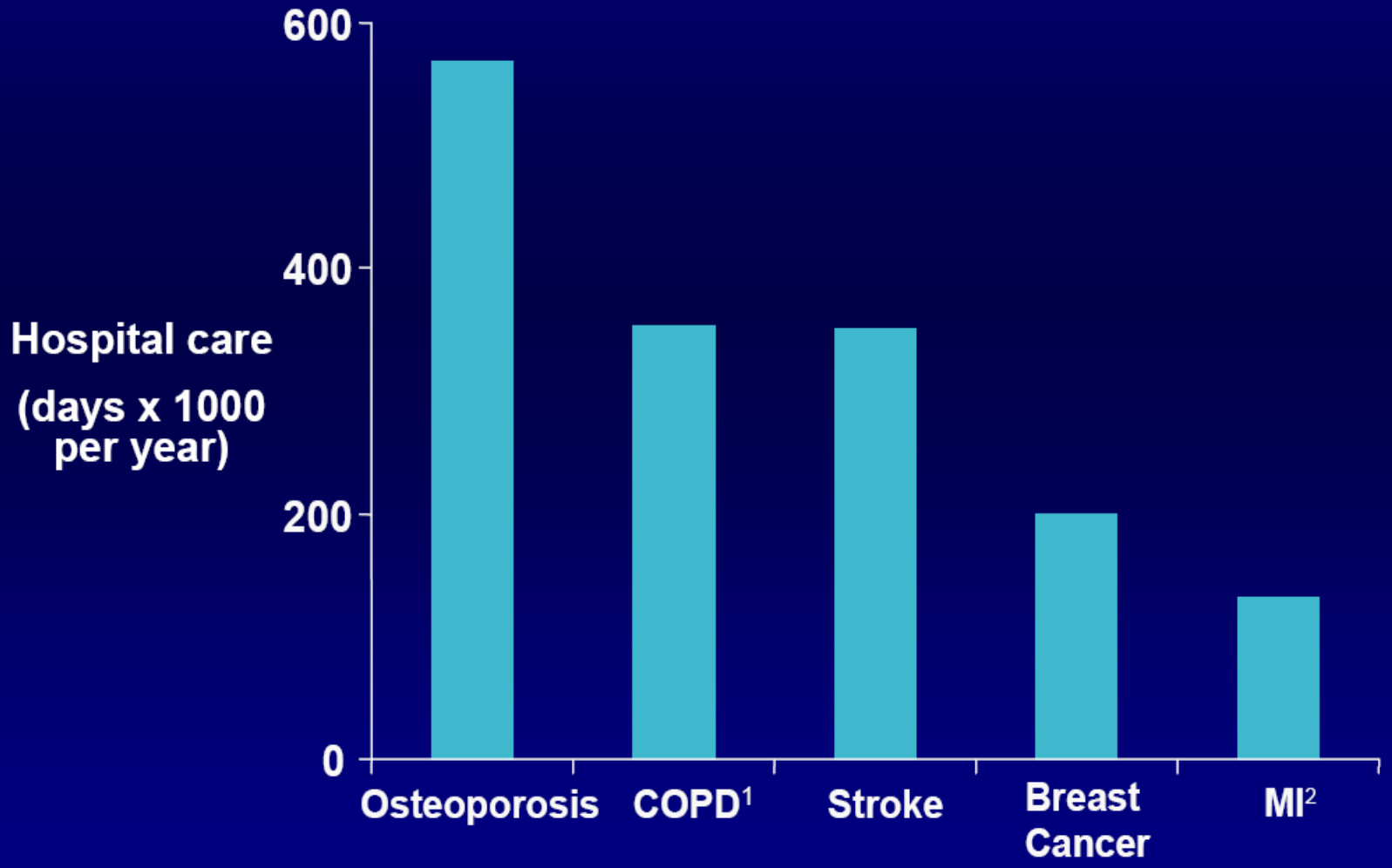
BMD & Survival free of CV death





Am J Med 1999;106:273-8

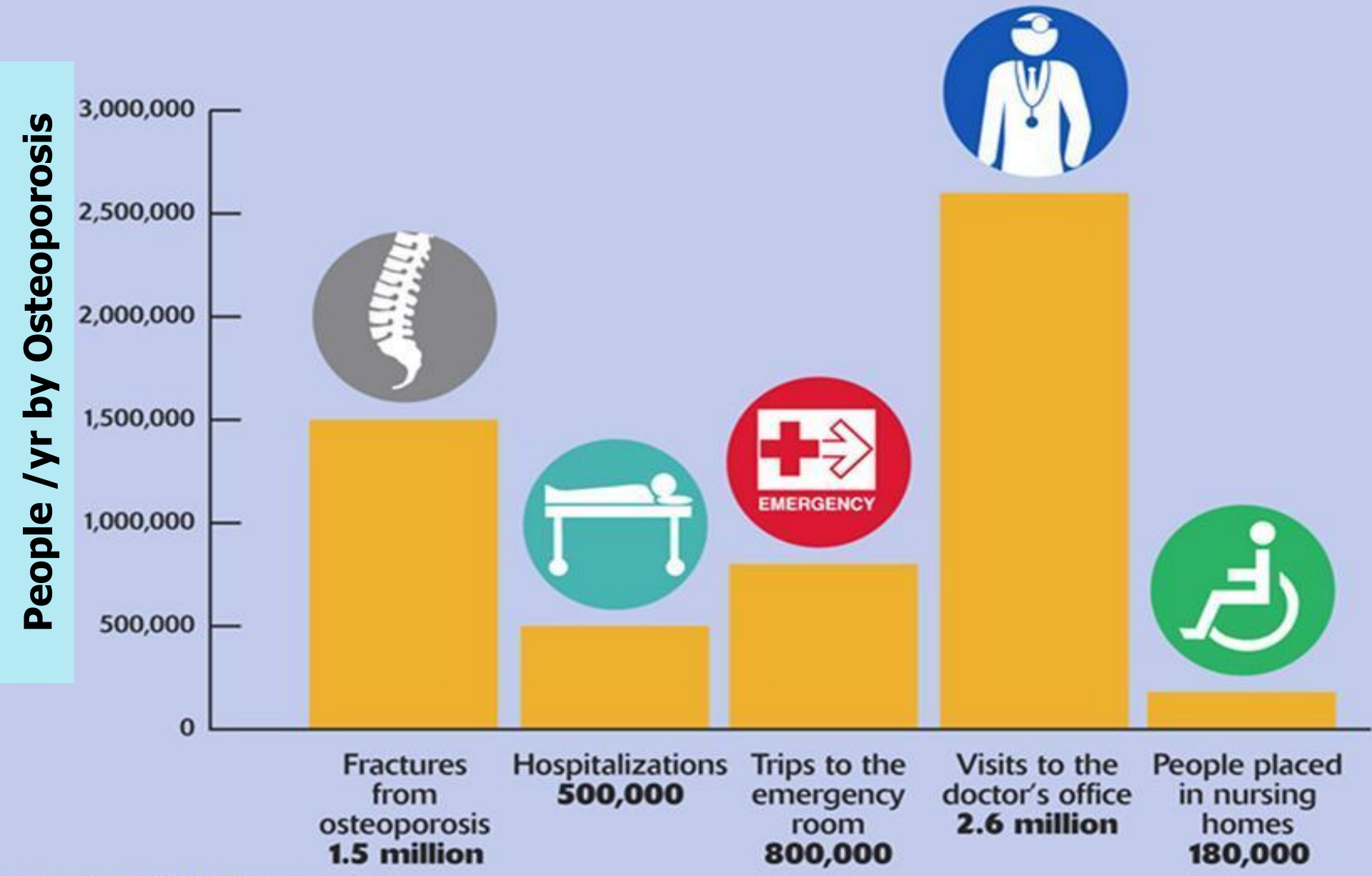
Osteoporosis-related Hospital Care



[1]Chronic obstructive pulmonary disease
[2]Myocardial infarction

Lippuner K, et al. *Osteoporos Int.* 19

Poor bone health is common and costly.



Source: U.S. Office of the Surgeon General

Vascular Calcification & Osteoporosis

- Epidemiology
- Risk factors and Mechanisms
- Clinical implication
- **Therapeutic, Preventive challenges**
- Summary

Clinical Factors on Bone & Artery Mineralization

Factor	Calcification	
	Bone	Artery
Estrogen	↑	↑
Bisphosphonates	—	↓
Diabetes	↓	↑
Hyperlipidemia	↓	↑
Hyperparathyroidism	↓	↑
Uremia	↓	↑
Warfarin*	↓	↑

*Includes vitamin K deficiency.

ATVB 2004;24:1161-70

Therapeutic Options for Dual-purposes

Clinical	
Statins	Anti-atherogenic Evidence for enhanced bone density Fracture reduction uncertain
Bisphosphonates	Anti-resorptive, enhance bone density, reduce fractures Diminish arterial calcification and in-stent intimal hyperplasia
Thiazolidinediones	Anti-atherogenic Increase adipogenesis and decrease osteoblastogenesis; Limit TNF-α effects on bone loss. Needs to be studied clinically for bone effects
Experimental	
Enzyme 12/15 LO	Pharmacological inhibition increases bone density Anti-atherogenic
OCN	Deficient genetic expression increases bone density
Modifying LRP5	To induce high bone mass
Deleting Wnt antagonist	Increases bone density
Therapy with OPG	Increases bone density
Mouse model deficient in low-density LRP treated with PTH	Increases bone density, decreases aortic valve calcification
Adiponectin	Improves diabetic state, anti-atherogenic

Q J Med 2005;98:467-84

Pros & Cons of BP in Atherosclerosis

Pros: inhibit the development of atherosclerosis

- Rosenblum IY, Flora L, Eisenstein R. The effect of disodium ethane-1-hydroxy-1,1-diphosphonate (EHDP) on a rabbit model of atheroarteriosclerosis.Atherosclerosis 197 5; 22: 411–424.
- Kramsch DM, Chan CT. The effect of agent interfering with soft tissue calcification and cell proliferation on calcific fibrous-fatty plaques in rabbits. Circ Res 1978; 42: 562 –571.
- Kramsch DM, Aspen AJ, Rozler LJ. Atherosclerosis: prevention by agents not affecting abnormal levels of blood lipids. Science 1981; 213:1511–1512.
- Ylitalo R, Oksala O, Yla-Herttuala S, Ylitalo P. Effects of clodronate (dichloro-methylene bisphosphonate) on the development of experimental atherosclerosis in rabbits. J Lab Clin Med 1994; 123:769–776.
- Zhu B-Q, Sun Y-P, Sievers RE, Isenberg WM, Moorhead TJ, Parmley WW. Effects of etidronate and lovastatin on the regression of atherosclerosis in cholesterol-fed rabb its. Cardiology 1994; 85:370–377.
- Price PA, Faus SA, Williamson MK. Bisphosphonates alendronate and ibandronate inhibitartery calcification at doses comparable to those that inhibit bone resorption. Art erioscler Thromb Vasc Biol 2001; 21:817–824.

Cons: not inhibit the development of atherosclerosis

- J.F. Bukowsky, C.C. Dascher, H. Das, 2005. Alternate bisphosphonate targets and mechanisms of action. Biochem. Biophys. Res. Commun. 328 (2005) 746–750.
- V. Kunzmann, E. Bauer, J. Feurle, et al., Stimulation of c/dT cells by aminobisphosphonates an in induction of antiplasma cell activity in multiple myeloma cells, Blood 96 (2000) 384–392.
- Shimshi M, Abe E, Fisher EA, Zaidi M, Fallon JT. Bisphosphonates induce inflammation and rupture of atherosclerotic plaques in apolipoprotein-E null mice. Biochem Biop hys Res Comm 2005; 328:790–793.
- Tanko LB, Qin G, Alexandersen P, Bagger YZ, Christiansen C. Effective doses of ibandronate do not influence the 3-year progression of aortic calcification in elderly osteo porotic women. Osteoporosis Int 2005; 16:184–190.

Statin & Arterial Calcification

Statin vs. Placebo

Effect of *Simvastatin (80 mg)* on Coronary and Abdominal Aortic Arterial Calcium (from the Coronary Artery Calcification Treatment with Zocor [CATZ] Study)

"Simvastatin treatment does not reduce progression of CAC or AAC compared with placebo."

Intensive (80mg) vs. Standard (10mg)

Effect of Intensive Versus Standard Lipid-Lowering Treatment With *Atorvastatin* on the Progression of Calcified Coronary Atherosclerosis Over 12 Months
A Multicenter, Randomized, Double-Blind Trial

"Intensive atorvastatin therapy was unable to attenuate CAC progression compared with standard atorvastatin therapy."

Estrogen Therapy & CAC

- WHI-CACS
- 1064 with hystrectomy at 50-59 yr
- 8.7 yr f/u

Coronary-Artery Calcium Score	Conjugated Equine Estrogens	Placebo	Odds Ratio (95% CI)		Multivariate P Value
			Unadjusted	Multivariate	
	no. (%)				
Intention-to-treat analyses†	N = 537	N = 527			
0 (referent)	299 (55.7)	266 (50.5)	1.00	1.00	
>0	238 (44.3)	261 (49.5)	0.81 (0.64–1.03)	0.78	0.09
<10 (referent)	348 (64.8)	302 (57.3)	1.00	1.00	
≥10	189 (35.2)	225 (42.7)	0.73 (0.57–0.93)	0.74	0.04
<100 (referent)	448 (83.4)	408 (77.4)	1.00	1.00	
≥100	89 (16.6)	119 (22.6)	0.68 (0.50–0.93)	0.69	0.04

- Esp. in ≥80% adherence to study medication

CAC	OR	P
>0	0.64	0.01
≥10	0.55	<0.001
≥100	0.46	0.001

NEJM 2007;356:2591-602

HRT & CAC in Postmenopausal

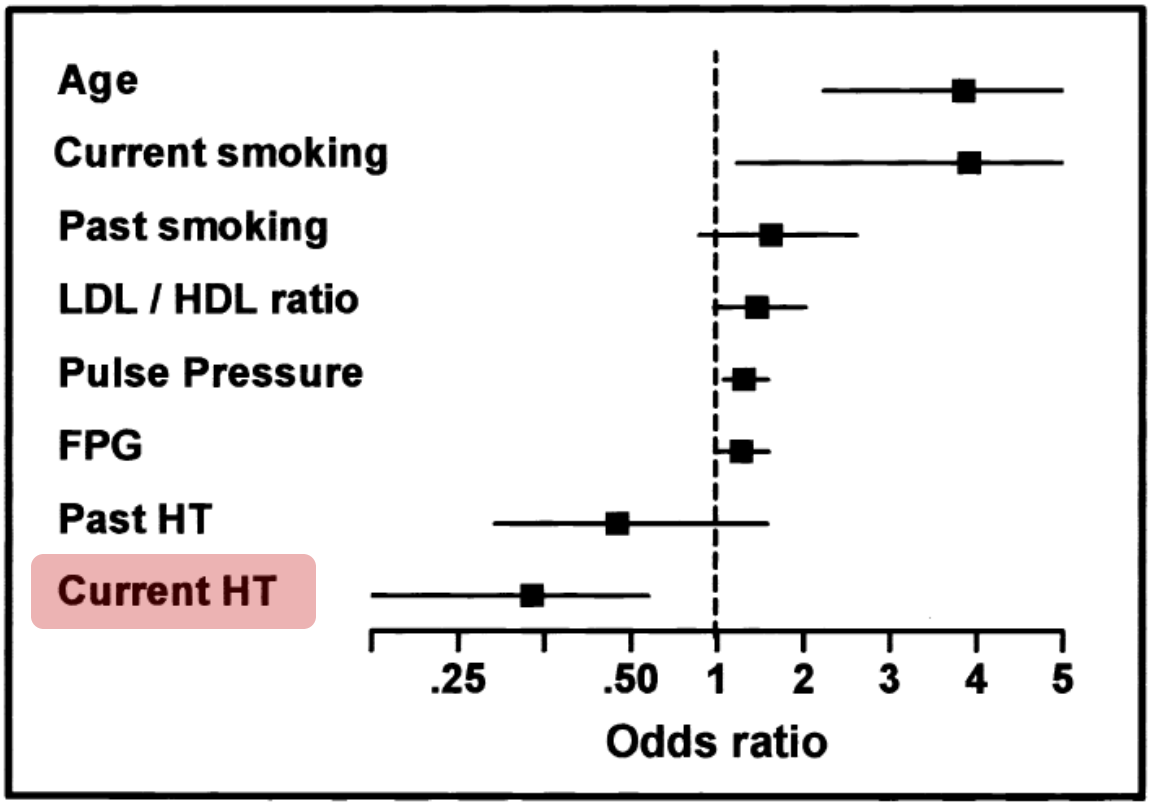
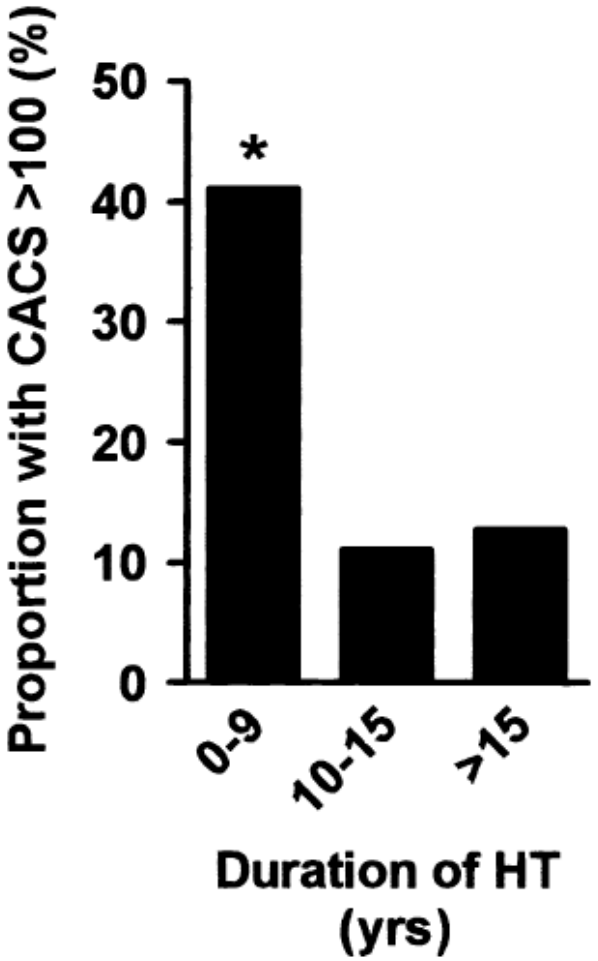


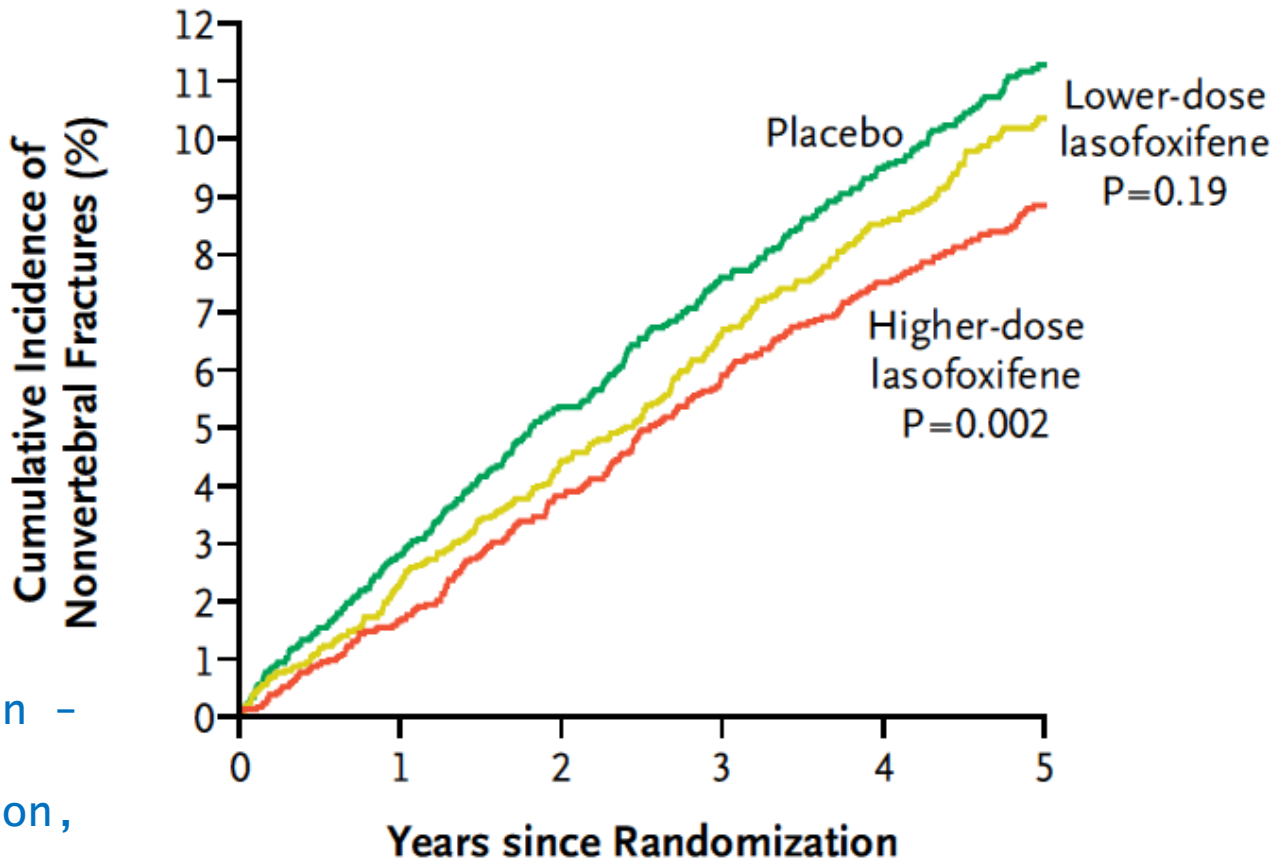
FIG. 1. Odds ratios for the association of *current* and *past* vs *never* HT and other CHD risk factors with increasingly severe coronary artery calcification among 204 asymptomatic postmenopausal women. Units: age = 10 y; LDL/HDL ratio = 1; pulse pressure = 10 mm Hg; FPG (fasting plasma glucose) = 20 mg/dL; current smoking = *yes* vs *no*.



Menopause 2005;12:40-48

SERM in Postmenopausal Osteoporosis

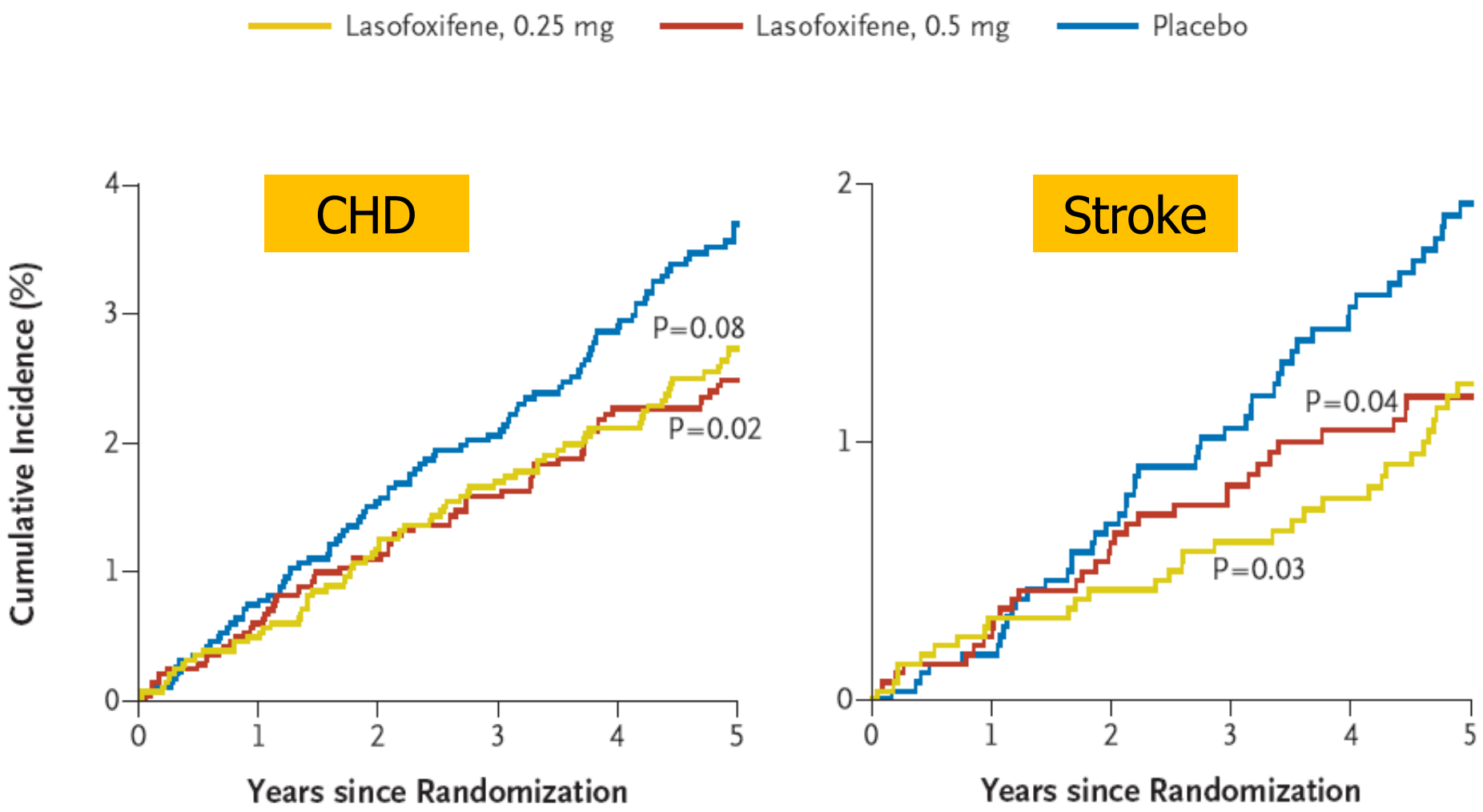
- PEARL trial
- 8556 women, 59-80 yr
- 5 yr f/u
- Lasofoxifene; newer selective estrogen-receptor modulator



*SERM: selective estrogen - receptor modulator
; Decrease bone resorption, bone loss, LDL-C
*PEARL: postmenopausal Evaluation and Risk-Reduction with Lasofoxifene

NEJM 2010;362:686-96

SERM in Postmenopausal Osteoporosis



SERM in Postmenopausal Osteoporosis