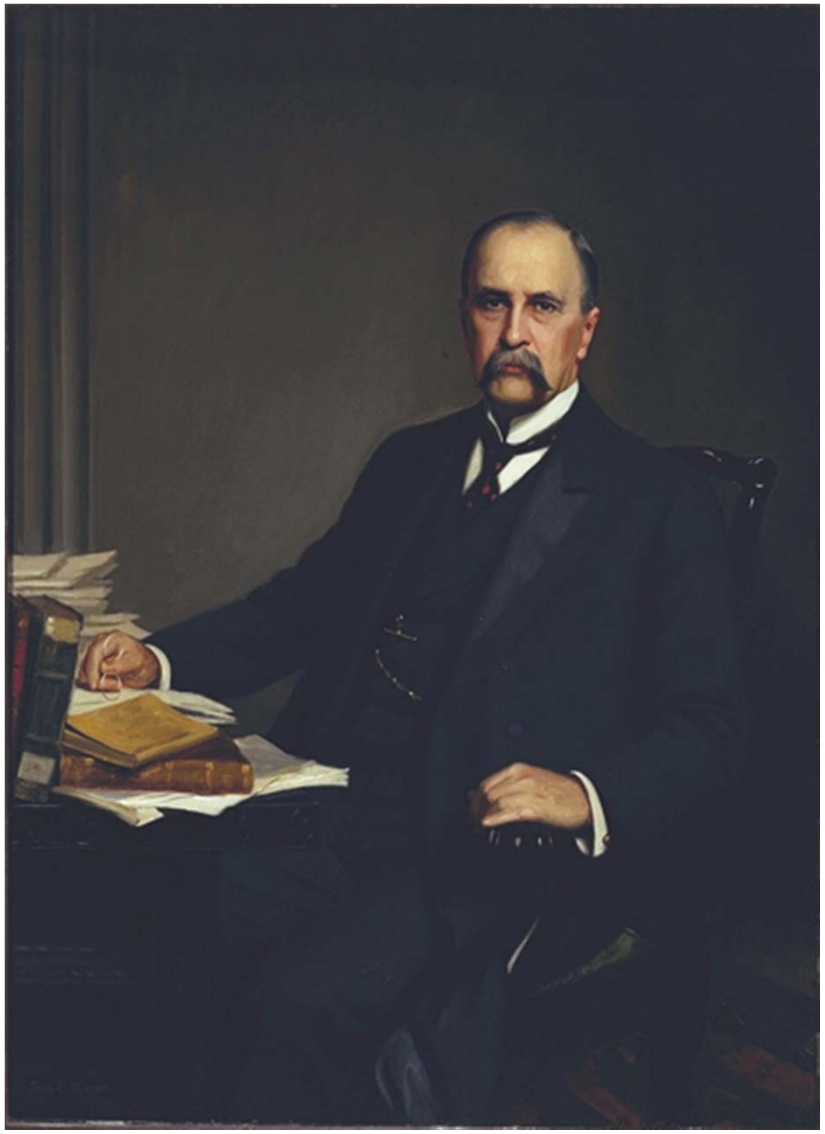
2011.4.16

How to Avert Vascular Calamity in Athero- and Arteriosclerosis?

Ju Han Kim

The Heart Center of Chonnam National University Hospital

Survivor or Death as aging



- **Longevity is a vascular question**

; Sir. William Osler (1849-1919)

- *The principles and practice*

of medicine (1898)

Origin of Terms

◆ **1755** - Von Haller used the Greek term, "**atheroma**", to describe a space filled with gruel-like material

◆ **1833** - Frenchman Jean Frederic Martin Lobstein first used the term " **arteriosclerosis**," Greek for "hardening of the arteries", to describe calcified arterial lesions

◆ **1852** - Johnson described the lesions of "**arteriolosclerosis**", a thickening of arterioles in the kidney in Bright's disease

◆ **1903** - M©nckeberg described "**medial calcific sclerosis**"

◆ **1904** - Marchand coined the term "**atherosclerosis**"

General Comments

- Arteriosclerosis
  - Thickening and loss of elasticity of arterial walls
  - Hardening of the arteries
  - Greatest morbidity and mortality of all human diseases via

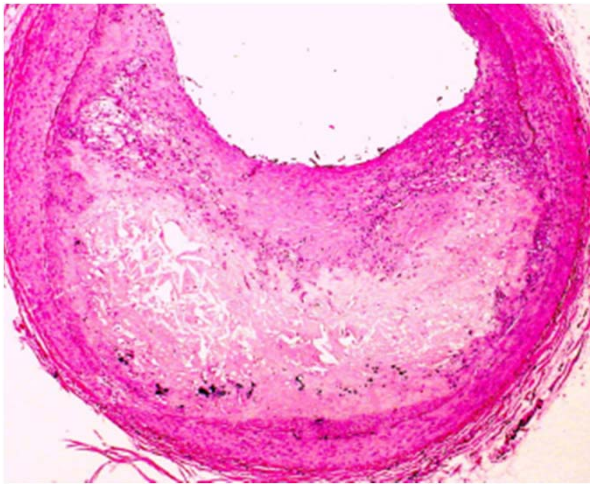
    Narrowing

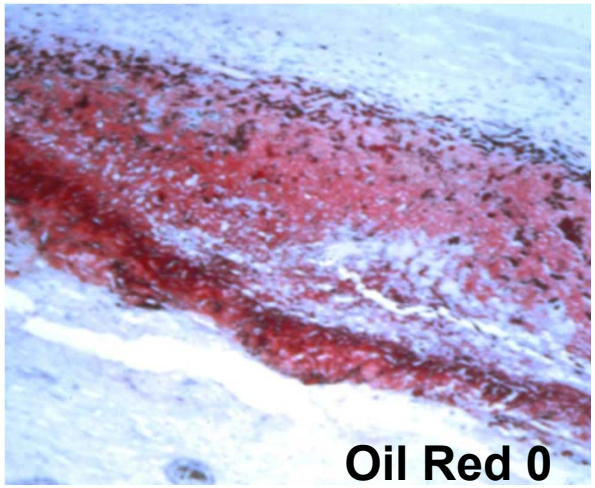
    Weakening

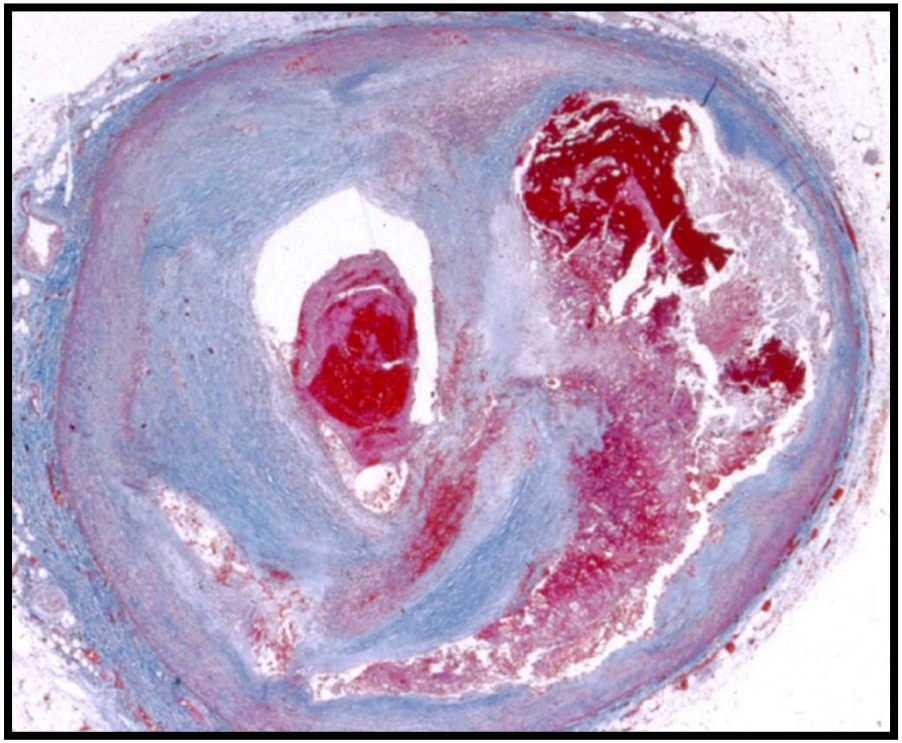
Three patterns of arteriosclerosis

- **Atherosclerosis**
  - The ***dominant pattern*** of arteriosclerosis
  - Primarily affects the elastic (aorta, carotid, iliac) and large to medium sized muscular arteries (coronary, popliteal)
- **Monckeberg medial calcific sclerosis**
- **Arteriolosclerosis** –small arteries and arterioles (hypertension and DM)

Atherosclerosis

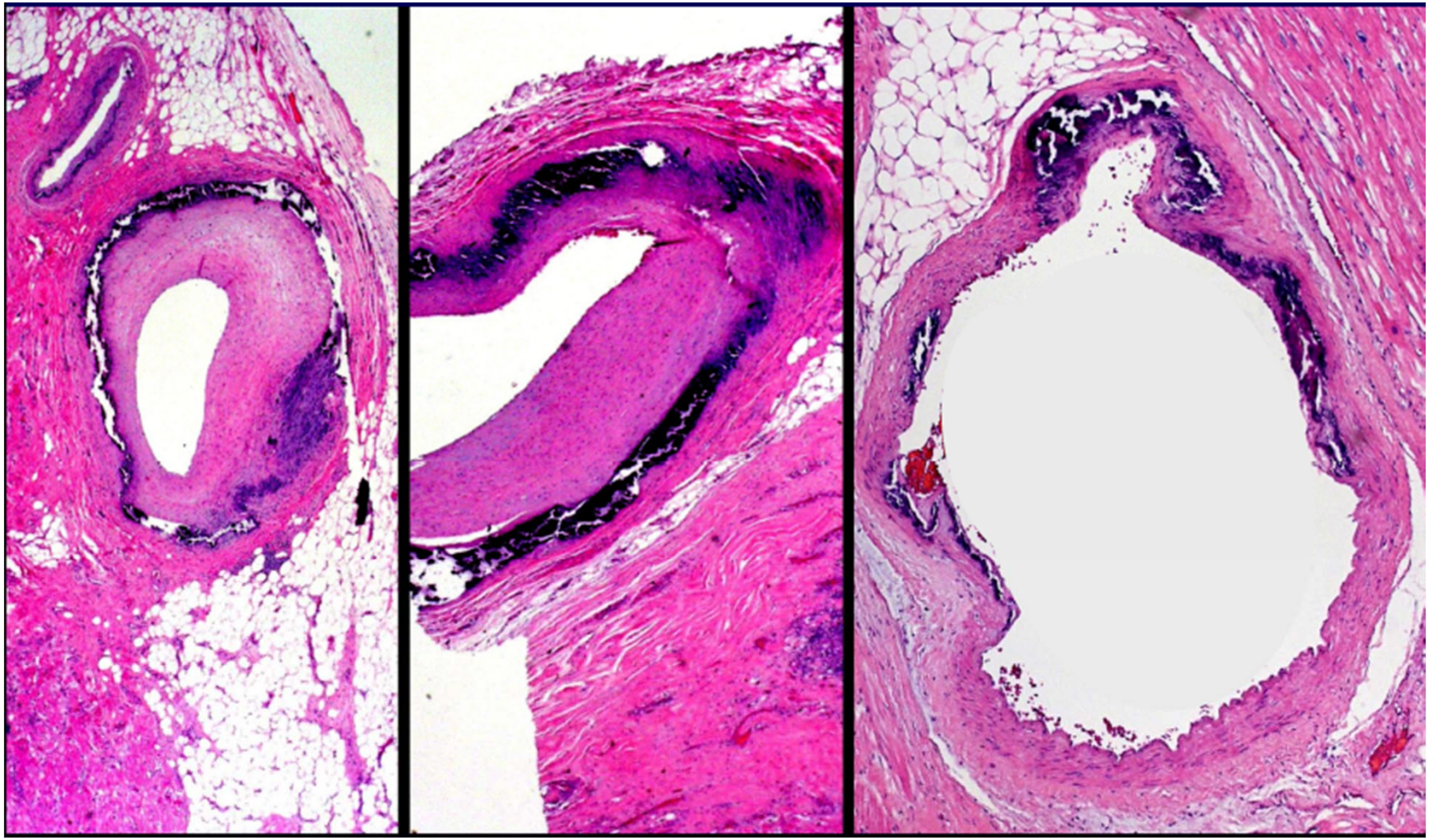




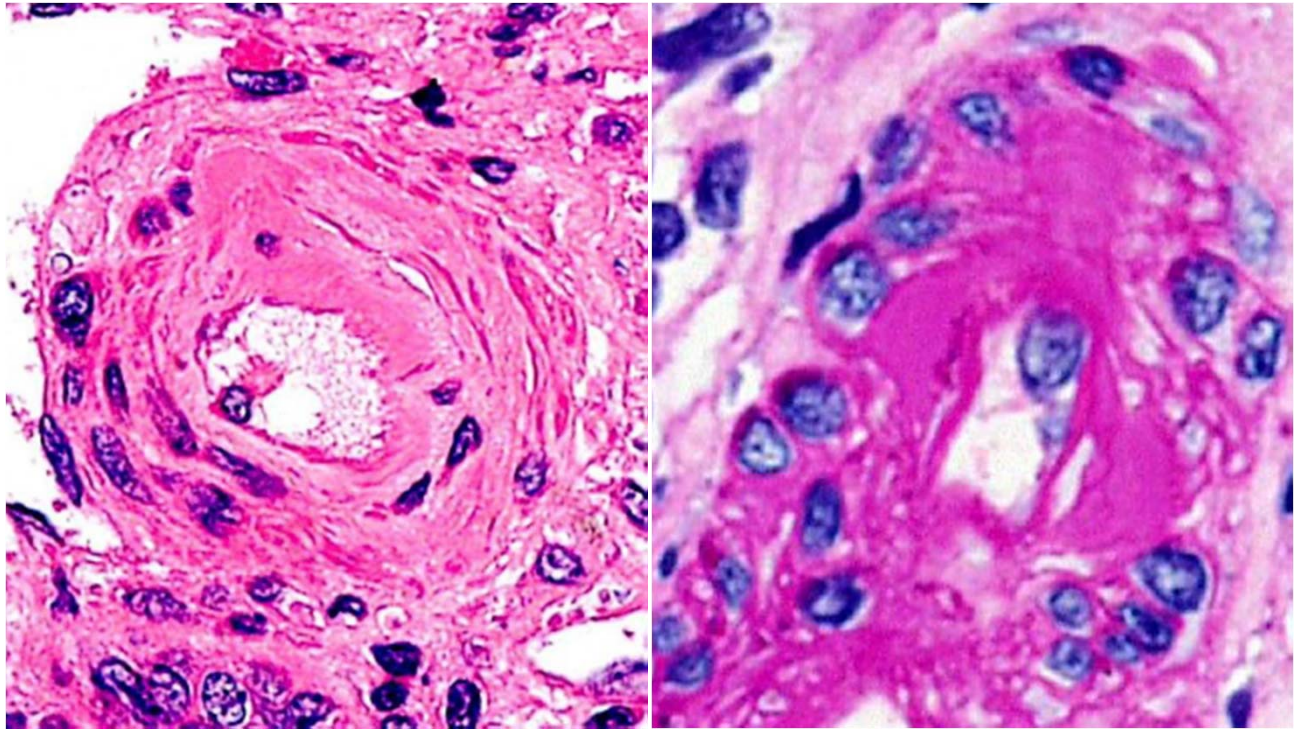


Ruptured, thrombosed, atherosclerotic plaque

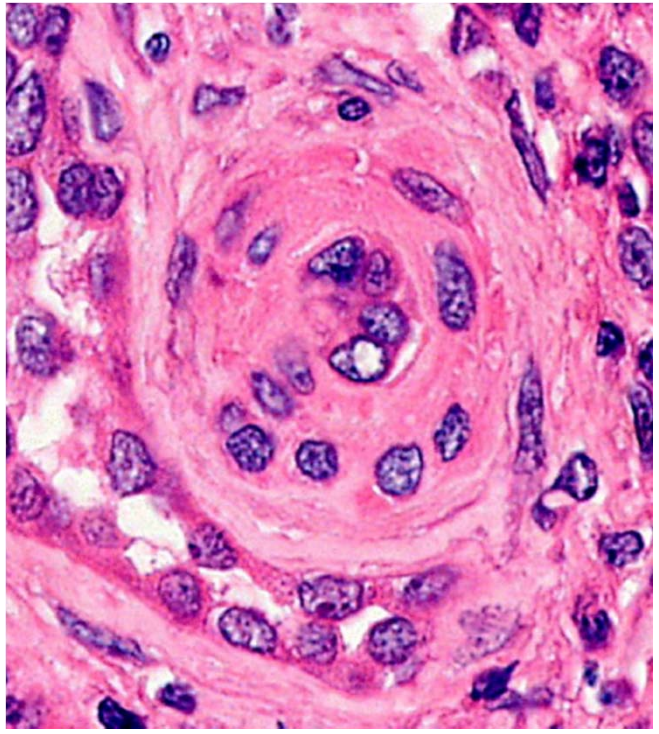
Monkeberg's Sclerosis of Coronary arteries



Arteriolosclerosis

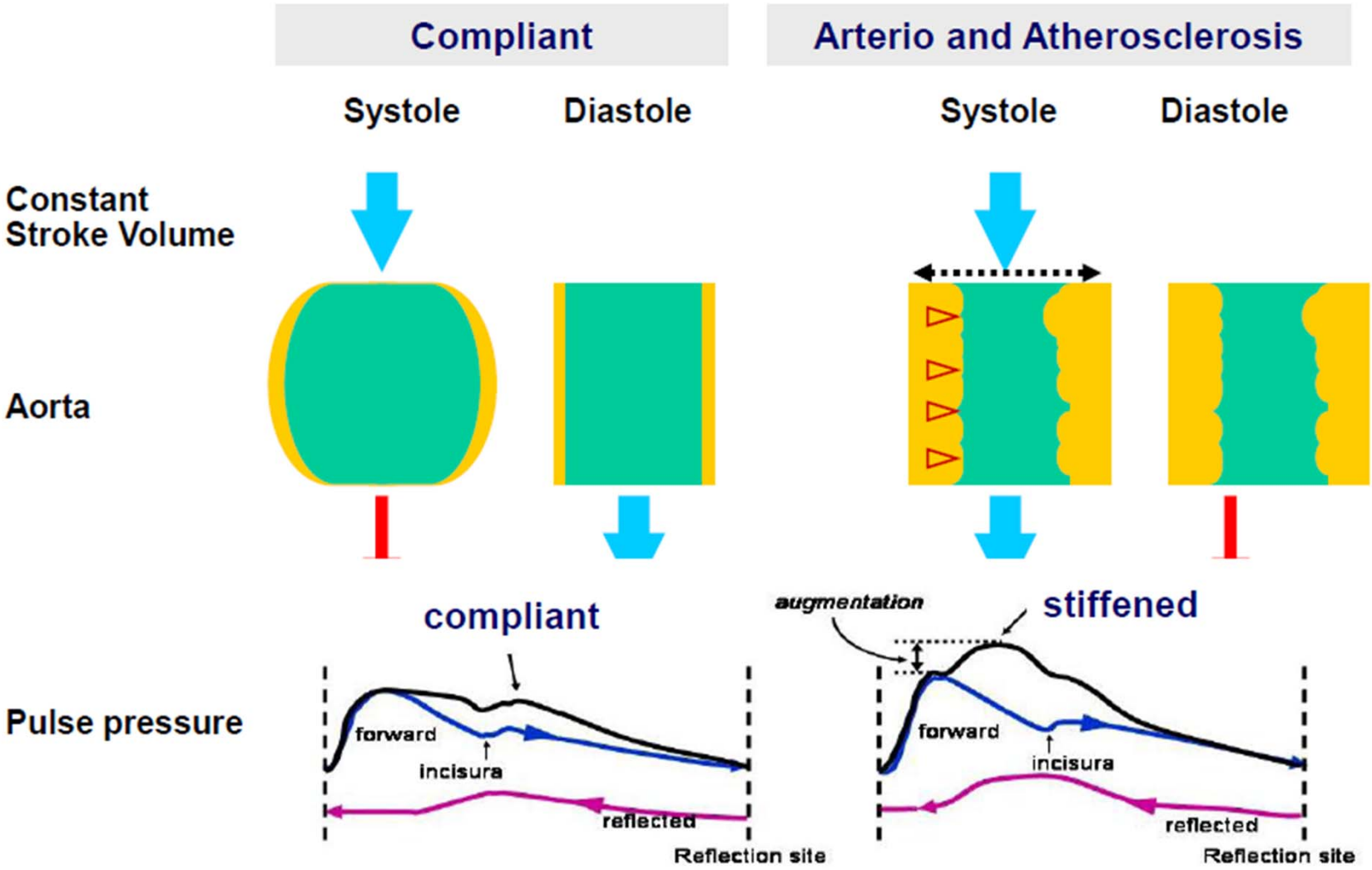


Hyaline type
- Intimal hyalinosis

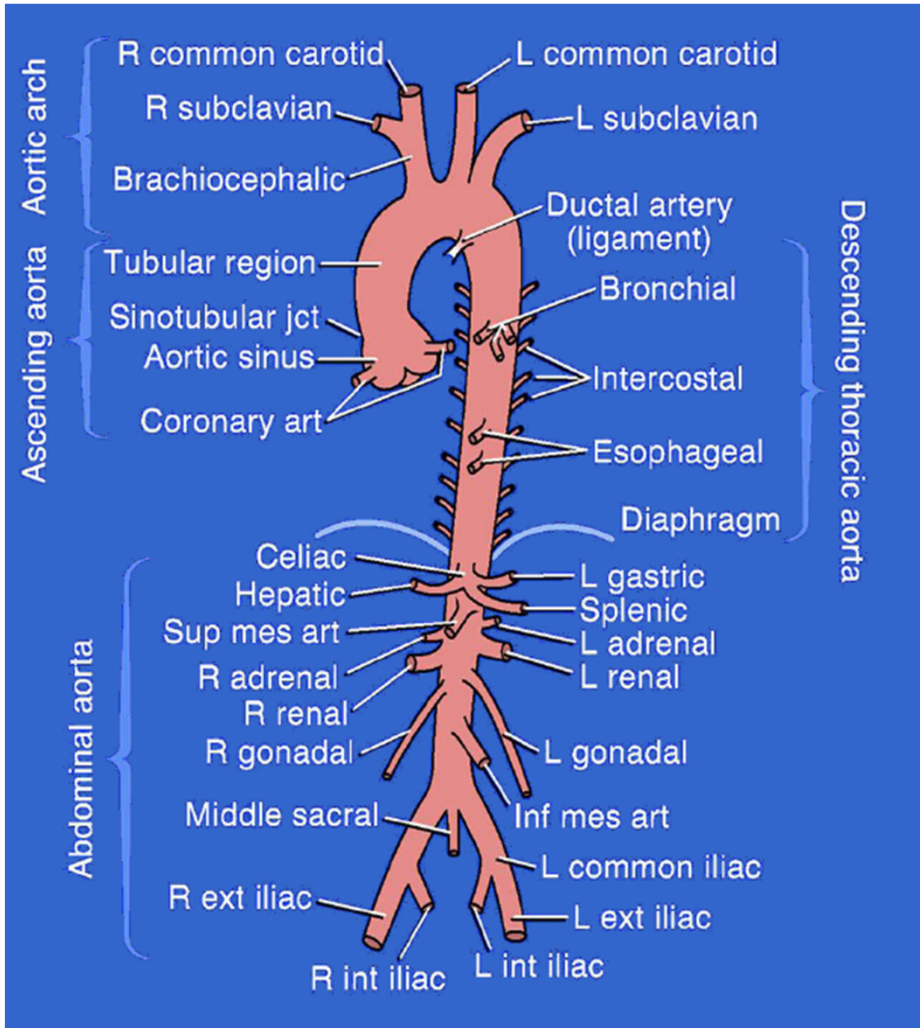


Hyperplastic type
- Intimal fibromuscular Hyperplasia

Arteriosclerosis and atherosclerosis



Artherosclerosis

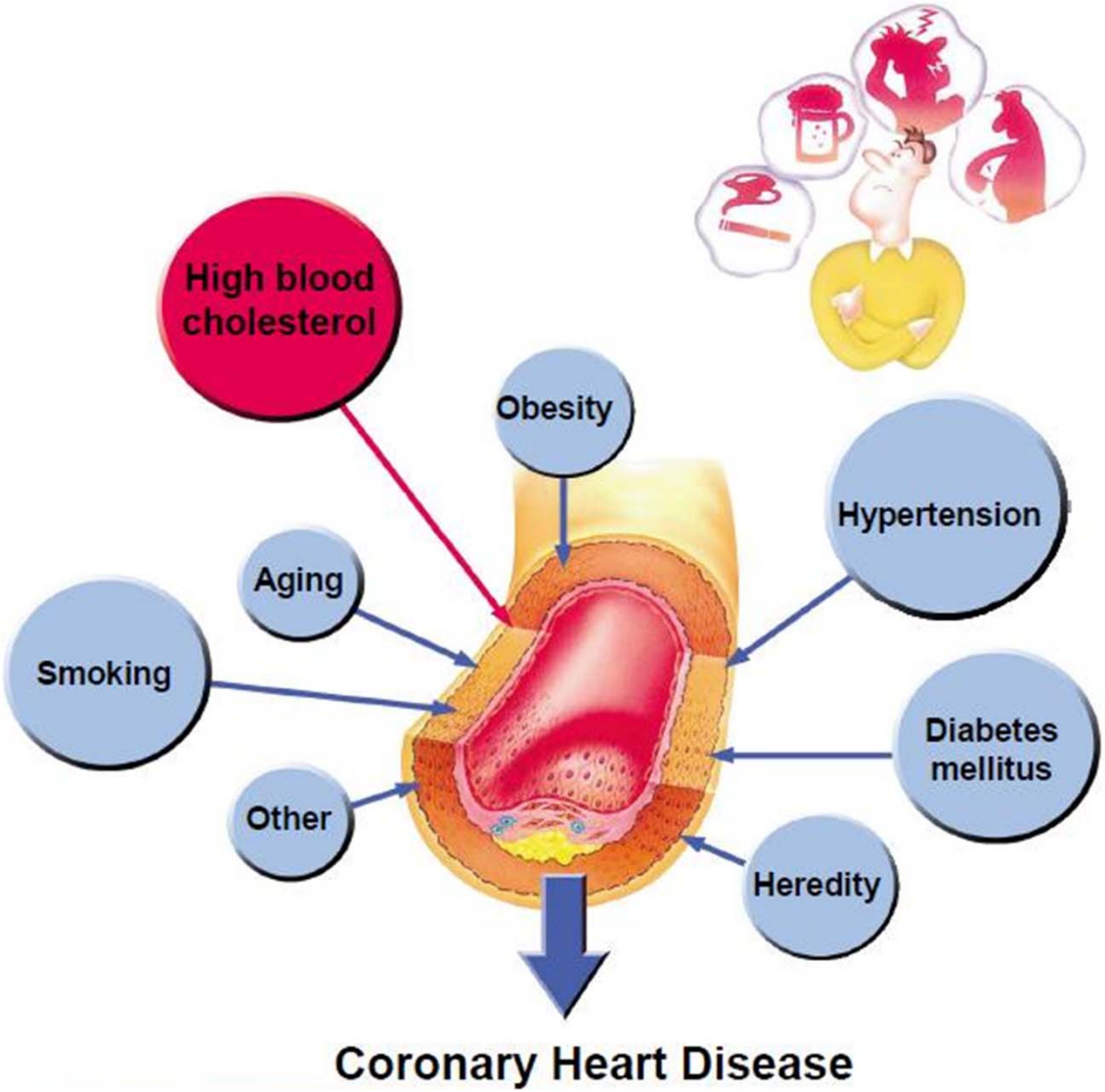


- Aorta
  - Abdominal
  - Thoracic
- Coronary artery and carotid artery
- Lower extremity arteries
- Upper extremity arteries

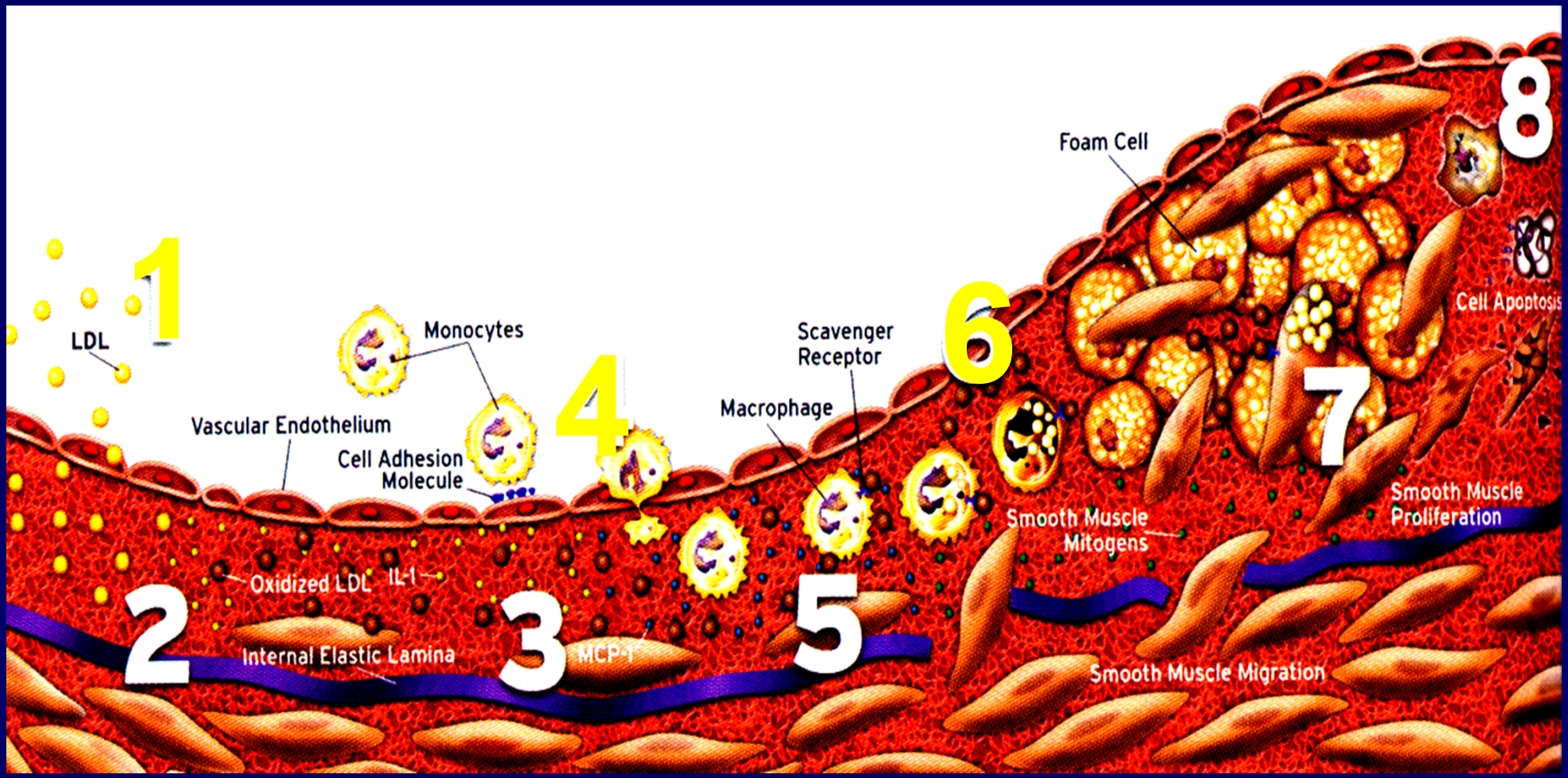
Early

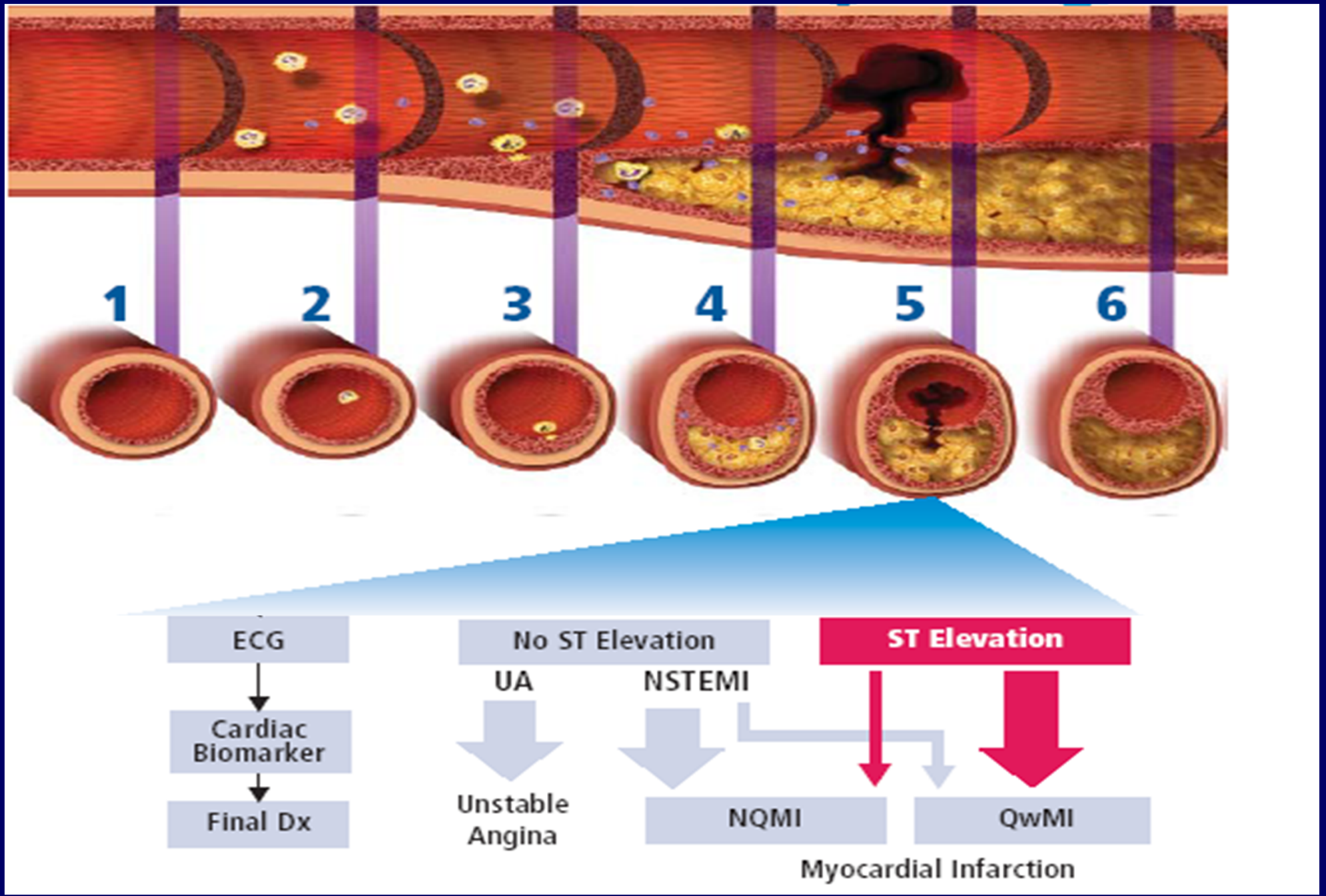
Late

Risk Factor of Atherosclerosis



Inflammatory Role in the Evolution of Atheromatous Plaque




1
2
3
4
5
6
ECG
Cardiac Biomarker
Final Dx
No ST Elevation
ST Elevation
UA
NSTEMI
Unstable Angina
NQMI
QwMI
Myocardial Infarction

Classical Atheromatous Plaque

Fibrin Cap

Lipid Core

Mechanisms

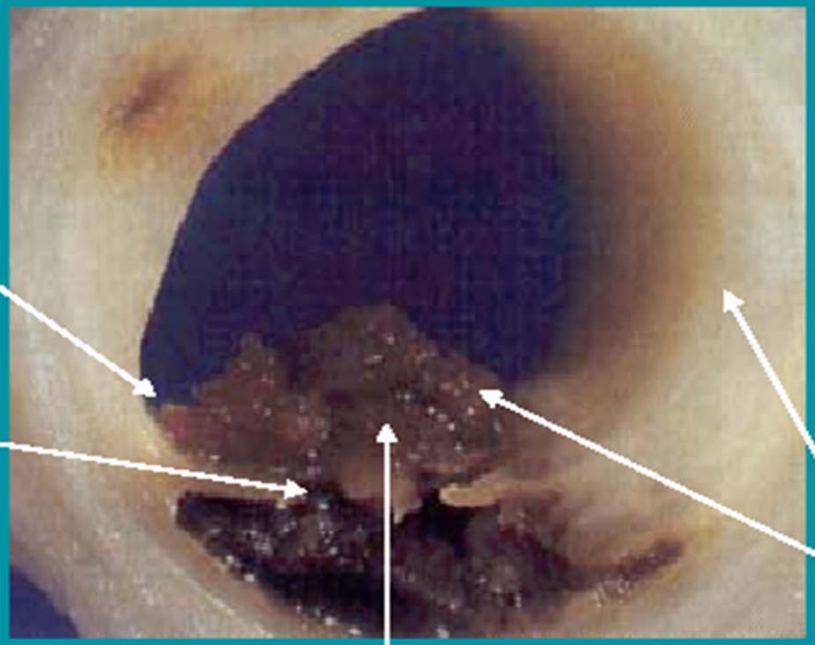
β-blockers

Targeted approaches

Inflammation

Plaque rupture
or erosion

Stent



Adapted from M.J Davies

Myocardial
Oxygen
Supply

Myoc
demand

PCI

Luminal narrowing

Nitrates
Ca antagonists

Vasospasm

Platelet aggregation

Aspirin

GpIIb/IIIa receptor inhib

Clopidogrel

Thrombosis

UH Heparin

LMWH

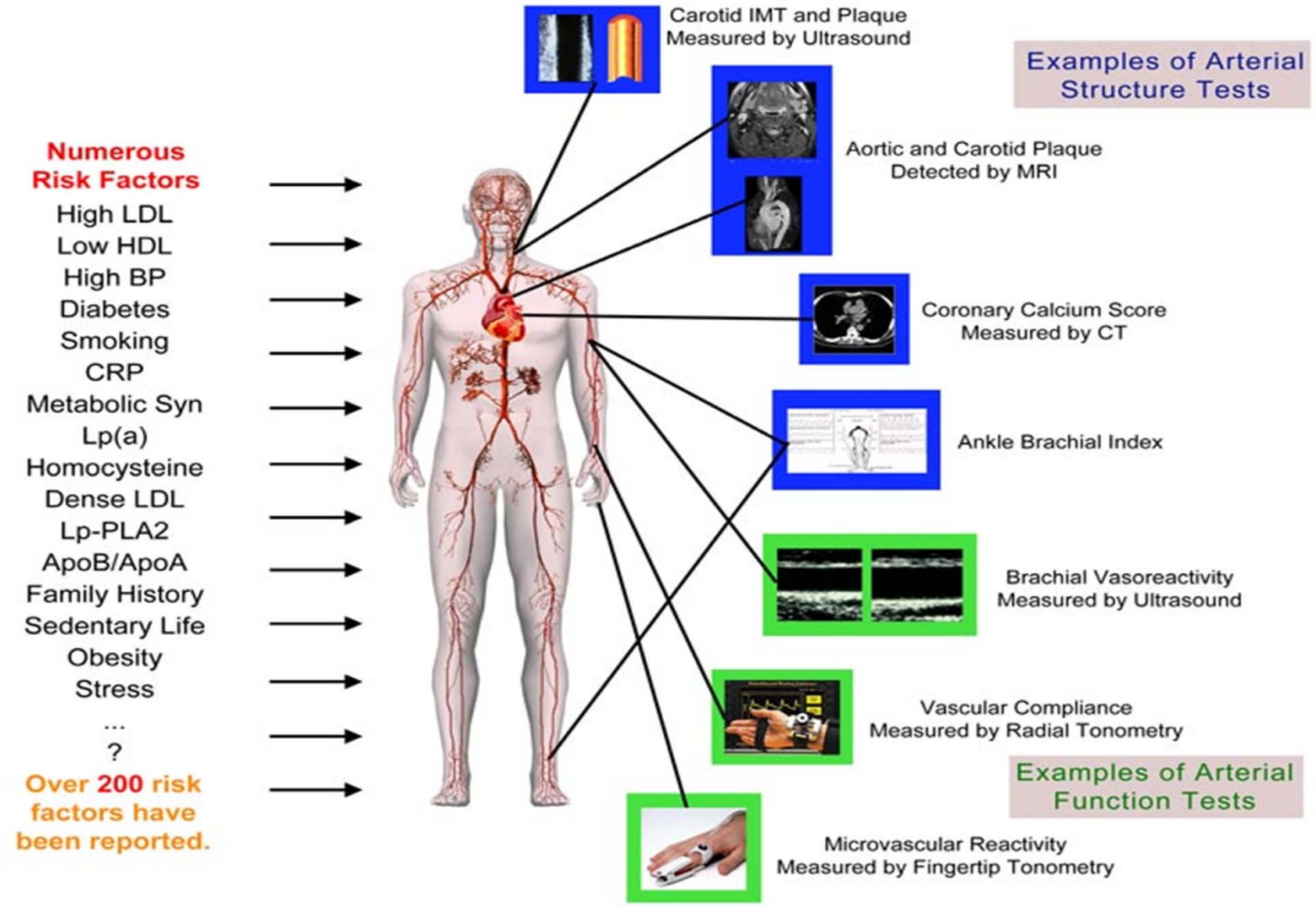
Recommended medications

Medication	Recommendation
Aspirin	All patients should take 75-150mg/day unless CIx
Clopidogrel	Should be prescribed for up to 12 months after ACS
β blocker	Should be prescribed for most Pt. after MI unless CIx : carvedilol, bisoprolol, metoprolol – should use in HF
ACE inhibitor	Should be given early after ACS
Statin	Should be initiated in hospital for all ACS patients
Warfarin	Recommended after MI for high risk thromboembolism : A. fib, mural thrombi, CHF or previous embolization Hx
Nitrates	All patients should be prescribed unless Cix
Insulin/OHA	Good glycemic control should be obtained and continued
Aldactone	Should be considered early after MI in those with HF

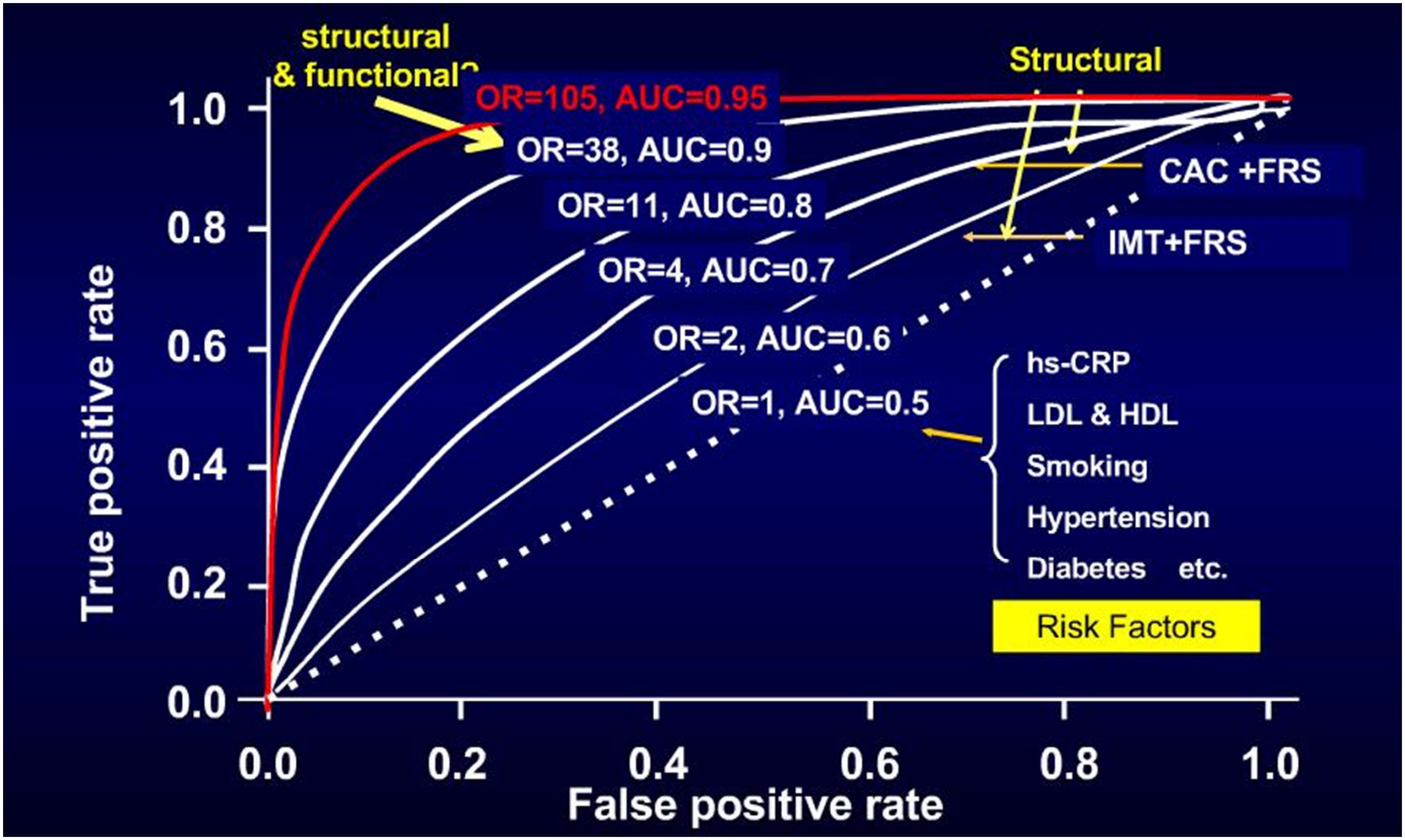
Other considerations

Factor	Recommendation
• Lifestyle advice	All patients should be given advice on lifestyle changes : smoking cessation, good nutrition, moderate alcohol, regular physical activity & weight management
• Rehabilitation	Should have access cardiac rehabilitation services
• Chest pain action plan	All patients should be provided with a action plan : sublingual NTG – aspirin – calling ambulance
• Fish oil	Omega-3 fatty acids from fish oil is recommended
• Psychosocial factors	All patients should be assessed for cormobid depression and level of social support
• Diabetes	Early glucose tolerance test should be considered
• ICD	Should be considered in persistent severe LV dysfunction

Screening for Atherosclerosis

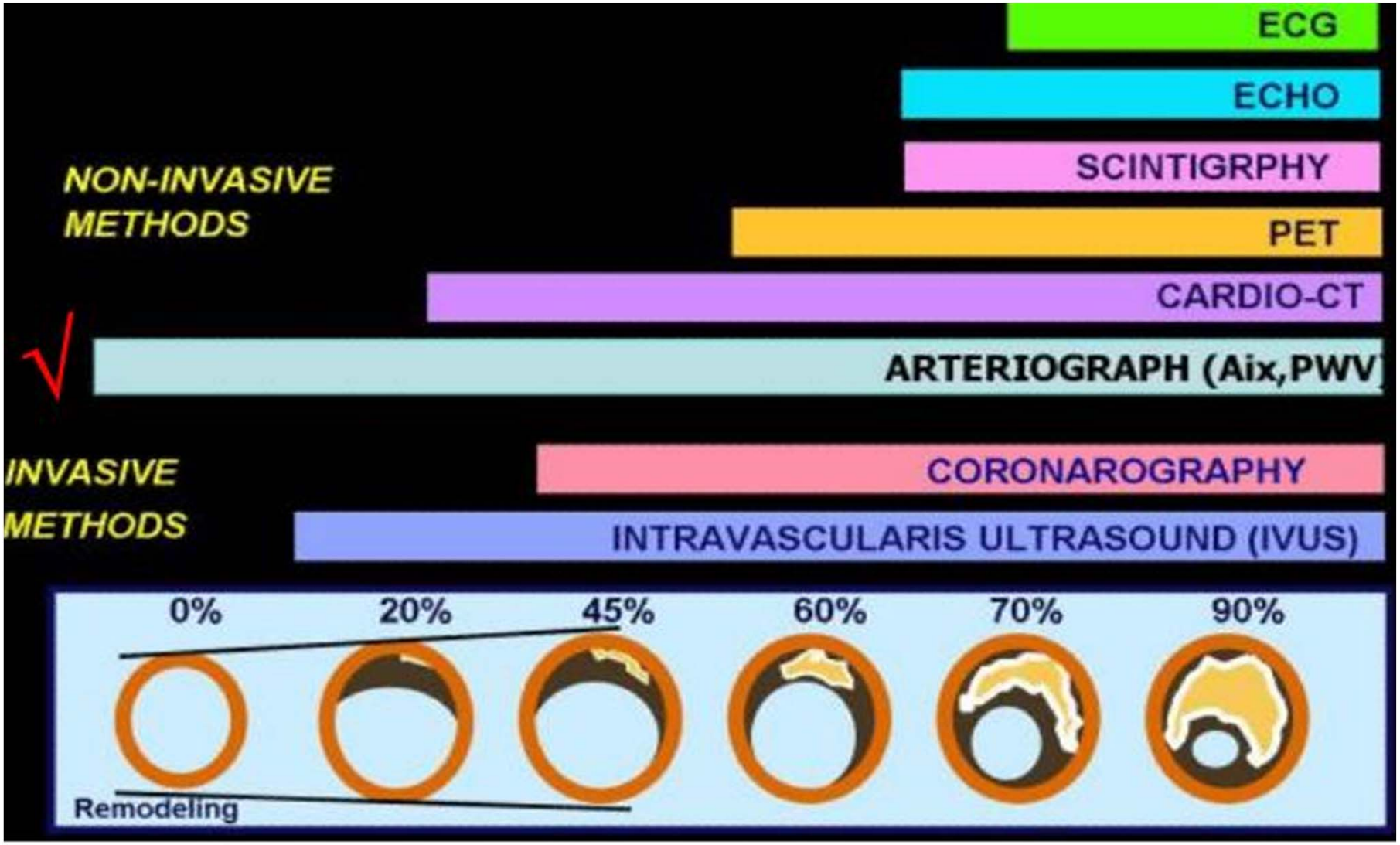


When in a New Prediction Marker Useful?



Pepe et al. Am J Epidemiol 2004; 159:882

Available methods for detecting Different stage of arteriosclerosis



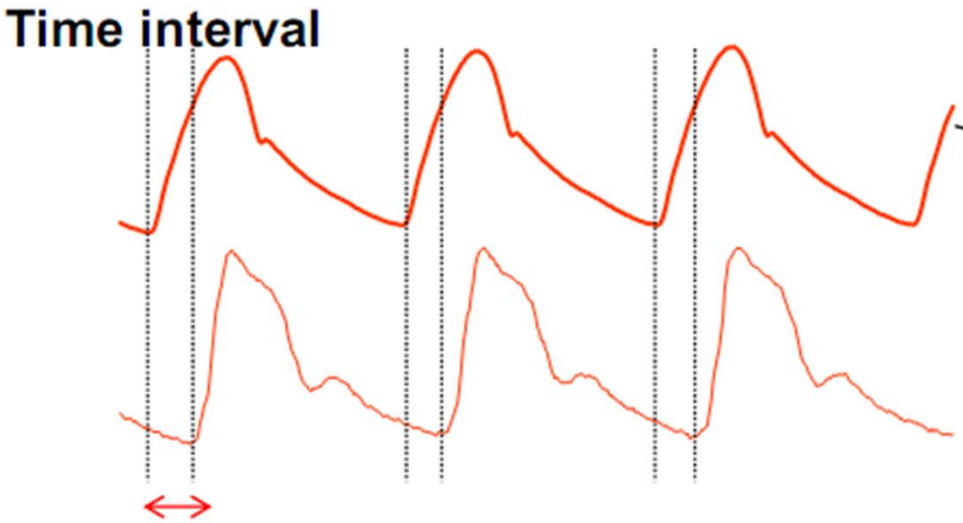
Nach Erbel. HERZ 1996;21,75-77

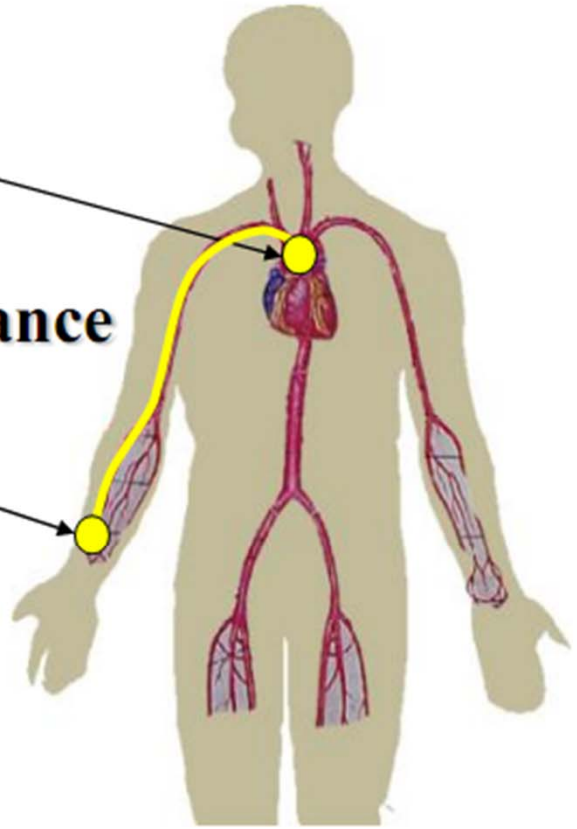
Comparison of Major methods used in the Noninvasive assessment of Arterial stiffness

	PWV	Arterial Ultrasound	MRI	SPCA	Carotid AIx	DPCA
Ease of use	++	+	+	+++	+++	+++
Quality of validation	++	++	+++	++	++	+
Affordability	+++	++	+	+++	+++	+++
Freedom from operator bias	++	+	+++	++	++	++
Evidence of prognostic value	+++	++	+	+	++	+
Endothelial function testing †	+	+++	+	+++	+++	++

Systolic Pulse Contour Ananlysis(SPCA), Diastolic Pulse Contour Analysis(DPCA)

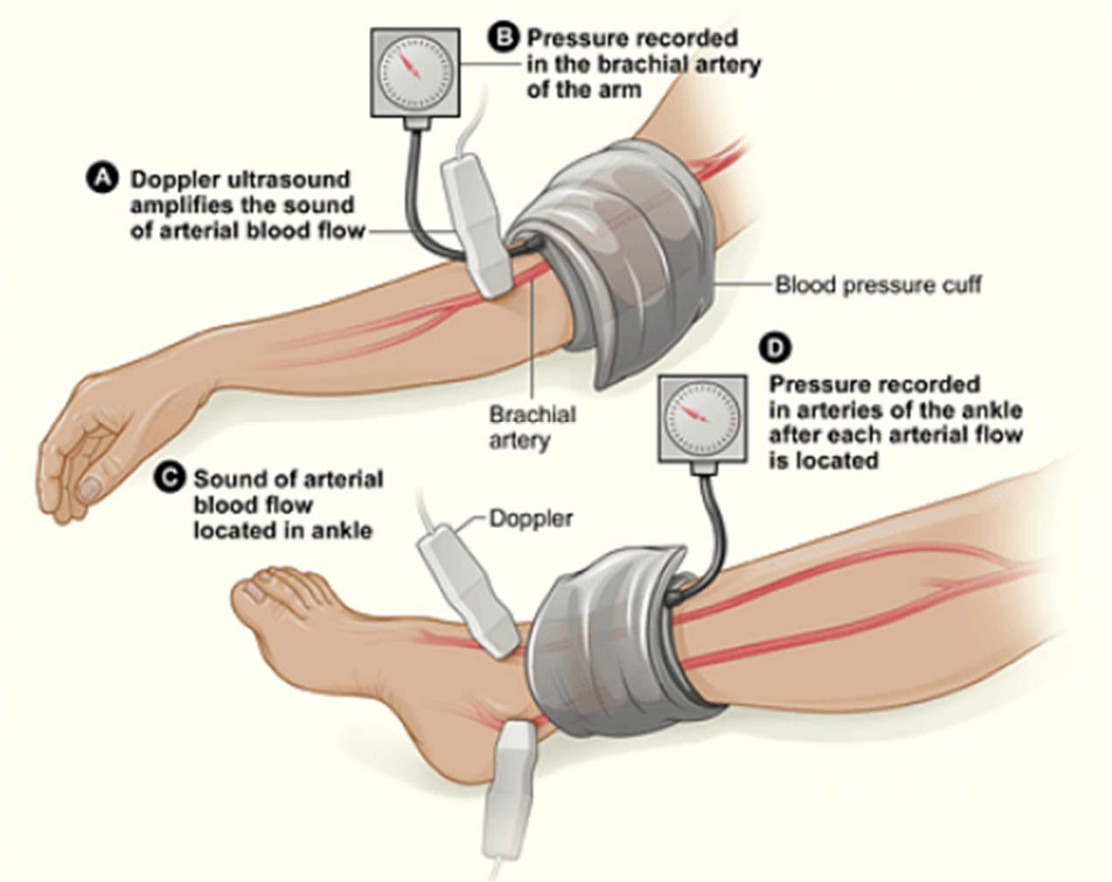
Pulse wave velocity (PWV)





Pulse Wave Velocity (PWV)
= Distance / time interval
Distance/Δt

Ankle-Brachial index(ABI)



ABI	Interpretation
> 1.2	Abnormal vessel hardening form PVD
1.0~1.2	Normal range
0.9~1.0	Acceptable
0.8~0.9	Some arterial disease
0.5~0.8	Moderate arterial disease
<0.5	Severe arterial disease

Cario-Ankle Vascular Index(CAVI)

CAVI = Pulse Wave Velocity(PWV) + Arterial compliance(stiffness)

Attach cuffs,
ECG electrodes,
PCG microphone

Pulse & Blood Pressure
Measurement at 4 limbs
+ ECG & PCG measurement

CAVI (Stiffness)
ABI (Stenosis, Occlusion)

Principle of CAVI

Expression of β with PWV using the relationship of velocity and elasticity (Bramwell-Hill's equation)

$$\beta = \left(\ln \frac{P_s}{P_d} \right) \left(\frac{D}{\Delta D} \right)$$

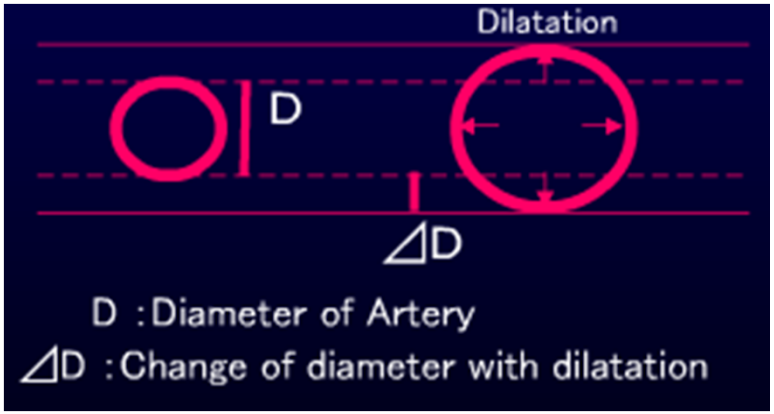
$$CAVI = \frac{2\rho}{\Delta P} \left[\ln \frac{Ps}{Pd} \right] PWV^2$$

$$PWV^2 = \frac{\Delta P}{\rho} \cdot \frac{V}{\Delta V}$$

$$= \frac{\Delta P}{2\rho} \cdot \frac{D}{\Delta D}$$

$$\Downarrow$$

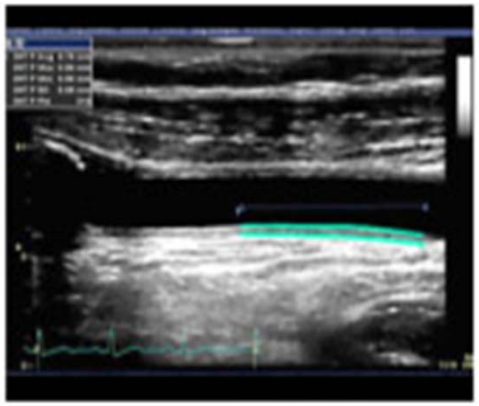
$$\frac{D}{\Delta D} = \frac{2\rho}{\Delta P} \cdot PWV^2$$

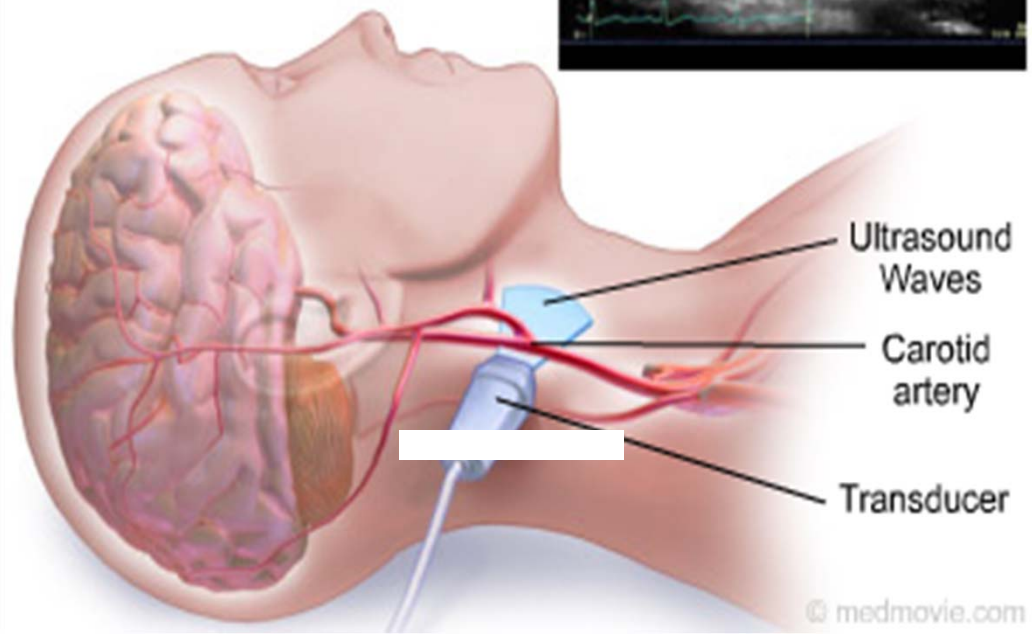


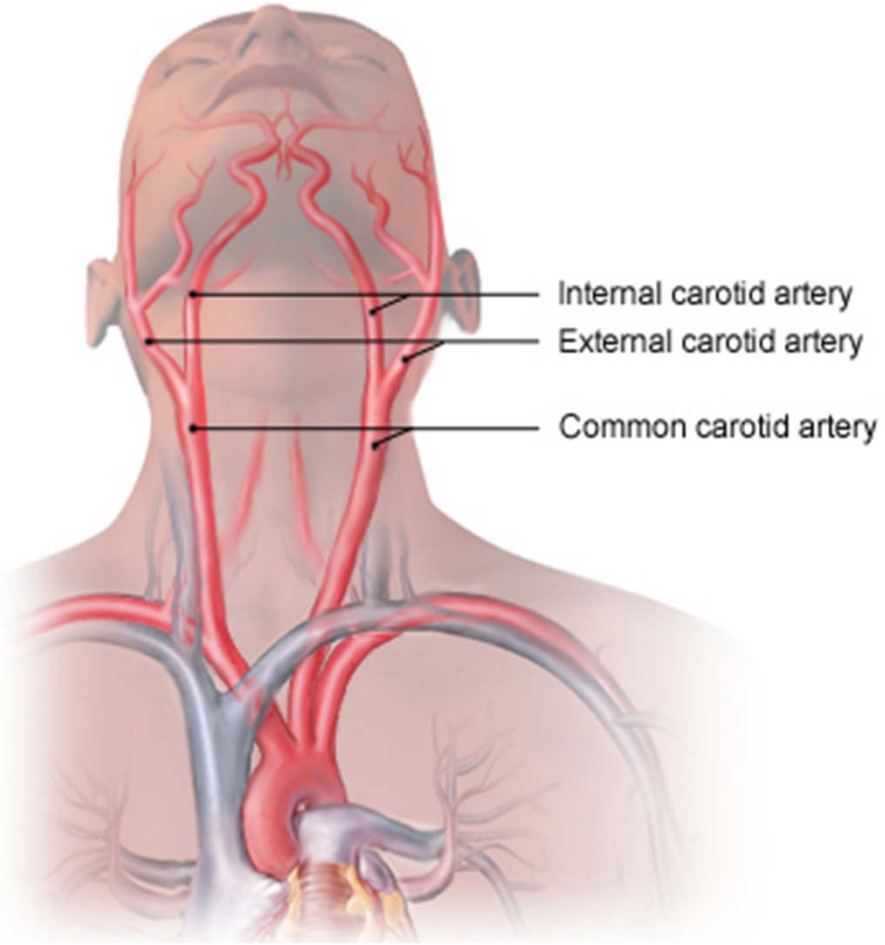
Blood-Pressure independent Atherosclerosis Index

Carotid Ultrasonogram

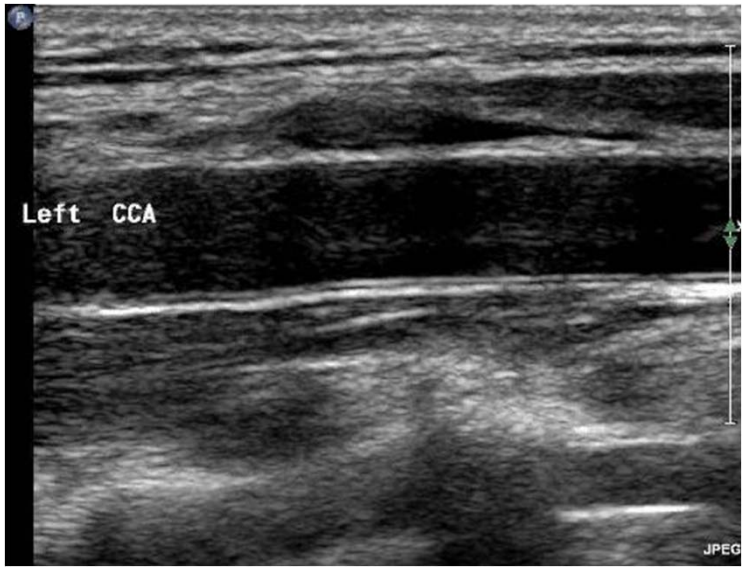
Carotid IMT uses sound waves to create images of the carotid artery. IMT measures the thickness of the inner artery wall to determine the presence of vascular disease.

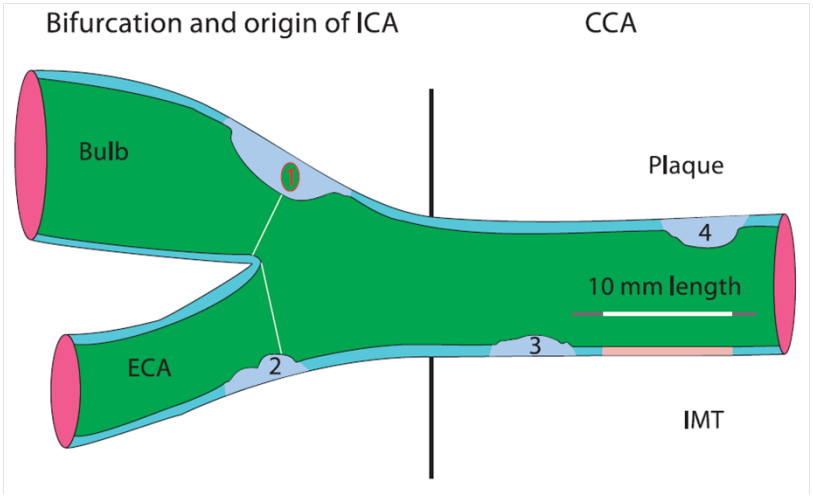






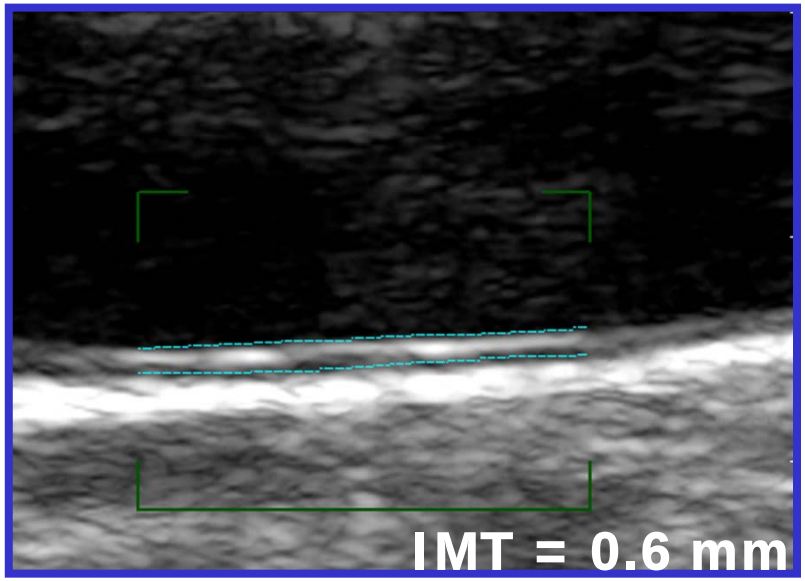
Carotid Ultrasonogram

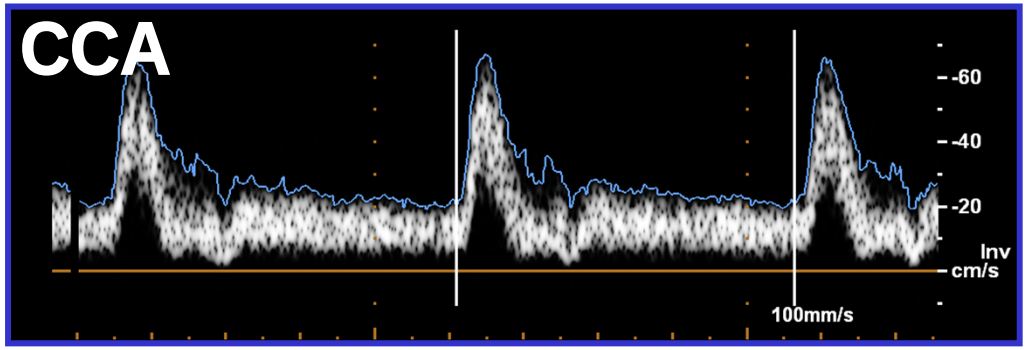


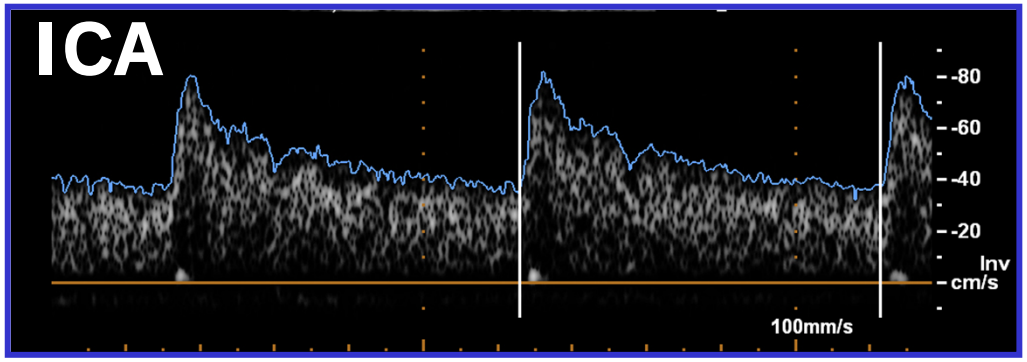


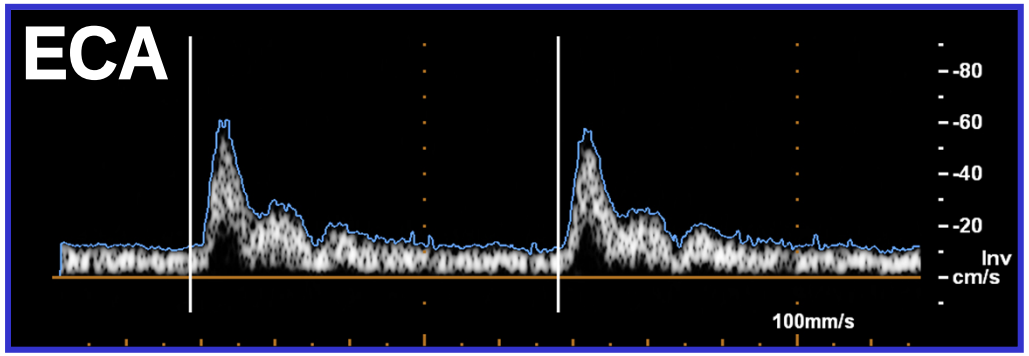
Mannheim Consensus. Cerebrovas Dis 2007

Carotid Ultrasonogram









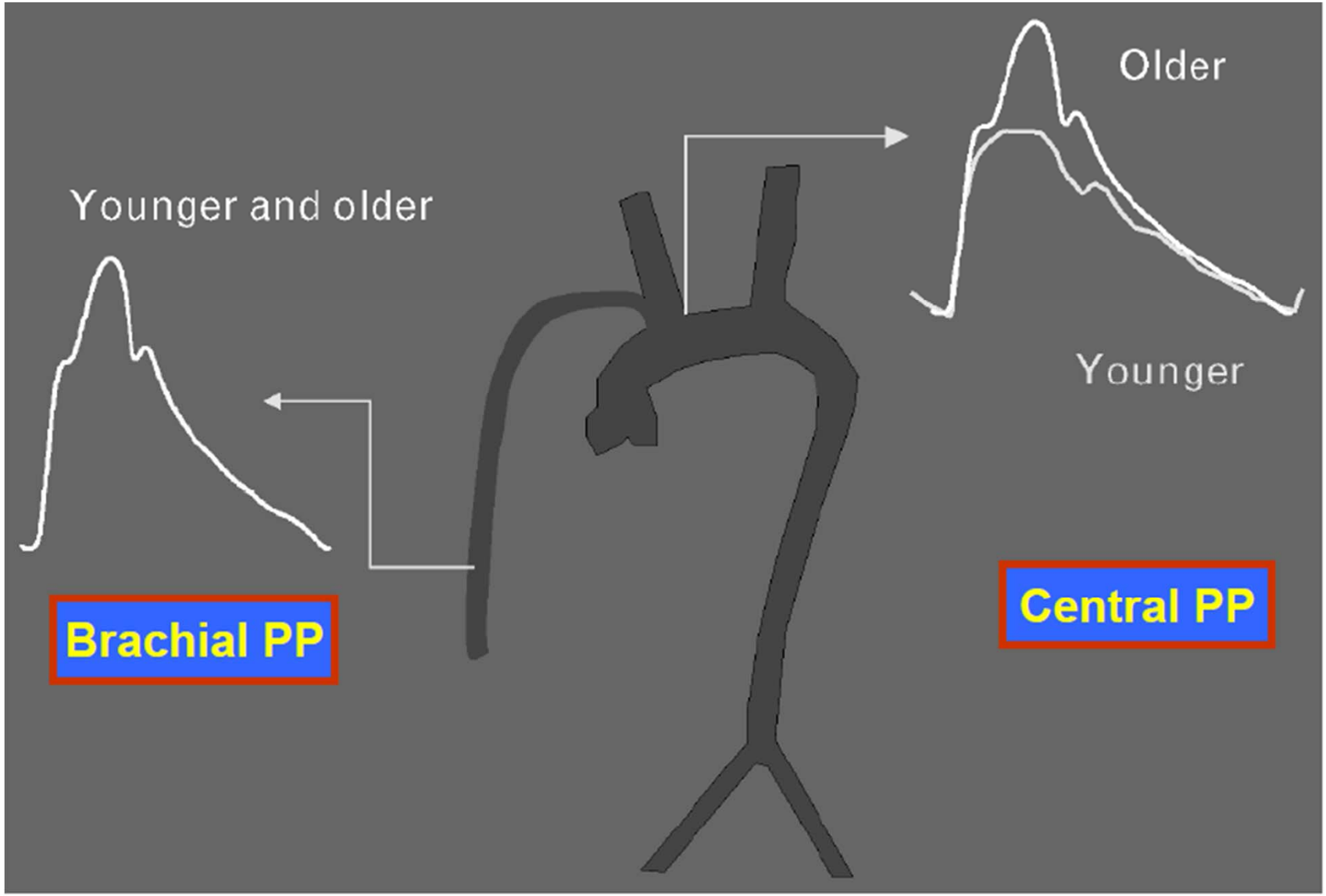
Carotid Plaque & Mortality

367 Living men (mean 78 yrs), 48 months F/U, 70 deaths

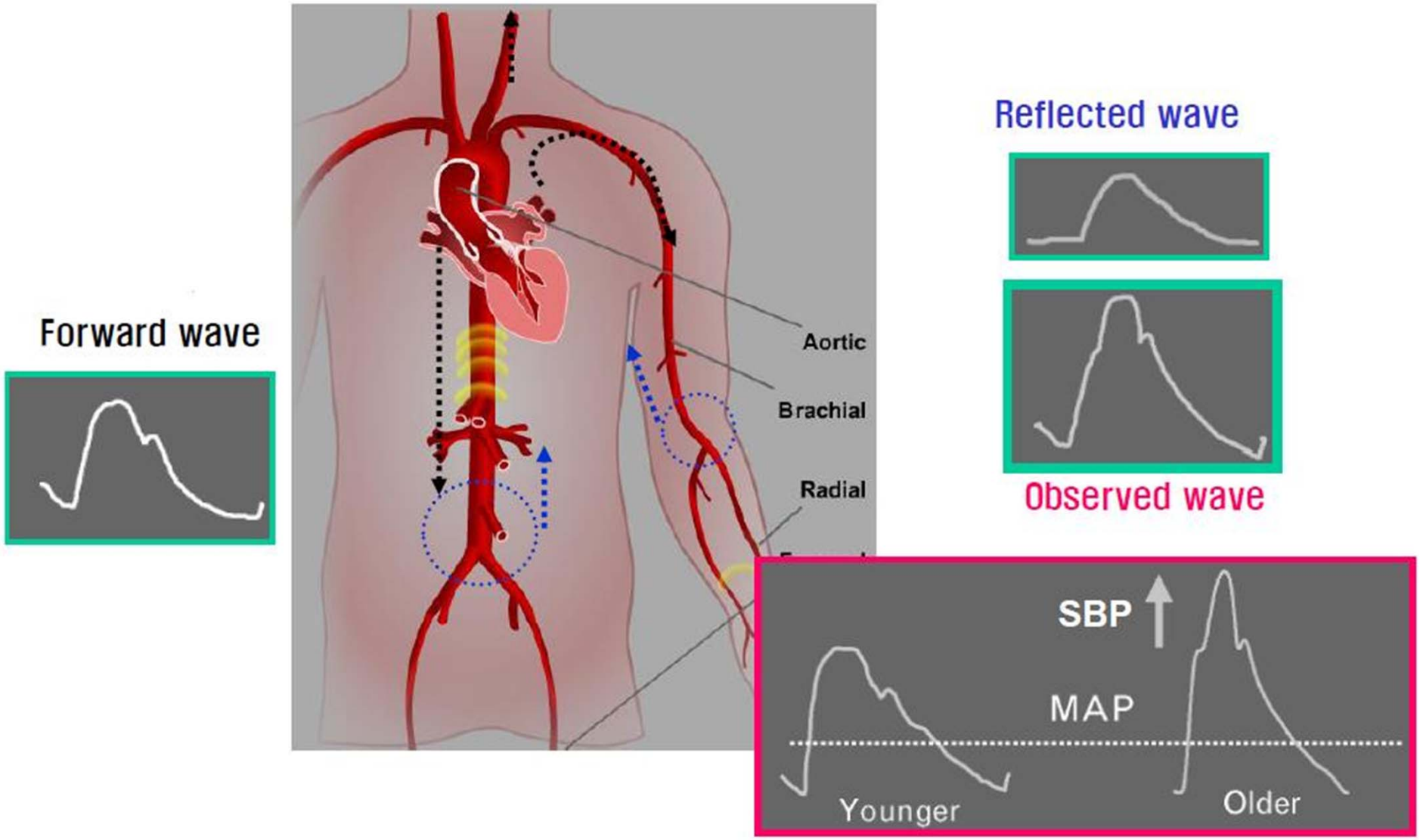
	Subjects at risk, n	Events, n	HR (95% CI)
Total plaque score			
No plaque	60	4	1.00
1~2 plaques	98	16	2.89 (0.96-8.69)
3~4 plaques	90	16	2.91 (0.97-8.73)
5~6 plaques	75	23	4.89 (1.69-14.15)
7~12 plaques	42	11	4.53 (1.44-14.23)
≥1 plaque on both sides	220	52	2.00 (1.15-3.46)
Any plaque	307	66	3.48 (1.27-9.54)

Stork et al. Circulation 2004;110:344~8

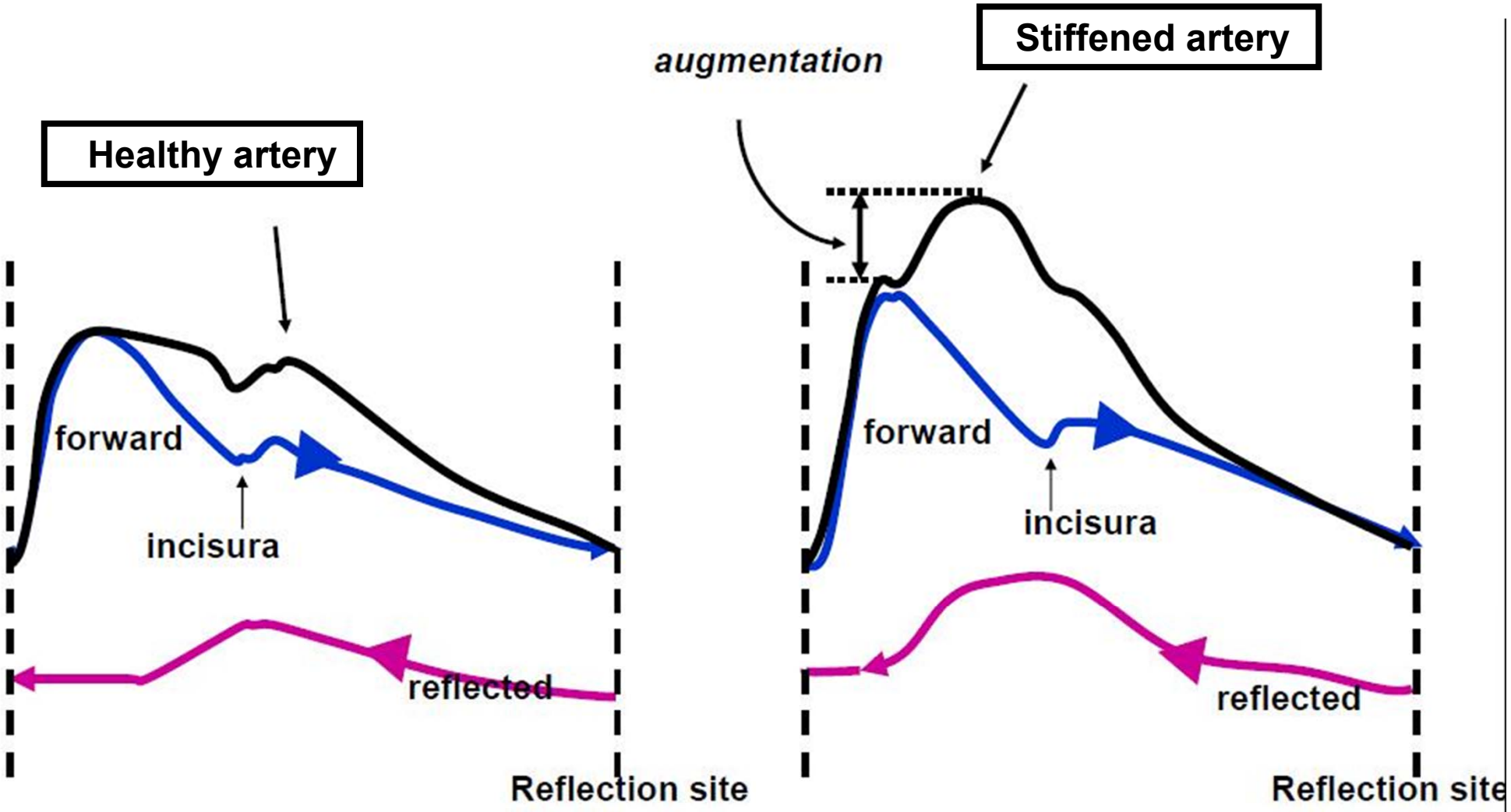
Central Blood Pressure



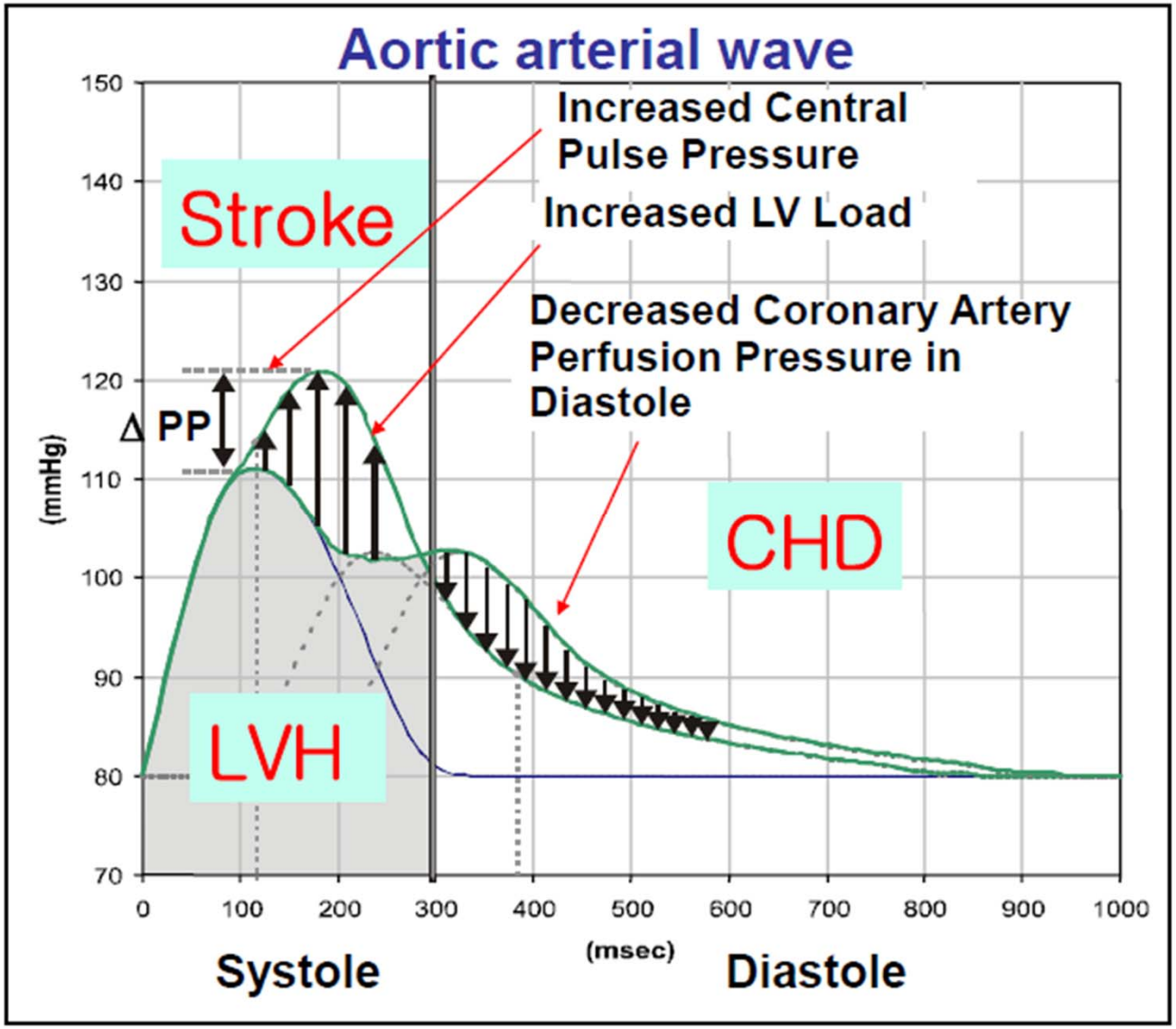
Pressure wave



Arterial stiffening



Stiffened artery and clinical implication



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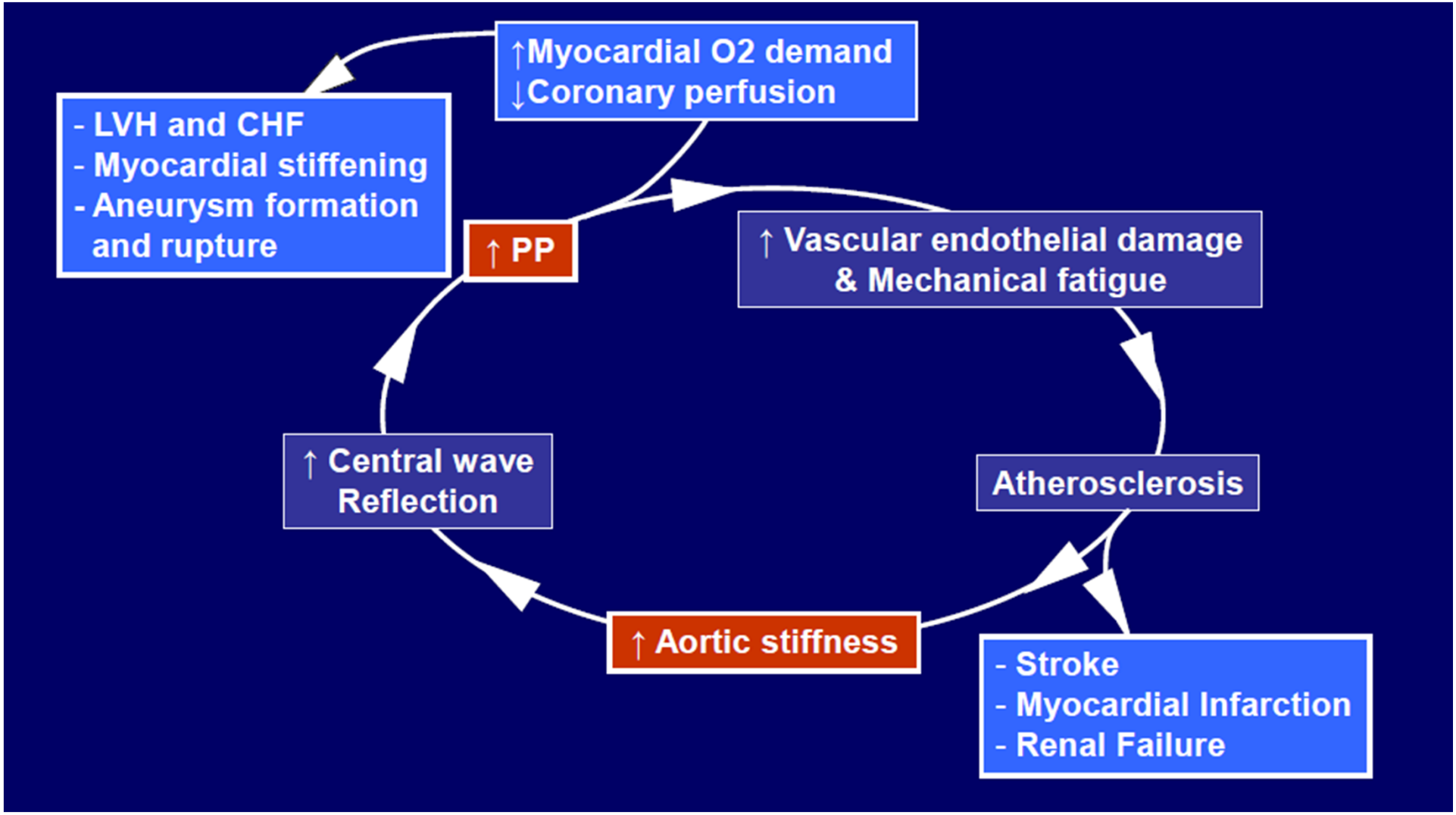
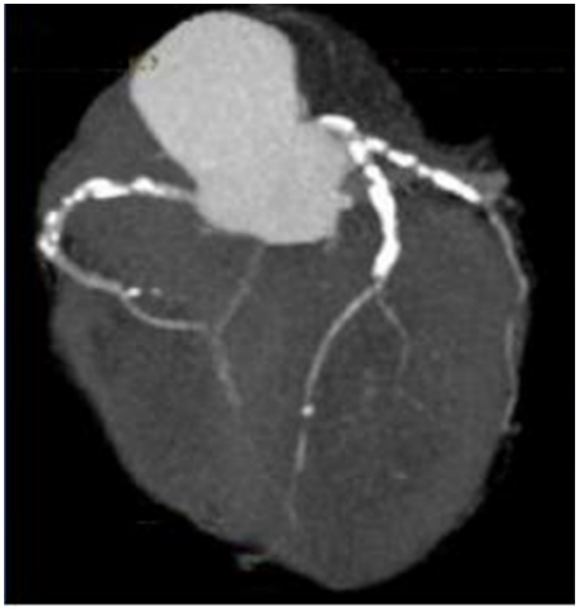


Coronary artery calcium

- A specific marker for coronary atherosclerosis
- Higher Ca^{++} → Higher coronary artherosclerotic burden
- Reproducible
- Predictor of coronary event



Scored By:	LMA	LAD	LCX	RCA	PDA	A	B	C	Total
AJ-130	0	474	272	462	0	0	0	0	1,208
Volume130	0	359	208	351	0	0	0	0	918

Cardiovascular risk based on CAC

Calcium score	Atherosclerotic plaque burden	Probability of significant CAD	Implications for CV risk
0	No detectable plaque	Very low (<5%)	Very low
1-10	Minimal detectable plaque burden	Very unlikely (<10%)	Low
11-100	Mild atherosclerotic plaque burden	Mild or minimal	Moderate
101-400	Moderate atherosclerotic plaque burden	High likelihood of nonobstructive CAD; possibility of obstructive disease	Moderately high
>400	Extensive atherosclerotic plaque burden	High likelihood of one or more significant obstructive lesion (>90%)	High

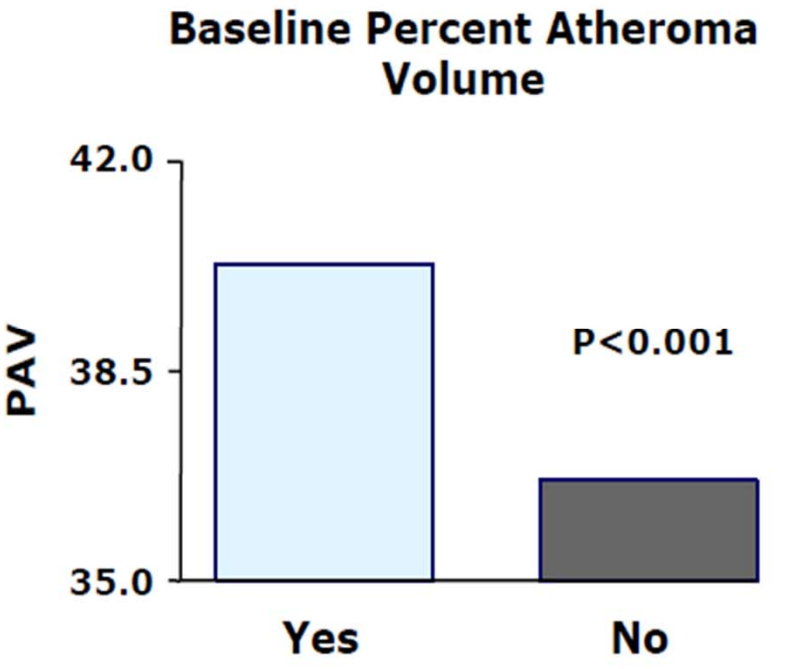
Rumberger et al. Mayo clin Proc 1999;74:243-252

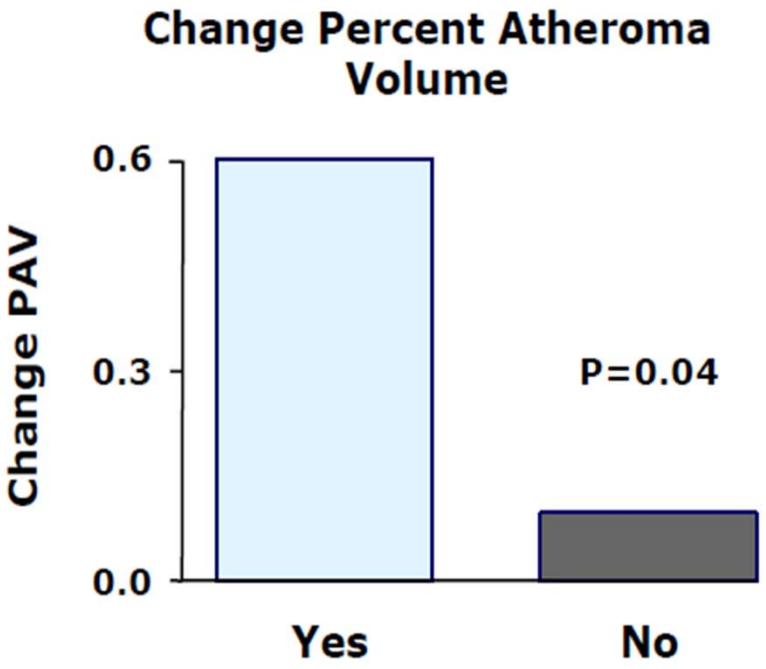
Cardiovascular risk based on CAC

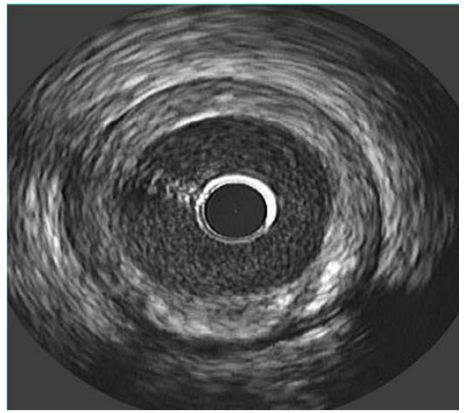
- Predictive value -

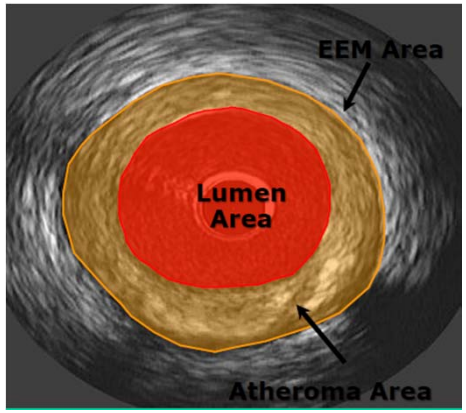
Author	Event	CAC score	RR	HR
Budoff (2009)	CHD	≤400	1	1
		>400	4.94	20.6 (11.8-36)
Becker (2008)	CVE (CD, MI)	0		
		0<CAC<75th		
		≥75th	5.2 (4.03-	
Folsom (2008)	CHD	0		1
		1-99		4.7 (2.5-8.7)
		100-399		11.5 (6.2-21.5)
		≥400		16.1 (8.5-30.8)

Atheroma burden and incident clinical event





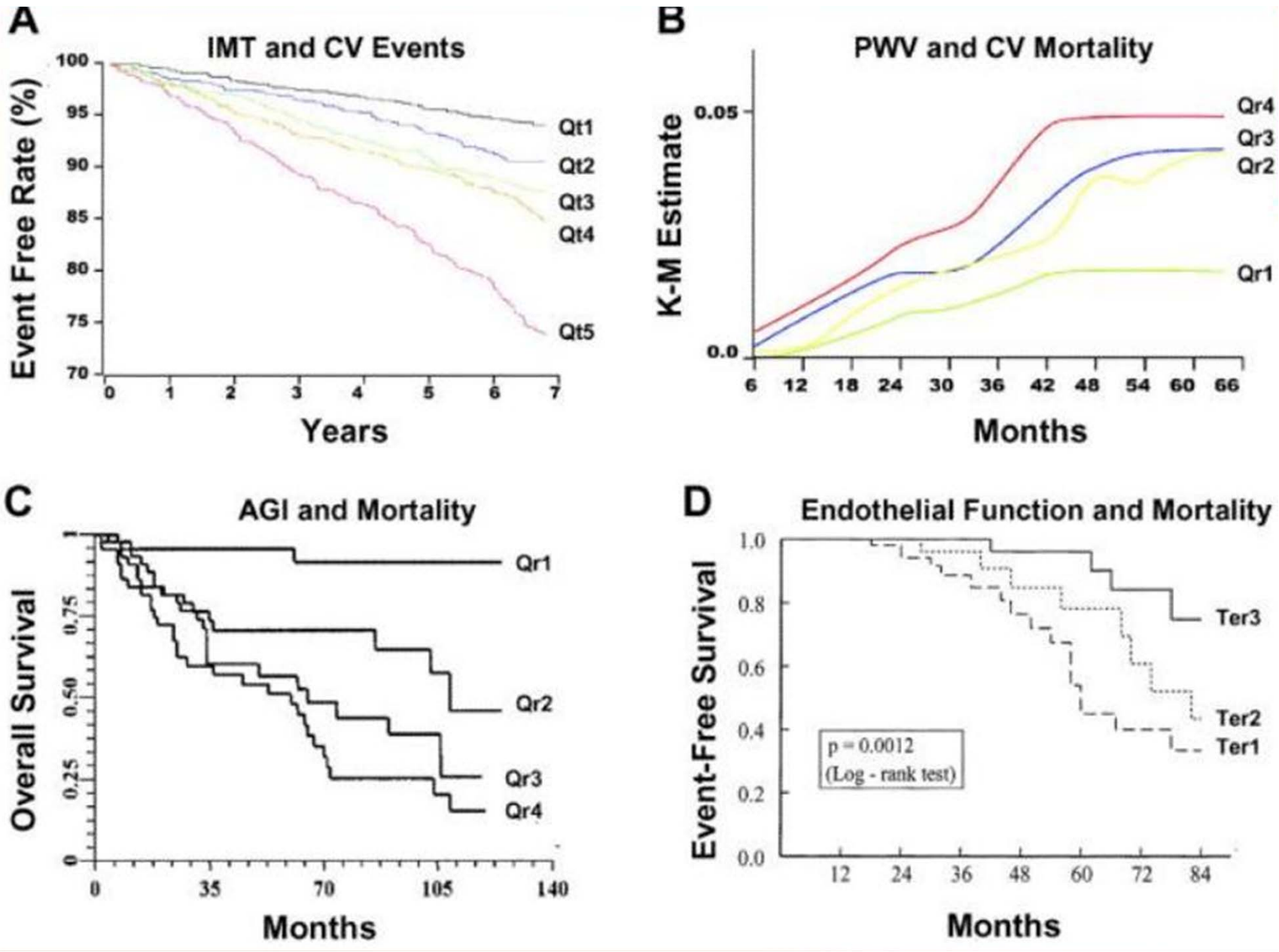




ILLUSTRATE (N =1180)

Incidence fo cardiovascular death, MI, hospitalization for unstable angina, stroke and coronary revascularization

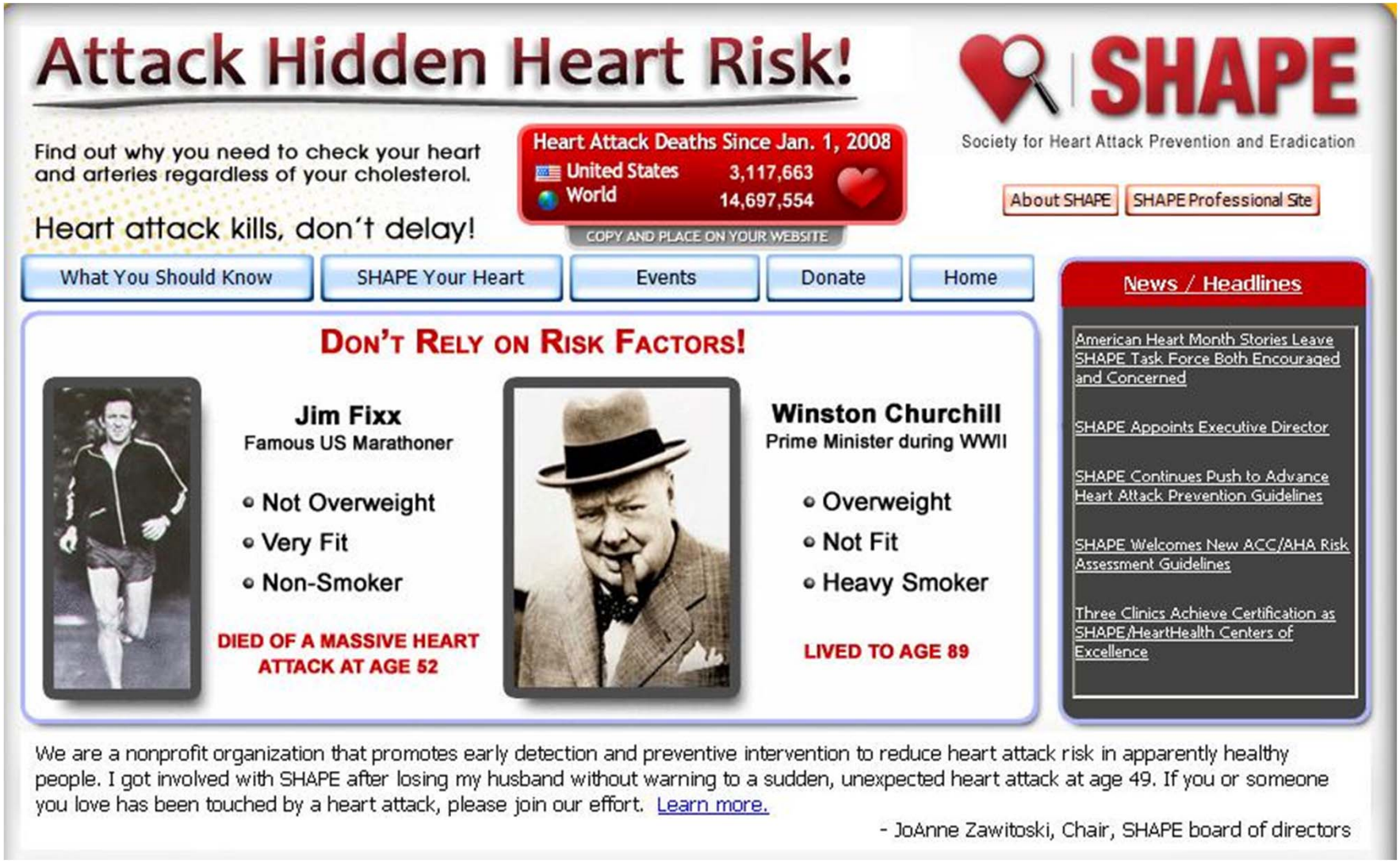
Nicholls S. AHA Scientific Sesseions 2007



Najjar SS et al. Hypertension 2005:46;454-62

The 1st S.H.A.P.E Guideline

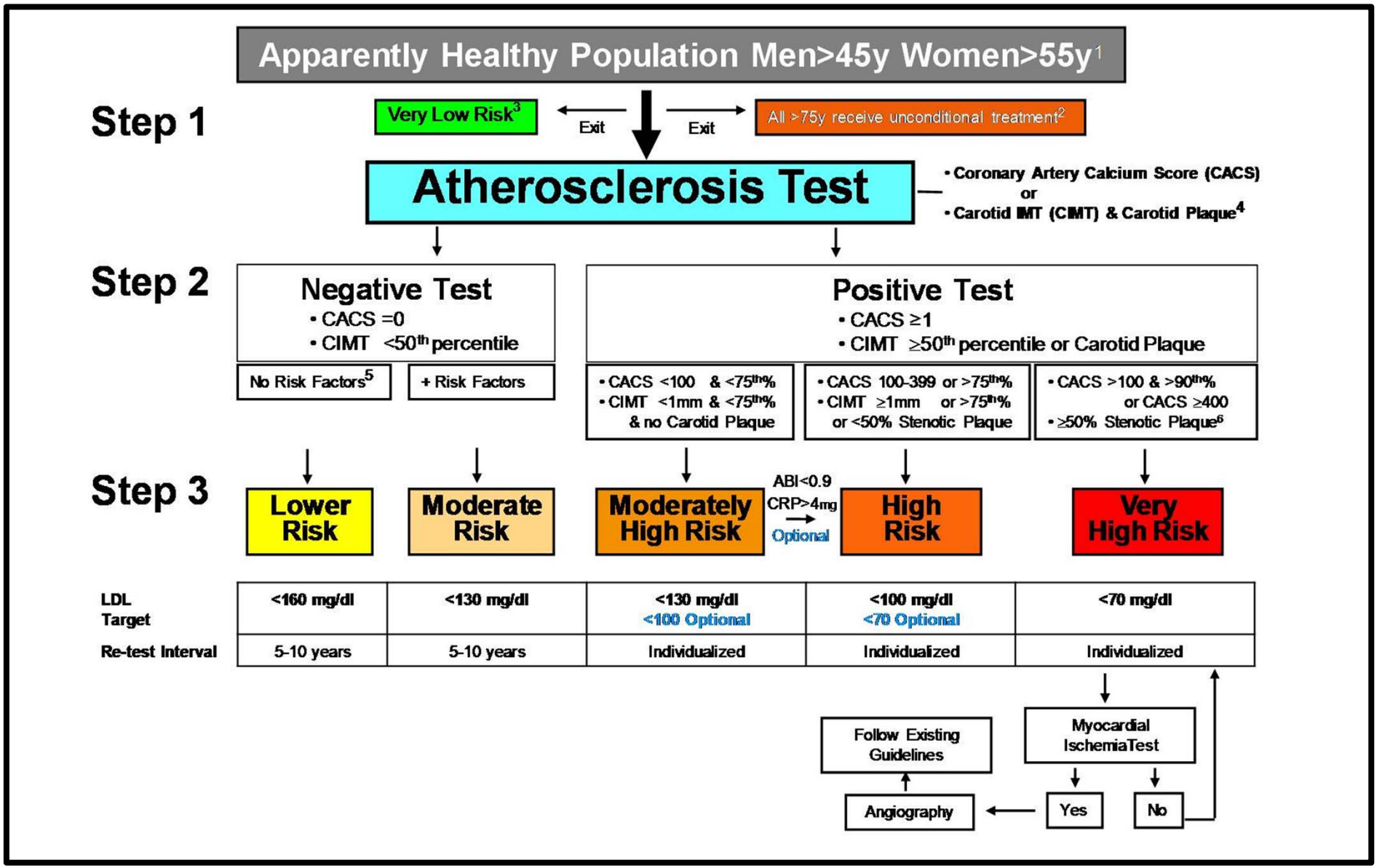
Towards the National Screening for Heart Attack Prevention and Education (SHAPE) Program



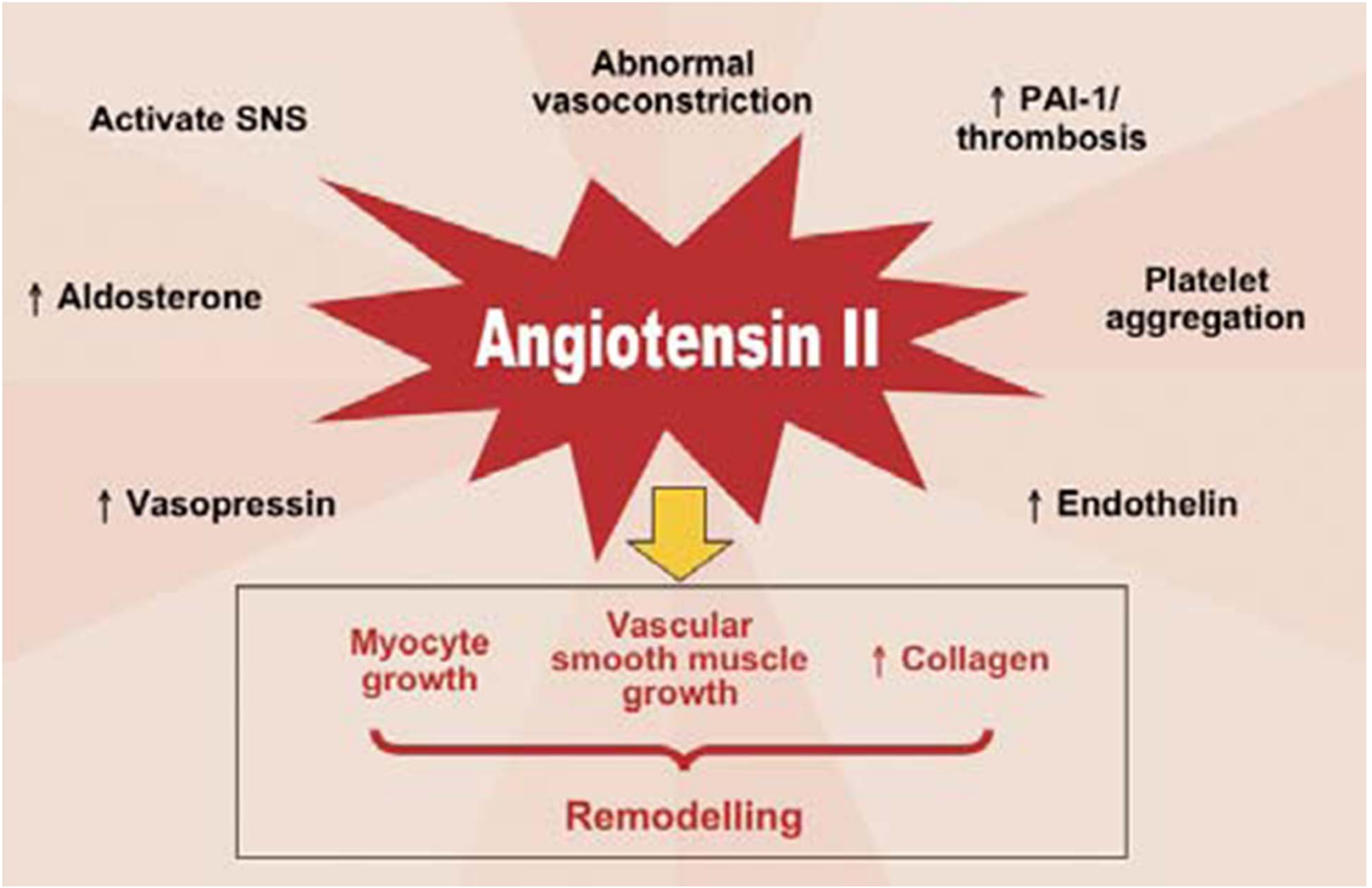
http://www. shapesociety.org

The 1st S.H.A.P.E Guideline

Towards the National Screening for Heart Attack Prevention and Education (SHAPE) Program



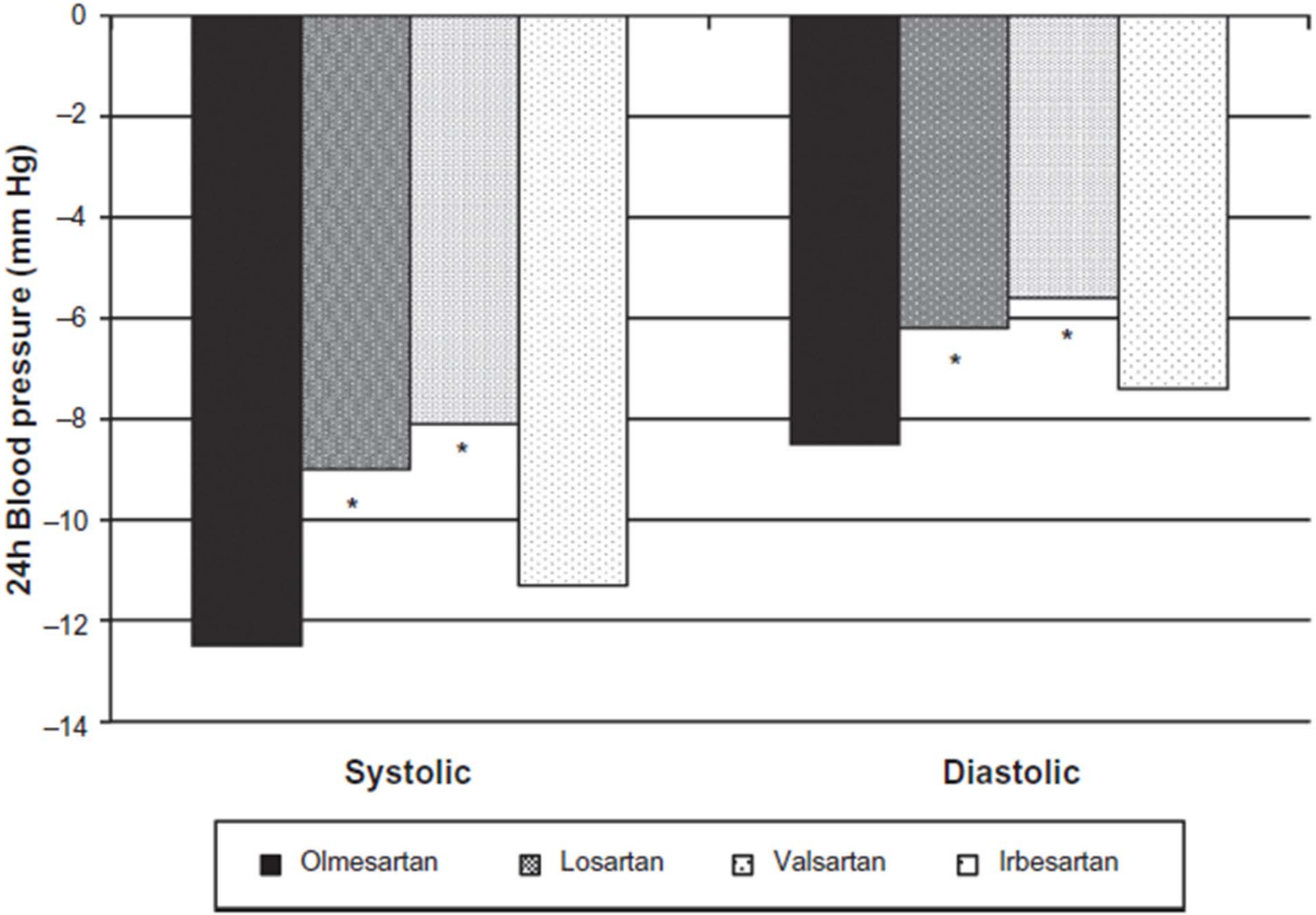
Deleterious effects of angiotesin II



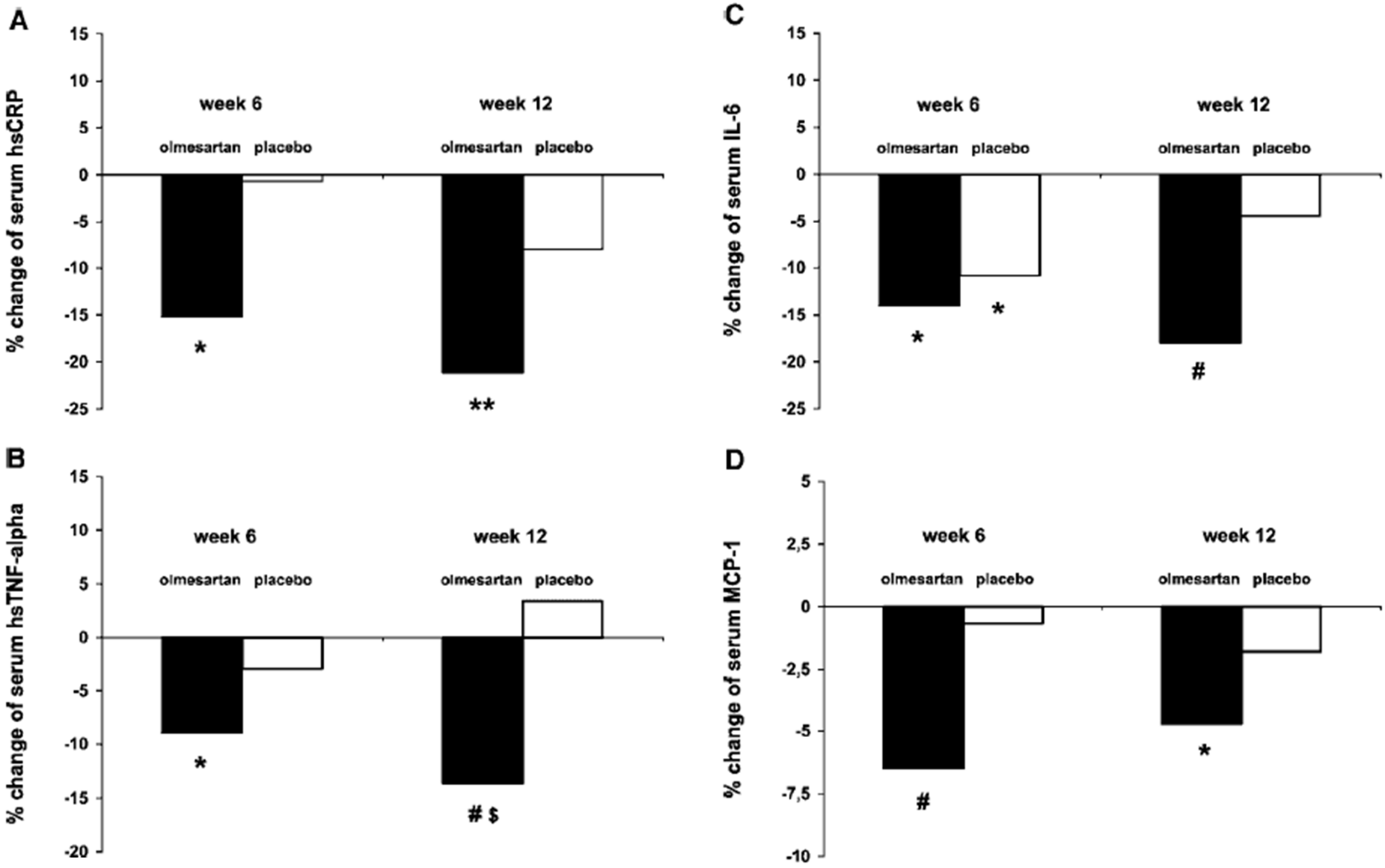
Burnier M, Brunner HR, Lancet 2000;355:637-45

,Brown NJ, Vaughn DE, Adv Intern Med 2000;45:419-29

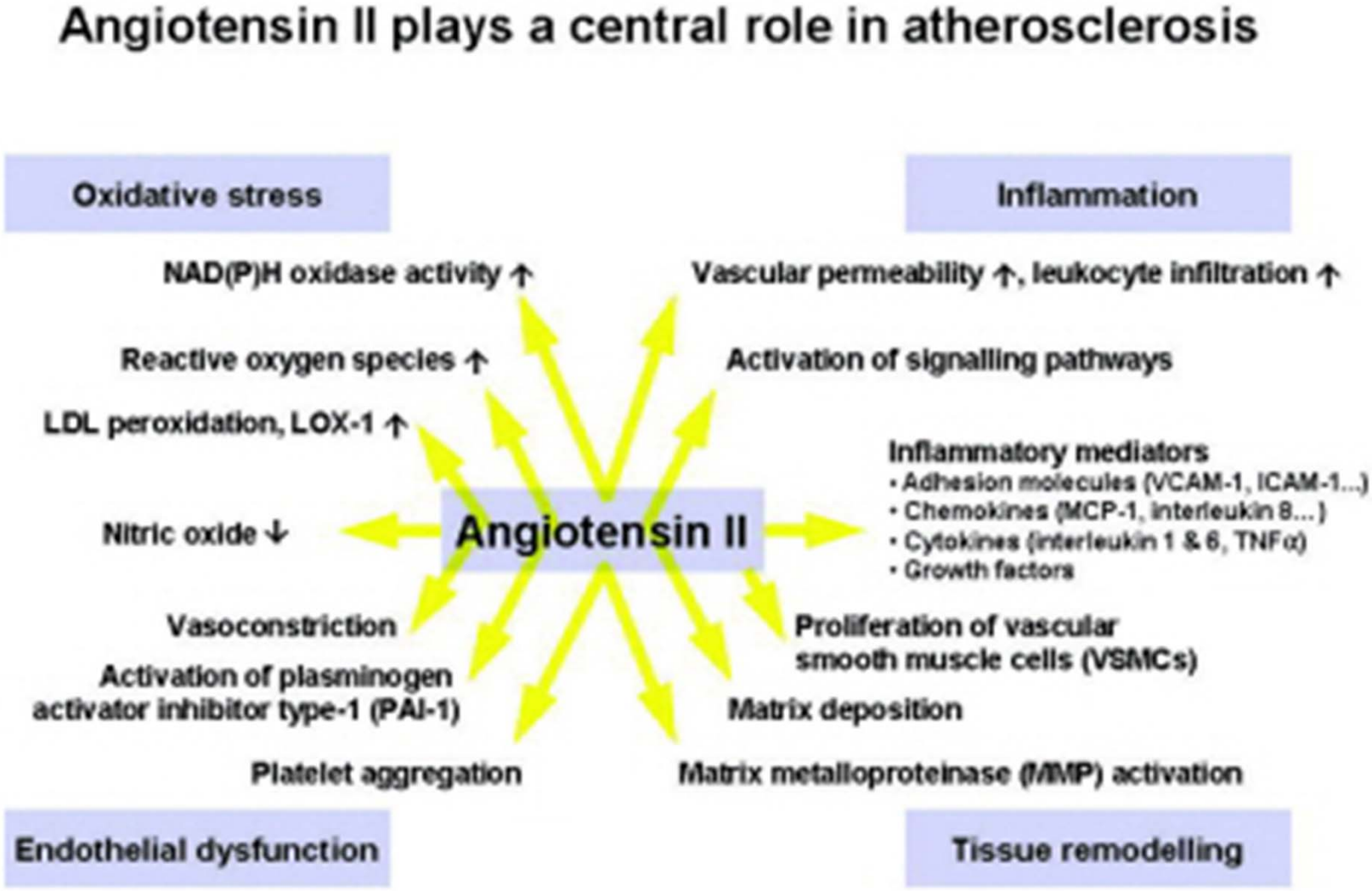
ARBs with Blood pressure



EUTOPIA (European Trial on Olmesartan and Pravastatin in Inflammation and Atherosclerosis) study



Role of angiotensin II in atherosclerosis



Schmieder et al. Lancet 2007;369:1208–19

VIOS study

Study design and primary end-point

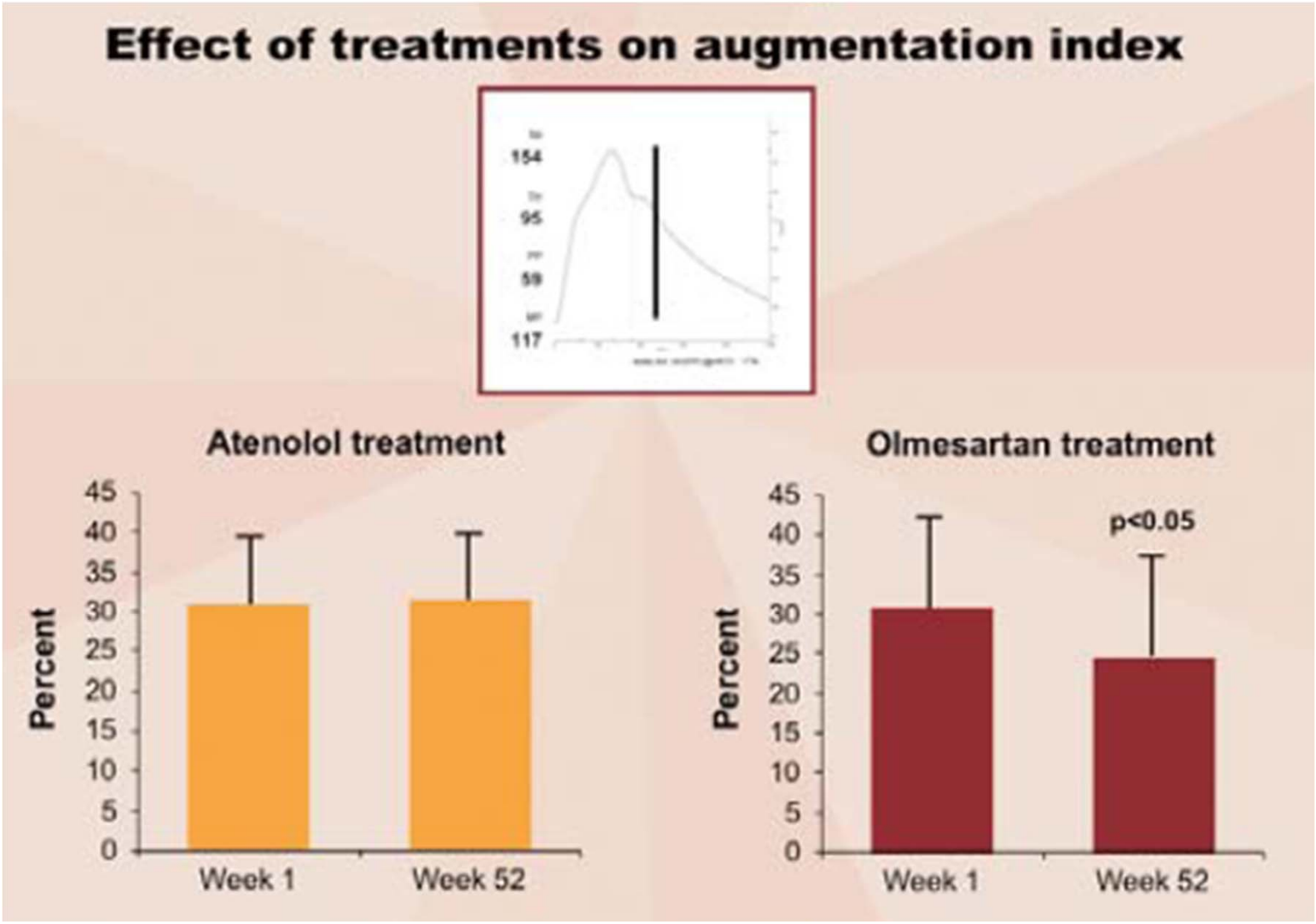
100 patients with stage I hypertension are characterized at baseline before being treated for 1 year to obtain a goal blood pressure of ≤120/80 mmHg as defined by JNC-7

Resistance vessel remodeling was determined using the gluteal fat biopsy technique in the hypertensive patients and a group of normotensive healthy volunteers

The primary end-point was the degree of vascular remodelling as obtained from changes in wall/lumen ratio of gluteal subcutaneous resistance vessels obtained from percutaneous biopsy of patients assigned to each of two treatment arms (olmesartan and atenolol) compared to the normal volunteers

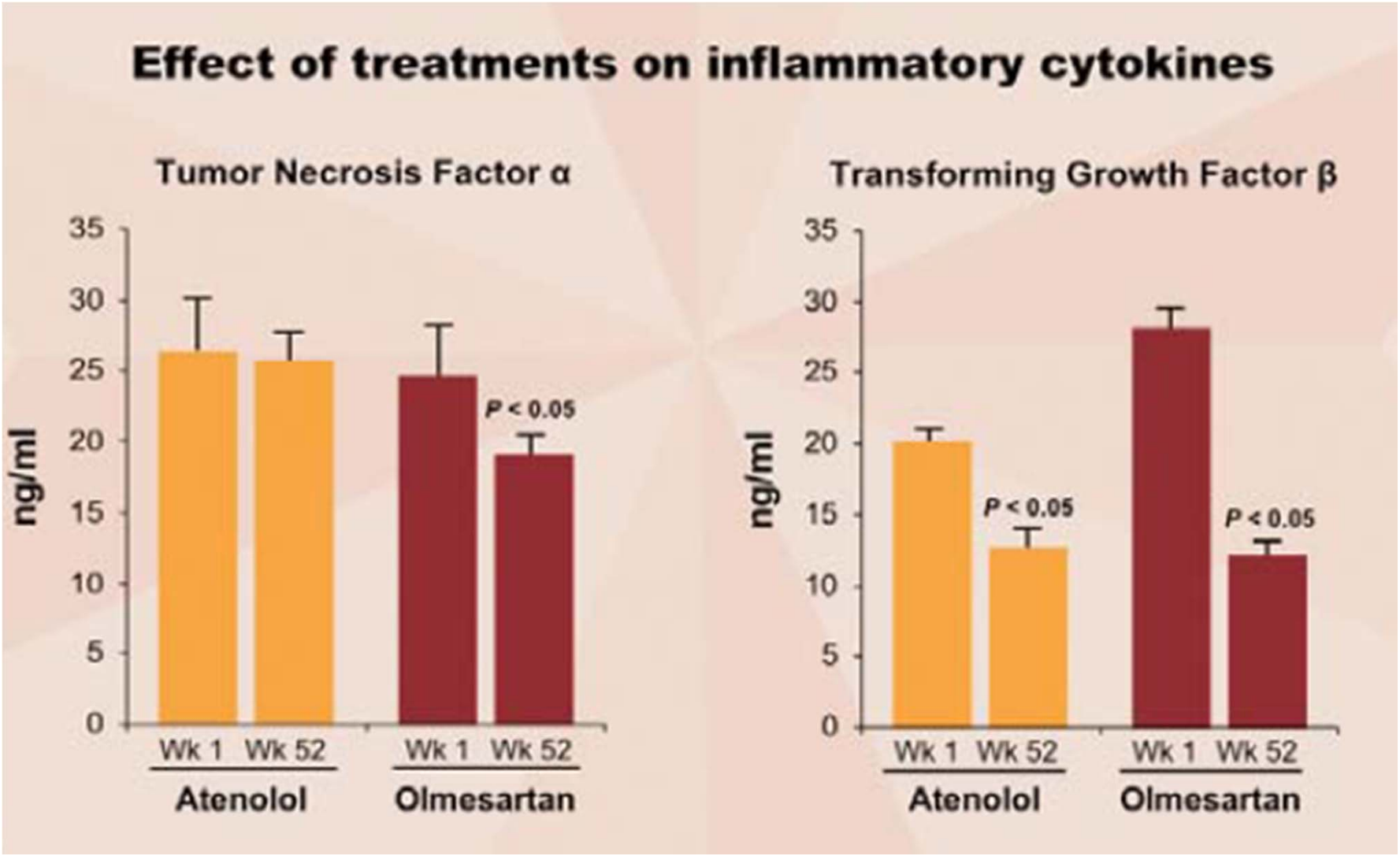
Smith RD, et al Am J Cardiovasc Drugs 2006;6:335-42

VIOS study



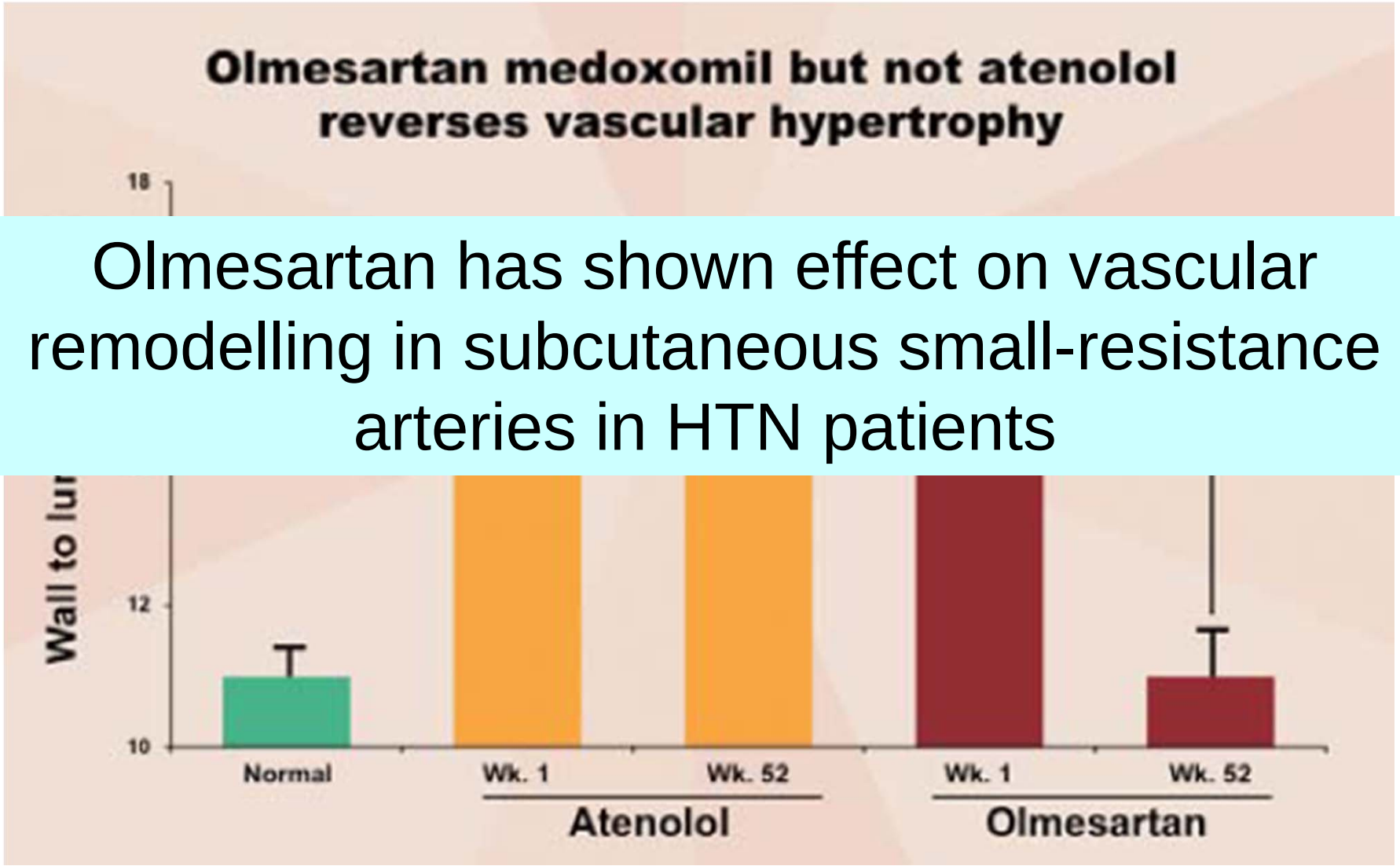
Smith RD, et al Am J Cardiovasc Drugs 2006;6:335-42

VIOS study



Smith RD, et al Am J Cardiovasc Drugs 2006;6:335-42

VIOS study

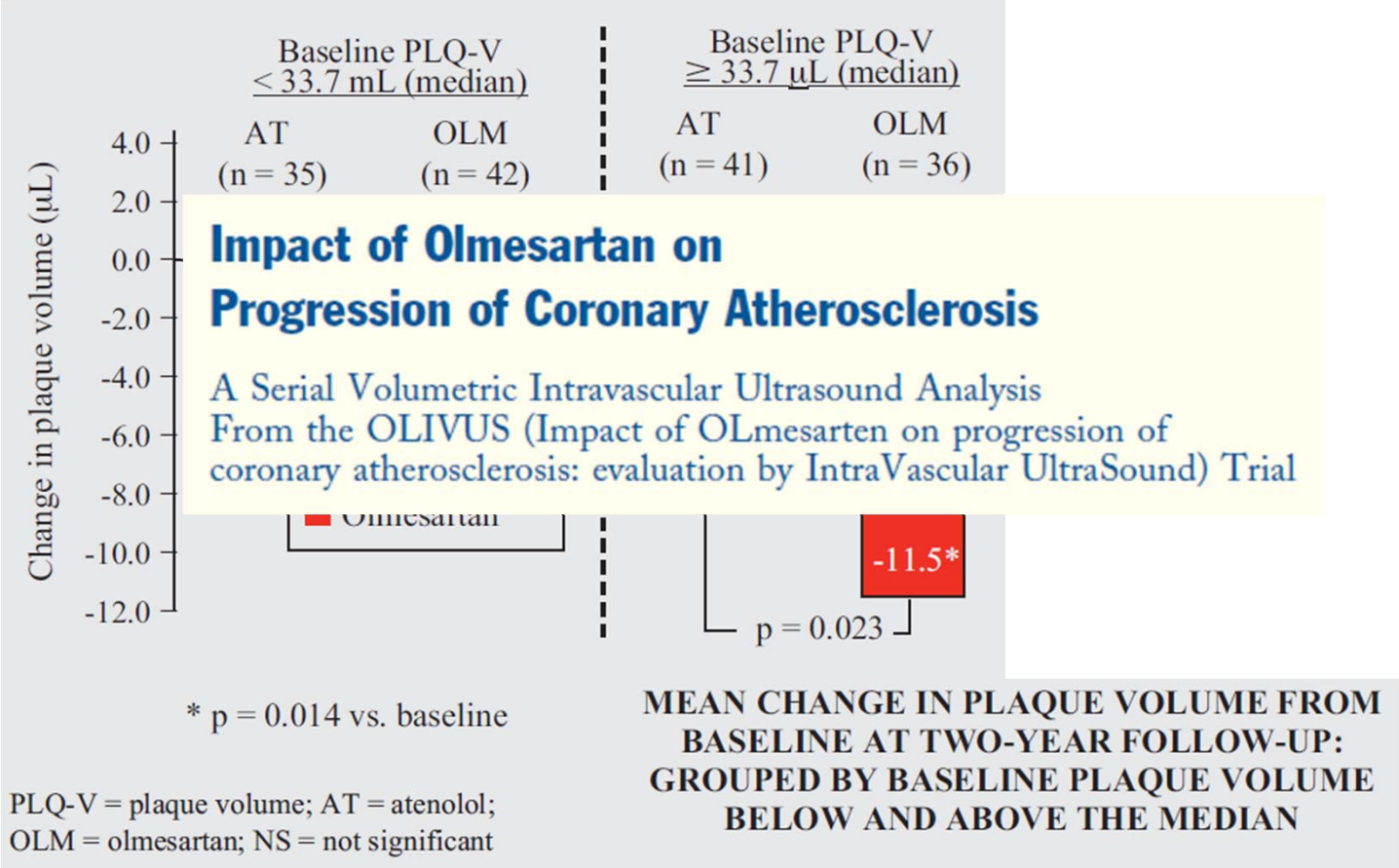


Olmesartan has shown effect on vascular remodelling in subcutaneous small-resistance arteries in HTN patients

Smith RD, et al Am J Cardiovasc Drugs 2006;6:335-42

MORE (Multicenter Olmesartan atherosclerosis Regression Evaluation) trial

Olmesartan has shown antiatherosclerotic effects



Stumpe KO, et al. MORE study. 2007

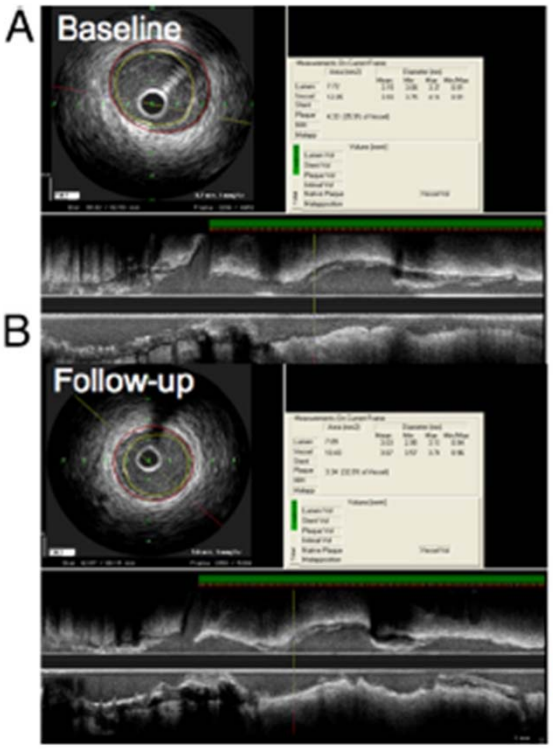
OLIVUS trial

Impact of Olmesartan on Progression of Coronary Atherosclerosis

A Serial Volumetric Intravascular Ultrasound Analysis
From the OLIVUS (Impact of OLmesarten on progression of coronary atherosclerosis: evaluation by IntraVascular UltraSound) Trial

Atsuhi et al. JACC 2010;55:976-82

OLIVUS trial



Baseline

Measured lengths = 52mm

Lumen Volume = 320.7 mm3
Plaque Volume = 207.4 mm3
Vessel Volume = 528.1mm3
Percent Plaque Volume = 39.3%

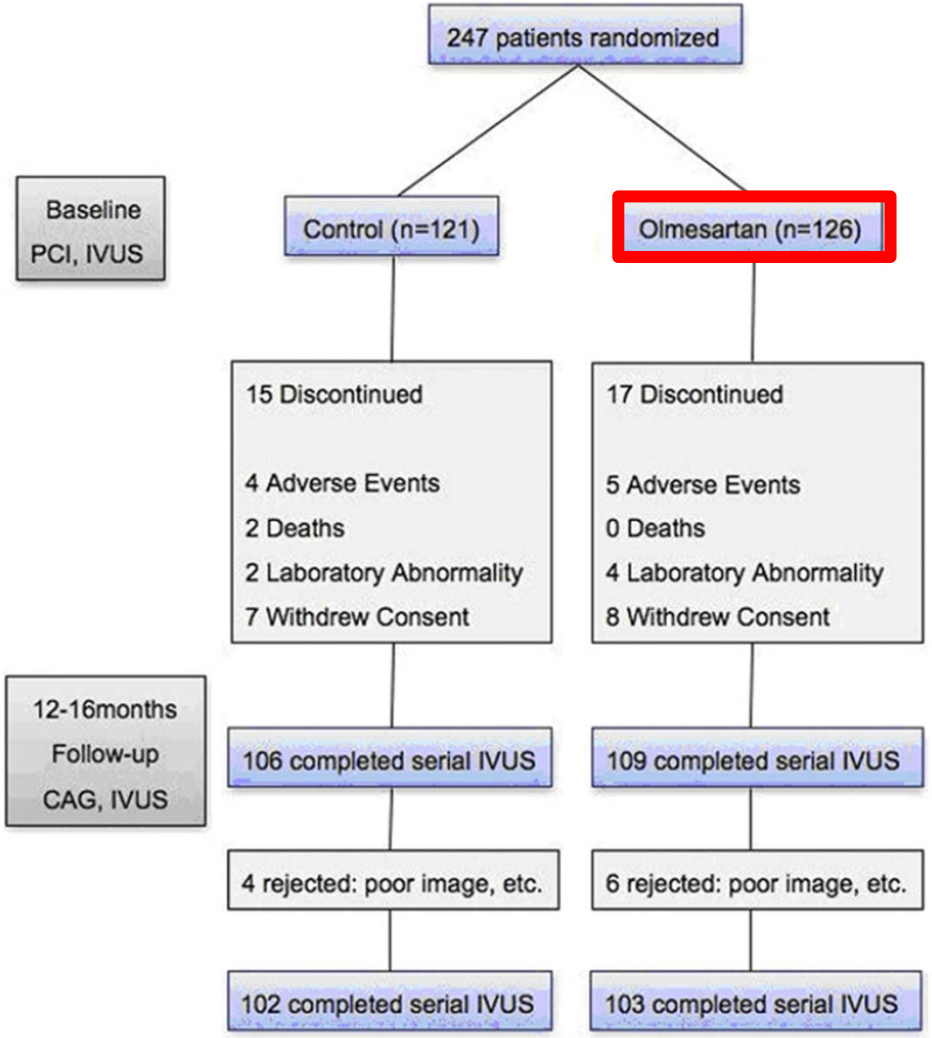
14-months Follow-up

Measured lengths = 52mm

Lumen Volume = 309.1 mm3
Plaque Volume = 221.2 mm3
Vessel Volume = 530.3mm3
Percent Plaque Volume = 41.7%

Percent Change in Plaque Volume = 6.6%
Change in Percent Plaque Volume = 6.2%

Prepresentative serial volumetric IVUS analysis in the control group



Atsuhi et al. JACC 2010;55:976-82

OLIVUS trial

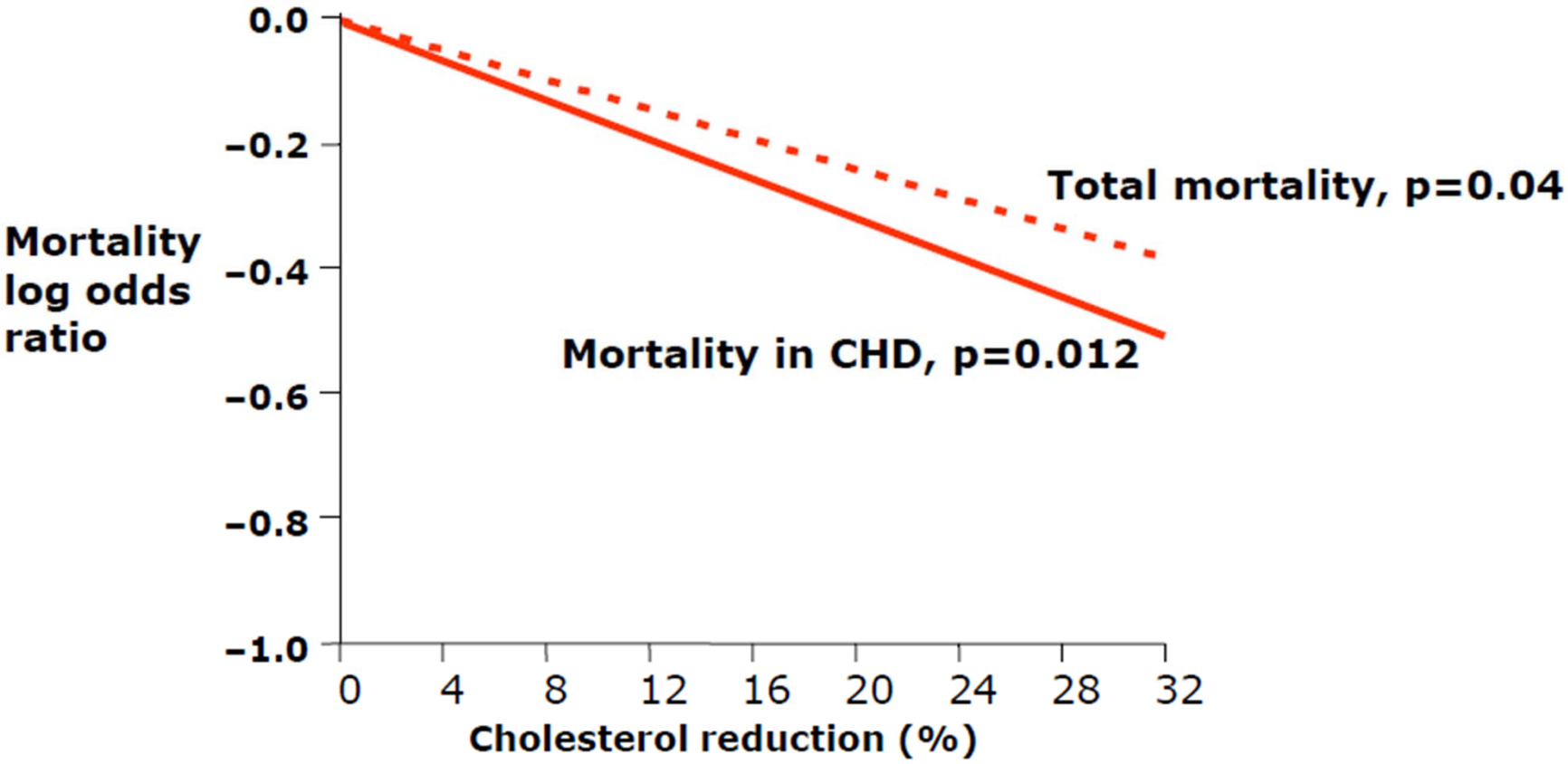
Table 6 Changes in IVUS Parameters From Baseline to Follow-Up

	Control (n = 121)	Olmesartan (n = 126)	p Value
Nominal change			
Atheroma volume (mm^3)	7.1 (1.8–12.4)*	−2.6 (−7.9–2.8)	0.011
Lumen volume (mm^3)	0.3 (−8.7–9.3)	0.4 (−7.6–8.3)	0.989
Vessel volume (mm^3)	7.8 (2.5–10.5)	−2.1 (−8.5–2.5)	0.178
PAV (%)	1.1 (0.1–2.1)†	−0.1 (−0.9–0.8)	0.085
Change in total atheroma volume and PAV			
Total atheroma volume (%)	5.4 (2.4–8.5)	0.6 (−1.9–3.1)	0.016
PAV (%)	3.1 (0.7–5.6)	−0.7 (−3.4–2.0)	0.038

Atsuhi et al. JACC 2010;55:976-82

Benefit of Lowering Cholesterol

Meta-analysis of 38 1° & 2° prevention trials, with ≥ 98,000 patients



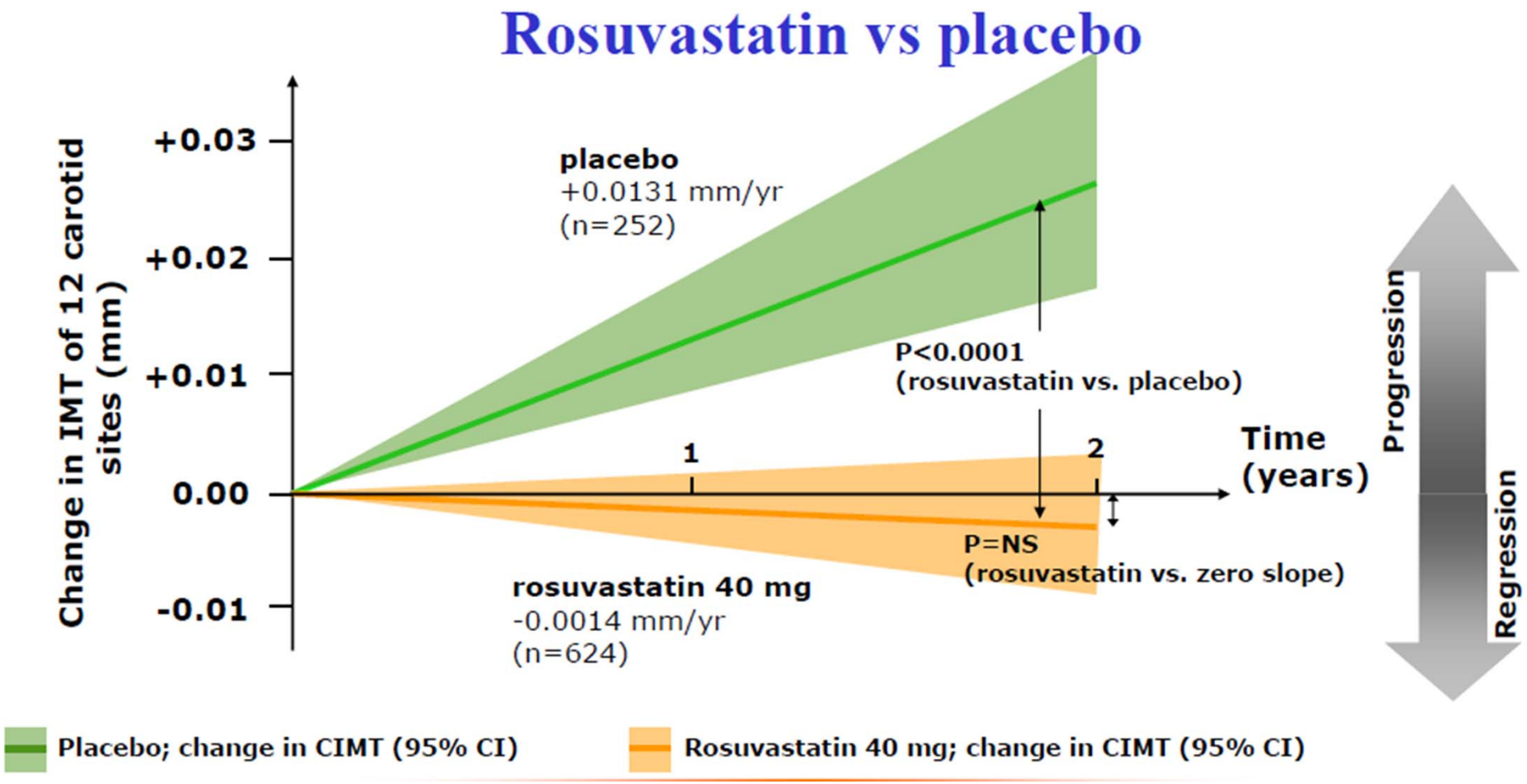
Gould AL et al. Circulation 1998;97:946-952

ADA/NECP ATP III

Recommendations for Lipid Goals in Patients

	Goals		
	LDL cholesterol (mg/dl)	Non-HDL cholesterol (mg/dl)	ApoB (mg/dl)
Highest-risk patients, including those with 1) known CVD or 2) diabetes plus one or more additional major CVD risk factor	<70	<100	<80
High-risk patients, including those with 1) no diabetes or known clinical CVD but two or more additional major CVD risk factors or 2) diabetes but no other major CVD risk factors	<100	<130	<90

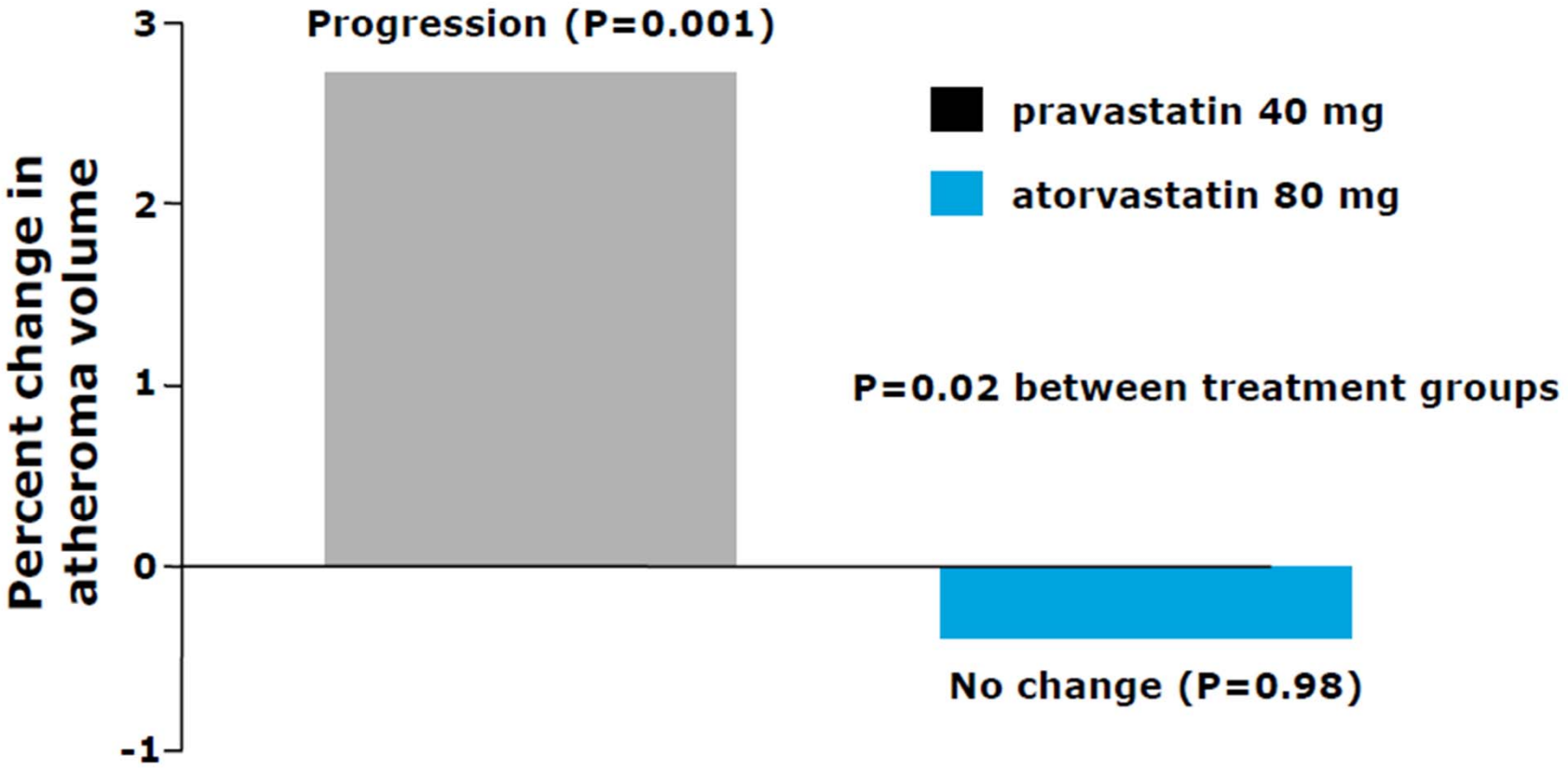
METEROR study



Crouse JR III et al. JAMA 2007;297:1344-1353

REVERAL

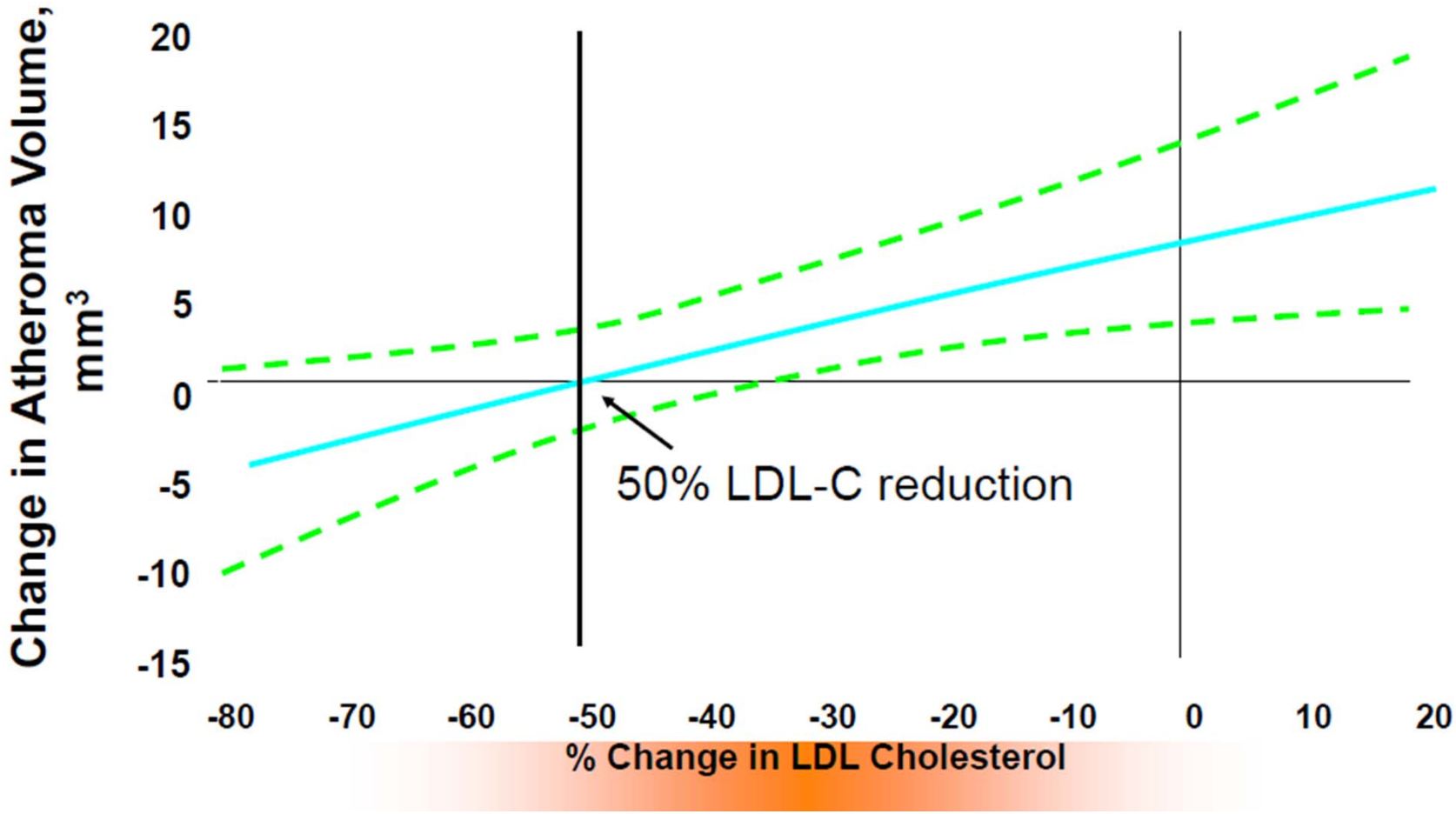
Benefit of Intensive LDLC Lowering on Plaque Progression



Nissen SE et al. JAMA 2004;291:1071-1080

REVERAL

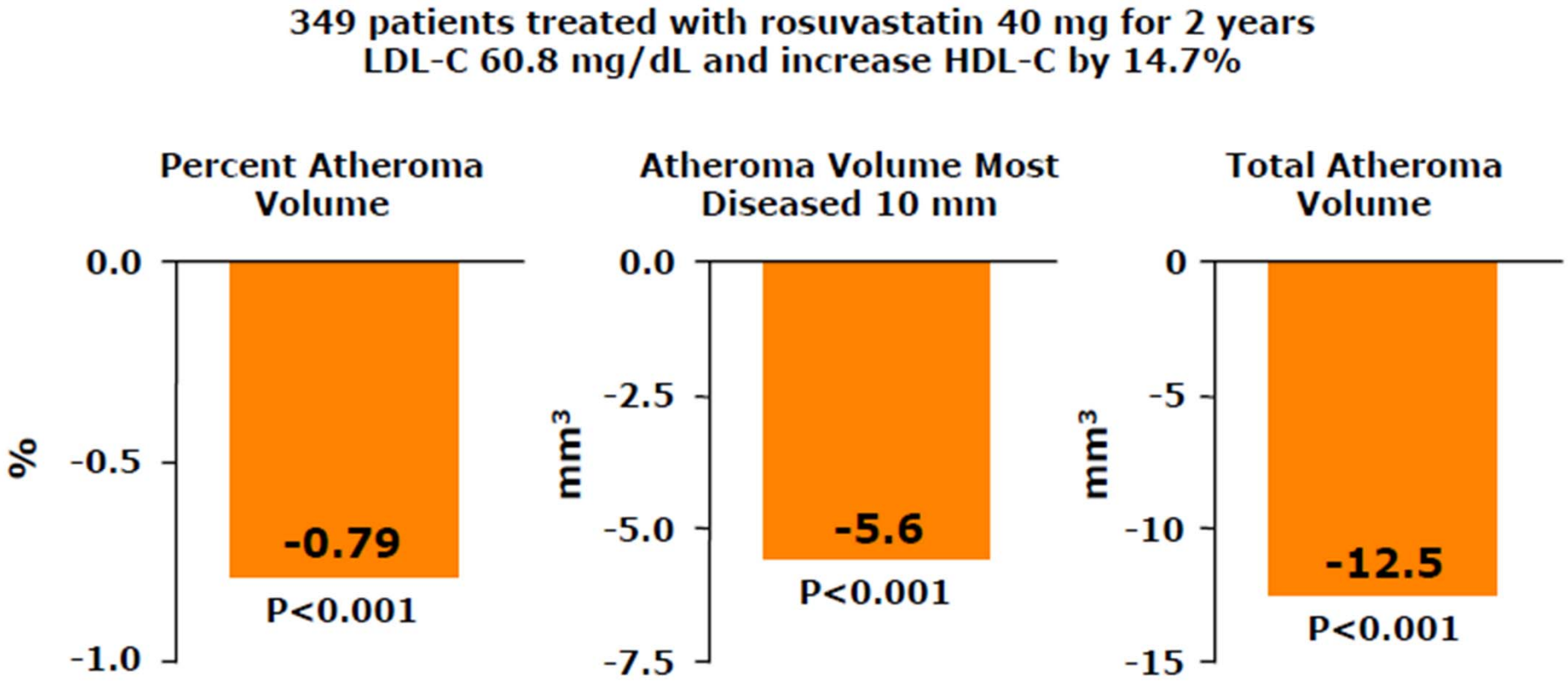
Comparision of % LDLCholesterol Reduction and Change in Atheroma Volume



Nissen SE et al. JAMA 2004;291:1071-1080

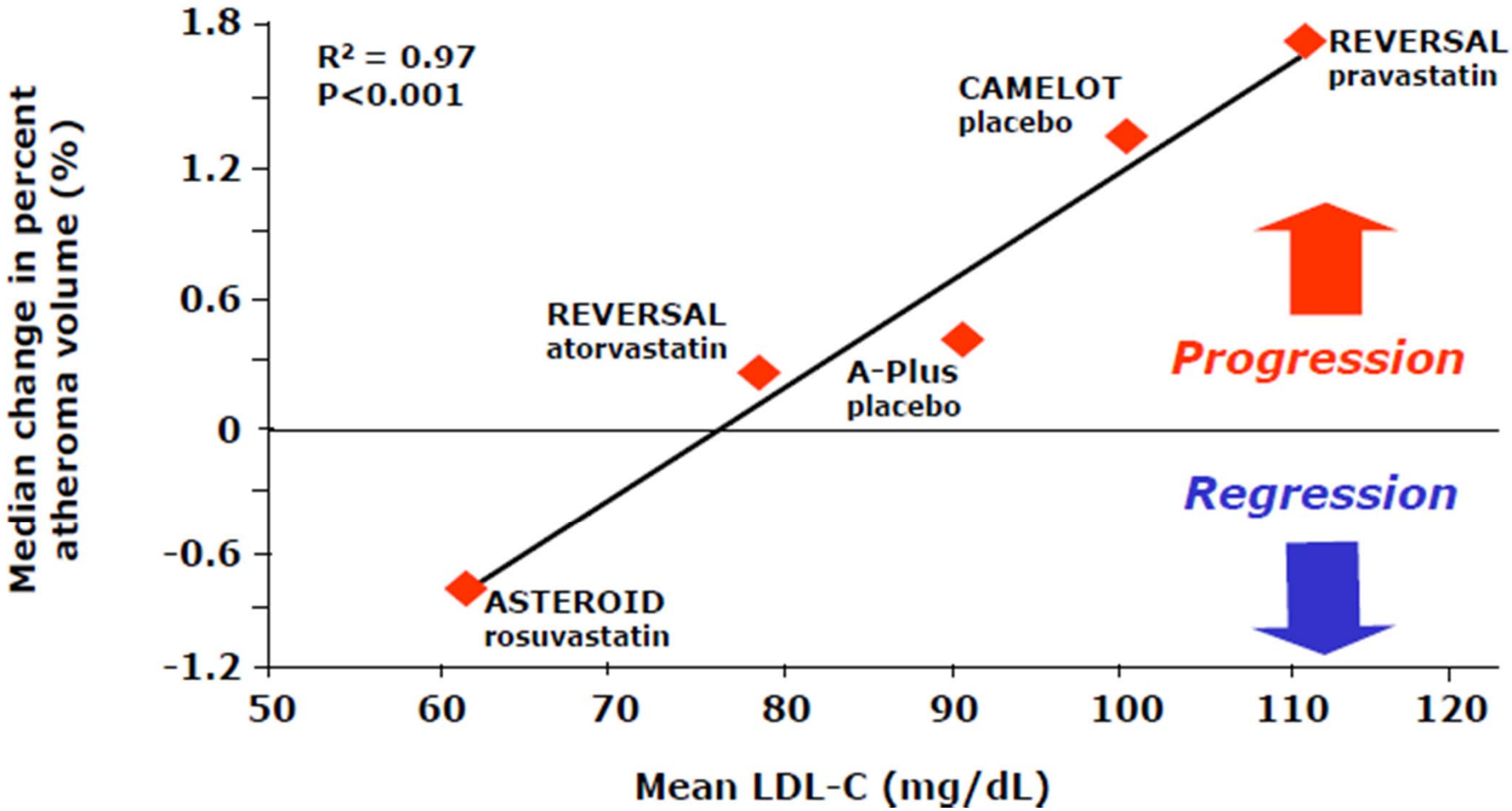
ASTEROID

Regression with High Dose Statin Therapy



Nissen SE, Nichollas et al. JAMA 2006;295:1555-1565

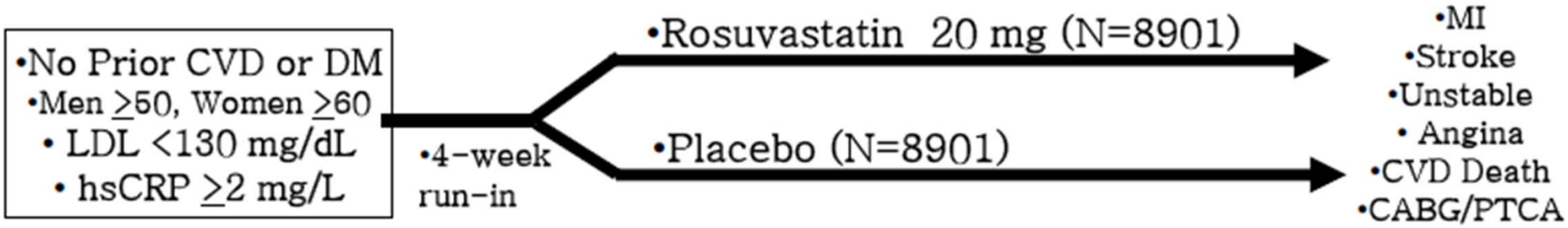
Relationship between LDLC Levels and Change in Percent Atheroma Volume for Several IVUS Trials



Nissen SE et al. JAMA 2006

JUPITER

Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP

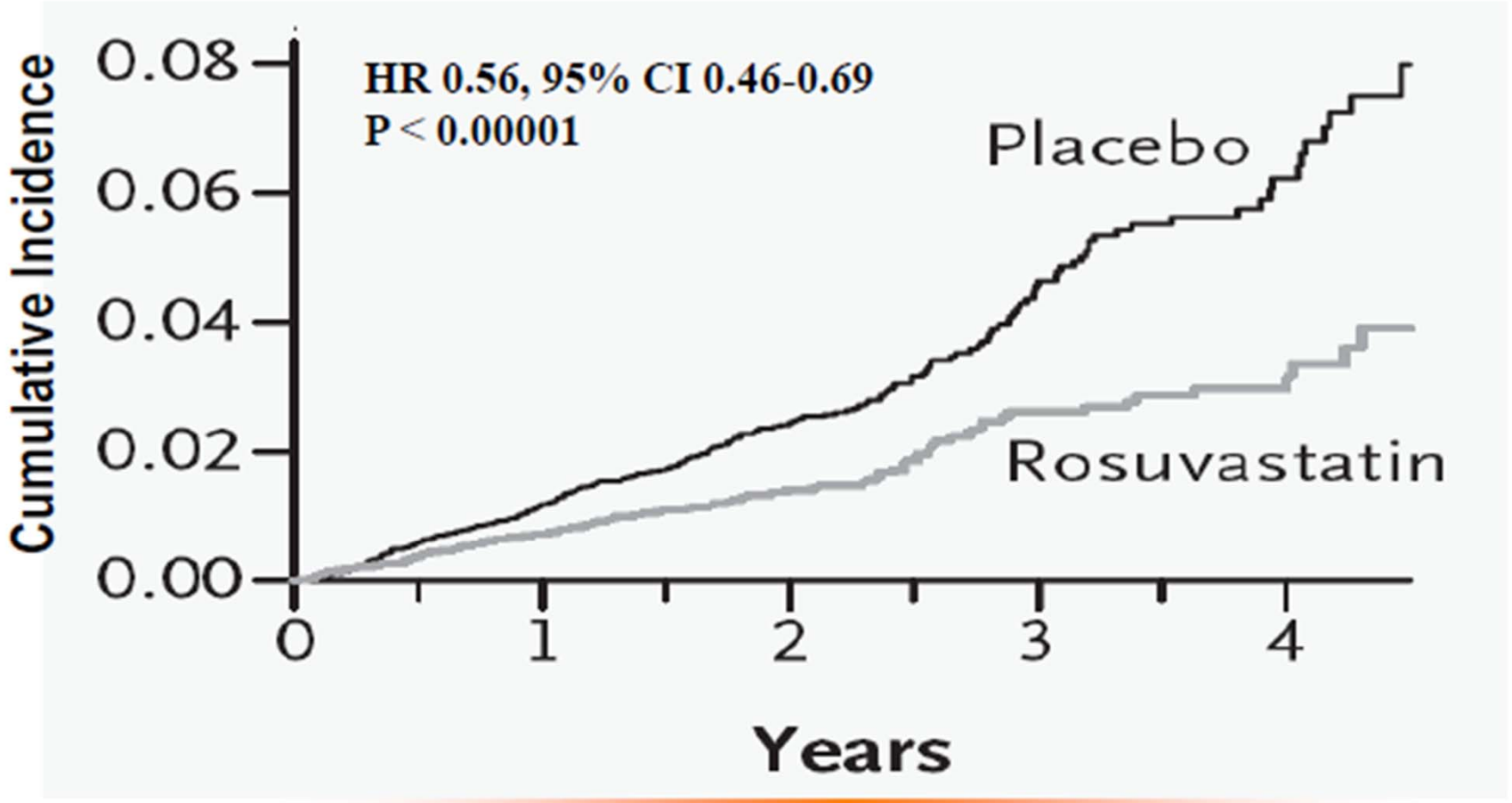


Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Ridker et al, Circulation 2003;108:2292-2297.

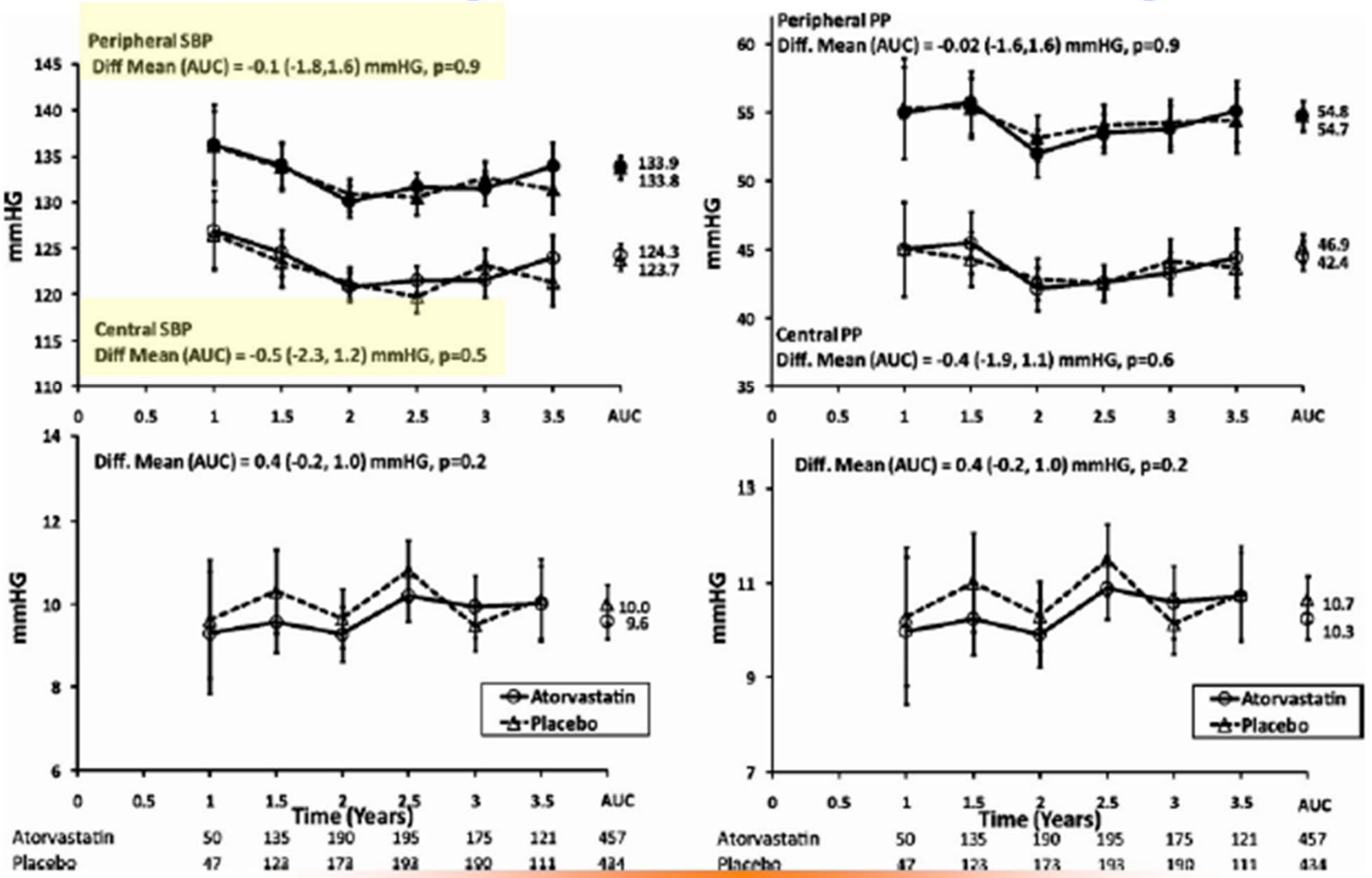
JUPITER Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

Number Needed to Treat (NNT5) = 25



Ridker et al. NEJM 2008;359(21):2280-2

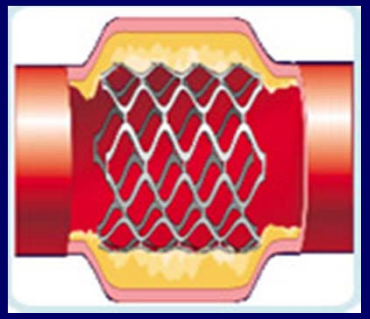
CAFE-LLA: Statin therapy does not influence central aortic pressure or hemodynamics



Williams, B. et al. Circulation 2009;119:53-61

Treatment of Atherosclerosis

Risk factor modulation



PCI

Plauqe rupture
Thrombosis
Stenosis

Drug

Vascular surgery

Modifiable Risk Factors (potentially controllable)

- Hyperlipidemia
- Hypertension
- Cigarette smoking
- Diabetes Mellitus
- Elevated Homocysteine
- Factors that affect hemostasis and thrombosis
- Infections: Herpes virus; Chlamydia pneumoniae
- Obesity, sedentary lifestyle, stress

Conclusions

- Risk factors evaluation
- PWV, AI, Carotid IMT
- Optimal BP control with ARB
- Optimal Lipid control with statin
- Others (?)

From Artherosclerosis without Atheroma

Thank You for Your Attention !