

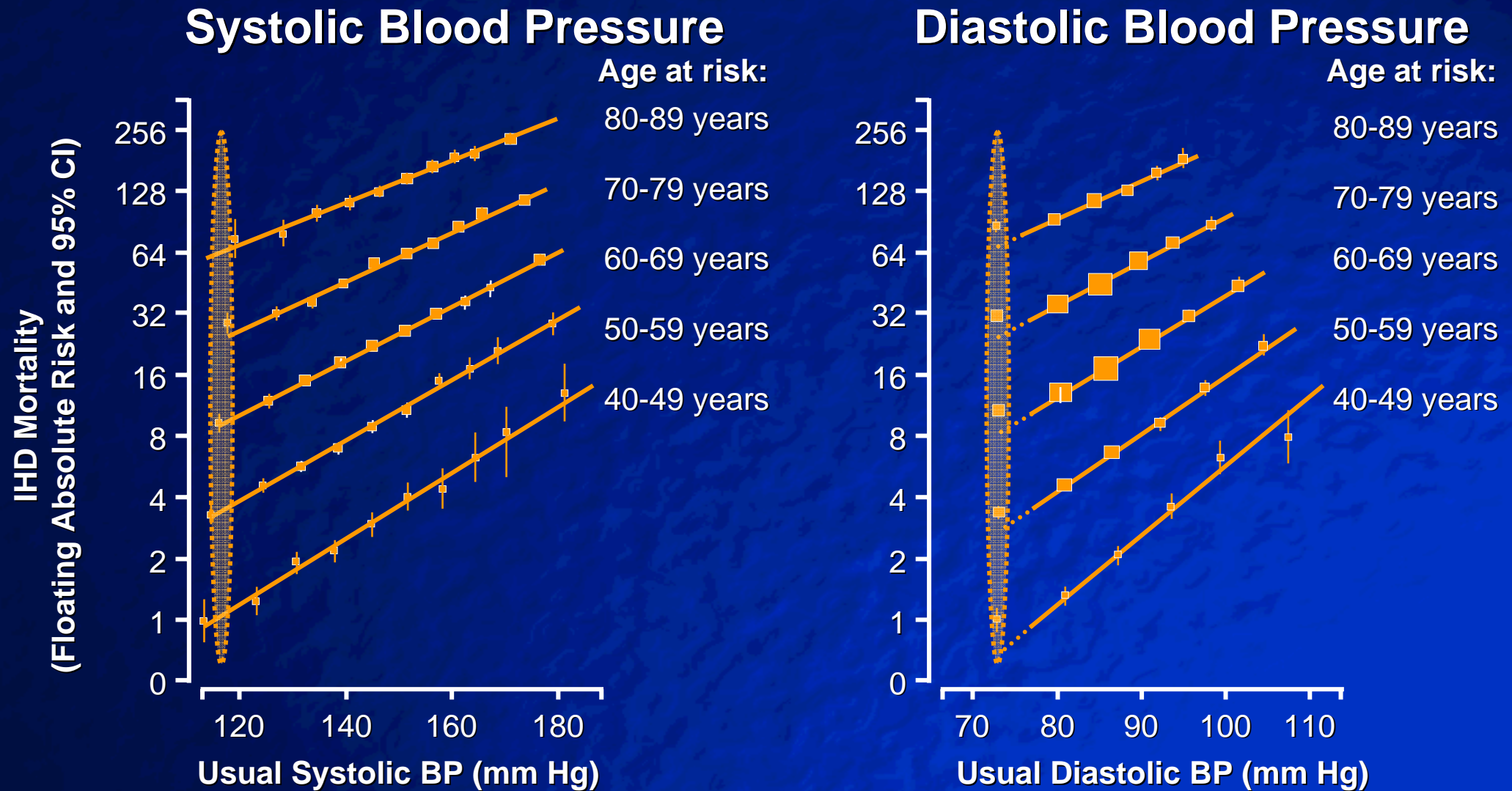
Optimizing the Treatment for Hypertensive Patients Led by Evidence: Is It All about Blood Pressure?

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12th Angioplasty Summit 2007-TCT Asia Pacific, 2007 Apr 25~27 at Seoul, Korea

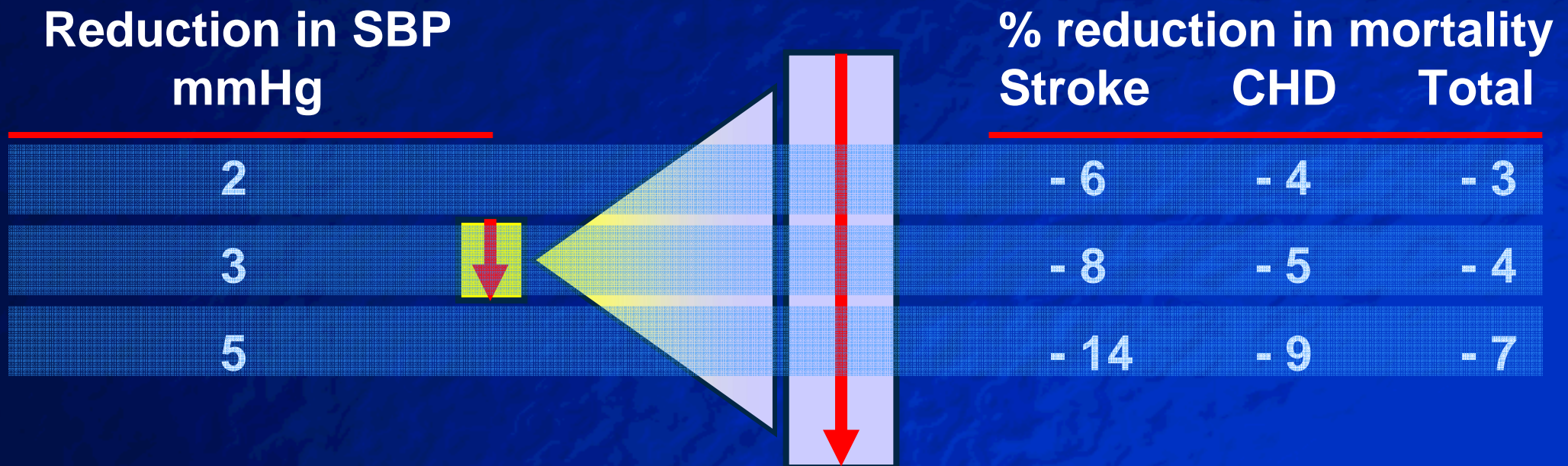
Ischemic Heart Disease Mortality and Usual BP by Age (Meta-analysis from 61 trials, 1,000,000 pts, 12,700,000 pt-yr)



Prospective Studies Collaboration. *Lancet*. 2002;360:1903-1913.

Lowering blood pressure reduces cardiovascular risk : JNC VII

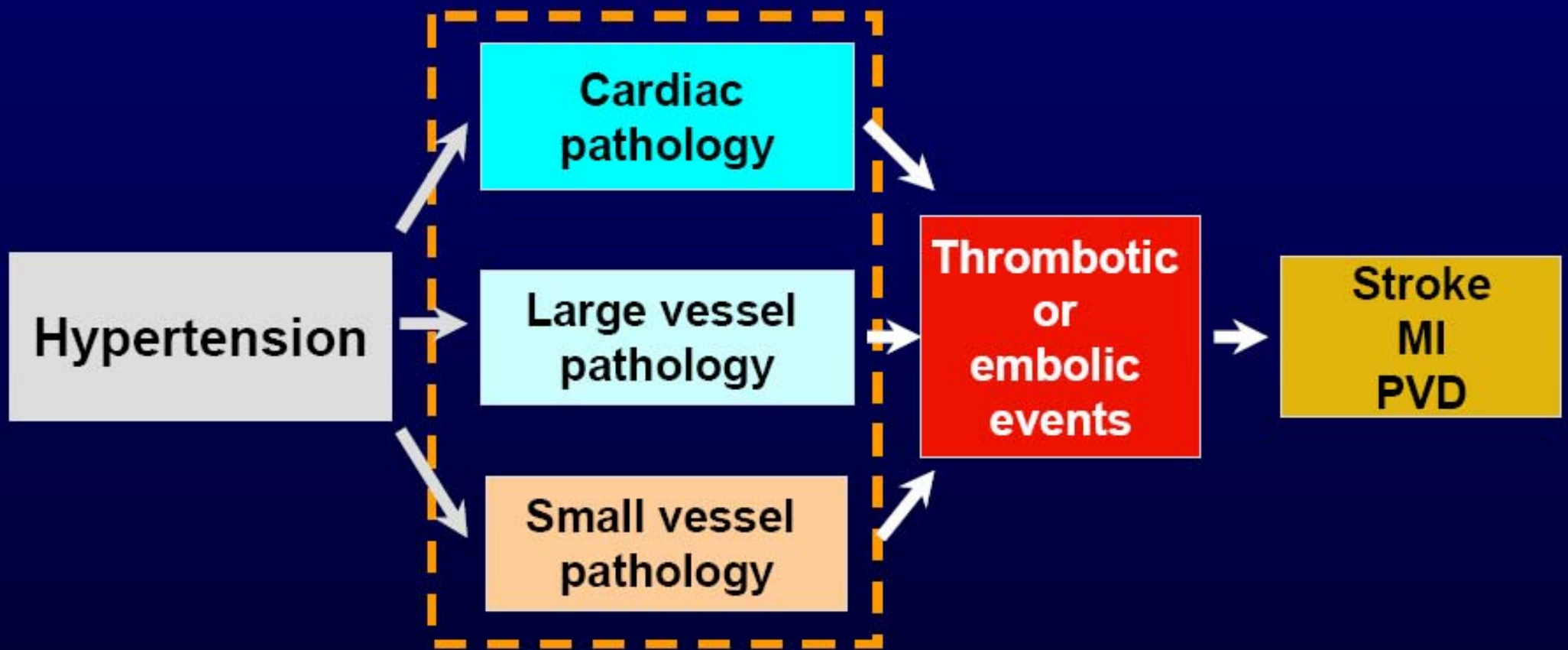
Small SBP reductions yield significant benefit !



Patients with CV risks, but BP already controlled < 140/90 mmHg

	BP change (c/w placebo)	primary end- point	P
Is It All about Blood Pressure?			
ACCEL (2000, NEJM)	(- 3/1 mmHg)	-11%	0.0003
EUROPA (ACEI) (2003, Lancet)	137/82→ 132/80 (- 5/2 mmHg)	-20%	0.0003
CAMELOT (CCB) (2004, JAMA)	129/78→ 124/75 (- 5/2.5 mmHg)	-31%	0.003

Understanding Hypertension and CV pathology as a Mechanism of “Beyond BP Lowering Effects”

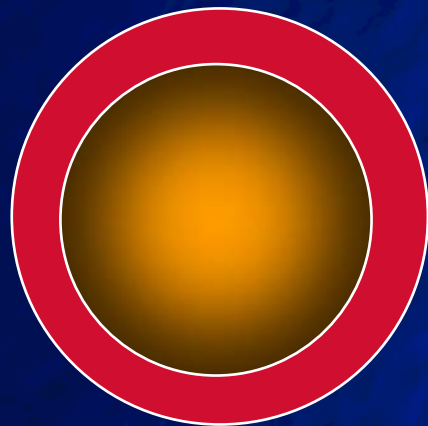


Cardio-Arterial changes in Hypertension

Normotension

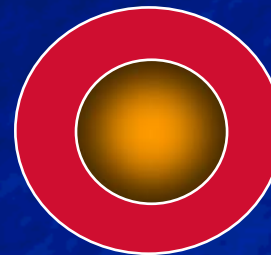
Hypertension

Hemodynamic:
pressure, flow, cyclic stress



Extra/intracellular stimuli:
Ang II, ET-1, NO⁻, O₂⁻ ...

Structure



large



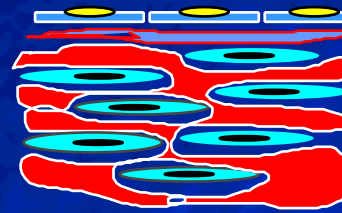
Hypertrophic

small



Eutrophic remodeling

Endothelium



Endothelial dysfunction

Elastin X

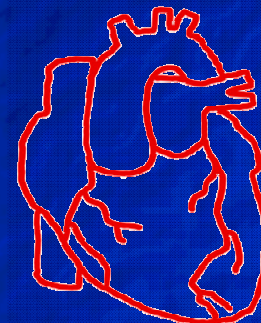


Altered vascular mechanics

Collagen ↑

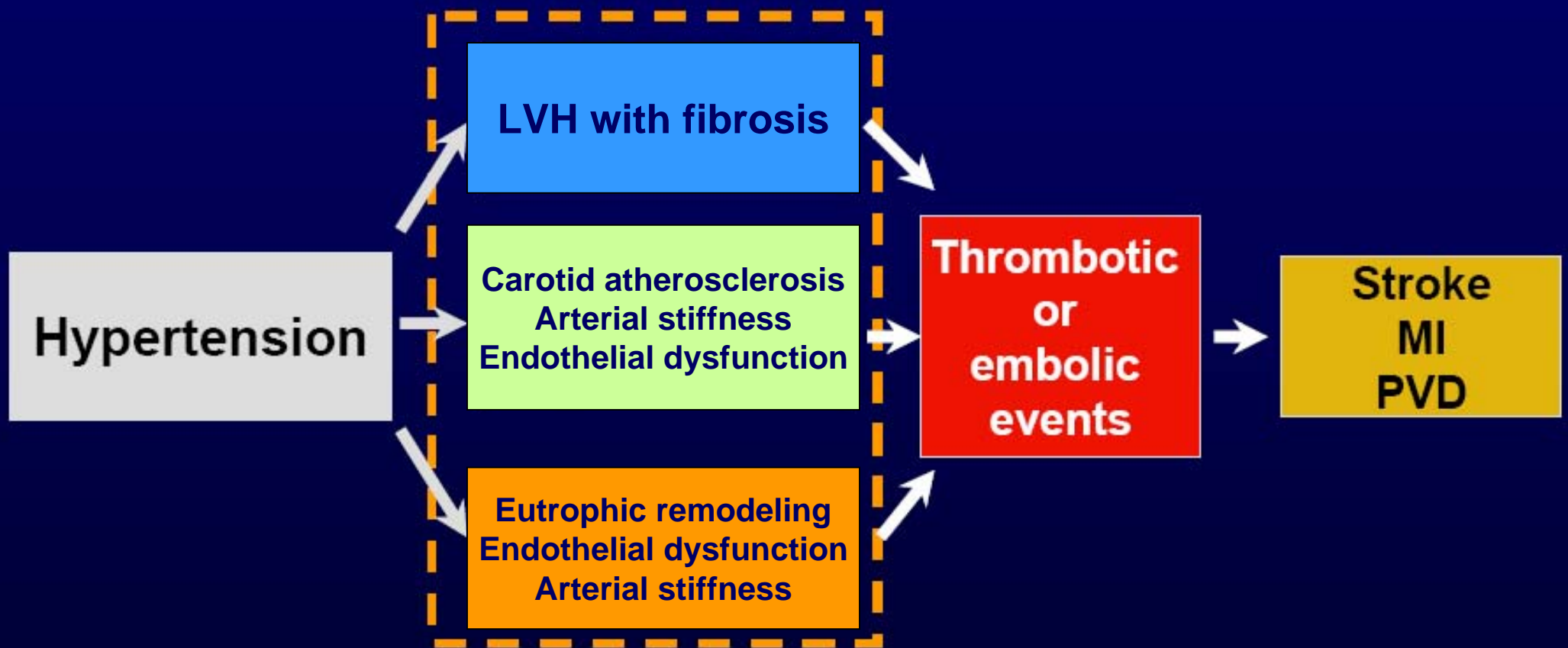


ECM deposition

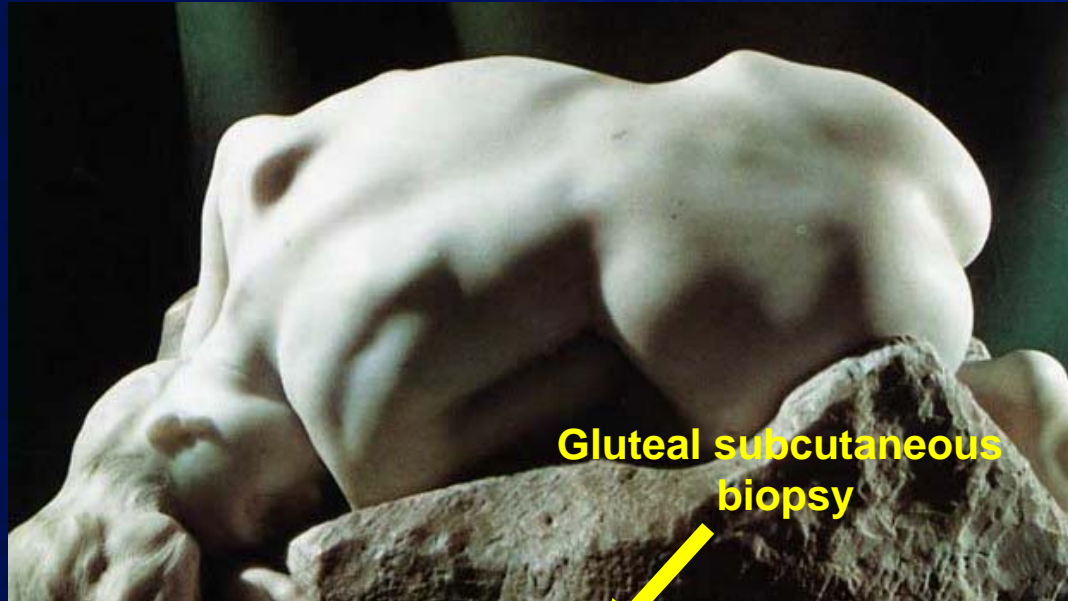


Cardiac Hypertrophy with fibrosis

Target organ damage as intermediate criteria for CV events “Beyond BP Lowering Effects”

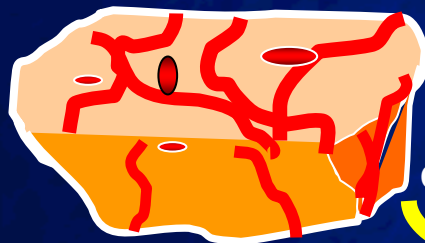


Resistance Artery Study in Human



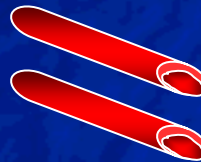
Gluteal subcutaneous biopsy

Subcutaneous fat

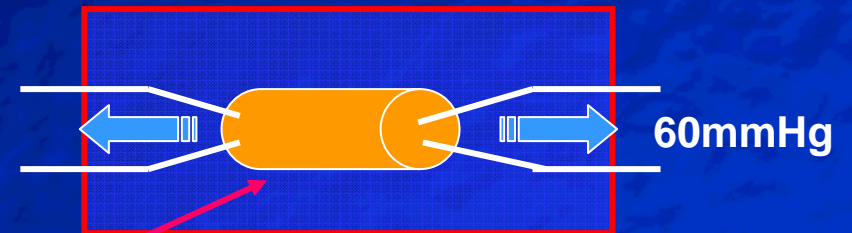


dissection

Peripheral resistance artery
(\varnothing 150 ~300 μ m)



Small artery studies (isobaric)



Structure; media to lumen ratio

Function; ach and nitroprusside

Mechanics

-intraluminal pressure = 3 - 140 mmHg

-lumen and media measurements

Small artery remodeling is the most prevalent (earliest?) form of target organ damage in mild essential hypertension.

	Hypertension	Prevalence (%)
Resistance Artery		
Vascular Remodeling	↑	63 - 97
- Media/Lumen ratio	↓	34 - 58
Endothelial Function	↔	No change
- Ach response	↗	26 - 34
Vascular Stiffness		
- E_{inc} vs stress		
LV Mass		
ECG/ECHO		

Small artery remodeling in hypertension ; eutrophic vs. hypertrophic

Normotensive

Hypertensive



Hypertrophic Remodeling

↑ Media/lumen
↑ CSA
(endothelin)

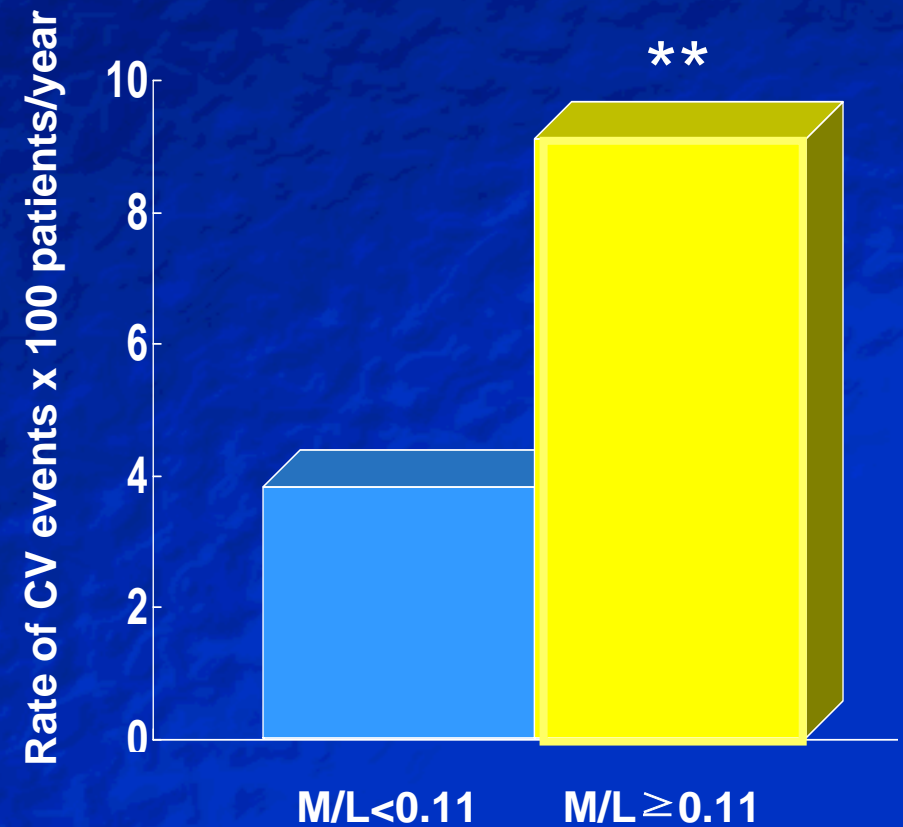
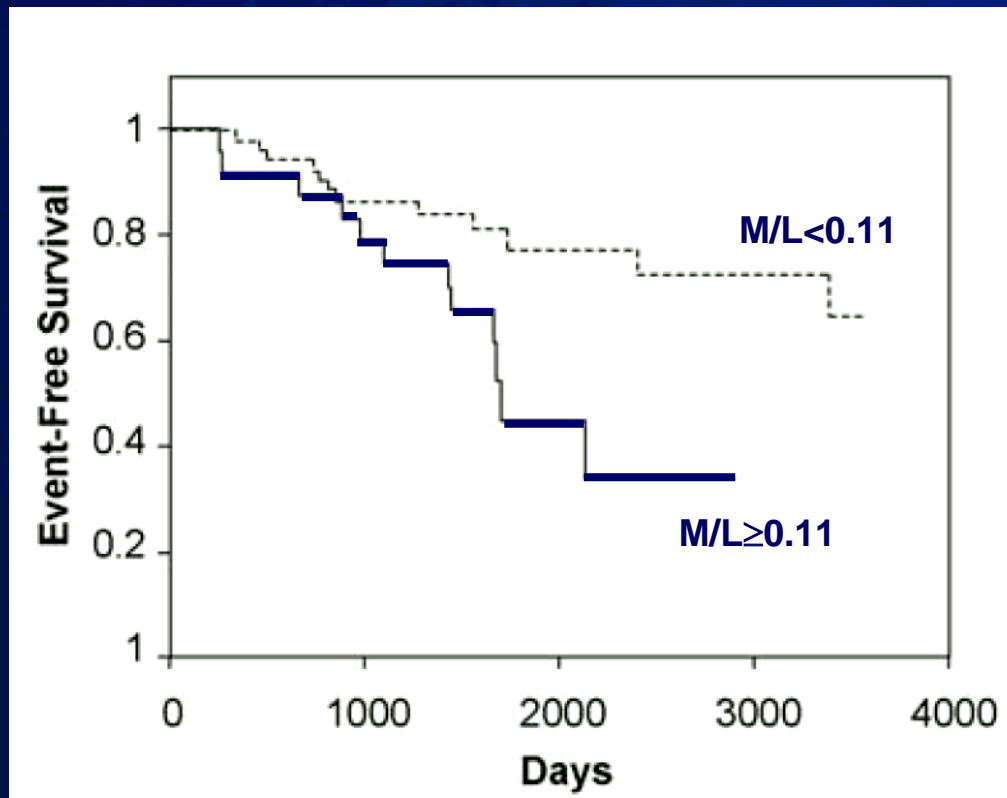
Eutrophic Remodeling

↑ Media/lumen
= CSA
(angiotensin II)

Poiseuille's law

$$\text{Resistance to flow} = \frac{8 \eta L}{\pi r^4}$$

Event-free survival in a group of patients with essential hypertension or diabetes mellitus and with a media–lumen (M/L) ratio of subcutaneous **small arteries** and Incidence of cardiovascular events



Correction of Arterial Structure and Endothelial Dysfunction in Human Essential Hypertension Angiotensin Receptor Antagonist Losartan

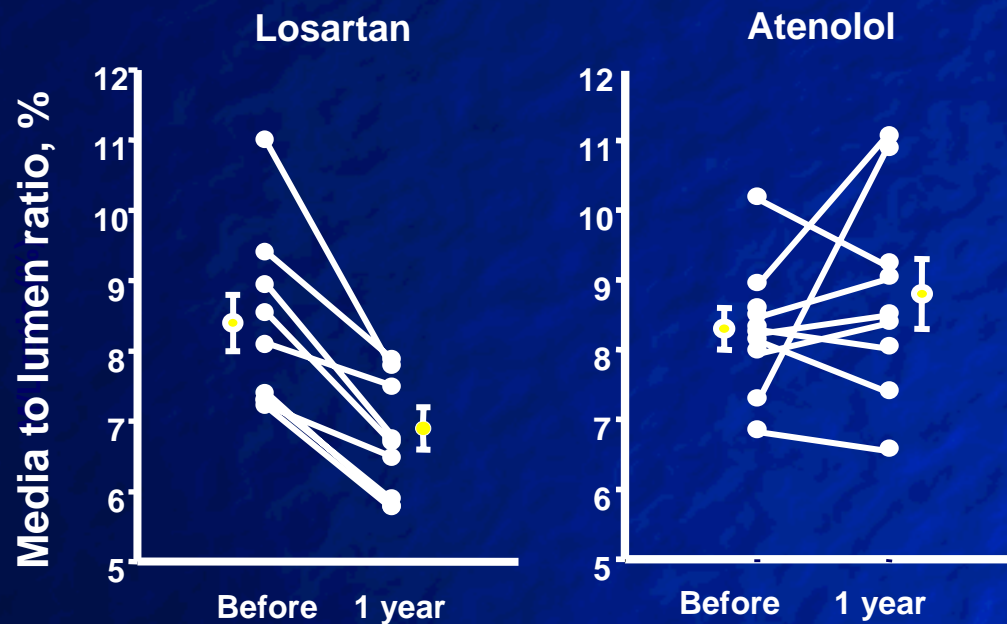
Ernesto L. Schiffrin, Jeong Bae Park,
Hope D. Intengan, Rhian M. Touyz

Circulation. 2000;101:1653-1659.

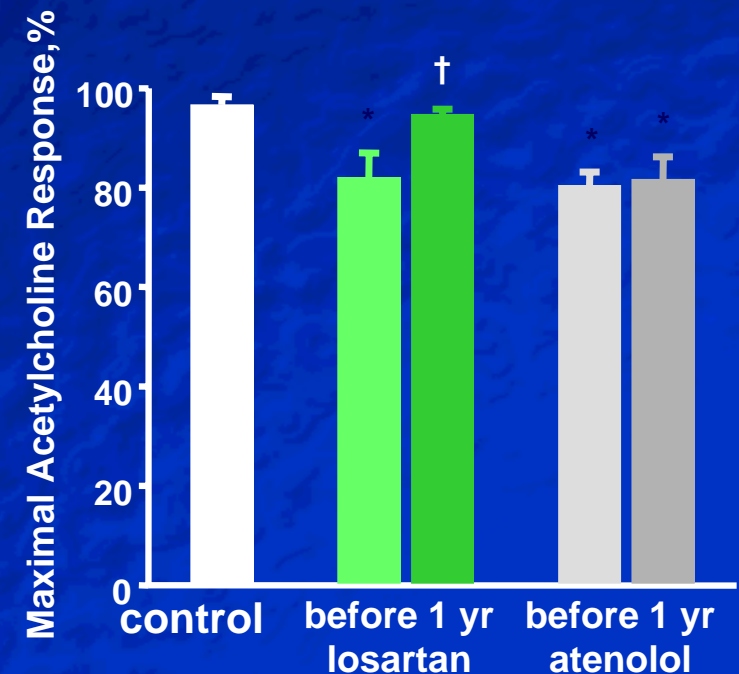
→ To test the hypothesis that the angiotensin receptor antagonist losartan, in contrast to the b-blocker atenolol, would correct resistance artery abnormalities in patients with essential hypertension.

Correction of Arterial Structure and Endothelial Dysfunction in Human Essential Hypertension by the Angiotensin Receptor Antagonist Losartan

Vascular structure

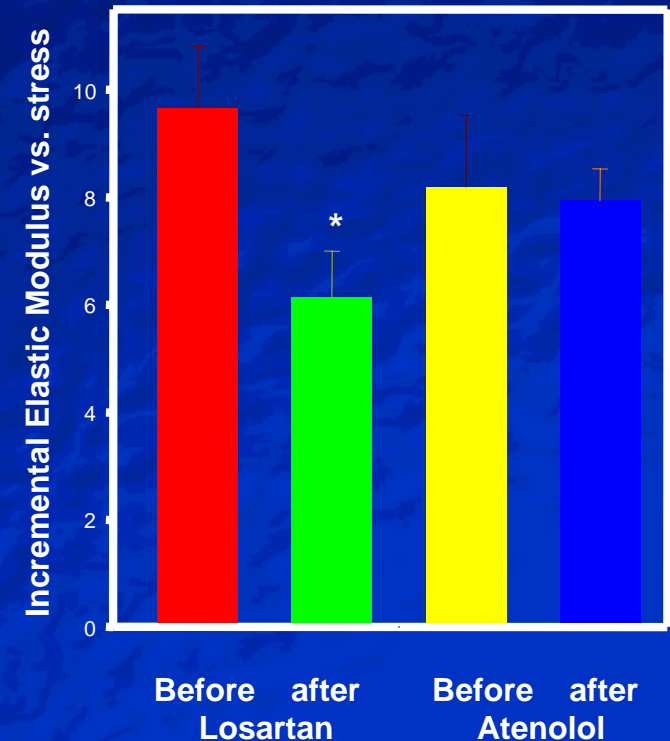
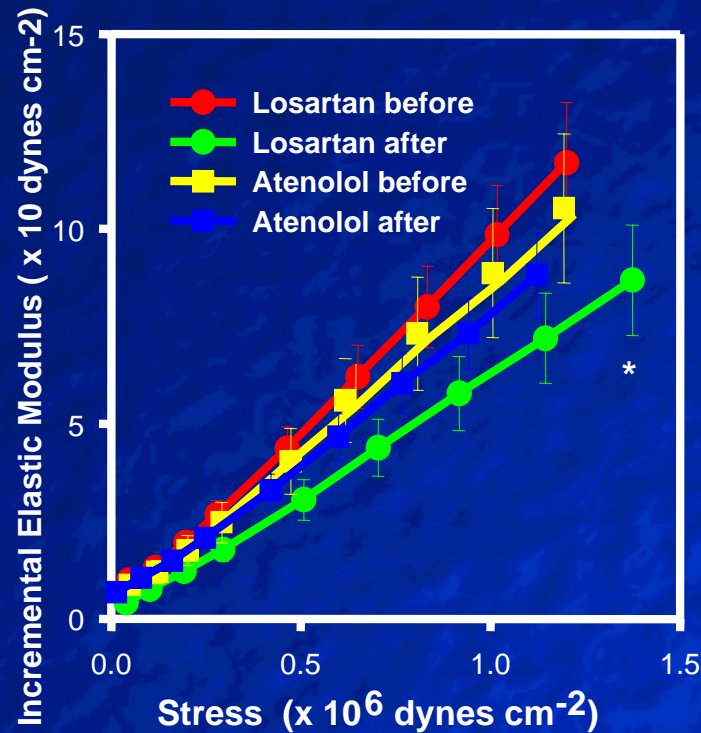
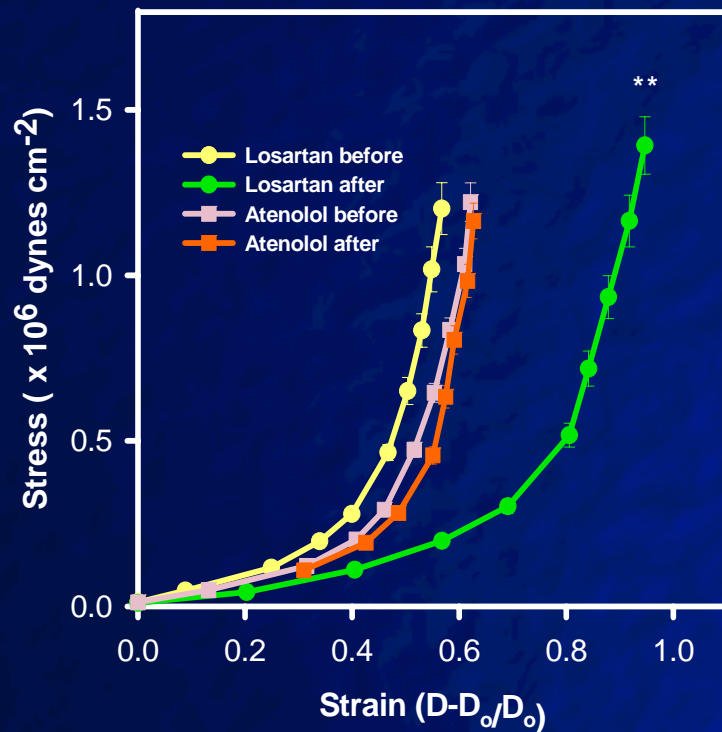


Vascular function

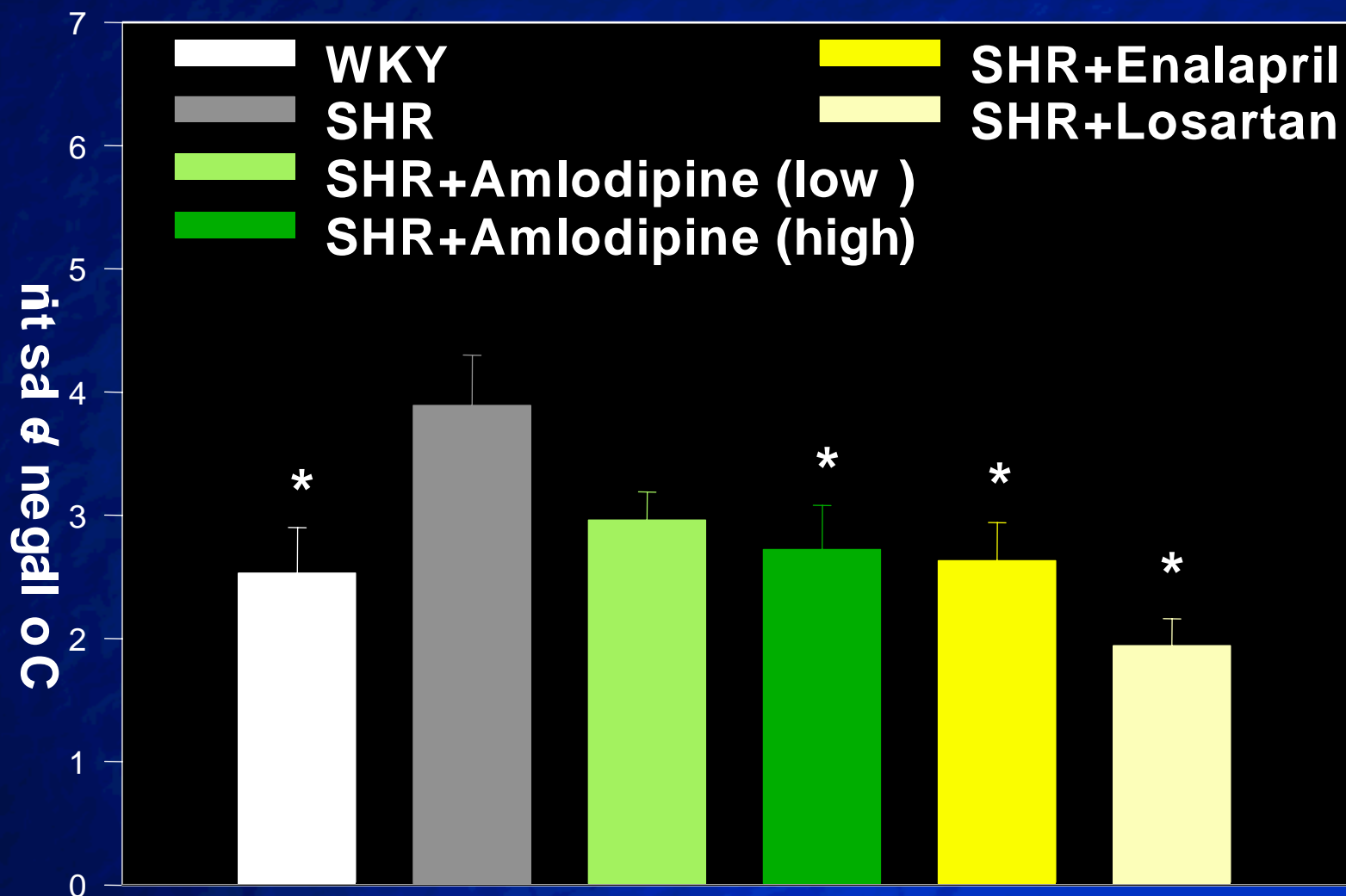


Schiffrin, Park et al. *Circulation* 2000;101:1653

Reduction of Resistance Artery Stiffness by Treatment with the AT₁ Receptor Antagonist Losartan in Essential Hypertension

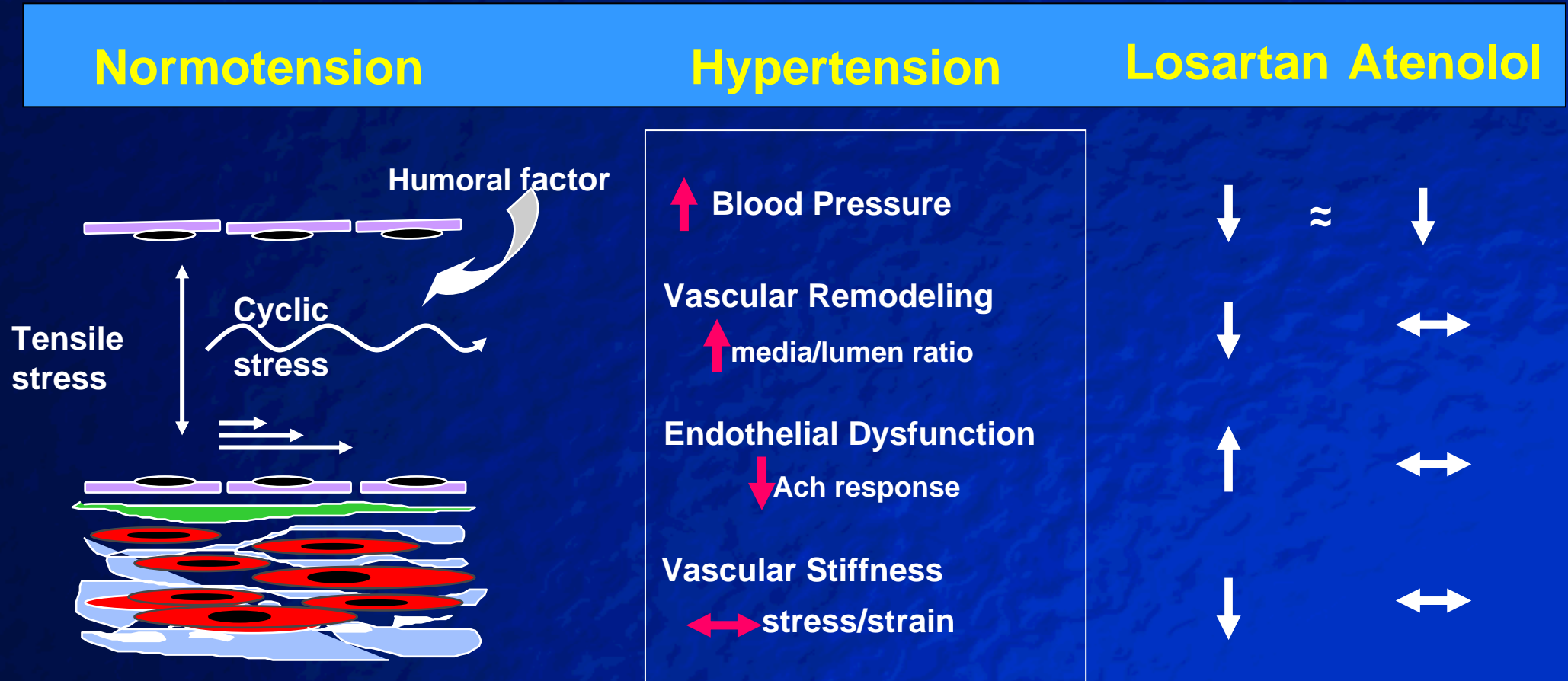


Ratio of collagen and elastin in small arteries of SHR after CCB , ACEi or ARB



Courtesy from Schiffrin EL

Differential Effects of Antihypertensive Therapy on Resistance Artery in Hypertension : 1-Year F/U



Park JB and Schiffrin EL et al. *Circulation, Hypertension, J Hypertens, Am J Hypertens, Curr Hypertens Reports, J Renin Angiotensin System...*

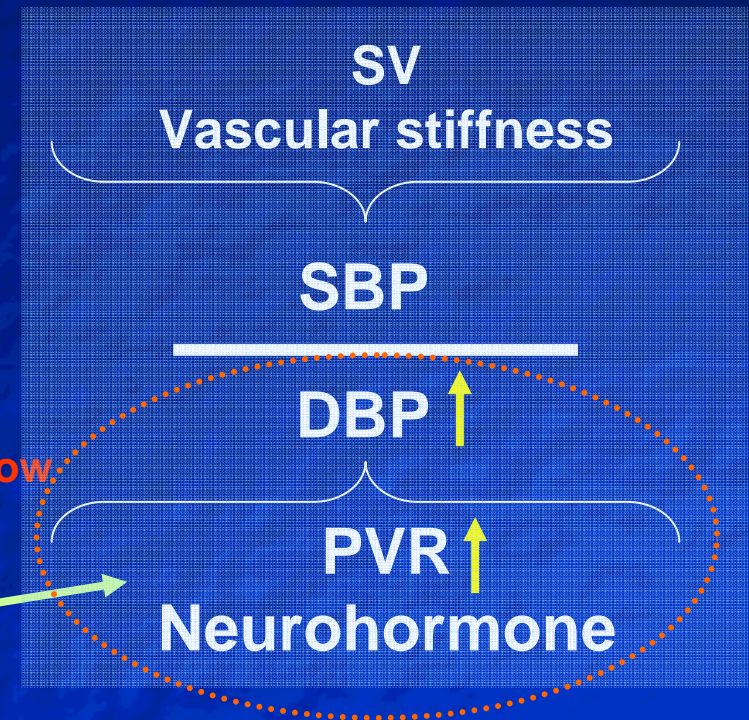
Implication of Small Artery Alterations in Hypertension

Small Artery Remodeling

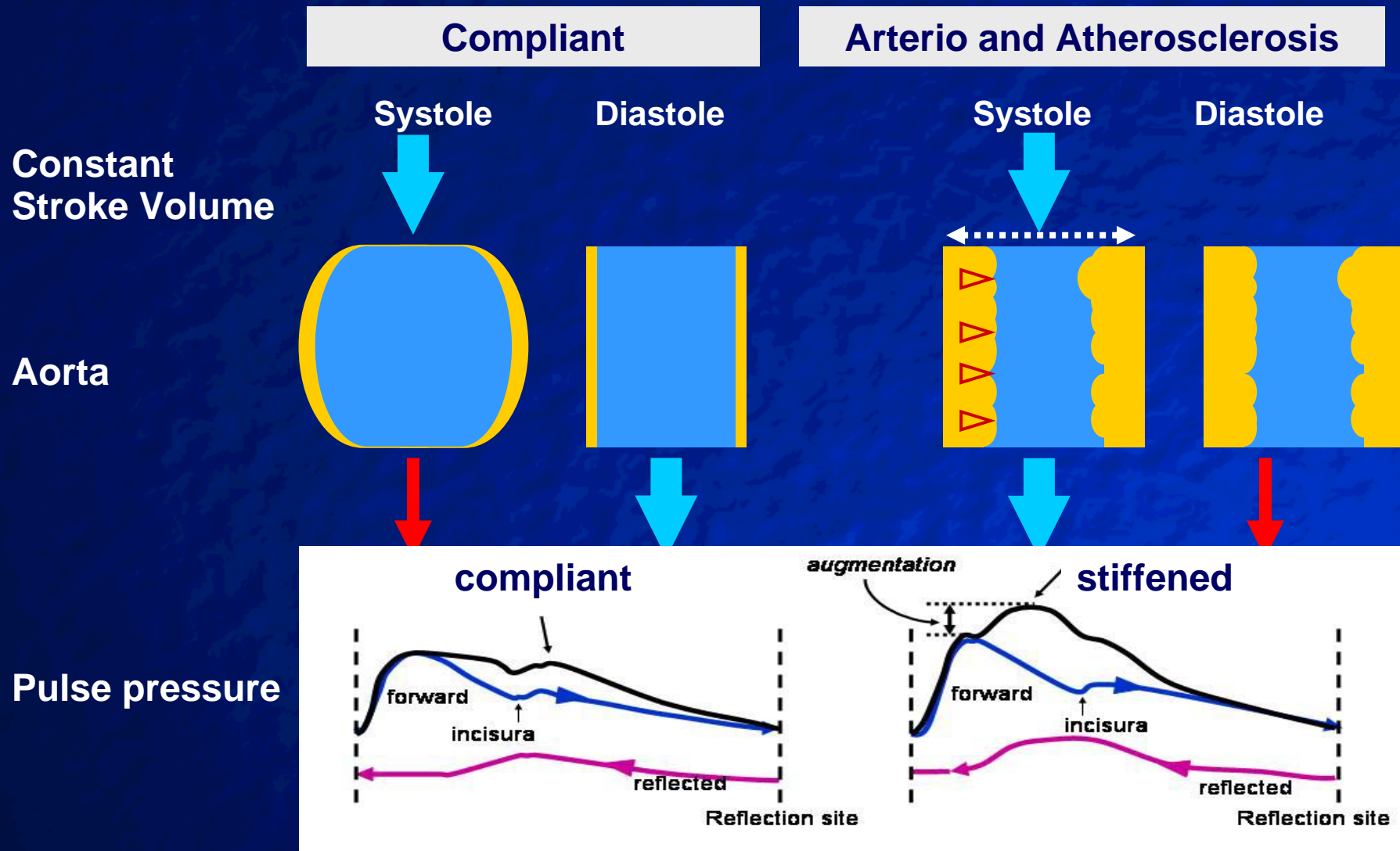
- Eutrophic remodeling
- Endothelial dysfunction
- Unaltered stiffness, initially
⇒ stiffened, later

Resistance to flow

$$= \frac{8 \eta L}{\pi r^4}$$



Arteriosclerosis and Atherosclerosis of Large Artery



Inhibition of Large Artery Stiffness and Prevention of Coronary Events

↘ arterial stiffness



↘ Aortic PP

↘ SBP

DBP

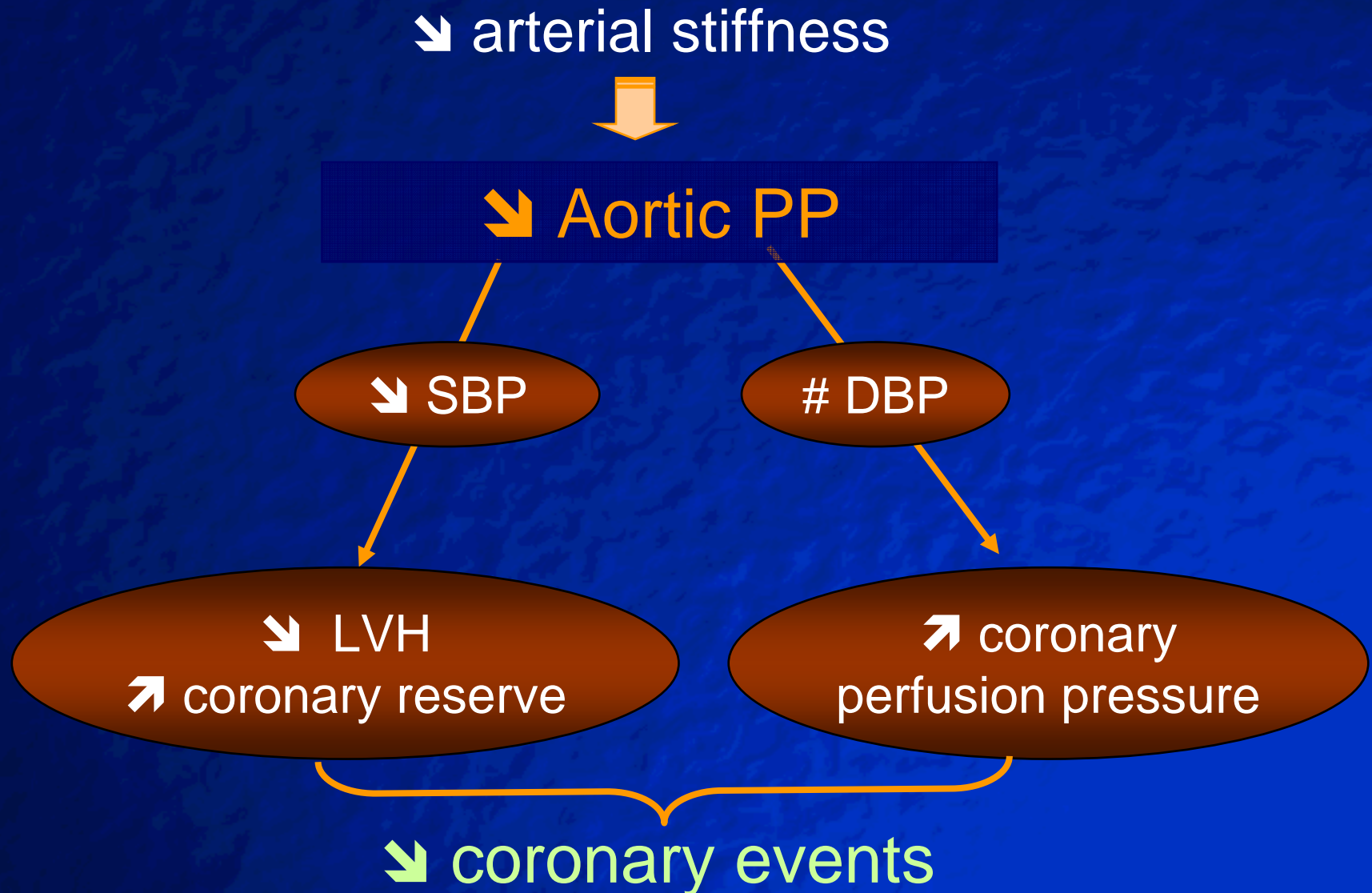
↘ LVH

↗ coronary reserve

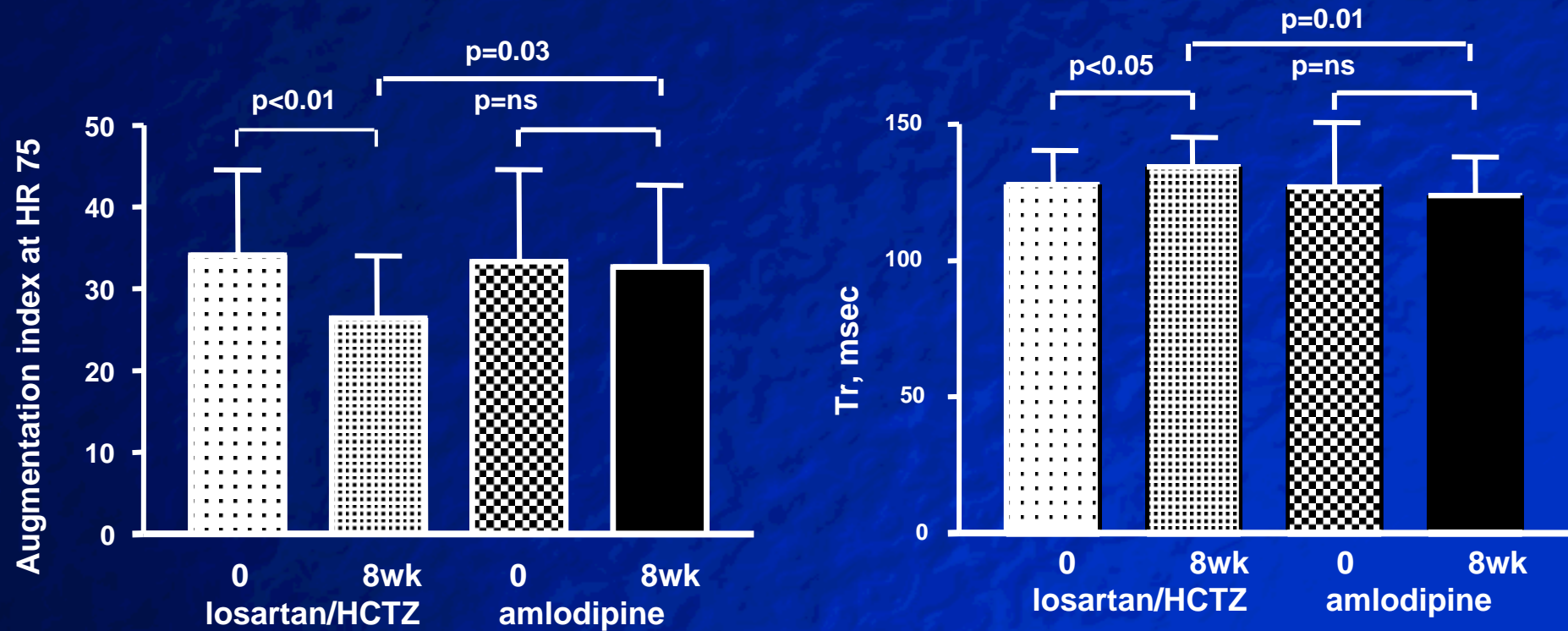
↗ coronary

perfusion pressure

↘ coronary events

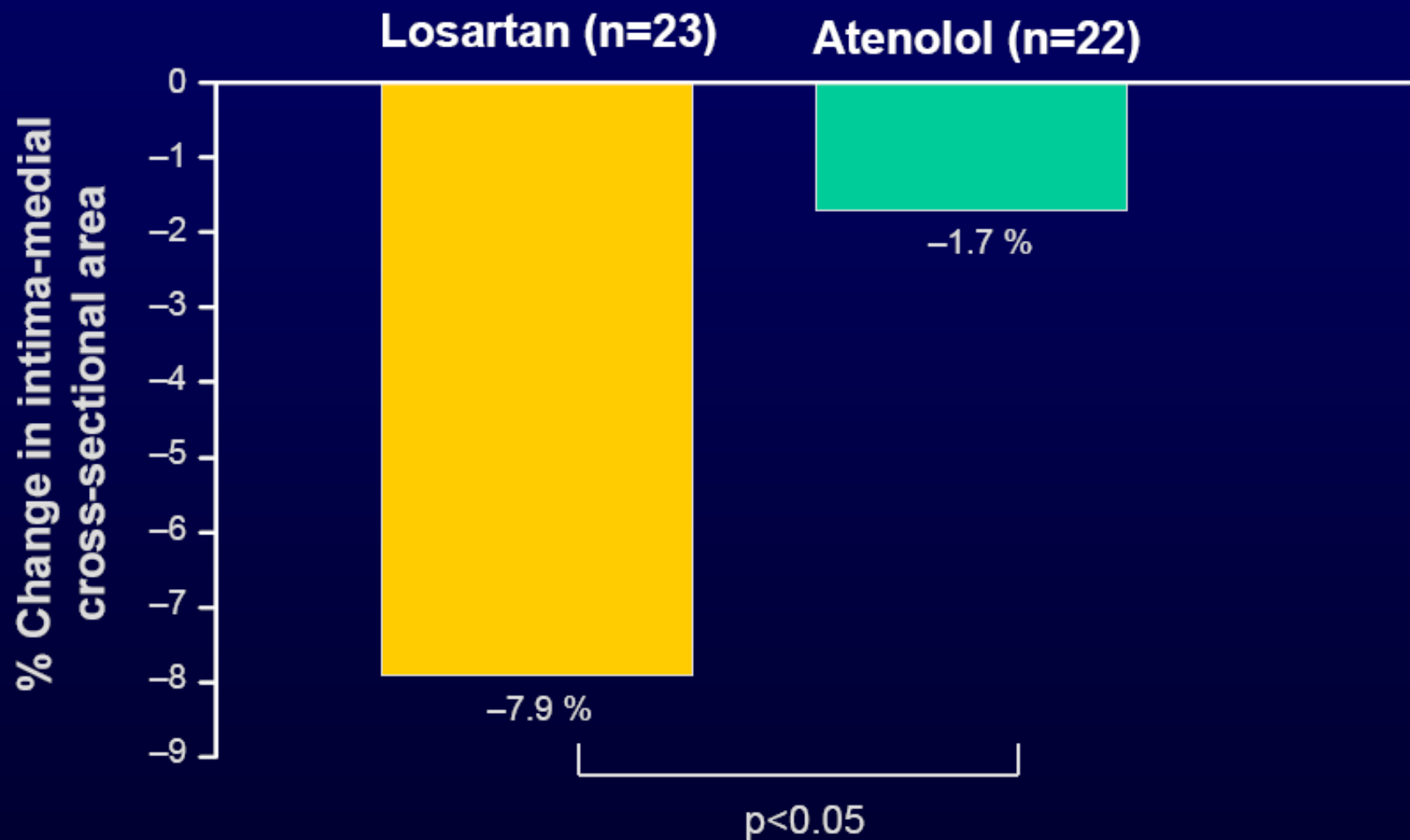


Reduction of arterial stiffness of losartan plus hydrochlorothiazide and amlodipine in patients with isolated systolic hypertension.





Losartan reduced carotid artery hypertrophy vs. atenolol :IMT changes from baseline at year 3





Beneficial Effect of Losartan over Atenolol in Prevention of Stroke in Hypertensive Patients with LVH

Hypertension



RAS block
by Losartan



LVH regression

10~15 %

4.8 year

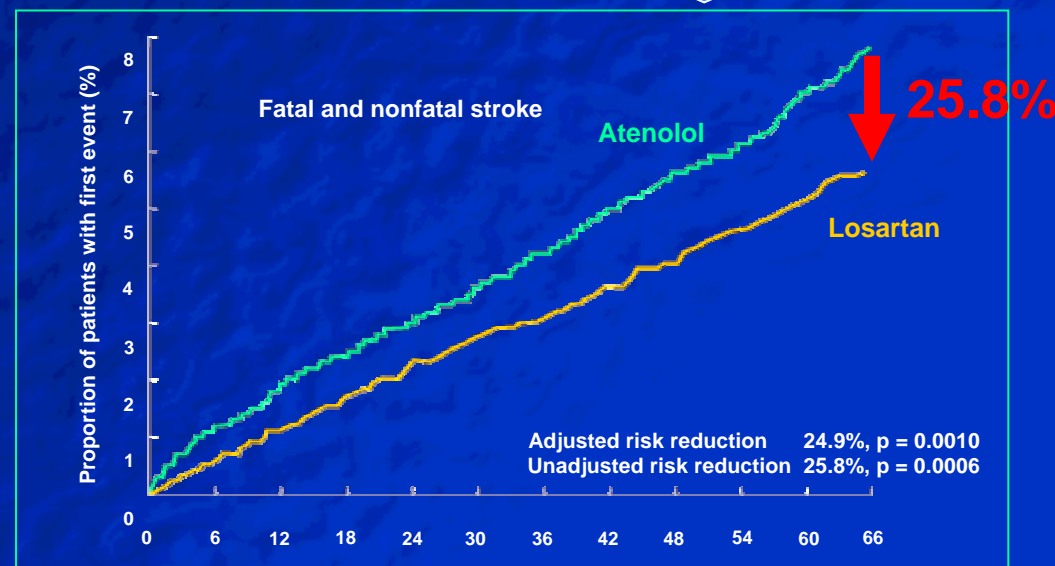
SNS block
by atenolol



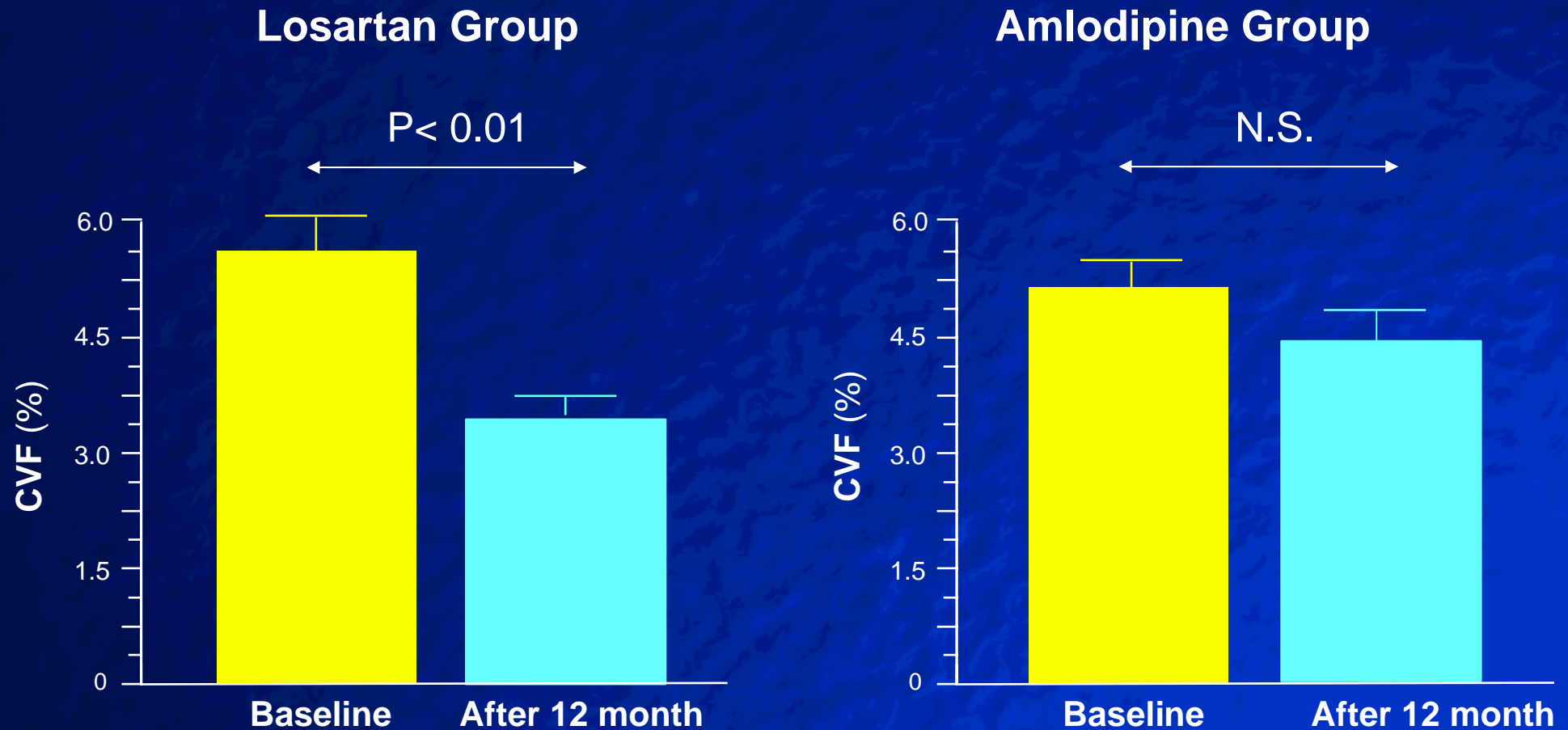
4~9 %



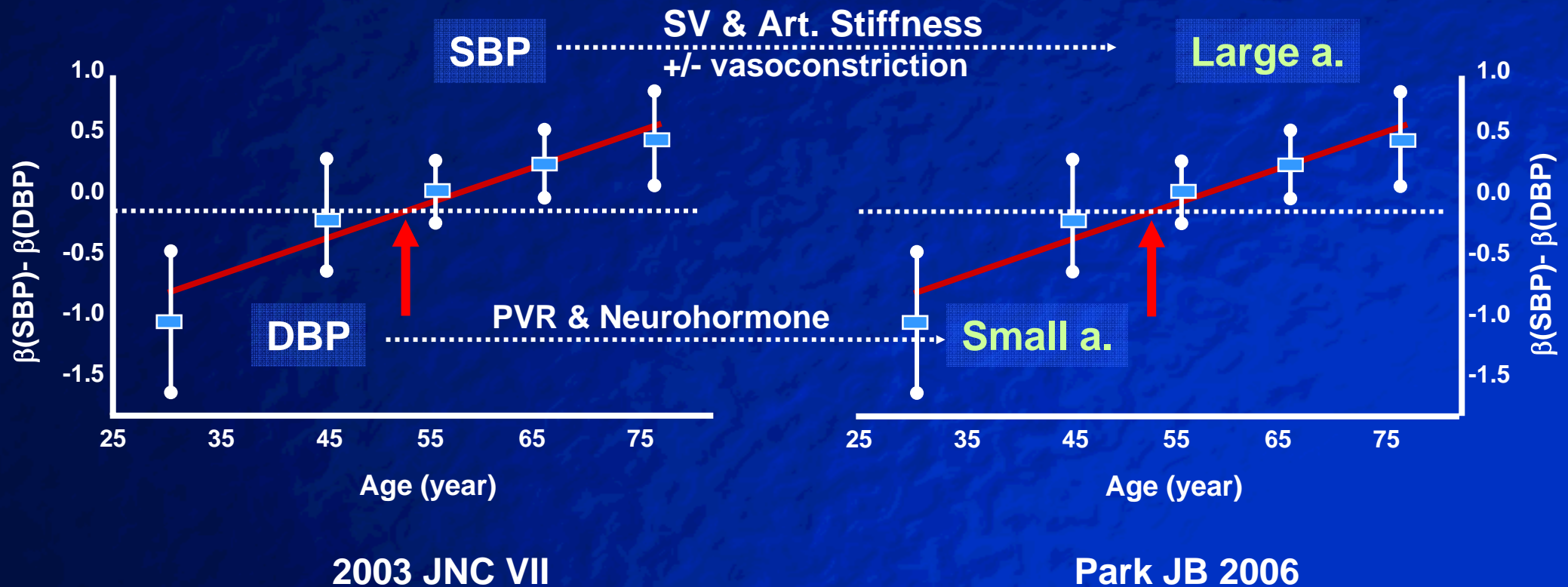
Hemodynamic factors
Nonhemodynamic
trophic factors
Demographic factors
Environmental factors
Impaired collagen
degradation



Effects of Antihypertensive Treatment on Myocardial Fibrosis in Hypertensives



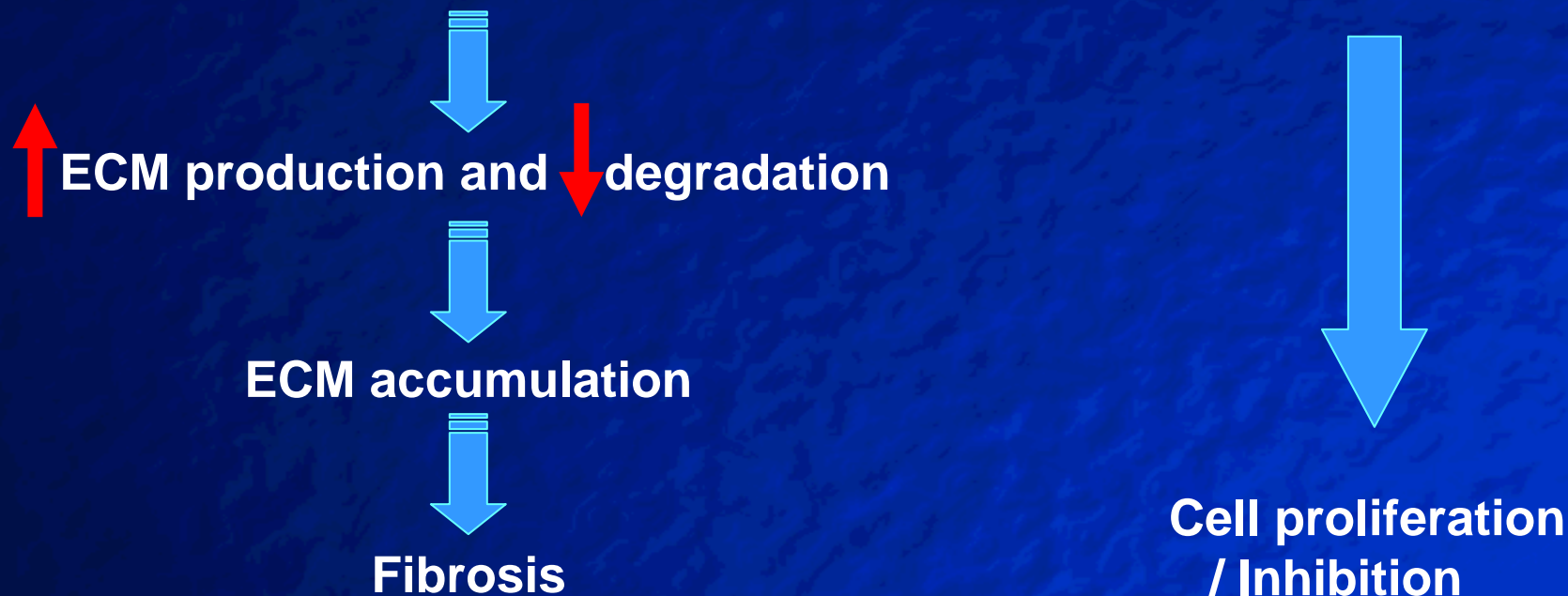
Difference of CVD prediction between systolic and diastolic BP as a function of age



Ang II regulates cell growth & fibrosis

Growth factors ; TGF β , PDGF, CTGF
Cytokines ; IL-6, TNF- α
Chemokines ; MCP-1
Other ; PAI-1, Metalloproteinases

Growth factor ;
-TGF- β , PDGF, EGF, CTGF
Other ; PTHrP



Cardio-Vascular Damage

Vascular and Tissue Dysfunction in Hypertension

