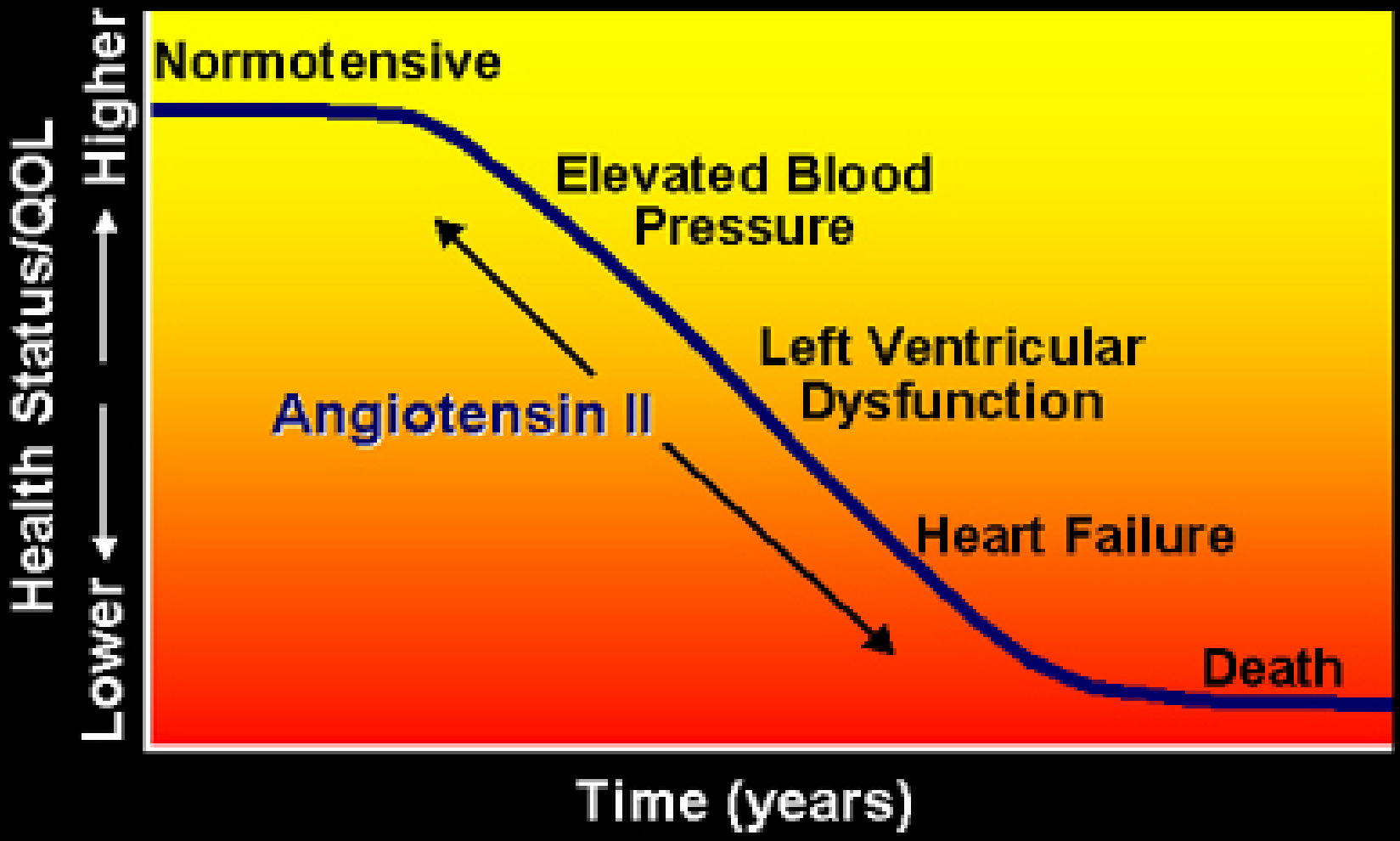
How Does Losartan Reduce the Risk of CVD “Beyond Blood Pressure”?

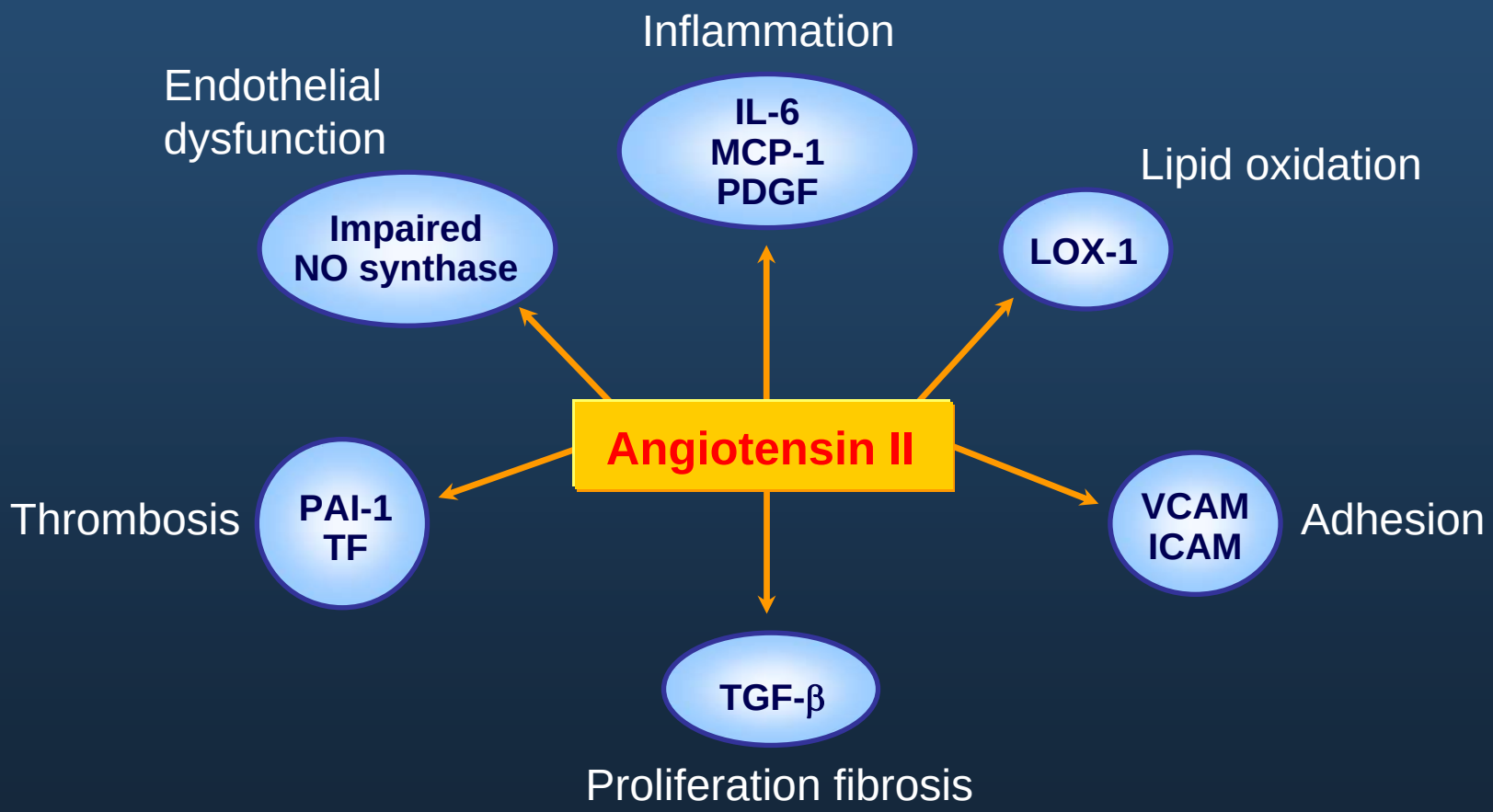
Hong-Seog Seo, M.D., Ph.D.

Cardiovascular Center
Korea University GURO-Hospital

The Cardiovascular Continuum: Hypertension to Heart Failure



Ang II and mechanisms of atherosclerosis

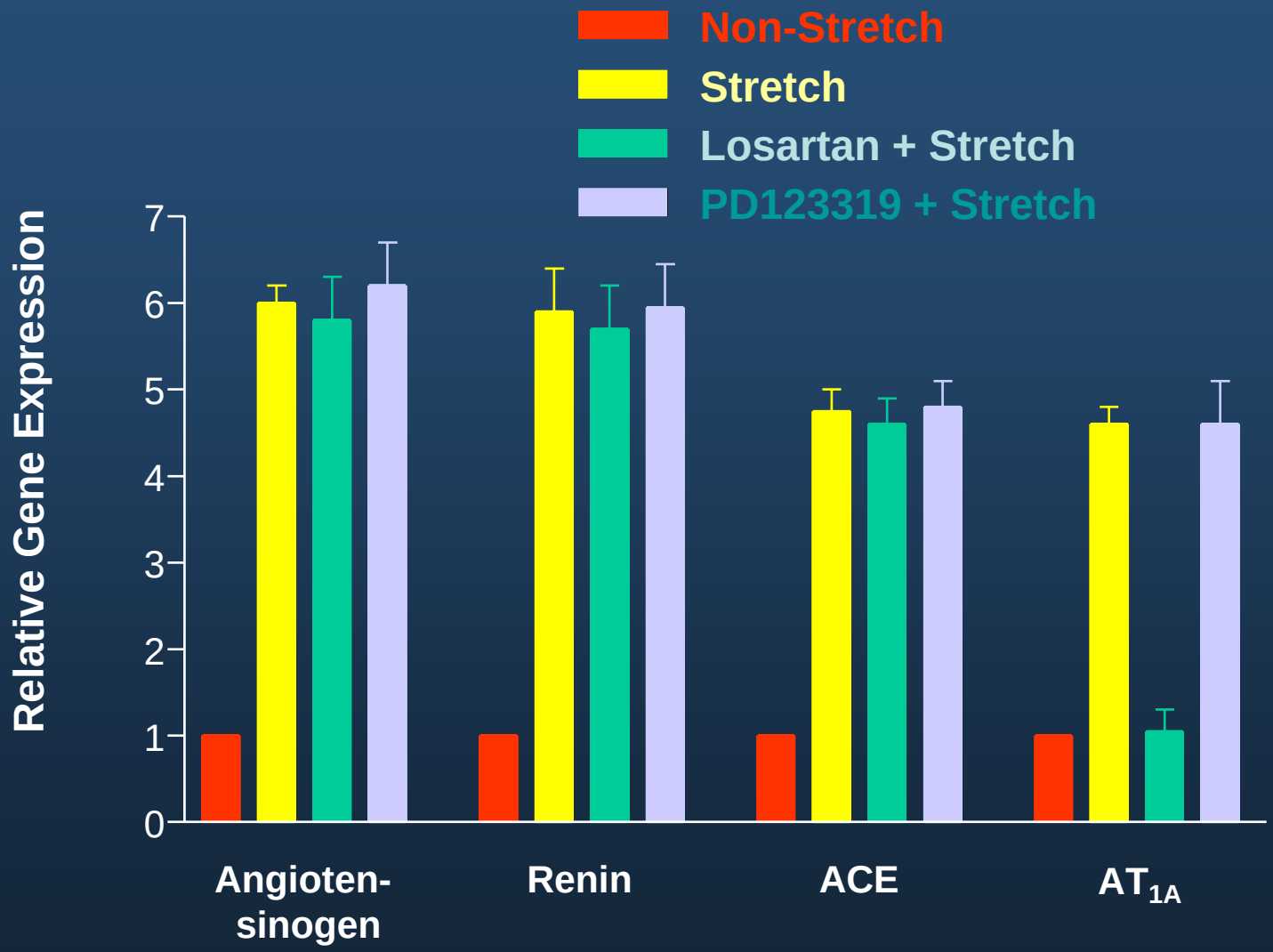


Jacoby DS, Rader DJ. *Arch Intern Med.* 2003;163:1155-64.

Mechanisms of Atrial Distension

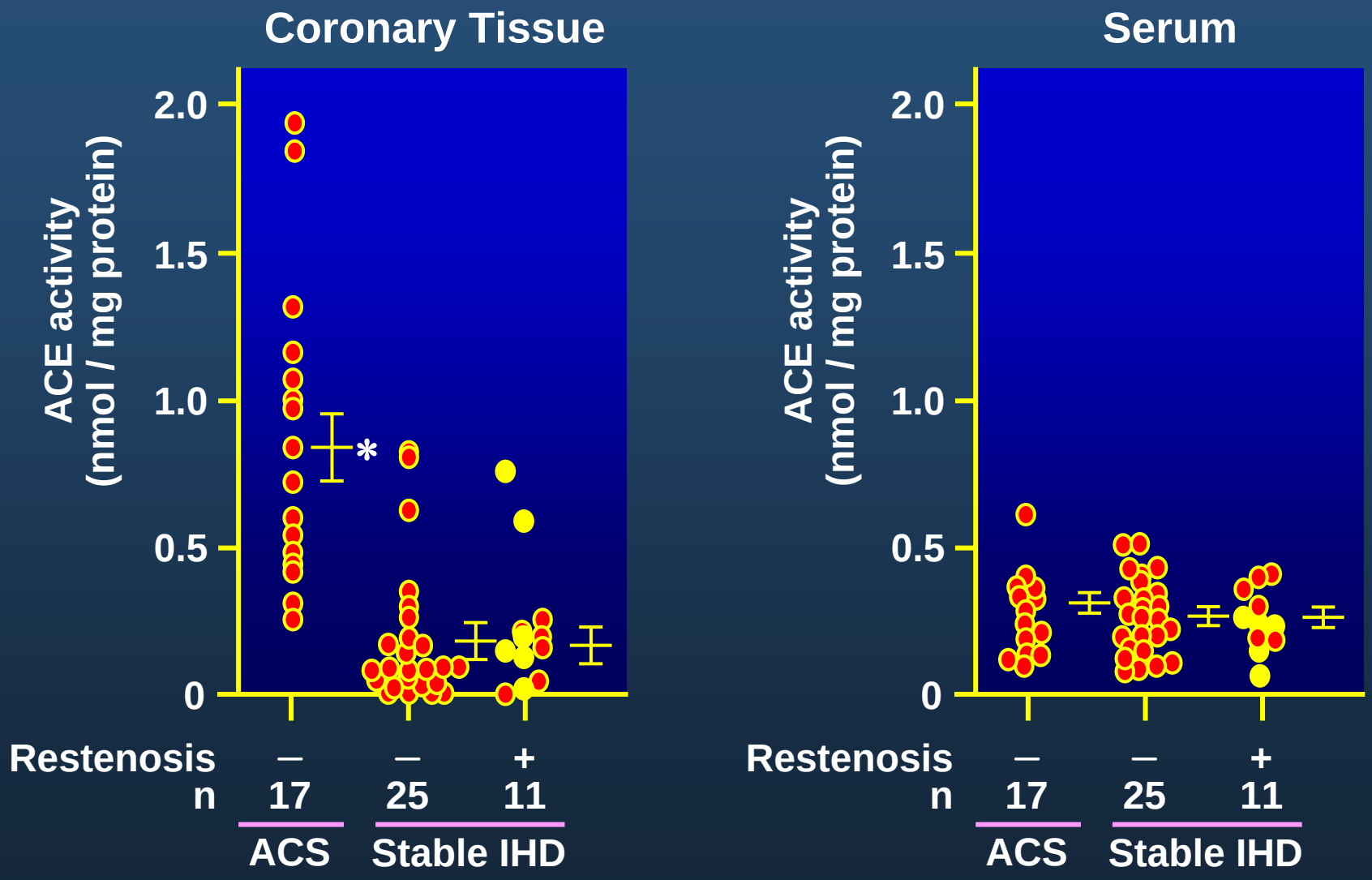
LV-Pressure (diast.)	–	++	+++
Atrial Stretch	–	++	+++
RAAS	–	++	+++

Myocardial Stretch and RAS Activation

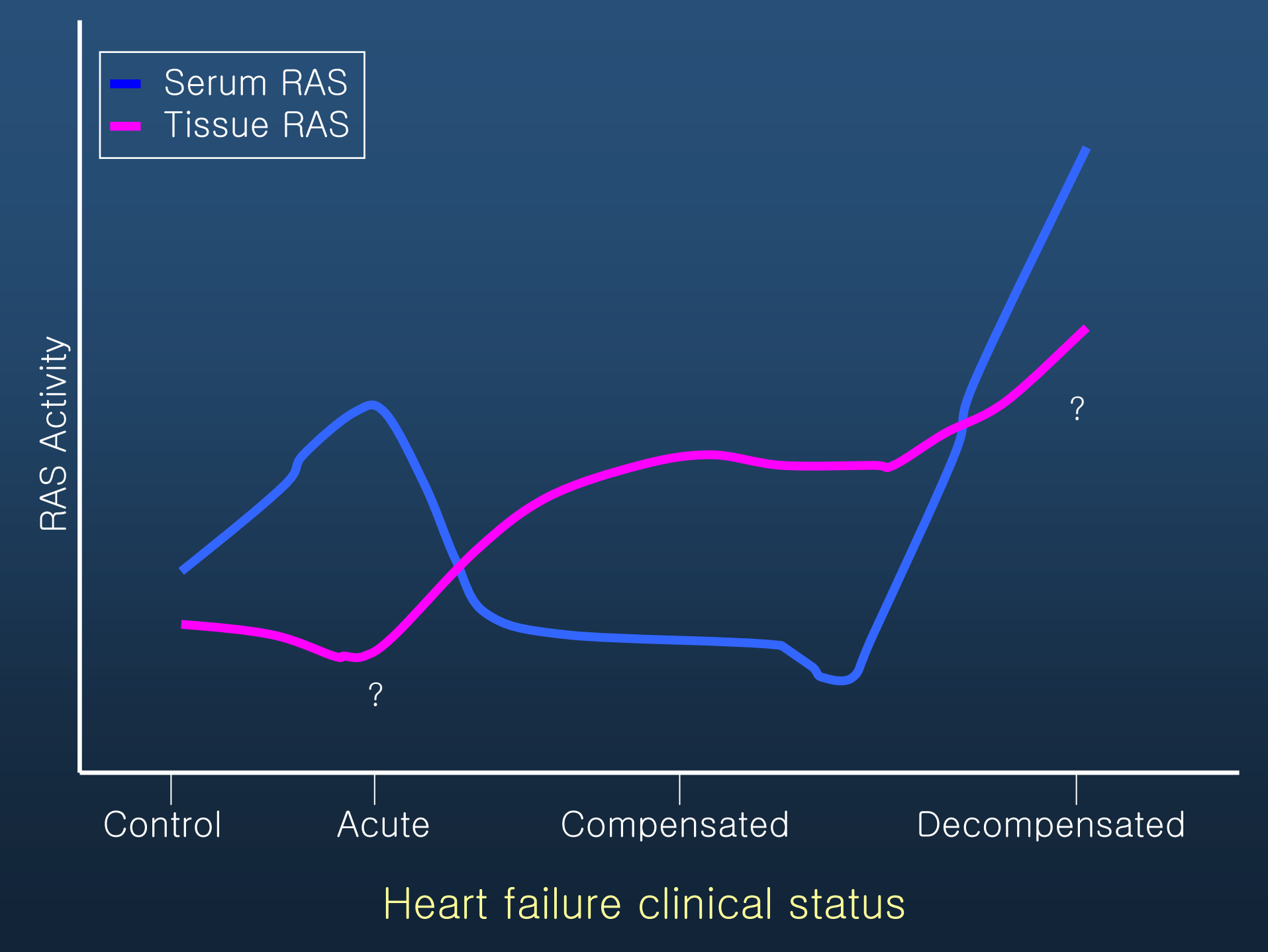


Malhotra et al., Circ Res 1999;85:137-146
Leri et al., J Clin Invest 101:1326-1346

ACE-Activity in Acute Coronary Syndromes



Hoshida et al, Circulation 103 (2001): 630-633


Serum RAS
Tissue RAS
RAS Activity
?
?
Control
Acute
Compensated
Decompensated
Heart failure clinical status

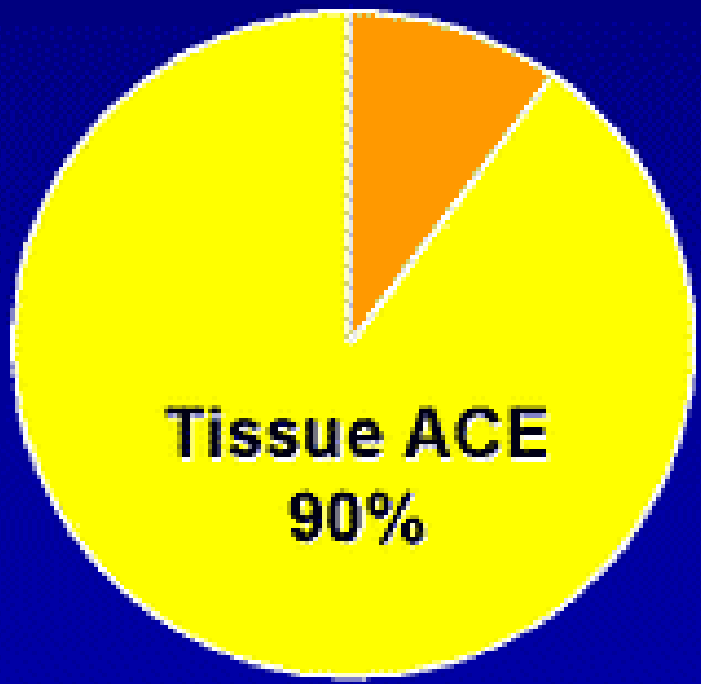
Regulation of the Endothelium: Circulating Versus Tissue ACE

Circulating ACE (endocrine)

- Plasma

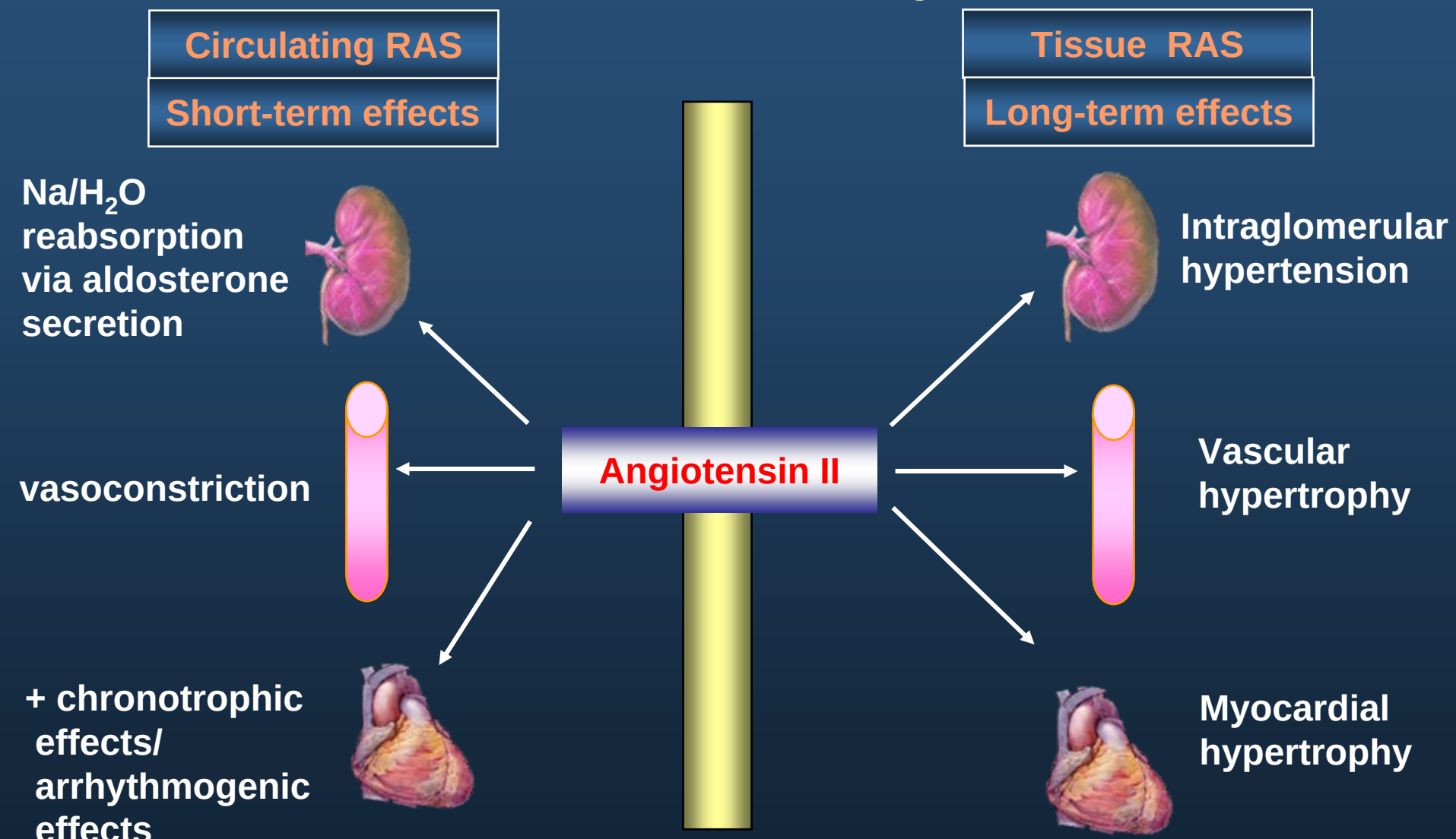
Tissue ACE (autocrine/paracrine)

- Vasculature (endothelium)
- CNS
- Adrenal
- Heart
- Kidney
- Reproductive organs
- Lung



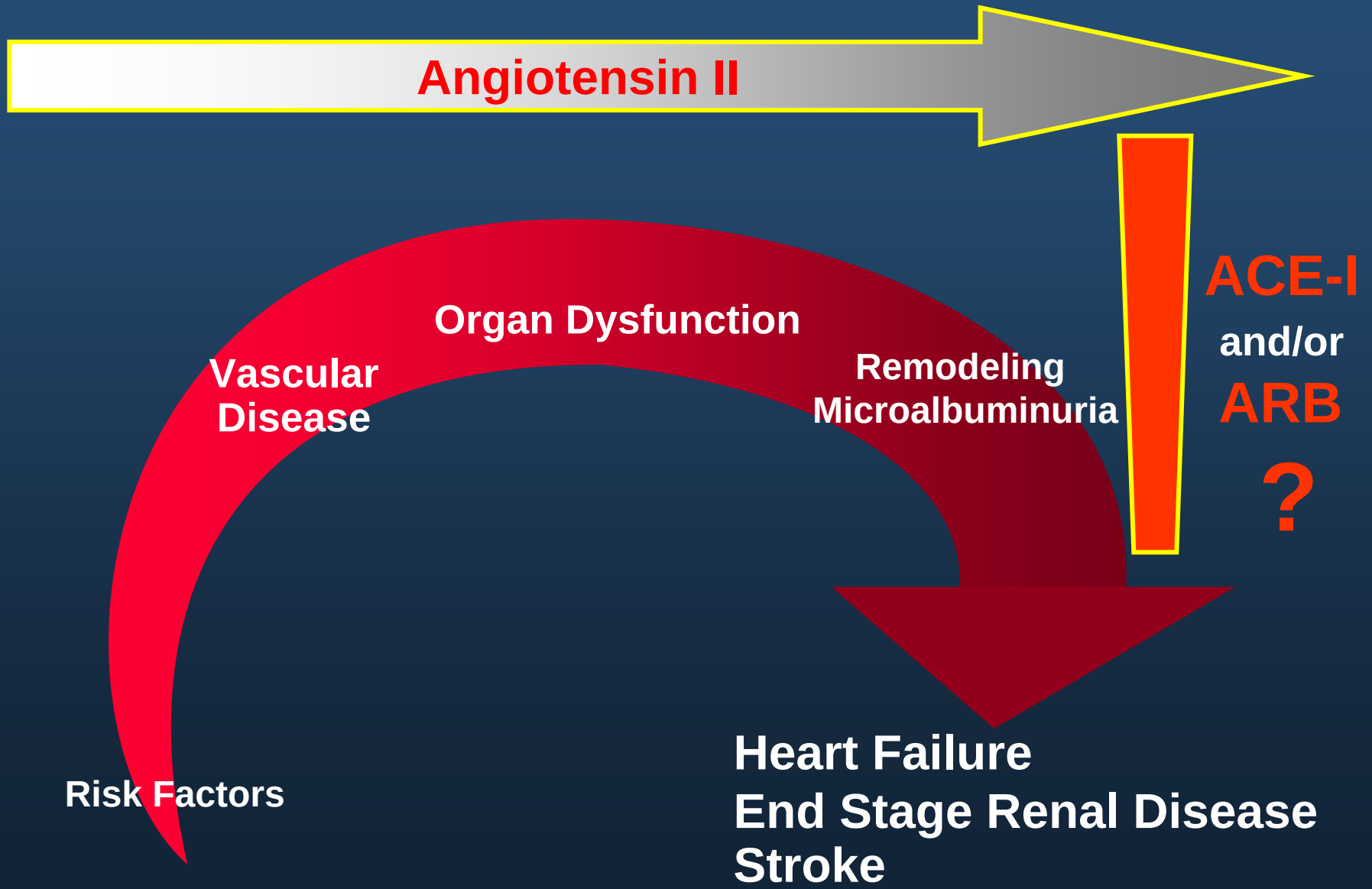
Dzau VJ. *Arch Intern Med.* 1993;153:937-942.

Circulating and Tissue RAS influence cardiovascular system

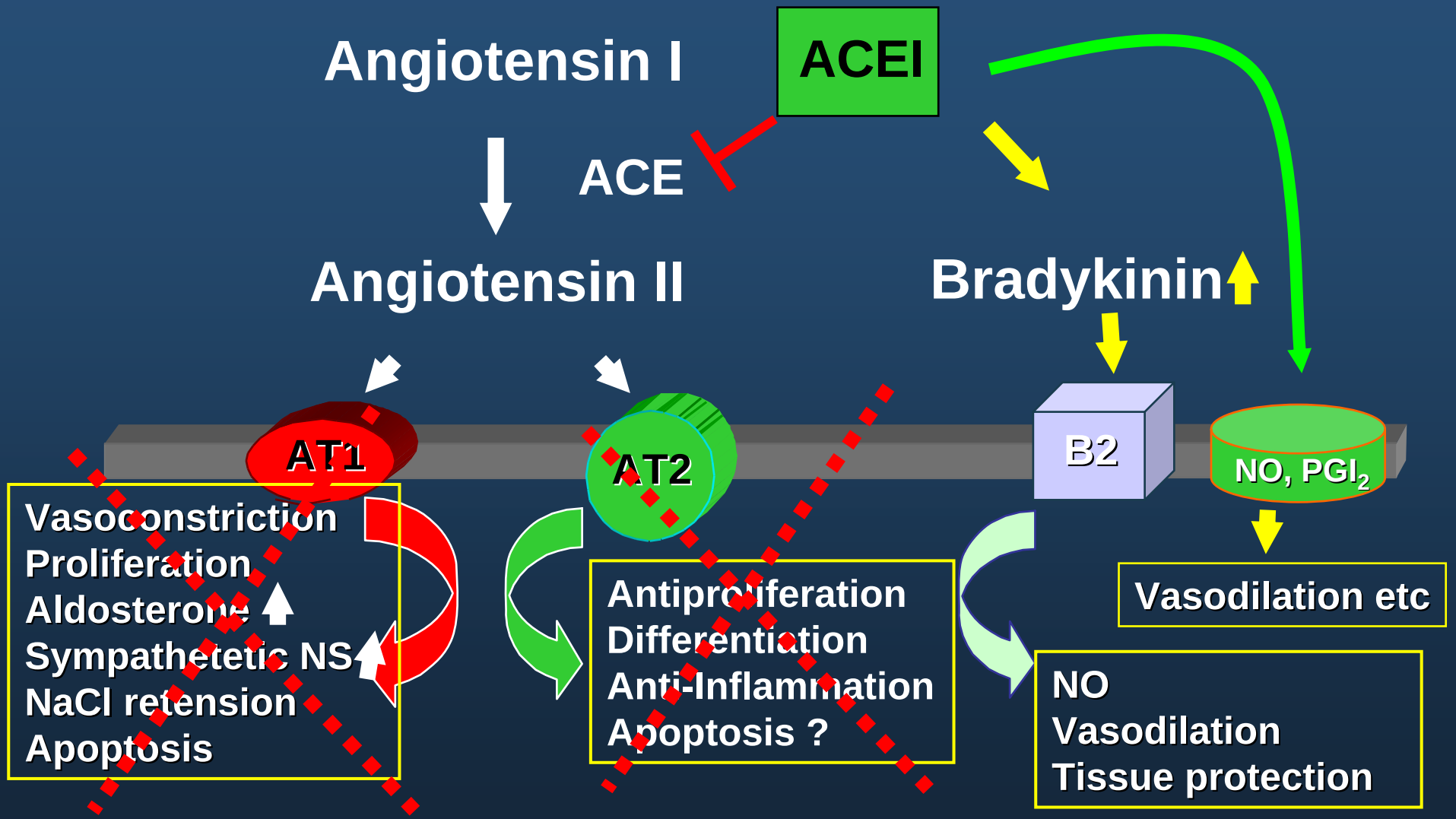


Dzau VJ. Arch Intern Med 1993;53:937-42

Cardiorenovascular Continuum - Pathophysiology



RAS-Inhibition by ACE-Inhibitors

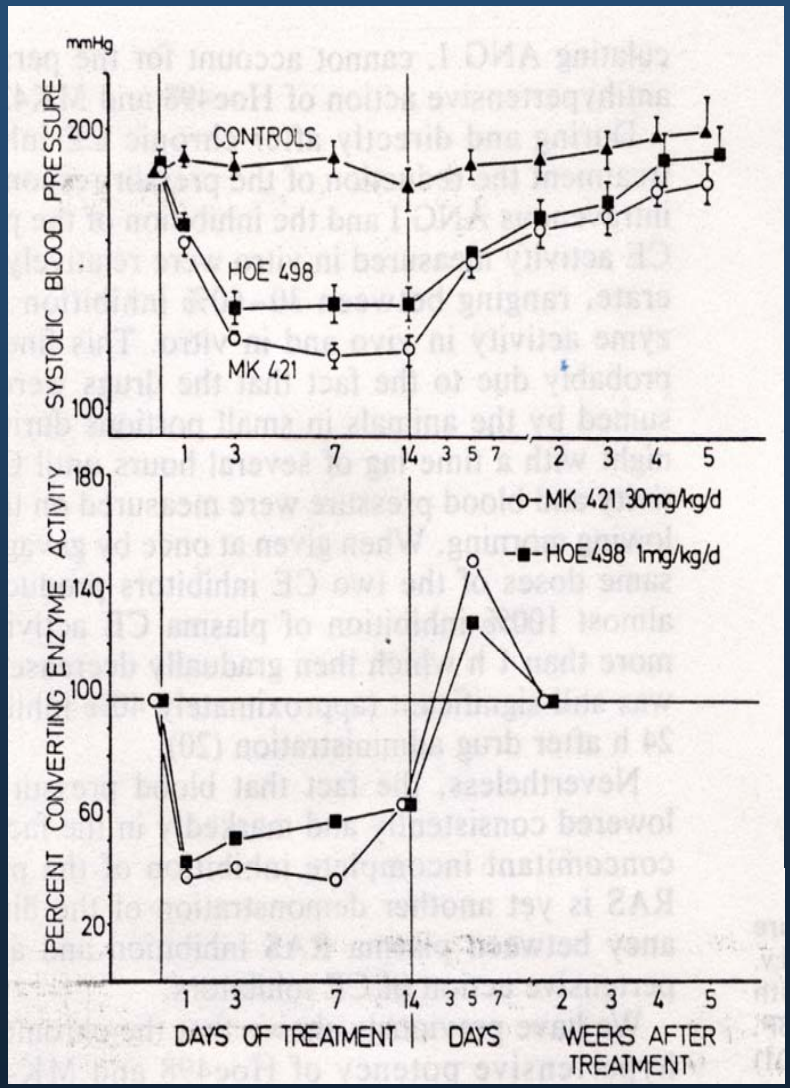


Steckelings UM, Kaschina E, Unger T. *Peptides* 26: 1401-1409, 2005

ACE inhibitor-induced changes in blood pressure and plasma converting enzyme activity in spontaneously hypertensive rats

BP

ACE activity

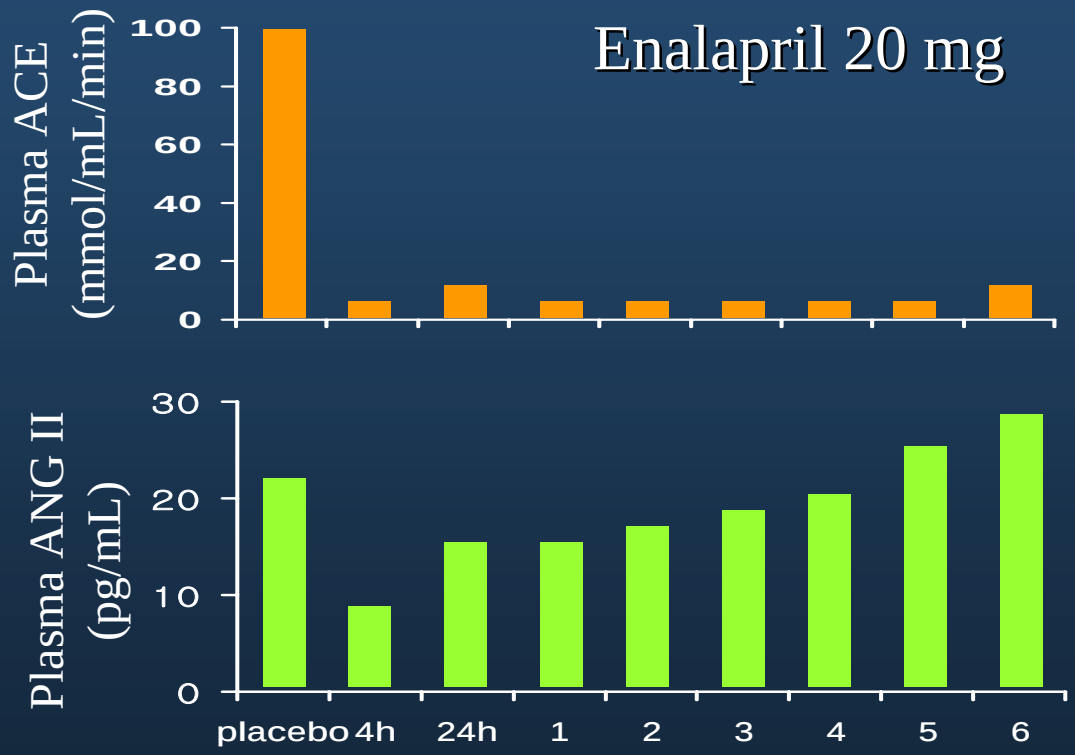


Hoe 498 - Ramipril

MK 421 - Enalapril

Unger T. et al. 1984 *J Cardiovasc Pharmacol*. 6:872-880

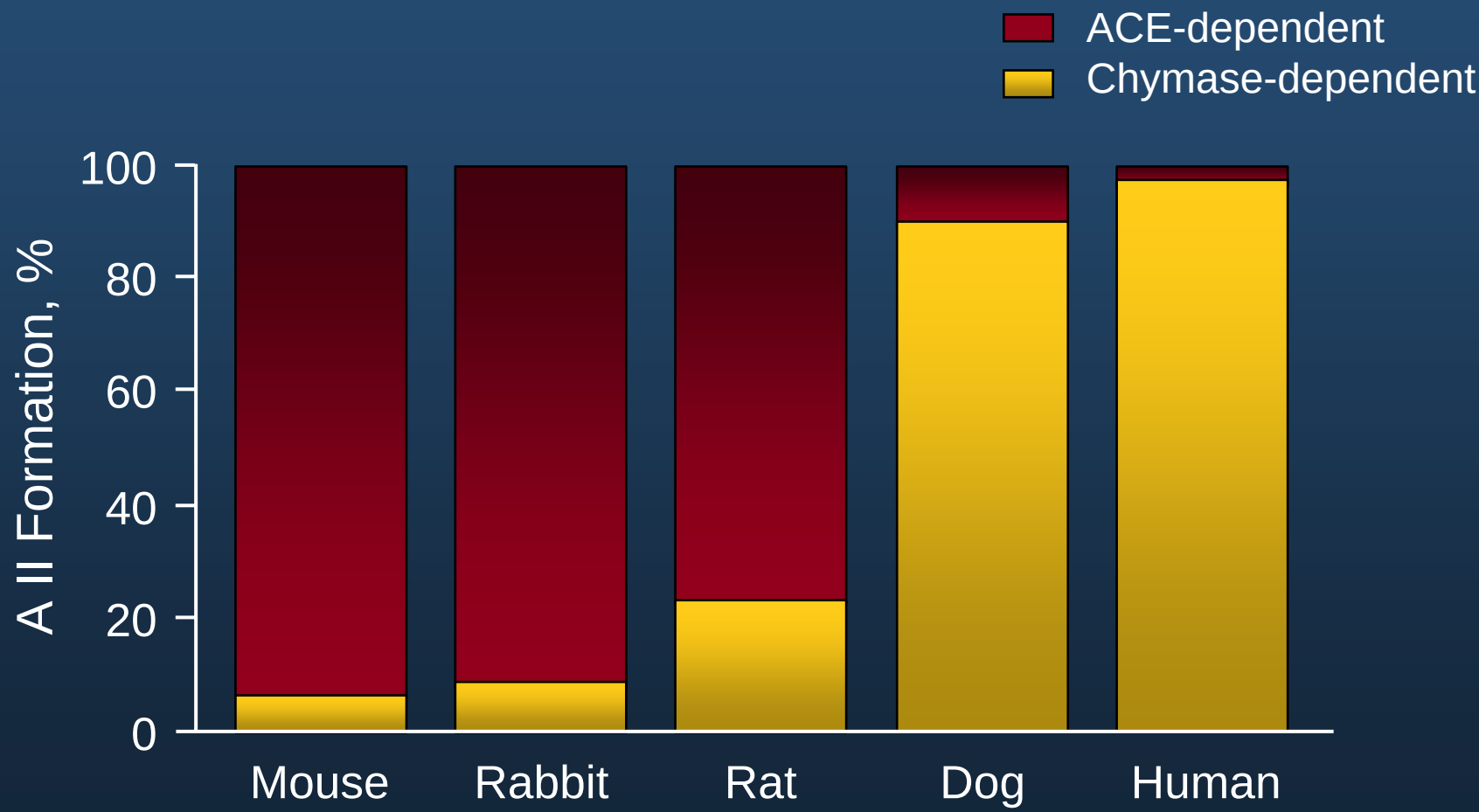
Long-Term Effects of ACE Inhibitor on Plasma ACE and Angiotensin II



P<0.001 vs. placebo

J Cardiovasc Pharmacol 1982;4:956

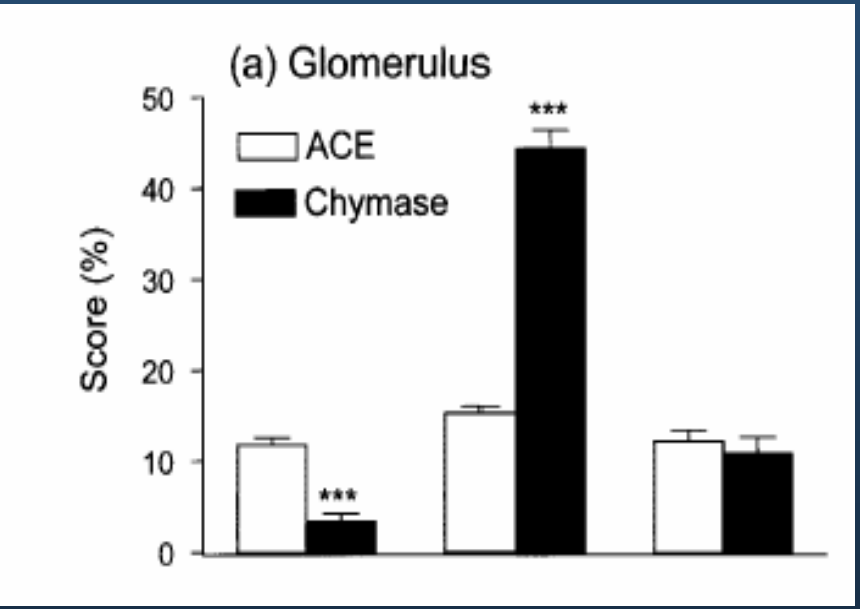
Chymase-dependent vs ACE-dependent A II Formation in Hearts of Various Species

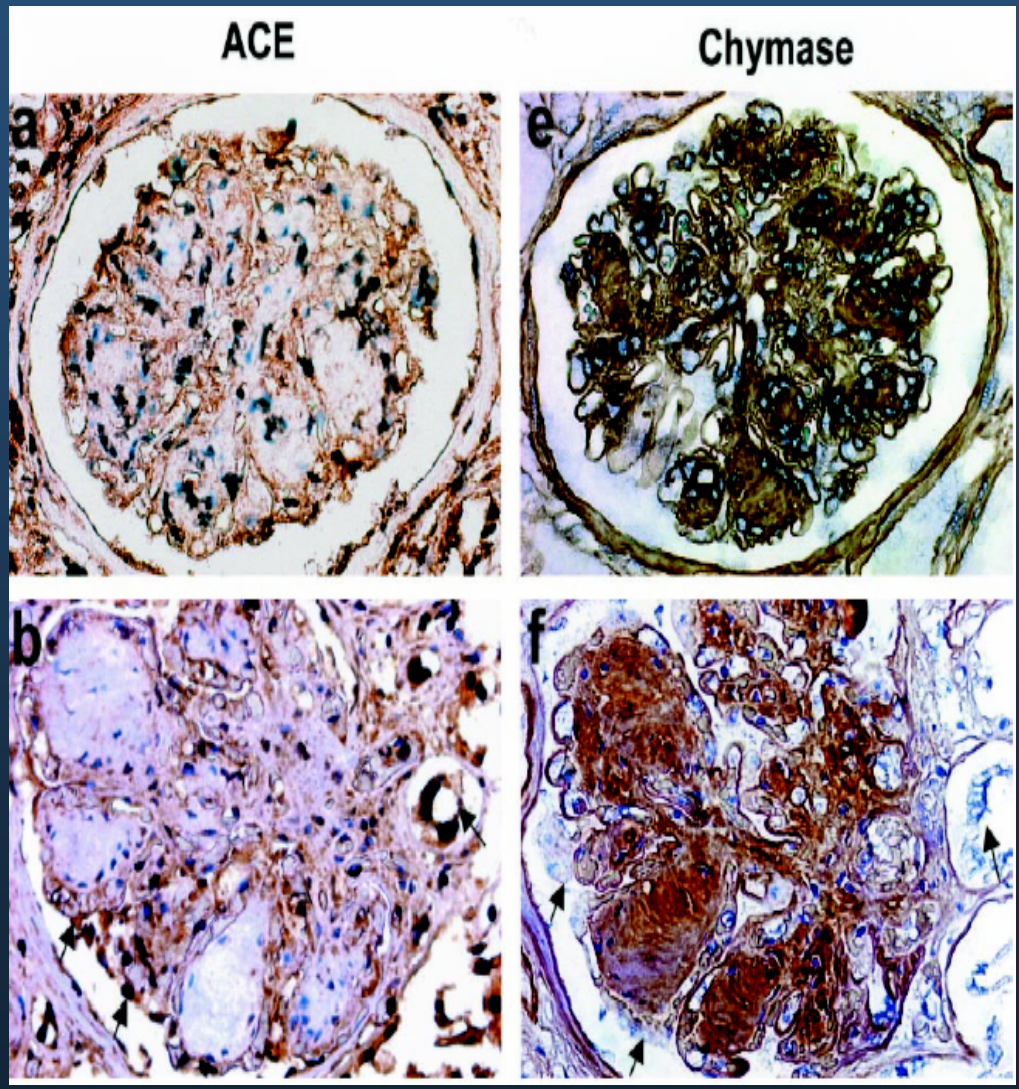


Reprinted with permission from Balcells E, et al. *Am J Physiol.* 1997;273:H1769–H1774.

Chymase is upregulated in diabetic nephropathy

Human biopsy in 44 patients with 4 mg/dl serum creatinine

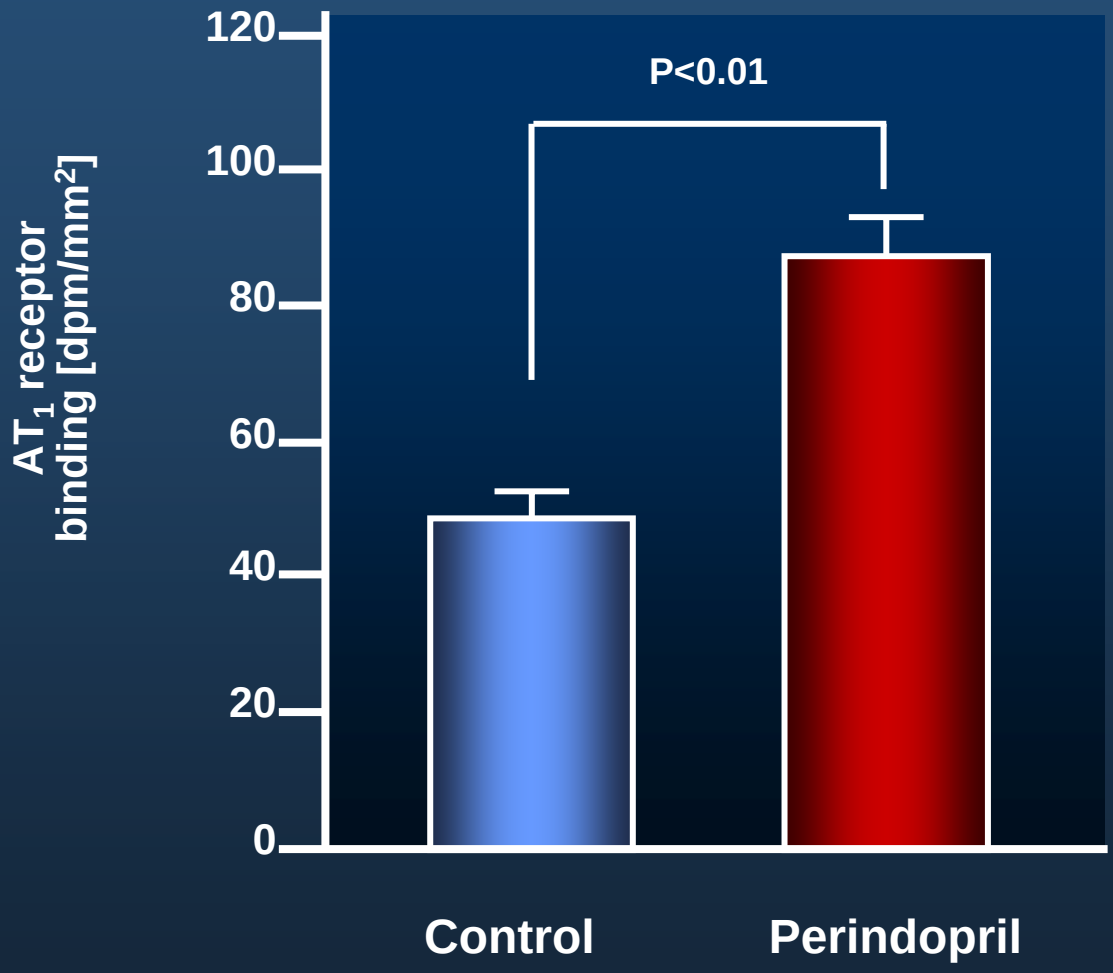




Hyp DN – hypertensive diabetic nephropathy
Norm DN – normotensive diabetic nephropathy

Huang XR et al. 2003 *JASN* 14:1738-1747

ACE and AT_1-Regulation Following ACE-Inhibitor in CHD



Zhuo et al, Hypertension 39 (2002): 634-638

Angiotensin II Reactivation / Aldosterone Escape

Plasma ACE-, Ang II- and Aldosterone-Levels under chronic ACE-Inhibition

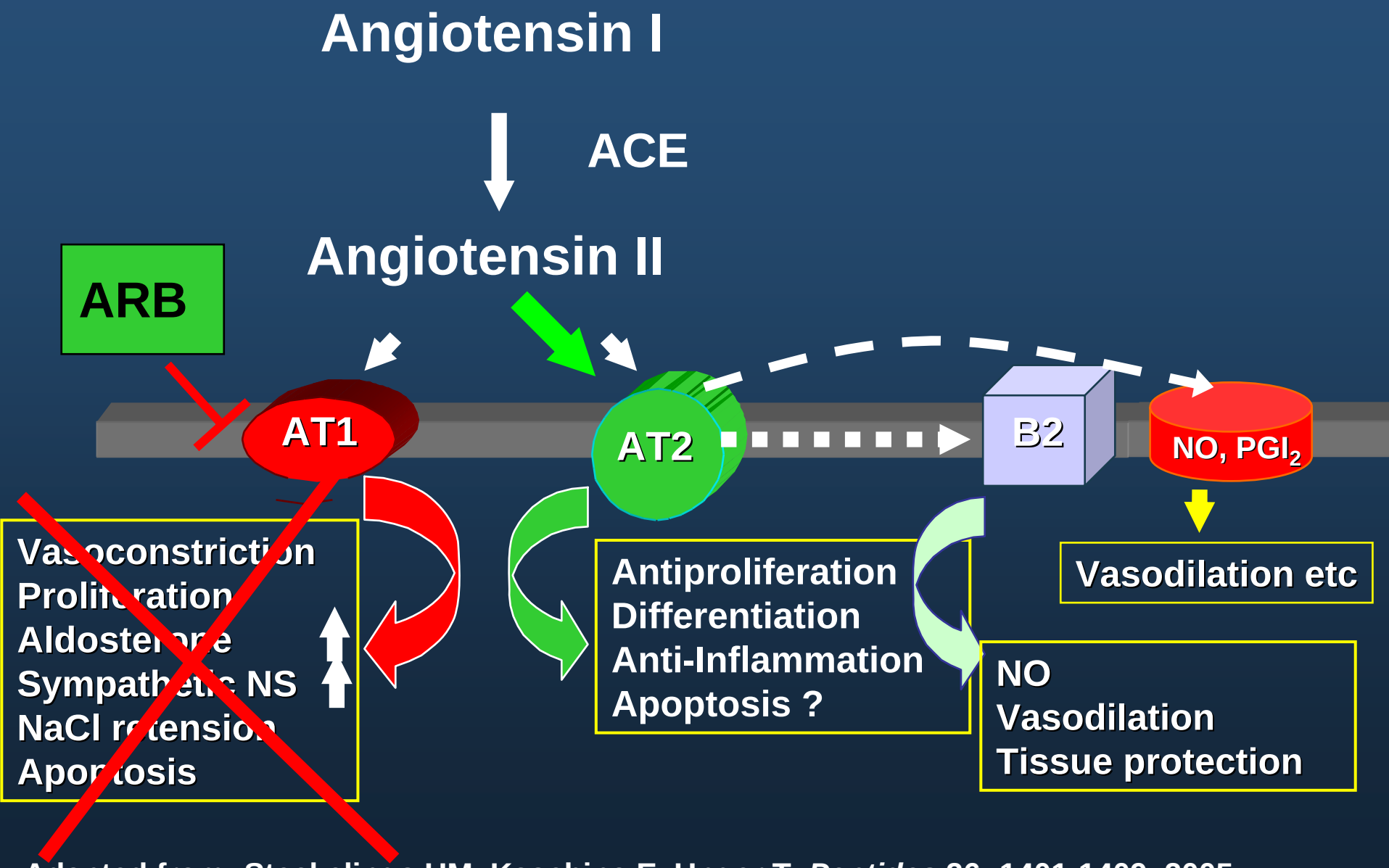
	n.d.	lowered / normal	increased
ACE	33%	34%	34%
Ang II	31%	49%	15%
Aldosterone	-	61%	38%

In at least one-third of patients, plasma-RAS is not suppressed !

MacFayden et al. 1999 *Heart*. 82:57-61

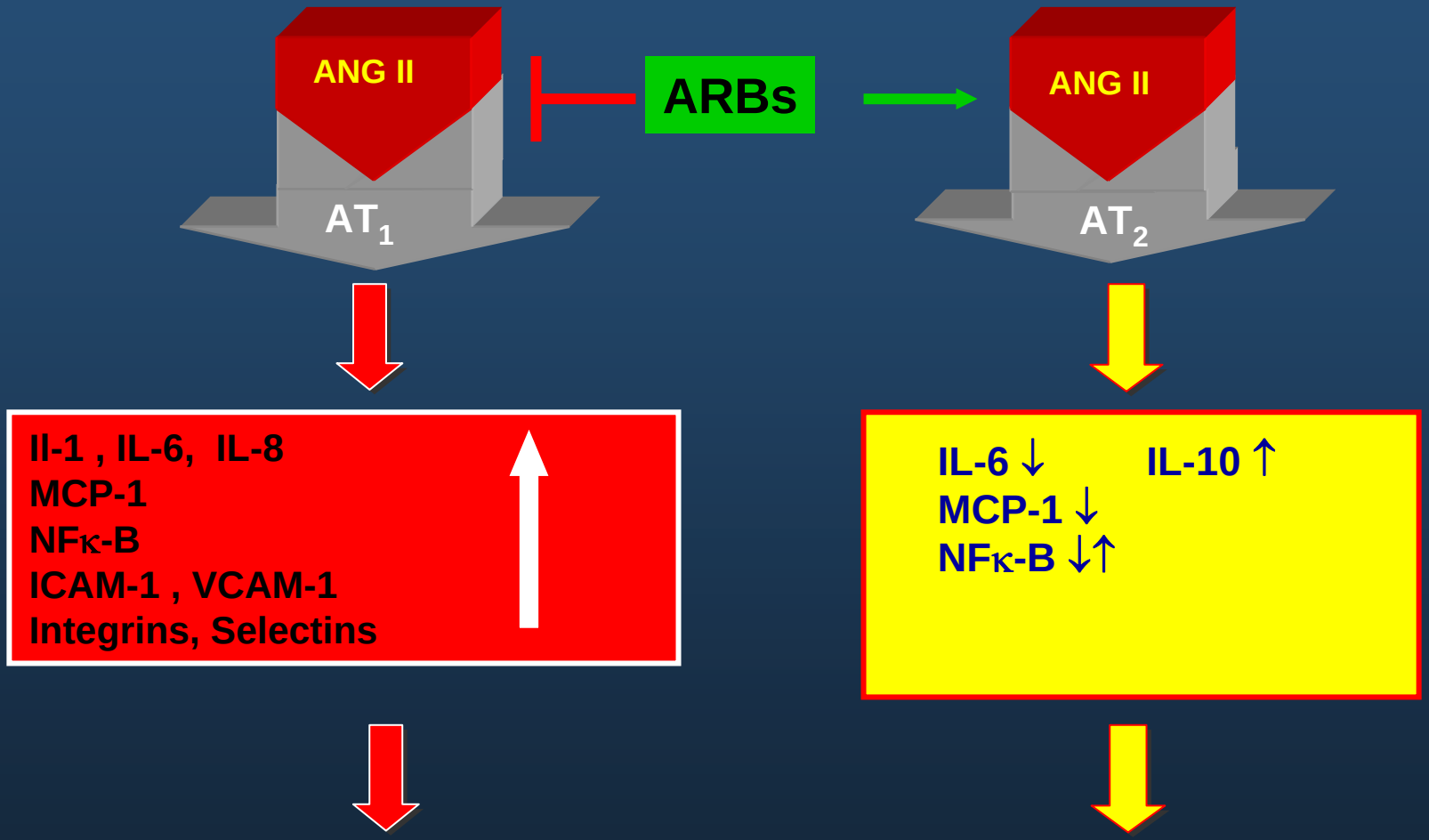
CCR

Selective AT1-blockade



Adapted from: Steckelings UM, Kaschina E, Unger T. *Peptides* 26: 1401-1409, 2005

Angiotensin Receptors and Inflammation

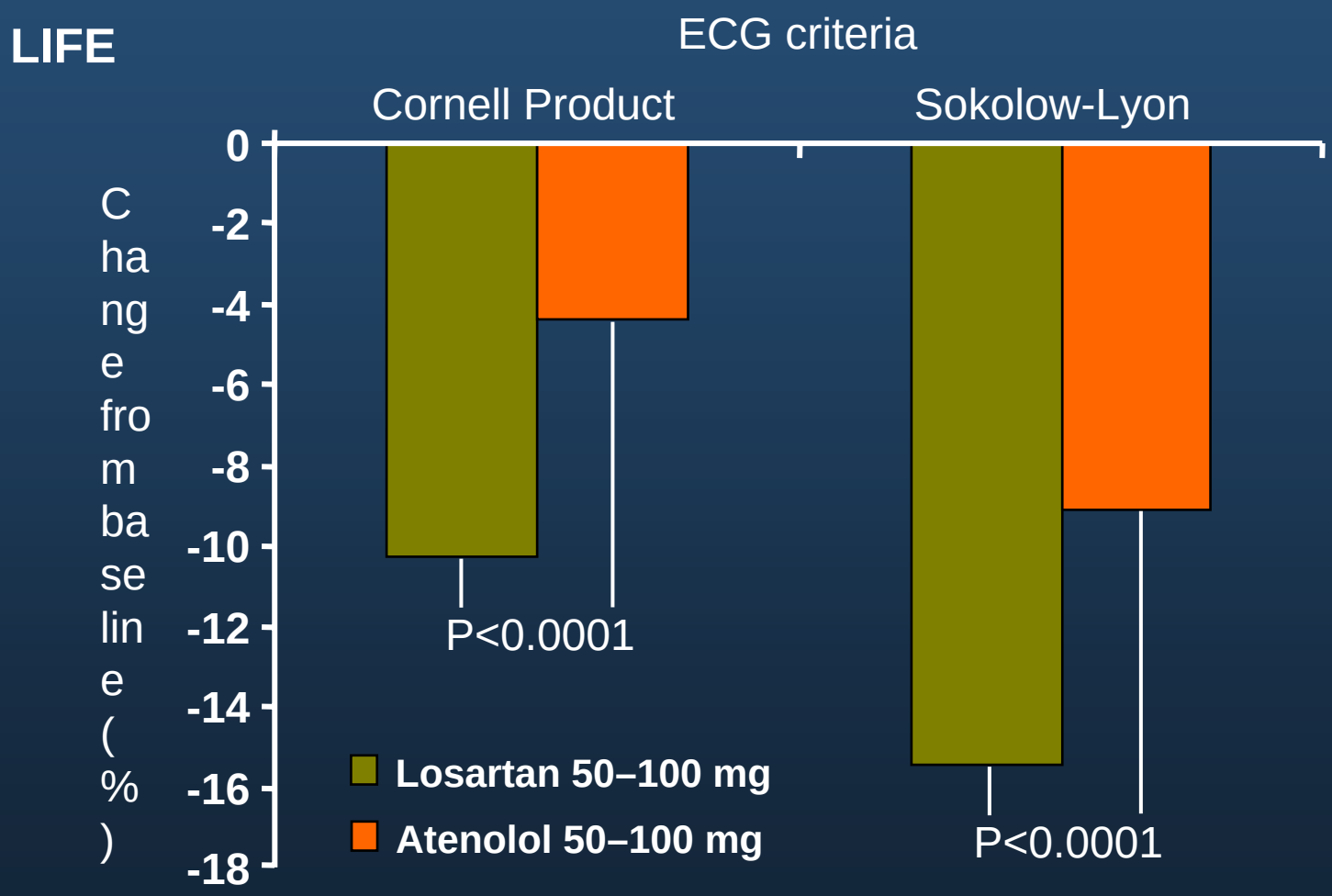


Suzuki et al. 2003 *Int J Biochem Cell Biol* 35:881-900

Class Effects of ARB

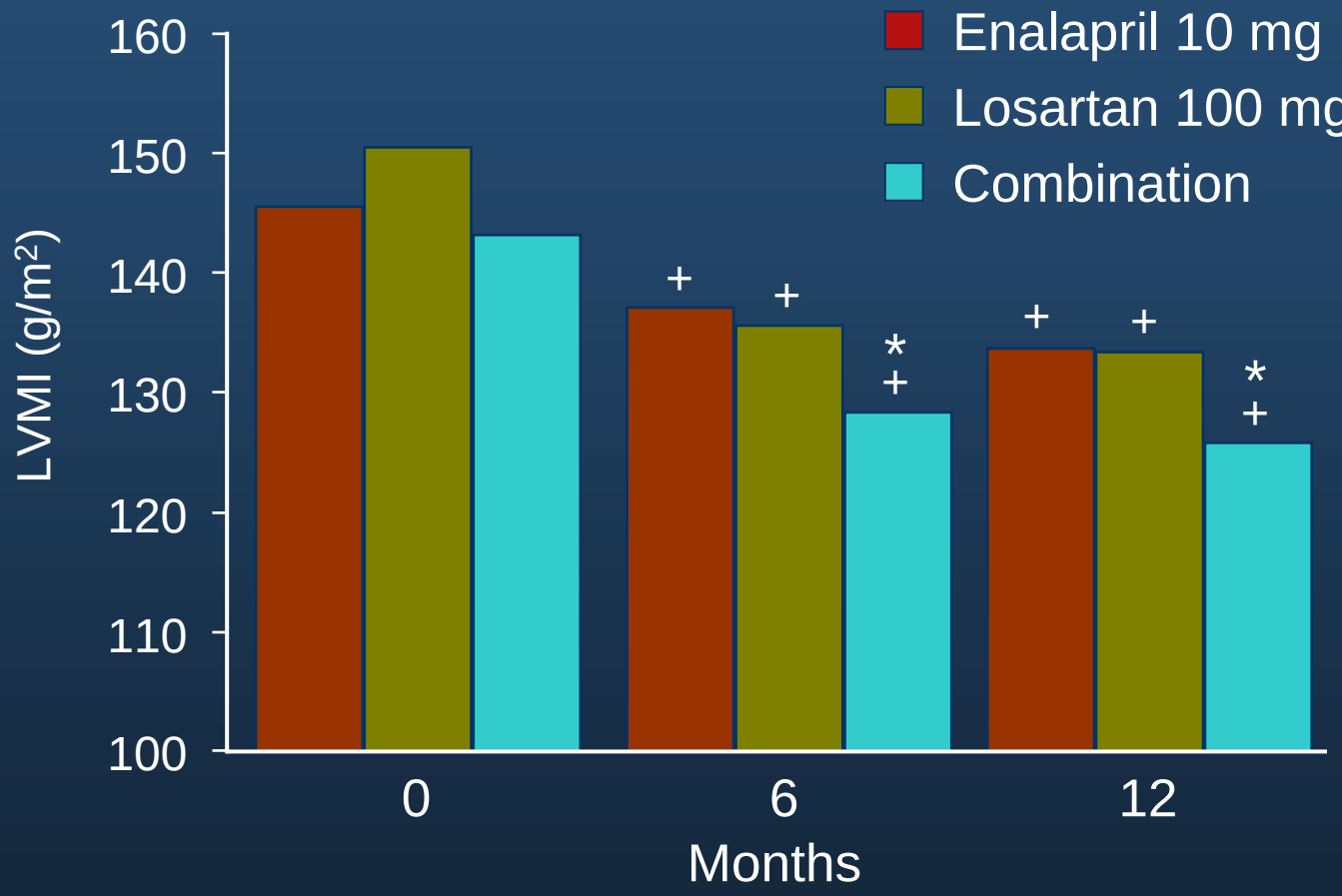
- Blood Pressure Lowering Effect
- Regression of LVH
- Prevention of New-onset DM
- Prevention of New-onset AF
- Renoprotective effects in DM
- Anti-atherosclerotic effects
- Neuroprotective effects

Losartan superior to atenolol in reducing LVH



Dahlöf et al. *Lancet* 2002;359:995–1003

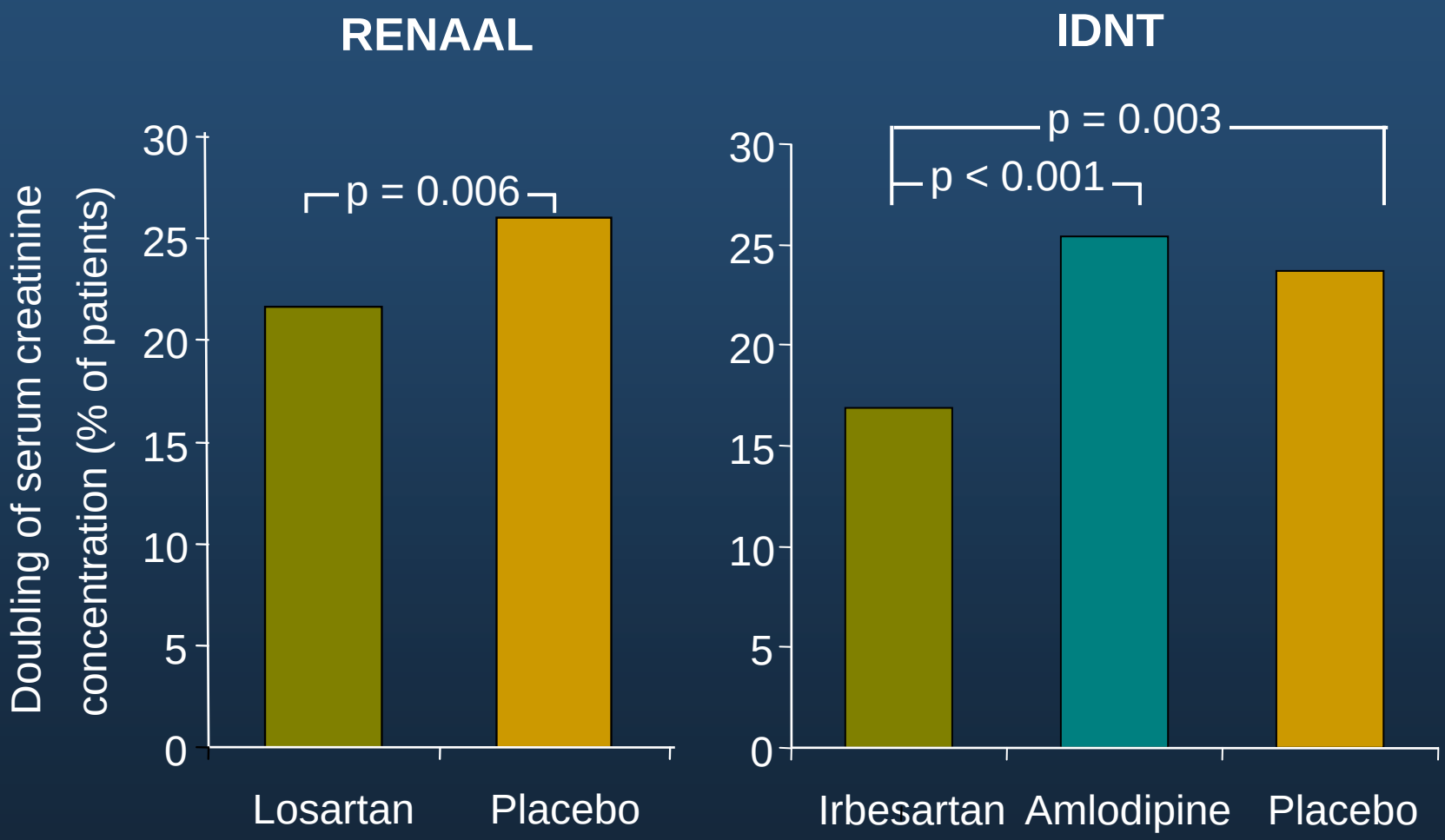
Reduction in LVM with Enalapril and Losartan Combination Therapy in Dialysis Patients



+P<0.05 vs baseline;
*P<0.05 vs monotherapies

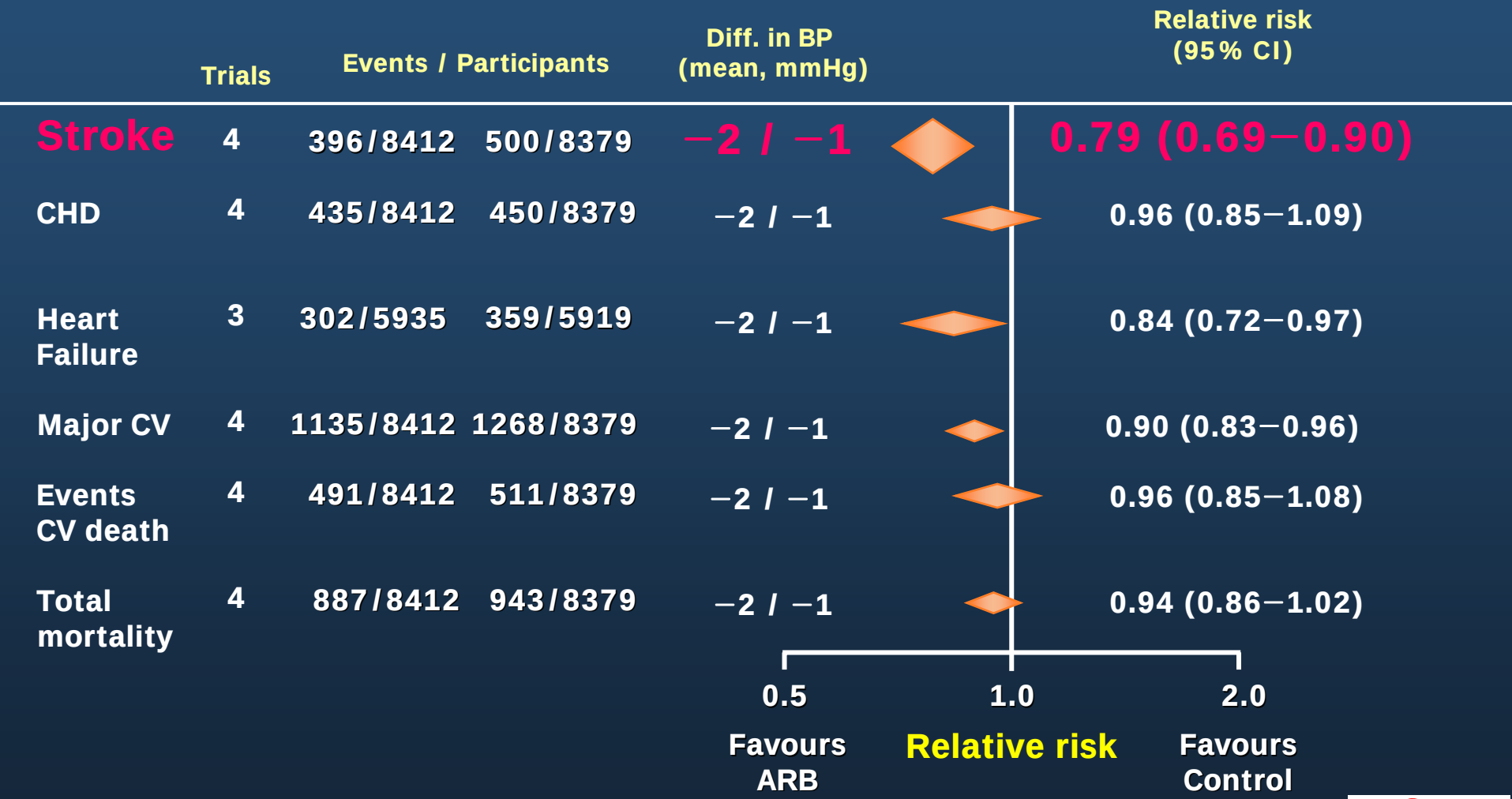
Suzuki et al. *Ther Apher Dial* 2004;8:320–327

ARBs slow progression in type 2 diabetes and macroproteinuria



Brenner et al. *N Engl J Med* 2001;345:861–869.
Lewis et al. *N Engl J Med* 2001;345:851–860.

Comparisons of ARB-Based Regimens With Control Regimens



BPLT Trialists' Collaboration. *Lancet*. 2003;362:1527–35.

Anti-inflammatory Effects of RAS Blockade in Coronary Artery Disease

		ACE inhibition	AT_1-receptor blockade
Anti-atherosclerotic effects	IL-10	⇧	
Pro-atherosclerotic surrogate markers elevated in CAD	MMP-9	⇩	
	IL-6	~	
Amplify inflammation	hsCRP	~	
Contribute to plaque's fibrous cap decomposition	TXA2-induced platelet aggregation	~	

More complete blockade of ANG II-proinflammatory and procoagulatory effects

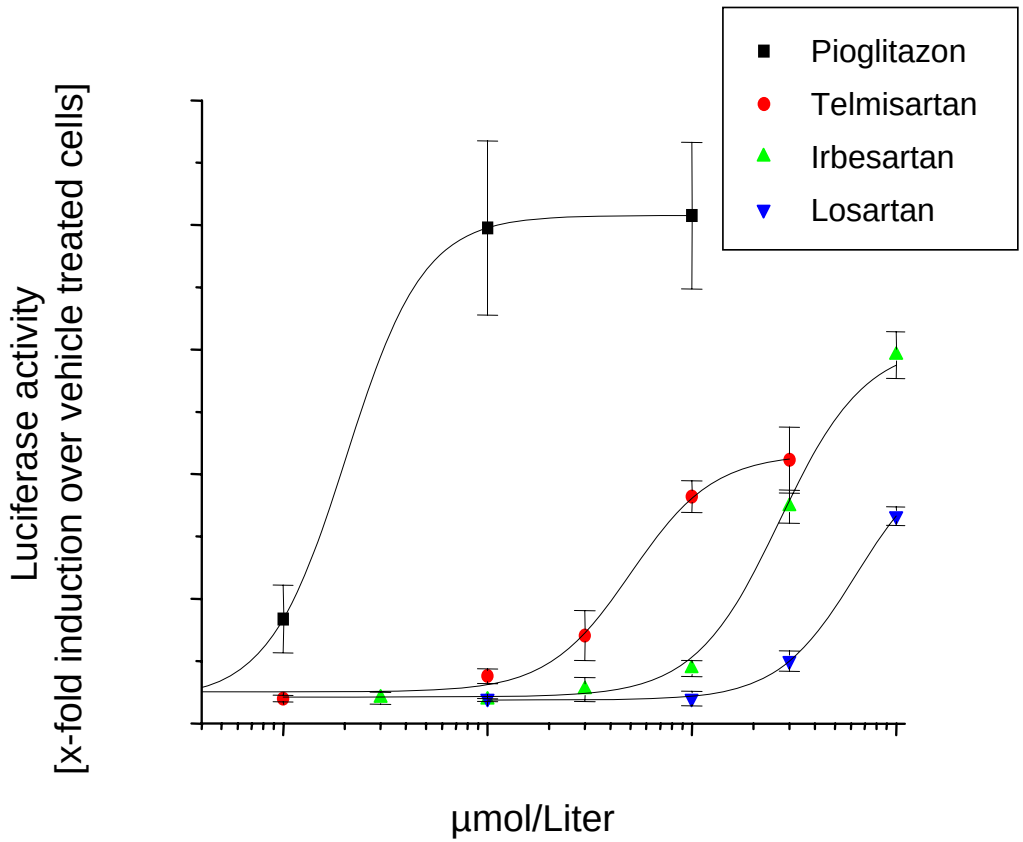
Atherosclerotic plaque progression and instability

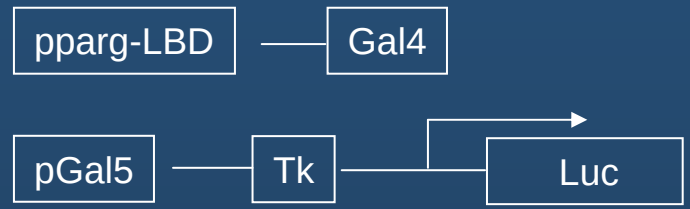
Schieffer B et al. J Am Coll Cardiol 2004; 44:362-368

ARBs and New-Onset Diabetes: Clinical Trials

Study	Population (age)*	Mean follow-up (years)	Incidence of type 2 diabetes RR (95% CI)
LIFE	9,193 patients with essential hypertension and left ventricular hypertrophy (55-80 years)	4.8	Losartan (6.0%) vs. Atenolol (8.0%) 0.75 (0.63-0.88)
CHARM	7,601 patients from 26 countries NYHA II-IV (≥18 years)	≥ 2	Candesartan (6.0%) vs. Placebo (7.4%) 0.78 (0.64–0·96)
VALUE	15,245 patients of high risk For cardiovascular events ≥ 50 years	≥ 4.2	Valsartan (13.1%) vs. Amlodipine (16.4%) 0.77 (0.69–0.86)

Interaction of ARBs with the PPARγ Ligand Binding Domain (LBD)





EC_{50} Pioglitazon	0.2 µmol/L
EC_{50} Telmisartan	5.02 µmol/L
EC_{50} Irbesartan	26.97 µmol/L
EC_{50} Losartan	>50 µmol/L

Schupp M. et al. 2004 *Circulation* 109: 2054 -7

AII antagonists have molecular specific effects which do not involve angiotensin II blockade?

- Inhibition of thromboxane A2–induced platelet aggregation

  Losartan, irbesartan

- PPARgama partial agonist activity

  Telmisartan, irbesartan, losartan (EXP3179)

- Inhibition of renal urate transport

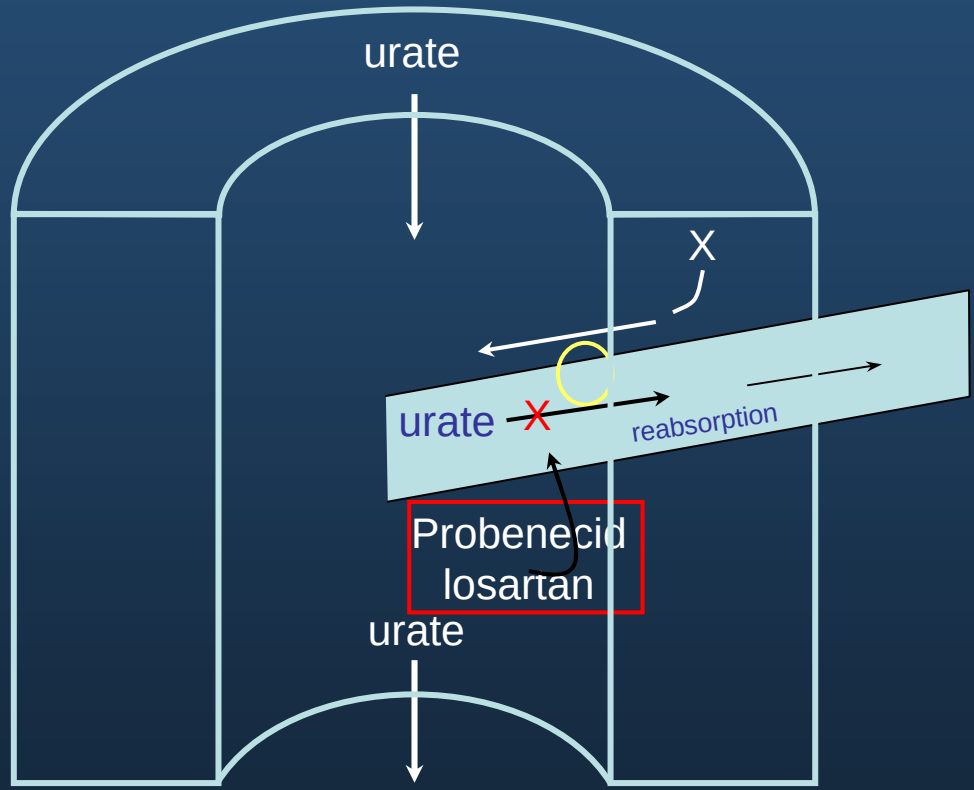
  Losartan

Drug-specific Effects of Losartan

- Uricosuric effect
- Neuroprotective effect
- Anti-thrombotic effect
- Others

Losartan Increases Urate Excretion by Inhibiting Urate/Anion Exchange

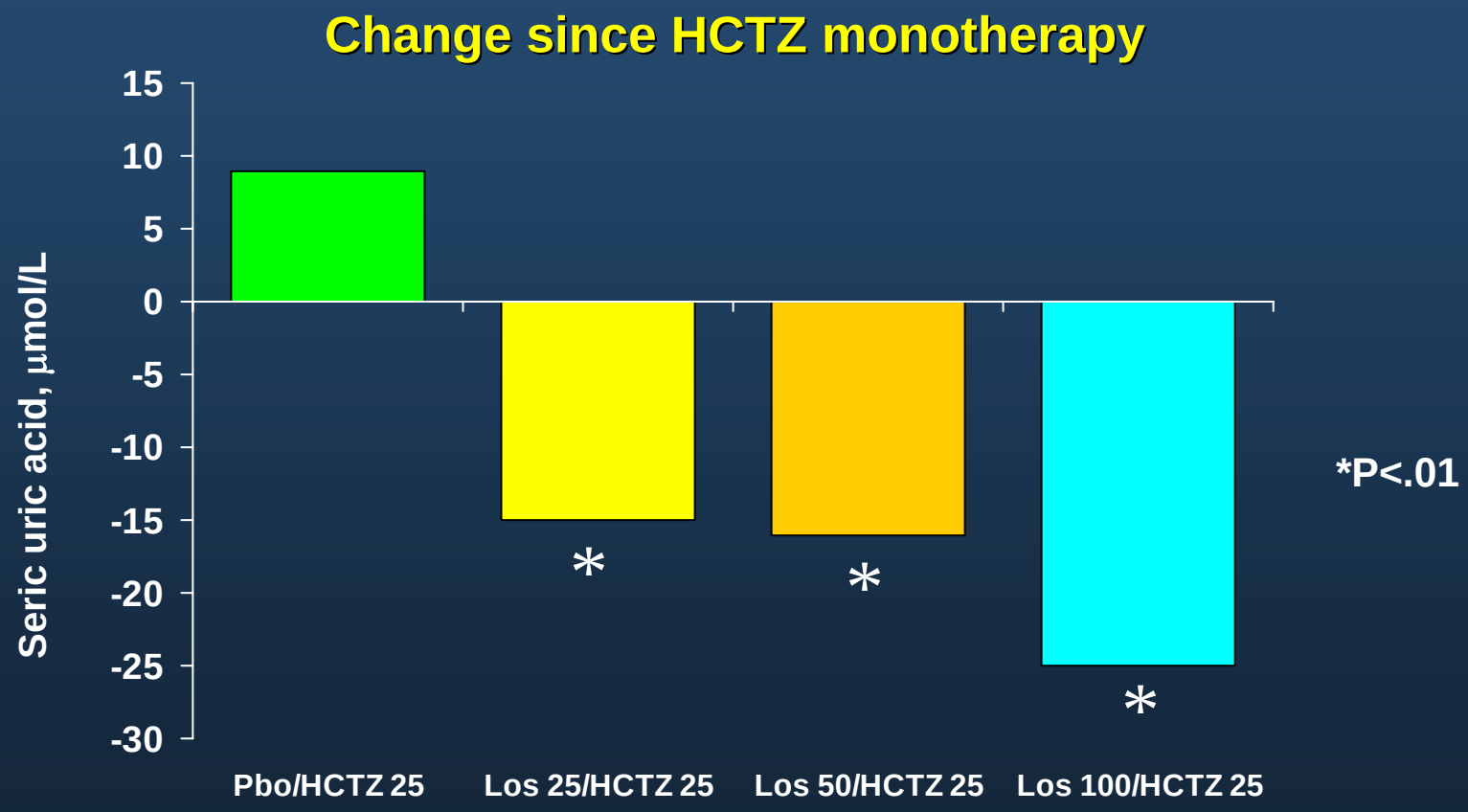
Proximal renal tubule



x=lactate, alpha-ketoglutarate, succinate beta-hydroxybutyrate, acetoacetate, nicotinate, etc.

Adapted from Burnier et al *Kidney Int* 1996;49:1787–1798.

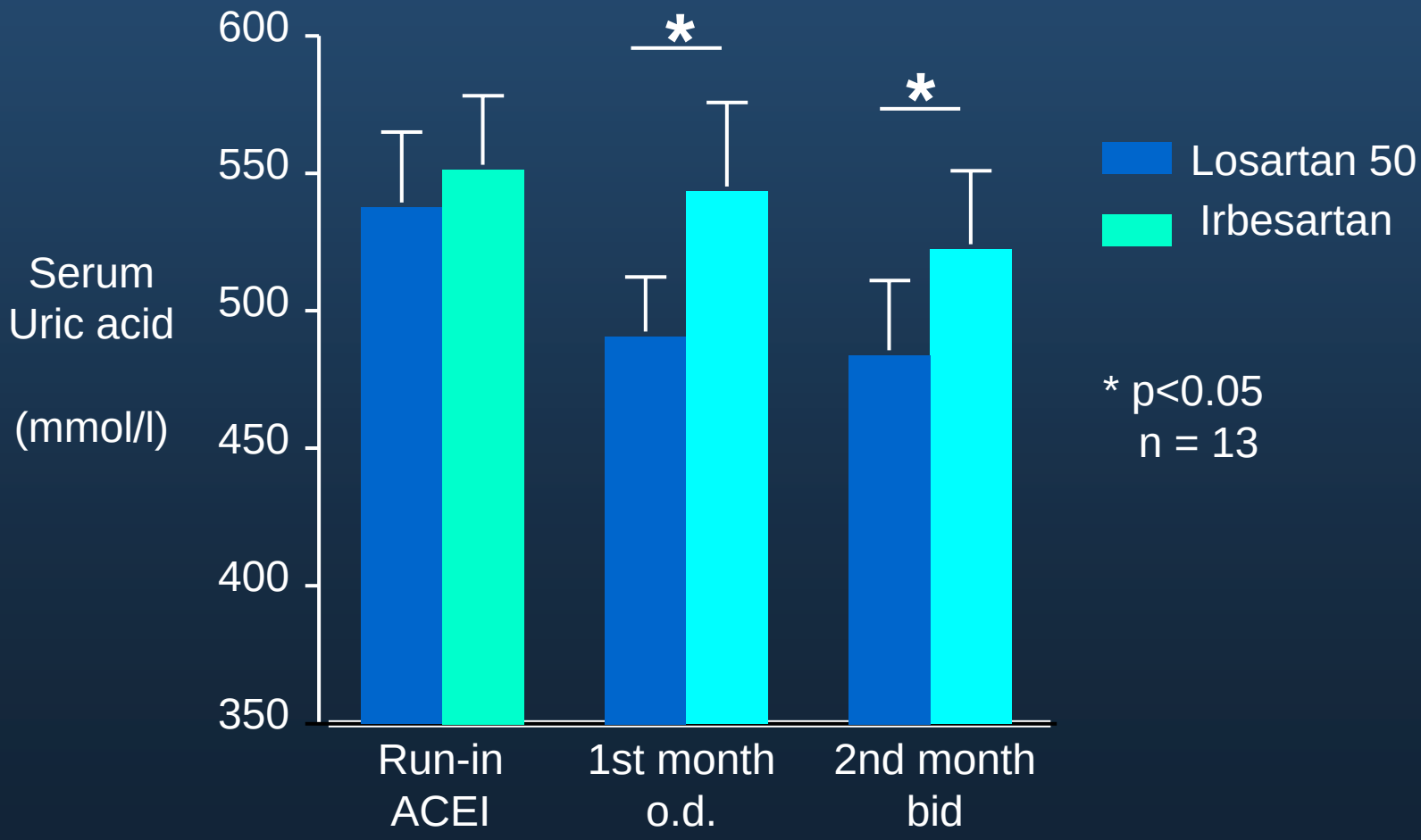
Without relevant metabolic alterations: Hyperuricemia



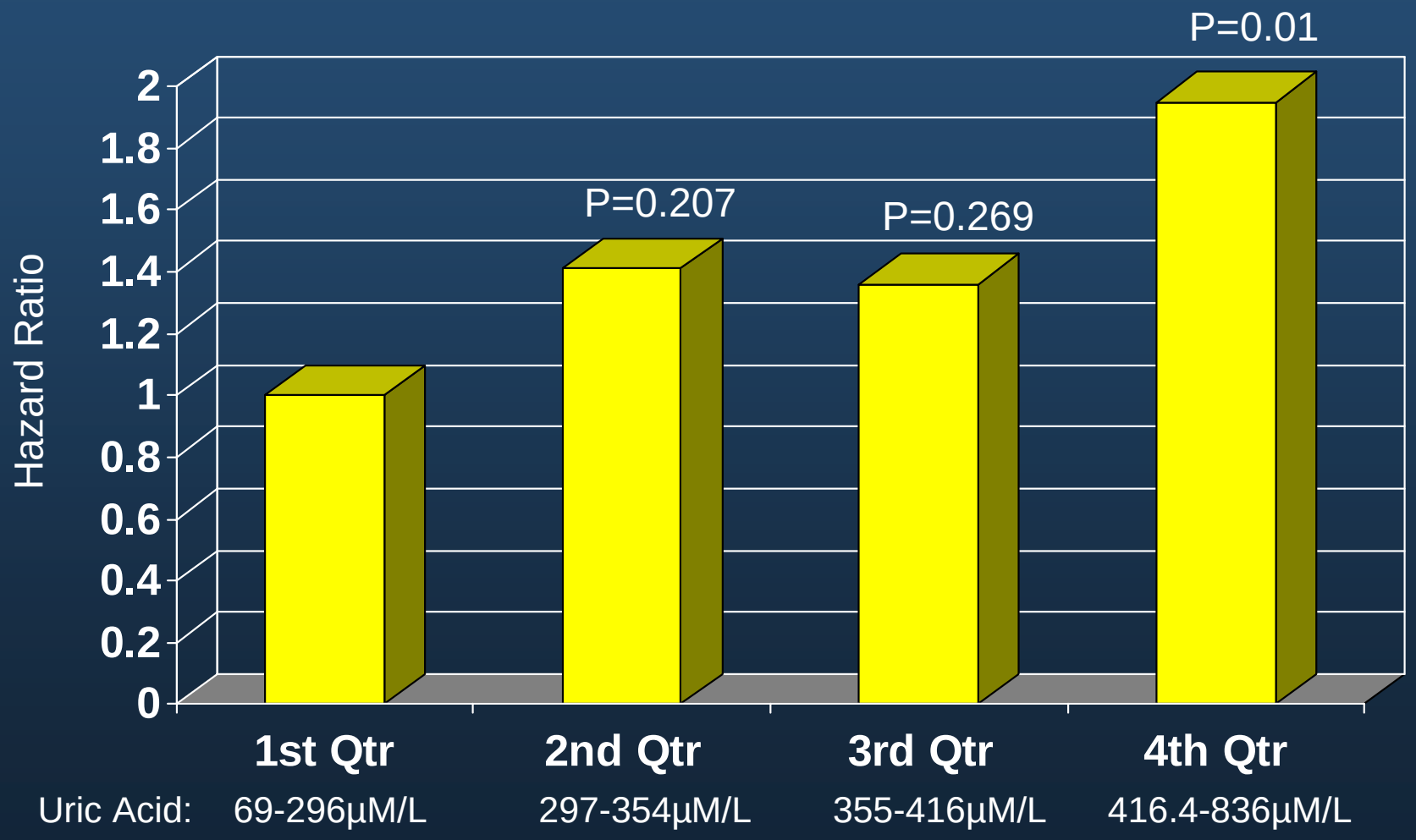
Soffer et al. Hypertension 1995, 26 (1): 112-117

Without relevant metabolic alterations: Hyperuricemia

Effect of Losartan and Irbesartan on Uric Acid Levels in Gouty Hypertensive Patients

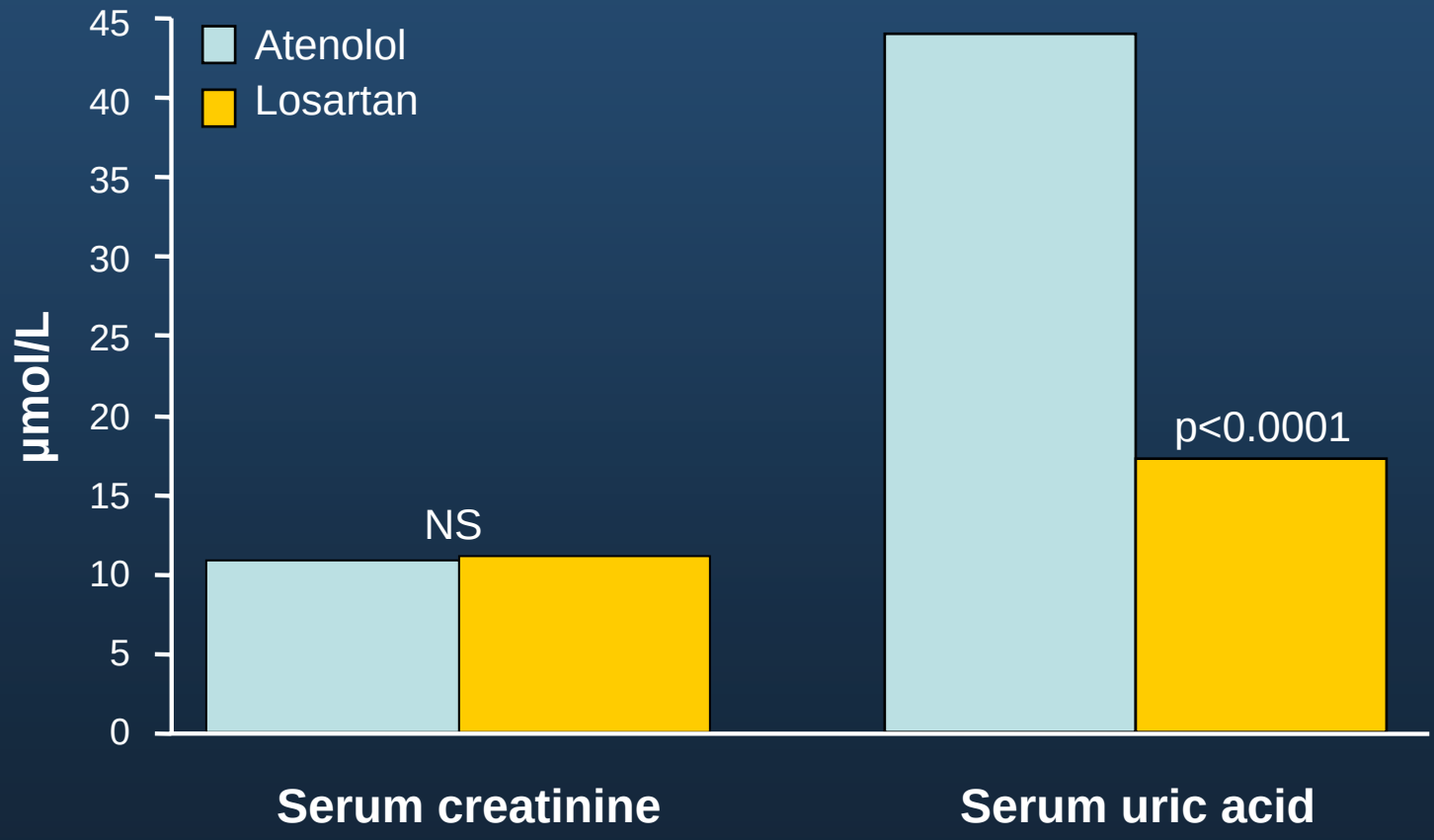


Serum Uric Acid at Year 4 in LIFE and Subsequent New-Onset AF (N=130)



Richard Devereux et al Unpublished 2006

LIFE: Losartan vs. Atenolol Reduced the Rise in Serum Uric Acid without Affecting Renal Function



Adapted from Høieggen A et al *Kidney Int* ;65:1–9, 2004

Without relevant metabolic alterations: Hyperuricemia

Uricosuric effect-Only Losartan

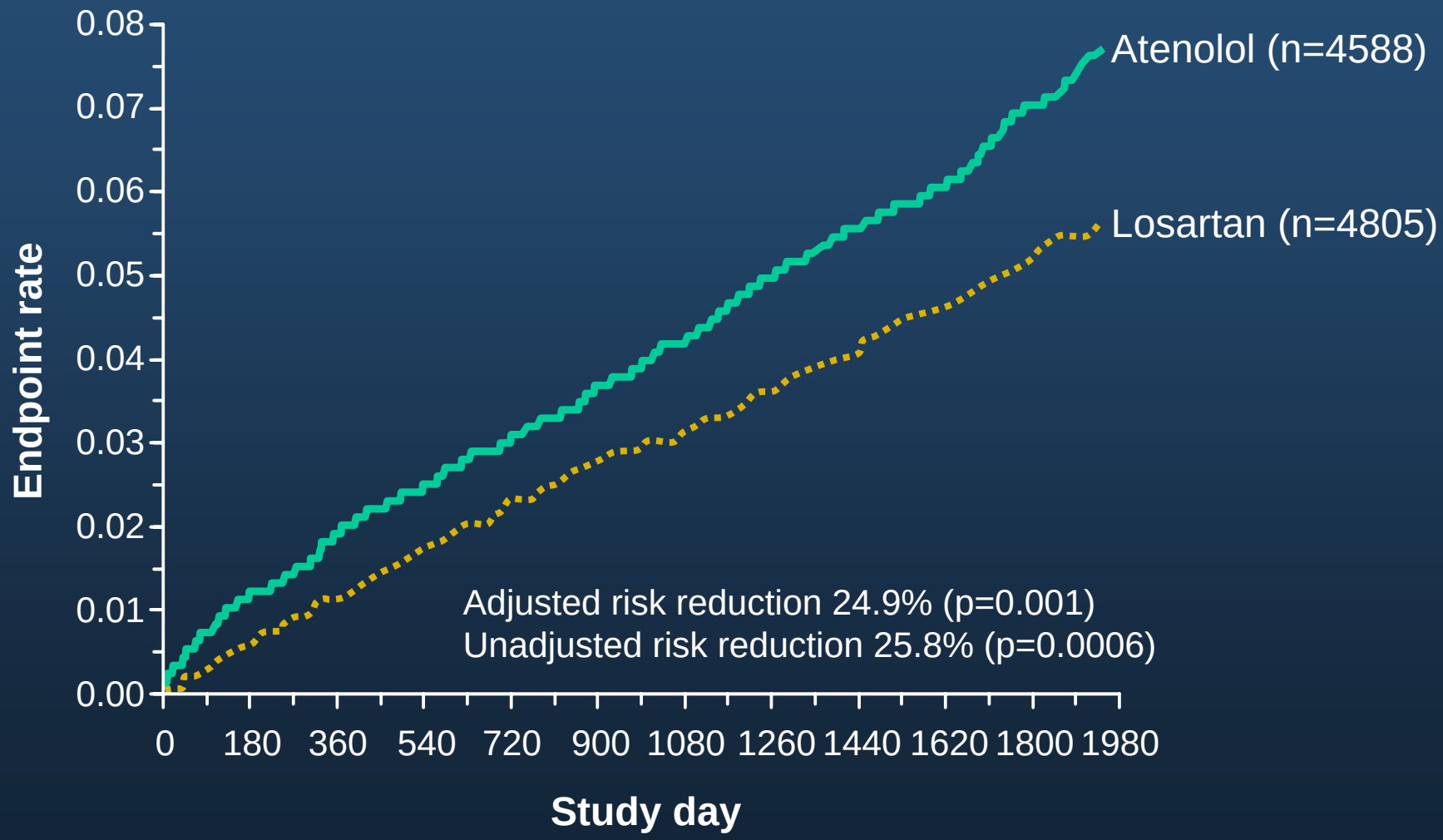
- Serum uric acid (SUA) :

  Independent risk factor for cardiovascular morbidity and death

- The contribution of SUA to the treatment effect of losartan

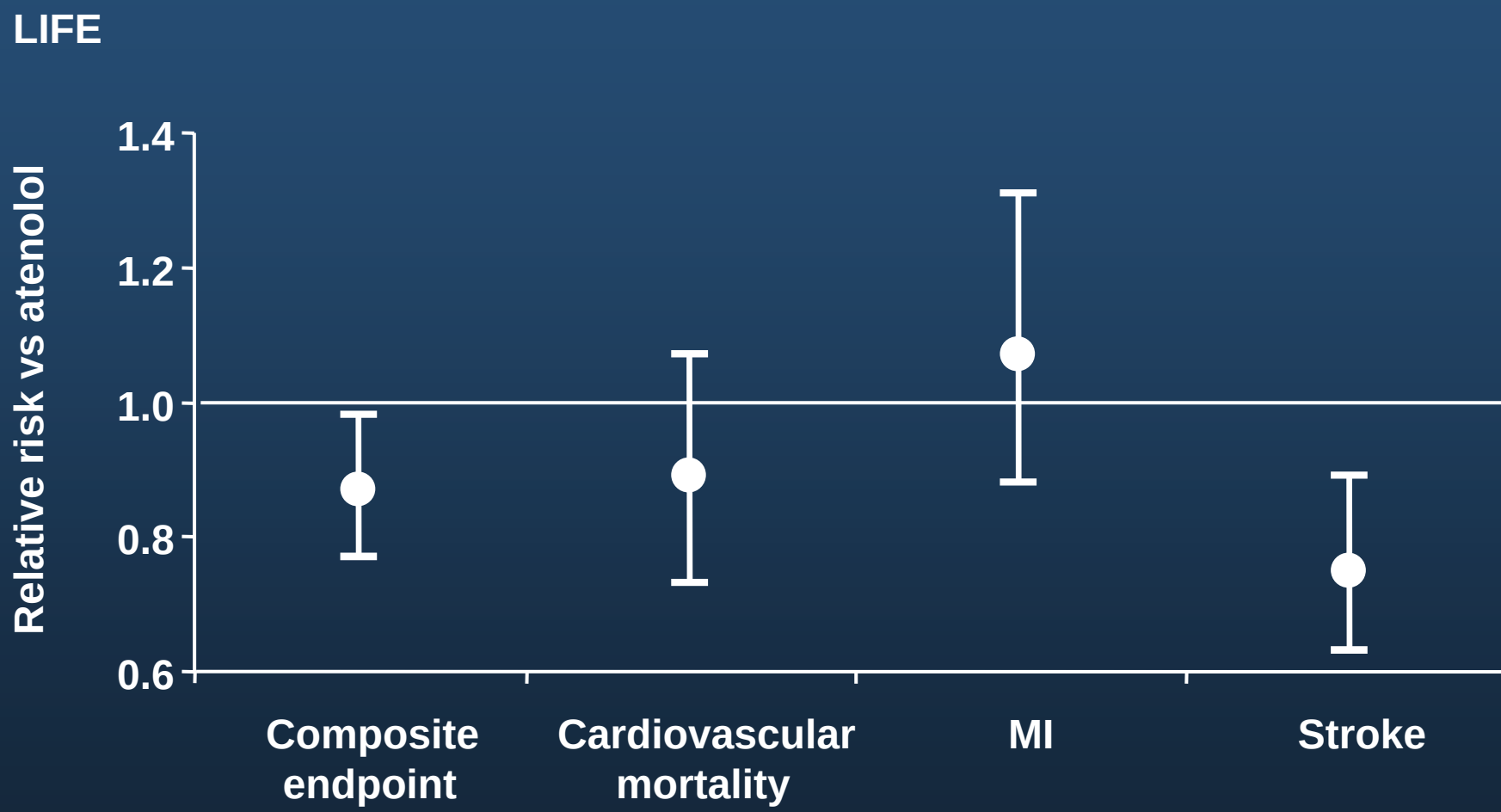
  in terms of the primary composite endpoint was 29% (p=0.004)

LIFE: Losartan Was Superior to Atenolol in Reducing the Risk of Fatal/Nonfatal Stroke



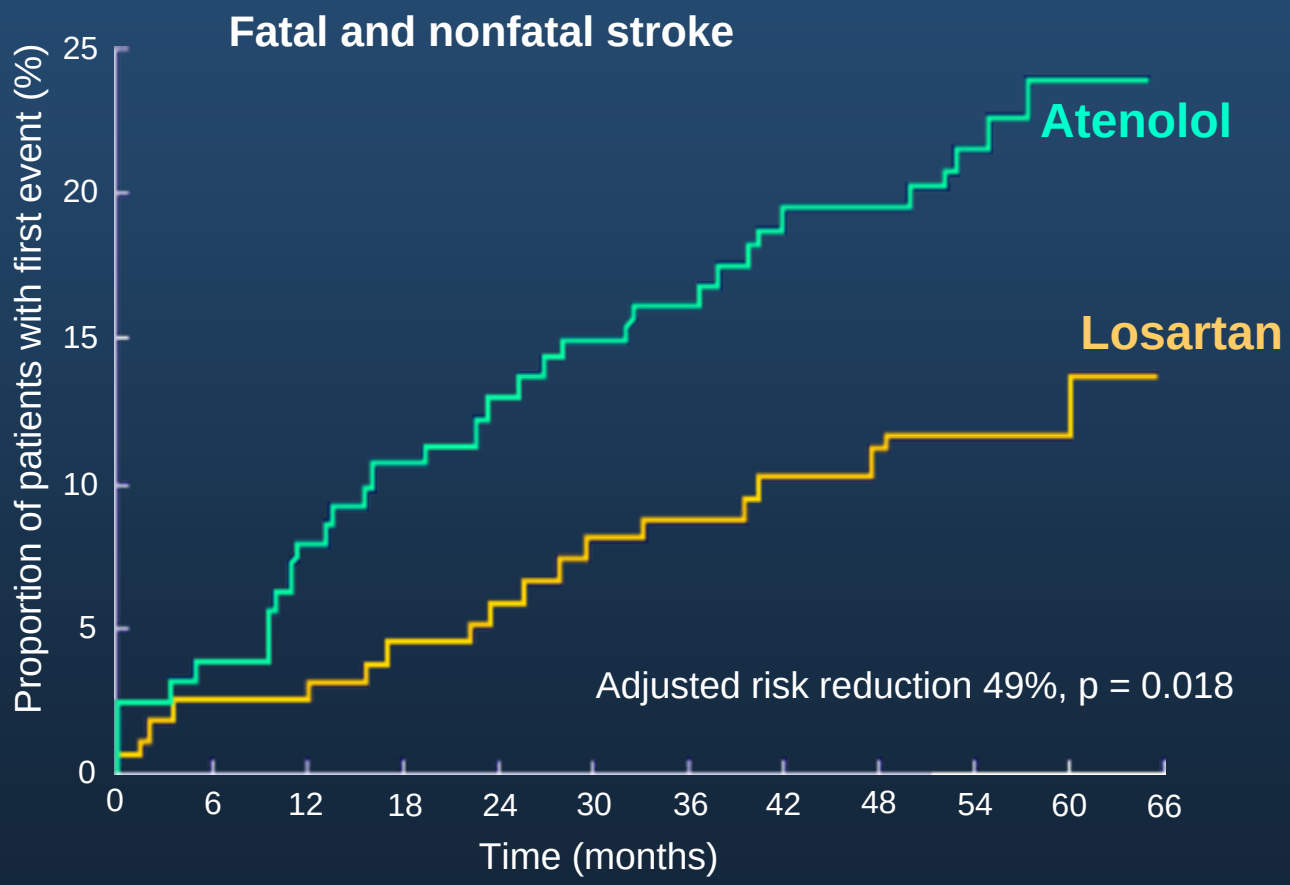
Adapted from Dahlöf B et al *Lancet* 2002;359:995–1003.

Cardiovascular effects of losartan primarily due to stroke reduction



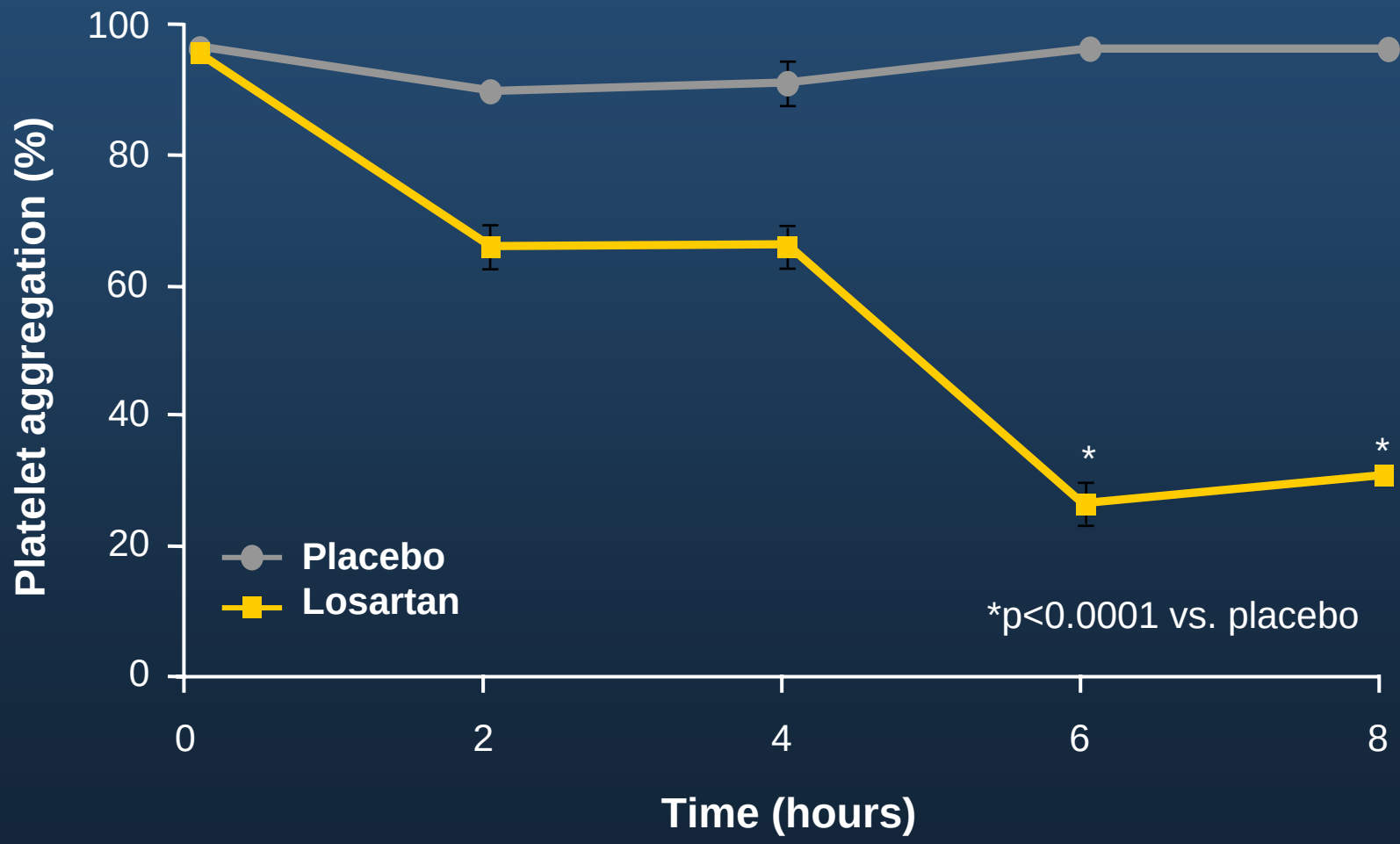
Dahlöf et al. *Lancet* 2002;359:995–1003

Reduction in Risk of Stroke in Patients with AF



Dalhöf B et al. Presented at the European Society of Cardiology Congress; Berlin, Germany; August 31–September 4, 2002. Poster 2163.

Losartan-Dependent Inhibition of Platelet Aggregation *in vivo*



Adapted from Krämer C et al *Circ Res* 2002;90:770–776.

Losartan Had Effects on Platelet Aggregation and Thrombus Formation

- Losartan
  - Reduced TXA_2–dependent platelet activation (platelets from 15 healthy men)
  - Reduced plasma levels of PAI-1 antigen, PAI-1 activity, and sTM level in 12 hypertensive patients
  - Increased the concentration of thrombin receptor-activating peptide (SRLRRN-NH2) required to induce platelet aggregation in 10 hypertensive patients
  - Reduced plasma PAI-1 levels in hypertensive postmenopausal women
  - Reduced the aggregatory response to thromboxane but not thrombin in hypertensive patients

Please refer to notes page for reference citations.

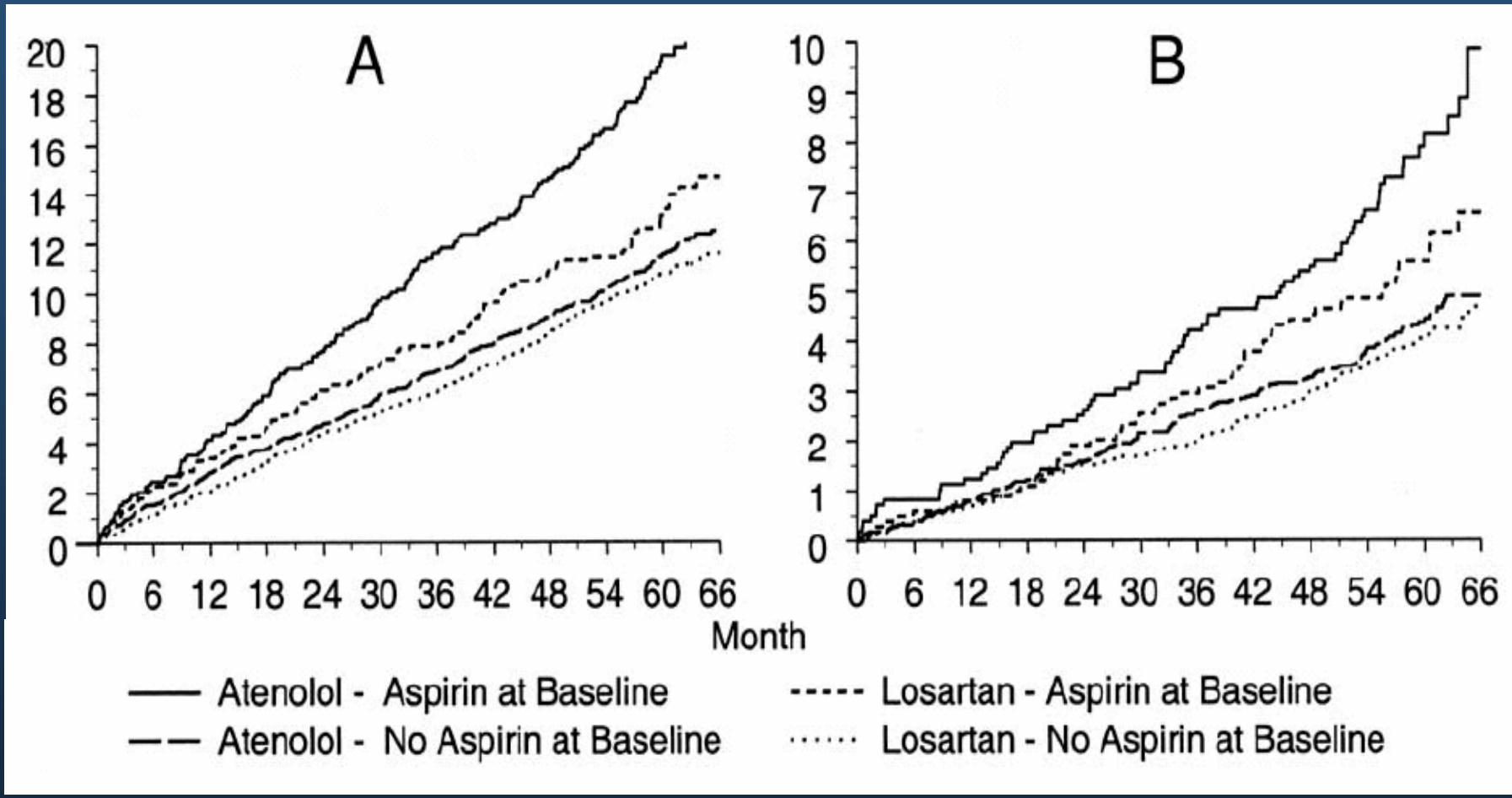
The Effect of Losartan Versus Atenolol on Cardiovascular Morbidity and Mortality in Patients With Hypertension Taking Aspirin

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study

CONCLUSIONS "There was a statistical interaction between Treatment and aspirin in the LIFE study, with significantly greater reductions for the CEP and MI with losartan in patients using aspirin than in patients not using aspirin at baseline. Further studies are needed to clarify whether this represents a pharmacologic interaction or a selection by aspirin use of patients more likely to respond to losartan treatment."

Fossum et al J Am Coll Cardiol 46:770-775, 2005

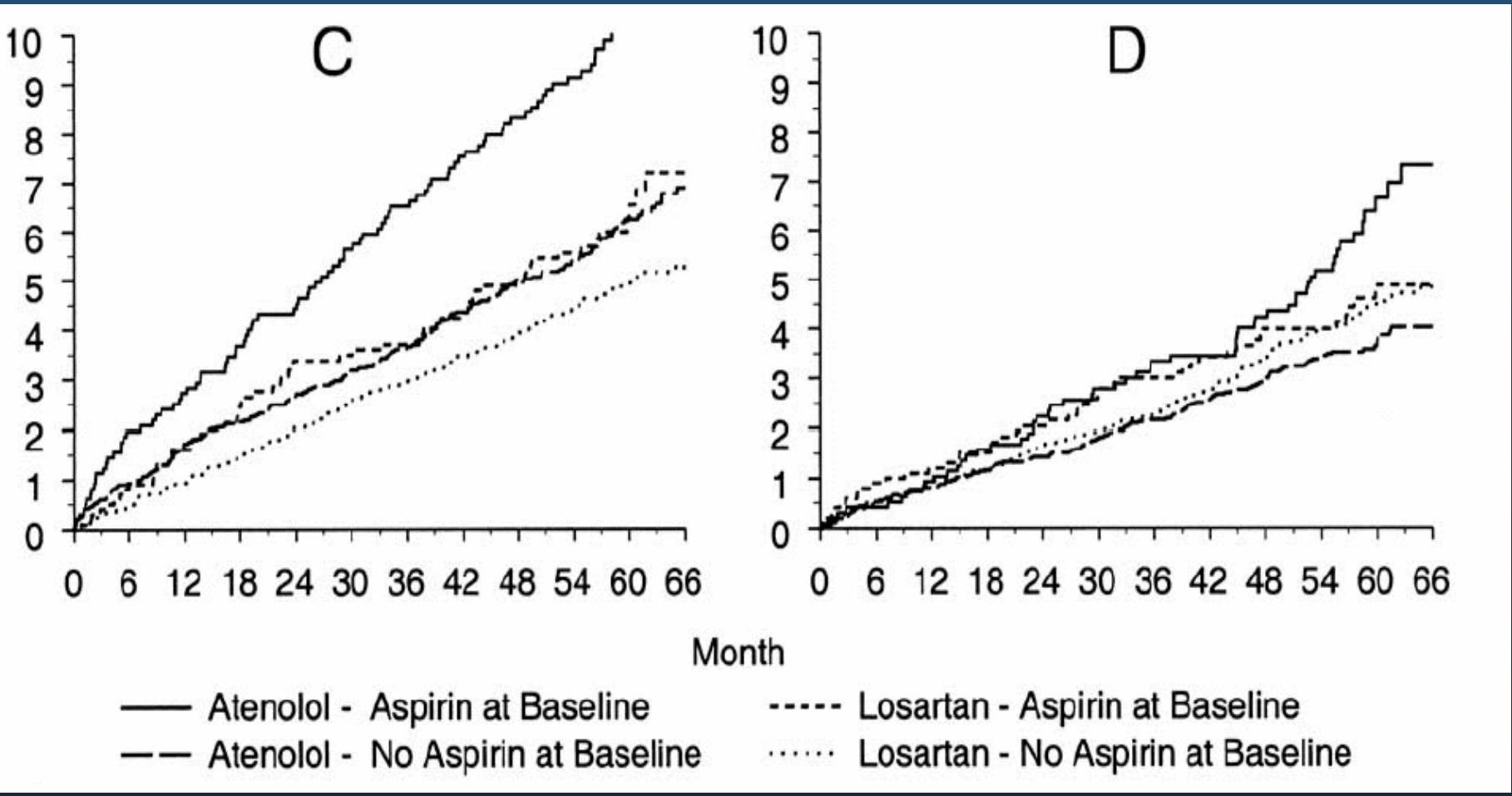
Endpoint Rate %



A Kaplan-Meier curves for the primary end point; p 0.016 for aspirin interaction.
B Kaplan-Meier curves for cardiovascular death.

Fossum et al J Am Coll Cardiol 46:770-775, 2005

Endpoint Rate %



C Kaplan-Meier curves for stroke.
D Kaplan-Meier curves for myocardial infarction; p 0.037 for aspirin interaction.

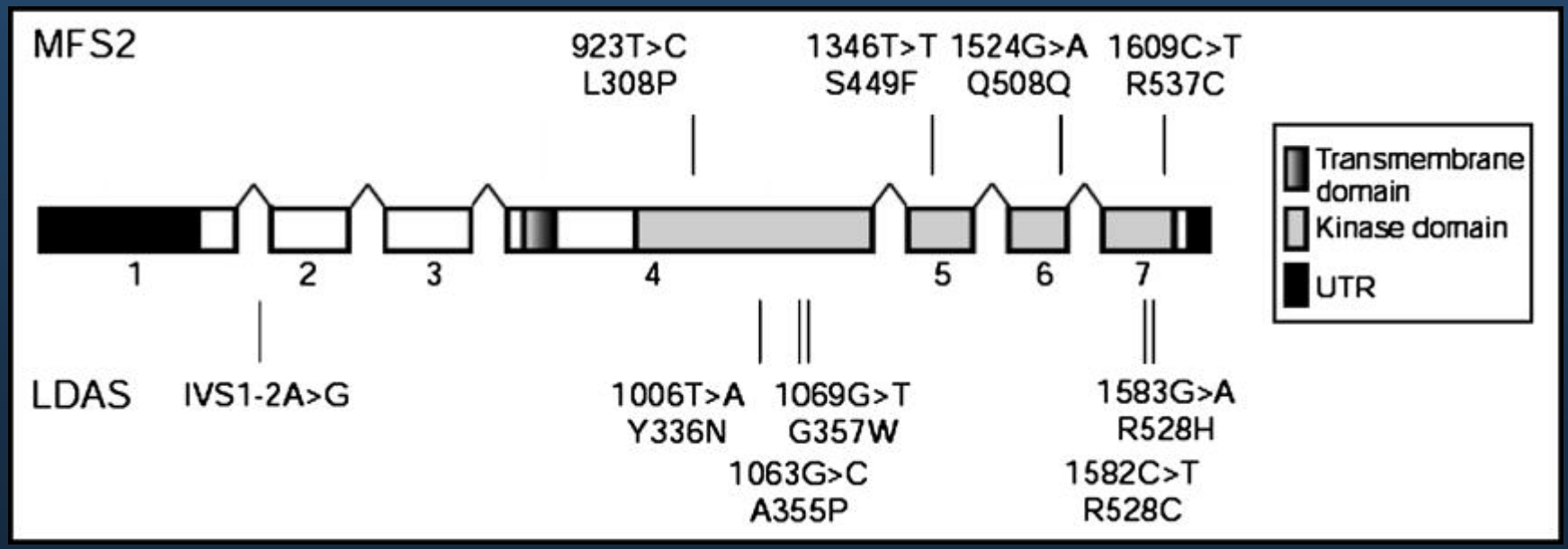
Fossum et al J Am Coll Cardiol 46:770-775, 2005

Losartan, an AT1 Antagonist, Prevents Aortic Aneurysm in a Mouse Model of Marfan Syndrome

Jennifer P. Habashi,[1*] Daniel P. Judge,[2*] Tammy M. Holm,[1] Ronald D. Cohn,[1] Bart L. Loeys,[1] Timothy K. Cooper,[1,3] Loretha Myers,[1] Erin C. Klein,[1] Guosheng Liu,[3] Carla Calvi,[2] Megan Podowski,[2] Enid R. Neptune,[2] Marc K. Halushka,[4] Djahida Bedja,[3] Kathleen Gabrielson,[3] Daniel B. Rifkin,[5] Luca Carta,[6] Francesco Ramirez,[6] David L. Huso,[3] Harry C. Dietz[1,2]†

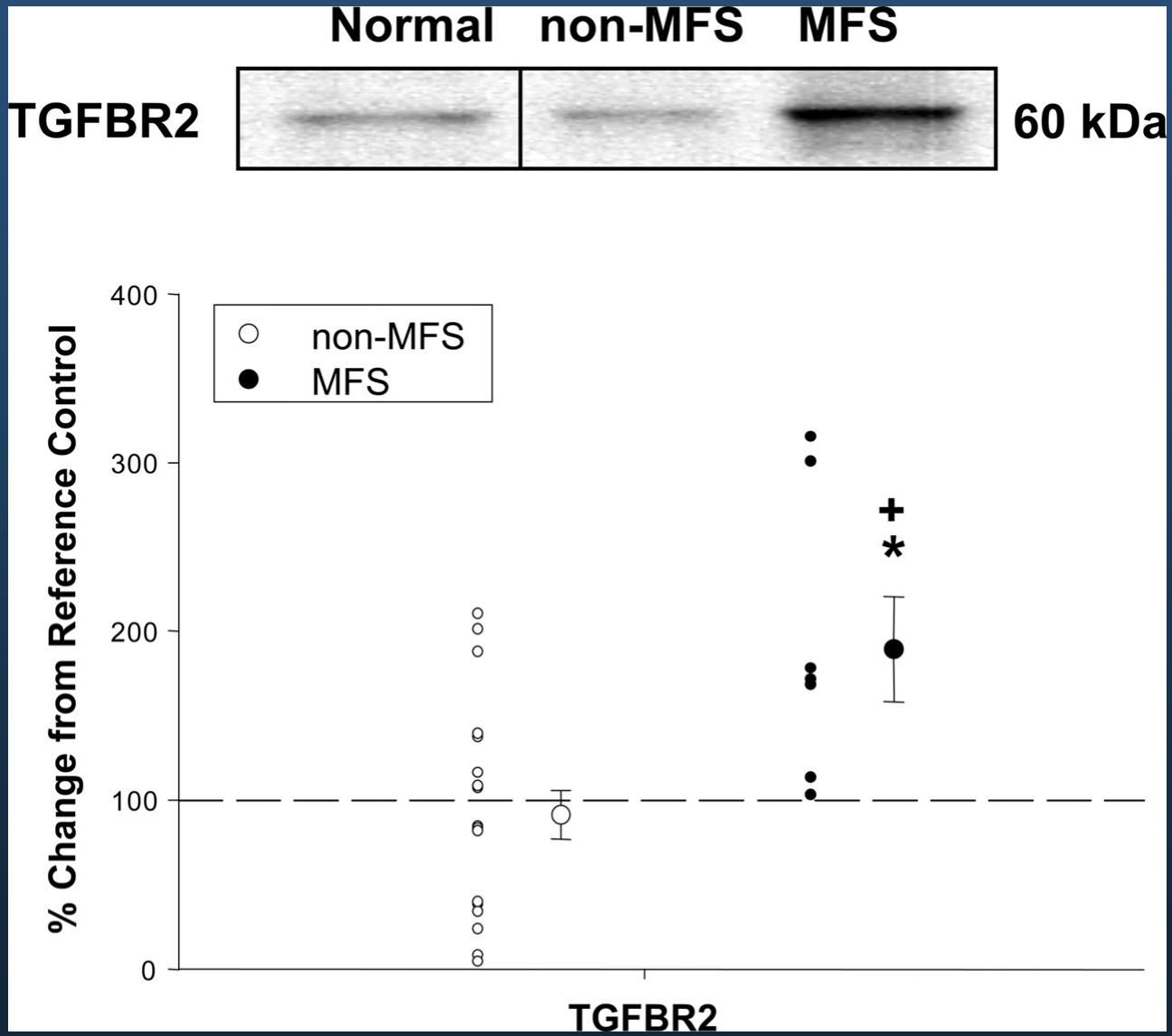
Aortic aneurysm and dissection are manifestations of Marfan syndrome (MFS), a disorder caused by mutations in the gene that encodes fibrillin-1. Selected manifestations of MFS reflect excessive signaling by the transforming growth factor–β (TGF-β) family of cytokines. We show that aortic aneurysm in a mouse model of MFS is associated with increased TGF-β signaling and can be prevented by TGF-β antagonists such as TGF-β–neutralizing antibody or the angiotensin II type 1 receptor (AT1) blocker, losartan. AT1 antagonism also partially reversed noncardiovascular manifestations of MFS, including impaired alveolar septation. These data suggest that losartan, a drug already in clinical use for hypertension, merits investigation as a therapeutic strategy for patients with MFS and has the potential to prevent the major life-threatening manifestation of this disorder.

Genomic structure of *TGFBR2* and mutations found in Marfan syndrome type II (MFS2) and Loeys-Dietz aortic aneurysm syndrome (LDAS).



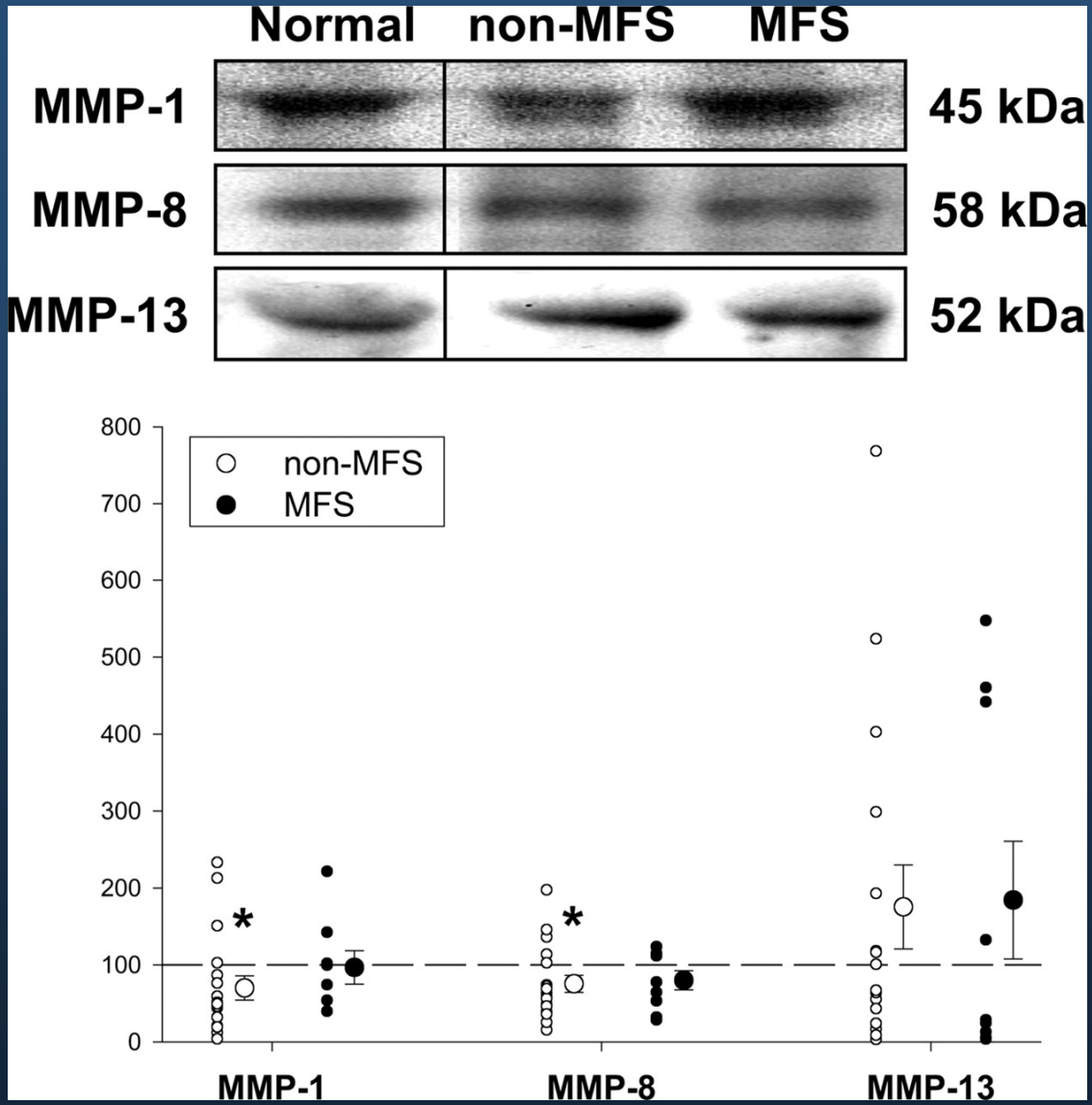
Boileau C et al Curr Opin Cardiol 2005:20:194-200

Analysis for TGFBR2 in aortic samples

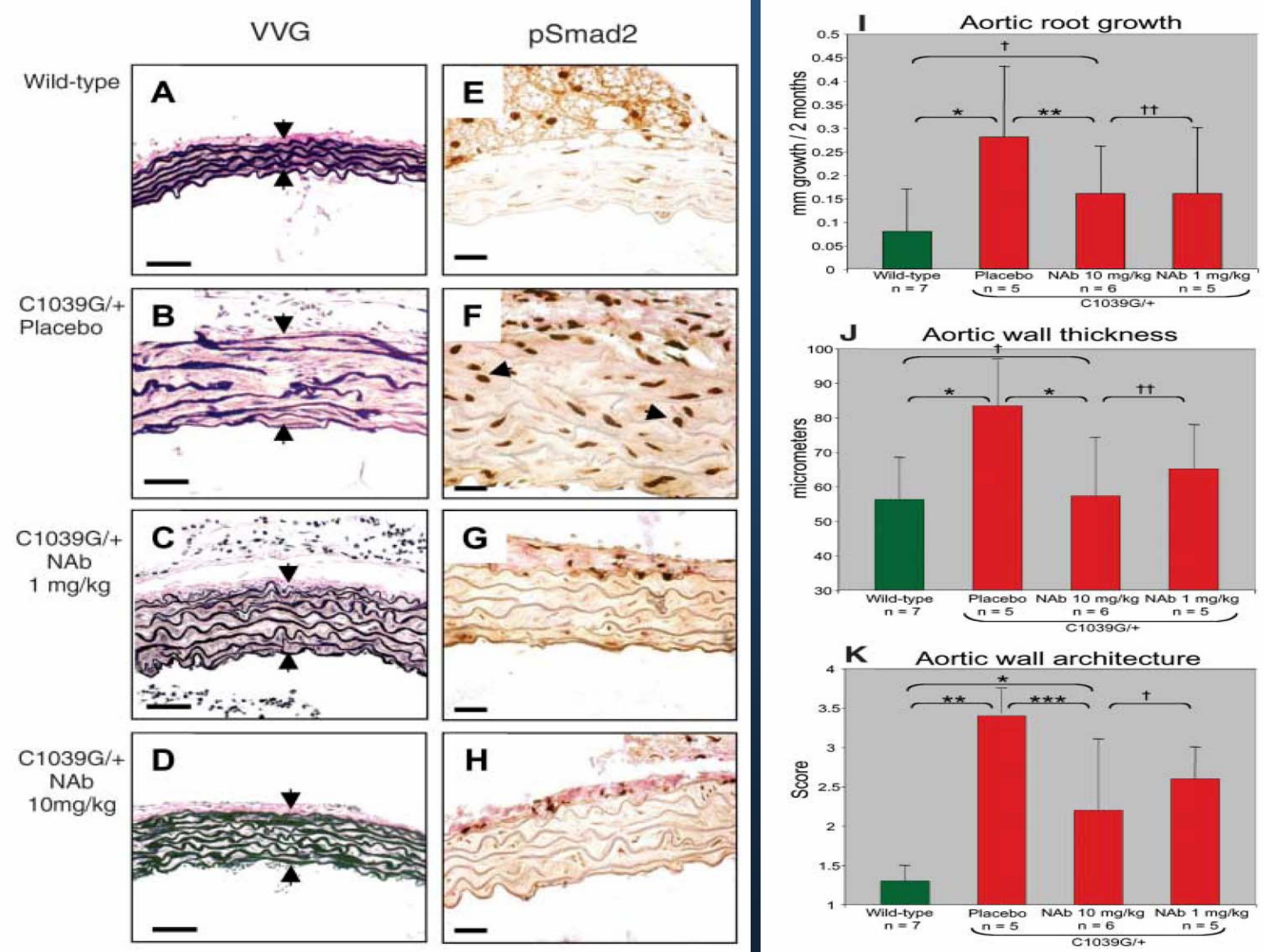


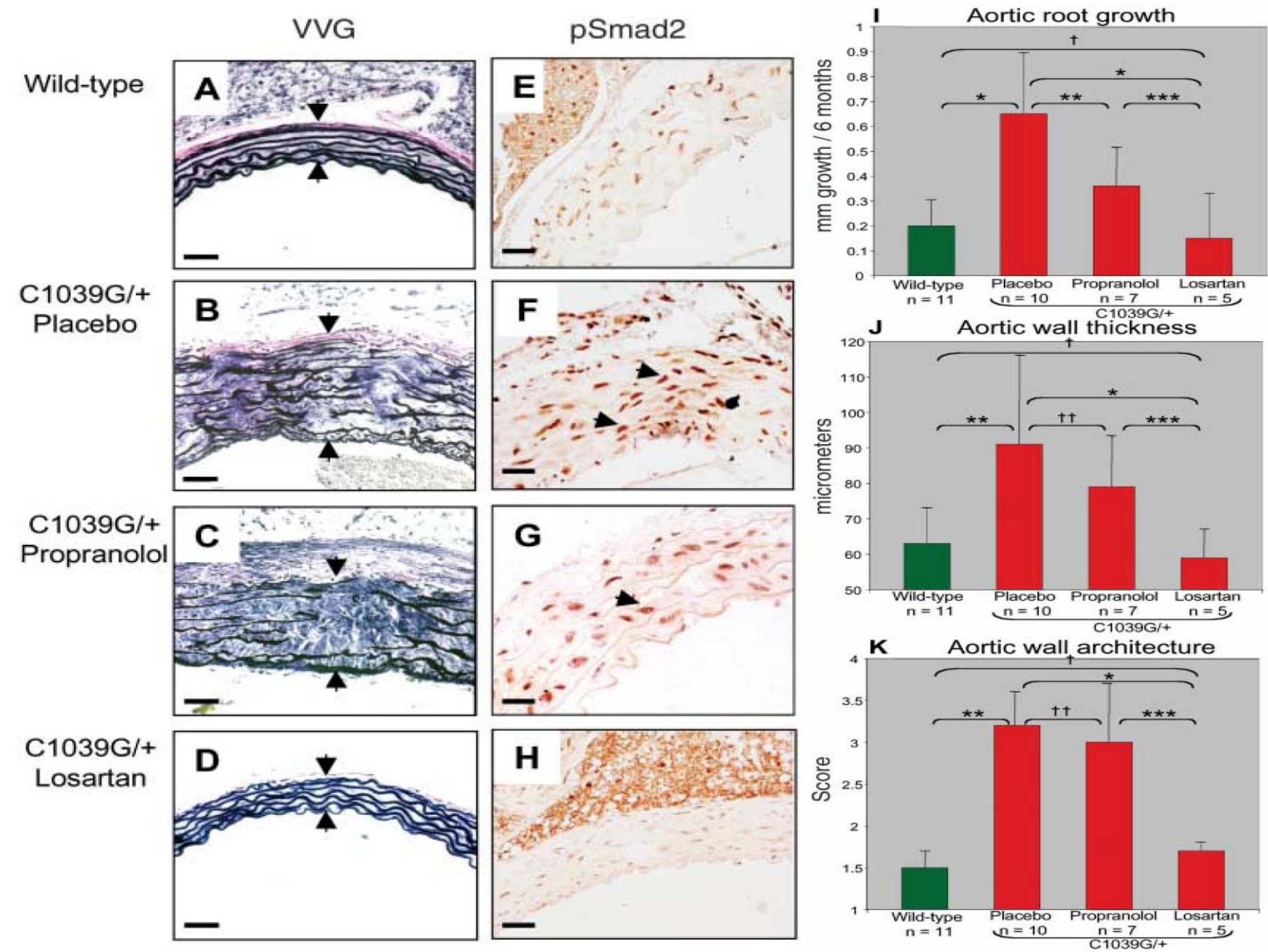
Ikonomidis, J. S. et al. Circulation 2006;114:I-365-I-370

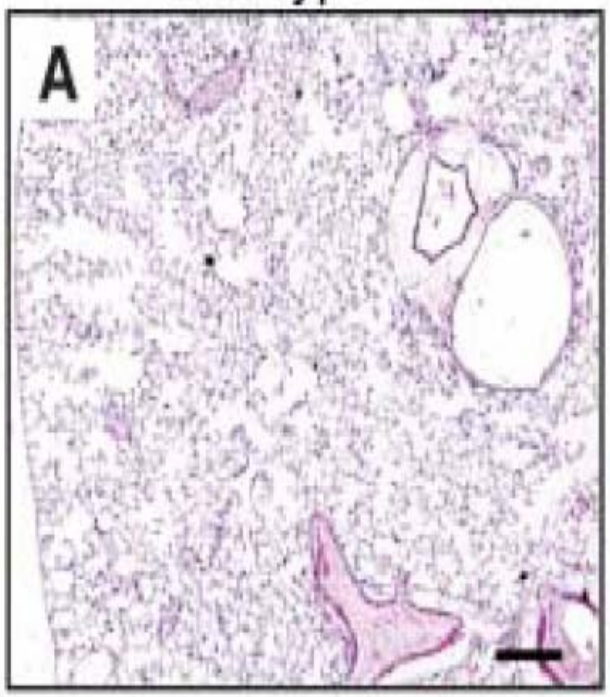
Collagenase analysis

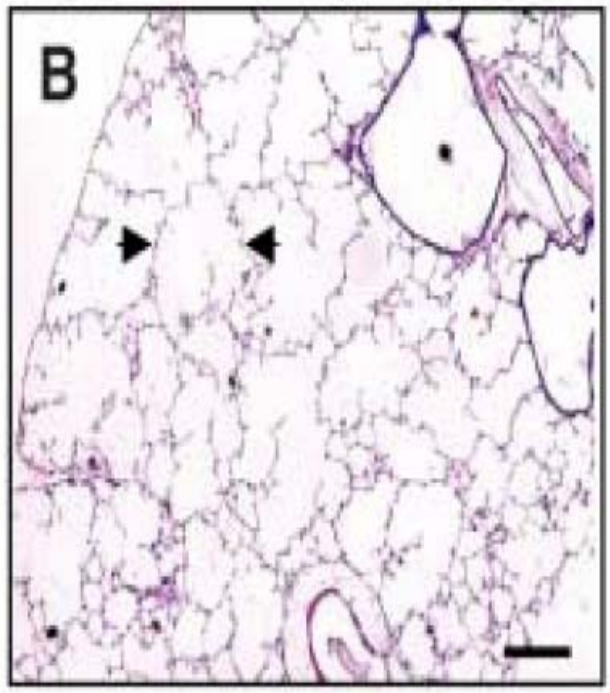


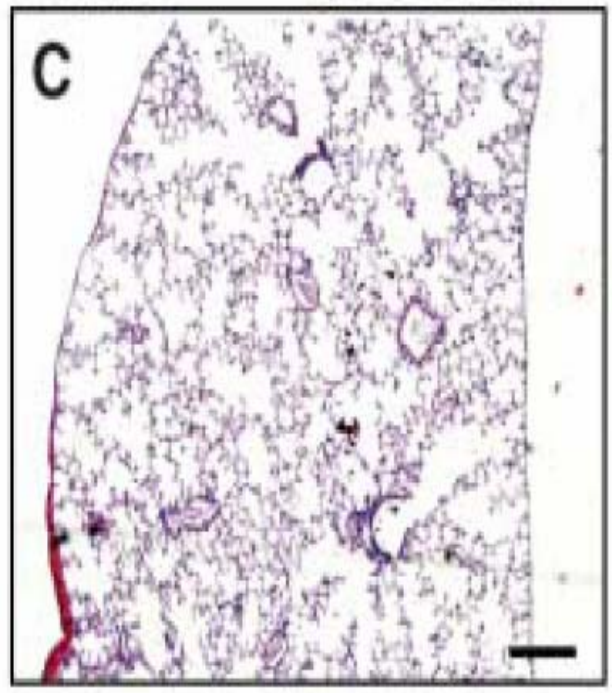
Ikonomidis, J. S. et al. Circulation 2006;114:I-365-I-370

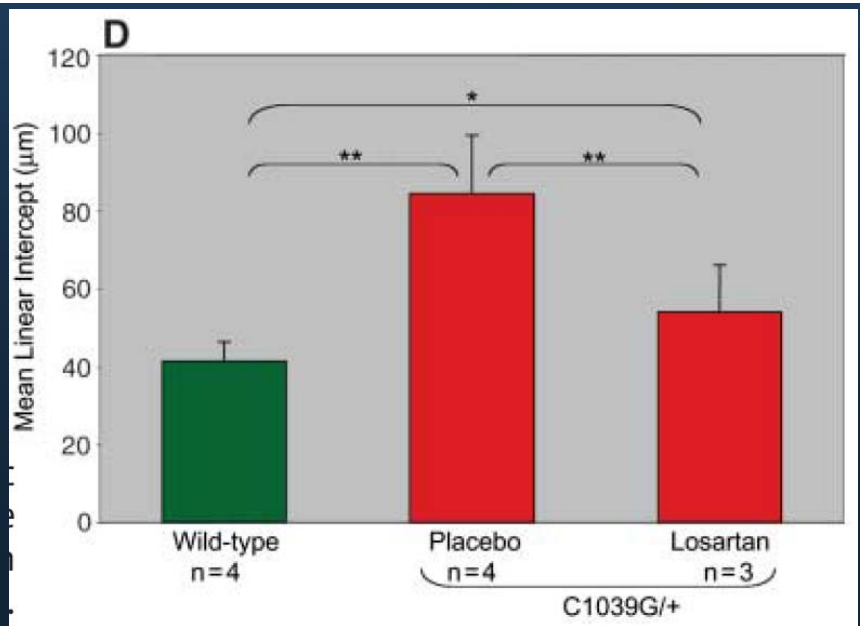

VVG
pSmad2
Wild-type
A
E
C1039G/+
Placebo
B
F
C1039G/+
NAb
1 mg/kg
C
G
C1039G/+
NAb
10mg/kg
D
H
I
Aortic root growth
mm growth / 2 months
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
†
*
**
††
Wild-type
n = 7
Placebo
n = 5
NAb 10 mg/kg
n = 6
NAb 1 mg/kg
n = 5
C1039G/+
J
Aortic wall thickness
micrometers
100
90
80
70
60
50
40
30
†
*
*
††
Wild-type
n = 7
Placebo
n = 5
NAb 10 mg/kg
n = 6
NAb 1 mg/kg
n = 5
C1039G/+
K
Aortic wall architecture
Score
4
3.5
3
2.5
2
1.5
1
*
**
***
†
Wild-type
n = 7
Placebo
n = 5
NAb 10 mg/kg
n = 6
NAb 1 mg/kg
n = 5
C1039G/+


VVG
pSmad2
Wild-type
C1039G/+ Placebo
C1039G/+ Propranolol
C1039G/+ Losartan
A
B
C
D
E
F
G
H
I
Aortic root growth
mm growth / 6 months
Wild-type n = 11
Placebo n = 10
Propranolol n = 7
Losartan n = 5
C1039G/+
J
Aortic wall thickness
micrometers
K
Aortic wall architecture
Score


Wild-type
A


Fbn1C1039G/+, Placebo
B


Fbn1C1039G/+, Losartan
C


D
Mean Linear Intercept (μm)
120
100
80
60
40
20
0
*
**
**
Wild-type
n=4
Placebo
n=4
Losartan
n=3
C1039G/+

Old Drug, New Hope for Marfan Syndrome

People with Marfan syndrome live with a ticking bomb. Their aortas, unless surgically replaced, gradually enlarge and weaken until they fatally rupture. But prompted by a new explanation of what causes Marfan syndrome, pediatric cardiologist Harry Dietz of Johns Hopkins University in Baltimore, Maryland, and his colleagues may have come up with a surprising tool to defuse this lethal situation: losartan, a drug already approved in the United States for use against high blood pressure. On page 117, they report that in a mouse model of Marfan syndrome, the drug prevents aortic aneurysms as well as lung problems sometimes seen in the condition.

"It's a beautiful story. It's one of the most classic examples of translational science I've seen in the cardiovascular arena," says Kenneth Chien, director of the Massachusetts General Boston. The study, he adds, "makes a very compelling case" that losartan should be tested immediately in people. In fact, Dietz's team has begun administering the drug to a few children with a severe form of Marfan syndrome who have rapidly deteriorating aortas. The National Institutes of Health (NIH) plans to start a large trial of the drug as soon as this fall.

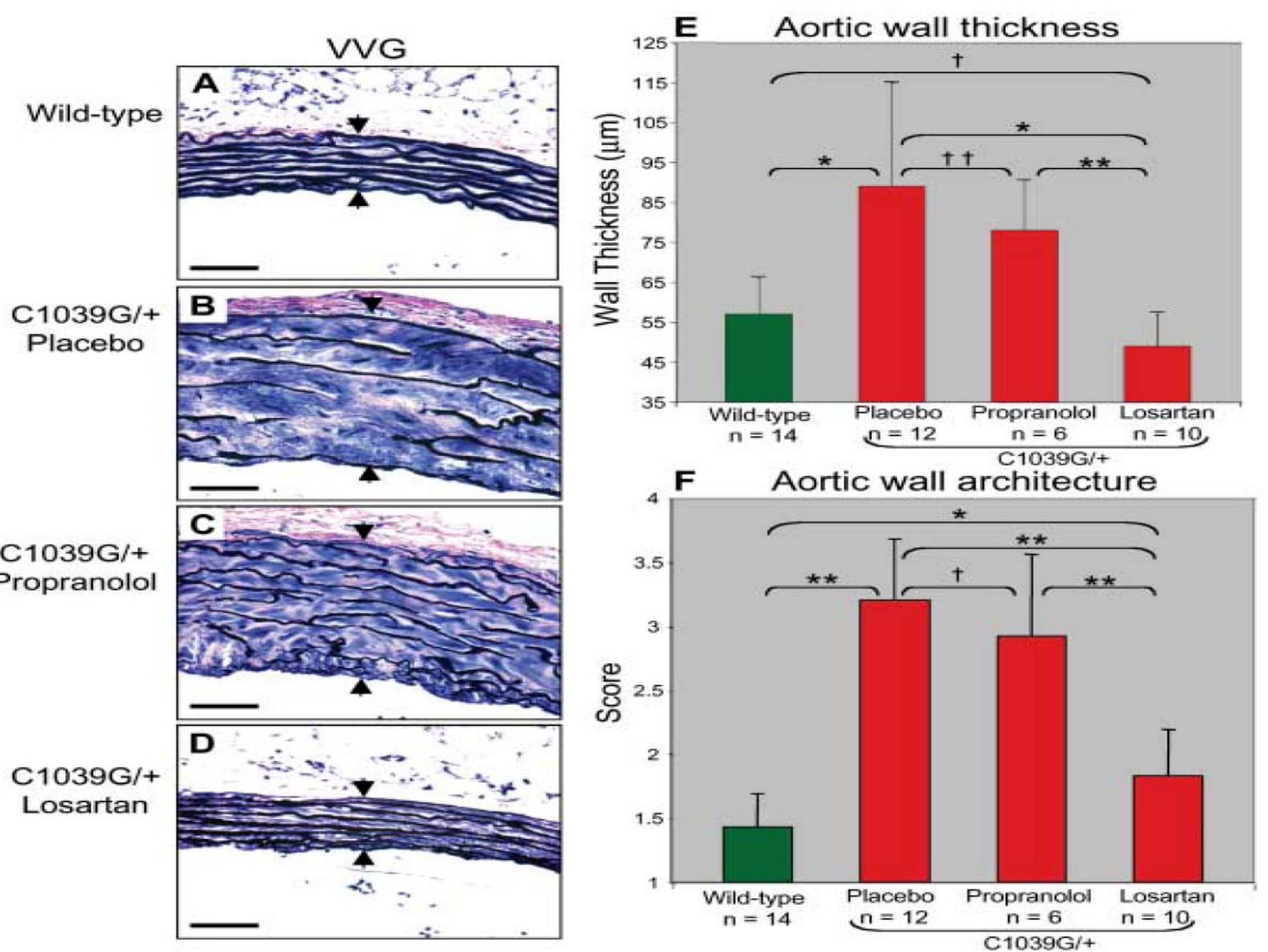
This enthusiasm is a far cry from the pessimism that has plagued the Marfan field. Experts once thought that a structural defect in connective tissue led to the aortic aneurysms, lung problems, and other features of Marfan syndrome. In 1991, Dietz and other researchers had reported that mutations in the gene encoding fibrillin-1 are responsible for the syndrome. This protein forms fibrils in the matrix outside cells, so the mutations were thought to rob elastic tissue of a key building

CONCLUSIONS

- Current data continue to support the therapeutic use of Losartan to lower blood pressure, beneficially modify tissue changes in hypertension and alter outcomes in hypertensive patients.

- Losartan continues to lead the clinical exploration of the pathological role of angiotensin II in cardiovascular morbidity and mortality.

감사합니다!


VVG
A
Wild-type
B
C1039G/+
Placebo
C
C1039G/+
Propranolol
D
C1039G/+
Losartan
E
Aortic wall thickness
Wall Thickness (μm)
125
115
105
95
85
75
65
55
45
35
†
*
*
††
**
Wild-type
n = 14
Placebo
n = 12
Propranolol
n = 6
Losartan
n = 10
C1039G/+
F
Aortic wall architecture
Score
4
3.5
3
2.5
2
1.5
1
*
**
**
†
**
Wild-type
n = 14
Placebo
n = 12
Propranolol
n = 6
Losartan
n = 10
C1039G/+