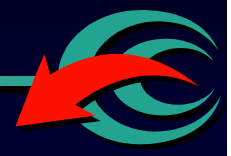
Mechanisms Linking Angiotensin II & Atherogenesis

Carlos M Ferrario, MD, FAHA,FACA, FACC
Professor and Director
Hypertension and Vascular Disease Center
Wake Forest University School of Medicine
Winston-Salem, North Carolina, USA

President and CEO
The Consortium for Southeastern Hypertension Control

Underlying Culprit: Inflammation



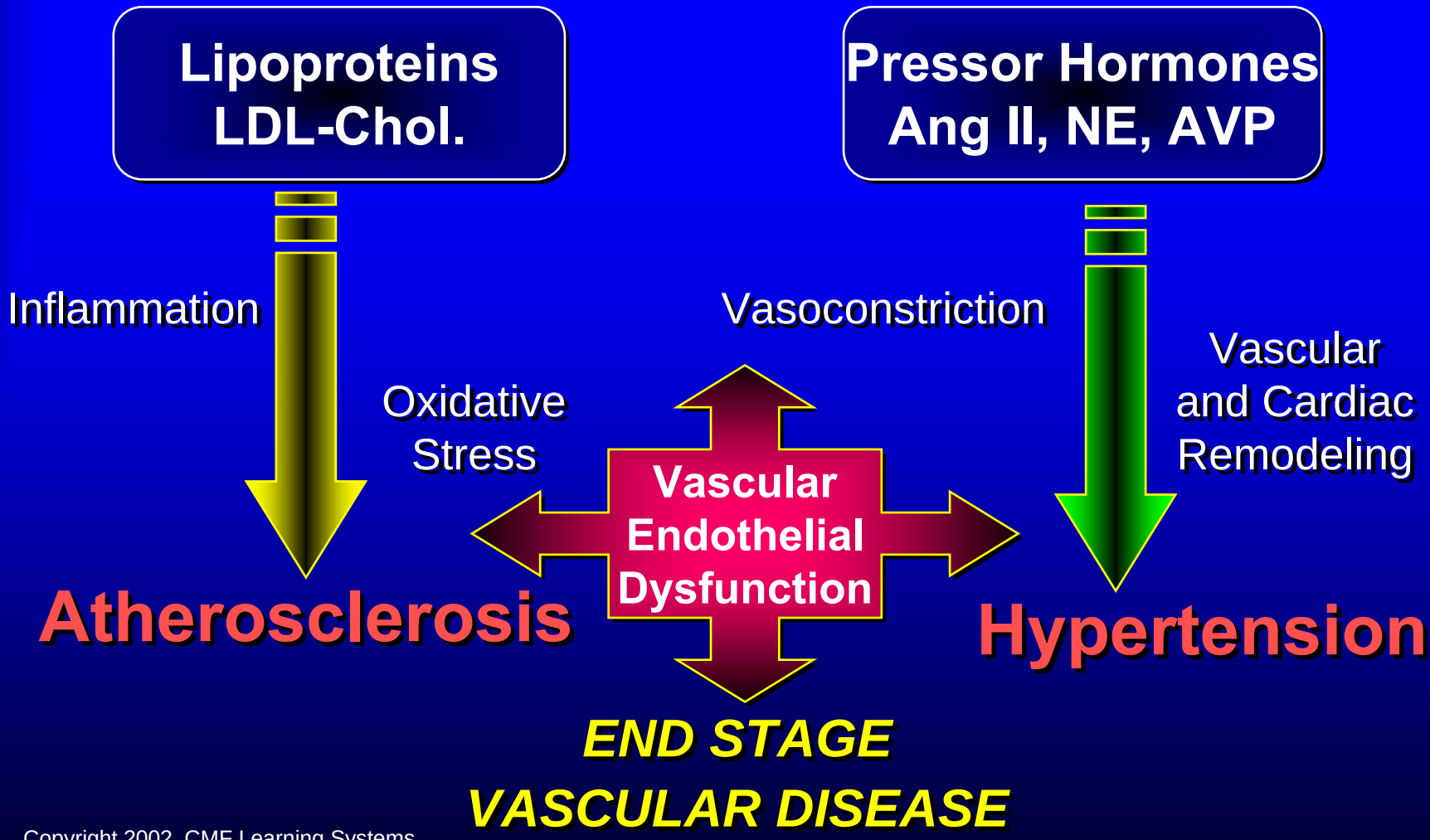
Hypertension

"…a pivotal role for inflammation in all phases of atherosclerosis from the initiation of the fatty streak to the culmination in acute coronary syndrome (plaque rupture)."

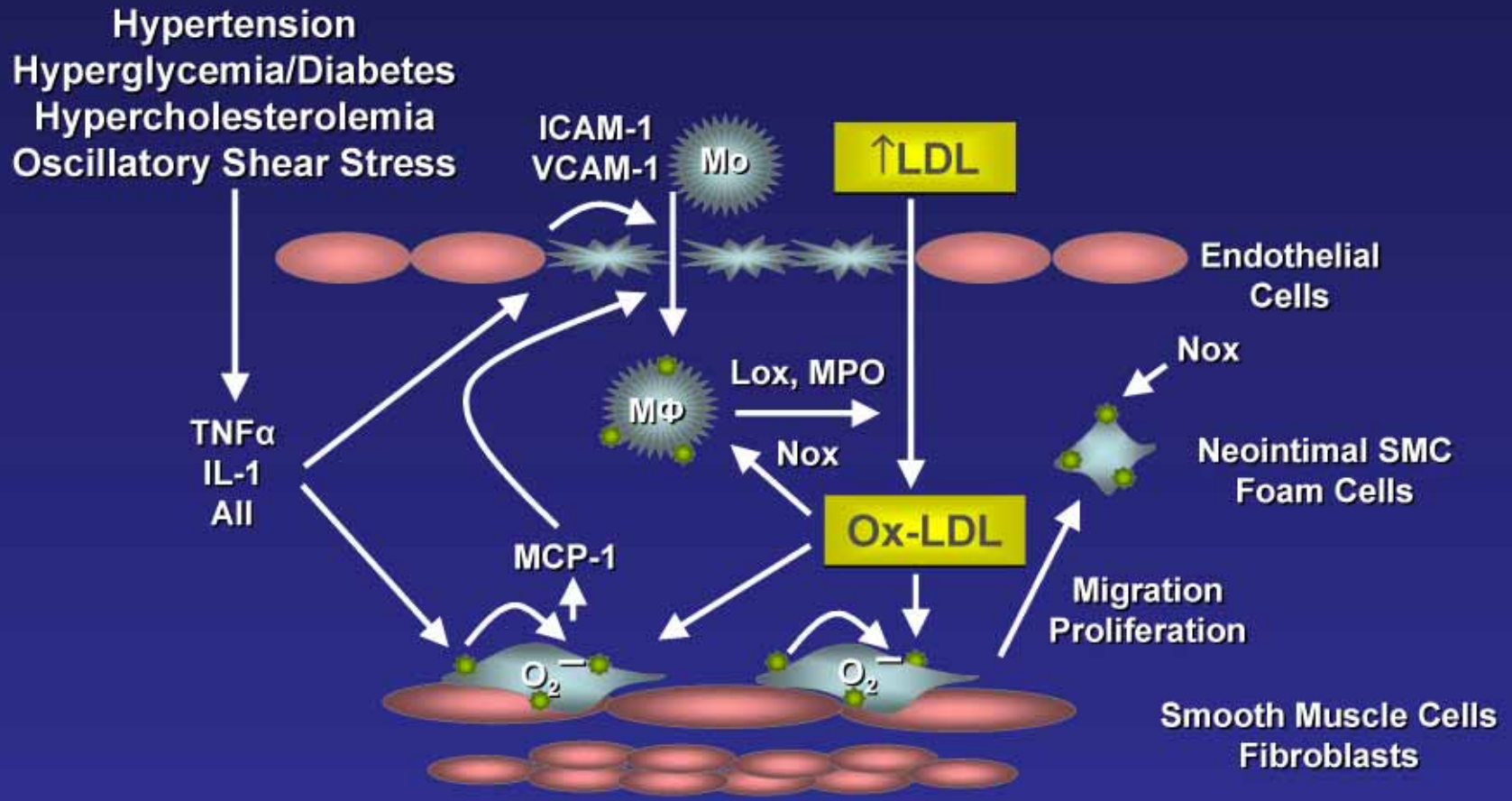
Dyslipidemia

Jialal et al. Hypertens 2004;44:6-11.

Current Concepts



Risk Factors, Oxidative Stress, and Early Atherosclerosis



Reprinted from *American Journal of Cardiology*, 87(suppl), Weiss D et al, Angiotensin II and atherosclerosis, 25C–32C, 2001, with permission from Excerpta Medica.

Managing Global Risks

Venus Consoling Love
Francois Boucher

Metabolic Syndrome

Truncal Obesity

(waist ≥ 40 M; ≥35 F)

Insulin Resistance

(fasting glucose > 110 mg/dL)

Dyslipidemia

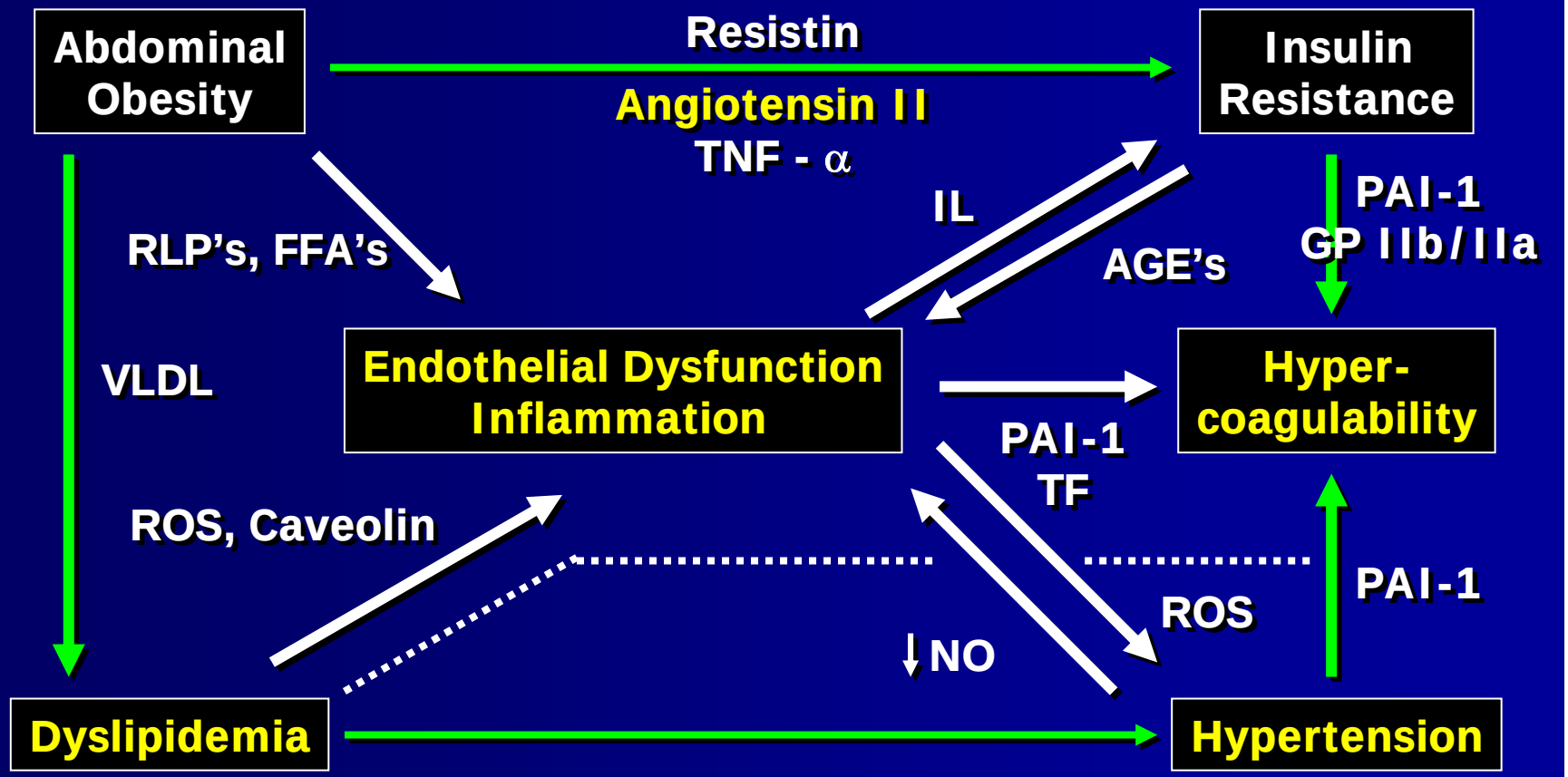
TG (150 mg/dL)
HDL-C (M < 40 mg/dL; F mg/dL)
Small dense LDL

Hypertension (≥ 130/85 mm Hg)

Hypercoagulability

Endothelial and Vascular Dysfunction

PATHOPHYSIOLOGY:
Metabolic Syndrome

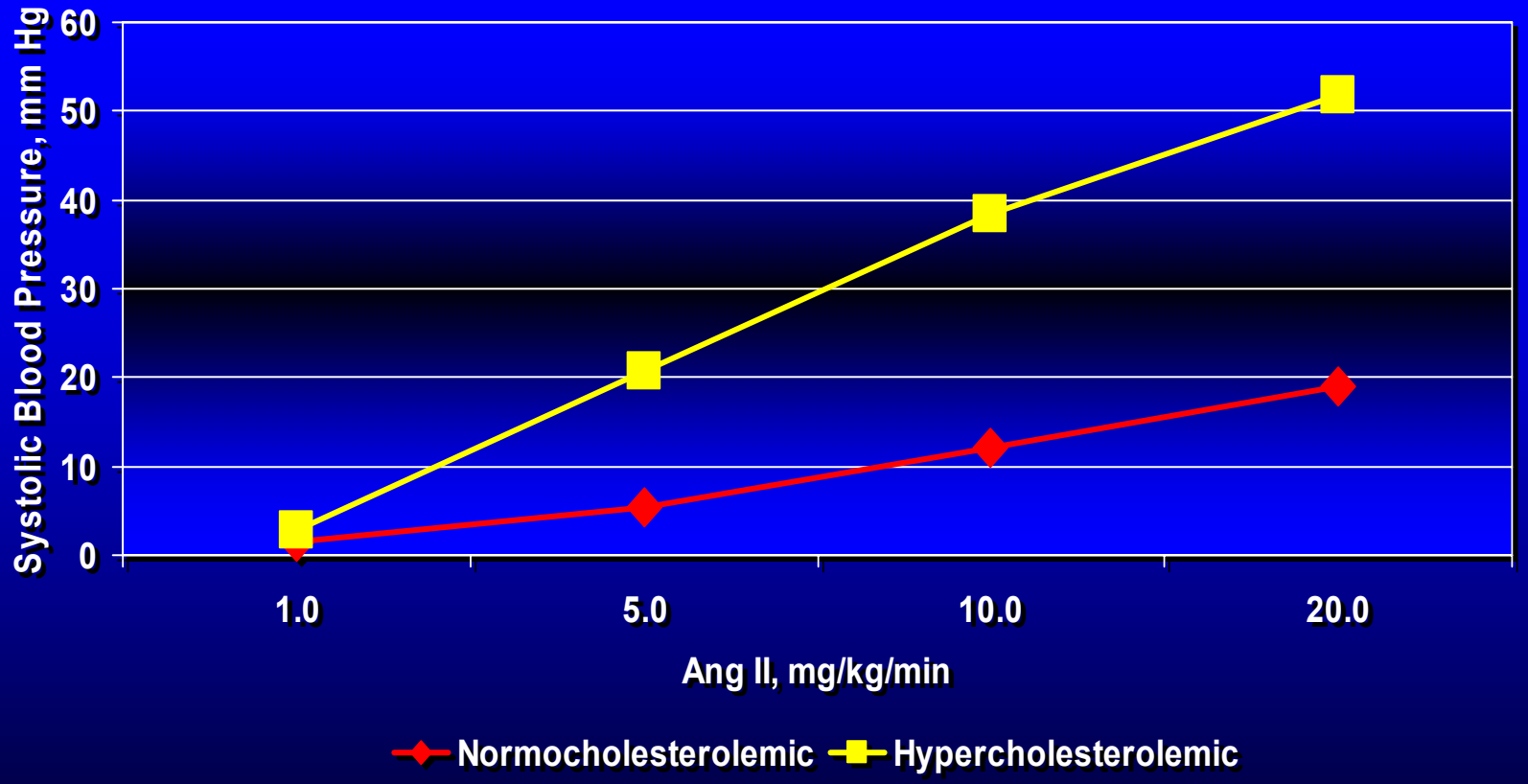


Adapted from R Vogel, MD

Vascular Actions of Ang II

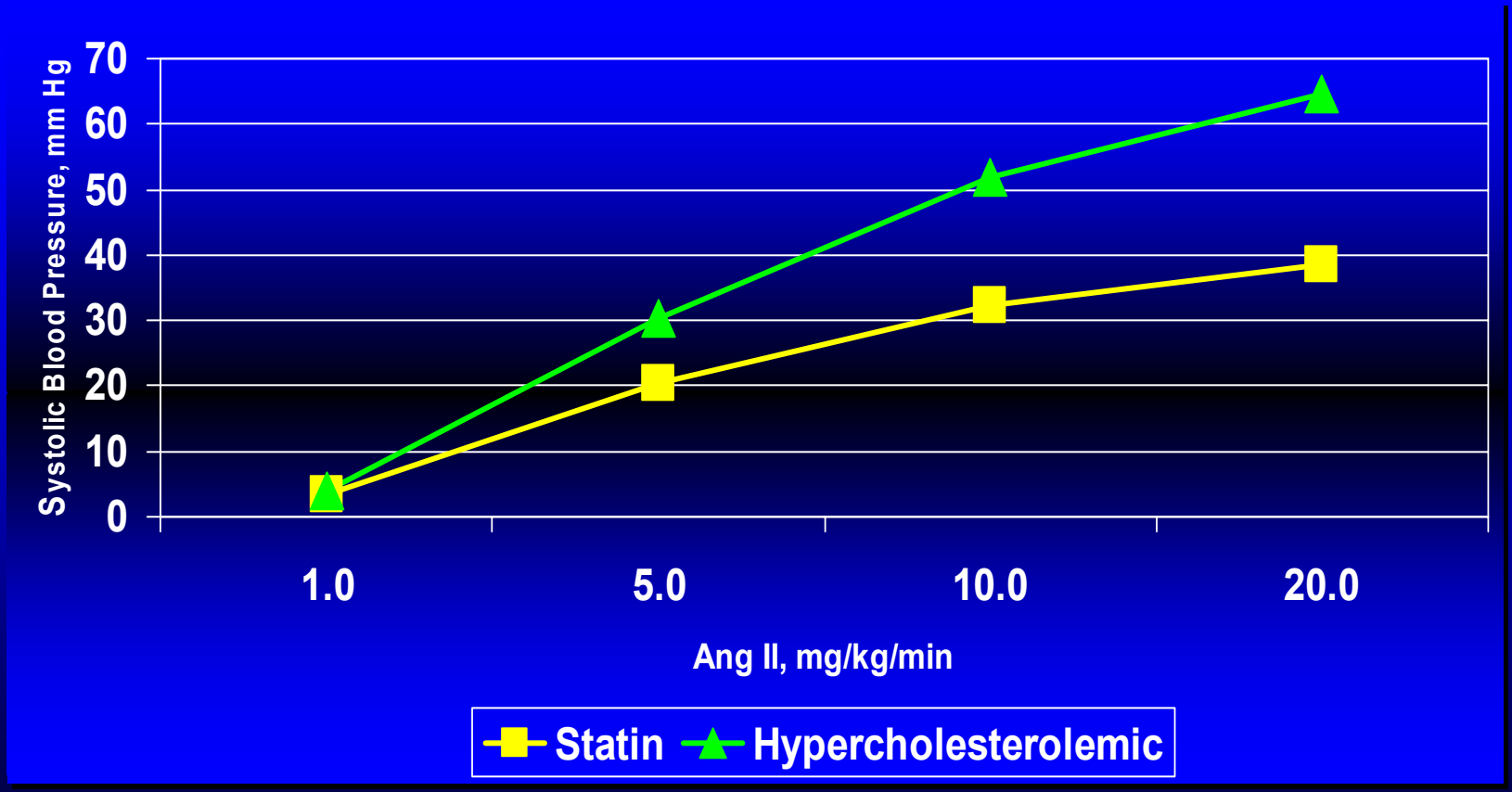
- Increase in superoxide anion production;
- Smooth muscle proliferation;
- Decrease in EDRF
- Increase monocyte adherence to endothelium
- Inhibition of plasminogen activation;
- Lipoxygenase production by macrophages;
- increase oxidase LDL;
- Increase activity of NADH/NADPH oxidase.

Hypercholesterolemia Augments Vasoconstrictor Responses to Ang II



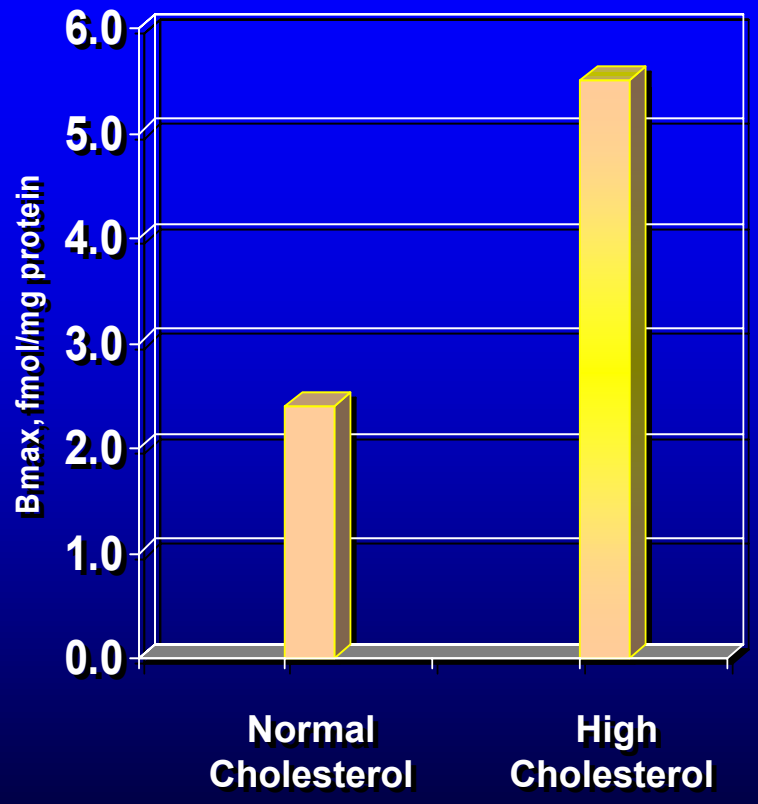
Nickenig et al. Circulation 1999;100:2131-2134

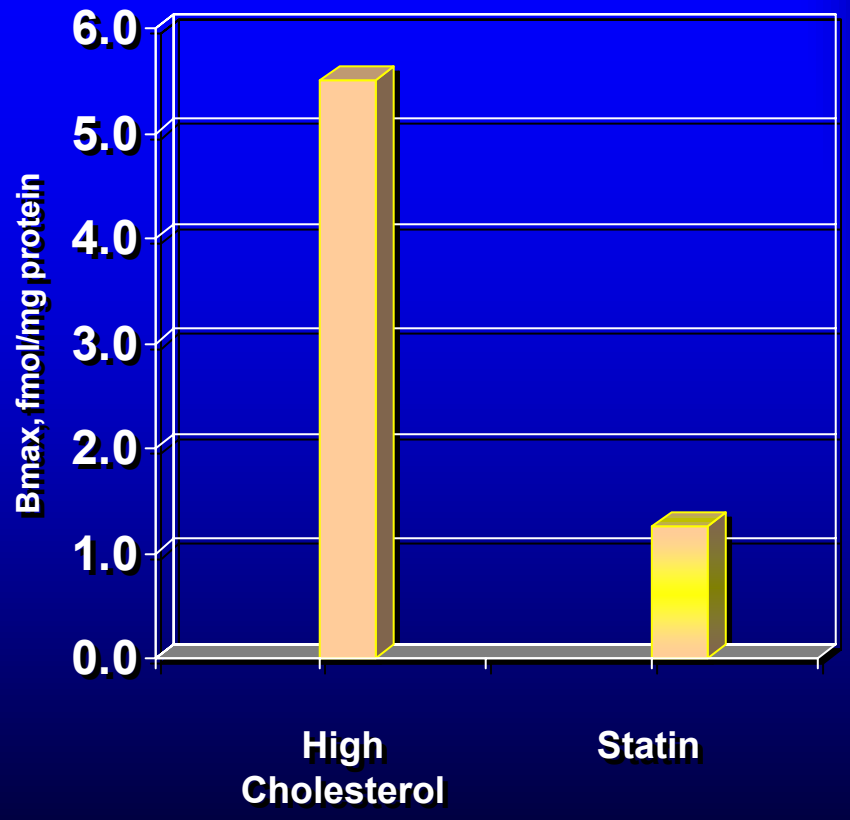
Statins Reduced Vasoconstrictor Responses to Ang II in Normotensive Hypercholesterolemic Subjects



Nickenig et al. Circulation 1999;100:2131-2134

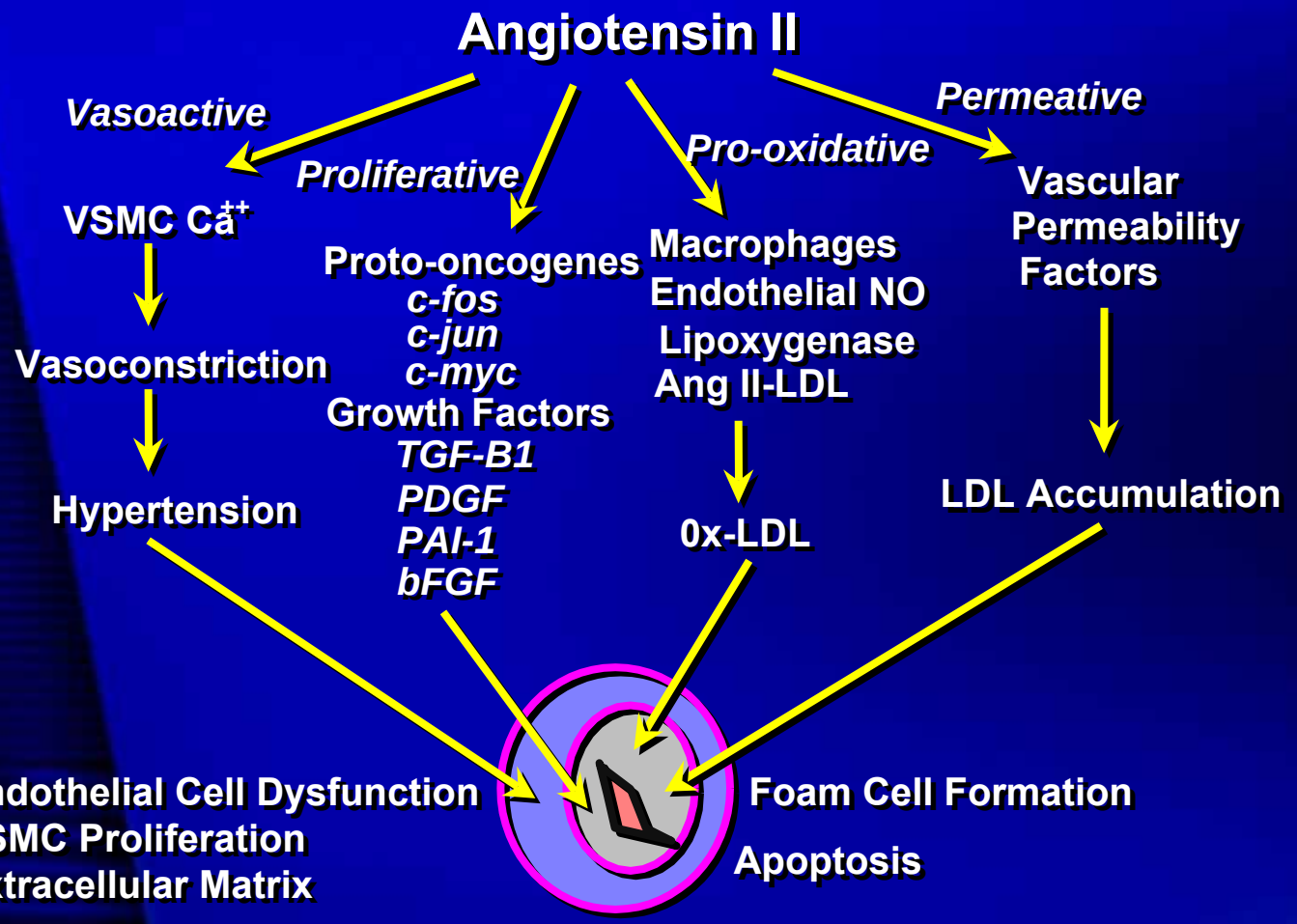
Effect of Cholesterol and Statins on Platelet AT_1 Receptor Density





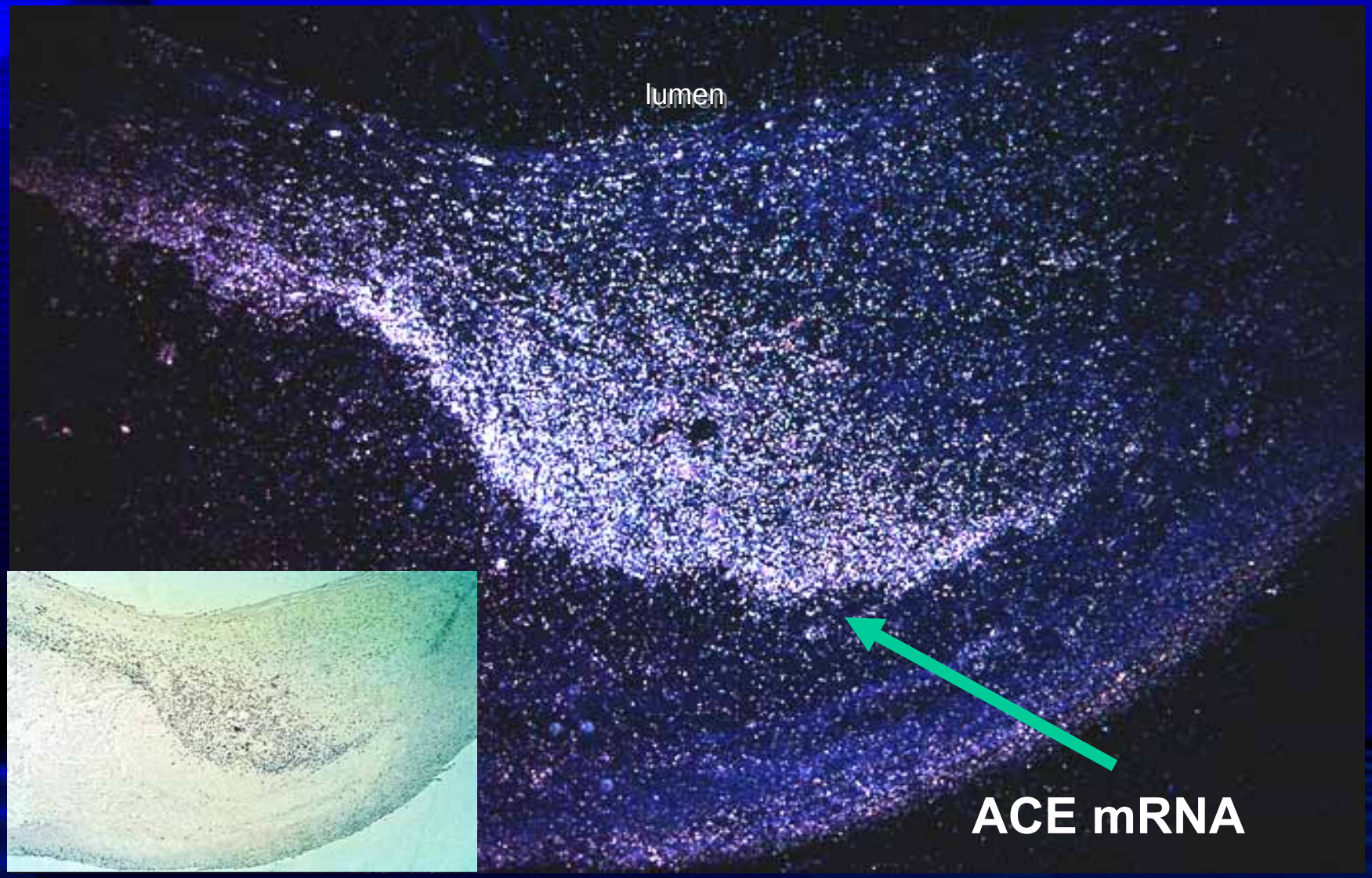
Nickenig et al. Circulation 1999;100:2131-2134

Ang II and Atherosclerosis



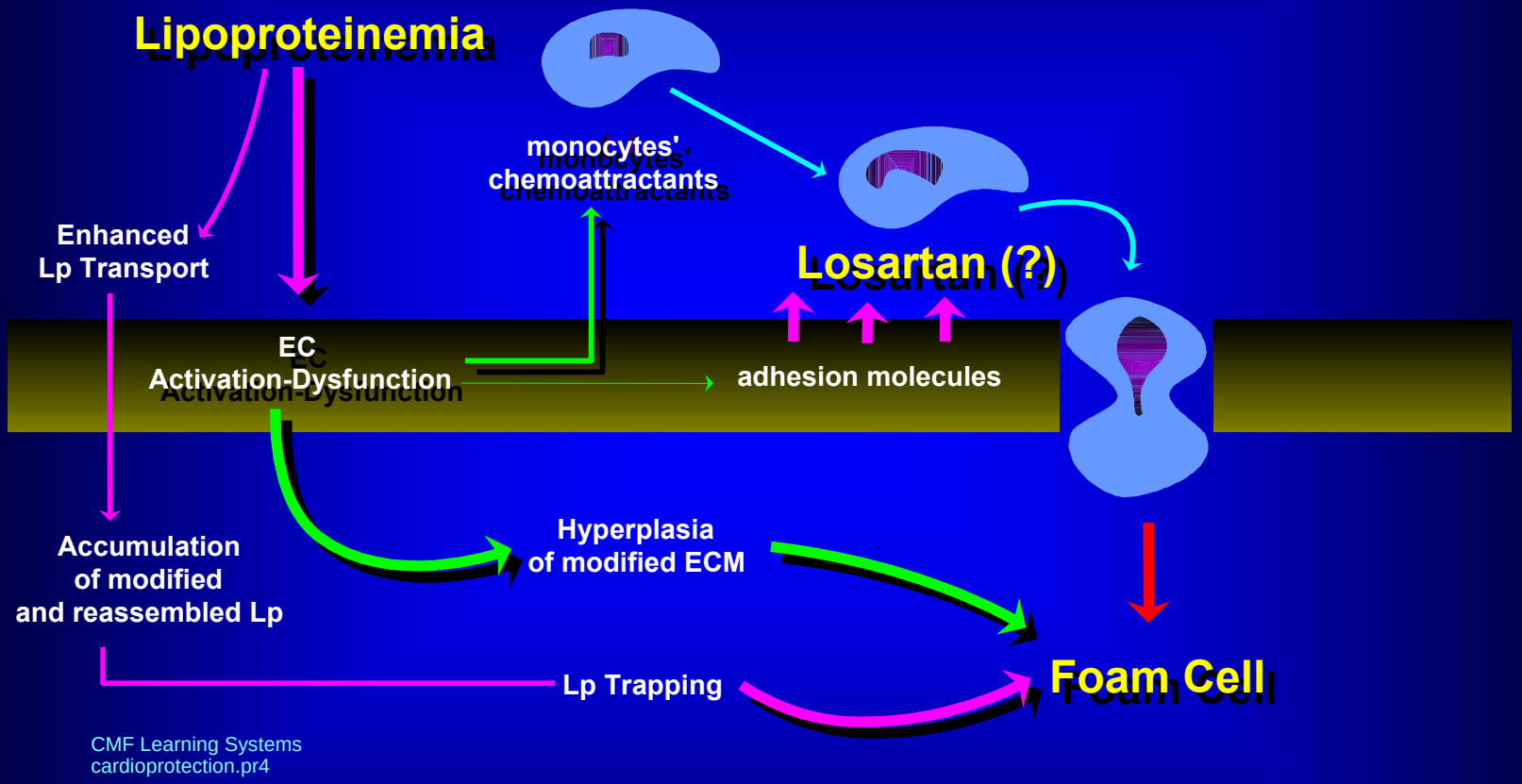
Occlusive Coronary Artery Atherosclerosis

VASCULAR RAS



Fukuhara et al. *Hypertension*. 2000;35:353-359

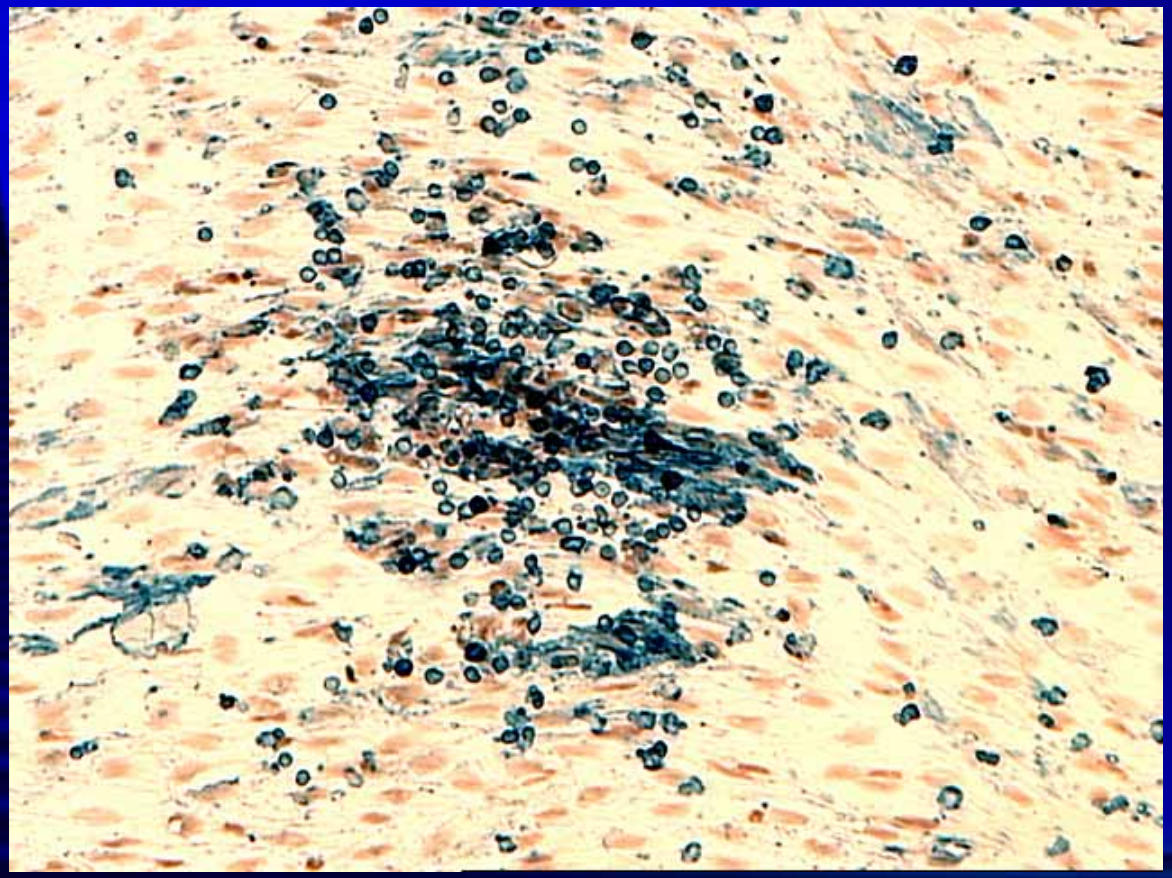
Ang II and Atherosclerosis



Strawn & Ferrario. J Cardiovasc Pharmacol 1998; 33:341-351

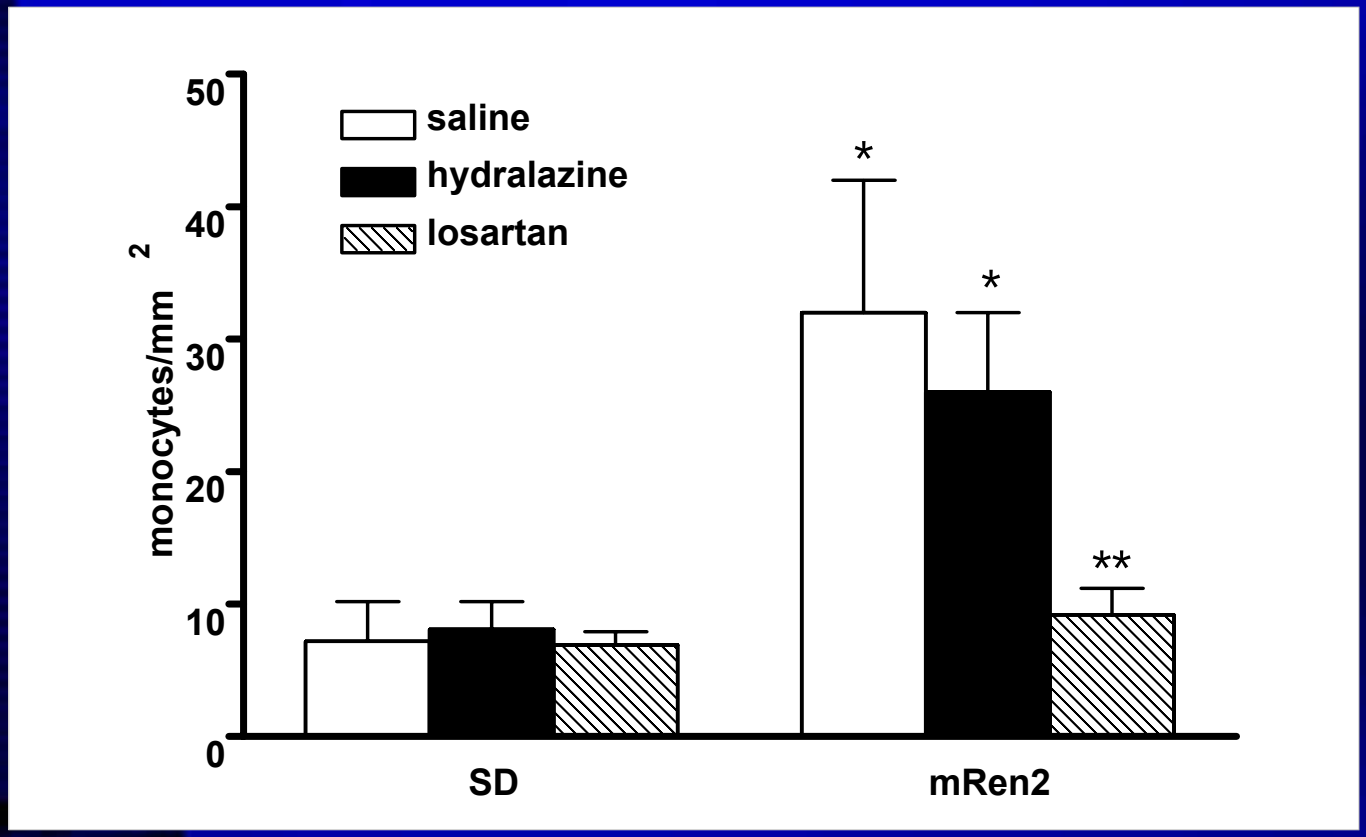
MONOCYTES ADHERENCE TO VASCULAR ENDOTHELIUM

[mRen2]27 Transgenic Hypertensive Rats



Strawn & Ferrario. J Cardiovasc Pharmacol 1998; 33:341-351

ARB and Vascular Protection



Number of monocytes adhered to vascular endothelium (Hautchen technique).

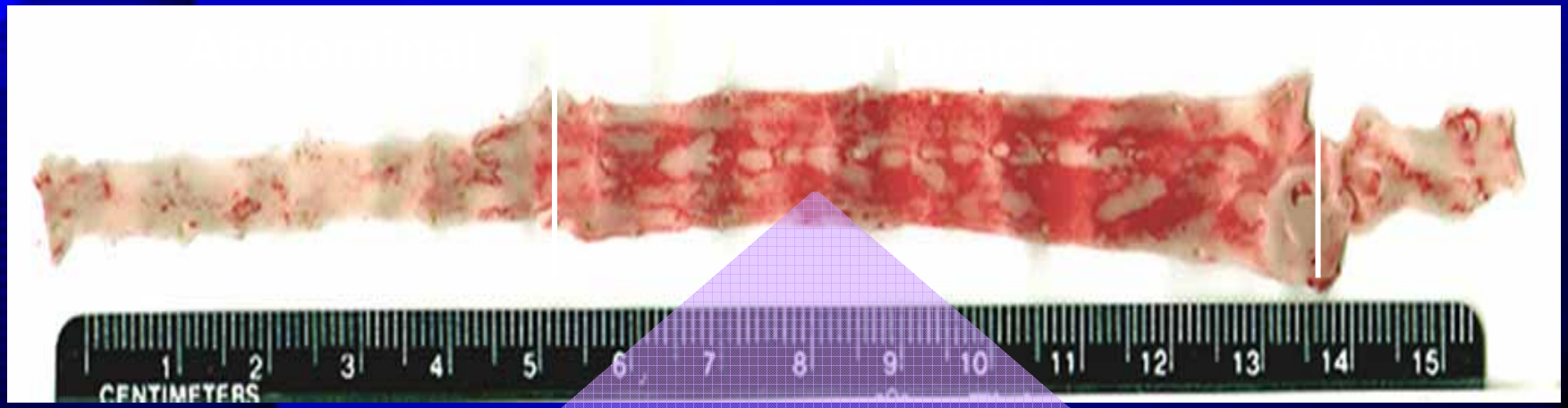
Strawn & Ferrario. J Cardiovasc Pharmacol 1998; 33:341-351

Experimental Atherosclerosis

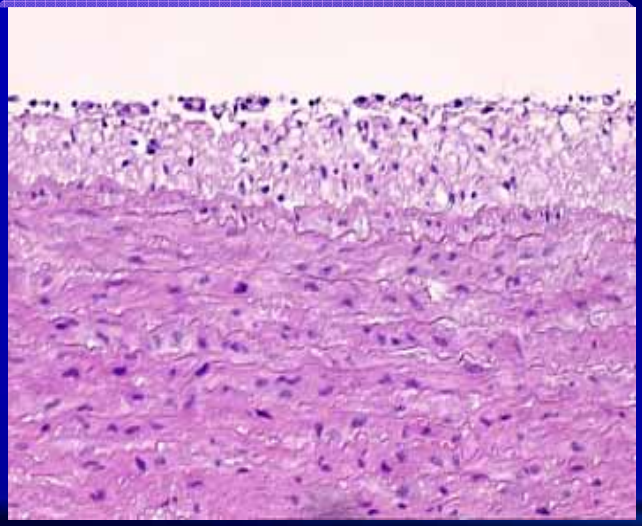
Cynomolgus Monkeys (Macaca Fascicularies)

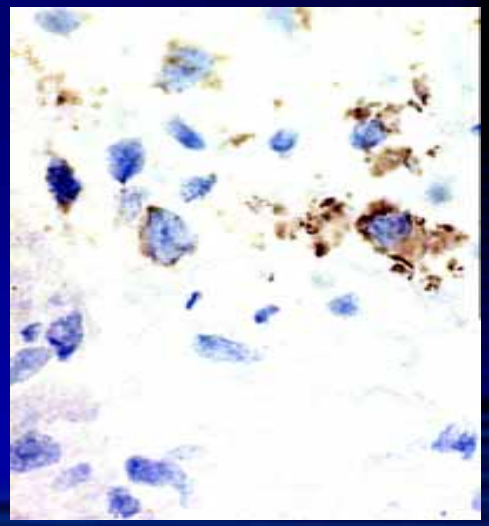
- Spontaneous atherosclerosis (Prathap, 1973);
- Diet-induced atherosclerosis bears high similarity with human lesions;
- Coronary lesions similar to humans (Stary and Manilow, 1982)
- Lesion progression from initial foam cell accumulation (Small et al., 1984)
- Carotid atherosclerosis correlates with plasma lipid concentrations (Kaplan et al., 1984)
- Plasma LDL uptake increased in aortas with diet-induced fatty streaks (Ghosh et al. 1987)

Aorta Fatty Streak in Cynomolgus Monkeys



- Fatty streak confined to intima
- Composed of macrophage foam cells

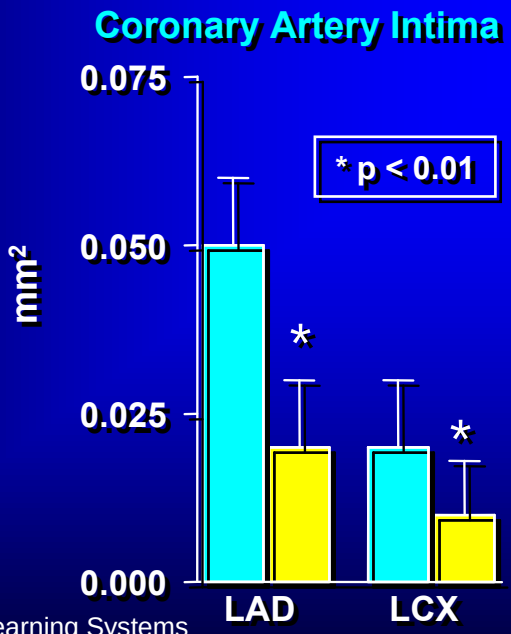


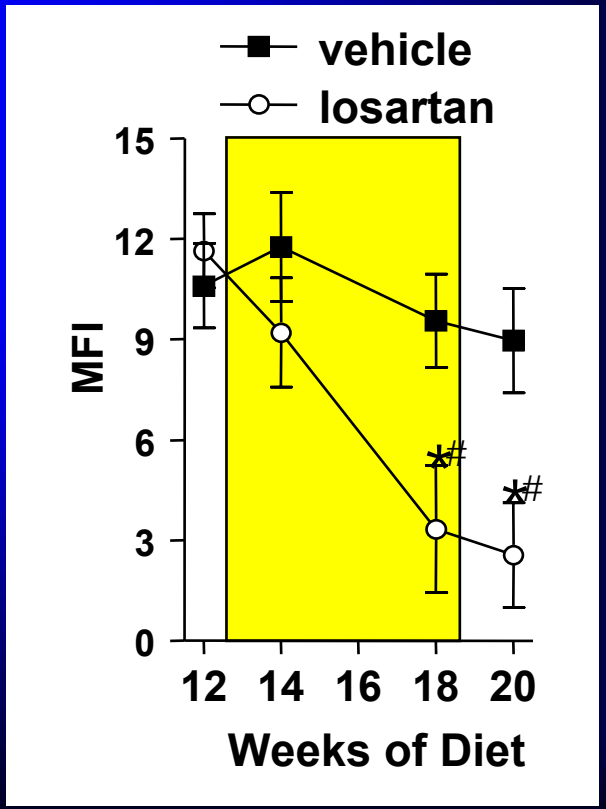


Losartan and Prevention of Atherosclerosis

Control

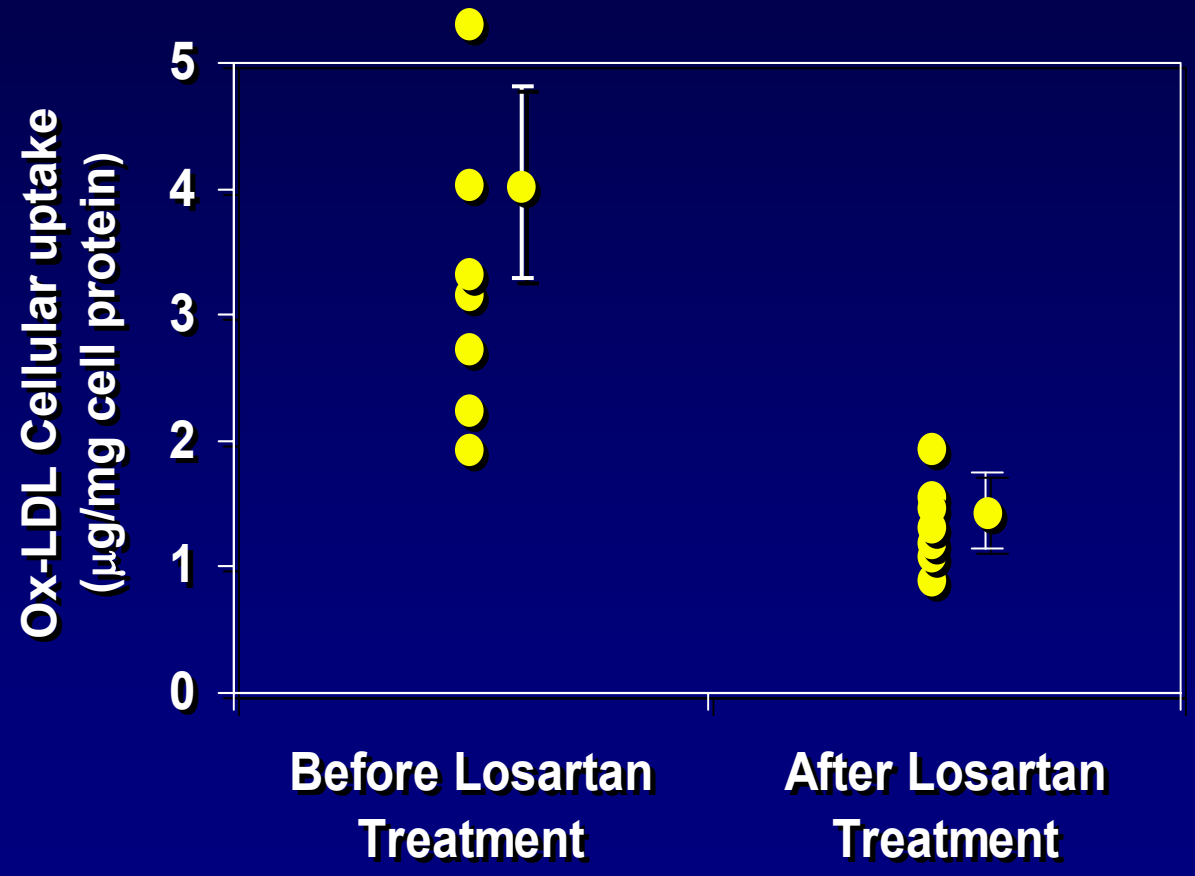
Losartan





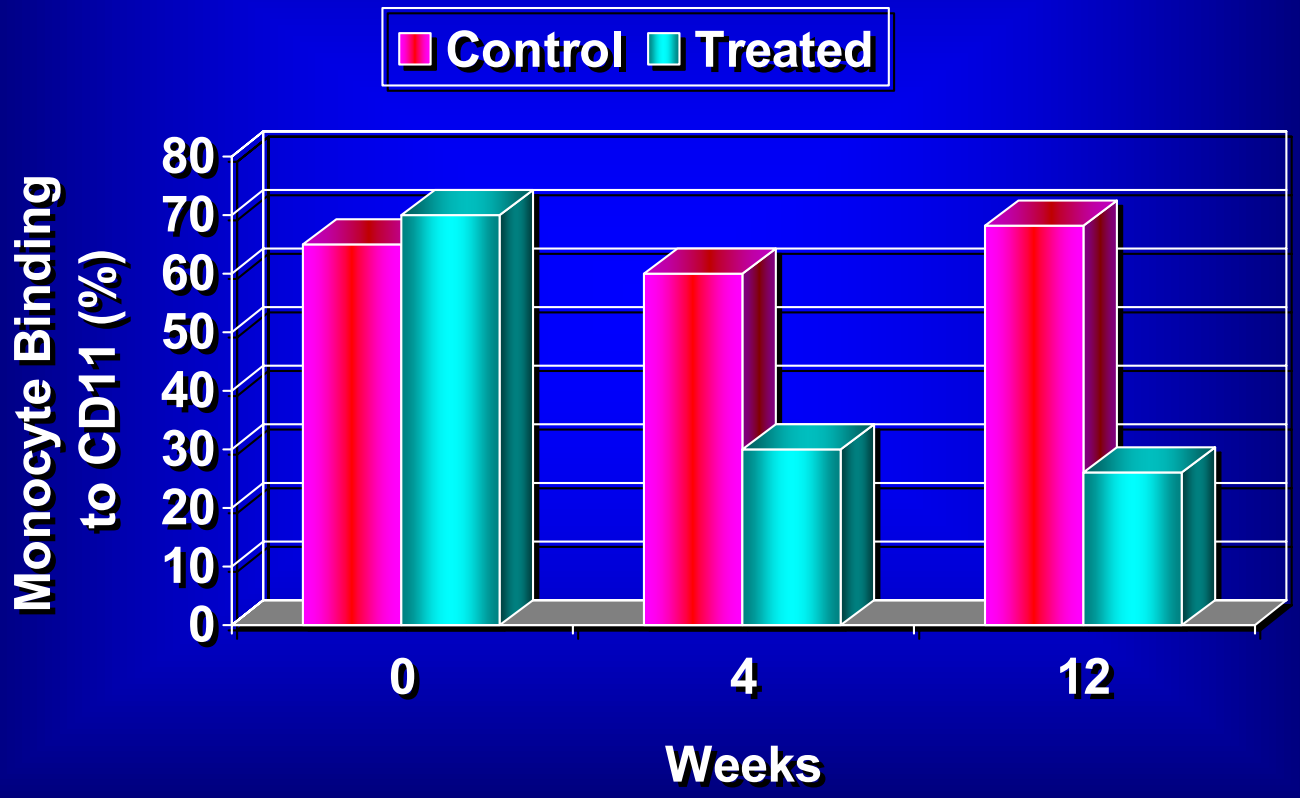
Strawn et al. Circulation, 2000

Monocyte-Derived Macrophages from Hypercholesterolemic Patients



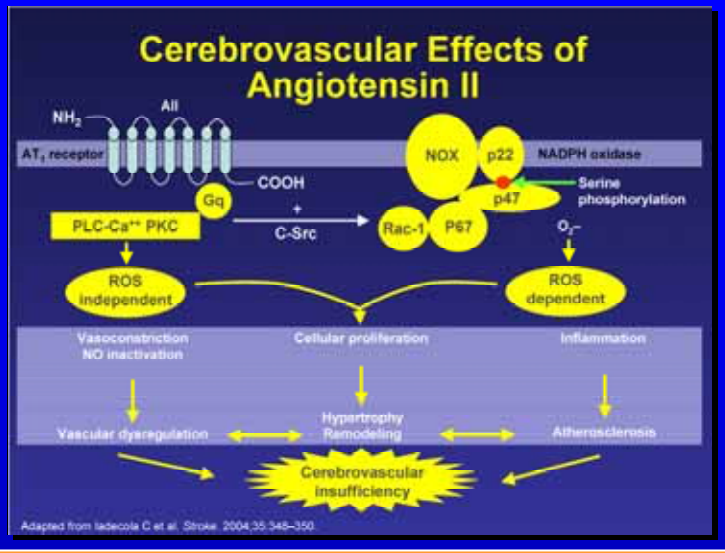
Hayek et al., BBRC 273:418, 2000

Angiotensin II AT_1 Receptor Blockade Reduces Monocyte CD11b Expression in Patients with Coronary Artery Disease



Khan et al., J Am Coll Cardiol 2001;38:1662-1667

EVIDENCE BASED MEDICINE



Can we translate basic mechanisms of the role of Ang II in atherogenesis to prevention of vascular disease?

THE LIFE TRIAL:
Stroke End-Points

Comparative Adjusted Risk Reduction (%)

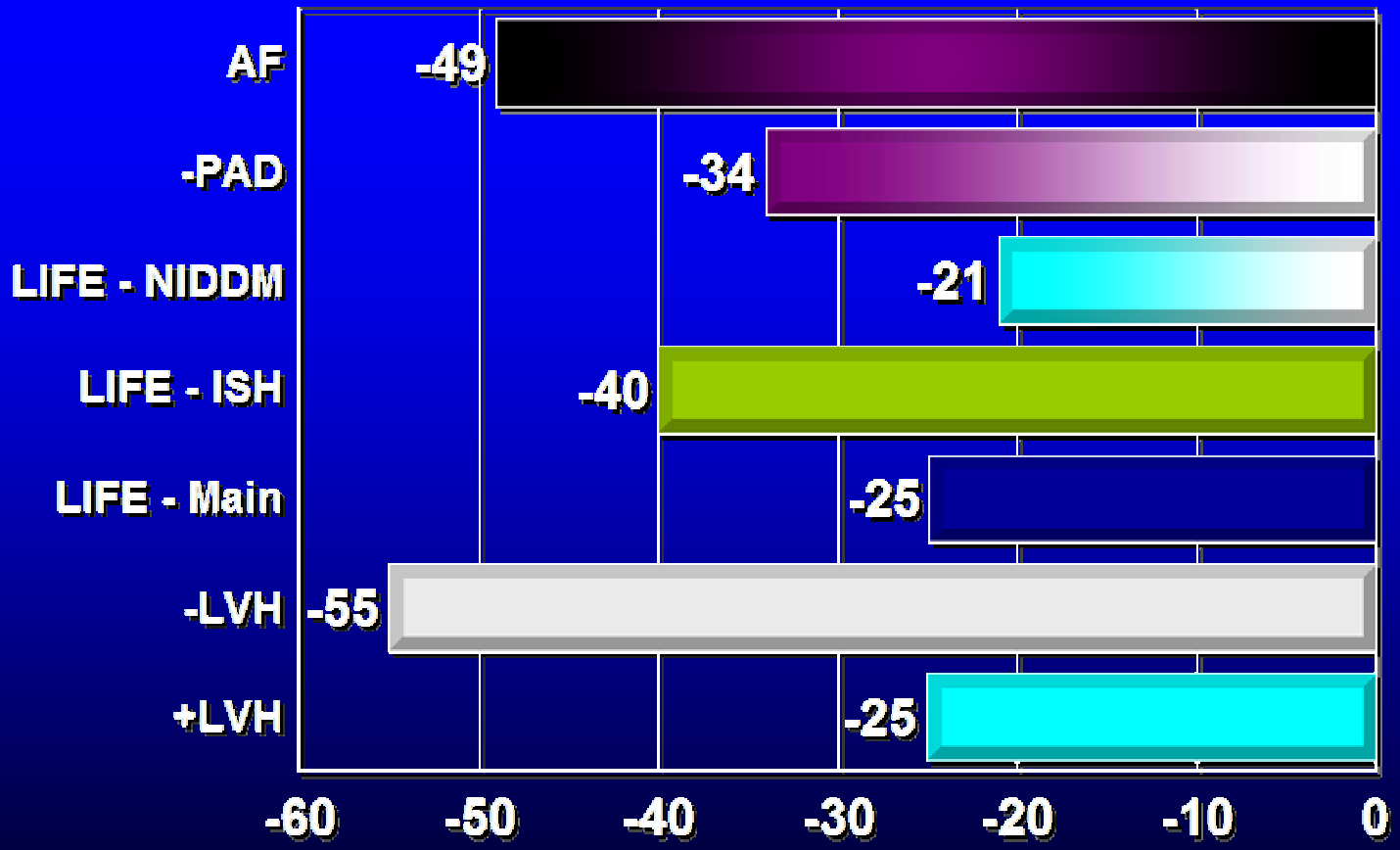
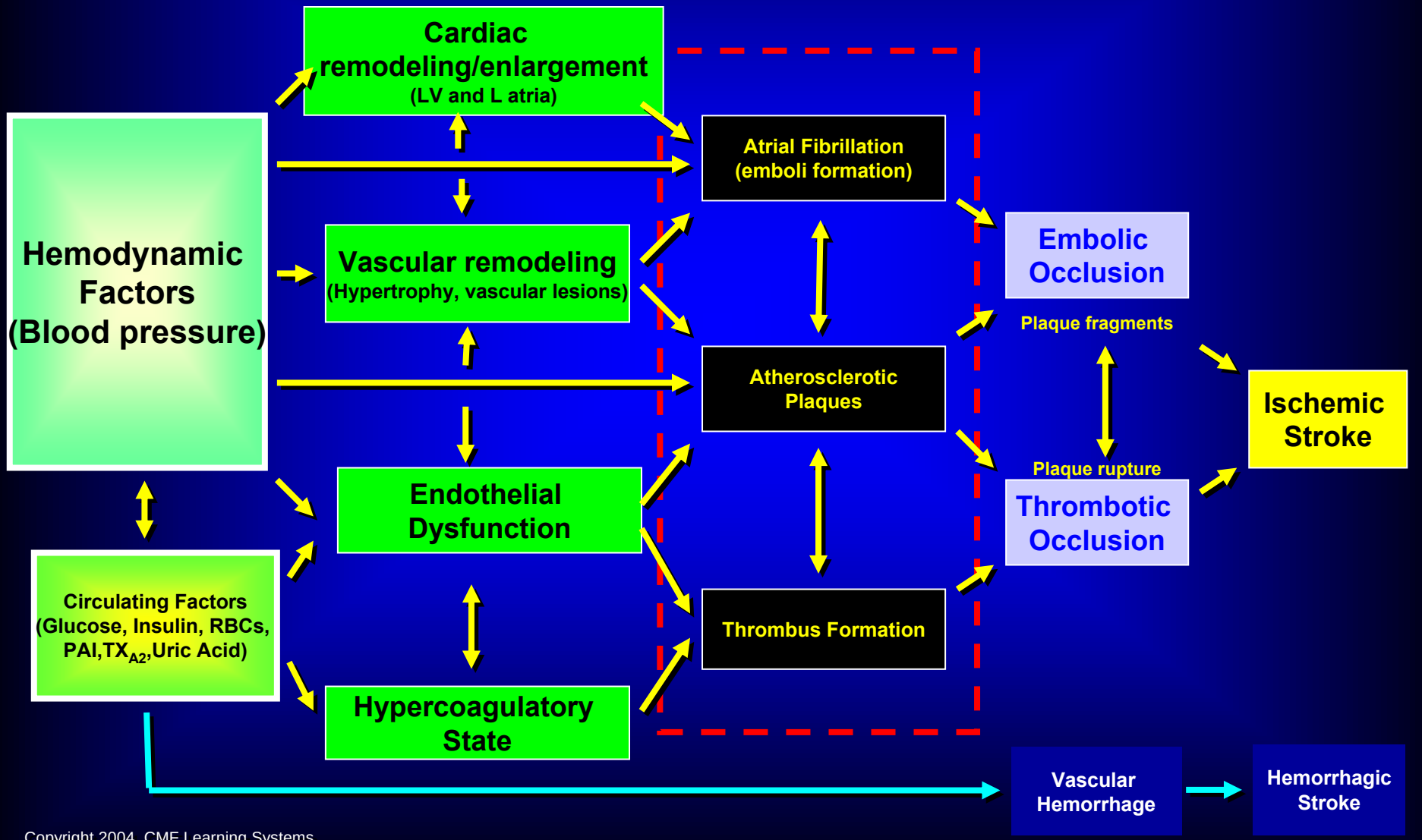


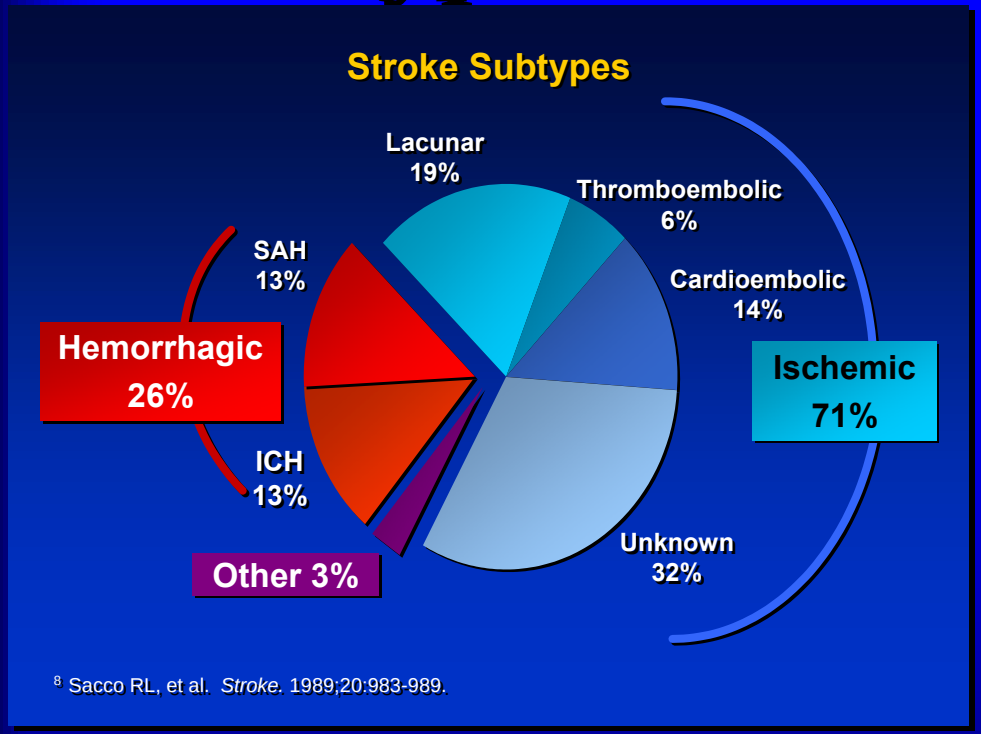
Chart Footnote

Understanding Vascular Atherosclerotic Disease

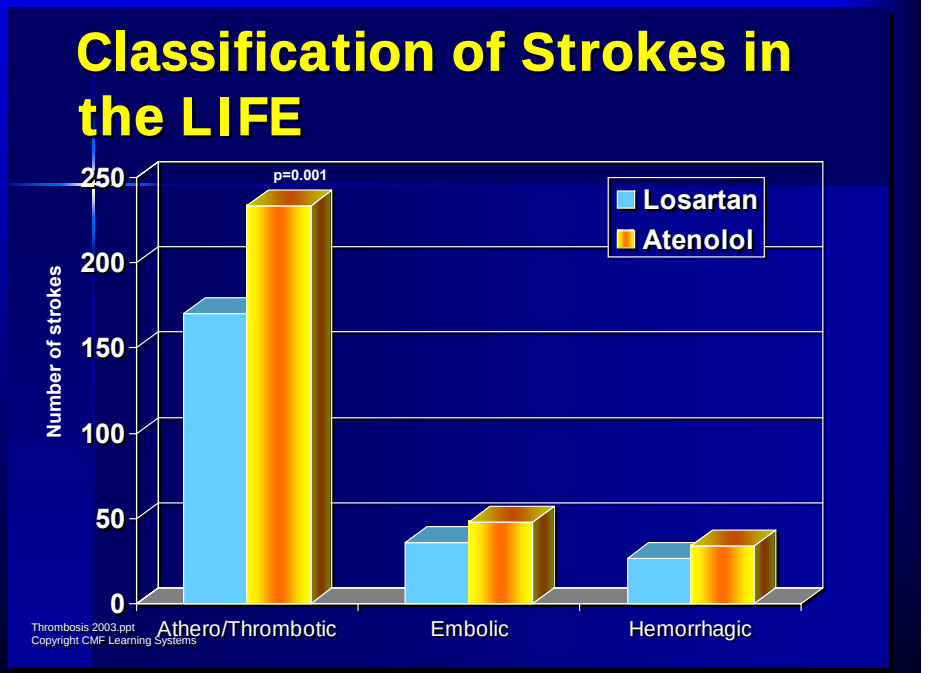
"STROKE: Mosaic of Interacting Factors"



Hypertension and Strokes

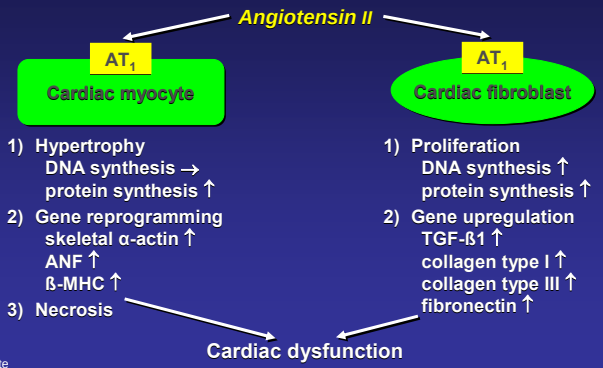


[8] Sacco RL, et al. *Stroke.* 1989;20:983-989.



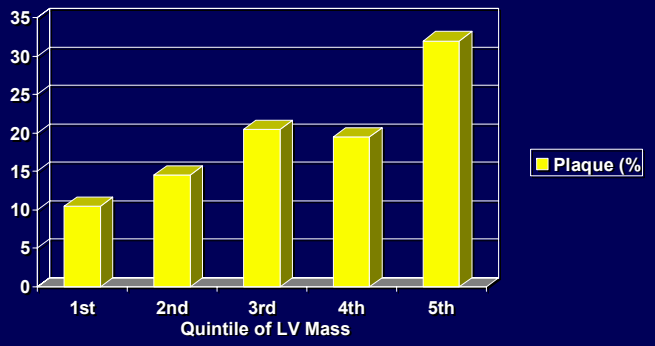
LOSARTAN AND CARDIOVASCULAR REMODELING

Angiotensin II (AII) and LVH



footnote
Adapted from Kim S et al. *Pharmacological Reviews*. 2000;52:11–34.

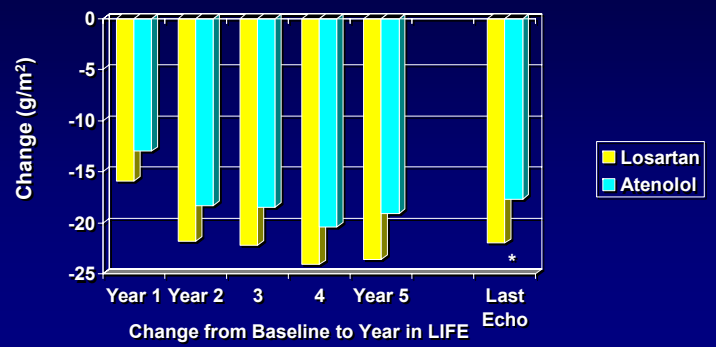
Association of Carotid Atherosclerosis with LV Mass in Employed Adults



Roman et al: *J Am Coll Cardiol* 1995;25:83-90

LIFE Echo: Change in LV Mass Index

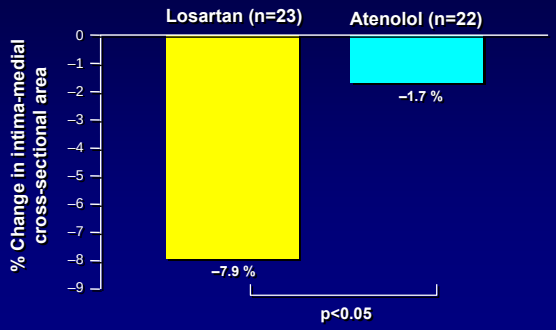
* p=0.021, adjusted for baseline LVMI and baseline & in treatment BP



6 Devereux et al.: *Circulation* 110: 1456-1462, 2004.

LIFE: Losartan vs. Atenolol Reduced Carotid Artery Hypertrophy

Intima-medial thickness—change from baseline at year 3



7 Olsen ML et al Circulation 106(19): II-574, 2002

Thrombosis

Platelets in Hypertension

1. **Morphological Changes**

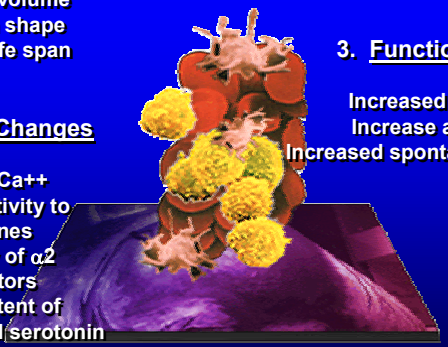
Increased volume
Change in shape
Reduced life span

2. **Biochemical Changes**

Elevated free Ca++
Increased sensitivity to catecholamines
Higher density of $\alpha 2$ adrenoreceptors
Decreased content of catecholamines and serotonin
Reduced uptake of catecholamines
Reduced nitric oxide

3. **Functional Changes**

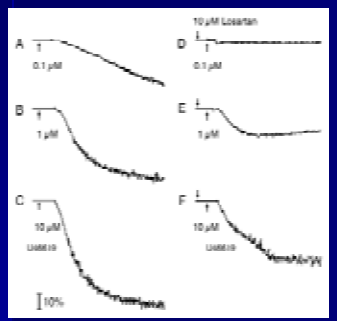
Increased aggregability
Increase adhesiveness
Increased spontaneous aggregation

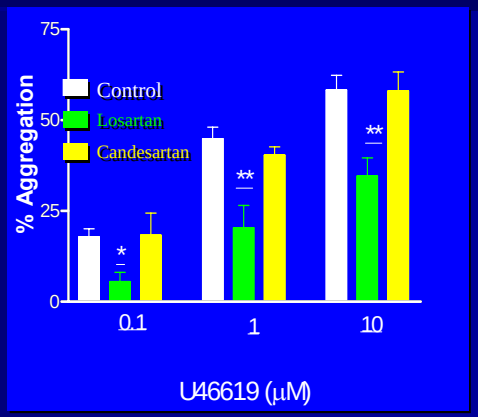


MSD.ppt

Ferrario, CM 2002

Losartan but not Candesartan Interacts with the Platelet TxA_2 receptor





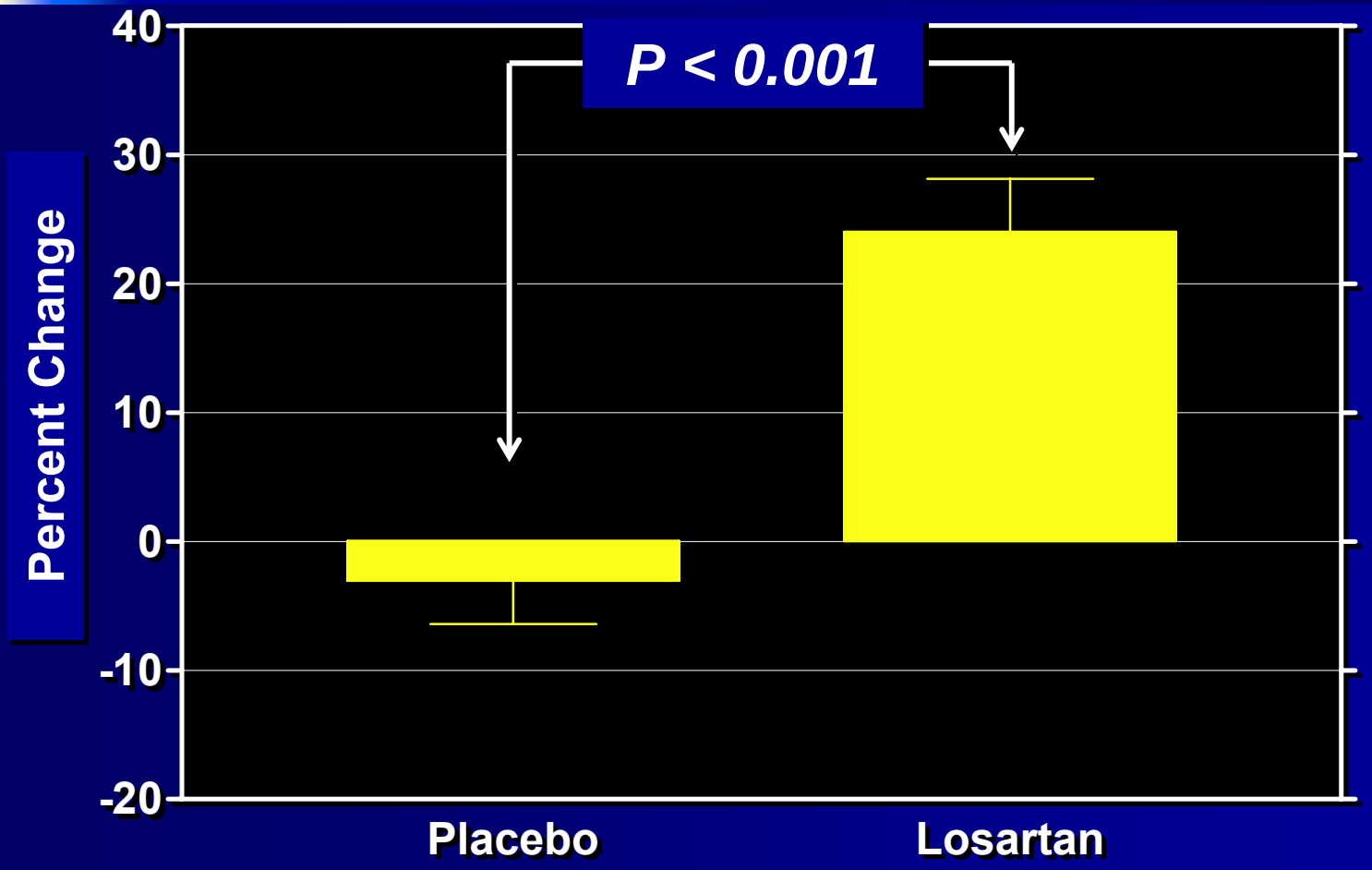
Li et al. J Pharmacol Exp Ther 1997; 281(3):1065-1070.
Li et al J Cardiovasc Pharmacol 1998; 32(2):198-205.

Li et al J Pharmacol Exp Ther 2000; 292(1):238-246.

CMFThromboxane.ppt

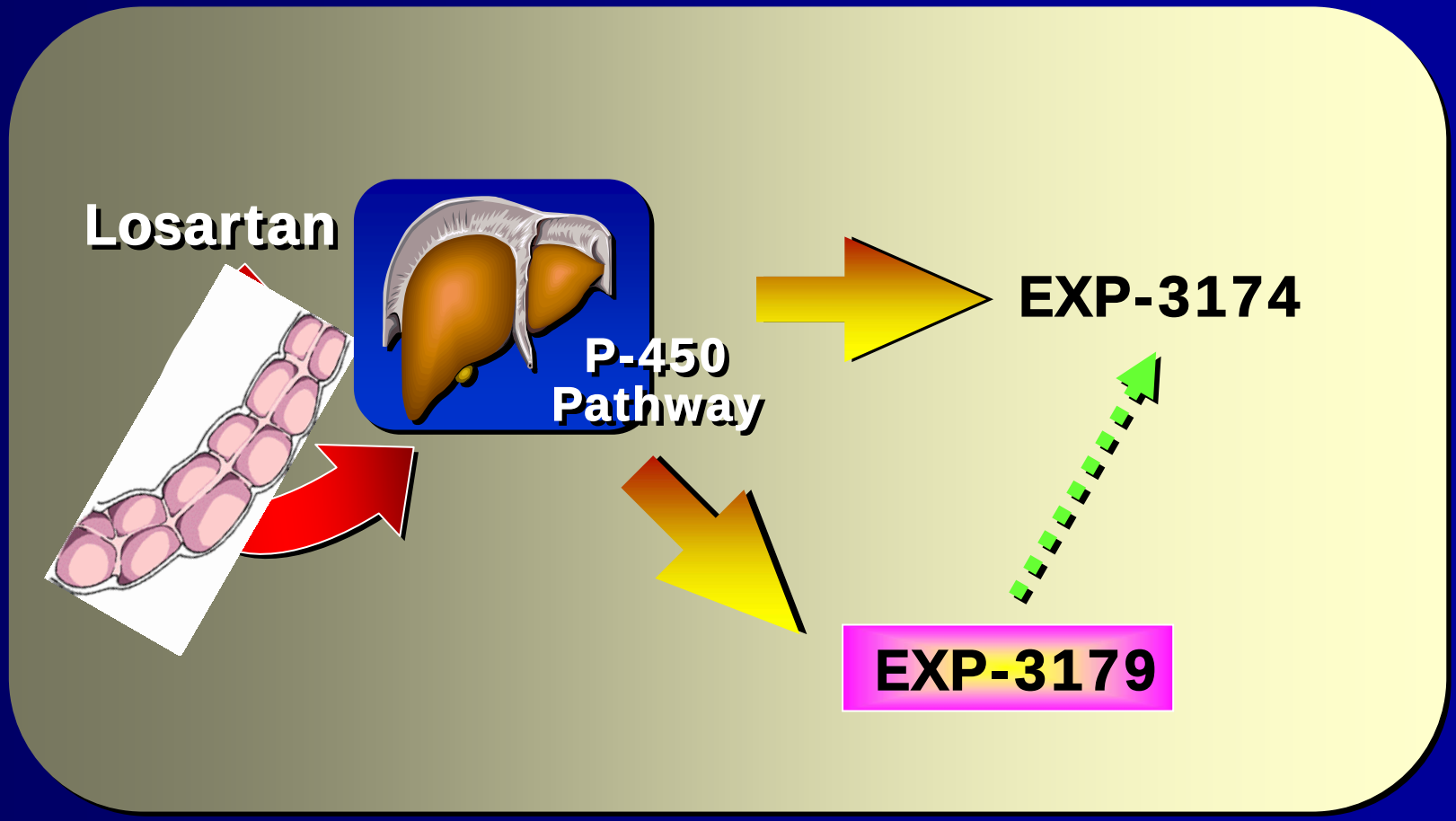
Life Thrombosis 2003.ppt

Changes in TRA-EC_{50} Extent



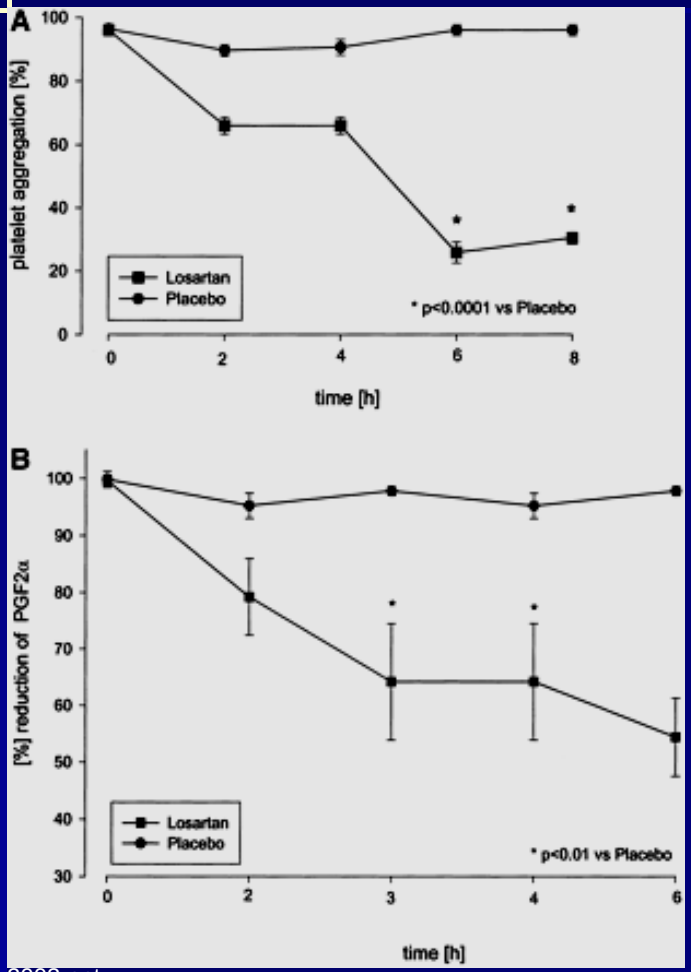
Levy et al. Am J of Cardiology, 2000

Novel Metabolite Inhibits TxA_2 and COX-2



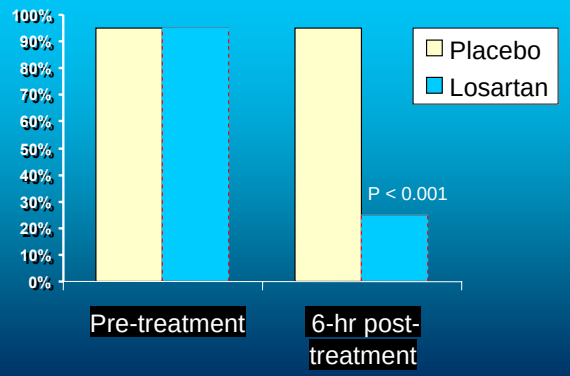
Ferrario, 2003

Effect of EXP3179 on Platelet Aggregation and COX-2



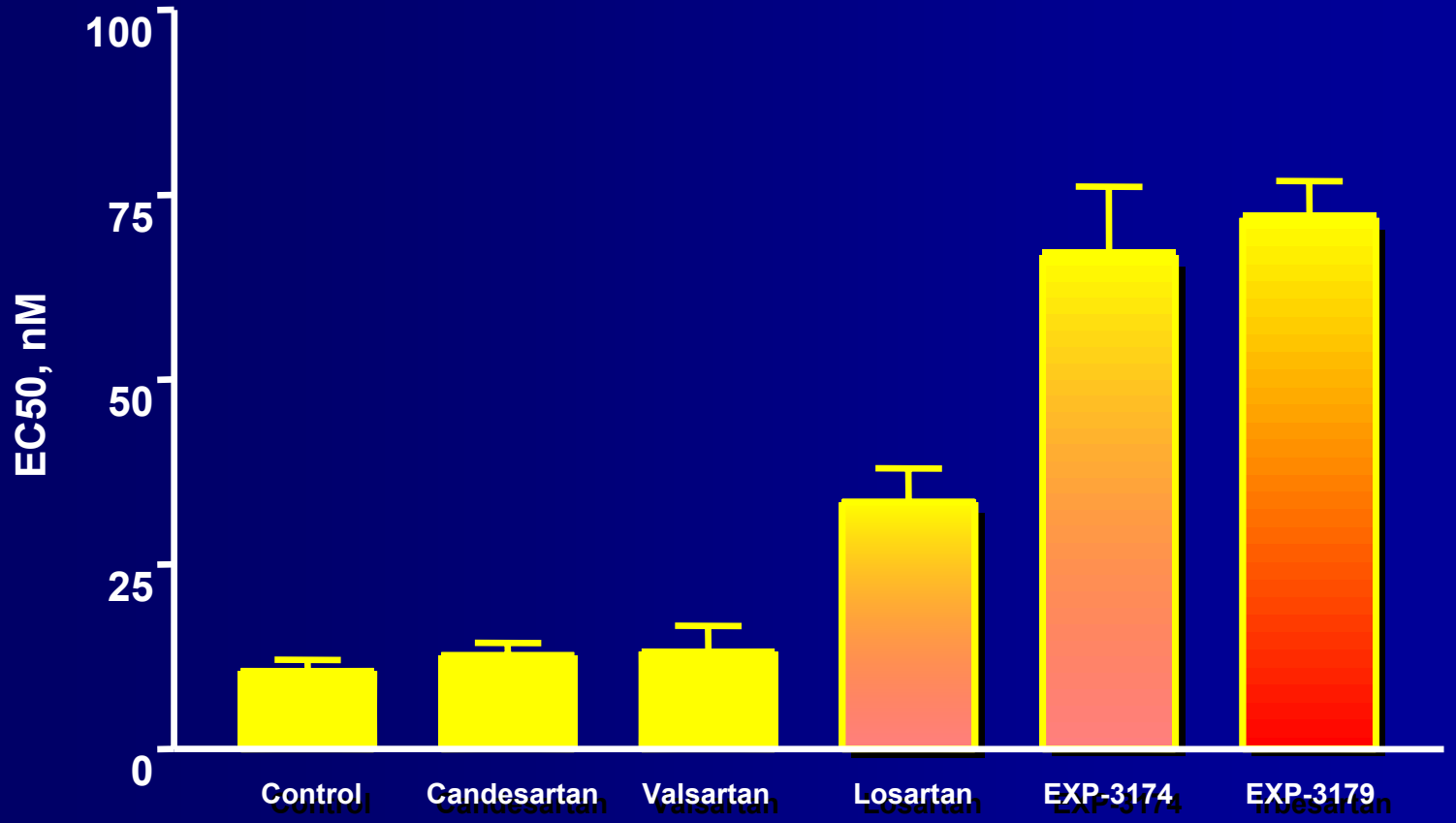
Losartan Inhibits Platelet Aggregation in Man (via EXP-3179?)

TxA_2-induced Platelet Aggregation



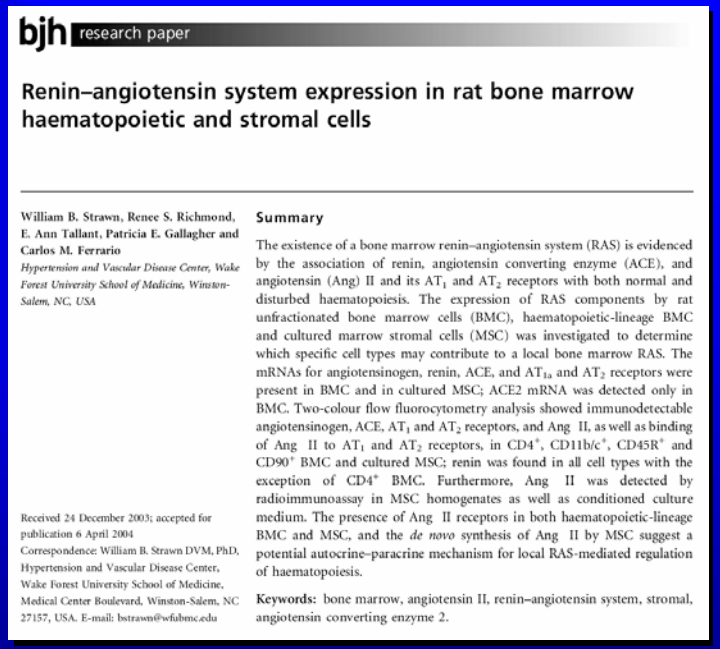
Krämer et al. Circulation Res 2002;90:770-776

Differential Actions Blockade of TxA_2 Receptors



Ferrario, CM. *Current Medical Research and Opinions* **20**, 1797-1804, 2004.

The Origin of Atherosclerosis



bjh research paper

Renin–angiotensin system expression in rat bone marrow haematopoietic and stromal cells

William B. Strawn, Renee S. Richmond, E. Ann Tallant, Patricia E. Gallagher and Carlos M. Ferrario

Hypertension and Vascular Disease Center, Wake Forest University School of Medicine, Winston-Salem, NC, USA

Summary

The existence of a bone marrow renin–angiotensin system (RAS) is evidenced by the association of renin, angiotensin converting enzyme (ACE), and angiotensin (Ang) II and its AT_1 and AT_2 receptors with both normal and disturbed haematopoiesis. The expression of RAS components by rat unfractionated bone marrow cells (BMC), haematopoietic-lineage BMC and cultured marrow stromal cells (MSC) was investigated to determine which specific cell types may contribute to a local bone marrow RAS. The mRNAs for angiotensinogen, renin, ACE, and AT_{1a} and AT_2 receptors were present in BMC and in cultured MSC; ACE2 mRNA was detected only in BMC. Two-colour flow fluorocytometry analysis showed immunodetectable angiotensinogen, ACE, AT_1 and AT_2 receptors, and Ang II, as well as binding of Ang II to AT_1 and AT_2 receptors, in $CD4^+$, $CD11b/c^+$, $CD45R^+$ and $CD90^+$ BMC and cultured MSC; renin was found in all cell types with the exception of $CD4^+$ BMC. Furthermore, Ang II was detected by radioimmunoassay in MSC homogenates as well as conditioned culture medium. The presence of Ang II receptors in both haematopoietic-lineage BMC and MSC, and the *de novo* synthesis of Ang II by MSC suggest a potential autocrine–paracrine mechanism for local RAS-mediated regulation of haematopoiesis.

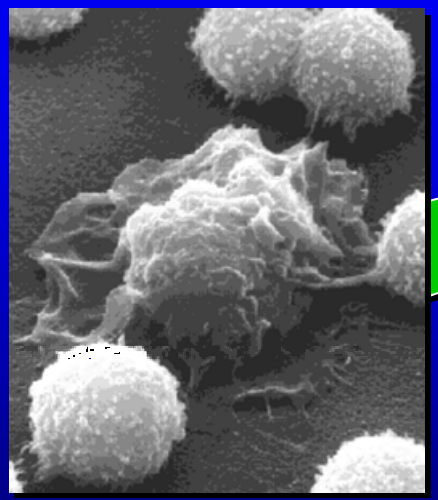
Keywords: bone marrow, angiotensin II, renin–angiotensin system, stromal, angiotensin converting enzyme 2.

Received 24 December 2003; accepted for publication 6 April 2004

Correspondence: William B. Strawn DVM, PhD, Hypertension and Vascular Disease Center, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA. E-mail: bstrawn@wfubmc.edu

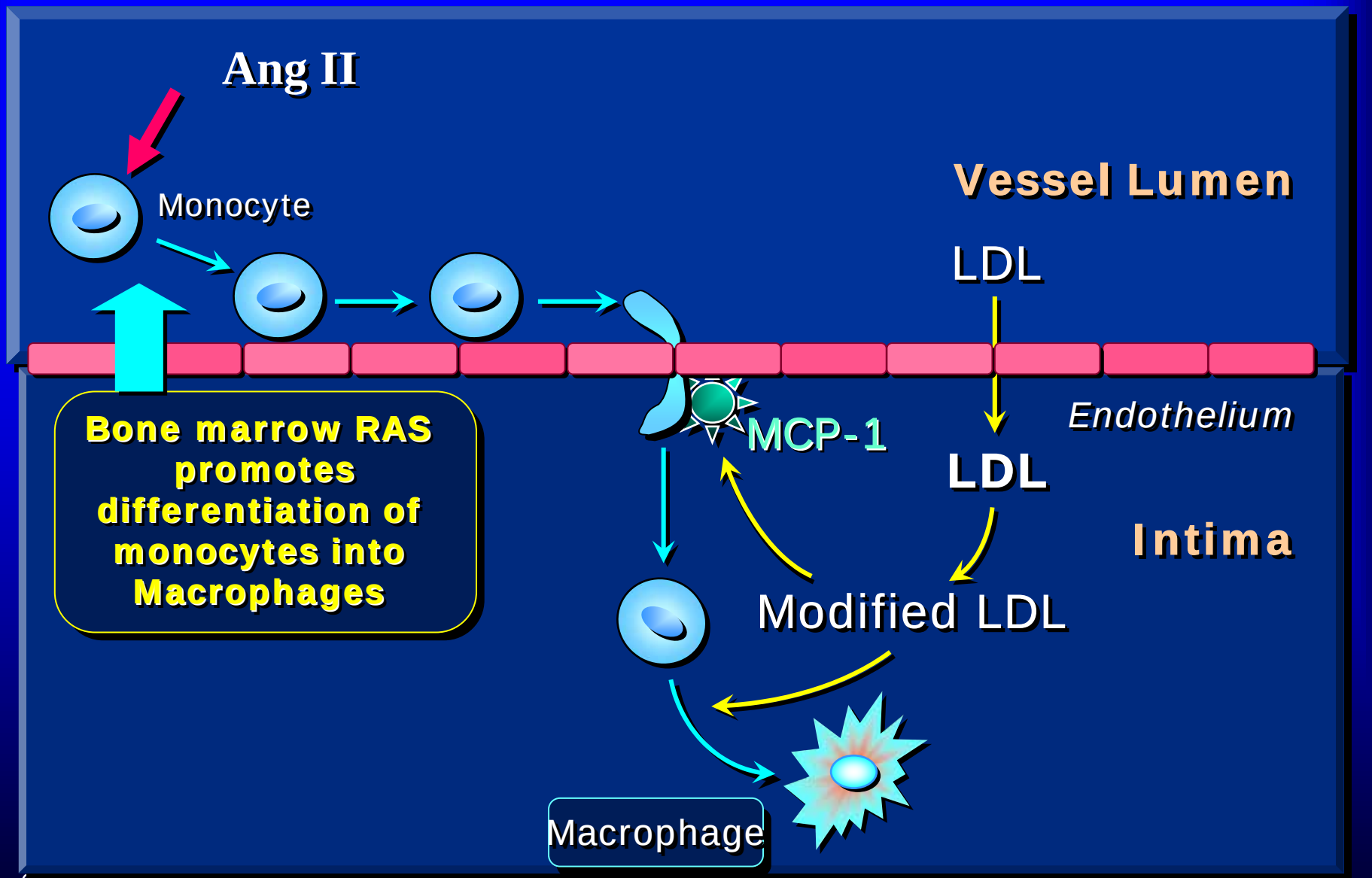
British Journal of Haematology, 126, 120–126, 2004

Monocytes
Bone Marrow Origin



Monocytes leave the blood stream to become macrophages engulfing antigens, debrids, and lipids

Is the BONE MARROW the



STEPS TO EVALUATING THE HYPOTHESIS

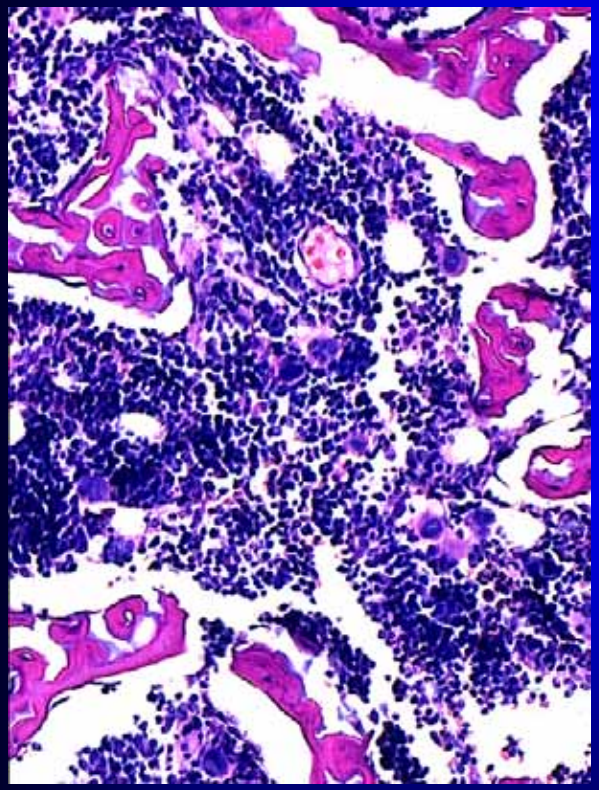
1. Does Ang II modulate hematopoiesis?
2. Is it a function of a local RAS?

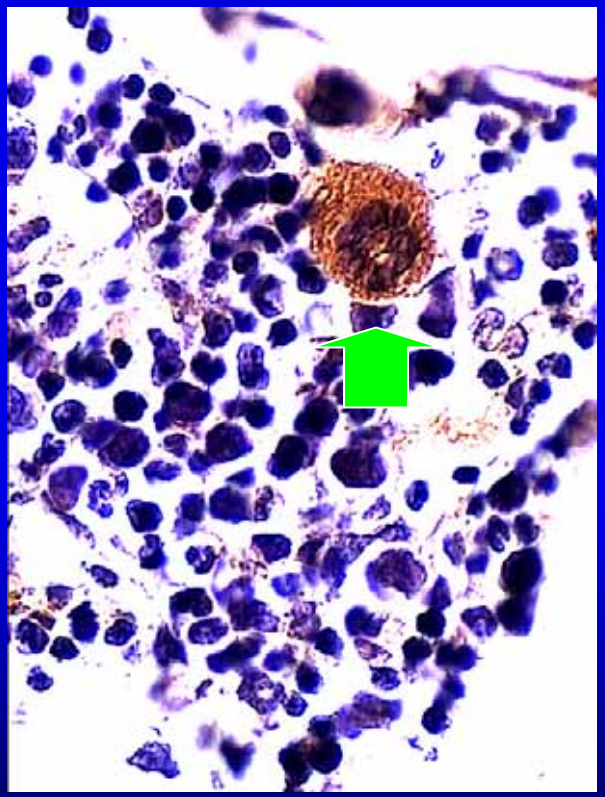
3. Do dyslipidemia affect the bone marrow RAS?

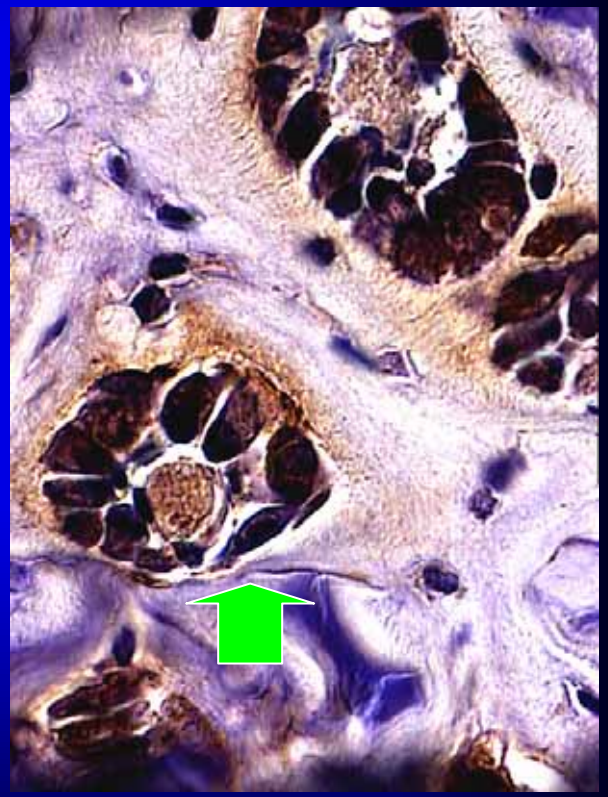
Ang II Immuno Reactive Products
Rat Bone Marrow

Hematopoietic Lineage

Stroma Osteoclasts

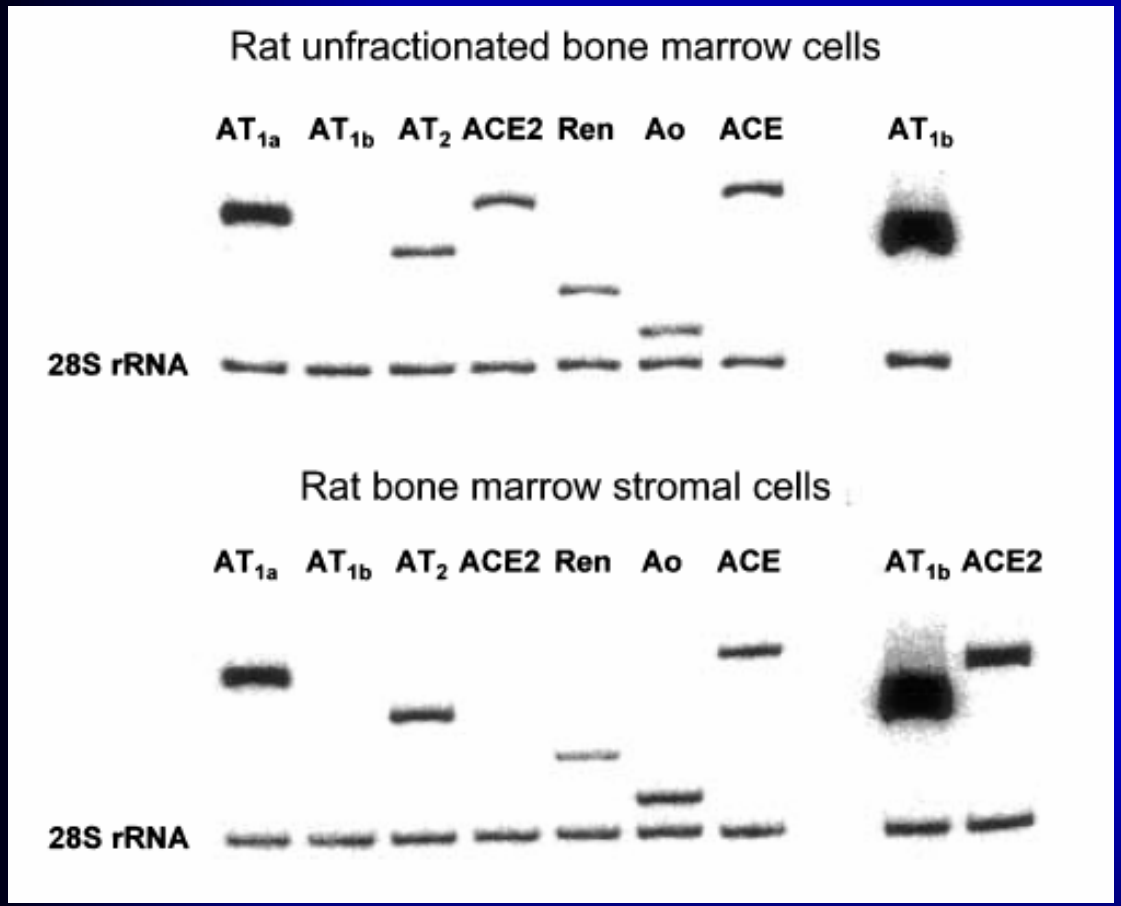


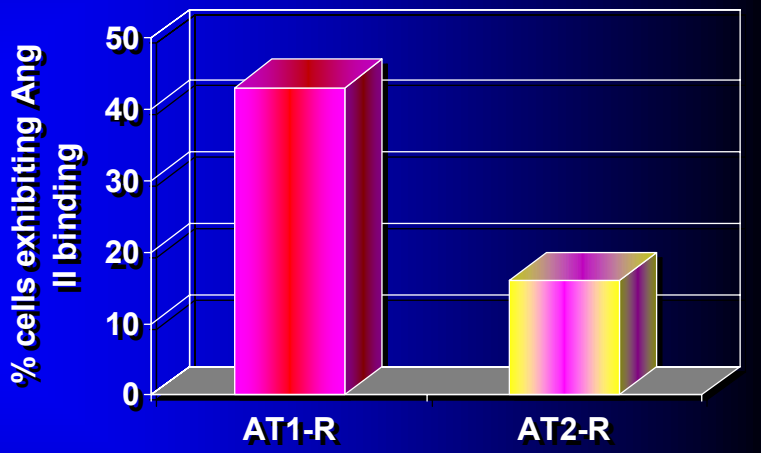




Expression of RAS Components

RAT BONE MARROW



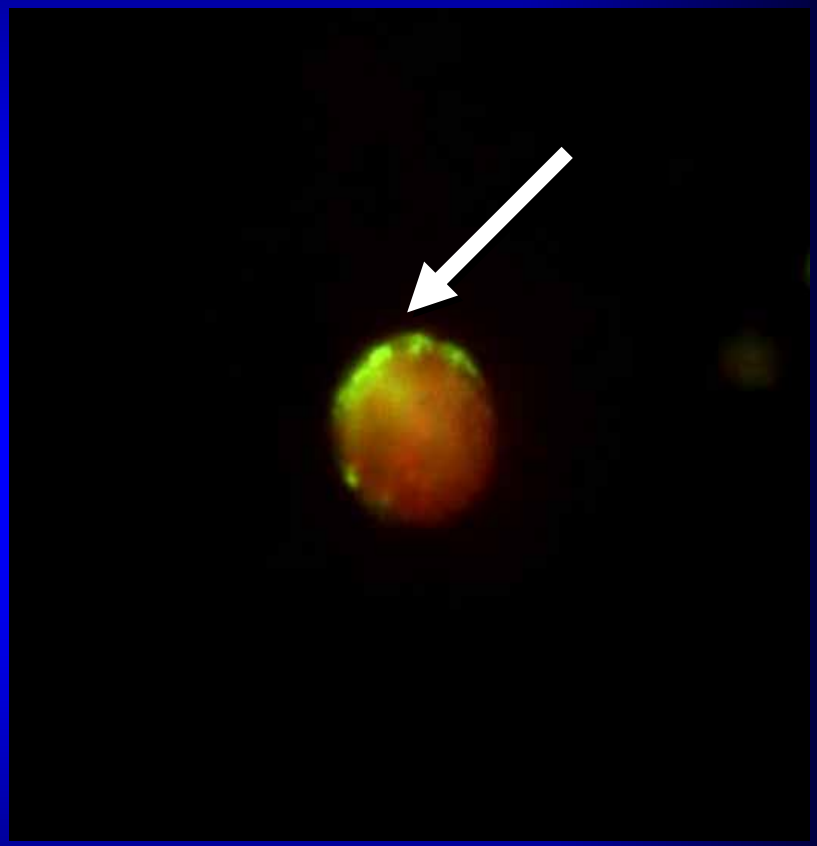


Strawn et al. British Journal of Haematology, 126, 120–126, 2004

BONE MARROW –PRIMATES-

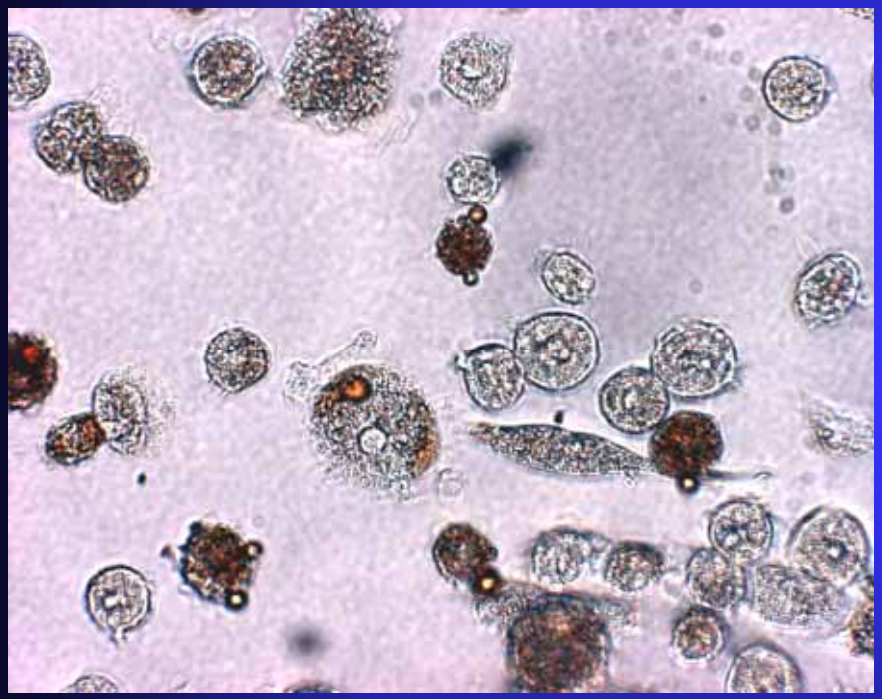
$CD34^+$ Progenitor Cells Express AT_1 Receptors

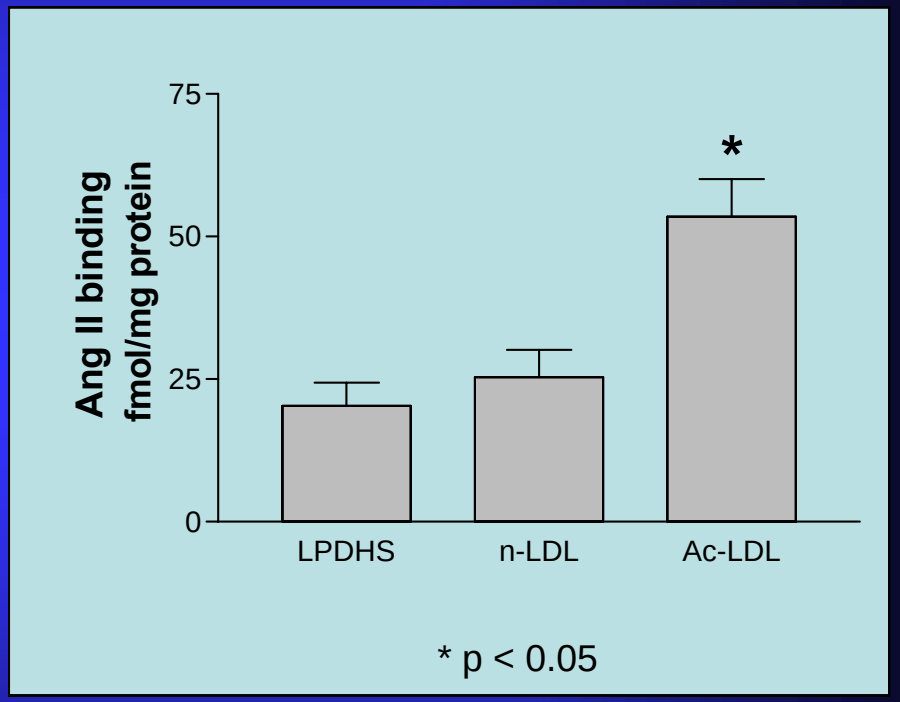
$CD34^+$ Cell



AT_1 Receptor Immunodetection on $CD34^+$ Cell

Acetylated LDL Increases Angiotensin II Binding to CD34^{+}-Derived Myeloid Precursors

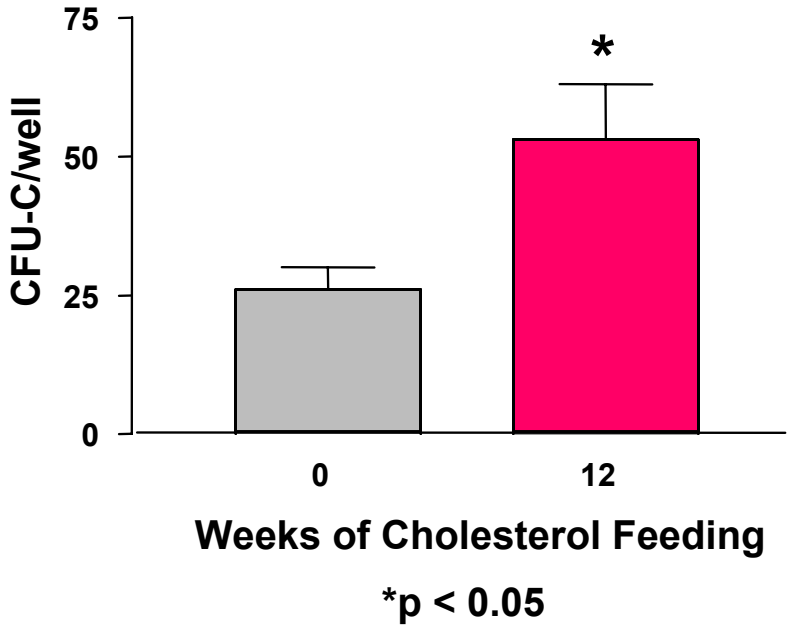




72 h incubation with 1.0 mg/mL Ac-LDL, Sudan IV, 400X

Strawn et al., Arterio Thromb Vasc Biol 2003; 23:a-56-57

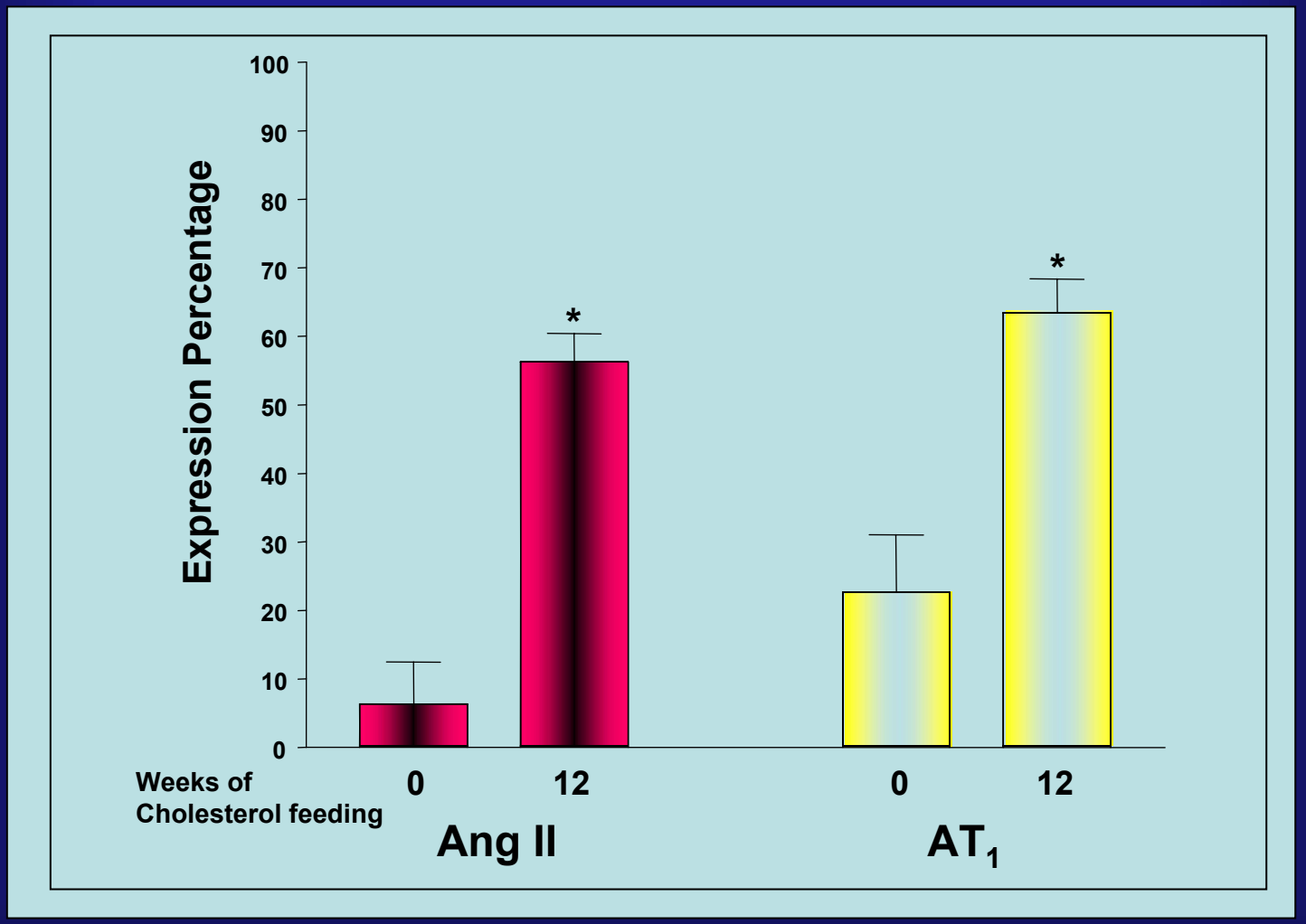
Induction of Hypercholesterolemia Increases Bone Marrow Hematopoietic Precursor Cell Proliferation



*p < 0.05

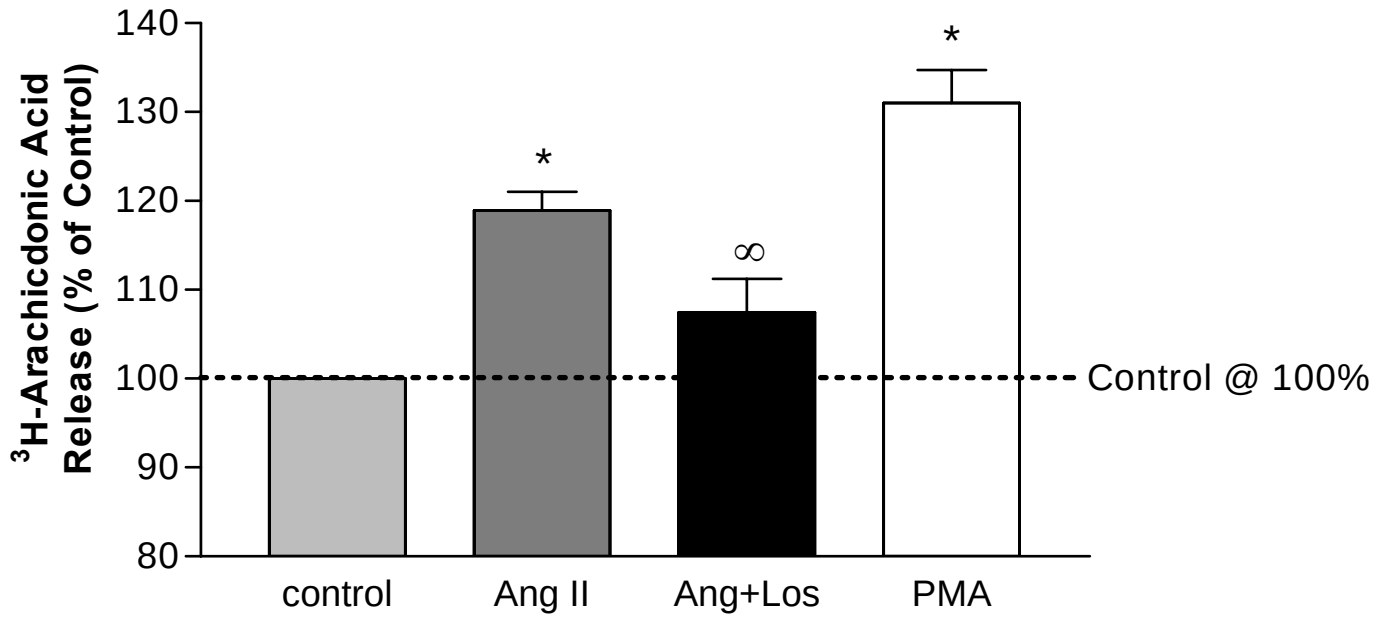
Strawn, Richmond & Ferrario, 2005

Immunodetectable Ang II and AT_1 Receptor Expression Increased by Cholesterol Feeding in Cynomolgus Monkey Bone Marrow Cells



Strawn, Richmond & Ferrario, 2005

Ang II-stimulated arachidonic acid release from HS-5 human bone marrow stromal cells



* p<0.0001 vs Control, ∞ p<0.001 vs Ang II
N = 21 experiments

Richmond et al. J Renin Angiotensin Aldosterone Syst. 2004 Dec;5(4):176-82.

SUMMARY

- Hyperlipidemia alters hematopoiesis, generating activated monocytic phenotypes
- The bone marrow RAS is activated by hyperlipidemia
- One result of bone marrow RAS activation by hyperlipidemia is the generation of activated monocytes that participate in atherogenesis
- The bone marrow RAS may be a target for diminishing end-organ pathology where inflammation is an early initiator

Acknowledgements

William Strawn, D.V.M., Ph.D.
Renee Richmond, Ph.D.
Linda Moore
Peg Gallagher, Ph.D.
Ann Tallant, Ph.D.