

NAM JUNE PAIK: *Rhapsody in Video*



혈관연구회 추계학회 2007.10.13

Renin-angiotensin-aldosterone System

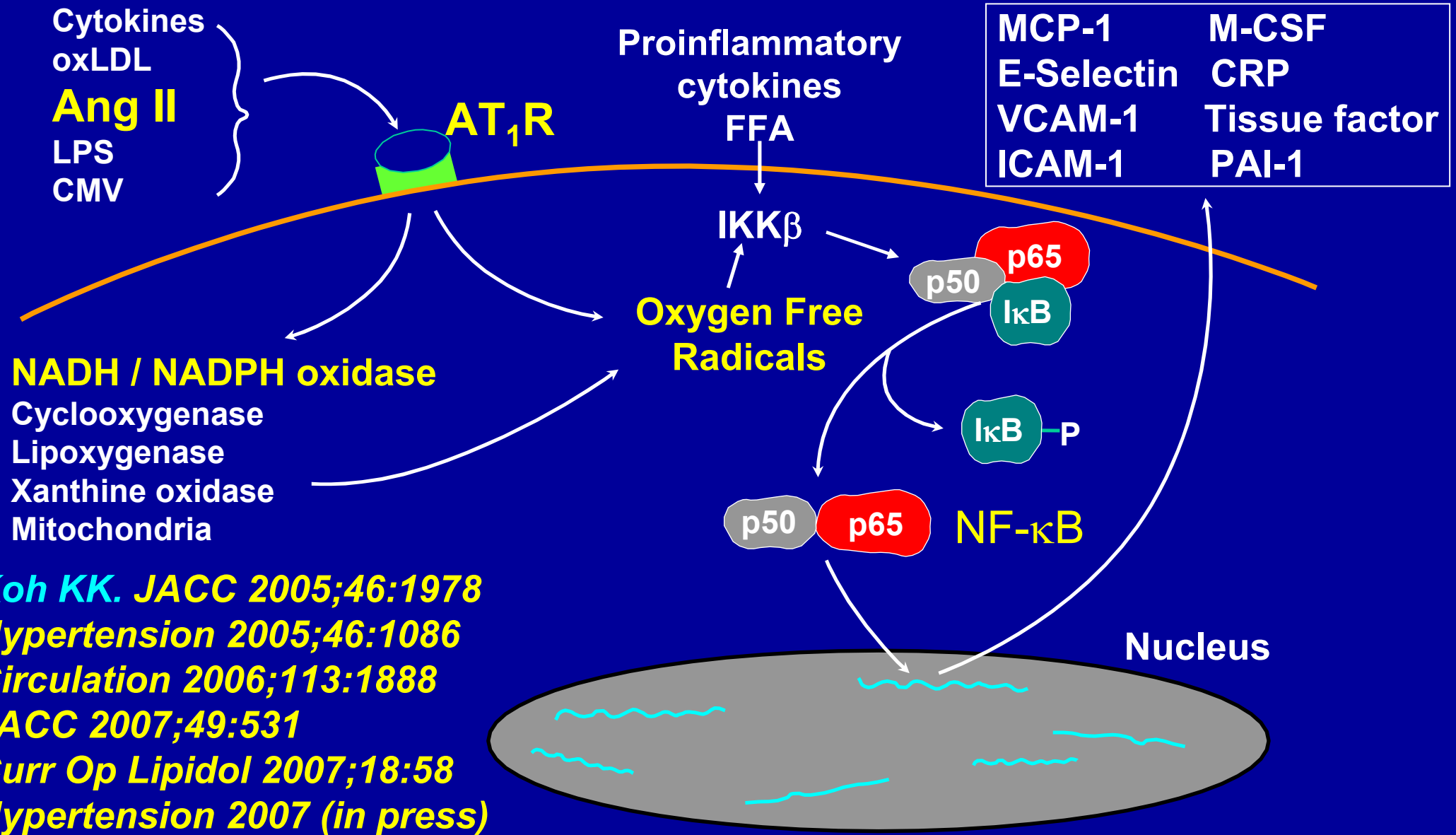
Kwang Kon Koh, MD, FACC, FAHA

Cardiology

Gachon University Gil Medical Center

Incheon, Korea

Activation of Nuclear Transcription Factor, NF- κ B



Koh KK. JACC 2005;46:1978
Hypertension 2005;46:1086
Circulation 2006;113:1888
JACC 2007;49:531
Curr Op Lipidol 2007;18:58
Hypertension 2007 (in press)

Combination Therapy for The Treatment of Atherosclerosis: Evidence from Novel Emerging Concepts

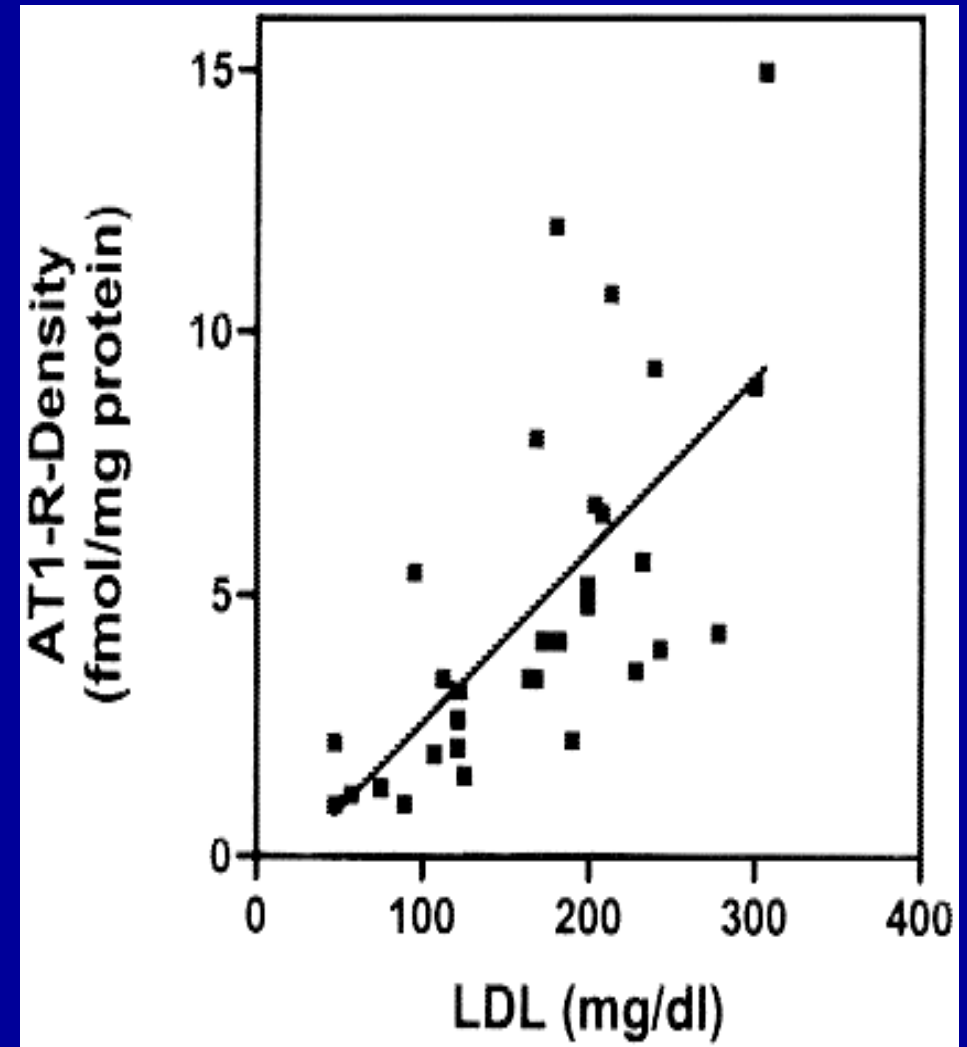
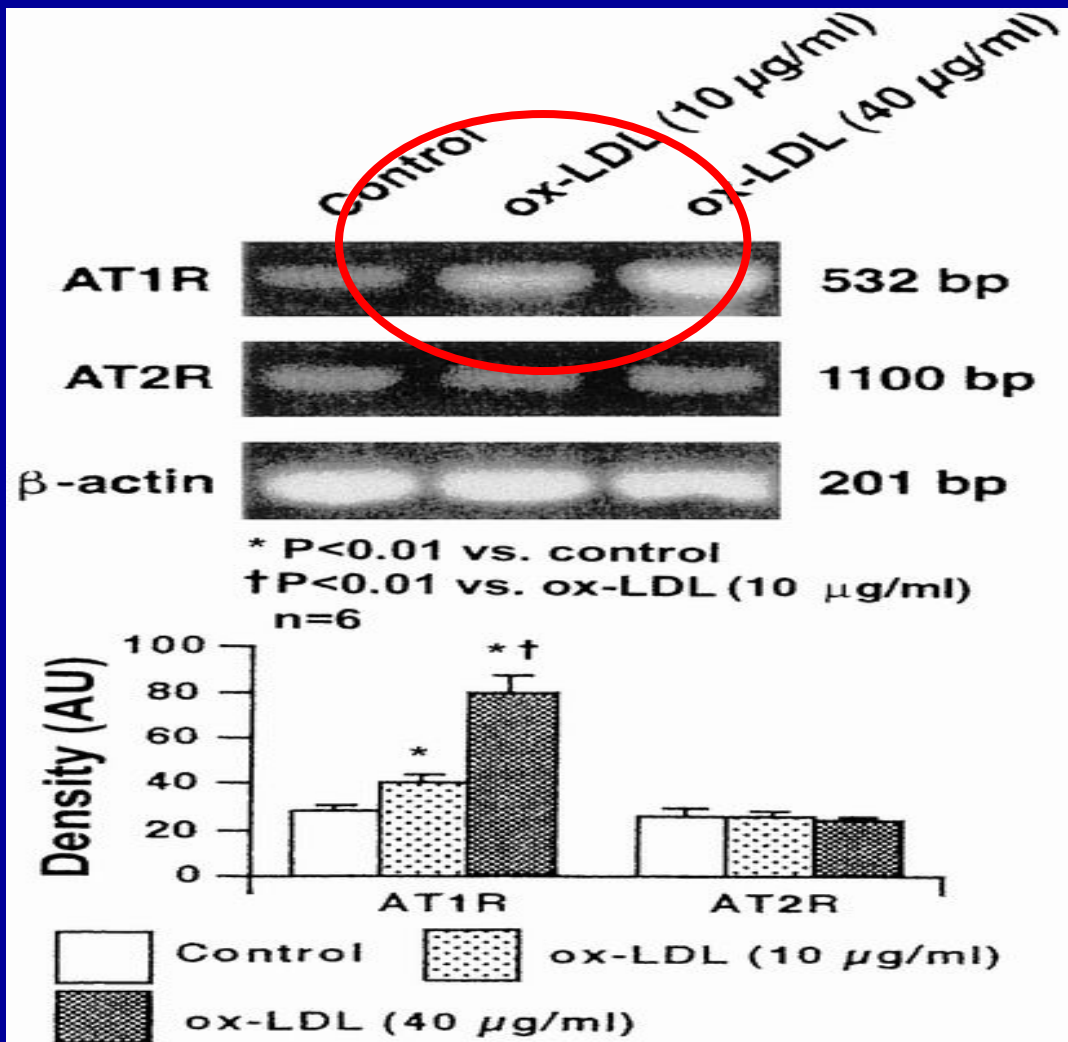
- **Nov 8: Methodist Hospital,
Baylor College of Medicine, Houston**
- **Dec 6: Cardiology Grand Rounds,
Brigham and Women's Hospital,
Harvard Medical School, Boston**
- **April 1: ACC 2008 Meeting, Chicago**

Cross-talk Between RAS and Statin

Upregulation of AT1R mRNA by ox-LDL, HCAECs

AT1R density in HC Men

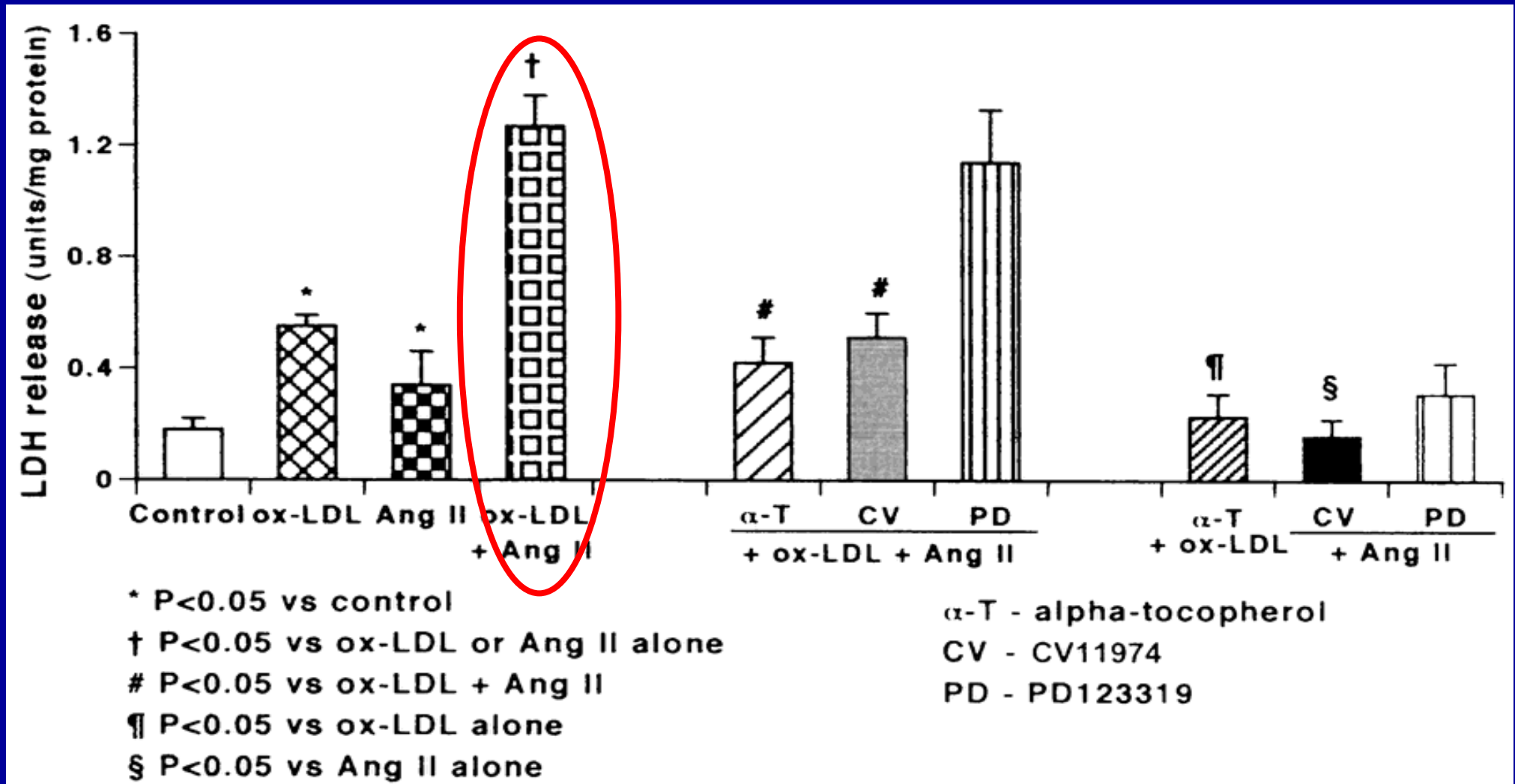
Regression analysis



Li et al, *Circulation* 2000;102:1970

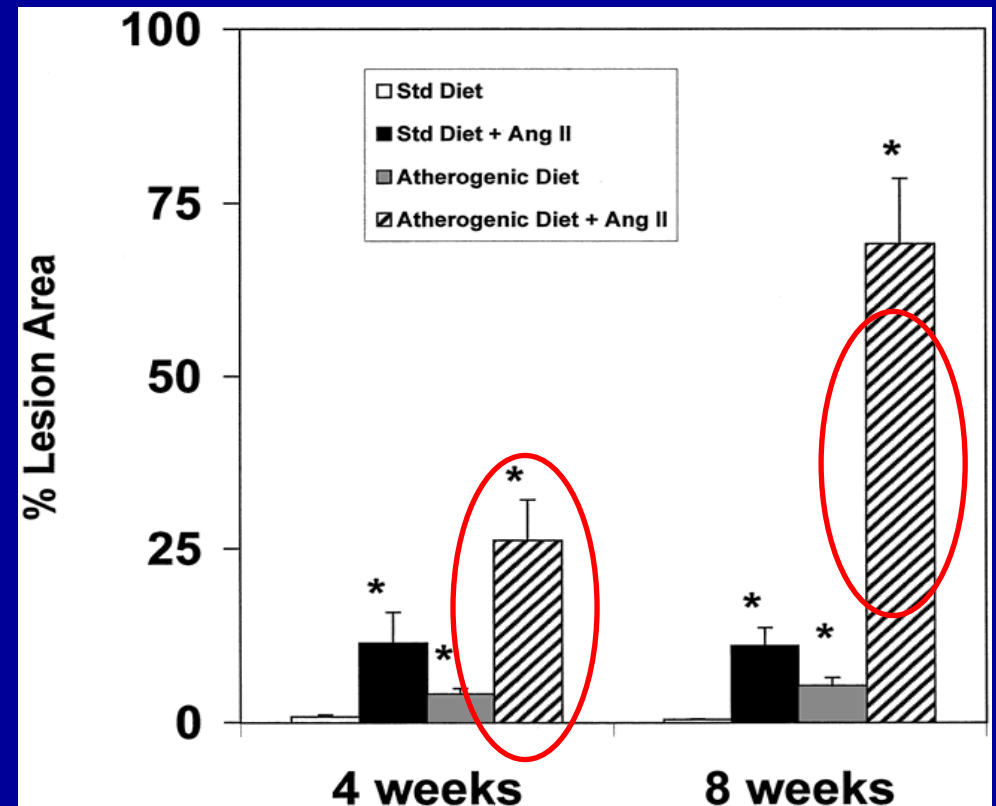
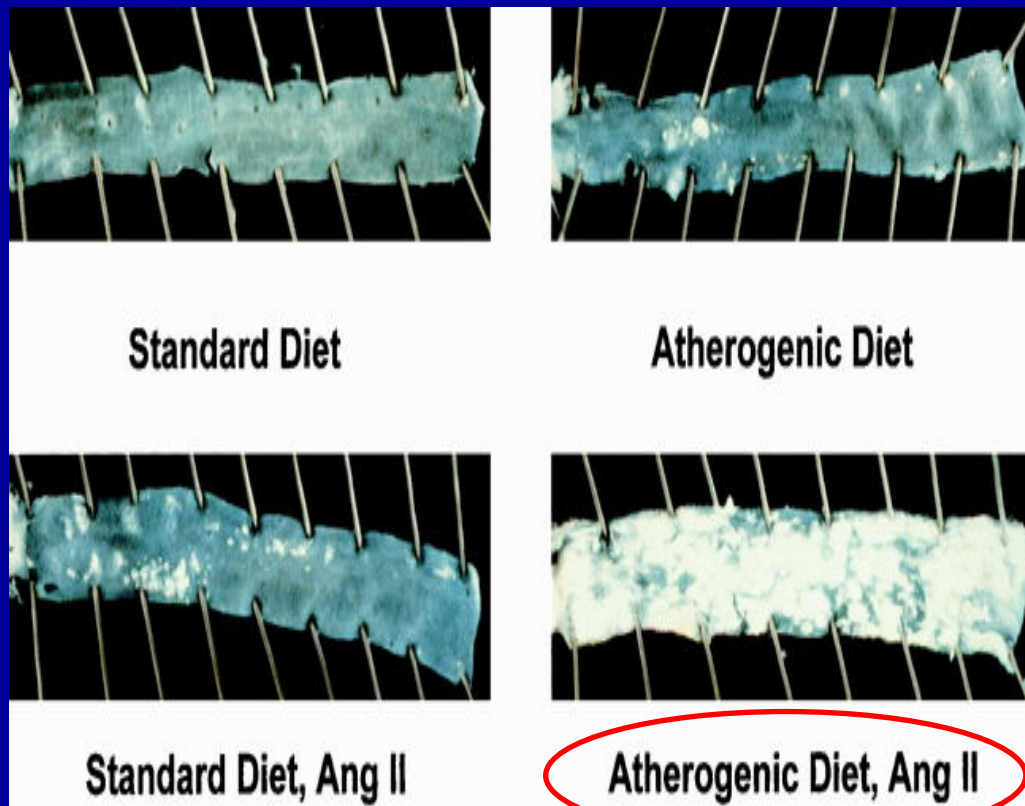
Nickenig et al, *Circulation* 1999;100:2131

Effect of ox-LDL and Ang II on endothelial cell injury measured as LDH release



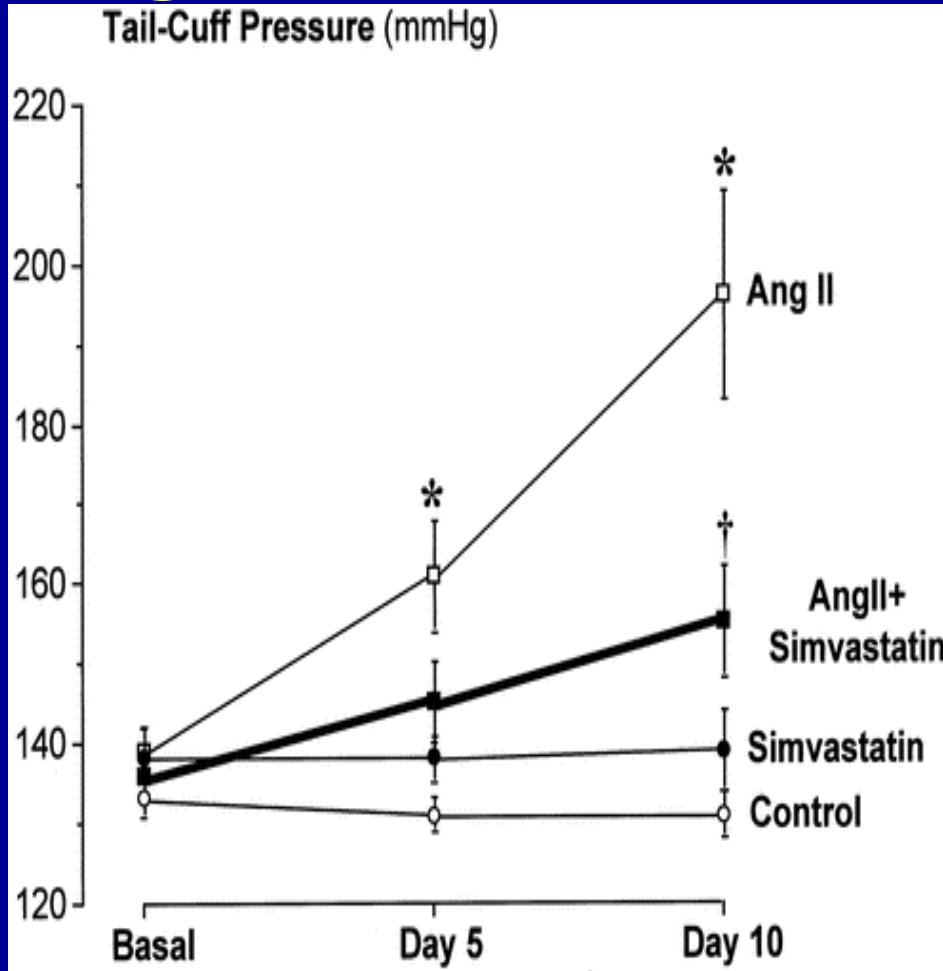
Ang II-Induced Hypertension Accelerates Atherosclerosis in ApoE-Deficient Mice

En face dissections of descending thoraco-abdominal aorta after 8 weeks of treatment



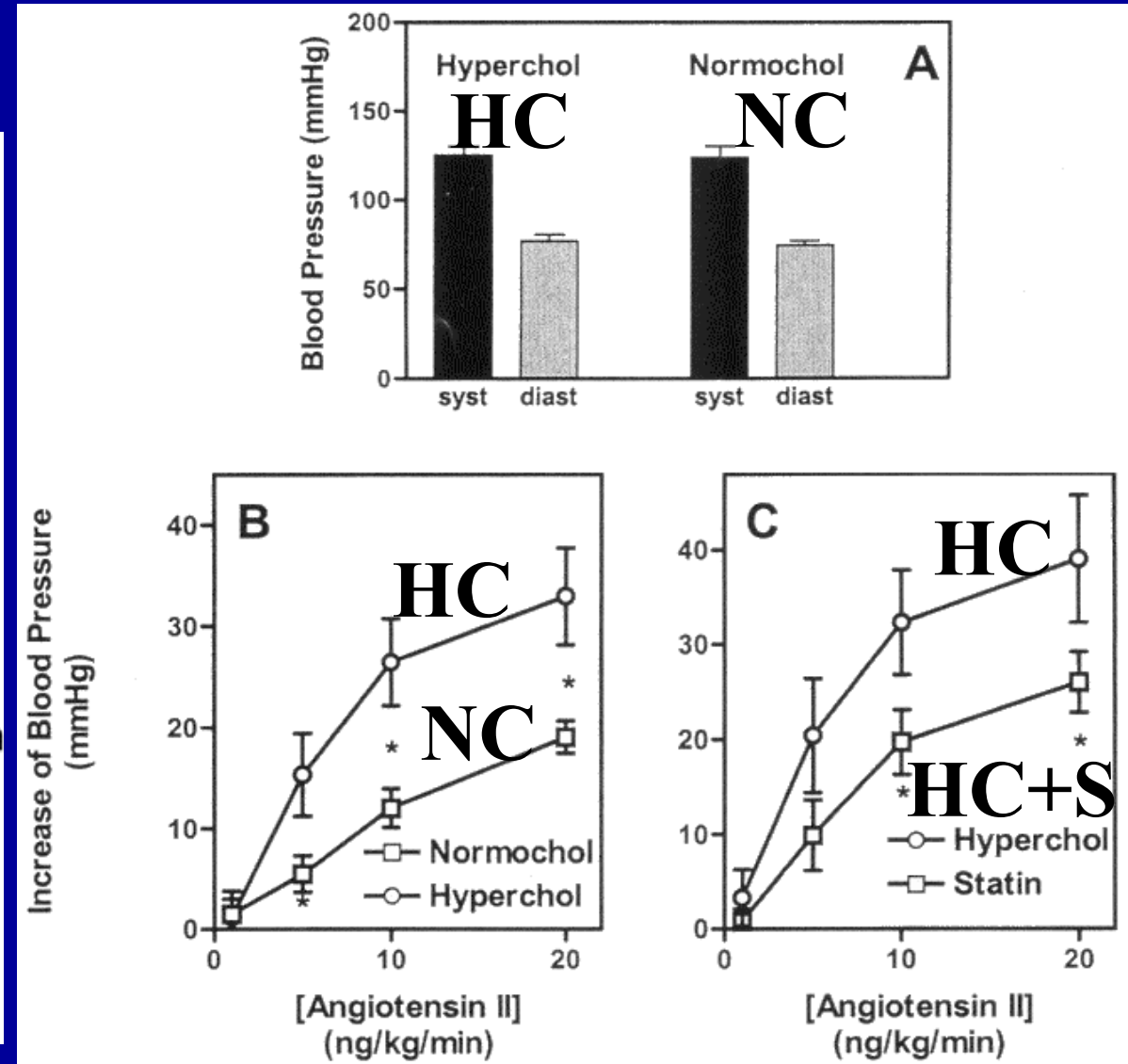
Weiss et al, *Circulation* 2001;103:448

Effect of Statin on tail-cuff Pr in Ang II HT in rats



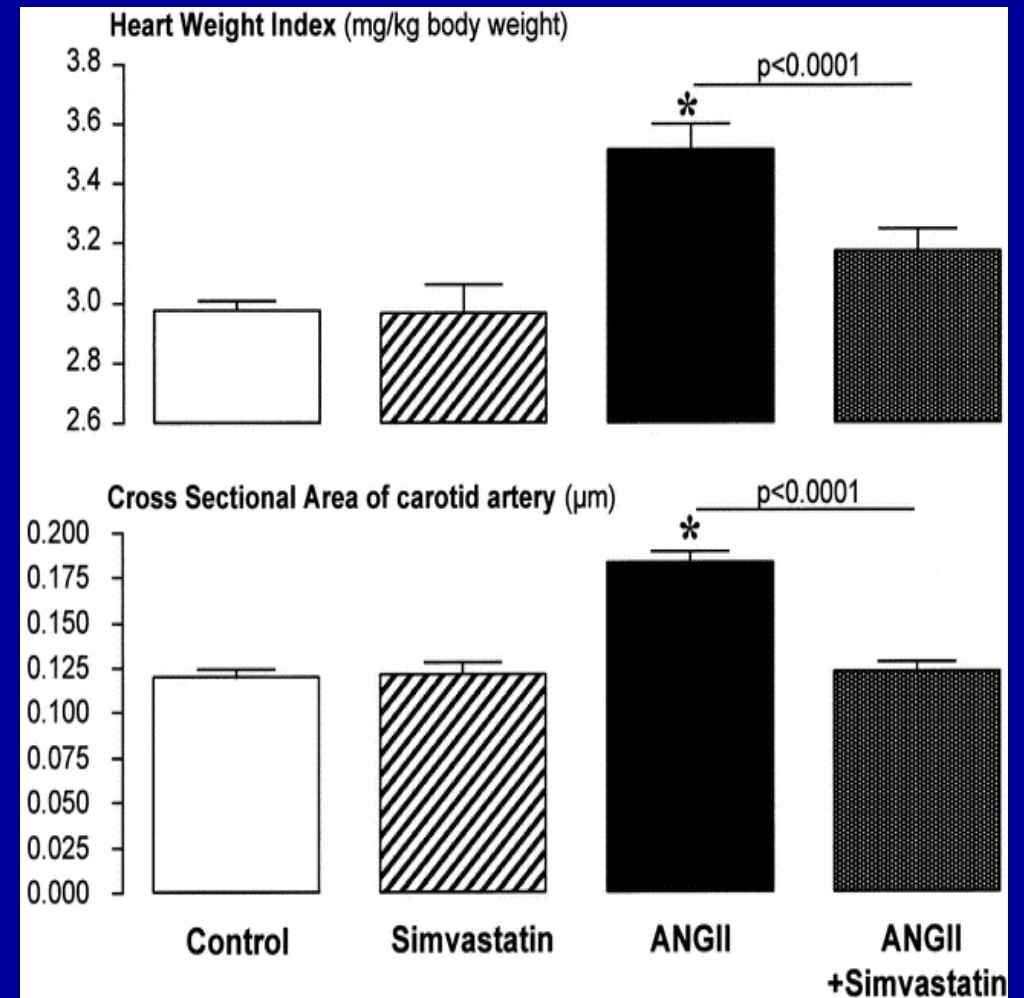
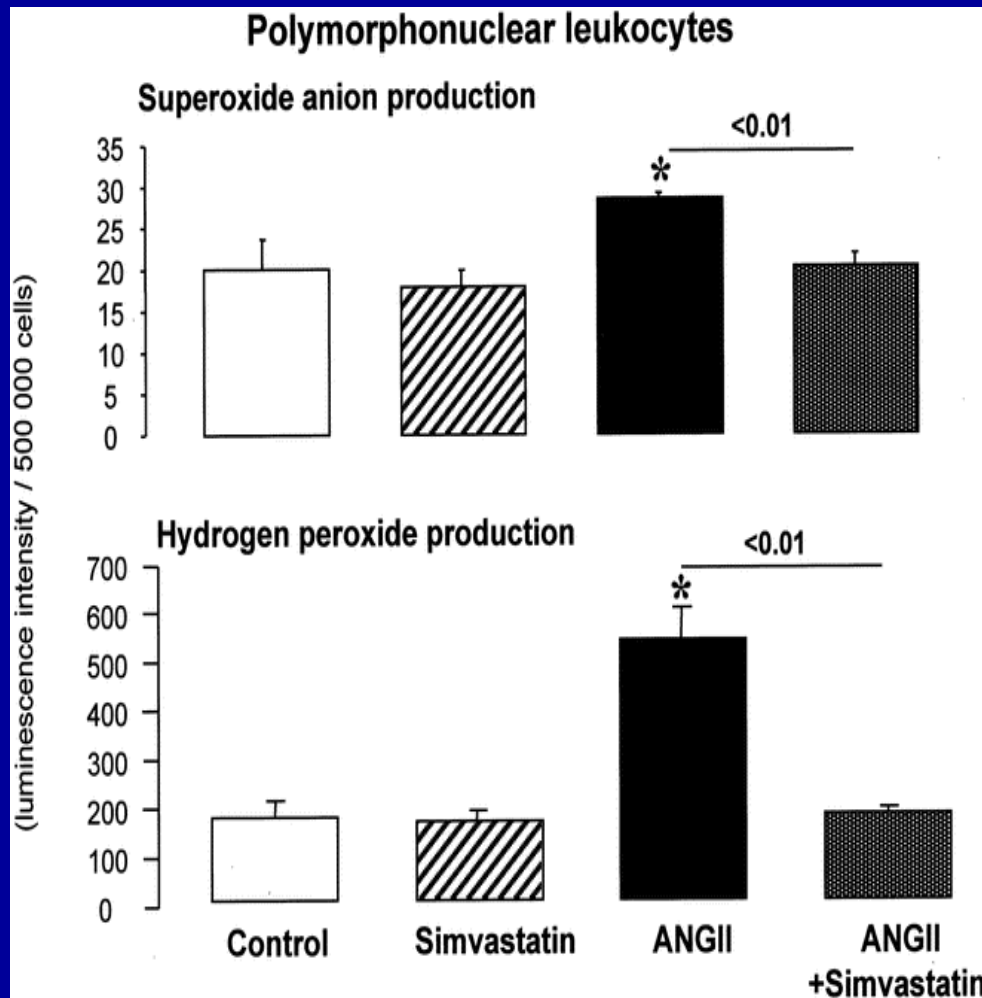
Delbosc et al, Hypertension 2002;40:142

Statin-Sensitive Dysregulated AT1R Function in HC Men

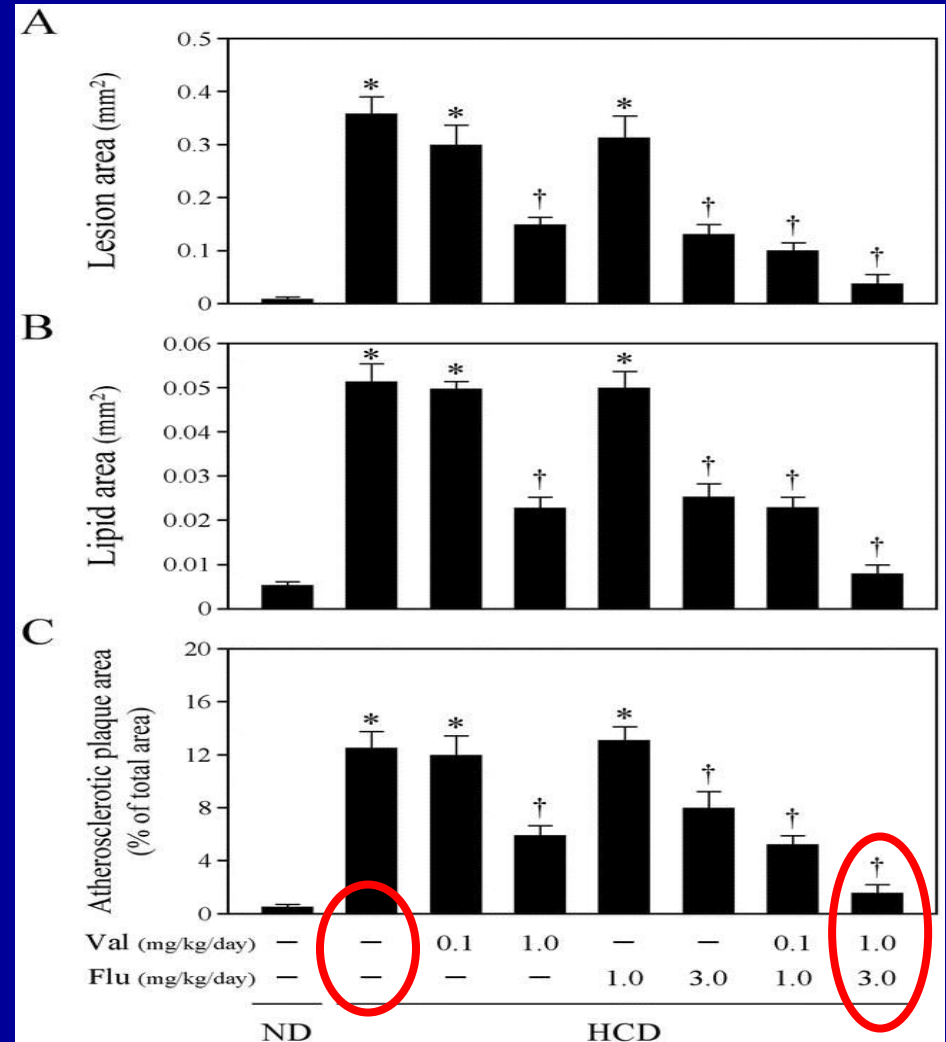
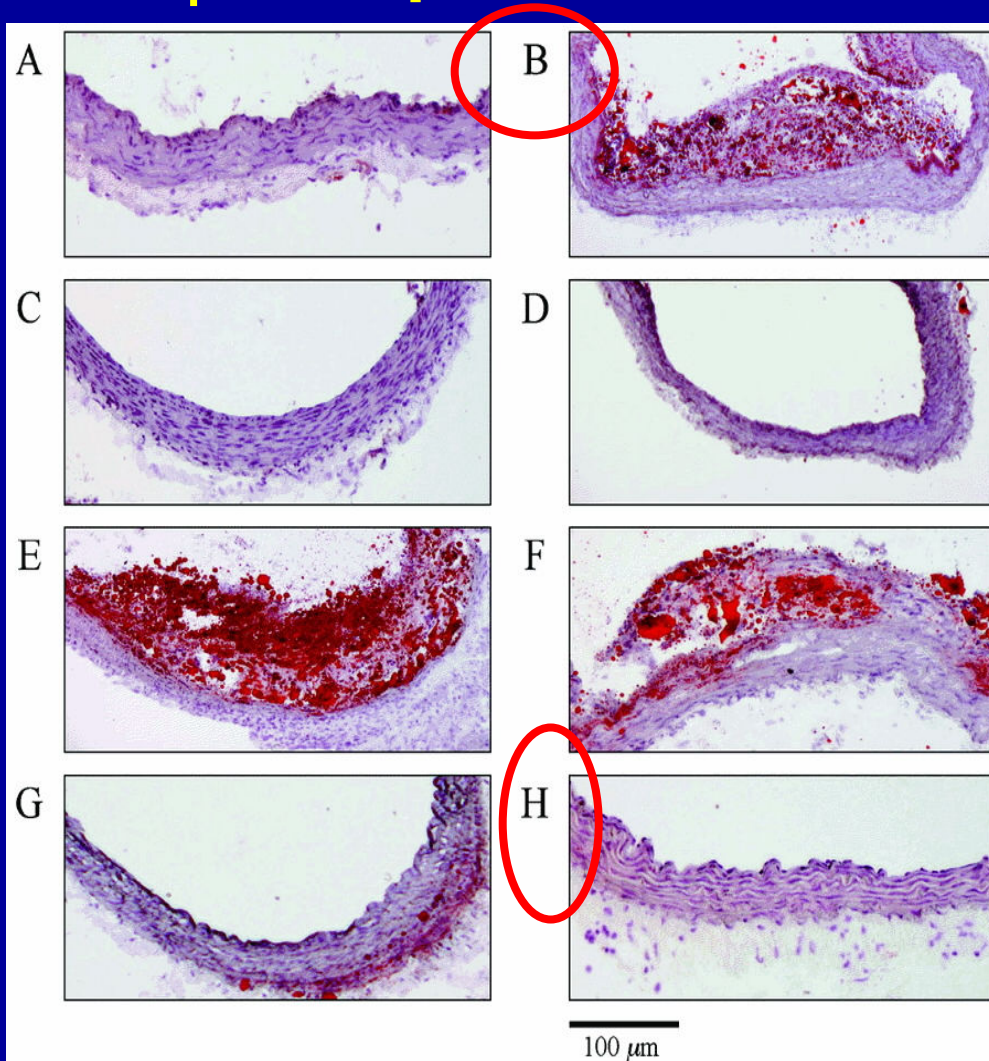


Nickenig et al, Circulation 1999;100:2131

Simvastatin prevents Ang II-induced Oxidative stress and cardiac hypertrophy



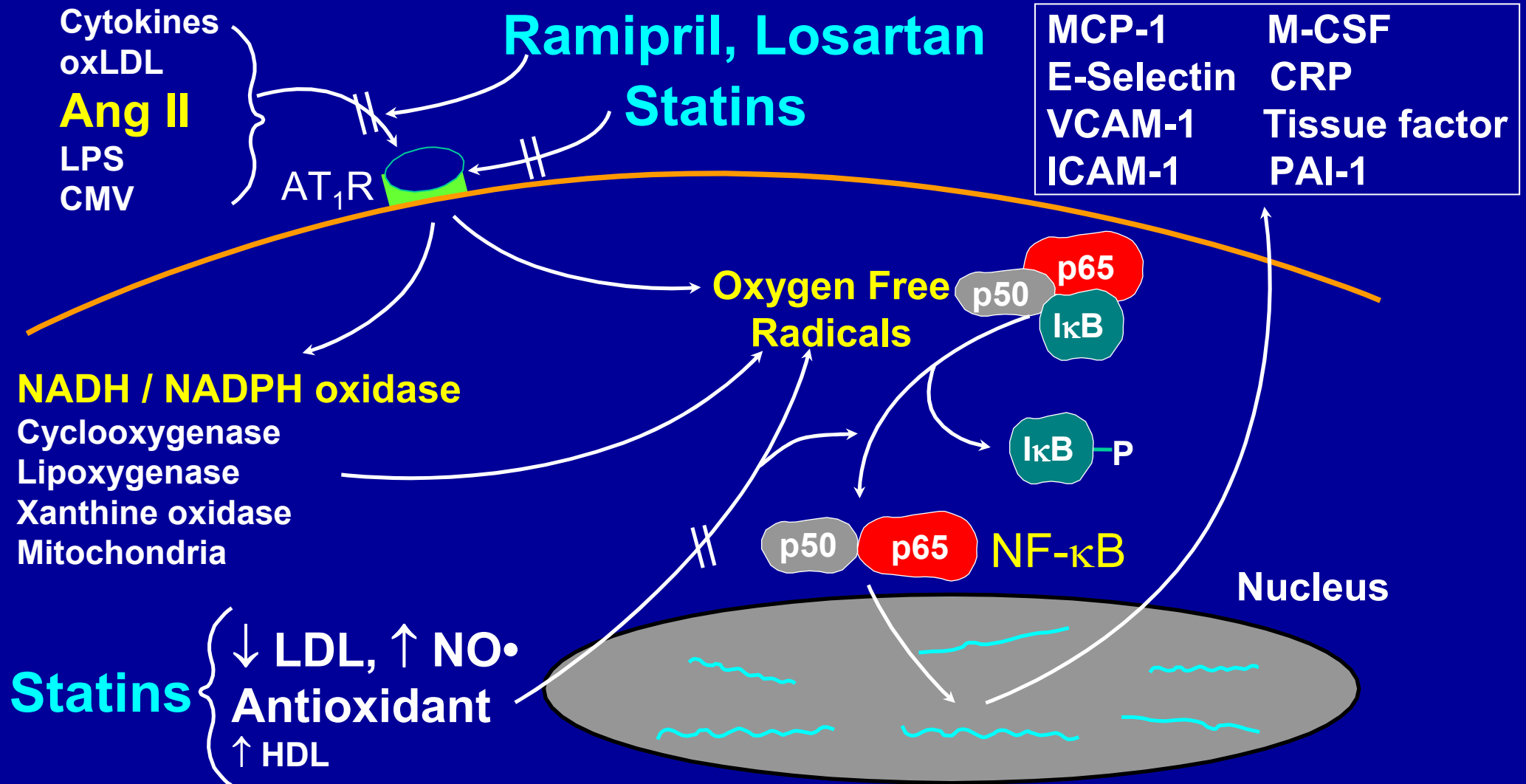
Fluvastatin Enhances the Inhibitory Effects of a Selective AT₁ Receptor Blocker, Valsartan, on Atherosclerosis



ApoE null (ApoEKO) Mice, 10 weeks
Independent of BP or Cholesterol Levels

A B E C F D G H

Activation of Nuclear Transcription Factor, NF- κ B



Koh KK. JACC 2005;46:1978, Hypertension 2005;46:1086, Circulation 2006;113:1888, JACC 2007;49:531, Curr Op Lipidol 2007;18:58, Hypertension 2007 (in press)

**Beneficial Vascular and Metabolic Effects of Combined
Therapy with Ramipril and Simvastatin in 50 Patients with
Type 2 Diabetes**

Kwang Kon Koh, Michael J. Quon*
Seung Hwan Han..... Eak Kyun Shin

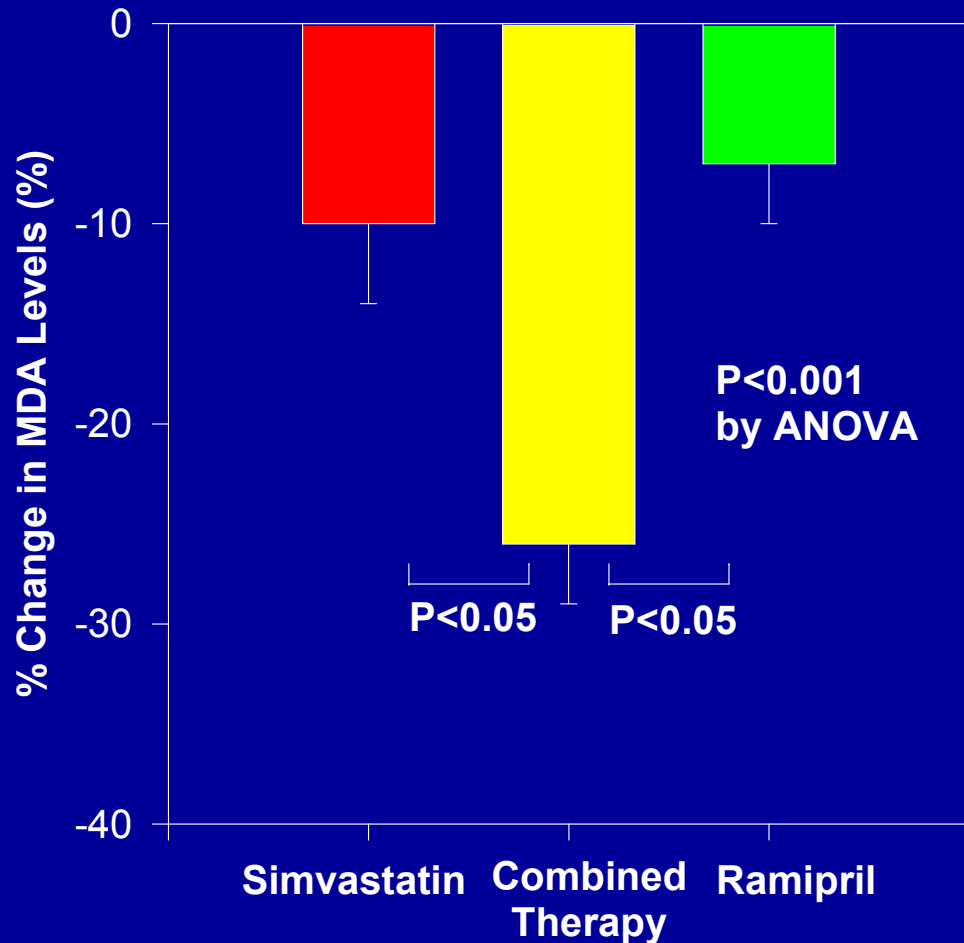
**Cardiology, Gachon Medical School, Korea
Diabetes Unit, NIH, USA***

Hypertension 2005;45:1088

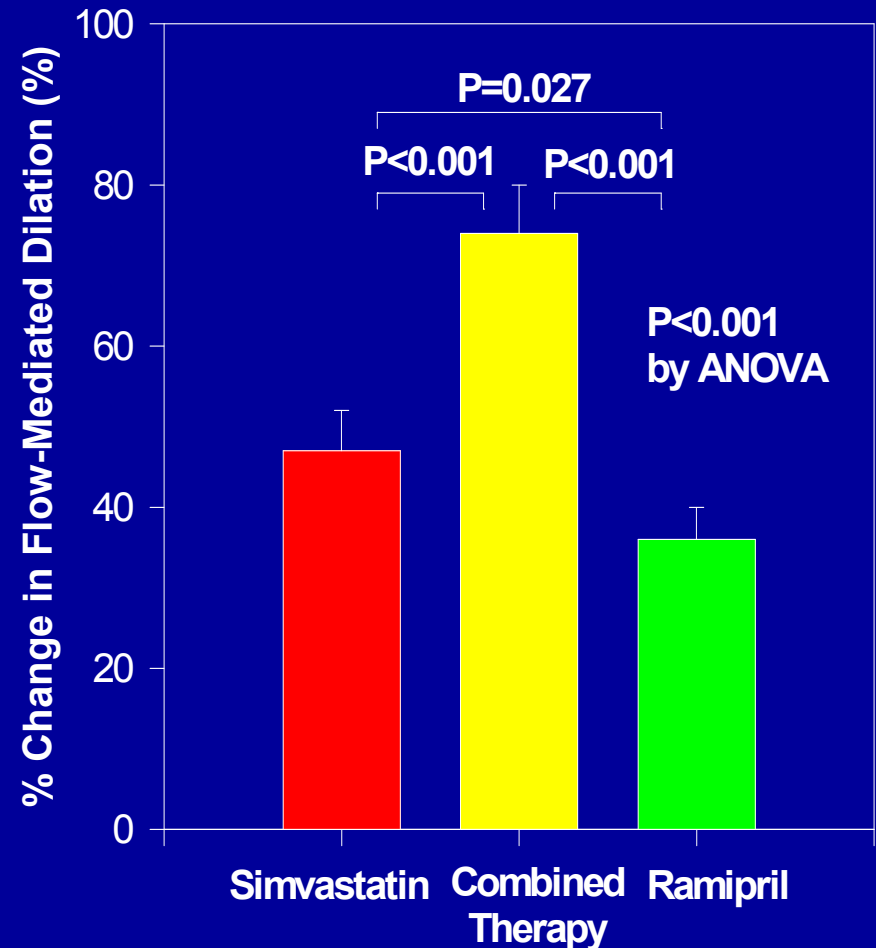
Reuters Health 2005-06-16

Effects of Simvastatin, Combined Therapy, and Ramipril on Flow-mediated Dilatation

Malondialdehyde

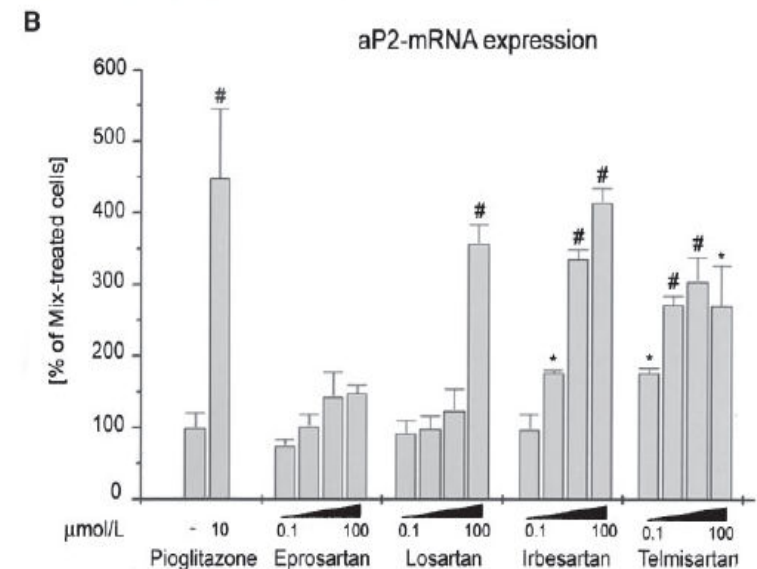
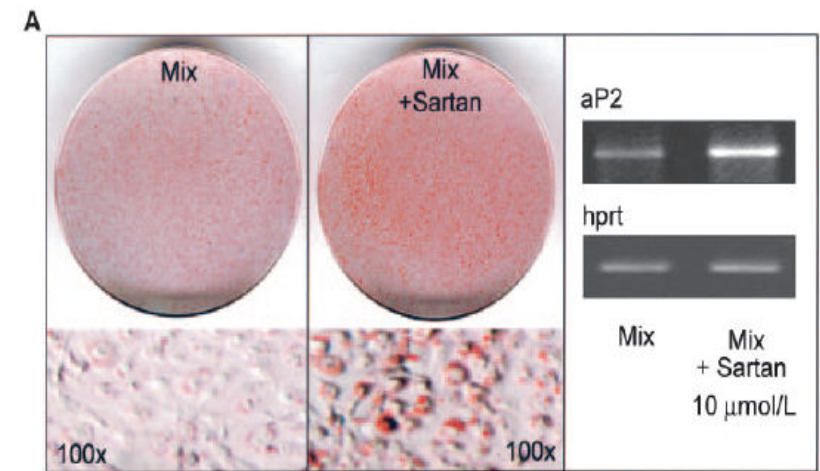
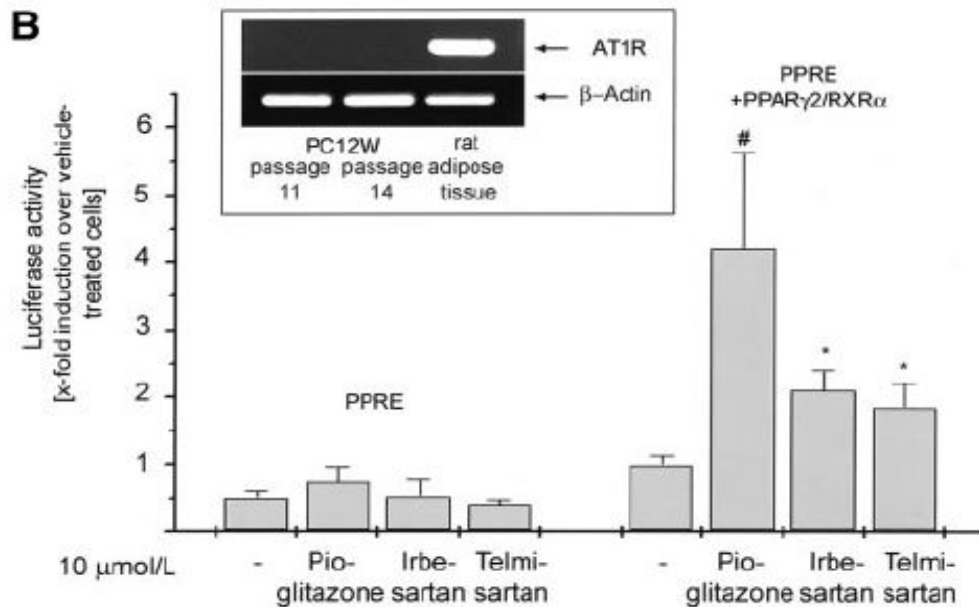
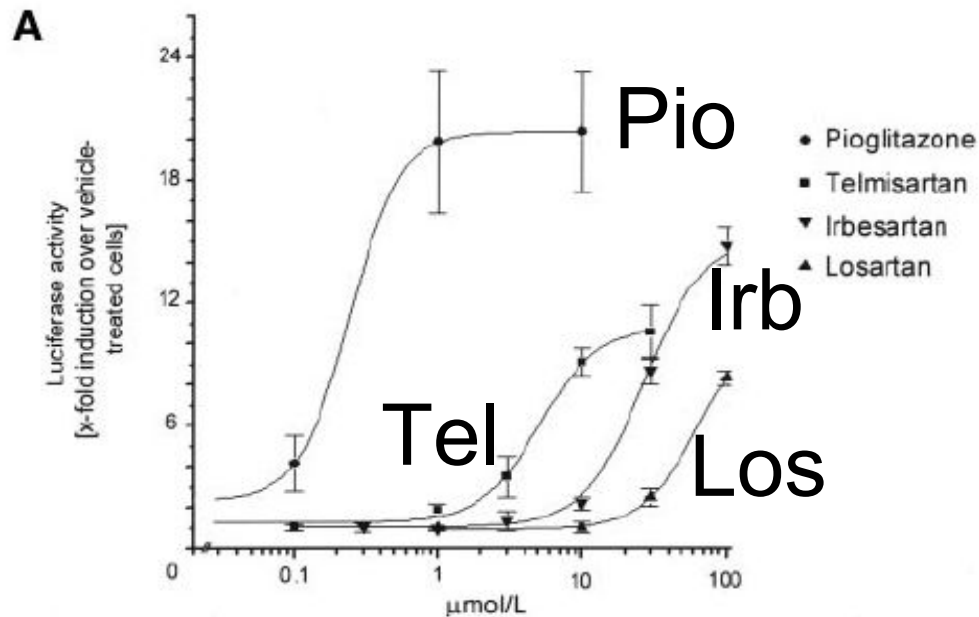


FMD



ARBs: PPAR γ Activity

ARBs Promote 3T3-L1 Adipocyte Differentiation



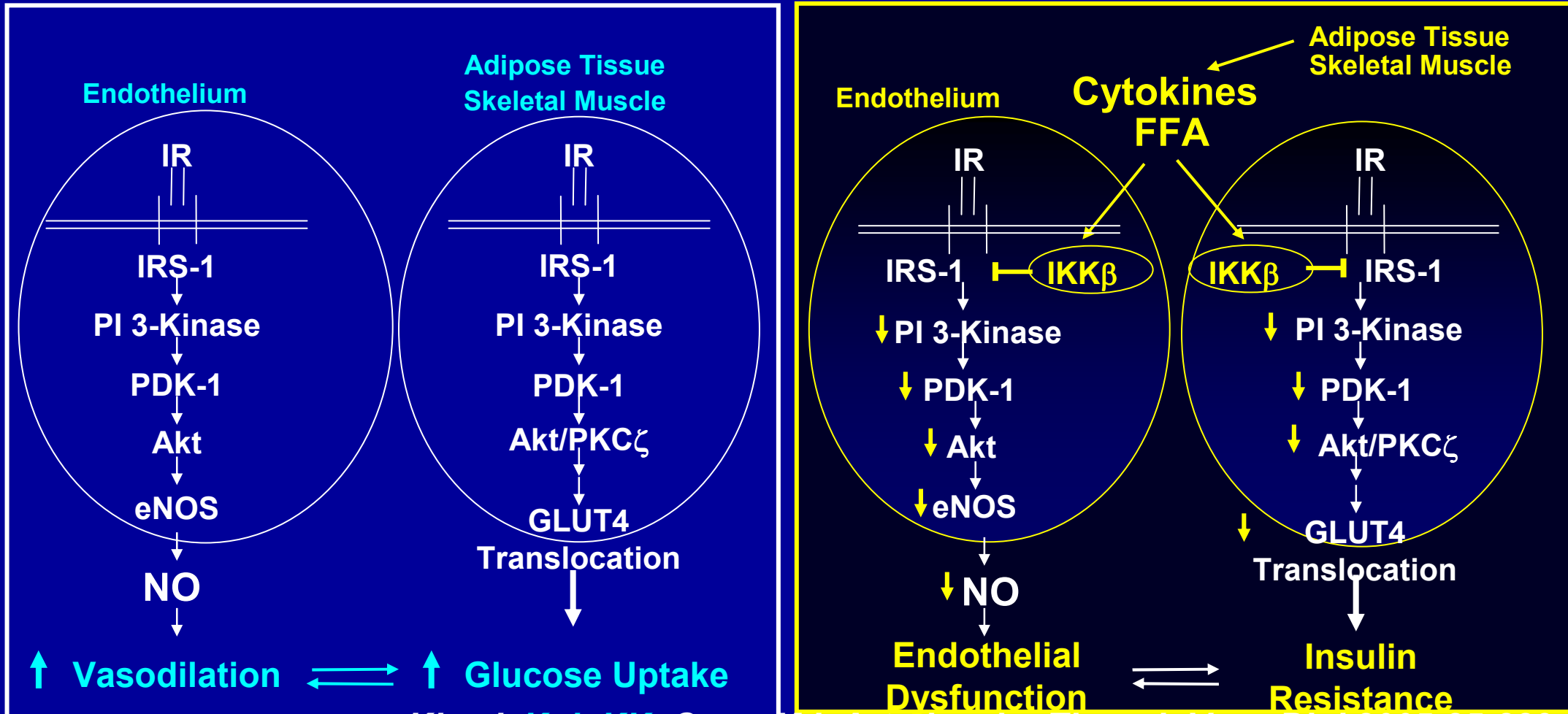
aP2: adipogenic marker gene, adipose protein 2
Schupp M, et al. *Circulation* 2004;107:2054

Cross-talk between inflammatory and insulin signaling pathways causes both **endo. dysfunction** and **metabolic insulin resistance** that synergize to cardiovascular disorders in **Met Syndrome**

Healthy

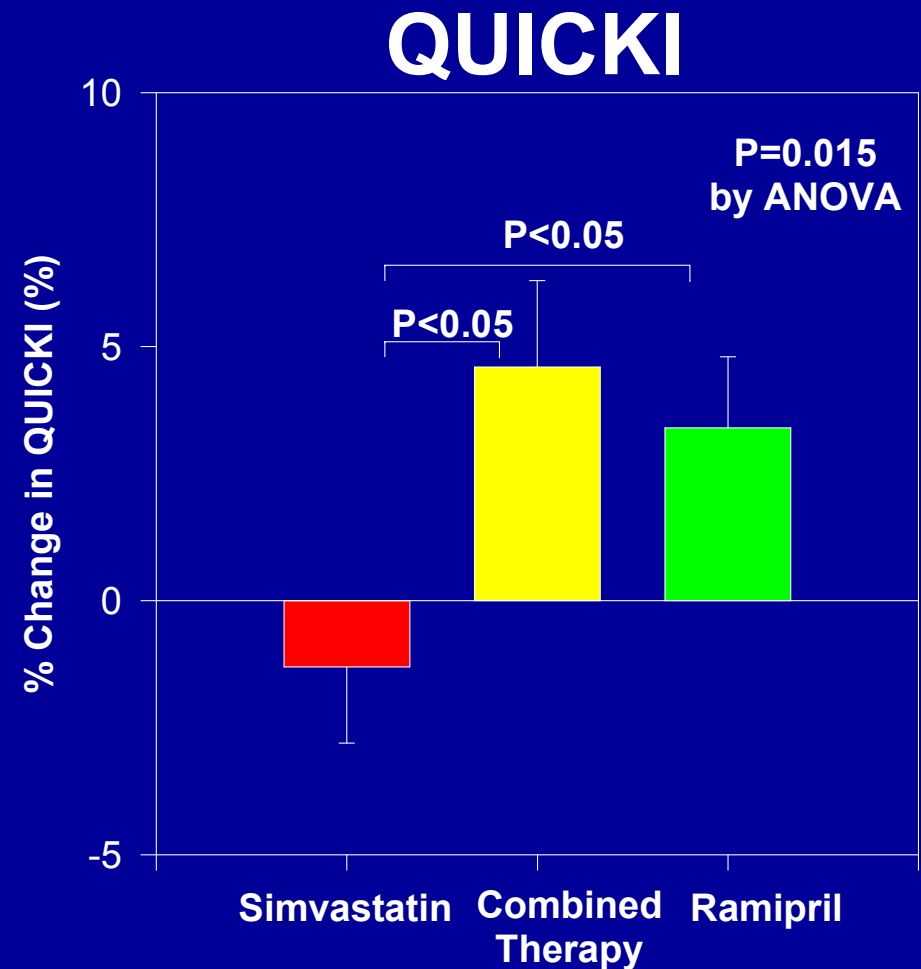
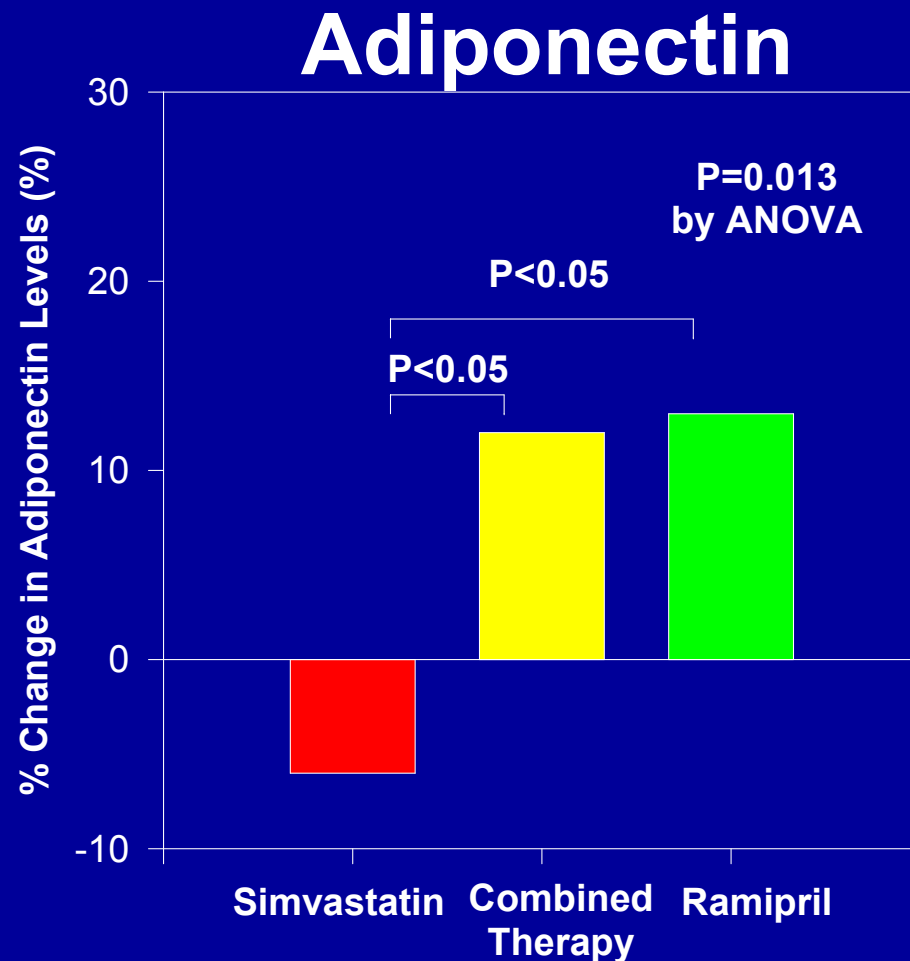
INFLAMMATION

Metabolic and Cardiovascular Diseases



Kim J, Koh KK, Quon MJ. *Arterioscler Thromb Vasc Biol* 2005;25:889.

Effects of Simvastatin, Combined Therapy, and Ramipril on Insulin Sensitivity



*QUICKI=Quantitative Insulin-Sensitivity Check Index, a surrogate index of insulin sensitivity, $QUICKI = 1/[\log(\text{insulin})+\log(\text{glucose})]$

Cross-talk Between RAS and PPAR

Beneficial Effects of Fenofibrate to Improve Endothelial Dysfunction and Raise Adiponectin Levels in Patients With Primary Hypertriglyceridemia

Kwang Kon Koh, Michael J. Quon*
Seung Hwan Han..... Eak Kyun Shin

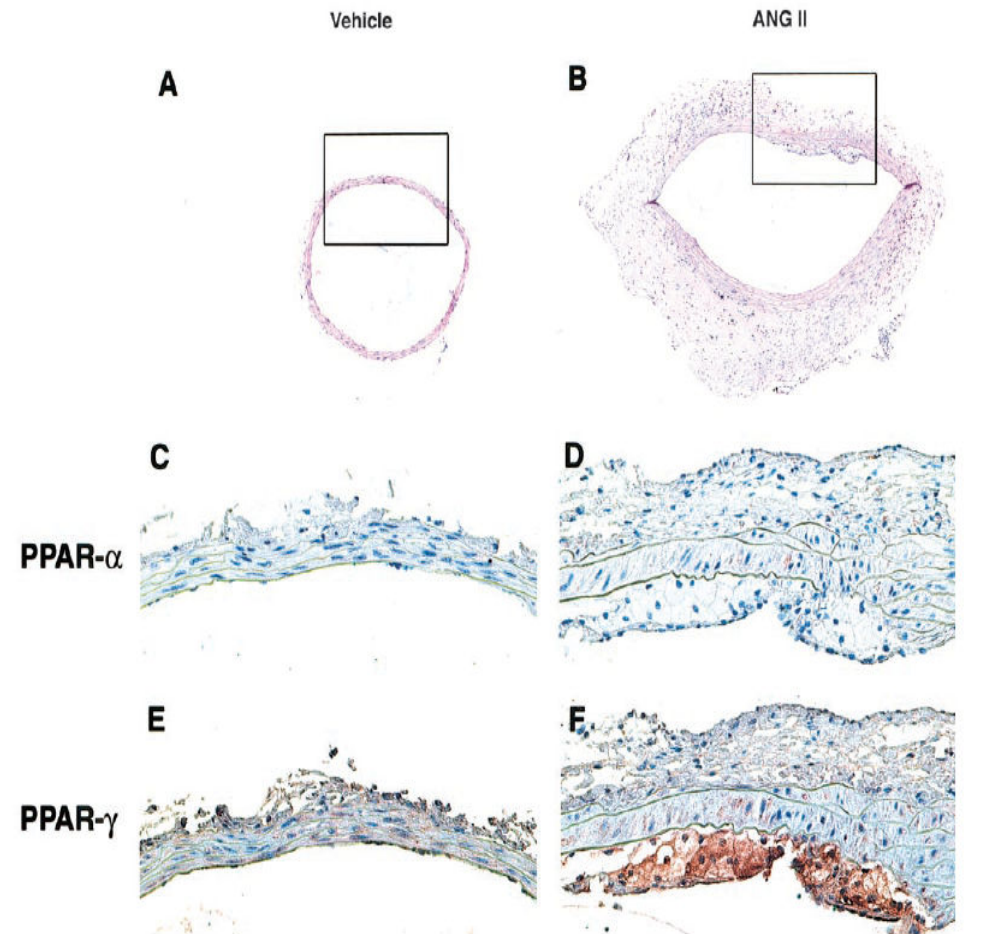
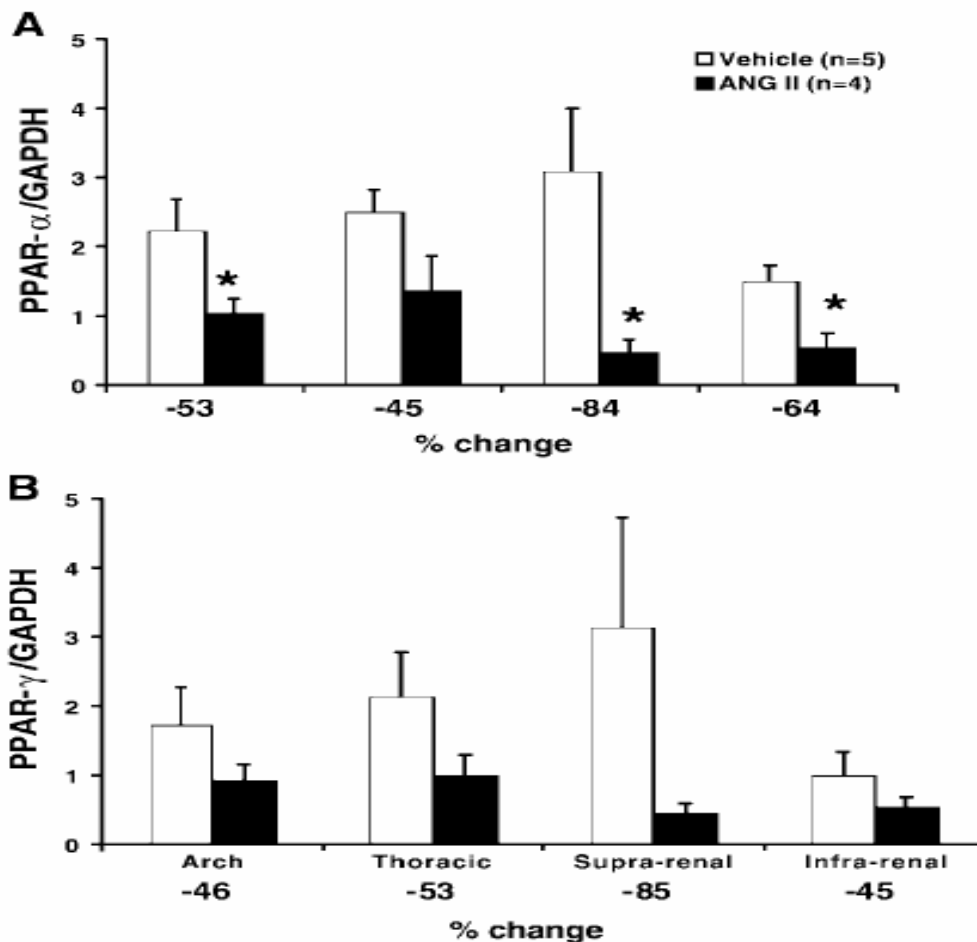
Cardiology, Gachon Medical School, Korea
Diabetes Unit, NIH, USA*

Diabetes Care 2005;28:1419

Downregulation of PPAR- α and PPAR- γ mRNA In Aortas of apoE-KO Mice Treated with ANGII

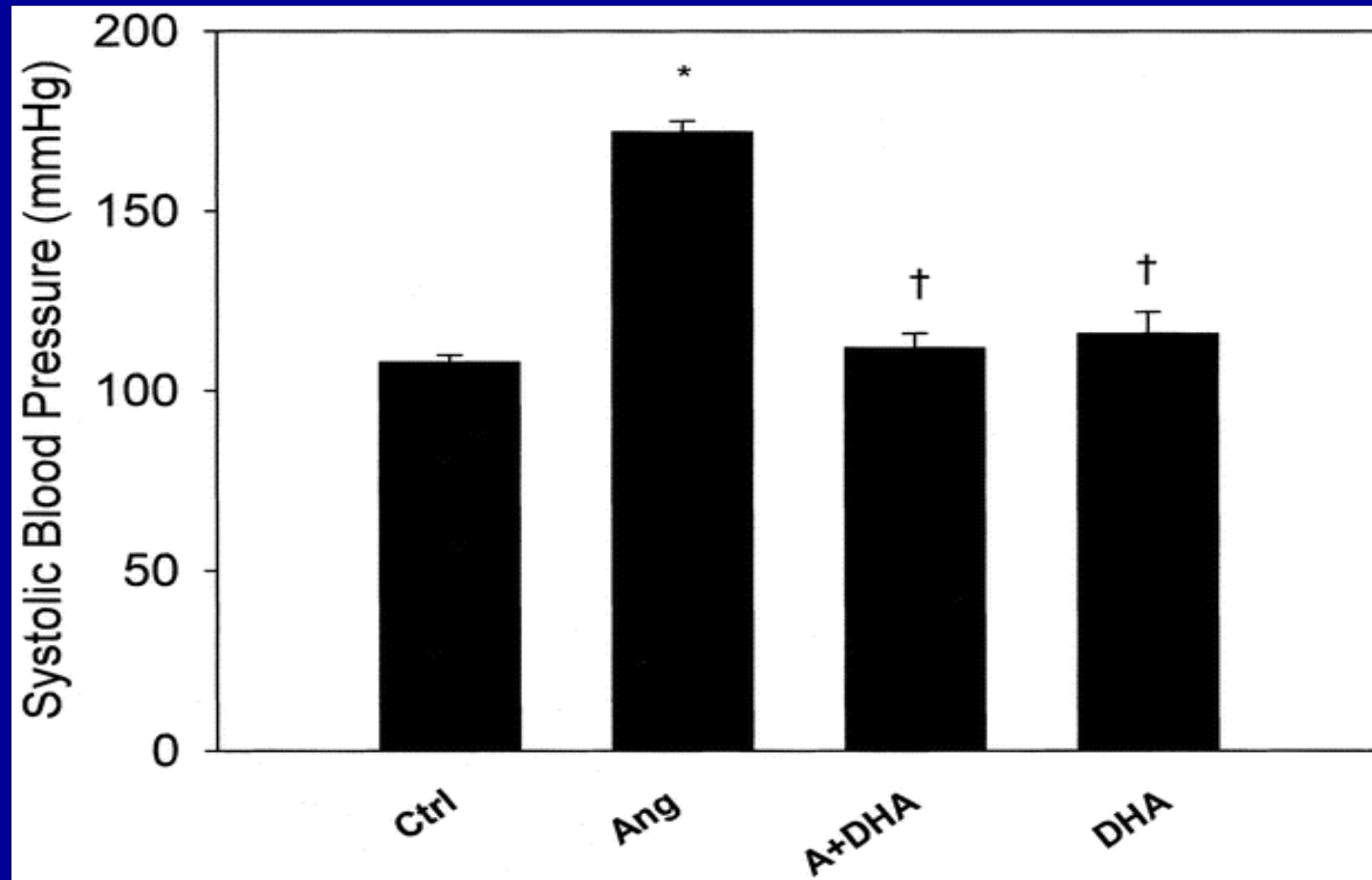
PPAR- α and PPAR- γ mRNA
In aortas of apo E-KO mice

Histo- and IH appearance of
suprarenal aorta



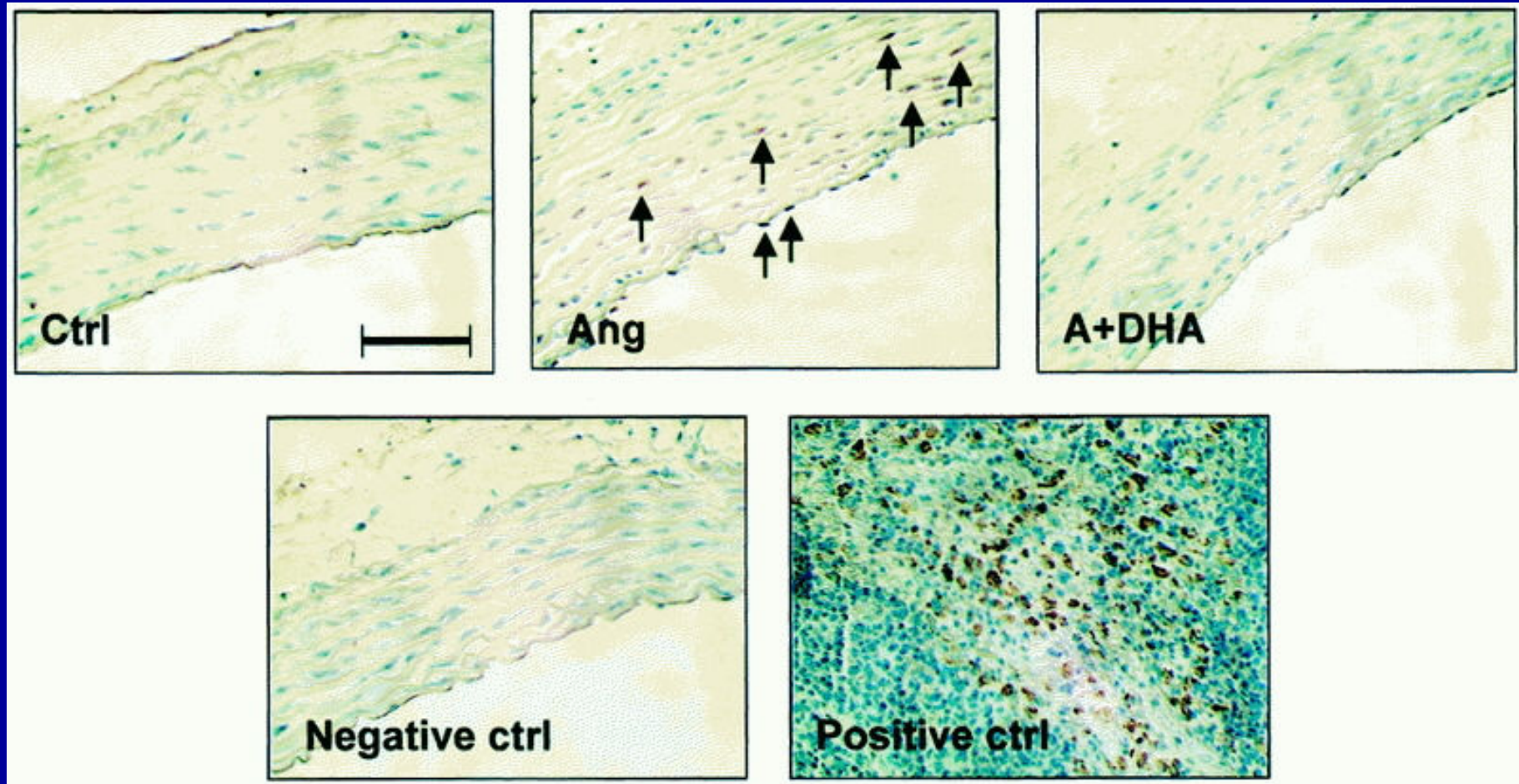
PPAR α Activator Effects on Ang II-Induced Vascular Oxidative Stress and Inflammation

Systolic BP in Ang II-infused rats treated with or without DHA (PPAR α activator, docosahexaenoic acid)

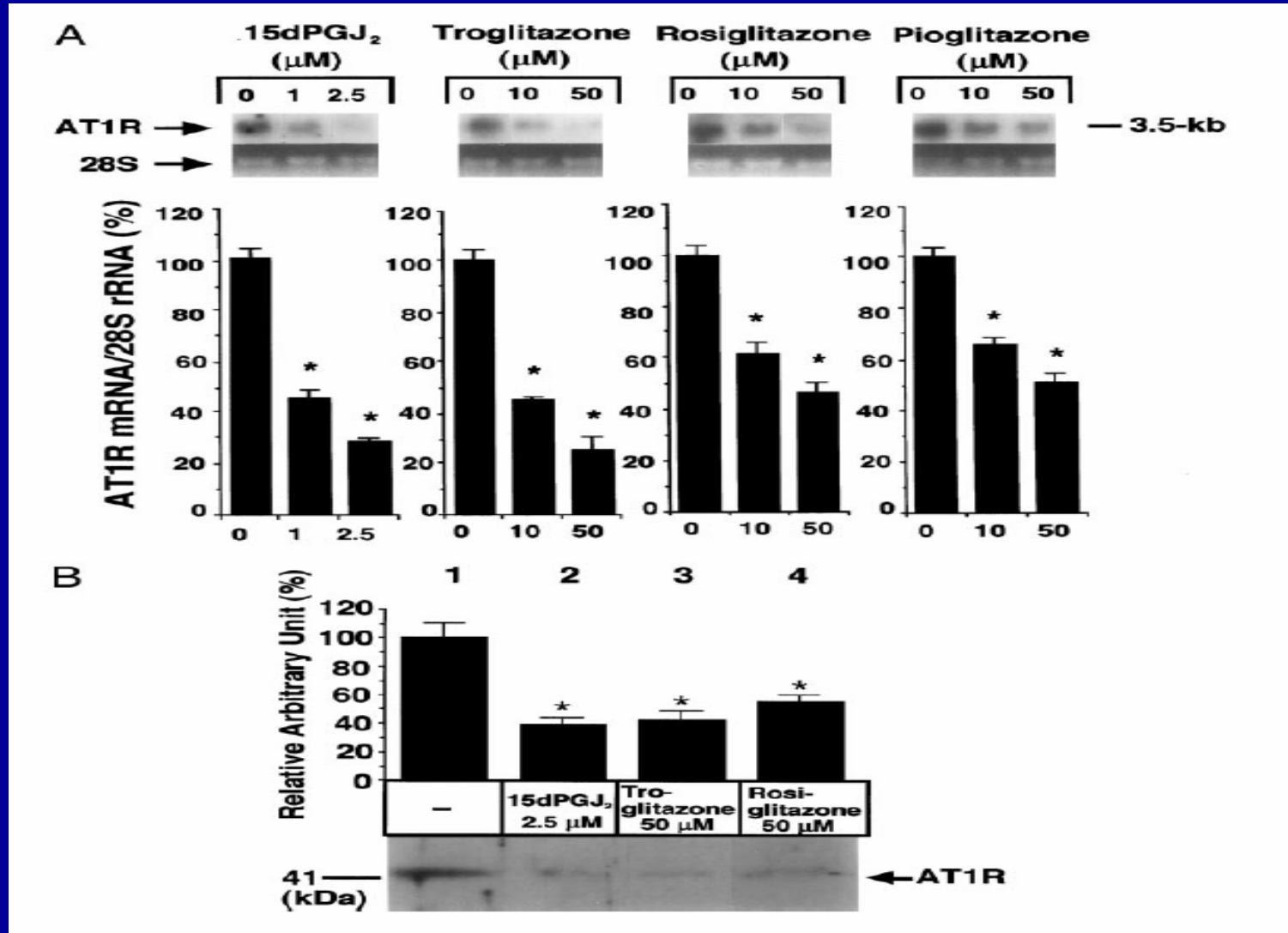


Diep et al, Hypertension 2002;40:866

Representative immunohistochemical Staining for ICAM in aorta of Ang II-infused rats with or without DHA



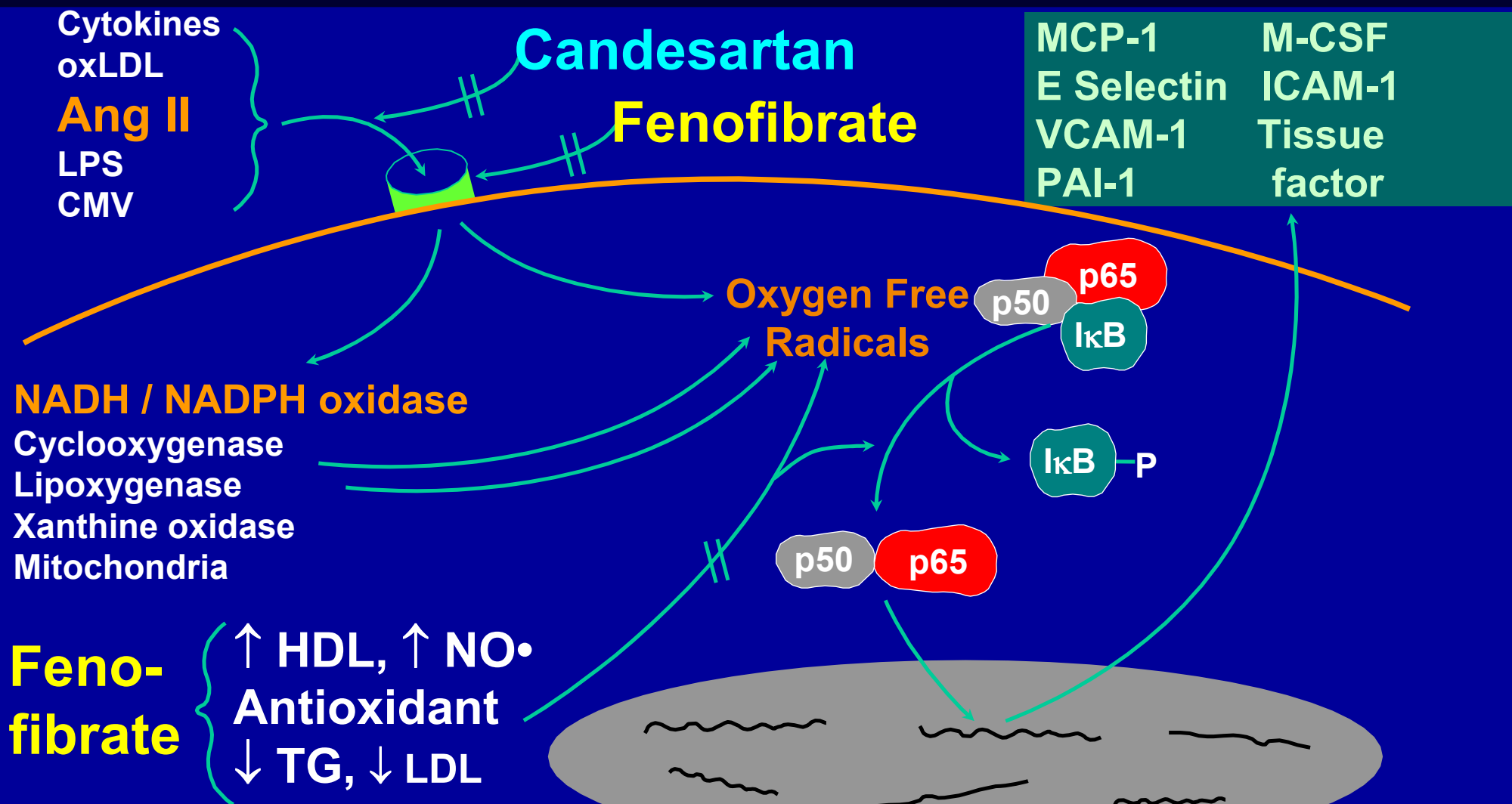
Transcriptional Suppression of AT₁R Gene Expression by PPAR- γ Ligands in VSMCs



AT₁R mRNA expression

AT₁R protein expression

Activation of Nuclear Transcription Factor, NF κ B



Koh KK, JACC 2005;46:1978 (Review)

Hypertension 2005;46:1086 (Review), Circulation 2006;113:1888 (Review)

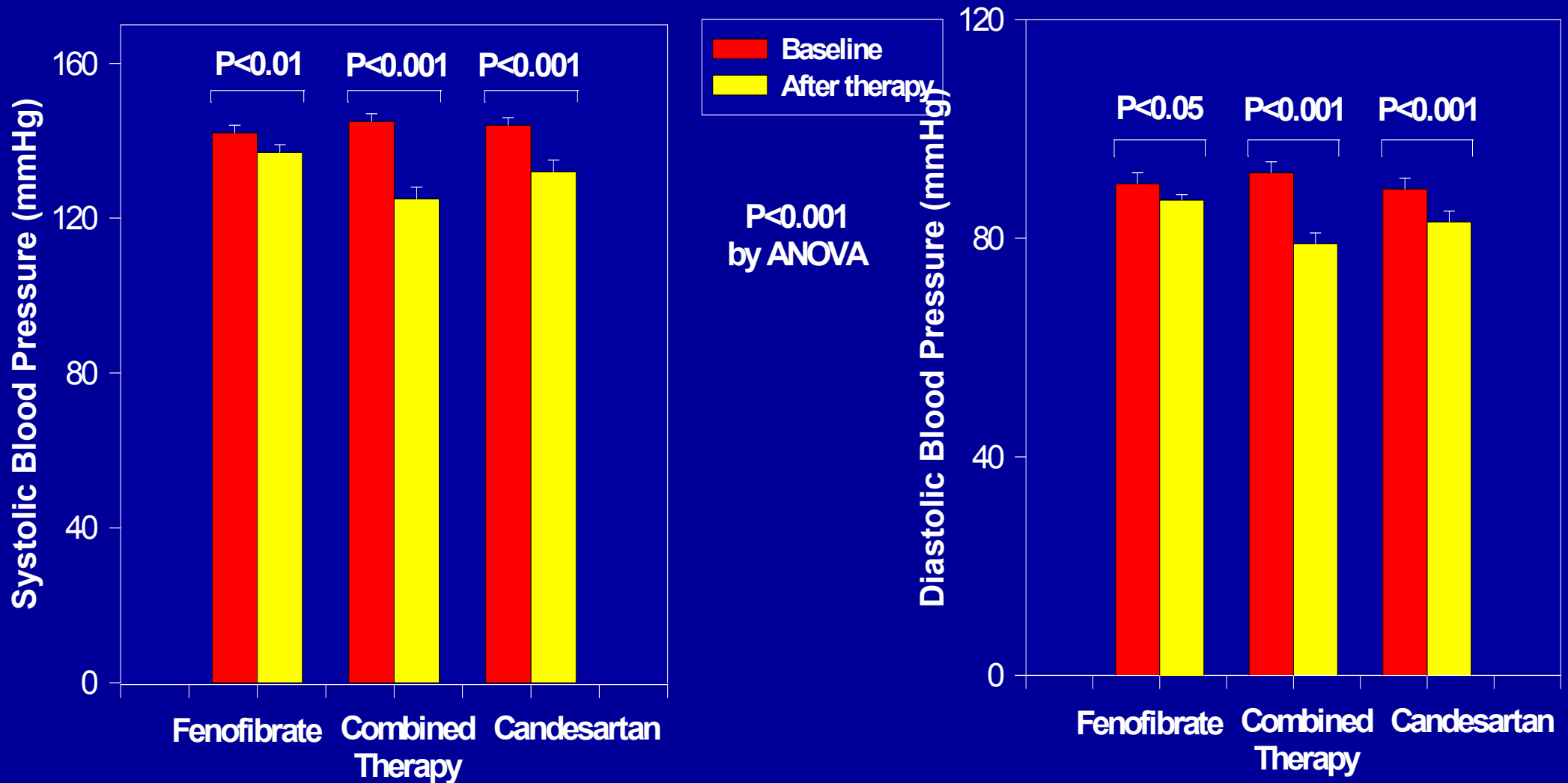
**Additive Beneficial Effects of Fenofibrate
Combined with Candesartan
In Treatment of Hypertriglyceridemic,
Hypertensive Patients**

Kwang Kon Koh, Michael J. Quon*
Seung Hwan Han..... Eak Kyun Shin

**Cardiology, Gachon Medical School, Korea
Diabetes Unit, NIH, USA***

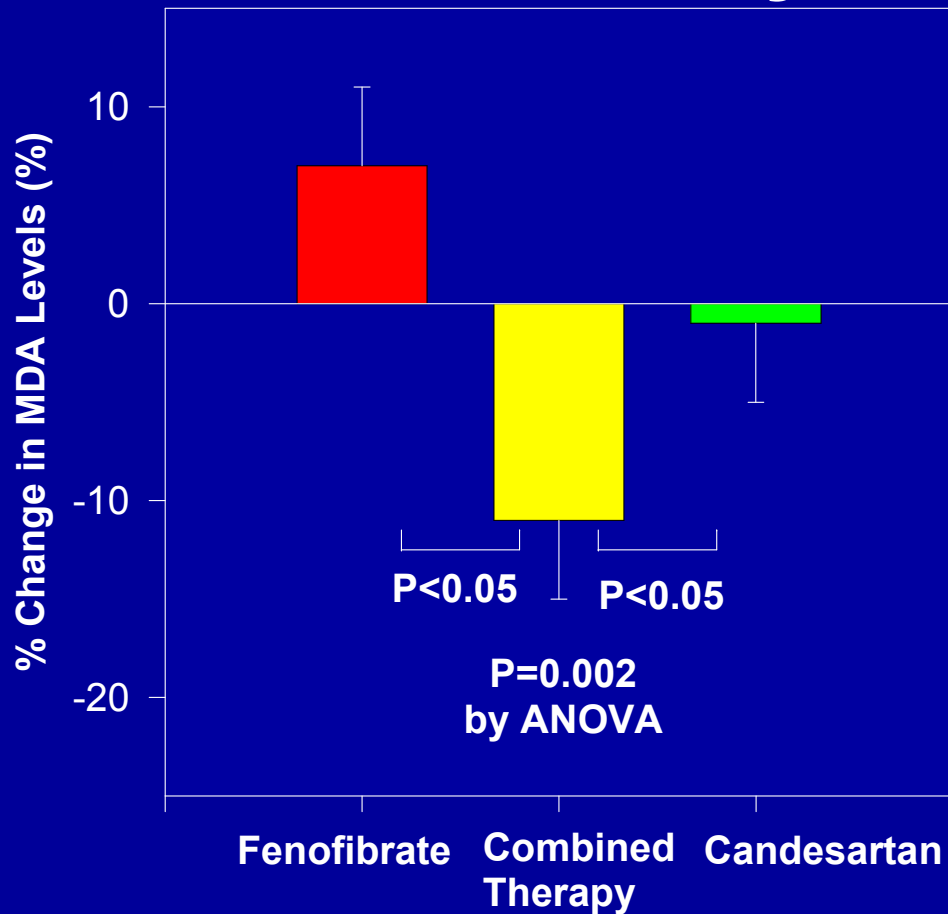
Diabetes Care 2006;29:195
Reuters Health 2006-02-27

Change in BP at Baseline and after Therapy In Hypertriglyceridemic, Hypertensive Patients

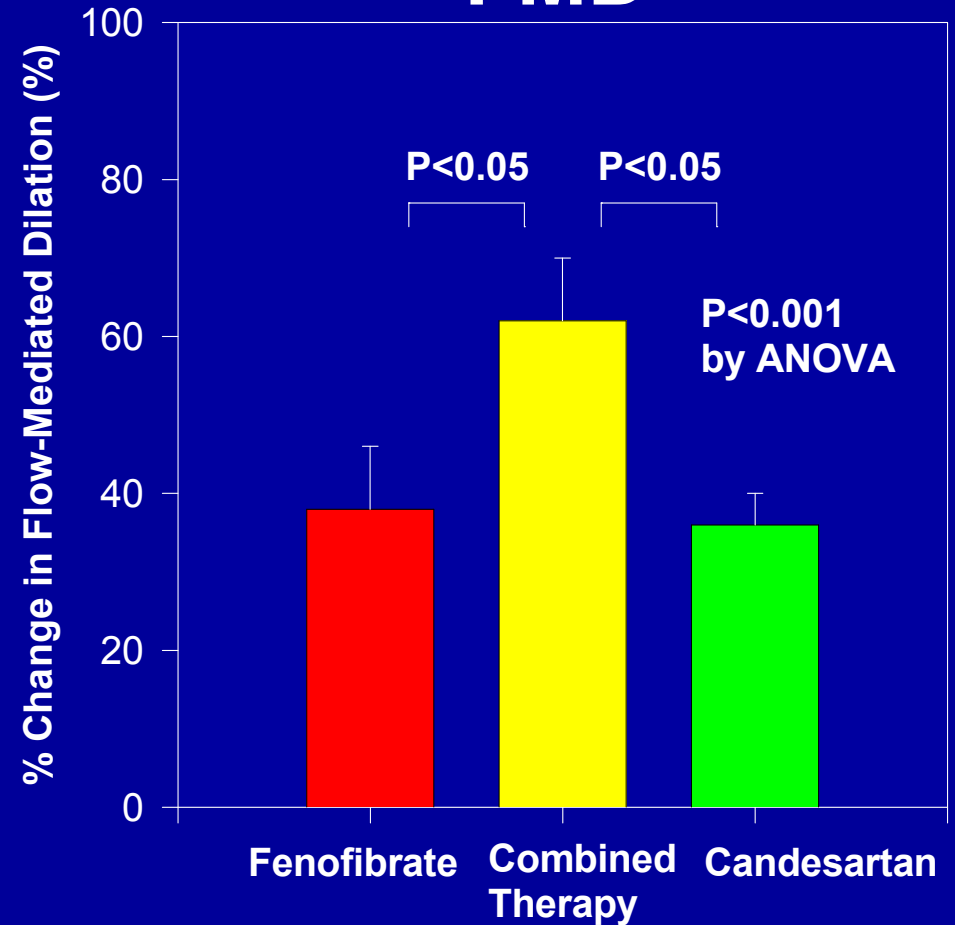


Combined Therapy Significantly Improves Flow-mediated Dilator Response

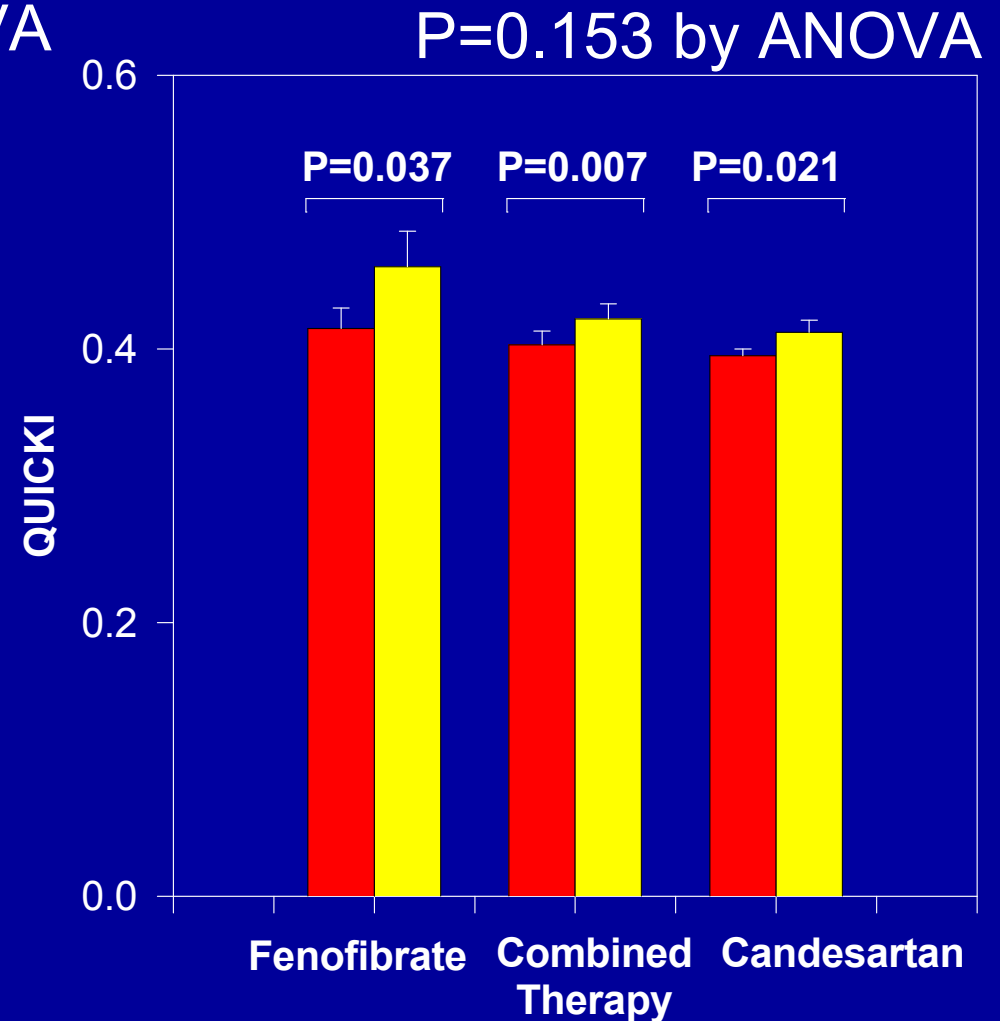
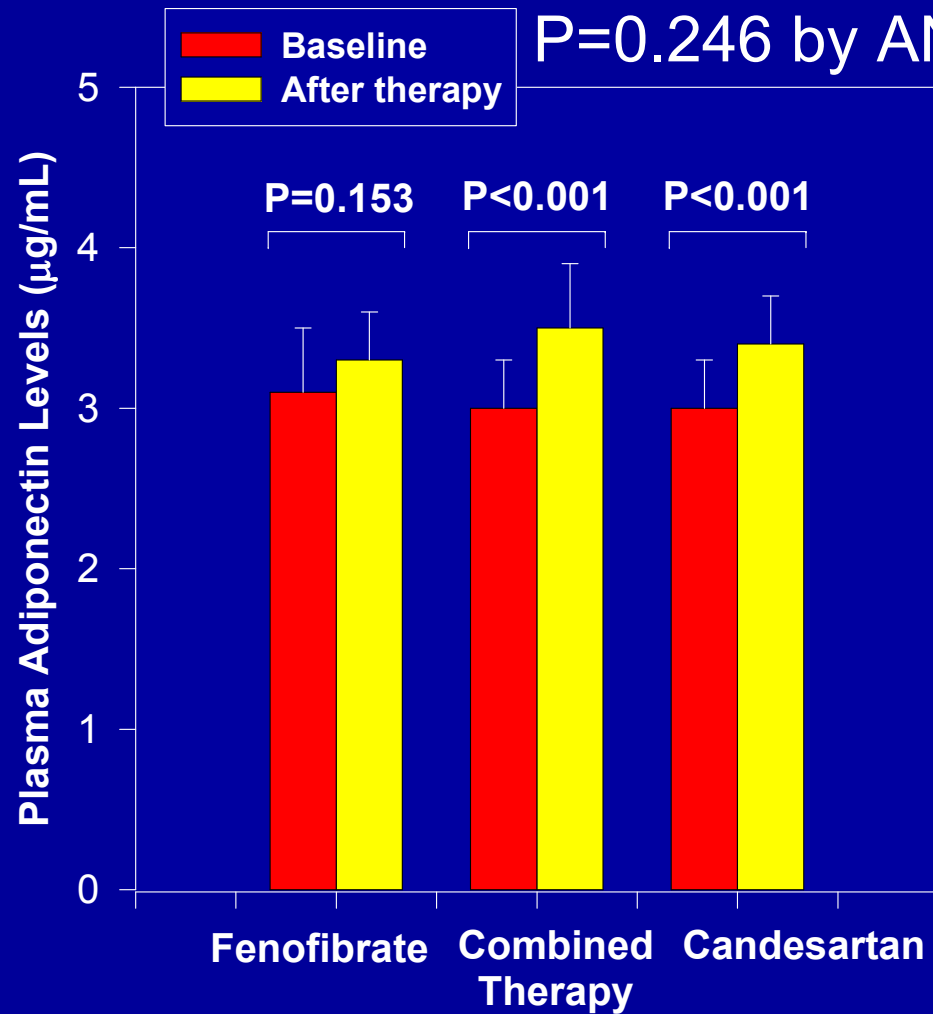
Malondialdehyde



FMD



Change in Insulin Sensitivity at Baseline and after Therapy in HyperTG, HT Patients



Shared and Interacting Mechanisms Underlie Reciprocal Relationships Between IR and ED

Glucotoxicity

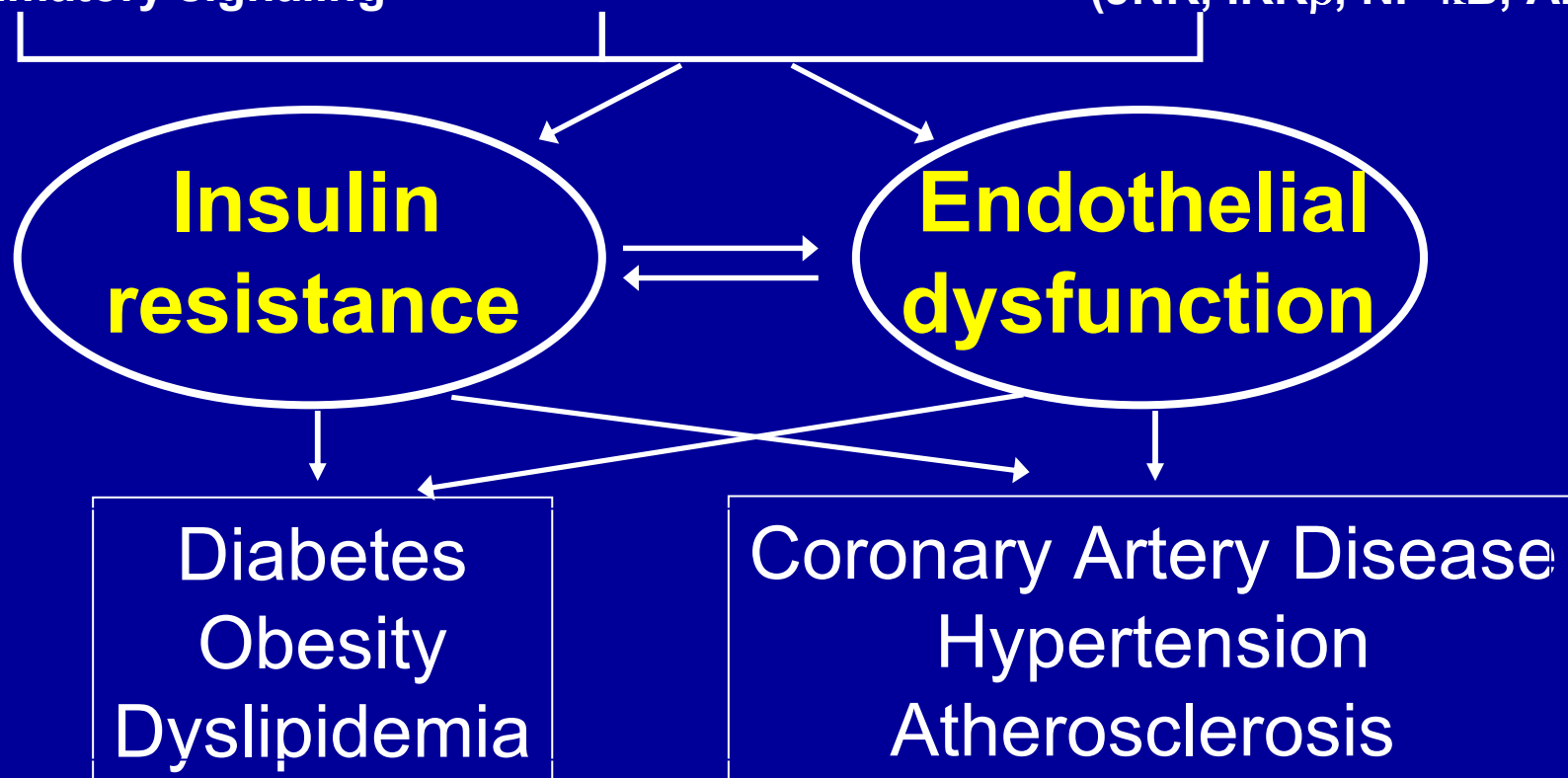
- Oxidative stress
- AGE formation
- Hexosamine Pathway
- Pro-inflammatory signaling

Lipotoxicity

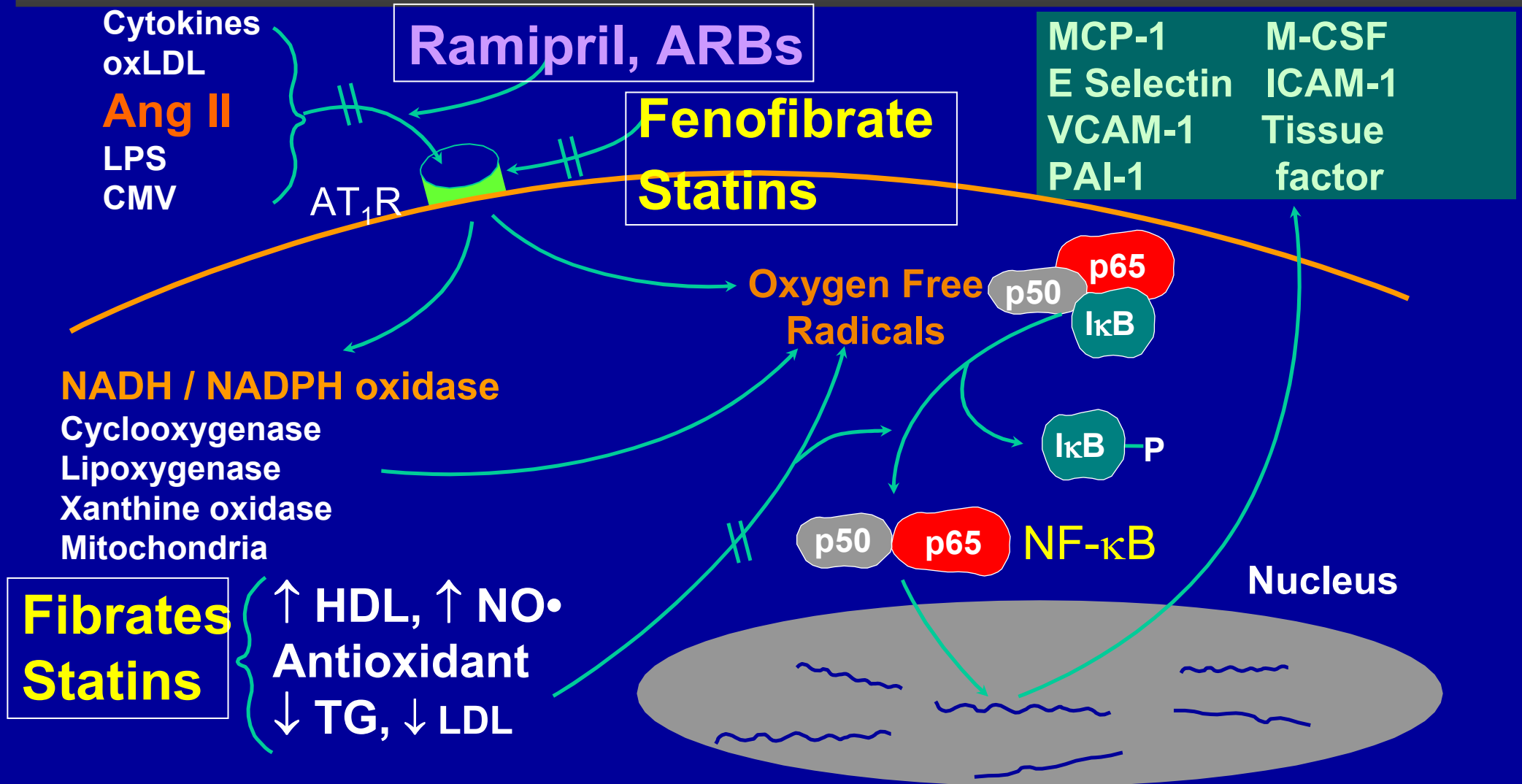
- Oxidative stress
- Pro-inflammatory signaling
- Ceramide

Inflammation

- Pro-inflammatory factors (TNF- α , IL-1 β , IL-6, CRP)
- Kinases/transcription factors (JNK, IKK β , NF- κ B, AP-1)



Combination Therapy for the Treatment of Atherosclerosis: Novel Emerging Concepts



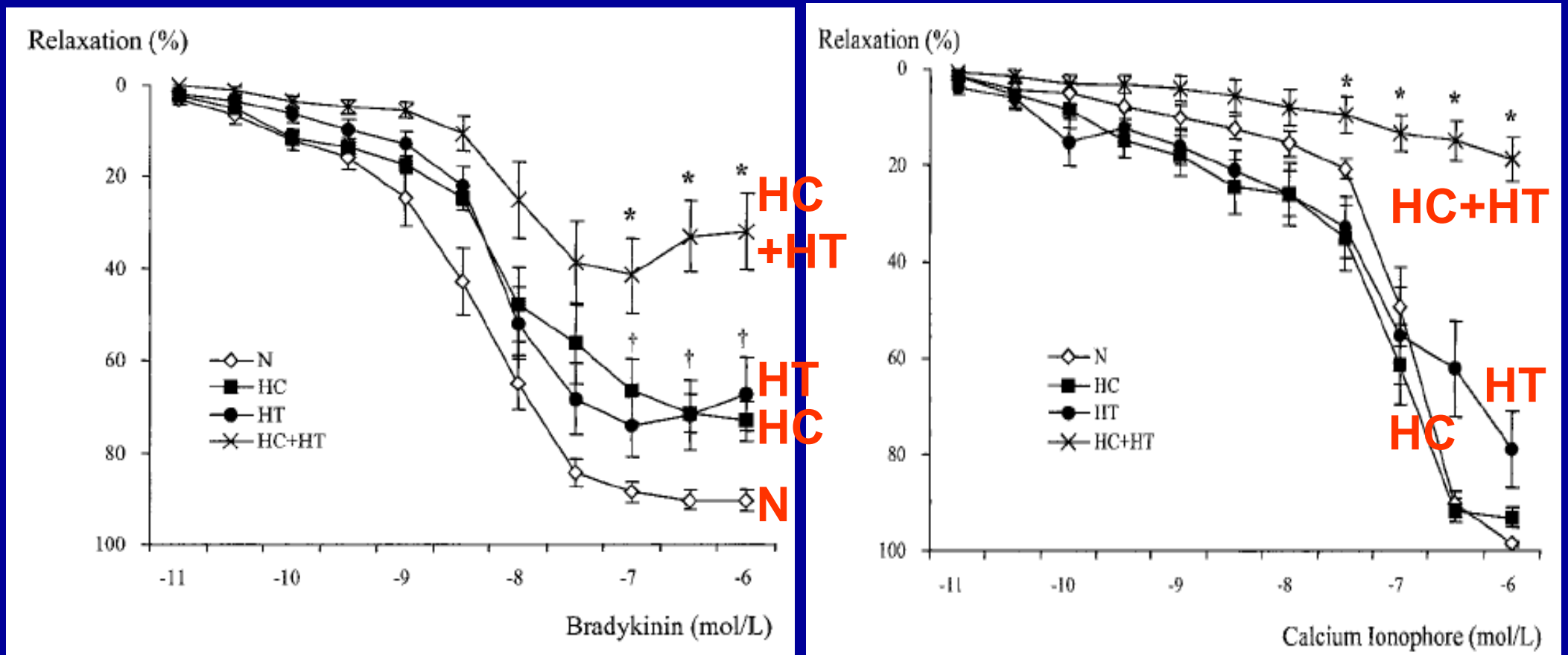
*Koh KK. JACC 2005;46:1978, Hypertension 2005;46:1086, Circulation 2006;113:1888
JACC 2007;49:531, Curr Op Lipid 2007;18:58, Hypertension 2007, Endo Review 2007*





Hypercholesterolemia and Hypertension Have Synergistic Deleterious Effects on Endo. Function

Epicardial arterial vasorelaxation response to Bradykinin and calcium ionophore in pigs



Adiponectin, cytokines secreted by adipose cells, Have insulin-sensitizing, anti-inflammatory, And anti-atherogenic properties

