순환기 추계학회 2006.10.12

The Power of *Ramipril* To Prevent CV Events and Diabetes: Evidence from HOPE and DREAM

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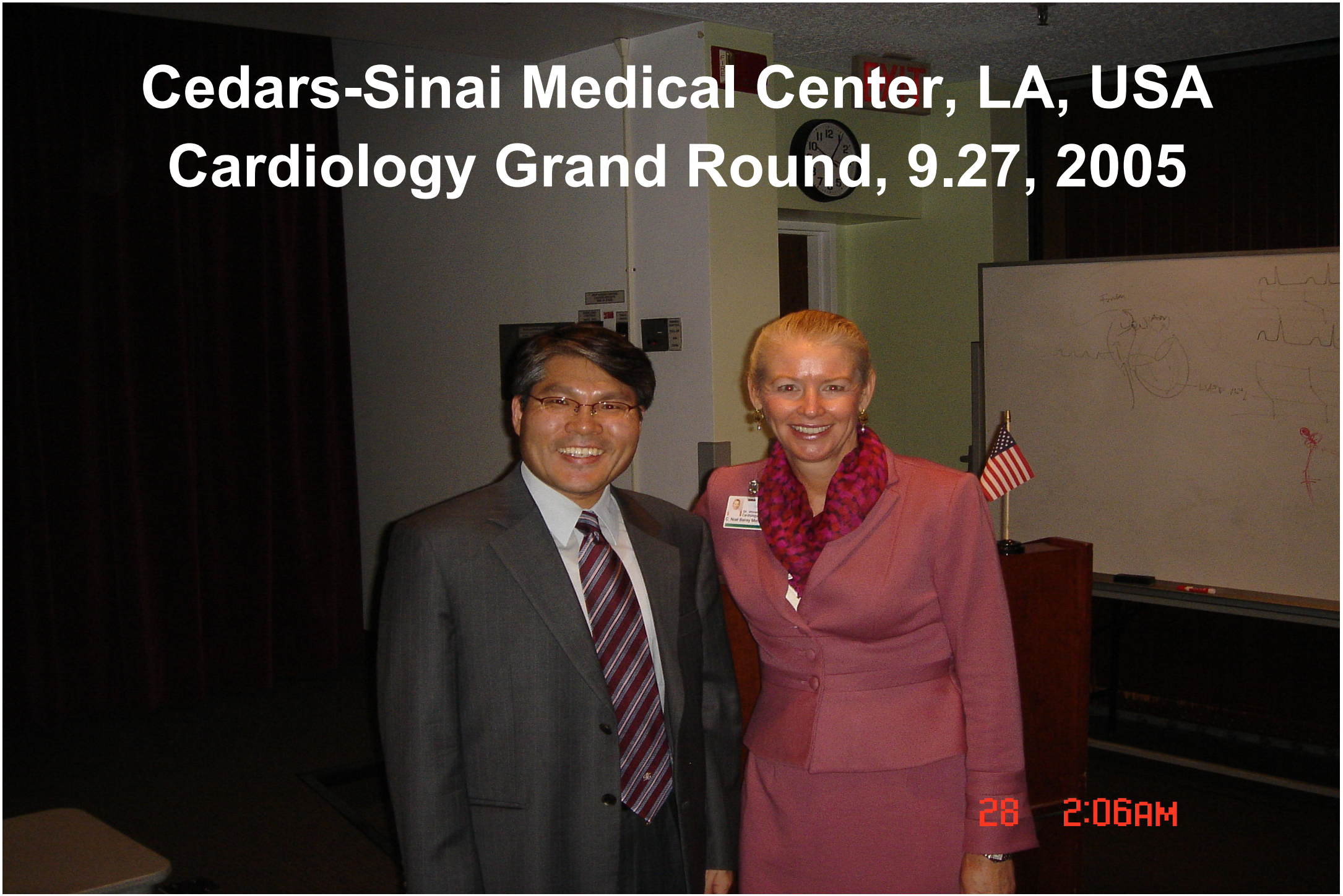
Cardiology, Gil Heart Center
Gachon Medical School
Incheon, Korea

2004 AHA Meeting, Hall G
Hypertension Special Symposium


Cedars-Sinai Medical Center, LA, USA
Cardiology Grand Round, 9.27, 2005
28 2:06AM


Northwestern Memorial Hospital, Chicago
Cardiology Seminar Lecture, Feb. 13, 2006
14 4:02AM

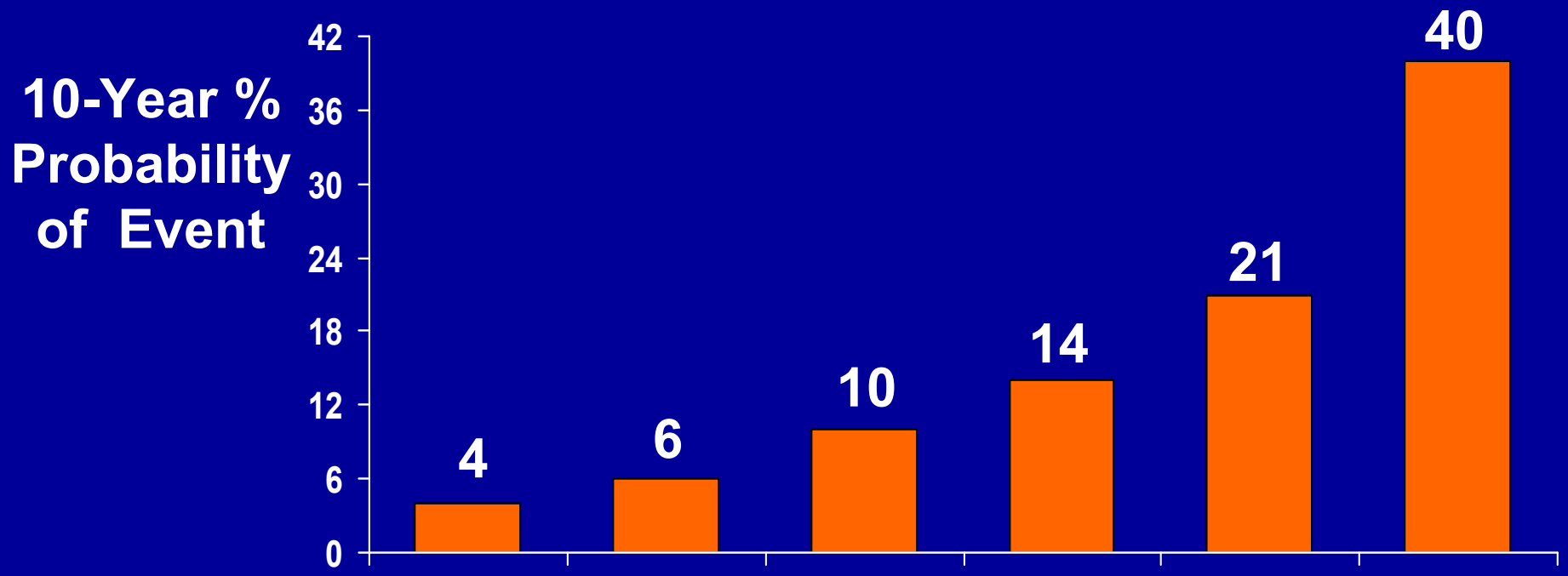
National Institutes of Health, Bethesda, USA
Cardiology Grand Round, 3.15, 2006

달리 생각합시다!!

The Power of *Ramipril*
To Prevent CV Events and Diabetes

- **HOPE, MICRO-HOPE, HOPE-TOO Study**
- **Plausible Mechanisms**
- **Mechanistic Clinical Studies**
- **Conclusions**

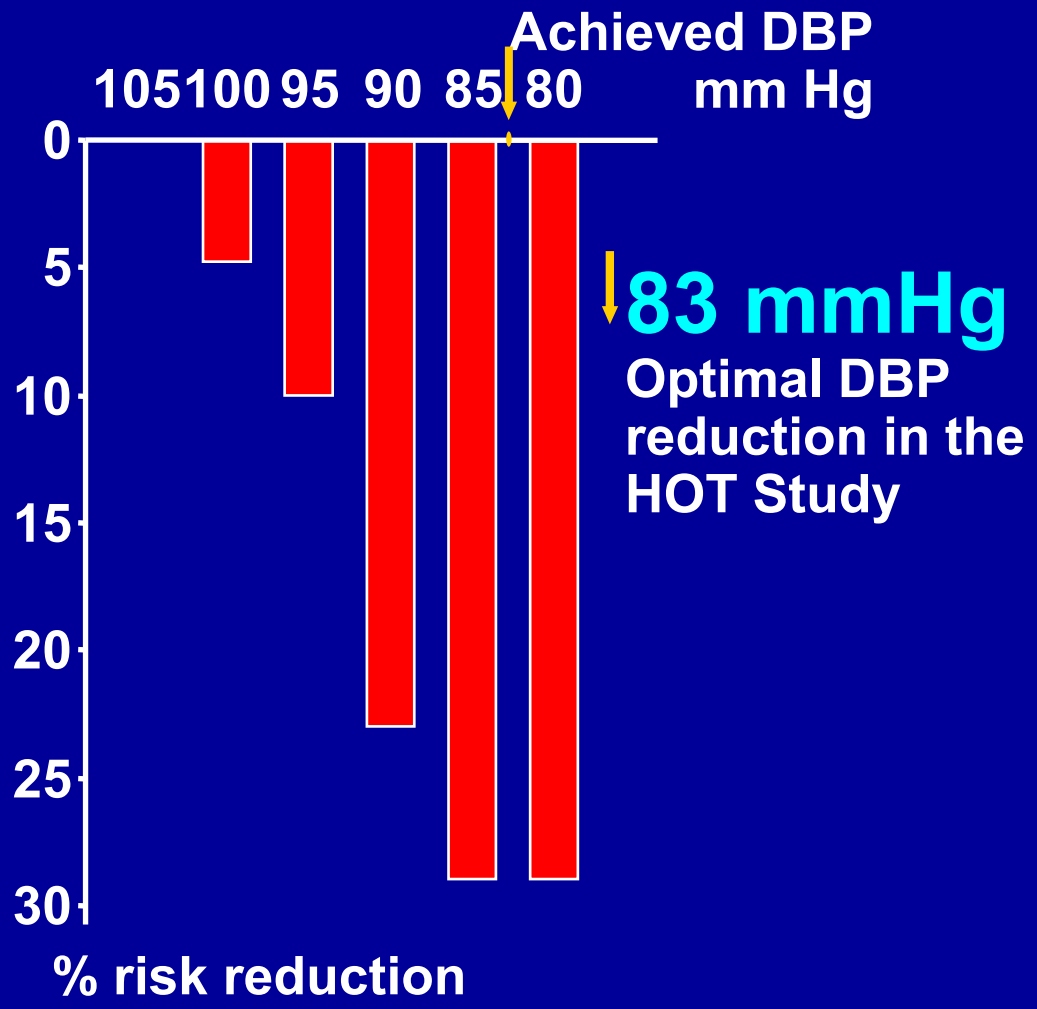
CAD Risk By Associated Risk Factors

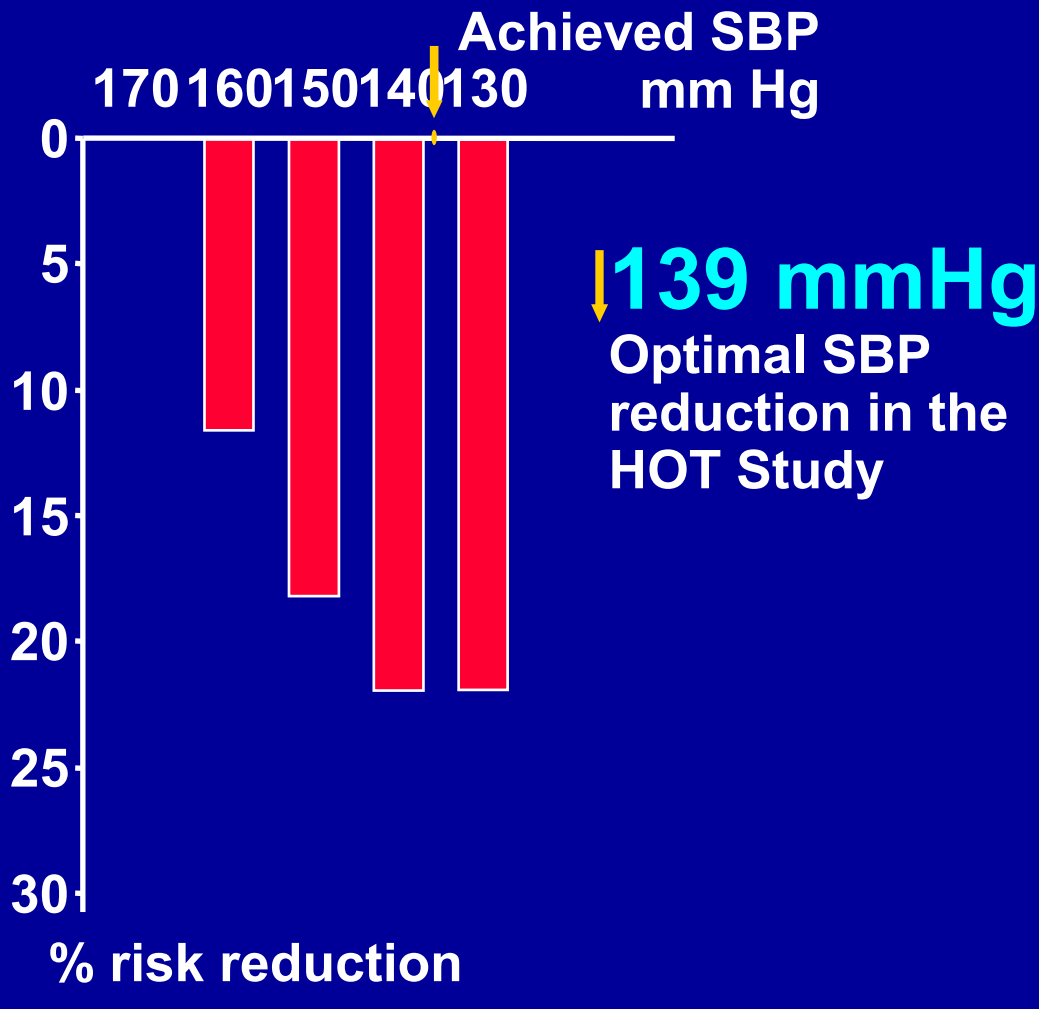


Systolic BP150-160	+	+	+	+	+	+
Cholesterol 240-262	-	+	+	+	+	+
HDL-C 33-35	-	-	+	+	+	+
Diabetes	-	-	-	+	+	+
Smoking	-	-	-	-	+	+
EKG-LVH	-	-	-	-	-	+

Kannel WB. Am J Hypertens. 2000;13:3S-10S.

HOT* Study: Risk of Major CV Event Reduced by 30% and 22%

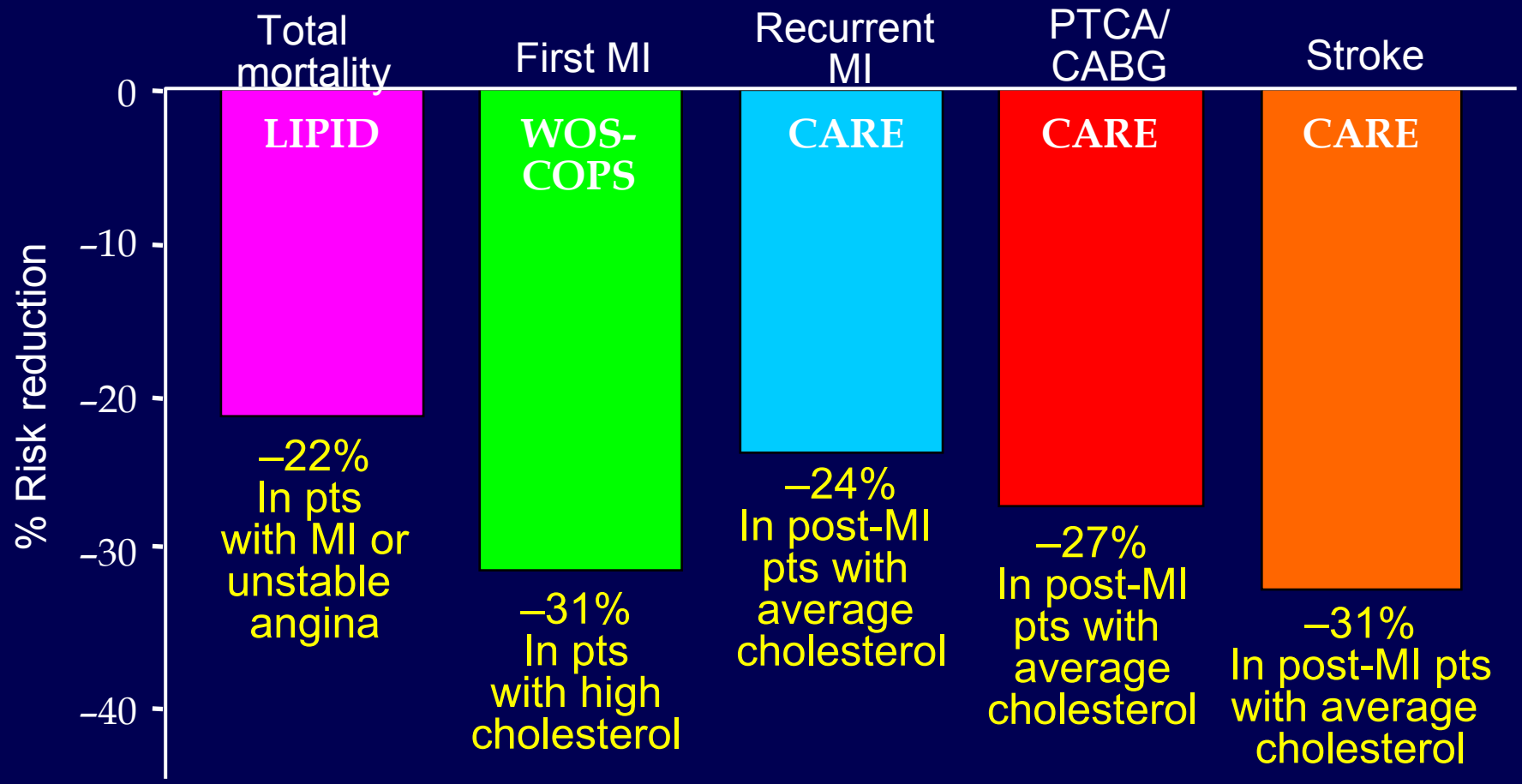




**HOT: Hypertension Optimal Treatment*

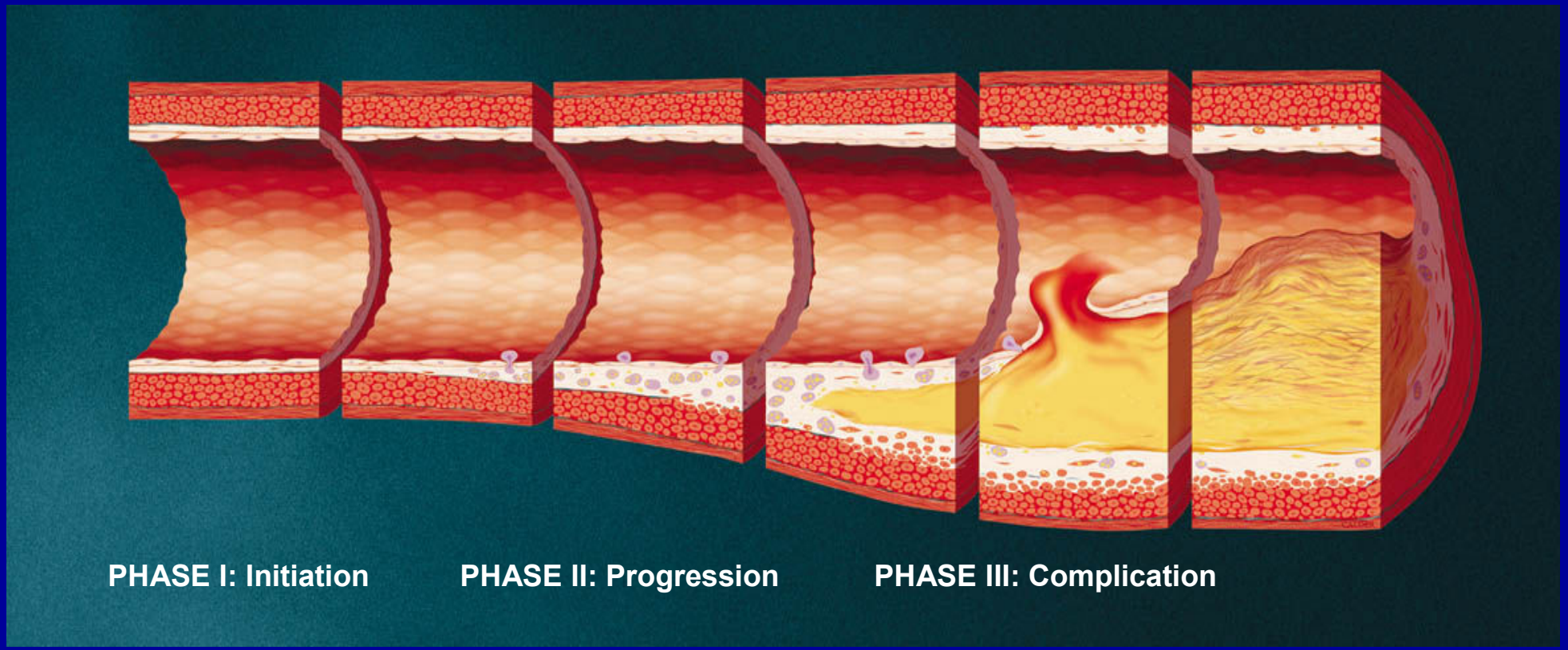
Lancet 1998;351:1755-62

Clinical Benefit of Pravastatin:
Evidence of Protection



Shepherd et al: *N Engl J Med* 1995;333:1301; The LIPID Study Group: *N Engl J Med* 1998;339:1349; Sacks et al: *N Engl J Med* 1996;335:1001

Atherosclerosis: A progressive process



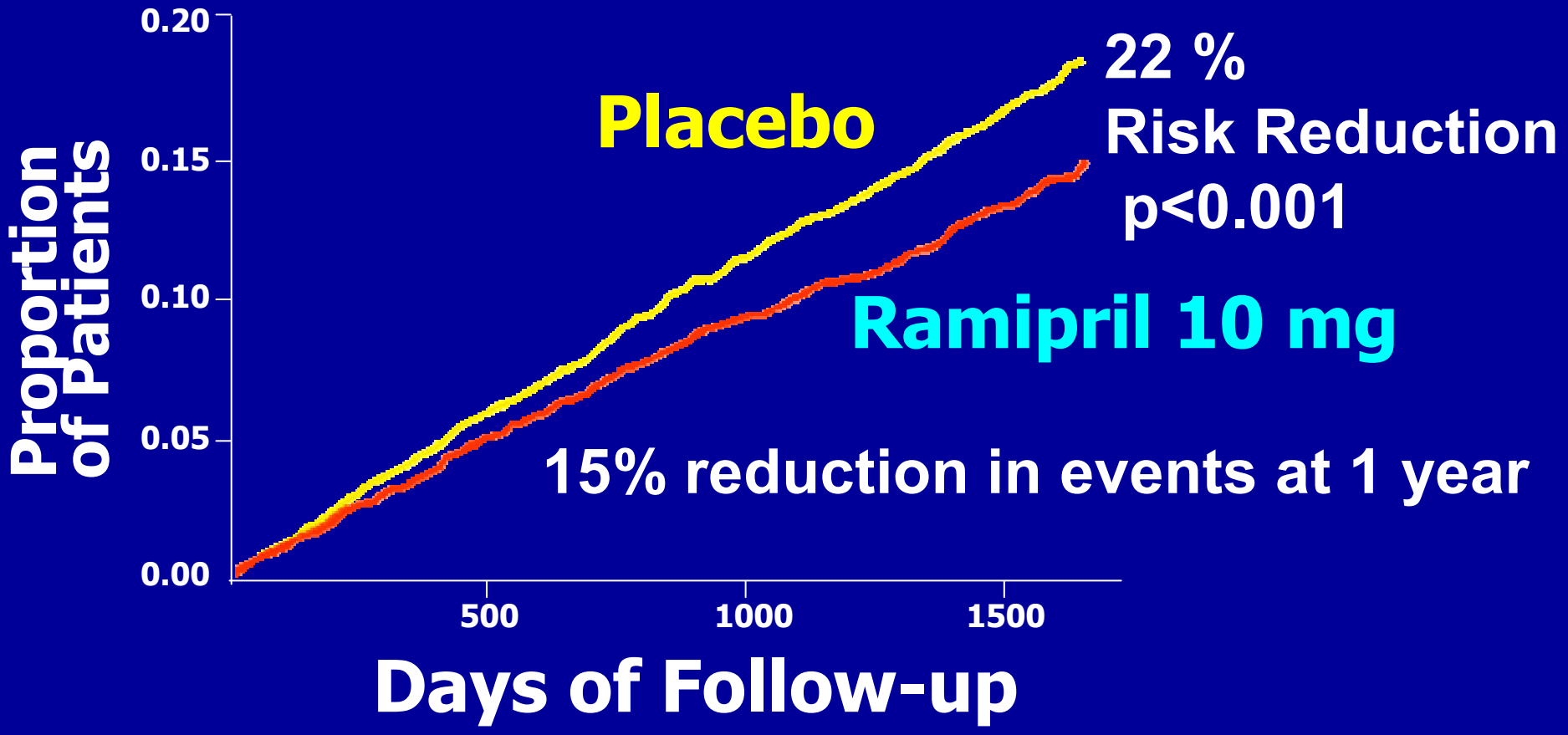
Disease progression

Regulatory Properties of Endothelium

- Vascular tone: Nitric oxide
- Inflammation
- Hemostasis
- Extracellular matrix
- Local cell growth
- Solute transport

Koh KK. Cardiovasc Res 2000;47:648 (Review)
Koh KK. Cardiovasc Res 2002;55:714 (Review)

Heart Outcomes Prevention Evaluation Study: MI/stroke/CV death



High risk patients with vascular disease or diabetes and additional risk factors

N Engl J Med, 2000;342:145.

BP Reduction and CV Risk in HOPE

- 22% relative risk reduction despite only a modest reduction in BP (-3.3 mmHg systolic)

- The benefits seen in HOPE were around **three times** greater than predicted from a meta-analysis of all trials

The benefits were **not due to reduced BP alone**

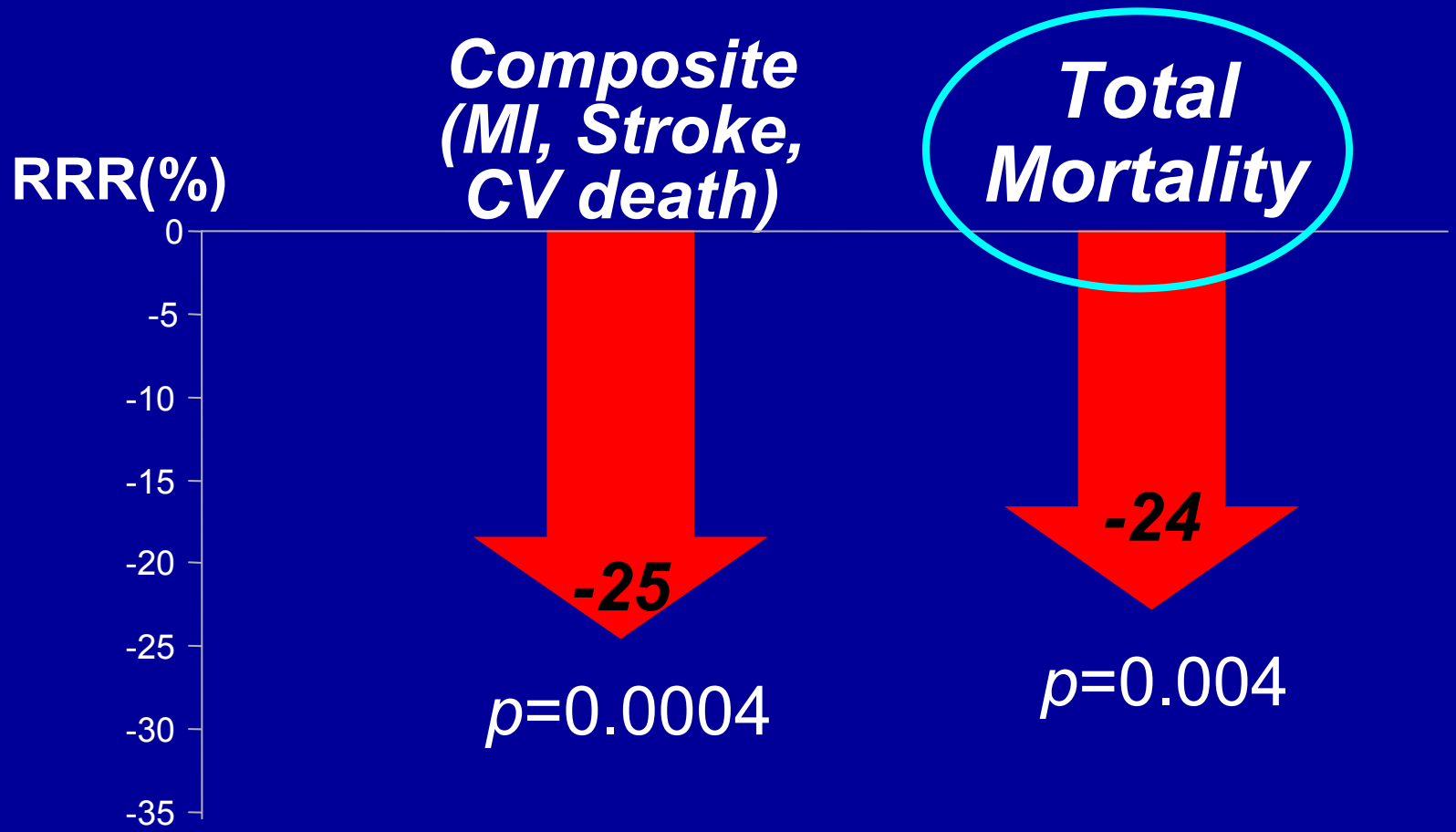
Sleight et al, Lancet 2001;358:2130

MICRO-HOPE Study

- MICRO-HOPE study investigated whether the addition of *ramipril* to the current medical regimen in high risk patients (3577) with diabetes mellitus can lower the risk of CV events.

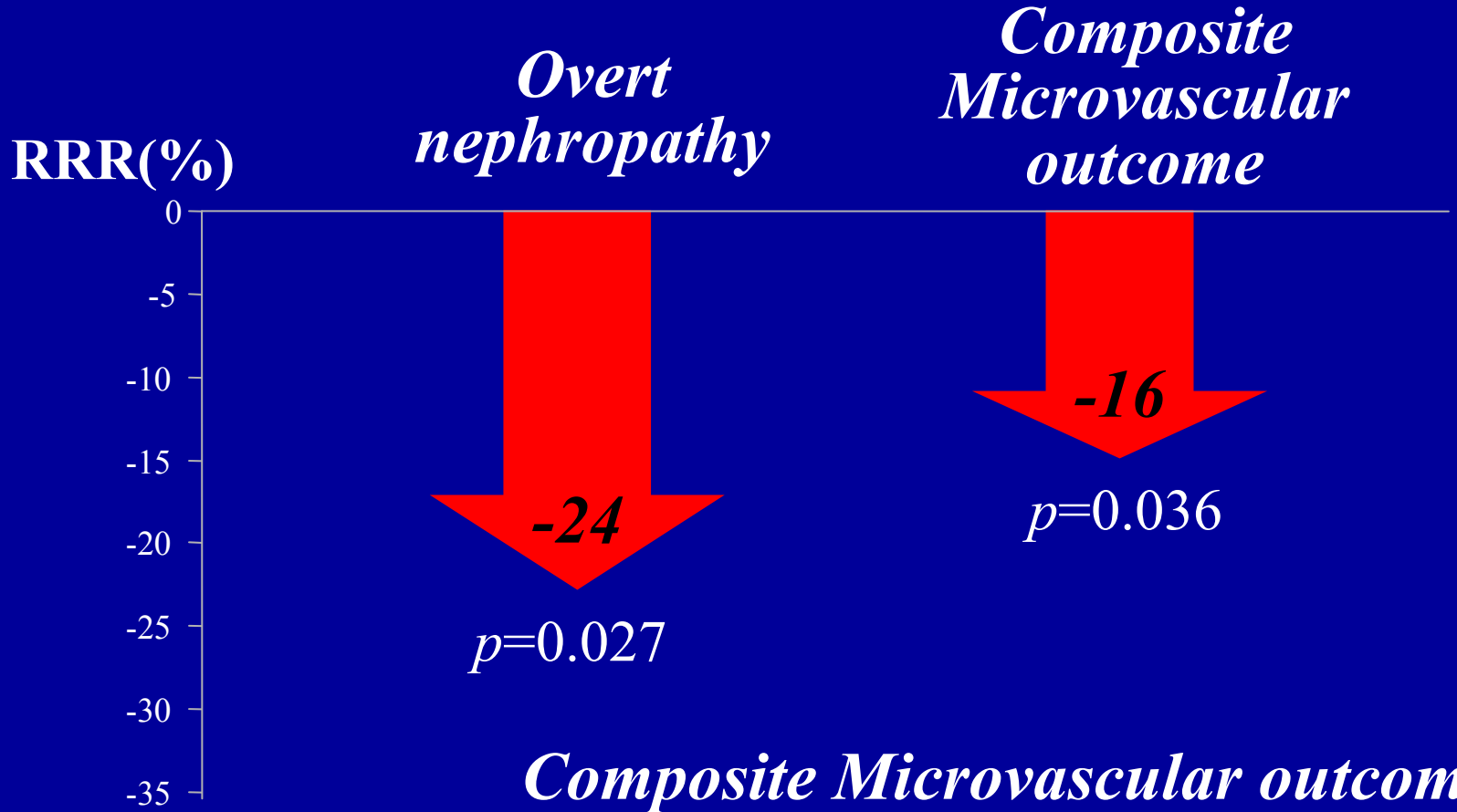
- High risk patients:
  - previous CVD (CAD, stroke, or PVD)
  - HT, TC>200 (5.2 mmol/l), HDL-C<35 (0.9 mmol/l), current smoking, known microalbuminuria
- Mean follow-up: 4.5 years

MICRO-HOPE : CV outcomes (I)



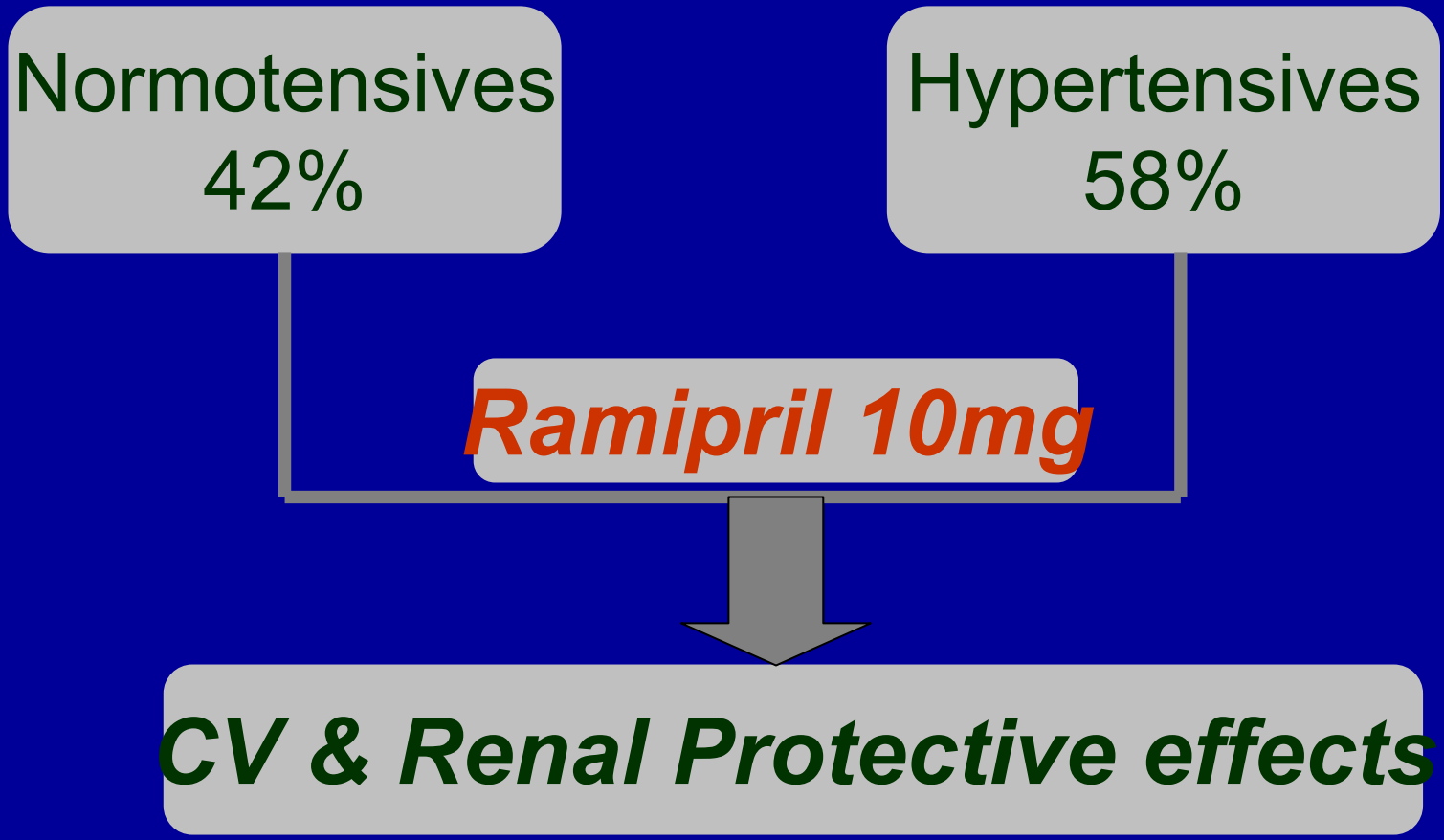
The Lancet, 2000; 355: 253

MICRO-HOPE : Microvascular Outcomes



Composite Microvascular outcome :
Overt nephropathy/ dialysis/ laser therapy

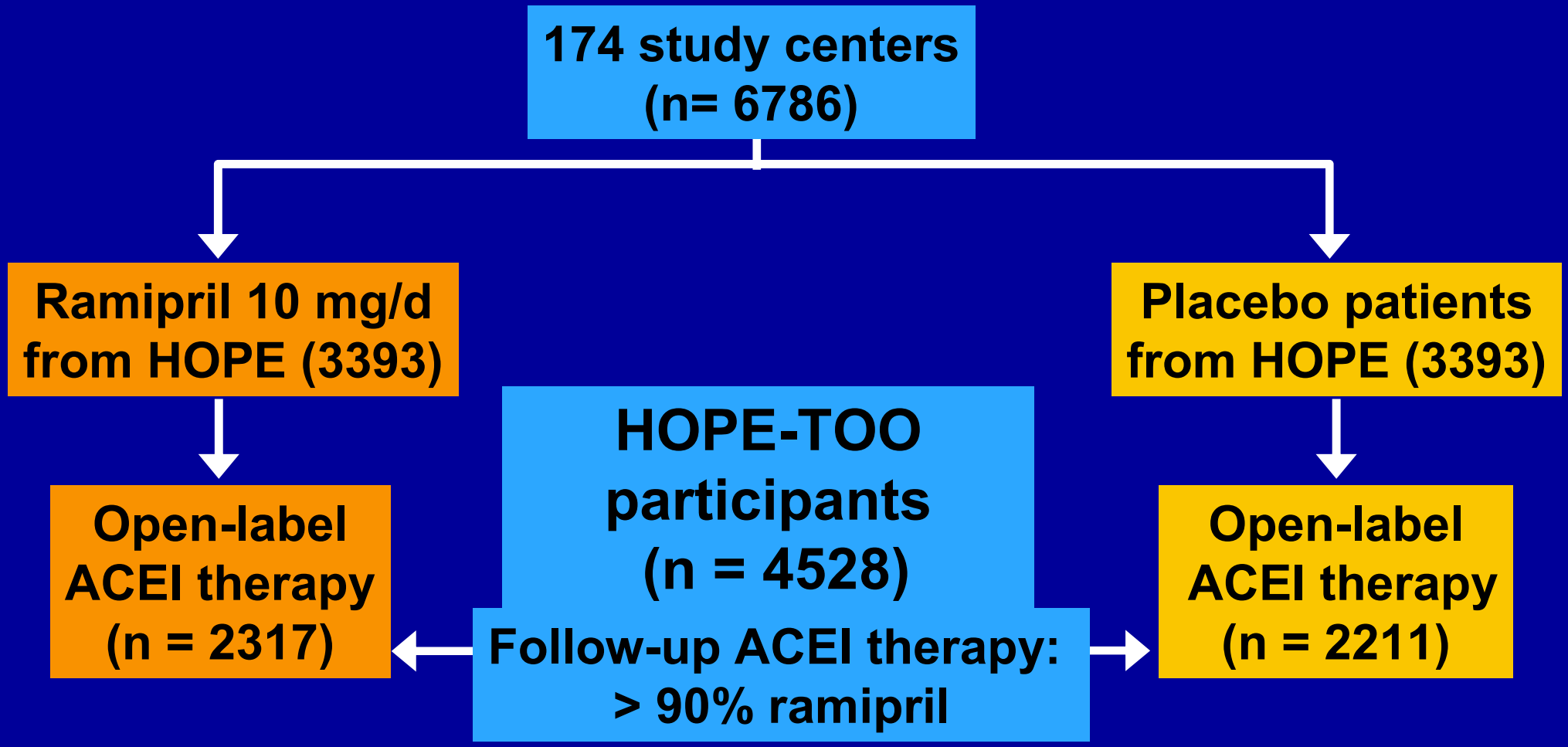
Effect in Normotensives and Hypertensives



HOPE Study Investigators, The Lancet, 2000; 355(22): 253-259

HOPE-TOO: Study design

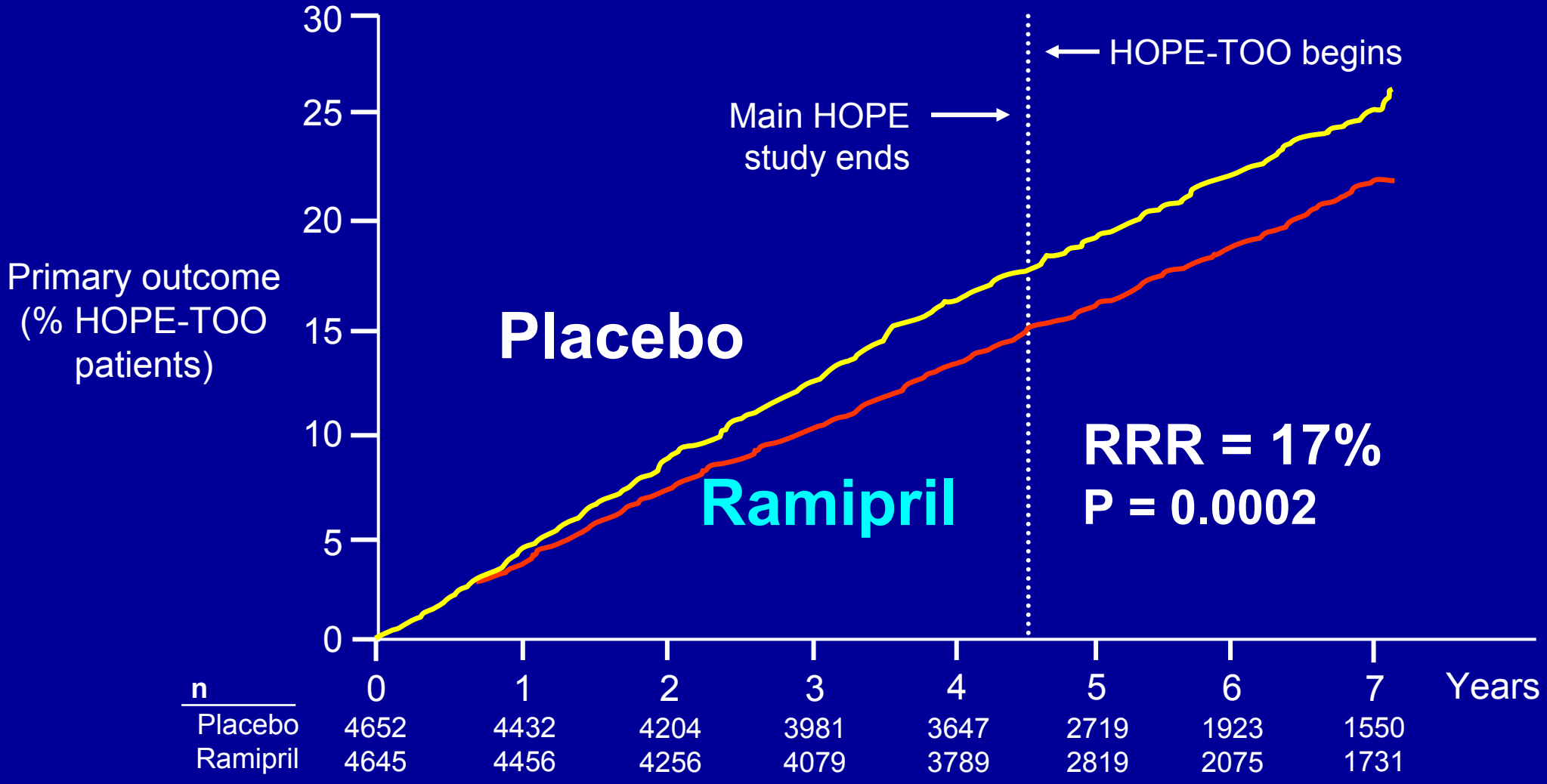
HOPE trial extension **2.6** years



HOPE-TOO = Heart Outcomes Prevention Evaluation – The Ongoing Outcomes

HOPE/HOPE-TOO Study Investigators. *Circulation*. 2005;112:1339-46.

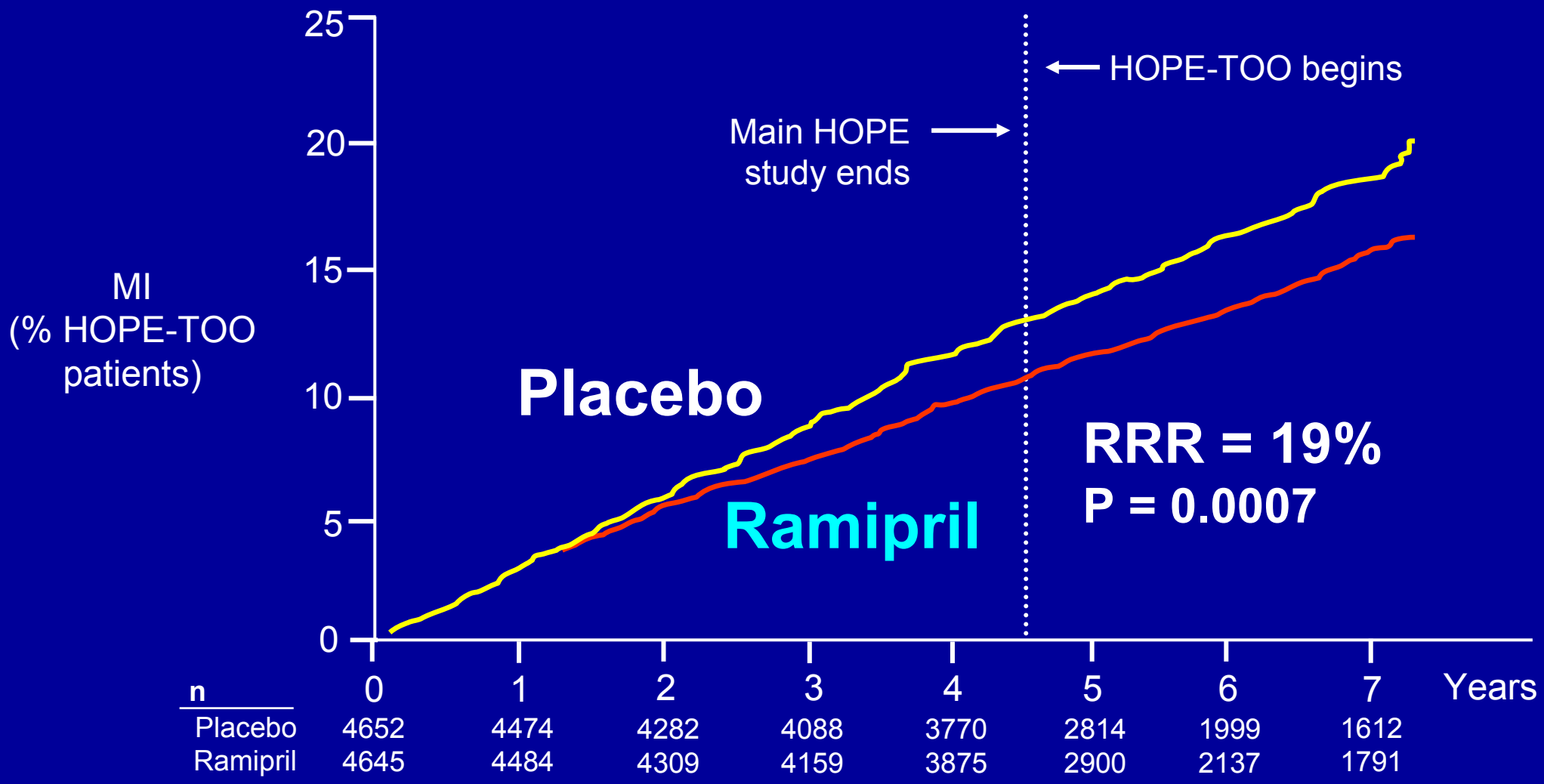
HOPE-TOO: Primary outcome (CV death, MI, stroke)



RRR = relative risk reduction

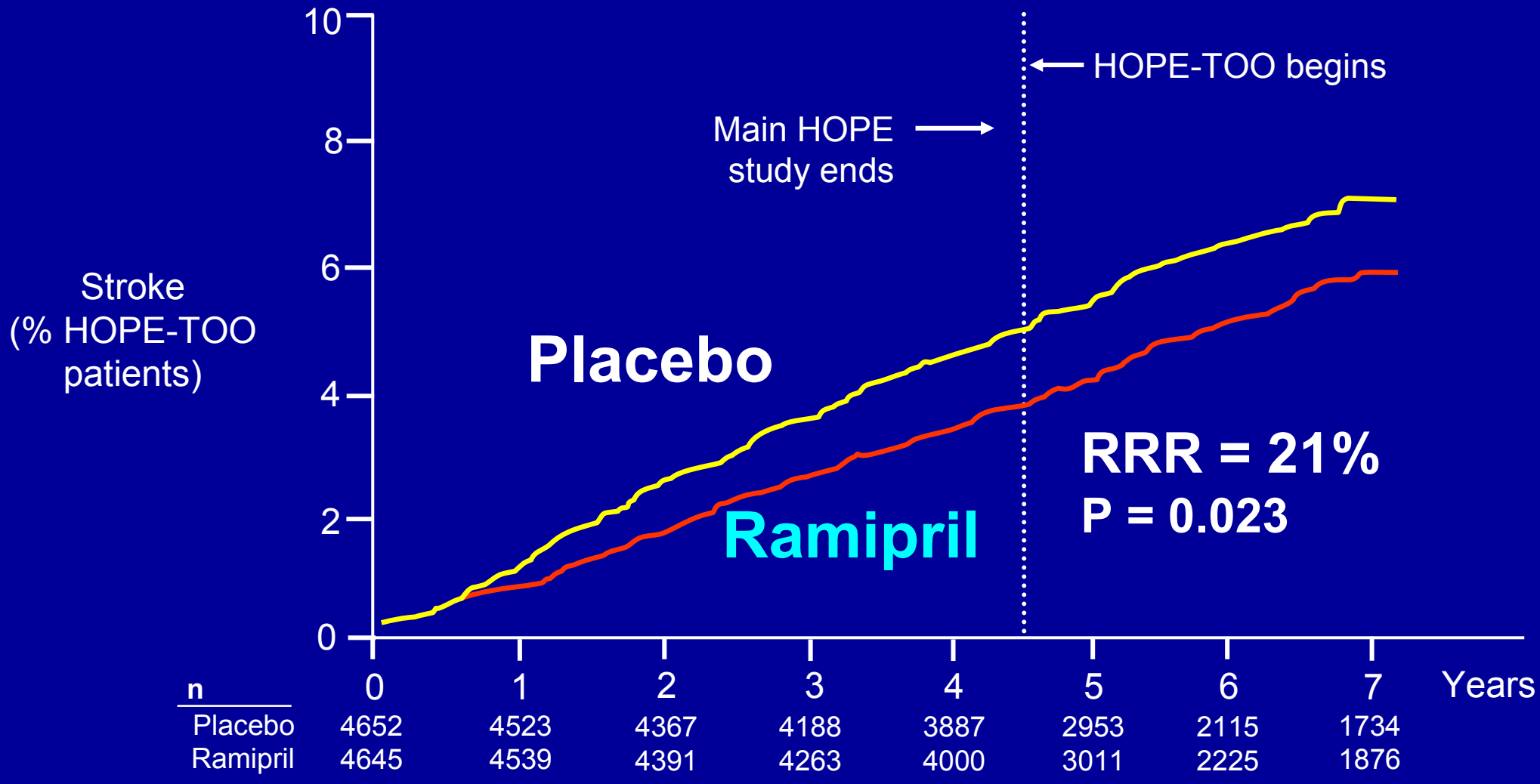
HOPE/HOPE-TOO Study Investigators. *Circulation*. 2005;112:1339-46.

HOPE-TOO: Additional reduction in MI



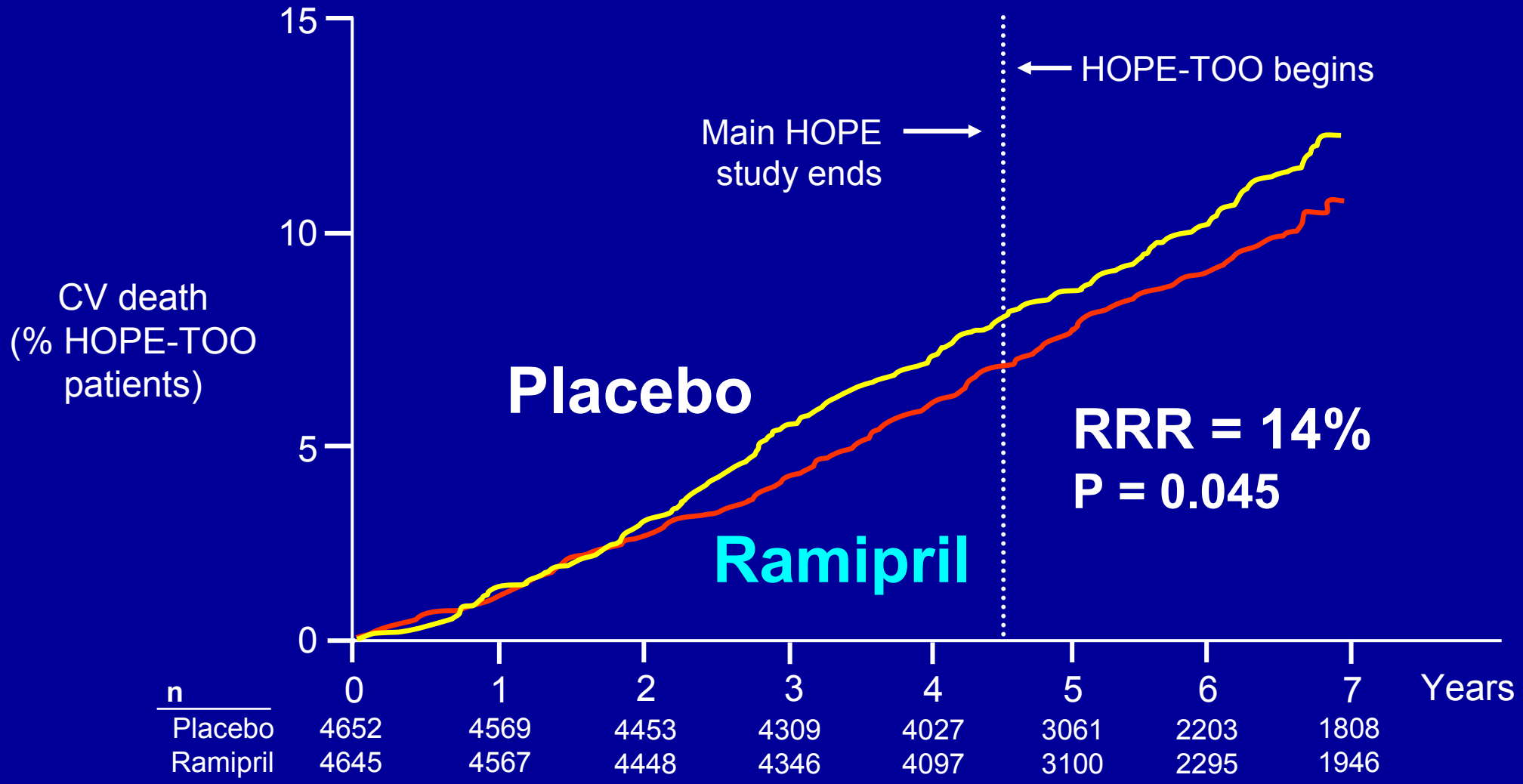
HOPE/HOPE-TOO Study Investigators. *Circulation*. 2005;112:1339-46.

HOPE-TOO:
Sustained reduction in stroke



HOPE/HOPE-TOO Study Investigators. *Circulation*. 2005;112:1339-46.

HOPE-TOO: Sustained reduction in CV death

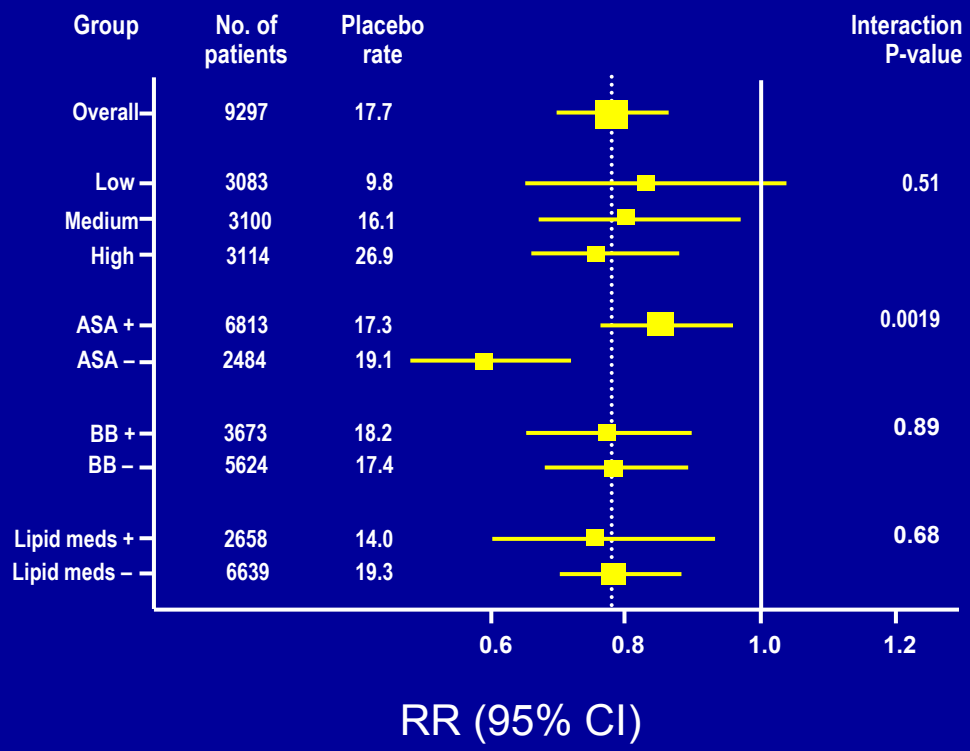


HOPE/HOPE-TOO Study Investigators. *Circulation*. 2005;112:1339-46.

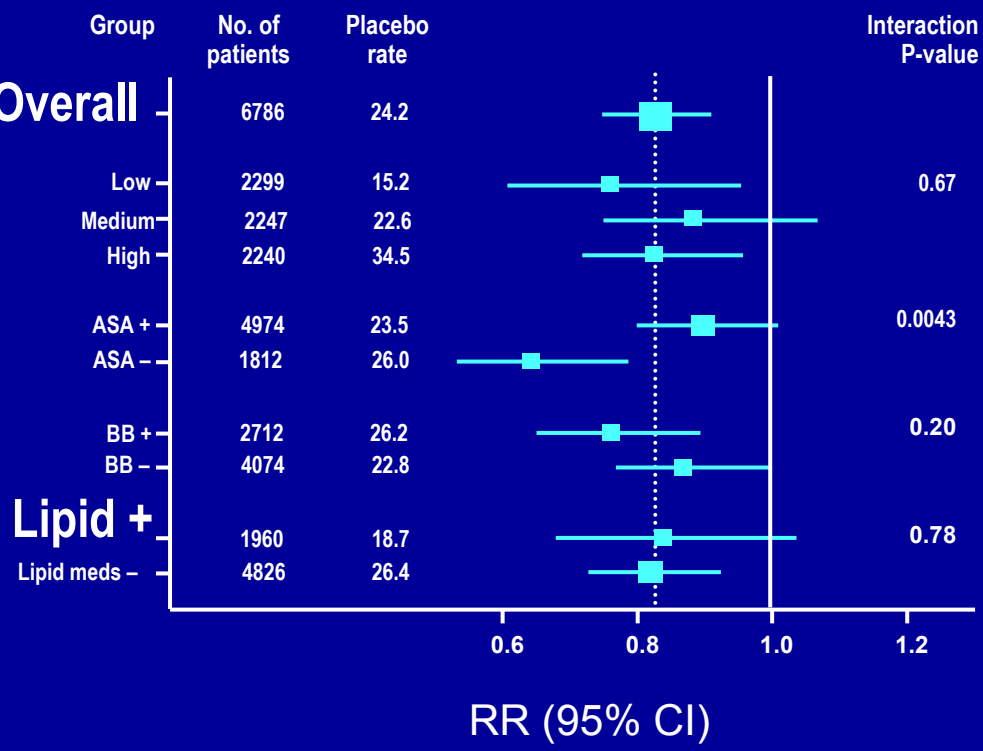
HOPE/HOPE-TOO: Benefits at all levels of risk and with other life-saving drugs

Primary outcome = CV death/MI/stroke

HOPE



HOPE-TOO



HOPE/HOPE-TOO Study Investigators. *Circulation*. 2005;112:1339-46.

HOPE/HOPE-TOO: Blood Pressure Differences

Study end

Blood pressure (mm Hg)	HOPE	HOPE-TOO
Ramipril allocated group	136/76	136/74
Placebo allocated group	139/77	136/74
Difference	3/1	None

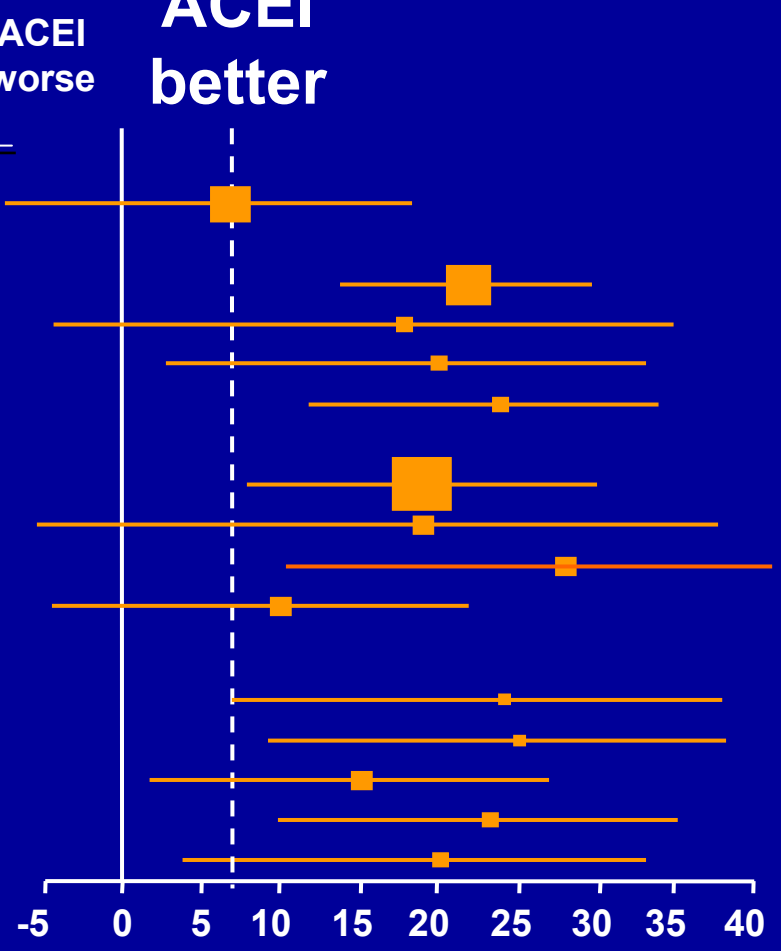
HOPE-TOO: Study conclusions

- Results support **earlier** vs later initiation of ACEI therapy.
- Benefit demonstrated across a **3-fold** range in baseline risk.
  (event rate: 1.9% – 6% per year)
- Benefits are **additive to other proven therapies** (ASA, β-blockers, lipid-lowering agents).

ACEIs Benefit a Broad Spectrum of CAD Patients

CV death,* nonfatal MI or stroke

Trial	Patients (n)	Annual rates in placebo groups	OR (95% CI)	P
PEACE	8290	2.13	**7** (-8 to 19)	0.328
HOPE total	9297	3.95	**25** (16 to 32)	0.0001
HOPE lower risk	3083	2.17	18 (-4 to 35)	
HOPE med risk	3100	3.58	20 (3 to 33)	
HOPE high risk	3114	5.98	24 (12 to 34)	
EUROPA	12218	2.60	**19** (8 to 28)	0.0007
EUROPA lower risk	3976	1.40	19 (-5 to 38)	
EUROPA med risk	3975	2.41	28 (11 to 41)	
EUROPA high risk	3975	4.00	10 (-4 to 22)	
AIRE	1986	22.6	24 (7 to 38)	0.0068
TRACE	1749	17.0	25 (9 to 33)	0.0028
SOLVD-P	4228	7.4	15 (2 to 27)	0.0252
SOLVD-T	2569	13.1	23 (10 to 33)	0.0009
SAVE	2231	9.8	20 (4 to 33)	0.0168



*Or total mortality for AIRE, TRACE, SOLVD, SAVE trials

Dagenais GR, et al. Lancet. 2006;368:581

ADA (2002) and JNC 7 (2003)

- In patients over aged 55 years, with/without HTN, but with another CV risk factor, an ACE inhibitor (***ramipril***) should be considered to reduce the risk of CVD events…

- The HOPE trial showed reductions in a variety of CVD events with ACEI (***ramipril***) compared with placebo in individuals with prior CVD, or DM.

- ***ACEI therapy (ramipril 10 mg) should be used in most patients with vascular disease or diabetes and additional risk factors.***

The Power of *Ramipril*
To Prevent CV Events and Diabetes

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- **Plausible Mechanisms**
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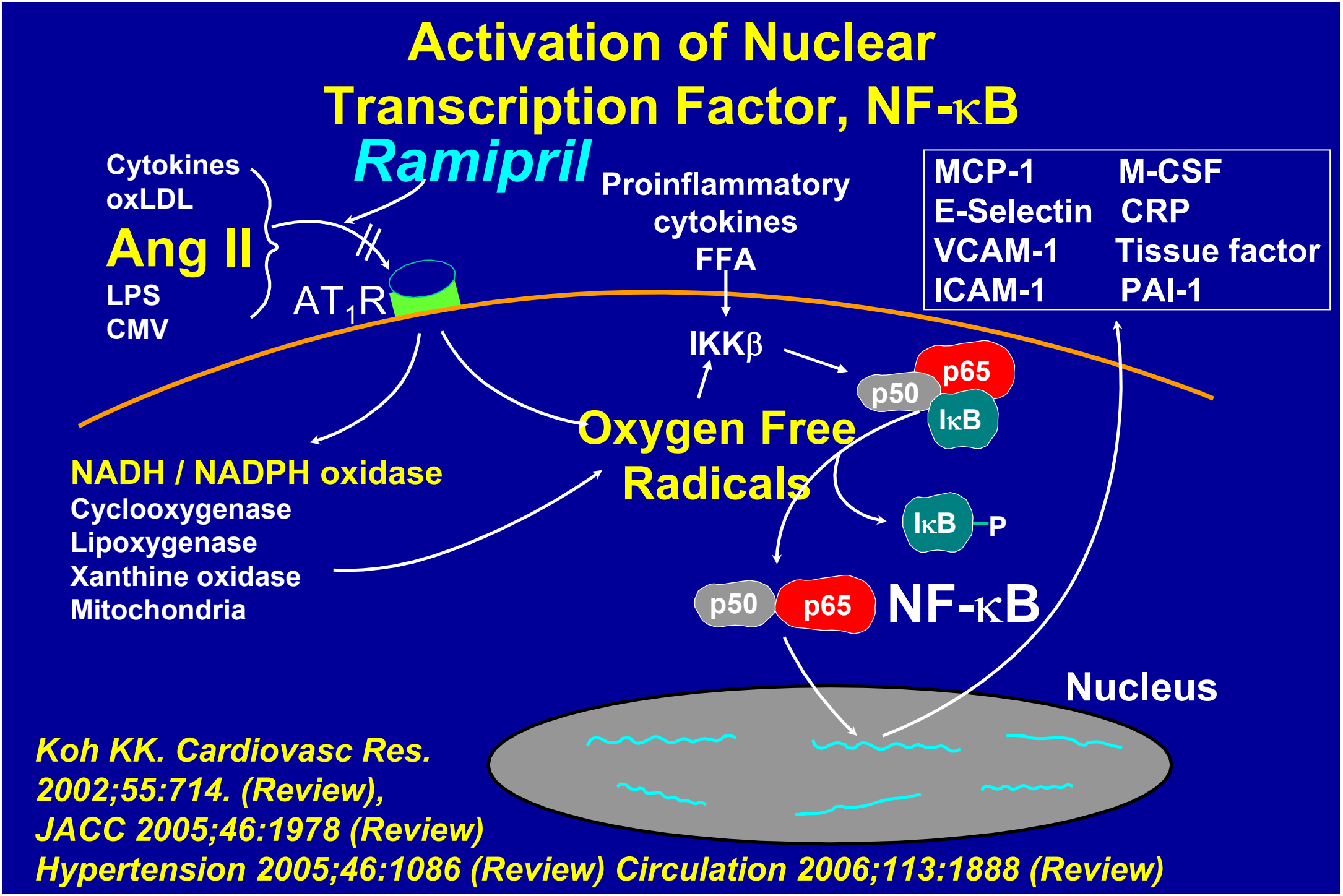
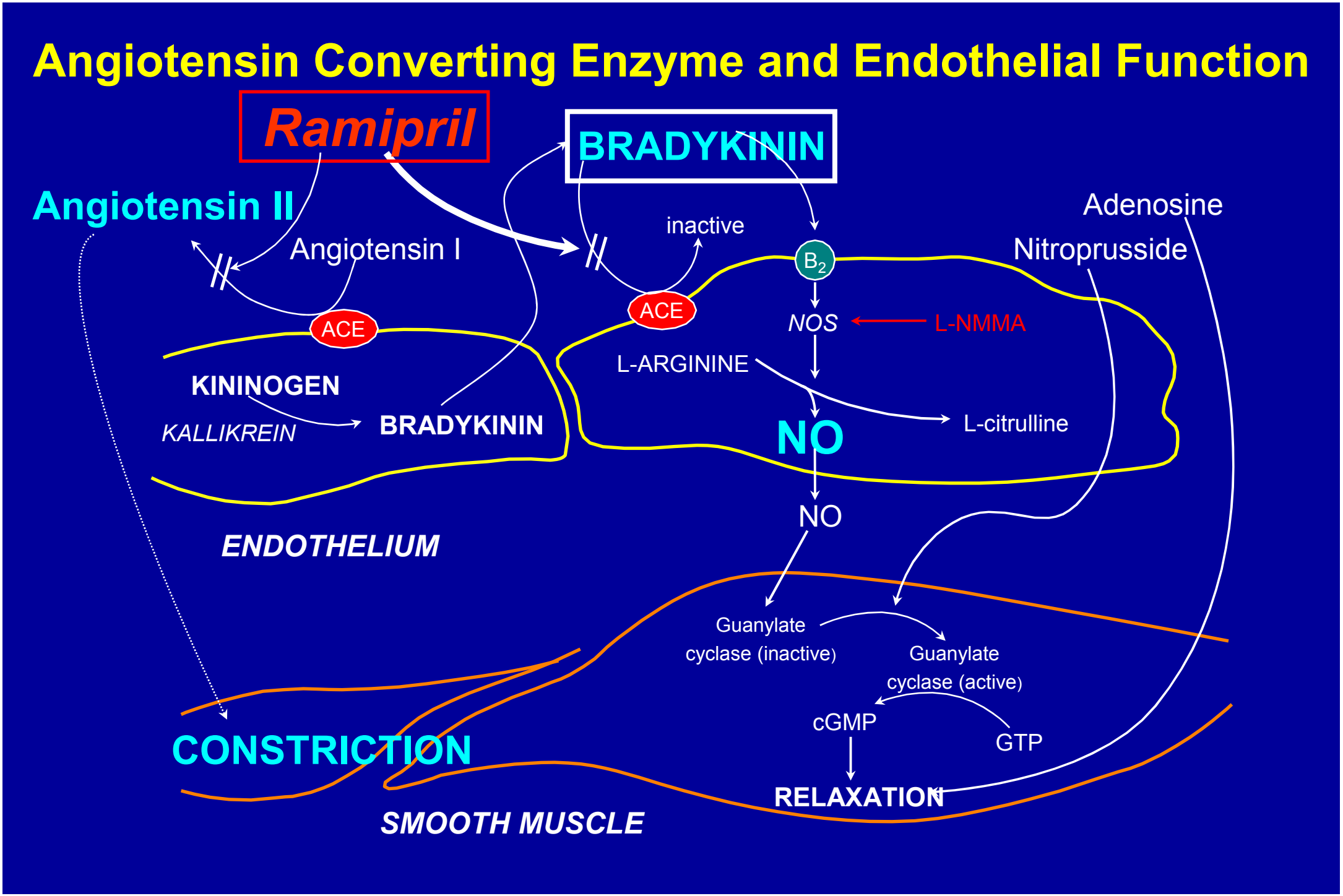
Activation of Nuclear Transcription Factor, NF-κB

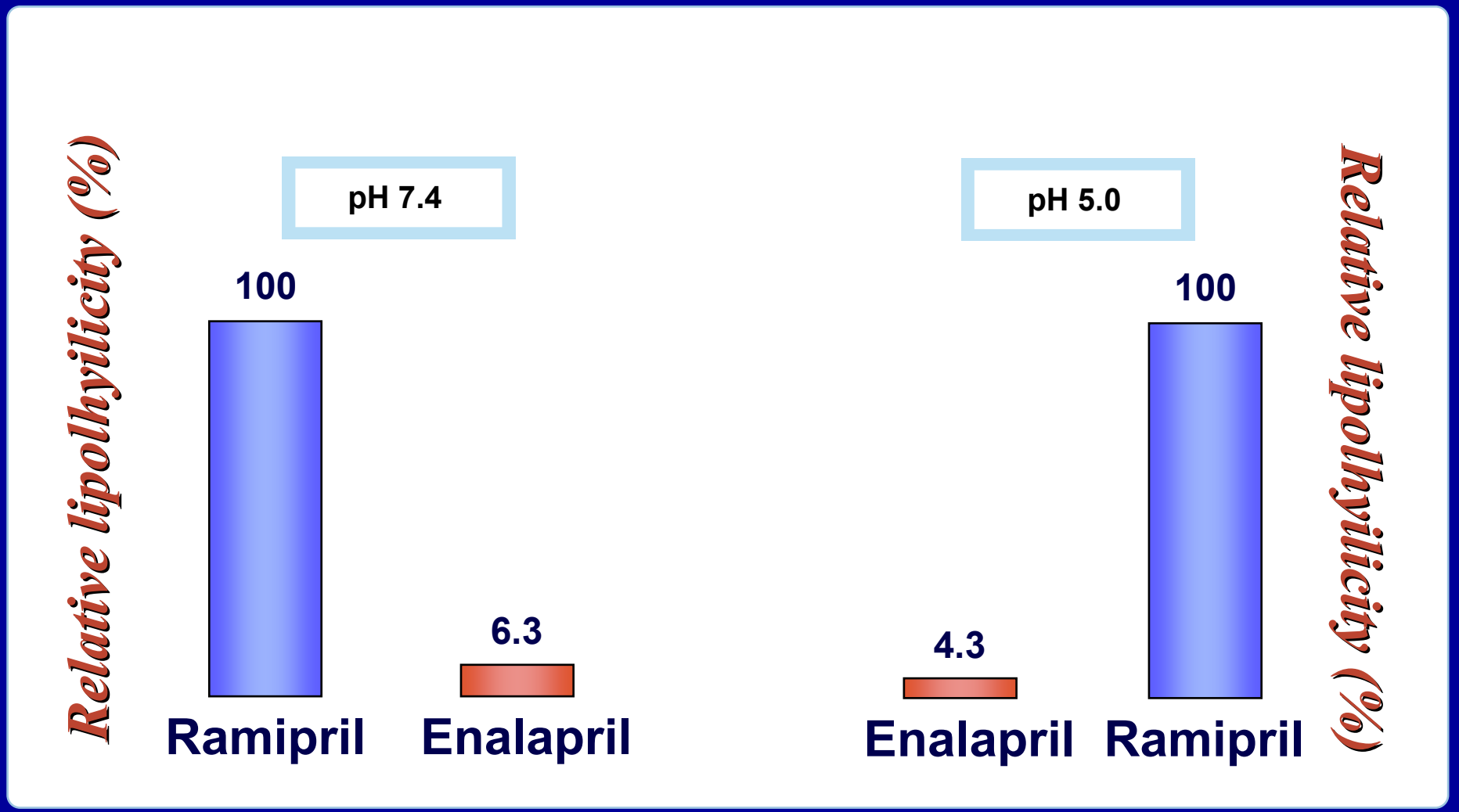


Koh KK. Cardiovasc Res. 2002;55:714. (Review),
JACC 2005;46:1978 (Review)
Hypertension 2005;46:1086 (Review) Circulation 2006;113:1888 (Review)

Angiotensin Converting Enzyme and Endothelial Function

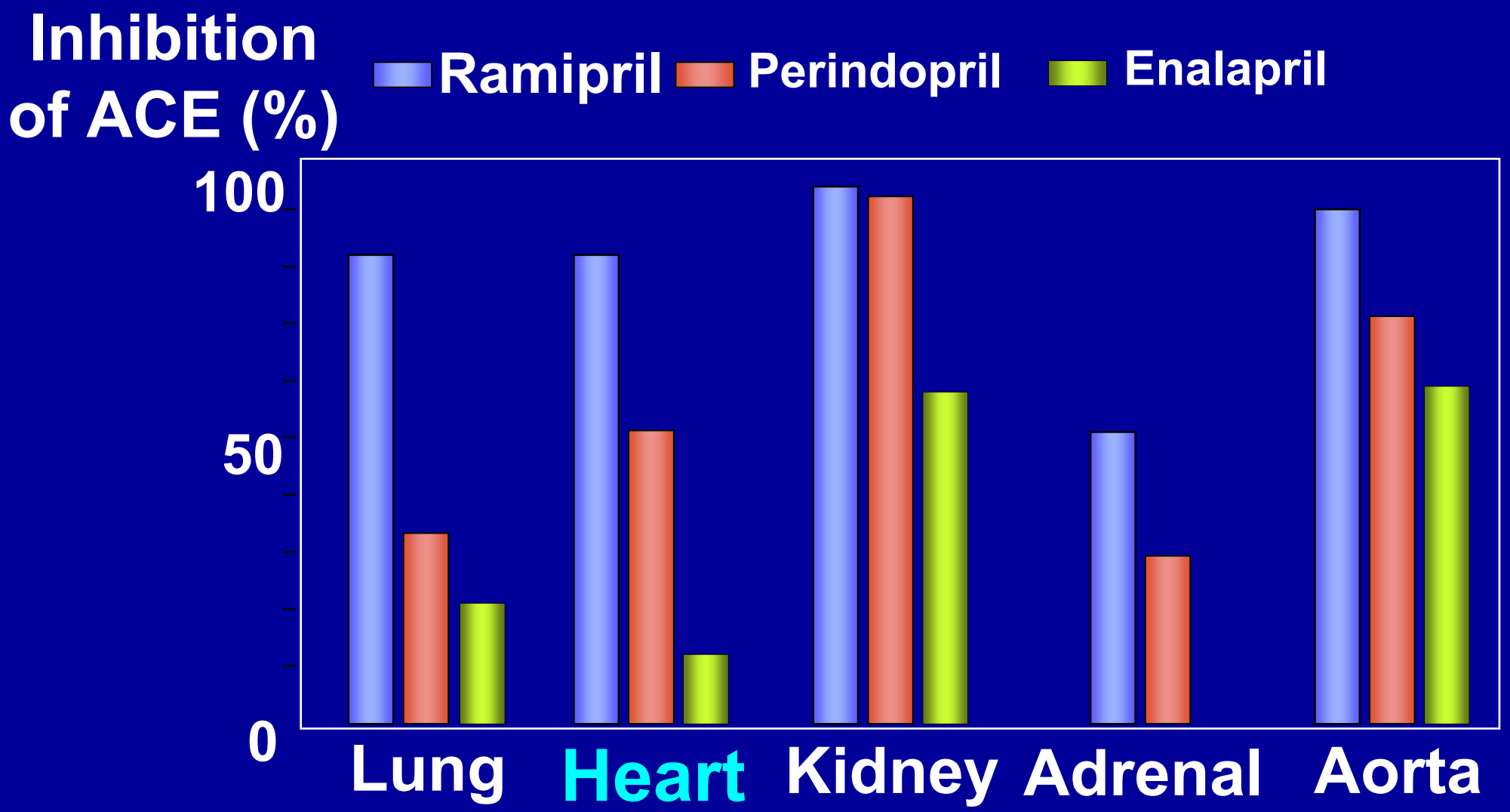


Outstanding Lipophilicity of Ramipril



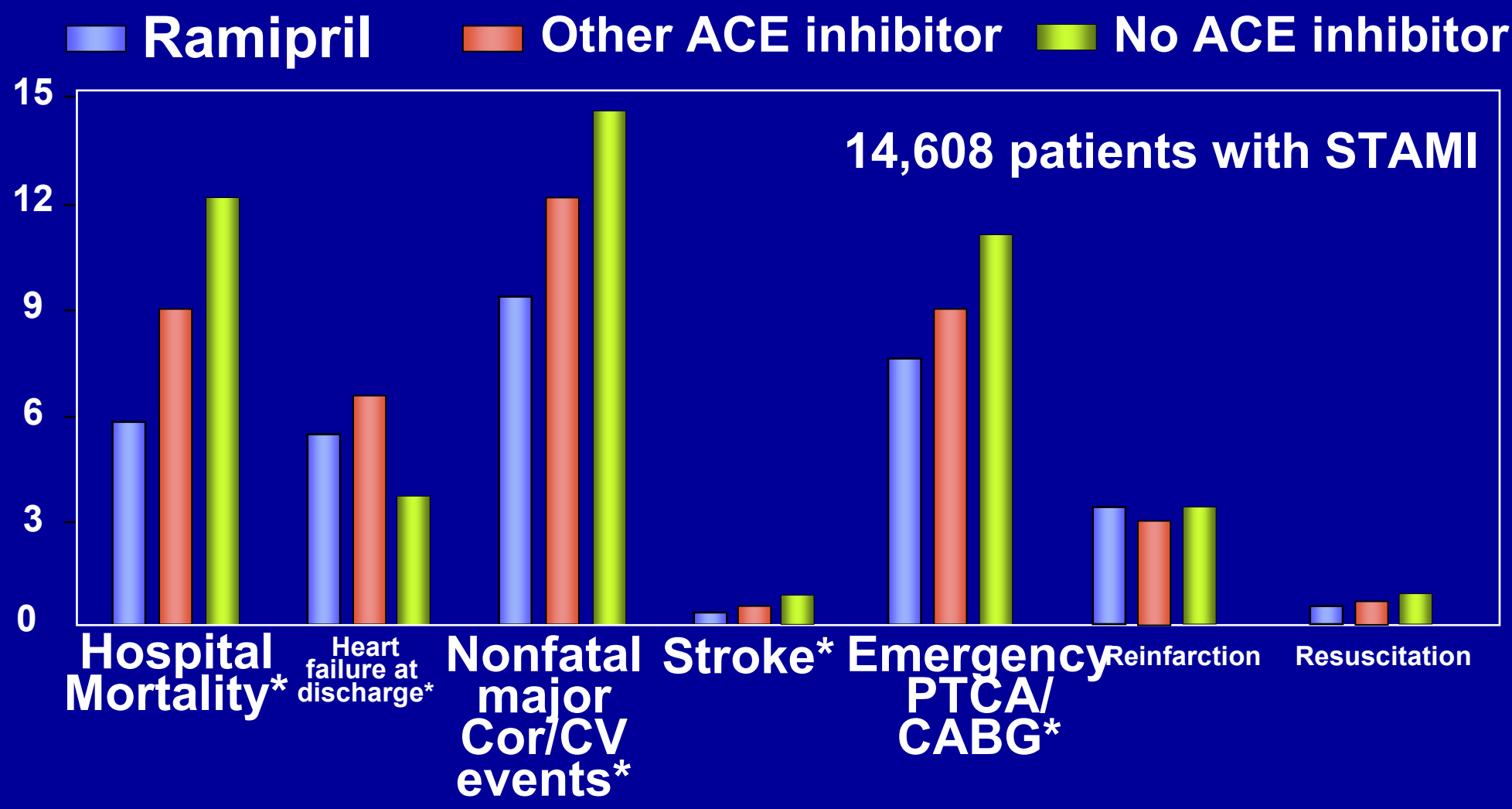
Bender et al. Clin Physiol Biochem 8, 1990

Tissue Specificity



Bender et al. *Clin Physiol Biochem* 1990; 8(suppl 1): 44-52

MITRA PLUS : Maximal Individual Therapy of Acute Myocardial Infarction PLUS registry

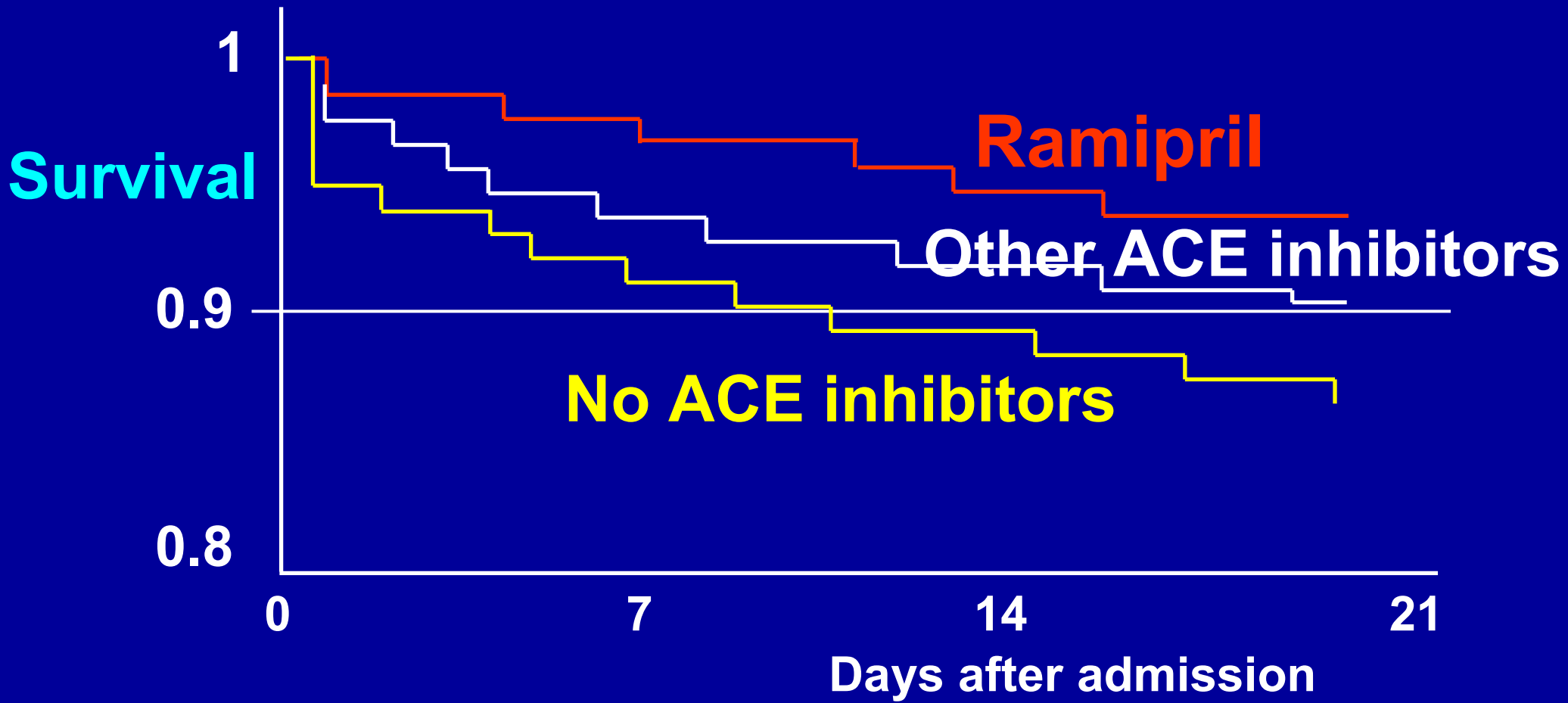


* P < 0.05, ramipril vs no ACE inhibitor
Cor/CV = Coronary/cerebrovascular

Wienbergen H, et al. Am J Cardiol. 2002;90:1045

MITRA PLUS : Impact on post-MI Survival Benefits of ramipril

14 608 patients with ST-elevation acute MI



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The Power of *Ramipril*
To Prevent CV Events and Diabetes

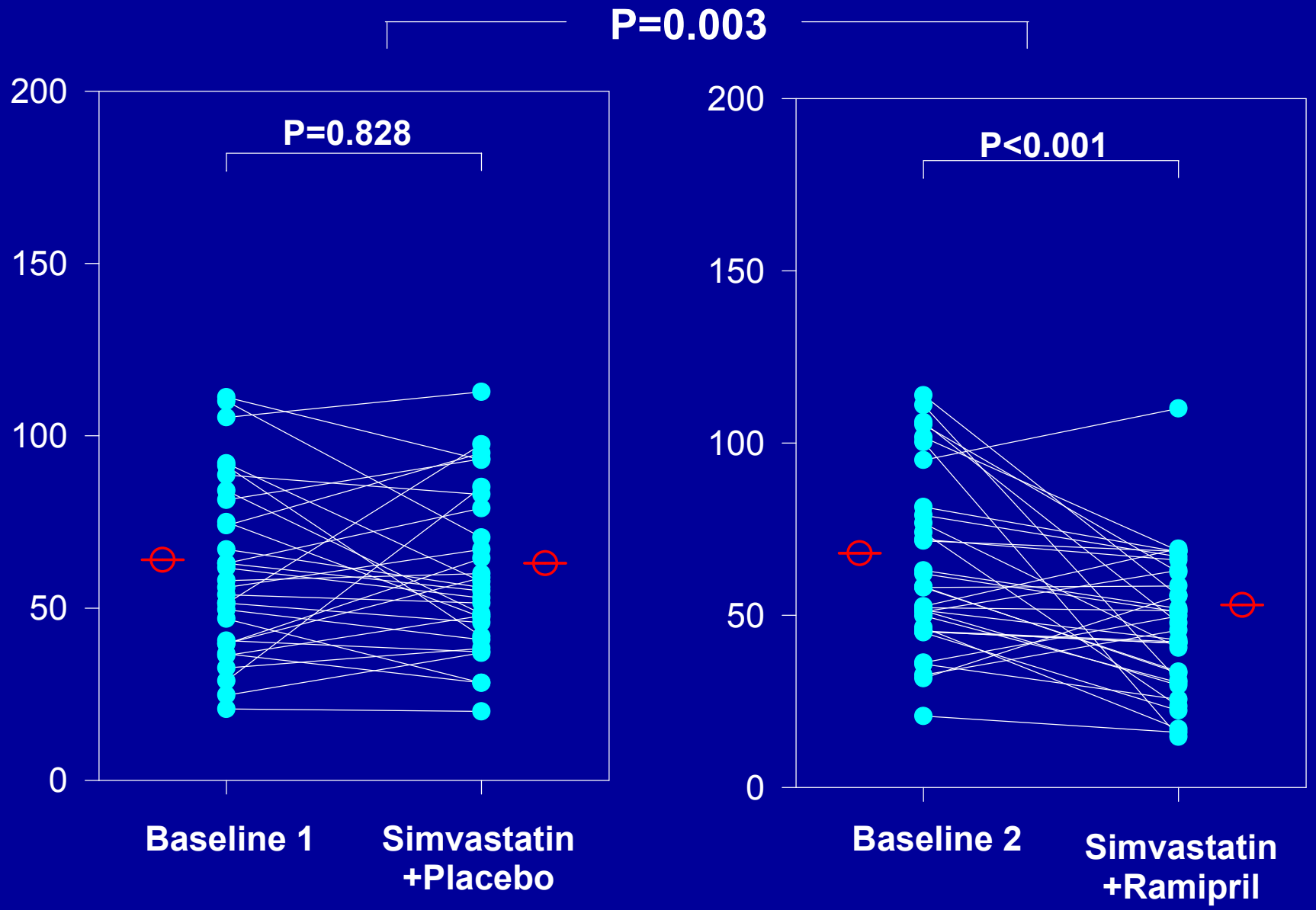
- HOPE, MICRO-HOPE, HOPE-TOO Study
- Plausible Mechanisms
- **Mechanistic Clinical Studies**
- Conclusions

Simvastatin Combined with *Ramipril* Treatment in 50 Hypercholesterolemic Patients

Koh KK, Han SH, Chung W-J, …Shin EK

Hypertension. 2004;44:180.

Simvastatin Combined with Ramipril on PAI-1 Antigen Levels (ng/ml) (HC)

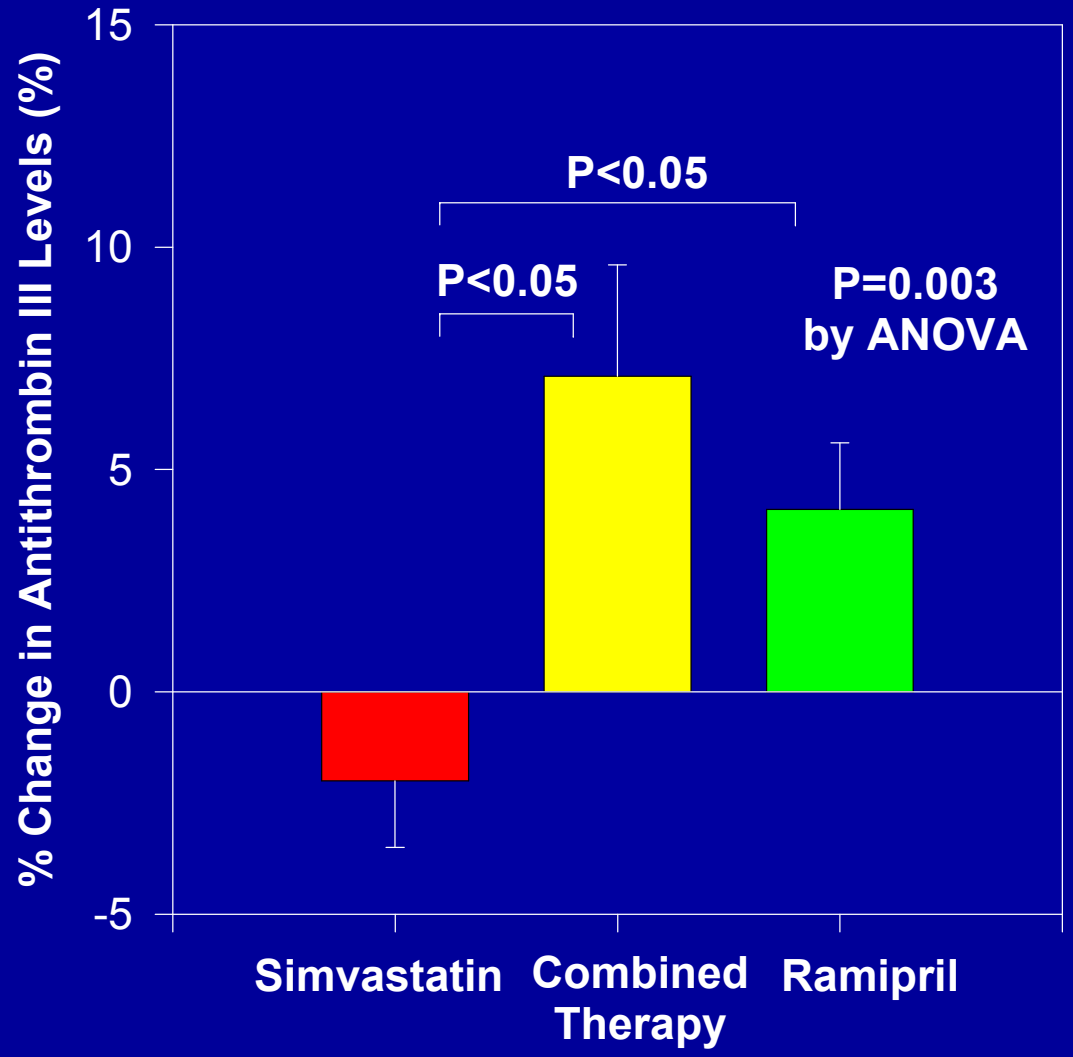


Effects of *Ramipril* and Simvastatin on Hemostasis in 50 Patients with Type 2 Diabetes

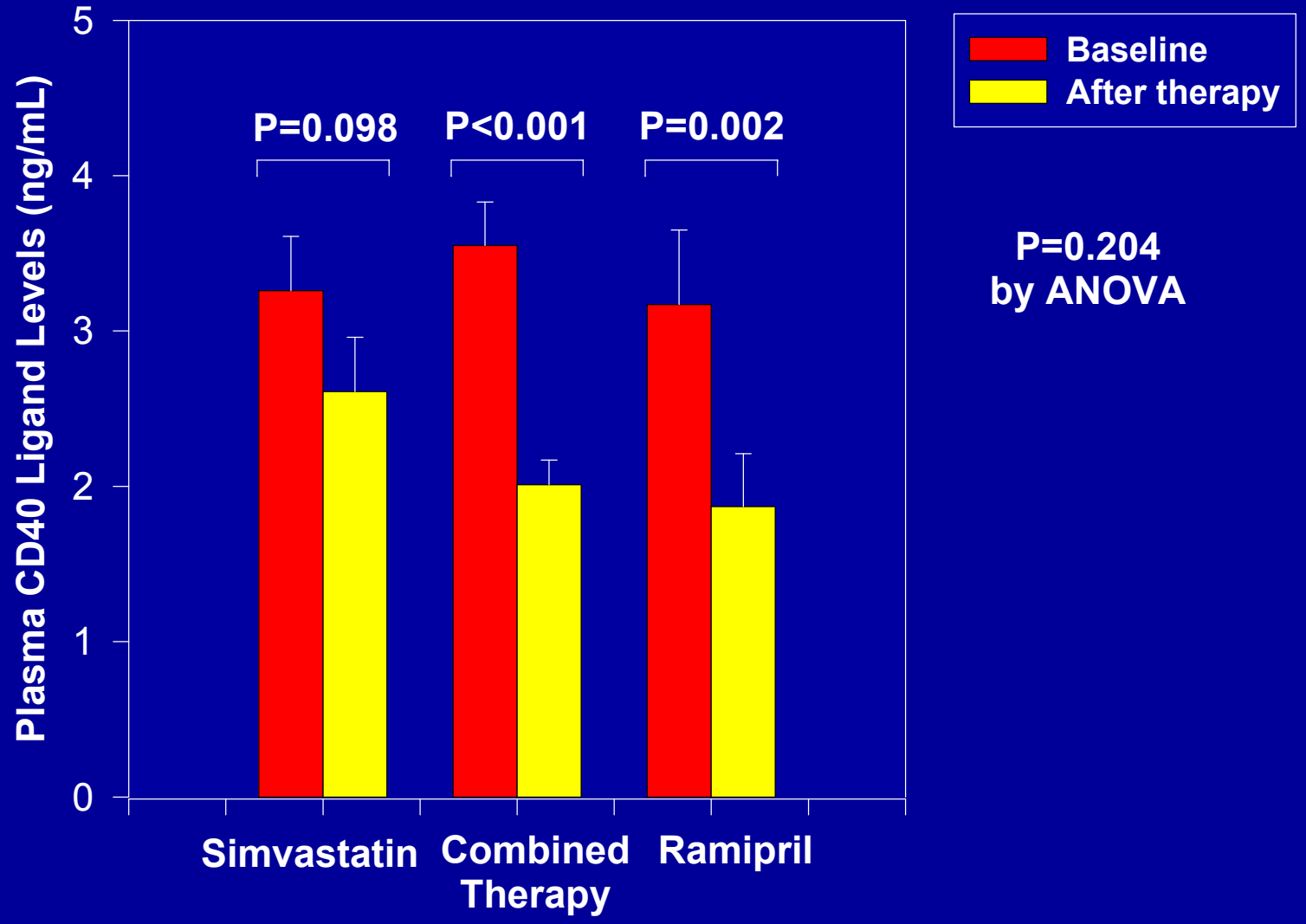
Koh KK, Han SH, …Shin EK

Atherosclerosis 2006 (in press)

Effects of Simvastatin, Combined Therapy, and Ramipril on Antithrombin III Levels



Change in sCD40L Levels at Baseline and after Therapy in Type 2 Diabetes



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

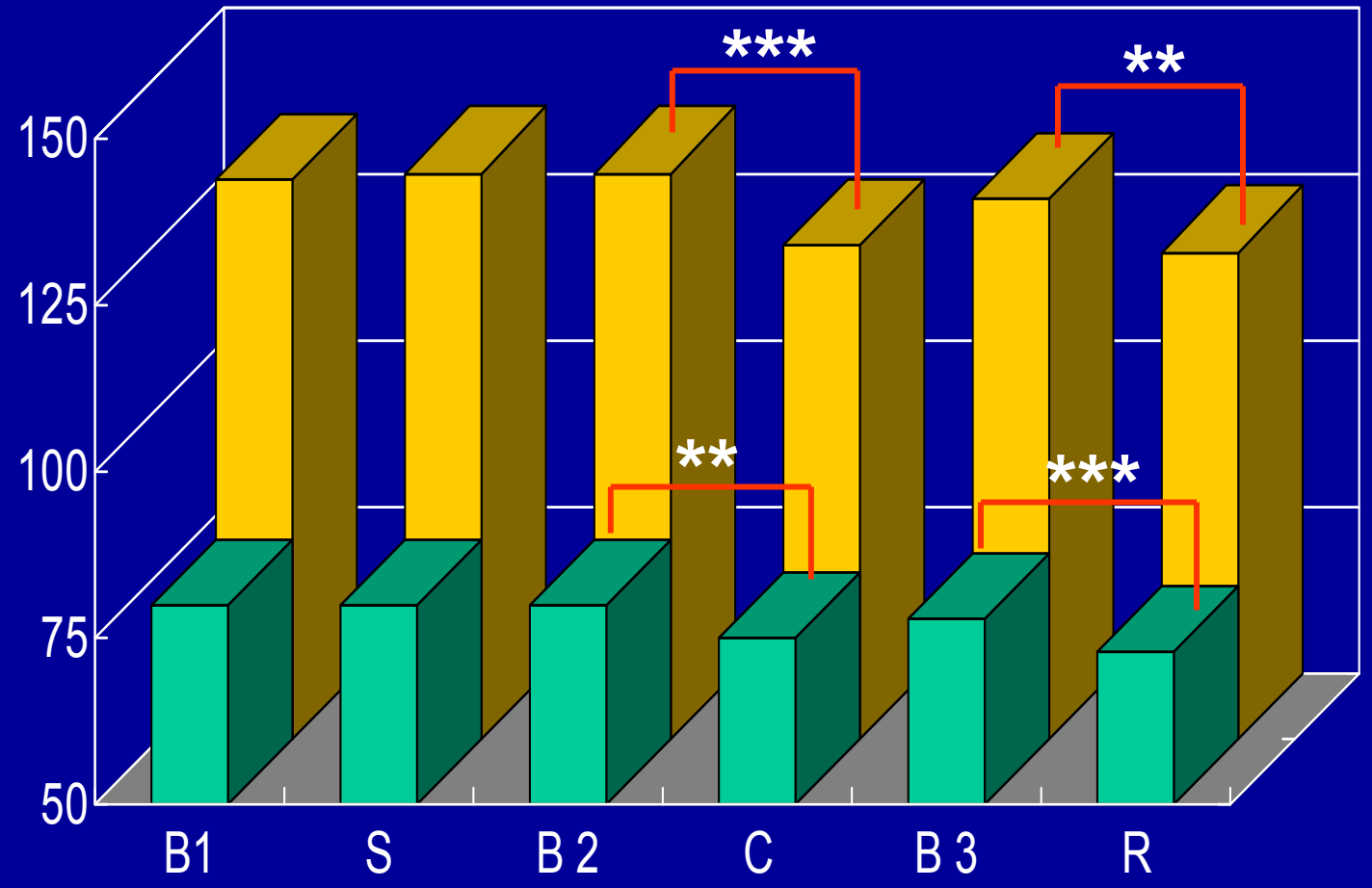
Cardiology, Gachon Medical School, Korea

Diabetes Unit, NIH, USA*

Hypertension 2005;45:1088

Reuters Health 2005-06-16

Ramipril Combined with Simvastatin on Blood Pressure (mmHg)



Systolic BP

ANOVA

p=0.003

Diastolic BP

ANOVA

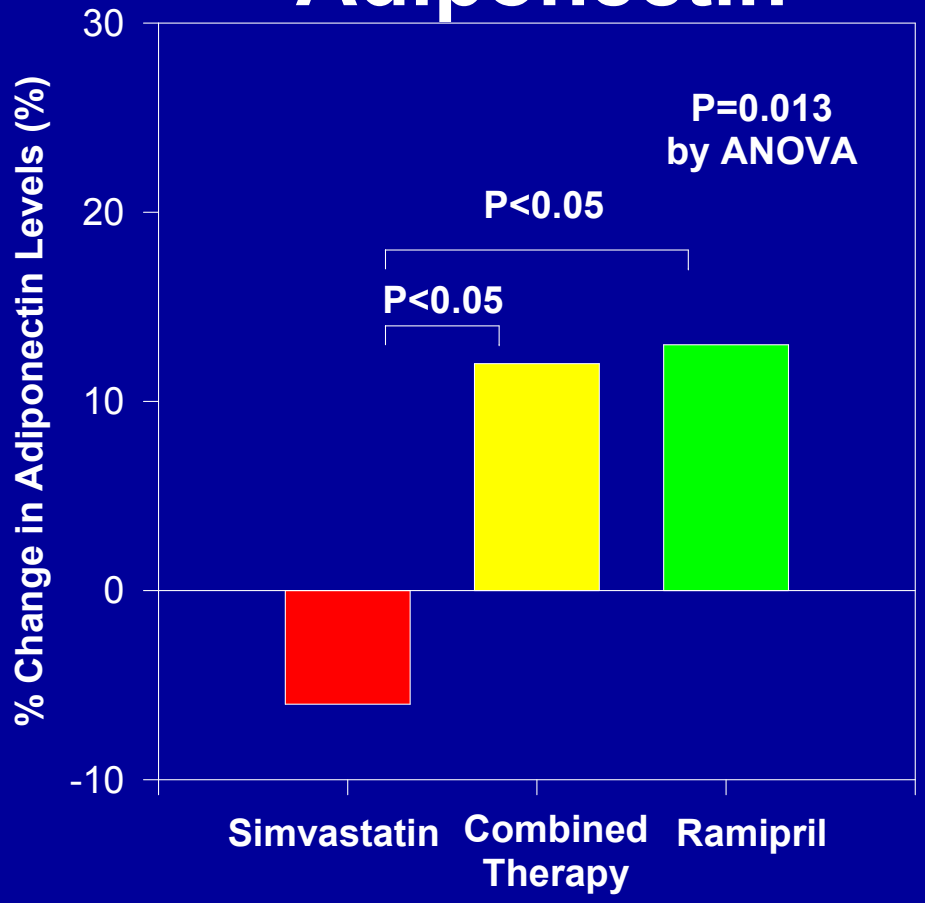
p=0.040

***=p<0.05; **=p<0.01; ***=p<0.001 vs. Baseline.**

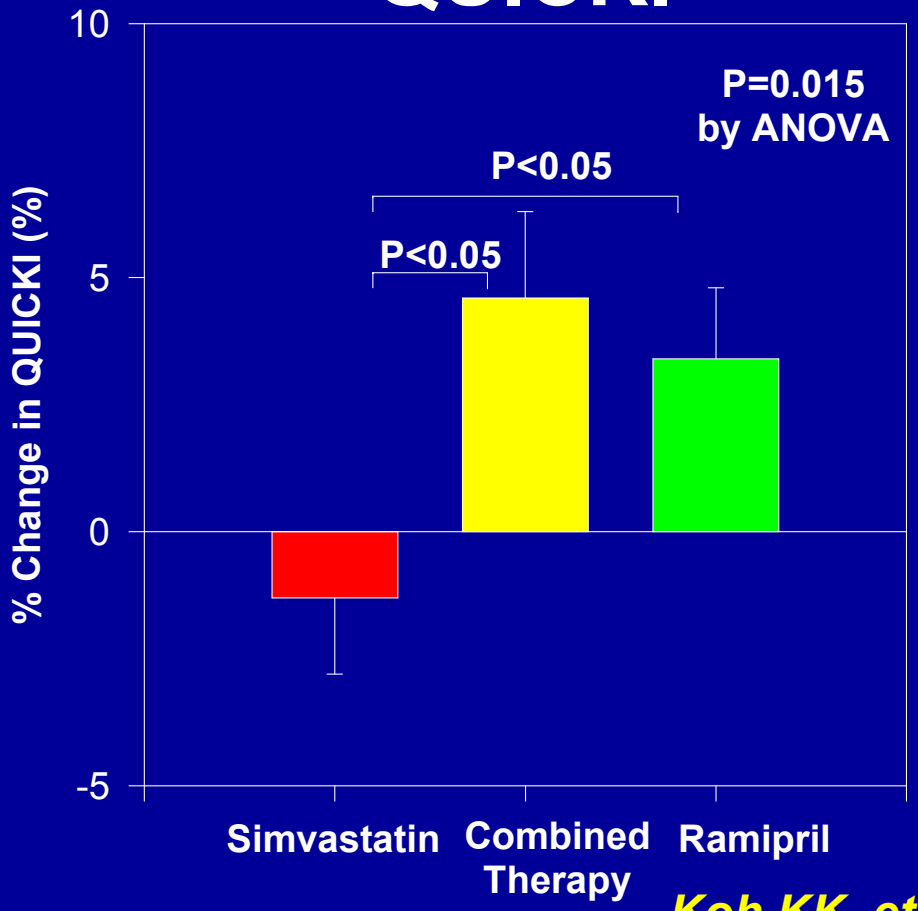
B= Baseline, S=simvastatin+placebo, C=simvastatin+ramipril, R=ramipril+placebo.

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

Adiponectin



QUICKI



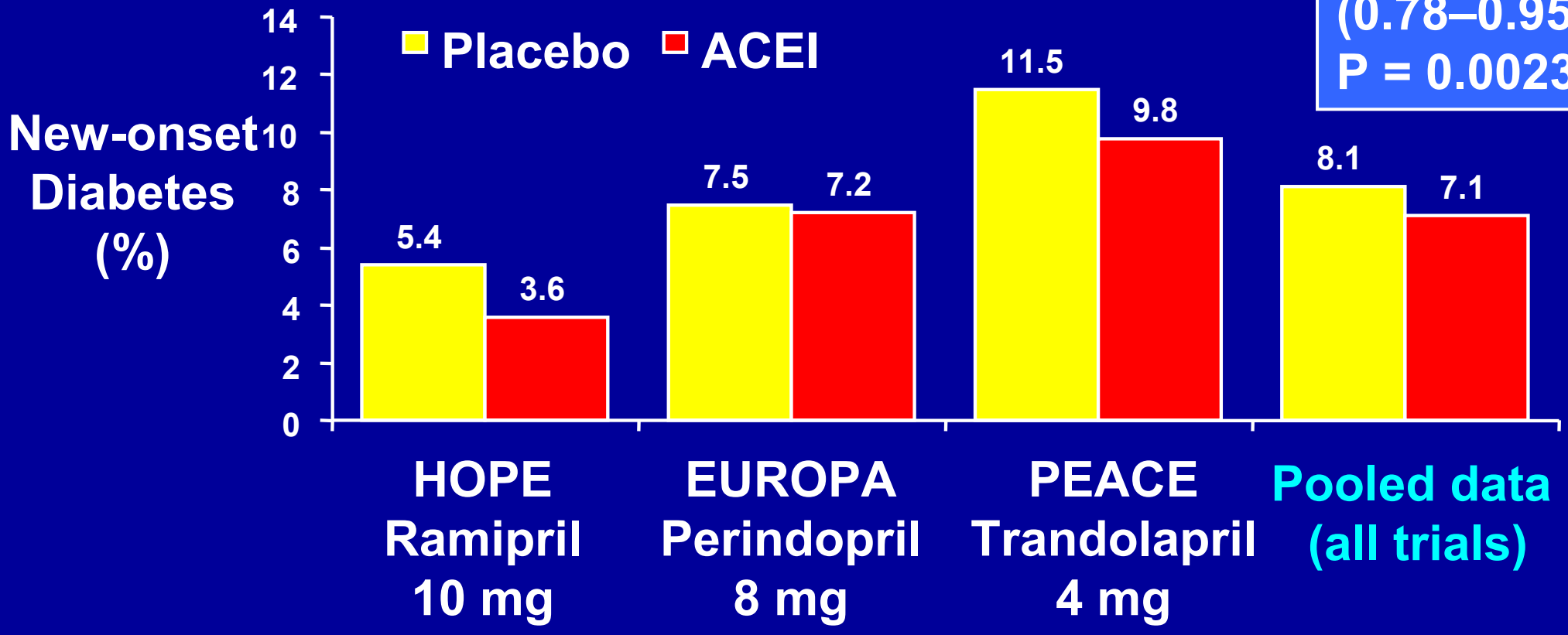
*QUICKI=Quantitative Insulin-Sensitivity Check Index, a surrogate index of insulin sensitivity, QUICKI = 1/[log(insulin)+log(glucose)]

Koh KK, et al. Hypertension 2005;45:1088

HOPE, EUROPA, PEACE:
Reduction in new-onset diabetes with ACEI

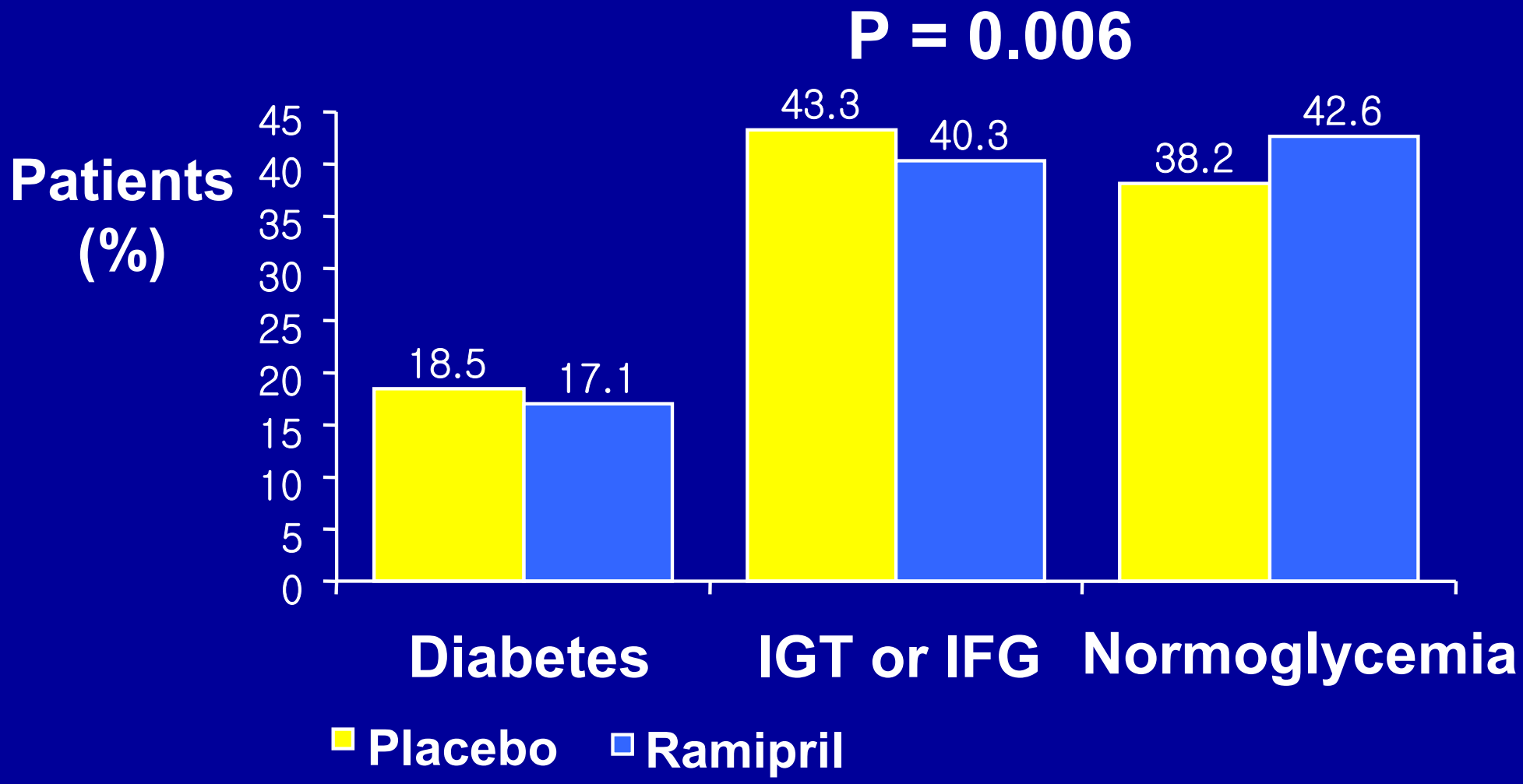
N = 23,340 free from diabetes at baseline

14% RRR
RR 0.86
(0.78–0.95)
P = 0.0023



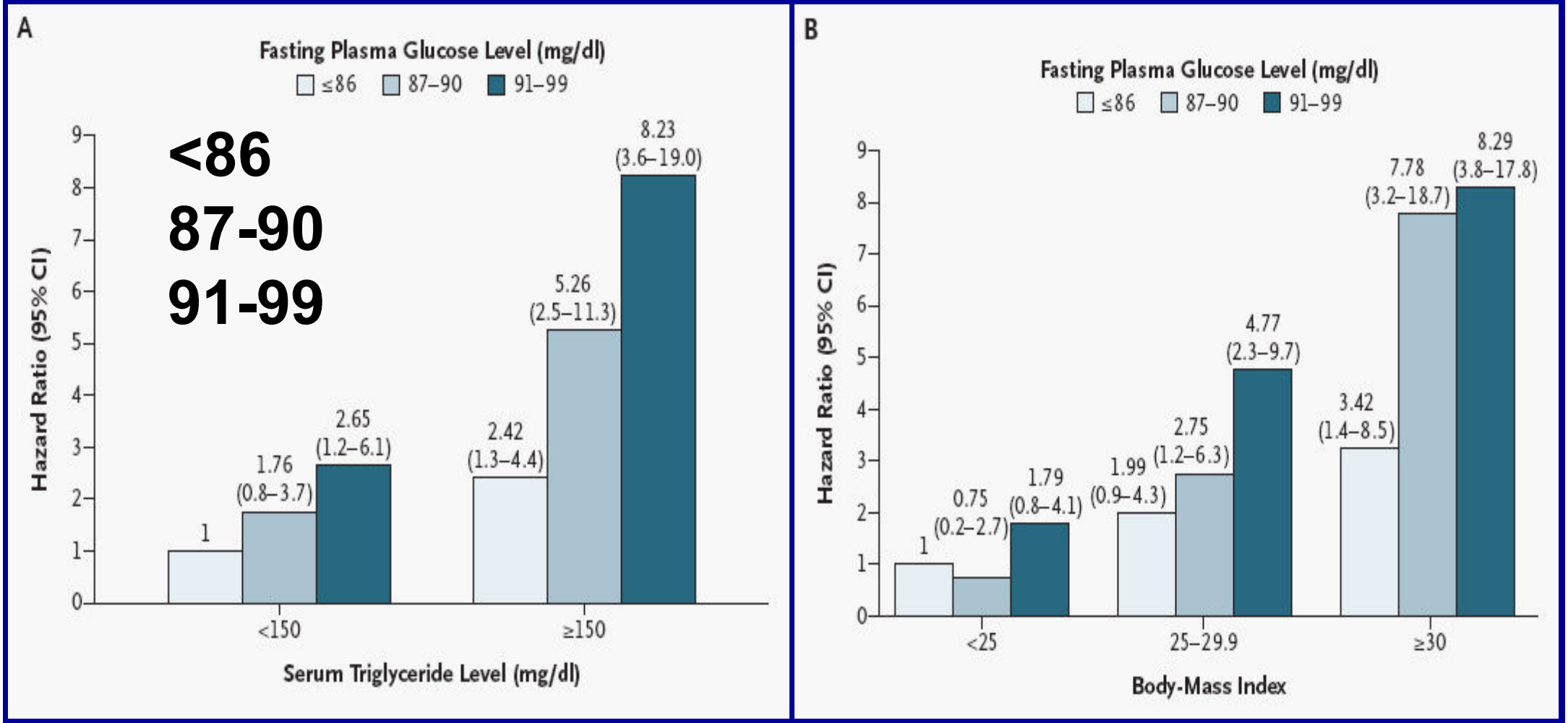
Dagenais GR, et al. Lancet. 2006;368:581

DREAM:
Ramipril Effect on Glycemic Categories



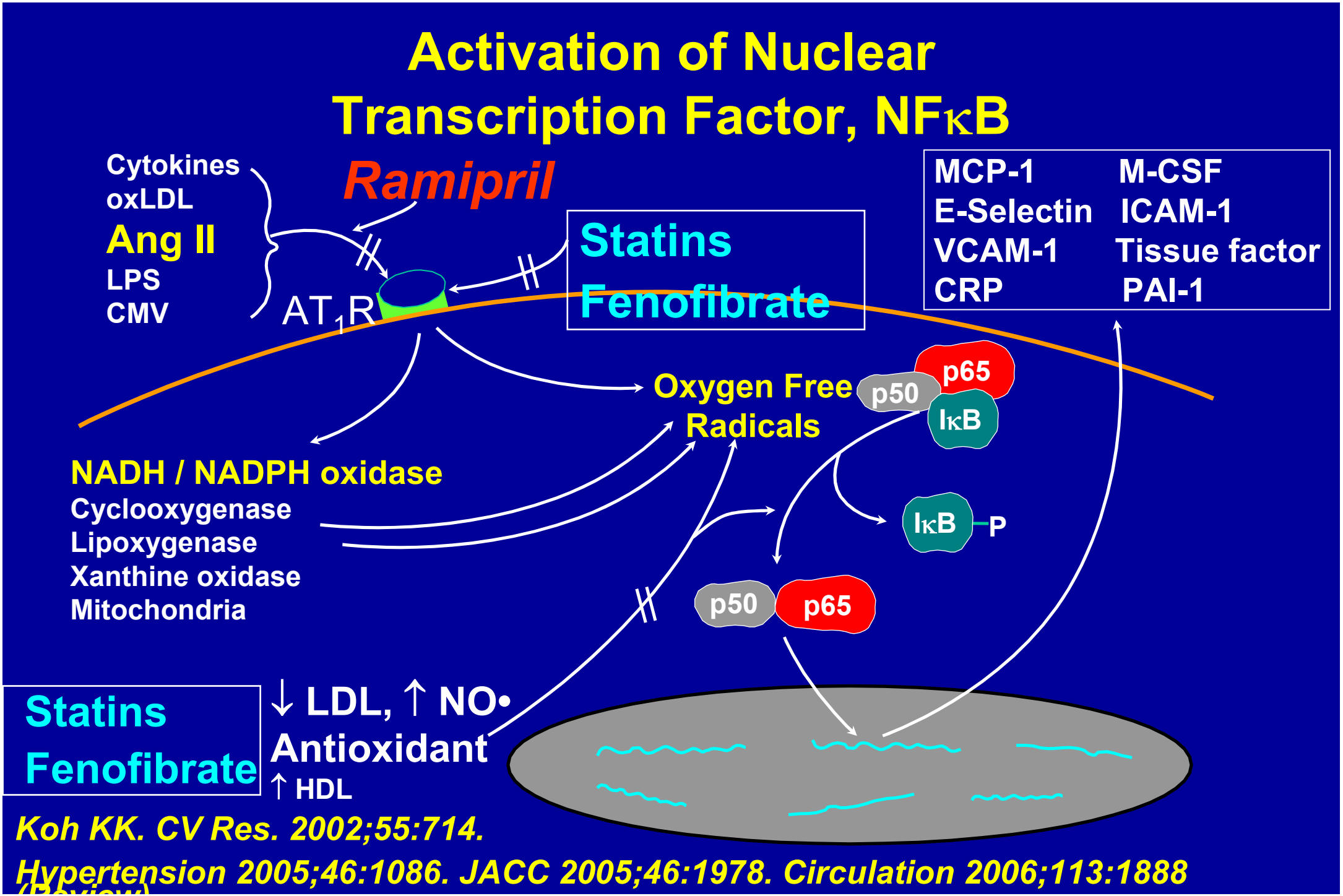
DREAM Trial Investigators. N Engl J Med. 2006;355.

Joint Effect of Fasting Plasma Glucose Levels, TG Levels, and BMI in Predicting Type 2 Diabetes Among 13,163 Young Men



Tirosh A, et al. N Engl J Med 2005;353:1454

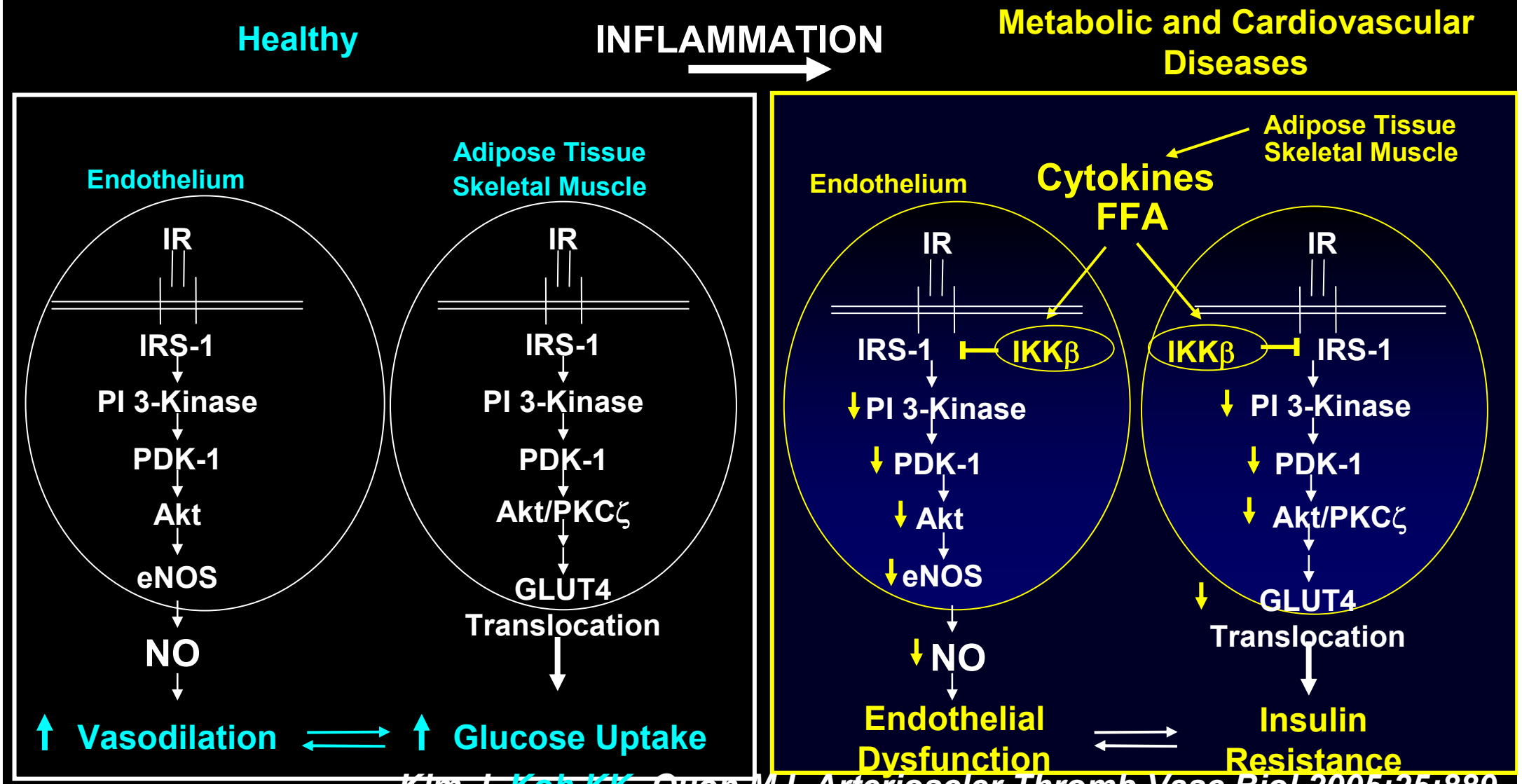
Activation of Nuclear Transcription Factor, NFκB



Koh KK. CV Res. 2002;55:714.

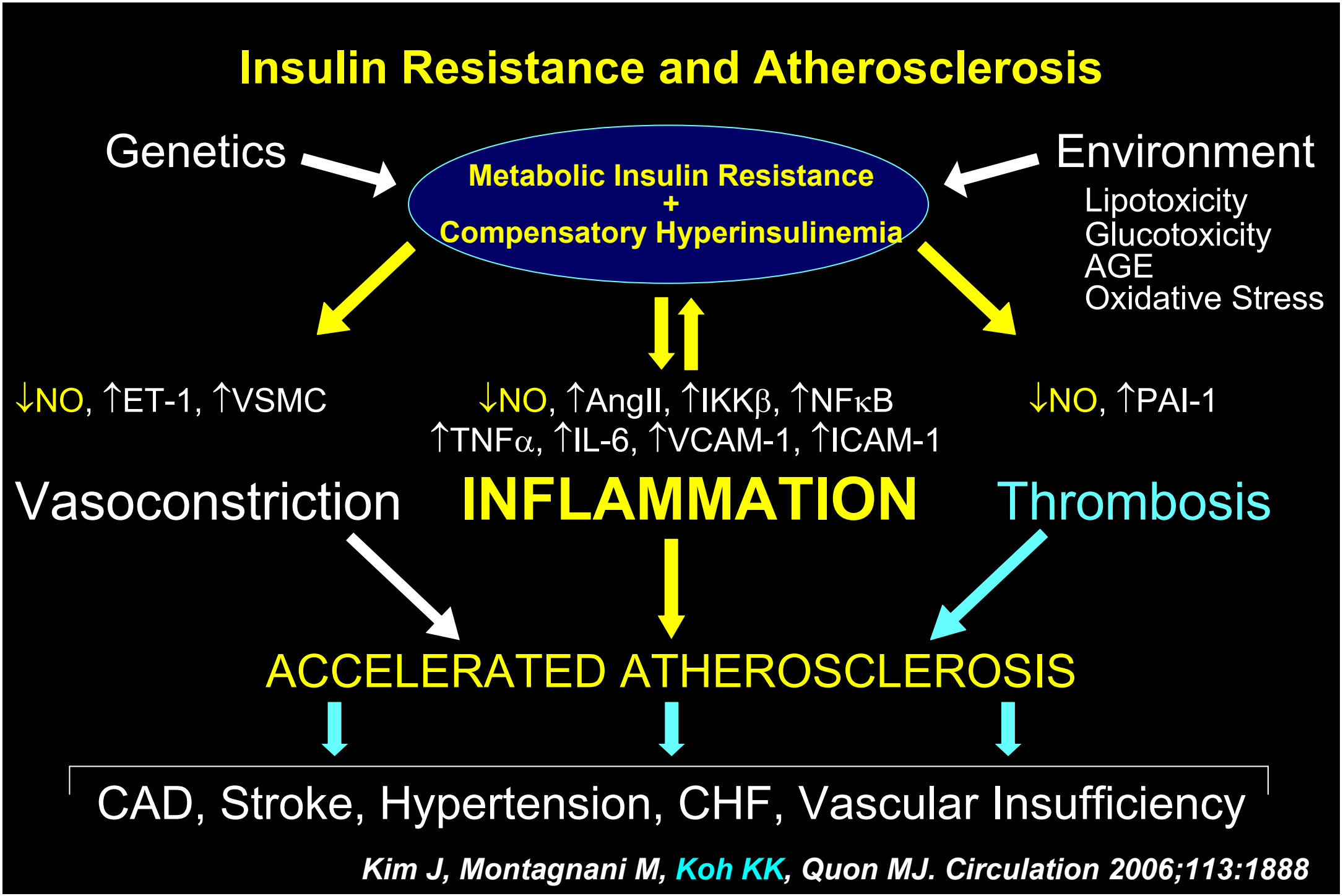
Hypertension 2005;46:1086. JACC 2005;46:1978. Circulation 2006;113:1888 (Review)

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



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

Insulin Resistance and Atherosclerosis



Kim J, Montagnani M, Koh KK, Quon MJ. Circulation 2006;113:1888

Conclusions

- ACEI therapy (ramipril 10 mg) should be used in most patients with vascular disease or diabetes and additional risk factors.
- The earlier initiation, the better outcomes.
- Benefits are additive to other therapies.
- Differences exist among ACE inhibitors.
- Ramipril - lower mortality than other ACEIs.

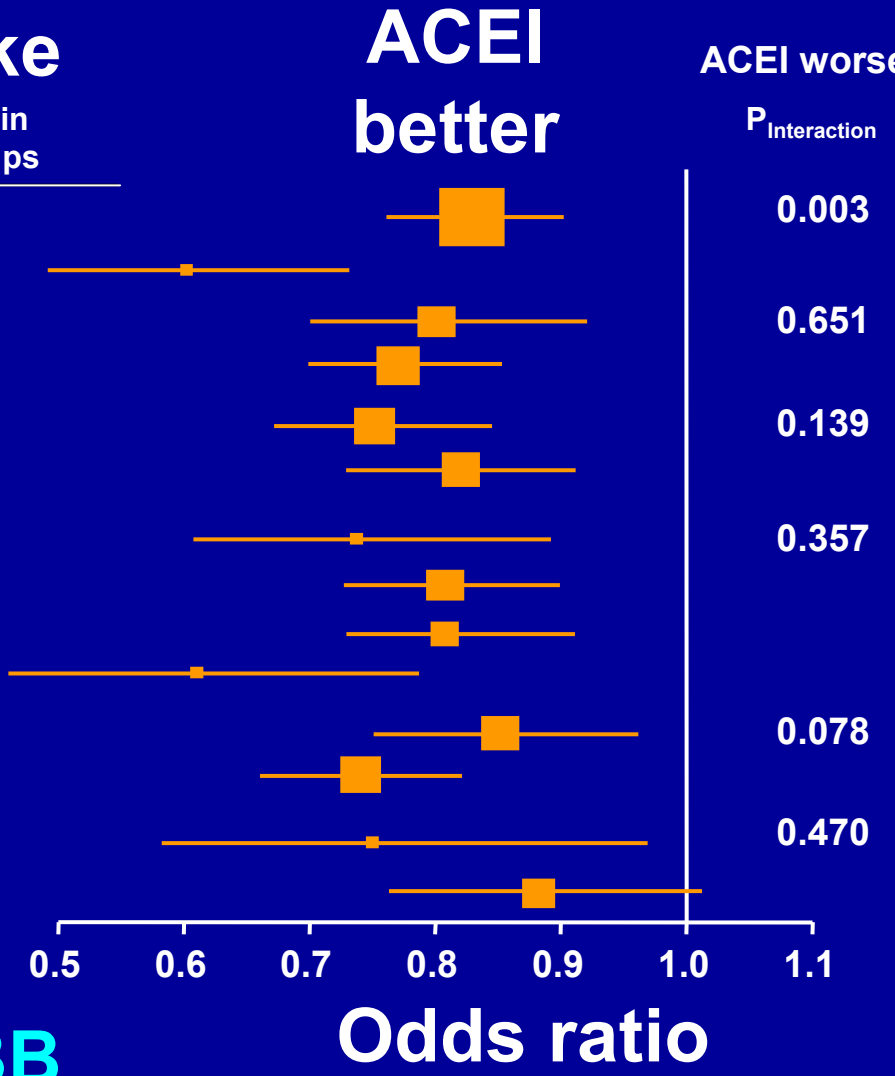

Symposium:10th Anniversary of Gil Heart Center
4, Gachon Hall, Gil Medical Center, Gachon Medical School

Q&A

Benefit of ACEI Regardless of Ancillary Treatment*

CV death, nonfatal MI, or stroke

Subgroup	Patients (n)	4-year rates in placebo groups	$P_{Interaction}$
Antiplatelets (ASA) +	18331	13.2	0.003
Antiplatelets –	3184	17.9	
Lipid-lowering agents (LL) +	9489	10.6	0.651
Lipid-lowering agents –	12026	16.4	
β blockers (BB) +	11323	13.4	0.139
β blockers –	10192	14.3	
All of the above	5103	10.4	0.357
One of the above	15314	12.6	
Two of the above	13093	12.0	
None of the above	1701	17.4	
Revascularization +	10394	11.5	0.078
Revascularization –	11123	16.0	
Revasc + ASA + LL + BB	2945	9.8	0.470
Revasc but no ASA, LL, or BB	7447	12.3	



*ASA, Lipid-lowering agents, BB

Dagenais GR, et al. Lancet. 2006;368:581