



Gachon international
symposium for
Atherosclerosis,
Hypertension
AND
Stem cell

GO AHEAD Symposium

10th Anniversary of Gil Heart Center

May 14, Saturday, 2005

Gachon Hall, Gil Medical Center

Program Director

Eak Kyun Shin, MD, PhD

Kwang Kon Koh, MD, PhD, FACC, FAHA



Welcome!

Mark

May 14, Sat!

2003 AHA Meeting, Educational Symposium



2004 AHA Meeting, Hypertension Symposium



2005.4.14

Pleiotropic Effects of *Ramipril* - Beyond Reduction in Blood Pressure

**Kwang Kon Koh,
MD, PhD, FACC, FAHA**

**Cardiology, Gil Heart Center,
Gachon Medical School,
Incheon, Korea**

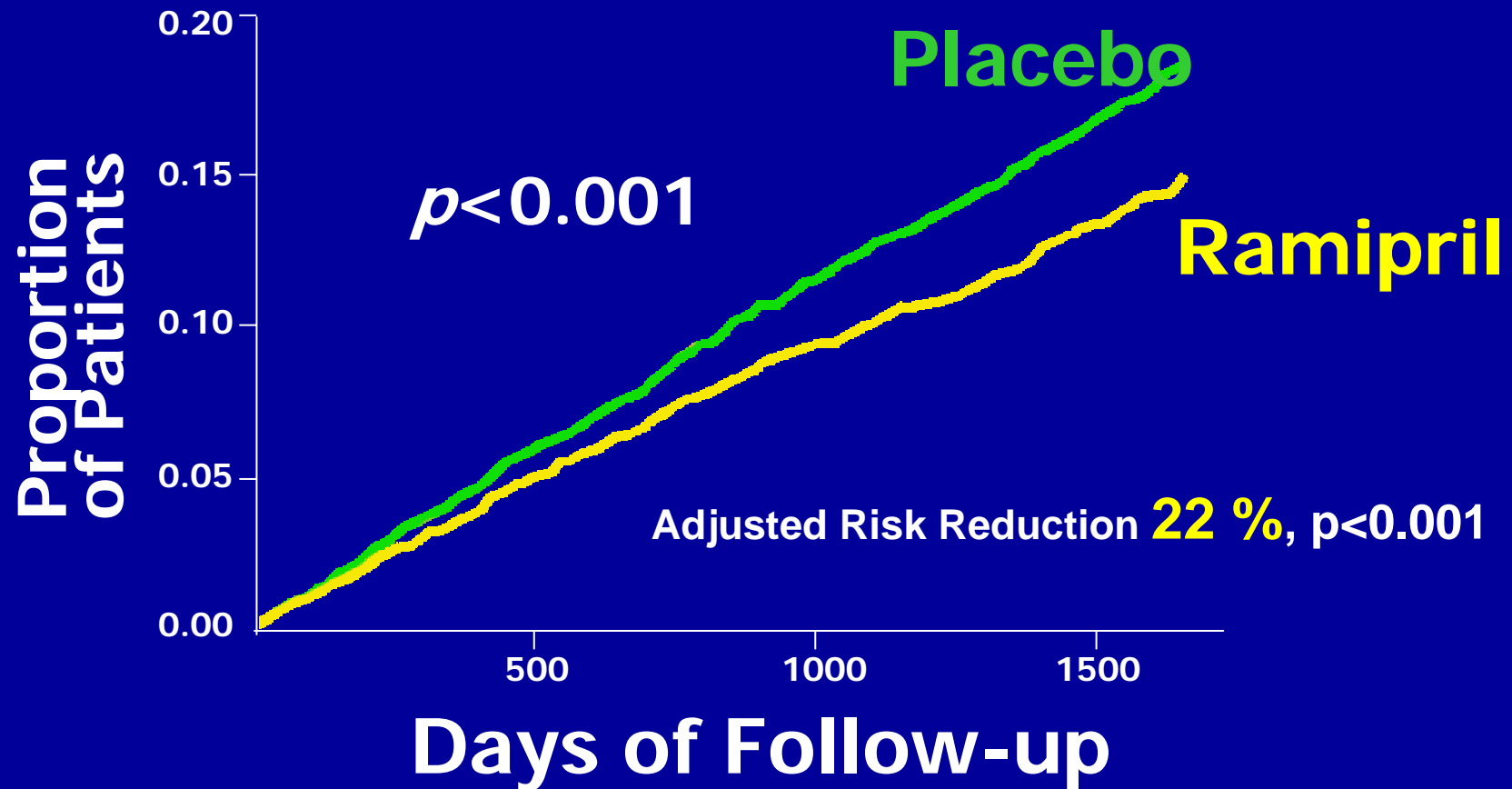


Pleiotropic Effects of *Ramipril*

- Beyond Reduction in Blood Pressure

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

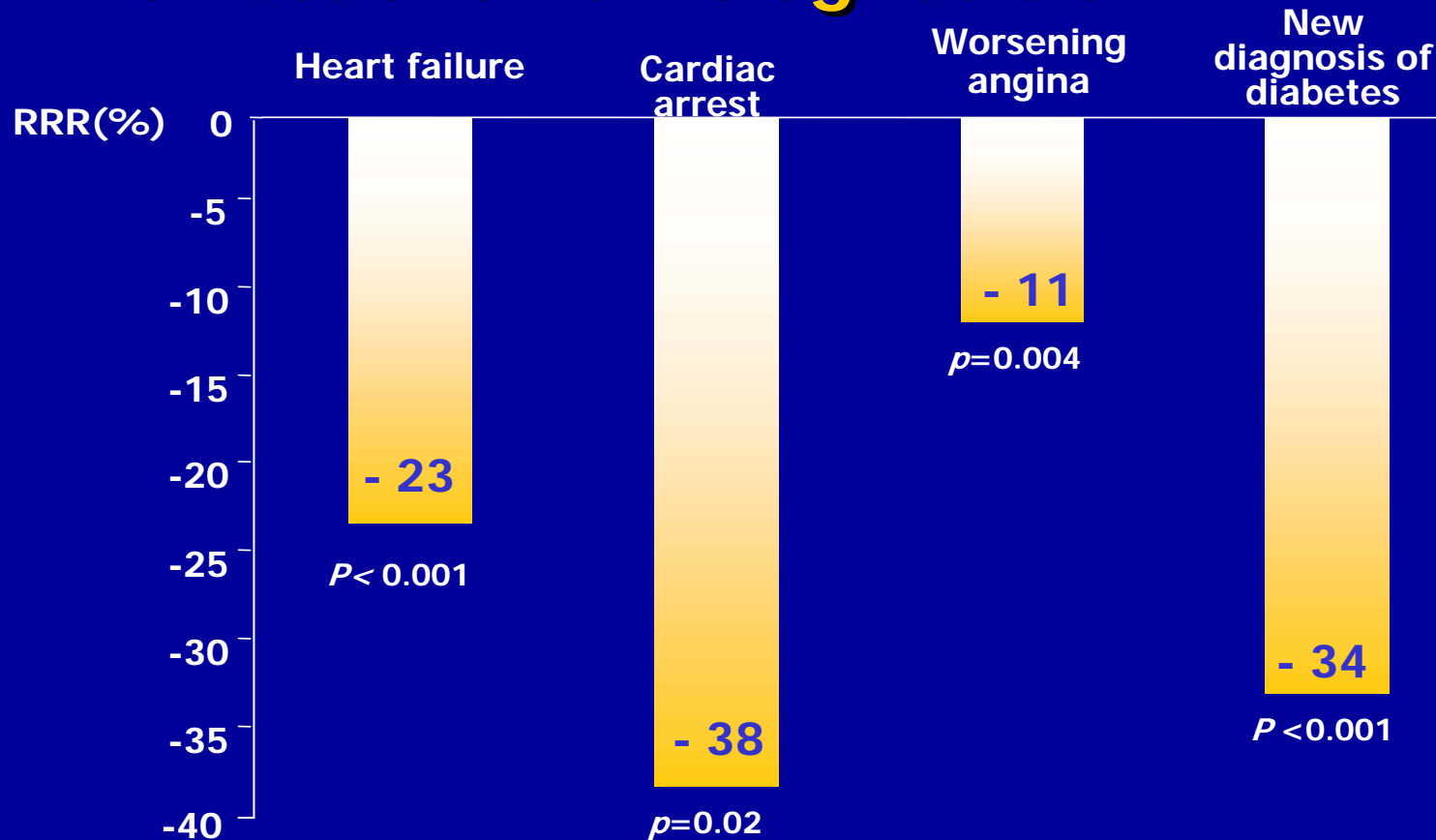
Heart Outomes Prevention Evaluation Study



Ramipril versus placebo Kaplan-Meier Estimates of Composite Primary Outcomes(%)

Heart Outcomes Prevention Evaluation (HOPE) Study

Lower incidences of heart failure, cardiac arrest and new diagnosis of DIABETES



Tritace versus Placebo Risk Reduction on Other Outcomes(%)⁸

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

Background of MICRO-HOPE Study

- **CVD: 70% of all deaths in diabetic patients**
- **Despite decreases in the incidence of CVD in the general population, the decline is much smaller in diabetic patients, and may even be rising in diabetic women.**

Gu K et al, JAMA 1999;281:1291

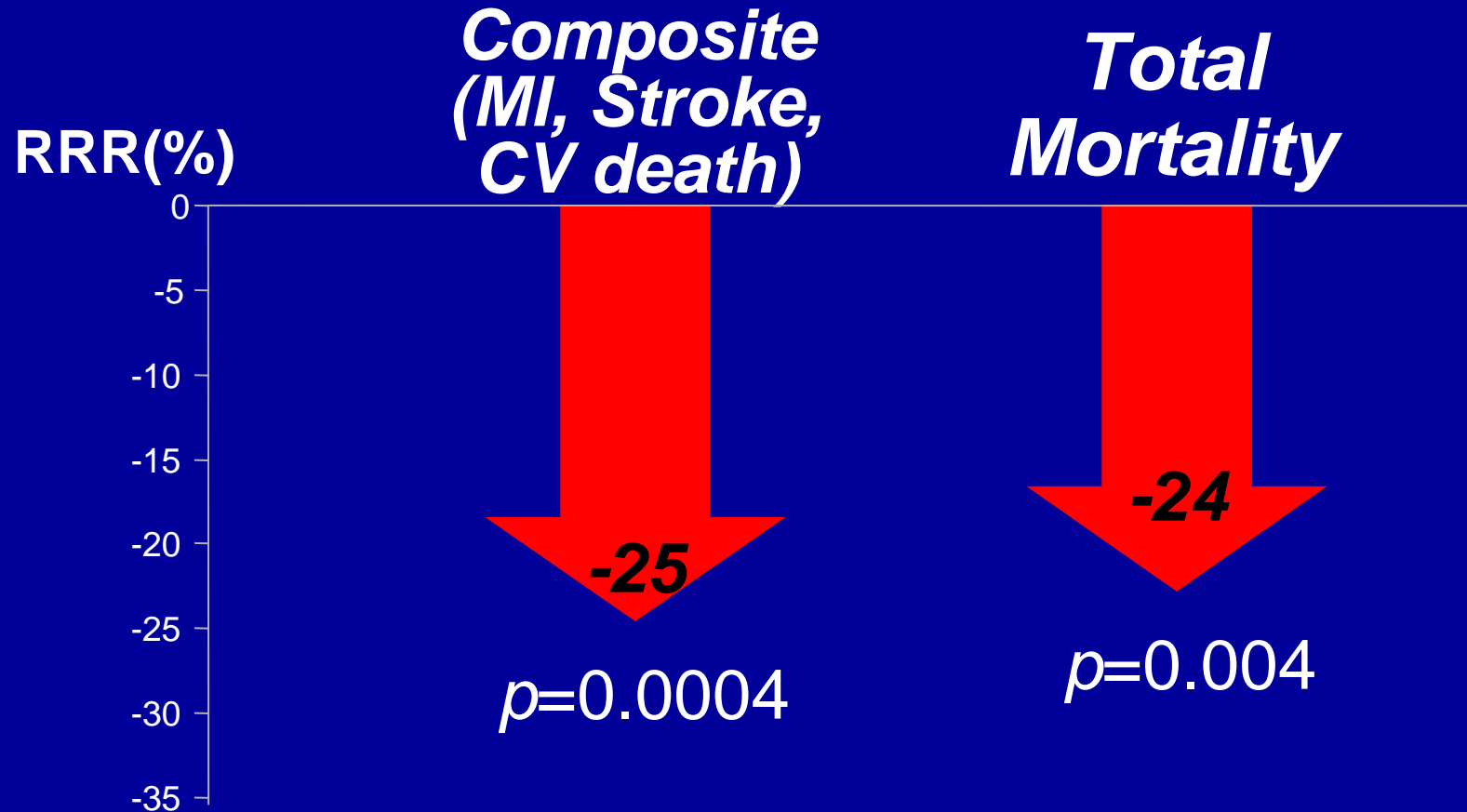
MICRO- HOPE

**(Microalbuminuria, Cardiovascular, and Renal Outcomes
in the Heart Outcomes Prevention Evaluation)**

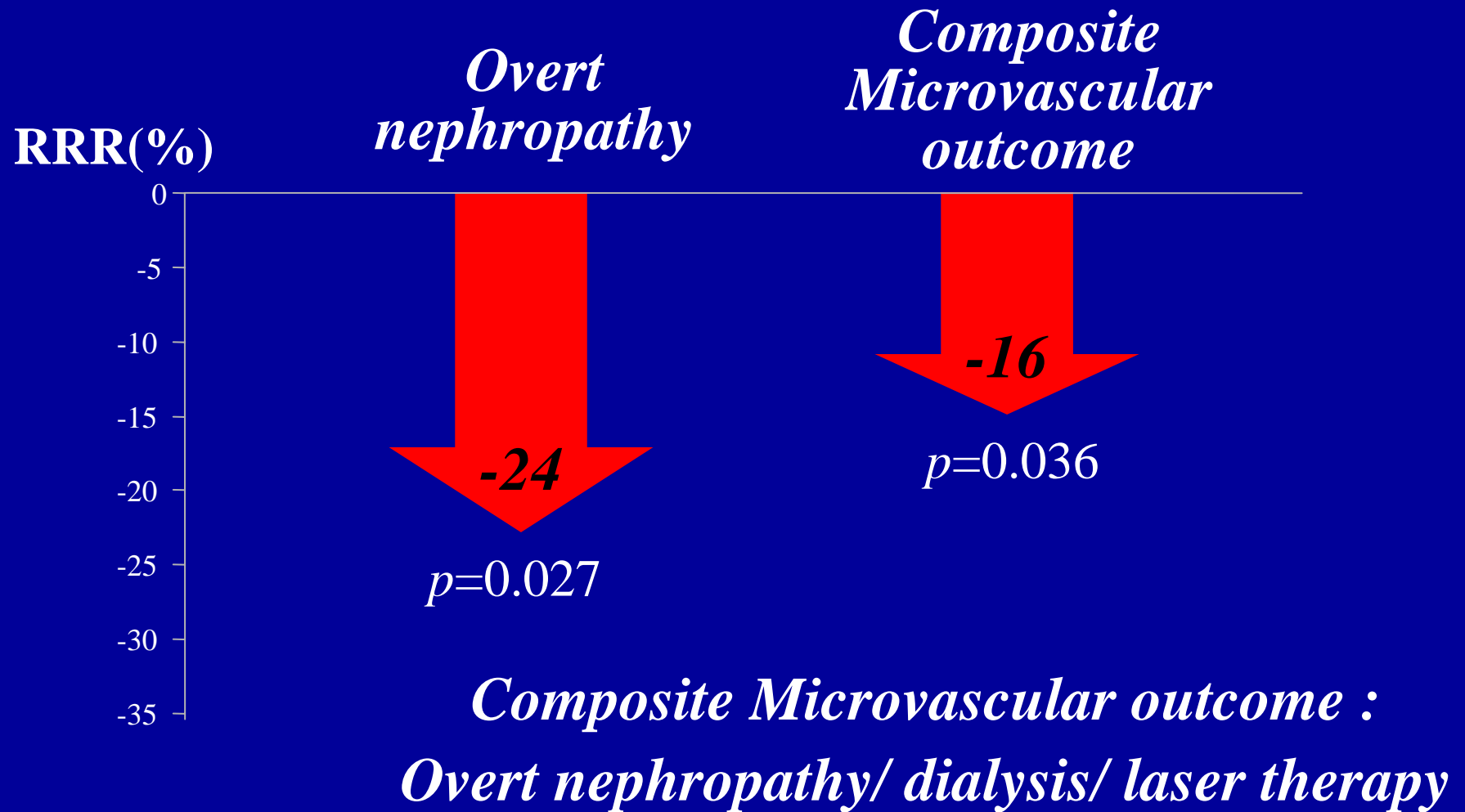
Hypothesis

- HOPE study investigated whether the addition of *ramipril* to the current medical regimen of high risk patients 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

MICRO-HOPE : CV outcomes (I)

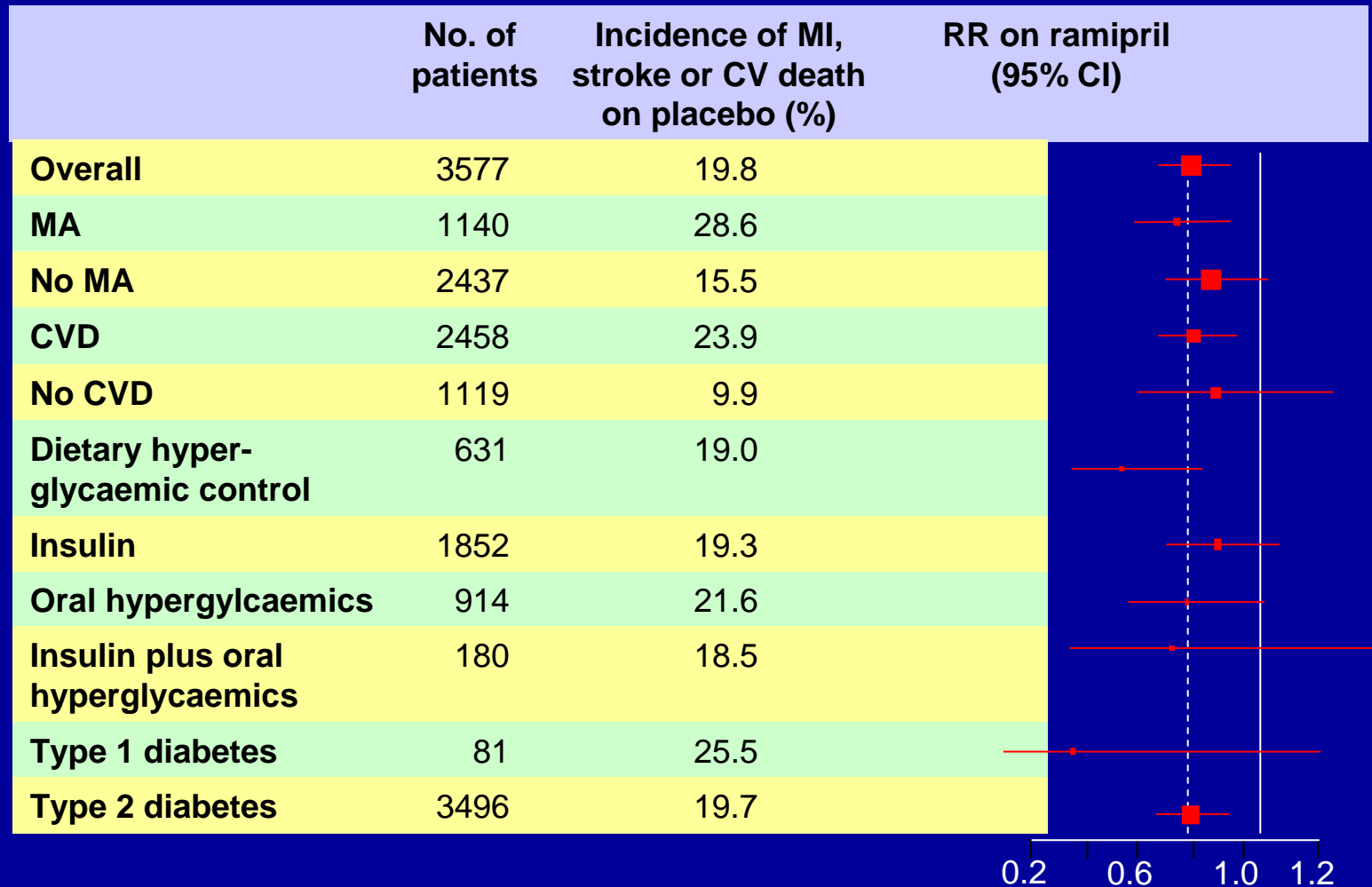


MICRO-HOPE : Microvascular Outcomes

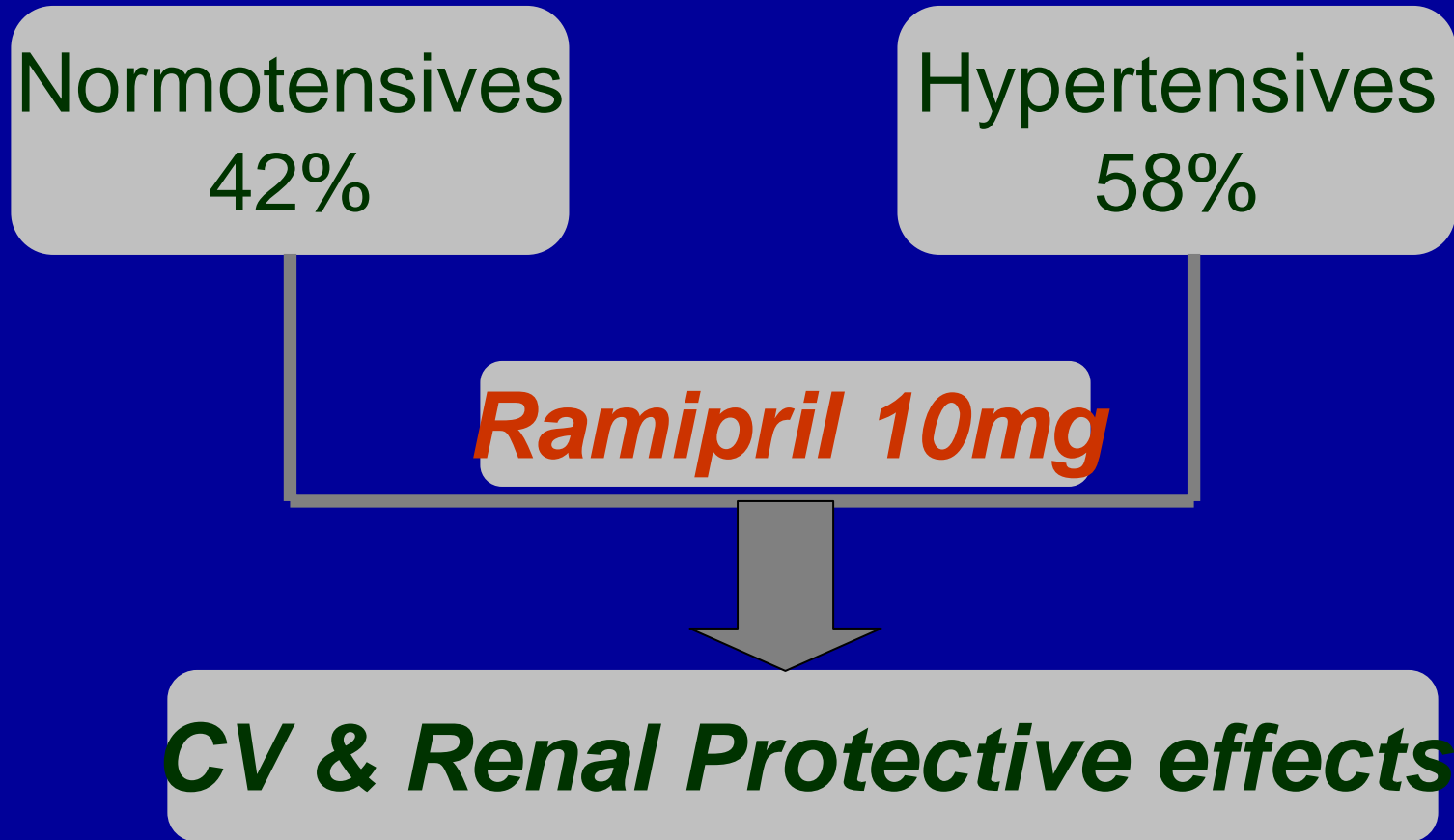


MICRO-HOPE:

Beneficial in all subgroups analyzed



Effect in Normotensives and Hypertensives



Additive Effect on top of all other Medications

Concomitant Medications

▪ Dietary alone	18%	Aspirin	54 %
▪ Oral agents	53%	Lipid lowering agents	23 %
▪ Insulin	24%	CCB	43%
▪ Insulin+oral agents	5%	Others: Beta-blockers	28 %
		Diuretics	19 %

HOPE, MICRO-HOPE: Summary

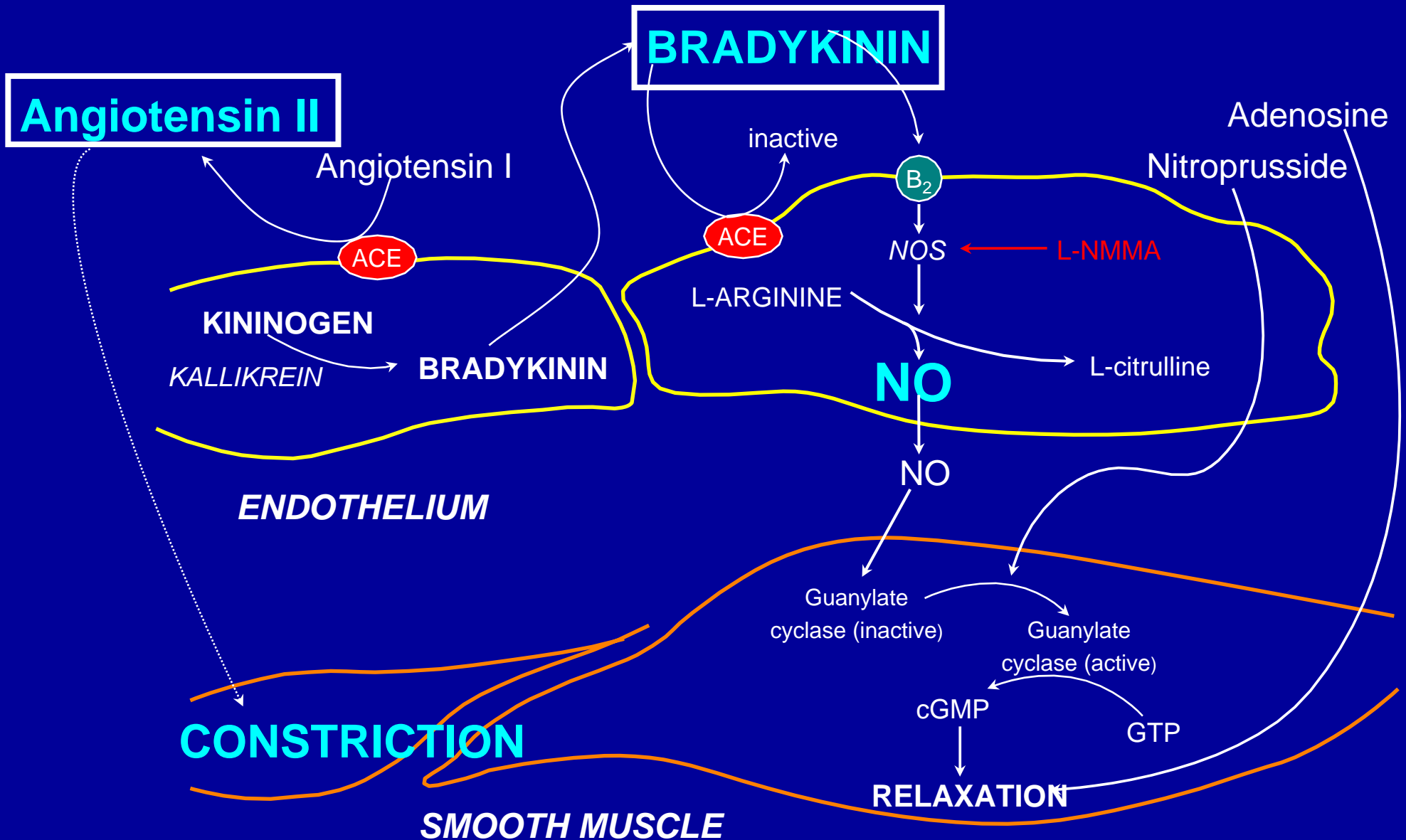
1. In diabetics at high risk, *Ramipril* prevented:
 - Major CV outcomes (death, MI, stroke)
 - Microvascular outcomes (nephropathy, retinopathy)
2. CV benefits (death, MI, stroke) were greater than expected for degree of BP-lowering.
Benefits: not due to reduced BP alone
3. Benefits were observed in addition to other effective therapies.

Pleiotropic Effects of Ramipril

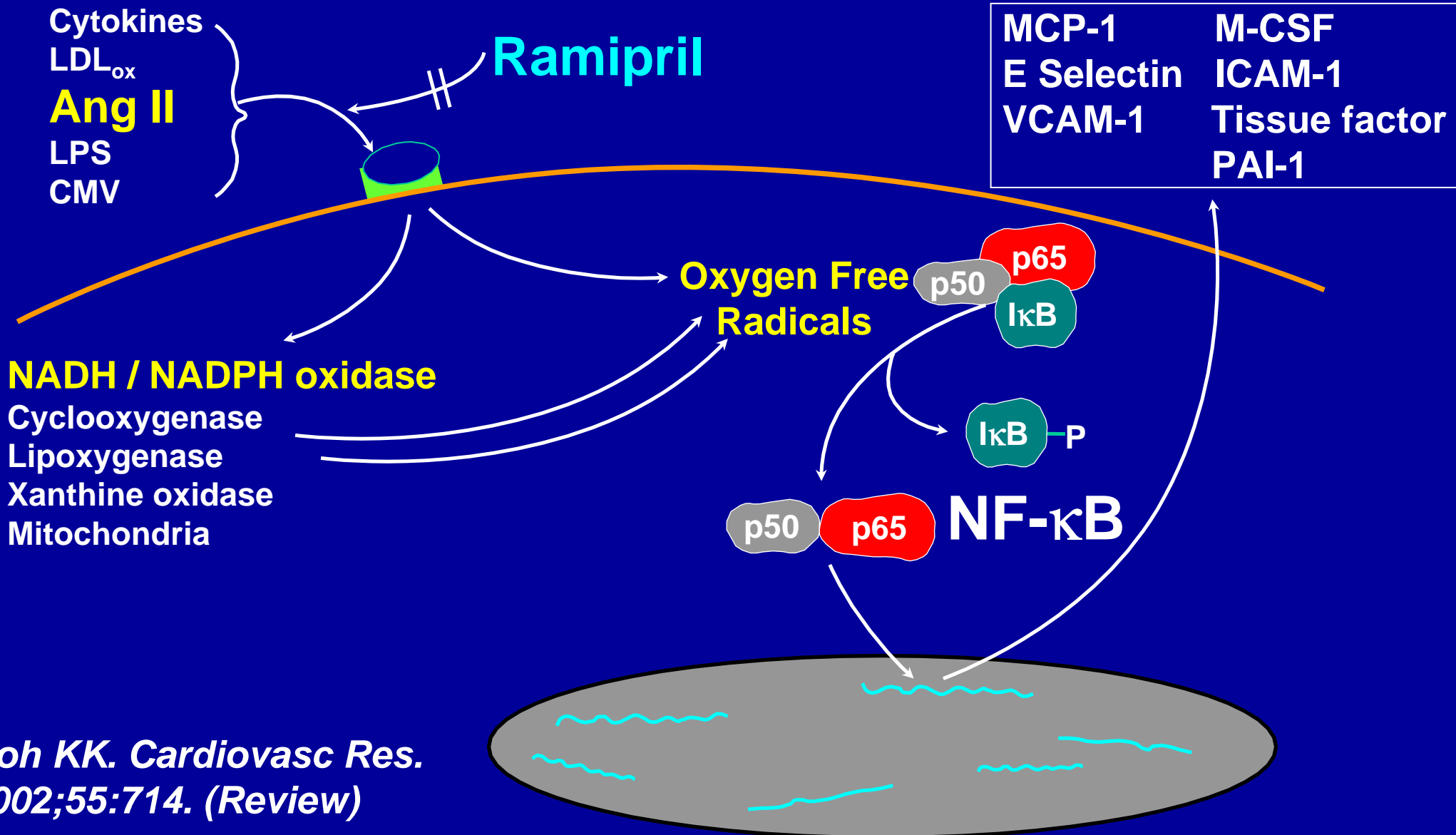
- Beyond Reduction in Blood Pressure

- Randomized Clinical Trials
- **Plausible Mechanisms**
- Mechanistic Clinical Studies
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Angiotensin Converting Enzyme and Endothelial Function

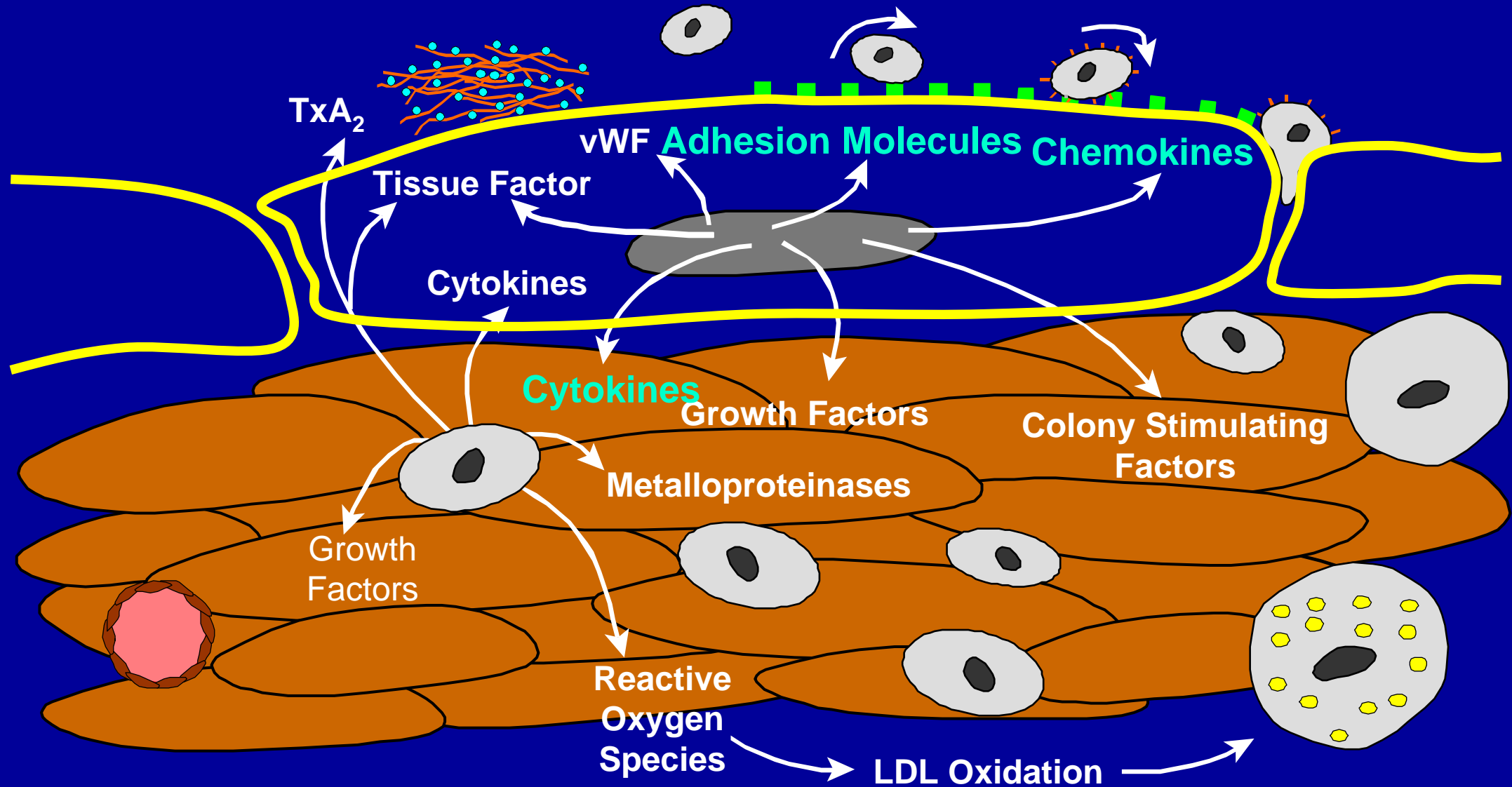


Activation of Nuclear Transcription Factor, NF κ B

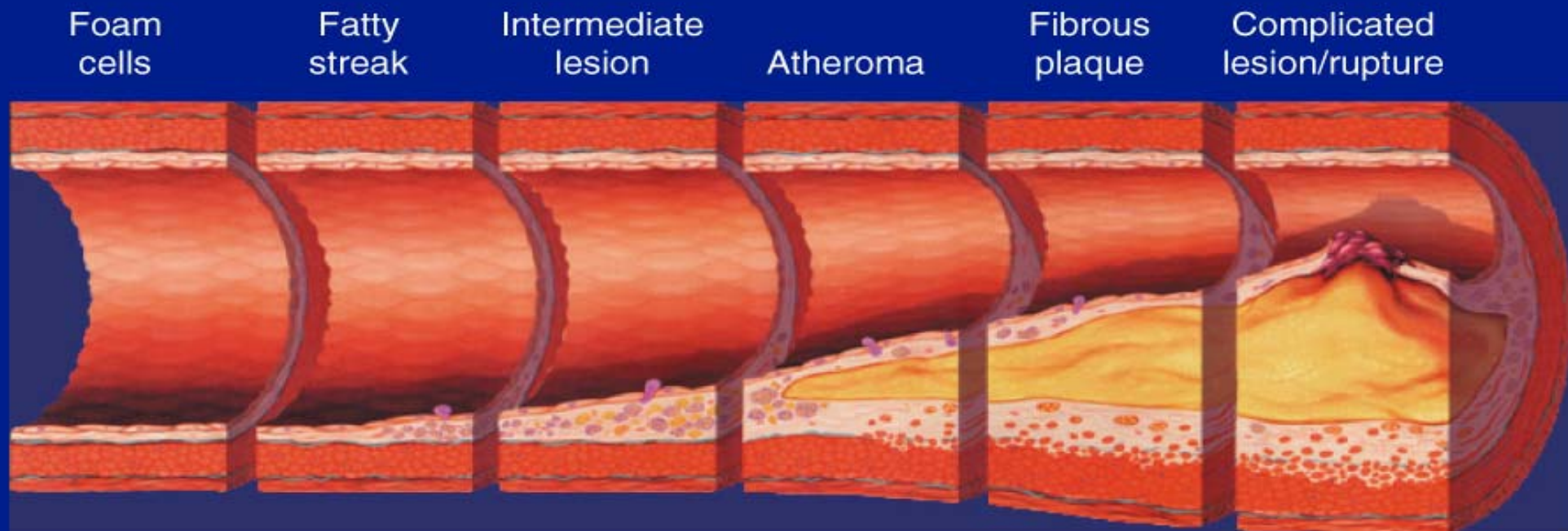


Koh KK. Cardiovasc Res. 2002;55:714. (Review)

Inflammatory Response to Injury



Atherosclerosis timeline



Endothelial dysfunction →

From first decade

From third decade

From fourth decade

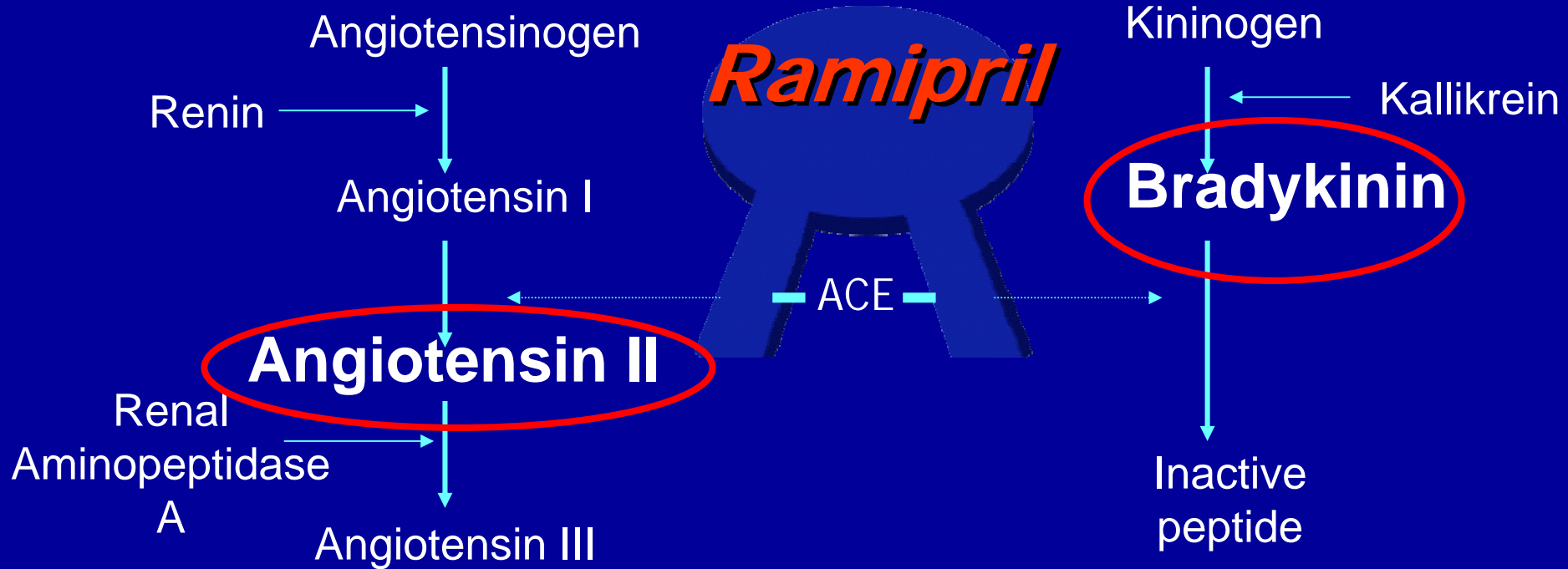
Growth mainly by lipid accumulation

Smooth muscle
and collagen

Thrombosis,
hematoma

Renin-angiotensin-aldosterone system

Kallikrein-kinin system



Pleiotropic Effects of *Ramipril*

- Beyond Reduction in Blood Pressure

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

Kwang Kon Koh, Seung Hwan Han

Eak Kyun Shin, Michael J. Quon*

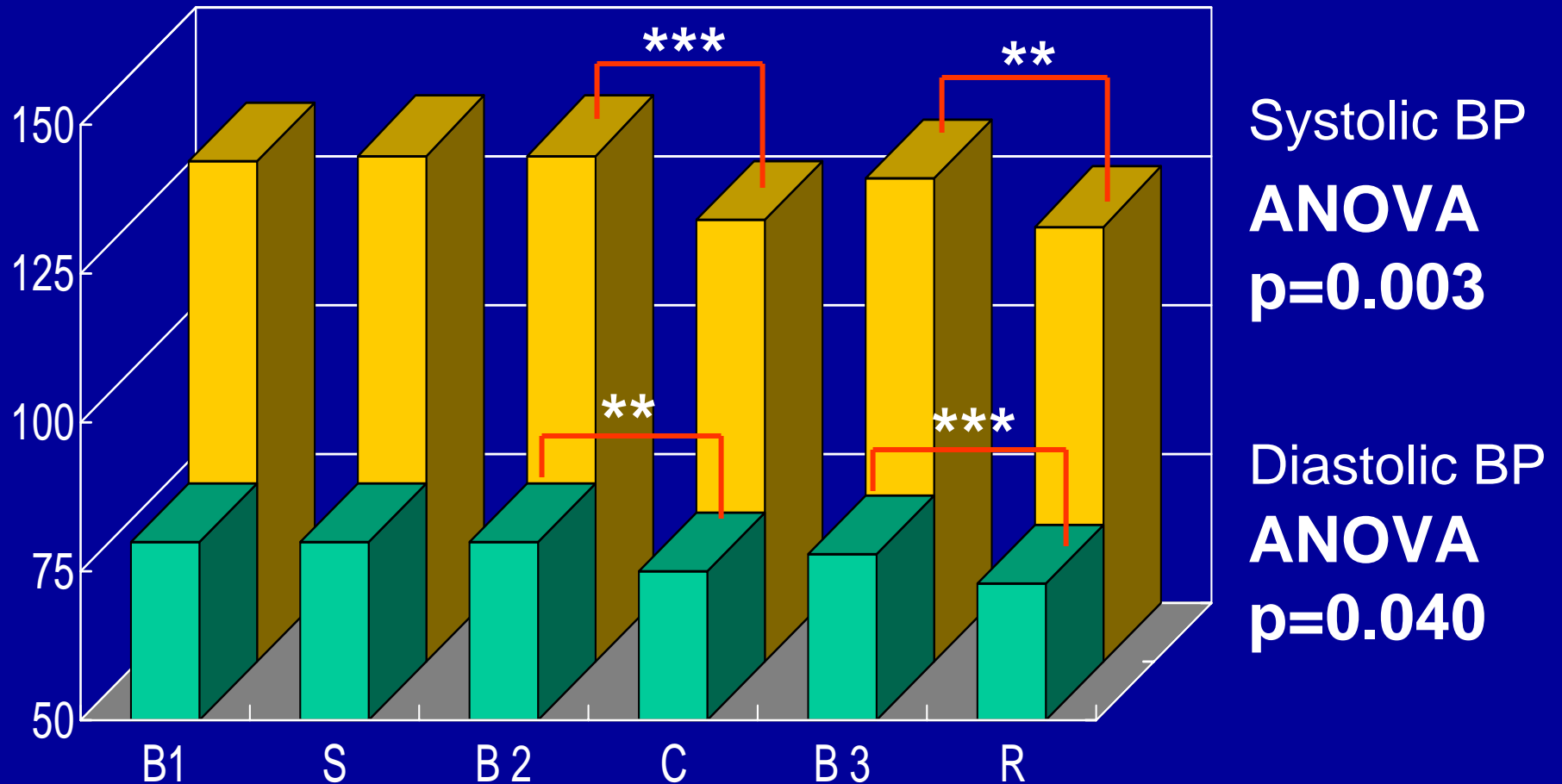
Cardiology Division, Gachon Medical School

Incheon, Korea

Diabetes Unit, NIH, USA*

AHA 2004, Hypertension 2005 (June)

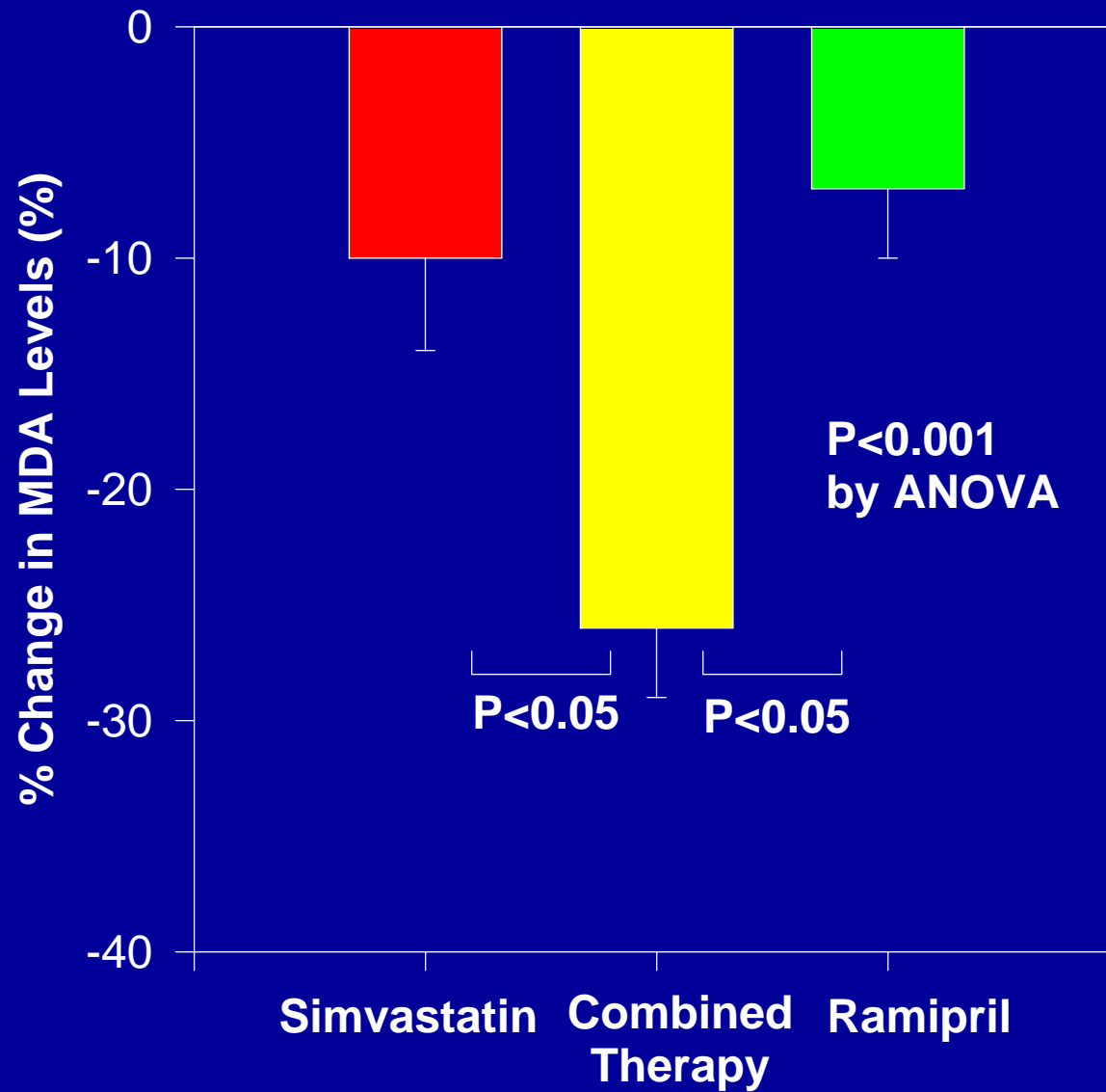
Ramipril Combined with Simvastatin on Blood Pressure (mmHg)



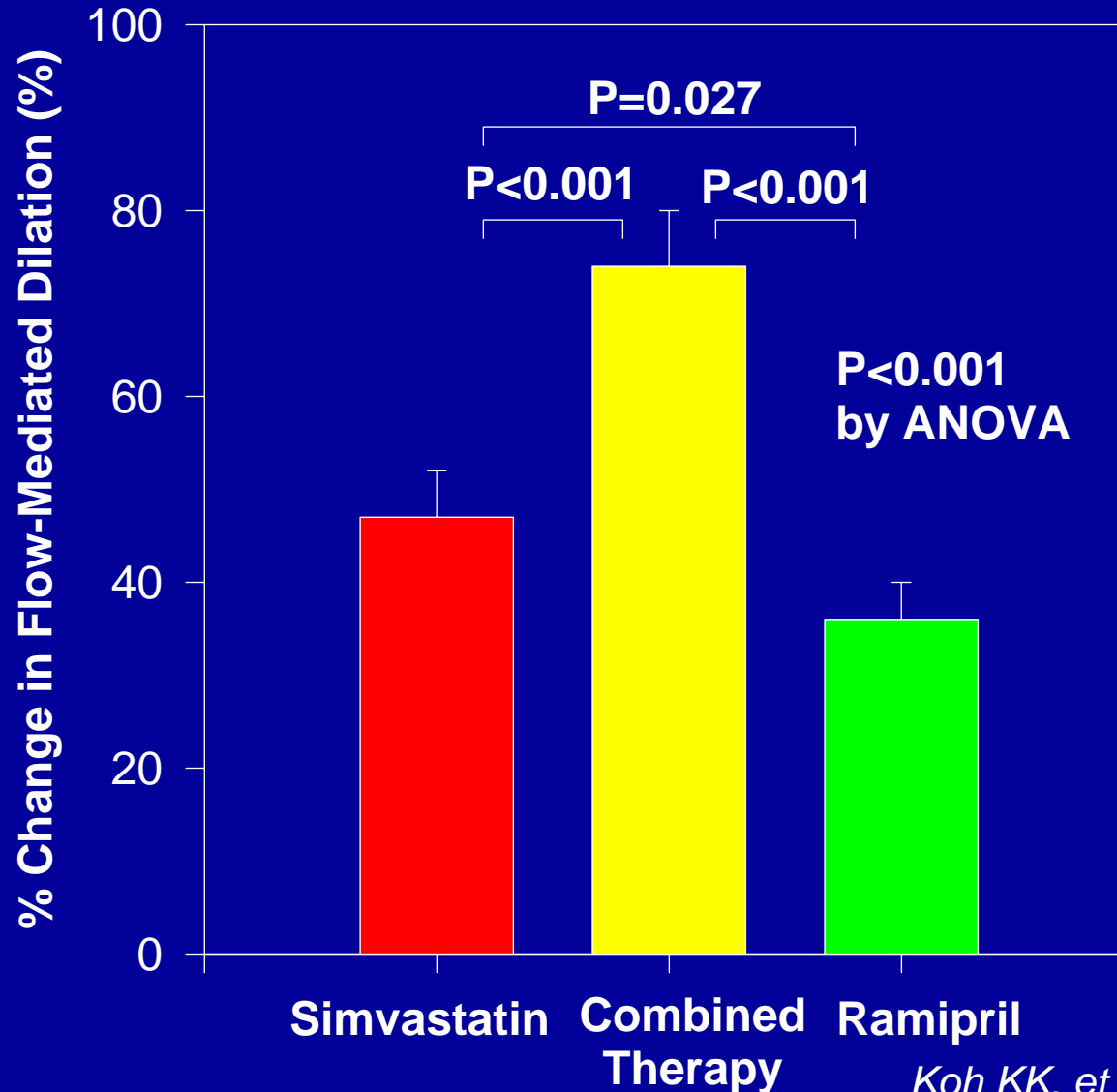
*= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.001$ vs. Baseline.

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

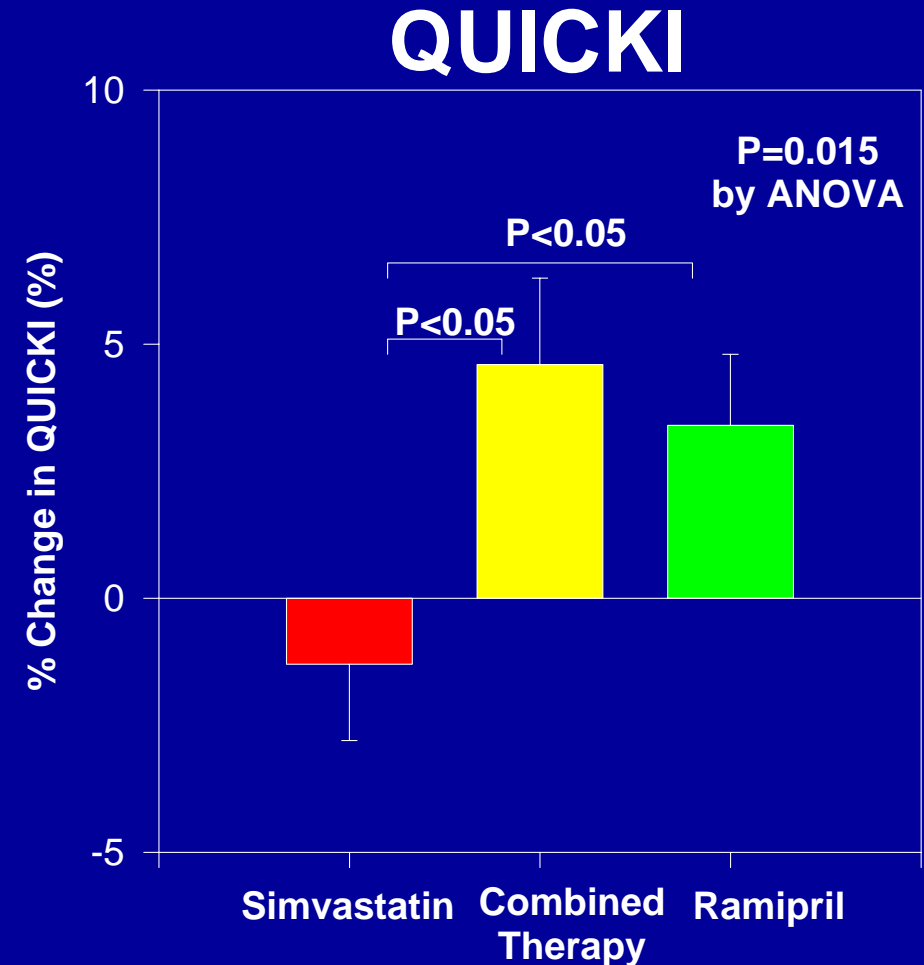
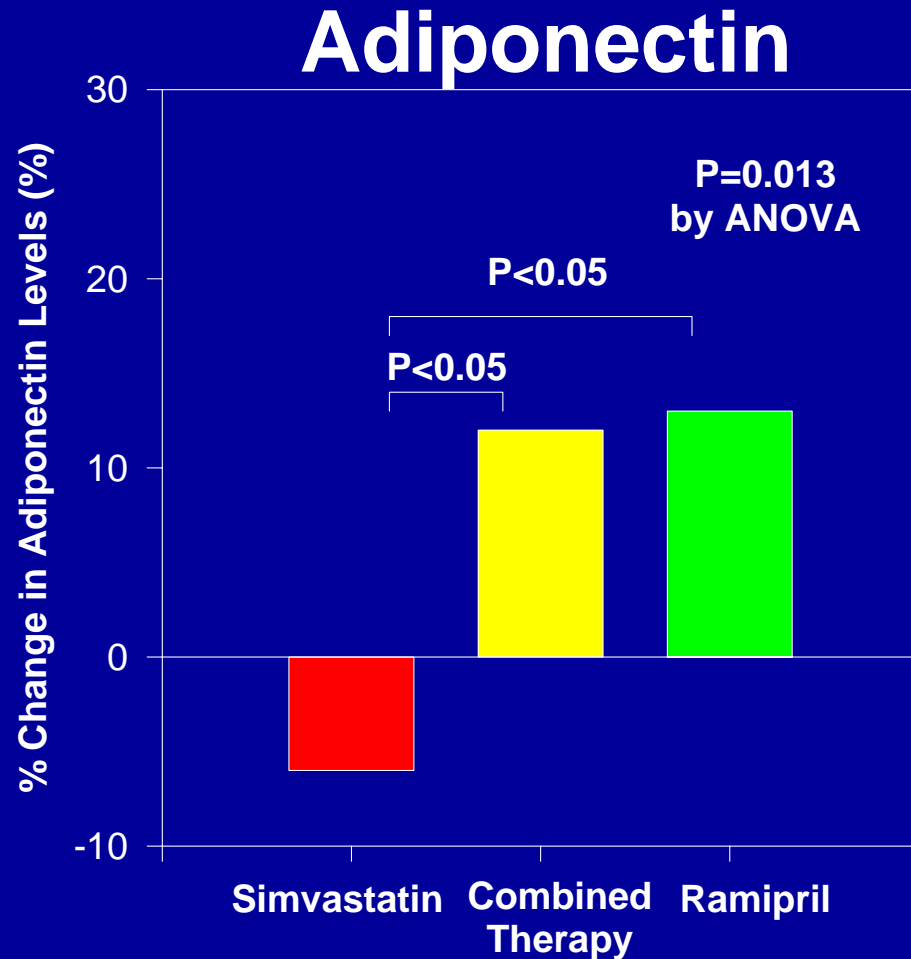
Effects of Simvastatin, Combined Therapy, and Ramipril on Malondialdehyde Levels



Effects of Simvastatin, Combined Therapy, and Ramipril on FMD



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



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

*Koh KK, et al.
Hypertension 2005
(June)*

Correlations Between Blood Pressure and FMD, MDA or CRP, and Insulin resistance

- There were **no significant correlations** between FMD, MDA, CRP, insulin resistance and reduction of systolic blood pressure (-0.201 r 0.276) and between these changes and reduction of diastolic blood pressure (-0.245 r 0.266).

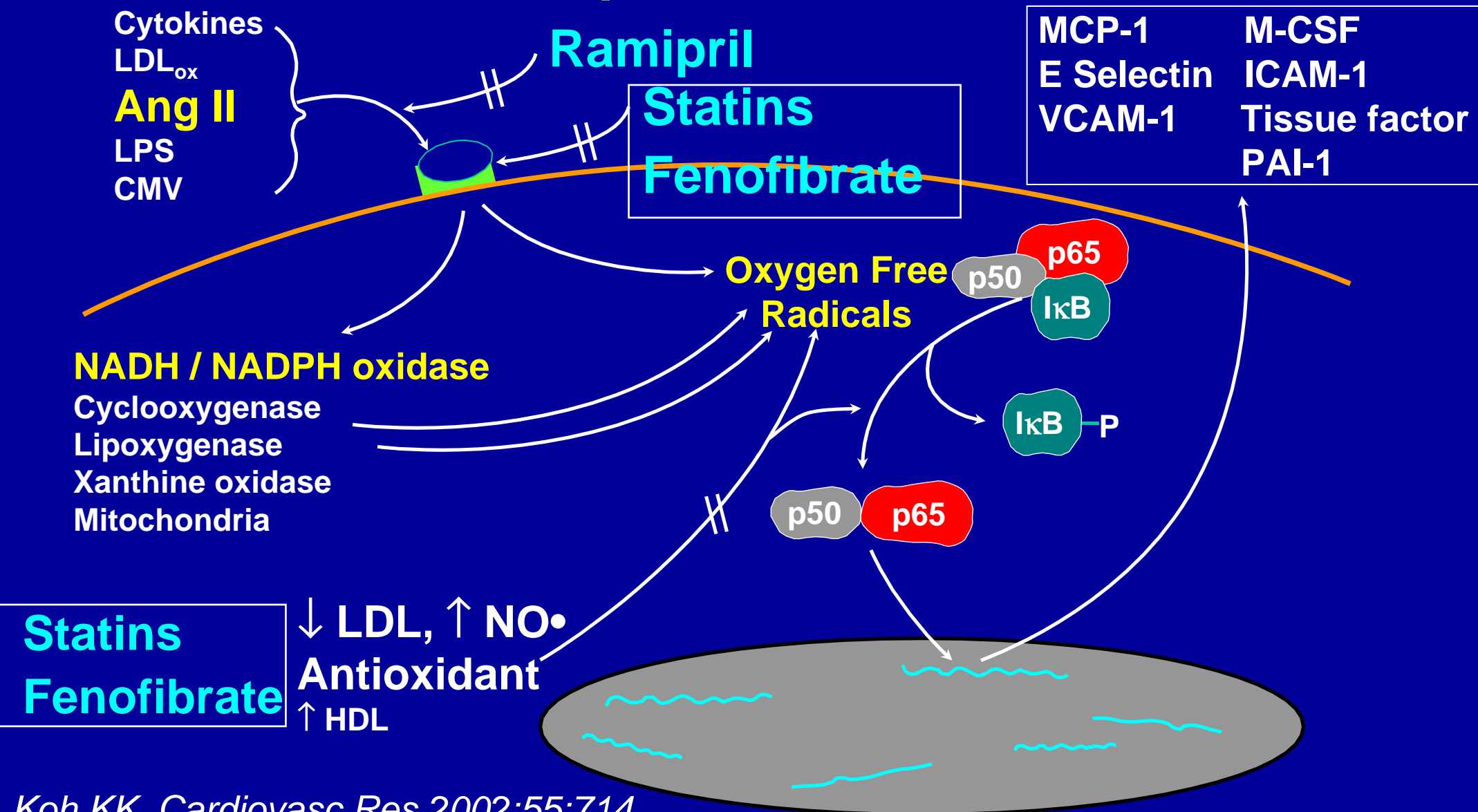
Future Research

Will *Ramipril* combined with Statins or Fenofibrate be better than monotherapy?

ASCOT trial. Lancet. 2003;361:1149.

Wald NJ, et al. BMJ. 2003;326:1419.

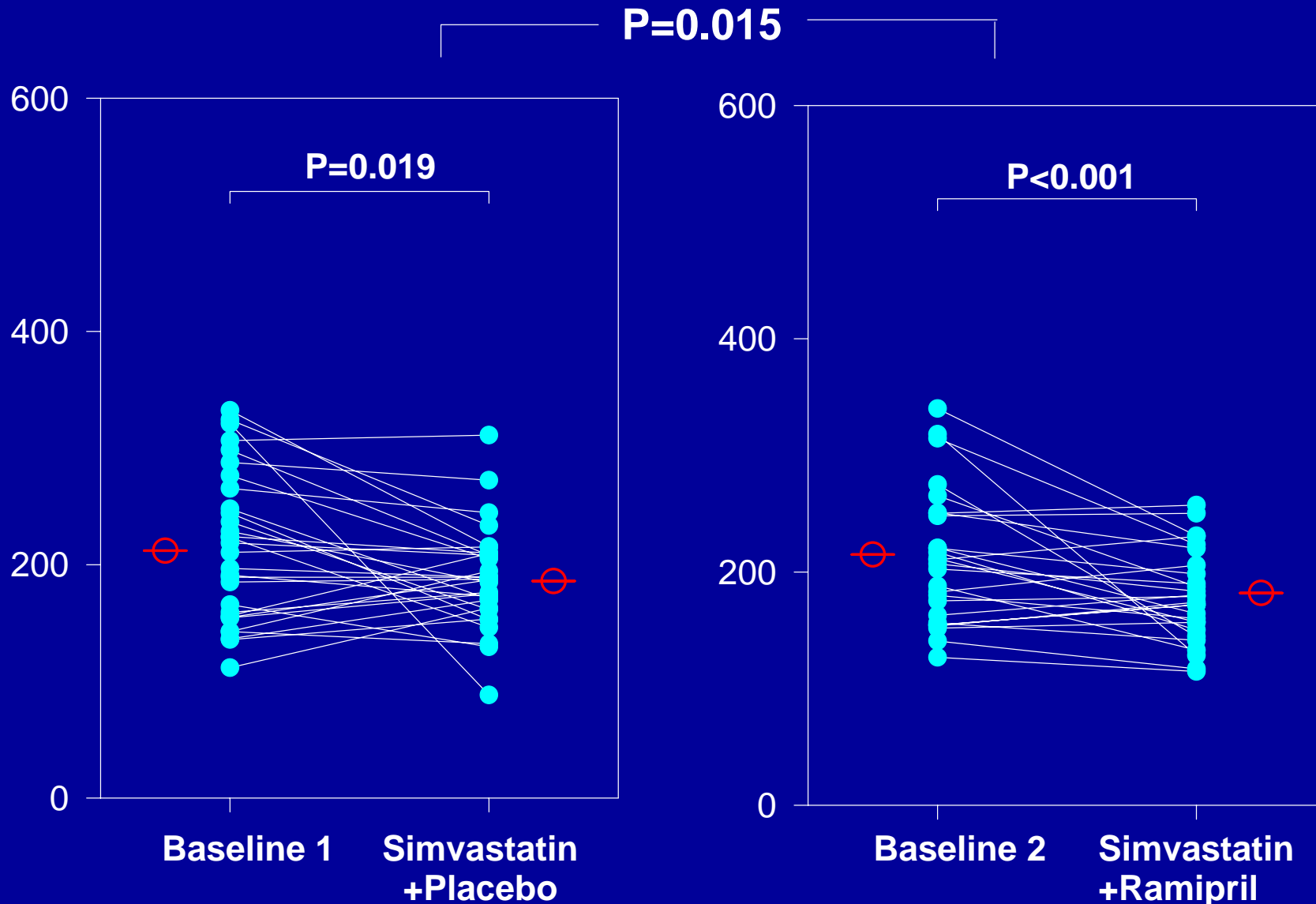
Activation of Nuclear Transcription Factor, NF κ B



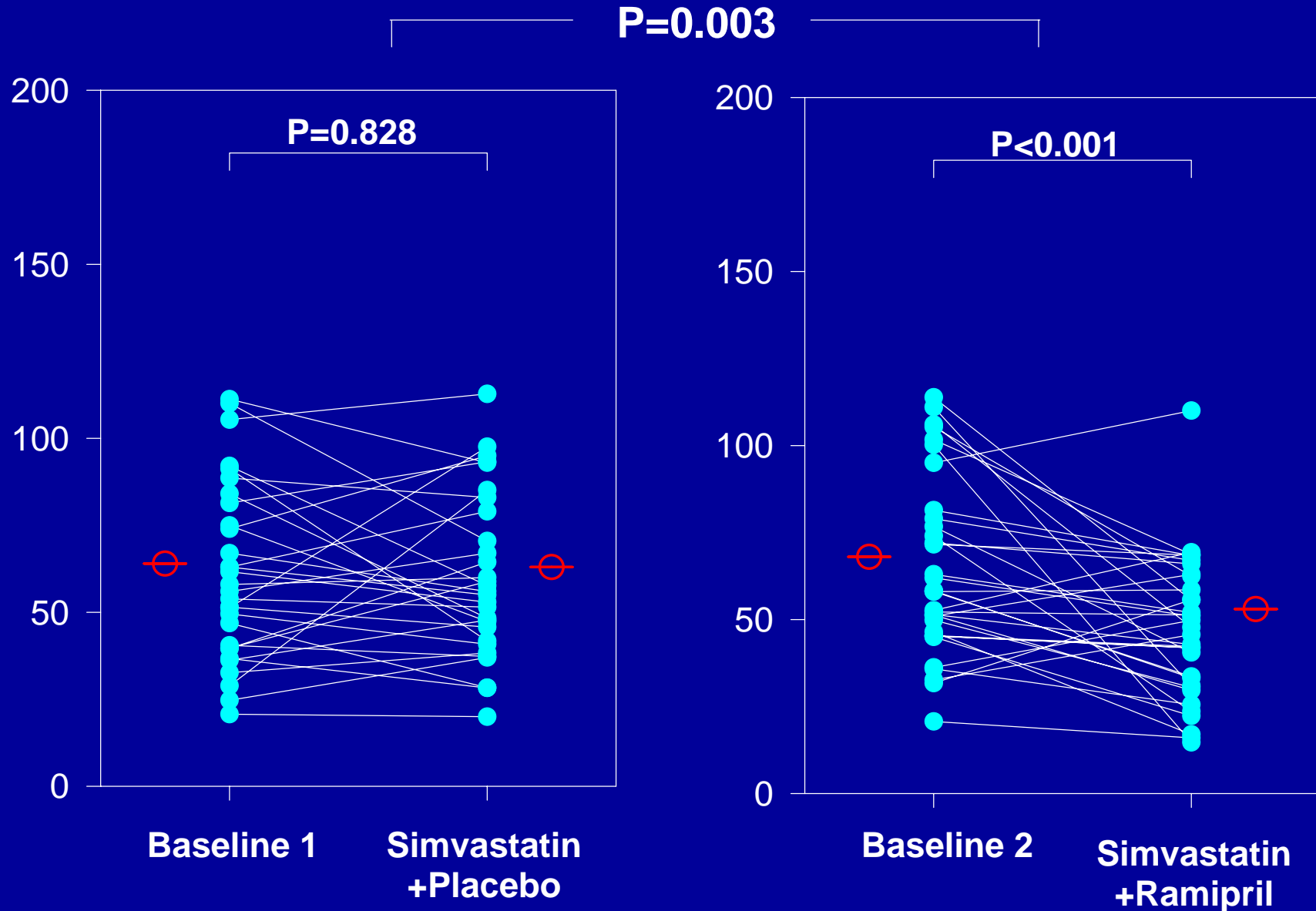
**Simvastatin Combined with
Ramipril Treatment in 50
Hypercholesterolemic Patients**

***Koh KK, Chung W-J, ...Shin EK
Hypertension. 2004;44:180.***

Ramipril Combined with Simvastatin on MCP-1 Levels (pg/ml) (HC)



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



**Additive Effects of *Ramipril*
Combined with Statin on
Inflammation and Fibrinolysis in
Patients with CAD**

***Koh KK, Han SH, ...Shin EK
Atherosclerosis. 2004;177:147***

Conclusions

- MICRO-HOPE study demonstrated that *ramipril* significantly prevented major CV outcomes (death, MI, stroke) and microvascular outcomes (nephropathy, retinopathy) in diabetics at risk.
- *Ramipril* (particularly high dose) has pleiotropic effects in vascular wall to improve impaired endothelial function and prevention of new onset of diabetes in high risk groups beyond reduction in blood pressure.

Tritace Plus!

Effective BP Control

with CV Protective Effect !!

Tritace Plus – The broadest range of patient by JNC 7

Recommended Drugs

Compelling indication	Thiaz	BB	CCB	ACEI	ARB	ALDO	ANT
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Heart failure

Post MI

High CAD risk

Diabetes

Chronic kidney Disease

Recurrent stroke prevention

Tritace Plus can be applied for patients with heart failure, high CAD risk, diabetes and stroke

Synergistic mechanism of ACEI and thiazide

ACEI
(ramipril)



Formation of Angiotensin II
Breakdown of bradykinin



**Dilatation of
Peripheral vessel**

Thiazide
(HCTZ)



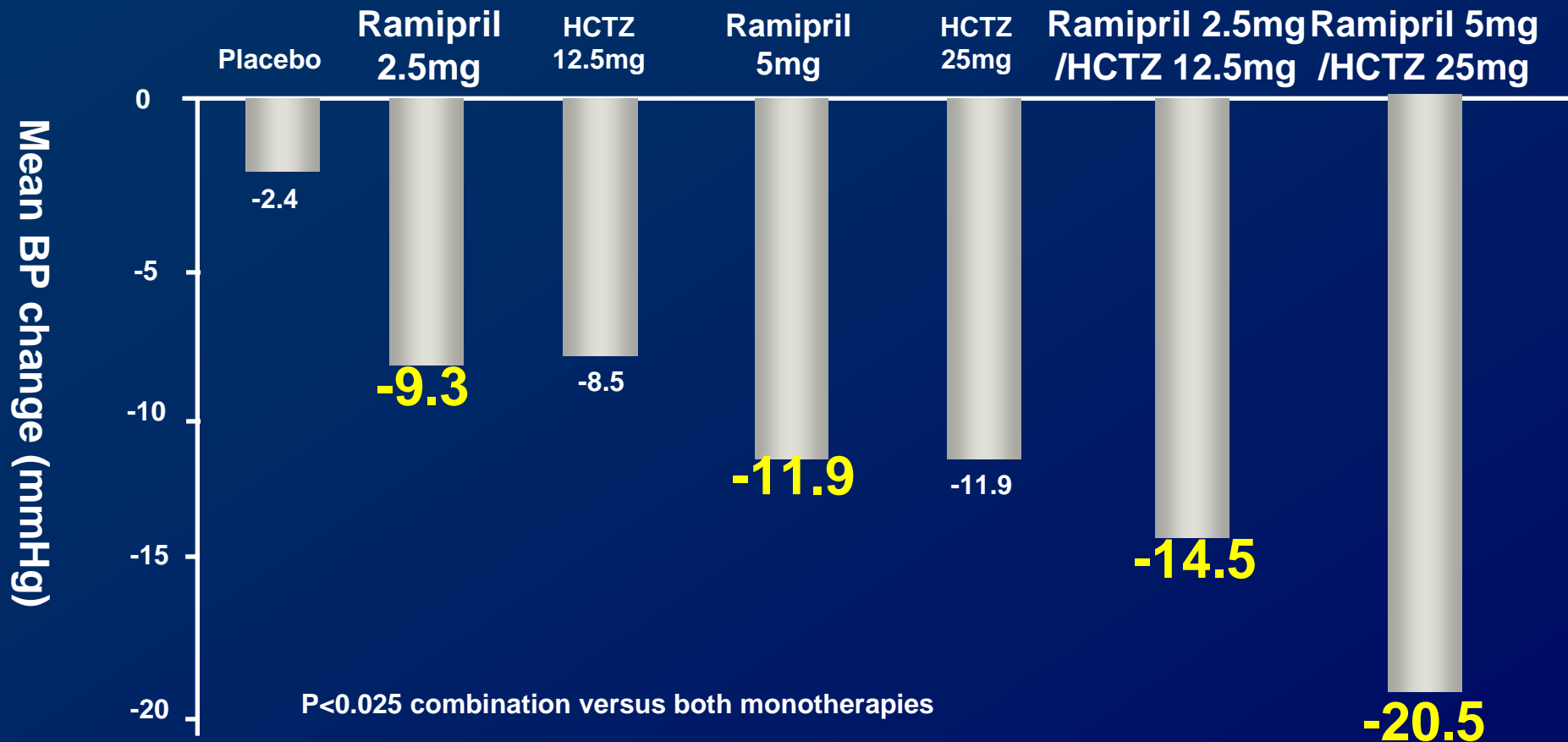
Renal excretion of electrolytes
and fluid



**Reduction of
Plasma volume**

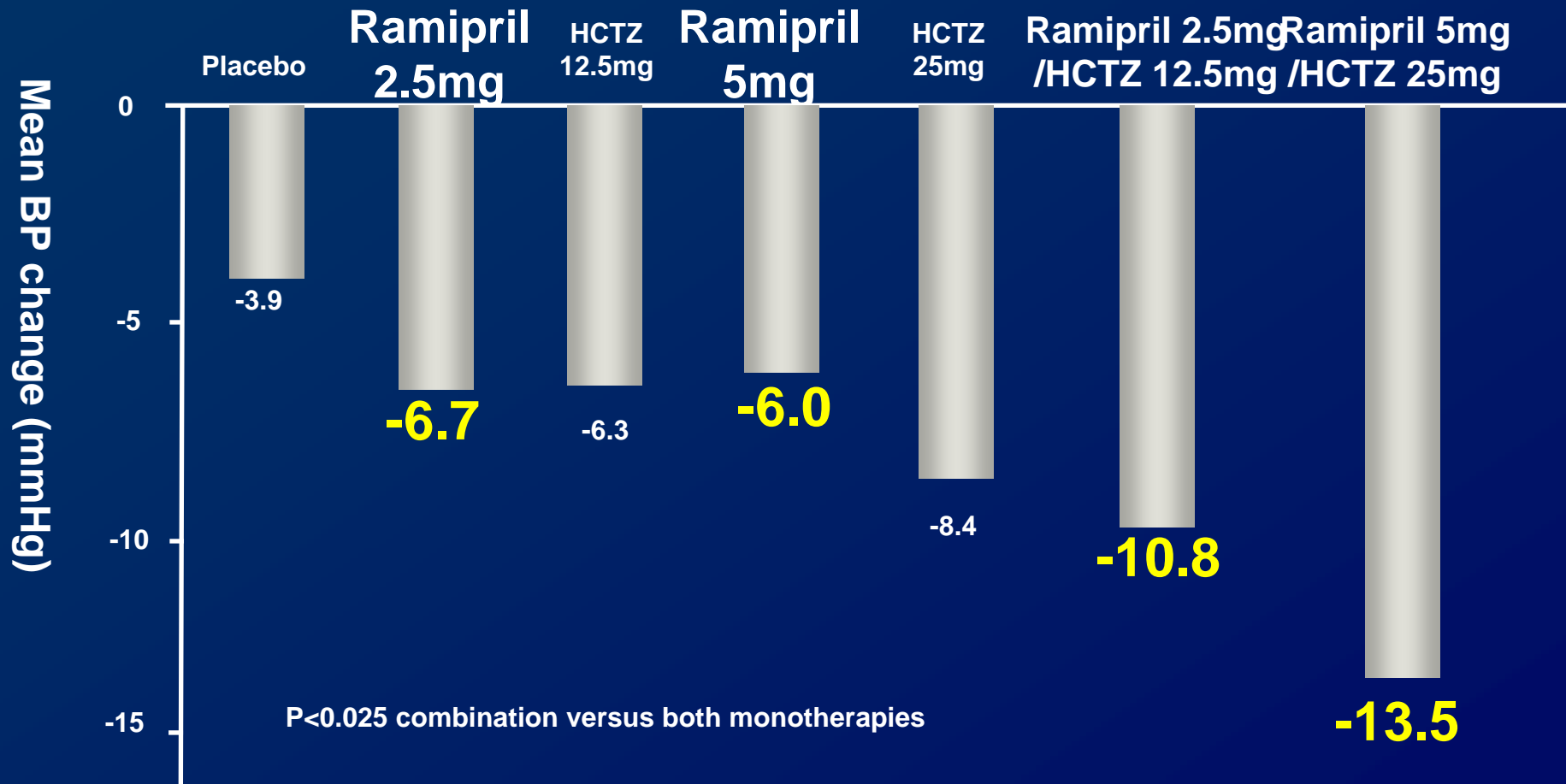
Greater BP decrease than monotherapy (1)

- Changes in supine SBP from baseline to end-point (n=534)



Greater BP decrease than monotherapy (2)

- Changes in supine DBP from baseline to end-point (n=534)

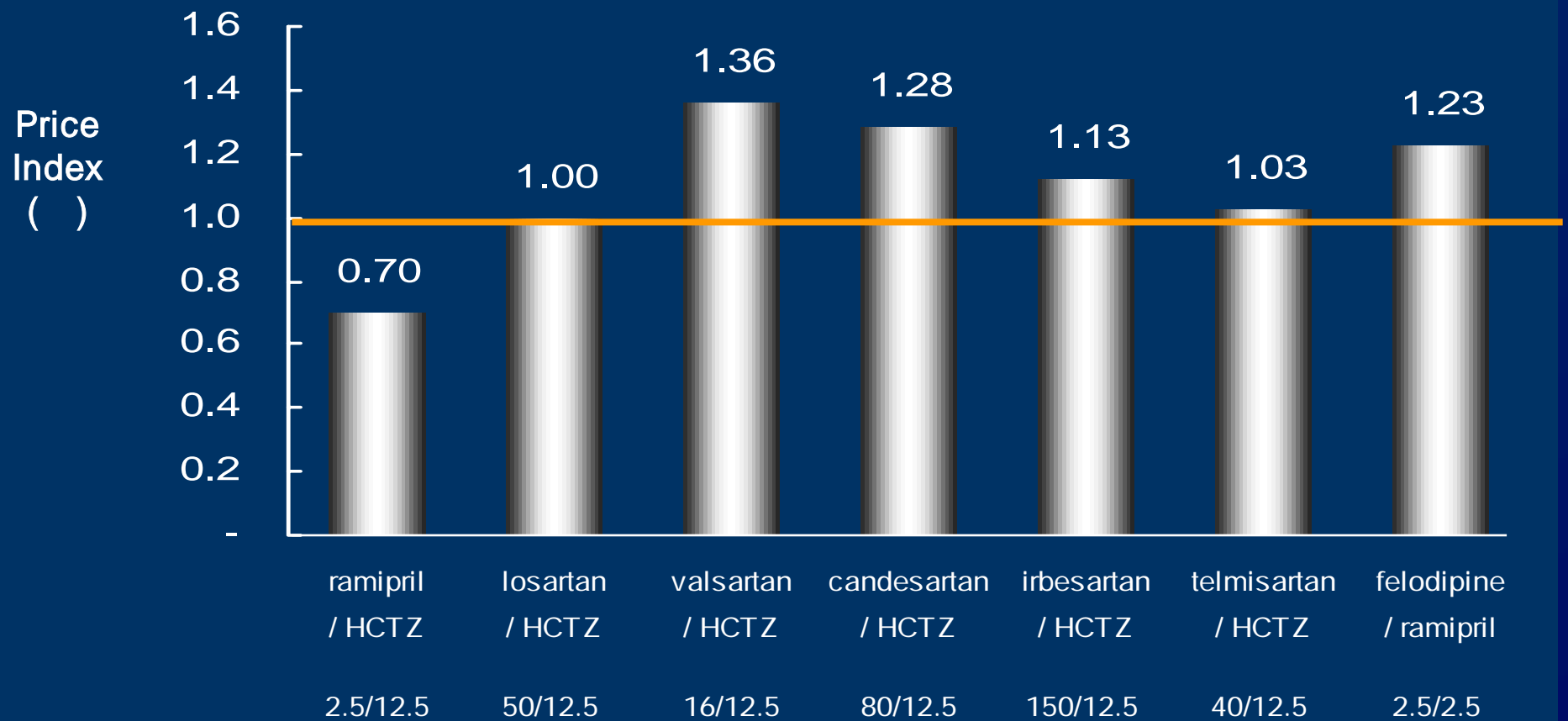


Tritace Plus – Less ADR

- Less major adverse drug reaction than monotherapy

	Combination (n=222)	Ramipril (n=218)	HCTZ (n=220)
ADR related therapy	8.1%	15.6%	10.9%
Cough	0.5%	3%	0.5%
Headache	1%	2%	1%

Economical Daily Treatment Cost



**Ramipril
/HCTZ**

Acknowledgment

- **Seung Hwan Han, MD**
- **Eak Kyun Shin, MD**
Cardiology
- **Jeong Yeal Ahn, MD**
Laboratory Medicine
- **Michael J. Quon, MD, PhD**
Diabetes Unit, NIH, USA



Free Registration. Join Us!
Enjoy your personal time with
Circulation Editorial Team!

HypErtension
AnD
Stem cell

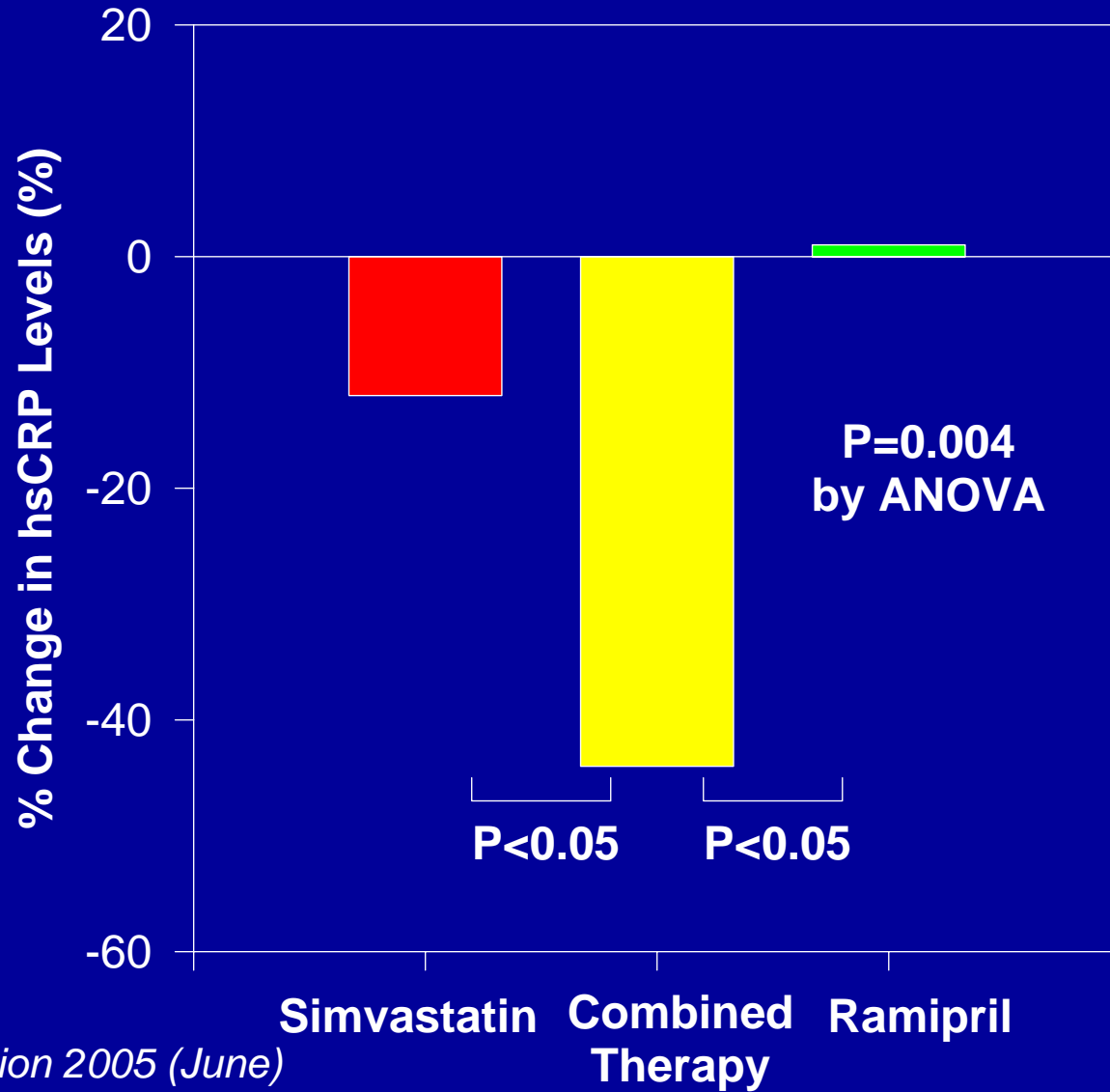
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Program Director
Eak Kyun Shin, MD, PhD
Kwang Kon Koh, MD, PhD, FACC, FAHA

The bottom of the poster features three circular logos: the Gil Medical Center logo, the Gachon University logo, and the Gil Heart Center logo.

Effects of Simvastatin, Combined Therapy, and Ramipril on hsCRP Levels



Why Is PEACE Trial Neutral?

1. Underpowered trial- only 8290 of a planned 14,100 patients were enrolled
2. Primary outcome was changed to include revascularization
3. Failure to reach maximal dose because of adverse effects

Meta-analysis of the HOPE, PEACE, and EUROPA data shows significant reductions in mortality, reinfarction, and stroke

Yusuf S, Pogue J. N Engl J Med 2005;352:937
Myers MG. N Engl J Med 2005;352:938

Meta-analysis of Data on Mortality from HOPE, EUROPA, and PEACE Trials

Trial	ACEI	Control	OR	P value
HOPE	10.4%	12.2%	0.83 (0.73-0.95)	0.005
EUROPA	6.1%	6.9%	0.89 (0.77-1.02)	0.098
PEACE	7.2%	8.1%	0.88 (0.75-1.04)	0.126
Total	7.8%	8.9%	0.86 (0.79-0.94)	<0.001

Meta-analysis shows significant reductions in mortality, reinfarction, and stroke