The Beneficial Role of Angiotensin-Converting Enzyme Inhibitor in Acute Myocardial Infarction

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Introduction

1. Cardiovascular disease is one of the leading causes of mortality in the world and most of the deaths are originated from the coronary artery disease.

2. Despite the proven beneficial effect of other drugs including aspirin, statin and β-blockers on the coronary heart disease, still the cardiovascular complications remains high.

ACE Inhibitors

3. Angiotensin-converting-enzyme (ACE) inhibitors have been introduced for an effective secondary preventive strategy to minimize these cardiovascular morbidity and mortality.

4. Traditionally, ACE inhibitors are known to be effective in reducing morbidity and mortality among patients with heart failure, left ventricular (LV) dysfunction, post myocardial infarction (MI), hypertension and other high risk patients.

Role of ACEI in AMI

** Two randomized trials involved patients with moderate to severe LV dysfunction

1) The SOLVD trial (Studies of Left Ventricular Dysfunction)

2) The SAVE trial (Survival And Ventricular Enlargement)

→ Post hoc analysis showed a reduction in the rate of AMI in patients who were treated with an ACE inhibitor.

Yusuf S et al. Lancet 1992;340:1173-8

HOPE - (Heart Outcomes Prevention Evaluation)

1. Objective

To investigate the effect of **Ramipril (*Tritace*)**
on the ***prevention of CV events in high-risk patients***

2. Study Design

2x2 factorial, double blind, randomized, placebo-controlled

9,297 patients enrolled

3. Follow-up

4.5 years (visits at 6 months)

HOPE Study Investigators. New Engl J Med 342:145-153, 2000

HOPE - *Patients*

1. Inclusion Criteria

Patients (age ≥55) at high risk for cardiovascular events because of

- any evidence of ***vascular disease (CHD, Stroke, PVD)***
  diabetes with one other risk factor

2. Exclusion Criteria

1) Low EF
2) Current use of ACE-I or Vitamin E

HOPE Study Investigators. New Engl J Med 342:145-153, 2000

HOPE – *Outcome Measures*

1. Primary Endpoint

Composite of MI/Stroke/CV death
(+ separate analysis of each)

2. Secondary Endpoint

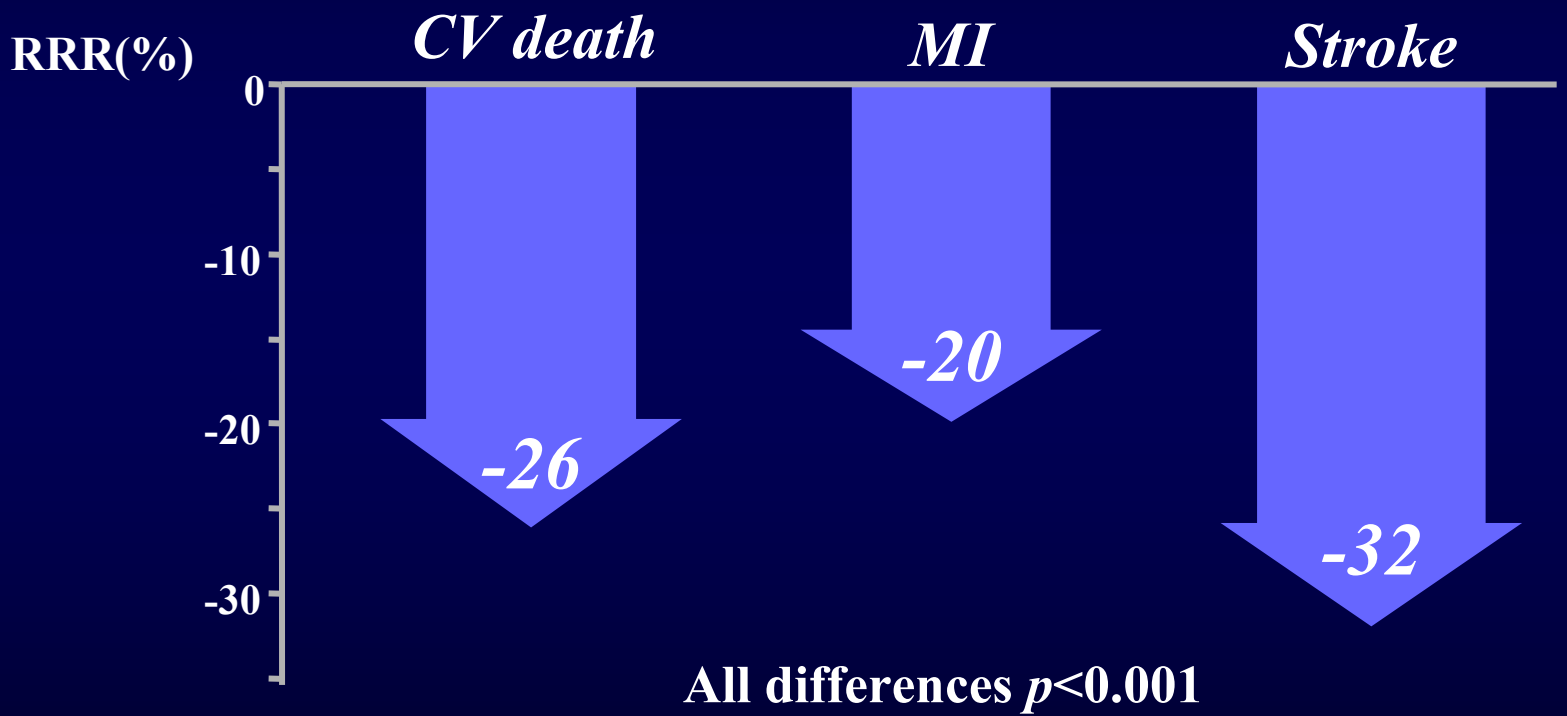
Total Mortality, Revascularization, **Diabetes Complications**

3. Other Endpoint

Onset of New Diabetes, Worsening angina/unstable angina, HF(including hospitalisations), Cardiac arrest

HOPE Study Investigators. New Engl J Med 342:145-153, 2000

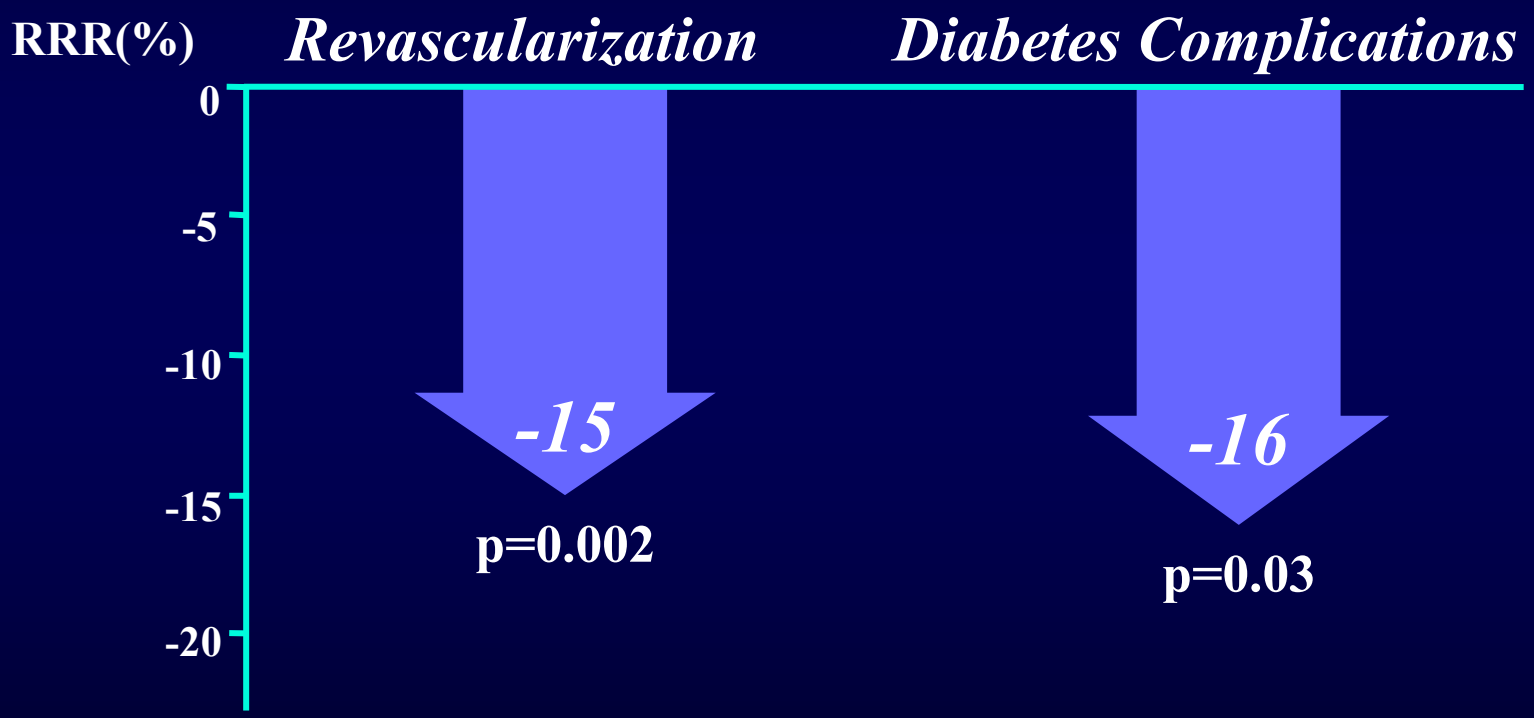
HOPE – *Result I: Primary Outcomes*



All differences $p<0.001$

HOPE Study Investigators. New Engl J Med 342:145-153, 2000

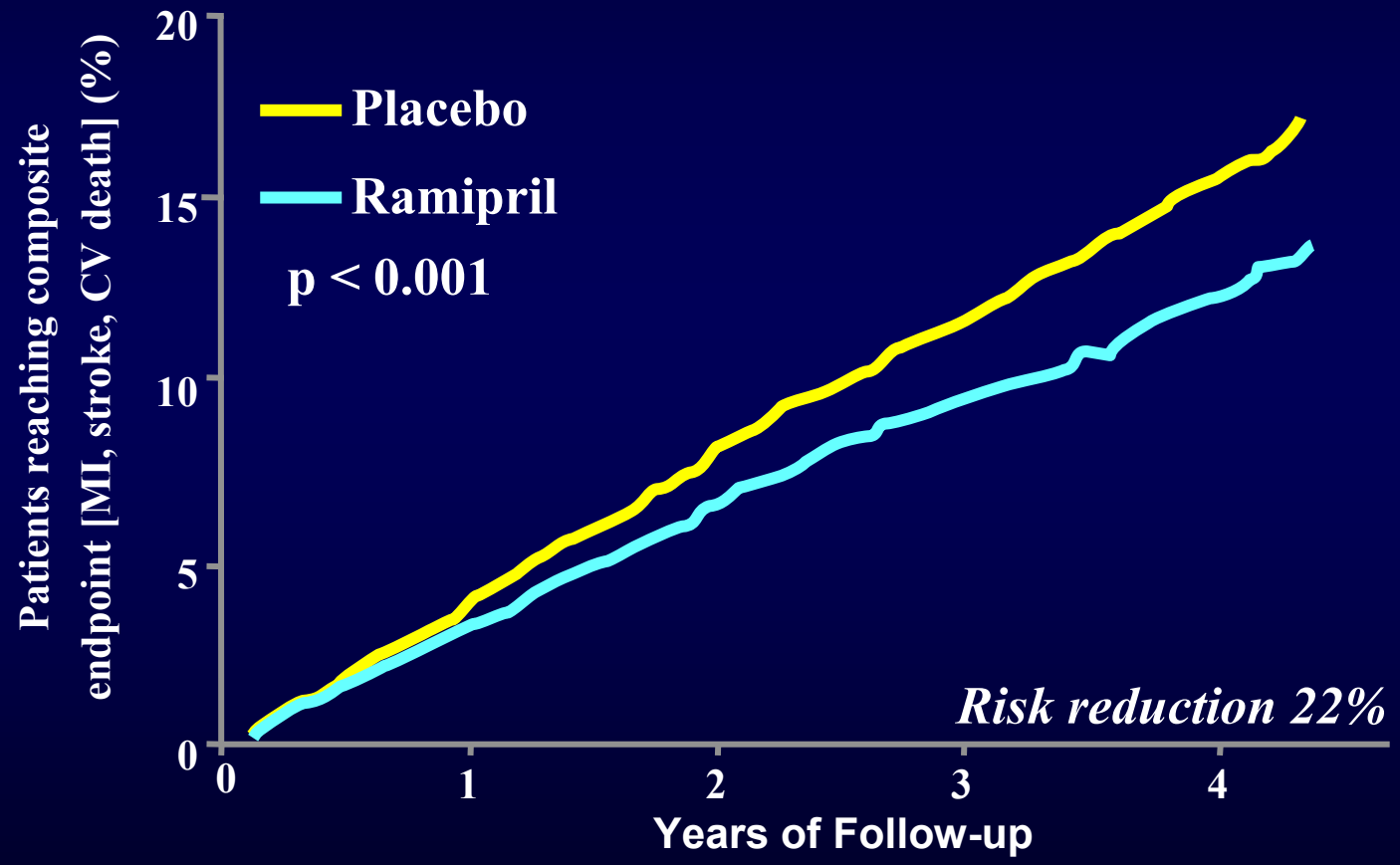
HOPE – *Result II: Secondary Outcomes*



HOPE Study Investigators. New Engl J Med 342:145-153, 2000

Effect of Ramipril in HOPE

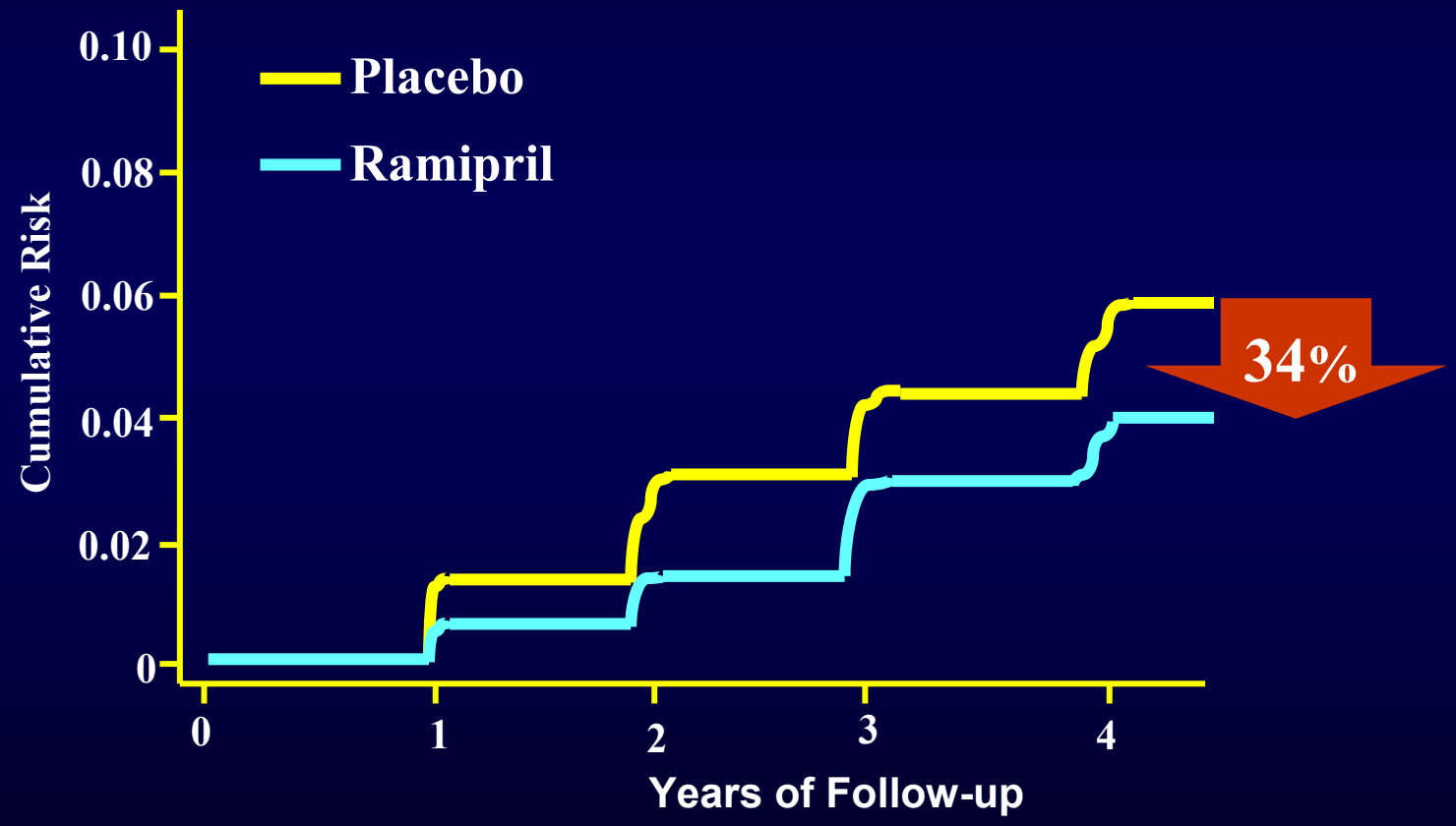
- increasing divergences with time



HOPE Study Investigators. New Engl J Med 342:145-153, 2000

HOPE-*Result III*

- significant reduction of new diagnosis of diabetes

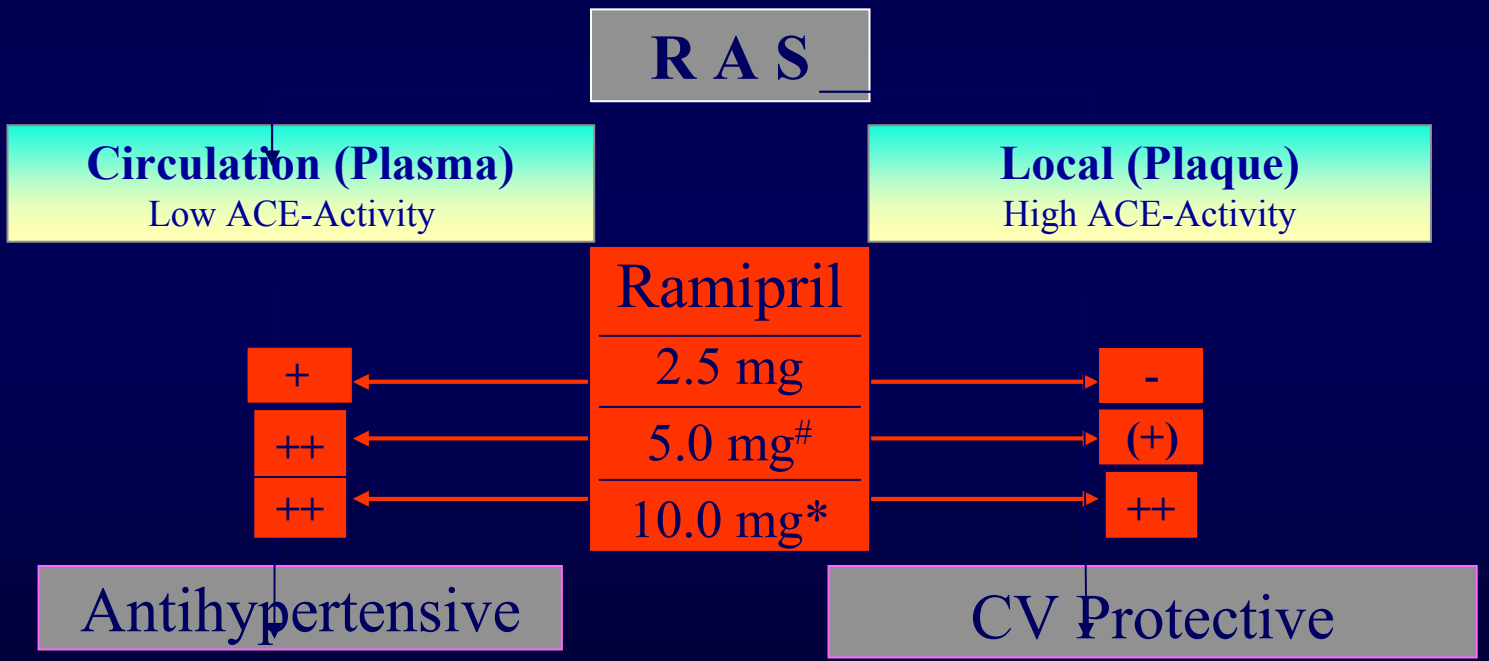


S. Yusuf et al. JAMA 286:1882-1885, 2001

Ramipril 10mg

- Direct dose dependent action of Ramipril on the RAS

➡ Role of 10 mg Ramipril:



* Based on the Clinical Results of the HOPE-Study

In Patient with Recommended Dose-Modification (ex. Renal Dysfunction.)

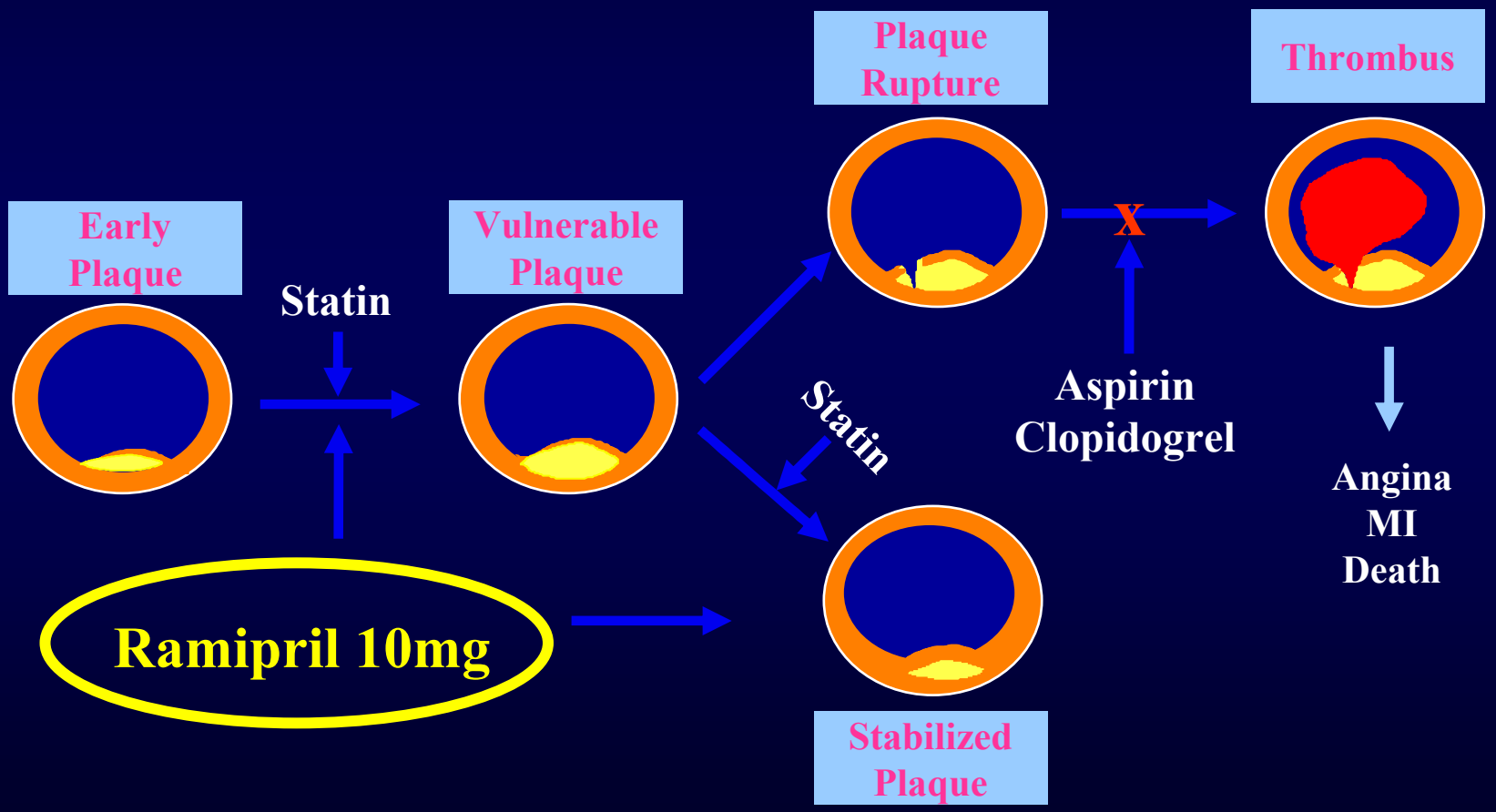
CV Protective Effect was *more than by BP Reduction*

1. Totally different from other clinical trials in the same effect in both *Normotensives* and *Hypertensives*

2. Much higher risk reduction than expected from general BP reduction

ACEI Ramipril 10mg

- the recent understanding of mechanism



- Across the spectrum of risk
- Efficacy beyond blood pressure control

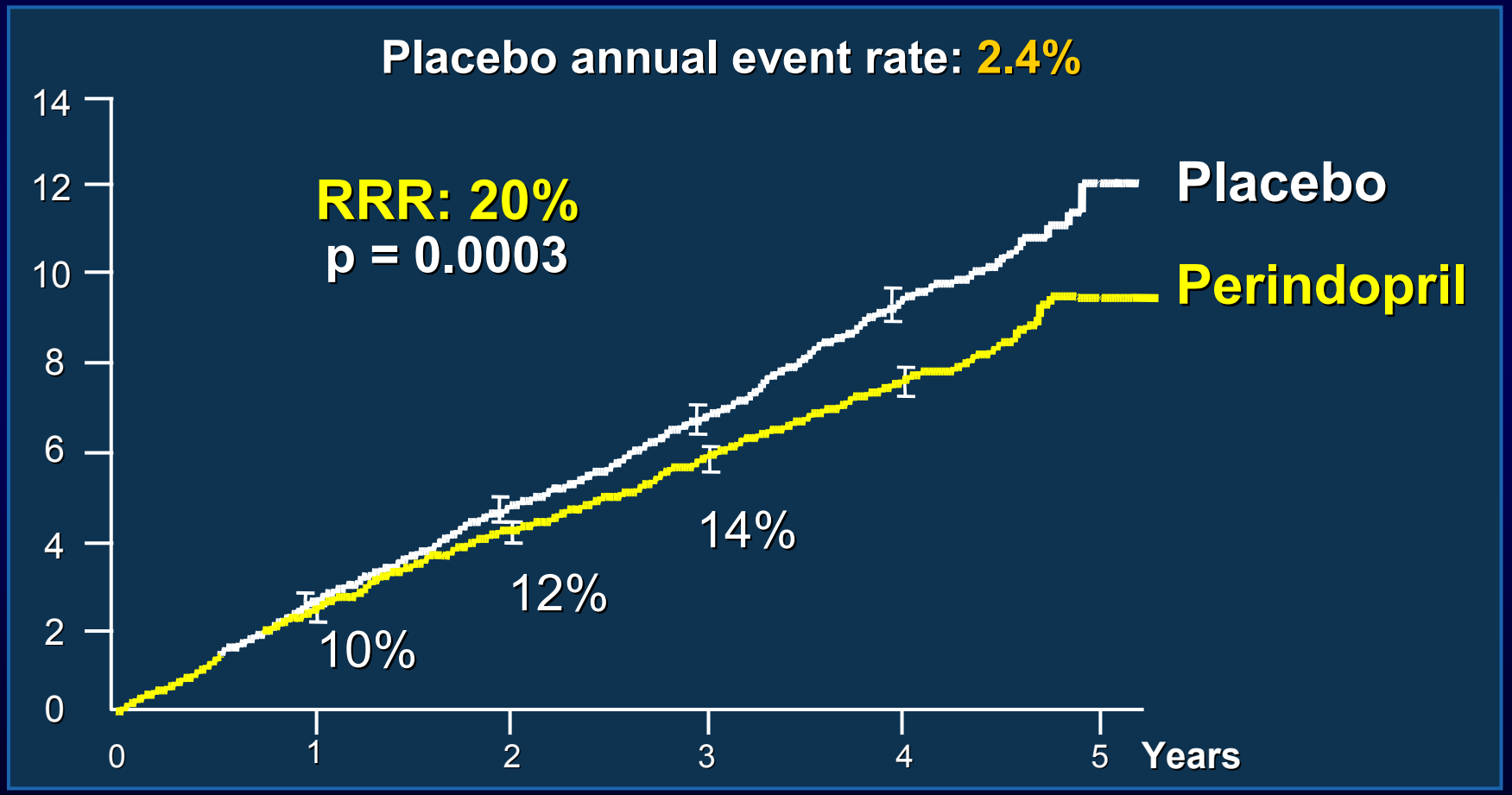
Risk assessment

In patients with stable coronary disease, after 4.2 years mean follow up, major cardiac events (death, MI) : 8 - 10%

- ***Risk assessment in these patients ?***
- ***Perindopril benefit at all levels of risk ?***

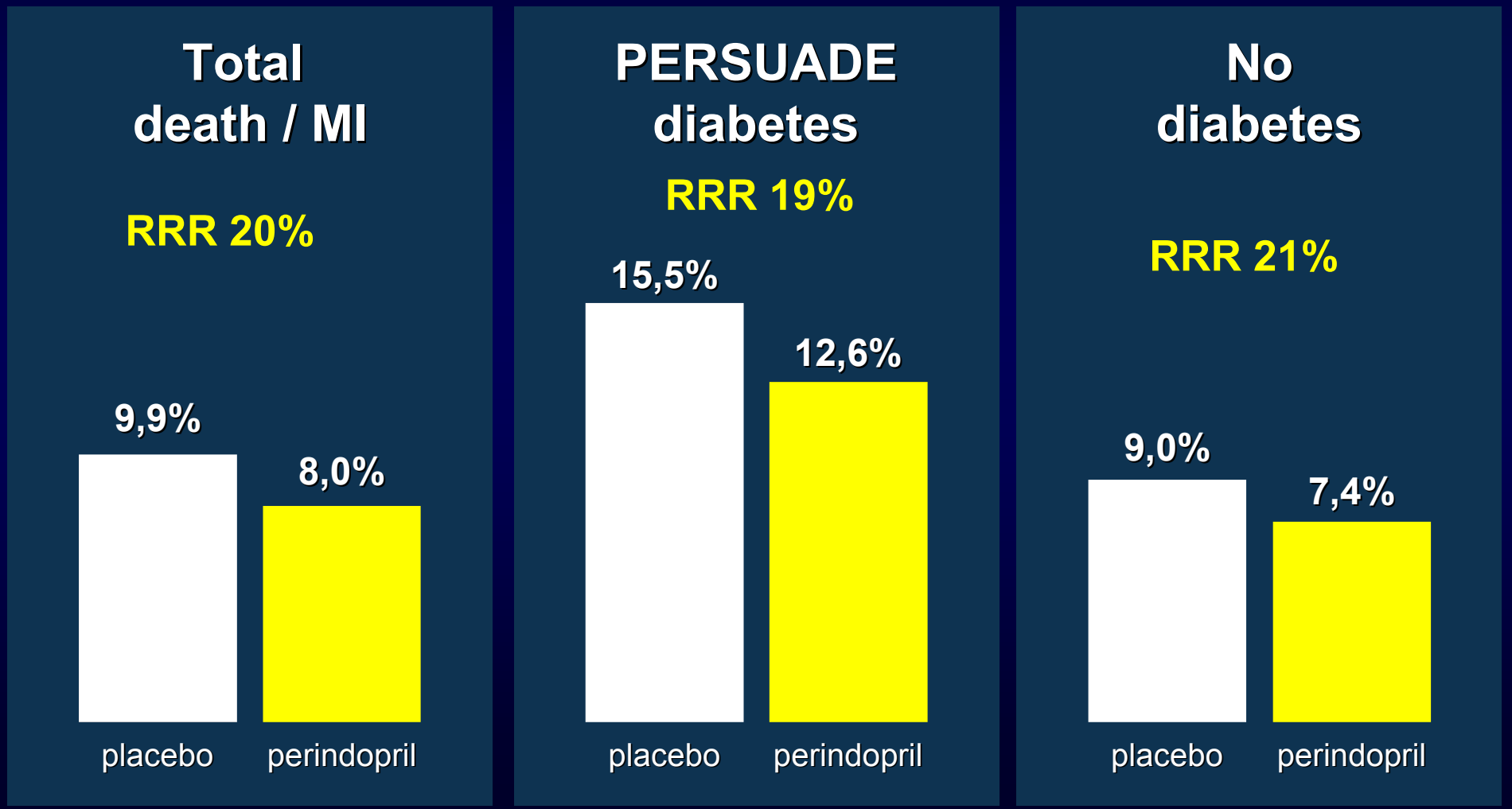
Primary endpoint

% CV death, MI or cardiac arrest



EUROPA Study Investigators *Lancet 2003;362:782-788*

Diabetes


Total death / MI
RRR 20%
9,9%
8,0%
placebo
perindopril
PERSUADE diabetes
RRR 19%
15,5%
12,6%
placebo
perindopril
No diabetes
RRR 21%
9,0%
7,4%
placebo
perindopril

Risk model

Risk factors in stable CAD :

- male
- age
- weight
- smoker
- diabetes
- BP
- cholesterol
- creatinine
- family history CAD
- stroke/TIA/PAD
- no revascularization

Risk model

	Score
Age	0 - 8
Chol	0 - 6
Weight	0 - 3
Creat	0 - 3
Systolic BP	0 - 2

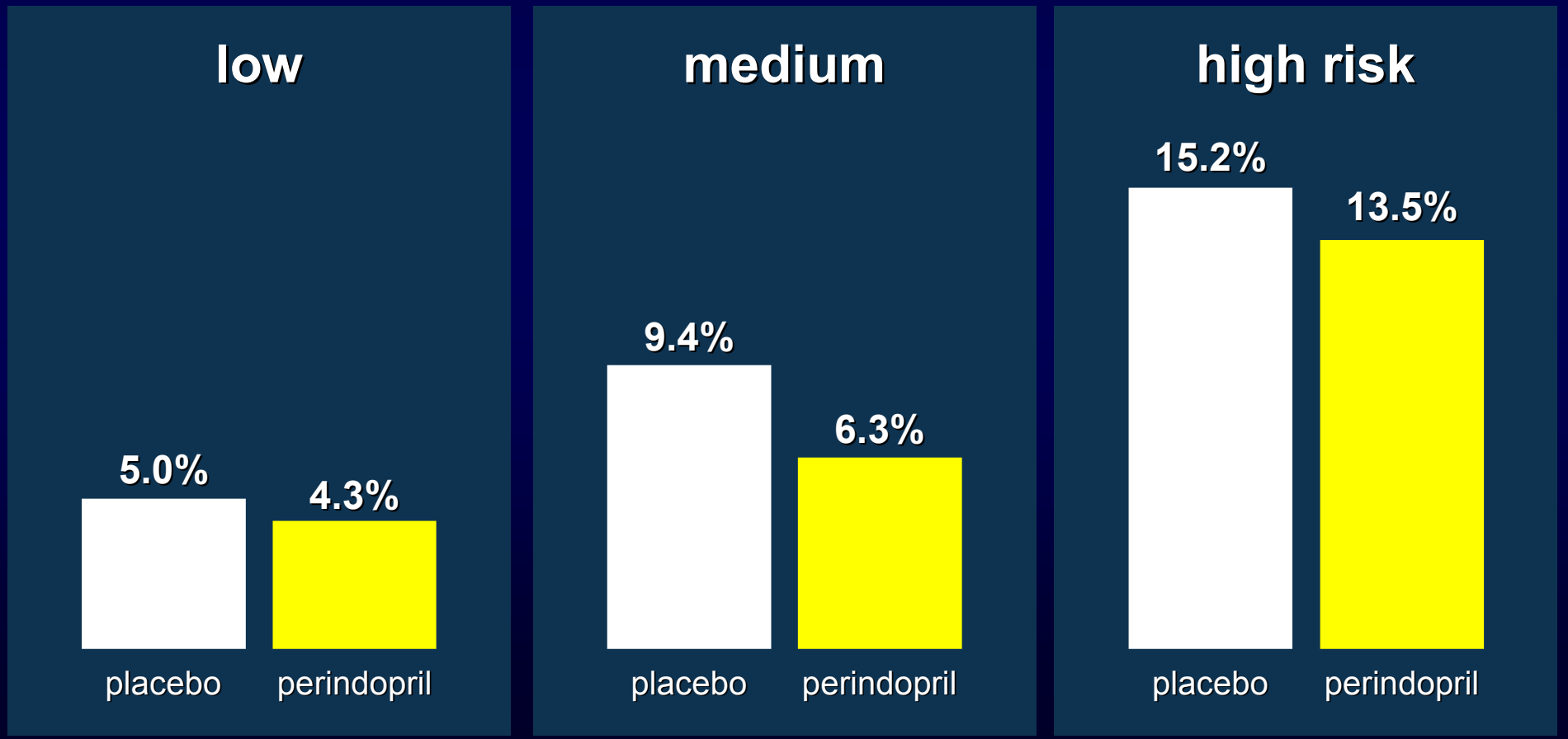
	Score
PAD/CVD	3
Male	2
Diabetes	2
Smoker	2
Fam Hist	1
Revasc	-1

Risk model

Risk level	low	mid	high
n=	3976	3975	3975
age (year)	57	59	64
Male (%)	78	89	90
Pre-MI (%)	41	71	81
Revasc. (%)	73	50	41
Syst. BP (mmHg)	133	137	142
Diabetes (%)	3	8	26
Creatinin level (μMol/l)	99	94	90

Treatment effect

Consistent risk reduction with perindopril



Treatment effect

Conclusion

Risk factors in stable CAD :

- male
- age
- weight
- smoker
- diabetes
- BP
- cholesterol
- creatinin
- family history CAD
- stroke/TIA/PAD
- no revascularization

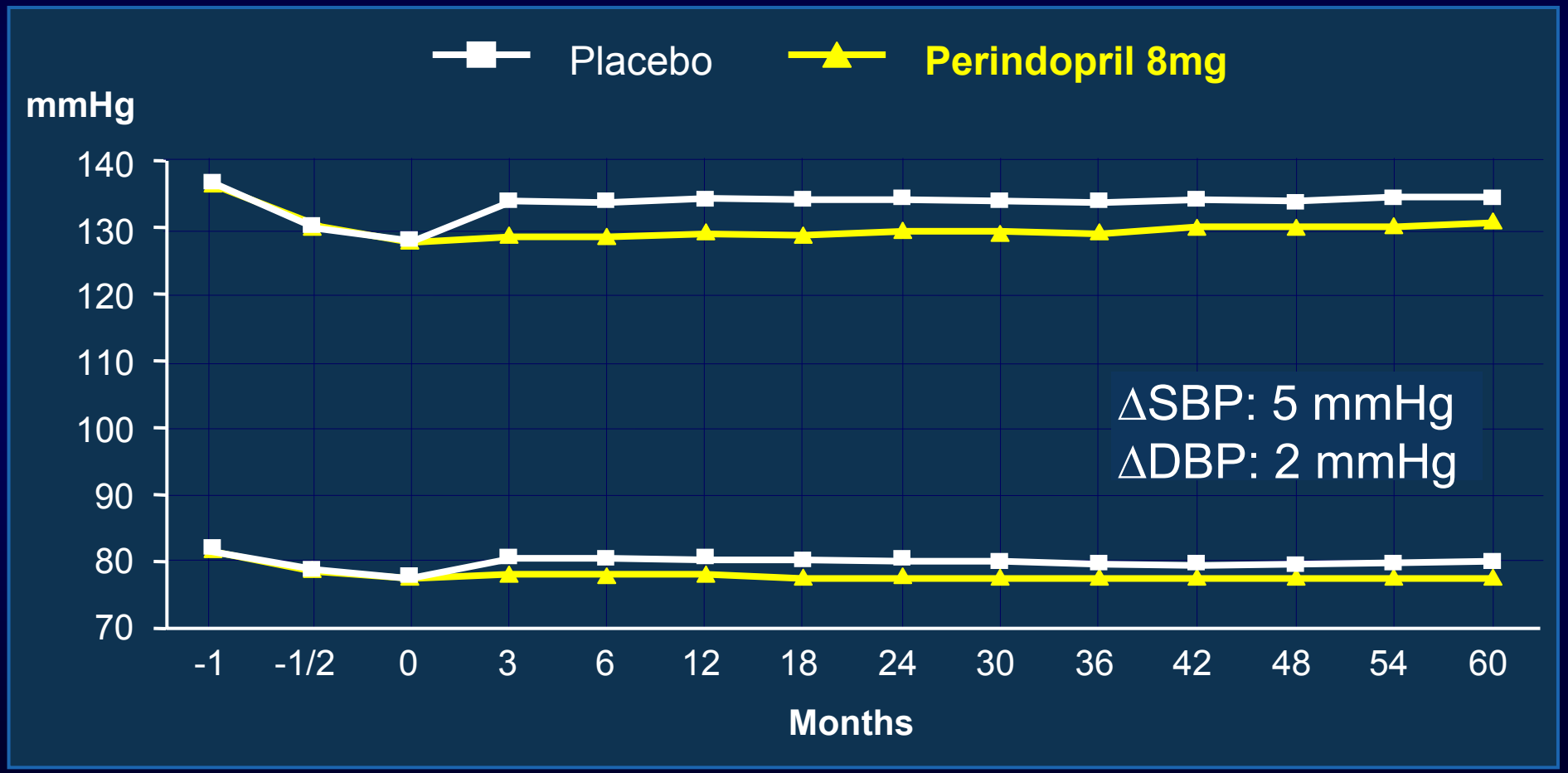
Perindopril treatment benefit consistent across all risk levels

ACE inhibition for secondary prevention of CAD

Rationale

- Anti-atherosclerotic effects
- Plaque rupture reduction
- Improvement in vascular endothelial function
- Enhanced fibrinolysis
- Modulation of neurohormonally-induced arterial vasoconstriction
- LV hypertrophy reduction
- **Blood pressure reduction**

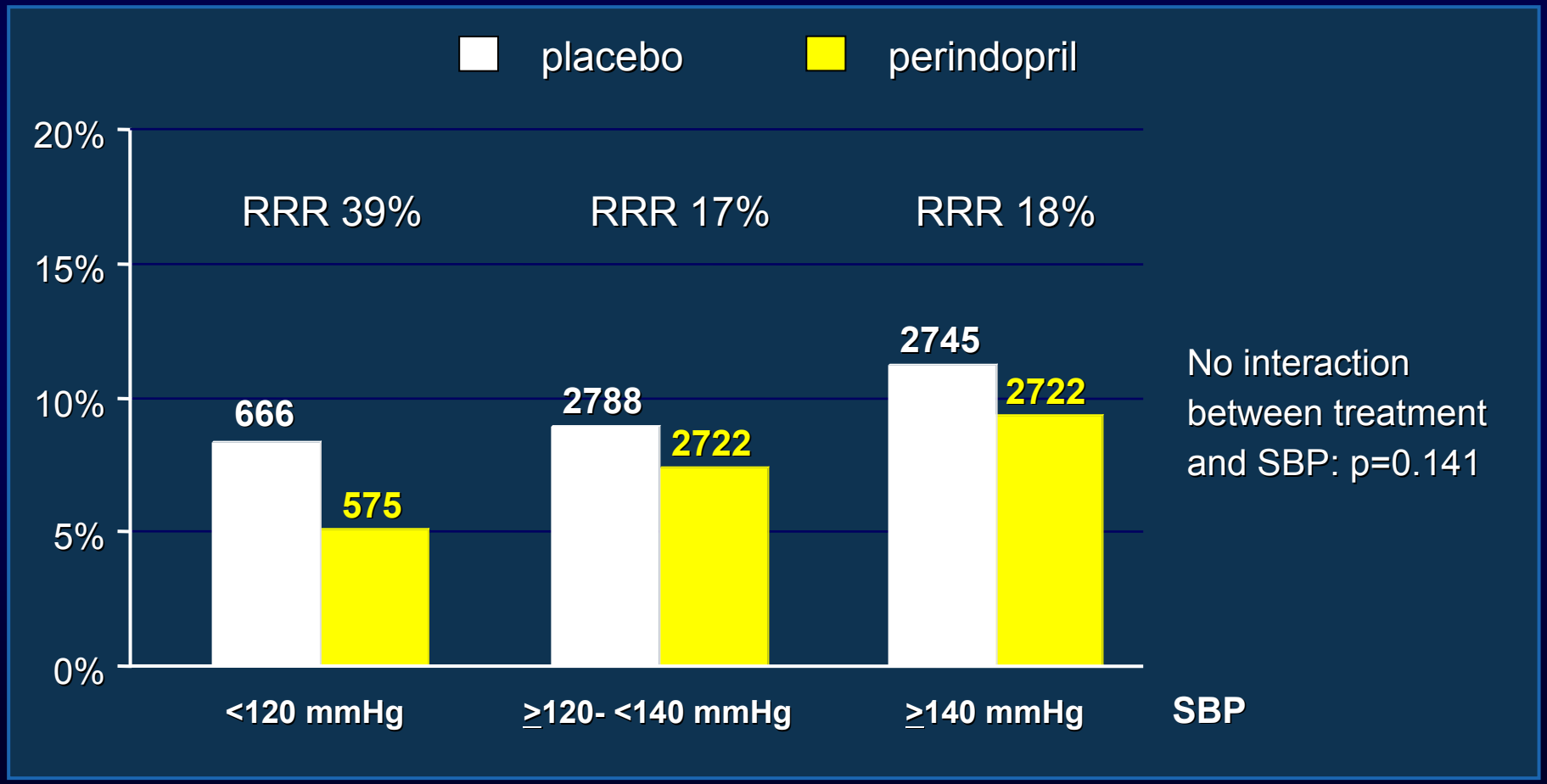
Blood pressure



Are the cardiovascular benefits observed in EUROPA the result of blood pressure lowering or could more specific anti-atherosclerotic effects be involved?

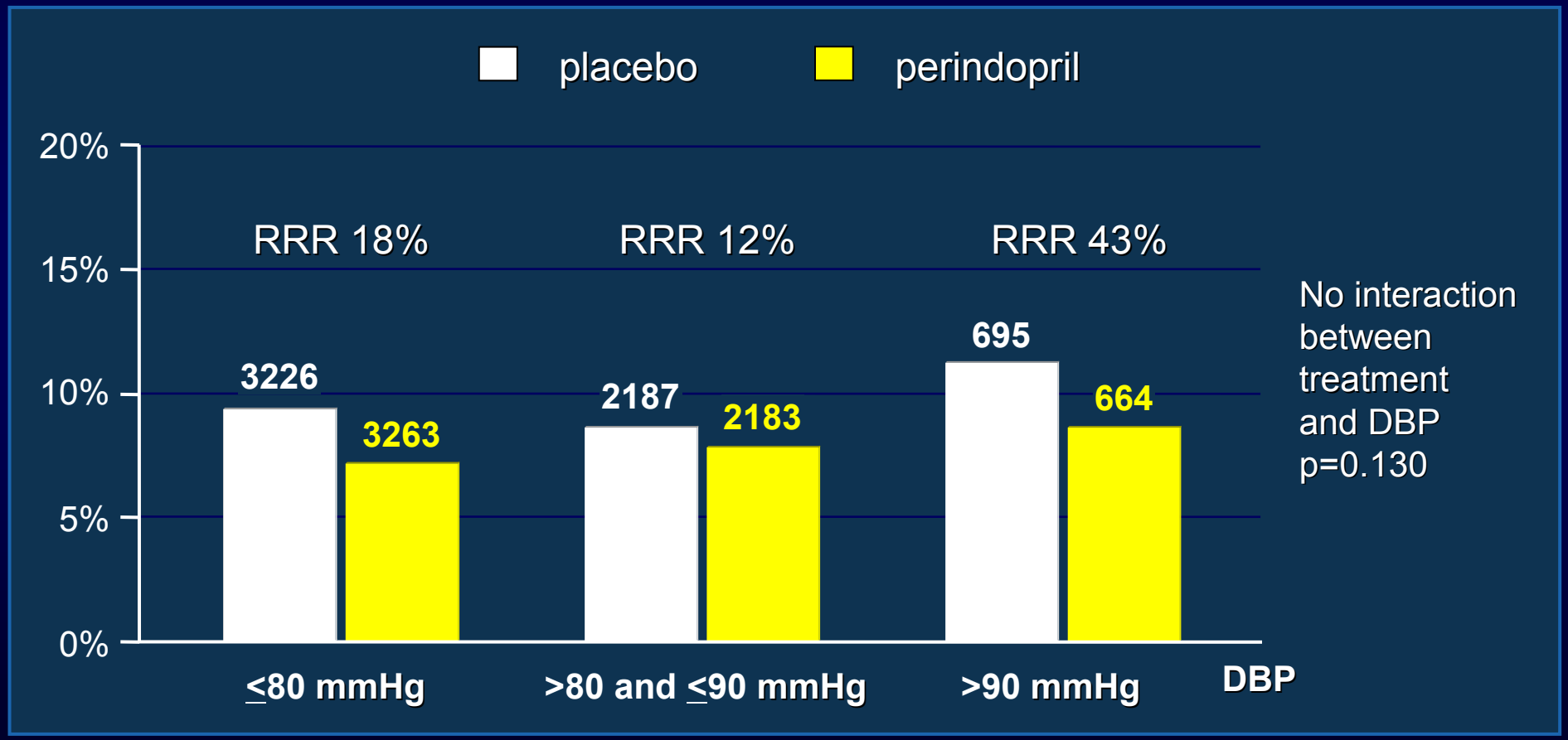
Effect of baseline systolic blood pressure on primary endpoint

Primary endpoint-risk reduction



Effect of baseline diastolic blood pressure on primary endpoint

Primary endpoint-risk reduction



EUROPA Conclusion

- Perindopril's benefit in **EUROPA** cannot be explained by blood pressure at baseline or blood pressure reduction alone
- Other mechanisms including direct vascular,anti-atherosclerotic effects and improvement of endothelial function of perindopril may play a role
- PERTINENT (a substudy of EUROPA): **PER**indopril - **T**hrombosis, **I**nflammatio**N**, **E**ndothelial dysfunction and **N**eurohormonal activation **T**rial

PEACE

1. PEACE Trial (Prevention of Events with Angiotensin Converting Enzyme Inhibition)

   ; Trandolapril

2. Study population

   1) In patients with stable coronary heart disease and preserved LV function who are receiving current standard therapy

   2) In whom the rate of cardiovascular events is lower than in previous ACE inhibitor trials in patients with vascular disease

PEACE Conclusion

In pts with *stable coronary heart disease* and *preserved LV function* who are receiving *"current standard" therapy* and in whom the rate of cardiovascular events is lower than in previous trials of ACEI in pts with vascular disease,

; ACE inhibitor provides no further benefit in terms of death from cardiovascular causes, MI or coronary revascularization.

Effect of ACEI in AMI Setting

1. Blood Pressure?
2. Cardiovascular protective effects?
3. LV remodeling?
4. Baroreflex sensitivity?
5. QT dispersion and tachyarrhythmia?
6. Angiogenesis?
7. No-reflow?

Angiotensin II

1. increases lipid peroxidation
2. increases oxyradical formation
3. stimulates the expression of proinflammatory genes (chemoattractant protein and leukocyte adhesion molecules)

   → endothelial dysfunction
4. improves vascular smooth-muscle proliferation
5. stimulates the production of PAI-I.

Bradykinin

1. counteracts the negative action of angiotensin II
2. improves endothelial function by increasing expression and activity of the constitutive nitric oxide synthase
3. antiproliferative effect; inhibits the expression of monocyte and adhesion molecules
4. stimulates the synthesis of tissue plasminogen activator

ACEI and LV remodeling in AMI

1. Inflammatory cytokines play an important role in the pathophysiology of LM remodeling and hs CRP is a predictor of LV remodeling in patients with AMI.
2. ACEI to AMI patients showing increased hs CRP levels during the early stage of the disease could prevent LV remodeling.
3. Early initiation of ACE inhibitor (Perindopril) reduces collagenase activity.

; beneficial effects on post MI remodeling

Suzuki H et al. Int Heart J. 2006;47(5):715-25.

ACEI and Baroreflex Sensitivity in AMI

1. Depressed barorelex sensitivity after AMI is considered an indication of decreased vagal and/or increased sympathetic tone.

2. ACE inhibitor *Captopril (Capril®)* appears to improve baroreflex sensitivity in the early phase of AMI.

Marakas SA et al. Eur Heart J 1995;16(7):914-21.

ACE Inhibitors, Angiotensin II Antagonists, and Platelet Function

ACE inhibitors			
Captopril 25 mg BID	Someya et al[78]	ADP-induced aggregation	Decreased
Captopril 25–50 mg BID	Birkebaek et al[79]	ADP-induced aggregation, PF4	No change
Quinalapril 20 mg BID	Gupta et al[80]	ADP-induced aggregation, PF4	No change
Enalapril 10–20 mg	Li-Saw-Hee et al[81]	ADP-induced aggregation, PF4	No change
Captopril 25–50 mg	Muller et al[82]	Platelet -adrenoceptors	Decreased
Enalapril 20 mg	Hernandez-Hernandez et al[83]	ADP-induced aggregation	Increased
Angiotensin II antagonists			
Losartan 50–100 mg	Li-Saw-Hee et al[81]	Soluble P-selectin	No change
Losartan 50–100 mg	Pathansali et al[91]	Megakaryocyte size and ploidy	Decreased
		Bleeding time	Increased
		Aggregation	No effect
Losartan 100 mg	Levy et al[84]	Platelet aggregation	Decreased
Losartan and valsartan	Kalinowski et al[77]	NO release in vitro	Increased
		Collagen-induced aggregation	Decreased

PF4 indicates platelet factor 4; NO, nitric oxide.

Blann, A. D. et al. Hypertension 2003;42:1-7

Indication for ACE-Is (US)

	HT	HF	LVD/HF after MI	MI	Reduction in Risk of MI Stroke and Death from Cardiovascular Cause	Reduction in mortality/morbidity for the indication
Benazepril	X					
Captopril	X	X*	X*	X*		V
Enalapril	X	X*				V
Fosinopril	X	X				
Lisinopril	X	X		X*		V
Moexipril	X					
Ramipril	X		X*		X*	V
Perindopril	X					
Quinapril	X	X				
Trandolapril	X		X*			V
No of Agents	10		7		1	5

*** includes documentation of improved long-term survival and clinical outcomes compared with placebo**

Curt D. et al. Circulation 2003:108:2608-2610

ACEI and QT dispersion in AMI

1. A prolonged QT dispersion is a marker of electrical instability predisposing to ventricular arrhythmia and sudden cardiac death.

2. ACE inhibitor *Enalapril* reduces the degree of ventricular dispersion of repolarization following AMI and sudden cardiac death can be reduced.

Kassotis J et al. Pacing Clin Electrophysiol. 2003;26(4 Pt 1):843-8.

ACEI and angiogenesis in AMI

1. Intravenous bFGF (basic fibroblast growth factor) may increase VEGF (vascular endothelial growth factor) and bFGF significantly, thus promoting the angiogenesis in the infarct zone and border zone in cardiac infarction as VEGF and bFGF are the potent angiogenic growth factors.

2. ACE inhibitor *Benazepril* may promote angiogenesis in the infarct zone and border zone in cardiac infarction.

Li DY et al. Biomed Environ Sci. 2004;17(4):442-51

ACEI and No-reflow in AMI

1. No-reflow phenomenon has been associated with severe myocardial injury, progressive LV remodeling, CHF and poor prognosis.

2. Pretreatment with ACE inhibitor (*Captopril*-M/C, Enalapril, Fosinopril) could preserve the microvascular integrity after AMI.

Zhao JL et al. Clin. Cardiol. 30.130-134 (2007).

Role of ACEI in AMI-Summary-

1. BP lowering effect
2. Direct cardiovascular protective effects
3. Decreasing LV remodeling
4. Improve Baroreflex sensitivity
5. Decrease QT dispersion
6. Increase Angiogenesis
7. Reduce No-reflow

Conclusion

1. The beneficial effects of ACE inhibitors in addition to other preventive measures including aspirin, ß-blockers and lipid-lowering drugs were consistent for the patients with AMI in all the previously published literature.

2. These results provide strong support for considering ACE inhibitors in all patients with AMI irrespective of cardiac function or risk factors.

Thank You for your attention!!

1. We have learned an incredible amount.
2. We are only limited by our imagination.