VALUE OF ACEI

IN THE MANAGEMENT

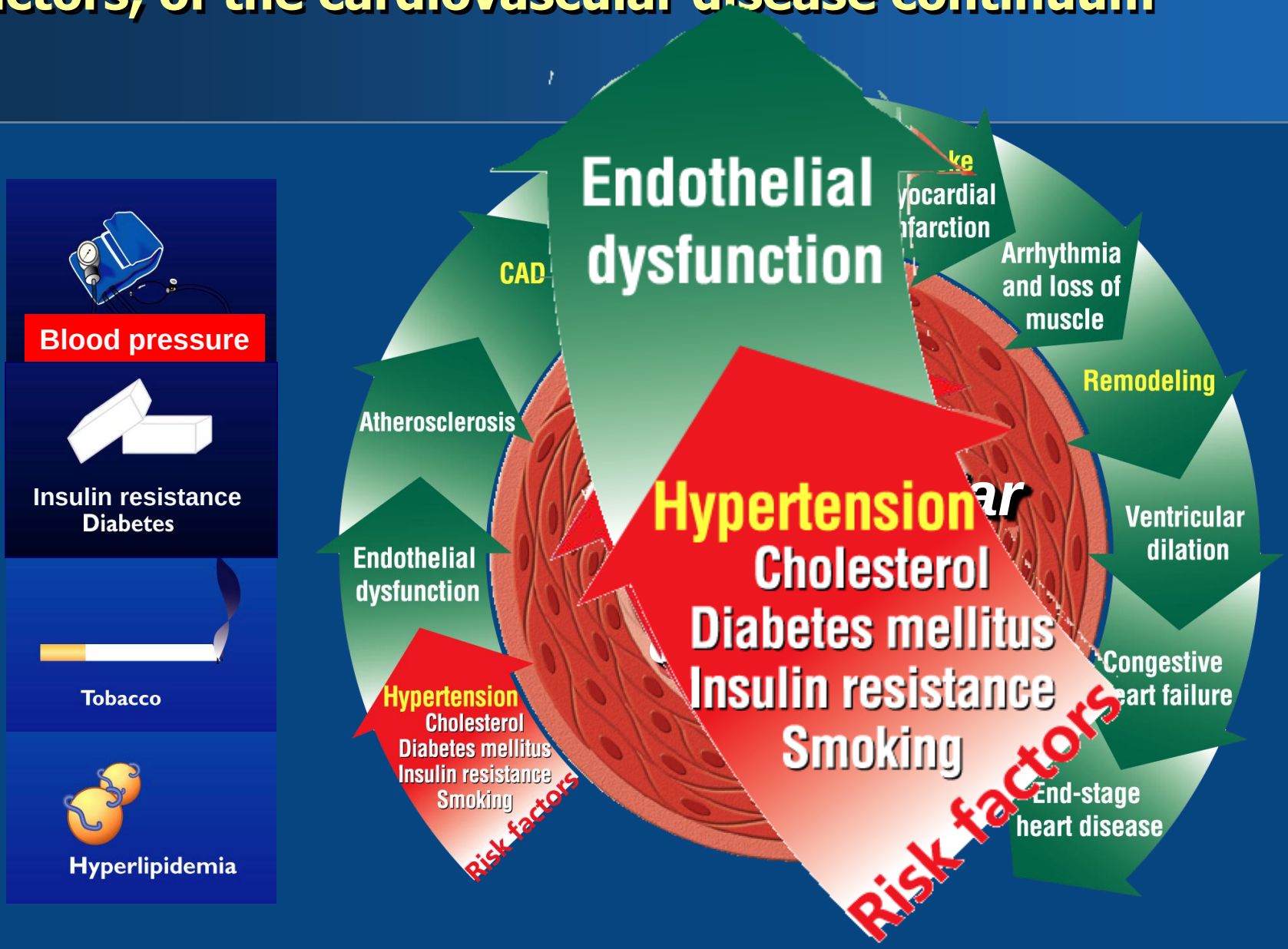
OF HYPERTENSION

Dr Catherine BESEME – Paris

6 th December 2005

6 th International Congress of Bangladesh Society of Medicine

Hypertension is a risk factor at the source, with other risk factors, of the cardiovascular disease continuum



The Renin Angiotensin System and Bradykinin

ANGIOTENSINOGEN

Renin (+)

Angiotensin I

ACE (+)

Angiotensin II

Kidney

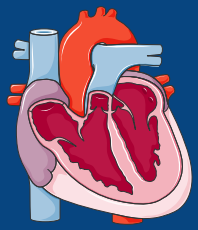
↗ Aldosterone
↗ Na+ water

AT Receptors

↗ Vasoconstriction
↗ Cell proliferation

Endothelium dysfunction

Heart

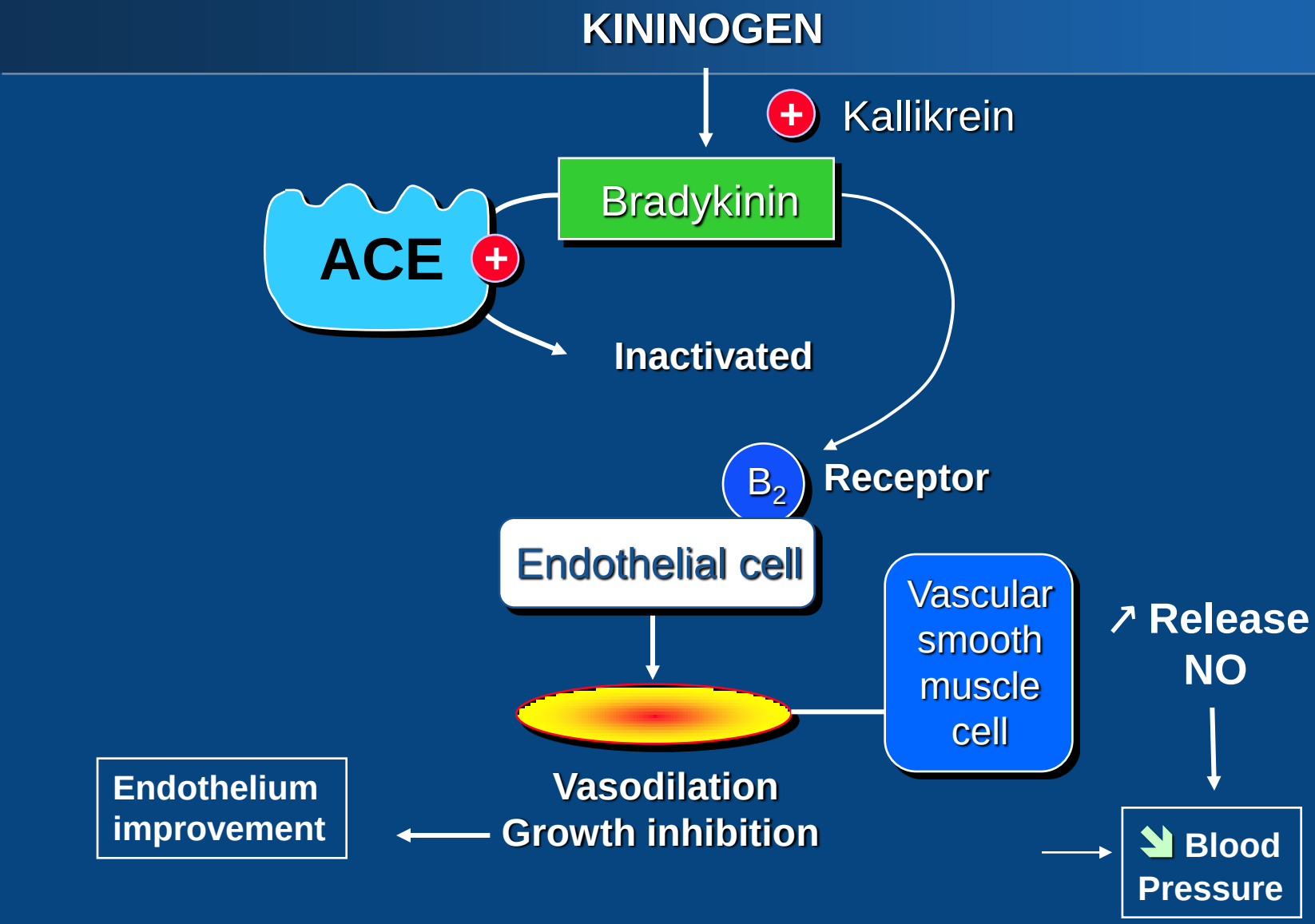


↗ Heart rate
↗ Contractility

↗ Blood Pressure

CMF Learning Systems in 2000, "Courtesy CM Ferrario, MD"

The Renin Angiotensin System and Bradykinin



CMF Learning Systems in 2000, "Courtesy CM Ferrario, MD"

RAAS

Main actions of AII and Bradykinin: one balances in one way, the other one counterbalances.

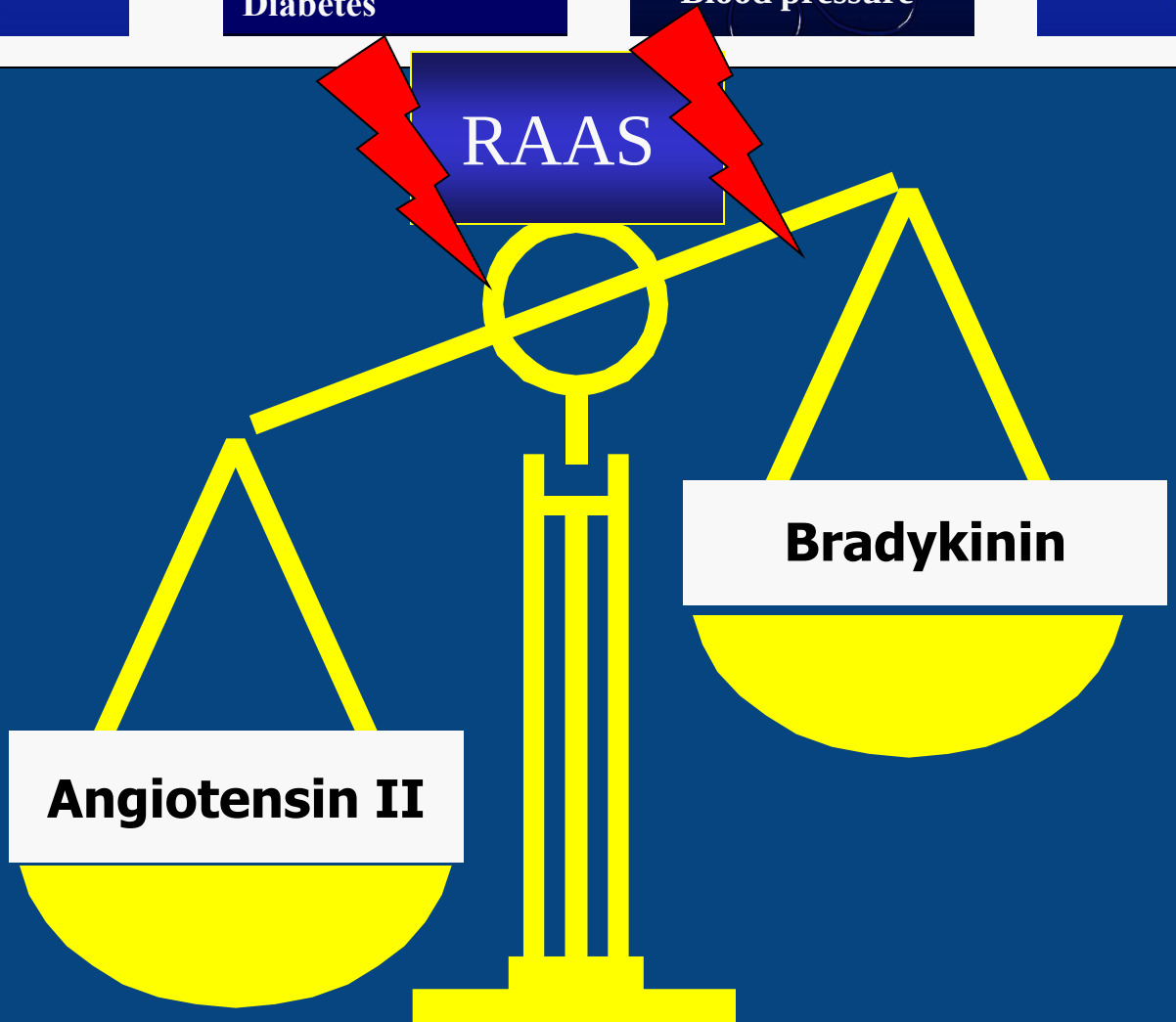
Angiotensin II

- Vasoconstriction, ↗ BP
- Proinflammatory, adhesion of cells
- SM cells growth, proliferation, migration
- Platelet aggregation
- Thrombogenesis

Bradykinin

- Vasodilation
- Anti-inflammatory, antiadhesion
- SM cells antigrowth, antiproliferation, antimigration
- Antiplatelet aggregation
- Fibrinolysis

Each of them modify the balance in favor of Angiotensin II



RAAS

In hypertensive patients, A II is increased whereas bradykinin is decreased .

Angiotensin II

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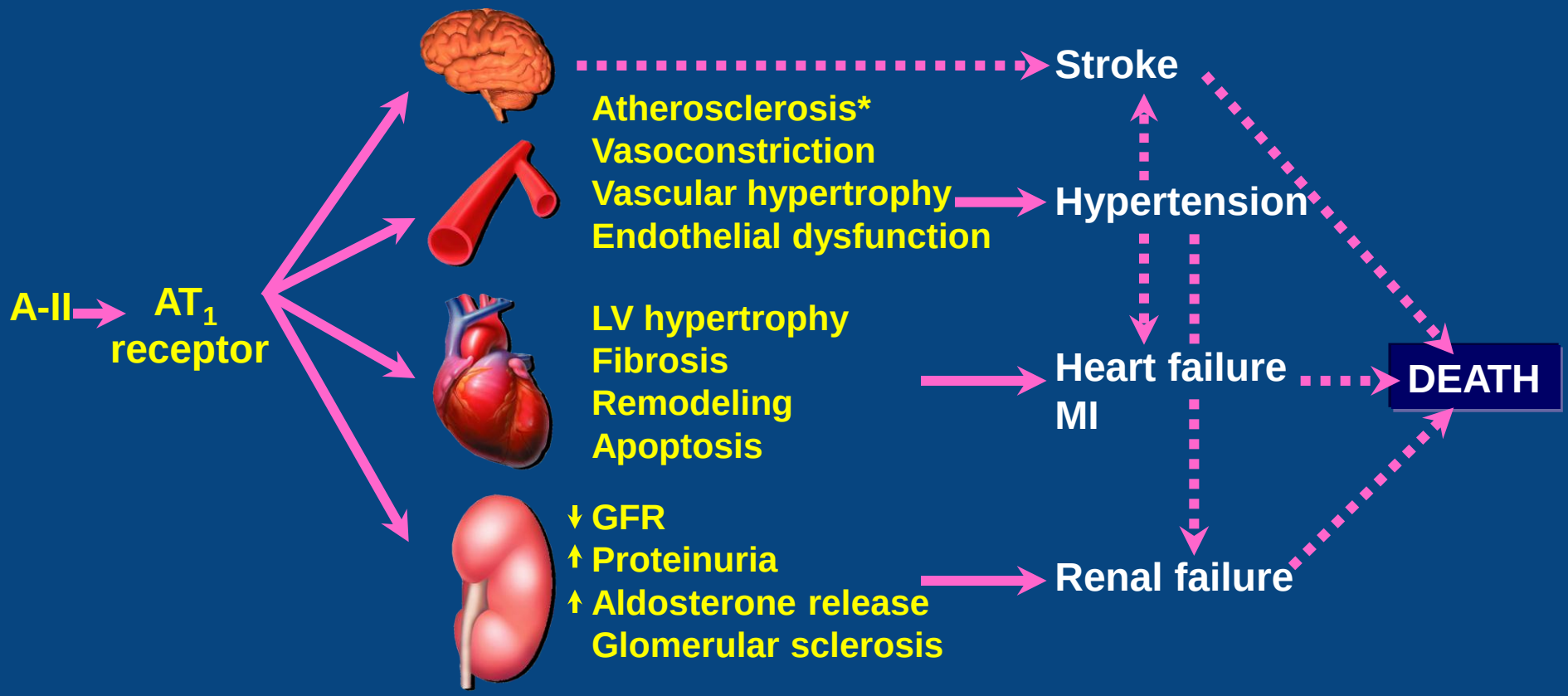
ACE inhibition

A continuum of benefits from hypertension to coronary artery disease

Immediate effects	Hemodynamic effects ↓ BP Bradykinin preservation ↑Nitric oxide ↓ Superoxide production
Intermediate effects	↓ Superoxide production Fibrinolytic stabilization ↓ PAI-1 ↑ t-PA ↓ Platelet activation
Late effects	↓ Platelet activation ↓ Cell migration ↓ Cell proliferation

Angiotensin-II Plays a Central Role in Organ Damage



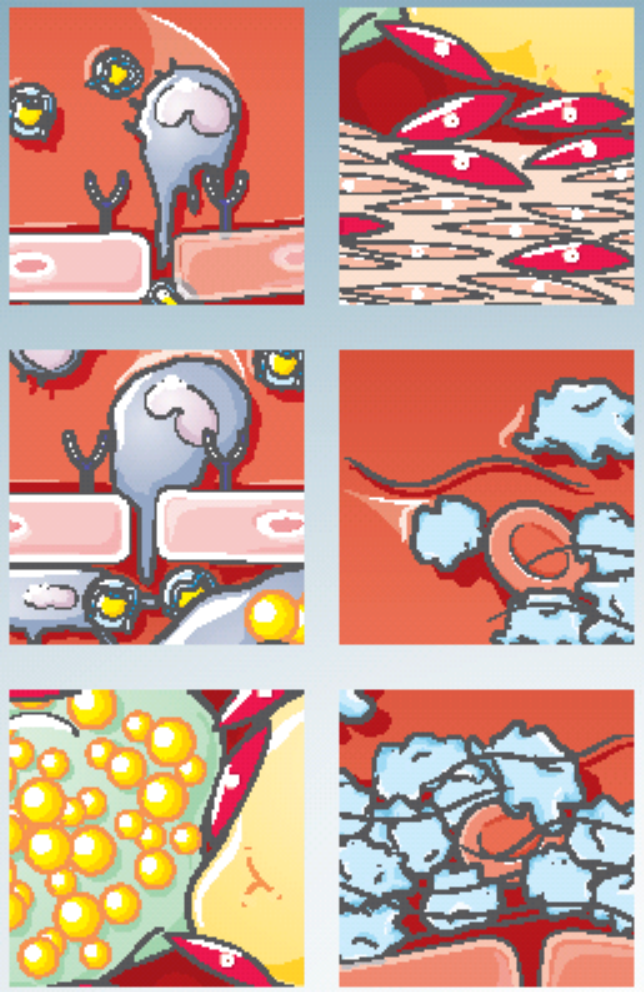
LV = left ventricular; MI = myocardial infarction; GFR = glomerular filtration rate

Angiotensin II stimulates phenomena responsible for endothelial dysfunction

a. Adhesion of monocyte cells

b. Endothelium permeability (penetration of cells and lipids)

c. SMC growth, proliferation, and migration

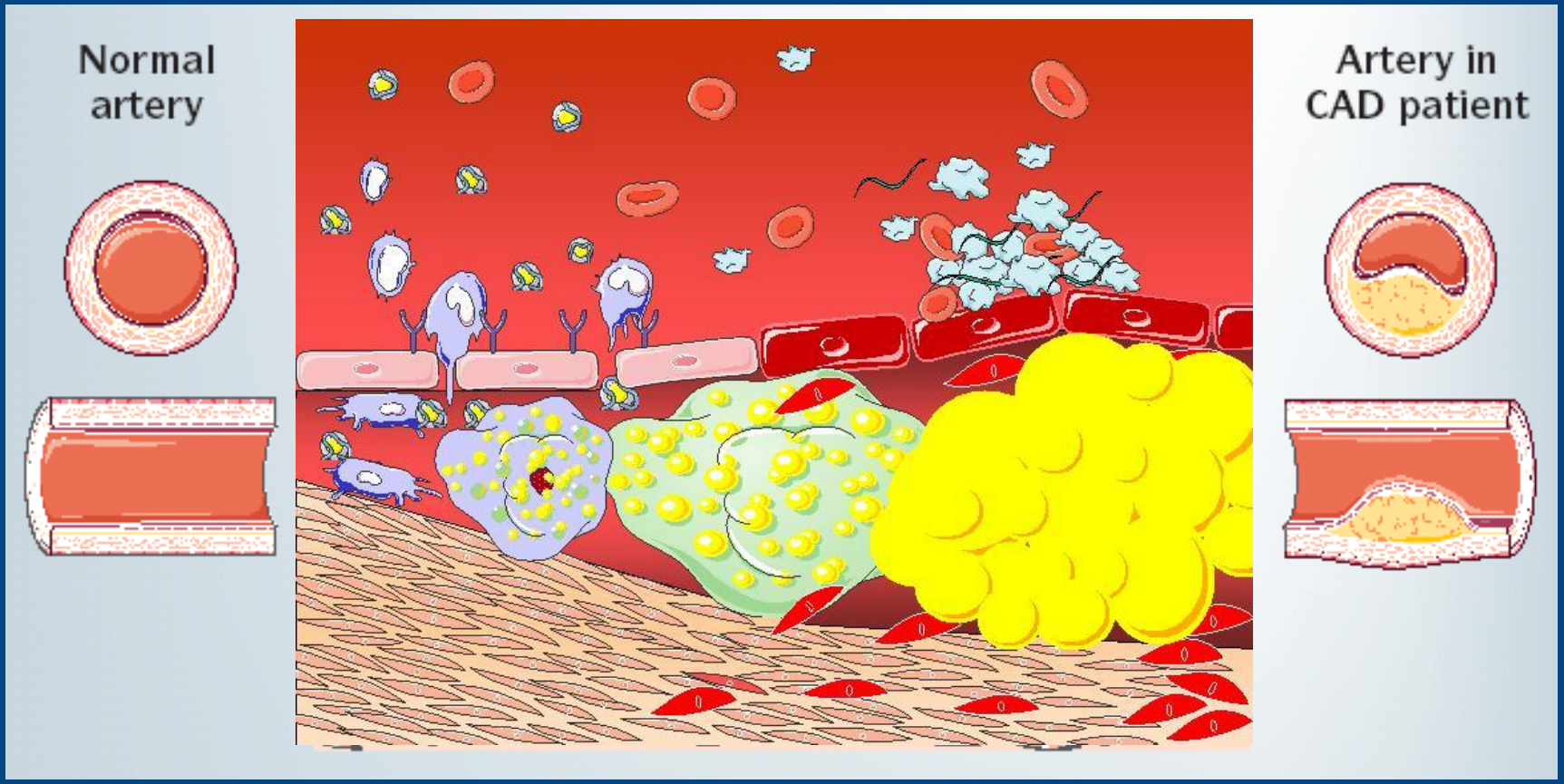


d. Lipid accumulation

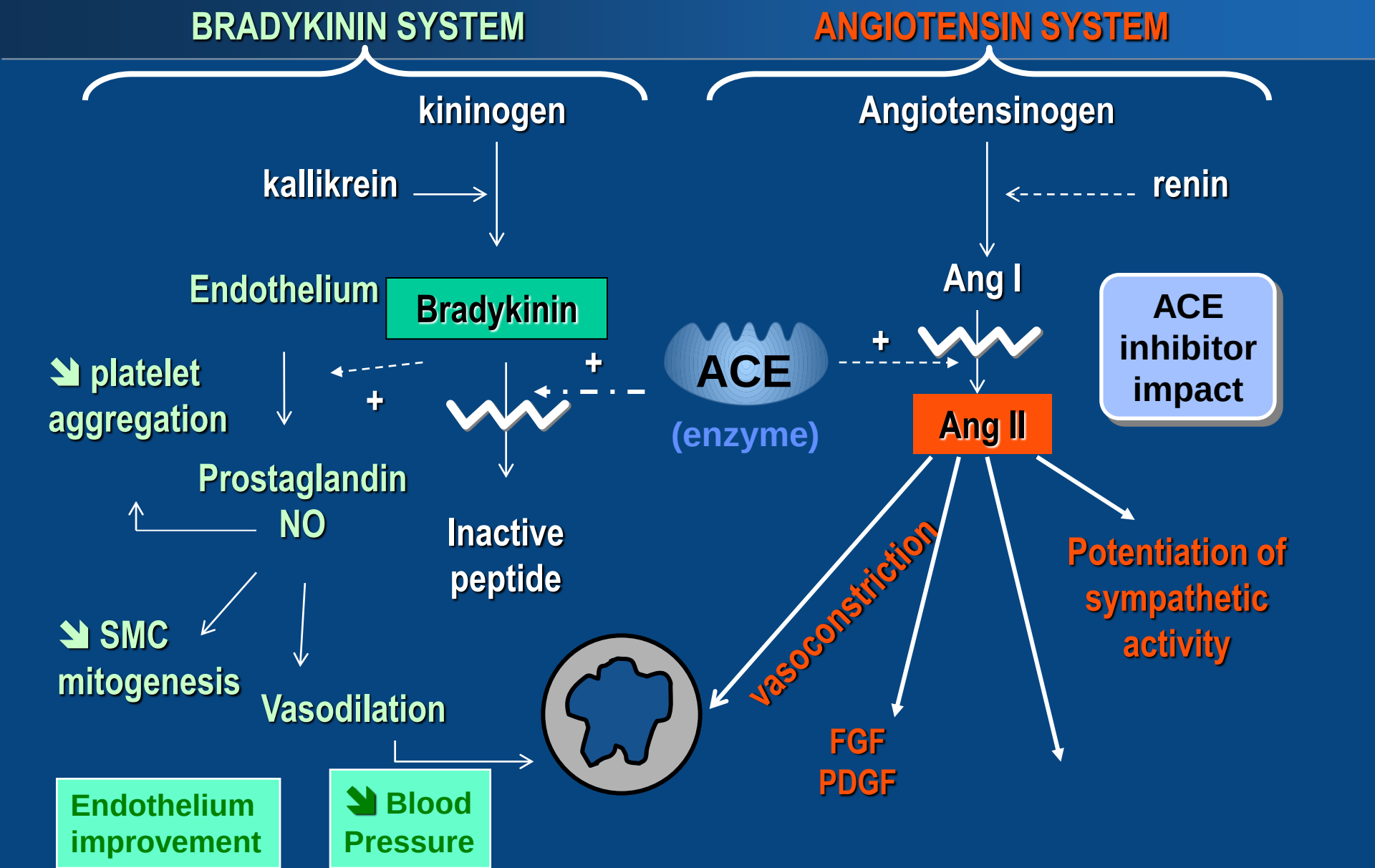
e. Platelet adhesion

f. Thrombogenesis

Detrimental effects of angiotensin II on arterial endothelium=initiation of atherosclerosis



Why ACE inhibition in the management of HT ?

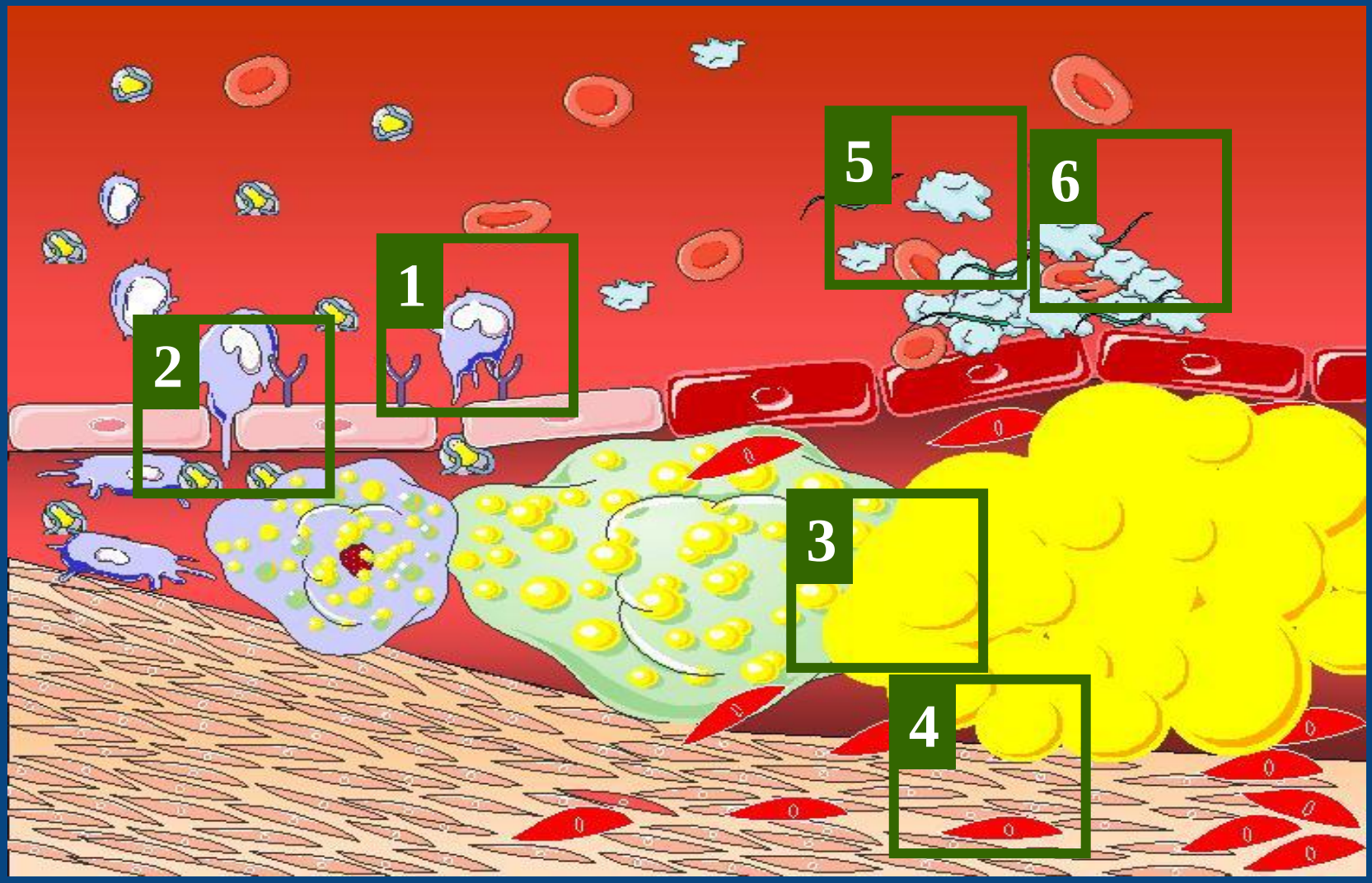


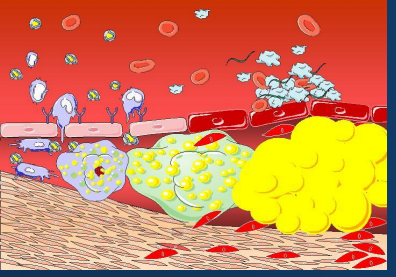
Pharmacokinetic properties of ACE inhibitors

	captopril	fosinopril	enalapril	lisinopril	ramipril	trandolapril	perindopril
Bioavailability	60	36	60	6-60	50-60	70	**66**
FDA T/P ratio (once daily)	60-70	50-80	40-60	30-70	50-63	50-90	**75-100**
Tissue ACE* Affinity	5	4	3		2		**1**
T max (h)	1-2	4	2-8	6-8	3	4-10	**3-6**
Duration of effects (h)	6-10	24	<24		12-24	24	**24**
Terminal 1/2 life (h)	2	12	30-35	6-8	>50	10	**30-120**
Inhibition of Plasma ACE	60% at 4h	80-100%	max 2- 8h	80%	80-100% at 4 h	80%	**80-95% still 60-80% at 24h**

Lionel H. Opie Angiotensin Converting Enzyme inhibitors (Third edition). *Ferrari R. *Dialog Cardiovasc Med* 2004;9:71-89.

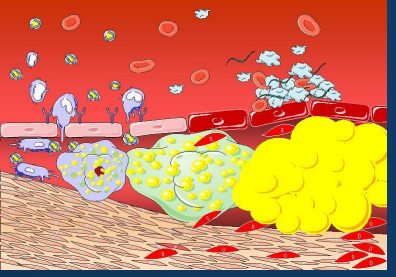
How does ACEI correct endothelial dysfunction?





How does ACEI correct endothelial dysfunction ?

ACEI decreases adhesion of monocyte cells



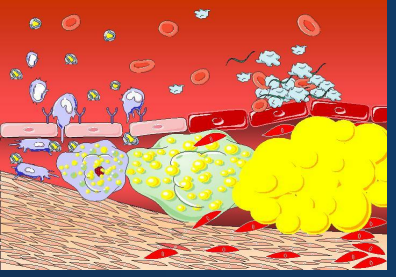
How does ACEI correct endothelial dysfunction ?

ACEI decreases adhesion of monocyte cells

ACEI restores endothelial permeability

(decrease of apoptosis)

and reduces penetration of cells and lipids



How does ACEI correct endothelial dysfunction ?

1

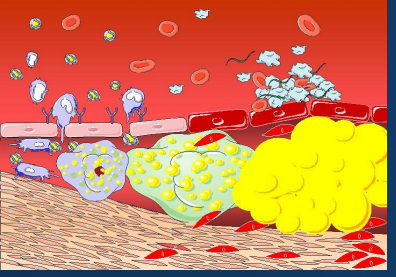
ACEI decreases adhesion of monocyte cells

2

ACEI restores endothelial permeability (decrease of apoptosis) and reduces penetration of cells and lipids

3

ACEI decreases lipid accumulation and prevents atherosclerosis development



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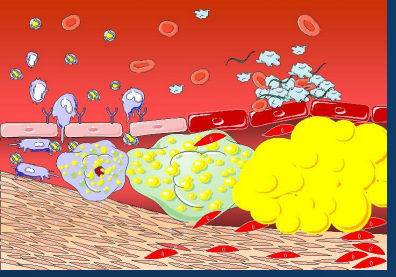
ACEI decreases lipid accumulation and prevents atherosclerosis development

ACEI decreases SMC growth, proliferation, and migration and thus stabalizes the plaques



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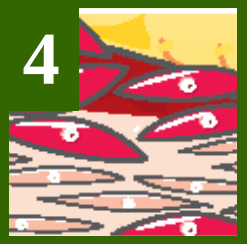
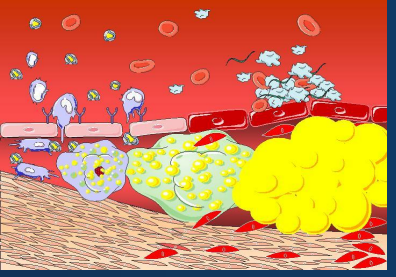


ACEI decreases SMC growth, proliferation, and migration and thus staba-lizes the plaques

5

ACEI decreases platelet aggregation



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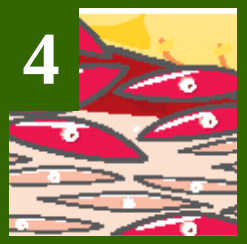

ACEI decreases SMC growth, proliferation, and migration and thus staba-lizes the plaques

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ACEI decreases platelet aggregation

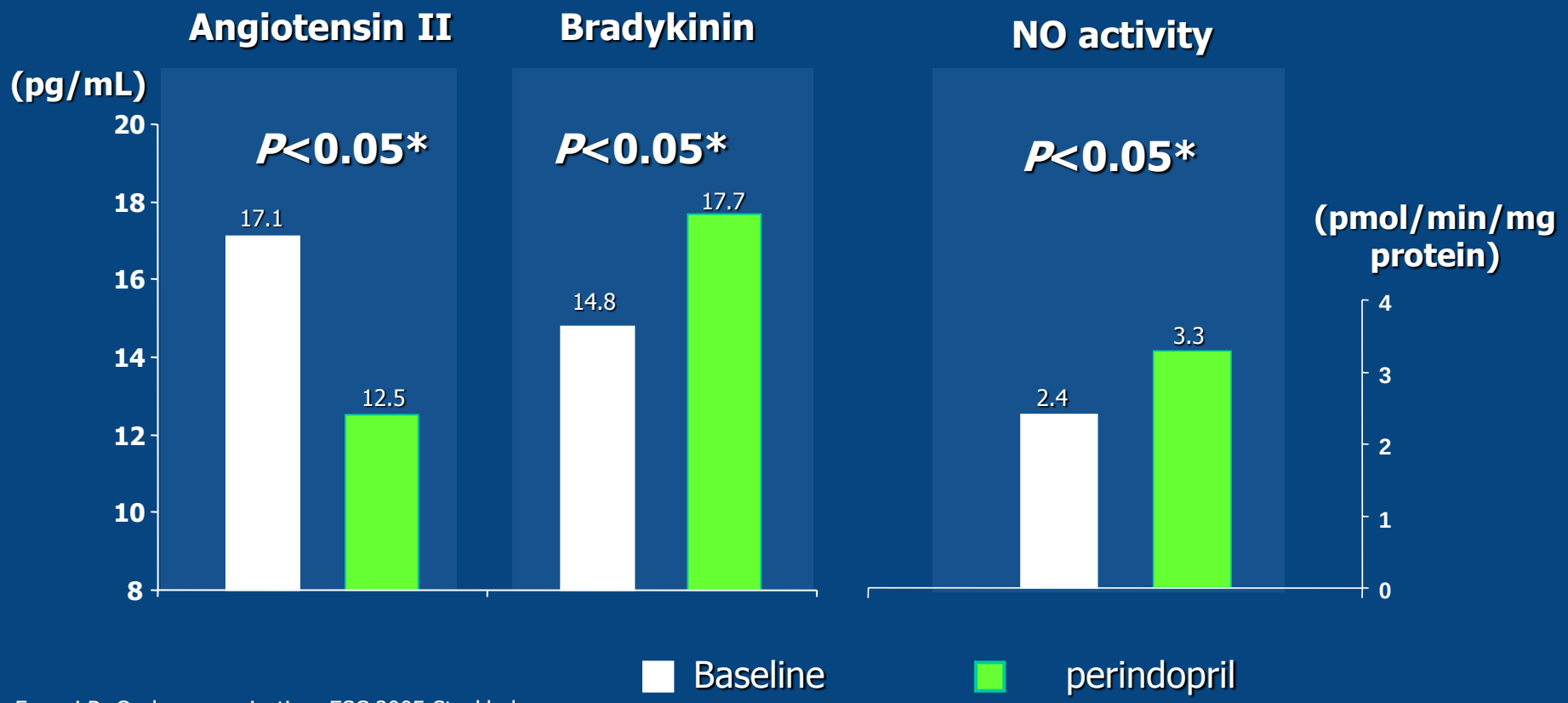
6

ACEI reduces thrombogenesis

EUROPA

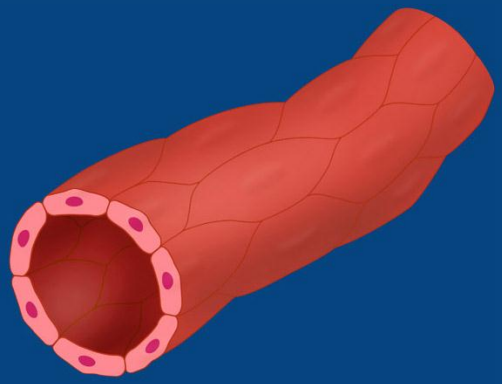
PERTINENT

In inhibiting ACE, perindopril corrects the angiotensin II/ bradykinin balance in favor of bradykinin and NO synthesis



Ferrari R. Oral communication. ESC 2005 Stockholm

Endothelial apoptosis is one of the main consequences of endothelial dysfunction



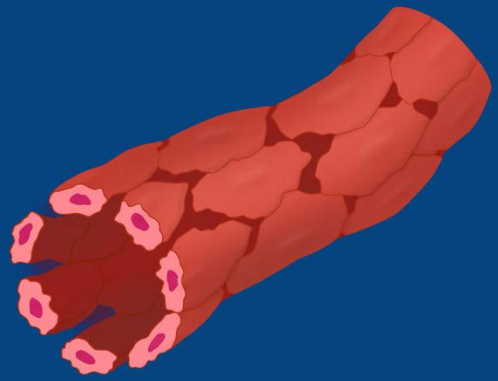
Normal rate of apoptosis: 3%

↓

Maintenance of endothelium layer

↓

Protection against atherosclerosis



Excess rate of apoptosis

(Endothelial suicide)

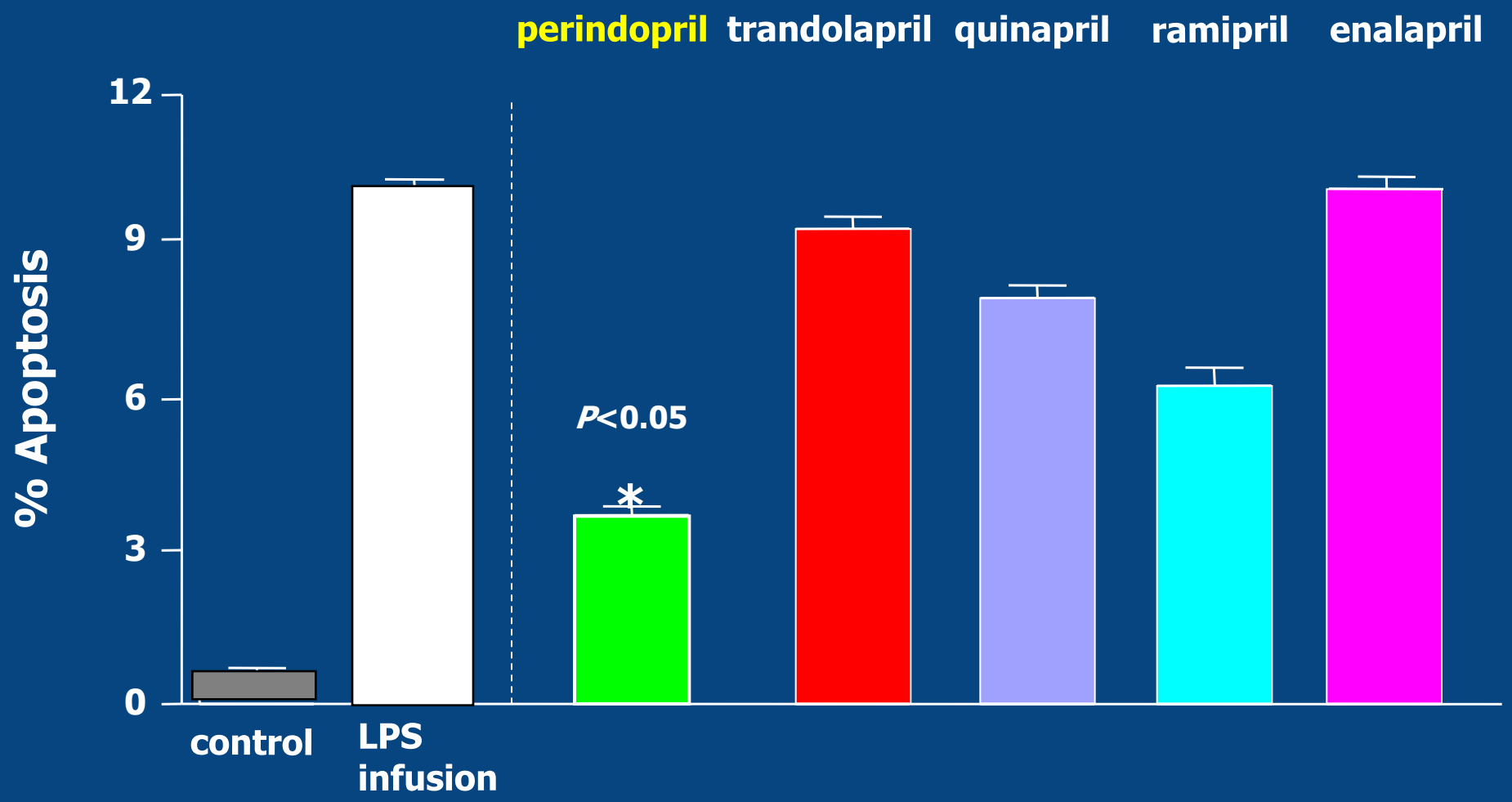
↓

Loss of endothelium continuity

↓

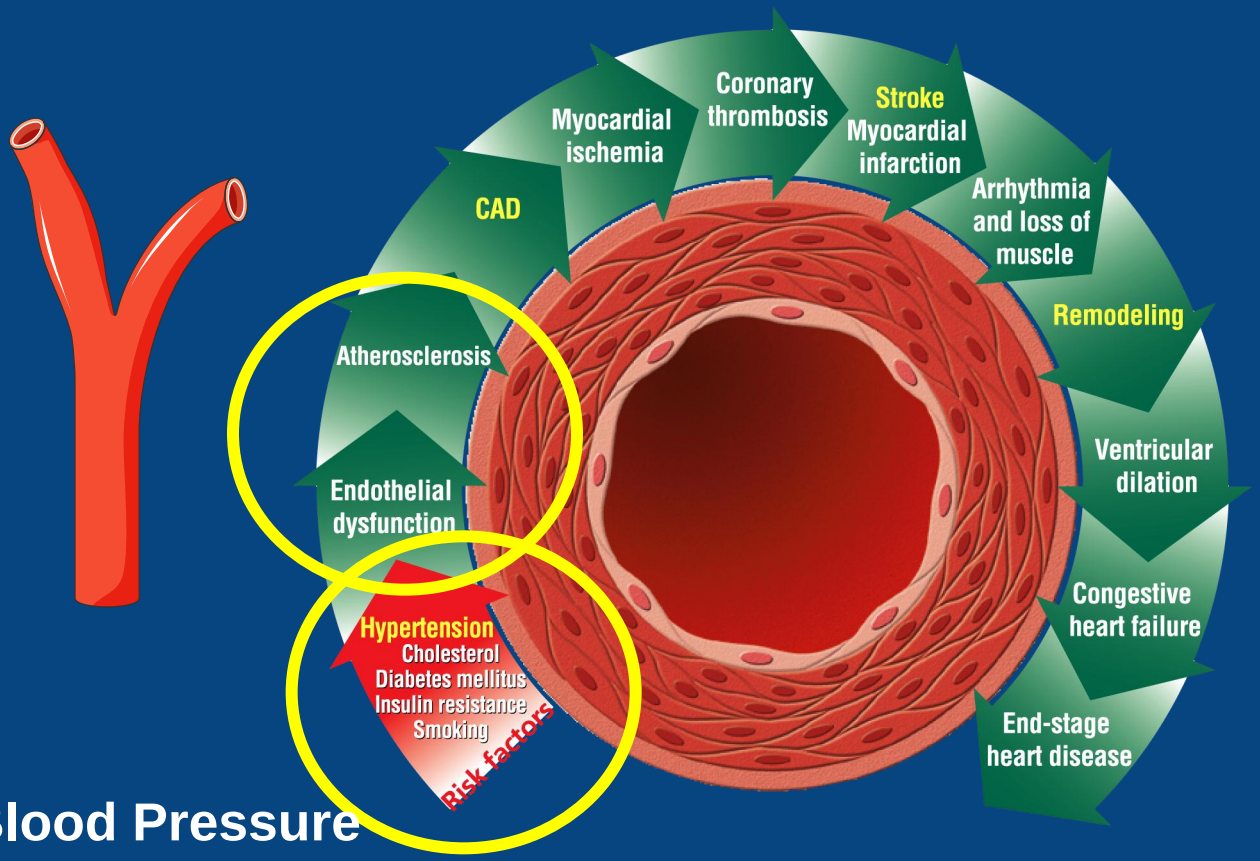
Onset of atherosclerosis

Each ACEi have different effect on reduction of endothelial apoptosis



ACE inhibition:

- lowers BP
- restores endothelial function at the arterial level and prevents cardiovascular mortality



↘ Blood Pressure

Four basic considerations for BP treatment

- Inhibiting of ACE is vital to reduce BP.
- To stop the silent and dramatic evolution of endothelium disease and thus avoiding cardiac and vascular events.
- This inhibition of RAAS has to be effective 24 hours a day otherwise endothelium protection remains incomplete.
- This efficacy has to result in a demonstrated improvement of clinical prognosis.

T/P ratio: long duration of action to provide a 24H effective coverage

US DATA sheet	T:P ratios as stated by FDA
perindopril	**75% to 100%**
Benazepril	≅ 50%
Quinapril	50%
Ramipril	50% to 60%
Lisinopril	"At all doses studied mean antihypertensive effect was substantially smaller 24H after dosing than 6H after dosing"
Enalapril	Not stated but once or twice daily dosage
Fosinopril	DBP = 50% to 60% ; SBP = 80%
Captopril	Not stated (twice or 3 times daily)
Trandolapril	50% to 90%

2004 *Physician's Desk Reference* (58th Edition), Thomson PDR, NJ

New US Study. *J Clin Hypertens 2004.*

10 425 patients mean age 56 newly diagnosed HT (50%)

Julius S. *J Clin Hyperten.* 2004;6:7-10.

Neutel JM et al. *Am J Cardiovasc Drugs.* 2004;4:335-341.

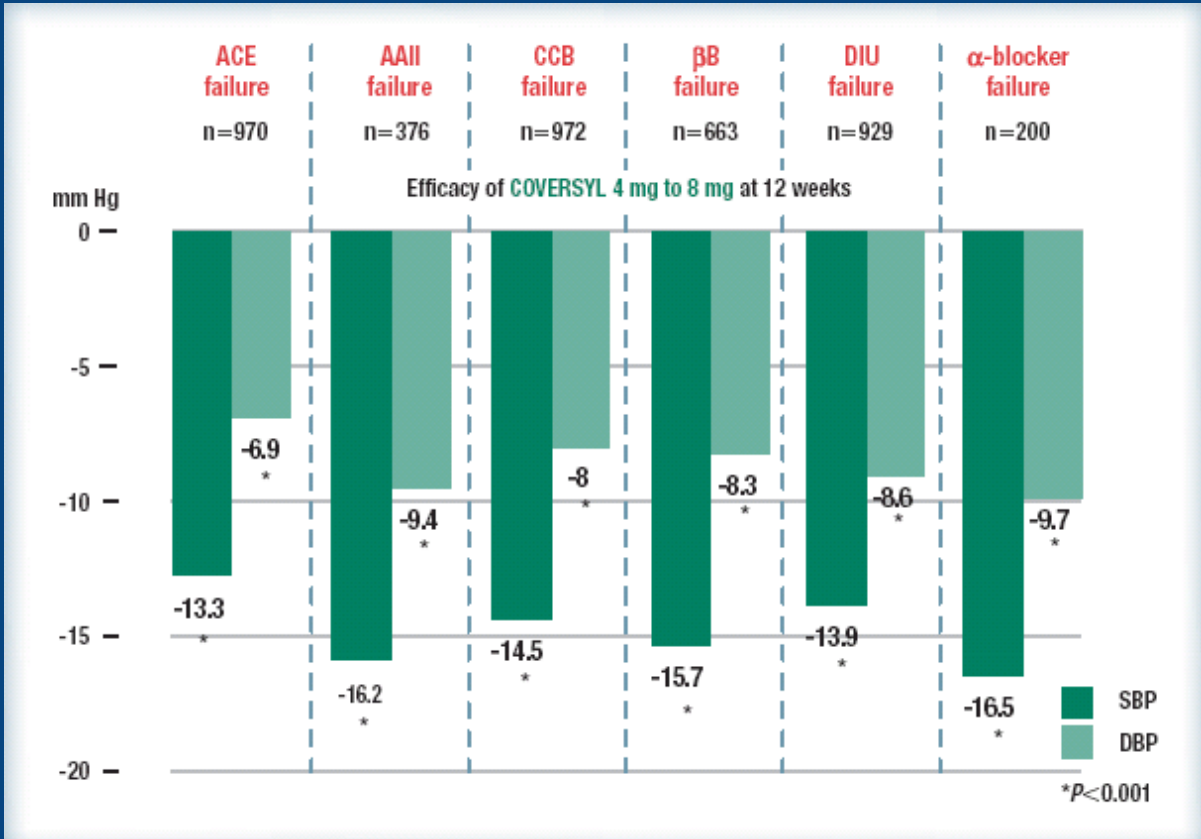
New US Study. *J Clin Hypertens 2004.*

Non responders to previous antihypertensive therapy, including ACEi or ARBs

10 425 patients mean age 56 newly diagnosed HT (50%)

-Inability to tolerate other antihypertensive drugs (20%)

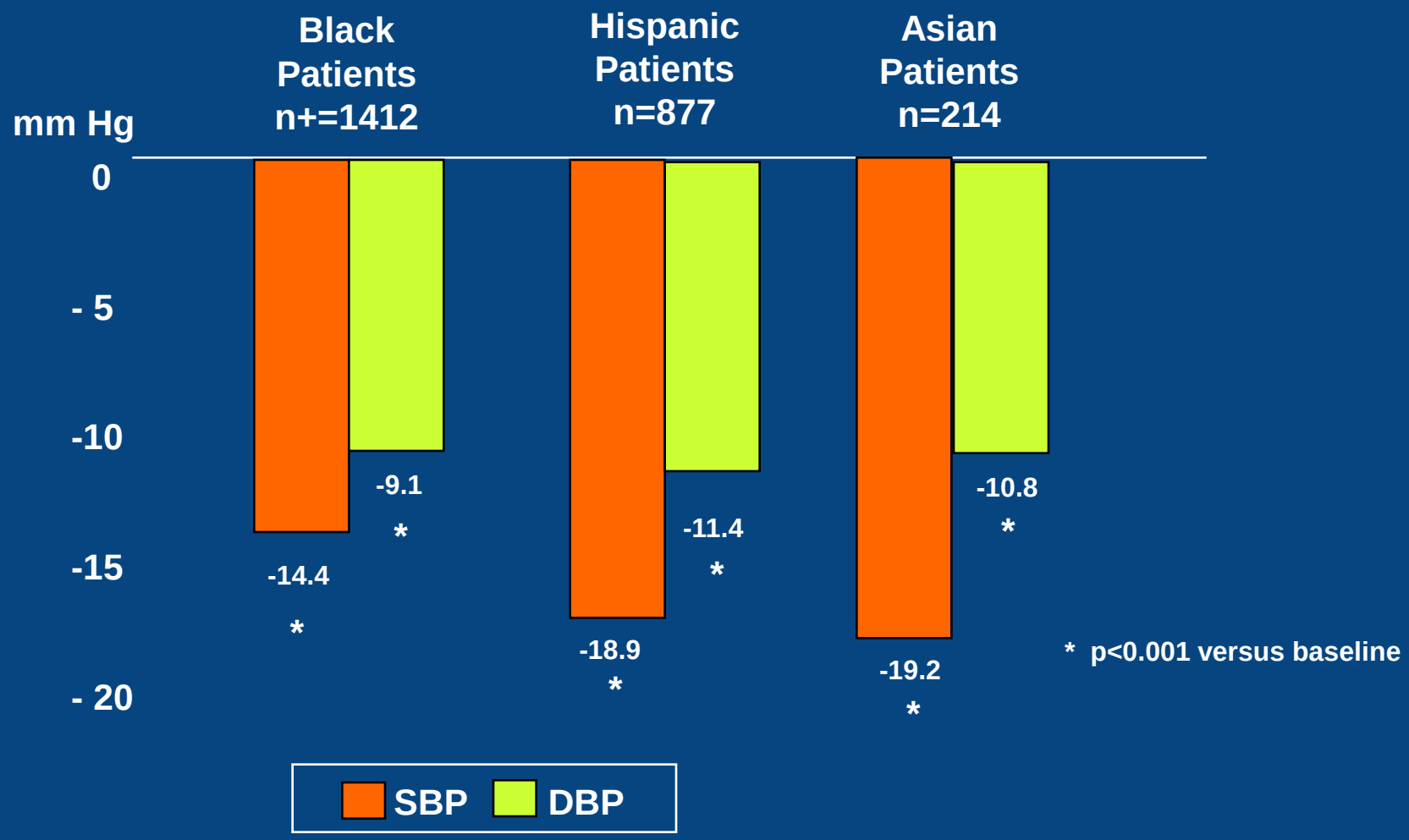
- Lack of BP control with any prior antihyper-tensive monotherapy, including ACEIs (30%)



Julius S. *J Clin Hyperten.* 2004;6:7-10.

New US Study. *J Clin Hypertens 2004.*

Perindopril decreases BP in all hypertensive patients



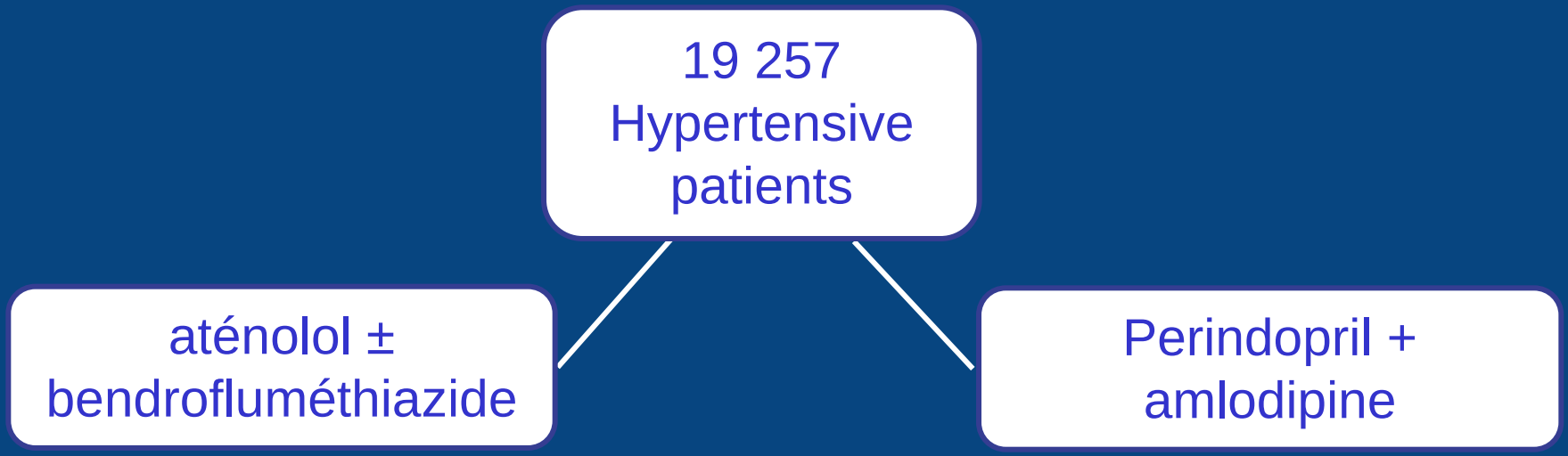
19 257 hypertensive patients

without cardiac disease

treated with

Perindopril + amlodipine

ASCOT-BPLA trial: Design



Controlled, randomised, multinational study

Anglo-Scandinavian ascot Cardiac Outcomes Trial

Inclusion criteria

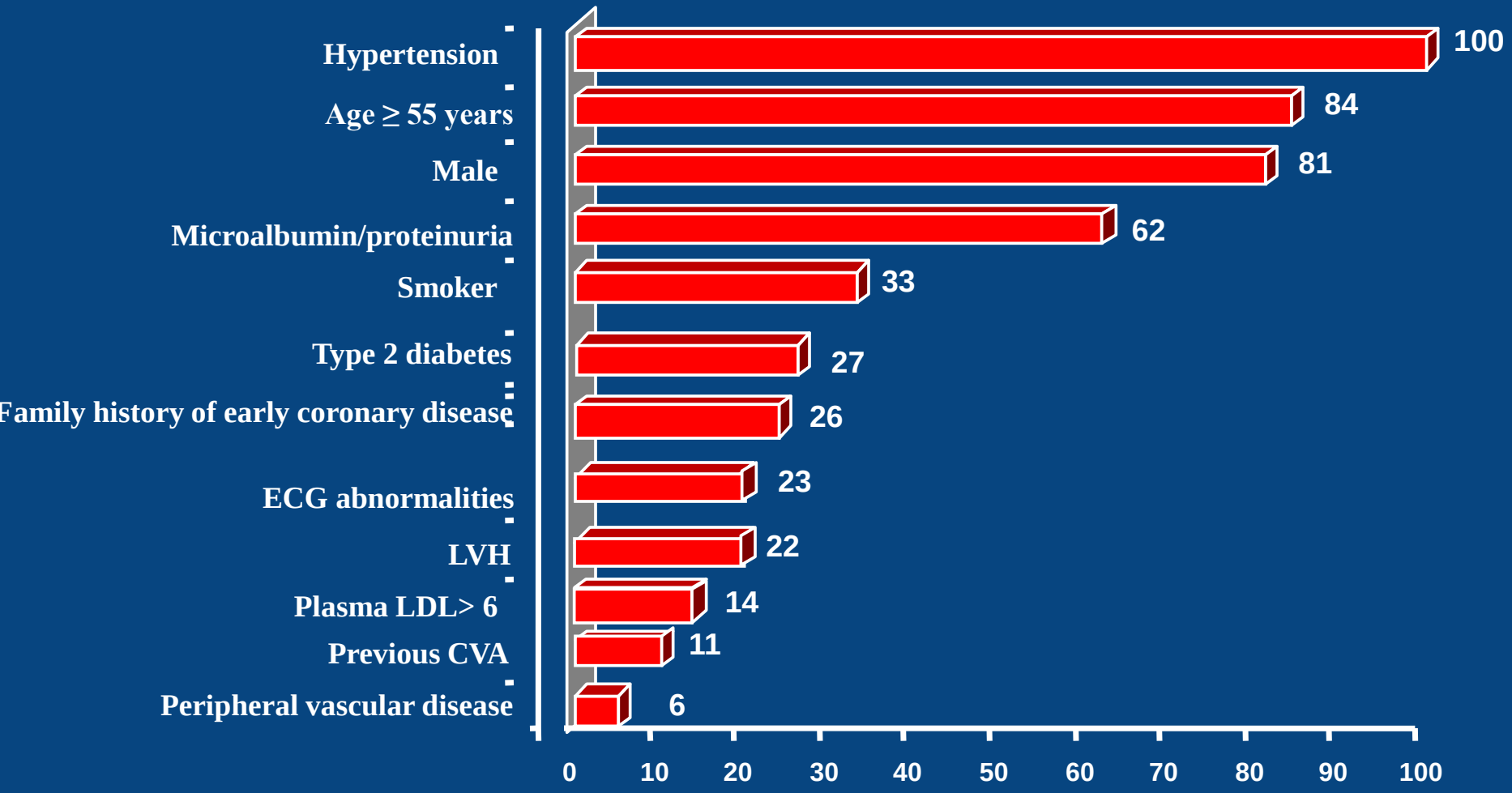
- **Hypertension** at baseline BP ≥ 160/100 mm Hg untreated or ≥ 140/90 mm Hg treated with one or more drugs
- Patients aged **40-79 years**
- Patients with **3 or more risk factors** for a future cardiovascular event

Male sex
Age > 55 years
LVH
NIDDM
Smoking
ECG abnormalities

History of cerebrovascular event
History of early CHD in first degree relative
Plasma TC/ HDL ratio ≥ 6
Peripheral vascular disease
Microalbuminuria/ proteinuria

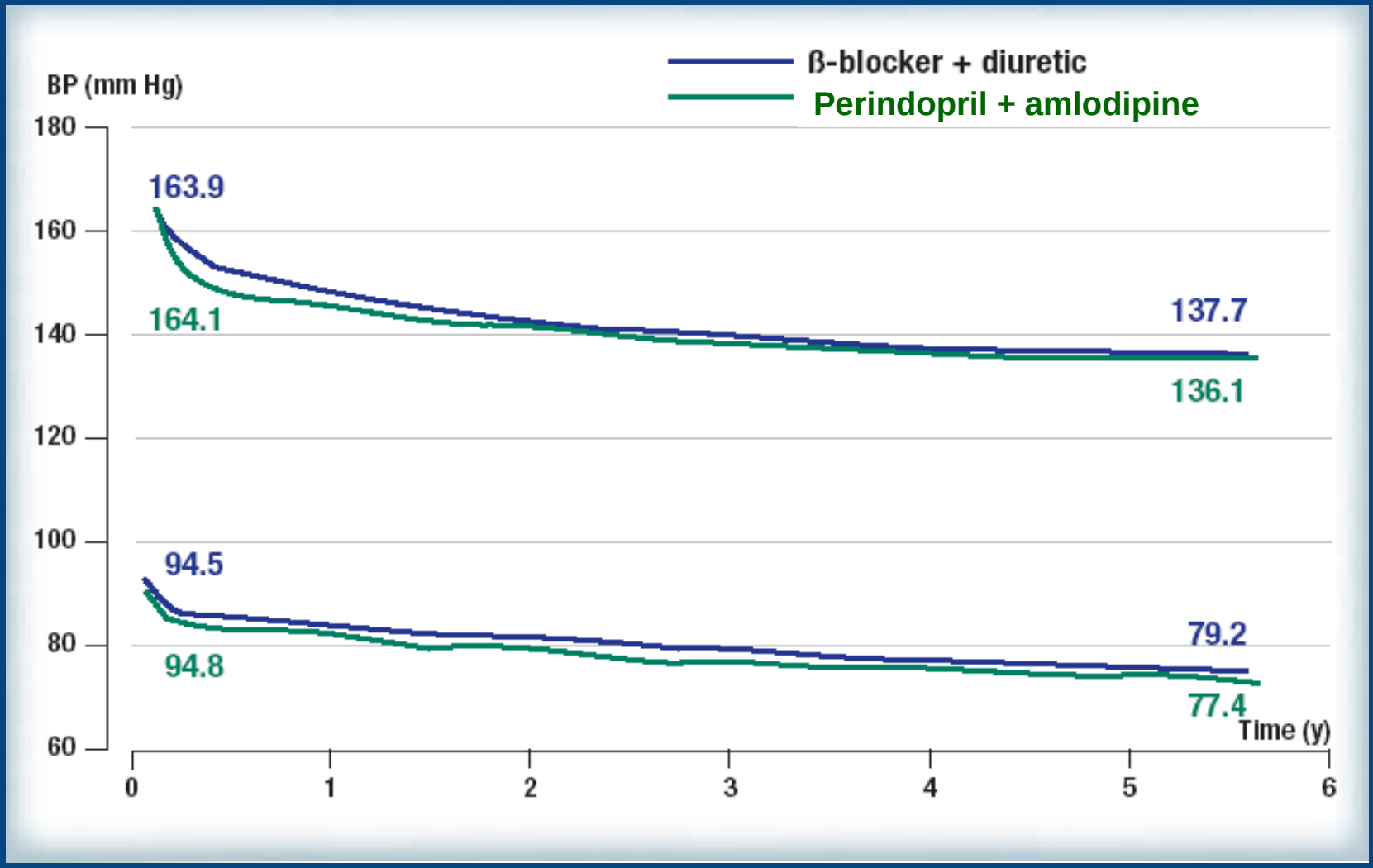
Anglo-Scandinavian ascot Cardiac Outcomes Trial

Risk factors at baseline



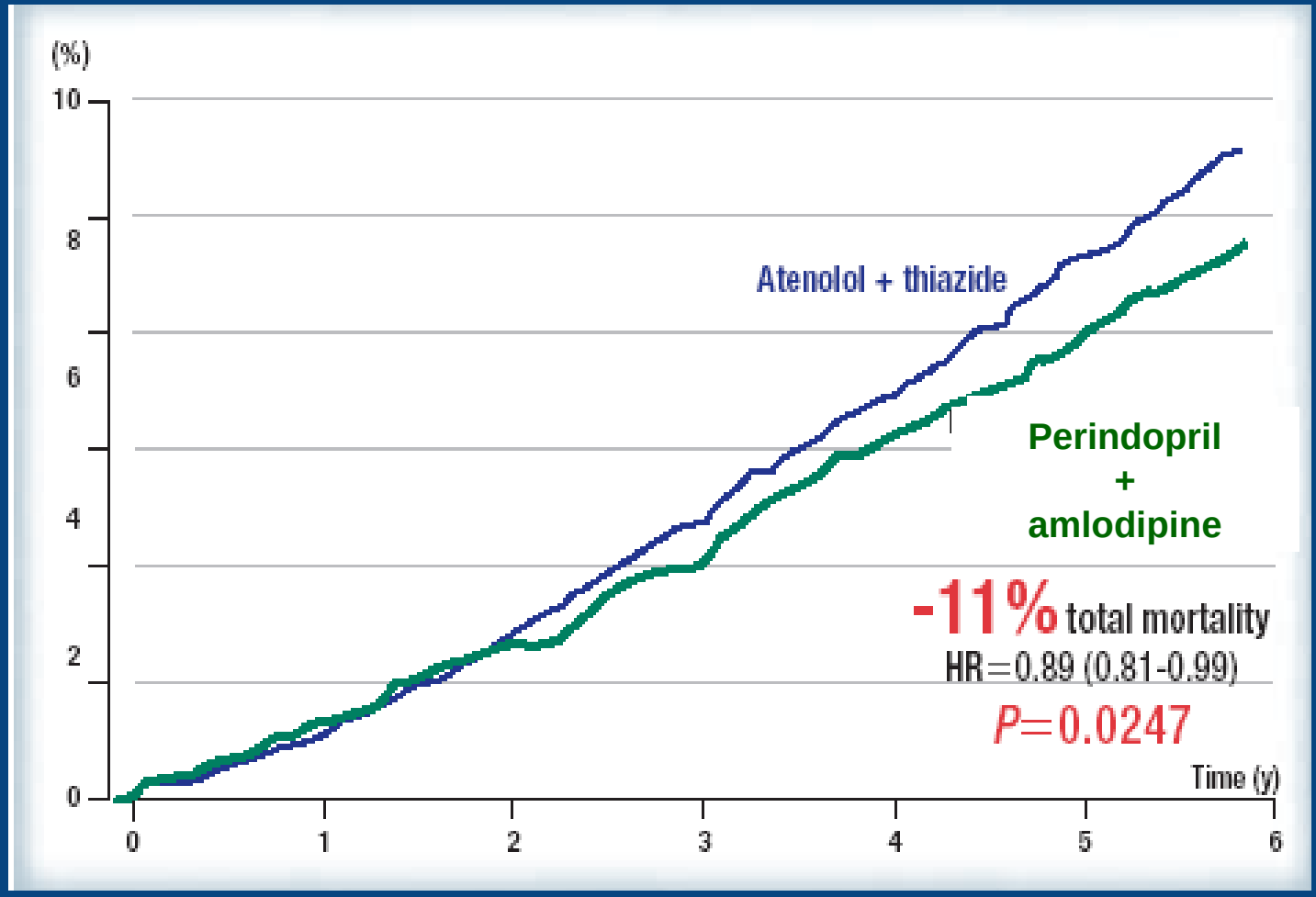
Anglo-Scandinavian ascot Cardiac Outcomes Trial

SBP and DBP by time



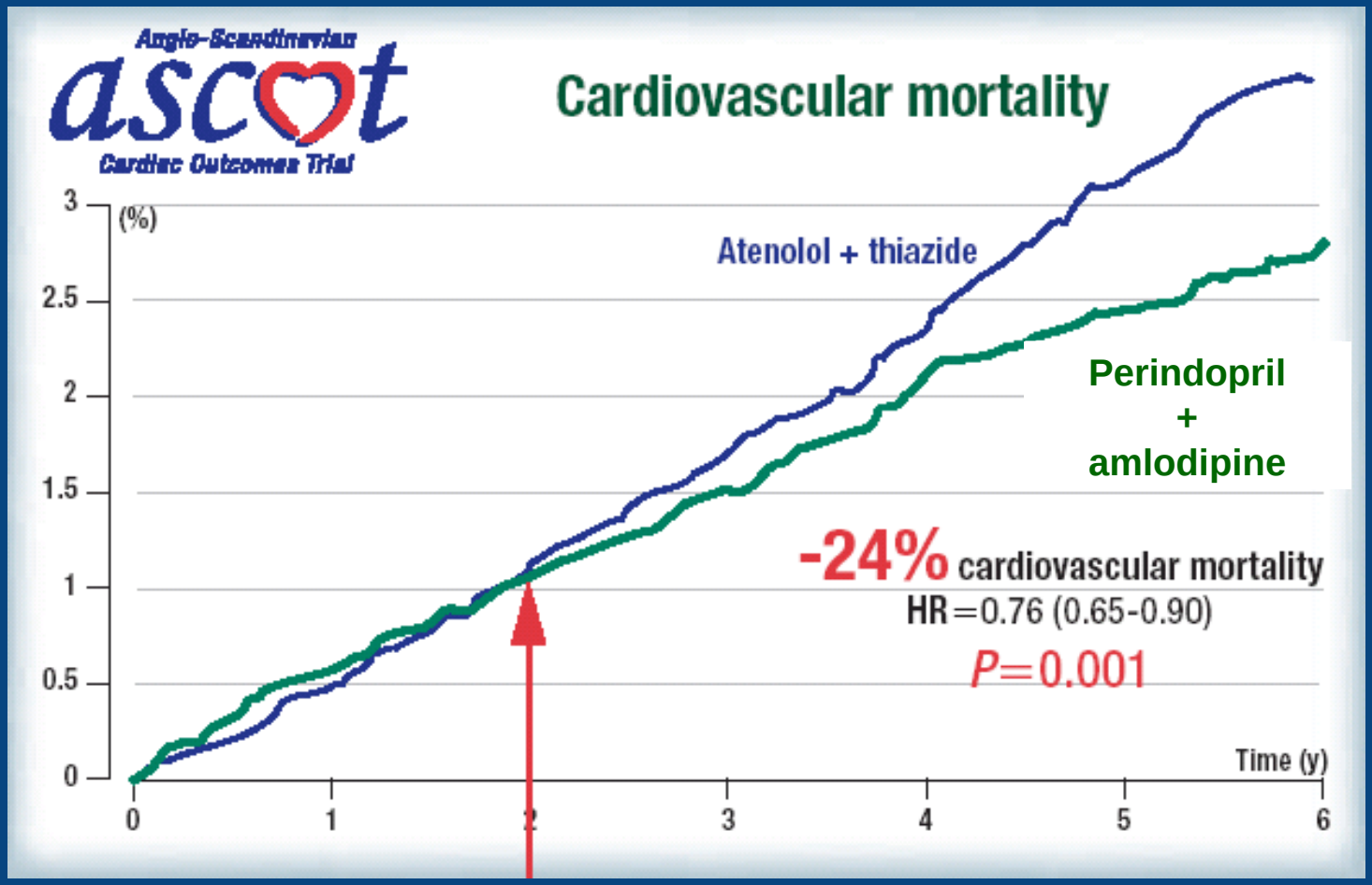
Anglo-Scandinavian ascot Cardiac Outcomes Trial

All-cause mortality: - 11%



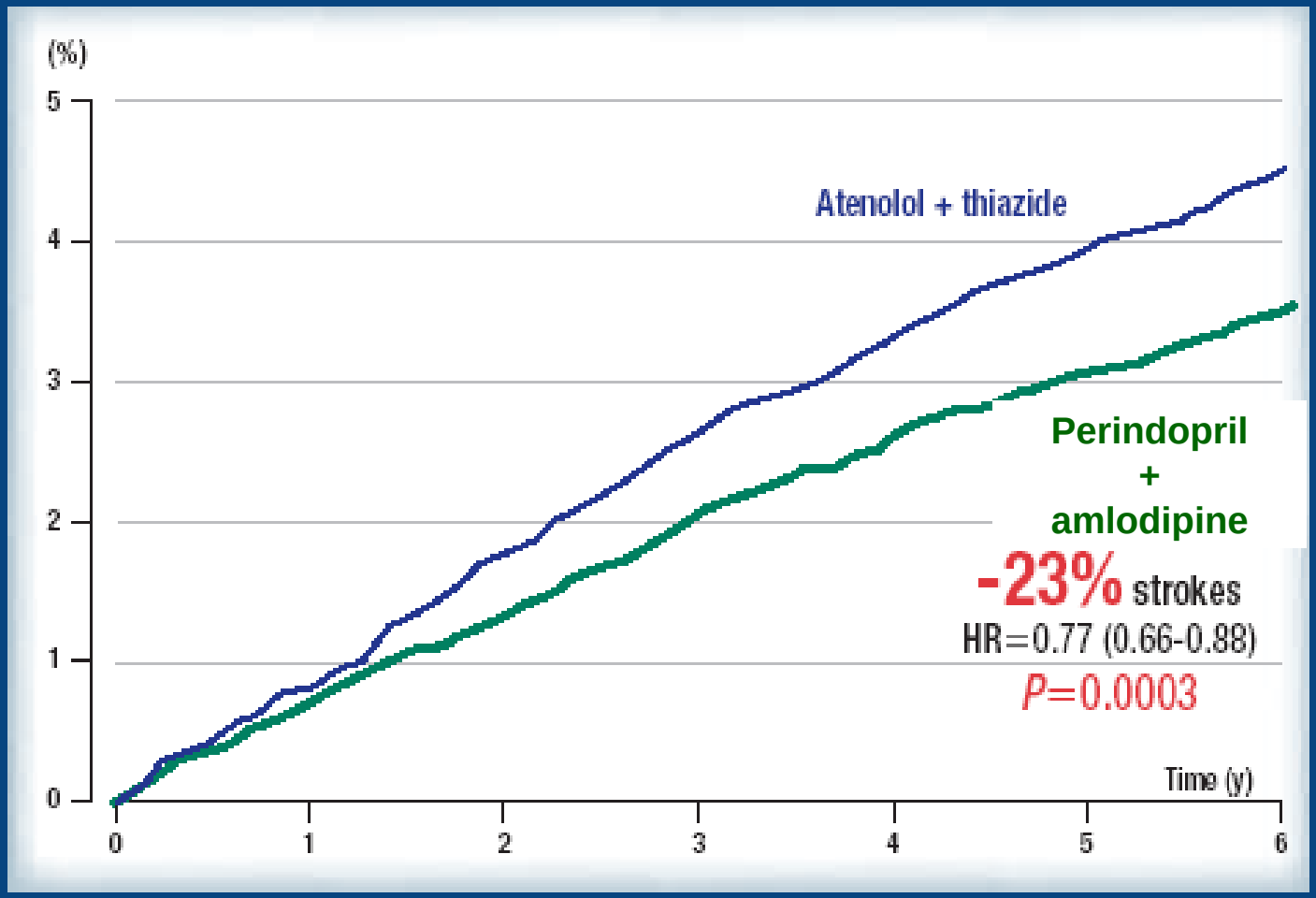
Anglo-Scandinavian ascot Cardiac Outcomes Trial

Cadiovascular mortality: - 24%



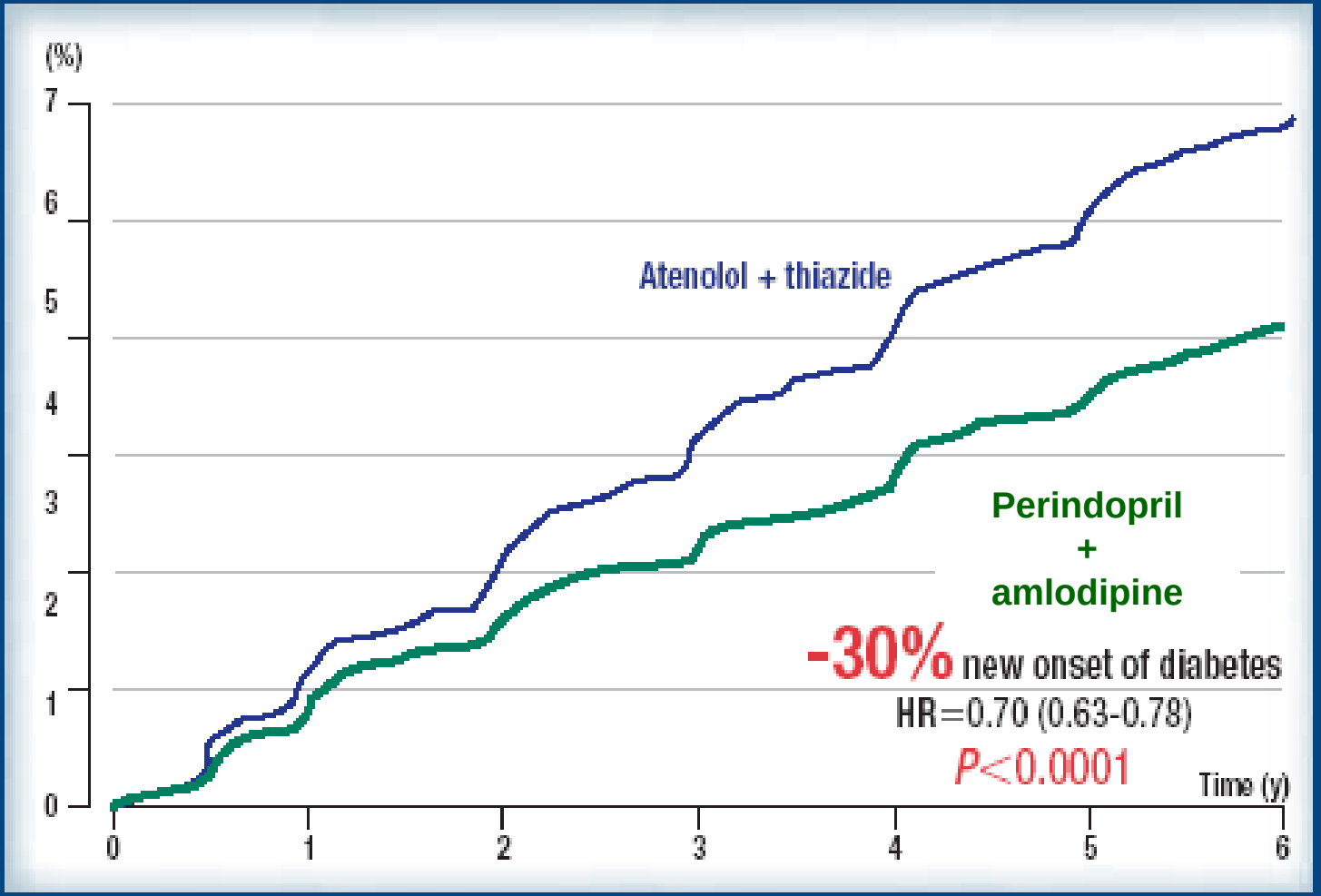
Anglo-Scandinavian ascot Cardiac Outcomes Trial

Fatal and nonfatal strokes: - 23%



Anglo-Scandinavian ascot Cardiac Outcomes Trial

New onset of diabetes: - 30%

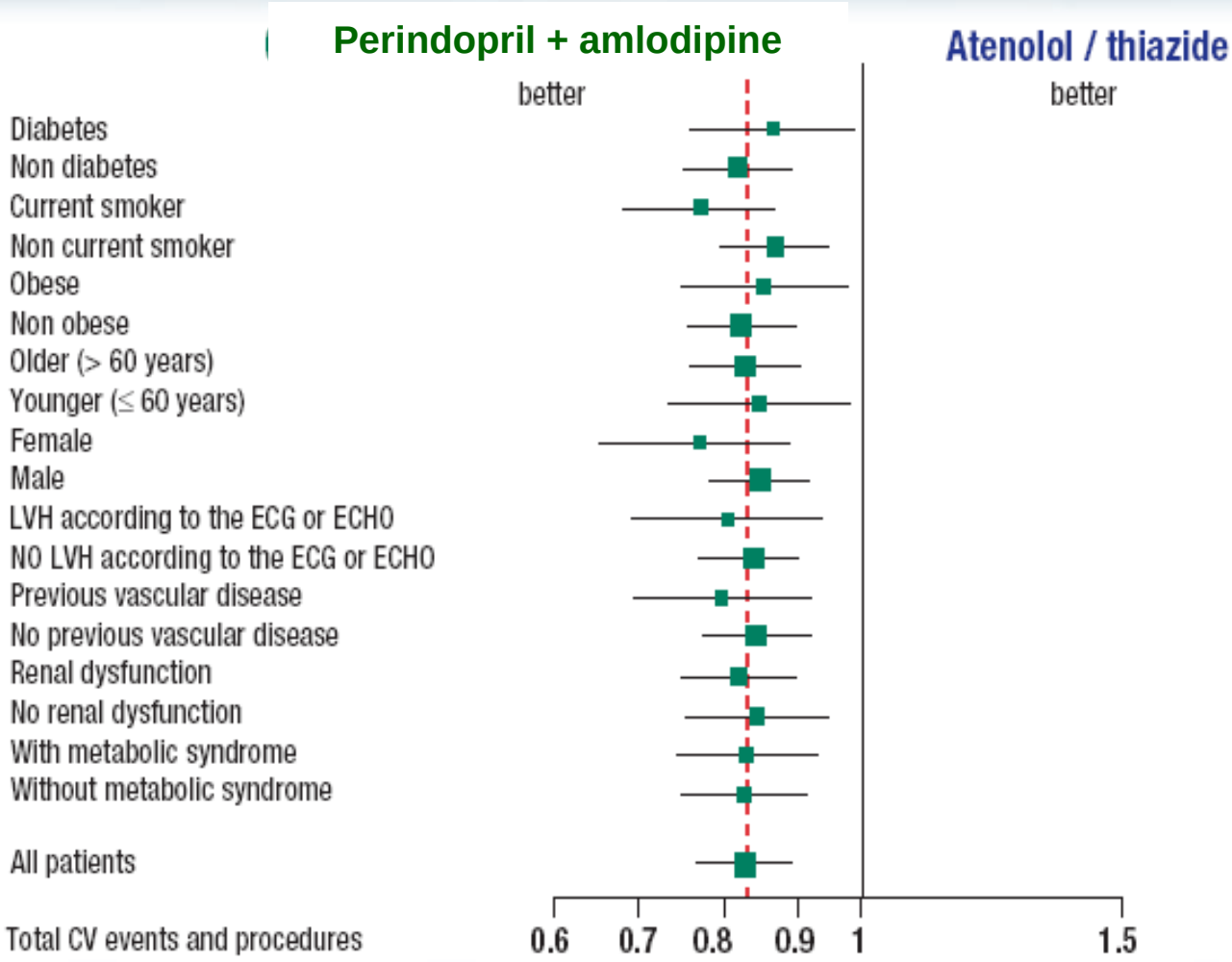


Despite good BP control and good use of β-blocker + thiazide, the newer treatment perindopril + amlodipine yielded better outcomes than traditional treatment

	Reduction in events	P
Nonfatal MI + CHD death	-10%	0.12
Cardiovascular mortality	-24%	<0.001
Total mortality	-11%	<0.001
Total coronary events	-13%	0.005
Fatal and nonfatal strokes	**-23%**	**<0.001**
Total CV events and procedures	-16%	<0.001
New onset of diabetes	**-30%**	**<0.001**

Anglo-Scandinavian ascot Cardiac Outcomes Trial

Total CV events and procedures among subgroups



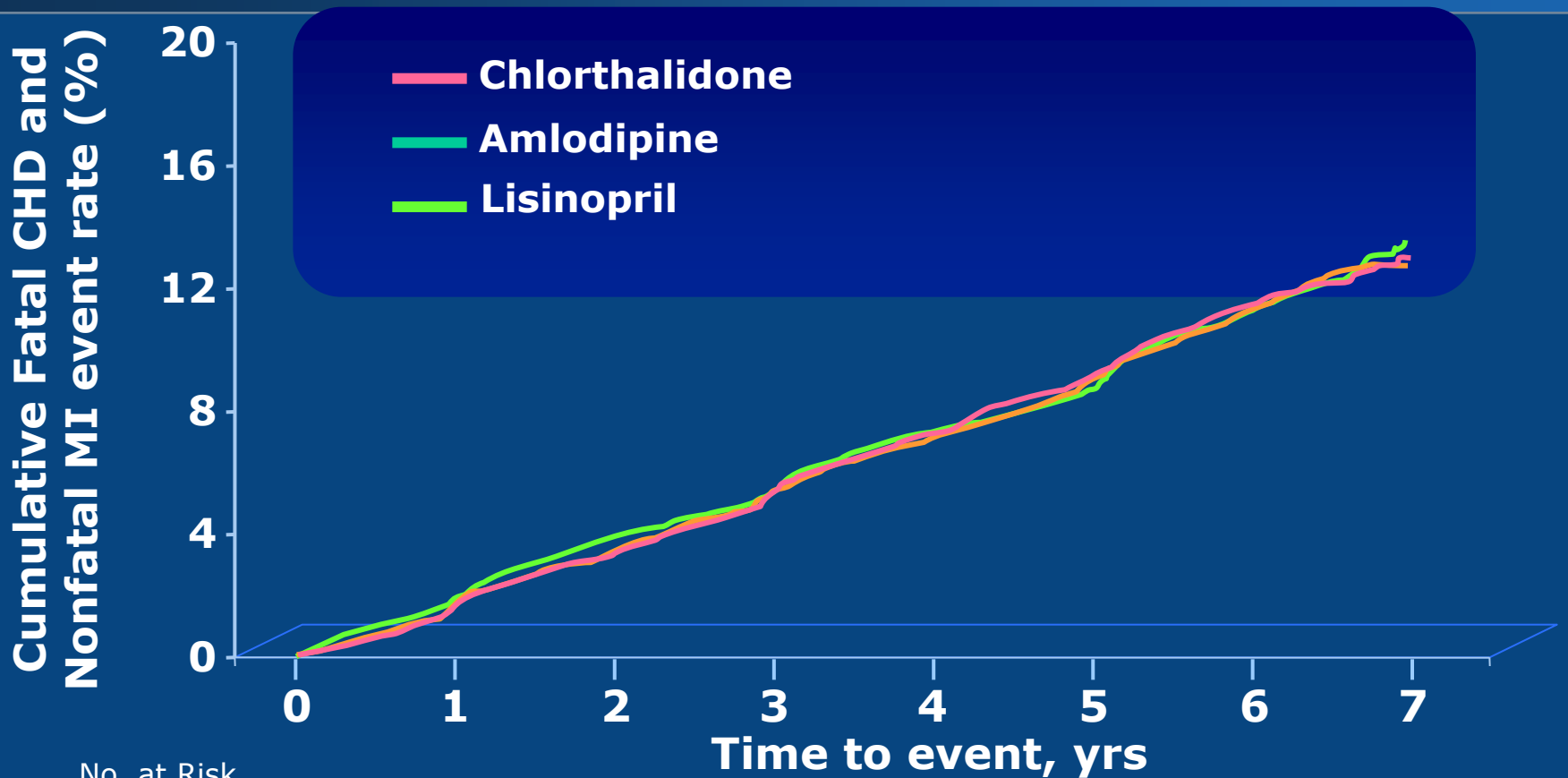
No ACEi or ARBs demonstrated superiority versus comparator, mainly diuretics+/- betablockers (or CCB) in hypertension on total and cardiovascular mortality

- Lisinopril — ALLHAT
- Enalapril — TOMHS
- ANBP2
- Enalapril or lisinopril — STOP 2
- Captopril — CAPPP
- Trandolapril — INVEST
- Losartan — LIFE
- Valsartan — VALUE

	ALLHAT Amlodipine + add-on (47%) n = 8 215		Anglo-Scandinavian ascot Cardiac Outcomes Trial Perindopril + amlodipine n = 9639	
CV death + nonfatal MI	RR=0.98 (*P*=0.6)	NS	RR=0.90 (*P*=0.1052)	NS
All-cause mortality	RR=0.96 (*P*=0.2)	NS	RR=0.89 (*P*=0.0247)	S
Combined CHD diseases	RR=1 (*P*=0.97)	NS	RR=0.87 (*P*=0,007)*	S
Combined CVD diseases	RR=1.04 (*P*=0.12)	NS	RR=0.84 (*P*<0.0001)	S
Strokes	RR=0.93 (*P*=0.28)	NS	RR=0.77 (*P*=0.0003)	S
Heart failure	RR=1.38 (*P*<0.001)	!	RR=0.84 (*P=0.1257*)	NS

*CV death

ALLHAT Primary Outcome by Treatment Group



No. at Risk								
Chlorthalidone	15255	14477	13820	13102	11362	6340	2956	209
Amlodipine	9048	8576	8218	7843	6824	3870	1878	215
Lisinopril	9054	8535	8123	7711	6662	3832	1770	195

ALLHAT Research Group. JAMA. 2002;288:2981-2997.

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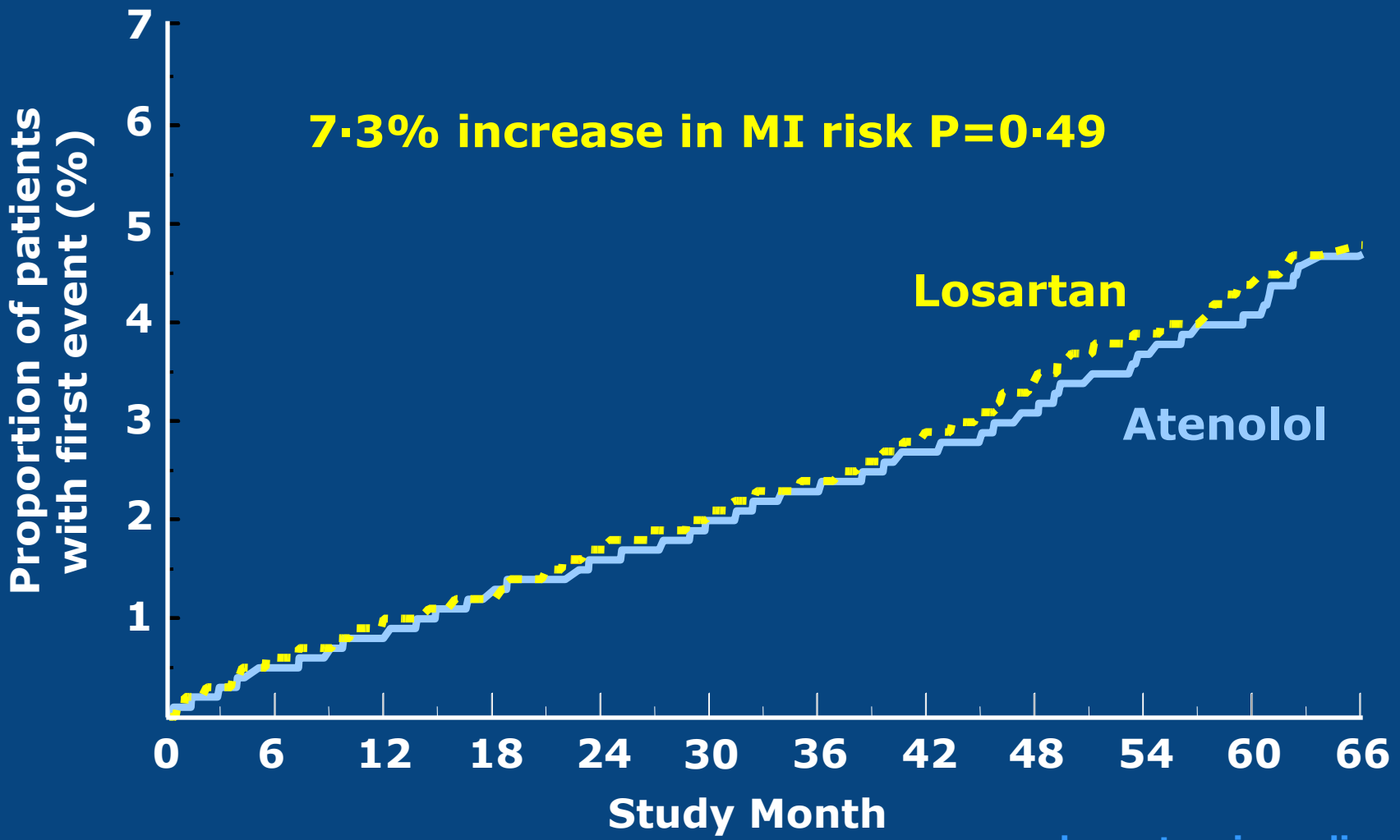
LIFE Study
Fatal and Non-Fatal Myocardial Infarction



Dahlof B, et al. Lancet. 2002;359:995-1003.
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www.hypertensiononline.org

VALUE

Anglo-Scandinavian ascot Cardiac Outcomes Trial

	Amlodipine + add-on (40.6%) n =7596	Perindopril + amlodipine n = 9639	
CV death + nonfatal MI	NS	RR=0.90 (*P*=0.12)	S
All-cause mortality	NS	RR=0.89 (*P*=0.0247)	S
Combined CHD diseases	NS	RR=0.87 (*P*=0.007) *	S
Combined CVD diseases	NS	RR=0.84 (*P*<0.0001)	S
Strokes	NS	RR=0.77 (*P*=0.0003)	S
Heart failure	!	RR=0.84 (*P=0.1257*)	NS

*CV death

Anglo-Scandinavian ascot Cardiac Outcomes Trial

Conclusions

- ✓ **Perindopril + amlodipine confers an advantage over atenolol/thiazide on all major CV end points, all-cause mortality and new-onset diabetes**

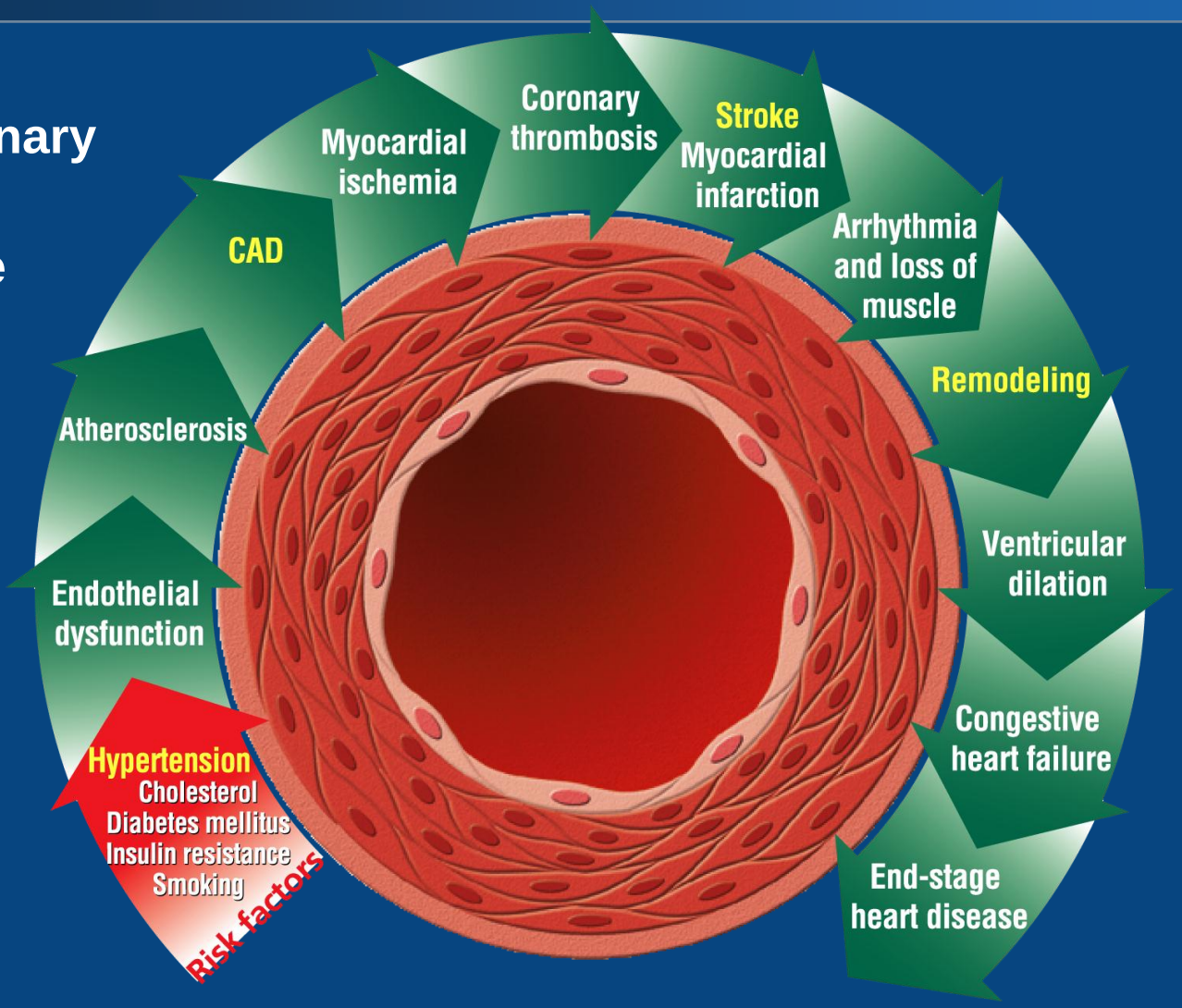
- ✓ **No other ACEi or ARBs demonstrated such a superiority versus diuretic/b-blockers**

"What is very interesting is that if you start on the wrong drug – it was lisinopril in ALLHAT, valsartan in VALUE, and atenolol in ASCOT – whether or not you increase the dose, or add second- and third-, or fourth-line drugs, you never seem to actually get there."

Prof Peter S. Sever (Imperial College London, CoChairman of the ASCOT trial)

The cardiovascular disease continuum

ACEi in Coronary Artery Disease



New US F.D.A. approval for CAD patients

"Perindopril is indicated in patients with stable coronary artery disease to **reduce the risk of cardiovascular mortality** or **non-fatal myocardial infarction.**

Perindopril can be used with **conventional treatment** for management of coronary artery disease such as antiplatelet, antihypertensive or lipid-lowering therapy."

1. The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. *Lancet*. 2003;362:782-788.
2. FPL for approval supplement NDA 20-184/S-011.

12 218 coronary artery disease patients

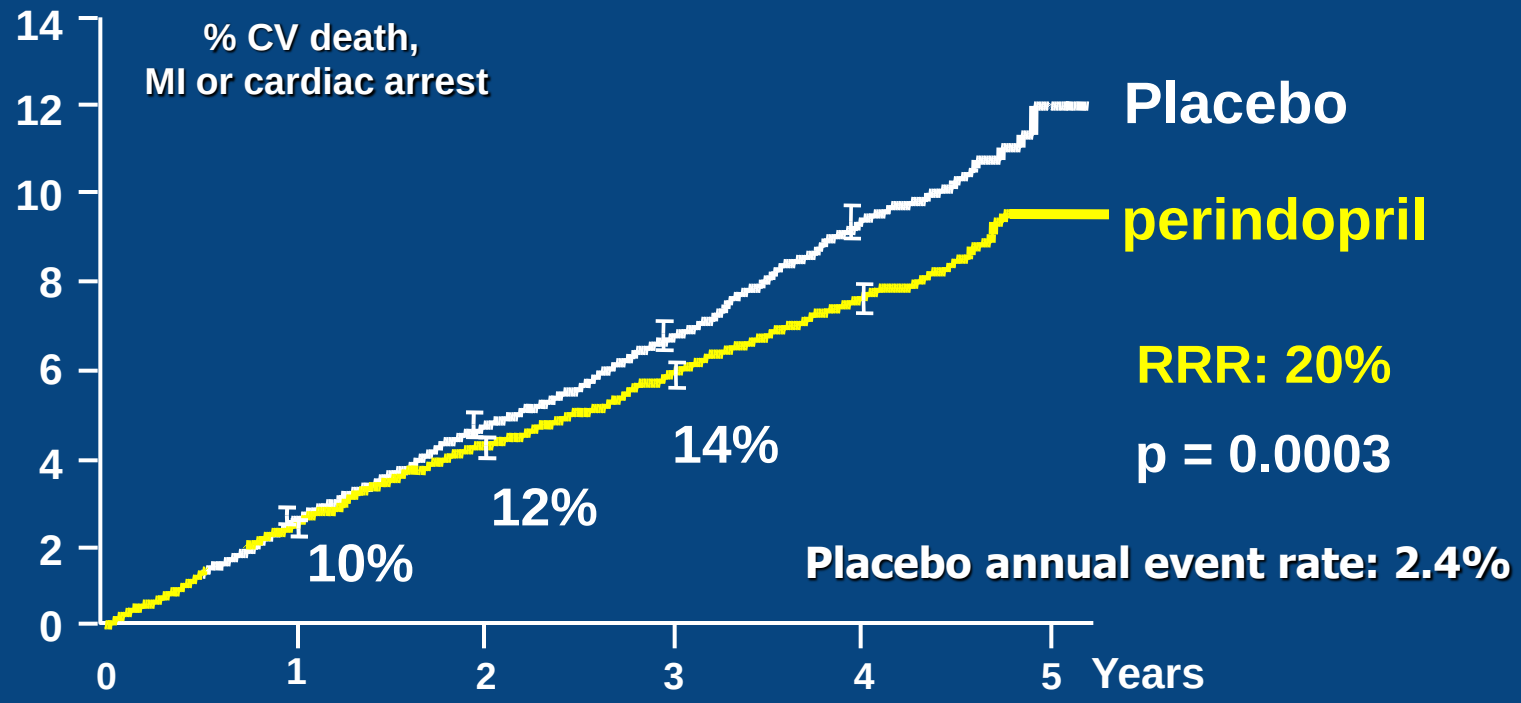
Age (y)	61
Known CAD (%)	100
Previous MI (%)	62
Diabetes (%)	12
Hypertension (%)	26
Hypercholesterolemia (%)	62
Antiplatelet drugs	91
β-blocker	62
Lipid-lowering agents	57

Optimal Standard Therapy

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

Primary end point: CV death, MI or cardiac arrest

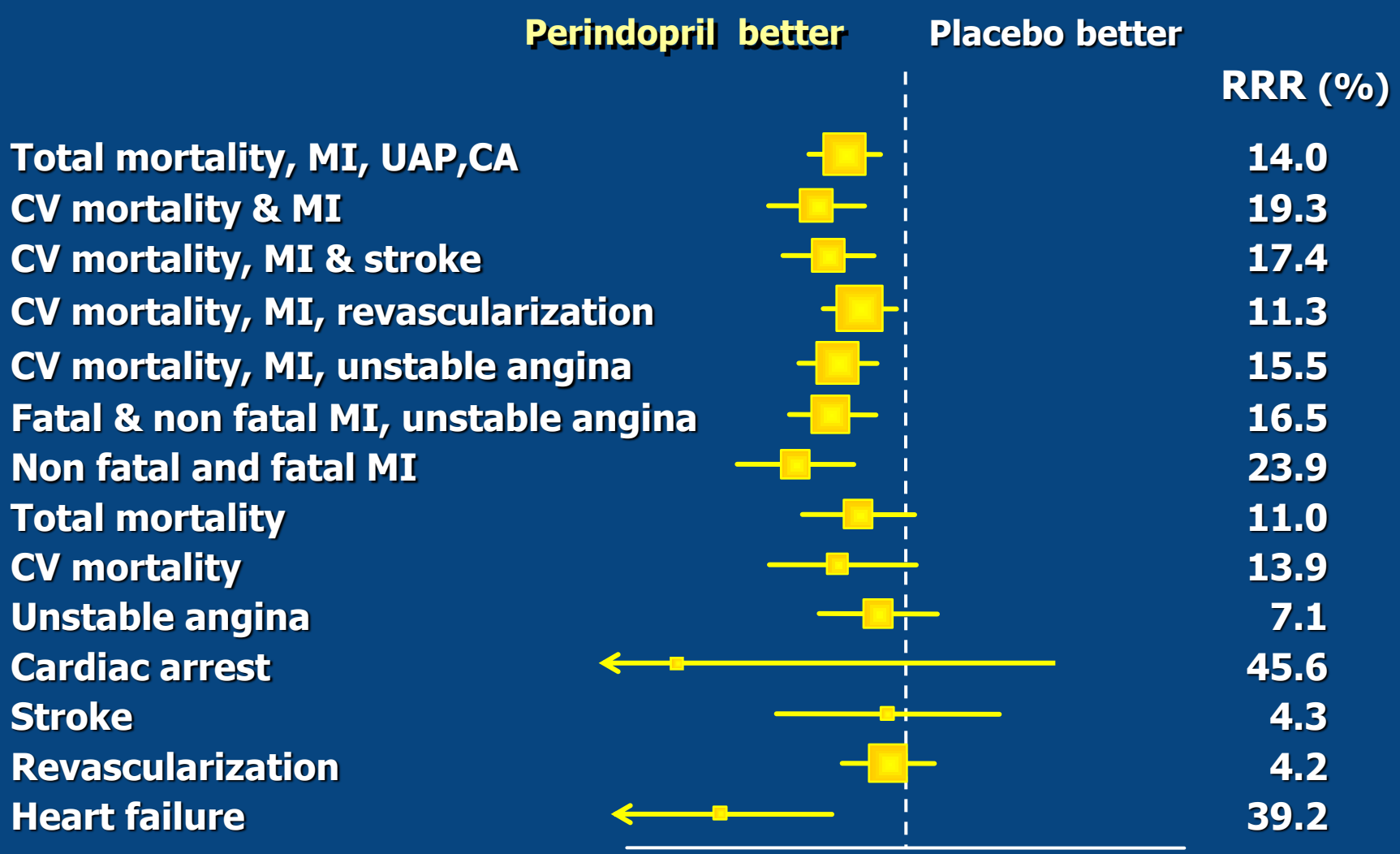
Coronary artery disease patients with normal LVEF



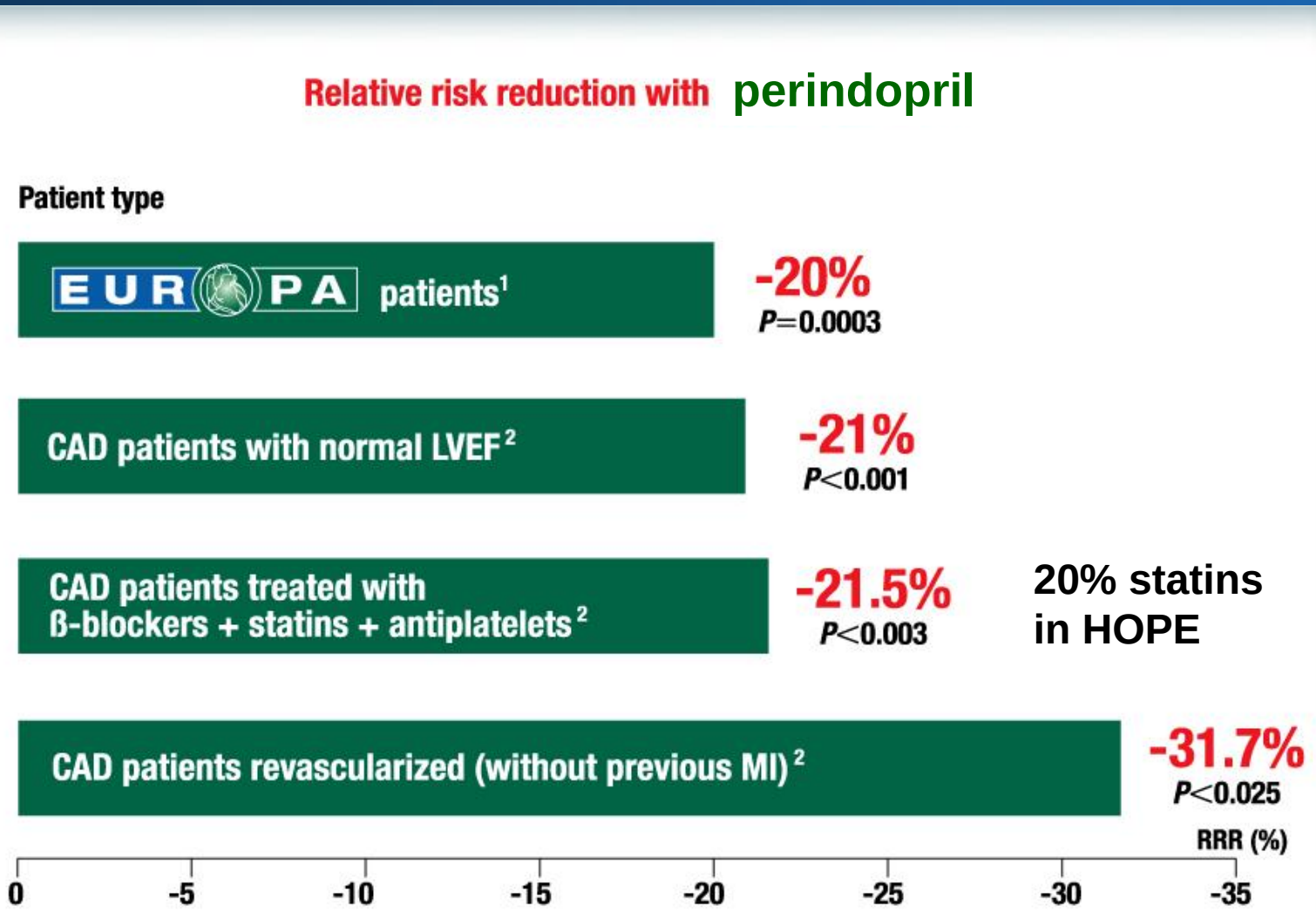
EUROPA Study Investigators *Lancet.* 2003;362:782-788.

Placebo annual event rate: 2.4%

Secondary endpoints

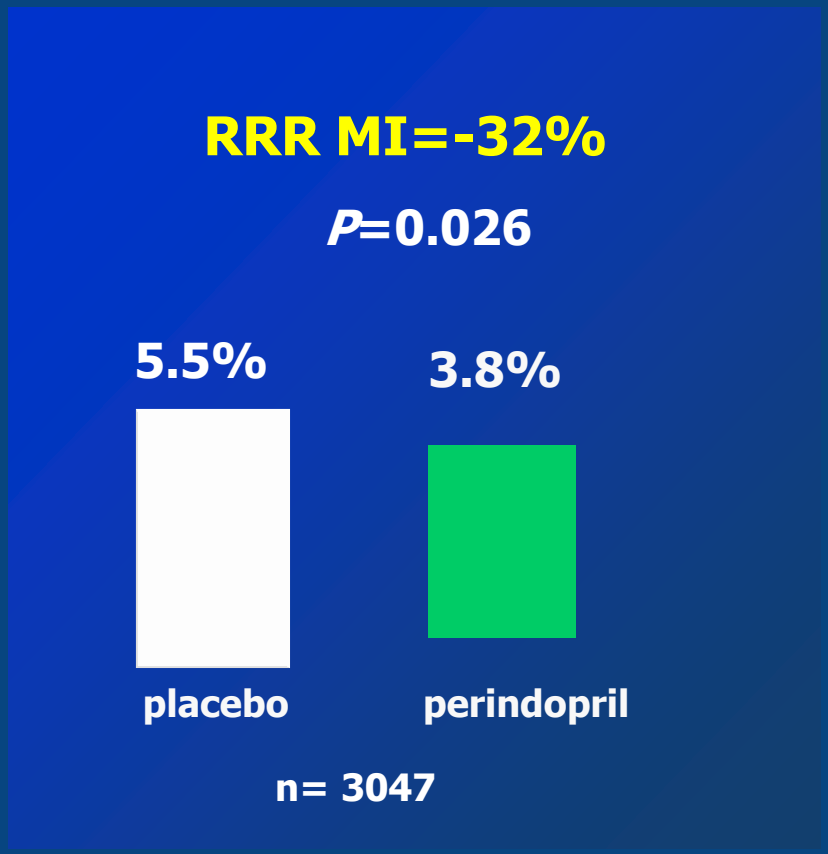


EUROPA Study Investigators. *Lancet.* 2003;362:782-788.

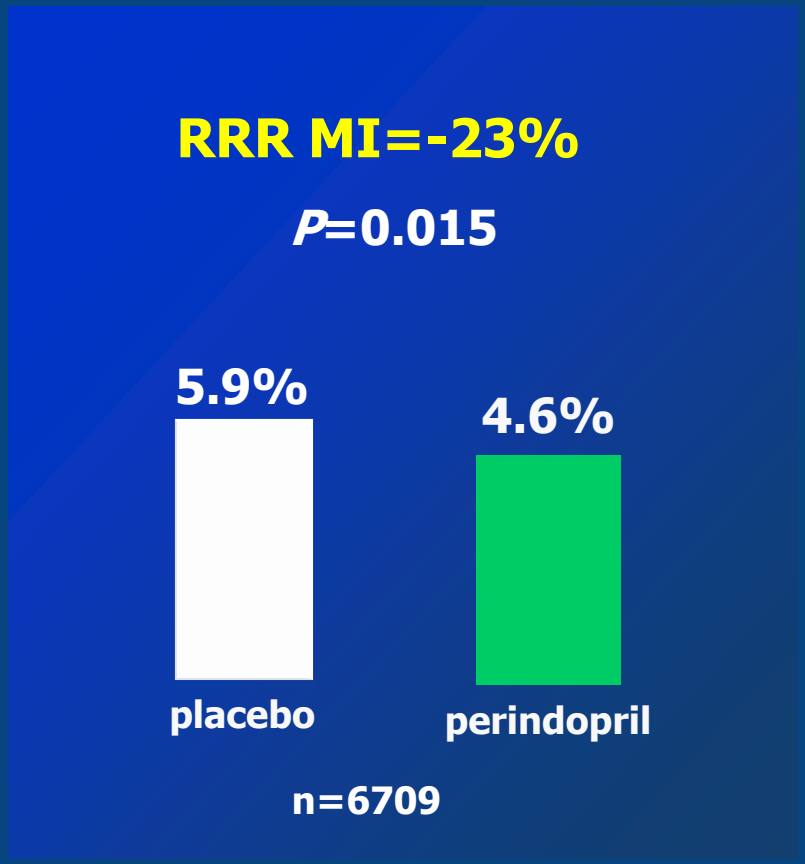

Relative risk reduction with perindopril
Patient type
EUROPA patients[1]
-20%
P=0.0003
CAD patients with normal LVEF[2]
-21%
P<0.001
CAD patients treated with ß-blockers + statins + antiplatelets[2]
-21.5%
P<0.003
20% statins in HOPE
CAD patients revascularized (without previous MI)[2]
-31.7%
P<0.025
RRR (%)
0
-5
-10
-15
-20
-25
-30
-35

perindopril decreases the risk of primary MI by 32% in revascularized CAD patients

Patients without previous MI



Patients with previous MI



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

Efficacy in reduction of cardiac events in CAD patients is neither shared by all the other ACEI

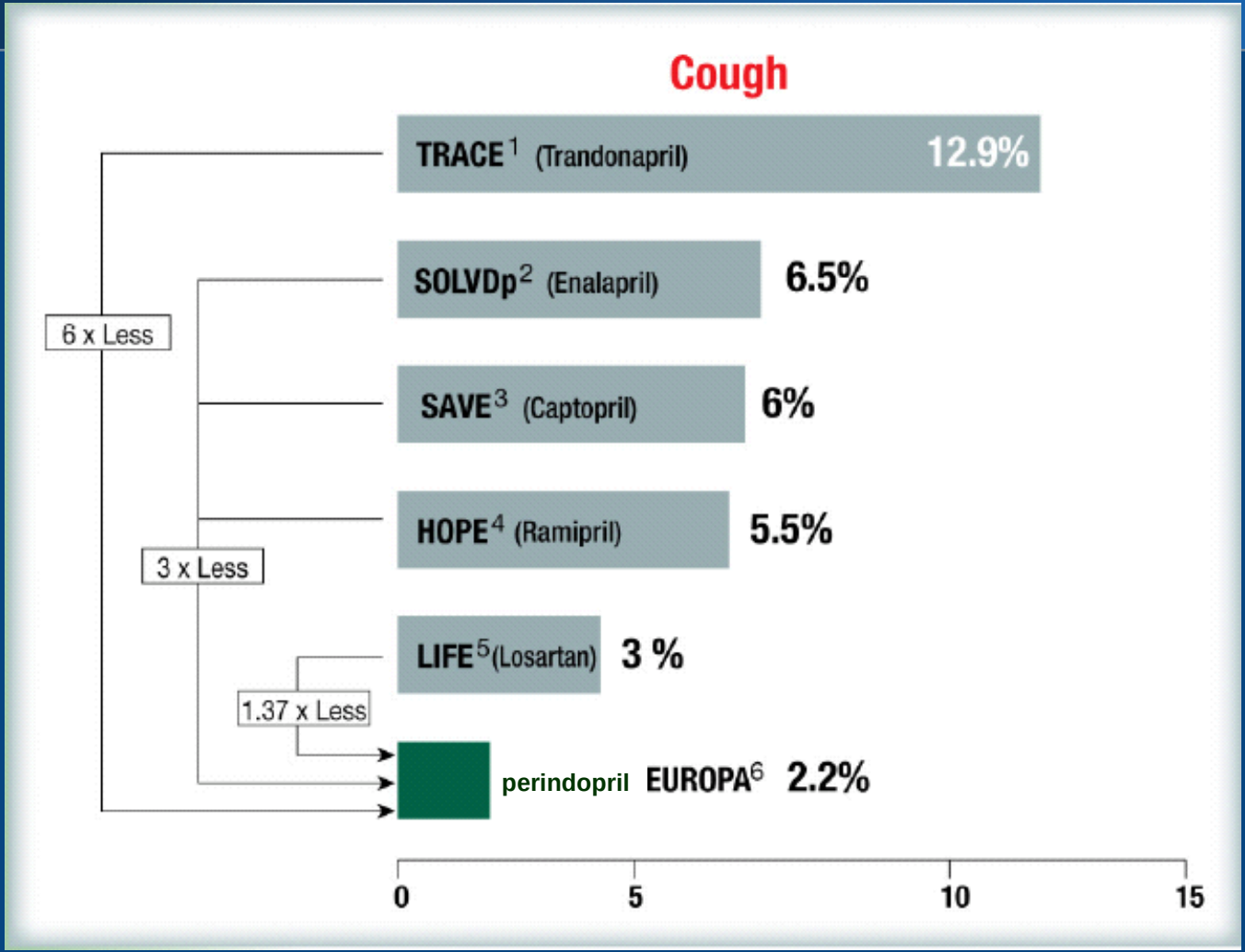
EUROPA	**perindopril**	**+**
HOPE	**ramipril**	**+**
PEACE	**trandolapril**	**-**
QUIET / IMAGINE	**quinapril**	**-**
CONSENSUS II	**enalapril**	**-**
GISSI-3	**lisinopril**	**-**

CAD patients Whatever the risk

High risk CAD patients

EUROPA Investigators.*Lancet*. 2003;362:782-8.
Pitt B et al. *Am J Cardiol*.2001;87:1058-63.
HOPE Study Investigators. *N Engl J Med.* 2000;342:145-53.
PEACE Trial Investigators. *N Engl J Med.* 2004;351:2058-68.

All ACEI do not produce similar cough !!



CONCLUSION

- Endothelium Dysfunction is the main contributor to CV mortality.
- Treatment of hypertension should address the global endothelium dysfunction.
- Evidence from large major clinical trial suggests that treatment with Perindopril blocks or reverses the progressive endothelial dysfunction along with lowering BP.