New approaches for Cardiovascular Protection

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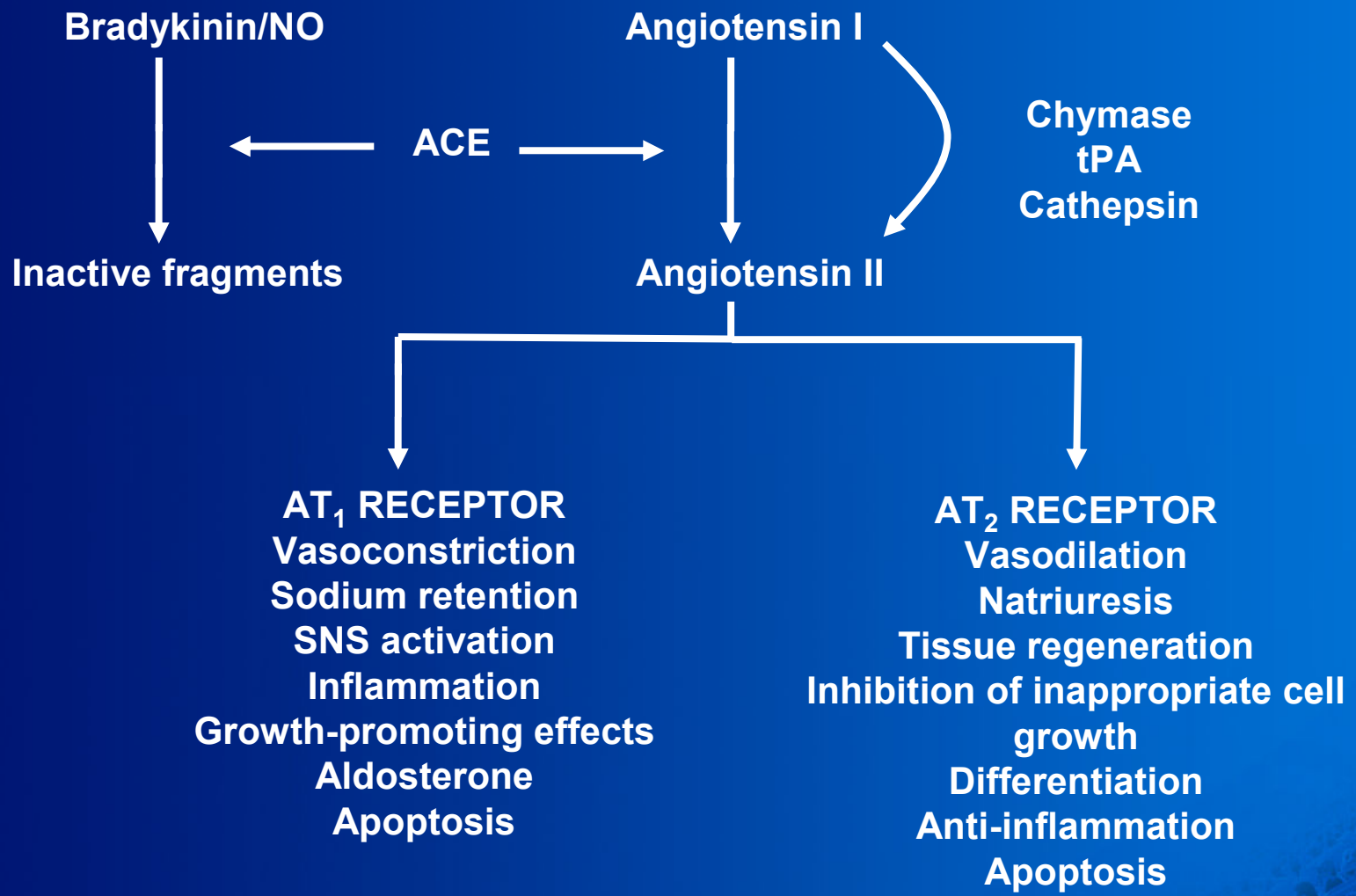
ONTARGET TELMISARTAN

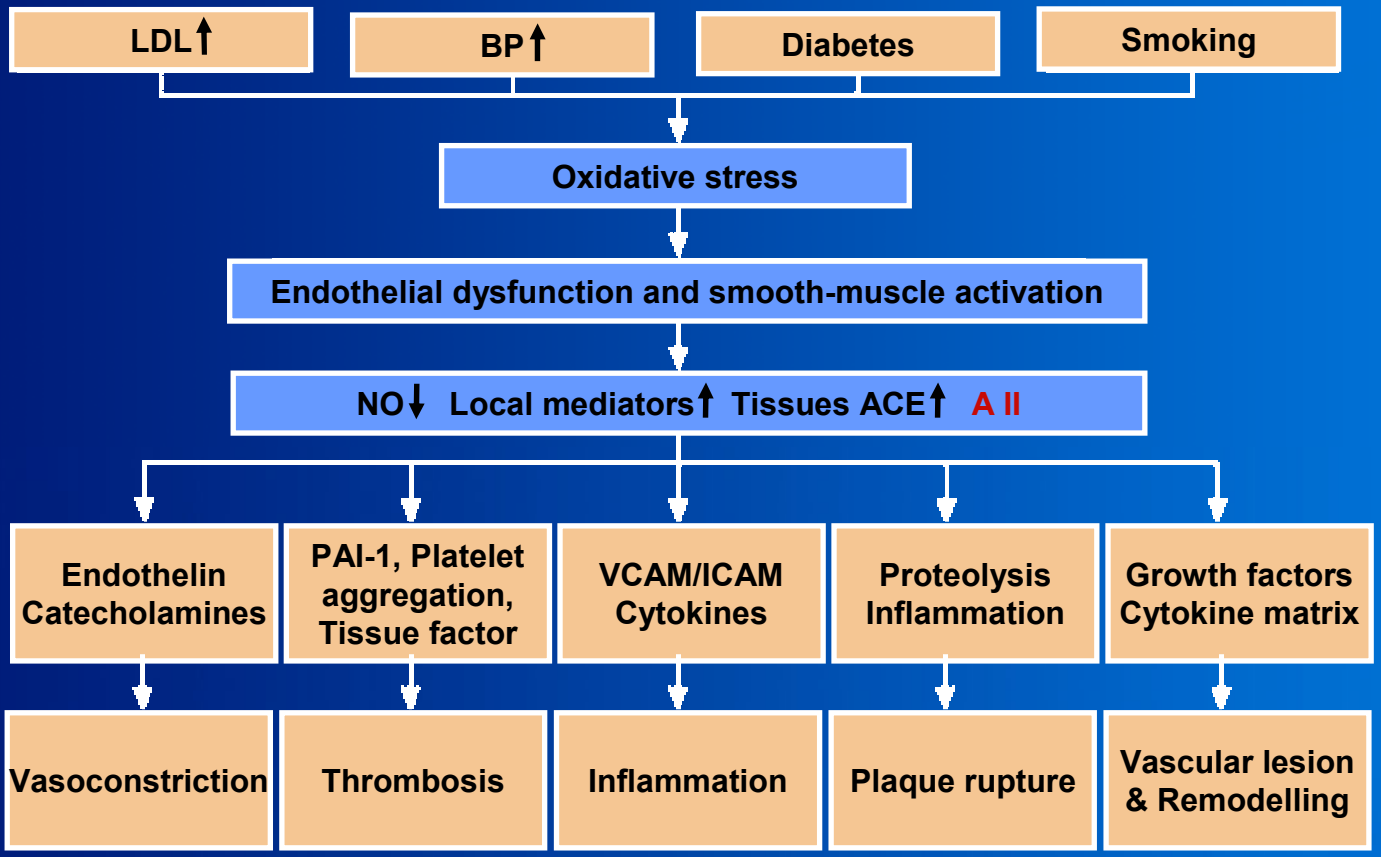
The renin–angiotensin system (RAS)



Hanon S., *et al.* J Renin Angiotensin Aldosterone Syst 2000;1:147–150; Chen R., *et al.* Hypertension 2003;42:542–547; Hurairah H., *et al.* Int J Clin Pract 2004;58:173–183; Steckelings U.M., *et al*. Peptides 2005;26:1401–1409

ONTARGET TELMISARTAN

Angiotensin II interaction with secondary mediators
Progression of CVD



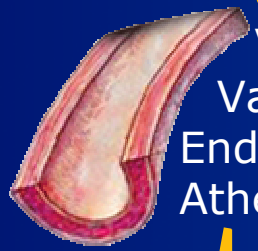
VCAM vascular cell adhesion molecule
ICAM intracellular adhesion molecule
NO nitric oxide
PAI-1 plasminogen activator inhibitor-1

Yusuf S., Am J Cardiol 2002;89(suppl):18A–26A

ONTARGET TELMISARTAN

Target-organ damage precedes clinical events

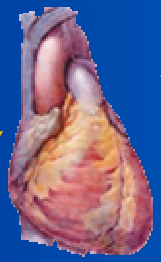
Risk factors: diabetes, obesity, smoking, age



Vasoconstriction
Vascular hypertrophy
Endothelial dysfunction
Atherosclerosis

Hypertension

Pro-thrombotic state

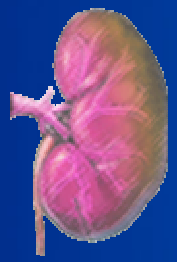


Apoptosis
LVH
Fibrosis

→ Arrhythmia
→ Heart failure
MI

Vascular disease

→ Stroke
→ Cognitive dysfunction



Decreased GFR
Proteinuria/albuminuria
Glomerulosclerosis

→ Renal failure

→ Death

Adapted from: Chung O. & Unger T., Am J Hypertens 1999;12:150S–156S

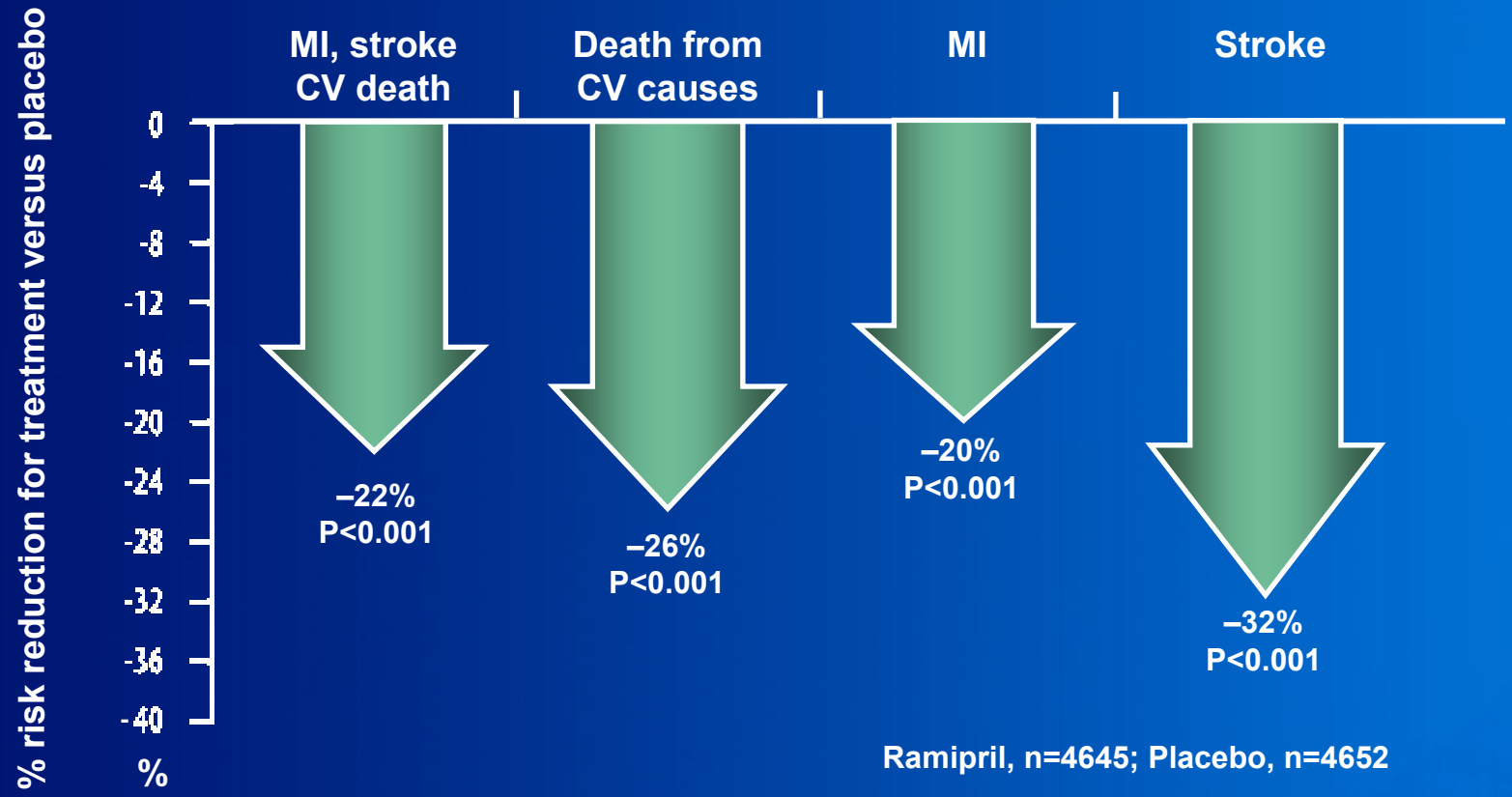
The Heart Outcomes Prevention Evaluation (HOPE) study

- *Heart Outcomes Prevention Evaluation (HOPE) was a landmark cardiovascular outcomes study*
- *Risk for MI, stroke or death from cardiovascular causes was compared between an ACE inhibitor (ramipril) and placebo*
- *Risk was determined as age >55 years, in conjunction with manifest atherosclerotic target-organ disease (heart, peripheral arteries, brain) or by the presence of diabetes, plus at least one other risk factor*
- *To avoid being just another hypertension or heart-failure trial, patients with heart failure or a known ejection fraction of <40% were excluded, as were patients with uncontrolled hypertension*

Yusuf S., *et al*. N Engl J Med 2000;342:145–153

ONTARGET TELMISARTAN

HOPE
Primary outcomes

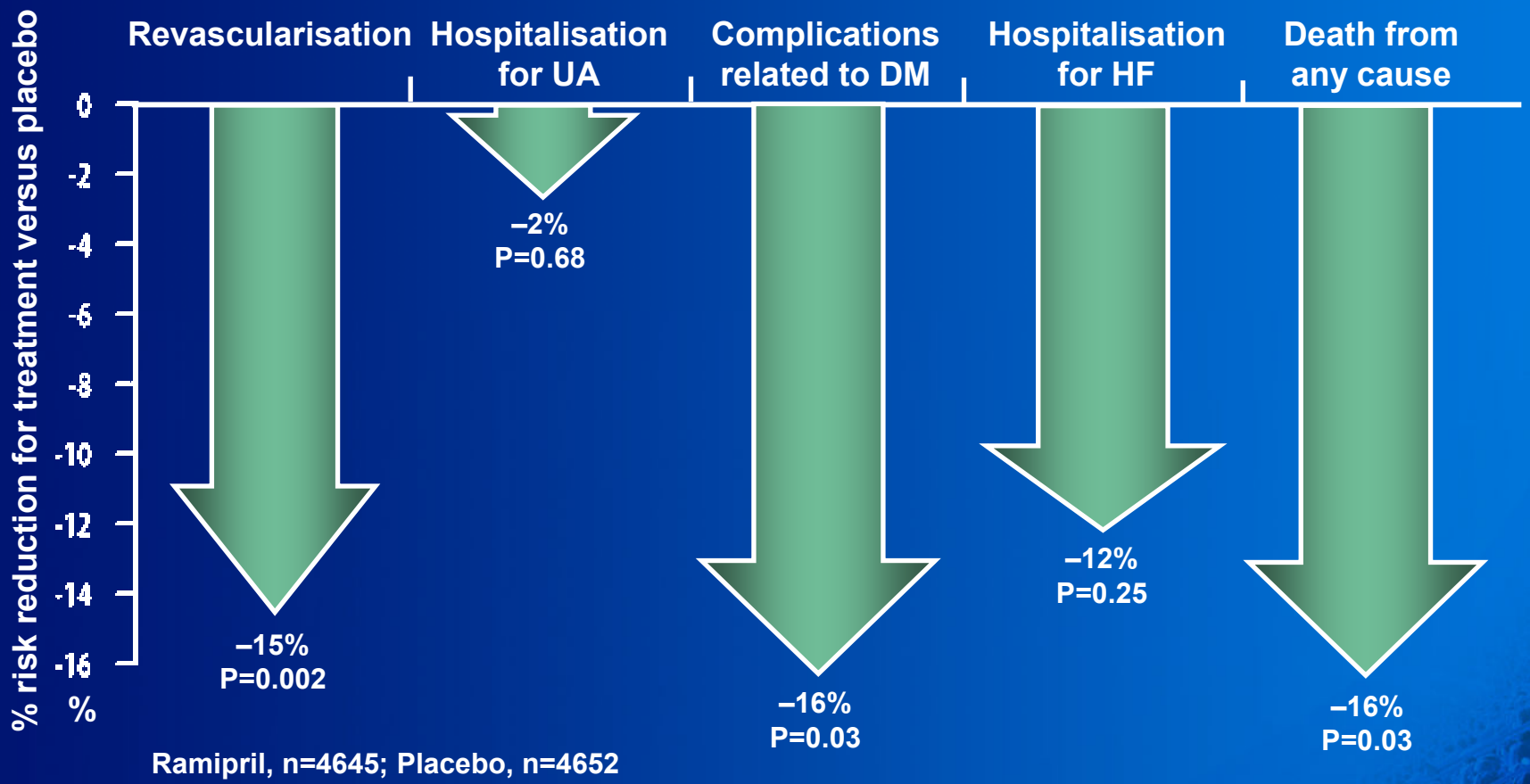


Ramipril, n=4645; Placebo, n=4652

Yusuf S., *et al*. N Engl J Med 2000;342:145–153

ONTARGET TELMISARTAN

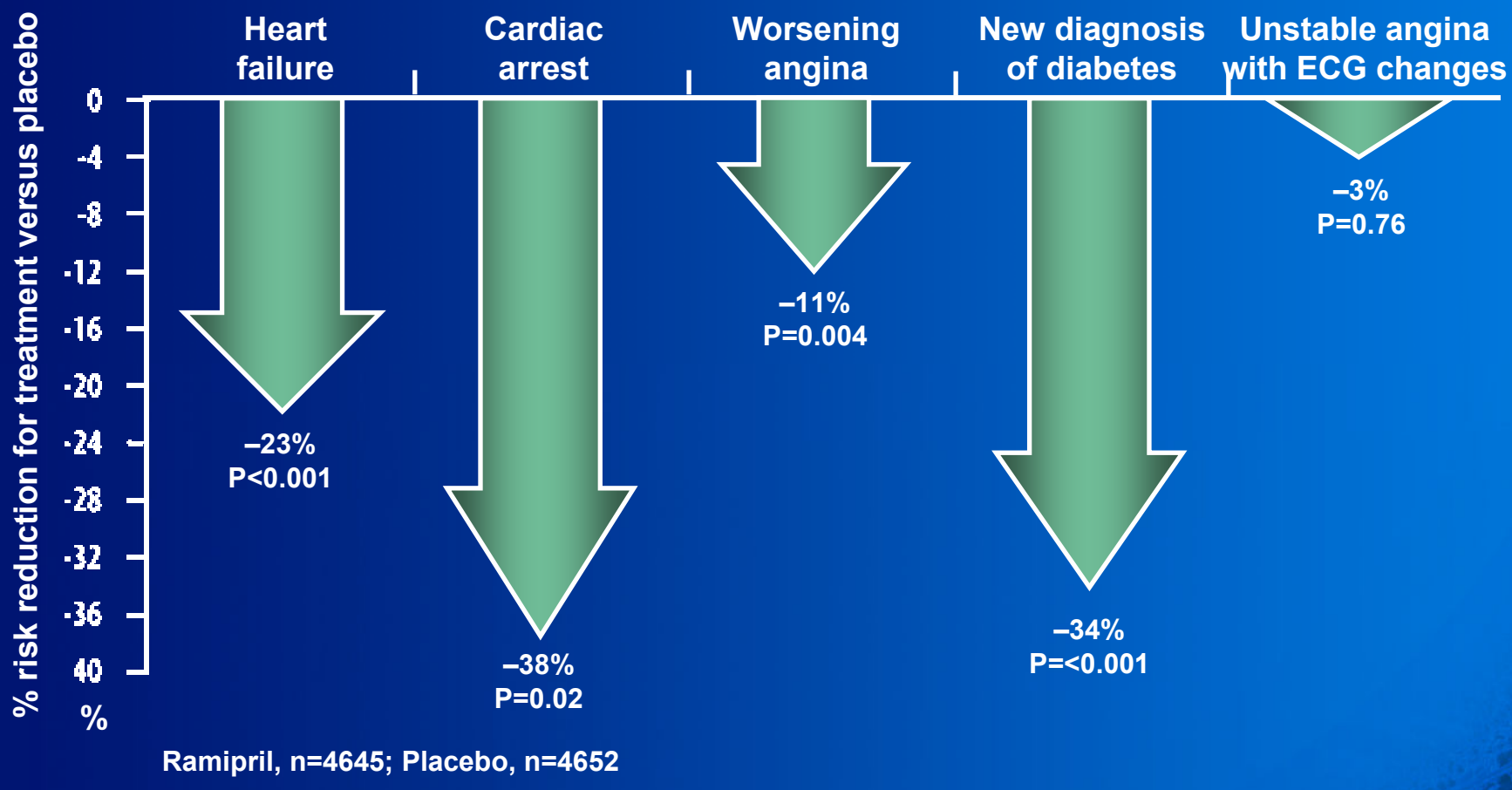
HOPE
Secondary outcomes



Yusuf S., *et al*. N Engl J Med 2000;342:145–153

ONTARGET TELMISARTAN

HOPE
Other outcomes



Ramipril, n=4645; Placebo, n=4652

Yusuf S., *et al*. N Engl J Med 2000;342:145–153

ONTARGET TELMISARTAN

What did we learn from HOPE?

- *Use of an ACE inhibitor is beneficial in a broad range of patients who are at a high risk of CV events*
- *Treatment with ramipril reduced the risk of myocardial infarction, stroke, CV death and the risk of complications related to diabetes*
- *There was a benefit of ACE treatment beyond simple blood pressure reduction, as hypertensive patients were already taking effective treatments and around 50% were not hypertensive at baseline*

Yusuf S., *et al*. N Engl J Med 2000;342:145–153; Mathew J., *et al*. Circulation 2001;104:1615–1621; Zimmermann M. & Unger,T., Expert Opin Pharmacother 2004;5:1201–1208

ONTARGET rationale
Blocking the RAS with ramipril, telmisartan or the combination for CVP

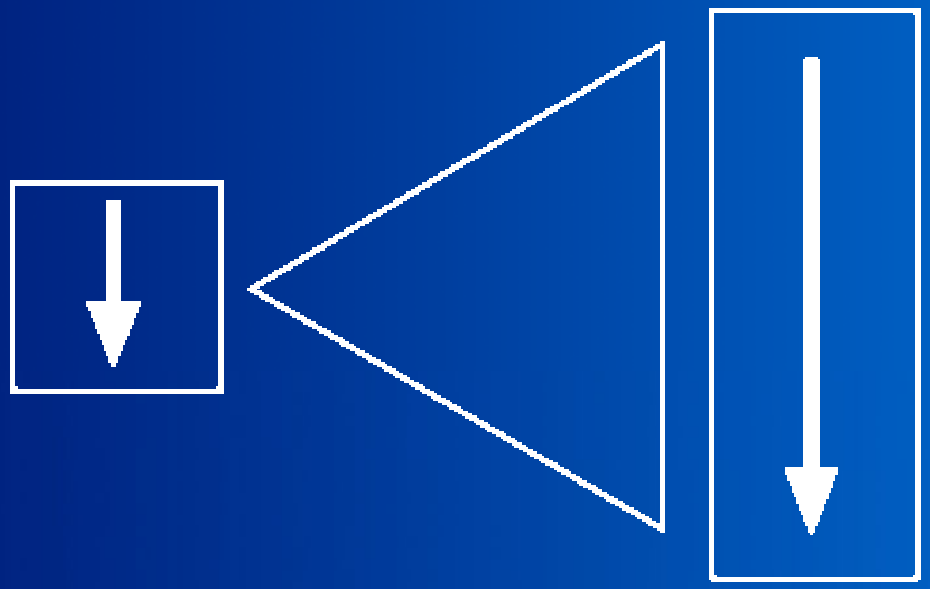
- *HOPE established the CV benefits of ACE inhibition with ramipril*
- *After HOPE, some questions remained open regarding the cardiovascular benefits of different ways to block the RAS*
  - *Do the different mechanisms of ARBs and ACE inhibitors translate to different clinical effects?*
  - *Would dual therapy provide additional benefit, especially in terms of cardiovascular protection (CVP)?*
  - *Which ARB could match the CV benefits shown in HOPE and elucidate the additional benefits of dual RAS blockade in CVP?*

Sica D.A., J Clin Hypertens 2007;9:78–85

ONTARGET TELMISARTAN

Is there conclusive evidence of CVP beyond BP reduction?

Lowering blood pressure reduces cardiovascular risk
Small SBP reductions yield significant benefit



- *Meta-analysis of 61 prospective, observational studies*
- *One million adults, 12.7 million person-years*

Adapted from Lewington S., *et al.* Lancet. 2002;360:1903–1913

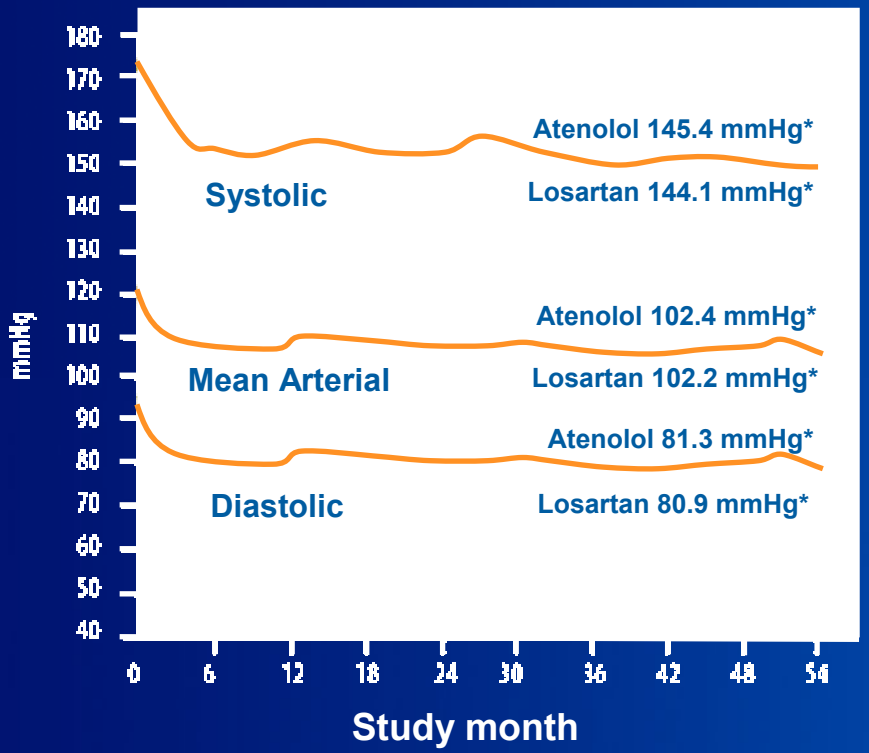
ONTARGET TELMISARTAN

Effect of ACE inhibition benefits beyond BP lowering?

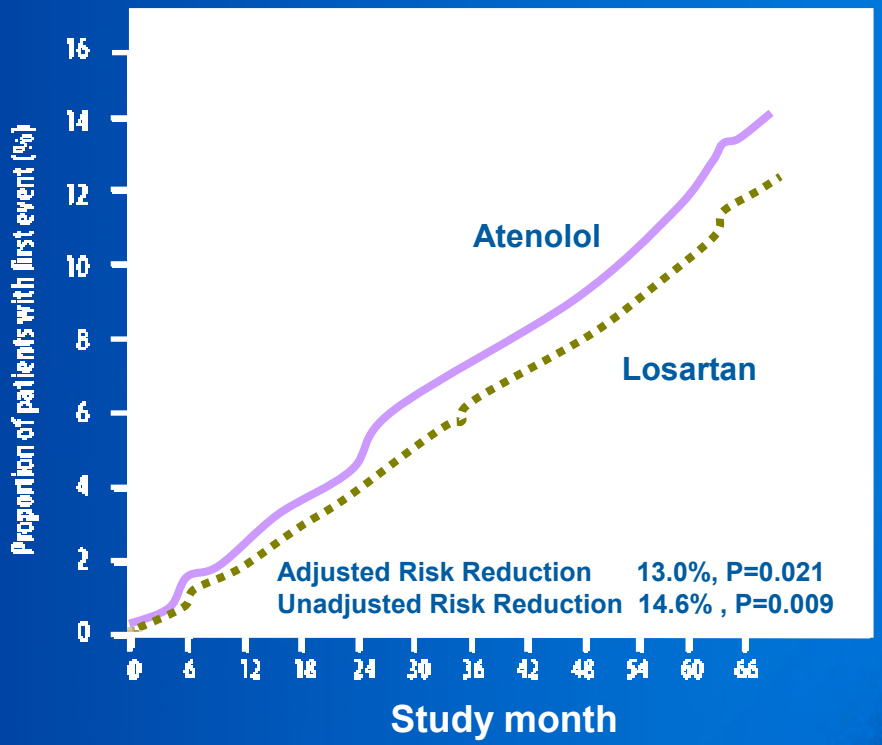
- *HOPE*
  - *RRR 22% in favour of ramipril*
  - *SBP/DBP diff. –3/–2 mmHg vs placebo*
  - *24 ABPM showed larger differences 12/5 mmHg*
- *EUROPA*
  - *RRR 20% in favour of Perindopril*
  - *SBP/DBP diff. –5/–2 mmHg vs placebo*
- *PROGRESS*
  - *RRR 5% with perindopril alone (NS)*
  - *SBP/DBP diff. –5/–3 mmHg vs placebo*
- *PEACE*
  - *RRR 4% with trandolapril (NS)*
  - *SBP/DBP diff. –3/–1.2 mmHg vs placebo*
- *CAMELOT*
  - *RRR 19% in favour of amlodipine vs enalapril (NS)*
  - *SBP/DBP diff. enalapril vs amlodipine +0.1/–0.1 mmHg*

Yusuf S., *et al*. N Engl J Med 2000;342:145–153; Svensson P., *et al*. Hypertension 2001;38: E28–E32; Fox K.M., Lancet 2003;362:782–788; The PEACE Trial Investigators. N Engl J Med 2004;351:2058–2068; Nissen S.E., *et al.* JAMA 2004;292:2217–2225; PROGRESS Collaborative Group. Lancet 2001;358:1033–1041

Superior results in the primary endpoint with the ARB at comparable levels of BP reduction



Composite of CV death, stroke and MI



	MONTH	0	6	12	18	24	30	36	42	48	54	60	66
Number at risk	Losartan	4605	4524	4160	4392	4312	4247	4189	4112	4047	3897	1889	901
	Atenolol	4588	4494	4114	4349	4289	4205	4135	4056	4992	3821	1854	876

Dahlöf B., *et al.* Lancet 2002;359:995–1003

ONTARGET TELMISARTAN

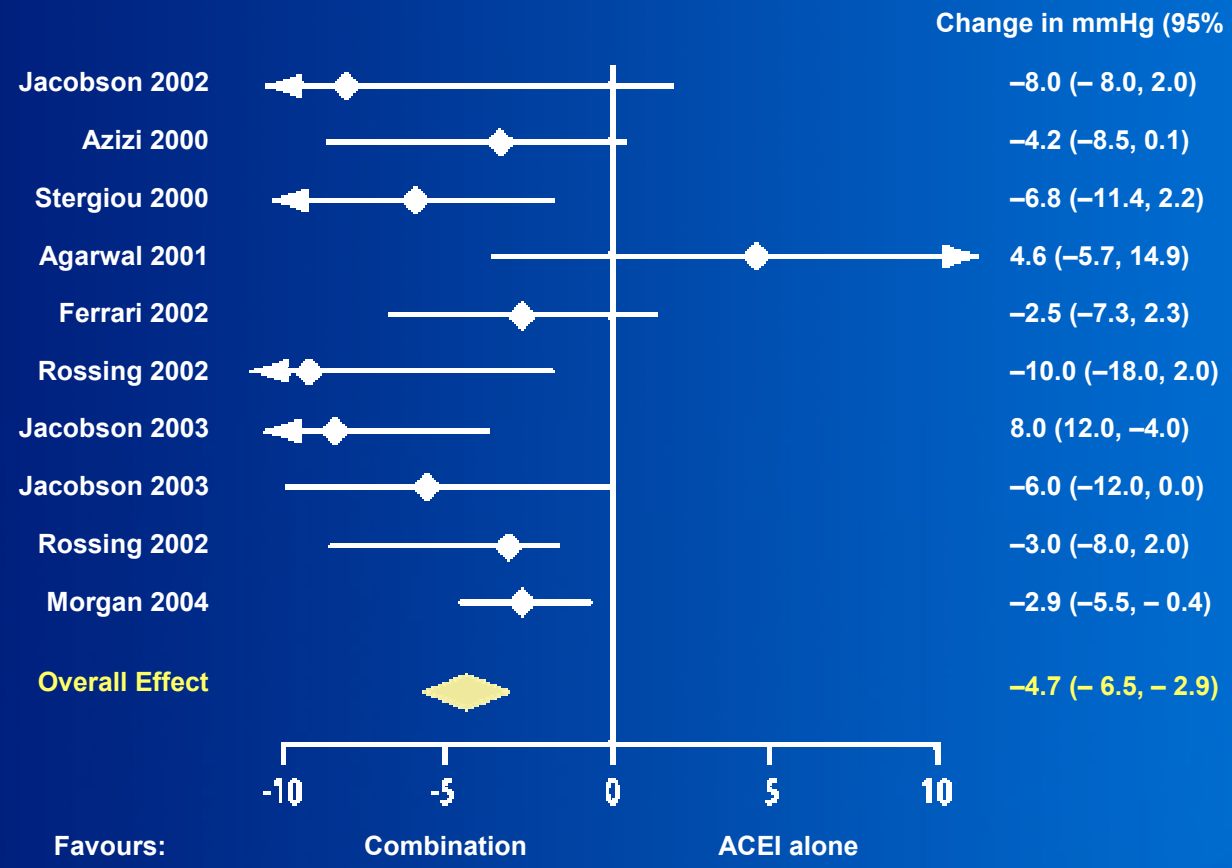
ARB and ACEI: Is there a role for combination?

Evaluation of combined ACE inhibitor/ ARB therapy

- *Blood pressure reduction*
- *Renal protection*
- *Cardiac effects*
- *Fatal and non-fatal cardiovascular outcomes*

ONTARGET TELMISARTAN

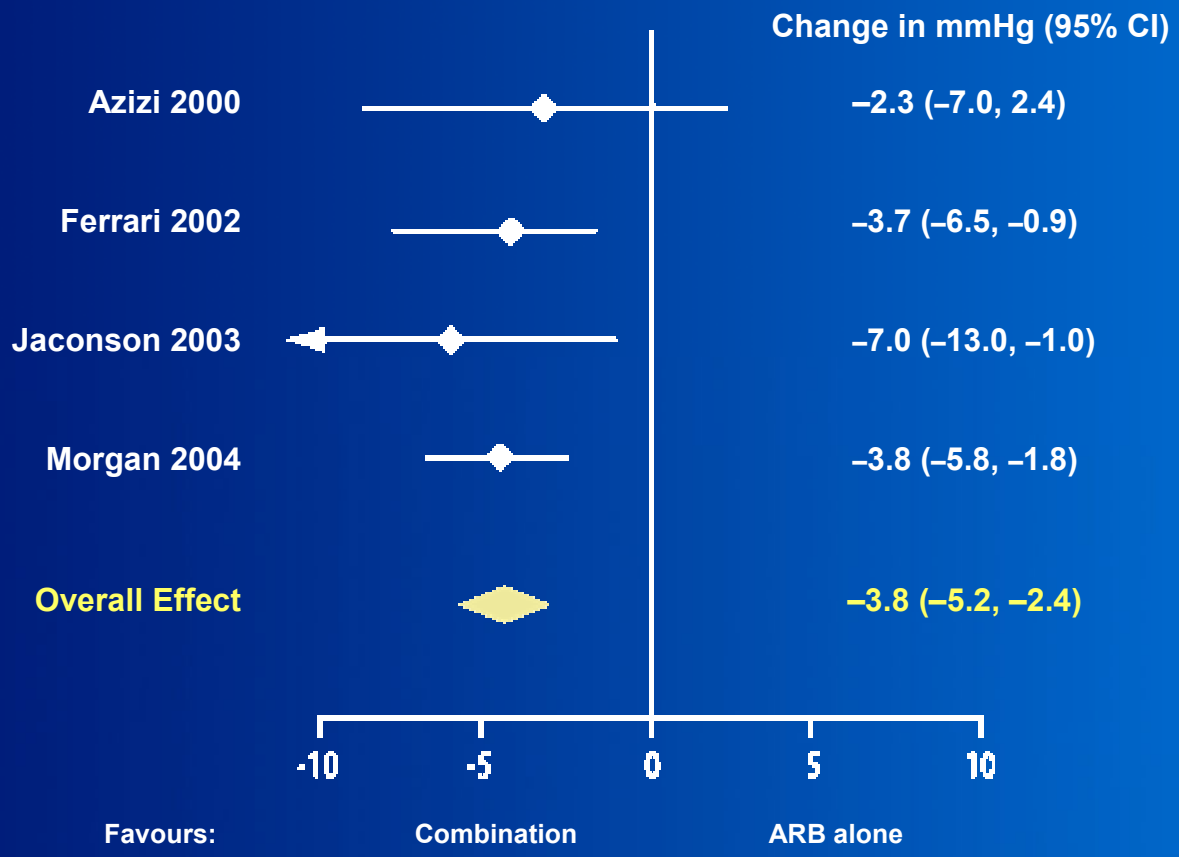
Meta-analysis of ACEI–ARB combination versus ACEI alone for ambulatory SBP



Doulton T.W., *et al*. Hypertension 2005;45:880–886

ONTARGET TELMISARTAN

Meta-analysis of ACEI–ARB combination vs ARB alone for ambulatory SBP

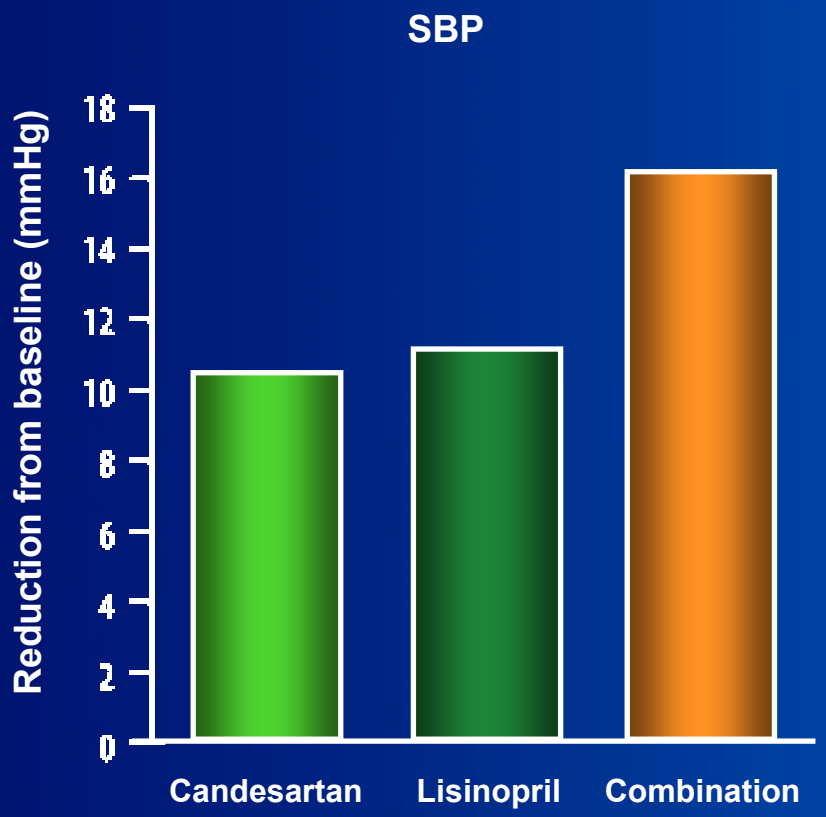


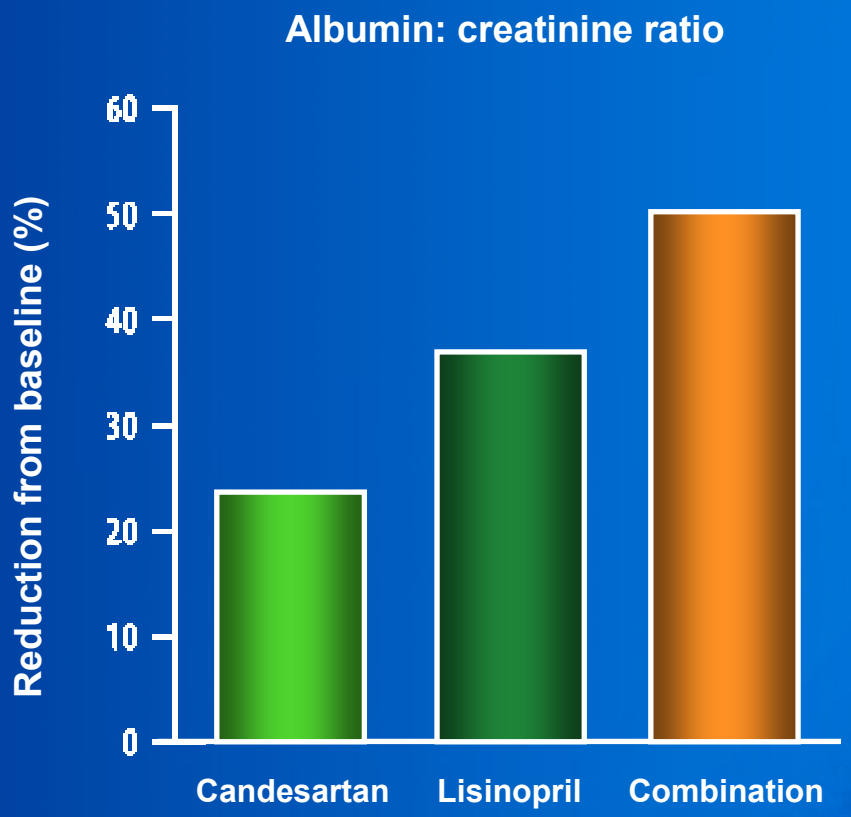
Doulton T.W., *et al*. Hypertension 2005;45:880–886

ONTARGET TELMISARTAN

Combination therapy provides additive benefit in proteinuria – CALM study

<u>But</u> differences in BP

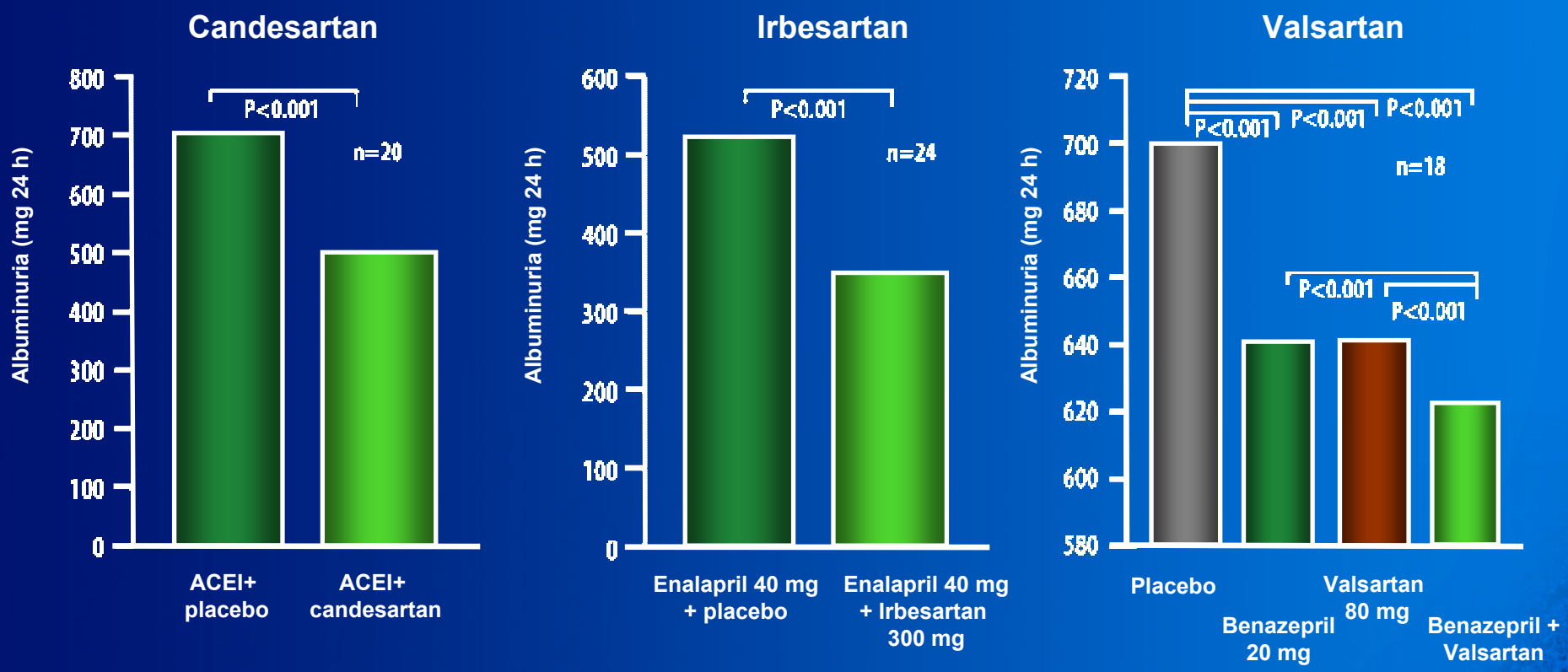




Mogensen C.E., *et al*. *BMJ* 2000;321:1440–1444

ONTARGET TELMISARTAN

Renoprotective effects of add-on ARB to ACEI in diabetic nephropathy in small trials

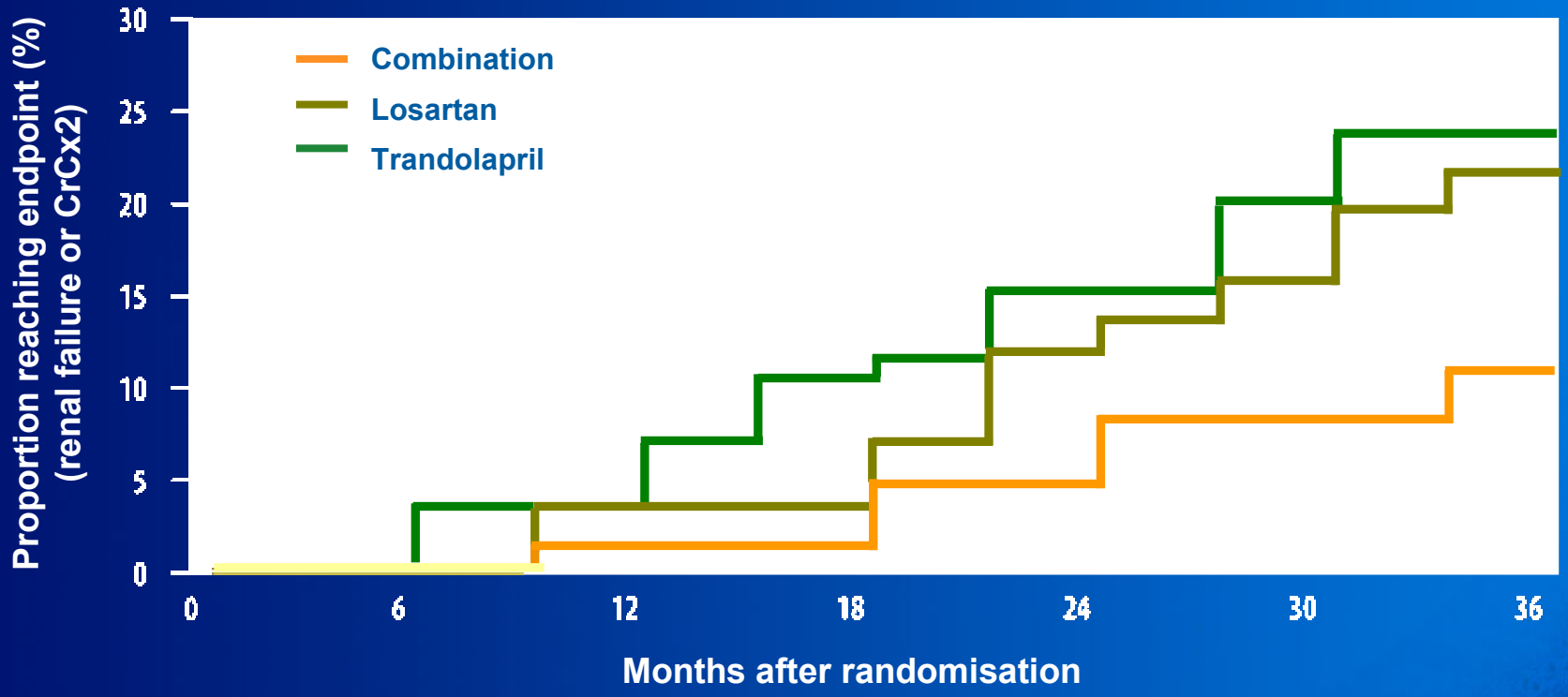


Jacobsen P., *et al*. J Am Soc Nephrol 2003;14:992–999; Rossing K., *et al*. Diabetes Care 2003;26:2268–2274; Jacobsen P., *et al.* Kidney Int 2003;63:1874–1880

ONTARGET TELMISARTAN

Combination ARB/ACEI therapy reduces risk of renal failure beyond changes in BP

COOPERATE



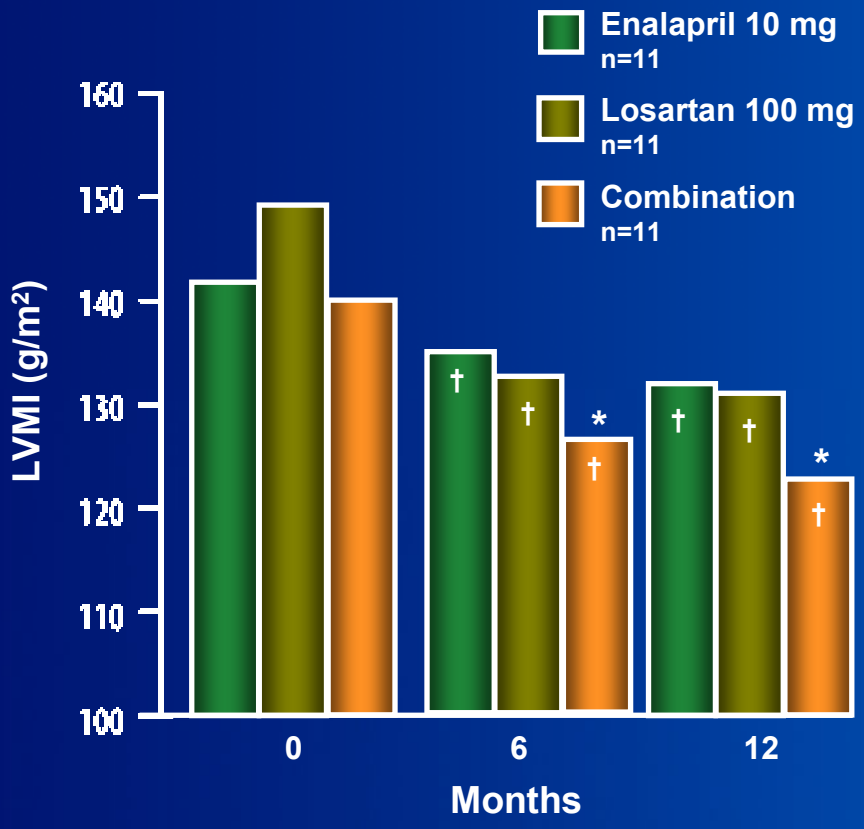
P = 0.018 combination vs trandolapril

P= 0.016 vs lorsartan

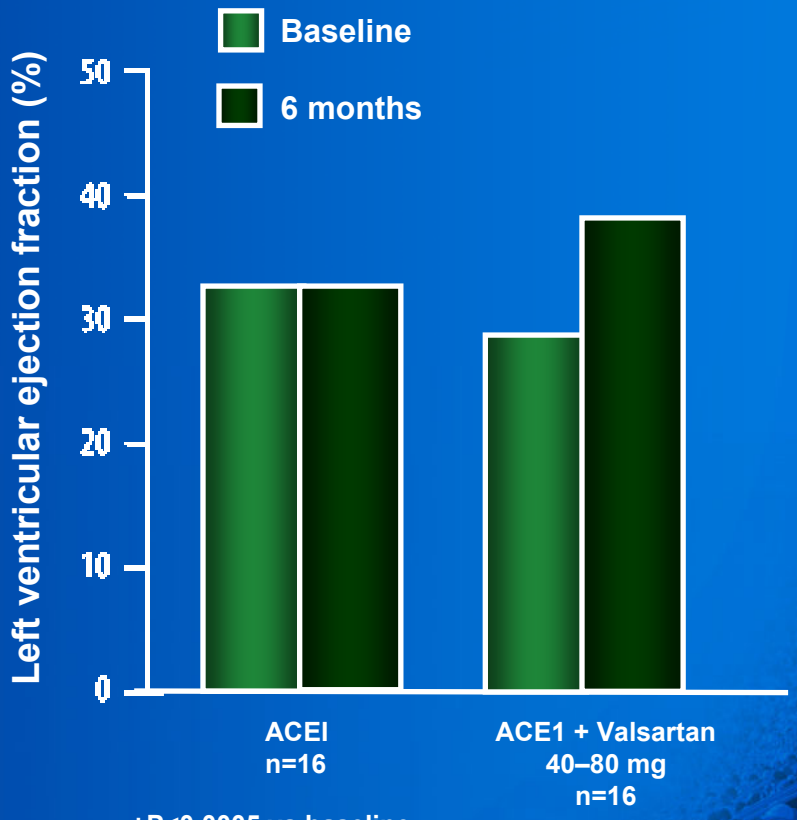
Nakao N., *et al*. Lancet 2003;361:117–124

ONTARGET TELMISARTAN

Add-on ARB to ACEI on LVM and function



+P<0.05 vs baseline
*P<0.05 vs monotherapies

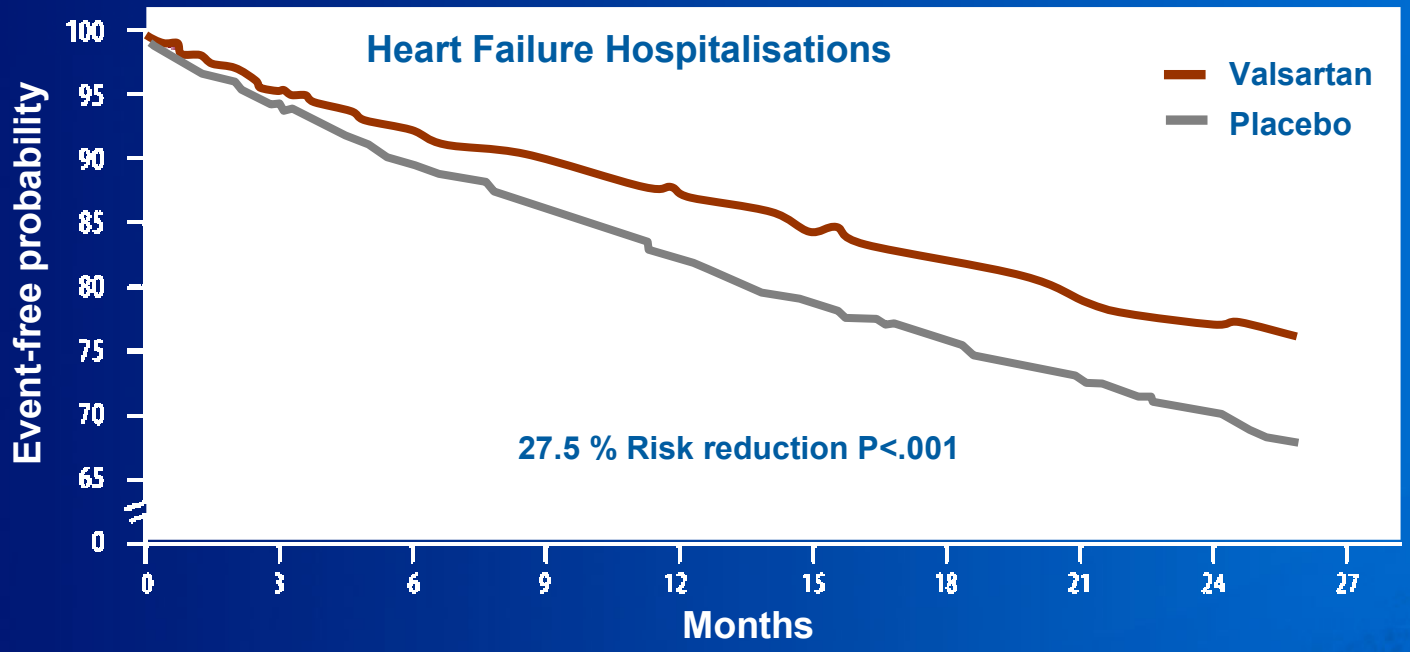


+P<0.0005 vs baseline

Suzuki H., *et al*. Ther Apher Dial 2004;8:320–327; Kasama S., *et al*. J Nucl Med 2003;44:884–890

Addition of Valsartan to ACE inhibition
Val-HeFT trial

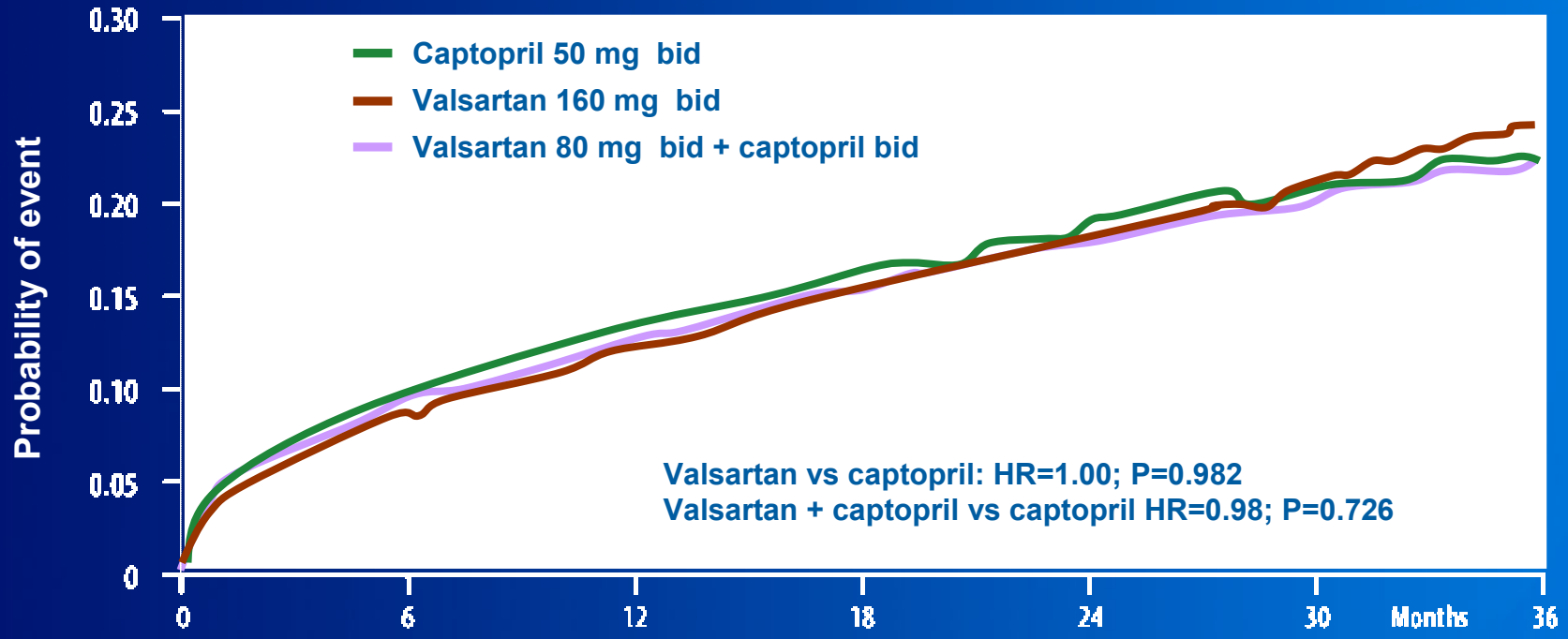
- *Valsartan 160 mg bid versus placebo on top of background therapy*
- *Almost 93% of patients were on ACE inhibitor therapy*
- *No difference in mortality between valsartan and placebo*
- *Valsartan reduced combined all-cause morbidity by 13.2% (P=0.009), mainly driven by reduced time to first HF hospitalisation by 27.5% (P<0.001)*



Cohn J.N., *et al*. N Engl J Med. 2001;345:1667–1675

ONTARGET TELMISARTAN

VALIANT: Effects of valsartan, captopril or their combination on all-cause mortality

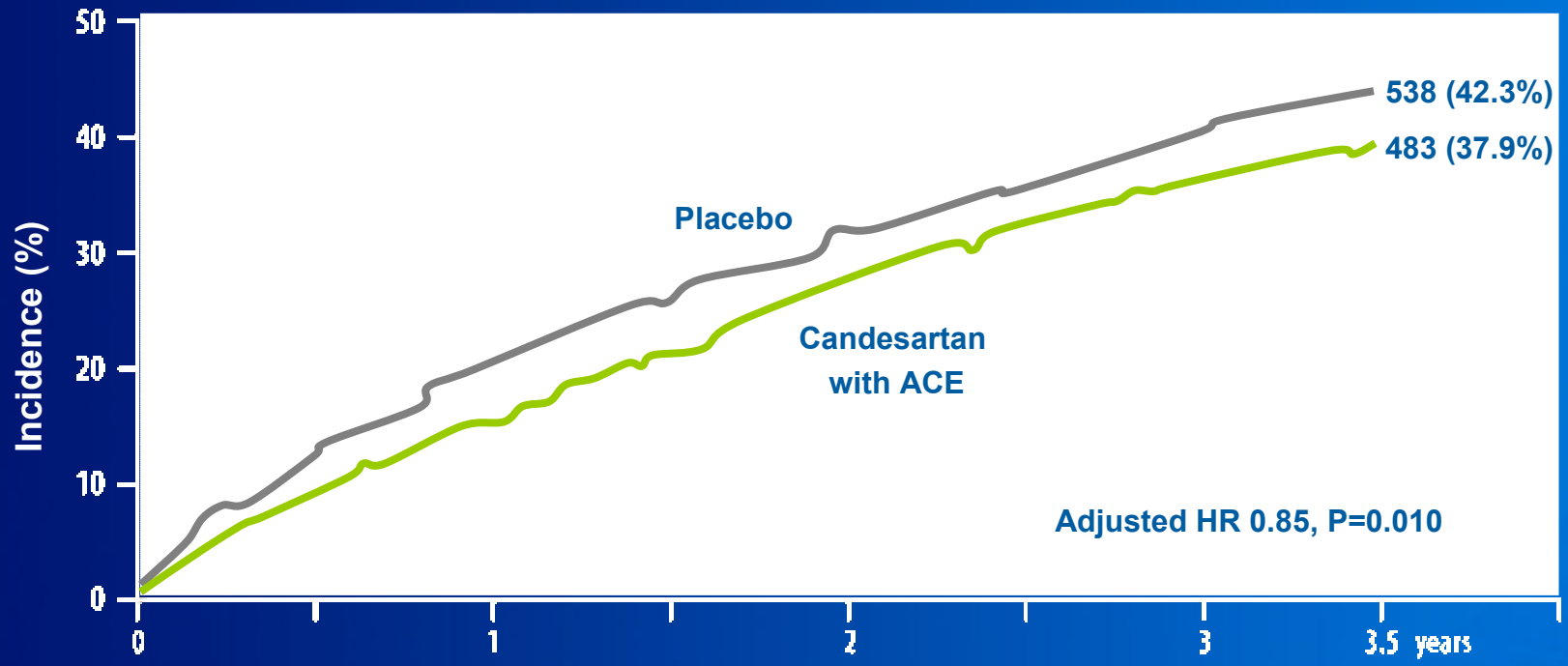


Captopril	4909	4428	4241	4018	2635	1432	364
Valsartan	4909	4464	4272	4007	2648	1437	357
Valsartan + Cap	4885	4414	4265	3994	2648	1435	382

Pfeffer M.A., *et al*. N Engl J Med. 2003;349:1893–1906

ONTARGET TELMISARTAN

CHARM-added: Addition of ARB to ACEI reduces risk of CV death or CHF hospitalisation in patients with CHF (class II-IV)

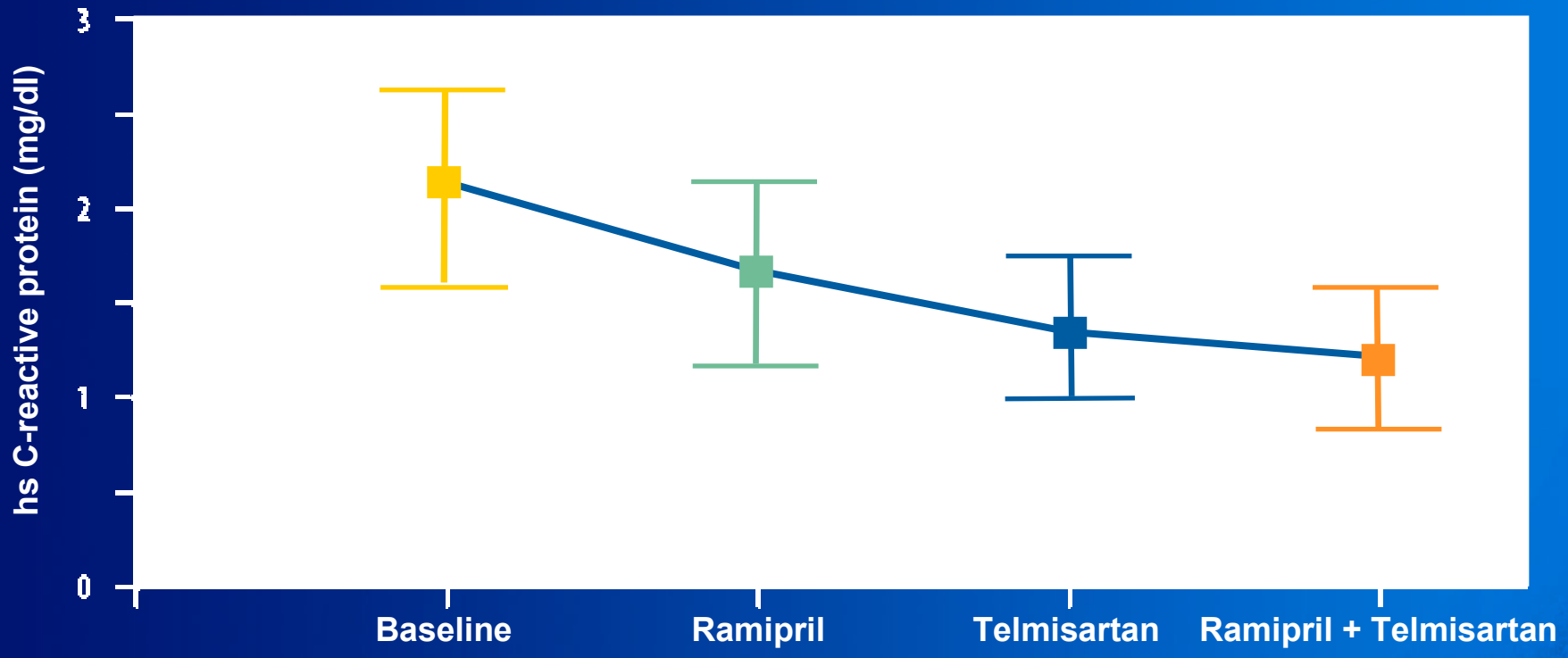


McMurray J.J., *et al*. Lancet 2003;362:767–771

Evaluation of combined ACE inhibitor/ ARB therapy

- *Blood pressure reduction*
  - *Some evidence for additive BP-lowering effects*
- *Renal protection*
  - *Some evidence in small trials for the additive beneficial effects on renal protection and proteinuria reduction*
- *Cardiac effects*
  - *Evidence for additive benefits in heart failure and LVH*
- *Fatal and non-fatal cardiovascular outcomes*
  - *Valiant and Val-HeFT have failed to show reductions in CV mortality with valsartan in addition to ACE inhibitors*
  - *In the Val-HeFT trial benefits come mainly from reduction in hospitalisations for heart failure*
  - *CHARM-added showed reductions in CV mortality with candesartan in addition to ACE inhibitors*

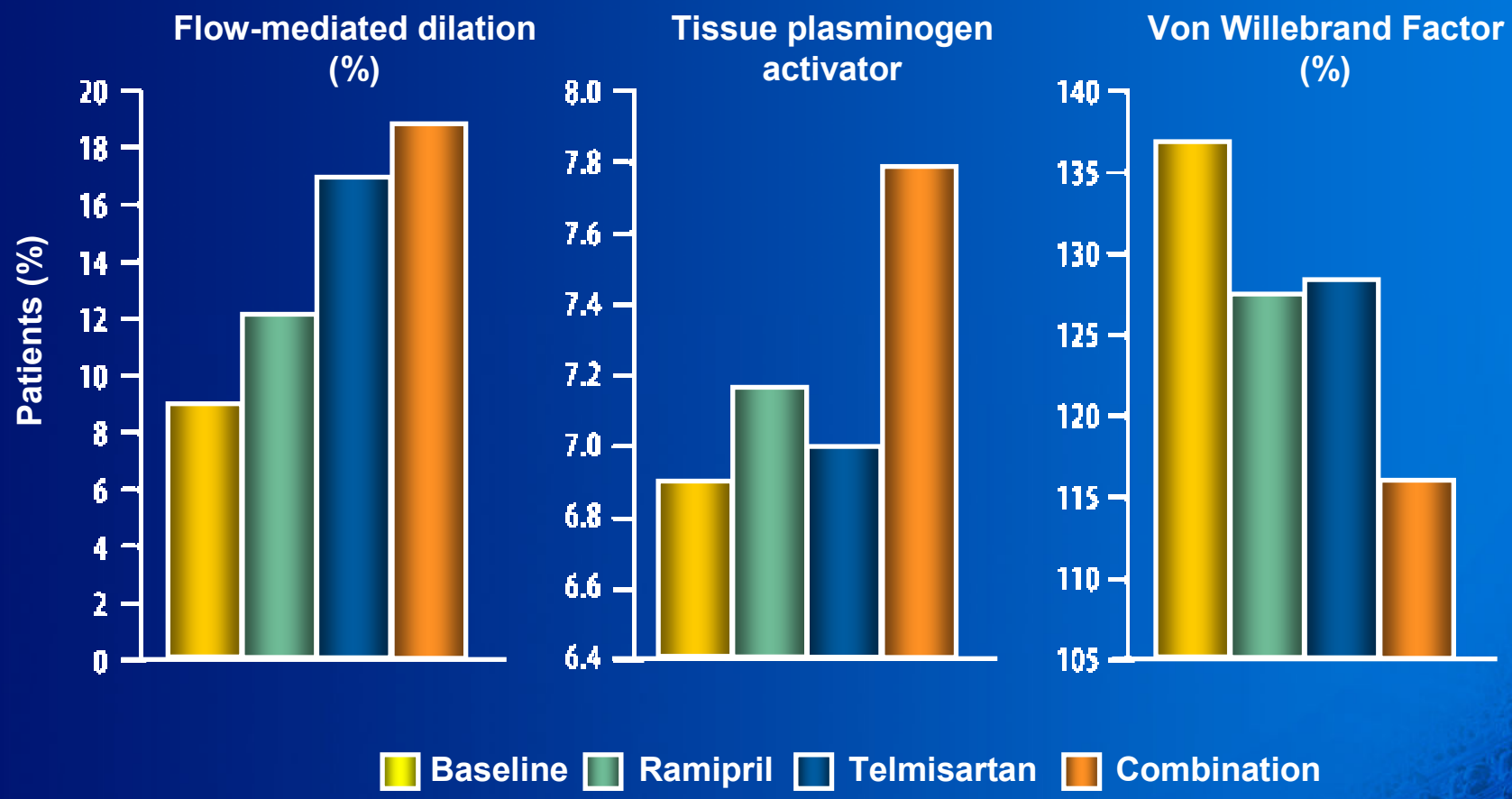
Effect of telmisartan, ramipril and the combination on inflammation (hs-CRP)



Koulouris S., *et al*. Am J Cardiol 2005;95:1386–1388

ONTARGET TELMISARTAN

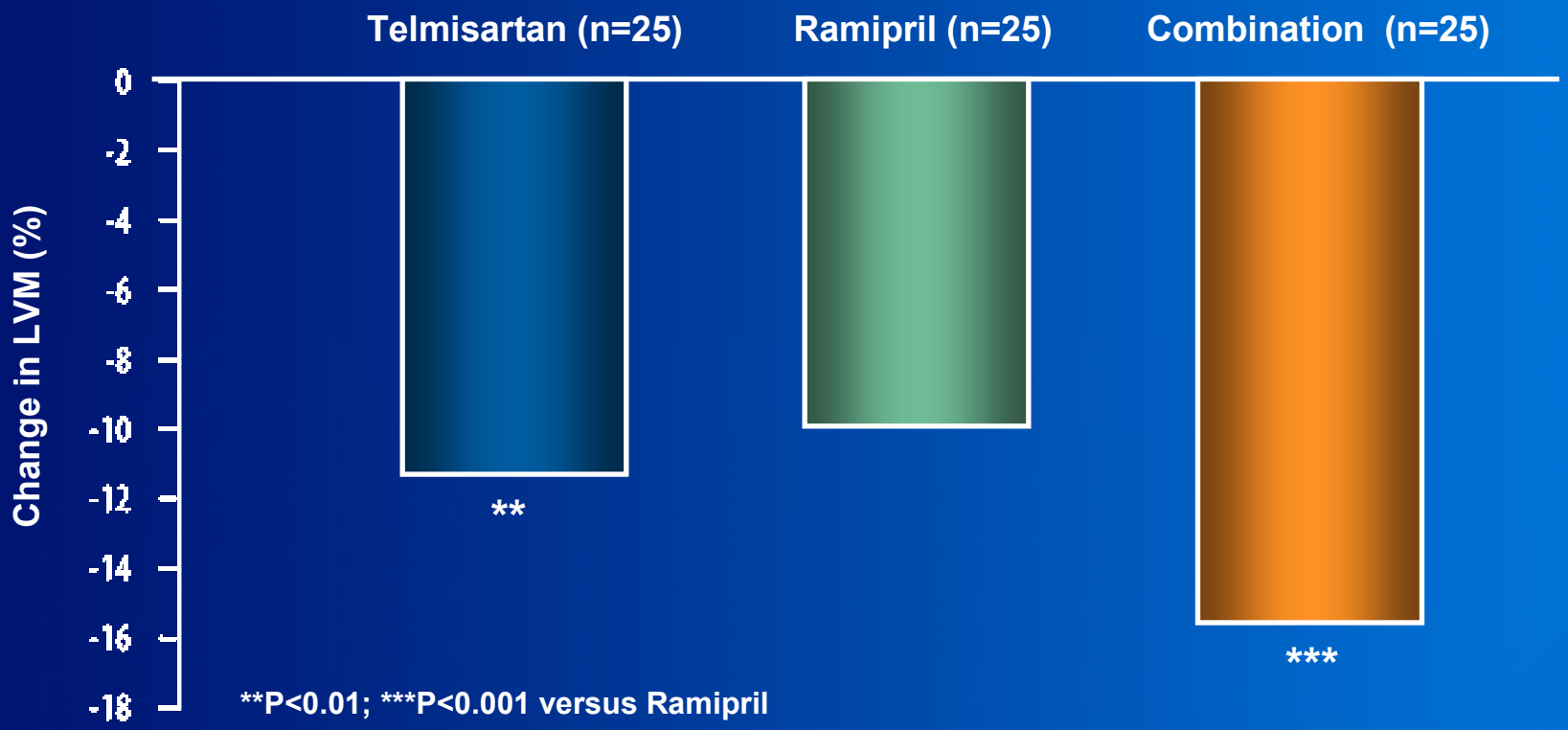
Endothelial function in diabetics further improved by combination of telmisartan with ramipril



Symeonides P., *et al.* J Am Coll Cardiol 2005;45(Suppl A):428A

ONTARGET TELMISARTAN

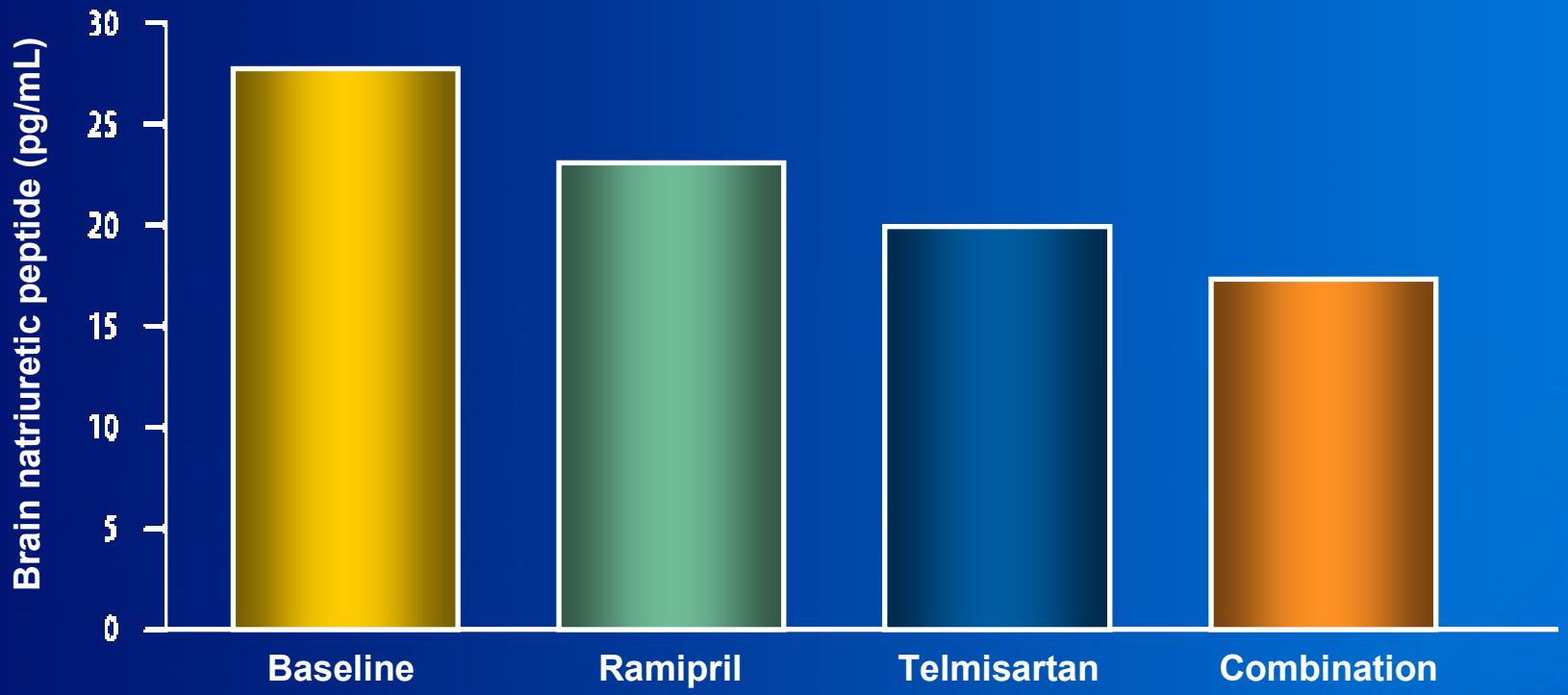
Combination of telmisartan and ramipril leads to regression in LVH



Petrovic I., *et al*. J Int Med Res 2005;33(Suppl 1):39A–49A

ONTARGET TELMISARTAN

Improvements in indices of early diabetic cardiomyopathy enhanced by dual therapy Effects additive to that of ramipril

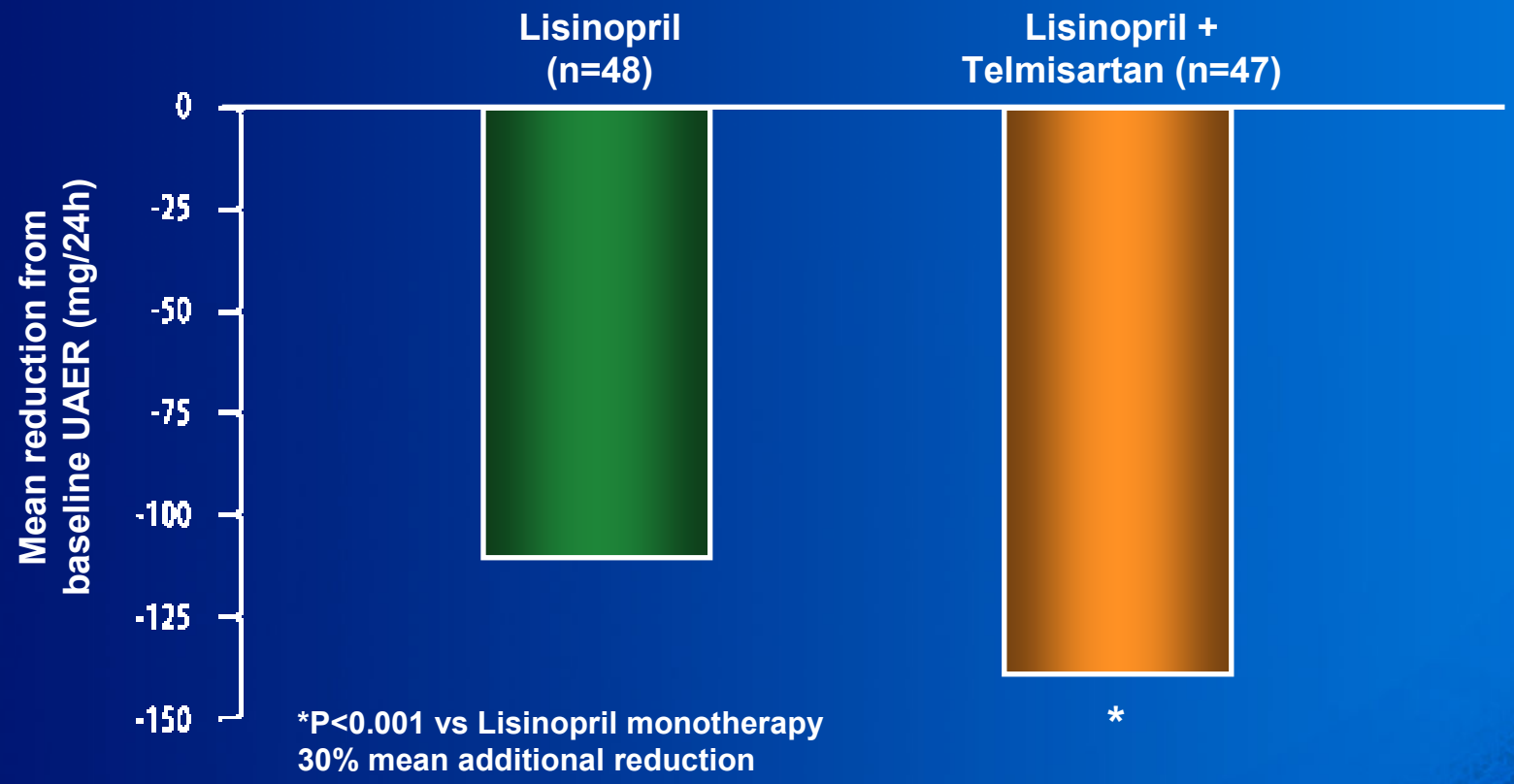


Koulouris S., *et al*. J Am Coll Cardiol 2005;45(Suppl A):170A

ONTARGET TELMISARTAN

Telmisartan – additional reductions in microalbuminuria when added to ACE inhibitor

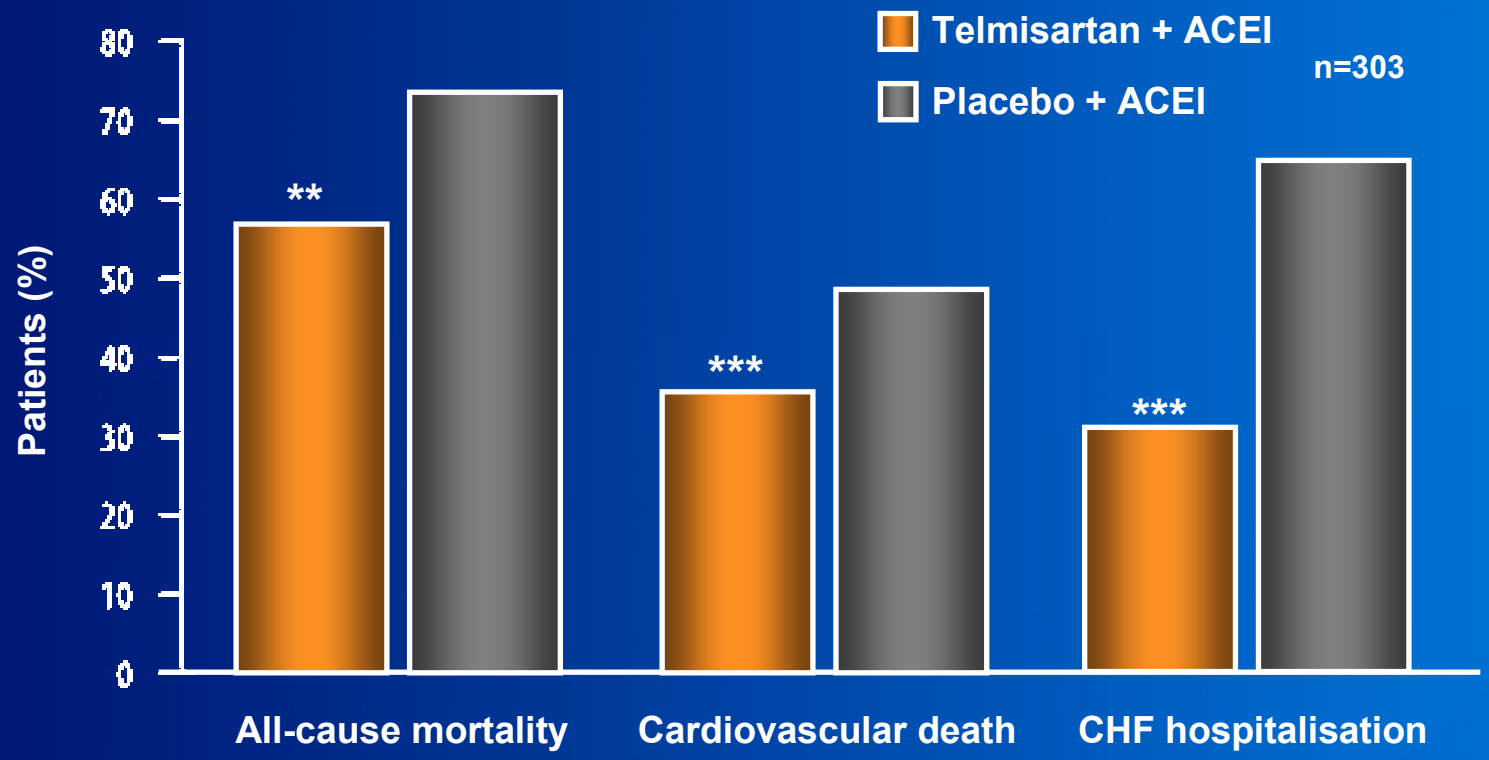
- *6 months of monotherapy + 6 months mono/combination therapy*



Sengul A.M., *et al*. Diabetes Res Clin Pract 2006;71:210–219

ONTARGET TELMISARTAN

Telmisartan added to ACEI therapy reduces CV risk in patients with ESRD and CHF



**P<0.01; ***P<0.001 versus placebo

Cice G., *et al*. Nephrol Dial Transplant 2005; 20(Supp 5):187

ONTARGET TELMISARTAN

ONTARGET Trial Programme: Investigating the combination of Telmisartan and Ramipril in cardiovascular protection

The ONTARGET Trial Programme
Rationale

- *ONTARGET is based on the positive results of HOPE, which investigated the effect of ramipril on cardiovascular risk reduction*
- *The rationale for the ONTARGET Trial Programme is based on three assumptions:*
  - *AT_1-receptor blockade by telmisartan should avert the negative consequences of angiotensin II escape*
  - *Due to the selectivity of telmisartan for the AT_1 receptors, any excess of angiotensin II will only act at the AT2 receptors. Stimulation of AT_2 receptors appears to be associated with beneficial effects*
  - *The potential tissue-protective properties associated with increased plasma bradykinin levels will be preserved*

Unger T., Am J Cardiol 2003;91(suppl):28G–34G; Zimmerman M. & Unger T. Expert Opin Pharmacother 2004;5:1201–1208

ONTARGET TELMISARTAN

The ONTARGET Trial Programme
Overview

- *The ONTARGET Trial Programme encompasses two randomised, double-blind studies: ONTARGET and TRANSCEND*
- *One of the largest and most ambitious, international, clinical study programmes ever undertaken (31,546 patients)*
- *Aims to investigate the role of the angiotensin II receptor blocker telmisartan in CVP*
- *Compares the efficacy and safety of the combination of telmisartan and ramipril with ramipril mono-therapy in the prevention of stroke, myocardial infarction, cardiovascular death and hospitalisation for CHF*

Yusuf S., *et al*. Am J Cardiol 2002;89(suppl):18A–26A; Unger T., *et al*. Am J Cardiol 2003;91 (suppl 1):28G–34G; Zimmerman M. & Unger T., Expert Opin Pharmacother 2004;5:1201–1208; Teo K., *et al*. Am Heart J 2004;148:52–61

ONTARGET TELMISARTAN

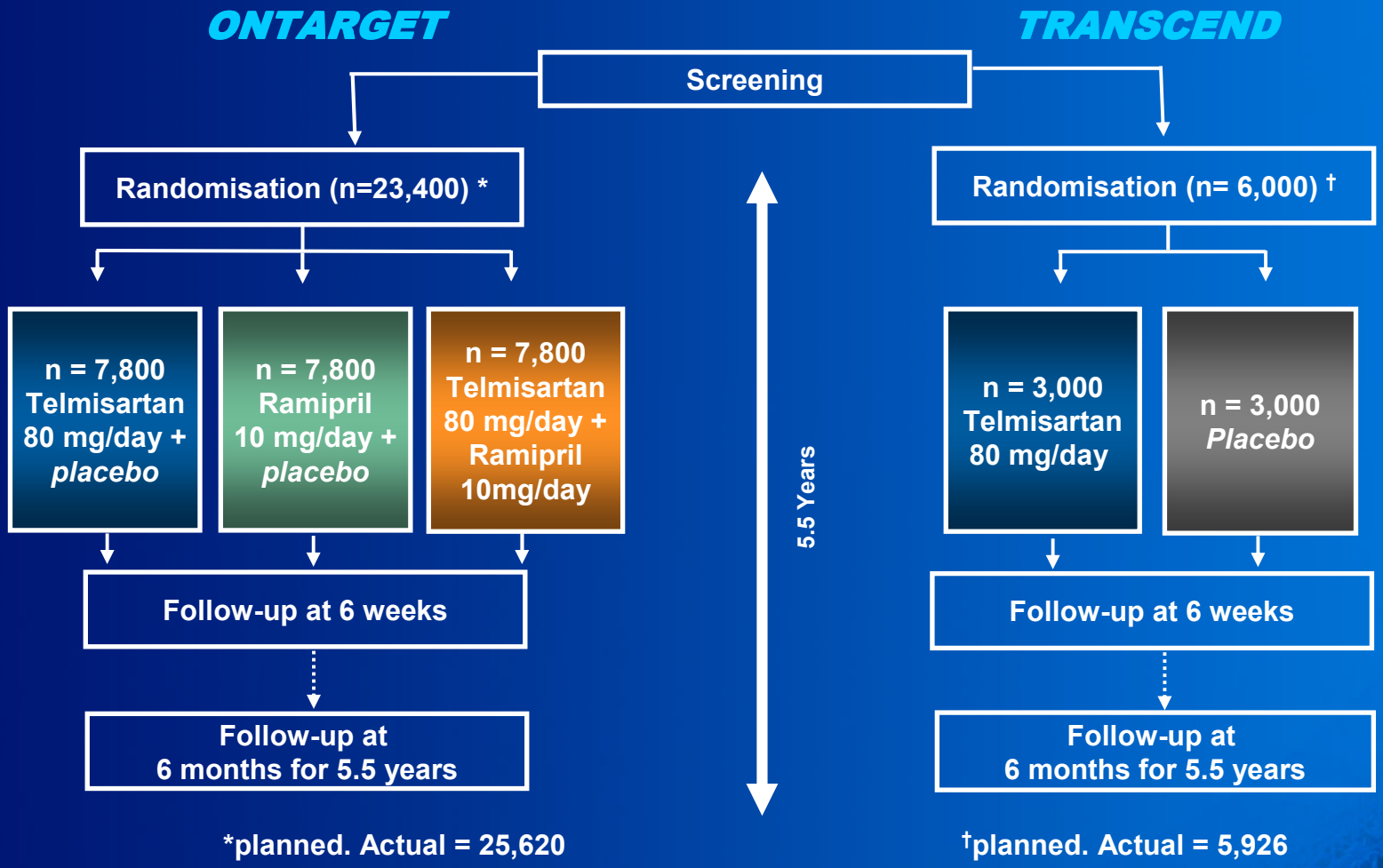
The ONTARGET Trial Programme
Objectives

- *To compare the efficacy of telmisartan with ramipril in preventing cardiovascular morbidity and mortality*
- *To determine any additional benefit of combining telmisartan with ramipril, compared with ramipril monotherapy*
- *With patients who are intolerant to an ACE inhibitor, the parallel TRANSCEND trial will compare the efficacy of telmisartan and placebo in addition to standard therapy in preventing cardiovascular morbidity and mortality*

Unger T., Am J Cardiol 2003;91(suppl):28G–34G; Zimmerman M. & Unger T., Expert Opin Pharmacother 2004;5:1201–1208

ONTARGET TELMISARTAN

The ONTARGET Trial Programme
Study design



Teo K., *et al*. Am Heart J 2004;148:52–61

The ONTARGET Trial Programme
Endpoints

- *Primary composite cardiovascular endpoint:*
  - *Cardiovascular mortality*
  - *Non-fatal myocardial infarction*
  - *Hospitalisation for congestive heart failure*
  - *Non-fatal stroke*
- *Secondary endpoints:*
  - *Newly diagnosed congestive heart failure*
  - *Cardiovascular revascularisation procedure*
  - *Newly diagnosed diabetes*
  - *Cognitive decline/dementia*
  - *New onset of atrial fibrillation*
  - *Nephropathy*
- *Other endpoints:*
  - *Non-cardiovascular death, total mortality*
  - *Unstable, new and worsening angina*
  - *Transient ischaemic attack*
  - *Microvascular complications of diabetes (laser therapy for diabetic retinopathy)*
  - *Non-fatal malignancy*

The ONTARGET Trial Programme
Inclusion criteria

- *Age ≥55 years*
- *At high risk of developing a CVD event, with a history of:*
  - *Coronary artery disease*
  - *Peripheral arterial occlusive disease (PAOD)*
  - *Cerebrovascular event*
  - *Diabetes mellitus with end-organ damage*
- *Intolerant to ACE inhibitors (TRANSCEND only)*

Teo K., *et al*. Am Heart J 2004;148:52–61

ONTARGET TELMISARTAN

The ONTARGET Trial Programme
Exclusion criteria

- *Cardiovascular disease*
  - *Symptomatic congestive heart failure*
  - *Uncontrolled hypertension on treatment (e.g. BP >160/100 mmHg)*
  - *Subarachnoid haemorrhage*
  - *Significant primary valvular or outflow tract obstruction*
  - *Others: Constrictive pericarditis, complex congenital heart disease, syncopal episodes of unknown aetiology, planned cardiac surgery or angioplasty within 3 months, heart transplant*
- *Significant renal disease*
  - *Creatinine clearance <0.6 ml/sec (<36 ml/min) or serum creatinine (>265 µmol/L; >3.0 mg/dL)*
  - *Documented significant renal artery stenosis*
  - *Hyperkalaemia: potassium >5.5 mmol/L*
  - *Proteinuria (for TRANSCEND only)*
- *Hepatic dysfunction*
  - *SGPT (ALT) or SGOT (AST) >4x upper limit of normal (ULN), additional criteria for hepatic impairment, total bilirubin >20 µmol/L, biliary obstructive disorders*

The ONTARGET Trial Programme
Baseline characteristics

	ONTARGET (n=25,620)	TRANSCEND (n=5,304*)
Demography		
Age (years)	66.4	67.0
Male (%)	73.3	57.5
Physical Exam		
BP at run-in (mm Hg)	143\82	142\82
BP at randomisation (mm Hg)	134\77	135\78
Body mass index	28.2	28.3
Waist–hip ratio	0.9	0.9
Medical History		
Hypertension	68.3	75.0
MI	48.7	46.3
Stable angina	34.8	36.5
Stroke/TIA	20.7	21.6
Claudication	11.8	10.2
Diabetes	37.3	35.0
Current smoker	12.5	9.5

* TRANSCEND as of January 2004. Final TRANSCEND recruitment, n=5,926

Teo K., *et al*. Am Heart J 2004;148:52–61

ONTARGET TELMISARTAN

The ONTARGET Trial Programme
Baseline characteristics – medication use

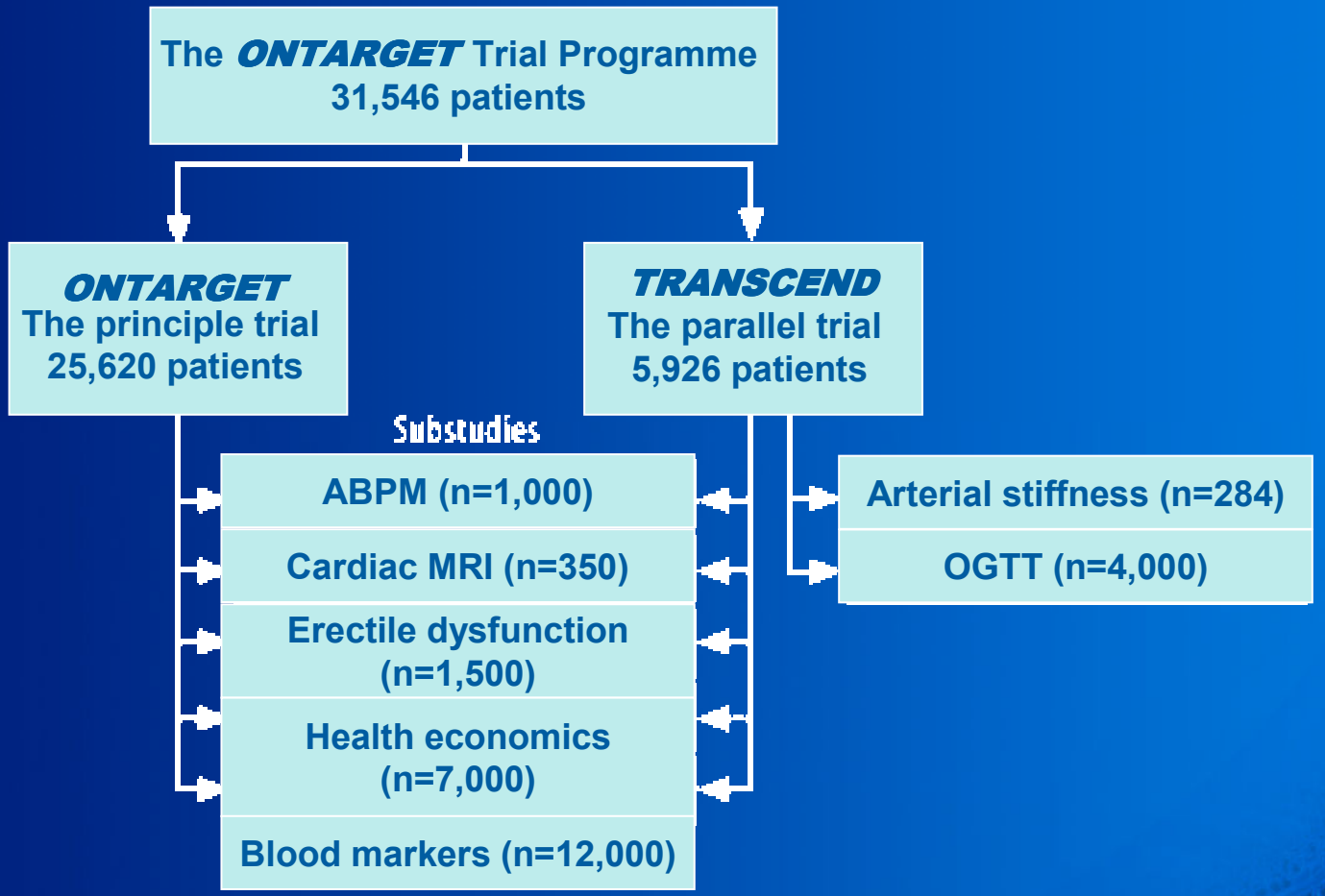
	ONTARGET (n=25,620)	TRANSCEND (n=5,304*)
Medications (% of patients)		
ACE Inhibitors	57.5	57.0
Angiotensin Receptor Blockers	8.6	30.0
Beta-blockers	56.9	57.6
Diuretics	27.9	32.6
Nitrates	29.2	34.5
Calcium channel blockers		
- Diltiazem/verapamil	9.7	10.1
- Other	23.8	31.0
Antiplatelets		
- ASA	75.6	74.3
- Ticlodipine	2.5	2.6
- Clopidogrel	8.5	8.0
Oral anticoagulants	7.6	7.2
Statins	60.7	54.4
Insulin	10.4	7.3
Oral hypoglycaemics	25.0	23.7

* TRANSCEND as of January 2004. Final TRANSCEND recruitment, n=5,926

Teo K., *et al*. Am Heart J 2004;148:52–61

ONTARGET TELMISARTAN

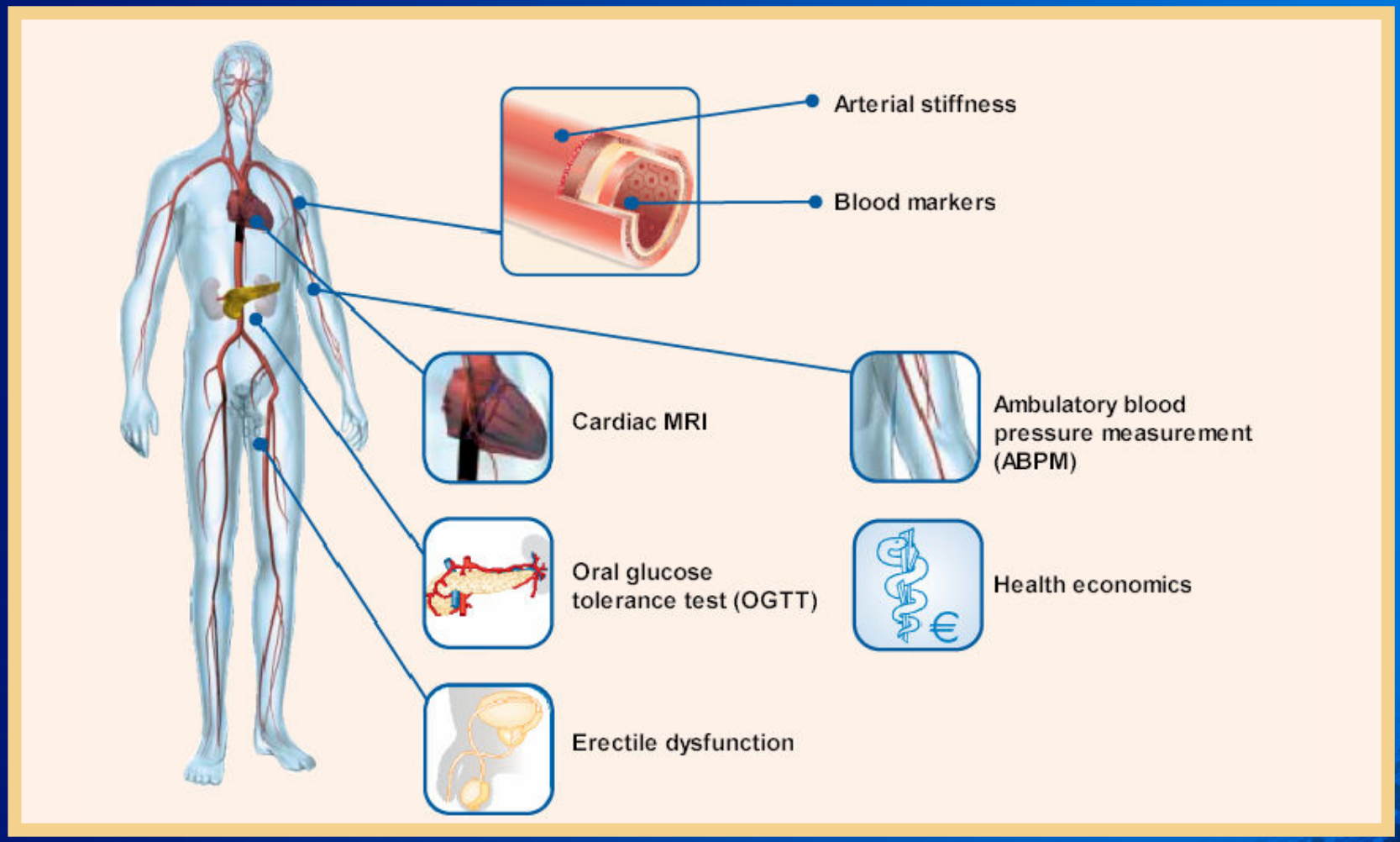
The ONTARGET Trial Programme
Sub-studies



Yusuf S., Am J Cardiol 2002;98(suppl):18A–26A; Unger T., Am J Cardiol 2003;91 (suppl):28G–34G; Zimmerman M. & Unger T., Expert Opin Pharmacother 2004;5:1201–1208

ONTARGET TELMISARTAN

The ONTARGET Trial Programme:
Sub-studies



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