

**Optimal blockade of the Renin-
Angiotensin-Aldosterone-
(RAA)-System
in chronic heart failure**

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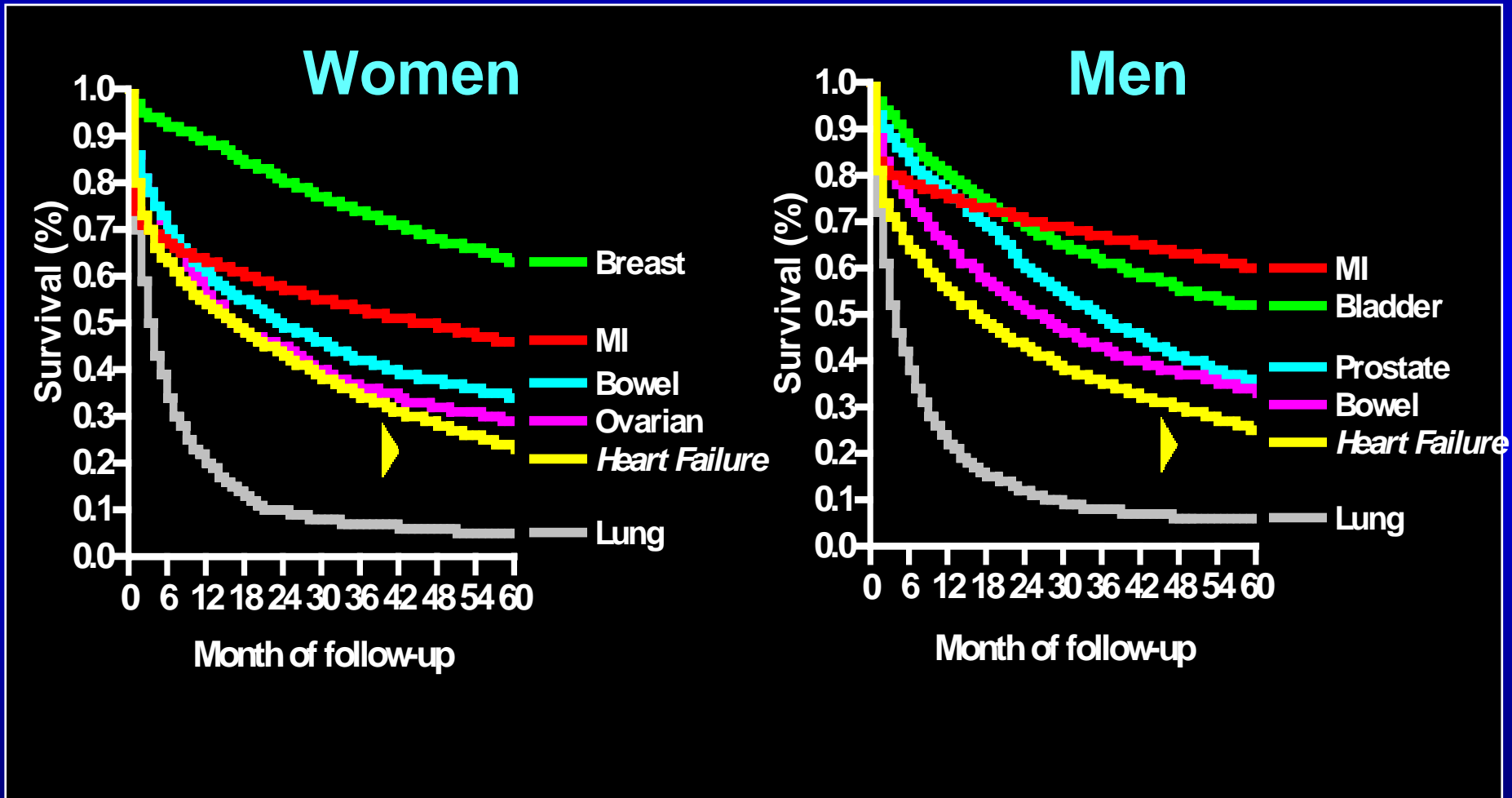
Stockholm, Sweden

Key Issues in Heart Failure

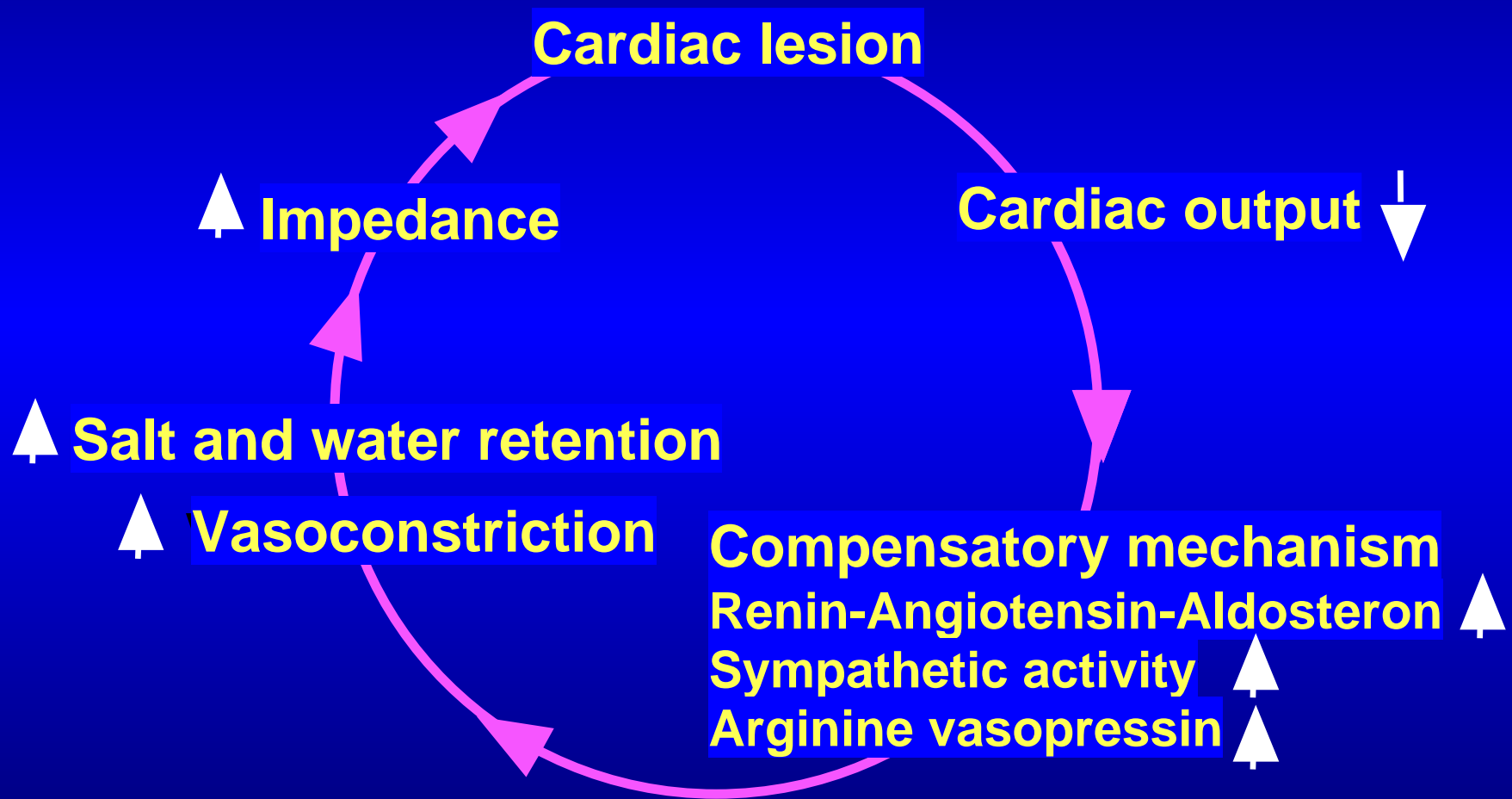
Chronic heart failure is:

- Common – 2% of the population
- Dangerous – high mortality
- Disabling – high morbidity
- Costly – 2% of health care budget
- Treatable – very successful pharmacological therapy developed

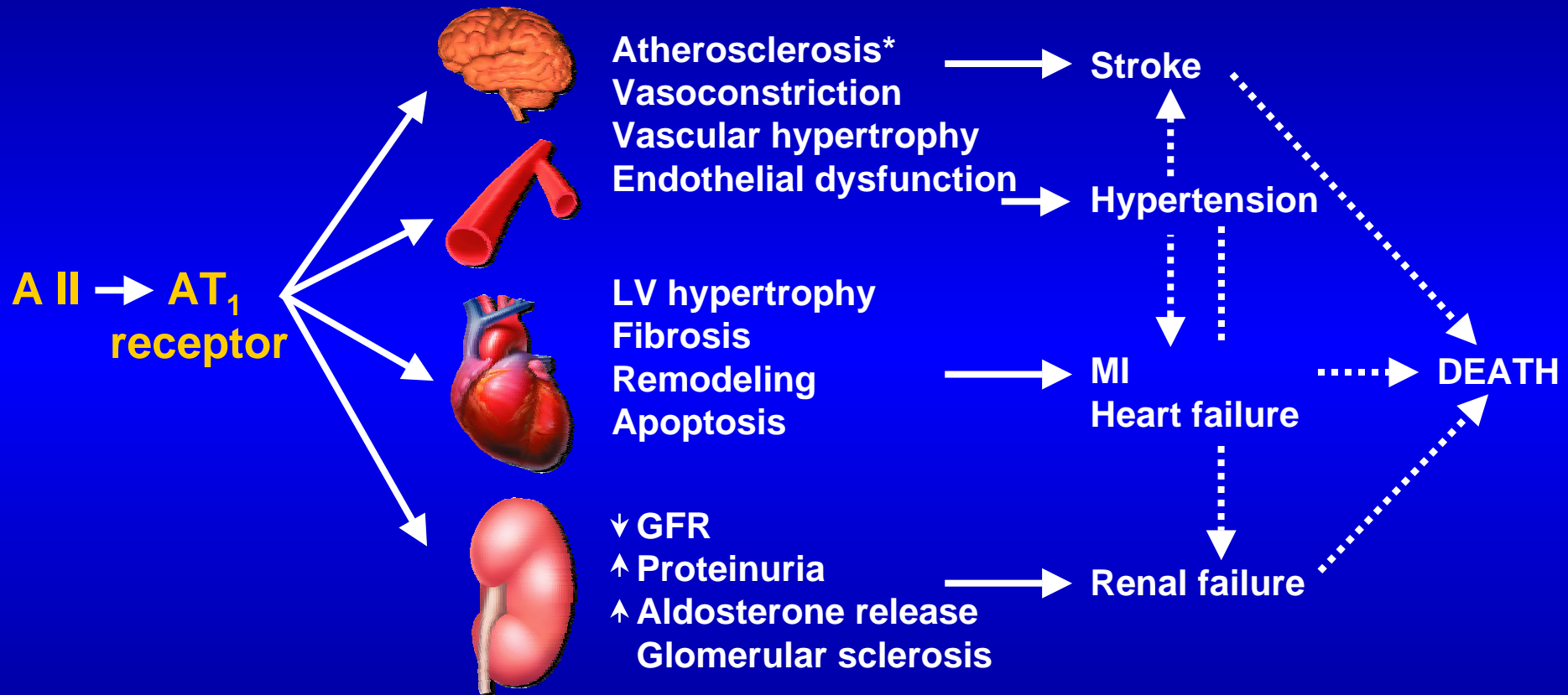
More malignant than cancer?



The Vicious Circle of Heart Failure



Angiotensin II Plays a Central Role in Organ Damage

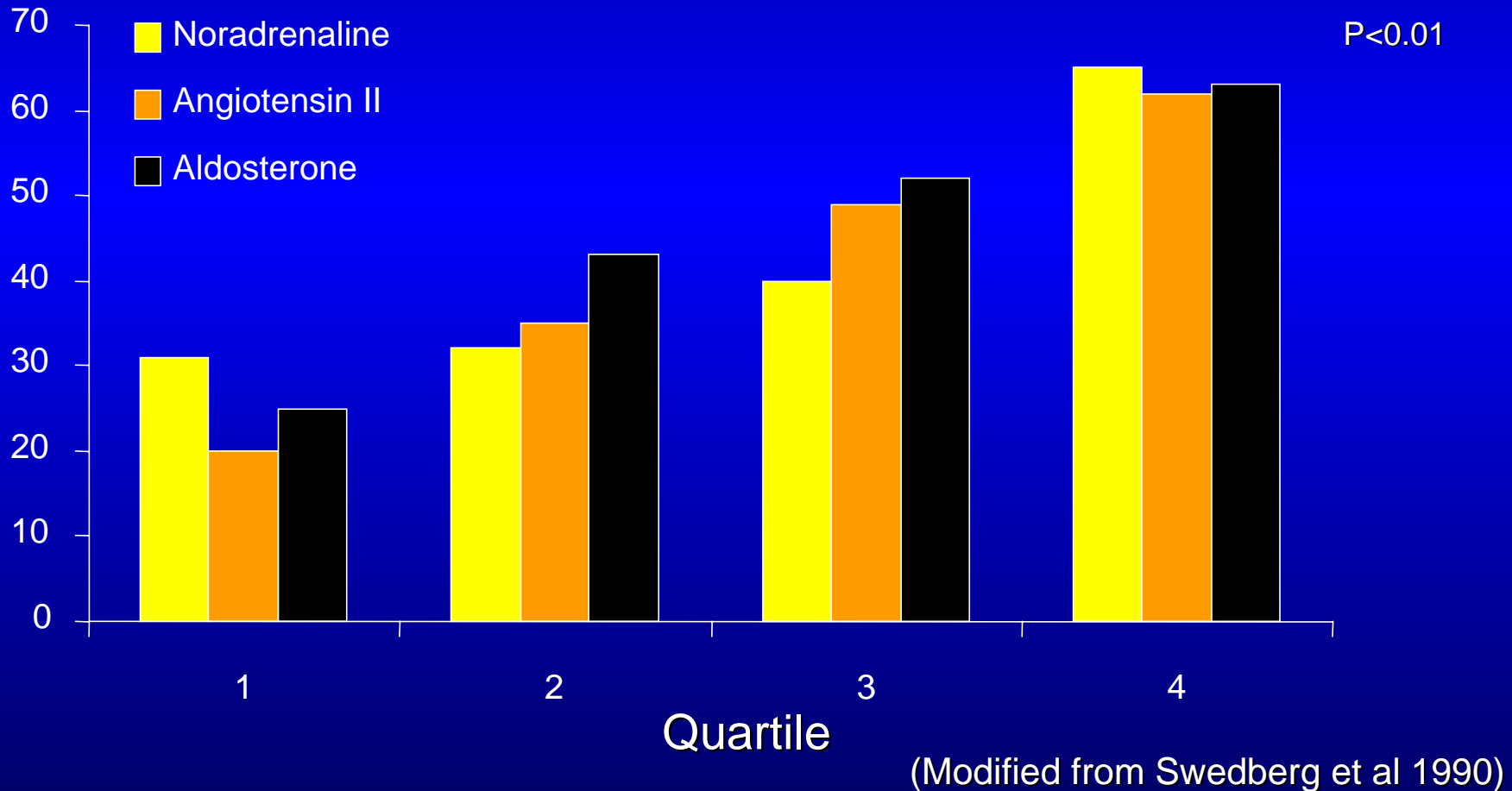


* Preclinical data

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

Neuroendocrine Activation and Mortality in Severe Heart Failure

Six month mortality (%) by plasma levels of hormones
From CONSENSUS I Placebo Group n=120



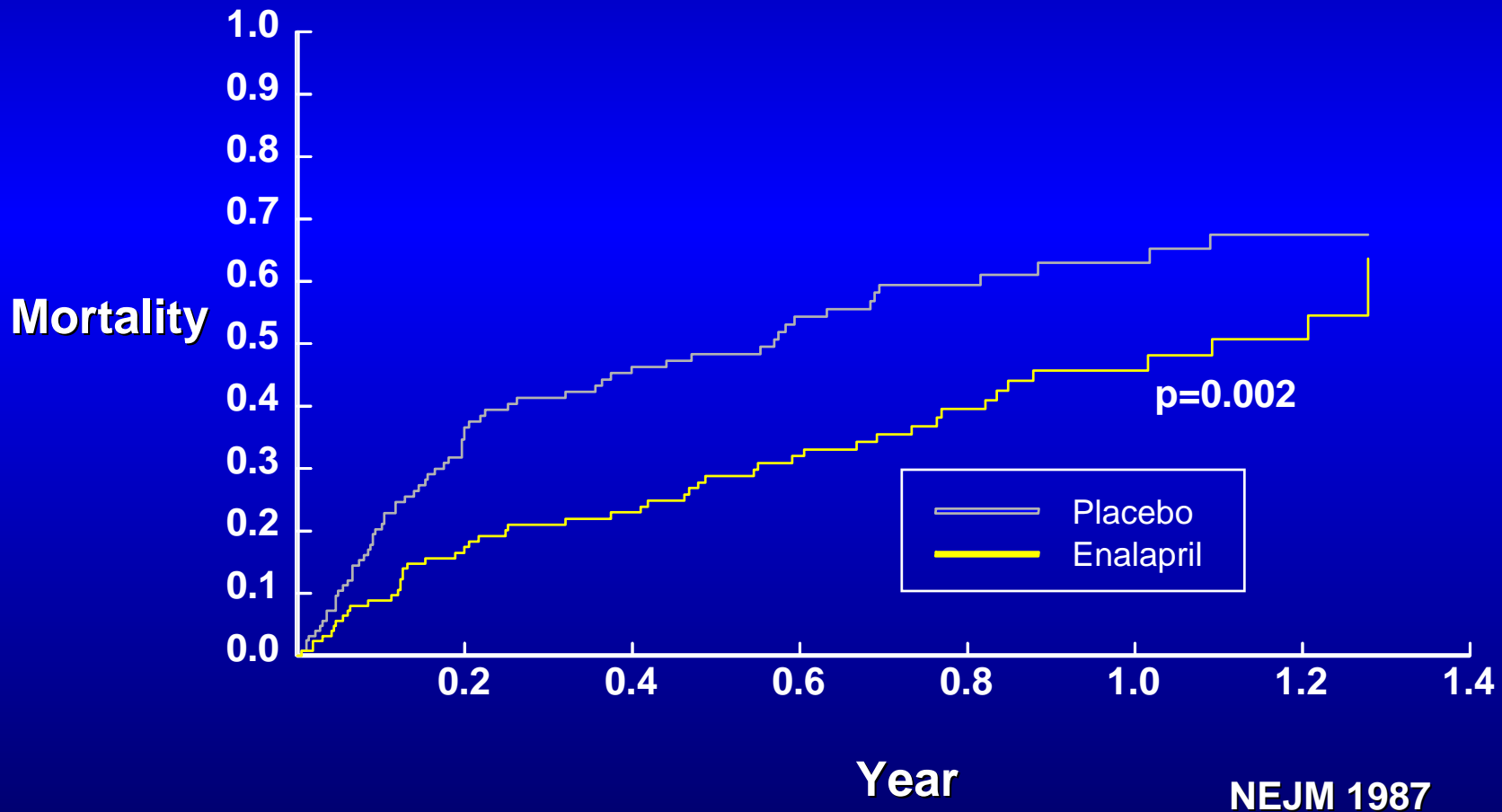
Inhibition of angiotensin II in chronic heart failure

ACE-inhibition

CONSENSUS

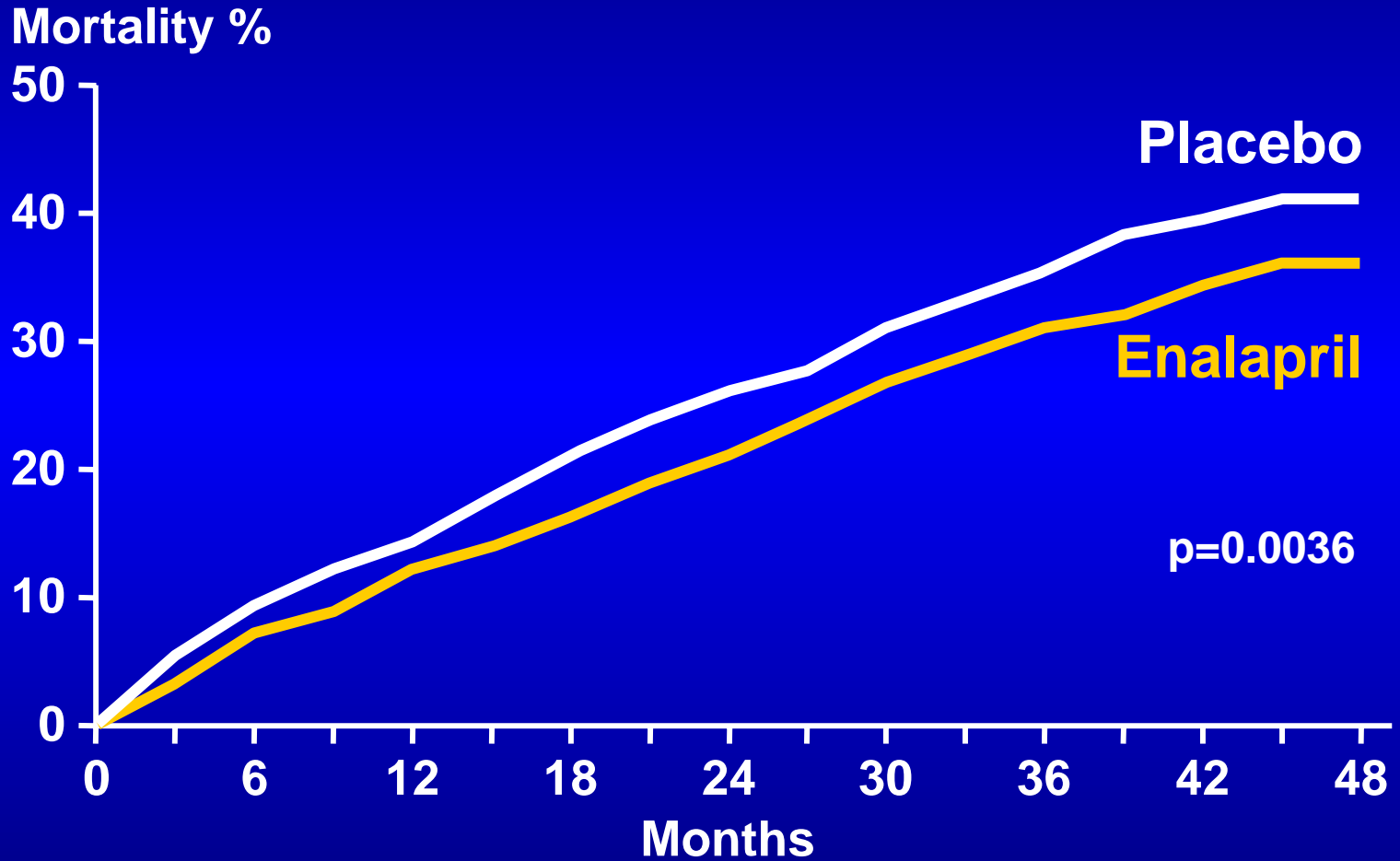
Original Study Result

253 patients in NYHA class IV. High doses of diuretics, nitrates, spiro.
Mean age 70. Study stopped by DSMB



SOLVD Treatment Trial

All Cause Mortality



Placebo	n = 1284	1159	1085	1005	939	819	669	487	299
Enalapril	n = 1285	1195	1127	1089	1010	891	697	526	333

Meta-analysis of Studies With ACE-Inhibitors in Heart Failure

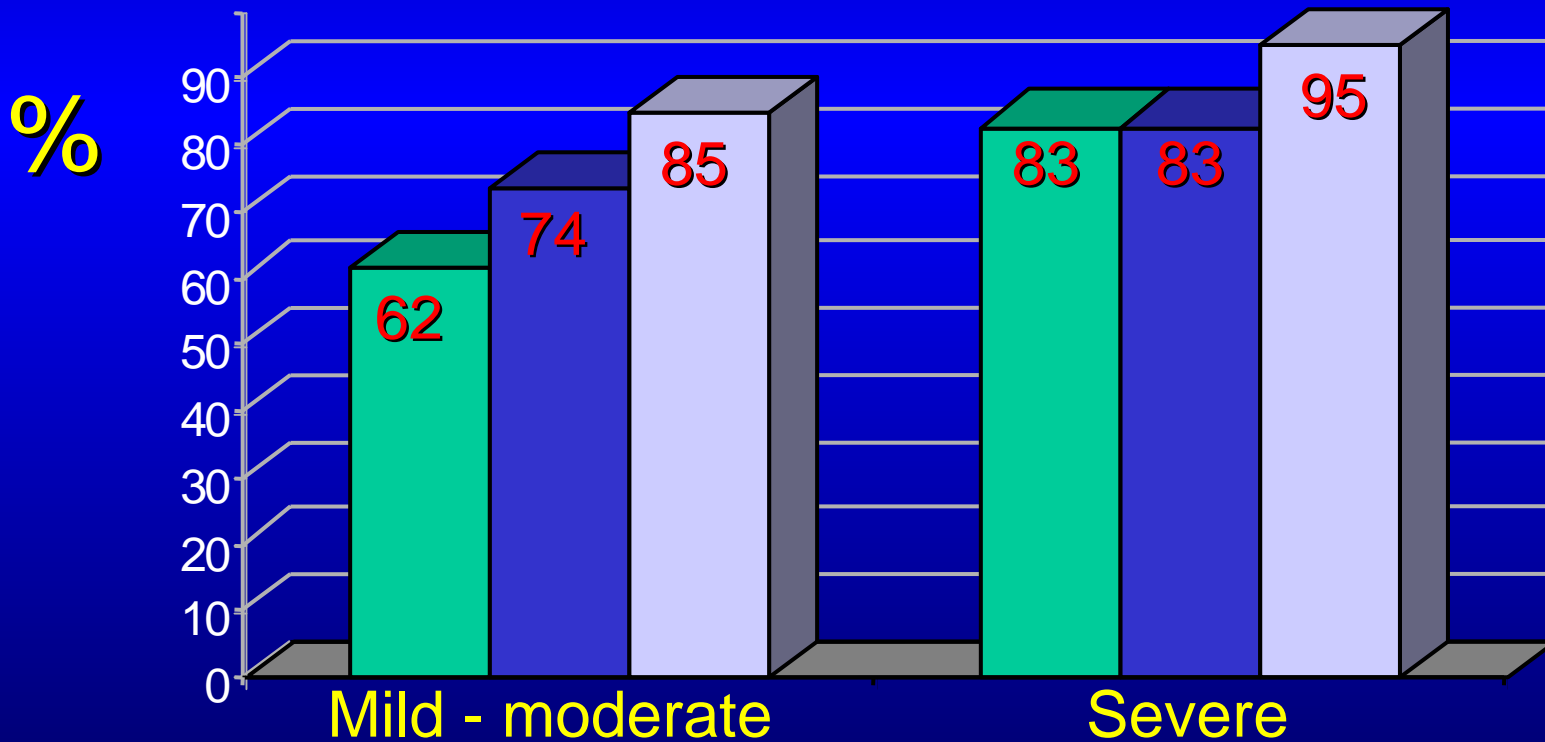
Study	Mortality (OR; 95% CI)	Mortality or hospitalisation for CHF (OR; 95% CI)
SOLVD	0.82 (0.70-0.97)	0.68 (0.59-0.80)
CONSENSUS	0.56 (0.34-0.91)	0.89 (0.51-1.57)
Total (32 trials)	0.77 (0.67-0.88)	0.65 (0.57-0.74)

(Garg & Yusuf JAMA 1995,273:1450)

ACE-inhibitors in heart failure

Prescription in relation to speciality

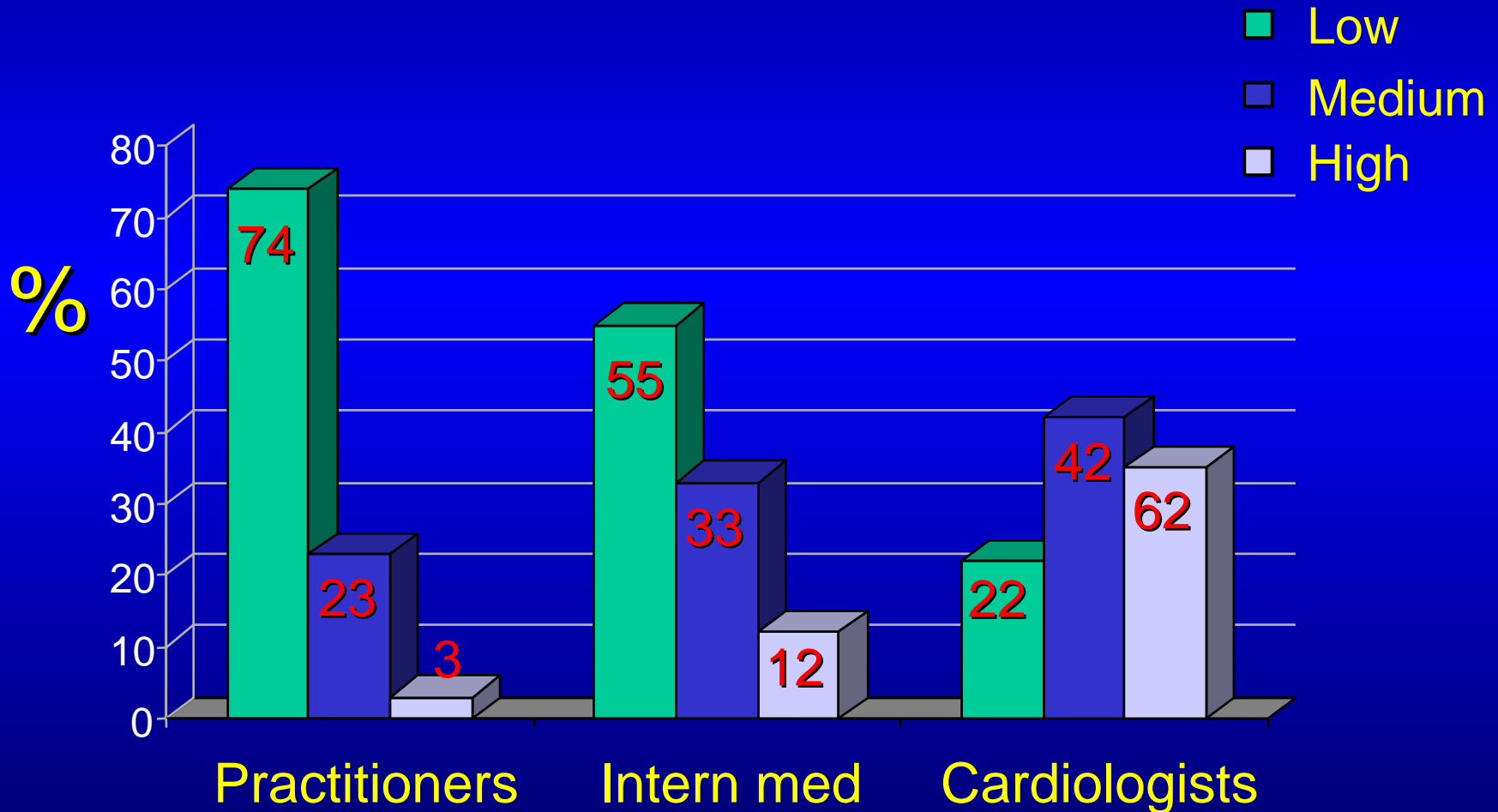
- Practitioners
- Internal med
- Cardiologists



(Edep et al. JACC 1997;30:518)

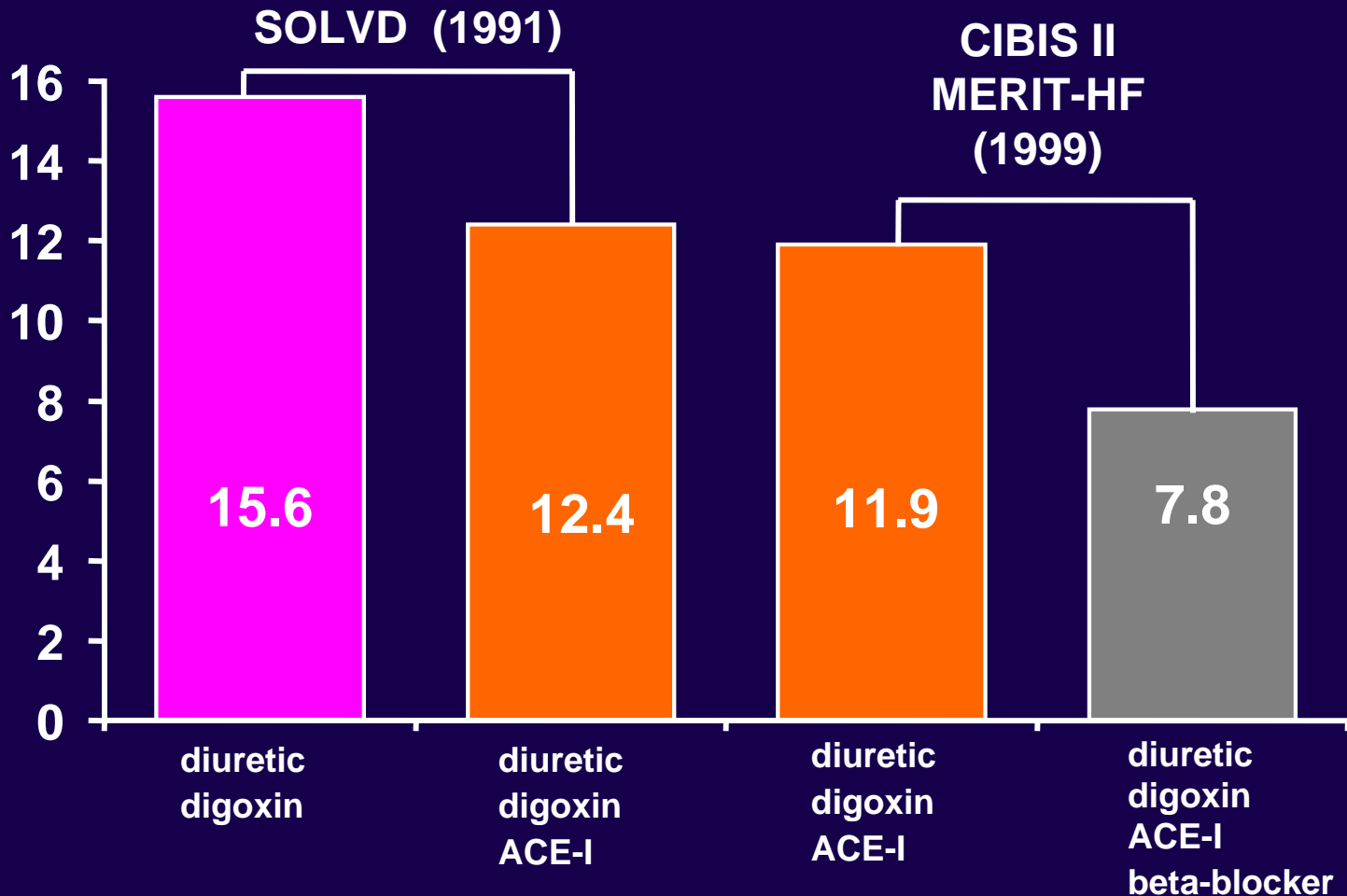
ACE-inhibitors in heart failure

Dose levels in relation to speciality



Mortality Benefit of Beta-blockers and ACE-inhibitors in CHF trials

% death at 1 year

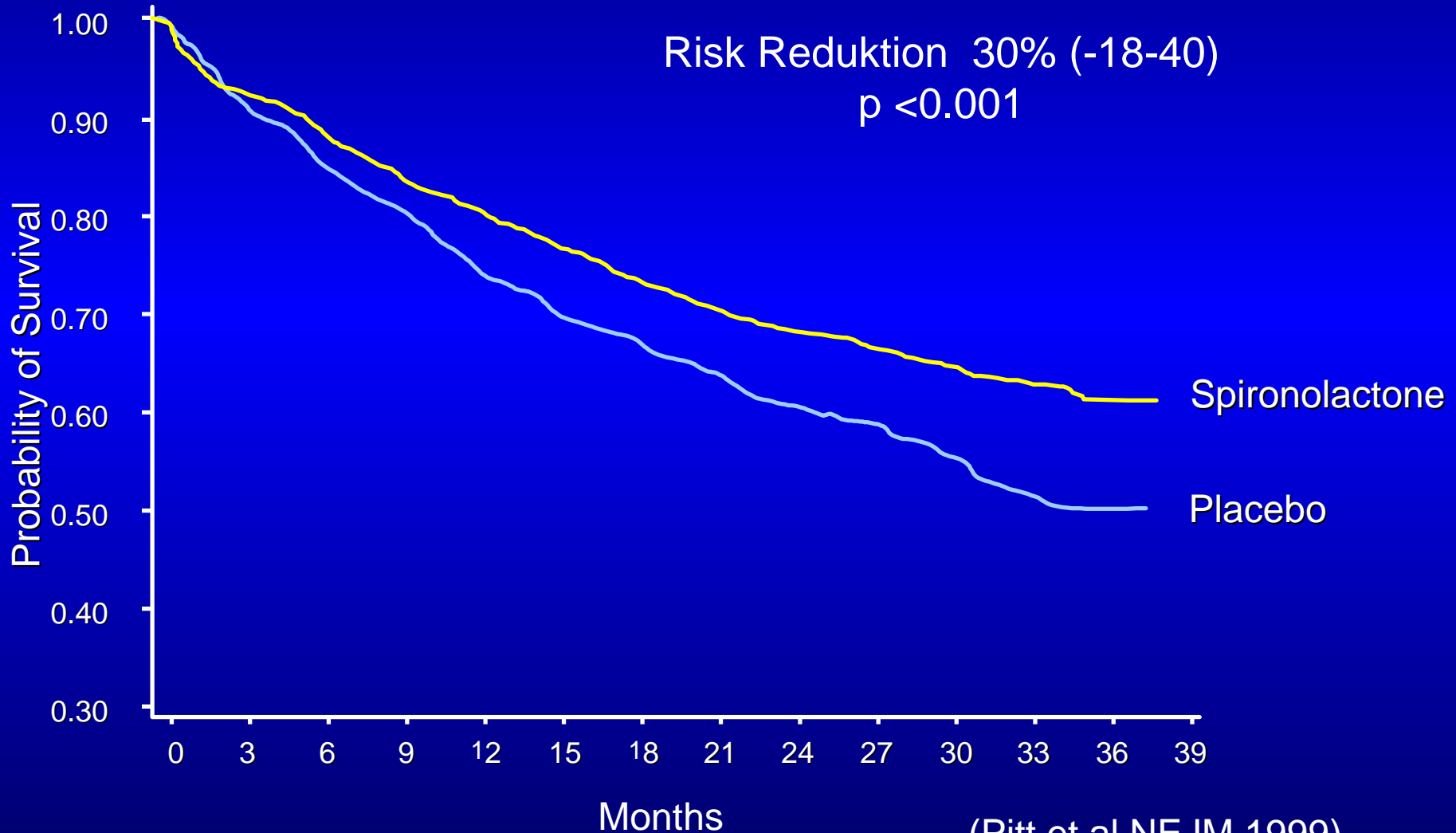


Further pharmacological manipulation of the Renin-Angiotensin-Aldosterone System in CHF

- Angiotensin II and Aldosterone is not optimally suppressed by ACE-inhibitors
- Blocking these molecules will add benefit

Rales

All-cause mortality



(Pitt et al NEJM 1999)

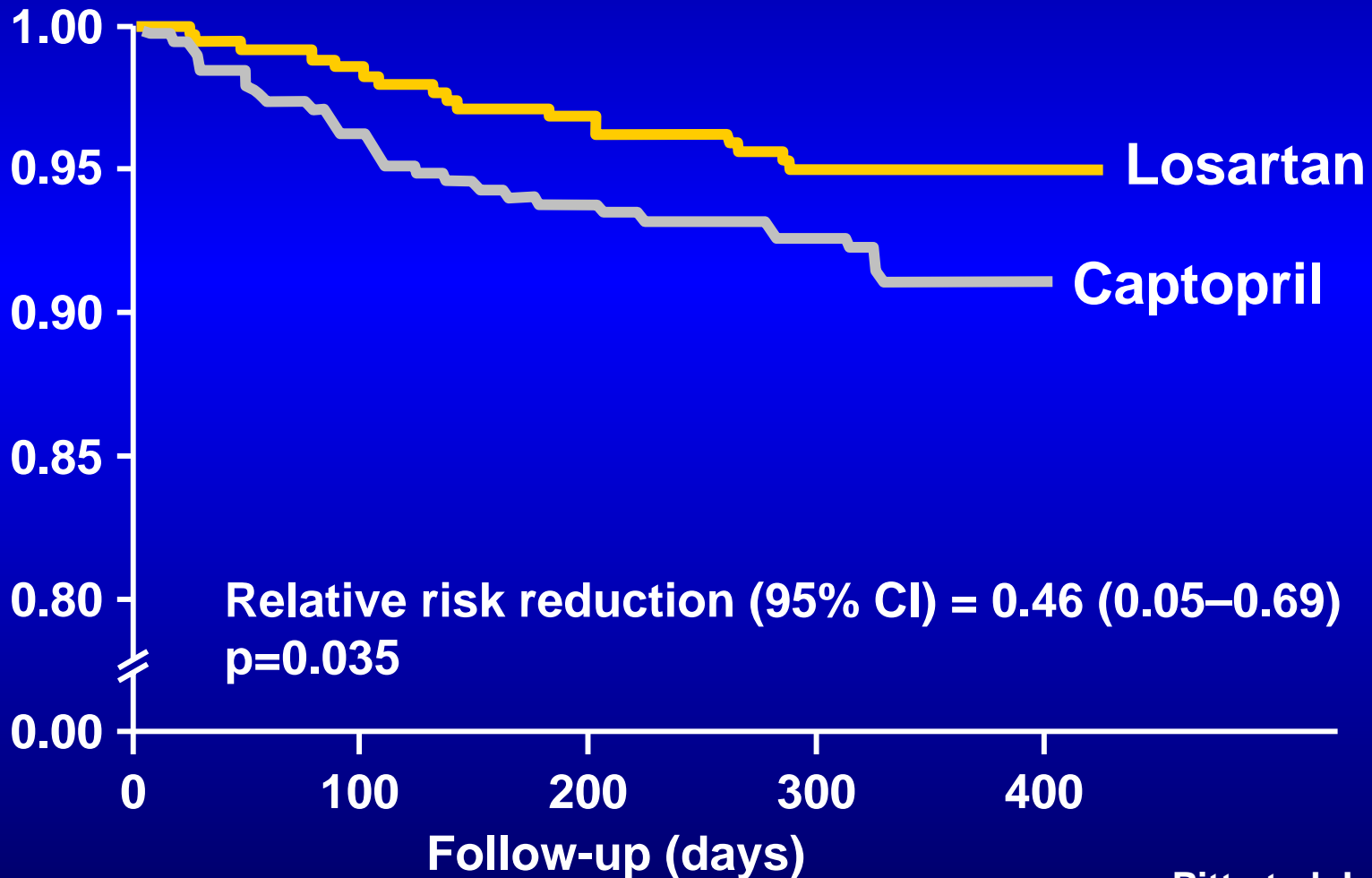
Inhibition of angiotensin II

AT₁-receptor blockade

May treatment of patients with heart failure improve even further?

Randomized trial of losartan vs captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE)

Probability of survival



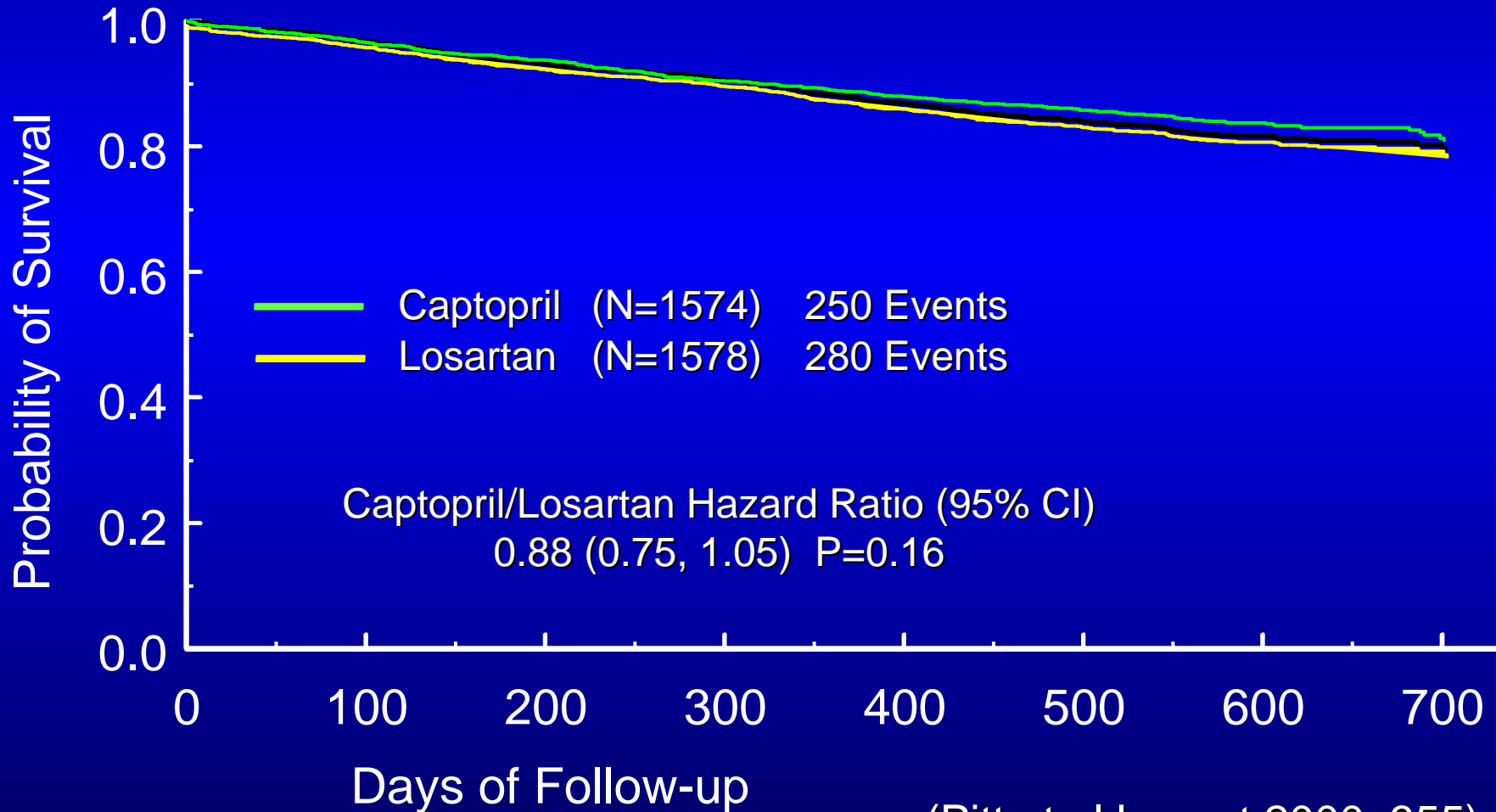
ELITE II

Losartan Heart Failure Survival Study

- 3152 pts HF (EF<40%) + >60 yrs
- Losartan target dose 50 mg vs
captopril target dose 150 mg
- Endpoint:
 - Total mortality

Losartan Heart Failure Survival Study ELITE II

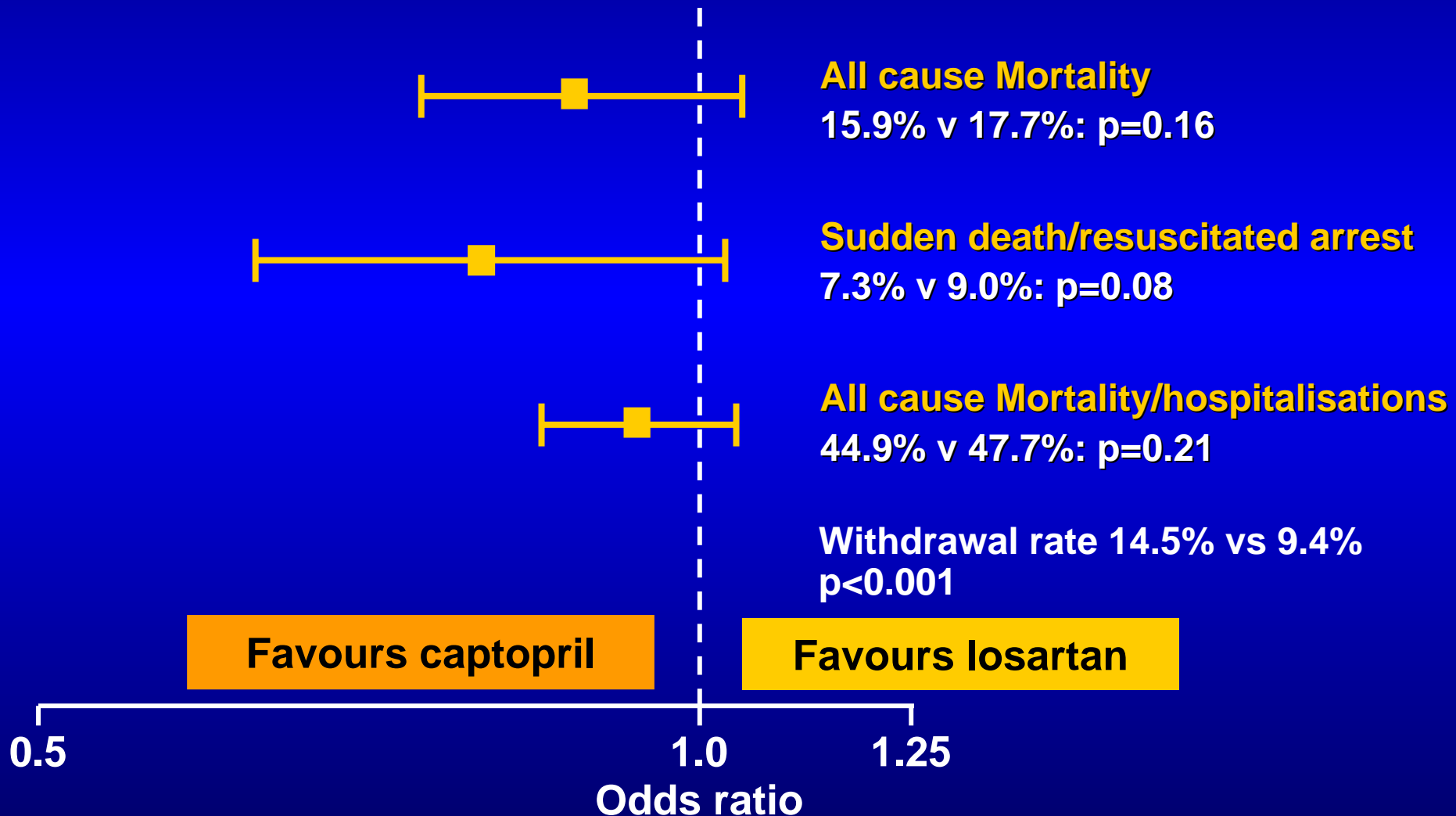
All cause mortality



(Pitt et al Lancet 2000, 355)

ELITE II: Summary of Major Findings

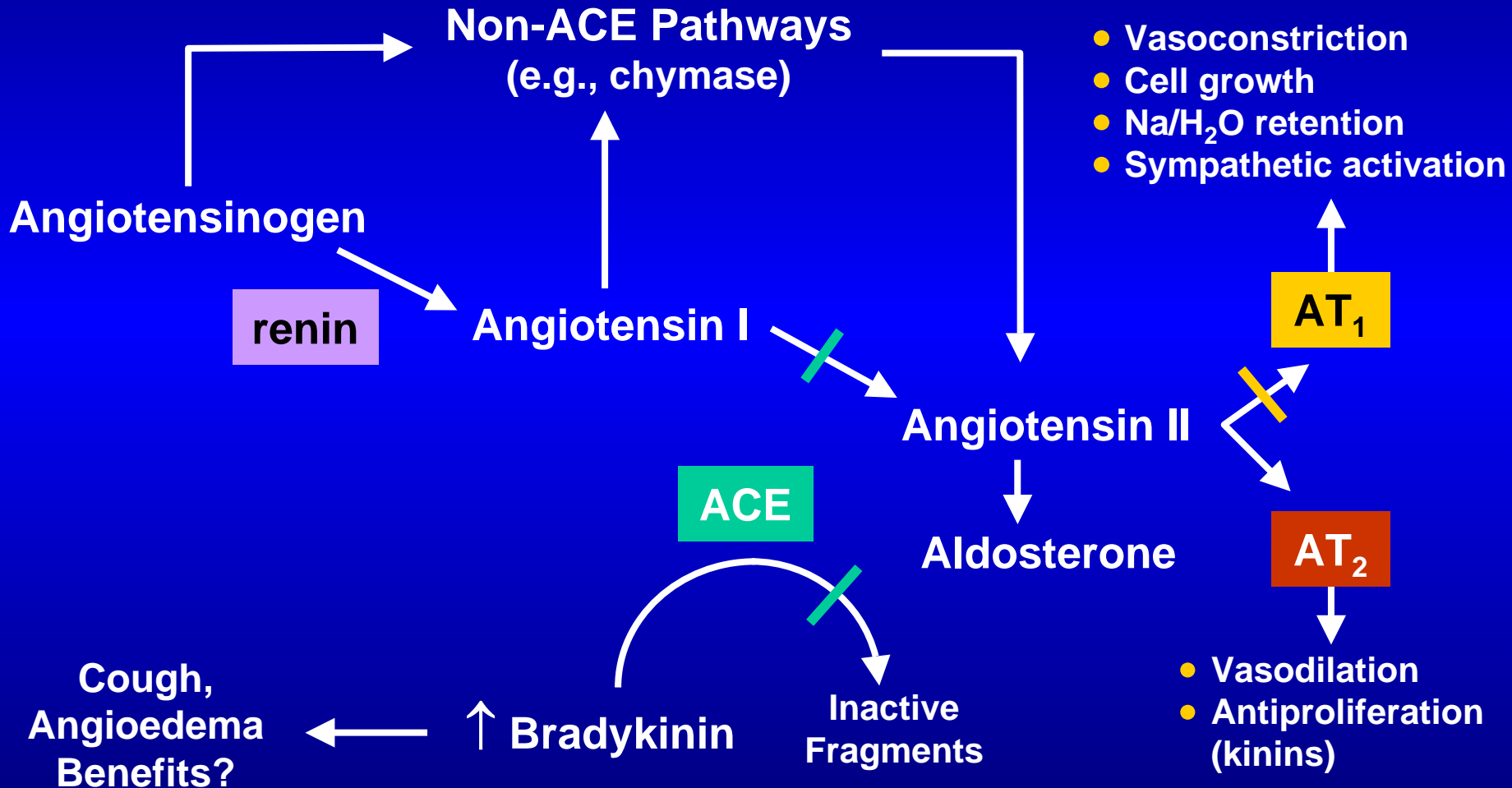
3152 elderly CHF patients randomised to losartan (50 mg od) or captopril (50 mg tid)



Combination of ACE Inhibitor and AT₁ Receptor Blocker

**Is it superior to ACE inhibitor
monotherapy?**

Renin-Angiotensin Aldosterone System



ACE inhibitor escape

- **Angiotensin II back to high pathologic pre-treatment levels after some time despite complete inhibition of circulating ACE**

Biollaz et al. J Cardiovasc pharmacol 1982;4:966-72

Rousseau et al. Am J Cardiol 1994;73:488-93

- **50% of ACE inhibitor treated CHF patients have escape and those patients have a worse prognosis**

Roig et al. Eur Heart J 2000;21:53-7

- **Probably due to non-ACE conversion of Ang I to Ang II**
- **Insufficient blockade of tissue ACE?**

Combination of ACE Inhibitor and AT₁ Receptor Blocker

- More complete inhibition of influence of Ang II
- Bradykinin accumulation benefits
- Combination therapy may therefore be superior to ACE inhibitor monotherapy

Val-HeFT

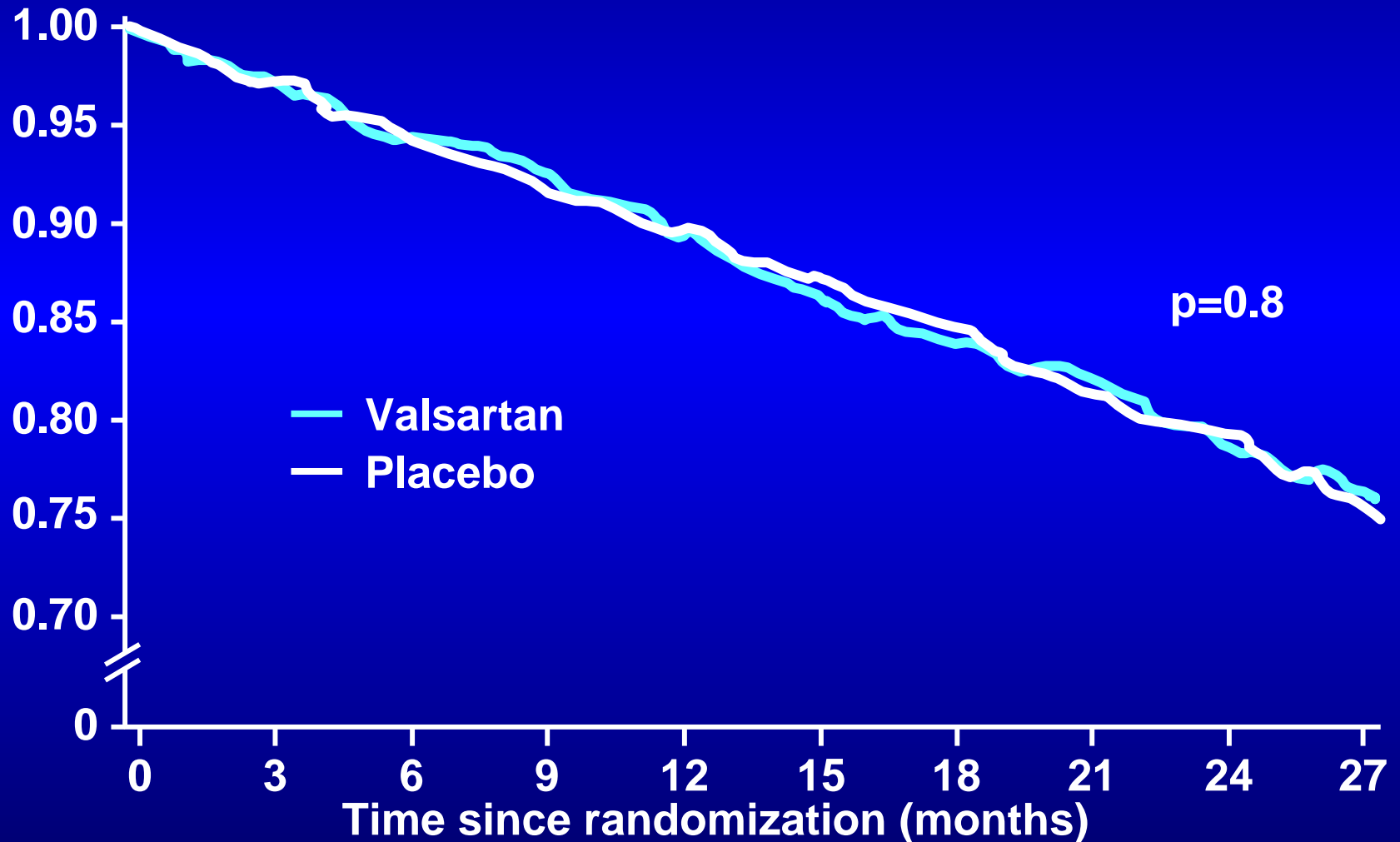
Valsartan Heart Failure Trial

- 5,010 pts HF (EF<40%) + LVED >2.9 cm/m²
- Valsartan target dose 320 mg vs placebo
- Patients on stable standard treatment (93%ACE-i, 1/3 beta-blockers)
- Endpoint:
 - Total mortality
 - Death or resuscitated sudden death, HF hospitalization, IV inotropics or vasodilators

Val-HeFT

All-Cause Mortality

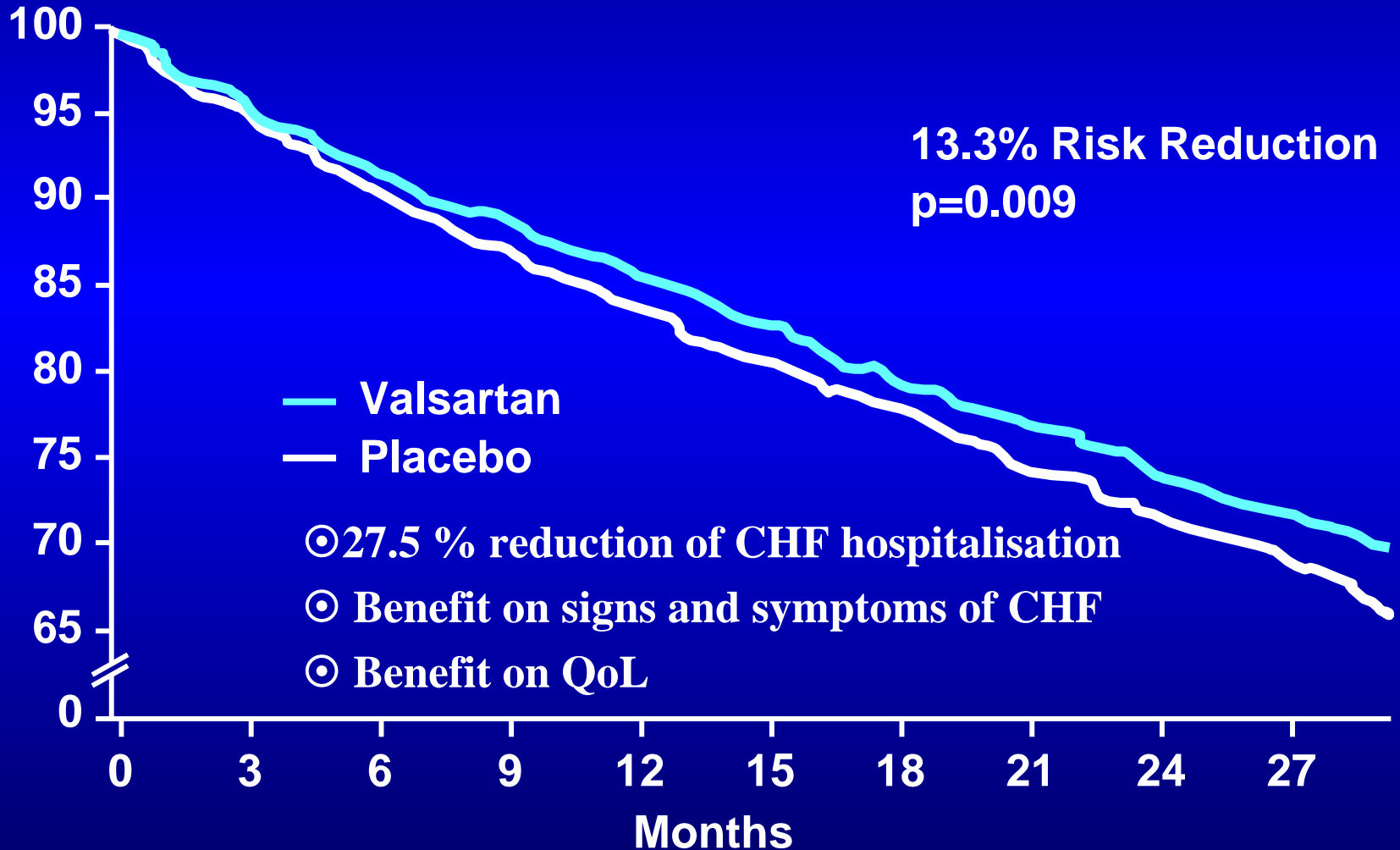
Survival probability



Val-HeFT

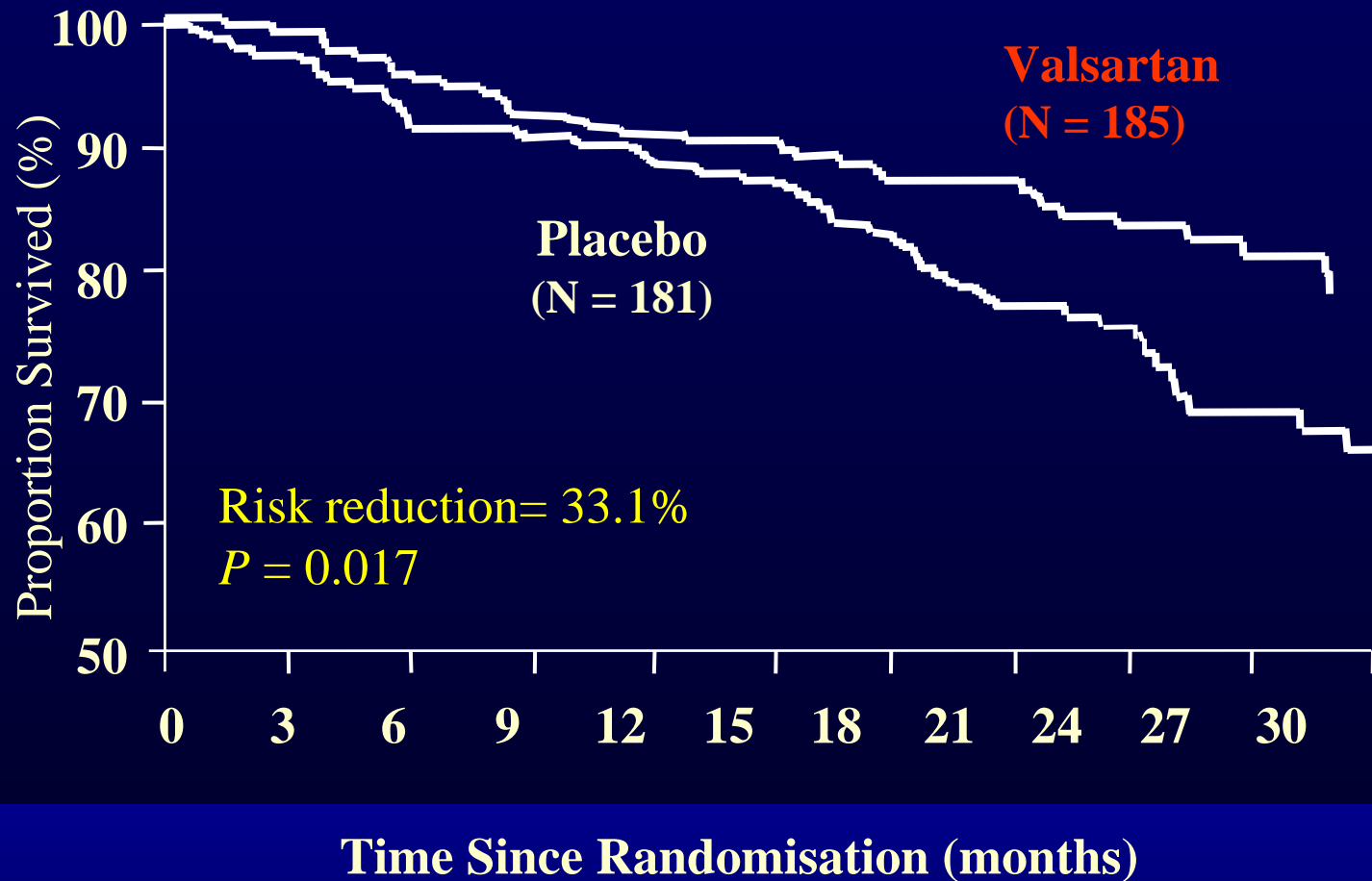
Combined All-Cause Mortality and Morbidity

Event free probability



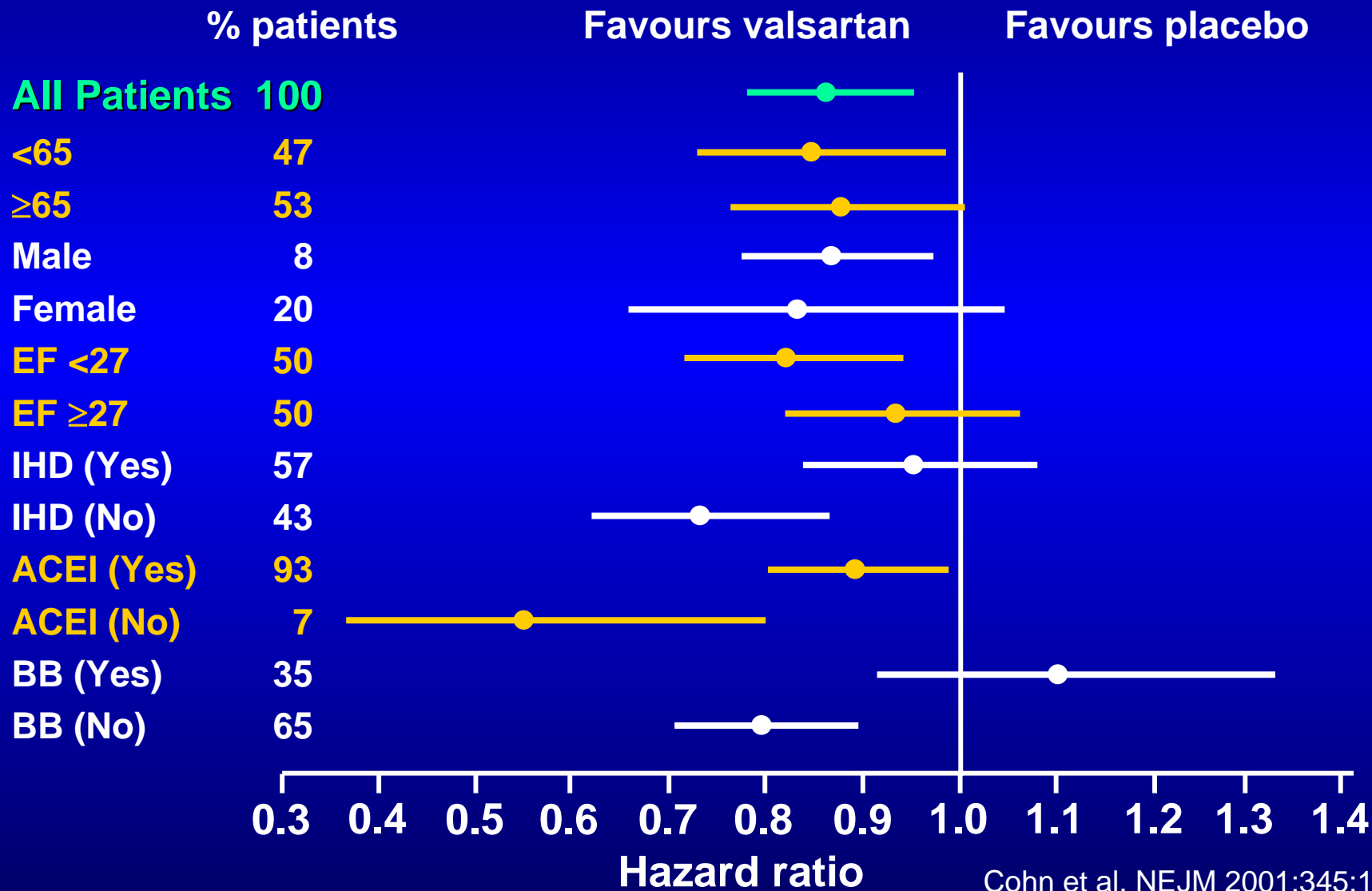
Val-HeFT

Reduction in Mortality (No ACEi)



Val-HeFT

Subgroup Combined Mortality/Morbidity



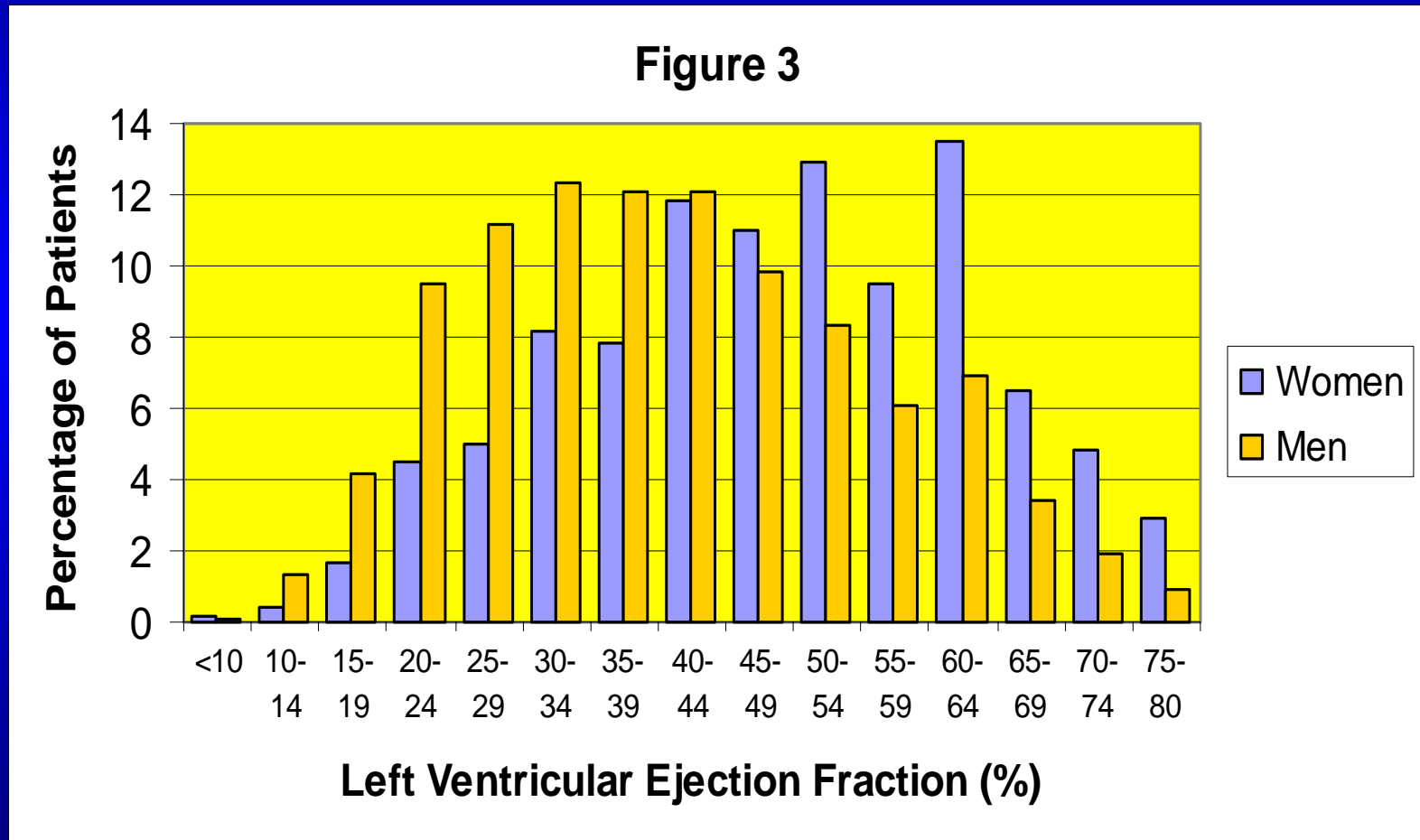
Questions remaining after ELITE II and Val-HeFT

- ARB in patients who don't tolerate an ACE-i?
- Is there a mortality benefit of combining ACE-i and ARB?
- Is "triple therapy" safe?
- May an ARB reduce morbidity and mortality in preserved left ventricular function CHF?

Euroheart Failure

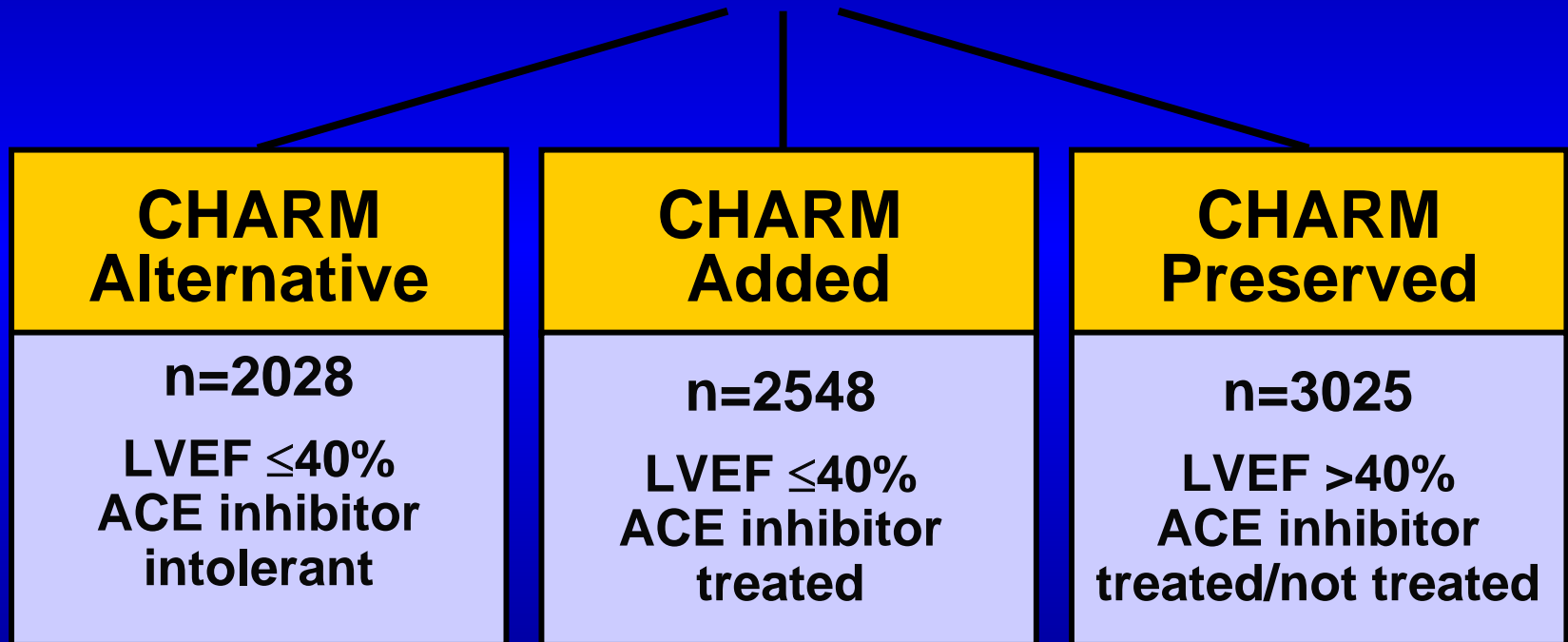
Distribution of left ventricular ejection fraction

11 322 patients from 115 hospitals in 24 countries



CHARM Programme

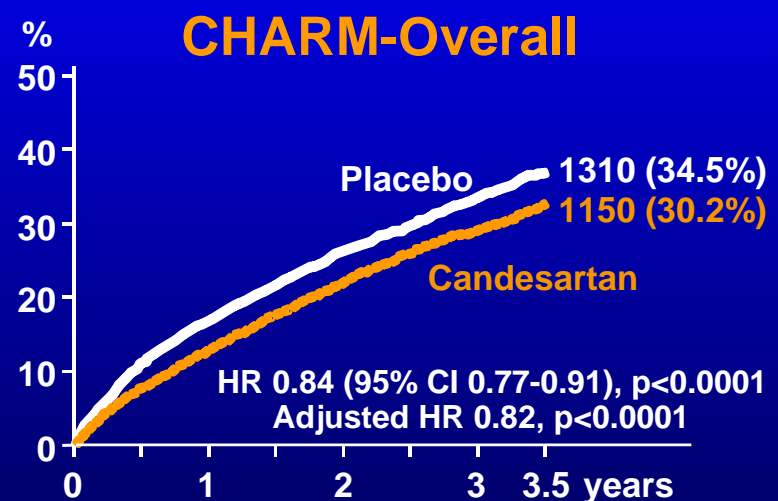
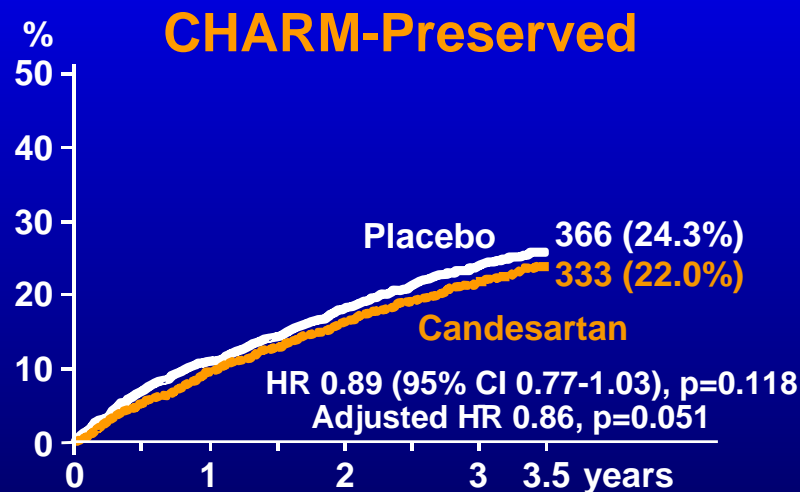
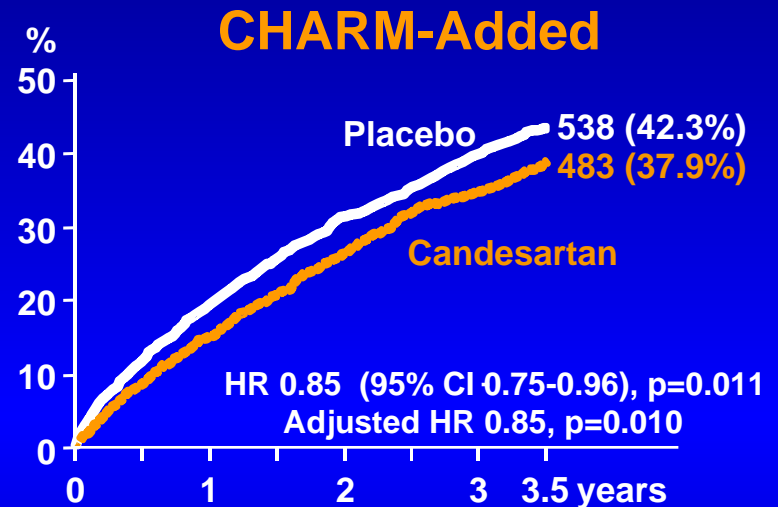
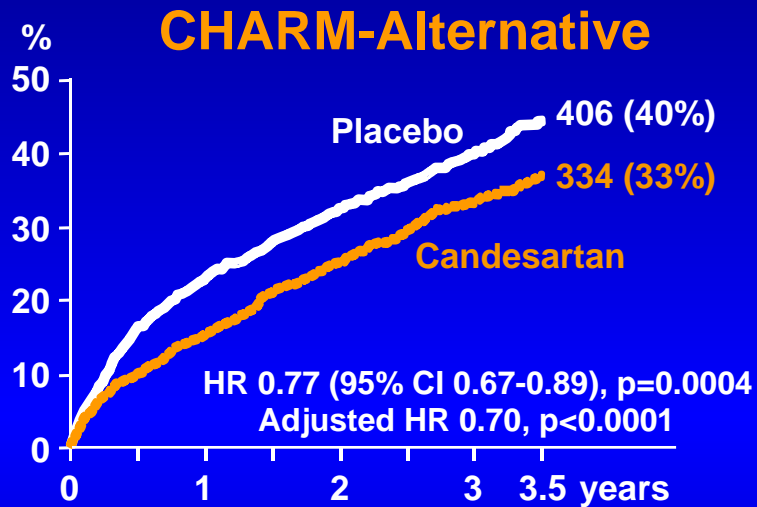
3 component trials comparing candesartan to placebo in patients with symptomatic heart failure



Primary outcome for each trial: CV death or CHF hospitalisation

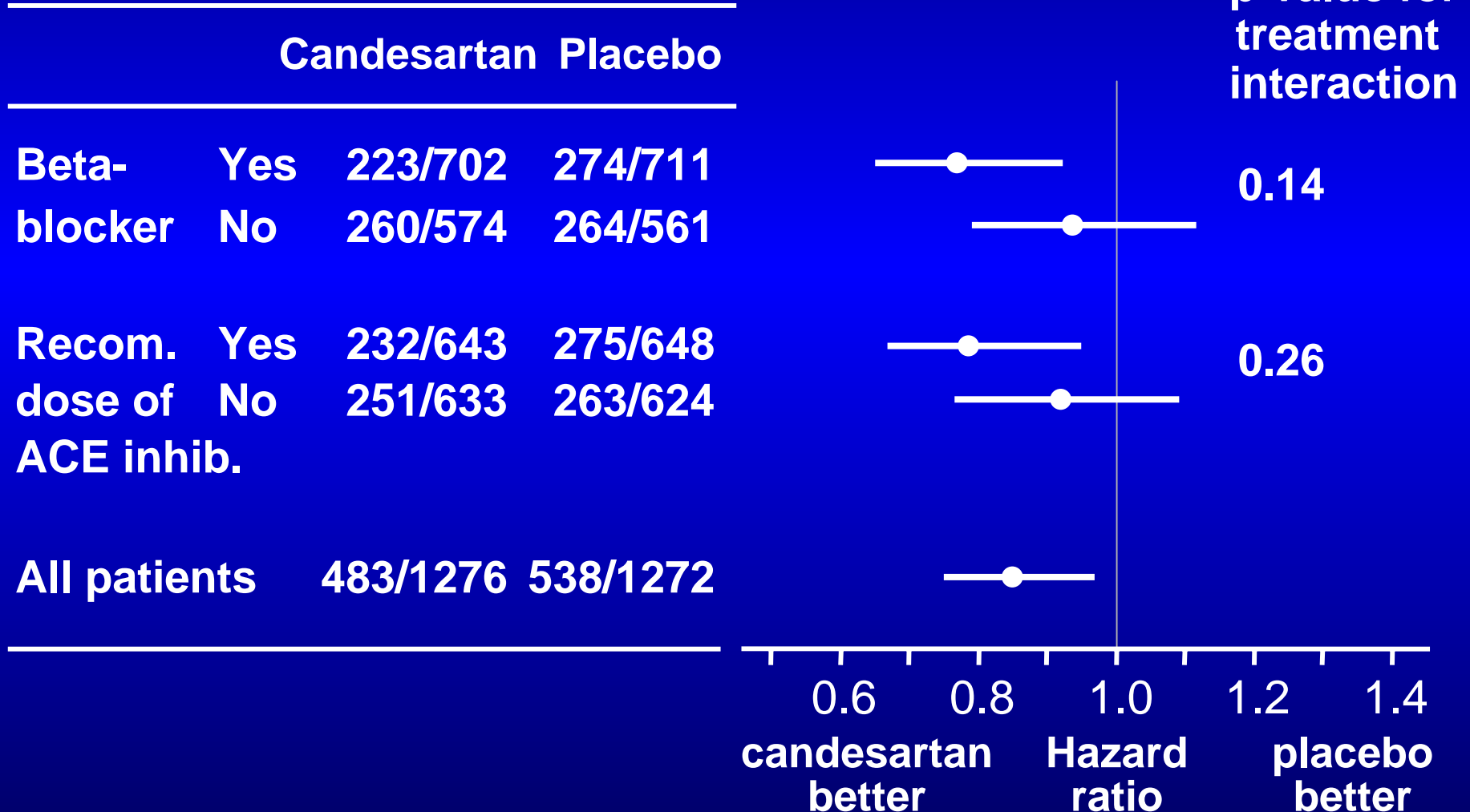
Primary outcome for Overall Programme: All-cause death

CHARM Programme:



CHARM-Added

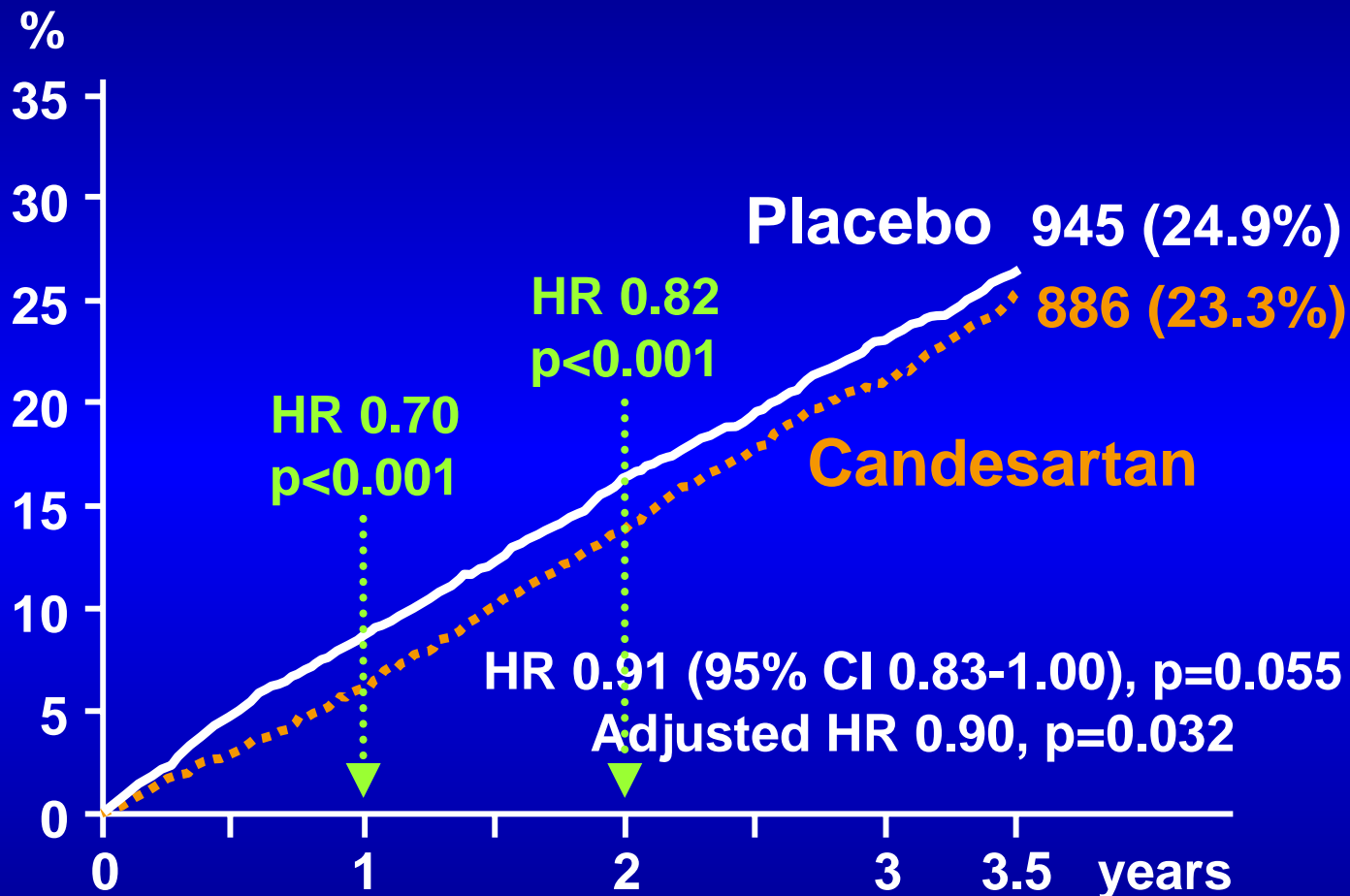
Prespecified subgroups, CV death or CHF hosp.





CHARM

CHARM-Overall: All-cause death



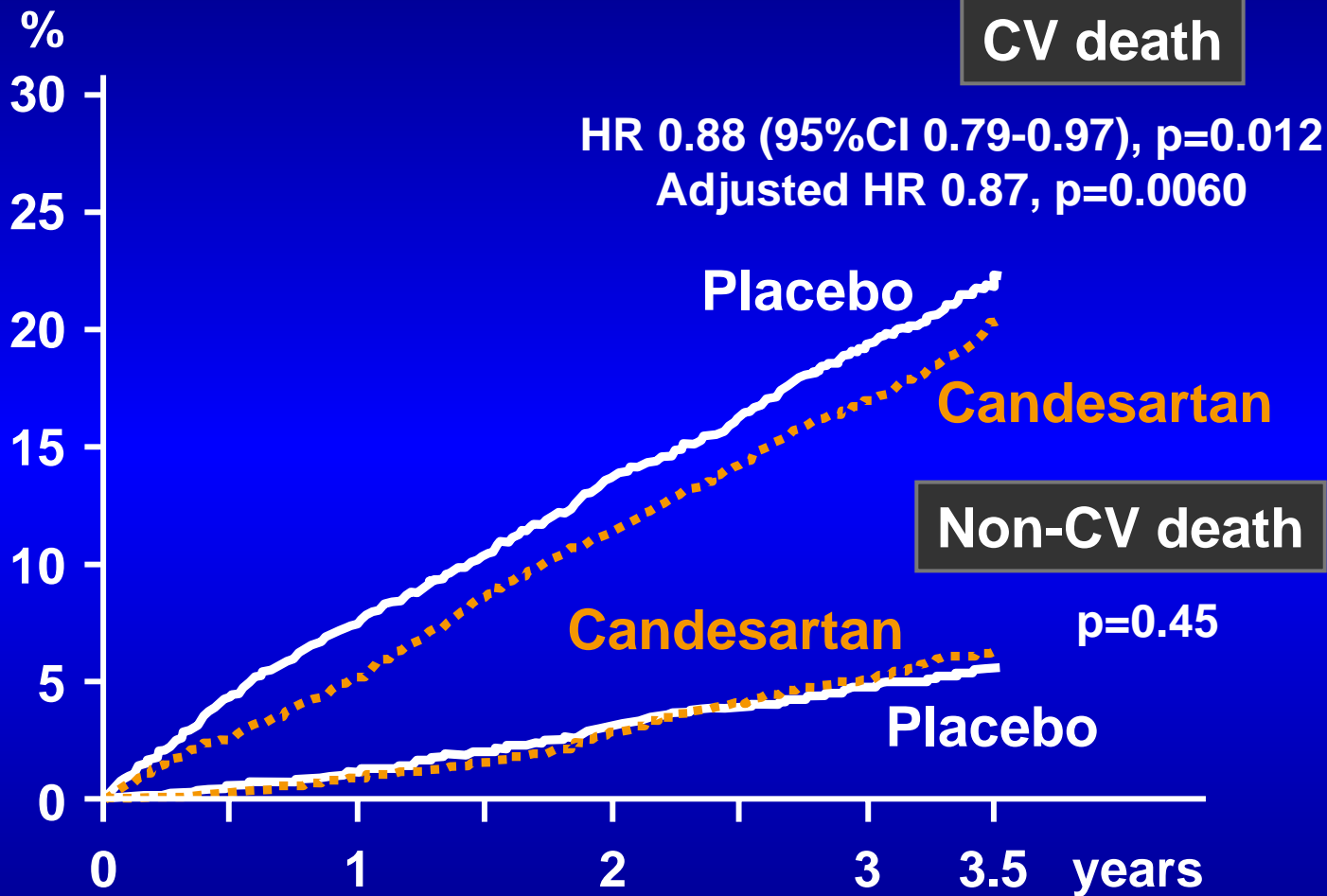
Number at risk

Candesartan	3803	3563	3271	2215	761
Placebo	3796	3464	3170	2157	743



CHARM

CHARM Overall: CV deaths and non-CV deaths



Number at risk

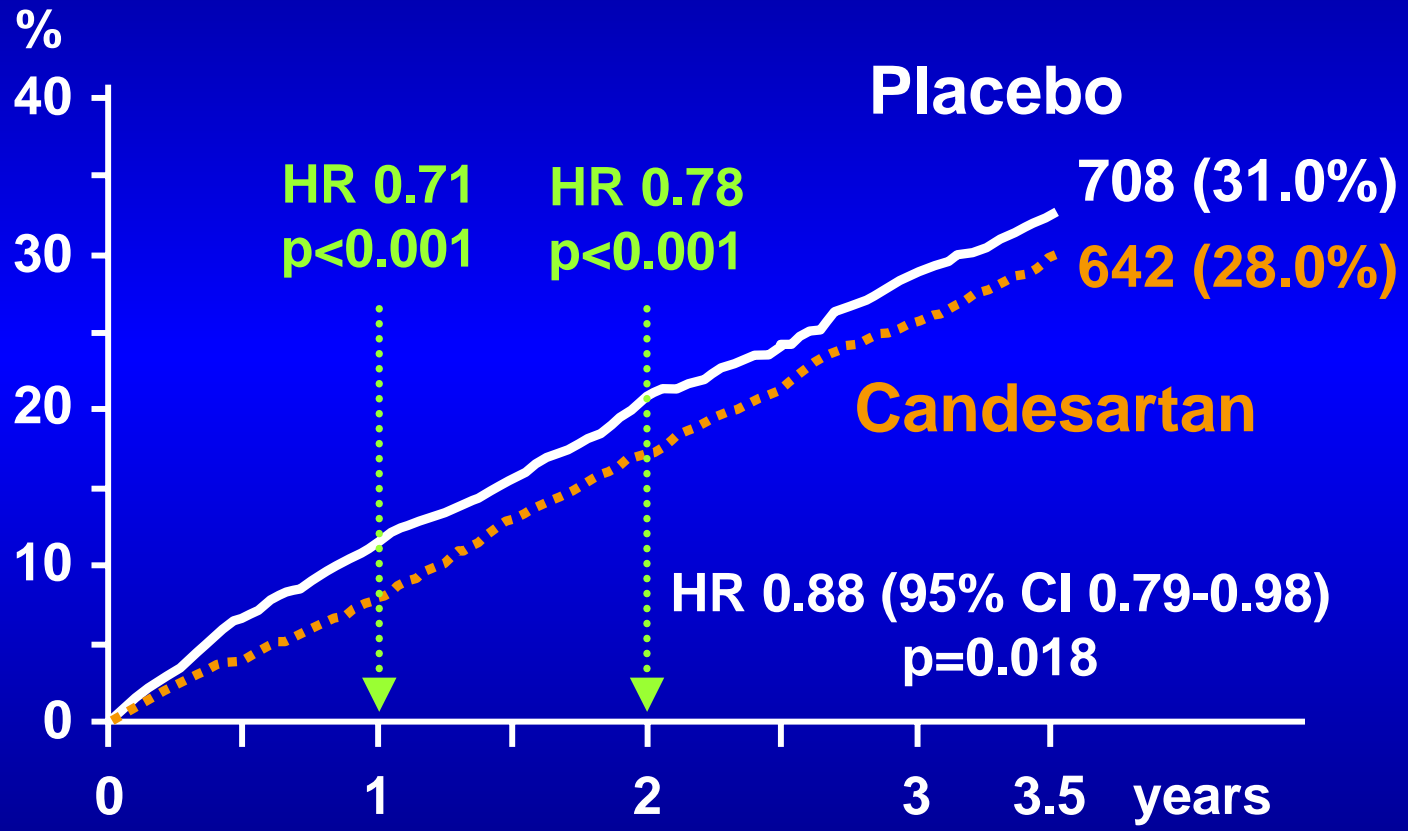
Candesartan	3803	3563	3271	2215	761
Placebo	3796	3464	3170	2157	743



CHARM

CHARM - Low EF (Alternative and Added)

All-cause death

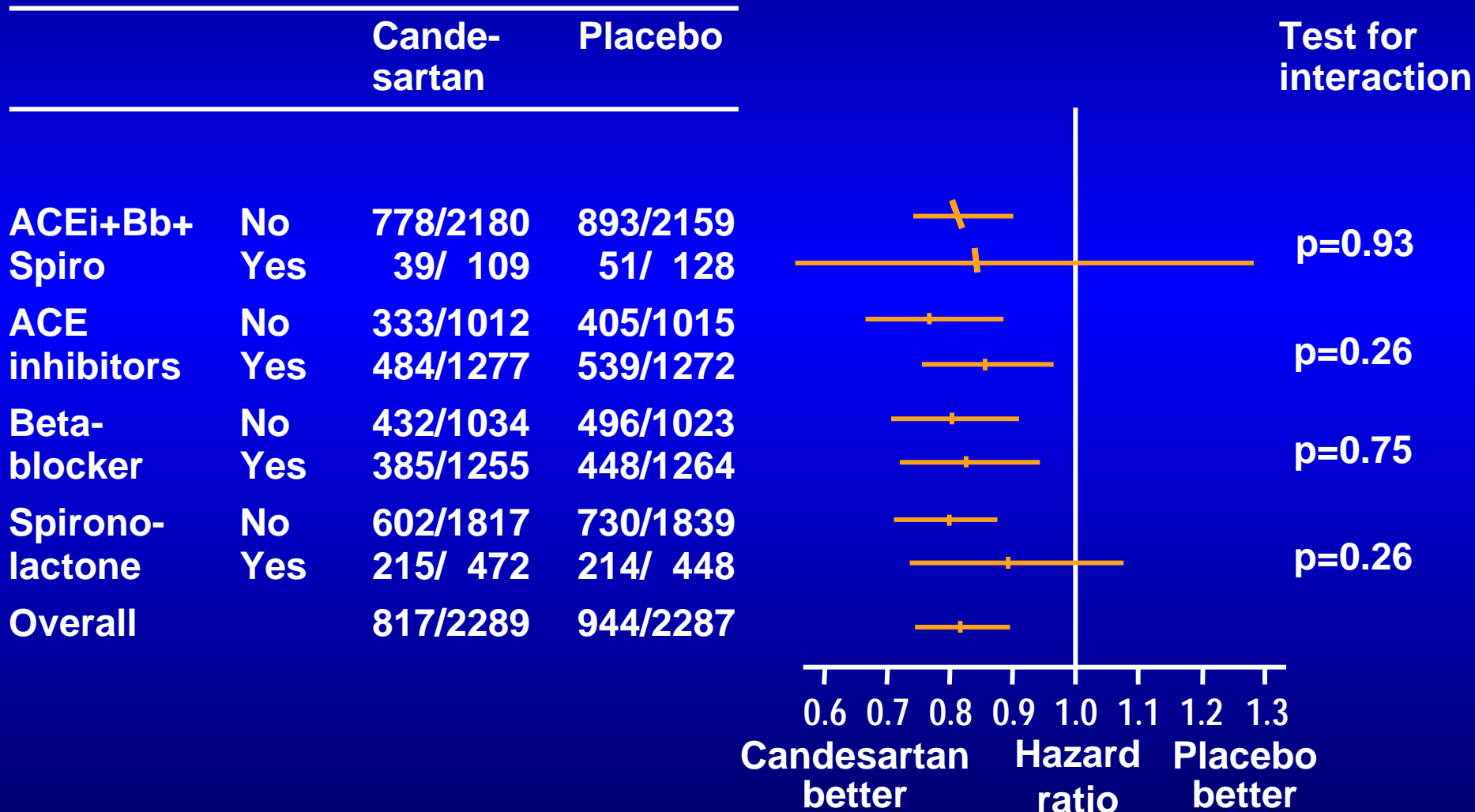


Number at risk

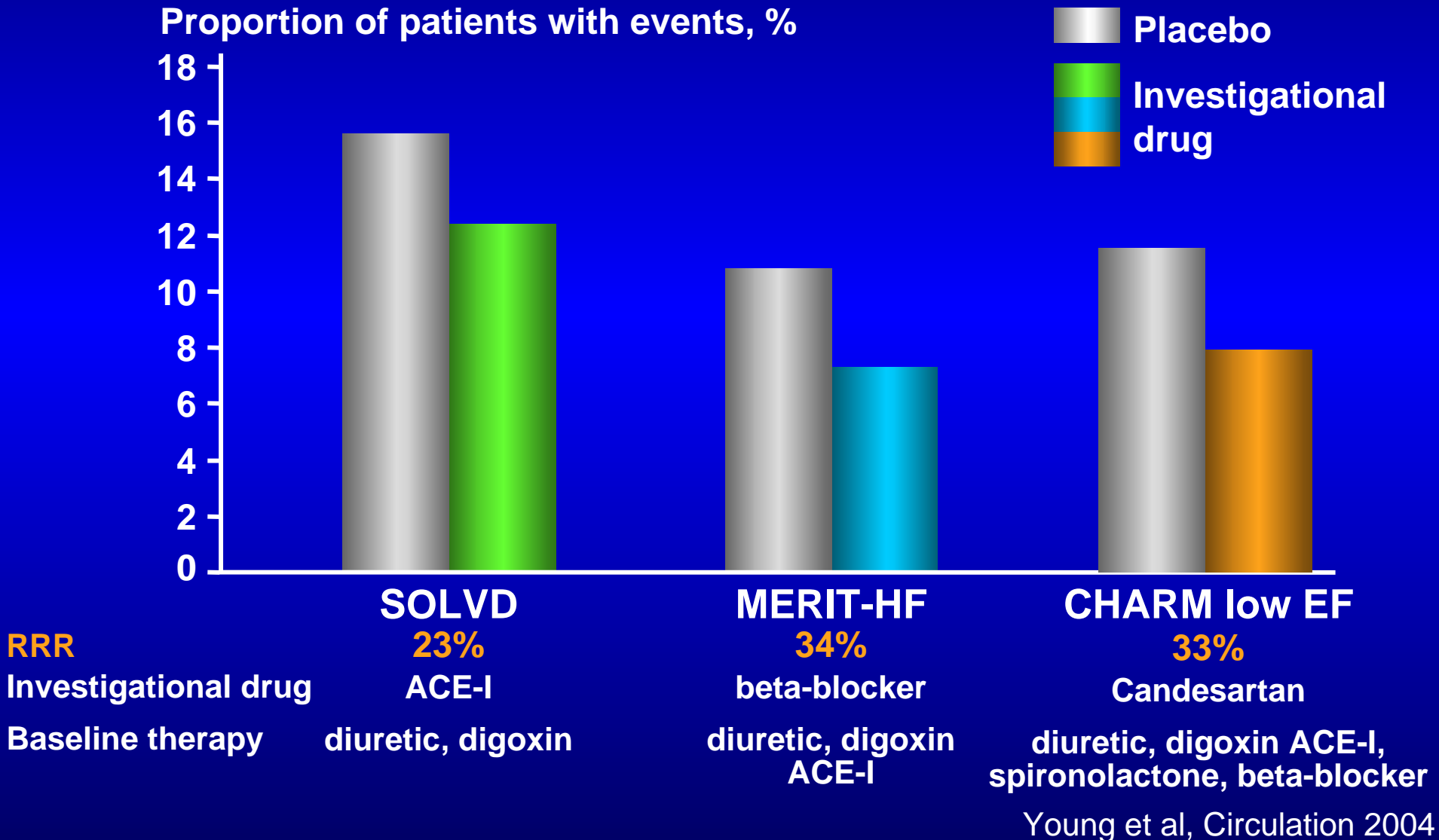
Candesartan	2289	2105	1894	1382
Placebo	2287	2023	1811	1333

CHARM - Low EF trials

CV death or CHF hospitalisation



All cause mortality and relative risk reduction (RRR) at 12 months



Optimal blockade of the RAA-System in chronic heart failure

- ACE-i should be used at maximal tolerated dose – if not tolerated an ARB should be given
- The combination of ACE-i/ARB more effective than ACE-i alone in symptomatic patients with CHF with LVEF<0.40
- Spironolactone should be added if patient has severe symptoms (class (III-)IV)

