

**Understanding and Development of
New Therapies for Heart Failure
- Lessons from Recent Clinical Trials -**

Clinical trials

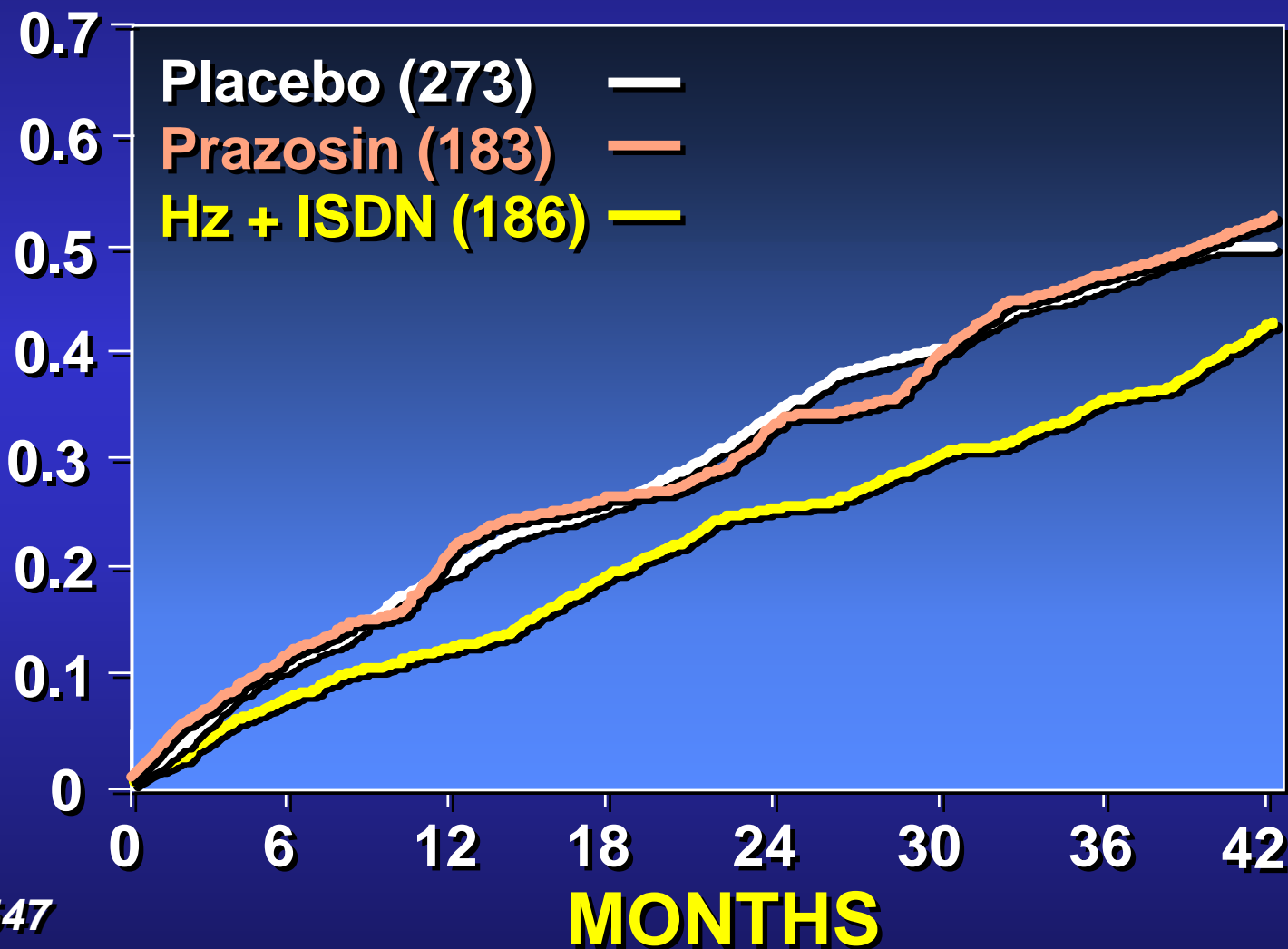
- Evidence-based medicine, clinical practice
- Impact upon
 - Understanding pathophysiology
 - Changing clinical practice through clarifying risk/benefit of intervention
- Cons
 - Cannot address all questions
 - “Art of medicine” not studied
 - Trial patients not like real-world patients
 - Long duration, expensive, ...

100 Large-scale Clinical Trials over 20 yrs

- ACE inhibitors
- Beta blockers
- Angiotensin receptor blockers (ARB's)
- CCB's, vasodilators, inotropes
- Anti-arrhythmic agents
- Device strategies like ICD, RCT
- Surgical intervention, immunomodulation, anticoagulation, exercise

VHefT - 1

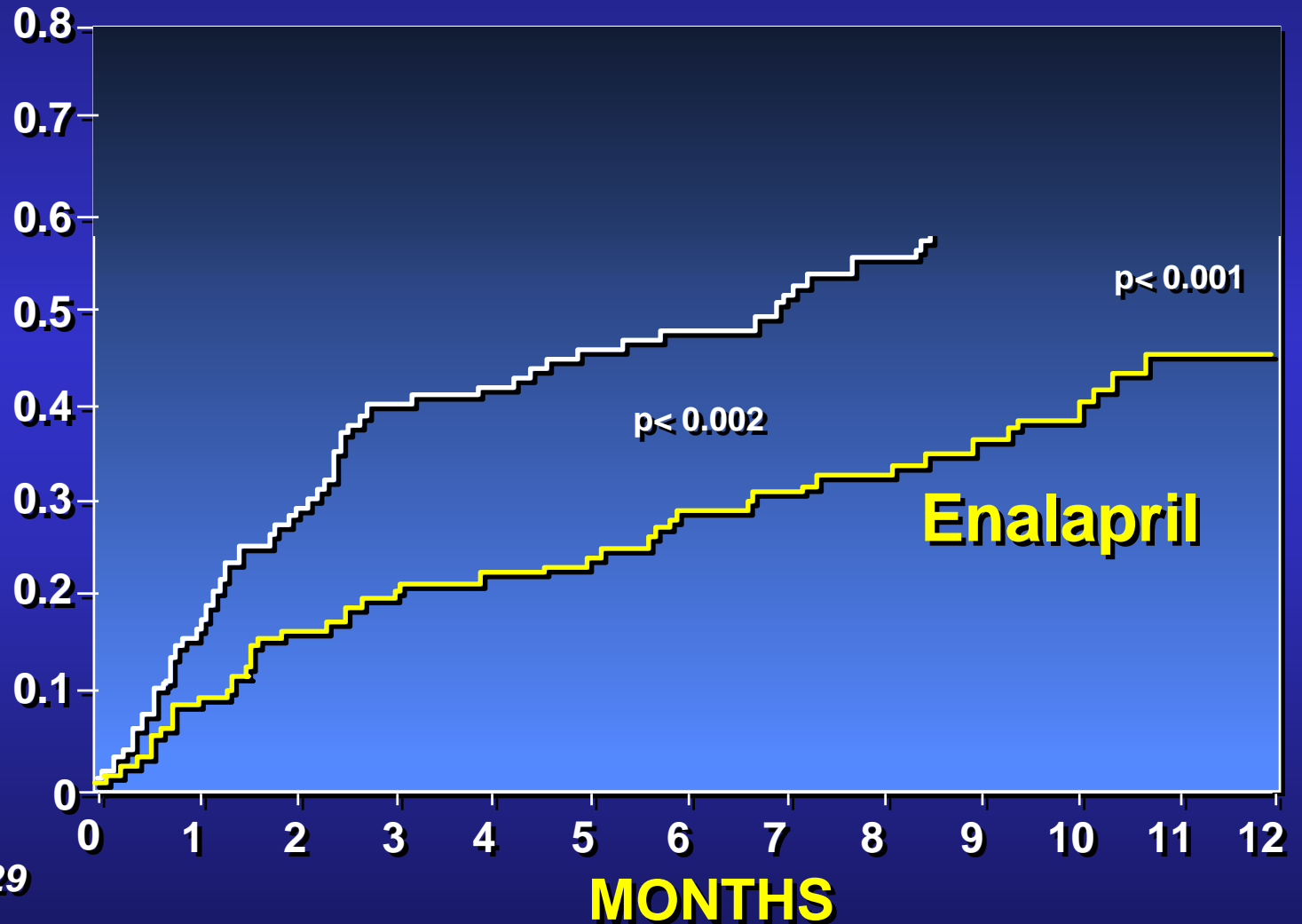
**PROBABILITY
OF
DEATH**



ACEI in Severe Heart Failure

PROBABILITY
OF
DEATH

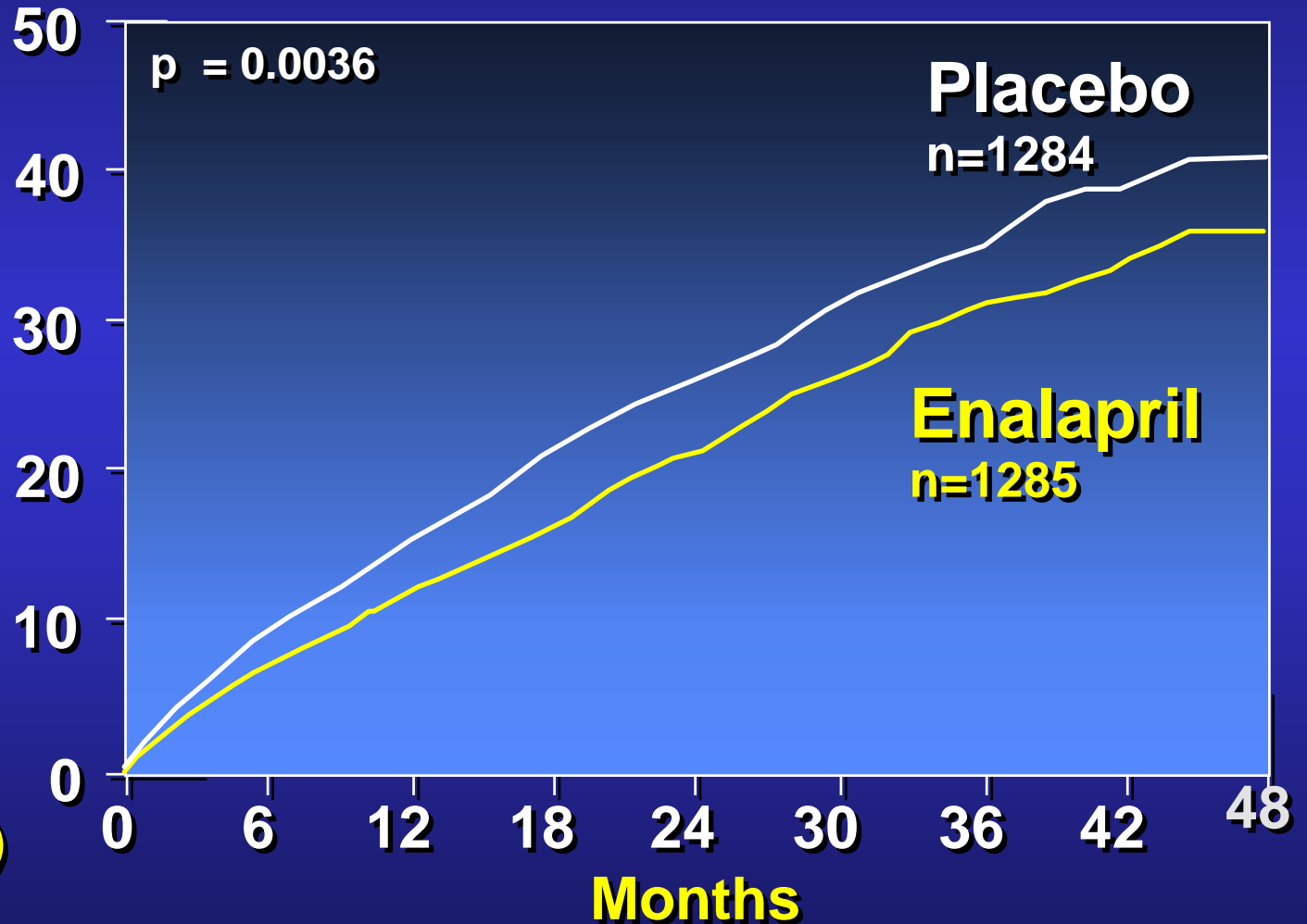
CONSENSUS



N Engl J Med 1987;316:1429

ACEI in Mild to Moderate Heart Failure

**%
MORTALITY**



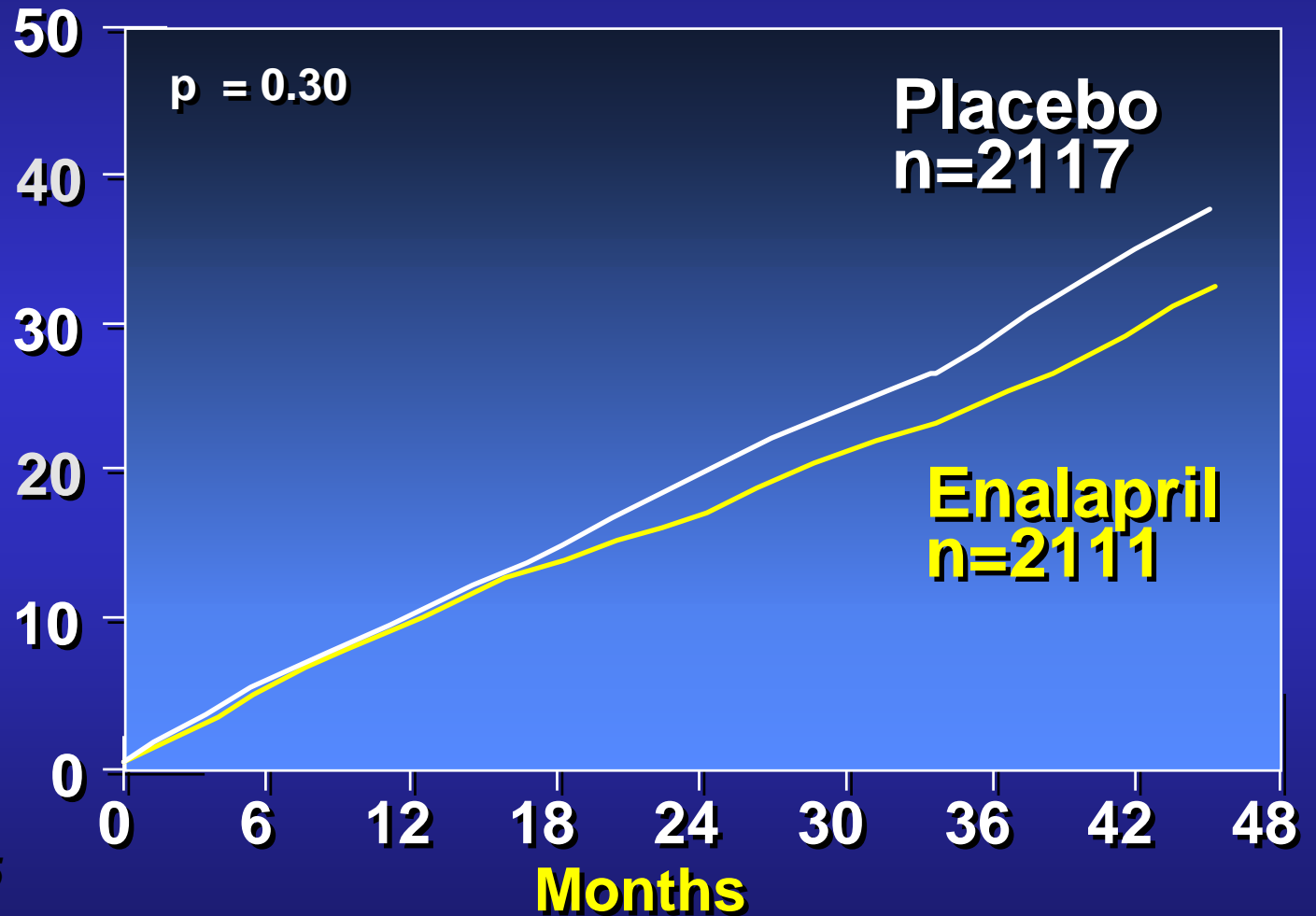
n = 2589
CHF
- NYHA II-III
- EF < 35

SOLVD (Treatment)

N Engl J M 1991;325:293

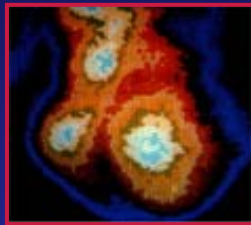
ACEI In Asymptomatic LV Dysfunction

**%
MORTALITY**



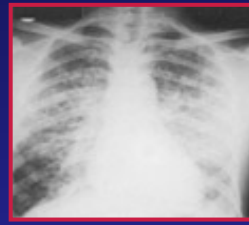
n = 4228
No CHF symptoms
EF < 35

SOLVD (Prevention)
N Engl J Med 1992;327:685



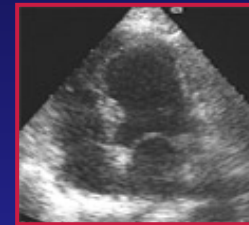
SAVE

Radionuclide
EF \leq 40%



AIRE

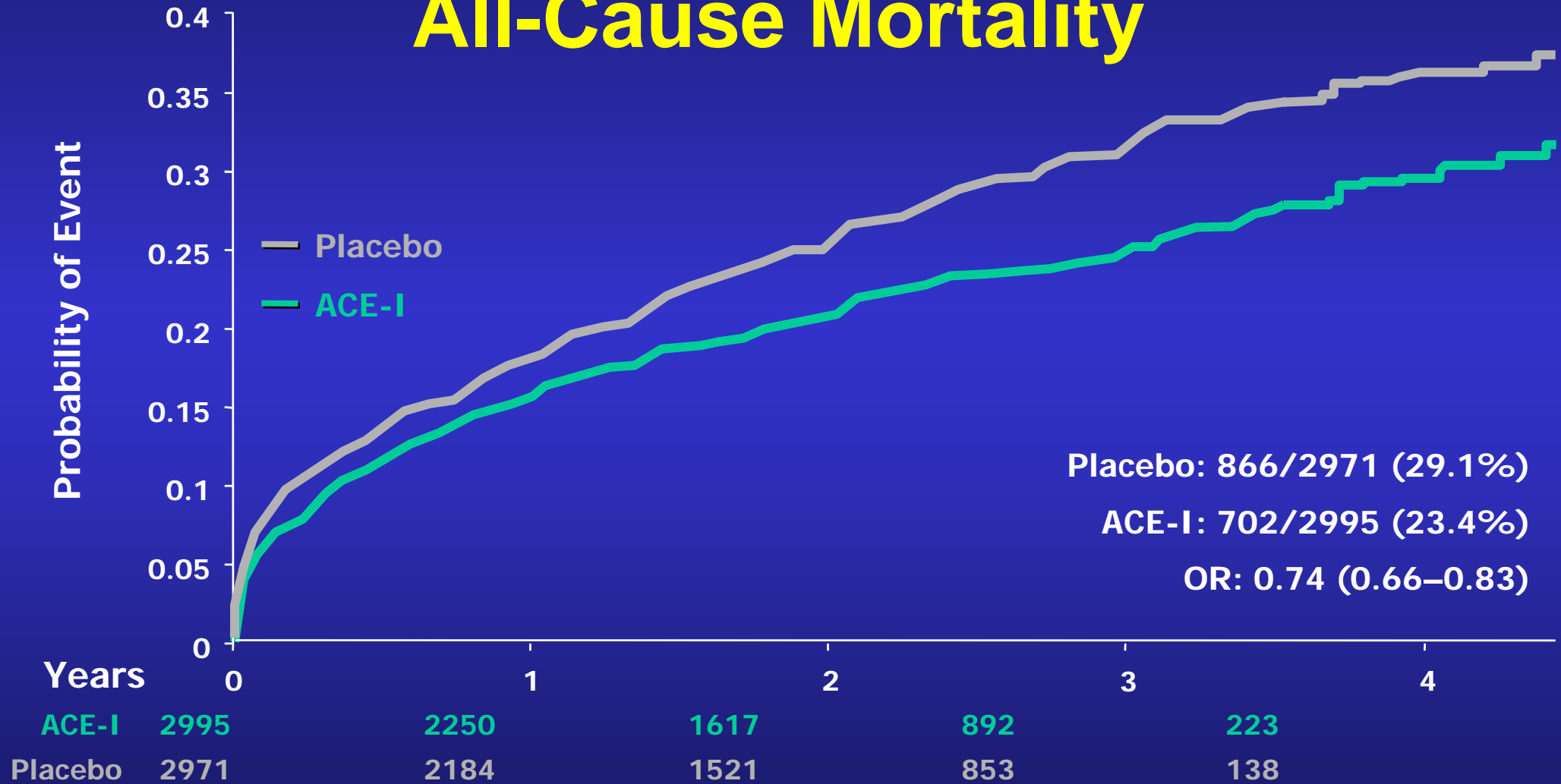
Clinical and/or
radiographic
signs of HF



TRACE

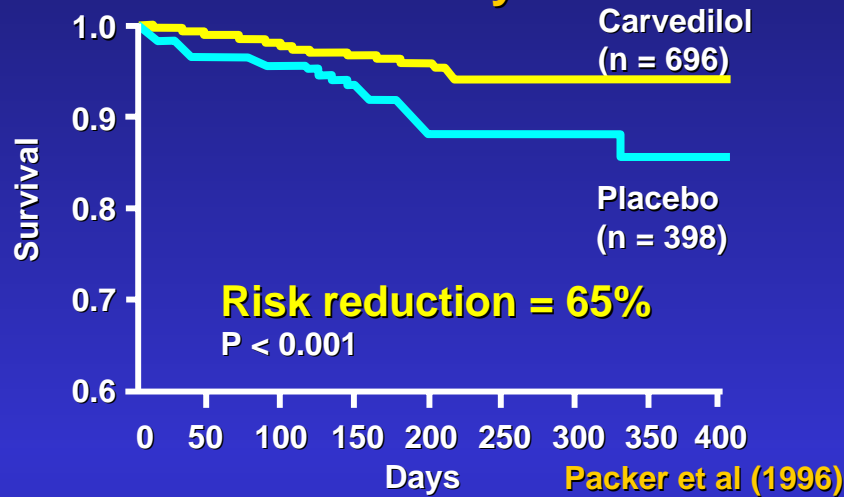
Echocardiographic
EF \leq 35%

All-Cause Mortality

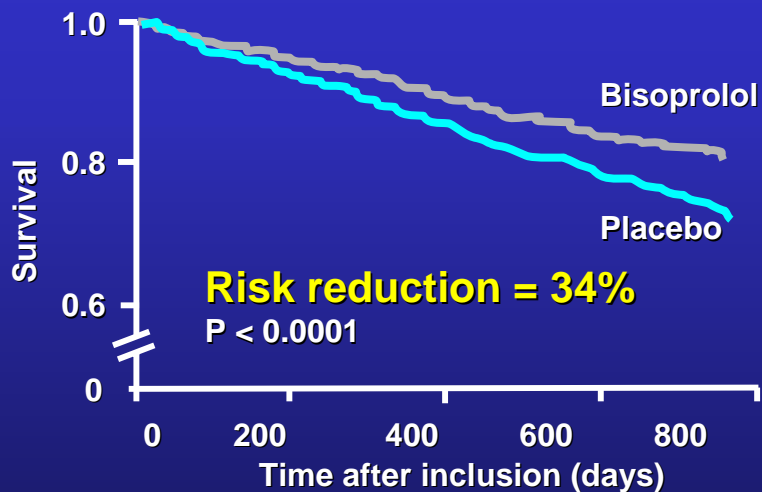


β blockers in CHF – All-cause Mortality

US Carvedilol Study

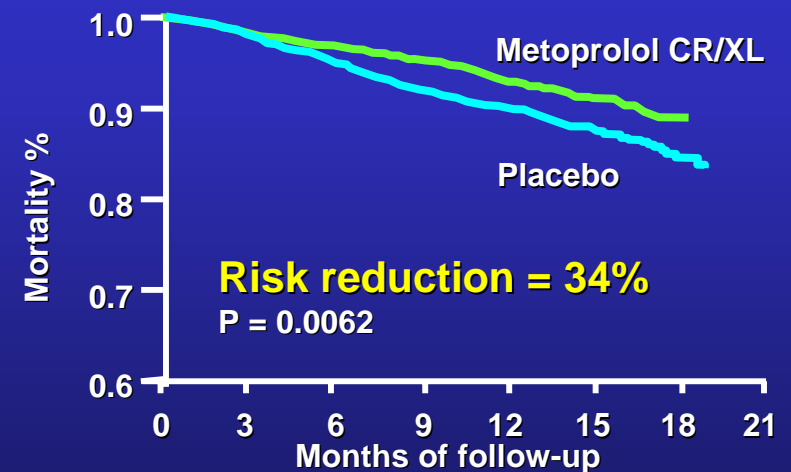


CIBIS-II



CIBIS-II Investigators (1999)

MERIT-HF



The MERIT-HF Study Group (1999)

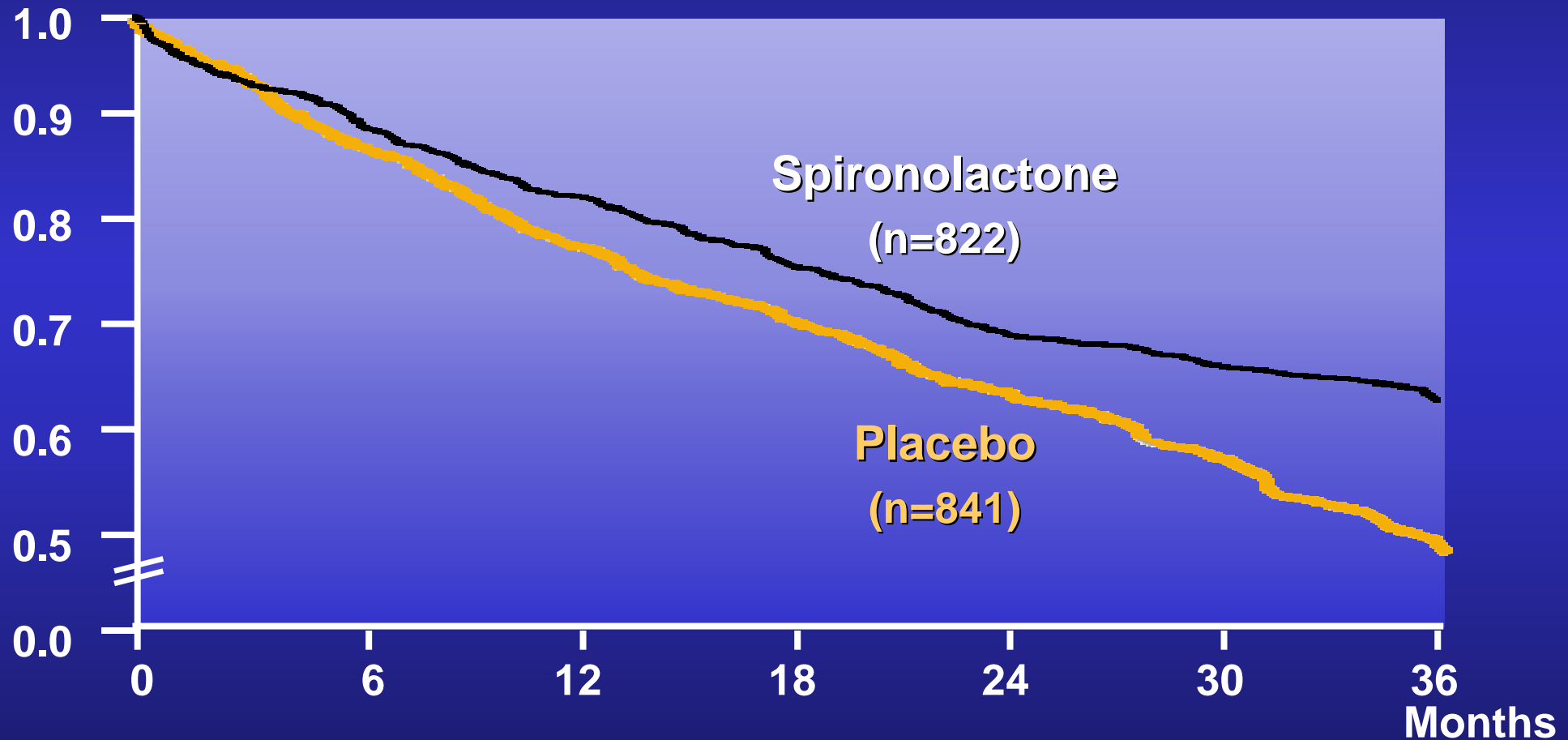
ARB's in heart failure

- **ELITE, ELITE-II**
 - Losartan vs. captopril in old patients
 - similar primary end point
- **RESOLVED**
 - candesartan

Spironolactone - RALES

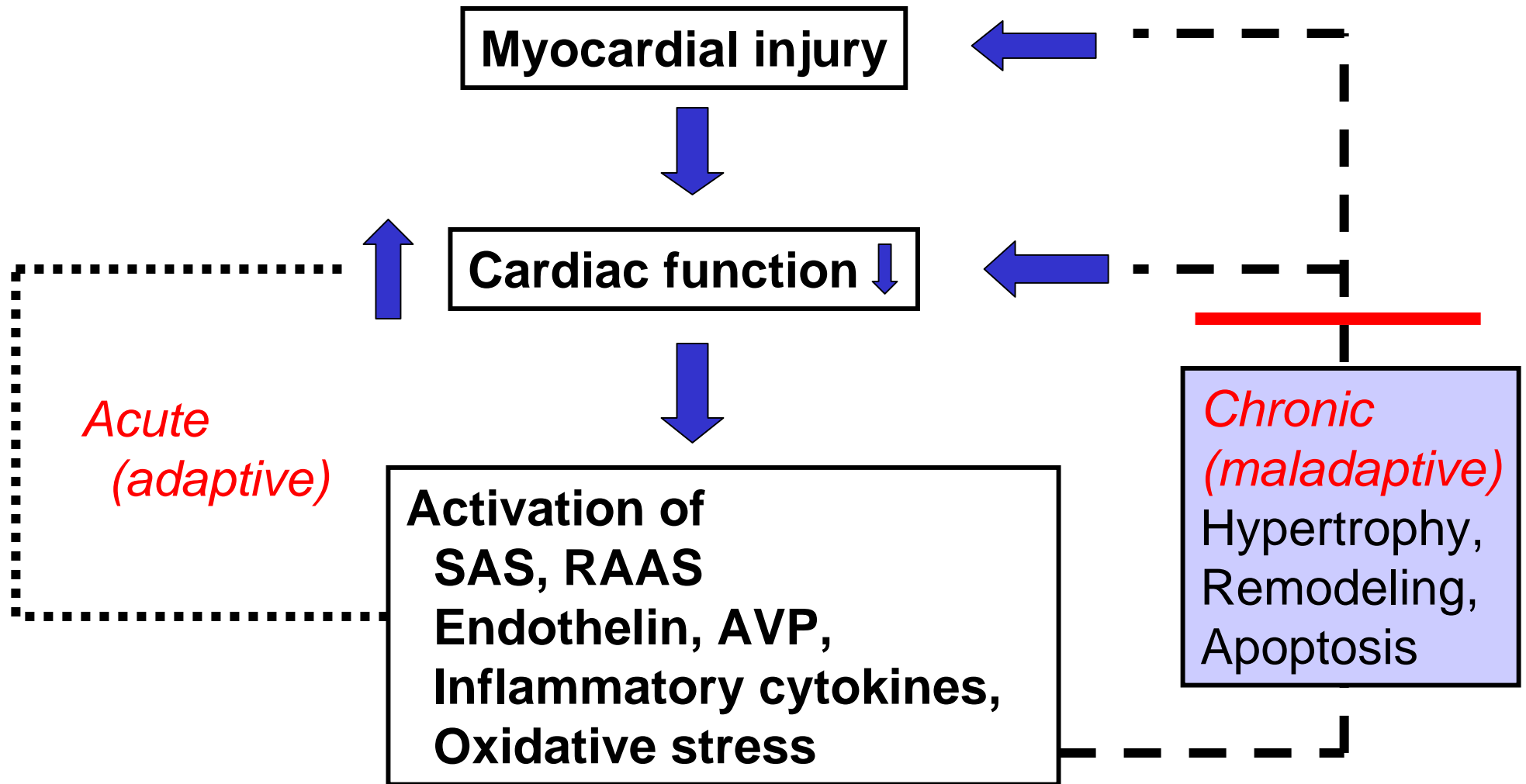
n=1,663, NYHA III-IV, EF 35%, 24months, Spironolactone 25-50 mg

Probability of Survival



Pitt B, et al. RALES study. N Engl J Med 1999;341:709.

Neurohormonal & cytokine adjustment



Established guideline from past clinical trials

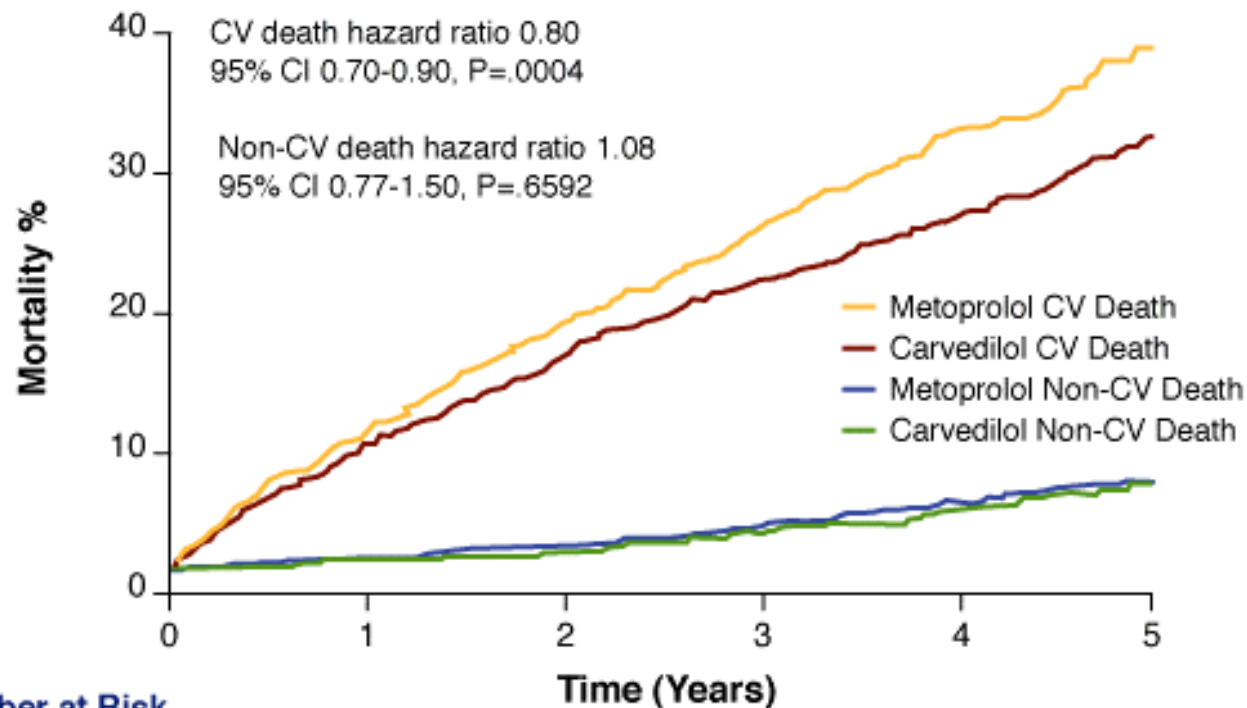
- **ACE inhibitors** in all patients with LV systolic dysfunction who can tolerate them
- **ARB's** in ACE inhibitor intolerant patients with LV systolic dysfunction
- **Beta blockers** in stable patients with mild to moderate symptoms without significant congestion
- **Aldosterone antagonists** in moderate to severe HF

Recent clinical trials impacting HF therapy

- **Beta blockers**
- **Angiotensin-aldosterone antagonists**
 - Angiotensin receptor blockers
 - Aldosterone antagonist
- **Other medical therapeutics**
 - NEP inhibitor
 - Anticytokines
 - Antiarrhythmic agent
 - t-type CCB's
- **Device**
 - ICD
 - RCT

COMET

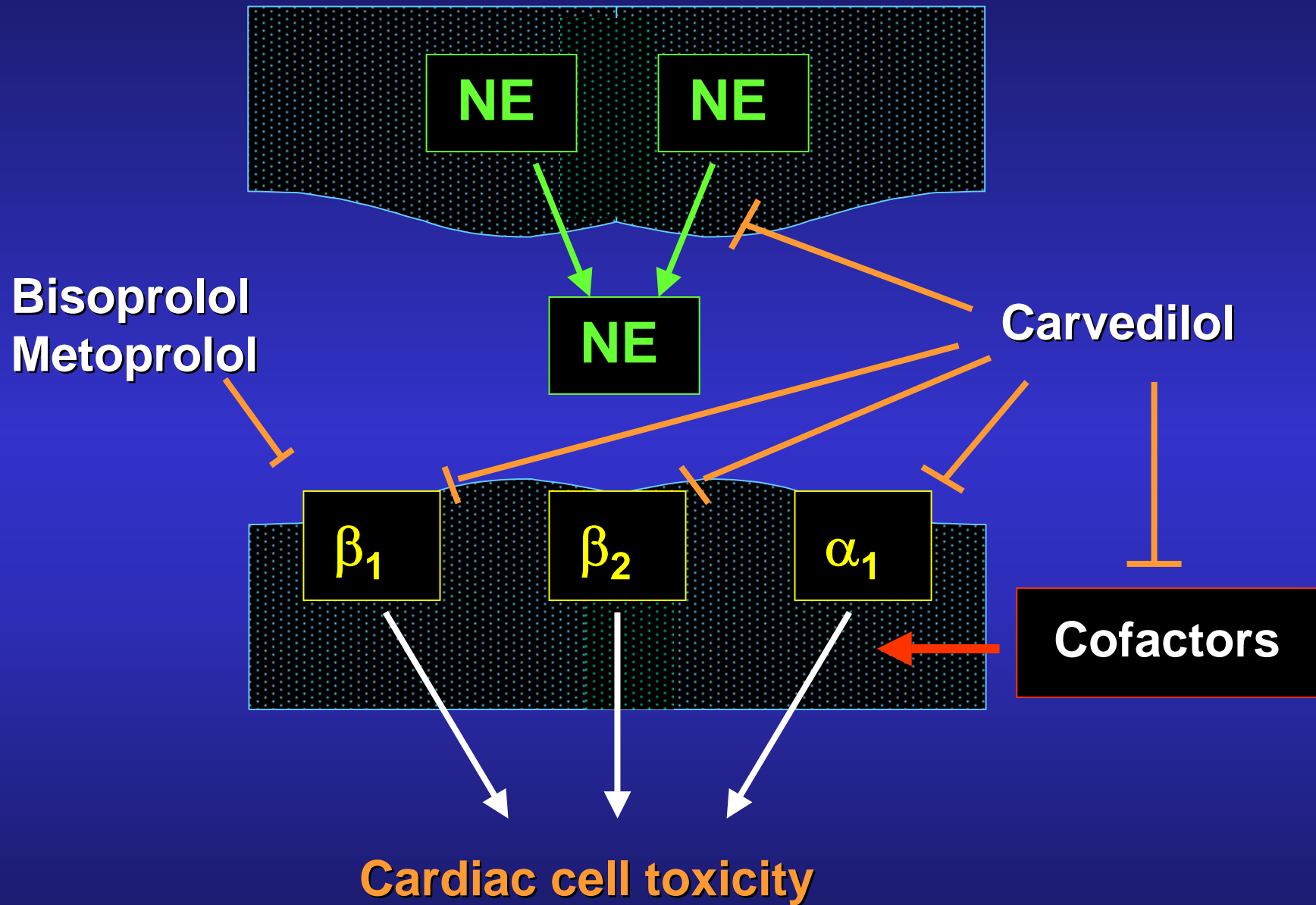
Cardiovascular and Non-Cardiovascular Death



Number at Risk

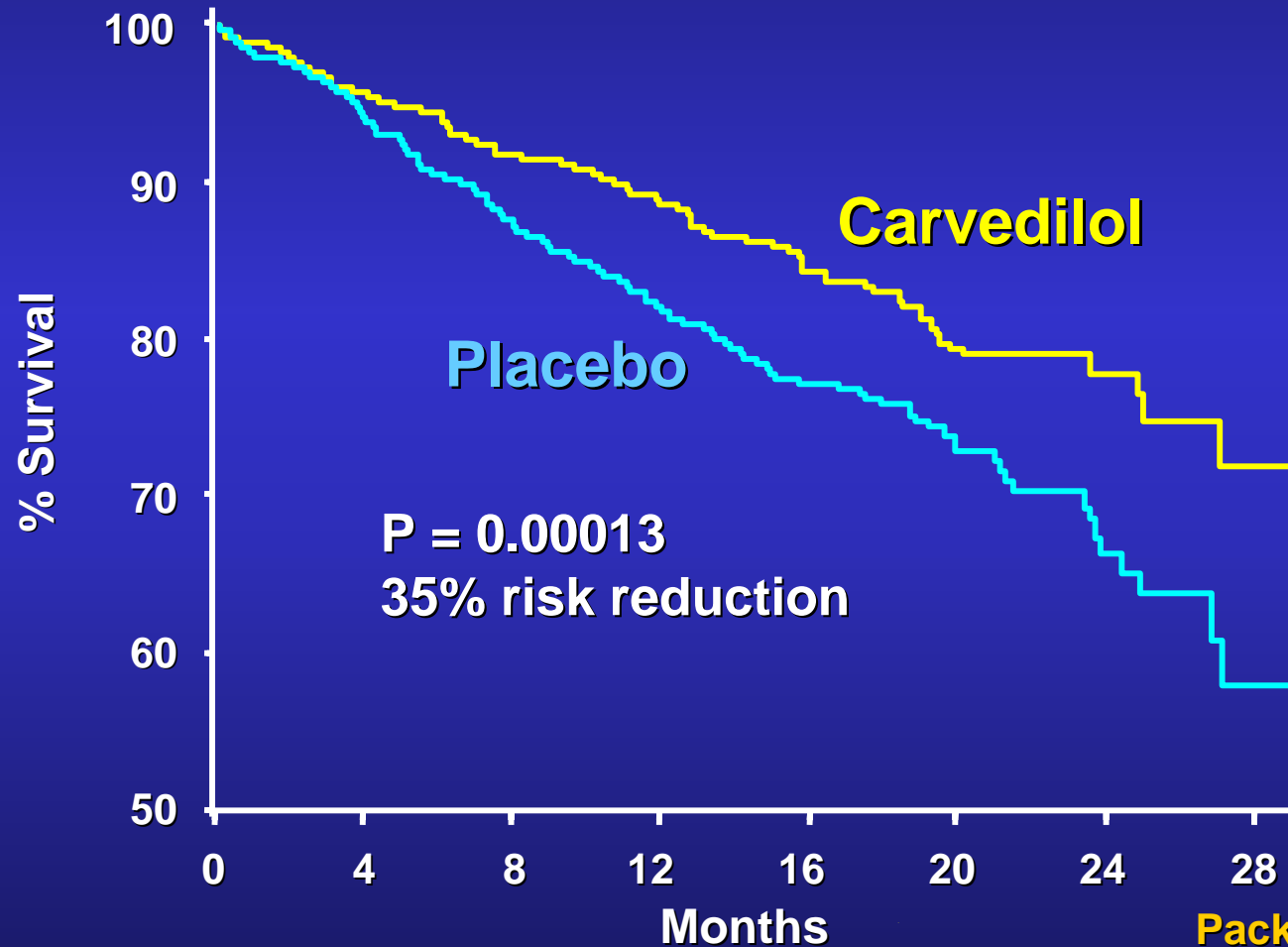
Metoprolol	1518	1359	1234	1105	933	352
Carvedilol	1511	1366	1258	1154	1002	382

Effects of Different β Blocking Agents



COPERNICUS

All-cause mortality



Packer et al. NEJM 2001

Recent beta blocker trials

- **COMET**, carvedilol vs. metoprolol
 - carvedilol is better
- **COPERNICUS**, carvedilol in severe (class IIIB & IV) HF
 - 35 % mortality reduction
- **CAPRICORN**, carvedilol in post-MI HF (EF < 40%)
 - 23 % reduction in all-cause mortality risk reduction
- **BEST**, bucindolol
 - Only non-statistically insignificant reduction in mortality and morbidity
- **MOXCON**, moxonidine, centrally acting beta blocker
 - Increased mortality

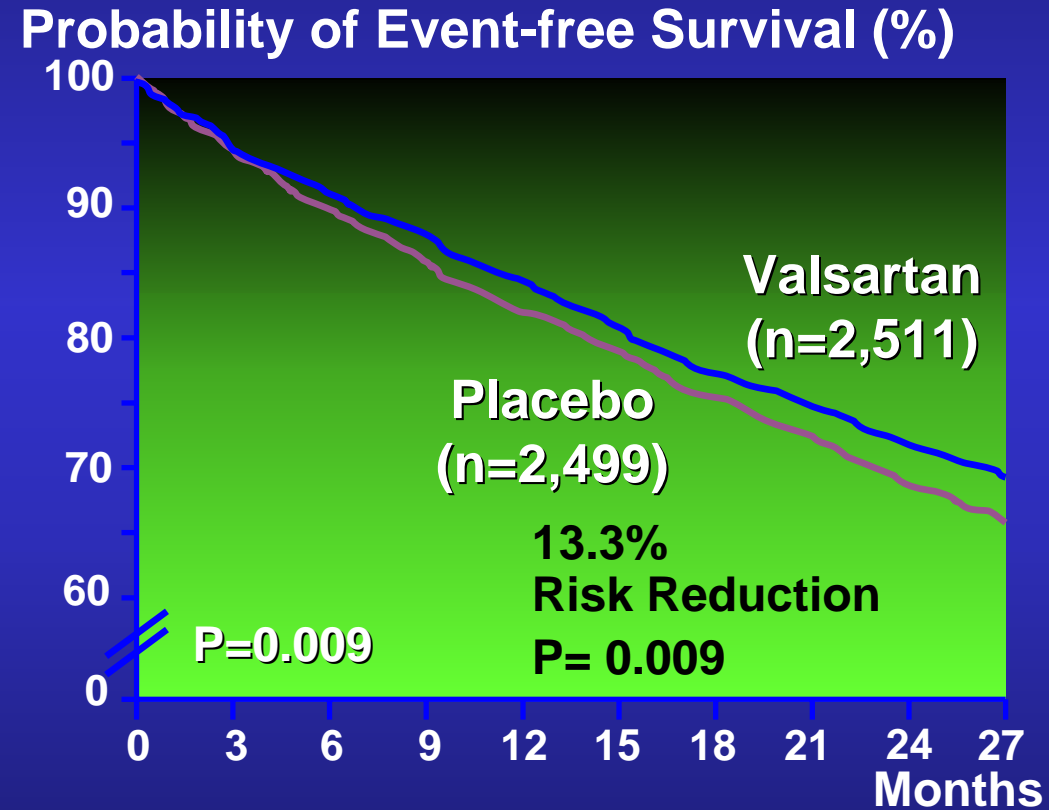
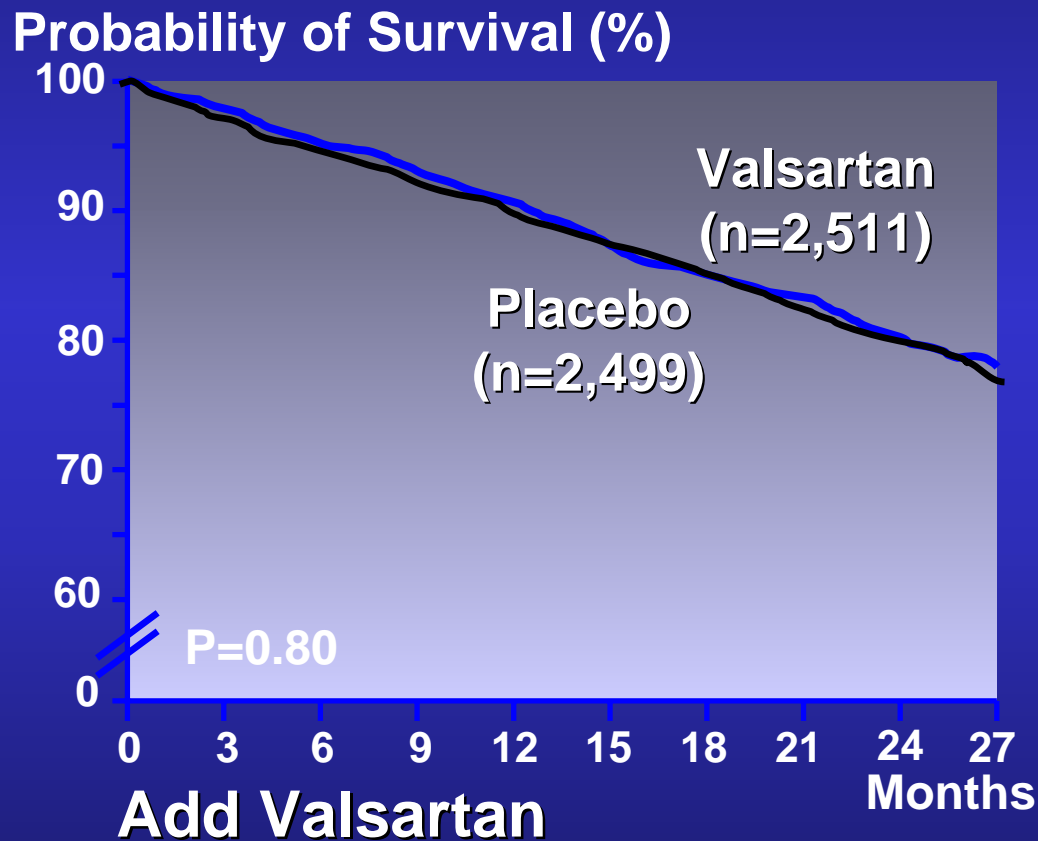
Recent Angiotensin-Aldosterone Antagonist Trials

- **Angiotensin receptor blockers**
 - OPTIMAAL : losartan in post-MI LV dysfunction
 - Valsartan : Val-HeFT, VALIANT
 - Candesartan : CHARM programme
- **Aldosterone antagonist**
 - Eplerenone : EPHESUS

Val-HeFT : Valsartan vs. Placebo

n=5,010, NYHA II-IV, EF 40%, 23months

Conventional Tx(including ACE inhibitors) + Valsartan 160mg bid



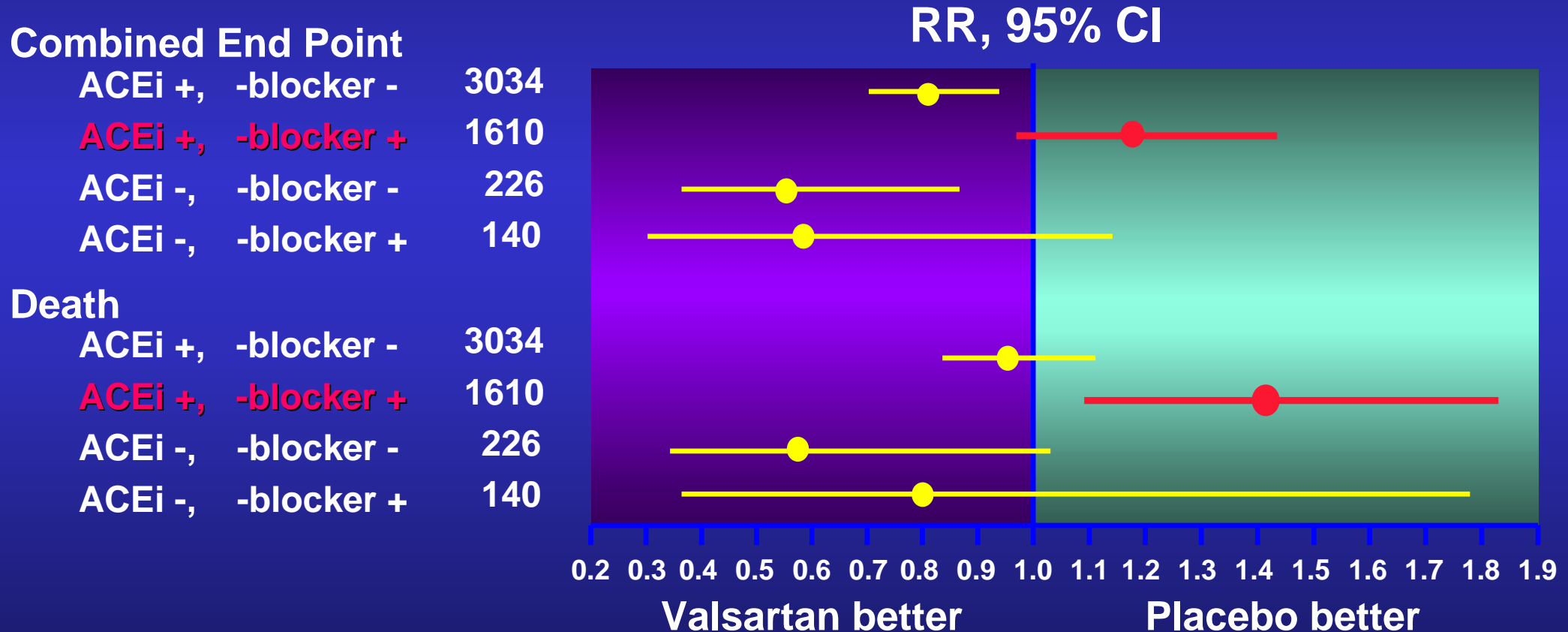
27.5% Hospitalization, Improvement of EF, NYHA class, Sx and Signs

Cohn JN, et al. N Engl J Med 2001;345:1667.

Val-HeFT : Valsartan vs. Placebo

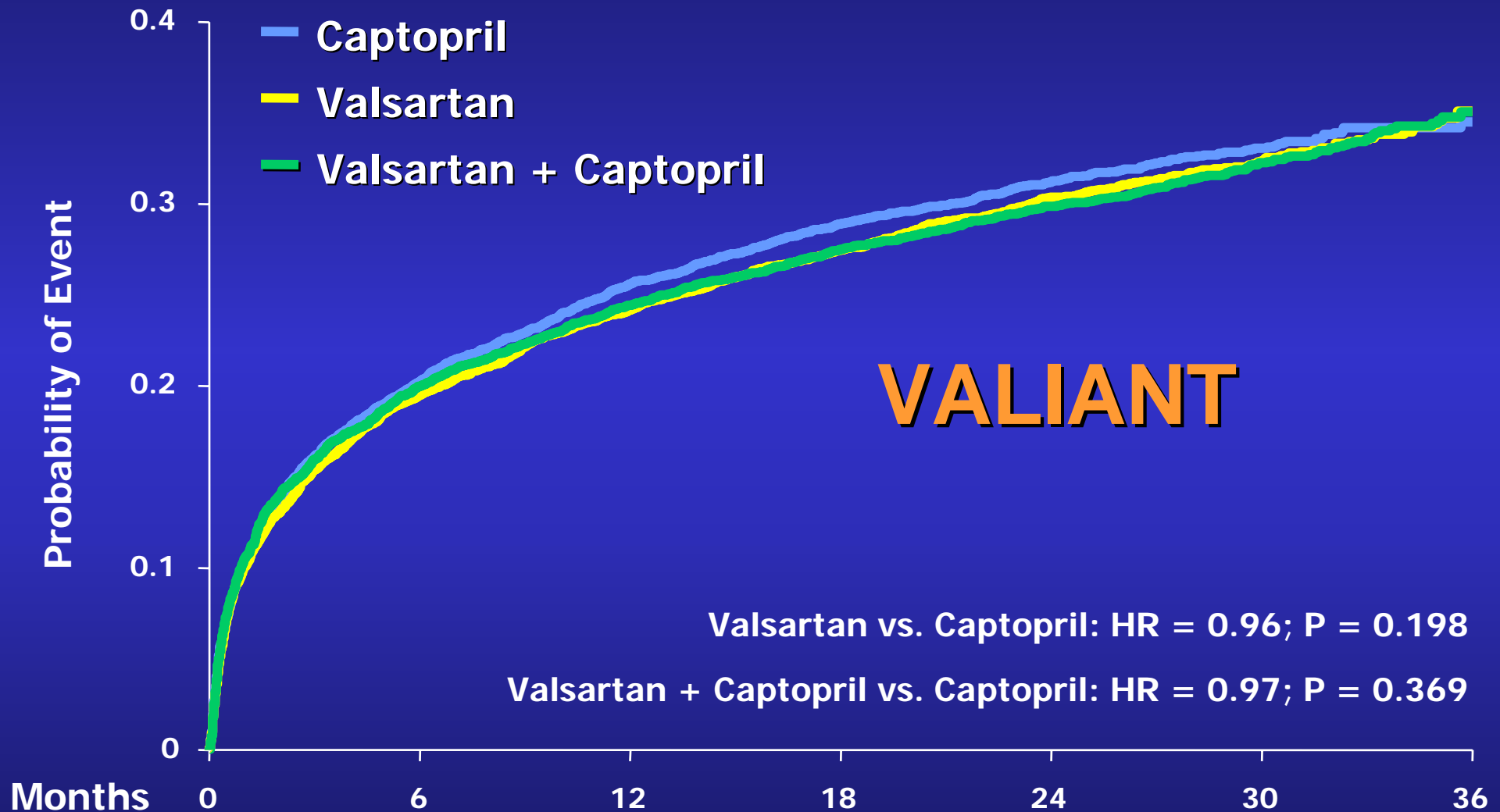
n=5,010, NYHA II-IV, EF 40%, 23months

Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening HF, IV Inotropes or Vasodilators)



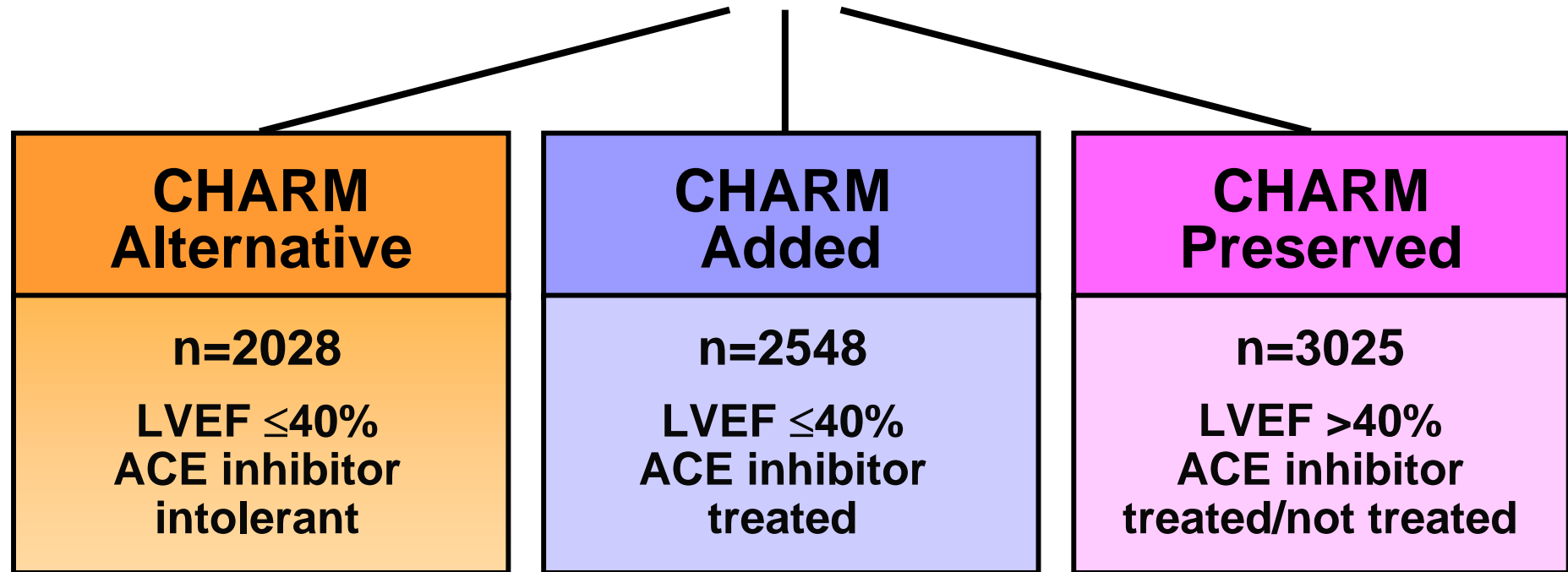
Cohn JN, et al. N Engl J Med 2001;345:1667.

CV Death, MI, or HF by Treatment



CHARM Programme

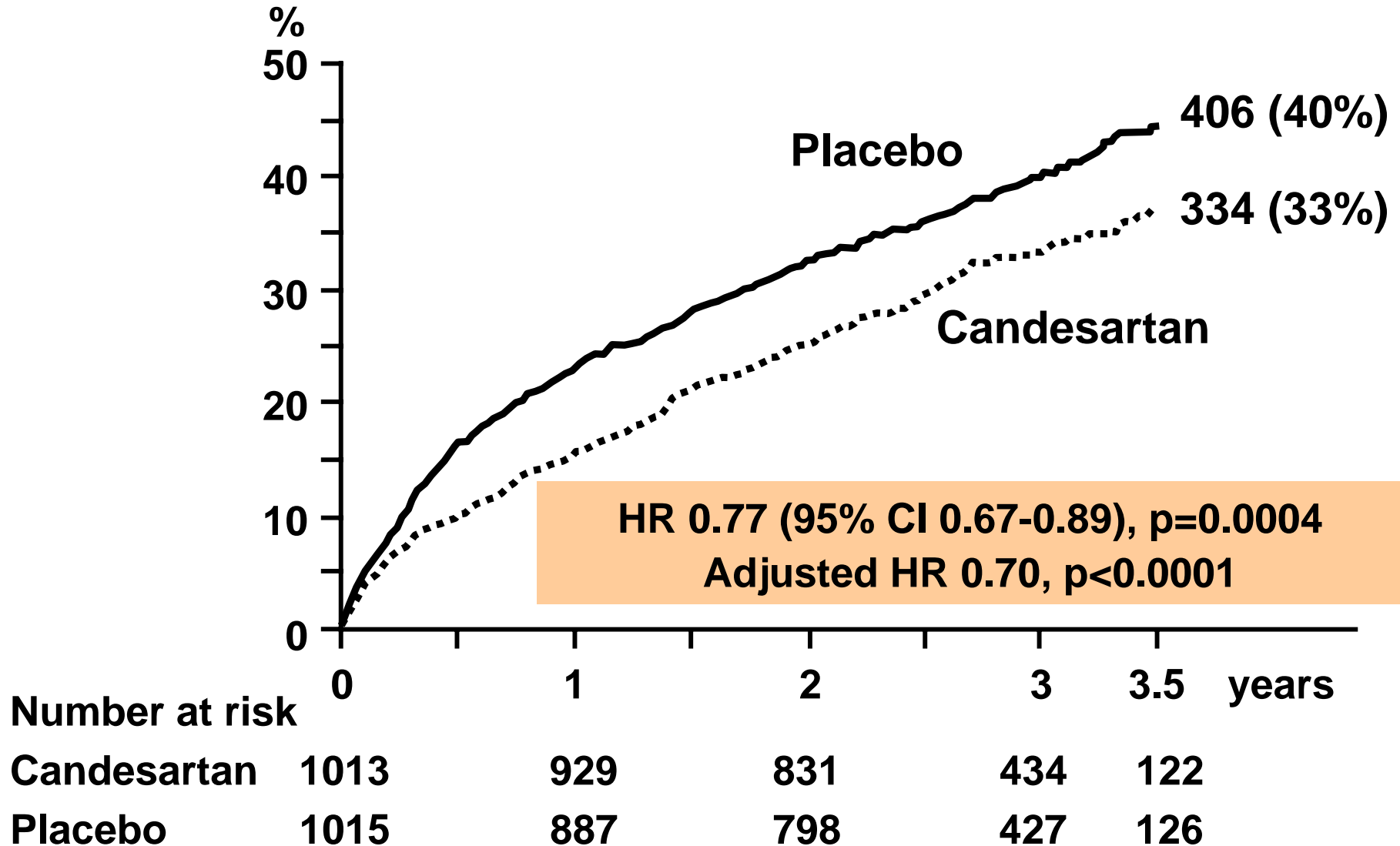
3 component trials comparing candesartan to placebo in patients with symptomatic heart failure



Primary outcome for each trial: CV death or CHF hospitalisation

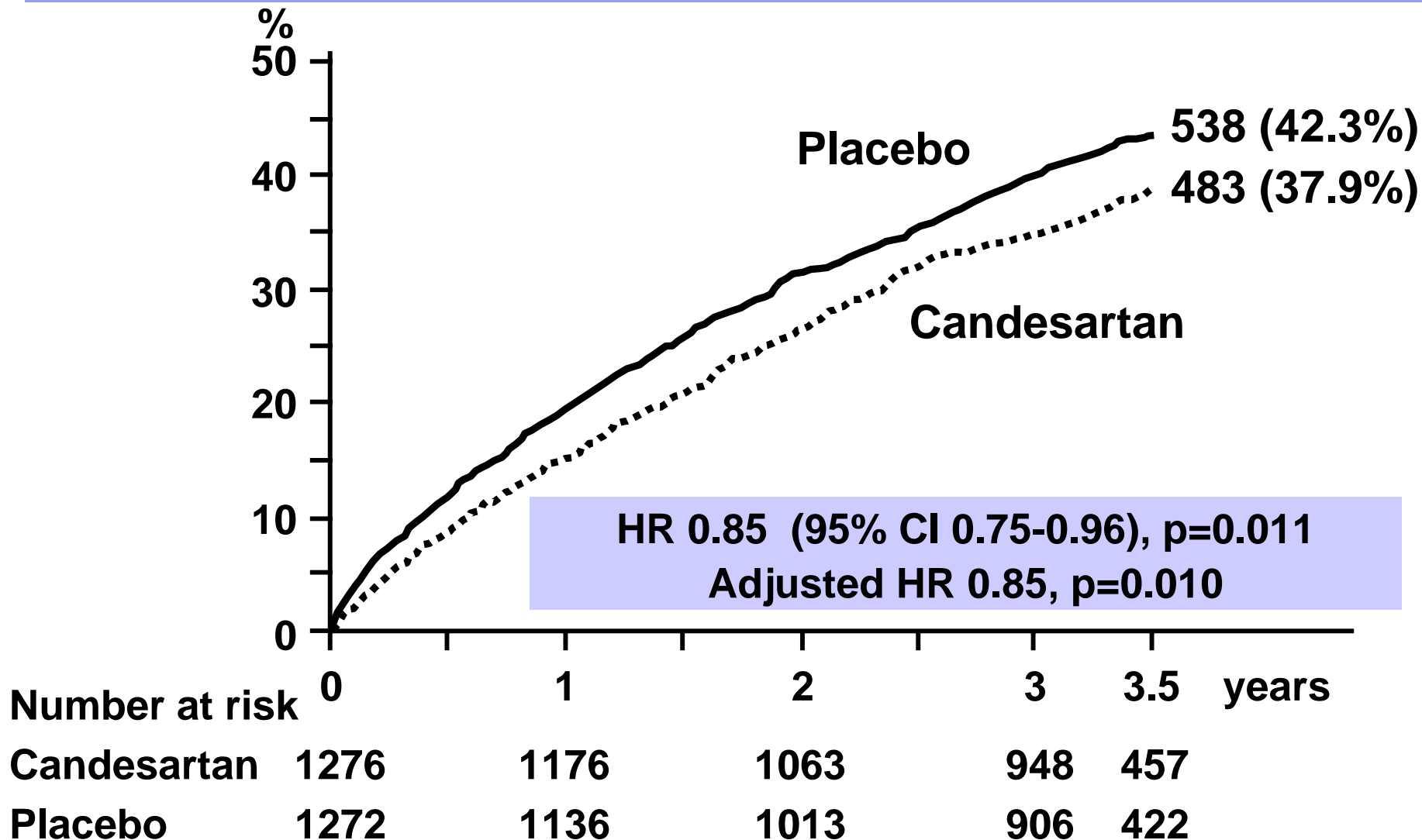
CHARM-Alternative

Primary outcome, CV death or CHF hospitalisation



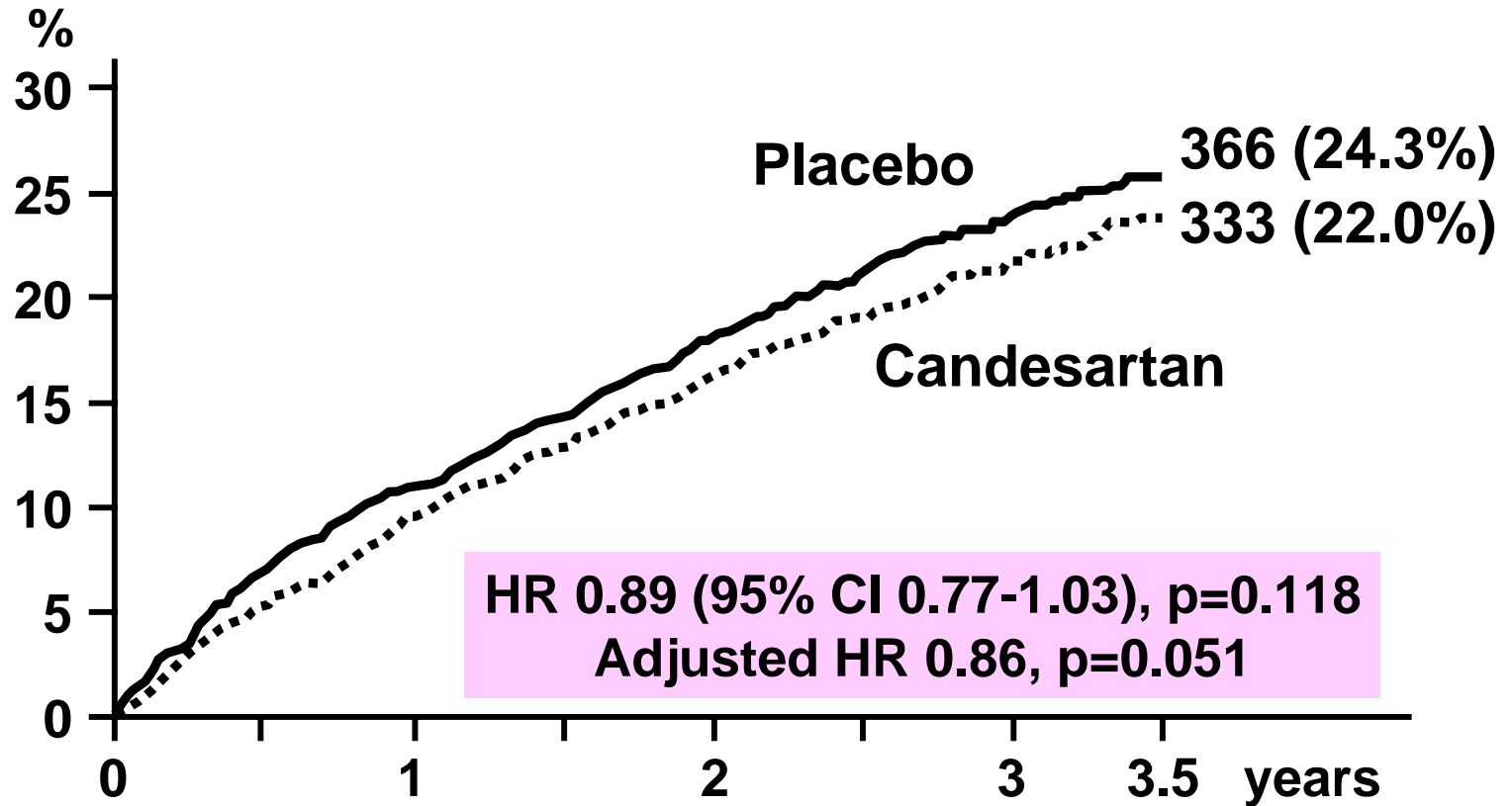
CHARM-Added

Primary outcome, CV death or CHF hospitalisation



CHARM-Preserved

Primary outcome, CV death or CHF hospitalisation



Number at risk

Candesartan	1514	1458	1377	833	182
Placebo	1509	1441	1359	824	195

ARB's in Heart Failure

esp. valsartan & candesartan

- Alternative in patients who are intolerant to ACE inhibitors
- Added to standard therapy
- Avoid using with both ACE inhibitor and beta blockers, esp. valsartan

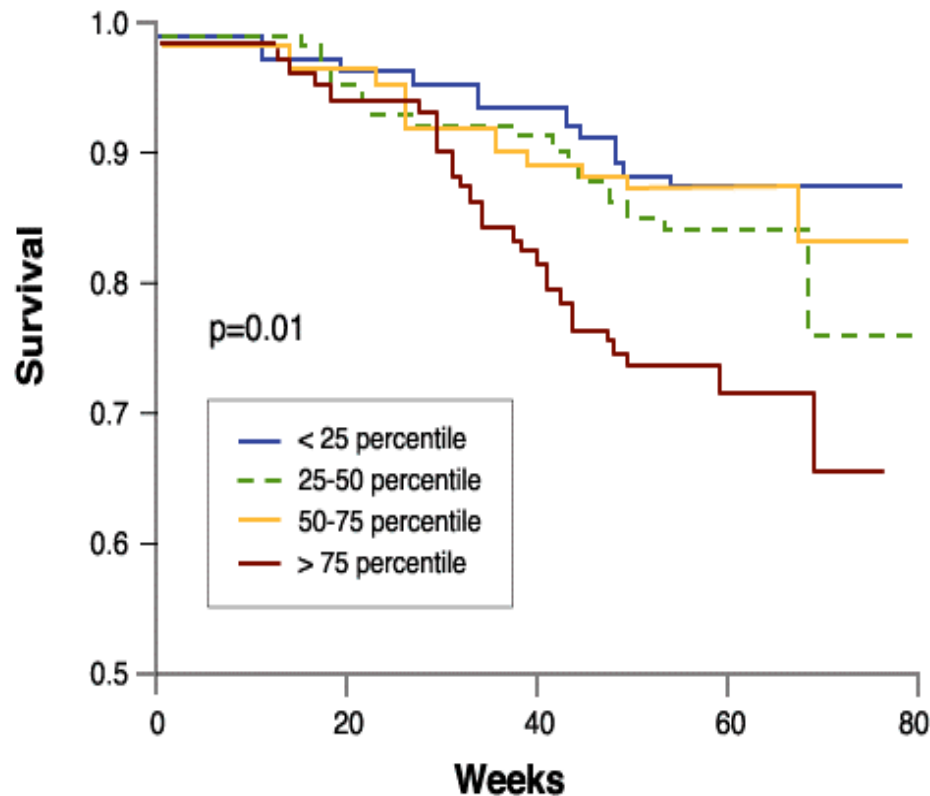
Recent clinical trials

– other medical therapeutics -

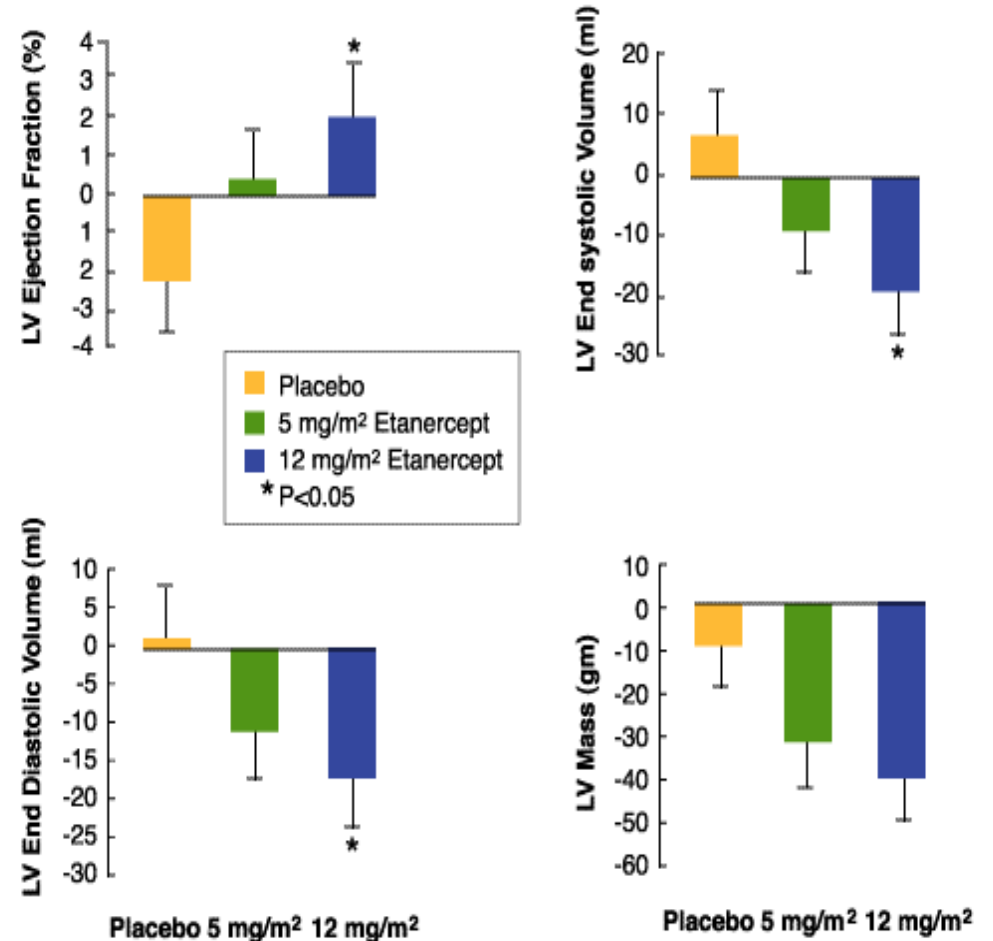
- **NEP inhibitor**
 - omapatrilat(OVERTURE)
- **Anticytokines**
 - Endothelin antagonists : bosentan, enrasentan
 - TNF-alpha antagonist : etanercept, infliximab
- **Antiarrhythmic agent**
 - Dofetilide
- **Calcium channel blockers**
 - Mibefradil – increased mortality by 11%

TNF in heart failure

Circulating Levels of TNF



Effect of Etanercept on LV Structure and Function



Recent clinical trials using device

- **ICD**
 - MADIT-II, SCD-HeFT
- **RCT(Resynchronization therapy) or bi-ventricular pacing**
 - MIRACLE, COMPANION

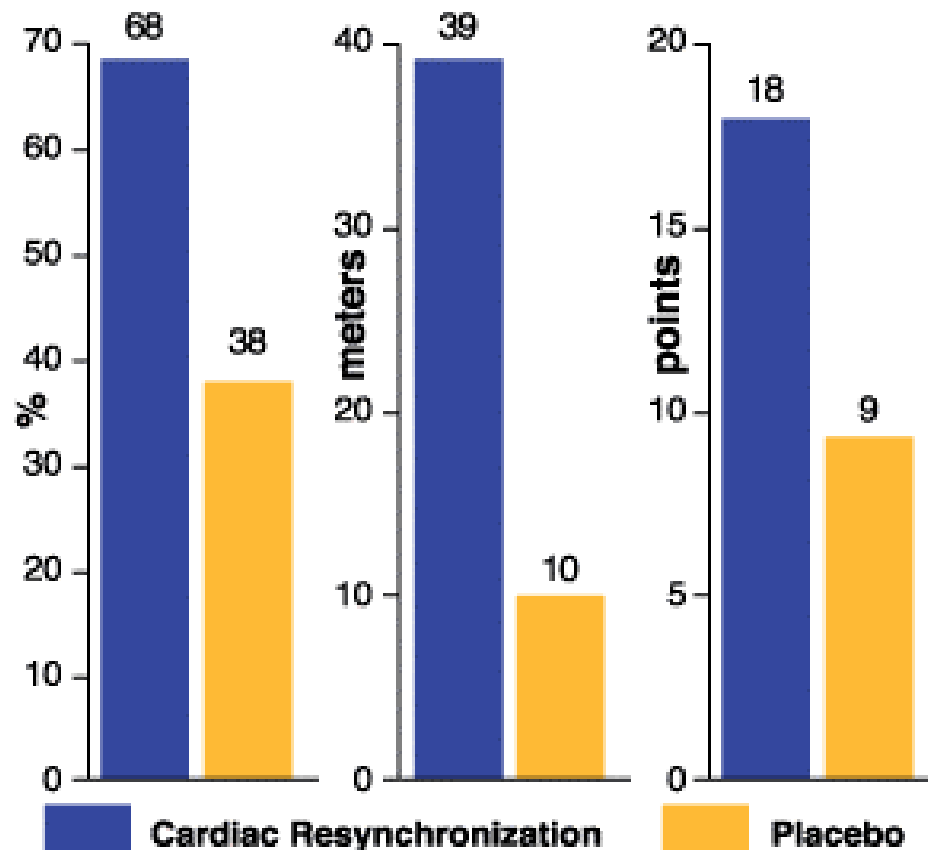
MIRACLE

Trial Design: MIRACLE was a double-blind, randomized trial of cardiac resynchronization (n=228) vs control (n=225) for 6 months in patients with moderate-to-severe heart failure and an intraventricular conduction delay. The primary endpoints were New York Heart Association functional class, quality of life, and the distance walked in 6 minutes at 6 month follow-up.

**Improvement by
≥1 NYHA Class
p<0.001**

**Distance walked
in 6 Minutes
p=0.005**

**Quality of Life
p=0.001**



www.cardiosource.com

Results

- Cardiac resynchronization therapy (CRT) was associated with improvements in all 3 primary endpoints compared with placebo (NYHA class, quality of life and walking distance; Figure)
- Device implantation unsuccessful in 8% of patients
- Secondary endpoints also improved with CRT: time on the treadmill during exercise testing (+81 vs +19 sec, p=0.001); peak oxygen consumption (+1.1 vs +0.2 ml/kg/min, p=0.009); ejection fraction (+4.6% vs -0.2%, p<0.001); QRS duration (-20 vs 0 msec, p<0.001) and need for hospital admission (8% vs 15%, p=0.02)
- Death or worsening heart failure requiring hospitalization ↓ in CRT arm (28% vs 44%; p=0.03)

Conclusions

- Among patients with chronic heart failure and ventricular dysynchrony, biventricular pacing was associated with improved functional class, increased 6-minute walk distance and maximal oxygen uptake, and improved quality of life
- Longer follow-up and larger trials of CRT pending

N Engl J Med 2002;346:1845-53

CRT

Cardiac Resynchronization Therapy

Clinical Consequences of Ventricular Dysynchrony

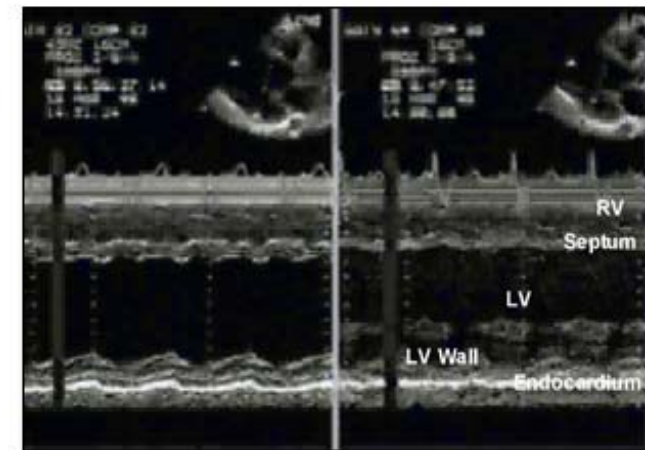
- Abnormal Interventricular Septal Wall Motion
- Reduced dP/dt
- Reduced Diastolic Filling Times
- Prolonged MR Duration



Proposed Mechanisms of Cardiac Resynchronization

Improved Contraction Pattern

- Improves Interventricular Synchrony
- Reduces Paradoxical Septal Wall Motion
- Improves LV Regional Wall Motion
- Lowers End-Systolic Volumes
- Improves LV dP/dt



Stimulation Off

Stimulation On

Resynch Off

Resynch On

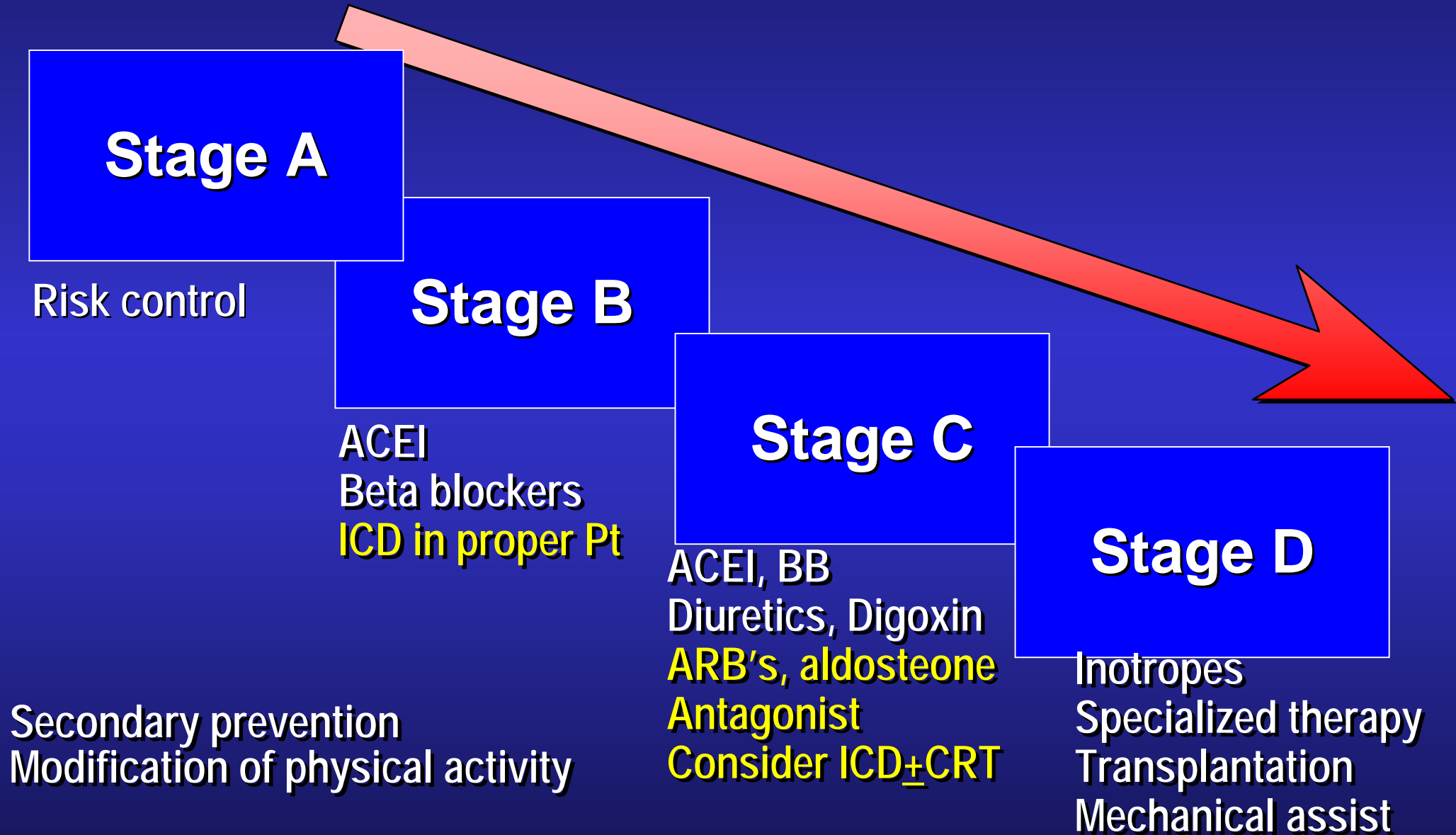
COMPANION

- Pharmacological therapy plus
 - **CRT** mortality ↓ 23.7 %
 - CRT + ICD mortality ↓ 43.4 %

CRT : Cardiac Resynchronization Therapy

ICD : Implantable cardioverter defibrillator

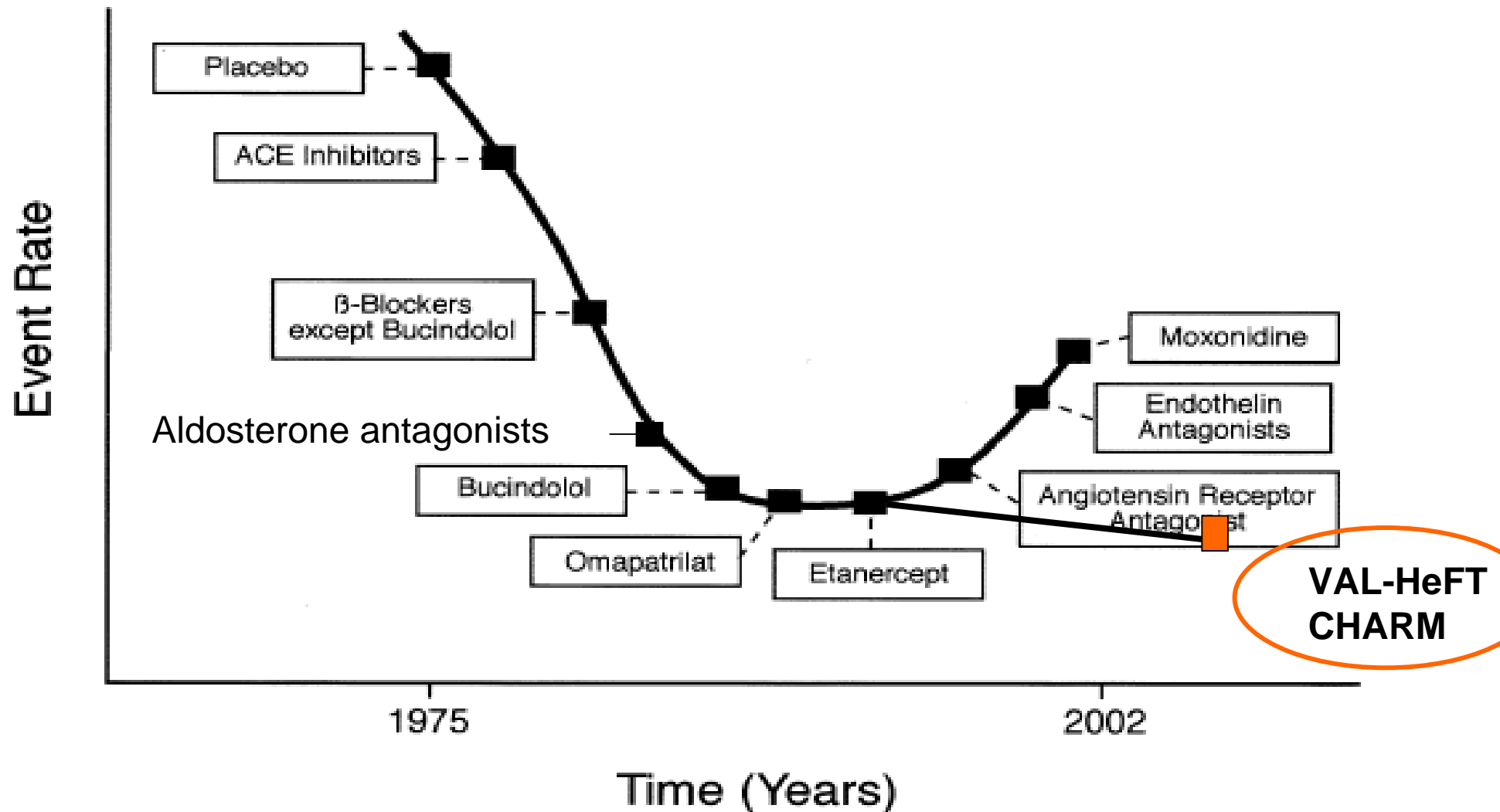
Treatment of Heart Failure



Lessons from Recent HF Clinical Trials

- Mortality and morbidity of HF is still high.
- Beta blockers
 - Carvedilol seems better than metoprolol
 - Added benefit with carvedilol even in post-MI and severe HF
- ARB's is valuable as an alternative to ACEI intolerant patients or can be added to standard therapy.
- CRT(bi-ventricular pacing) coupled with ICD is superior to medical therapy alone in selected HF population.
- **More aggressive blockade of neurohormonal or cytokine activation is not necessarily beneficial.**

Saturation of Benefit with Incremental Neurohormonal Blockade in Chronic Heart Failure



Potential Therapeutic Target Beyond Neurohormonal Activation

