What do the antagonists of aldosteronereceptors have to offer in the treatment of heart failure?

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Heart Failure: Pathophysiology

LVSD

- ↓ CO
- ↓ Systemic perfusion
- ↑ Pulmonary pressure
- ↑ Pulmonary congestion

Neurohormonal Adaptation

- ↑ Sympathetic nervous system
  - ↑ **HR**
  - ↑ **Contractility**
  - ↑ **CO**

Stimulation of RAA system

↑ AngII, *aldosterone*

Na^+ and H_2O retention
Endothelial dysfunction
Organ fibrosis
LV dilatation and hypertrophy
Oxidative stress
Vascular remodeling
Immune system activation

Aims of Heart Failure Patient Management

- Alleviate symptoms
- Improve quality of life
- Delay disease progression
- Prolong patient survival
- Reduce sudden cardiac death
- Minimise hospital admissions/hospital care (costs)

Heart Failure Drug Treatment Options

Symptom Relieving

- Diuretics
- Digoxin

Disease Modifying

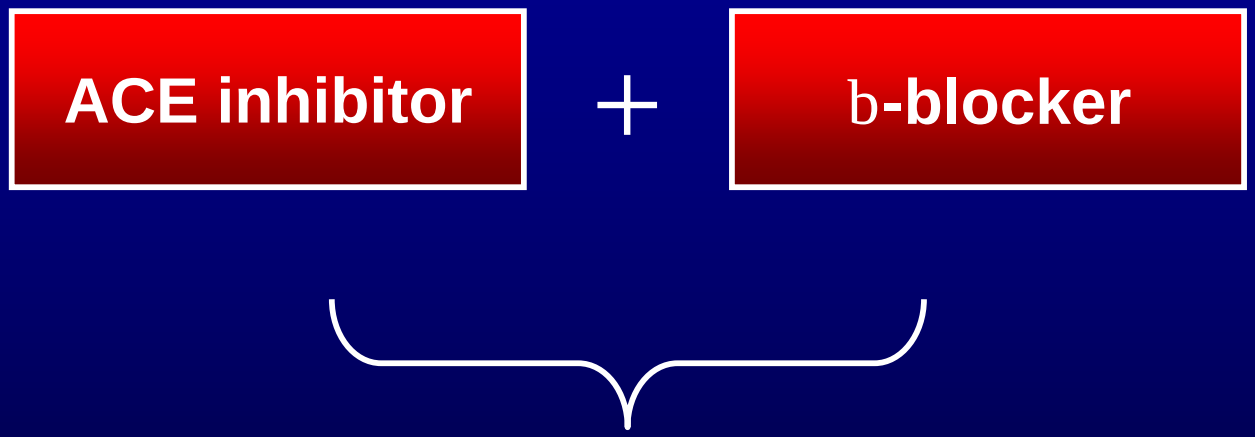
- ACE inhibitors /angiotensinII receptor antagonists
- Beta-blockers
- Aldosteronereceptor antagonists

Present Challenges in Treatment

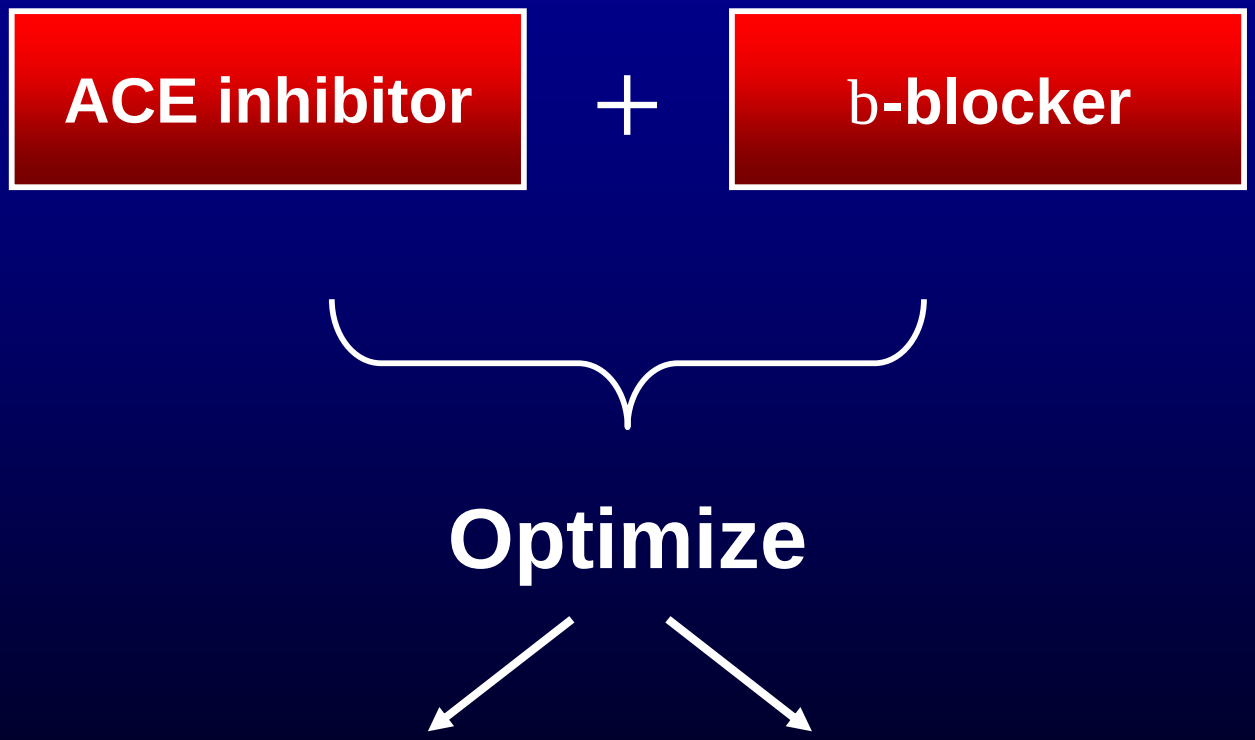
Despite use of ACE inhibitors + b-blockers

- **Risk of death remains high (≥12% per year)**
- **Risk of death or cardiovascular hospitalization remains high (≥25% per year)**
- **Risk of disability remains high**

What Is the Next Step?



What Is the Next Step?



Optimization of ACE Inhibition

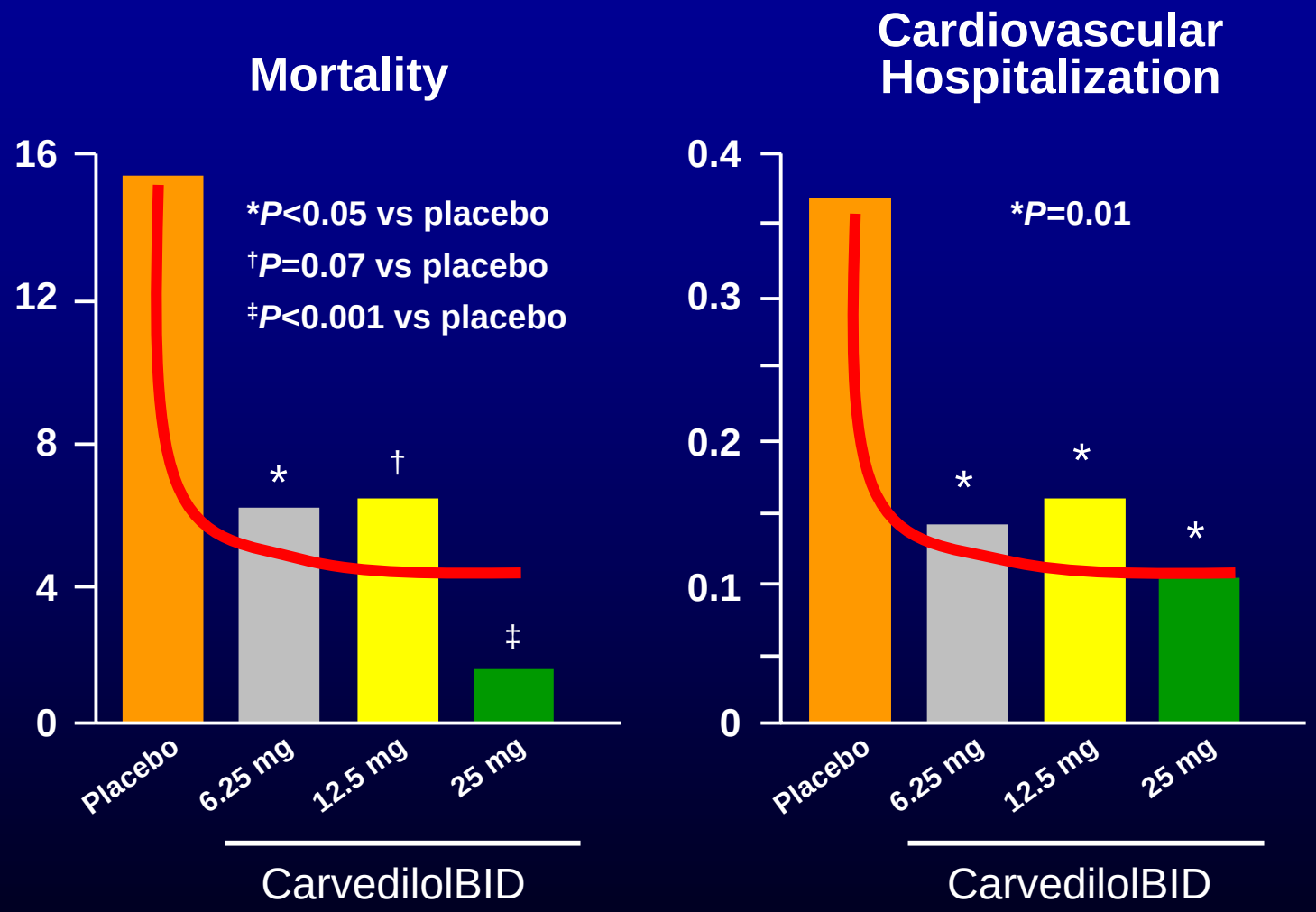
ATLAS Trial

Randomized comparison of low dose (2.5 mg to 5 mg daily) and high-dose lisinopril (32.5 mg to 35 mg daily)

- 8% lower risk of death (*P*=0.128)
- 15% lower risk of death or hospitalization for heart failure (*P*=0.001)
- Greater risk of hypotension, renal insufficiency, and hyperkalemia with high dose

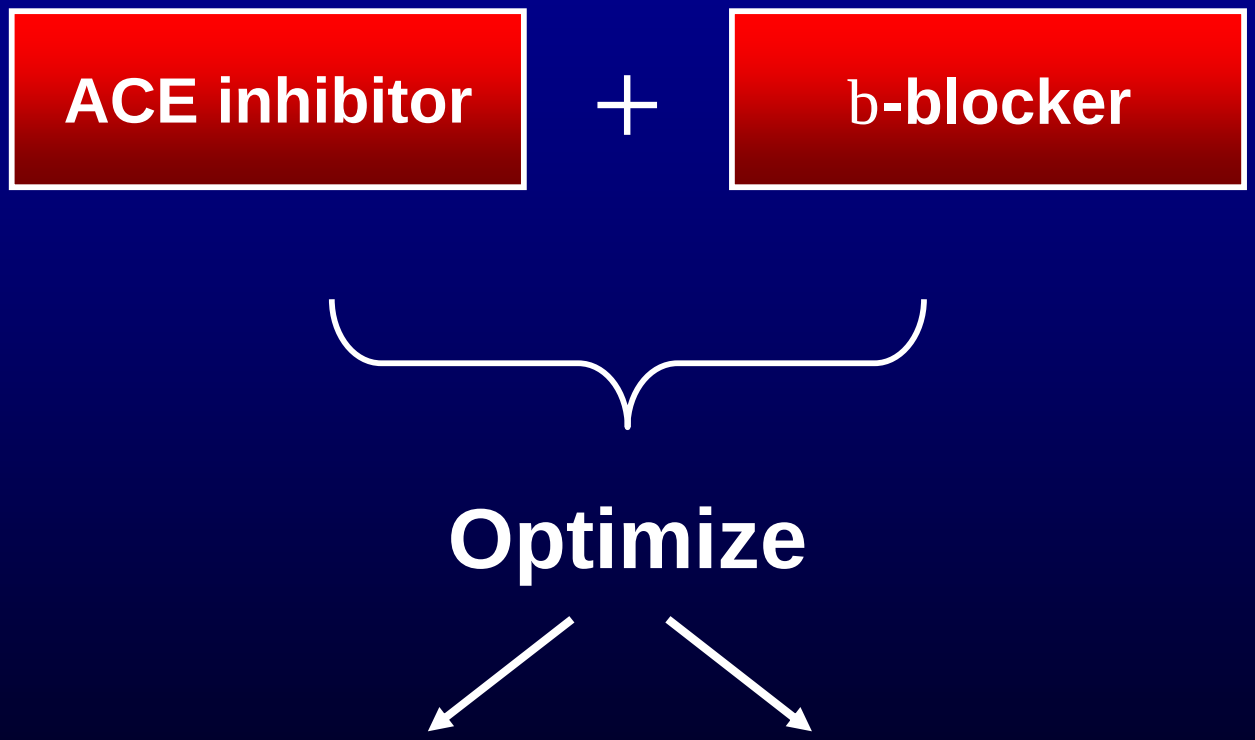
Packer M, et al. *Circulation*. 1999;100:2312-2318.

Effect of Different Doses of Carvedilol on Morbidity and Mortality (MOCHA)



Bristow MR, et al. *Circulation*. 1996;94:2807-2816.

What Is the Next Step?



ACE Inhibitors vs Angiotensin Receptor Blockers in Multicenter Trials

	Captopril	Losartan	Hazard Ratio	*P* Value
OPTIMAAL[1] (post-MI CHF)	447/2,733	499/2,744	1.13 (0.99,1.28)	0.07
ELITE II[2] (chronic HF)	250/1,574	280/1,578	1.13 (0.95,1.35)	0.16

1.Dickstein K, et al. *Lancet*. 2002;360:752-760.
2.Pitt B, et al. *Lancet*. 2000;355:1582-1587.

Optimization of b-Blockade

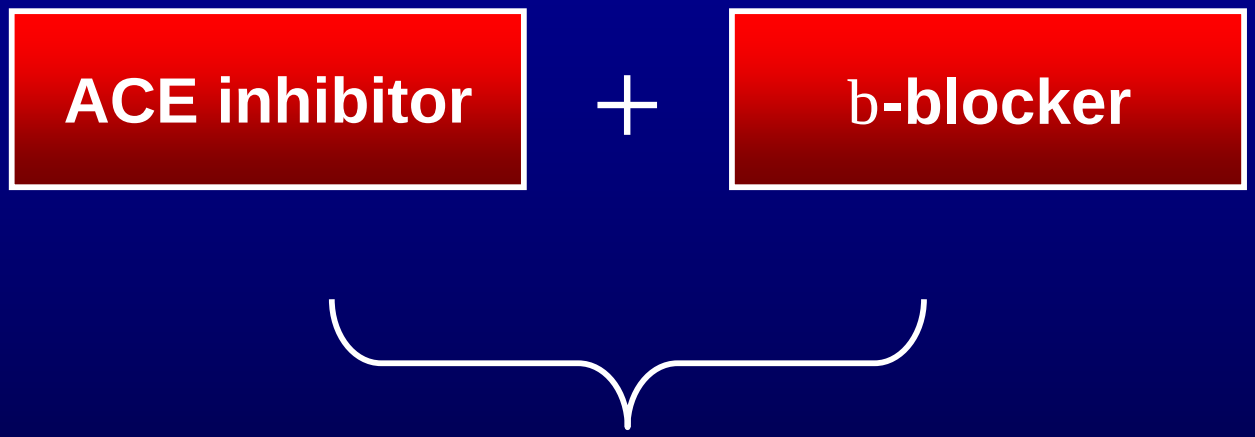
COMET Trial

Randomized comparison of metoprolol (50 mg BID) and carvedilol(25 mg BID)

- 17% lower risk of death (*P*=0.0017)
- 11% lower risk of death or hospitalization for heart failure (*P*=0.02)
- Similar risk of adverse events

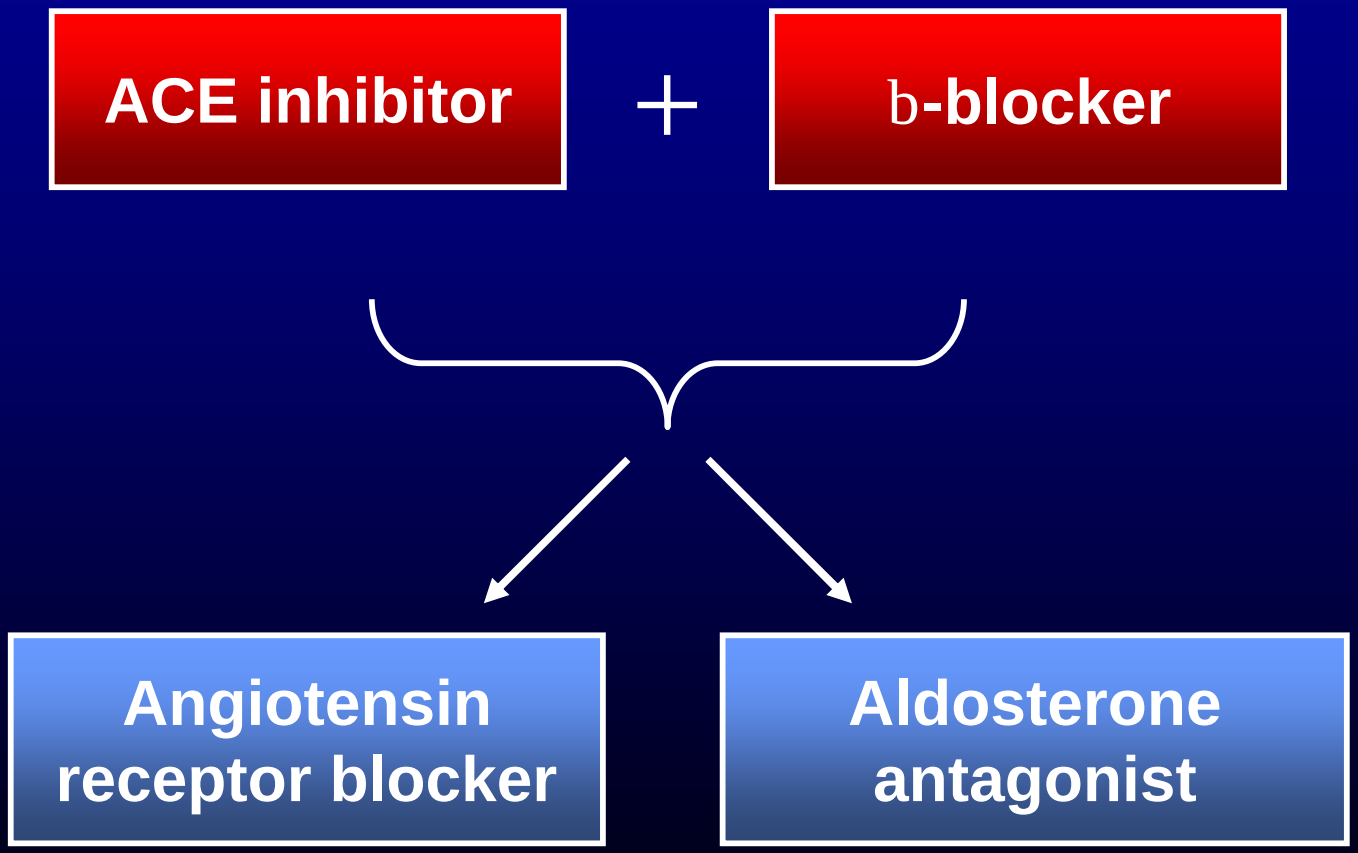
Poole-Wilson PA, et al. *Lancet*. 2003;362:7-13.

What Is the Next Step?



Add a third agent

What Is the Next Step?



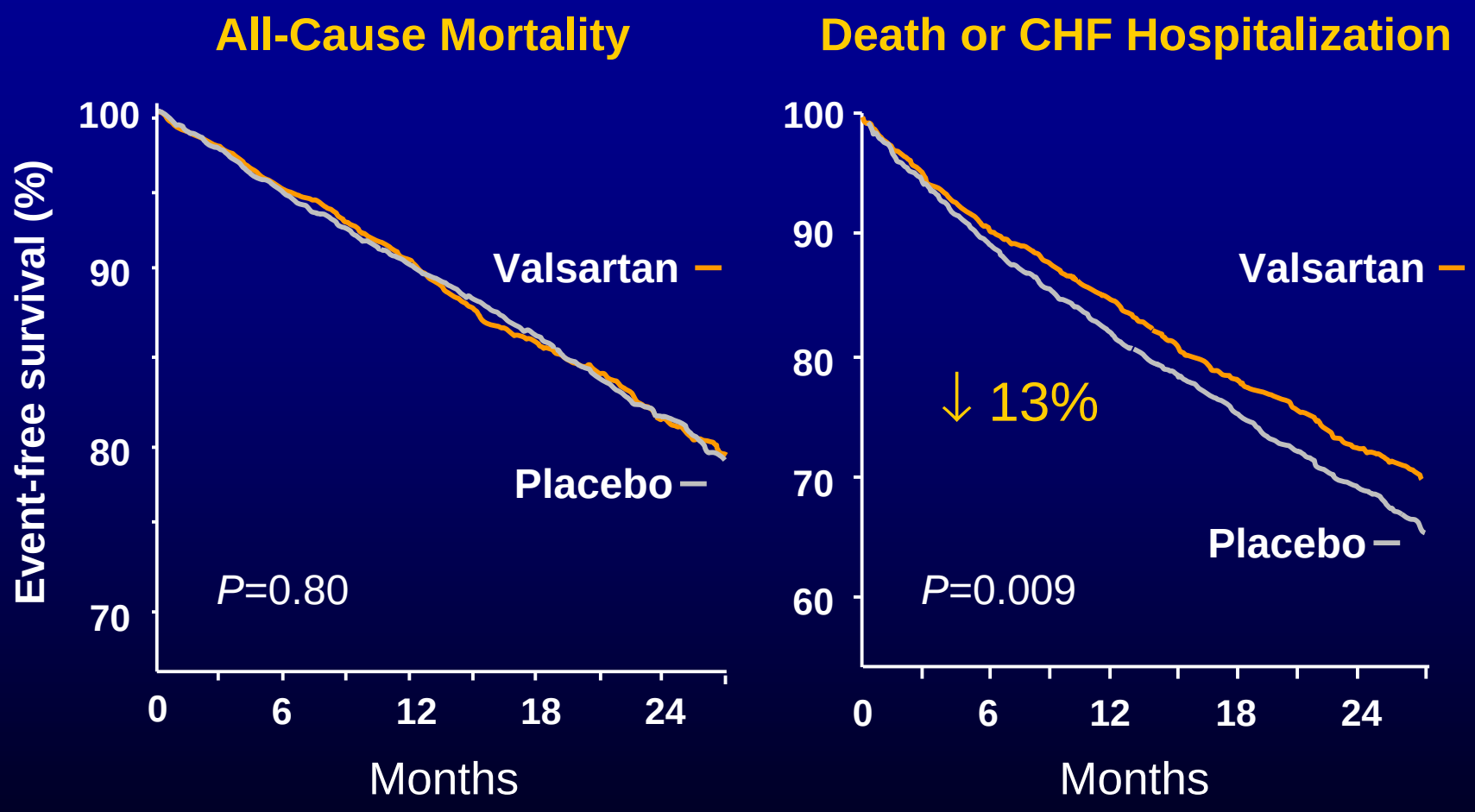
What Is the Next Step?

ACE inhibitor + **b-blocker**

Angiotensin receptor blocker

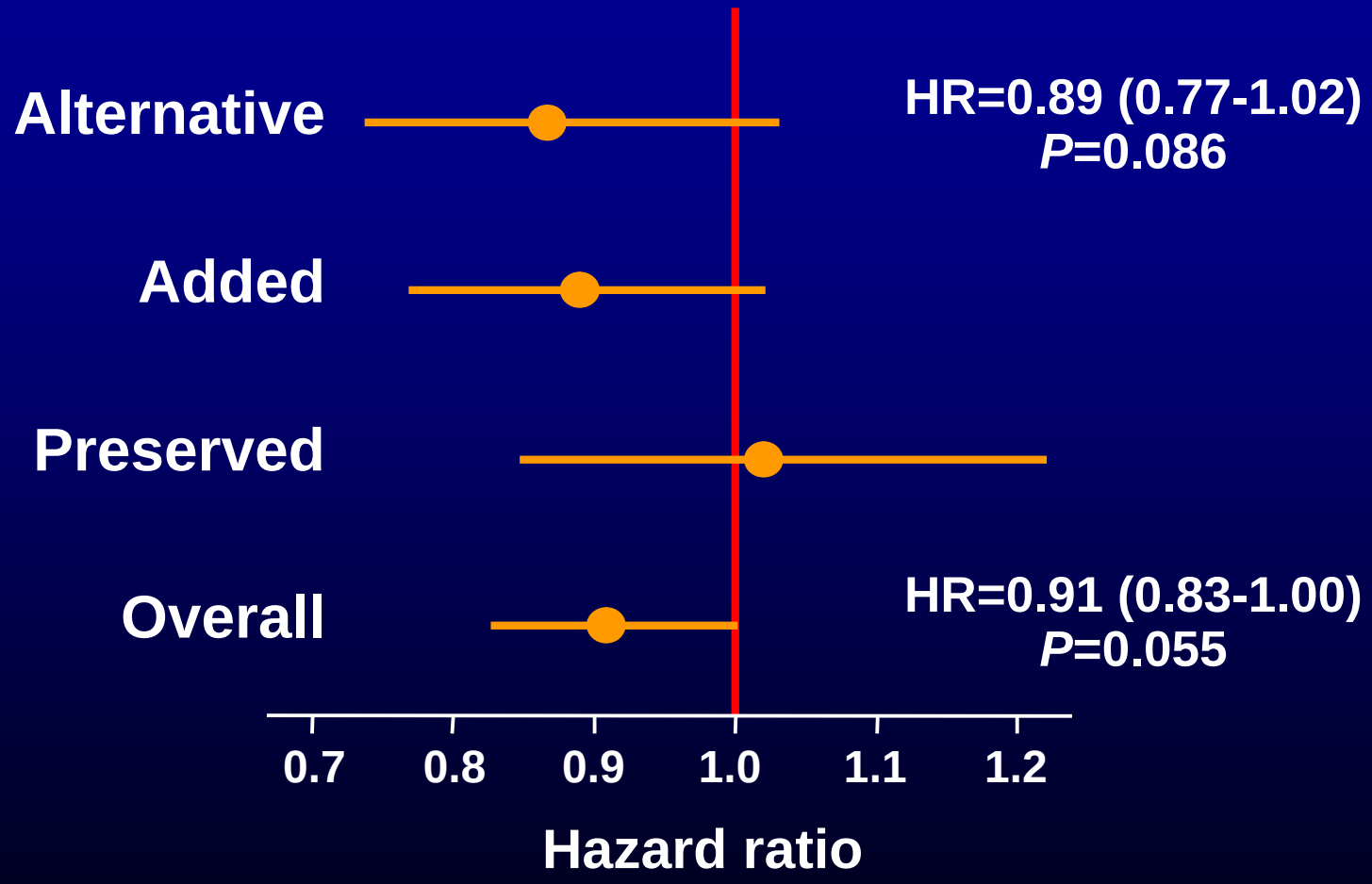
- Val-HeFT
- CHARM
- VALIANT

Val-HeFT: ARBs Added to ACE Inhibitors



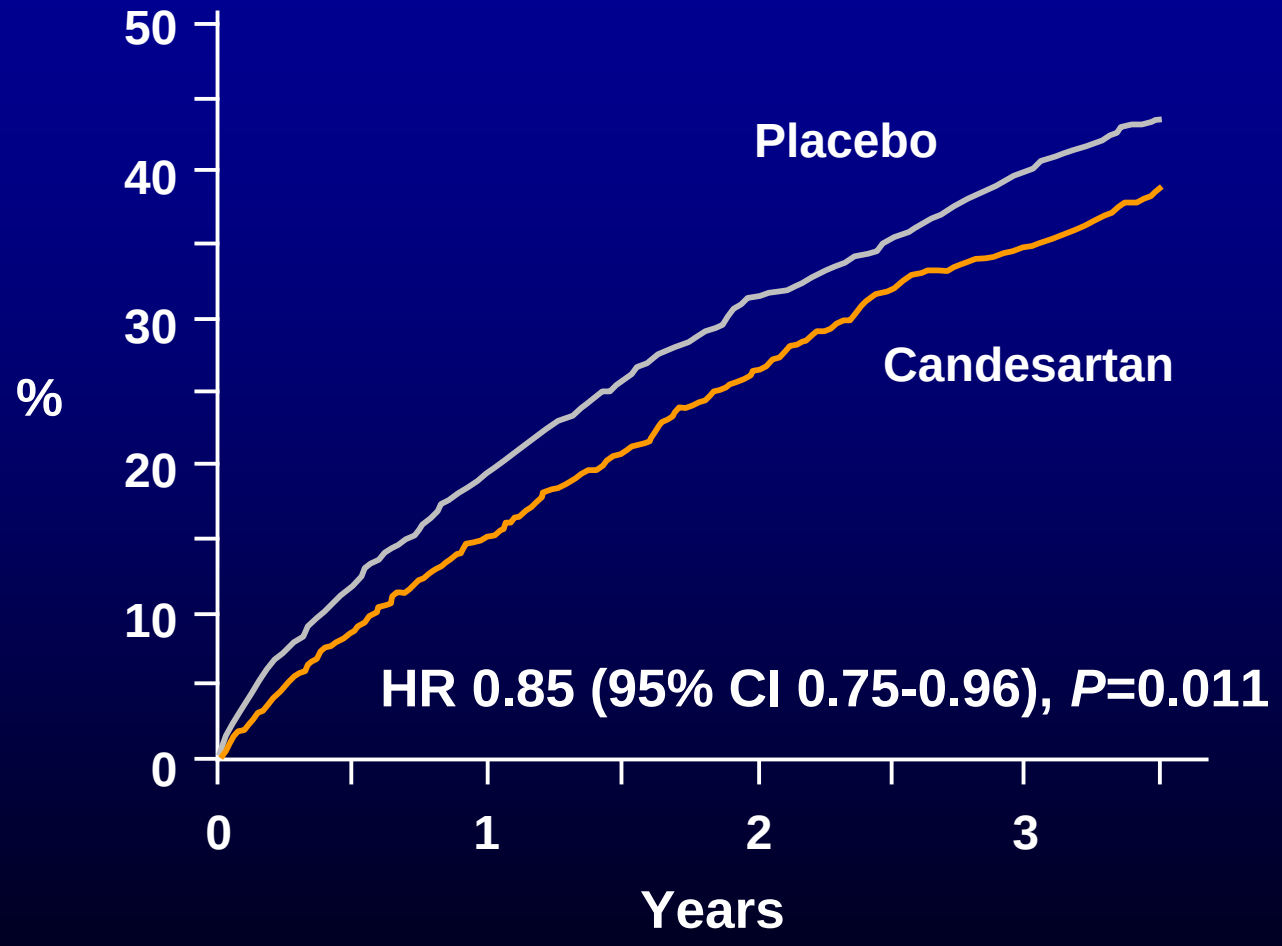
Cohn JN, et al. *N Engl J Med*. 2001;345:1667-1675.

CHARM Program: All-Cause Mortality



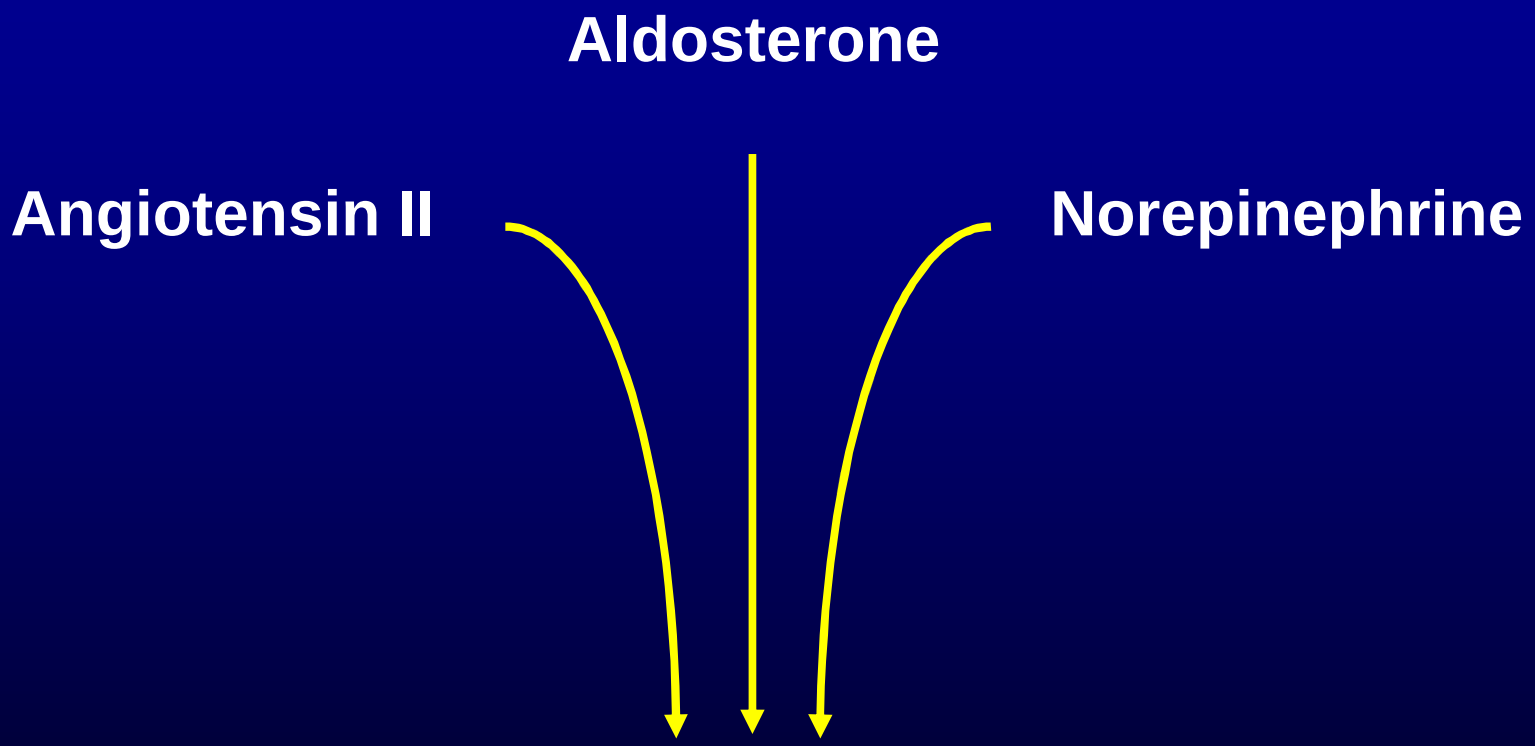
PfefferMA, et al. *Lancet*. 2003;362:759-766.

CHARM-Added: Cardiovascular Death or Hospitalization for CHF



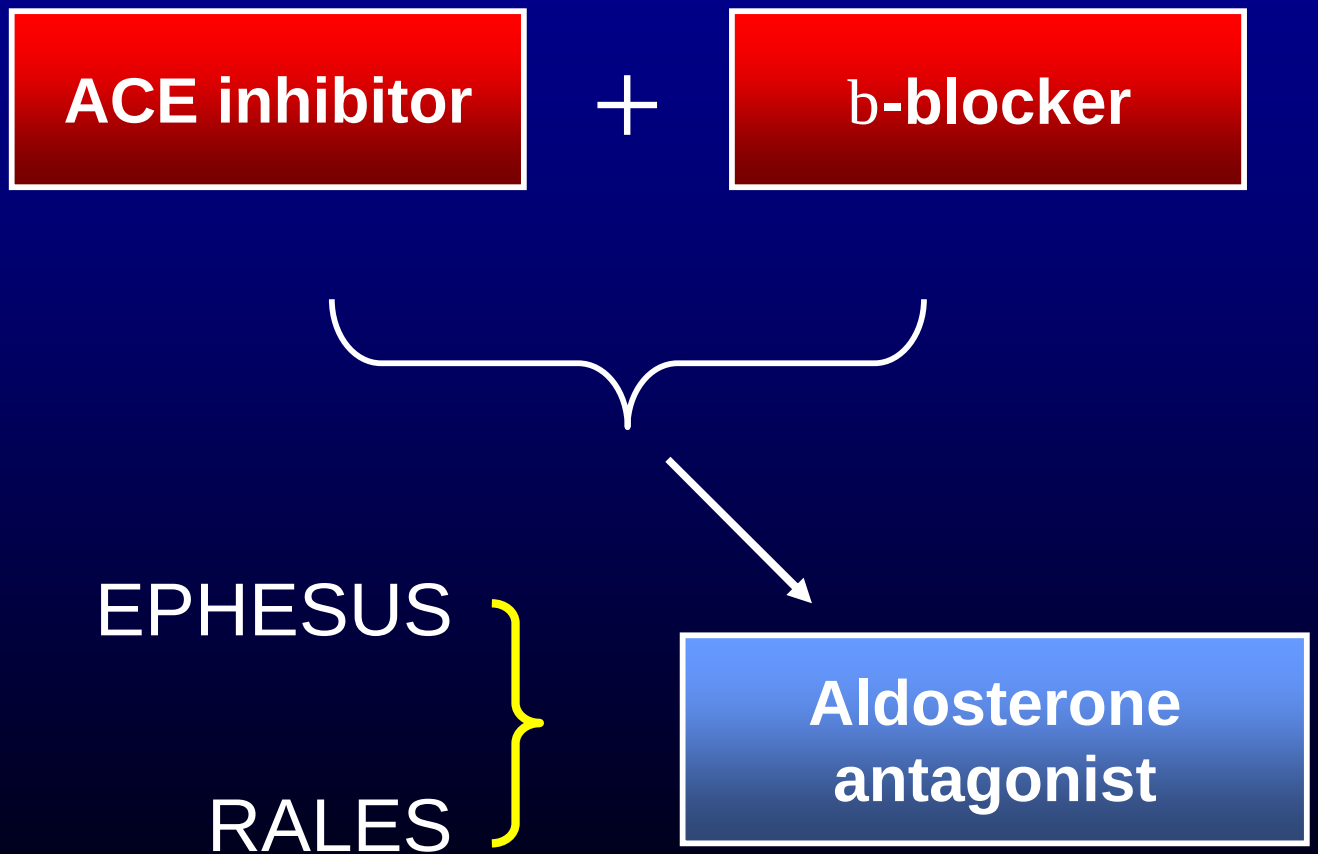
McMurray JJV, et al. *Lancet*. 2003;362:767-771.

The Pathophysiology of Heart Failure Results from Neurohormonal Activation

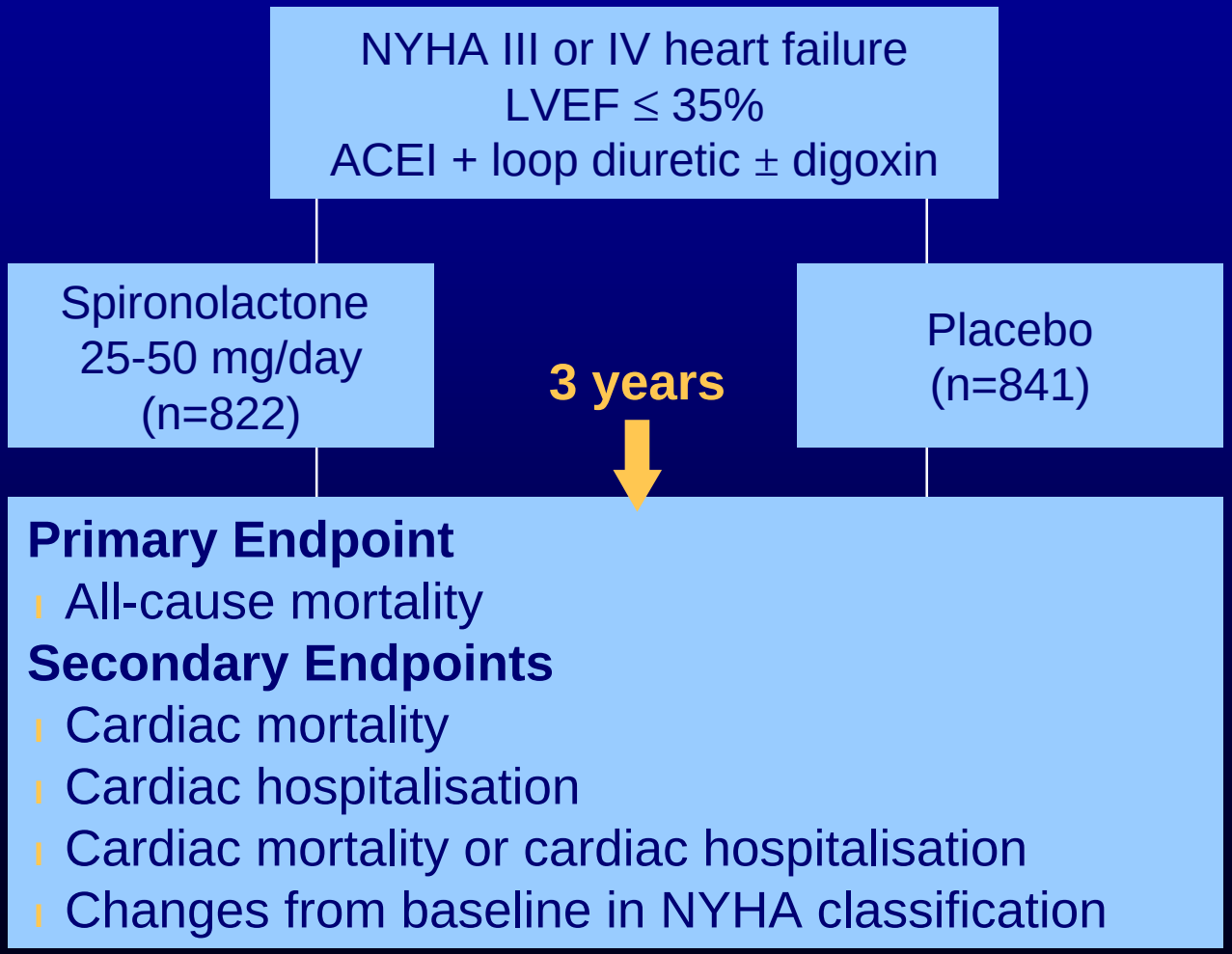


Hypertrophy, apoptosis, ischemia,
arrhythmias, remodeling, fibrosis

What Is the Next Step?

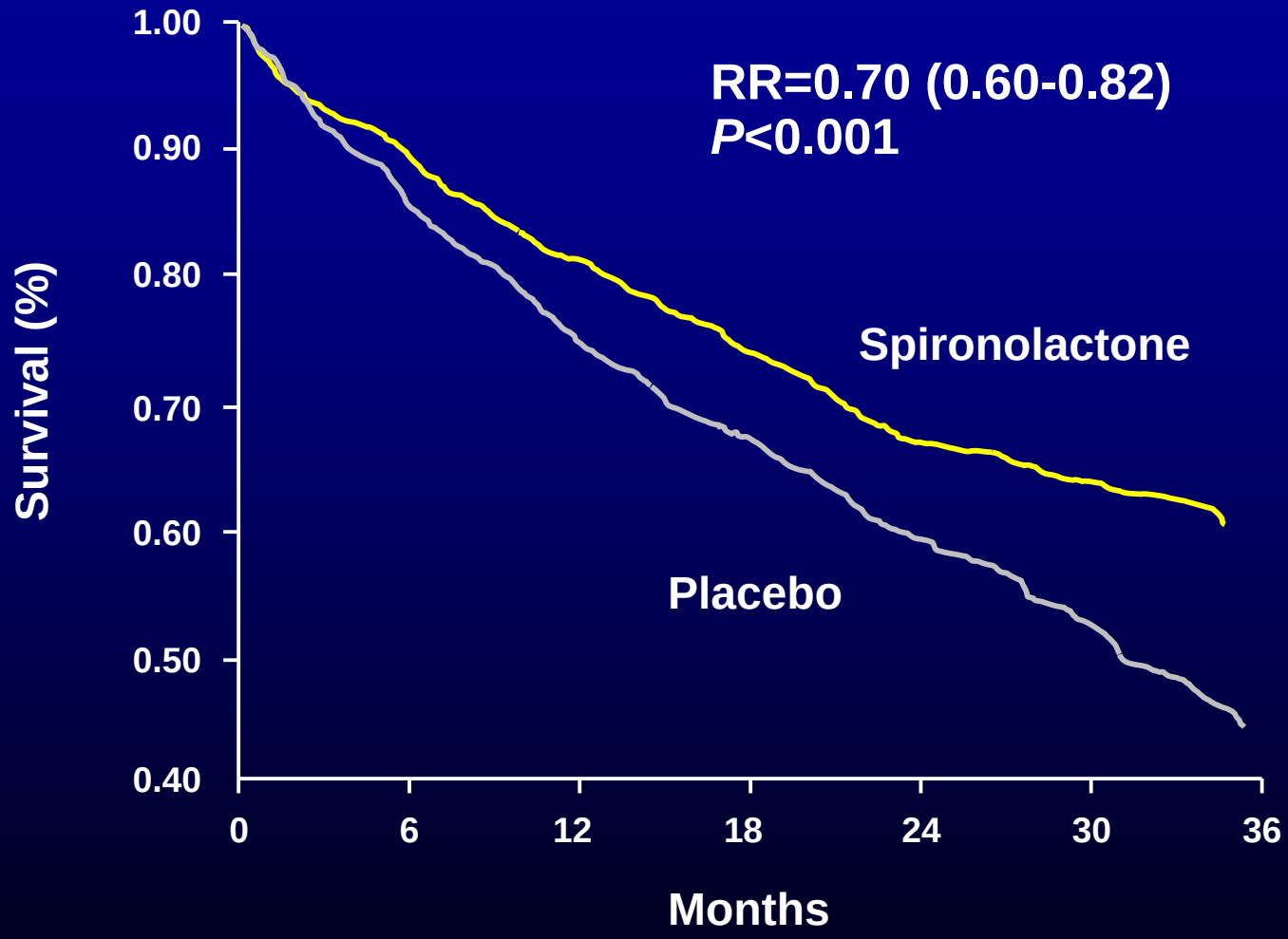


Randomized Aldactone Evaluation Study : Study Design



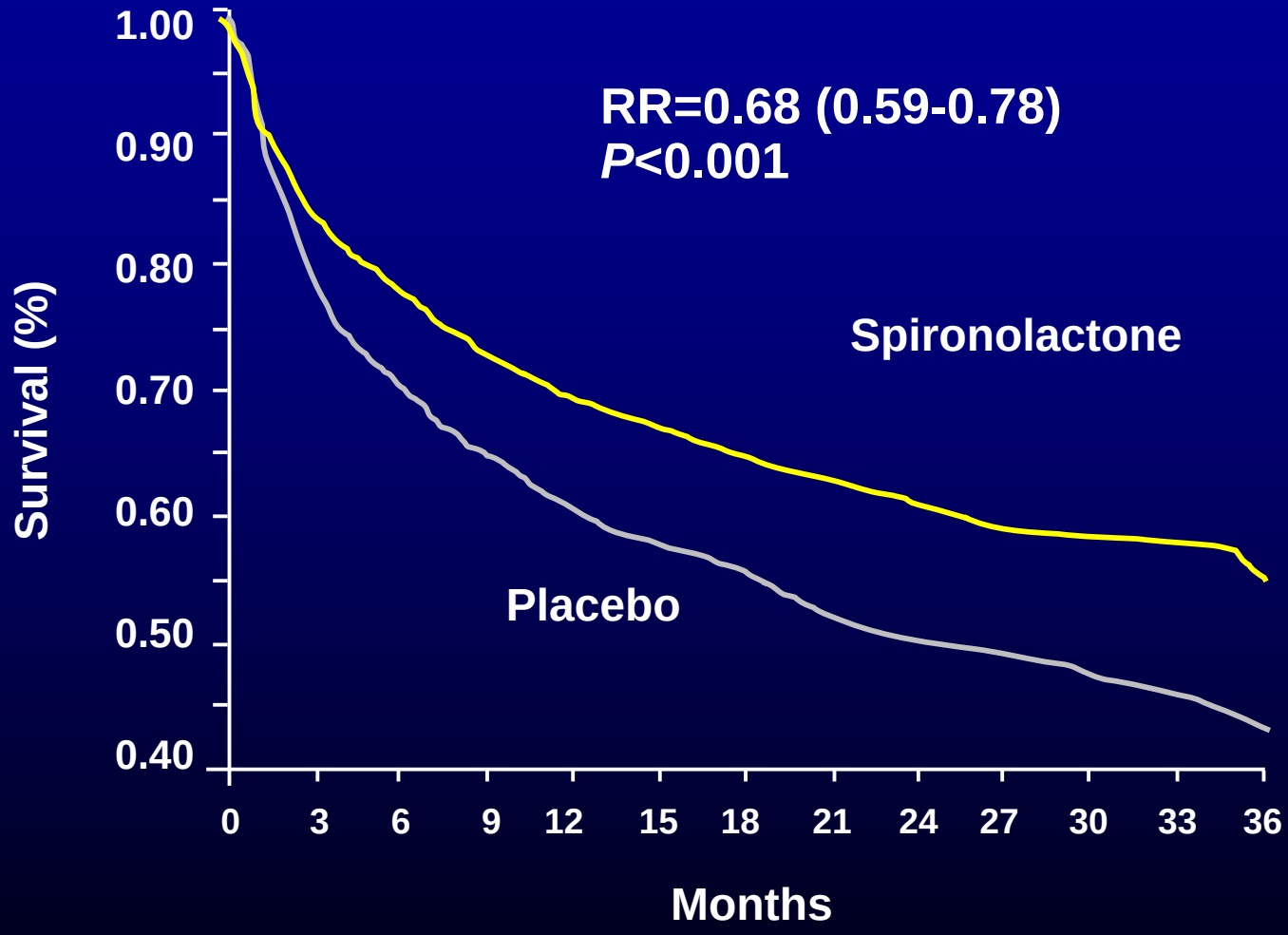
Pitt B et al, N EnglJ Med 1999; 341: 709-717

RALES: All-Cause Mortality



Pitt B, et al. *N Engl J Med*. 2003;341:709-717.

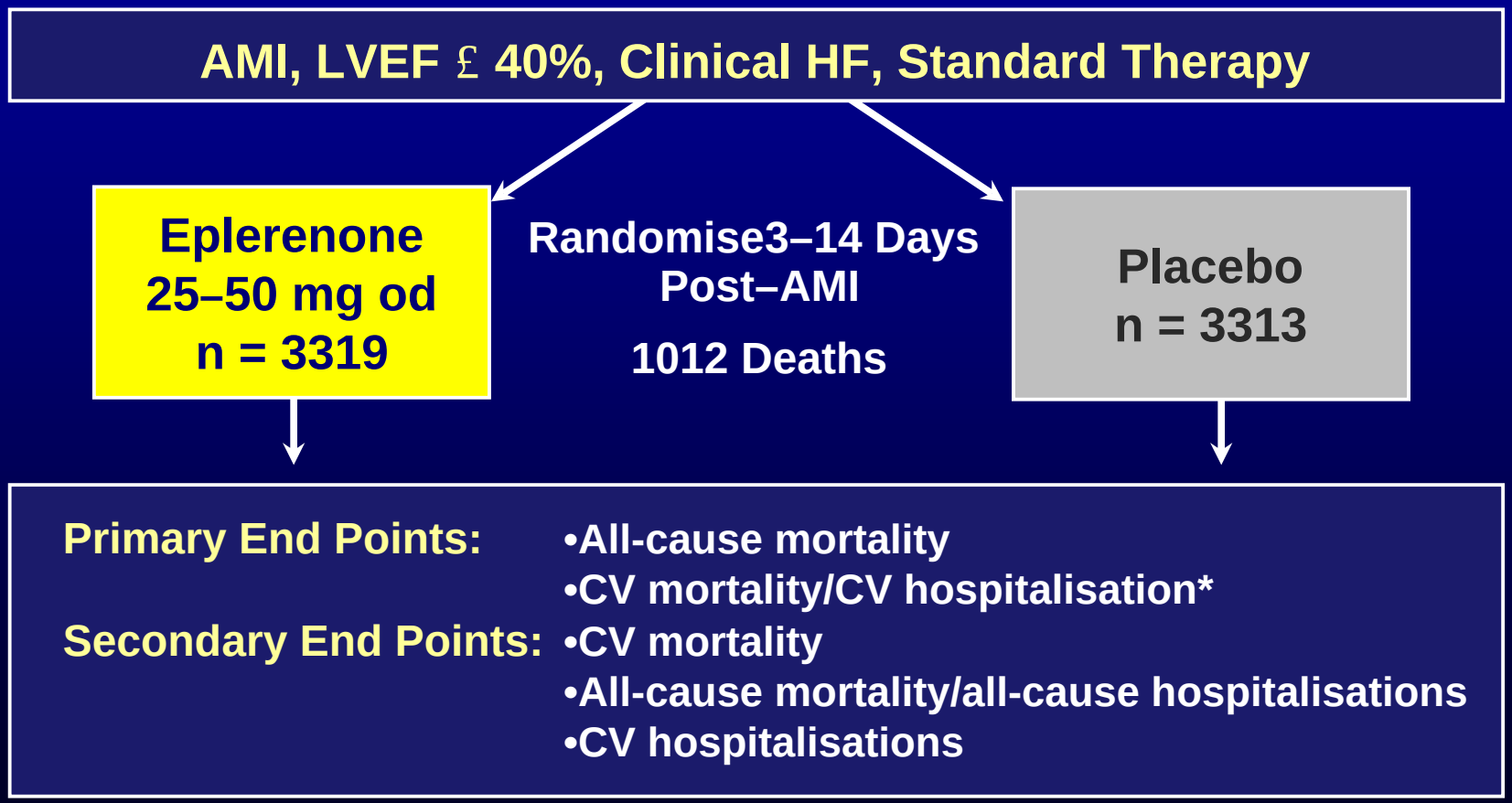
RALES: Cardiovascular Mortality or Cardiovascular Hospitalization



Pitt B, et al. *N Engl J Med*. 2003;341:709-717.

EPHESUS

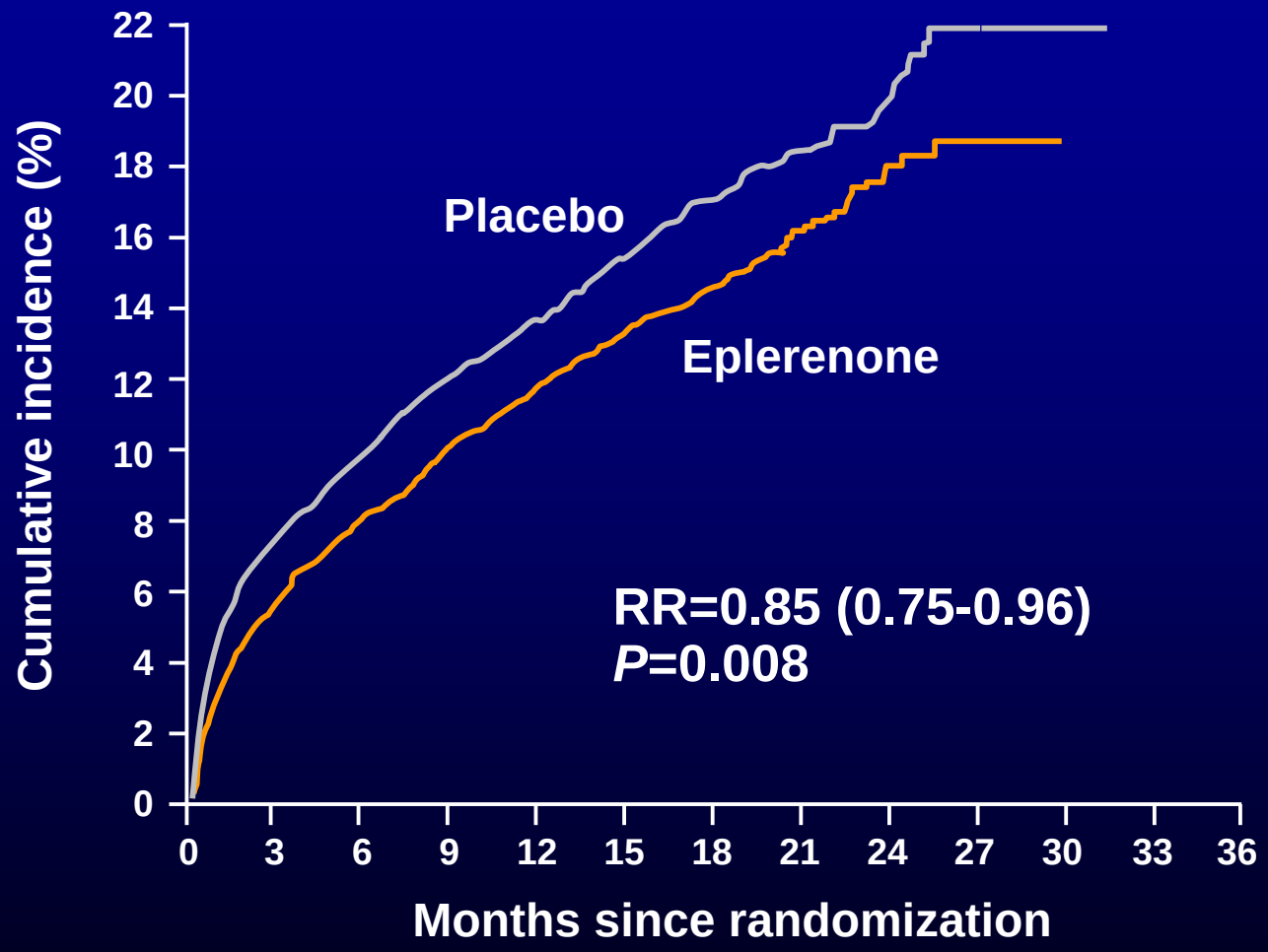
Study Design



*CV hospitalisation= hospitalisationfor heart failure, MI, stroke, or ventricular arrhythmia

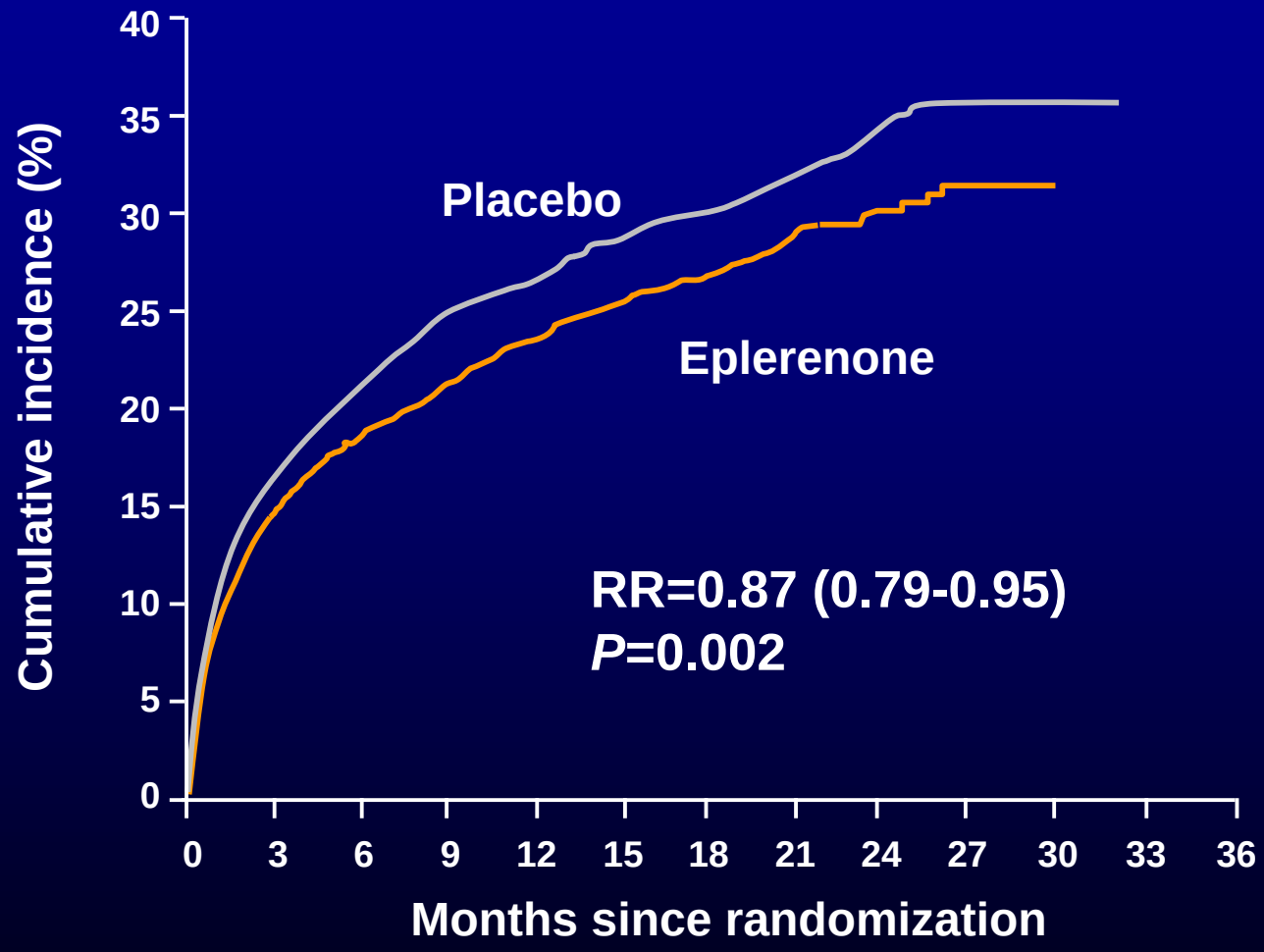
Pitt B et al. CardiovascDrugs and Therapy 2001; 15: 79-87

EPHESUS: All-Cause Mortality



Pitt B, et al. *N Engl J Med*. 2003;348:1309-1321.

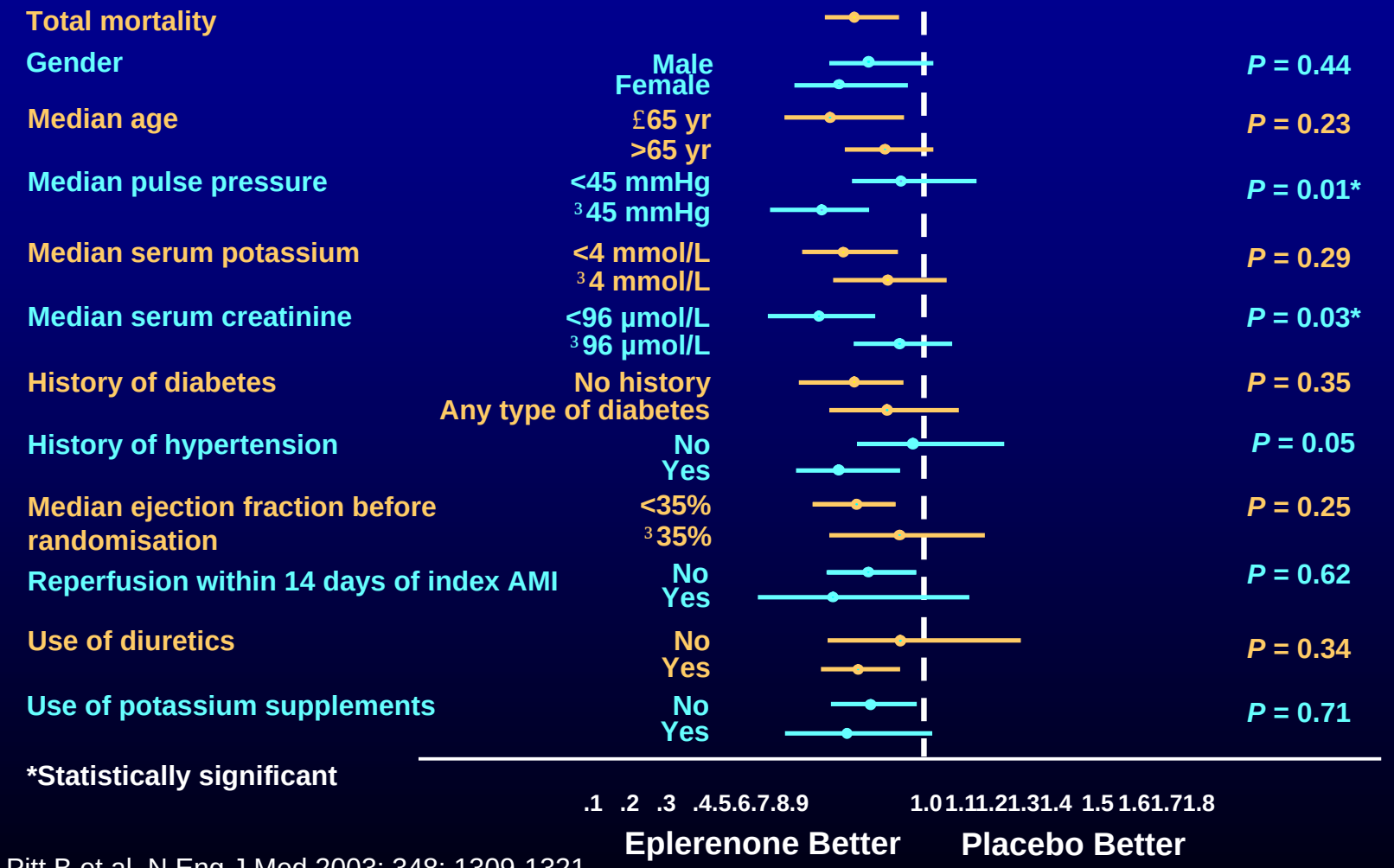
EPHESUS: Combined Risk of Cardiovascular Mortality or Cardiovascular Hospitalization



Pitt B, et al. *N Engl J Med*. 2003;348:1309-1321.

EPHESUS

All-Cause Mortality Subgroup Analysis



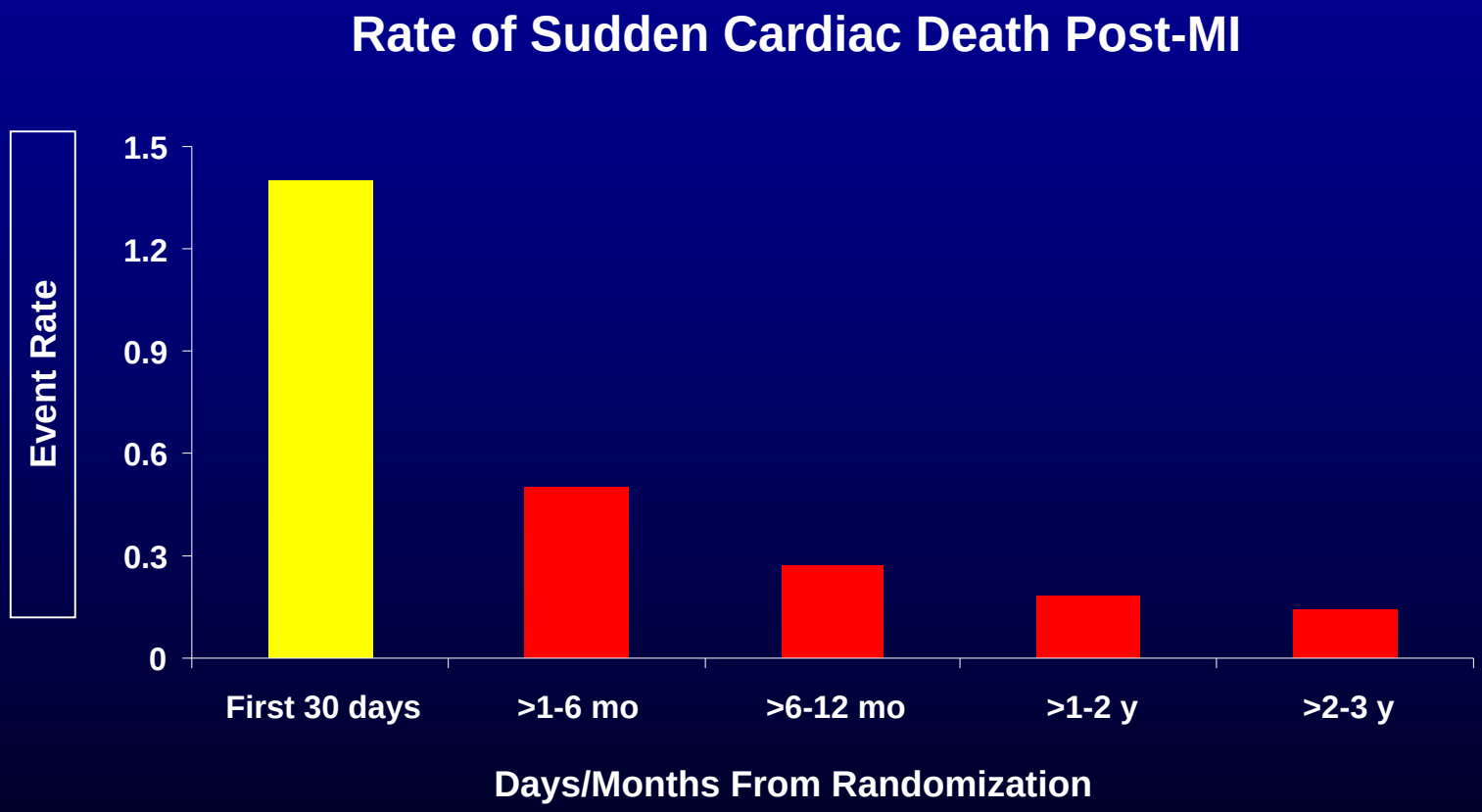
Pitt B et al. N Eng J Med 2003; 348: 1309-1321

EPHESUS™: 30-Day Analysis

Objective: To assess the impact of eplerenone on mortality 30 days after randomization in patients after acute myocardial infarction (AMI) with a left ventricular ejection fraction (LVEF) ≤40%and clinical signs of heart failure (HF)

Pitt B, White H, NicolauJ, et al. *J Am CollCardiol.* 2005;46:425-431.

Why Are 30-day Mortality Data Important?



Study of 14,609 patients with LVD, HF, or both after MI to assess the timing of sudden cardiac death, using the VALIANT database.

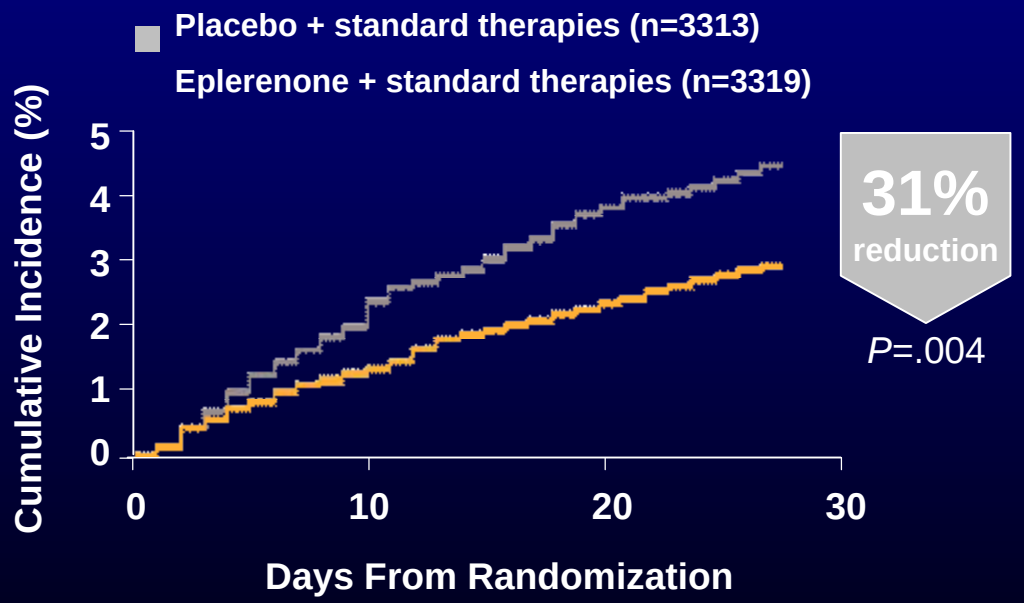
Adapted from Solomon SD, Zelenkofske S, McMurray JJV, et al. *N EnglJ Med.* 2005;352:2581-2588.

EPHESUS™: All-Cause Mortality at 30 Days Post-Randomization

- Risk reduction in all-cause mortality seemed to occur as early as 10 days post-randomization

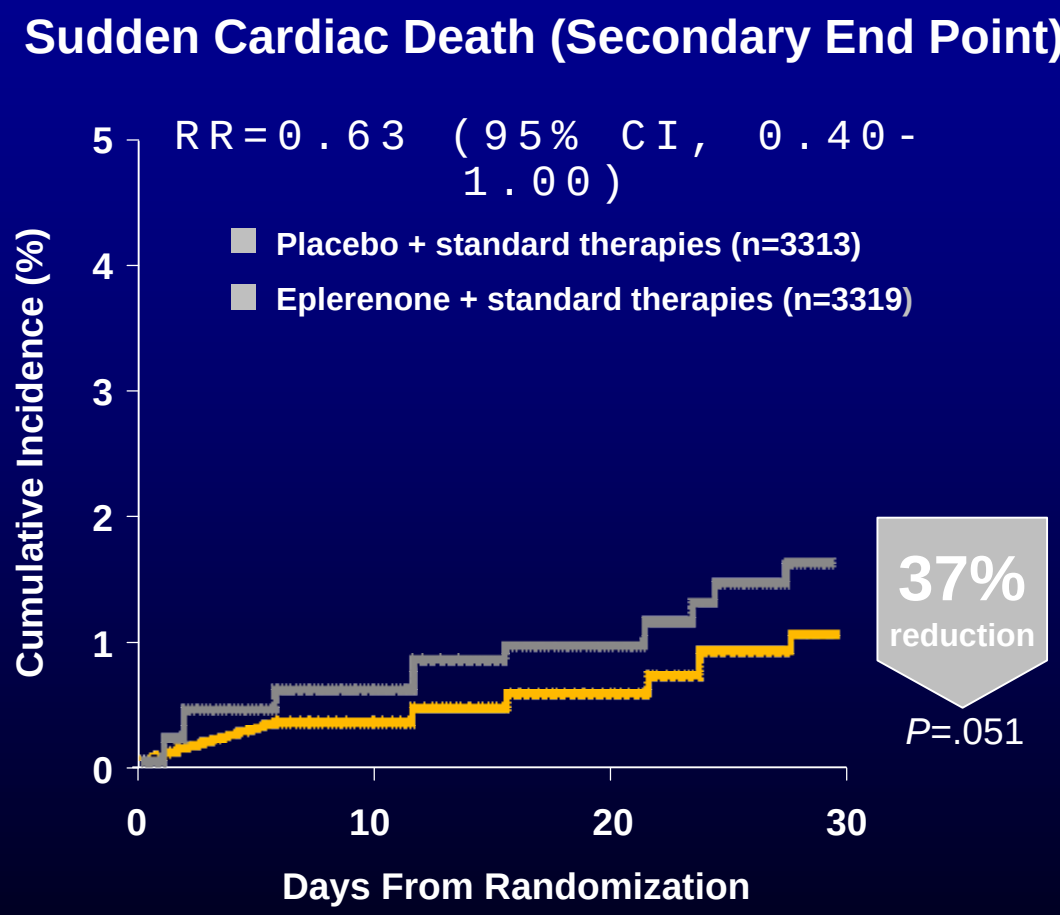
All-Cause Mortality (Primary End Point)

RR=0.69 (95% CI, 0.54-0.89)



Pitt B, White H, NicolauJ, et al. *J Am CollCardiol.* 2005;46:425-431.

EPHESUS™: Sudden Cardiac Death at 30 Days Post-Randomization



Pitt B, White H, NicolauJ, et al. *J Am CollCardiol.* 2005;46:425-431.

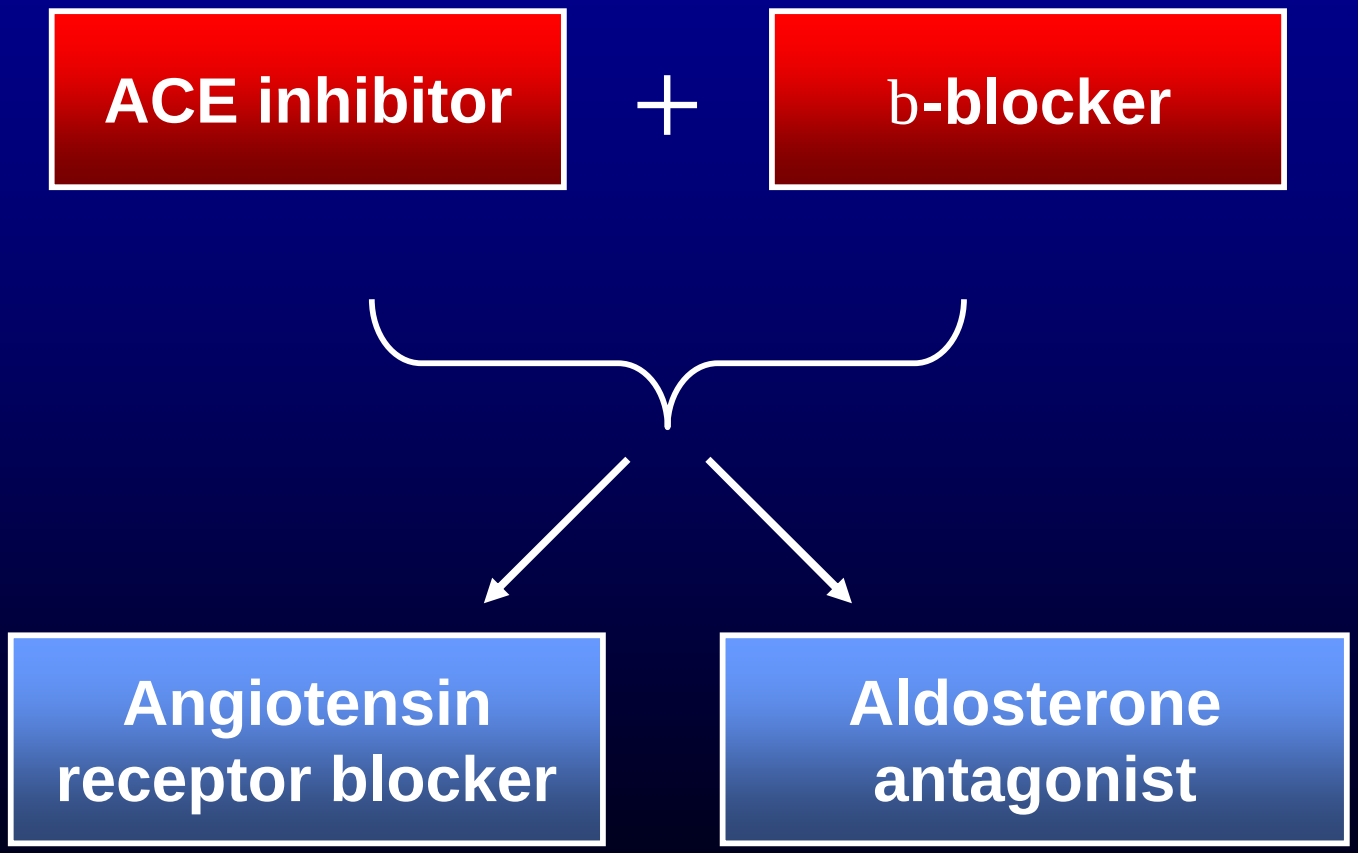
Aldosterone Antagonism

EPHESUS and RALES Trials

Placebo vs eplerenone or spironolactone added to ACE inhibitor and β-blocker in post-MI CHF or class III-IV heart failure

- 15% to 30% lower risk of death ($P<0.01$)
- 15% to 30% lower risk of death or hospitalization for heart failure in both trials, both $P<0.001$
- Higher risk of renal insufficiency and hyperkalemia

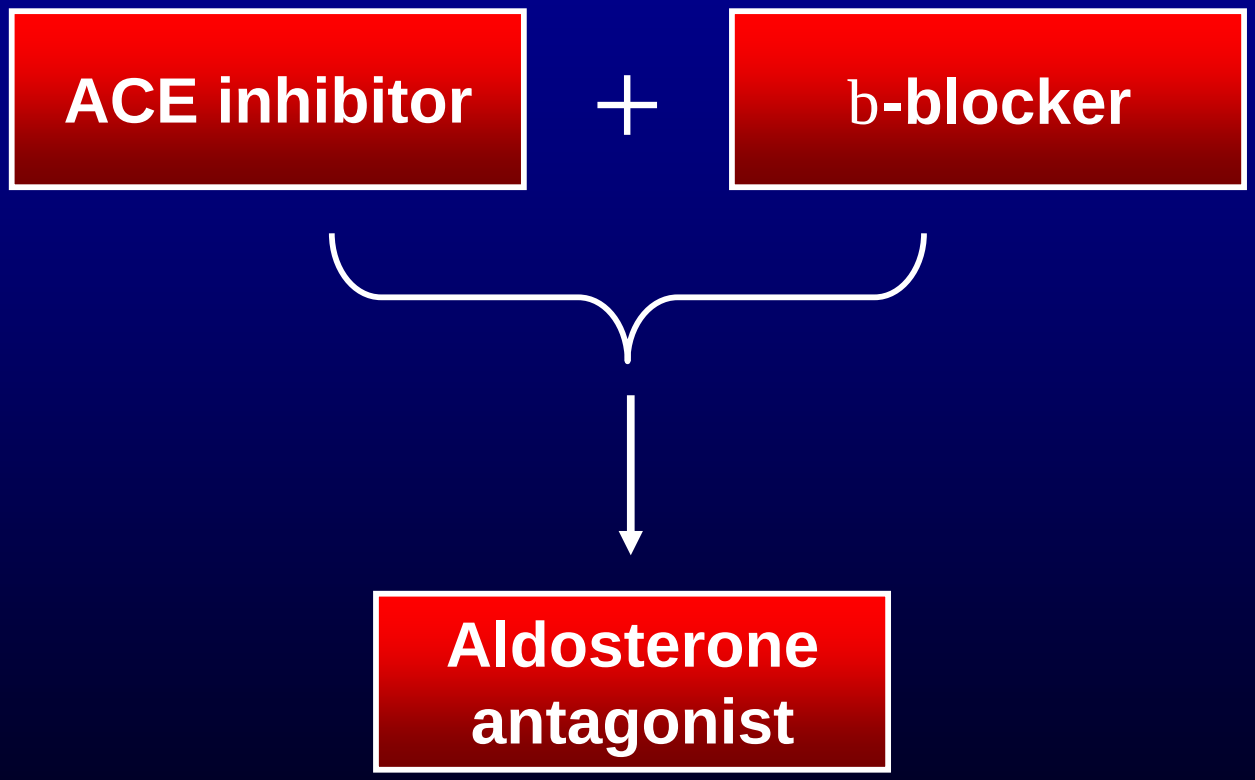
What Is the Next Step?



Should an Aldosterone Antagonist Be the Next Step After ACE Inhibitor + b-Blocker?

	Aldosterone Antagonist	Angiotensin Receptor Blocker
Effect on mortality	15%-30%	5%-10%
Effect on risk of death or CHF hospitalization	15%-30%	10%-15%
Effect on blood pressure	No change	Decrease
Other safety	Renal insufficiency Hyperkalemia	Renal insufficiency Hyperkalemia

What Is the Next Step?



ESC GUIDELINES FOR HEART FAILURE (UPDATE 2005)

- *Aldosteroneantagonists such as eplerenoneare recommended in addition to ACEiand β-blockers in post-MI LV dysfunction with or without symptoms of HF (level of evidence IB).*

- **Check serum potassium <5 and creatinine<2.5. Add low dose Eplerenone25 mg. After 4-6 days if potassium is 5-5.5 reduce dose 50%. If potassium > 5.5 stop the drug. If symptoms persists and normokalaemiaexists after one month, increase to 50 mg daily. Check biochemicsafter one week.**

Post-MI LV **Dysfunction**: Current therapeutic strategies

- **ACE inhibitors (SAVE, AIRE, TRADE)**
- **Carvedilol (CAPRICORN)**
- **ARBs** alternatively to ACEi **(VALIANT)**
- **Eplerenone (EPHESUS)**

- **Statins**
- **Aspirine**
- **Nitrates?**