Optimal blockade of RAA in Heart Failure

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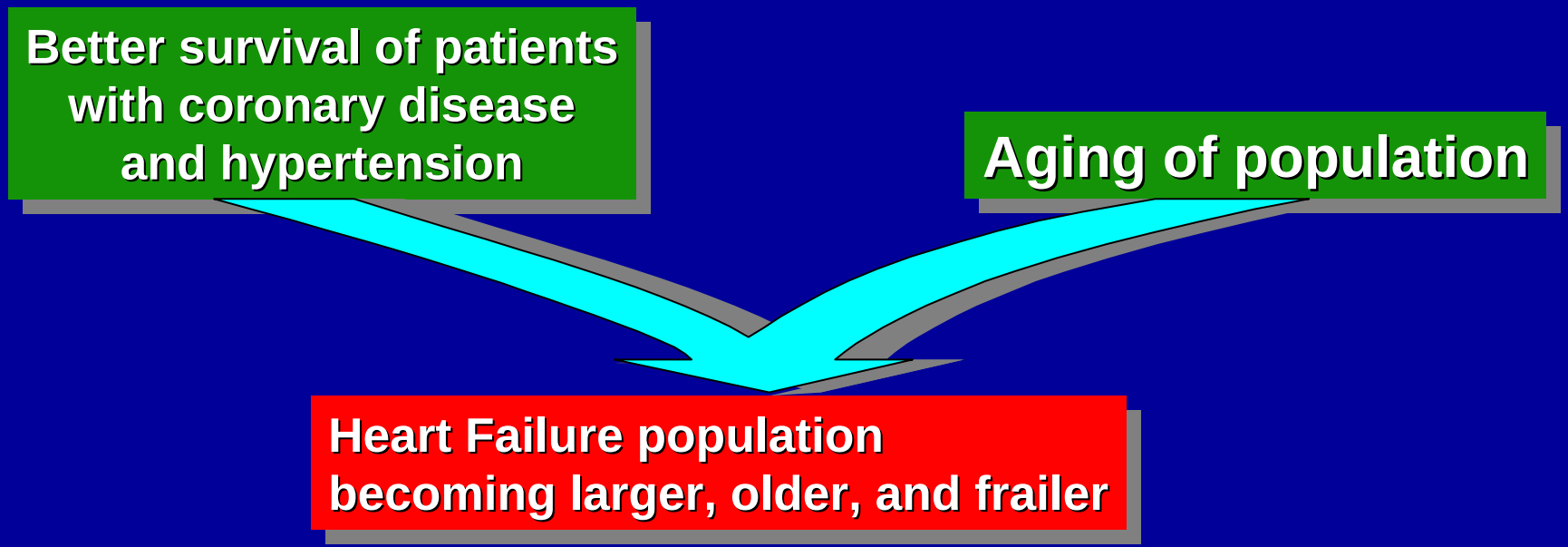
Contents

- RAA system in heart failure
- RAA block trials in heart failure
- Conundrum

Heart Failure Problem



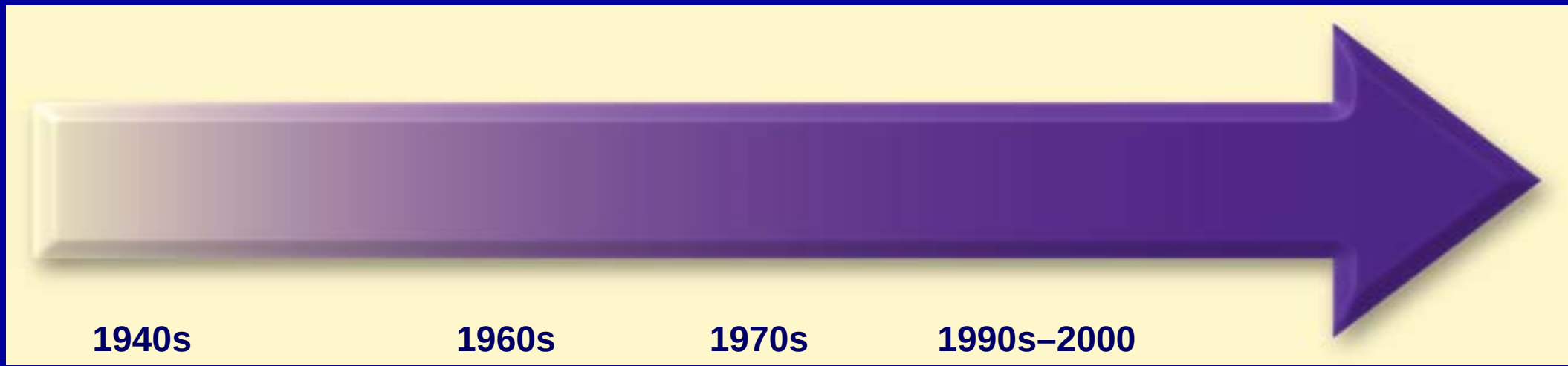
- *Classic paradox*
  - *improvement in one area of medicine leads to increases in diseases in another*

Evolving Models of CHF

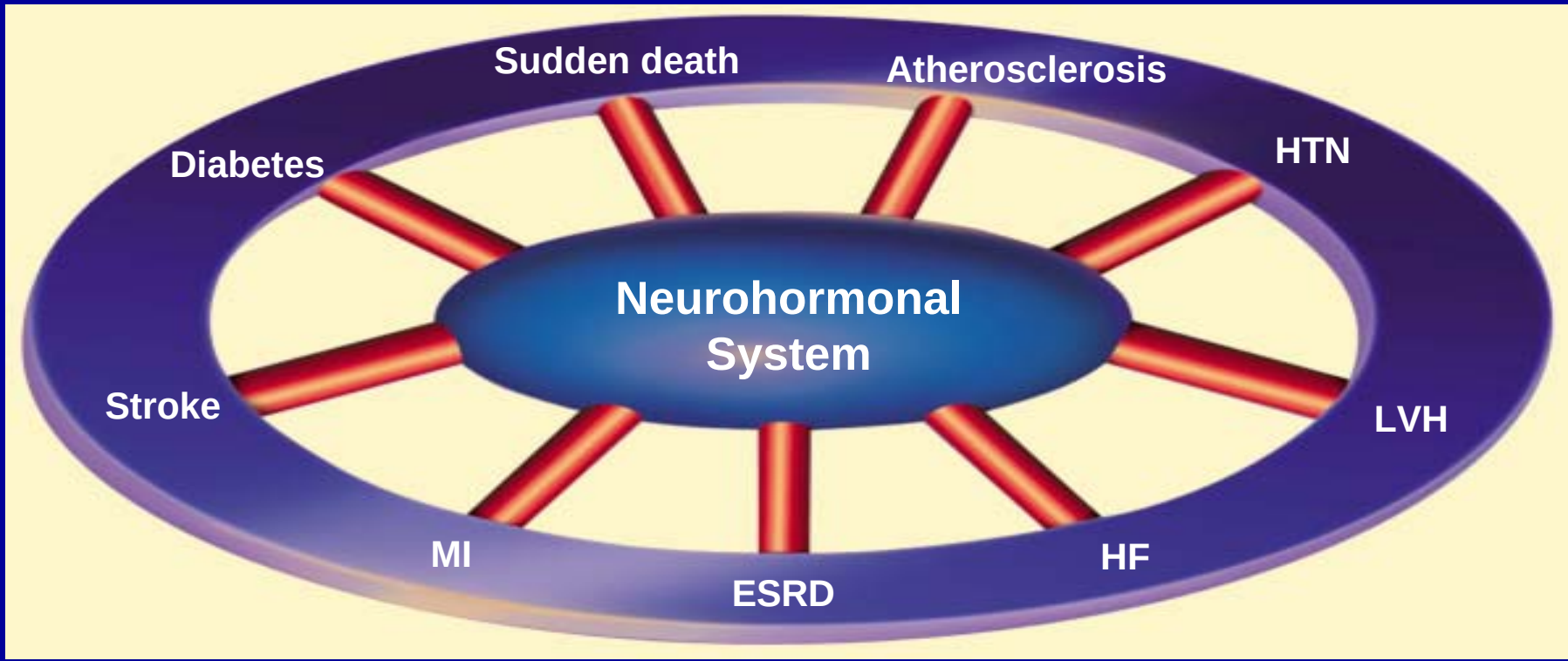
Cardiorenal
Digitalis and diuretic to perfuse kidneys

Hemodynamic
Vasodilators or positive inotropes to relieve ventricular wall stress

Neurohormonal
ACE inhibitors, beta blockers, and other agents to block neurohormonal activation



Neurohormonal System - Center CV Risk

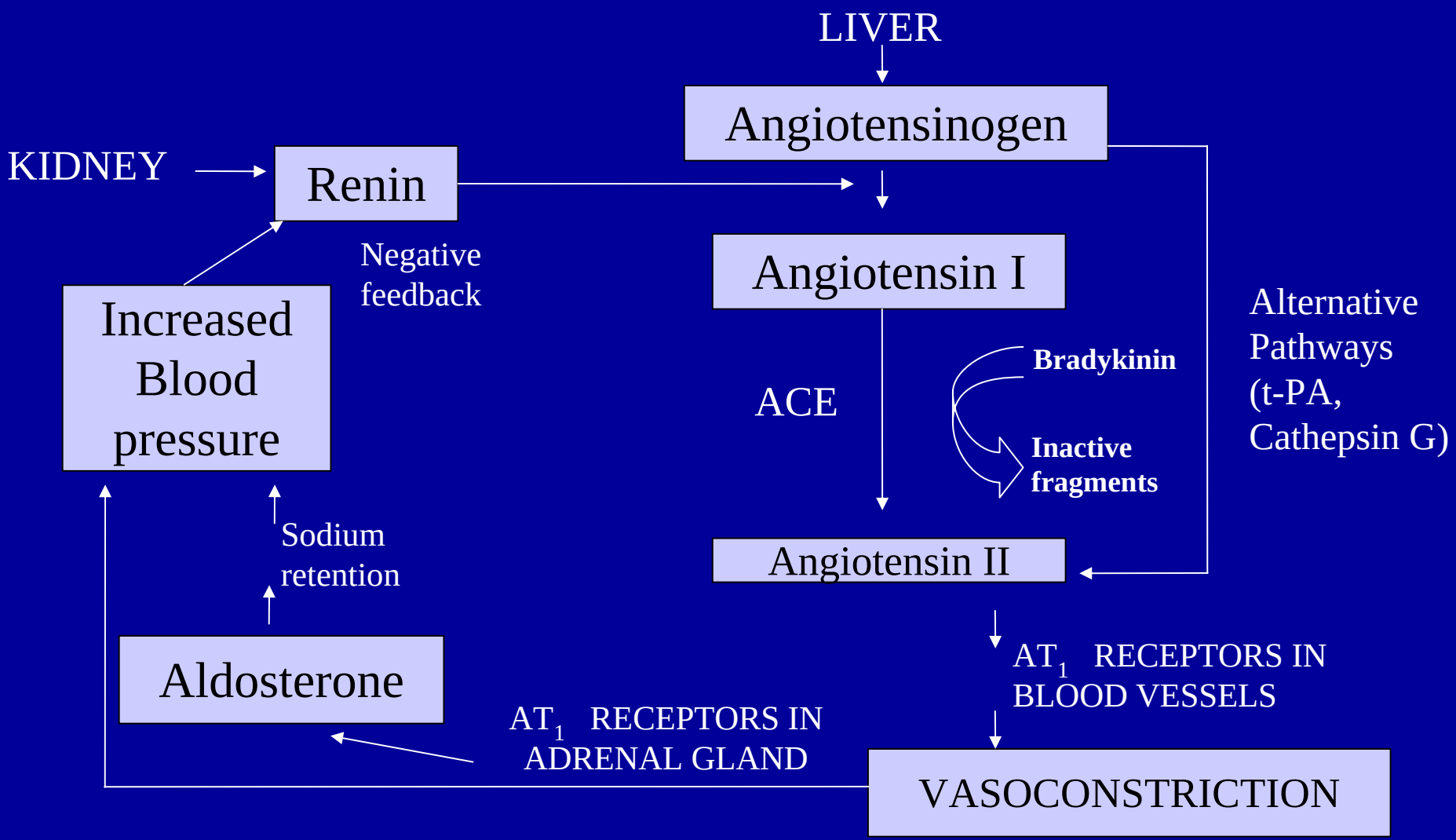


ESRD = End-stage renal disease, HF = Heart failure, HTN = Hypertension
LVH = Left ventricular hypertrophy, MI = Myocardial infarction

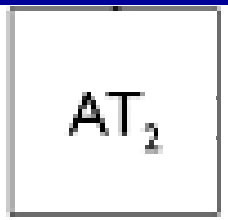
Neurohormonal System in CHF

- BNP
- Angiotensin II
- Norepinephrine
- Aldosterone
- Endothelin
- Vasopressin

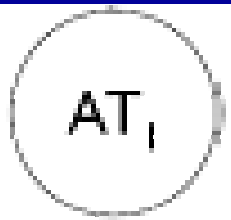
The renin-angiotensin system



AT receptors

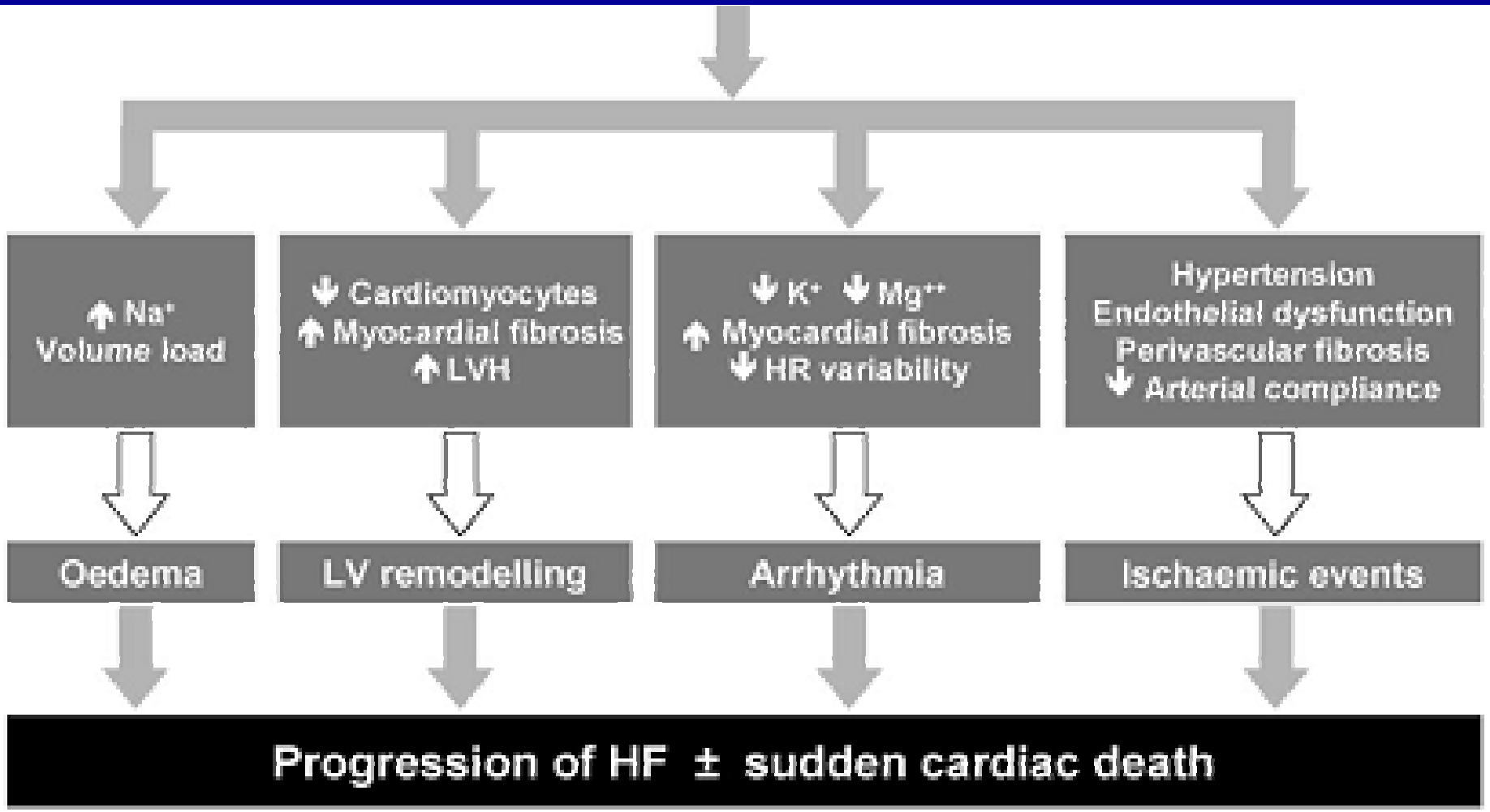


- Systemic/renal vasodilation
- Decreased renal sodium reabsorption
- Decreased inflammation
- Decreased mitogenesis
- Decreased myocyte hypertrophy
- Decreased cardiac fibrosis

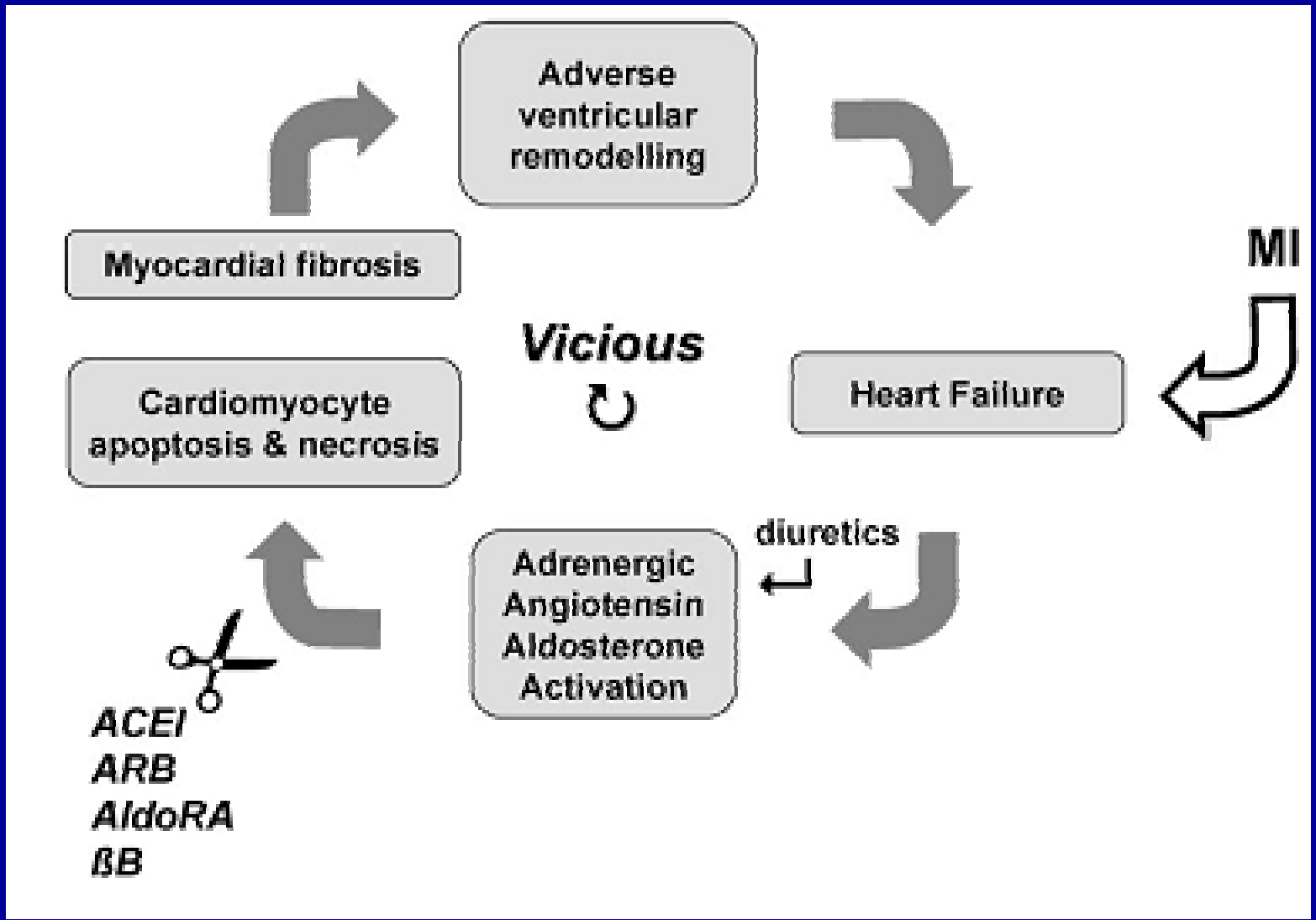


- Systemic/renal vasodilation
- Increased renal sodium reabsorption
- Activation of inflammatory cytokines
- Vascular smooth muscle growth
- Oxidative stress
- Endothelial dysfunction
- Increased PAI-1 activity/ thrombosis

Aldosterone



Heart failure

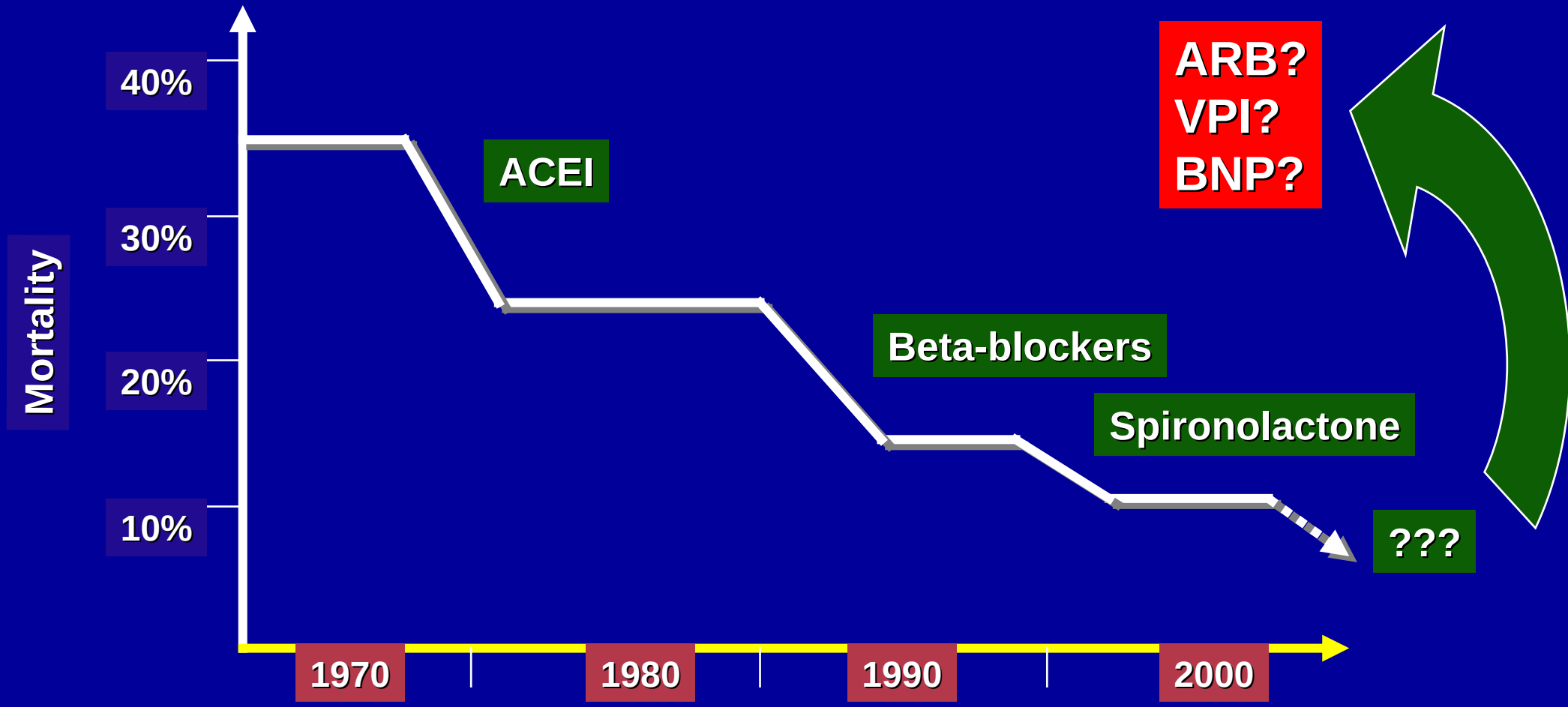


RAA block trials in heart failure

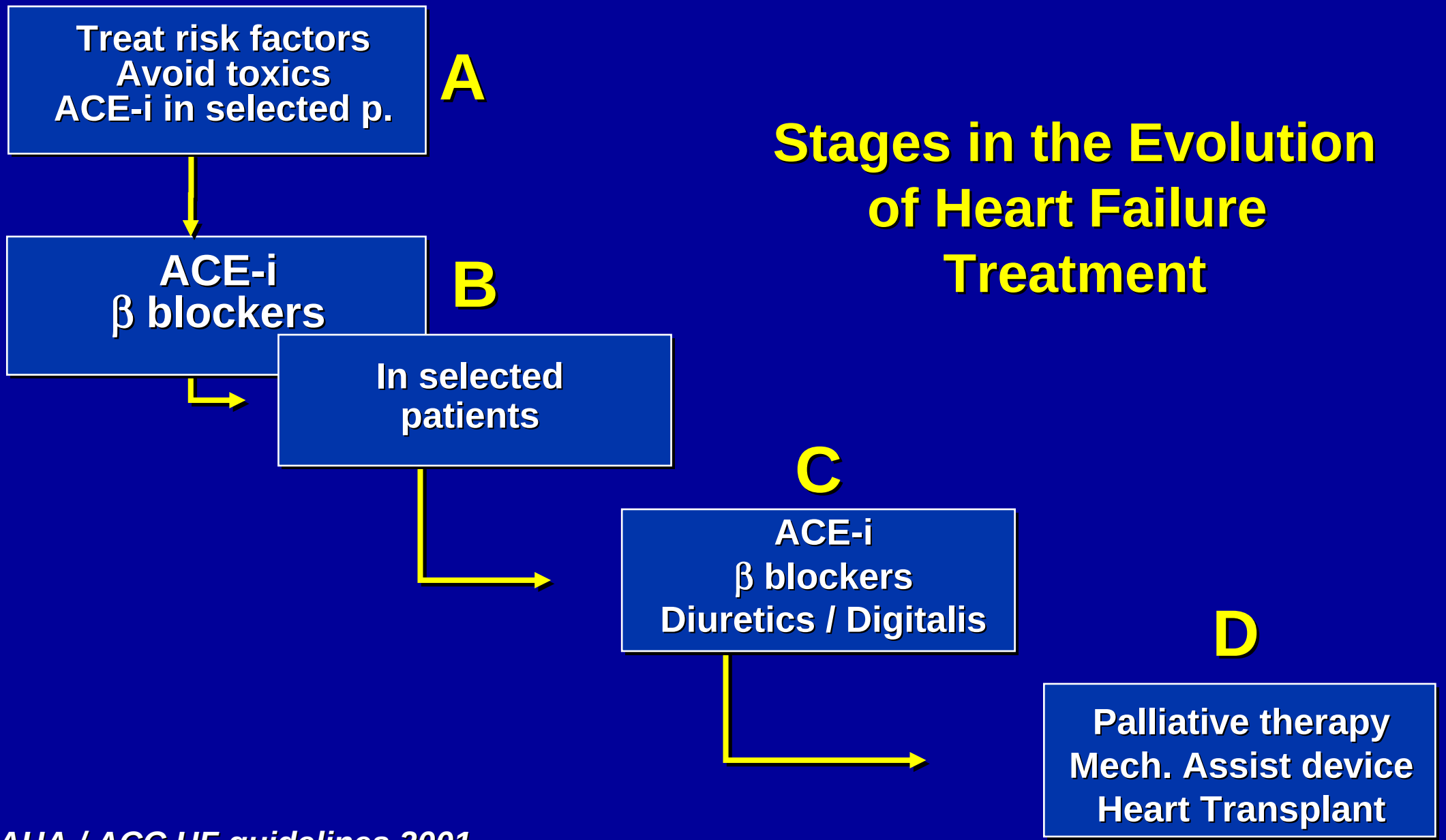
CHF treatment through the ages

- 1920 - Organomercurial diuretics
- 1958 - Thiazide diuretics introduced
- 1967 - Heart transplantation (C Barnard)
- 1975 - β blockers first used in heart failure (F Waagstein et al)
- 1987 - CONSENSUS shows survival benefits from ACE inhibitors (K Swedberg et al)

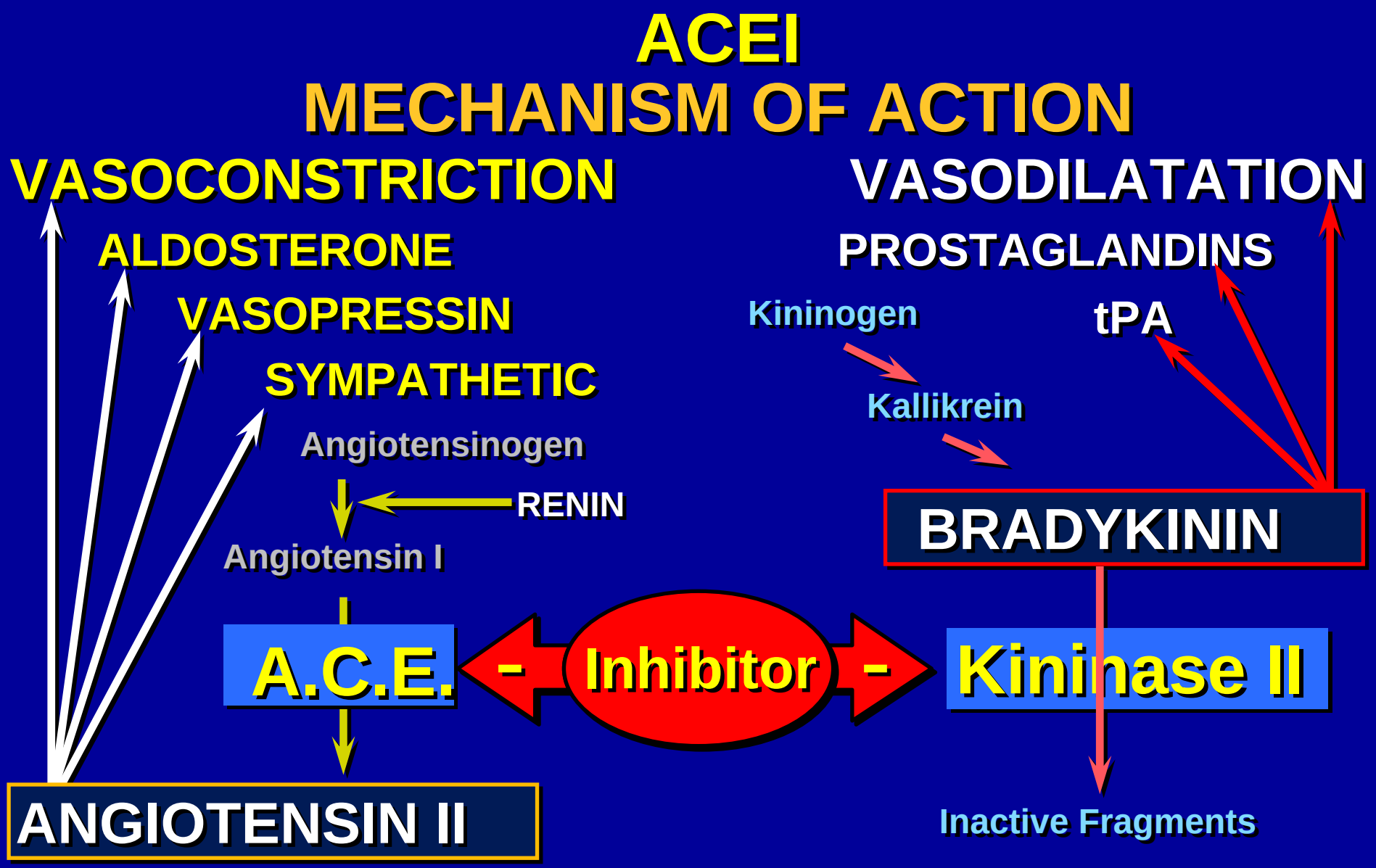
Medical Therapy for CHF



Stages in the Evolution of Heart Failure Treatment



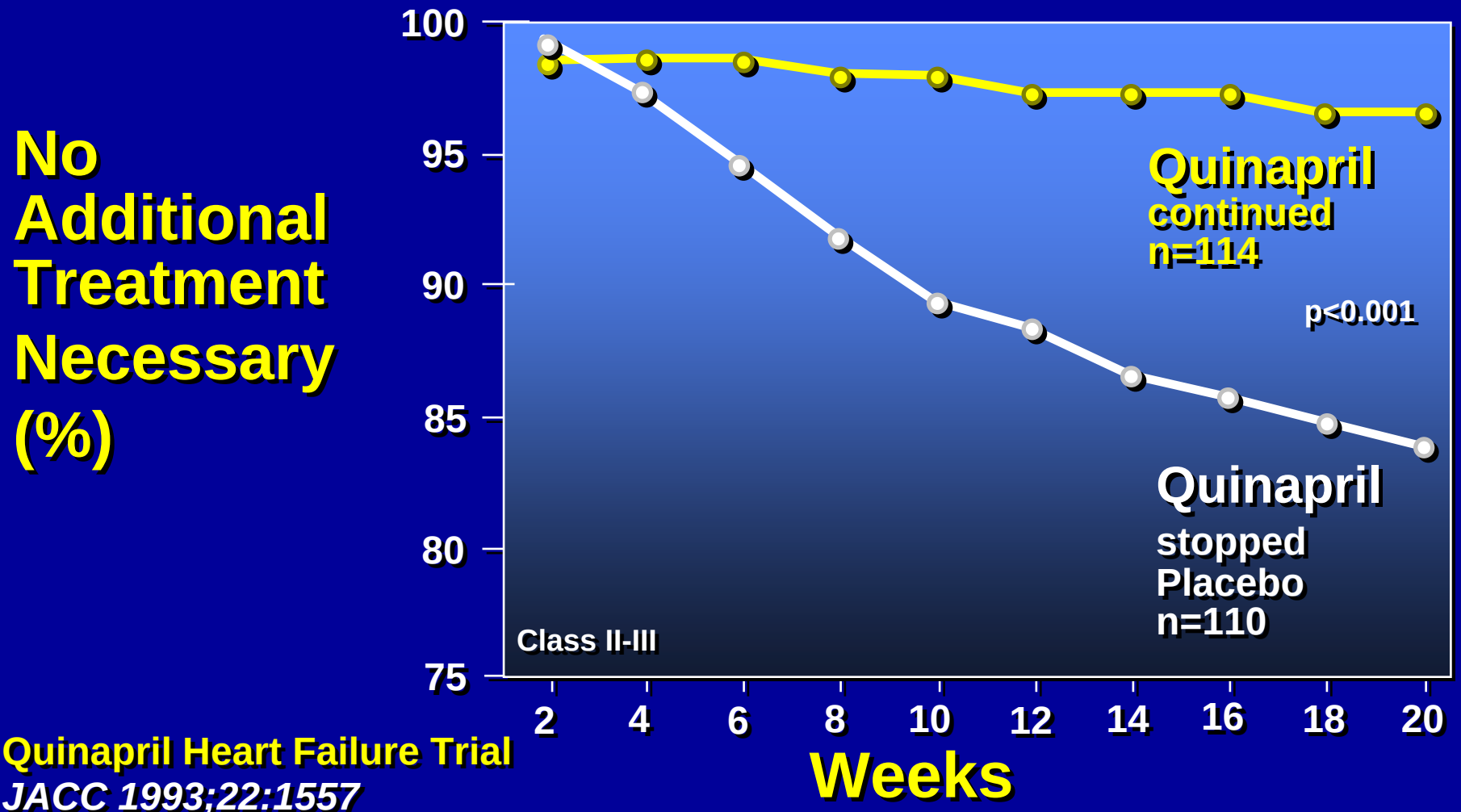
AHA / ACC HF guidelines 2001


ACEI
MECHANISM OF ACTION
VASOCONSTRICTION
VASODILATATION
ALDOSTERONE
VASOPRESSIN
SYMPATHETIC
PROSTAGLANDINS
Kininogen
tPA
Kallikrein
Angiotensinogen
RENIN
BRADYKININ
Angiotensin I
A.C.E.
Inhibitor
Kininase II
ANGIOTENSIN II
Inactive Fragments

ACEI
HEMODYNAMIC EFFECTS

- Arteriovenous Vasodilatation
  - ↓PAD, PCWP and LVEDP
  - ↓SVR and BP
  - ↑CO and exercise tolerance
- No change in HR / contractility
- ↓MVO_2
- ↑Renal, coronary and cerebral flow
- Diuresis and natriuresis

ACEI
FUNCTIONAL CAPACITY



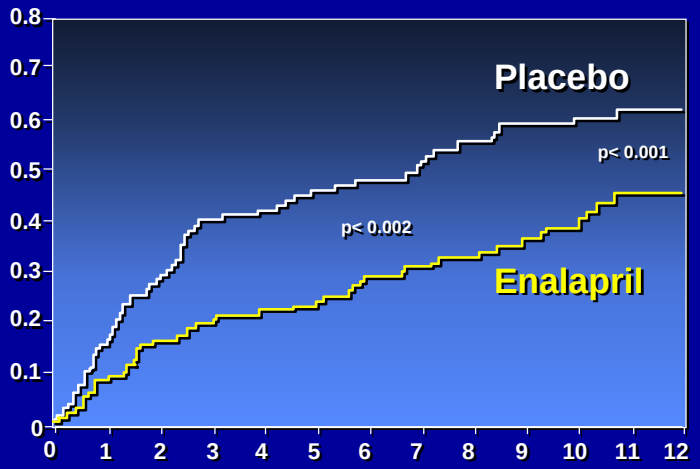
Quinapril Heart Failure Trial
JACC 1993;22:1557

ACEI
ADVANTAGES

- Inhibit LV remodeling post-MI
- Modify the progression of chronic CHF
  - ⬆ Survival
  - ⬇ Hospitalizations
  - Improve the quality of life
- In contrast to others vasodilators, do not produce neurohormonal activation or reflex tachycardia
- Tolerance to its effects does not develop

ACEI Survival

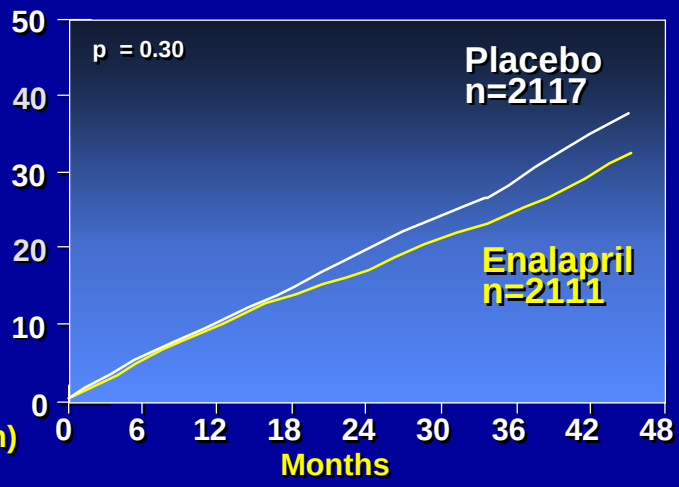
PROBABILITY OF DEATH



CONSENSUS
N Engl J Med 1987;316:1429

% MORTALITY

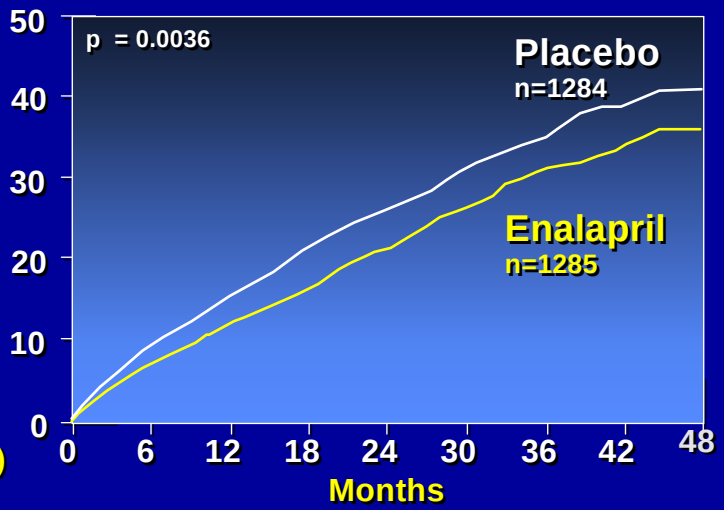
n = 4228
No CHF symptoms
EF < 35



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

% MORTALITY

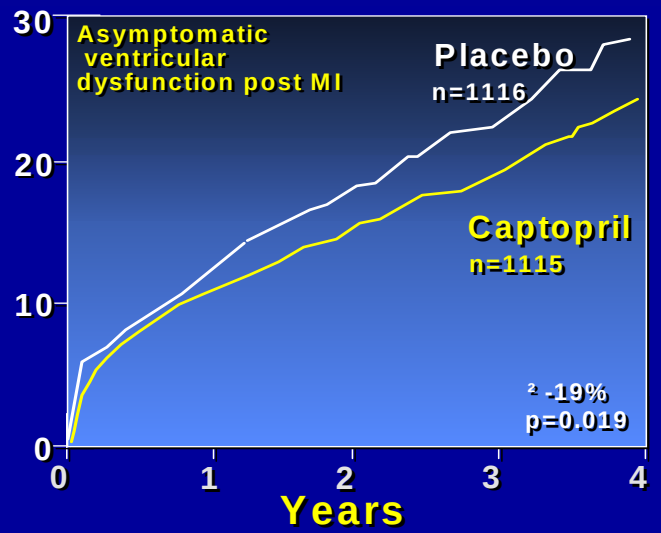
n = 2589
CHF
- NYHA II-III
- EF < 35



SOLVD (Treatment)
N Engl J M 1991;325:293

Mortality, %

n = 2231
3 - 16 days post AMI
EF < 40
12.5 --- 150 mg / day



SAVE
N Engl J Med 1992;327:669

ACEI
UNDESIRABLE EFFECTS

- **Inherent in their mechanism of action**
  - Hypotension
  - Hyperkalemia
  - Angioneurotic edema
  - Dry cough
  - Renal Insuff.
- **Due to their chemical structure**
  - Cutaneous eruptions
  - Neutropenia, thrombocytopenia
  - Digestive upset
  - Dysgeusia
  - Proteinuria

ACEI
CONTRAINDICATIONS

- Renal artery stenosis
- Renal insufficiency
- Hyperkalemia
- Arterial hypotension
- Intolerance (due to side effects)

ALDOSTERONE INHIBITORS INDICATIONS

FOR DIURETIC EFFECT

- Pulmonary congestion (dyspnea)
- Systemic congestion (edema)

FOR ELECTROLYTE EFFECTS

- Hypo K^+, Hypo Mg^+
- Arrhythmias
- Better than K^+ supplements

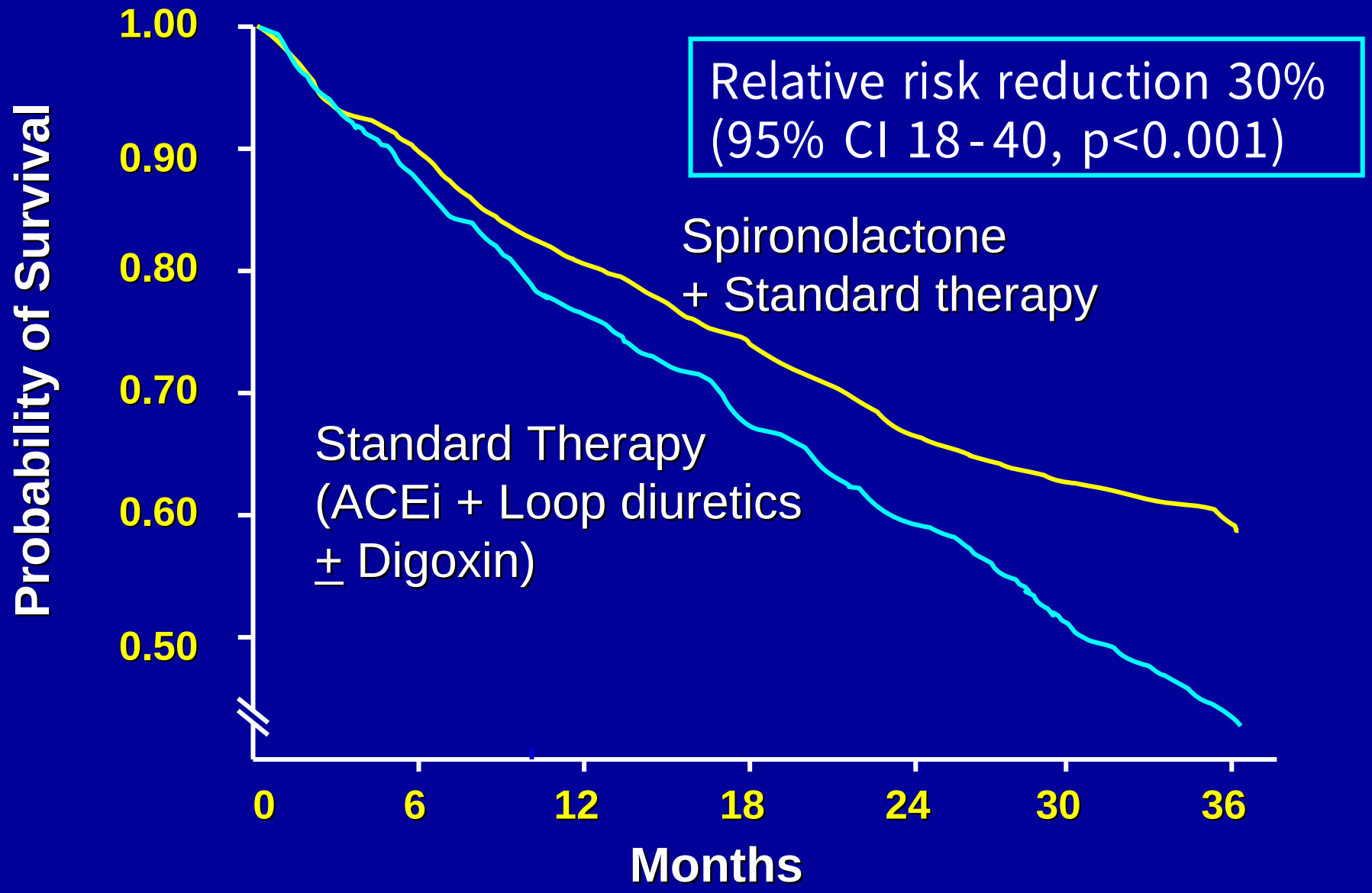
FOR NEUROHORMONAL EFFECTS

- Please see RALES results,
  N Engl J Med 1999:341:709-717

Benefits of Aldosterone Receptor Blockade

- Are not primarily due to a diuretic effect, but are most likely the result of other antialdosterone effects
- Include:
  - Decreased myocardial and vascular fibrosis
  - Increased myocardial NE reuptake
  - Improved arterial compliance
  - Improved endothelial dysfunction
  - Improved baroreceptor function
  - Improved potassium and magnesium homeostasis

RALES


Probability of Survival
1.00
0.90
0.80
0.70
0.60
0.50
0
6
12
18
24
30
36
Months
Relative risk reduction 30%
(95% CI 18-40, p<0.001)
Spironolactone
+ Standard therapy
Standard Therapy
(ACEi + Loop diuretics
± Digoxin)

EPHESUS

Eplerenone Post-AMI Heart Failure Efficacy and SUrvival Study: Primary Results of the EPHESUS Trial

B. Pitt[1†], W. Remme[2], F. Zannad[3†], J. Neaton[4†], F. Martinez[5], B. Roniker[6], R. Bittman[6], S. Hurley[6], J. Kleiman[6], M. Gatlin[6] for the Eplerenone Post-AMI Heart Failure Efficacy and Survival Study Investigators

[1]University of Michigan, Ann Arbor, MI, USA
[2]STICARES,Cardiovascular Research Foundation, Rotterdam, the Netherlands
[3]Centre d'Investigation Clinique de Nancy, Nancy, France
[4]University of Minnesota, Minneapolis, MN USA
[5]Fundación Rusculleda, Cordoba, Argentina
[6]Pharmacia Corporation Skokie, IL, USA

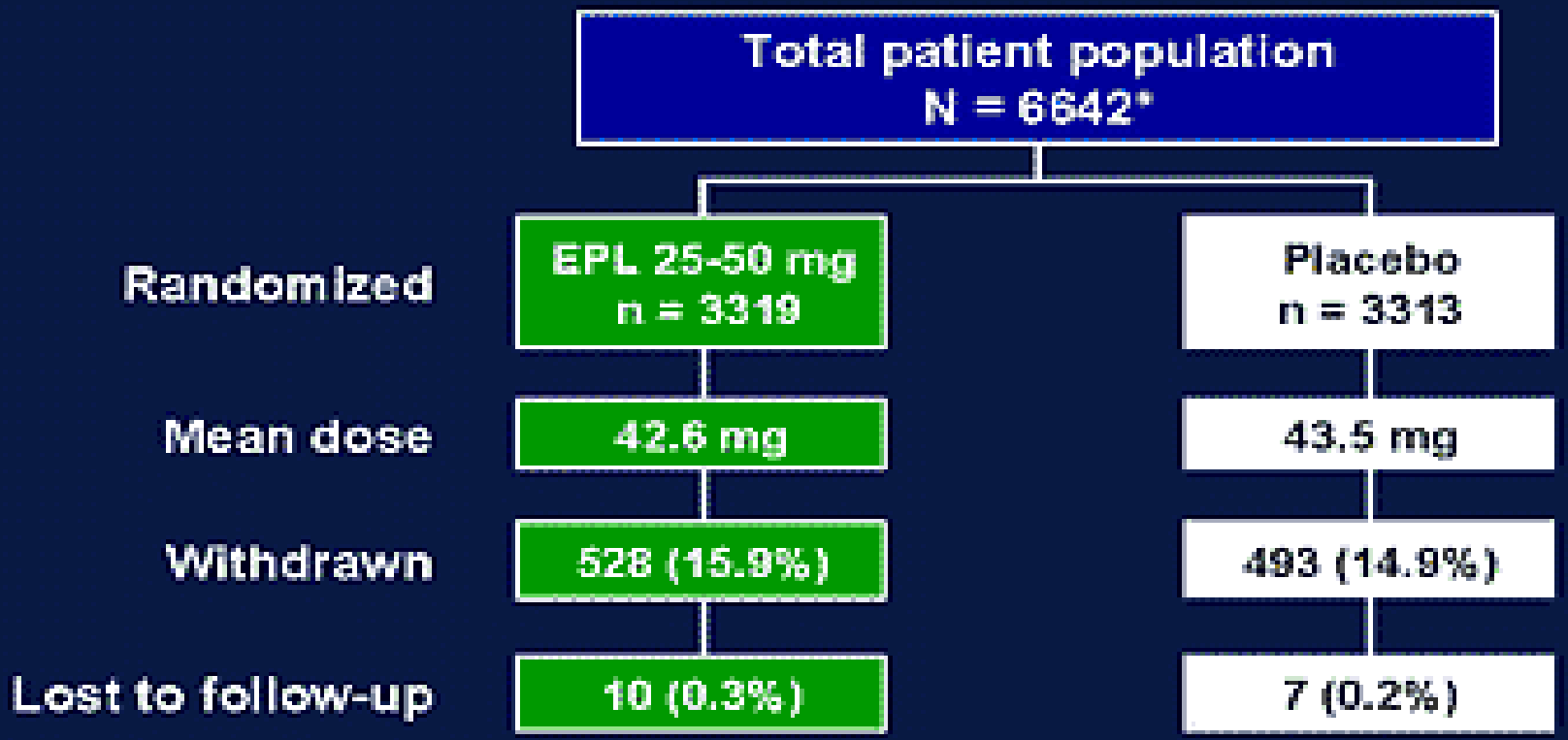
Supported by a grant from Pharmacia Corporation, Peapack, NJ

www.NEJM.org

[†]Consultant to Pharmacia

EPHESUS

EPHESUS: Disposition of Patients

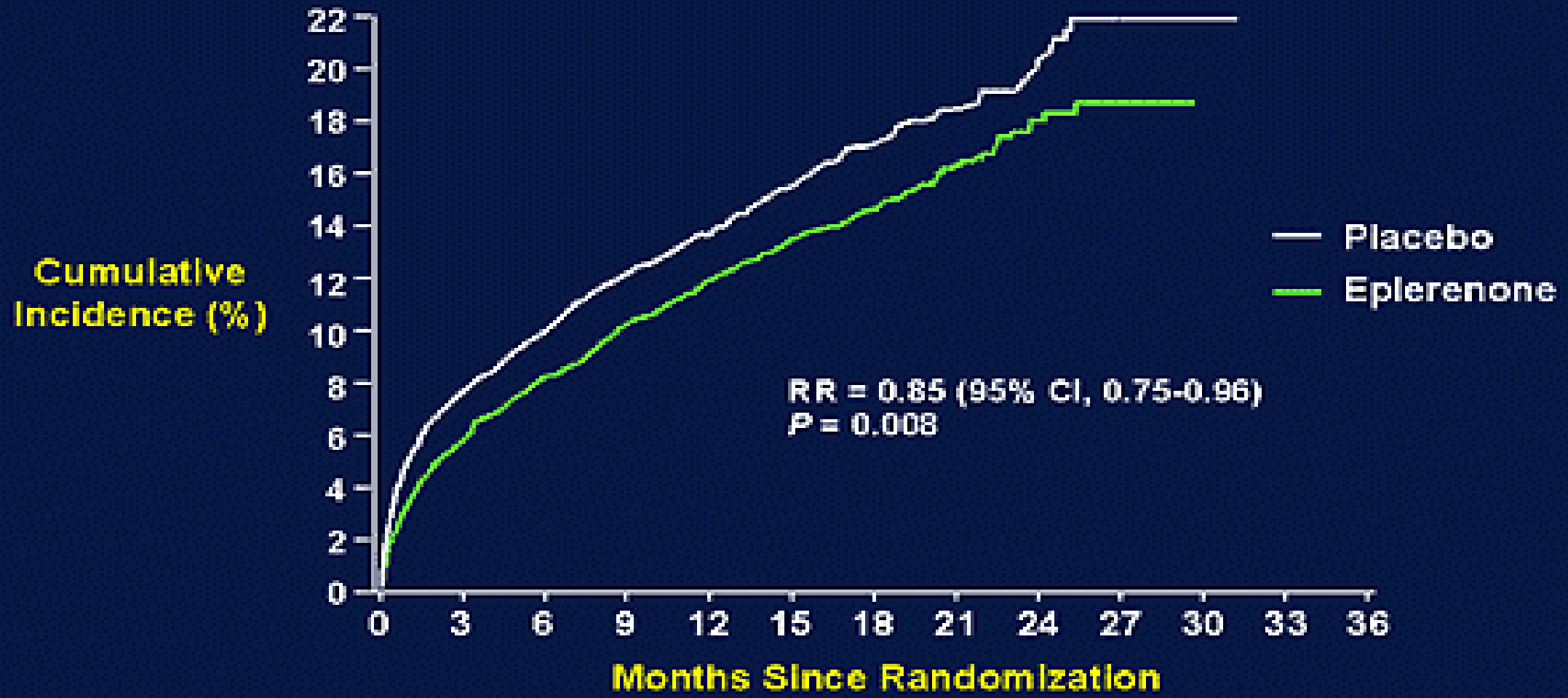


Mean duration of follow-up 16 months (range 0-33)

* 10 patients removed from analysis prior to unblinding due to data quality issues at one center

EPHESUS

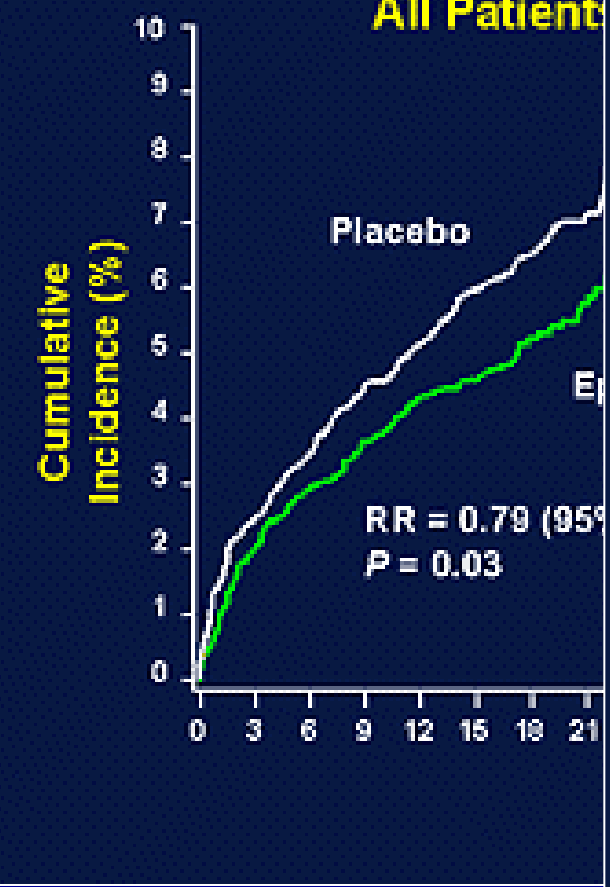
Relative Risk of Total Mortality



Placebo	3313	3064	2983	2830	2418	1801	1213	709	323	99	2	0	0
Eplerenone	3319	3125	3044	2896	2463	1857	1260	728	336	110	0	0	0

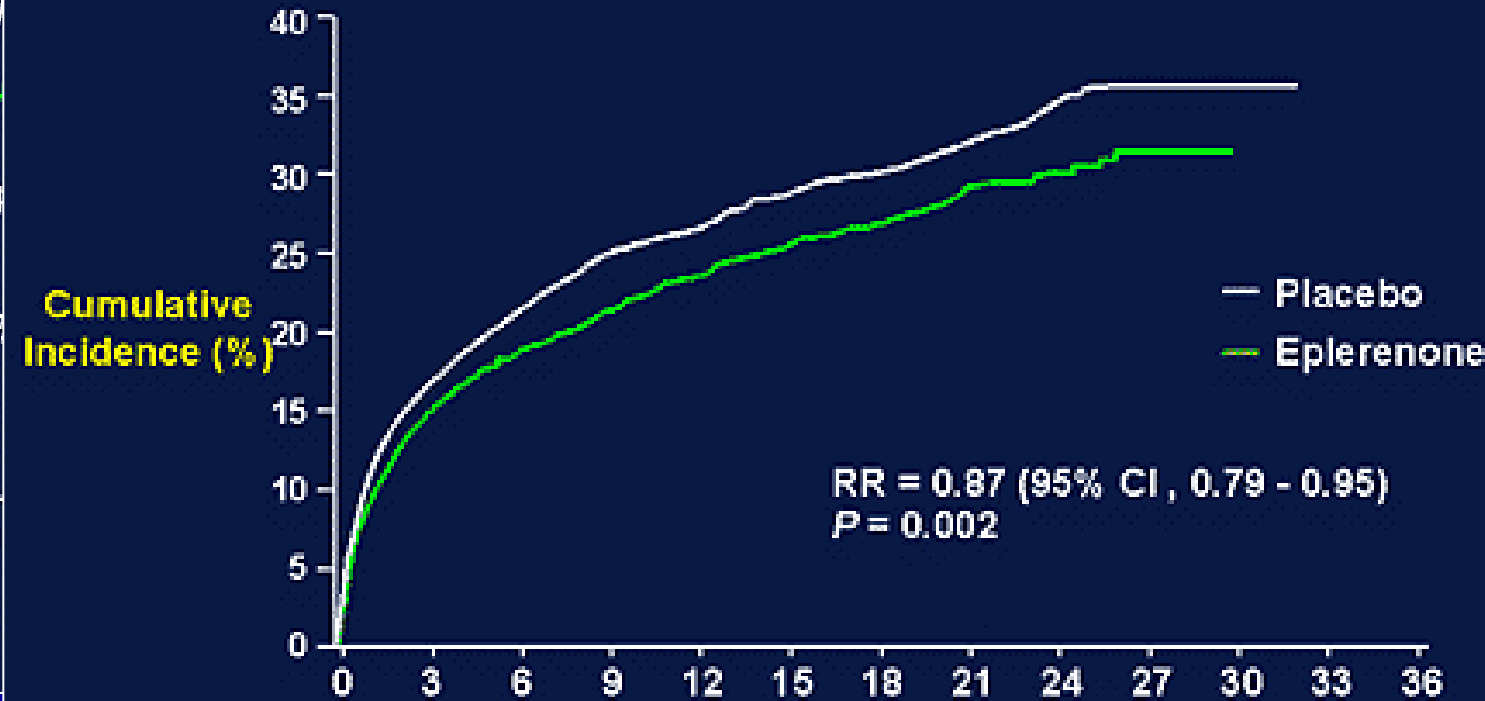
EPHESUS

Relative Risk of Sudden Cardiac Death



EPHESUS

Relative Risk of CV Mortality/CV Hospitalization



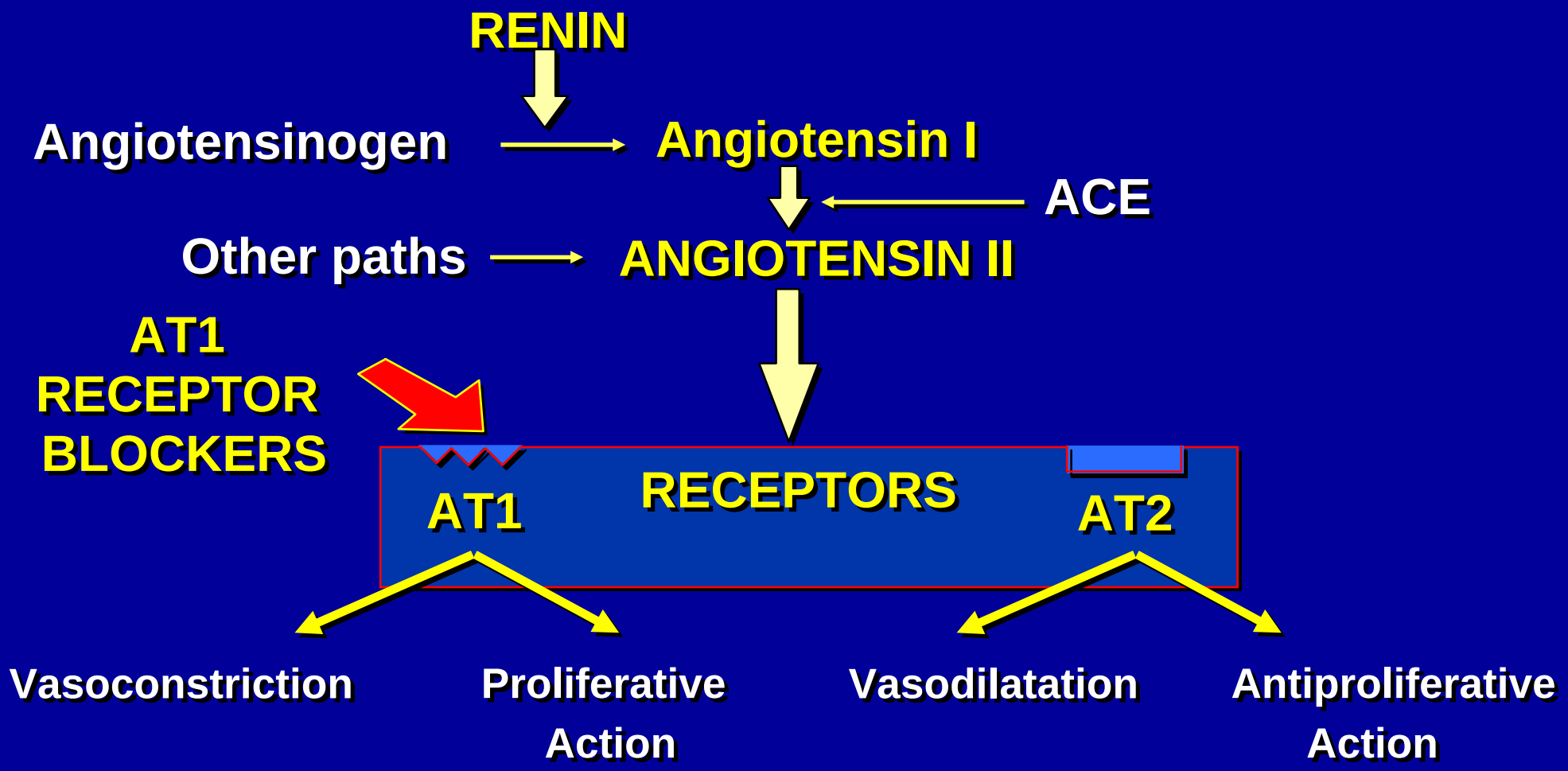
Placebo	3313	2754	2580	2388	2013	1494	995	558	247	77	2	0	0
Eplerenone	3319	2816	2680	2504	2096	1564	1061	594	273	91	0	0	0

EPHESUS

EPHESUS Summary

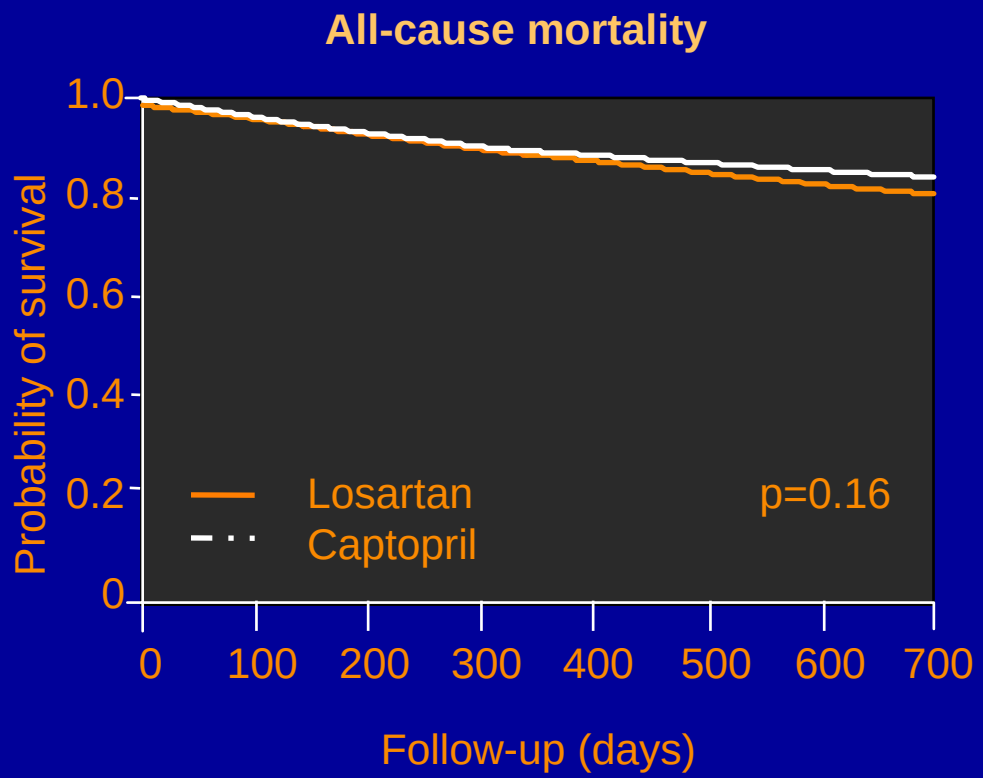
- Treatment with eplerenone was safe and well tolerated and resulted in:
  - no excess gynecomastia, impotence, or menstrual disorder
  - a 1.6% absolute increase of serious hyperkalemia and a 4.7% decrease of hypokalemia
  - 1 life saved per year for every 50 patients treated
  - 1 episode of CV mortality/CV hospitalization prevented per year for every 33 patients treated

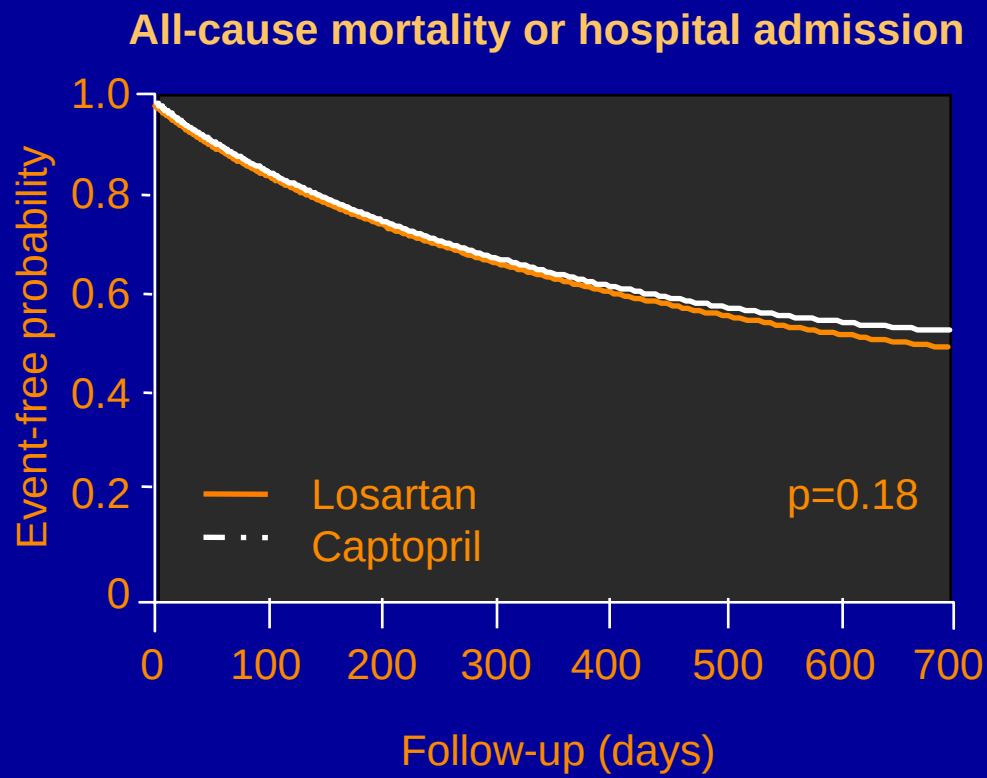
ANGIOTENSIN II INHIBITORS
MECHANISM OF ACTION



ELITE II: Endpoint Results

All-Cause Mortality or Hospital Admission

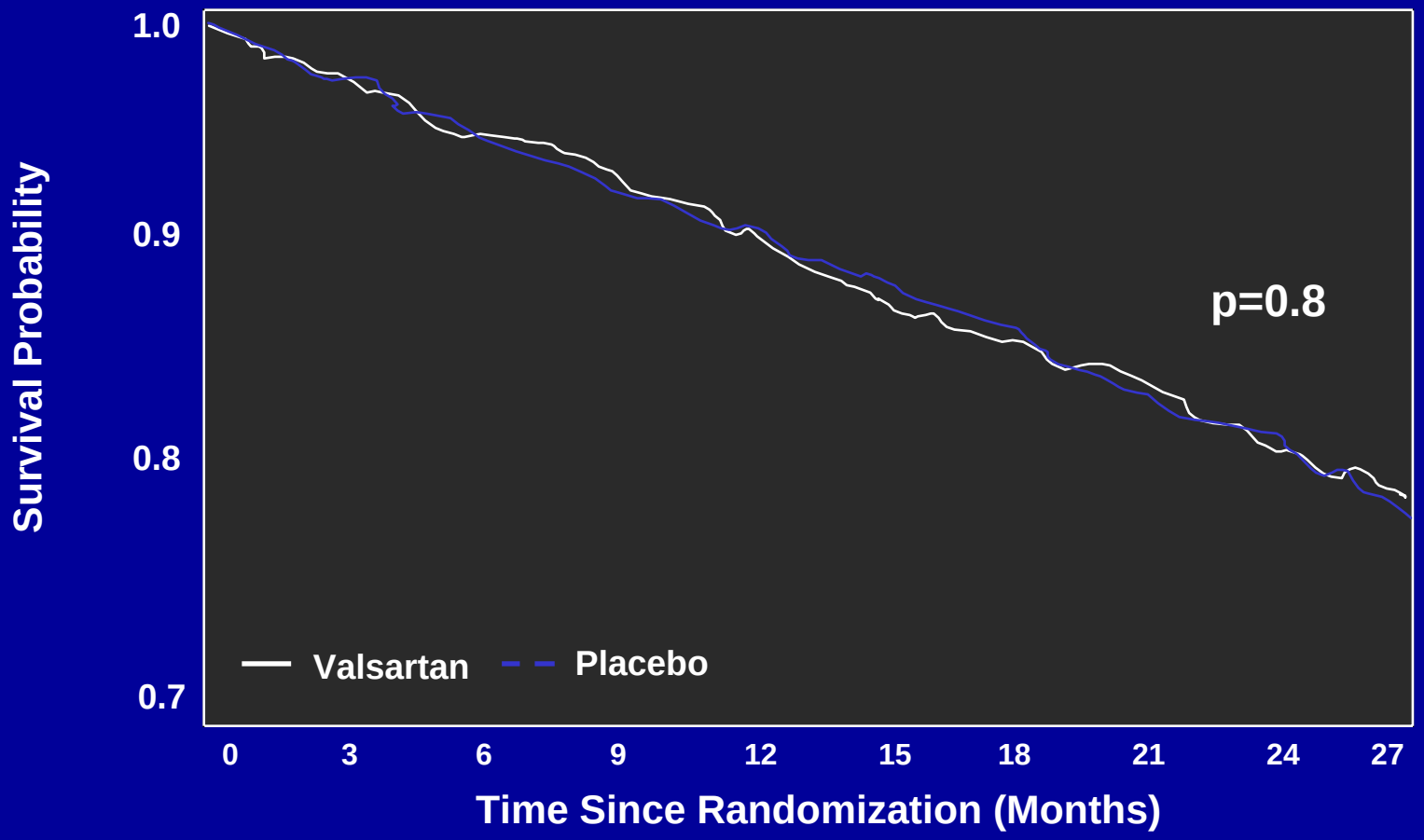




Pitt B, et al. *Lancet* 2000;**355**;1582-87

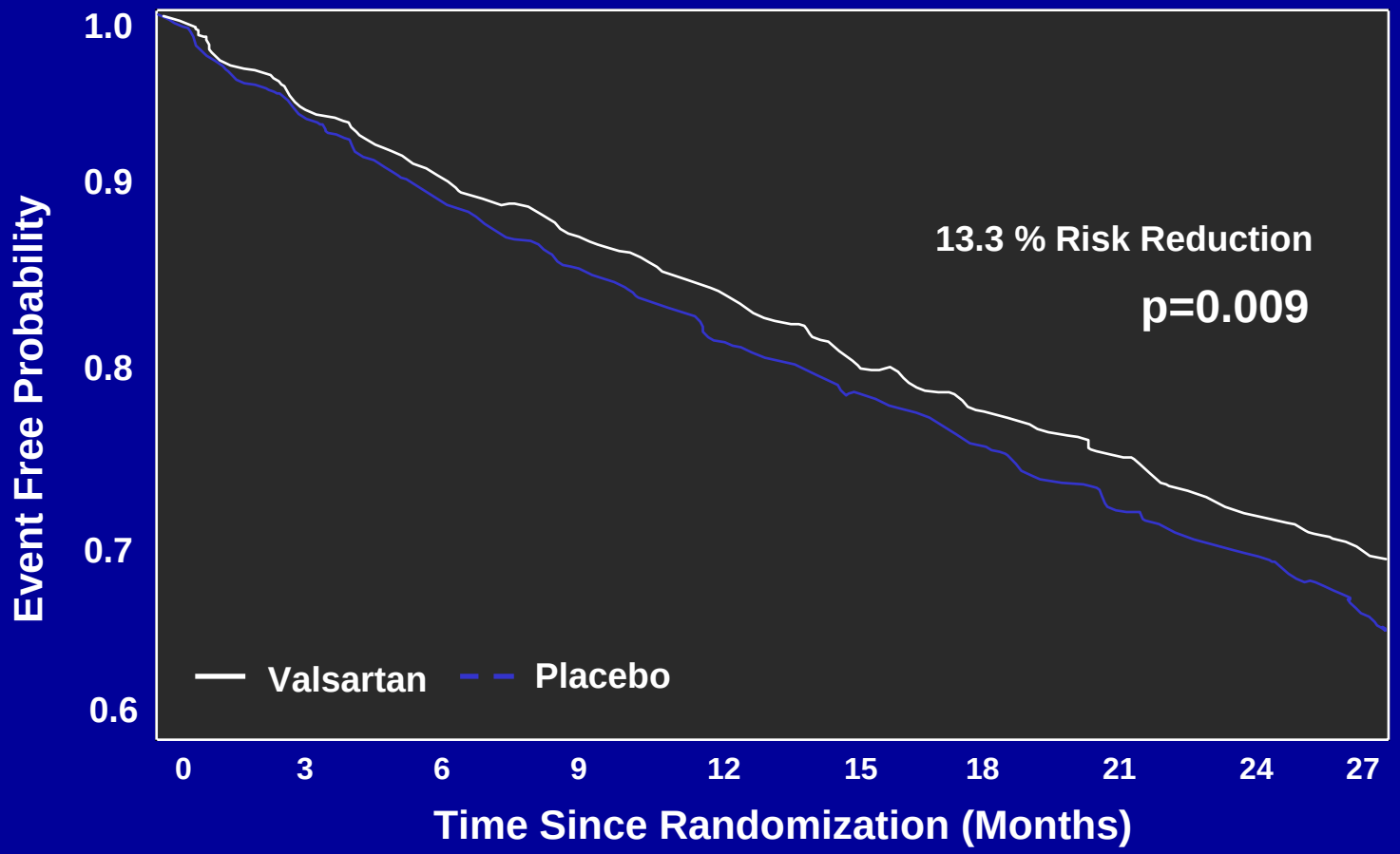
Val-HeFT Results

Primary Endpoint: All Cause Mortality



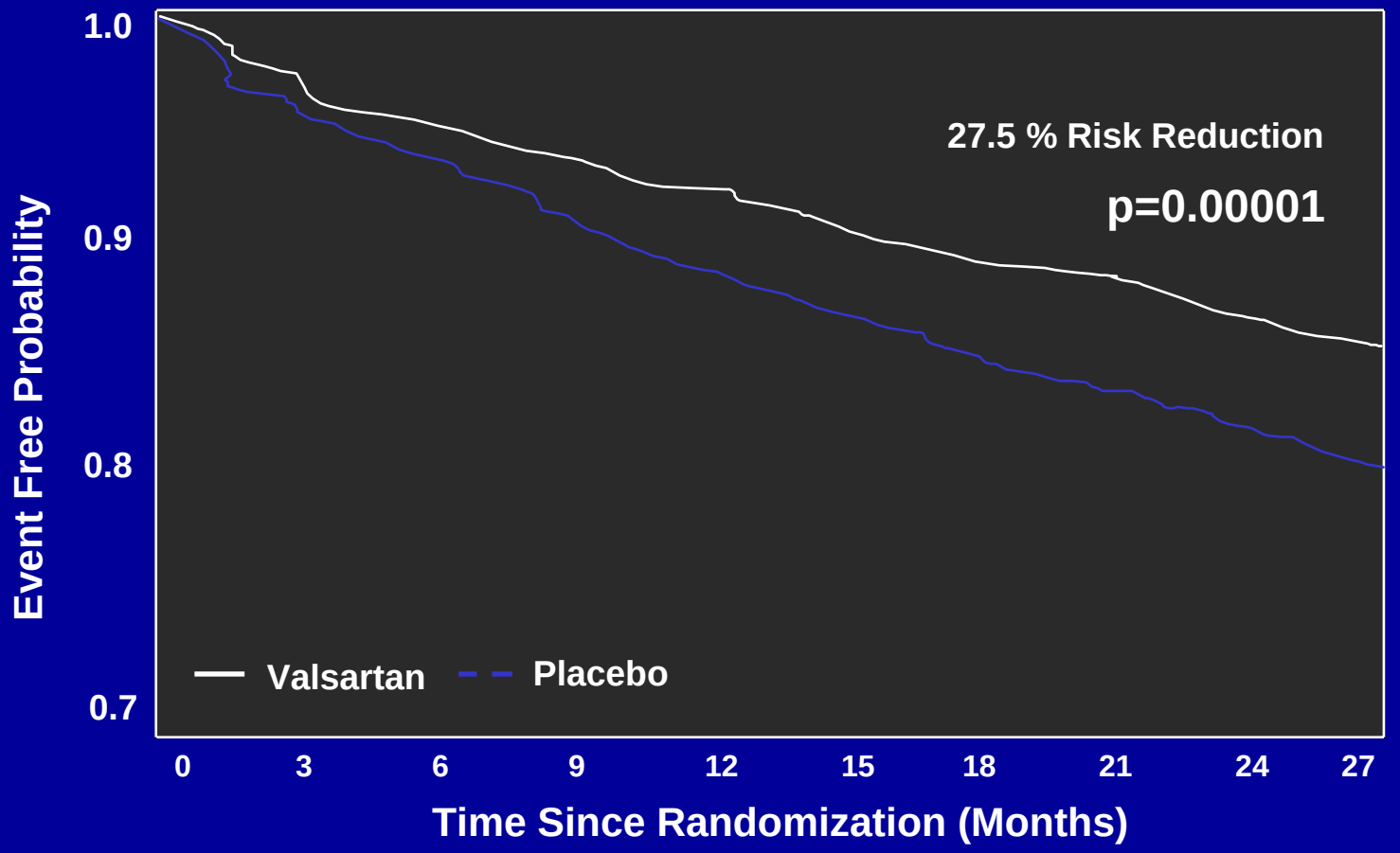
Val-HeFT Results

Primary Endpoint: Combined All Cause Mortality and Morbidity



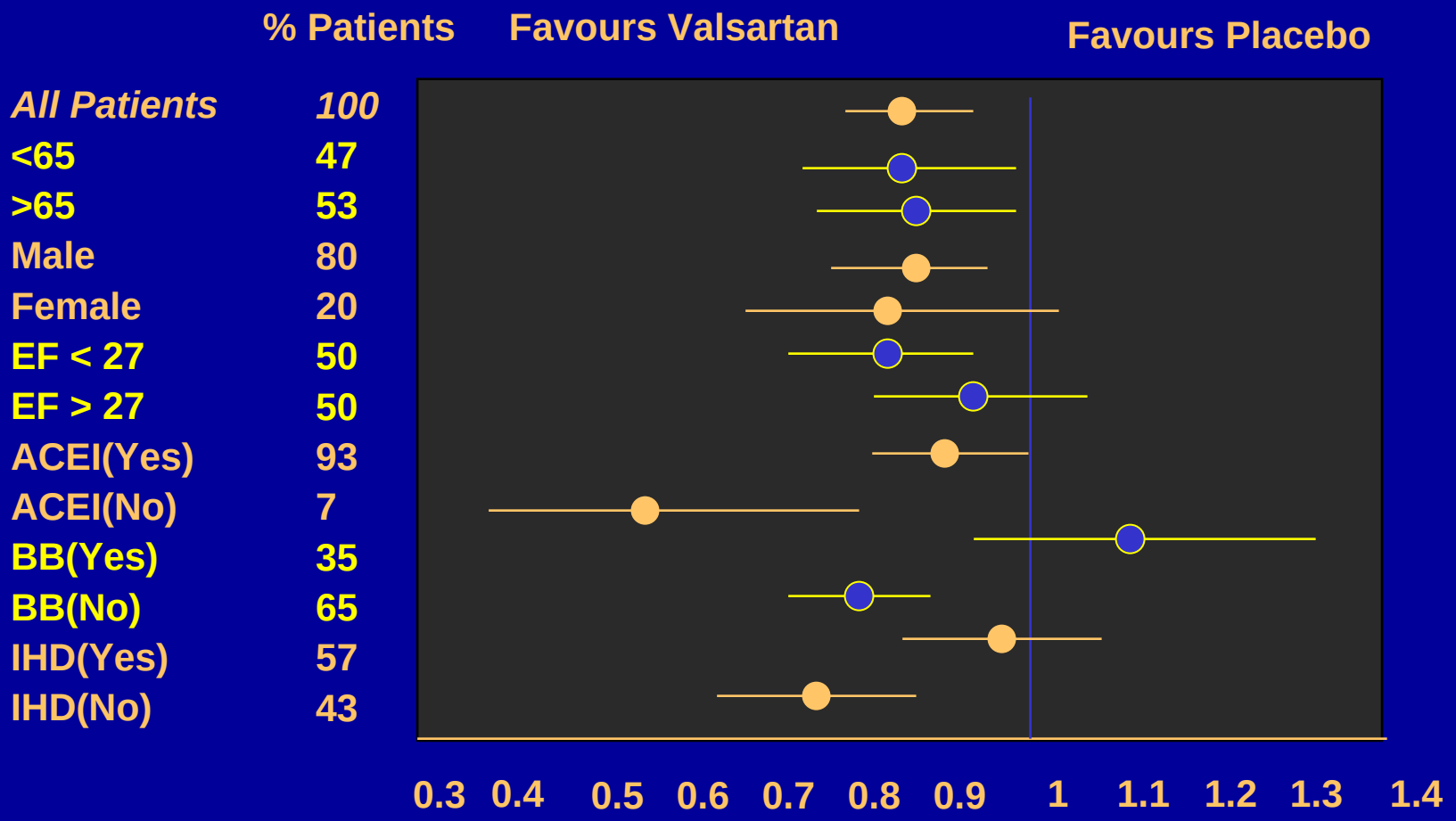
Val-HeFT Results

Secondary Endpoint: HF Hospitalization



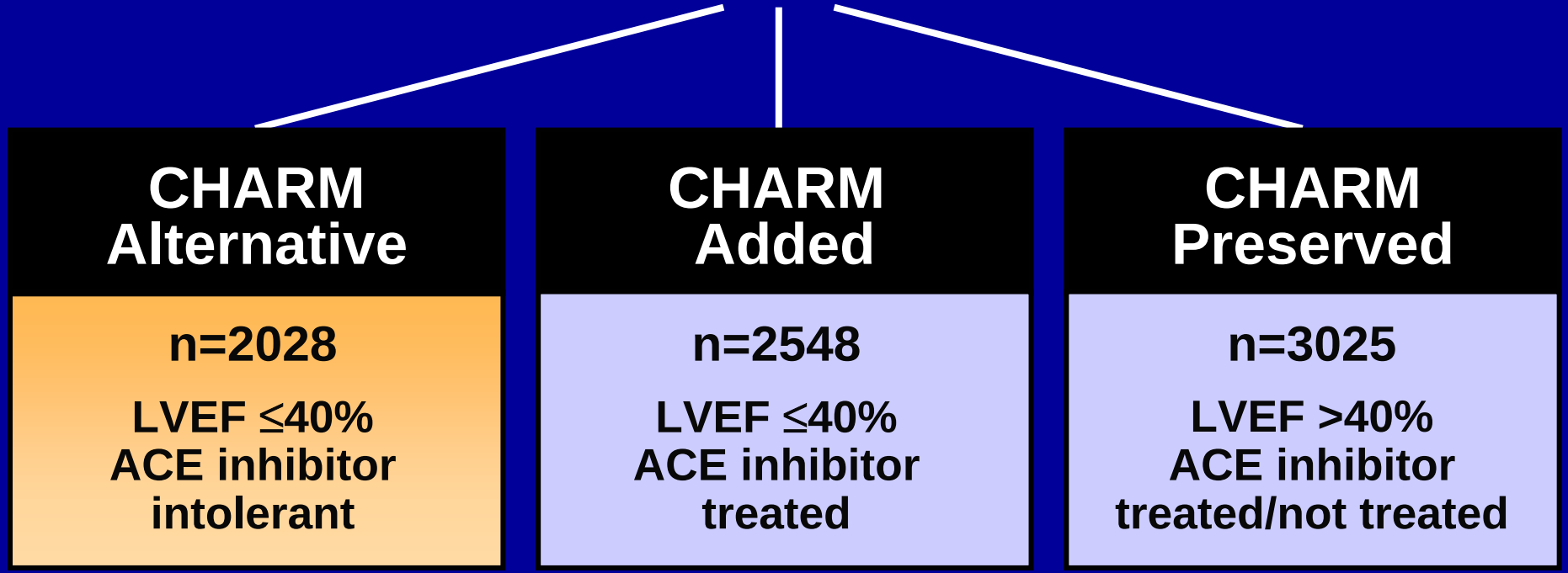
Val-HeFT Results

Combined Morbidity/Mortality in Subgroups



CHARM Programme

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



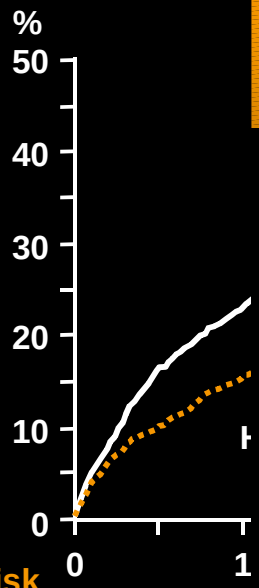
Primary outcome for each trial: CV death or CHF hospitalisation

Primary outcome for Overall Programme: All-cause death

Pfeffer et al, Lancet 2003

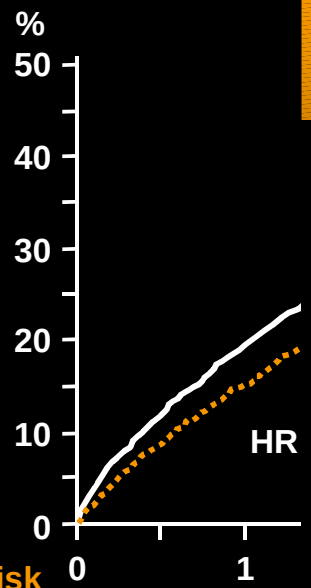
CHARM results

CHARM-Alternative
Primary outcome, CV death or CHF hospitalisation



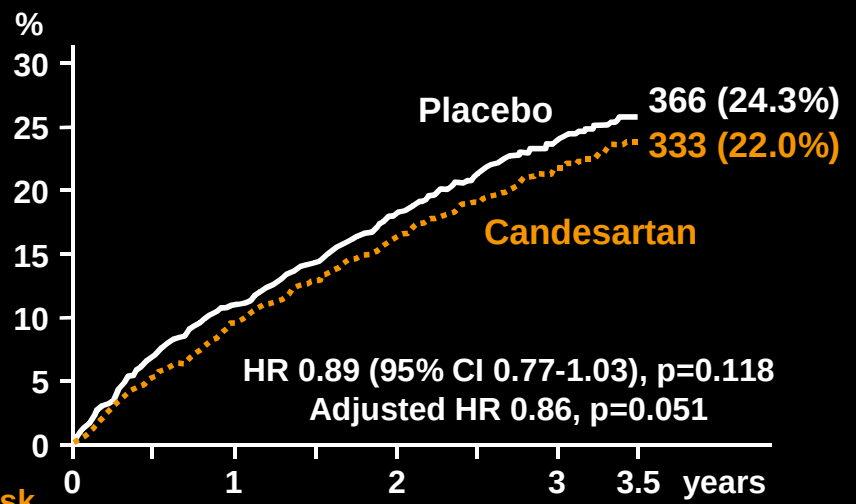
Number at risk		
Candesartan	1013	92
Placebo	1015	88

CHARM-Added
Primary outcome, CV death or CHF hospitalisation



Number at risk		
Candesartan	1276	1176
Placebo	1272	1136

CHARM-Preserved
Primary outcome, CV death or CHF hospitalisation



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

Yusuf et al, Lancet 2003

Post-MI heart failure

- OPTIMAAL
- VALIANT

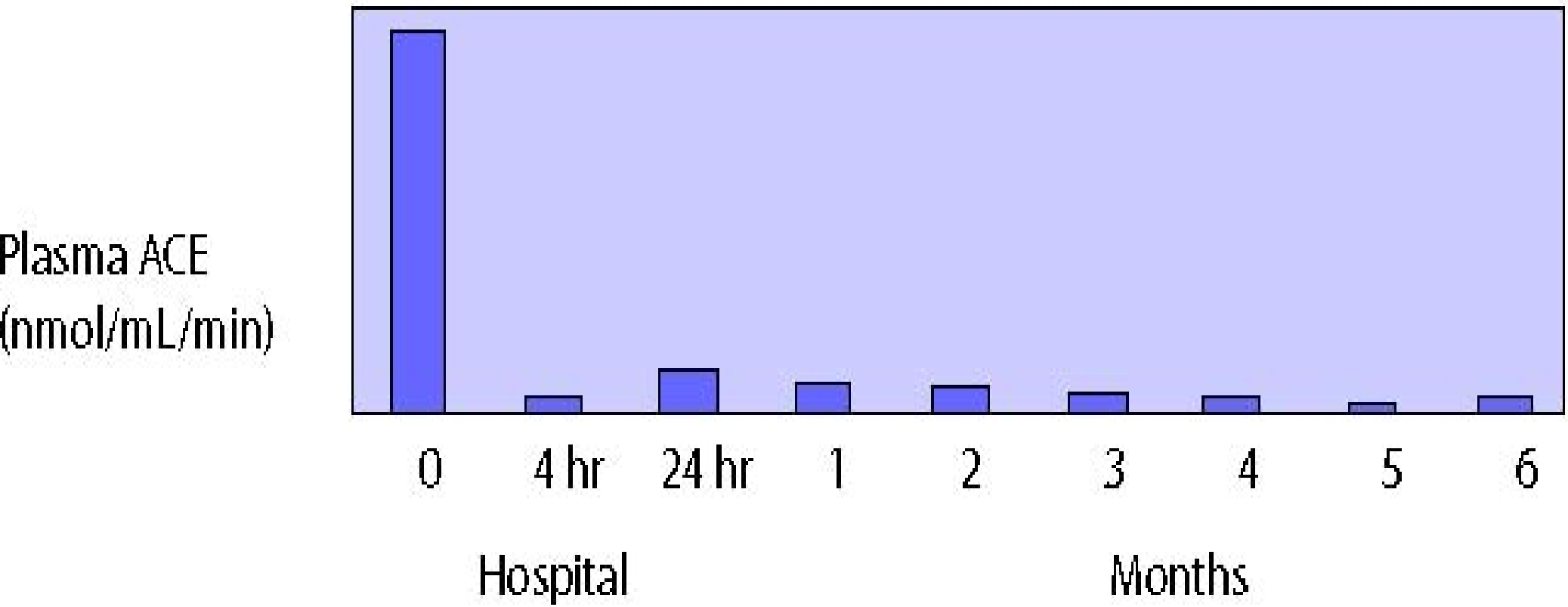
New drugs?

- Renin inhibitors

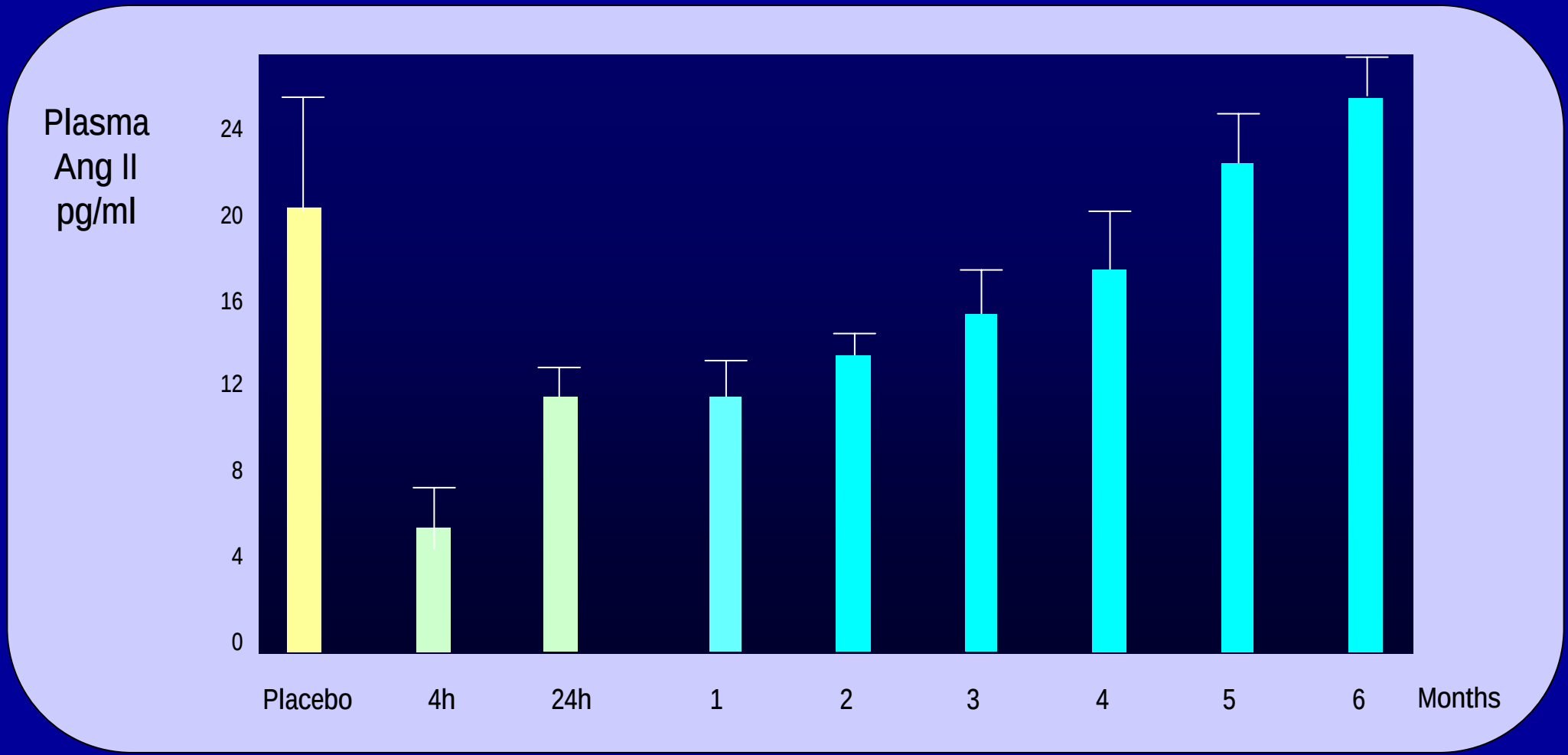
Conundrum

- To combine or not to combine?
- Which first?; ACEi vs BB, ARB vs Aldo antag
- Hit the bottom?
- Optimal dosage

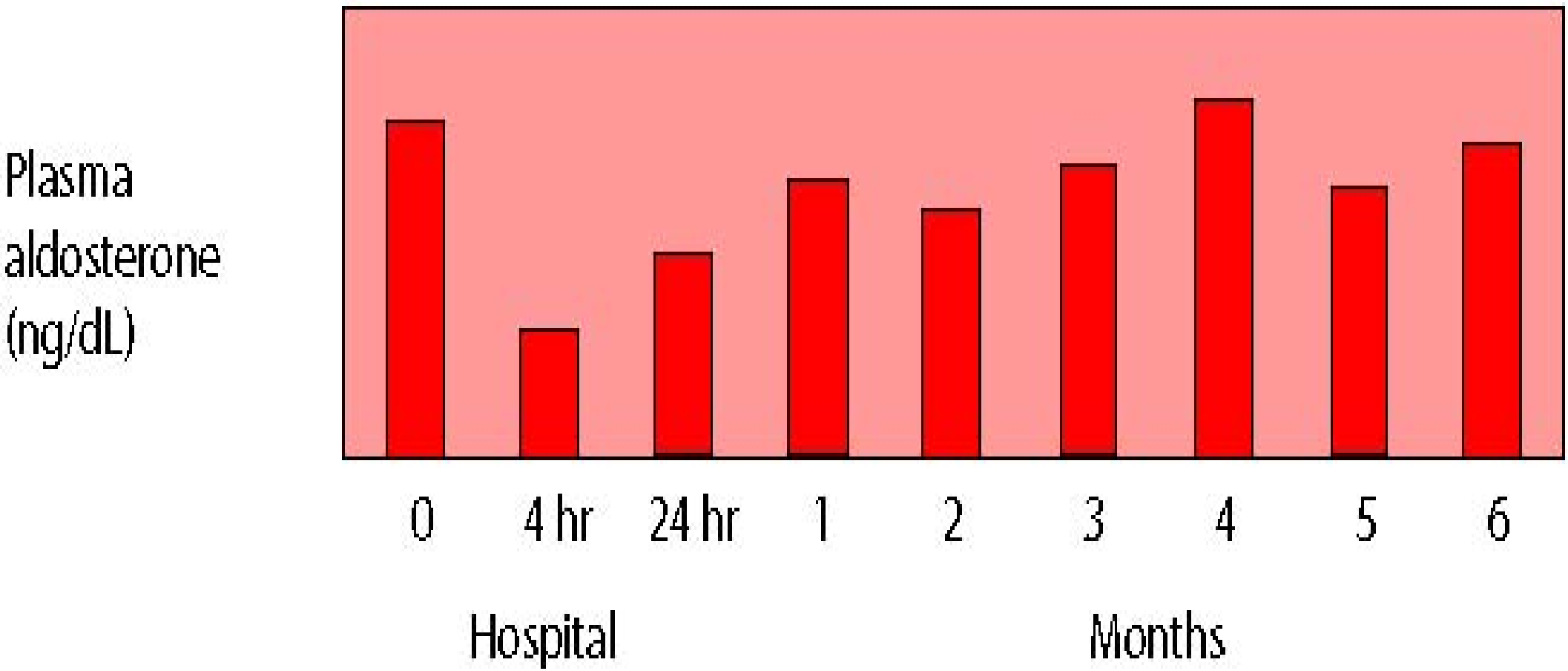
ACE
Post-MI: Enalapril 20 mg BID



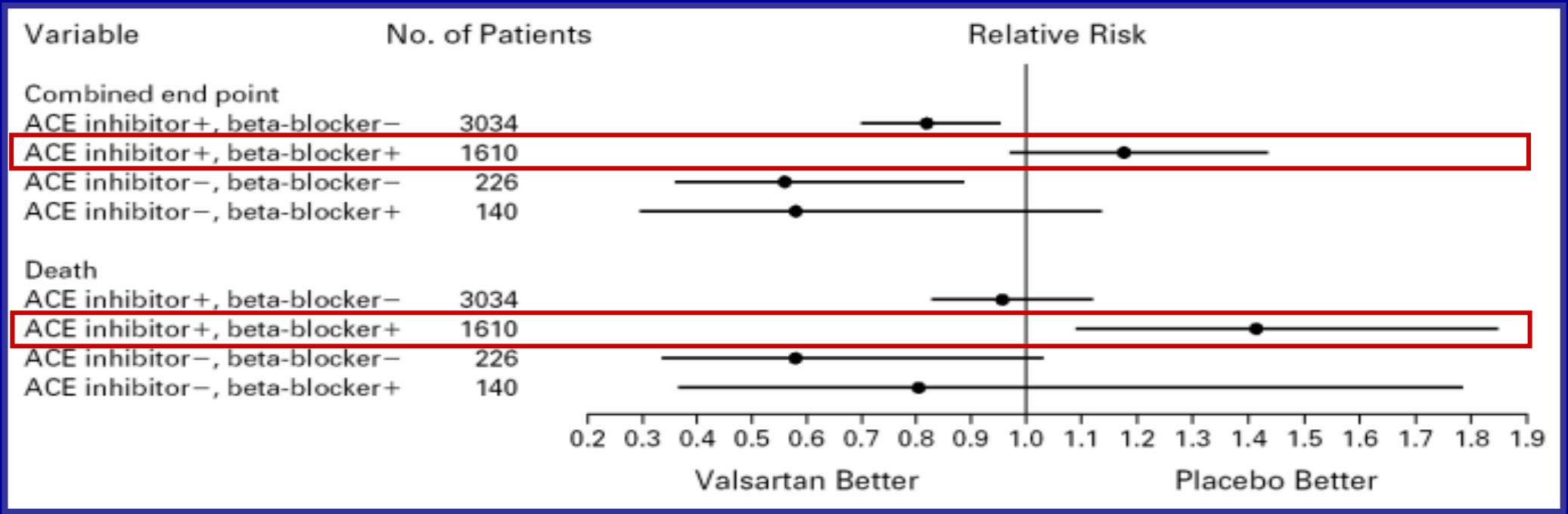
ACE escape


Plasma
Ang II
pg/ml
24
20
16
12
8
4
0
Placebo
4h
24h
1
2
3
4
5
6
Months

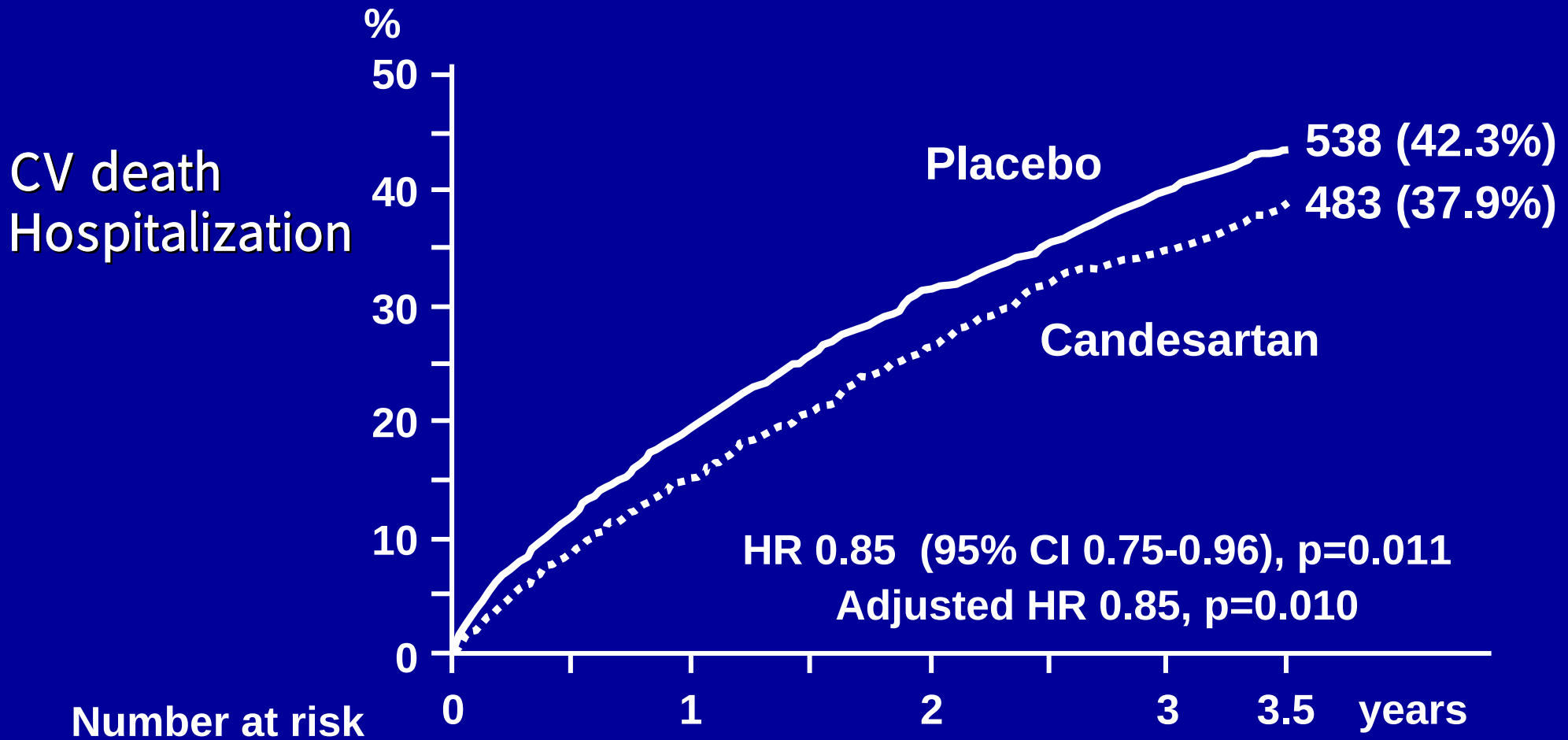
Aldosterone escape



Combine ARB, ACEI & β-blocker : Val-HeFT



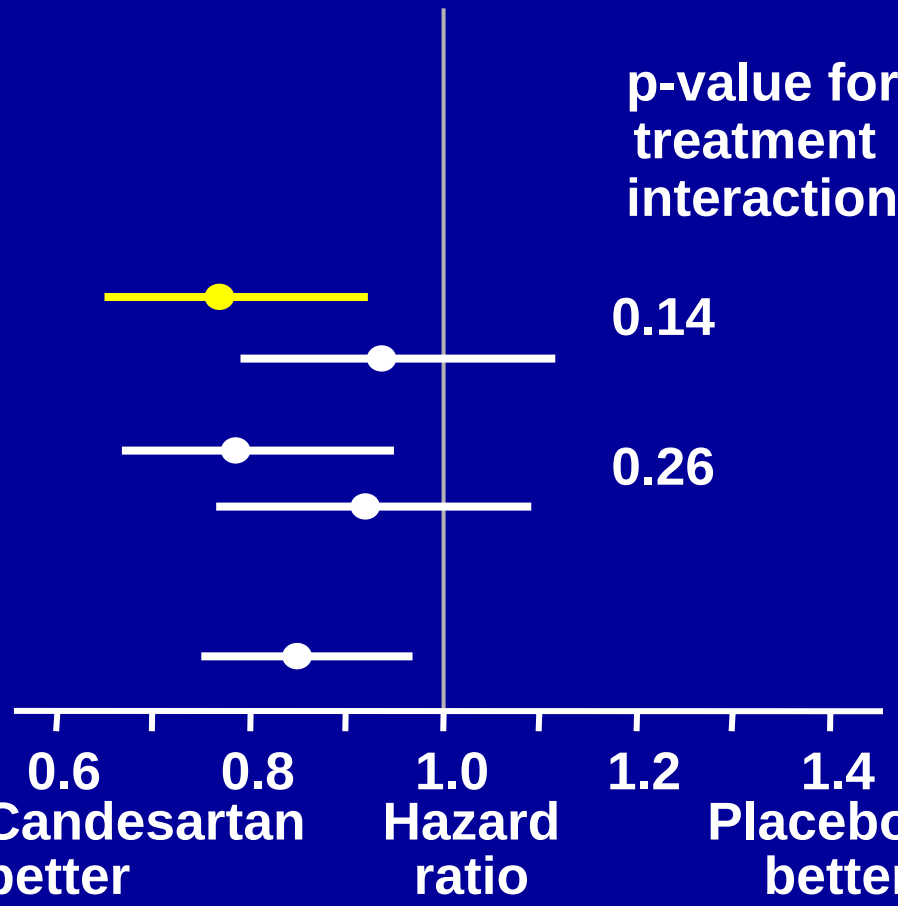
Combine ARB, ACEI & β-blockers: CHARM-Added



CHARM-Added

Prespecified subgroups, CV death or CHF hospitalisation

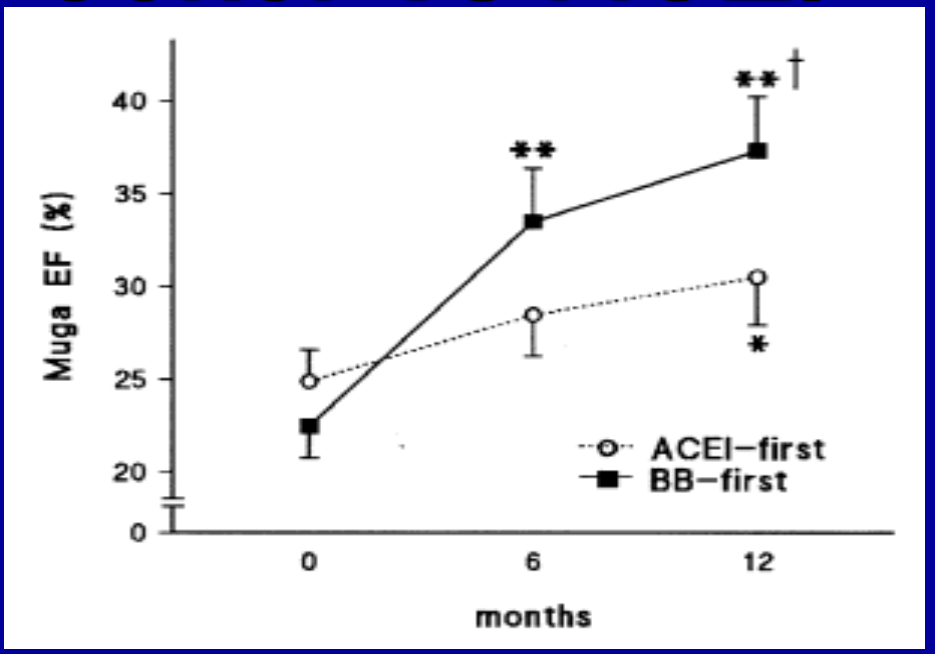
		Candesartan event/n	Placebo event/n	p-value for treatment interaction
Beta-blocker	Yes	223/702	274/711	0.14
	No	260/574	264/561	
Recom. dose of ACE inhib	Yes	232/643	275/648	0.26
	No	251/633	263/624	
All patients		483/1276	538/1272	

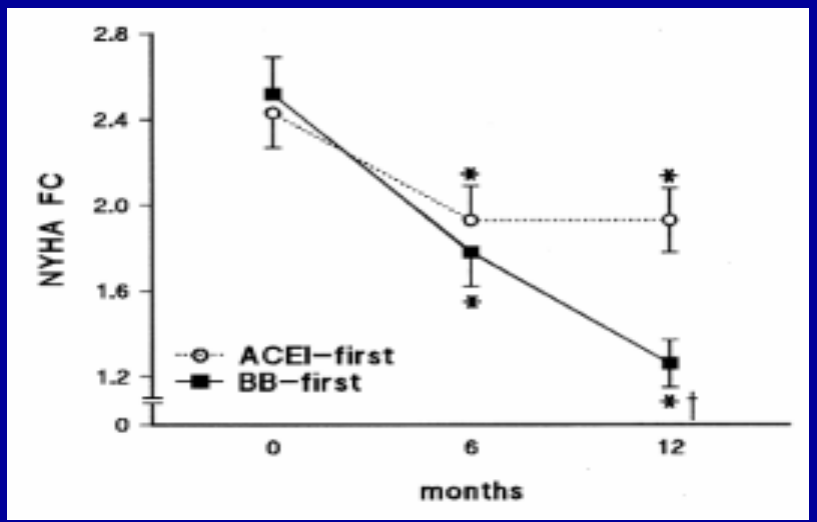


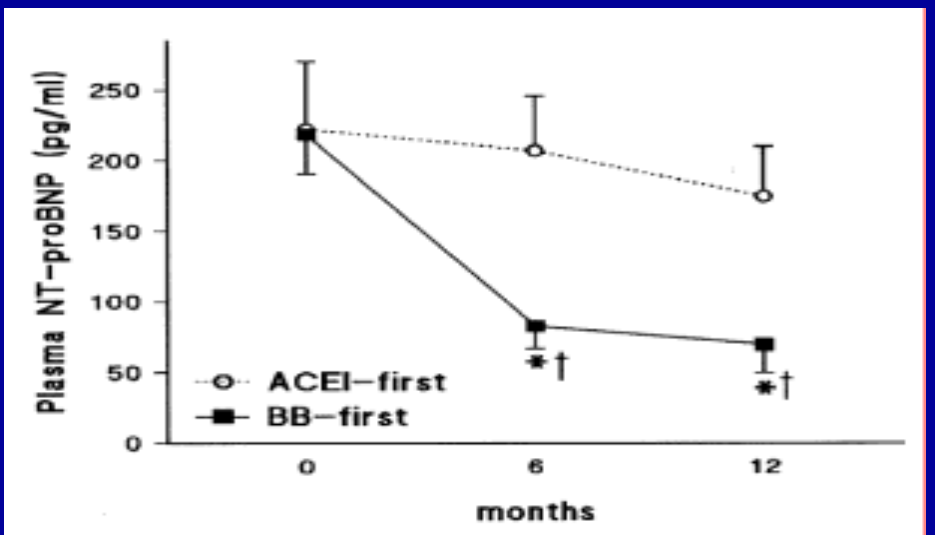
McMurray et al, Lancet 2003

Which first? : β-blocker vs ACEI

- 78 idiopathic DCM
- NYHA FC II to III
- Digoxin & diuretics for 7 days
  - ACEI-first group (40)
    - Perindopril for 6 Mo
    - Carvedilol add for 6 Mo
  - BB-first group (38)
    - Carvedilol for 6 Mo
    - Perindopril add for 6 Mo







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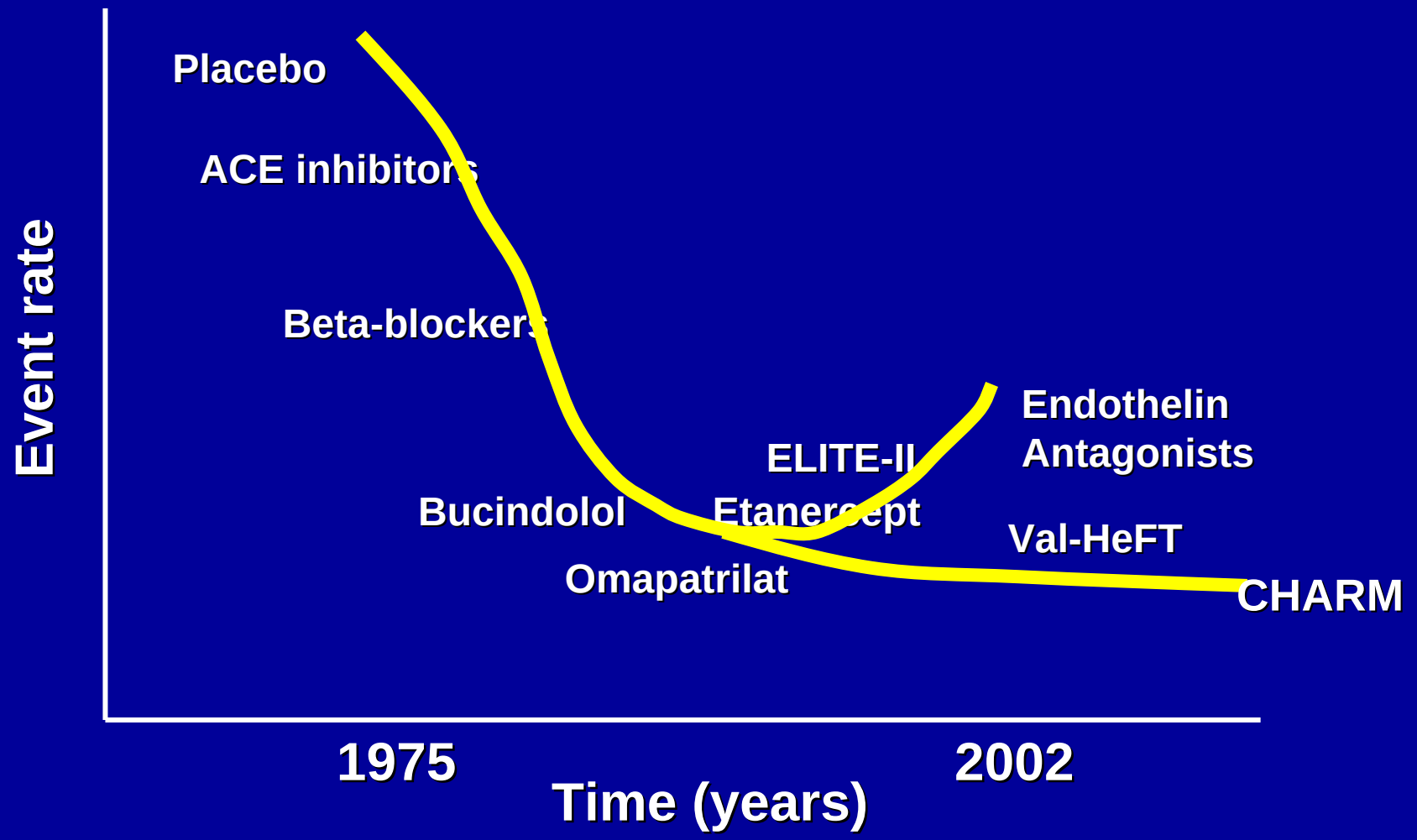

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Optimal Dosage

용량의존(Dose-dependency)

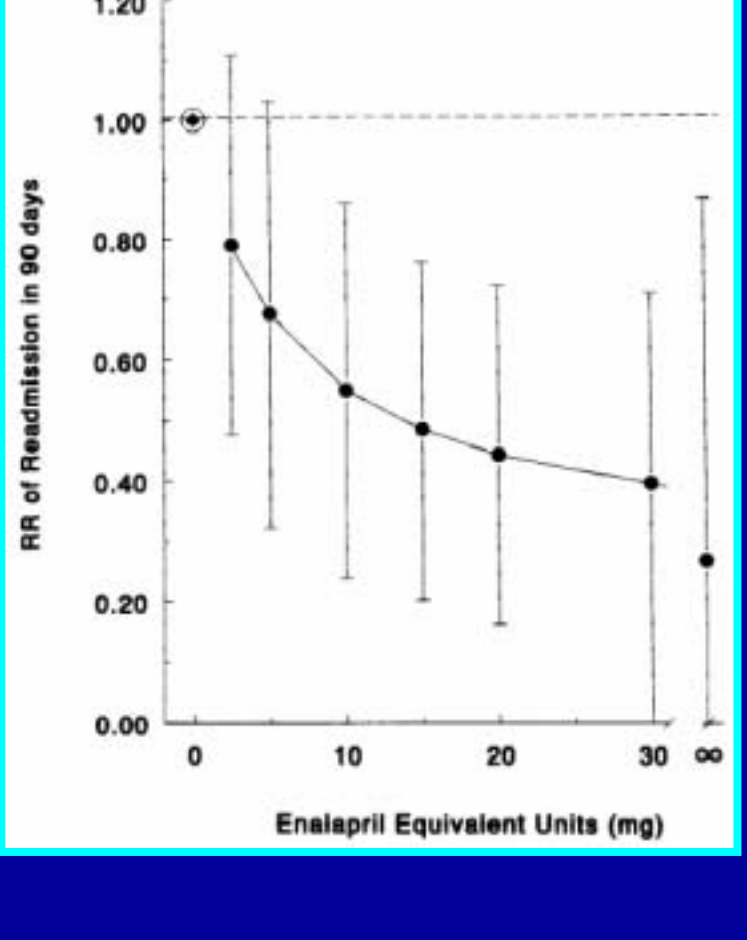
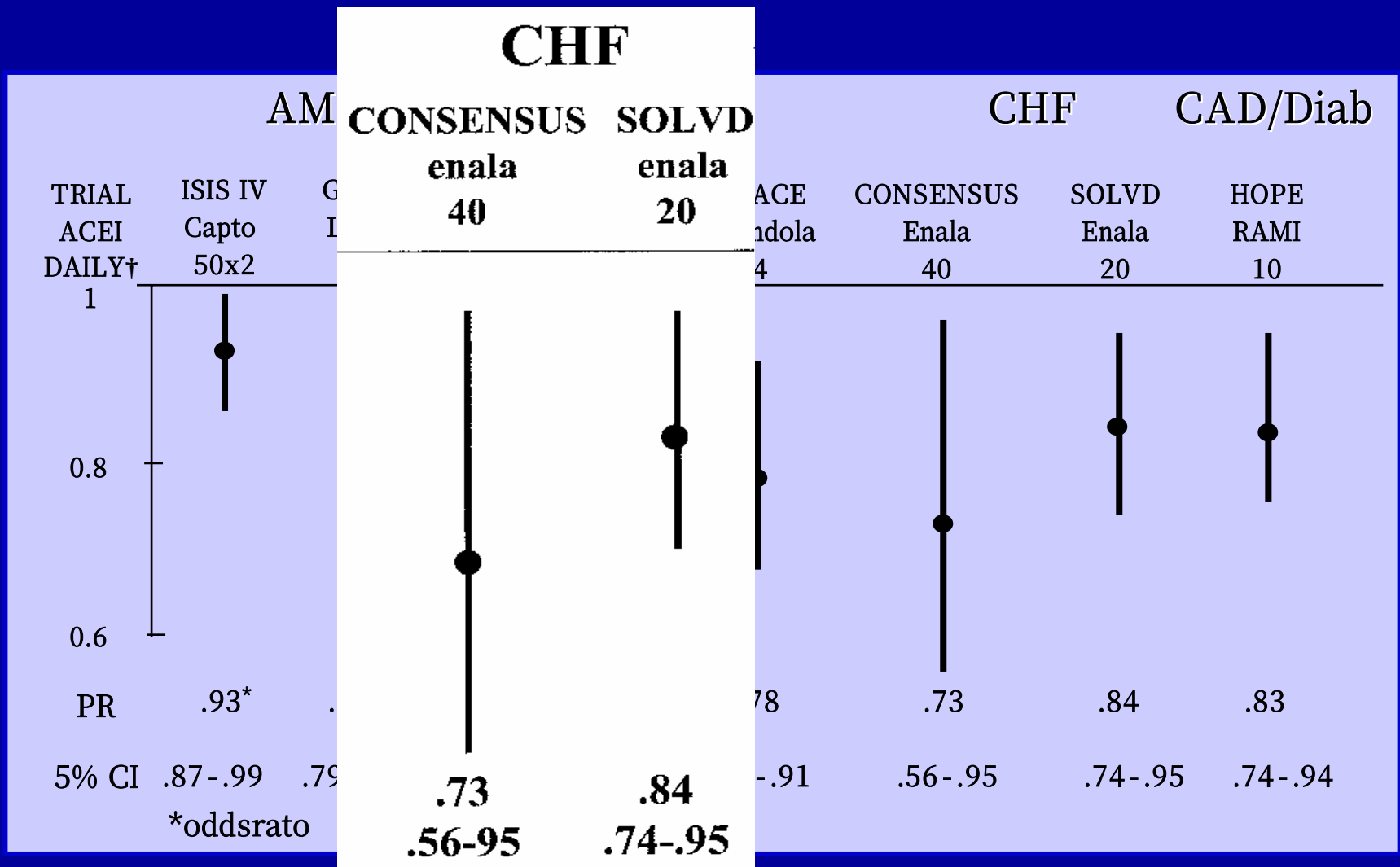


TABLE III Modeled Minimum and Maximum Effective Daily Dose Ranges

ACE Inhibitor	Daily Dose (mg)	
	Minimum Effective Dose	90%–95% Maximum Effect Dose Range
Enalapril	10	100–200
Captopril	75	750–1,500
Lisinopril	10	100–200
Quinapril	20	200–400

(Luzier AB, et al:Am J Cardiol 1998;82:465–469

Proven ACE inhibitors



Potential target beyond neurohormonal model