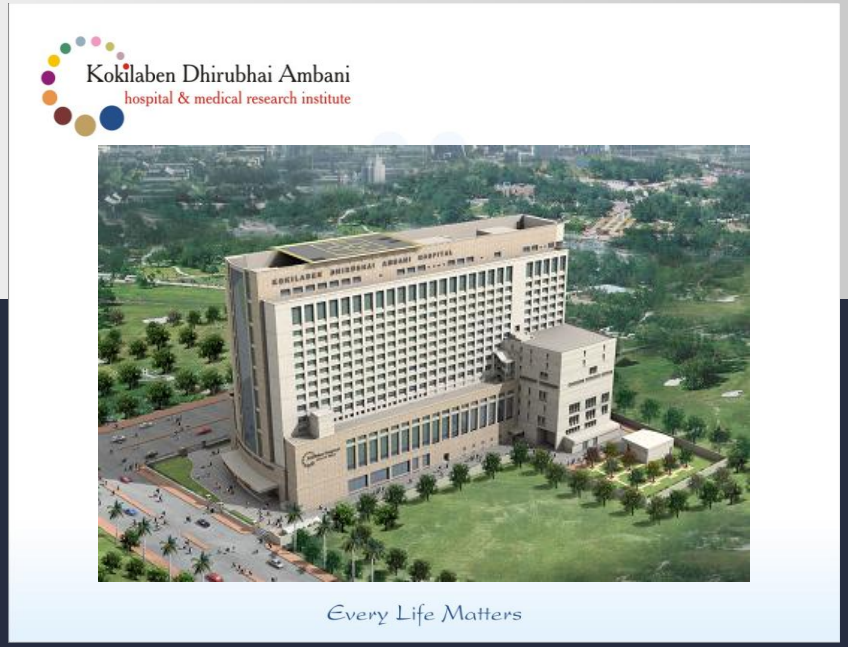
Post-AMI Remodeling



Dr J J Dalal

MD,DM,PhD

Director-Centre for Cardiac Sciences

Cardiac remodeling

- Cardiac remodeling can be defined clinically in relation to the changes in ventricular size, shape, and function that occur after myocardial injury, pressure, or volume overload.
- These clinical changes are determined at the tissue level through altered genome expression and molecular, cellular, and interstitial changes regulated principally by hemodynamic load and neurohormonal activation.
- Ventricular remodeling may be physiologic and adaptive during normal growth, or pathologic because of myocardial infarction, hypertension, or valvular heart disease

It is a Precursor of Heart failure

Cardiac remodeling

Ventricular remodeling implies a decline in function . (even though the word "remodeling" usually implies improvement).

Could be termed as “adverse remodeling”.

The term "reverse remodeling" in cardiology implies an improvement in ventricular mechanics and function after a remote injury.

Cardiac remodeling

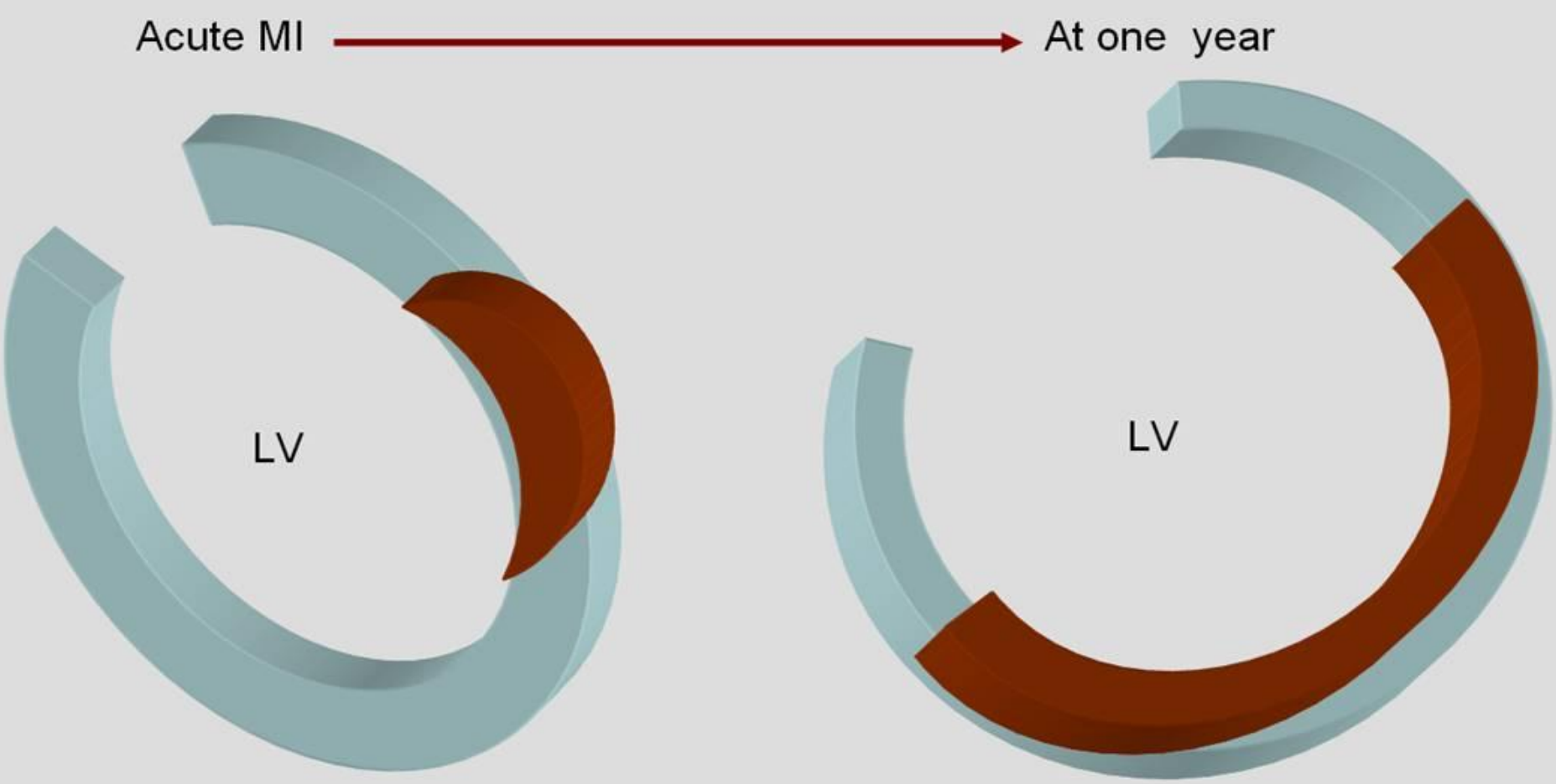
- Due to continuous remodeling myocardial dysfunction is a progressive condition. Even if the initial event is so mild that it causes no immediate cardiac dysfunction (e.g. a small myocardial infarction), the remodeling process is triggered.

- Although the remodeling process can be adaptive, the process becomes maladaptive when the stimuli are continuous and pathological.

- Though heart failure may develop acutely eg, after an acute MI, the progressive changes in myocardial structure and deterioration of myocardial function can go on silently for a very long time and overt heart failure may develop several years after an initial insult, even if there are no further events.

It is necessary to identify patients with an ongoing remodeling process and to effectively counteract it.

Progressive adverse LV remodeling



Alteration in Myocyte architecture , Size, Shape and Contractility

Cardiac remodeling

Processes Occurring in Ventricular Remodeling

- Cardiomyocyte lengthening and wall thinning
- Infarct expansion rather than extension occurs
- Reabsorption of necrotic tissue with scar formation
- Continued expansion of infarct zone
- Dilation and reshaping of the left ventricle
- Myocyte hypertrophy and ongoing myocyte loss
- Excessive accumulation of collagen

Cardiac remodeling

THE MAIN COMPONENTS OF CARDIAC REMODELING

Cardiac myocytes

Myocytes are believed to be fundamentally involved in the remodeling process.

Fibroblast proliferation

Fibroblast stimulation increases collagen synthesis and causes fibrosis of both the infarcted and noninfarcted regions of the ventricle.

Collagen degradation

The myocardium consists of myocytes tethered and supported by a connective tissue network composed largely of fibrillar collagen, this is degraded by interstitial fibroblasts.

Apoptosis

Hypothesis for the role of apoptosis in HF is that progressive LV dysfunction occurs, in part, as a result of ongoing myocyte cell death

Differences in remodeling between Hypertensive Heart Disease and ischemic Heart disease

The difference can be judged by the manner in which geometric remodeling of the LV occurs .

Patient with HHD

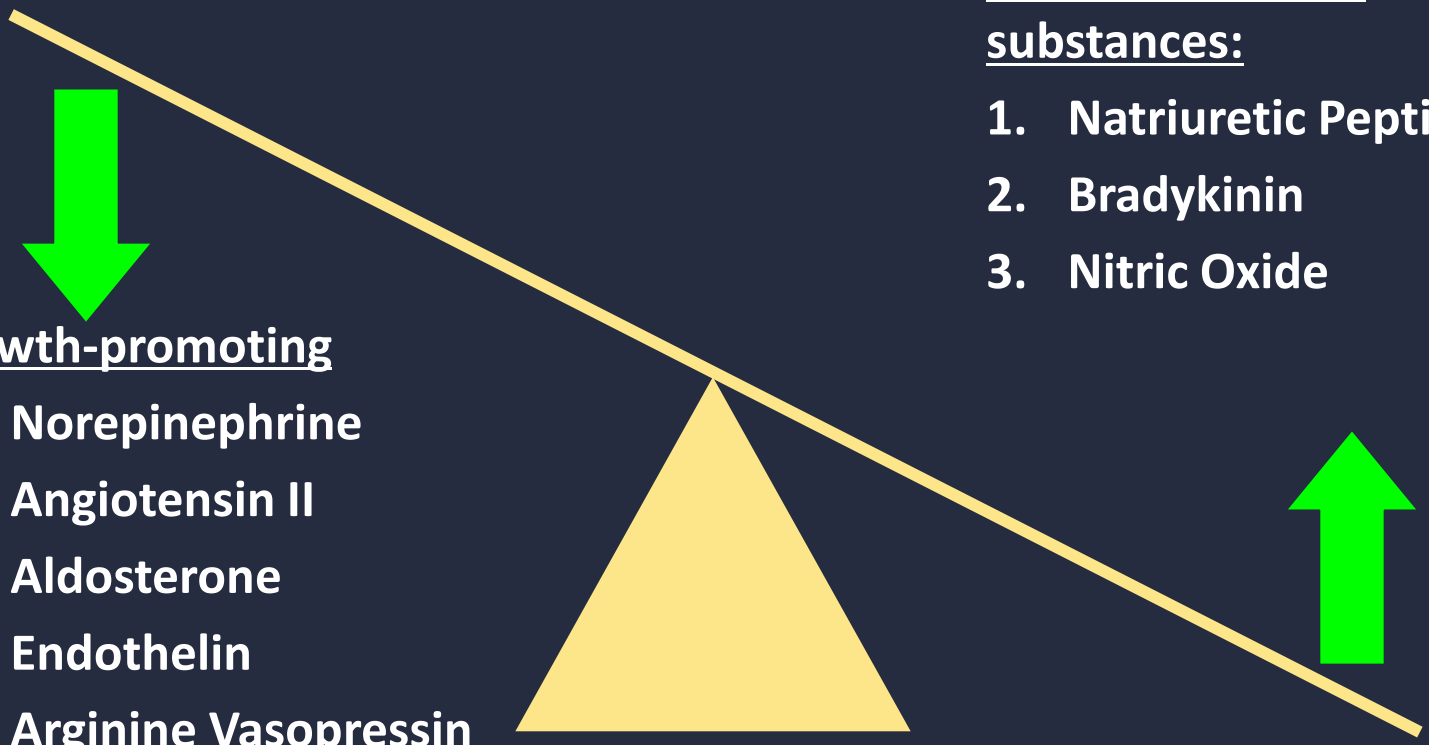
Patients with HHD usually present with LV hypertrophy (LVH) but have a normal-sized LV chamber and preserved systolic function (ejection fraction greater than 50%).

Ischemic or idiopathic disease

Patients with remodeling secondary to ischemia or idiopathic cardiomyopathy usually have an enlarged, dilated LV chamber and more frequently also have RV enlargement .

J. Clin. Invest. 117:568–575 (2007).

Neuroendocrine Imbalance in HF-Pivotal in Cardiac Remodeling



Anti-Proliferative substances:

1. Natriuretic Peptides
2. Bradykinin
3. Nitric Oxide

Growth-promoting

1. Norepinephrine
2. Angiotensin II
3. Aldosterone
4. Endothelin
5. Arginine Vasopressin

Effects of the RAAS.

- All major components of the RAAS — Renin, ANG II, and Aldosterone — exert pro-fibrotic effects on cells.

- Renin and Prorenin increase the synthesis of Tissue Growth Factor- in mesangial cells.

- Renin also enhances the synthesis of fibronectin, collagen I, and plasminogen activator inhibitor-1.

The actions of Renin are independent of ANG II.

ANG II is the dominant hormone responsible for cardiac fibrosis in HHD.

Am. J. Physiol.Cell Physiol. 2007 292:C82–C97.

Role for aldosterone in cardiac fibrosis and Remodeling

● Aldosterone stimulates adverse cardiac remodeling, as a result of

- Endothelial dysfunction and inflammation
- myocyte apoptosis
- myocardial fibrosis

● Aldosterone antagonists significantly reduce cardiac fibrosis in acute or chronic heart failure and improve LV function.

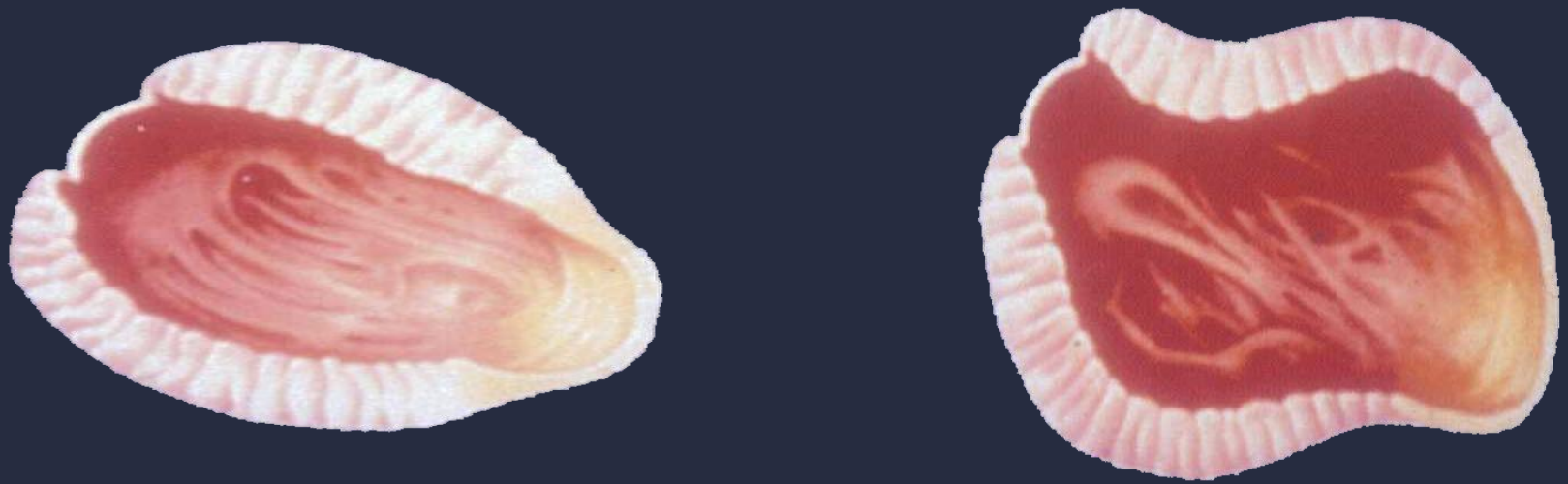
● The addition of an aldosterone antagonist significantly improves morbidity and mortality among patients with :

- ➢ Heart failure post-myocardial infarction (eplerenone)
- ➢ Patients with moderate-to-severe chronic heart failure (spironolactone)

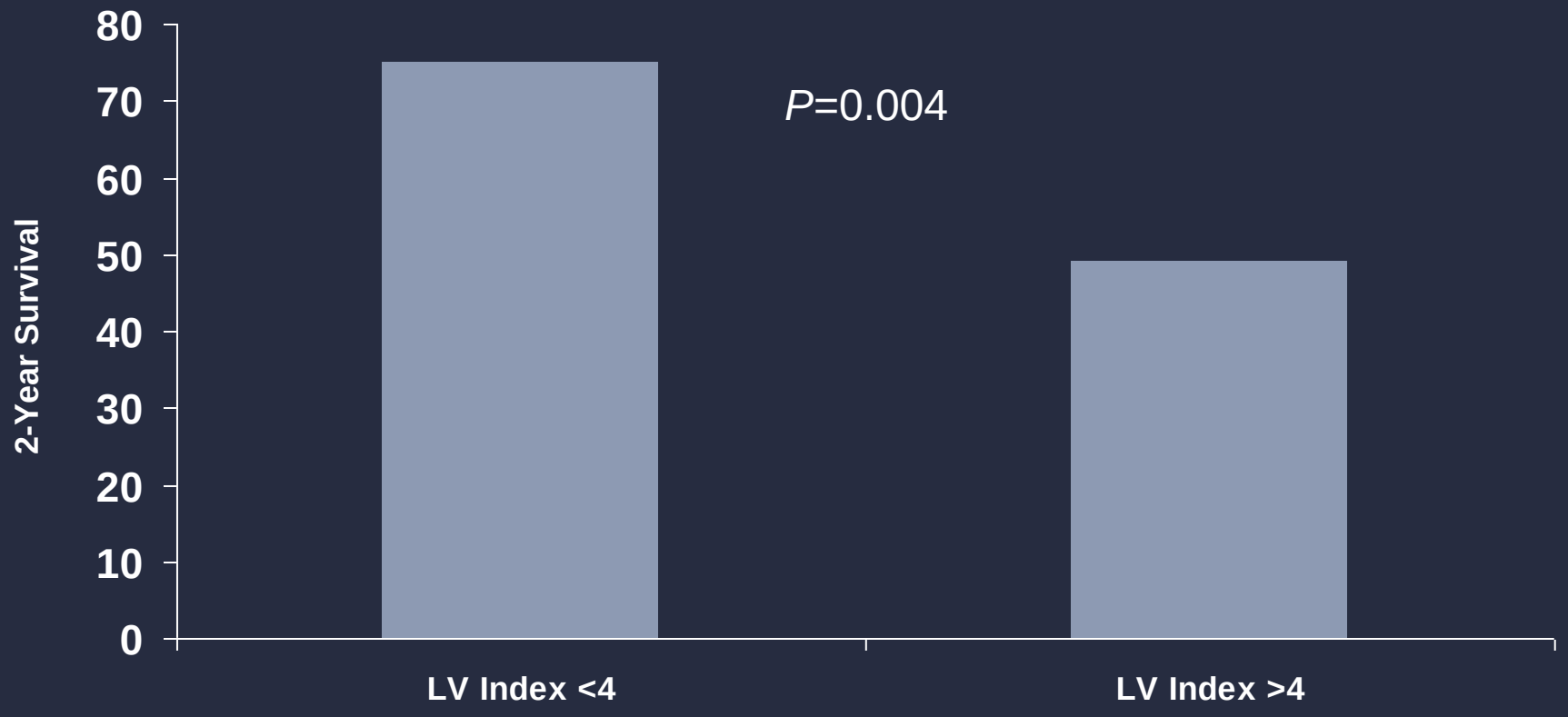
Allan D Struthers *Br J Cardiol* 2005;12:211–18

LV Remodeling Post MI

- Almost 25% of patients develop limited LV dilatation within 4 weeks after infarction, which helps to restore cardiac and stroke index and to preserve exercise performance and therefore remains compensatory.
- A smaller group (20%) develops progressive structural LV dilatation, progressing to noncompensatory dilatation, and finally results in severe global LV dysfunction.
- In these patients, depression of global ejection fraction probably results from impairment of function of initially normally contracting myocardium.

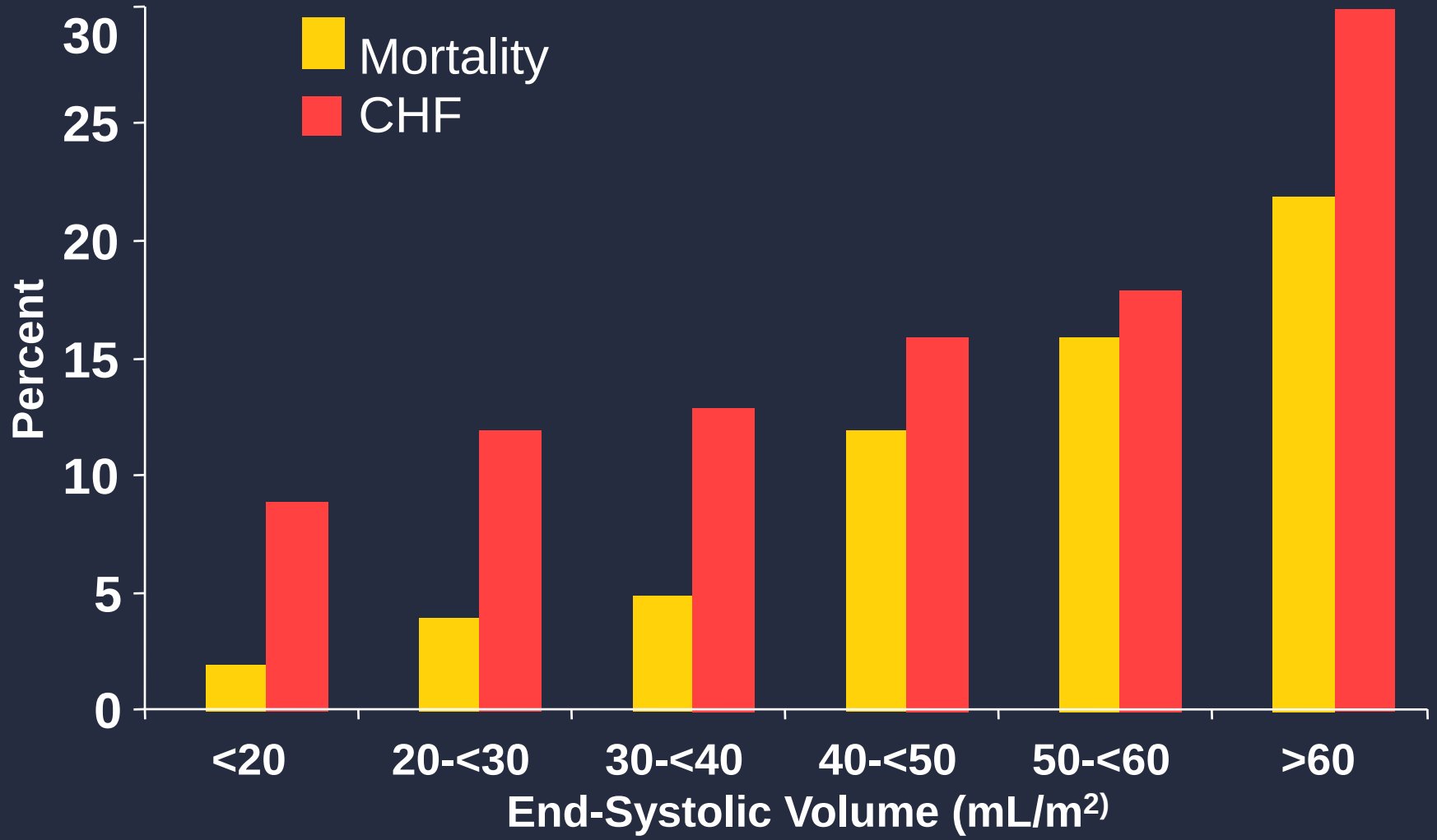


Relation Between LV Size and Outcome in Heart Failure



Lee TH et al. *Am J Cardiol.* 1993;72:672-676.

Relation Between Post-MI End Systolic Volume and Natural History Outcomes

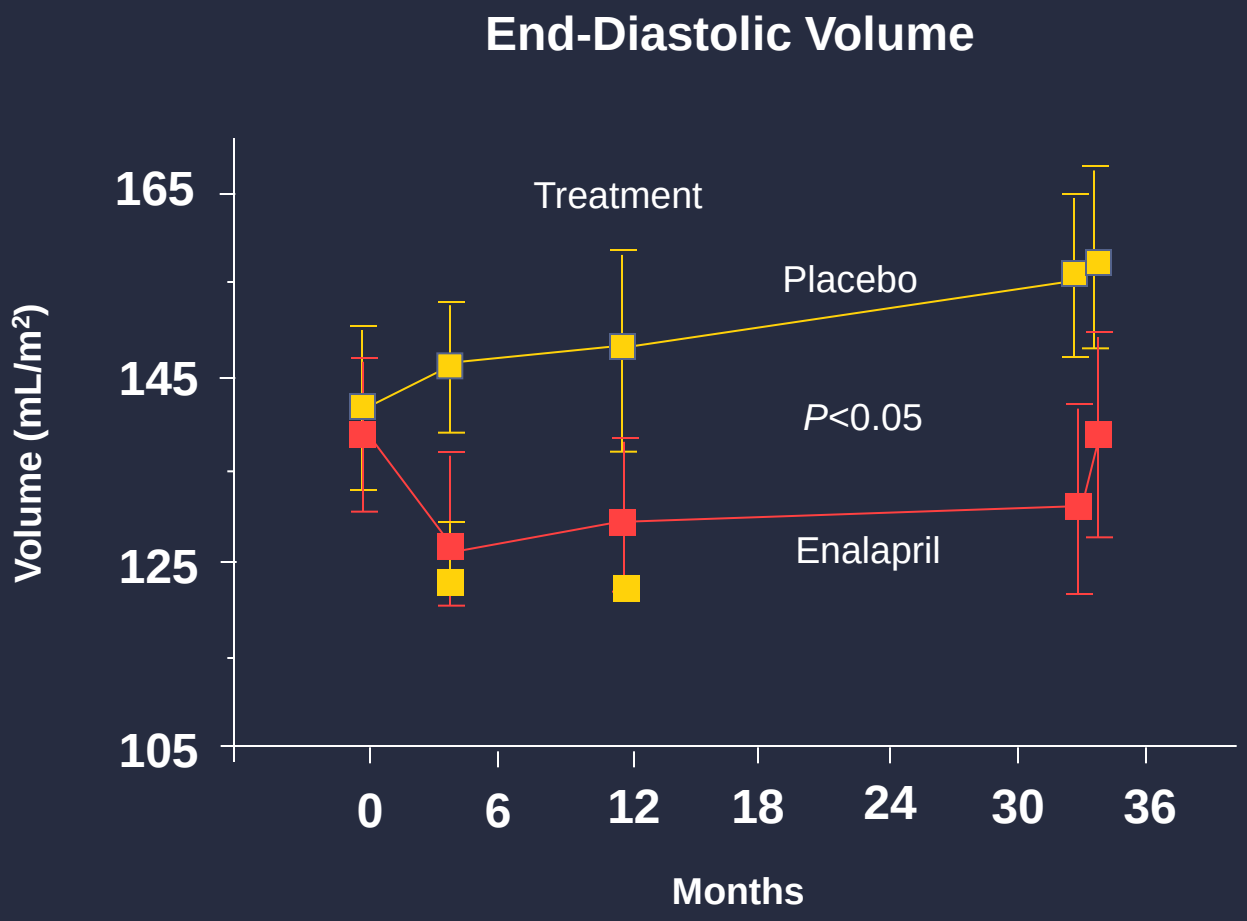


Migrino RO et al. *Circulation.* 1997;96:116-121.

Neurohormonal Modulation in treatment of LV remodeling

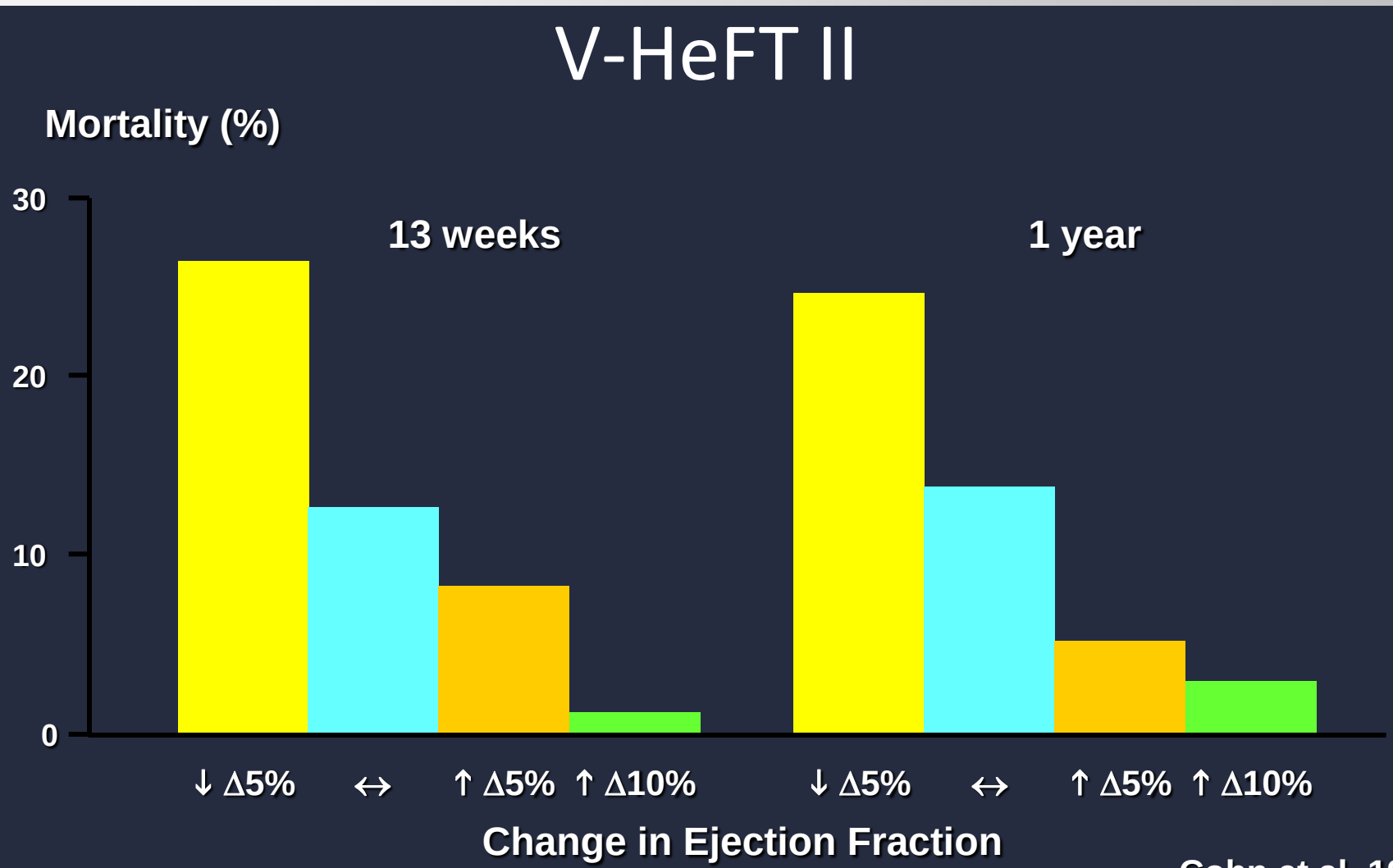
- ACE inhibitor – the first choice?
- β Blocker (± α blockade)
- Aldosterone antagonist
- Angiotensin AT_1 blocker
- Endothelin antagonist
- Vasopeptidase inhibitor
- Cytokine antagonist
- Neutral Endopeptidase Inhibitor
- Vasopressin antagonist
- h-BNP
- DA_2/α_2 agonist
- Dopamine β hydroxylase inhibitor

ACE Inhibitor Effect on Ventricular Remodeling



Konstam MA et al. *Circulation.* 1993;88:2277-2283.

Degree of Improvement in EF with ACE Inhibition Relates to Survival



Cohn et al. 1993

SAVE study

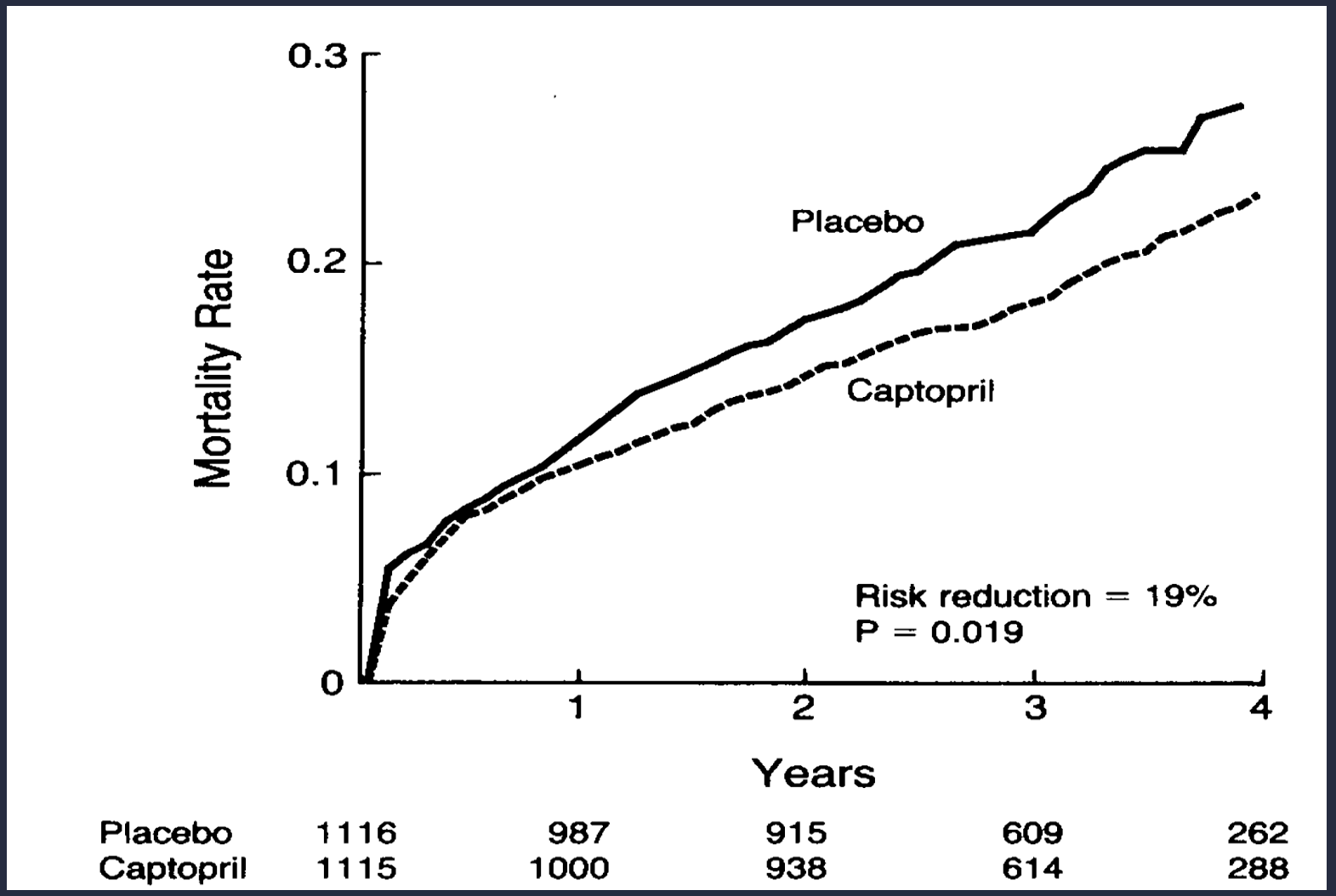
The New England
Journal of Medicine

Volume 327 SEPTEMBER 3, 1992 Number 10

EFFECT OF CAPTOPRIL ON MORTALITY AND MORBIDITY IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION AFTER MYOCARDIAL INFARCTION

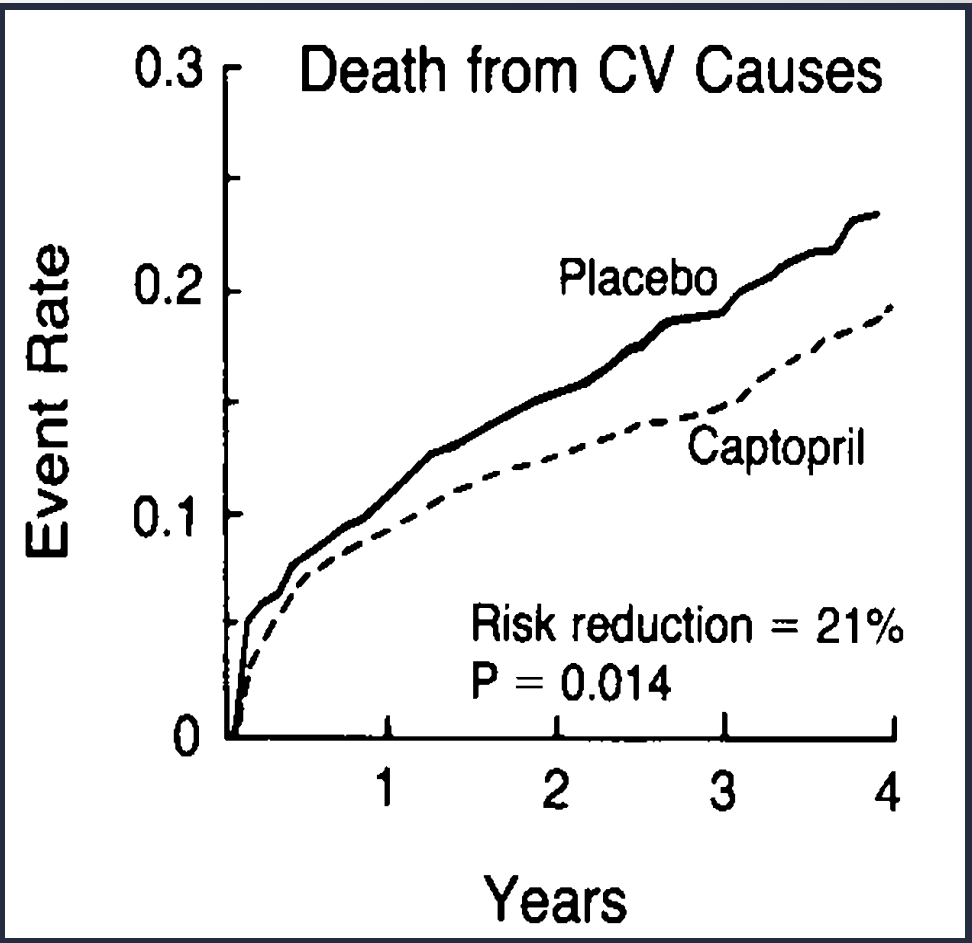
Double blind randomized study, 3 – 16 days of AMI
LVEF ≤ 40% without overt HF were randomized to –
Captopril (n=1116) Placebo (n =1115)
Follow up 42 months

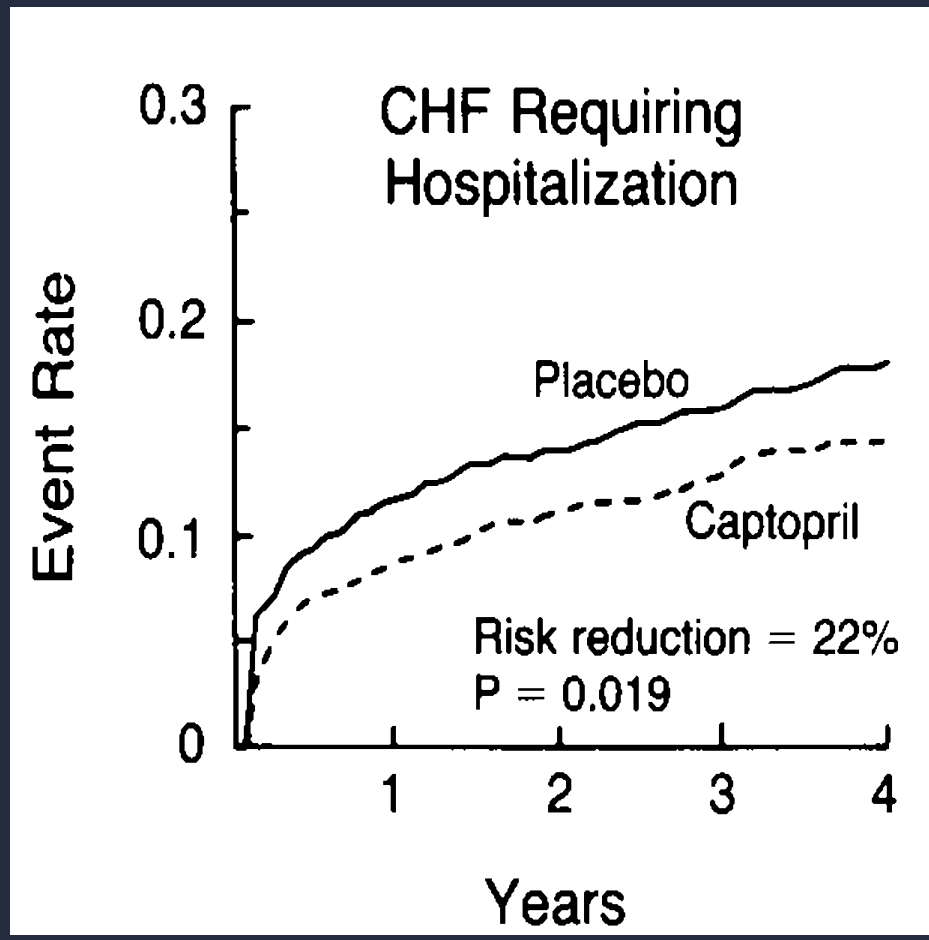
All Cause Mortality



Placebo	1116	987	915	609	262
Captopril	1115	1000	938	614	288

Other End Points





Conclusion

* In patients with asymptomatic LV dysfunction after AMI, long term administration of captopril was associated with improvement in survival and reduced mortatliy and morbidity due to major cardiovascualar events.

Another Evidence: Enalapril

Vol. 327 No. 10 ENALAPRIL FOR REDUCED LEFT VENTRICULAR EJECTION FRACTION — SOLVD 685

EFFECT OF ENALAPRIL ON MORTALITY AND THE DEVELOPMENT OF HEART FAILURE IN ASYMPTOMATIC PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS

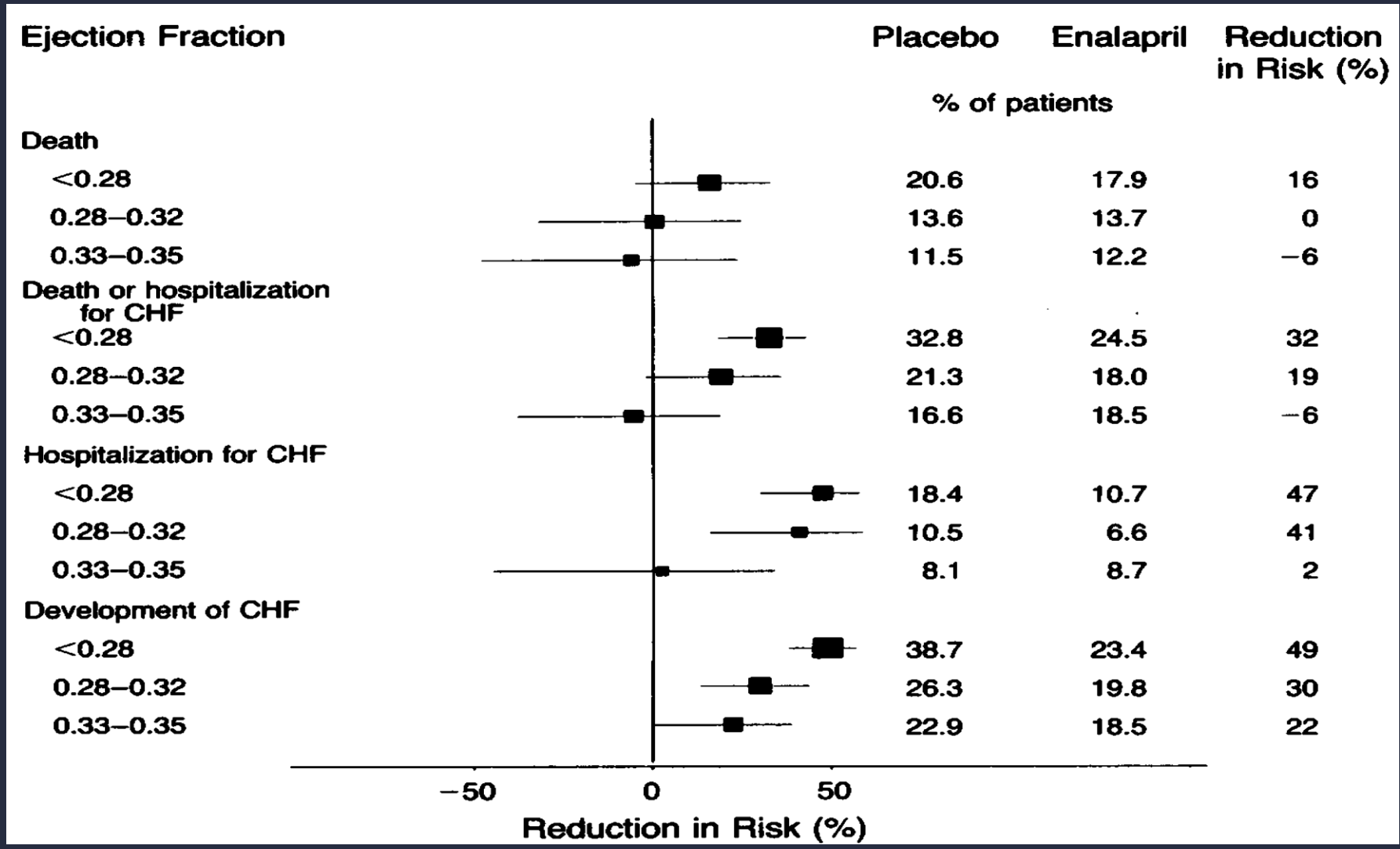
THE SOLVD INVESTIGATORS*

- Double blind randomized study following AMI –

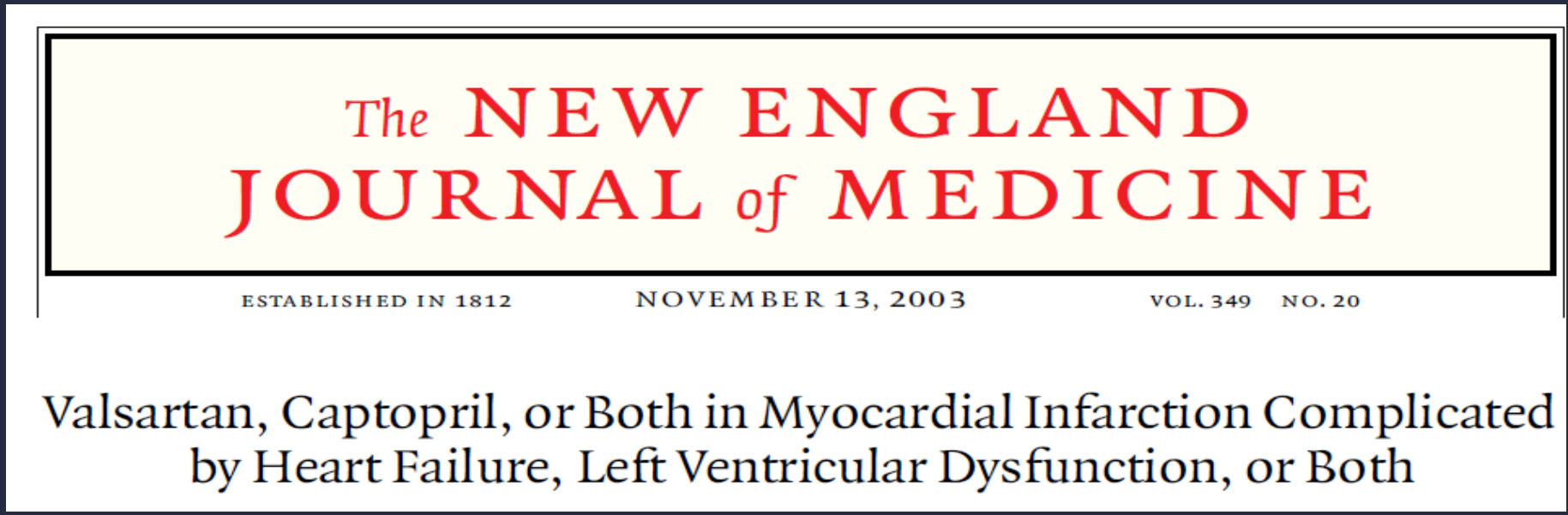
  Enalapril (n=2111) Placebo (n = 2117)

- Follow up 37 months

Overall risk reduction



ARBs: Valsartan



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 13, 2003 VOL. 349 NO. 20

Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both

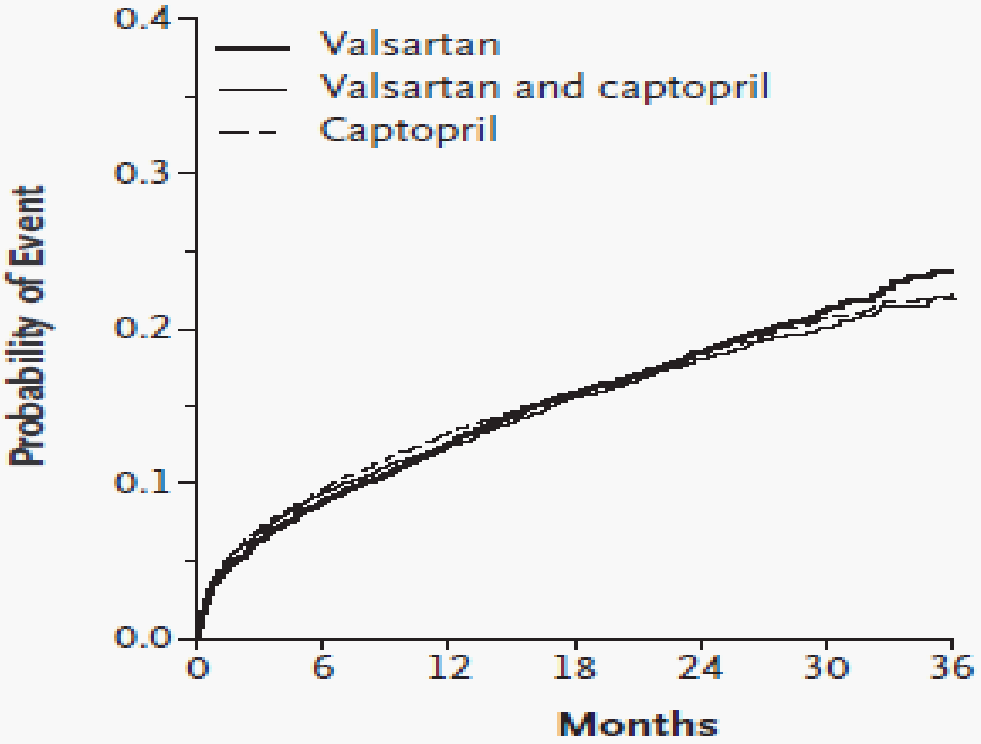
Patients receiving conventional therapy were assigned, 0.5 to 10 days after AMI, to additional therapy with

- **Valsartan (4909 patients)**
- **Valsartan plus captopril (4885 patients)**
- **Captopril (4909 patients)**

N Engl J Med 2003;349:1893-906

Results

A Death from Any Cause

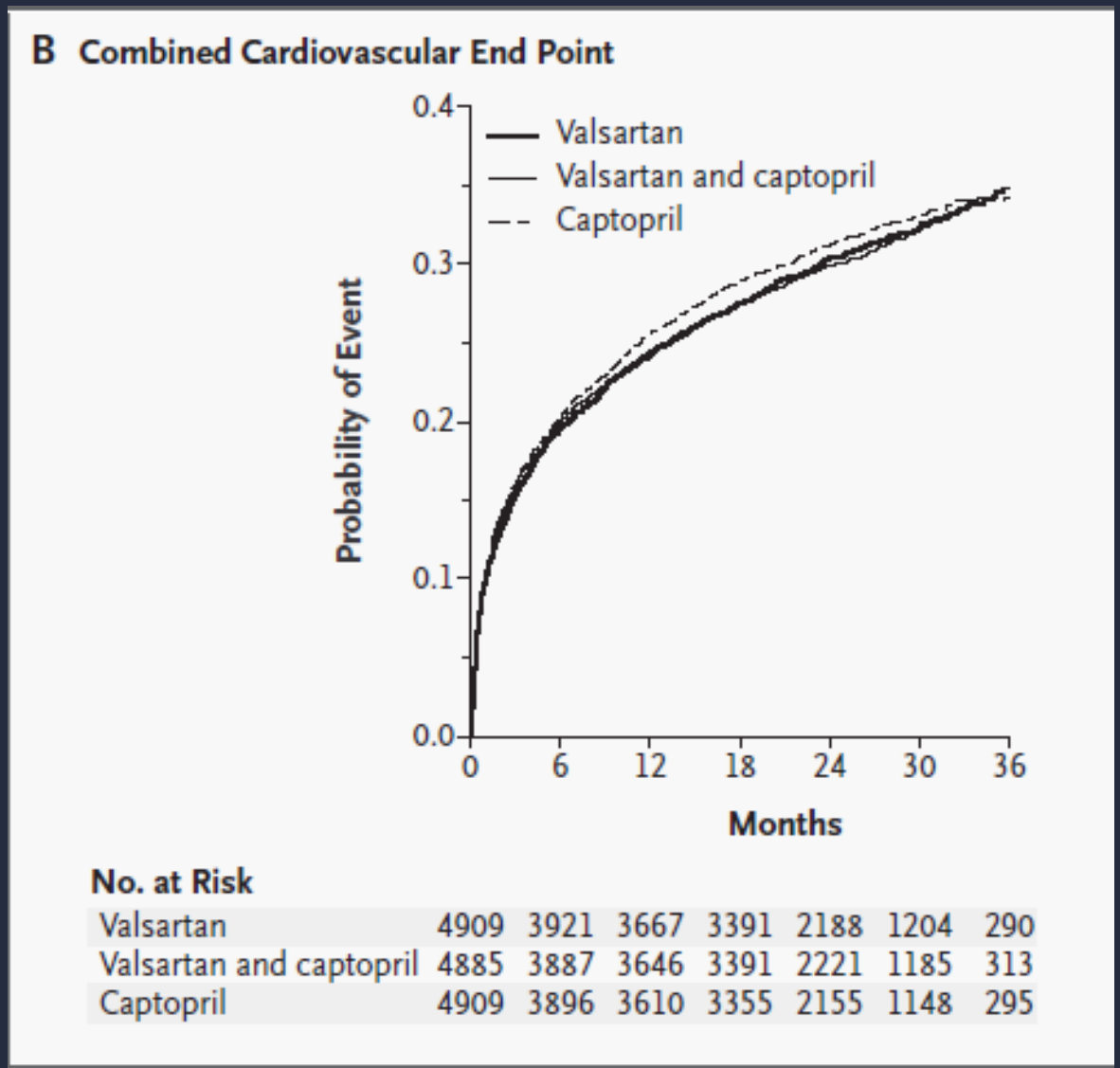


No. at Risk

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

Valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after myocardial infarction.

Combining valsartan with captopril increased the rate of adverse events without improving survival.



No. at Risk

Valsartan	4909	3921	3667	3391	2188	1204	290
Valsartan and captopril	4885	3887	3646	3391	2221	1185	313
Captopril	4909	3896	3610	3355	2155	1148	295

OPTIMAAL: Optimal Trial In Myocardial Infarction with the Angiotensin Antagonist Losartan

-5466 patients aged ≥50 years with AMI and evidence of heart failure or left ventricular dysfunction (LVEF<35%)

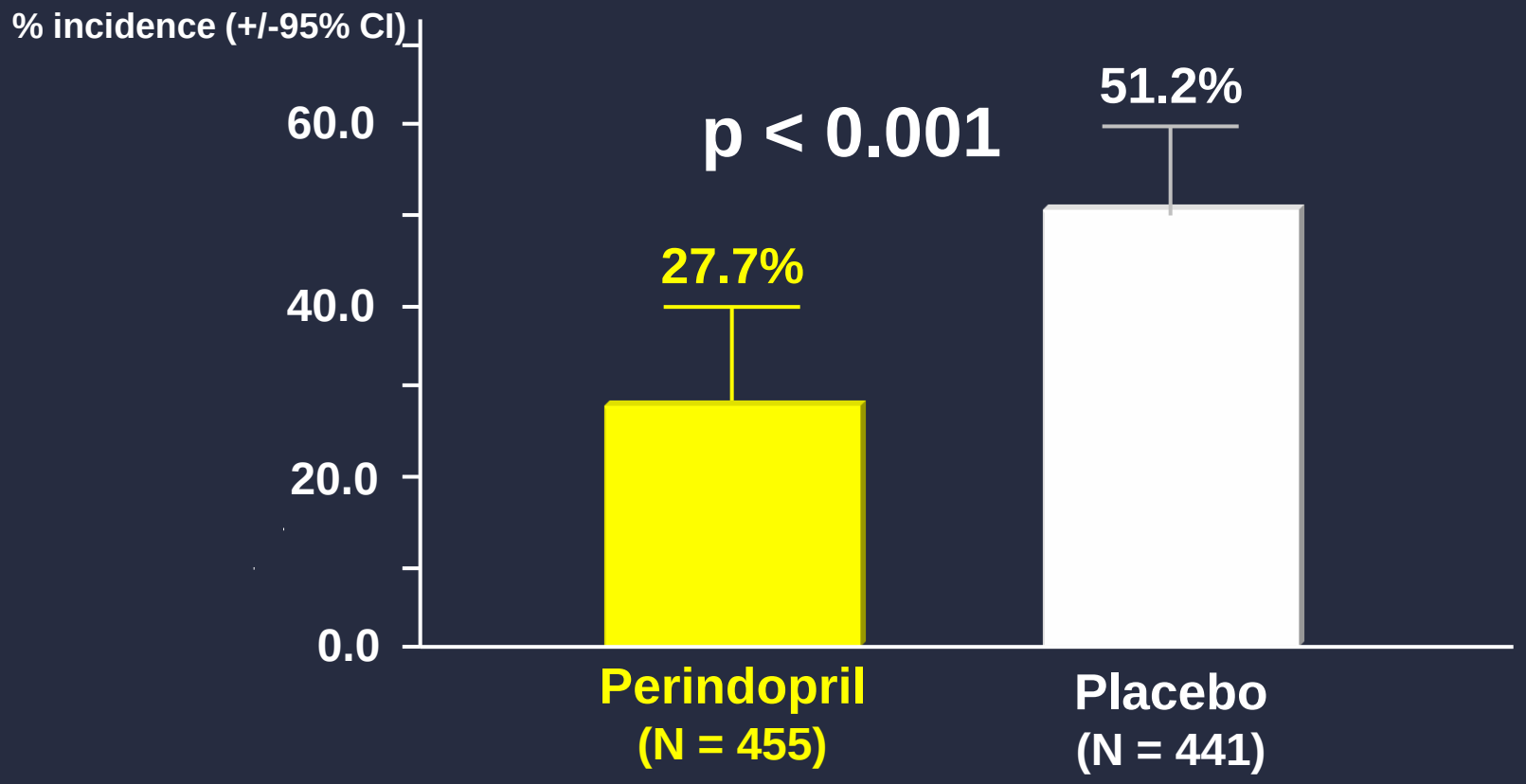
The three major endpoints

	Captopril (n=2733) No. (%)	Losartan (n=2744) No. (%)	Relative risk (95% CI)	P
All-cause mortality	447 (16.4)	499 (18.2)	1.13 (0.99–1.28)	0.069
Sudden cardiac death or resuscitated cardiac arrest	203 (7.4)	239 (8.7)	1.19 (0.99–1.43)	0.072
Myocardial reinfarction (fatal or nonfatal)	379 (13.9)	384 (14)	1.03 (0.89–1.18)	0.722

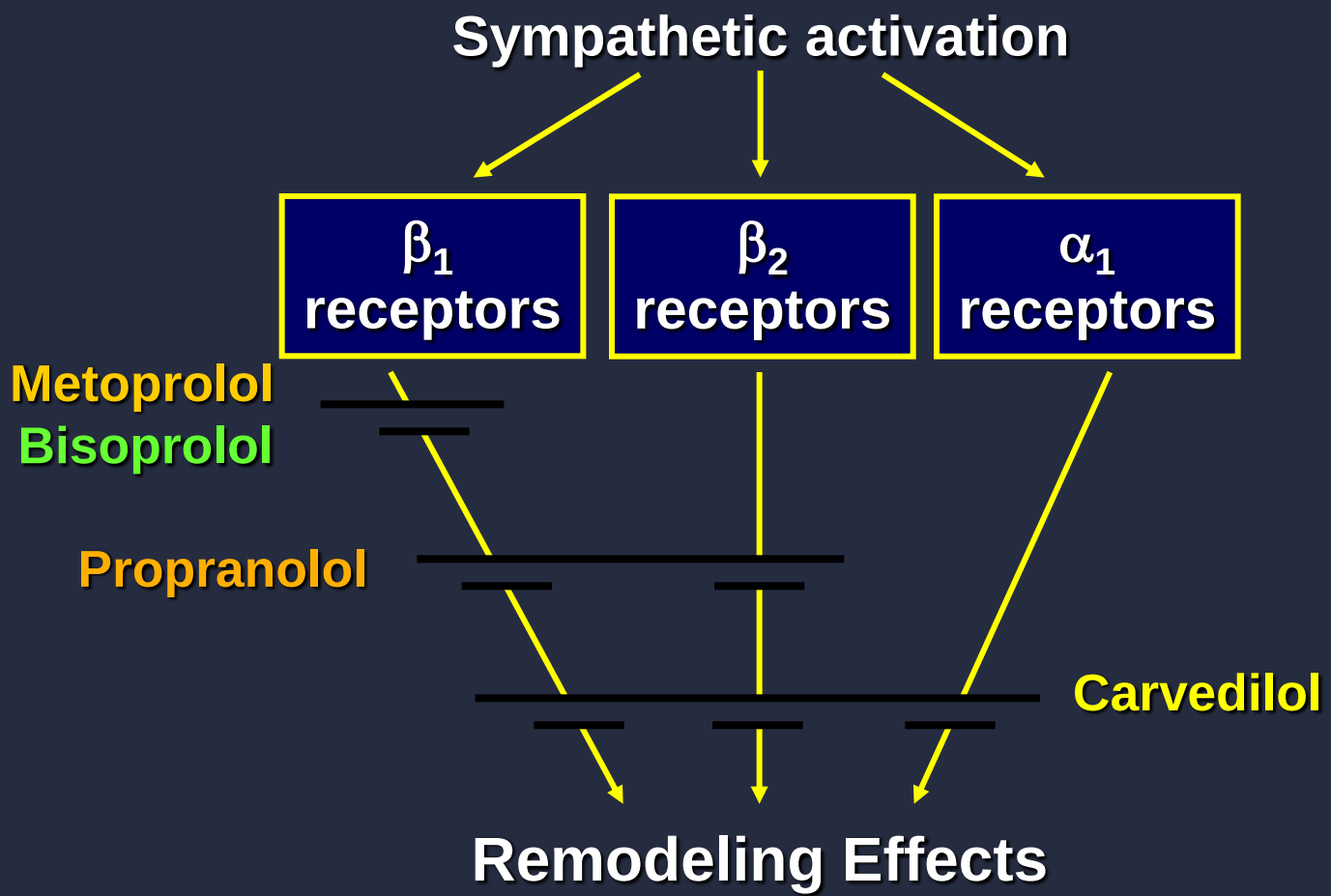
In patients with acute MI and evidence of heart failure or LV dysfunction, losartan 50 mg daily, conferred no further benefit in comparison with captopril but was better tolerated than captopril

PREAMI
Perindopril and Remodelling in Elderly with Acute Myocardial Infarction

1-year ACE-inhibition with perindopril (8 mg/day) in 1252 elderly (≥65 years) patientswith AMI and preserved LV function (EF ≥40%). The primary end point - a composite of death, hospitalization for heart failure, and LV remodeling (defined as ≥ 8% increase in LV end diastolic volume), was significantly reduced by 38% in patients on perindopril (P < .001) .



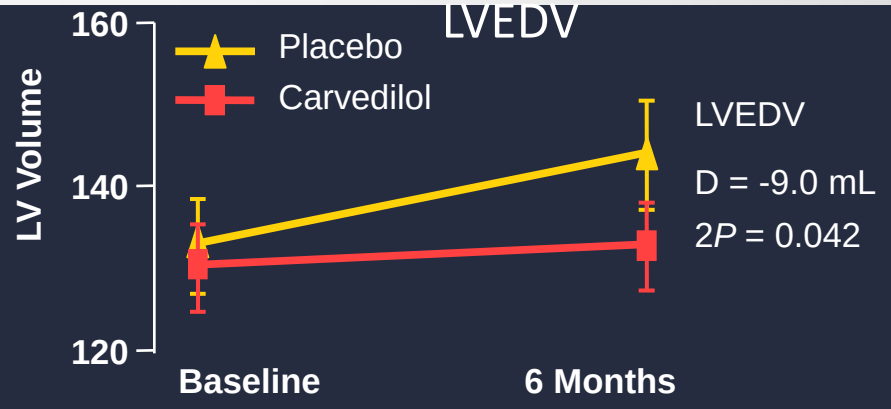
Antiadrenergic Therapy by β Blockade

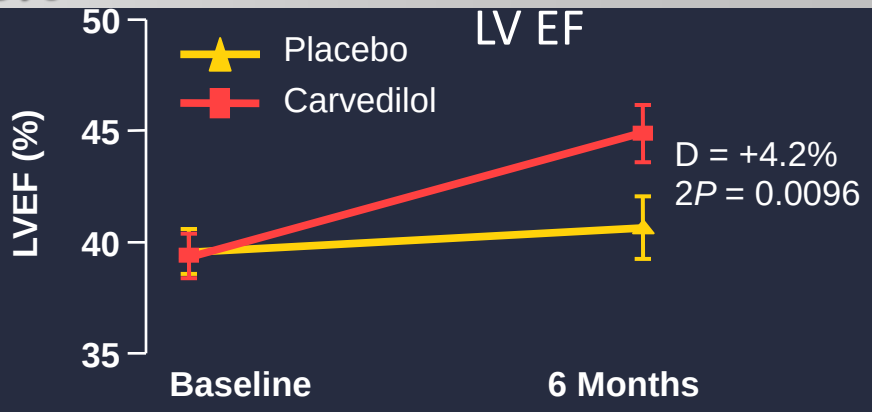


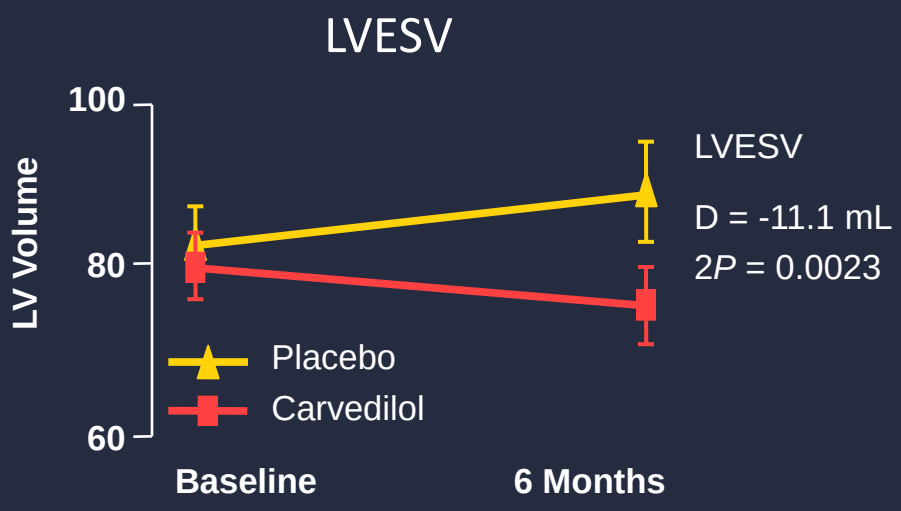
CAPRICORN

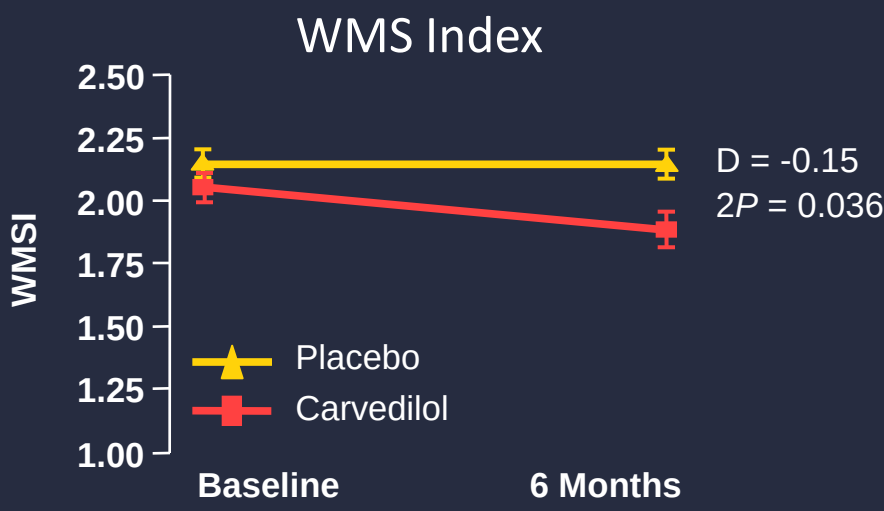
Effect of Carvedilol on LV Function on Top of ACEI-1,959 patients post MI

LVEF ≤ 40%







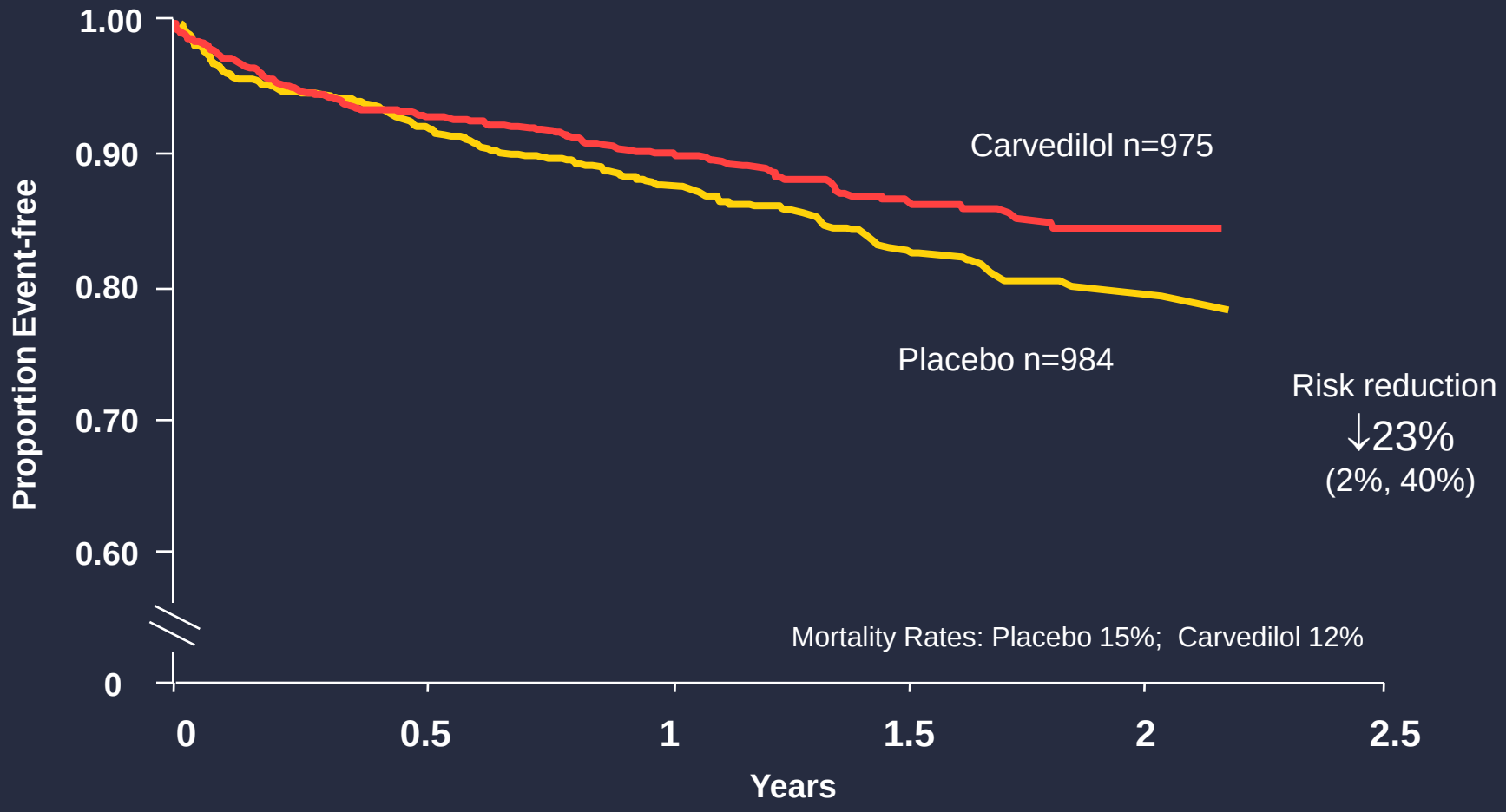


LVEDV=left ventricular end-diastolic volume.

Doughty RN et al. *Circulation*. 2001

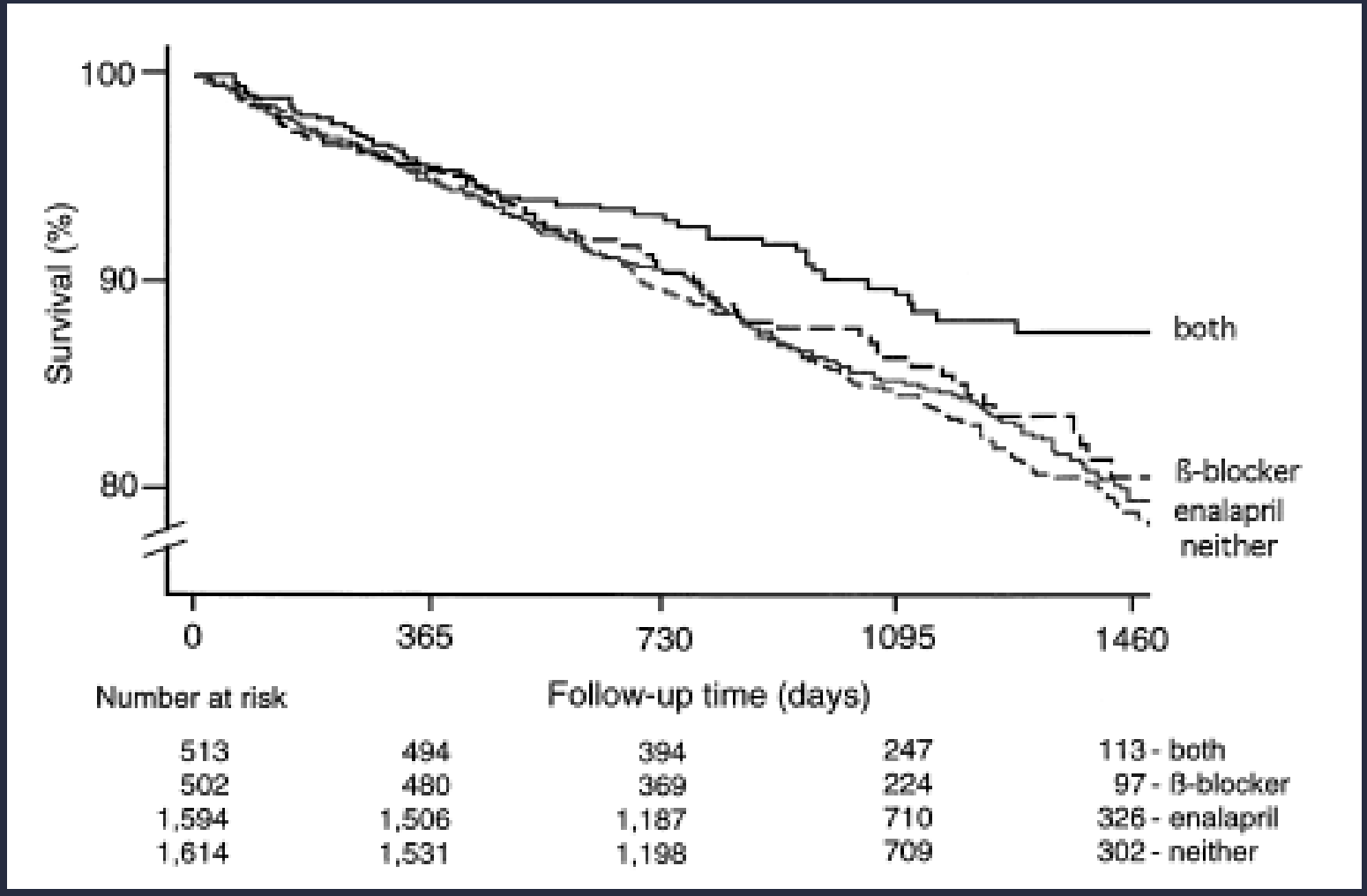
CAPRICORN All-Cause Mortality

Carvedilol Post-Infarct Survival Control in LV Dysfunction



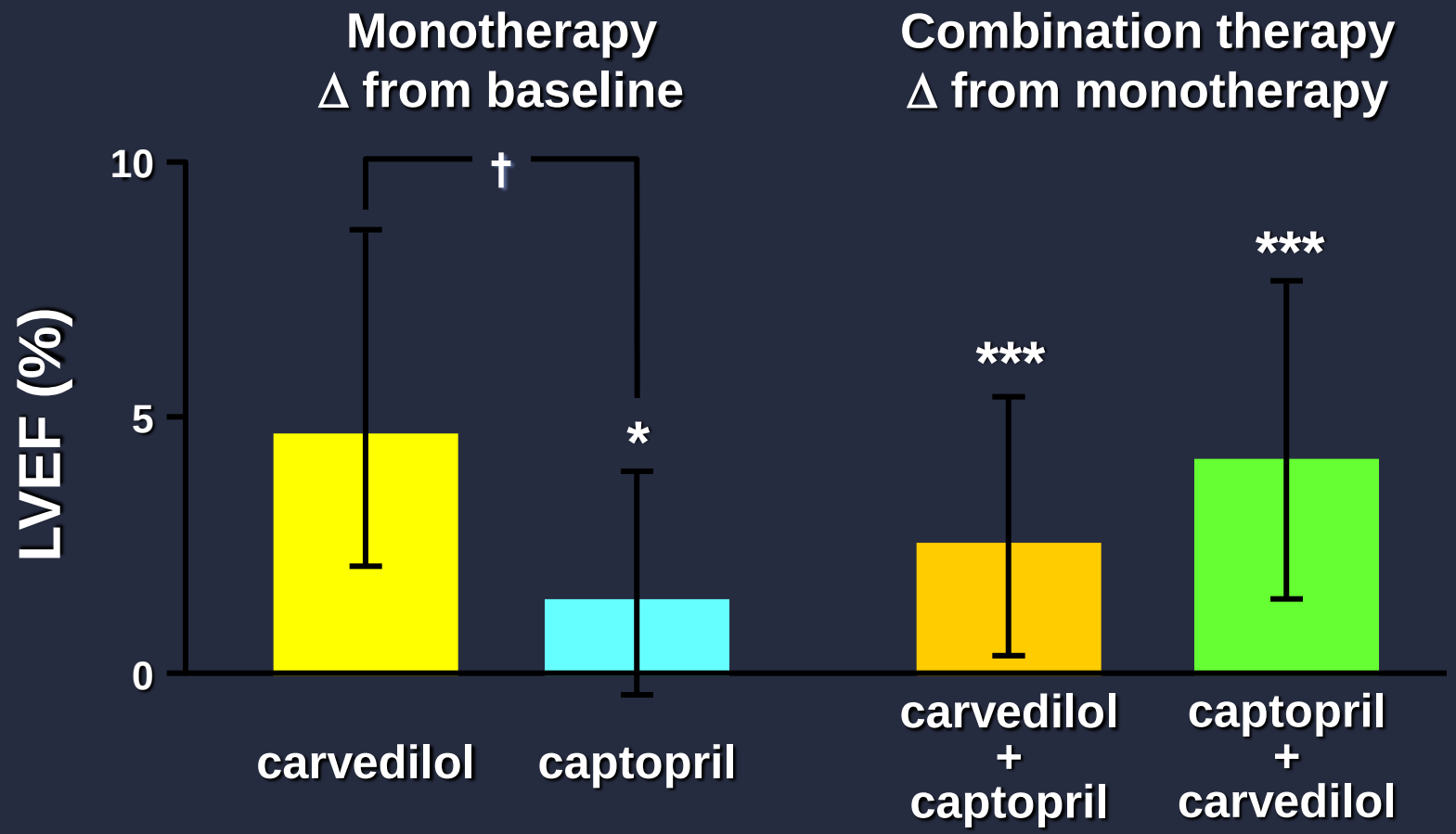
The CAPRICORN Investigators. *Lancet*. 2001;357:1385-1390.

ACEI / BB – Alone or both?



JACC Vol. 33, No. 4, 1999: 916 - 23

Median Changes in LVEF With Carvedilol and Captopril From Baseline to Monotherapy to Combination



Comparisons within groups: * P < 0.05; *** P < 0.001
Comparison between groups: † P < 0.05

Khattar R et al. Am Heart J

Eplerenone post MI - EPHESUS

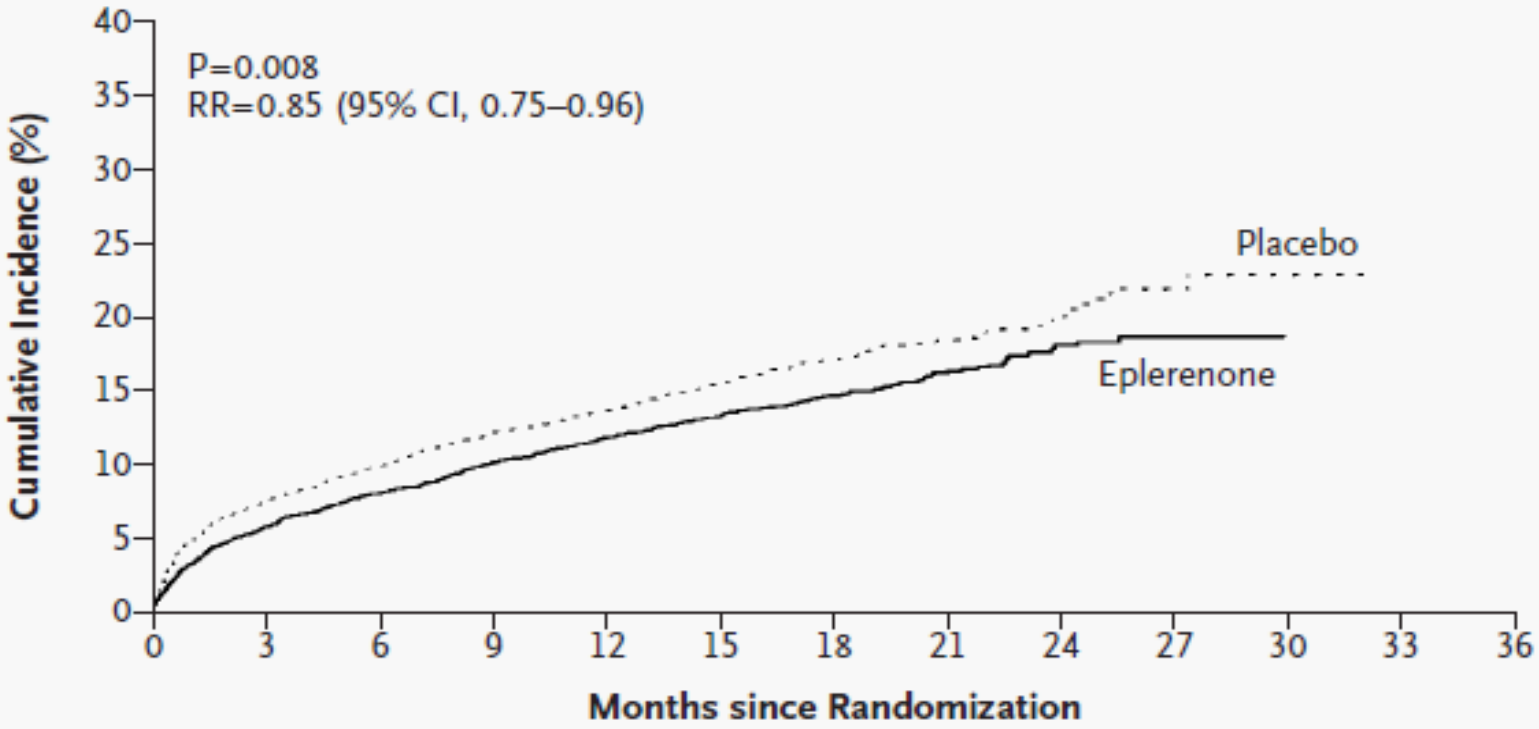
- Multicenter, randomized, double-blind, placebo-controlled trial.
- Eplerenone (25 mg per day) for four weeks, and increased to a maximum of 50 mg per day.

  or matching placebo.

- Inclusion: AMI in last 3 – 14 days with LVEF < 40% or lower on Echo &/or documented HF.
- Exclusion: Sr. Creat > 2.5mg/dL or Sr. K+ > 5.0mmol/L.

N Engl J Med 2003;348:1309-21.

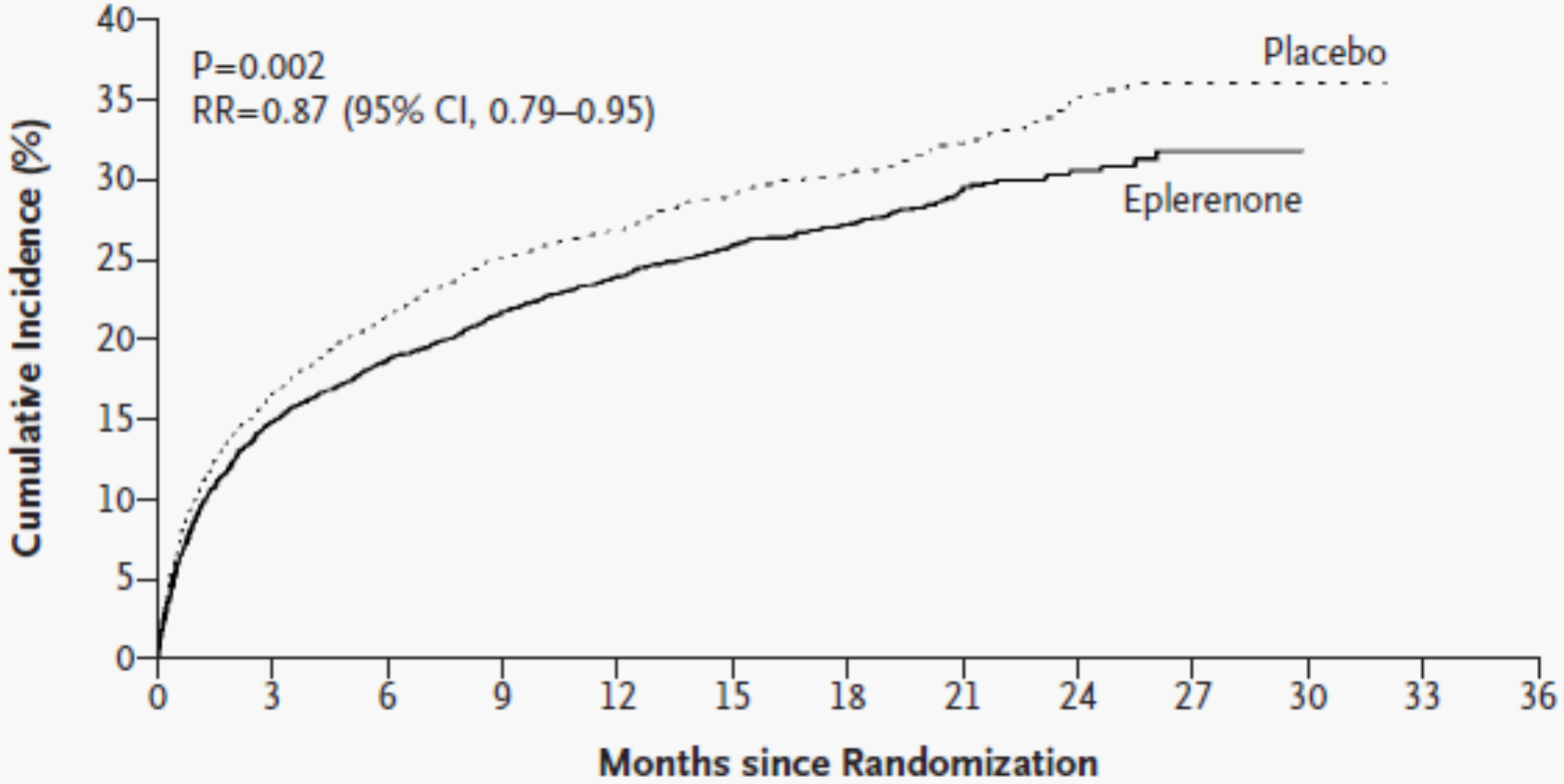
Results: EPHESUS
I Primary EP: Death from any cause



No. at Risk													
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

N Engl J Med 2003;348:1309-21.
N Engl J Med 2003;348:1309-21.

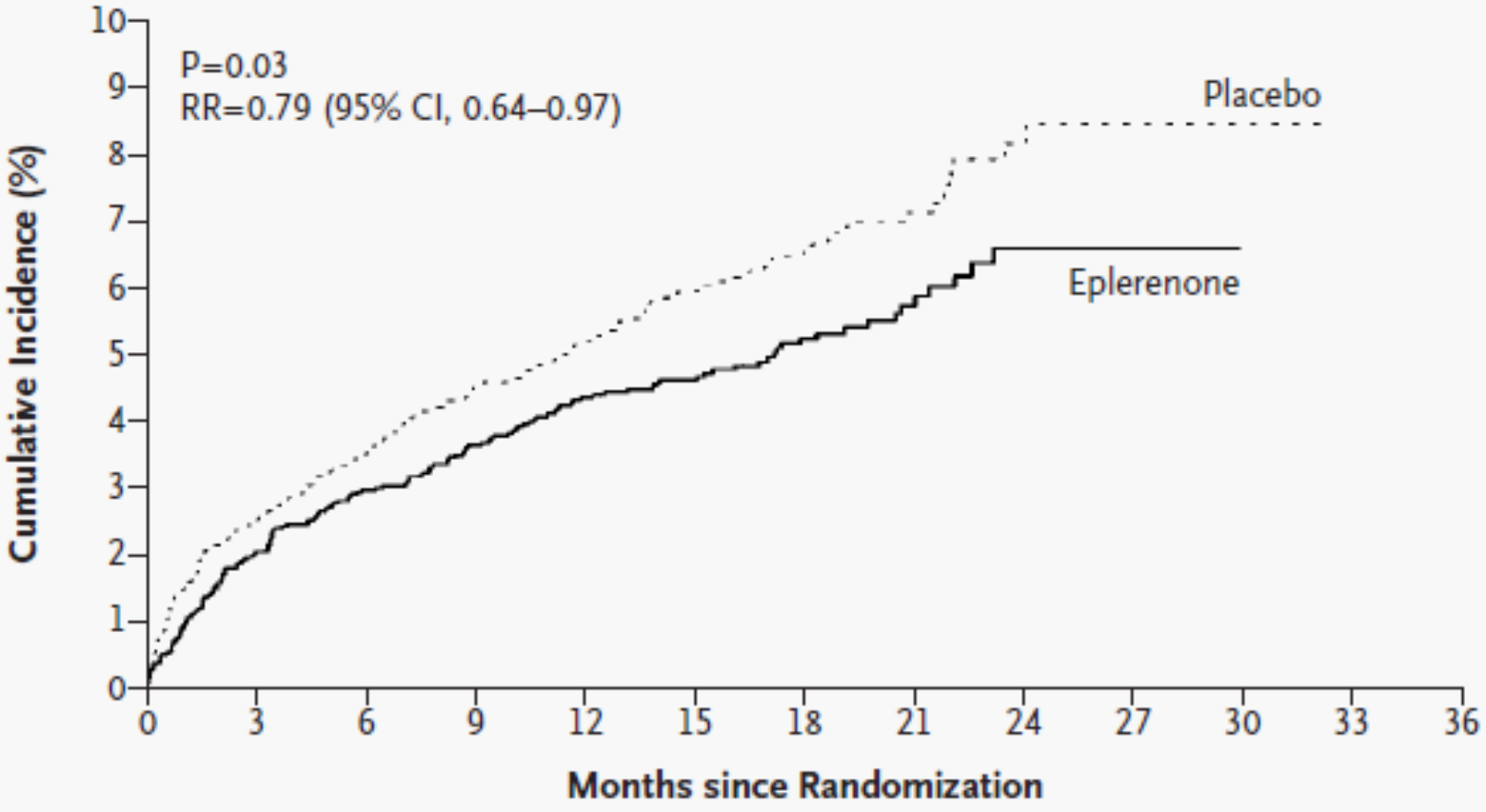
Results: EPHESUS
II Primary EP: Death from CVS cause



No. at Risk													
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

N Engl J Med 2003;348:1309-21.

Results: Secondary End point Sudden Cardiac death



No. at Risk													
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

N Engl J Med 2003;348:1309-21.

Metablocically active drugs

- Trimetazidine
- L Carnitine
- Ranolazine
- Coenzyme Q 10

Role of Statins in Remodeling

Statin therapy on LV remodeling after MI using cardiac magnetic resonance imaging.

* **BACKGROUND** Statin therapy has been shown to reduce cardiac hypertrophy in vitro and in vivo, but the influence on LV post-MI remodeling is largely unknown.

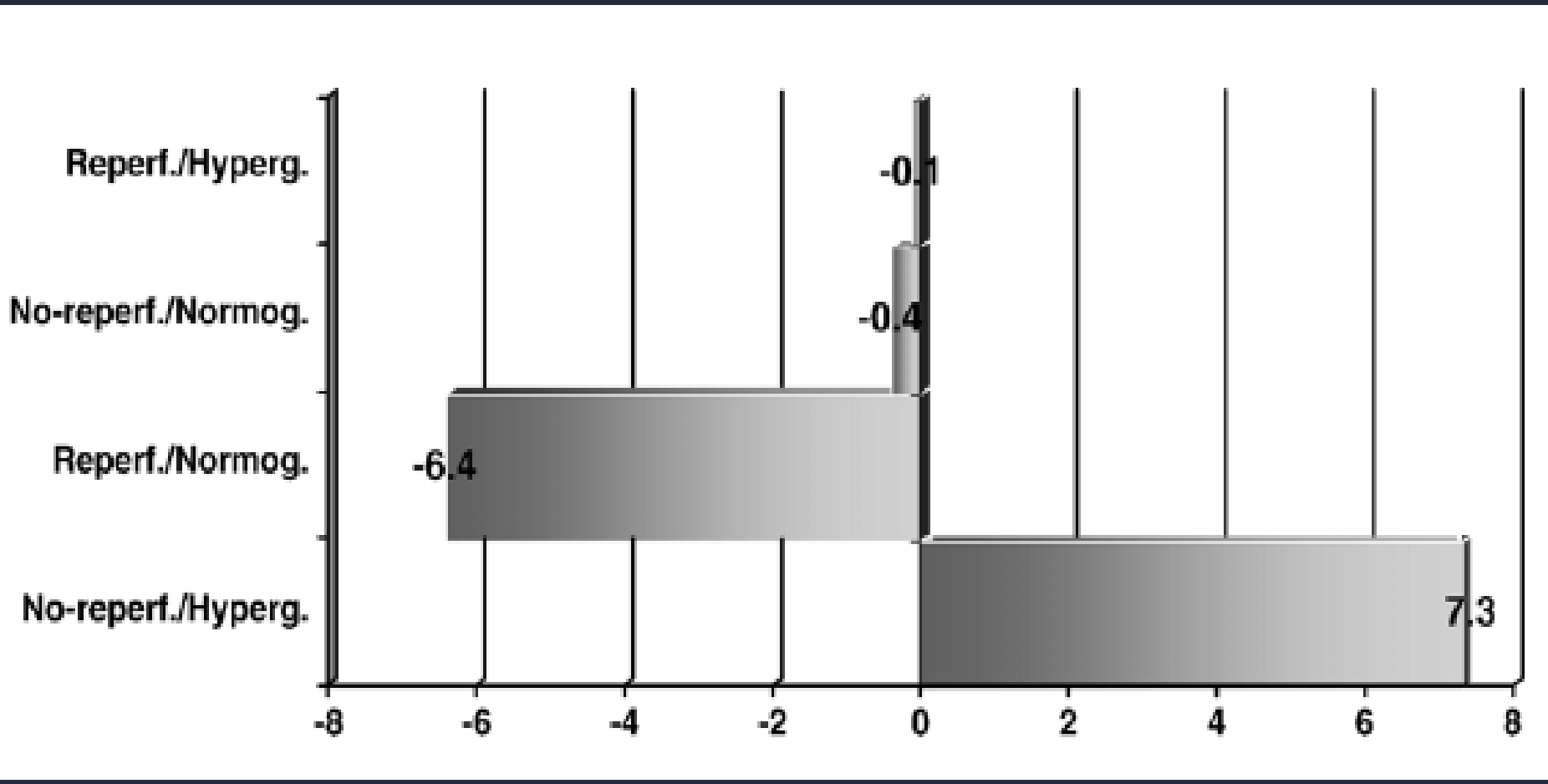
* **METHODS** The CMRI measurements were taken four and 12 weeks after left coronary artery ligation

* **RESULTS** Administration of cerivastatin attenuated hypertrophy after MI, and this effect was completely abolished by NOS inhibition

* **CONCLUSIONS** LV remodeling was profoundly changed by statin treatment. Hypertrophy was attenuated, and global function was improved.

J Am Coll Cardiol 2002;40:1695–700

Reperfusion and Hyperglycemia



J.C. Nicolau et al. / Journal of Diabetes and Its Complications 21 (2007) 294– 299

Biventricular pacing

Studies demonstrate that reverse LV remodeling is sustained to 12 months with Cardiac Resynchronization Therapy in patients with moderate to severe heart failure.

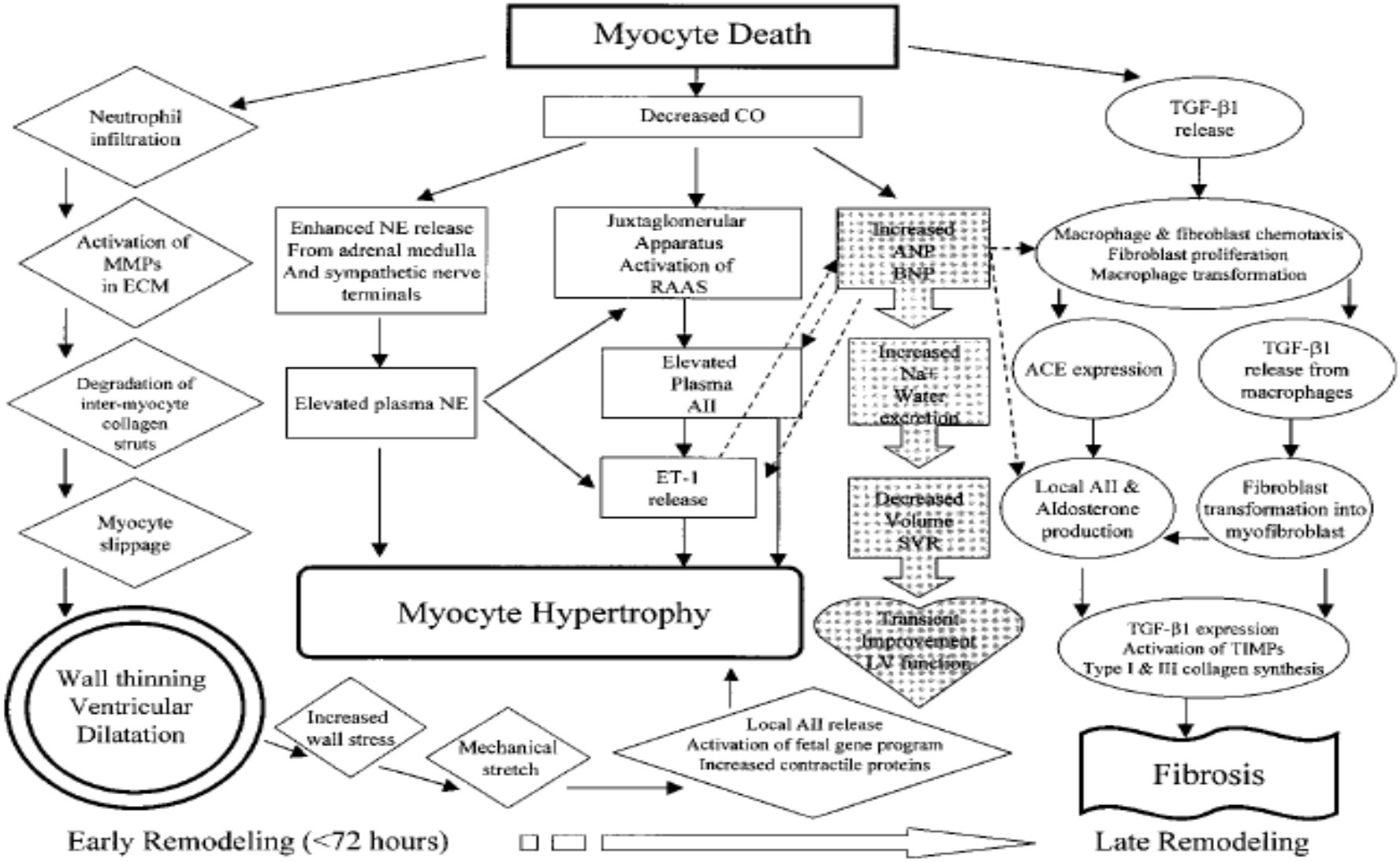
The sustained improvement in NYHA symptom class, 6-minute walk distance, and QoL reflects the ongoing favorable structural and functional LV remodeling.

The percentage of patients demonstrating improvement was strongly influenced by etiology, the greater reduction in LV volumes observed in nonischemic versus ischemic patients.

This late recurrent LV dilatation in patients with ischemic heart failure may relate to the deterioration in LV function due to repetitive episodes of ischemia and progressive regional loss of viable myocardium

Device Therapy

Diagrammatic representation of the many factors involved in the pathophysiology of ventricular remodeling.



Strategies for Remodeling

Long-term Management of Heart Failure or LV Dysfunction

Recommendations	Class	LOE
Oral beta-blockers in all patients without contraindications	I	A
ACE-inhibitors in all patients without contraindications	I	A
ARB (valsartan) in all patients without contraindications who do not tolerate ACE-inhibitors	I	B
Aldosterone antagonists if EF ≤ 40% and signs of heart failure or diabetes if creatinine is < 2.5 mg/dL (221 µmol/L) in men and < 2.0 mg/dL (177 µmol/L) in women and potassium < 5.0 mmol/L	I	B

Thank you

Aim- Prevention and Regression of Remodelling