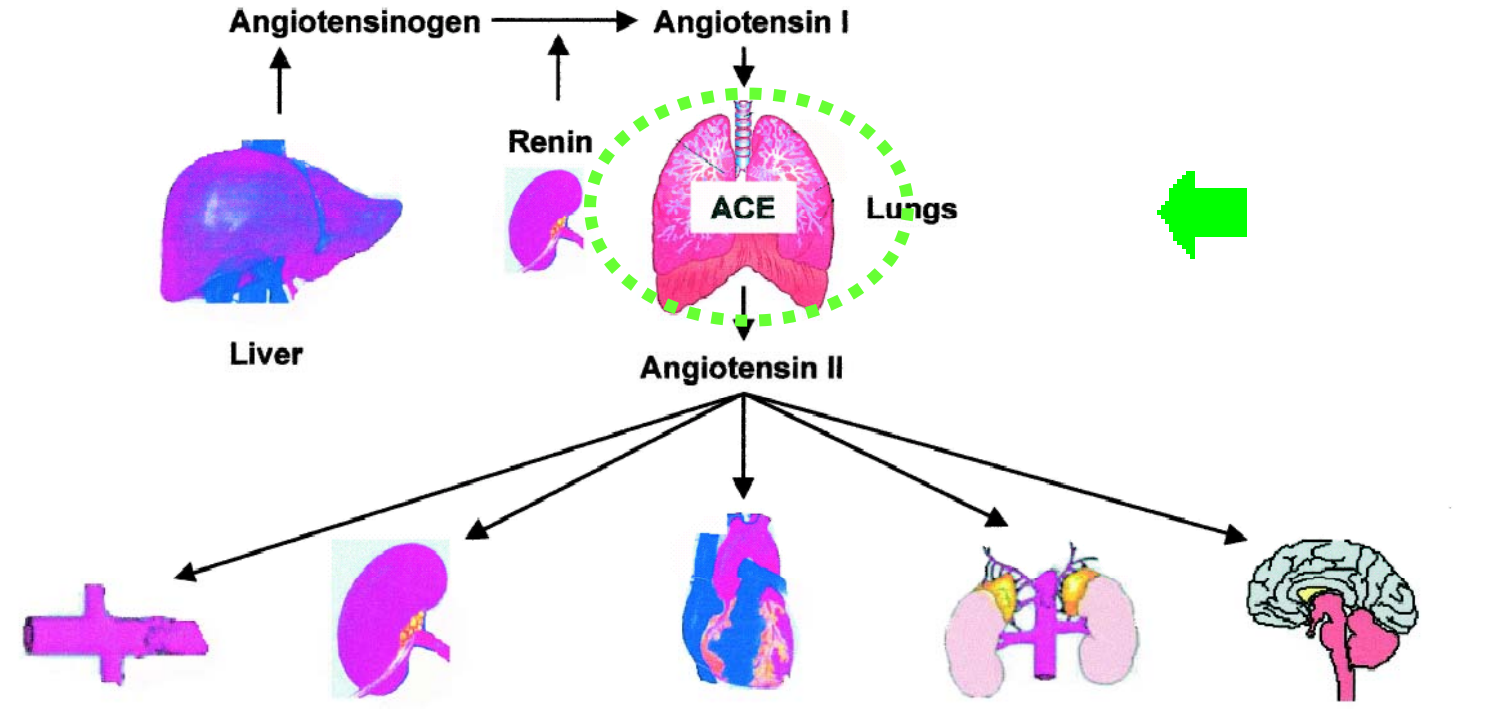
A to Z of RAAS blockade in heart failure

John McMurray
BHF Cardiovascular Research Centre
University of Glasgow.

RAAS inhibition in CHF



Blood vessel
Vasoconstriction
SMC hypertrophy
Superoxide generation
Endothelin secretion
Monocyte activation
Inflammatory cytokines
Reduced fibrinolysis

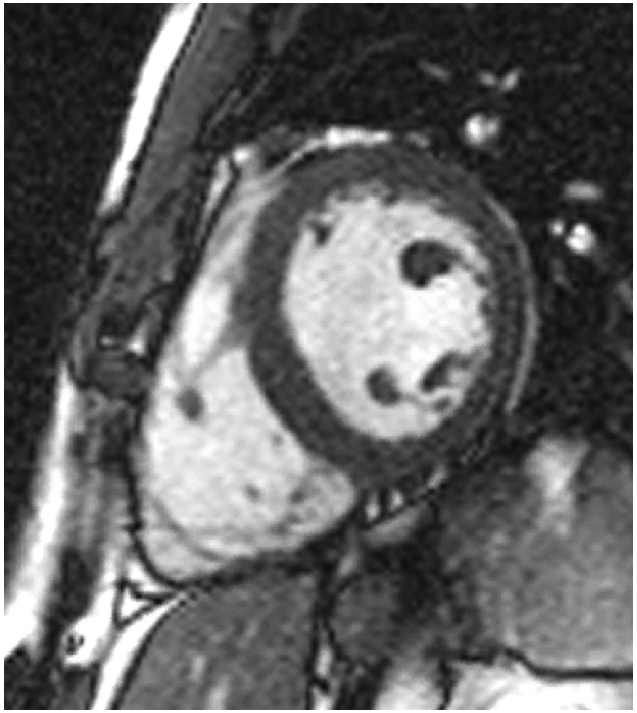
Kidney
Sodium and water retention
Efferent arteriolar vasoconstriction
Glomerular and interstitial fibrosis

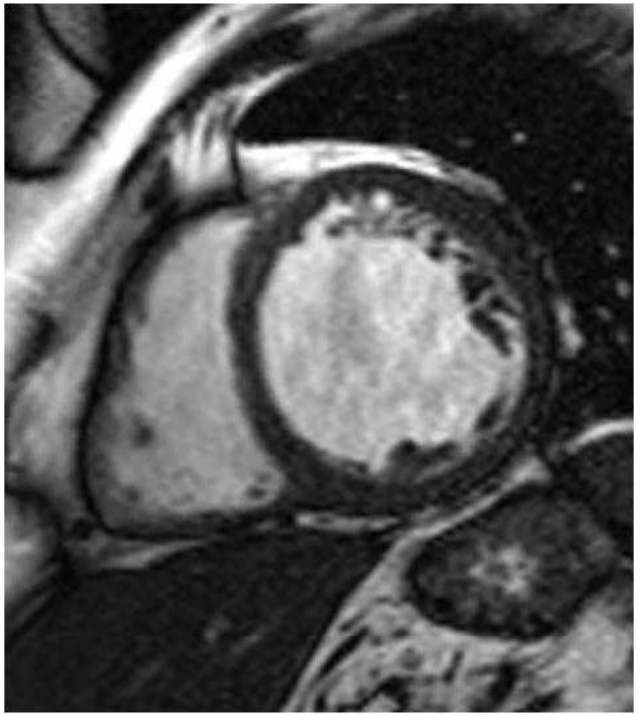
Heart
Cellular hypertrophy
Myocyte apoptosis
Myocardial fibrosis
Inflammatory cytokines
Coronary vasoconstriction
Positive inotropy
Proarrhythmia

Adrenal gland
Aldosterone secretion

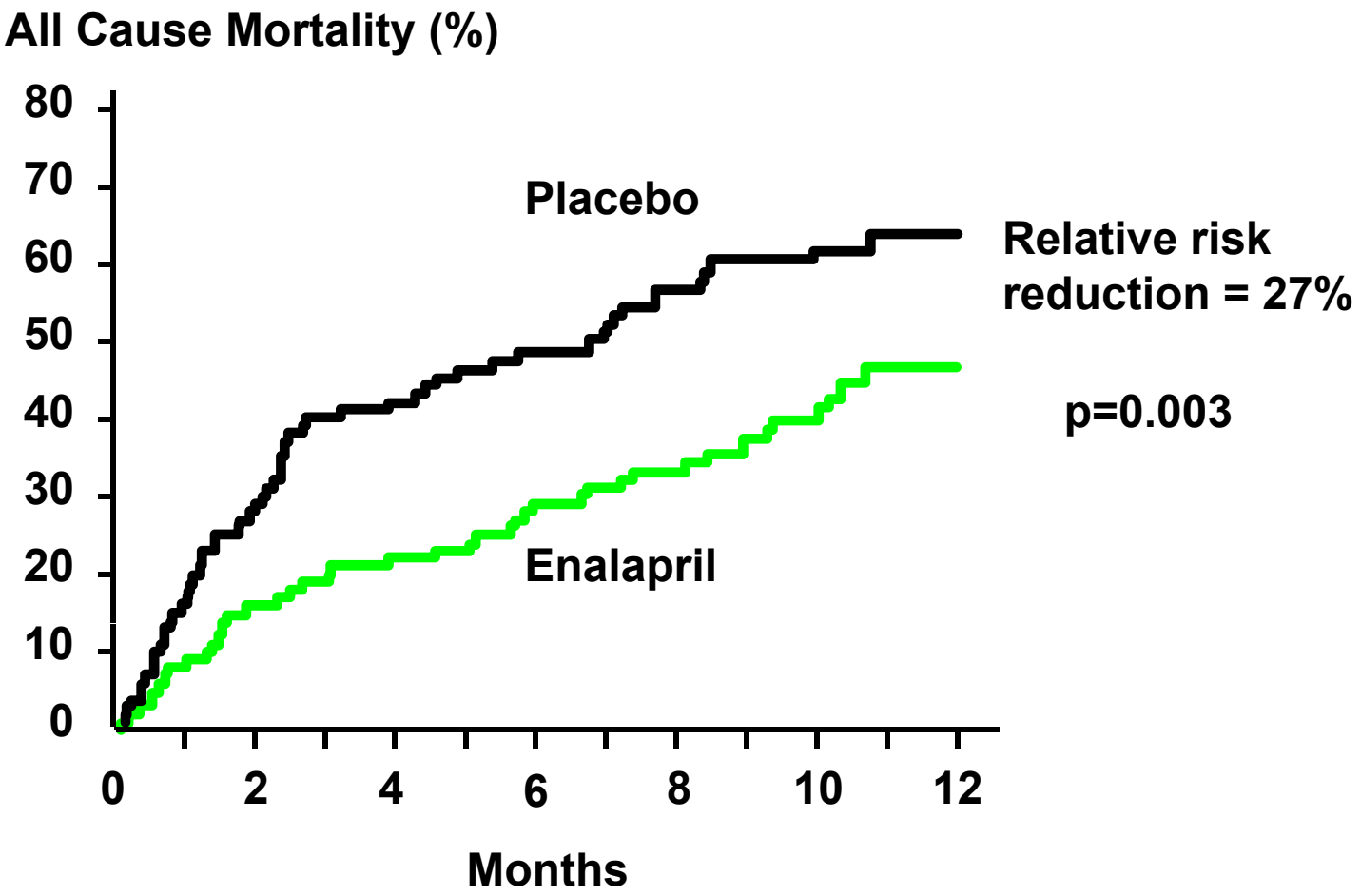
Brain
Vasopressin secretion
Sympathetic activation

ACE inhibition in patients with low LVEF CHF





CONSENSUS
Enalapril in severe HF

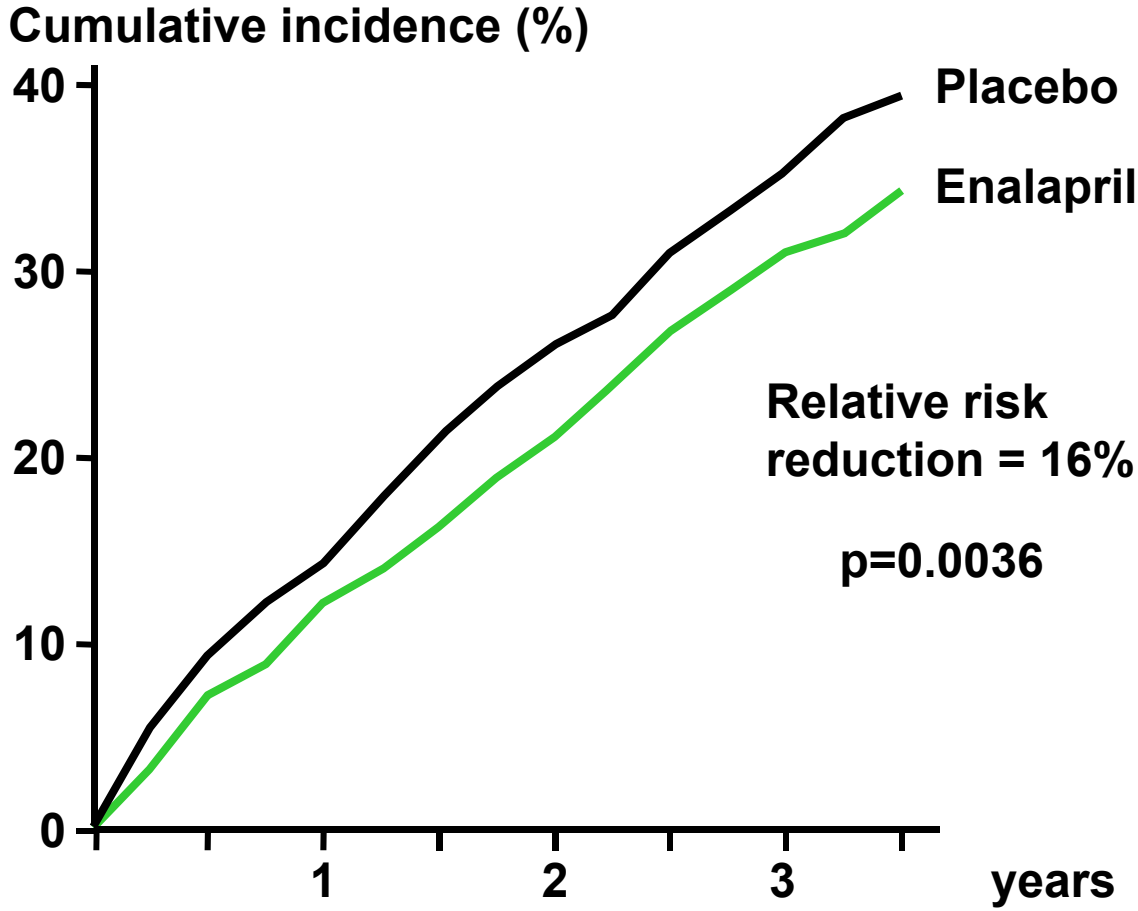


Swedberg et al NEJM 1987

CONSENSUS: background therapy

Drug therapy	
Digitalis	93%
Beta-blocker	3%
Diuretic	
Furosemide (mean dose)	98% (205mg)
Spironolactone (mean dose)	53% (80mg)

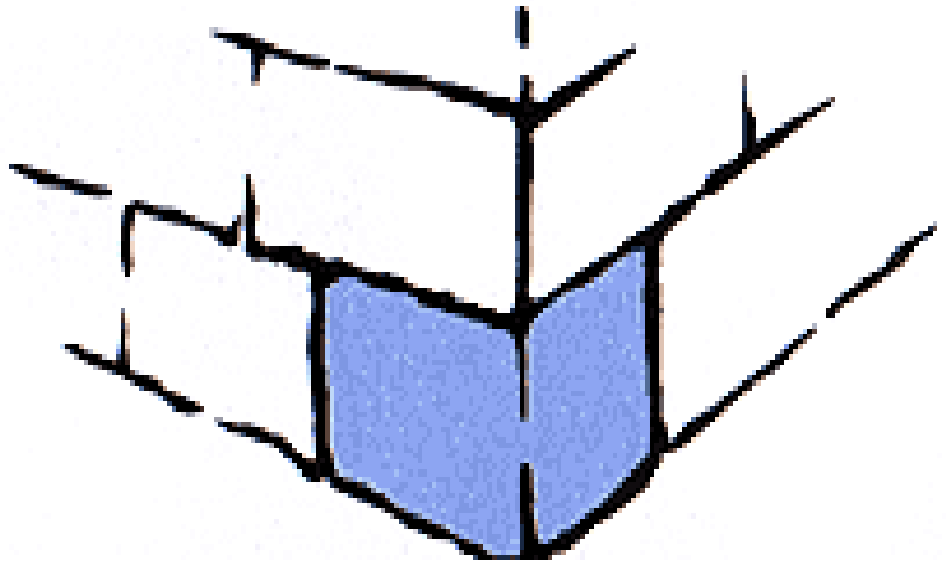
SOLVD Treatment Trial
All Cause Death



Number at risk					
Enalapril	1285	1127	1010	697	526
Placebo	1284	1085	939	669	487

SOLVD Investigators NEJM

The cornerstone of therapy



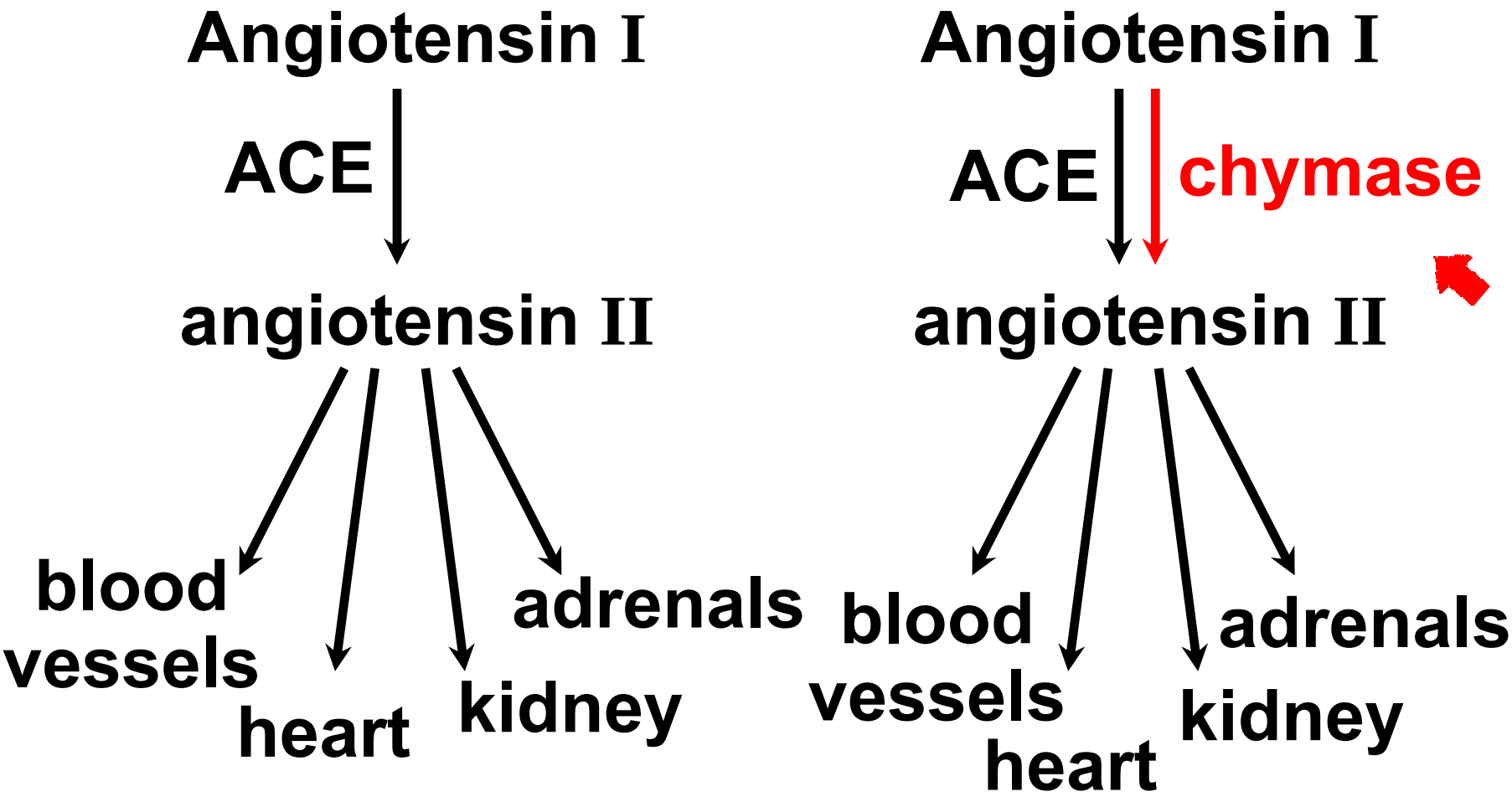
ACE inhibitor
(Beta-blocker)

Can we do better than an ACE inhibitor?

ARB versus ACE inhibitor

Head to head comparison of an ACE inhibitor and ARB: Coke vs. Pepsi?

Why use an ARB instead of an ACE inhibitor?



Bradykinin – good or bad?

Cough
Angioedema?
Renal impairment?

Vasodilatation?
Growth inhibition?
Other?

Evaluation of Losartan In The Elderly ELITE 2

Study Design

≥60 years; NYHA II-IV; EF ≤40%
ACEI/AIIA naive or <7 days in 3 months prior to entry
Standard Rx (± Dig/Diuretics), β-blocker stratification

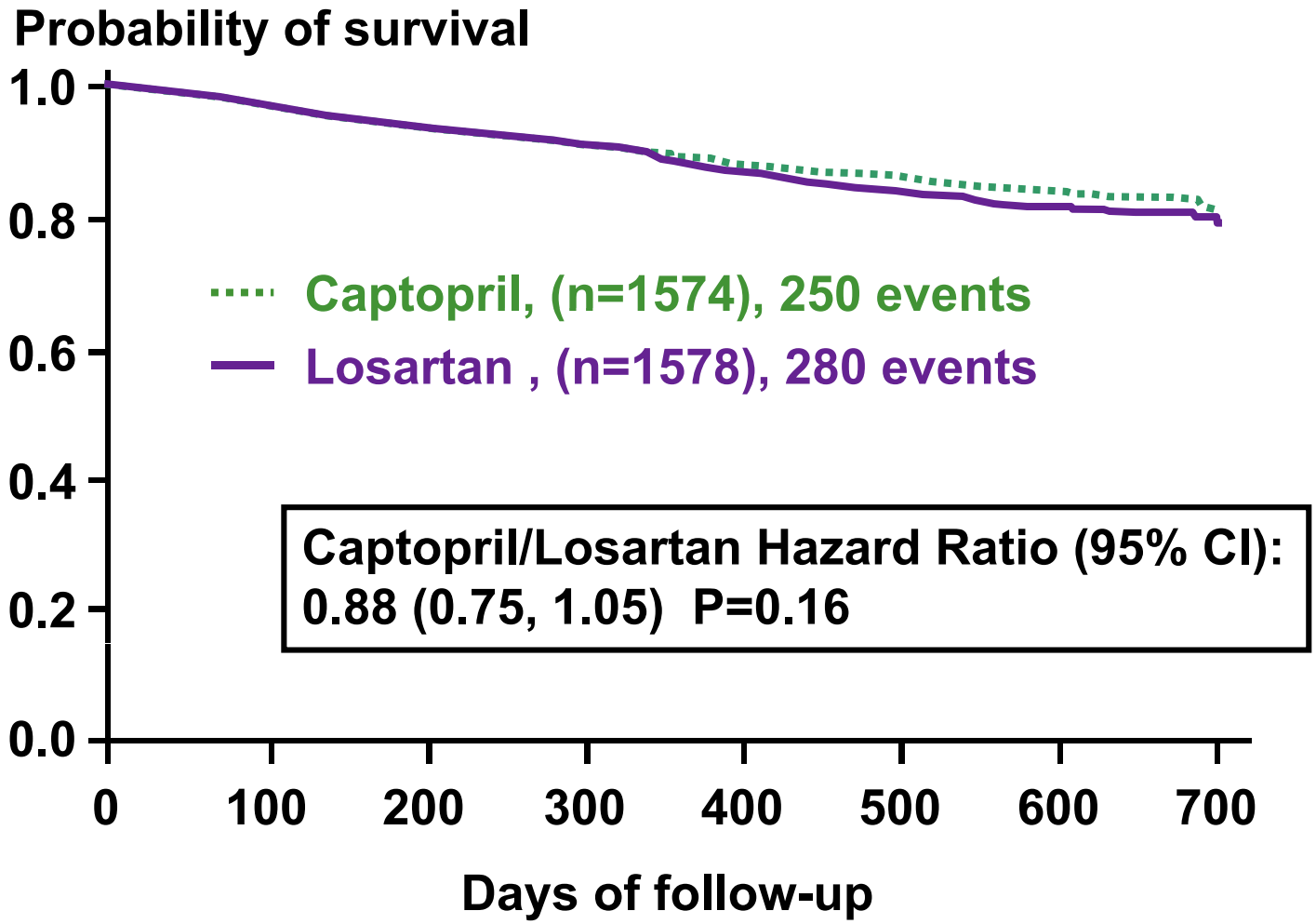
Captopril
50 mg 3 times daily
(n=1574)

Event-driven
(Target 510 Deaths)
~2 years

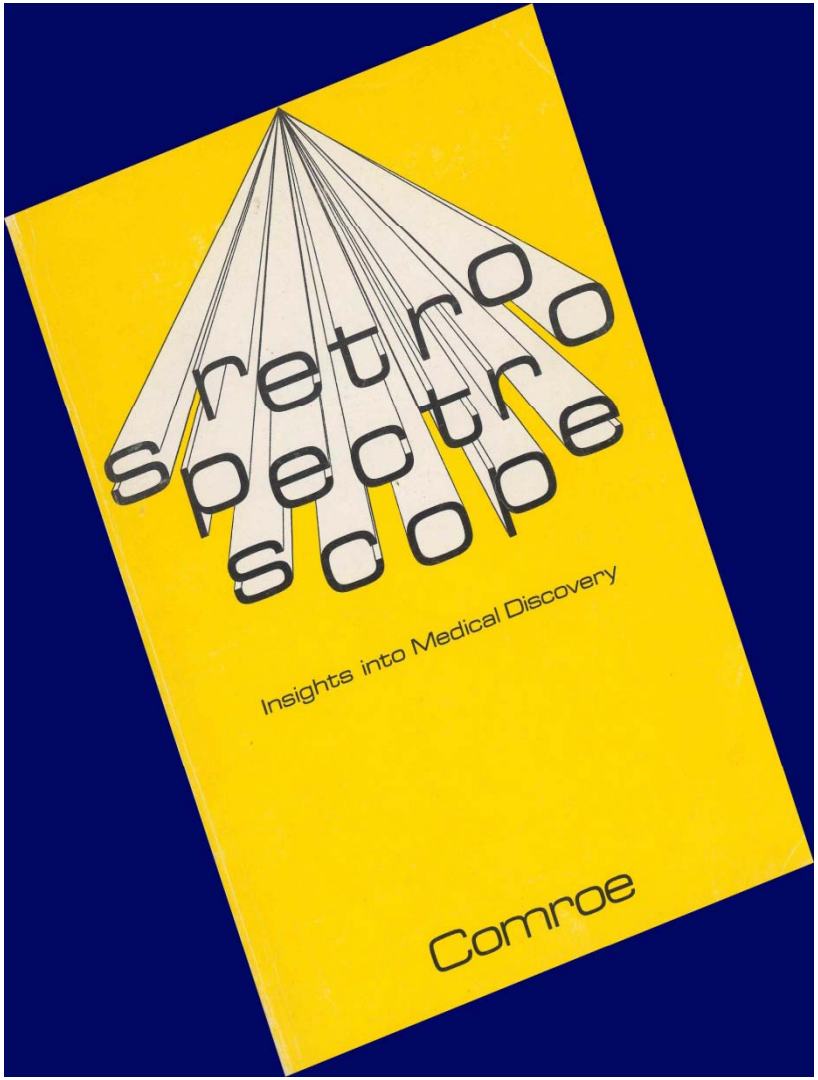
Losartan
50 mg daily
(n=1578)

Primary Endpoint: All-Cause Mortality
Secondary Endpoint: Sudden Cardiac Death and/or Resuscitated Arrest
Other Endpoints: All-Cause Mortality/Hospitalizations
Safety and Tolerability

Losartan Heart Failure Survival Study: ELITE II
Primary Endpoint – All-Cause Mortality



The Retrospectroscope - A widely used instrument



Published by Julius Comroe in1977

Was the Dose of Losartan Too Low?

"Neutral trials"	"Positive trials"
ELITE II mean dose: 41 mg	RENAAL mean dose: 86 mg
OPTIMAAL mean dose: 45 mg	LIFE mean dose: 82 mg

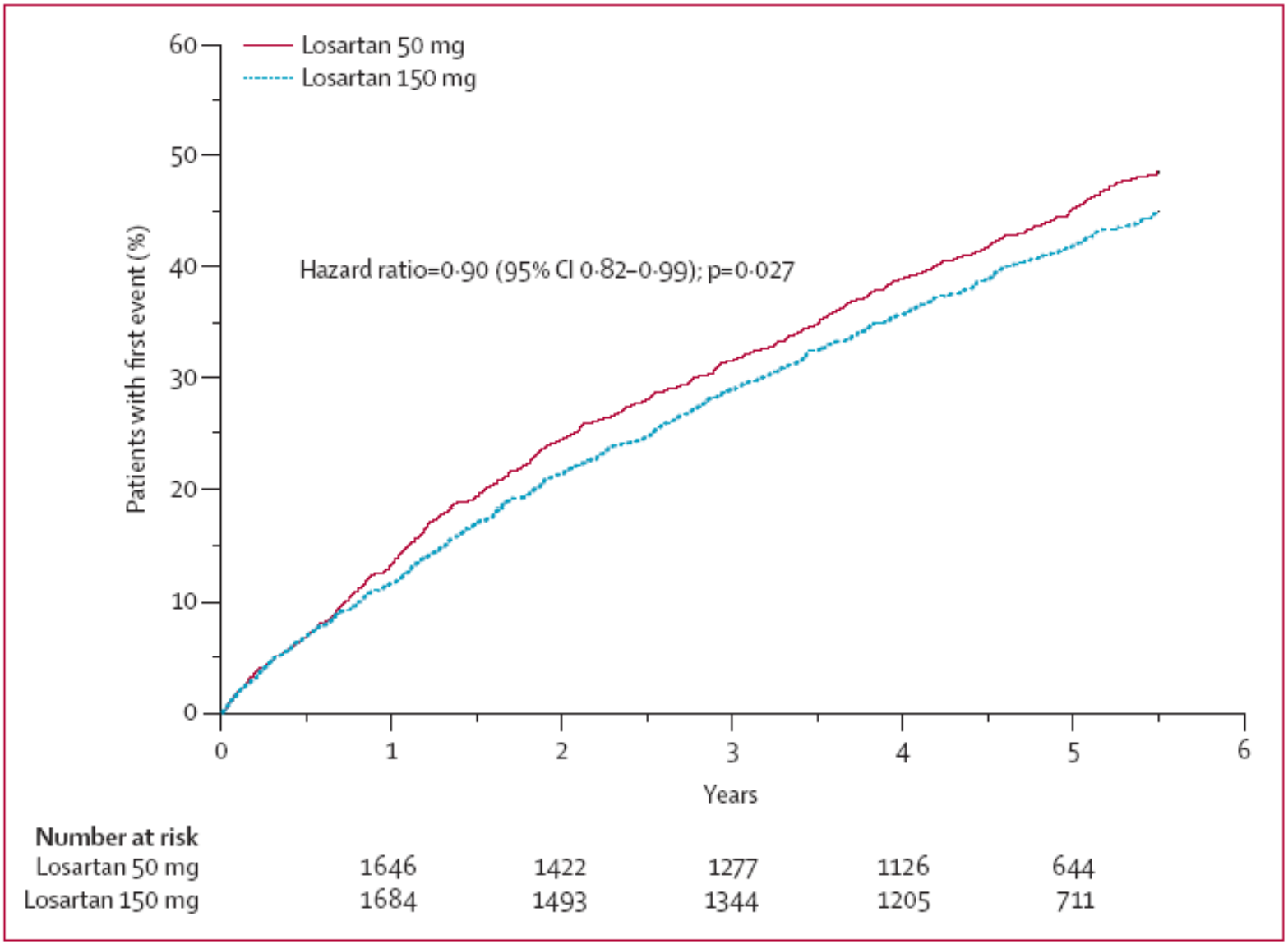
HEAAL: high *versus* low dose losartan

Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial

Marvin A Konstam, James D Neaton, Kenneth Dickstein, Helmut Drexler, Michel Komajda, Felipe A Martinez, Gunter A J Riegger, William Malbecq, Ronald D Smith, Soneil Guptha, Philip A Poole-Wilson,† for the HEAAL Investigators‡*

Published online November 17, 2009

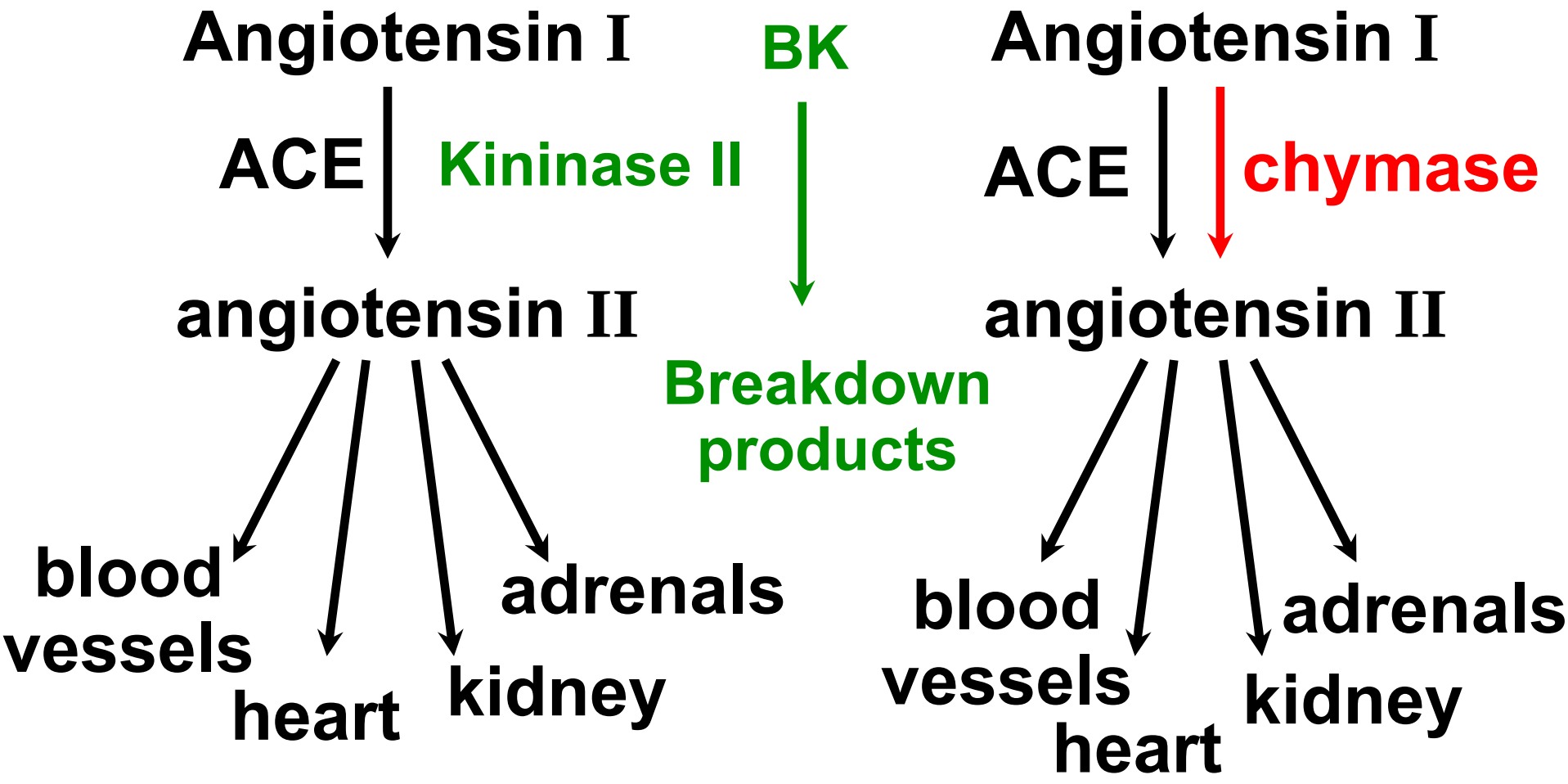
HEAAL: death or HF hospitalisation



Can we do better than an ACE inhibitor?

ARB *added to* an ACE inhibitor

Why add an ARB to an ACE inhibitor?



CHARM

Candesartan in **H**eart failure: **A**ssessment of **R**eduction in **M**ortality and morbidity

THE LANCET

www.thelancet.com

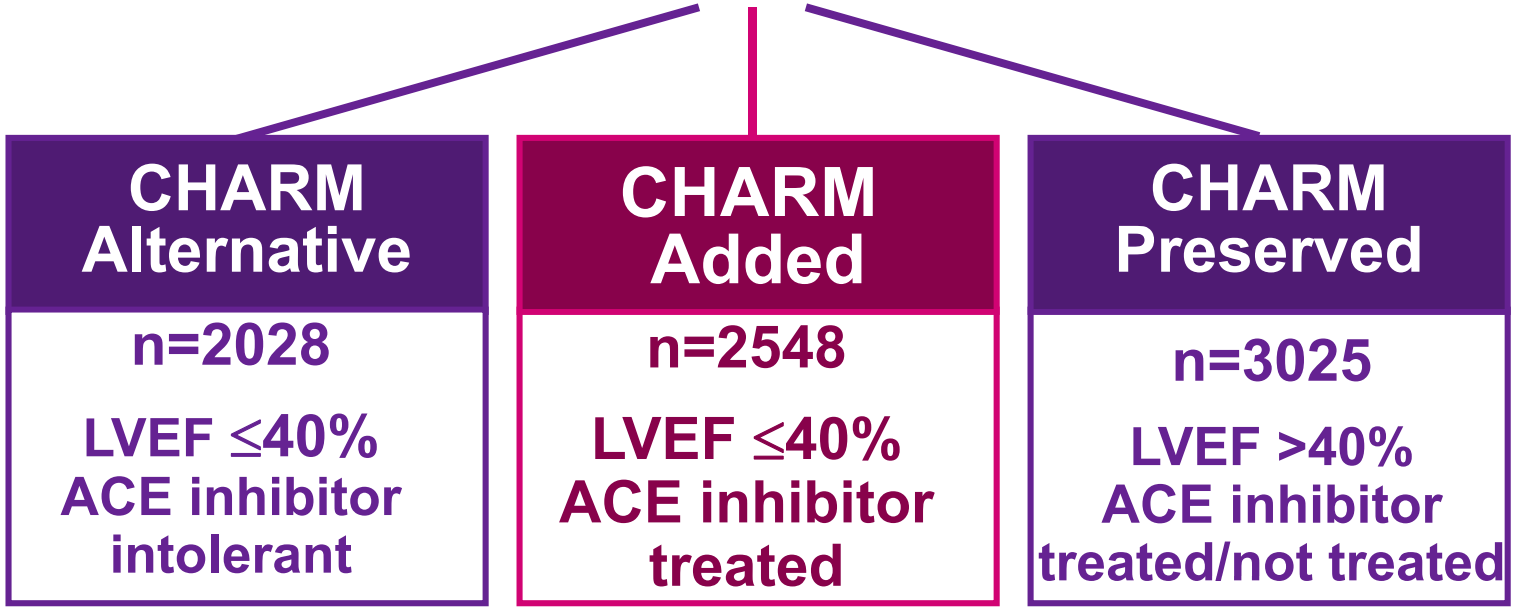
Volume 362, Number 9386 • Founded 1823 • Published weekly • Saturday September 6, 2003

Contents list continues inside

CHARM

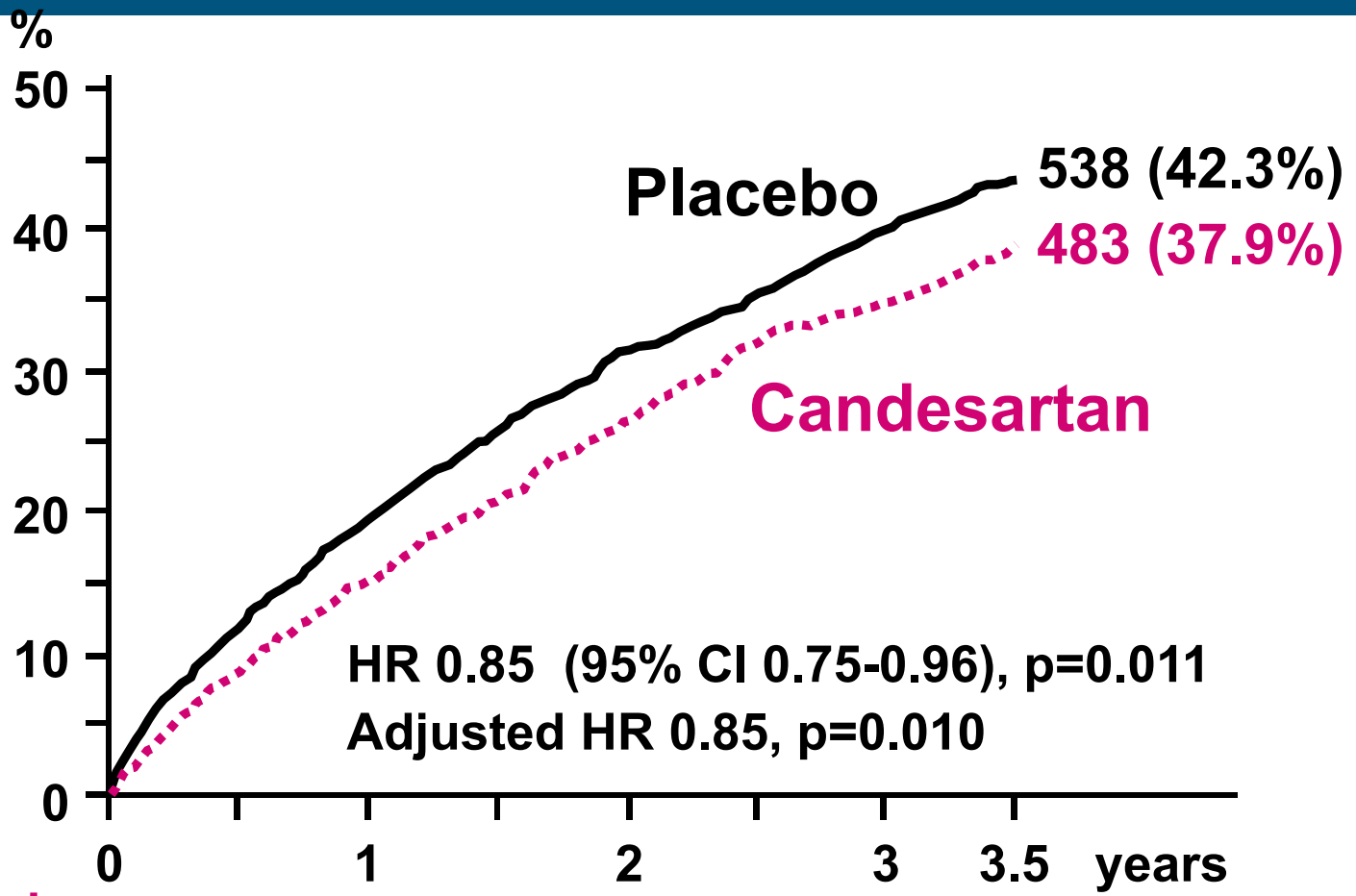
Candesartan in **H**eart failure: **A**ssessment of **R**eduction in **M**ortality and morbidity

3 component trials comparing candesartan to placebo



Primary outcome:
CV death or CHF hosp

CHARM-Added: Primary outcome
CV death or CHF hospitalisation



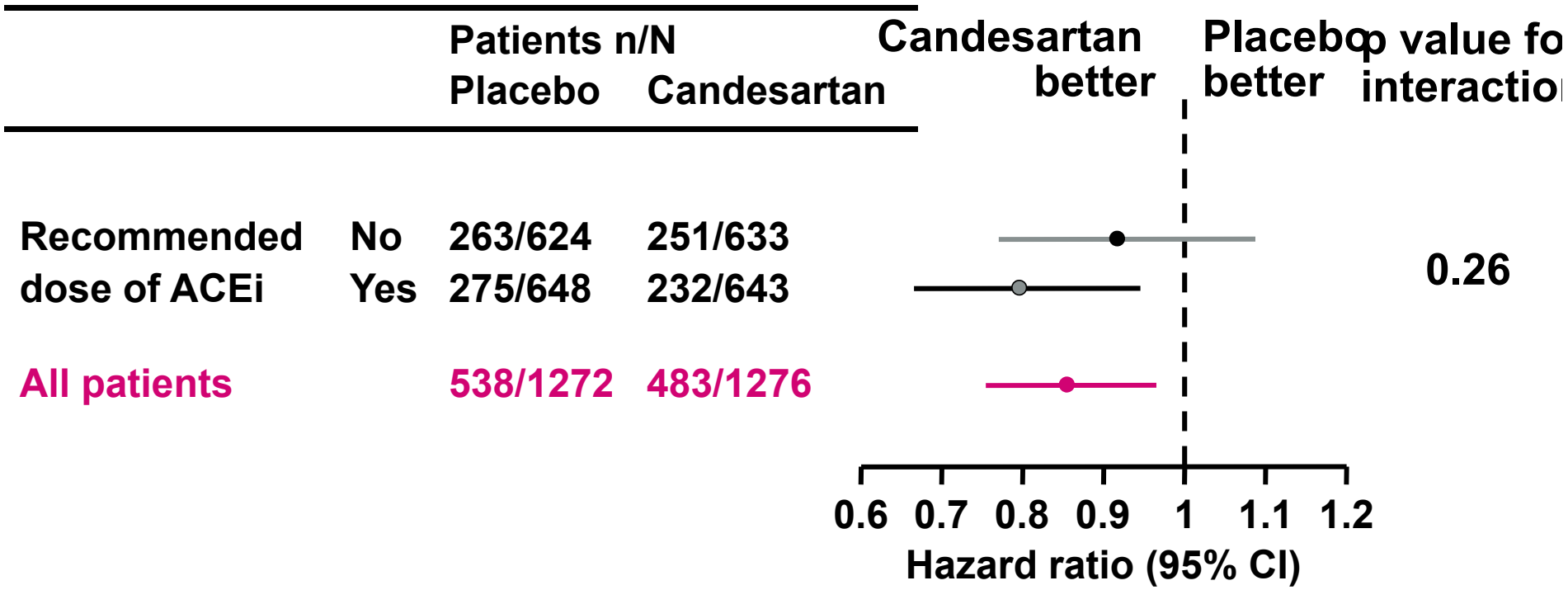
Number at risk

Candesartan	1276	1176	1063	948	457
Placebo	1272	1136	1013	906	422

NNT = 23

CHARM-Added
Pre-specified Subgroup analysis

CV Death or CHF Hospitalisation



McMurray et al. Lancet 2003;362:767-71

Maximising RAS blockade

- Would we achieve he same effect by increasing the dose of an ACE inhibitor as adding an ARB (or renin inhibitor)?

RAS blockers

ACE inhibitor **ARB**

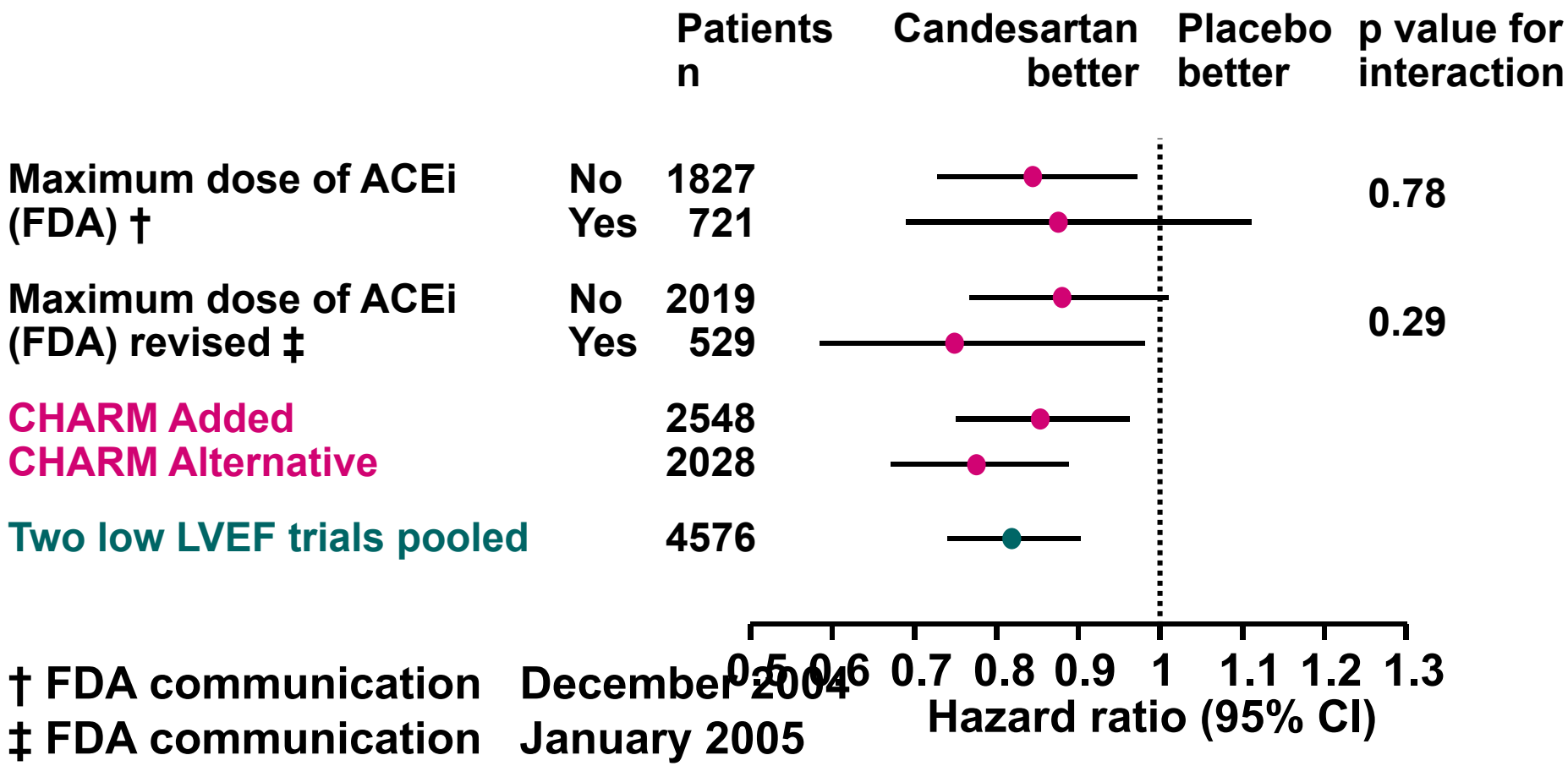
FDA set a higher bar

U.S. Department of Health and Human Services
Food and Drug Administration

FDA requested analyses of CHARM-Added

ACE inhibitor	% on Rx	Dose in CHARM-Add (mg/d)	≥Maximum (FDA),† n = 721		≥Maximum (FDA revised),‡ n = 529	
			Dose (mg/d)	Patients (%)	Dose (mg/d)	Patients (%)
Enalapril	27	17	20	52	40	10
Lisinopril	19	18	40	15	20	52
Captopril	17	83	150	21	300	2
Ramipril	11	7	10	39	10	39
Trandolapril	6	2.5	4	27	4	27
Perindopril§	6	4	16	1	16	1
Quinapril	5	25	80	7	80	7
Fosinopril	5	20	40	20	40	20
Benazepril§	3	26	80	5	80	5
Other§‖	1	–				
All	100			28.30		20.80

CHARM-Added: FDA-requested analyses by ACE-inhibitor dose

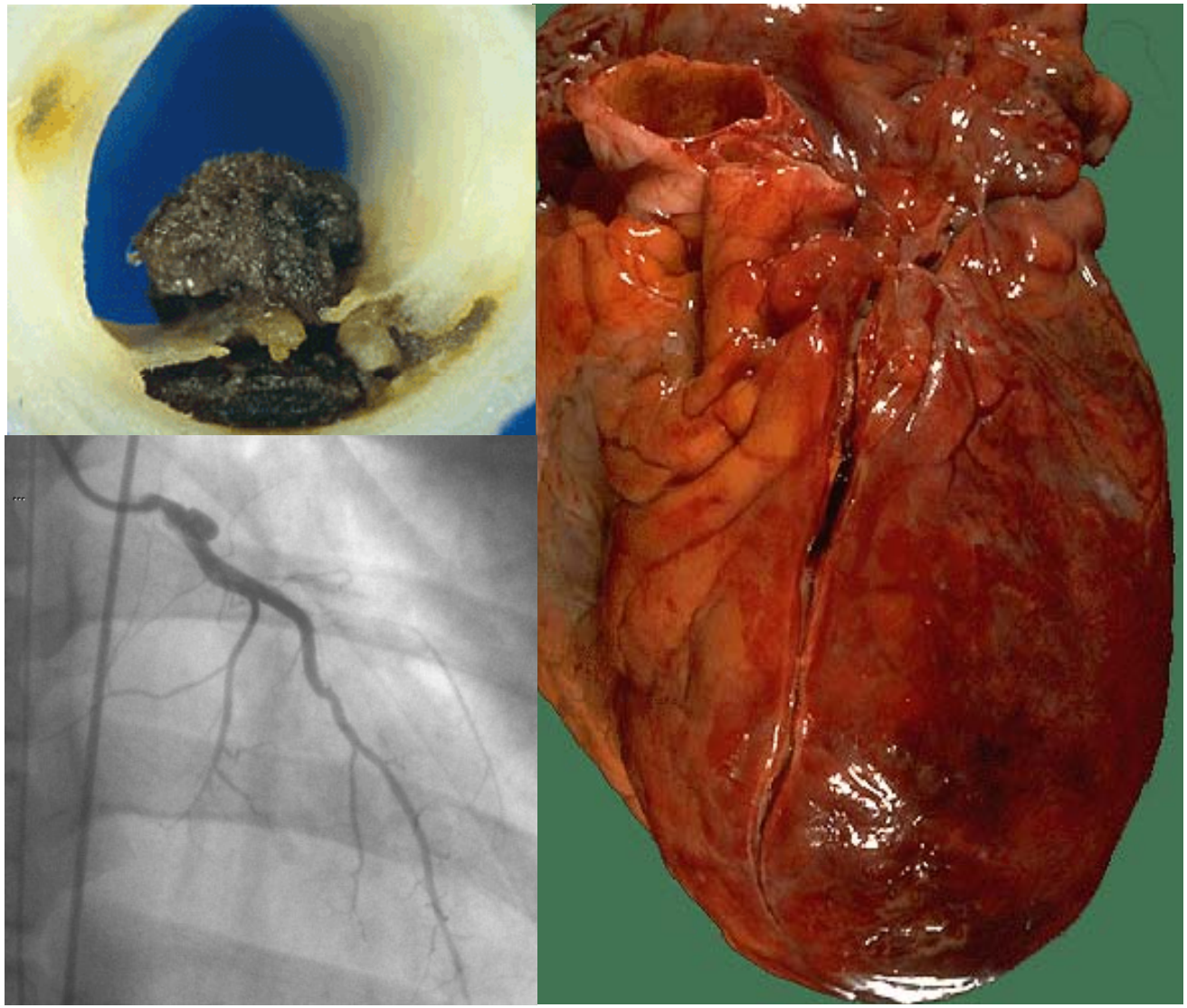


† FDA communication December 2004

‡ FDA communication January 2005

McMurray et al. Am Heart J 2006

Maximising RAS blockade after acute MI



VALIANT

The NEW ENGLAND JOURNAL of MEDICINE

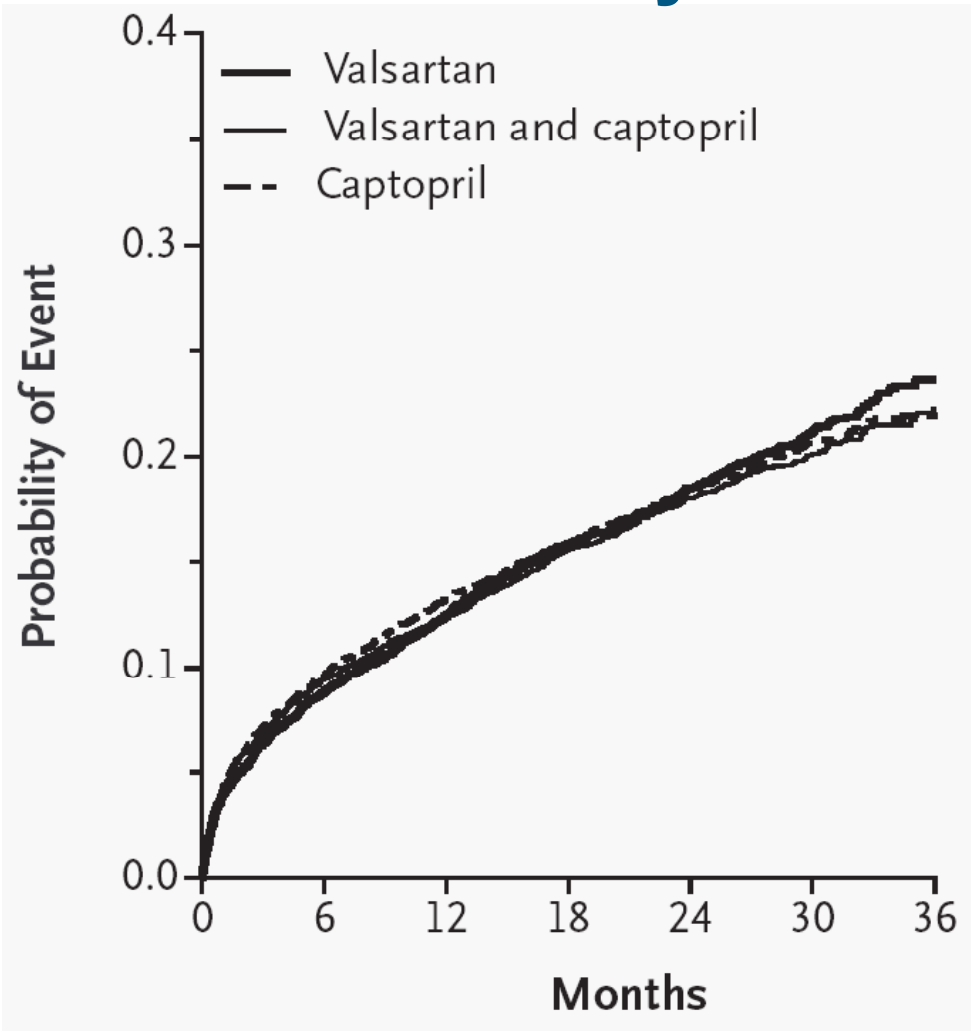
ESTABLISHED IN 1812 NOVEMBER 13, 2003 VOL. 349 NO. 20

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

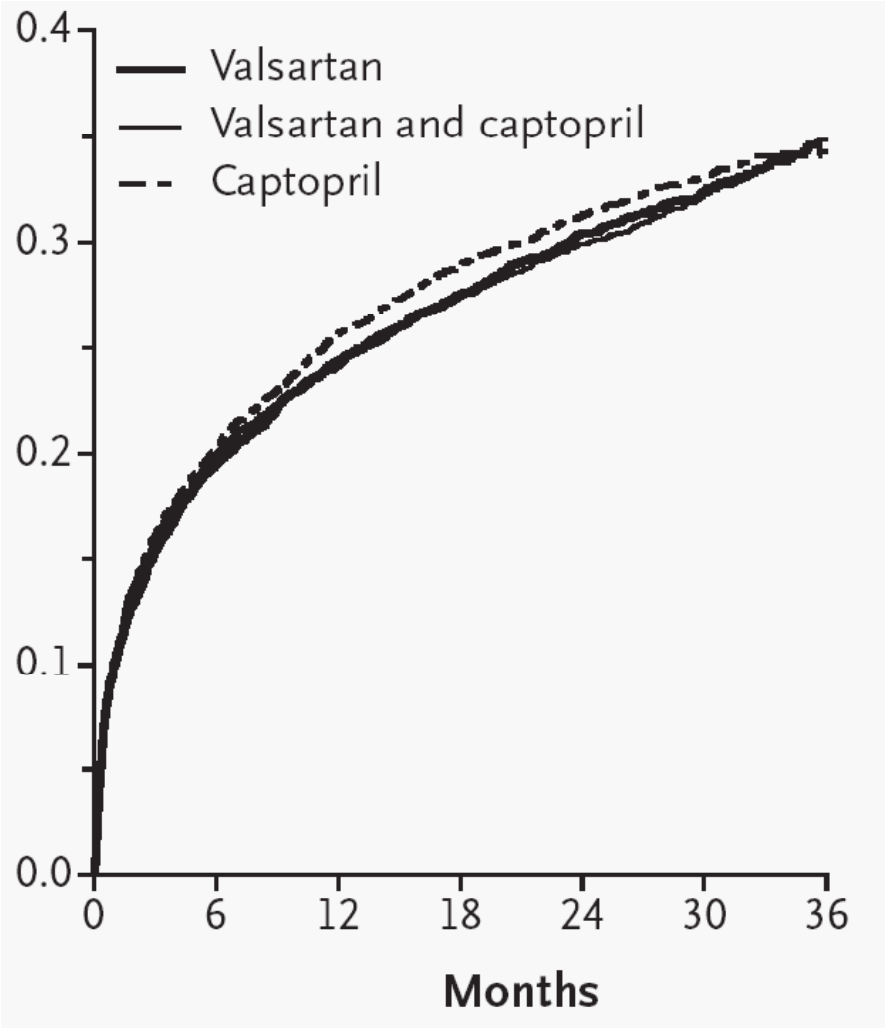
Marc A. Pfeffer, M.D., Ph.D., John J.V. McMurray, M.D., Eric J. Velazquez, M.D., Jean-Lucien Rouleau, M.D., Lars Køber, M.D., Aldo P. Maggioni, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., Frans Van de Werf, M.D., Ph.D., Harvey White, D.Sc., Jeffrey D. Leimberger, Ph.D., Marc Henis, M.D., Susan Edwards, M.S., Steven Zelenkofske, D.O., Mary Ann Sellers, M.S.N., and Robert M. Califf, M.D., for the Valsartan in Acute Myocardial Infarction Trial Investigators*

VALIANT: clinical outcomes

Mortality



CV death, MI or HF



ONTARGET

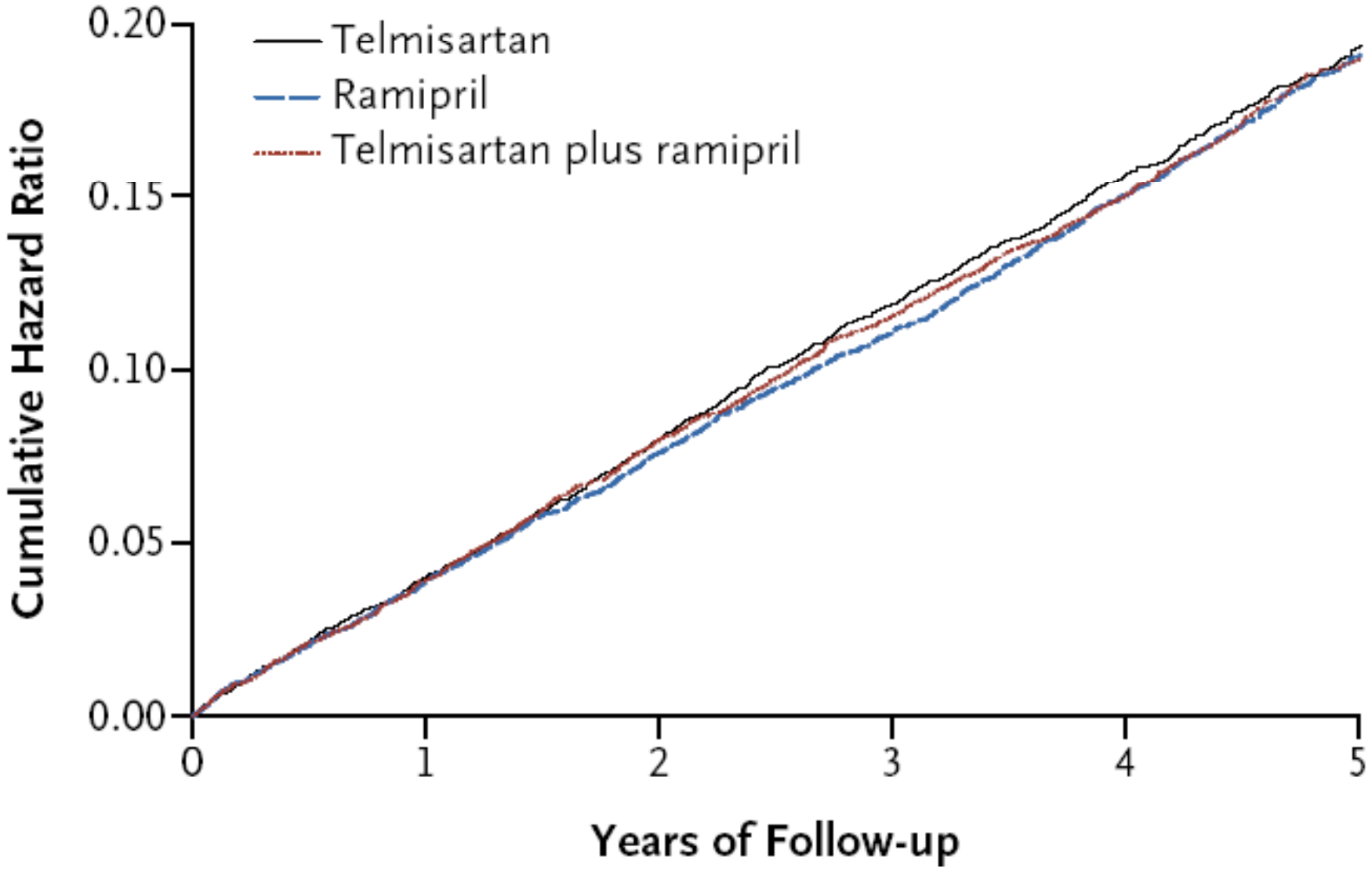
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 10, 2008 VOL. 358 NO. 15

Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

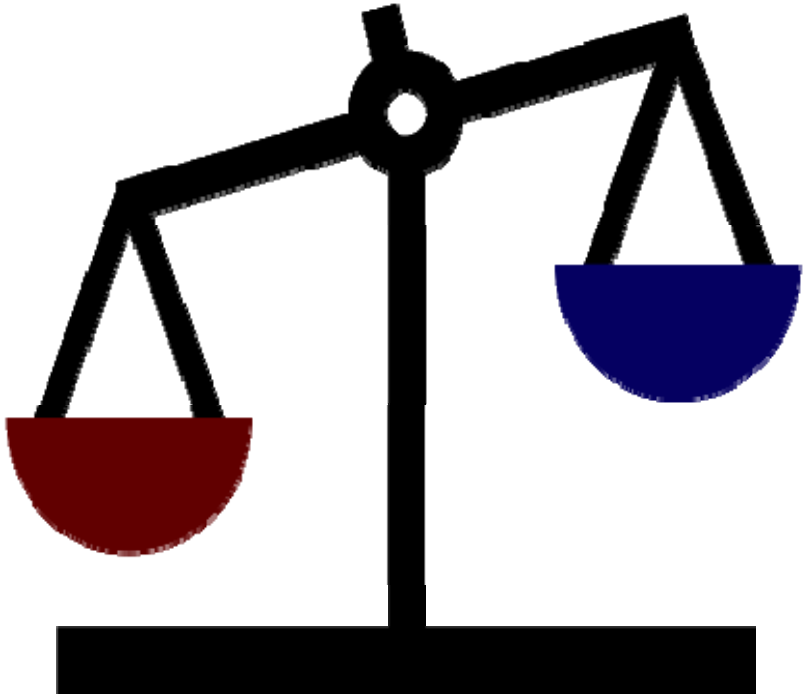
The ONTARGET Investigators*

ONTARGET: Primary endpoint



More intense RAS inhibition in ONTARGET: did we reach the limit?

No clinical benefit



More adverse events

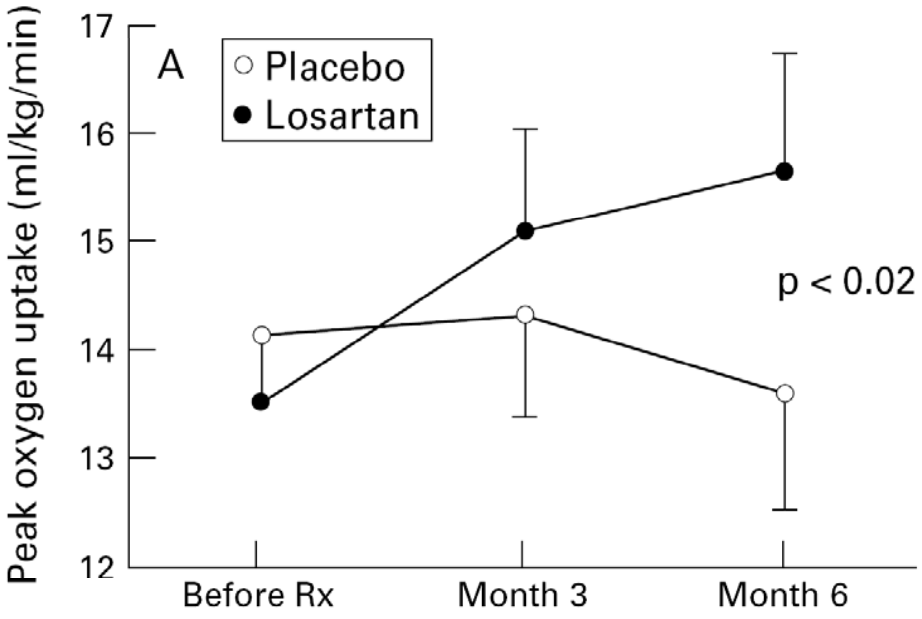
Why is CHARM (and Val-HeFT) different from VALIANT and ONTARGET?

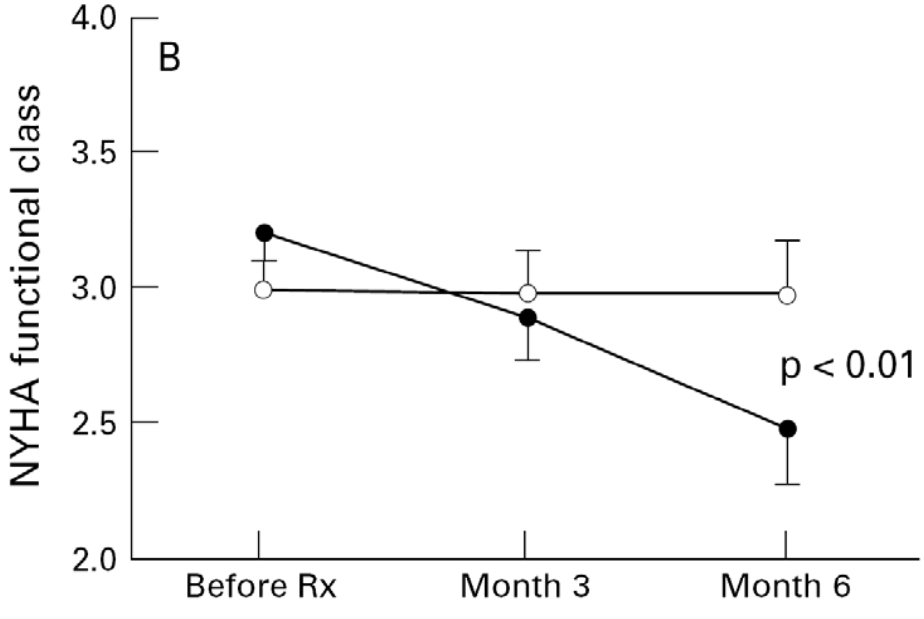
Is heart failure different?

CHF: losartan added to ACE-I

33 patients, severe CHF, maximum dose of ACE-I, randomized to placebo or losartan 50mg

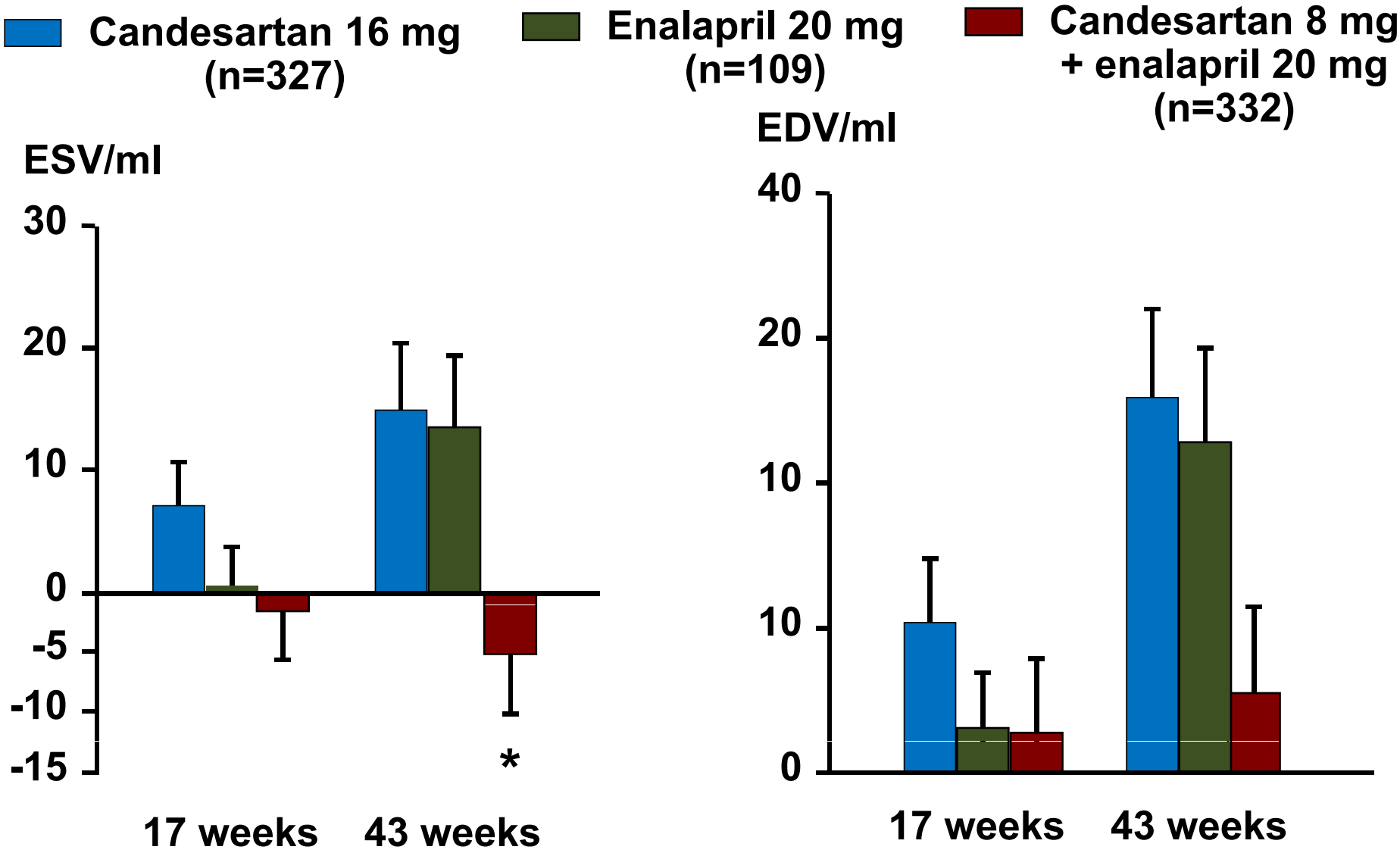
Mean daily dose (losartan/placebo group):
captopril 175/115mg; enalapril 36/28mg





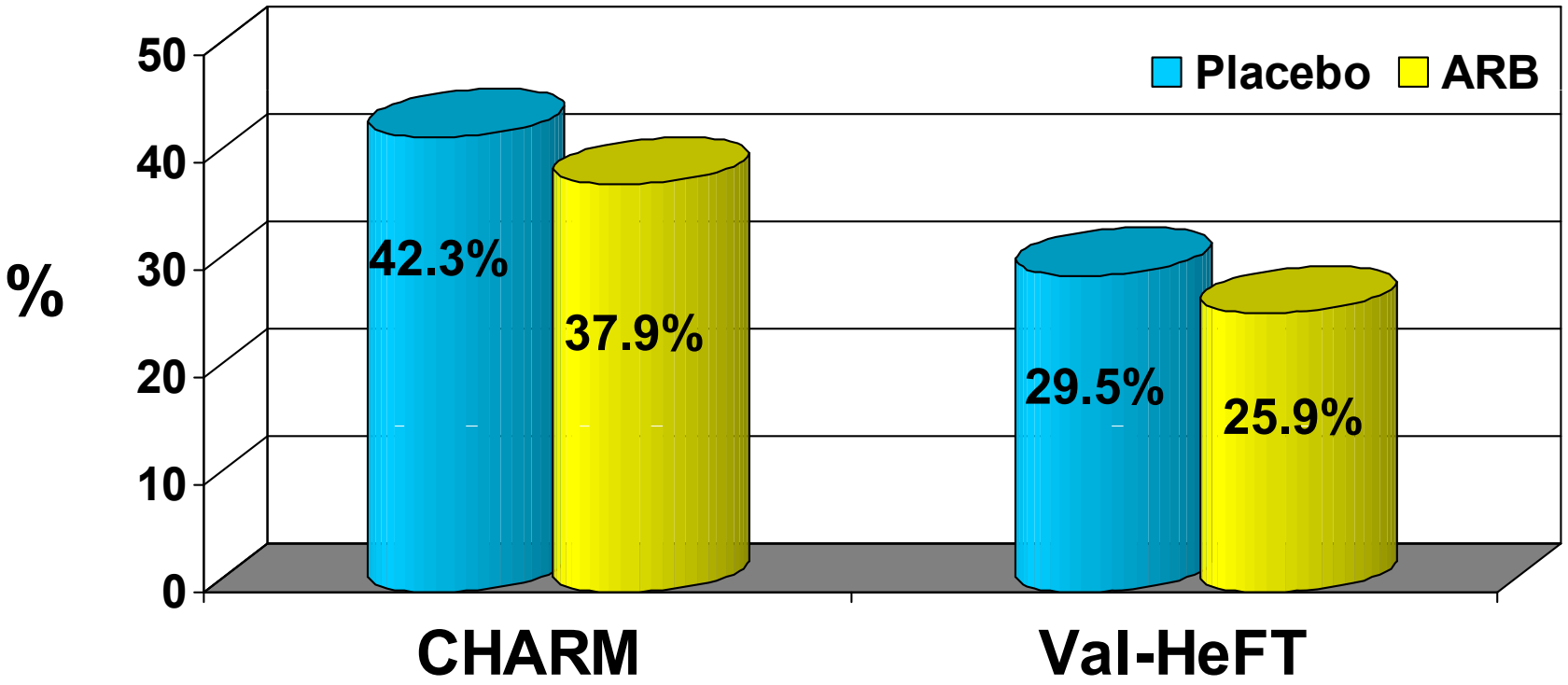
Hamroff et al Circulation1999

RESOLVD: Change in LV volumes



CHARM-Added *vs.* Val-HeFT

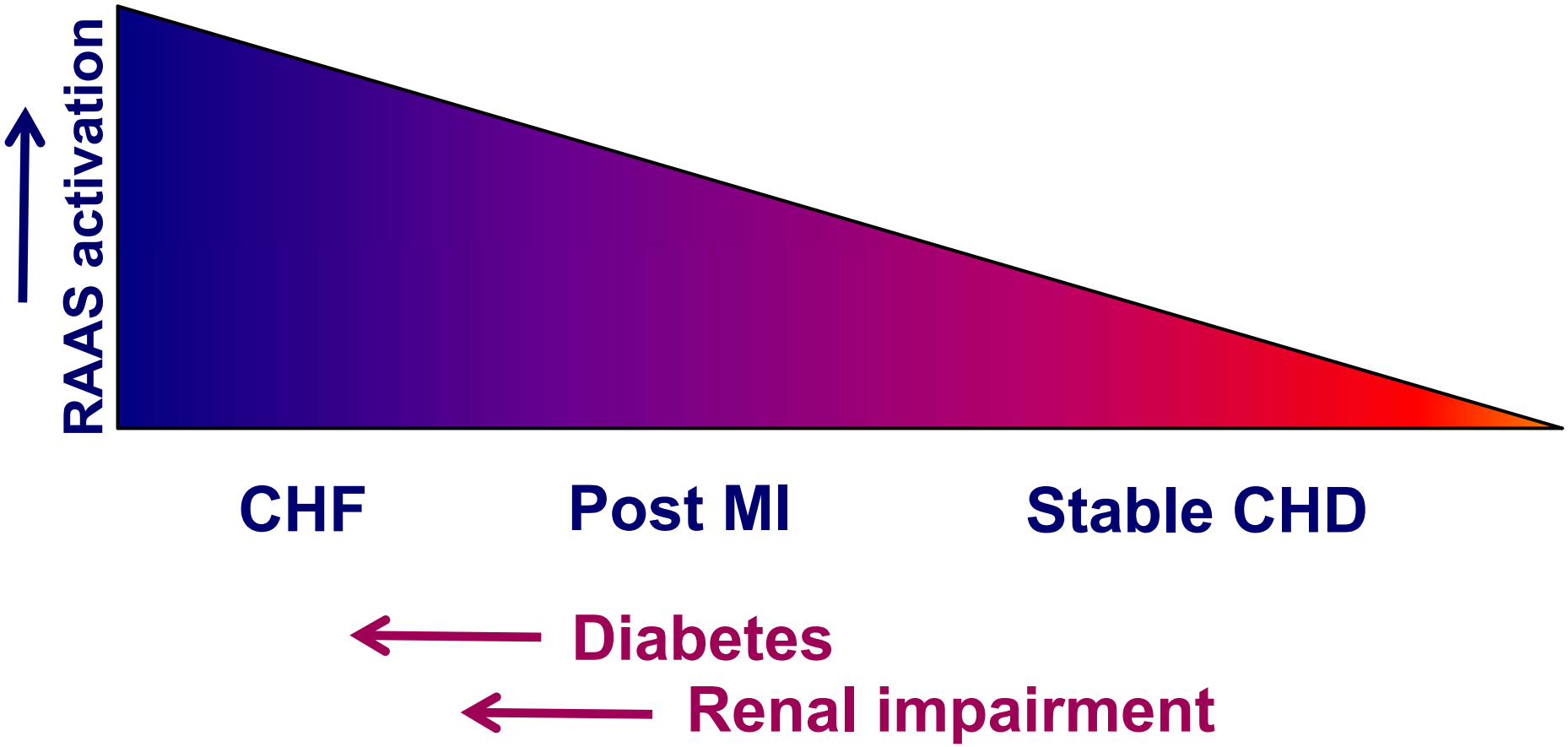
CV death or HF hospitalisation

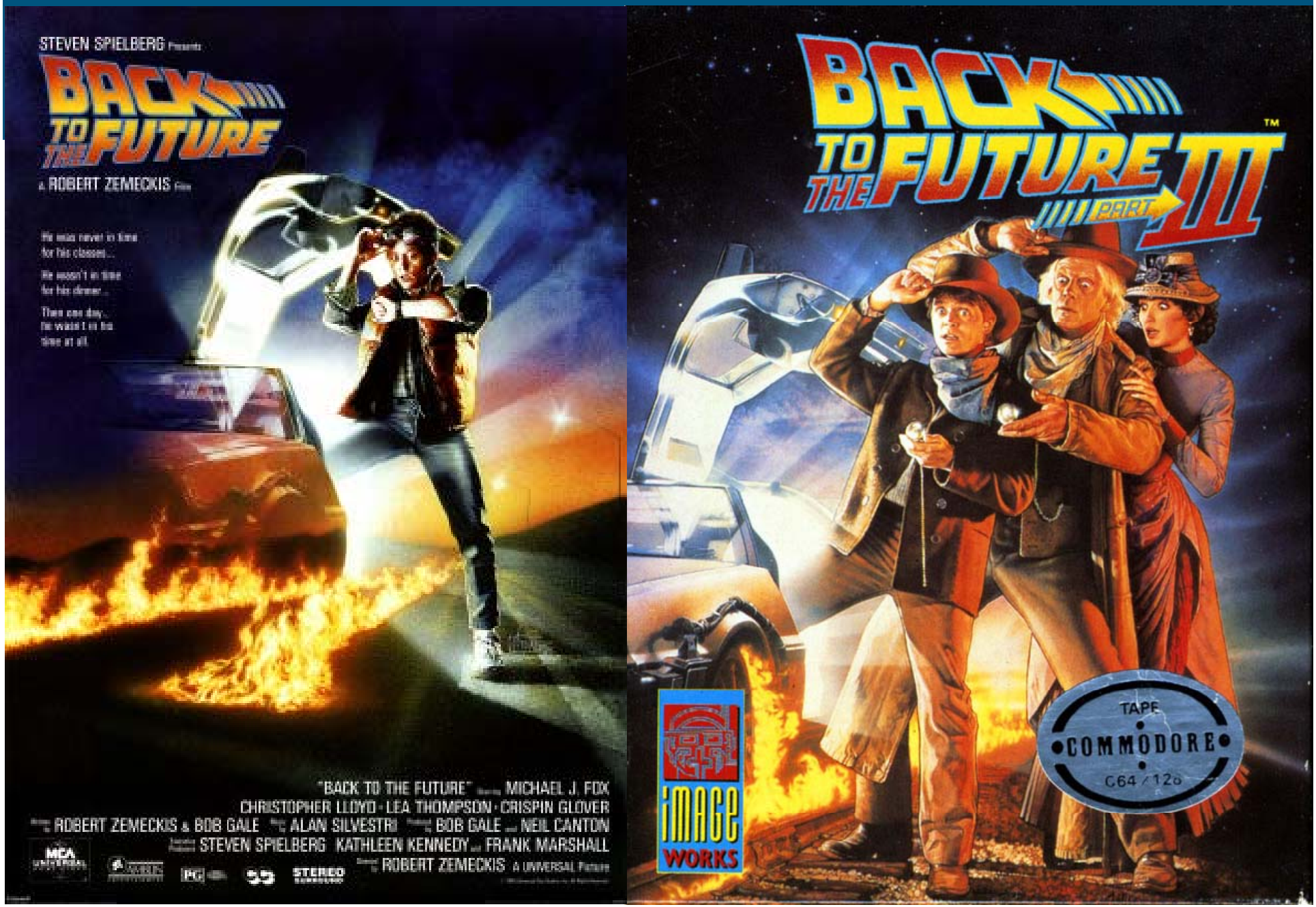


CHARM
HR 0.85
95% CI 0.75-0.96
P=0.011

Val-HeFT
HR 0.86
95% CI 0.77-0.95
P=0.004

Hypothesis: effectiveness of RAAS blockade



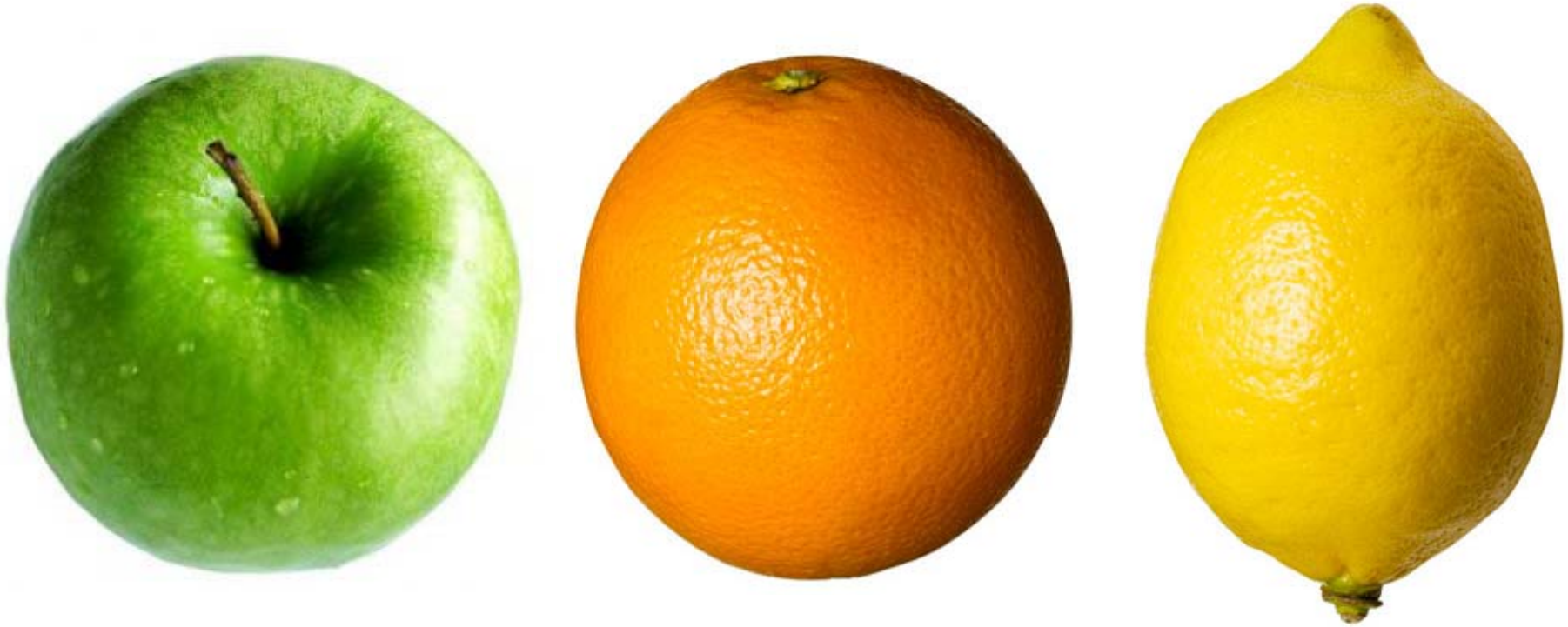

STEVEN SPIELBERG Presents
BACK TO THE FUTURE
A ROBERT ZEMECKIS Film
He was never in time for his classes...
He wasn't in time for his dinner...
Then one day... he wasn't in time at all.
"BACK TO THE FUTURE" Starring MICHAEL J. FOX
CHRISTOPHER LLOYD · LEA THOMPSON · CRISPIN GLOVER
Written by ROBERT ZEMECKIS & BOB GALE Music by ALAN SILVESTRI Produced by BOB GALE and NEIL CANTON
Executive Producer STEVEN SPIELBERG KATHLEEN KENNEDY and FRANK MARSHALL
Directed by ROBERT ZEMECKIS A UNIVERSAL Picture
MCA UNIVERSAL
PG
55
STEREO
BACK TO THE FUTURE PART III ™
image WORKS
TAPE
COMMODORE
C64 / 128

Why a renin inhibitor?

- **Was the original aim in the development of RAAS inhibitors!**
- **Renin is the rate limiting enzyme in RAAS cascade**
- **Highly specific for its substrate (angiotensinogen)**
- **Difficulty in developing a potent and orally active (absorbed) inhibitor**

RAS blockers

ACE inhibitor **ARB** **Renin inhibitor**



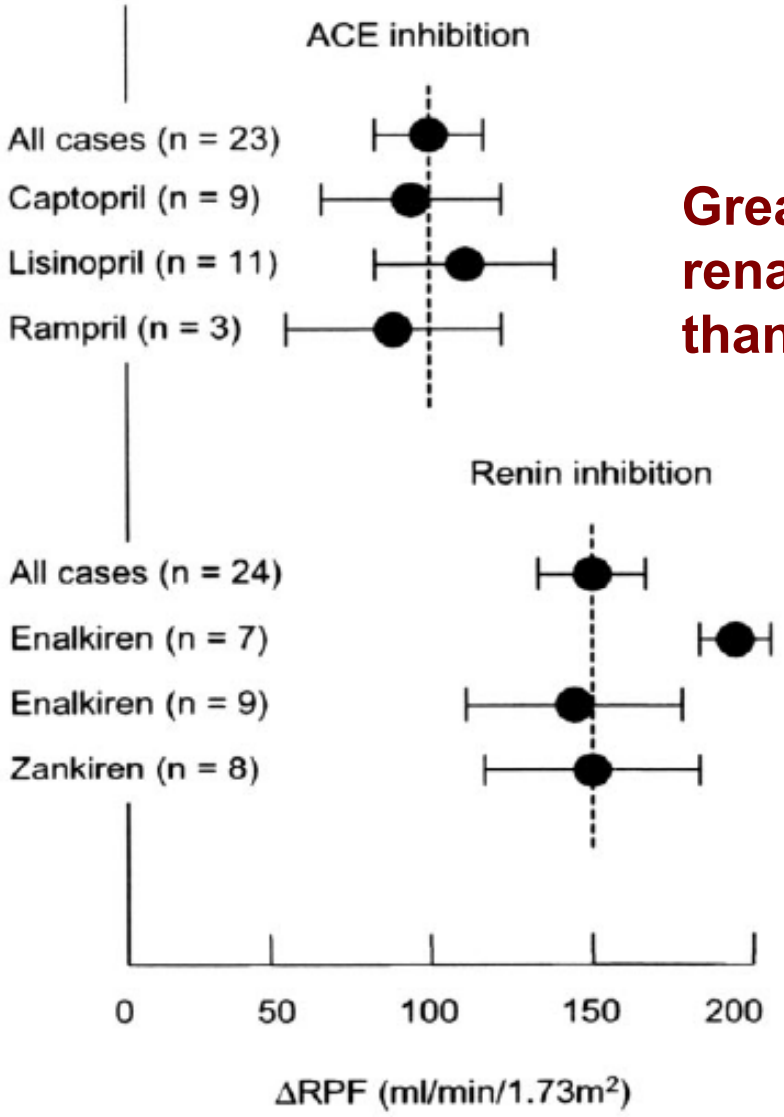
RAS blockers

ACE inhibitor **ARB** **Renin inhibitor**

Profile of action of different inhibitors of inhibitors of the RAAS

DRUG	Renin	Angiotensin I	Angiotensin II
ACE inhibitor	↑	↑	↓
ARB	↑	↑	↑
Renin inhibitor	↓	↓	↓

Tissue selectivity? Renal blood flow



Greater increase in renal blood flow with RI than with ACE-I

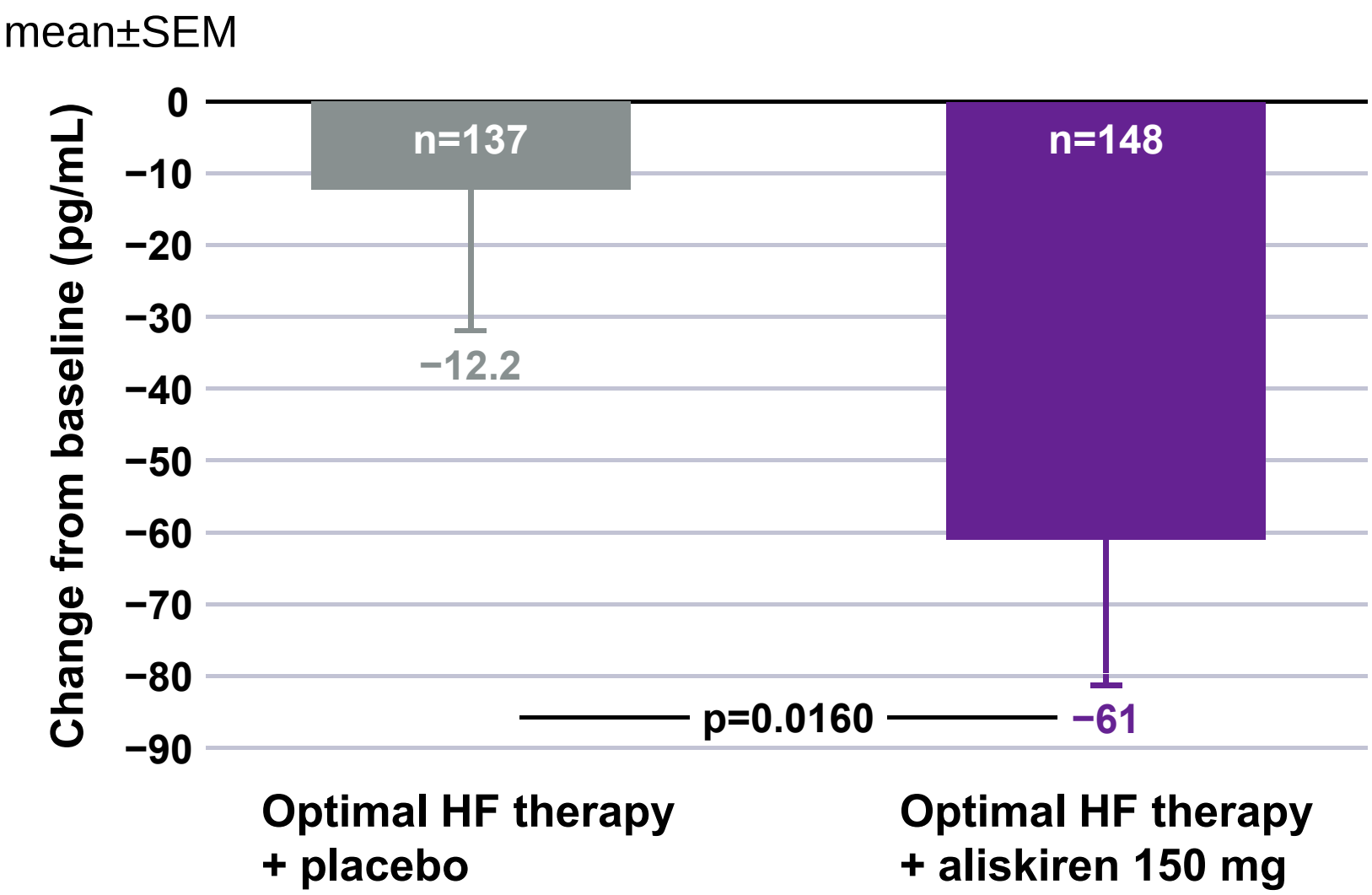
Fisher & Hollenberg

J Am Soc Nephrol 16: 592–599, 2005

ALOFT: Why add a renin inhibitor to an ACE inhibitor?

- RAAS blockade is beneficial in heart failure (HF)
- ACE inhibitors and ARBs induce loss of negative feedback inhibition of renin secretion
- Consequent compensatory rise in renin and other downstream components of RAAS may result in loss of RAAS blockade
- Direct renin inhibitors should block this compensatory response to loss of negative feedback
- ALOFT tested the safety and efficacy of adding a direct renin inhibitor in patients with HF already treated with an ACE inhibitor (or ARB) and beta-blocker

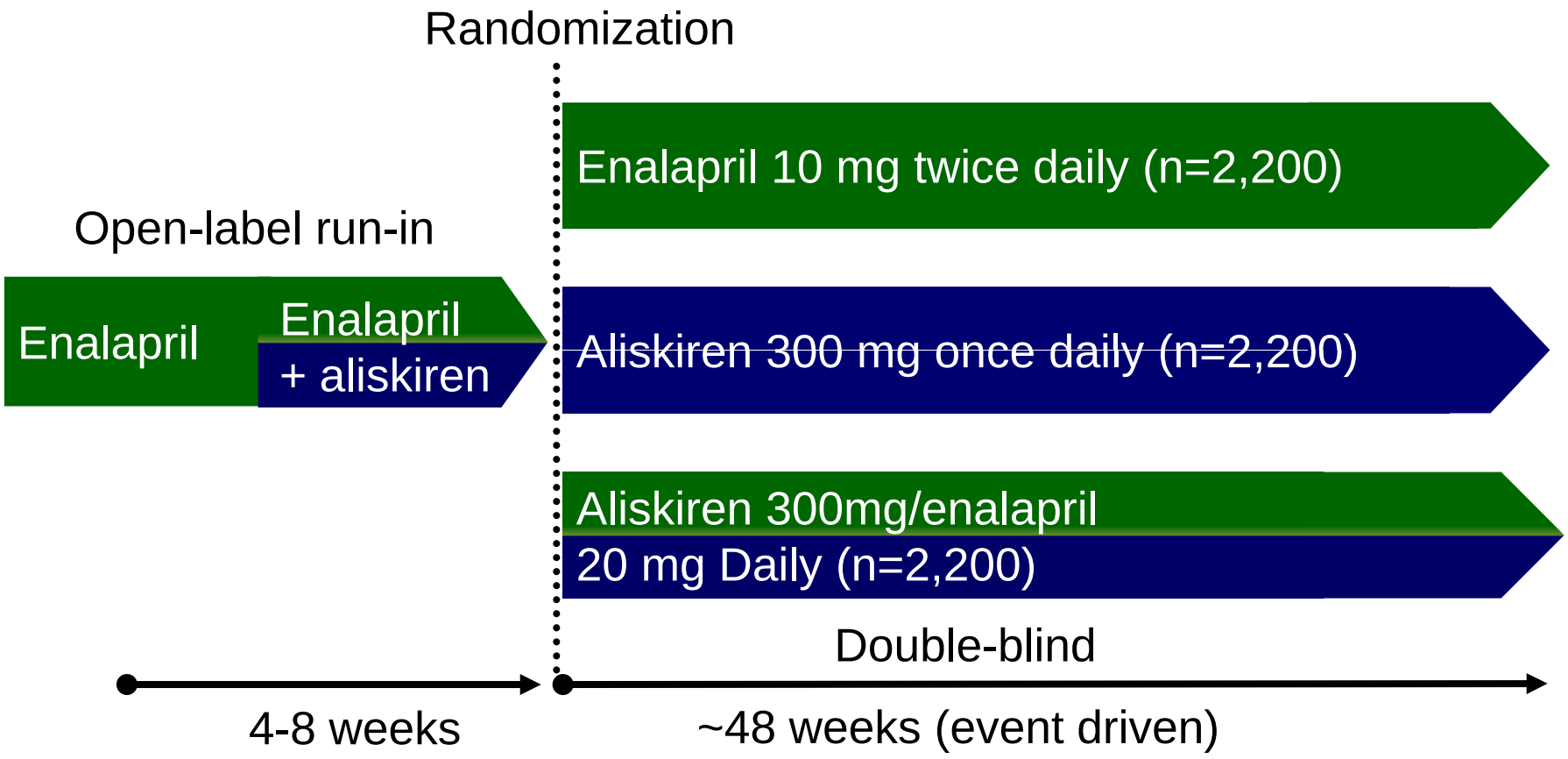
ALOFT findings: significant reduction in BNP levels



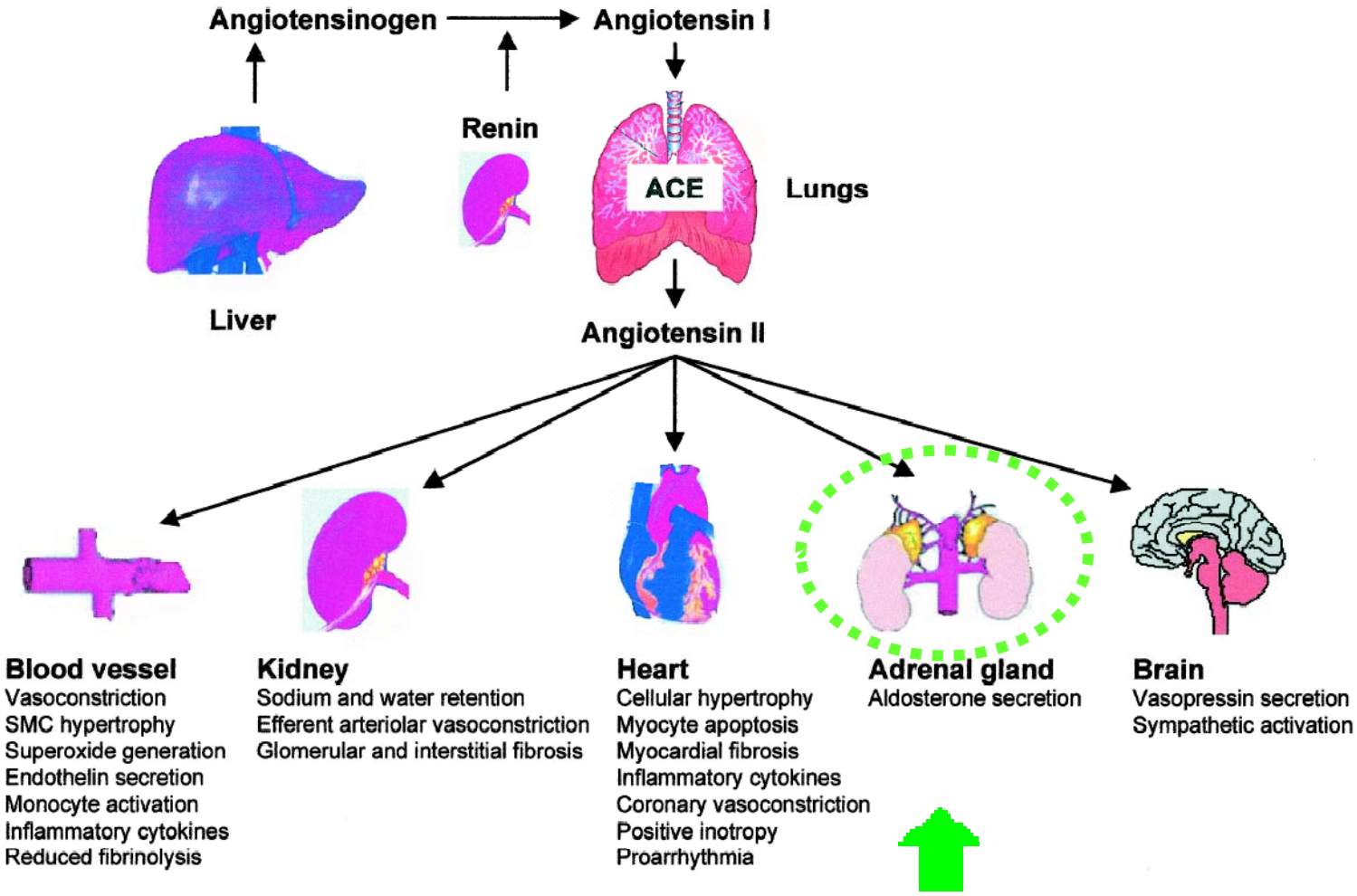
ATMOSPHERE: design overview

Primary outcome: CV death or heart failure hospitalization

(event driven: 2162 patients)

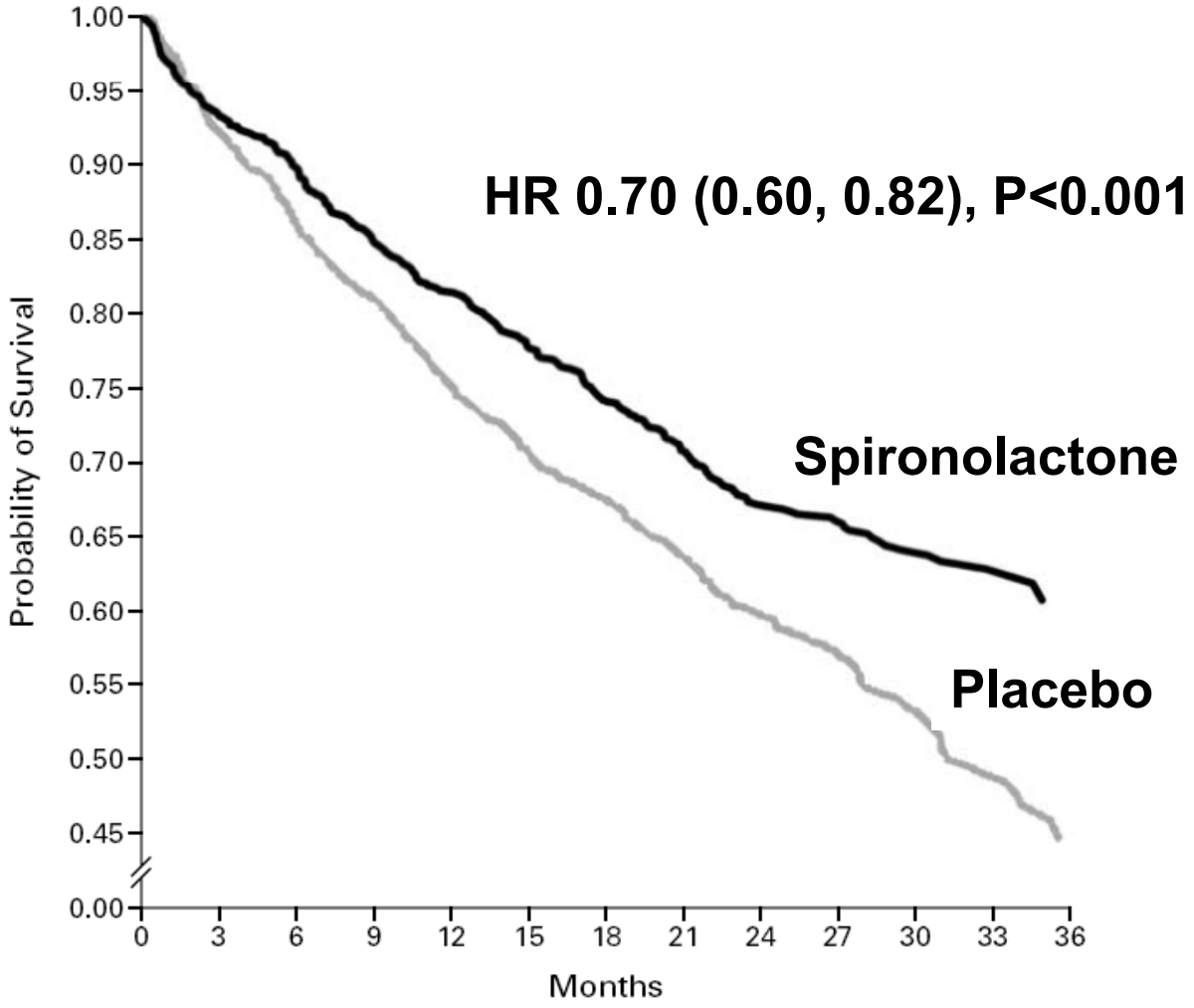


RAAS inhibition in CHF



RALES

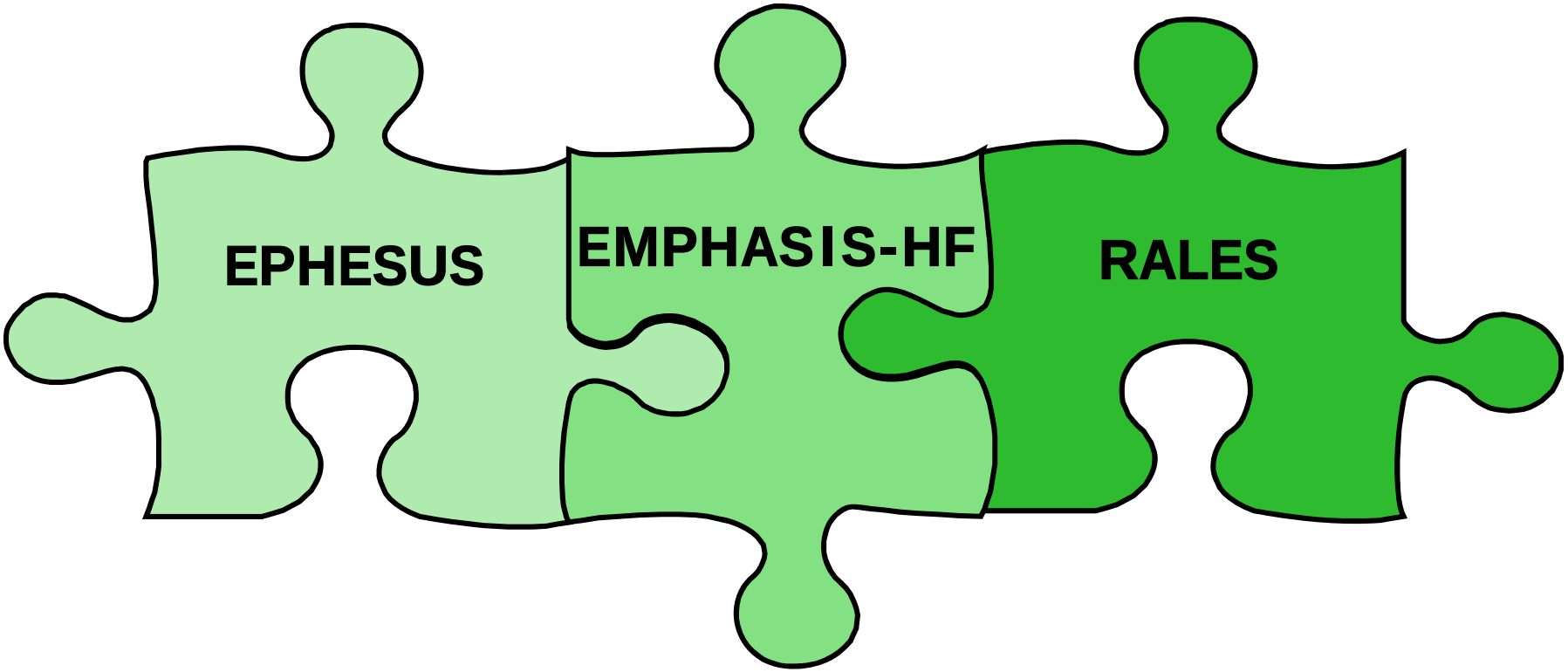
24 months follow-up
94.5% ACE-I
10.5% Beta-blocker



No. at Risk													
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

The missing piece of the aldosterone-antagonist jigsaw

LVSD/HF after AMI **Mild CHF** **Severe CHF**

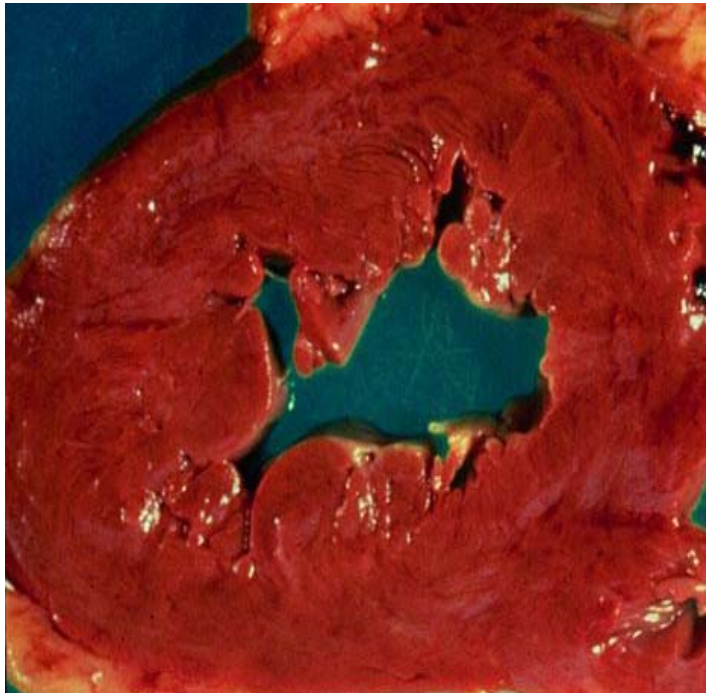


EMPHASIS-HF

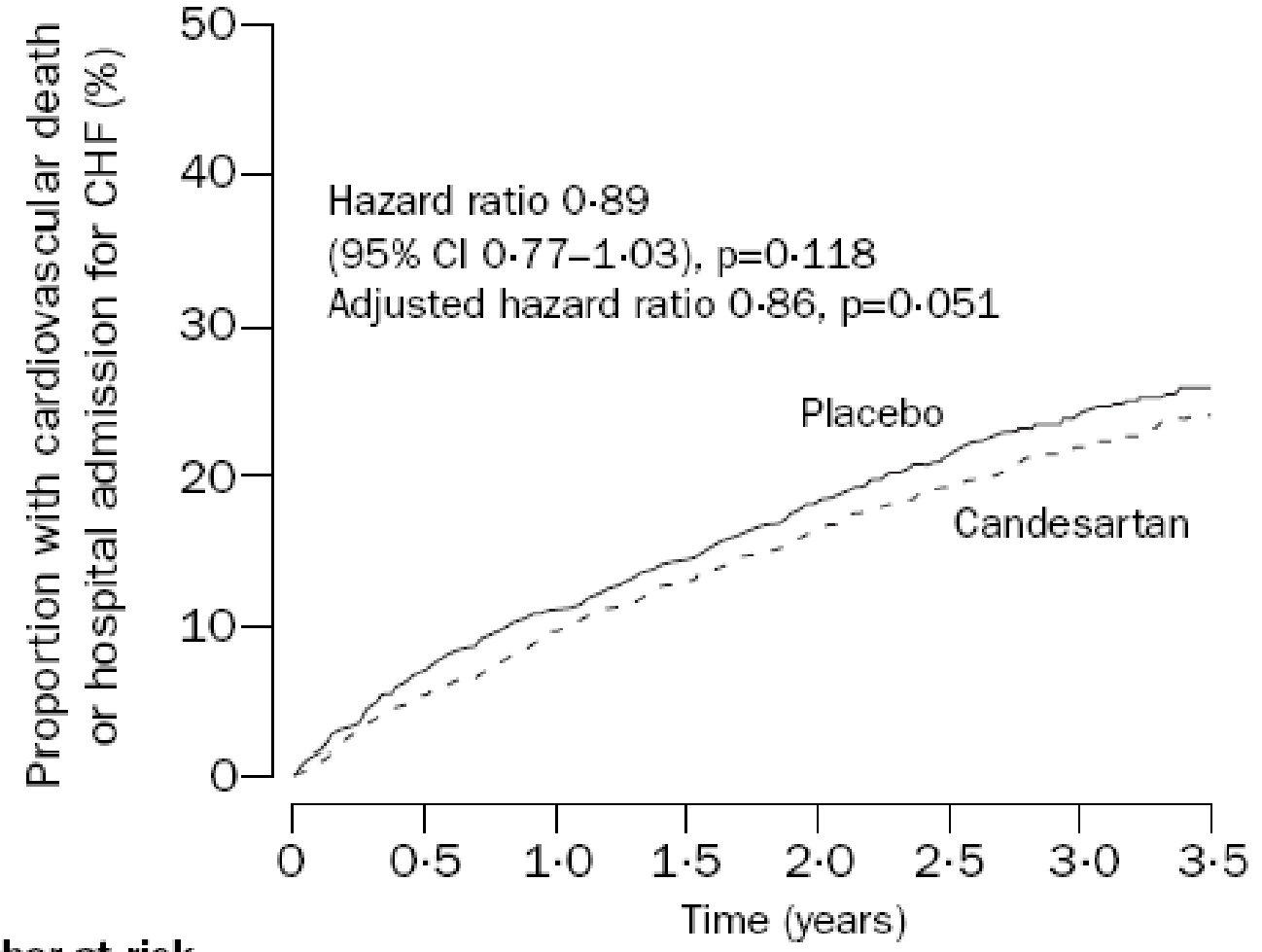
- **Hypothesis:** Aldosterone antagonism with eplerenone will be of benefit in patients with mild HF and LV systolic dysfunction
- **Population:** ~3100 patients ≥60 years with NYHA II HF and LVEF ≤30%(or LVEF 31-35% and QRS duration >130 msec.). CV hospitalisation within 90 days (or BNP ≥250 pg/ml or NT-proBNP ≥500 pg/ml in men/ ≥750 pg/ml in women.
- **Intervention:** Eplerenone (50 mg) vs Placebo
- **Primary endpoint:** CV death or HF hospitalisation – event driven (813 events)
- **Status:** Randomisation started Q2 2006

HF with preserved EF

We still do not have evidence-based treatment



CHARM-Preserved



Number at risk

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

Are ARBs beneficial in HF-PEF?

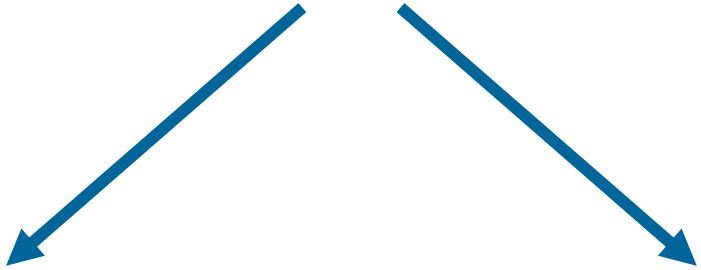
i-PRESERVE

Irbesartan in Heart Failure with **Preserve**d Systolic Function

I-PRESERVE: Inclusion Criteria

Age ≥60 years

LVEF ≥0.45



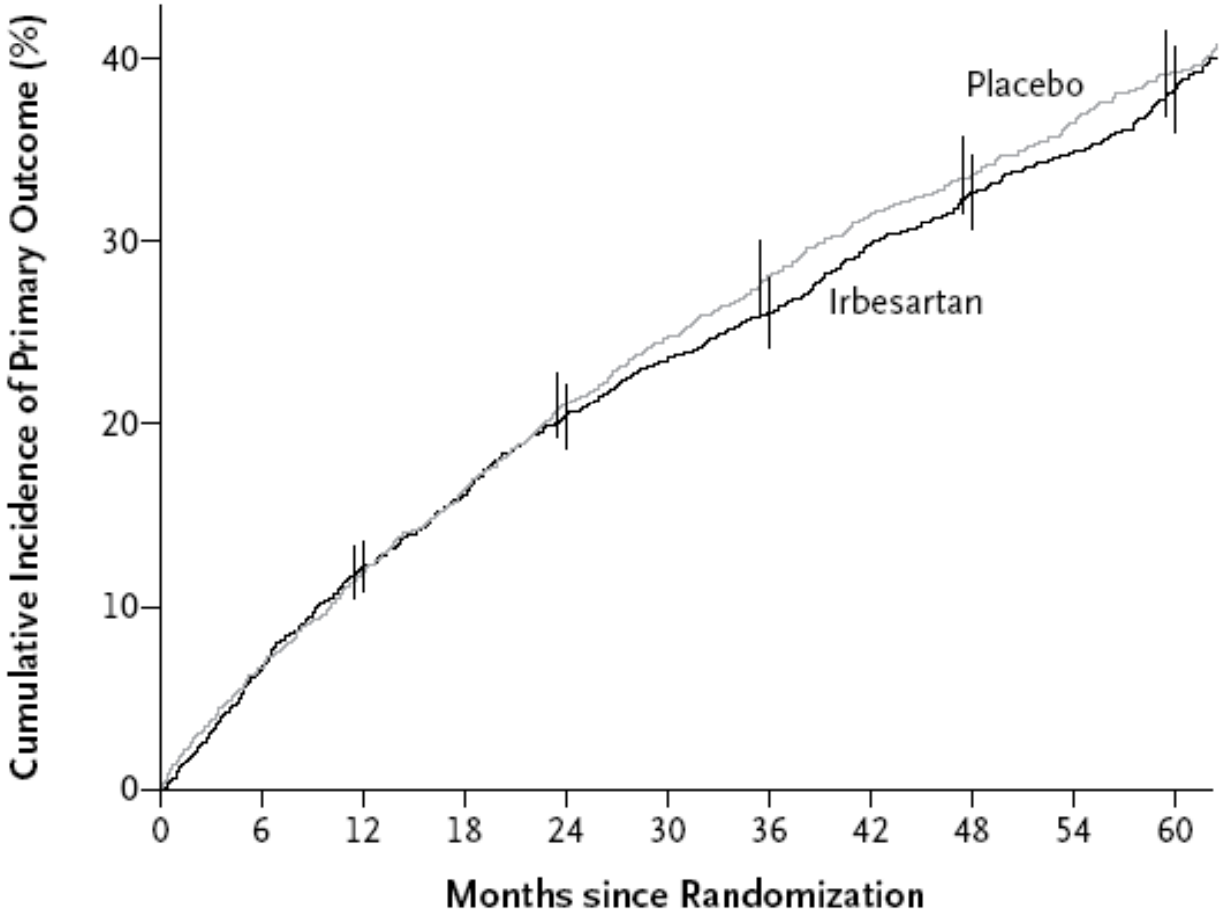
NYHA class II - IV

- **CHF hosp. ≤6 months**

NYHA Class III/IV

- **CXR (p.congestion)**
- **ECG (LVH, LBBB)**
- **echo (LVH, enlarged LA)**

I-PRESERVE

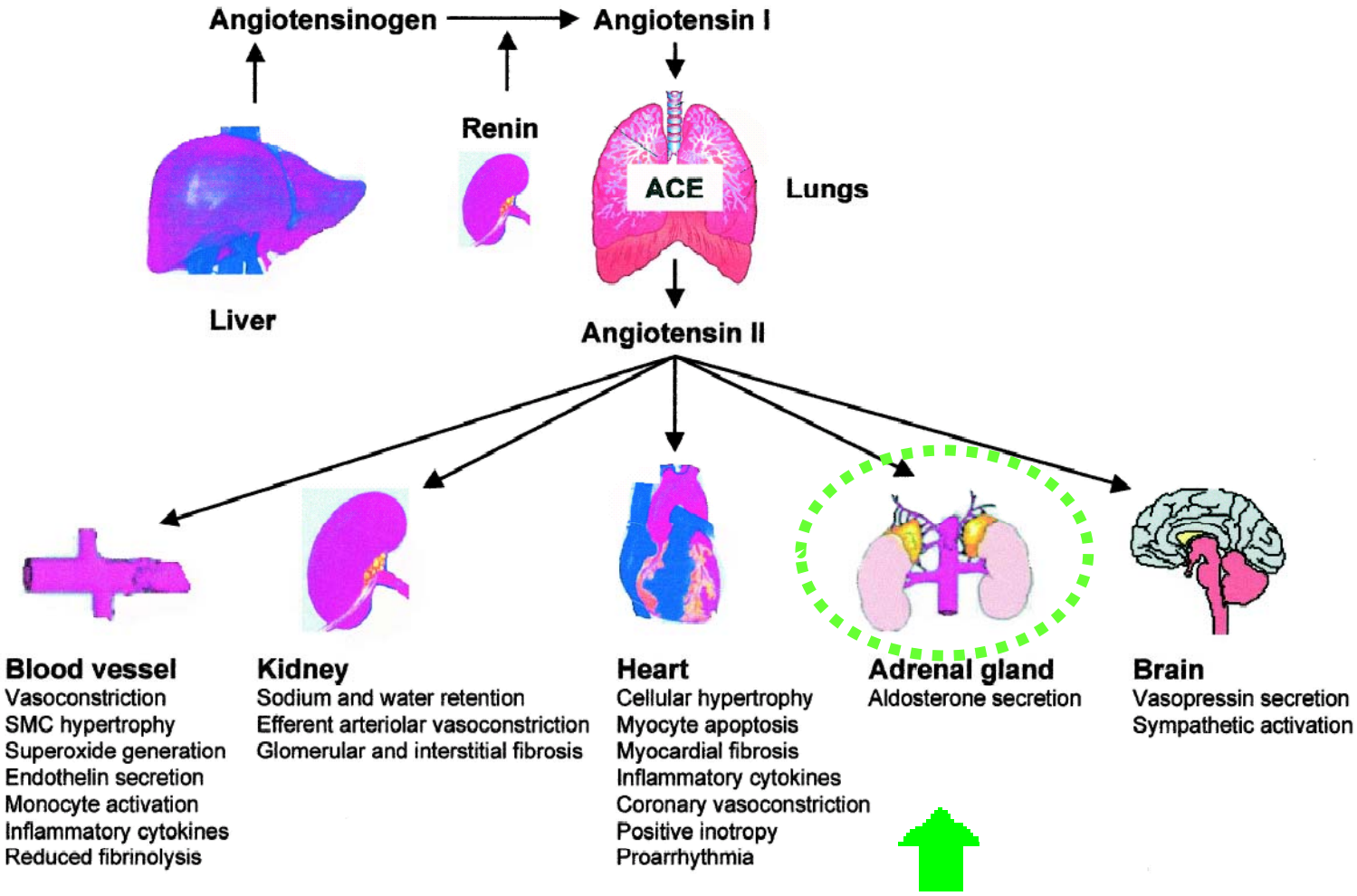


No. at Risk											
Irbesartan	2067	1929	1812	1730	1640	1569	1513	1291	1088	816	497
Placebo	2061	1921	1808	1715	1618	1539	1466	1246	1051	776	446

Why did CHARM-Preserved and I-PRESERVE differ?

- They may not be different – p value in CHARM-Preserved was not significant
- The patients were different – CHARM had patients with a LVEF 41-45% (“mild systolic dysfunction”?)
- The treatment was different – different ARB; dose may not have been equivalent - 8mg candesartan=150mg irbesartan in clinical pharmacology studies (Belz et al J CV Pharmacol 2002) and reduction in BP was 6.9/2.9 mmHg in CHARM-Preserved vs. 3.6/1.9 mmHg in I-PRESERVE.

RAAS inhibition in CHF



Aldosterone antagonist for HF-PEF?

Funded by the NHLBI

Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist

TOPCAT

- **Hypothesis:** Spironolactone will reduce morbidity and mortality in mild HF and preserved LV function
- **Population:** 4500 patients >50 yrs with NYHA II HF (and admission or elevated BNP), EF ≥45%
- **Intervention:** Spironolactone (15-45 mg) vs placebo
- **Primary endpoint:** CV death, RCA, HF hospitalisation
- **Status:** Recruitment started 2008; slow; expected completion uncertain

RAAS blockade: past present and future

Robert Tigerstedt

The kidney and circulation

Niere und Kreislauf.[1]

Von

Robert Tigerstedt und **P. G. Bergman.**

(Aus dem physiologischen Laboratorium des Carolinischen medico-chirurgischen Instituts in Stockholm.)

Einleitung.

Der geistreiche Gedanke Brown-Séquard's, dass verschiedene Organe dem Blute Stoffe abgeben, welche nicht zu den gewöhnlichen Dissimilationsproducten gehören, sondern durch eine specifische Thätigkeit der Gewebe gebildet werden und für die Gesammtleistungen des Körpers eine durchgreifende Bedeutung haben, hat sich durch die zahlreichen hierüber angestellten Untersuchungen aufs Glänzendste bewährt.

In Bezug auf die Niere suchten Brown-Séquard und d'Arsonval im Jahre 1892 nachzuweisen, dass sie, ausser ihrer Aufgabe als Excretionsorgan, noch durch eine „innere Secretion" der oben definirten Art die Vorgänge im Körper mächtig beeinflusste.

Scand Arch Physiol 1898; 8: 223-71