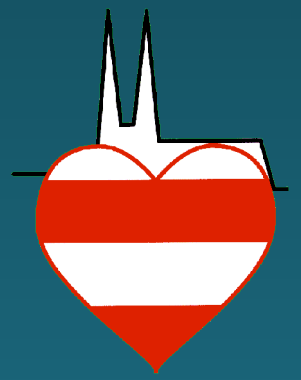
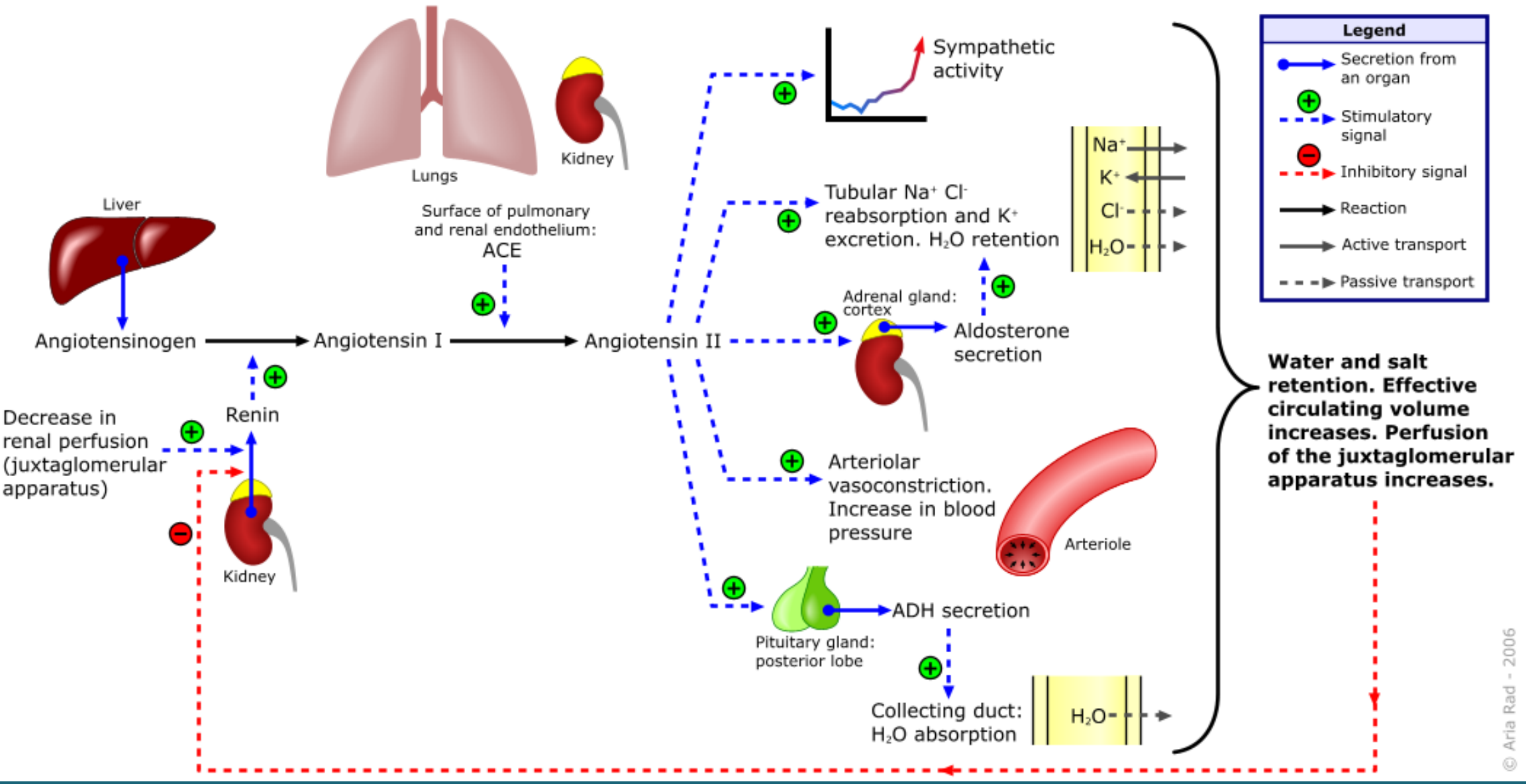
Stříbrná svatba srdečního selhání a blokády systému RAAS

Jiří Vítovec

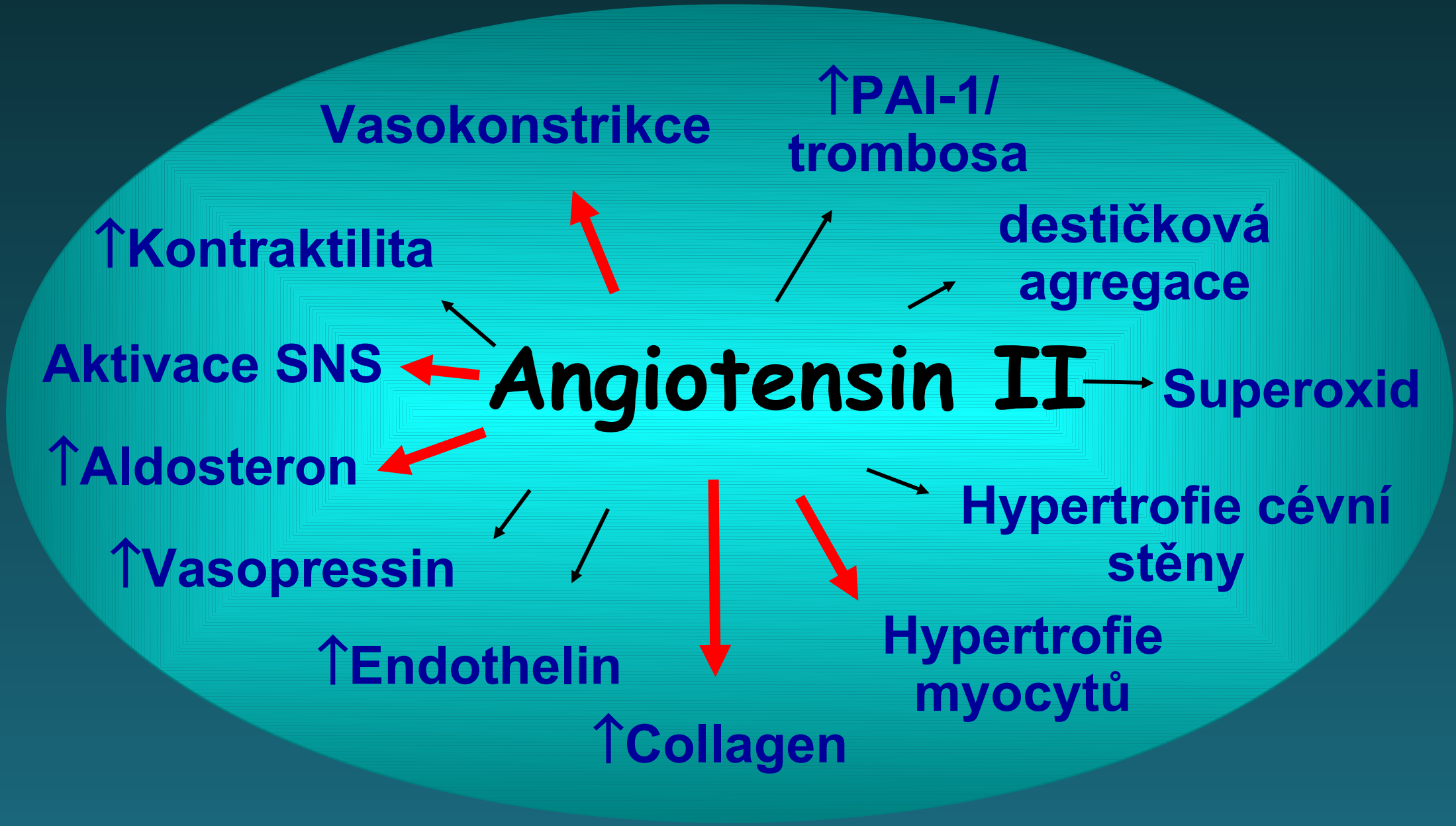
LF MU a ICRC FN u sv.Anny



Renin-angiotensin-aldosterone system



Patofysiologický efekt angiotensinu II



Modified after Burnier & Brunner Lancet 2000


JULY 27, 1987
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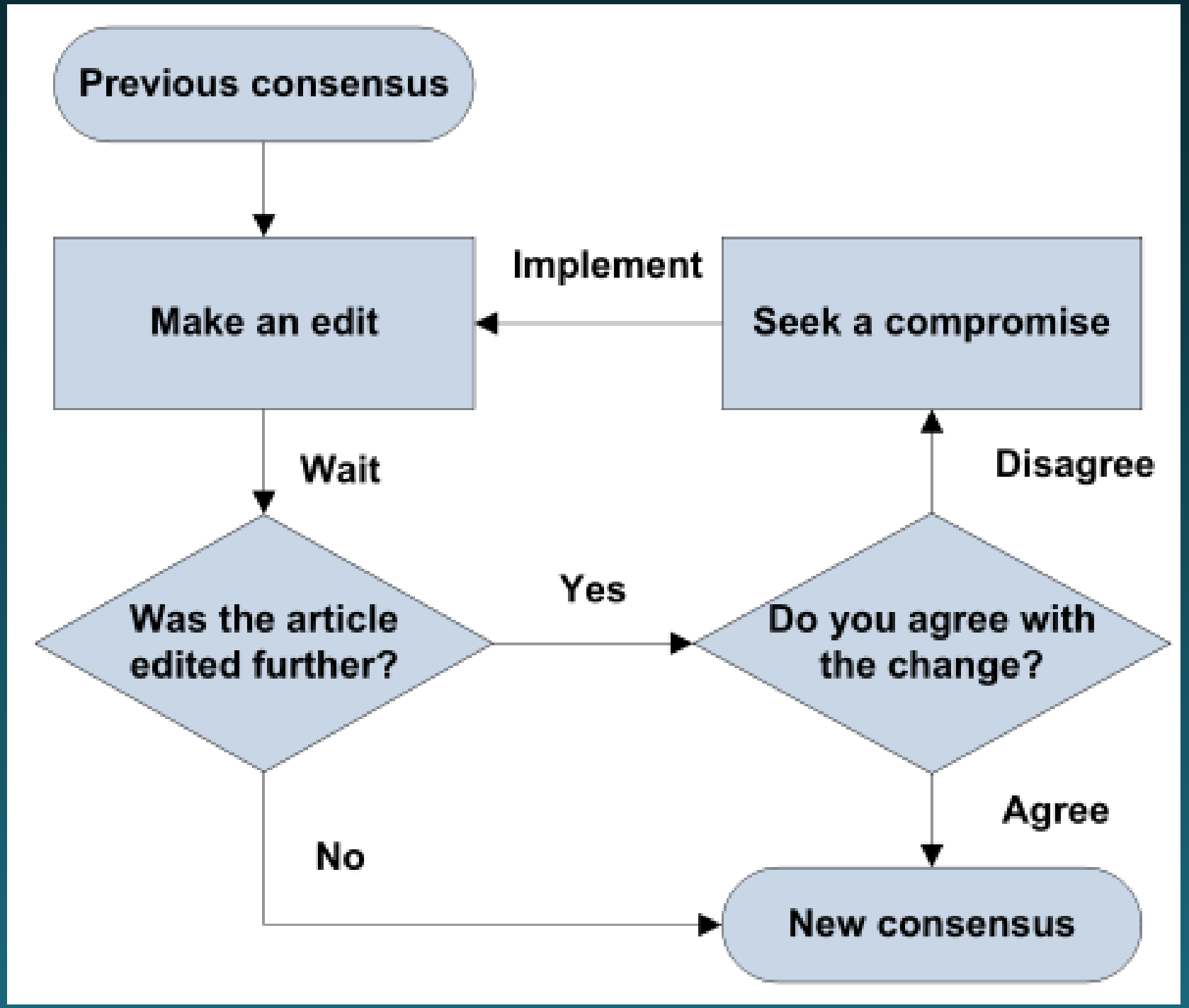
TIME
Poindexter Takes the Rap
Gorbachev's Revolution
Can He Make It Work?
Is the Cold War Fading?


Previous consensus
Make an edit
Implement
Seek a compromise
Wait
Disagree
Was the article edited further?
Yes
Do you agree with the change?
Agree
No
New consensus

The New England
Journal of Medicine

Volume 316 JUNE 4, 1987 Number 23

EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

THE CONSENSUS TRIAL STUDY GROUP*

N Engl J Med 1987;316:1429–35

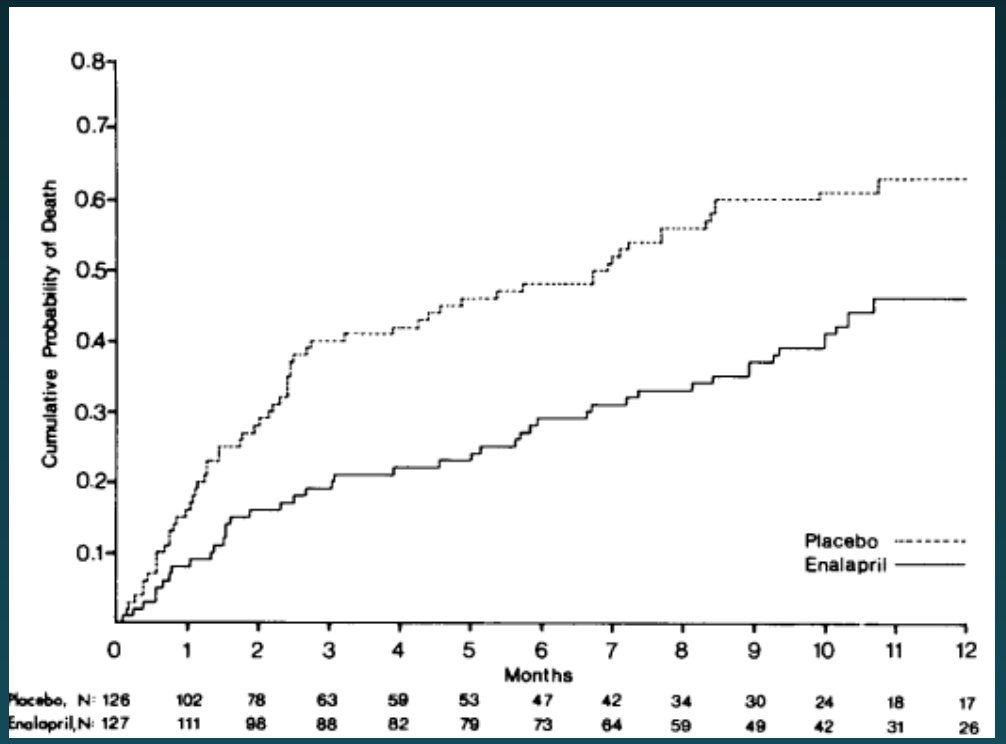
EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

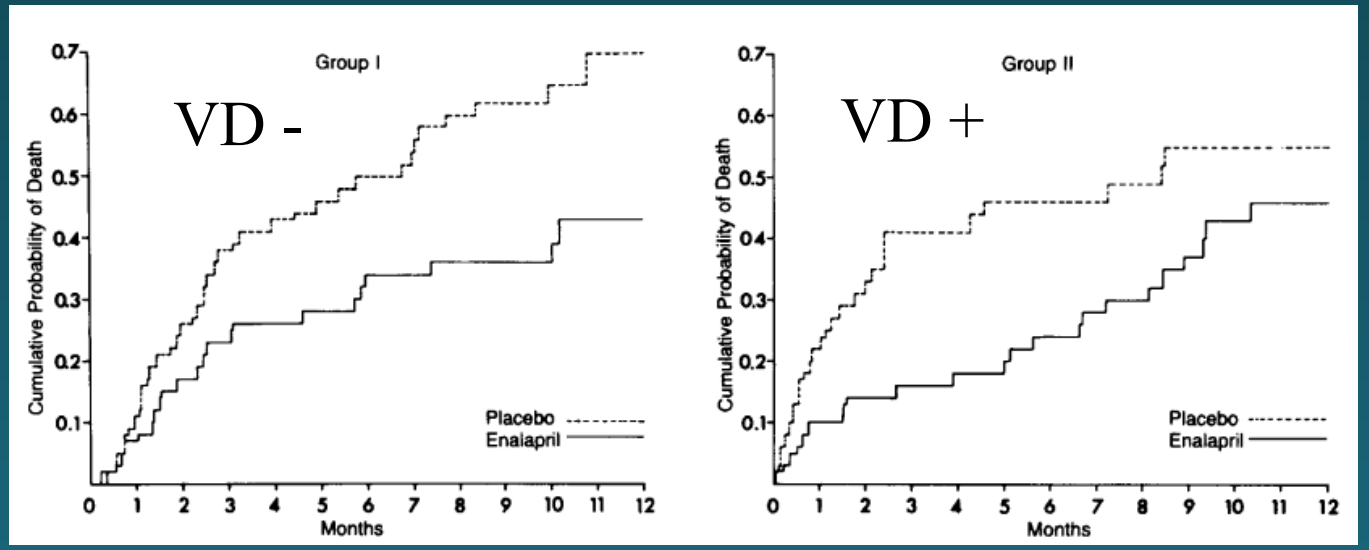
Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

THE CONSENSUS TRIAL STUDY GROUP*

Cílem bylo určit ACE inhibitoru **enalaprilu** (**2.5 to 40 mg** /den) na prognózu těžkého srdečního selhání, randomizováno bylo 253 pacientů dvojitě slepě buď na placebo (n = 126) či enalapril (n = 127).
Konvenční léčba srdečního selhání byla: digitalis, diuretika, včetně **vasodilatancií (nitrates, prazosin, hydralazine**).
Follow-up byl průměrně **188 dní** (od 1 dne do 20 měsíců).
Diagnóza ChSS byla stanovena na základě klinických kriterií: anamnéza srdečního onemocnění se symptomy dušnosti, únavy, dále známkami retence tekutin při vyloučení primárního plicního onemocnění
Nemocní byli klidově symptomatičtí (**NYHA IV**).
Srdeční velikost byla určena RTG > 600 ml/ m^2 u mužů (norma <550) a u žen > 550 ml/ m2 (norma <500).

N Engl J Med 1987;316:1429–35

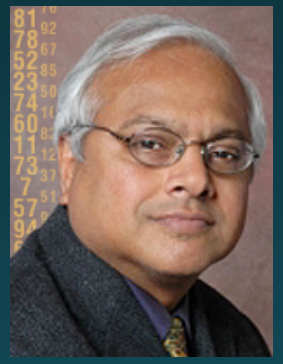




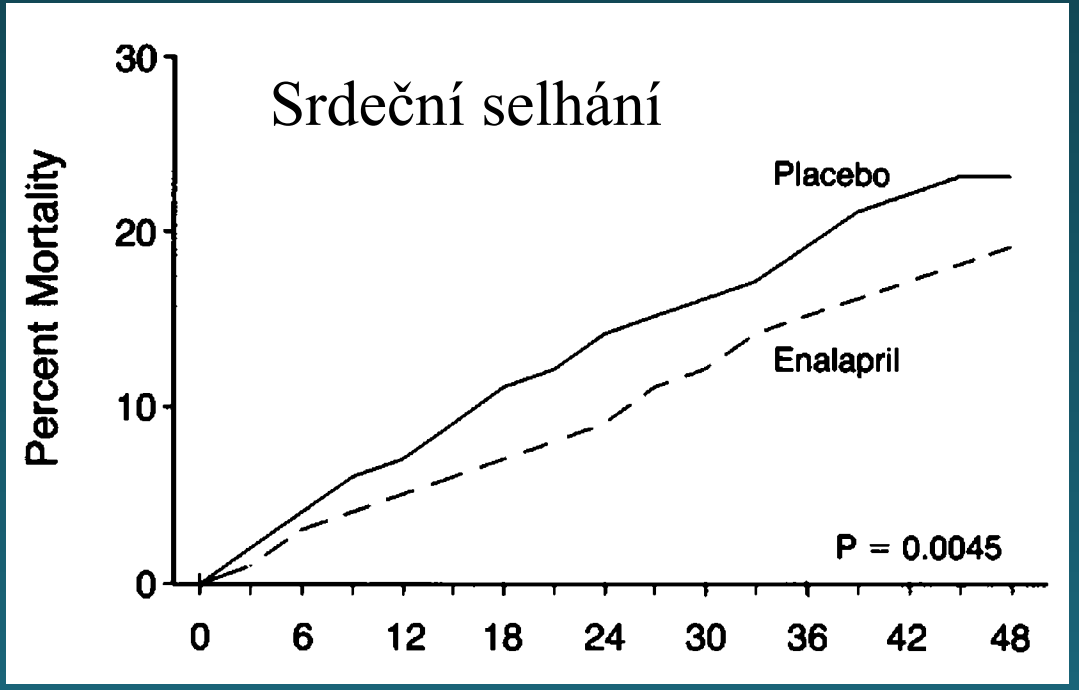
N Engl J Med 1987;316:1429–35

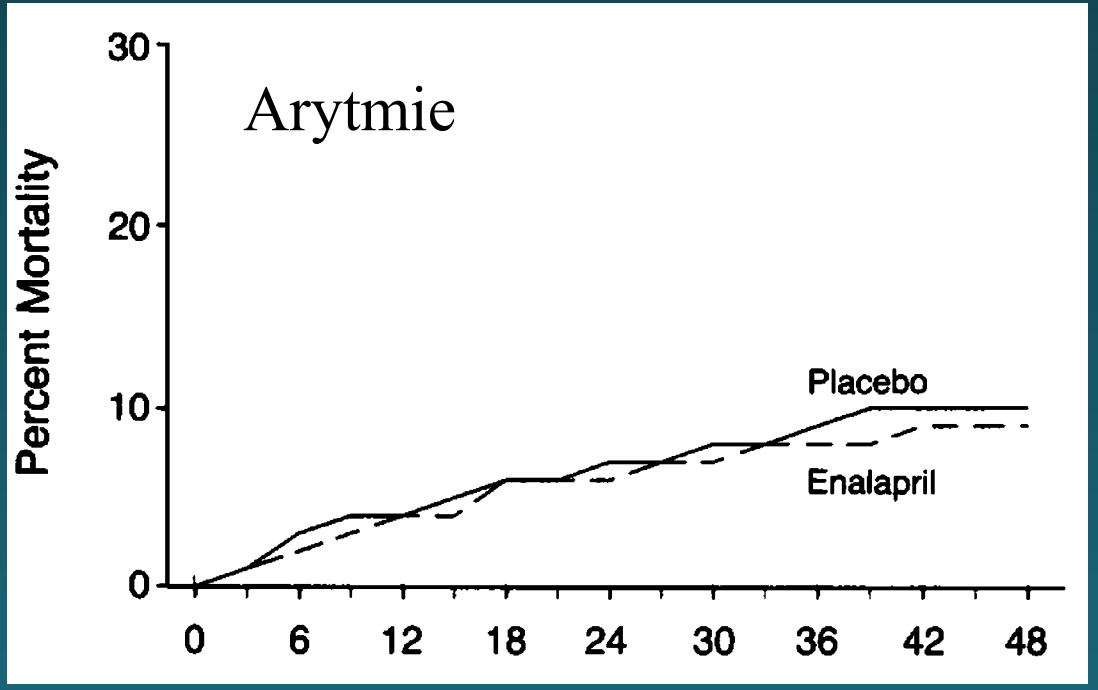
EFFECT OF ENALAPRIL ON SURVIVAL IN PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS AND CONGESTIVE HEART FAILURE

THE SOLVD INVESTIGATORS*



Patients receiving conventional treatment for heart failure were randomly assigned to receive either placebo (n = 1284) or enalapril (n = 1285) at doses of 2.5 to 20 mg per day. Approximately 90 percent of the patients were in **NYHA classes II and III. EF less than 35%** Primary endpoint was mortality.

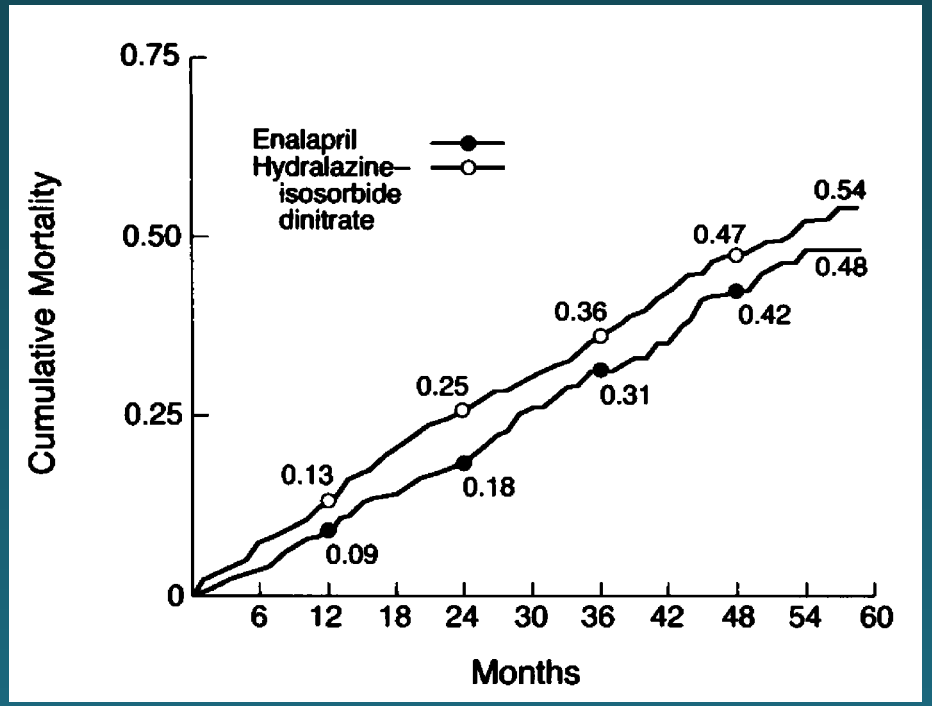


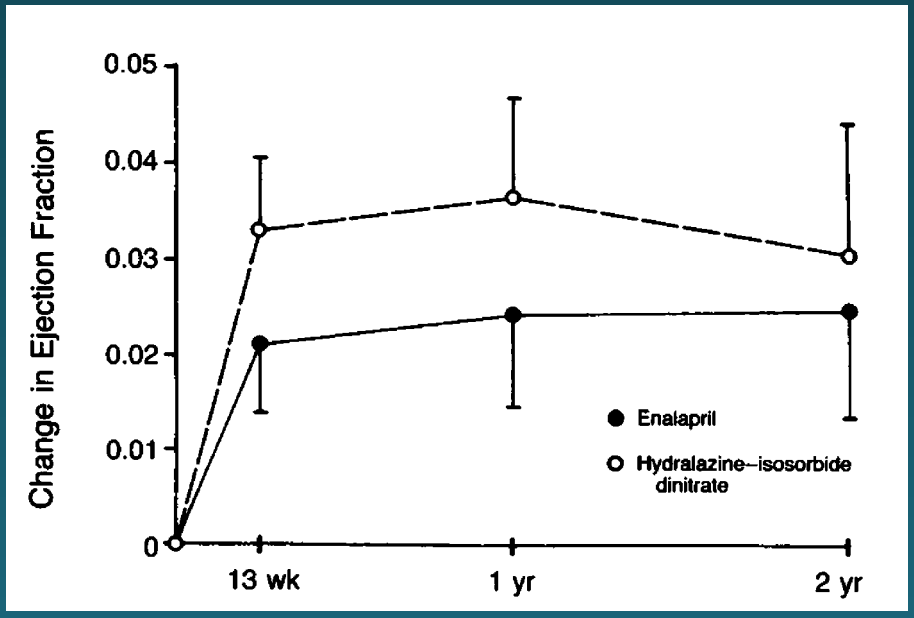


N Eng J Med 1991; 325: 293-302

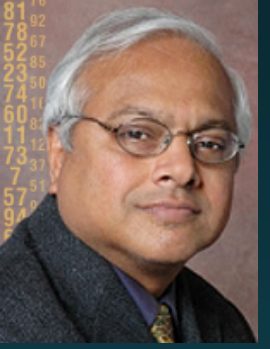
A COMPARISON OF ENALAPRIL WITH HYDRALAZINE–ISOSORBIDE DINITRATE IN THE TREATMENT OF CHRONIC CONGESTIVE HEART FAILURE

Compared the effects of hydralazine and isosorbide dinitrate with those of enalapril in 804 men receiving digoxin and diuretic therapy for heart failure. The patients NYHA II-III, EF 30% were randomly assigned in a double-blind manner to receive **20 mg ENP or 300 mg HZ + 160 mg ISDN daily**.





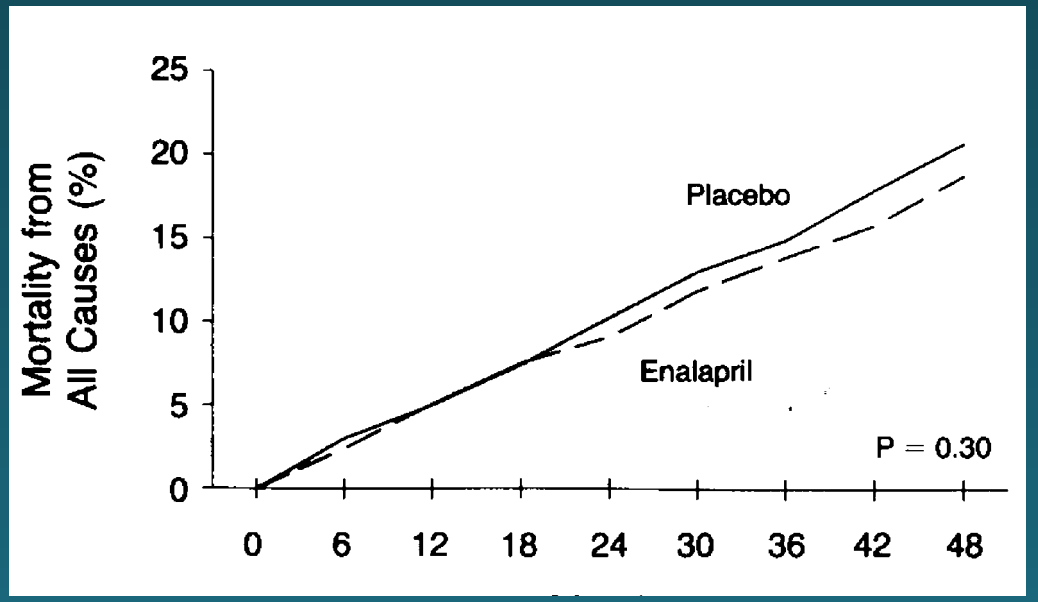
N Eng J Med 1991; 325:303-310

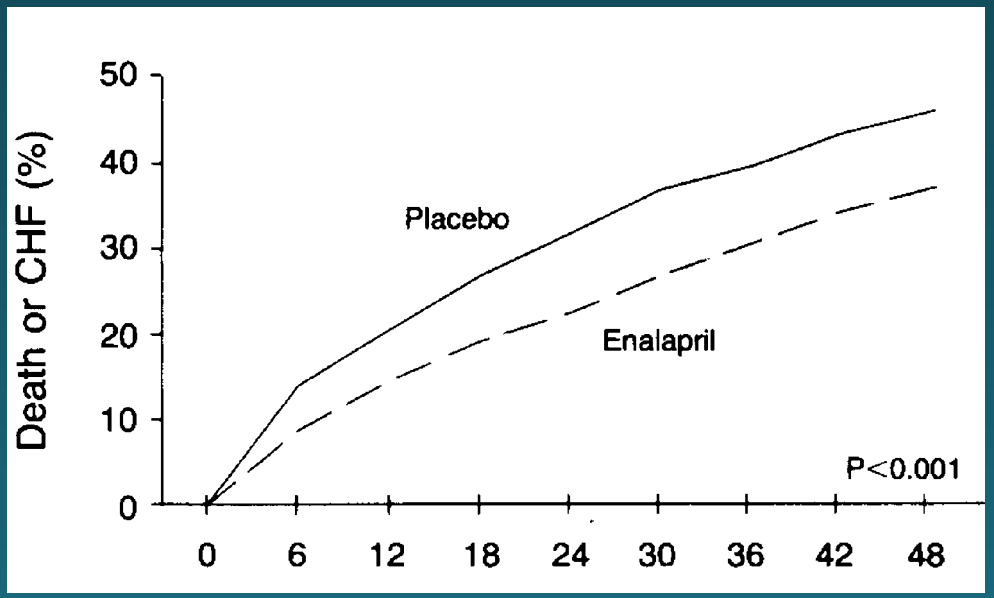


EFFECT OF ENALAPRIL ON MORTALITY AND THE DEVELOPMENT OF HEART FAILURE IN ASYMPTOMATIC PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS

THE SOLVD INVESTIGATORS*

Studied the effect of an ACE I, enalapril, on total mortality and mortality from cardiovascular causes, the development of heart failure, and hospitalization for heart failure among patients with **EF of 0.35 or less** who were not receiving drug treatment for heart failure. **NYHA I patients** were randomly assigned to receive either placebo (n = 2117) or enalapril (n = 2111) at doses of 2.5 to 20 mg per day in a double-blind trial. Follow-up averaged 37.4 months.



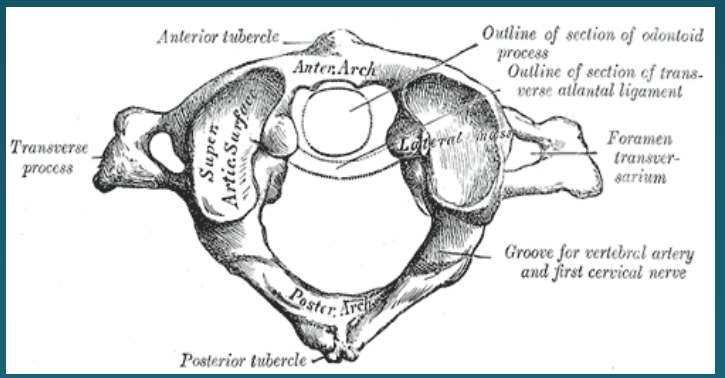


N Eng J Med 1992; 327: 685-691

Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure

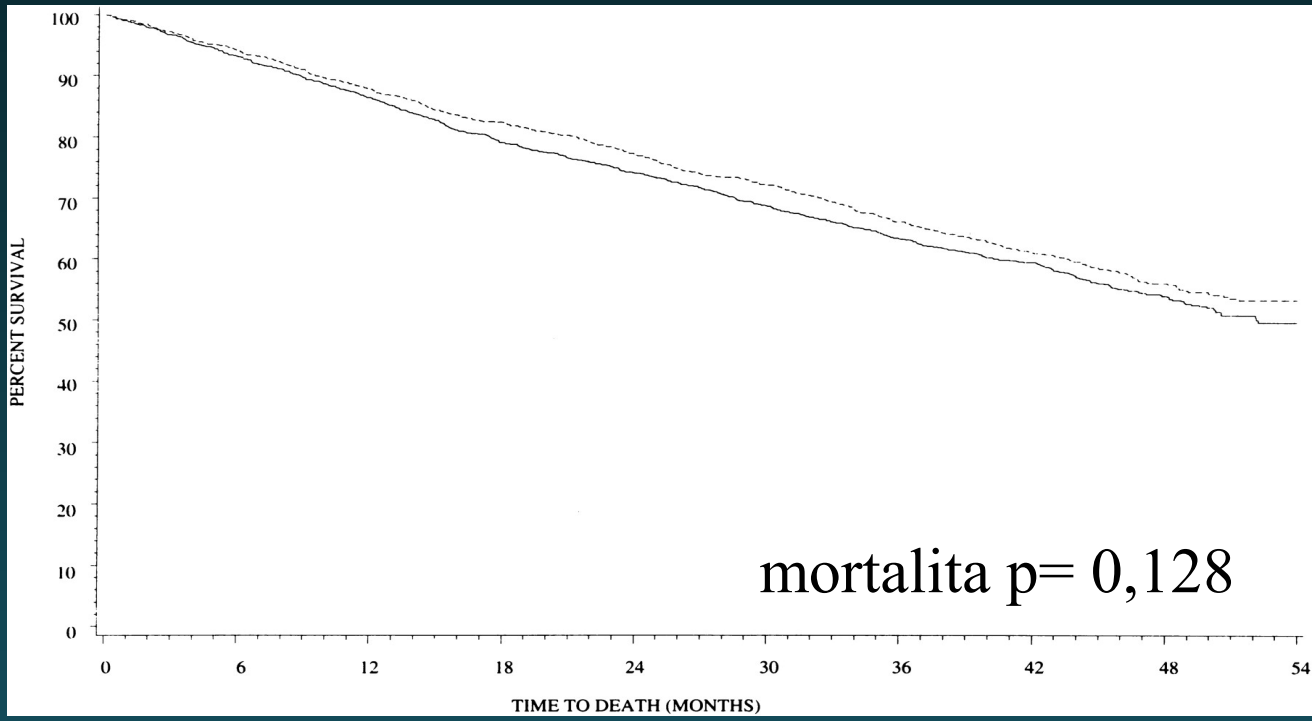
Milton Packer, MD; Philip A. Poole-Wilson, MD; Paul W. Armstrong, MD; John G.F. Cleland, MD; John D. Horowitz, MD; Barry M. Massie, MD; Lars Rydén, MD; Kristian Thygesen, MD; Barry F. Uretsky, MD; on behalf of the ATLAS Study Group*

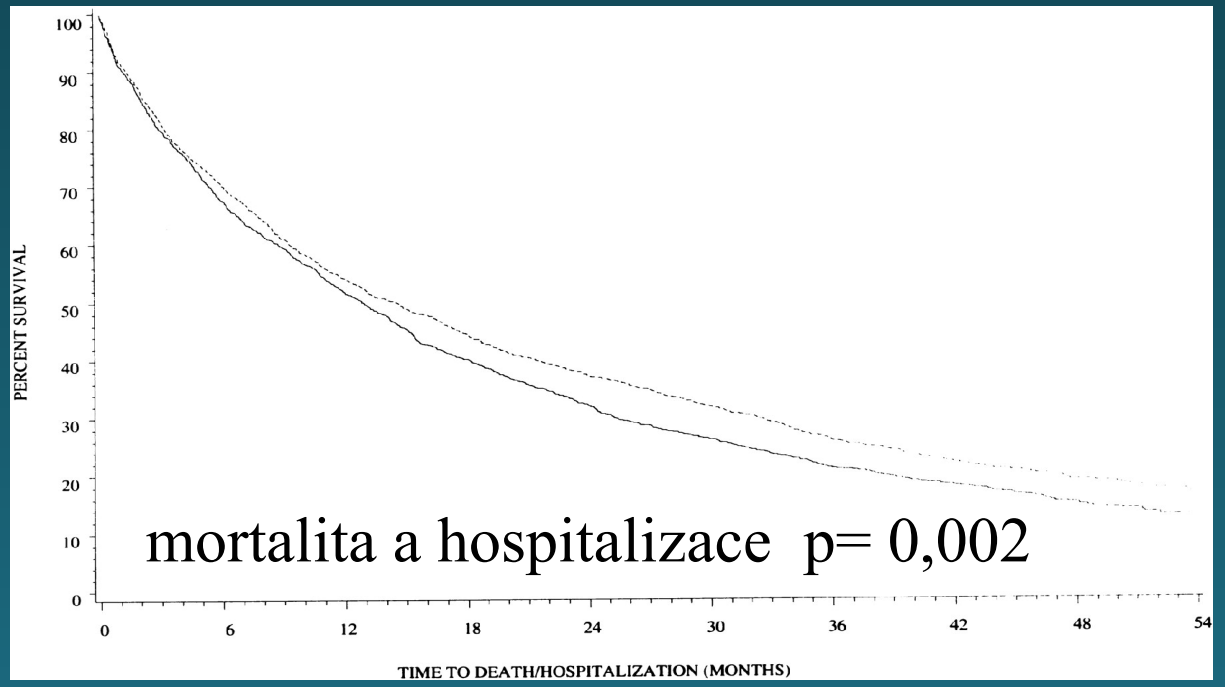
We randomly assigned 3164 patients with **NYHA II to IV** heart failure and an ejection fraction less than 30% to double-blind treatment with either low doses (2.5 to 5.0 mg daily, n=1596) or high doses (32.5 to 35 mg daily, n=1568) of the ACE inhibitor, lisinopril, for 39 to 58 months, while background therapy for heart failure was continued.



Circulation 1999; 100: 2312-2318

ATLAS





Packer M et al. Circulation 1999;100:2312-23

Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE)

*Bertram Pitt, Robert Segal, Felipe A Martinez, Georg Meurers, Alan J Cowley, Ignatius Thomas, Prakash C Deedwania, Dawn E Ney, Duane B Snavely, Paul I Chang, on behalf of ELITE Study Investigators**

Randomly assigned 722 ACE inhibitor naive patients (aged 65 years or more) with **NYHA II–IV** heart failure and EF of 40% or less to double-blind losartan (n=352) titrated to 50 mg once daily or captopril (n=370) titrated to 50 mg three times daily, for 48 weeks. **The primary endpoint was the tolerability measure of a persisting increase in serum creatinine of 26·5 µmol/L or more (0·3 mg/dL) on therapy**

Lancet 1997; 349: 747-752

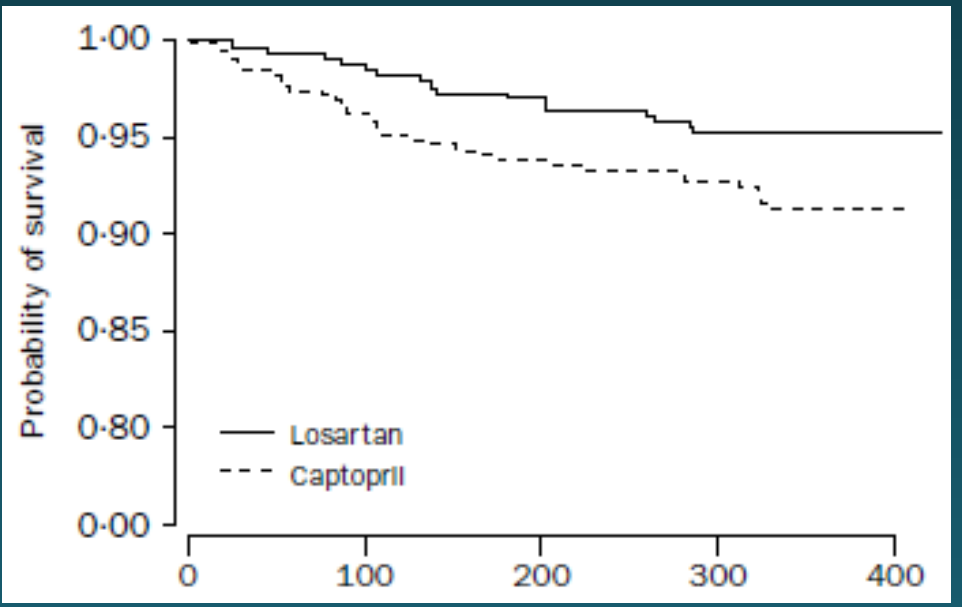
Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE)

*Bertram Pitt, Robert Segal, Felipe A Martinez, Georg Meurers, Alan J Cowley, Ignatius Thomas, Prakash C Deedwania, Dawn E Ney, Duane B Snavely, Paul I Chang, on behalf of ELITE Study Investigators**

Age	Treatment	No	Event rate*
All patients	Losartan	352	37 (10·5%)
	Captopril	370	39 (10·5%)
<70	Losartan	95	8 (8·4%)
	Captopril	119	10 (8·4%)
⩾70	Losartan	257	29 (11·3%)
	Captopril	251	29 (11·6%)

*Defined as a rise of 26·5 μmol/L (0·3 mg/dL) or more, confirmed within 5–14 days.

Table 2: **Frequency of increases in serum creatinine**



Lancet 1997; 349: 747-752

Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II

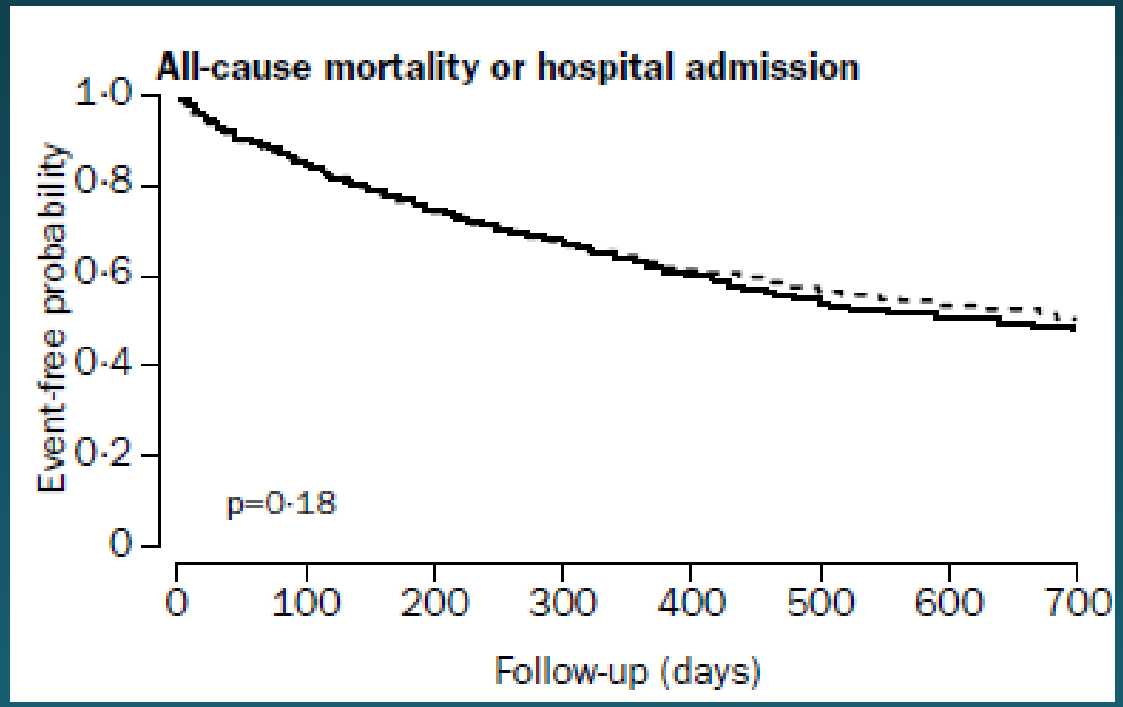
Bertram Pitt, Philip A Poole-Wilson, Robert Segal, on behalf of the ELITE II investigators

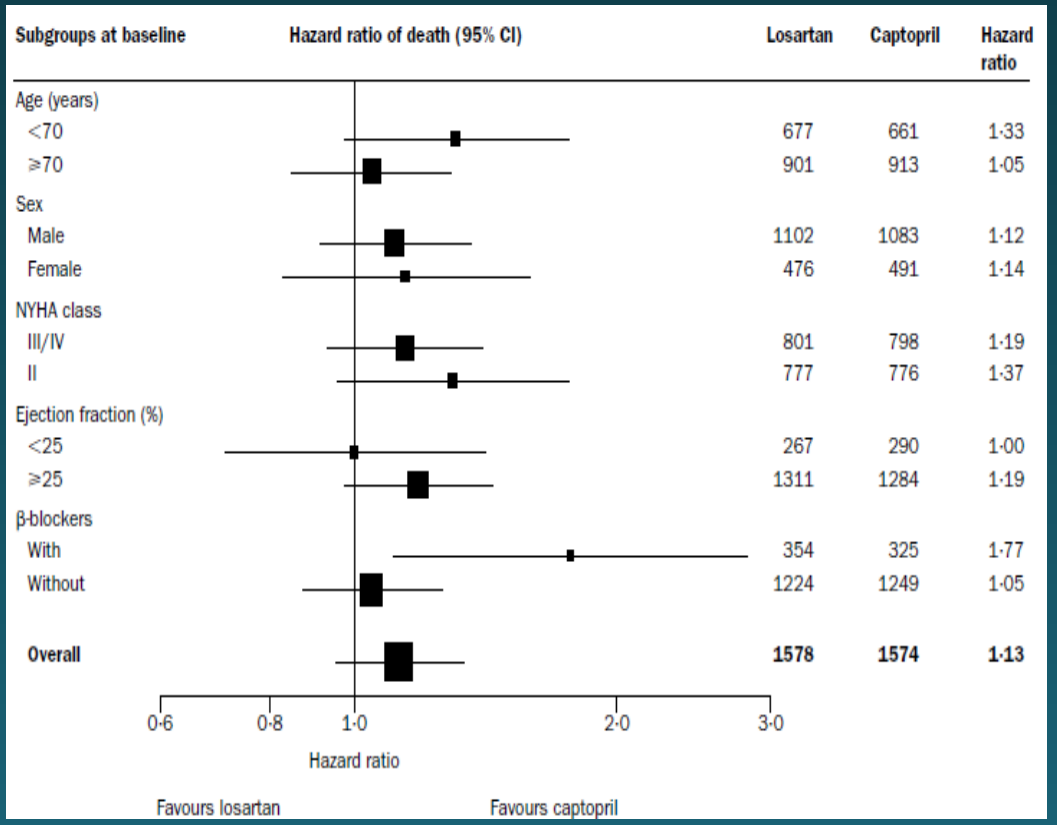
Randomised of 3152 patients aged 60 years or older with **NYHA II–IV** heart failure and EF of 40% or less. Patients, stratified for - betablocker use, were randomly assigned **losartan (n=1578) titrated to 50 mg** once daily or **captopril (n=1574) titrated to 50 mg three times daily**. The primary and secondary endpoints were all-cause mortality, and sudden death or resuscitated arrest.

Lancet 2000; 355: 1582-87

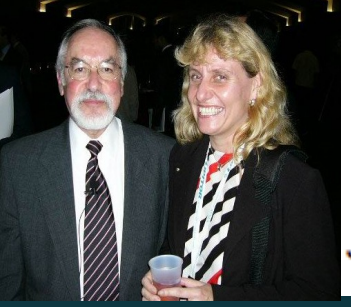
Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II

Bertram Pitt, Philip A Poole-Wilson, Robert Segal, on behalf of the ELITE II investigators





Lancet 2000; 355: 1582-87



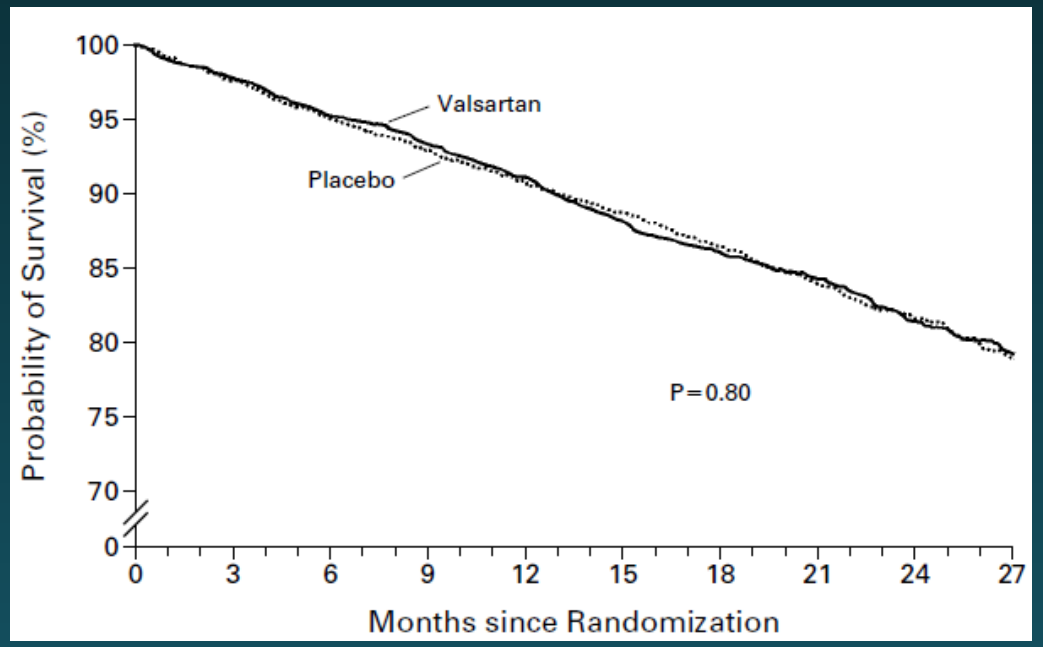
A RANDOMIZED TRIAL OF THE ANGIOTENSIN-RECEPTOR BLOCKER VALSARTAN IN CHRONIC HEART FAILURE

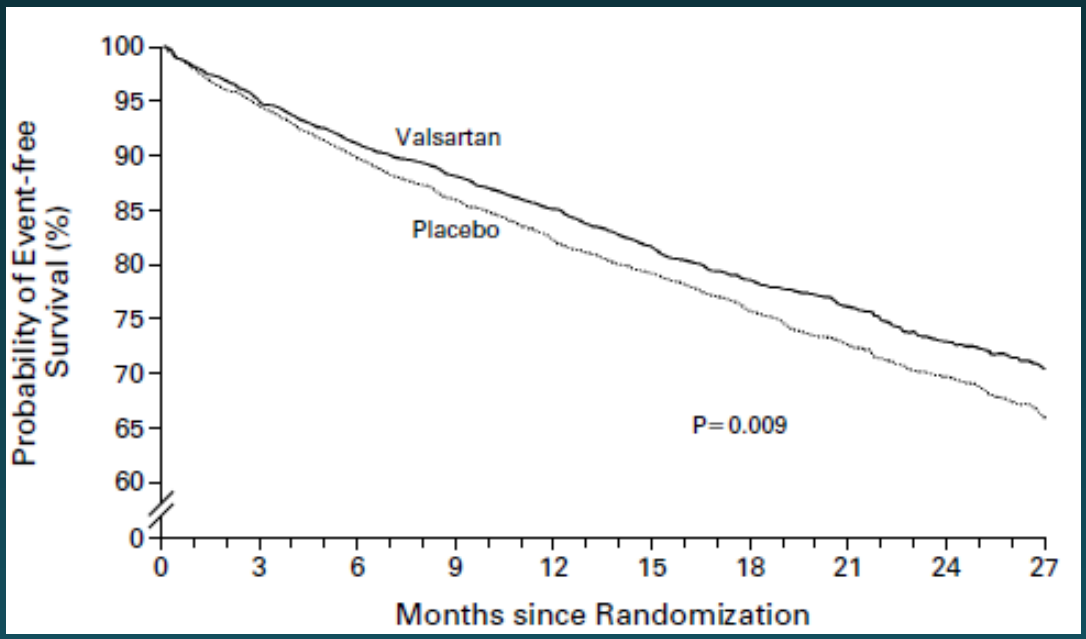
JAY N. COHN, M.D., AND GIANNI TOGNONI, M.D., FOR THE VALSARTAN HEART FAILURE TRIAL INVESTIGATORS*

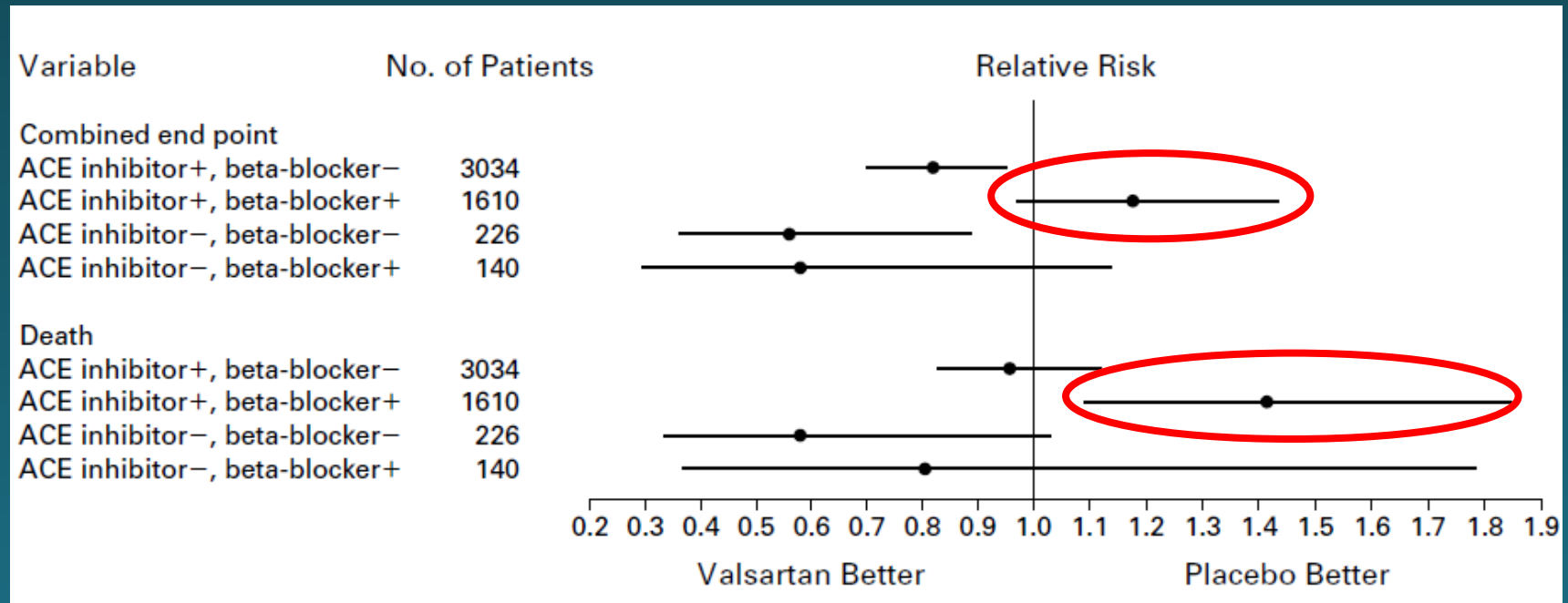
A total of 5010 patients with heart failure of **NYHA II, III, or IV** were randomly assigned to receive 160 mg of valsartan or placebo twice daily. The primary outcomes were mortality and the combined end point of **mortality and morbidity**, defined as the incidence of **cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least four hours.**

N Eng J Med 2001; 345: 1667-75

VAL - HEFT


Probability of Survival (%)
100
95
90
85
80
75
70
0
Valsartan
Placebo
P=0.80
0
3
6
9
12
15
18
21
24
27
Months since Randomization


Probability of Event-free Survival (%)
100
95
90
85
80
75
70
65
60
0
Valsartan
Placebo
P=0.009
0
3
6
9
12
15
18
21
24
27
Months since Randomization


Variable
No. of Patients
Relative Risk
Combined end point
ACE inhibitor+, beta-blocker−
3034
ACE inhibitor+, beta-blocker+
1610
ACE inhibitor−, beta-blocker−
226
ACE inhibitor−, beta-blocker+
140
Death
ACE inhibitor+, beta-blocker−
3034
ACE inhibitor+, beta-blocker+
1610
ACE inhibitor−, beta-blocker−
226
ACE inhibitor−, beta-blocker+
140
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
Valsartan Better
Placebo Better

Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme

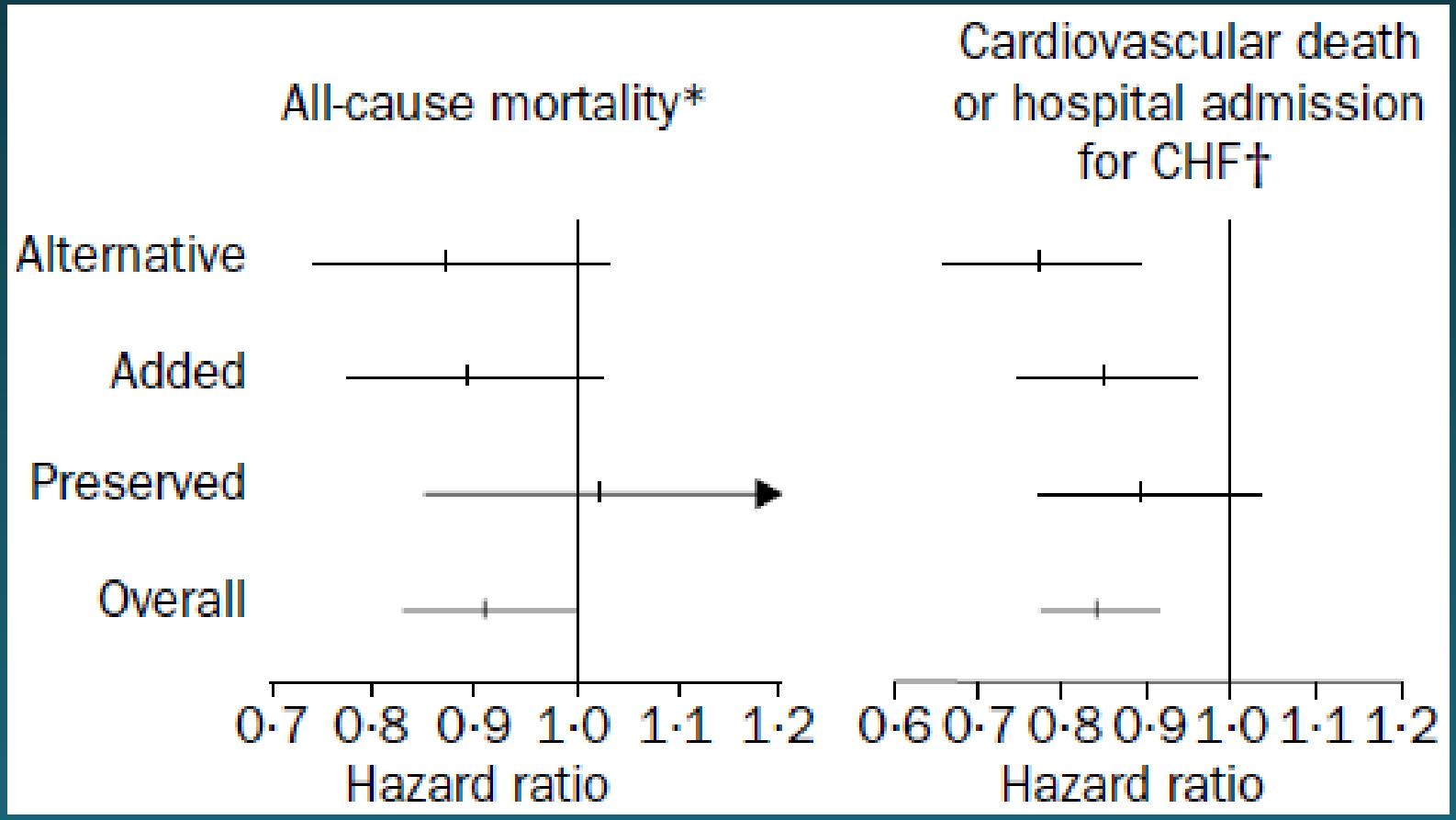
*Marc A Pfeffer, Karl Swedberg, Christopher B Granger, Peter Held, John J V McMurray, Eric L Michelson, Bertil Olofsson, Jan Östergren, Salim Yusuf, for the CHARM Investigators and Committees**

Clinical trials was compared candesartan with placebo in three distinct populations. We studied patients with **LVEF < 40%** who were **not receiving ACE inhibitors** because of previous intolerance **or** who were **currently receiving ACE inhibitors**, and patients with **LVEF > 40%.** Overall, 7601 patients (7599 with data) were randomly assigned candesartan (n=3803, titrated to 32 mg once daily) or matching placebo (n=3796), and followed up for at least 2 years. The primary outcome of the overall programme was all-cause mortality, and for all the component trials was cardiovascular death or hospital admission for CHF

Lancet 2003; 362: 759-66

Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme

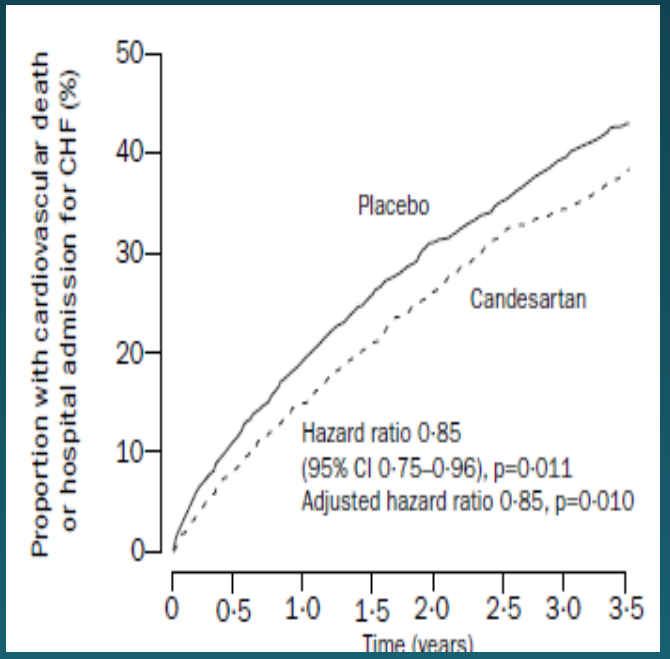
*Marc A Pfeffer, Karl Swedberg, Christopher B Granger, Peter Held, John J V McMurray, Eric L Michelson, Bertil Olofsson, Jan Östergren, Salim Yusuf, for the CHARM Investigators and Committees**

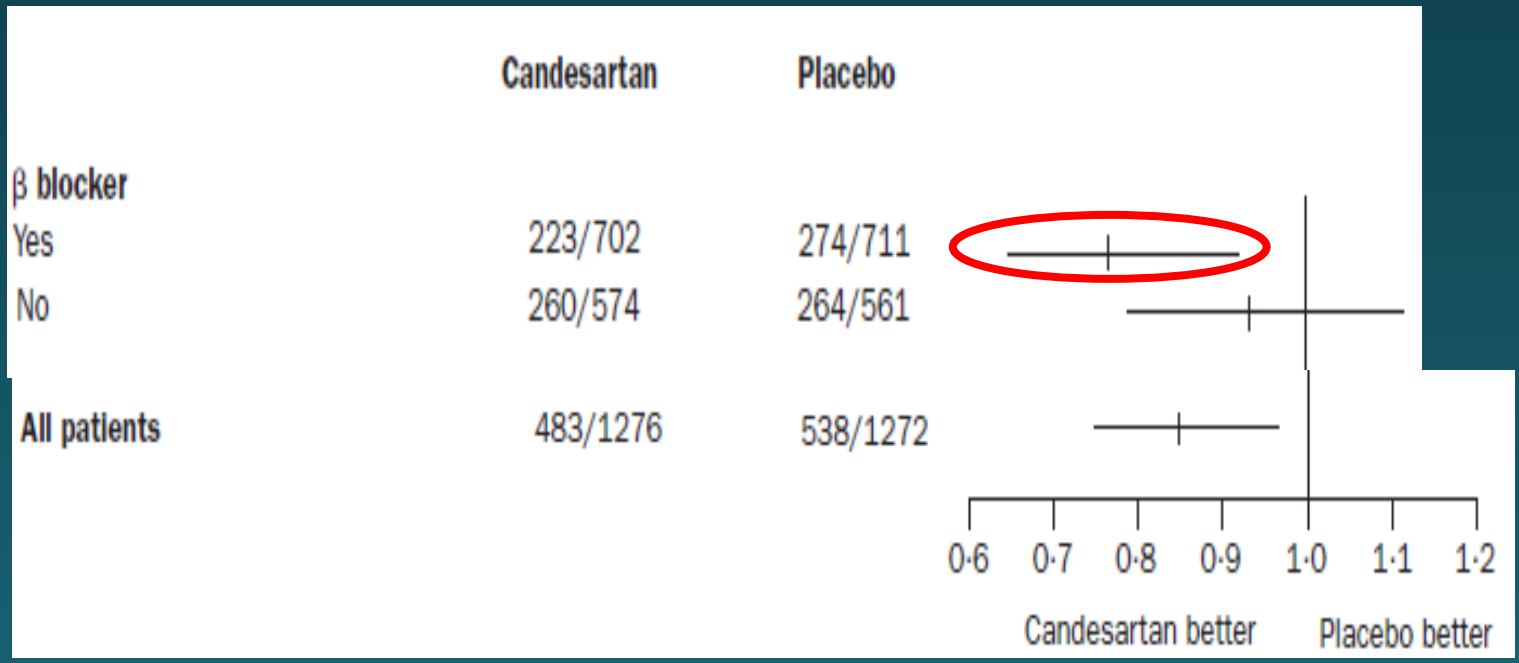


Lancet 2003; 362: 759-66

Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial

Candesartan (n=1276) či placebo (n=1272)



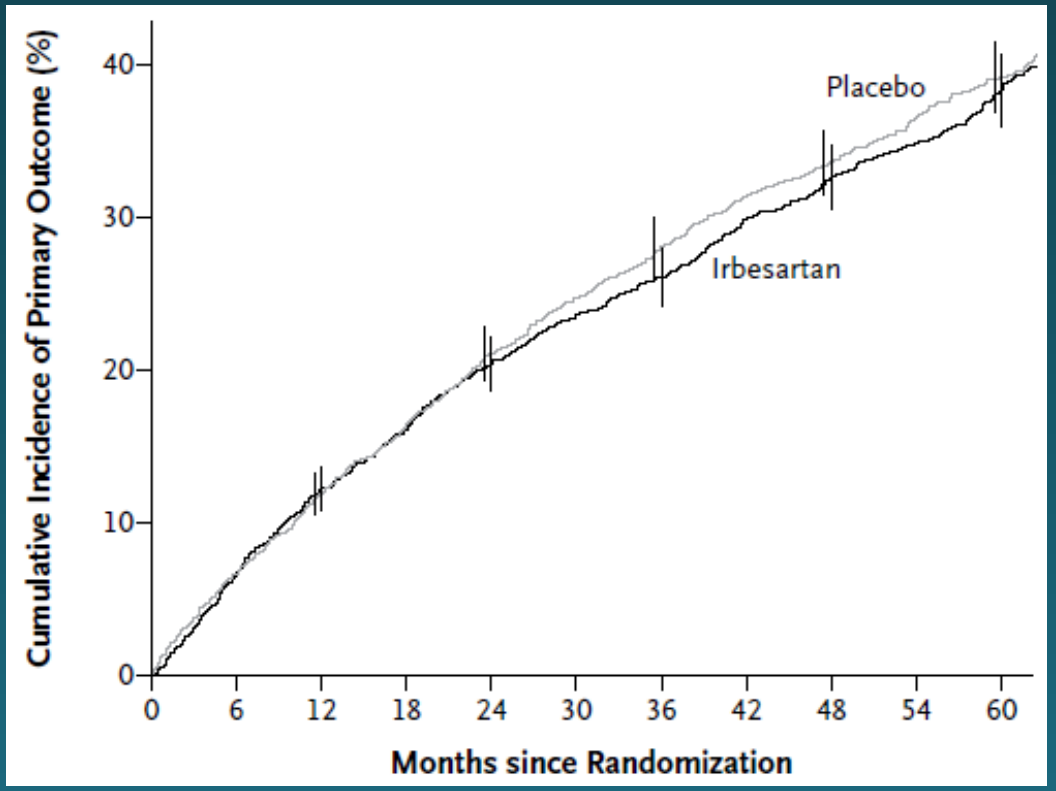


Lancet 2003; 362: 767-71

Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction

Barry M. Massie, Peter E. Carson, John J. McMurray, for the I-PRESERVE Invest.

Enrolled 4128 patients who were at least 60 years of age and had New York Heart Association class II, III, or IV heart failure and an ejection fraction of at least 45% and randomly assigned them to receive 300 mg of irbesartan or placebo per day



N Eng J Med 2008; 359: 2456-67

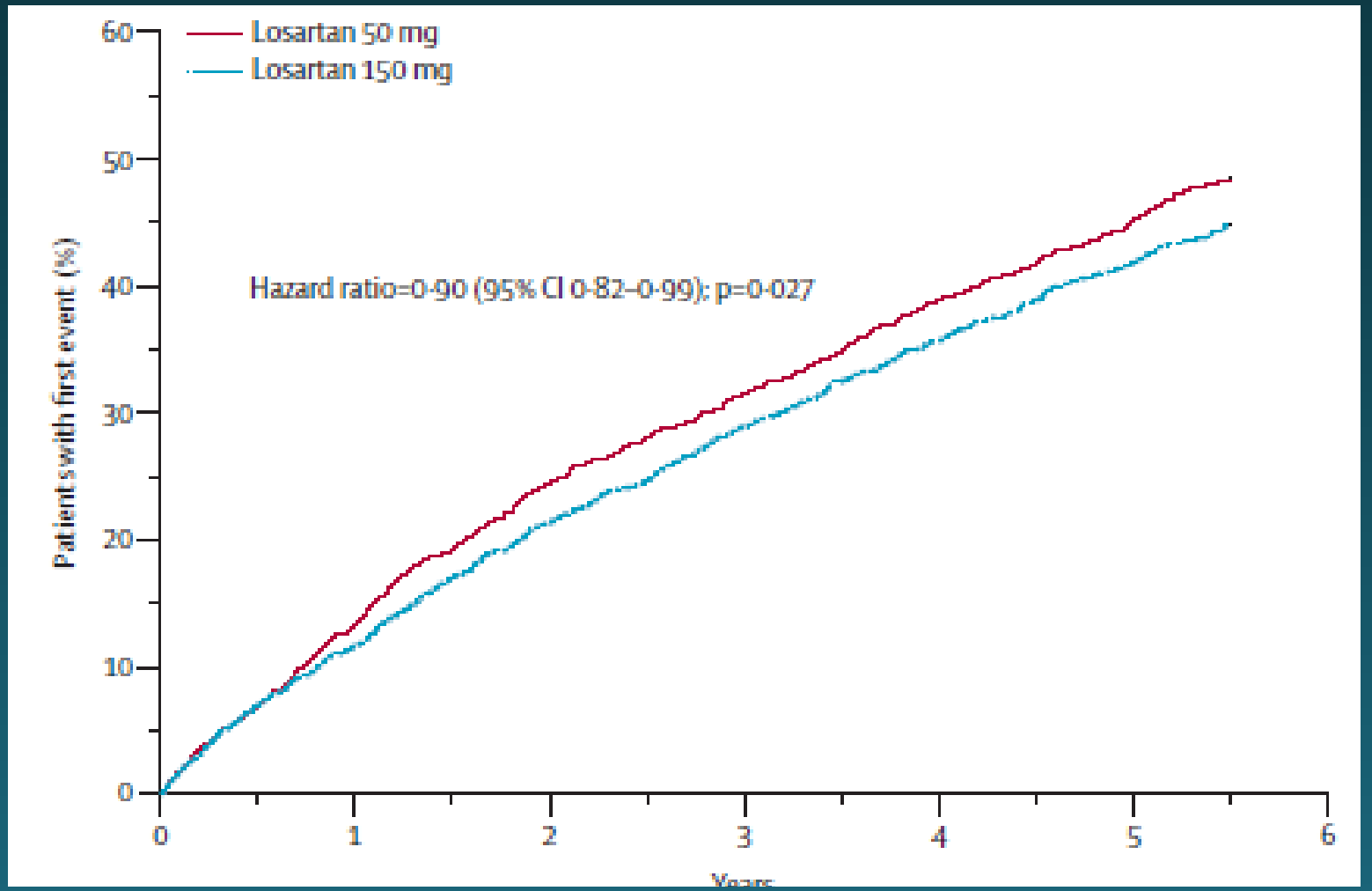
Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial

Marvin A Konstam, James D Neaton, Kenneth Dickstein, for the HEAAL Investigators‡

This double-blind trial. 3846 patients with heart failure of NYHA II–IV, LVEF 40% or less, and intolerance to ACE inhibitors were randomly assigned to losartan 150 mg (n=1927) or 50 mg daily (n=1919). The primary endpoint was death or admission for heart failure.

Lancet 2009; 374: 1840-48

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

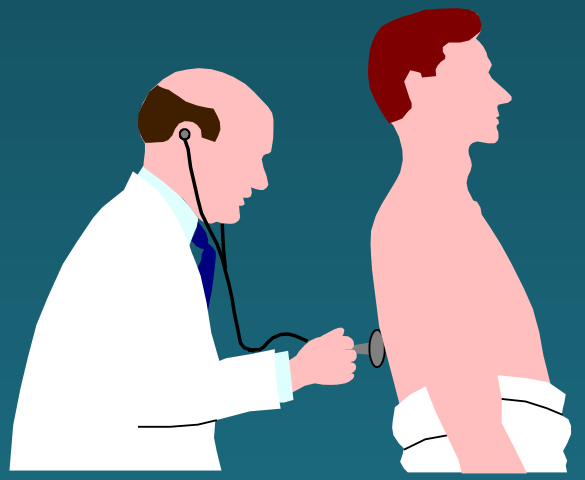


Lancet 2009; 374: 1840-48

THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*

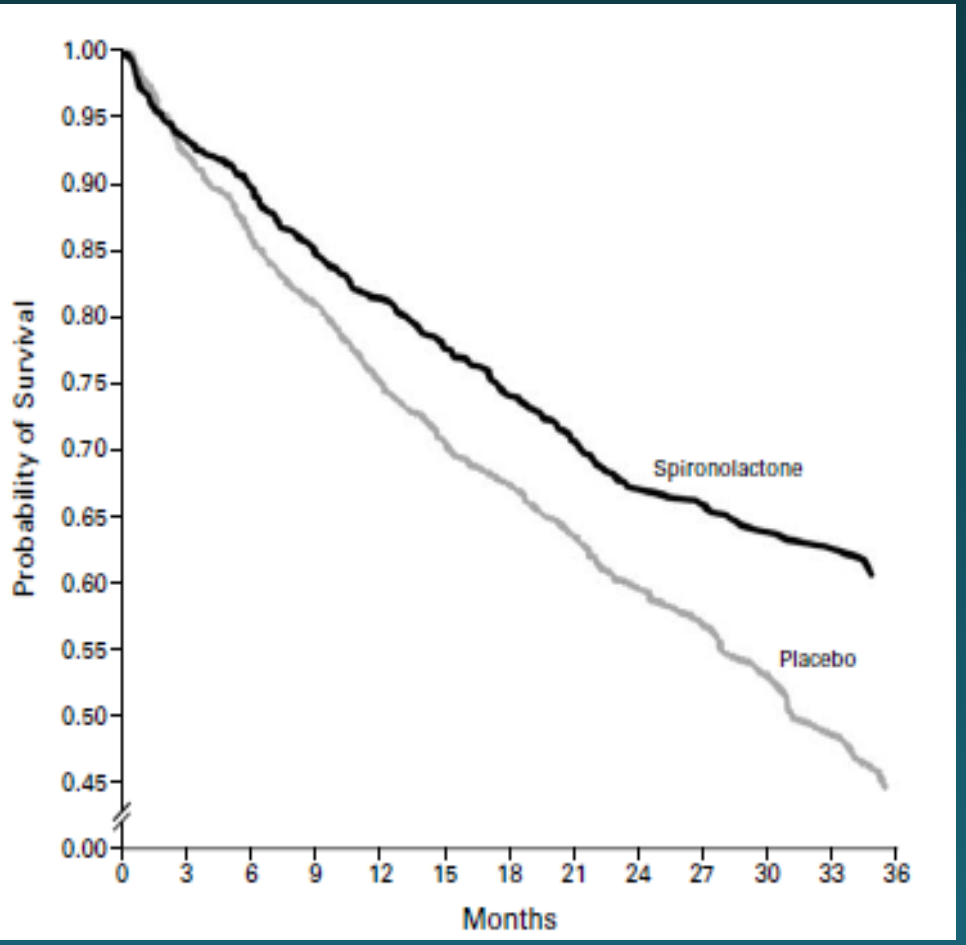
Enrolled 1663 patients NYHA II-IV who had severe heart failure and a LVEF of no more than 35 percent and who were being treated with an ACE I, a loop diuretic, and in most cases digoxin. A total of 822 patients were randomly assigned to receive 25 mg of spironolactone daily, and 841 to receive placebo. The primary end point was death from all causes.

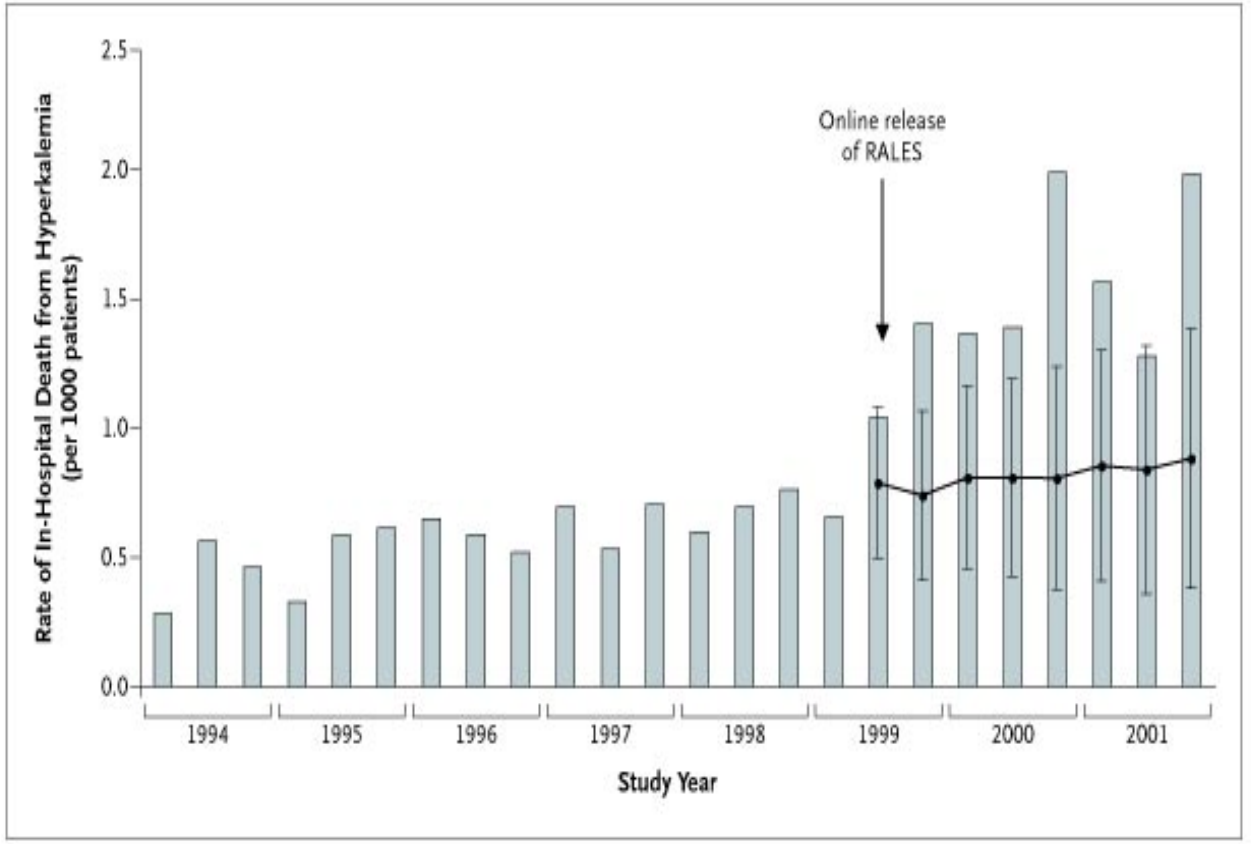


N Eng J Med 1999; 341: 709-712

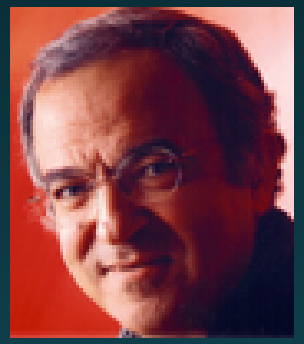
THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*





N Eng J Med 1999; 341: 709-712



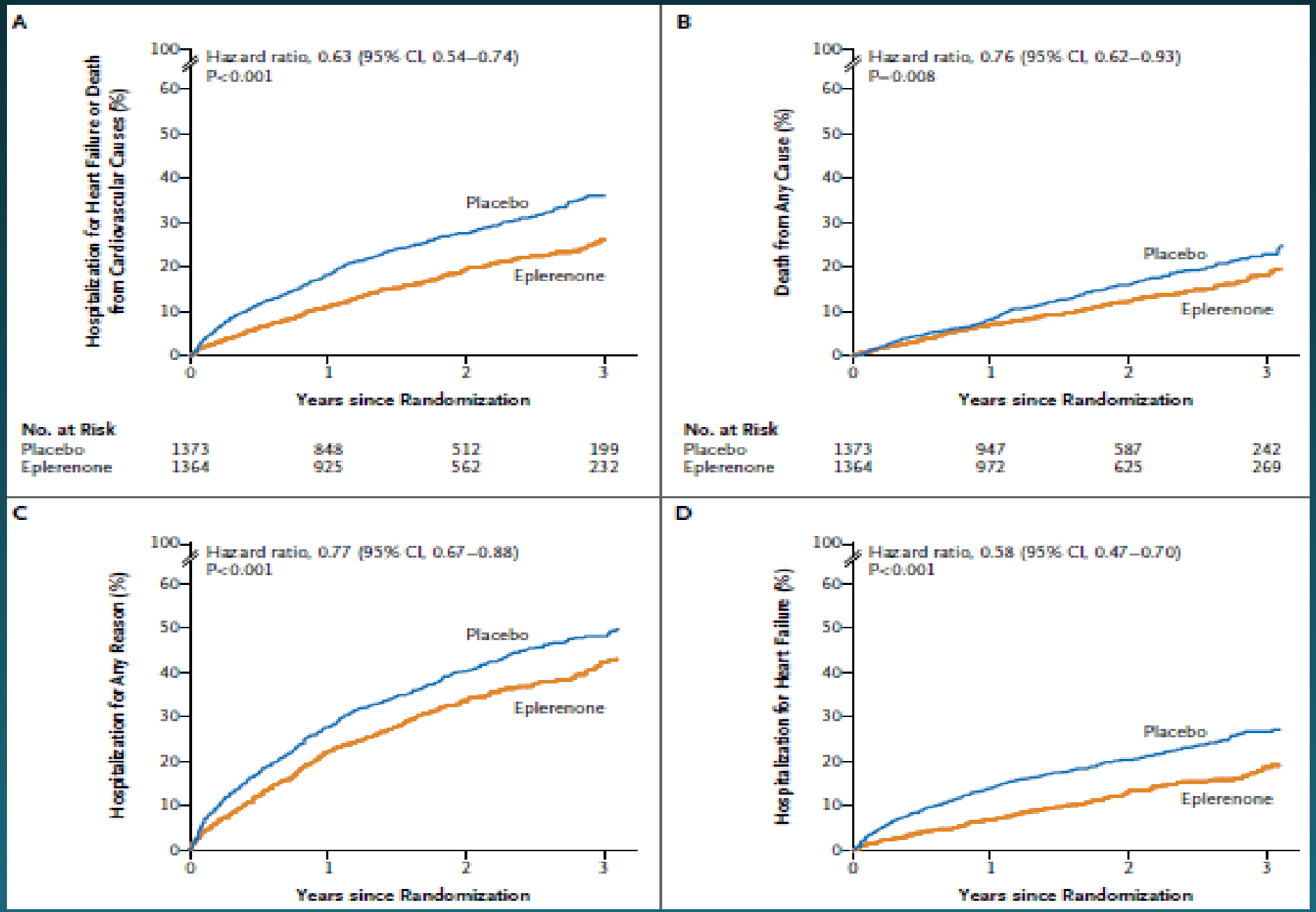
Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D, Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D., for the EMPHASIS-HF Study Group*

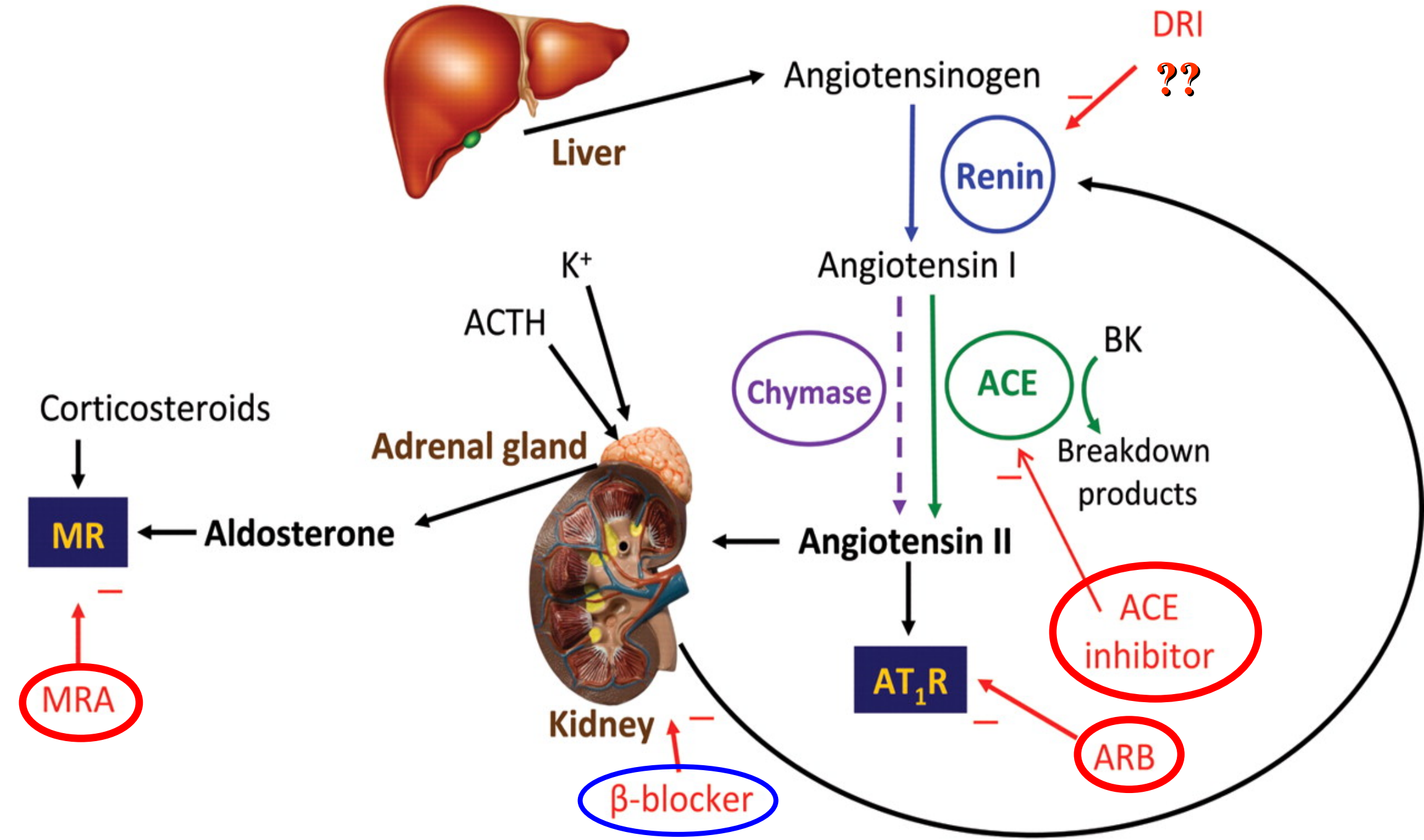
In this randomized, double-blind trial, we randomly assigned 2737 patients with New York Heart Association class II heart failure and an ejection fraction of no more than 35% to receive eplerenone n=1364 (up to 50 mg daily) or placebo n=1373, in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

N Eng J Med 2011; 364: 11-21

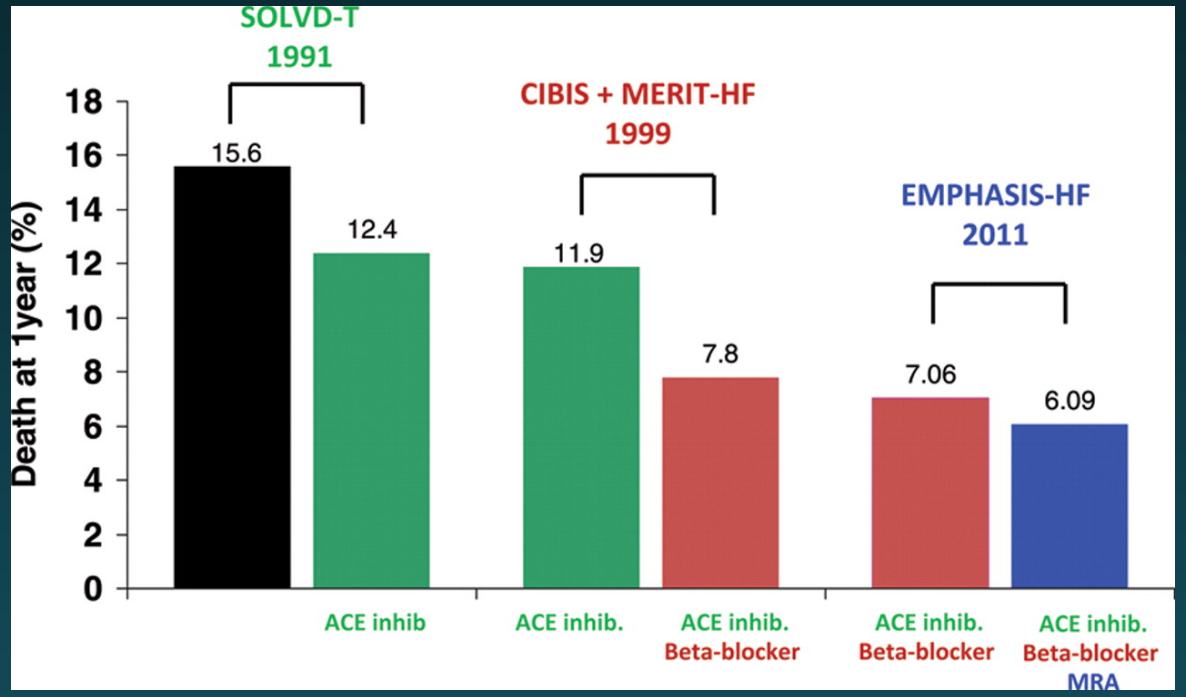
EMPHASIS-HF



N Eng J Med 2011; 364: 11-

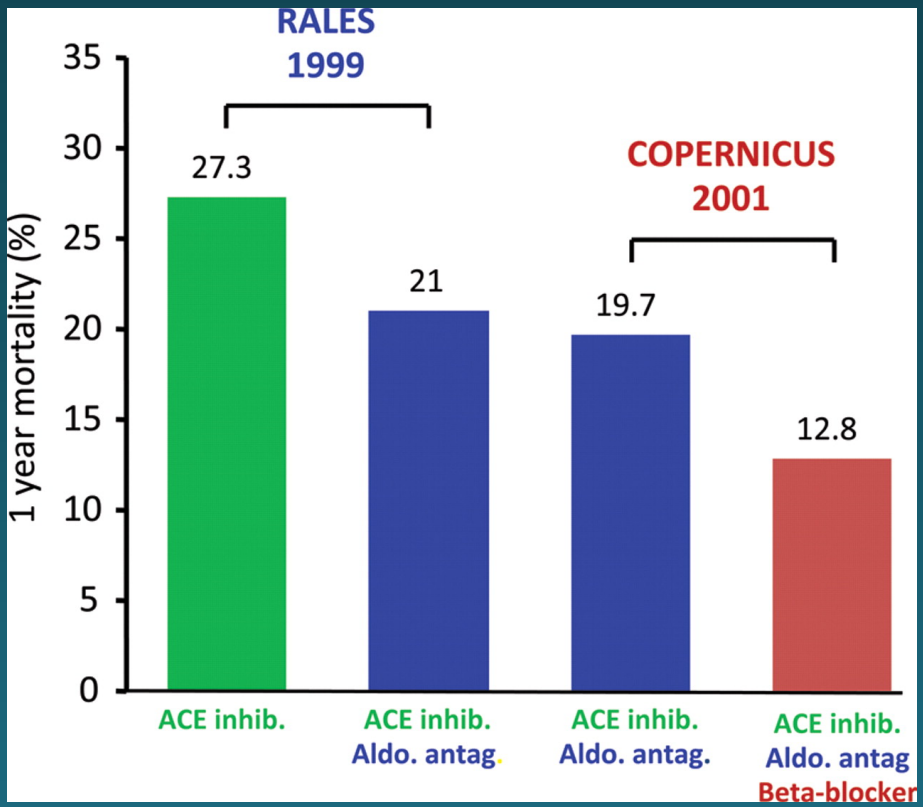


DRI, direct renin inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist;
K^+ potassium ion; ACE, angiotensin converting enzyme; ACTH, adrenocorticotropic hormone (corticotropin); BK, bradykinin;
AT_1R, angiotensin II type 1 receptor; MR, mineralcorticoid receptor



NYHA I-II

NYHA III-IV




(AS SHOWN)
Happy
25th
Anniversary