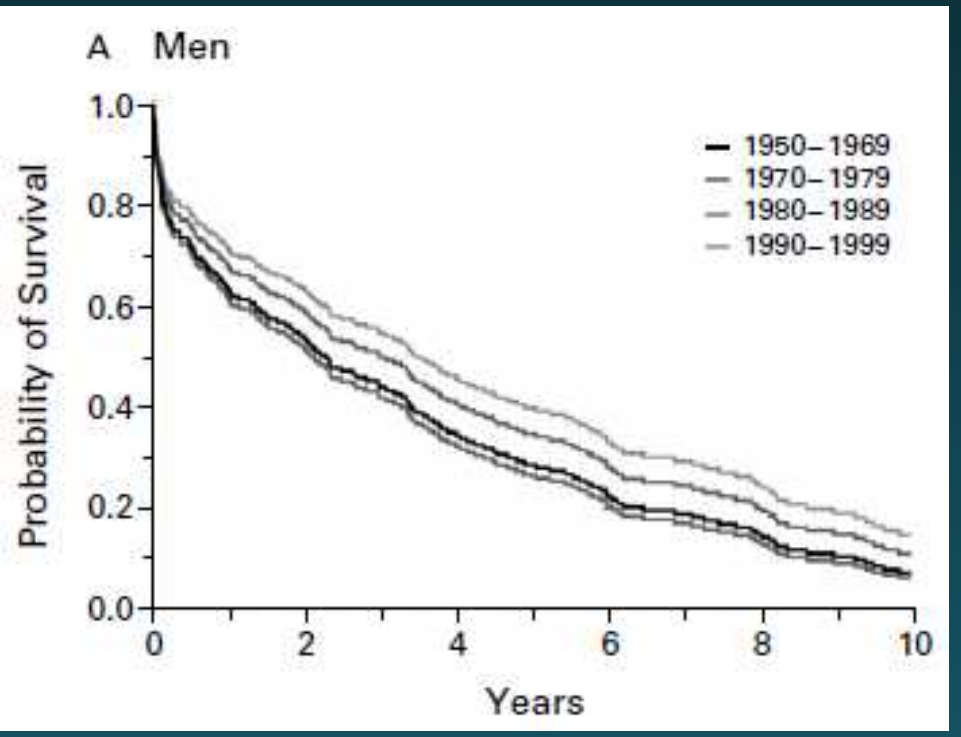
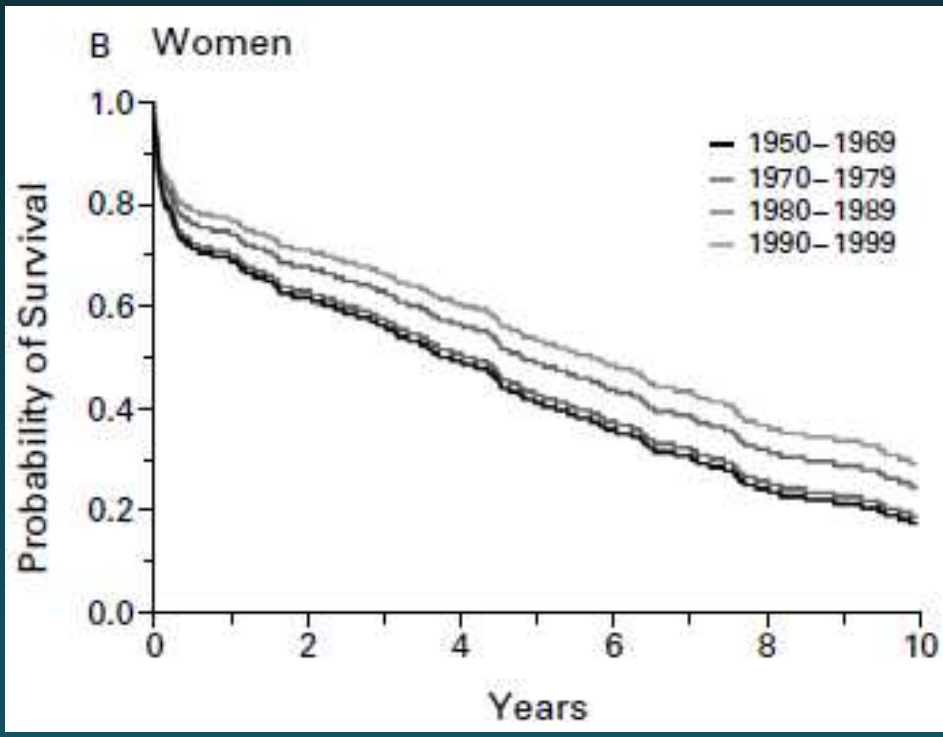
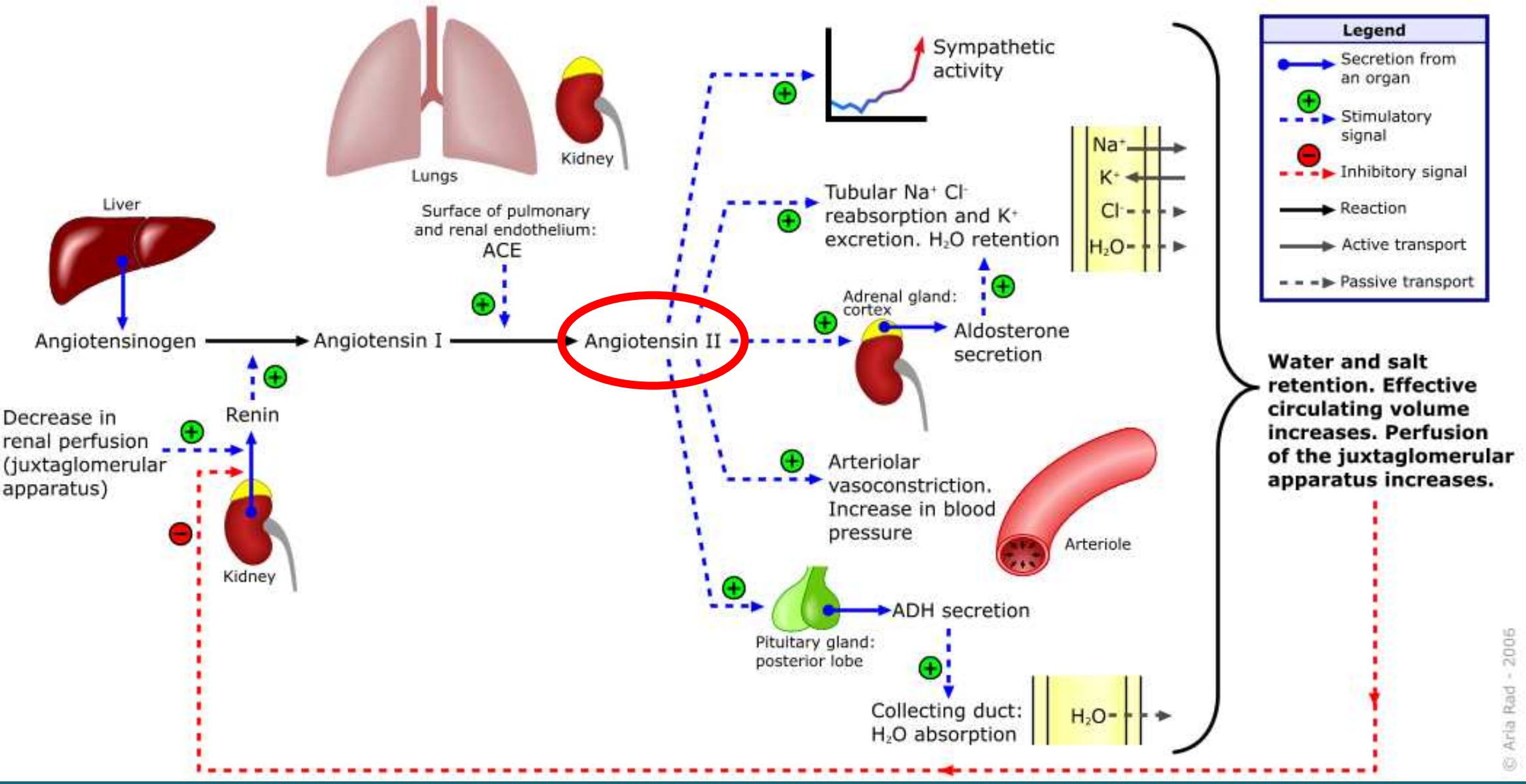
Blokáda systému RAAS v léčbě srdečního selhání

Jiří Vítovec
IKAK LF MU a FN u sv.Anny

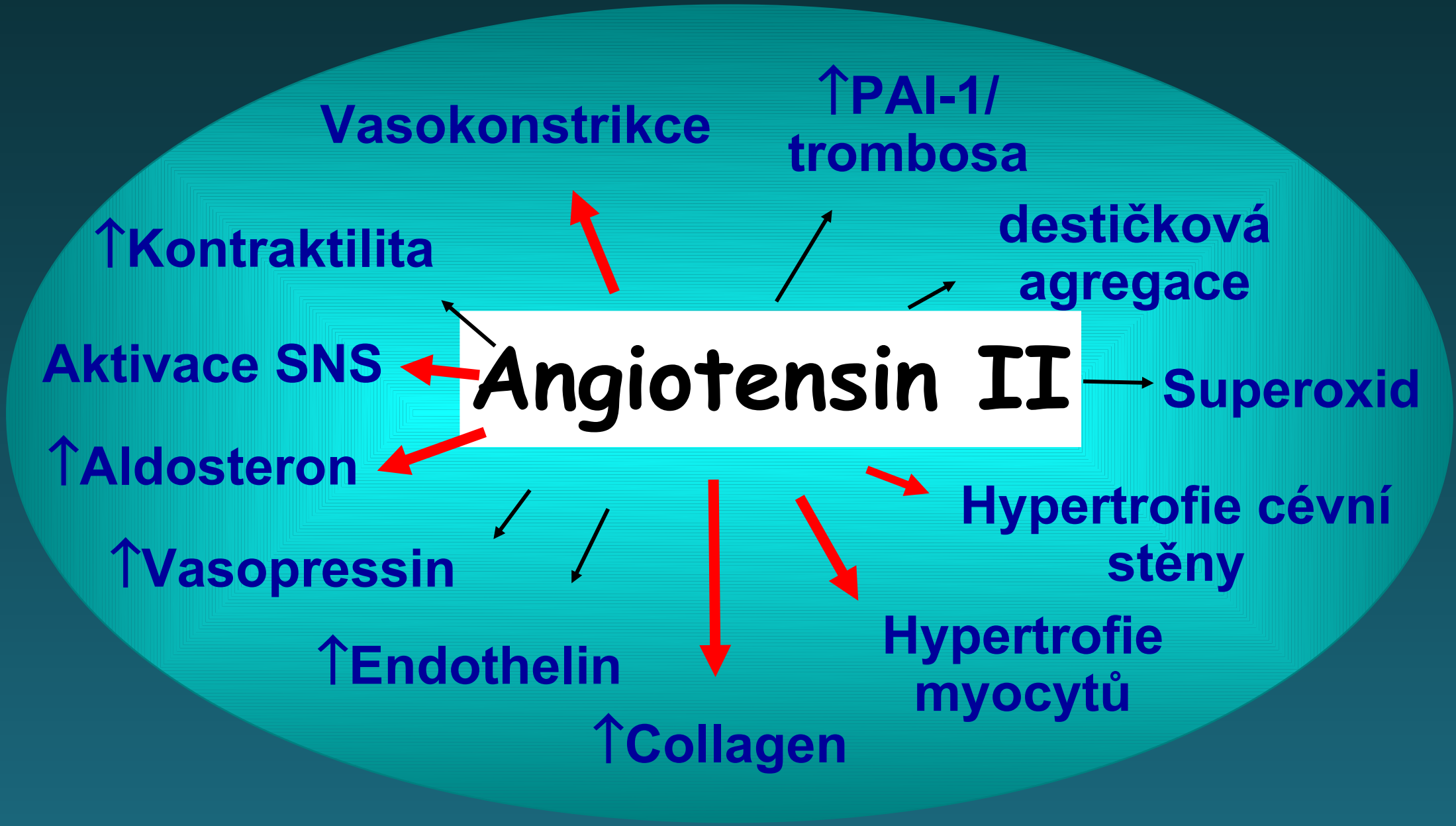

A Men
Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Years
1950–1969
1970–1979
1980–1989
1990–1999


B Women
Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Years
1950–1969
1970–1979
1980–1989
1990–1999

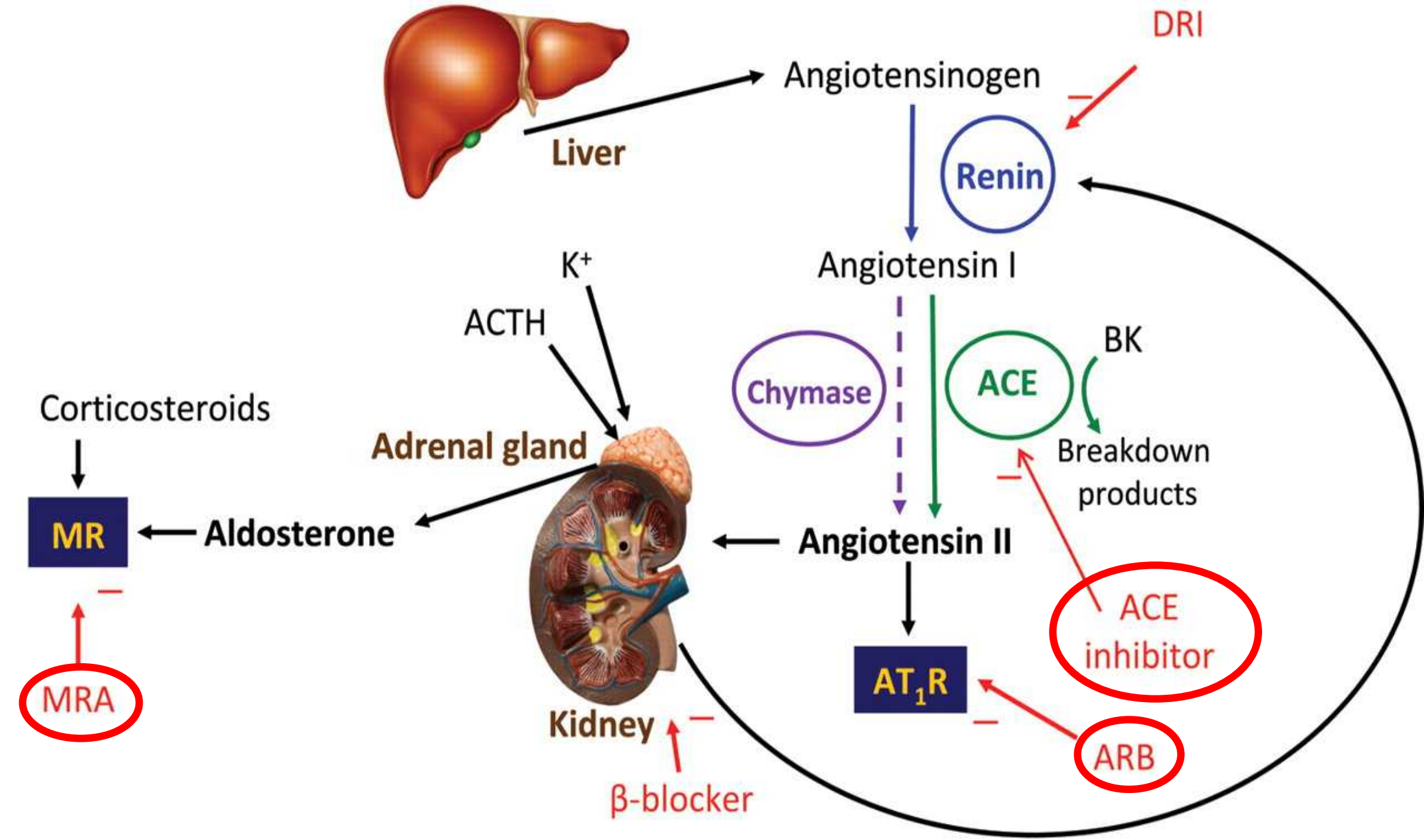
Renin-angiotensin-aldosterone system



Patofysiologický efekt A II



Modified after Burnier & Brunner Lancet 2000



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

The New England
Journal of Medicine

Volume 316 JUNE 4, 1987 Number 23

EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

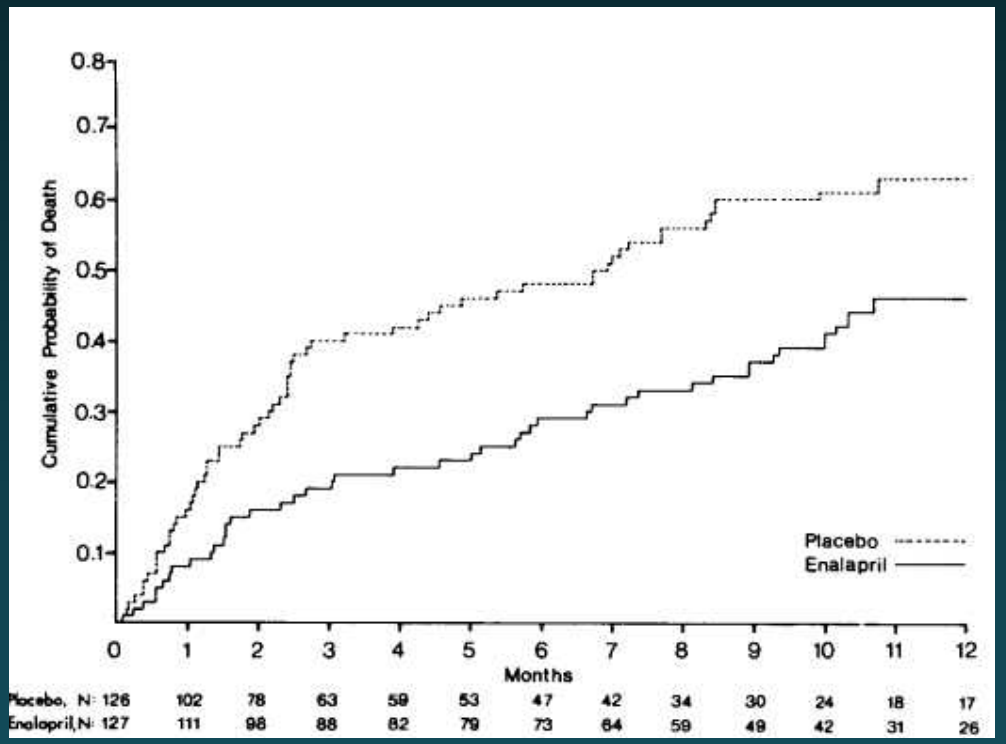
Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

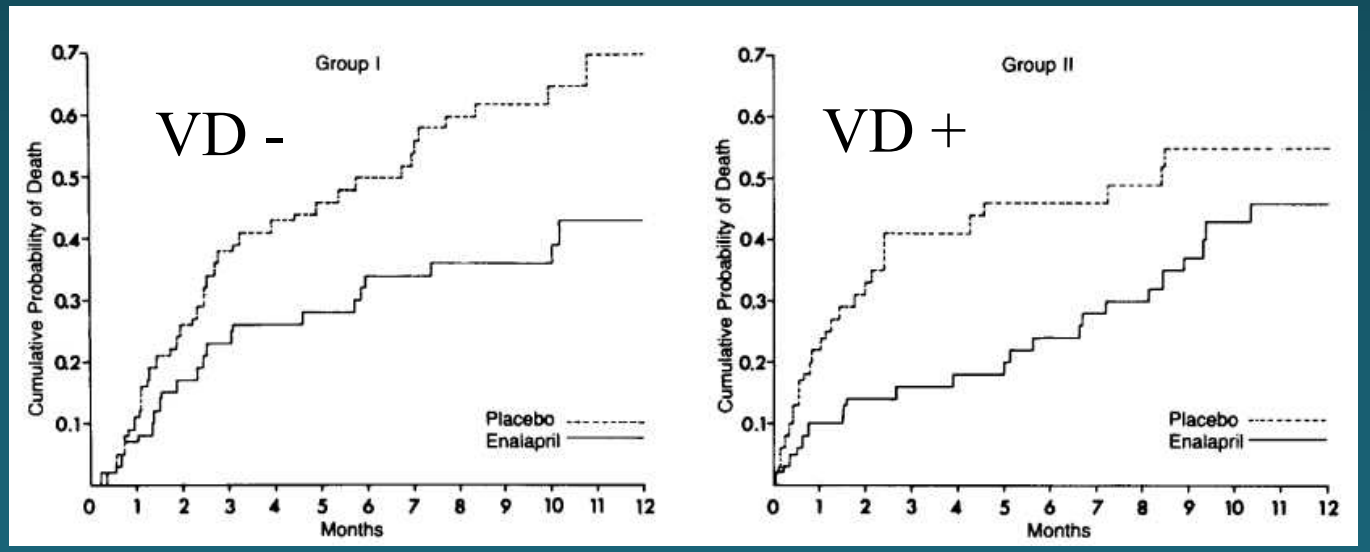
THE CONSENSUS TRIAL STUDY GROUP*

N Engl J Med 1987;316:1429–35

To evaluate the influence of the ACE inhibitor **enalapril** (**2.5 to 40 mg** per day) on the prognosis of severe CHF, randomly assigned 253 patients in a double-blind study to receive either placebo (n = 126) or enalapril (n = 127). Conventional treatment for heart failure, including **vasodilators (**e.g., nitrates, prazosin, hydralazine) , was continued in both groups. **Follow-up averaged 188 days** (range, 1 day to 20 months). The diagnosis of congestive heart failure was based on clinical criteria: a history of heart disease with symptoms of dyspnea or fatigue or both, together with signs of fluid retention and no evidence of primary pulmonary disease. The patients were symptomatic at rest (NYHA functional class IV). The heart size as determined radiologically had to be more than 600 ml per square meter of body-surface area in men (normal, <550) or more than 550 ml per square meter in women (normal, <500).

N Engl J Med 1987;316:1429–35



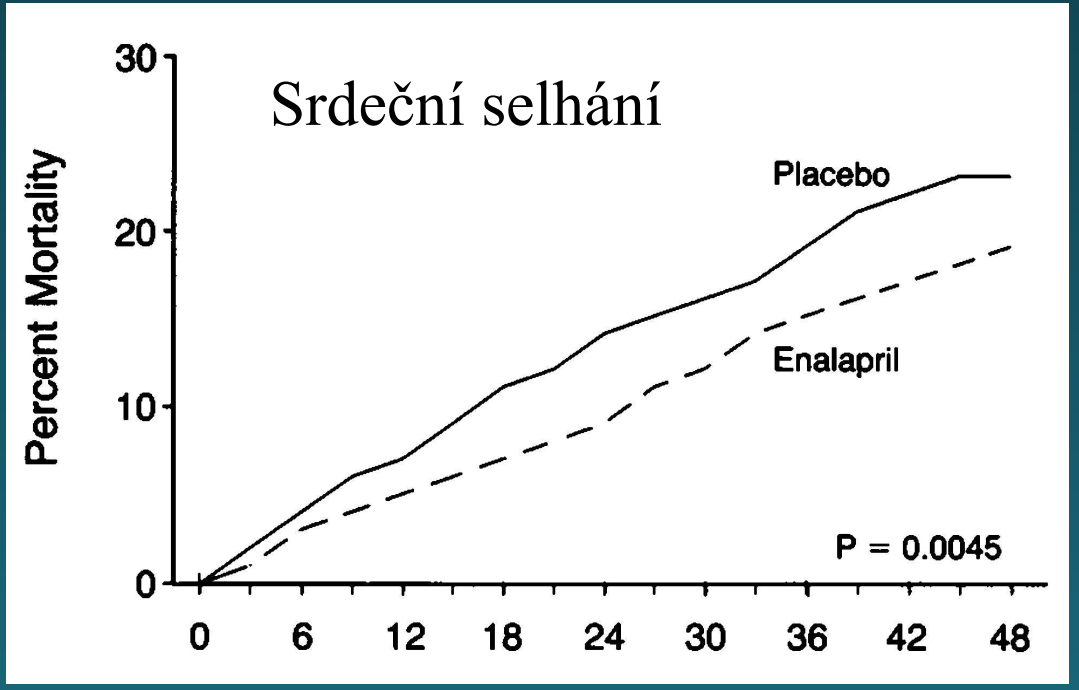


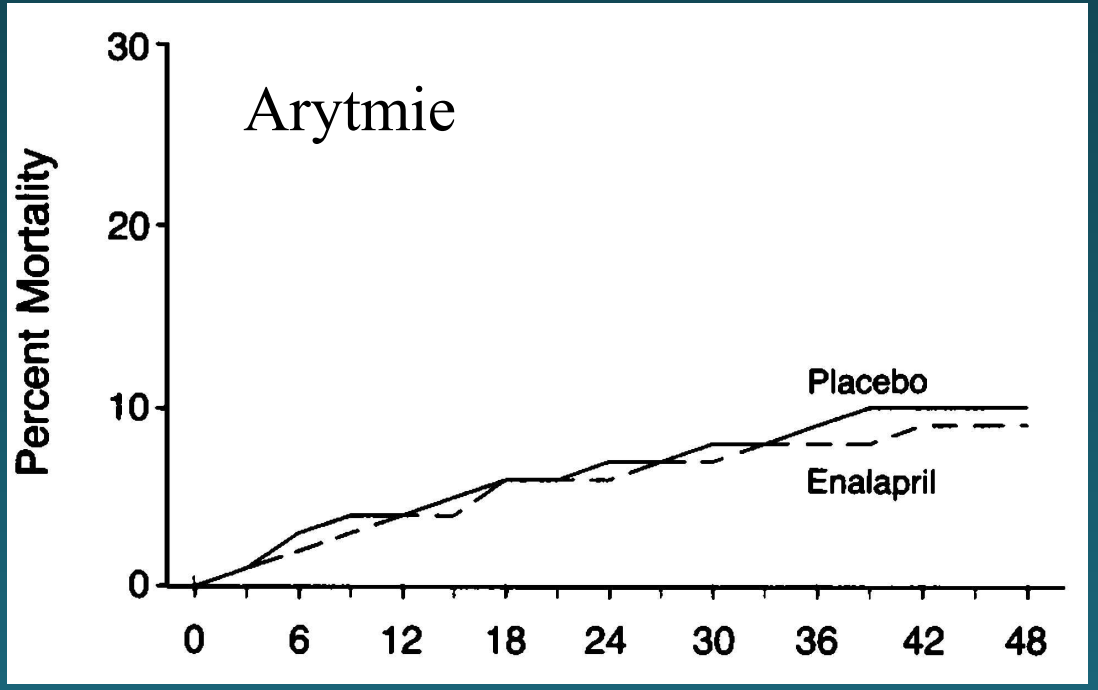
N Engl J Med 1987;316:1429–35

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 New York Heart Association functional classes II and III. EF less than 35% Primary endpoint was mortality.

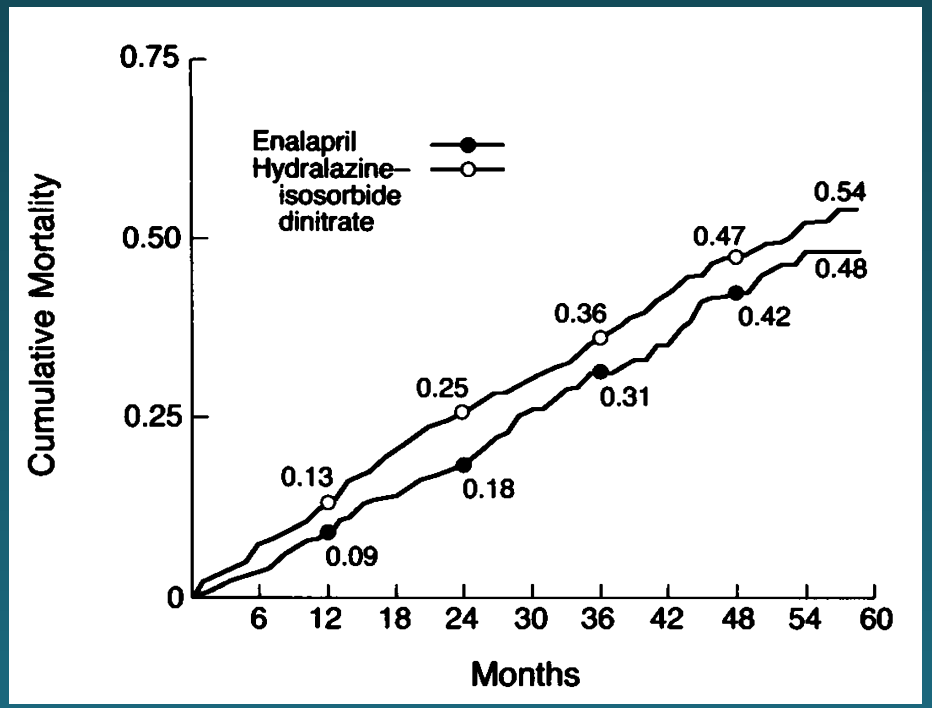


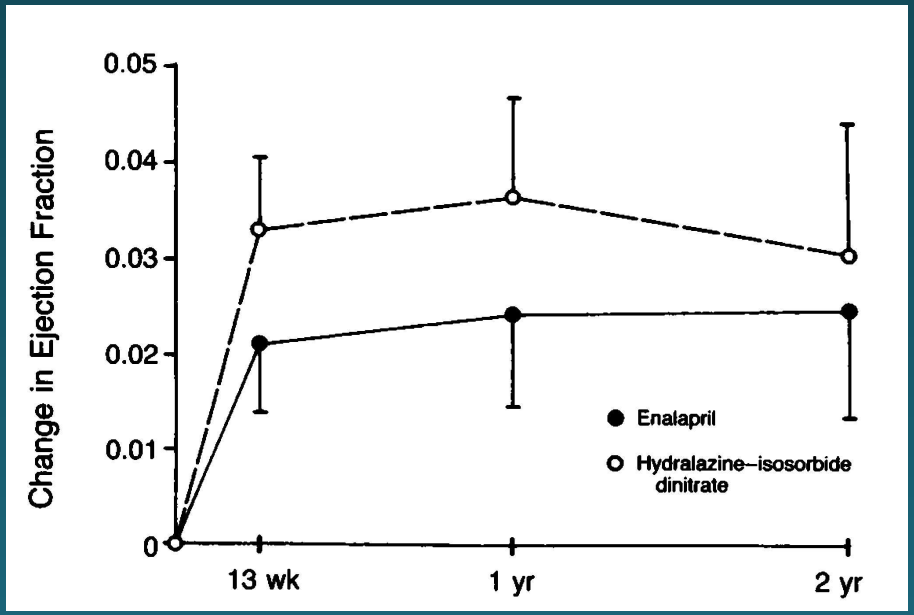


N Eng J Med 1991; 325: 293-302

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 were randomly assigned in a double-blind manner to receive 20 mg of enalapril daily or 300 mg of hydralazine plus 160 mg of isosorbide dinitrate daily.



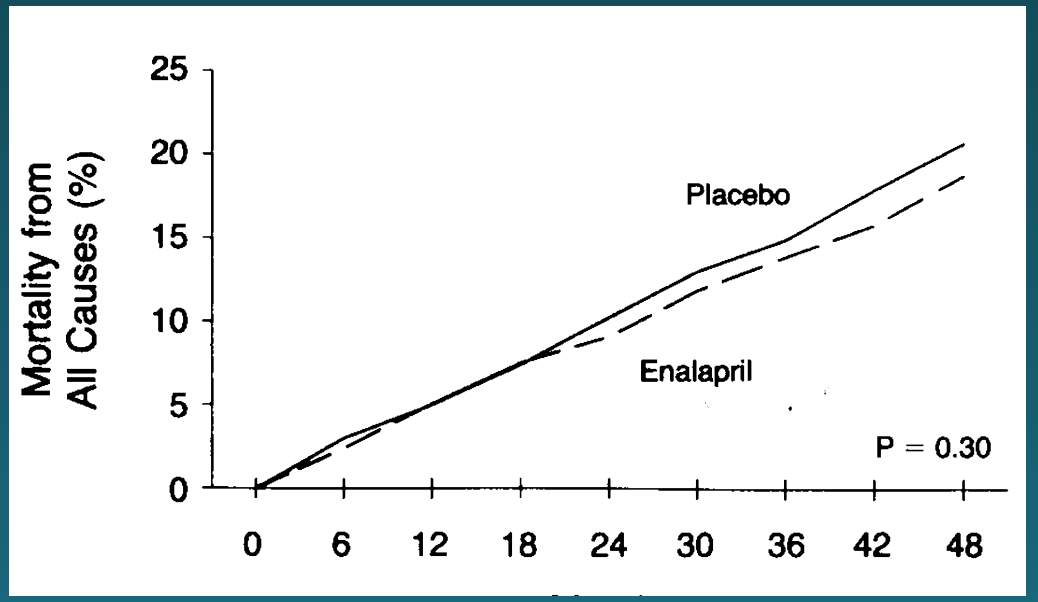


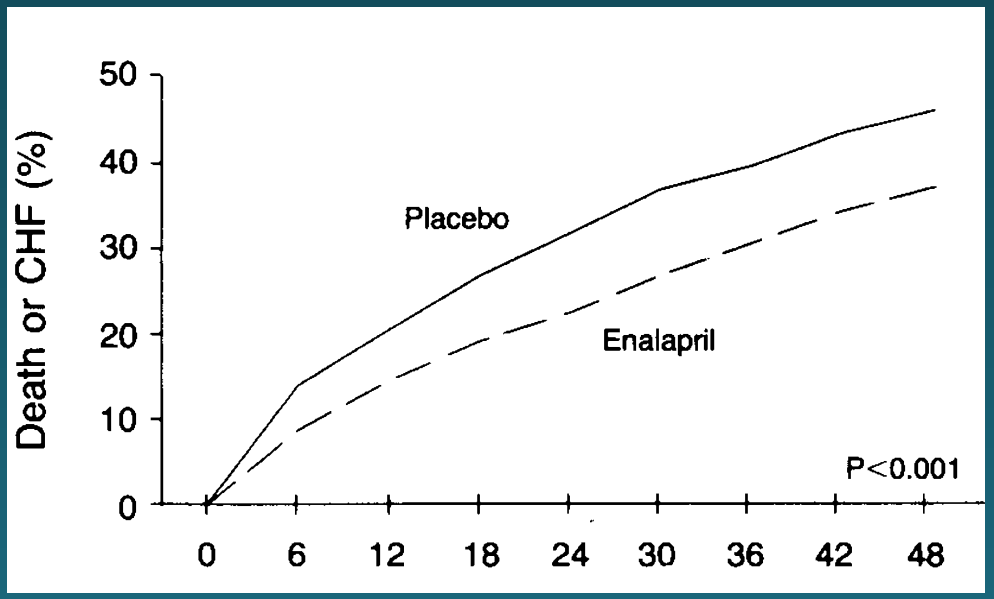
N Eng J Med 1991; 325:303-310

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.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

Vedlejší a nežádoucí účinky ACEi

1. Hyperkalemie, zvláště v kombinaci s MRA
2. Hypotenze
3. Snížení renálních funkcí
4. Dráždivý kašel
5. Angioedém - vzácně

Odlišná reakce AT_1 a AT_2 receptorů na AII

Vazokonstrikce
Vaskulární proliferace
Sekrece aldosteronu
Proliferace myocytů
Zvýšený sympatický tonus

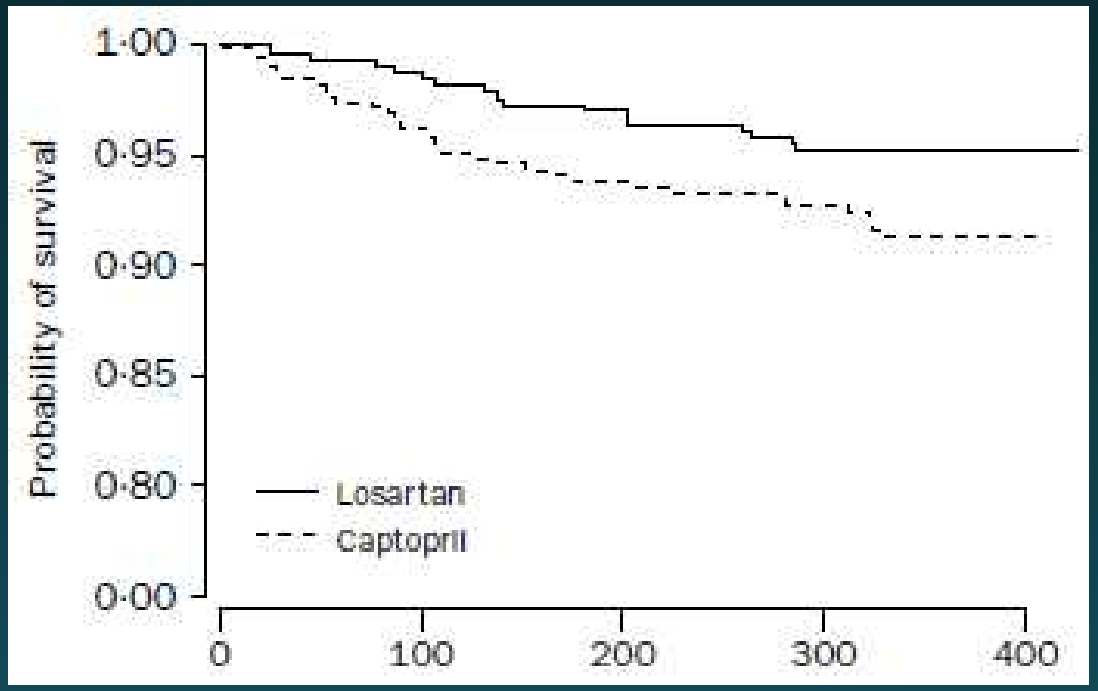
Antiproliferativní
Účinek
Apoptóza
Diferenciace, regenerace
Vazodilatace

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.

Lancet 1997; 349: 747-752



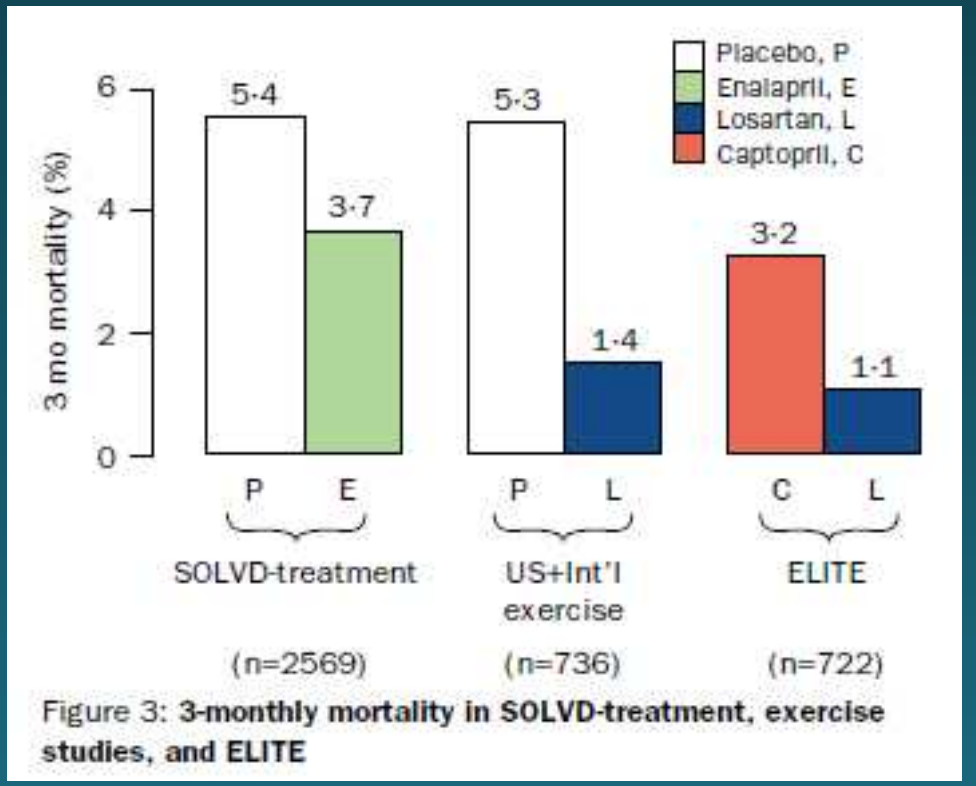


Figure 3: **3-monthly mortality in SOLVD-treatment, exercise studies, and ELITE**

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

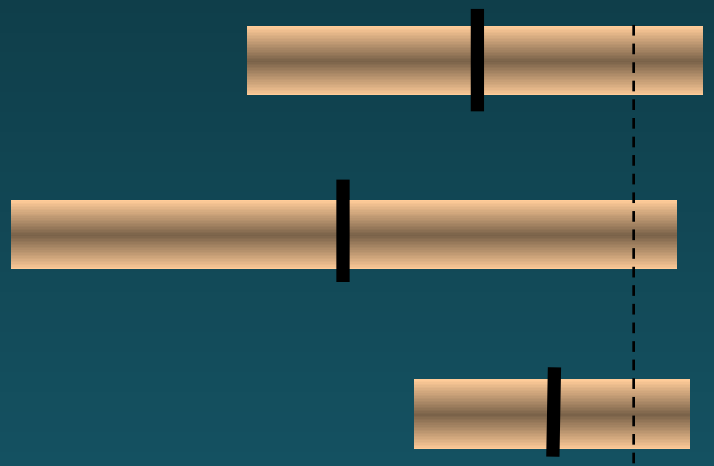
Bertram Pitt, Philip A Poole-Wilson, Robert Segal, on behalf of the ELITE II investigators

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

ELITE II

losartan (1x 50 mg) vs captopril (3x 50 mg)

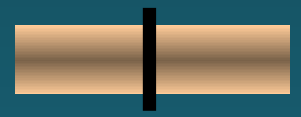


Celková úmrtnost
(15.9% vs 17.7%: $p = 0.16$)

Náhlá smrt/KPR
(7.3% vs 9.0%: $p = 0.08$)

Úmrtnost/Hospitalizace
(44.9% vs 47.7%: $p = 0.21$)

Vysazení pro NUL
(14.5% vs 9.4%: $p < 0.001$)



Favors Captopril

Favors Losartan

0.5 **1.0** **1.25**

Odds Ratio

ARB in congestive heart failure

Recommended to reduce the risk of HF hospitalization and the risk of premature death in patients with an EF ≤40% and **unable to tolerate an ACE inhibitor because of cough** (patients should also receive a beta-blocker and an MRA)

I A

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 EHJ 2012

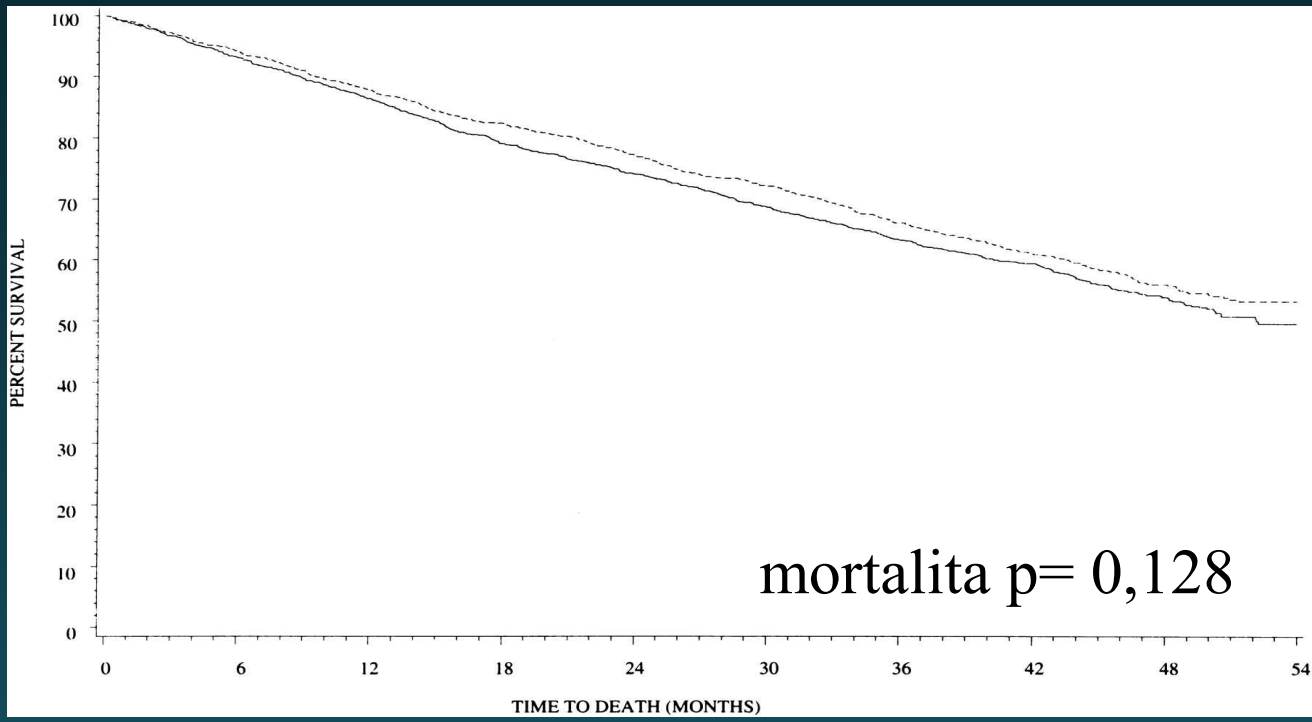
Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure

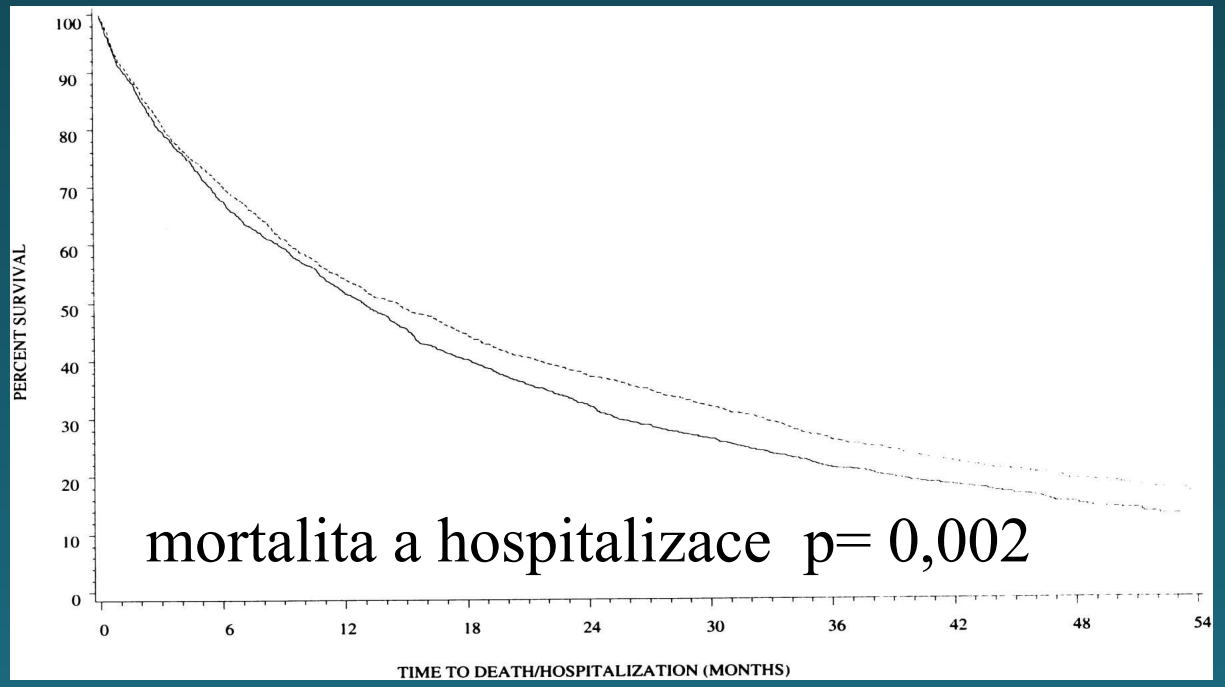
Milton Packer, MD; Philip A. Poole-Wilson, MD; Paul W. Armstrong, MD; John G.F. Cleland, MD; John D. Horowitz, MD; Barry M. Massie, MD; Lars Rydén, MD; Kristian Thygesen, MD; Barry F. Uretsky, MD; on behalf of the ATLAS Study Group*

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





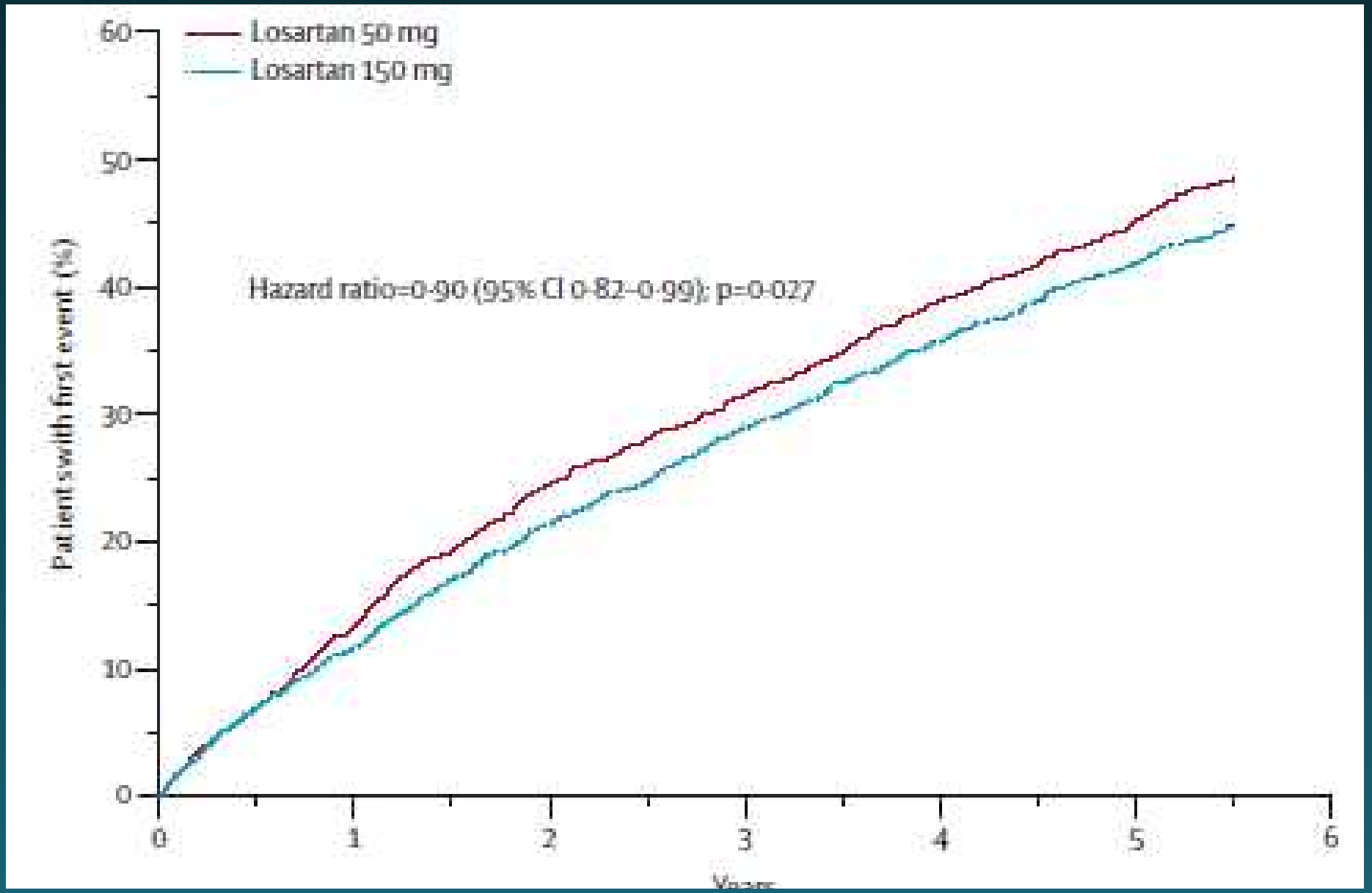
Packer M et al. Circulation 1999;100:2312-23

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‡

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



Lancet 2009; 374: 1840-48

Jak mám si vybrat jednu (jeden),
holky (ACE i/ARB) já mám všechny rád!

captopril, cilazapril, enalapril, fosinopril, imidapril ,**lisinopril**, moexipril, **perindopril**, quinapril, **ramipril**, spirapril, **trandolapril**

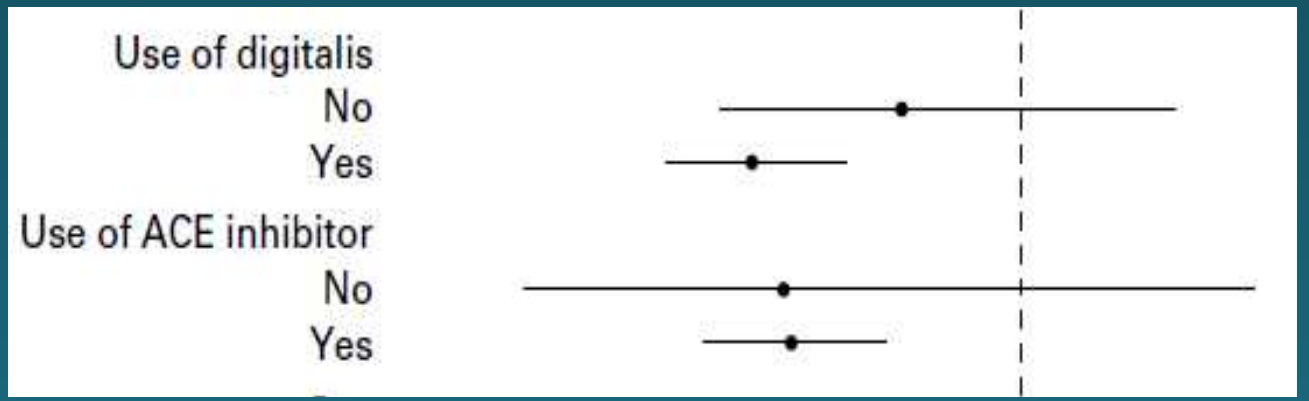
candesartan,eprosartan,inbesartan, **losartan**, telmisartan,**valsartan**

žlutě – doporučeny k léčbě srdečního selhání

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 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.



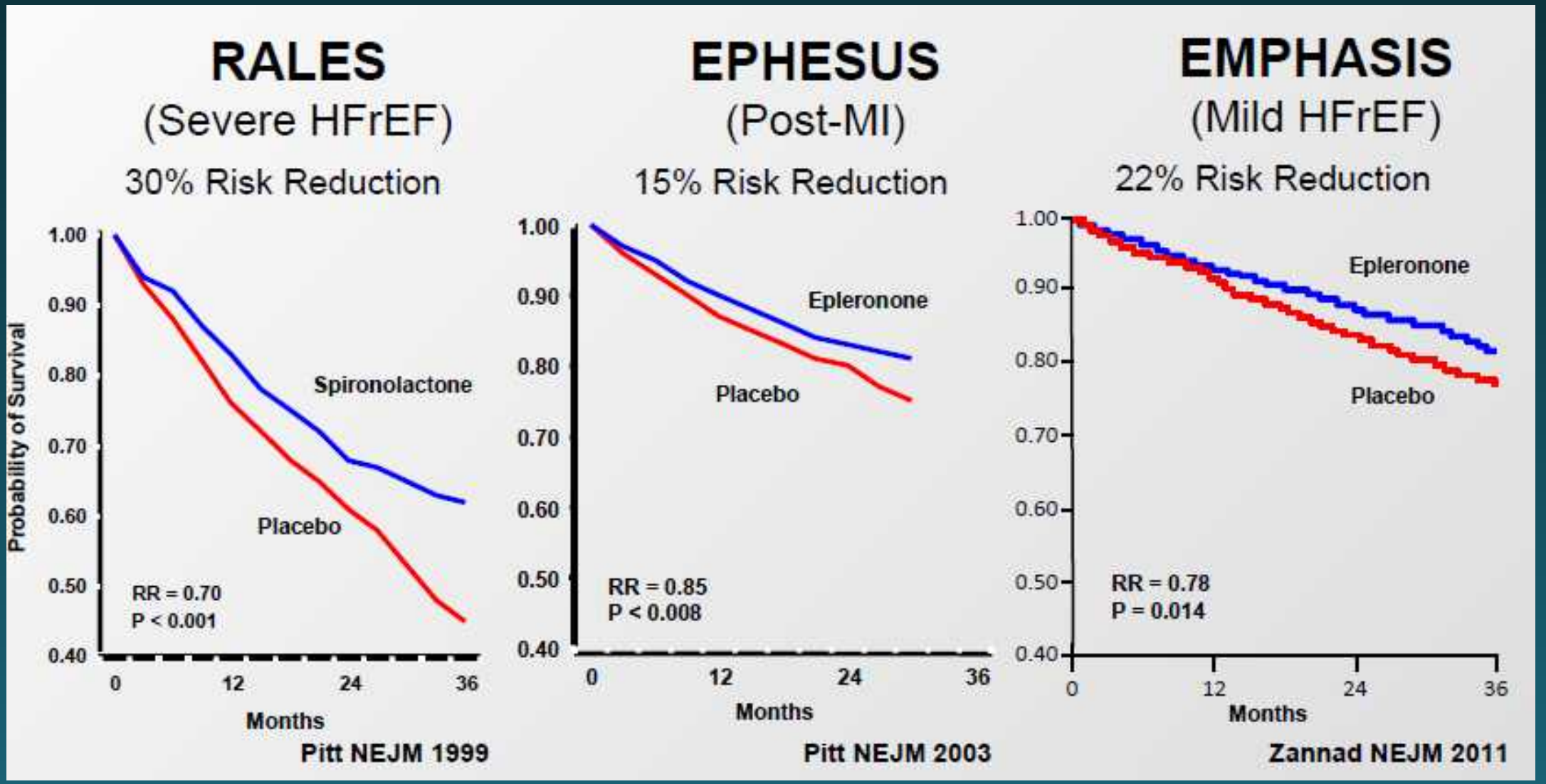
N Eng J Med 1999; 341: 709-712

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*

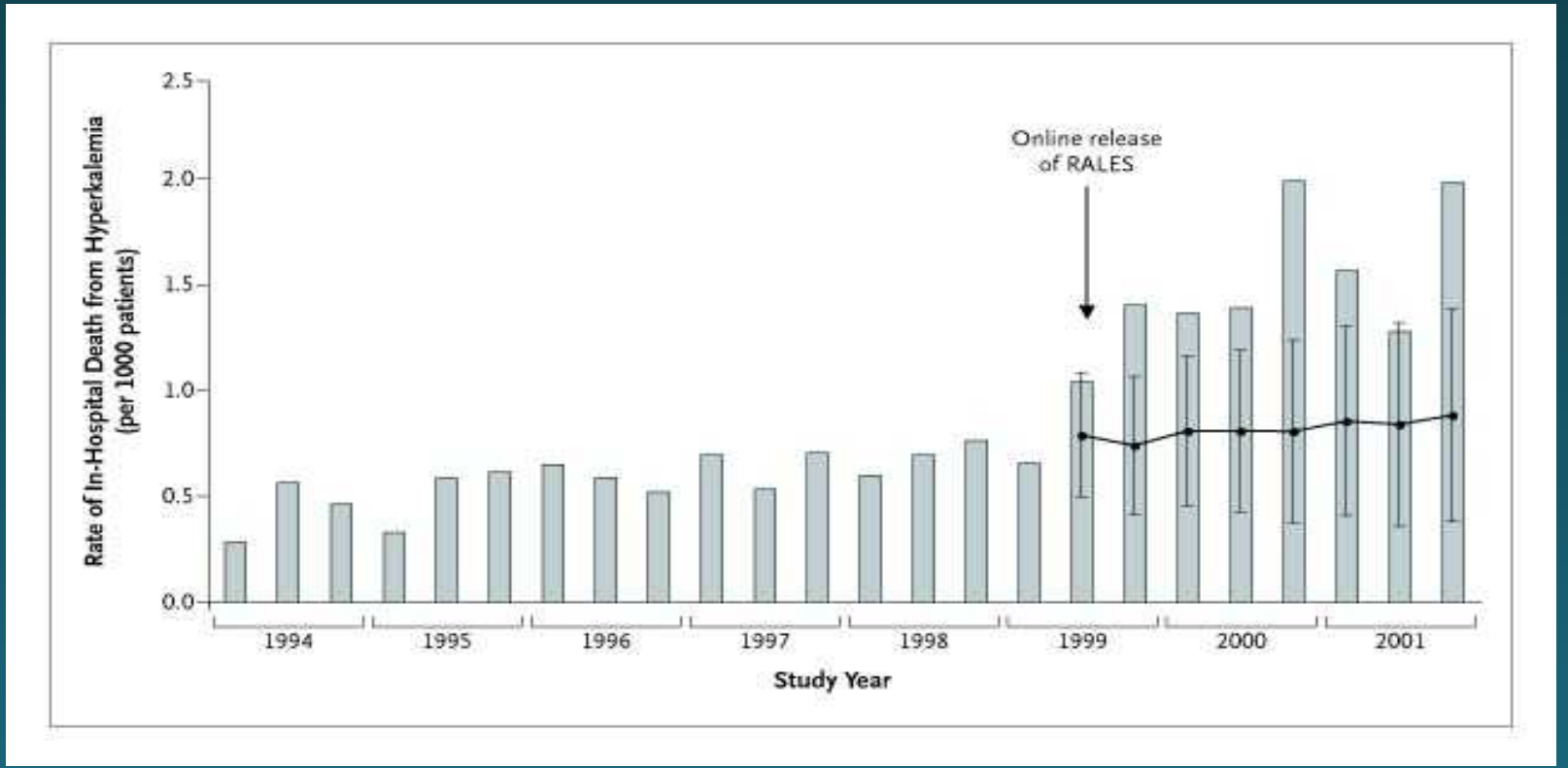
In this randomized, double-blind trial, we randomly assigned 2737 patients with New York Heart Association class II heart failure and an ejection fraction of no more than 35% to receive **eplerenone n=1364 (up to 50 mg daily) or placebo n=1373, in addition to recommended therapy**. The primary outcome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

N Eng J Med 2011; 364: 11-21


RALES
(Severe HFrEF)
30% Risk Reduction
Probability of Survival
1.00
0.90
0.80
0.70
0.60
0.50
0.40
Spironolactone
Placebo
RR = 0.70
P < 0.001
0
12
24
36
Months
Pitt NEJM 1999
EPHESUS
(Post-MI)
15% Risk Reduction
Epleronone
Placebo
RR = 0.85
P < 0.008
Pitt NEJM 2003
EMPHASIS
(Mild HFrEF)
22% Risk Reduction
Epleronone
Placebo
RR = 0.78
P = 0.014
Zannad NEJM 2011

Blokátory mineralokortikoidních receptorů

1. Srdeční selhání II-IV
2. Stav po infarktu myokardu s nízkou EF
3. Rezistentní hypertenze

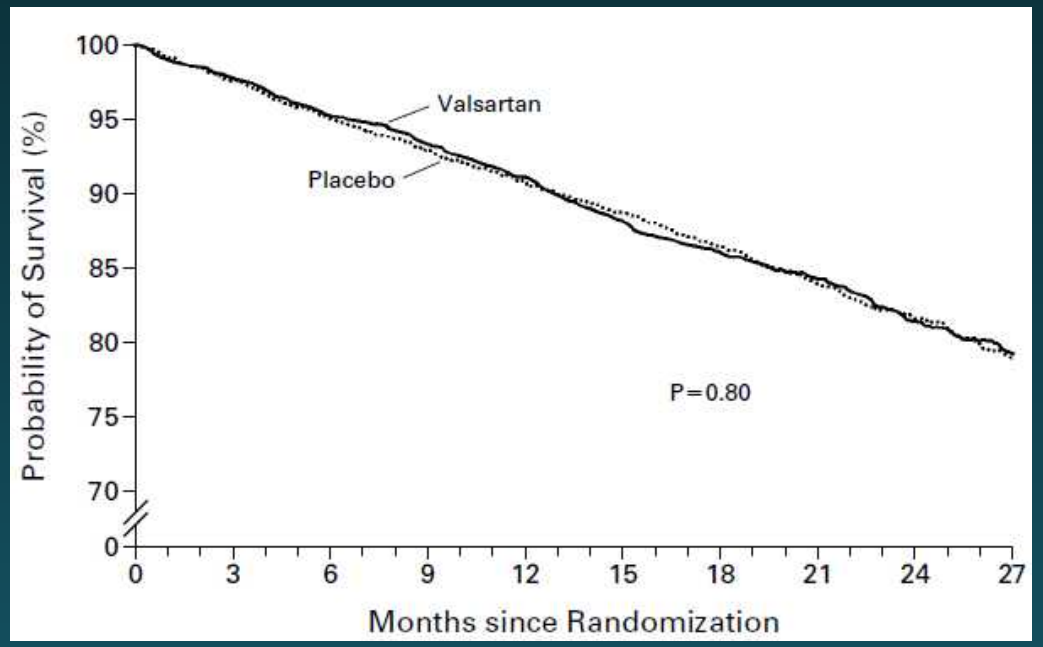


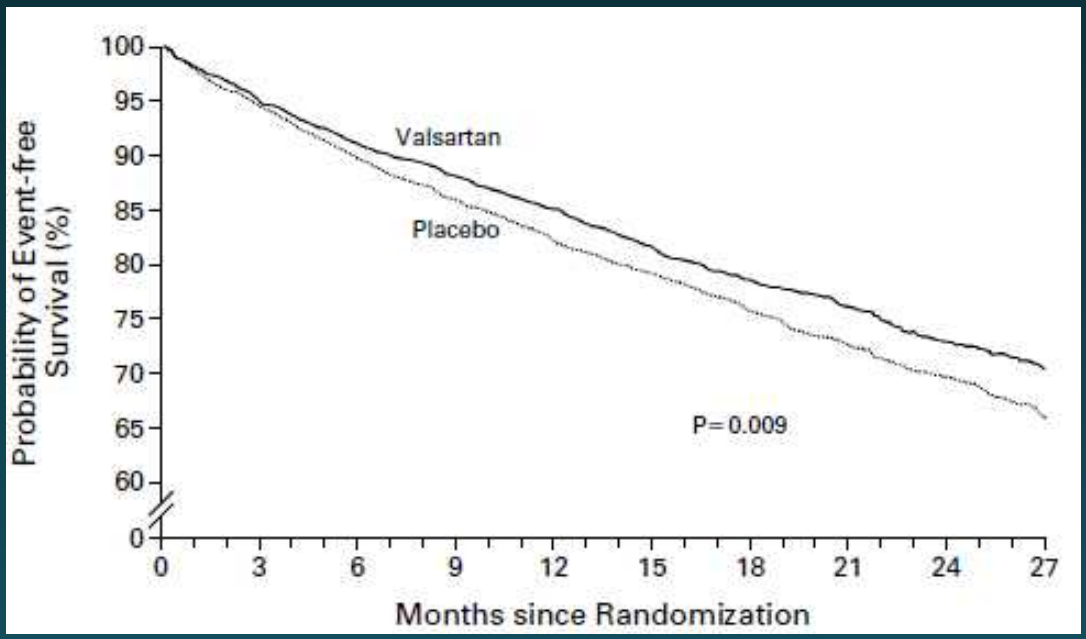
A RANDOMIZED TRIAL OF THE ANGIOTENSIN-RECEPTOR BLOCKER VALSARTAN IN CHRONIC HEART FAILURE

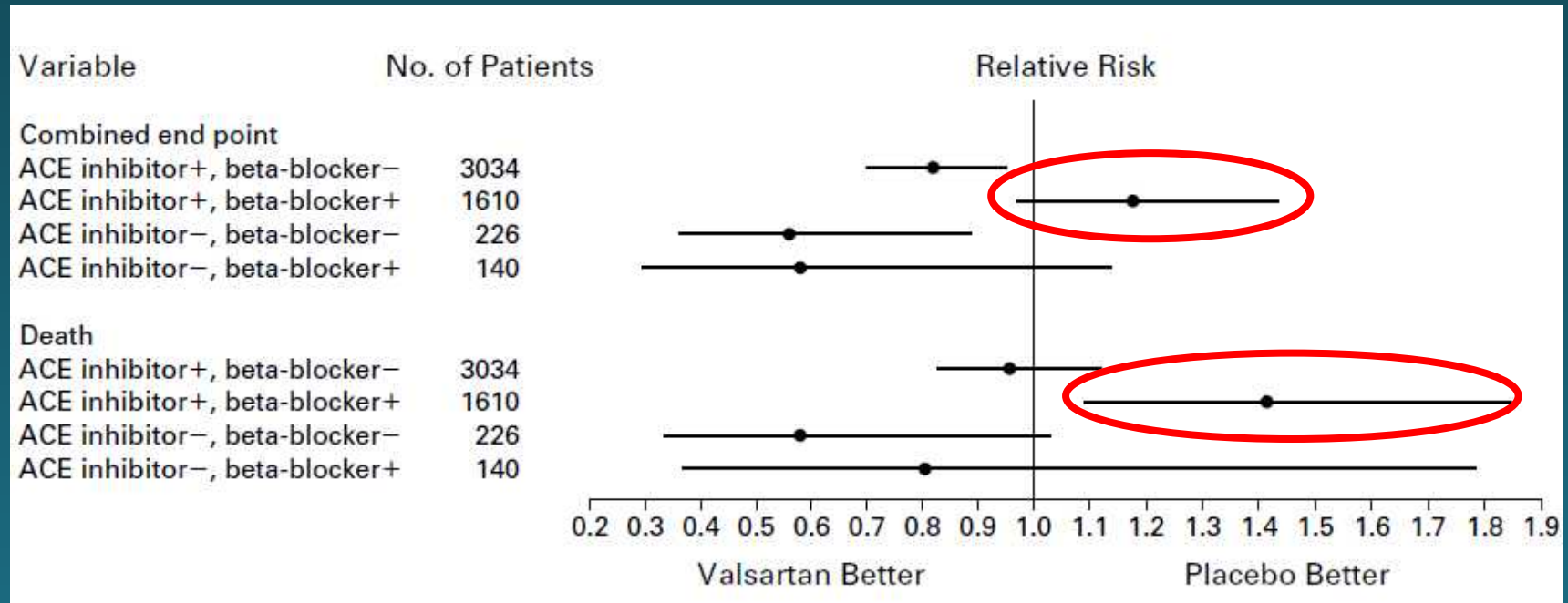
JAY N. COHN, M.D., AND GIANNI TOGNONI, M.D., FOR THE VALSARTAN HEART FAILURE TRIAL INVESTIGATORS*

A total of 5010 patients with heart failure of New York Heart Association (NYHA) class 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.

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

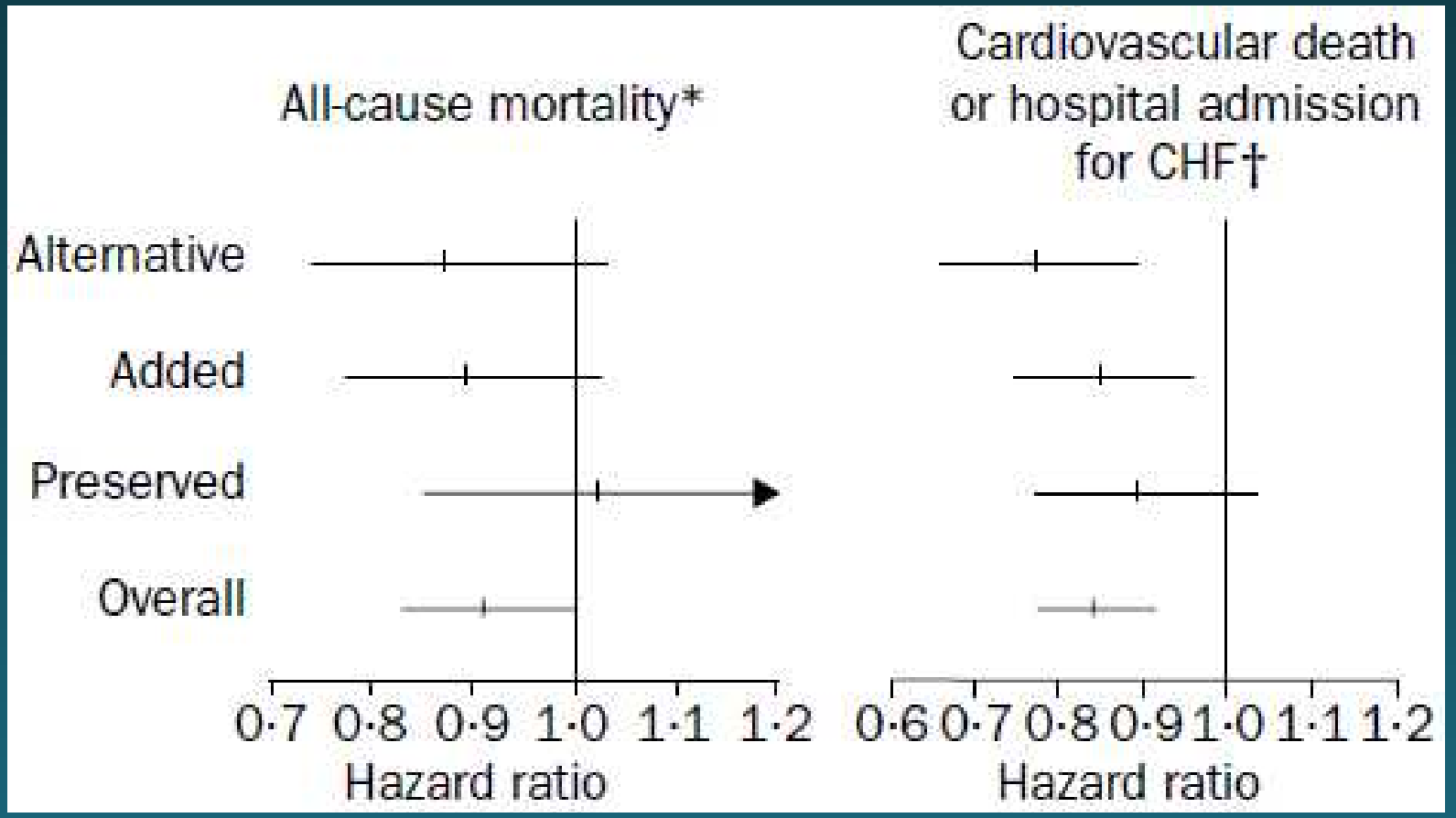
*Marc A Pfeffer, Karl Swedberg, Christopher B Granger, Peter Held, John J V McMurray, Eric L Michelson, Bertil Olofsson, Jan Östergren, Salim Yusuf, for the CHARM Investigators and Committees**

We studied patients with LVEF 40% or less who were not receiving ACE inhibitors because of previous intolerance or who were currently receiving ACE inhibitors, and patients with LVEF higher than 40%. Overall, 7601 patients were randomly assigned candesartan (n=3803, titrated to 32 mg once daily) or placebo (n=3796), and followed up 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

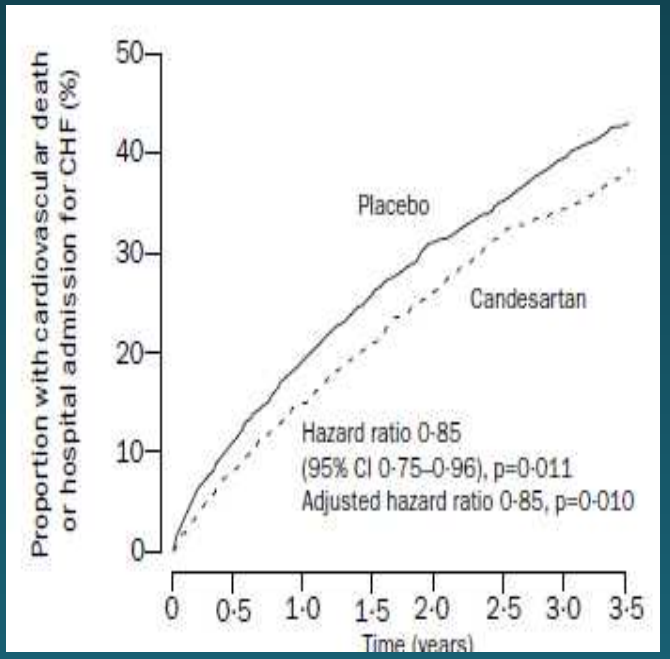
*Marc A Pfeffer, Karl Swedberg, Christopher B Granger, Peter Held, John J V McMurray, Eric L Michelson, Bertil Olofsson, Jan Östergren, Salim Yusuf, for the CHARM Investigators and Committees**

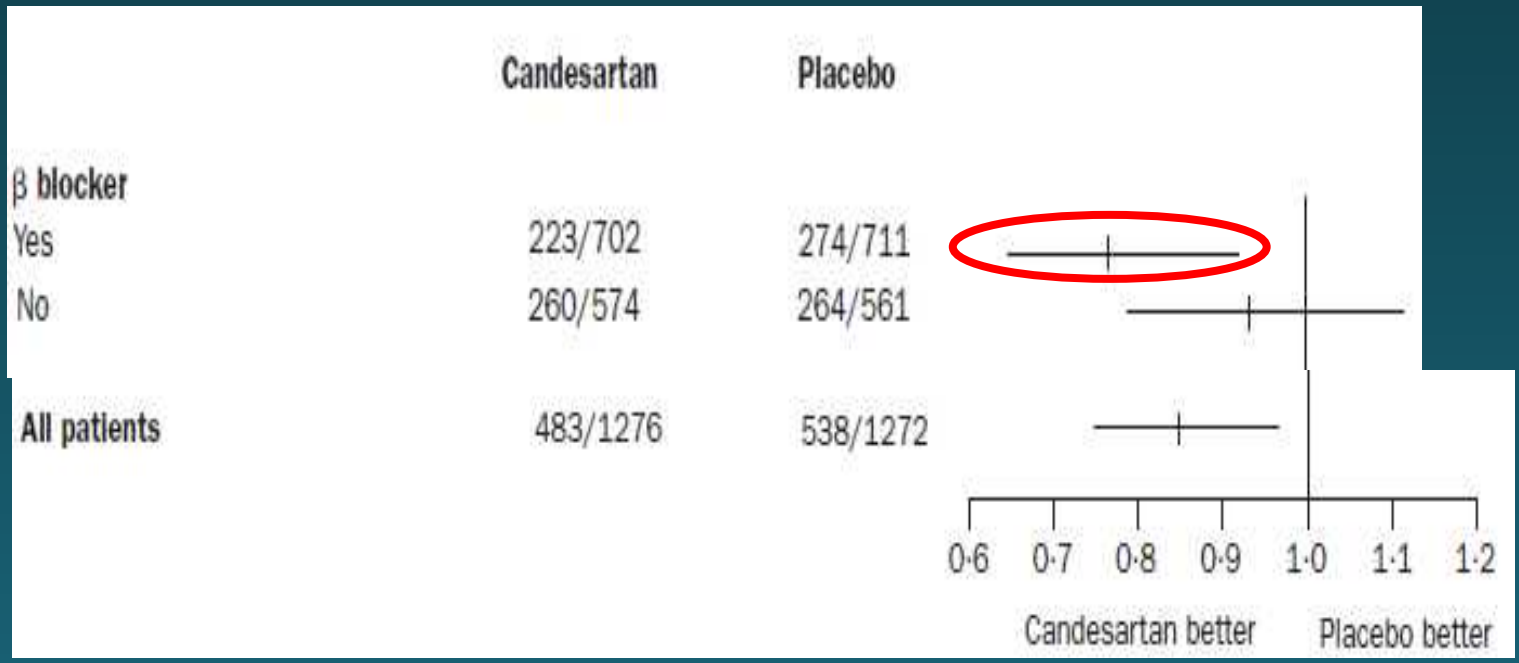


Lancet 2003; 362: 759-66

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)





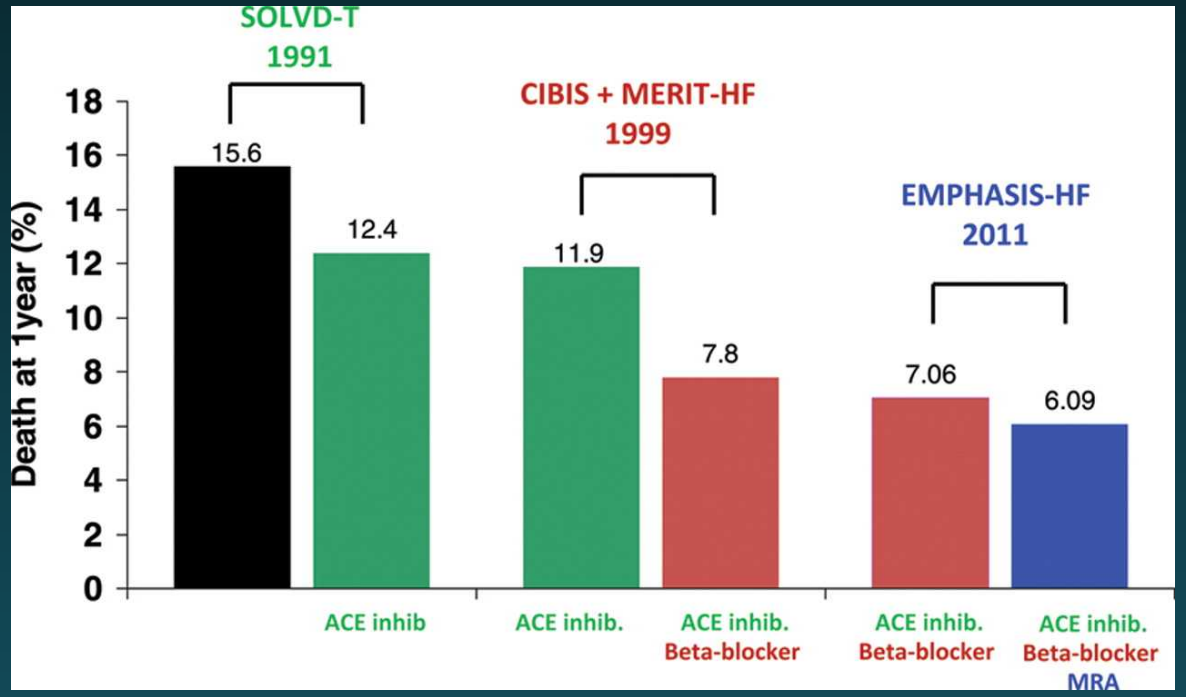
Lancet 2003; 362: 767-71

ACE i + ARB u srdečního selhání

Recommended to reduce the risk of HF hospitalization in patients with an EF ≤40% and persisting symptoms (NYHA class II–IV) despite treatment **with an ACE inhibitor and a beta-blocker who are unable to tolerate an MRA**.

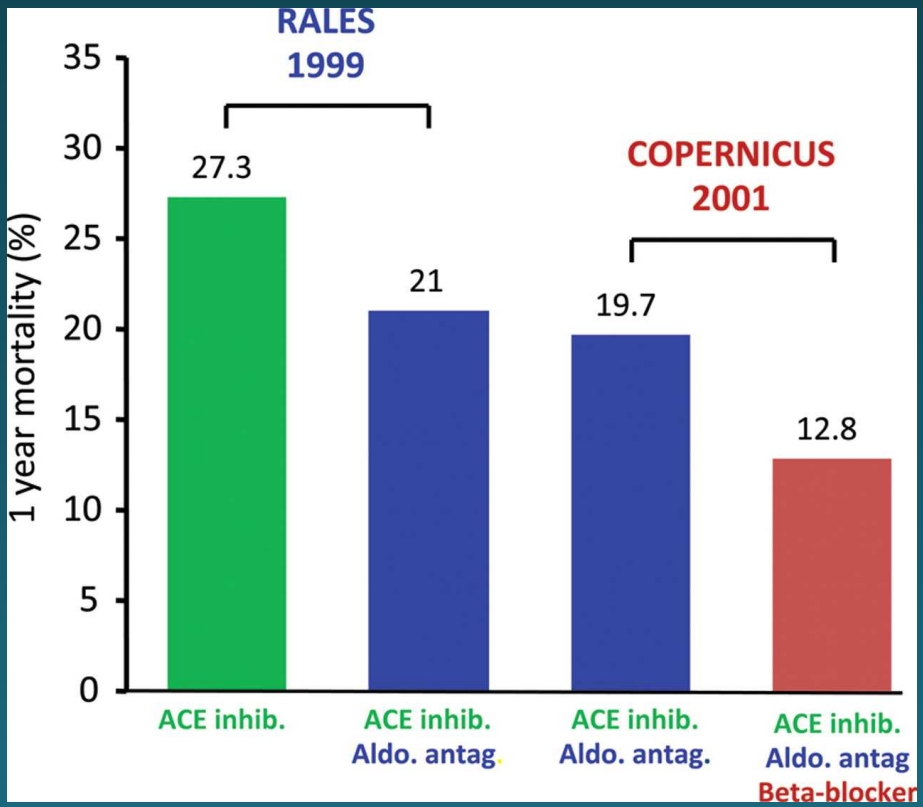
I A

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 EHJ 2012



NYHA II

NYHA III-IV

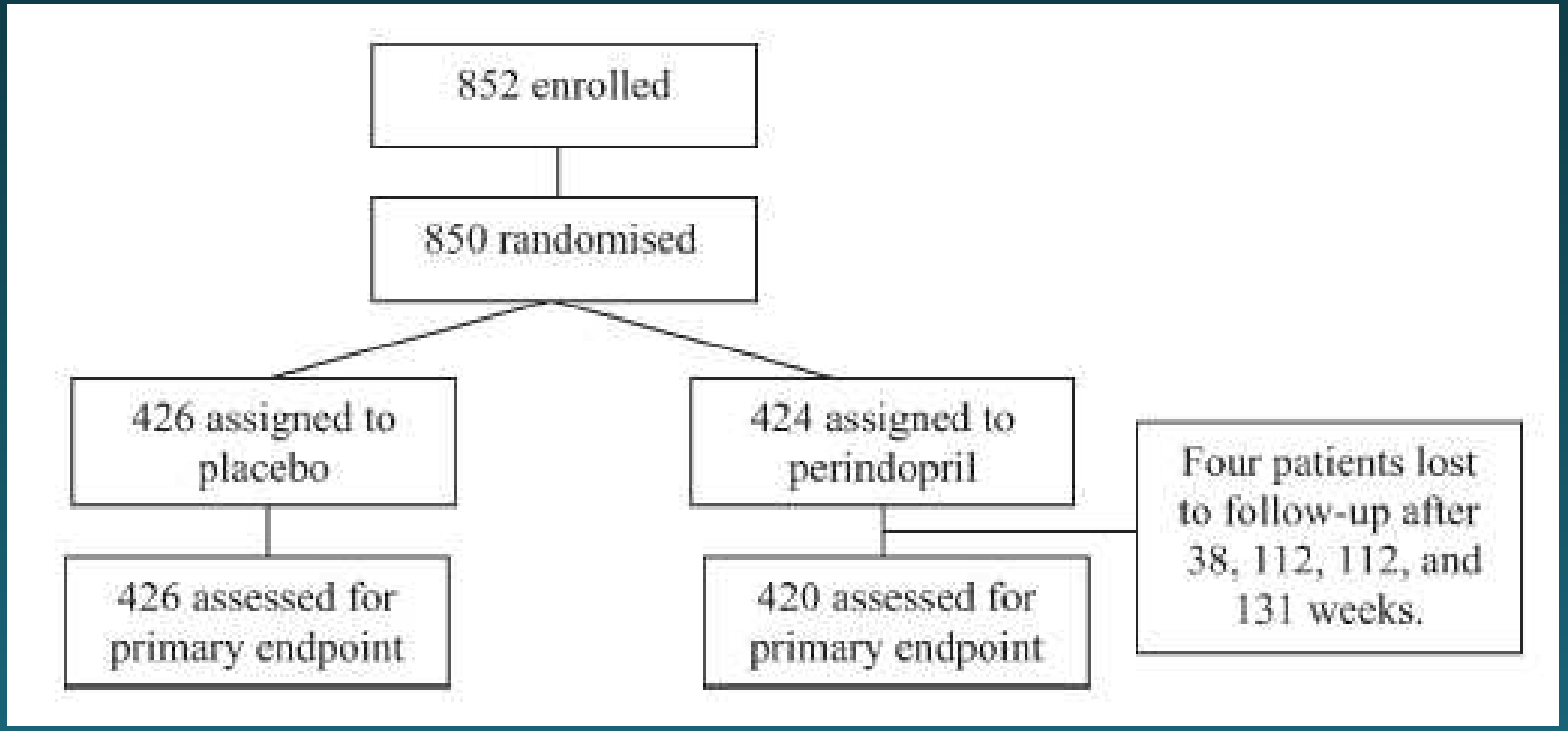


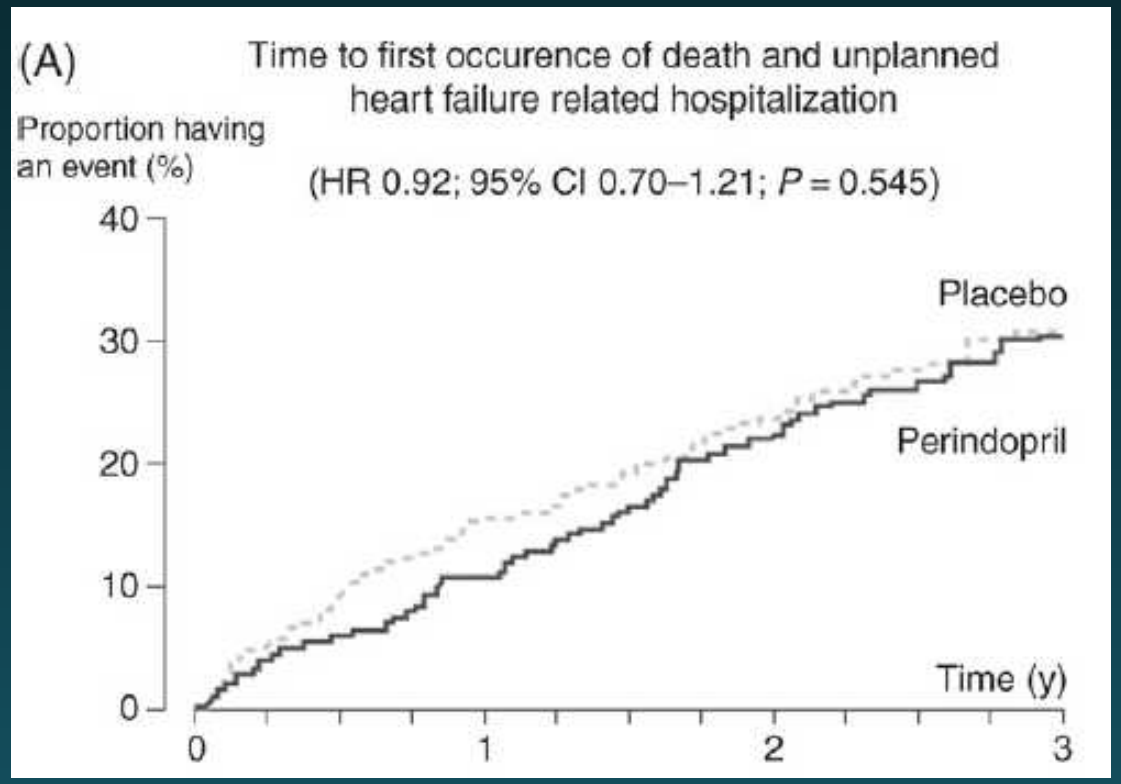
Srdeční selhání se zachovalou EF a jak reaguje na blokádu RAAS

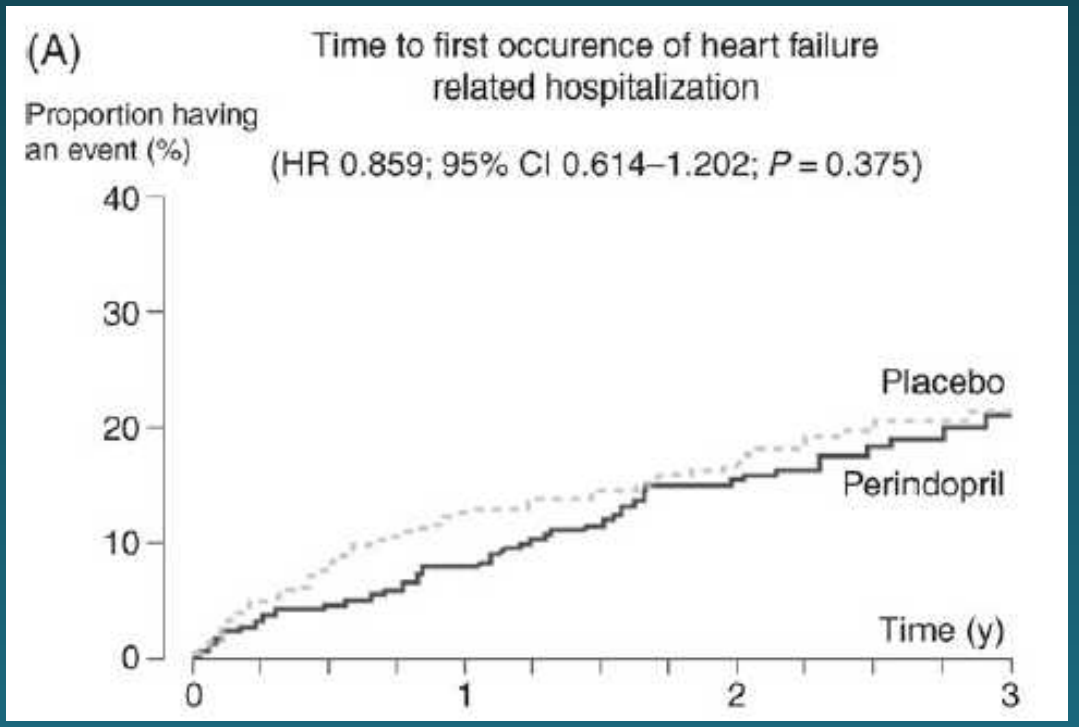
Srdeční dysfunkce může být diastolická, kdy se srdeční komory špatně plní krví, nejčastěji při poklesu jejich poddajnosti (= vzestupu tuhosti) a zhoršené roztažitelnosti. Při postižení pouze diastolické funkce se srdeční selhání také nazývá srdeční selhání se zachovanou ejekční frakcí (HFPEF – heart failure with preserved ejection fraction).

FASTTRACK The perindopril in elderly people with chronic heart failure (PEP-CHF) study

John G.F. Cleland[1*], Michal Tendera[2], Jerzy Adamus[3], Nick Freemantle[4], Lech Polonski[5], and Jacqueline Taylor[6] on behalf of PEP-CHF Investigators



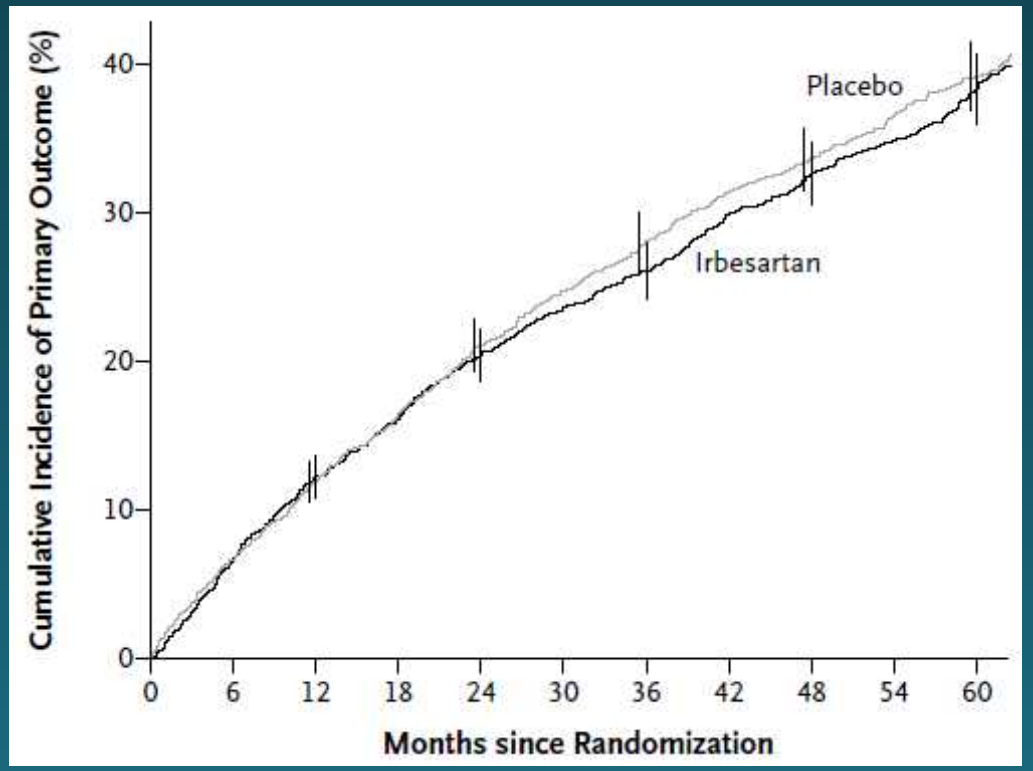

(A)
Time to first occurence of death and unplanned heart failure related hospitalization
Proportion having an event (%)
(HR 0.92; 95% CI 0.70–1.21; P = 0.545)
40
30
20
10
0
Placebo
Perindopril
Time (y)
0
1
2
3


(A)
Time to first occurence of heart failure related hospitalization
Proportion having an event (%)
(HR 0.859; 95% CI 0.614–1.202; P = 0.375)
40
30
20
10
0
Placebo
Perindopril
Time (y)
0
1
2
3

Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction

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

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

Treatment **O**f **P**reserved **C**ardiac Function Heart Failure with an **A**ldosterone an**T**agonist **(TOPCAT)**

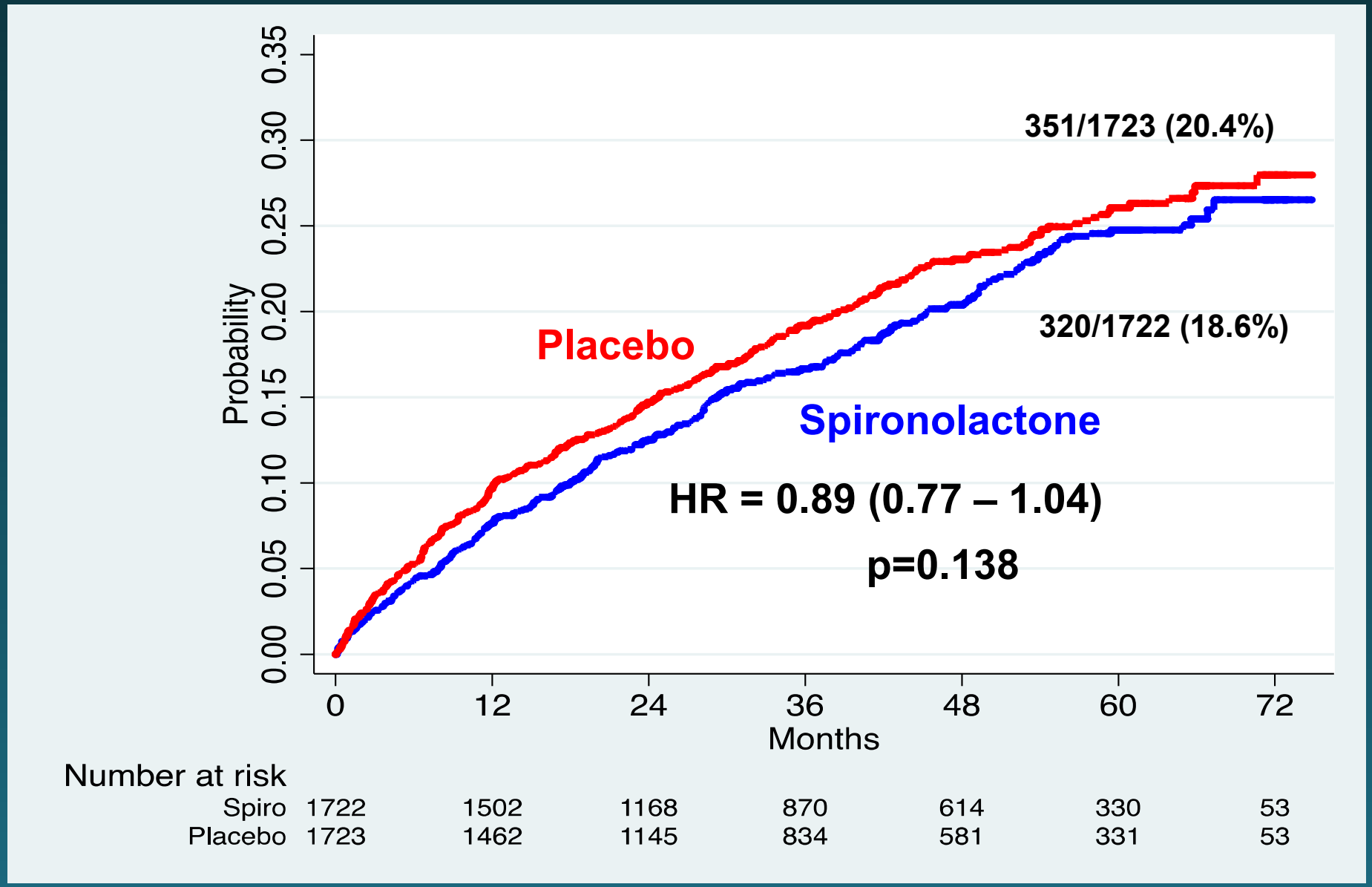
- Objective
  - **To determine if treatment with spironolactone can produce a clinically meaningful reduction in the composite endpoint of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure, compared with placebo, in adults with HF-Preserved EF.**
- Inclusions:

  Symptomatic Heart Failure, Age ≥ 50, LVEF ≥ 45%, stratified according to:
  - **Hospitalization within the past year for management of heart failure, or**
  - **Elevated natriuretic peptides (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL)**
- Major Exclusions:

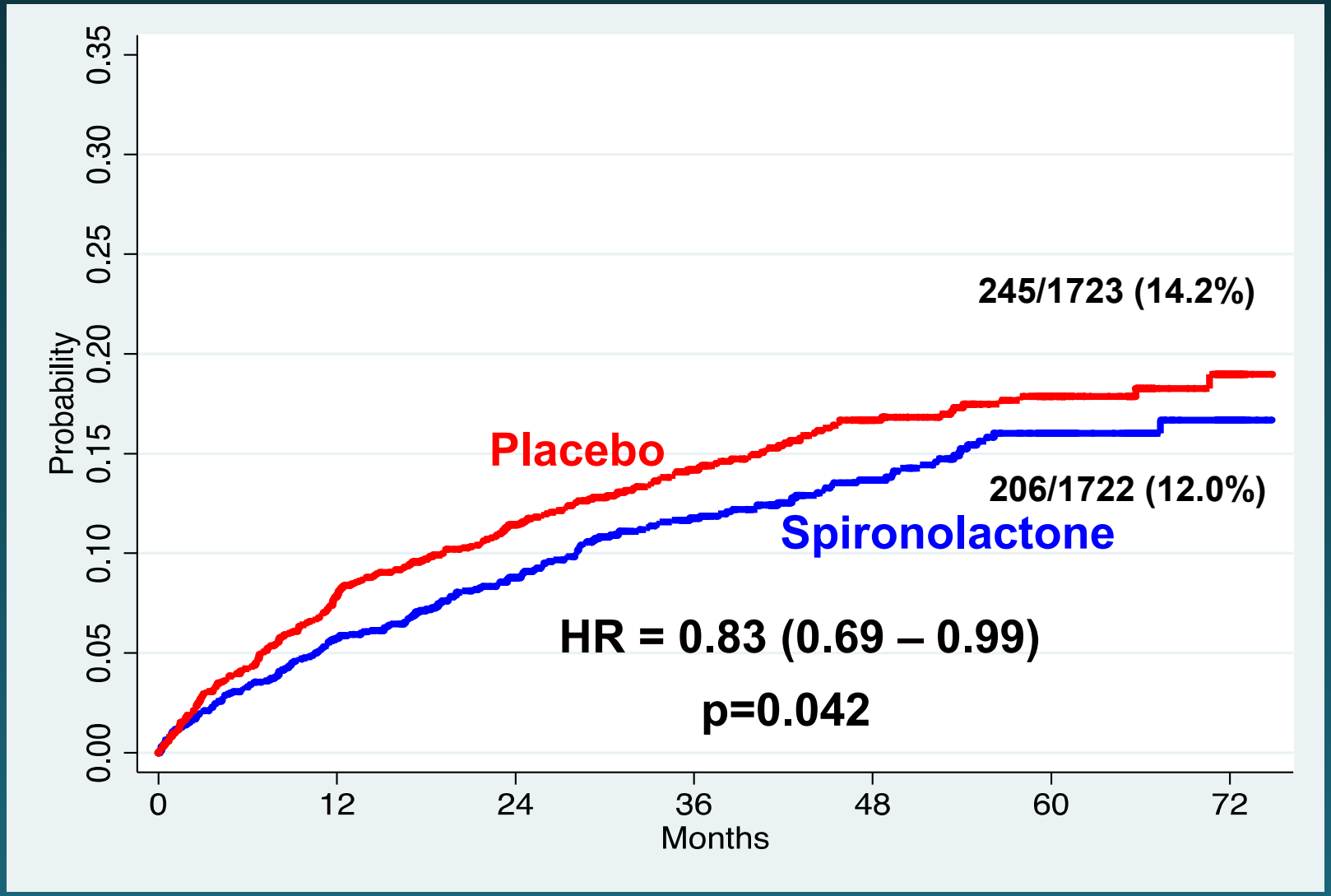
  eGFR<30 mL/min/1.7m^2, serum potassium ≥5 mmol/L, uncontrolled hypertension, AF with rate > 90/min, recent ACS, restrictive, infiltrative, or hypertrophic cardiomyopathy

Rationale and design: (A. Desai, Am Heart J 2011)

Primární cíl
(CV Death, HF Hosp, or CPR)



Hospitalizace pro srdeční selhání



Indikace blokátorů RAAS u CHSS

1. ACEi/ARB již od NYHA I až po IV
2. MRA od NYHA II-IV a po IM s dysfunkcí LK
3. Kombinace ACEi a ARB jen v případě KI MRA
4. Sledovat TK, renální funkce a kalemii
5. U nemocných s HFPEF individuální přístup