

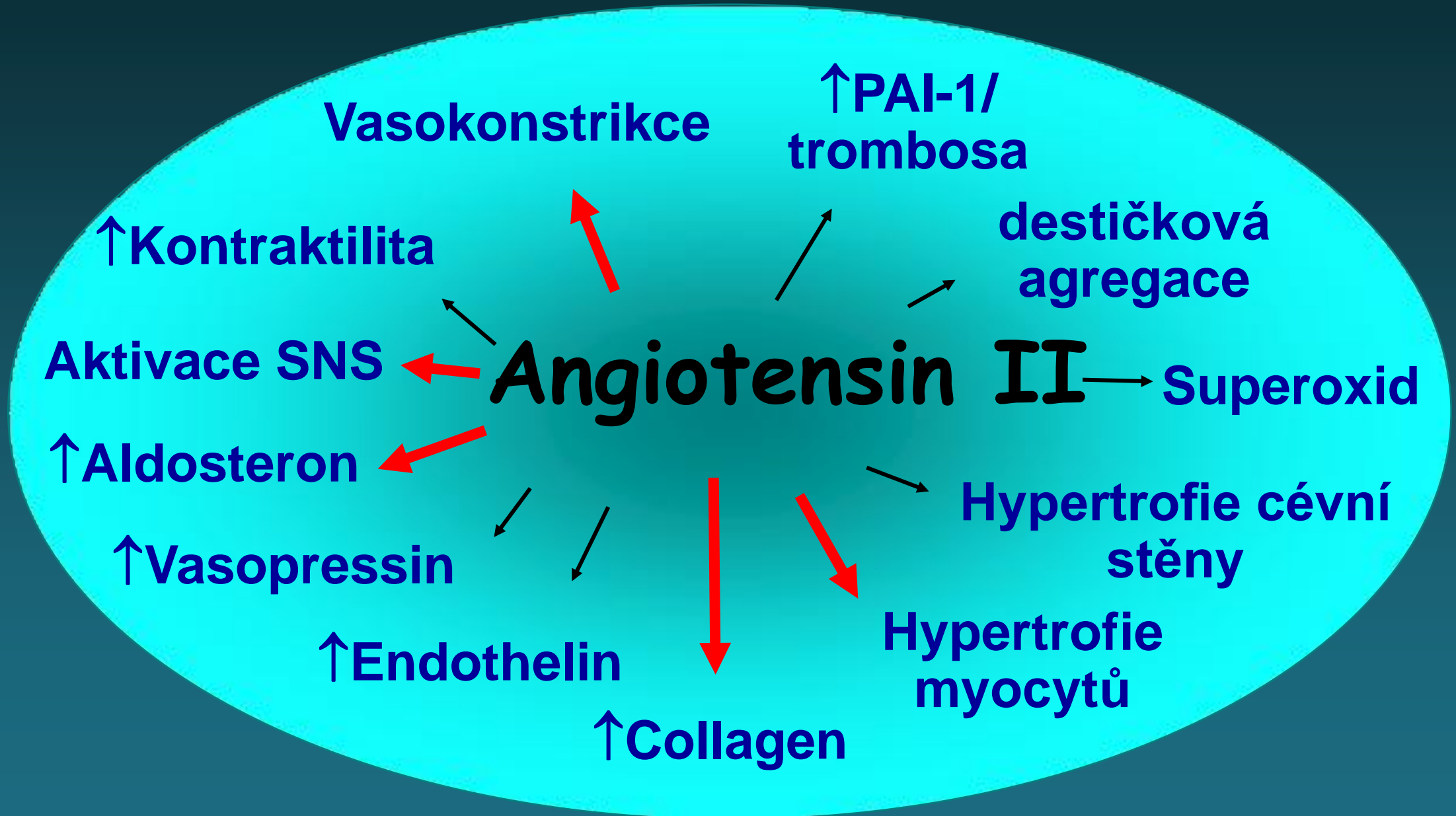
# Stříbrná svatba srdečního selhání a blokády systému

## RAAS

Jiří Vítovec

LF MU a ICRC FN u sv. Anny

# Patofysiologický efekt angiotensinu II



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**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 dvojité slepě buď na placebo (n = 126) či enalapril (n = 127).

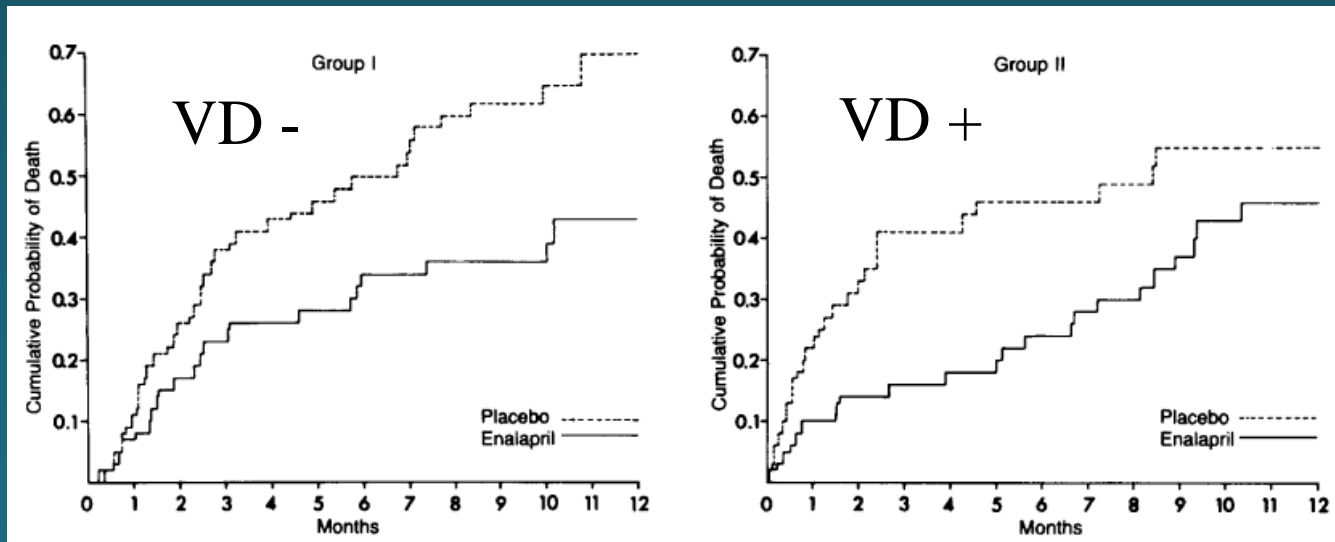
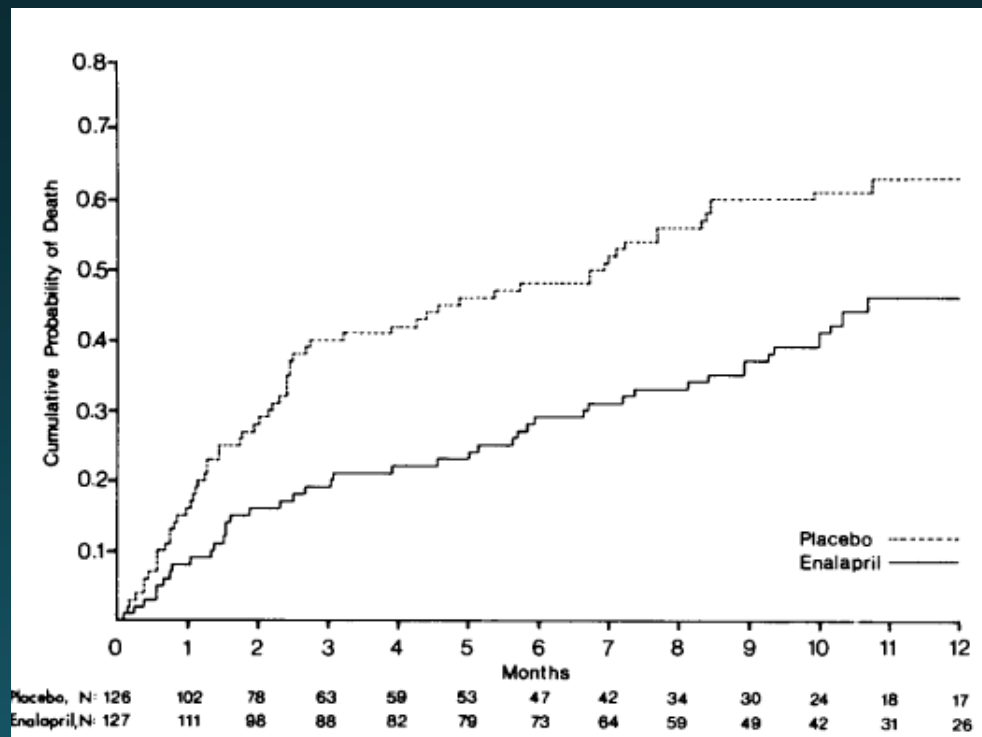
Konvenční léčba srdečního selhání byla: digitalis, diuretika, včetně **vasodilatancií (nitrates, prazosin, hydralazine)**.

**Follow-up** byl průměrně **188 dní** (od 1 dne do 20 měsíců).

Diagnóza ChSS byla stanovena na základě klinických kritérií: anamnéza srdečního onemocnění se symptomy dušnosti, únavy, dále známkami retence tekutin při vyloučení primárního plicního onemocnění

Nemocní byli klidově symptomatictí (**NYHA IV**).

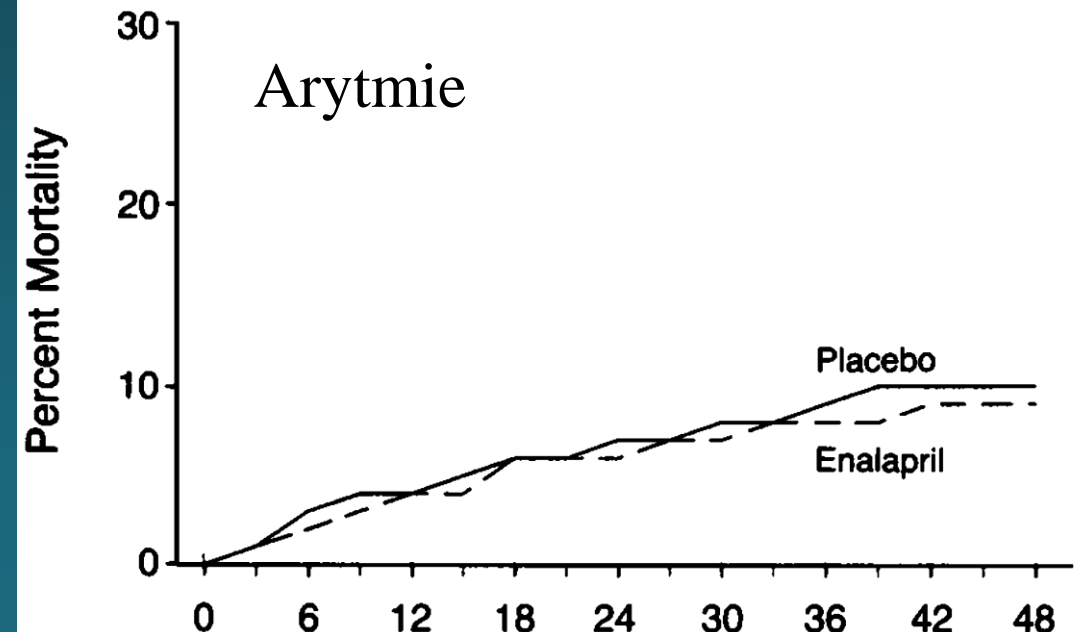
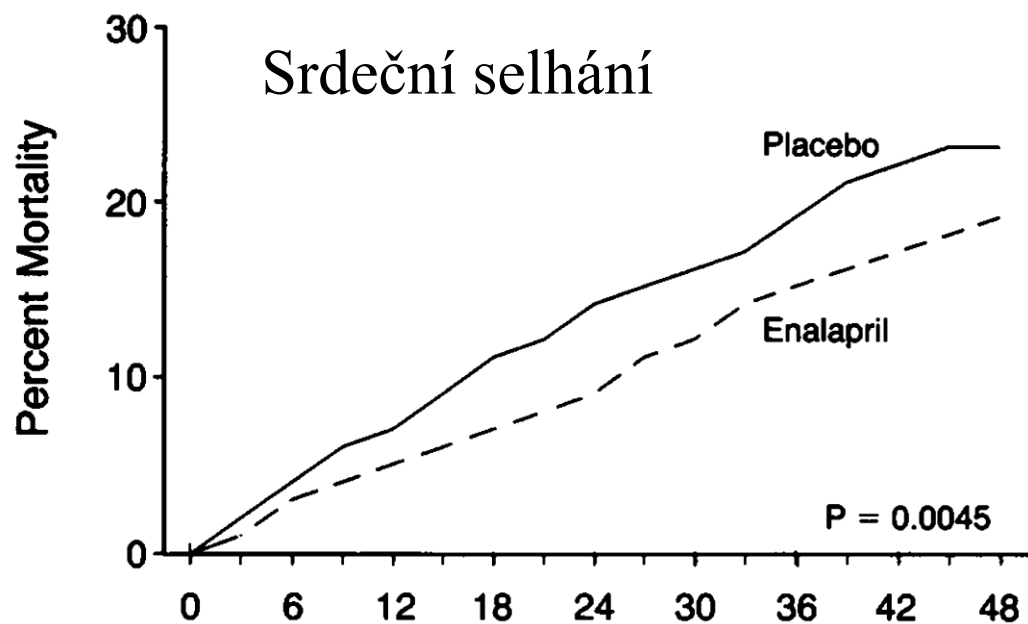
Srdeční velikost byla určena RTG  $> 600 \text{ ml/ m}^2$  u mužů (norma  $<550$ ) a u žen  $> 550 \text{ ml/ m}^2$  (norma  $<500$ ).



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

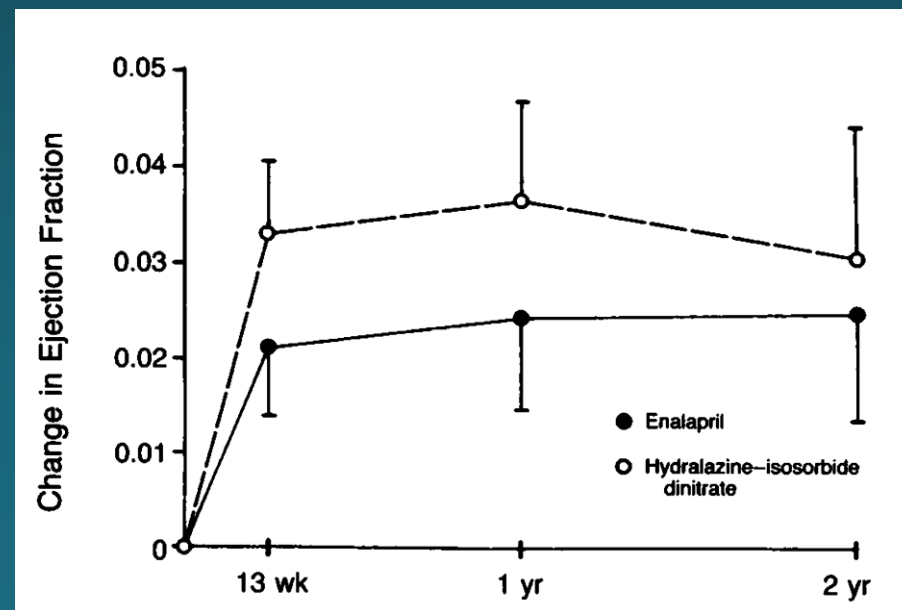
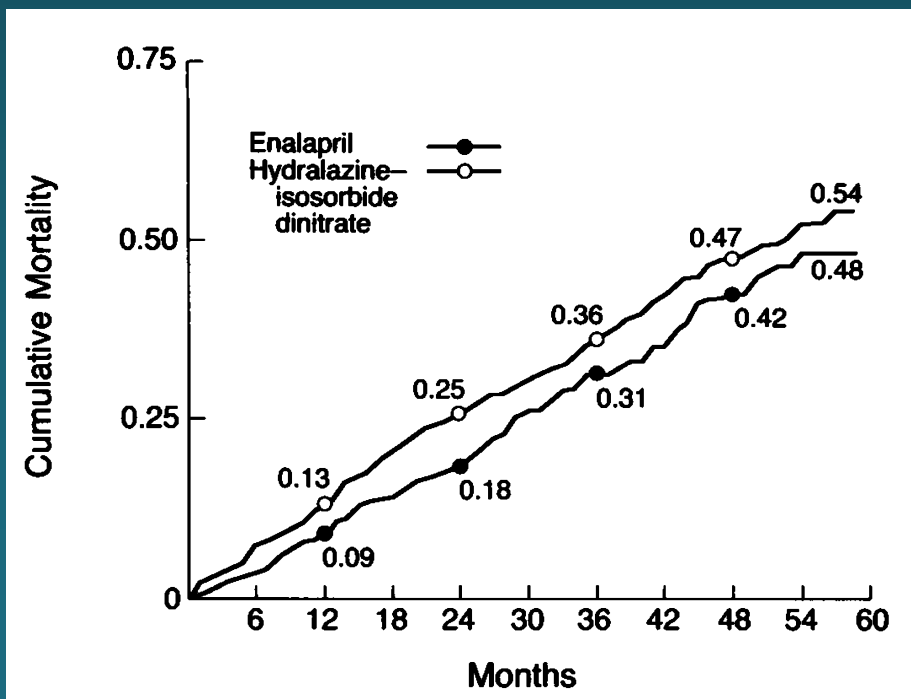
THE SOLVD INVESTIGATORS\*

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.



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

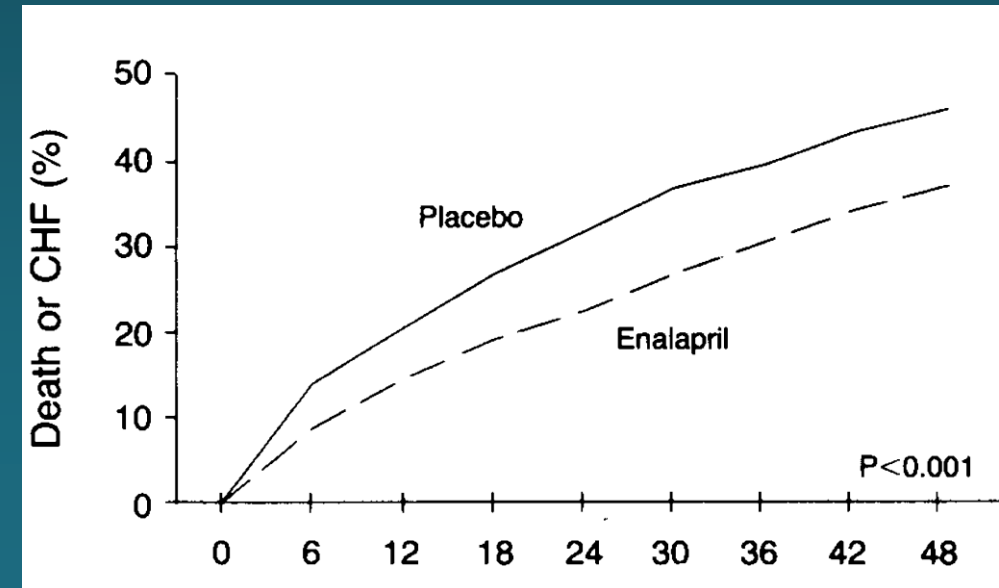
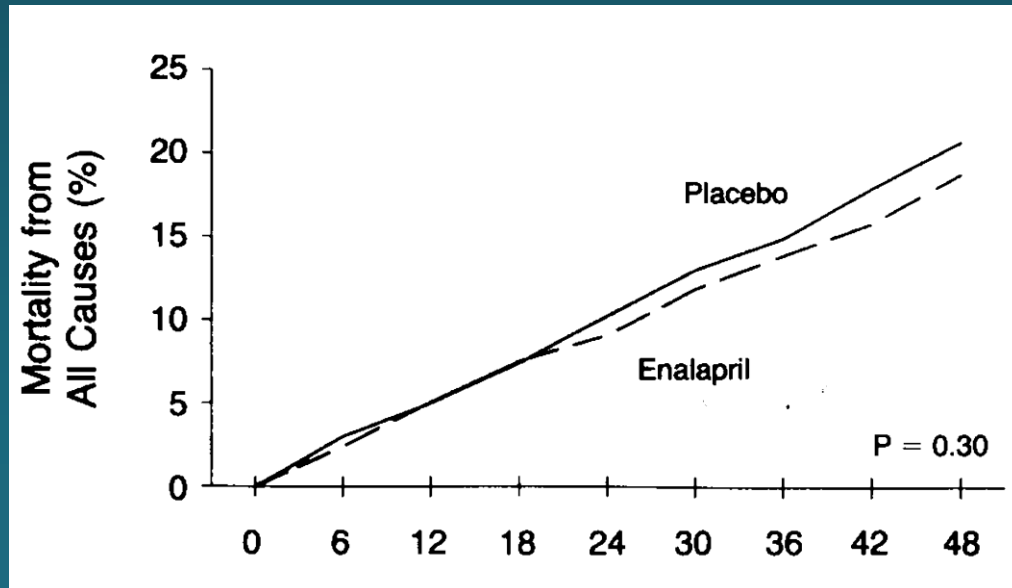
Compared the effects of hydralazine and isosorbide dinitrate with those of enalapril in 804 men receiving digoxin and diuretic therapy for heart failure. The patients were randomly assigned in a double-blind manner to receive 20 mg of enalapril daily or 300 mg of hydralazine plus 160 mg of isosorbide dinitrate daily.



## 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.



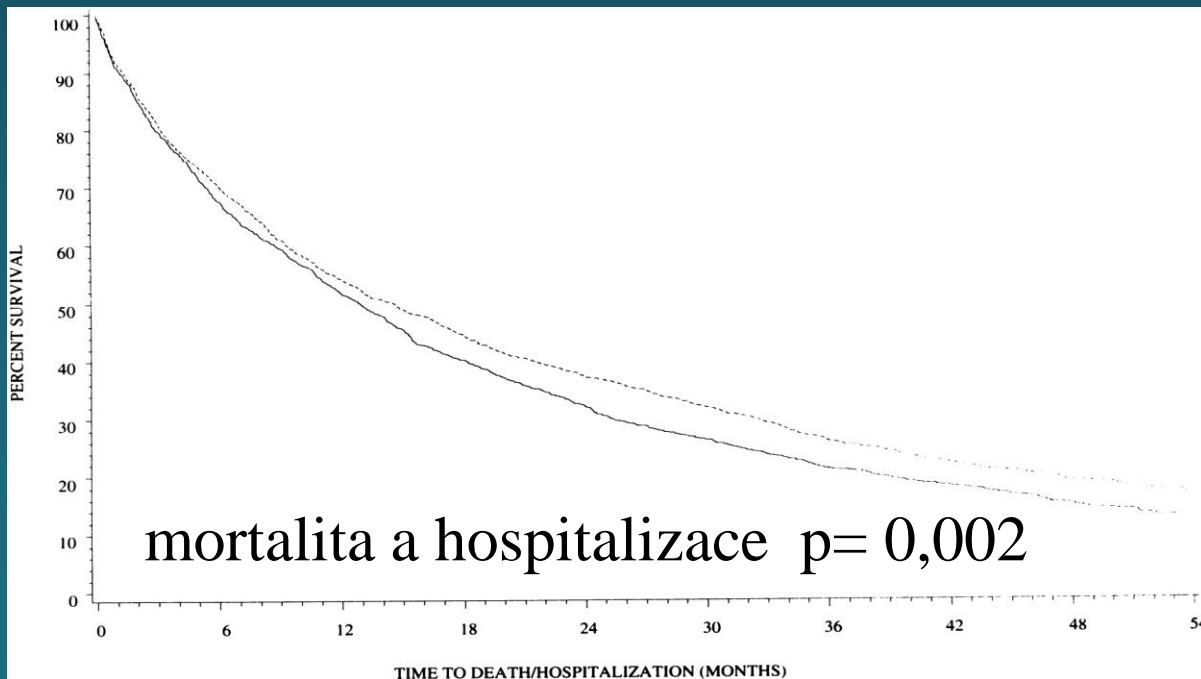
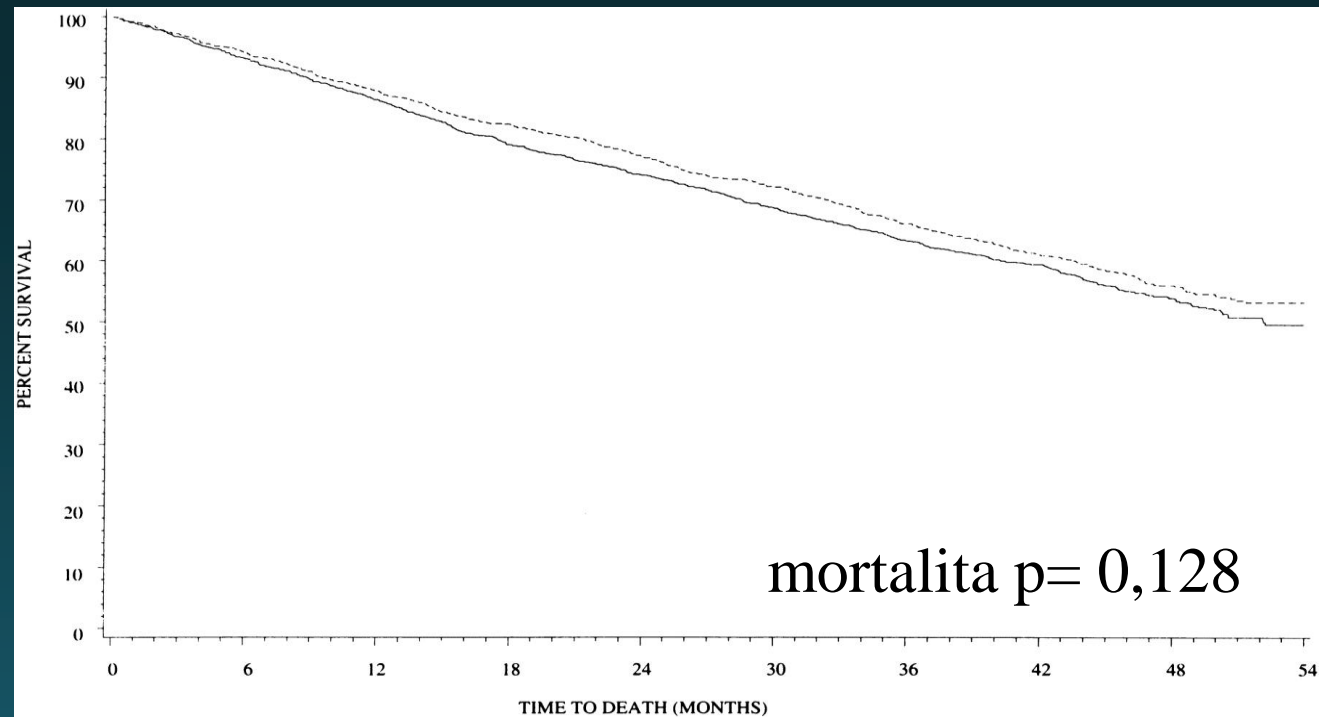


# **Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure**

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.

# ATLAS



# 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.

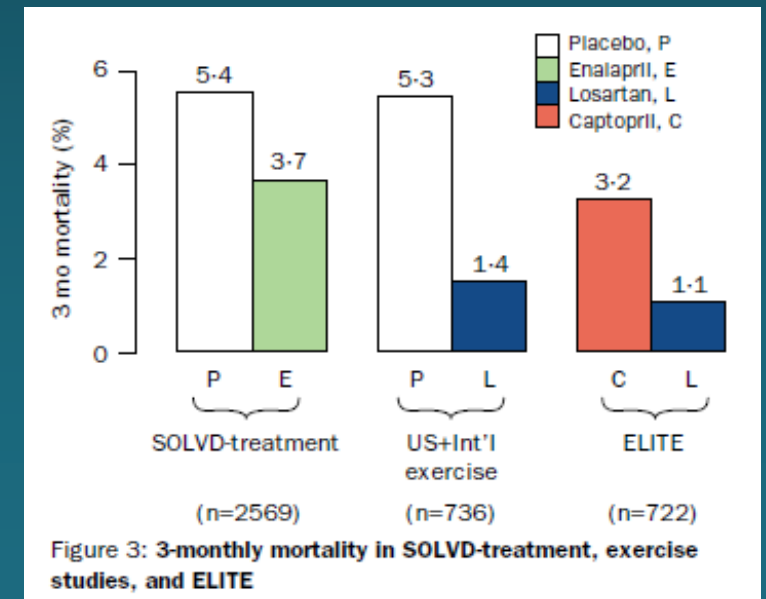
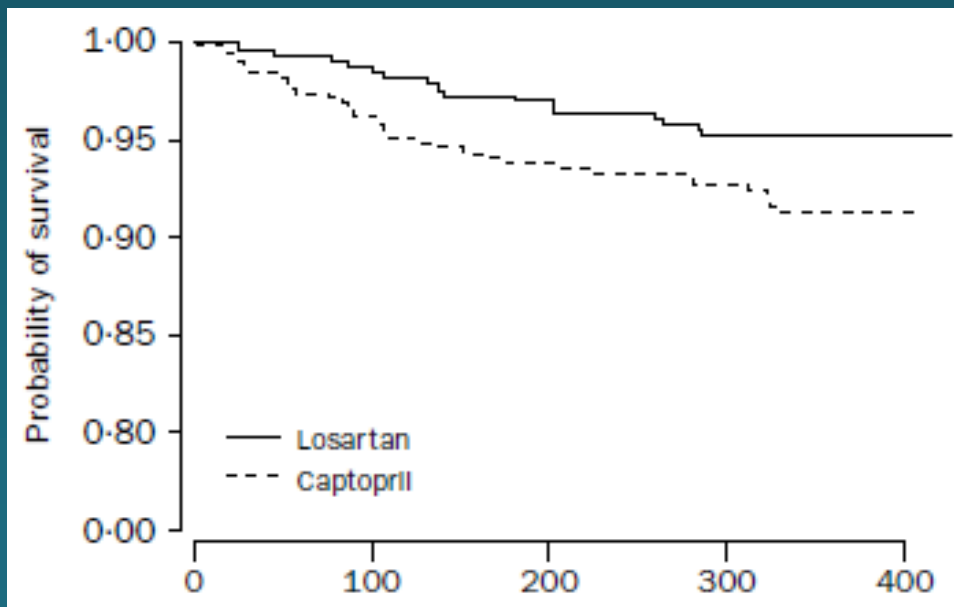
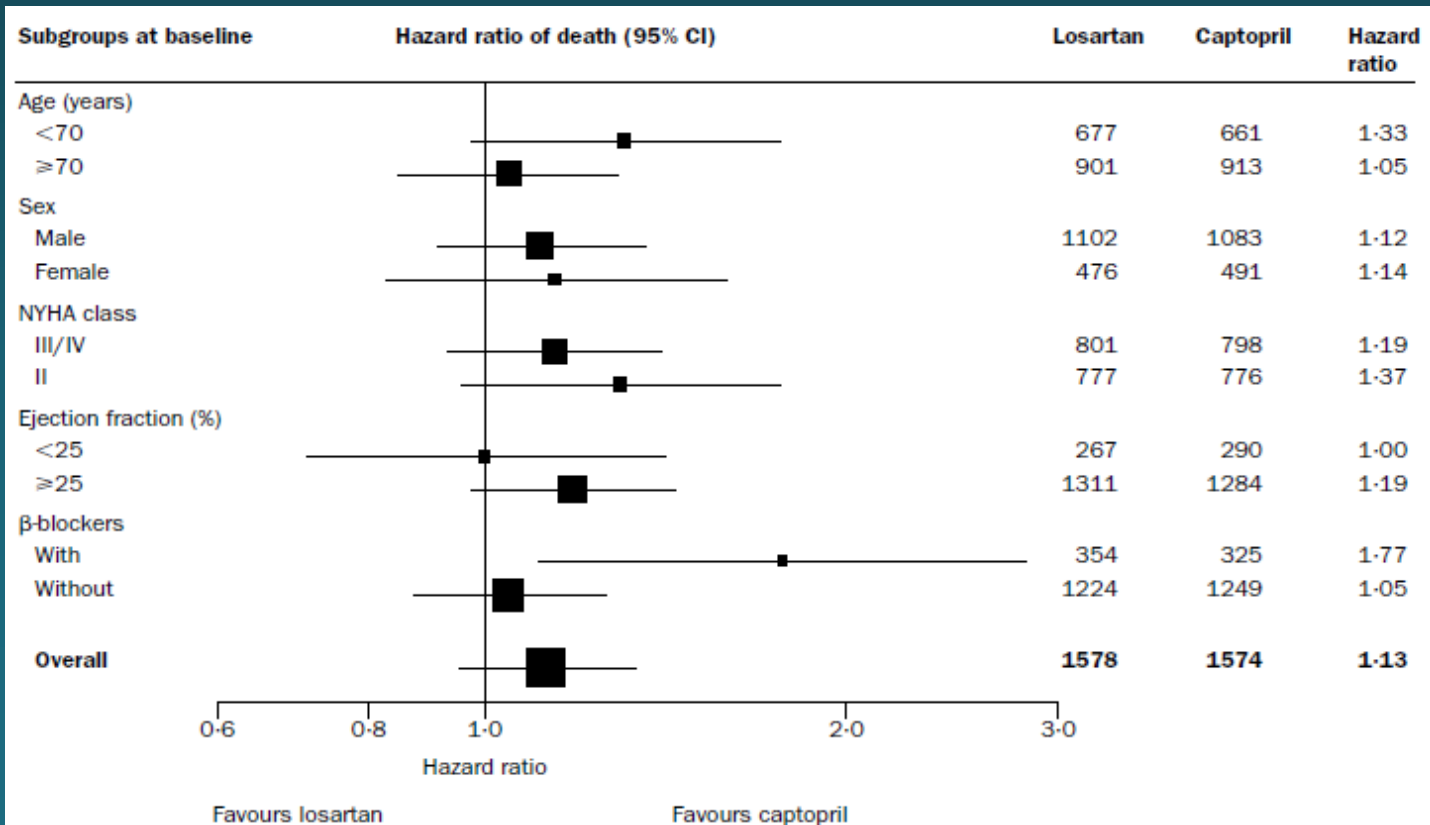


Figure 3: 3-monthly mortality in SOLVD-treatment, exercise studies, and ELITE

# 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.

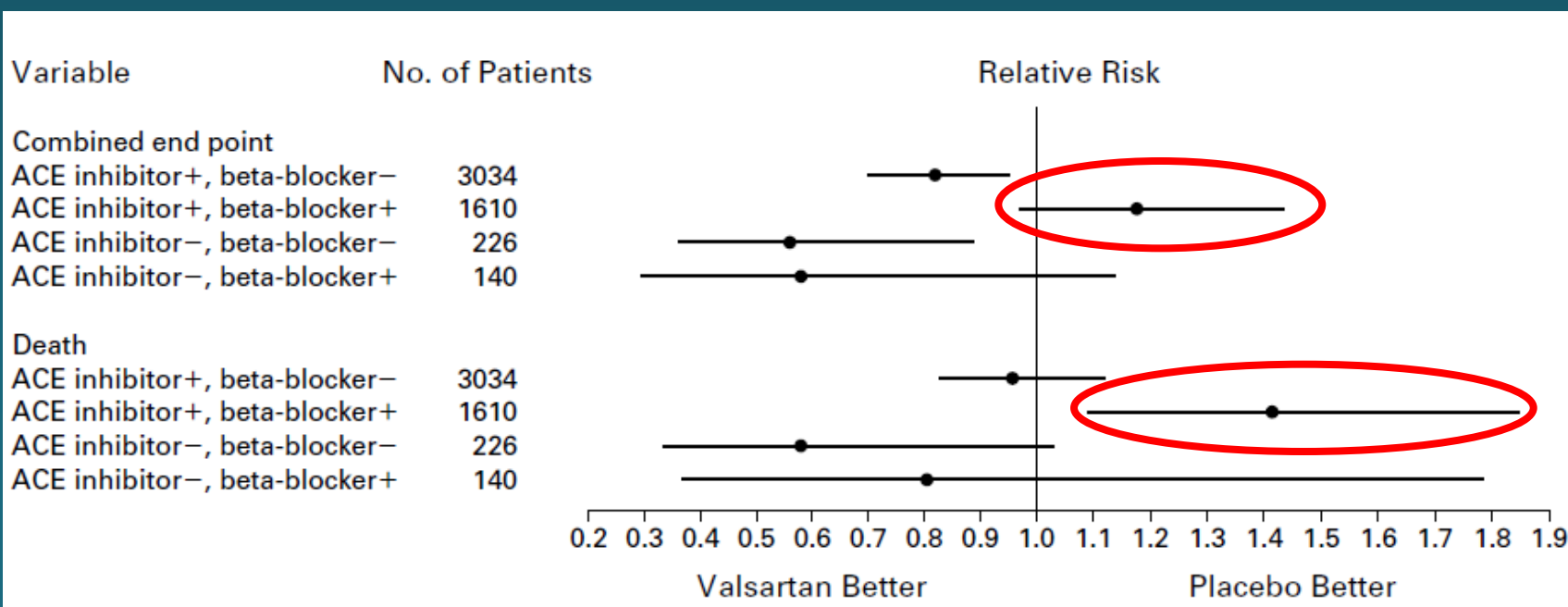
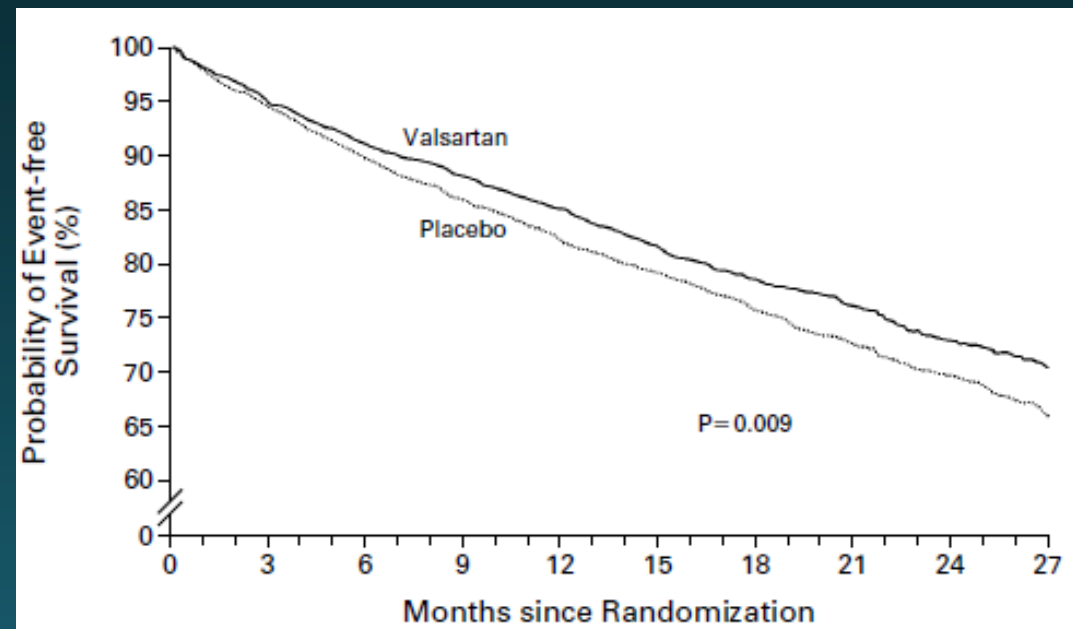
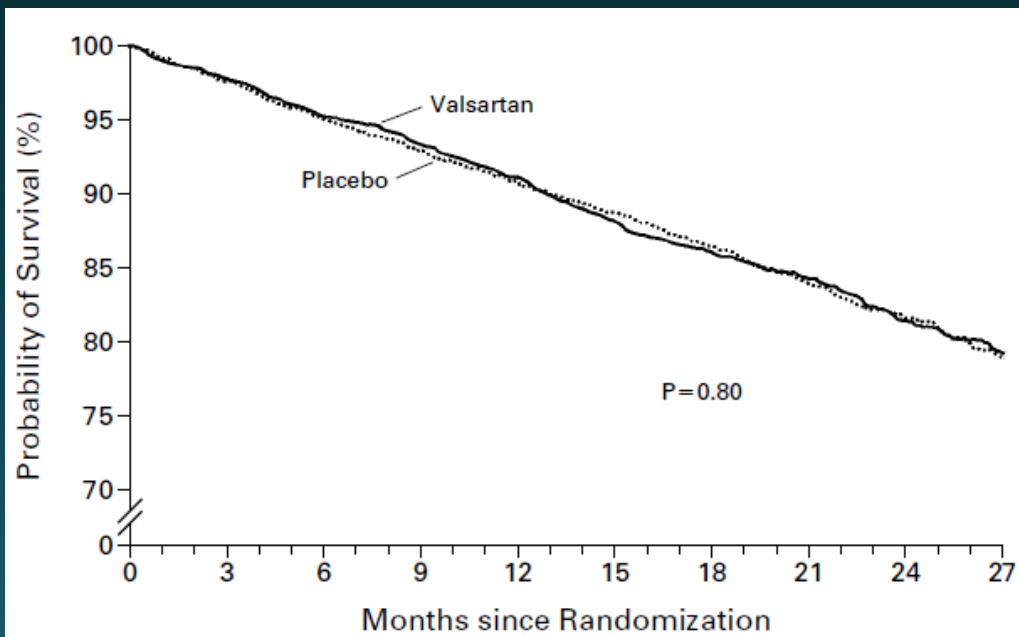


**A RANDOMIZED TRIAL OF THE ANGIOTENSIN-RECEPTOR BLOCKER  
VALSARTAN IN CHRONIC HEART FAILURE**

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



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

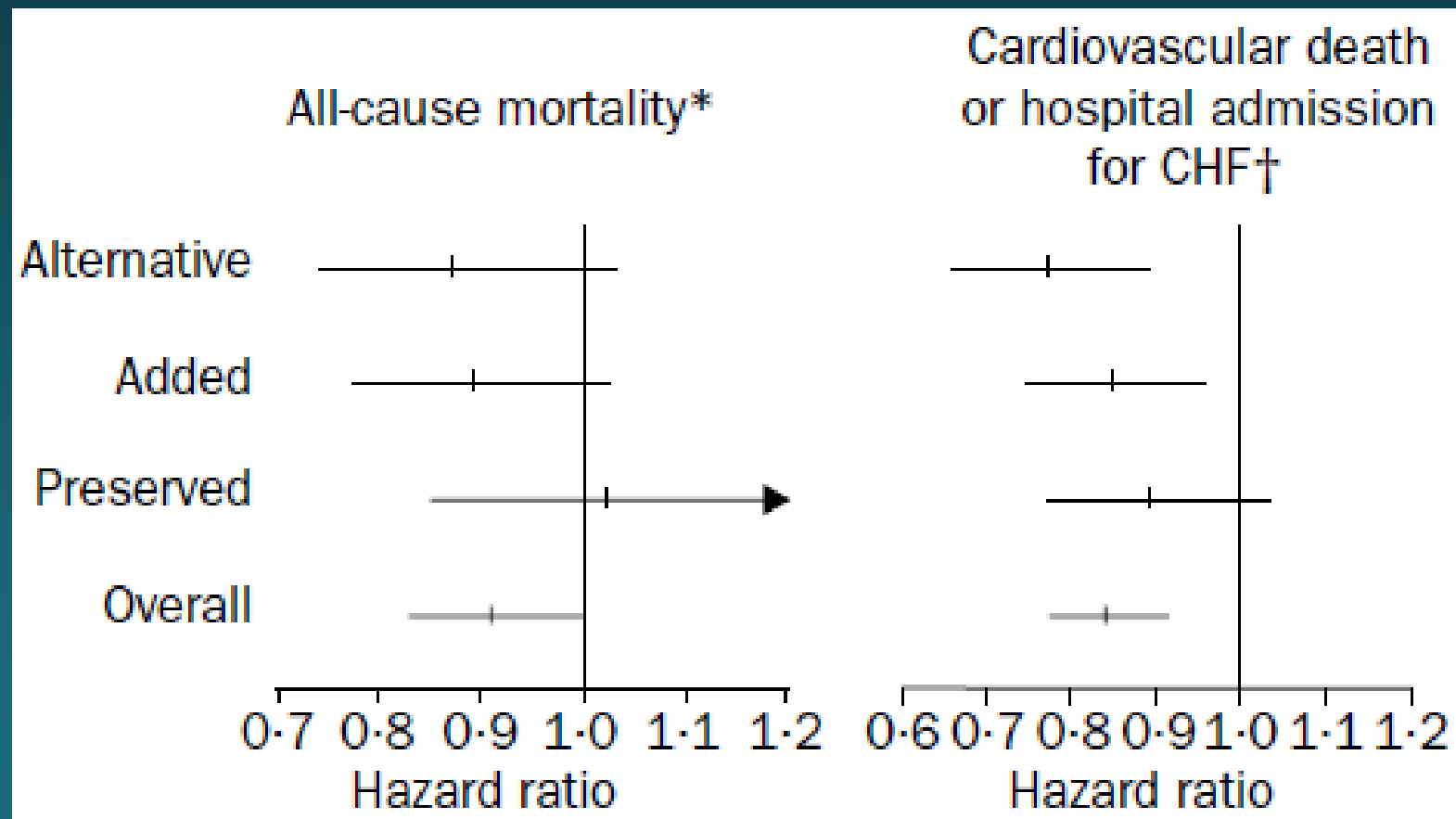
*Marc A Pfeffer, Karl Swedberg, Christopher B Granger, Peter Held, John J V McMurray, Eric L Michelson, Bertil Olofsson, Jan Östergren, Salim Yusuf, for the CHARM Investigators and Committees\**

In parallel, randomised, double-blind, controlled, clinical trials we compared candesartan with placebo in three distinct populations. We studied patients with left-ventricular ejection fraction (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 (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



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

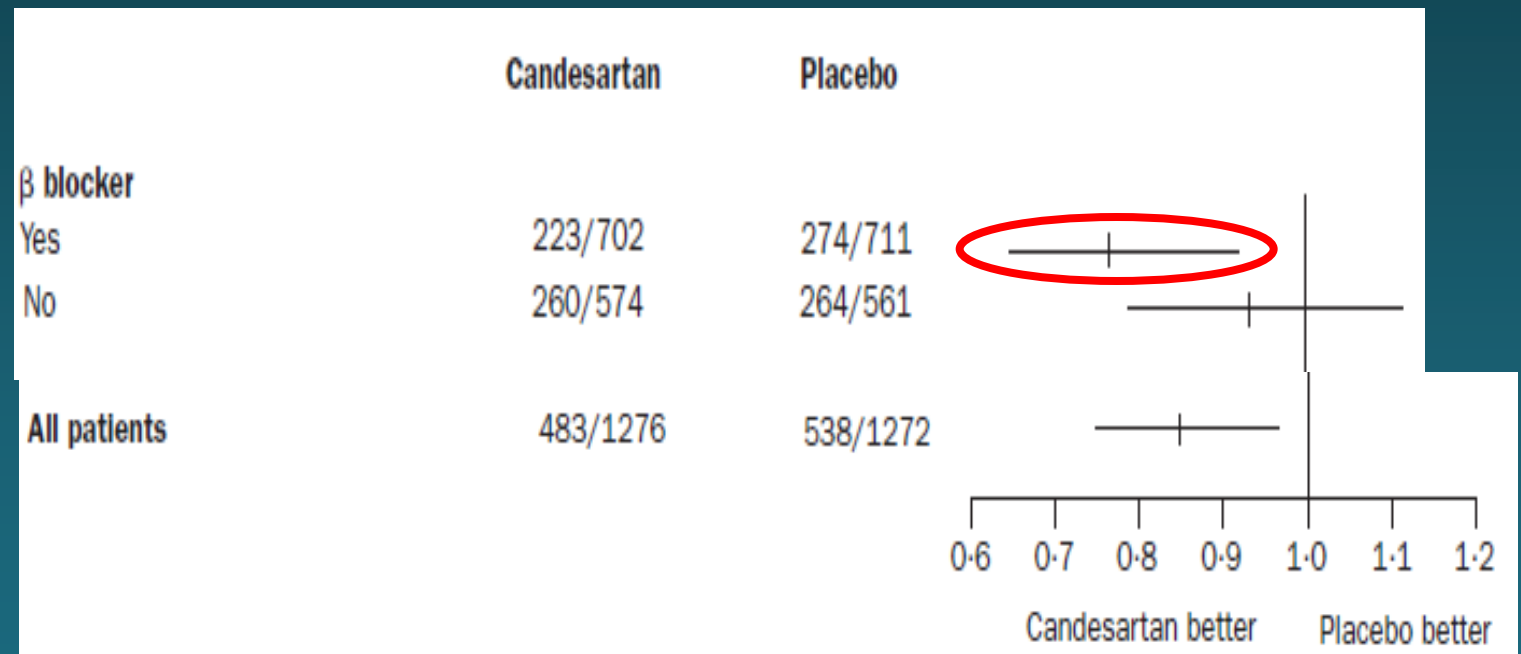
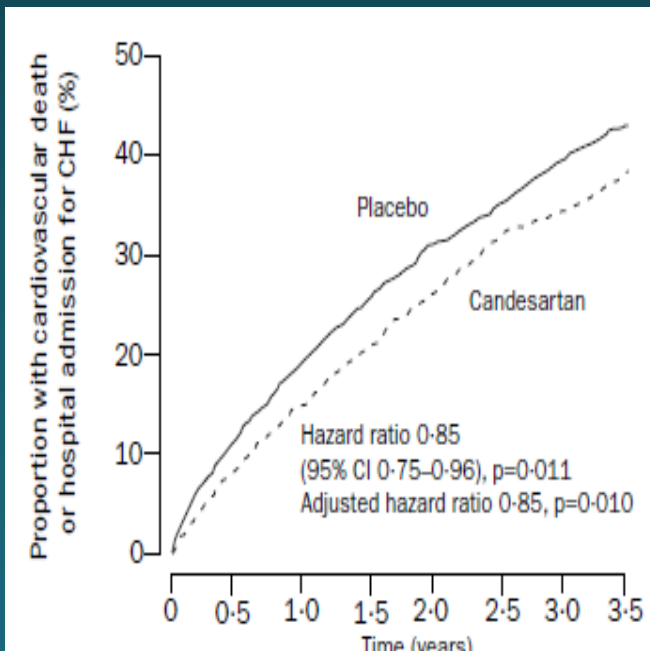
Marc A Pfeffer, Karl Swedberg, Christopher B Granger, Peter Held, John J V McMurray, Eric L Michelson, Bertil Olofsson, Jan Östergren, Salim Yusuf, for the CHARM Investigators and Committees\*





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

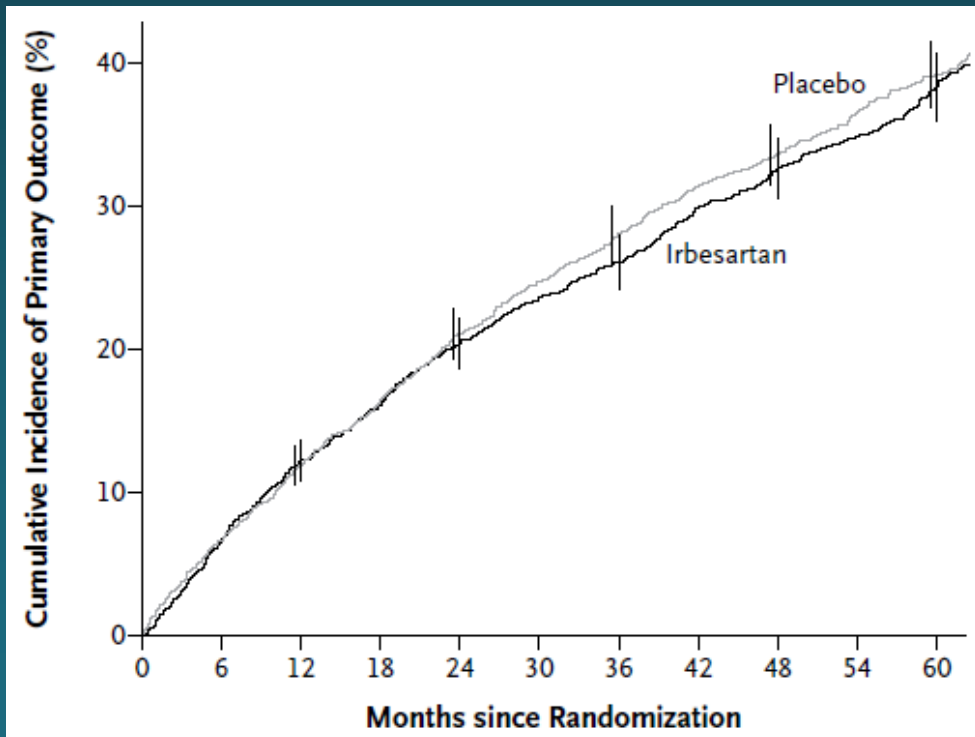
Candesartan (n=1276) či placebo (n=1272)



# 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

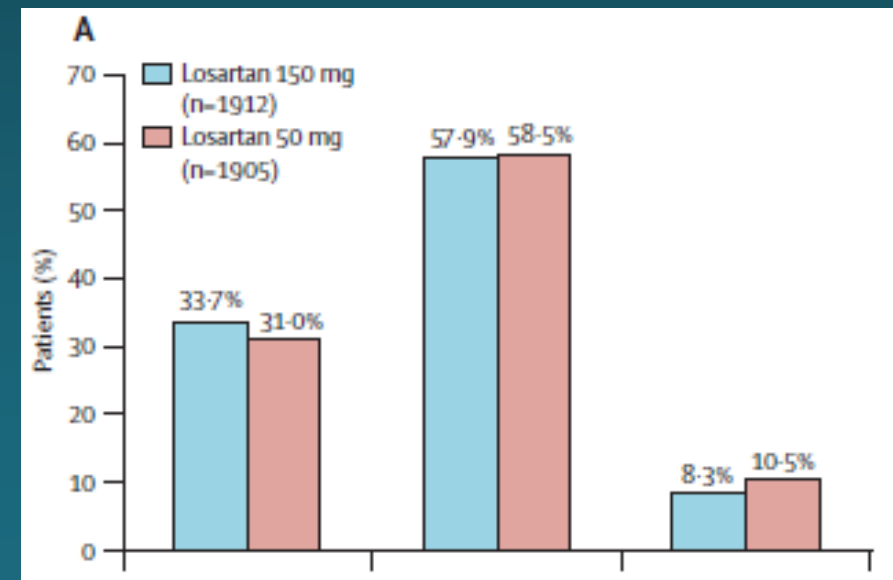
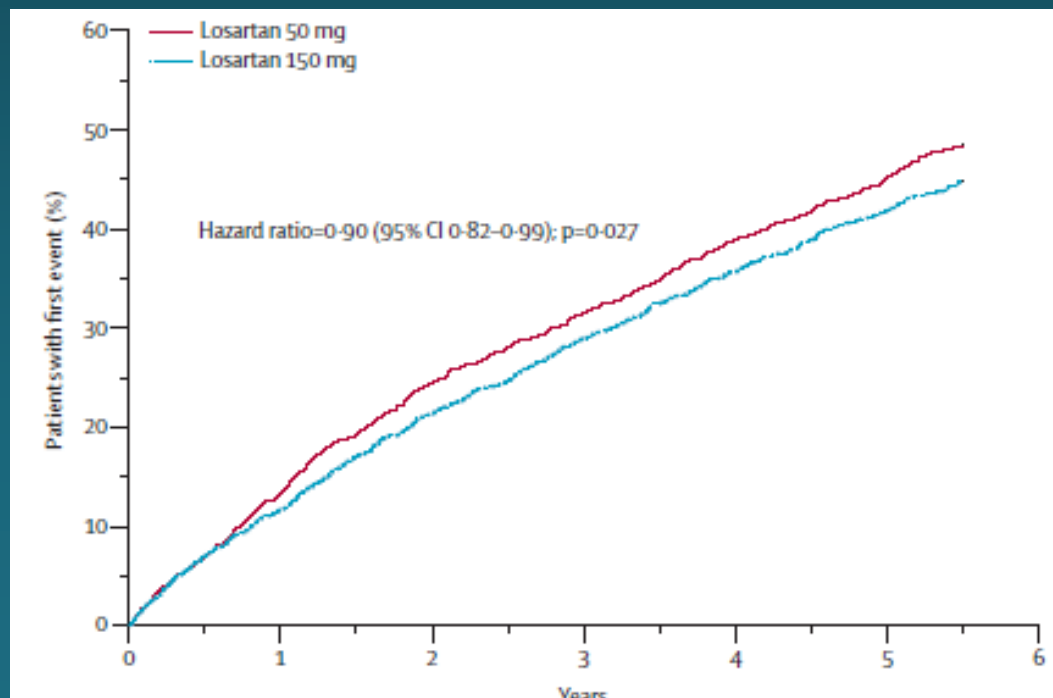


Subgroup	Irbesartan no. of patients/no. of events (%)	Placebo no. of patients/no. of events (%)	Hazard Ratio (95% CI)
All patients	742/2067 (36)	763/2061 (37)	0.97 (0.87-1.08)
Age			
<65 yr	86/376 (23)	86/364 (24)	1.03 (0.81-1.31)
65-75 yr	331/994 (33)	322/981 (33)	0.99 (0.88-1.11)
>75 yr	325/697 (47)	355/716 (50)	0.94 (0.81-1.09)
Sex			
Female	392/1227 (32)	420/1264 (33)	0.98 (0.87-1.10)
Male	350/840 (42)	343/797 (43)	0.97 (0.87-1.08)
Ejection fraction			
≤59%	433/1054 (41)	423/1027 (41)	0.98 (0.88-1.09)
>59%	309/1011 (31)	339/1033 (33)	0.94 (0.83-1.06)
Use of ACE inhibitor			
No	529/1529 (35)	566/1551 (36)	0.97 (0.87-1.08)
Yes	213/538 (40)	197/510 (39)	1.05 (0.91-1.21)
Use of beta-blocker			
No	299/842 (36)	336/859 (39)	0.93 (0.83-1.04)
Yes	443/1225 (36)	427/1202 (36)	0.99 (0.89-1.10)
Diabetes			
No	491/1495 (33)	494/1496 (33)	0.99 (0.89-1.10)
Yes	251/570 (44)	269/564 (48)	0.92 (0.81-1.05)
Hospitalization for heart failure within 6 mo			
No	323/1157 (28)	334/1155 (29)	0.97 (0.87-1.08)
Yes	419/910 (46)	429/906 (47)	0.98 (0.88-1.09)
Geographic region			
Europe	518/1475 (35)	534/1464 (36)	0.97 (0.87-1.08)
North America	87/190 (46)	99/195 (51)	0.91 (0.78-1.06)
Other	137/402 (34)	130/402 (32)	1.04 (0.91-1.18)

# 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

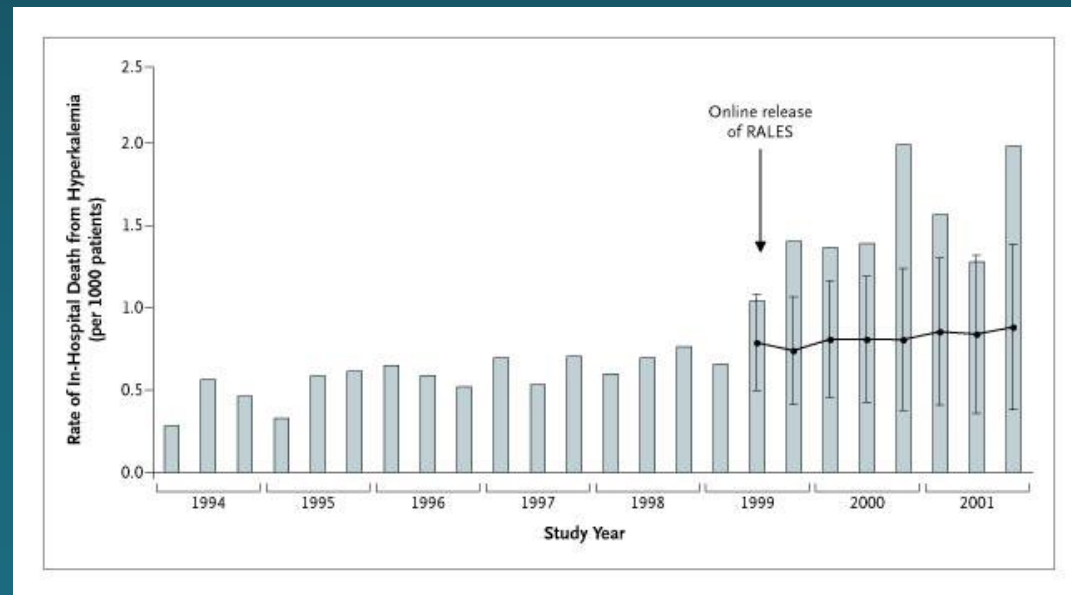
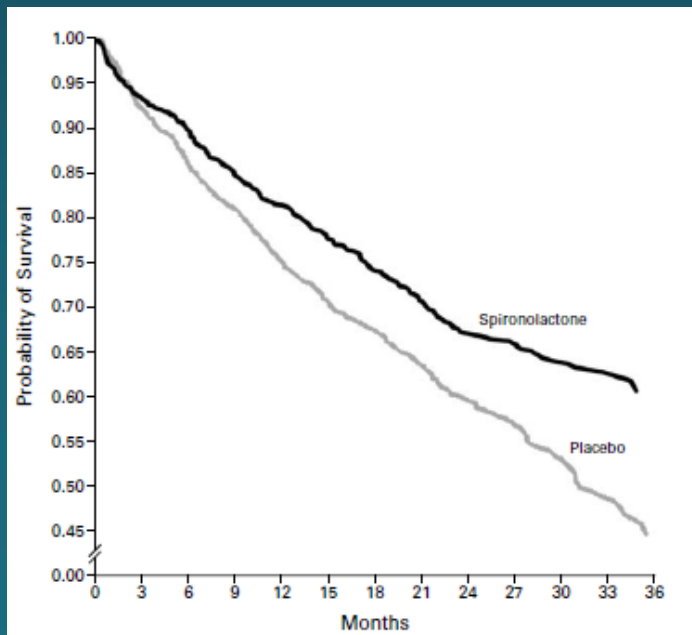
# Role aldosteronu u kardiovaskulárních onemocnění



# 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.



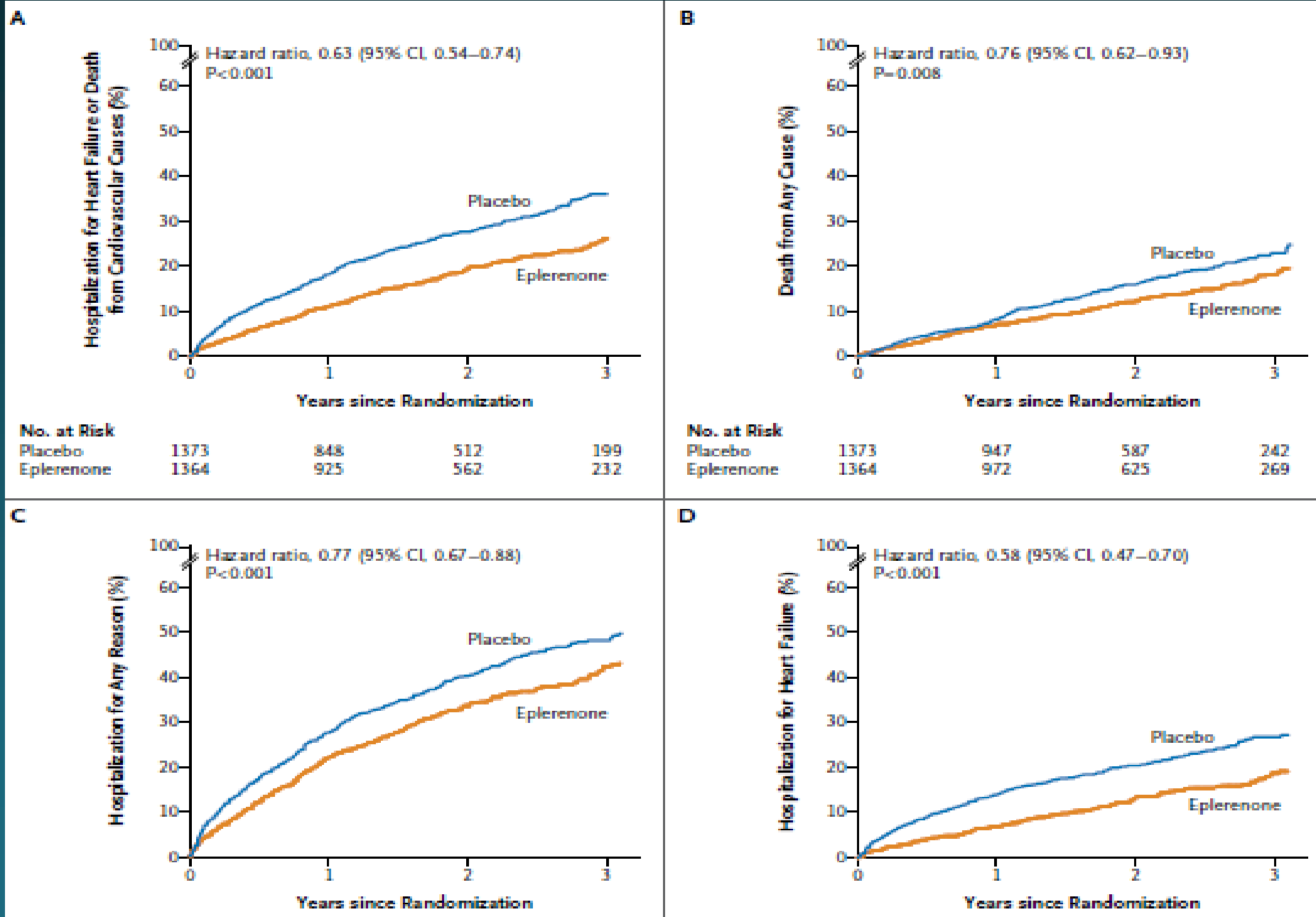
# Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

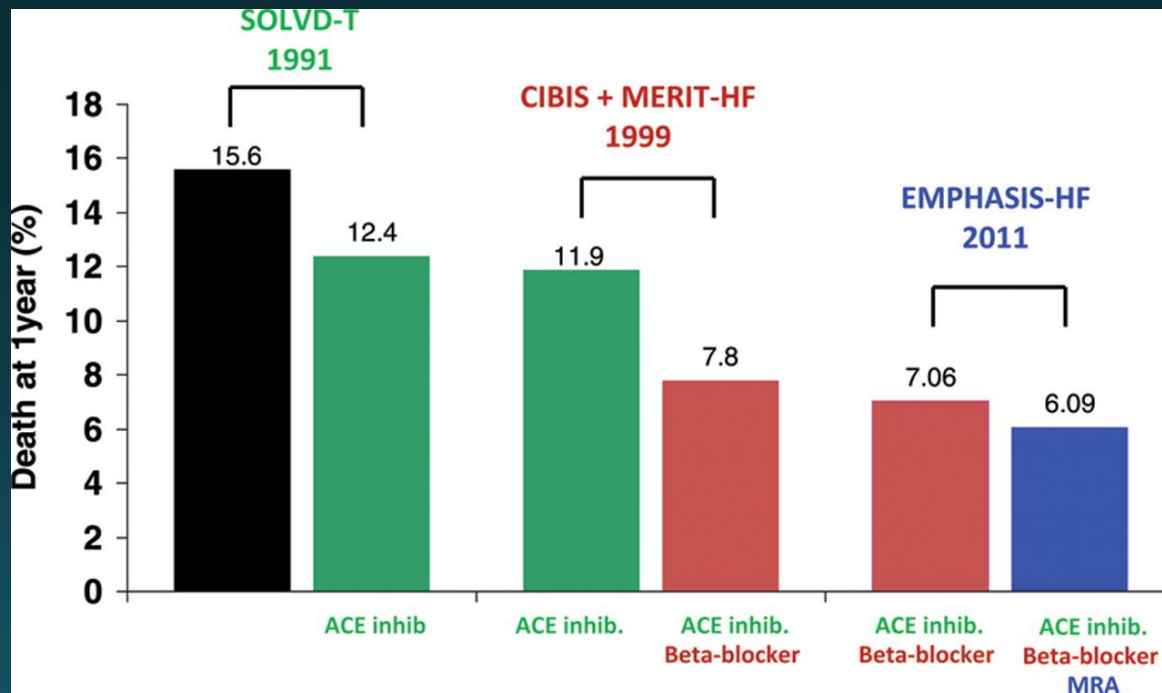
Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D.,  
for the EMPHASIS-HF Study Group\*

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





## NYHA I-II

## NYHA III-IV

