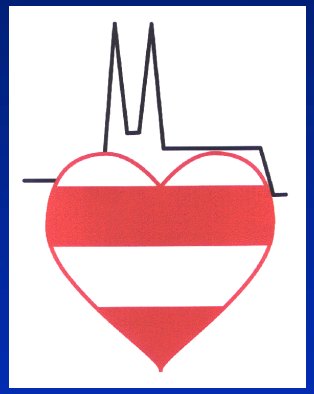
Novinky ve farmakoterapii srdečního selhání

Špinar J.
Brno, Česká republika



Novinky ve farmakoterapii srdečního selhání

akutní

chronické

vazodilatace

duální inhibice

Současná léčba ASS

IV Diuretika

Snižují objem
Předtížení

Kličková diuretika

ANO

Vazodilatace

Snižují předtížední
i dotížení

Nitroglycerin
Nitroprusside
Nesiritide

Ularitid
Serelaxin

Inotropika

Zvyšují
kontraktilitu

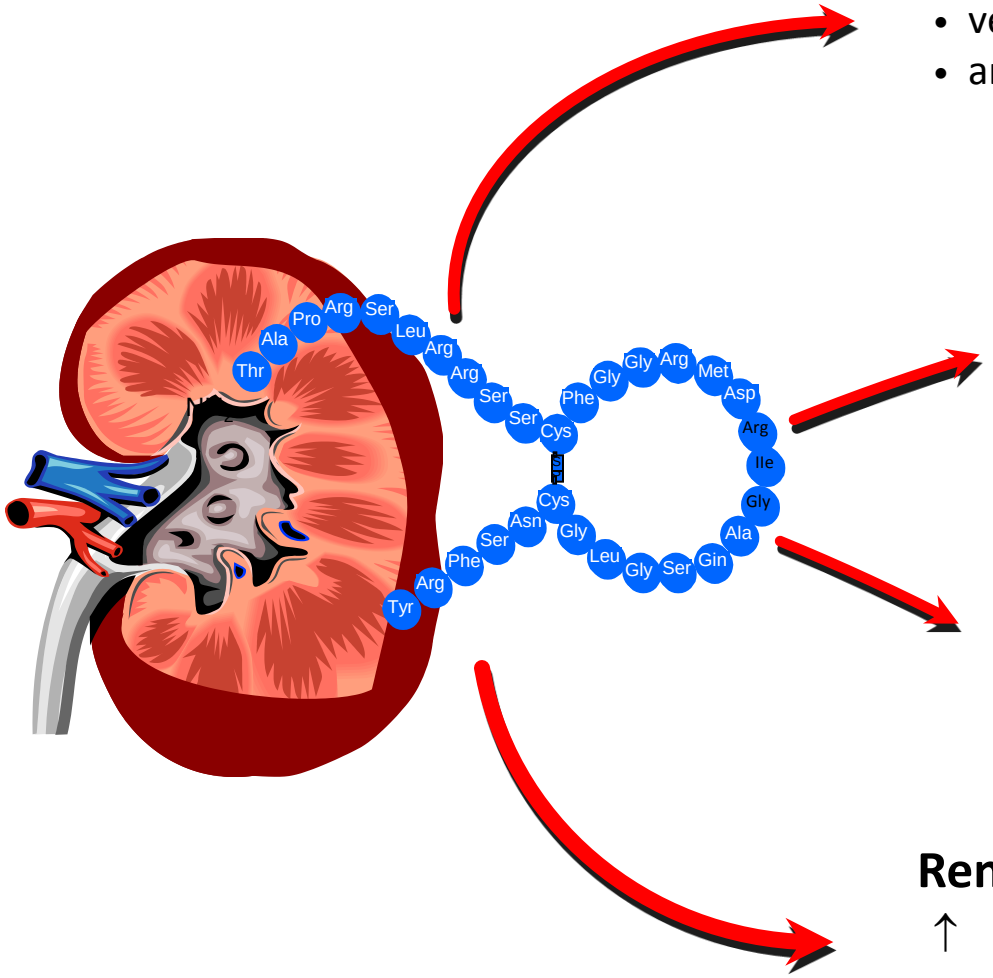
Dobutamine
Milrinone

Zklamání

Ularitide

Souhrn farmakologických účinků Ularitidu

CARDIORENTIS



Hemodynamické (vasodilatace)

- venozní
- arteriální

Carstens JT, Clin Sci. 1997;92:397-407
Bestle, MH, Am J Physiol, 1999, R684-R695

Bronchodilatace

•Tracheální hladké svaly - relaxace

Flüge T, Regul.Pept. 1995;59:357-70.

Neurohumorální

↓ renin
↓ angiotensin
↓aldosterone
↓endothelin

Carstens JT, Clin Sci. 1997;92:397-407
Bestle, MH, Am J Physiol, 1999, R684-R695
Meyer M, Am J Physiol,1996;271(40);F489-497

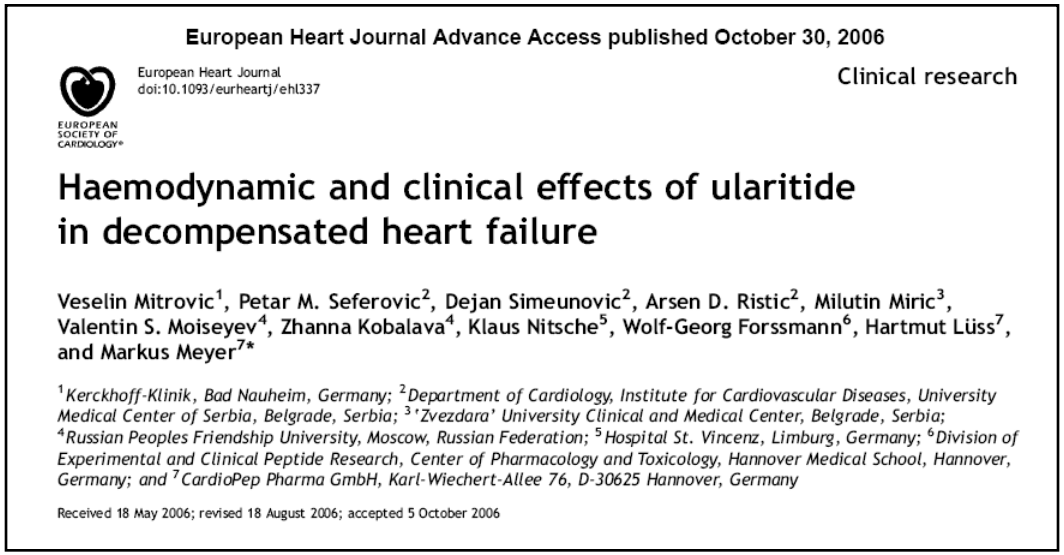
Renální

↑ diuréza
↑ natriuréza

Carstens JT, Clin Sci. 1997;92:397-407
Bestle, MH, Am J Physiol, 1999, R684-R695

Safety and efficacy of an Intravenous placebo controlled Randomised Infusion of Ularitide in a prospective double-blind Study in patients with symptomatic, decompensated chronic heart failure (Phase IIb)

SIRIUS II



European Heart Journal Advance Access published October 30, 2006

European Heart Journal
doi:10.1093/eurheartj/ehl337

Clinical research

Haemodynamic and clinical effects of ularitide in decompensated heart failure

Veselin Mitrovic[1], Petar M. Seferovic[2], Dejan Simeunovic[2], Arsen D. Ristic[2], Milutin Miric[3], Valentin S. Moiseyev[4], Zhanna Kobalava[4], Klaus Nitsche[5], Wolf-Georg Forssmann[6], Hartmut Lüss[7], and Markus Meyer[7]*

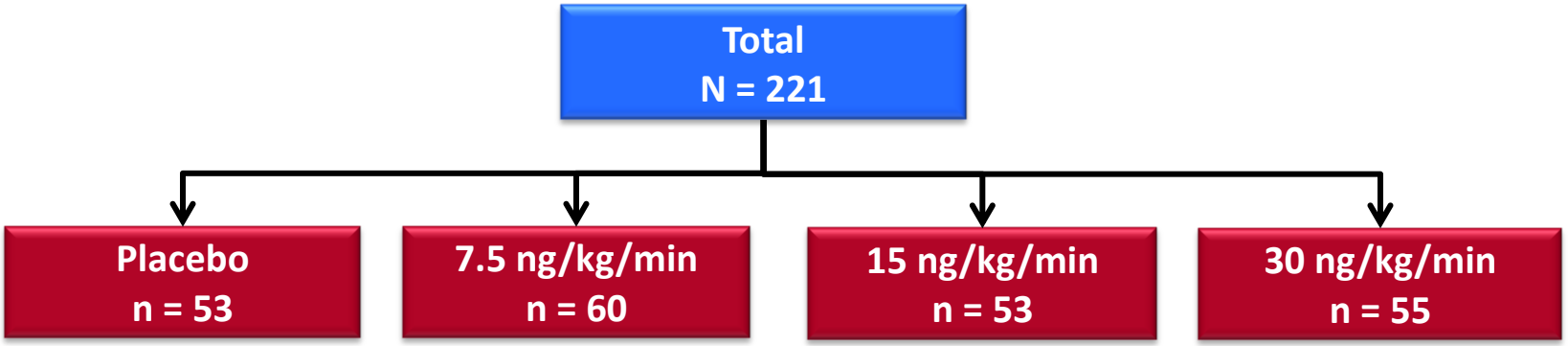
[1]*Kerckhoff-Klinik, Bad Nauheim, Germany;* [2]*Department of Cardiology, Institute for Cardiovascular Diseases, University Medical Center of Serbia, Belgrade, Serbia;* [3]*'Zvezdara' University Clinical and Medical Center, Belgrade, Serbia;* [4]*Russian Peoples Friendship University, Moscow, Russian Federation;* [5]*Hospital St. Vincenz, Limburg, Germany;* [6]*Division of Experimental and Clinical Peptide Research, Center of Pharmacology and Toxicology, Hannover Medical School, Hannover, Germany; and* [7]*CardioPep Pharma GmbH, Karl-Wiechert-Allee 76, D-30625 Hannover, Germany*

Received 18 May 2006; revised 18 August 2006; accepted 5 October 2006

Mitrovic V, et al. *Eur Heart J* 2006; (23):2823-32

SIRIUS II – Study design

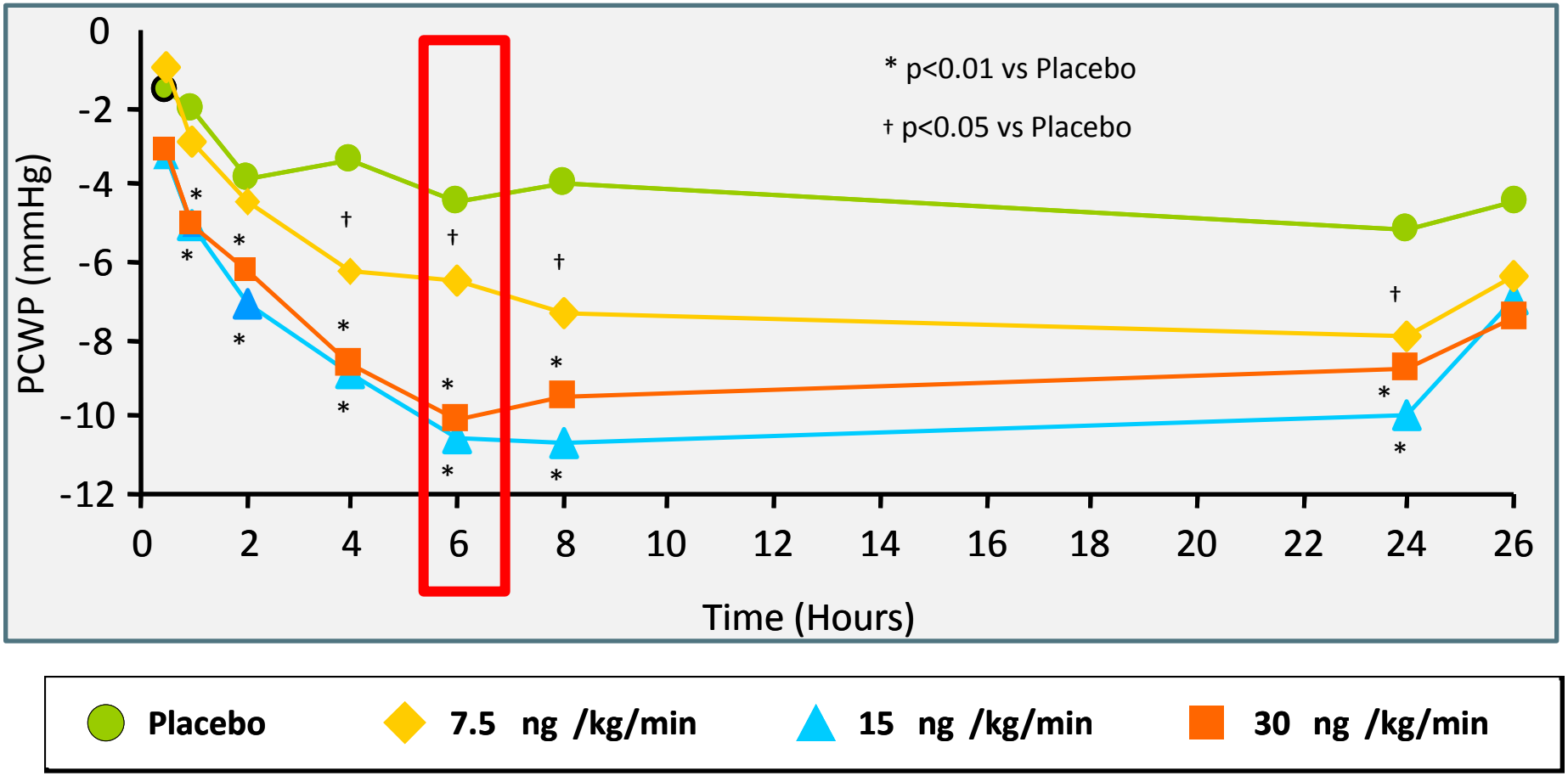
- Randomised, placebo controlled, double-blind, study with 3 active dosing and 1 placebo group
- Infusion of Ularitide 7.5, 15, and 30 ng/kg body weight/min, or placebo over 24 hours
- Patients with decompensated heart failure requiring hospitalisation as well as right heart catheterisation were included into the study
- **Distribution**



Mitrovic V, et al. *Eur Heart J* 2006; (23):2823-32

First Primary Endpoint

Ularitide Reduces PCWP



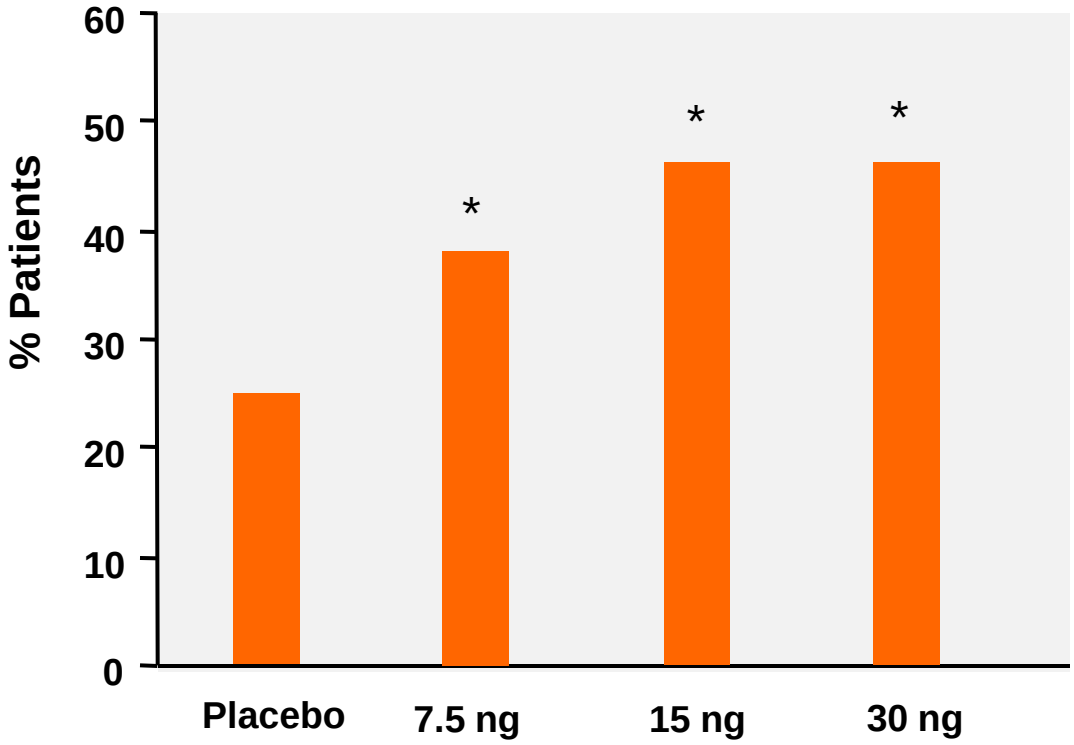
Mitrovic V, et al. *Eur Heart J* 2006; (23):2823-32

Second Primary Endpoint

Ularitide Improves Dyspnea Categories

CARDIORENTIS

Patient-assessed dyspnea at 6 hrs: moderately or markedly better



* p<0.05 vs Placebo

Mitrovic V, et al. *Eur Heart J* 2006; (23):2823-32

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2015) **36**, 715–723
doi:10.1093/eurheartj/ehu484

REVIEW

Clinical update

Ularitide for the treatment of acute decompensated heart failure: from preclinical to clinical studies

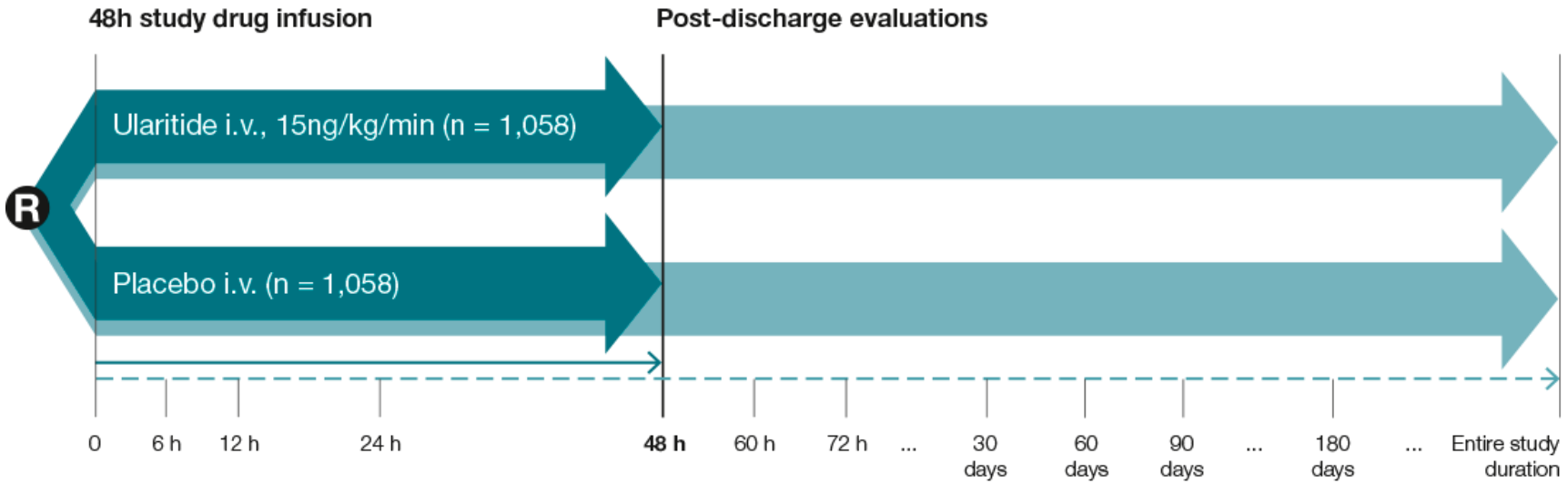
Stefan D. Anker[1]*, Piotr Ponikowski[2], Veselin Mitrovic[3], W. Frank Peacock[4], and Gerasimos Filippatos[5]

[1]Department of Innovative Clinical Trials, University Medical Centre Göttingen, Göttingen, Germany; [2]Medical University, Wroclaw, Poland; [3]Department of Cardiology, Kerckhoff-Klinik, Bad Nauheim, Germany; [4]Emergency Medicine, Baylor College of Medicine, Houston, TX, USA; and [5]Athens University Hospital Attikon, Athens, Greece

Received 14 July 2014; revised 20 November 2014; accepted 1 December 2014; online publish-ahead-of-print 10 February 2015

Design and Key Efficacy Measures

TRUE-AHF



PRIMARY ENDPOINTS	
	A **composite score** that assesses the symptoms and **clinical course**
	Cardiovascular mortality over time

CARDIORENTIS

TRUE-AHF

2 152 nemocných

17.5.2015

Alert Mail – Notification on upcoming recruitment closure

Subject: **TRUE-AHF study 2152 patients randomized**

Dear Investigator,

We are very happy to inform you that today we have randomized the 2152nd patient in our study and therefore we have reached the number of patients required for the TRUE-AHF study. Thank you all very very much for your unrelenting support in making this happen.

On 17 May 2015 at 06:00 p/m GMT you will receive a notification through IXRS that the system is closed and you will no longer be able to access the IXRS system. However, between now and the exact time of closing of the IXRS system, any ongoing screening activities may continue and randomization of these patients will still be allowed.

Effect of Serelaxin on Cardiac, Renal and Hepatic Biomarkers in the Relaxin in Acute Heart Failure- (RELAX-AHF) Development Program

Prof. Marco Metra, MD et al.

Journal of American College of Cardiology

2013; 61:196-206

Pregnancy & the Heart

Parameter	Pregnancy
Cardiac Output (L/min)	20% Increase
Systemic Vascular Resistance ($dyn.s.cm^2$)	30% Decrease
Global Arterial Compliance (mL/mm Hg)	30% Increase
Renal Blood Flow ($mL/min/1.73m^2$)	50-85% Increase
Creatinine Clearance ($mL/min/1.73m^2$)	40-65% Increase

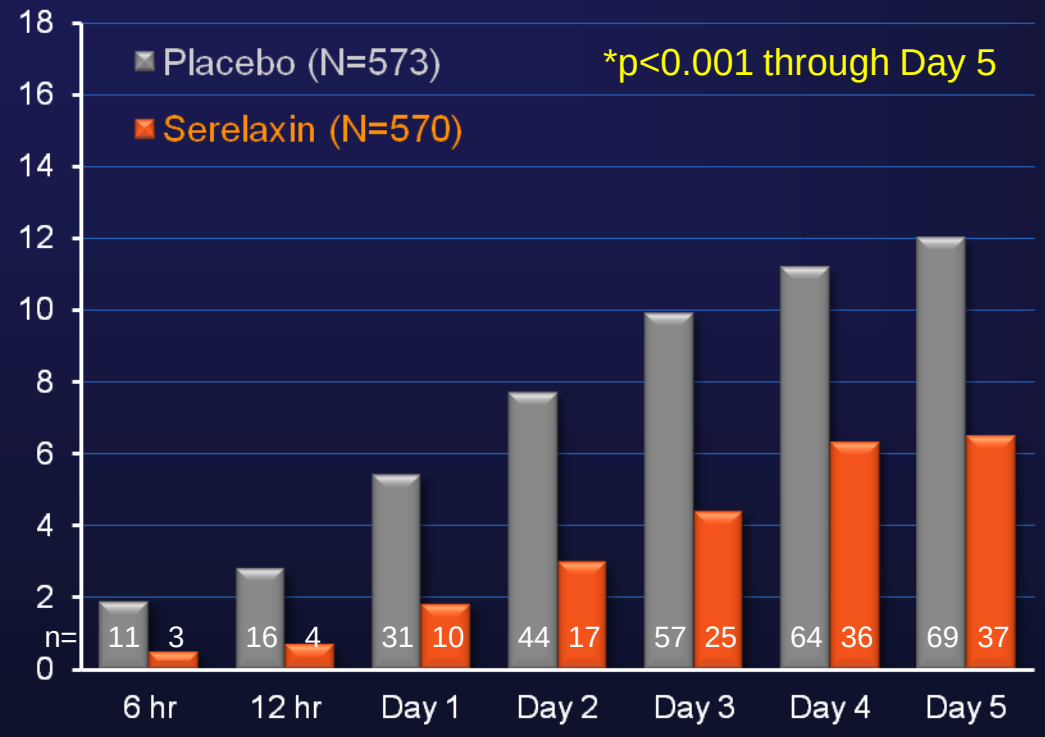
- Relaxin has been shown to mediate these changes, as well as to have anti-ischemic, anti-inflammatory, anti-fibrotic effects.
- Relaxin is elevated through 9 months of pregnancy and mediates physiologic hemodynamic adjustments to growing baby
- Pharmacologic use of serelaxin may produce these beneficial effects in acute heart failure

Baylis, C. *Am J Kid Dis* 1999; Schrier, RW, et al. *Am J Kid Dis* 1987; Jeyebalan, A, et al. *Adv Exp Med Biol* 2007; Teichman SL et al. *Curr Heart Fail Rep* 2010;7:75–82.
Helal I, et al. *Nature Reviews* 2012;293-300.

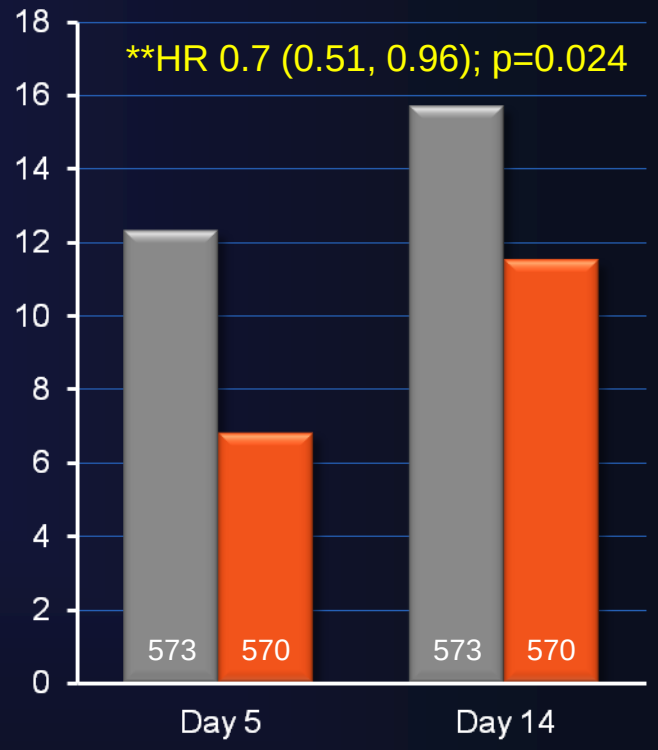
RELAX AHF studie

Worsening of Heart Failure

Cumulative proportion of worsening heart failure to Day 5 (%)



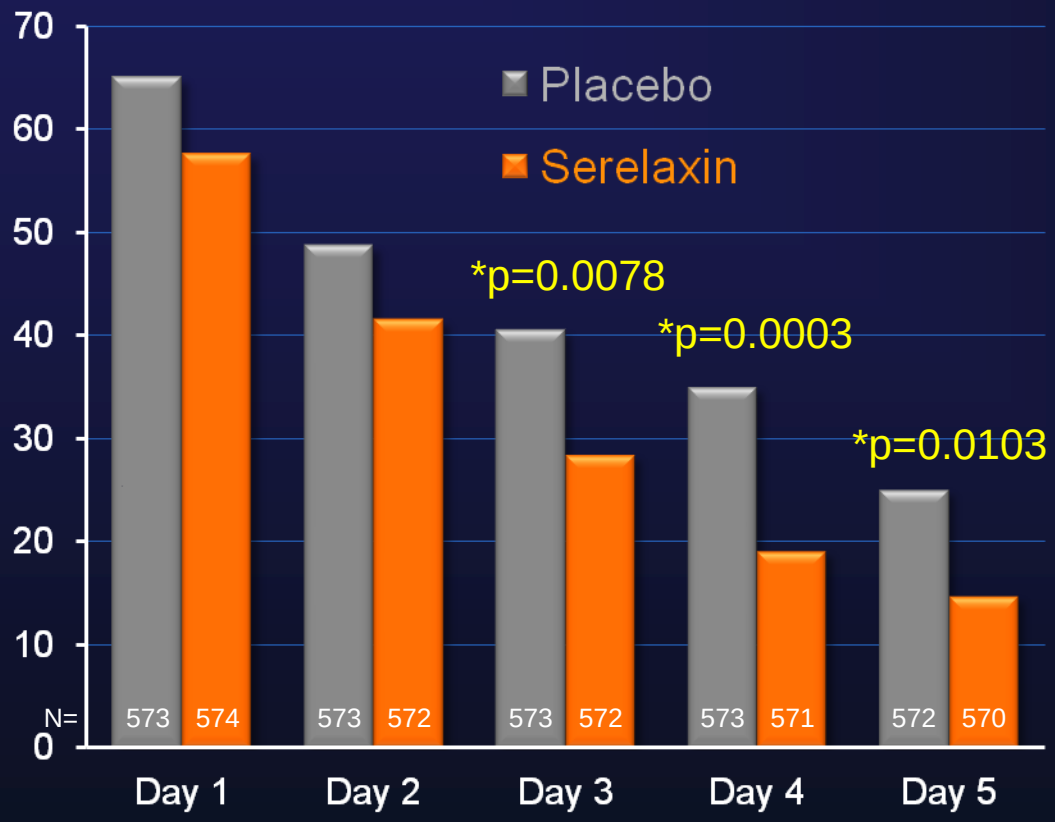
Kaplan-Meier estimate D14 for time to WHF (%)



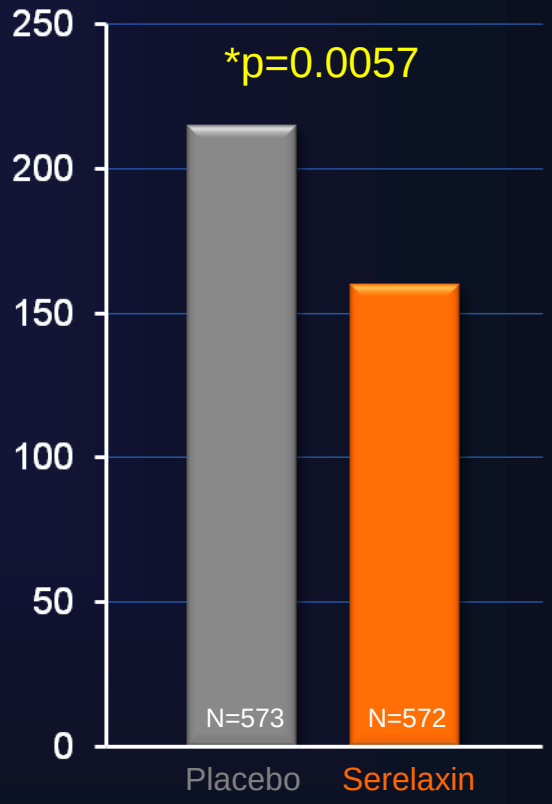
Worsening Heart Failure (WHF) was defined as worsening signs and/or symptoms of HF that required an intensification of IV therapy for heart failure or mechanical ventilatory or circulatory support.
*p value by Wilcoxon test
**p value by log rank test for Serelaxin vs. Placebo; HR estimate by Cox model, HR<1.0 favors Serelaxin

Intravenous Diuretic Use

Total daily dose IV diuretics (mg)

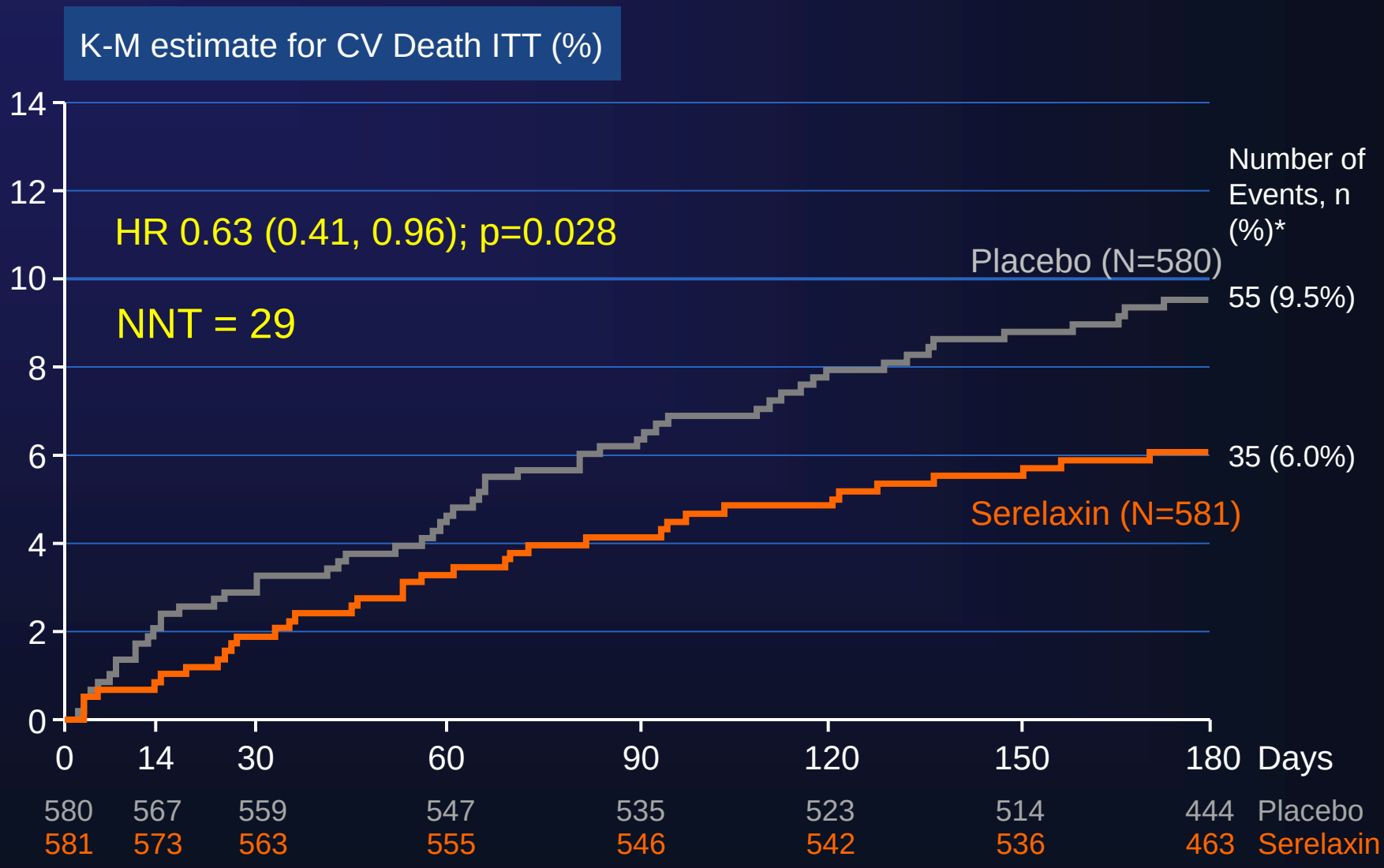


IV diuretics use (cumulative total dose from day 1-5; mg)



*p value by t test

CV Death through Day 180

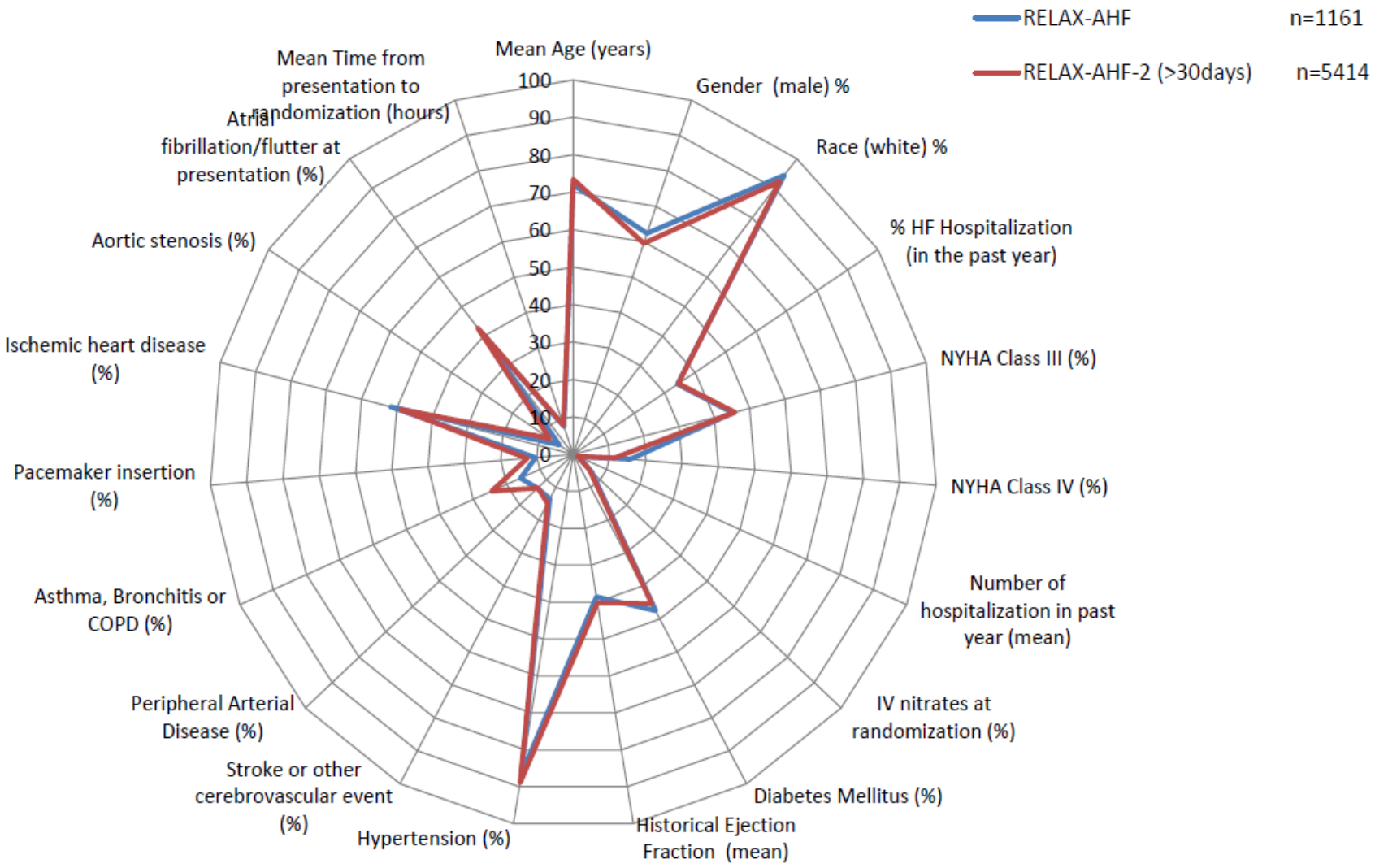


RLX030A2301 Study Milestones

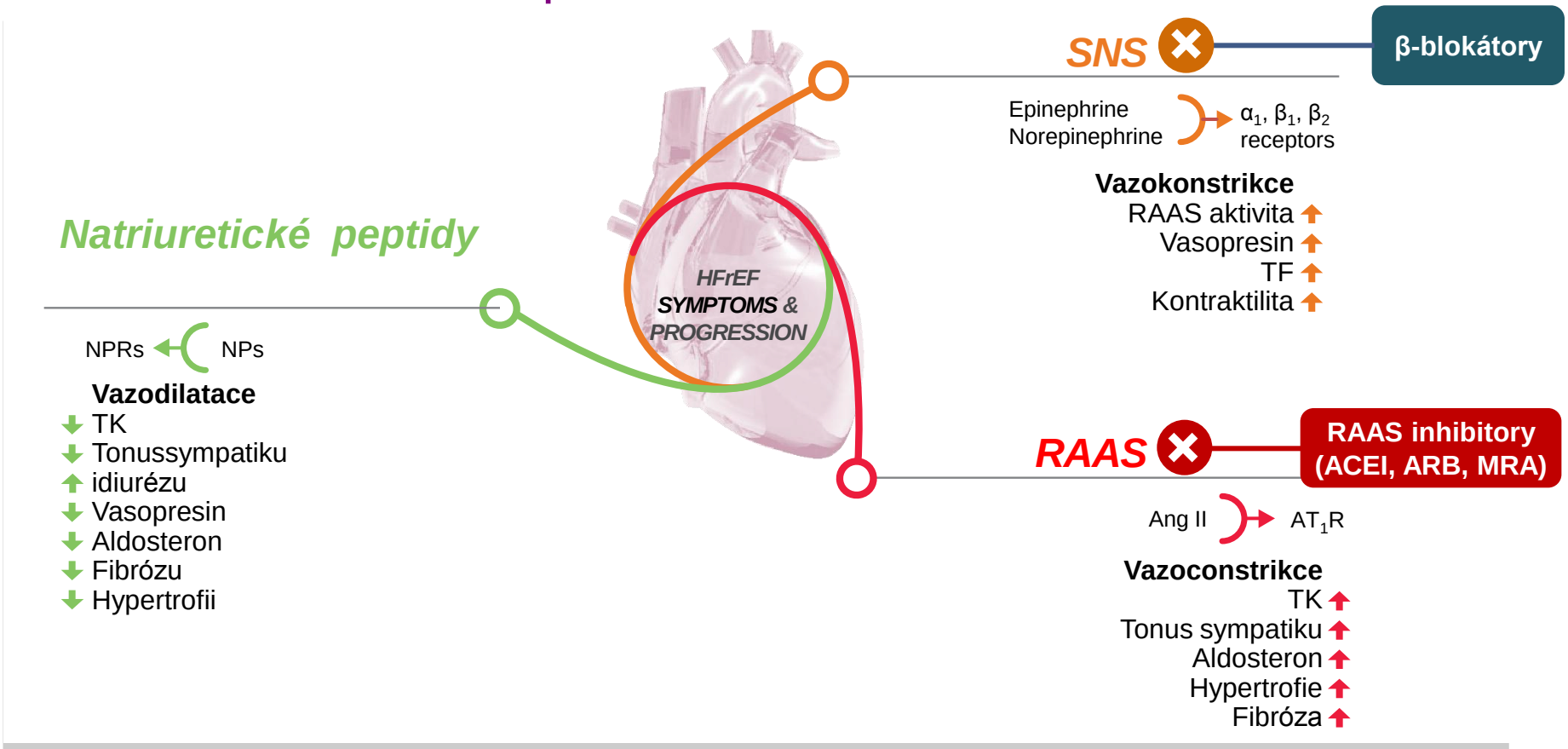
6,800 Patients

Final Protocol	24-May-13
FPFV	2-October-13
Interim Analysis	7-November-15
75% Patients Recruited	1-December-15
Last Patient First Visit	29-July-16
Last Patient Last Visit	31-January-17
Clinical DBL	15-March -17

RELAX – AHF - 2

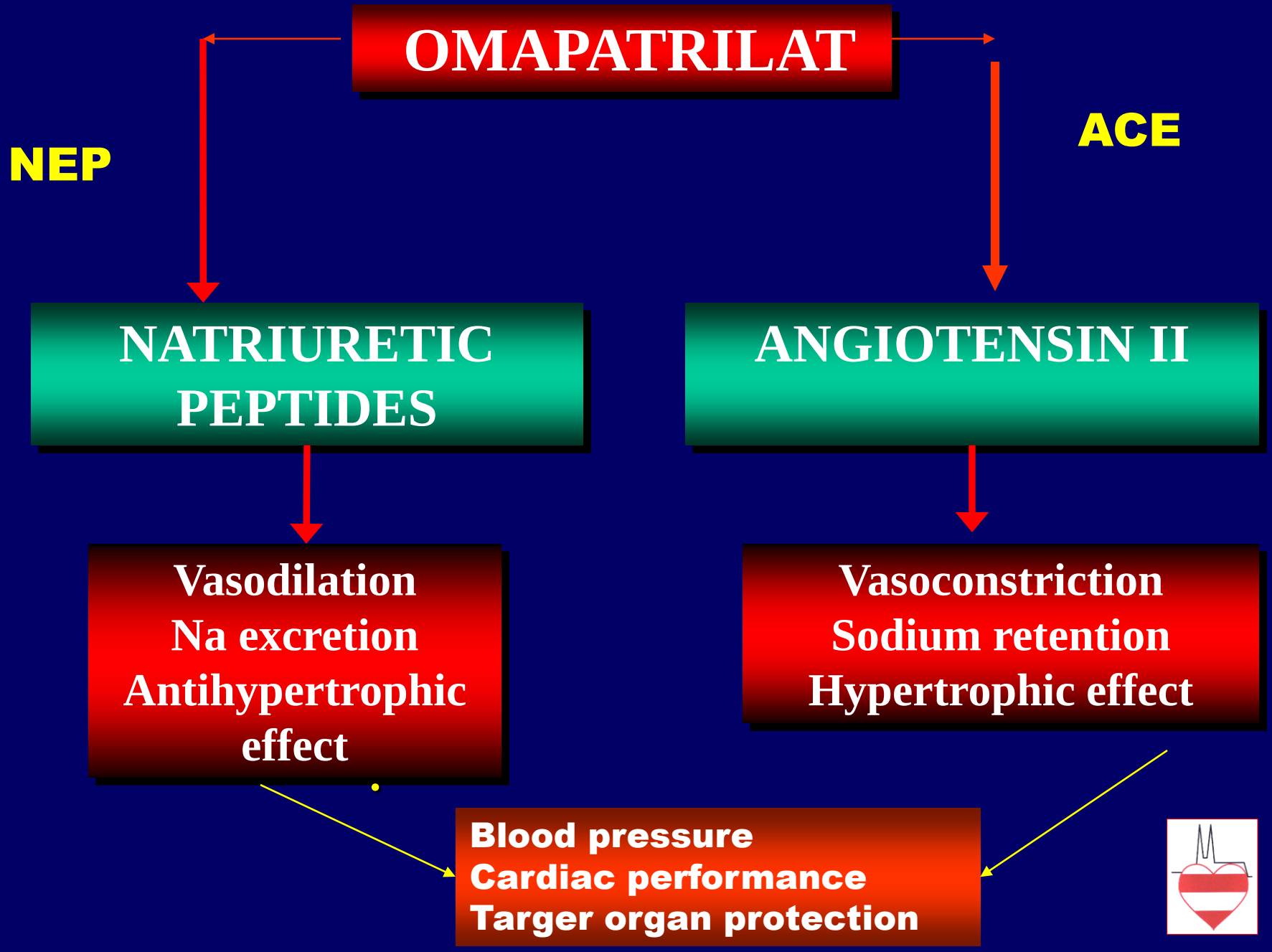

RELAX-AHF n=1161
RELAX-AHF-2 (>30days) n=5414
Mean Age (years)
Gender (male) %
Race (white) %
% HF Hospitalization (in the past year)
NYHA Class III (%)
NYHA Class IV (%)
Number of hospitalization in past year (mean)
IV nitrates at randomization (%)
Diabetes Mellitus (%)
Historical Ejection Fraction (mean)
Hypertension (%)
Stroke or other cerebrovascular event (%)
Peripheral Arterial Disease (%)
Asthma, Bronchitis or COPD (%)
Pacemaker insertion (%)
Ischemic heart disease (%)
Aortic stenosis (%)
Atrial fibrillation/flutter at presentation (%)
Mean Time from presentation to randomization (hours)
100
90
80
70
60
50
40
30
20
10
0

Nadměrná RAAS a SNS je škodlivá u CHSS, její ovlivnění je základem farmakoterapie

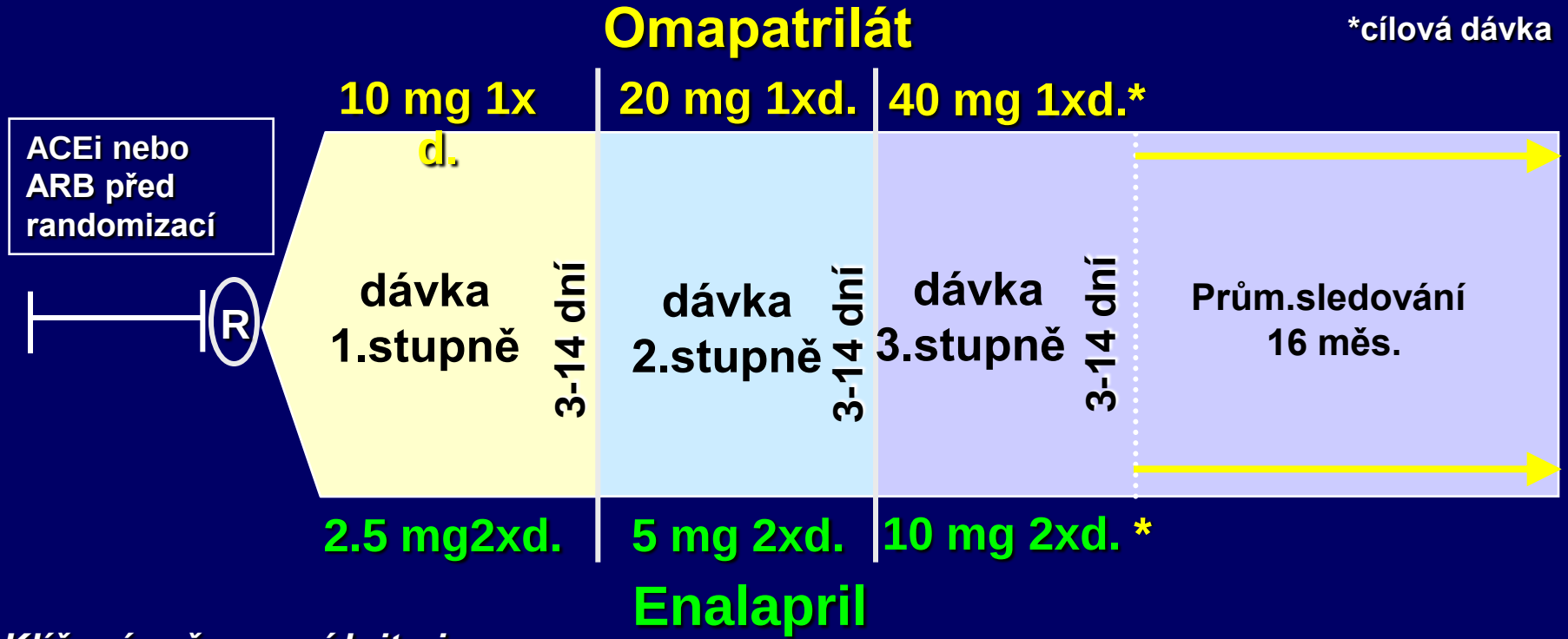


- Základním význam RAAS je podpořen příznivým účinkem ACEIs, ARBs a MRA[1]
- Prospěch β-blokátorů ukazuje, že SNS hraje také klíčovou roli

1. McMurray et al. Eur Heart J 2012;33:1787–847
Figure references: Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Kemp & Conte. Cardiovascular Pathology 2012;365–371; Schrier & Abraham. N Engl J Med 2009;341:577–85;


OMAPATRILAT
NEP
ACE
NATRIURETIC PEPTIDES
ANGIOTENSIN II
Vasodilation
Na excretion
Antihypertrophic effect
Vasoconstriction
Sodium retention
Hypertrophic effect
Blood pressure
Cardiac performance
Targer organ protection

OVERTURE
4 420 pts



Klíčová zařazovací kriteria:

- **NYHA třída srdečního selhání II, III nebo IV ; EF LK ≤30%; hospitalizace pro srdeční selhání v průběhu předchozích 12 měsíců**

Primární cíl:

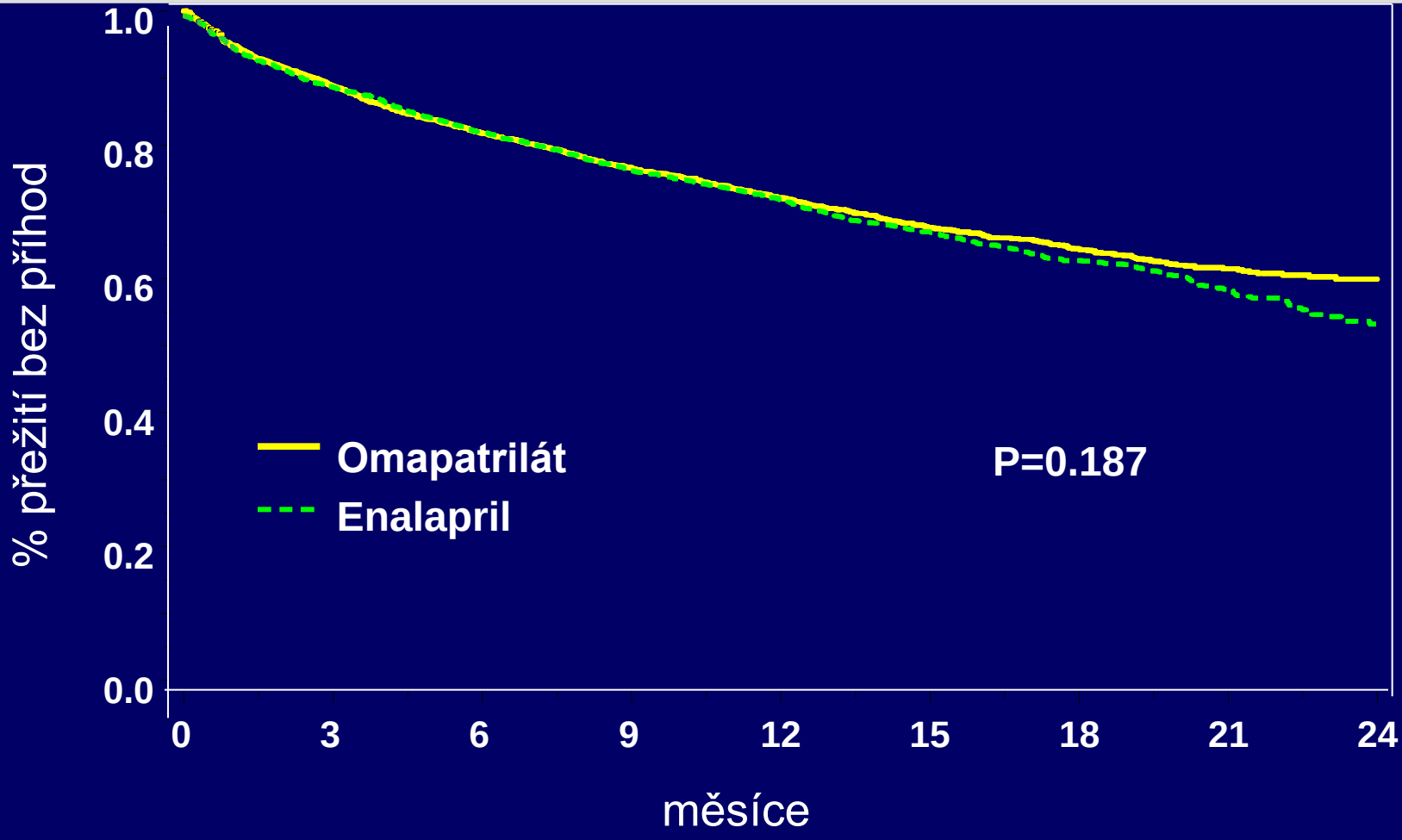
- mortalita ze všech příčin + hospitalizace pro srdeční selhání

Sekundární cíl:

- mortalita ze všech příčin

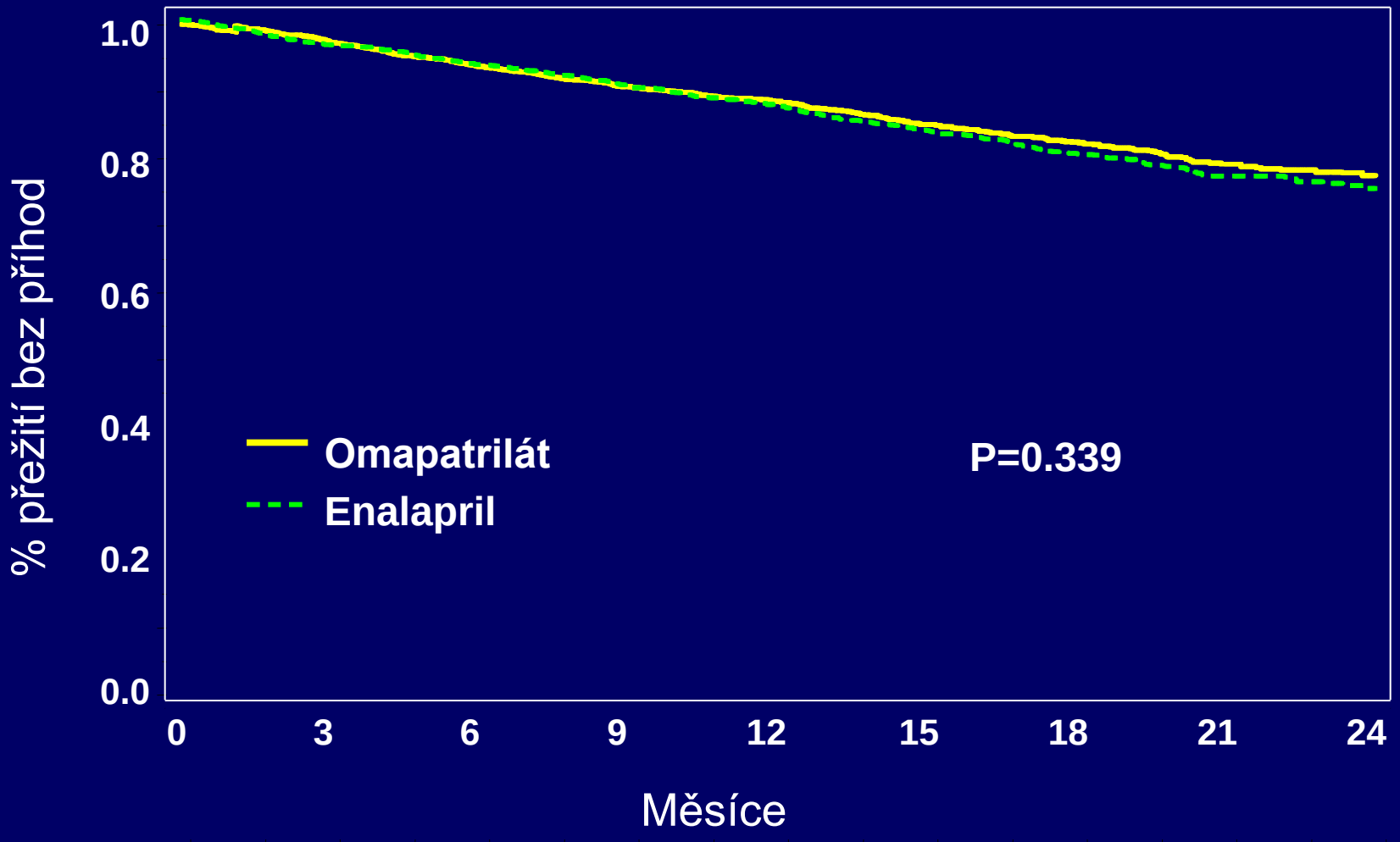
Data on file, Bristol-Myers Squibb.

OVERTURE: primární cíl úmrtí nebo hospitalizace pro srdeční selhání



Data on file, Bristol-Myers Squibb.

OVERTURE: sekundární cíl mortalita ze všech příčin



Data on file, Bristol-Myers Squibb.

OVERTURE: předběžné závěry

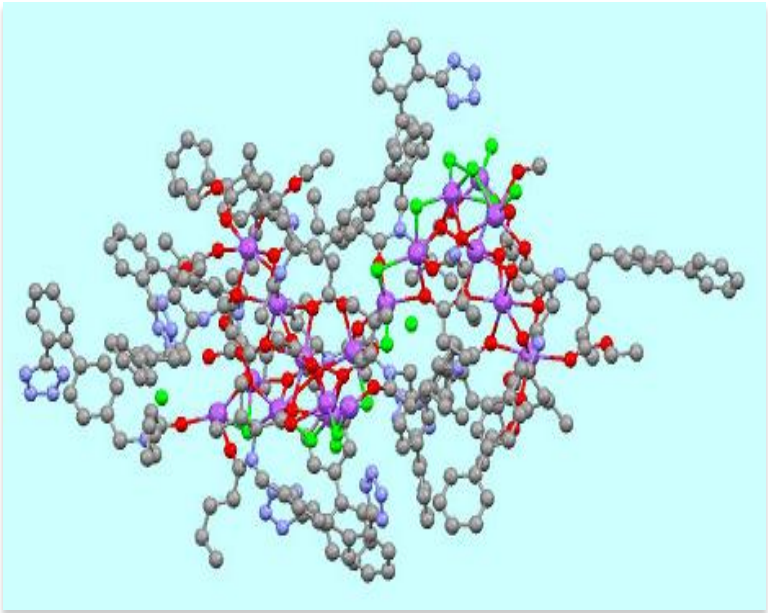
Kombinovaná inhibice ACE a NEP omapatrilátem vede k poklesu morbidity a mortality u nemocných s těžkým srdečním selháním, která je ekvivalentní, ale ne signifikantně větší než inhibice ACE sama.

Data on file, Bristol-Myers Squibb.

LCZ696 je první ve třídě angiotensin receptor neprilysin inhibitor (ARNI)

- LCZ696 je nový lék který současně inhibuje neprilysin a blokuje AT_1 receptor [1–3]
- LCZ696 je komplex soli, který obsahuje dvě aktivní substance:[2,3]
  - sacubitril (AHU377) – pro-drug; dále metabolizovaný na inhibitor neprilysinu LBQ657
  - valsartan – blokátor AT_1 receptoru

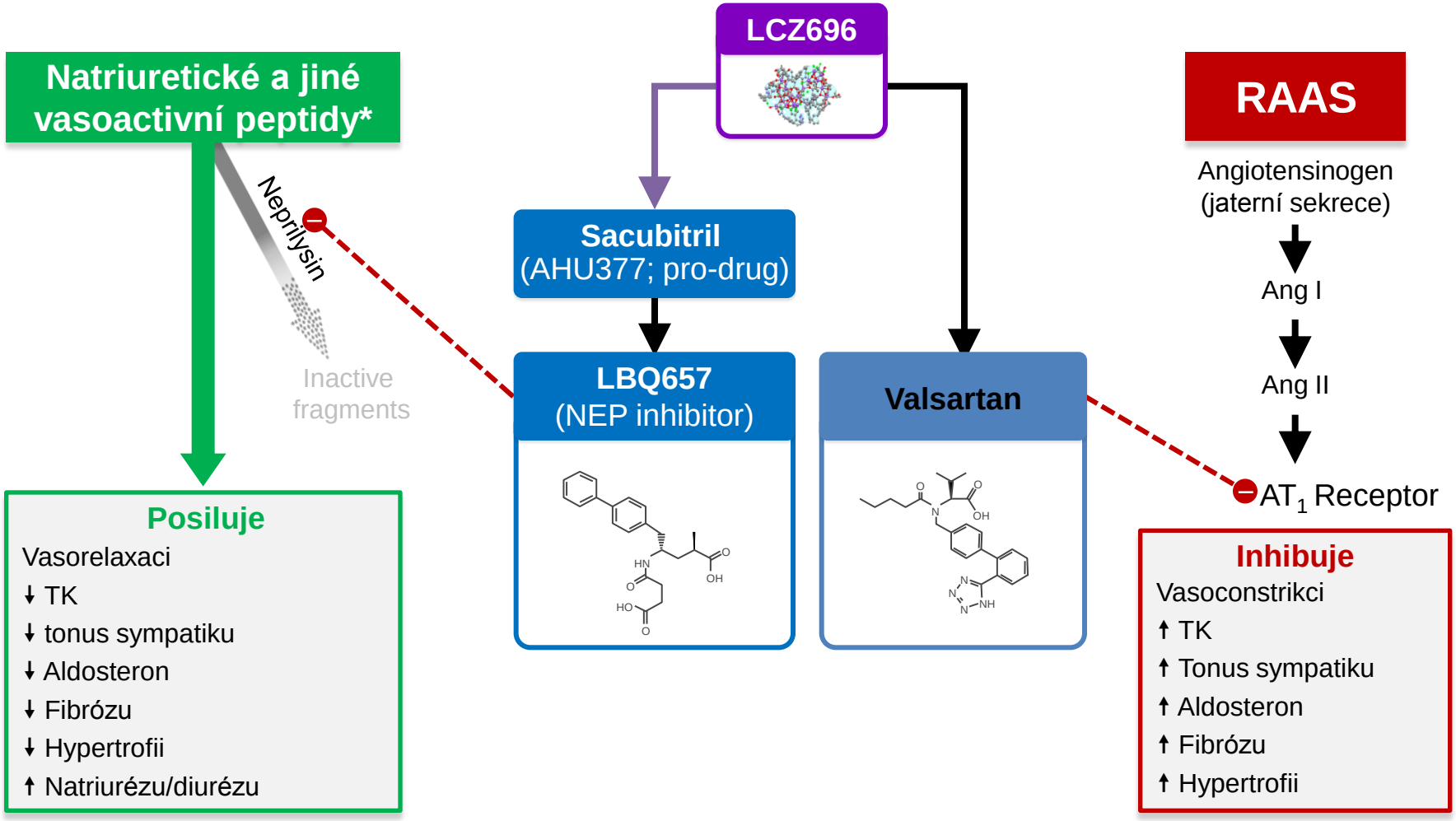
  V molárním poměru 1:1



3D LCZ696 struktura[2]

1. Bloch, Basile. J Clin Hypertens 2010;12:809–12; 2. Gu et al. J Clin Pharmacol 2010;50:401–14; 3. Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9

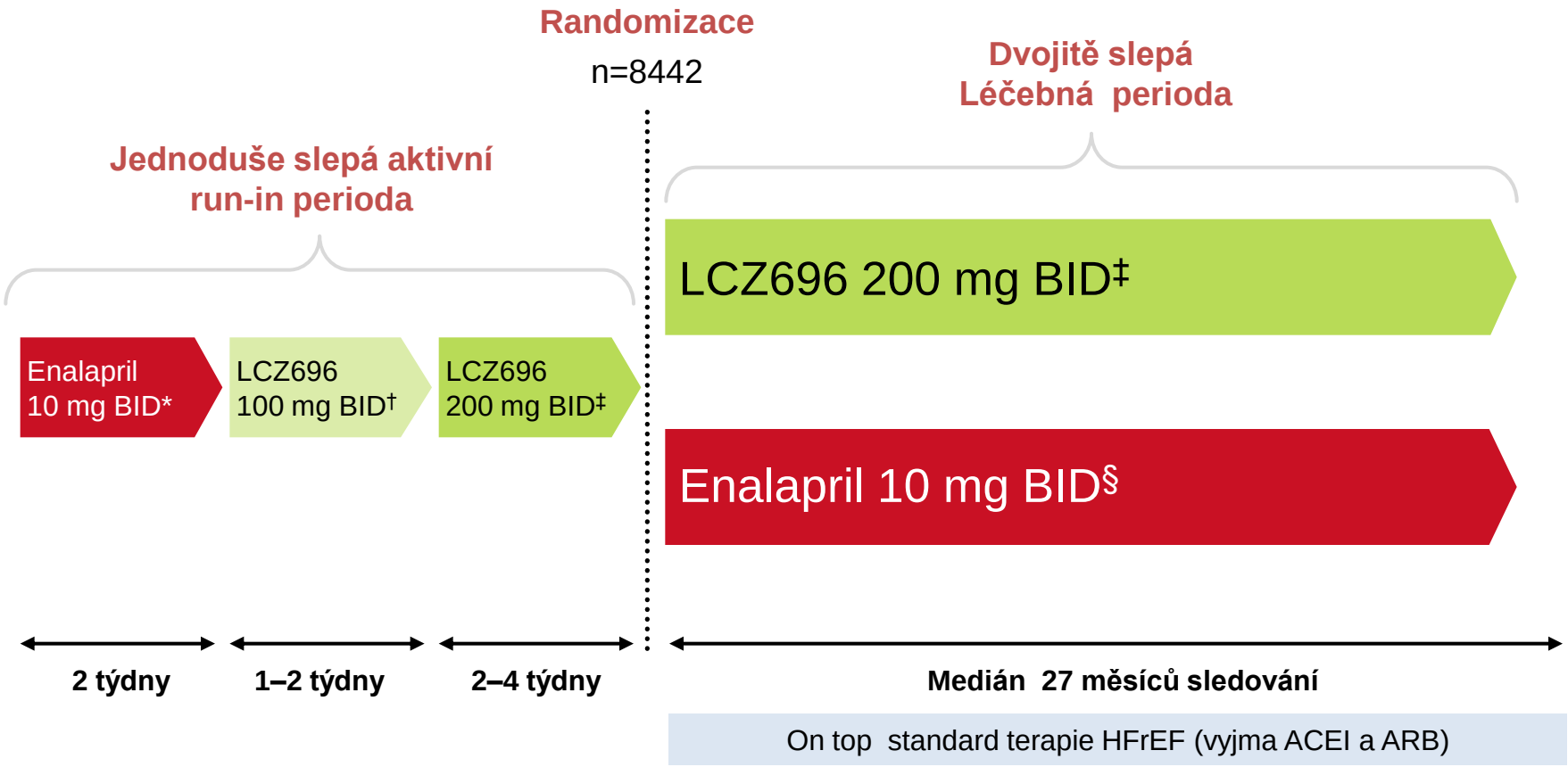
LCZ696 sooučasně inhibuje NEP (via LBQ657) a blokuje AT_1 receptor (via valsartan)



*Neprilysin substrates listed in order of relative affinity for NEP: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP

Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42;
Schrier & Abraham N Engl J Med 2009;341:577–85; Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9;
Feng et al. Tetrahedron Letters 2012;53:275–6

PARADIGM-HF: Design studie

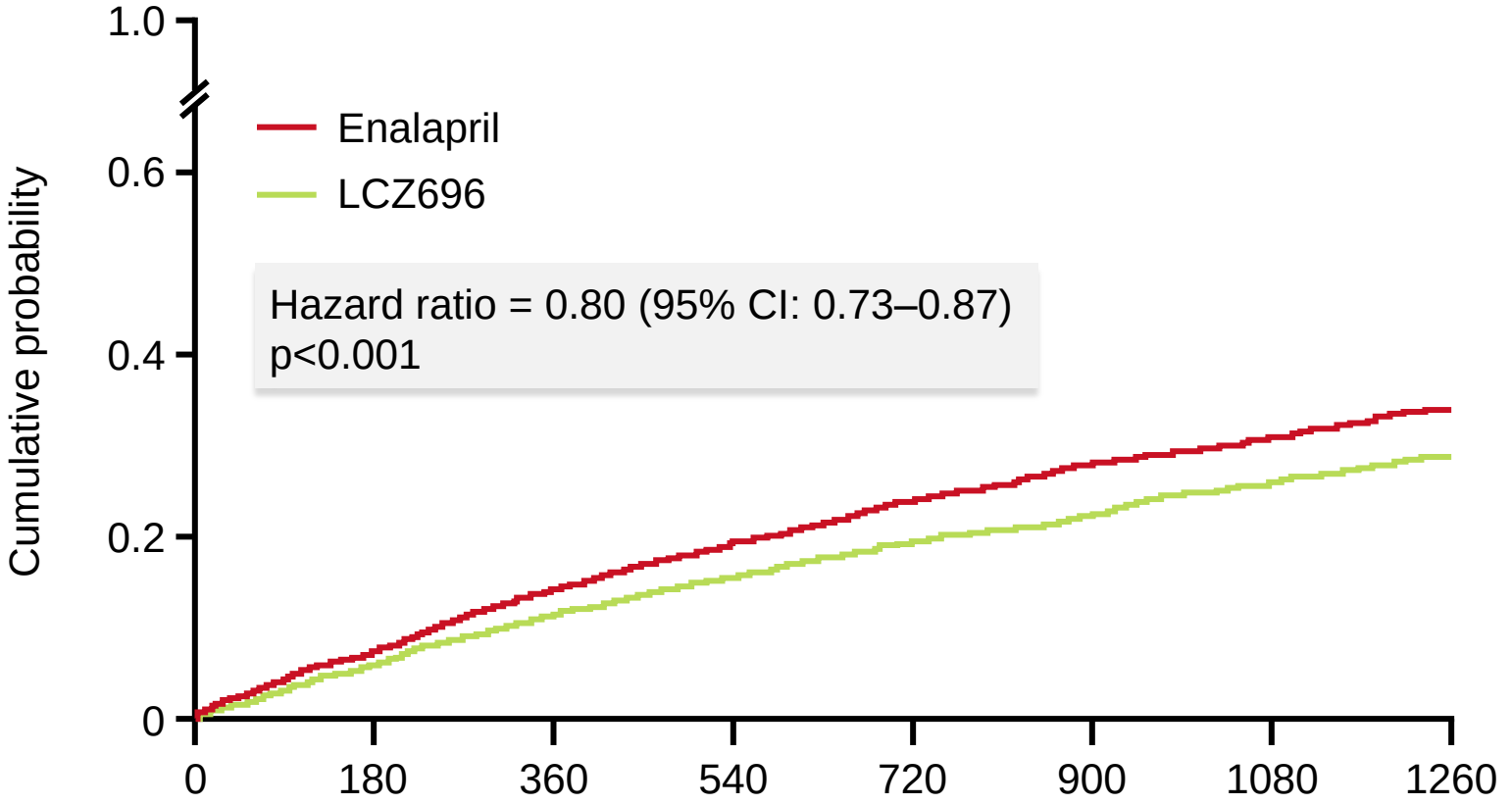


*Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; †200 mg TDD; ‡400 mg TDD; §20 mg TDD.

McMurray et al. Eur J Heart Fail. 2013;15:1062–73; McMurray et al. Eur J Heart Fail. 2014;16:817–25; McMurray, et al. N Engl J Med 2014; ePub ahead of print: DOI: 10.1056/NEJMoa1409077.

Primární endpoint:

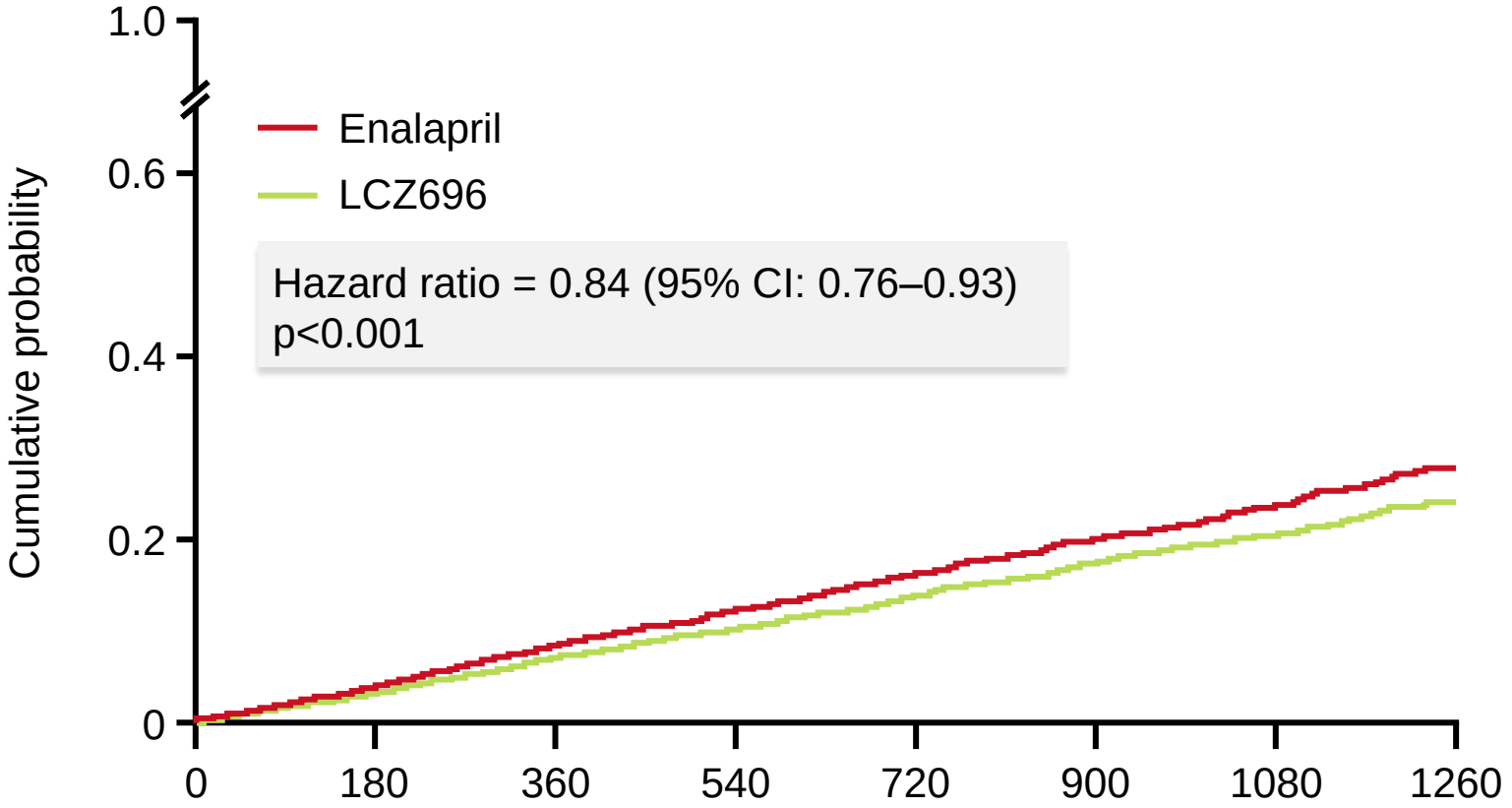
KV úmrtí nebo první hospitalizace pro SS



No at risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

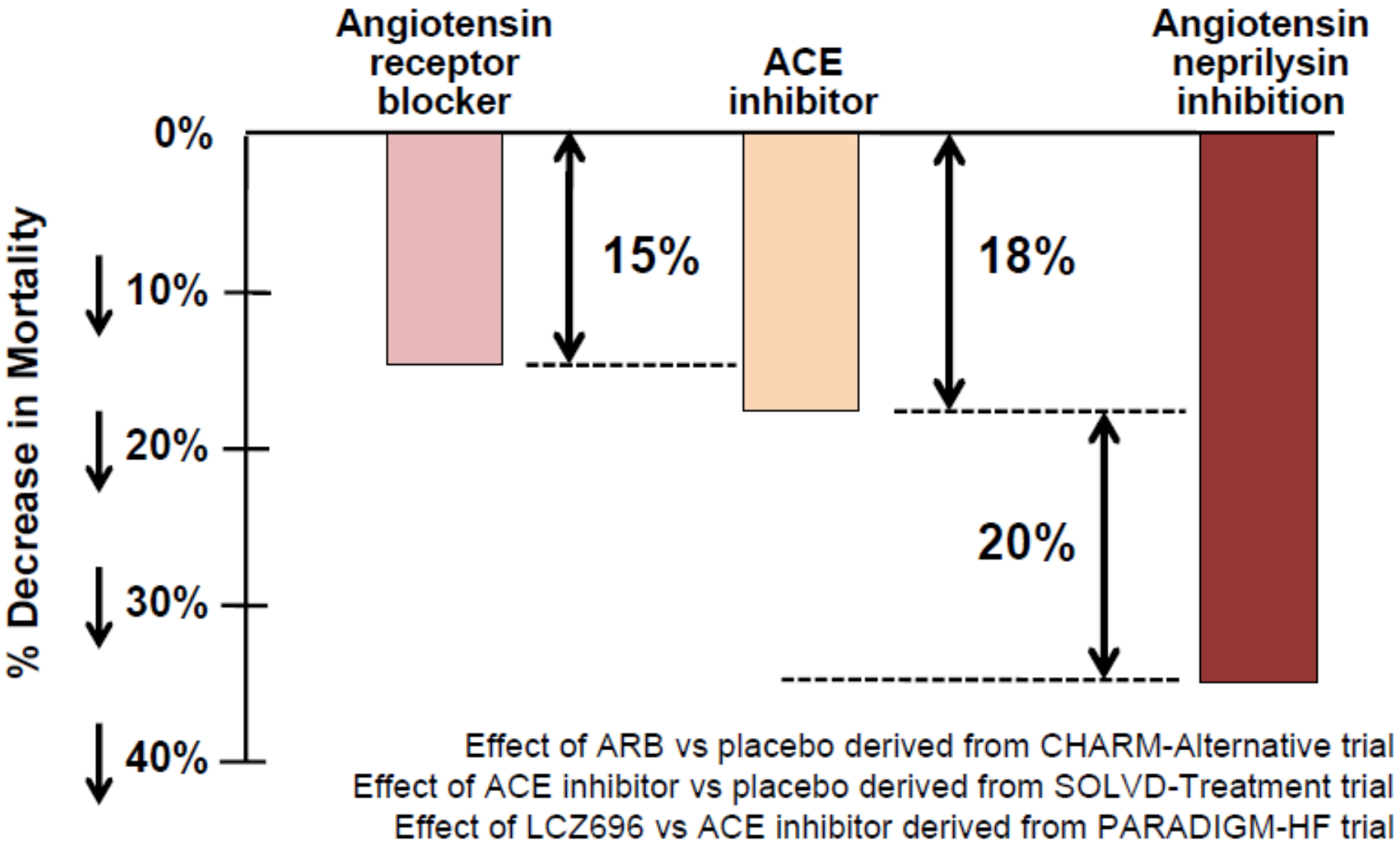
McMurray, et al. N Engl J Med 2014; ePub ahead of print: DOI: 10.1056/NEJMoa1409077.

Sekundární cíl: Úmrtí z jakékoliv příčiny



No at risk								
LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

McMurray, et al. N Engl J Med 2014; ePub ahead of print: DOI: 10.1056/NEJMoa1409077.



M.Packer: ESC Congress 2014

Užívání ACEI po více než 25 let s efektem na snížení KV mortality o 18% jim dalo mandát být na prvním místě v léčbě SS.

LCZ měl efekt na KV mortalitu o 20% oproti ACEI, není tedy čas uvažovat o náhradě ACEI tímto lékem?

M.Packer: ESC Congress 2014
L.Špinarová, ČKS Congress 2015

Děkuji za pozornost