Akutní srdeční selhání
Novinky ve farmakoterapii

Špinar J.
Brno, Česká republika

The 2012 ESC heart failure guidelines

European Heart Journal (2012) **33**, 1787–1847
doi:10.1093/eurheartj/ehs104

ESC GUIDELINES

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

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: John J.V. McMurray (Chairperson) (UK)*, Stamatis Adamopoulos (Greece), Stefan D. Anker (Germany), Angelo Auricchio (Switzerland), Michael Böhm (Germany), Kenneth Dickstein (Norway), Volkmar Falk (Switzerland), Gerasimos Filippatos (Greece), Cândida Fonseca (Portugal), Miguel Angel Gomez-Sanchez (Spain), Tiny Jaarsma (Sweden), Lars Køber (Denmark), Gregory Y.H. Lip (UK), Aldo Pietro Maggioni (Italy), Alexander Parkhomenko (Ukraine), Burkert M. Pieske (Austria), Bogdan A. Popescu (Romania), Per K. Rønnevik (Norway), Frans H. Rutten (The Netherlands), Juerg Schwitter (Switzerland), Petar Seferovic (Serbia), Janina Stepinska (Poland), Pedro T. Trindade (Switzerland), Adriaan A. Voors (The Netherlands), Faiez Zannad (France), Andreas Zeiher (Germany).

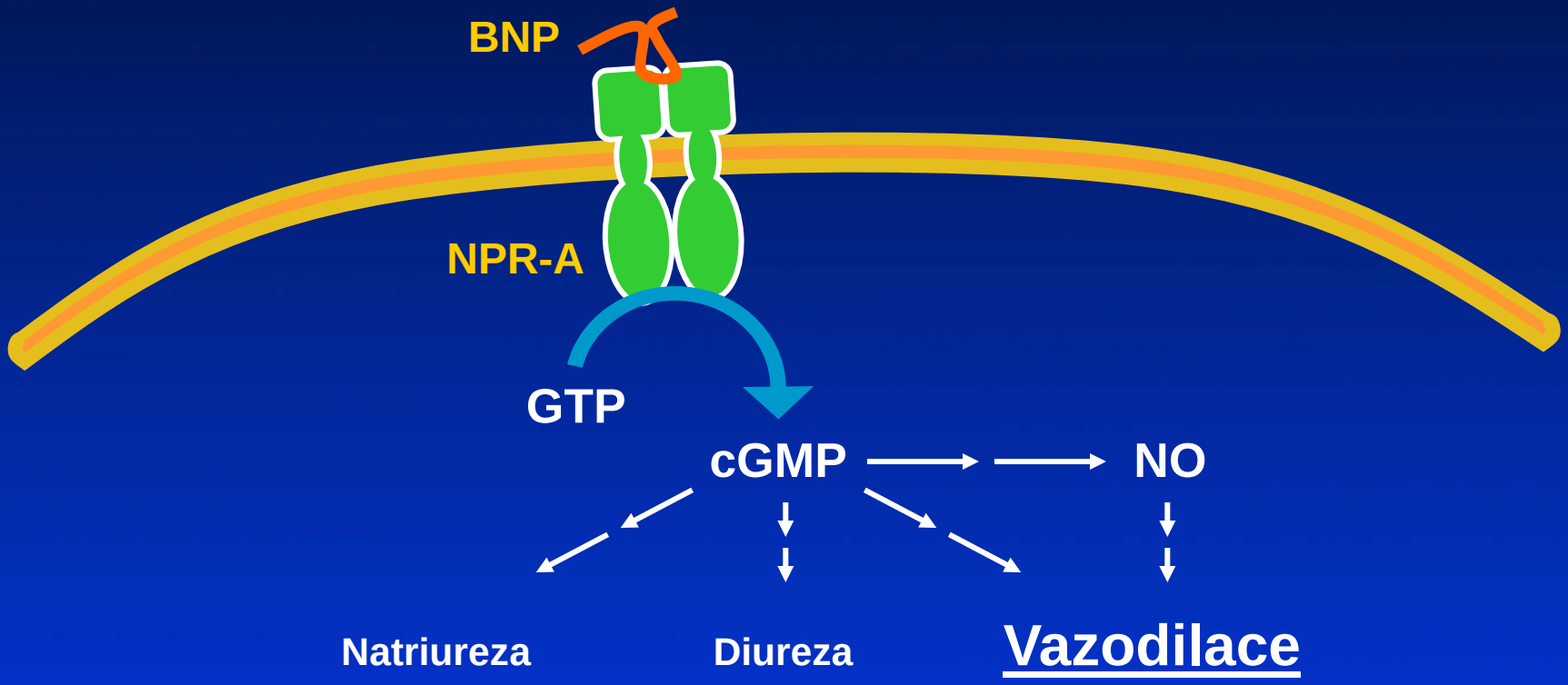
Současná léčba ASS

IV Diuretika	Vazodilatace	Inotropika
Snižují objem Předtížení	**Snižují předtížední i dotížení**	**Zvyšují kontraktilitu**
Kličková diuretika	**Nitroglycerin Nitroprusside Nesiritide**	**Dobutamine Milrinone**

McBride BF, et al. *Pharmacotherapy*. 2003;23:997-1020.

Nesiritide Mechanismus účinku

- Recombinantní lidský B-typ natriuretický peptide (BNP)



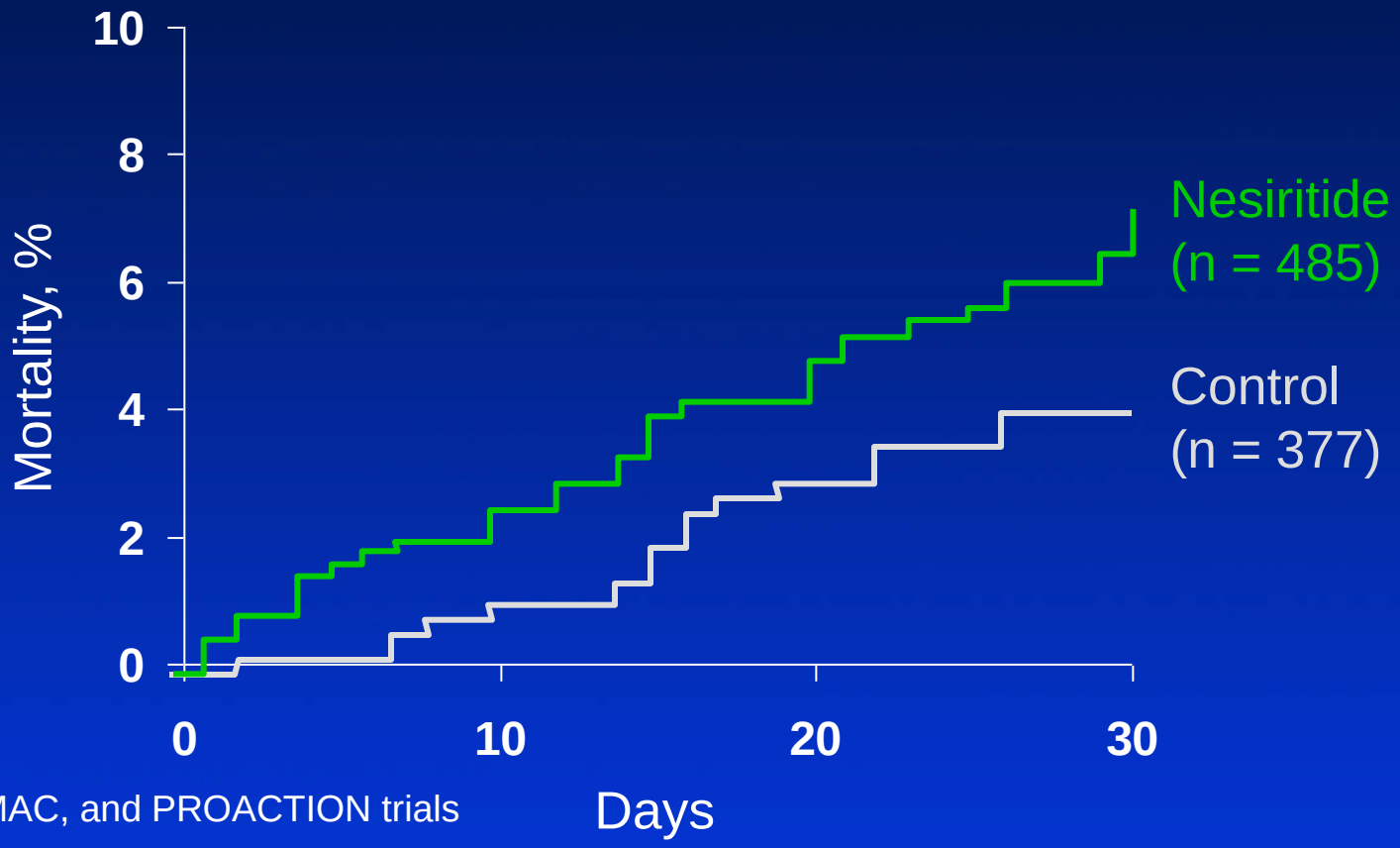
Kuhn M. *Circ Res.* 2003;93:700-709.

Effect of Nesiritide on Mortality

Meta-Analysis of 3 Nesiritide Trials*

Unadjusted: hazard ratio 1.86 (95% CI, 1.02-3.41), *P*=0.04

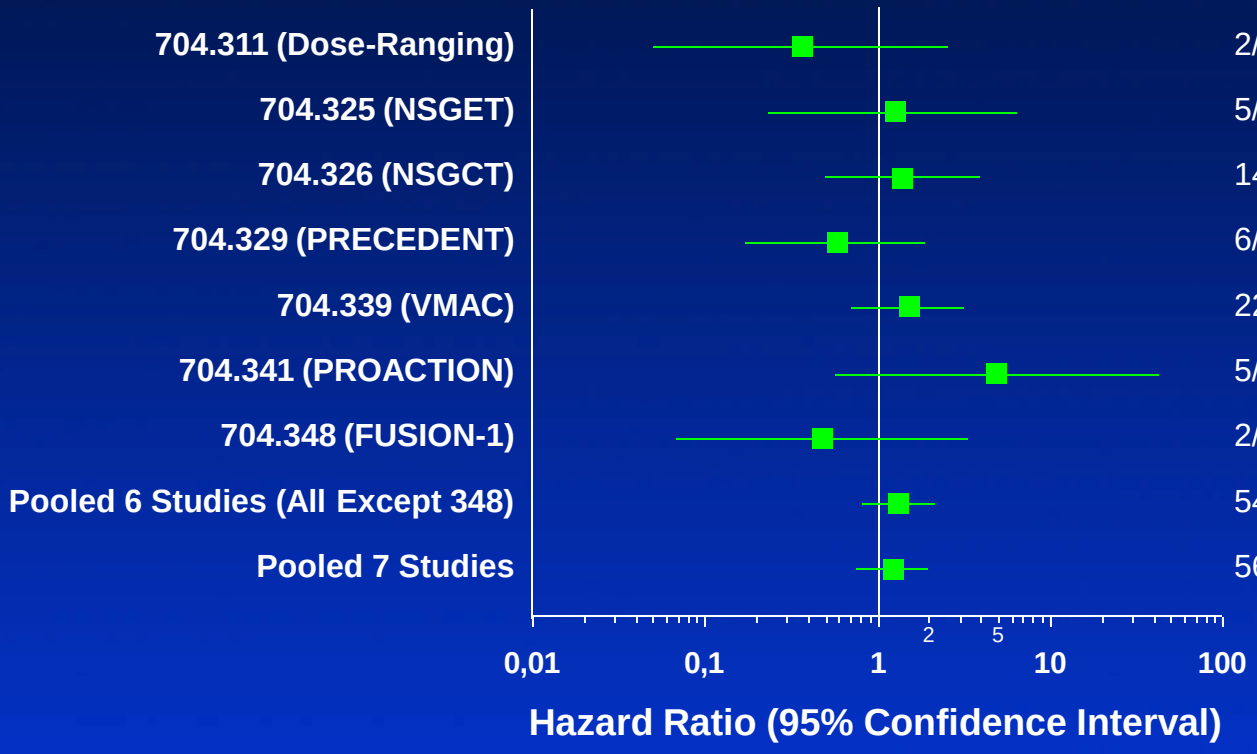
Adjusted for study: hazard ratio 1.80 (95% CI 0.98-3.31), *P*=0.057



*NSGET, VMAC, and PROACTION trials

Sackner-Bernstein JD, et al. *JAMA.* 2005;293:1900-1905.

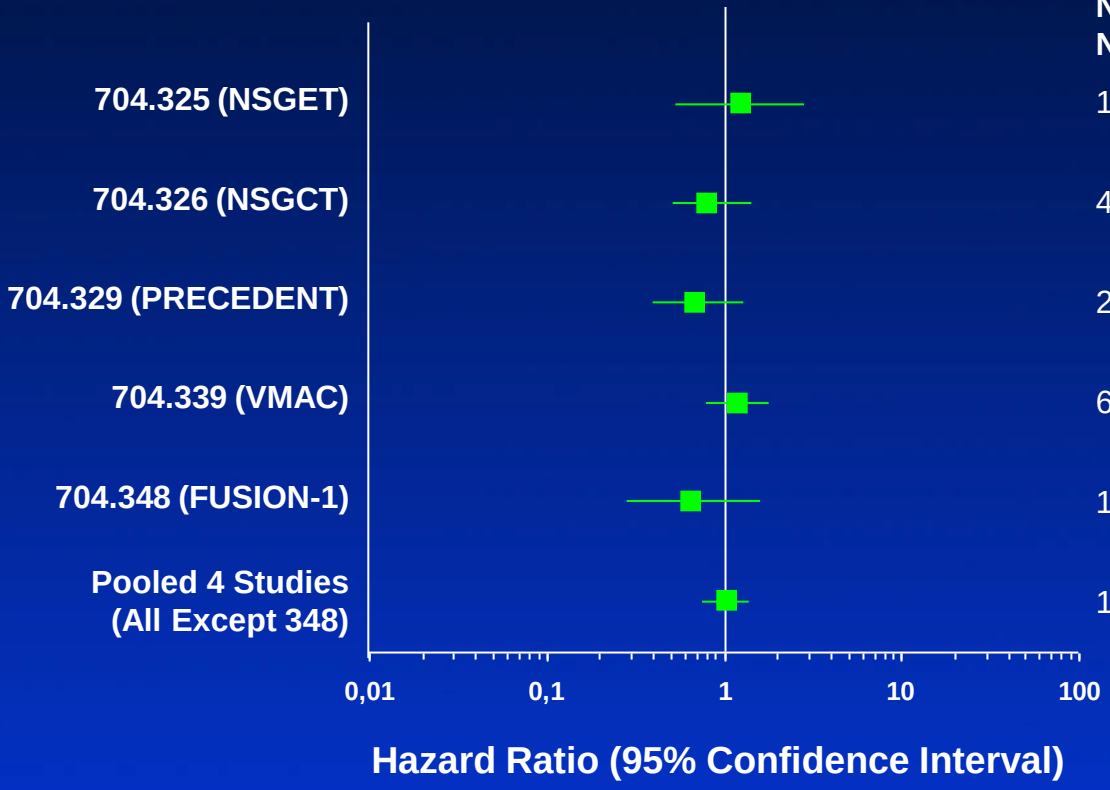
Efekt of Nesiritidu na 30 denní mortalitu



	Nesiritide N (%)	Control N (%)
704.311 (Dose-Ranging)	2/74 (2.7%)	2/29 (7.5%)
704.325 (NSGET)	5/85 (5.9%)	2/42 (4.8%)
704.326 (NSGCT)	14/203 (6.9%)	5/102 (4.9%)
704.329 (PRECEDENT)	6/163 (3.7%)	5/83 (6.1%)
704.339 (VMAC)	22/273 (8.1%)	11/216 (5.1%)
704.341 (PROACTION)	5/120 (4.2%)	1/117 (0.9%)
704.348 (FUSION-1)	2/141 (1.4%)	2/69 (2.9%)
Pooled 6 Studies (All Except 348)	54/918 (5.9%)	26/589 (4.4%)
Pooled 7 Studies	56/1059 (5.3%)	28/658 (4.3%)

Natrecor [package insert]. Fremont, Calif: Scios Inc; 2005.

Efect of Nesiritidu na 180 denní mortalitu

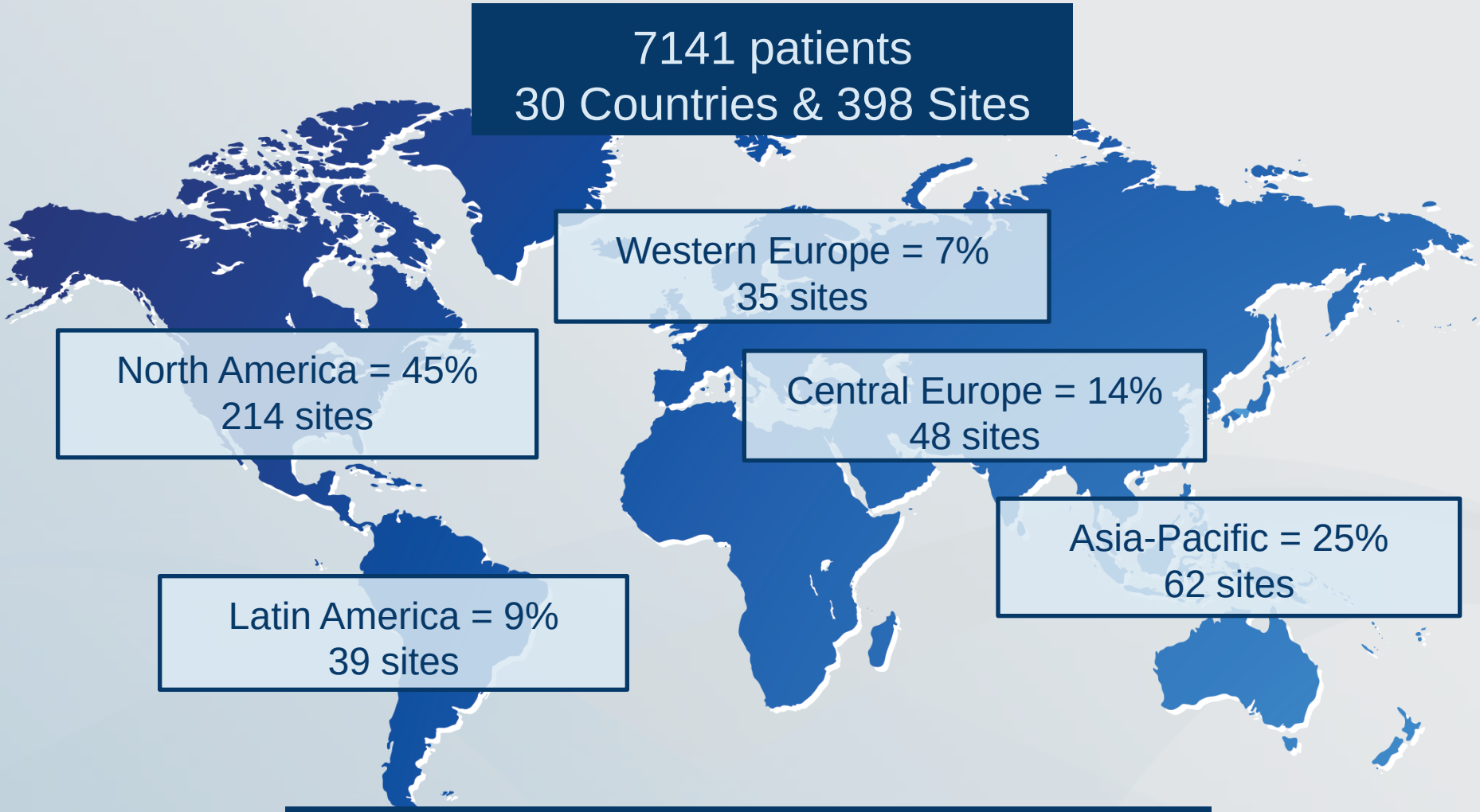


	Nesiritide N (%)	Control N (%)
704.325 (NSGET)	19/85 (23.1%)	8/42 (19.3%)
704.326 (NSGCT)	42/203 (20.8%)	24/102 (23.5%)
704.329 (PRECEDENT)	26/163 (16.3%)	18/83 (22.2%)
704.339 (VMAC)	67/273 (25.1%)	44/216 (20.8%)
704.348 (FUSION-1)	13/141 (9.4%)	9/69 (13.5%)
Pooled 4 Studies (All Except 348)	154/724 (21.7%)	94/443 (21.5%)

Natrecor [package insert]. Fremont, Calif: Scios Inc; 2005.

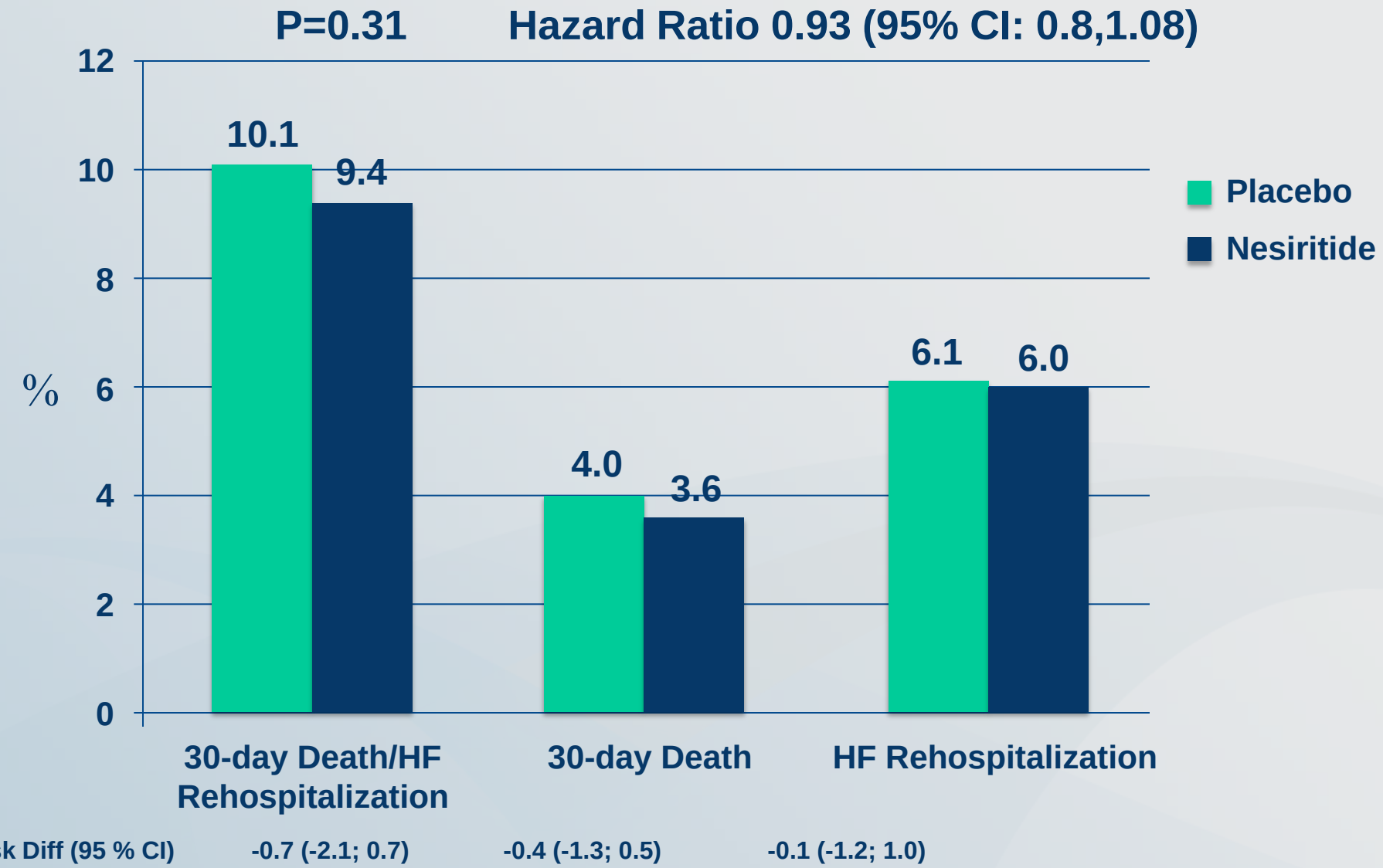
Enrollment

ASCEND-HF
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure



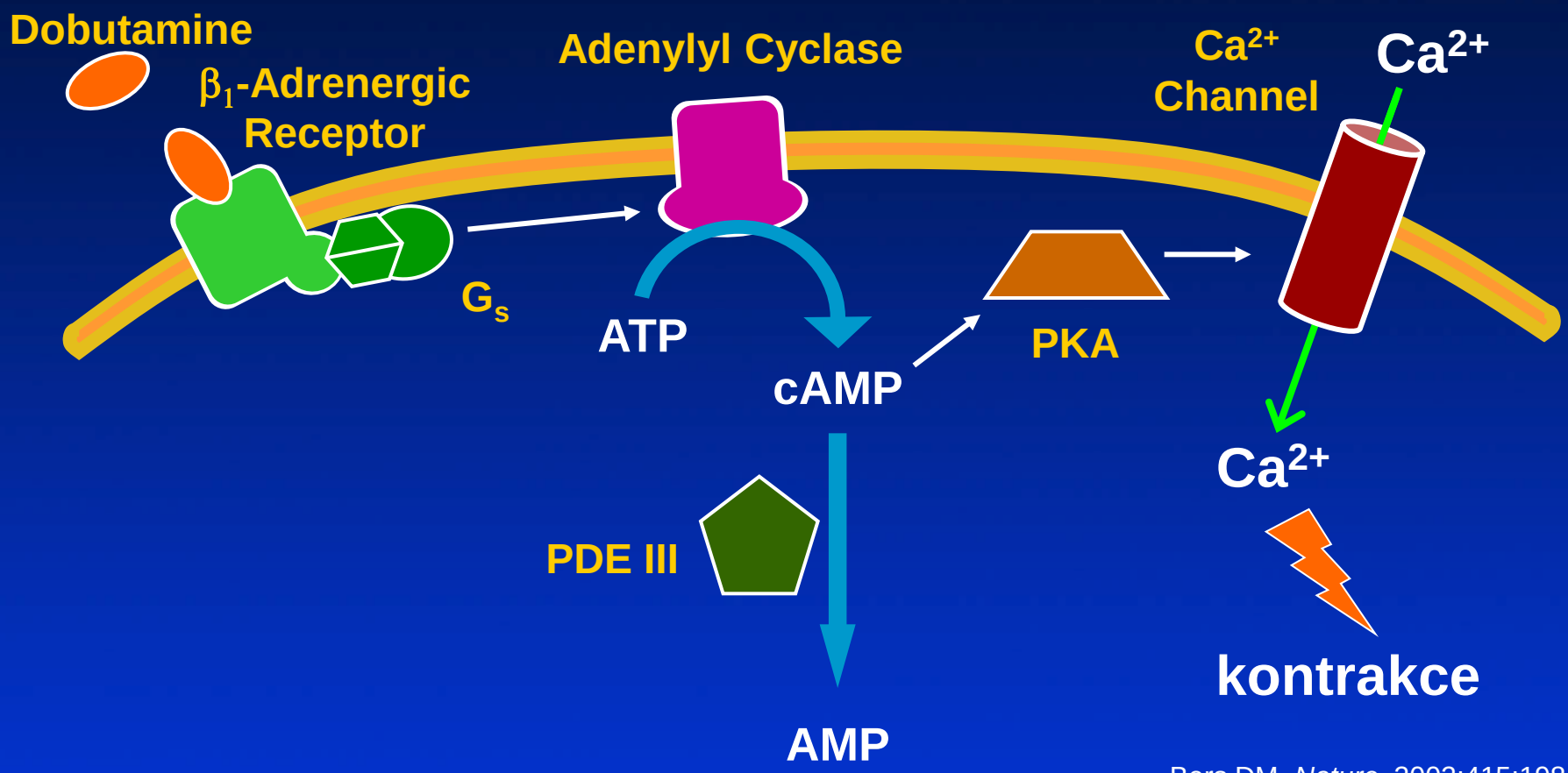
Co-Primary outcome: 30-day all-cause mortality or HF rehospitalization

ASCEND-HF
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure



Risk Diff (95 % CI)	-0.7 (-2.1; 0.7)	-0.4 (-1.3; 0.5)	-0.1 (-1.2; 1.0)

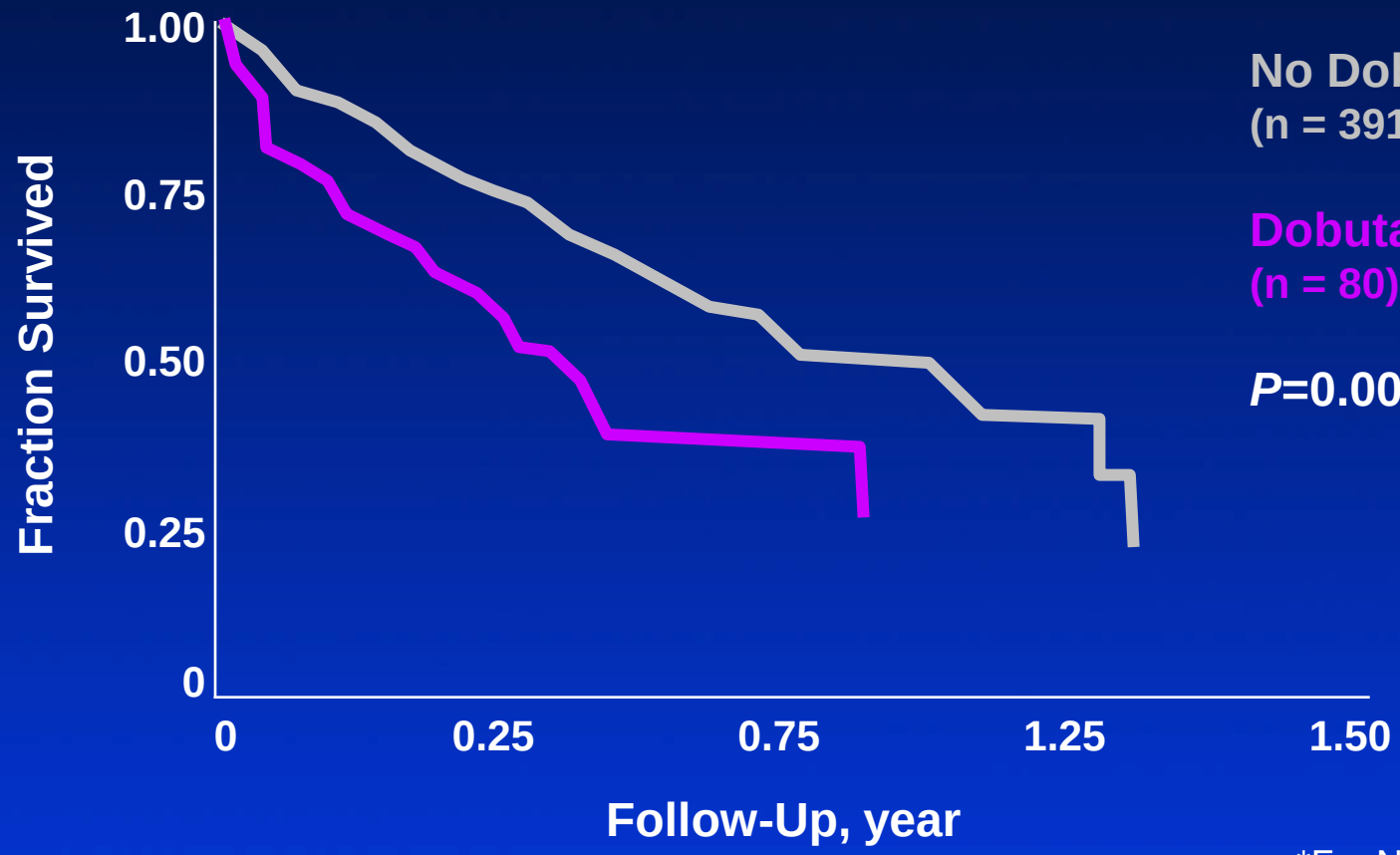
Dobutamine mechanismus účinku



Bers DM. *Nature.* 2002;415:198-205.
Movsesian MA. *J Card Fail.* 2003;9:475-480.
McBride BF, et al. *Pharmacotherapy.* 2003;23:997-1020.

Effect of Dobutamine on Survival

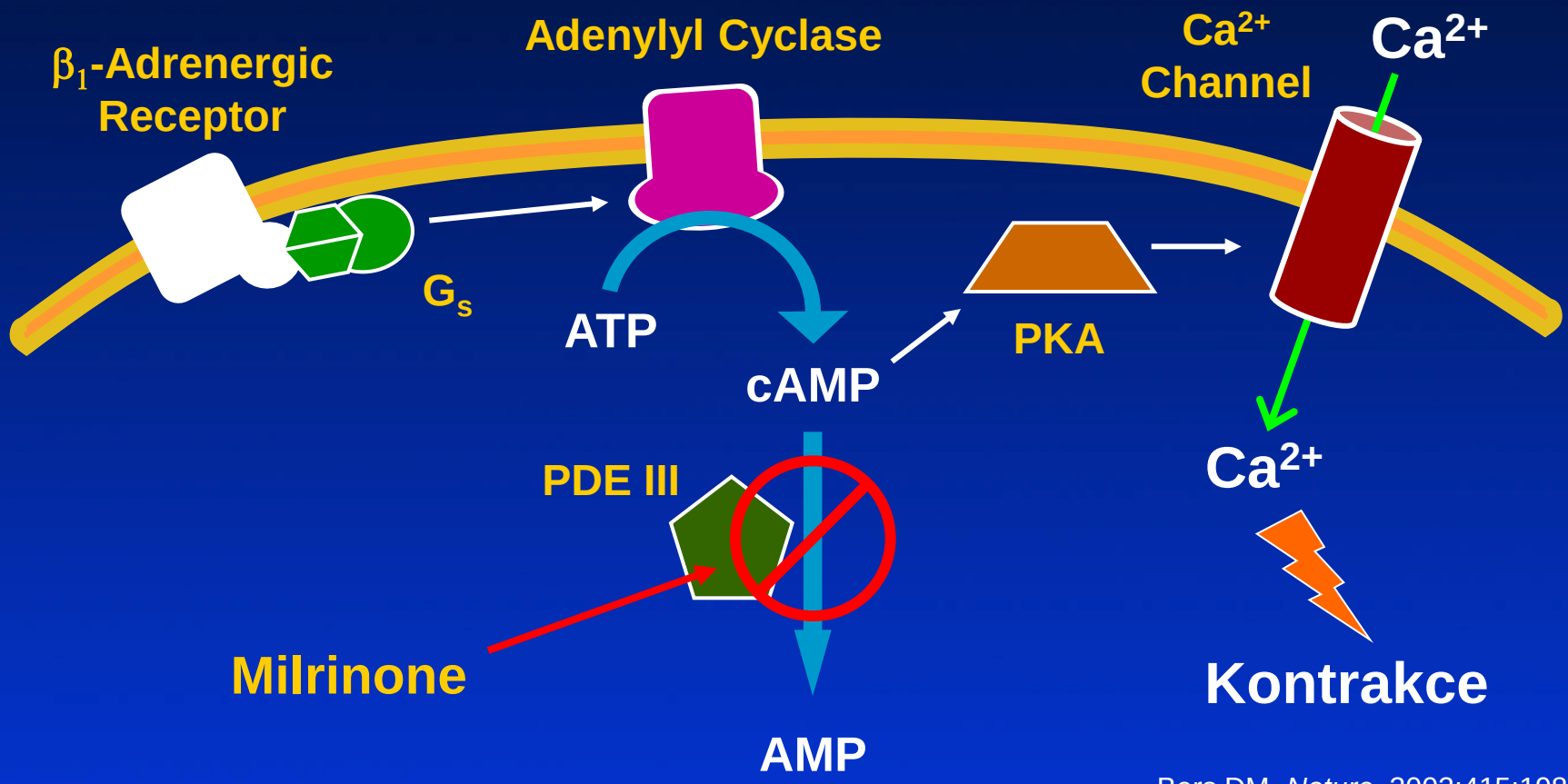
FIRST Trial: Adjusted Survival



*For NYHA III-IV patients.

O'Connor CM, et al. *Am Heart J*. 1999;138:78-86.

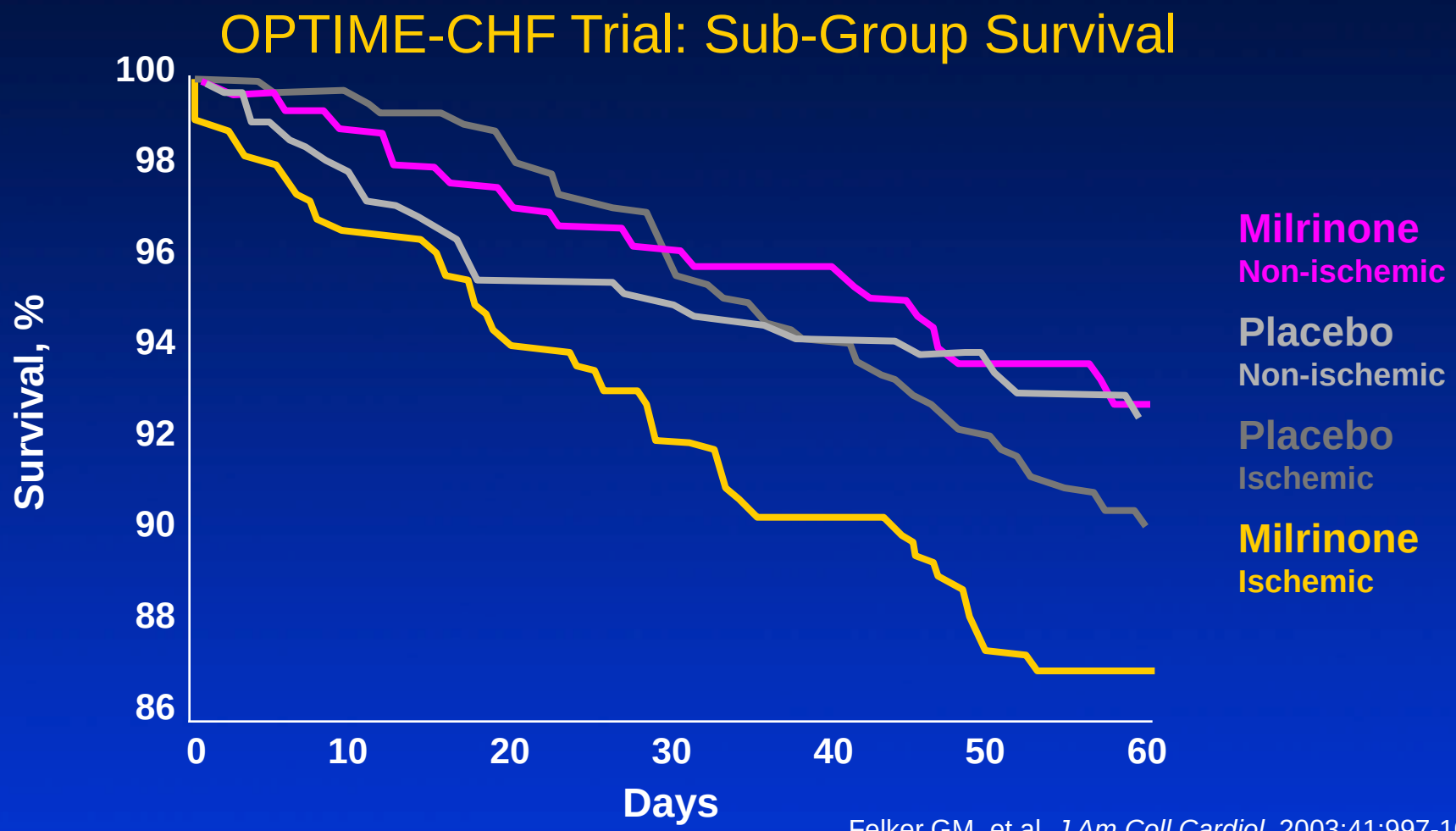
Milrinone mechanismus účinku



Bers DM. *Nature.* 2002;415:198-205.
Movsesian MA. *J Card Fail.* 2003;9:475-480.
McBride BF, et al. *Pharmacotherapy.* 2003;23:997-1020.

Effect of Milrinone on Survival

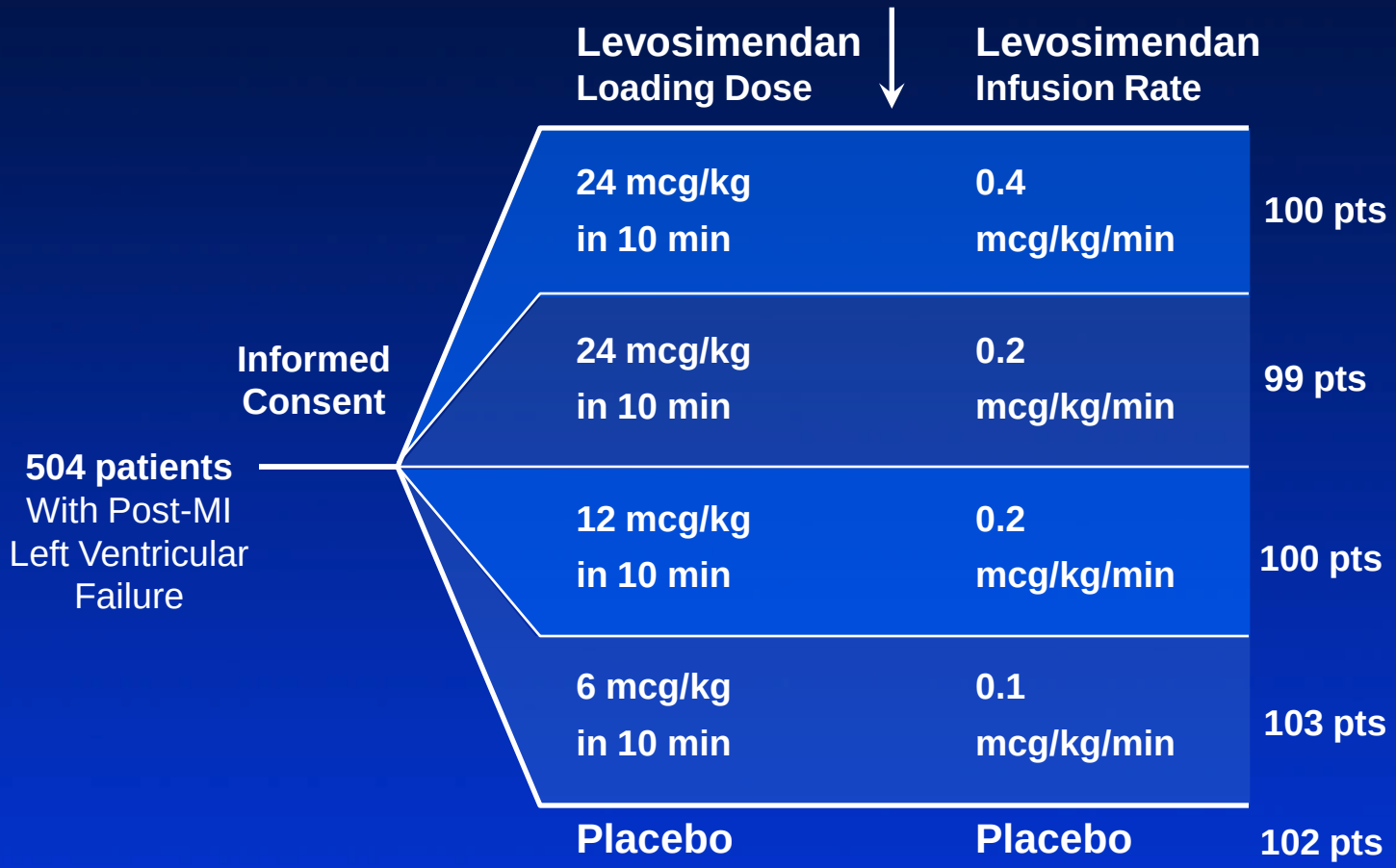
Kaplan-Meier Survival Curves to 60 Days by Heart Failure Etiology and Treatment Assignment



Felker GM, et al. *J Am Coll Cardiol*. 2003;41:997-1003.
Cuffe MS, et al. *JAMA*. 2002;287:1541-1547.

Levosimendan

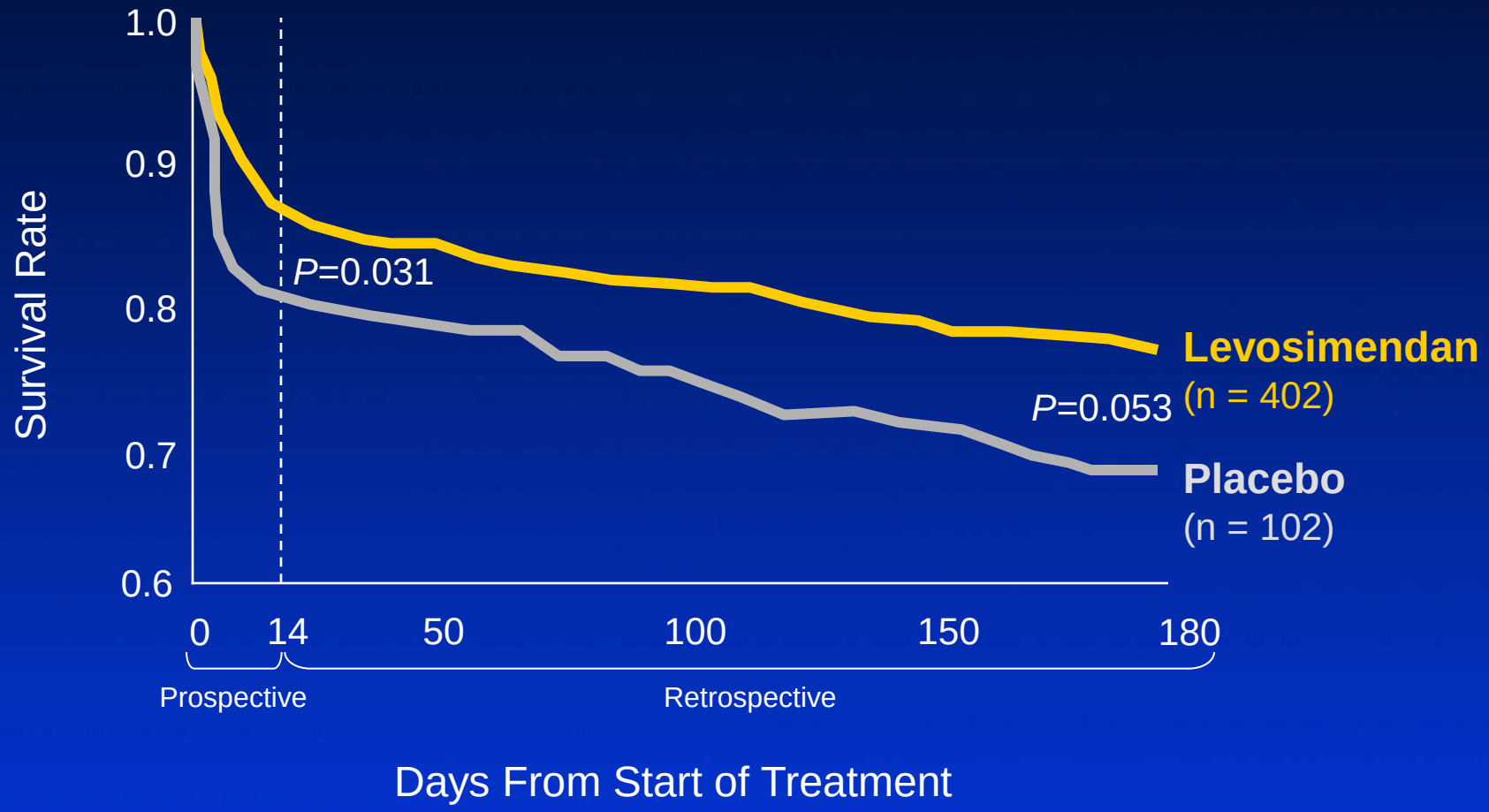
RUSSLAN Study Design



Total infusion time: 6 hours

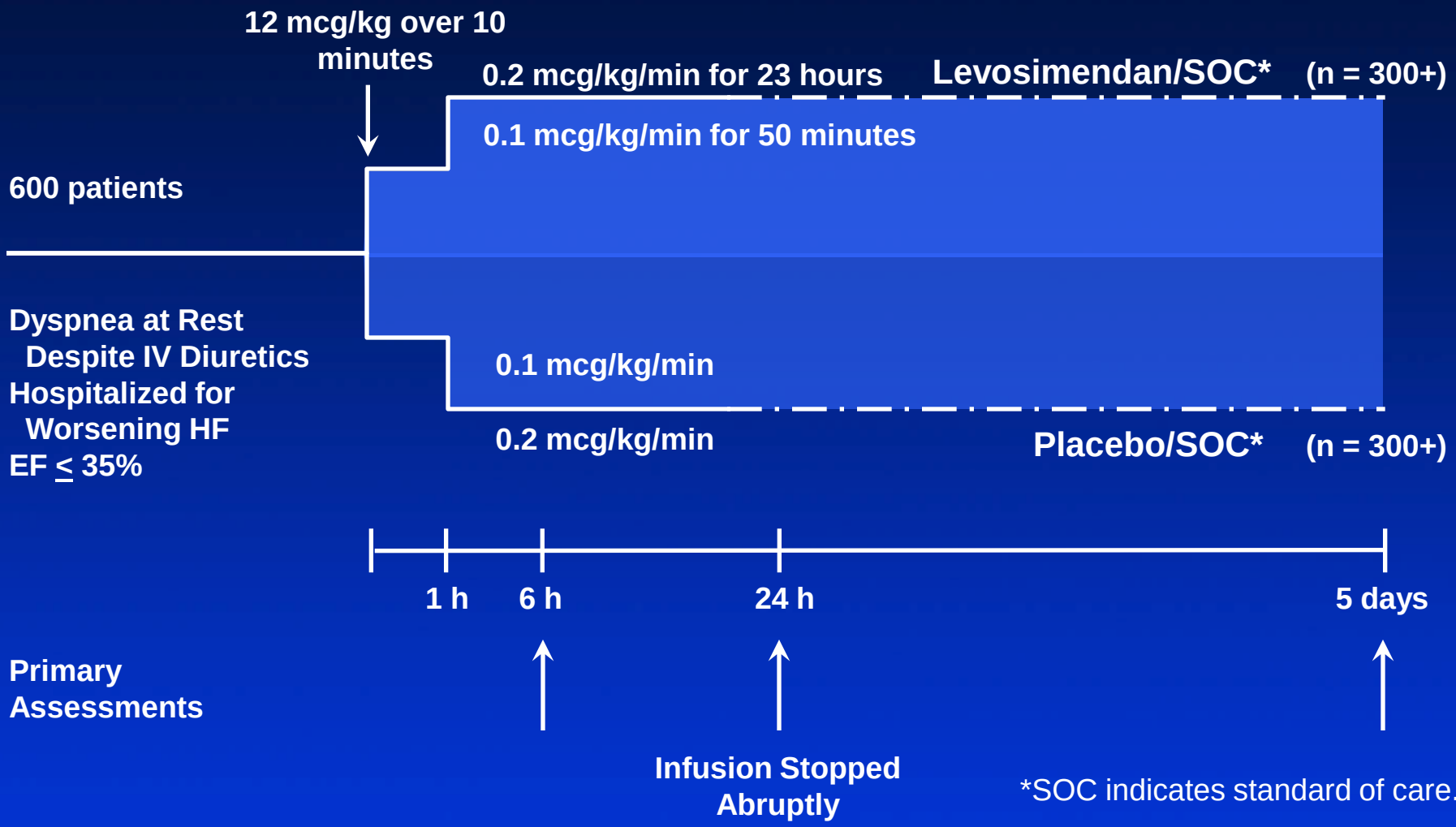
Moiseyev VS, et al. *Eur Heart J*. 2002;23:1422-1432.

RUSSLAN All-Cause Mortality



Moiseyev VS, et al. *Eur Heart J*. 2002;23:1422-1432.

REVIVE II Study Design

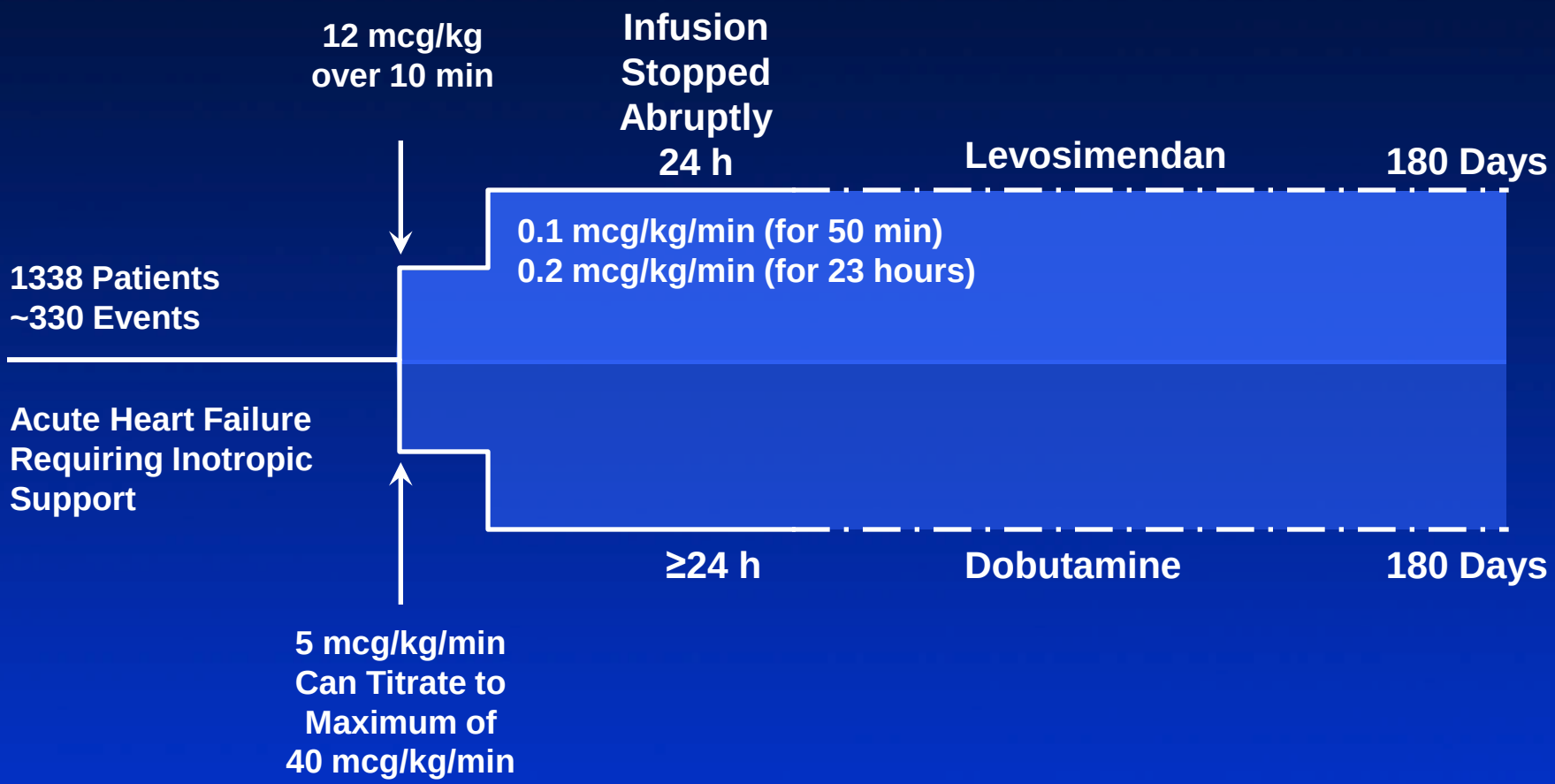


*SOC indicates standard of care.

Effect of Levosimendan on Mortality

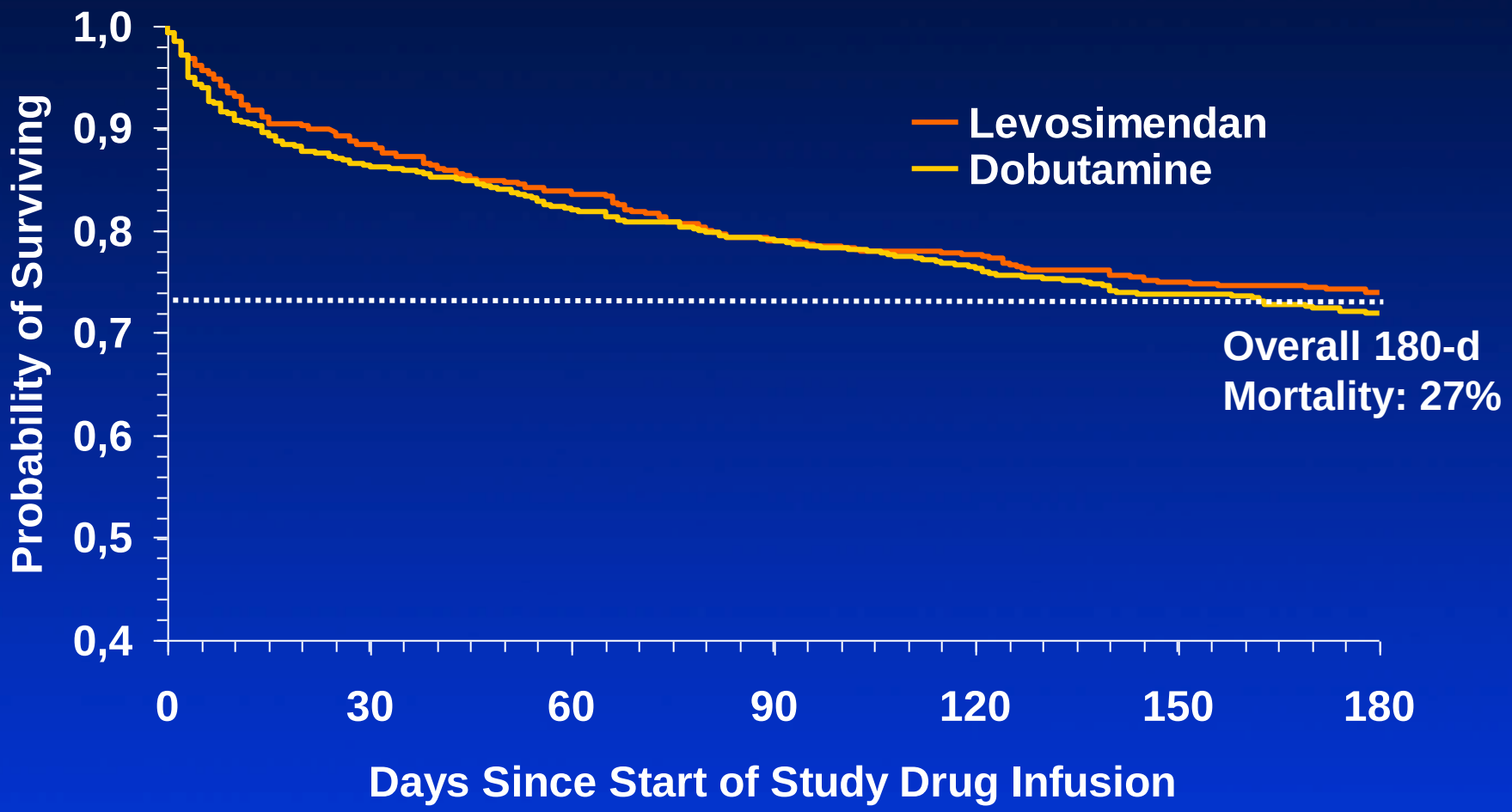
	Days Following Randomization			
	5	**14**	**31**	**90**
REVIVE II				
Placebo	1	5	12	35
Levosimendan	5	14	20	45
REVIVE I				
Placebo	0	1	4	5
Levosimendan	0	1	1	4
REVIVE I + II				
Placebo	1	6	16	40
Levosimendan	5	15	21	49

SURVIVE Study Design



SURVIVE

180-Day All-Cause Mortality



Co je zkoušeno v roce 2016 ???

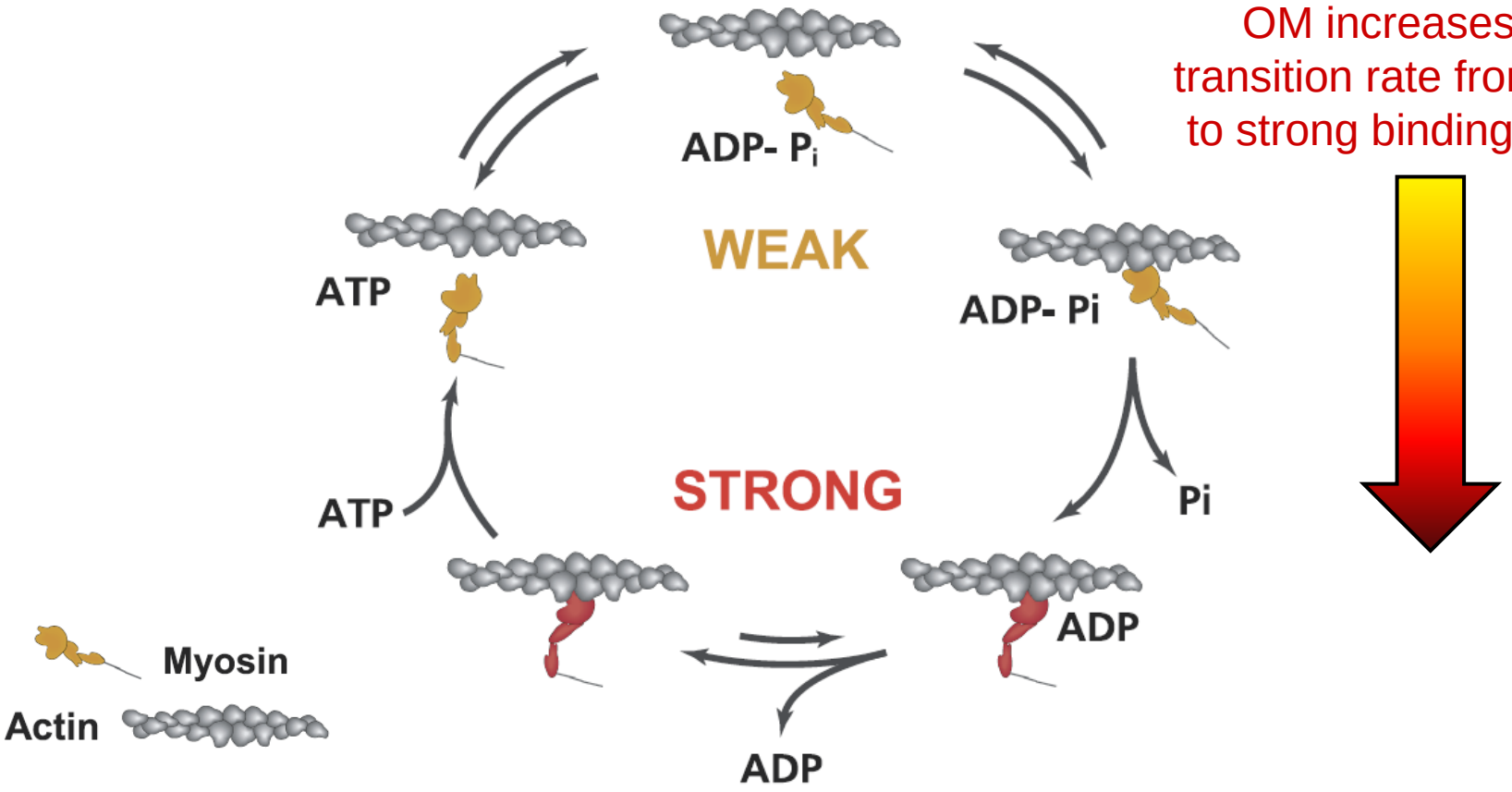
Omecantiv mecarbil

Ularitide

Serelaxin

omecamtiv mecarbil

The actin-myosin cycle



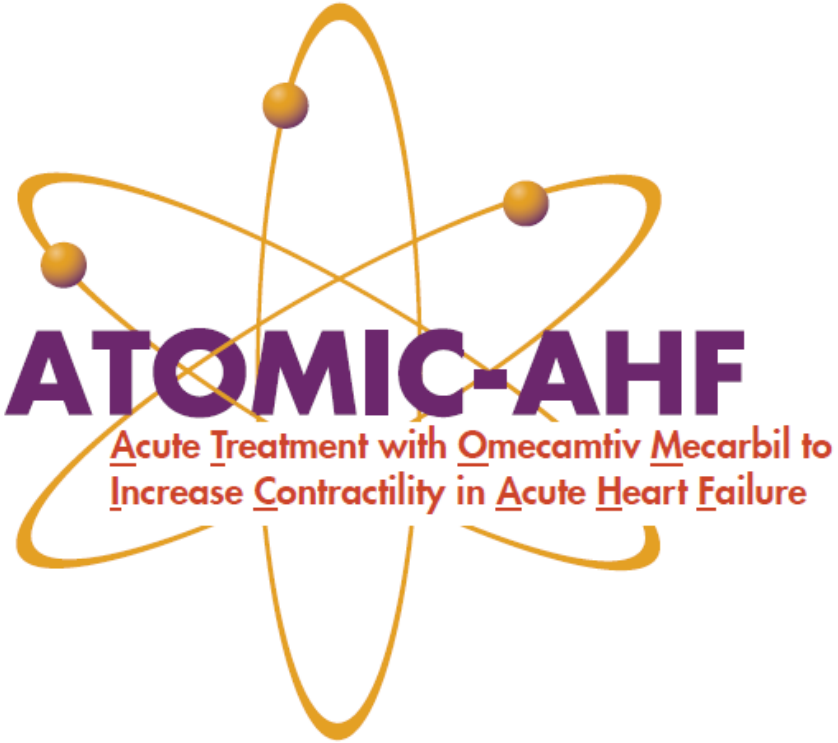
OM increases the transition rate from weak to strong binding states

Omecamtiv mecarbil increases the number of independent force generators (myosin heads) interacting with the actin filament

"More hands pulling on the rope"

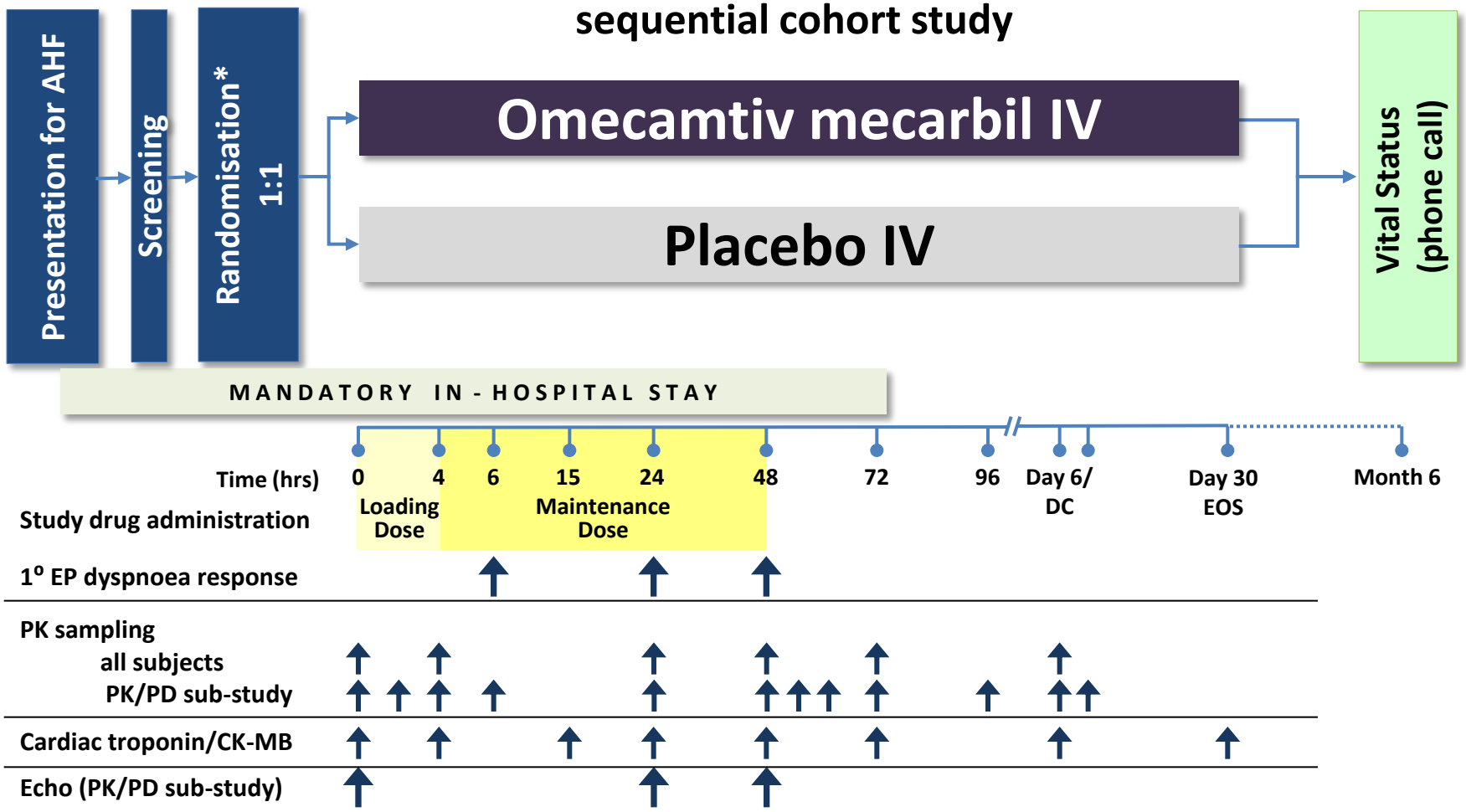
Malik FI, et al. Science 2011

Omecamtiv mecarbil



Study Design

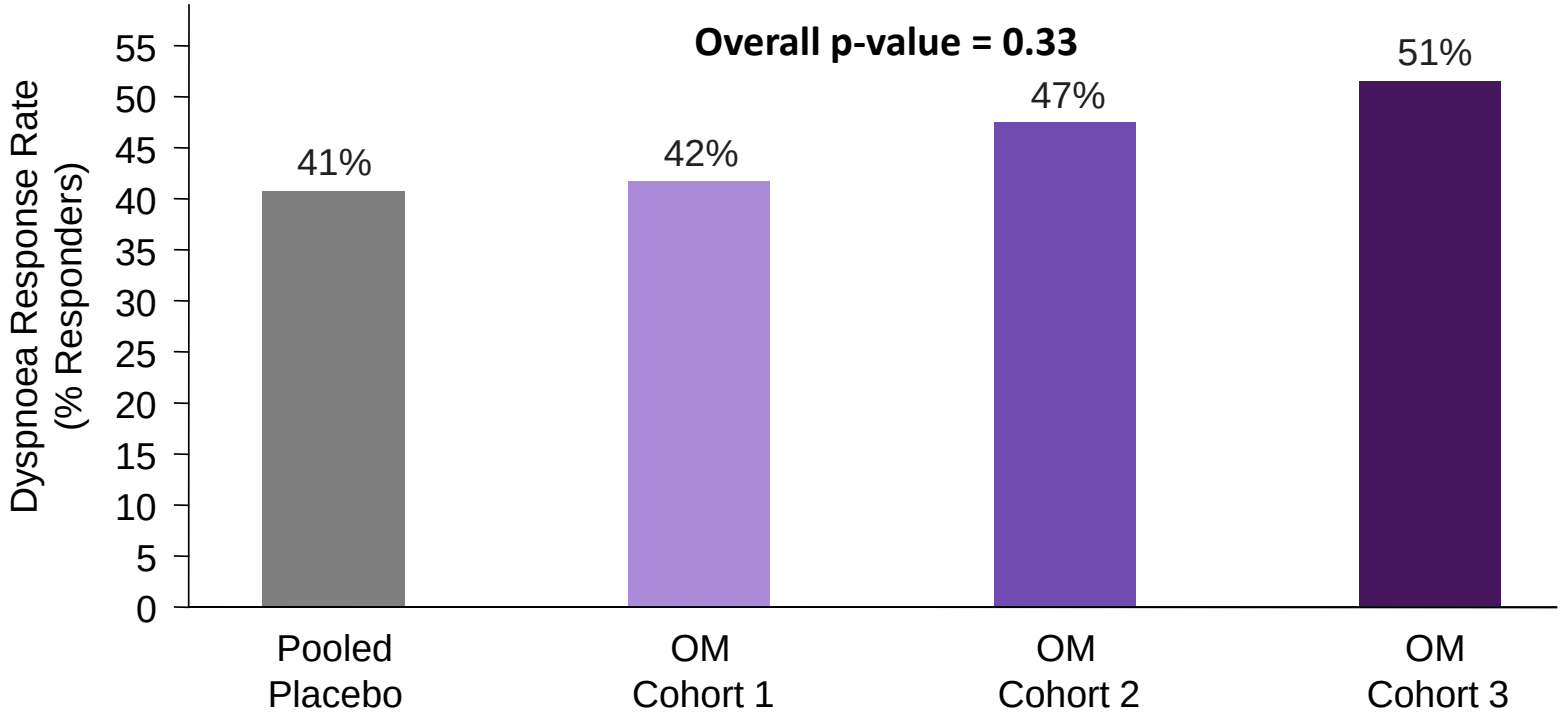
Randomised, double-blind, placebo-controlled, sequential cohort study



* Randomisation within 24 hours of initial IV diuretic (Amendment 2)

Primary Efficacy Endpoint: Dyspnoea Response (Likert Scale)

Pooled Placebo



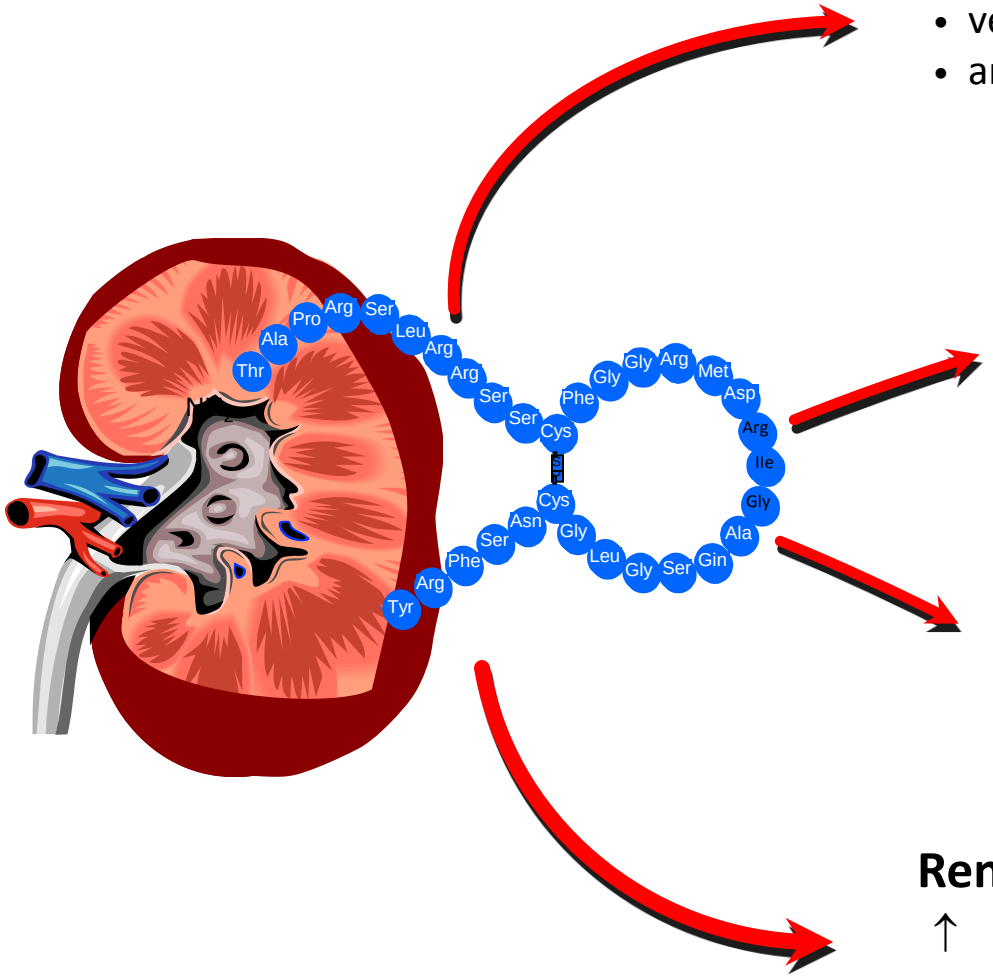
Response Rate Ratio*	**1.03**	**1.15**	**1.23**
95% CI	**(0.79, 1.35)**	**(0.90, 1.47)**	**(0.97, 1.55)**

*Ratio of response rate to Pooled Placebo
p-value of a CMH test among all 3 Placebo arms = 0.32

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

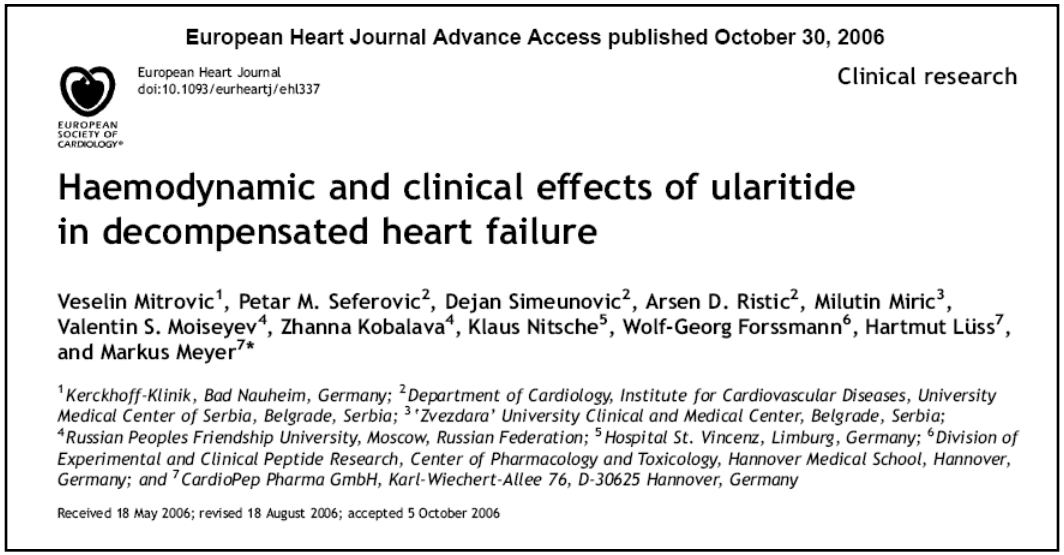
Renální

↑ 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*

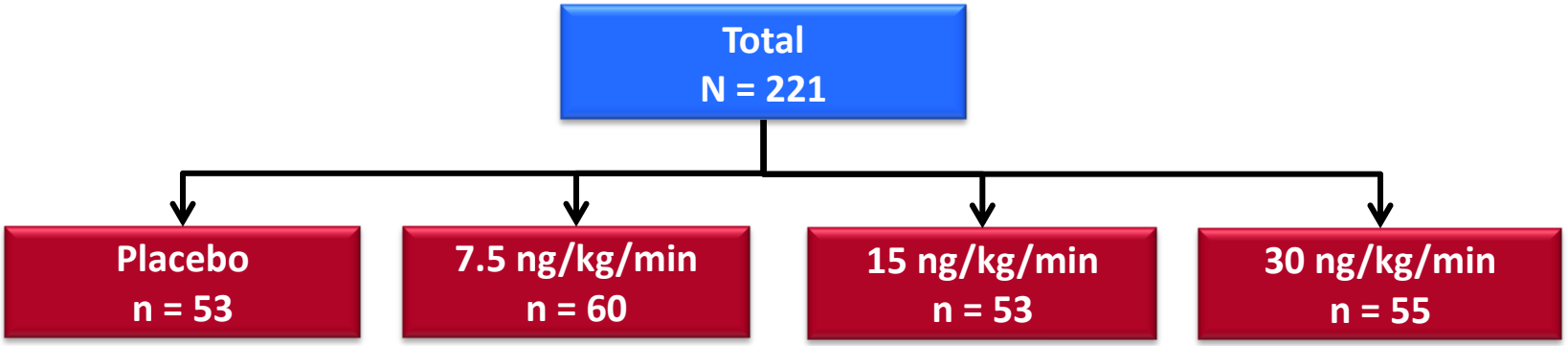
Received 18 May 2006; revised 18 August 2006; accepted 5 October 2006

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

SIRIUS II – Study design

CARDIORENTIS

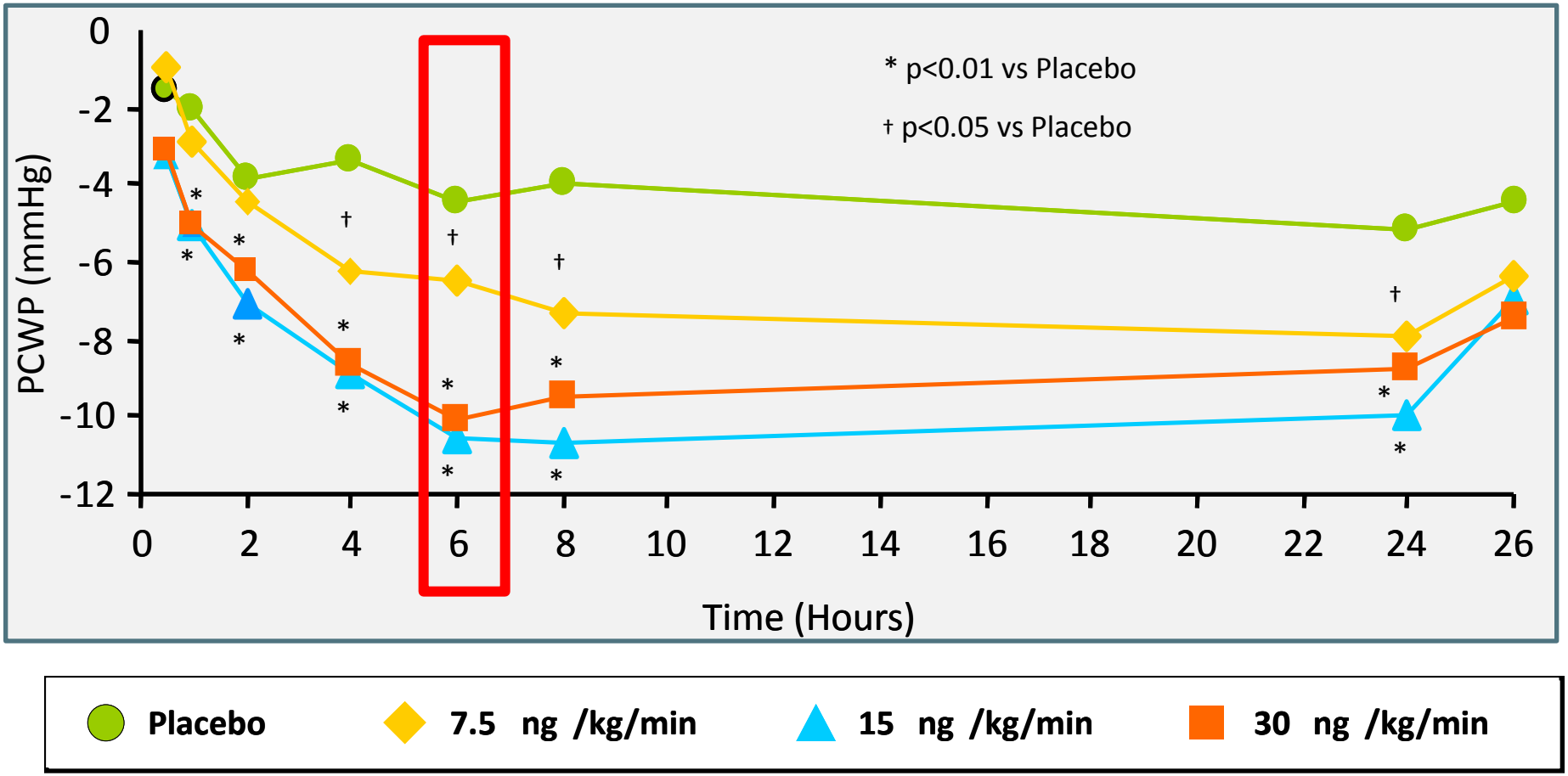
- Randomised, placebo controlled, double-blind, study with 3 active dosing and 1 placebo group
- Infusion of Ularitide 7.5, 15, and 30 ng/kg body weight/min, or placebo over 24 hours
- Patients with decompensated heart failure requiring hospitalisation as well as right heart catheterisation were included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

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

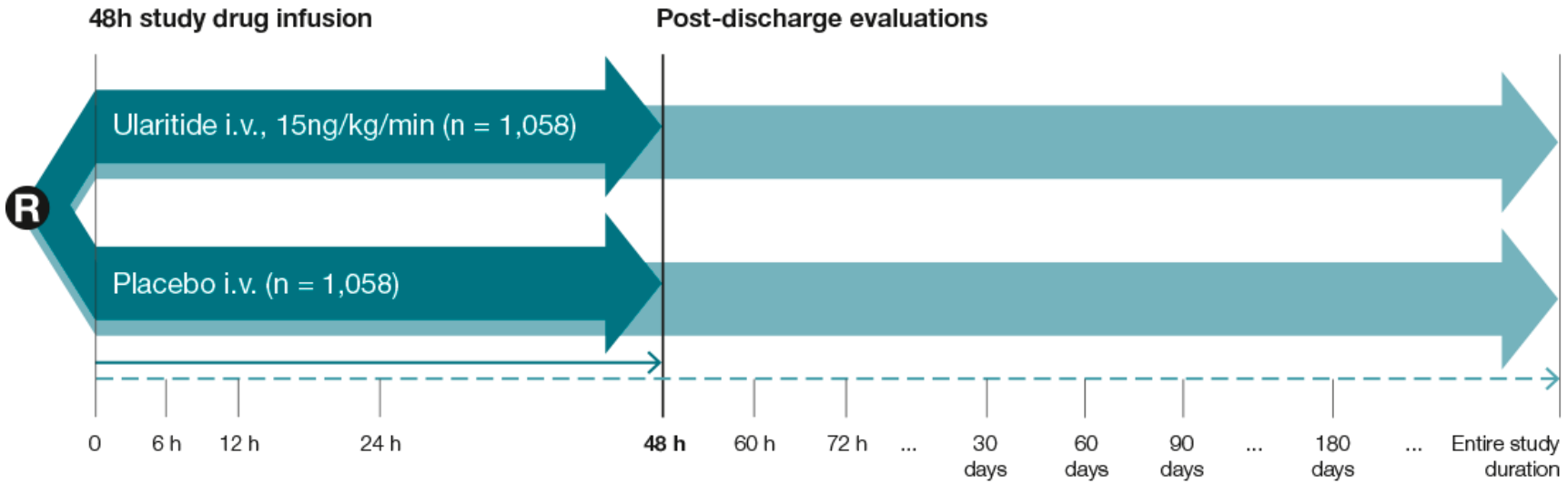
Stefan D. Anker[1]*, Piotr Ponikowski[2], Veselin Mitrovic[3], W. Frank Peacock[4], and Gerasimos Filippatos[5]

[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

BNP 1464 pg/ml
NT-proBNP 6905 pg/ml

4,7x

Age 68,4 let
eGFR 63,7 ml/min/1,73

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

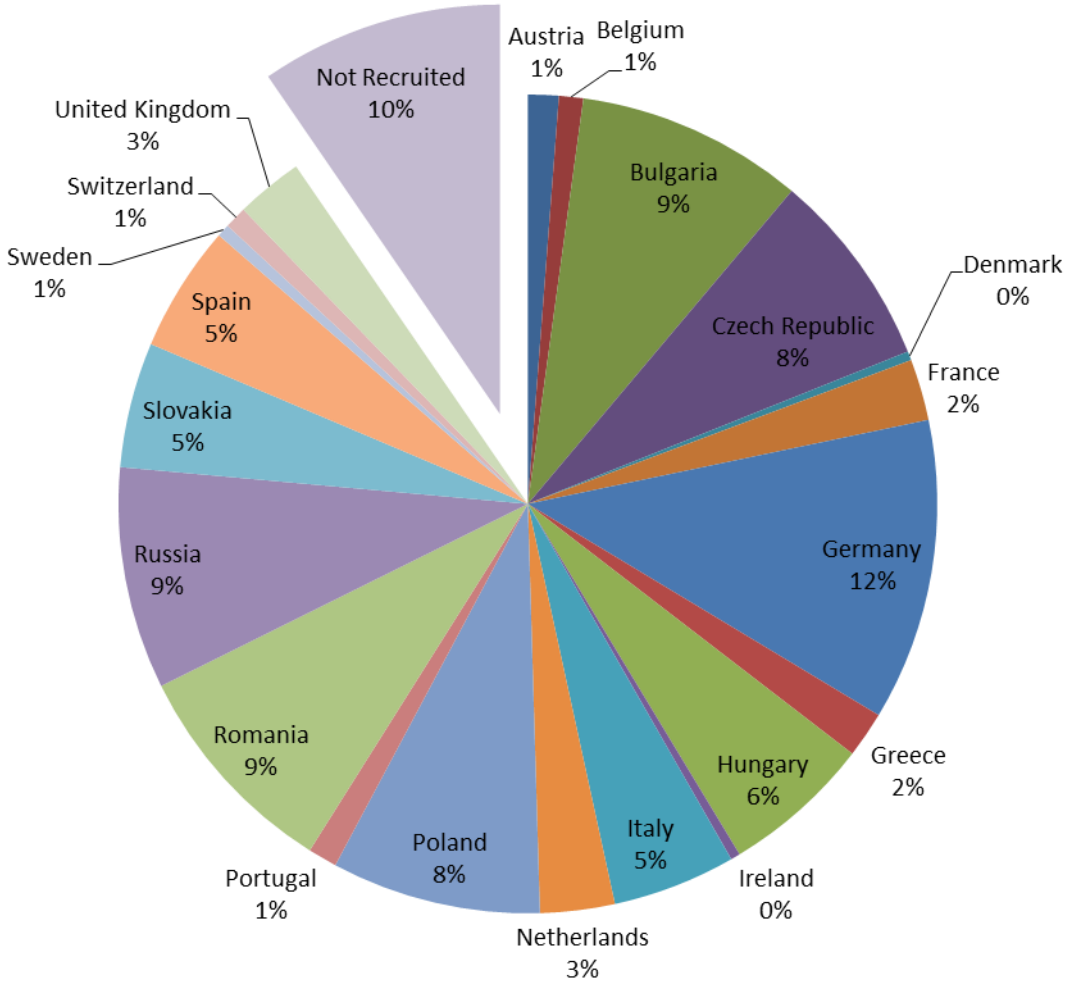
Baylis, C. *Am J Kid Dis* 1999; Schrier, RW, et al. *Am J Kid Dis* 1987; Jeyebalan, A, et al. *Adv Exp Med Biol* 2007; Teichman SL et al. *Curr Heart Fail Rep* 2010;7:75–82.
Helal I, et al. *Nature Reviews* 2012;293-300.

RELAX-AHF-2 Study -Update

Check Republic March 2016

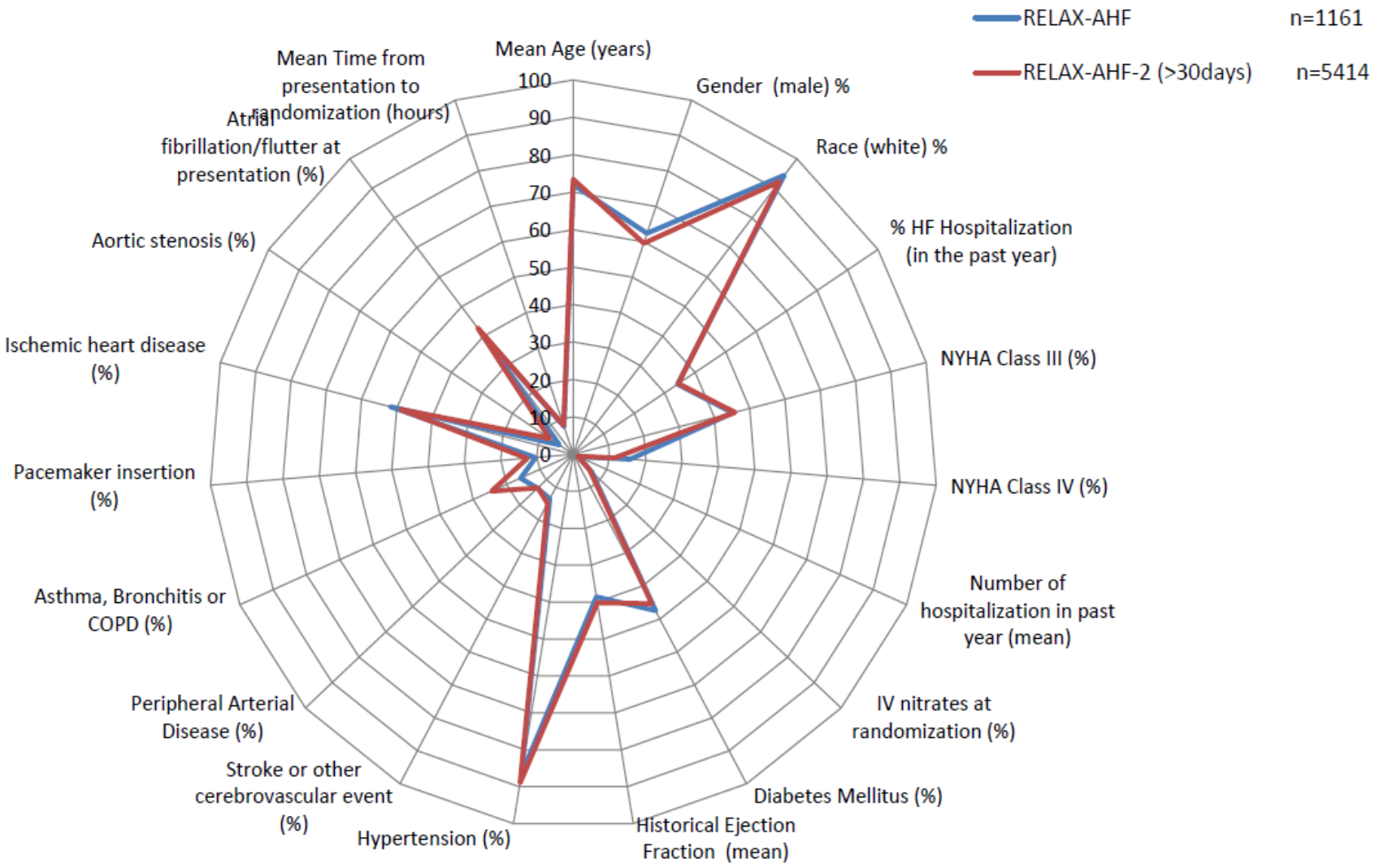
RLX030A2301 Region Europe Recruitment

April 6, 2016



Globally < 1,000 patients to complete the trial

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

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

Děkuji za pozornost