UPDATE: NEW TRIALS OF PHARMACOLOGICAL THERAPY IN HEART FAILURE

Hans-Dirk Düngen

3rd Cardiology Highlights
Dubrovnic, Croatia 2013

Conflict of Interest - Disclosure

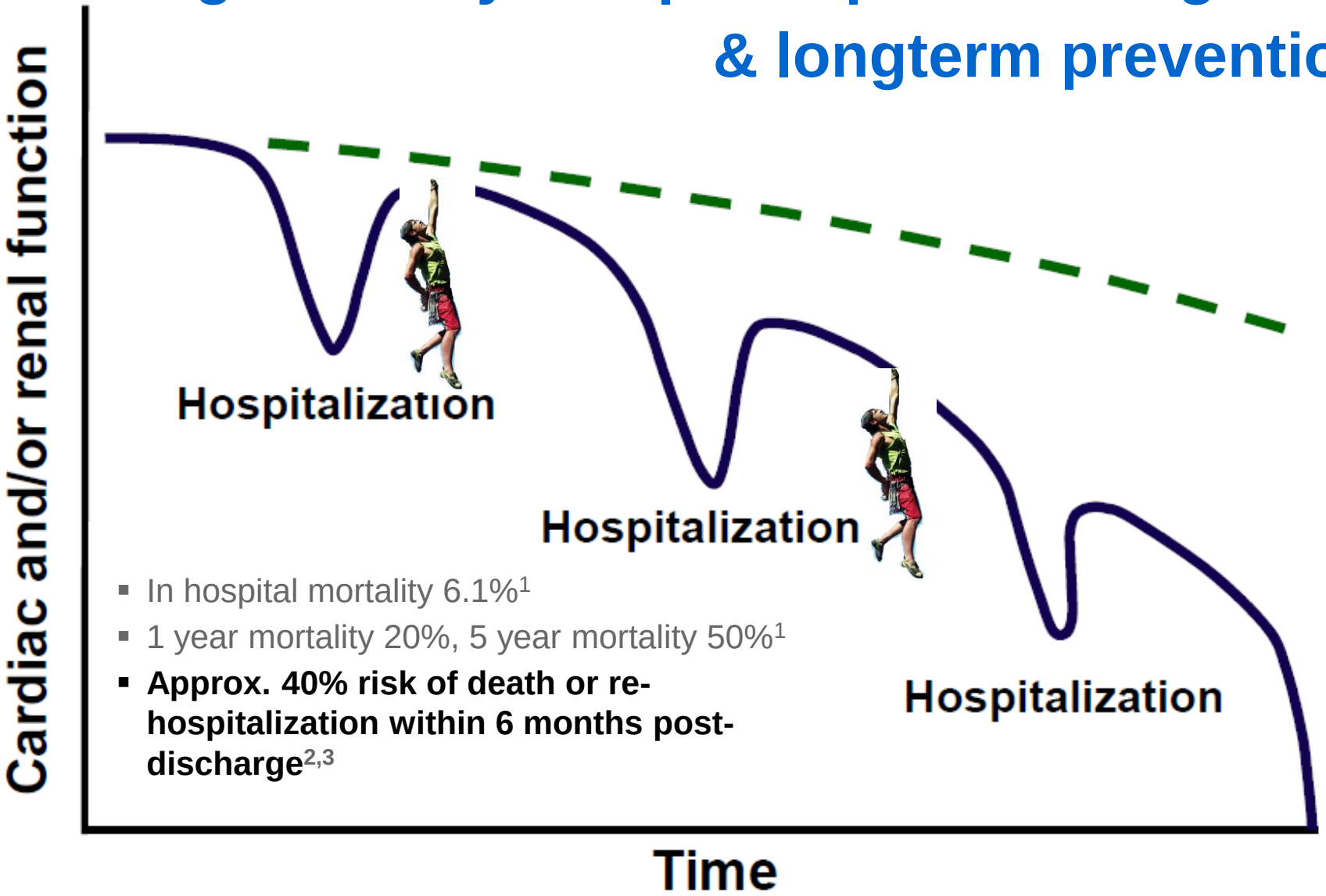
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed

Affiliation/Financial Relationship	Company
1. Honoraria for lectures	Servier, Novartis, Berlin Chemie
2. Honoraria for advisory board activities	Novartis, Servier
3. Participation in clinical trials Roche,	Novartis, Schering Plough, Astra Zeneca, Brahms, Novartis, Getemed, Fresenius, Celladon, Amgen
4. Research funding	Brahms, Novartis, Getemed, Fresenius
5. Financial shares and options	None

Overview

- Update and highlights &
- Chronic heart failure &
- Acute decompensated heart failure
  - SHIFT: Ivabradine
  - EMPHASIS: Eplerenone
  - DIG: Digoxin
  - ASTRONAUT/ATMOSPHERE: Aliskiren
  - RED HF: Darbepoetin alfa
  - RELEX: Serelaxin
  - COSMIC: Omecamtiv Mecarpil
  - CUPID: Mydicar

Cliffhangers: early and preemptive strategies & longterm prevention



- In hospital mortality 6.1%[1]
- 1 year mortality 20%, 5 year mortality 50%[1]
- **Approx. 40% risk of death or re-hospitalization within 6 months post-discharge[2,3]**

modified from Gheorghiade M et al. Am J Cardiol. 2005; 96:11G-17G

SHIFT : heart rate as risk factor in chronic heart failure

I_f current inhibitor ivabradin vs. placebo in chronic HF

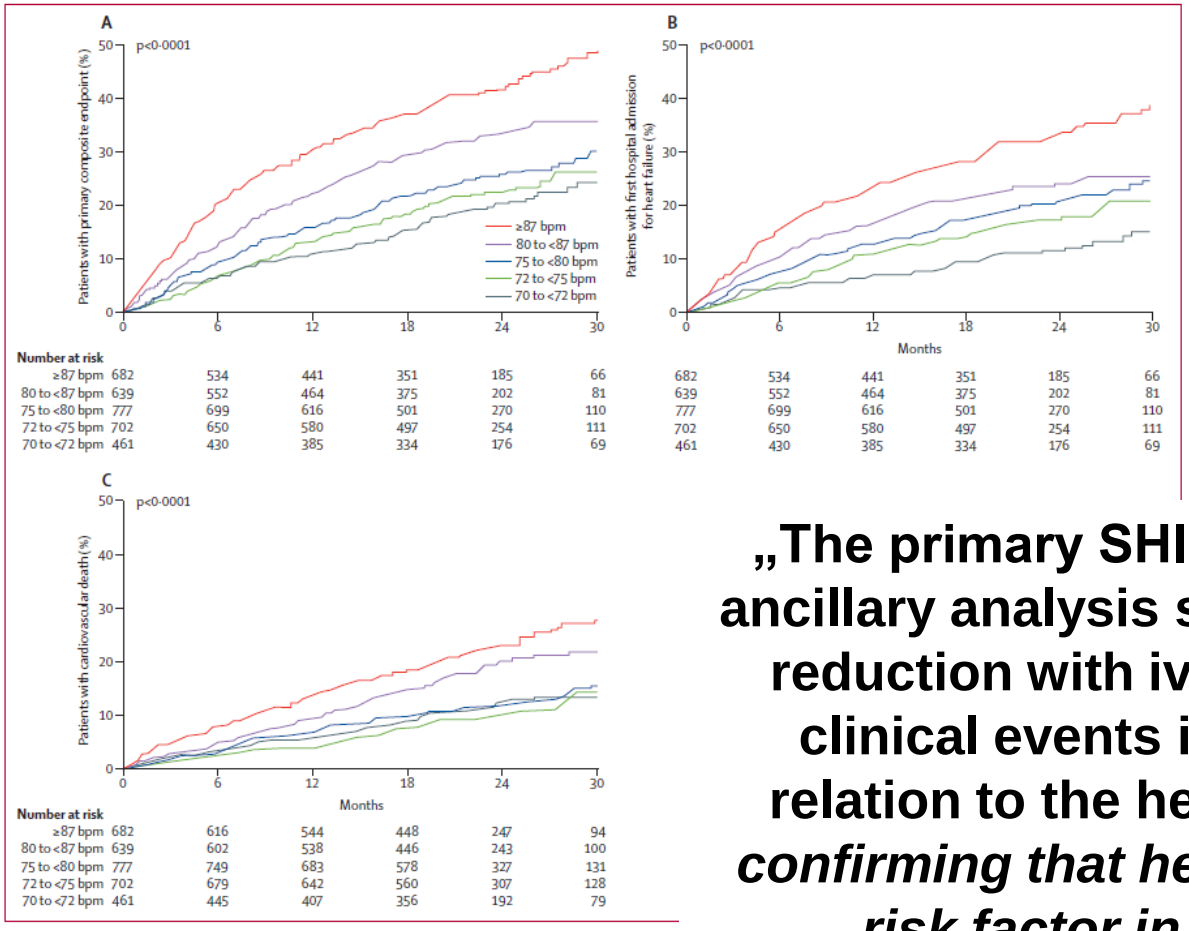
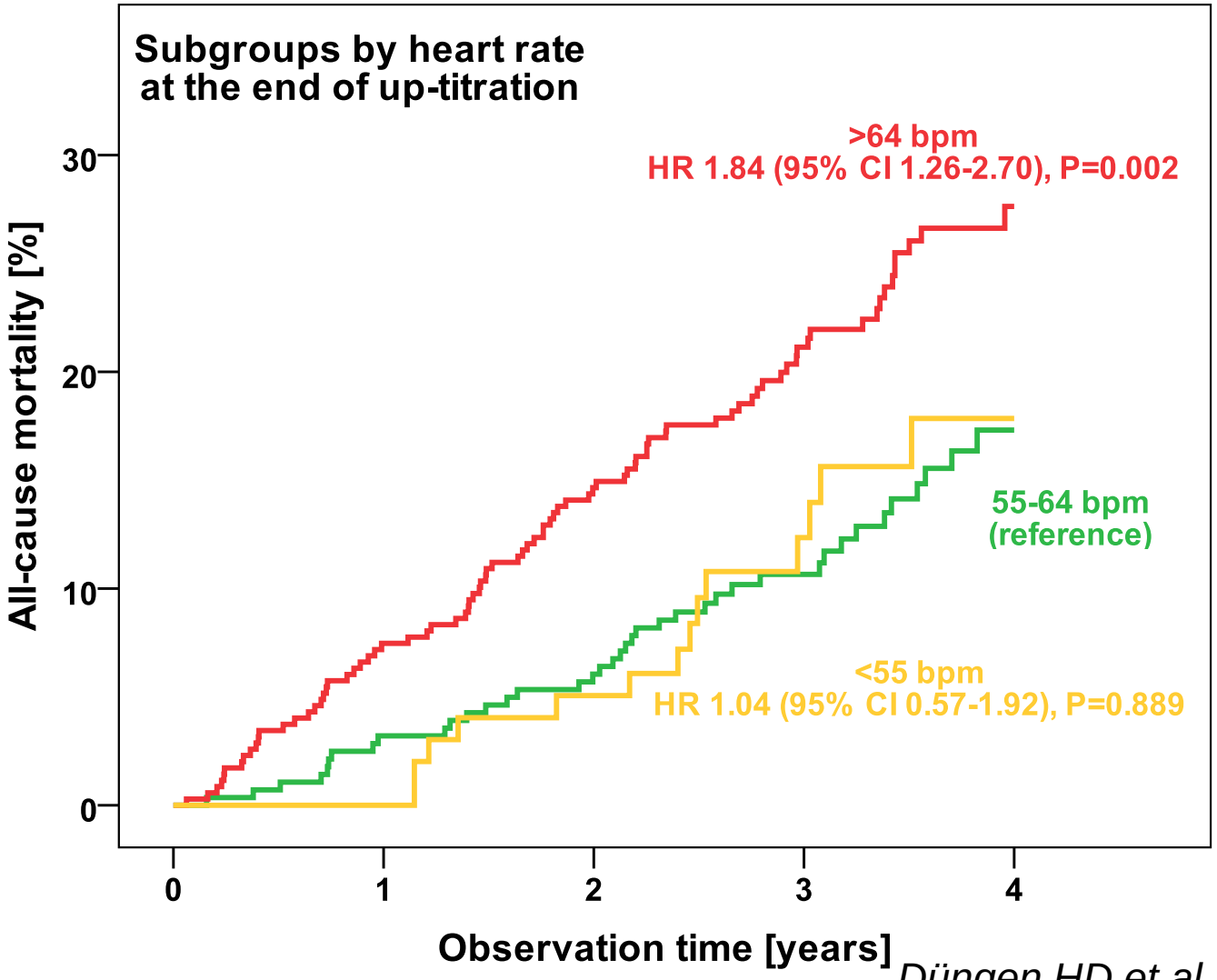


Figure 1: Kaplan-Meier cumulative event curves for (A) the primary composite endpoint, (B) first hospital adr
group,* according to groups defined by quintiles of heart rate at baseline
Primary composite endpoint includes cardiovascular deaths and hospital admissions for worsening heart failure. Th
*n=3264.

„The primary SHIFT results and our ancillary analysis show that heart-rate reduction with ivabradine reduces clinical events in heart failure in relation to the heart rate achieved, *confirming that heart rate is clearly a risk factor in heart failure*.“

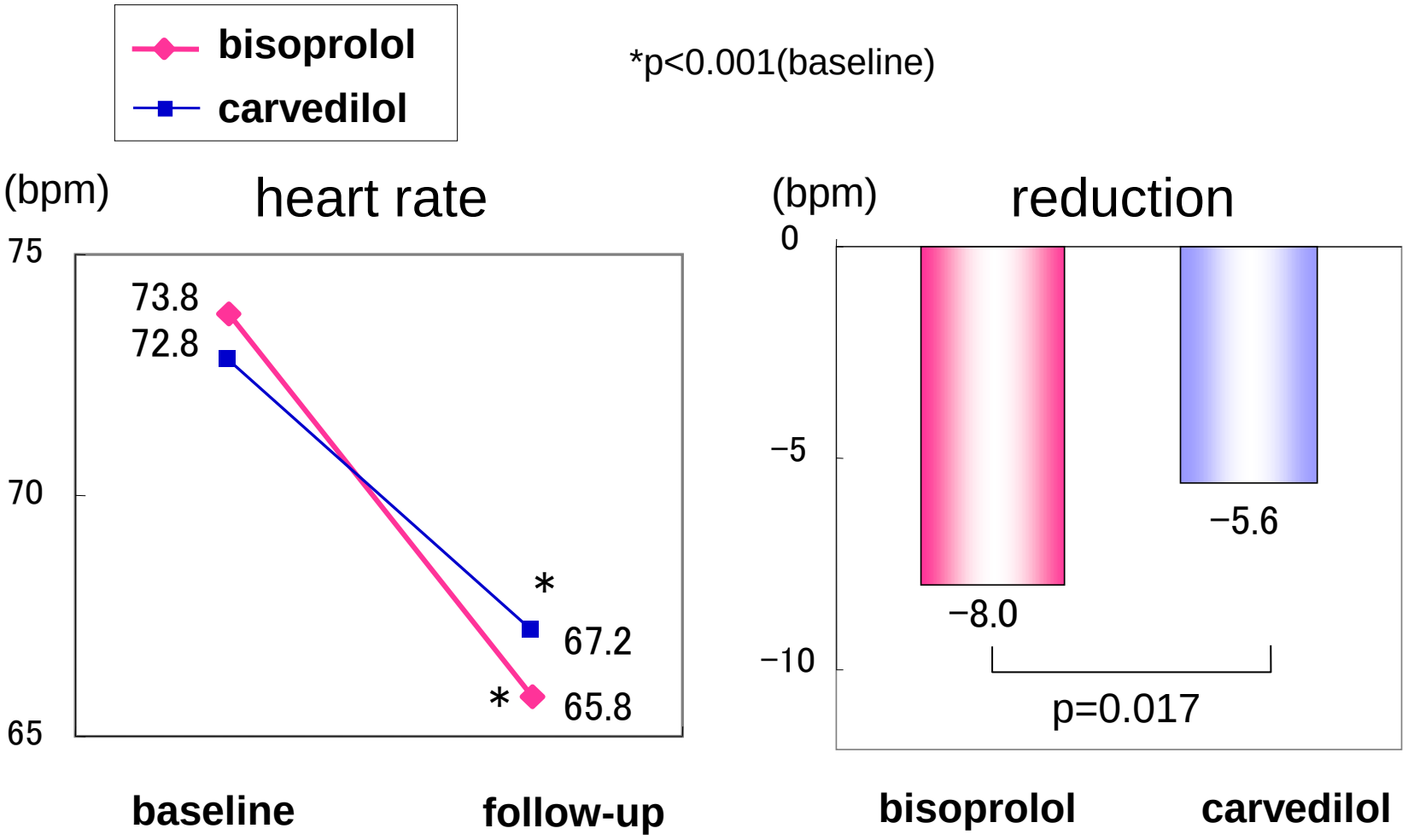
- Böhm et al. Lancet 2010

Heart rate lowering with... beta blockers!



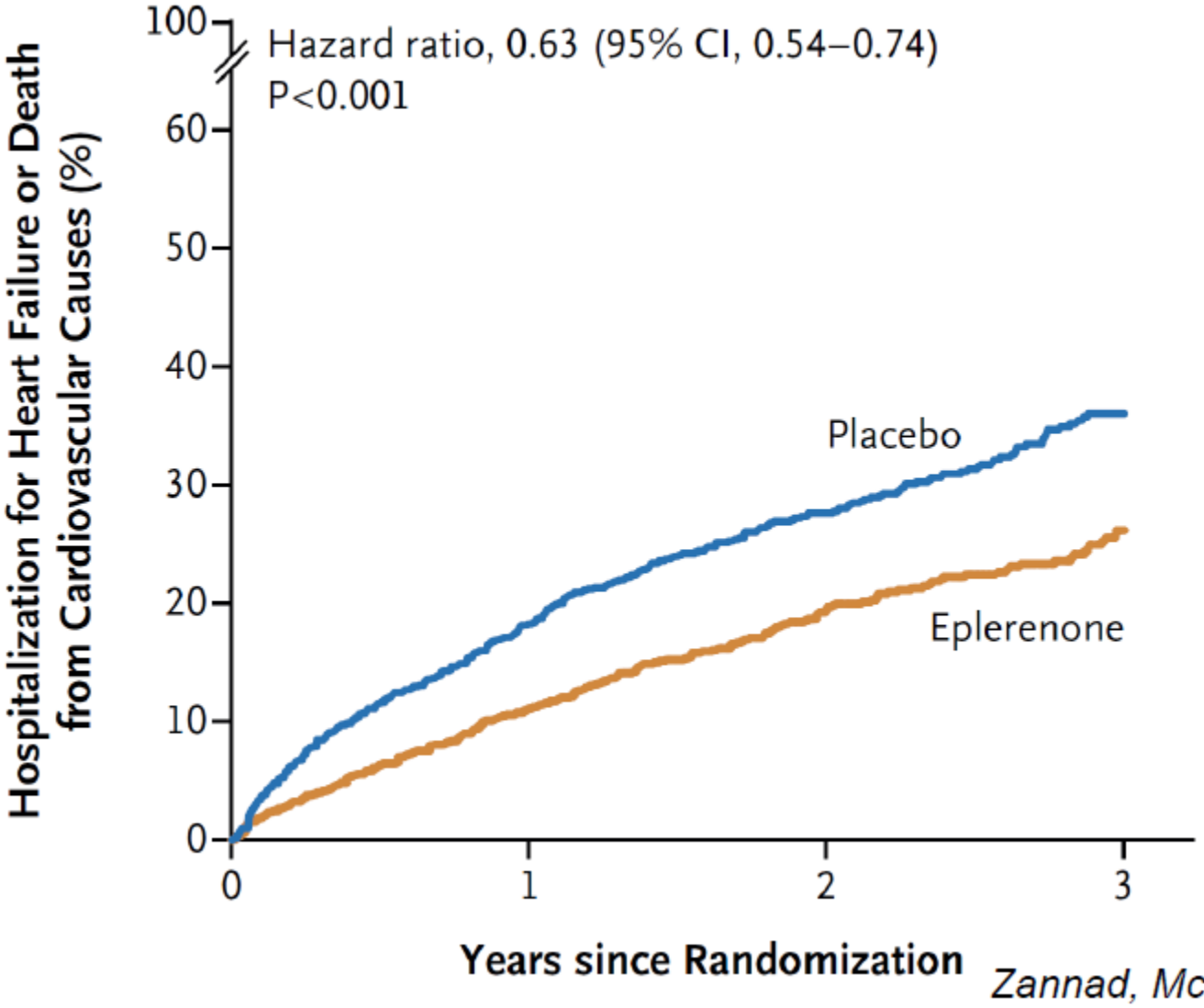
Düngen HD et al ESC HFA 2013

Bisoprolol vs. carvedilol



Düngen et al. 2011 EJHF

EMPHASIS



Eplerenon vs. placebo in mild HF
n=2737
≥ 55 years

NYHA II hospitalised within past 6 months or elevated BNP

LVEF ≤30% or ≤35% + QRS<130ms

21 month median follow-up

Zannad, McMurray et al NEJM 2011

DIG Subanalysis

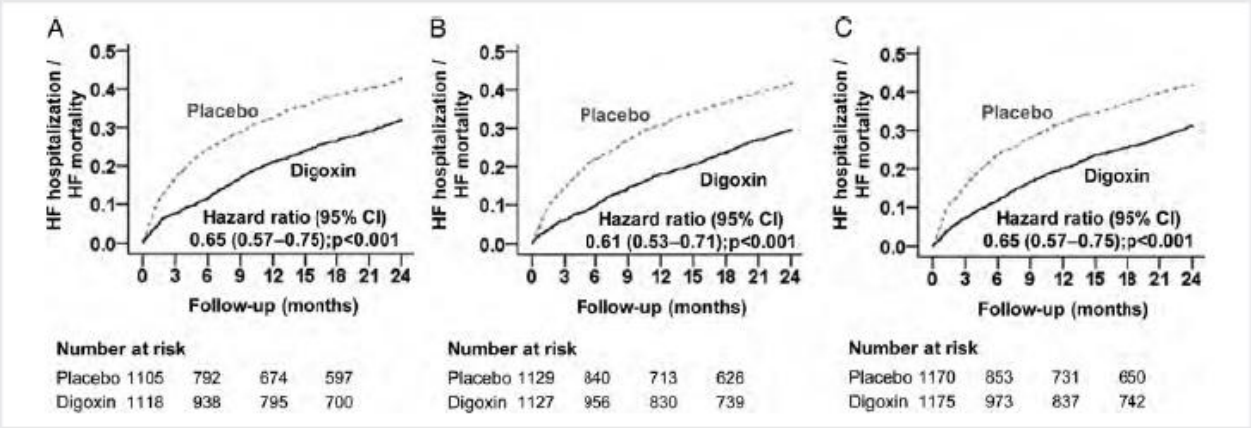


Figure 1 Kaplan–Meier plots for heart failure (HF) mortality or HF hospitalization by treatment groups in high-risk patients with chronic HF in the DIG trial: (*A*) NYHA class III–IV, (*B*) LVEF <25%, and (*C*) cardiothoracic ratio >55%. CI, confidence interval.

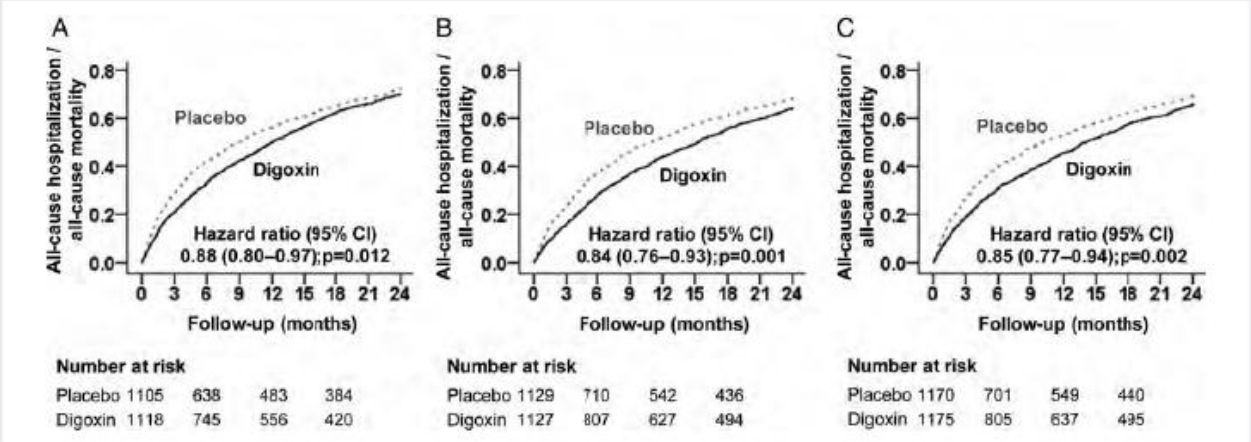


Figure 2 Kaplan–Meier plots for all-cause mortality or all-cause hospitalization by treatment groups in high-risk patients with chronic heart failure (HF) in the DIG trial: (*A*) NYHA class III–IV, (*B*) LVEF <25%, and (*C*) cardiothoracic ratio >55%. CI, confidence interval.

Reduction in 2-year composite endpoint (HF-mortality or HF-hospitalisation)

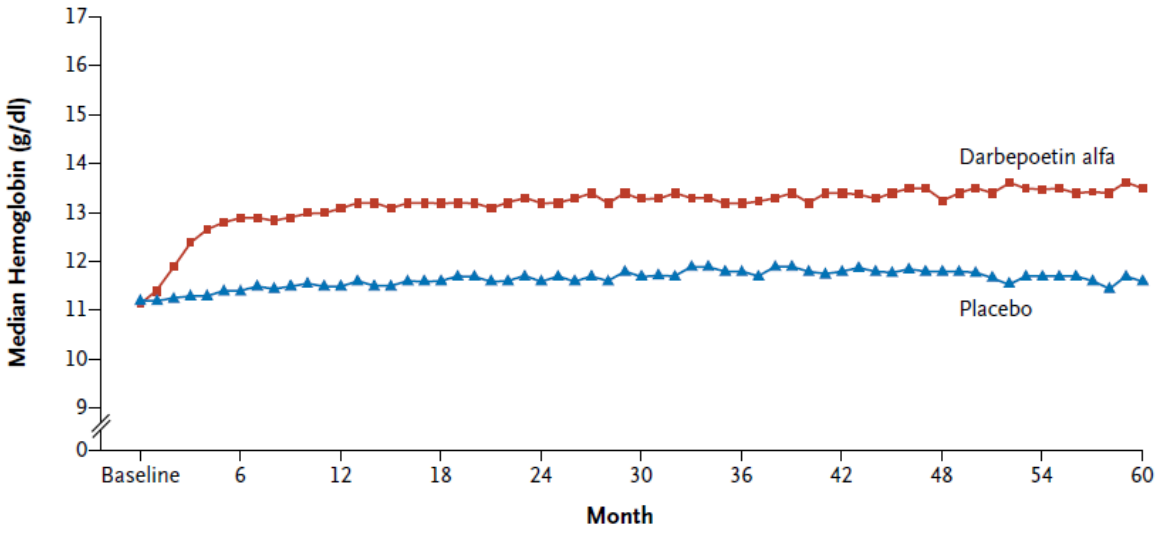
n=6800, placebo-controlled double-blind digoxin vs. placebo

Digoxin improves outcomes in high risk chronic HF patients with:
NYHA class III–IV,
or
LVEF <25%
or
cardiothoracic ratio >55%

Gheorghiade M et al EJHF 2013

RED-HF 1

- randomized, double-blind trial of darbepoetin alfa vs. placebo in chronic systolic heart failure patients with mild-to-moderate anemia (9.0-12.0 g/dl)



No. at Risk

Placebo	1140	966	803	676	560	459	377	265	182	140	99
Darbepoetin alfa	1133	959	827	673	569	465	372	289	208	158	115

Figure 1. Monthly Hemoglobin Levels through 60 Months According to Study Group.

n=2278
LVEF ≤ 40%
Hemaglobin 9.0-12.0 g/dl

Patients receiving darbepoetin had higher hemaglobin

but…

Swedberg et al. NEJM 2013

RED-HF 2

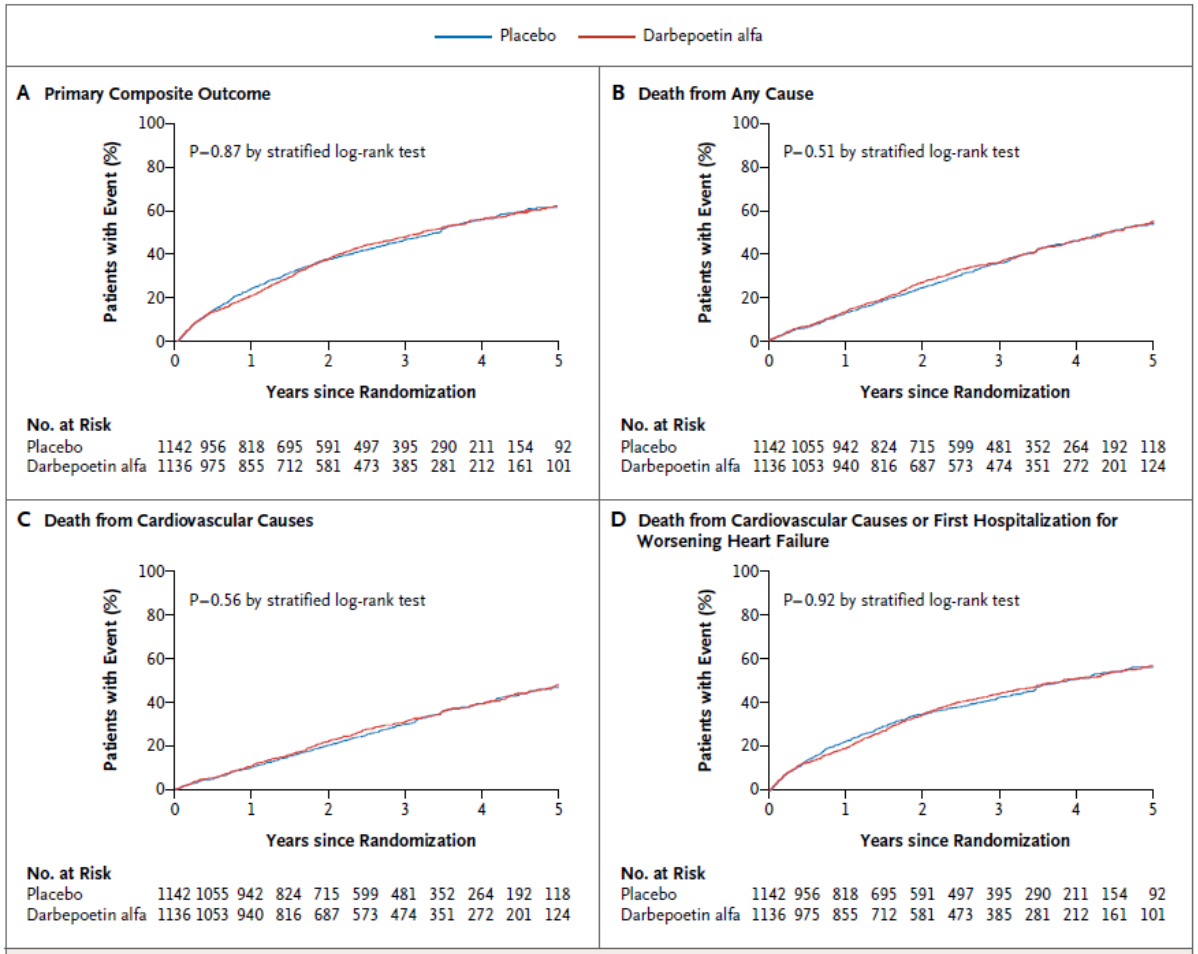


Figure 2. Kaplan–Meier Estimates of the Probability of the Primary and Secondary Outcomes.

Shown are the primary composite outcome of death from any cause or first hospitalization for worsening heart failure (Panel A) and secondary outcomes of death from any cause (Panel B), death from cardiovascular causes (Panel C), and death from cardiovascular causes or first hospitalization for heart failure (Panel D). P values have not been adjusted for multiple comparisons.

No improvement in primary composite outcome (all-cause death/HF-hospitalisation)

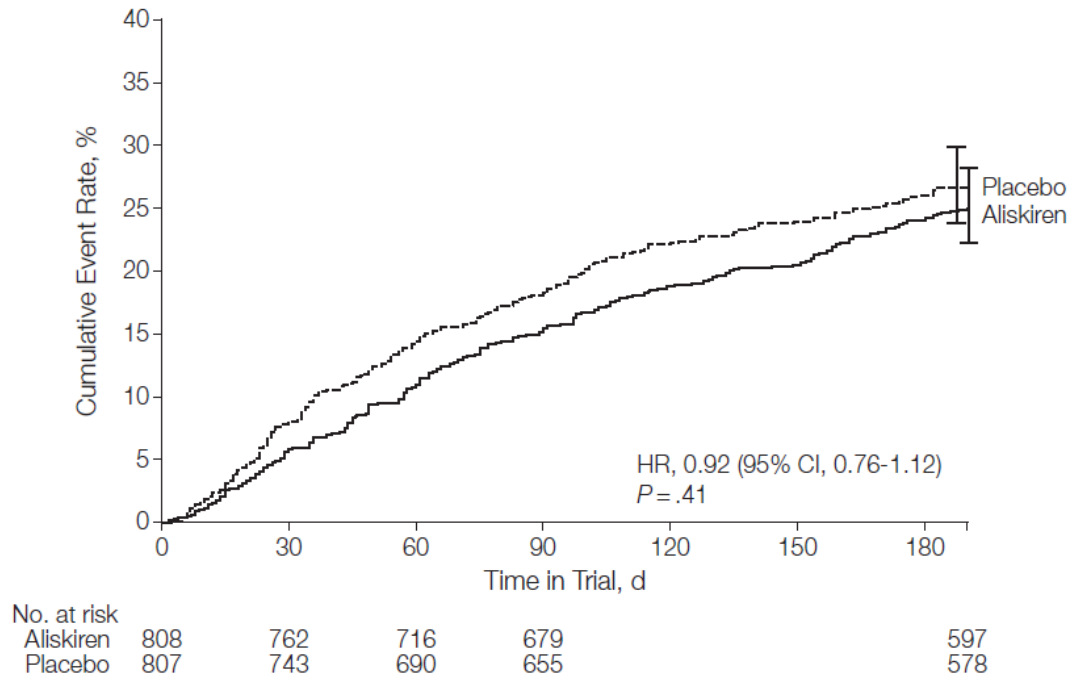
More thromboembolic adverse events in darbepoitin group (13.5% vs 10.0%, p=0.01)

No difference in non-fatal and fatal stroke rate

ASTRONAUT

- double-blind, aliskiren vs. placebo in hemodynamically stable inpatients

Figure 2. Kaplan-Meier Analyses of the Cumulative Event Rate for Cardiovascular Death or Heart Failure Hospitalization at 6 Months



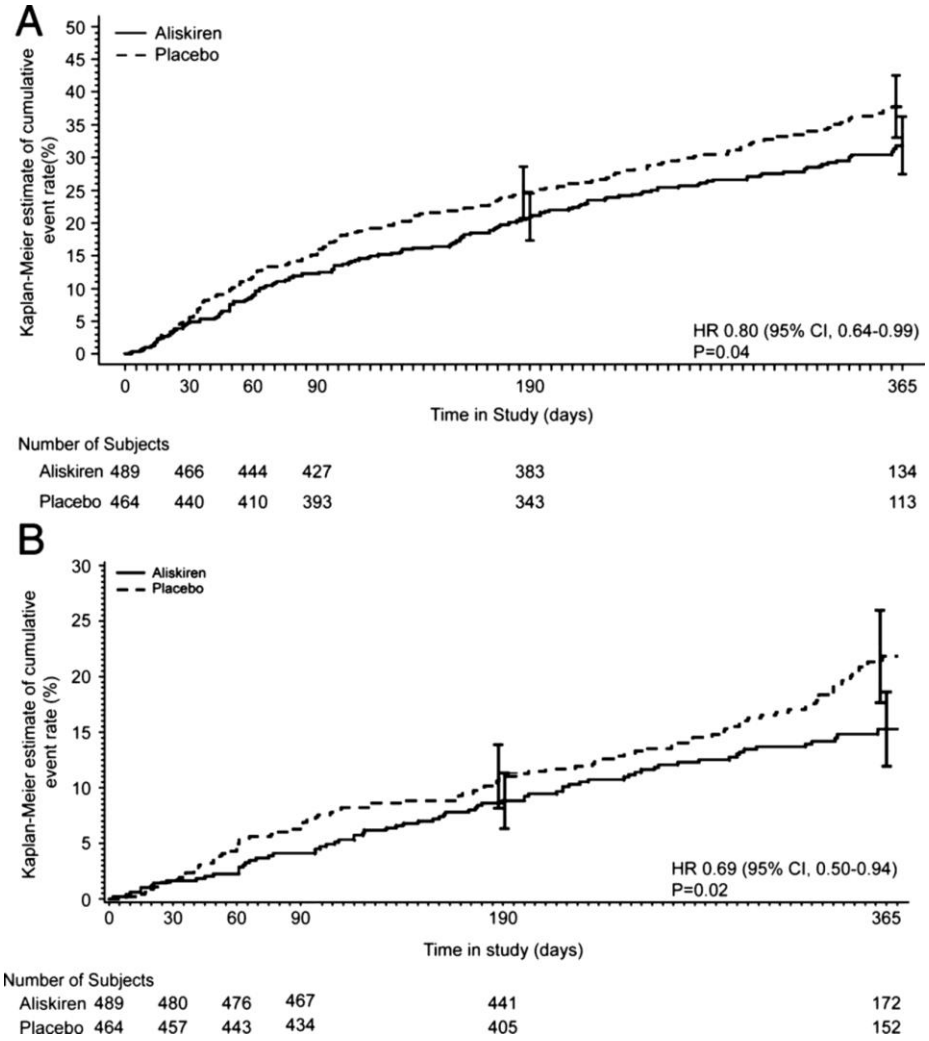
For the analysis of events within 6 months, a Cox-regression model was used. Error bars indicate 95% CIs for the Kaplan-Meier estimate at day 190.

- n=1639
- LVEF ≤ 40%
- BNP≥ 400pg/ml or NT-proBNP ≥ 1600pg/ml
- signs and symptoms of fluid overload

No improvement in primary endpoint CV death or HF-rehospitalization at 6 months or 12 months post discharge

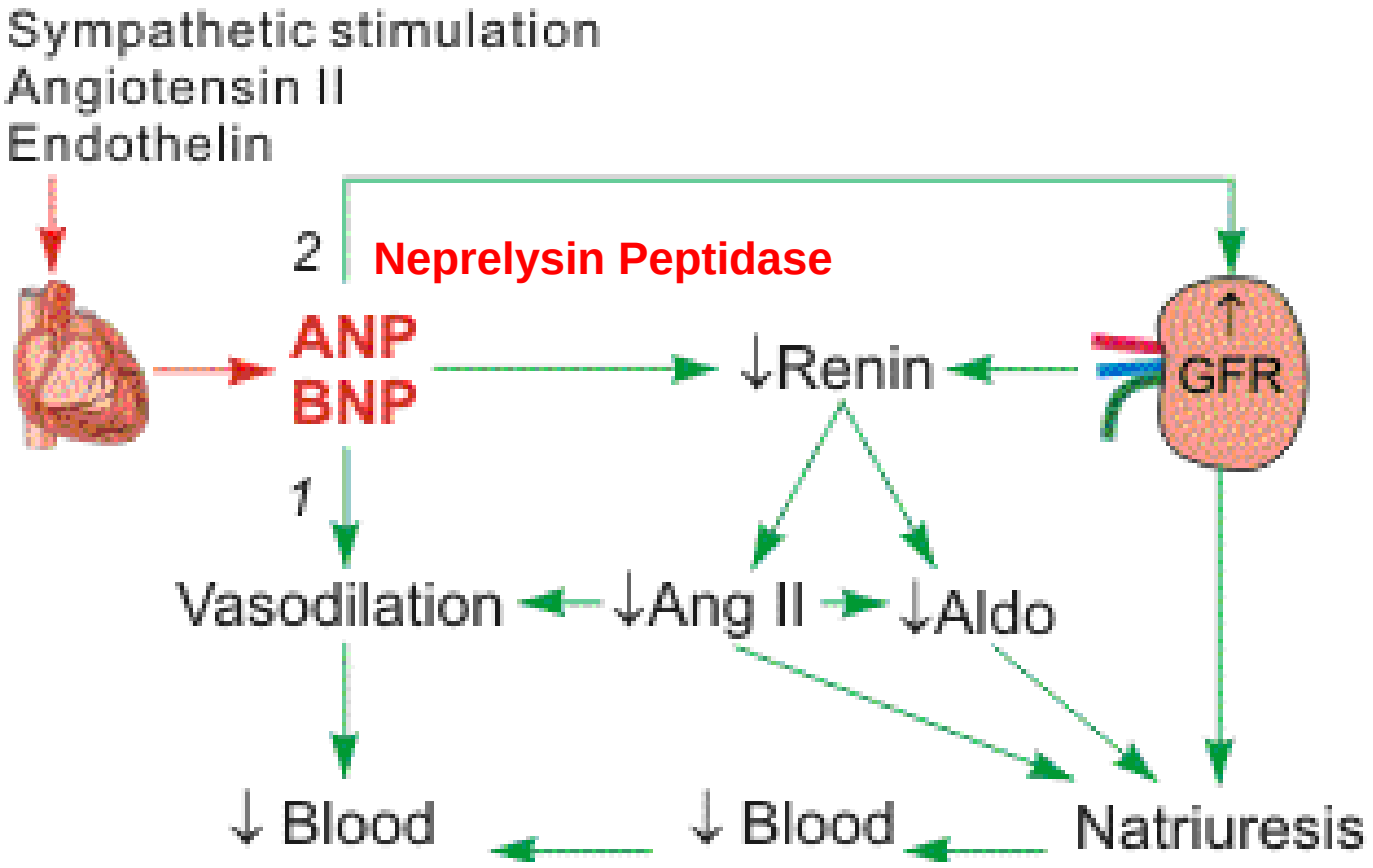
Gheorghiade M et al JAMA 2013

Kaplan–Meier analysis of the cumulative event rate of cardiovascular death or heart failure hospitalization (A) and all-cause death (B) within 12 months in patients without baseline diabetes mellitus.



Maggioni A P et al. Eur Heart J 2013

Natriuretic peptides



PARADIGM

ARNi

Angiotensin **R**eceptor

Neprelysin **i**nhibitor

LCZ696: complex of

ARB (Valsartan) and NEP inhibitor

Primary objective: time to first occurence of CV mortality or HF hospitalisation in HFREF

Secondary objective: allcause mortality, eGFR change, QoL

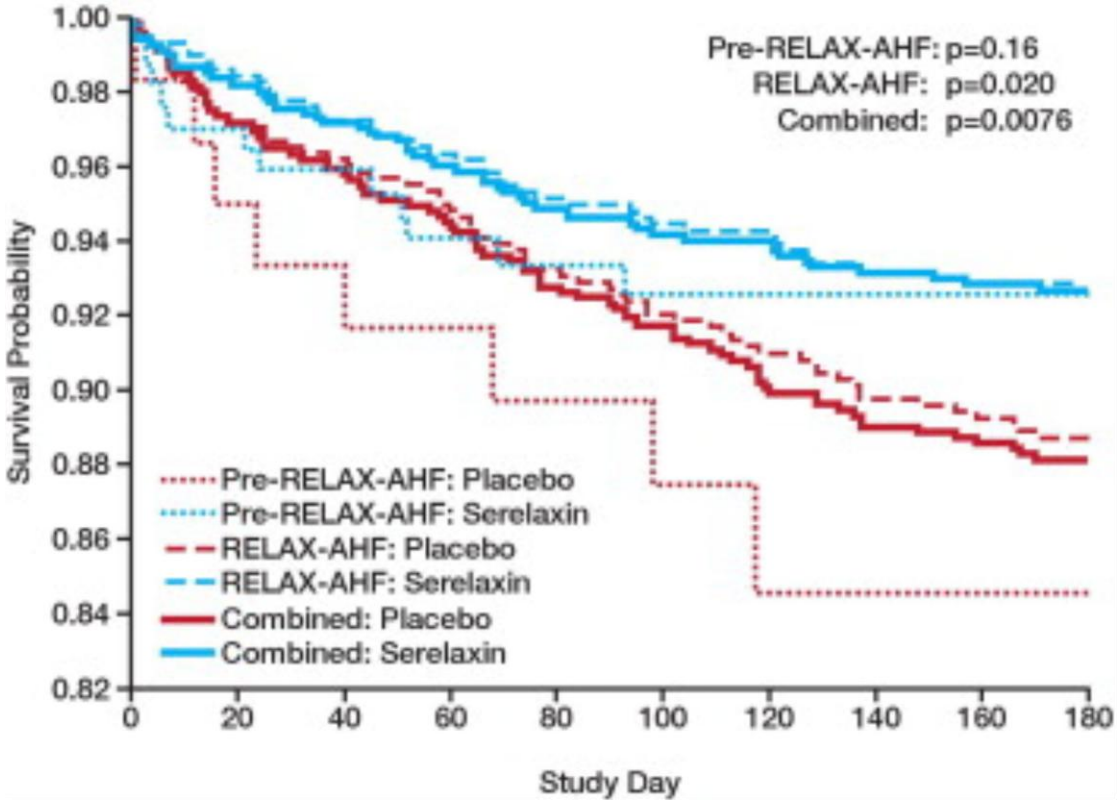
Population: n=8.436 (randomisation completed), EF<40, Ntpro>600, hospitalisation within last 12 mths

Intervention: LCZ696 vs. Enalapril

Clinical trials in worsening heart failure

Trial	Agent	Pts	Effects on Outcome	Effects on Symptoms
OPTIME-CHF	Milrinone	951	↑AEs	No
VERITAS	Tezosentan	1.448	No	No
EVEREST	Tolvaptan	4.133	No	Yes
LIDO	Levosimendan vs. Dobutamine	203	Yes	No
Survive	Levosimendan vs. Dobutamine	1.327	No	No
PROTECT	Rolofylline	2.033	No	No
VMAC	Nesiritide	489	-	Yes

An unexpected favorite: the rise of Serelaxin



Risk for All-Cause Mortality in Pre-RELAX-AHF, RELAX-AHF, and combined results

Metra et al. JACC 2013

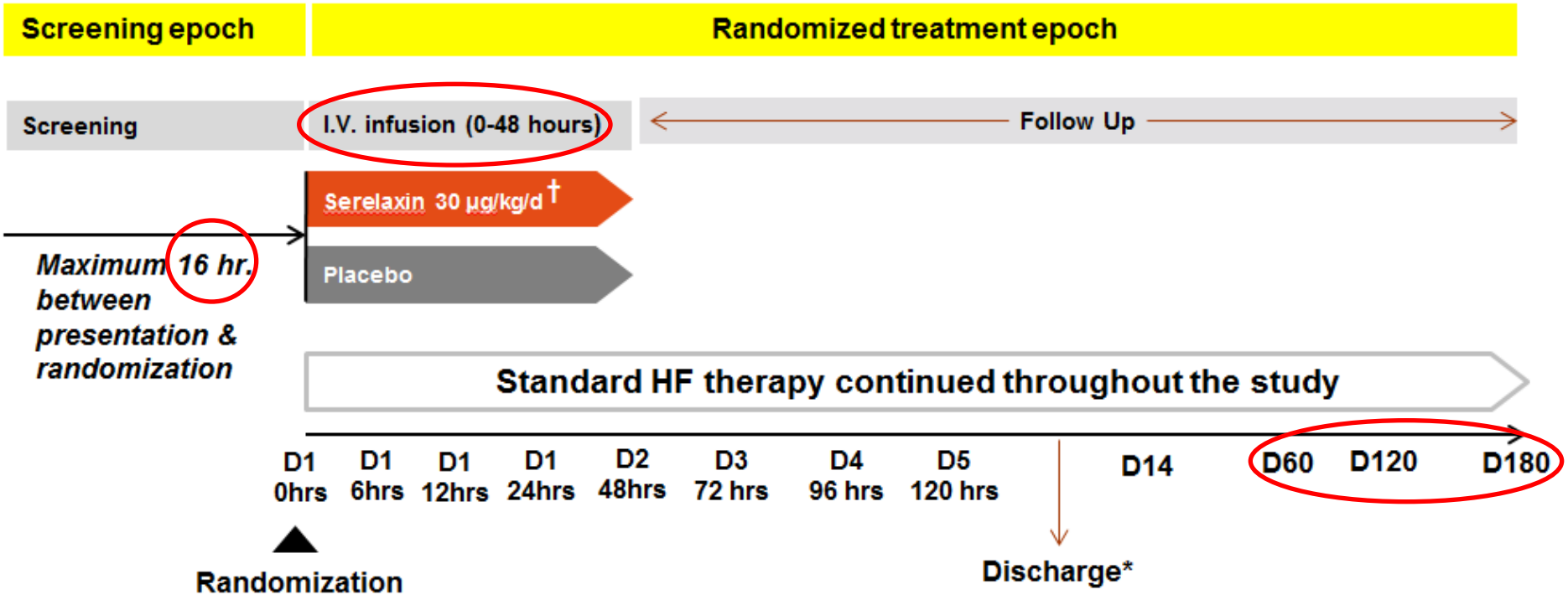
Studie RLX030A2301

A multicenter, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy, safety and tolerability of Serelaxin when added to standard therapy in acute heart failure patients

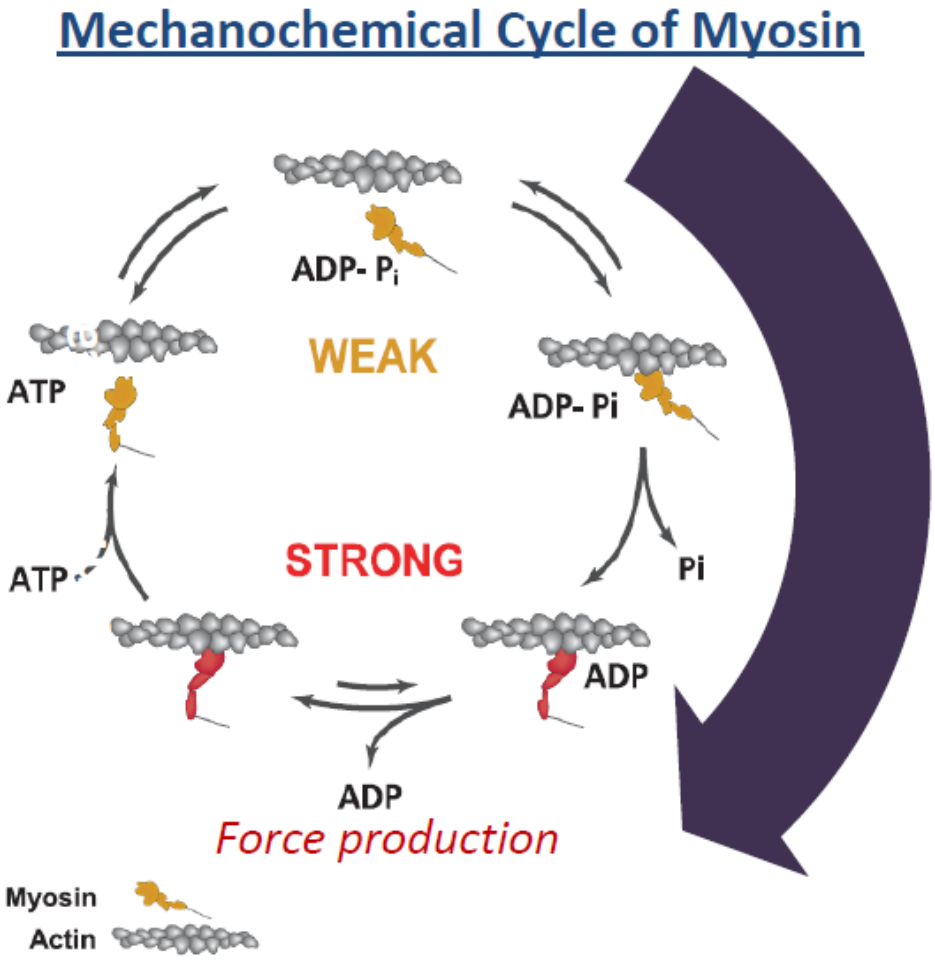
- EudraCT-Nr.: 2013-001498-25
- Akronym: RELAX2, RELAX AHF 2, RLX2,...
- N=6375 patients in 550 center

The primary objective of this study is to demonstrate that serelaxin is superior to placebo in reducing cardiovascular mortality in AHF patients during a follow-up period of 180 days

Studiendesign RLX030A2301



Rethinking positive inotropes: Omecamtiv Mecarbil



Malik FI, *et al.* *Science* 2011; 331:1439-43.

ATOMIC HF: Dyspnoe relief in highest dose but safety concerns

COSMIC HF: oral modified release formulation of omecamtiv mecarbil in subjects with HF and left ventricular systolic dysfunction
N=420
chronic stable HF
elevated NT-proBNP
LVEF ≤ 40%

Cardiac myosin activator
Increases entry rate of myosin into force producing state with actin

„more hands pulling on the rope“

New targets: SERCA2a gene transfer

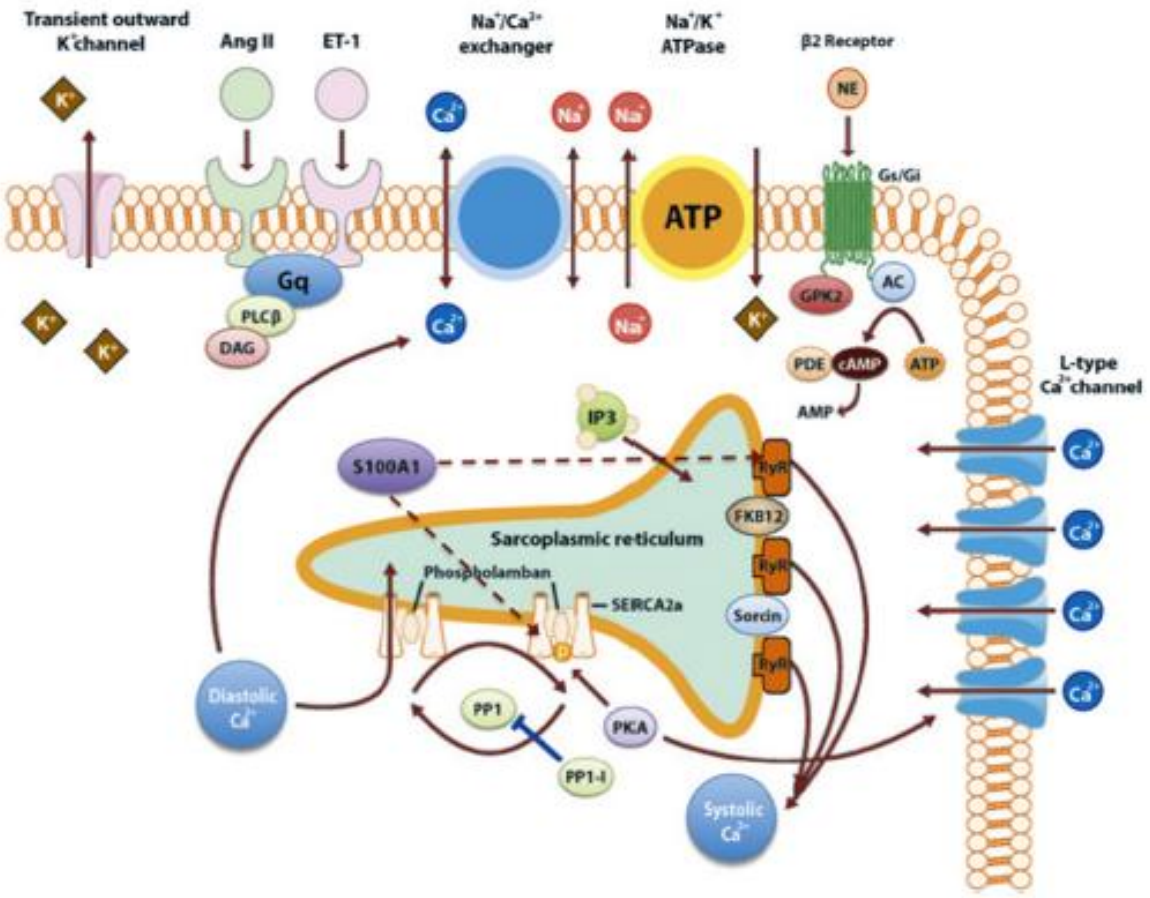
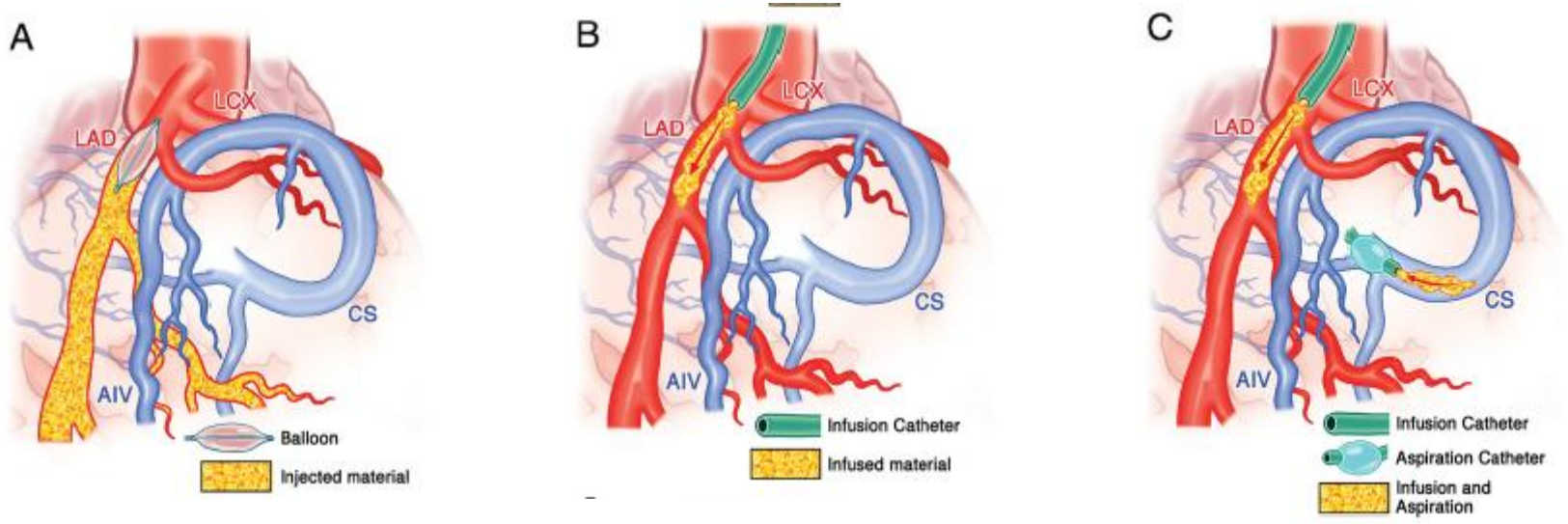


Figure 4 Targets Within Cardiac Myocytes

Kawase et al JACC 2011

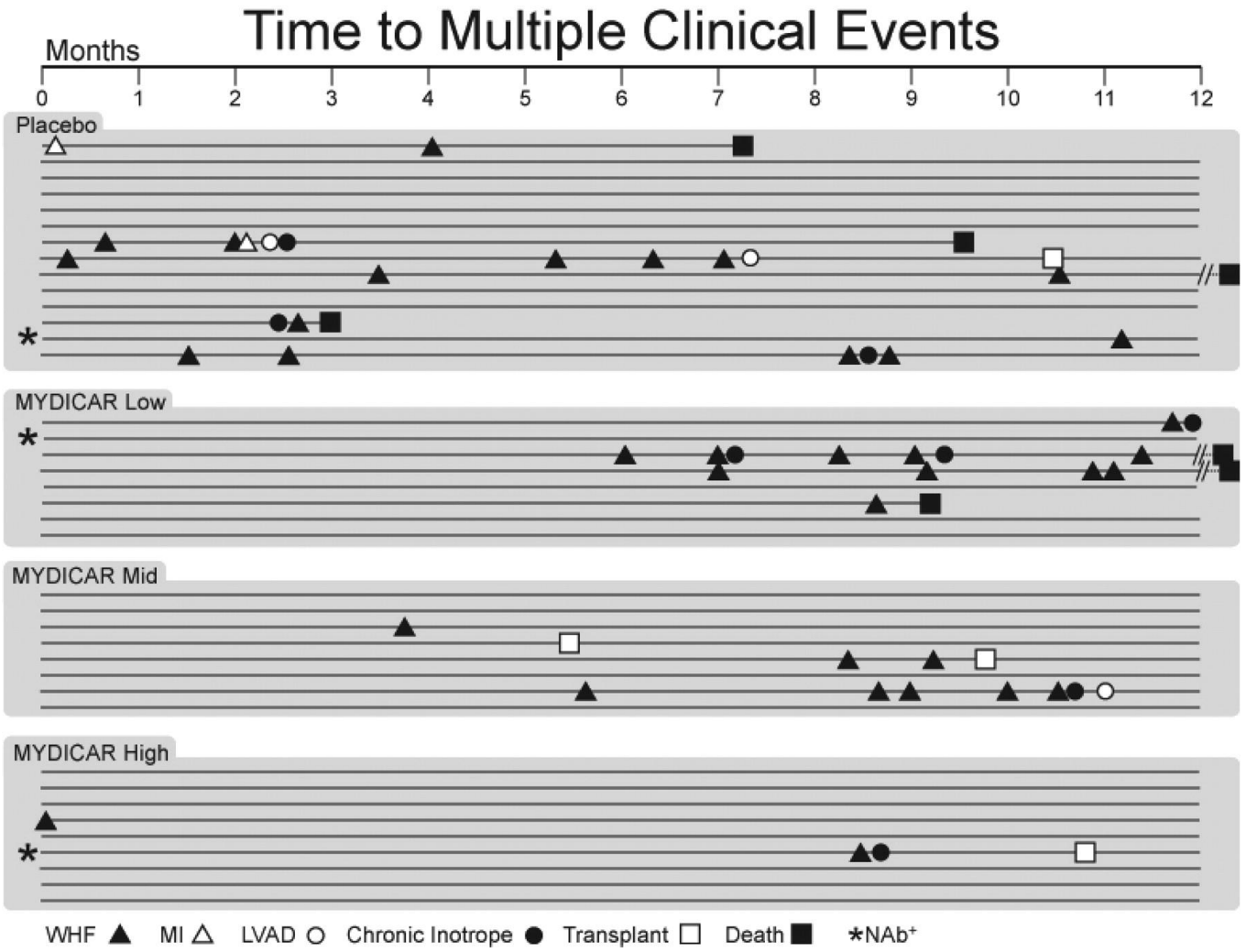
CUPID

- Phase 2b, Double-Blind, Placebo-Controlled, Randomized Study of Safety and Efficacy of Intracoronary Administration of MYDICAR® (AAV1/SERCA2a) in Subjects with Heart Failure.
  - N=200 (LVEF)
  - chronic systolic heart failure ≤35%,
  - all-cause death, heart transplant, LVAD implantation, any hospitalization and outpatient treatment for worsening heart failure



Jessup M et al. Circulation 2011;124:304-313, Kawase et al JACC 2011

Multiple cardiovascular events at 12 months.

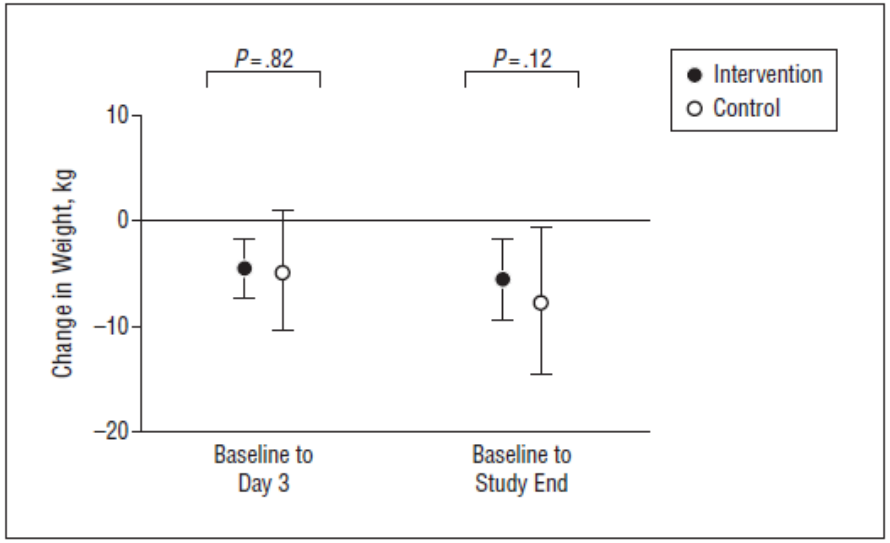


Jessup M et al. Circulation 2011

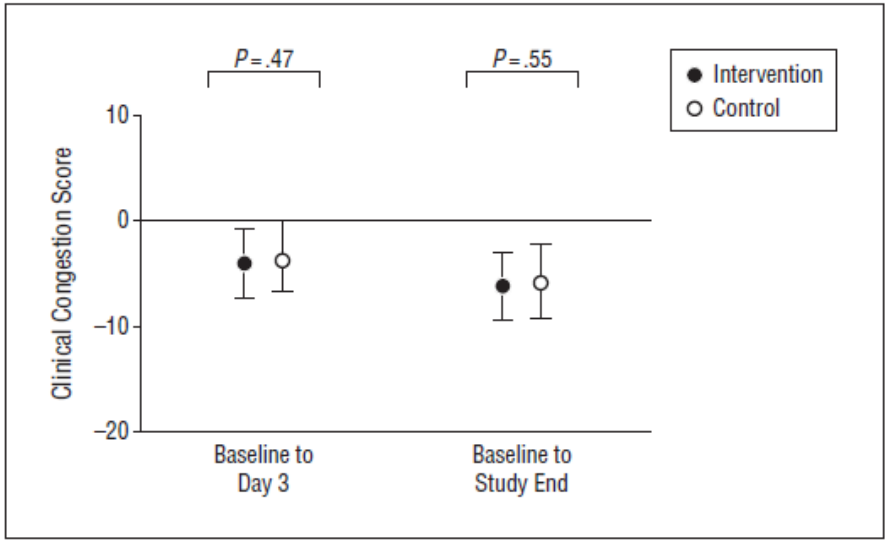
Rethinking non-pharmacological treatment

Randomized, parallel-group clinical trial with blinded outcome assessments.

- No effect of fluid-restricted (max. 800 mL/d) and sodium-restricted (max. 800 mg/d) diet on weight loss and clinical stability during a 3-day period in 75 patients hospitalized with ADHF compared with unrestricted diet (control). Mean EF 26%
- Aggressive fluid and salt restriction associated with significant increase in perceived thirst.



Change in body weight



Change in clinical congestion score

Badin et al JAMA Intern Med 2013

Thank you very much for your attention!

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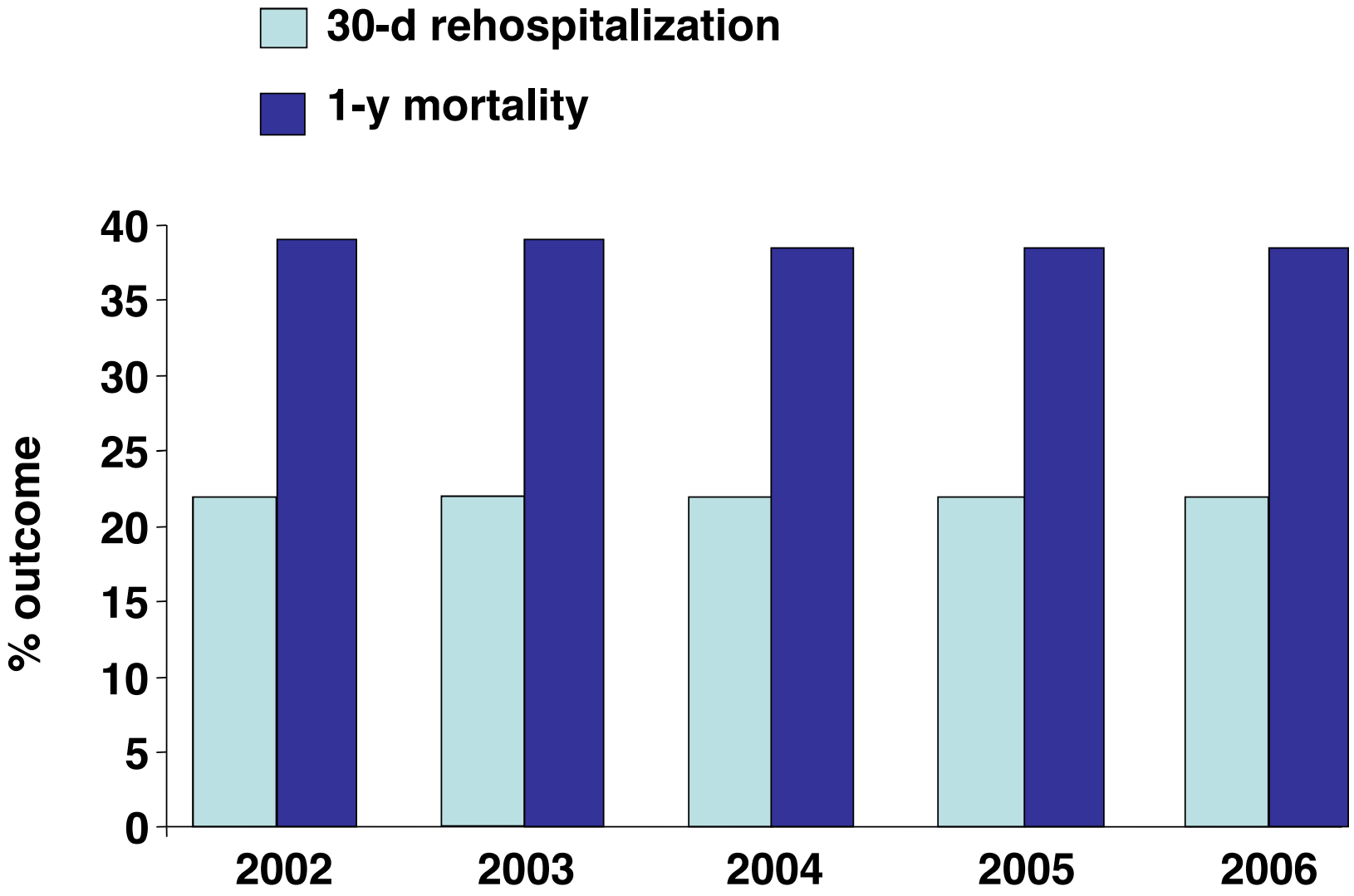
Event rate remains high: „stable“ situation?



Fonarow and Peterson JAMA 2009;302:792-794