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:

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

If current inhibitor ivabradin vs. placebo in chronic HF

„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!

Subgroups by heart rate at the end of up-titration

- >64 bpm: HR 1.84 (95% CI 1.26-2.70), P=0.002
- 55-64 bpm (reference)
- <55 bpm: HR 1.04 (95% CI 0.57-1.92), P=0.889

Observation time [years]

Düngen HD et al ESC HFA 2013
Bisoprolol vs. carvedilol

(p<0.001 (baseline))

Düngen et al. 2011 EJHF
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

Hazard ratio, 0.63 (95% CI, 0.54–0.74)
P<0.001

Zannad, McMurray et al NEJM 2011
DIG Subanalysis

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)

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

Patients receiving darbepoetin had higher hemaglobin but…

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

Swedberg et al. NEJM 2013
RED-HF 2

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

More thromboembolic adverse events in darbepoetin 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**

- 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

Sympathetic stimulation
Angiotensin II
Endothelin

Neprelysin Peptidase

ANP
BNP

↓ Renin

GFR

Vasodilation
↓ Ang II
↓ Aldo

↓ Blood

↓ Blood

Natriuresis
PARADIGM

ARNi
Angiotensin Receptor
Neprelysin inhibitor

LCZ696: complex of
ARB (Valsartan) and NEP inhibitor

Primary objective: time to first occurrence of CV mortality or HF hospitalisation in HFREF
Secondary objective: all-cause 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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Pts</th>
<th>Effects on Outcome</th>
<th>Effects on Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTIME-CHF</td>
<td>Milrinone</td>
<td>951</td>
<td>↑AEs</td>
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<tr>
<td>VERITAS</td>
<td>Tezosentan</td>
<td>1.448</td>
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<td>No</td>
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<tr>
<td>EVEREST</td>
<td>Tolvaptan</td>
<td>4.133</td>
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<td>Yes</td>
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<td>LIDO</td>
<td>Levosimendan vs. Dobutamine</td>
<td>203</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Survive</td>
<td>Levosimendan vs. Dobutamine</td>
<td>1.327</td>
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<td>No</td>
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<tr>
<td>PROTECT</td>
<td>Rolofylline</td>
<td>2.033</td>
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<tr>
<td>VMAC</td>
<td>Nesiritide</td>
<td>489</td>
<td>-</td>
<td>Yes</td>
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</table>
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*
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

Screening epoch

- Screening
- I.V. infusion (0-48 hours)
- Serelaxin 30 µg/kg/d
- Placebo

Maximum 16 hr. between presentation & randomization

Randomized treatment epoch

- Follow Up
- Standard HF therapy continued throughout the study

Randomization

Discharge*

D14
D60
D120
D180
Rethinking positive inotropes: Omecamptiv Mecarbil

Mechanochemical Cycle of Myosin

ATOMIC HF: Dyspnoe relief in highest dose but safety concerns

COSMIC HF: oral modified release formulation of omecamptiv 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

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

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