« New drugs »
Postgraduate Course Heart Failure Session

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Service de cardiologie
Hôpitaux Universitaires de Genève

Joint annual meeting SSC/SSCS-SSP 15.06.2016
Lausanne
“Before I begin, one of the acronyms I’m going to use is completely made up. See if you can figure out which one.”
HFrEF
Positive drug, device and other trials 2001-2014

Slide courtesy of John McMurray
GUIDELINES – what’s new?

Future - HFrEF

Future – HFpEF /HFmrEF

Future - Acute HF
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Yancy, CW, et al.
Heart Failure Focused Update on Pharmacological Therapy

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America
Sacubitril-Valsartan – PARADIGM-HF

McMurray J et al, EJHF 2015
Sacubitril-Valsartan – PARADIGM-HF

8442 patients
NYHA II-III-IV – EF ≤40%
Enalapril 10 mg x 2 and OMT
→ LCZ696 (200x2) vs enalapril (10x2)

1°: composite of death from CV cause and hospital admission for HF

Stopped after 27 months because of overwhelming benefit of LCZ 696 for primary (20% reduction) and secondary endpoints (16-29% reduction).

McMurray J et al, NEJM 2014
Treatment algorithm for patients with HFrEF

ESC Guidelines 2016

ESC Guidelines for diagnosis and treatment of acute and chronic heart failure 2016
Neprilysin, cardiovascular, and Alzheimer’s diseases: the therapeutic split?

Nicolas Vodovar¹, Claire Paquet¹, Alexandre Mebazaa¹,³,⁴, Jean-Marie Launay¹,⁵,⁶, Jacques Hugon¹,²,⁴, and Alain Cohen-Solal¹,⁴,⁷*

¹UMRS 942 Inserm, 75010 Paris, France; ²Clinical and Research Memory Center, Lariboisière Hospital, Paris, France; ³Department of Anesthesiology and Intensive Care, Lariboisière Hospital, Paris, France; ⁴Paris Diderot University, Sorbonne Paris Cité, Paris, France; ⁵Department of Biochemistry, Lariboisière Hospital, Paris, France; ⁶Centre for Biological Resources, Lariboisière Hospital, Paris, France, and ⁷Department of Cardiology, Lariboisière Hospital, 2, Rue Ambroise Paré, 75475 Paris Cedex 10, France

Received 23 October 2014; revised 12 January 2015; accepted 13 January 2015; online publish-ahead-of-print 30 January 2015

Neprilysin \( \rightarrow \) degradation of amyloid A\( \beta \) responsible of Alzheimer’s disease

Metabolite of LCZ696 does not seem to cross the blood-brain barrier

LONG TERM SAFETY CONCERN

Vodovar N et al, EHJ 2015
**Sacubitril-Valsartan – CH**

**DOSE**
- start: 100mg (or 50mg) 2x/d
- double at 2-4 weeks
- target: 200mg 2x/d

**CI**
- ACEI (36h), aliskiren (diab et IR)
- Clcreat <10ml/min/1.73²

**SE**
- hypotension, renal impairment, hyperkalemia, angioedema

**PRICE**
- 8.16 Frs/day
- 230.- Frs/month

**FOLLOW-UP**
- use NT-proBNP

**Dates**
- FDA July 2015
- Swissmedic for HFrEF September 2015
- OFSP (reimbursement) November 2015
- EU November 2015
Levosimendan – advanced CHF

**LEVO-REP** (2014, 120 patients) – **LION-HEART** (HF congress 2015, 69 patients)
1° no change in 5-min walk test
2° reduced combined HF hosp and death endpoint (but not mortality alone)

**LAICA study** (HF congress 2016, 97 patients)
1° hospital admission for AHF → no difference
2° mortality → reduction in levosimendan group

**STILL NOT MENTIONED IN THE GUIDELINES**

- Safety ok
- Contrasting results regarding HF hospital admission and mortality
  → Large RCT with mortality endpoint needed
GUIDELINES – what’s new?

Future - HFrEF

Future – HFpEF/HFmrEF

Future - Acute HF
Soluble guanylyl cyclase (sGC) stimulator → increase cGMP

Key role in HFrEF and HFp/mrEF

Slide courtesy of John McMurray
SOCRATES-REDUCED – phase II

NT-proBNP level change from baseline  

CV death or HF hospital admission

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**Ratio of Geometric Means for Change From Baseline of NT-proBNP Level**

- **Vericiguat Group:**
  - 1.25 mg
  - 2.5 mg
  - 2.5 to 5 mg
  - 2.5 to 10 mg
  - Pooled 2.5/5/10 mg groups

- **P**-values:
  - P < .02$^a$
  - P < .05$^b$

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**Proportion of Patients Experiencing the Composite of CV Death and HF Hospitalization**

- **Placebo group**
- **Vericiguat 2.5-10mg group**

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*Gheorghiade M et al, JAMA 2015*
Empagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus at High Cardiovascular Risk

Silvio E Inzucchi, Christoph Wanner, John M Lachin, David Fitchett, Stefan Hantel, Michaela Mattheus, Theresa Devins, Odd Erik Johansen, Hans J Woerle, Uli C Broedl, Bernard Zinman

Patients with event/analysed

<table>
<thead>
<tr>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86</td>
<td>(0.74, 0.99)*</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87</td>
<td>(0.70, 1.09)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24</td>
<td>(0.92, 1.67)</td>
</tr>
</tbody>
</table>

Zinman et al. NEJM 2015
Fitchett et al, EHJ 2016

Empagliflozin – HFrEF

SGLT2 inhibitors – inhibits proximal tubular glucose reabsorption, cause diuresis and natriuresis, lower BP and reduce weight

EMPA-REG-OUTCOME diabetes study 7,020 patients with T2DM and CV disease/risk factors 38% reduction in CV death 35% reduction in hospital admission for HF
GUIDELINES – what’s new?

Future - HFrEF

Future – HFpEF/HFmrEF

Future - Acute HF
RCT – HFP/mrEF

PEP-CHF
- 107/426 (25.1%)
- 100/424 (23.6%)
- HR (CI) 0.92: (0.70–1.21)
- P=0.55

CHARM-Preserved
- 366/1509 (24%)
- 333/1514 (22%)
- HR (CI) 0.89: (0.77–1.03)
- P=0.12

I-PRESERVE
- 763/2061 (37%)
- 742/2067 (36%)
- HR (CI) 0.95: (0.86–1.05)
- P=0.35

TOPCAT
- HR (CI) 0.89: (0.77–1.04)
- P=0.14
PARAGON-HF
Prospsective comparison of ARni with Arb Global Outcomes in heart failure with preserved ejection fraction

Target patient population: ~4,300 patients with symptomatic HF (NYHA Class II–IV) and LVEF ≥45%

Active run-in period

Screening
Valsartan 80 mg BID*

LCZ696 100 mg BID

up to 2 weeks

3–8 weeks

Double-blind treatment period

LCZ696 200 mg BID
Randomization 1:1
Valsartan 160 mg BID

On top of optimal background medications for co-morbidities (excluding ACEIs and ARBs)

~240 weeks

Primary outcome: CV death and total (first and recurrent) HF hospitalizations (anticipated ~1,721 primary events)

*Valsartan 40 mg BID (up to 2 weeks) followed by valsartan 80 mg BID as an optional starting run-in dose for those patients being treated with less than the minimum dose of ACEi or ARB at Visit 1. ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BID=twice daily; CV=cardiovascular; HF=heart failure; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association.
GUIDELINES – what’s new?

Future - HFrEF

Future – HFpEF/HFmrEF

Future - Acute HF
SERELAXIN - AHF

Multiple actions through Endothelin and NO

VASODILATATION $\rightarrow$ lower BP, increased CO
INCREASES RENAL PERFUSION $\rightarrow$ diuresis
DECREASES INFLAMMATION
DECREASES OXYDATIVE STRESS
DECREASES FIBROSIS
RELAX-AHF (2013)
phase III, 1161 patients with AHF
30ug/kg/d or placebo
1° dyspnea (day 5)
2° CV death and readmission (day 60)

→ improvement of dyspnea, no
difference in 2°
→ 180-day mortality, no hypotension,
less renal impairment

Teerlink JT et al, Lancet 2013
**RELAX – AHF 2**

### Design
Randomized, double-blind, placebo-controlled, Phase III outcome study in patients with AHF

### Population
Patients hospitalized for AHF with key inclusion and exclusion criteria largely similar to RELAX-AHF-1

### Primary endpoint
CV mortality through a follow-up period of 180 days

### Key 2nd efficacy endpoints
- All-cause mortality through a follow-up period of day 180
- Worsening heart failure (WHF) through Day 5
- Length of index hospitalization
- Composite of CV mortality or re-hospitalization due to WHF/renal failure through 180 days

### Sample size
N= 6,375 (513 CV deaths) provides 80% power to detect 22% RRR at α=2.6% (one-sided), assuming placebo CV death rate of 5%. One interim analysis considered at approx. 60% of overall accumulated primary events (308 CV deaths) to stop for overwhelming efficacy benefit ( Lan-DeMets spending function with an O’Brien-Fleming stopping boundary)

**EXPECTED COMPLETION 2017**

NCT01870778 (https://clinicaltrials.gov/ct2/show/NCT01870778), Courtesy of McMurray, Heart Failure Congress 2016
SERELAXIN - AHF

**WHY LONG TERM EFFECT?**

1° LESS ORGAN DAMAGE
2° LESS WHF
3° BETTER DECONGESTION

Filippatos G et al, EHJ 2014
Natriuretic peptide (kidney) → inhibits Na reabsorption
Natruresis – Vasodilatation – Bronchodilatation – Neurohormonal (- RAA Endothelin)

**TRUE-AHF** - RCT PHASE III, 2157 patients AHF, 15ng/kg/d 48h vs placebo
1° A. Composite score of clinical outcome and symptoms during perfusion
   B. CV mortality during entire trial (180 days)

RESULTS IN ROME IN AUGUST 2016

Anker SD et al, EHJ 2015
Heart Failure Congress Florence 2016*
Omecamtiv mecarbil – AHF/HFrEF

Intravenous - AHF

Oral- HFrEF

Teerlink JT et al, JACC 2016
FUTURE...

PHASE III – NEAR FUTURE

SACUBITRIL-VALSARTAN (HFp/mrEF)
SERELAXIN (AHF – (HFrEF?)
ULARITIDE (AHF)

TO BE FOLLOWED...

VERICIGUAT (HFrEF – HFP/mrEF?)
EMPAGLIFLOZINE (HFrEF – HFP EF)
OMECAMTIV MECARBIL (HFrEF – AHF)
FINERENONE (HFP EF)
NYTROXYL DONORS (AHF – HFP EF)
ISTAROXIME (AHF)

...
Most innovations in the last decades are in the field of HFrEF (drugs, devices)

Sacubitril-valsartan is the only new drug incorporated into the guidelines ESC guidelines since 2012 (HFrEF)

What about levosimendan for repetitive doses in advanced HFrEF?

In HFp/mrEF no new drug, but waiting for PARAGON-HF (sacubitril-valsartan)

In acute HF no new drug, but waiting for RELAX-AHF2 (serelaxin) and TRUE-AHF (ularitide)

Many drugs under phase II-III planned (vericiguat, empagliflozine, omecamtiv mecarbil, istoroxime, nitroxy1 donors, finerenone, and more)

Take home messages
Thank you for your attention
498 patients
No difference in tolerability, better reach of target dose with « conservative » regimen for low-dose initial ACEI

Senni M et al, EJHF 2016
**SHIFT (2010)**

6658 patients
NYHA II-III, EF≤35%, on OMT

→ Ivabradine ad 7.5mg x2 vs placebo + OMT

1° composite HF death and hospital admission

Swedberg K et al, Lancet 2010
Levosimendan – AHF

**Calcium sensitizer**
Inotropic – Lusitropic – Vasodilation
No increase of O2 consumption

**LIDO trial (2002) phase II**
103 patients – RCT with levosimendan vs dobutamine
1° Hemodynamic effect (30% increase in CO, 25% decrease in PCWP) at 24h

**SURVIVE study (2007) phase III**
1327 patients – RCT with levosimendan (with loading dose) vs dobutamine
1° All cause mortality at 180 days

Survival advantage in subgroup of CHF patients receiving beta blockers
Class IIb, level C
Preferred molecule for CHF patients receiving BB

Mebazza et al, JAMA 2007
Primary outcome: CV death or heart failure hospitalization
(event driven: target 2318 patients [2369 accrued])

- Enalapril 5-10mg bid
- Enalapril + Aliskiren 150mg qd
- Aliskiren 300mg qd
- Enalapril 5-10mg bid + Aliskiren 300mg qd

*89% 10mg bid
†Target dose (titrated from 150mg qd)

Prior ACEi use discontinued

Median follow-up = 36.6 months

### ATMOSPHERE - Design

**Graph:**
- **Graph Title:** Combination vs Enalapril
- **Hazard ratio (95% CI):** 0.934 (0.846, 1.030)
- **2-sided p-value:** 0.1724
- **Aliskiren vs Enalapril**
- **Hazard ratio (95% CI):** 0.994 (0.902, 1.097)
- **2-sided p-value:** 0.9118

**Cumulative event rate [%]**

<table>
<thead>
<tr>
<th>Time since randomization [days]</th>
<th>Cumulative event rate [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>180</td>
<td>1</td>
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<td>360</td>
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<td>540</td>
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<td>900</td>
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<td>1080</td>
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<td>1260</td>
<td>13</td>
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<td>1440</td>
<td>15</td>
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<tr>
<td>1620</td>
<td>17</td>
</tr>
<tr>
<td>1800</td>
<td>19</td>
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</table>

**Patients at risk**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination</td>
<td>2340</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>2340</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2336</td>
</tr>
</tbody>
</table>

Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial

Faiez Zannad¹, Barry Greenberg², John G.F. Cleland³, Mihai Gheorghiade⁴, Dirk J. van Veldhuisen⁵, Mandeep R. Mehra⁶, William M. Byra⁷, Min Fu⁷, and Roger M. Mills⁷*
Hypothesis: Rivaroxaban will reduce morbidity and mortality in pts with HF due to CHD.

Population: 5000 patients; symptomatic HF; CHD; EF ≤40%; BNP ≥200 pg/ml or NT-proBNP ≥ 800 pg/ml; recent exacerbation of HF.

Intervention: Rivaroxaban (2.5mg bid) vs placebo.

Primary endpoint: Death, MI or stroke.

Status: Started 2013.
TRV (120)027: a biased angiotensin II type 1 receptor (AT1R) ligand

Boerrigter G et al. Circ Heart Fail 2011;4:770-778
BLAST-HF
Biased Ligand of the Angiotensin receptor Study in acute Heart Failure

• **Hypothesis:** To test the efficacy and safety of TRV027, a novel biased ligand of the angiotensin II type 1 receptor.

• **Population:** 500 patients hospitalized with AHF (systolic blood pressure ≥120 mm Hg and ≤200 mm Hg within 24 h of presentation.

• **Intervention:** 3 doses of iv TRV027 (1, 5, or 25 mg/h) or placebo (1:1:1:1) for <48 h and ≥96 h.

• **Primary endpoint:** composite of 5 clinical endpoints (dyspnea, worsening heart failure, length of hospital stay, 30-day rehospitalization, and 30-day mortality) combined using an average z-score.
Sacubitril-valsartan – HFpEF

PARAMOUNT (Phase II)
301 patients – LVEF ≥45%
Sacubitril-valsartan vs valsartan alone
1° change in NT-proBNP level at 12 weeks
2° reduction in LA size at 36 weeks
HFpEF... what else?

Vericiguat (sGMP stimulator)
SOCRATES-PRESERVED (Phase II)
477 patients
5 arms (2 low doses, 2 uptitration, 1 placebo)
Completed september 2015 – No results

Empagliflozine (SGLT-2 inhibitor)
EMPA-REG (phase III, diabetics)
Application in HFpEF

Finerenone (non-steroidal mineralocorticoid receptor antagonist)
ARTS-HF (phase II)
1002 patients - Finerenone (different dose groups (5) vs eplerenone)
Equal reduction in pro-BNP - less hypekaliemia
Trend to better event-free survival (small groups)
## SERELAXIN - AHF

### Pre-RELAX-AHF (2009)
Phase II RCT, 234 patients with AHF
- 4 doses (48h) or placebo
- Decrease dyspnea (immediate and 14 days)
- Suggestion of beneficial effect on congestion, worsening HF, length of stay, death and readmission at 60 days, 180-day CV mortality

### ULARITIDE

#### SIRIUS-I (2005) and SIRIUS-II (2006)
24 and 221 patients in AHF, 3 doses and placebo
- Reduces PCWP, mortality
- Improves CI and symptoms
- No impairment of renal function
**Omecamtiv mecarbil** (cardiac myosin activator – ATOMIC-AHF study (IV))
Initropic effect without increase in O2 consumption – no proarrythmia
1° no change in dyspnea, but trend towards reduced WHF
2° safe

**Istaroxime** (Na/K-ATPase inhibitor – HORIZON-HF)
Inotropic and lusitropic effect – no proarrythmia
1° decreases effectively PCWP, no phase III trial

**Nitroxyll donor (HNO)**
Inotropic, lusitropic and vasodilator (unlike NO, only vasodilator)
Also potential use in HfpEF