Training course:
All About Clinical Trials

UPCOMING AND ONGOING CLINICAL TRIALS:
Heart Failure

Claudio Ceconi
Declaration of Conflict Of Interest

The existence of potential conflicts of interest does not necessarily indicate a bias. However it is our ethical obligation to inform organisers and participants so that they are made aware of any relationship that might cause unintentional bias. A potential conflict of interest may arise from various relationships, past or present, such as employment, consultancy, investments and stock ownerships, funding for research, family relationship etc.

✓ I have no potential conflict of interest to report

☐ I have the following potential conflict(s) of interest to report

<table>
<thead>
<tr>
<th>Type of affiliation / financial interest</th>
<th>Name of commercial company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of grants/research supports:</td>
<td></td>
</tr>
<tr>
<td>Receipt of honoraria or consultation fees:</td>
<td></td>
</tr>
<tr>
<td>Participation in a company sponsored speaker’s bureau:</td>
<td></td>
</tr>
<tr>
<td>Stock shareholder:</td>
<td></td>
</tr>
<tr>
<td>Spouse/partner:</td>
<td></td>
</tr>
<tr>
<td>Other support (please specify):</td>
<td></td>
</tr>
</tbody>
</table>
Unmet needs

- Effective treatments in Acute Heart Failure
- Effective treatments in Heart Failure with preserved heart LV function
The failure of new therapies
### Inotropic mechanism

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium-potassium-ATPase inhibition</td>
<td>Digoxin</td>
</tr>
<tr>
<td>β-Adrenoceptor stimulation</td>
<td>Dobutamine, dopamine</td>
</tr>
<tr>
<td>Phosphodiesterase inhibition</td>
<td>Enoximone, milrinone</td>
</tr>
<tr>
<td>Calcium sensitization</td>
<td>Levosimendan</td>
</tr>
<tr>
<td>Sodium-potassium-ATPase inhibition plus SERCA activation</td>
<td>Istaroxime</td>
</tr>
<tr>
<td>Acto-myosin cross-bridge activation</td>
<td>Omecamtiv mecarbil</td>
</tr>
<tr>
<td><strong>SERCA activation</strong></td>
<td>Gene transfer</td>
</tr>
<tr>
<td>SERCA activation plus vasodilation</td>
<td>Nitroxyl donor; CXL-1020</td>
</tr>
<tr>
<td>Ryanodine receptor stabilization</td>
<td>Ryanodine receptor stabilizer; S44121</td>
</tr>
<tr>
<td>Energetic modulation</td>
<td>Etomoxir, pyruvate</td>
</tr>
</tbody>
</table>
Gene transfer in the future for HF therapy?
SERCA2a gene therapy in HF
MYDICAR Reduced Adjudicated CV Clinical Events: 3-Year Follow-up

Clinical Events
- Worsening Heart Failure
- Heart Transplant
- Myocardial Infraction
- Chronic Use of Inotrope
- Insertion of LVAD
- All-Cause Death


- 13 Deaths in Phase 2 Trial
- 6 in Placebo
- 3 in Low Dose
- 3 in Mid Dose

- MYDICAR Reduced Adjudicated CV Clinical Events:
  - Year 1
  - Year 2
  - Year 3

- Placebo
- MYDICAR Low
- MYDICAR Mid
- MYDICAR High

- Withdrew Consent
CUPID 2: A Phase 2b Confirmatory Ongoing International Study – Data April 2015

Study Population
- 18-80 years of age
- Systolic HF
- Ischemic or non-ischemic
- EF ≤35%
- NYHA Class II to IV
- Maximal, optimized HF regimen

MYDICAR 1x10^13 DRP, N=125

<table>
<thead>
<tr>
<th>Placebo, N=125</th>
</tr>
</thead>
</table>

Sample Size/Power:
N=125 per treatment group with 186 recurrent events provides:
83% power, 0.05 two-sided significance level, to detect at least a 45% risk reduction (HR=0.55)

All Subjects Followed Quarterly for Clinical Events Until:
- Last enrolled subject completes 12 months of observation AND
- 186 adjudicated HF-related hospitalizations have occurred

Primary Endpoint
- Time to recurrent HF-related hospitalizations in presence of terminal events (all-cause death, heart transplant, and LVAD implantation)

Secondary Endpoint
- Time to first terminal event (all-cause death, heart transplant, LVAD implantation)

Additional Endpoints
- Symptoms, Exercise Capacity and Quality of Life

Enrolment
- Conduct (12 Months of Study)
- Analysis 3 Months

3 Months
- 54 centers in Belgium, Denmark, Germany, Hungary, Israel, The Netherlands, Poland, Sweden, UK & US

Recurrent analysis showed inefficacy p=0.98
SERCA2a story is not over yet...

Istaroxime phase III in acute heart failure
Cardiopoietic Stem Cell Therapy Improved Left Ventricular Remodeling - Longitudinal Results from the CHART-1 Study

John R. Teerlink, MD, HFA Congress 2017

- Intramyocardial injections using retention-enhanced catheter (C-Cathez®)
- Up to 20 injections of 0.5 mL each spaced ~1 cm apart over LV where ≥ 8 mm thick
  - ≤ 16 injections n=29
  - 17/18/19 n=35
  - ≥ 20 n=56
- Sham procedure did not have intramyocardial injections

Changes in LVEDV and LVESV at Week 52 by number of cardiopoietic cell injections

In this population of patients with advanced HF, intramyocardial administration of cardiopoietic stem cells induced significant reverse LV remodeling. Effects on remodeling appear most pronounced in patients who received a moderate number of injections.

John R. Teerlink, MD, HFA Congress 2017
### Inotropic mechanism

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium-potassium-ATPase inhibition</td>
<td>Digoxin</td>
</tr>
<tr>
<td>β-Adrenoceptor stimulation</td>
<td>Dobutamine, dopamine</td>
</tr>
<tr>
<td>Phosphodiesterase inhibition</td>
<td>Enoximone, milrinone</td>
</tr>
<tr>
<td>Calcium sensitization</td>
<td>Levosimendan</td>
</tr>
<tr>
<td>Sodium-potassium-ATPase inhibition plus SERCA activation</td>
<td>Istaroxime</td>
</tr>
<tr>
<td>Acto-myosin cross-bridge activation</td>
<td>Omecamtiv mecarbil</td>
</tr>
<tr>
<td>SERCA activation</td>
<td>Gene transfer</td>
</tr>
<tr>
<td>SERCA activation plus vasodilation</td>
<td>Nitroxyll donor; CXL-1020</td>
</tr>
<tr>
<td>Ryanodine receptor stabilization</td>
<td>Ryanodine receptor stabilizer; S44121</td>
</tr>
<tr>
<td>Energetic modulation</td>
<td>Etomoxir, pyruvate</td>
</tr>
</tbody>
</table>

*Note: The diagram shows the cumulative percentage of different therapies.*
Omecamtiv Mecarbil (OM)
Selective Cardiac Myosin Activator

Omecamtiv mecarbil is a small molecule that directly activates cardiac myosin.

OM binds directly to the enzymatic domain of cardiac myosin and, during systole, increases its rate of ATP hydrolysis.

- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in $dP/dt_{\text{max}}$
- No increase in MVO$_2$

Omecamtiv Mecarbil: A Cardiac Myosin Activator

Omecamtiv Mecarbil Binds to the Mechanochemical Domain of Myosin


Omecamtiv Mecarbil (MW = 401.43)

Omecamtiv Mecarbil: Preclinical Pharmacology in Dog Heart

Increases in Duration of Cardiac Contraction Underlie Increases in Cardiac Function

Time-dependent Elastance [E(t)]

MVO₂ Increased

MVO₂ Unchanged

Dobutamine

Baseline

Omecamtiv mecarbil

Baseline

Increase in systolic ejection time underlies increase in cardiac function

Δ Stroke Volume (mL)
Δ Fractional Shortening (% points)
Δ Ejection Fraction (% points)

Δ = placebo corrected change from baseline
Mean ± SEM

Healthy Volunteers vs. Heart Failure Patients

Omecamtiv Mecarbil: Overview of Development Program

**PHASE 1-2a**
- PK/PD, tolerability
- Healthy Volunteers
- Stable HF Patients
  - EF < 40%
  - Stable therapy

**DOSE RANGING**

**DOSE FINDING**

**PHASE 1-2a**
- PK, tolerability
- Healthy Volunteers
- Stable HF Patients
  - EF < 40%
  - Stable therapy

**PHASE 3 CV OUTCOMES**
**GALACTIC-HF**
N = 8000
- Oral dosing
- Evaluate clinical efficacy
- Establish safety and tolerability

**ATOMIC-AHF**
N = 613
- IV PK in Acute HF
- Evaluate safety, tolerability, echo PD, and clinical efficacy

Evaluation across a range of heart failure patient populations
14 phase 1 and 2 studies completed; > 1000 subjects dosed
GALACTIC-HF

**Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility (in Heart Failure)**

A Double-blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects With Chronic Heart Failure With Reduced Ejection Fraction

---

**Major Inclusion Criteria:**
- Chronic heart failure
- NYHA II-IV
- LVEF ≤ 35%; ↑ BNP/NT-proBNP
- Managed with Standard of Care therapy
- Current hospitalization for HF or history of hospitalization or ER/ED visit for HF within 12 months

---

**Study Visits:**
- D1, W2, W4, W6, W8, W12, W24, W36, W48, Q16W

---

**Endpoints:**
- Primary endpoint: Time to CV death or first HF event
- Event driven trial
Mithocondrial therapies
Healthy Mitochondrial Structure

Diseased Mitochondrial Structure

Cardiolipin shapes mitochondrial structure
- Foundation of electron transport chain (ETC)
- Maintains healthy ATP levels and minimal ROS production

Bendavia reestablishes healthy mitochondrial structure and function in disease
- Electrostatic interaction with cardiolipin, maintaining ETC
- Restoring healthy ATP and ROS levels
- Modifying disease

Bendavia

Improves Mitochondrial Structure and Function

E TC

Normal ATP

Increased ROS

Restores normal ATP levels and decreases ROS in disease

Healthy Cardiolipin

Diseased Cardiolipin

Electrostatic interaction with cardiolipin, maintaining ETC
Restoring healthy ATP and ROS levels
Modifying disease

Bendavia

Working Group
Cardiovascular Pharmacotherapy
Bendavia in Acute Coronary Syndrome
EMBRACE Clinical Study

- Clinical outcomes and heart failure
  - Bendavia reduces the incidence of heart failure during the initial day after ACS
  - No differences in clinical safety and patient tolerability

Left Ventricular Ejection Fraction (LVEF)

<table>
<thead>
<tr>
<th>Group</th>
<th>LVEF (±)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>41.9 ± 10.4</td>
<td>55</td>
</tr>
<tr>
<td>Bendavia</td>
<td>44.0 ± 11.0</td>
<td>52</td>
</tr>
</tbody>
</table>

p=0.16
The hypothesis CONFIRM HF

Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†

Piotr Ponikowski1,2, Dirk J. van Veldhuisen3, Josep Comin-Colet4, Georg Ertl5,6, Michel Komajda7, Viacheslav Mareev8, Theresa McDonagh9, Alexander Parkhomenko10, Luigi Tavazzi11, Victoria Levesque12, Claudio Mori12, Bernard Roubert12, Gerasimos Filippatos13, Frank Ruschitzka14, and Stefan D. Anker15, for the CONFIRM-HF Investigators

ESC Working Group Cardiovascular Pharmacotherapy

6 MWT Difference FCM vs placebo 33 (SE11) metres

Week 24
Clinicaltrials.gov identifier: NCT01453608

P=0.002

LSM change in 6MWT distance from baseline (m)
Choosing Quality vs Quantity of Life in Heart Failure

• ... there was a "strong preference for the symptom relief afforded by inotropes over the better survival promise of optimal medical therapy (42% vs 26%, p<0.001)" MacIver J, J Heart Lung Transplant 2008;

• ... pts with HF 61% preferred QOL.

"The majority of HF patients attach more weight to quality of life over longevity" Kraai IH, European J Heart Failure 2013;15, 1113–1121.

Preferences of heart failure patients in daily clinical practice: quality of life or longevity?

Quality of life in patients with heart failure: Ask your patients what matters most
FAIR-HF-2

Design: Multi-centre, international, randomised (1:1), double-blind, placebo-controlled

Main inclusion criteria:
- CHF with LVEF ≤ 45% and NYHA class II / III
- HF hospitalisation within 6 mo or BNP/NT-proBNP >100/>300 pg/mL or MRproANP>120 mmol/L
- Iron deficiency: serum ferritin <100 µg/L or ferritin 100-299ng/mL with TSAT <20%
- Hb: ≤ 14.0 g/dL

FCM up to 2000mg
(2x1000mg)

Treatment continues every 4 months if ID is not corrected

Primary endpoint
- Rate of recurrent hospitalisations for heart failure or CV death during follow-up.
Vericiguat
The soluble guanylate cyclase stimulator reduced the composite endpoint of CV death or heart failure hospitalization compared with placebo when given on top of standard therapies. No additional details were provided.

Monday, November 18, 2019
Antidiabetic drugs in HF: the case of SGLT-2inh

DAPA-HF Trial, *NEJM* 2019

- Empaglifozin (23) and Canaglifozin (5)
- Mechanisms?
- HFrEF vs. HFpEF?
Many other stories going on...

- Praliciguat
- Cimlanod
- Neucardin
- K+ binders
- Etomoxir
- Ryanodine receptor stabilizers
- Neuregulin 1β3
- A pletora of biosensors
- ...

ESC Working Group
Cardiovascular Pharmacotherapy
The great thing in this world is not so much where we stand, as in what direction we are moving.

Oliver Wendell Holmes 1841-1935