Recent advances and future directions in the treatment of heart failure

Focus of pharmacological therapy

John McMurray
BHF Cardiovascular Research Centre, University of Glasgow & Queen Elizabeth University Hospital, Glasgow.
My employer, Glasgow University, is currently or has recently been paid for my time as a member of the Executive or Steering Committees of trials testing treatments in CV disease/CKD/diabetes, including acarbose (ACE – Oxford University/Bayer), albiglutide (Harmony Outcomes – GSK), aliskiren (ATMOSPHERE - Novartis), atrasentan (SONAR – Abbvie), dapagliflozin (AstraZeneca), daprodustast (ASCEND, GSK), omecamtiv mecarbil (COSMIC-HF, GALACTIC-HF - Amgen/Cytokinetics), ularitide (TRUE-AHF - Cardiorentis) and sacubitril/valsartan (PARADIGM-HF, PARAGON-HF, PARADISE-MI, PERSPECTIVE - Novartis).

My employer has also been paid for meetings and presentations related to these trials and treatments.

Study sponsors have paid for my travel and accommodation for some meetings related to these trials/treatments.
Heart failure with reduced ejection fraction

- New guidelines
- New evidence since the guidelines
- Emerging treatments
ESC 2016 and ACC/AHA/HFSA 2016 Heart failure guidelines/update

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

Authors/Task Force Members: Piotr Ponikowski (Chairperson) (Poland), Adriaan A. Voors (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Vollmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Piecke (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

ACC/AHA/HFSA Focused Update

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

85 page guideline

36 page update
Treatment of HF with reduced ejection fraction (HF-REF)
What is new in the treatment of HF-REF?

- **Drugs:**
  - Ivabradine (USA/Canada)
  - Sacubitril/valsartan
  - Intravenous iron

- **Devices:**
  - No major update
Progress in HF-REF since 2000

Positive drug, device and other trials 2001-2014

- COMET
- CHARM-Alt
- CHARM-Add
- Val-HeFT
- A-HeFT
- SENIORS
- AF-CHF
- SHIFT
- PARADIGM-HF
- HF-ACTION
- EMPHASIS-HF
- COMPANION
- SCD-HeFT
- CARE-HF
- MADIT-CRT
- Heart Mate II
- RAFT
- STICH

Key:
- H-ISDN
- MRA
- Beta-blocker
- Surgery
- ARNI
- Angiotensin receptor blocker (ARB)
- Ivabradine
- Implantable cardioverter defibrillator/cardiac resynchronization therapy (ICD/CRT)

Head-to-head comparison
Dose-response study

1. Rate vs. rhythm control in atrial fibrillation (AF)
2. Exercise prescription
Can we change the paradigm?

- Harness endogenous protective systems as well as inhibit the harmful ones?
- Replacing an existing treatment and not adding a new one?
Heart failure: a state of “neurohumoral imbalance”

Vasoconstrictor/anti-natriuretic/pro-mitotic mediators

Vasodilator/natriuretic/anti-mitotic mediators
A paradigm shift: from “neuro-humoral inhibition” to “neuro-humoral modulation”

Vasoconstrictor/anti-natriuretic/pro-mitotic mediators

Vasodilator/natriuretic/anti-mitotic mediators
Natriuretic peptides: How the heart protects itself

- The heart is an endocrine organ
- It secretes A and B type natriuretic peptides into the circulation where they act on the blood vessels, kidneys, adrenal glands, brain etc
- These peptides protect the heart from volume and pressure overload
Angiotensin receptor neprilysin inhibition (ARNI)

Sacubitril-valsartan (LCZ696)

Neprilysin inhibition

AT₁ Receptor blocker
**Angiotensin Receptor Neprilysin Inhibition (ARNI)**

**Sacubitril-valsartan (LCZ696)**

- **sacubitril**
  - Natriuretic peptides (BK, ADM, Subs-P, VIP, CGRP)
  - Vasodilation
  - Natriuresis
  - Diuresis
  - Inhibition of pathologic growth/fibrosis
- **valsartan**
  - AT$_1$ Receptor
  - Vasoconstriction
  - Sodium/water retention
  - Fibrosis/hypertrophy

**Neprilysin**
- Degradation products
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

- Age ≥18 years. NYHA class II-IV. LVEF ≤0.40 (amended to ≤0.35).
- BNP ≥150 pg/ml (NTpro-BNP ≥600 pg/ml) or if HF hosp. within 12 mo. BNP ≥100 pg/ml (NTpro-BNP ≥400 pg/ml)
- Background RAS blocker therapy equivalent to enalapril ≥10 mg/d
- Beta-blocker and MRA as recommended by guidelines
- SBP ≥100 mmHg run-in/ ≥95 mmHg at randomization
- eGFR ≥30 ml/min/1.73m²/no decrease >25% (amended to 35%)
- Potassium ≤5.2 mmol/l run-in/ ≤5.2 mmol/l at randomization

**Single-blind period**
- Enalapril 5-10 mg bid
- LCZ 100 mg bid
- LCZ 200 mg bid

**Double-blind period**
- LCZ696 200 mg BID (n=4187)
- Enalapril 10 mg BID (n=4212)

N = 8442 (1:1 randomization)

Outcome driven (CV death): Stopped early for benefit

Median follow-up = 27 months

Prior ACEi/ARB use discontinued

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td><strong>Women (%)</strong></td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td><strong>Ischemic cardiomyopathy (%)</strong></td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td><strong>LV ejection fraction (%)</strong></td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td><strong>NYHA functional class II / III (%)</strong></td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td><strong>N-terminal pro-BNP (pg/ml)</strong></td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td><strong>B-type natriuretic peptide (pg/ml)</strong></td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Digitalis</strong></td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td><strong>Beta-adrenergic blockers</strong></td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td><strong>Mineralocorticoid antagonists</strong></td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td><strong>CRT</strong></td>
<td>7.0%</td>
<td>6.7%</td>
</tr>
<tr>
<td><strong>ICD</strong></td>
<td>15%</td>
<td>15%</td>
</tr>
</tbody>
</table>
The primary outcome
PARADIGM-HF: Primary outcome
Cardiovascular death or heart failure hospitalization

HR: 0.80 (0.73, 0.87)
\[ p = 0.0000004 \]

Cumulative Proportion of Patients with Primary End Point (%)

Days after Randomization

At risk
Enalapril: 4212 3883 3579 2922 2123 1488 853 236
LCZ696: 4187 3922 3663 3018 2257 1544 896 249

PARADIGM-HF: Components of the primary outcome

Death from CV causes
20% risk reduction

HF hospitalization
21% risk reduction

HR: 0.80 (0.71, 0.89)
P = 0.00008

McMurray, Packer et al. NEJM 2014
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Death from any cause
16% risk reduction

Cumulative Proportion of Patients Who Died from Any Cause (%)

Days after Randomization

HR: 0.84 (0.76, 0.93)
P = 0.0009

Enalapril (n=4212)
LCZ696 (n=4187)
Effect of LCZ696 on the two major modes of death in HF

Sudden death

Death due to worsening HF

HR=0.80 (0.68, 0.94)  
P=0.008

HR=0.79 (0.64, 0.98)  
P=0.034

Desai et al. Eur Heart J 2015;36:1990-7
Safety

Pre-defined safety assessments
## PARADIGM-HF: Safety

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypotension (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td>14.0</td>
<td>9.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>symptoms and SBP &lt; 90 mmHg</td>
<td>2.7</td>
<td>1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Renal impairment (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr ≥ 2.5 mg/dl</td>
<td>3.3</td>
<td>4.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Cr ≥ 3.0 mg/dl</td>
<td>1.5</td>
<td>2.0</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Hyperkalaemia (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺ &gt; 5.5 mmol/l</td>
<td>16.2</td>
<td>17.4</td>
<td>0.15</td>
</tr>
<tr>
<td>K⁺ &gt; 6.0 mmol/l</td>
<td>4.3</td>
<td>5.6</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Cough (%)</strong></td>
<td>11.3</td>
<td>14.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Angioedema:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not hospitalized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment/antihistamines n, (%)</td>
<td>10 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Catecholamines/corticosteroids n, (%)</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No airway compromise n, (%)</td>
<td>3 (0.1)</td>
<td>1 (0.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise n, (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
</tbody>
</table>

Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA.

ACE, angiotensin converting enzyme; MRA, mineralocorticoid receptor antagonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction

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**Recommendation for sacubitril/valsartan in ESC 2016 heart failure guidelines**

<table>
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<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
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<td>Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA</td>
<td>I</td>
<td>B</td>
</tr>
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</table>

*Ponikowski et al. Eur Heart J 2016*
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

In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.¹⁹
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; CRT, cardiac resynchronisation therapy; H-ISDN, hydralazine/isosorbide dinitrate; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid (aldosterone) receptor antagonist; VAD, ventricular assist device
Treatment of HF-REF 2017?

ARNI, angiotensin receptor neprilysin inhibition; CABG, coronary artery bypass graft surgery; CRT, cardiac resynchronisation therapy; H-ISDN, hydralazine/isosorbide dinitrate; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid (aldosterone) receptor antagonist; VAD, ventricular assist device.
Using sacubitril/valsartan

- **Why:** Is a superior alternative to an ACEi/ARB.
- **Who:** HFrEF (LVEF ≤40%), NYHA class II-IV, treated with an ACE-I/ARB, SBP ≥100 mmHg, eGFR >30 ml/min/1.73 m², K⁺ <5.2mmol/l.
- **When:** Sooner rather than later – rapid onset of benefit.
- **How:** 36 hour wash-out if on ACEi. Up-titrate to target dose of 97/103 mg (=200 mg of LCZ696).
- **Where:** Outpatient setting.
- **Monitoring:** For hypotension (rarely serious), angioedema (rare). Remember – is also a RAAS blocker (renal dysfunction, hyperkalaemia).
What is new in the treatment of HF-REF?

- **Drugs:**
  - Ivabradine (USA/Canada)
  - Sacubitril/valsartan
  - Intravenous iron

- **Devices:**
  - No major update
Intravenous iron therapy in heart failure

Dietary iron

Utilisation

Duodenum (average, 1–2 mg per day)

Utilisation
Other iron-containing enzymes (100 mg)

Bone marrow (300 mg)

Bone marrow (300 mg)

Muscle (myoglobin) (300 mg)

Plasma transferrin (3 mg)

Liver parenchyma (1000 mg)

Storage iron

Circulating erythrocytes (Hb) (1800 mg)

Reticuloendothelial macrophages (600 mg)

Iron loss 1–2 mg/day

Sloughed mucosal cells, desquamation, menstruation, other blood loss

FAIR-HF
Ferric carboxymaltose Assessment in patients with Iron deficiency and chronic Heart Failure

- **Design:** Multicentre, randomised, placebo-controlled; blinded?

- **Inclusion criteria:** N=459. NYHA class II & LVEF ≤40% or NYHA III & ≤45%. Hb: 9.5–13.5 g/dL. Iron deficiency (serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%)

- **Intervention:** 200 mg of IV iron or infused saline every 4 weeks up to week 24

- **Primary endpoints:** 1) Self-reported Patient Global Assessment at week 24 and 2) NYHA functional class at week 24

- **Secondary endpoints:** 6-minute walk test; KCCQ & EQ-5D at weeks 4, 12, and 24.
CONFIRM-HF
ferric CarboxymaltOse evaluation on performance in patients with iron deficiency in combination with chronic Heart Failure

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

Clinicaltrials.gov identifier: NCT01453608

6 MWT Difference
FCM vs placebo 33 (SE11) metres

P=0.002

Week 24
**Recommendation for iv iron in ESC 2016 heart failure guidelines**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
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<tbody>
<tr>
<td>Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin &lt;100 μg/L, or ferritin between 100–299 μg/L and transferrin saturation &lt;20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.</td>
<td>Ila</td>
<td>A</td>
</tr>
</tbody>
</table>

FCM = ferric carboxymaltose; HF, heart failure; HFrEF, heart failure with reduced ejection fraction

*Ponikowski et al. Eur Heart J 2016*
Heart failure with reduced ejection fraction

- New guidelines
- New evidence since the guidelines
- Emerging treatments
Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure (EFFECT-HF)

Dirk J. van Veldhuisen, Piotr Ponikowski, Marco Metra, Michael Böhm, Peter van der Meer, Artem Doletsky, Adriaan A. Voors, Iain MacDougall, Bernard Roubert, Stefan D. Anker, Alain Cohen Solal for the EFFECT-HF Investigators.

Sponsor: Vifor Pharma Ltd.

Dept. of Cardiology, University Medical Center Groningen
Groningen, The Netherlands
Primary endpoint analysis: Change in peak VO$_2$ from baseline to Week 24

**Full analysis set (N=172)**

Contrast FCM vs placebo for $\Delta$ pVO$_2$:
LS means $\pm$ SE difference of 1.04 $\pm$ 0.44 mL/kg/min
(95% CI: 0.164, 1.909)

$P=0.02$

**Per-protocol set (N=146)***

Contrast FCM vs placebo for $\Delta$ pVO$_2$:
LS means $\pm$ SE difference of 1.32 $\pm$ 0.51 mL/kg/min
(95% CI: 0.306, 2.330)

$P=0.01$

*population consisted of all subjects who, in addition to the full analysis set criteria, had no major protocol violations.

FCM, ferric carboxymaltose; LOCF, last observation carried forward; LSM, least-square means
What about oral iron?

**Oral Iron Repletion effects on Oxygen UpTake in Heart Failure (IRONOUT)**

**Gregory D. Lewis, M.D.**
on behalf of
The NHLBI Clinical Heart Failure Network

- 225 patients with NYHA Class II-IV HF symptoms and LVEF≤0.40
- Serum ferritin between 15-100 ng/ml or serum ferritin between 100-299 ng/ml with transferrin saturation <20%
- Hemoglobin 9.0-13.5 g/dL in females, 9.0-15 g/dL in males
- Stable evidence-based medical therapy for HF
- Able to perform cycle/treadmill exercise testing with achievement of a respiratory exchange ratio of at least 1.0

Oral iron polysaccharide
150 mg bid
New mortality/morbidity trials with intravenous iron

**IRON-MAN¹**

- **Population:** 1300 patients. LVEF <45%, NYHA class II – IV. Iron deficient - TSAT <20% and/or ferritin <100 ug/L. Evidence of higher risk: current or recent HF hospitalisation OR out-patients with NT-proBNP >250 ng/L in (>1,000 ng/L in AF) (or BNP of > 75 pg/mL/300 pg/mL)
- **Intervention:** Intravenous iron (III) isomaltoside vs placebo.
- **Primary endpoint:** CV death or HF hospitalisation.

**Affirm-AHF²**

- **Population:** 1100 patients; hospitalized for acute HF; EF <50%; serum ferritin <100 ng/mL or ≤299 ng/mL if transferrin saturation (TSAT) <20%. Hb must be >8g/dL.
- **Intervention:** Intravenous ferric carboxymaltose vs placebo.
- **Primary endpoint:** CV death and HF hospitalization: at 52 weeks (recurrent events).

ClinicalTrials.gov ¹NCT02642562 ²NCT02937454
What is new in the treatment of HF-REF?

- **Drugs:**
  - Ivabradine (USA/Canada)
  - Sacubitril/valsartan
  - Intravenous iron

- **Devices:**
  - No major update
Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

1116 non-ischaemic HF patients in NYHA class II/III with LVEF ≤35% (ACEi/ARB 96%, BB 92%, MRA 58%, CRT 58%)

All-cause mortality

Hazard ratio, 0.87 (95% CI, 0.68–1.12)
P = 0.28

significant treatment-by-subgroup interaction for age (P = 0.009)

Heart failure with reduced ejection fraction

- New guidelines
- New evidence since the guidelines
- Emerging treatments
What else is in the pipeline? (Phase 3 mortality/morbidity trials)

**COMMANDER-HF**

- **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

**VICTORIA**

- **Hypothesis:** Vericiguat will be superior to placebo, added to SOC, in patients with symptomatic chronic HF-REF (LVEF <45%)
- **Population:** 4872 patients; iv therapy for exacerbation of HF in past 3 months/hospitalization within 6 months and elevated NPs
- **Primary endpoint:** CV death or HF hospitalization: target 1561 events (powered for CV death).

¹NCT01877915 ²NCT02861534
Omecamtiv mecarbil – a cardiac-specific myosin activator

Mechanochemical Cycle of Myosin

OM increases the entry rate of myosin into the tightly-bound, force-producing state with actin

“More hands pulling on the rope”

- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt_{max}
- No increase in MVO_{2}

Inhibit proximal tubular glucose reabsorption, cause diuresis and natriuresis, lower BP and reduce weight. Also renoprotective (in diabetes)?
Phase-3 Mortality/morbidity trials

Jardiance® (empagliflozin) to be studied for the treatment of people with chronic heart failure

- New studies will evaluate the effect of Jardiance® for the treatment of chronic heart failure
- There are approximately 26 million people worldwide, and 5.7 million people in the U.S., suffering from chronic heart failure
- The studies build on results from the landmark EMPA-REG OUTCOME® trial

Ingelheim, Germany and Indianapolis, US, 19 April, 2016 – Boehringer Ingelheim and Eli Lilly and Company

AstraZeneca announces two new phase IIIb trials for Forxiga in chronic kidney disease and chronic heart failure

Published
12 September 2016
Recent disappointments

- **SERVE-HF:** Adaptive Servo-Ventilation
- **ATMOSPHERE:** Renin inhibition (aliskiren)
- **REM-HF:** Remote monitoring/management
What is new in treatment?

- HF with reduced ejection fraction (HFrEF)
- HF with preserved ejection fraction (HFpEF)
- Acute heart failure
HF with preserved EF (HF-PEF)

We still do not have evidence-based treatment

McMurray et al. Eur Heart J 2012;33:1787–1847
Key large RCTs in HF-PEF

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

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

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

**TOPCAT**
- HR (CI) 0.89: (0.77–1.04) P=0.14
- 351/17231 (20.4)%
- 320/1722 (18.6)%
PARAGON-HF
Prospective comparison of ARni with Arbit 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

Randomization 1:1

LCZ696 200 mg BID

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
What is new in treatment?

- HF with reduced ejection fraction (HFrEF)
- HF with preserved ejection fraction (HFpEF)
- Acute heart failure
Acute heart failure

Ultrafiltration: Aqual natriuresis

Bilevel or continuous positive airway pressure: Preload reduction

Nitrates, nitroprusside, dobutamine: Arterial vasodilation

Dobutamine, dopamine, milrinone: Increased inotropy

Nitrates, morphine: Venodilation

Furosemide: Natriuresis
New treatments in acute heart failure

International Non-proprietary Name (INN)

carperitide
nesiritide
ularitide

Relaxin
Anti-oxidant/
Anti-apoptotic

Anti-proliferative/
Anti-inflammatory

Vasodilator
What else is in the pipeline? (Phase 3 mortality/morbidity trials)

TRUE-AHF\(^1\)

- **Hypothesis:** Ularitide will lead to clinical improvement in patients with acute "decompensated" HF (ADHF).
- **Population:** ~2000 patients hospitalized with ADHF SBP ≥110 mmHg. Dyspnoea at rest despite ≥40 mg furosemide.
- **Intervention:** placebo or ularitide 15 ng/kg/min started within 12 hours of admission for 48 hrs.
- **Co-primary endpoint:** 1) moderate or marked improvement in a clinical composite outcome at 6 h, 24 h and 48 h. 2) CV mortality.

RELAX-AHF \(^2\)

- **Hypothesis:** Serelaxin will lead to clinical improvement in patients with acute "decompensated" HF (ADHF).
- **Population:** ~6,400 patients; hospitalized with ADHF SBP ≥125 mmHg. Dyspnoea at rest/minimum exertion despite ≥40 mg furosemide.
- **Intervention:** Placebo or serelaxin 30 µ/kg/d started within 16 hours of admission for 48 hrs.
- **Co-primary endpoint:** 1) All-cause mortality at 180 days. 2) Worsening HF day 5

1. NCT01661634 (https://clinicaltrials.gov/ct2/show/NCT01661634)
2. NCT01870778 (https://clinicaltrials.gov/ct2/show/NCT01870778)
Rationale for and design of the TRUE-AHF trial: the effects of ularitide on the short-term clinical course and long-term mortality of patients with acute heart failure

Milton Packer¹*, Richard Holcomb², William T. Abraham³, Stefan Anker⁴, Kenneth Dickstein⁵, Gerasimos Filippatos⁶, Henry Krum⁷, Aldo P. Maggioni⁸, John J.V. McMurray⁹, Alexandre Mebazaa¹⁰, Christopher O’Connor¹¹, Frank Peacock¹², Piotr Ponikowski¹³, Frank Ruschitzka¹⁴, Dirk J. van Veldhuisen¹⁵, and Johannes Holzmeister¹⁴,¹⁶, on behalf of the TRUE-AHF Investigators and Committees
TRUE-AHF: Co-primary endpoint

- **Ularitide**: 236 deaths
- **Placebo**: 225 deaths

**HR = 1.03**

(96% CI: 0.85-1.25)

**P = 0.75**

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Ularitide</th>
<th>Placebo</th>
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<tr>
<td>1088</td>
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</tbody>
</table>
TRUE-AHF: Co-primary endpoint

- Improved
- Unchanged
- Worse

P=0.82
Acute heart failure trials – new drugs

Milrinone
Tolvaptan
Tezosentan
Levosimendan
Adenosine antagonists
Nesiritide
Ularitide

REST IN PEACE
GUIDE-IT: NT proBNP guided therapy after acute HF hospitalization

- Hospitalization for heart failure
  - LVEF ≤ 40 within 12 months
  - NTproBNP > 2000 pg/mL or BNP > 400 pg/mL during index hospitalization

- Randomized within 2 weeks of hospital discharge

- Usual Care
  - N= 550

- Follow up: 2 wks, 6 mos, 12 mos, 18 mos, 24 mos

- Changes in therapy

- Endpoints: All-cause mortality
  - Total days alive and out of hospital during follow-up
  - CV mortality or CV hospitalization
  - Safety
  - Health related quality of life
  - Resource utilization, costs, cost-effectiveness

**Stopped for futility September 23, 2016**
Chronic heart failure: Recent advances

- A new treatment (an ARNI) has potentially replaced one of the current gold-standards (an ACE inhibitor)
- Confirmatory study with intravenous iron (CONFIRM-HF) and two new mortality/morbidity studies planned/underway
- Many more trials of novel therapies underway including a NOAC, SGLT2 inhibitors, a soluble guanylate cyclase stimulator and a selective cardiac myosin activator; also two influenza vaccination trials
- Still no breakthrough in HF-PEF but new trial with an ARNI ongoing (PARAGON-HF)
AHF: summary and conclusions

• Current treatment is not based on robust evidence (i.e. based upon placebo-controlled RCTs).

• Several disappointing trials in acute "decompensated" HF: milrinone, levosimendan, tezosentan, nesiritide, tolvaptan, adenosine antagonists, ultrafiltration

• Large trial with ularitide disappointing

• Relaxin looks more promising and a large confirmatory trial is underway

• Several other drugs at an earlier stage of development.
## PARADIGM-HF: Intensive care management

### Intensive management in hospital

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 N=4187 n (%)</th>
<th>Enalapril N=4212 n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients requiring intensive care</strong></td>
<td>549 (13.1)</td>
<td>623 (14.8)</td>
<td>0.87 (0.78, 0.98) P=0.019</td>
</tr>
<tr>
<td><strong>Total number of stays in intensive care</strong></td>
<td>768</td>
<td>879</td>
<td>0.82 (0.72, 0.94) P=0.005</td>
</tr>
<tr>
<td><strong>Patients receiving IV positive inotropic drugs</strong></td>
<td>161 (3.8%)</td>
<td>229 (5.4%)</td>
<td>0.69 (0.57, 0.85) P &lt; 0.001</td>
</tr>
</tbody>
</table>
What about other outcomes?
PARADIGM-HF: Pre-specified endpoints

- **Primary**: Cardiovascular death or heart failure hospitalization
  - Cardiovascular death
  - Heart failure hospitalization

- **Secondary**:
  - Death from any cause
  - KCCQ (CSS - symptoms and physical limitations)
  - New onset atrial fibrillation
  - Decline in renal function
What about the patient’s perspective?

So far I’ve discussed death, admission, ED visits and treatment changes made by physicians - but the patient lives with heart failure every day.
Kansas City Cardiomyopathy Questionnaire (KCCQ)

23 items covering 5 domains

- Symptoms
- Physical limitation
- Self-efficacy
- Quality of life
- Social interference

Flynn K et al. Am Heart J. 2012;163:88-94
KCCQ: Significance of a 5-point change

- A 5-point change in KCCQ overall score corresponds to:
  - 112 metre change in 6-minute walking distance and
  - 2.50 ml/kg/min change in peak VO₂ in HF-REF patients

- A 5-point decrease in KCCQ overall score corresponds to a deterioration in the patient’s condition

Flynn K et al. Am Heart J. 2012;163:88-94
PARADIGM-HF: Percent of patients with at least 5 Points deterioration in KCCQ clinical summary score*

- **Odds ratio (Month 8):** 0.82 (0.74, 0.90), P<0.001
- **Number needed to treat (Month 8):** 23

Clinical summary score based on the physical limitation and total symptom score domains. The analysis included all patients with at least one KCCQ data. For patients who died the KCCQ scores are imputed by zero at all subsequent scheduled visits.

* Post hoc analysis
1116 non-ischaemic HF patients in NYHA class II/III with LVEF ≤35% (ACEi/ARB 96%, BB 92%, MRA 58%, CRT 58%)

All-cause mortality

Hazard ratio, 0.87 (95% CI, 0.68–1.12)  
P = 0.28

significant treatment-by-subgroup interaction for age (P = 0.009)
Heart failure with reduced ejection fraction

- New guidelines, new evidence
- Emerging treatments
What’s in the pipeline?

Focus on on-going large-scale mortality/morbidity outcome studies
MEDICAL INTELLIGENCE

CURRENT CONCEPTS

Cardiac Decompensation

ALBERTO RAMÍREZ, M.D., AND WALTER H. ABELMANN, M.D.

THE NEW ENGLAND JOURNAL OF MEDICINE  Feb. 28, 1974

- Morphine
- Oxygen (NIV)
- Loop diuretic (tourniquet/phlebotomy)
- Inotropes (digitalis/aminophylline/isoproterenol)
- Nitroglycerin/nitroprusside/phenolamine
- Cardioversion/pacing/IABP

Plus ça change, plus c’est la même chose
• **Hypothesis:** Ularitide will lead to clinical improvement in patients with acute HF.

• **Population:** 2,157 patients 18-85 yr hospitalized with AHF (dyspnoea at rest, CXR evidence of HF and BNP >500 pg/mL or NT-pro BNP >2000 pg/mL); SBP ≥110 mmHg. Dyspnoea at rest despite ≥40 mg furosemide.

• **Intervention:** Placebo or ularitide 15 ng/kg/min started within 12 hours of admission for 48 hrs.

• **Co-primary endpoint:** 1) moderate or marked improvement in a clinical composite outcome ("Packer") at 6 h, 24 h and 48 h. 2) CV mortality.

NCT01661634 (https://clinicaltrials.gov/ct2/show/NCT01661634)
RCT-IVVE: Influenza Vaccine to prevent adverse Vascular Events

- **Hypothesis:** Influenza vaccine more effective than placebo in preventing CV events in patients with HF.
- **Population:** 3500 patients; HF NYHA class II-IV
- **Intervention:** Trivalent influenza vaccine vs. placebo
- **Primary endpoint:** CV death, MI, stroke or hospitalizations for heart failure
- **Status:** Recruiting.

NCT02762851
Hypothesis: High dose trivalent influenza vaccine more effective than standard dose quadrivalent influenza vaccine.

Population: 9300 patients; hospitalization for myocardial infarction within 1 year of enrolment OR a history of hospitalization for heart failure within 2 years of enrolment plus additional risk factors.

Intervention: High vs standard dose vaccine.

Primary endpoint: All-cause death or cardiopulmonary hospitalization.

Status: Recruiting.
Urodilatin is synthesized in the distal tubule cells...is luminally secreted...binds downstream in the inner medullary collecting duct to NPR-A and acts via cGMP...and inhibits Na⁺ reabsorption
Summary of the pharmacological effects of urodilatin/ularitide

- **Haemodynamic (vasodilation)**
  - veins
  - arteries

- **Bronchodilation**

- **Neurohumoral**
  - ↓ RAAl
  - ↓ Aldosterone

- **Diuresis**
  - ↑ Natriuresis
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

SIRIUS-1

• Phase 2a randomised, double-blind, ascending-dose study. 24 patients with AHF received 24 hour IV infusion of placebo or ularitide at 7.5, 15, or 30 ng/kg/min in addition to standard therapy

Sirius-2

• Phase 2b placebo-controlled, double-blind, parallel-group study; 221 AHF patients randomized to 1 of 3 different ularitide doses of 7.5 ng/kg/min (n=60), 15 ng/kg/min (n=53) and 30 ng/kg/min (n=55) or to placebo (N=53), administered in addition to standard therapy

### SIRIUS 1 (n=24)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>More patients in each ularitide group had marked/moderate improvement over baseline in self-assessed dyspnoea at 6 hours than in the placebo group</td>
<td></td>
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<tr>
<td>Proportion of subjects with marked or moderate improvement was greater in the 15 and 30 ng/kg/min groups than in the 7.5 ng/kg/min group</td>
<td></td>
</tr>
<tr>
<td>Mortality at day 30 was 5.6% (1 of 18 patients) across the three ularitide groups and 16.7% (1 of 6 patients) in the placebo group</td>
<td></td>
</tr>
<tr>
<td>The most frequently reported AEs were hypotension, a confused state, restlessness and dyspnoea</td>
<td></td>
</tr>
</tbody>
</table>

### SIRIUS 2 (n=221)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 hours all 3 ularitide doses produced greater decreases in PCWP vs. placebo</td>
<td></td>
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<tr>
<td>At 6 hours, 39.7%, 47.1% and 45.5% of subjects, respectively, in the 7.5, 15, and 30 ng/kg/min dose groups had marked/moderate improvement in self-assessed dyspnoea vs. 24.5% with placebo (p &lt;0.05 for each dose).</td>
<td></td>
</tr>
<tr>
<td>LOS in the 15 and 30 ng/kg/min groups was 122 and 158 hours, respectively vs. 201 and 192 hours in the placebo and 7.5 ng/kg/min groups</td>
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<tr>
<td>Mortality at day 30 was 3% in the 3 ularitide groups vs.13.2% with placebo</td>
<td></td>
</tr>
<tr>
<td>The most frequent drug-related AEs across the 3 ularitide groups were hypotension and dose-dependent decreases in blood pressure</td>
<td></td>
</tr>
</tbody>
</table>
Acute heart failure: an evidence-free zone
Rationale and Design of the GUIDE-IT Study

Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure

G. Michael Felker, MD, MHS,*† Tariq Ahmad, MD, MPH,*† Kevin J. Anstrom, PhD,† Kirkwood F. Adams, MD,‡ Lawton S. Cooper, MD, MPH,§ Justin A. Ezekowitz, MB BCH, MSc,|| Mona Fiuzat, PHARM D,*† Nancy Houston-Miller, RN, BSN,¶ James L. Januzzi, MD,# Eric S. Leifer, PhD,§ Daniel B. Mark, MD, MPH,*† Patrice Desvigne-Nickens, MD,§ Gayle Paynter, BS, RN,† Ileana L. Piña, MD, MPH,** David J. Whellan, MD, MHS, Christopher M. O’Connor, MD*†

J Am Coll Cardiol HF 2014;2:457-65
GUIDE-IT: NT proBNP guided therapy after acute HF hospitalization

**Screening**
- Hospitalization for heart failure
  - LVEF ≤ 40 within 12 months
  - NTproBNP > 2000 pg/mL or BNP > 400 pg/mL during index hospitalization

**Randomization**
- Randomized within 2 weeks of hospital discharge
  - Usual Care
    - N=550
  - Biomarker Guided
    - NTproBNP < 1000 pg/mL
    - N=550

**Follow-up**
- Follow up: 2 wks, 6 wks, 3 months, then Q3 month for 12-24 mos
- Additional 2 week follow up after changes in therapy

**Endpoints**
- Primary endpoint: Time to CV death or first HF hospitalization
- Secondary Endpoints: All-cause mortality
  - Total days alive and out of hospital during follow-up
  - CV mortality or CV hospitalization
  - Safety
  - Health related quality of life
  - Resource utilization, costs, cost-effectiveness
What else is in the pipeline? (Phase 3 mortality/morbidity trials)

**RELAX-AHF**

- **Hypothesis:** Serelaxin will lead to clinical improvement in patients with acute "decompensated" HF (ADHF).
- **Population:** ~6,400 patients; hospitalized with ADHF SBP ≥125 mmHg. Dyspnoea at rest/minimum exertion despite ≥40 mg furosemide.
- **Intervention:** Placebo or serelaxin 30 µ/kg/d started within 16 hours of admission for 48 hrs.
- **Co-primary endpoint:** 1) All-cause mortality at 180 days. 2) Worsening HF day 5

1. NCT01870778 (https://clinicaltrials.gov/ct2/show/NCT01870778)
2. NCT01661634 (https://clinicaltrials.gov/ct2/show/NCT01661634)

**TRUE-AHF**

- **Hypothesis:** Ularitide will lead to clinical improvement in patients with acute "decompensated" HF (ADHF).
- **Population:** ~2000 patients hospitalized with ADHF SBP ≥110 mmHg. Dyspnoea at rest despite ≥40 mg furosemide.
- **Intervention:** Placebo or ularitide 15 ng/kg/min started within 12 hours of admission for 48 hrs.
- **Co-primary endpoint:** 1) moderate or marked improvement in a clinical composite outcome at 6 h, 24 h and 48 h. 2) CV mortality.
**What else is in the pipeline?**
*(Phase 3 mortality/morbidity trials)*

### RELAX-AHF 2¹
- **Hypothesis:** Serelaxin will lead to clinical improvement in patients with acute "decompensated" HF (ADHF).
- **Population:** ~6,400 patients; hospitalized with ADHF SBP ≥125 mmHg. Dyspnoea at rest/minimum exertion despite ≥40 mg furosemide.
- **Intervention:** Placebo or serelaxin 30 µ/kg/d started within 16 hours of admission for 48 hrs.
- **Co-primary endpoint:** 1) All-cause mortality at 180 days. 2) Worsening HF day 5

1. NCT01870778 (https://clinicaltrials.gov/ct2/show/NCT01870778)
2. NCT01661634 (https://clinicaltrials.gov/ct2/show/NCT01661634)

### TRUE-AHF²
- **Hypothesis:** Ularitide will lead to clinical improvement in patients with acute "decompensated" HF (ADHF).
- **Population:** ~2000 patients hospitalized with ADHF SBP ≥110 mmHg. Dyspnoea at rest despite ≥40 mg furosemide.
- **Intervention:** placebo or ularitide 15 ng/kg/min started within 12 hours of admission for 48 hrs.
- **Co-primary endpoint:** 1) moderate or marked improvement in a clinical composite outcome at 6 h, 24 h and 48 h. 2) CV mortality.
Relaxin: RELAX-AHF

- Anti-oxidant/
  Anti-apoptotic

- Anti-proliferative/
  Anti-inflammatory

Vasodilator
Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

John R Teerlink, Gad Cotter, Beth A Davison, G Michael Felker, Gerasimos Filippatos, Barry H Greenberg, Piotr Ponikowski, Elaine Unemori, Adriaan A Voors, Kirkwood F Adams Jr, Maria I Dorobantu, Liliana R Grinfeld, Guillaume Jondeau, Alon Marmor, Josep Masip, Peter S Pang, Karl Werdan, Sam L Teichman, Angelo Trapani, Christopher A Bush, Rajnish Saini, Christoph Schumacher, Thomas M Severin, Marco Metra, for the RELAXin in Acute Heart Failure (RELAX-AHF) Investigators

Lancet 2013; 381: 29–39
RELAX-AHF
RELAXin in Acute Heart Failure trial

• **Hypothesis:** Serelaxin will improve dyspnoea and other outcomes, compared to placebo in patients with AHF.

• **Population:** 1161 patients with acute HF. Must have dyspnoea, had ≥40 mg furosemide & be randomized within 16 h of presentation. Also required: CXR congestion, increased BNP/NT pro BNP, eGFR 30-75ml/min/1.73m² and SBP >125 mm Hg. Nitrates allowed if SBP >150mm Hg.

• **Intervention:** 48-h intravenous infusions of placebo or serelaxin (30 μg/kg per day).

• **Co-primary endpoints:** 1) Change in dyspnoea (VAS AUC) from BL to day 5 and 2) proportion of patients with moderate or marked dyspnoea improvement measured by Likert scale during the first 24 h.
RELAX-AHF: Primary endpoint – dyspnoea AUC analysis

A

- Serelaxin (n=581): AUC with serelaxin, 2756 (SD2588) mm×h
- Placebo (n=580): AUC with placebo, 2308 (SD3082) mm×h

p=0.007
RELAX-AHF: Co-primary endpoint – dyspnoea Likert scale

- Placebo-Serelaxin 6 h
  - Markedly improved: 22.7%
  - Moderately improved: 26.0%
  - Minimally improved: 37.5%
  - No change: 16.4%
  - Minimally worsened: 24.7%
  - Markedly worsened: 8.7%
  - Total: 100%

- Placebo-Serelaxin 12 h
  - Markedly improved: 28.0%
  - Moderately improved: 33.9%
  - Minimally improved: 35.0%
  - No change: 14.5%
  - Minimally worsened: 7.8%
  - Markedly worsened: 16.4%
  - Total: 100%

- Placebo-Serelaxin 24 h
  - Markedly improved: 36.4%
  - Moderately improved: 42.1%
  - Minimally improved: 22.8%
  - No change: 7.3%
  - Minimally worsened: 63.1%
  - Markedly worsened: 25.8%
  - Total: 100%

Significance levels:
- Placebo-Serelaxin 6 h vs. Placebo-Serelaxin 12 h: p=0.113
- Placebo-Serelaxin 12 h vs. Placebo-Serelaxin 24 h: p=0.051
- Placebo-Serelaxin 24 h vs. Placebo-Serelaxin 6 h: p=0.086
CV death or re-hospitalization for HF/RF at day 60

Placebo: 75 events (13.0%)
Serelaxin: 76 events (13.2%)

HR 1.02 (95% CI 0.74-1.41)
p=0.89

HF/renal re-admissions
50 placebo
60 serelaxin
RELAX-AHF: All-cause mortality

1161 patients, hospitalised for acute HF, diuretic treatment, still dyspnoeic at rest/minimal exertion, pulmonary congestion on CXR, elevated BNP/NT proBNP, renal dysfunction, SBP >125 mm Hg, randomised within 16 hr.

Teerlink et al Lancet 2012
RELAX-AHF2: Study Design

Randomized, placebo-controlled study in AHF

**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 2° efficacy endpoints**
- All-cause mortality through a follow-up period of day 180
- Worsening heart failure (W HF) 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=2.5% (one-sided), assuming placebo CV death rate of 9%. 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)
RELAX-AHF-2

• **Hypothesis:** Serelaxin will lead to clinical improvement in patients with acute HF

• **Population:** ~6,800 patients; hospitalized with AHF; persistent dyspnoea at rest/minimum exertion despite ≥40 mg furosemide; pulmonary congestion on CXR; BNP ≥500 pg/ml/NT-proBNP ≥2000 pg/ml (patients ≥ 75 yr or AF: BNP ≥ 750 pg/ml/NT-proBNP ≥ 3,000 pg/ml); SBP ≥125 mmHg.

• **Intervention:** Placebo or serelaxin 30 µ/kg/d started within 16 hours of admission for 48 hrs.

• **Co-primary endpoint:** 1) All-cause mortality at 180 days. 2) Worsening HF day 5

NCT01870778 (https://clinicaltrials.gov/ct2/show/NCT01870778)
Anticoagulation in heart failure

ACS

Stroke
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.
What else is in the pipeline? (Phase 3 mortality/morbidity trials)

**COMMANDER-HF**

- **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

**VICTORIA**

- **Hypothesis**: Vericiguat will be superior to placebo, added to SOC, in patients with symptomatic chronic HF-REF (LVEF <45%)
- **Population**: 4872 patients; iv therapy for exacerbation of HF in past 3 months/hospitalization within 6 months and elevated NPs
- **Primary endpoint**: CV death or HF hospitalization: target 1561 events (powered for CV death).

1NCT01877915 2NCT02861534
Other methods to increase cGMP: Soluble guanylyl cyclase (sGC) stimulation
Original Investigation

Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction

The SOCRATES-REDUCED Randomized Trial

Mihai Gheorghiade, MD; Stephen J. Greene, MD; Javed Butler, MD, MPH, MBA; Gerasimos Filippatos, MD; Carolyn S. P. Lam, MBBS; Aldo P. Maggioni, MD; Piotr Ponikowski, MD; Sanjiv J. Shah, MD; Scott D. Solomon, MD; Elisabeth Kraigher-Krainer, MD; Eliana T. Samano, MD; Katharina Müller, DiplStat; Lothar Roessig, MD; Burkert Pieske, MD; for the SOCRATES-REDUCED Investigators and Coordinators

Omecamtiv mecarbil

**ATOMIC-AHF**
Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure

**COSMIC-HF**
Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure

intravenous  oral
Effects of omecamtiv mecarbil (OM)

**Stroke Volume**
- PK-Titration Group
- Placebo, 25 mg, 25 mg (no titration), 25 → 50 mg, All PK Titration
- LS Mean (SE) Change (mL)
  - Placebo: p = 0.004
  - 25 mg (no titration): p = 0.022

**LVESV**
- Placebo, 25 mg, 25 mg (no titration), 25 → 50 mg, All PK Titration
- LS Mean (SE) Change (mL)
  - Placebo: p = 0.019
  - 25 mg: p = 0.005

**Heart Rate**
- Placebo, 25 mg, 25 mg (no titration), 25 → 50 mg, All PK Titration
- LS Mean (SE) Change (bpm)
  - Placebo: p = 0.218
  - 25 → 50 mg: p = 0.007

**NT-proBNP**
- Placebo, 25 mg, 25 mg (no titration), 25 → 50 mg, All PK Titration
- LS Mean (SE) Change (pg/mL)
  - Placebo: p = 0.021
  - All PK Titration: p = 0.007
The decision to advance omecamtiv mecarbil into Phase 3 was based on positive results from COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure), a Phase 2 trial evaluating the treatment in patients with chronic heart failure, which were presented as a Late-Breaking Clinical Trial at the American Heart Association (AHA) Scientific Sessions in November 2015. This first chronic dosing trial of omecamtiv mecarbil met its primary pharmacokinetic objective and demonstrated significant improvement in all pre-specified secondary measures of cardiac function in the treatment group employing pharmacokinetic-based dose titration.
IRON-MAN: Intravenous iron (III) isomaltoside

Effectiveness of Intravenous iron treatment vs standard care in patients with heart failure and iron deficiency: a randomised, open-label multicentre trial (IRON-MAN)

CV mortality or hospitalisation for worsening heart failure (analysis will include first and recurrent hospitalisations)

- 1300 patients
- LVEF <45%, NYHA class II - IV
- Iron deficient - TSAT <20% and/or ferritin <100 ug/L
- Evidence of higher risk:
  - Current or recent (within 6 months) HF hospitalisation
  - Out-patients with NT-proBNP >250 ng/L in sinus rhythm or >1,000 ng/L in AF (or BNP of > 75 pg/mL/300 pg/mL)
Affirm-AHF: Ferric carboxymaltose in patients with acute heart failure and iron deficiency

- **Hypothesis:** Intravenous iron will reduce morbidity and mortality in patients with acute HF and iron deficiency.

- **Population:** 1100 patients; hospitalized for acute HF; EF <50%; serum ferritin <100 ng/mL or ≤299 ng/mL if transferrin saturation (TSAT) <20%. Hb must be >8g/dL.

- **Intervention:** Ferric carboxymaltose vs placebo.

- **Primary endpoint:** HF hospitalizations or CV death up to 52 weeks after randomization; recurrent events

- **Status:** Not started
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

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New evidence on prevention
New approaches to reducing blood glucose

Incretins
- (GIP)
- GLP-1

Stimulate insulin release
Inhibit glucagon release

DPP4
Breakdown products

GLP-1 agonists/analogues
e.g. exenatide

DPP4 inhibitors ("gliptins")

Reduce blood glucose
Inhibit renal re-absorption
(SGLT2 inhibitors)

Inhibit gastrointestinal absorption
(α-glucosidase inhib’s)
SGLT-2 inhibitors

Inhibit proximal tubular glucose reabsorption, cause diuresis and natriuresis, lower BP and reduce weight. Also renoprotective (in diabetes)?
EMPA-REG Outcome

7,020 patients with T2DM and CV disease/risk factors

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D.,
David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D.,
Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H.,
Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D.,
and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

EMPA-REG Outcome:
Primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Patients with event/analysed</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>Empagliflozin 490/4687, Placebo 282/2333</td>
<td>0.86</td>
<td>(0.74, 0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>Empagliflozin 172/4687, Placebo 137/2333</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>Empagliflozin 213/4687, Placebo 121/2333</td>
<td>0.87</td>
<td>(0.70, 1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>Empagliflozin 150/4687, Placebo 60/2333</td>
<td>1.24</td>
<td>(0.92, 1.67)</td>
<td>0.1638</td>
</tr>
</tbody>
</table>

Zinman et al. NEJM published on line Sept 17, 2015
EMP A-REG Outcome: Heart failure

Hospitalization for or death from heart failure

HR 0.61
(95% CI 0.47, 0.79)
p = 0.0002

Zinman et al. NEJM published on line Sept 17, 2015
Empagliflozin should be considered in patients with type 2 diabetes order to prevent or delay onset of HF and prolong life.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin should be considered in patients with type 2 diabetes order to prevent or delay onset of HF and prolong life.</td>
<td>Ila</td>
<td>B</td>
</tr>
</tbody>
</table>
SGLT-2 inhibitors

• How do they work?
  – Diuretic/natriuretic effect?
  – Improved myocardial metabolism?
  – Improved renal function?

• Can they be used to treat established HF?
  – Existing trials largely about prevention of incident HF
  – Just HF patients with diabetes or all HF patients?
Jardiance® (empagliflozin) to be studied for the treatment of people with chronic heart failure

- New studies will evaluate the effect of jardiance® for the treatment of chronic heart failure
- There are approximately 26 million people worldwide, and 5.7 million people in the U.S., suffering from chronic heart failure
- The studies build on results from the landmark EMPA-REG OUTCOME® trial

Ingenheim, Germany and Indianapolis, US, 19 April, 2016 – Boehringer Ingelheim and Eli Lilly and Company

AstraZeneca announces two new phase IIIb trials for Forxiga in chronic kidney disease and chronic heart failure

Published
12 September 2016
Remote management of heart failure using implanted devices and formalized follow-up procedures (REM-HF)

Primary endpoint: Death or CV hospitalization

HR 1.01 (0.87-1.18)
P=0.87
PARADIGM-HF: Adverse events leading to permanent study drug discontinuation

- Any adverse event: Enalapril 516, LCZ696 449 (p = 0.03)
- Hypotension: Enalapril 29, LCZ696 36 (p = 0.38)
- Renal reasons: Enalapril 59, LCZ696 29 (p = 0.002)
- Hyperkalaemia: Enalapril 15, LCZ696 11 (p = 0.56)