Heart failure: What’s new in drug therapy?

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BHF Cardiovascular Research Centre,
University of Glasgow & Queen Elizabeth
University Hospital, Glasgow.
Scottish Intercollegiate Guidelines Network (SIGN)
Special Article

The Canadian Cardiovascular Society Heart Failure Companion: Bridging Guidelines to Your Practice

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for the Canadian Cardiovascular Society Heart Failure Guidelines Panels

Canadian Journal of Cardiology 32 (2016) 296—310

15 page guideline!
Treatment of HF with reduced ejection fraction (HF-REF)
What is new in the treatment of HF-REF?

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

- **Devices:**
  - No major update
Positive drug, device and other trials 2001-2016

Angiotensin receptor neprilysin inhibition (ARNI)

Sacubitril-valsartan (LCZ696)

Neprilysin inhibition

AT₁ Receptor blocker
Angiotensin Receptor Neprilysin Inhibition (ARNI)

Sacubitril-valsartan (LCZ696)

Natriuretic peptides
- BK, ADM
- Subs-P, VIP, CGRP

Angiotensin II
- Vasodilation
- Natriuresis
- Diuresis
- Inhibition of pathologic growth/fibrosis

Neprilysin
- Degradation products

AT\textsubscript{1}R Receptor
- Vasoconstriction
- Sodium/water retention
- Fibrosis/hypertrophy

McMurray Eur J Heart Fail. 2015;17:242-7
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 (NTpro ≥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/ ≤5.4mmol/l at randomization

Prior ACEi/ARB use discontinued

# PARADIGM-HF: Baseline Characteristics

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Target dose, mg</th>
<th>Mean daily dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS (1987)*</td>
<td>127</td>
<td>20 bid</td>
<td>18.4</td>
</tr>
<tr>
<td>SOLVD-T (1991)†</td>
<td>1284</td>
<td>10 bid</td>
<td>16.6</td>
</tr>
<tr>
<td>V-HeFT II (1991)</td>
<td>403</td>
<td>10 bid</td>
<td>15.0</td>
</tr>
<tr>
<td>OVERTURE (2002)</td>
<td>2884</td>
<td>10 bid</td>
<td>17.7</td>
</tr>
<tr>
<td>CARMEN (2004)</td>
<td>190 E only</td>
<td>10 bid</td>
<td>16.8</td>
</tr>
<tr>
<td></td>
<td>191 E+Carv</td>
<td>10 bid</td>
<td>14.9</td>
</tr>
<tr>
<td>CIBIS-3 (2005)</td>
<td>505 E first</td>
<td>10 bid</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td>505 Bisop first</td>
<td>10 bid</td>
<td>15.8</td>
</tr>
<tr>
<td>PARADIGM-HF</td>
<td>4212</td>
<td>10 bid</td>
<td>18.9</td>
</tr>
</tbody>
</table>

† N.B. active run-in; 49% reached target dose. *22% reached target dose.
PARADIGM-HF: The primary outcome
PARADIGM-HF: Primary outcome
Cardiovascular death or heart failure hospitalization

HR: 0.80 (0.73, 0.87)
p = 0.0000004

Enalapril (n=4212)
Sacubitril/valsartan (n=4187)

PARADIGM-HF: Primary outcome
Cardiovascular death or heart failure hospitalization

Cumulative Proportion of Patients with Primary End Point (%)

Days after Randomization

HR: 0.80 (0.73, 0.87)  
p = 0.0000004

0.65 (0.45, 0.93)  
P=0.019

At risk
Enalapril: 4212 3883 3579 2922 2123 1488 853 236
Sac/val: 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

PARADIGM-HF: Number of hospital admissions (including repeats) by cause

Number of hospital admissions by cause:
- **All causes**: 4053
- **CV causes**: 2537
- **Worsening HF**: 1079

**Number of hospital admissions**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Enalapril</th>
<th>Sacubitril/valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>4053</td>
<td>3564</td>
</tr>
<tr>
<td>CV causes</td>
<td>2537</td>
<td>2216</td>
</tr>
<tr>
<td>Worsening HF</td>
<td>1079</td>
<td>851</td>
</tr>
</tbody>
</table>

**Relative Risk (RR)**
- **All causes**: RR = 0.84, p < 0.001
- **CV causes**: RR = 0.84, p < 0.001
- **Worsening HF**: RR = 0.77, p < 0.001

PARADIGM-HF: First and repeat heart failure hospitalizations

Patients hospitalised for heart failure

<table>
<thead>
<tr>
<th>Number</th>
<th>Enalapril</th>
<th>Sacubitril/valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 admission</td>
<td>418</td>
<td>367</td>
</tr>
<tr>
<td>2 admissions</td>
<td>143</td>
<td>110</td>
</tr>
<tr>
<td>3 admissions</td>
<td>53</td>
<td>33</td>
</tr>
<tr>
<td>≥4 admissions</td>
<td>44</td>
<td>27</td>
</tr>
</tbody>
</table>

PARADIGM-HF: Cause/mode of death

All causes | CV causes | Sudden | Worsening HF
---|---|---|---
835 | 711 | 693 | 558
311 | 250 | 184 | 147

HR p = 0.84 < 0.001 0.80 < 0.00008 0.80 0.008 0.79 0.034

<table>
<thead>
<tr>
<th></th>
<th>Sacubitril/valsartan (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;90mmHg</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 ≥2.5mg/dl</td>
<td>3.3</td>
<td>4.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Cr ≥3.0mg/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;5.5mmol/l</td>
<td>16.1</td>
<td>17.3</td>
<td>0.15</td>
</tr>
<tr>
<td>K⁺ &gt;6.0mmol/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: not hospitalised</strong></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><strong>Angioedema: hospitalised</strong></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>
PARADIGM-HF: Adverse events leading to permanent study drug discontinuation

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

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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<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>
</tbody>
</table>

ACE, angiotensin converting enzyme; MRA, mineralocorticoid receptor antagonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction
Treatment of HF-REF: The current situation

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; CRT, cardiac resynchronisation therapy; HF-REF, heart failure with reduced ejection fraction; H-ISDN, hydralazine/isosorbide dinitrate; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid (aldosterone) receptor antagonist; VAD, ventricular assist device

Treatment of HF-REF: The future?

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

What is new in the treatment of HF-REF?

- **Drugs:**
  - Ivabradine
  - Sacubitril/valsartan
  - Intravenous iron

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

Dietary iron

Utilisation

Duodenum (average, 1–2 mg per day)

Plasma transferrin (3 mg)

Muscle (myoglobin) (300 mg)

Liver parenchyma (1000 mg)

Storage iron

Utilisation

Other iron-containing enzymes (100 mg)

Bone marrow (300 mg)

Sloughed mucosal cells, desquamation, menstruation, other blood loss

Iron loss 1–2 mg/day

Circulating erythrocytes (Hb) (1800 mg)

Reticuloendothelial macrophages (600 mg)

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

Piotr Ponikowski\textsuperscript{1,2,*}, Dirk J. van Veldhuisen\textsuperscript{3}, Josep Comin-Colet\textsuperscript{4}, Georg Ertl\textsuperscript{5,6}, Michel Komajda\textsuperscript{7}, Viacheslav Mareev\textsuperscript{8}, Theresa McDonagh\textsuperscript{9}, Alexander Parkhomenko\textsuperscript{10}, Luigi Tavazzi\textsuperscript{11}, Victoria Levesque\textsuperscript{12}, Claudio Mori\textsuperscript{12}, Bernard Roubert\textsuperscript{12}, Gerasimos Filippatos\textsuperscript{13}, Frank Ruschitzka\textsuperscript{14}, and Stefan D. Anker\textsuperscript{15}, for the CONFIRM-HF Investigators
CONFIRM-HF: Primary endpoint
- 6MWT at 24 weeks

Difference FCM vs placebo 33 (SE11) metres

P=0.002

Week 24

FCM (N=150)
Placebo (N=151)
CONFIRM-HF: Secondary endpoints

KCCQ over 52 weeks

EQ-5D VAS over 52 weeks
Recommendation for iv iron in ESC 2016 heart failure guidelines

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<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
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)

- 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, respectively)
New evidence on prevention

Prevention is better than cure
Standard vs intensive BP lowering in non-diabetic hypertensives

- 9361 patients ≥50 yrs with SBP 130-180 mmHg and additional CV risk (clinical/subclinical CVD, eGFR 20-60, age ≥75 yrs or FRS for CVD ≥ 15%).
- Target SBP of 140 (standard) vs. 120 mmHg (intensive).

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

Published November 26, 2015
SPRINT: Primary Outcome (CV death, ACS, stroke or HF)

Baseline BP 140/78 mmHg
Decrease in BP 14.8/7.6 mmHg
Median follow-up 3.26 years

Hazard ratio with intensive treatment, 0.75 (95% CI, 0.64–0.89)

No. at Risk
Standard treatment  4683  4437  4228  2829  721
Intensive treatment  4678  4436  4256  2900  779
## SPRINT: Primary outcome and components (event rates and hazard ratios)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Intensive No. of Events</th>
<th>Intensive Rate, %/year</th>
<th>Standard No. of Events</th>
<th>Standard Rate, %/year</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>243</td>
<td>1.65</td>
<td>319</td>
<td>2.19</td>
<td>0.75 (0.64, 0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All MI</td>
<td>97</td>
<td>0.65</td>
<td>116</td>
<td>0.78</td>
<td>0.83 (0.64, 1.09)</td>
<td>0.19</td>
</tr>
<tr>
<td>Non-MI ACS</td>
<td>40</td>
<td>0.27</td>
<td>40</td>
<td>0.27</td>
<td>1.00 (0.64, 1.55)</td>
<td>0.99</td>
</tr>
<tr>
<td>All stroke</td>
<td>62</td>
<td>0.41</td>
<td>70</td>
<td>0.47</td>
<td>0.89 (0.63, 1.25)</td>
<td>0.50</td>
</tr>
<tr>
<td>All HF</td>
<td>62</td>
<td>0.41</td>
<td>100</td>
<td>0.67</td>
<td>0.62 (0.45, 0.84)</td>
<td>0.002</td>
</tr>
<tr>
<td>CVD death</td>
<td>37</td>
<td>0.25</td>
<td>65</td>
<td>0.43</td>
<td>0.57 (0.38, 0.85)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
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 Matteus, 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

SGLT-2 inhibitors

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

Heart failure Hospitalization

Cardiovascular mortality

Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P=0.002

Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P<0.001
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

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

Boehringer Ingelheim

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

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- 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
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.
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 MVO₂

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

**COMMANDER-HF²**
- **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

**VICTORIA³**
- **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).
Other methods to increase cGMP: Soluble guanylyl cyclase (sGC) stimulation
HF with preserved EF (HF-PEF)

We still do not have evidence-based treatment
Key large RCTs in HF-PEF

**PEP-CHF**
- HR (CI) 0.92: (0.70–1.21)
- P=0.55

**CHARM-Preserved**
- HR (CI) 0.89: (0.77–1.03)
- P=0.12

**I-PRESERVE**
- 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**
Prospective 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

- **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)

- **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
MEDICAL INTELLIGENCE

CURRENT CONCEPTS
Cardiac Decompensation

Alberto Ramírez, M.D., and Walter H. Abelmann, M.D.

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

- **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

- **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 µg/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

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Summary and conclusions

- Exciting times in heart failure!
- We continue to make progress in HFREF – new treatment reducing mortality (sacubitril/valsartan)
- New mechanisms and new trials
- Large trial in HFPEF nearly completed enrollment
- Results of two large trials in acute HF imminent