Rapidfire update:
New heart failure therapies & late breaking trials for HFpEF and HFpEF

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Disclosures / COI / RWI / RWA

• Available online: thecvc.ca
Research burns bright
Pathophysiology and Epidemiology

• ....are no substitute for RCT

Robert M Califf @califf001 · Aug 6
Fantastic depiction of why randomization is essential. This should be required reading. @dukeforge Workplace Wellness Programs Don’t Work Well. Why Some Studies Show Otherwise.

Workplace Wellness Programs Don’t Work Well. Why Some Studies Show Otherwise.

Randomized controlled trials, despite their flaws, remain a powerful tool.

By Aaron E. Carroll

Aug. 6, 2018

The gold standard of medical research, the randomized controlled trial, has been taking a bit of a beating lately.
Step 1: Out with the antiquated

...10 million leeches / year....

NY Times 2017
Step 2: in with the new...
Sacubitril / valsartan (HFpEF)

PARAGON
HF-PEF and sacubitril/valsartan

PARAMOUNT
HF-PEF with elevated NPs

No change in QOL

Figure 2: NT-proBNP at 4, 12, and 36 weeks in the LCZ696 and valsartan groups

Solomon, Lancet 2012
Target patient population: ~4,800 patients with symptomatic HF (NYHA Class II–IV) and LVEF ≥45%

PARAGON (HFpEF)

Active run-in period
- Screening
- Valsartan 80 mg BID*
- LCZ696 100 mg BID

Double-blind treatment period
- LCZ696 200 mg BID
- Valsartan 160 mg BID

On top of optimal background medications for comorbidities (excluding ACEIs and ARBs)

Primary outcome: CV death and total (first and recurrent) HF hospitalizations (anticipated ~1,721 primary events)
Mechanisms with SGTL2 inhibitors

Evidence supporting potential mechanisms is sparse

There has been considerable discussion about three potential mechanisms
• Improvements in hemodynamics
• Super-fuel hypothesis
• Improved oxygen delivery

CV, cardiovascular; SGLT2, sodium-glucose cotransporter-2
## Differences in study designs

<table>
<thead>
<tr>
<th></th>
<th>DAPA-HF(^1)</th>
<th>EMPEROR-Reduced(^2)</th>
<th>SOLOIST-WHF</th>
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</thead>
<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td></td>
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<tr>
<td>• Patients with NYHA class II-IV heart failure with Reduced EF (&lt;40%) and elevated NT-proBNP</td>
<td>• Patients with NYHA class II-IV heart failure with Reduced EF (&lt;40%) and elevated NT-proBNP</td>
<td>• Patients with NYHA class II-IV heart failure with ANY EF and elevated NT-proBNP</td>
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<tr>
<td>• eGFR ≥ 30 mL/min/1.73 m(^2)</td>
<td>• eGFR ≥ 20 mL/min/1.73 m(^2)</td>
<td>• eGFR ≥30 mL/min/1.73 m(^2)</td>
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<tr>
<td>• Diabetes and no Diabetes</td>
<td>• Diabetes and no diabetes</td>
<td>• Diabetes only</td>
<td></td>
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<tr>
<td><strong>Sample size</strong></td>
<td>N=4500</td>
<td>N=2850</td>
<td>N=4000</td>
</tr>
<tr>
<td><strong>Study duration</strong></td>
<td>33 months</td>
<td>38 months</td>
<td>32 months</td>
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<tr>
<td><strong>Primary outcome</strong></td>
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<td>• Time to first occurrence of any component of the composite:</td>
<td>• Time to the first occurrence of any of the components of the composite:</td>
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<tr>
<td>• CV death</td>
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<td>• or hHF</td>
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<tr>
<td>• or an urgent HF visit</td>
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<td><strong>Secondary outcomes</strong></td>
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<tr>
<td>• Time to first occurrence of hHF</td>
<td>• Total number of hHF</td>
<td>• Total number of hHF incl recurrent events</td>
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<tr>
<td>• Time to first occurrence of CVD</td>
<td>• eGFR slope change from baseline</td>
<td>• eGFR slope change from baseline</td>
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<tr>
<td>• Total number of hHF and CVD</td>
<td>• Time to occurrence of sustained reduction of eGFR</td>
<td>• Time to occurrence of sustained reduction of eGFR</td>
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<tr>
<td>• Change in KCCQ at 8 months</td>
<td>• Time to first hHF</td>
<td>• Time to first hHF</td>
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<tr>
<td>• Time to the composite of ≥5% decline in eGFR, reaching ESRD or renal death</td>
<td>• Time to CVD</td>
<td>• Time to CVD</td>
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<tr>
<td>• All-cause mortality</td>
<td>• Time to all-cause mortality</td>
<td>• Time to all-cause mortality</td>
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<td></td>
<td>• Time to diabetes onset</td>
<td>• Time to diabetes onset</td>
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<td></td>
<td>• Change in KCCQ at 12 months</td>
<td>• Change in KCCQ at 12 months</td>
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<tr>
<td></td>
<td>• Total all-cause hospitalisation</td>
<td>• Total all-cause hospitalisation</td>
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<td></td>
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<td>• Above and EF&lt;50%</td>
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</table>
Soluble guanylate cyclase modulators

VICTORIA VITALITY
Different cGMP-augmenting pathways

ARNI

Natriuretic peptides

NO

NO / sGC: causal lesion

GTP

cGMP

extracellular secretion

5’GMP

modified after Senni et al., Eur Heart J. 2014 Oct 21;35(40):2797-815

ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CNP, c-type natriuretic peptide; NO, nitric oxide; PDE5, phosphodiesterase-5; pGC, particulate guanylyl cyclase; sGC, soluble guanylyl cyclase.

NPs: compensatory mechanism

Endothelial function
Soluble guanylate cyclase modulators

Vasodilation
Antifibrosis
Anti-inflammation
Antiproliferation

SMCs / VSMCs
Fibroblasts
Cardiomyocytes

VERICIGUAT

potassium channels / L-type
calcium channels, IRAG,
Phospholamban, MLCK/MLCP,
Titin, ...

sNOS
Arg → Cit

αβγδ

GTP → cGMP

PKG

HF-PEF and SGCm

Vericiguat vs placebo

Improved QOL
KCCQ – physical limitation score
Dose dependent

VITALITY: Phase 2b RCT near completion

Fillipatos, EJHF 2017
HFrEF and SGCm

Change in NT-proBNP at 12 weeks (per protocol analysis)

-24.5% -23.3% -27.4% -29.8% -41.0% -33.1%

p=0.048 p=0.15

N=456 pts
HFrEF <45%
Post D/c HF

Gheorghiade, JAMA 2015
HFrEF
EF<45%
Post D/C HF

Vericiguat 10 mg target dose + Standard HF therapy
1:1, total N = 4872
Placebo + Standard HF therapy

Event-driven study duration
Estimated median follow-up 18 months

Screening
0-30 days 2 weeks 2 weeks 12 weeks 16 weeks Every 16 weeks until planned number of events is reached 14 days

Interim Analysis
Final Visit
Final Phone Call

FULLY ENROLLED
Omecamtiv mecarbil

GALACTIC-HF
Omecamtiv mecarbil

• Direct cardiac myosin activator
• Increases duration of systole by
  • Increasing entry rate of myosin into force-producing state→increasing overall # of active cross-bridges
• Increases stroke volume
• No increase in MVO2 observed

1. Teerlink J. Heart Fail Rev. doi:10.1007/s10741-009-9135-0.
Omecamtiv mecarbil

Healthy Volunteers vs. Heart Failure Patients

Δ Stroke Volume (mL)

Δ Fractional Shortening (% points)

Δ Ejection Fraction (% points)

Δ = placebo corrected change from baseline
Mean ± SEM

Change from Baseline

Healthy Volunteers

SET Heart Failure

[Omecamtiv mecarbil] (ng/mL)

SET (msec)

[Image 570x304 to 701x370]

[Image 12x11 to 66x58]


~8000 patients randomized 1:1 to *omecamtiv mecarbil* versus placebo, stratified by inpatient versus outpatient at randomization

*Omecamtiv mecarbil* started at 25 mg BID: PK-guided dose optimization to one of 3 target doses (25, 37.5, 50mg BID)

Event-driven; patients will be followed indefinitely until CV death events have accumulated (90% powered for CV Mortality)
IV Iron

HEART-FID
Iron Deficiency and HF

- The prevalence of iron deficiency in HF is >40-50%
  - Ferritin <100 ng/mL
  - Ferritin 100-300 ng/mL + transferrin saturation [TSAT] <20%
- In patients with and without anemia

Mechanisms of Iron Deficiency

Daily Recommended Iron intake:
8-18 mg = 0.25% of body stores

Iron Absorption:
- Duodenum
  Iron Absorption: 5-35%

Iron Bioavailability:
- Reticulo Endothelial System
  - IFN-γ
  - TNFα
  - Transferrin
  - RBC

Hepcidin
- Circulating Iron-bound to transferrin (3-5mg)
- "Free" iron → toxic
- Ferritin Complexes (1000-1500mg)
- Hemoglobin (2,500mg)

Bone Marrow
- Erythropoiesis

Iron loss (bleeding)

Lewis GD. Circ HF 2016
Improvements in NYHA class, PGA, QoL, with FCM was detected with statistical significance observed from Week 24 onwards.

Reduction in HF hosp
HR 0.39 (0.19-0.82)
P = 0.009

Patients with HFrEF, EF < 40%, iron deficiency (tsat <20%, ferritin < 100)

**HEART-FID**

Ferric carboxymaltose
(Dosing at Day 0 and Day 7 then every 6 mos as applicable)

N ~ 3014

Placebo + Standard of care (excluding IV iron)

1° endpoint: Mortality, HF hosp Δ 6MWD (6 mos)

*20+ sites across Canada
Sometimes we don’t get it right in research:
? Asked the wrong question
? Engaged the wrong people
? Lost in translation
Other lines of research

- MRAS in HFpEF, pragmatic trials
  - SPIRIT, SPIRRIT
- Apelin peptides
- VADs
- SODIUM-HF
- Gut microbiome
- Telehome monitoring / App-based management
- Personalized medicine
Summary/Conclusions

- >25000 patients in RCT underway
- Future is bright
- Sunrise not sunset for medical therapy