



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

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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,

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has been taking a bit of a beating lately.

Step 1: Out with the antiquated

....10 million leeches / year.... NY Times 2017



Effectiveness of Congesting Cuffs ("Rotating Tourniquets") in Patients with Left Heart Failure

PHILIP A. HABAK, ALLYN L. MARK, J. MICHAEL KIOSCHOS, DONALD R. MCRAVEN, and FRANCOIS M. ABBOUD

Originally published 1 Aug 1974 | https://doi.org/10.1161/01.CIR.50.2.366 | Circulation. 1974;50:366–371







Step 2: in with the new...





Sacubitril / valsartan (HFpEF)

PARAGON

HF-PEF and sacubitril/valsartan



Figure 2: NT-proBNP at 4, 12, and 36 weeks in the LCZ 696 and valsartan groups

PARAMOUNT HF-PEF with elevated NPs

No change in QOL

Solomon, Lancet 2012

PARAGON (HFpEF)

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





SGLT2i EMPA DAPA SOTA

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



JAMA Cardiology September 2017 Volume 2, Number 9

Differences in study designs

	DAPA-HF ¹	EMPEROR-Reduced ²	SOLOIST-WHF
Patient populatio n	 Patients with NYHA class II-IV heart failure with Reduced EF (<40%) and elevated NT-proBNP eGFR ≥30 mL/min/1.73 m² Diabetes and no Diabetes 	 Patients with NYHA class II-IV heart failure with Reduced EF (<40%) and elevated NT-proBNP eGFR ≥20 mL/min/1.73 m² Diabetes and no diabetes 	 Patients with NYHA class II-IV heart failure with ANY EF and elevated NT-proBNP eGFR ≥30 mL/min/1.73 m² Diabetes only *hospital
Sample size	N=4500	N=2850	N=4000
Study duration	33 months	38 months	32 months
Primary outcome	 Time to first occurrence of any component of the composite: CV death or hHF or an urgent HF visit 	Time to the first occurrence of any of the components of the composite:CV deathor hHF	Time to the first occurrence of any of the components of the composite:CV deathor hHF
Secondary outcomes	 Time to first occurrence of hHF Time to first occurrence of CVD Total number of hHF and CVD Change in KCCQ at 8 months Time to the composite of ≥5% decline in eGFR, reaching ESRD or renal death All-cause mortality 	 Total number of hHF eGFR slope change from baseline Time to occurrence of sustained reduction of eGFR Time to first hHF Time to CVD Time to all-cause mortality Time to diabetes onset Change in KCCQ at 12 months Total all-cause hospitalisation 	 Total number of hHF incl recurrent events eGFR slope change from baseline Time to occurrence of sustained reduction of eGFR Time to first hHF Time to CVD Time to all-cause mortality Change in KCCQ at 12 months Total all-cause hospitalization Above and EF<50%



Soluble guanylate cyclase modulators VICTORIA VITALITY

Different cGMP-augmenting pathways



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.

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

Soluble guanylate cyclase modulators



HF-PEF and SGCm



Vericiguat vs placebo

Improved QOL KCCQ – physical limitation score Dose dependent

VITALITY: Phase 2b RCT near completion

Figure 2 Kansas City Cardiomyopathy Questionnaire (KCCQ) item analysis. Mean change from baseline to week 12 compared with placebo for physical limitation (A) and symptom domain (B) items. KCCQ individual items are scored in concordance with the instrument scoring instructions on a 0–100 scale; the respective domain scores are the mean of the contributing items. The labels of the item give a shortened version of the full questions found in Green et al.¹⁶.

Fillipatos, EJHF 2017

HFrEF and SGCm

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





Gheorghiade, JAMA 2015

Dose group

VICTORIA







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



Teerlink J. *Heart Fail Rev.* doi:10.1007/s10741-009-9135-0.
 Malik FI, et al. *Science*. 2011;331:1439-43.

Omecamtiv mecarbil



GALACTIC-HF

- ~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)



2 years enrollment, approx. 4 years total follow-up/study period





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





¹Iron loss (bleeding) Lewis GD. Circ HF 2016

CONFIRM-HF



FCM 150

140

131

126

77

Ponikowski et al. Eur Heart J. 2015

HEART-FID

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



*20+ sites across Canada



玻璃栈道 小心滑倒 Glass ladder rank, carefully slip.

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