Canadian **VIGOUR** Centre
Bridging Hearts and Minds

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

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May somethingorother 2019

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

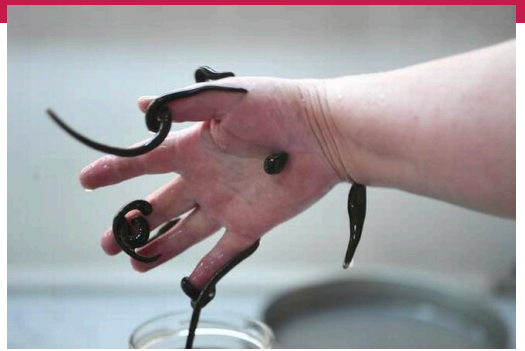
Aug. 6, 2018

167

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



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

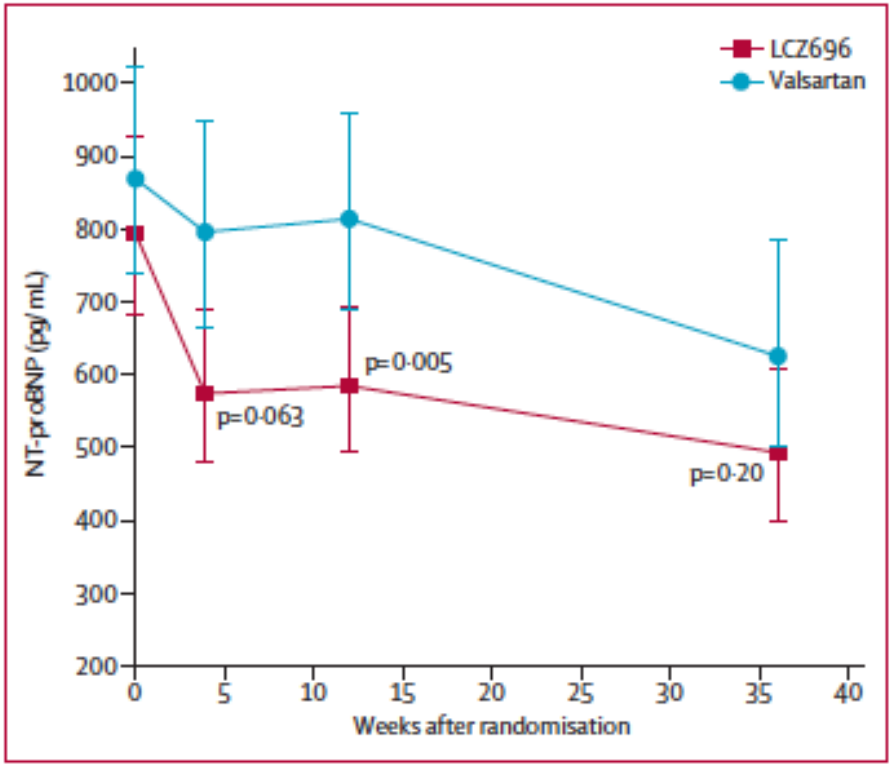


Figure 2: NT-proBNP at 4, 12, and 36 weeks in the LCZ696 and valsartan groups

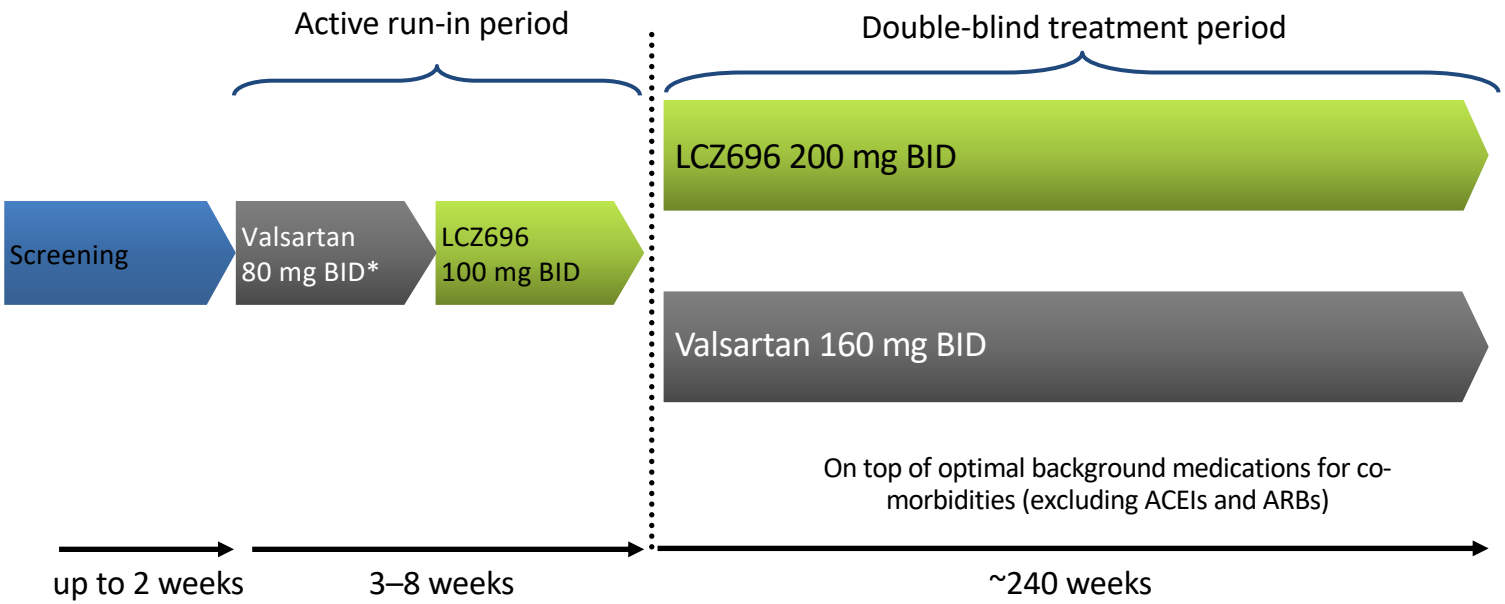
PARAMOUNT
HF-PEF with elevated NPs

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%

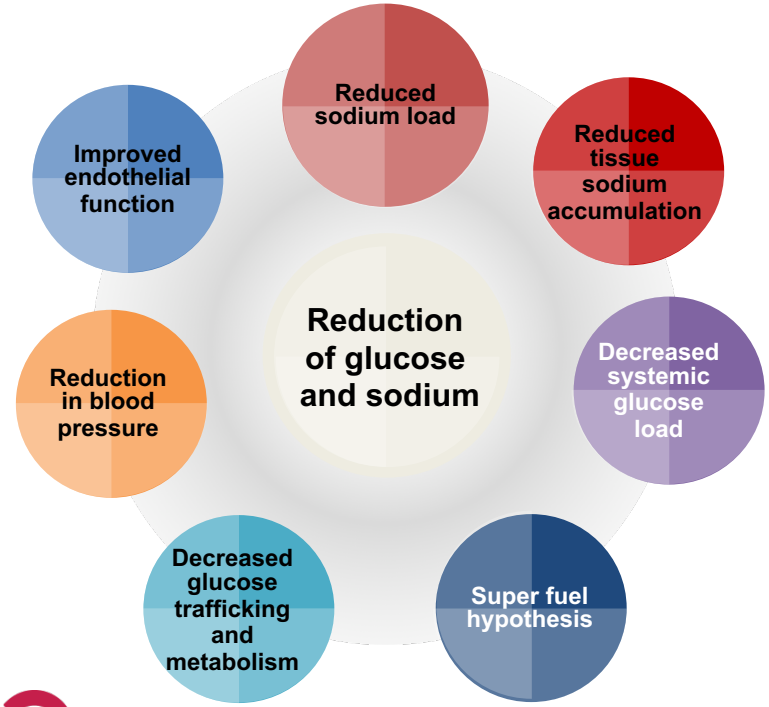


Primary outcome: CV death and total (first and recurrent) HF hospitalizations (anticipated ~1,721 primary events)

SGLT2i

EMPA
DAPA
SOTA

Mechanisms with SGTL2 inhibitors



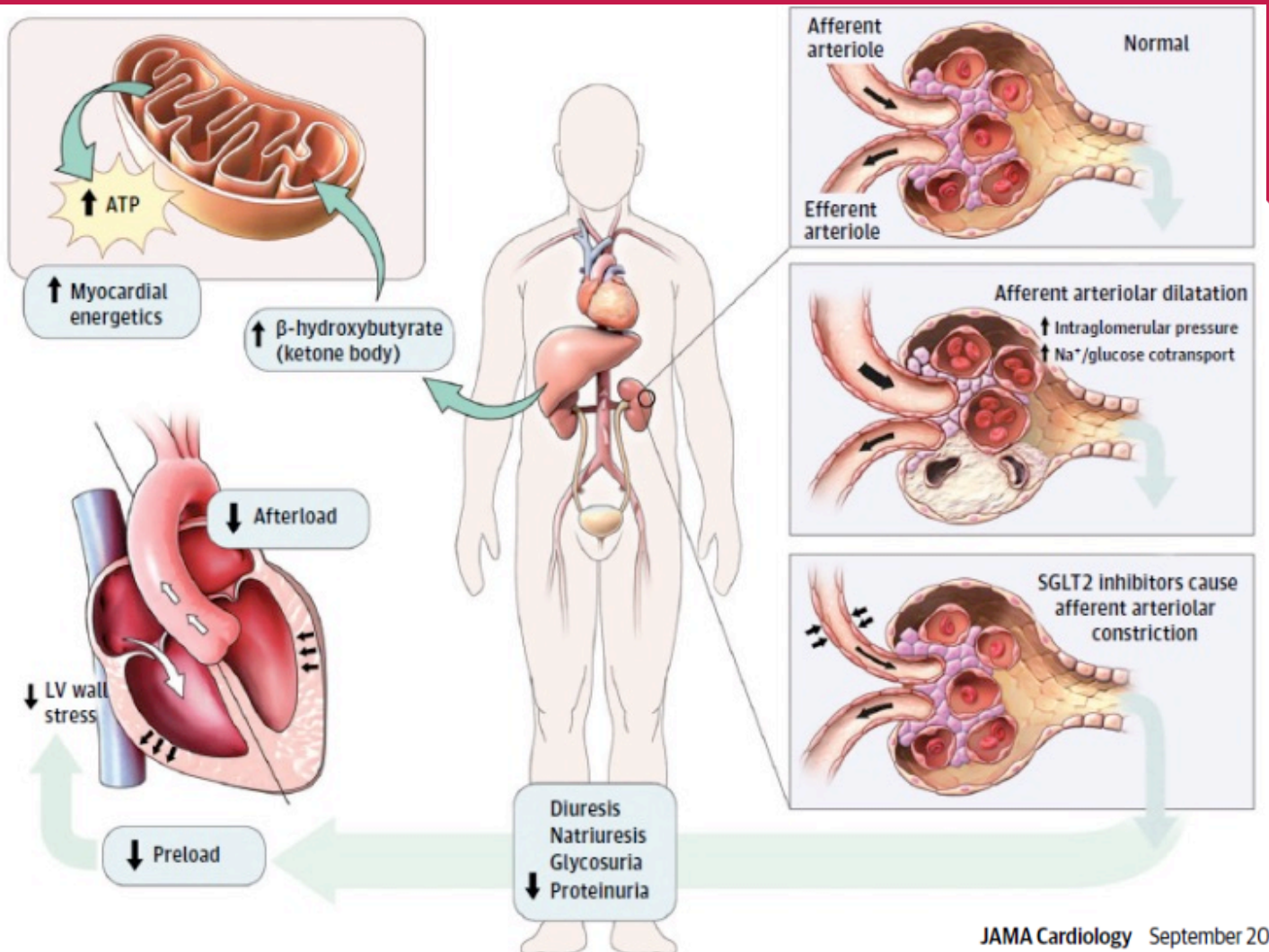
Evidence supporting potential mechanisms is sparse

There has been considerable discussion about three potential mechanisms

- **Improvements in hemodynamics**
- **Super-fuel hypothesis**
- **Improved oxygen delivery**

CV, cardiovascular; SGLT2, sodium-glucose cotransporter-2

Mudaliar S, et al. *Diabetes Care.* 2016;39:1115–1122.


ATP
Myocardial energetics
β-hydroxybutyrate (ketone body)
Afterload
LV wall stress
Preload
Diuresis
Natriuresis
Glycosuria
Proteinuria
Afferent arteriole
Normal
Efferent arteriole
Afferent arteriolar dilatation
Intraglomerular pressure
Na+/glucose cotransport
SGLT2 inhibitors cause afferent arteriolar constriction

Differences in study designs

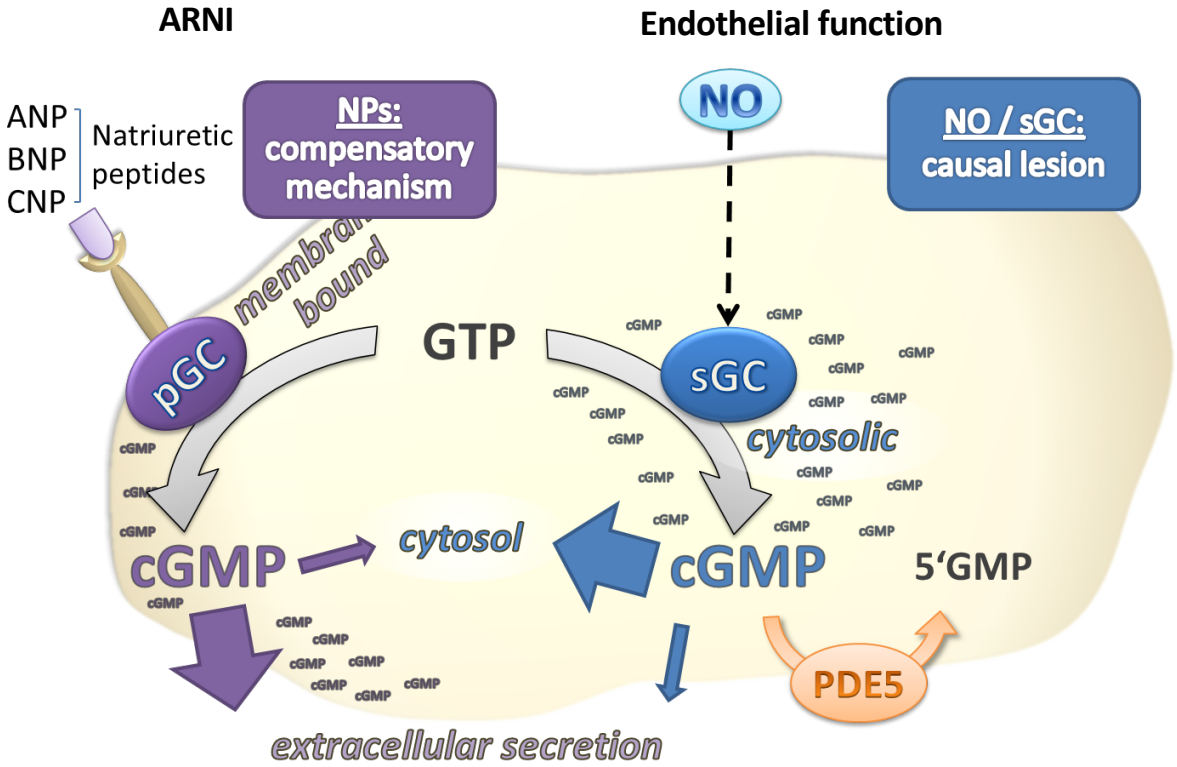
	DAPA-HF[1]	EMPEROR-Reduced[2]	SOLOIST-WHF
Patient population	• Patients with NYHA class II-IV heart failure with Reduced EF (<40%) and elevated NT-proBNP • eGFR ≥**30** mL/min/1.73 m^2 • **Diabetes and no Diabetes**	• Patients with NYHA class II-IV heart failure with Reduced EF (<40%) and elevated NT-proBNP • eGFR ≥**20** mL/min/1.73 m^2 • **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 m^2 • **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 death • or hHF	Time to the first occurrence of any of the components of the composite: • CV death • or 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%

1. I

Soluble guanylate cyclase modulators

VICTORIA
VITALITY

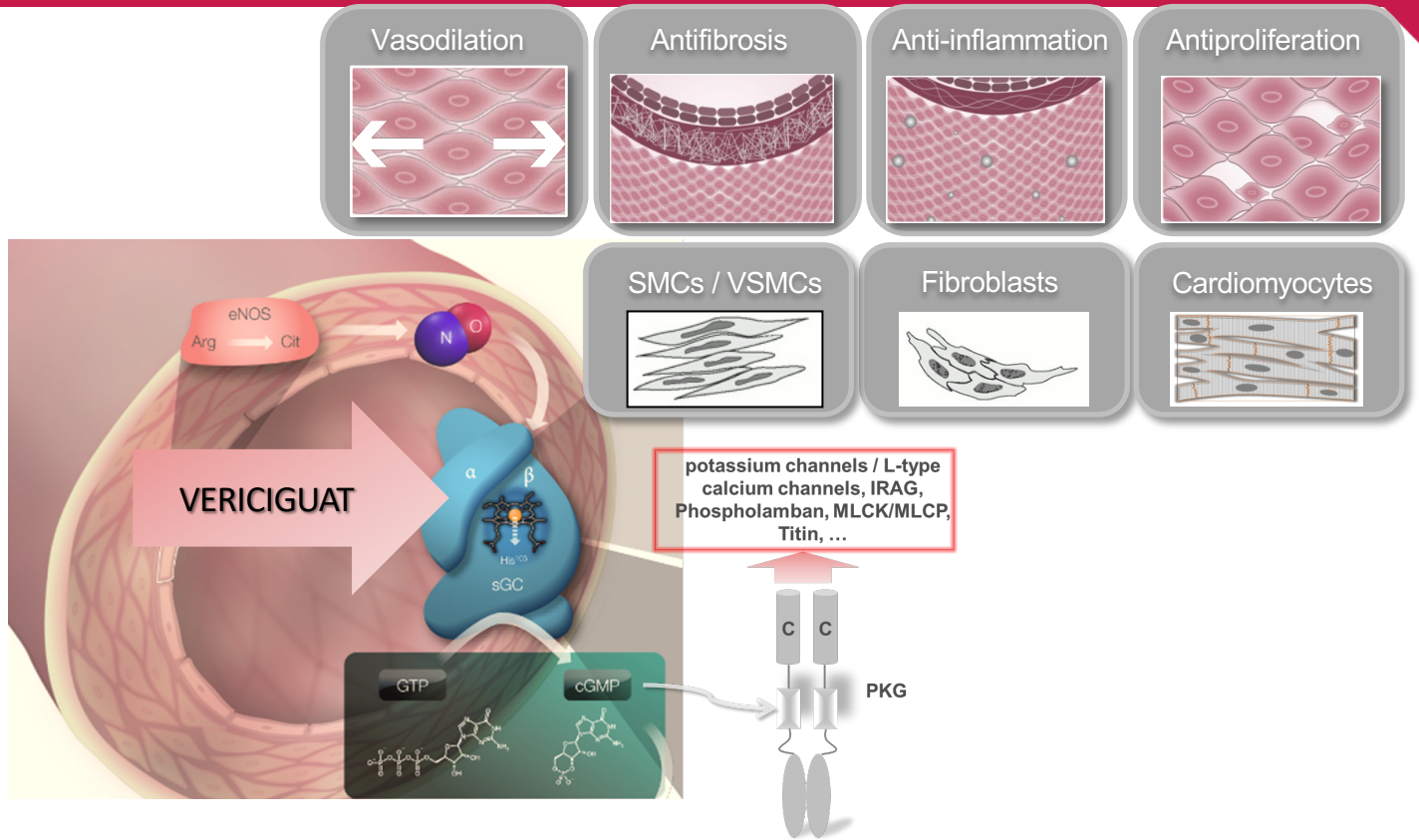
Different cGMP-augmenting pathways



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



Refs: C. Fiocchi: Am J Physiol 1997, G769-G775

HF-PEF and SGCm

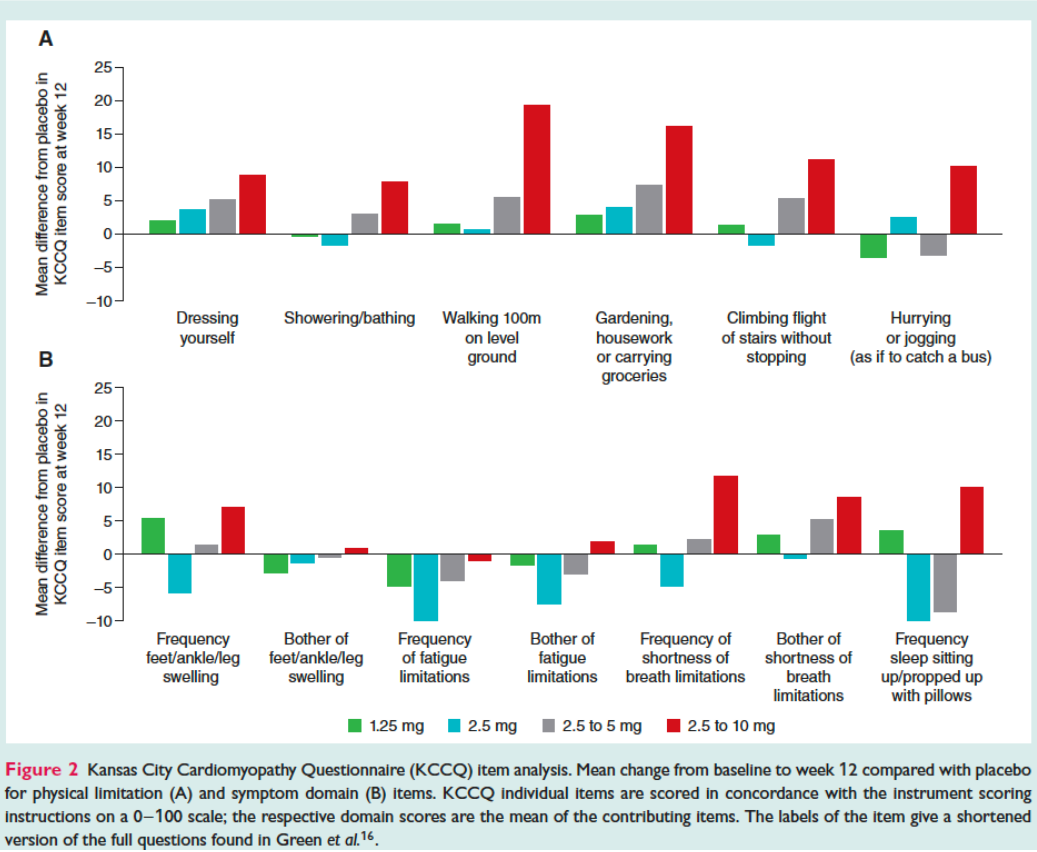


Figure 2 Kansas City Cardiomyopathy Questionnaire (KCCQ) item analysis. Mean change from baseline to week 12 compared with placebo for physical limitation (A) and symptom domain (B) items. KCCQ individual items are scored in concordance with the instrument scoring instructions on a 0–100 scale; the respective 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].

Vericiguat vs placebo

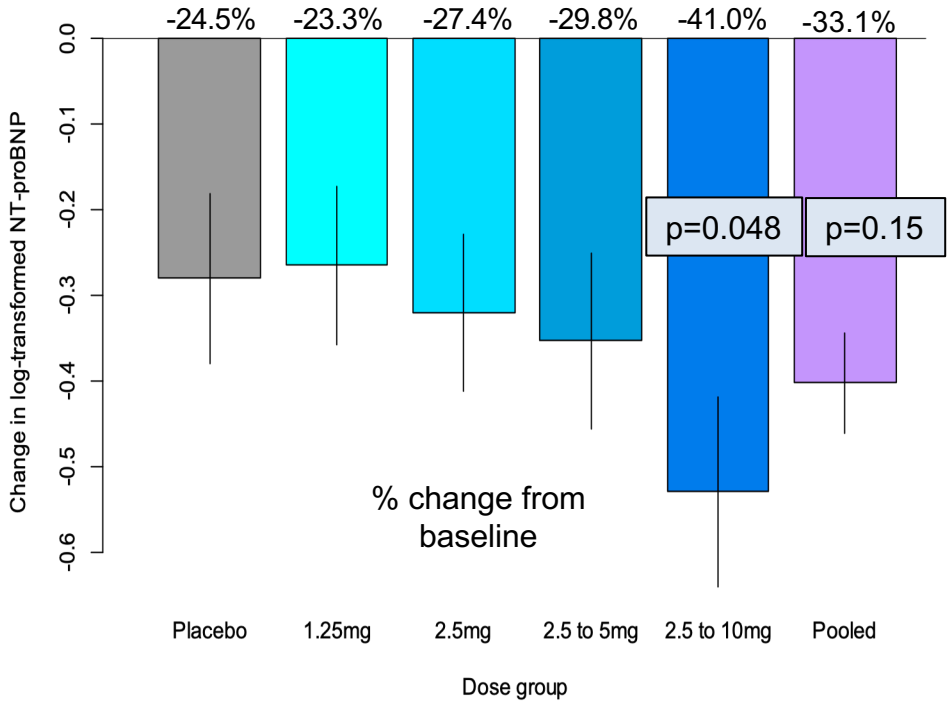
Improved QOL
KCCQ – physical limitation score
Dose dependent

VITALITY: Phase 2b RCT near completion

Fillipatos, EJHF 2017

HFrEF and SGCm

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



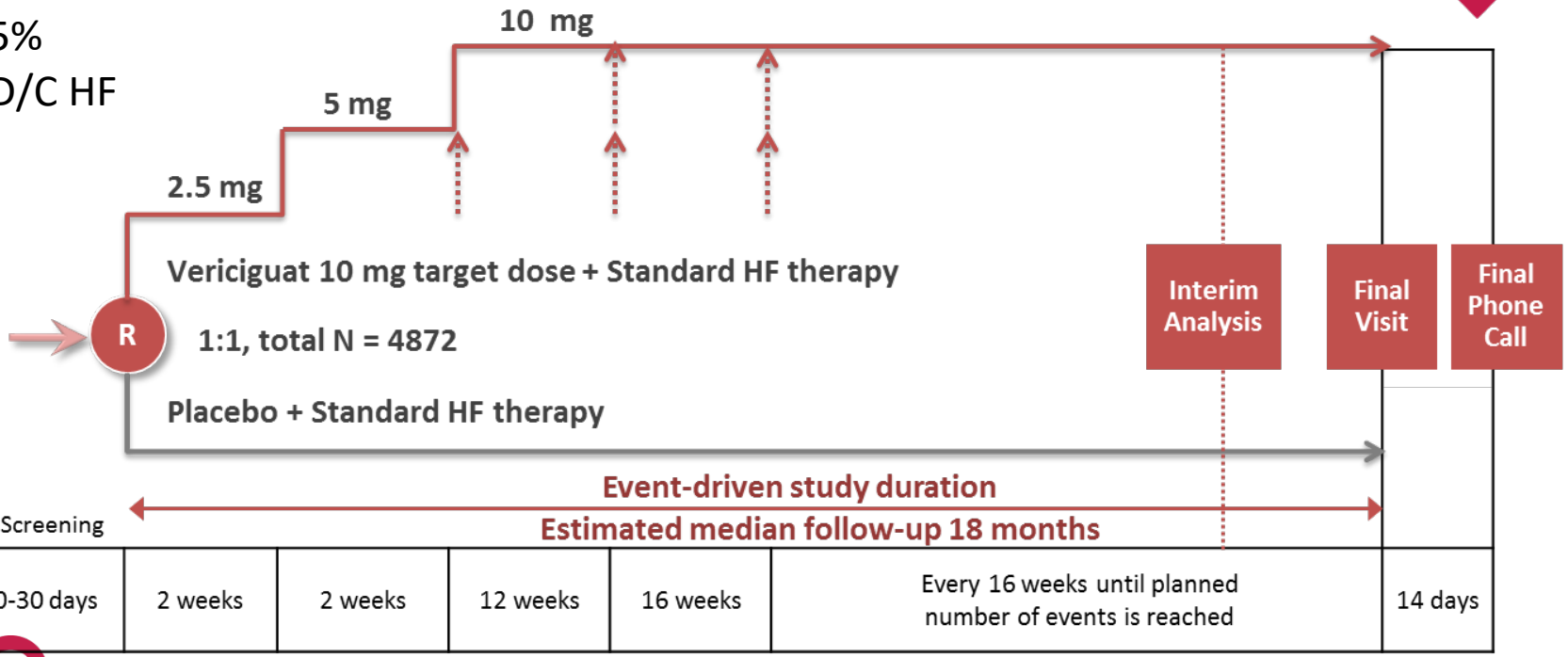
N=456 pts
HFrEF <45%
Post D/c HF

Gheorghiade, JAMA 2015

VICTORIA

FULLY ENROLLED

HFrEF
EF<45%
Post D/C HF



Omecamtiv mecarbil

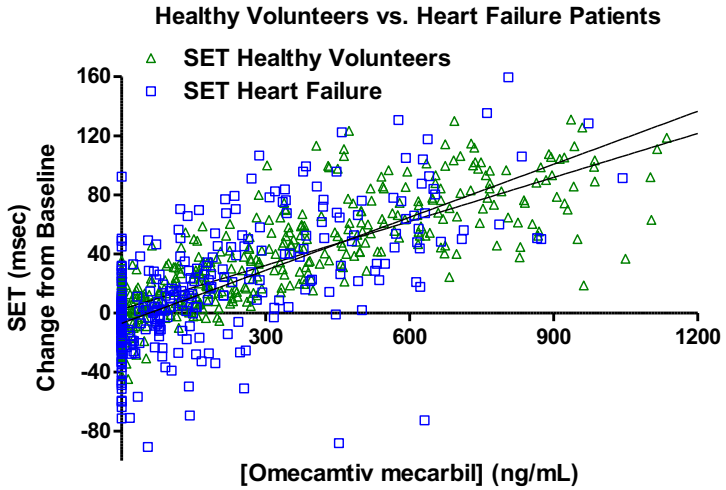
GALACTIC-HF

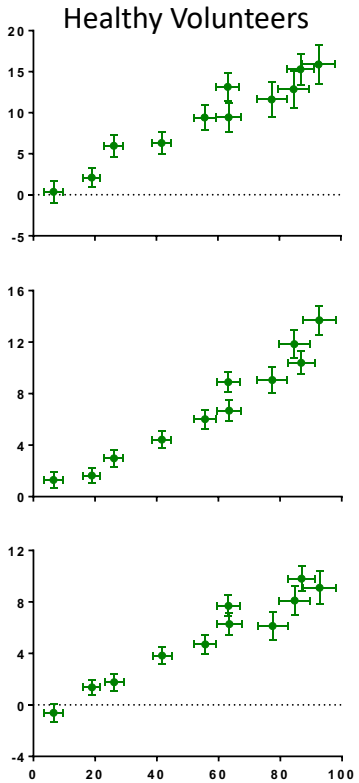
Omecamtiv mecarbil

- 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.
2. Malik FI, et al. *Science.* 2011;331:1439-43.

Omecamtiv mecarbil





Δ Stroke Volume (mL)

Δ Fractional Shortening (% points)

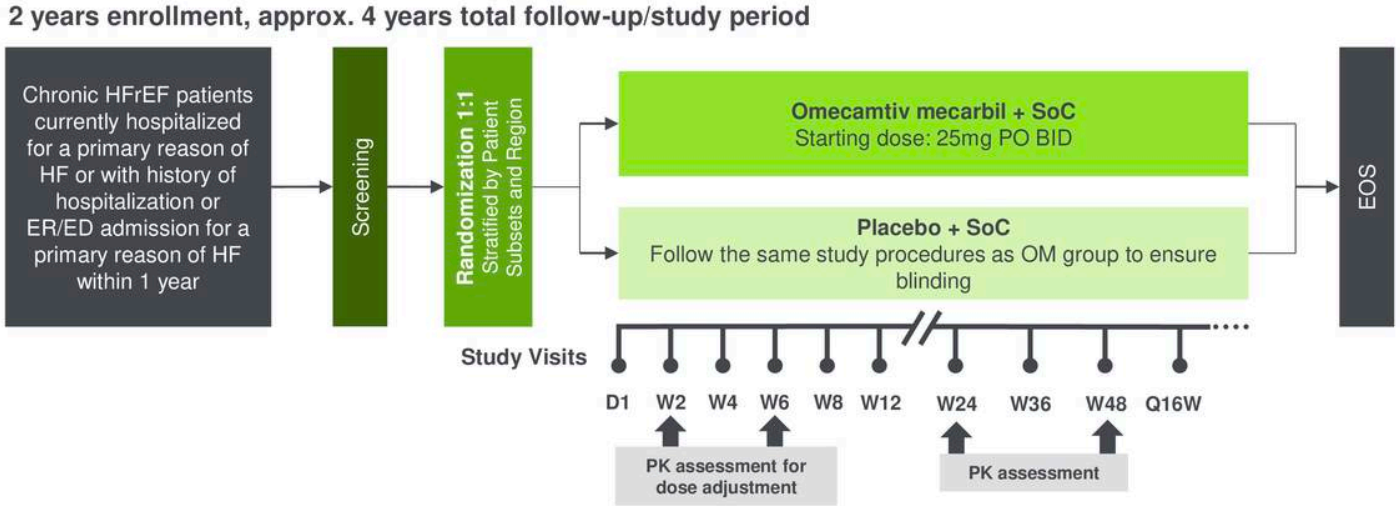
Δ Ejection Fraction (% points)

Teerlink JR, et al. *Lancet* 2011; 378: 667–75.
Cleland JGF, et al. *Lancet* 2011; 378: 676–83.

Δ = placebo corrected change from baseline Mean ± SEM

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)

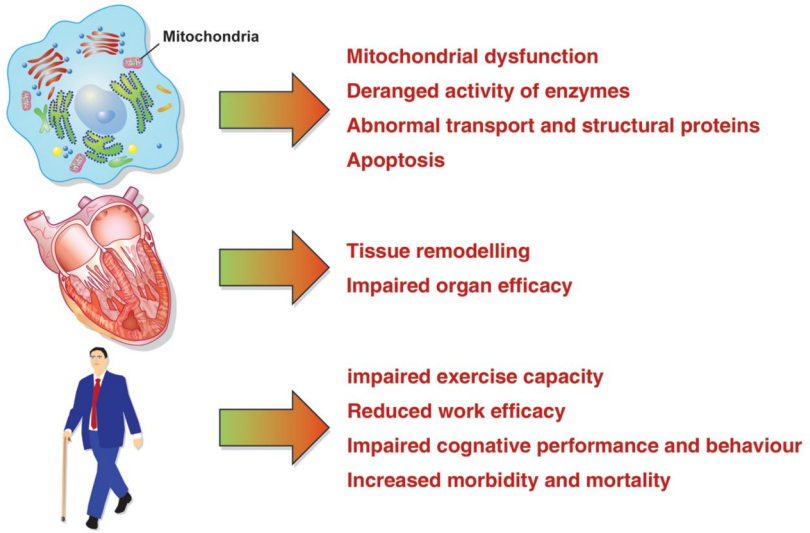


IV Iron

HEART-FID

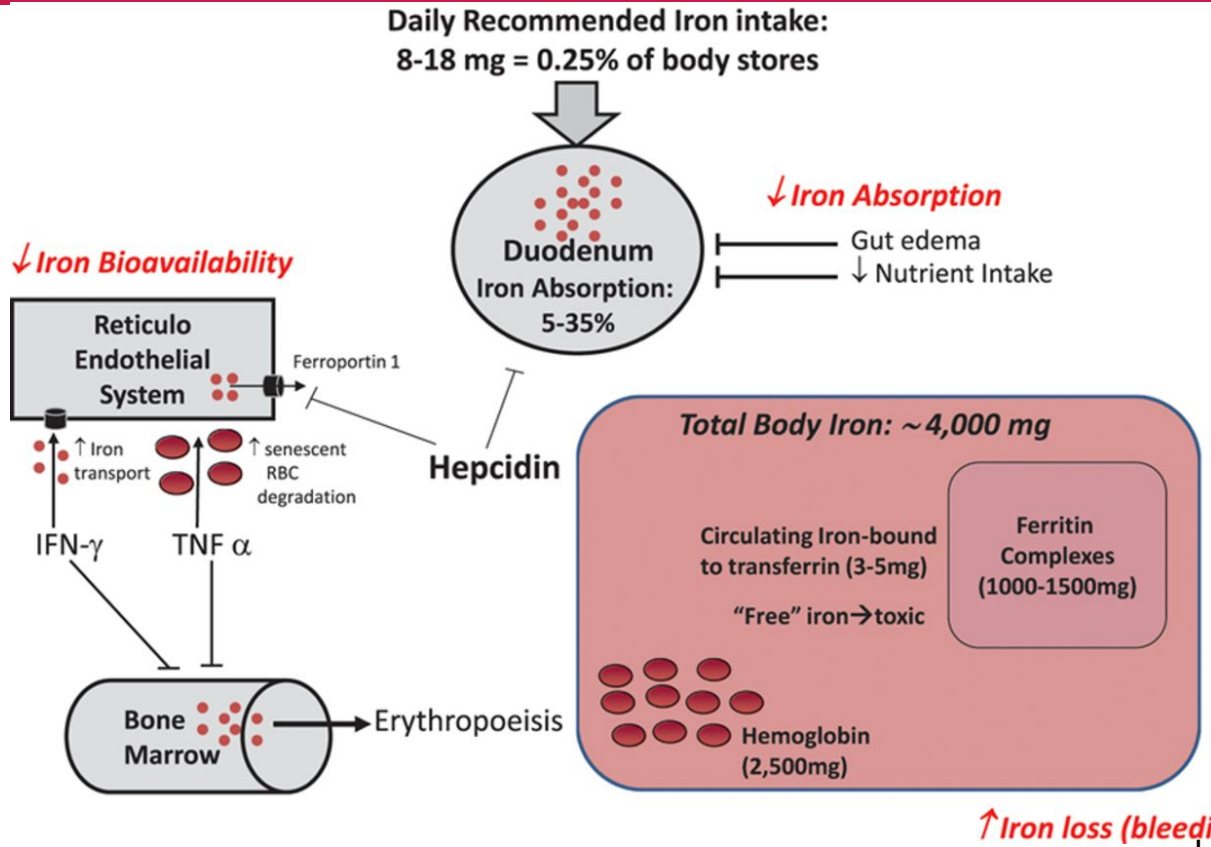
Iron Deficiency and HF

- 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



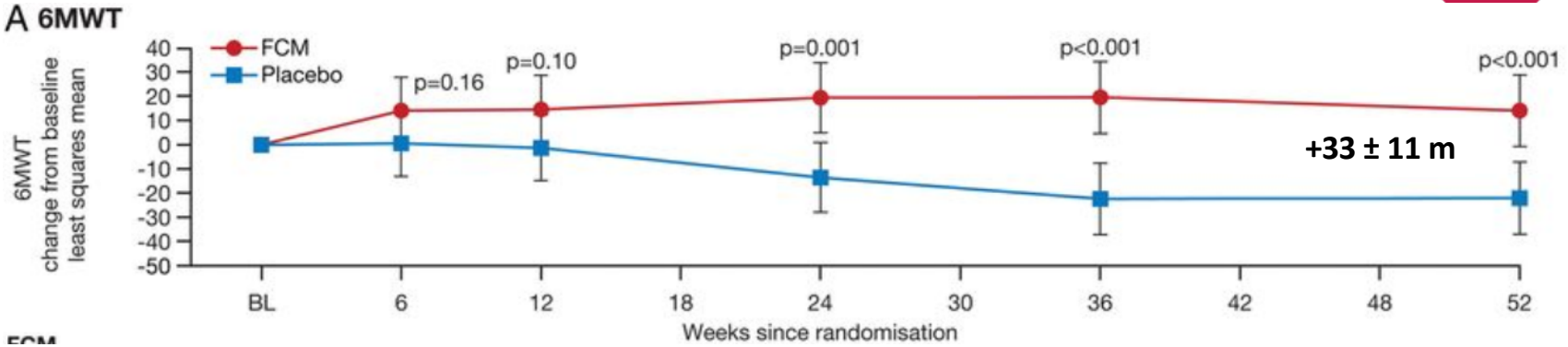
Jankowska EA et al. *Eur Heart J*. 2013 Mar;34(11):816-29.

Mechanisms of Iron Deficiency

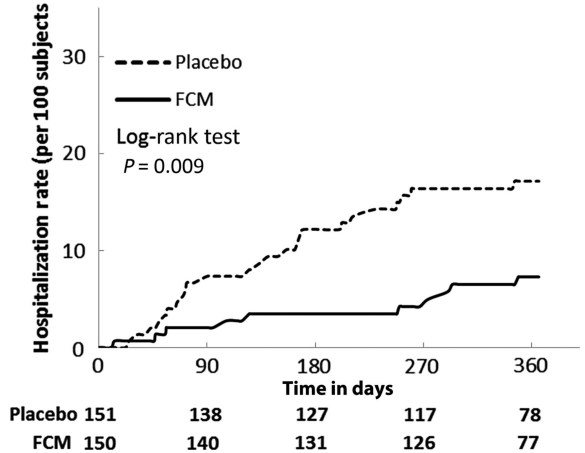


Lewis GD. Circ HF 2016

CONFIRM-HF



Improvements in NYHA class, PGA, QoL, with FCM was detected with statistical significance observed from Week 24 onwards

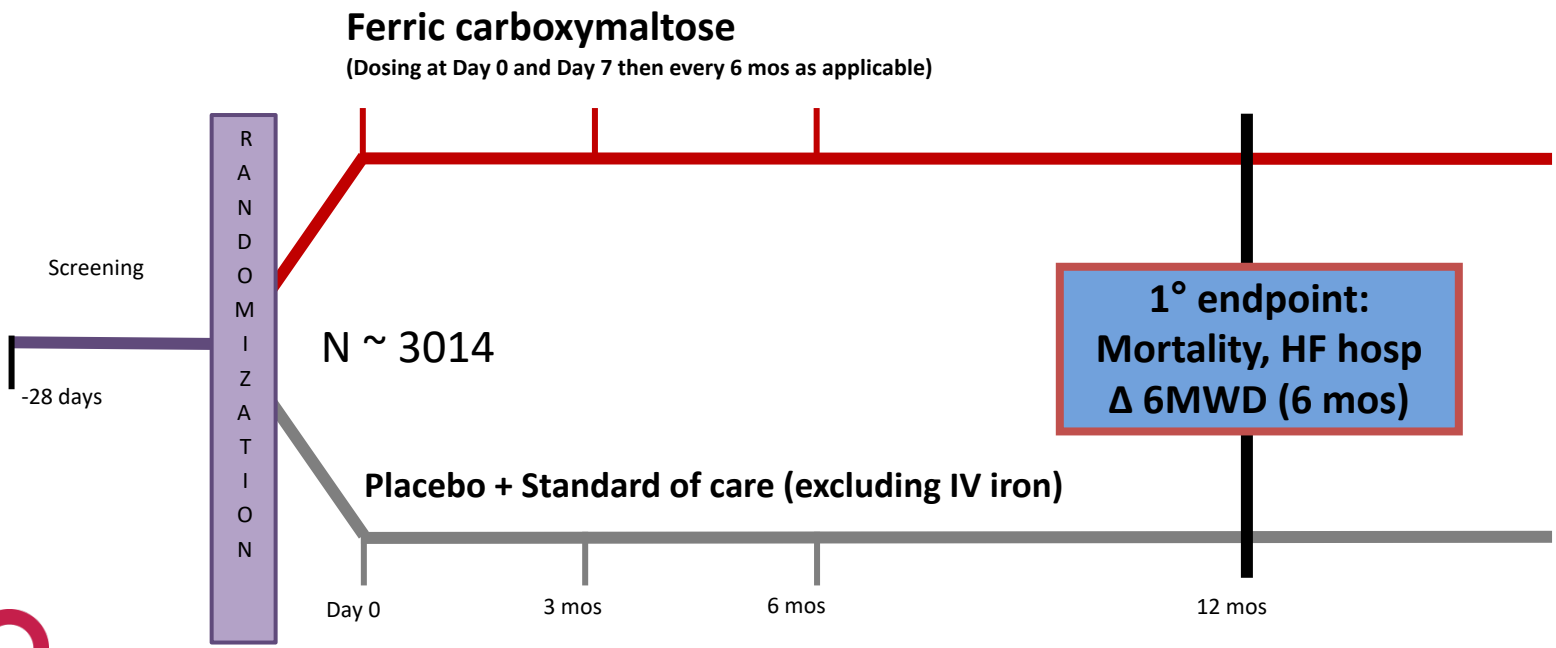


Reduction in HF hosp
HR 0.39 (0.19-0.82)
P = 0.009

Ponikowski et al. *Eur Heart J*. 2015

HEART-FID

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



*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