IRONOUT-HF TRIAL: ORAL VS IV

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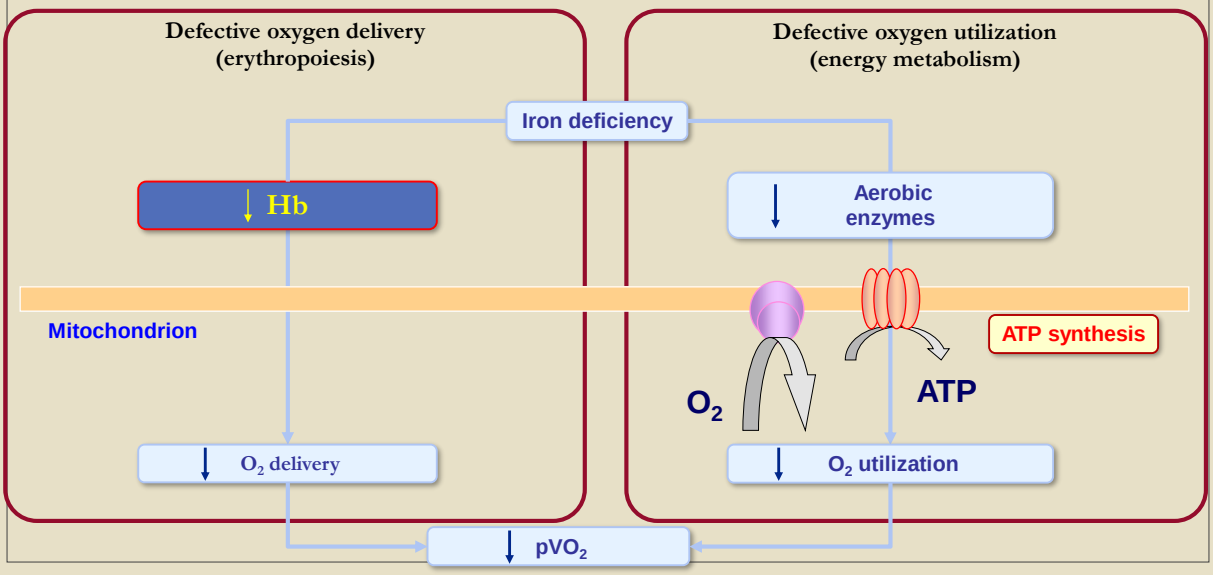
Iron deficiency

- Most common nutritional deficiency worldwide
- In HF:
  - A common comorbidity (50%)
  - Contributes to cardiac and peripheral muscle dysfunction
  - Strong predictor of poor clinical outcome

Dual effects of iron deficiency in HF



Iron as a target for HF treatment

- Iron deficiency associated with:
  - Low VO2 and exercise capacity.
  - Depression in men irrespective of HF severity, neurohormonal activation, Hb and inflammation
  - Poor prognosis
  - Dysfunction of the skeletal and cardiac muscles.

IRONOUT HF Trial

- "Oral Iron Repletion Effects ON Oxygen UpTake in Heart Failure"
- Aim: (August 2014 – April 2016)
- Oral Fe polysaccharide is superior to oral placebo in improving functional capacity measured by change in peak VO_2 by CPET in pts with HFrEF and Fe deficiency at 16 weeks.
- Primary outcome:
  - Change in Peak VO2 (ml/min) [Baseline and Week 16]
- Secondary outcomes:
  - Change in Submaximal exercise capacity (O2 uptake kinetics and ventilatory efficiency measured by CPET and 6MWT)
  - Change in NT-pro BNP
  - Change in Health Status: KCC Questionnaire (KCCQ)

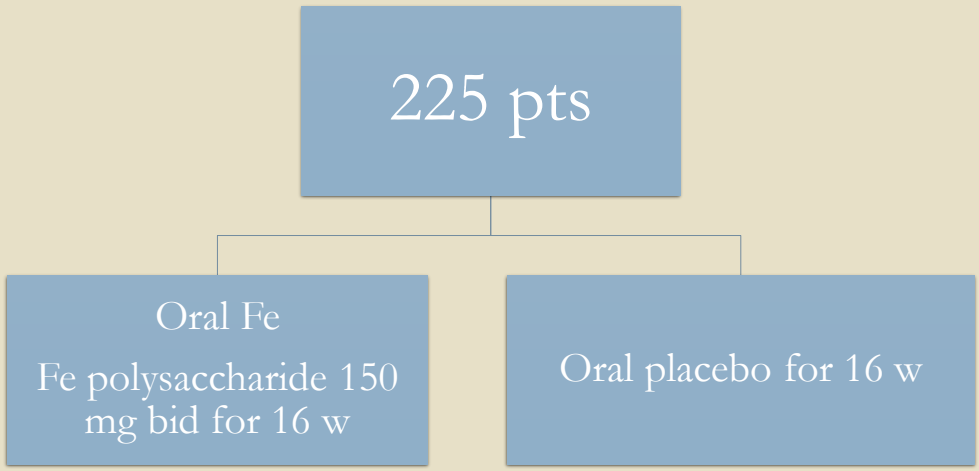
IRONOUT HF Trial

- Inclusion Criteria:
  - Age >18 years
  - HF NYHA Class II-IV symptoms, LVEF≤0.40 within 2 years, and ≥3 months after a major change in cardiac status (i.e. CABG or CRT).
  - Serum ferritin 15-100 ng/ml OR 100-299 ng/ml + transferrin saturation <20%
  - Hb 9.0-13.5 g/dL at time of enrollment
  - Stable EBMT for HF (BB and ACE-I/ARB unless intolerant, and diuretics as necessary)

IRONOUT HF Trial

- Exclusion Criteria:
  - N/M, orthopedic or other non-cardiac condition that prevents exercise testing
  - Severe renal or liver disease
  - Gl conditions impairing Fe absorption (i.e. inflammatory bowel disease)
  - Active infection/ GI bleeding / malignancy
  - Anemia with known cause other than Fe deficiency or chronic disease
  - Fe overload disorders (i.e. hemochromatosis or hemosiderosis)
  - H/O of erythropoietin, Fe therapy, or blood transfusion in previous 3 months.
  - Previous adverse reaction to Fe preparations
  - Known or anticipated pregnancy within 4 m
  - Cardiac conditions:
    - VADs
    - Expected cardiac transplantation within 4 m
    - Cardiomyopathy: HCM, infiltrative, acute myocarditis, constrictive pericarditis or tamponade.

IRONOUT HF Trial



IRONOUT HF Trial

	Treatment difference	p
Peak VO2 at 16 w	21 ml/min	0.46
Peak VO2 at 16 w (wt adjusted)	0.3 ml/kg/min	0.3

IRONOUT HF Trial

	Oral iron	Standard ttt	p
Adverse events	35%	39%	0.5
Death/ CV rehospitalization	13%	11%	0.63
6MWT	19 m	32 m	0.19
KCCQ	3.1 points	3 points	0.57

IRONOUT HF Trial

- Response of iron stores: minimal

	IRONHF	FAIR-HF
Ferritin	11 ng/ml	20 x
TSAT	3%	4 x

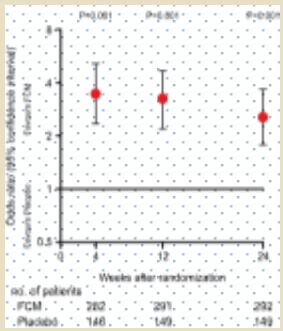
IV IRON TRIALS

FAIR-HF Trial

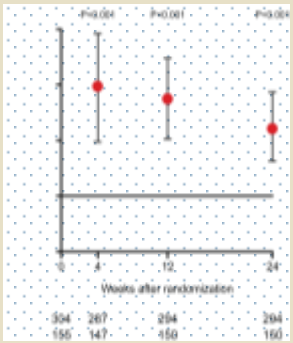
- IV Ferric carboxymaltose vs placebo (459 pts, 2:1)
- Increased QOL, NYHA and 6MWT at 6 months
- In both anemic and non-anemic patients

FAIR-HF

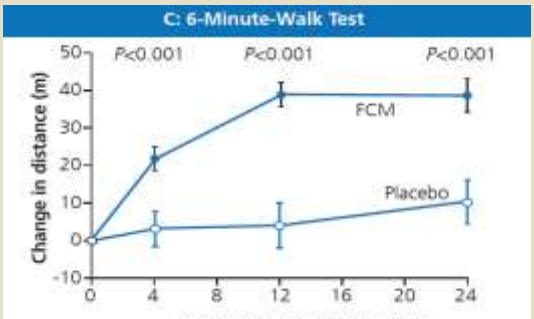
Patient Global Assessment



NYHA functional class



FAIR-HF Trial

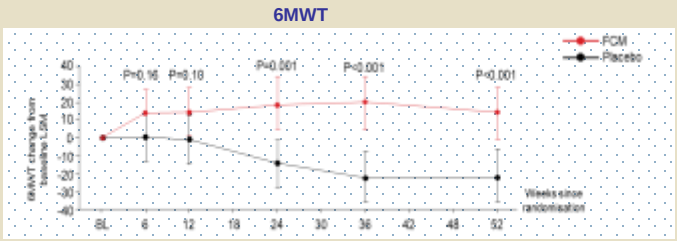


FACM				
No. of patients	303	284	280	268
Mean distance (m)	274±6	294±7	312±6	313±7
Placebo				
No.of patients	155	144	141	134
Mean distance (m)	269±9	269±10	277±10	277±10
Mean study-treatment effect	21±6	37±7		35±8

CONFIRM HF Trial

- **304 pts, received IV ferric carboxymaltose (median = 1500 mg) vs placebo**
  - ↑ exercise capacity at 12 m (p<0.001)
  - ↑QOL (p<0.001) and NYHA symptoms (p<0.001)
  - 2ry endpoints: ↓ hospitalization for worsening HF (HR: 0.39, p = 0.009)
  - Death was similar in both groups.

CONFIRM-HF

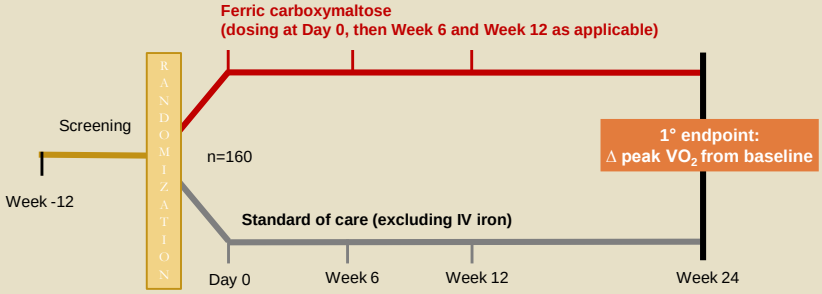


Meta-analysis of trials

- **↓ Hospitalization**
- **↓ HF symptoms**
- **↑ Exercise capacity**
- **↑ QOL**
- **No change in mortality or adverse events.**

EFFECT-HF

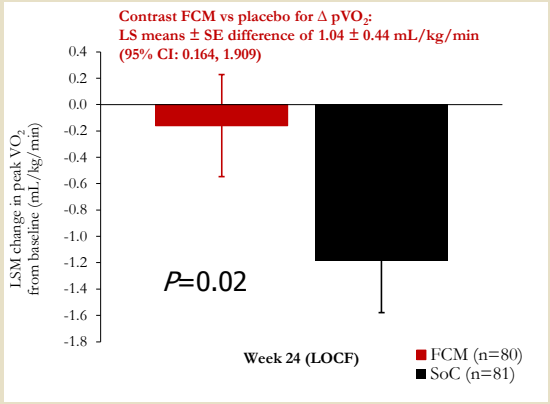
- **Design:** Multicenter, randomized (1:1), open label, assessor/endpoint-blinded, standard of care-controlled
- **174 pts**
- **Main inclusion criteria**
  - ✓ NYHA class II/III
  - ✓ LVEF ≤45%
  - ✓ Peak VO_2 10-20 mL/kg/min (reproducible)
  - ✓ BNP >100 pg/mL and/or NT-proBNP >400 pg/mL
  - ✓ Fe deficiency: ferritin <100 µg/L OR 100–300 µg/L if TSAT <20%
  - ✓ Hb <15 g/dL



EFFECT-HF: Iron-related parameters

	FCM (N=86)		SoC (N=86)		Contrast: FCM – SoC**	
Parameter	Baseline	Week 24	Baseline	Week 24	Change from baseline	P-value between groups
Ferritin ng/mL*	62.06 (60.64)	283.17 (150.28)	64.72 (51.44)	92.31*** (65.43)	188.7 (17.27)	0.0001
TSAT %*	19.65 (13.71)	26.54 (8.25)	20.07 (9.63)	21.90 (10.17)	4.7 (1.35)	0.0007
Hb g/dL*	12.93 (1.30)	13.90 (1.30)	12.99 (1.46)	13.19 (1.47)	0.74 (0.17)	<0.0001

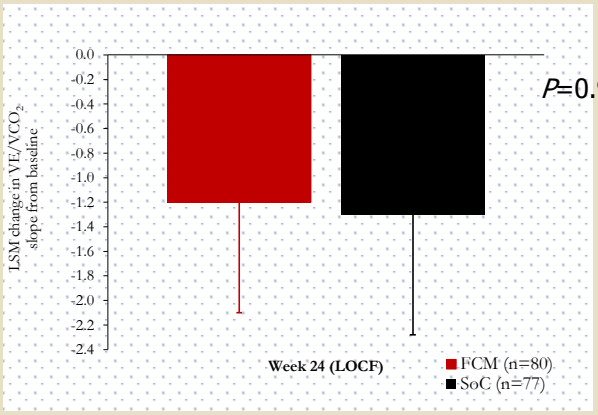
EFFECT-HF: 1ry endpoint



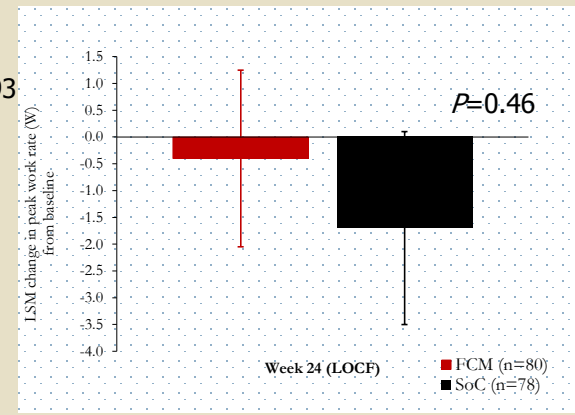
Full analysis set (N=172)

EFFECT-HF: 2ry endpoint

VE/VCO_2 slope

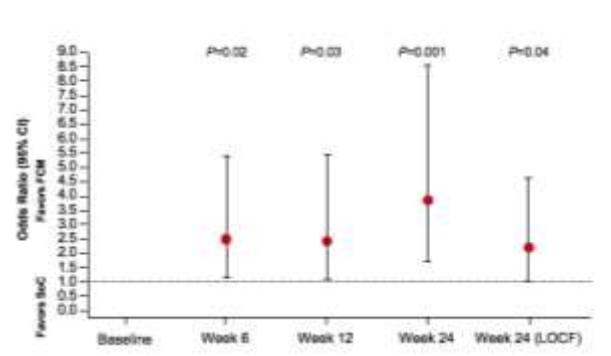


Peak work rate (W)

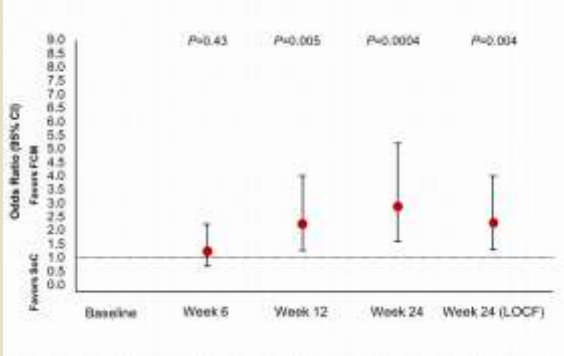


EFFECT-HF

New York Heart Association Functional (NYHA) class



Self-reported Patient Global Assessment (PGA) score



EFFECT-HF

<u>However</u>

- ↑ hospitalization rates
  - Worsening of HF (12.5% vs7.1%)
  - Another CV event (13.6% vs 3.5%)

EFFECT-HF: Conclusion

- In symptomatic patients with HF and Fe deficiency, treatment with IV FCM over a 24-week period resulted in significantly better peak VO2 compared with standard of care (irrespective of baseline anaemia).
- This confirms the results of previous studies (FAIR-HF and CONFIRM-HF).

Take Home Message

- Almost all patients have resistance to oral iron uptake.
- Patients are given oral iron based on evidence from studies using IV iron.
- Intravenous Fe can replenish stores, increase functional capacity and QOL but does not affect mortality.

Recommendations for the treatment of other co-morbidities in patients with heart failure

Recommendations	Class[a]	Level[b]	Ref[c]
Iron deficiency			
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 μg/L, or ferritin between 100–299 μg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A	469, 470

Thank you