

*discussion of*



# **Oral Iron Repletion effects on Oxygen UpTake in Heart Failure (IRONOUT)**

*Lewis GD et al.*

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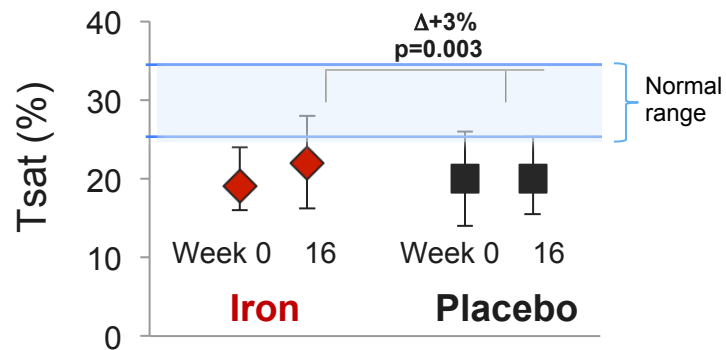
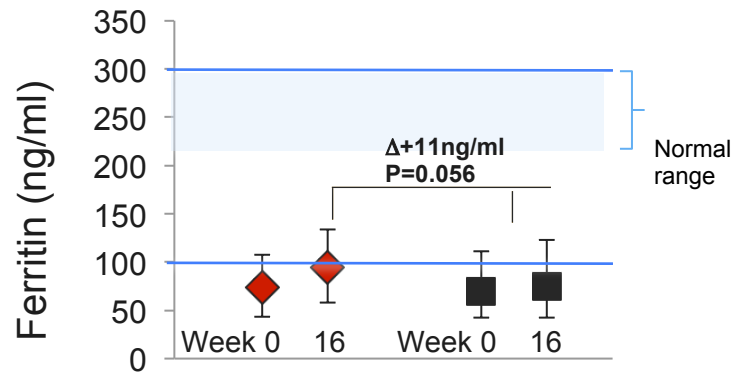
Dol: Consultancy for Vifor, Luitpold, Novartis, Bayer, ASTRA, Pfizer; Grants from Vifor & Abbott Vascular; Investigator for EFFECT-HF; PI of Fair-HF & Fair-HF2

## Summary

- Well done trials by expert teams
- IRONOUT: Oral iron does not work in patients with chronic heart failure.
- Iron that is not getting into the body cannot exert effects.

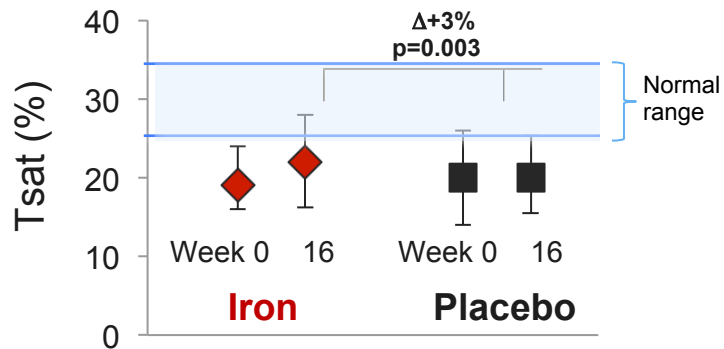
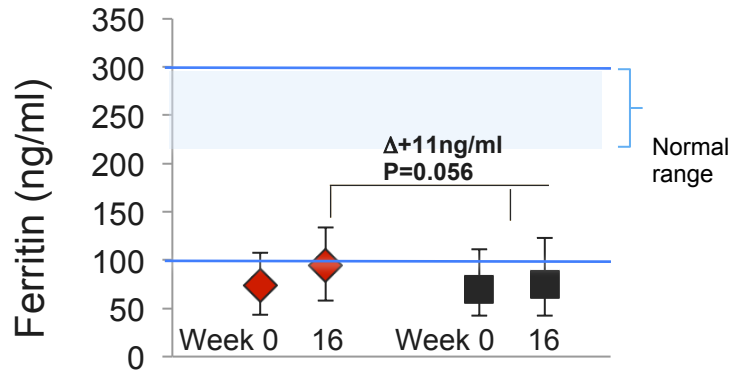
# Results on hematinics in different trials. Change from baseline to week 16 / week 24.

## IRONOUT-HF

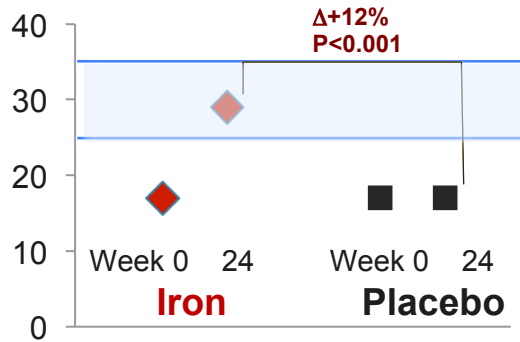
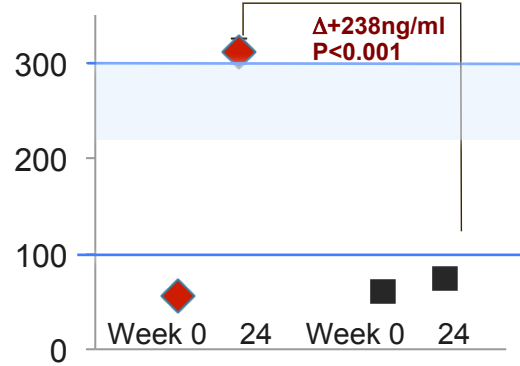


# Results on hematinics in different trials. Change from baseline to week 16 / week 24.

## IRONOUT-HF



## vs. FAIR-HF (IV Iron)

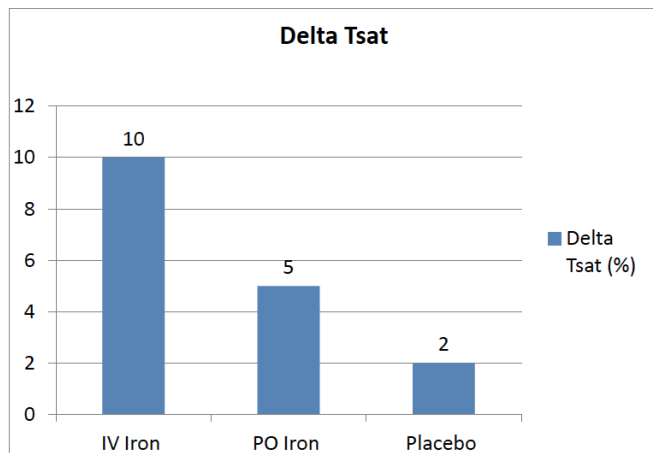


## vs. CONFIRM-HF (IV Iron)

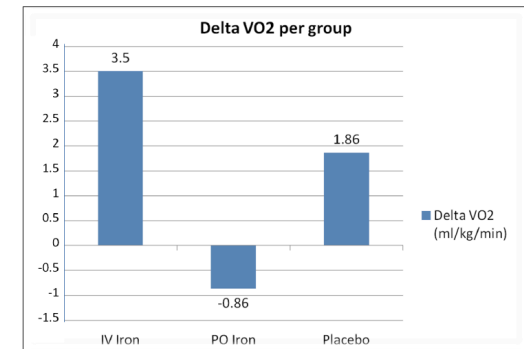
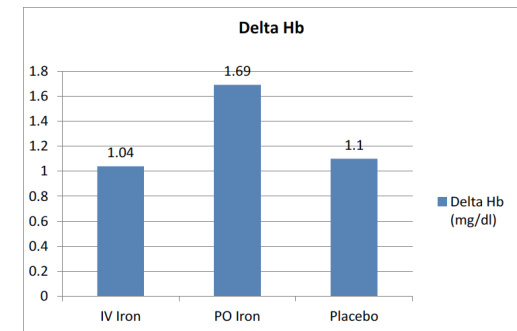
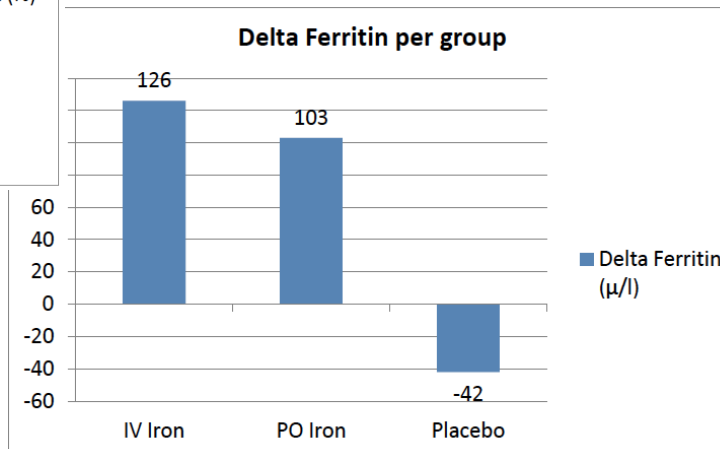
<b>Ferritin:</b>	<b>FCM 57</b>	$\Delta+265\text{ng/ml}$
	<b>Plac 57</b>	$P<0.001$
<b>TSAT:</b>	<b>FCM 20</b>	$\Delta+9\%$
	<b>Plac 18</b>	$P<0.001$

# Results on hematinics in different trials. One randomised trial of oral iron vs IV iron.

Oral iron: ferrous sulfate 200 mg tid for 8 weeks (here ron polysaccharide 150 mg bd for 16 weeks)  
IV iron: iron sucrose i.v. 200 mg, once a week, for 5 weeks



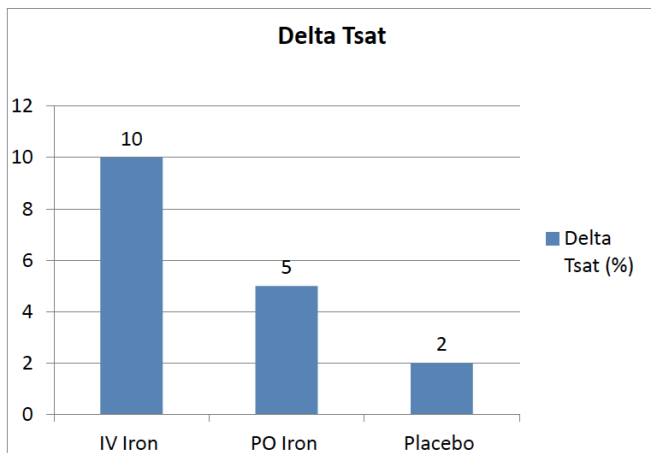
Oral iron: n=7  
IV iron: n=10  
Placebo: n=6



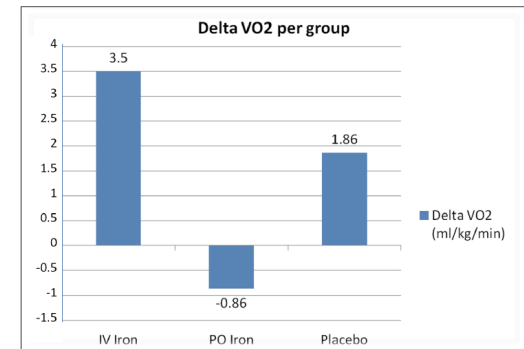
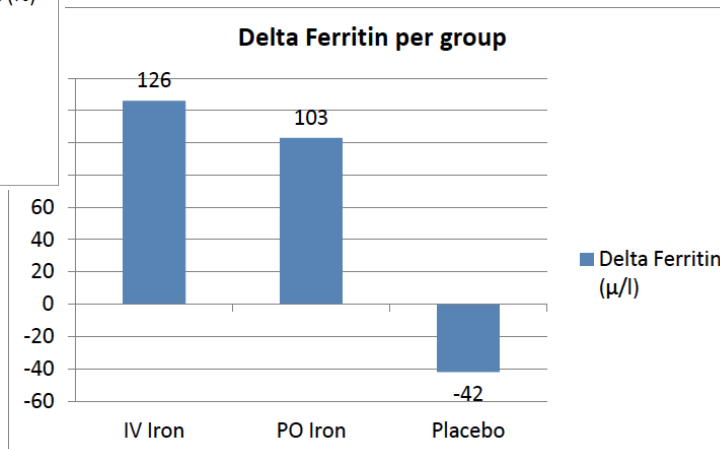
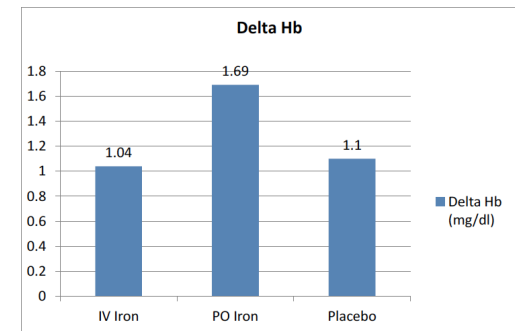
Beck-da-Silva L et al.  
Int J Cardiol 2013.

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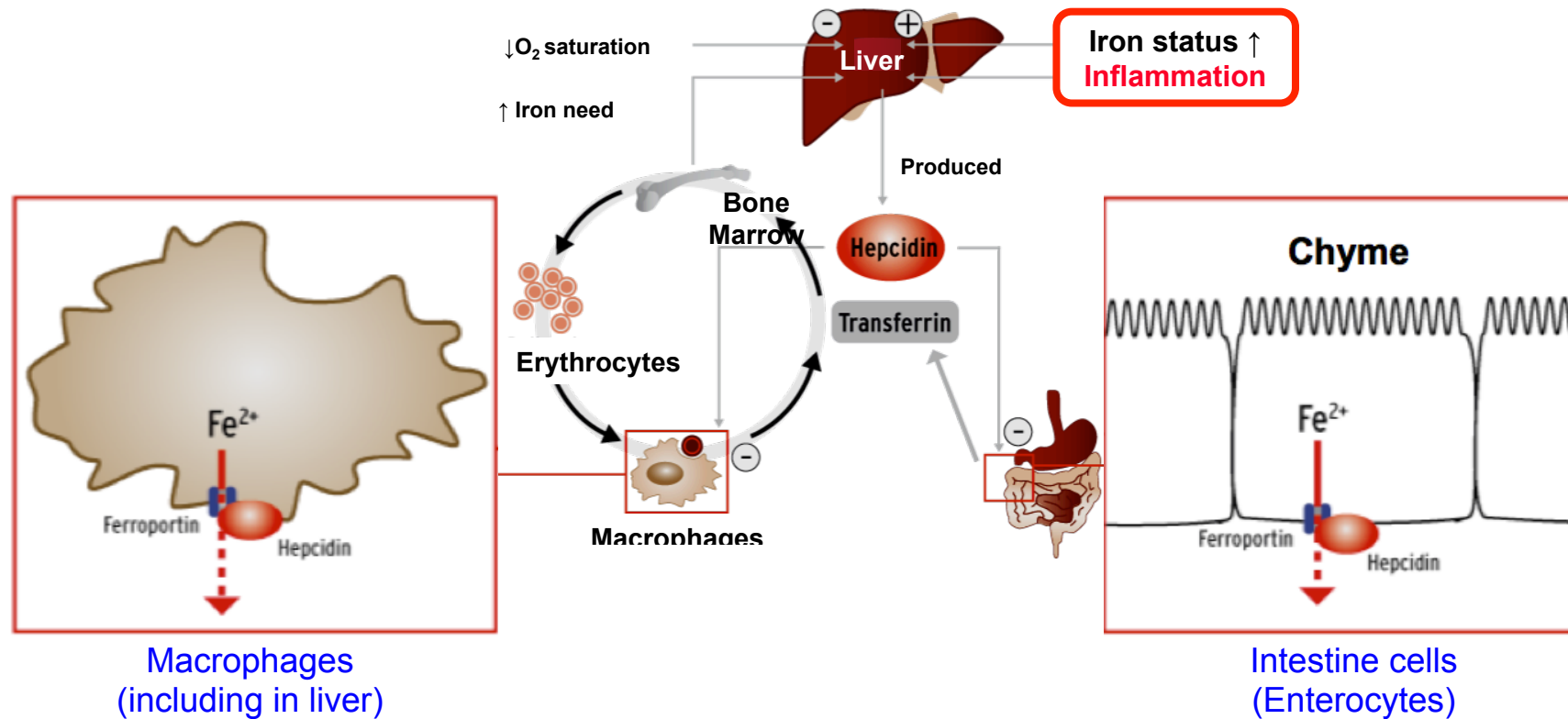
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Some suggest to use iron  
Absorption tests in CHF.  
Levy WC. JACC 2008

Beck-da-Silva L et al.  
Int J Cardiol 2013.

# The pathophysiology of iron deficiency: inflammation, hepcidin, ferroportin & the regulation of iron metabolism



Hentze MW et al. *Cell* 2004;117:285–297

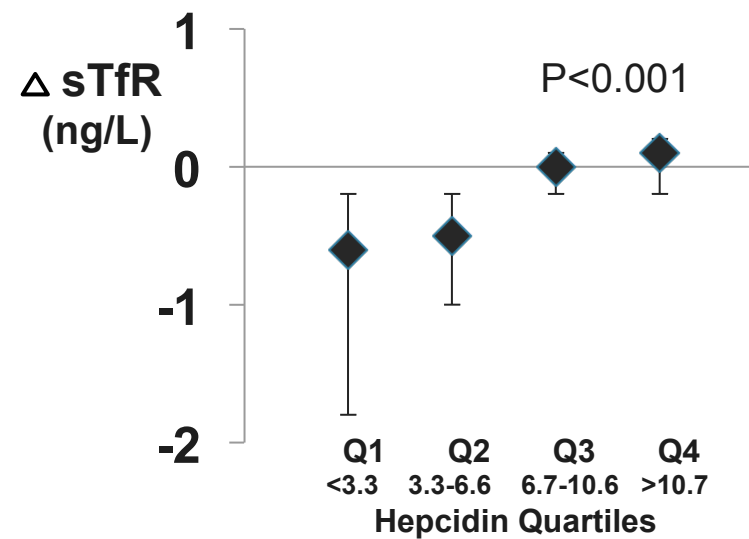
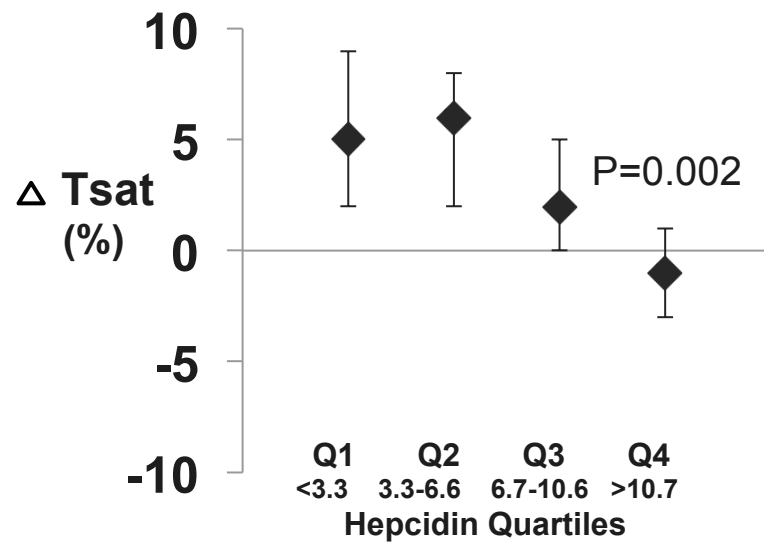
# IRONOUT-HF – Hepcidin levels predict responsiveness to oral iron from baseline to week 16.

## Hepcidin at baseline, ng/mL

Placebo (n=114)	6.5 (3.3–11.1)
Oral Iron (n=111)	6.6 (3.3–10.8)

## sTfR at baseline, ng/mL

Placebo (n=114)	3.8 (3.3–4.8)
Oral Iron (n=111)	3.8 (2.9–4.8)



Higher baseline hepcidin levels were related to:  
 ↓ Δ cellular iron levels: Δ sTr  $r=0.49$ ,  $p<0.001$

sTfR at baseline in  
 EFFECT-HF: 4.6 ng/mL



## Statistical methods – Handling of Dropouts and Missing Data

- If the patient is missing any of the required data such that a difference cannot be calculated, **multiple imputation will be used to address the missing data.**
- **Three sensitivity analyses** will be performed that accounts for missing data differently.
  - **Complete Case Analysis:** If the patient is missing any of the required data such that a difference cannot be calculated, the patient is excluded from that particular analysis.
  - **Repeated Measures:** A repeated measures model will be used with baseline peak  $VO_2$  as a response instead of a covariate.
  - **Worst rank analysis:** Observed change in peak  $VO_2$  will be ranked from smallest to largest. Any patient that died or had a LVAD will be assigned the worst rank.

### **Statistical Tests:**

- A general linear model (PROC GLM in SAS) to compare the treatment groups.
- A mixed model (PROC MIXED) will be used to generate the repeated measures models.

## Conclusions

- Oral iron does not work in patients with chronic heart failure.
- Iron that is not getting into the body cannot exert effects.
- New therapeutic modalities that can overcome the resistance to enteral iron uptake may have a chance.
- Double-blind trials make for clearer results, and hence are preferable whenever possible.
- Outcome trials in HF patients are needed.  
Fair-HF2 – a trial of FCM vs placebo – is about to start.