Iron Deficiency in Heart Failure

Hartfalendag

Zeist – 27 sept 2019

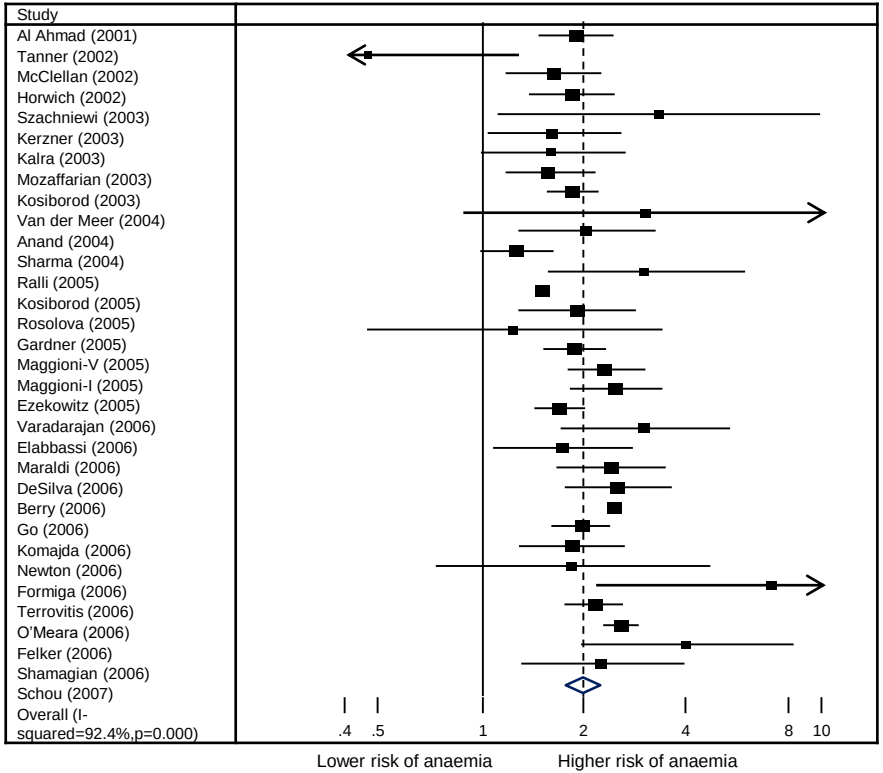
Peter van der Meer, cardioloog

Disclosures

Research grants and/or consultancy fees:

Astra Zeneca, Vifor Pharma, Novartis, Pfizer, Ionis, Servier

Anaemia and mortality



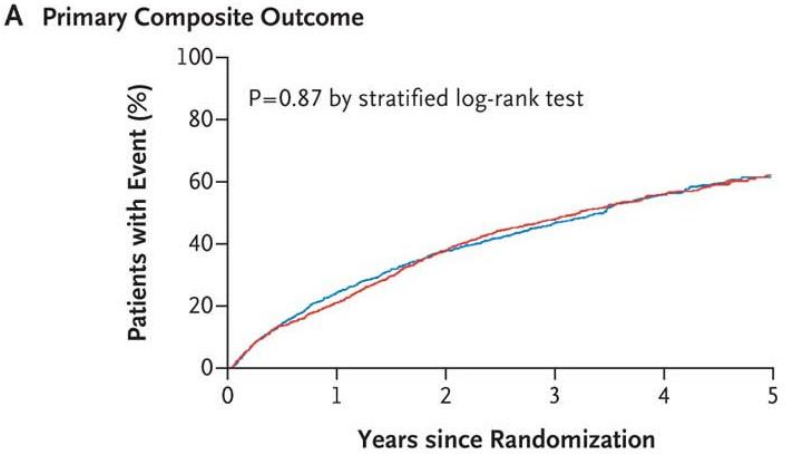
34 studies included

- **150,000 patients**
- **37.8% had anaemia**
- **Odds ratio: 1.96** [1.74–2.21, *p*<0.001]
- **Adjusted HR: 1.46** [1.26–1.69, *p*<0.001]
- **Similar outcome in systolic/diastolic HF**

Groenveld HF. J Am Coll Cardiol 2008;52:818–27

ORIGINAL ARTICLE

Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure



No. at Risk

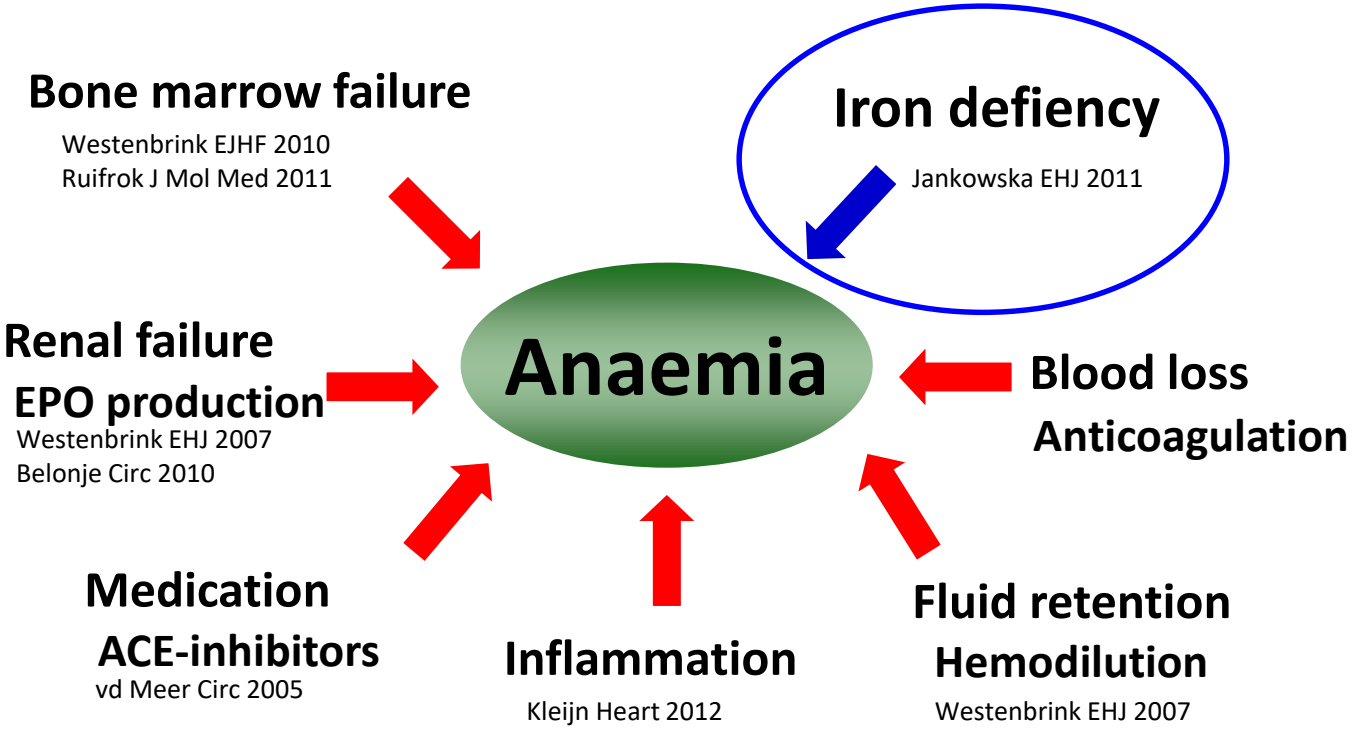
Placebo	1142	956	818	695	591	497	395	290	211	154	92
Darbepoetin alfa	1136	975	855	712	581	473	385	281	212	161	101

PHASE 3 TRIAL (RED-HF)

Inclusion Criteria

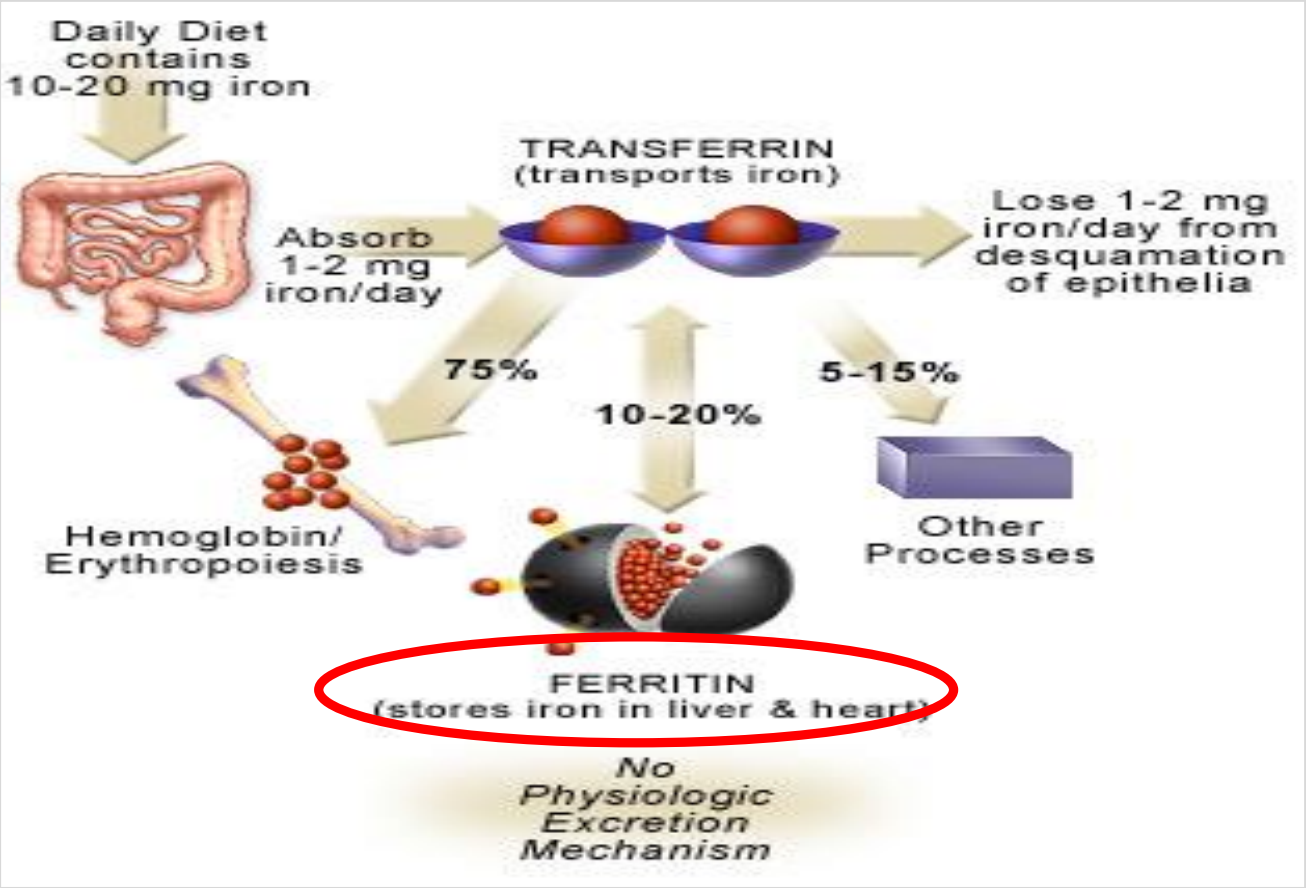
- LVEF < 40%
- Hb 9-12.0 g/dL
- T-SAT: > 15%
- Kreat: <265 umol/L

Possible aetiologies of anaemia in heart failure



van der Meer P. Eur Heart J 2004;25:285–91

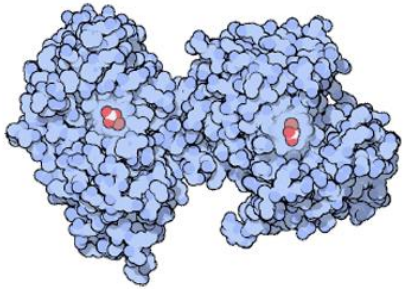
The “life cycle of iron”



How to diagnose iron deficiency

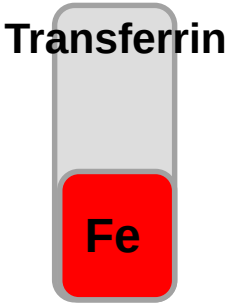
Ferritin = storage of iron

Iron deficiency in HF <100 ug/L



Transferrin-saturation (T-sat)

$$\frac{\text{iron}}{\text{Transferrin}} \times 100 = \text{T-SAT\%}$$



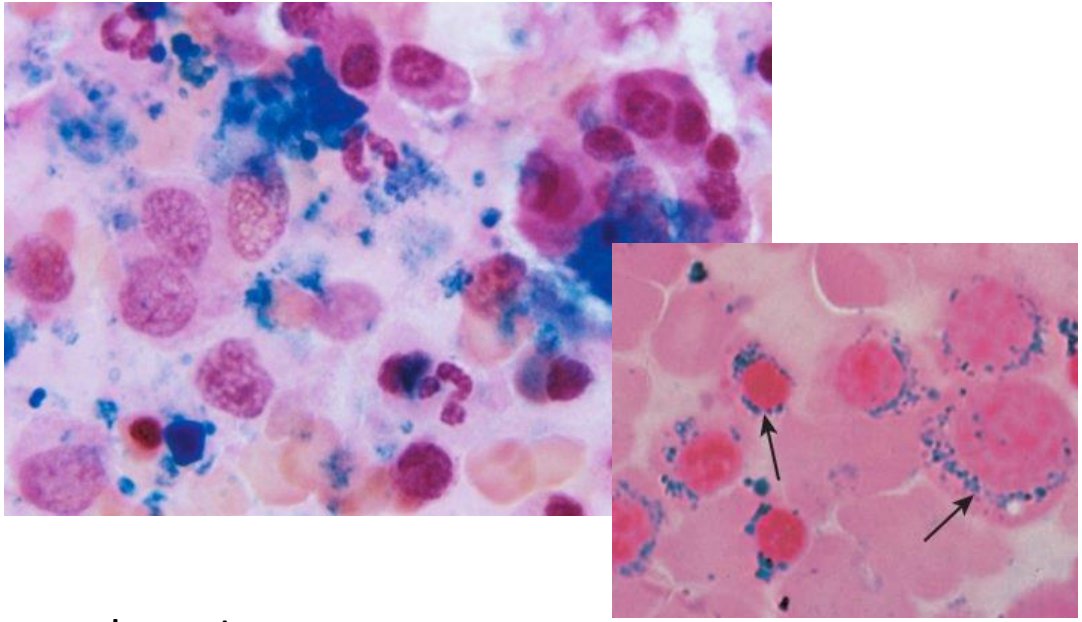
Ferritin < 100 OR Ferritin 100-300 AND T-SAT < 20%

Welke lab-waarden zijn naast ferritine nodig om ijzer status te meten in patienten met hartfalen?

1) Serum ijzer + transferrine
2) Transferrine + hemoglobine
3) Hemoglobine + MCV
4) Serum ijzer + zuurstof saturatie
5) Hemoglobine + hepcidine

Beenmergaspiratie

- Prussian Blue-staining



- Iron stores
- Iron incorporation sideroblasts

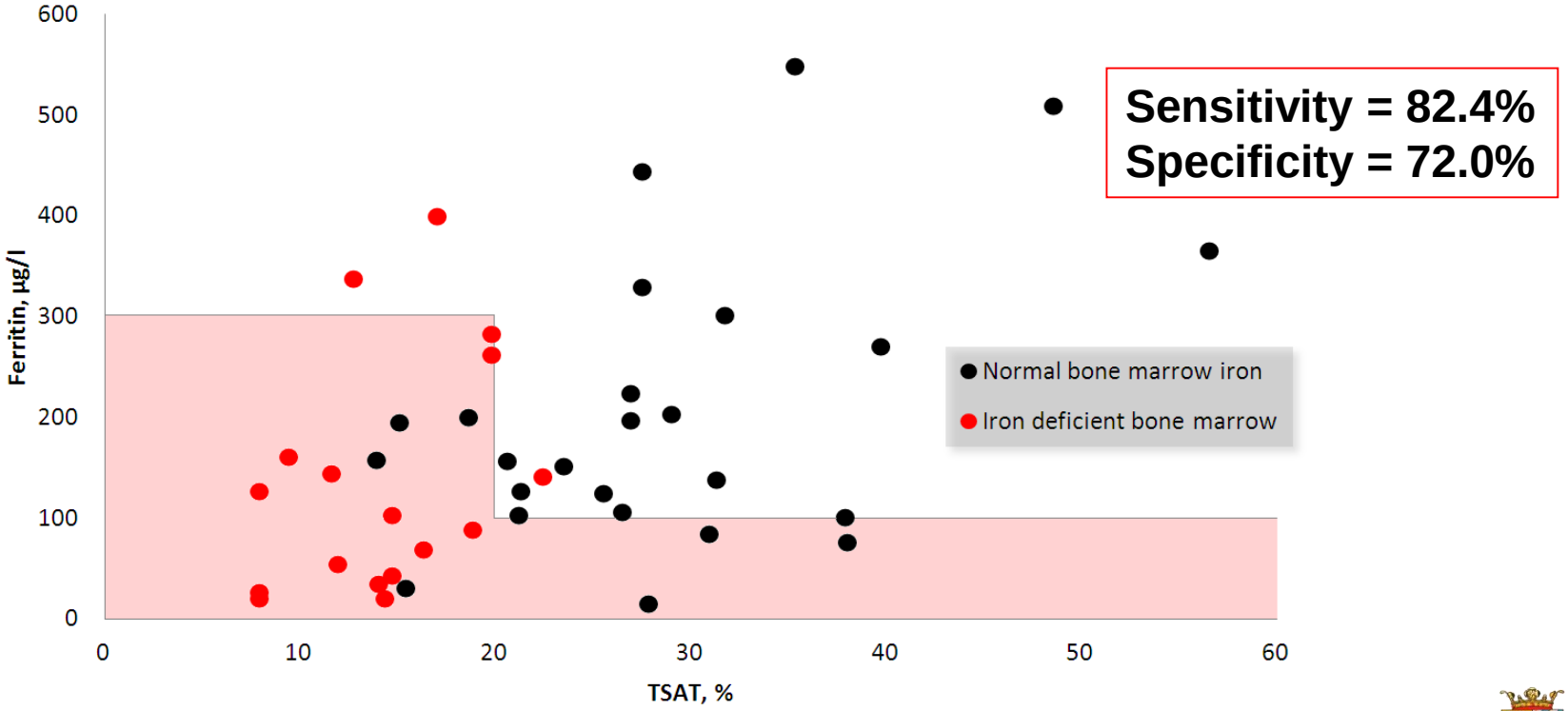
Baseline

Variable	Total
N	42
Age, y	68.0 ± 9.5
Female gender	10 (24%)
BMI, kg/m2	28.6 ± 3.8
SBP (mmHg)	131.5 ± 16.5
NYHA class	
1	8 (19%)
2	21 (50%)
3	12 (29%)
4	1 (2%)
LVEF, %	37.8 ± 7.0
Comorbidities	
Previous MI	20 (48%)
Diabetes mellitus	22 (52%)
Atrial fibrillation	12 (29%)
Hypertension	32 (76%)
Hypercholesterolemia	39 (93%)
ID (FAIR-HF)	21 (50%)
Anemia	7 (17%)
Medication	
Anti-platelets	33 (79%)
Diuretics	22 (52%)
B-Blocker	32 (76%)
ACEi or ARB	38 (90%)

Variable	Total
Laboratory values	
NT-proBNP, ng/l	914 (454, 1755)
eGFR, ml/min/1.73m2	77.9 ± 18.8
CRP, mg/l	2.0 (0.9, 4.5)
Hematology	
Hemoglobin, g/dl	14.0 ± 1.3
MCV, fl.	90.1 ± 5.3
Ferritin, µg/dl	144 (85, 263)
TSAT, %	20.9 (14.7, 27.8)

Grote Beverborg, … Van der Meer Circ HF 2018

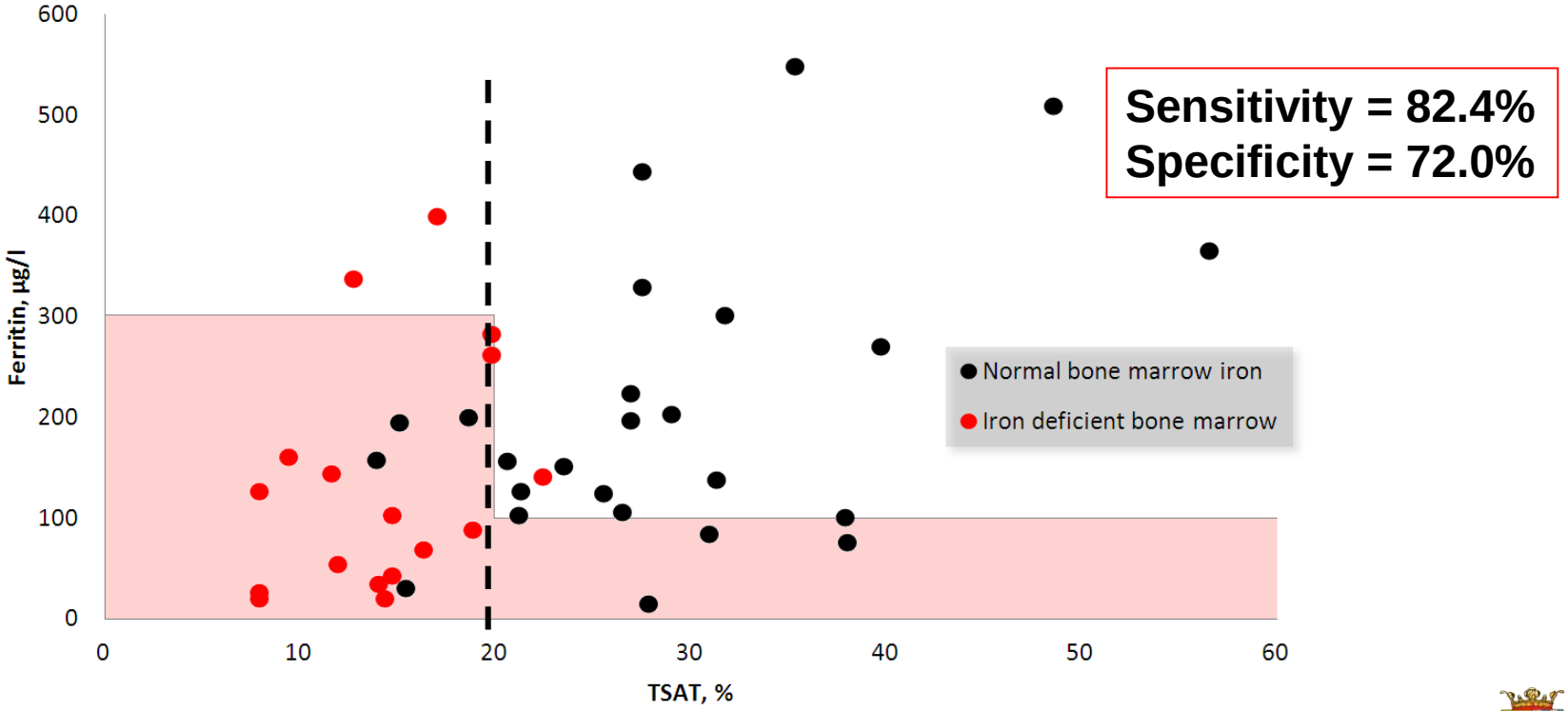
FAIR-HF vs. bonemarrow



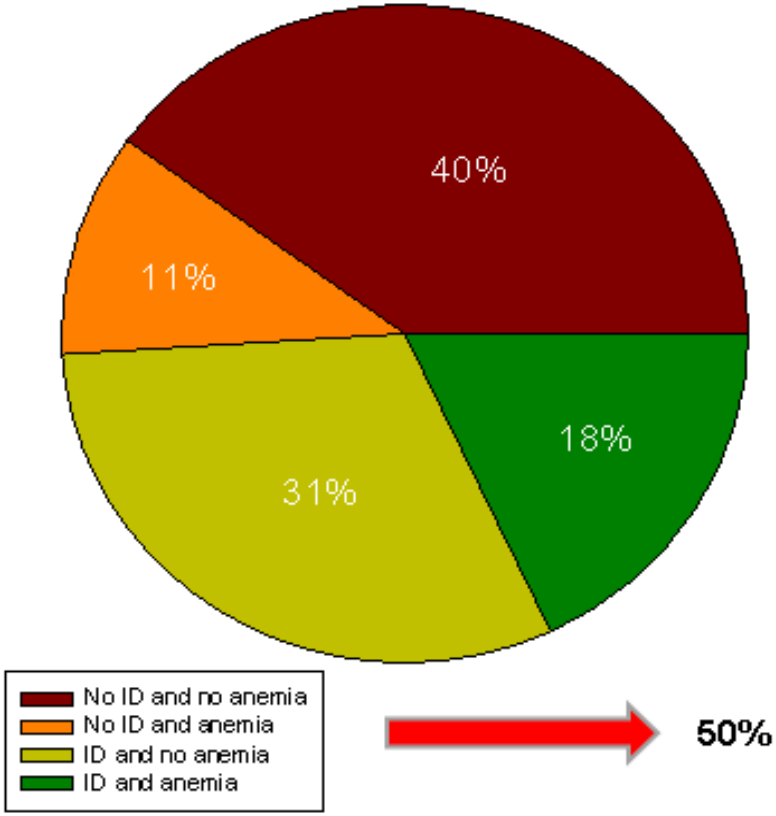
Receiver operating characteristics (ROC)

Variables for prediction of ID	AUC ± SE	Cut-off value	Sensitivity	Specificity
Hemoglobin, g/dl	0.820 ± 0.064	≤14.2	94.1%	48.0%
Hematocrit, %	0.716 ± 0.081	≤0.41	70.6%	58.3%
Reticulocytes, $x10^9$/l	0.586 ± 0.095	≥13.1	64.7%	58.3%
RPI	0.618 ± 0.091	≤60.2	82.4%	50.0%
MCV, fl	0.645 ± 0.090	≤90.1	76.5%	62.5%
MCH, fmol	0.719 ± 0.084	≤1879	75.0%	66.7%
MCHC, g/dl	0.773 ± 0.080	≤20.9	75.0%	66.7%
RDW, %	0.733 ± 0.083	≥13.5	58.8%	75.0%
HYPO, %	0.687 ± 0.091	≥0.2	64.7%	78.3%
RET-He, pg	0.821 ± 0.066	≤32.2	76.5%	73.9%
RBC-He, pg	0.706 ± 0.086	≤30.0	82.4%	69.6%
Delta-He, pg	0.776 ± 0.076	≤1.8	58.8%	91.3%
Ferritin, µg/l	0.666 ± 0.089	≤145	70.6%	60.0%
TSAT, %	0.932 ± 0.036	≤19.8	94.1%	84.0%
Transferrin, mg/l	0.515 ± 0.096	≤250	58.8%	68.0%
Iron, µg/dl	0.922 ± 0.044	≤13	94.1%	88.0%
sTfR, mg/l	0.679 ± 0.089	≥1.06	70.6%	56.0%
sTfR-index	0.706 ± 0.090	≥0.19	58.8%	92.0%
Hepcidin, nM	0.541 ± 0.111	≤6.1	52.9%	84.0%

T-SAT < 20% goede voorspeller van ijzer deficientie



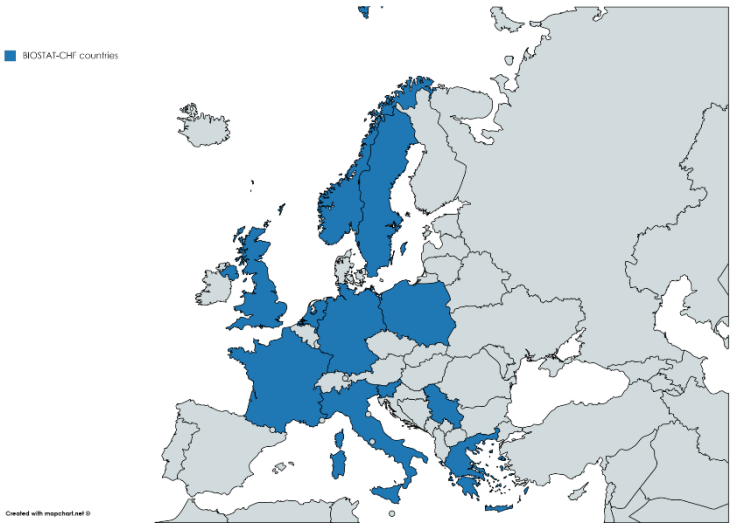
Prevalence of iron deficiency in large cohort



- NYHA class I-IV
- 1506 patients
- 86% were HFrEF
- ID:
  Ferritin < 100 µg/L or ferritin 100-299 µg/L when TSAT <20%
- Anemia WHO criteria

50% of HF patients are iron deficient

Why are patients with heart failure iron deficient?



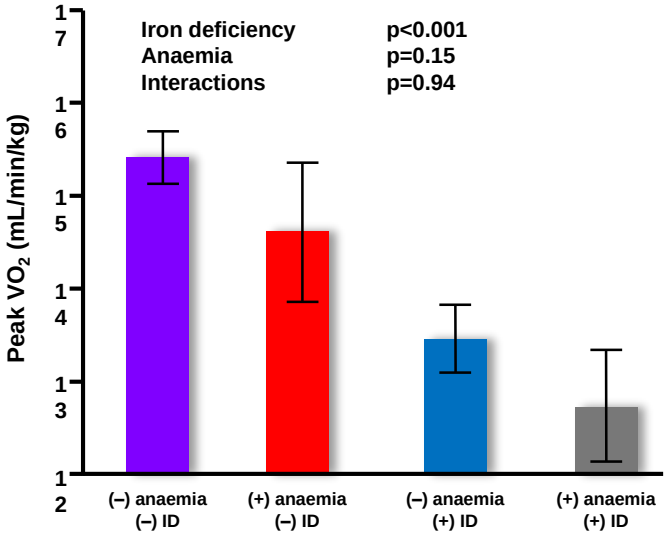
- N = 2352 patients with worsening HF
- Mean age 69 years and 26% women
- Median NTproBNP: 4300 ng/L
- 62% of the patients are iron deficient

Predictors of iron deficiency

Determinants of iron deficiency in heart failure		
Iron uptake	Iron storage	Iron loss
Malnutrition	Inflammation	$P2Y_{12}$ inhibitor use
Fluid overload	Renal disease	
Female sex		

Van der Wal, … Van der Meer Eur Heart J in press

Iron deficiency leads to impaired exercise tolerance.

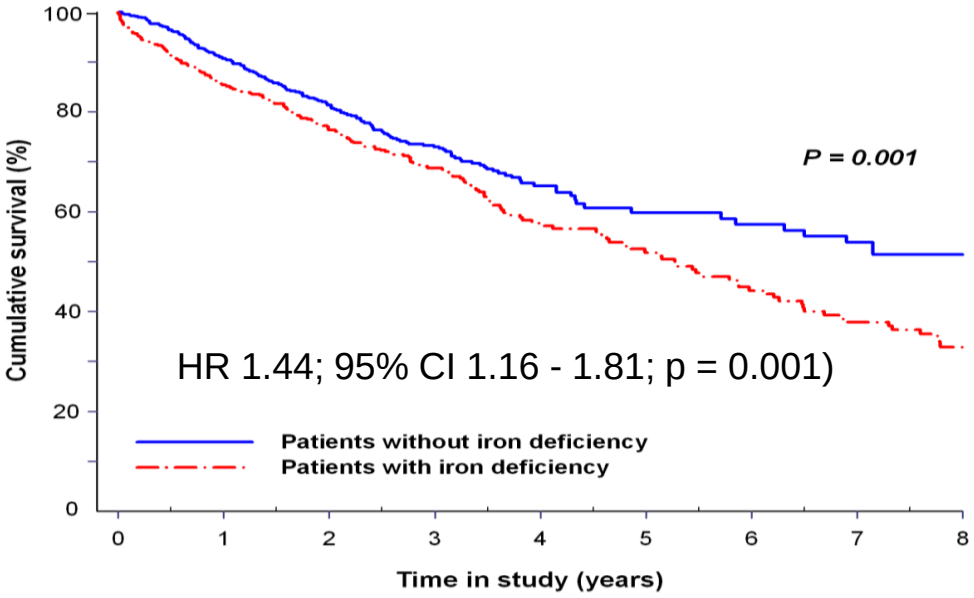


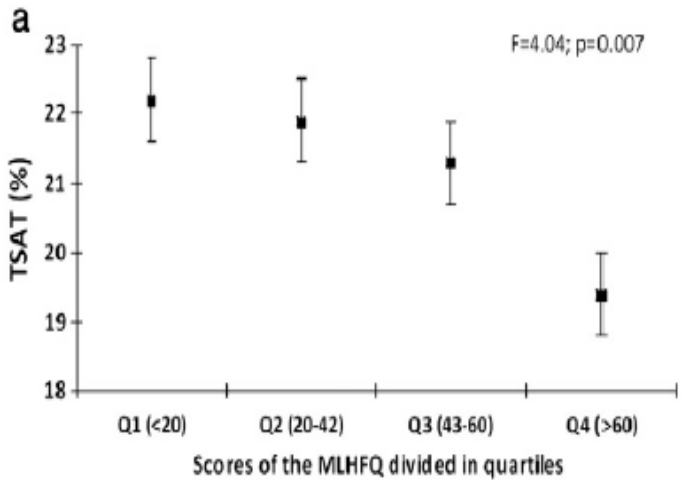
- **443 patients with stable systolic CI**
- **age 54 ± 10 years,**
- **males 90%,**
- **LV ejection fraction 26 ± 7%,**
- **NYHA: I/II/III/IV 49/188/180/26)**

- Iron deficiency defined as serum ferritin <100µg/L, or serum ferritin 100–300µg/L with TSAT <20%
- Anaemia defined as haemoglobin level <12g/dL in women and <13g/dL in men

Jankowska EA, et al. J Cardiac Fail 2011;17:899–906

Iron deficiency associated with lower QoL and higher mortality





Klip J. Am Heart J 2013 accepted

Heeft het zin om ijzerdeficientie in hartfalen te behandelen?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

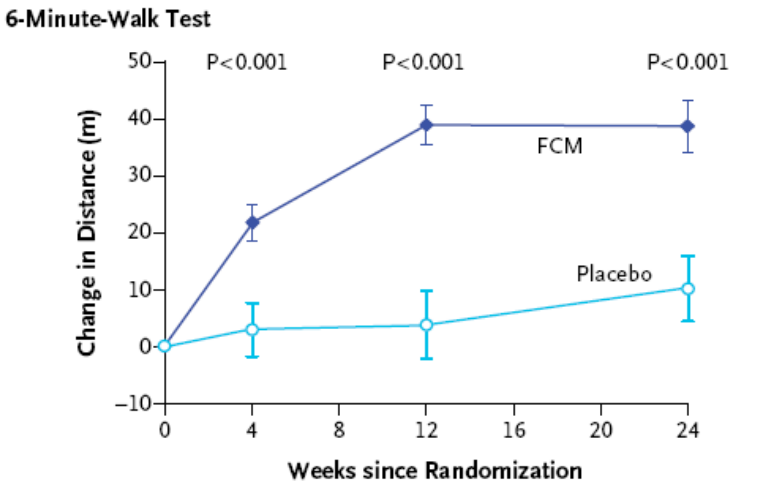
Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

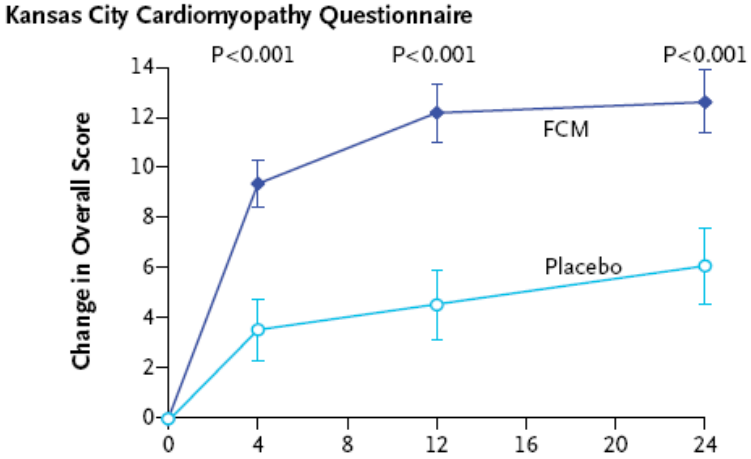
hypothesis

the Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial, to determine whether the correction of iron deficiency with the use of intravenous iron (ferric carboxymaltose) confers symptomatic benefits in patients with chronic heart failure.

Anker, .. Ponikowksi. NEJM 2009

Iron deficiency in chronic heart failure



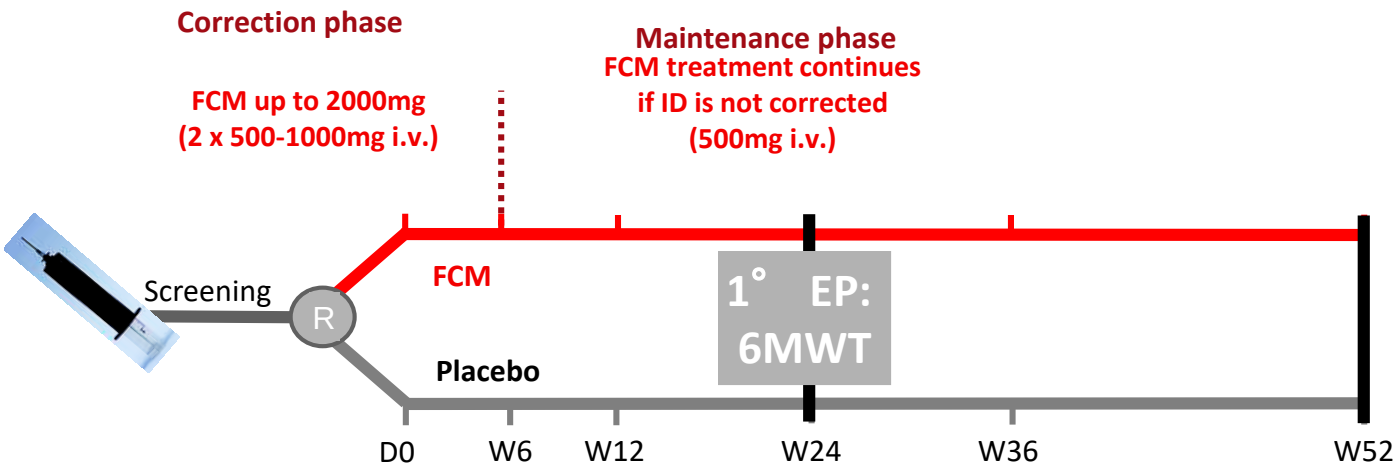


Self-Reported Patient Global Assessment

Subgroup	Ferric Carboxy-maltose	Placebo	Odds Ratio (95% CI)	P Value for Interaction
	no. of patients			
Hemoglobin				0.98
≤120 (g/liter)	146	74		
>120 (g/liter)	146	75		
Median ferritin				0.45
≤39 (μg/liter)	153	72		
>39 (μg/liter)	139	77		
Estimated GFR				
<60 (ml/min/1.73 m^2 of body-surface area)	119	67		0.22
≥60 (ml/min/1.73 m^2 of body-surface area)	173	82		
Median age				0.10
≤69.7 yr	149	75		
>69.7 yr	143	74		
Sex				0.99
Male	140	68		
Female	152	81		
NYHA class				0.66
Class II	52	27		
Class III	240	122		
Median LV ejection fraction				0.86
≤33%	169	70		
>33%	123	79		

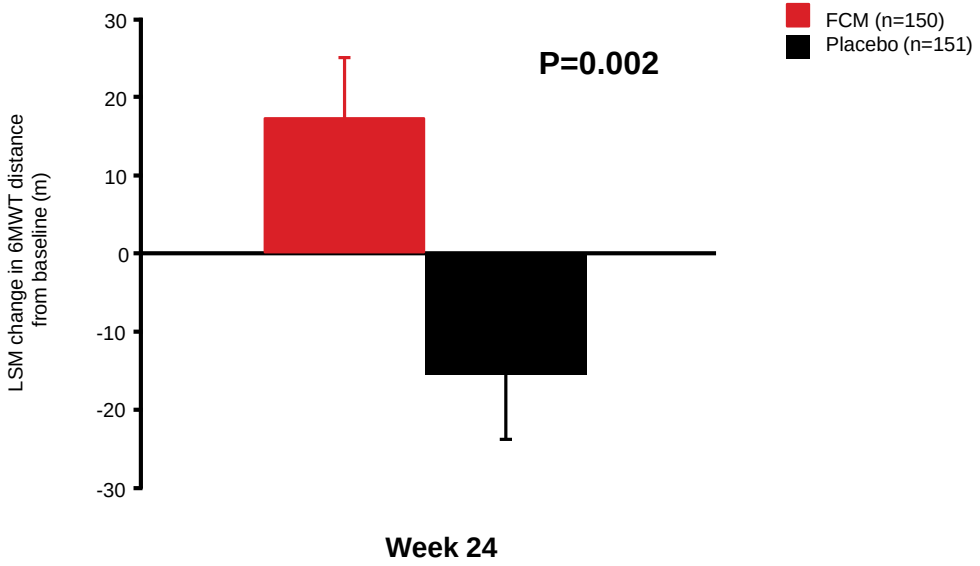
CONFIRM-HF

- **Design:** Multicentre, randomised (1:1), double-blind, placebo-controlled
- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤45%
  - BNP > 100 pg/mL or NT-proBNP > 400 pg/mL
  - **Iron deficiency: serum ferritin <100 ng/mL or 100-300 ng/mL if TSAT <20%**
  - Hb < 15 g/dL



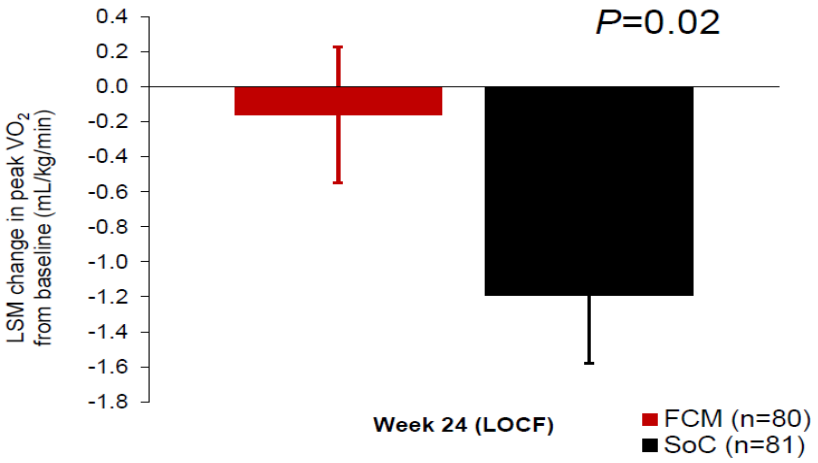
Primary endpoint:
6-minutes walking distance at week 24

- FCM improved 6MWT at week 24:
- FCM vs placebo: 33 ± 11 m (least squares mean ± standard error)



EFFECT-HF

- Open label (Ferinject vs. OMT)
- N=161
- Iron deficiency
- HFrEF
- Change peak VO2 at 24wk



Circulation 2017

Werkt oraal ijzer net zo goed?

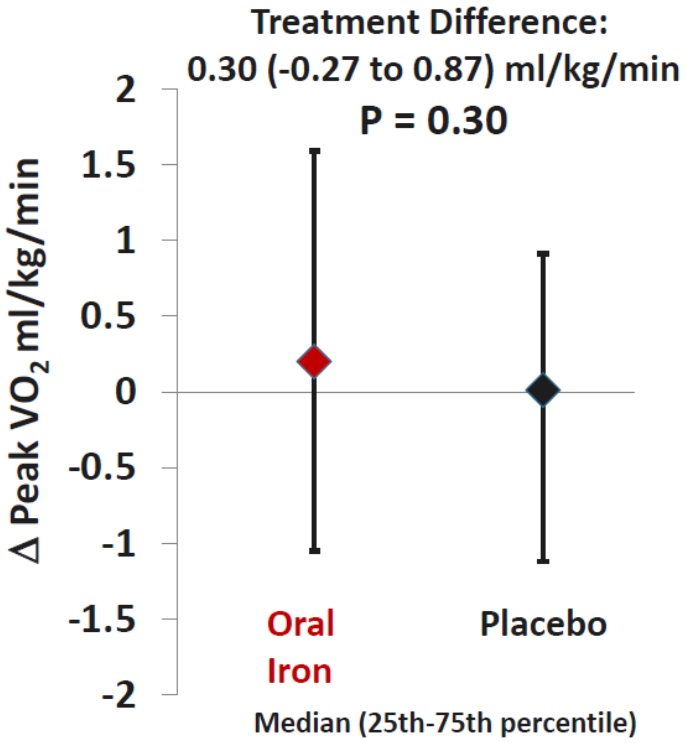
IRON OUT

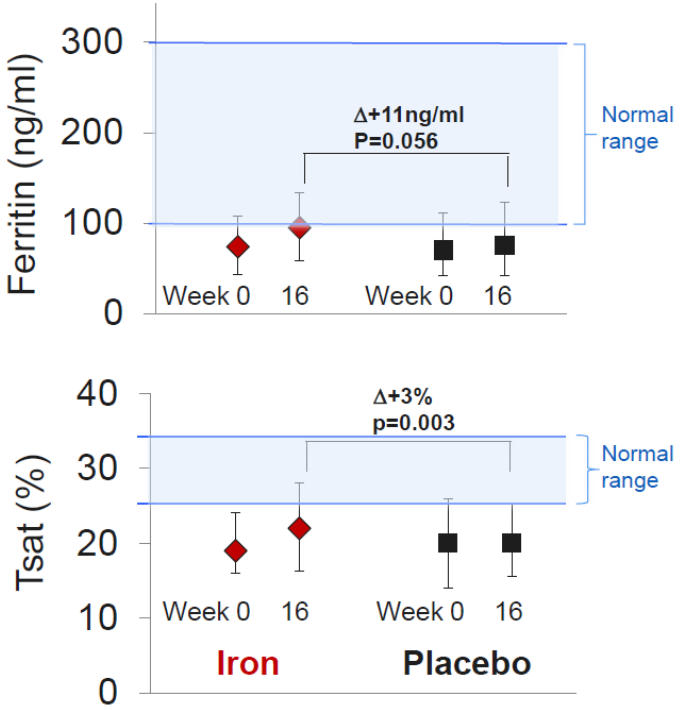
Oral iron vs. placebo

- Double blind placebo controlled
- N=225
- Iron deficiency + Hb (9-13.5 g/dL)
- LVEF <40%

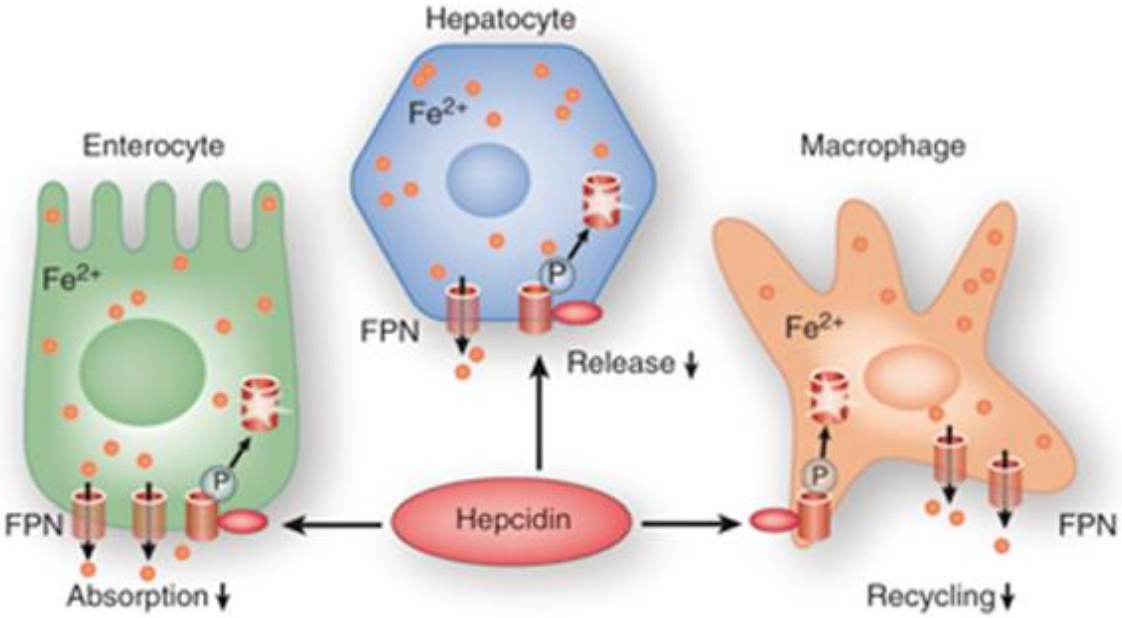
- Oral iron [2dd150mg feramax vs. Placebo]

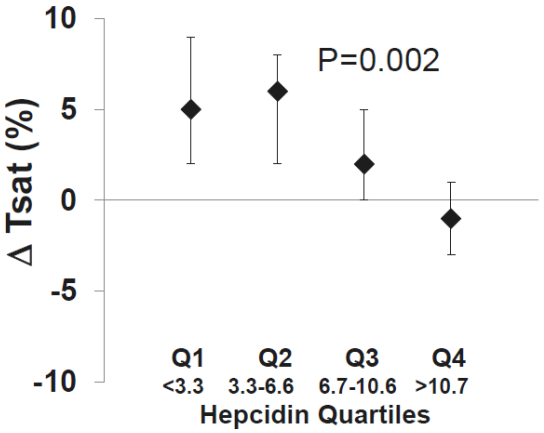
- Primary endpoint change peak VO2 at 16wks


Treatment Difference:
0.30 (-0.27 to 0.87) ml/kg/min
P = 0.30
Δ Peak VO2 ml/kg/min
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
Oral Iron
Placebo
Median (25th-75th percentile)


Ferritin (ng/ml)
300
200
100
0
Δ+11ng/ml
P=0.056
Normal range
Week 0
16
Week 0
16
Tsat (%)
40
30
20
10
0
Δ+3%
p=0.003
Normal range
Week 0
16
Week 0
16
Iron
Placebo

Iron deficiency – Inflammation - Uptake



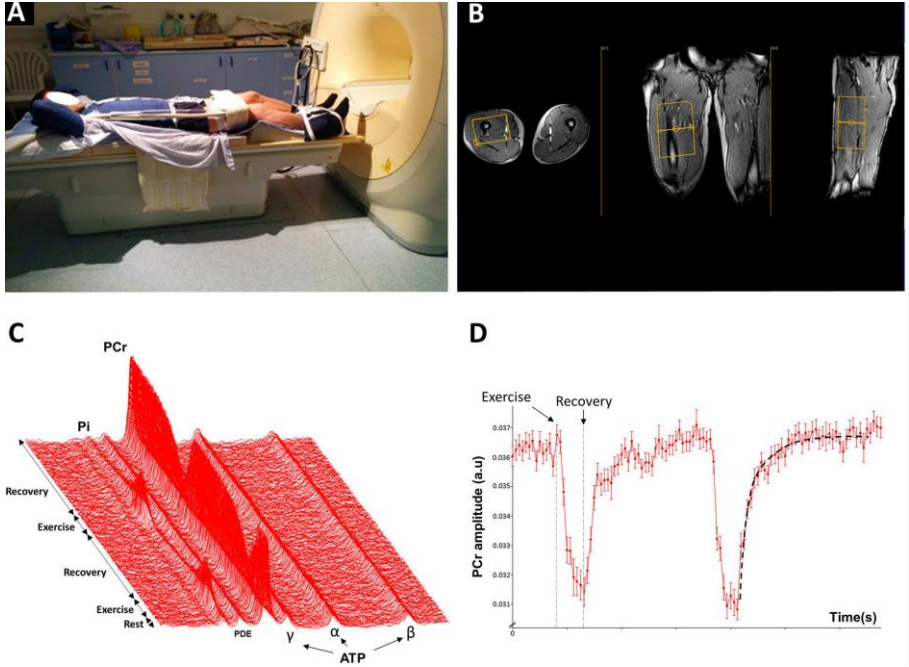


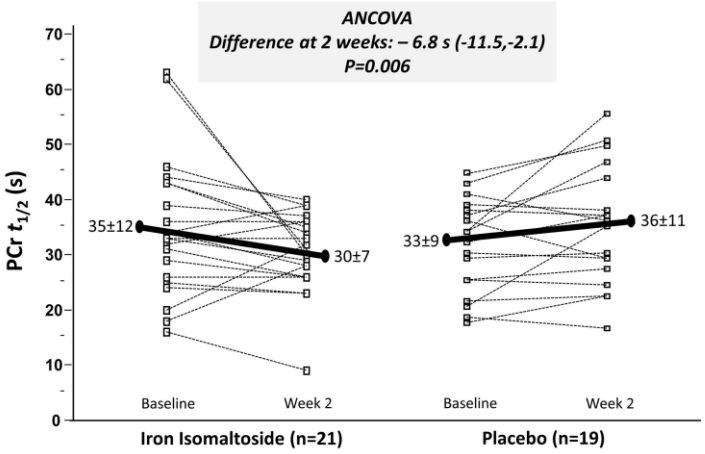
Behandeling van ijzerdeficientie in hartfalen

a) Eerst oraal ijzer en indien niet effectief i.v. ijzer
b) Alleen i.v. ijzer is bewezen effectief
c) Effect oraal ijzer en i.v. ijzer zijn niet onderzocht in hartfalen

IV iron improves skeletal muscle performance in HF patients

^{31}P MRI scan

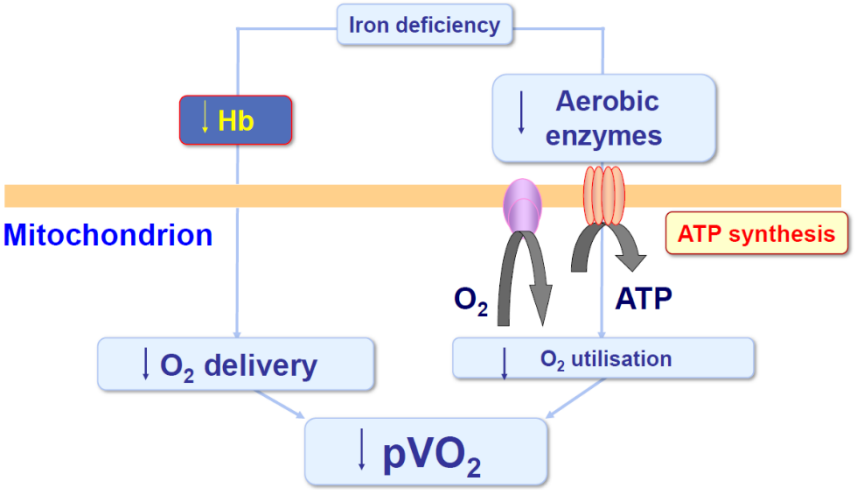


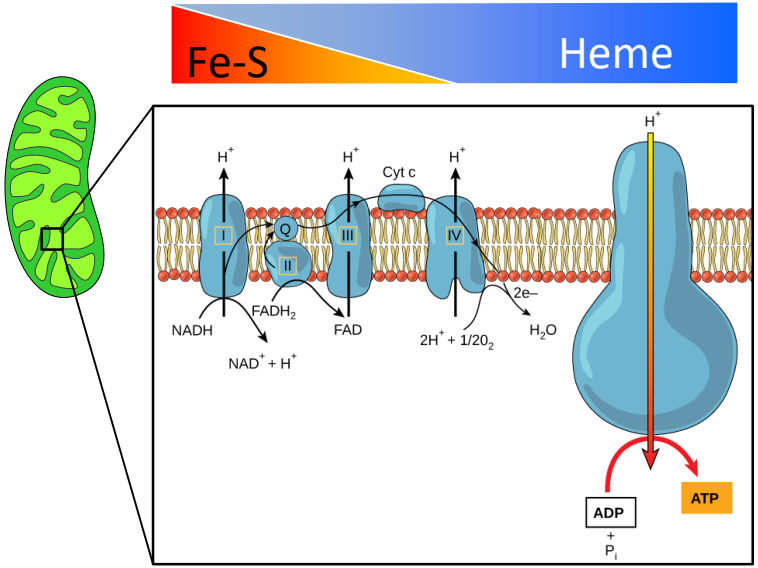


Charles-Edwards G et al. *Circulation.* 2019;139:2386-98

Iron deficiency impairs contractility of human cardiomyocytes through decreased mitochondrial function

Martijn F. Hoes[1†], Niels Grote Beverborg[1†], J. David Kijlstra[1], Jeroen Kuipers[2], Dorine W. Swinkels[3], Ben N.G. Giepmans[2], Richard J. Rodenburg[4], Dirk J. van Veldhuisen[1], Rudolf A. de Boer[1], and Peter van der Meer[1*]

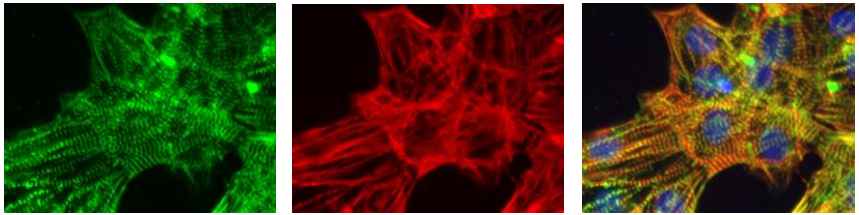


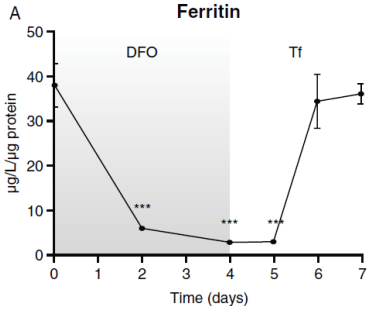


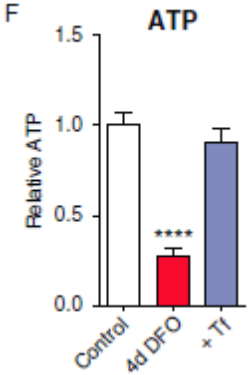
Hoes MF et al. *Eur J Heart Fail.* 2018;20:910–9

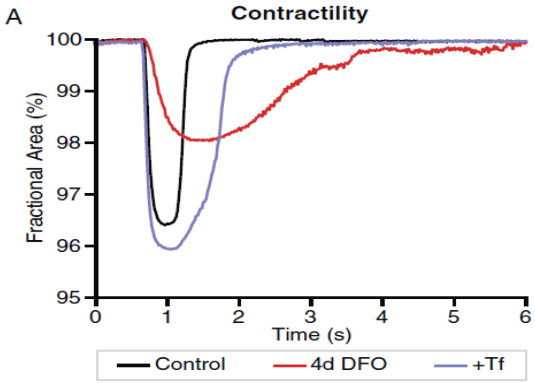
Iron deficiency – more than haemoglobin

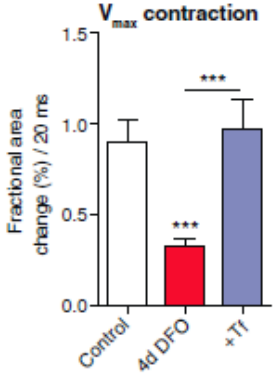
α-actinin cTnT DNA











Hoes MF et al. *Eur J Heart Fail*. 2018;20:910–9

CONCLUSIONS

- Iron deficiency is observed in 50% of HF patients
- Iron deficiency relates to a reduced exercise tolerance
- Iron deficiency is associated with a substantial higher mortality risk
- 3 trials showed beneficial effects of i.v. iron on soft endpoints
- Oral iron does not improve peak VO2.
- Several ongoing iron trials will investigate the effect on morbidity/mortality (AFFIRM, FAIR-HF2, IRONMAN, HEART-FID