The iron link in the vicious circle of heart failure

Peter van der Meer

Prevalence and definition of anaemia

Anaemia is common in patients with chronic heart failure

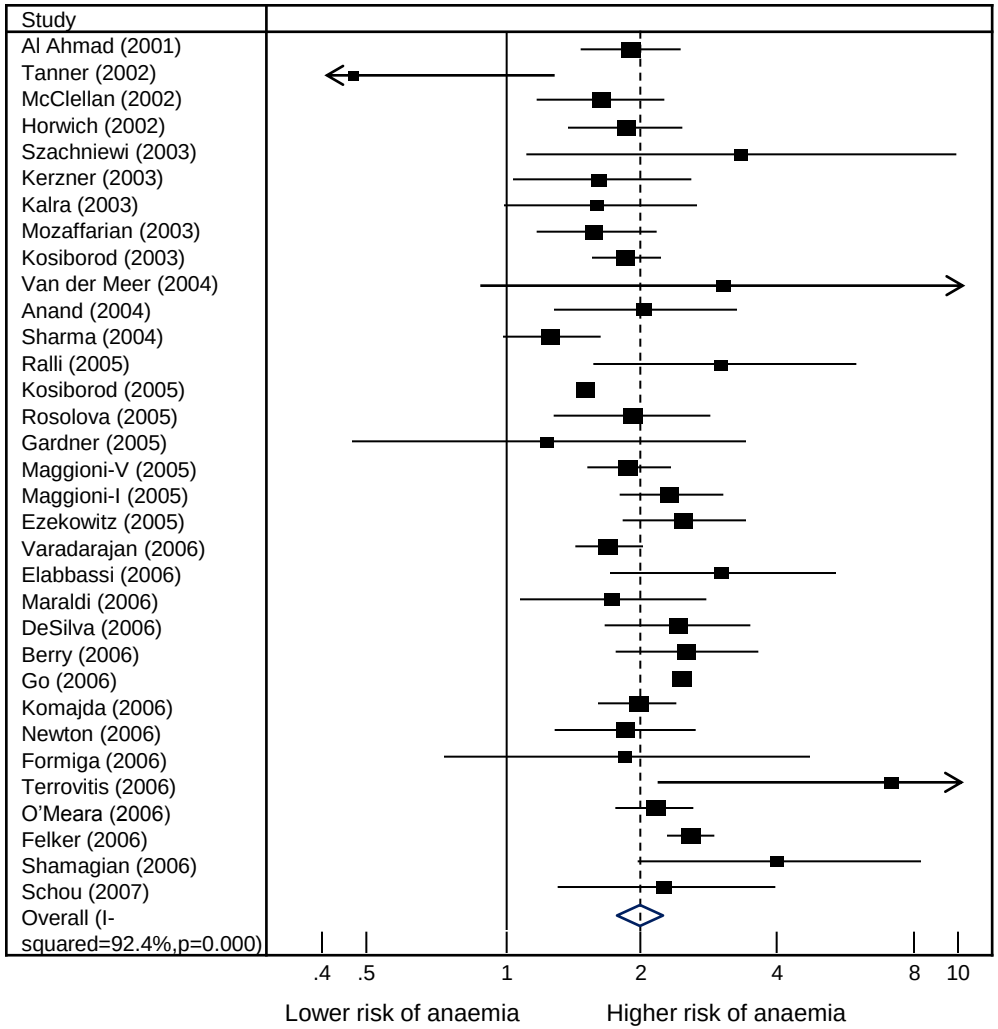
Prevalence 14–79%

Prevalence of anaemia depends on:

- Severity of HF
- Definition of anaemia
  - WHO definition: – male <13.0 g/dL (8.1 mmol/L)
    – female <12.0 g/dL (7.5 mmol/L)

van der Meer P. Heart 2009;95:1808–12

Anaemia and mortality

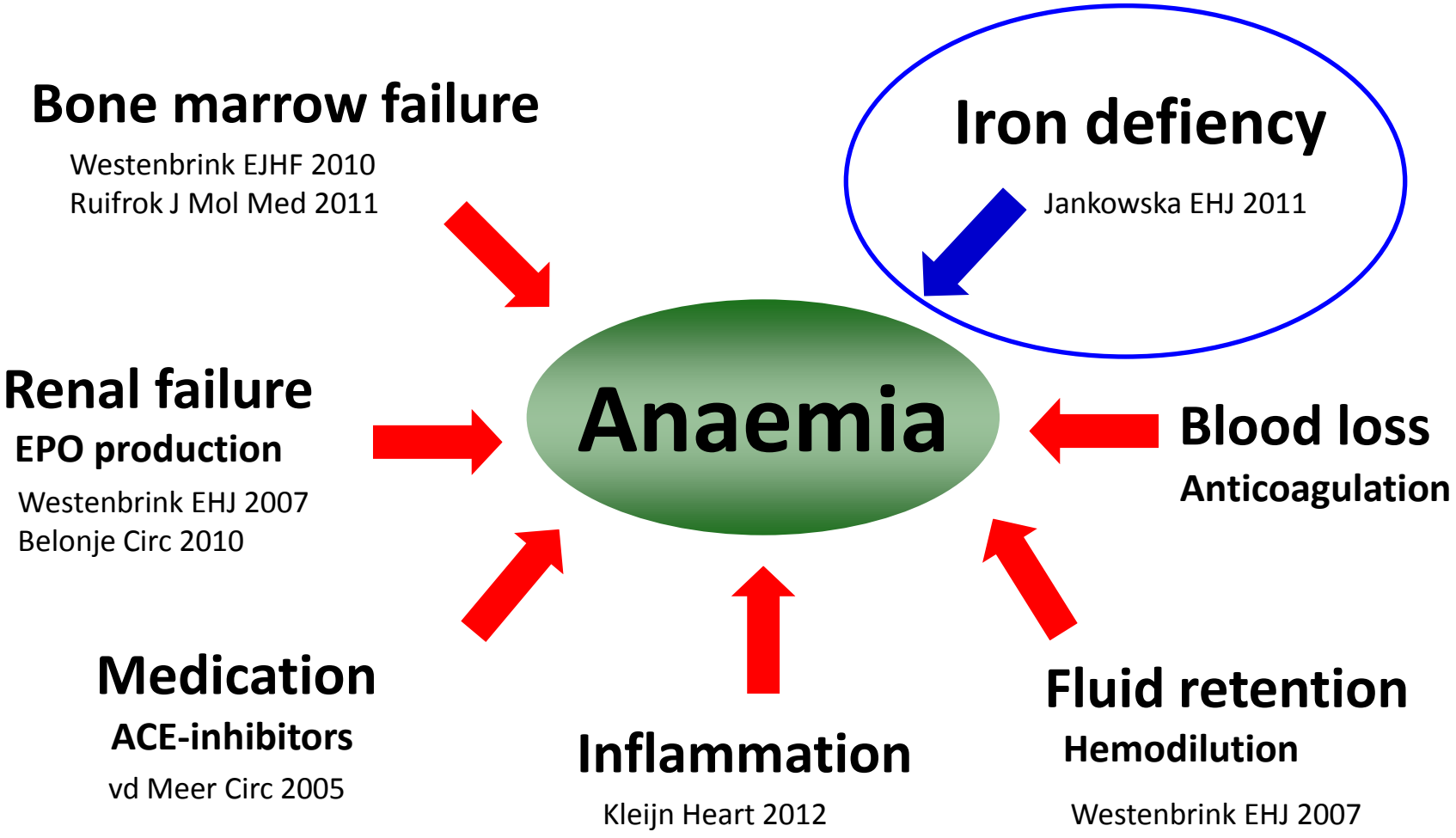


34 studies included

- **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

Possible aetiologies of anaemia in heart failure

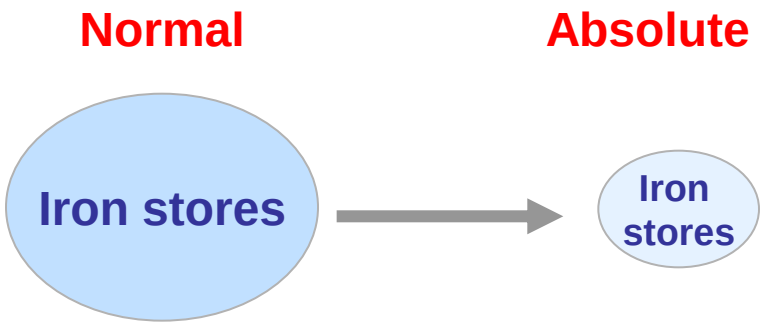


van der Meer P. Eur Heart J 2004;25:285–91

Definition of iron deficiency

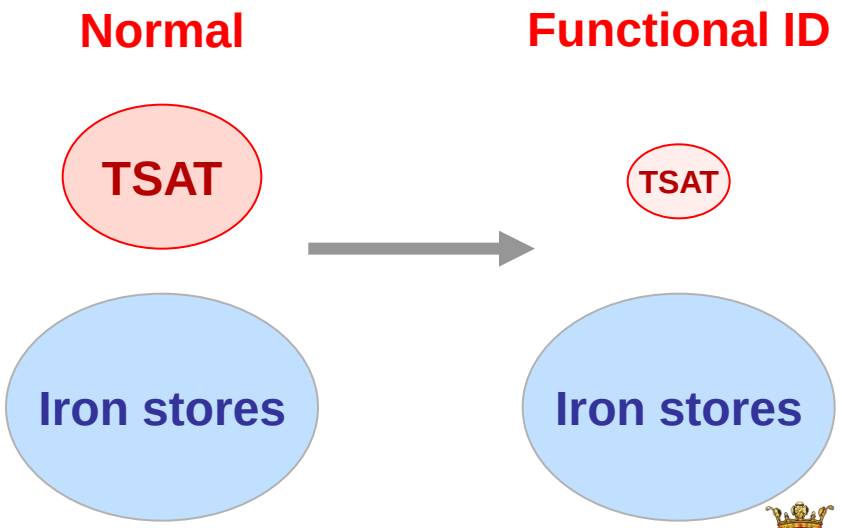
- **Absolute ID**
  - Depletion of iron available in the circulation (bound to transferrin) and iron stores (ferritin in the liver and iron in the RES)
  - Caused by chronic blood loss

Strict: Ferritin < 30 µg/L
FAIR-HF: Ferritin < 100 µg/L
Nephro: Ferritin < 100 µg/L

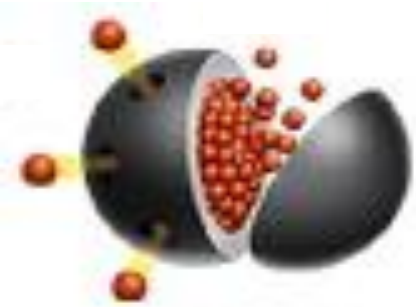


- **Functional ID**
  - Depletion of iron available in the circulation (bound to transferrin) but not iron stores
  - Caused by inflammation induced by elevated hepcidin levels

Strict: Ferritin < 30-99 µg/L when TSAT < 20%
FAIR-HF: Ferritin < 100-299 µg/L when TSAT < 20%
Nephro: TSAT < 20%

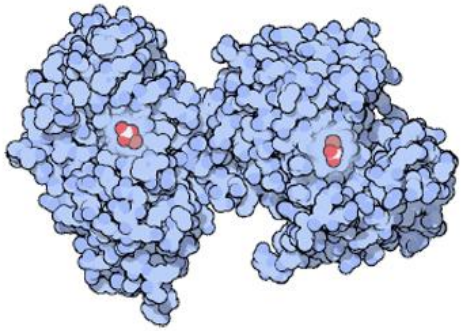


Ferritin: Storage iron

Parameter measured	Advantages	Limitations
• Storage iron[1] (serum ferritin) 	• The most useful indirect estimate of body iron stores[2] • In healthy individuals, serum ferritin correlated with body iron stores[2]	• Normal or high ferritin does not exclude functional ID or absolute ID[3] • Gender differences (normally lower in women)[1] • Acute-phase reactant[1] • Can be elevated by concomitant inflammatory conditions, infection, malignancy or liver disease[2,3]

1. Wish JB. Clin J Am Soc Nephrol 2006;1:S4–8
2. Crichton RR et al. Iron therapy with special emphasis on intravenous administration (4th edition) 2008
3. Macdougall IC. Curr Opin Nephrol Hyperten 1994;3:620–5

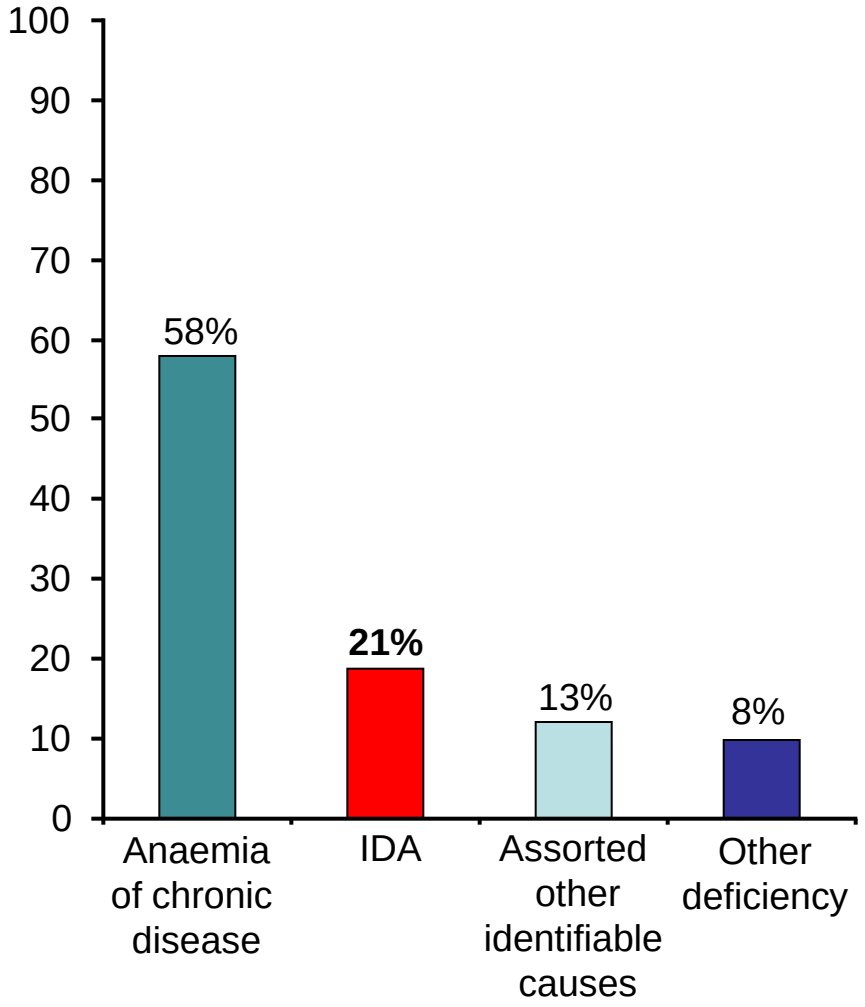
TSAT: Circulation iron

Parameter measured	Advantages	Limitations
• Amount of iron available for erythropoiesis[1] • TSAT = serum iron divided by total iron binding capacity (amount of transferrin) x 100[2]	• Absence (or near absence) of stainable iron in bone marrow correlates with TSAT <20%[2]	• Marked diurnal variation[1,2] • Transferrin is an acute-phase reactant[2] • Influenced by inflammation, malnutrition and chronic disease[2]  Transferrin

1. Macdougall IC. Curr Opin Nephrol Hyperten 1994;3:620–5
2. Wish JB. Clin J Am Soc Nephrol 2006;1:S4–8

Iron deficiency is a common cause of anaemia

- A population-based cohort of patients with new-onset HF
  - n=12 065
- Anaemia identified in 17% of patients who tended to be:
  - older
  - female
  - hypertensive
  - chronically renal insufficient
- ID is the cause in 21% of patients with anaemia

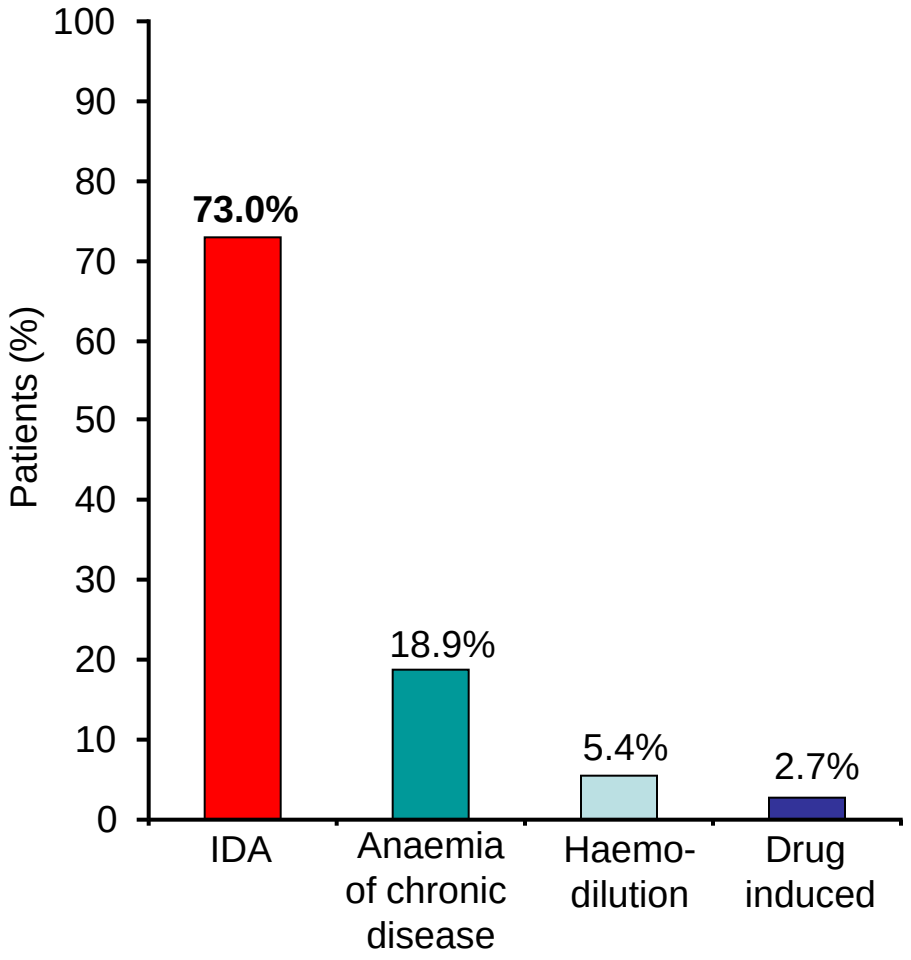


Ezekowitz JA. Circulation 2003;107:223–5

Iron deficiency is common in heart failure

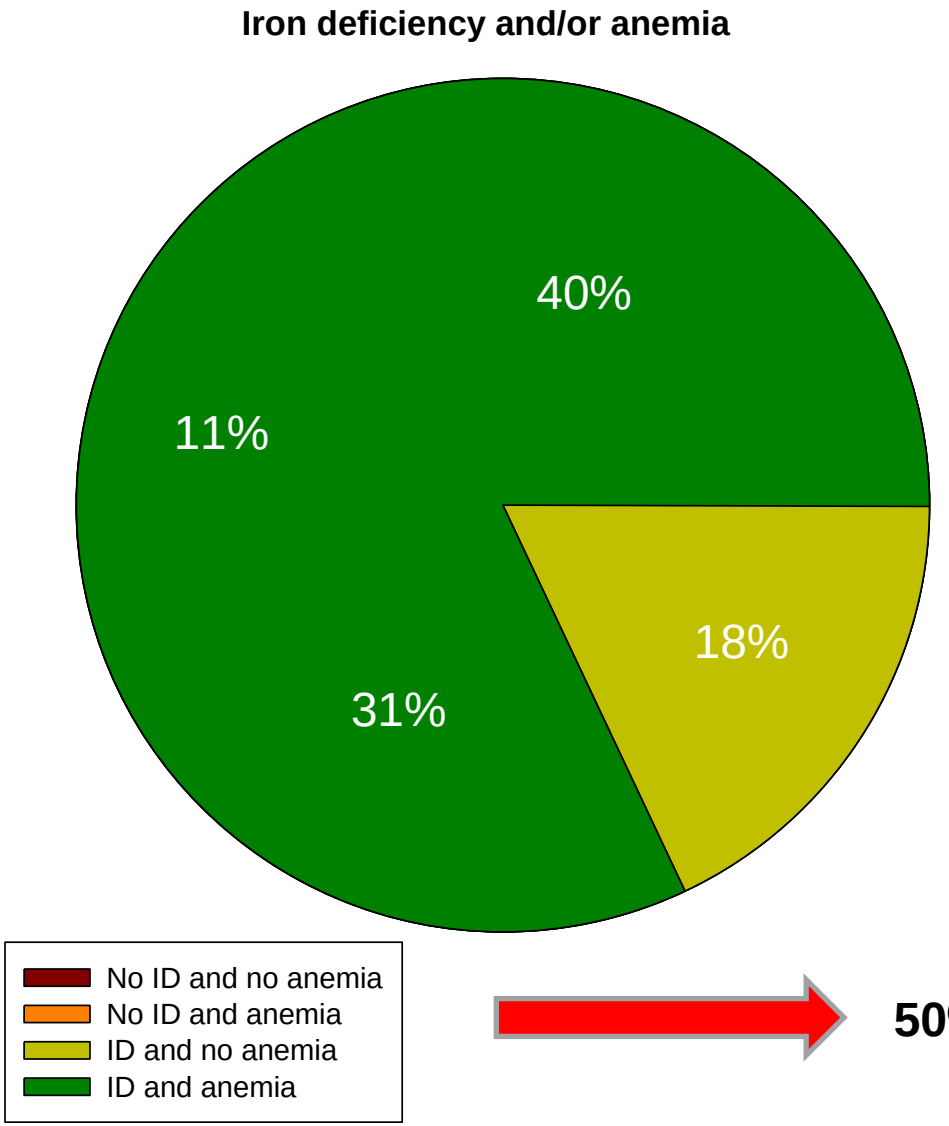
Bone marrow biopsy "the golden standard"

- Patients with anaemia and advanced chronic HF
  - n=37
  - NYHA: IV
  - LVEF: 22%
  - Ferritin: 113 ng/mL
- Bone-marrow biopsy confirmed ID in 73% (27/37) of patients
- MCV, MCHb and serum ferritin concentration significantly lower in patients with ID compared with patients without ID



Nanas JN. J Am Coll Cardiol 2006;48:2485–9

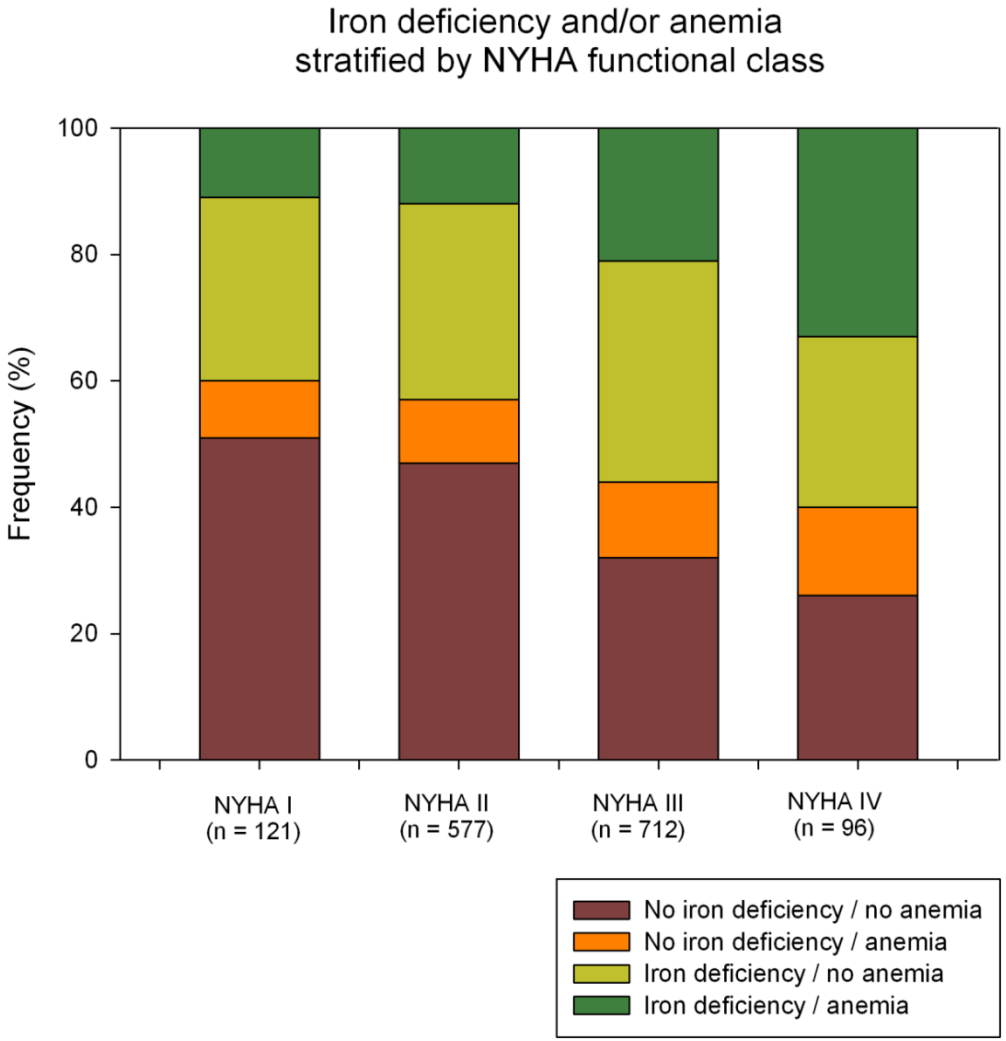
Prevalence of iron deficiency in large cohort



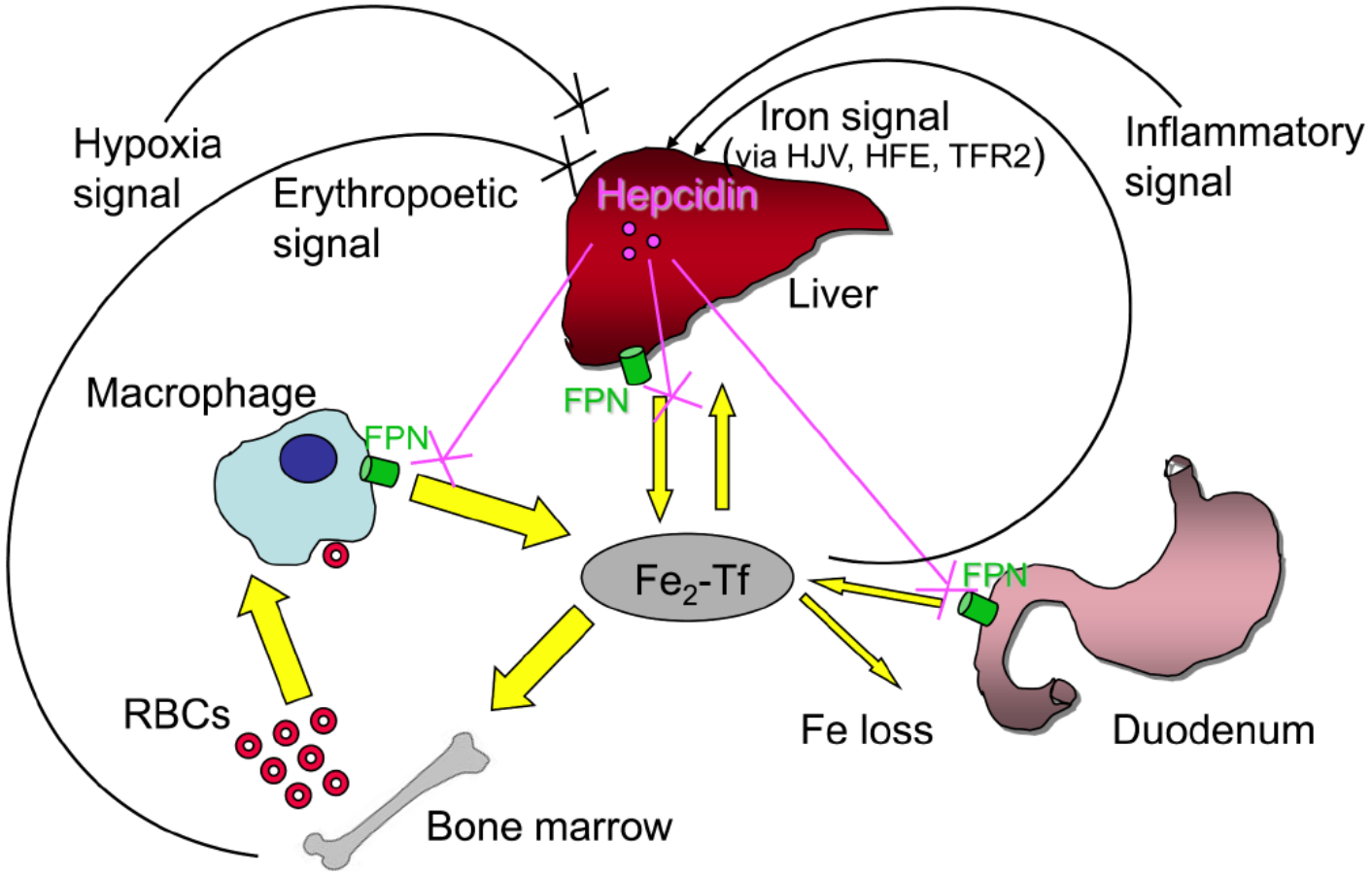
- NYHA class I-IV
- 1506 patients
- 86% were HFrEF
- ID:
  Ferritin < 100 µg/L or ferritin 100-299 µg/L when TSAT <20%
- Anemia WHO criteria

50% of HF patients are iron deficient

Iron deficiency increases with severity of HF



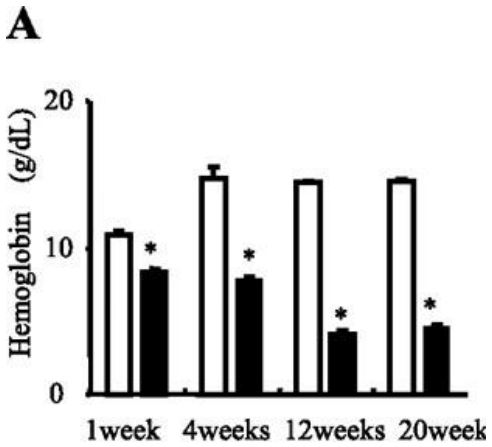
Mechanism of iron deficiency in HF

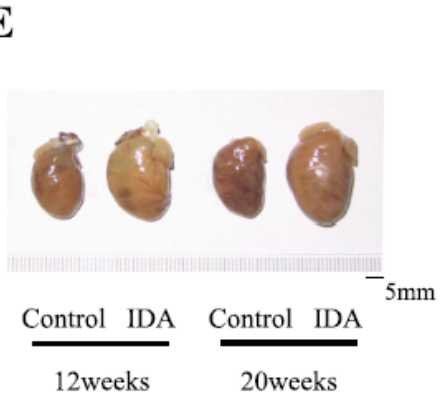


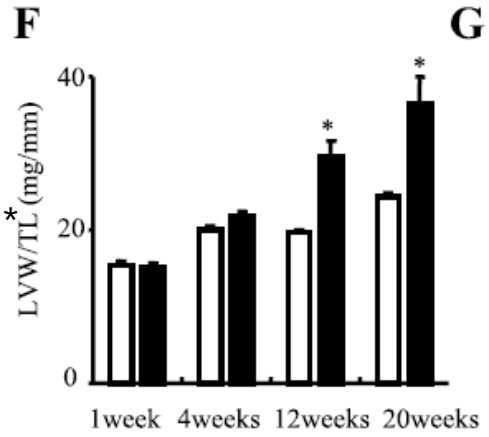
FPN=ferroportin; HFE=hemochromatosis; HJV=haemojuvelin; RBC=red blood cell; TFR=transferrin receptor

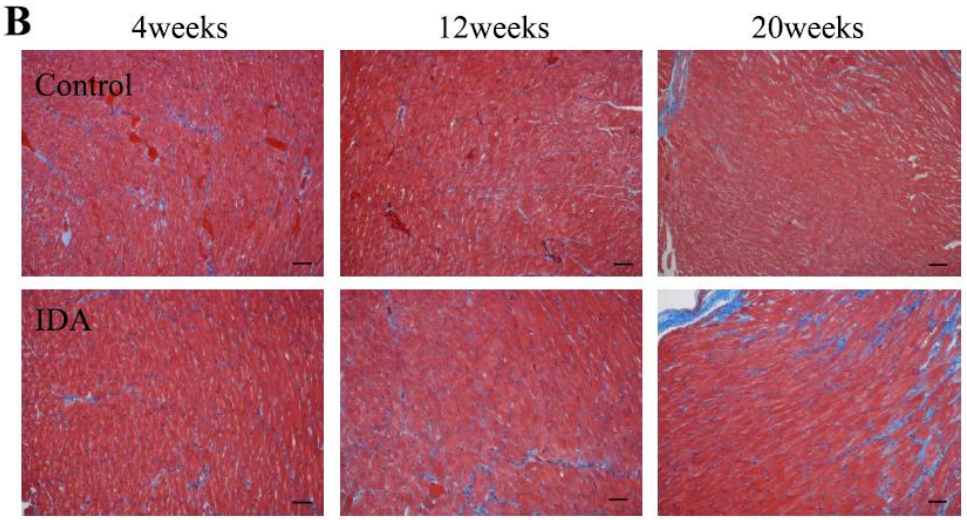
Babitt JL. Am J Kidney Dis 2010;55:726–41

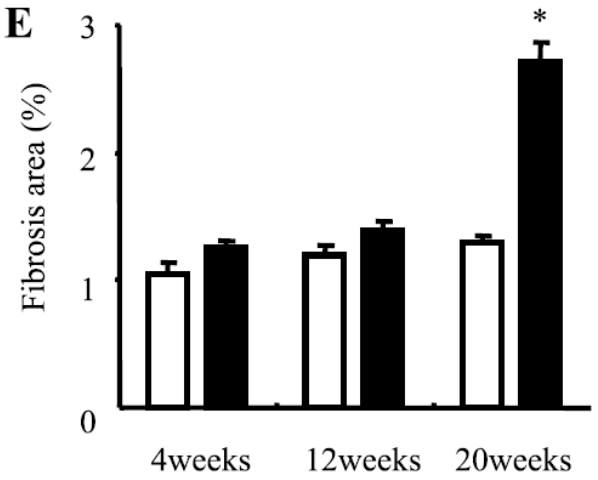
Effect of iron deficiency anemia on cardiac structure







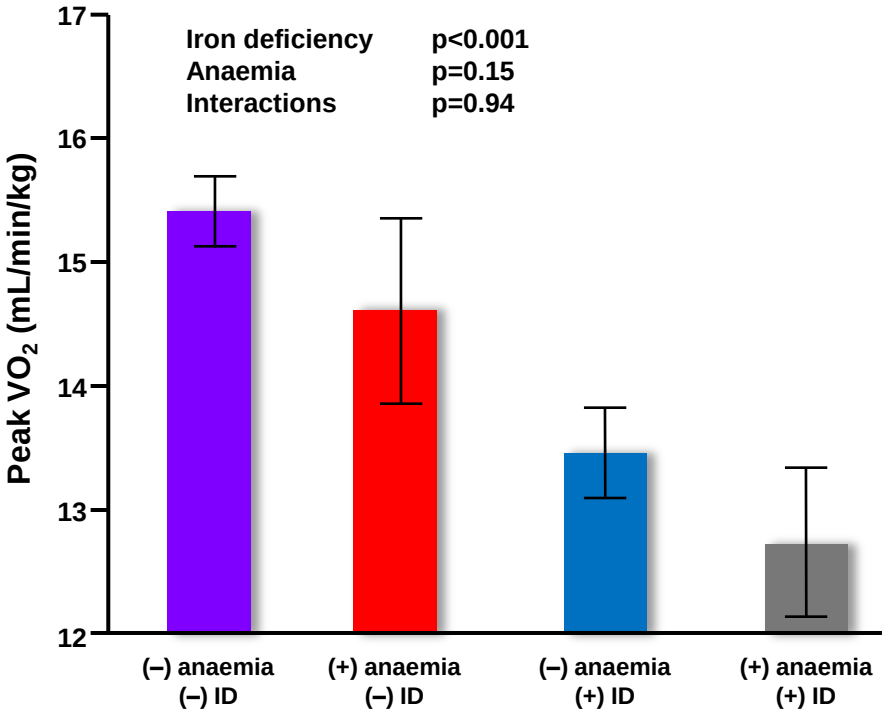




Naito Y. Am J Physiol Heart Circ Physiol 2009;296:H585-93

Iron deficiency is associated with reduced exercise capacity

Peak oxygen consumption

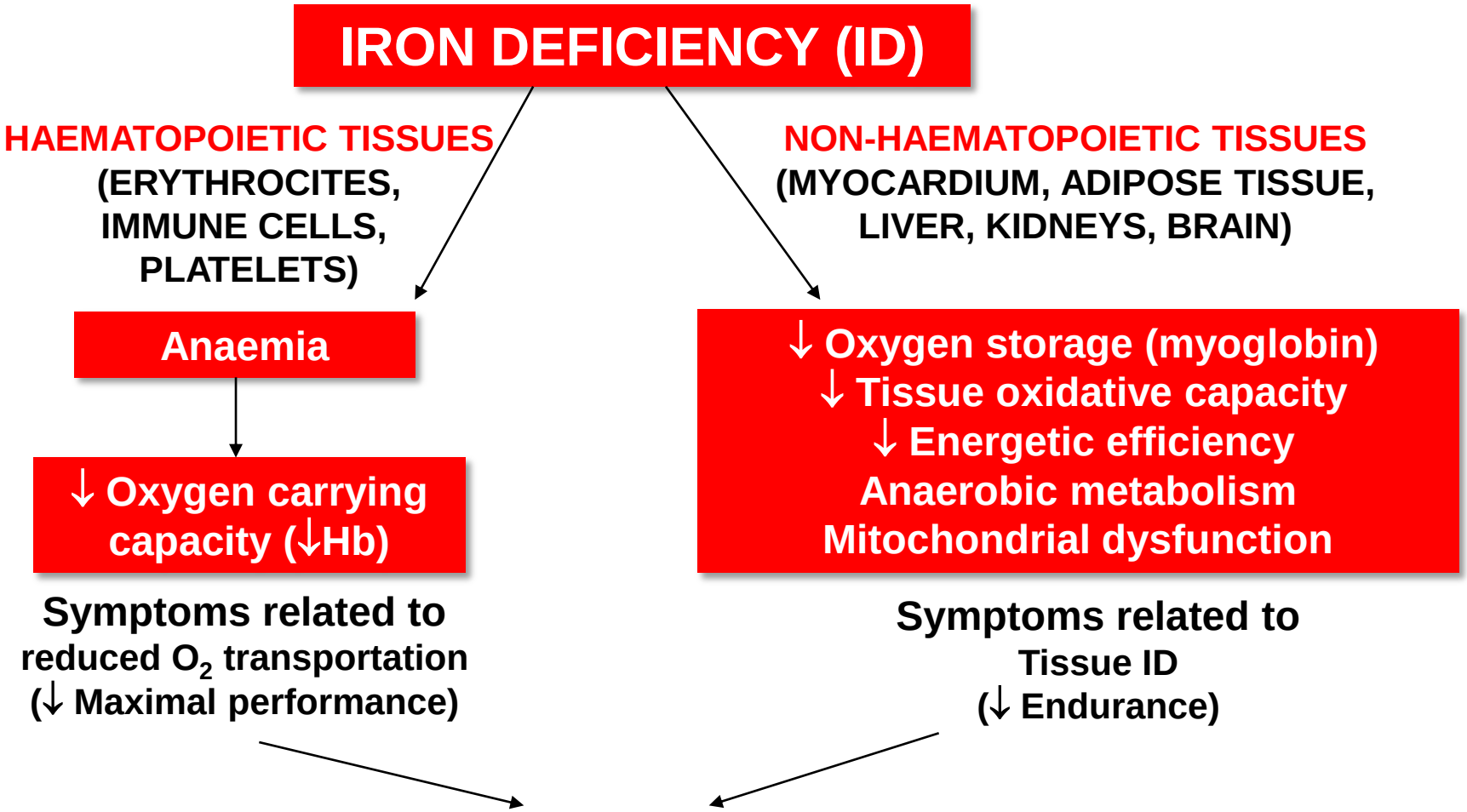


- 443 patients with stable systolic CHF
- age 54 ± 10 years,
- males 90%,
- LV ejection fraction 26 ± 7%,
- NYHA: I/II/III/IV 49/188/180/26)

- 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

Impact of iron deficiency on exercise intolerance

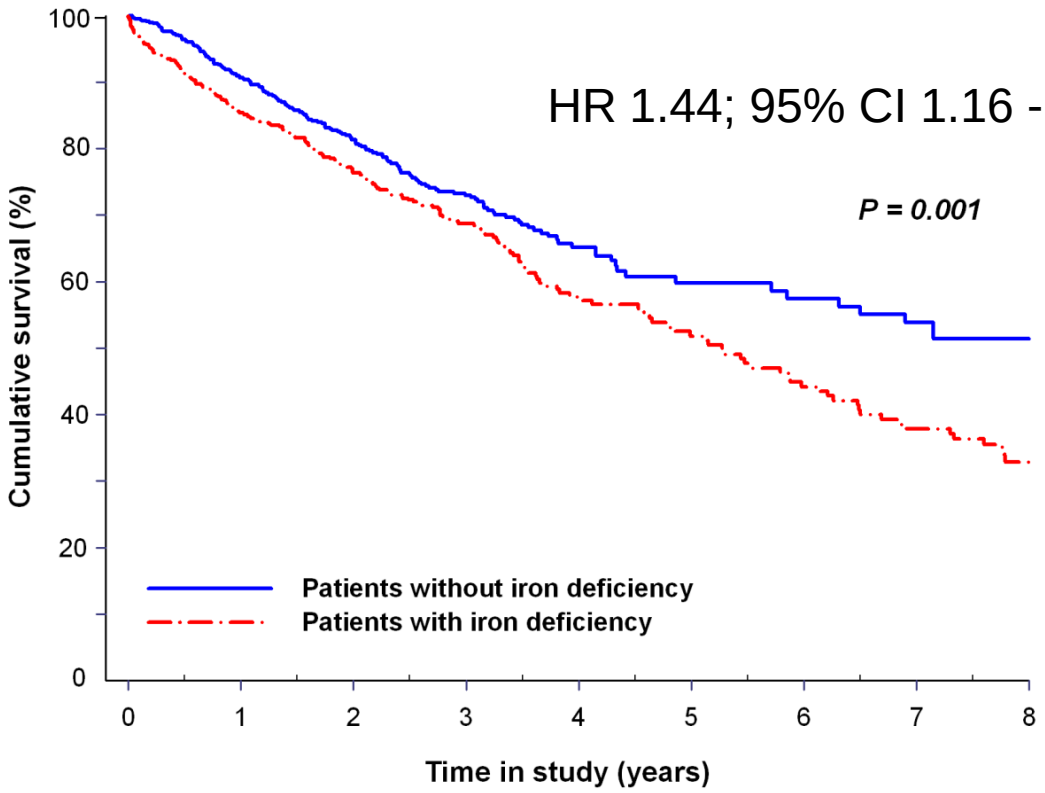


van Veldhuisen D. Nat Rev Cardiol 2011; 8:485-93

Predictor of iron deficiency

Variables	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Female vs. male	1.85 (1.45 - 2.35)	< 0.001	1.67 (1.17 - 2.31)	0.005
NYHA functional class				
III vs. I/II	1.73 (1.41 - 2.14)	< 0.001	1.61 (1.25 - 2.11)	< 0.001
IV vs. I/II	2.07 (1.34 - 3.20)	0.001	1.80 (1.02 - 3.20)	0.022
Comorbidities				
Anemia, yes vs. no*	2.06 (1.63 - 2.61)	< 0.001	1.68 (1.20 - 2.38)	0.033
Laboratory				
MCV, per 1 fL†	0.99 (0.98 - 0.99)	0.001	0.99 (0.98 - 0.99)	< 0.001
NT-proBNP, per 1 log pg/mL	1.21 (1.12 - 1.32)	< 0.001	1.15 (1.05 - 1.34)	0.010

Iron deficiency associated with adverse clinical outcome



HR 1.44; 95% CI 1.16 - 1.81; p = 0.001)

Numbers at risk:

ID absent	753	386	104	63	40
ID present	753	343	100	49	33

CONCLUSIONS

- Iron deficiency and anaemia are both commonly observed comorbidities in HF
- Iron deficiency is observed in almost 50% of HF patients
- Iron deficiency relates to a reduced exercise tolerance
- Iron deficiency is associated with a substantial higher mortality risk