Adverse consequences of iron deficiency and the importance of its correction

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CoI: Vifor – research grants, consultancy, fees for speaking;
Amgen – research grants, consultancy

Relevant co-morbidities in CHF that require medical attention

- CAD / ischemia
- Hypertension
- Diabetes mellitus
- Depression / other neurological disease
- Renal dysfunction and kidney injury
- **Anemia and iron defficiency**
- COPD
- Liver & bowel dysfunction

Mechanisms of Anemia in Chronic Heart Failure & Chronic Kidney Failure

Haemodilution
Plasma Volume ↑

Forward failure
Bone marrow dysfunction

Iron deficiency
Fe^{++} uptake ↓
inflammation induced
malabsorption
chron. bleeding (aspirin)

Chronic immune activation
TNF alpha - production of Epo ↓
- Epo activity in BM ↓

Drugs
ACE-I: Epo synthesis ↓
Epo activity in BM ↓

Chronic kidney failure
Production of Epo ↓
Loss in urine ↑

Iron Metabolism

Iron stores: 35-45 mg/kg BW

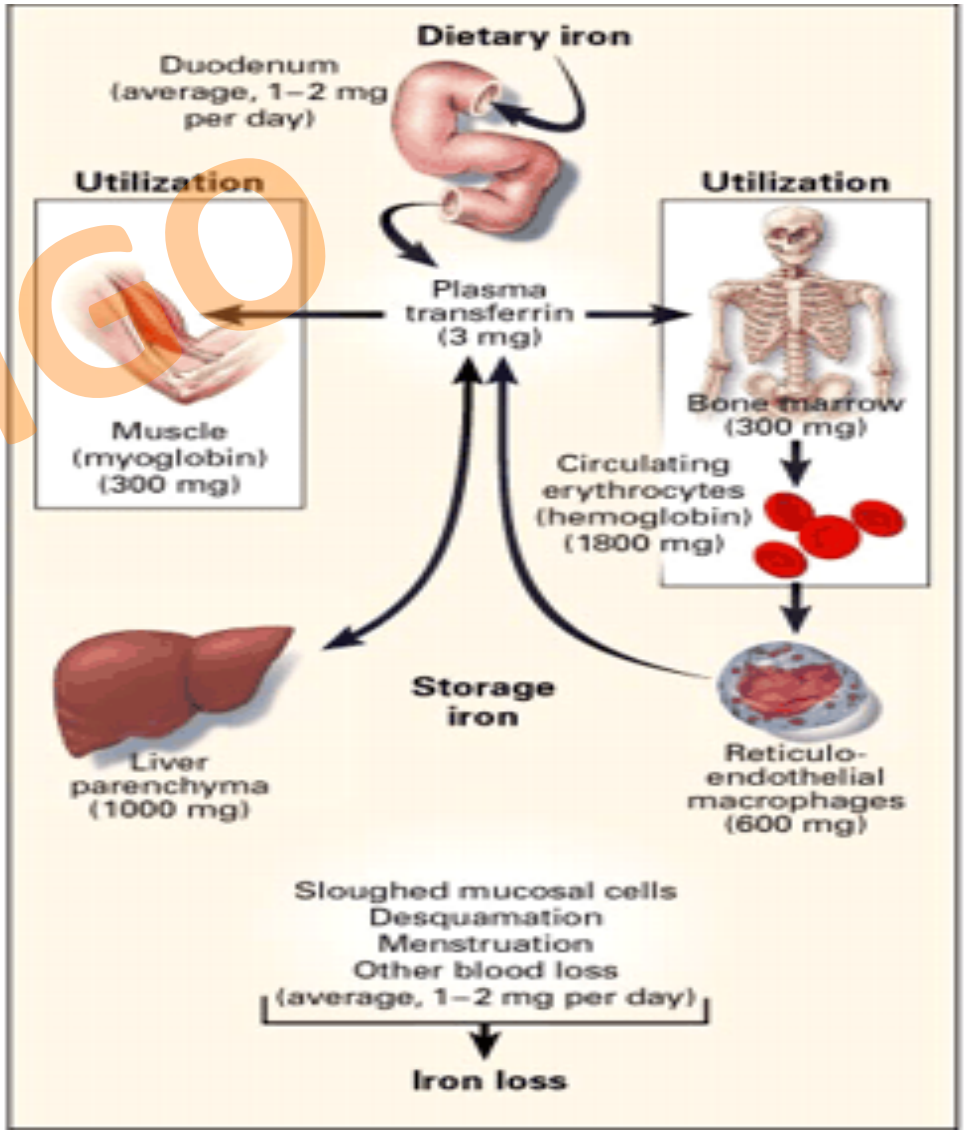
Iron distribution:

- Blood – Transferrin (3 mg)
- Hemoglobin (bone marrow & erythrocyts, 1800 mg)
- Storage: mainly liver (1000 mg) & RES (600 mg)
- Muscle – Myoglobin (300 mg)

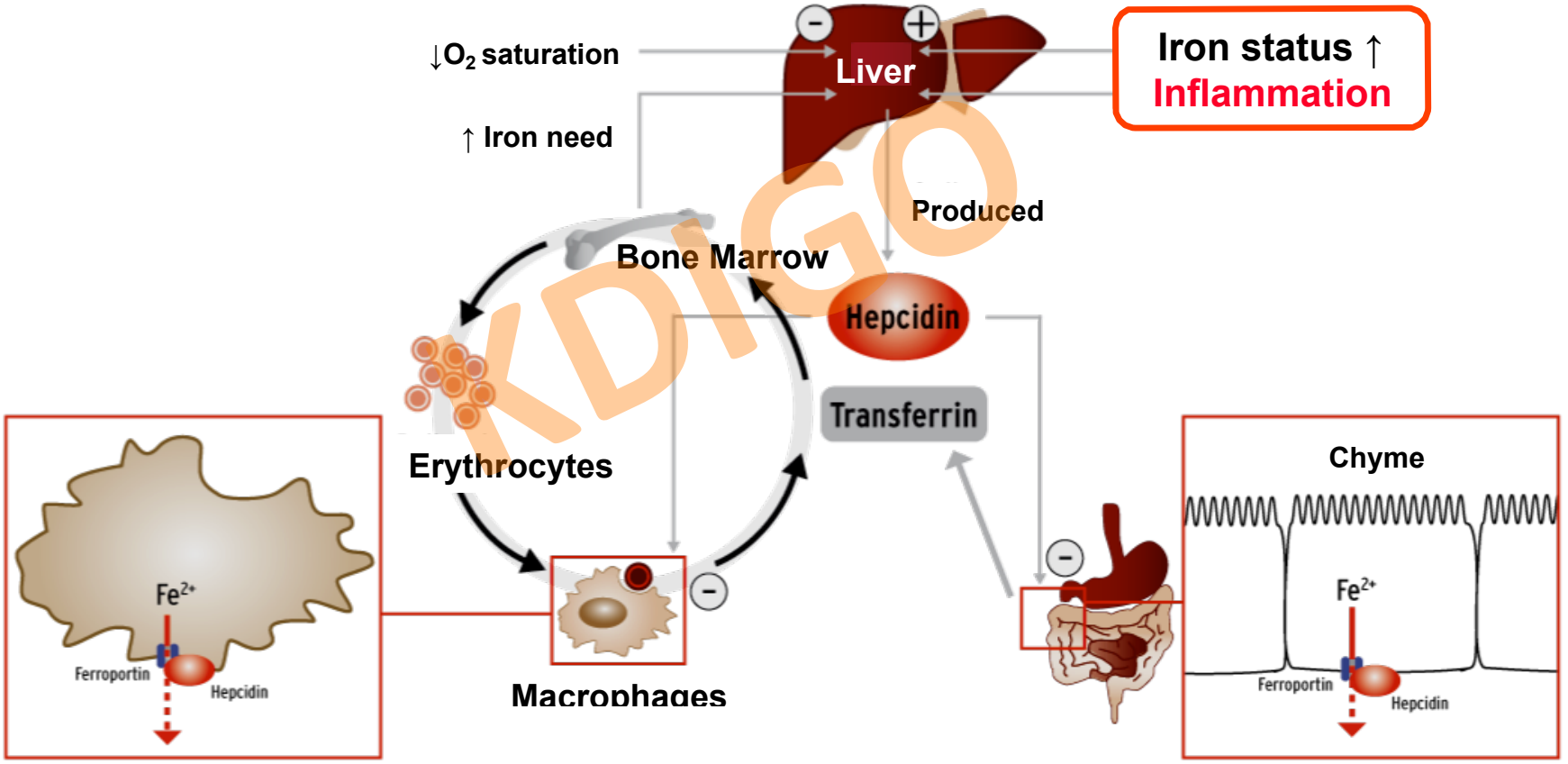
Iron loss: 1-2 mg / 24 h
(every day !)

Iron uptake: 1-2 mg / 24 h
(critical !)

Andrews NC, NEJM 1999



Inflammation, Hepcidin, Ferroportin & the regulation of iron metabolism



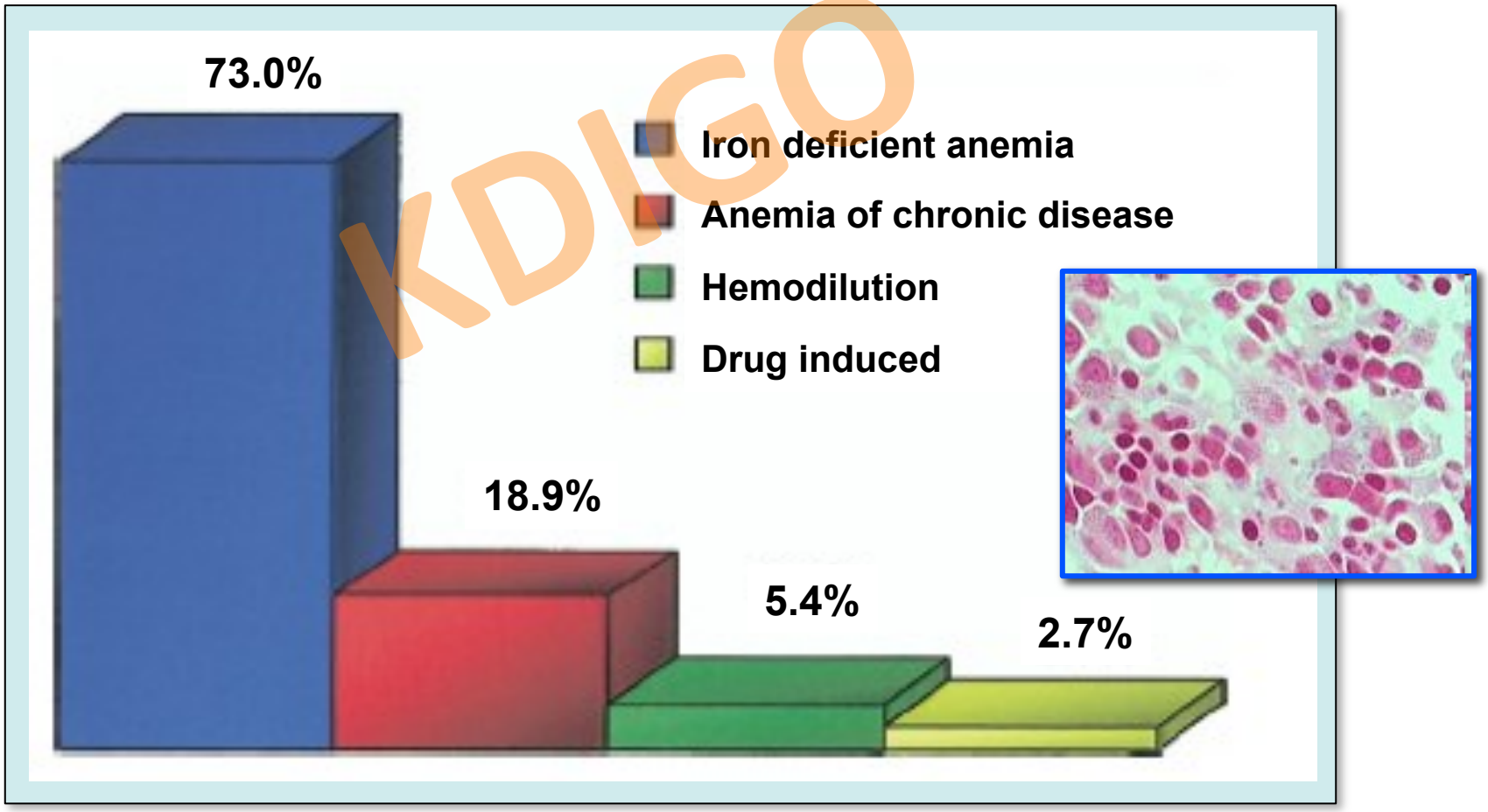
Macrophages
(including in liver)

Intestine cells
(Enterocytes)

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

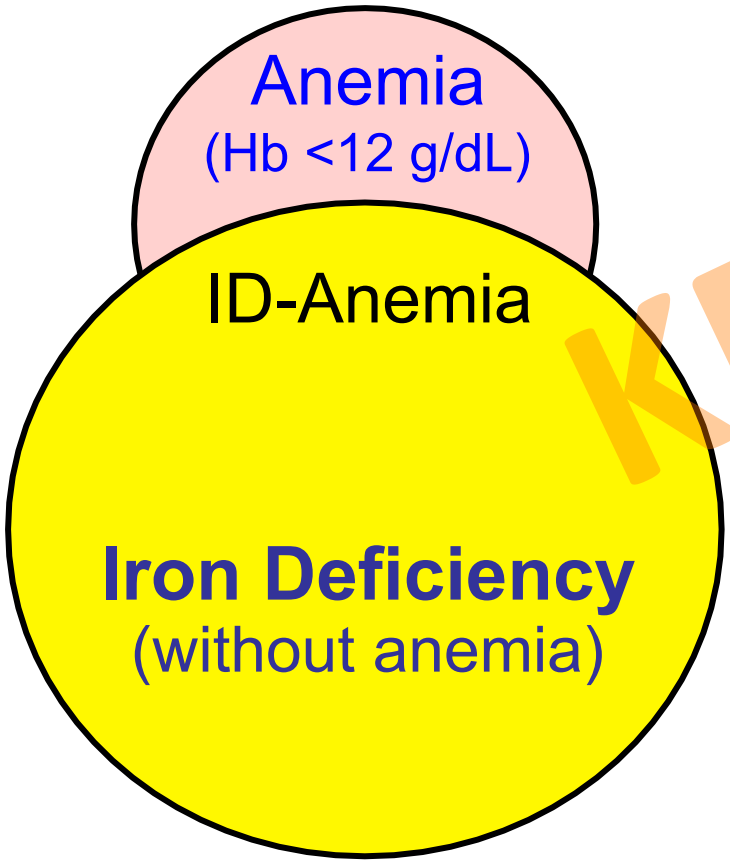
Patients with congestive HF: 10-20% with anemia
Cause of anemia: in 20-30% of cases iron deficiency

- 37 anemic patients with severe CHF, NYHA IV, LVEF – 22%
- bone marrow biopsy confirmed iron deficiency (ID) in 27 of 37 pts



Nanas JN et al.; JACC 2006

Absolute & functional iron deficiency – definitions



1. Absolute iron deficiency

(Reduction in iron stores)

- Causes: chronic blood loss (aspirin), malnutrition, malabsorption
- Diagnosis: low serum ferritin level <30 µg/L

2. Functional iron deficiency

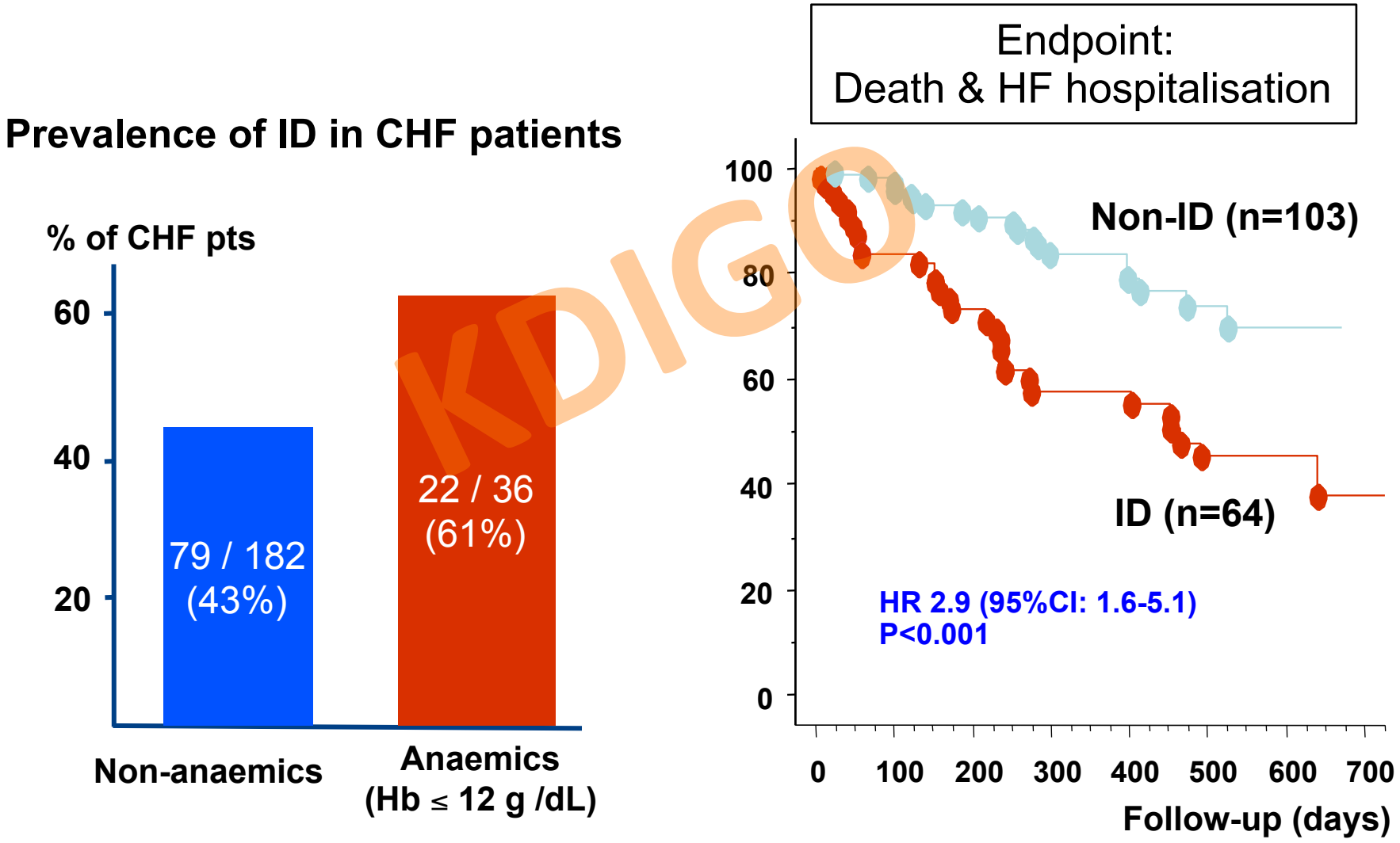
(Disturbed iron metabolism in bone marrow; iron stores =/↓)

- Causes: chronic inflammation & kidney dysfunction
- Diagnosis: serum ferritin 30–99 µg/L or serum ferritin 100–299 µg/L and TSAT<20%

1. Wish JB. *Clin J Am Soc Nephrol* 2006;1:S4–8. 2. Muñoz M, et al. *World J Gastroenterol* 2009;15:4617–26.

Functional Iron Deficiency = poor Prognosis

definition: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%

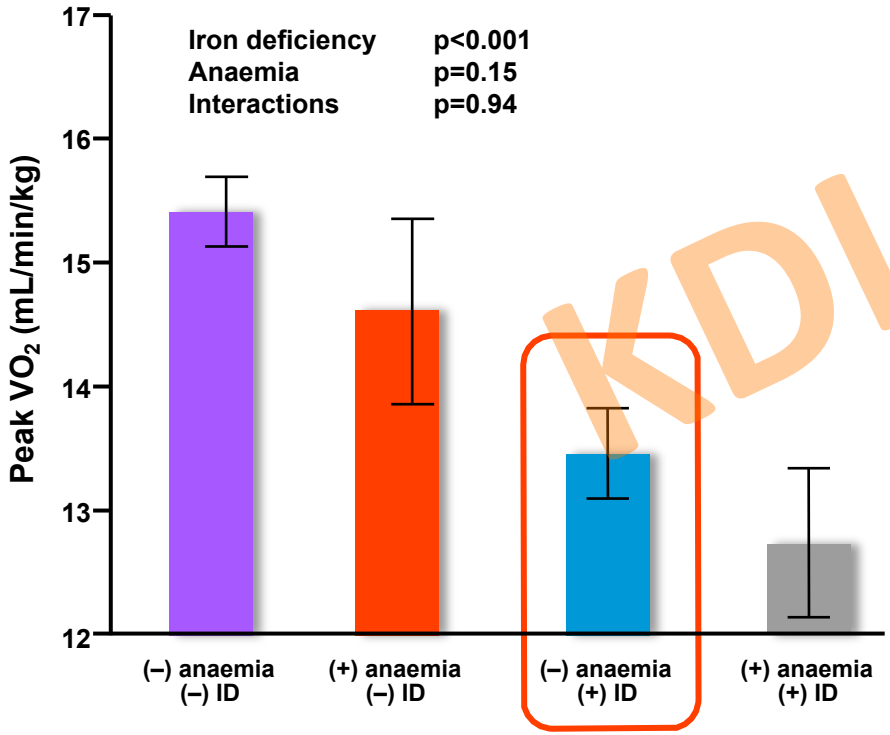


Jankowska et al., EHJ 2010

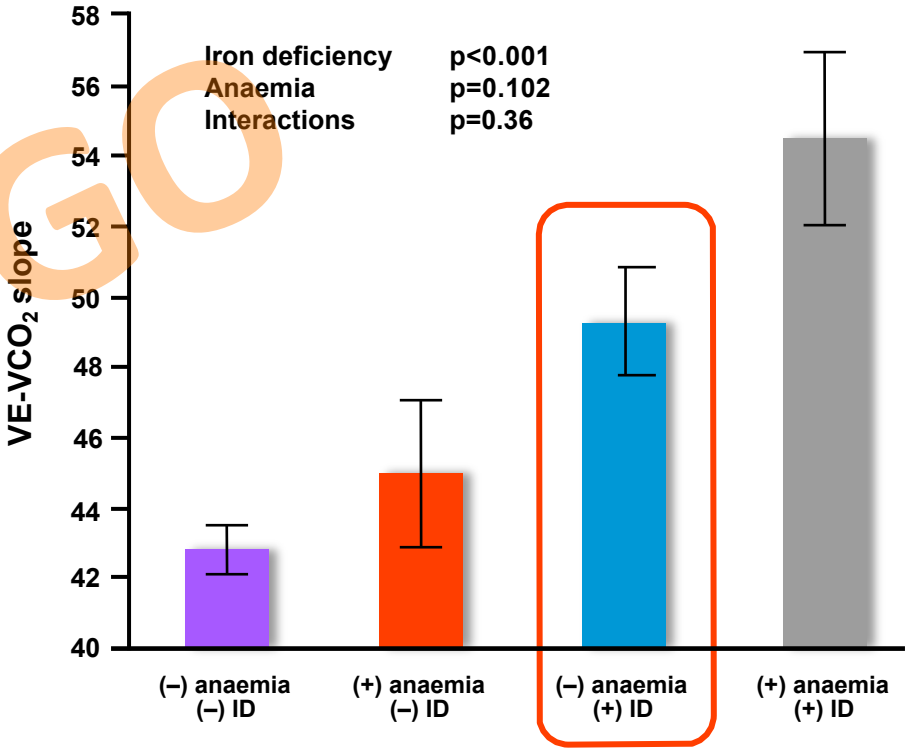
Grzeslo A et al. (abstract at HFA 2006)

Iron deficiency but not anaemia is associated with reduced exercise capacity in CHF patients

Peak oxygen consumption



Ventilatory response to exercise

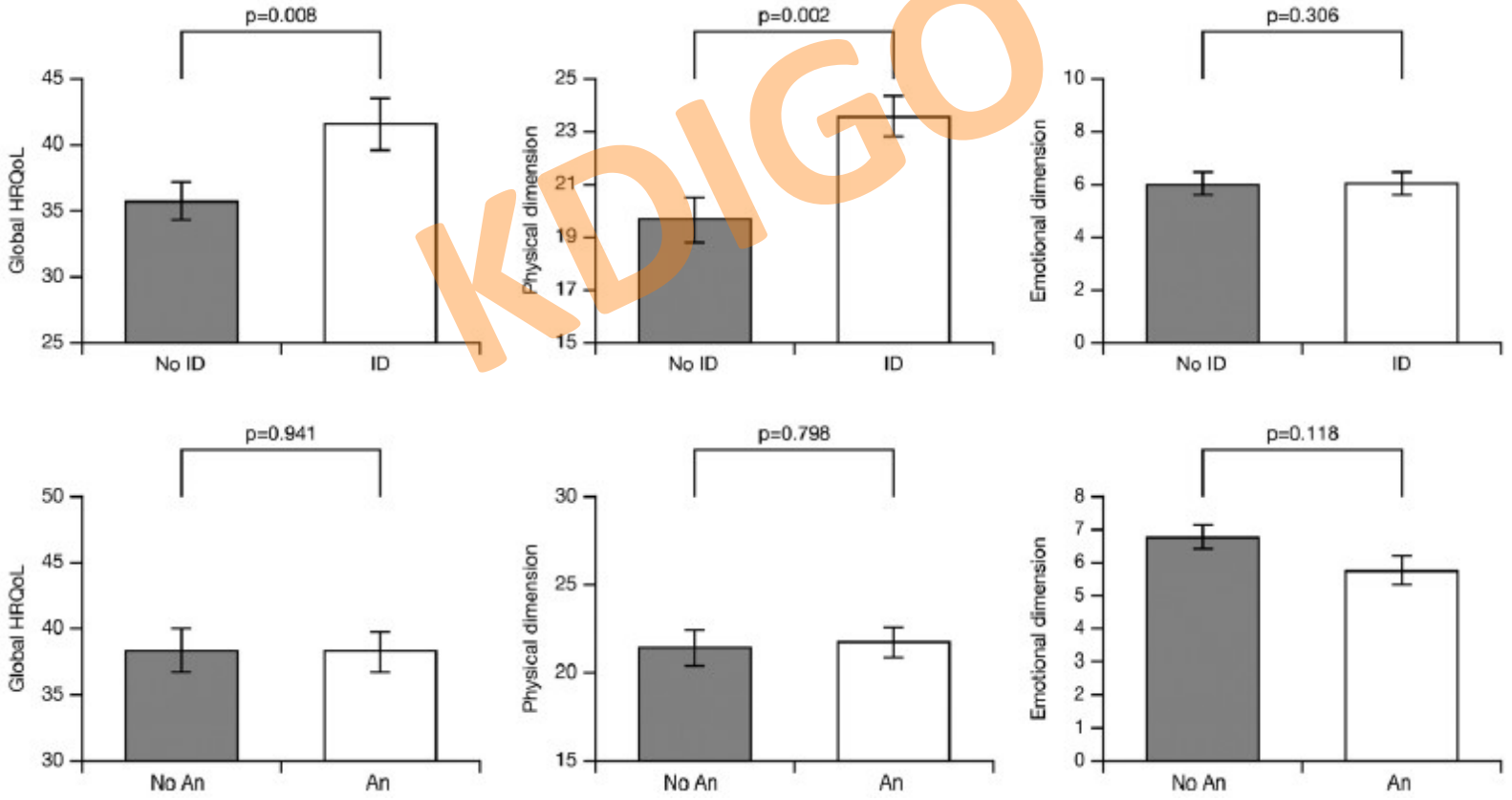


- Iron deficiency = serum ferritin <100µg/L, or serum ferritin 100–300µg/L with TSAT <20%
- Anaemia = haemoglobin level <12g/dL in women and <13g/dL in men

Jankowska et al. J Cardiac Fail 2011

Iron deficiency but not anaemia is associated with reduced QoL in CHF patients

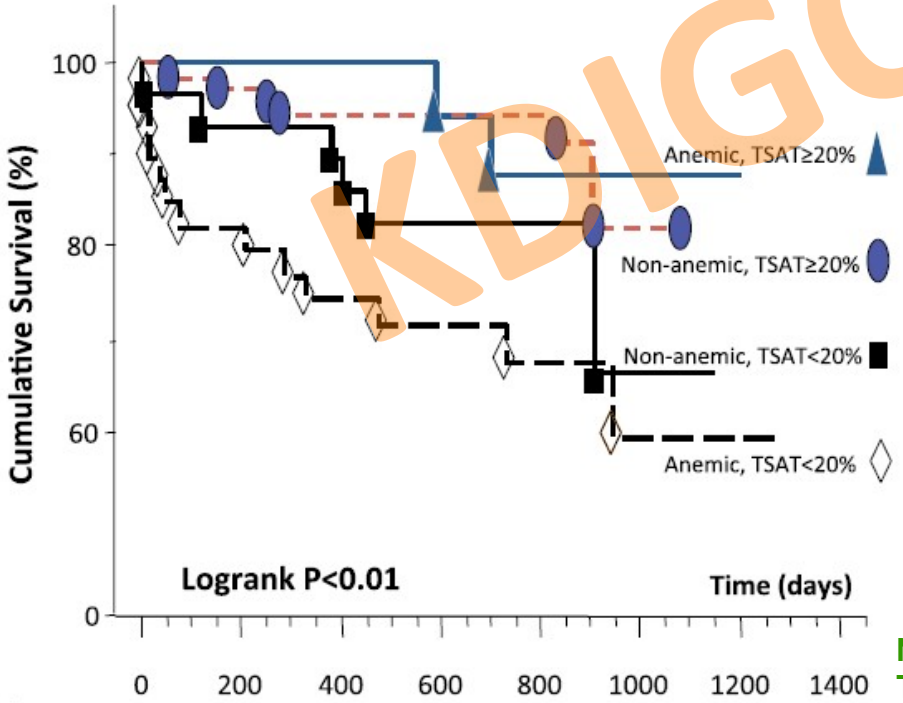
- HRQoL test: Minnesota Living with Heart Failure Questionnaire (MLHFQ)
- Results adjusted for anaemia, ID and other covariates



Comin-Colet et al. Eur J Heart Fail 2013

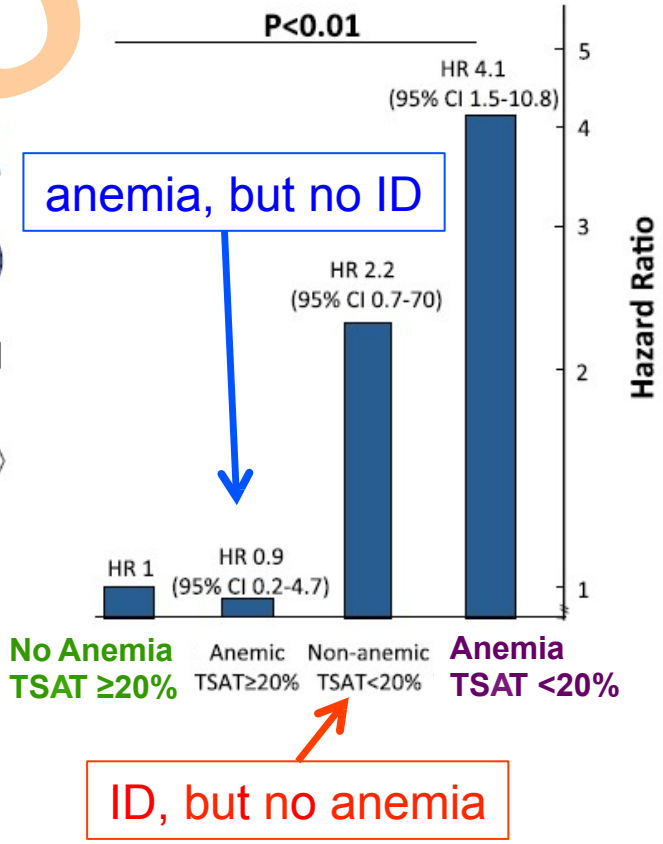
Iron deficiency is a bigger problem than anemia

- 157 consecutively eligible patients with CHF
- 2-fold greater risk for mortality in iron-deficient non-anemic patients vs. iron-replete anemic subjects
- 3-fold escalated risk for death irrespective of anaemic status



Numbers at Risk

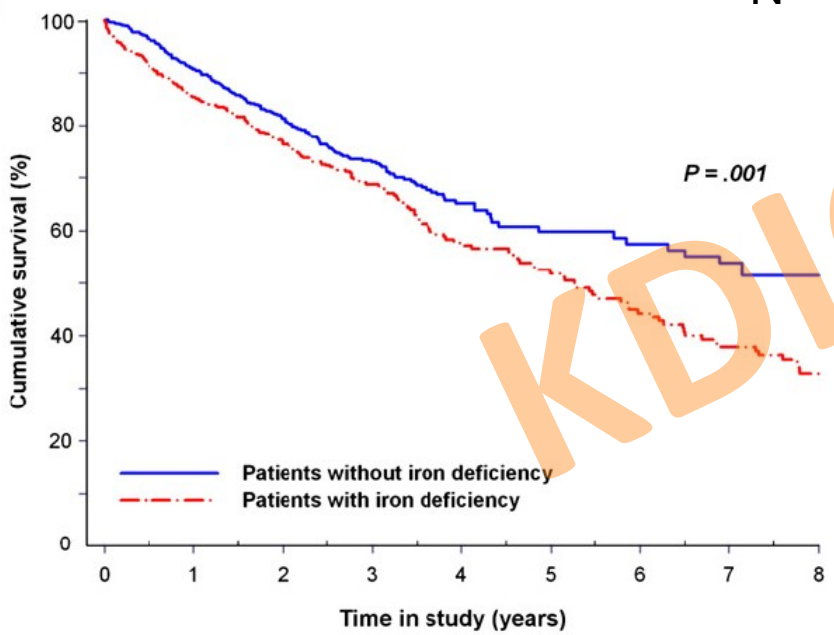
Non-anemic, TSAT≥20%	67	65	63	51	36	3	0
Anemic, TSAT≥20%	22	22	22	17	11	3	0
Non-anemic, TSAT<20%	29	27	25	23	14	1	0
Anemic, TSAT<20%	39	32	29	22	13	6	1

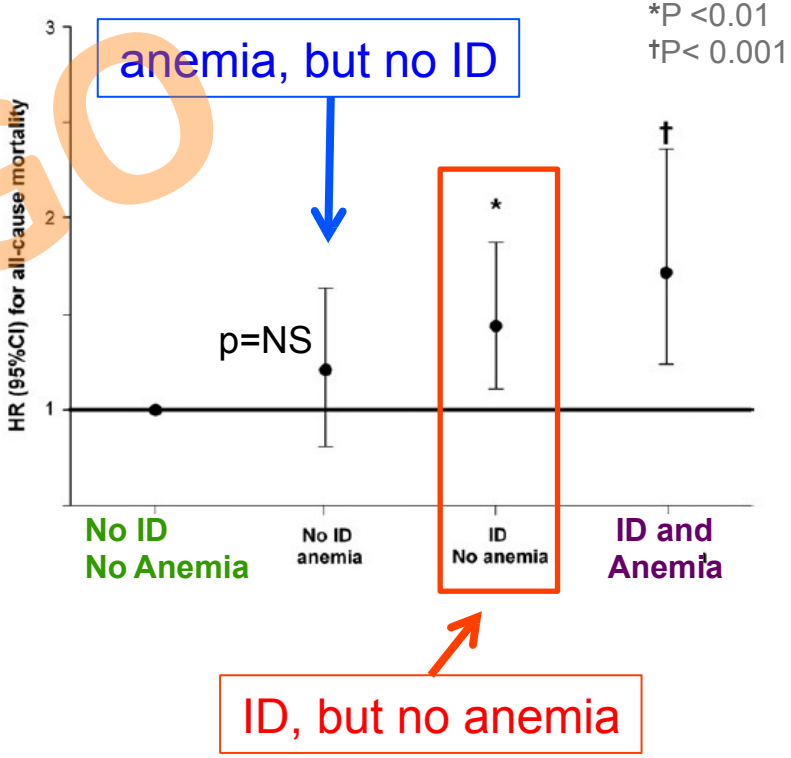


Okonko et al. JACC 2011

Iron deficiency & anaemia – not 1, but 2 problems

N= 1506



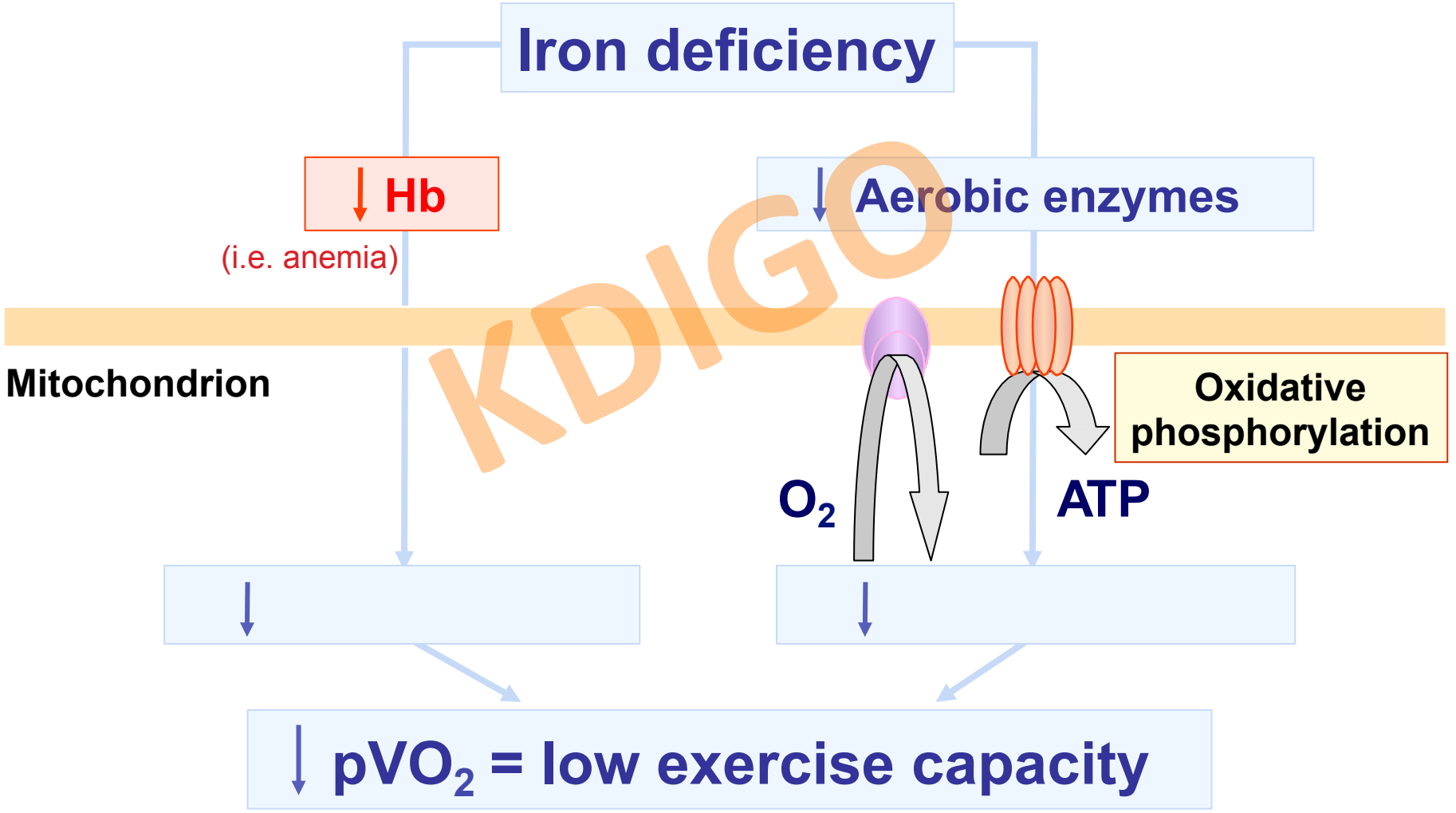


Mortality increases when ID is present

ID is a negative prognostic factor stronger than anemia

Klip IT, et al. *Am Heart J* 2013;165:575-82.

Anemia & iron deficiency & exercise capacity



Haas JD & Brownlie T. *J Nutr* 2001;131(2 suppl 2):676S–690S; Dallman PR. *J Intern Med* 1989;226:367–372;
Willis WT & Dallman PR. *Am J Physiol* 1989;257:C1080–1085;
Figure adapted from: Anker et al. EJHF 2009

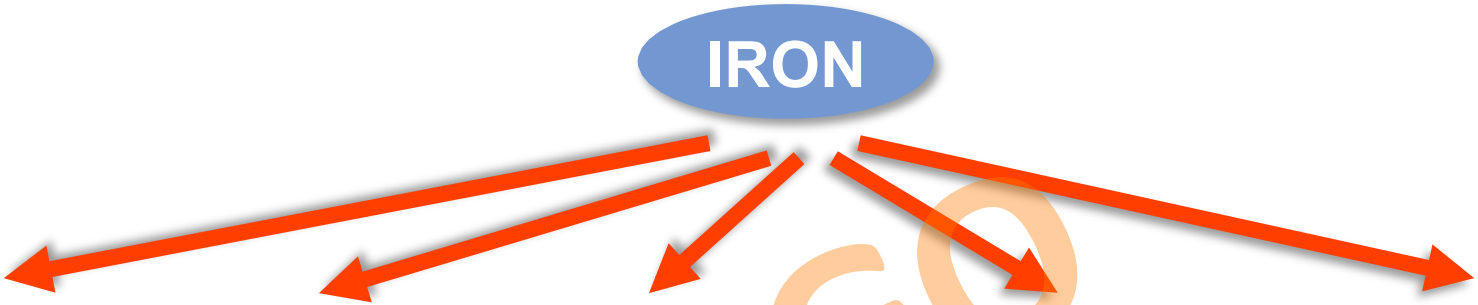
Iron is an essential element for cellular functions[1–3]

Function	Protein
Oxygen transport and storage	Haemoglobin, myoglobin
Mitochondrial electron transport	Respiratory complex I-III
	Cyt-c, Cyt-c oxidase
Metabolism	Mitochondrial aconitase, lipoate synthase, tyrosine hydroxylase, thyroid peroxidase
Nucleic acid processing	Phosphoribosyl-pyrophosphate-amidotransferase
DNA replication	DNA primase
Cell signalling	Guanylate cyclase
Antioxidative activity	Myeloperoxidase, catalase, peroxidases, NO synthase

Cyt, cytochrome; NO, nitric oxide

1. Crichton. Iron metabolism – from molecular mechanisms to clinical consequences. London: John Wiley & Sons Ltd; 2009;
2. Evstatiev & Gasche. *Gut* 2012;61:933–52; 3. Meyer-Klaucke *et al. Eur J Biochem* 1996;241:432–9;
4. Crichton *et al.* UNI-MED Verlag AG, 2008

Iron is essential for growth and survival



CELLS

- Mitochondrial dysfunction
- Deranged enzyme activity
- Abnormal transport and structural proteins
- Apoptosis

TISSUES

ORGANS

- Tissue remodelling
- Impaired organ efficacy

BODY

- Impaired exercise capacity
- Reduced work efficiency
- Impaired cognitive performance and behaviour
- Increased morbidity and mortality

POPULATION

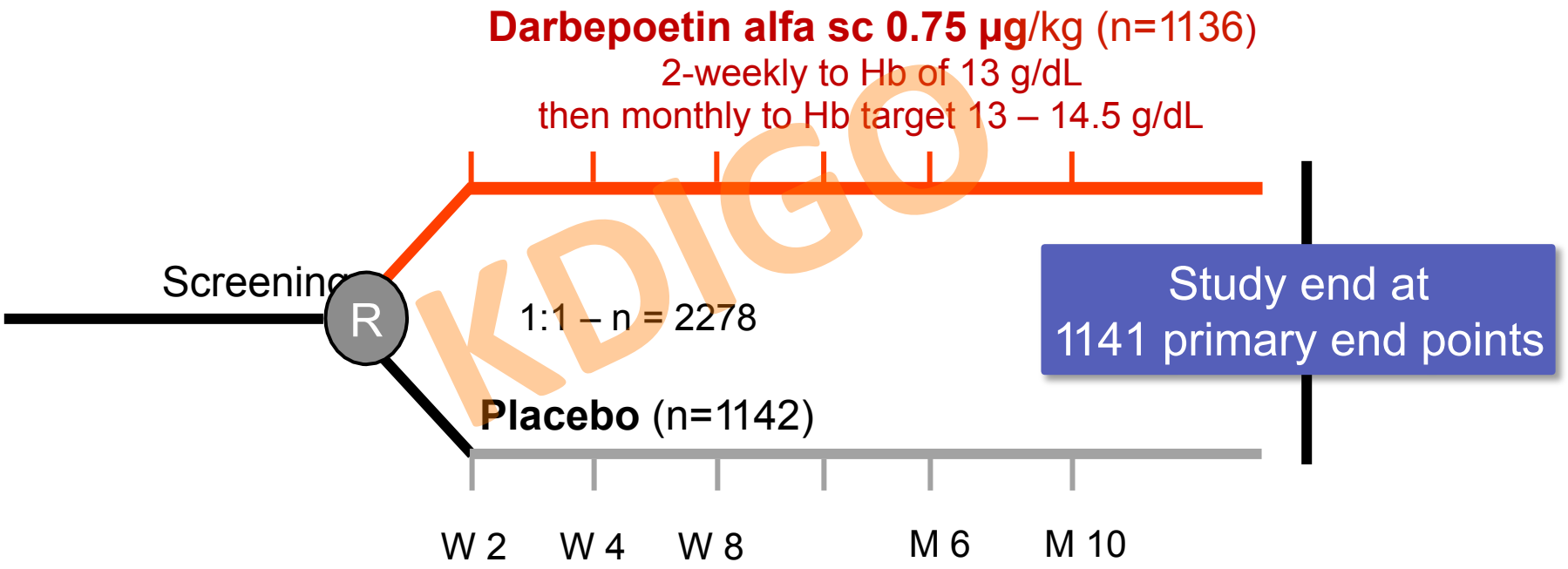
Iron is particularly important for cells of high mitogenic potential and high energy demand
(e.g. skeletal myocytes and cardiomyocytes)

Andrews N Engl J Med 1999
Cairo et al. Genes Nutr 2006
Zimmermann, Hurrell. Lancet 2007

Treatment of CRS, anemia & iron deficiency
– Options –

- Blood transfusion (in severe anemia, if Hgb <9 d/dL, rare in CHF)
  - Demetri GD et al. Br J Cancer 2001
- EPO in combination with iv iron or with Vitamin B12 / folic acid
  - Silverberg D et al. J Am Coll Cardiol 2000 + 2001
  - Mancini DM et al., Circulation 2003
- ESAs alone (in some cases also with [mostly oral] iron)
  - Amgen Study Programme (Phase 3: RED-HF)
- Iron (oral or iv)
  - 3 PoC / Phase 2 studies have been reported
  - Phase 3: FAIR-HF

RED-HF
Design



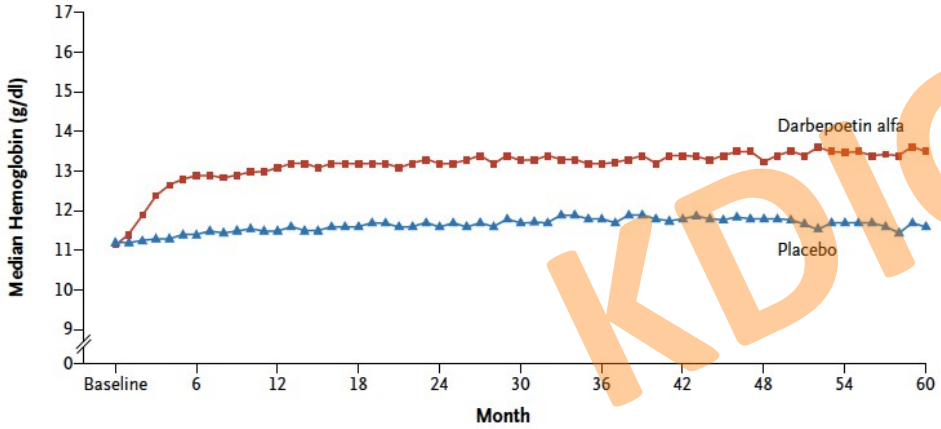
Inclusion criteria:

- NYHA II-IV (in NYHA II also CV hosp in last 12 months)
- LVEF ≤ 40%; CHF for ≥ 3 months
- Hb 9-12 g/dL
- TSAT ≥15%

Swedberg K, et al. N Engl J Med 2013;368:1210-9.

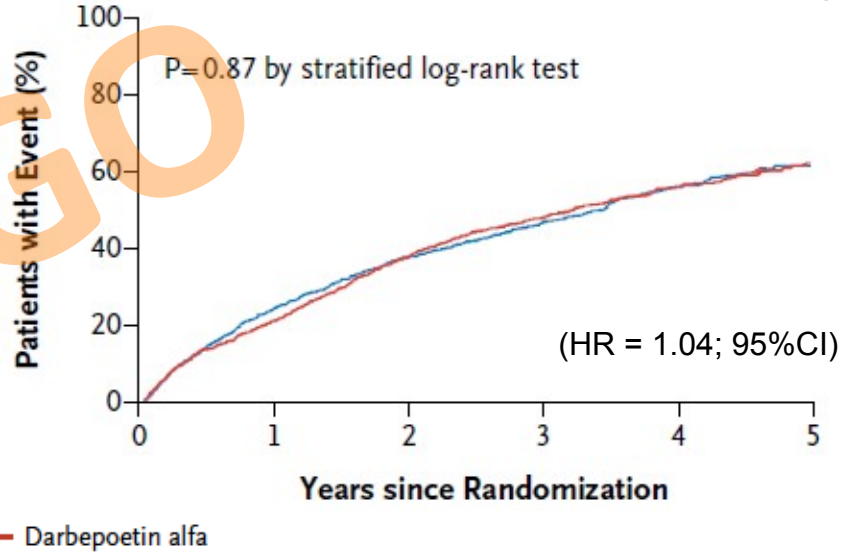
RED-HF
Main results

Haemoglobin



Primary endpoint

Death from any cause or first hospitalization for worsening HF



- ESA leads to correction of anaemia
- ESA does not lead to improvements in survival or QoL
- ESA shows somewhat increased risk for thromboembolic adverse events
- Cancer-related adverse events similar in both groups

ESA = Erythropoeisis stimulating agent

Swedberg K, et al. N Engl J Med 2013;368:1210-9.

RED-HF
and the iron status

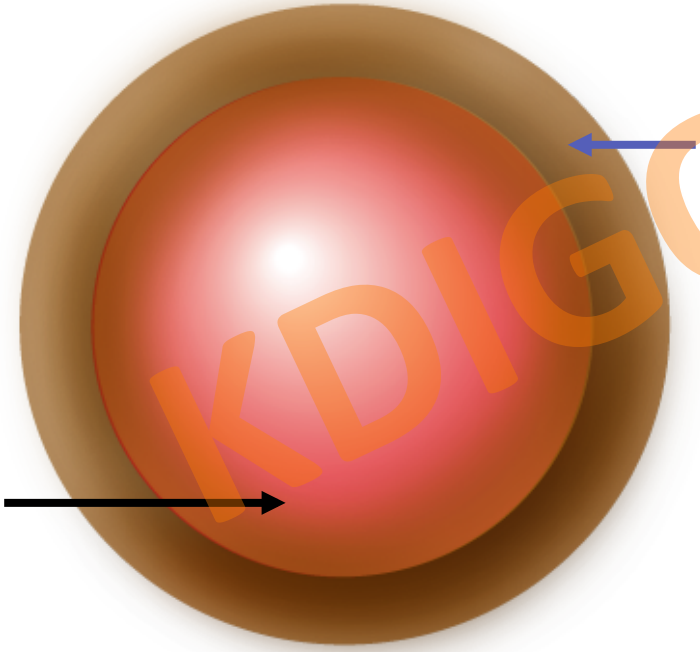
- Exclusion criterion: TSAT <15%, no ferritin assessed
- Baseline: median TSAT: 24% (19-31)
  median ferritin: 102 µg/L (53-194)
- When TSAT <20%, iron supplementation was considered, no ferritin cut-off value:
  - i.v. iron: 4.9% (D) vs 5.6% (P), p=0.47
  - p.o. iron: 72.3% (D) vs 73.5% (P), p=0.52

↠~50% were iron deficient at time of randomization according to the current definition (ESC HF GLs 2012)

↠Predominant treatment with oral iron

Zannad F, et al. Eur J Herat Fail 2013;15:1082-94.
Swedberg K, et al. N Engl J Med 2013;368:1210-9.

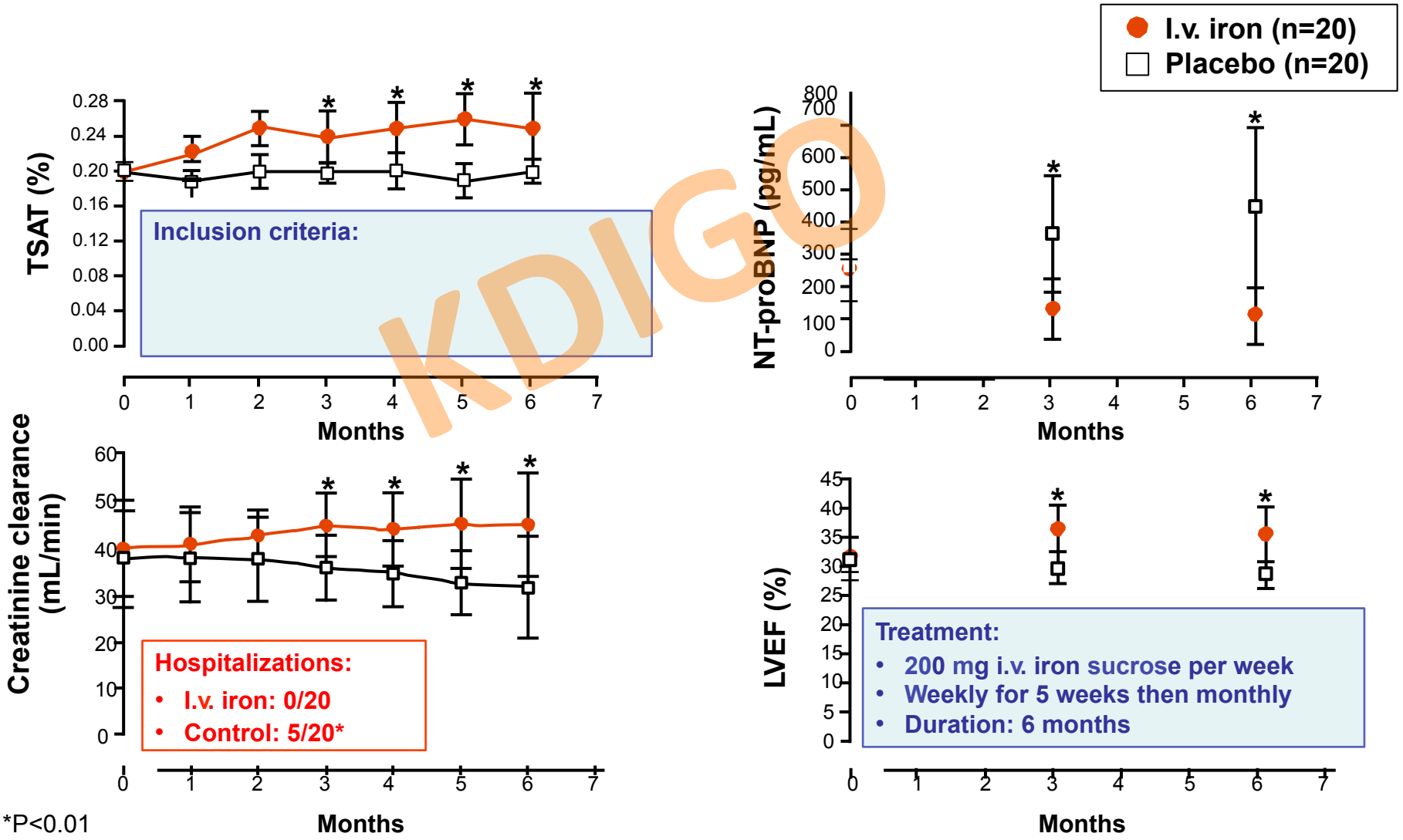
The structure of intravenous iron



- Dextran can cause anaphylactic reactions
- Larger/heavier iron–carbohydrate complexes are more stable than smaller/lighter complexes

Macdougall IC. *J Ren Care* 2009;35 Suppl 2:8–13.

i.v. Iron Sucrose Improves Kidney Function in Patients with CHF and Iron Deficiency

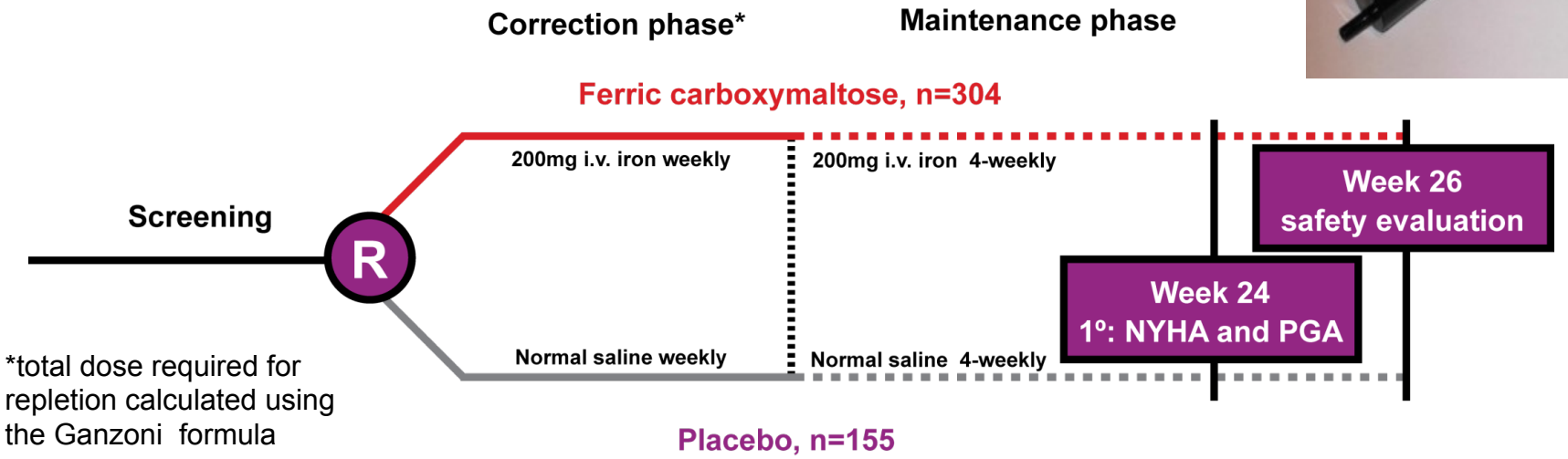


*P<0.01

Toblli JE et al. *J Am Coll Cardiol* 2007;50:1657–65

FAIR-HF Trial -- Study Design

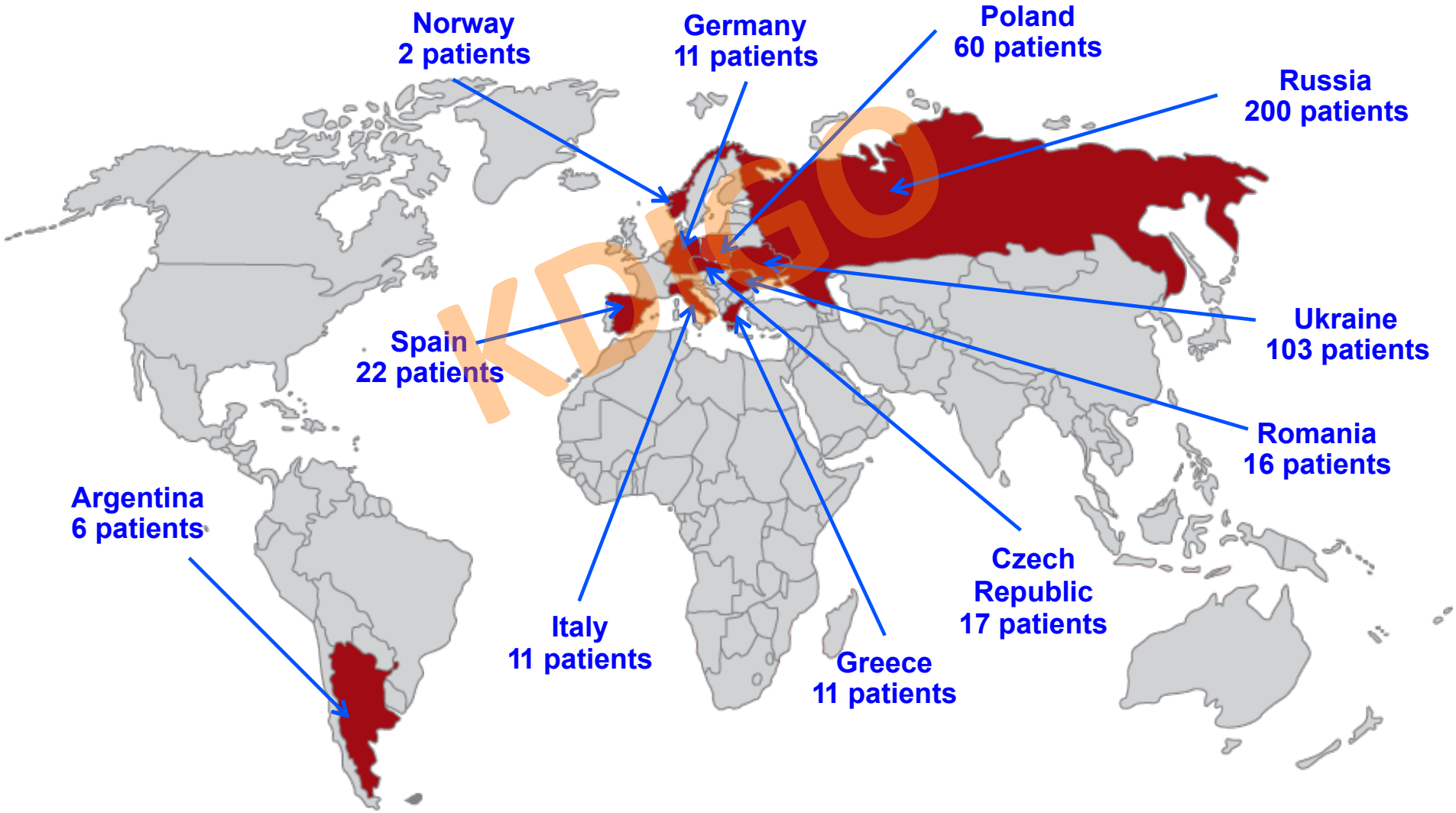
- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - Hb: 9.5–13.5g/dL
  - **Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%**
- **Treatment adjustment algorithm:**
  - Interruption: Hb>16.0g/dL or ferritin>800µg/L or ferritin>500µg/L, if TSAT>50%
  - Restart: Hb <16.0g/dL and serum ferritin <400µg/L and TSAT<45%
- **Blinding:**
  - Clinical staff: unblinded and blinded personnel
  - Patients: usage of curtains and black syringes for injections



*total dose required for repletion calculated using the Ganzoni formula

Anker *et al, Eur J Heart Failure* 2009;11:1084-1091

75 centers from 11 countries

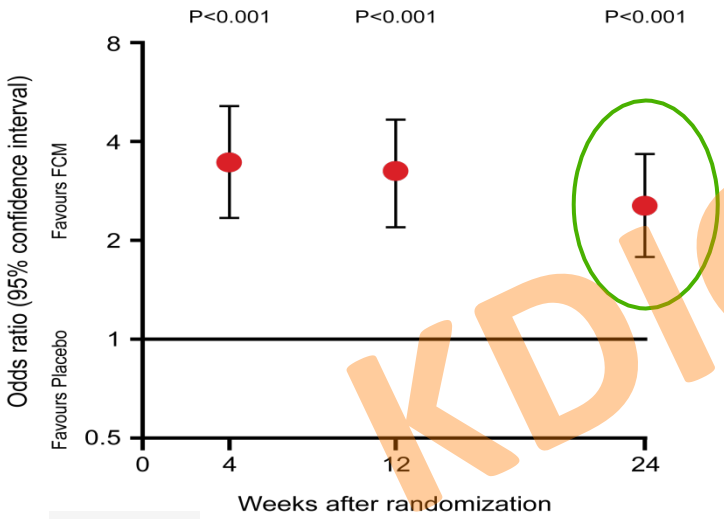


Patient Details

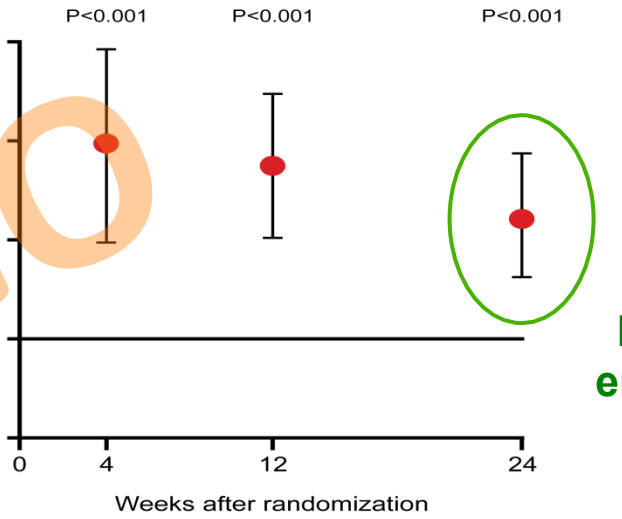
	FCM (N=304)	Placebo (N=155)
Age (years)	68	67
Gender (% female)	52	55
NYHA class III, n (%)	251 (82.6)	126 (81.3)
6-min walk test distance (m)*	274 ± 105	269 ± 109
Ischemic etiology (%)	81	79
Estimated GFR (mL/min/1.73m^2)*	64 ± 21	65 ± 25
LVEF (%)	32	33
Hb (g/L)*	119 ± 13	119 ± 14
Serum ferritin (µg/L)*	53 ± 55	60 ± 67
ACEi/ARB (%)	92	91
Beta-Blocker (%)	86	83
Diuretics (%)	92	90

NYHA, PGA, QoL, 6min-Walking-Test
-- Week 4, 12 & 24 --

Patient Global Assessment

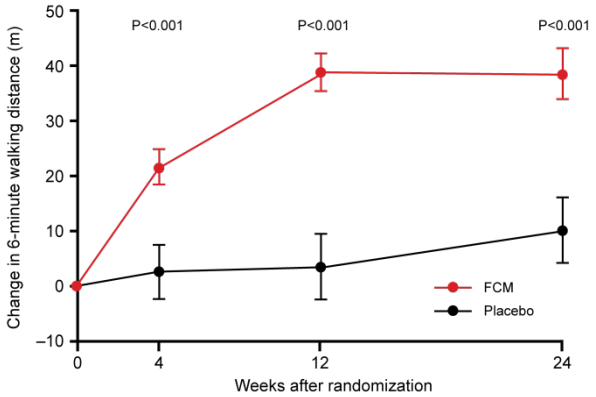


NYHA functional class

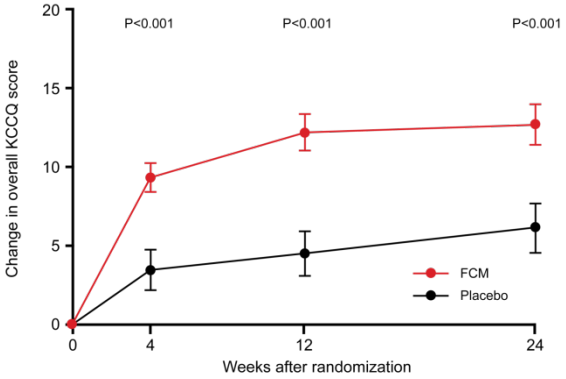


Primary endpoints

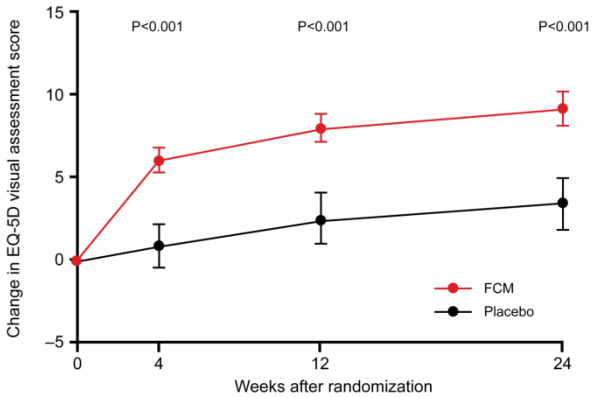
6-minute walk test



KCCQ overall score



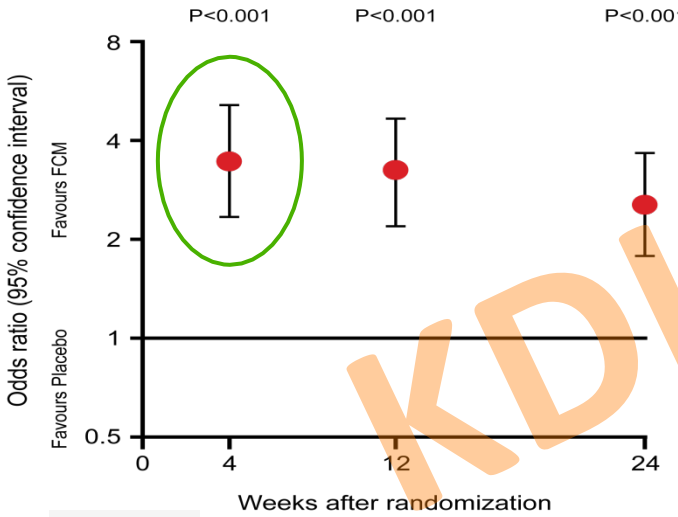
EQ-5D VAS score



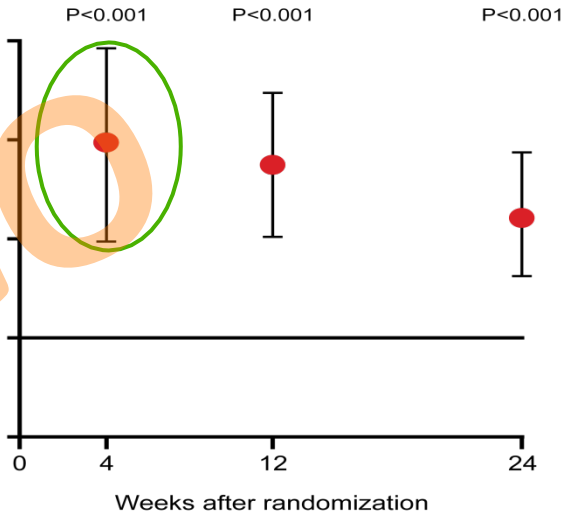
Anker *et al, NEJM* 2009;361:2436-2448

NYHA, PGA, QoL, 6min-Walking-Test
-- Week 4, 12 & 24 --

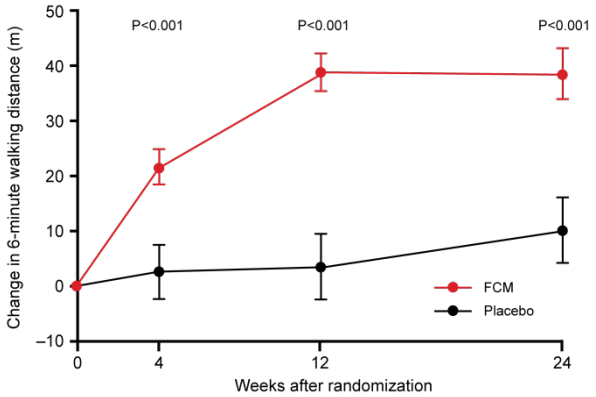
Patient Global Assessment



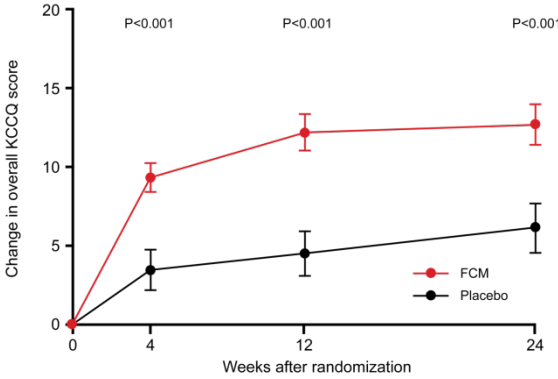
NYHA functional class



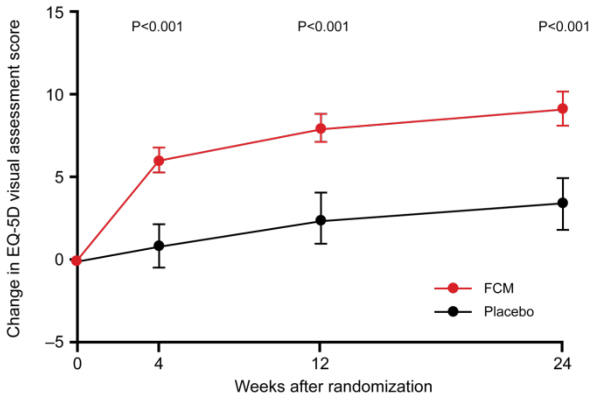
6-minute walk test



KCCQ overall score

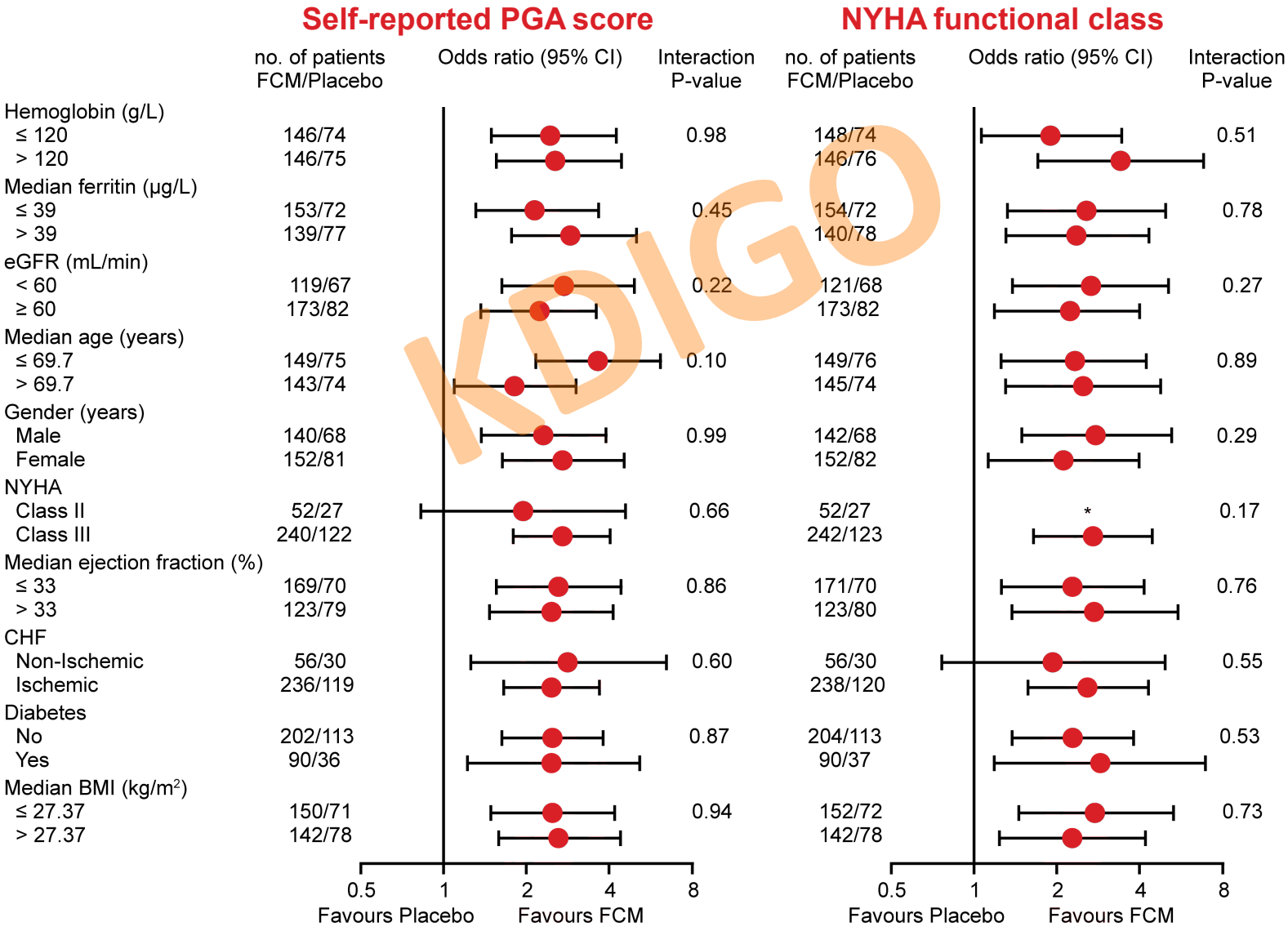


EQ-5D VAS score

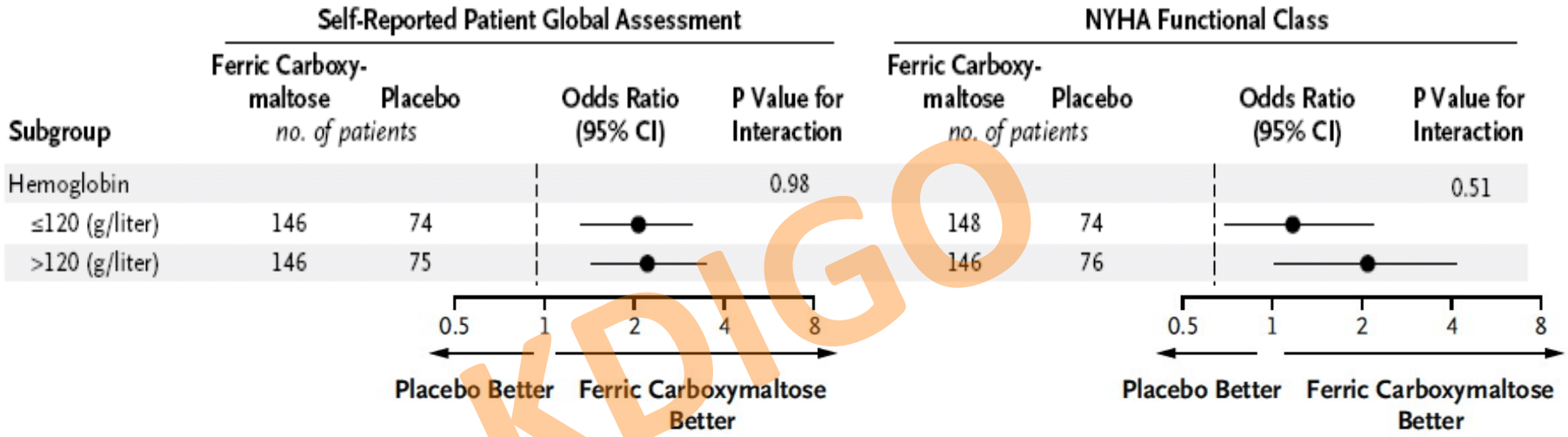


Anker *et al, NEJM* 2009;361:2436-2448

Secondary Endpoints: PGA & NYHA in pre-defined subgroups



iv-FCM improves PGA & NYHA class in CHF patients with and without anemia

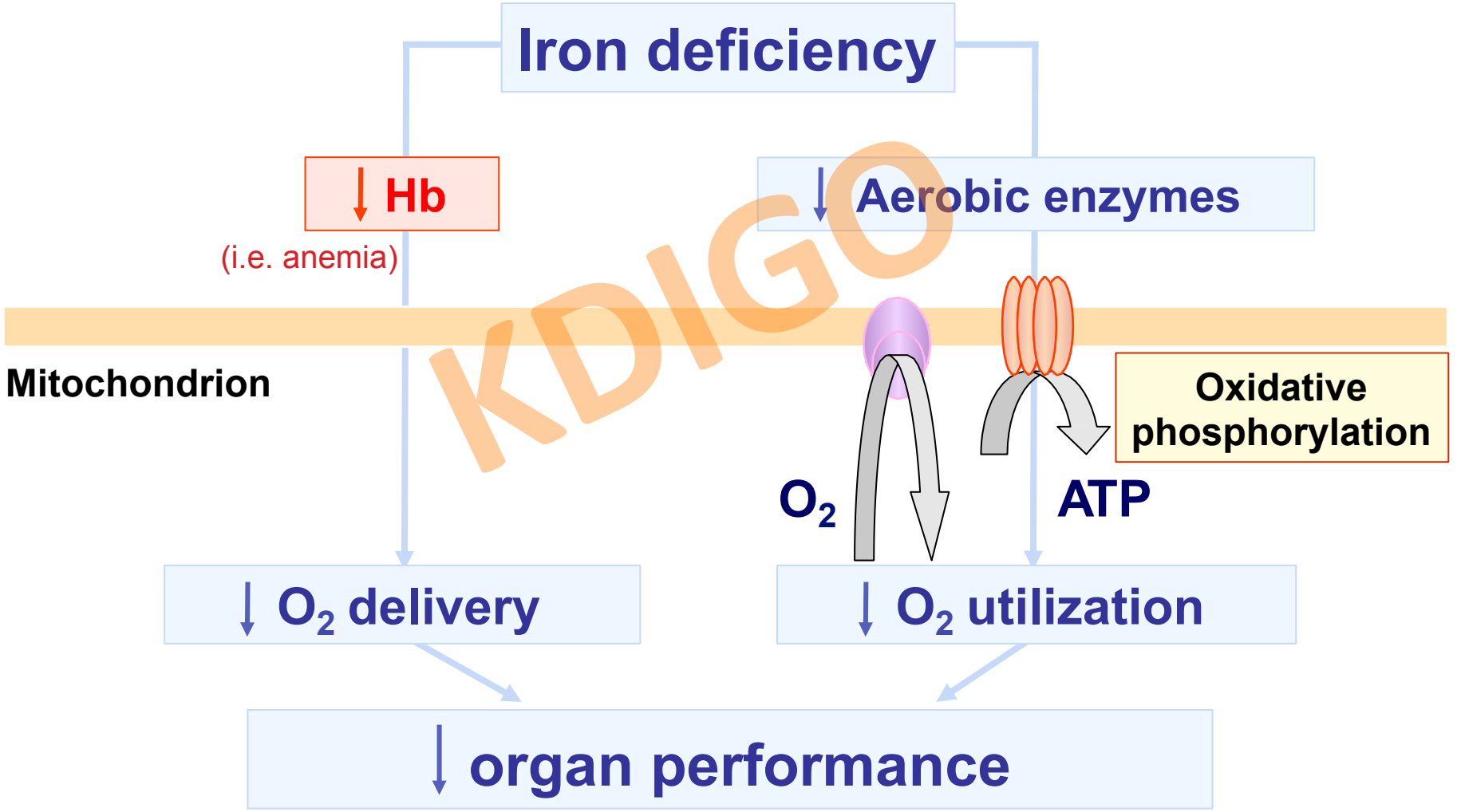


week 24 results	FCM	Placebo	p value*
Patients with anaemia (at BL)			
Serum ferritin (µg/L)	275±18	68±11	<0.001
TSAT (%)	29±1	17±1	<0.001
Haemoglobin (g/L)	127±1	118±2	<0.001
Patients without anaemia (at BL)	349±19	80±11	<0.001
Serum ferritin (µg/L)			
TSAT (%)	30±1	22±1	<0.001
Haemoglobin (g/L)	133±1	132±1	0.21

*Mean treatment effect, adjusted for the baseline value

Anker *et al, NEJM* 2009;361:2436-2448

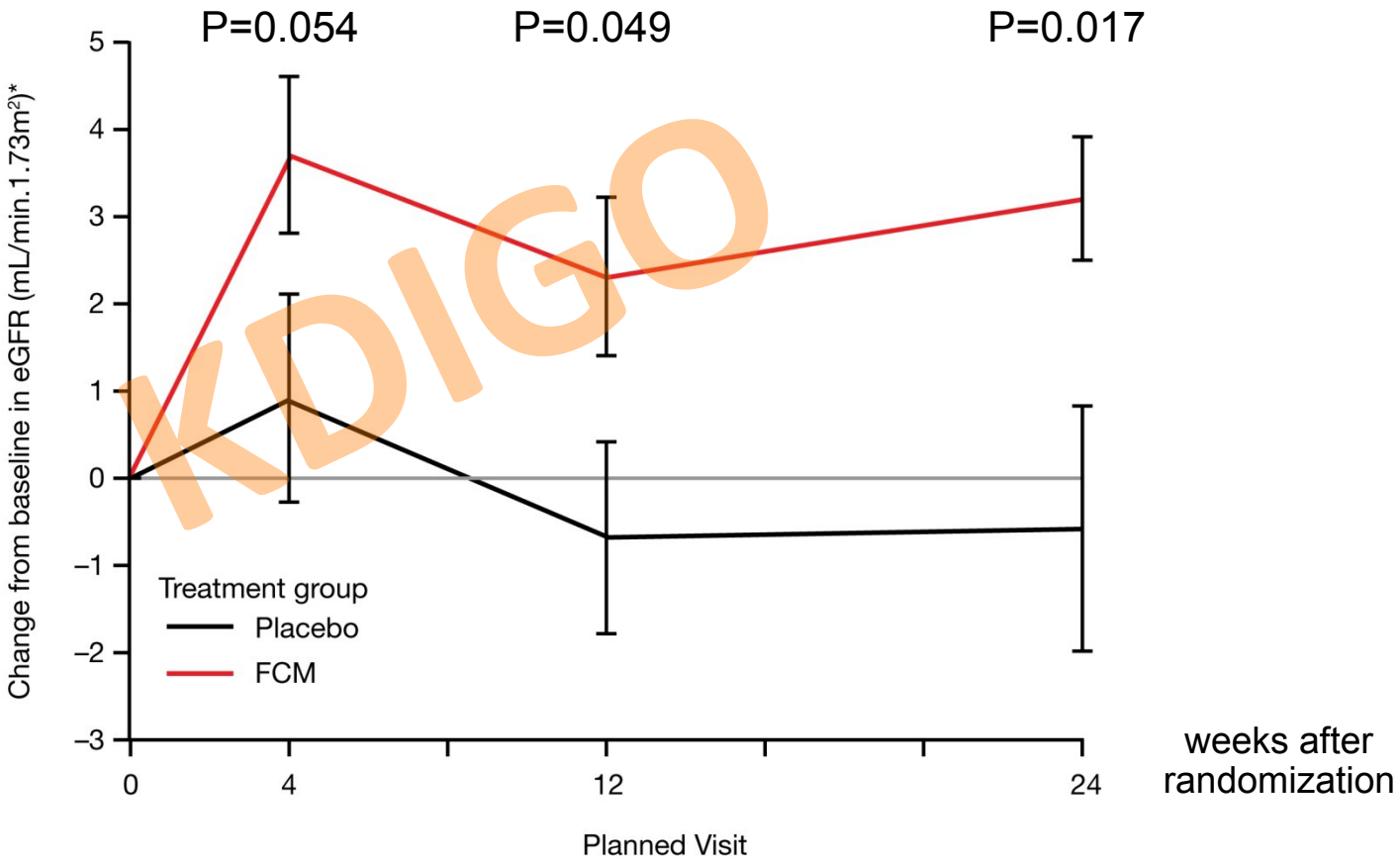
Anemia & iron deficiency & organ performance



Haas JD & Brownlie T. *J Nutr* 2001;131(2 suppl 2):676S–690S; Dallman PR. *J Intern Med* 1989;226:367–372;
Willis WT & Dallman PR. *Am J Physiol* 1989;257:C1080–1085;
Figure adapted from: Anker et al. EJHF 2009

Effect of iv-iron on kidney function

Change in eGFR from baseline (mL/min.1.73m²)



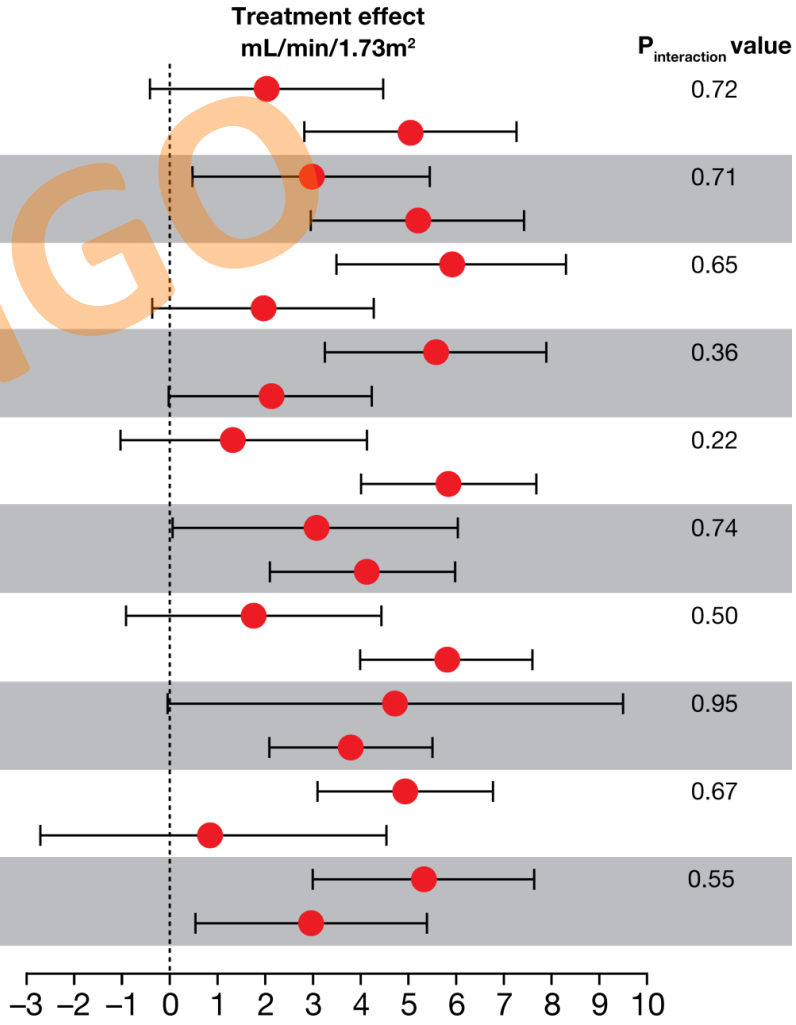
Treatment effect (mL/min/1.73m²):*	2.8 ± 1.5	3.0 ± 1.5	4.0 ± 1.7

* LSM mean ± SE

Ponikowski *et al. 2014 (submitted)*

Treatment effect on renal function in pre-specified subgroups

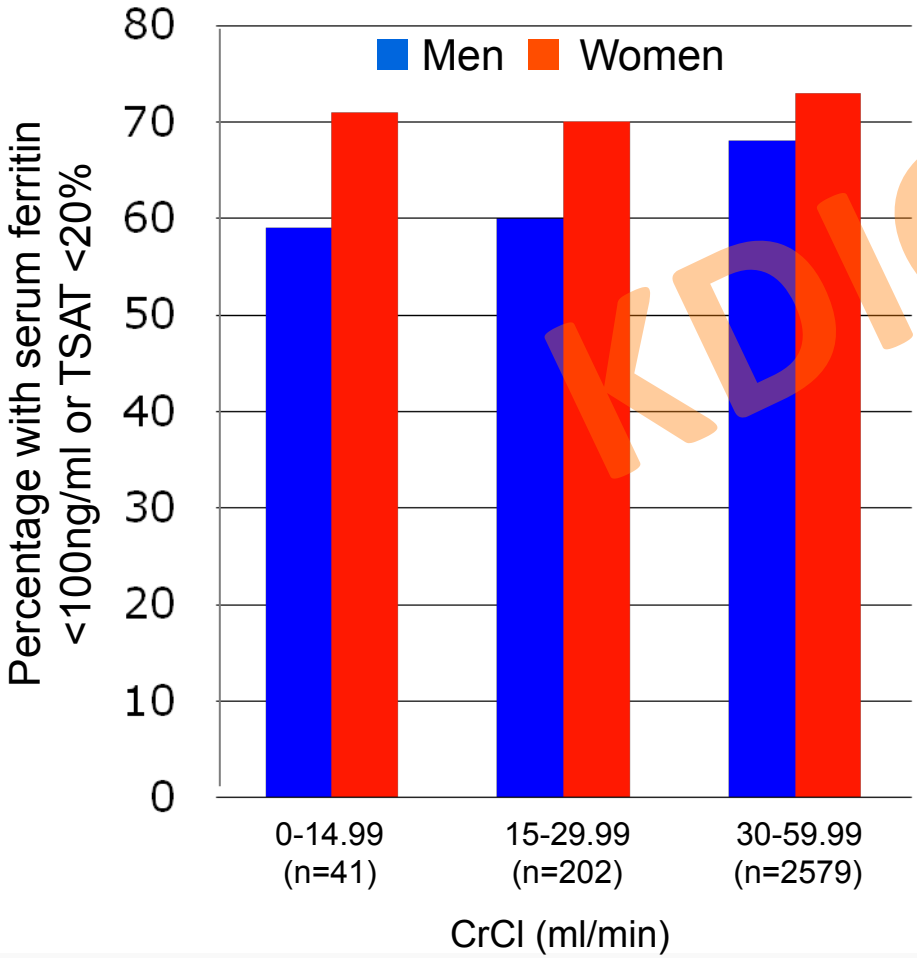
Endpoint (Week 24)	FCM	Placebo	$P_{interaction}$ value
eGFR <60 mL/min/1.73 m²	8.19 ± 1.42	6.13 ± 2.00	0.72
eGFR ≥60 mL/min/1.73 m²	−0.24 ± 1.23	−5.31 ± 1.87	
Hb ≤12 g/dL	4.11 ± 1.42	1.10 ± 2.04	0.71
Hb >12 g/dL	2.76 ± 1.22	−2.46 ± 1.86	
Ferritin ≤39 ng/mL	4.35 ± 1.30	−1.58 ± 2.02	0.65
Ferritin >39 ng/mL	2.32 ± 1.34	0.36 ± 1.88	
Age ≤69.7 years	3.22 ± 1.42	−2.64 ± 2.15	0.36
Age >69.7 years	3.61 ± 1.21	1.45 ± 1.75	
Male	3.29 ± 1.54	2.02 ± 2.40	0.22
Female	3.46 ± 1.09	−2.41 ± 1.52	
NYHA Class II	1.31 ± 1.63	−1.80 ± 2.45	0.74
NYHA Class III	3.88 ± 1.09	−0.20 ± 1.60	
LVEF ≤33%	4.21 ± 1.41	2.45 ± 2.31	0.50
LVEF >33%	2.44 ± 1.11	−3.40 ± 1.46	
Non-ischaemic HF	5.40 ± 2.73	0.64 ± 3.89	0.95
Ischaemic HF	2.97 ± 0.95	−0.86 ± 1.42	
Non diabetic	3.30 ± 1.07	−1.63 ± 1.50	0.67
Diabetic	3.77 ± 1.88	2.88 ± 3.19	
BMI ≤27.37kg/m²	3.66 ± 1.25	−1.67 ± 1.90	0.55
BMI >27.37kg/m²	3.08 ± 1.39	0.12 ± 1.98	



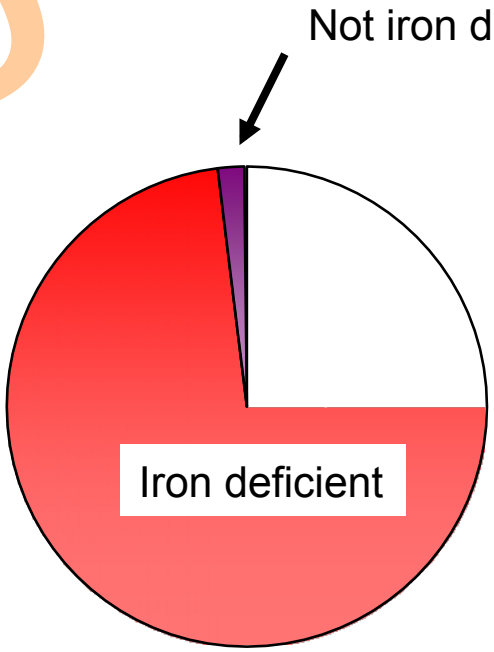
Ponikowski et al. HFA Congress 2010

Prevalence of Iron Deficiency in CKD

NHANES program (1988-2004)[1]



Bone marrow biopsy revealed severe iron deficiency in 46 of 47 CKD patients (Hb <12 g/dl)[2]



NHANES, National Health and Nutrition Examination Survey
CrCl = creatinine clearance; TSAT = transferrin saturation

1. Adapted from Fishbane S et al. Clin J Am Soc Nephrol 2009; 4: 57-61;
2. Gotloib L et al. J Nephrol 2006; 19: 161-67

Safety Endpoints

FAIR-HF

	Patients with events (Incidence per 100-patient years at risk)		
	FCM (N=305)	Placebo (N=154)	P
Death	5 (3.4)	4 (5.5)	0.47
CV death	4 (2.7)	4 (5.5)	0.31
Death due to worsening HF	0 (0.0)	3 (4.1)	-
First hospitalization	25 (17.7)	17 (24.8)	0.30
Hospitalization for any CV reason	15 (10.4)	14 (20.0)	0.08
First hospitalization for worsening HF	6 (4.1)	7 (9.7)	0.11
Any hospitalization or death	30 (21.2)	19 (27.7)	0.38
Hospitalization for any CV reason or death	20 (13.9)	16 (22.9)	0.14
First hospitalization for worsening HF or death	11 (7.5)	10 (13.9)	0.15

Reported Adverse Events

FAIR-HF

	Patients with events (Incidence per 100-patient years at risk)		
	FCM (N=305)	Placebo (N=154)	P
Cardiac disorder	38 (27.6)	33 (50.2)	0.01
Gastrointestinal disorder	24 (16.9)	5 (6.9)	0.06
General disorder or administration site condition	23 (16.2)	6 (8.3)	0.14
Injection site pain or discoloration	6 (4.1)	0 (0.0)	-
Infection or infestation	50 (37.0)	24 (35.8)	0.97
Abnormal laboratory test, vital sign, physical finding	32 (23.0)	10 (14.0)	0.17
Nervous system disorder	22 (15.6)	14 (20.3)	0.44
Respiratory, thoracic or mediastinal disorder	9 (6.2)	10 (14.2)	0.06
Vascular disorder	20 (14.0)	11 (15.7)	0.80

No severe or serious hypersensitive reactions

Adverse events are classified by the Medical Dictionary for Regulatory Activities (MedDRA) and are reported by system organ class when they occurred for more than 4% of patients in total.

The 2012 ESC heart failure guidelines

European Heart Journal
doi:10.1093/eurheartj/ehs104

ESC GUIDELINES

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: John J. V. McMurray (Chairperson) (UK)*, Stamatis Adamopoulos (Greece), Stefan D. Anker (Germany), Angelo Auricchio (Switzerland), Michael Böhm (Germany), Kenneth Dickstein (Norway), Volkmar Falk (Switzerland), Gerasimos Filippatos (Greece), Cândida Fonseca (Portugal), Miguel Angel Gomez Sanchez (Spain), Tiny Jaarsma (Sweden), Lars Køber (Denmark), Gregory Y. H. Lip (UK), Aldo Pietro Maggioni (Italy), Alexander Parkhomenko (Ukraine), Burkert M. Pieske (Austria), Bogdan A. Popescu (Romania), Per K. Rønnevik (Norway), Frans H. Rutten (The Netherlands), Juerg Schwitter (Switzerland), Petar Seferovic (Serbia), Janina Stepinska (Poland), Pedro T. Trindade (Switzerland), Adriaan A. Voors (The Netherlands), Faiez Zannad (France), Andreas Zeiher (Germany).

New ESC Guidelines HF 2012

Measurement of iron parameters are newly recommended (1C) as standard for the diagnosis in ambulatory patients suspected of having HF:

"*In addition to standard biochemical [sodium, potassium, creatinine/ estimated glomerular filtration rate (eGFR)] and haematological tests (haemoglobin, haematocrit, **ferritin**, leucocytes, and platelets), …*"

Measurement of blood chemistry (including sodium, potassium, calcium, urea/blood urea nitrogen, creatinine/estimated glomerular filtration rate, liver enzymes and bilirubin, ferritin/TIBC) and thyroid function is recommended to: (i) Evaluate patient suitability for diuretic, renin–angiotensin–aldosterone antagonist, and anticoagulant therapy (and monitor treatment) (ii) Detect reversible/treatable causes of HF (e.g. hypocalcaemia, thyroid dysfunction) and co-morbidities (e.g. iron deficiency) (iii) Obtain prognostic information.	I	C

TSAT= Serum iron/TIBCx100 TIBC

= Total Iron-Binding Capacity

McMurray JJ, et *al. Eur J Heart Fail* 2012:14:803–869

Iron Deficiency Treatment Recommendations

11.14 Iron deficiency

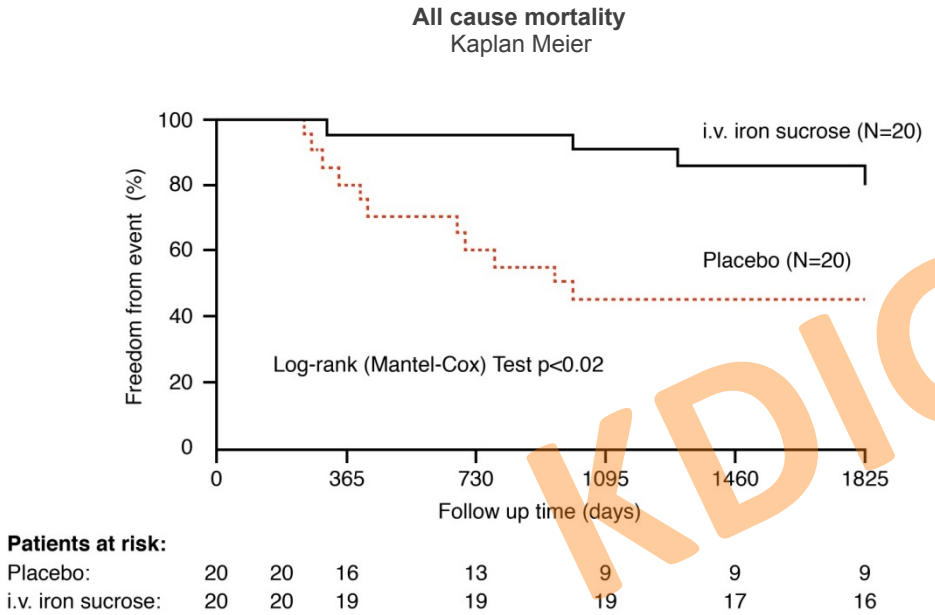
Iron deficiency may contribute to muscle dysfunction in HF and causes anaemia. In a single RCT, 459 patients with NYHA class II or III systolic HF, a haemoglobin concentration between 9.5 and 13.5 g/dL, and iron deficiency (see below) were randomized 2:1 to i.v. ferric carboxymaltose or saline. In this trial, iron deficiency was diagnosed when serum ferritin was <100 µ/L or when the ferritin concentration was between 100 and 299 µg/L and transferrin saturation was <20%.[208] Over 6 months of treatment, iron therapy improved self-reported patient global assessment and NYHA class (as well as 6-min walk distance and health-related quality of life) and may be considered as a treatment for these patients. The effect of treating iron deficiency in HF-PEF and the long-term safety of iron therapy in HF is unknown.

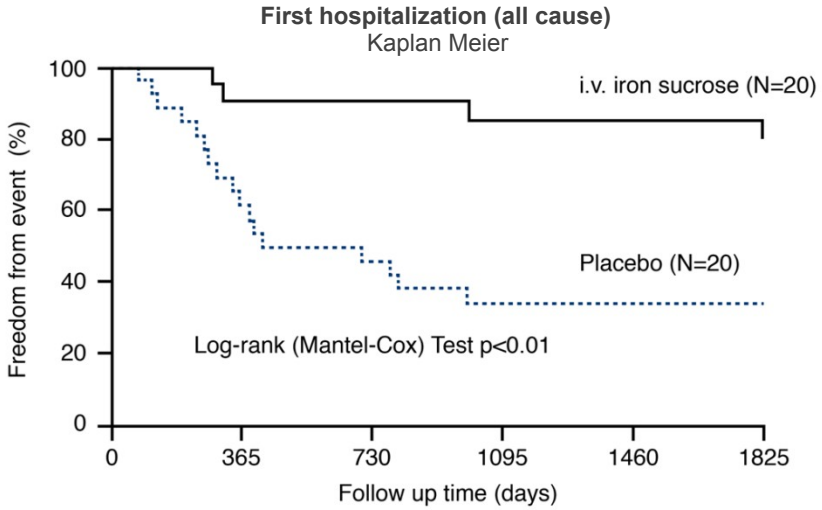
Limitations of the FAIR-HF study

- The FAIR-HF study:
  - Promising results, but the only double-blind, placebo-controlled clinical trial
    - Results need to be replicated
  - Primary endpoint: NYHA and PGA: optimal decision?
    - Studies need to evaluate different endpoints

      (CONFIRM-HF & EFFECT-HF ongoing -- 1000 mg injections in 1 min)
  - Relatively short study duration (6 months)
    - Studies need longer follow-up (patients exposition), with more safety data
  - Repeated 200mg doses
    - Higher single doses (up to 1000 mg) to be evaluated

Mortality and hospitalization in CHF with i.v. iron sucrose





LVEF < 35%

Anaemia: Hb <12.5 g/dl (men);
Hb <11.5 g/dl (women)

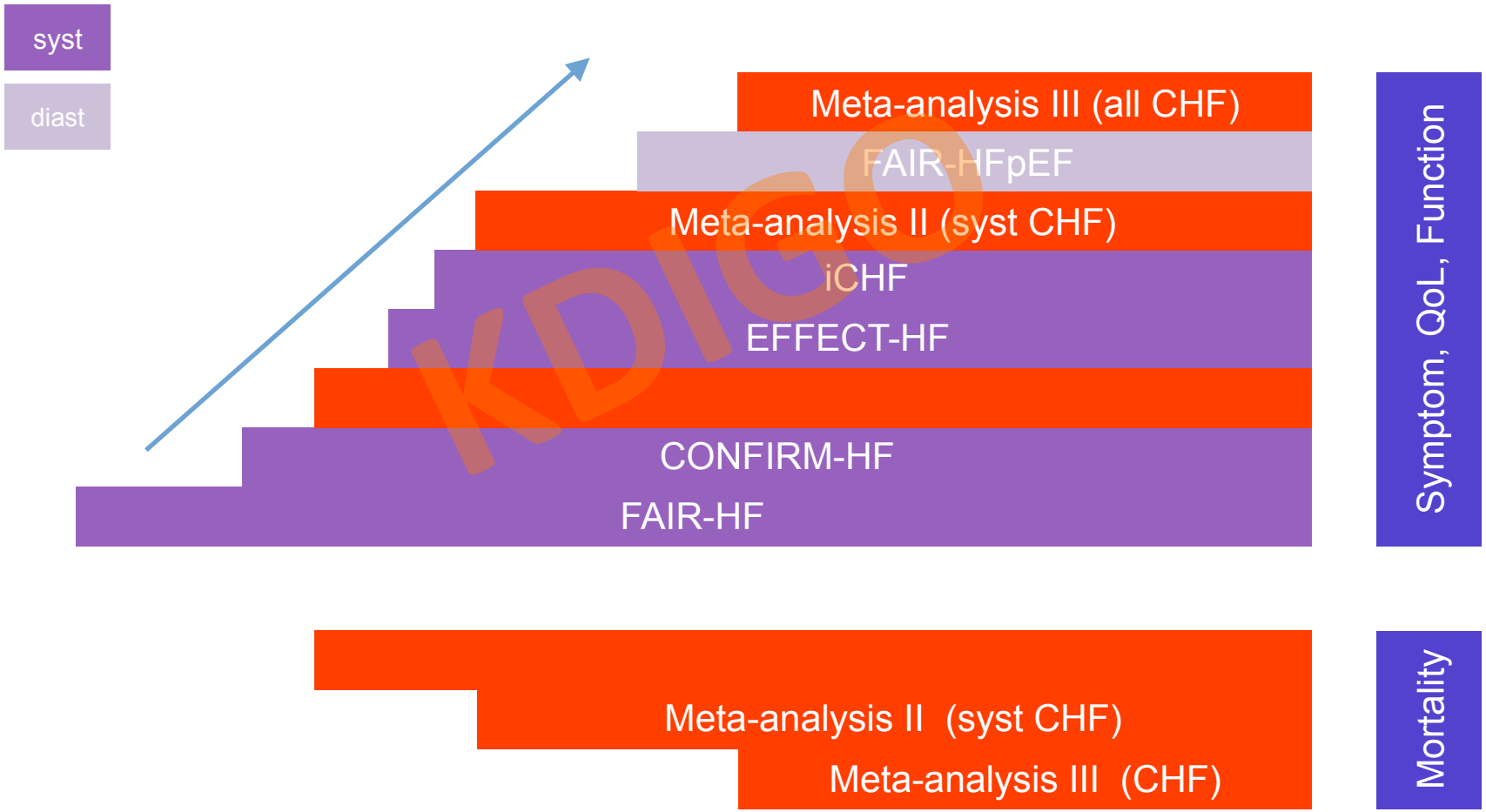
ID: Ferritin <100 ng/mL or TSAT <20%

Treatment:

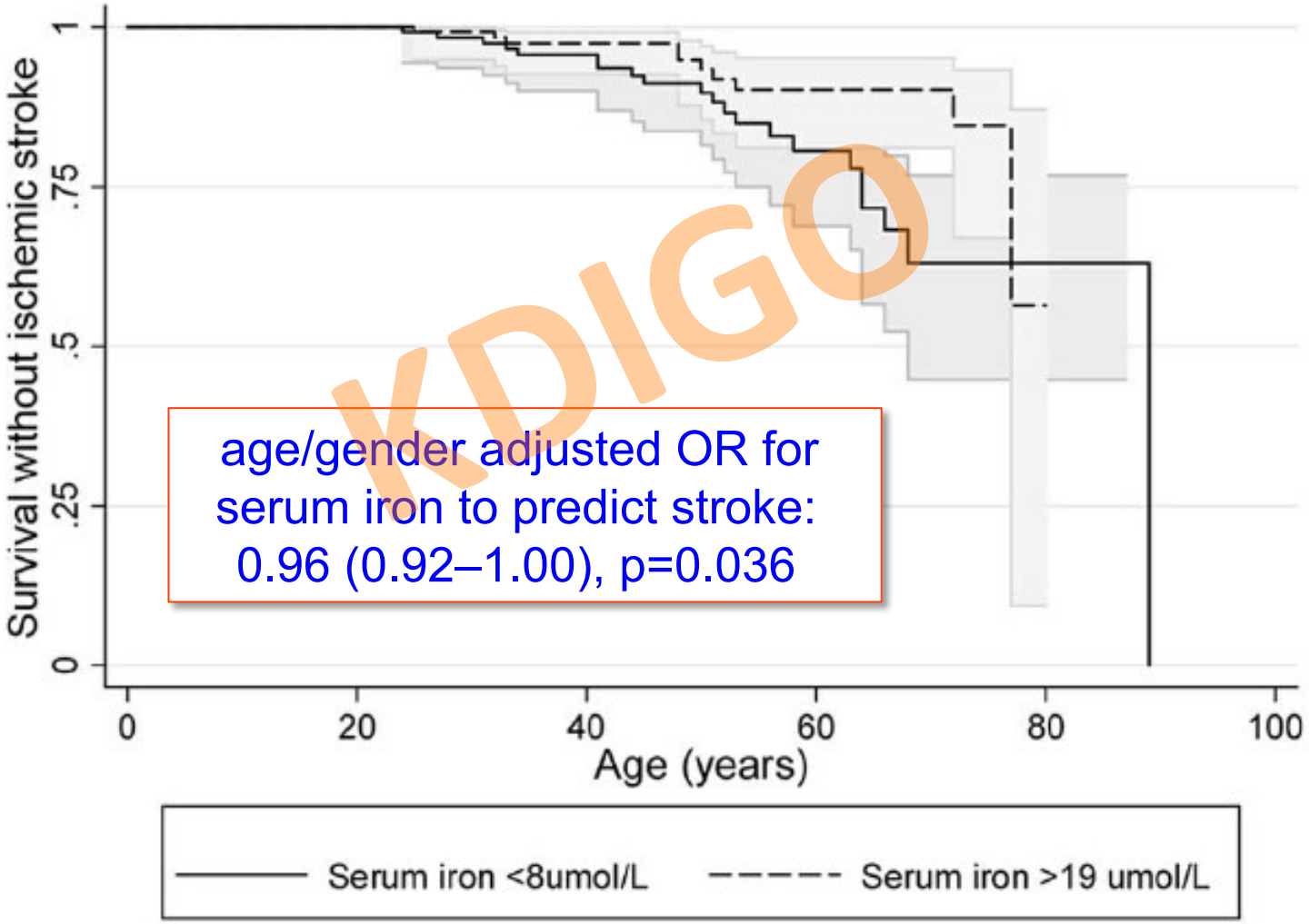
- i.v. iron group: 200mg/wk for 5wks, after 6 mt 200mg if Hb <11.0 g/dl and/or TSAT < 20%
- No oral iron and/or ESA given in both groups

Toblli JE, et al.
Abstract (Poster) AHA 2012.

CHF – Consolidating the Evidence



ID and stroke

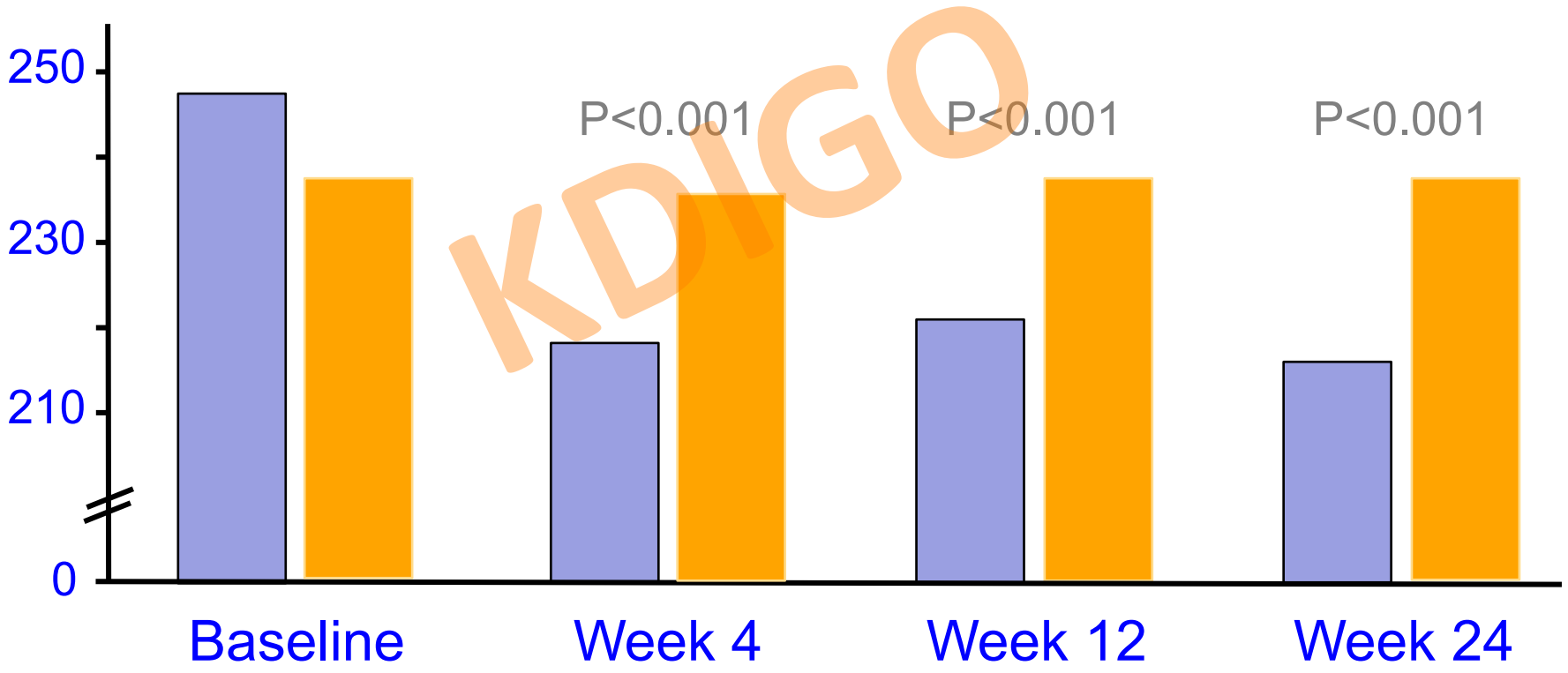


age/gender adjusted OR for serum iron to predict stroke: 0.96 (0.92–1.00), p=0.036

Shovlin CL, et al.
PLOS ONE 2014.

iv iron therapy reduces platelet numbers

FAIR-HF data



Von Haehling S. et al.
Abstract (Poster) ASN 2012

Iron Therapy is Under-Utilized in ND-CKD

European Best Practice Guidelines state:

"All CKD patients with renal anemia undergoing treatment with an erythropoiesis stimulating agent (ESA) should be given supplementary iron ...regardless of dialysis status"[1]

... but 33% of patients with non-dialysis CKD are NOT given iron therapy when starting ESA therapy

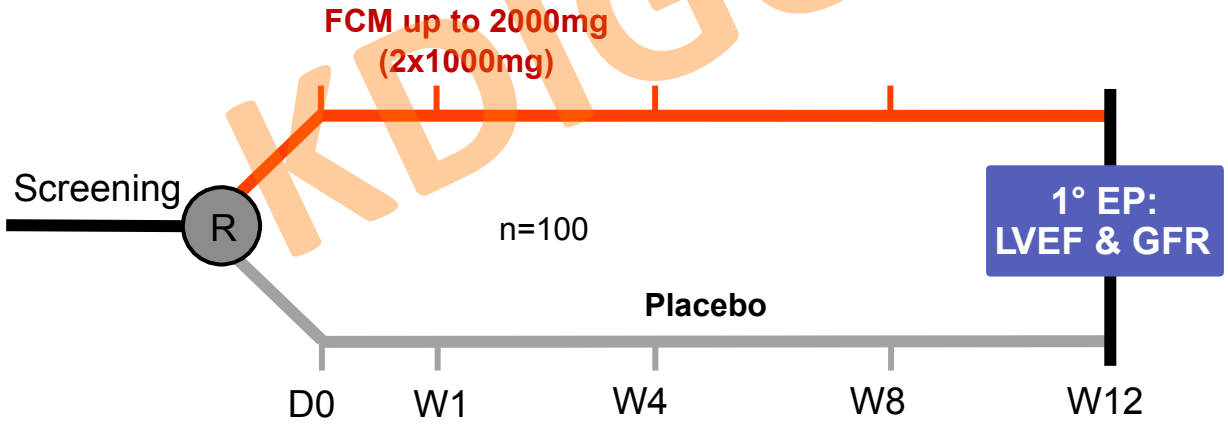
- Data from 1,060 patients with ND-CKD receiving ESA therapy[2]

Retrospective data from 1,997 patients starting dialysis 1999-2000 at 779 centers.
ESA = erythropoiesis stimulating agent

1. Locatelli F et al. Nephrol Dial Transplant 2004; 19(Suppl 2): ii1–ii47
2. Valderrábano F et al. Nephrol Dial Transplant 2003; 18: 89-100

iCHF
Design

- **Design:** Multicentre, randomized (1:1), double-blind, placebo-controlled
- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤40%
  - Iron deficiency: serum ferritin <100 µg/L or 100-300 µg/L, if TSAT <20%
  - Hb: 9.5–13.5g/dL

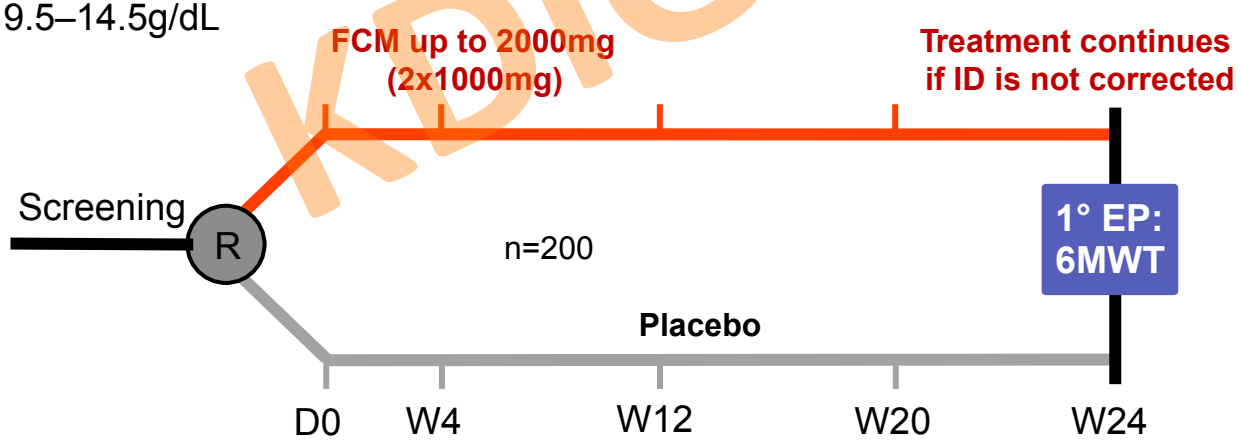


- **Primary endpoint**
  - Change in LVEF determined by cardiac MRI at week 12
  - Change in GFR determined by radionuclide Chromium-51-EDTA at week 12
- **Secondary endpoints**
  - Changes in biomarkers for iron deficiency, renal function, cardiac function, NYHA functional class, PGA and QoL
  - Overall safety over the treatment period

Clinicaltrials.gov identifier: NCT01837082.

FAIR-HFpEF
Design

- **Design:** Multicentre, randomized (1:1), double-blind, placebo-controlled
- **Main inclusion criteria:**
  - NYHA class II / III, LVEF > 45%
  - BNP > 100 pg/mL or NT-proBNP > 300 pg/mL
  - 6MWT < 450m
  - Iron deficiency: serum ferritin <100 µg/L or TSAT <20%
  - Hb: 9.5–14.5g/dL



- **Primary endpoint**
  - Change in 6MWT at week 24
- **Secondary endpoints**
  - Change in biomarkers for iron deficiency, renal function, cardiac function, NYHA functional class, PGA and QoL
  - Overall safety over the treatment period

Implications for clinical practice

Anemia in CHF patients:

- Sign of poor morbidity and mortality
- Increased Hgb: QoL, symptoms, ex.capacity not improved
- Treatment with ESAs: RED-HF trial (for M&M) neutral

Iron deficiency in CHF patients (with CKD):

- New significant therapeutic target (in patients ± anemia)
- Can easily be detected using ferritin & TSAT:
  a) ferritin<100, b) ferritin <300 & TSAT <20%
- ESC/HFA HF GL 2012: iv FCM "may be considered as a treatment for these patients"

McMurray JJ et al, EHJ & EJHF 2012

Problems & solution in iron therapy

- Iron overlaod
  - checking for ferritin & %TSAT after iron application
- Hypersensitivity & iron
  - inclusion / exclusion criteria
  - in reality, not observed in CHF trails
- Infections & iron
  - inclusion / exclusion criteria (CrP>10 excluded)
  - in reality, not observed in CHF trails