Carenza ed Eccesso di Ferro:
nuove conoscenze ed approccio terapeutico

Terapia delle carenze marziali: quali e quando

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Disclosure

- Member of advisory board for:
  - Novartis
  - Sanofi Genzyme
  - Celgene

ID and ID(A): Definition

Iron Deficiency

- Depleted iron stores

Absolute Iron Deficiency (no iron stores)

- Low Transferrin Saturation (**TSAT<20%**)
- **Serum ferritin low (<20ng/ml** – or <100ng/ml in case of inflammation)
- Elevated Serum Transferrin Receptor (sTfR)

Functional Iron Deficiency (full iron stores but ID in erythroid bone marrow)

- Low TSAT (**TSAT<20%**)
- **Serum ferritin normal or elevated (>20 ng/ml** – or >100ng/ml in case of inflammation)
- Normal sTfR

Iron Deficiency Anaemia

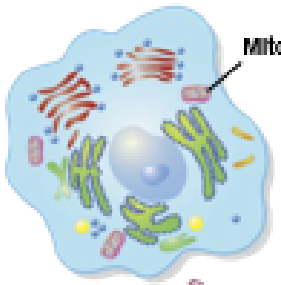
- Depleted iron stores
- Haemoglobin (Hb) concentration falls below defined lower limit (12g/dl for women, 13 g/dl for men)

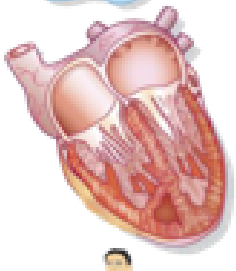
Adapted from Hush R. and Schaefer R. Pocket Atlas Special. Thiene 2006 and Prof. IY. Beguin oral communication. Parallel Symposia at EHA congress 2014, Milan, Italy

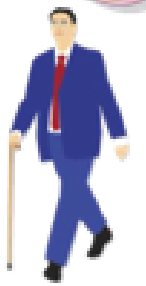
Rationale to treat the ID/ID(A)

Importance of Iron

Iron is critical for optimal functioning and survival of living structures:







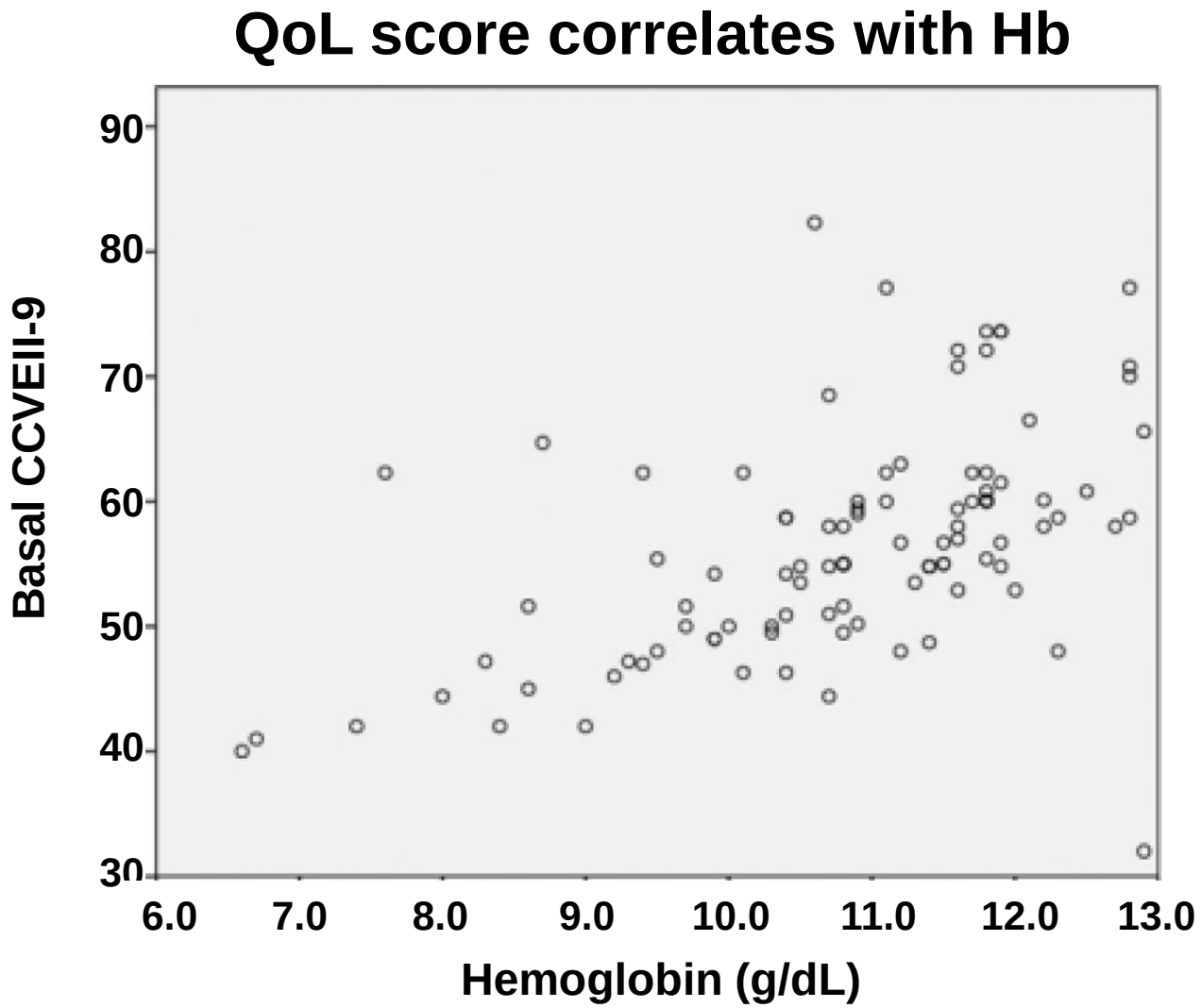
Iron deficiency results in:

- Mitochondrial dysfunction
- Deranged activity of enzymes
- Abnormal transport and structural proteins
- Apoptosis

- Tissue remodeling
- Impaired organ efficacy

- Impaired exercise capacity
- Reduced work efficacy
- Impaired cognitive performance and behavior
- Increased morbidity and mortality

Impact of anemia on quality of life



Linear correlation coefficient 0.51; determination coefficient 0.26

p <0.0001

QoL, Quality of Life

CCVEII-9 short ended 9-item questionnaire

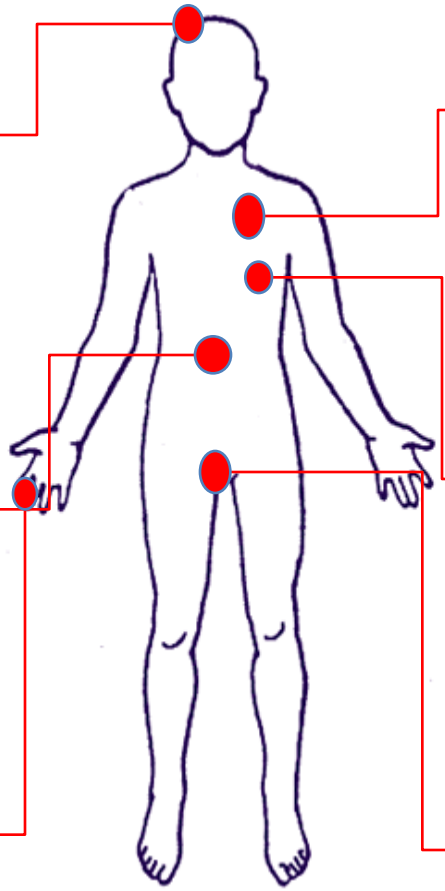
Gisbert JP, et al. *Inflamm Bowel Dis* 2009;15:1485-91.

Clinical consequences of anaemia and of ID(A)

Central nervous system
- *Fatigue*
- *Dizziness*
- *Depression*
- *Impaired cognitive function*

Gastrointestinal system
- *Anorexia*
- *Nausea*

Vascular system
- *Low skin temperature*
- *Pallor of skin*



Immune system
- *Impaired T-cell and macrophage function*

Cardio-respiratory system
- *Exertion dyspnoea*
- *Tachycardia, palpitations*
- *Hypertrophy*
- *Risk of cardiac failure*

Genital tract
- *Menstruation problems*
- *Loss of libido*

Ludwig H, et al. Semin Oncol 1998;25:35-44.

Available treatment options

VS

Oral Iron

i.v. Iron

Treatment – General Principles

Oral iron

- *No* underlying chronic diseases
- *No* malabsorption
- *Small* amounts of iron required
- Replenishment not time critical

I.V. iron

- With underlying *chronic disease*
- With underlying *malabsorption*
- *Moderate-to-large* amounts of iron required
- *Rapid repletion* required

RBC transfusion

- As last resort for unstable, bleeding patient

ESA

- Low endogenous EPO levels (eg CKD)
- Blunted erythropoiesis (inflammation; hepcidin block)
- Only if iron stores are repleted

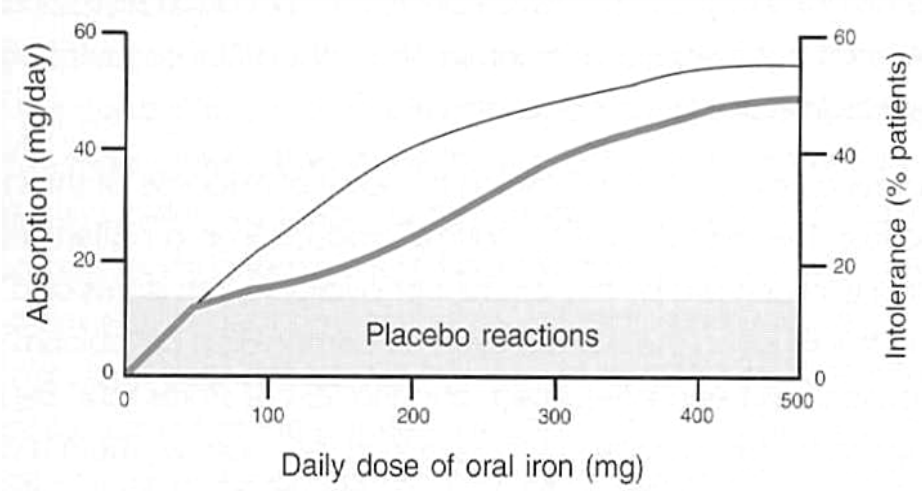
Table 3. Major Iron Formulations Available and Current Treatments for ID

Treatment	Agent	Dosage	Amount of Fe administrated (mg)	Adverse Events	Reccomandations	Ref.
Oral Iron Suppl.	Ferrous Sulphate	1 tablet/day	(Fe^{++}) 85-105 mg	• Nausea • Vomit • Epigastric discomfort • Constipation/diarrhoea • Metallic taste • Dark colored stools	• Healthy population after treatment of underlying cause of IDA; • Elderly if Hb > 8 g/dL < 12 g/dL; **Gray area:** Every day or alternative day schedule.	3, 5, 6, 14, 26, 51, 52, 53, 54, 56, 60
	Ferrous Gluconate	1 tablet/day	(Fe^{++}) 75-80 mg			
	Na^{+} Ferrigluconate	1 fl/day	(Fe^{++}) 62.5 mg			
	Fe-glycine sulphate	1 tablet/day	(Fe^{++}) 100 mg			
	Fe-bisglycinate	1-3 tablet/day	(Fe^{2+}) 25 mg			
	Lyposomial Fe-pyroph and Vit. C	1-2 tablet/day	(Fe^{++}) 30 mg and Vit. C 70 mg			
I.v. Iron Suppl.	Na^{+} Ferrigluconate	1-2 fl/day-diluted in FS	(Fe^{+++}) 62.5 mg	• Nausea • Vomit • Pruritus • Headheache and flushing • Myalgia and arthralgia • Back and chest pain (resolution within 48 hrs) **Notes** • Avoid iv Fe Suppl. during the first trimester of pregnancy (no data available on safety) • Test-dose is NOT informative on possible severe AEs.	**Strong indication in:** • CKD stage 5D • IBD with active disease • Malasorption • CHF • Hb ≤8 g/dL • IRIDA • IDA with intolerance to oral Fe Suppl. **Suggested in:** • CKD stage 3D-5D **Gray area:** IDA in elderly	3, 5, 6, 13, 14, 26, 31, 36, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 63, 64
	Ferric carboximaltoside	500-1000 mg diluted in SS	(Fe^{+++}) 100 -500 mg			
	Fe-saccharate	1fl/day diluted in SS	(Fe^{+++}) 100 mg			
	Ferumoxytol	510 mg	(Fe^{+++}) 510 mg			

Vit C: Vitamine C; fl: SS: saline solution; i.v.: intravenous; CKD: chronic kidney disease; CHF: chronic heart failure; IBD: inflammatory bowel disease; Hb: hemoglobin; IDA: iron deficiency anemia; Hamp: hepcidin; IRIDA: iron refractory iron deficiency anemia; hrs: hours; D: disease; suppl: supplementation.
Ganzoni formula calculates the amounts of iron required to restore desire Hb levels: iron deficit (mg)=body weight (Kg) x (target Hb-actual Hb) (g/dL) x 2.4 + iron storage depot (mg).

De Franceschi L et al submitted

Oral iron therapy



- **200 mg** iron per day
- **Ferrous salts** :Ferric compounds less absorbed (better tolerated)
- Absorption **improves** when given **between meals**
  Absorption **decreases** with **inflammation, renal failure, cancer, poor transit…**
- Duration of regimen : **3–6 months**
  - Anemia corrects with first 3 months
  - Iron Stores get replenished with second 3 months

- Tolerance **improves** when given **with meals**
  Side effects : **GI** (intolerance, diarrhea, constipation, black stools…)

Causes of Oral Therapy Failure

Causes of treatment failure in oral iron therapy

Lack of adherence to therapy or insufficient length of therapy for the degree of iron deficit

Concomitant/causal underlying blood loss pathology not resolved

Poor duodenal absorption:

- Concomitant GI pathology (inflammatory bowel disease or any other cause or chronic inflammation; malignancy)
- Insufficient gastric acidity (pharmacological blockade of gastric secretion)
- Chemical inhibition of absorption (lead-aluminum)

Side effects:

- Nausea
- Constipation
- Upper GI irritation

Iron-refractory iron deficiency anaemias (IRIDA)

Indications for i.v. Iron

Main indications for IV iron treatment
Cancer related anaemia
Post-partum iron deficiency anaemia
Anaemia of pregnancy
Anaemia of chronic kidney disease
Anaemia of inflammatory bowel disease
Anaemia in patients treated in an intensive care unit
To increase blood donation before surgery in elective orthopedic patients
In iron malabsorption syndromes (post gastrectomy, Biermer disease, IRIDA)
Intolerance of or non-compliance with oral iron treatment
Severe iron deficiency anaemia with continuous bleeding (Osler-Weber-Rendu disease)

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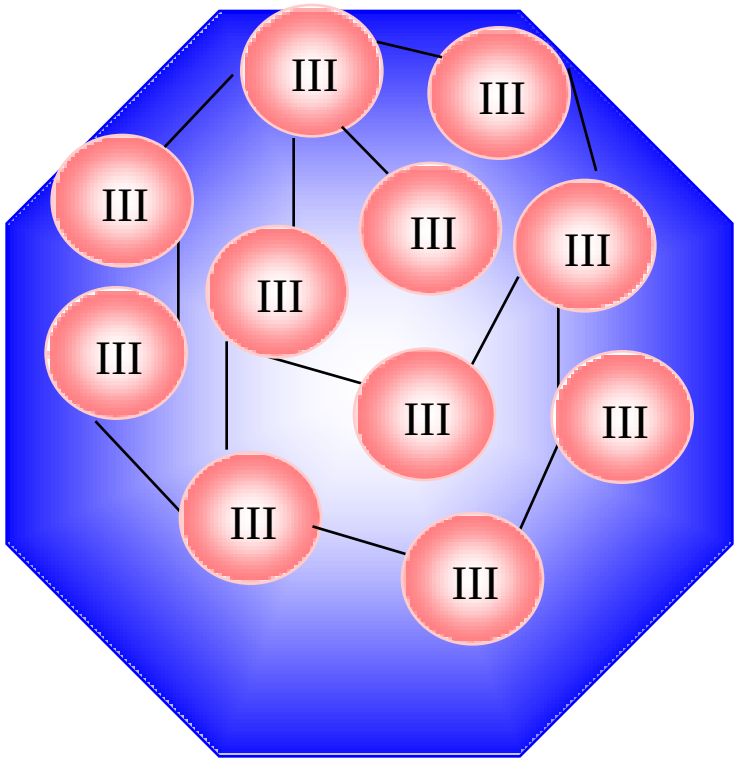
De Franceschi L et al submitted

Advances on i.v. iron

Iron Core



Carbohydrate shell

1947: Fe-Saccharide

↓

1954: Fe-Dextran (HMW)

↓

1999: Fe-Gluconate

↓

2000: Fe-Sucrose

↓

2009: Ferumoxytol

↓

2011: Fe-Carboymaltose

Intravenous iron compounds

	Iron gluconate	Iron sucrose	Ferumoxytol	Iron carboxymaltose	Iron dextran	Iron isomaltoside
Maximum single iron dose	125 mg*	200 mg**	510 mg	20 mg/kg bw*** (1000 mg)	20 mg/kg bw	20 mg/kg bw
Route for max dose	Injection or infusion	Injection or infusion**	Injection	Injection or infusion	Infusion	Infusion
Time for maximum dose	Infusion: 1 hour  Injection: 5 min	Infusion: 30 min  Injection:10 min	Injection: 17 sec 	Infusion: 15 min  Injection: 15min	Infusion: 4–6 h 	Infusion: 1 hour 
Dosing interval	Max 3 times a week	Max 3 times a week	3–8 days	Weekly	2–3 times a week	Weekly

* 125mg can be administered in some countries
** 500 mg can be administered in some countries
***only for infusion, 15 mg/kg bw for injection

Prof. Y. Beguin oral communication. Parallel Symposia at EHA congress 2014, Milan, Italy. Table generated from single product's SmPC.

Iron Sucrose

(Venofer)

- Preparations contain **20 mg** iron/mL
- Approved for **IV** use only
- **Safety and efficacy** profile **similar** to that of **ferric gluconate** (dialysis, non-dialysis CKD, IBD, chemotherapy-induced anemia, peripartum period, gastric bypass, heavy uterine bleeding…)
- **Test dose not indicated**, but **recommended** in patients who are **sensitive** to iron dextran or have other **drug allergies**

Iron Sucrose

Venofer

- **<u>Recommended dose:</u>**
  - Anemic **cancer** patients receiving **erythropoiesis-stimulating agents** is **200 mg** infused over 60 minutes, repeated every two to three weeks
  - It is routinely given as a **200 mg** IV bolus over two minutes in **dialysis** centers
- While approved as a 500 mg infusion over longer periods of time (hours), single doses greater than 300 mg are **not recommended**

Ferric Carboxymaltose

Ferrinject

- **Novel** stable iron complex for **IV** use
- Can be given at **single doses** of up to **1000 mg** of elemental iron per week over a recommended infusion time of **15 minutes**
- A number of trials have shown **efficacy and safety** of this agent in iron deficient patients in a number of different settings (eg, heavy uterine bleeding, postpartum women, chronic renal failure, inflammatory bowel disease, heart failure, nonresponse to oral iron)
- It was shown to be effective in **alleviating symptoms** of **congestive heart failure** and was the first agent to demonstrate **efficacy** in **chemotherapy-associated anemia** when administered **without** concomitant use of an **erythropoiesis-stimulating agent**

Ferric Carboxymaltose

Ferinject®

- **Licensed** for use in Europe, Asia, and New Zealand

- **Approved** for use in the United States in patients with **IDA** and **intolerance** or **unsatisfactory** response to oral iron and for treatment of **IDA** in adults with **nondialysis-dependent** CKD

- Based on the preponderance of published evidence, ferric carboxymaltose is **safe and effective**, with a **side effect** profile **similar** to the **other** available intravenous iron formulations

Iron toxicity (limiting dose) depends on stability of the iron/carbohydrate complex

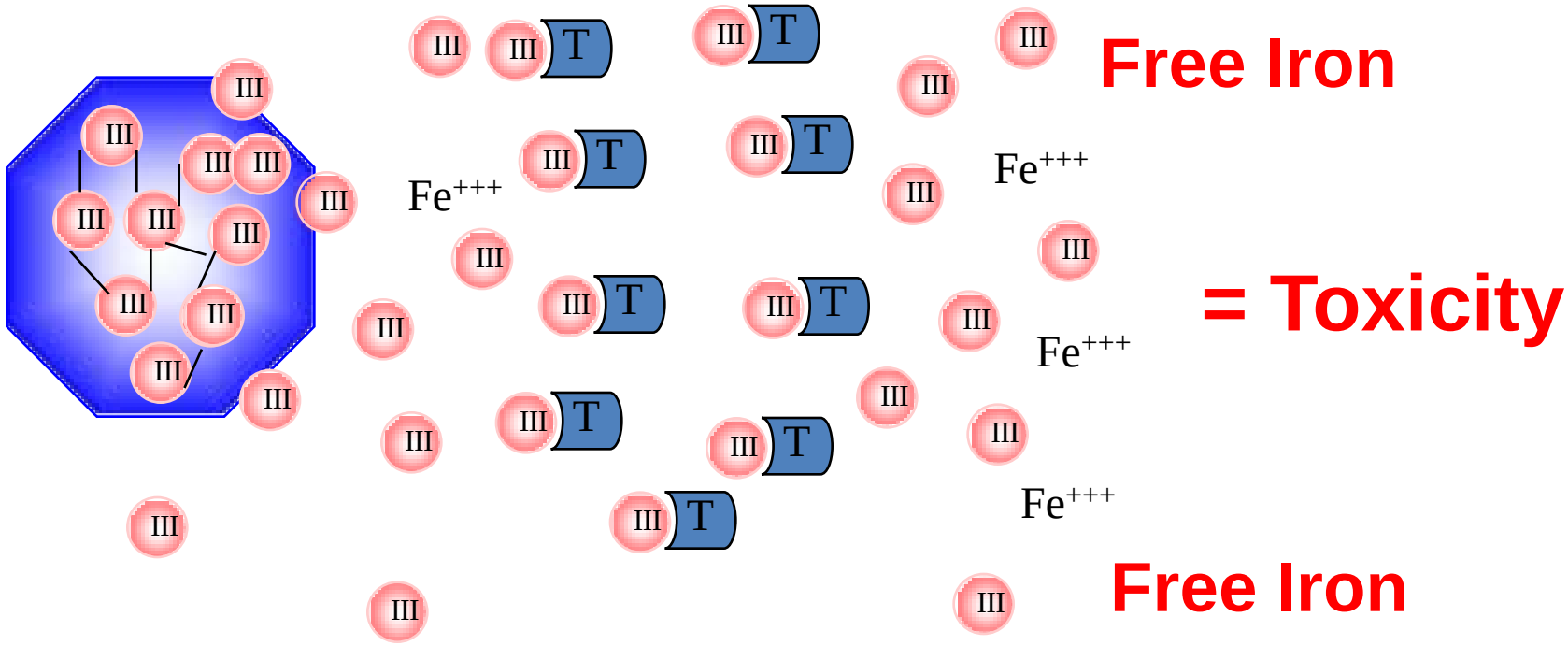


Table 2. Diagnosis and Therapeutic Options in Special Subset of Patients affected by mycrocitic anemia related to ID							
Disease		**Causes of ID**	**Diagnosis**	**Clinical Management**	**Follow-up**	**Notes**	**Ref.**
GI disorders	Occult Blood loss Malassorbition	• NSAID use • Colon carcinoma • Benign gastric ulcer • Gastric cancer • Coelic disease • Gastrectomy • Infection (HP, Giardia l.)	Mycrotic anemia SF <30 ng/mL TST < 20%	• Remove the cause • Oral Fe suppl. • i.v. Fe suppl is indicated.	Hb levels after 4 weeks and then every 3 months the iron related indices for the first year then once/y	- Verify tolerability and patient adherence to oral Fe suppl. - Consider iv Fe suppl. if failure after 6 months suppl.	3, 6, 15, 23, 24, 25, 26, 27, 28, 29
	IBD (Disease activity)	• Quiescent D. • Active D.	Mycrocitic anemia SF <30 ug/L TST < 20% Mycrocitic anemia SF <100 ng/mL TST < 20%	i.v. Fe suppl. is preferred Treat the active IBD Absolute indication for i.v. Fe suppl are: • Hb< 10 g/dL • Intolerance to oral Fe suppl. • Inadequate response to oral Fe suppl. • Severe intestine D.	Hb levels after 4 weeks and then every 3 months the iron related indices for the first year then once/y	Mycrocitic anemia is still undertreated in IBD patients	
CKD		• Reduced Fe absorption related to chronic	**Not yet on HD:** Mycrocitic anemia SF < 100 ng/mL	Oral Fe Suppl.: 30% of pts shows GI side effects: consider i.v. Fe	• Hb levels after 4 weeks with 1-2 gr/month increase	Functional ID: Normocytic anemia SF:100-800	3, 30, 31, 32,

De Franceschi I et al.submitted

		inflammatory state • Relative EPO deficiency • Uremic induced inhibition of erythropoiesis	TST < 20% **On HD:** Mycrocitic anemia SF < 200 ng/mL	suppl. i.v. Fe Suppl.: well tolerated.	• Evaluation of pts QoL improvement • ↓%hypochromic RBCs	ng/mL TST: >20%	33, 34, 35, 36
Chronic Heart Failure (CHF)		• Reduced Fe absorption related to chronic inflammatory state • Nutritional factors • Suboptimal mesenteric blood flow	SF*<100ng/mL SF:100-300 ng/mL and TST < 20%	i.v. Fe suppl has to be considered due to: • low pts adherence to oral therapy • suboptimal mesenteric blood flow (↓ absorption and politherapy)	Hb levels after 4 weeks and then every 3 months the iron related indices for the first year then once/y In anemic pts consider Hb target > 7 g/dL	ESAs should be considered only in presence of chronic renal failure	3, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 64
Elderly		• Malnutrition • Delay gastric emptying • occult blood loss • Presence of chronic inflammatory diseases	Mycrocitic anemia SF < 30 ng/mL TST < 20% Anemia SF < 30-100 ng/mL TST < 20% ↑ CRP	• Identify and remove the cause; • Oral Fe suppl. fractioned in small doses. i.v. Fe suppl. has to be considered if: • GI intolerance to oral Fe formulation • GI disorders • Presence of co-morbidities: CKD, HD, IBD RBC transfusion should be considered if Hb levels • <6 g/dL (acute	Hb levels after 4 weeks and then every 3 months the iron related indices for the first year then once/y Hb target > 8 g/dL	- Functional ID as normocytic anemia: • SF: >100ng/mL • TST: >20% • ↑ CRP - Unexplained normochromic normocytic hypoproliferative anemia, possibly related to stem cell disorder(s) and characterized by: • ↓ CRP	3, 22, 47, 48, 49, 50

				setting) • 7-8 g/dL (chronic setting)			
IRIDA	Autosomal recessive condition	Mutations in TMPRSS6 gene	Mycrocitic anemia SF ≥ 30 ng/mL TST < 20%	Oral Fe Suppl.: high possibility of failure Consider i.v. Fe Suppl.	Hb levels after 4 weeks and then every 3 months the iron related indices for the first year then once/y	Hamp ➔↑	5, 6, 9, 12,13, 15,

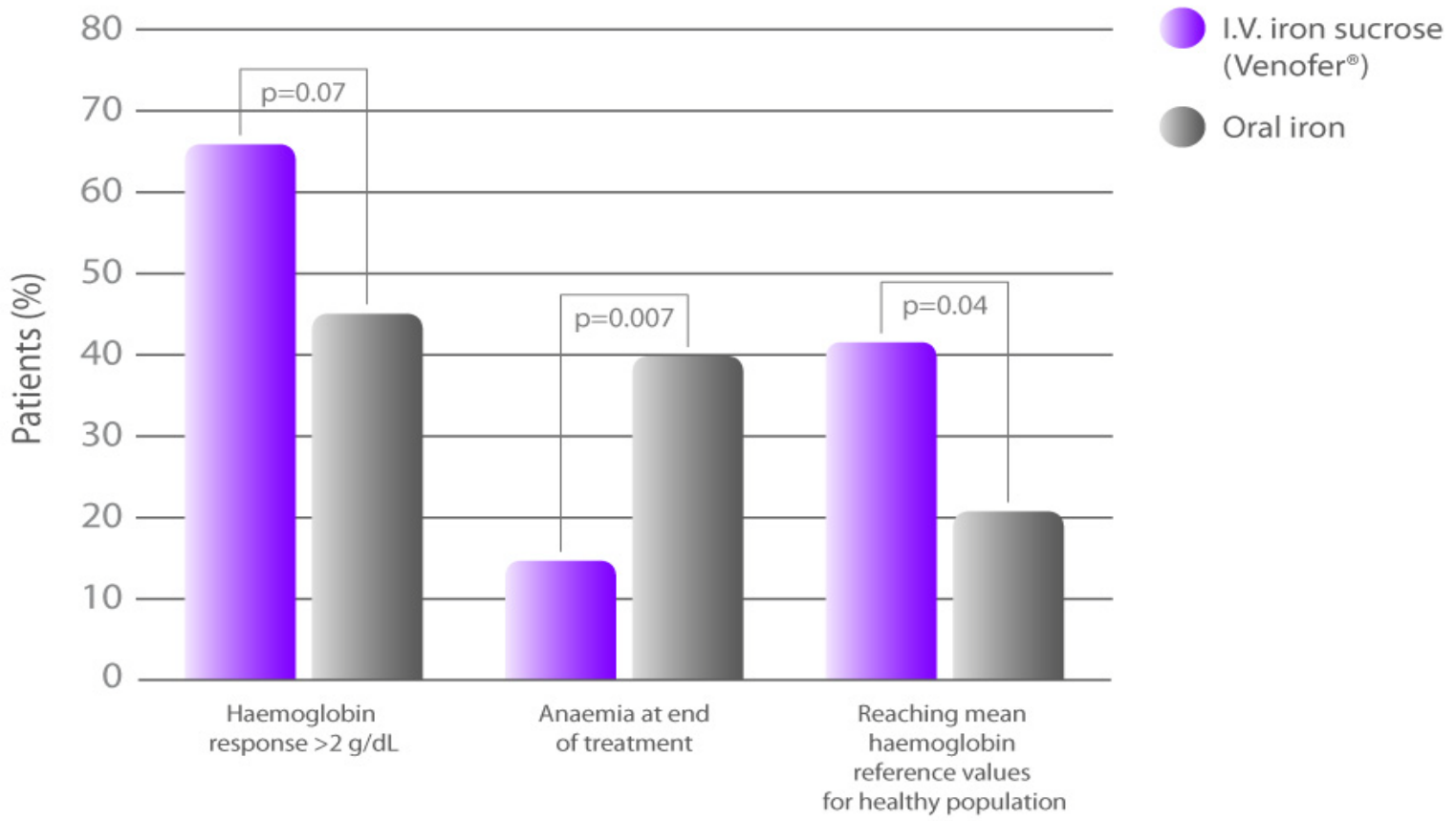
Treatment – Indications for I.V. Iron Therapy

	Advantages	Disadvantages
Oral iron	Relatively low cost, suitable for almost all women	Compliance issues associated with gastrointestinal adverse events (e.g., diarrhea, constipation, nausea/vomiting) and oxidative stress (in particular for ferrous salts)
I.V. iron	Beneficial for patients who cannot tolerate oral supplements, only effective therapy to supply enough iron for erythropoiesis, may be rapidly administered, provides rapid increase in iron stores, ferritin and Hb levels	Risk of local and systemic adverse events and anaphylactic reactions (iron dextran), hypotension, nausea, cramps
Transfusion	Can be life-saving	Involves a variety of inherent risks and complications (infection, immune reaction), high cost, shortage in supply, administrative errors

Examples

Anemia In Inflammatory Bowel Disease (IBD)

Superiority of I.V. over oral iron in IBD



Reproduced from Lindgren S *et al*. *Scand J Gastroenterol* 2009

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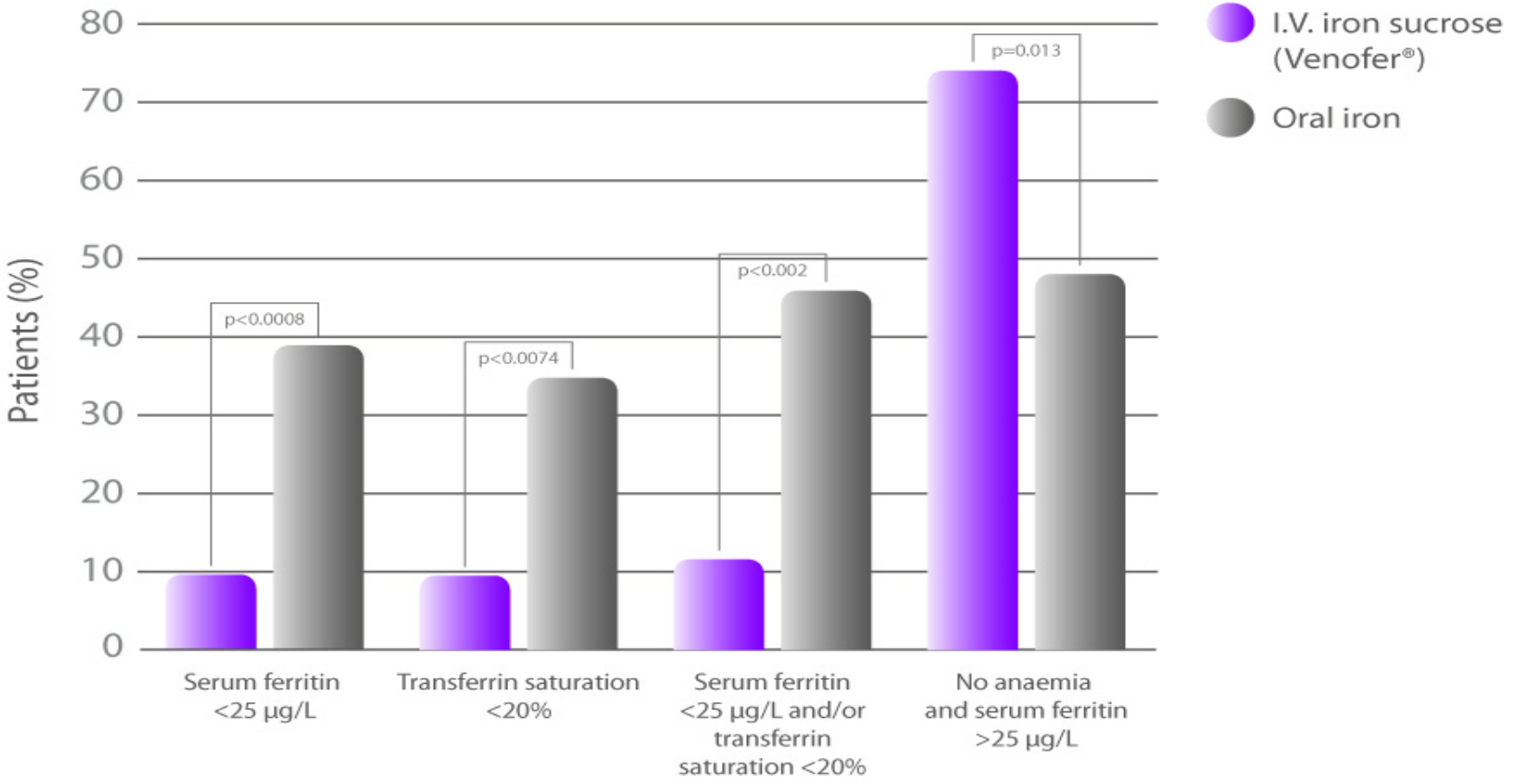


Reproduced from Lindgren S *et al*. *Scand J Gastroenterol* 2009;44:7; 838-845

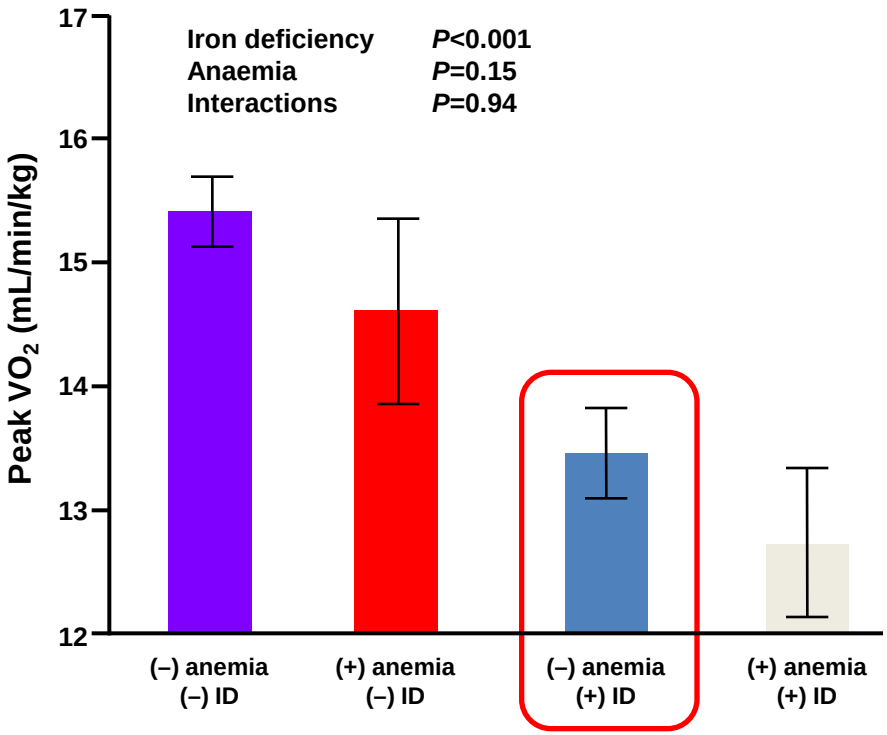
Iron deficiency beyond targeting anemia

Iron plays a key role in oxygen uptake, transport, and storage, as well as oxidative metabolism in the skeletal muscle; it also is involved in erythropoiesis.[8,9] Traditionally, iron deficiency has been considered to have clinical consequences only in the presence of anemia. Alternatively, a reduced hemoglobin level can be viewed as the end result of a process beginning with the gradual depletion of iron stores.[9,10] Iron deficiency in patients with or without anemia attenuates aerobic performance and is accompanied by reports of fatigue and exercise intolerance.[11] The repletion of iron in patients who have iron deficiency without heart failure improves cognitive, symptomatic, and exercise performance.[12,13]

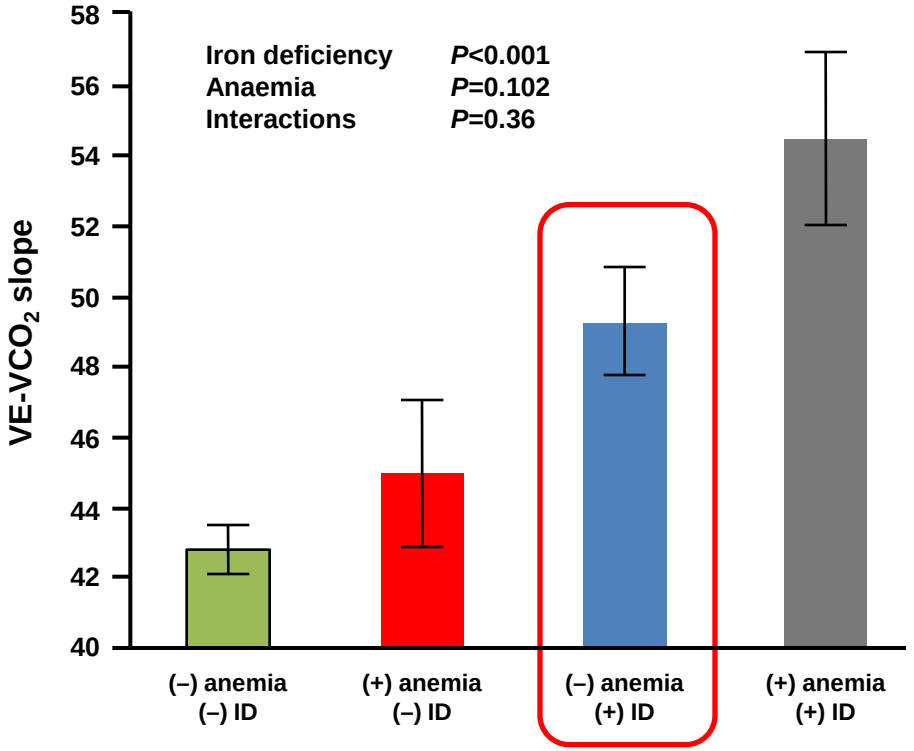
N Engl J Med 2009;361:2436-48.

ID is associated with reduced exercise capacity in heart failure (HF) patients (1)

Peak oxygen consumption



Ventilatory response to exercise



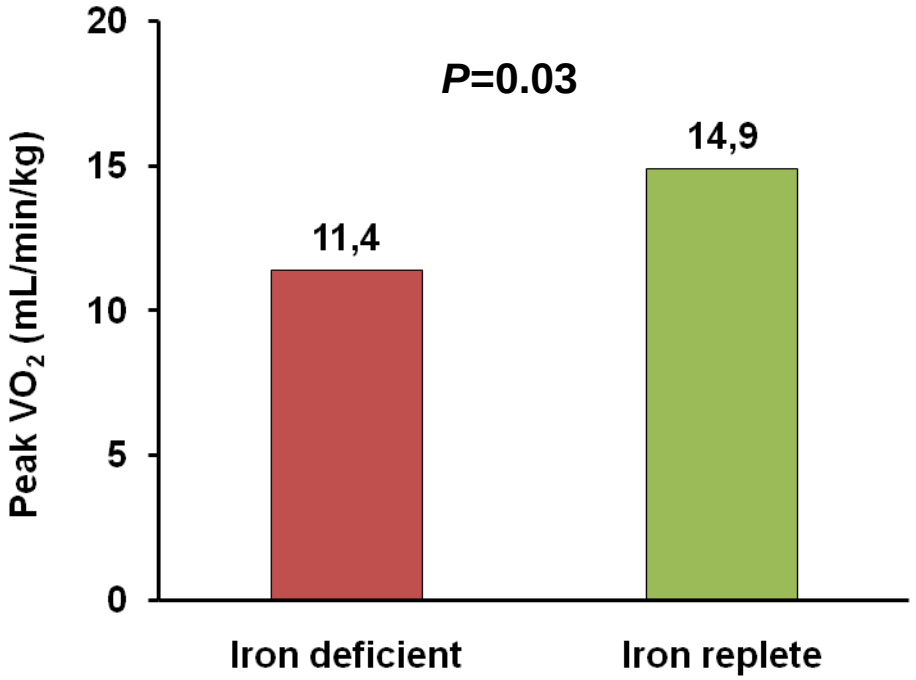
- Iron deficiency defined as serum ferritin <100 µg/L, or serum ferritin 100–300 µg/L with TSAT <20%
- Anemia defined as haemoglobin level <12 g/dL in women and <13 g/dL in men
- Iron deficiency was present in 35% of patients

TSAT, transferrin saturation

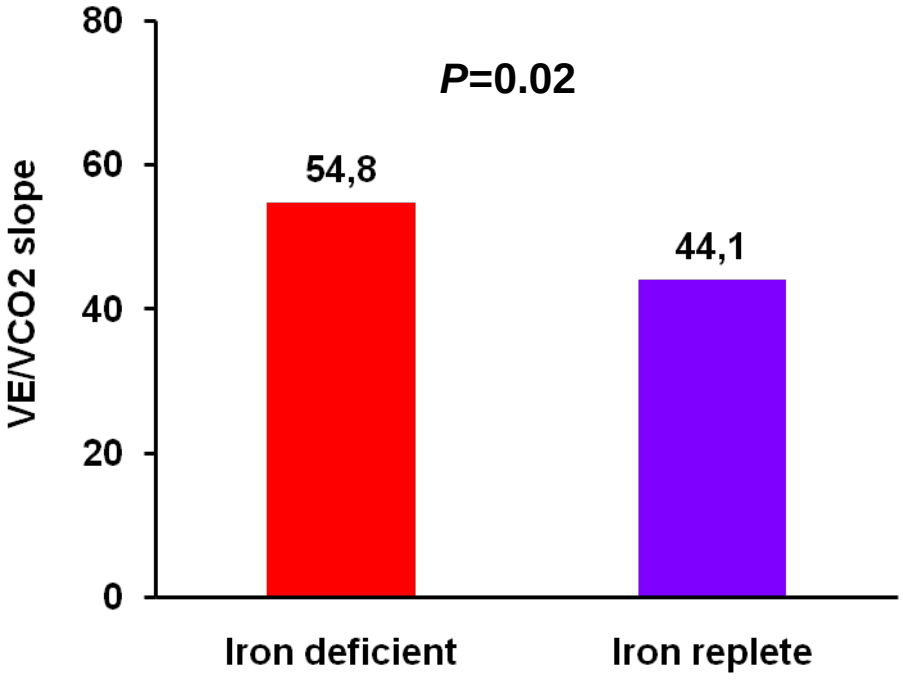
Jankowska EA, et al. J Cardiac Fail 2011;17:899–906

ID is associated with reduced exercise capacity in HF patients (2)

Peak oxygen consumption



Relationship between ventilation and VCO_2



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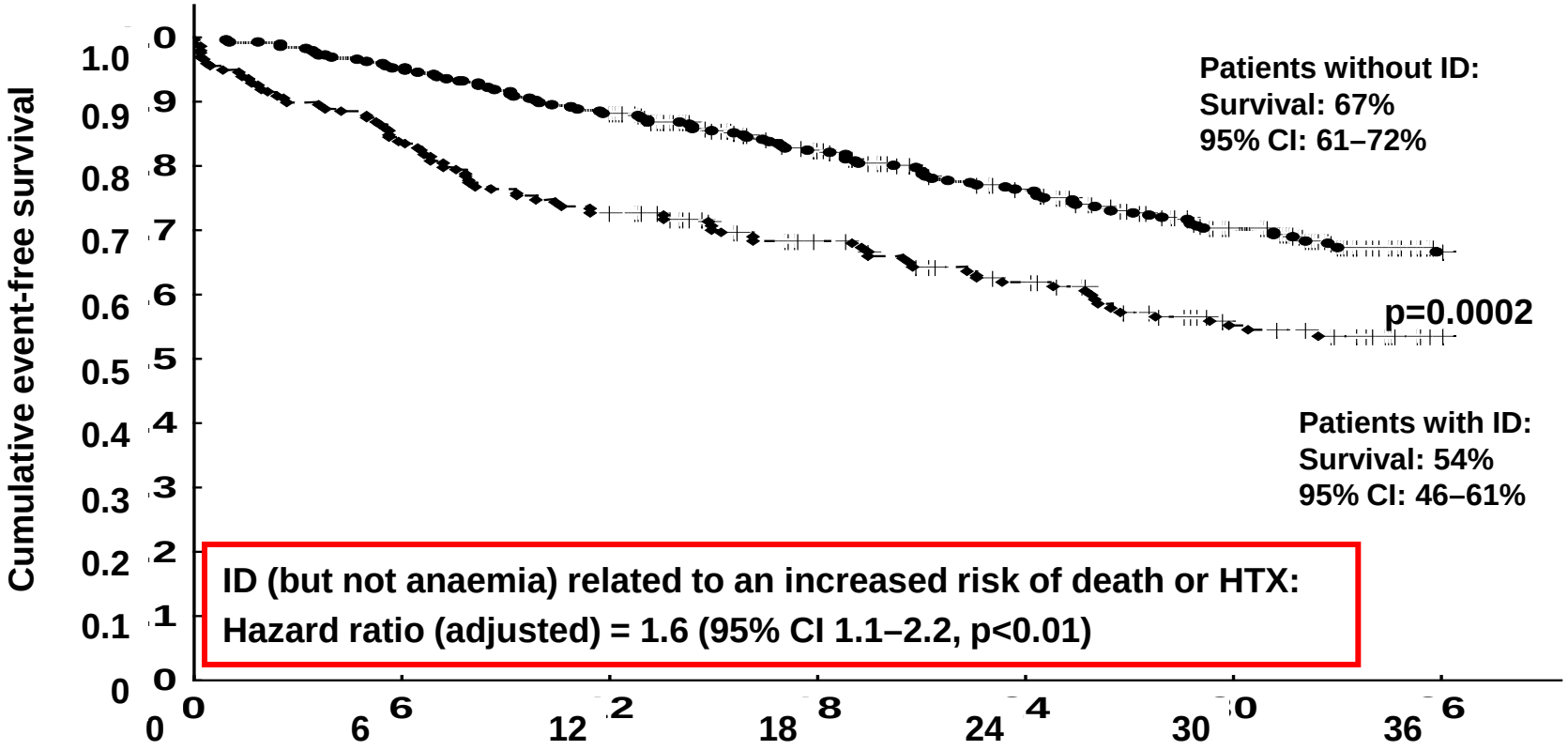
Okonko DO, et al. J Am Coll Cardiol 2011;58:1241–51

Iron deficiency
An ominous sign in patients with CHF

- Prospective observational study, 546 patients with stable systolic CHF
- ID: serum ferritin <100 µg/L, or 100–300 µg/L with TSAT <20%



Jankowska EA, *et al. Eur Heart J* 2010;31:1872–80.

HTX=heart transplantation

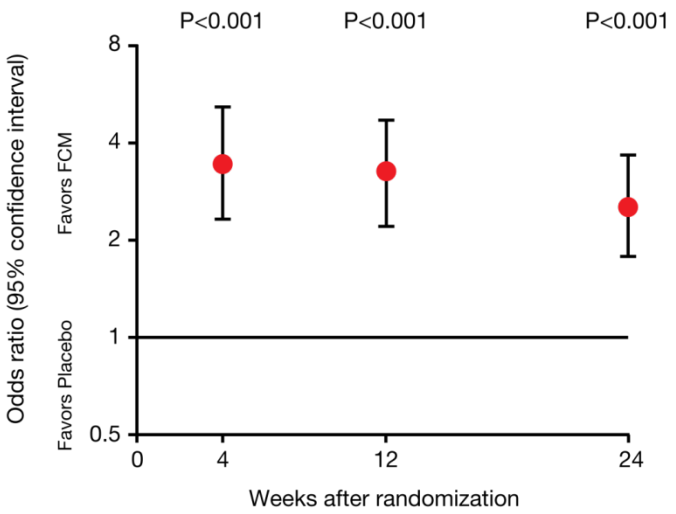
Clinical Trials…

- FAIR – HF : NEJM 2009
- CONFIRM – HF: 2014
- EFFECT – HF: 2014

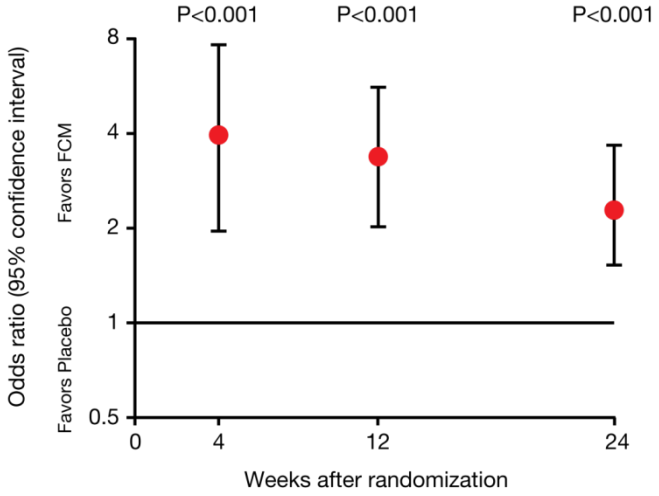
FCM in patients with CHF – Over time

FAIR-HF

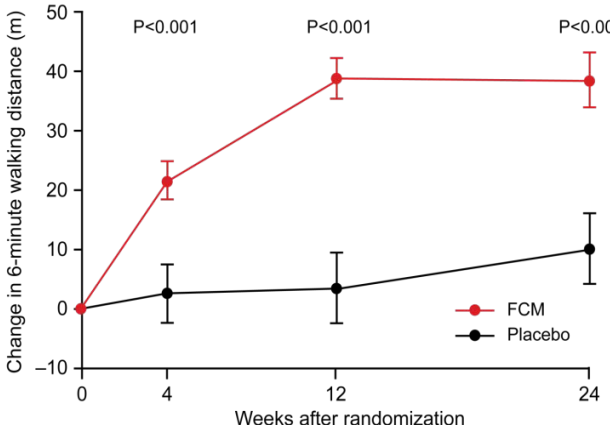
Patient Global Assessment



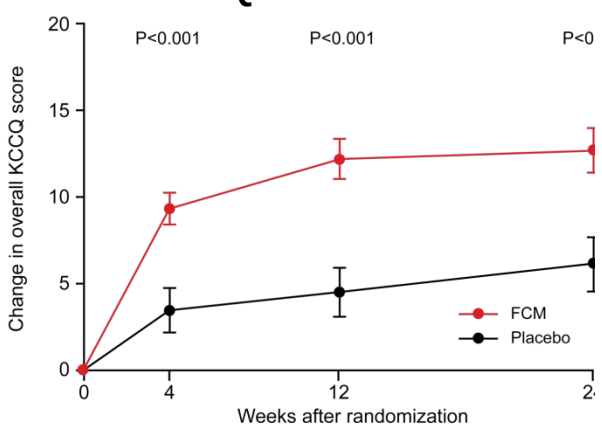
NYHA functional class



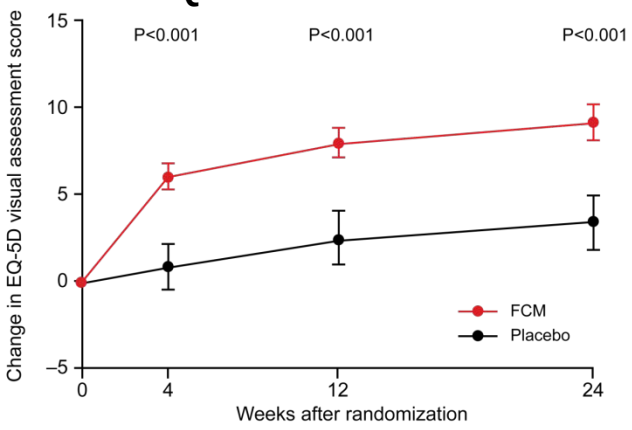
6-minute walk test



KCCQ overall score



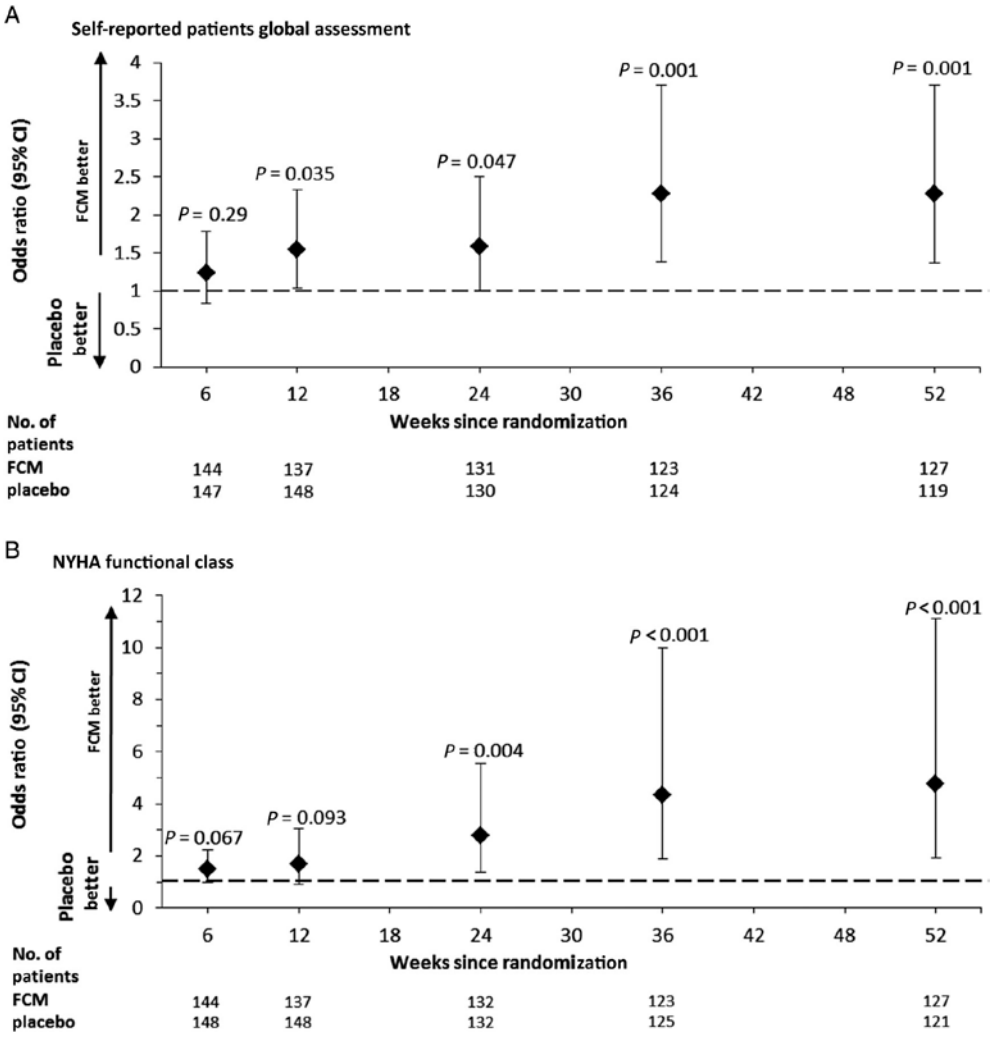
EQ-5D VAS score



EQ-5D=European Quality of Life 5-Dimensions; FCM=ferric carboxymaltose; KCCQ=Kansas City Cardiomyopathy Questionnaire; VAS=visual analogue scale

Anker SD, *et al. N Engl J Med* 2009;361:2436–48.

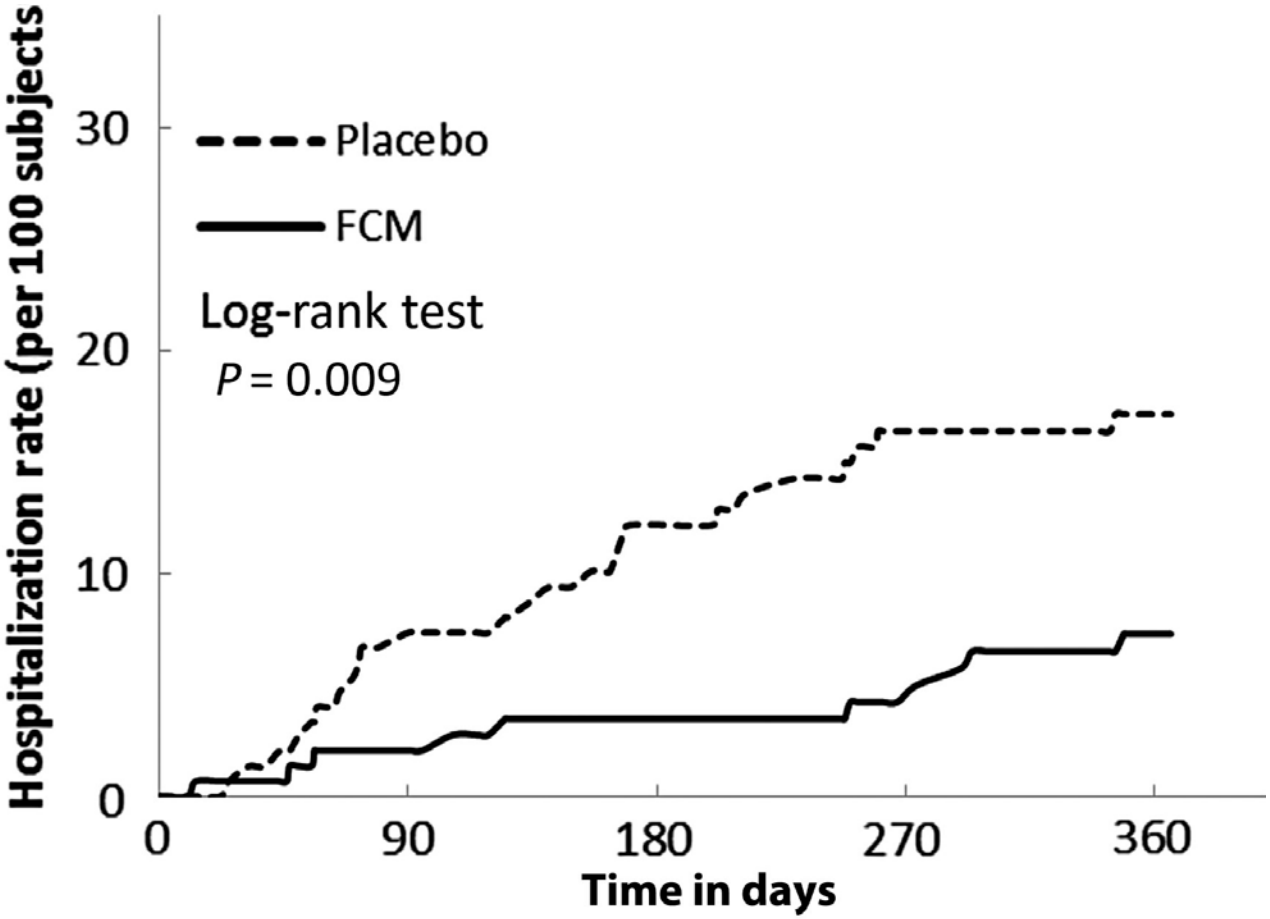
Patient Global Assessment and NYHA Functional Class over Time (full-analysis set).



Ponikowski P et al. Eur Heart J 2014;eurheartj.ehu385

European Heart Journal

Time to first hospitalization due to worsening heart failure.



Placebo	151	138	127	117	78
FCM	150	140	131	126	77

Ponikowski P et al. Eur Heart J 2014;eurheartj.ehu385

European Heart Journal

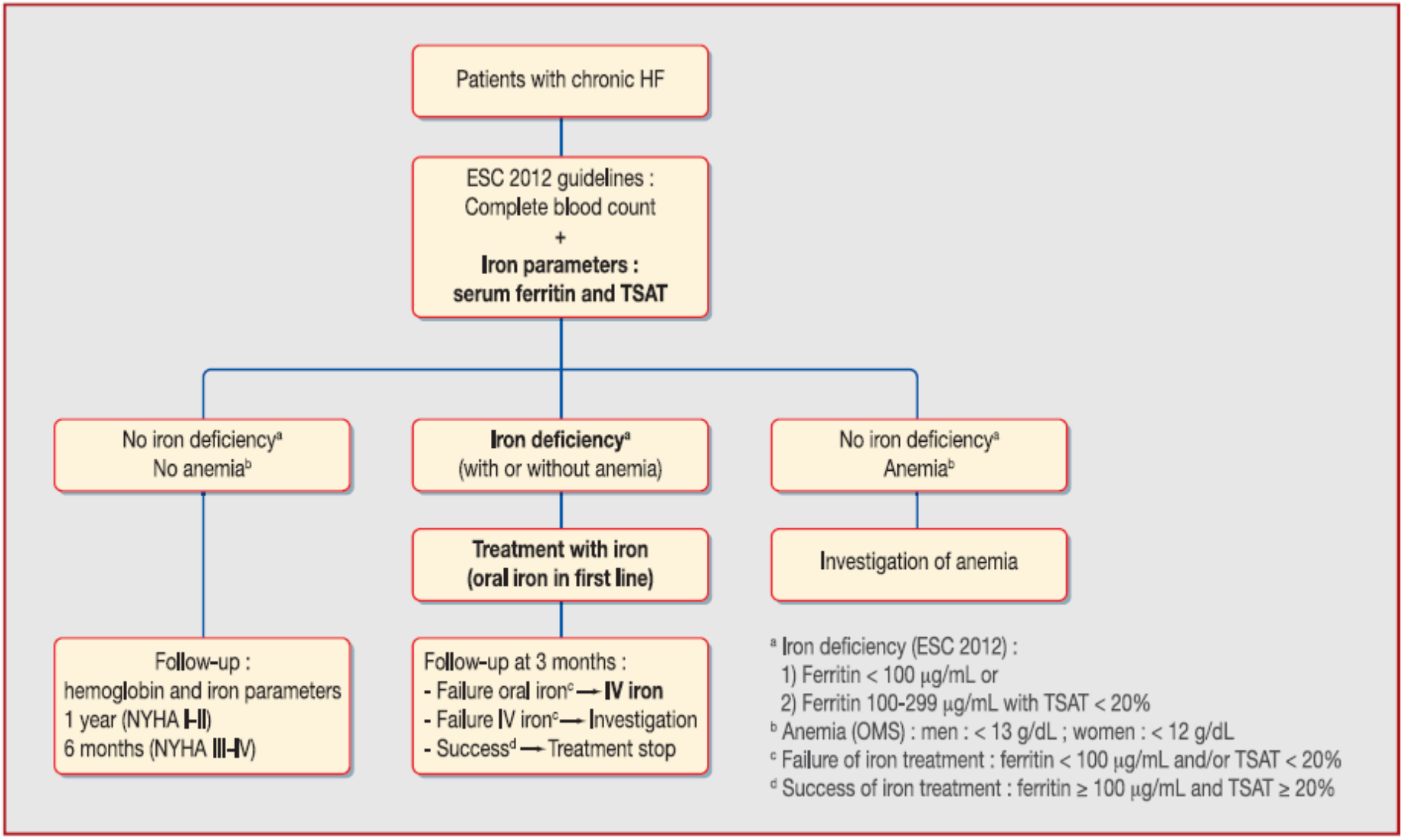


Figure 1. Assessment of iron variables and treatment of iron deficiency in chronic heart failure. ESC: European Society of Cardiology; HF: heart failure; IV: intravenous; NYHA: New York Heart Association; OMS: Organización Mundial de la Salud (World Health Organization); TSAT: transferrin saturation.

A. Cohen-Solala et al. Archives of Cardiovascular Disease (2014) **107, 563—571**

Treatment of iron deficiency during pregnancy

	Advantage	Disadvantage
Oral iron[1,2]	Relatively low cost, suitable for almost all women	Compliance issues associated with gastrointestinal adverse events (eg diarrhoea, constipation, nausea/vomiting) and oxidative stress (in particular for ferrous salts)
I.V. iron[1]	Beneficial for patients who cannot tolerate oral supplements, only effective therapy to supply enough iron for erythropoiesis, may be rapidly administered, provides rapid increase in iron stores, ferritin and Hb levels	Risk of local and systemic adverse events and anaphylactic reactions (iron dextran), hypotension, nausea, cramps
Transfusion[3]	Can be life-saving	Involves a variety of inherent risks and complications (infection, immune reaction), high cost, shortage in supply, administrative errors

1. Bashiri A et al. *Eur J Obstet Gynecol Reprod Biol* 2003;110:2–7; 2. Dresow B et al. *Biometals* 2008; 21:273-276;
3. Breymann C & Huch R. Anaemia in pregnancy and the puerperium. 2008 UNI-MED

Treatment recommendations on use of I.V. iron in pregnancy/postpartum

Period	Treatment
1st Trimester	I.V. iron contraindicated[1] (except for Ferric Carboxymaltose) **Slight to moderate IDA (Hb 9–10.5 g/dL):** oral iron 160–200 mg/day[2,3]
2nd Trimester	Start with oral iron[4] **Slight to moderate IDA:** If Hb increases < 0.5 g/dL[4] or < 1 g/dL[2,3] in 2 weeks, consider I.V. iron at > 14 weeks gestation **Severe IDA (Hb < 9 g/dL):** I.V. iron in separate doses of up to 1,000 mg iron until Hb is > 10.5 g/dL[2,3]
3rd Trimester	First option: I.V. iron[3,4]
Postpartum	**Mild anaemia (Hb 9.5-12 g/dL):** oral iron 80-200 mg/day[2] **Moderate to severe anaemia (Hb 8.5-9.5 g/dL):** up to 1,000 mg iron once weekly until Hb is >10 g/dL, followed by oral iron for Hb maintenance[2] **Severe anaemia (Hb <8 g/dL):** consider adding an ESA to I.V. iron[2] **Critical anaemia (Hb <6 g/dL):** consider RBC transfusion[2,4]

ESA – Erythropoiesis stimulating agent
RBC – red blood cell

1. SPC Ferinject®. http://emc.medicines.org.uk/. Accessed 24 Nov 2009
2. Breymann C et al. *Expertenbrief* 2007;22;
3. Milman N. *Ann Hematol* 2008;87:949–959;
4. Beris P et al. *TATM* 2007;9:29

Thank You

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