Iron metabolism – anemia and beyond

Jacek Lange

Perm, 8 October 2016

Overview

1. Iron metabolism
2. CKD – Chronic Kidney Disease
3. Iron deficiency beyond anemia and CKD
4. Conclusions

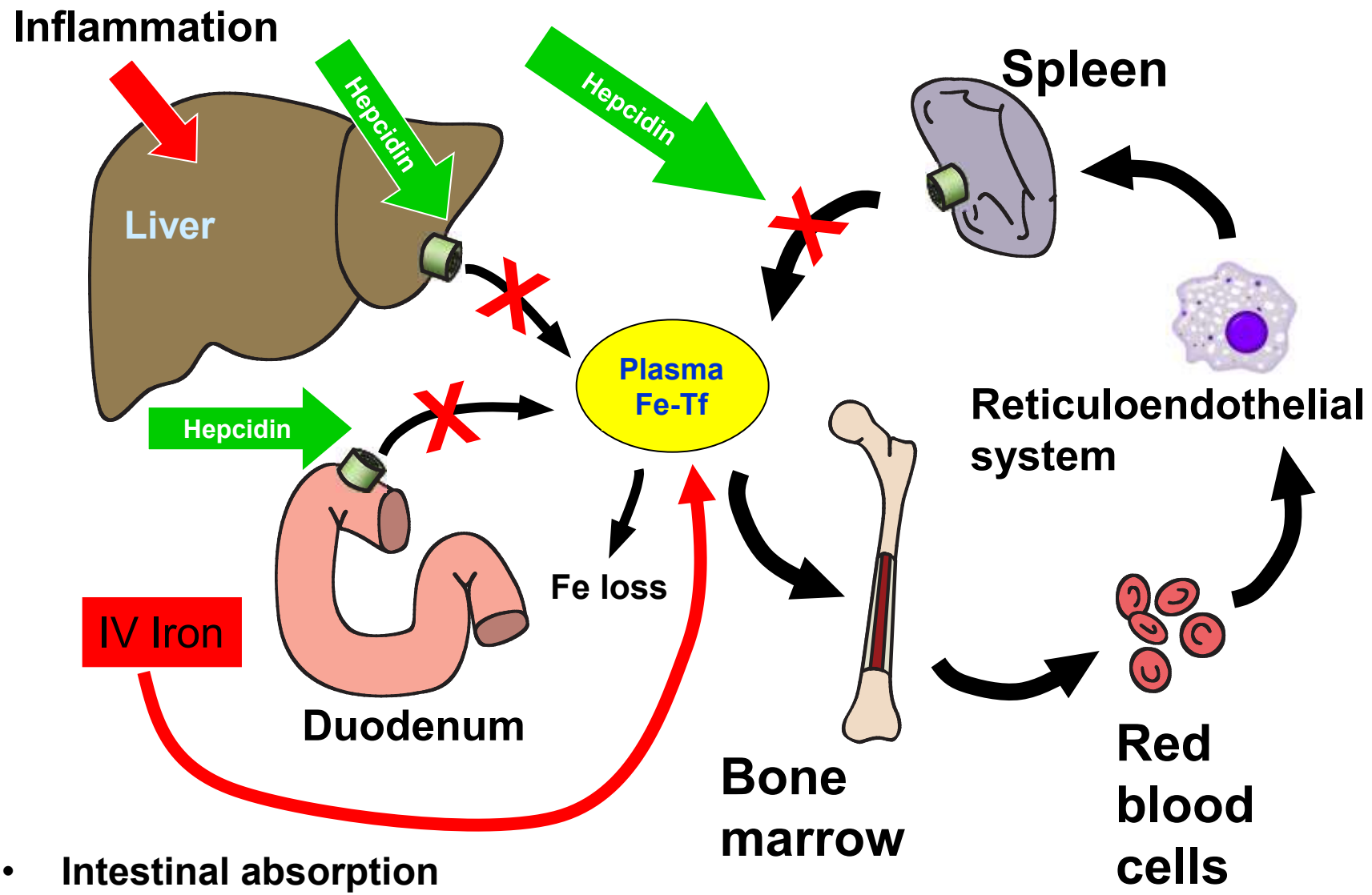
Why iron deficiency in CKD?

1. Impaired iron absorption
   - Level of intoxication – local inflammation in digestional tract
   - General inflammation due to uremia
   - Hepcidin

2. Iron loss
   - Loss of few mls in every HD session = * 156 times / year
   - Loss through digestional tract
   - Other bleedings (Heparin, LMWH, local inflammation)

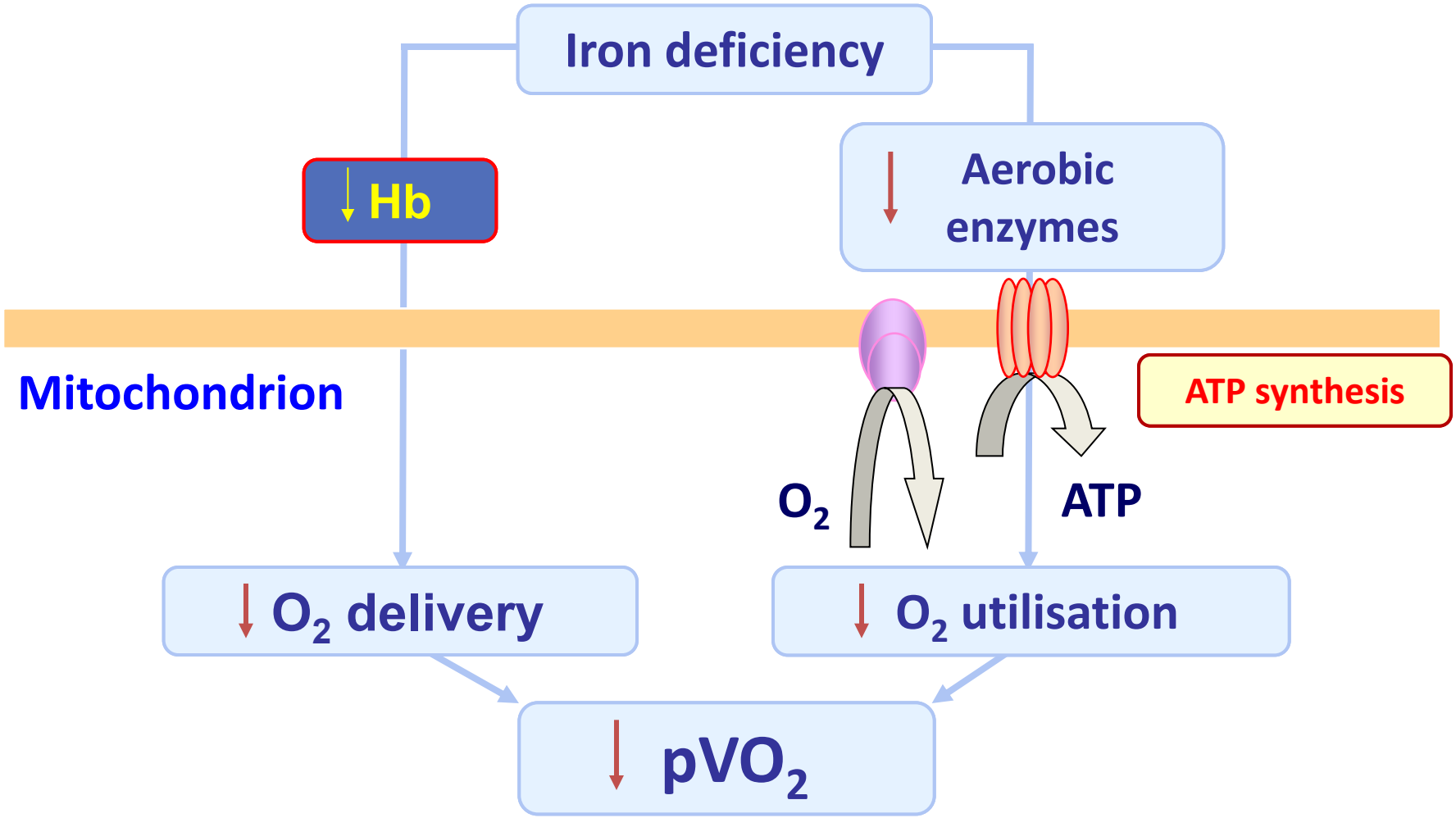
3. Functional iron deficiency due to ESA

Absorption of oral iron in inflammation

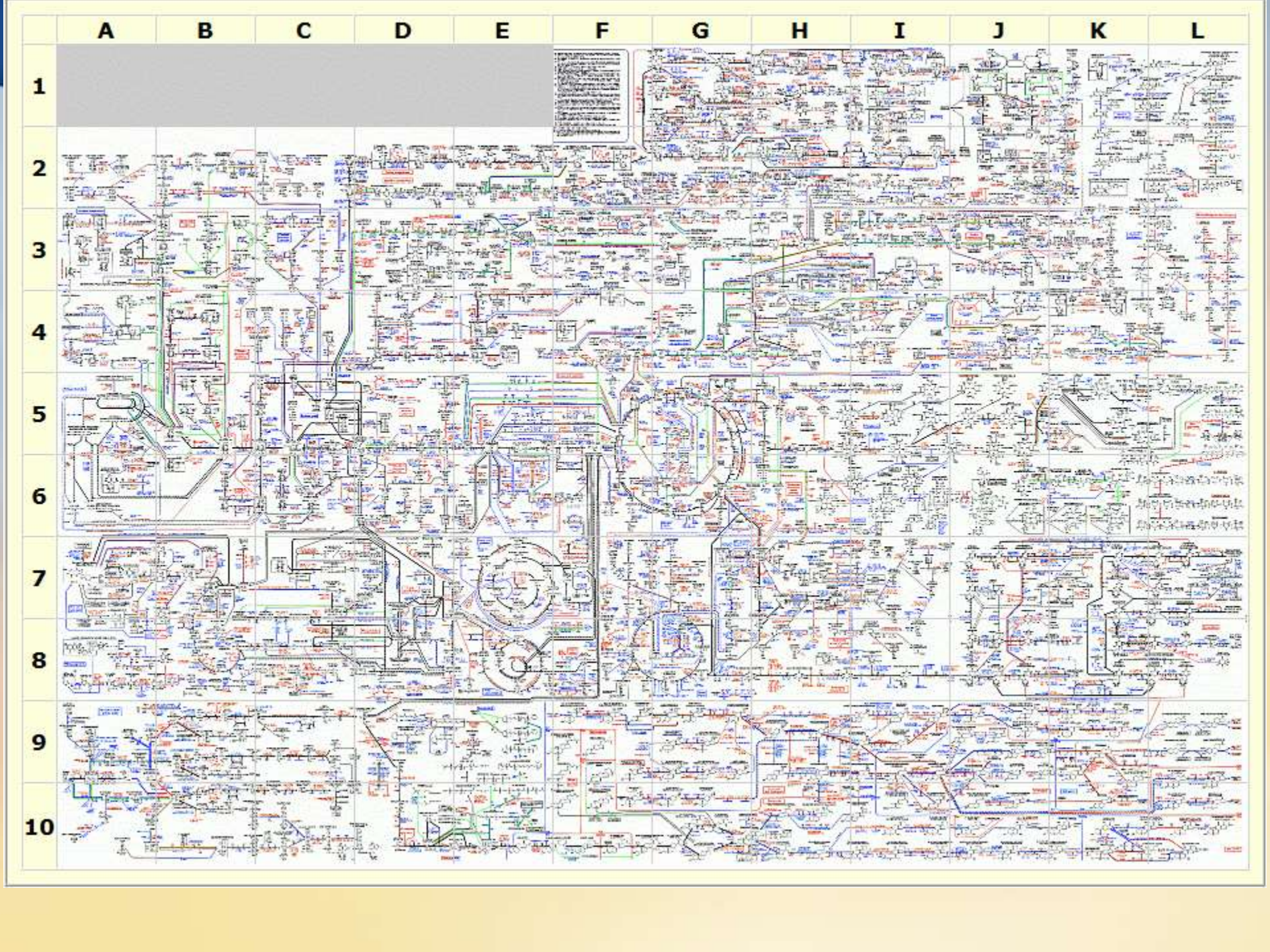


- Intestinal absorption
- Release from hepatic cells and macrophages

Dual effects of iron deficiency: defective oxygen delivery and utilization



Anker SD, et al. Eur J Heart Fail 2009
Haas JD, Brownlie T IV. J Nutr 2001
Dallman PR. J Intern Med 1989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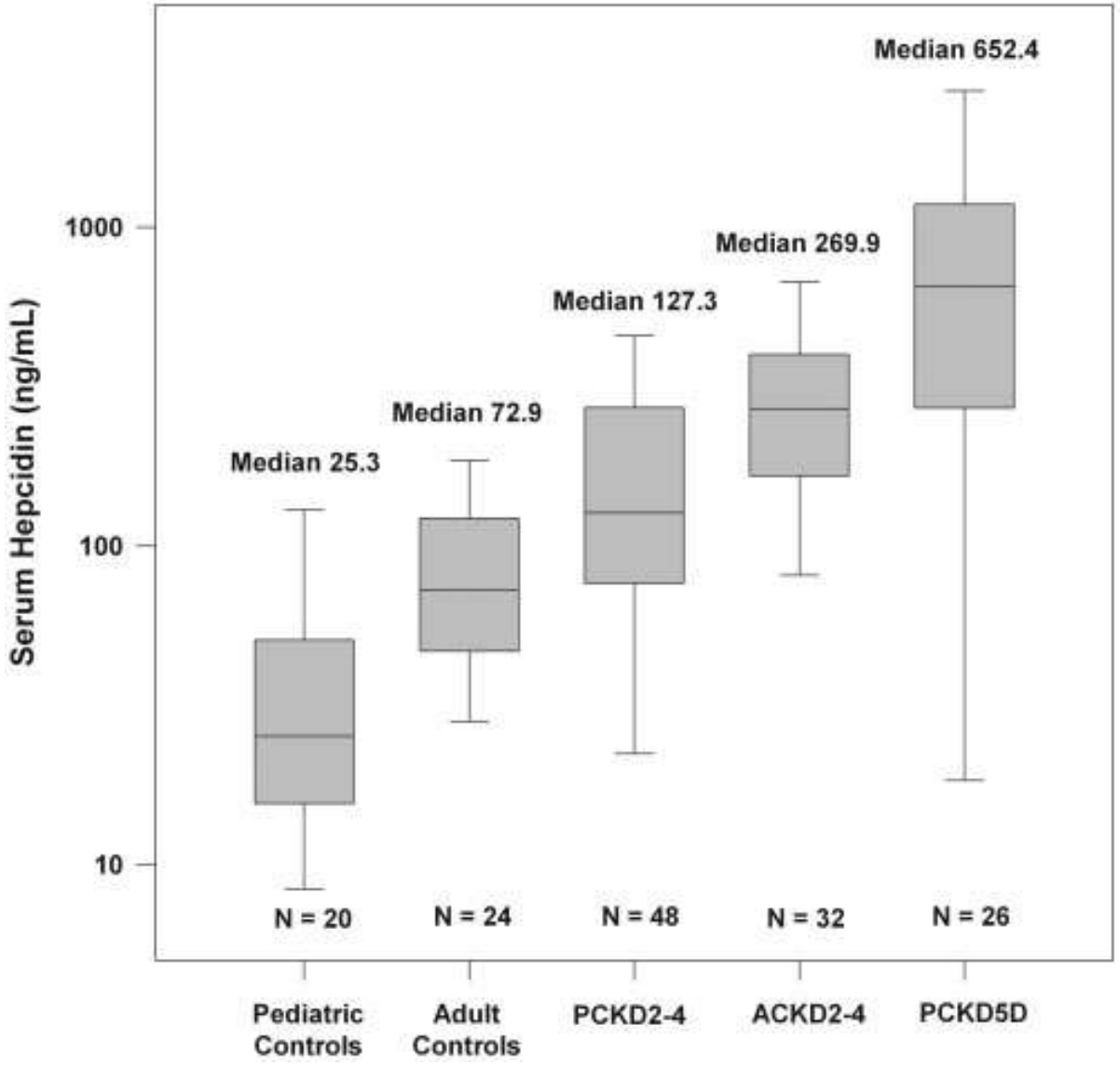
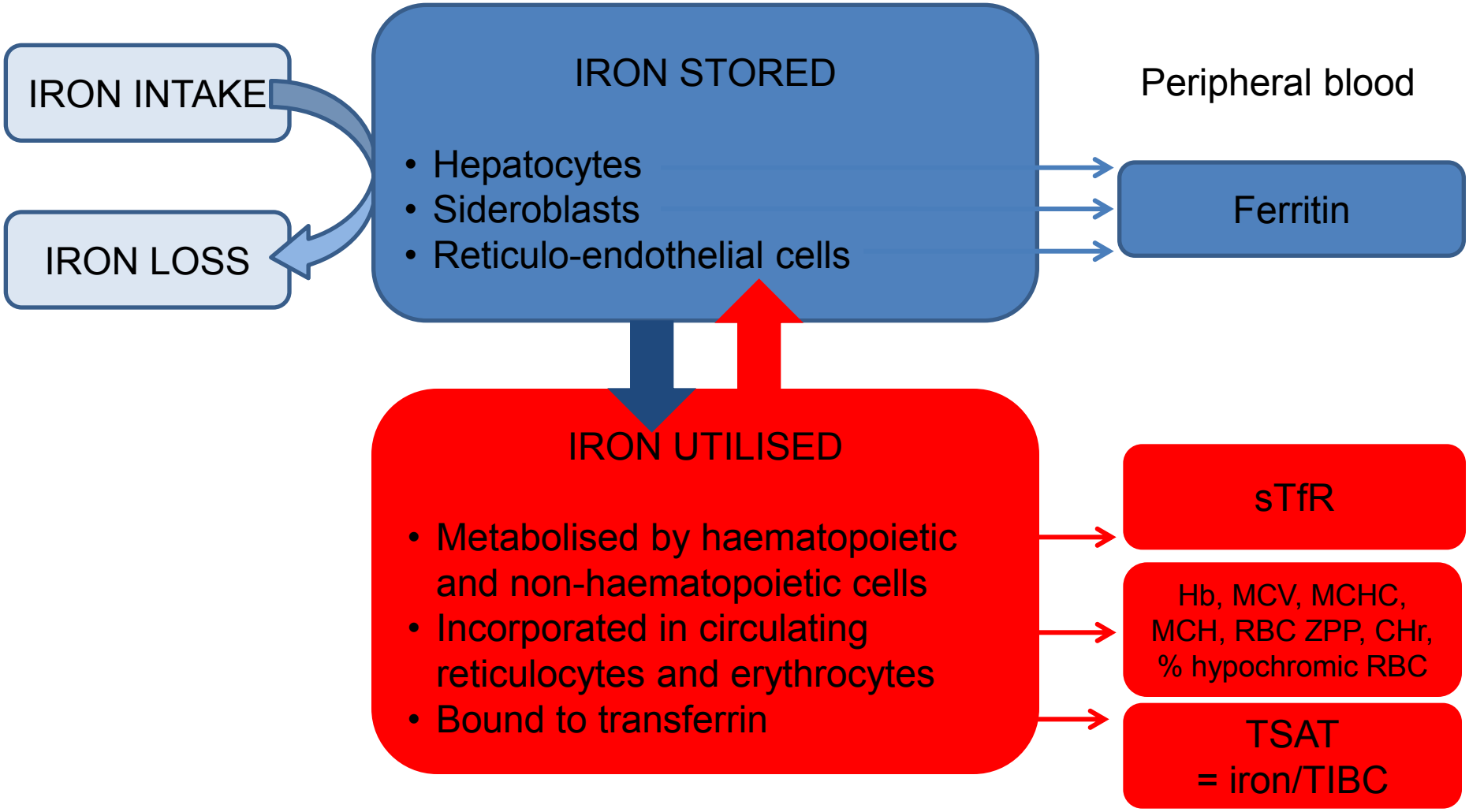
Hepcidin – a potential biomarker of Iron status in Chronic Kidney Disease



Zaritsky J et al.:
Clin J Am Soc Nephrol
2009;4:1051-1056

Iron storage and utilisation: interpretation of circulating biomarkers



Modified from Jankowska et al. Eur. Heart J 2013

Iron sucrose (Venofer®) facilitates ESA dose optimalization in HD patients

Study	Design	n	Venofer® dose	Baseline Hb (g/dL)	Duration	Change in ESA dose vs baseline
Richardson 2001	Consecutive patients Single-center	386	N x50 mg iron as Venofer®	11.3	24 months	**~47%** reduction
Li 2008	Randomized Single-center	26	200 mg iron/week for 4 weeks then 200 mg iron every 2 weeks for 4 weeks	8.9	8 weeks	**~20%** reduction
Schiesser 2006	Single-arm Multicenter	50	24 x50 mg iron as Venofer® weekly	12.1	6 months	**~38.5%** reduction (darbepoetin) 6.3/8.3% (epoetin alfa/beta)
Descombes 2000	Single arm Single-center	25	Dose adjusted by serum ferritin level	11.5	18 months	**~32%** reduction
Hussain 1998	Two arm Single-center	20	100 mg iron as Venofer® twice weekly or oral iron	7.8-8.0	3 months	**~25%** reduction versus oral iron

Richardson D et al. Am J Kidney Dis 2001;38:109-117
Li H et al. Blood Purif 2008;26:151-6
Schiesser D et al. Nephrol Dial Transplant 2006;21:2841-2845
Descombes E et al. Nephron 2000;84:196-197
Hussain R et al. Nephrology 1998;4:105-108

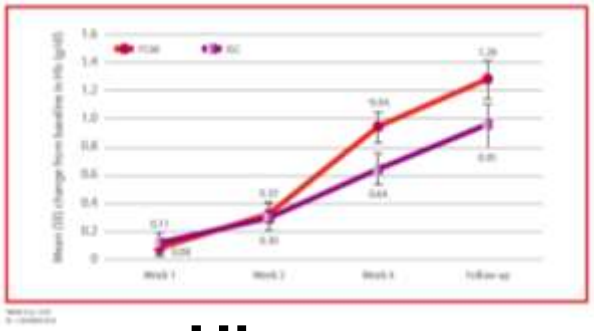
Iron sucrose in hemodialysis – extensive safety profile – 13,5 mln patients

Study	Dosing	n	Duration	Safety outcomes
Aronoff[1] 2004	10x100 mg iron as Venofer®	665	Mean 101 days	No serious or life-threatening adverse events reported
Charytan[2] 2001	10x100 mg iron as Venofer®	77	8 weeks	No serious adverse events or withdrawals due to drug-related adverse events observed
Richardson[3] 2001	N x50 mg iron as Venofer®	386	24 months	Venofer® withheld in only 2 out of 386 patients. Good safety profile
Schiesser[4] 2006	24 x50 mg iron as Venofer® weekly	50	6 months	No serious adverse events or hypotensive episodes. Only one AE was classified as possibly related to Venofer®
Hussain[5] 1998	100 mg iron as Venofer® twice weekly	10	3 months	No adverse events reported

1. Aronoff GR et al. Kidney Int 2004;66:1193-1198
2. Charytan C et al. Am J Kidney Dis 2001;37:300-307
3. Richardson D et al. Am J Kidney Dis 2001;38:109-117
4. Schiesser D et al. Nephrol Dial Transplant 2006;21:2841-2845
5. Hussain R et al. Nephrology 1998;4:105-108

FCM in HD patients (Evenpoel 2009)

200 mg of iron 2-3 times a week according to requirements, FCM (n = 119) vs. IS (n = 118)



Hb conc.

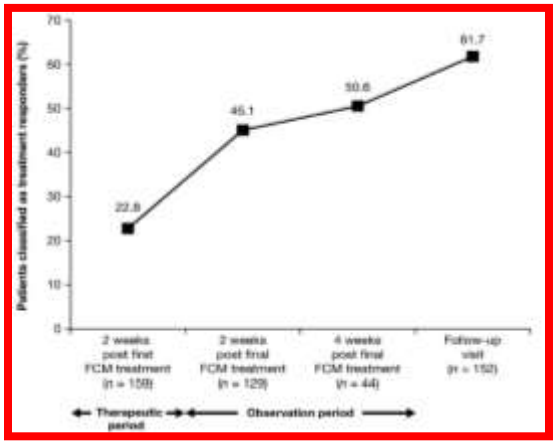
Serum ferritin conc.

TSAT

Evenepoel A et al. Abstract/Poster ASN 2009 San Diego

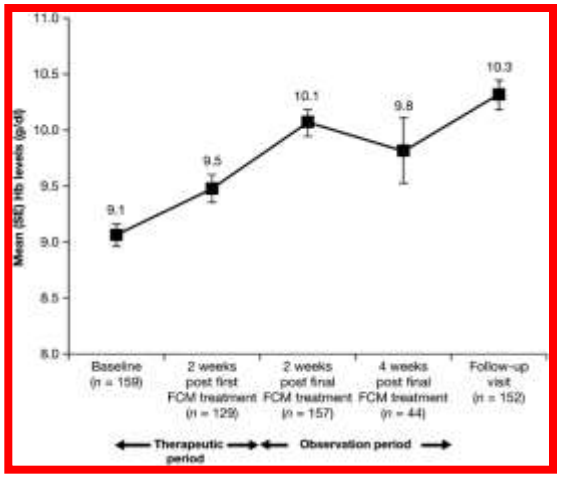
FCM in HD (Covic et al., 2010)

Responders = Proportion of patients attaining an increase in Hb ≥1.0 g/dl

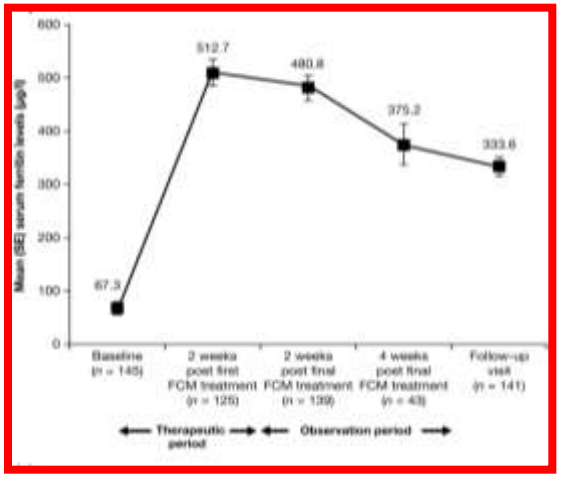


- FCM 100-200 mg at each HD session for a max. 6 weeks.
- n=163
- 120 patients –> ESA
- 63 patients –> no ESA

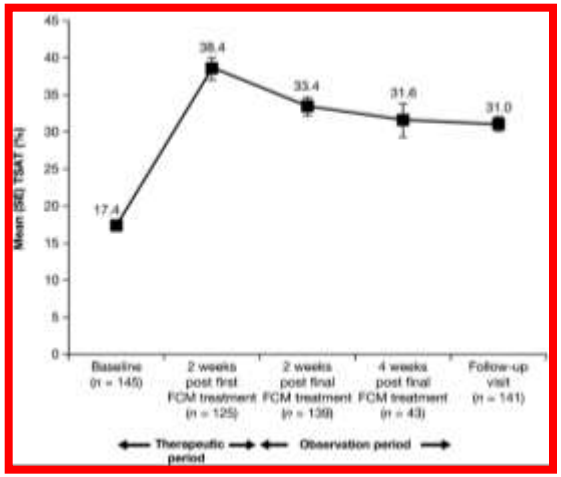
Hb



Ferritin



TSAT



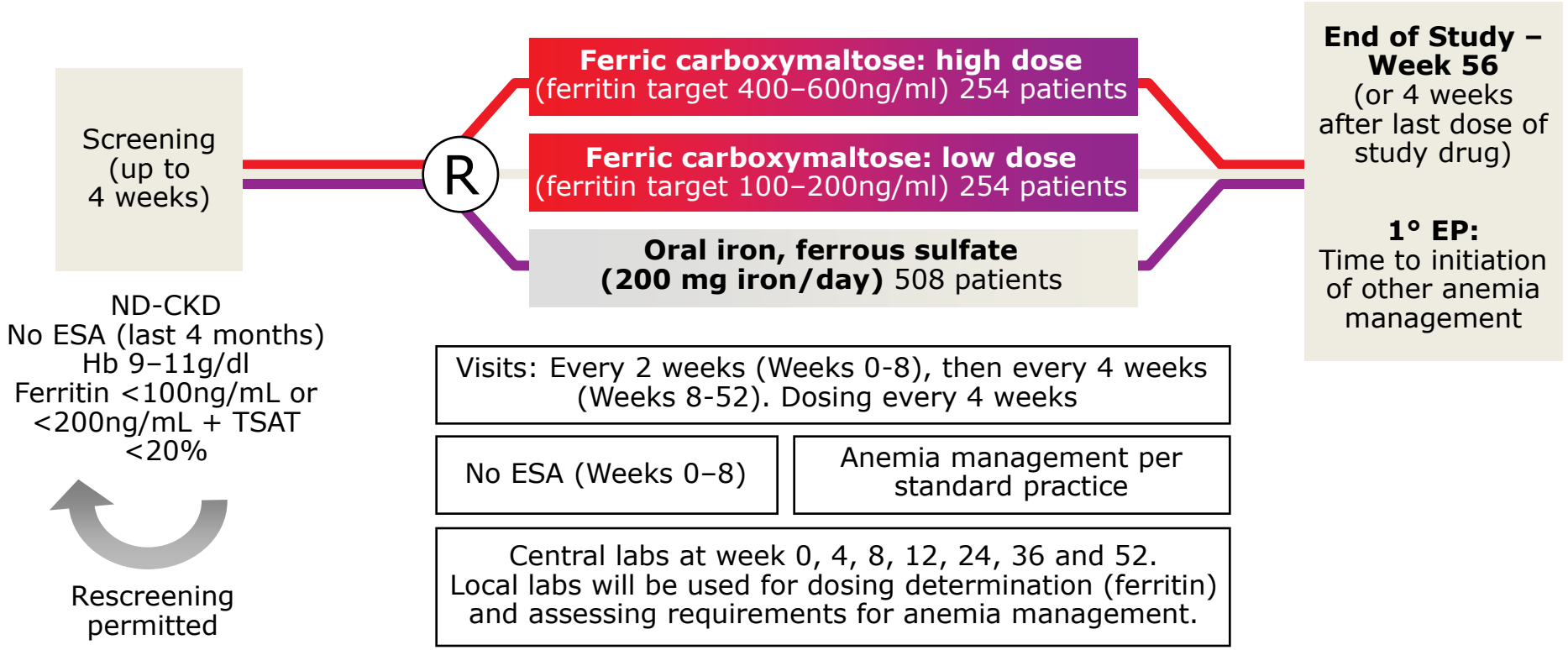
Covic A et al. Nephrol Dial Transplant 2010 25: 2722–2730

FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia

Iain C. Macdougall[1], Andreas H. Bock[2], Fernando Carrera[3], Kai-Uwe Eckardt[4], Carlo Gaillard[5], David Van Wyck[6], Bernard Roubert[7], Jacqueline G. Nolen[7] and Simon D. Roger[8] on behalf of the FIND-CKD Study Investigators[†]

NDT Advance Access published June 2, 2014

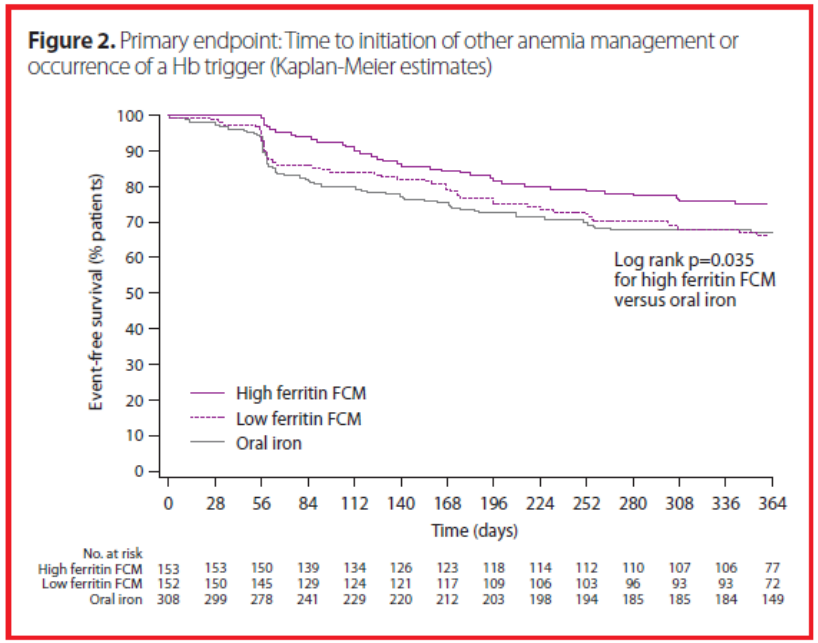
FIND-CKD: Study design



- Primary endpoint:
  Time to initiation of other anemia management (e.g. ESA or blood transfusion)

Macdougall IC et al. J Am Soc Nephrol 2009; 20: 660A (SA-PO2402)

Results – primary endpoint



1. The increase in the Hb level – significantly greater with high sF FCM versus oral iron.

2. The hematological response – **faster**, and the proportion of patients with an increase in Hb level ≥ 1 g/dL significantly greater with high sF FCM versus oral iron or low sF FCM.

Results – secondary endpoint

Table 2. Secondary efficacy endpoints

	High ferritin FCM (n=153)	Low ferritin FCM (n=152)	Oral iron (n=308)
Blood transfusion, n (%)	12 (7.8)	11 (7.2)	26 (8.4)
Hb increase ≥1 g/dL, n (%)	87 (56.9)*	52 (34.2)	99 (32.1)
Change from baseline to month 12 (least squares mean [SE])			
Hb, g/dL[a]	1.4 (0.1)**	0.9 (0.1)	1.0 (0.1)
Ferritin, µg/L[b]	451 (10)***	81 (11)***	137 (8)
TSAT, %[b]	15.8 (1.3)	8.5 (1.3)†	13.8 (1.0)
eGFR, mL/min/1·73m^2[c]	0.4 (0.8)	-1.6 (0.8)	-1.1 (0.6)

[a] Prior to first initiation of other anemia management
[b] Measured up to the point at which other anemia therapy was initiated and/or study drug was discontinued
[c] MDRD formula
* p<0.001 versus low ferritin FCM and oral iron (Kaplan-Meier estimates, log rank test)
** p=0.014 versus oral iron
*** p<0.001 versus oral iron
†p=0.001 versus oral iron

VIEWS & REVIEWS

Restless legs syndrome associated with major diseases

A systematic review and new concept

Neurology, March 2016

Claudia Trenkwalder, MD
Richard Allen, PhD
Birgit Högl, MD
Walter Paulus, MD
Juliane Winkelmann, MD

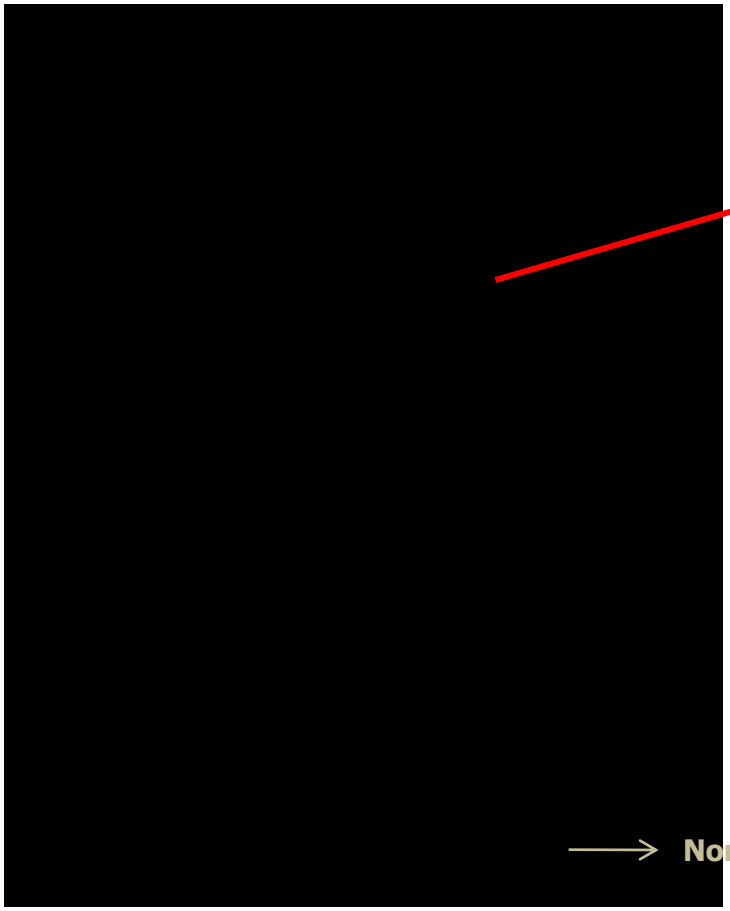
ABSTRACT

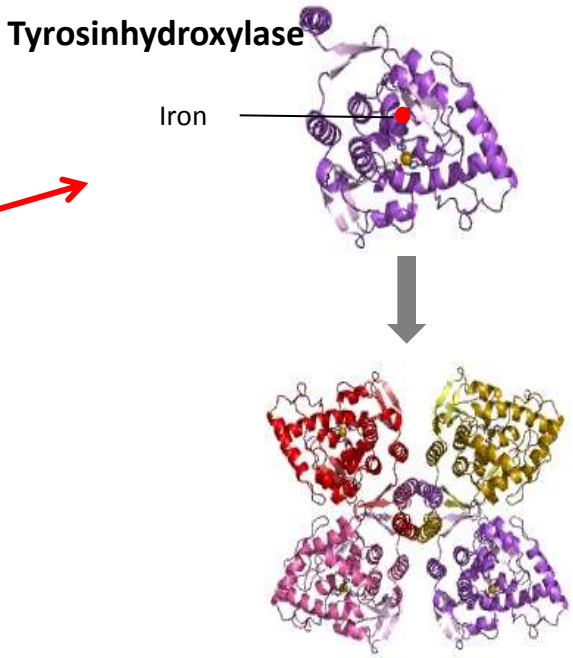
Recent publications on both the genetics and environmental factors of restless legs syndrome (RLS) defined as a clinical disorder suggest that overlapping genetic risk factors may play a role in primary (idiopathic) and secondary (symptomatic) RLS. Following a systematic literature search of RLS associated with comorbidities, we identified an increased prevalence of RLS only in iron deficiency and kidney disease. In cardiovascular disease, arterial hypertension, diabetes, migraine, and Parkinson disease, the methodology of studies was poor, but an association might be possible. There is insuf-

- **Kidney disease**
- **Pregnancy**
- **Cardiovascular disease and arterial hypertension**
- With some association:
- Polyneuropathy und painsyndroms
- Parkinson Syndromes including.
- Multiple Sclerosis, Migraine

Iron deficiency with and without anemia above all of that ??

Dopamine and Iron





→ Noradrenalin → Adrenalin

Iron deficiency and COPD

Open Access Research

BMJ Open

To cite: Nickol AH, Frise MC, Cheng H-Y, *et al*. A cross-sectional study of the prevalence and associations of iron deficiency in a cohort of patients with chronic obstructive pulmonary disease. *BMJ Open* 2015;**5**: e007911. doi:10.1136/bmjopen-2015-007911

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2015-007911).

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Accepted 15 June 2015

A cross-sectional study of the prevalence and associations of iron deficiency in a cohort of patients with chronic obstructive pulmonary disease

Annabel H Nickol,[1,2] Matthew C Frise,[2] Hung-Yuan Cheng,[2] Anne McGahey,[1] Bethan M McFadyen,[1] Tara Harris-Wright,[1] Nicole K Bart,[2] M Kate Curtis,[2] Shivani Khandwala,[3] David P O'Neill,[2] Karen A Pollard,[2] F Maxine Hardinge,[1] Najib M Rahman,[1] Andrew E Armitage,[3] Keith L Dorrington,[2] Hal Drakesmith,[3] Peter J Ratcliffe,[4] Peter A Robbins[2]

- Non-anaemic iron deficient patients more hypoxaemic
- Essential role of iron as a factor of key cellular pathways

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

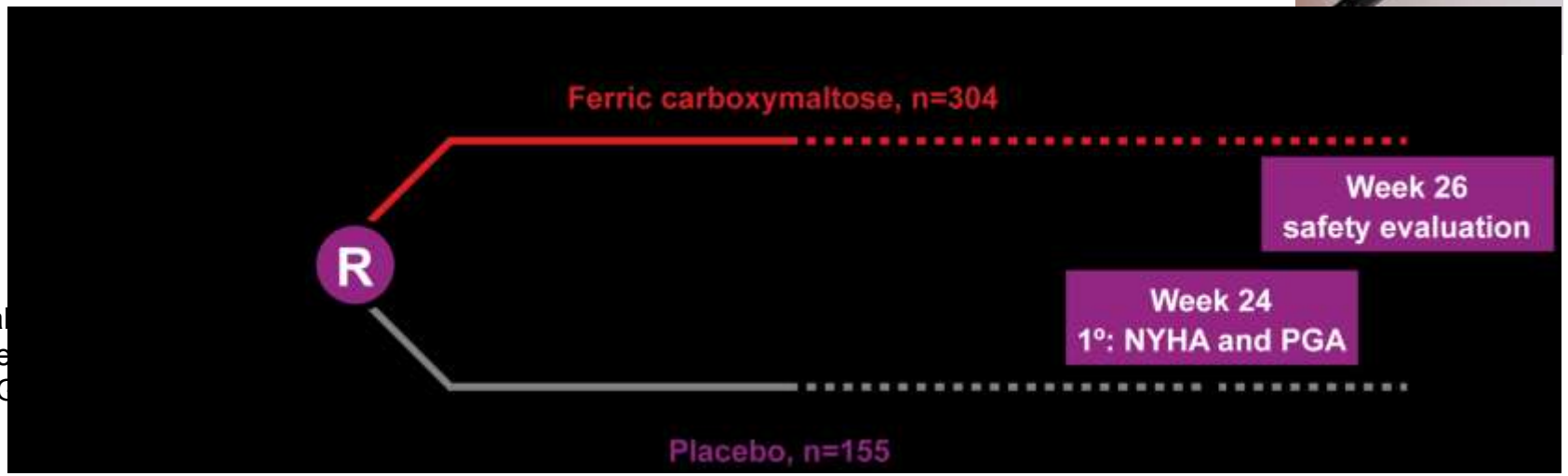
Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D.,
Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D.,
Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D.,*
Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D.,
Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D.,
Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D.,
Philip A. Poole-Wilson, M.D.,* and Piotr Ponikowski, M.D., Ph.D.,
for the FAIR-HF Trial Investigators†

NEJM 2009

FAIR-HF study design

- **Main inclusion criteria:**
  - NYHA class II/III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - Hb: 9.5–13.5 g/dL
  - **Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%**
- **Treatment adjustment algorithm:**
  - Interruption: Hb >16 g/dL or serum ferritin >800 µg/L or serum ferritin >500 µg/L, if TSAT >50%
  - Restart: Hb <16 g/dL and serum ferritin <400 µg/L and TSAT<45%
- **Blinding:**
  - Clinical staff: unblinded and blinded personnel
  - Patients: usage of curtains and black syringes for injections



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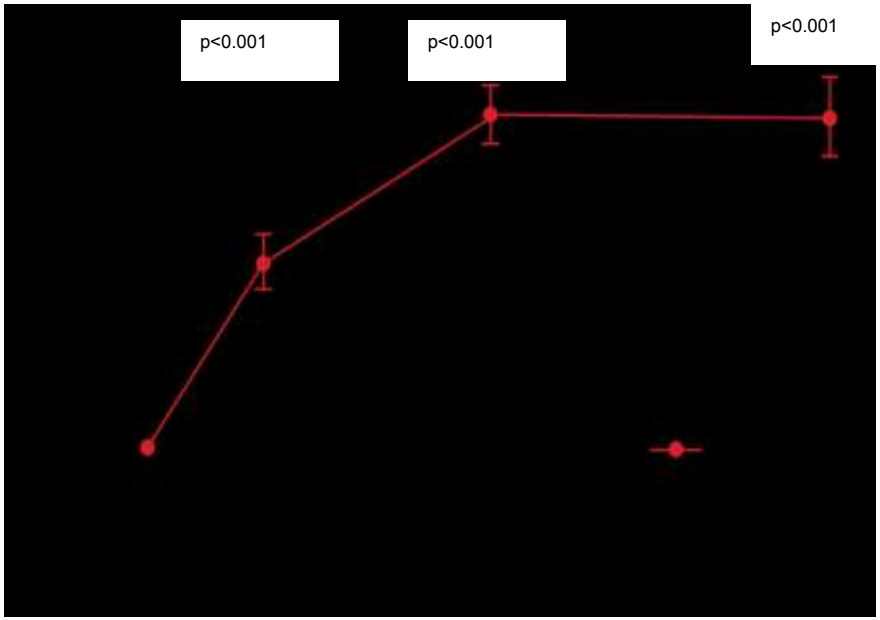
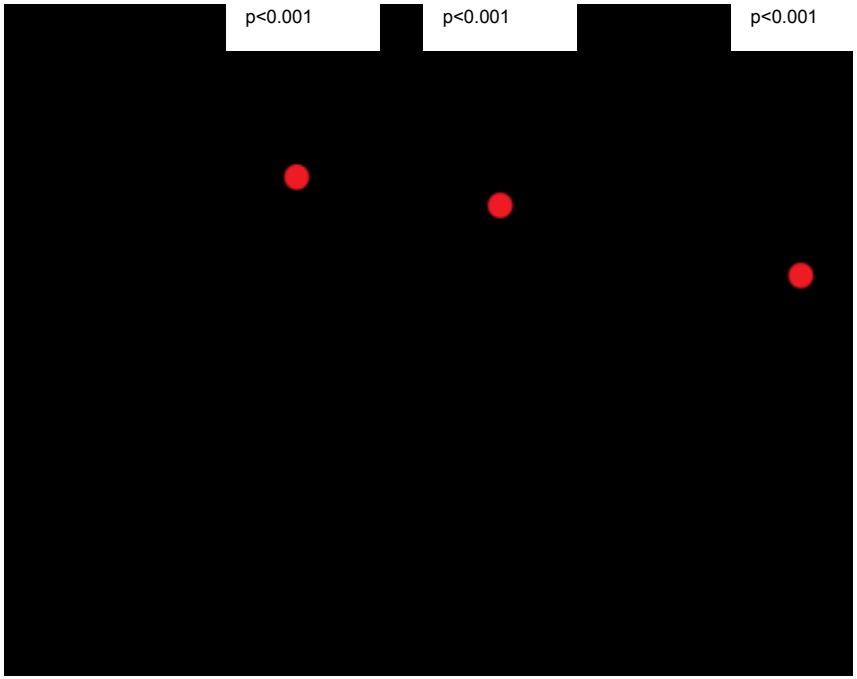
Anker SD, et al. N Engl J Med 2009;361:2436–48.

FAIR-HF results



6-minute walk test

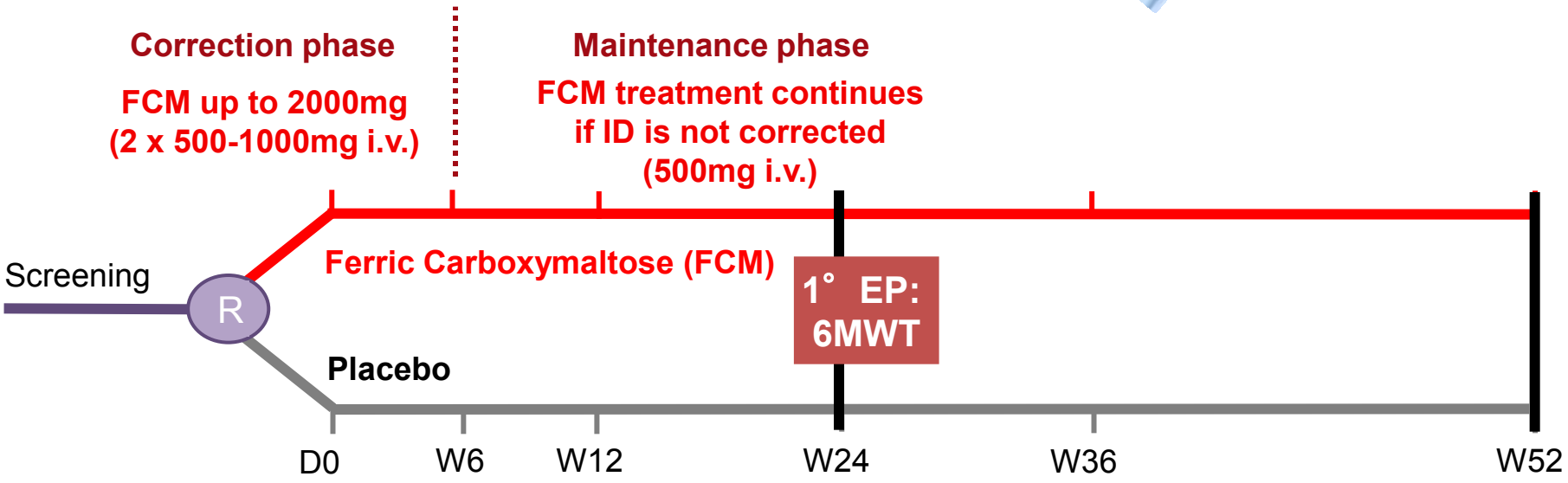


NYHA functional class

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

CONFIRM-HF
Study design

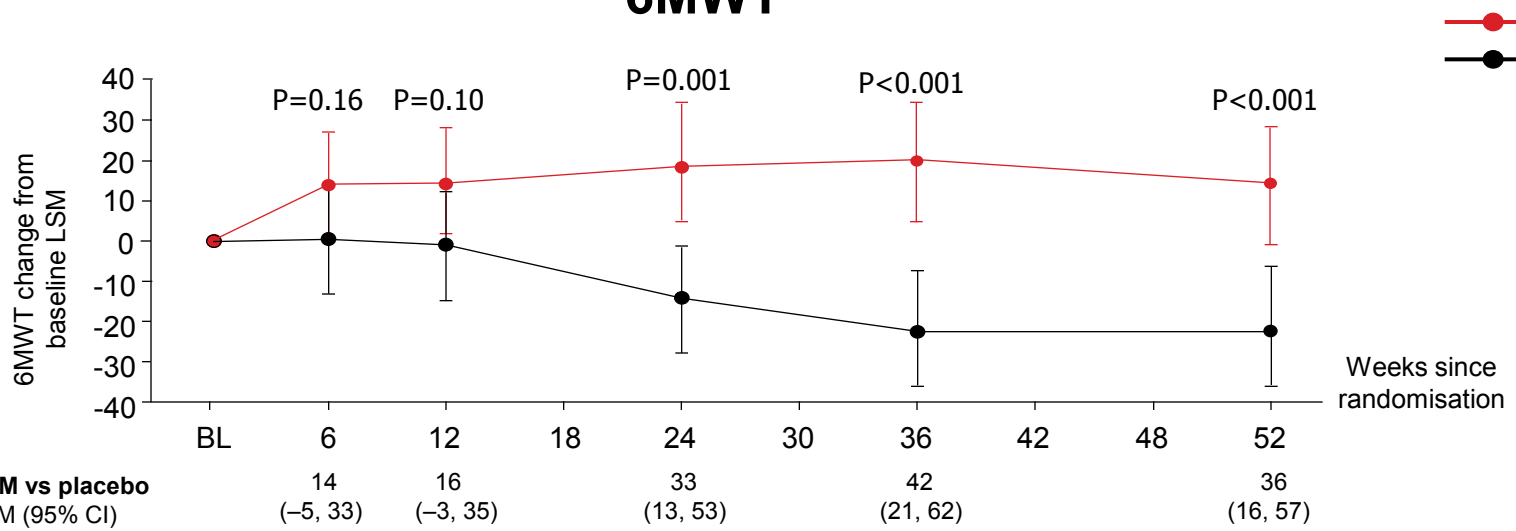
- **Design:** Multicentre, randomised (1:1), double-blind, placebo-controlled
- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤45%
  - BNP > 100 pg/mL or NT-proBNP > 400 pg/mL
  - Iron deficiency: serum ferritin <100 ng/mL or 100-300 ng/mL if TSAT <20%
  - Hb < 15 g/dL
- **Blinding:**
  - Clinical staff: unblinded and blinded personnel
  - Patients: usage of curtains and black syringes for injections



Ponikowski P et al. *Eur Heart J* 2014; Epub ahead of print

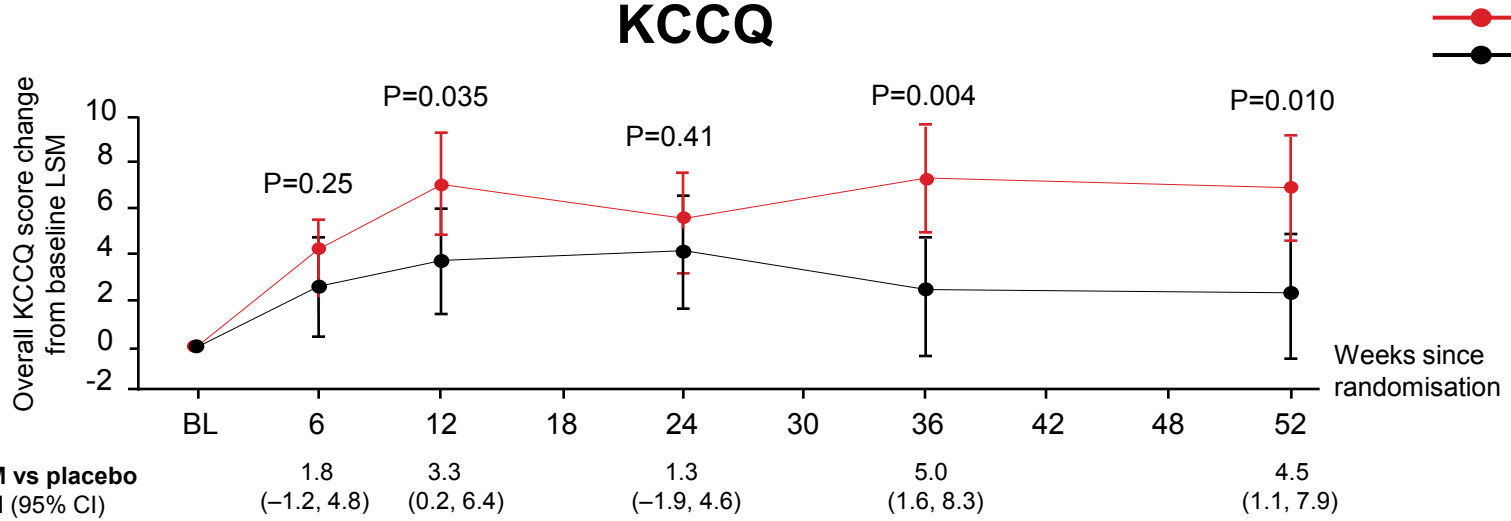
Secondary endpoints: Changes in 6MWT distance and QoL over time

6MWT



FCM vs placebo LSM (95% CI)	6	12	24	36	52
	14 (–5, 33)	16 (–3, 35)	33 (13, 53)	42 (21, 62)	36 (16, 57)

KCCQ



FCM vs placebo LSM (95% CI)	6	12	24	36	52
	1.8 (–1.2, 4.8)	3.3 (0.2, 6.4)	1.3 (–1.9, 4.6)	5.0 (1.6, 8.3)	4.5 (1.1, 7.9)

KCCQ – Kansas City Cardiomyopathy Questionare

Ponikowski P et al. *Eur Heart J* 2014; Epub ahead of print

Secondary endpoints: Outcome events

	FCM (N=150)		Placebo (N=151)			
End-point or event	**Total events (n)**	**Incidence/ (100 patient risk-year)**	**Total events (n)**	**Incidence/ (100 patient risk-year**	**Time to first event Hazard ratio 95% CI**	**P-value**
Death for any CV reason	11	11 (8.1)	12	12 (8.5)	0.96 (0.42 – 2.16)	0.91
Hospitalisation for any CV reason	26	21 (16.6)	51	33 (26.3)	0.63 (0.37 – 1.09)	0.097

FCM reduced the risk of recurrent hospitalisations due to worsening HF (post hoc):
Hazard Ratio (95% CI) – 0.30 (0.14-0.64), p=0.0019

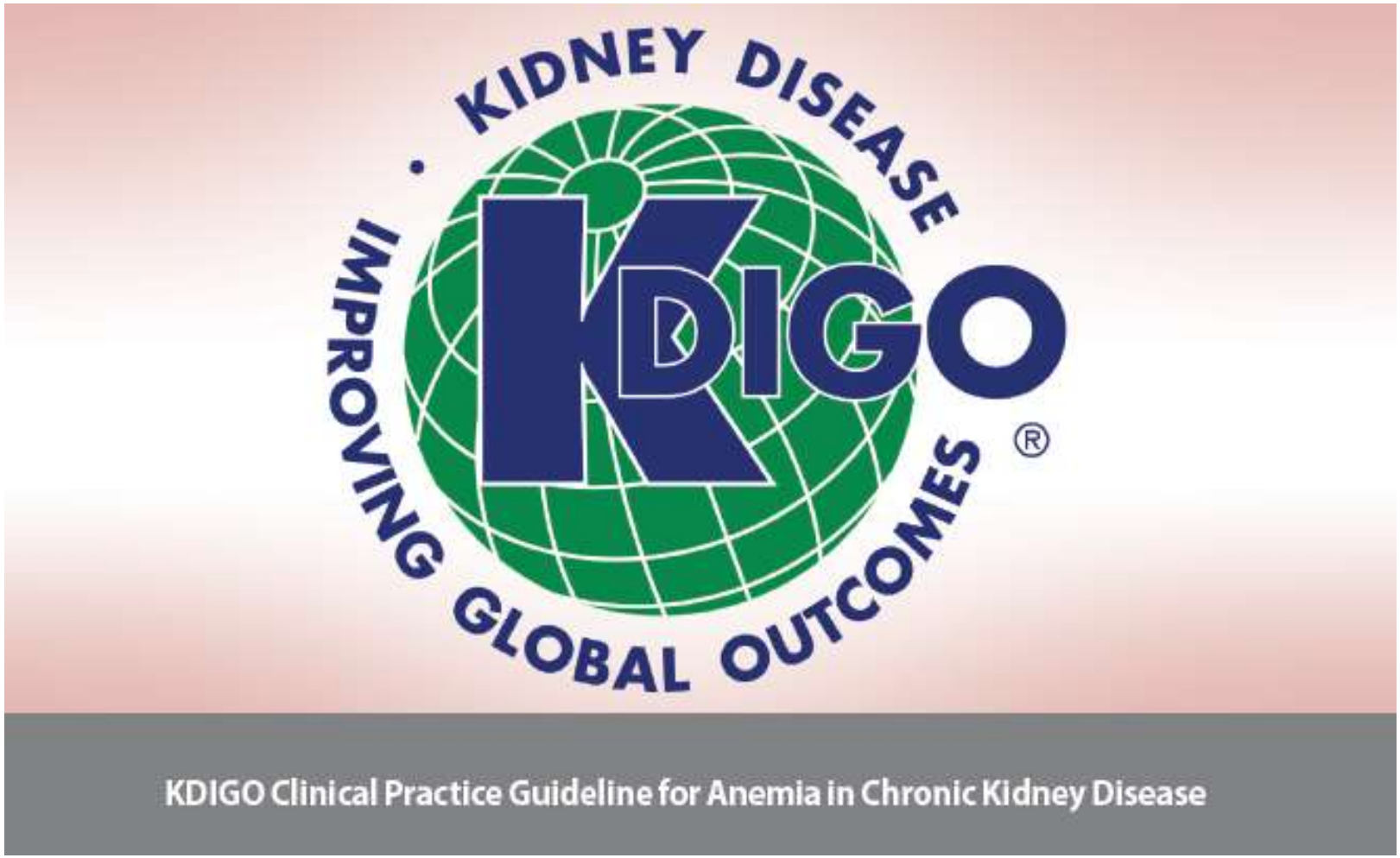
Ponikowski P et al. *Eur Heart J* 2014; Epub ahead of print

ESC Guidelines HF 2016

Recommendations for the treatment of other co-morbidities in patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
Iron deficiency			
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A	469, 470

KDIGO Anemia Guideline



KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease . Kid Int Suppl (2012) 2, 283–287

KDIGO Anemia Guideline

2.1.1 When prescribing iron therapy, balance the potential benefits of avoiding or **minimizing blood transfusions**, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). *(Not Graded)*

2.1.2 For adult CKD patients with anemia **not on iron or ESA** therapy we suggest a **trial of IV iron** (or in CKD ND patients alternatively a 1-3 month trial of oral iron therapy) if *(2C)*:

2.1.3 For adult CKD patients **on ESA therapy** who are not receiving iron supplementation, we suggest **a trial of IV iron** (or in CKD ND patients alternatively a 1-3 month trial of oral iron therapy) if *(2C)*:

Goals:
- an increase in Hb concentration without starting ESA treatment and
- TSAT is ≤ 30% and ferritin is ≤ 500 ng/ml

KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease . Kid Int Suppl (2012) 2, 283–287

Conclusions

1. Can we use IV iron in CKD patients (RLS? COPD? CHF?) ?

YES, WE CAN. We even have to.

2. Is oral iron possible to be used?

Yes, it is.

BUT

- in most cases the ID is 1,5 – 2,0 g;
- absorbtion of 1-2 mg/day;

Compliance?

3. Is every iron the same?

No, there is a individualization needed.

4. **Iron deficiency** is not only **Iron deficiency anemia** !!!

Спасибо Большое

Thank you for your attention