Iron metabolism – anemia and beyond

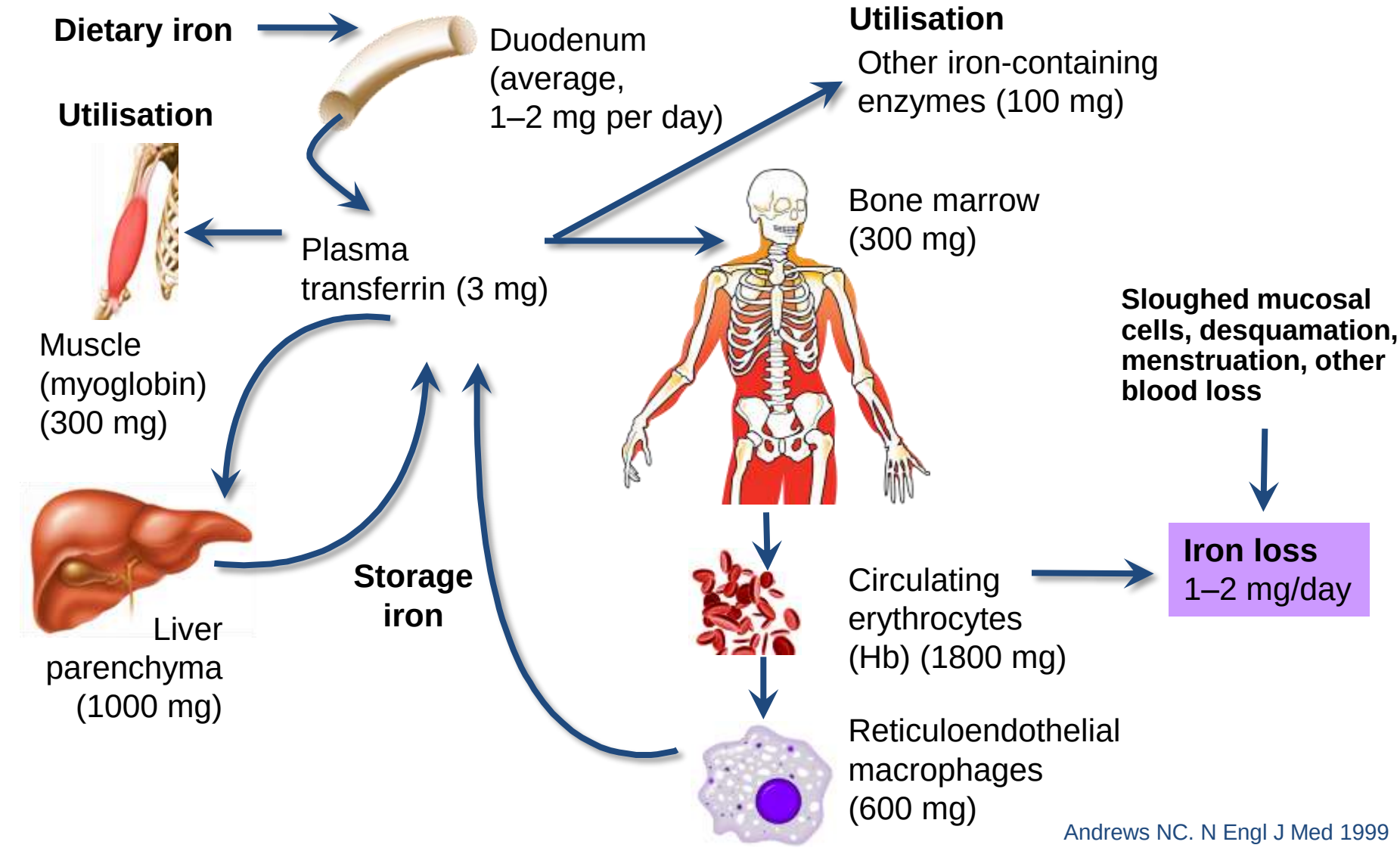
Jacek Lange

Khabarovsk, October 2015

Overview

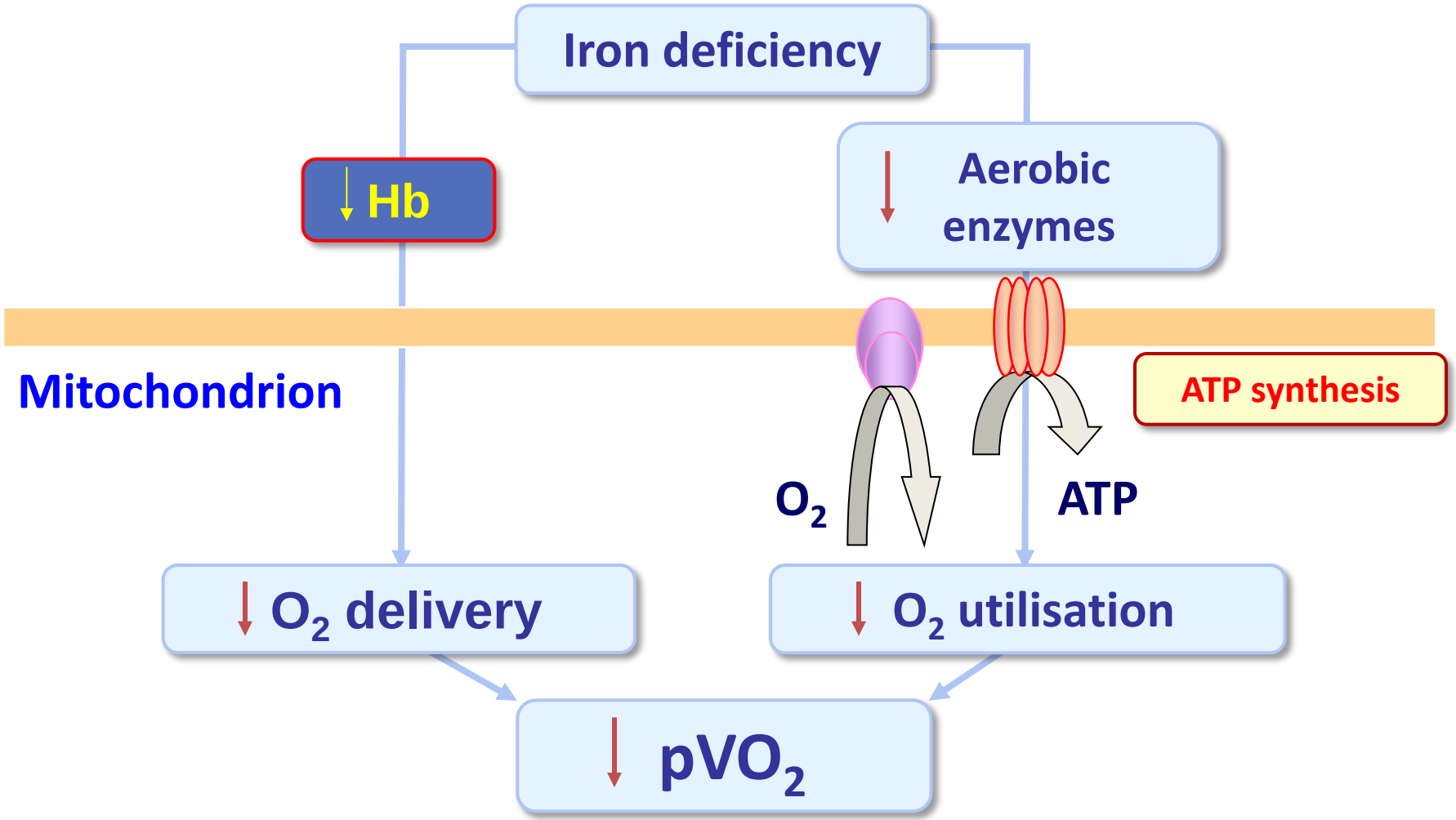
1. Iron metabolism
2. CKD
3. CHF
4. Conclusions

Under normal healthy conditions, daily iron intake equals daily iron loss (1–2 mg/day)



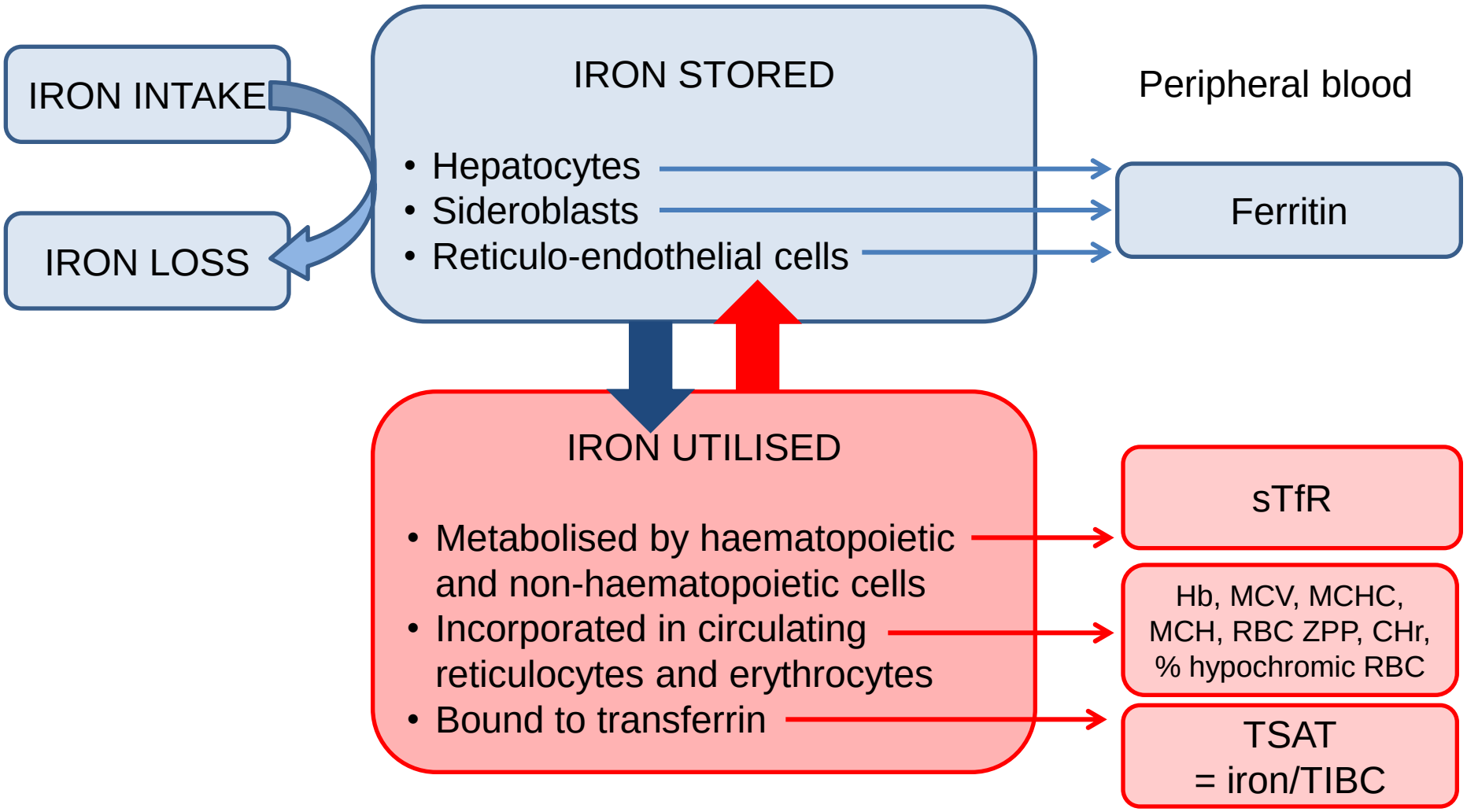
Andrews NC. N Engl J Med 1999

Dual effects of iron deficiency: defective oxygen delivery and utilization



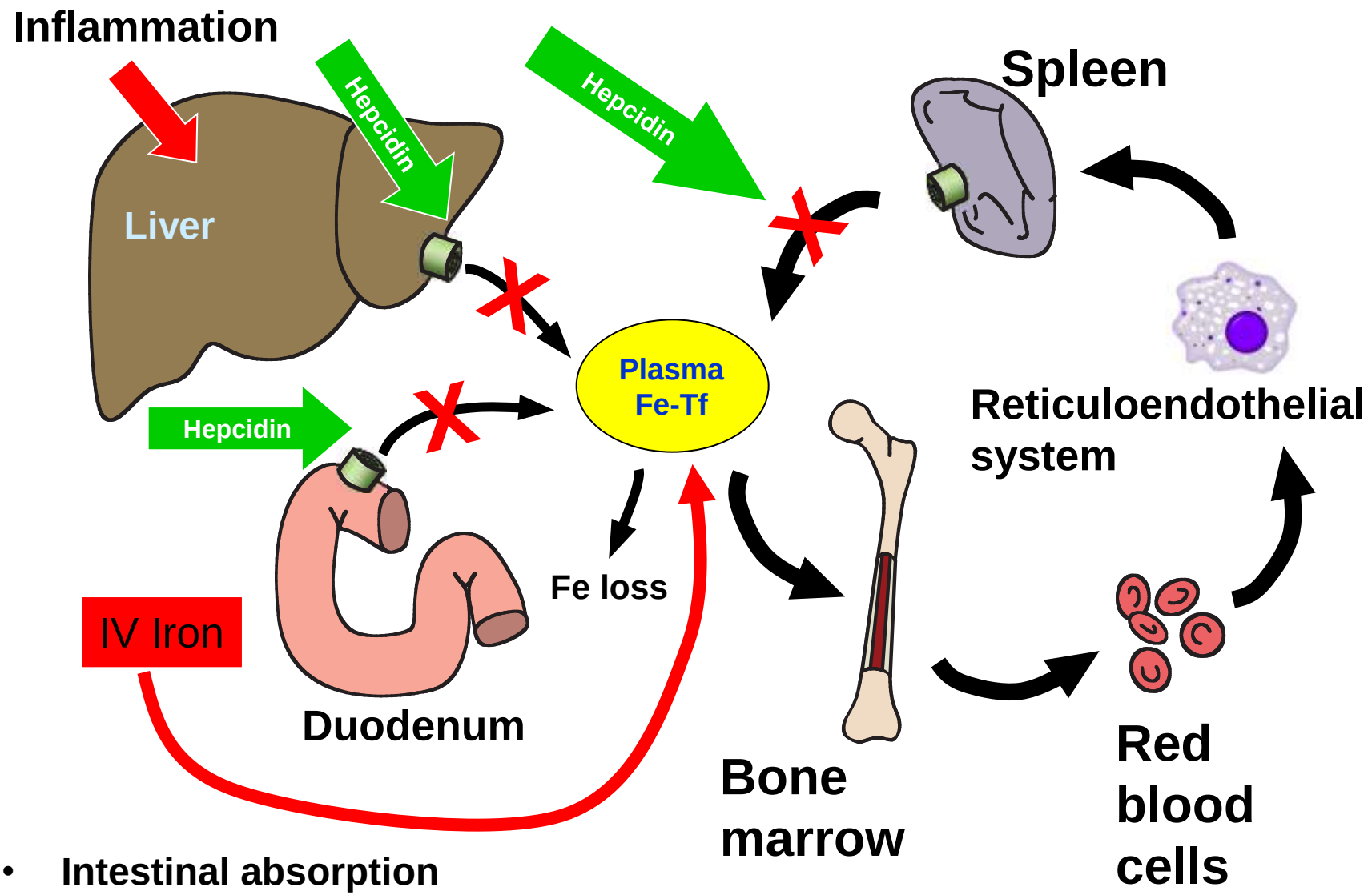
Anker SD, et al. Eur J Heart Fail 2009
Haas JD, Brownlie T IV. J Nutr 2001
Dallman PR. J Intern Med 1989

Iron storage and utilisation: interpretation of circulating biomarkers



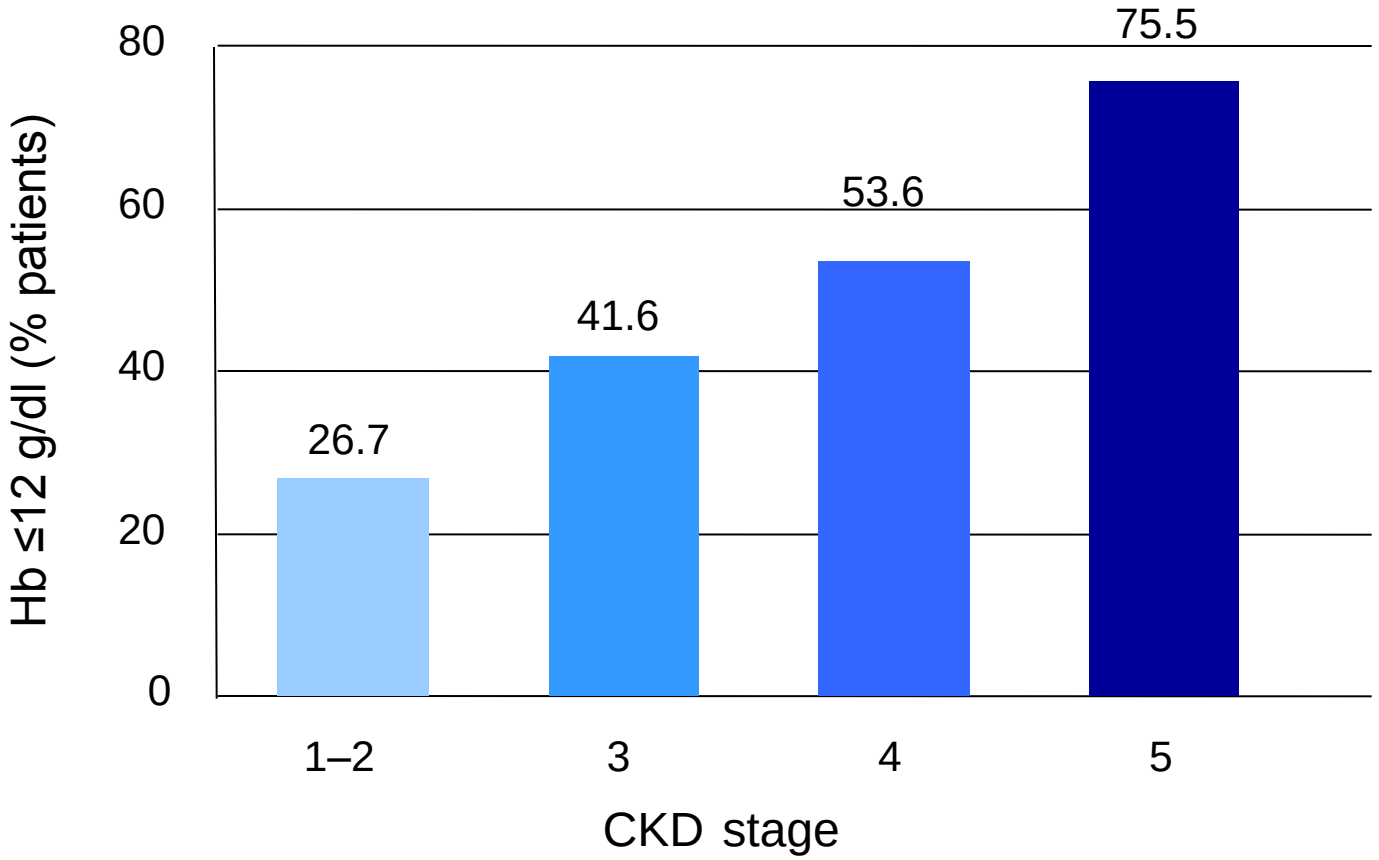
Modified from Jankowska et al. Eur. Heart J 2013

Absorption of oral iron in inflammation



- Intestinal absorption
- Release from hepatic cells and macrophages

Anemia is frequent in patients with CKD



Cross-sectional, US multicenter survey of 5,222 adult patients at 237 physician practices

McClellan W et al. Curr Med Res Opin 2004; 20: 1501-1510

Why anemia in CKD?

1. EPO
   - Impaired production
   - Impaired receptors' function

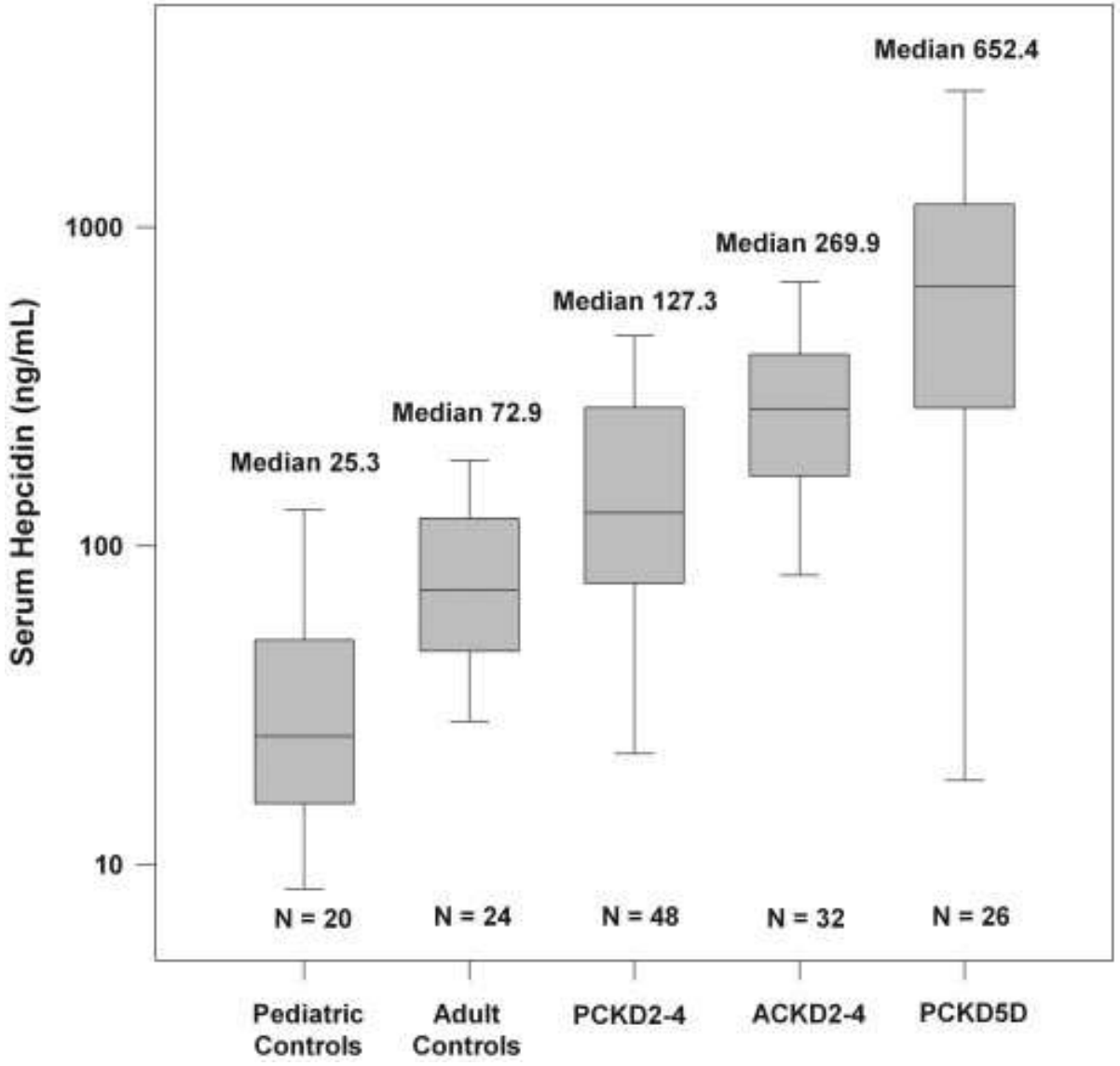
2. Impaired iron absorption
   - Level of intoxication – local inflammation in digestional tract
   - General inflammation due to uremia
   - Hepcidin

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

4. Functional iron deficiency due to ESA & inflammation

5. Impaired vitamins' intestinal absorption – Vit B12, folic acid

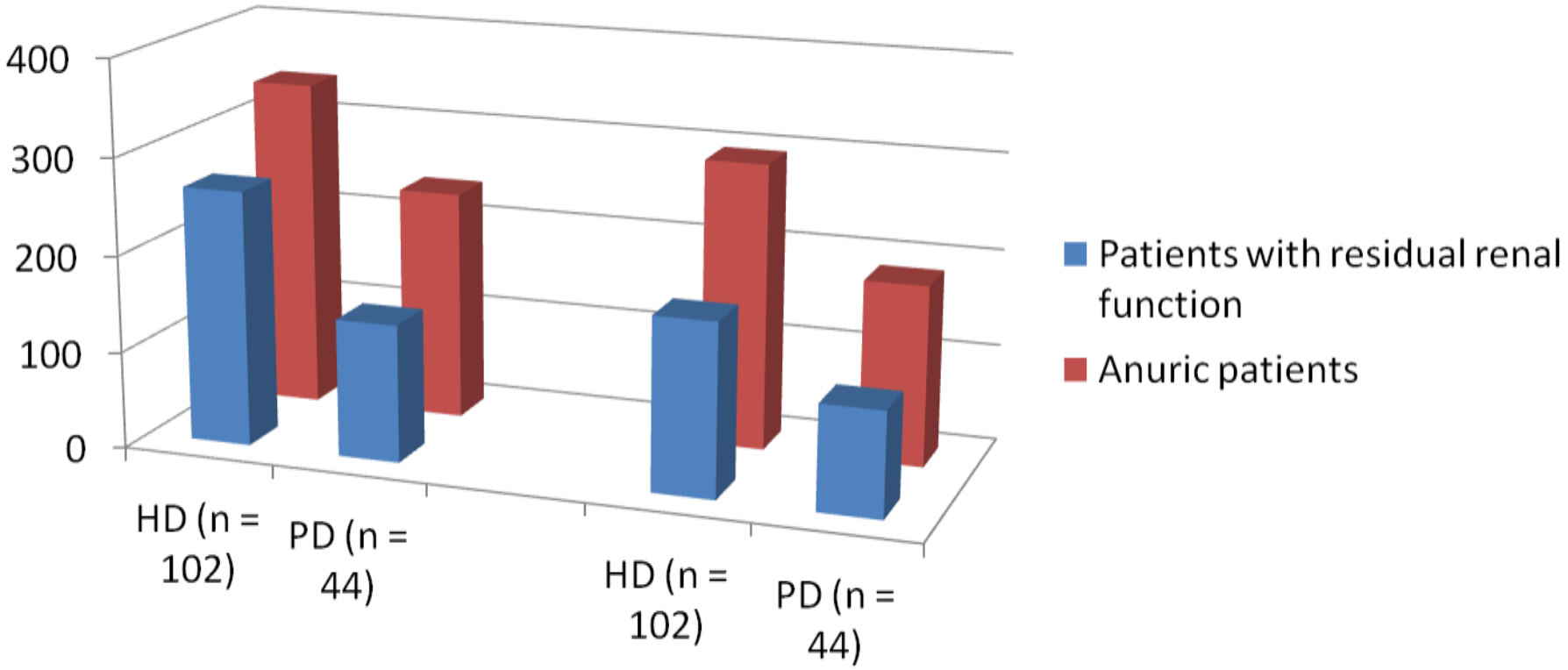
Hepcidin – a potential novel biomarker of Iron status in Chronic Kidney Disease



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

Inflammation vs. iron balance in PD and HD patients

Assessment of prohepcidin and hepcidin in serum, urine, and ultrafiltrate/peritoneal effluent



Malyszko J et al.: Type of renal replacement therapy and residual renal function may affect prohepcidin and hepcidin. Ren Fail 2009;31(10):876-883

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

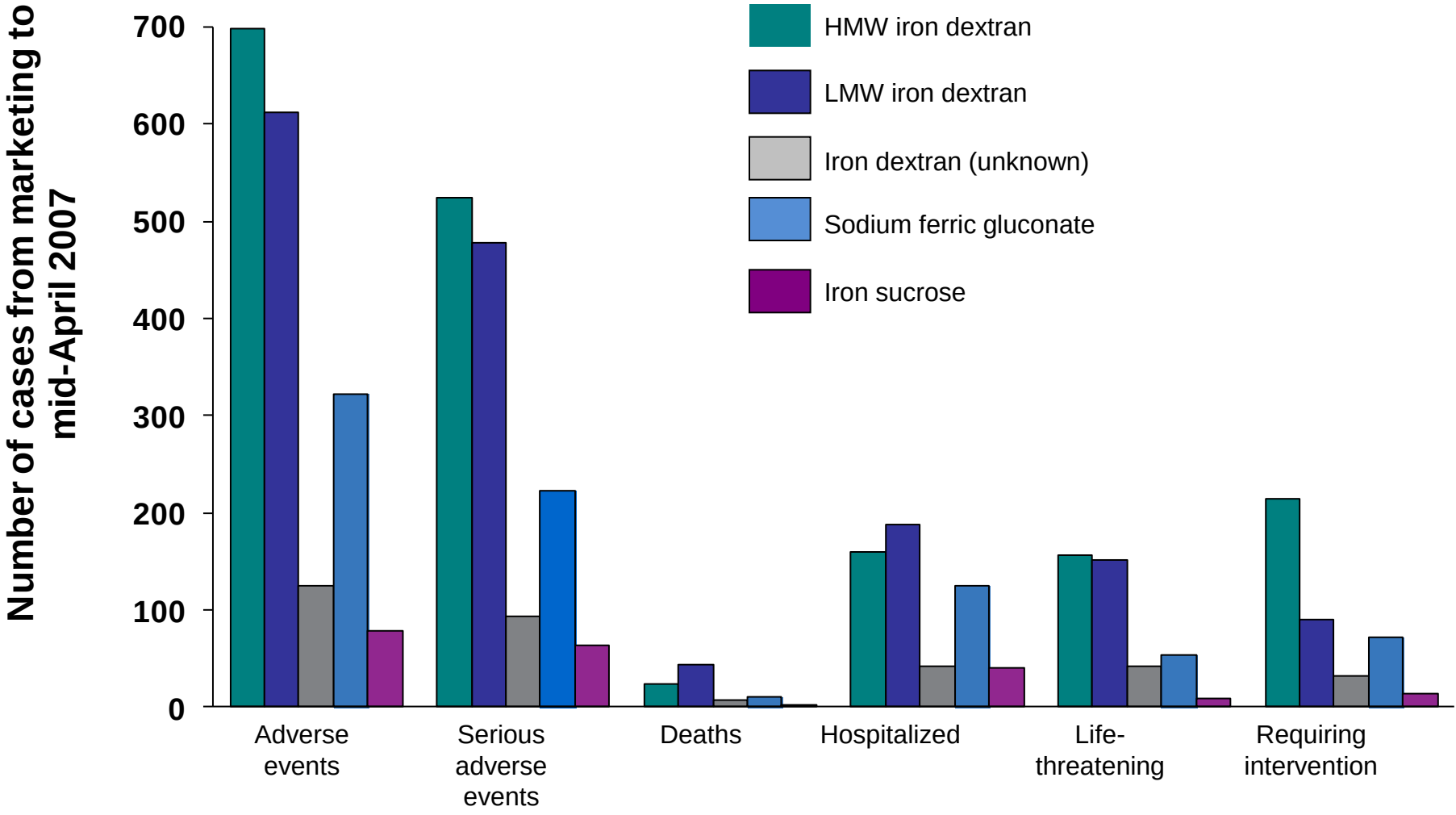
Safety comparison of I.V. iron preparations
Switch from Iron Dextran/Iron Gluconate to Iron Sucrose

Study	Design	n	History of intolerance	Safety outcomes
Van Wyck 2000[1]	Single-arm Multi-center	23	Iron dextran	No serious adverse drug reactions or drug discontinuation due to any drug-related adverse event
Charytan 2004[2]	Pooled data from 4 prospective studies	130	Iron dextran and/or iron gluconate	No serious adverse events
Aronoff 2004[3]	Single-arm Single-center	80*	Iron dextran and/or iron gluconate	No drug-related serious adverse events
Haddad 2009[4]	Single-arm Single-center	15	Iron dextran	No hypersensitivity reaction to Venofer®

*80 patients among a total population of 665

1. Van Wyck DB et al. Am J Kidney Dis 2000;36:88-97
2. Charytan C et al. Nephron Clin Pract 2004;96:c63-66
3. Aronoff GR et al. Kidney Int 2004;66:1193-1198
4. Haddad A et al. Saudi J Kidney Dis 2009;20:208-211

Wysowski et al, 2010



Wysowski DK et al. Am J Hematol 2010;85:650-654

Properties of ferric carboxymaltose (Ferinject®)

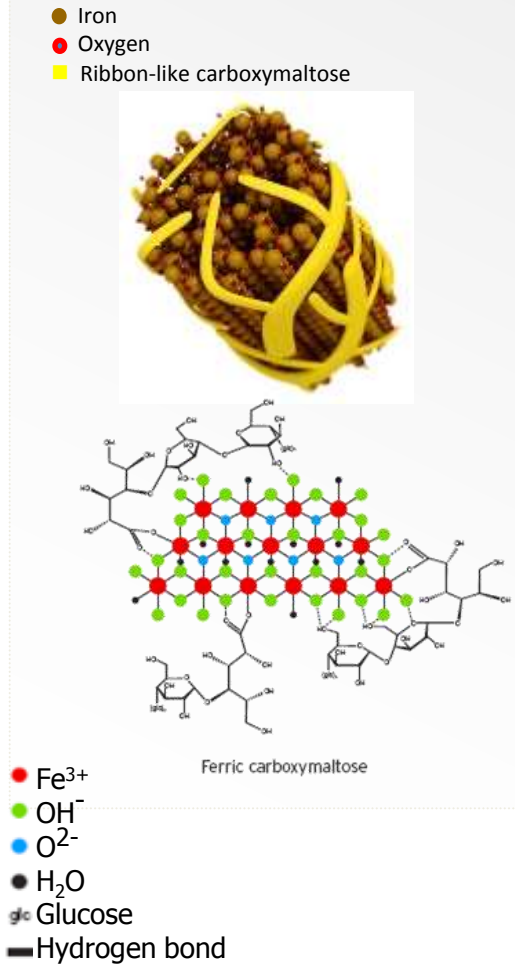
Ferric Carboxymaltose:

- Water soluble
- Macromolecular complex of polynuclear iron(III)-oxohydroxide stabilised by a carboxymaltose ligand

- Molecular weight of approximately 150 kDa
  - ensuring minimal renal elimination

Geisser P. Port J Nephrol Hypert 2009; 23:1 11–16
Ferric carboxymaltose, SmPCs, EU

Characteristics of ferric carboxymaltose (Ferinject®)



Effective correction of iron deficiency

- **High single doses (up to 1000 mg iron*)**
- **Rapid administration**
  - **200 mg iron bolus push**
  - **1000 mg iron infusion in 15 min**
- **Selective delivery to bone marrow**

Low immunogenic potential

- **Free of dextran derivatives**
- **No cross-reaction with dextran antibodies**

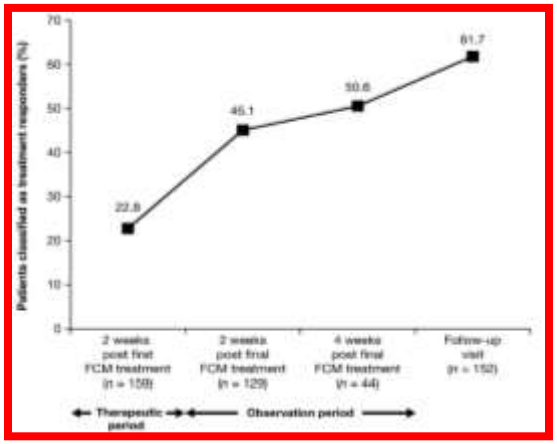
➢ **No test dose required**

*max 15 mg/kg bw

Geisser P. *Port J Nephrol Hypert* 2009;23:11–6

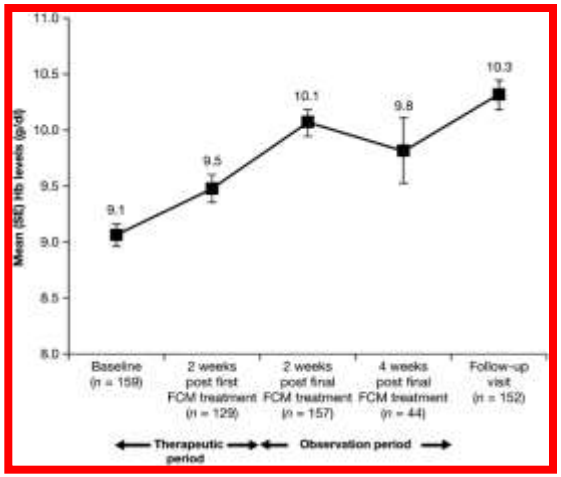
With FCM Hb and iron parameters in HD (Covic et al., 2010)

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

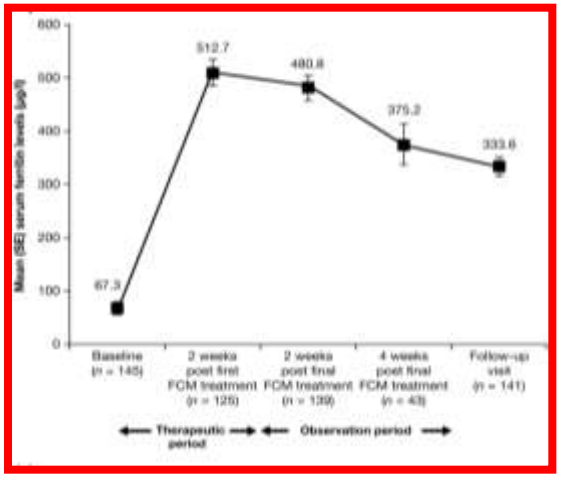


- FCM 100-200 mg at each HD session for a max. 6 weeks.
- n=163
- 120 patients –> ESA
- 63 patients –> no ESA

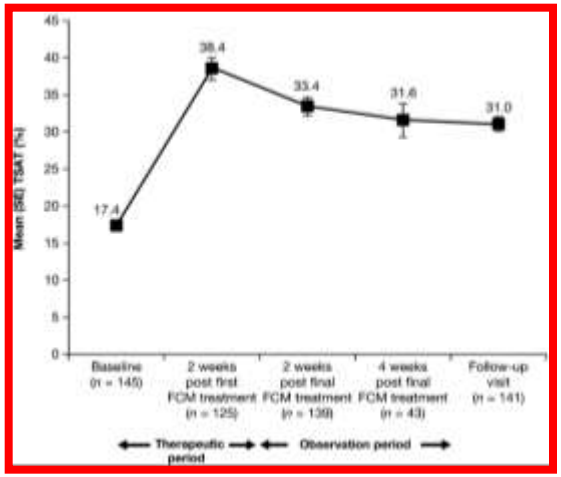
Hb



Ferritin



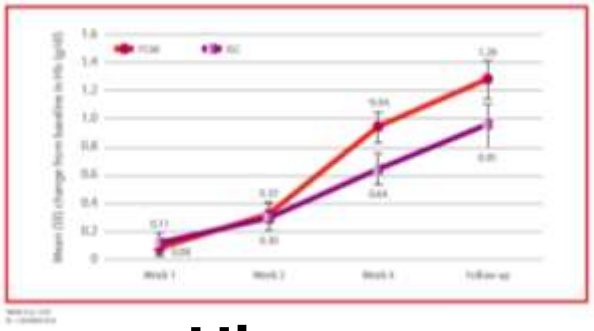
TSAT



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

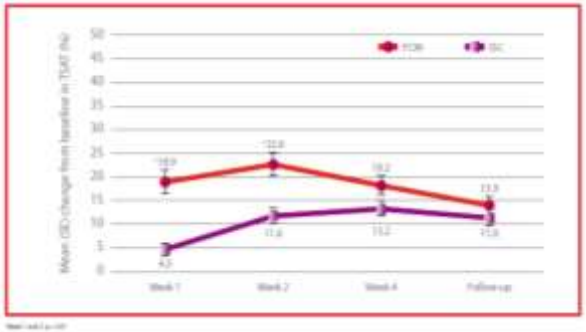
FCM in HD patients – Hb level

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

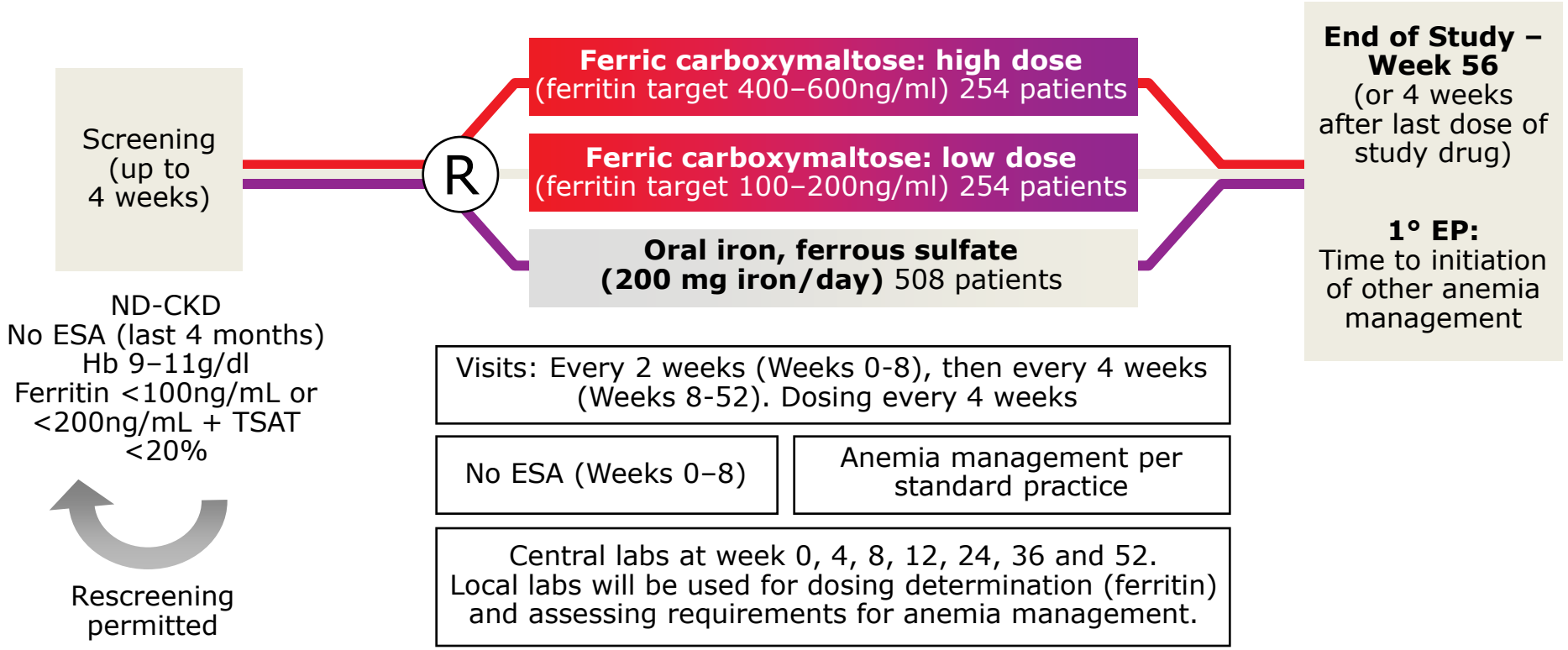
Evenepoel A et al. Abstract/Poster ASN 2009 San Diego

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

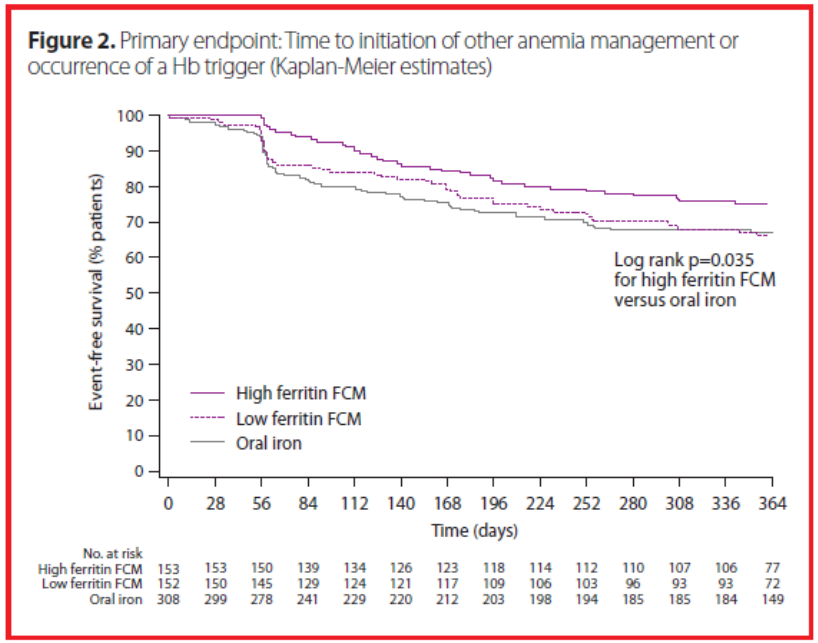
FIND-CKD: Study design



- 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/1·73m²[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

The NEW ENGLAND JOURNAL of MEDICINE

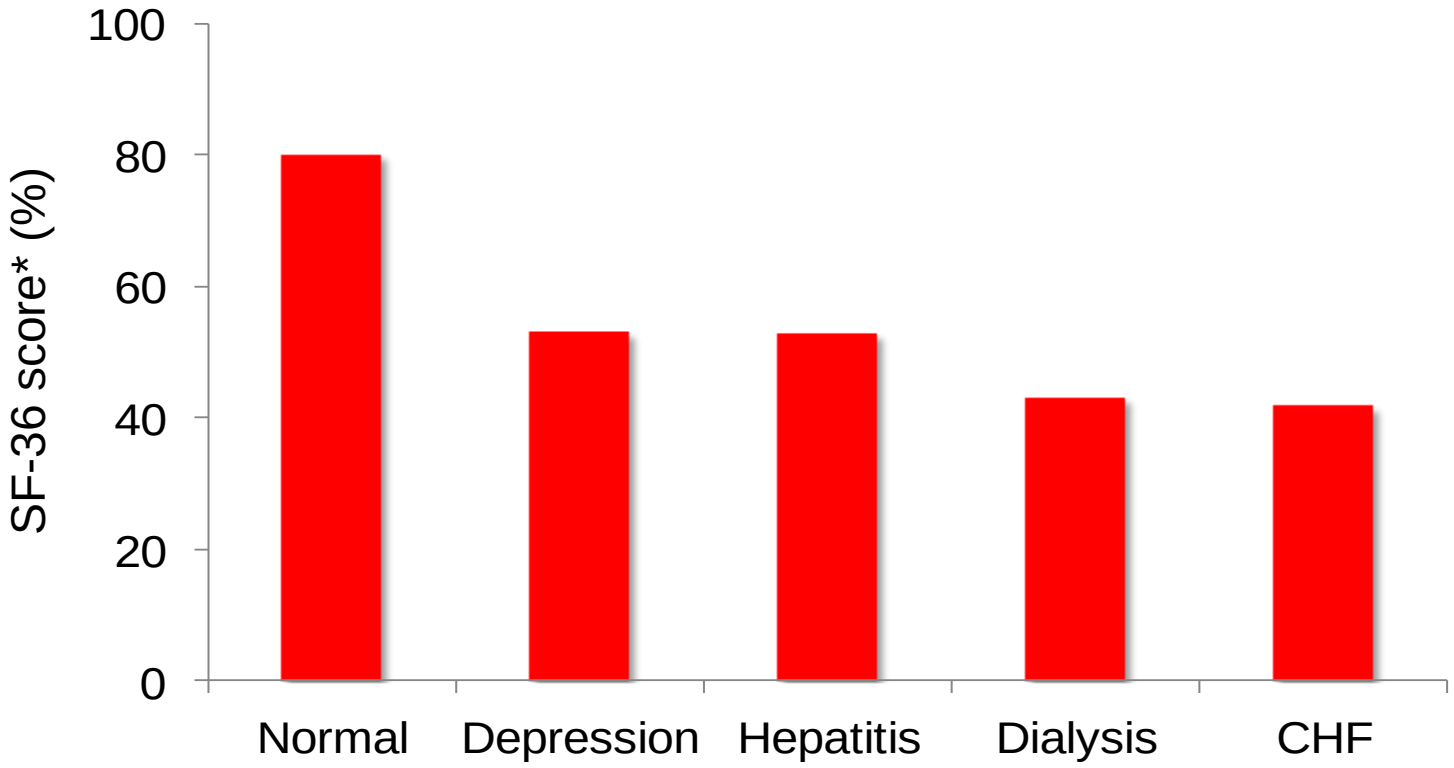
ORIGINAL ARTICLE

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

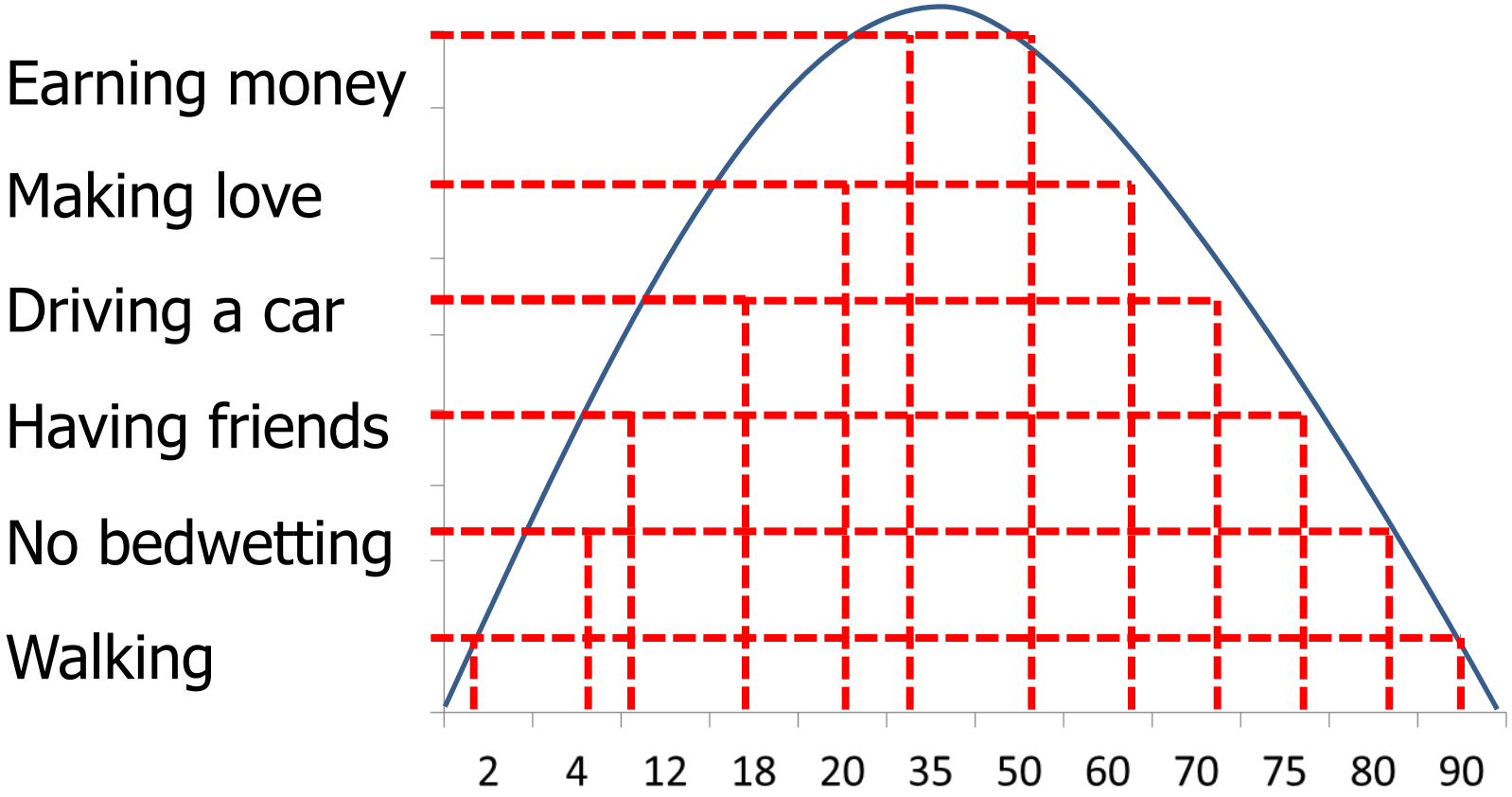
Quality of life in HF patients



* General health perceptions

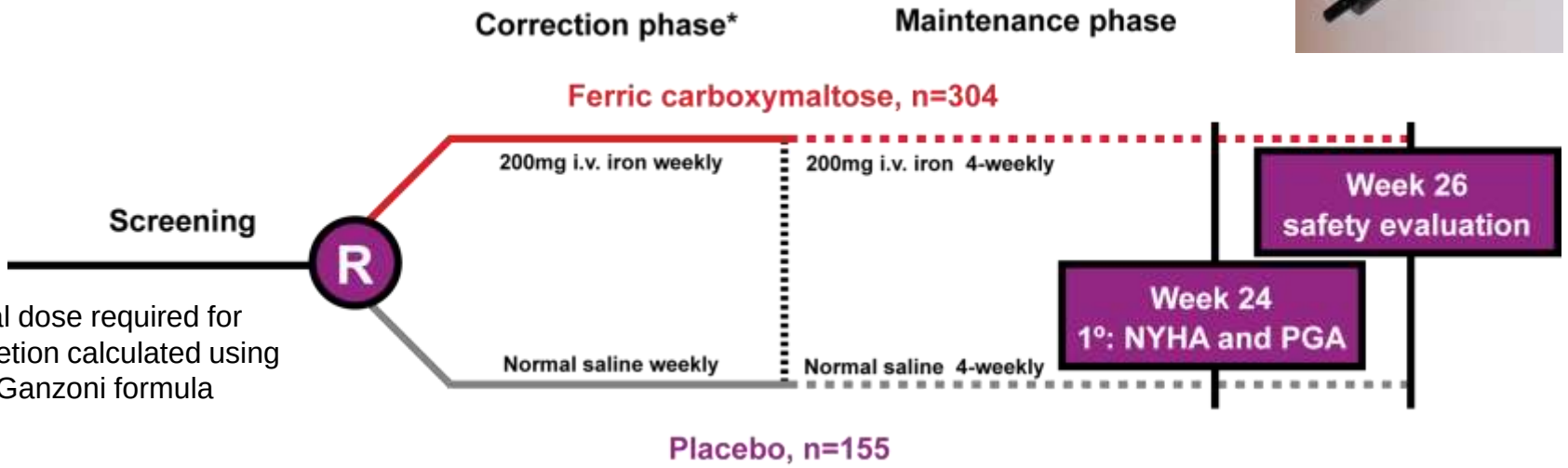
1. Ekman I, et al. Heart Lung 2002;31:94–101; 2. Lesman-Leegte I, et al. J Card Fail 2009;15:17–23;
3. Stewart AL, et al. J Clin Epidemiol 1994;47:719–30; 4. Juenger J, et al. Heart 2002;87:235–41.

Preferences



FAIR-HF study design

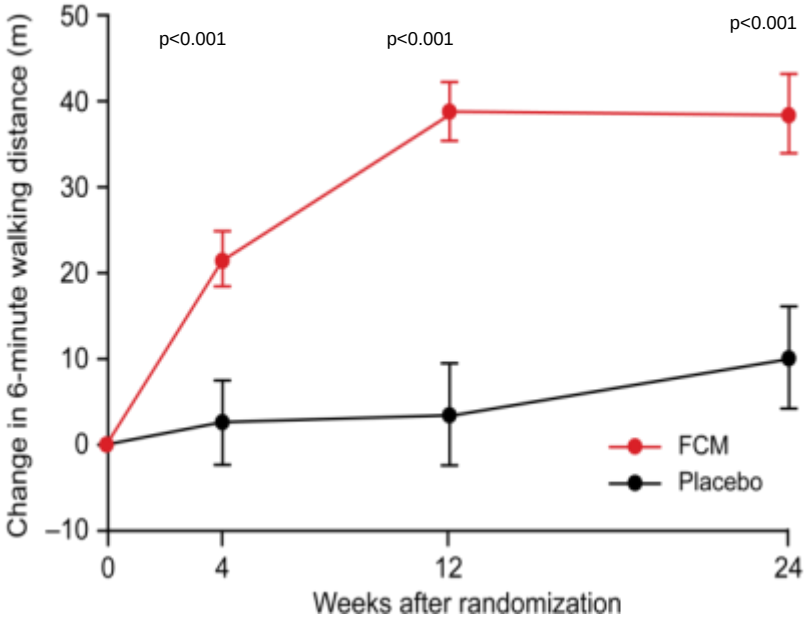
- **Main inclusion criteria:**
  - NYHA class II/III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - Hb: 9.5–13.5 g/dL
  - **Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%**
- **Treatment adjustment algorithm:**
  - Interruption: Hb >16 g/dL or serum ferritin >800 µg/L or serum ferritin >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

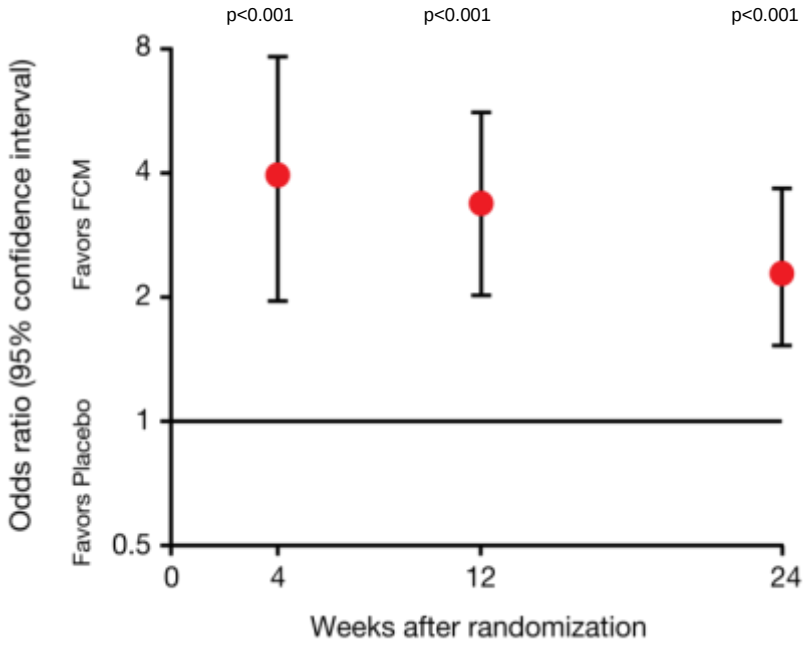


* Total dose required for repletion calculated using the Ganzoni formula

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

FAIR-HF results





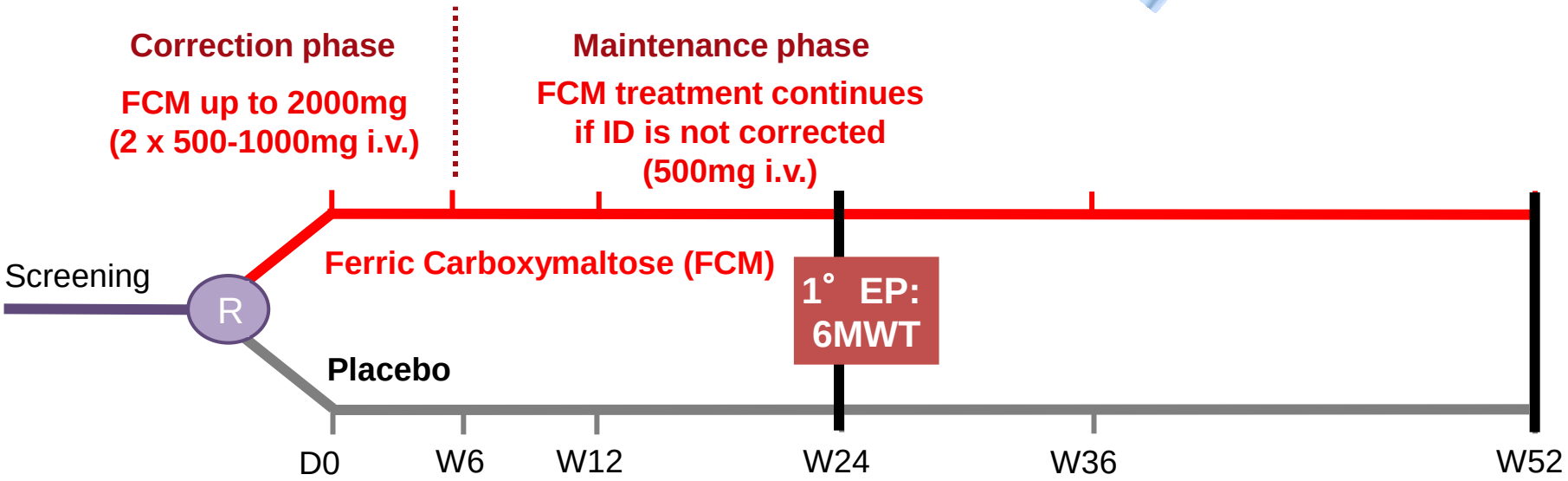
6-minute walk test

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

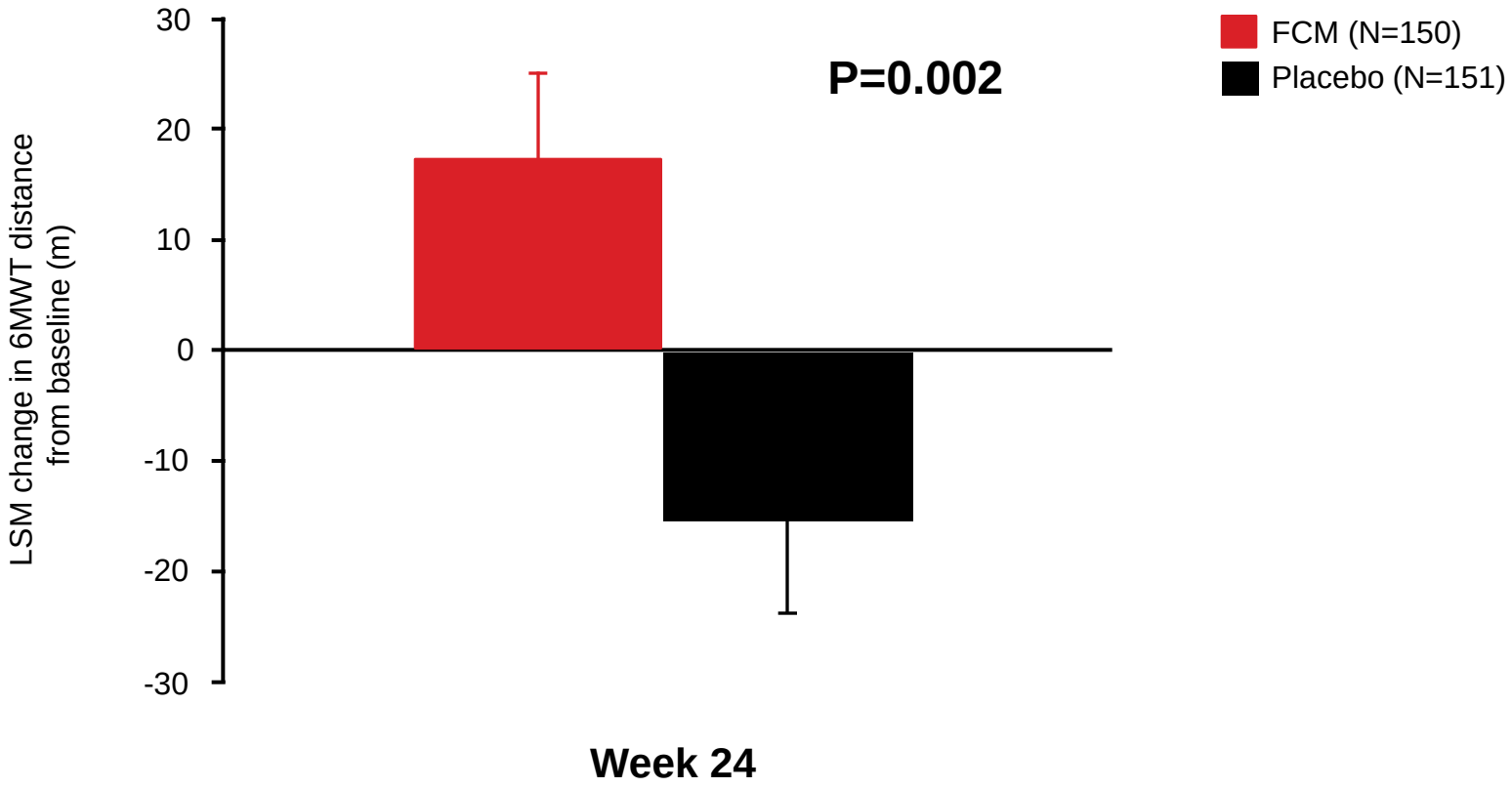


Ponikowski P et al. *Eur Heart J* 2014

Primary endpoint: Change in 6MWT at Week 24

FCM improved 6MWT at week 24

FCM vs placebo: 33 ± 11 m *(least squares mean ± SE)*

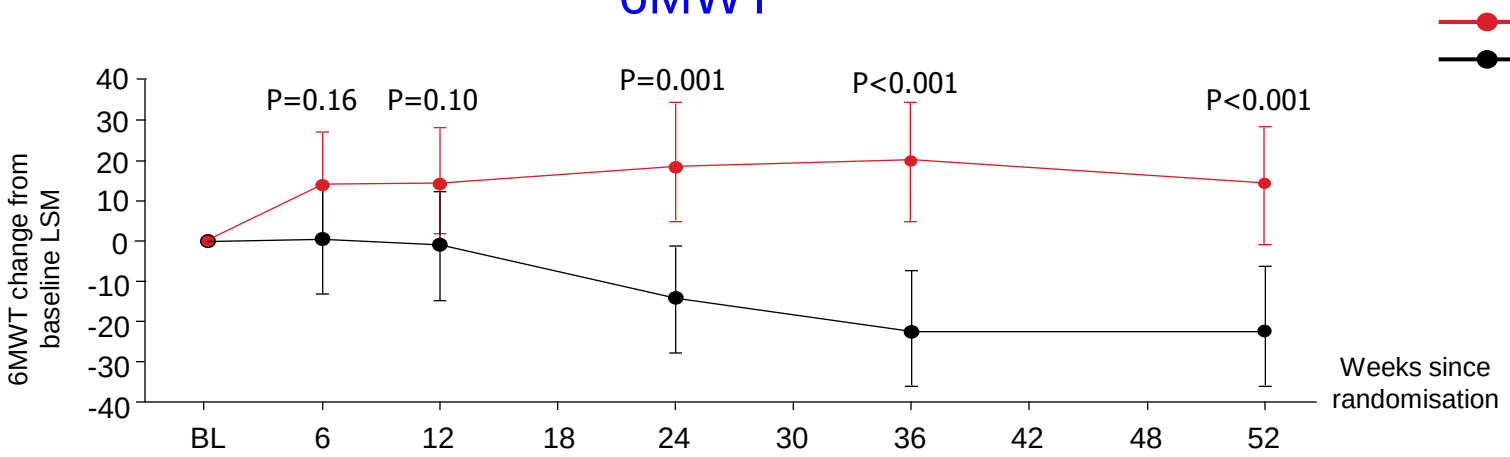


Ponikowski P et al. *Eur Heart J* 2014

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

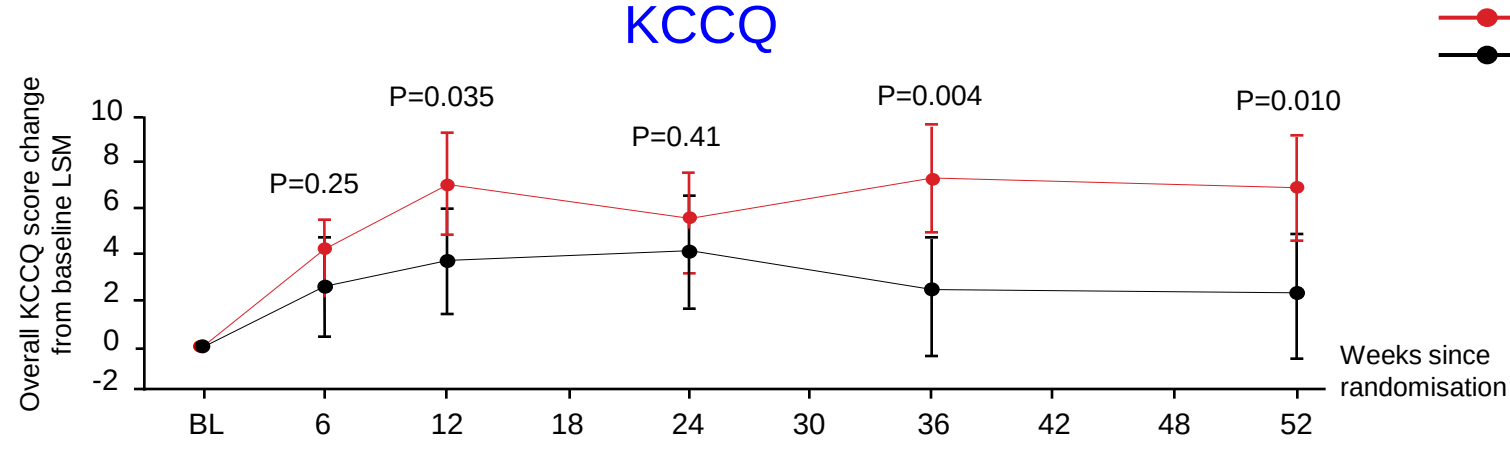
CONFIRM-HF

6MWT



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

KCCQ



FCM vs placebo LSM (95% CI)	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)

Ponikowski P et al. *Eur Heart J* 2014

Secondary endpoints: Outcome events

CONFIRM-HF

	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	12	12 (8.9)	14	14 (9.9)	0.89 (0.41 – 1.93)	0.77
Death for any CV reason	11	11 (8.1)	12	12 (8.5)	0.96 (0.42 – 2.16)	0.91
Hospitalisation	46	32 (26.3)	69	44 (37.0)	0.71 (0.45 – 1.12)	0.14
Hospitalisation for any CV reason	26	21 (16.6)	51	33 (26.3)	0.63 (0.37 – 1.09)	0.097
Hospitalisation due to worsening HF	**10**	**10 (7.6)**	**32**	**25 (19.4)**	**0.39 (0.19 – 0.82)**	**0.009**

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;

Controversies on Iron Management in CKD Conference
March 27-30, 2014, San Francisco

Steering Committee

Glenn Chertow, USA – Conference Co-Chair

Iain Macdougall, UK – Conference Co-Chair

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Roger (AU)	Simon	Vaziri (US)	Nick	Tentori (US)	Francesca	Rottembourg (FR)	Jacques
Rostoker (FR)	Guy	Wheeler (UK)	David	Wiecek (PL)	Andrzej	Spinowitz (US)	Bruce
Singh (US)	Ajay			Winkelmayer (US)	Wolfgang C.		

Controversies on Iron Management in CKD – Conclusions

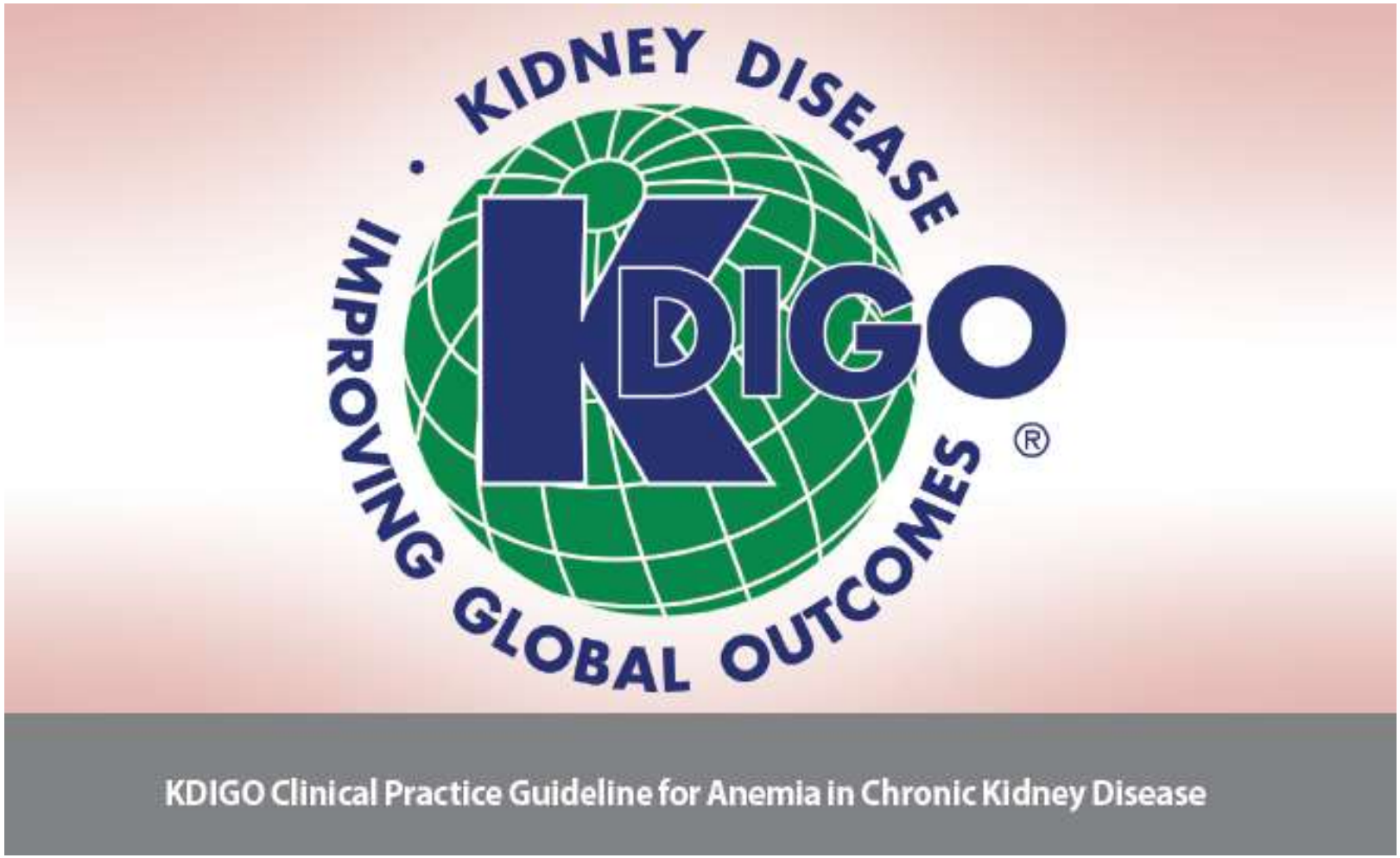
1. While there are **potential risks** associated with iron therapy, **appropriate use** of iron to treat iron deficiency **can help minimise** these risks and **result in benefits** for patients.

2. The **benefits** of iron therapy outweigh the risks.

3. Preliminary consensus from the controversies conference suggests there is **not sufficient new information** that requires updating the current *KDIGO anemia management guideline.*

4. The conference reinforced the importance of clinicians using the **guidelines** in clinical practice. **KDIGO guidelines still valid.**

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

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Conclusions

1. Can we use IV iron in CKD patients?

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