Efficacy of intraoperative Iron Isomaltoside 1000 on Hemoglobin Response

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Why intravenous iron dosing is an issue?

Intravenous (IV) iron

- IV iron has been widely used
- A highly effective means of replacing iron deficits
- *Indications*
  - Surgical patients: pre and postoperative period
  - Chronic kidney disease (with or without receiving hemodialysis)
  - Heart failure
  - Inflammatory bowel disease
  - Cancer, chemotherapy-related anemia, etc

- ***Optimum dose* remains *uncertain***

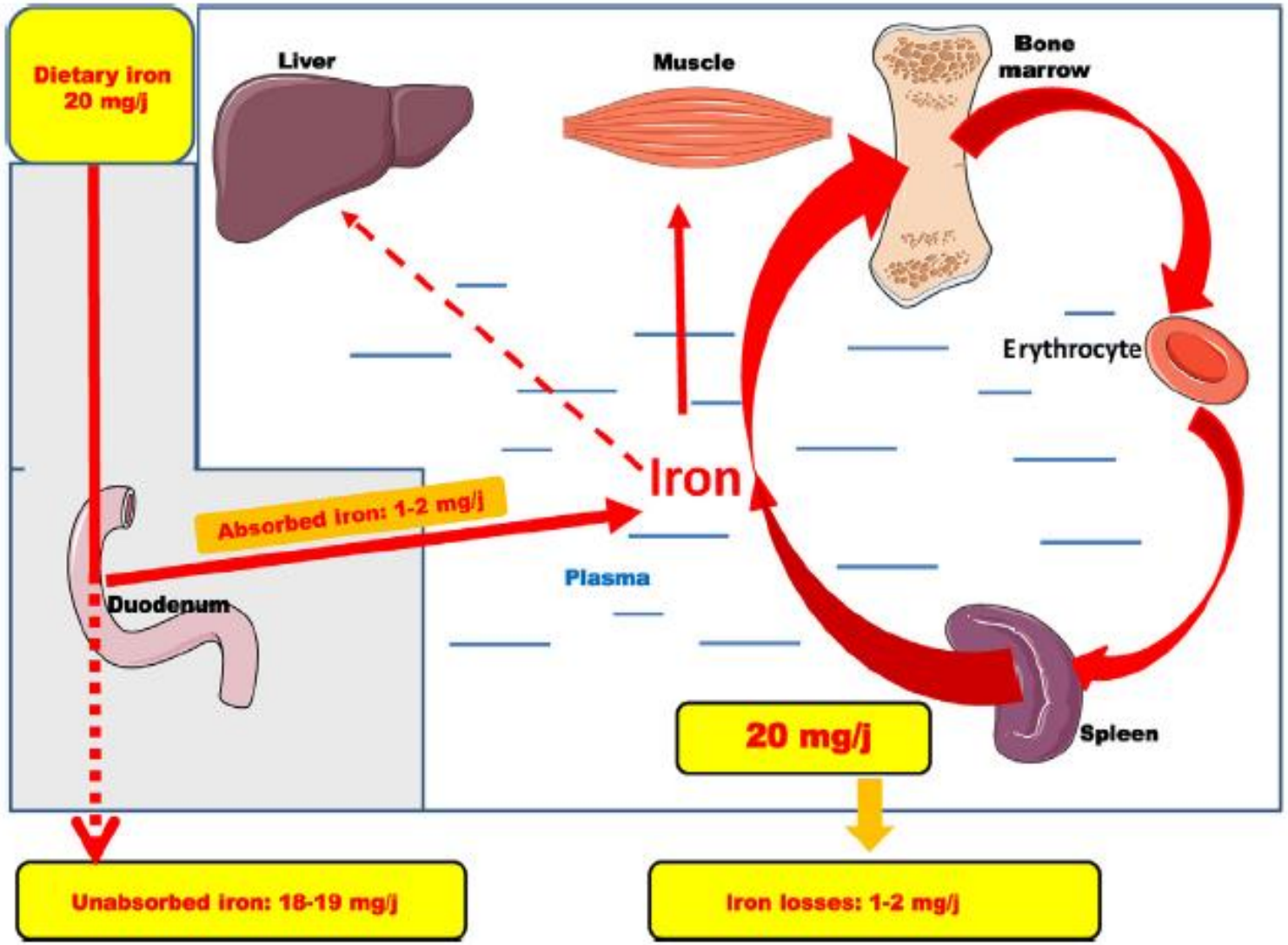

Fig. 1. Iron homeostasis. The two sources of plasma iron are dietary iron absorption and iron recycling from the spleen. Iron losses (digestive, urinary, cutaneous) and intake (digestive) are quantitatively equal, and much lower than recycled iron. Modified from Brissot et al. [1].

Iron homeostasis

➢ *Circulating iron*

- Hemoglobin-bounded iron (erythrocytic iron)
- Plasma iron bound to transferrin (each transferrin can bind up to two iron atoms)
- Transferrin forms: apotransferrin, mono-ferric transferrin, di-ferric transferrin
- **Plasma transferrin saturation (TSAT) : key index**

➢ *Stored iron*

- Ferritin: intracellular iron-storage protein
  - Maintain labile cellular iron levels within a safe range

P. Brissot et al. Transfusion Clinique et Biologique 26 (2019) 80–88

Iron homeostasis

- Hepcidin
  - Key iron-regulatory protein synthesized in the liver
  - ↓Plasma iron levels - ↓ Hepcidine production
  - ↑Plasma iron levels - ↑ Hepcidine production
  - Upregulated during Inflammation and infection

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Vulnerability of iron homeostasis

1) Risk of **iron deficiency**
   - Humans cannot **synthesize iron**
   - Entirely dependent on dietary intake

2) Risk of **iron overload**
   - Limited ability to increase iron excretion
   - Excessive intake (oral or parenteral) can accumulate

➢ Intravenous iron
   - Bypass the normal physiologic hepcidin-regulated intestinal absorption
   - Carries a potential risk of iron overload

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IV iron preparation and dosing methods

	Iron sucrose (IS)	Iron isomaltoside 1000 (IIM) or ferric derisomaltose (FDI)	Ferric carboxymaltose (FCM)
Concentration of elemental iron	20 mg/ml	100 mg/ml	50 mg/ml
Max dose in sing administration for pts > 35 kg	200 mg	20 mg/kg with (Max.dose: 1500 mg) EU, UK, New Zealand (Max.dose: 1000 mg) ≥50kg, US 20 mg/kg: < 50kg, US	20 mg/kg with (Max.dose of 1000 mg)
Total dose single infusion	No	Yes (< 20 mg/kg)	No (unless total body iron deficit is ≤ 1000 mg)
Frequency of administration	≤ 3 times/week	More than 20 mg/kg, 7 days apart	7 days apart
Infusion time for maximum dose	15 min – 30 min	15 min – 30 min	15 min

Jahn et al , European j. of pharmaceutics and biopharmaceutics 78 (2011) 480-491

Qassim et al. Aust N Z J Obstet Gynaecol 2018; 58: 22–39.

Dosing methods

Total iron dose (**Ganzoni formula**)

= [actual body weight (kg) x (15 – actual Hb)] x 2.4 + iron stores

1. Modified Ganzoni formula

Total iron dose = [actual body weight x (13 – actual Hb)] x 2.4 + iron stores

(Iron stores: approximately 500 mg)

Ex> Hb 9.5, body weight 70 kg: 1088 mg

- Administration
  - Multi-fractionated infusion
  - Single high-dose administration

2. **Fixed-dose:** single high-dose, body weight and Hb

Wt < 50 kg: Ganzoni formula
Body weight 50-70 kg

Table 1. Total Iro… …ose Regimen

Hb (g/dL)	Body weight <70 kg	Body weight ≥70 kg
≥10	1000 mg	1500 mg
7–10	1500 mg	2000 mg

NOTE. Total dosage was administered in single infusions of 500 mg or 1000 mg iron as FCM. For patients with a body weight <67 kg, single doses of 500 mg were given.

Evstatiev et al. GASTROENTEROLOGY 2011;141:846–853

FERGIcor, a Randomized Controlled Trial on Ferric Carboxymaltose for Iron Deficiency Anemia in Inflammatory Bowel Disease

RAYKO EVSTATIEV,* PHILIPPE MARTEAU,‡ TARIQ IQBAL,§ IGOR L. KHALIF,‖ JÜRGEN STEIN,¶ BERND BOKEMEYER,# IVAN V. CHOPEY,** FLORIAN S. GUTZWILLER,‡‡ LISE RIOPEL,§§ and CHRISTOPH GASCHE,* for the FERGI Study Group

*Department of Medicine 3, Division of Gastroenterology and Hepatology, Christian Doppler Laboratory for Molecular Cancer Chemoprevention, Medical University of Vienna, Vienna, Austria; ‡AP-HP, Département medico-chirurgical de pathologie digestive Hôpital Lariboisière & Université Denis Diderot- Paris 7, Paris, France; §University Hospital, Birmingham, United Kingdom; ‖State Scientific Centre of Coloproctology, Moscow, Russia; ¶Department of Gastroenterology and Clinical

- Dosing

✓FCM: up to 3 infusions of 1000 mg or 500 mg each

✓IS: Ganzoni-calculated, up to 11 infusions of 200 mg each

- Hb response (Hb increase ≥ 2 g/dl)
  - ✓ FCM: 65.8%
  - ✓ IS: 53.6%
  - ✓ Difference: + 12.2% (P=0.004)
- Hb normalization
  - ✓ FCM: 72.8%
  - ✓ IS: 61.8%
  - ✓ Difference: +11.0 % difference (P = 0.015)

The simple FCM-based fixed dosing regimen showed better efficacy and compliance

Evstatiev et al. GASTROENTEROLOGY 2011;141:846–853

Clinical efficacy evidence

Low-dose, multi-fractionated vs High-dose, single infusion

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§University Hospital, Birmingham, United Kingdom; ‖State Scientific Centre of C
Nutrition and Crohn Colitis Centre Rhein Main, Frankfurt/Main, Germany; #Gastr
Uzhgorod, Ukraine; ‡‡Institute of Pharmaceutical Medicine (ECPM), University o

See Covering the Cover synopsis on page 783.

BACKGROUND & AIMS: Iron deficiency anemia (IDA) i
common in chronic diseases and intravenous iron is a
effective and recommended treatment. However, dose calcu
lations and inconvenient administration may affect compl
ance and efficacy. We compared the efficacy and safety of
novel fixed-dose ferric carboxymaltose regimen (FCM) wit
individually calculated iron sucrose (IS) doses in patient
with inflammatory bowel disease (IBD) and IDA. **METH
ODS:** This randomized, controlled, open-label, multicente
study included 485 patients with IDA (ferritin <100 μg/l
hemoglobin [Hb] 7–12 g/dL [female] or 7–13 g/dL [male]
and mild-to-moderate or quiescent IBD at 88 hospitals an
clinics in 14 countries. Patients received either FCM in
maximum of 3 infusions of 1000 or 500 mg iron, or Gan
zoni-calculated IS dosages in up to 11 infusions of 200 m
iron. Primary end point was Hb response (Hb increase ≥
g/dL); secondary end points included anemia resolution an
iron status normalization by week 12. **RESULTS:** The re
sults of 240 FCM-treated and 235 IS-treated patients wer
analyzed. More patients with FCM than IS achieved H
response (150 [65.8%] vs 118 [53.6%]; 12.2% difference, P =
.004) or Hb normalization (166 [72.8%] vs 136 [61.8%]; 11.0
difference, P = .015). Both treatments improved quality o
life scores by week 12. Study drugs were well tolerated an
drug-related adverse events were in line with drug-specifi
clinical experience. Deviations from scheduled total iro
dosages were more frequent in the IS group. **CONCLU
SIONS:** The simpler FCM-based dosing regimen showe
better efficacy and compliance, as well as a good safet
profile, compared with the Ganzoni-calculated IS dose reg

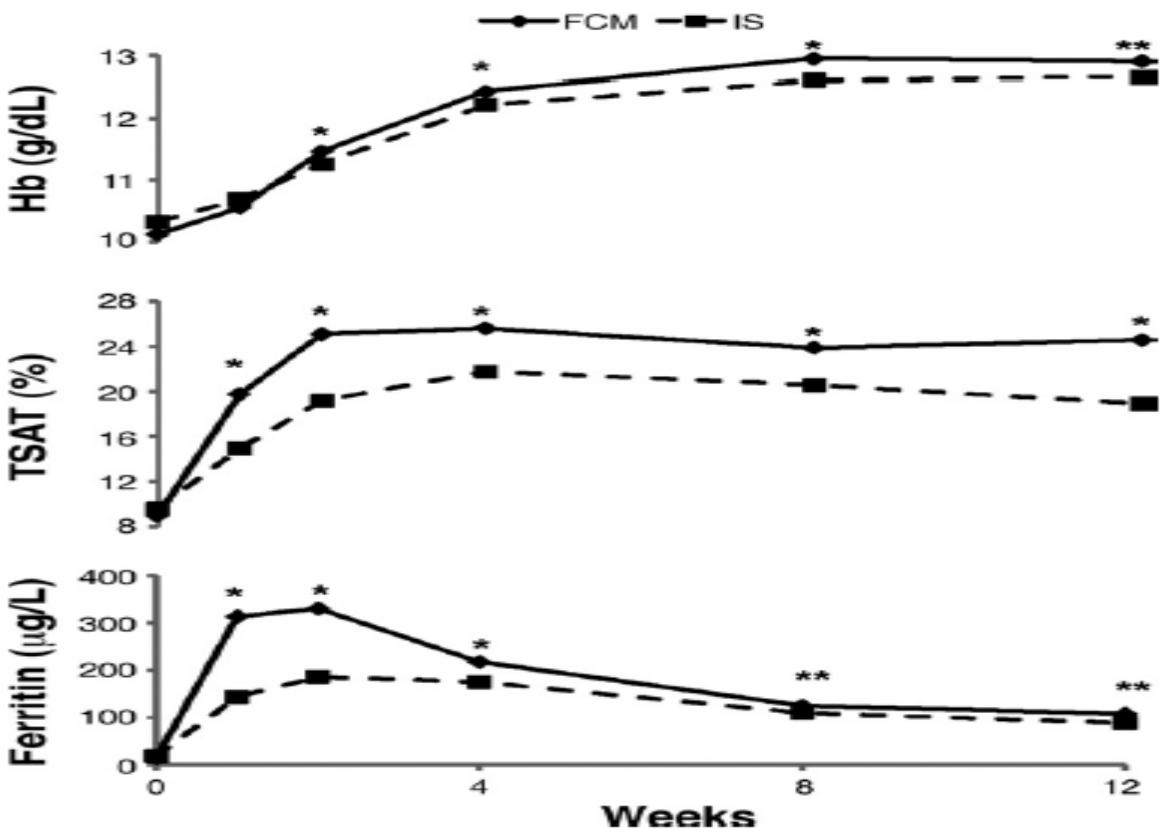


Figure 2. Time courses of patients' Hb, TSAT, and ferritin levels show earlier and consistently better improvement of Hb and iron status with the FCM regimen compared with the IS regimen.
*P < .001 and **P ≤ .015 for changes vs baseline.

Evstatiev et al. GASTROENTEROLOGY 2011;141:846–853

Nephrol Dial Transplant (2014) 29: 833–842
doi: 10.1093/ndt/gft251
Advance Access publication 20 August 2013

ndt
Nephrology Dialysis Transplantation

Original Articles

Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial

- Stratification factors
  - Baseline Hb ≤9.0 / 9.1-10.0 / ≥10.1 g/dl
  - Baseline cv risk, region, ESA use and CKD stage

- **Dosing**
- **FCM**
  - 15 mg/kg, max 750 mg per dose,
  - Two infusions: **a max total dose of 1500 mg** (Days 0 and 7)
- **IS**
  - 200 mg
  - 5 infusions (total **1000 mg)** (Days 0, 7, and 14)

Ferric carboxymaltose in patients with iron-defi and impaired renal function: the REPAIR-IDA t

able 3. Proportion of subjects with an increase in hemoglobin ≥1.0 g/dL between baseline ar opulation)

	Study group	
	FCM (n = 1249)n/N (%)	Iron sucrose (n = 1244)
Overall	607/1249 (48.60%)	510/1244 (41.00%)
Baseline Hb, g/dL		
≤9.0	63/100 (63.00%)	57/96 (59.38%)
9.1–10.0	152/280 (54.29%)	144/279 (51.61%)
≥10.1	392/869 (45.11%)	309/869 (35.56%)
Use of ESA		
No	491/1024 (47.95%)	411/1034 (39.75%)
Yes	116/225 (51.56%)	99/210 (47.14%)
CKD stage		
2	43/68 (63.24%)	41/77 (53.25%)
3–4	533/1091 (48.85%)	433/1067 (40.58%)
5	31/90 (34.44%)	36/100 (36.00%)

KD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; FCM, ferric carboxymaltose; Hb, hemoglobi Confidence interval based on the normal approximation to the binomial with Wald continuity correction.

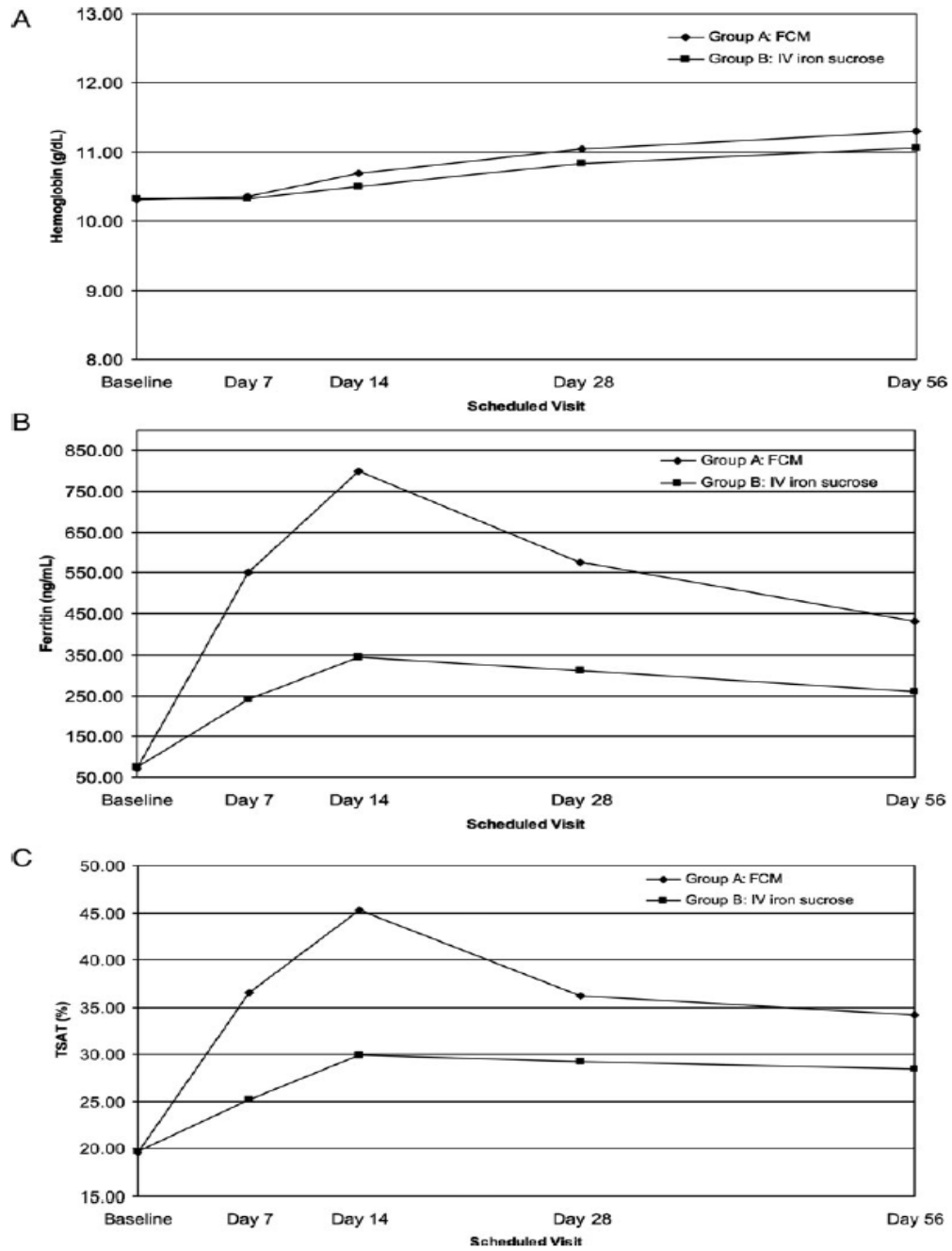


FIGURE 2: (A) Mean hemoglobin values at each scheduled visit. (B) Mean ferritin values population; n = 2493). (C) Mean TSAT values at each scheduled visit (modified intent-to-tre

RESEARCH ARTICLE

A prospective, multi-center, randomized comparison of iron isomaltoside 1000 versus iron sucrose in patients with iron deficiency anemia; the FERWON-IDA trial

Cumulative dose of iron : 1000 mg

Michael Auerbach[1] | Lars L. Thomsen[5] | Joh

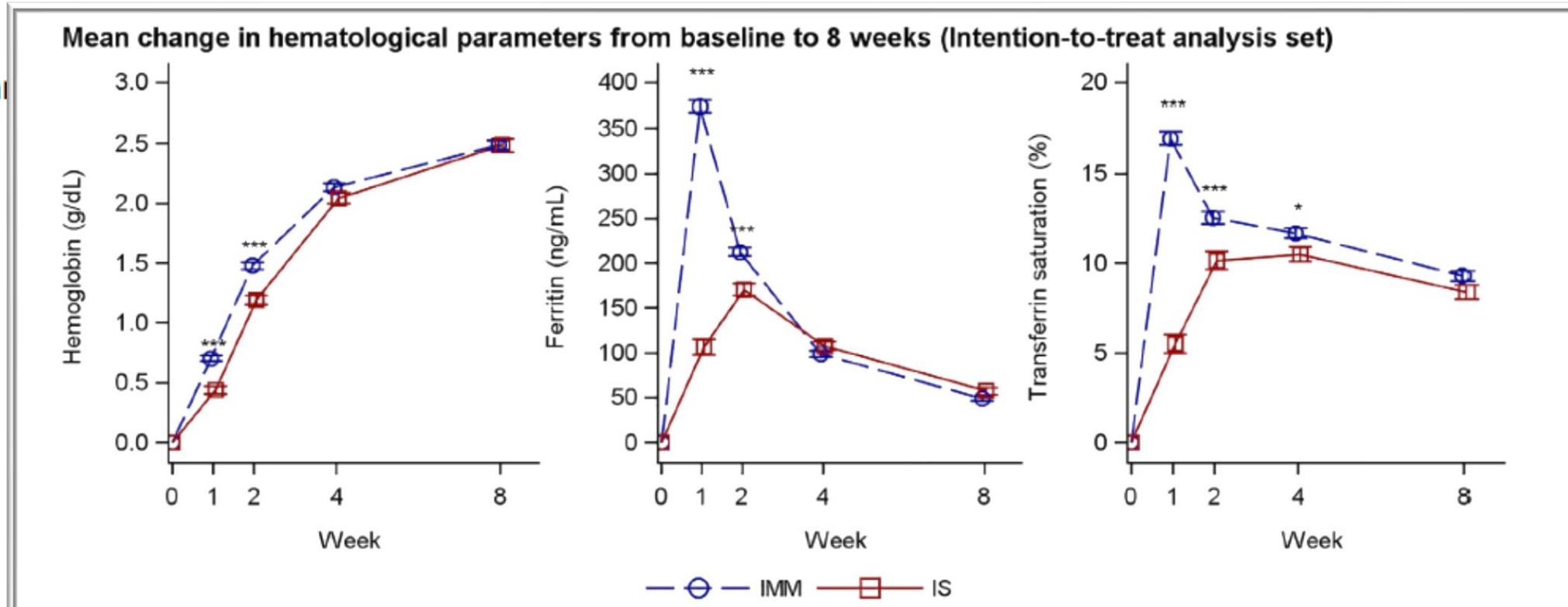
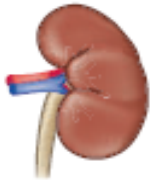
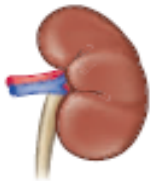
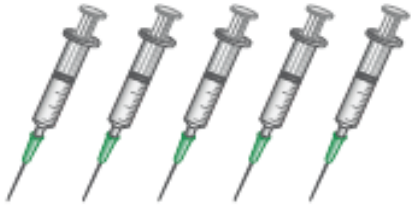


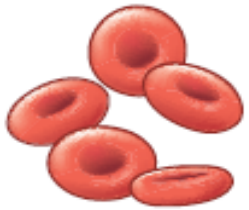
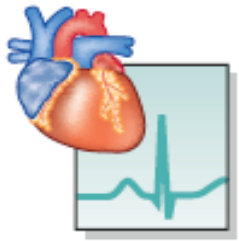
FIGURE 2 Hemoglobin, *s*-ferritin, and transferrin saturation over time by treatment group (intention to treat analysis set). Estimates (mean and SE) from a mixed model with repeated measures with strata, treatment and time as factors, treatment*time and baseline value*time interactions and baseline value as covariate. IMM, iron isomaltoside 1000/ferric derisomaltose; IS, iron sucrose. *$P < .05$, **$P < .001$, ***$P < .001$

GRAPHICAL ABSTRACT

RCT
CKD

In patients with CKD, single high dose iron isomaltoside 1000/ferric derisomaltose has comparable efficacy with fewer cardiovascular events compared to repeated doses of iron sucrose: the FERWON–NEPHRO trial

	CKD	Iron		Hyper-sensitivity	Haemo-globin	CV events
N = 1027 38.4% ♂ 68.3 ± 12.3 years Hb 9.7±1.1 g/dL	 eGFR 35.7 (SD 18.3)	 Iron isomaltoside, 1000 mg; 1 dose	 8 weeks	0.3%	+1.22 g/dL	4.1%
N = 511 35.6% ♂ 69.3 ± 12.3 years Hb 9.7±1.1 g/dL	 eGFR 35.2 (SD 18.6)	 Iron sucrose, 1000 mg; median 5 doses of 200 mg		0% p > 0.05	+1.14 g/dL p = 0.27	6.9% p = 0.025

ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Bhandari, S et al. NDT (2019)
@NDTSocial

Bhandari et al. Nephrol Dial Transplant (2021) 36: 111–120

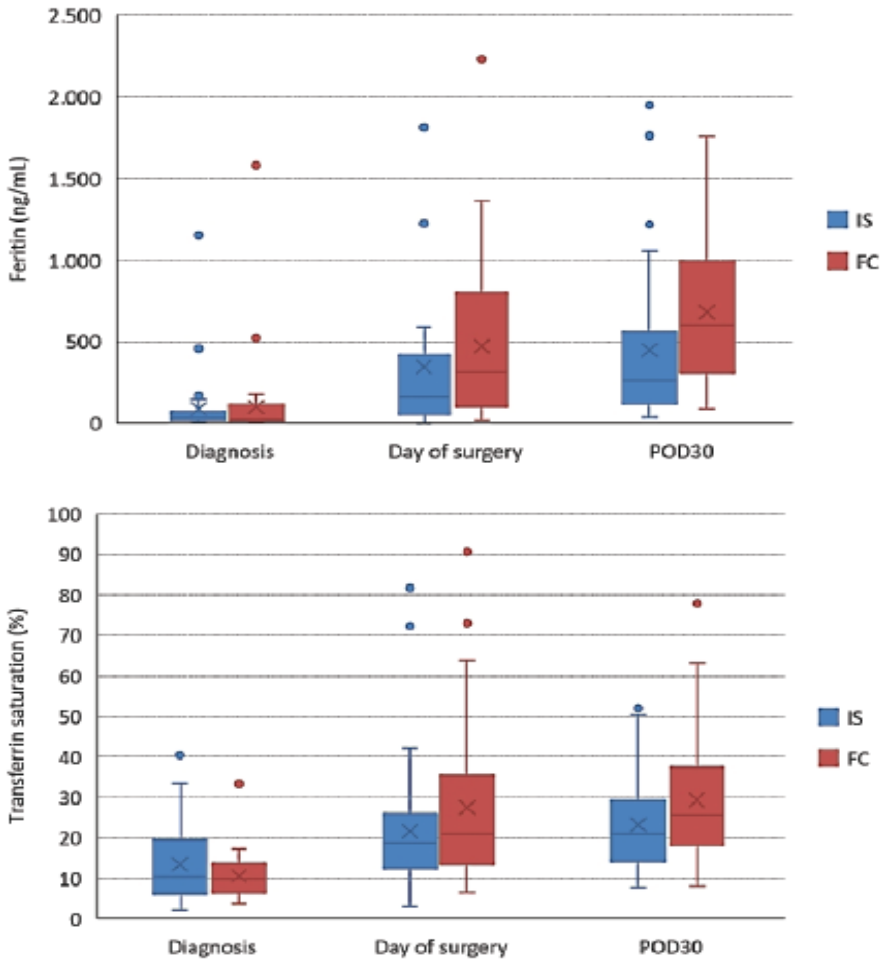


Figure 2 - Ferritin and transferrin saturation at diagnosis of colorectal cancer (CRC), day of surgery, and postoperative day 30 (POD30)
IS: iron sucrose; FC: ferric carboxymaltose.

Table IV - *Surgery complicat and hospital length*

Blood transfusion
Subjects transfused, n (%)
1 unit **2 units** **3 units** **4 units**
Transfusion index*
Infections
Patients with any infection, n (%) **Infection of the surgical wound** **Intra-abdominal abscess** **Urinary tract infection** **Bacteraemia** **Respiratory infection**
Haemorrhagic complications, n (%)
Cardiovascular complications, n (%)
Length of hospital stay (days), mean (SD **All patients** **Transfused patients**

*Units/patient transfused. IS: iron sucrose; FC postoperative day 30; Hb: haemoglobin.

Single-dose intravenous ferric carboxymaltose infusion *versus* multiple fractionated doses of intravenous iron sucrose in the treatment of post-operative anaemia in colorectal cancer patients: a randomised controlled trial

María J. Laso-Morales[1], Roser Vives[2], Elvira Bisbe[3], José A. García-Erce[4,5,6], Manuel Muñoz[7], Fernando Martínez-López[1], Federico Carol-Boeris[1], Caridad Pontes-García[2]

Background - Recent clinical guidelines suggest that treatment of postoperative anaemia in colorectal cancer surgery with intravenous iron reduces transfusion requirements and improves outcomes. The study aimed at comparing two intravenous iron regimens in anaemic patients after colorectal cancer surgery.
Materials and methods - This was a single-centre, open-label, randomised, controlled trial in patients undergoing elective colorectal cancer surgery. Patients with moderate to severe anaemia (haemoglobin [Hb] <11 g/dL) after surgery were randomly assigned 1:1 to receive ferric carboxymaltose (FC; 1,000 mg, single dose) or iron sucrose (IS; 200 mg every 48 hours until covering the total iron deficit or discharge). Randomisation was stratified by Hb level: <10 g/dL (Group A) or ≥10–10.9 (Group B). The primary endpoint was the change in Hb concentration at postoperative day 30. Secondary endpoints included iron status parameters, transfusion requirements, complications, and length of hospital stay.
Results - From September 2015 to May 2018, 104 patients were randomised (FC 50, IS 54). The median intravenous iron dose was 1,000 mg and 600 mg in the FC and IS groups, respectively. There were no between-group differences in mean change in Hb from postoperative day 1 to postoperative day 30 (FC: 2.5 g/dL, 95% CI: 2.1-2.9; IS: 2.4 g/dL, 95% CI: 2.0-2.8; p=0.52), in transfusion requirements or length of stay. The infection rate was lower in the FC group compared with the IS group (9.8% *vs* 37.2%, respectively).
Discussion - The administration of approximately 500 mg of IS resulted in an increase in Hb at postoperative day 30 similar to that of 1,000 mg of FC, but it was associated with a higher infection rate. Future research will be needed to confirm the results, and to choose the best regime in terms of effectiveness and side effects to treat postoperative anaemia in colorectal cancer patients.

Keywords: *postoperative anaemia, colorectal cancer, intravenous iron.*

Laso-Morales MJ et al. Blood Transfus. 2022 Jul;20(4):310-318.

- FCM vs IS
- Dosing
  - ✓The mean iron deficit (Ganzoni) = approximately 1000 mg
  - ✓The median IV iron dose: FCM 1000 mg vs IS 600 mg
- Efficaty
  - Mean Hb increase from POD1 → POD30
  - FCM: +2.5 g/dl, IS:+ 2.4 g/dl
  - No significant differences in transfusion requiremtns
  - ~500 mg IS = 1000 mg FCM in Hb response
- Safety
  - Infection rate: FCM < IS (9.8% vs 37.2%)

Laso-Morales MJ et al. Blood Transfus. 2022 Jul;20(4):310-318.

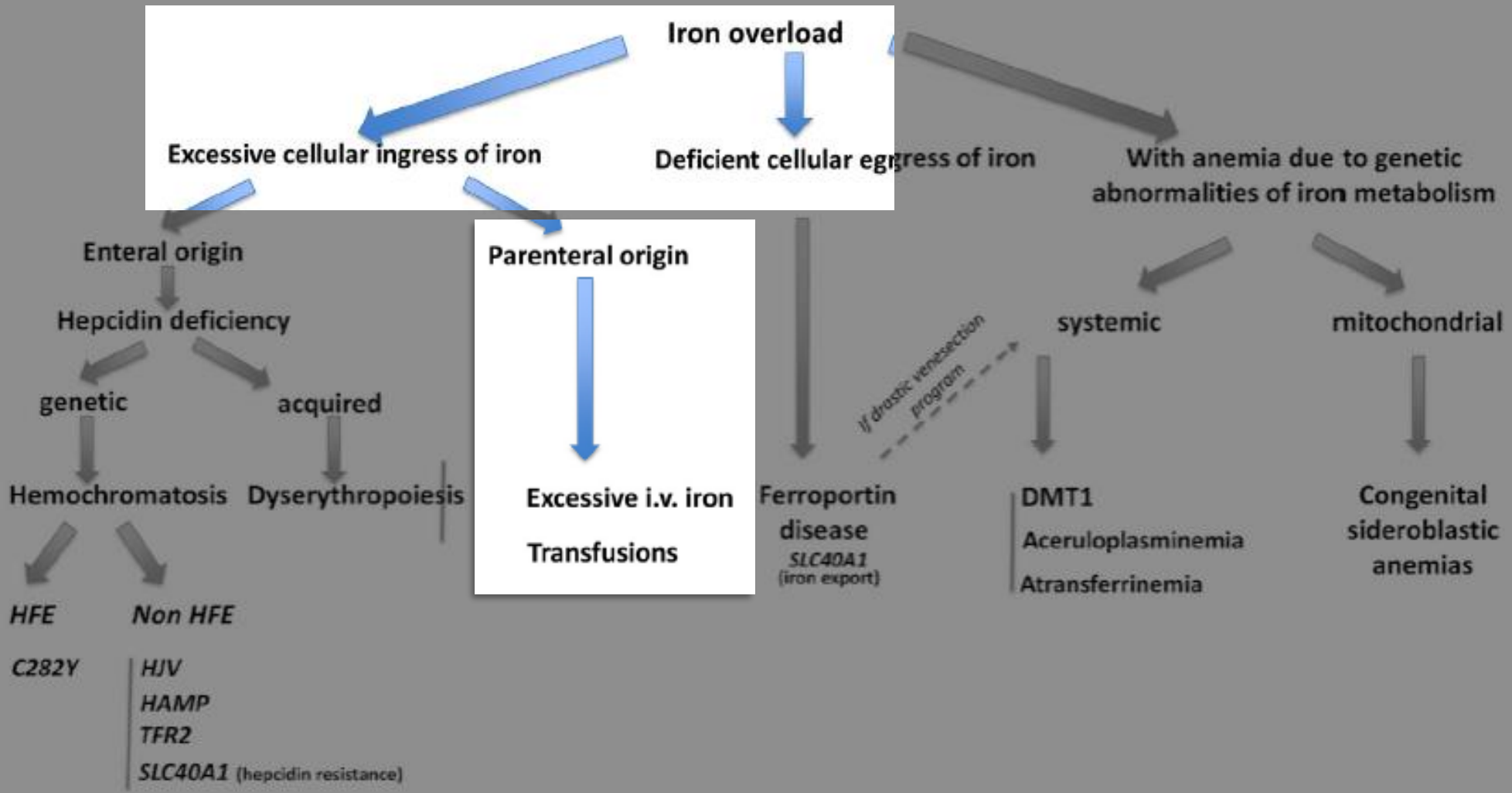


Fig. 4. Pathophysiological classification of iron overload (hematological look). Gene mutations are written in italics. i.v.: intravenous. [21].

Potential safety concerns of IV iron

1. Iron overload and toxicity
2. Infection risk
3. Hypersensitivity reactions
4. Hypophosphatemia

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1 Iron overload and toxicity

➢**Iron overload**

- Condition of increased total body iron content
- Time-dependent risk of organ dysfunction
- Pathologic iron overload: organ injury caused by excess iron

➢TSAT > 45% : non-transferrin bound iron(NTBI) → parenchymal iron deposition

- TSAT > 78-80%
  - Labile plasma iron, reactive plasma iron
  - Generate oxygen radical species

  ➔Damage cell membrane, intracellular organells, DNA

➢Ferritin > 1000 ng/l: liver parenchymal injury

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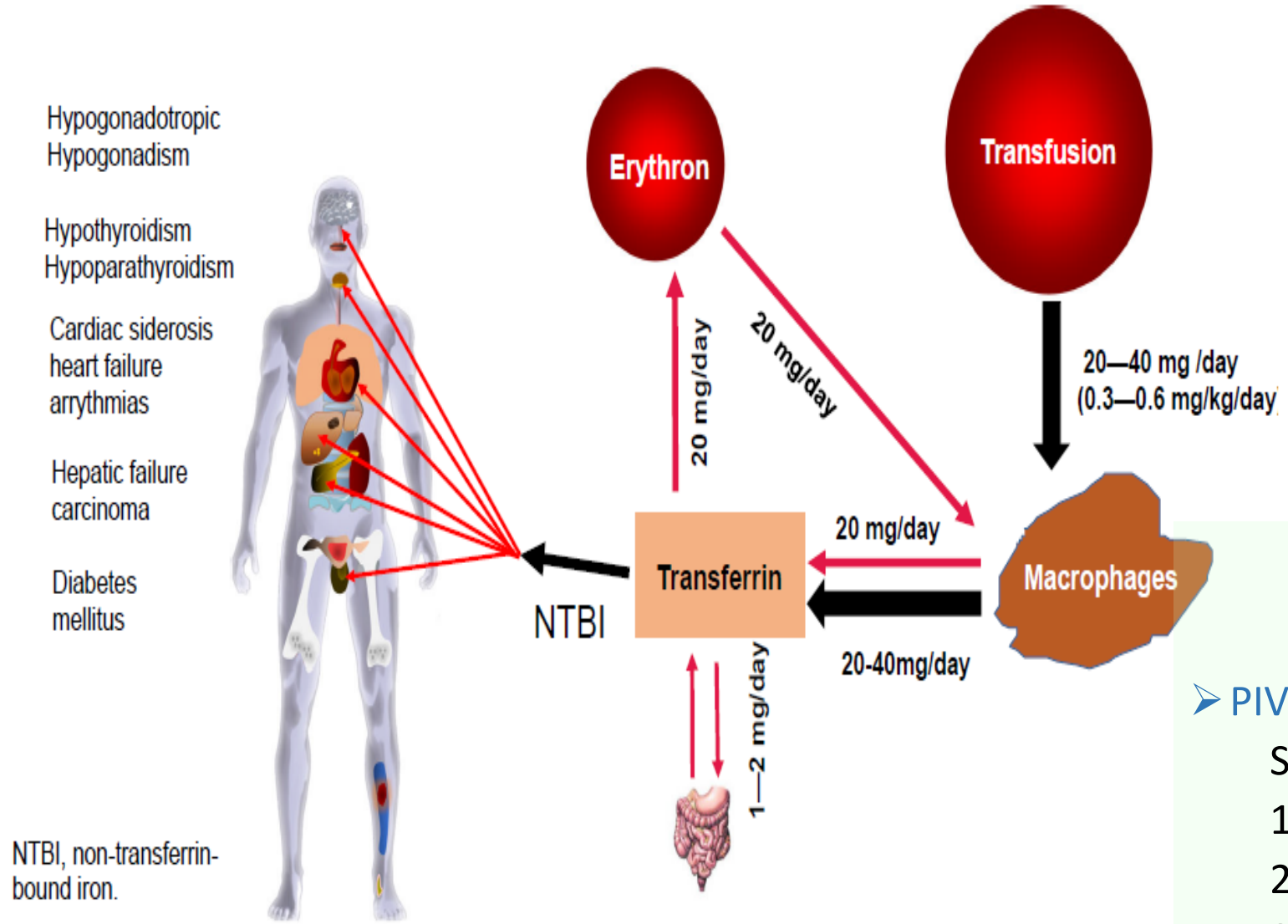


Fig 2. Iron loading and distribution in transfusion-dependent patients. The addition of blood transfusion increases iron for recycling by 20–40 mg/ day. Transferrin once saturated > 70% will result in the development of NTBI which causes end organ.

- PIVOTAL study: ferritin < 400 ng/l, TSAT < 30%

  Stop:

  1) ferritin >200 ng/l + TSAT > 20%
  2) ferritin > 70 ng/l
  3) TSAT ≥ 40%

Safety and efficacy of iron isomaltoside 1000/ferric derisomaltose versus iron sucrose in patients with chronic kidney disease: the FERWON-NEPHRO randomized, open-label, comparative trial

Cumulative dose of iron : 1000 mg

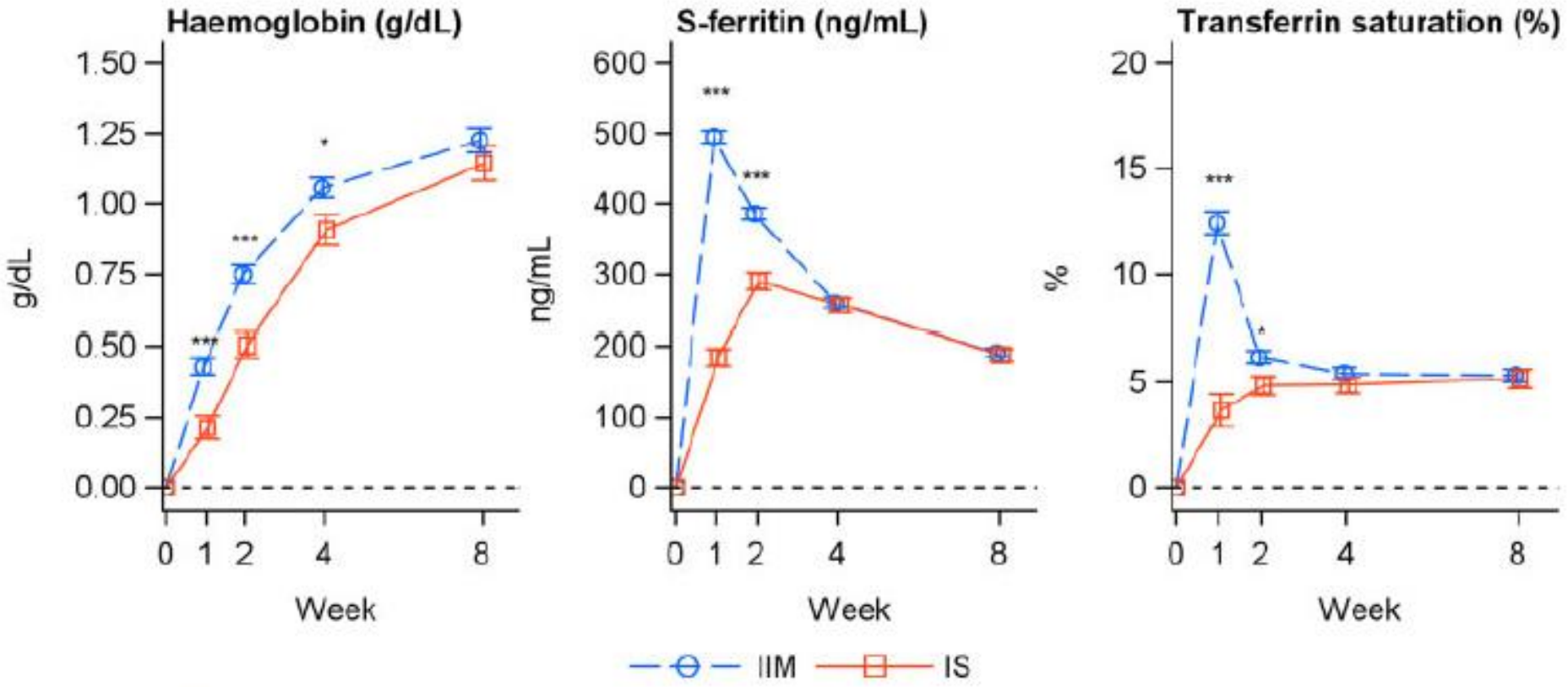


FIGURE 3: Change in Hb (g/dL), serum ferritin (ng/mL) and TSAT (%) from baseline to Weeks 1, 2, 4 and 8 (intention-to-treat analysis set). Estimated (LS mean and SE) from a mixed model with repeated measures with treatment, strata and time as factors, treatment × time and baseline value × time interactions and baseline value as covariate. *P < 0.05; ***P < 0.001.

Bhandari et al. Nephrol Dial Transplant2021 Jan 1;36(1):111-120.

Original Report: Patient-Oriented, Translational Research

Nephrology American Journal of

Am J Nephrol 2018;48:260–268
DOI: 10.1159/000493551

Received: August 11, 2018
Accepted: September 6, 2018
Published online: October 10, 2018

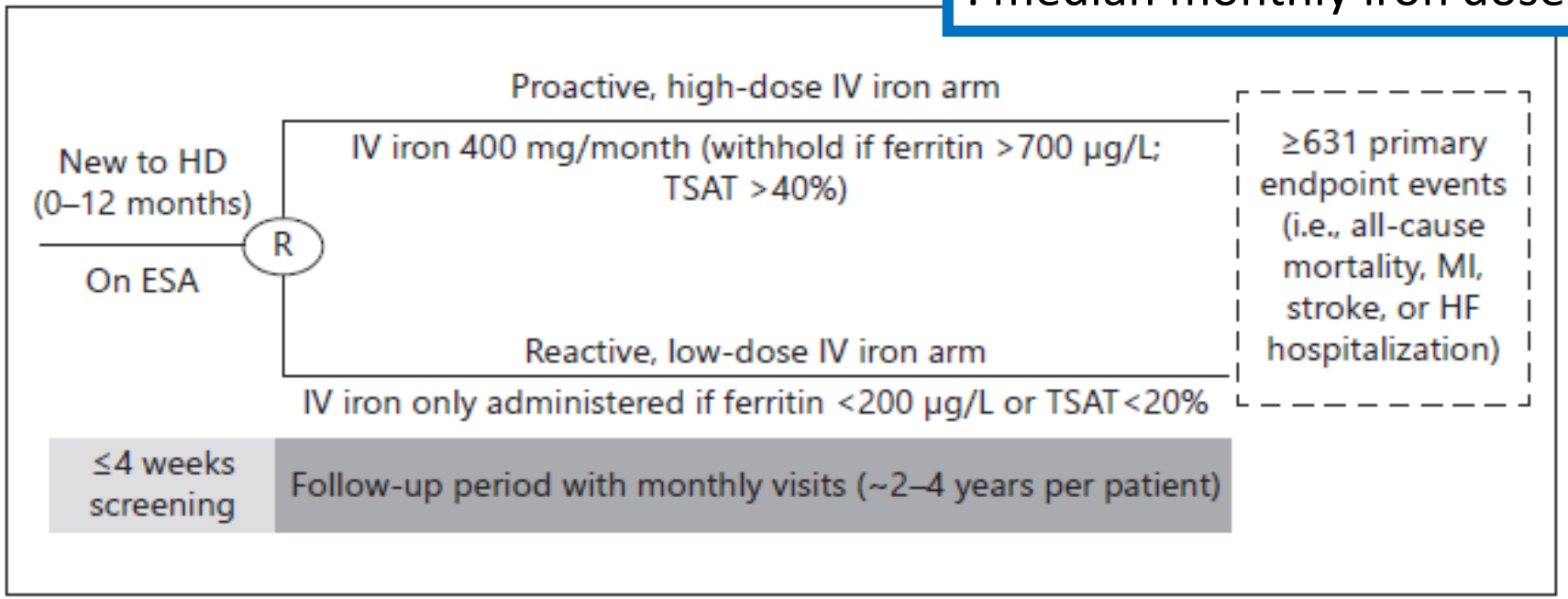
Randomized Trial Comparing Proactive, High-Dose versus Reactive, Low-Dose Intravenous Iron Supplementation in Hemodialysis (PIVOTAL): Study Design and Baseline Data

- Monthly assessments of serum ferritin and TSAT
- Proactive, High-dose group

: median monthly iron dose: 264 mg [200-336]

- Restrictive, Low-dose group

: median monthly iron dose: 145 mg/ [100-190]



(ESA) were eligible. Enrolled patients were randomized to a proactive, high-dose IV iron arm (iron sucrose 400 mg/month

low-up is 2–4 years. ***Results:*** Of the 2,589 patients screened across 50 UK sites, 2,141 (83%) were randomized. At base-

1 Iron overload and toxicity

- Cardiovascular risk
  - Atherosclerosis
  - Arterial remodeling
- Hepcidin and CV risk
  - Mechanism
  - ↑Hepcidin: prevent mobilization of iron from macrophages
  - Monocyte chemoattractant protein-1 release
  - Promotes vascular damage, especially in metabolic disease

2 Infection risk and IV iron

- Microbial growth
- Promotes proliferation & pathogenicity of bacteria, viruses, parasites, helminths, and fungi
- Clinical evidence
  - Controversial results: some show ↑ or no significant association

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Sinead Stoneman did a nice visual abstract for this week's discussion.

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis.

Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, et al.
N Engl J Med. 2019 31;380(5):447-458.

#NephJC

2141

- Adults with ESKD
- On hemodialysis ≤ 12 months
- Ferritin < 400 µg/L TSAT < 30%
- Receiving ESA

PROACTIVE

IRON SUCROSE 400 mg → HELD IF ABOVE → Monthly labs Ferritin 700 µg/L TSAT 40%

1093

29%

Composite Primary Outcome: Death, MI, Stroke, Heart Failure

29,757 IU
Median monthly ESA dose

967
Total RCC units transfused

P<0.001 for non-inferiority

REACTIVE

IRON SUCROSE 0-400 mg → TO MAINTAIN → Monthly labs Ferritin 200 µg/L TSAT 20%

1048

32%

Composite Primary Outcome: Death, MI, Stroke, Heart Failure

38,805 IU
Median monthly ESA dose

1122
Total RCC units transfused

@Stones__

Nephrol Dial Transplant (201
doi: 10.1093/ndt/gft251
Advance Access publication 2

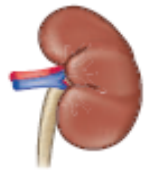
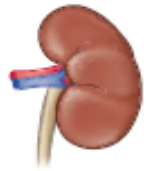
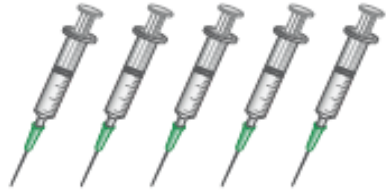
Original Art

Ferric carbo
and impaire

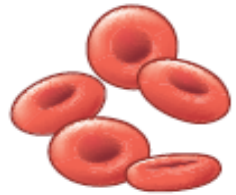
GRAPHICAL ABSTRACT

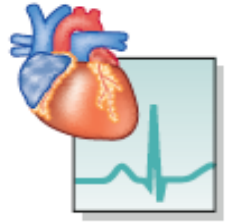
RCT CKD

In patients with CKD, single high dose iron isomaltoside 1000/ferric derisomaltose has comparable efficacy with fewer cardiovascular events compared to repeated doses of iron sucrose: the FERWON–NEPHRO trial

	CKD	Iron	Hyper-sensitivity	Haemo-globin	CV events
N = 1027 38.4% ♂ 68.3 ± 12.3 years Hb 9.7±1.1 g/dL	 eGFR 35.7 (SD 18.3)	 Iron isomaltoside, 1000 mg; 1 dose	0.3%	+1.22 g/dL	4.1%
N = 511 35.6% ♂ 69.3 ± 12.3 years Hb 9.7±1.1 g/dL	 eGFR 35.2 (SD 18.6)	 Iron sucrose, 1000 mg; median 5 doses of 200 mg	0% p > 0.05	+1.14 g/dL p = 0.27	6.9% p = 0.025

8 weeks





ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Bhandari, S et al. NDT (2019)
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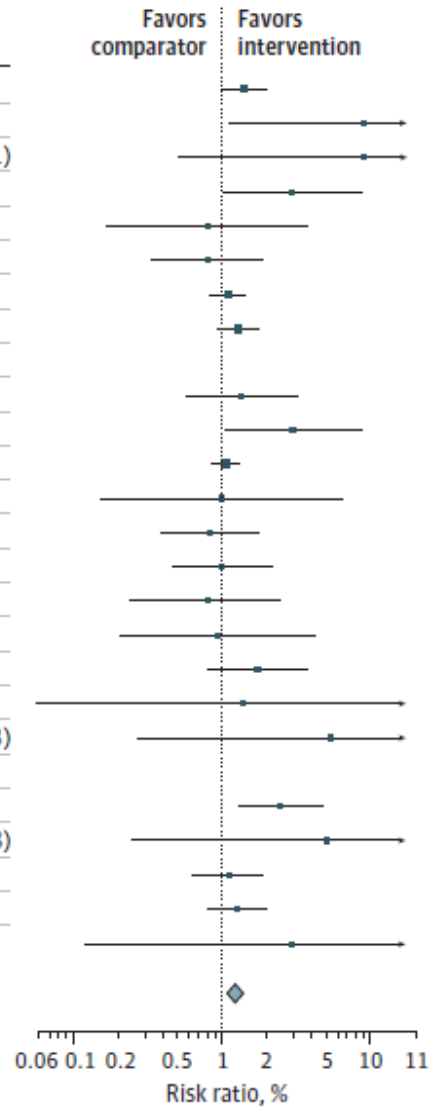
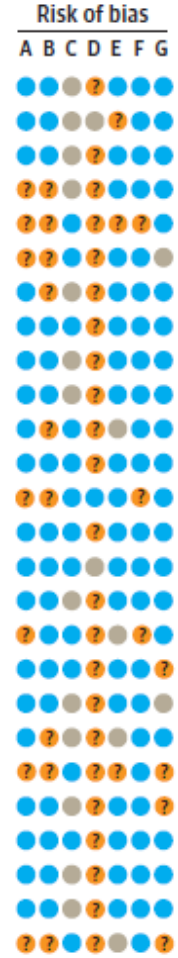
Figure 2. Association Between Risk of Infection and Intravenous Iron When Compared With Oral Iron

Study	Experimental No. of events	Experimental Total No.	Control No. of events	Control Total No.	Risk ratio (95% CI)	Weight, %
Agarwal et al,[34] 2015	37	67	27	69	1.41 (0.98-2.03)	10.6
Bencaiova et al,[53] 2009	9	130	1	130	9.00 (1.16-70.03)	0.4
Bisbe et al,[61] 2014	4	60	0	62	9.30 (0.51-169.01)	0.2
Breymann et al,[63] 2008	19	277	4	177	3.04 (1.05-8.77)	1.6
Fishbane et al,[86] 1995	2	25	5	50	0.80 (0.17-3.84)	0.8
Henry et al,[95] 2007	6	41	16	88	0.80 (0.34-1.91)	2.4
Kalra et al,[100] 2016	56	112	53	117	1.10 (0.84-1.45)	15.8
Keeler et al,[103] 2017	36	55	31	61	1.29 (0.94-1.76)	13.2
Khalafallah et al,[105] 2010	0	92	0	91	Not estimable	
Kulnigg et al,[114] 2008	18	137	6	63	1.38 (0.58-3.31)	2.4
Lindgren et al,[118] 2009	12	45	4	46	3.07 (1.07-8.80)	1.6
MacDougall et al,[120] 2014	114	304	111	312	1.05 (0.86-1.30)	21.2
Meyer et al,[124] 1996	2	21	2	21	1.00 (0.16-6.45)	0.5
Mudge et al,[128] 2012	10	51	12	51	0.83 (0.40-1.75)	3.2
Neogi et al,[132] 2019	13	934	13	947	1.01 (0.47-2.18)	3.0
Padmanabhan et al,[138] 2019	4	20	5	20	0.80 (0.25-2.55)	1.4
Pollak et al,[143] 2001	2	10	4	19	0.95 (0.21-4.32)	0.8
Qunibi et al,[148] 2011	20	147	8	103	1.75 (0.80-3.82)	2.9
Reinisch et al,[150] 2013	1	233	0	109	1.41 (0.06-34.34)	0.2
Schröder et al,[155] 2005	2	22	0	24	5.43 (0.28-107.33)	0.2
Singh et al,[161] 1998	0	30	0	30	Not estimable	
Steensma et al,[165] 2011	28	164	11	163	2.53 (1.30-4.91)	3.9
Van Wyck et al,[175] 2005	2	79	0	82	5.19 (0.25-106.38)	0.2
Van Wyck et al,[174] 2007	24	174	22	178	1.12 (0.65-1.91)	5.6
Vanobberghen et al,[176] 2021	32	114	25	116	1.30 (0.83-2.05)	7.5
Verma et al,[184] 2011	1	75	0	75	3.00 (0.12-72.49)	0.2
Total (95% CI)		**3419**		**3204**	**1.26 (1.09-1.44)**	**100.0**
Total events	**454**		**360**			

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 26.04$, $df = 23$ ($P = .30$); $I^2 = 12\%$
Test for overall effect: $z = 3.24$ ($P = .001$)
Test for subgroup differences: not applicable





A Random sequence generation (selection bias)
B Allocation concealment (selection bias)
C Blinding of participants and personnel (performance bias)
D Blinding of outcome assessment (detection bias)
E Incomplete outcome data (attrition bias)
F Selective reporting (reporting bias)
G Other bias

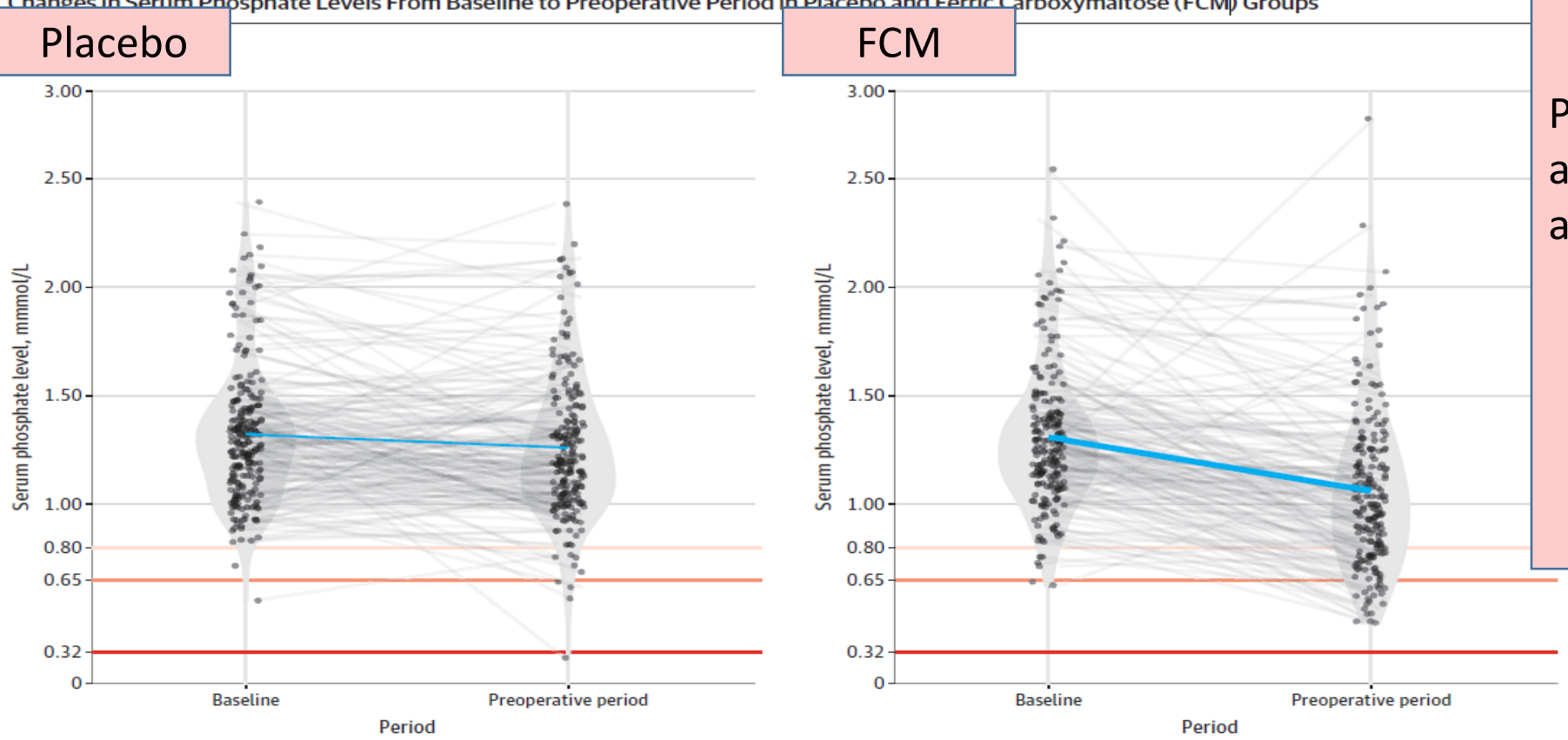
Potential safety concerns of IV iron

1. Iron overload, toxicity
2. Infection risk
3. Hypersensitivity reactions

31

4 Hypophosphatemia

Figure. Changes in Serum Phosphate Levels From Baseline to Preoperative Period in Placebo and Ferric Carboxymaltose (FCM) Groups



This figure displays the changes in serum phosphate levels from baseline to the preoperative period for both the placebo (A) and FCM treatment (B) groups. Each black dot represents an individual participant's serum phosphate level at baseline and the preoperative period. The gray lines connect the baseline and preoperative values for each participant, with a mean line (blue) showing the trend of serum phosphate changes within individuals. The horizontal lines indicate critical thresholds of serum phosphate levels: tan indicates moderate hypophosphatemia at <0.80 mmol/L; orange, mild at <0.65 mmol/L; and red, severe at <0.32 mmol/L.

JAMA Network Open. 2025;8(4):e253093. doi:10.1001/jamanetworkopen.2025.3093 April 17, 2025 1/4

PREVENTT study

Preoperative treatment for anemia before major open abdominal surgery

IV FCM 1000 mg (n = 244)

Placebo (saline) (n = 243)

4 Hypophosphatemia

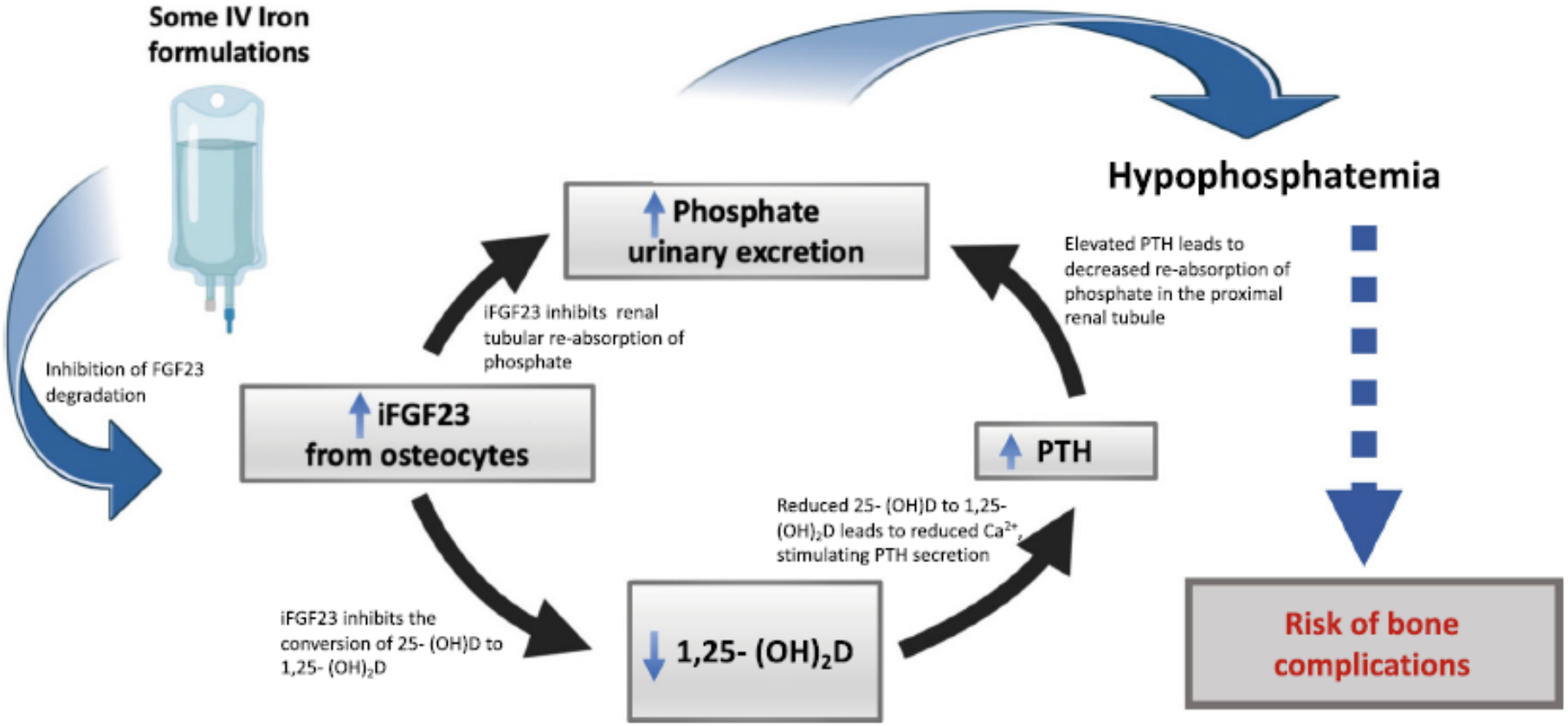
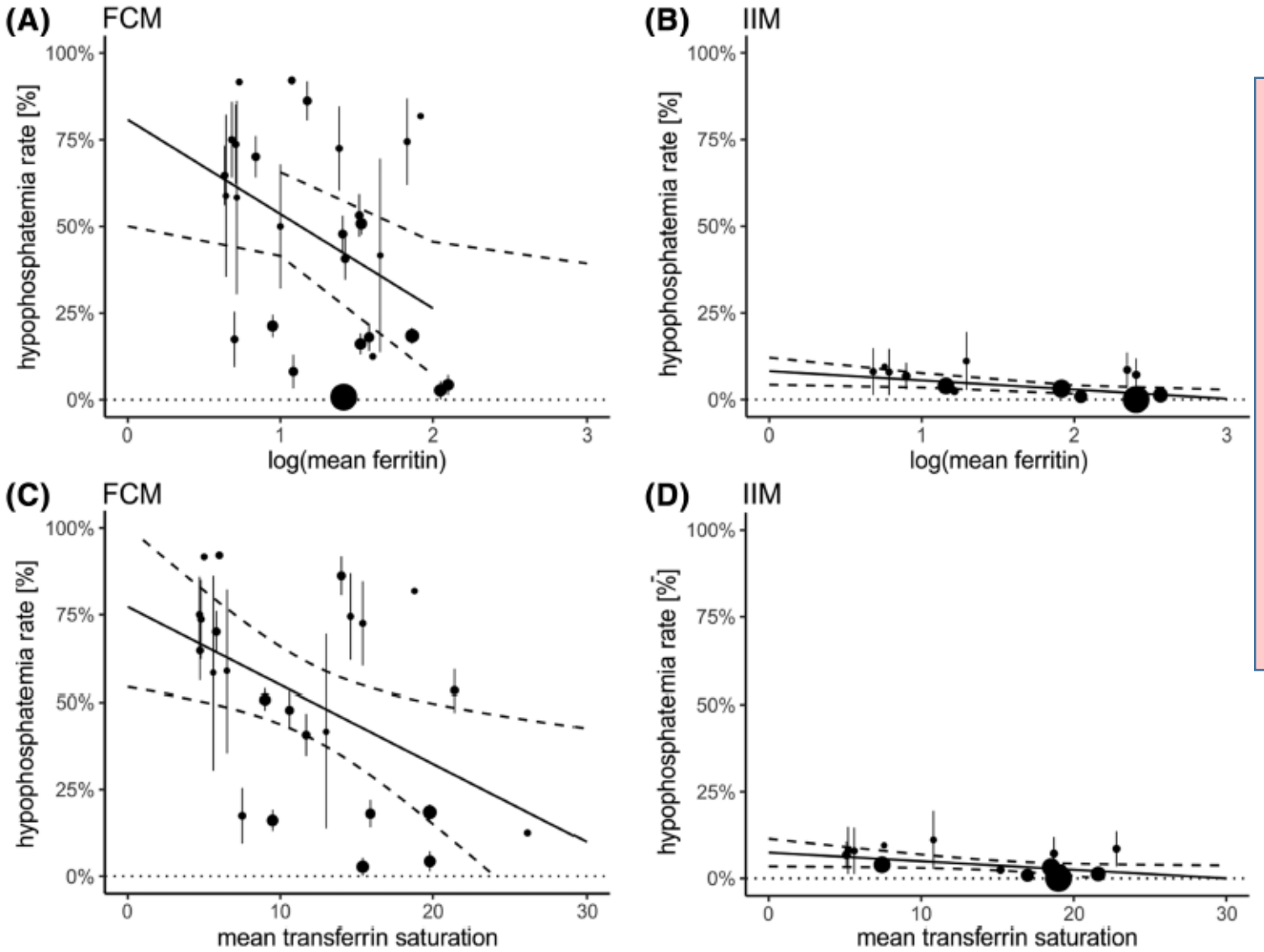


FIGURE 3 Mechanism of treatment- emergent hypophosphatemia, adapted from Blumenstein et al.[64] iFGF23, intact fibroblast growth fact 23. Following administration of some intravenous iron formulations there is a sharp rise in the plasma intact FGF23 (iFGF23) which triggers a pathophysiological cascade of renal phosphate wasting, calcitriol deficiency, and secondary hyperparathyroidism frequently culminating in hypophosphatemia even after iFGF23 levels have normalized. [Color figure can be viewed at wileyonlinelibrary.com]



Risk factors

- ✓ FCM > IIM or FID
- ✓ Low baseline ferritin & TSAT

FIGURE 4 Meta regression of hypophosphataemia rate in relation to either log (mean ferritin) (A,B) or mean transferrin saturation (C,D) in studies on FCM (A,C) or IIM (B,D). Numerical outputs are reported in Table S1

- Initial high-dose IV iron
  - Faster correction of deficits
  - Improving erythropoiesis

- Multiple low-dose iv iron
  - Similar Hb response
  - Lower convenience & compliance

- Iron deficiency: ↓ Physiologic reserve, ↓ Iron overload risk

- Follow-up

Iron deficit dose in clinical studies

The required dose to replace the iron deficit is usually > 1000 mg

Study	Patient population	Calculated mean iron deficit based on the modified Ganzoni Formula (mg)	SD	No. of patients
Van Wyck et al	Postpartum	1458	330	182
Van Wyck et al	Heavy ut.bleeding	1608	383	251
Seid et al	Postpartum	1539	351	143
Barish et al	IDA various etiologies	1520	342	348
Hussain et al	IDA various etiologies	1508	359	161

Koch et al. Anemia. 2015, article ID 763576, 10 pages

Patient population	Treatment	Calculated mean iron deficit (mg)	SD	No. of patients	Total mean (mg)
IDA various etiologies	1500 mg IV iron vs Oral iron	1340 vs 1344	356 vs 360	246 vs 253	1496
	1500 mg IV iron vs IV standard of care	1600 vs 1703	460 vs 482	252 vs 245	
NDD-CKD (REPAIR-IDA)	1500 mg IV iron vs 1000 mg IV iron	1355 vs 1349	401 vs 403	1275 vs 1285	1352
Overall mean		1392		3556	

Koch et al. Anemia. 2015, article ID 763576, 10 pages

Nephrol Dial Transplant (2014) 29: 833–842
doi: 10.1093/ndt/gft251
Advance Access publication 20 August 2013

ndt
Nephrology Dialysis Transplantation

Original Articles

Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial

Jane E. Onken[1], David B. Bregman[2], Robert A. Harrington[1,3], David Morris[4], John Buerkert[5], Douglas Hamerski[6], Hussain Iftikhar[7], Roberto Mangoo-Karim[8], Edouard R. Martin[9], Carlos O. Martinez[10], George Edward Newman[11], Wajeh Y. Qunibi[12], Dennis L. Ross[13], Bhupinder Singh[14], Mark T. Smith[15], Angelia Butcher[16], Todd A. Koch[16] and Lawrence T. Goodnough[3,17]

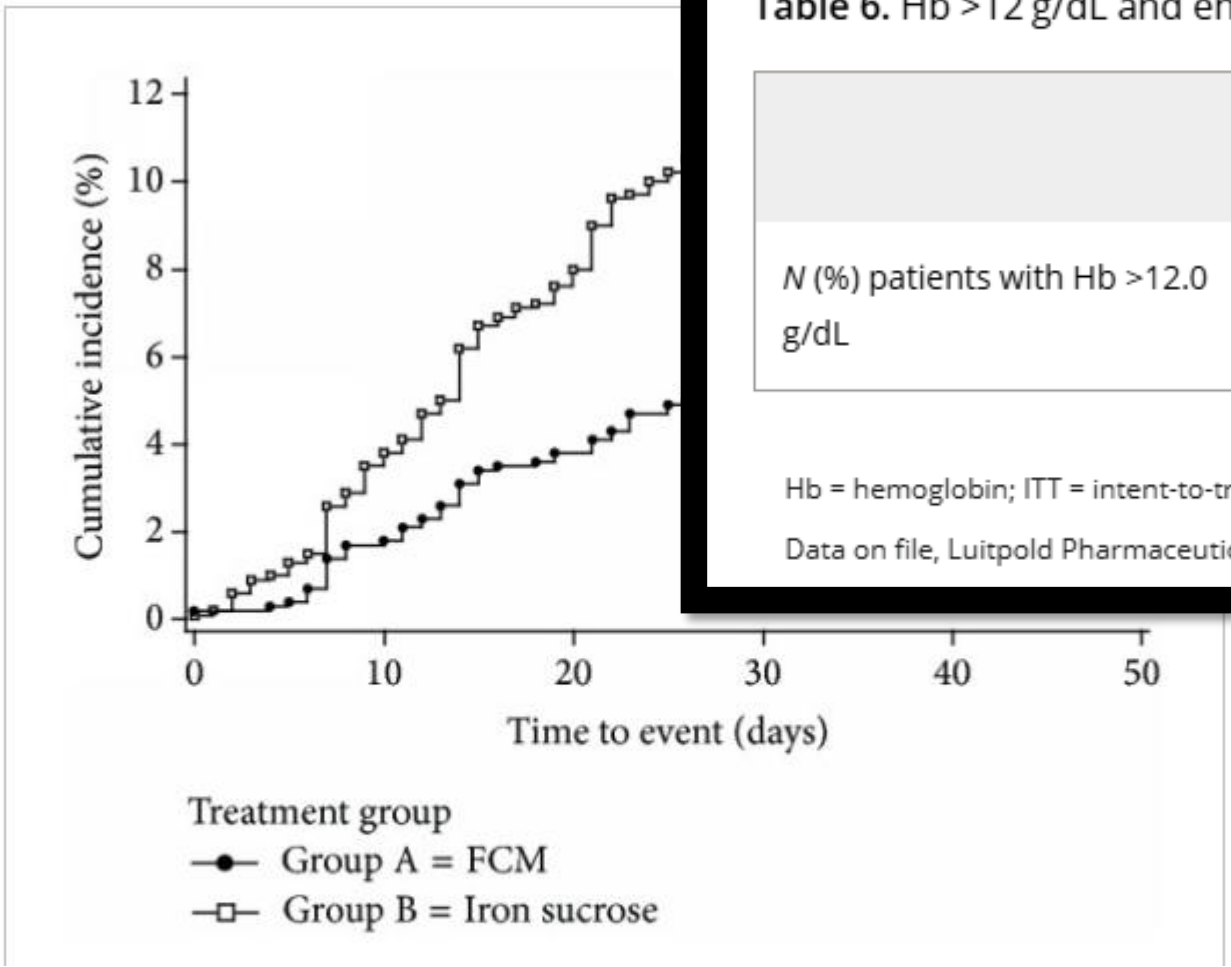


Table 6. Hb >12 g/dL and end of treatment (Day 56) from clinical Study 7 (ITT population).

	1500 mg IV iron (*n* = 1249)	1000 mg IV iron (*n* = 1244)	*p* value
N (%) patients with Hb >12.0 g/dL	265 (24.4%)	169 (15.6%)	*p* = 0.001

Hb = hemoglobin; ITT = intent-to-treat.

Data on file, Luitpold Pharmaceuticals, Inc.

Hb < 11 g/dl + ferritin ≤ 100 ng/ml
or ferritin ≤ 300 + TSAT <30%

Table 5. Retreatment between Days 56–90 in clinical Study 7 (Safety Population).

	1500 mg IV iron (*n* = 1276)	1000 mg IV iron (*n* = 1285)	*p* value
N (%) patients retreated	71 (5.6%)	142 (11.1%)	*p* < 0.001

Koch et al. Anemia. 2015, article ID 763576, 10 pages

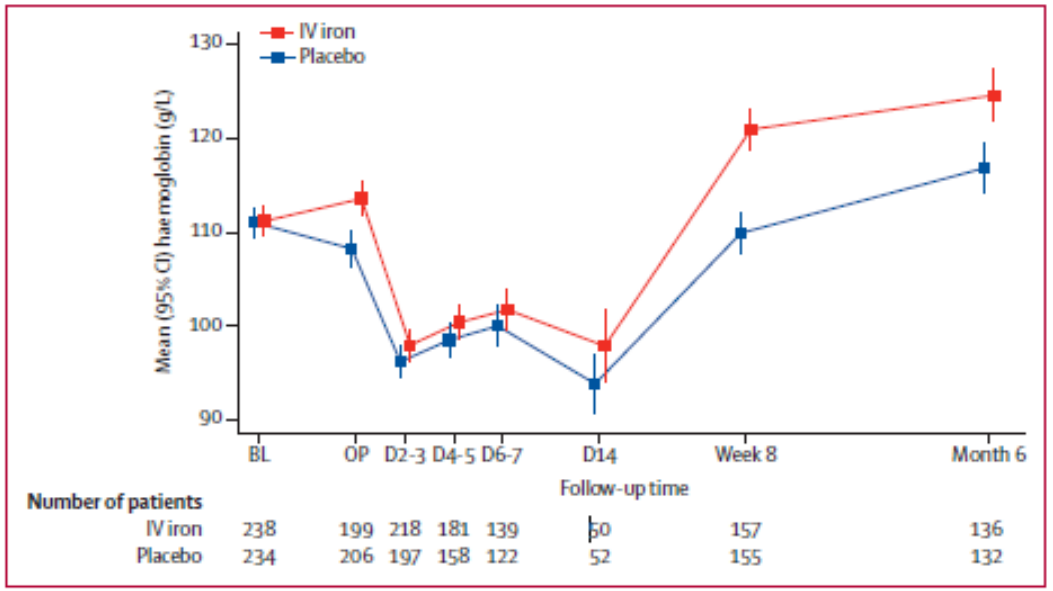


Figure 2: **Mean haemoglobin concentrations of the trial participants by randomised treatment group**
Error bars show 95% CI. BL=baseline prerandomised treatment. OP=day of operation before surgery. D=day post operation (eg, D2–3=day 2 or 3 post operation). D2–3, D4–5, D6–7, and D14 measurements are only available for patients still hospitalised at that time. IV=intravenous.

Lancet 2020; 396: 1353–61

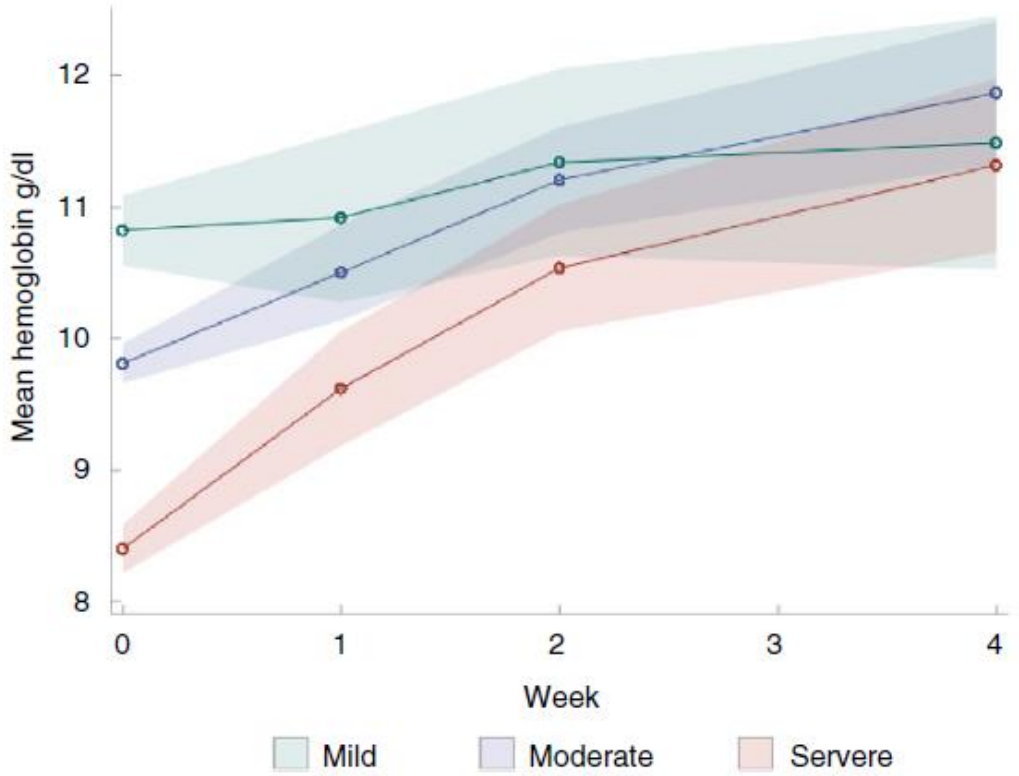
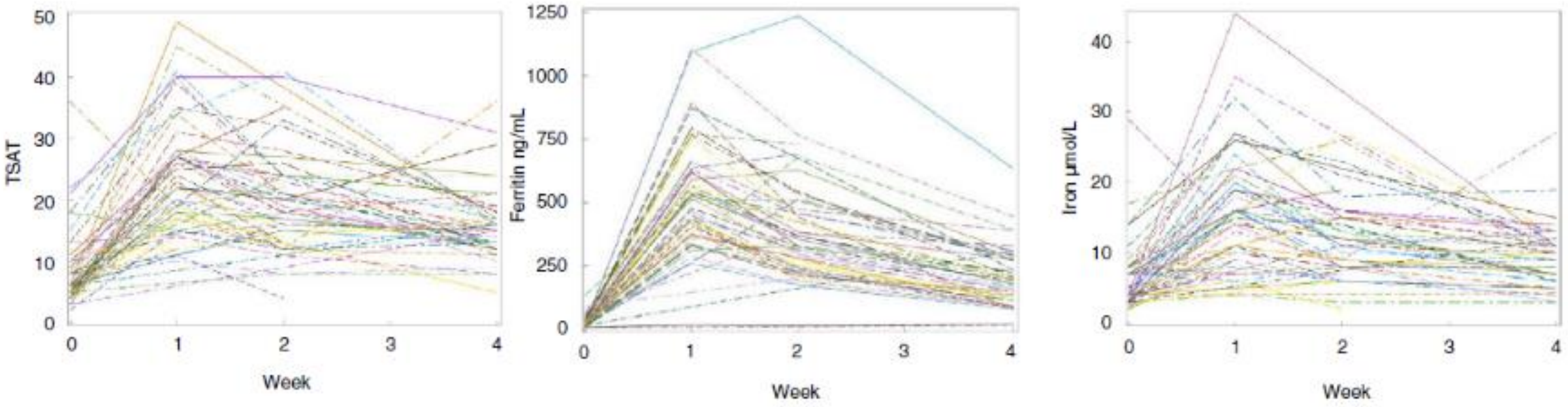


FIGURE 3 The means of the increase in haemoglobin over time depending on the severity of anaemia at baseline with 95% confidence intervals. *x*-axis: time in weeks. *y*-axis: haemoglobin in g/dl. Green, mild (>10.31 g/dl); blue, moderate (9.02–10.31 g/dl); red, severe (<9.02 g/dl). 95% confidence interval marked by the opaque area

Colorectal Disease. 2021;23:2550–2558

The dynamic effects of preoperative intravenous iron in anaemic patients undergoing surgery for colorectal cancer

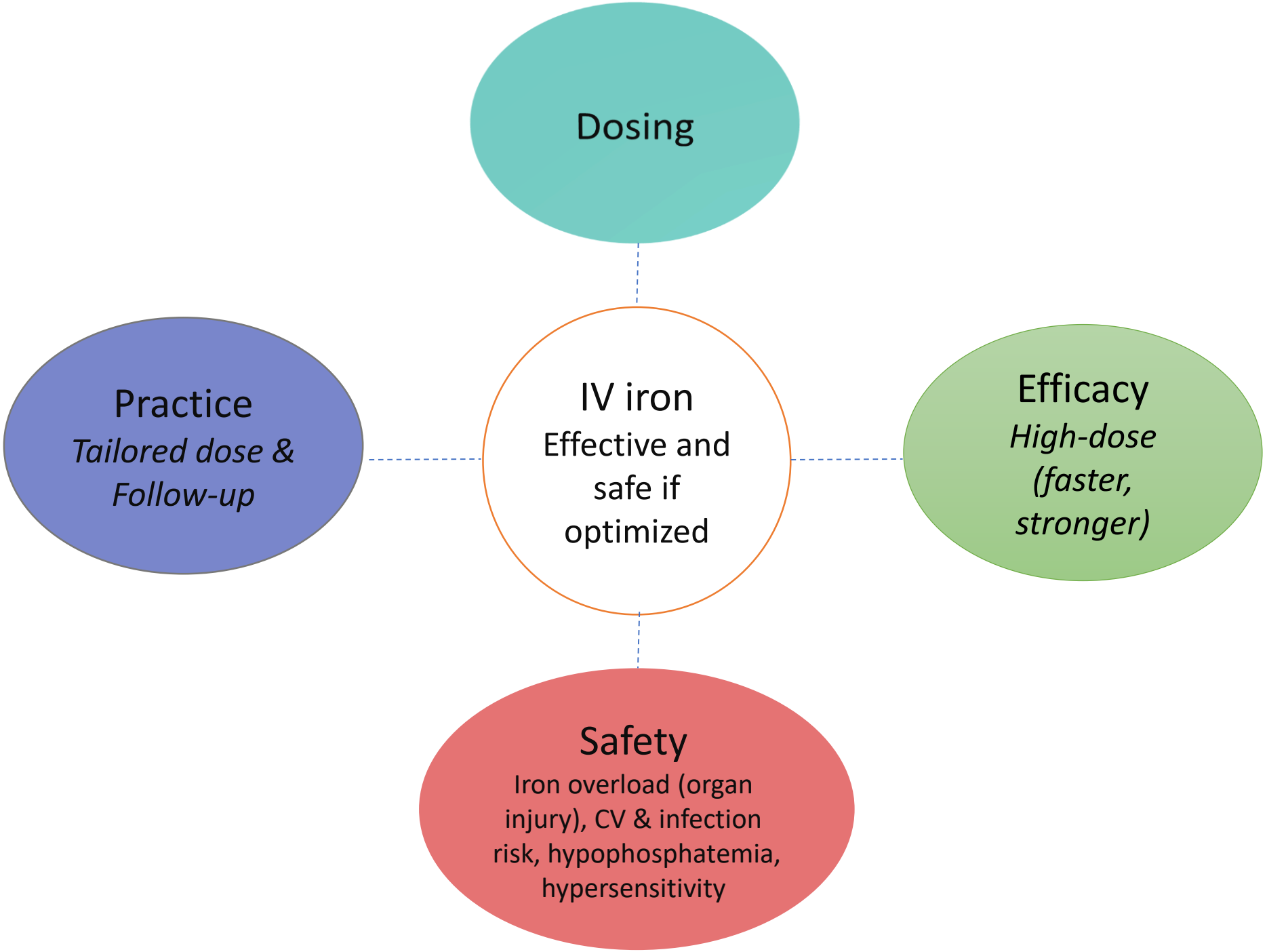
Rasmus Dahlin Bojesen[1,2] | Jens Ravn Eriksen[3] | Rasmus Peuliche Vogelsang[2] |



Hb, weight adjusted dose + 20 mg/kg
Iron isomaltoside: median dose of 1500 mg

saturation (TSAT), ferritin and iron over time. Each patient is
bin in g/dl, TSAT in percentage, ferritin in ng/ml and iron in µmol/l

Colorectal Disease. 2021;23:2550–2558


Dosing
Practice
Tailored dose & Follow-up
IV iron
Effective and safe if optimized
Efficacy
High-dose (faster, stronger)
Safety
Iron overload (organ injury), CV & infection risk, hypophosphatemia, hypersensitivity