Safety of Intravenous Iron

AIM for the future

AIM FOR THE FUTURE 2015

Michael Auerbach MD, FACP

- Private Practice, Baltimore, Maryland
- Clinical Professor of Medicine
- Georgetown University School of Medicine

Intravenous Iron: history, administration, safety and efficacy

Michael Auerbach, MD, FACP
Private Practice, Baltimore, Maryland
Clinical Professor of Medicine
Georgetown University School of Medicine
Washington, DC

Disclosures

- This presentation contains published studies of unapproved methods of administration

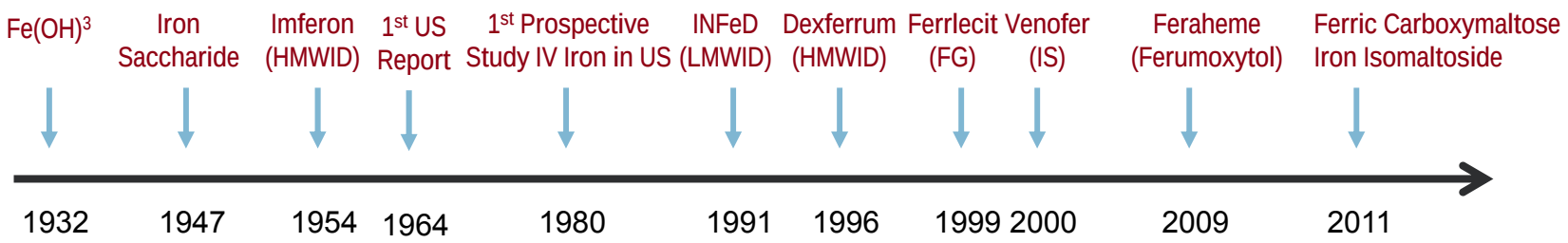
Disclosures

- I have no financial disclosures

My Experience since 1986

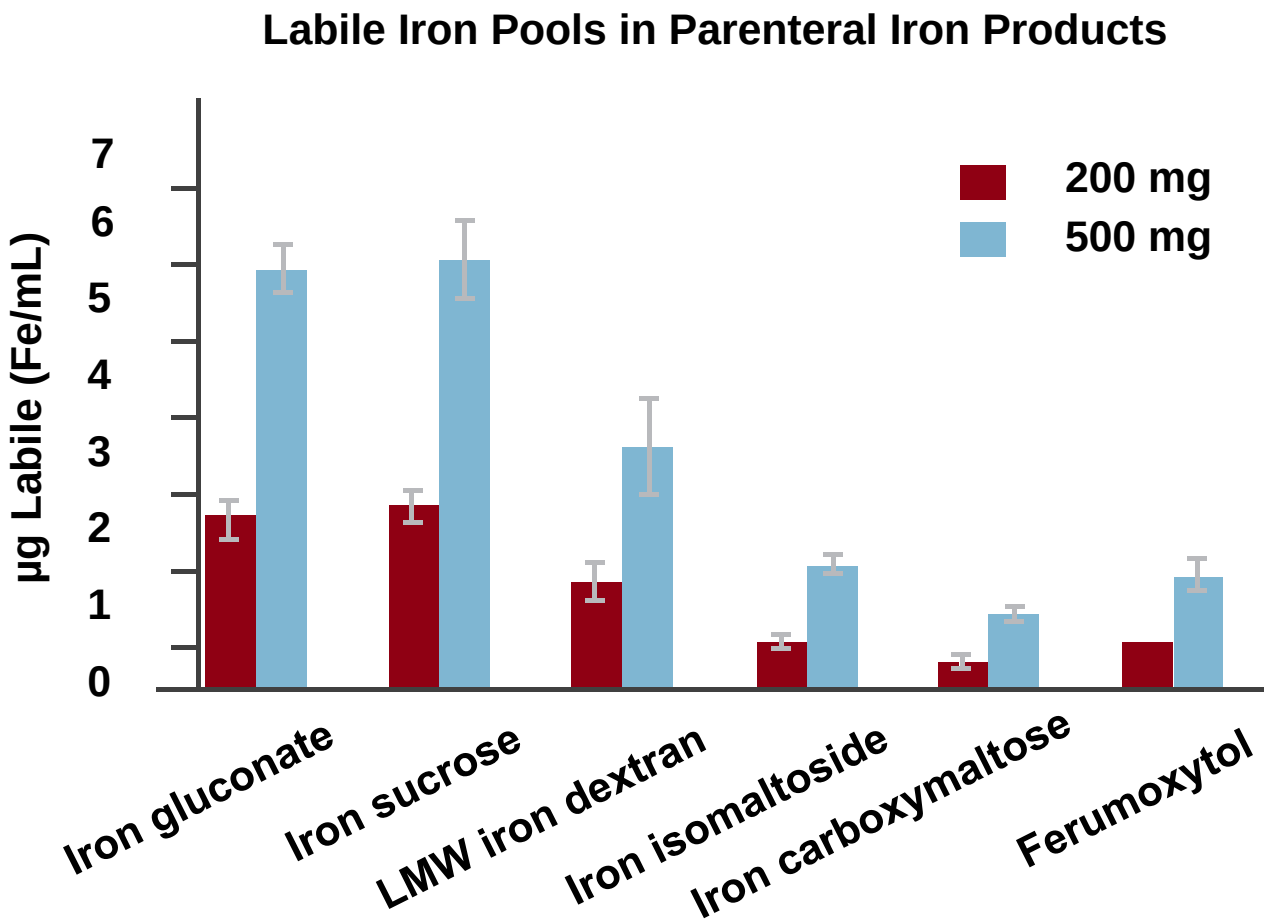
- >30,000 treated patients
- >1700 gravidas
- Data based on use of all formulations except HMW iron dextran
- About 1:200 minor infusion reactions
- Zero SAEs

History of IV Iron



FG = ferric gluconate. HMWID = high-molecular-weight iron dextran. IS = iron sucrose. IV = intravenous. LMWID = low-molecular-weight iron dextran.

Labile Iron Content in Parenteral Iron Products



Jahn MR, et al. *Eur J Pharm Biopharm*. 2011;78:480-491.

Comparative Studies

- 2 prospective studies: LMWID and iron sucrose[1,2]
- 1 meta-analysis[3]
- 1 prospective study: Iron sucrose and ferumoxytol[4]
- 1 retrospective study: all but HMWID[5]
- No statistically significant difference in AEs

1. Moniem KA, Bhandari S. *TATM*. 2007;9:37-42. 2. Sav T, et al. *Ren Fail*. 2007;29:423-426. 3. Critchley J, Dundar Y. *TATM*. 2007;9:8-36
4. MacDougall I, et al. *J Am Soc Nephorol.* 2011; Abstract LB-PO3156. 5. Okam MM, et al. *Am J Hematol.* 2012;87:E123-E124.

Comparative Rates of AEs with Different Formulations of IV Iron: Methods

- A retrospective review was performed of all adult patients (age ≥18 years) who received IV iron at the Dana-Faber/Brigham and Women's Cancer Center from April 1, 2008 to March 31, 2010
- Patients on dialysis were excluded
- Occurrence of AEs and management of AEs were obtained from nursing records
- Each administration of LMWID or HMWID was preceded by a test dose followed by a 1-hour observation, and a full-dose of 1-2 g of LMWID or HMWID was completed over a 2.5–3-hour period
- AEs were defined as any undesirable sign, symptom, medical condition, or experience occurring during or shortly after IV iron administration

Okam MM, et al. *Am J Hematol.* 2012;87:E123-E124.

Comparative Rates of AEs with Different Formulations of IV Iron: Conclusions

- The mean age of patients was 50.7 years; 619 unique patients received at least 1 treatment cycle of IV iron, and a total of 3174 infusions of IV iron were given
- All AEs were mild to moderate, and no severe AEs or anaphylactic-type reactions were noted; all were easily managed, and none were complicated by long-term sequelae
- In a multivariate model with AEs as outcome, there was no difference between LMWID and ferric gluconate; however, iron sucrose had a significantly higher odds ratio for AEs

	HMWID (Dexferrum)	Ferric gluconate	LMWID (INFeD)	Iron sucrose
Number of patients (%)	**9 (1.5)**	**393 (63.5)**	**121 (19.5)**	**96 (15.5)**
AEs	**4 (44.4)**	**12 (3.6)**	**3 (2.5)**	**11 (11.5)**
Urticaria/rash	**3**	**1**	**3**	**2**
Chest pressure/pain	**1**	**1**	**1**	**1**
Nausea			**2**	**1**
Facial flushing			**1**	**2**
Perioral paresthesia			**1**	
Rigors		**1**		
Lightheadedness			**3**	**1**
Fevers			**1**	**1**
Swelling and erythema at injection site			**2**	**3**

PHARMACOSMOS

Okam MM, et al. *Am J Hematol.* 2012;87:E123-E124.

FDA Review of IV Iron Anaphylactic Reactions

- IMS database, FDA Adverse Event Reporting System, death certificates, and ER visits
- Reactions with all products possible
- Using current system, it is not possible to determine relative rates of SAEs, absent head-to-head trials

IMS = Intercontinental Medical Statistics.

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

AEs and IV Iron Therapy: Recent FDA Medwatch Reports

- Obtained from Freedom of Information, all AEs from 1/1/07 to 12/31/09
- Iron dextran
  - HMW ID had 116 AEs; 88 unidentifiable
  - LMW ID had 127 AEs; 75 unidentifiable
  - IMS data base: approximately five times as many doses LMW ID sold during this period

Pseudoanaphylaxis (Fishbane Reaction)

- Minor chest and back tightness
- *No* tachycardia, hypotension, wheezing, stridor, periorbital edema
- Resolves without treatment
- Does not require intervention
  - Do *not* intervene with epinephrine or diphenhydramine

Auerbach M, Ballard H, Glaspy J. *Lancet*. 2007;369:1502-1504.

Premedication and SAEs

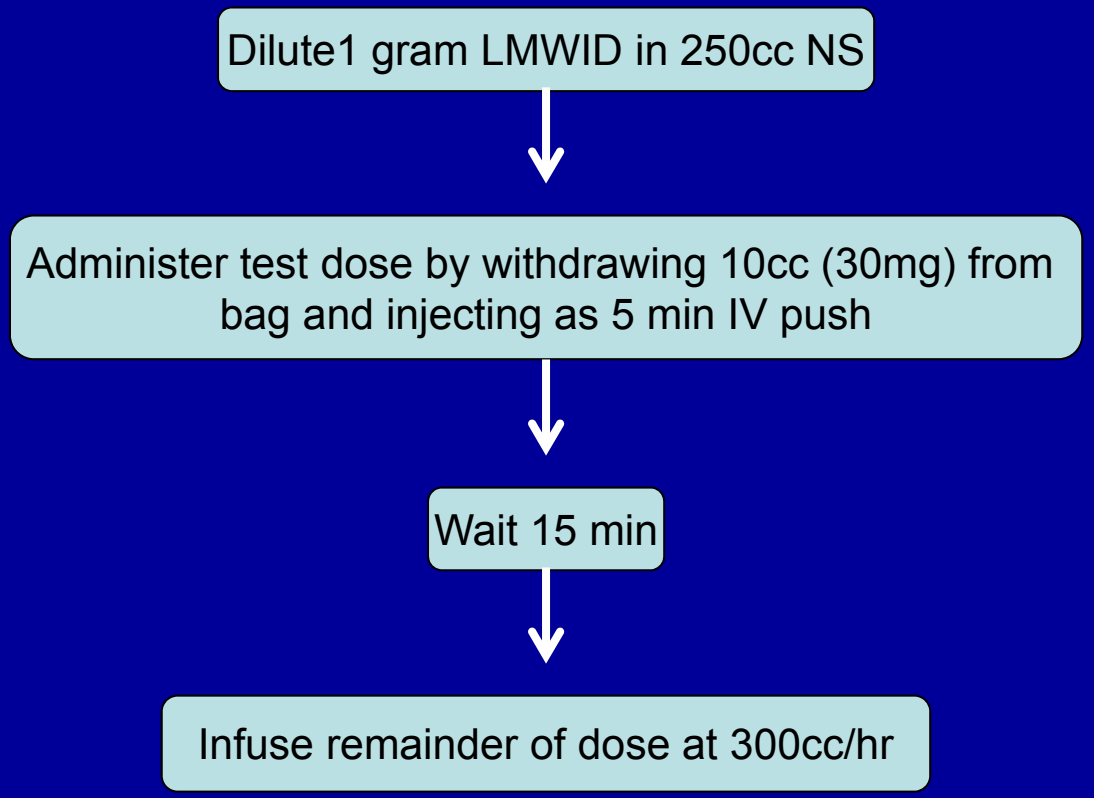
- Patients **should not** be premedicated with diphenhydramine, which can cause hypotension, flushing, somnolence, and supraventricular tachycardia
- Inappropriate intervention can cause severe SAE
- Minor chest and back tightness, usually after test dose, first described by Dr. Steve Fishbane is **not** a SAE
- Resolves without treatment: do **not** intervene with epinephrine or diphenhydramine
- An SAE should consist of hypotension, tachypnea, tachycardia, wheezing, stridor, or periorbital edema
- Premedication with steroids only for allergic diatheses

Auerbach M, et al. *Lancet*. 2007;369:1502-1504.

Picture of a Patient with Minor Infusion Reaction to IV Iron

Picture of the Same Patient after 3.5 Minutes with Infusion Reaction Resolved

Rapid (one hour) infusion of 1000 mg of LMW ID



Auerbach et al. Blood 2009;114(Suppl):1555.

Hemoglobin Levels

	Baseline Hb, g/dL	Follow-up Hb, g/dL	Change from Baseline, g/dL	Period between IV iron and Follow-up Hb, weeks
Mean (SD)	10.7 (1.6)	11.7 (1.3)	1.2 (1.2)*	5.0 (3.8)
Range	6.2 – 15.3	7.9 – 15.9	-1.6 – 5.6	1 - 21
95% CI	10.4 – 10.9	11.5 - 11.9	1.0 – 1.4	4.3 – 5.6

* p-value < 0.001

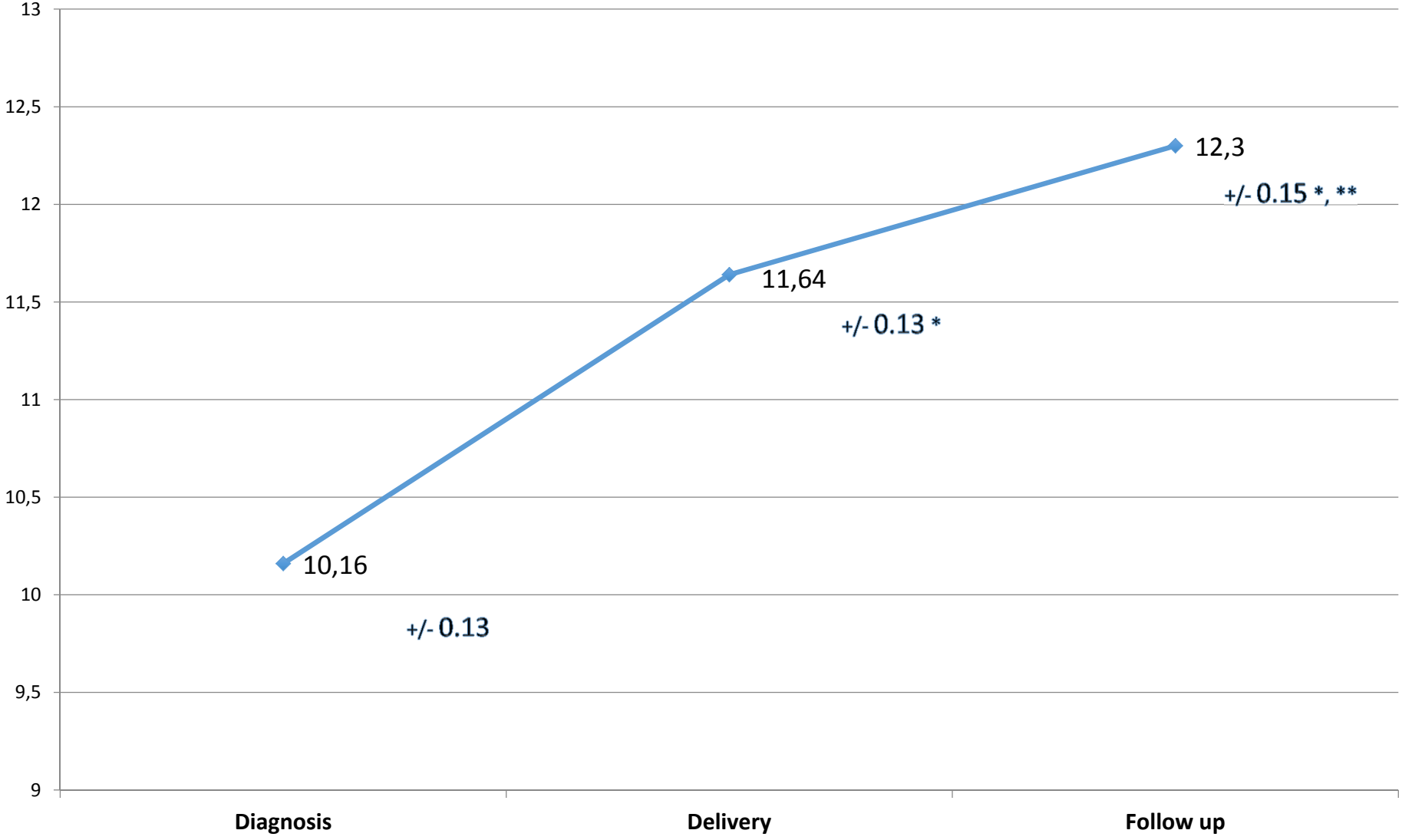
Auerbach et al. Blood 2009;114(Suppl):1555

Adverse Events

Number of Patients	189
All Adverse Events	33 in 19 patients
Related Adverse Events	24 in 12 patients
Serious Adverse Events	0 patients
Discontinued IV iron due to AE	1 patient
Adverse Events with ≥1% incidence, n (%)	
Back pain	5 (2.6%)
Headache	4 (2.1%)
Nausea	3 (1.6%)
Myalgia	2 (1.1%)
Nasal congestion	2 (1.1%)

Auerbach et al. Blood 2009;114(Suppl):1555.

Figure 1. Change in mean hemoglobin concentration (g/dL) +/- SE from diagnosis to delivery to postpartum follow up.



***** **P < 0.0001 vs Diagnosis**

****** **P < 0.0001 vs Delivery**

TDI is a convenient alternative to IV bolus in many clinical settings

- Nephrology
  - Non–dialysis-dependent CKD patients
  - Peritoneal dialysis patients
- Inflammatory bowel disease
- Rheumatic diseases
- Perioperative
- Peri- and postpartum; Menorrhagia
- Otherwise well patients intolerant of oral iron
- Gastric Bypass and hereditary hemorrhagic telangiectasia
- Restless Legs syndrome

Auerbach M, Ballard H, Glaspy J. *Lancet*. 2007;369:1502-1504.
Ondo WG. *Sleep Med.*2010;11:494-494.

IV Iron and Risk of Infection

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Safety and Efficacy of IV Iron Systematic Review and Primary Meta-analysis – Increased Risk of Infection?

- IV iron resulted in a significant increase in mean Hgb concentration (6.5 g/L, 95% CI 5.1 g/L to 7.9 g/L) compared with oral iron or no iron supplementation
- IV iron therapy reduced the risk (relative risk 0.74, 95% CI 0.62 to 0.88) of patients requiring allogeneic RBC transfusion
- No significant difference in mortality or SAEs was observed with IV iron
- IV iron was associated with a significant increase in risk of infection of 1.33 (95% CI1.10 to 1.64)

"Infection was not a **predefined endpoint in many pooled studies**, and it is possible that **missing data could have created unmeasured bias** in our analysis. Furthermore, we could not find a significant association between iron dose and risk of infection, and, overall, serious adverse events and mortality were not significantly increased in those receiving intravenous iron compared with oral or no iron."

Litton E, et al. *BMJ*. 2013;347:f4822.

Association of IV Iron with Mortality and Infection

- Increased mortality (relative risk, 1.11) among 5833 HD patients receiving >10 vials of IV iron dextran over 6 months (*P*=0.05 vs. ≤10 vials)[1]
- Subsequent analysis suggested inadequate controlling for confounding variables (including likelihood that patients receiving IV iron have more advanced illness)
- No increased morbidity associated with IV iron

1. Feldman HI, et al. *J Am Soc Nephrol*. 2002;13:734-744.

No Effect of IV Iron Administration on Risk of Infection in Dialysis Patients

- **Hoen, et al[1]**
  - 988 HD patients in 19 European centers were followed for 6 months
  - 51 episodes of bacteremia (0.11 episode/year)
  - Multivariable analysis of risk factors for infection

	Relative Risk
History of infection	7.3
Catheter access	7.6
Immunosuppression	3.0
Anemia	1.4 per 1 g/dL decrement in Hgb
Any use of iron	No detected association
Ferritin	No detected association

- **Hoen, et al[2]**
  - IV iron administration not associated with bacteremia

1. Hoen B, et al. *J Am Soc Nephrol*. 1998;9:869-876. 2. Hoen B, et al. *Clin Nephrol*. 2002;57:457-461.

Does IV Iron Increase the Risk of Infection as Concluded by Litton E, *et al*?

Limitations of the Review and Meta-analysis

- Data from studies on different populations (medical and surgical) with various pathologies receiving different IV iron formulations with different dosing regimens are pooled (eg, only 2 randomized controlled trials were included)
- Without a reliable measure of infection rates and amidst no difference in serious adverse outcomes, it is impossible to determine the impact of IV iron on clinically significant infections, and no inference can be made
- The search strategy was incomplete since published relevant trials (some dating back to 2000) were overlooked

"The conclusions of the meta-analysis by Litton, *et al*. are unfortunately undermined by the limitations of their study and are somewhat contradictory to the litany of other studies."

Munoz M, et al. Available at: http://www.bmj.com/content/347/bmj.f4822/rr/661826. Accessed October 25, 2013.

What are the Strengths of FIND-CKD?

- It is the largest and longest trial ever conducted evaluating IV versus oral iron in patients with NDD-CKD

- It is the largest and longest study ever conducted evaluating IV iron in patients with NDD-CKD not receiving ESA therapy

- The primary endpoint was not a change in Hb level

Macdougall IC, et al. *Nephrol Dial Transplant*. 2014.

Study Treatment

	High Ferritin FCM	Low Ferritin FCM	Oral iron
Target	Serum ferritin 400-600 µg/L	Serum ferritin 100-200 µg/L	
Day 0	1,000 mg iron*	200 mg iron	Ferrous sulphate 200 mg iron/day†
Weeks 4-52	**Serum ferritin** — **Iron dose***** <200 µg/L — 1000 mg iron every 4 weeks to week 48** 200 to <400 µg/L — 500 mg iron every 4 weeks to week 48 ≥400 µg/L — No iron	**Serum ferritin dose***** <100 µg/L — 200 mg iron every 4 weeks to week 48 ≥100 µg/L — No iron	

*Patients ≤66 kg: 500 mg iron on Days 0 and 7; **Patients ≤66 kg: 500 mg iron on day of visit and 500 mg iron one week later; ***No administration if TSAT level ≥40%; †Oral iron was withheld if ferritin >200 µg/L and restarted if/when ferritin <100 µg/L; The last dose of FCM was administered at Week 48, and the last dose of oral iron was administered at week 52

PHARMACOSMOS

Macdougall IC, et al. *Nephrol Dial Transplant*. 2014.

Serious Adverse Events, N (%)

	High ferritin FCM (N=154)	Low ferritin FCM (N=150)	Oral iron (N=312)
Cardiac disorders	10 (6.5)	7 (4.7)	14 (4.5)
Acute myocardial infarction	2 (1.3)	0 (0)	4 (1.3)
Cardiac failure	1 (0.6)	0 (0)	3 (1.0)
Infections	6 (3.9)	5 (3.3)	12 (3.8)
Pneumonia	0 (0)	1 (0.7)	4 (1.3)
Injury, poisoning & procedural complications	4 (2.6)	3 (2.0)	8 (2.6)
Neoplasms (benign & malignant)	8 (5.2)	3 (2.0)	2 (0.6)

Macdougall IC, et al. *Nephrol Dial Transplant*. 2014.

IV iron Safety

- A recent systematic review aimed to compile all available evidence regarding the safety of intravenous (IV) iron preparations, in order to provide a true balance of efficacy and safety
- All randomized control trials comparing IV iron to another comparator were included
- All electronic databases until 1/2014 were reviewed.

IV iron Safety

- A total of 103 trials performed between 1965 and 2013were included
- Pooled together, 10,390 patients were treated with IV iron and were compared to
  - 4,044 patients treated with oral iron
  - 1,329 with no iron
  - 3,335 with placebo
  - 155 with IM iron

IV iron Safety

- Type of Iron preparation:
  - Iron sucrose (IS) was used in 57 trials
  - Ferric carboxymaltose (FCM) in 15
  - Ferric gluconate (FG) in 7
  - Iron Dextran in 14
  - Ferumoxytol in 4
  - Iron polymaltose in 3
  - Iron isomaltoside in 2

IV iron Safety

- Overall, there was no increase in the risk of severe adverse events (SAEs) with IV iron compared to control, RR 1.04 (95% CI 0.93-1.17, 97 trials, I^2=9%)

TABLE 1. Primary Outcomes[a,b]

SAE	RR (95% CI)	NNH or NNP (95% CI)
All studies	1.04 (0.93-1.17)	NA
By indication		
Chronic heart failure	**0.45 (0.29-0.70)**	**NNP, 10 (6-25)**
Obstetrics and gynecology	**2.0 (1.15-3.62)**	**NNH, 119 (61-1725)**
By comparator		
Placebo	0.83 (0.64-1.08)	NA
No iron	1.06 (0.90-1.25)	NA
Oral iron	1.13 (0.95-1.35)	NA
Intramuscular iron	1.36 (0.22-8.49)	NA
By compound		
IS	1.33 (0.96-1.83)	NA
FCM	0.82 (0.64-1.06)	NA
FML	1.04 (0.71-1.53)	NA
ISM or IPM	1.09 (0.43-2.80)	NA
ID	1.05 (0.77-1.45)	NA
FG	1.12 (0.96-1.30)	NA
By system involved		
Infections	0.96 (0.63-1.46)	NA
Gastrointestinal	1.03 (0.64-1.66)	NA
Cardiovascular	0.94 (0.60-1.46)	NA
Thromboembolic	0.99 (0.52-1.86)	NA
Respiratory	0.91 (0.27-3.86)	NA
Neurologic	1.05 (0.47-2.36)	NA
By infusion reaction		
All	**2.47 (1.43-4.28)**	**NNH, 292 (164-1316)**
IS	1.75 (0.69-4.43)	NA
FCM	1.47 (0.40-5.39)	NA
FML	2.26 (0.19-26.22)	NA
ISM or IPM	1.00 (0.99-1.01)	NA
ID	3.10 (0.86-11.22)	NA
FG	**5.32 (1.49-18.99)**	**NNH, 118 (68-423)**
Placebo comparator	**2.96 (1.16-7.51)**	**NNH, 255 (136-1910)**

[a]FCM = ferric carboxymaltose; FG = ferric gluconate; FML = ferumoxytol; ID = iron dextran; IPM = iron polymaltose; IS = iron sucrose; ISM = iron isomaltoside; NA = not applicable; NNH = number needed to harm; NNP = number needed to prevent; RR = relative risk; SAE = severe adverse event.

[b]Statistically significant results are presented in bold.

IV iron Safety

- There was no increased risk of serious infections with IV iron, RR 0.96 (95% CI 0.63-1.46, I^2=8.2%).
- The risk of cardiovascular, neurological, thromboembolic or gastrointestinal SAEs was not increased with IV iron

TABLE 2. Secondary Outcomes[a,b]

AE	RR (95% CI)	NNH or NNP (95% CI)
Mortality	1.06 (0.81–1.39)	NA
Any	1.04 (0.99–1.08)	NA
Treatment related	1.08 (0.96–1.21)	NA
Requiring discontinuation		
Total	0.92 (0.76–1.12)	NA
FCM	**0.69 (0.46–1.00)**	**NNP, 127 (60–1377)**
Infections	1.17 (0.83–1.65)	NA
Gastrointestinal		
Total	**0.55 (0.51–0.61)**	**NNP, 10 (8–14)**
ID	**0.28 (0.14–0.53)**	**NNP, 15 (6–32)**
FCM	**0.57 (0.48–0.68)**	**NNP, 15 (8–173)**
IS	**0.38 (0.32–0.45)**	**NNP, 7 (5–12)**
Placebo	**1.39 (1.13–1.71)**	**NNH, 54 (34–128)**
No iron	**0.84 (0.72–0.92)**	**NNP, 24 (12–738)**
Oral iron	**0.33 (0.29–0.38)**	**NNP, 6 (5–7)**
Infusion reaction		
Total	**2.74 (2.13–3.53)**	**NNH, 64 (44–115)**
IS	**3.59 (2.30–5.61)**	**NNH, 44 (25–183)**
FCM	**3.36 (2.08–5.44)**	**NNH, 46 (29–110)**
FG	**5.85 (1.53–22.30)**	**NNH, 141 (79–627)**
Placebo	**2.42 (1.50–3.91)**	**NNH, 92 (52–422)**
Oral iron	**3.49 (2.22–5.49)**	**NNH, 50 (32–113)**
No iron	**2.19 (1.05–4.56)**	**NNH, 92 (52–422)**
Cardiovascular		
Total	0.99 (0.83–1.17)	NA
FCM	**0.57 (0.42–0.79)**	**NNP, 28 (17–71)**
FG	**1.33 (1.05–1.69)**	**NNH, 39 (21–235)**
Respiratory	1.14 (0.72–1.81)	NA
Neurologic		
Total	**1.35 (1.13–1.61)**	**NNH, 78 (44–336)**
IS	**1.63 (1.10–2.42)**	**NNH, 71 (30–237)**
Oral iron	**2.14 (1.54–2.98)**	**NNH, 50 (33–100)**
Intramuscular iron	**0.09 (0.03–0.26)**	**NNP, 14 (4–42)**
Thromboembolic	0.92 (0.62–1.38)	NA
Hypotension		
Total	**1.39 (1.09–1.77)**	**NNH, 97 (58–305)**
IS	**3.01 (1.12–8.11)**	**NNH, 68 (37–364)**
No iron	**3.83 (1.33–11.02)**	**NNH, 50 (25–100)**
Skin	**1.60 (1.05–2.45)**	**NNH, 99 (59–304)**
Muscle or skeletal		
Total	**1.58 (1.15–2.17)**	**NNH, 36 (28–53)**
FCM	**3.42 (2.02–5.79)**	**NNH, 32 (23–49)**
Hypertension	**2.25 (1.00–5.08)**	**NNH, 36 (28–51)**
Constitutional	1.35 (0.97–1.87)	NA
Electrolytes	**2.45 (1.84–3.26)**	**NNH, 19 (11–67)**
Abnormal laboratory results	1.57 (0.91–2.71)	NA
Iron overload	1.40 (0.95–2.07)	NA

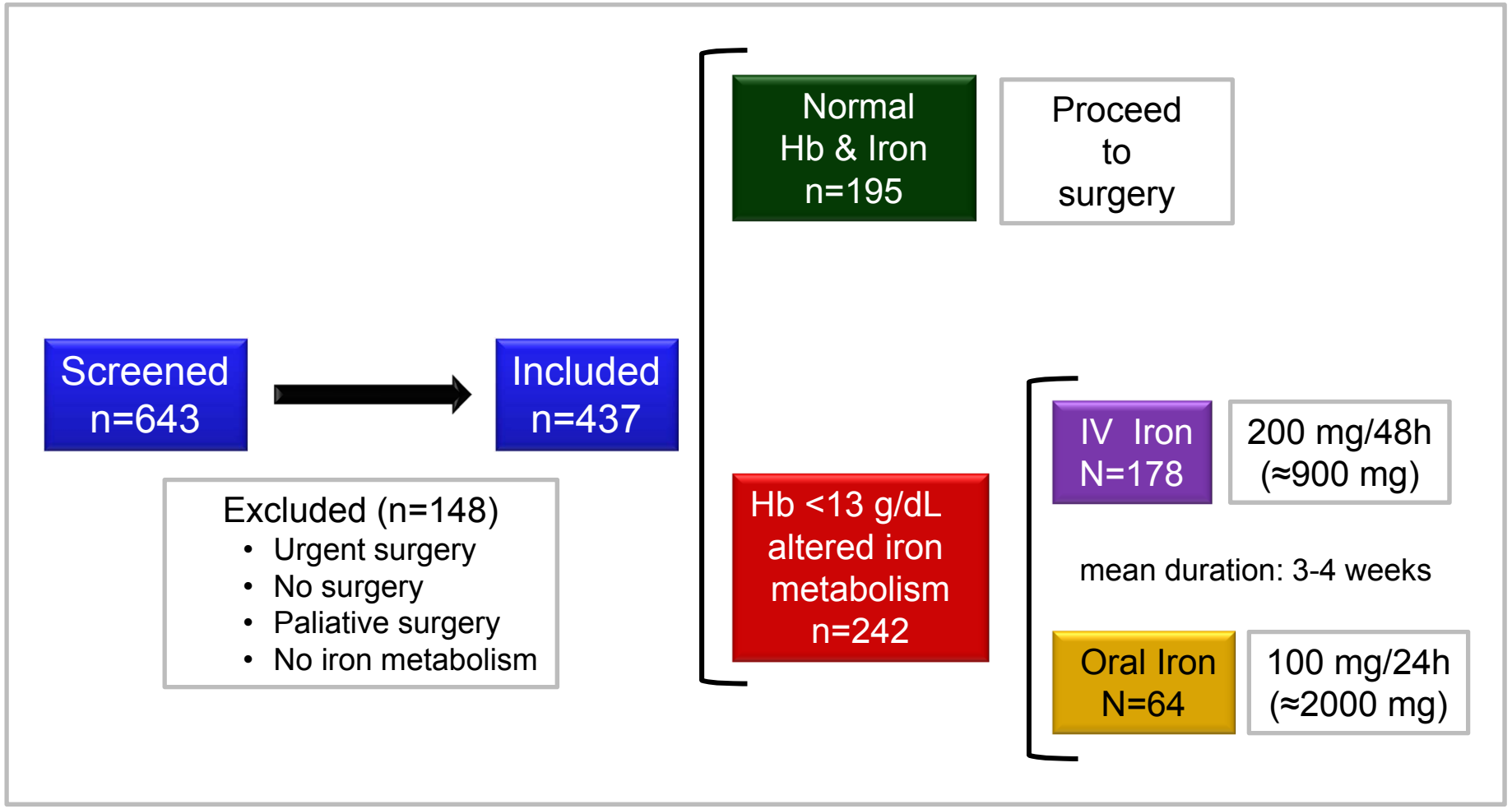
[a]AE = adverse event; FCM = ferric carboxymaltose; FG = ferric gluconate; ID = iron dextran; IS = iron sucrose; NA = not applicable; NNH = number needed to harm; NNP = number needed to prevent; RR = relative risk.
[b]Statistically significant results are presented in bold.

IV iron Safety

- In conclusion, according to this recent large meta-analysis of 103 trials published in *Mayo Clinic Proceedings* , IV iron therapy is not associated with an increased risk of severe adverse events or infections.

Preoperative optimization of Hb: CRC

Corporació Sanitari Parc Tauli. Sabadell, Barcelona (Spain)
5-years restrospective audit

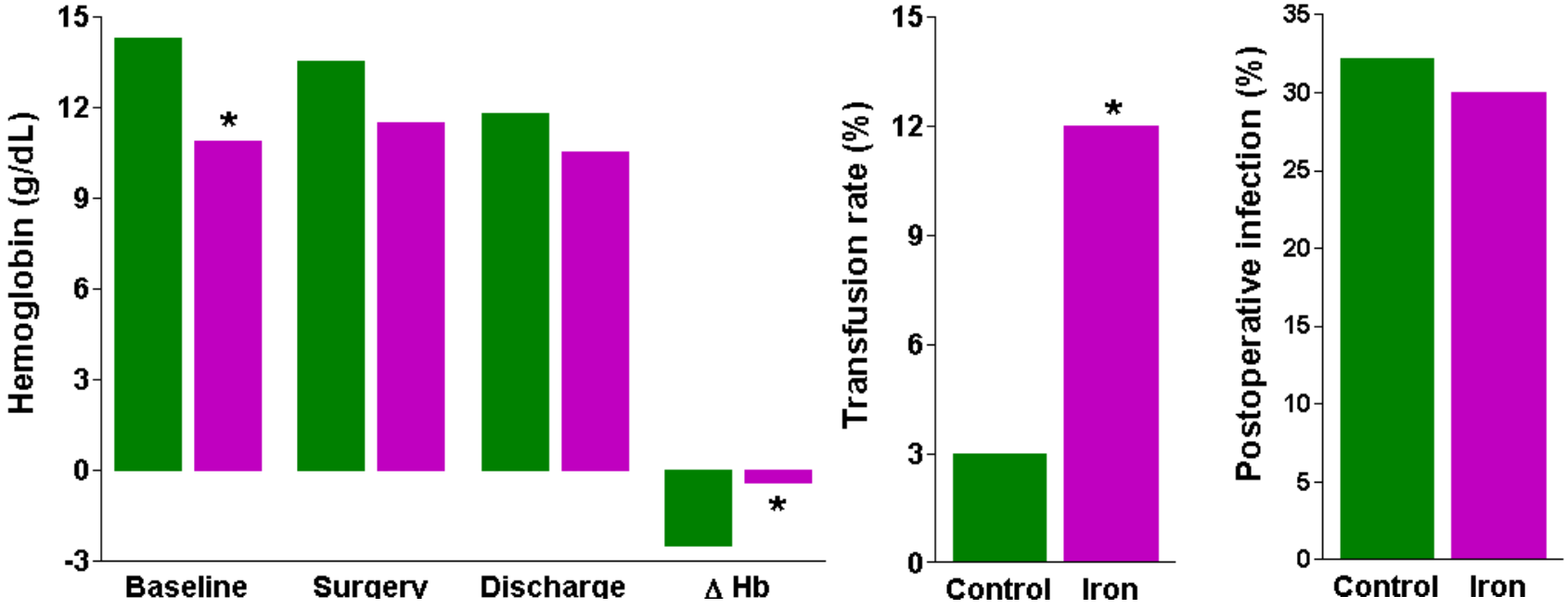


Diaz-Espallardo C, et al. Cir Esp 2011; 89:392-399

Preoperative optimization of Hb: CRC

5-years restrospective audit

- Preoperative iron administration in CRC patients:
  - Reduced perioperative haemoglobin loss.
  - Resulted in low transfusion rate in the anaemic group.
  - Did not increase postoperative infection rate.
  - No serious IV iron side-effects were witnessed.



Diaz-Espallardo C, et al. Cir Esp 2011; 89:392-399

GIEMSA

Perioperative IV iron

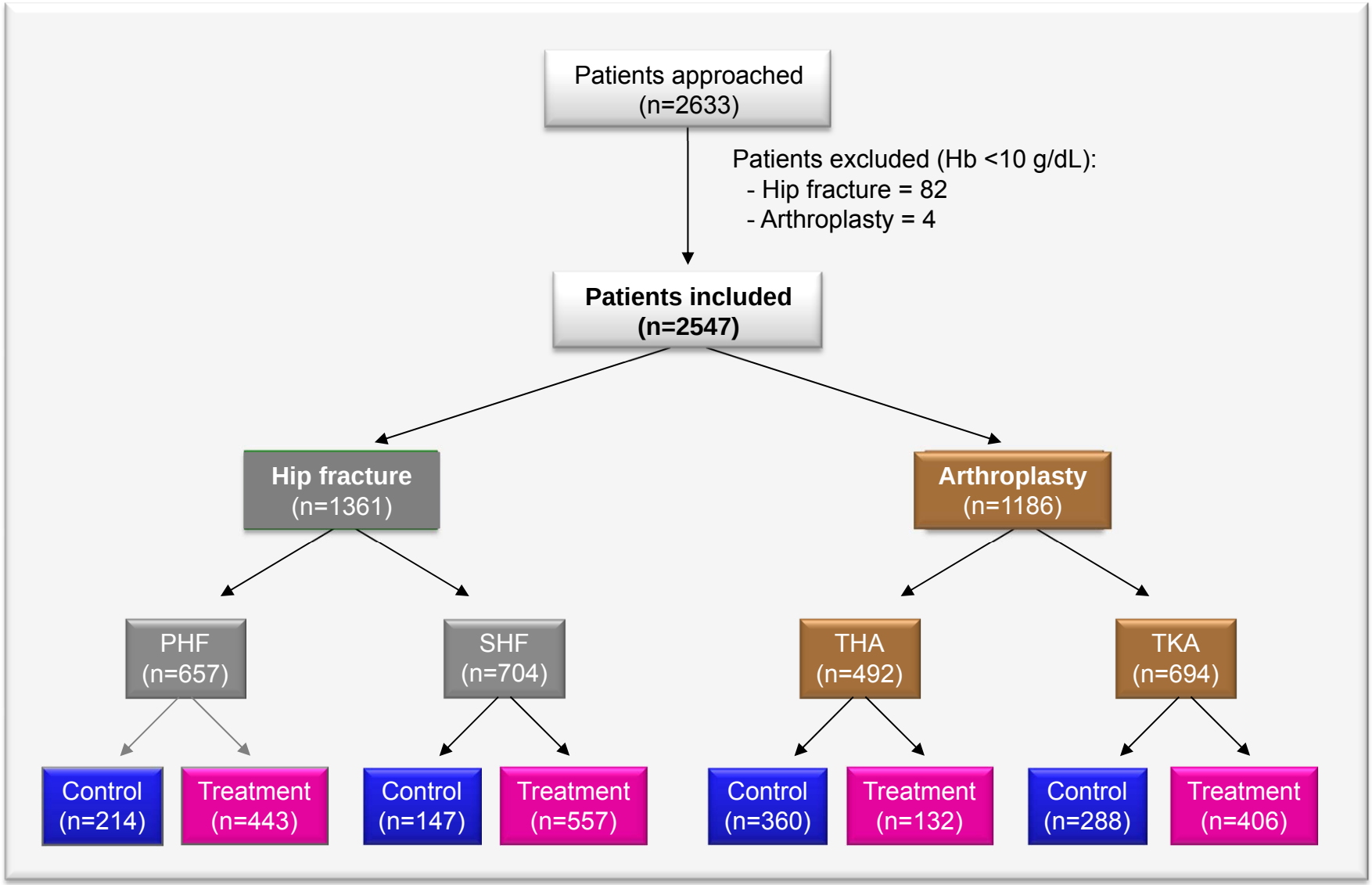
ORIGINAL ARTICLE

Very-short-term perioperative intravenous iron administration and postoperative outcome in major orthopedic surgery: a pooled analysis of observational data from 2547 patients

Manuel Muñoz, Susana Gómez-Ramírez, Jorge Cuenca, José Antonio García-Erce, Daniel Iglesias-Aparicio, Sami Haman-Alcober, Daniel Ariza, and Enrique Naveira

Transfusion. 2014; 54(2): 289 - 299

Patients, procedures and groups



GIEMSA

Perioperative IV iron ESAs

Treatment

- **Iron sucrose**: doses of 100 to 200 over 30 to 60 minutes up to three times perioperatively (either 2-5 days preoperatively and/or 2-3 days postoperatively). Some patients received 3 postoperative doses 200 mg ferric carboxymaltose instead of iron sucrose.

- **rHuEPO:** single preoperative dose (40,000 IU, sc) was administered at the orthopaedic ward to some patients presenting with preoperative Hb level of less than 13 g/dL.

- Most patients were managed with a restrictive transfusion trigger (Hb < 8 g/dL).

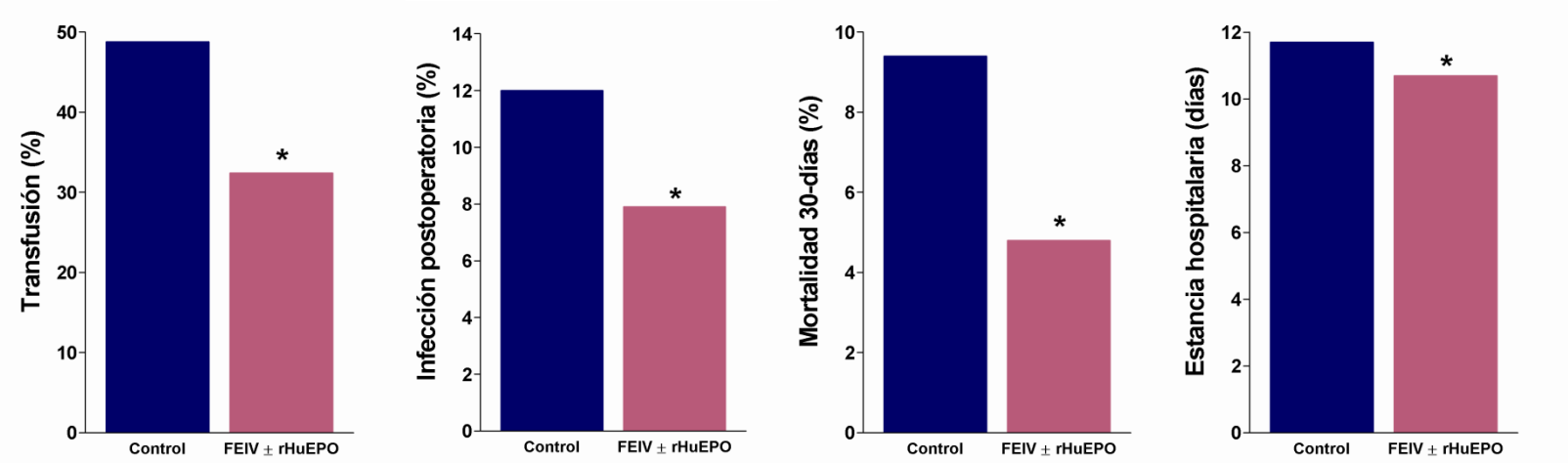
- **No other blood conservation measure was used.**

GIEMSA

Perioperative IV iron ESAs

Results

- Very short-term perioperative IV iron administration, with or without rHuEPO, significantly reduced (*p<0.01):



- No clinically relevant AEs attributable to IV iron or rHuEPO were observed.
- Mean compensated perioperative Hb loss was 3.8 g/dL. Thus, the **scheduled IV iron dose** (200-600 mg) may not cover total iron loss, especially in patients with preoperative iron deficiency.
- **Preoperative rHuEPO** was only administered in 351 out of 1059 patients presenting with Hb level <13 g/dL and no contraindication.

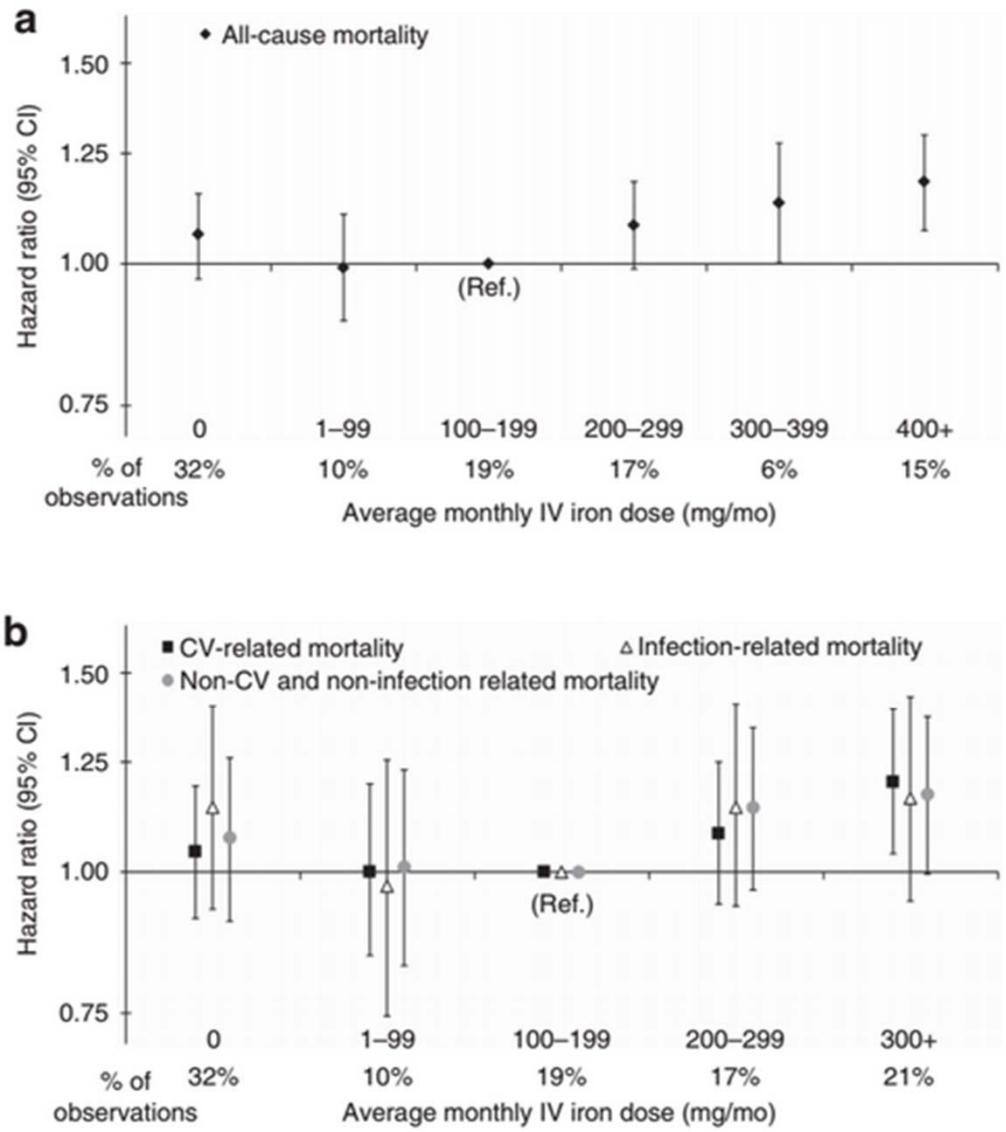
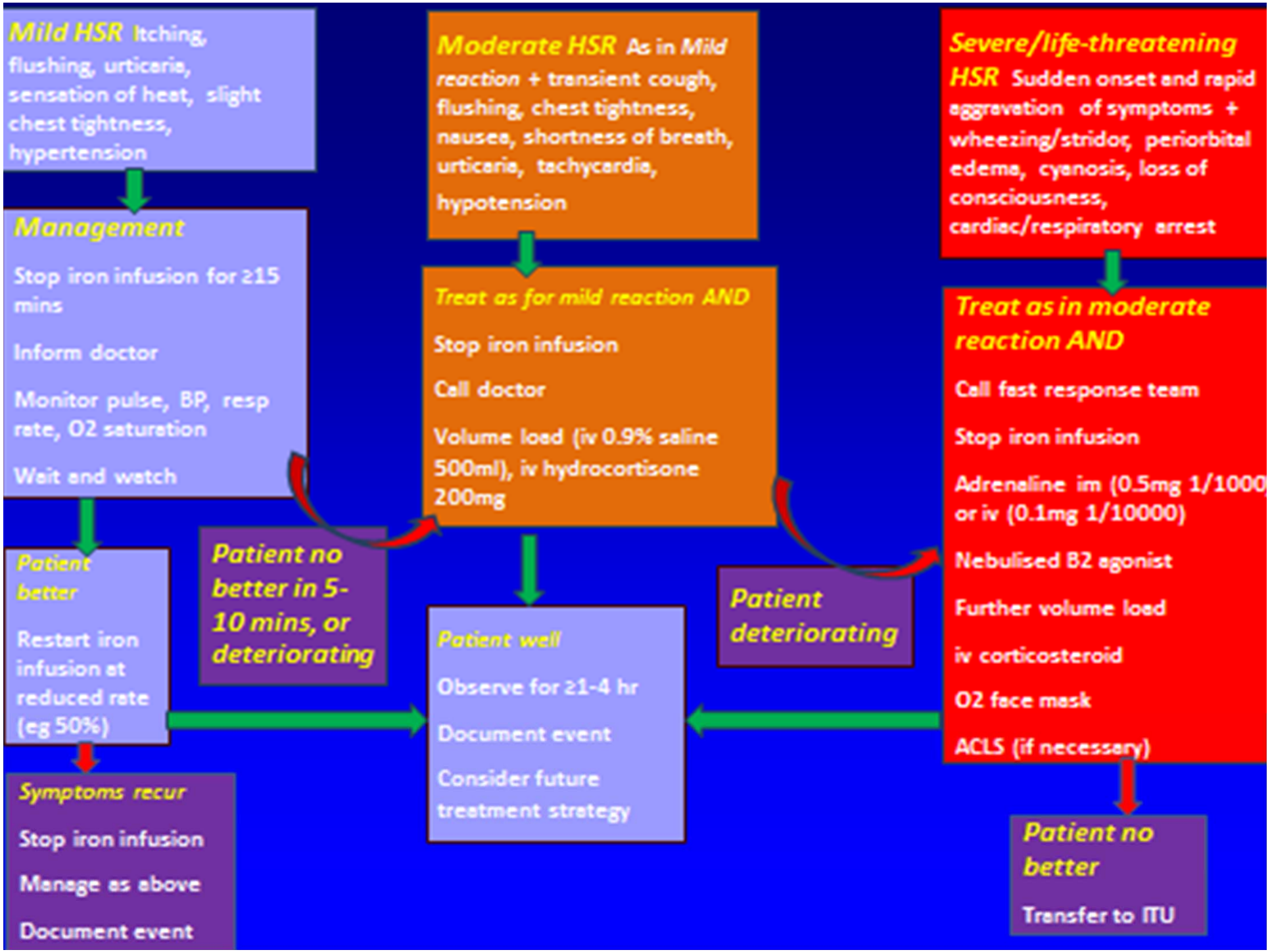


Figure 1 | Associations of intravenous (IV) iron dose categories with (a) all-cause mortality and (b) cause-specific mortality. IV iron dose is the total 4-month dose, expressed as average mg/month. Model details are provided in text. Adjustments and effect estimates (95% confidence interval (CI)) are as per Model 6 in Table 2. CV, cardiovascular.

Bailie, et al. *Kidney International*. 2014.


Mild HSR Itching, flushing, urticaria, sensation of heat, slight chest tightness, hypertension
Management
Stop iron infusion for ≥15 mins
Inform doctor
Monitor pulse, BP, resp rate, O2 saturation
Wait and watch
Patient better
Restart iron infusion at reduced rate (eg 50%)
Symptoms recur
Stop iron infusion
Manage as above
Document event
Moderate HSR As in Mild reaction + transient cough, flushing, chest tightness, nausea, shortness of breath, urticaria, tachycardia, hypotension
Treat as for mild reaction AND
Stop iron infusion
Call doctor
Volume load (iv 0.9% saline 500ml), iv hydrocortisone 200mg
Patient no better in 5-10 mins, or deteriorating
Patient well
Observe for ≥1-4 hr
Document event
Consider future treatment strategy
Patient deteriorating
Severe/life-threatening HSR Sudden onset and rapid aggravation of symptoms + wheezing/stridor, periorbital edema, cyanosis, loss of consciousness, cardiac/respiratory arrest
Treat as in moderate reaction AND
Call fast response team
Stop iron infusion
Adrenaline im (0.5mg 1/1000 or iv (0.1mg 1/10000)
Nebulised B2 agonist
Further volume load
iv corticosteroid
O2 face mask
ACLS (if necessary)
Patient no better
Transfer to ITU

Conclusions

- Intravenous is safe
- Serious adverse events are vanishingly rare
- If premedication and interventions for minor infusion reactions are avoided, SAEs are not seen
- It is possible that the overwhelming number of SAEs ostensibly attributed to IV iron are iatrogenic