PIA FONDAZIONE DI CULTO E RELIGIONE CARD. G. PANICO

Gestione del deficit di ferro nel paziente con malattia renale cronica

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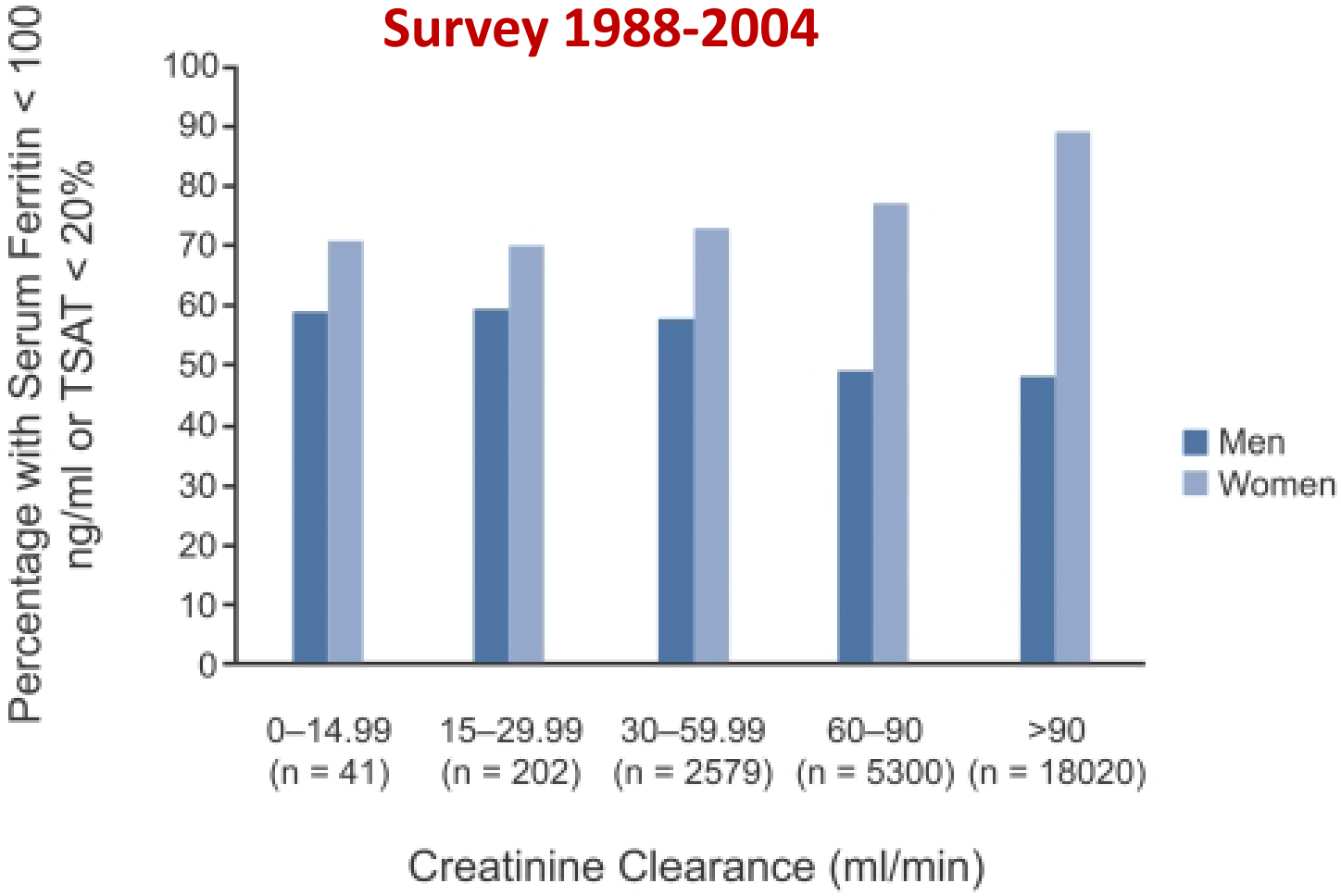
Parma 18 Novembre 2016

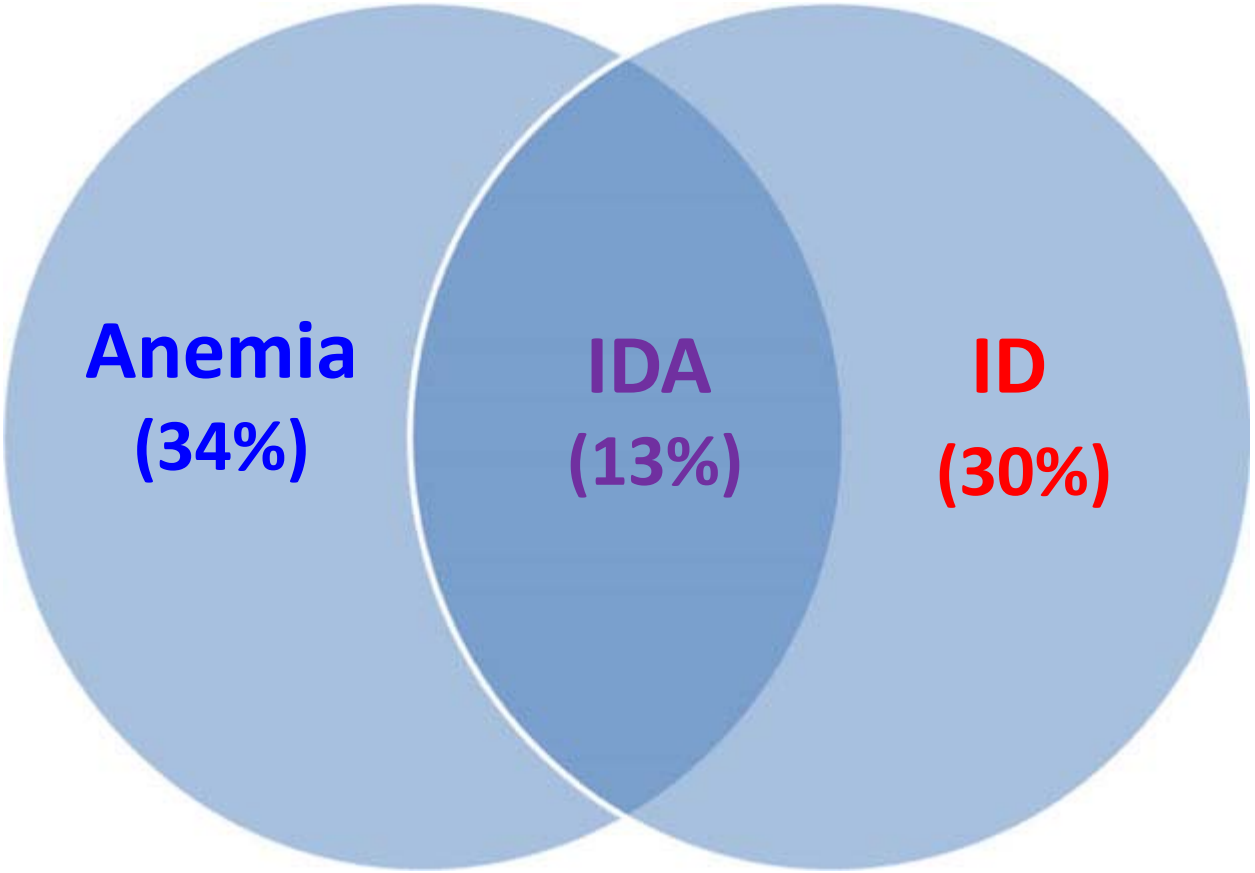
Iron indices in chronic kidney disease in the National Healt And Nutritional Examination Survey 1988-2004



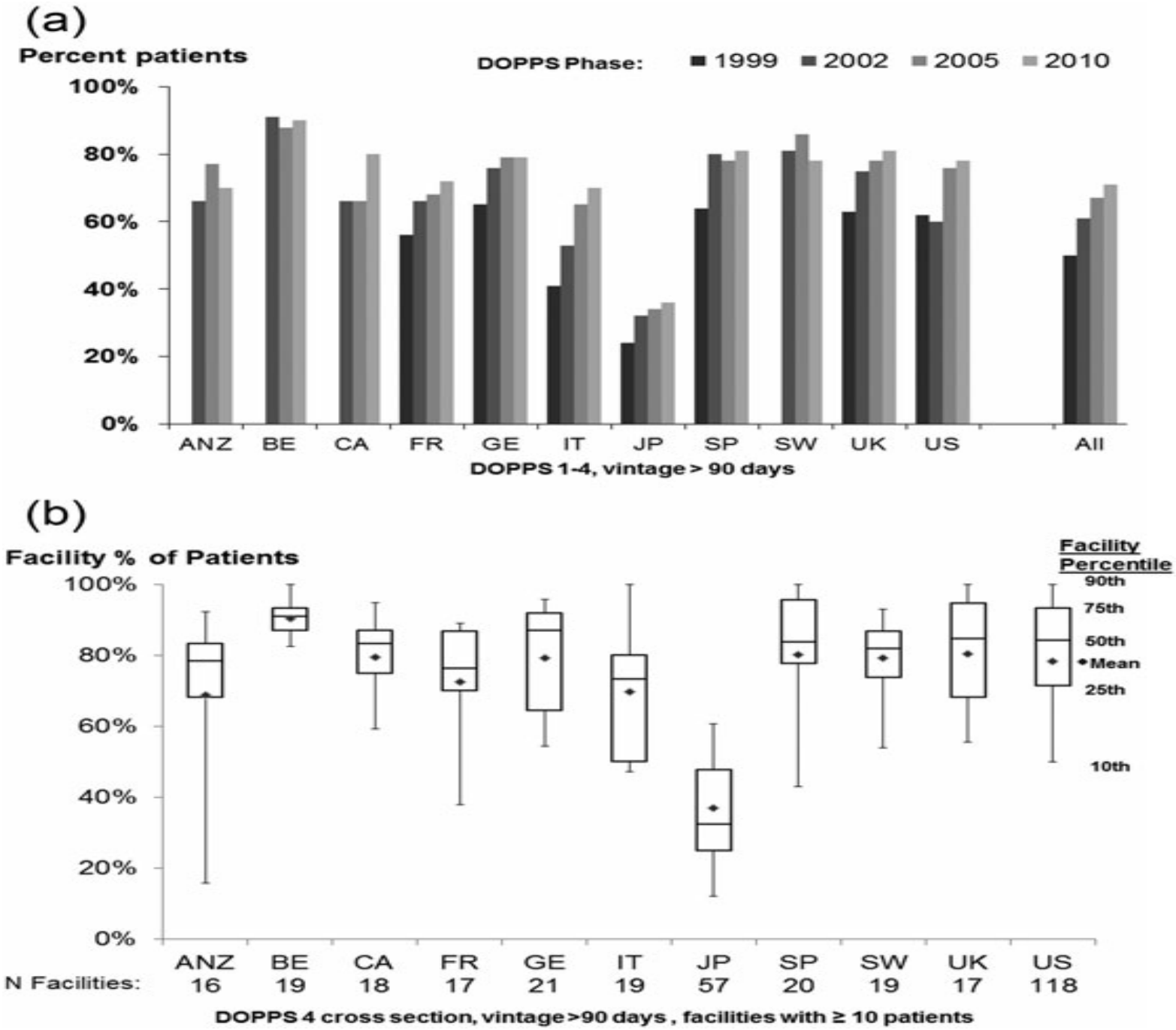
CJASN

S. Fishbane et al. Clin J Am Soc Nephrol 4: 57-61, 2009

Anemia and iron deficiency in renal transplant recipients

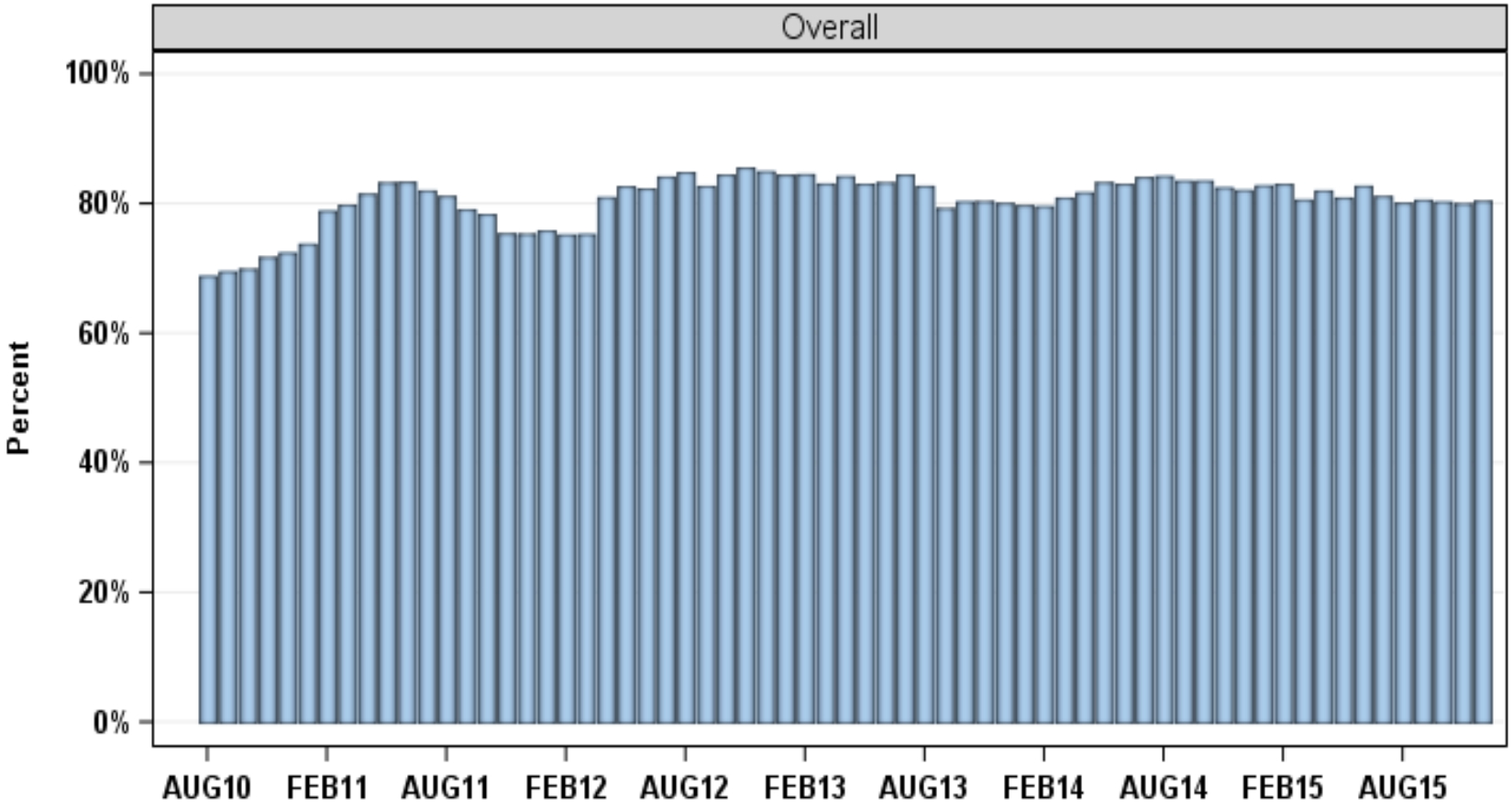


M. F. Eisenga et al. Transplant International 2016; 29: 1176–1183


(a)
Percent patients
DOPPS Phase: 1999 2002 2005 2010
100%
80%
60%
40%
20%
0%
ANZ BE CA FR GE IT JP SP SW UK US All
DOPPS 1-4, vintage > 90 days
(b)
Facility % of Patients
Facility Percentile
90th
75th
50th
Mean
25th
10th
100%
80%
60%
40%
20%
0%
ANZ BE CA FR GE IT JP SP SW UK US
N Facilities: 16 19 18 17 21 19 57 20 19 17 118
DOPPS 4 cross section, vintage >90 days , facilities with ≥ 10 patients

IV iron use, last 3 months

National sample

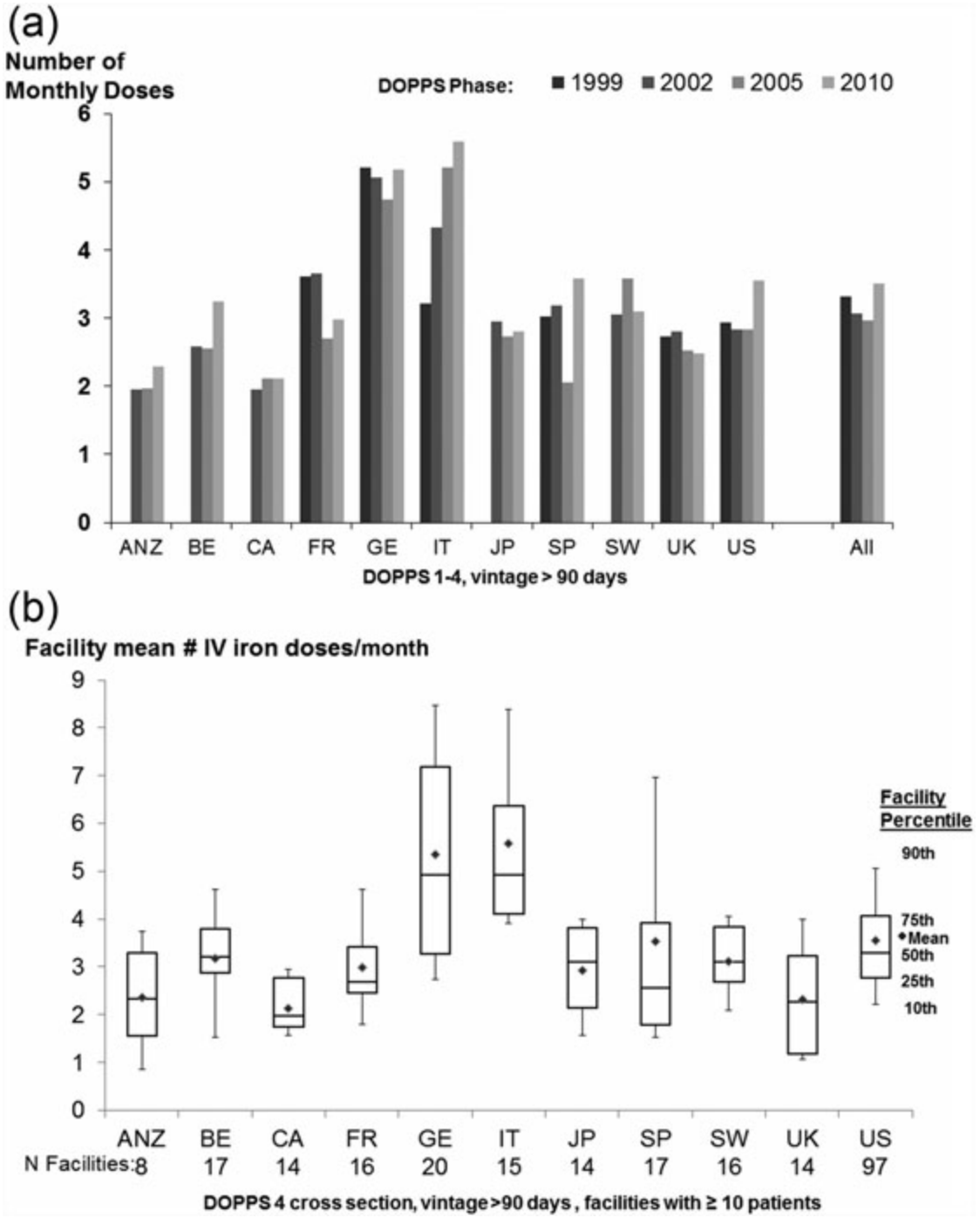


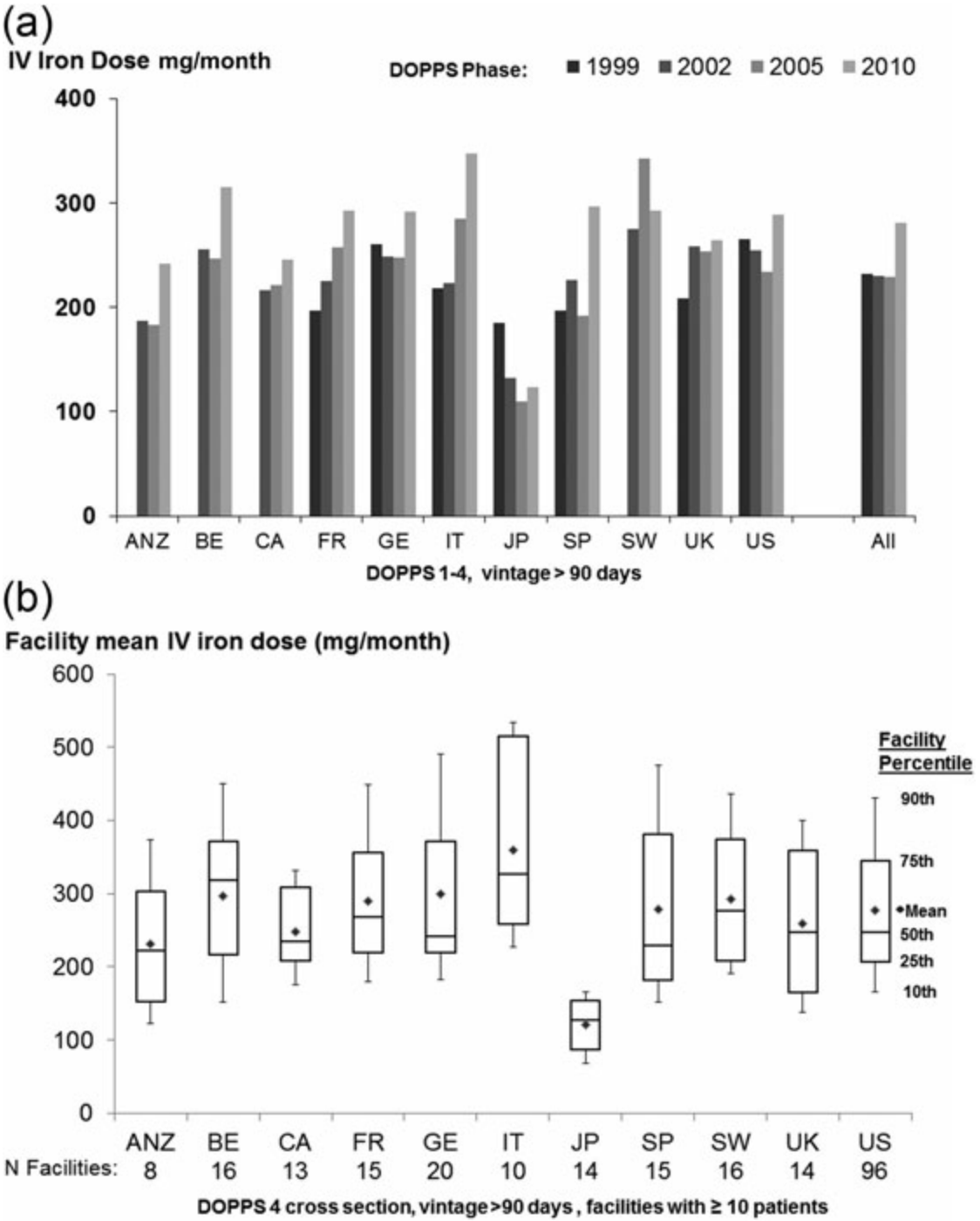
Values for each month reflect any prescription during prior three months

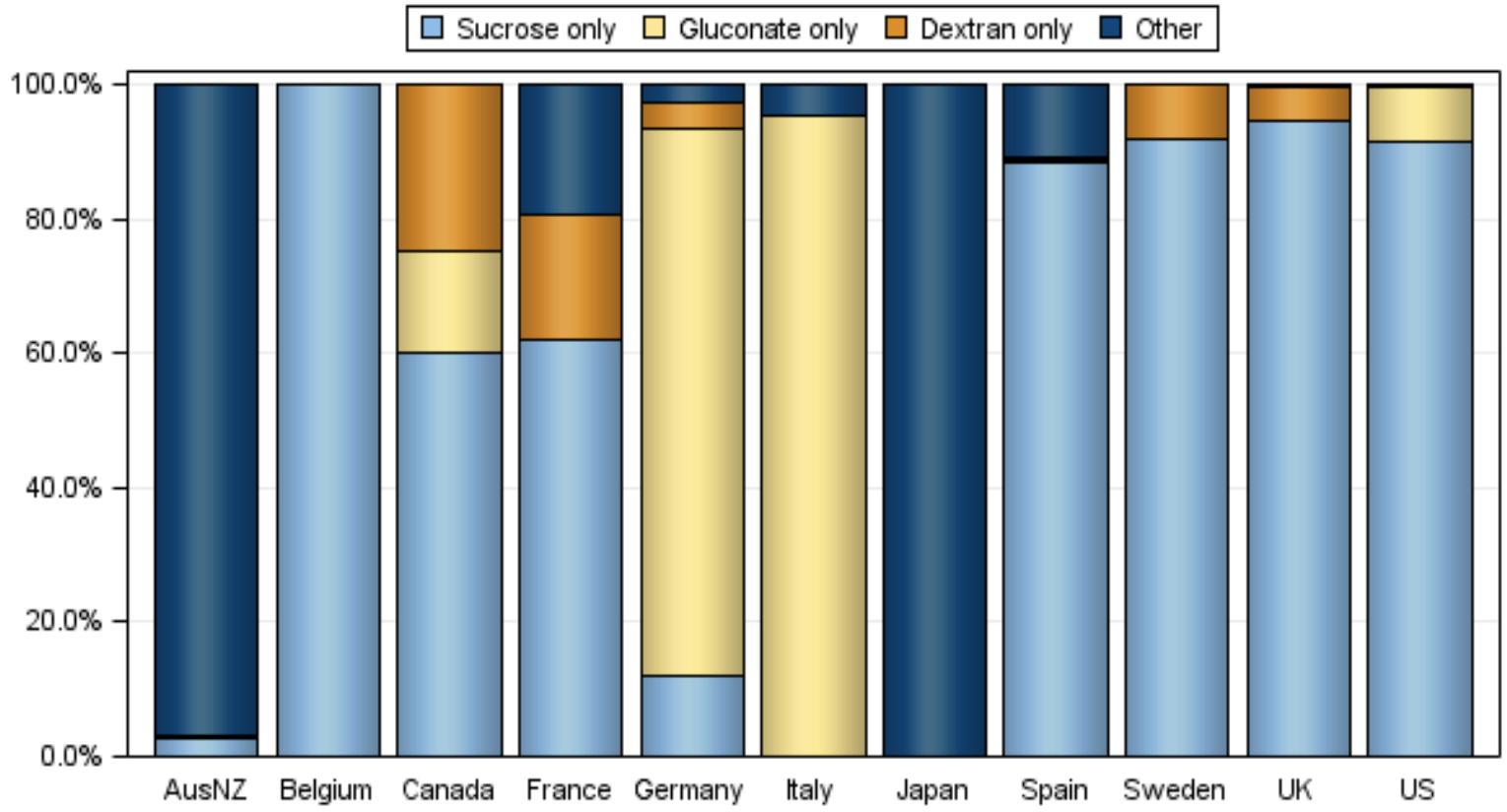
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods").

Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").

Source: US-DOPPS Practice Monitor, April 2016; http://www.dopps.org/DPM


(a)
Number of Monthly Doses
DOPPS Phase: 1999 2002 2005 2010
6
5
4
3
2
1
0
ANZ BE CA FR GE IT JP SP SW UK US All
DOPPS 1-4, vintage > 90 days
(b)
Facility mean # IV iron doses/month
9
8
7
6
5
4
3
2
1
0
Facility Percentile
90th
75th
Mean
50th
25th
10th
ANZ BE CA FR GE IT JP SP SW UK US
N Facilities: 8 17 14 16 20 15 14 17 16 14 97
DOPPS 4 cross section, vintage >90 days , facilities with ≥ 10 patients


(a)
IV Iron Dose mg/month
DOPPS Phase: 1999 2002 2005 2010
400
300
200
100
0
ANZ BE CA FR GE IT JP SP SW UK US All
DOPPS 1-4, vintage > 90 days
(b)
Facility mean IV iron dose (mg/month)
600
500
400
300
200
100
0
Facility Percentile
90th
75th
Mean
50th
25th
10th
ANZ BE CA FR GE IT JP SP SW UK US
N Facilities: 8 16 13 15 20 10 14 15 16 14 96
DOPPS 4 cross section, vintage >90 days , facilities with ≥ 10 patients

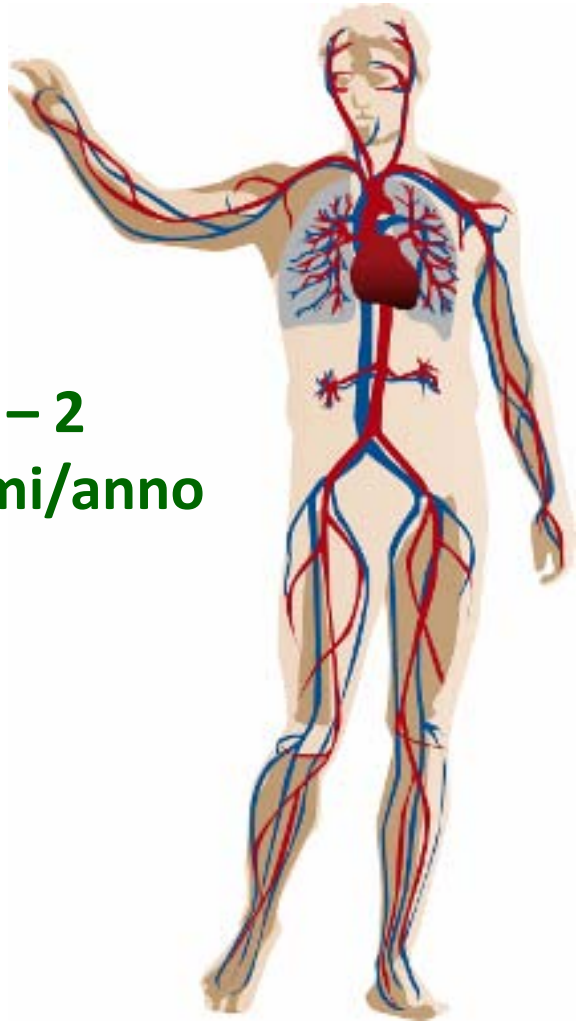


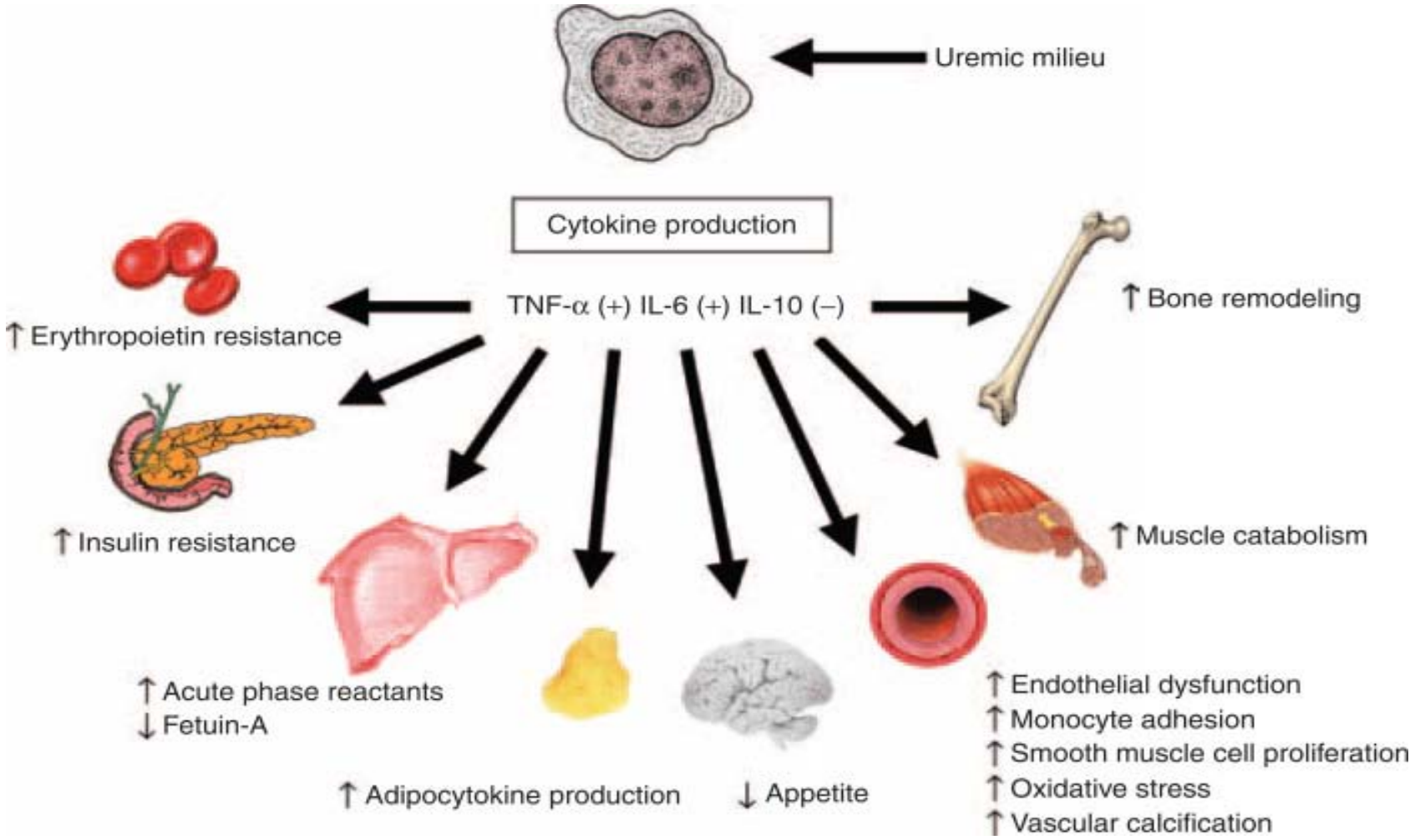
		AusNZ	Belgium	Canada	France	Germany	Italy	Japan	Spain	Sweden	UK	US
Sucrose only	(N Ptnts)	7	373	184	200	61	0	0	365	318	331	2,744
Sucrose only	(Wgtd %)	2.7%	100.0%	60.1%	62.0%	11.9%	0.0%	0.0%	88.2%	91.9%	94.4%	91.6%
Gluconate only	(N Ptnts)	1	0	73	1	379	413	0	3	0	0	234
Gluconate only	(Wgtd %)	0.6%	0.0%	15.0%	0.2%	81.5%	95.2%	0.0%	0.7%	0.0%	0.0%	8.0%
Dextran only	(N Ptnts)	0	0	67	36	26	0	0	1	34	27	22
Dextran only	(Wgtd %)	0.0%	0.0%	24.9%	18.5%	4.0%	0.0%	0.0%	0.2%	8.1%	5.2%	0.4%
Other	(N Ptnts)	255	0	0	59	16	18	621	59	0	2	0
Other	(Wgtd %)	96.7%	0.0%	0.0%	19.4%	2.7%	4.8%	100.0%	11.0%	0.0%	0.3%	0.0%

Cause di deficit di ferro nella MRC

- Stato infiammatorio cronico
- Ridotto assorbimento intestinale (alti livelli di epcidina, uso di chelanti del fosforo, inibitori della pompa protonica)
- Ridotto intake alimentare (scarso appetito, dieta ipoproteica, malnutrizione)
- Prelievi, ospedalizzazioni
- Perdite gastrointestinali (uso di farmaci antiaggreganti orali, eparina in dialisi)
- Perdite ematiche legate alle procedure dialitiche o per sanguinamenti dell'accesso vascolare)

1 – 2 grammi/anno



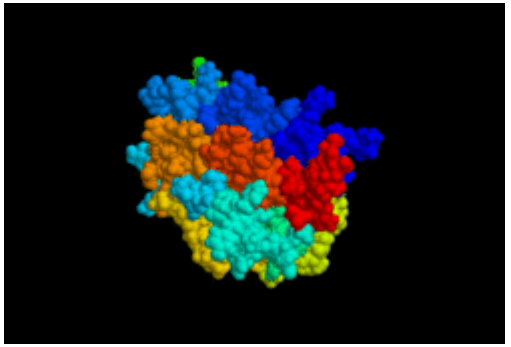

Uremic milieu
Cytokine production
TNF-α (+) IL-6 (+) IL-10 (–)
↑ Erythropoietin resistance
↑ Bone remodeling
↑ Insulin resistance
↑ Muscle catabolism
↑ Acute phase reactants
↓ Fetuin-A
↑ Adipocytokine production
↓ Appetite
↑ Endothelial dysfunction
↑ Monocyte adhesion
↑ Smooth muscle cell proliferation
↑ Oxidative stress
↑ Vascular calcification

The role of chronic inflammation and hepcidin in renal anaemia

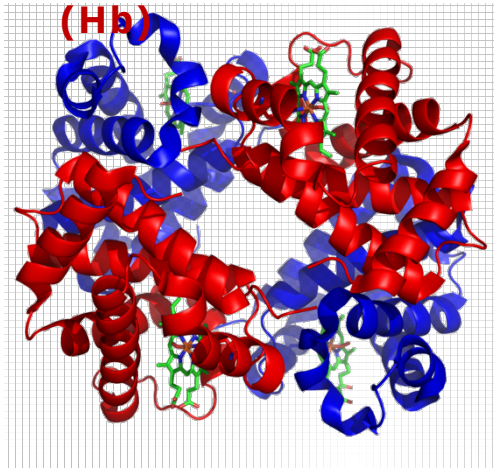
- Inflammatory cytokines (e.g. TNF-α and IFN-γ) reduce erythropoiesis directly by inhibiting growth of erythroid progenitor cells and blunting response to EPO[1]
- Inflammatory cytokines increase levels of hepcidin[2]. Hepcidin inhibits Hb production by blocking iron export[2] from the:

1. RES cells into the plasma, restricting release of recycled iron
2. Enterocytes into the plasma, limiting dietary iron uptake
3. Hepatocytes, limiting release of storage iron

The EPO molecule

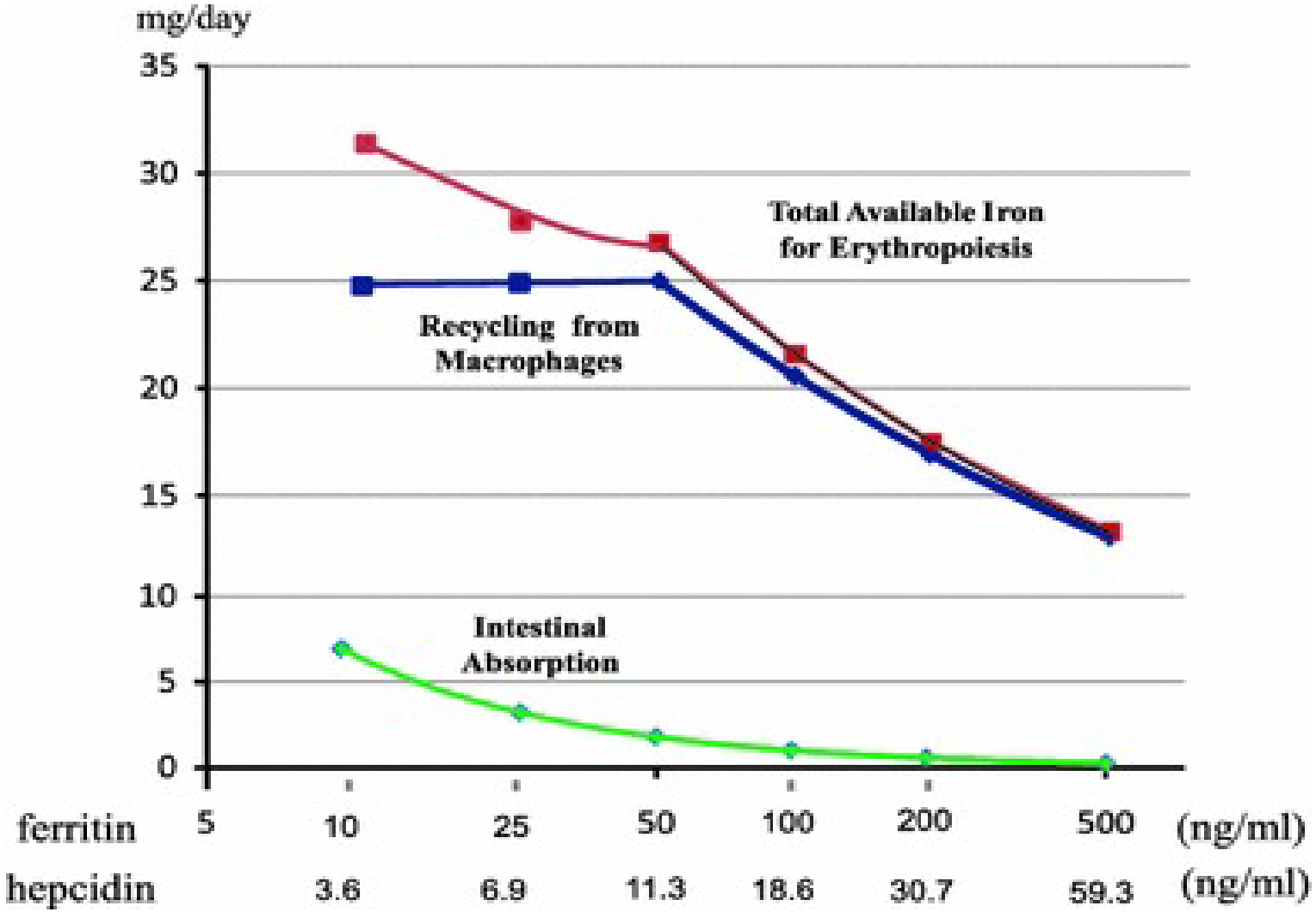


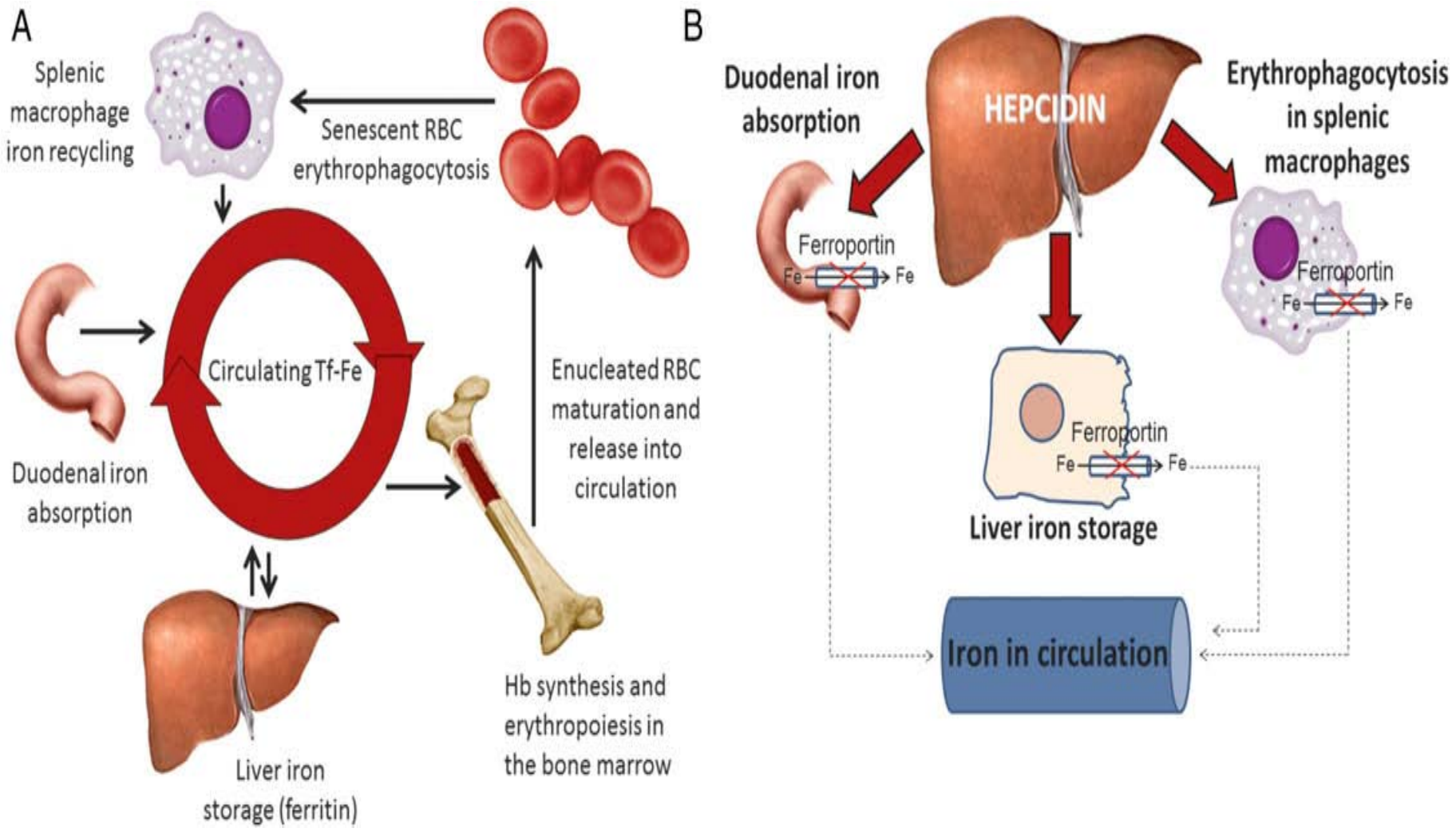
Haemoglobin (Hb)



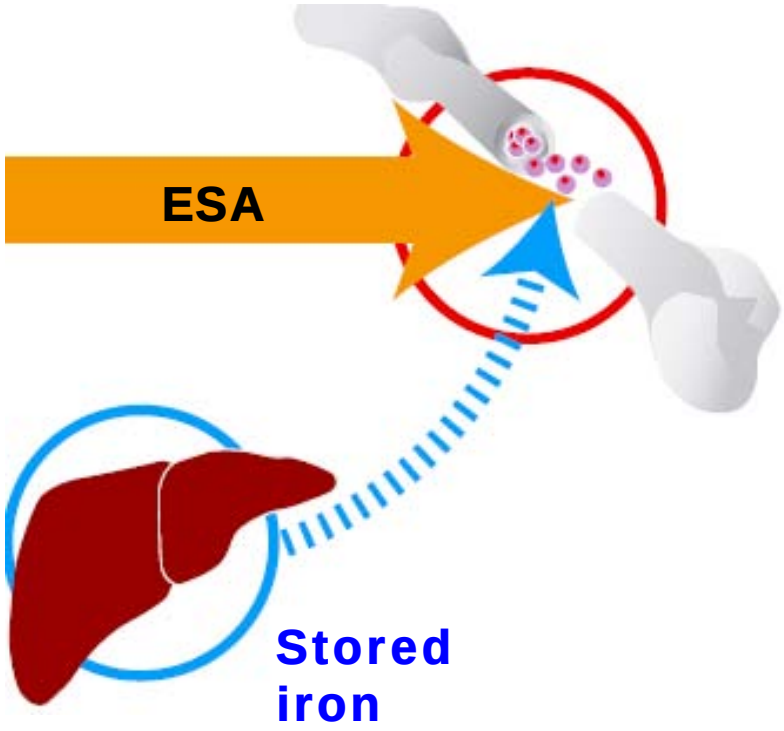
EPO, erythropoietin

1. Weiss G. Blood Reviews 2002; 16: 87-96
2. Handelman GJ et al. Heart Fail Rev 2008; 13: 393-404


mg/day
35
30
25
20
15
10
5
0
Total Available Iron
for Erythropoiesis
Recycling from
Macrophages
Intestinal
Absorption
ferritin
5
10
25
50
100
200
500
(ng/ml)
hepcidin
3.6
6.9
11.3
18.6
30.7
59.3
(ng/ml)


A
Splenic macrophage iron recycling
Senescent RBC erythrophagocytosis
Circulating Tf-Fe
Duodenal iron absorption
Enucleated RBC maturation and release into circulation
Hb synthesis and erythropoiesis in the bone marrow
Liver iron storage (ferritin)
B
Duodenal iron absorption
HEPCIDIN
Erythrophagocytosis in splenic macrophages
Ferroportin
Fe
Fe
Ferroportin
Fe
Fe
Ferroportin
Fe
Fe
Liver iron storage
Iron in circulation

Increased need for iron during ESA therapy



- ESA increases the need for iron for synthesis of new red blood cells
- In the first 3 months of ESA therapy, a haemodialysis patient needs up to 30mg supplemental iron/24h (about 1000mg per month)
- Adequate iron availability increases erythropoiesis and reduces ESA requirements

ESA, erythropoiesis stimulating agent

European Best Practice Guidelines. Nephrol Dial Transplant 2004; 19 (Suppl 2): ii6-15

Sensitivity and specificity of iron measures for detecting functional iron deficiency in patients with CKD

Reference	Patients	Iron measures	Sensitivity (%)	Specificity (%)
Stancu et al	CKD	BM iron (-)	65	65
Fishbane et al.	HD	Ferritin < 100 mg TSAT < 21%	48 81	75 63
Tessitore et al.	HD	Ferritin < 100 mg TSAT < 19%	35 59	78 78
Mittman et al	HD	Ferritin < 100 mg TSAT < 20% CHr <28 pg	38 50 78	53 60 71
Tarng et al	HD	CHr<28 pg	78	87
Tarng et al	HD	TfR-F >0.6	90	79

Hung and Tarng AJKD vol 55, N° 4 (April), 2010: pp 617-621

Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following pubblication of the Trial to reduce Cardiovascular Events with Aranesp Therapy (TREAT) Study

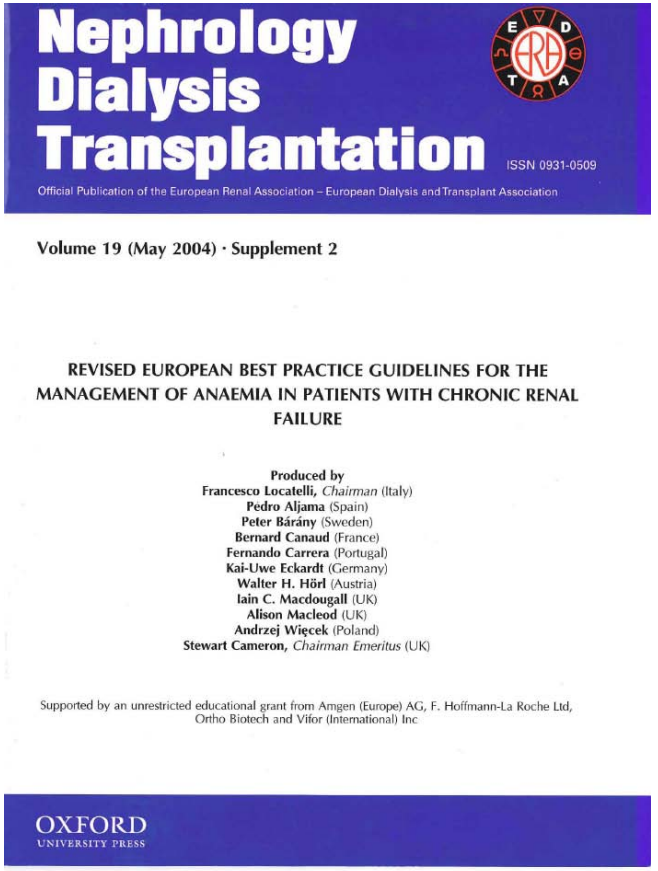
- Iron administration is an important factor for the successful treatment with any kind of ESA in order to use the lowest dose for reaching and maintaining the desidered Hb target
- ESA treatment should not be started in patients who are iron-deficient
- Iron replacement should be used first in any CKD patient who is proven or likely to be iron-deficient, and only once the iron stores are replete should ESA therapy be initiated

NDT Nephrology Dialysis Transplantation

Locatelli F. et al. Nephrol Dial Transplant (2010) 25: 2846-2850

European Best Practice Guidelines: Recommendations for route of iron supplementation

- "I.v. administration is the optimal route for the delivery of iron to patients with CKD, as oral iron is poorly absorbed in uraemic individuals"
- "There is strong evidence from randomised, controlled trials that treatment with i.v. iron is more effective than oral iron in renal failure patients"



European Best Practice Guidelines. Nephrol Dial Transplant 2004; 19 (Suppl 2): ii6-131

La terapia marziale nella MRC: linee guida

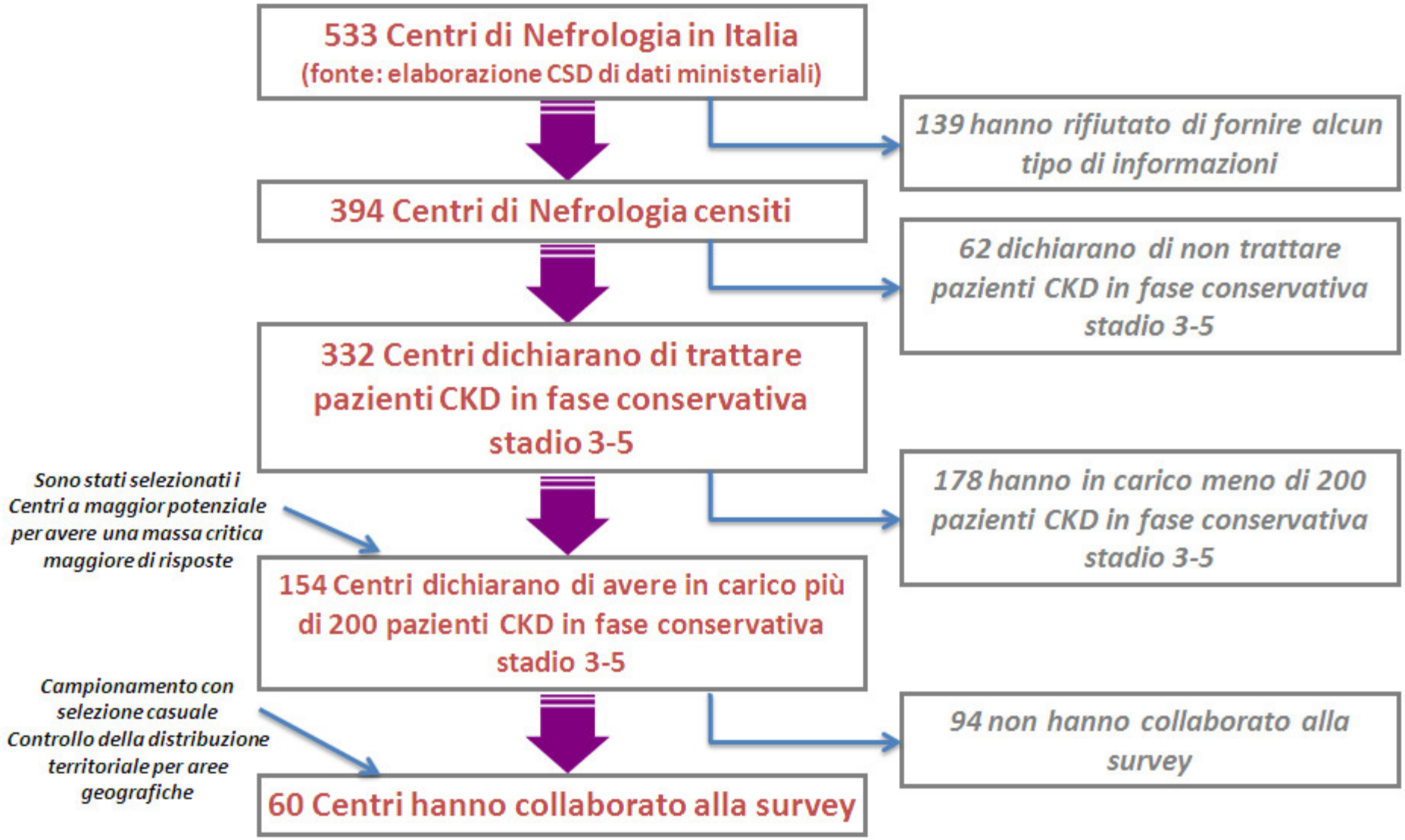
KDOQI	**A trial of iron treatment could be considered when TSAT is ≤ 30% even if ferritin is > 500 ng/ml**
KDIGO	A trial of iron treatment is suggested in patients with TSAT ≤ 30% and ferritin ≤ 500 ng/ml
KHA-CARI	Target levels: TSAT > 20% (prior to ESA), 20-30% (during ESA) Ferritin > 100 ng/ml (prior to ESA), 200-500 ng/ml (during ESA)
ERBP	Thresholds for iron overload: Ferritin > 500 ng/ml and TSAT > 30%
CSN	Target levels: TSAT > 20% Ferritin > 100 ng/ml (ND and PD), > 200 ng/ml (HD)
JSDT	Target levels: TSAT > 20% Ferritin > 100 ng/ml

Giornale Italiano di Nefrologia

PegasoNews

Diagnosi e trattamento dell'anemia sideropenica in pazienti con CKD non-dialitica

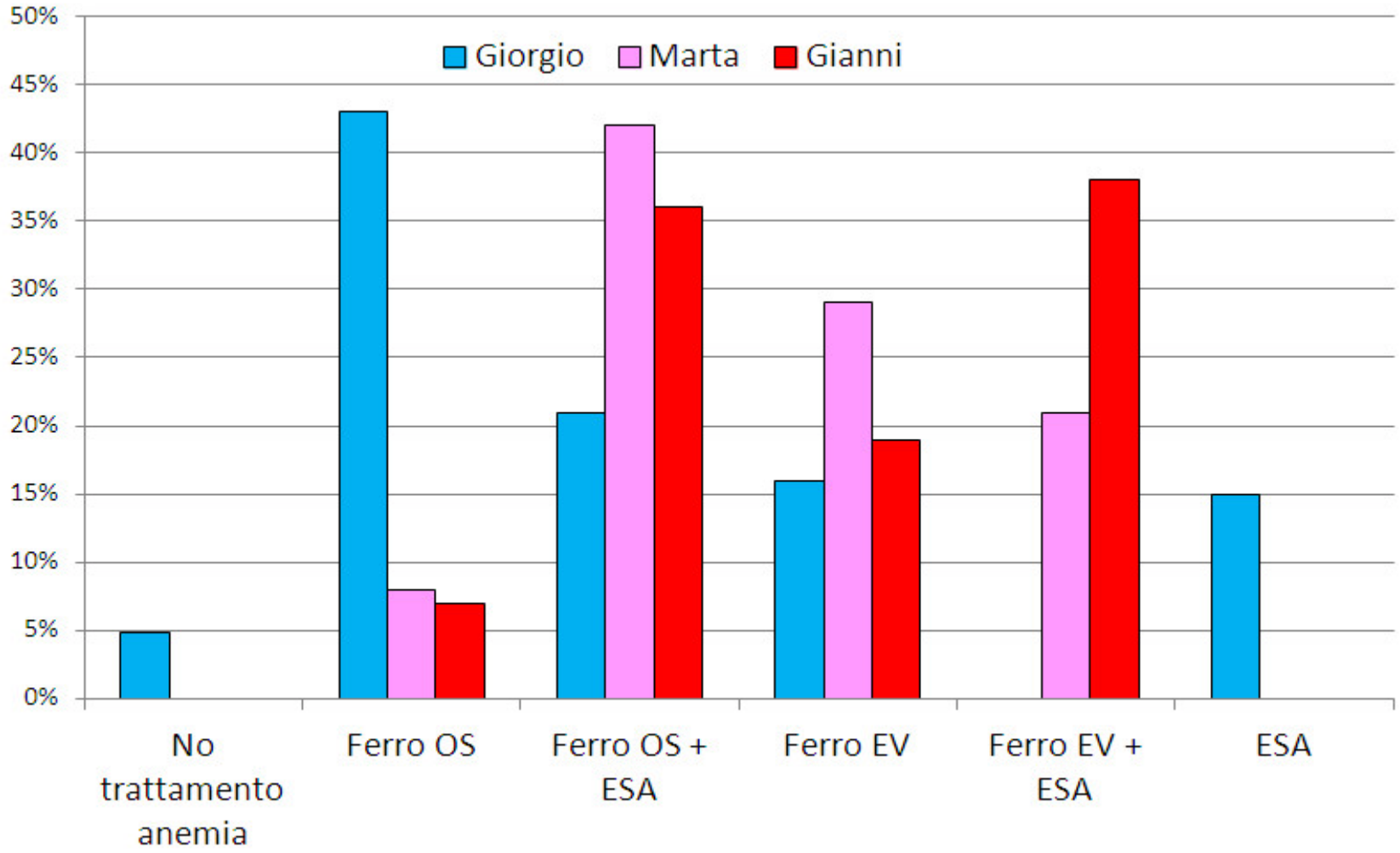
Locatelli F. et al. G Ital Nefrol 2013; 30 (6) 1:18


533 Centri di Nefrologia in Italia
(fonte: elaborazione CSD di dati ministeriali)
139 hanno rifiutato di fornire alcun tipo di informazioni
394 Centri di Nefrologia censiti
62 dichiarano di non trattare pazienti CKD in fase conservativa stadio 3-5
332 Centri dichiarano di trattare pazienti CKD in fase conservativa stadio 3-5
Sono stati selezionati i Centri a maggior potenziale per avere una massa critica maggiore di risposte
178 hanno in carico meno di 200 pazienti CKD in fase conservativa stadio 3-5
154 Centri dichiarano di avere in carico più di 200 pazienti CKD in fase conservativa stadio 3-5
Campionamento con selezione casuale
Controllo della distribuzione territoriale per aree geografiche
94 non hanno collaborato alla survey
60 Centri hanno collaborato alla survey

Frequenza (%) della terapia marziale nella MRC

Terapia/ Stadio CKD	Stadio 3	Stadio 4	Stadio 5 NoD
Ferro orale	43	33	25
Ferro EV	2	7	13
ESA (EPO)	26	47	58
Altro	2	1	2
Niente	28	12	1

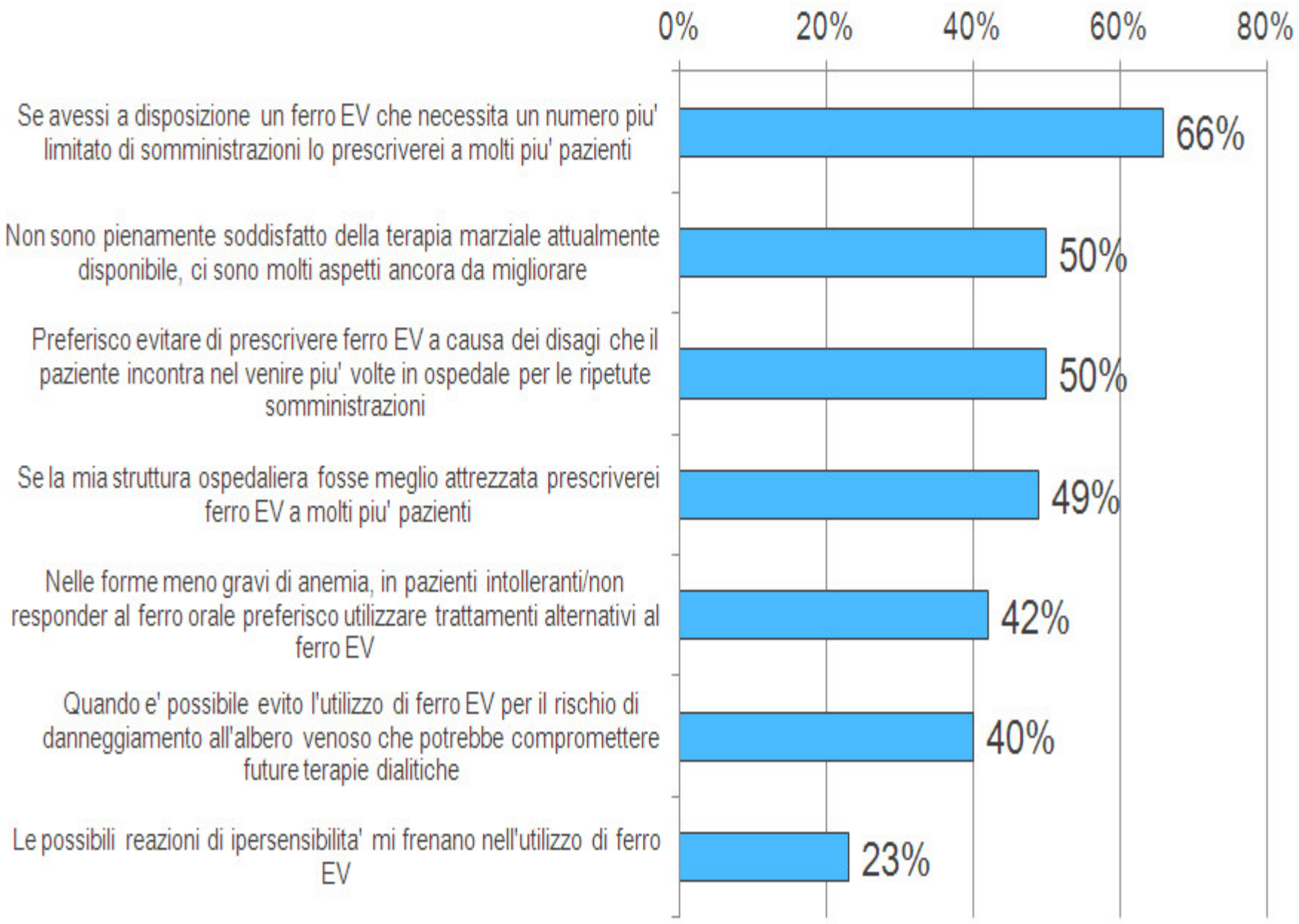
Locatelli F. et al. G Ital Nefrol 2013; 30 (6) 1:18



Giornale Italiano di Nefrologia

Motivi del mancato utilizzo ferro ev

Motivazioni	Totale	Giorgio	Marta	Gianni
Difficile gestione della somministrazione/utilizzo in ospedale	33.8	28.1	40.9	35.3
Anemia modesta/lieve	11.3	21.9	4.5	-
Intolleranza/effetti collaterali	8.5	6.3	13.6	5.9
Non ancora necessario	7	6.3	9.1	5.9
Attesa per capire se ferro os corregge deficit marziale	7	9.4	4.5	5.9
Per salvaguardare il patrimonio venoso	5.6	6.3	4.5	5.9
Costo	4.2	3.1	4.5	5.9
Scarsa efficacia	4.2	3.1	4.5	5.9
Altro	14	12.6	4.5	29.5
Non indica	16.9	15.6	18.2	17.6


0%
20%
40%
60%
80%
Se avessi a disposizione un ferro EV che necessita un numero piu' limitato di somministrazioni lo prescriverei a molti piu' pazienti
66%
Non sono pienamente soddisfatto della terapia marziale attualmente disponibile, ci sono molti aspetti ancora da migliorare
50%
Preferisco evitare di prescrivere ferro EV a causa dei disagi che il paziente incontra nel venire piu' volte in ospedale per le ripetute somministrazioni
50%
Se la mia struttura ospedaliera fosse meglio attrezzata prescriverei ferro EV a molti piu' pazienti
49%
Nelle forme meno gravi di anemia, in pazienti intolleranti/non responder al ferro orale preferisco utilizzare trattamenti alternativi al ferro EV
42%
Quando e' possibile evito l'utilizzo di ferro EV per il rischio di danneggiamento all'albero venoso che potrebbe compromettere future terapie dialitiche
40%
Le possibili reazioni di ipersensibilita' mi frenano nell'utilizzo di ferro EV
23%

Pharmacological characteristics of the main i.v iron complexes

	Sodium ferric gluconate	Iron sucrose	Ferric carboxymaltose
Trade name	Ferrlicit	Venofer	Ferinject
Carbohydrate shell	Gluconate	Sucrose	Carboxymaltose
Molecular weight	37500	34000-60000	150000
Classification	Type III	Type II	Type I
Iron content (mg/ml)	12.5	20	50
Half-life (hours)	1	6	7-12
Maximum single dose (mg)	125	200	15 mg/Kg (max 1000 mg)
Reactivity with transferrin	High	Medium	Low
Test dose required	No	No	No
In vitro percentage iron donation to transferrin	5.8	4.5	2.4-3.4

PIA FONDAZIONE DI CULTO E RELIGIONE CARD. G. PANICO

Esperienza del ferro e.v nel paziente con malattia renale cronica non in dialisi

Caratteristiche cliniche basali

Variabili	Soggetti (n=6)
Età (anni)	78.5 ± 8.8
Sesso F/M (n)	5/1
Hb (g/dl)	9.1 ± 0.9
Ferritina (ng/ml)	57.9 ± 103
TSAT (%)	7.6 ± 3.01
Creatinina (mg/dl)	2.56 ± 0.5
eGFR (ml/m/1.73m2-MDRD)	21.1 ± 5.2
Terapia con ESA (n)	3
Ferro per os (n)	5

Ferrocarbossimaltosio e.v

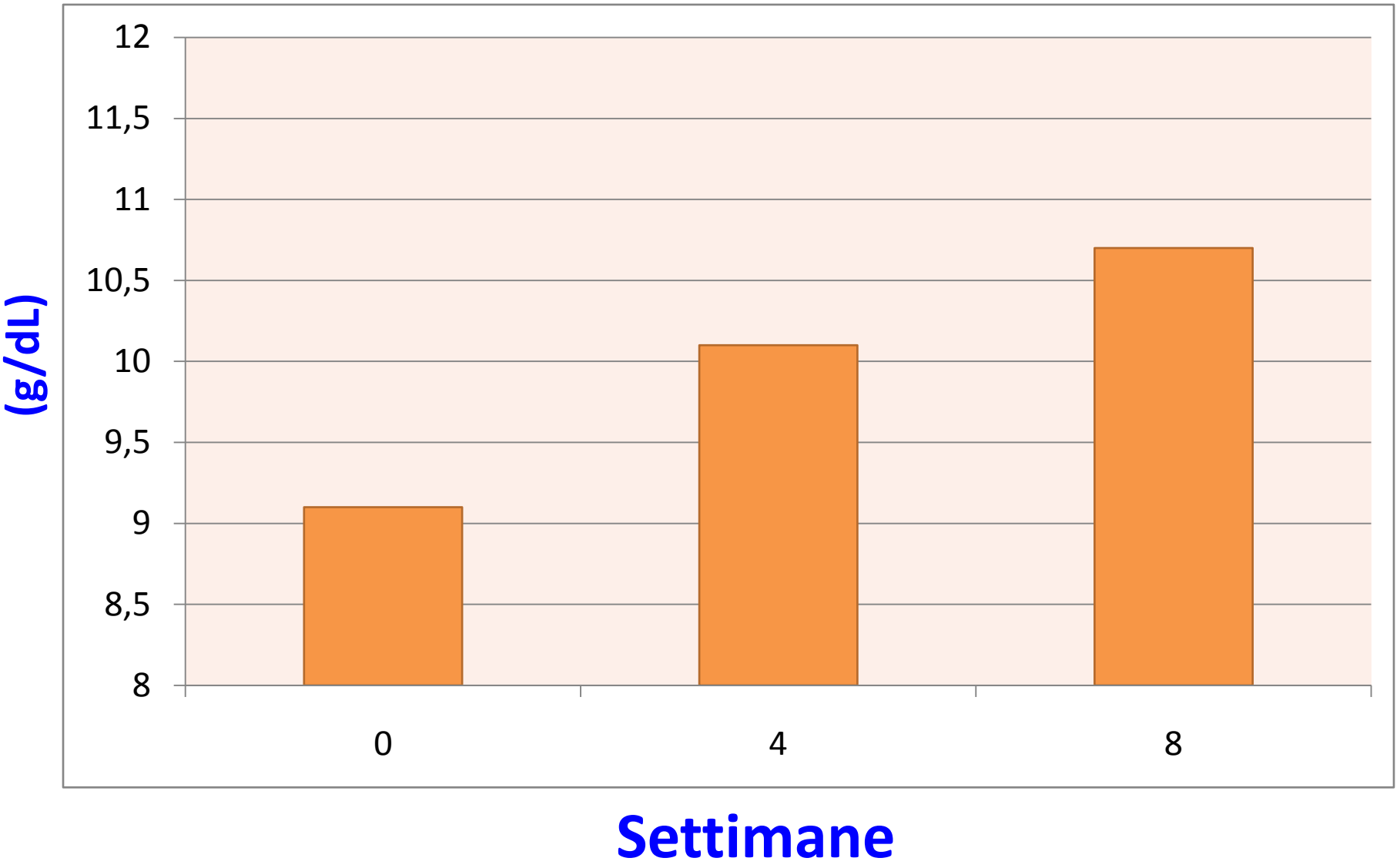
N° fiale somministrate

2.66 ± 0.51

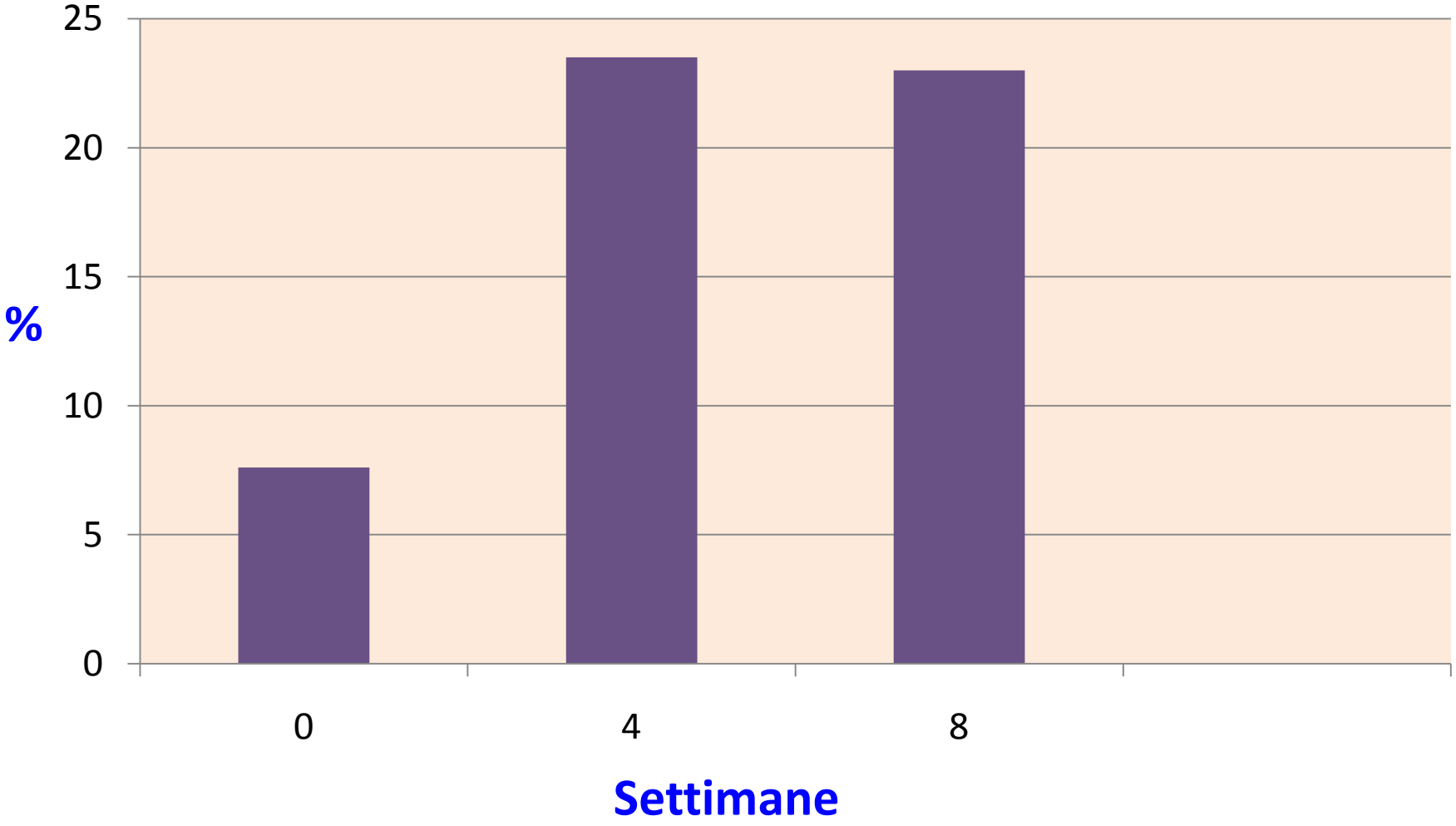
Dosaggio

800 ± 178.8 mg

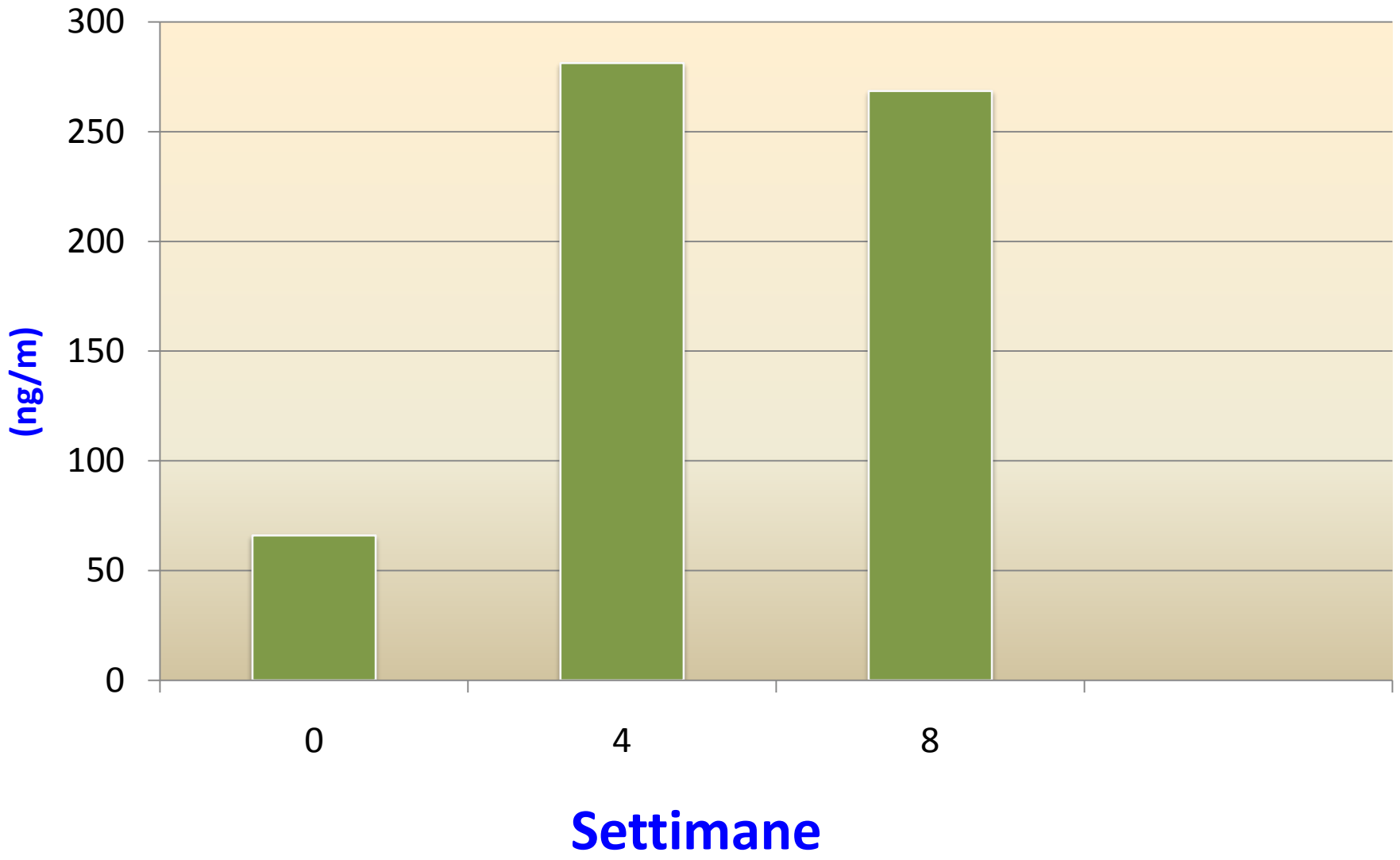
Hb



TSAT



Ferritina



PIA FONDAZIONE DI CULTO E RELIGIONE CARD. G. PANICO

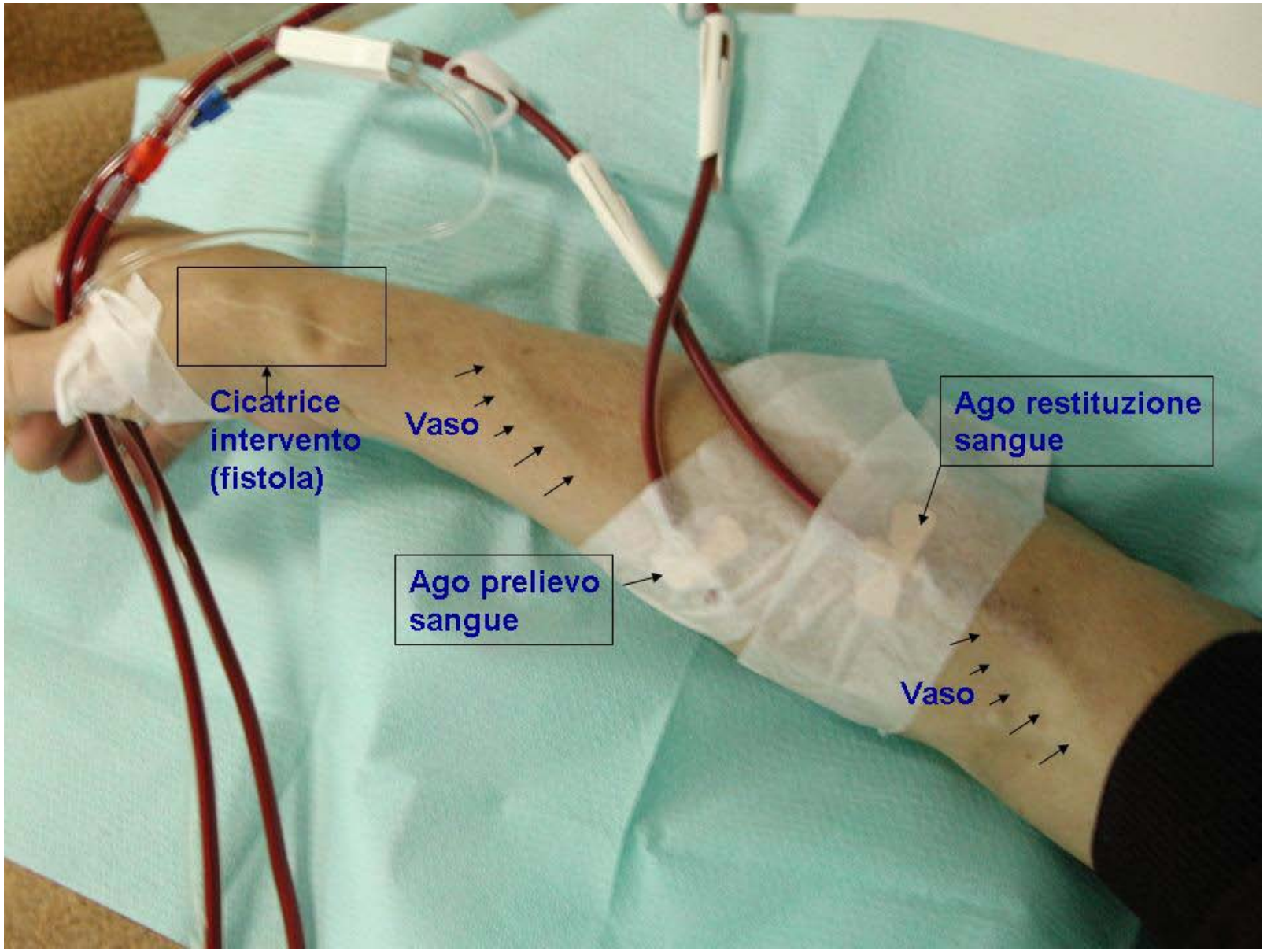
Esperienza del ferro e.v nel paziente emodializzato

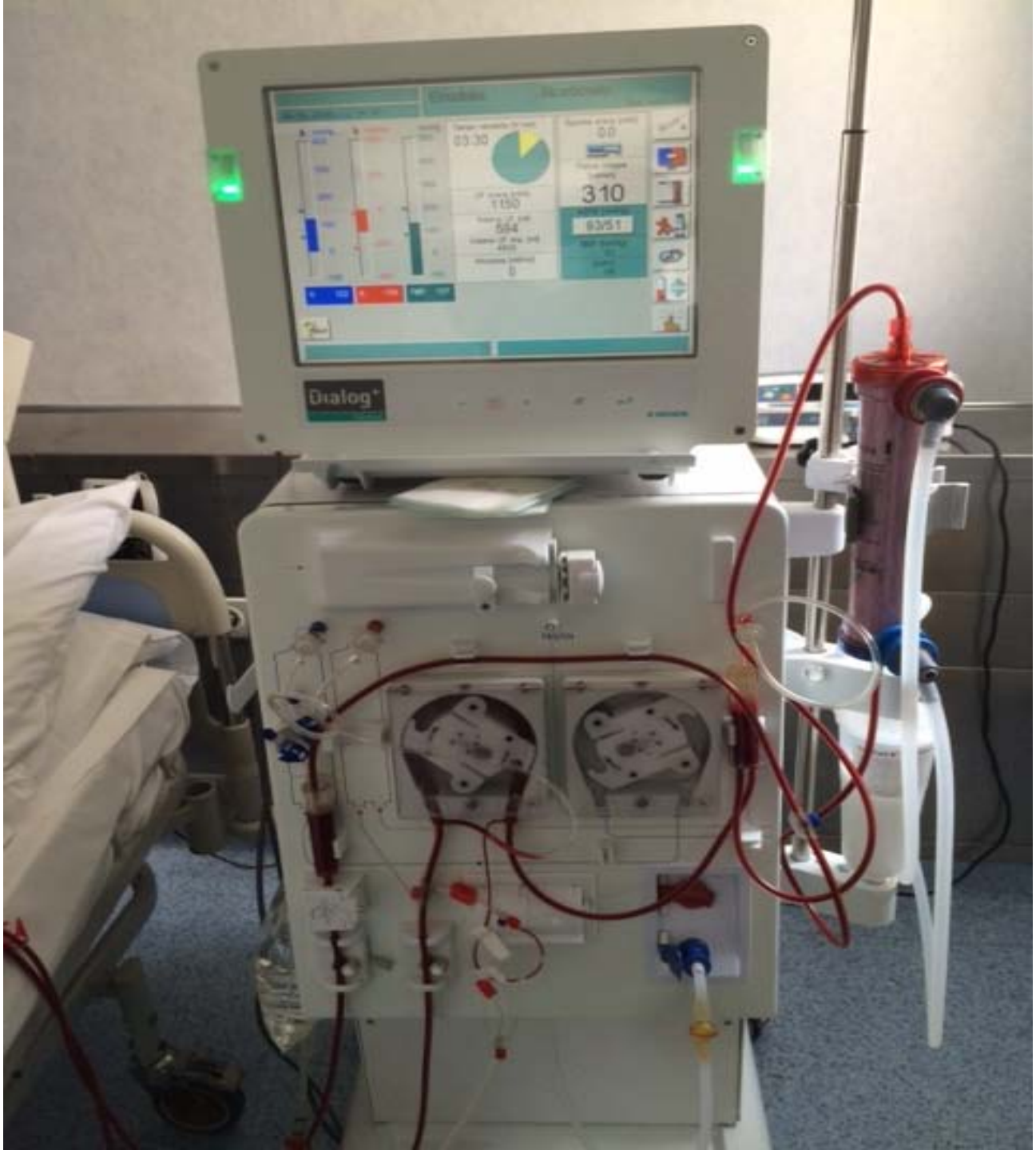
		Ferro carbossimaltosio (n=83)	Ferro saccarato (n=11)	Ferro gluconato (n=17)	ANOVA (valore p)
Età (anni)	Media	66.5	67.6	72.2	0.292
	DS	14.3	11.4	11.0	
Anzianità HD (mesi)*	Mediana	51	36	72	0.494*
	Min	3	21	10	
	Max	324	324	240	
Peso (Kg)	Media	66.5	71.6	68.7	0.457
	DS	13.9	14.1	11.0	
Durata terapia (mesi) *	Mediana	3	4	4	0.802*
	Min	1	1	1	
	Max	12	6	12	
Numero fiale *	Mediana	15	14	23	0.048*
	Min	4	7	4	
	Max	49	26	53	
Hb T0	Media	10.0	10.1	10.0	0.888
	DS	0.8	0.7	0.8	
Saturazione T0	Media	14.5	19.6	15.3	0.081
	DS	6.2	7.1	6.4	
Ferritina T0	Mediana	67	36	92	0.979*
	Min	6	10	10	
	Max	436	245	242	

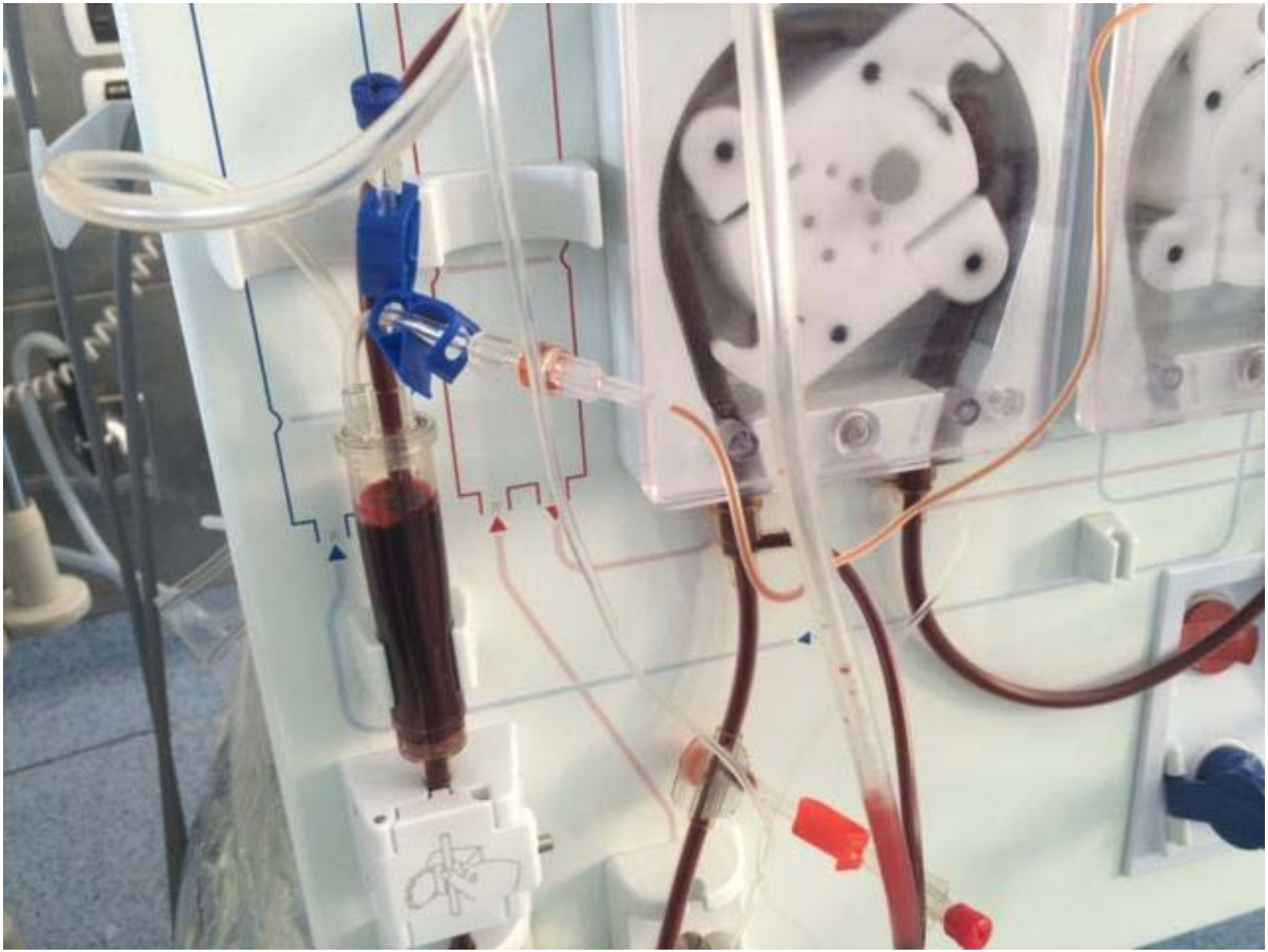
*dopo trasformazione logaritmica

Dosaggio del ferro e.v

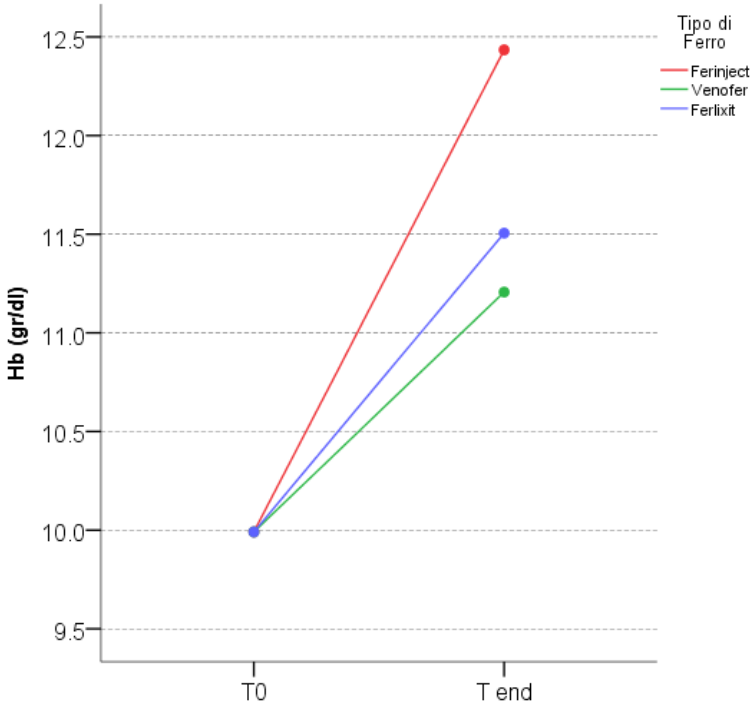
- Ferrocarbossimaltosio: 100 – 200 mg/settimana, 100 mg/settimana, 100 mg ogni 15 giorni
- Ferro saccarato: 100 – 200 mg/settimana, 100 mg/settimana, 100 mg ogni 15 giorni
- Ferro gluconato: 62.5 – 187.5 mg/settimana, 62.5 mg/settimana, 62.5 mg ogni 15 giorni

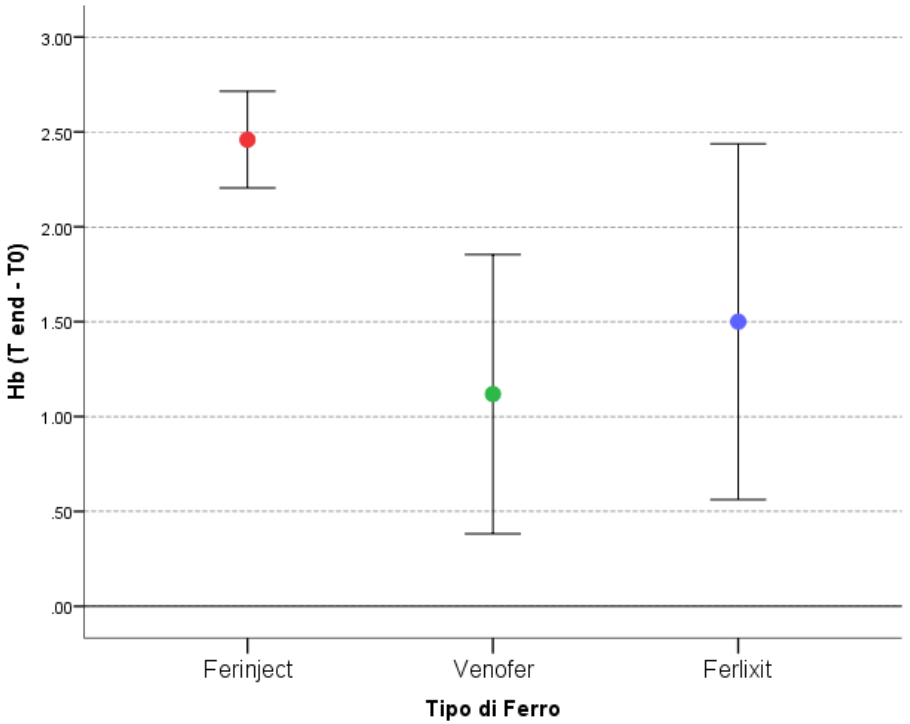

Cicatrice intervento (fistola)
Vaso
Ago restituzione sangue
Ago prelievo sangue
Vaso


Dialog+
310



Hb



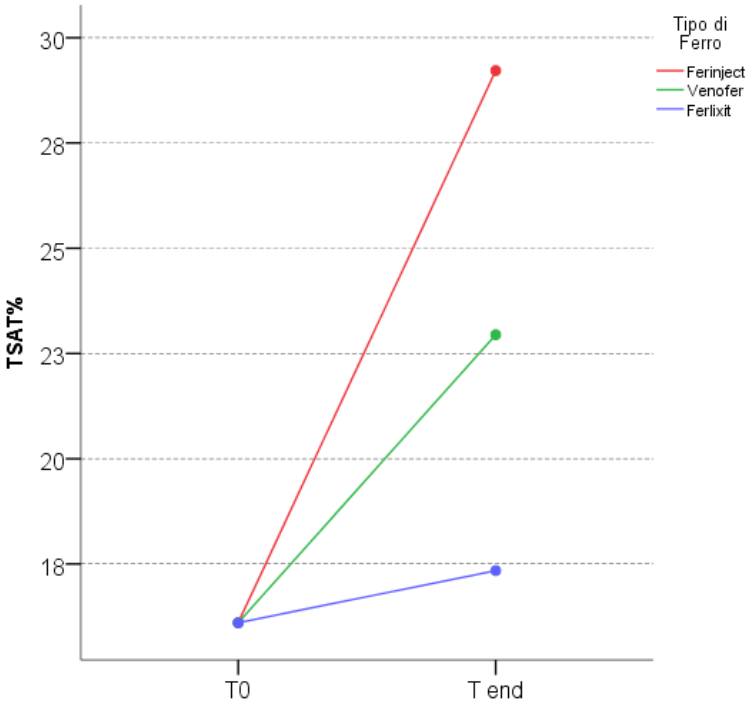


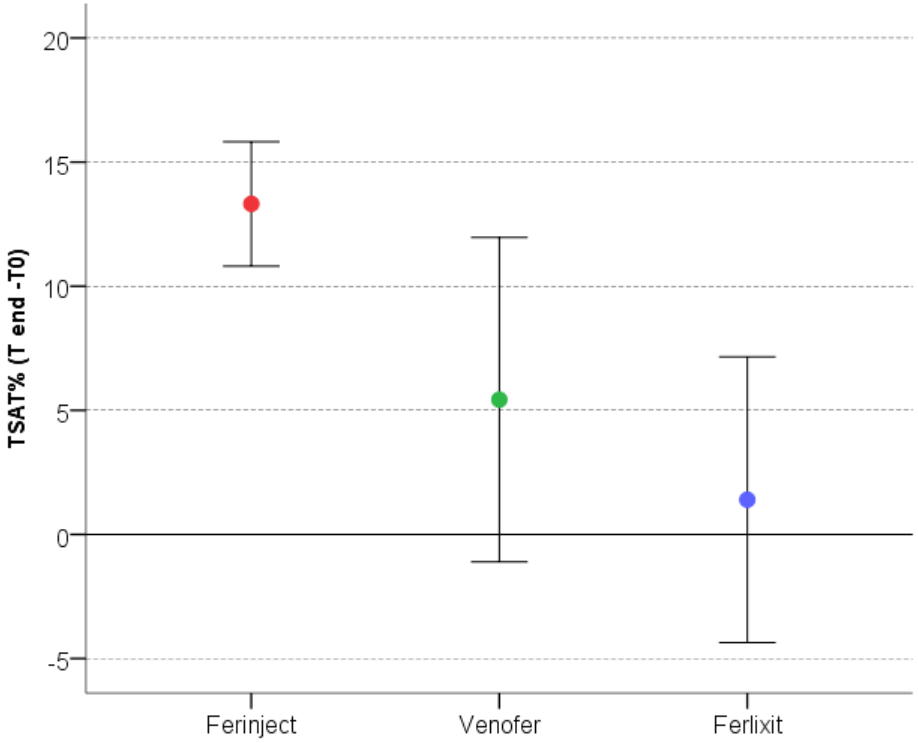
Bonferroni

Dependent Variable: hb_diff

(I) Tipo di Ferro	(J) Tipo di Ferro	Sig.
Ferinject	Venofer	.004
	Ferlixit	.017

TSAT



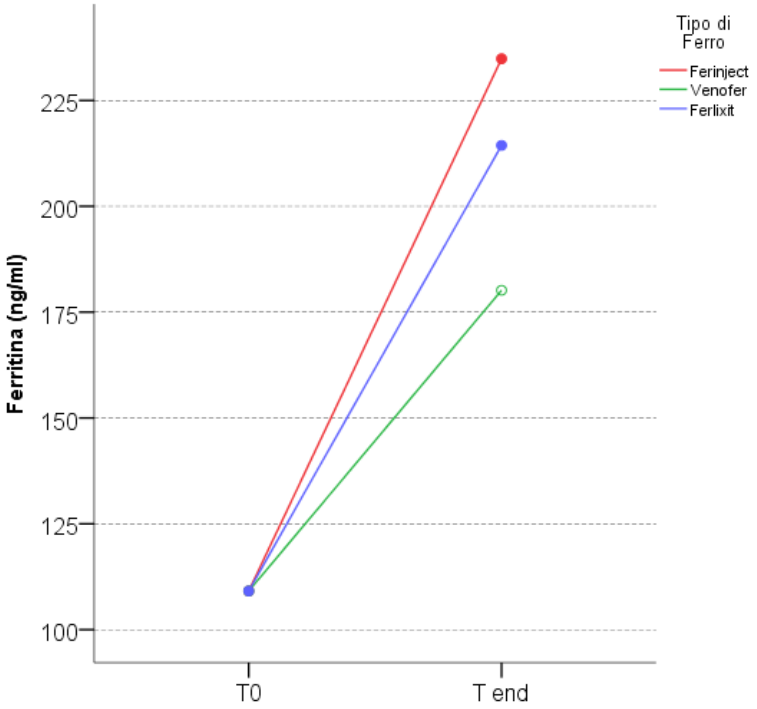


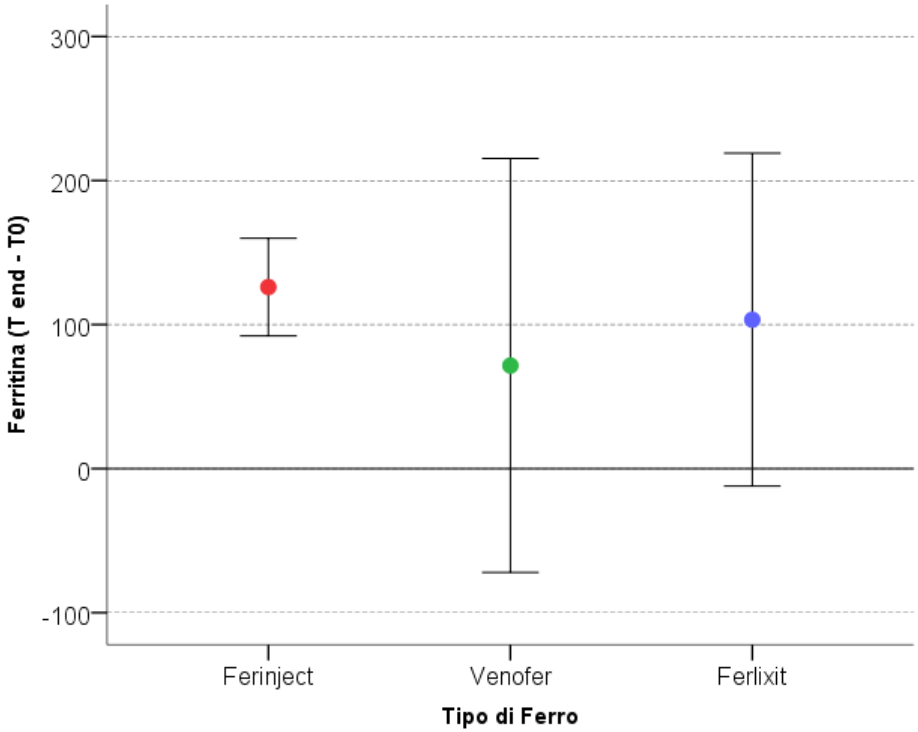
Bonferroni

Dependent Variable: saturazione_diff

(I) Tipo di Ferro	(J) Tipo di Ferro	Sig.
Ferinject	Venofer	.052
	Ferlixit	.000

Ferritina



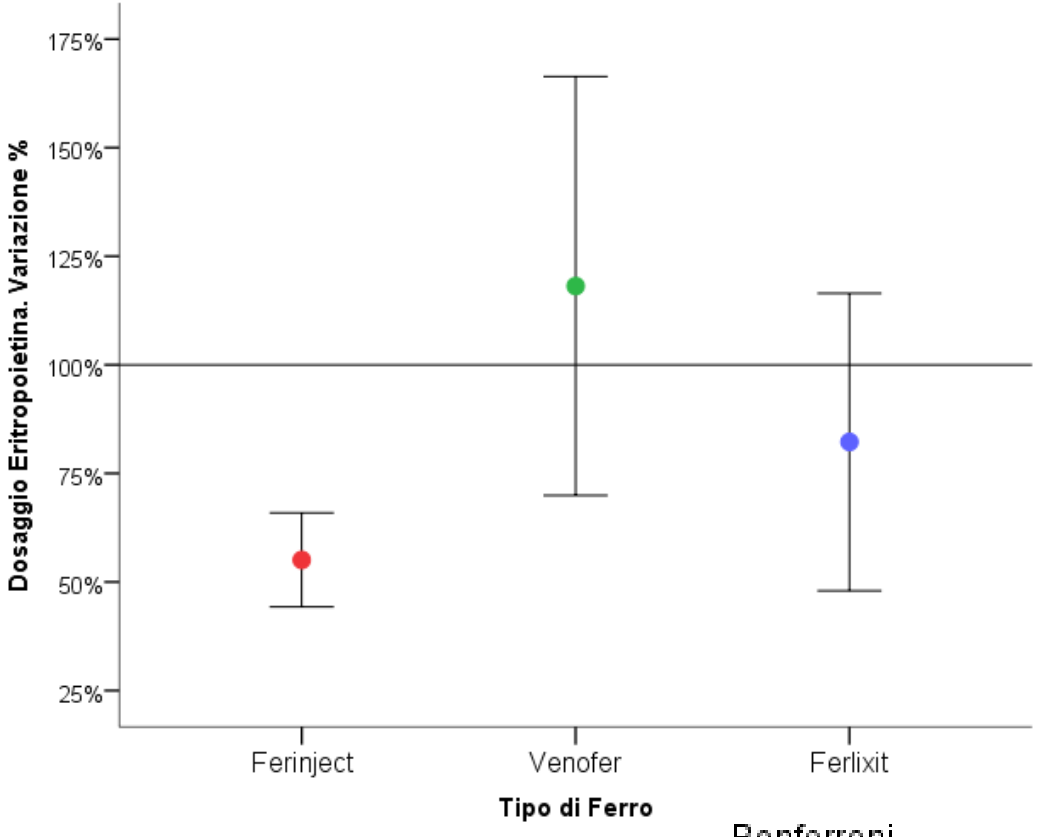


Bonferroni

Dependent Variable: ferritina_diff

(I) Tipo di Ferro	(J) Tipo di Ferro	Sig.
Ferinject	Venofer	.861
	Ferlixit	1.000

Eritropoietina



Bonferroni

Dependent Variable: eritropoietina_change

(I) Tipo di Ferro	(J) Tipo di Ferro	Sig.
Ferinject	Venofer	.002
	Ferlixit	.174

Eritropoietina

Ferro e.v	Pazienti (n)	Pazienti in EPO a T0 (n)	Riduzione dosaggio (n)	Stop EPO (n)	Aumento dosaggio (n)	Nessuna variazione dosaggio (n)
Ferinject	83	68 (81.9%)	46 (67.6%)	8 (11.7%)	3 (4.4%)	11 (16.1%)
Venofer	11	9 (81.8%)	3 (33.3%)	0 (0%)	4 (44.4%)	2 (22.2%)
Ferlixit	17	15 (88.2%)	3 (20%)	3 (20%)	3 (20%)	6 (40%)

Chi-quadro=24.257, p=0.0005

Effetti collaterali

- Ferro gluconato: edema del volto in un paziente

- Ferrocarbossimaltosio – Ferro gluconato: nessun paziente ha presentato segni clinici di rilievo dopo l'infusione del ferro

Conclusioni

La carenza di ferro è una condizione frequente nei pazienti con malattia renale cronica, soprattutto negli emodializzati in cui è indicato l'uso del ferro e.v. con ricorso a molecole che offrano un adeguato profilo in termini di sicurezza ed efficacia clinica (minore tossicità da ferro libero, minore induzione dello stress ossidativo, minore accumulo tissutale, minore rischio infettivo, minore sviluppo di reazioni da ipersensibilità)

Conclusioni

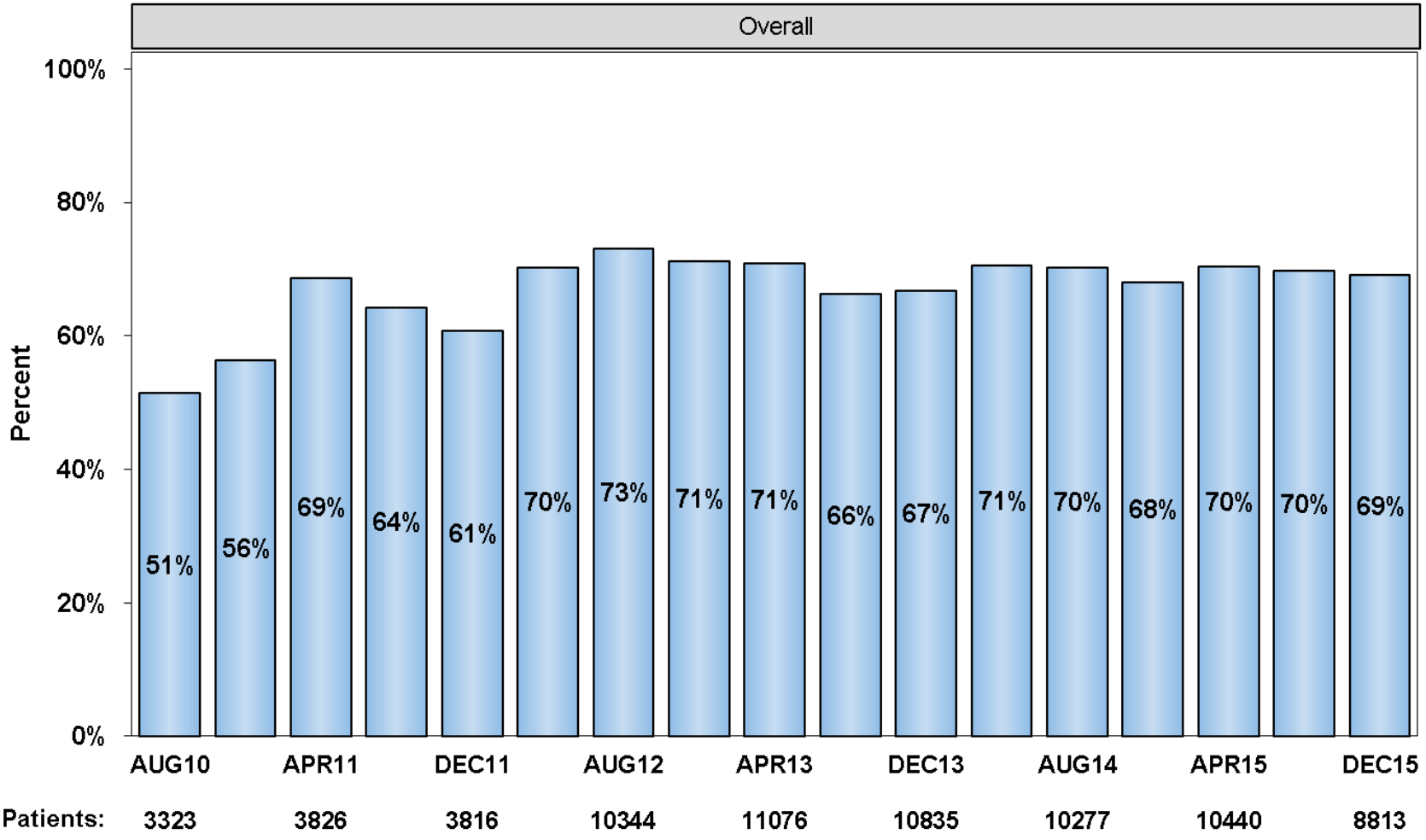
La nostra esperienza clinica nella gestione del deficit marziale nei diversi stadi della malattia renale cronica ha evidenziato l'efficacia e la sicurezza clinica del Ferrocarbossimaltosio con adeguata e progressiva correzione degli indici del deficit di ferro e dei valori di emoglobina in assenza di eventi clinici avversi. Il Ferrocarbossimaltosio presenta infatti delle caratteristiche favorevoli poiché favorisce l'uptake del ferro dal sistema reticolo endoteliale in modo controllato e graduale con conseguente minor rilascio di ferro libero e minore attivazione del complesso di eventi che determinano lo stress ossidativo e non mostra una cross reattività con i destrani.

Conclusioni

E’ risultato poi di indubbia utilità nei nefropatici non in dialisi anche per il ridotto numero di somministrazioni con conseguente minor disagio per il paziente, minore sfruttamento del patrimonio vascolare e minore rischio di tossicità da ferro libero. Nei pazienti in trattamento emodialitico un ulteriore beneficio indotto dalla terapia marziale è derivato infine da una importante riduzione dei dosaggi di eritropoietina e quindi dei costi sanitari che ne derivano.

IV iron use, last 1 month

National sample

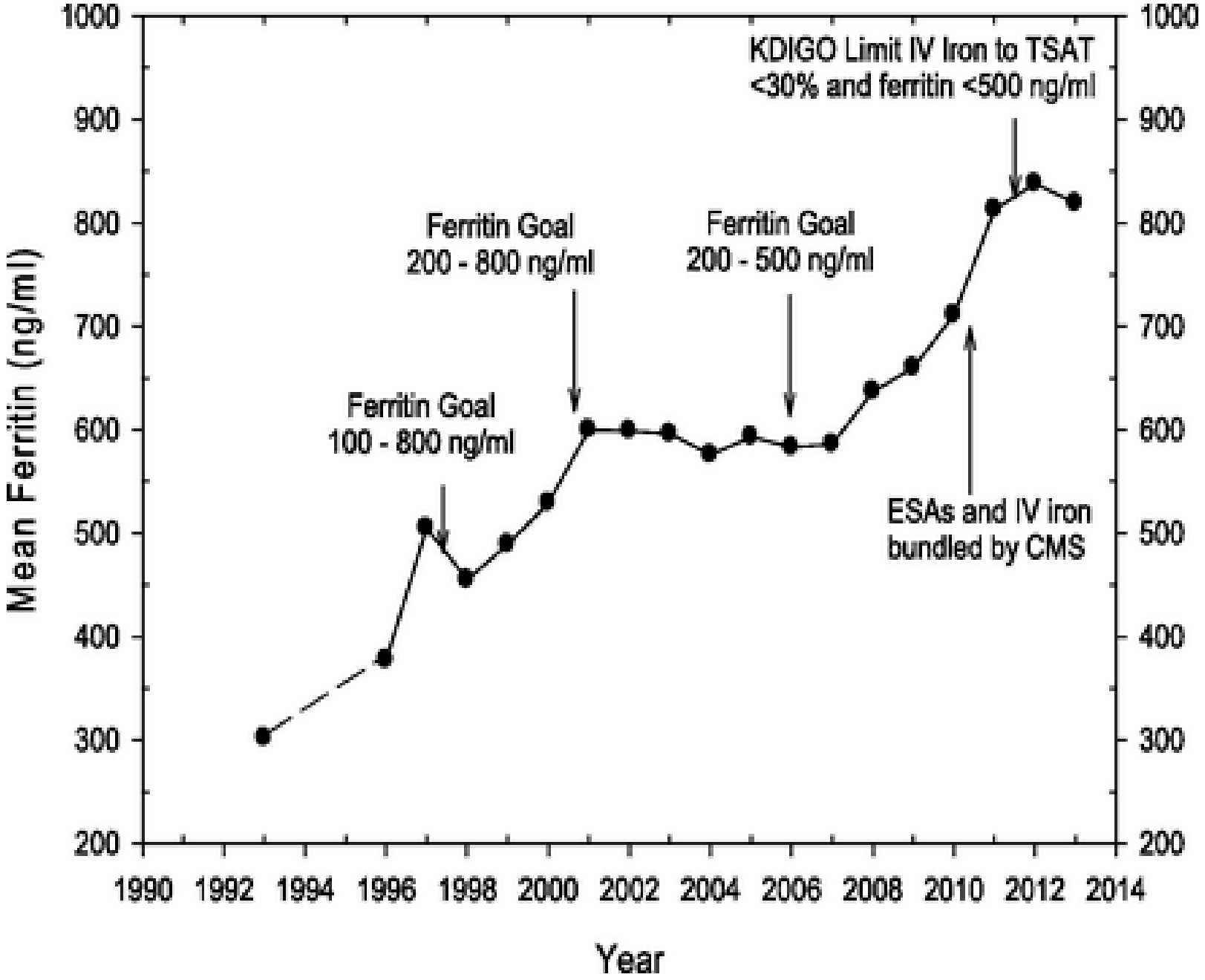


Values for each month reflect prescription at end of study month (2010, 2011) or anytime during study month (2012+)

Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods").

Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").

Source: US-DOPPS Practice Monitor, April 2016; http://www.dopps.org/DPM


Mean Ferritin (ng/ml)
Year
1000
900
800
700
600
500
400
300
200
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
KDIGO Limit IV Iron to TSAT
<30% and ferritin <500 ng/ml
Ferritin Goal
200 - 800 ng/ml
Ferritin Goal
200 - 500 ng/ml
Ferritin Goal
100 - 800 ng/ml
ESAs and IV iron
bundled by CMS

Safety of intravenous iron in clinical practice: implications for anemia management protocols

- Does iv iron therapy increase mortality or morbidity?
- Does iv iron therapy increase risk of infection?
- Does iv iron therapy increase risk of cardiovascular disease?
- What level of serum ferritin is too high for further iv iron therapy?
- Acute adverse events after iv iron: allergy or toxic reaction?

JASN George R. Aronoff J Am Soc Nephrol 15: S99-S106, 2004

Global Action. Local Change.

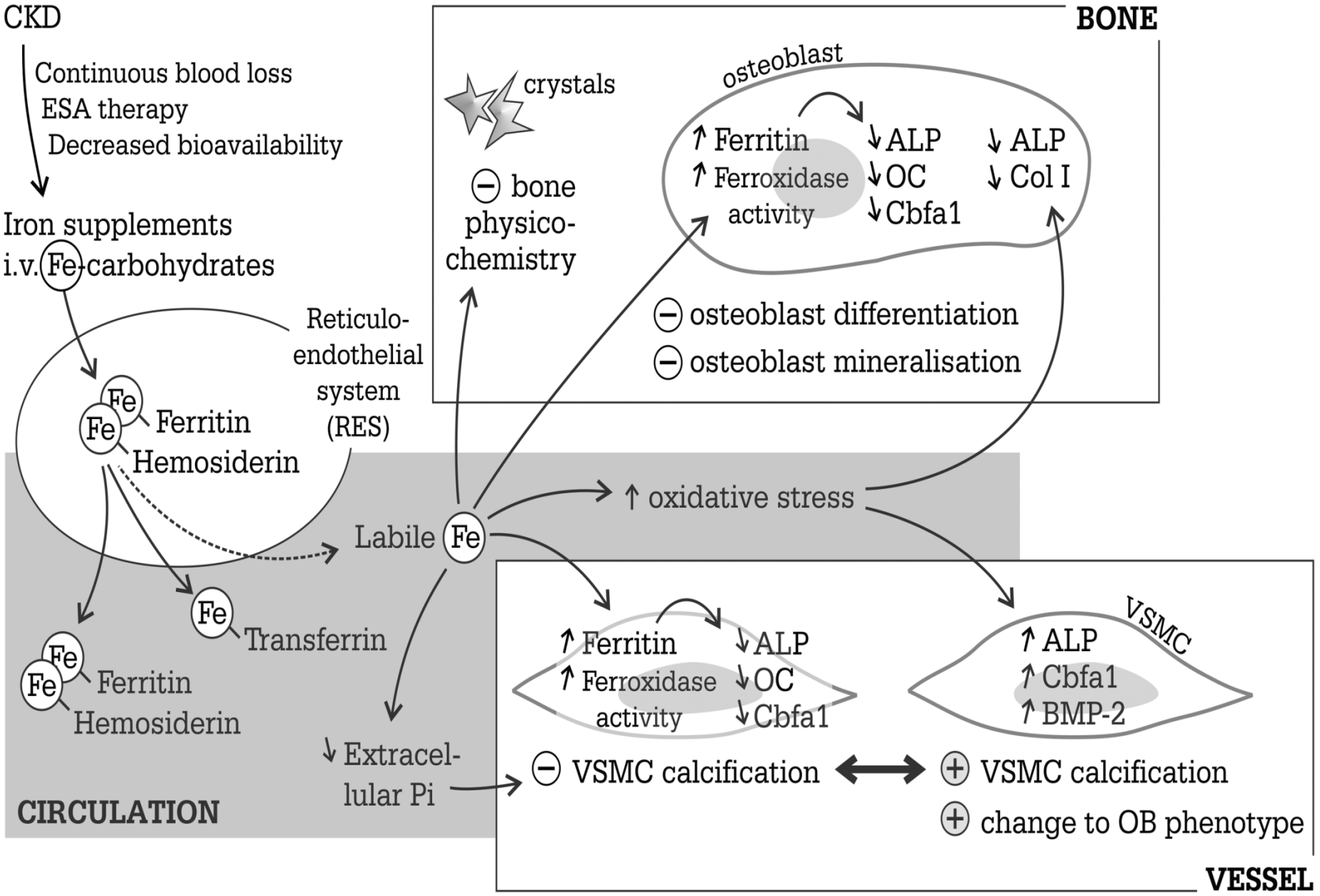
Iron overload
Inflammation and oxidative stress
Iron and infections
Hypersensitivity reactions

KDIGO Controversies Conference on

Iron Management in Chronic Kidney Disease

March 27-30, 2014

San Francisco, USA


CKD
Continuous blood loss
ESA therapy
Decreased bioavailability
Iron supplements
i.v. Fe-carbohydrates
Reticulo-endothelial system (RES)
Fe
Ferritin
Hemosiderin
Transferrin
Labile Fe
CIRCULATION
BONE
crystals
bone physico-chemistry
osteoblast
↑ Ferritin
↑ Ferroxidase activity
↓ ALP
↓ OC
↓ Cbfa1
↓ ALP
↓ Col I
osteoblast differentiation
osteoblast mineralisation
↑ oxidative stress
↓ Extracel-lular Pi
VSMC
↑ ALP
↑ Cbfa1
↑ BMP-2
VSMC calcification
VSMC calcification
change to OB phenotype
VESSEL

Giornale Italiano di Nefrologia

PegasoNews

Virtual visit

- Paziente 1: **Giorgio**, uomo di 45 anni, affetto da CKD stadio 3 e ipertensione arteriosa controllata
- Paziente 2: **Marta**, donna con diabete tipo 2, 50 anni, affetta da CKD stadio 4 e ipertensione controllata, manifestava anemia sideropenica causata da malassorbimento intestinale come conseguenza di una disautonomia , non rispondente al ferro orale
- Paziente 3: **Gianni**, uomo di 85 anni con carcinoma prostatico, affetto da CKD stadio 5 ed ipertensione controllata con anemia sideropenica causata da macroematurie, non rispondente al ferro orale

Iron saccharate injecton (12 hemodialysis patients)

Sample time point	S-Transferrin (g/l)	S-Fe (mmo/l)	Transferrin saturation (%)	BDI (µmol/l) Bleomycin-detectable iron
Before i.v iron injecton	1.7 ± 0.4	8 ± 4	20 ± 12	0.03 ± 0.02
5 min	1.7 ± 0.4	28 ± 9	67 ± 29	0.14 ± 0.28
30 min	1.8 ± 0.4	25 ± 10	59 ± 28	0.07 ± 0.11
90 min	1.8 ± 0.4	28 ± 10	66 ± 27	0.12 ± 0.24
210 min	1.8 ± 0.4	37 ± 14	83 ± 27	0.29 ± 0.34
2 to 3 days after i.v. iron	1.8 ± 0.4	10 ± 7	20± 16	0.02 ± 0.01
Reference values	1.8 – 3.1	7 - 30	17 - 52	< 0.10

NDT Nephrology Dialysis Transplantation

Parkkinen J. Et al. NDT (2000) 15: 1827 - 1834


INFUSIONE
100 ml/h
+ REGOLARE -
ADULTO UTI
VOLUME
0.47 ml
0h 11m 38s
PRESSIONE
147
300 mmHg
VOLUME
VOI
Alaris
CC
25
30
35

Monitoraggio della terapia marziale

Frequenza	Stadio 3	Stadio 4	Stadio 5 ND
Mensilmente	-	3	53
Ogni 2-3 mesi circa	15	58	35
Ogni 4-5 mesi circa	4	32	12
Ogni 6-7 mesi circa	37	5	-
Ogni 8-9 mesi circa	3	2	-
Ogni 12 mesi circa	5	-	-
Ogni quanti mesi (in media)?	**5.4**	**3.4**	**1.9**

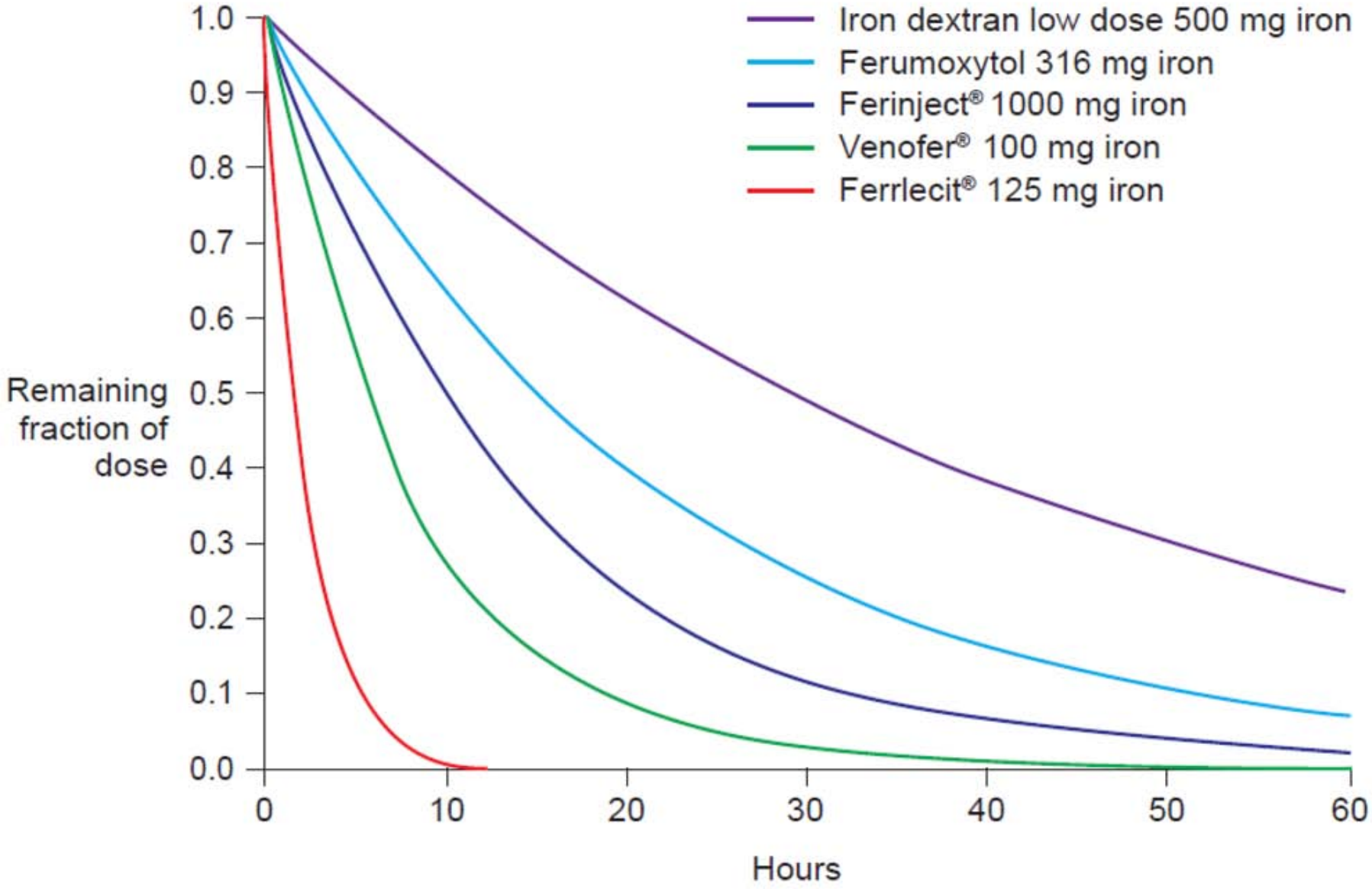
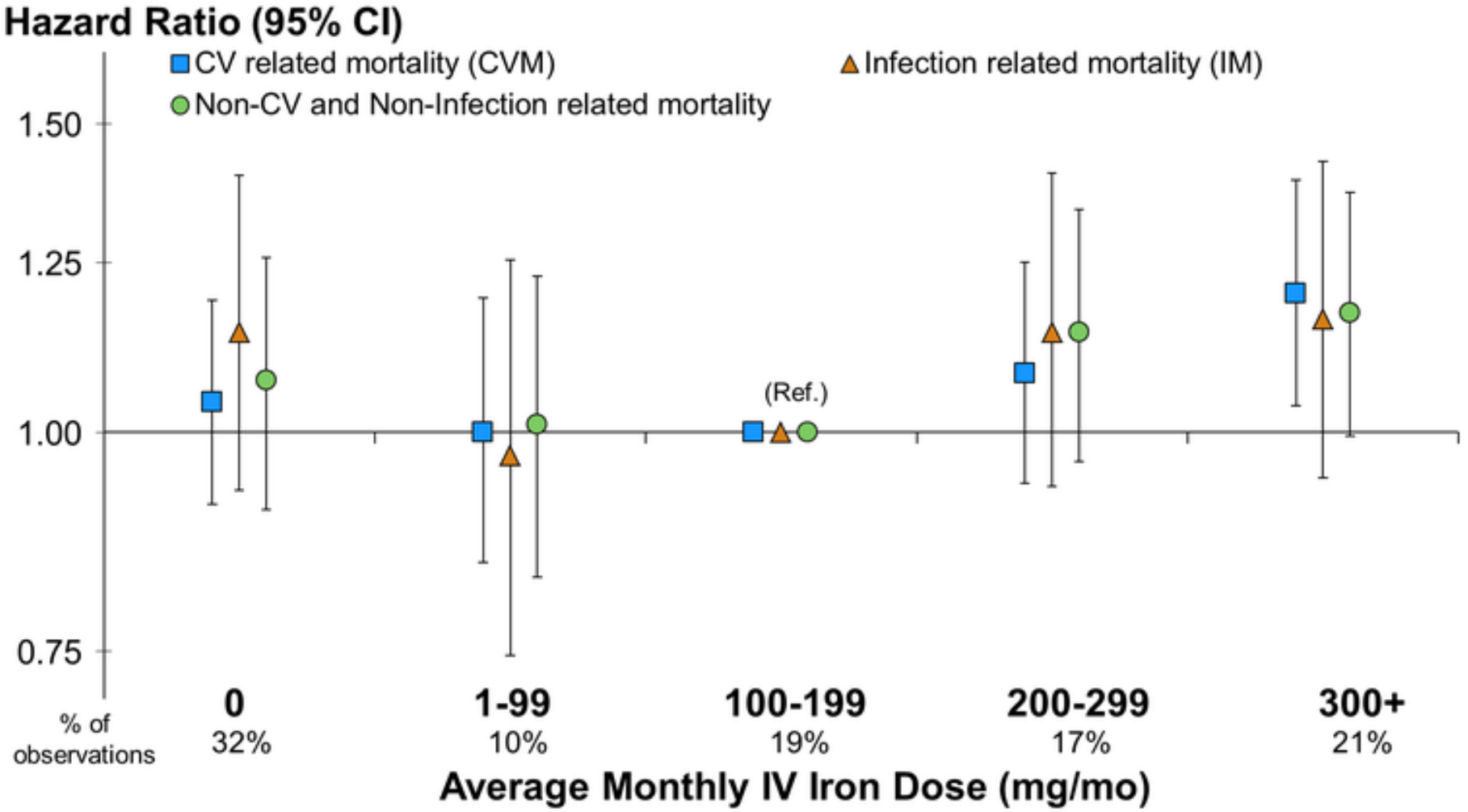

Iron dextran low dose 500 mg iron
Ferumoxytol 316 mg iron
Ferinject® 1000 mg iron
Venofer® 100 mg iron
Ferrlecit® 125 mg iron
Remaining fraction of dose
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
Hours

Figure 1B

IV iron dose categories and cause-specific mortality



IV iron dose is total 4-month dose, expressed as average mg/month.
Adjustments and effect estimates (95% CI) are as per Model 6 in Table 2.

DOPPS

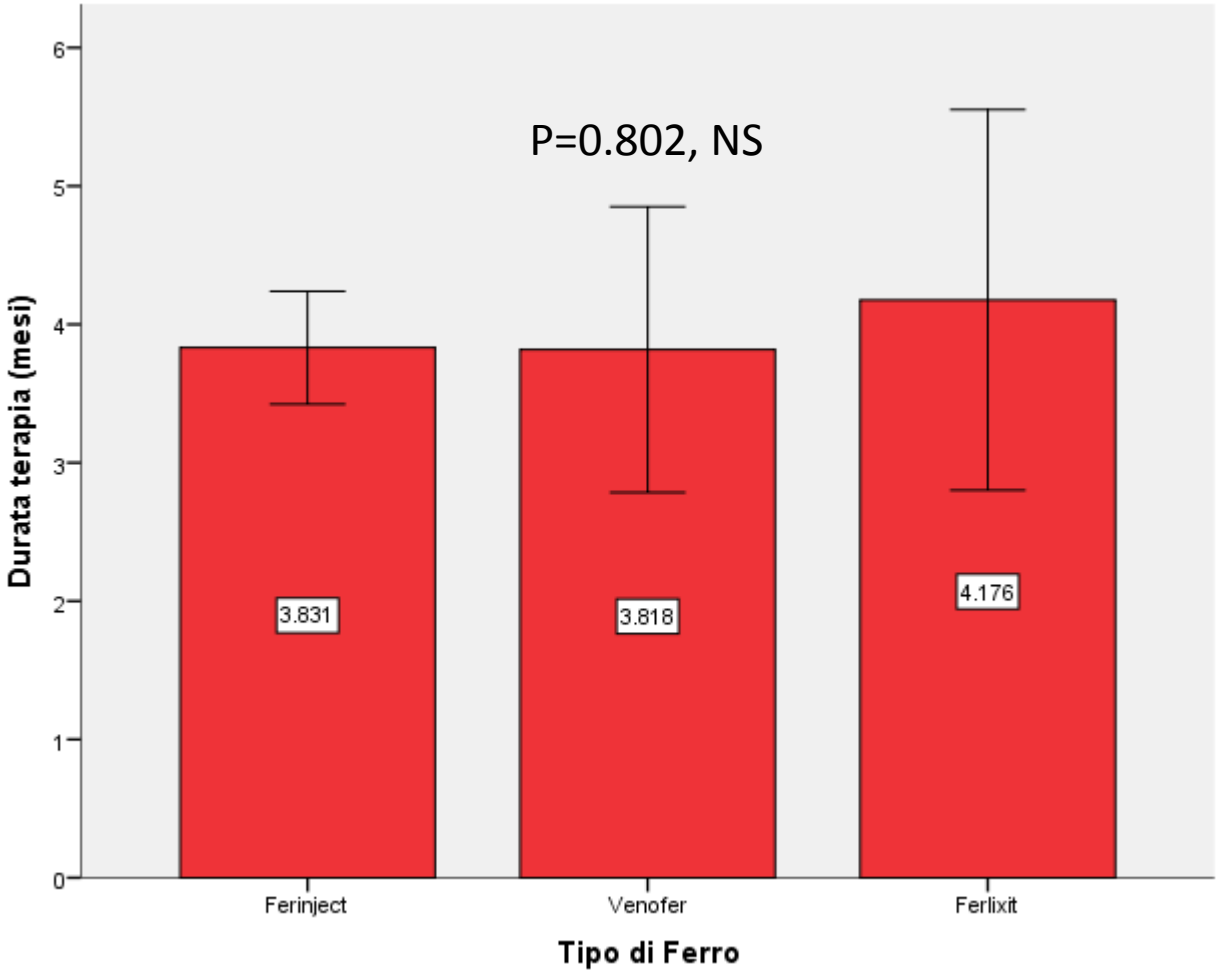
Bailie et al. *Kidney Int. 2015 Jan;87(1):162-8.*

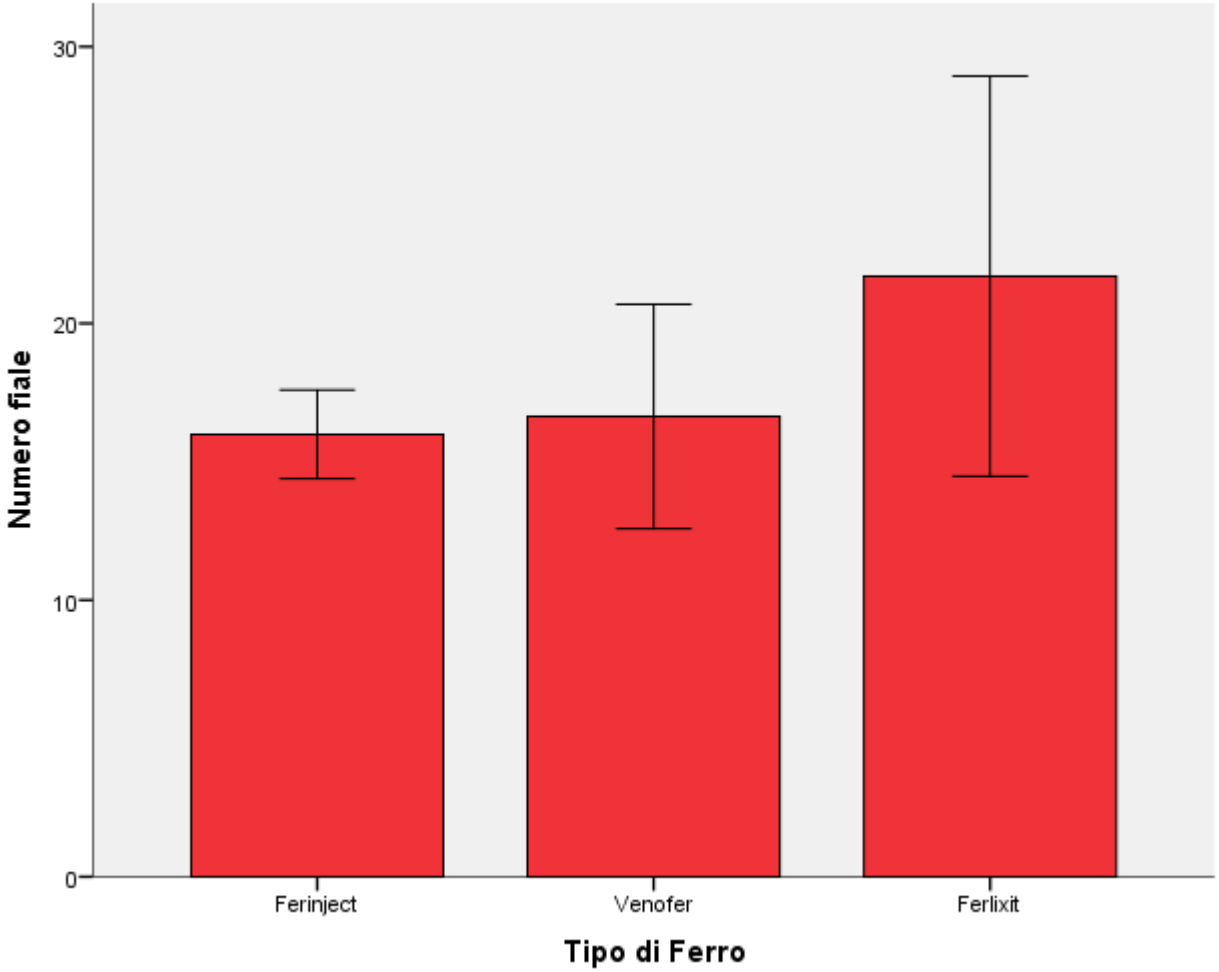
Numero medio di pazienti a centro

	Media	%	St.dev.	Mediana	Min-Max
Pazienti CKD-ND 3-5	521	100	237	410	220-1200
Pazienti con anemia sideropenica	208	**40**	130	177	37-590
Pazienti intolleranti alla terapia marziale	39	**19**	43	26	4-240
Pazienti non reponders alla terapia marziale orale	39	**19**	45	23	5-180

Giornale Italiano di Nefrologia

Locatelli F. et al. G Ital Nefrol 2013; 30 (6) 1:18


P=0.802, NS
Durata terapia (mesi)
0
1
2
3
4
5
6
3.831
3.818
4.176
Ferinject
Venofer
Ferlixit
Tipo di Ferro



Dependent Variable: Numero fiale

Bonferroni

(I) Tipo di Ferro	(J) Tipo di Ferro	Sig.
1 Ferinject	2 Venofer	1.000
	3 Ferlixit	.042