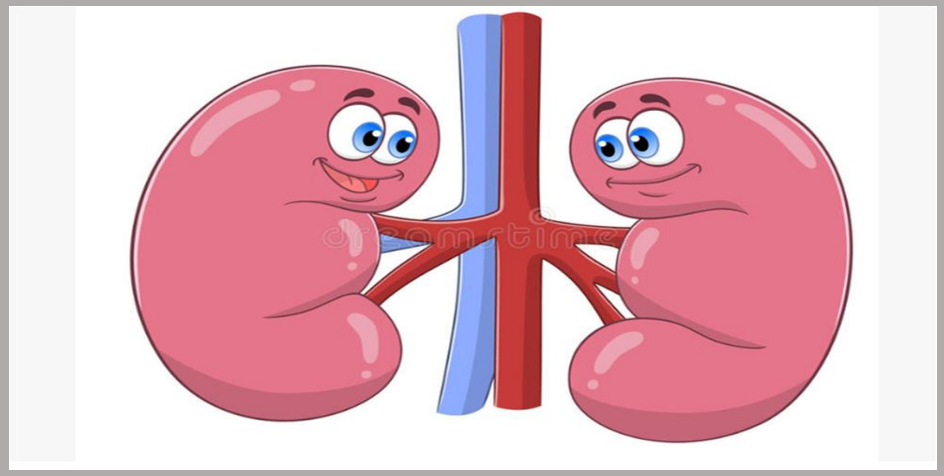
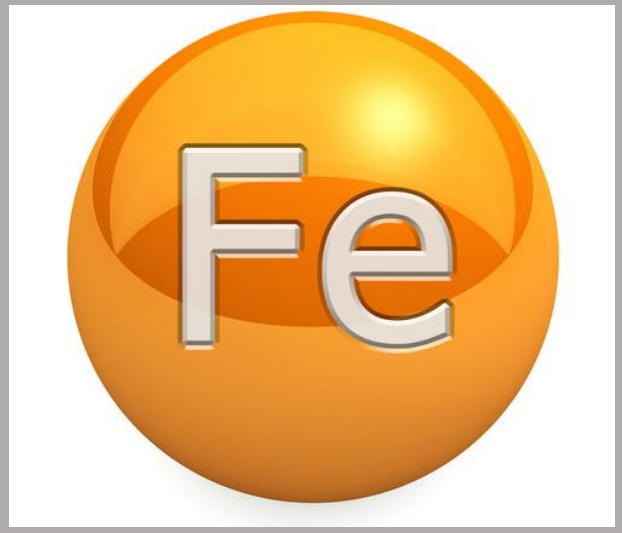
Chiara Brunati
UO Nefrologia dialisi e trapianti
ASST Grande Ospedale Metropolitano Niguarda
Milano

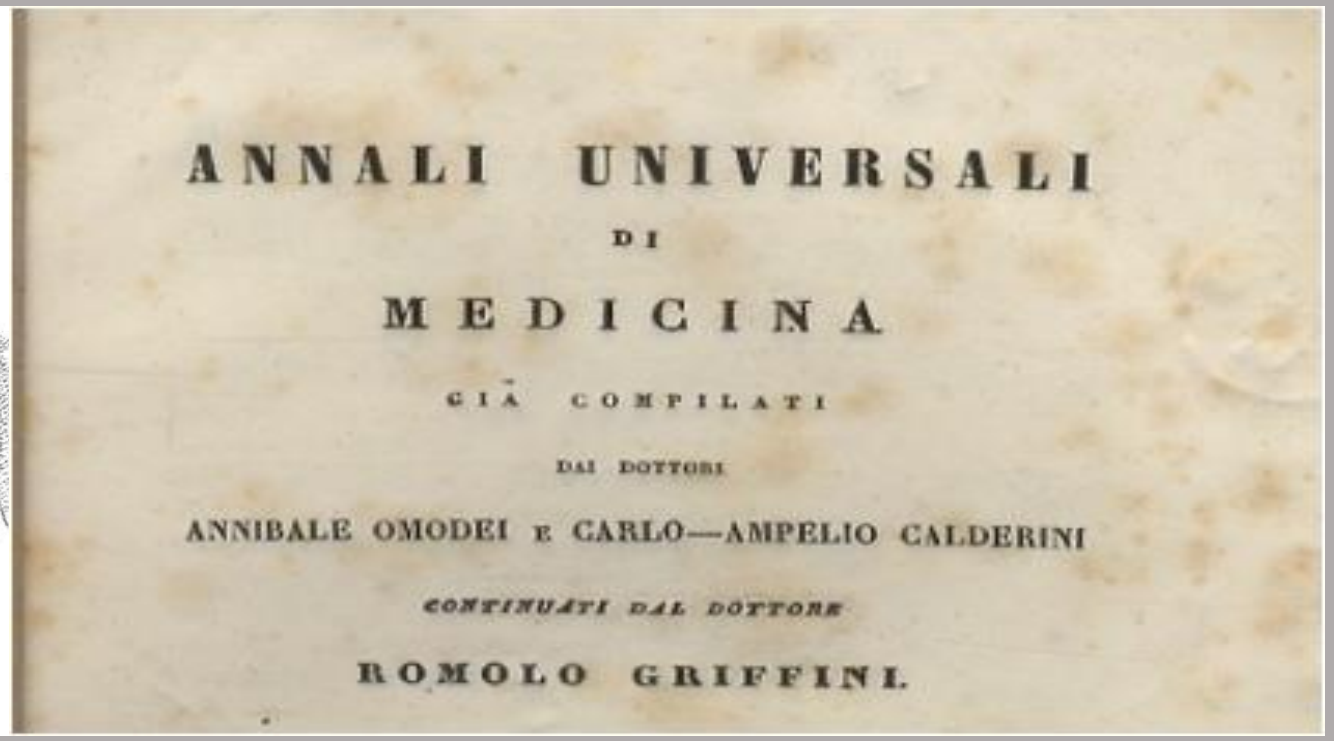


+

……opzioni terapeutiche in un paziente complesso

+

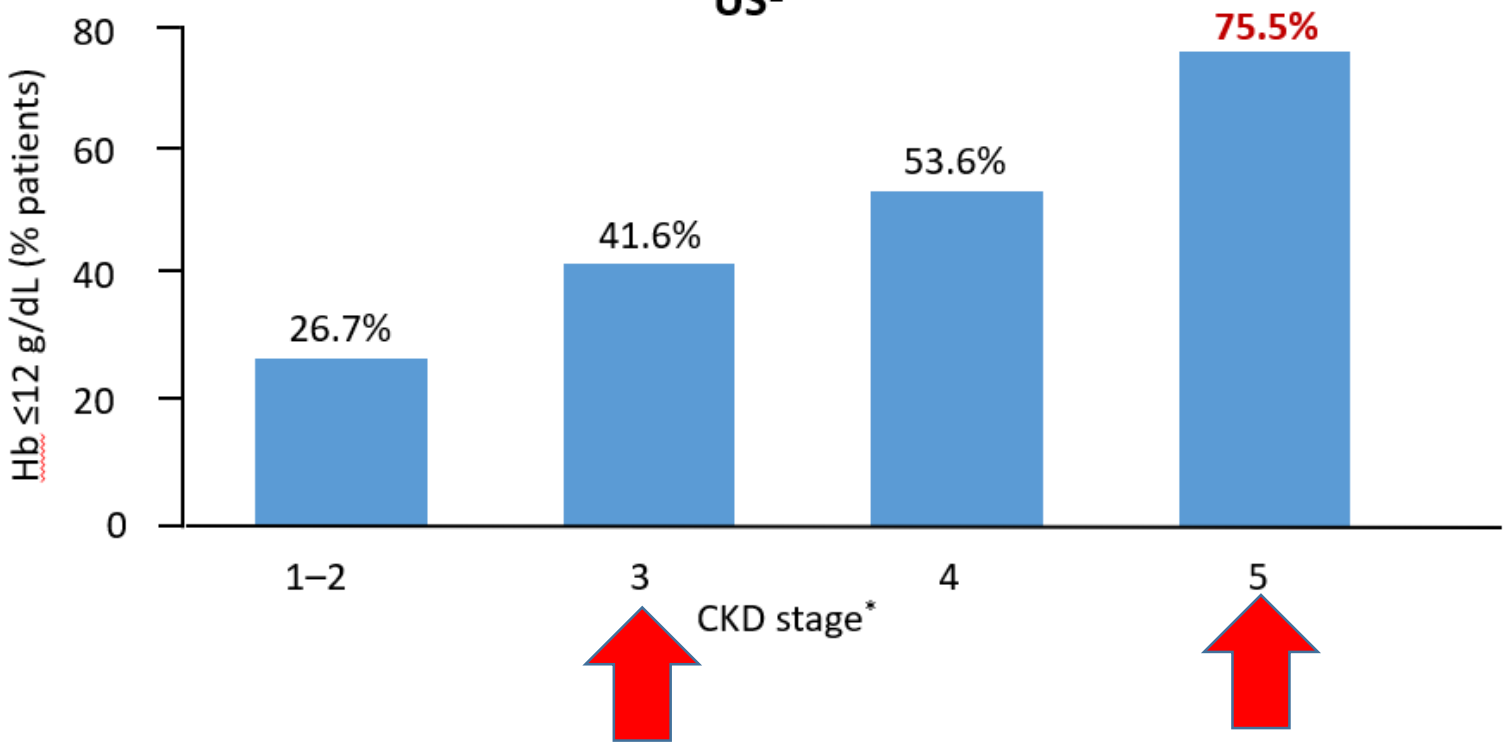




……. la proporzione di ematosina nel sangue mi sembra costituire uno dei piu' sicuri criteri per giudicare dei progressi dell'alterazione organica dei reni ..... **Dott Annibale Omodei,1839**

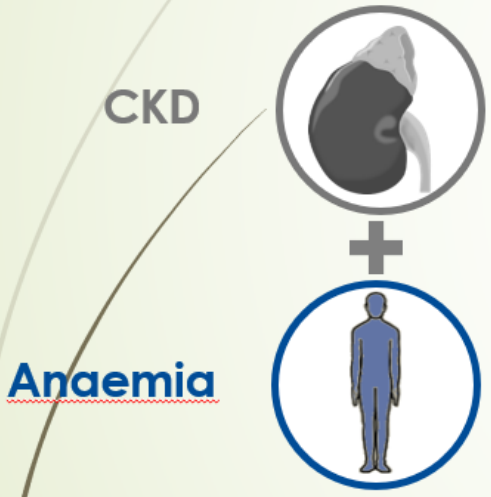
Rising burden of anaemia as CKD progresses

Cross-sectional survey of 5222 adult patients at 237 physician practices in the US[1]



1. McClellan W *et al. Curr Med Res Opin* 2004;20:1501–1510; 2. Astor BC *et al. Arch Intern Med* 2002;162:1401–1408; 3. NKF Kidney Foundation. *Am J Kidney Dis* 2005;45:S71–S80

Anaemia in CKD: A risk amplifier for adverse outcomes



Risk of CHD* — x 2.74[1]

Fold increase of CHD events

Risk of stroke — x 5.43[3]

Fold increase of events

Mortality† — x 2.96[4]

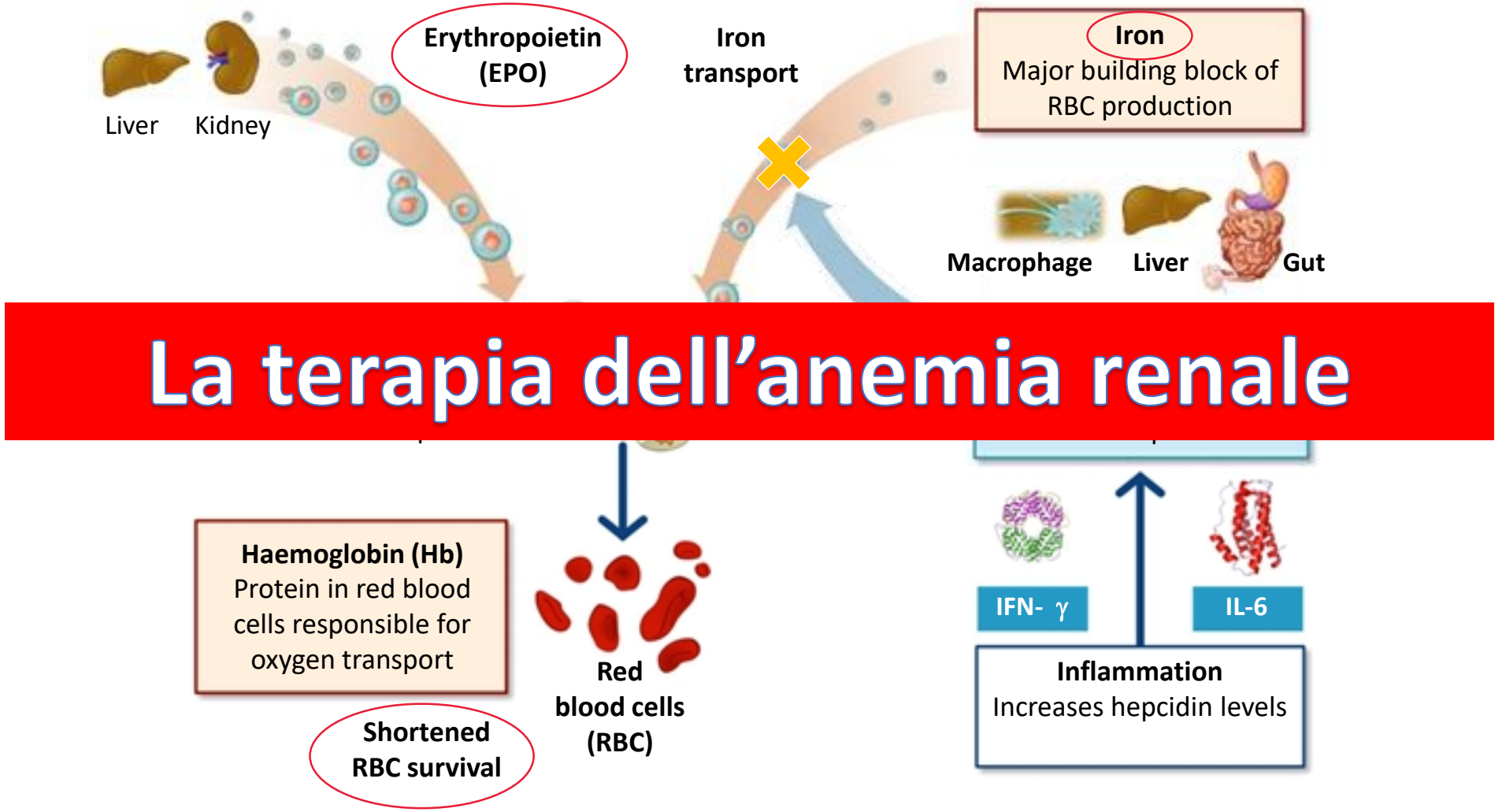
Progression to ESKD† — x 2.10[4]

Fold increase of events

1. Jurkovitz C et al. J Am Soc Nephrol 2003;14:2919–2925; 2. Herzog TB et al. J Am Coll Cardiol 2002;39:1780–1786; 3. Abramson JL et al. Kidney Int 2003;64:610–615; 4. Kovesdy CP et al. Kidney Int 2006;69:560–564; 5. Kazory A, Ross EA. Am Coll Cardiol 2009;53:639–647; 6. Johnson E et al. Am J Kidney Dis 2007;50:559–565

«Anemia renale» : patogenesi

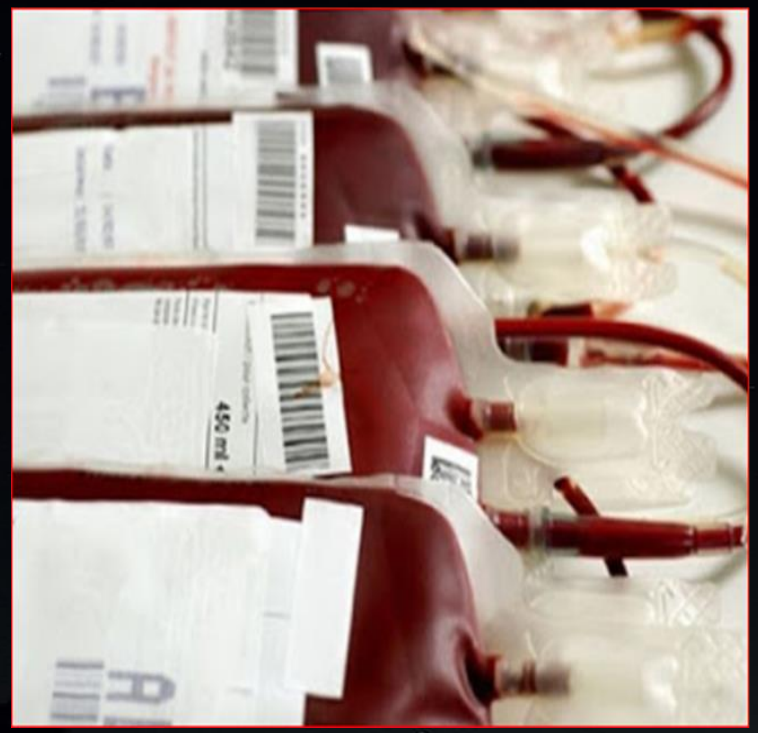
Mechanisms of anaemia in CKD



Adapted from: 1. Ganz T, Nemeth E. *Hematology Am Soc Hematol Educ Program* 2011;2011:538–542; 2. Goodnough L. *Transfusion* 2012;52:1584–1592; 3. Malyszko J, Mysliwiec M. *Kidney Blood Press Res* 2007;30:15–30; 4. Weiss G, Goodnough LT. *N Engl J Med.* 2005;352:1011–1023


Prima e un dopo 1987

Prima del 1987….



Sovraccarico marziale

Infezioni

Anticorpi

SeattleX

1987

Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin

Joseph W. Eschbach, M.D., Joan C. Egrie, Ph.D., Michael R. Downing, Ph.D., Jeffrey K. Browne, Ph.D., and John W. Adamson, M.D.

N Engl J Med 1987; 316:73-78 | January 8, 1987 | DOI: 10.1056/NEJM198701083160203

Dal 1987 : la «golden era» della Eritropoietina

Dal 1987-2000 «golden era» dell'eritropoietina

Pz politrasfusi in dialisi……CKD

Kidney International, Vol. 61, Supplement 80 (2002), pp. S44–S48

Influence of target hemoglobin in dialysis patients on morbidity and mortality

ALLAN J. COLLINS

Il sogno…..

prevenire la cardiopatia uremica

Correzione totale dell'anemia pre dialitica

EPO

2009

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 19, 2009 VOL. 361 NO. 21

A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D., Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D., John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D., Ajay K. Singh, M.D., Scott D. Solomon, M.D., and Robert Toto, M.D., for the TREAT Investigators*

Table 2. Composite and Component End Points.*

End Point	Darbepoetin Alfa (N=2012)	Placebo (N=2026)	Hazard Ratio (95% CI)	P Value†
	number (percent)			
Primary end points				
Cardiovascular composite end point‡	632 (31.4)	602 (29.7)	1.05 (0.94–1.17)	0.41
Death from any cause	412 (20.5)	395 (19.5)	1.05 (0.92–1.21)	0.48
Myocardial infarction§	124 (6.2)	129 (6.4)	0.96 (0.75–1.22)	0.73
Stroke§	101 (5.0)	53 (2.6)	1.92 (1.38–2.68)	<0.001
Heart failure§	205 (10.2)	229 (11.3)	0.89 (0.74–1.08)	0.24
Myocardial ischemia	41 (2.0)	49 (2.4)	0.84 (0.55–1.27)	0.40
Renal composite end point (ESRD or death)	652 (32.4)	618 (30.5)	1.06 (0.95–1.19)	0.29
ESRD	338 (16.8)	330 (16.3)	1.02 (0.87–1.18)	0.83
Additional adjudicated end points				
Death from cardiovascular causes	259 (12.9)	250 (12.3)	1.05 (0.88–1.25)	0.61
Cardiac revascularization	84 (4.2)	117 (5.8)	0.71 (0.54–0.94)	0.02

* ESRD denotes end-stage renal disease.
† P values have not been adjusted for multiple comparisons.
‡ A patient may have had multiple cardiovascular events of different types. The cardiovascular composite end point reflects only the first occurrence of any of the components.
§ This category includes both fatal and nonfatal events.

r%

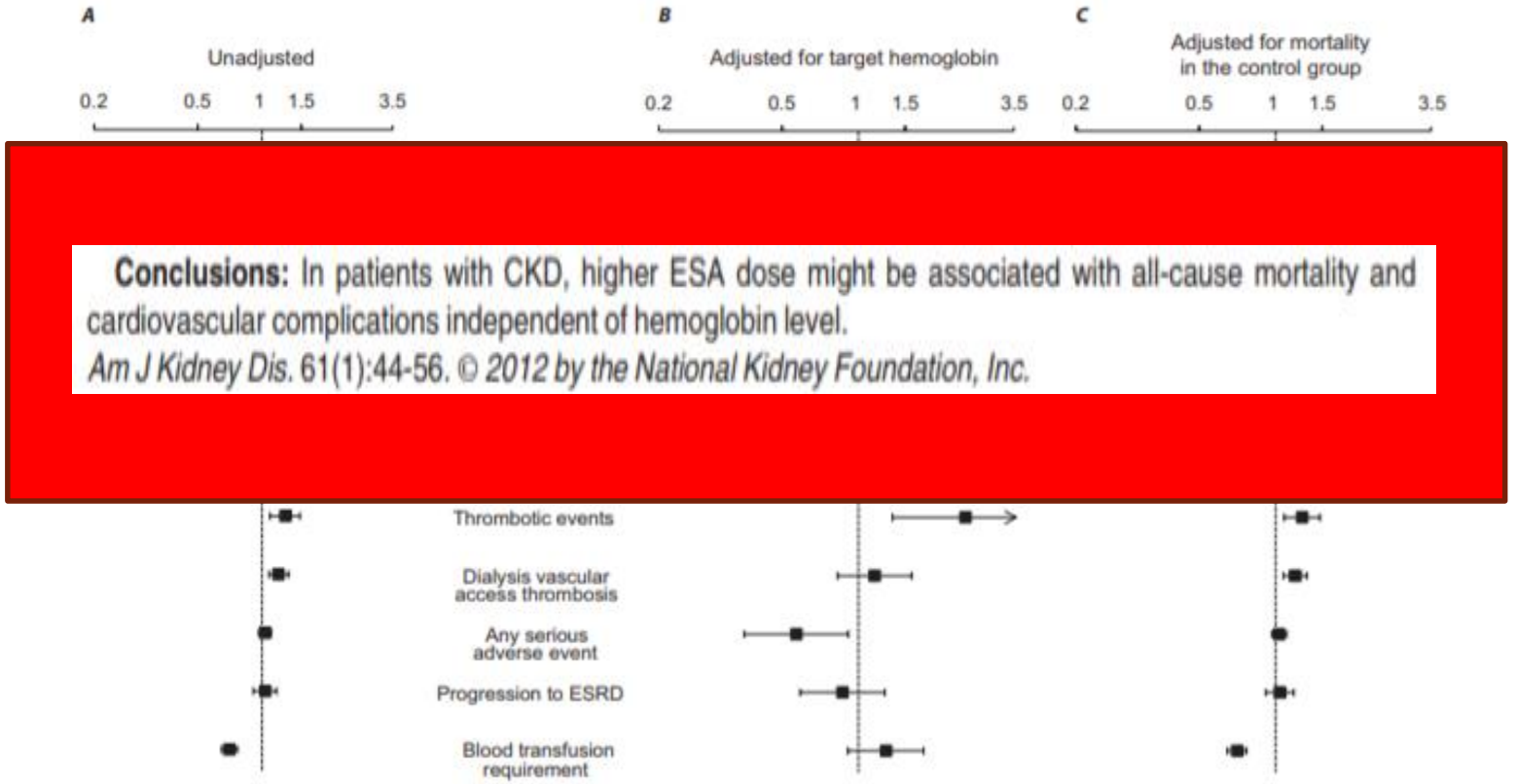
d evento CV

La normalizzazione dei livelli di Hct nell'uremico non e' indicata

Study	US NHCT[1]	CREATE[2]	CHOIR[3]	TREAT[4]
Patients	HD patients with CHF or IHD (1998)	CKD stage 3-4 (2006)	06)	CKD, diabetes, anaemia (2009)
Target	HCT 42% or 30%	Hb 13–1	dL or dL	Hb 13 g/dL
Study drug	EPO-a			Darbepoetin-a
Primary endpoint			Composite of death, MI, stroke, HF hospitalisation	Composite of death or CV events, ESRD
Result		difference in first CV events	High Hb more events than low Hb (*P*=0.03)	Higher Hb more strokes (HR 1.92)
Concerns	Administration of EPO to raise their HCT to 42% not recommended	More rapid progression to requiring RRT	Increased risk with no QoL benefit	Increased risk of stroke with EPO (*P*<0.001)

Cautela!!!

1. Besarab A *et al. N Engl J Med* 1998;339:584–590; 2. Drueke T *et al. N Engl J Med* 2006;355:2071–2084; 3. Singh AK *et al. N Engl J Med* 2006;355:2085–2098; 4. Pfeffer MA *et al. N Engl J Med* 2009;361:2019–2032



Conclusions: In patients with CKD, higher ESA dose might be associated with all-cause mortality and cardiovascular complications independent of hemoglobin level.

Am J Kidney Dis. 61(1):44-56.

Figure 4. Metaregression analyses examining the association of total-study-period erythropoiesis-stimulating agent dose (per epoetin alfa–equivalent 10,000 U/wk increment) with the secondary outcomes ([A] unadjusted, [B] adjusted for target hemoglobin level, and [C] adjusted for mortality rate [expressed per 1,000 person-years] in the control group). Incidence rate ratio (IRR) and 95% confidence interval (CI) are displayed on a logarithmic scale. Abbreviation: ESRD, end-stage renal disease.

Le conseguenze ..... I targets

1) Evitare la **«normalizzazione» dei livelli di Hb**

Target inferiore Hb :

- ***9 gr% - 10 gr%***

Target maggiore Hb :

- ***11-12 gr%***

KDIGO 2012 (Kidney Disease : Improving Global Outcomes)= organizzazione internazionale destinata a migliorare la cura e gli outcomes dei pazienti nefropatici

Le conseguenze …… la dose

1) Evitare dosi elevate di EPO

- Dose usuali 20UI-50 UI/Kg x 3 vv alla settimana sc o ev
- Risposta clinica Δ > 1 gr/4 sett
- Iporesponsivita' ad Epo se non si ottiene risposta clinica raddoppiando la dose iniziale….

KDIGO 2012 (Kidney Disease : Improving Global Outcomes)= organizzazione internazionale destinata a migliorare la cura e gli outcomes dei pazienti nefropatici

2010 ➡ Ferro

Perdite nell'emodialializzato

Circuito extracorporeo

Prelievi

7 mg/HD = 1300 mg/yrs*

Perdite GE

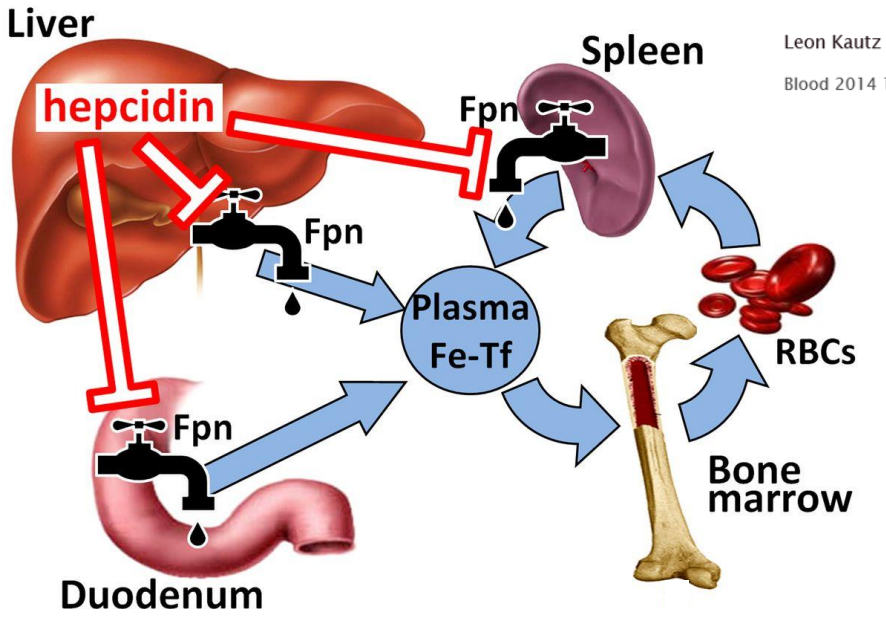
6,27 ml/die= 700 mg/yrs**

200 mg/mese
Tot = 2000 mg /yre

*Sargent (2004)
** Rosemblatt (1982)

Trattare bene il paziente nefropatico con il ferro e'…… difficile

La ferrocinetica nel dializzato e’ estremamente complessa



Molecular liaisons between erythropoiesis and iron metabolism

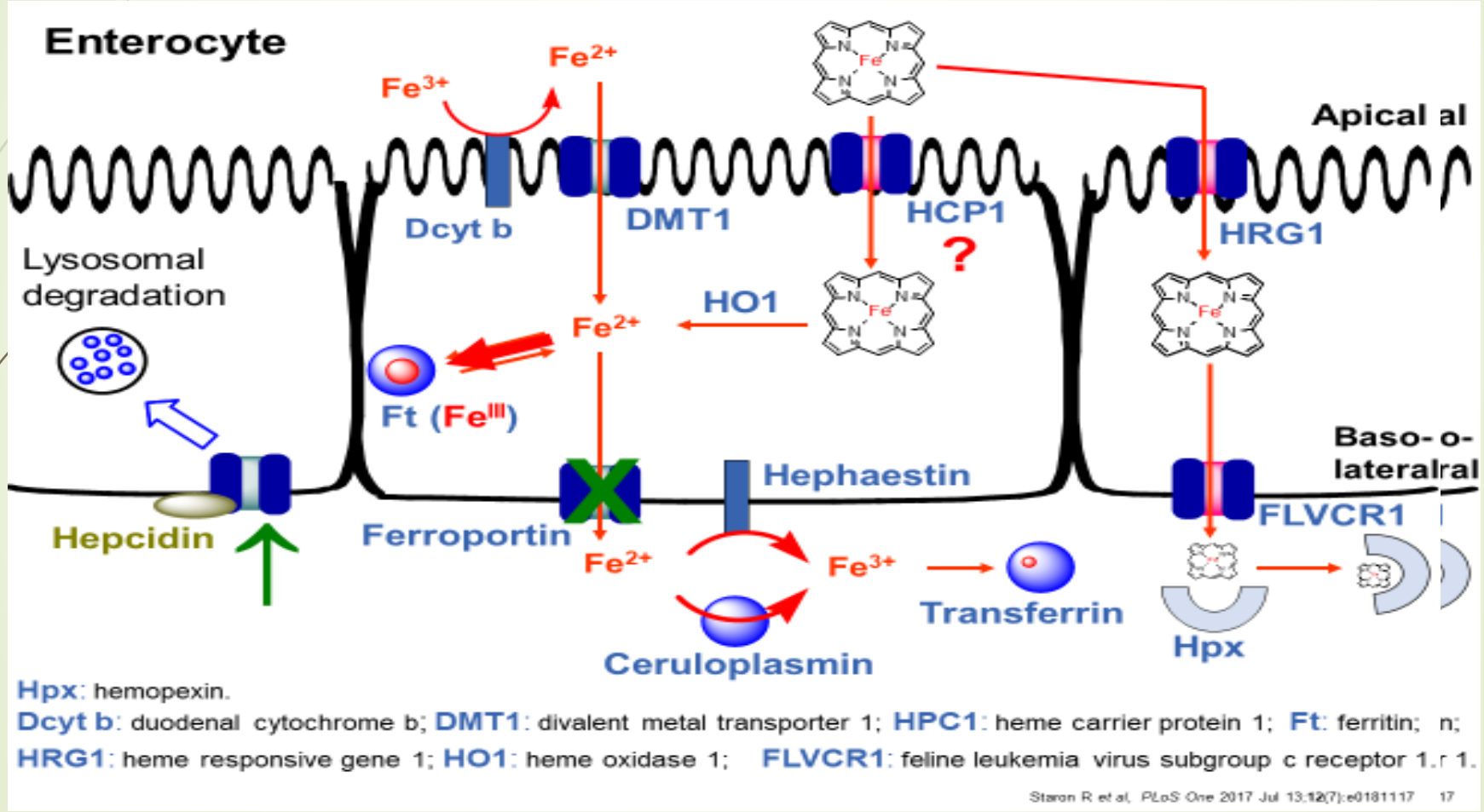
Leon Kautz and Elizabeta Nemeth

Blood 2014 124:479-482; doi: https://doi.org/10.1182/blood-2014-05-516252

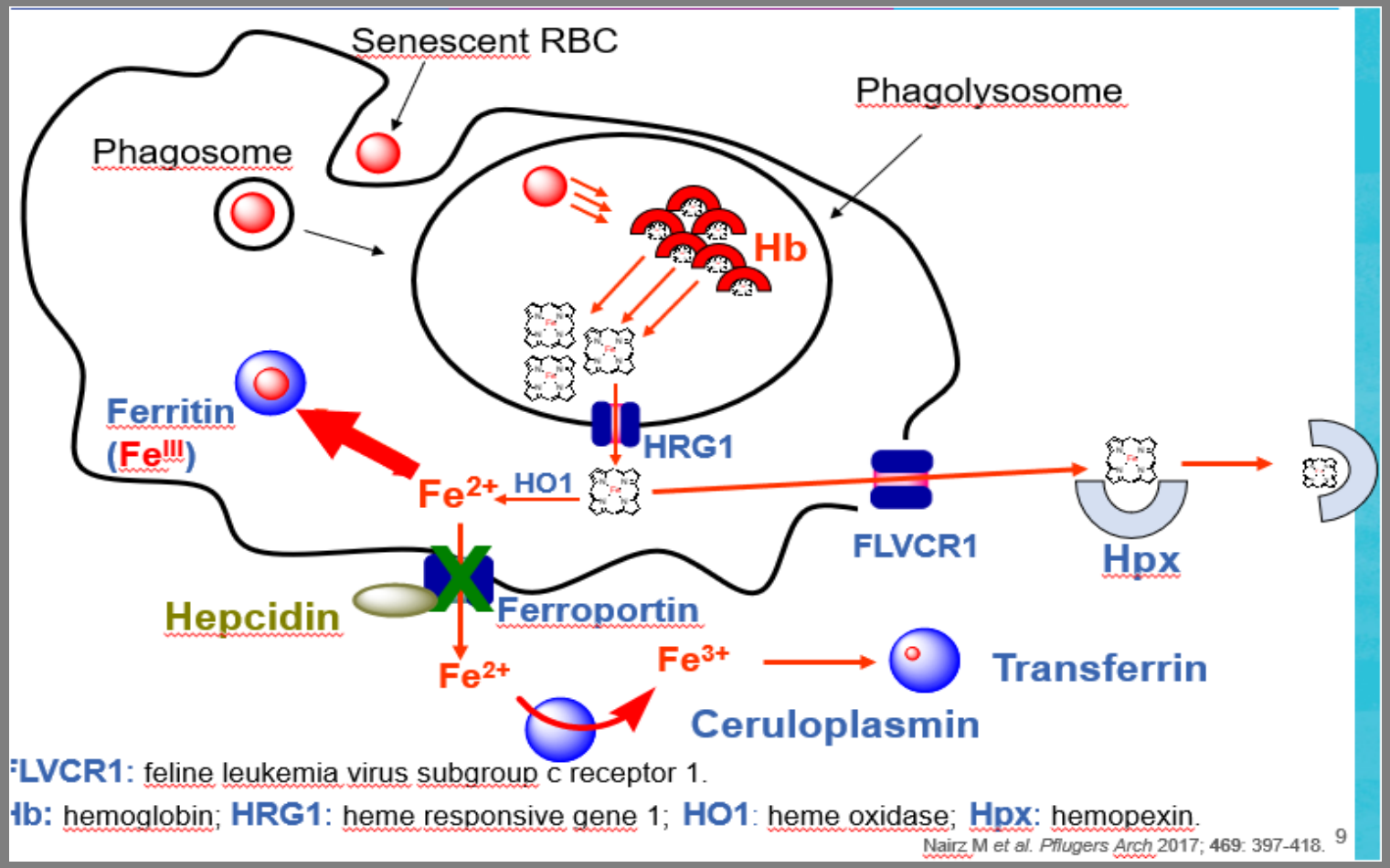
Nel paziente in dialisi esiste una grave compromissione
a carico dei due «snodi» cruciali della regolazione del ferro

- Epcidina =Aumentata per effetto IL, tossina uremica
- Eritrone = carenza di Epo

Lo scarso assorbimento GE del ferro

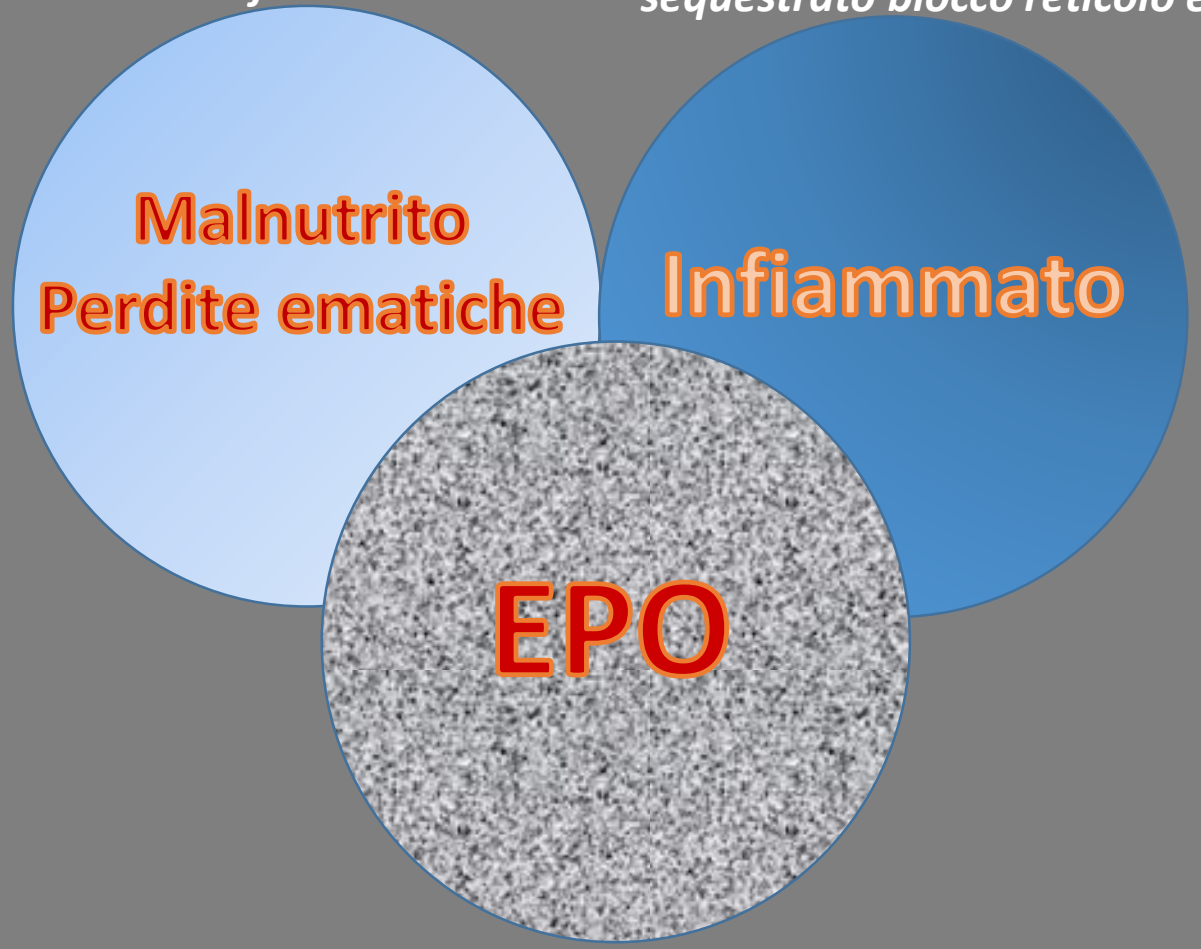


Il blocco reticoloendoteliale



Carenza di ferro assoluta

Carenza di ferro funzionale (ferro sequestrato blocco reticolo endoteliale)



Carenza di ferro funzionale in corso di stimolazione con EPO

La difficolta’ della diagnosi della condizione dell’assetto marziale: gli indicatori

I marcatori dello stato del ferro in nefrologia

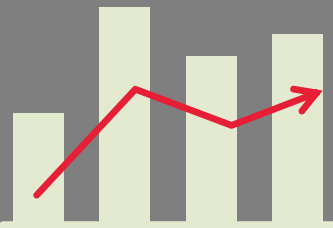
Serum ferritin: A measure of iron storage

Laboratory parameter

Serum ferritin

Enters circulation after secretion from iron storage sites or as a result of cell death (mainly macrophages)

What it measures



The balance between the secretion/leakage of tissue ferritin and its clearance (mainly in liver)

Storage iron[2]

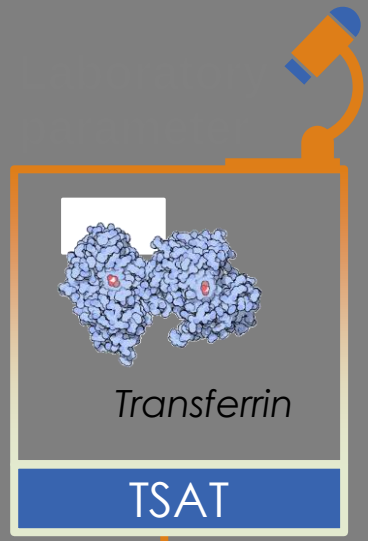
ADVANTAGES

- Correlates with body iron stores in healthy individuals[1]
- Low levels are highly specific for iron deficiency[2]
- Easy to use, testing widely available, moderate cost

LIMITATIONS

- Acute-phase reactant: Inflammation, infection and liver dysfunction may interfere with SF levels
- Normal or high SF does not exclude functional iron deficiency[3]
- Gender-related differences (normally lower in women)[4]

Transferrin saturation: A measure of functional iron reserve, but with limitations



What it measures

Iron available for erythropoiesis[1]

ADVANTAGES

- More reliable than SF[1]
- Higher sensitivity than SF[1]
- The absence (or near absence) of sustainable iron in the bone marrow correlates with TSAT <20%[2,3]
- High levels (>40–50%) suggests iron overload conditions, bone marrow suppression and liver disease[3]
- Easy to use and testing widely available

LIMITATIONS

- Negative acute-phase reactant such that TSAT levels are reduced by inflammation, infection, malignancy and progesterone[1,4]
- Limited sensitivity and specificity in patients for predicting bone marrow iron stores in CKD[5]

Con quali valori di ferritina e indice di saturazione della transferrina conviene iniziare una terapia marziale?

Paziente non in EPO

- Paziente non anemizzato se FS ≤100 mcg/l IST ≤20% (carenza assoluta)
- Paziente anemizzato **non in dialisi** se FS ≤200 mcg/l e IST ≤ 25%
- Paziente anemizzato **in dialisi** se FS ≤ 300 mcg/l e IST ≤ 25%

Paziente in EPO (tutti)

- Paziente se FS ≤ 300 mcg/l e IST ≤ 25%

Non superare FS ≥500 mic/L e IST >30%

KDIGO 2012 (Kidney Disease : Improving Global Outcomes)= organizzazione internazionale destinata a migliorare la cura e gli outcomes dei pazienti nefropatici

Come somministrare il ferro?
Il problema della via di somministrazione

Nel paziente pre dialisi……i vantaggi de ferro ev

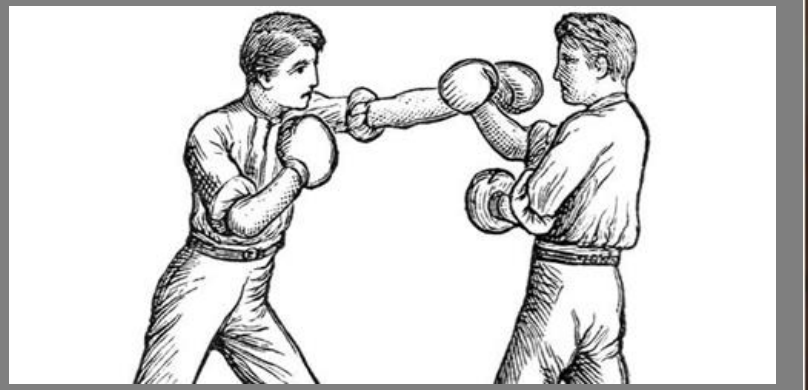
????

1) Il ferro *ev by passa il problema dell'assorbimento gastroenterico*
2) *Il ferro ev offre un'ottima compliance*

Nel paziente pre dialisi…gli svantaggi

????

1) Il ferro *per os potrebbe essere ancora efficace* rendendo non indicato esporre il paziente ad eventuali effetti acuti collaterali (reazioni anafilattoide o immunogeniche)
2) Problemi di tipo *organizzativo*
3) Problema *dell'accesso vascolare* (la vena e' patrimonio nel paziente nefropatico)



Dr MacDougall

Dr Agarwal

Nephrol Dial Transplant (2014) 29: 2075–2084
doi: 10.1093/ndt/gfu201
Advance Access publication 2 June 2014

ndt
NEPHROLOGY DIALYSIS TRANSPLANTATION
Basic and clinical renal science

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], Simon D. Roger[8] on behalf of the FIND-CKD Study Investigators[†]

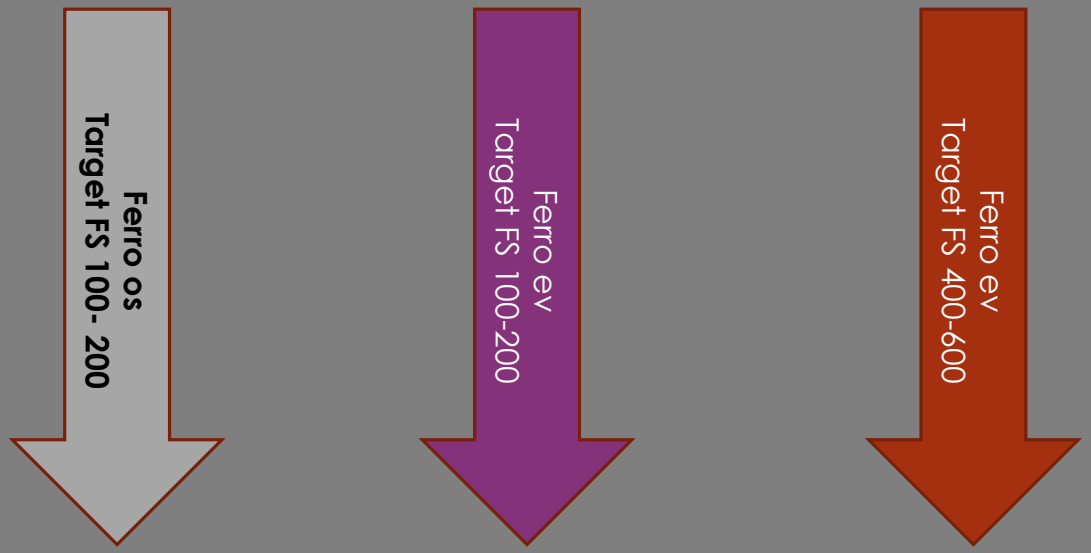
[1]Department of Renal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK, [2]Department of Nephrology, Kantonsspital Aarau, Aarau, Switzerland, [3]Eurodial, DaVita, Leiria, Portugal, [4]Department of Nephrology and Hypertension, University of Erlangen-Nürnberg, Erlangen, Germany, [5]Department of Nephrology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands, [6]DaVita Healthcare Partners Inc., Denver, CO, USA, [7]Vifor Pharma, Glattbrugg, Switzerland and [8]Renal Research, Gosford, NSW, Australia

Ferrocarbossimaltosio

- Poco diluente
- Dosi alte in un'unica sommistrazione

Disegno dello studio

Studio randomizzato in pazienti con anemia da carenza di ferro e IRC III-IV stadio

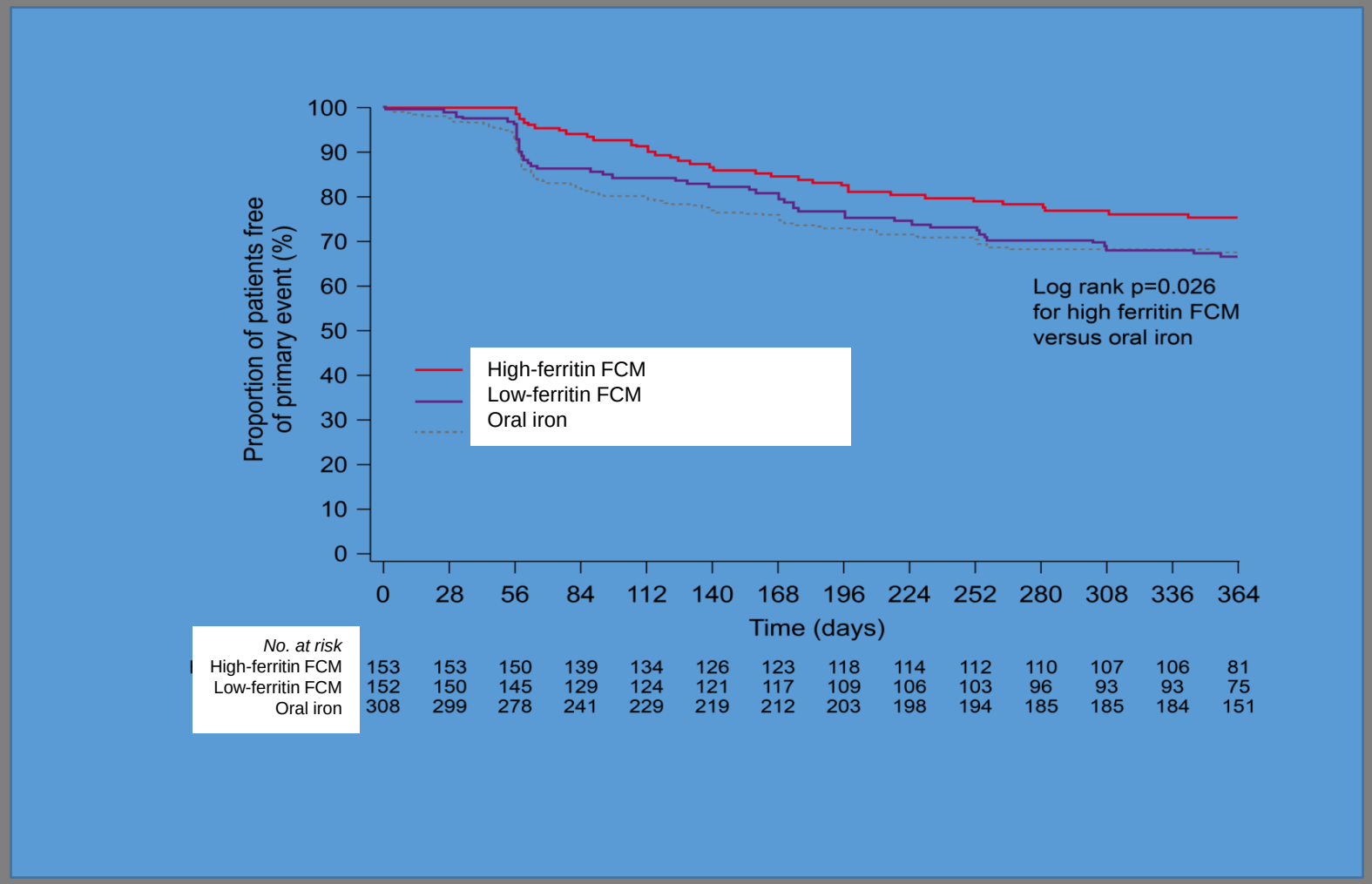


56 settimane

L'end point primario del FIND-CKD

Quale e' il migliore schema di terapia marziale per ritardare e/o evitare l'impiego di eritropoietina nei pz con IRC non in dialisi?

L'end point primario del FIND-CKD



Supplementary Table 1. Cumulative number of adverse events and serious adverse events during the total study period to the final follow-up visit (safety population)

	High ferritin FCM (n=154) (138.5 PY)	Low ferritin FCM (n=150) (129.0 PY)	Oral iron (n=312) (242.8 PY)
Duration of follow-up (months)			
Mean (SD)	12.1 (2.7)	12.2 (2.5)	11.5 (3.5)
Median (IQR)	12.9. (12.9–13.0)	12.9 (12.9–13.0)	12.9 (12.8–13.0)
Adverse events			
No. events	678	640	1432
No. events per 100 PY	436.3	421.6	480.4
Serious adverse events			
No. events	76	69	195
No. events per 100 PY	48.9	45.5	65.4
Serious adverse events classified as cardiac disorders			
No. events	15	11	35
No. events per 100 PY	9.7	7.2	11.7
Serious adverse events classified as infections			
No. events	8	5	34
No. events per 100 PY	5.1	3.3	11.4

IQR, interquartile range; PY, patient years
The safety population included all patients who received ≥1 dose of randomized treatment

AJKD

Editorial

Oral Iron Therapy: After Three Centuries, It Is Time for a Change

Am J Kidney Dis. 2016;68(5):665-666

Studio REVOKE, AGARWAL 2015

Studio randomizzato monocentrico

Due braccia trattamento : ferro saccarato vs ferro per os

136 pz randomizzati : 69 oral vs 67 os

Carenza di ferro : FS ≤100 mic/L IS ≤25% ,Hb fino 8 gr% anch
andamento rapidamento evolutivo della IRC

End point primario : andamento della funzione renale

Dose : ferro IV 1000 mg in 5 somministrazioni in 8 sett

Ferro per os 325 mg ferrosolfato x 3 vv al giorno

Follow up : 2 anni

Table 2 | Serious adverse events reported following randomization

Event type	Oral iron ($n=69$) Subjects (n)	Events (n)	Incidence rate (events/100 PY)	IV iron ($n=67$) Subjects (n)	Events (n)	Incidence rate (events/100 PY)	Incidence rate ratio, IV/oral (95% CI)	P	Adjusted incidence rate ratio, IV/oral (95% CI)	P
Overall SAEs	40	176	168.4	37	201	199	1.18 (0.97–1.45)	0.106	1.60 (1.28–2.00)	<0.0001
Infections	11	27	25.8	19	37	36.6	1.42 (0.86–2.33)	0.168	2.12 (1.24–3.64)	0.006
Skin	6	6	5.7	7	11	10.9	1.90 (0.70–5.13)	>0.2	3.79 (1.32–10.87)	0.013
Bone	2	7	6.7	3	4	4	0.59 (0.17–2.02)	>0.2		
Lung	4	4	3.8	8	11	10.9	2.85 (0.91–8.94)	0.073	4.35 (1.23–15.39)	0.022
UTI	3	5	4.8	3	5	4.9	1.03 (0.30–3.57)	>0.2	2.37 (0.60–9.34)	>0.2
Sepsis	1	2	1.9	5	5	4.9	2.59 (0.50–13.33)	>0.2	122.15 (0.89–16819.84)	0.056
Other	2	3	2.9	1	1	1	0.34 (0.04–3.32)	>0.2		
Cardiovascular	19	36	34.4	17	55	54.4	1.58 (1.04–2.41)	0.033*	2.51 (1.56–4.04)	<0.001
CHF	9	15	14.3	9	28	27.7	1.93 (1.03–3.62)	0.040*	2.07 (1.04–4.11)	0.038
Angina	2	2	1.9	2	2	2	1.03 (0.15–7.35)	>0.2		
MI	8	9	8.6	8	9	8.9	1.03 (0.41–2.61)	>0.2	1.25 (0.41–3.82)	>0.2
Stroke	0	0	0	2	2	2	2.0e+07 (0.00 -.)	>0.2		
Arrhythmia	4	4	3.8	4	5	4.9	1.29 (0.35–4.82)	>0.2		
PVD	1	2	1.9	2	3	3	1.55 (0.26–9.29)	>0.2		
Other	4	4	3.8	5	6	5.9	1.55 (0.44–5.50)	>0.2		
Renal	18	29	27.7	14	28	27.7	1.00 (0.59–1.68)	>0.2	1.39 (0.78–2.47)	>0.2
AKI	15	22	21	12	21	20.8	0.99 (0.54–1.80)	>0.2		
Hyperkalemia	5	6	5.7	2	4	4	0.69 (0.19–2.44)	>0.2		
Other	1	1	1	3	3	3	3.10 (0.32–29.84)	>0.2		
Cancer related	4	4	3.8	4	8	7.9	2.07 (0.62–6.87)	>0.2		
Other	31	69	66	25	61	60.4	0.91 (0.65–1.29)	>0.2		
PRBC transfusion	12	17	16.3	12	19	18.8	1.16 (0.60–2.22)	>0.2		
GI bleed	5	7	6.7	0	0	0	NA	NA		
Hyperglycemia	1	1	1	2	2	2	2.07 (0.19–22.82)	>0.2		
Hypoglycemia	3	5	4.8	0	0	0	NA	NA		
Diabetic retinopathy	1	2	1.9	1	5	4.9	2.59 (0.50–13.33)	>0.2		
Hypertensive crisis	1	1	1	3	5	4.9	5.17 (0.60–44.28)	0.134		
Urinary retention	2	3	2.9	2	3	3	1.03 (0.21–5.13)	>0.2		
Miscellaneous	21	33	31.6	20	27	26.7	0.85 (0.51–1.41)	>0.2		
ESRD	7	7	6.7	6	6	5.9	0.89 (0.30–2.64)	>0.2	1.04 (0.25–4.24)	>0.2
Death	4	4	3.8	6	6	5.9	1.55 (0.44–5.50)	>0.2	1.60 (0.28–9.07)	>0.2
CV related	2	2	1.9	2	2	2	1.03 (0.15–7.35)	>0.2		
Non-CV related	2	2	1.9	4	4	4	2.07 (0.38–11.30)	>0.2		

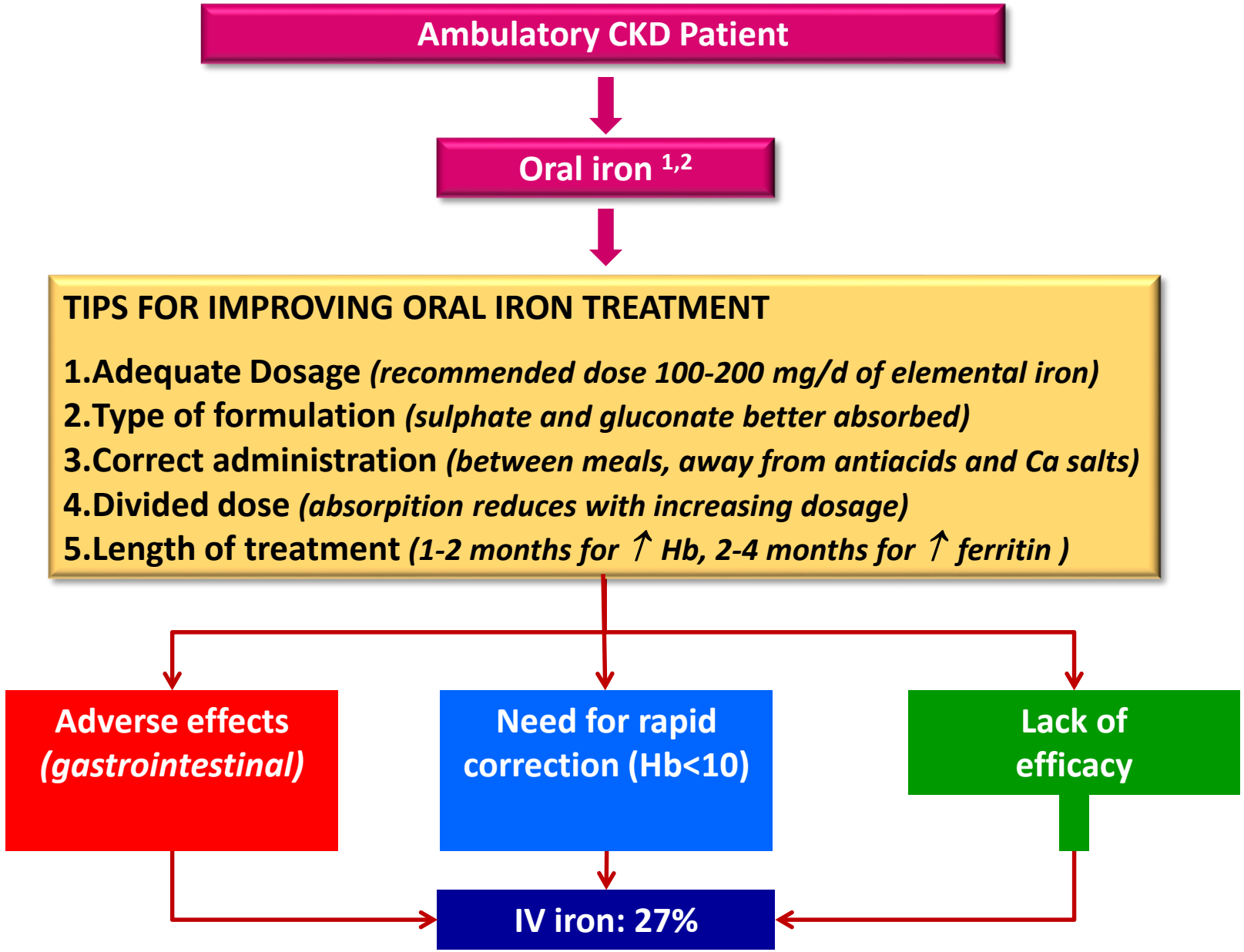
Abbreviations: AKI, acute kidney injury; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; ESRD, end-stage renal disease; GI, gastrointestinal; IV, intravenous; MI, myocardial infarction; NA, not available; SAE, serious adverse event; PRBC, packed red blood cell; PVD, peripheral vascular disease; PY, patient-years; UTI, urinary tract infection.
Oral iron exposure: 104.5 PY, and IV iron exposure: 101 PY. Adjustments for overall serious adverse events, cardiovascular events, renal events, AKI, hyperkalemia, and ESRD, death: age, sex, black race, stratum of proteinuria, baseline estimated glomerular filtration rate (GFR), diabetes, cardiovascular disease, tobacco use, systolic blood pressure (BP), statin use, antiplatelet therapy, angiotensin-converting enzyme (ACE) or angiotensin receptor blocker (ARB) use. Adjustments for CHF events: all the above adjustments except cardiovascular disease replaced by history of hospitalization for CHF. Adjustments for MI events: all the above adjustments except cardiovascular disease replaced by history of MI. Adjustments for infection events: all the above adjustments except dropped systolic BP, statin use, antiplatelet therapy, ACE or ARB use, and added history of hospitalized infection. Adjustments for skin infection events: all the adjustments for infection except that history of hospitalized infection replaced by prior history of hospitalized cellulitis. Adjustments for lung infection events: all the adjustments for infection except that history of hospitalized infection replaced by prior history of hospitalized pneumonia. Adjustments for urinary infection events: all the adjustments for infection except that history of hospitalized infection replaced by prior history of hospitalized UTI. Adjustments for sepsis events: all the adjustments for infection except that history of hospitalized infection replaced by prior history of hospitalized sepsis.

Aumento eventi avversi seri (sia cardiovascolari che infettivi)

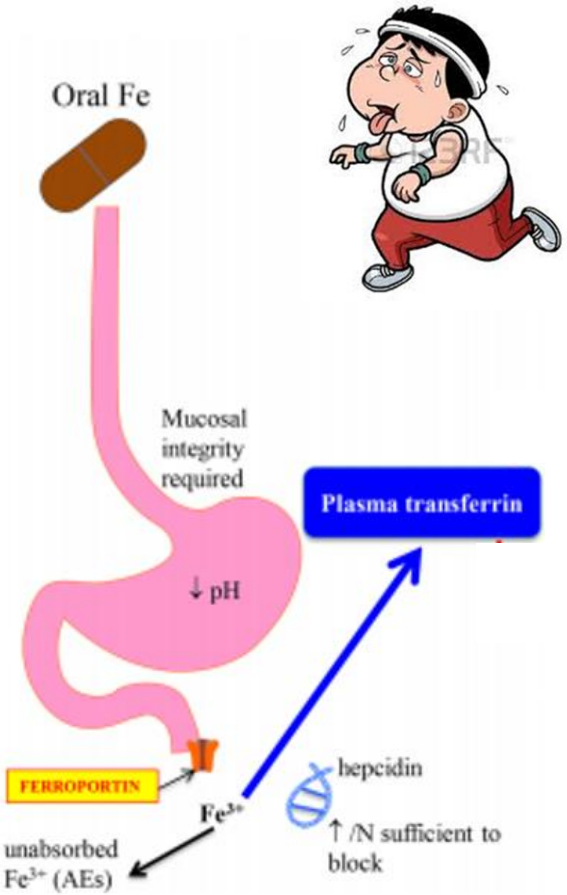
Tipologia di trattamento

Tipologia dei pazienti

Algorithm of treatment with iron for ambulatory CKD patients



Il ferro per os puo' non farcela



- ***Ferroportina intestinale*** ……
  trasporto di piccole quantita' di ferro (1-2 mg/di)
- Lievi aumenti di epcidina sono sufficienti per inibirla

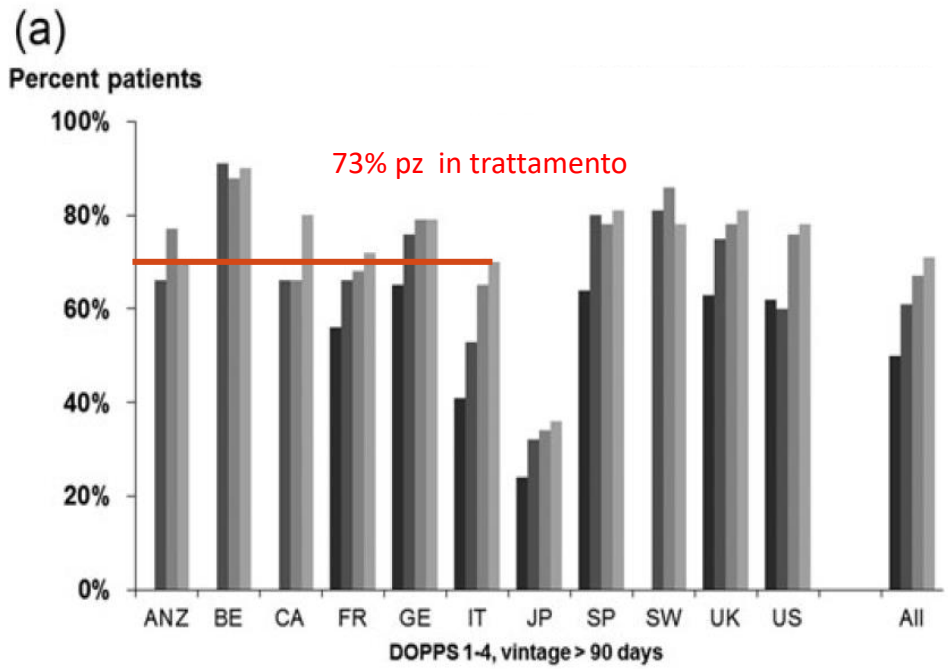
Meccanismo finemente regolato

*Il ferro per bocca **non funziona****
*Nel pz **dializzato** sempre : L'USO DEL FERRO ENDOVENA E' UNIVERSALMENTE RICONOSCIUTO*
*Nel dializzato il problema diventa la dose e la frequenza e cioe' lo **schema terapeutico** da usare per evitare gli effetti collaterali di un uso sconsiderato del ferro endovena*

Alta percentuale di pazienti trattati con ferro endovena……

DOPPS

DIALYSIS OUTCOMES AND PRACTICE PATTERNS STUDY



Nephrol Dial Transplant. 2013 Oct;28(10):2570-9. doi: 10.1093/ndt/gft062.

Effetti collaterali del ferro endovena

- **Effetti collaterali cronici**

1) Il rischio di positivizzazione del bilancio di ferro (sovraccarico ma

Quale dose usare?

2) Effetto aterogenetico
   - aumentata mortalita'
   - possibile accelleratore del peggioramento della IRC

3) Un aumentato rischio di infezioni

Dose ferro e mortalita' cardiovascolare

2005-2015

Table 2 Characteristics of epidemiological studies on IV iron and CV-related events among HD patients

First author	Study year	Country	Databases	N	Iron formulation	Exposures	Follow-up	HR (95% CI)	CV risk[a]
Kalantar-Zedeh (2005)[52]	2001 to 2003	United States	USRDS and DaVita	58,058	Ferric gluconate, iron sucrose, iron dextran	<400 vs. 0 mg/mo	2 y	200 to 399: between 0.5 and 0.6[b]	–
						≥400 vs. 0 mg/mo		≥400: between 1.1 and 1.3	+
Kuo (2012)[53]	2004 to 2005	Taiwan	Prospective study at Excelsior Renal Service Co	1,239	Ferric chloride hexahydrate	40 to 800 vs. 0 mg/6 mo	12 mo	1.7 (1.0–2.7)	+
						840 to 1600 vs. 0 mg/6 mo		3.5 (1.9–6.1)	+
						1640 to 2400 vs. 0 mg/6 mo		5.1 (3.0–9.7)	+
Kshirsagar (2013)[54]	2004 to 2008	United States	USRDS and DaVita	117,050	Ferric gluconate, iron sucrose, iron dextran	Bolus vs. maintenance[c]	3 mo	1.03 (0.99–1.07)	*
						High vs. low (> 200 vs. ≤200 mg/1 mo)		0.99 (0.96–1.03)	*
Miskulin (2014)[27]	2003 to 2008	United States	USRDS and Dialysis Clinic Inc.	14,078	All formulations[d]	vs. >0 to 150/1 mo	≤4 y	>350: 0.95 (0.70–1.29)	*
						vs. >0 to 450/3 mo		>1050: 1.02 (0.74–1.41)	
						vs. >0 to 900/6 mo		>2100: 1.17 (0.76–1.79)	
Susantitaphong (2014)[51]	Through December 2012	Multi-country	24 single-arm studies and 10 parallel-arm RCTs	2,658	Multiple formulations[e]	NA	NA	NA	*
Bailie (2015)[55]	2002 to 2011	12 countries	DOPPS	32,435	Multiple formulations[f]	Average dose over 4 mo (mg/mo): 0, 1 to 99, 100 to 199 (reference), 200 to 299, 300 to 399, 400+	Median (IQR): 1.7 (1.0–2.4) y	Increased risks with ≥300; ≥6 vs. 1 to 2 mg/kg per mo: 1.35 (1.12–1.62)	+

[a]Symbol representation: + = increased risk; – = decreased risk; * = no difference.
[b]Obtained from a figure in the article, the exact estimates were not available.
[c]Bolus dosing: consecutive doses ≥ 100 mg exceeding 600 mg during 1 month; maintenance: all other iron doses during the month.
[d]No further explanation provided in the article.
[e]Iron sucrose, ferric gluconate, iron dextran, iron saccharate, iron polymaltose, iron oxide, ferrous colloid, ferumoxytol.
[f]Iron sucrose, ferric gluconate, iron dextran, iron saccharate, iron polymaltose, chondroitin sulfate iron complex, citeferron.
IV = intravenous; CV = cardiovascular; HD = hemodialysis; US = the United States; USRDS = the United States Renal Data System; IQR = interquartile range; CI = confidence interval; HR = hazard ratio; DOPPS = Dialysis Outcomes and Practice Patterns Study.

Lo studio Pivotal

The NEW ENGLAND JOURNAL of MEDICINE

Follow up medio 2.1 anni

Nr pz randomizzati 2141

End point primario :

mortalita'

infarto miocardico

Stroke o ospedalizzazioni per scompenso

Uso del ferro ev anche in dosi elevate (400 mg mese) con target di ferritina fino a 700 mic/l possa garantire una riduzione significativa di morbilita' e mortalita'

Ian Ford, Ph.D., for the PIVOTAL Investigators and Committees*

Nephrol Dial Transplant (2019) 1–3
doi: 10.1093/ndt/gfz052

ndt
Nephrology Dialysis Transplantation

Will the results of the Proactive IV Iron Therapy in Haemodialysis Patients trial impact the anaemia guidelines?

Francesco Locatelli and Lucia Del Vecchio

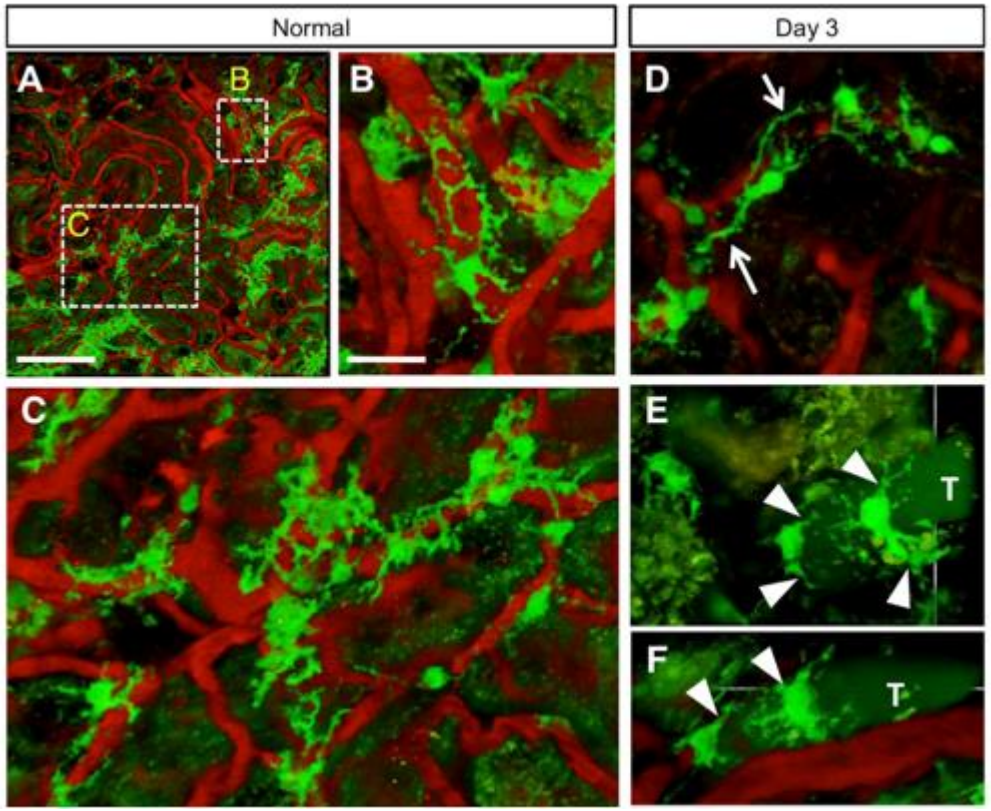
…..Lo studio Pivotal autorizza in accordo alle raccomandazioni delle KDIGO di usare anche dosi elevate di ferro con target di ferritine fino a 700 mic/L per ottenere una riduzione significativa di mortalita' e morbilita' cardiovascolare…….

Il futuro…..
…stabilizzatori del fattore inducente ipossia (HIF)

Roxadustat (FG-4592): Correction of Anemia in Incident Dialysis Patients

Anatole Besarab,* Elena Chernyavskaya,† Igor Motylev,‡ Evgeny Shutov,§ Lalathaksha M. Kumbar,‖ Konstantin Gurevich,¶ Daniel Tak Mao Chan,** Robert Leong,* Lona Poole,* Ming Zhong,* Khalil G. Saikali,* Marietta Franco,* Stefan Hemmerich,* Kin-Hung Peony Yu,* and Thomas B. Neff*

J Am Soc Nephrol 27: 1225–1233, 2016.



REP (Epo Producing Cell) nella corticale renale che vanno incontro ad una evoluzione verso fibroblasti in corso di CKD

Ossigeno

Stabilizzazione

idrossiprolinasi

HIF alfa + HIF beta (fattore di transcrizione)

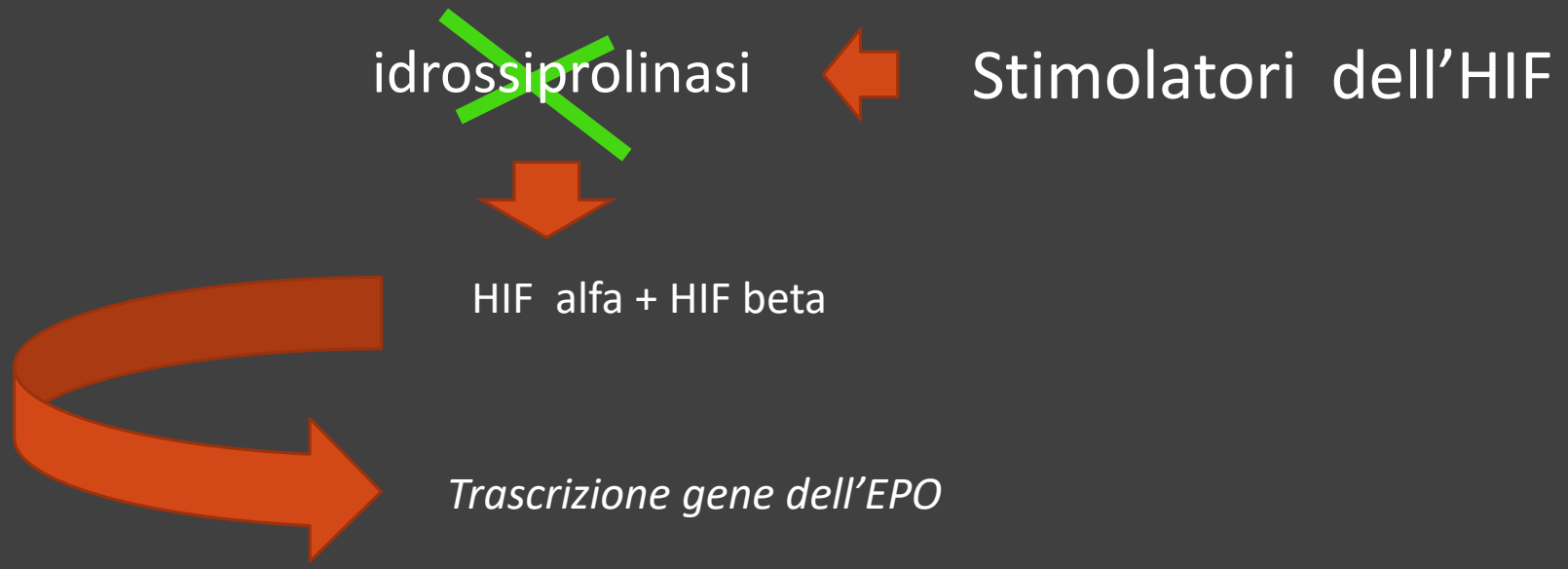
Trascrizione gene dell'EPO

Ipossia

idrossiprolinasi

HIF alfa + HIF beta

Trascrizione gene dell'EPO


idrossiprolinasi
Stimolatori dell’HIF
HIF alfa + HIF beta
Trascrizione gene dell’EPO

Effetti degli stimolatori dell'HIF

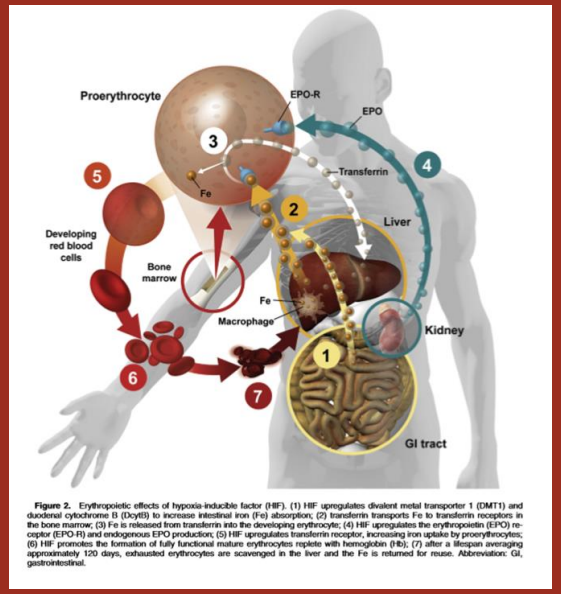


Figure 2. Erythropoietic effects of hypoxia-inducible factor (HIF). (1) HIF upregulates divalent metal transporter 1 (DMT1) and duodenal cytochrome B (Dcytb) to increase intestinal iron (Fe) absorption; (2) transferrin transports Fe to transferrin receptors in the bone marrow; (3) Fe is released from transferrin into the developing erythrocyte; (4) HIF upregulates the erythropoietin (EPO) receptor (EPO-R) and endogenous EPO production; (5) HIF upregulates transferrin receptor, increasing iron uptake by proerythrocytes; (6) HIF promotes the formation of fully functional mature erythrocytes replete with hemoglobin (Hb); (7) after a lifespan averaging approximately 120 days, exhausted erythrocytes are scavenged in the liver and the Fe is returned for reuse. Abbreviation: GI, gastrointestinal.

Meccanismo di azione: inibizione della degradazione di HIF-α (attivatori della trascrizione dell'EPO) che stimola la produzione endogena di EPO

- *Riattivazione della produzione di eritropoietina nelle REP*
- *Riduzione dell'epcidina*
- *Attivazione epatica dei geni regolatori produzione d transferrina,recettore della trasferrina, ceruloplasmina*
- *Attivazione citocromo duodenale B e attivatore del trasporto dei metalli divalenti*

Ripristina una corretta comunicazione fra eritrone e depositi di ferro

Clinical outcome ?

- Il trattamento con HIF –PGI induce un incremento minore dei livelli di Epo rispetto alla terapia con ESA ricombinante
  (fatto pos)

- Esistono molti geni non correlati con l'eritropoiesi che sono potenzialmente attivati dai HIF-PGI tipo VEGF (proangiogenetico tumorogenesi, retinopatia proliferativa diabetica)
  (fatto che crea dubbi)

- *Fra i possibili geni attivati da HIF-PGI esistono molti altri geni coinvolti nel controllo vasomotorio*
  Molidustat *effetto ipotensivo simile ad enalapril,*
  Roxadustat *10% dei pazienti hanno ridotto la terapia antipertensiva*


Anemia e IRC una storia da riscrivere
una volta...

Grazie!