



**PATIENT BLOOD MANAGEMENT
DALLA TEORIA ALLA PRATICA
16 FEBBRAIO 2018**

EPO e Ferro in Emodialisi: Il PBM al suo esordio

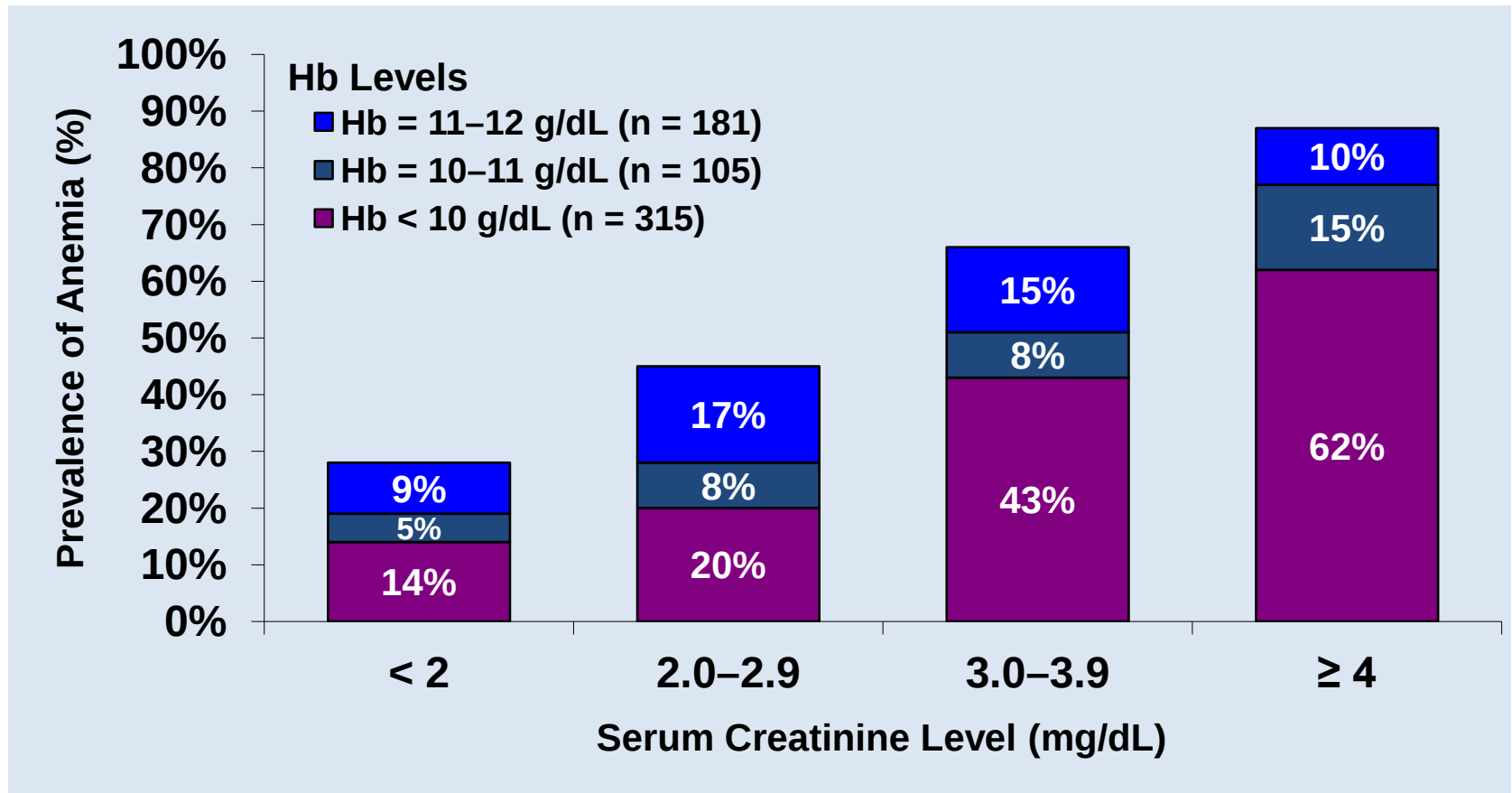
Lucia Del Vecchio

**Divisione di Nefrologia e Dialisi
Ospedale A. Manzoni, ASST Lecco**

Perché i malati con CKD sviluppano anemia?

- **Primary cause**
 - Low erythropoietin production
- **Secondary cause**
 - Iron deficiency
 - Hyperparathyroidism
 - Chronic inflammation
 - Infection
 - Nutritional deficiency
 - Bleeding

Anemia Worsens as Kidney Function Declines



Hb = hemoglobin

Adapted from Kausz AT, et al. *Dis Manage Health Outcomes*. 2002;10:505-513.

Anemia treatment in CKD patients

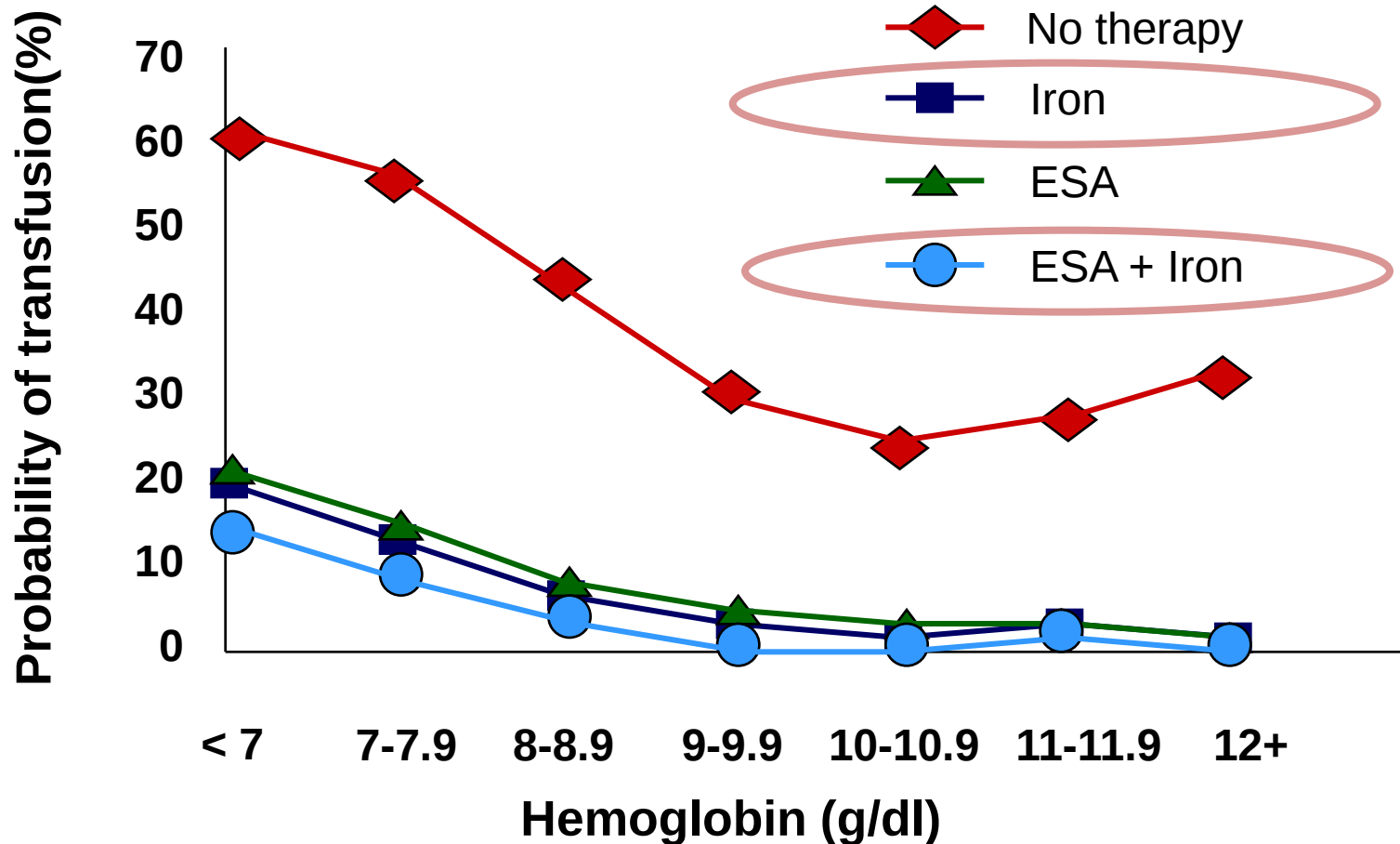
- **ESA**
- **Iron**
- **Both**
- **Blood transfusion**





Transfusion rates by Hb level according to the treatment status

- Retrospective analysis between 2002 and 2007
- 97,636 patients with CKD not on dialysis and anemia



The early times of dialysis

Locatelli F, Del Vecchio L. Am J Nephrol 2010;31(6):557-60



*The 'lucky 13' first chronic haemodialysis patients
Royal Free Hospital, January 1st 1965*





Early nineties

rHuEPO become available in everyday clinical practice



Label indication:

“Treatment of anemia associated with chronic renal failure, including patients on dialysis (end stage renal disease) and patients not on dialysis.”



EFFECT OF HUMAN ERYTHROPOIETIN DERIVED FROM RECOMBINANT DNA ON THE ANAEMIA OF PATIENTS MAINTAINED BY CHRONIC HAEMODIALYSIS

Winearls CG et al.

ABSTRACT

Ten patients with end-stage renal failure and anaemia (mean haemoglobin 6·1 g/dl, range 4·6-8·8 g/dl) on thrice-weekly haemodialysis were treated with human erythropoietin derived from recombinant DNA (rHuEPO). This was given as an intravenous bolus after each dialysis in rising doses within the range 3-192 IU/kg. All patients showed increases in reticulocyte numbers and haemoglobin concentration and after the first week of treatment none of the four previously transfusion-dependent patients needed further transfusions. In nine patients treated for 12 weeks haemoglobin rose to a mean of 10·3 g/dl, range 9·5 to 12·8 g/dl. Thereafter the dose of erythropoietin was adjusted to avoid a further rise in haemoglobin. During treatment one patient

ANEMIA

Fattore di rischio ?

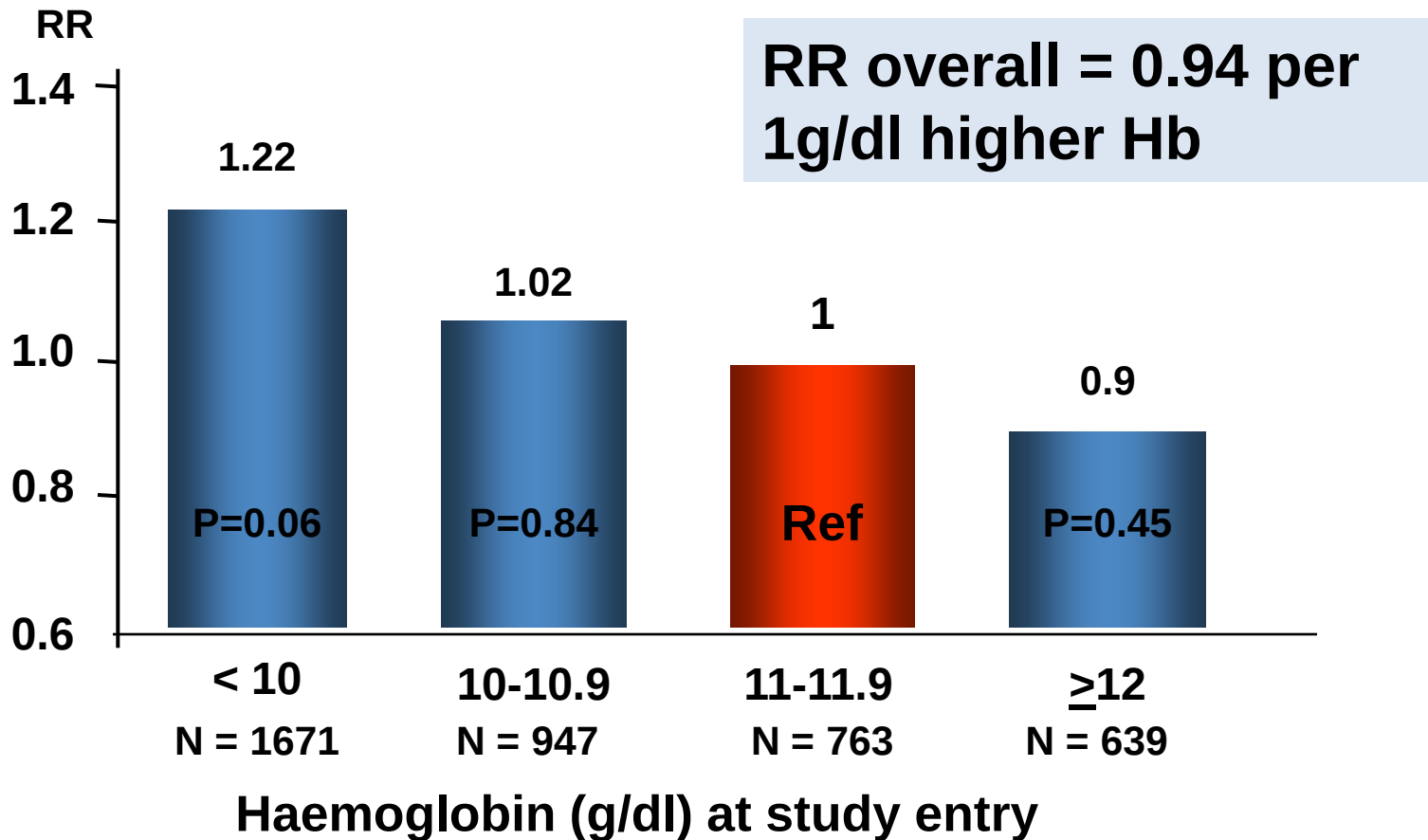
Marker di comorbidità?



Mortality and hospitalisation risks and anemia



Relative Risk of Death



Hemoglobin target and ESA

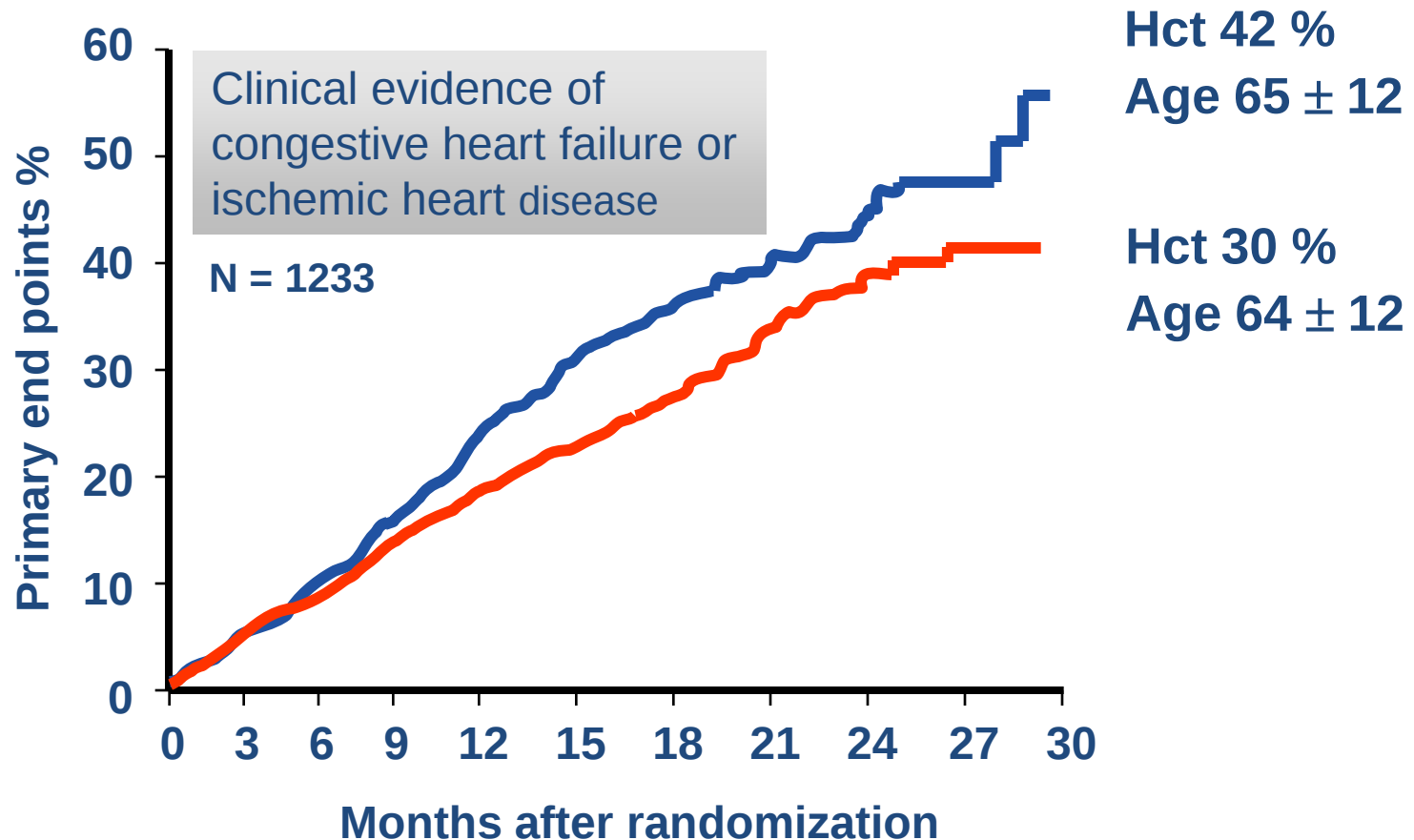
The higher the better?



**Complete anemia
correction did not give
the awaited results**

Probability of death or first non - fatal myocardial infarction

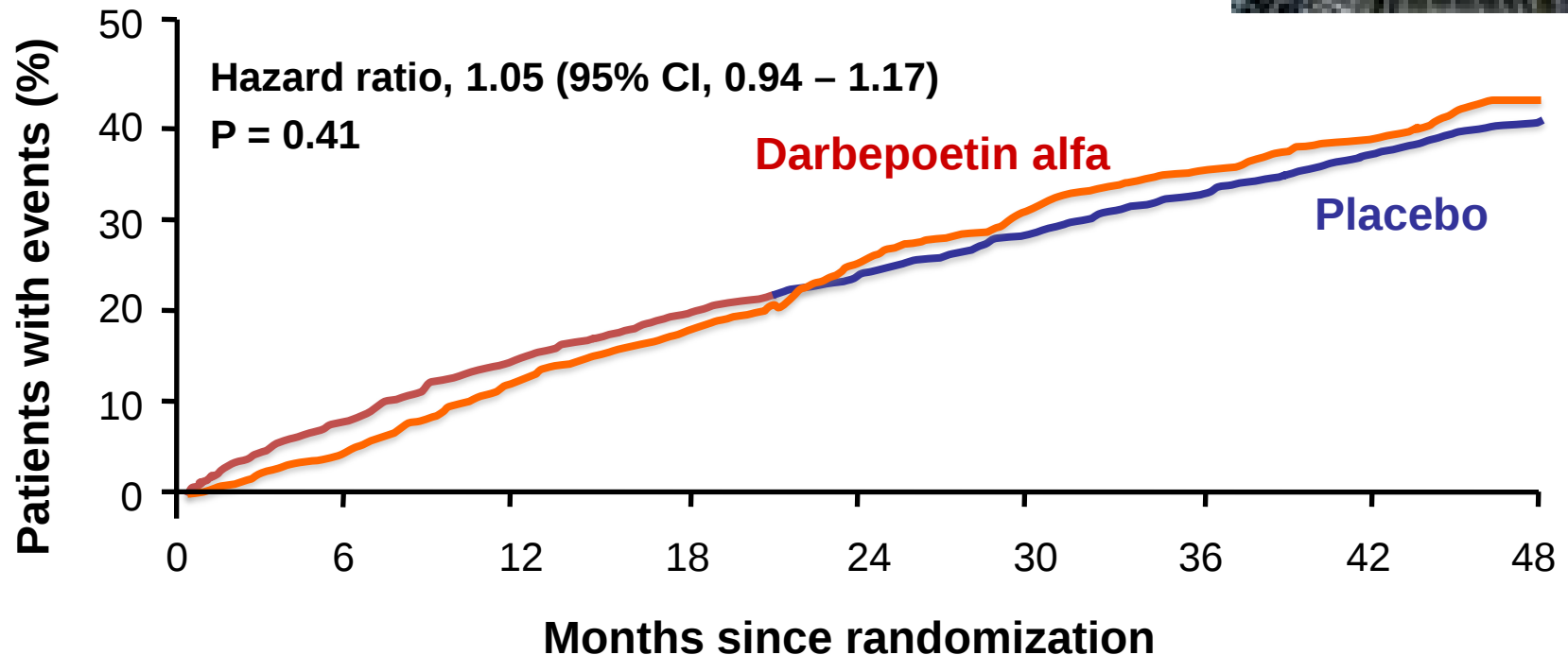
Normal versus low haematocrit



The TREAT Study

Cardiovascular composite end point (ITT)

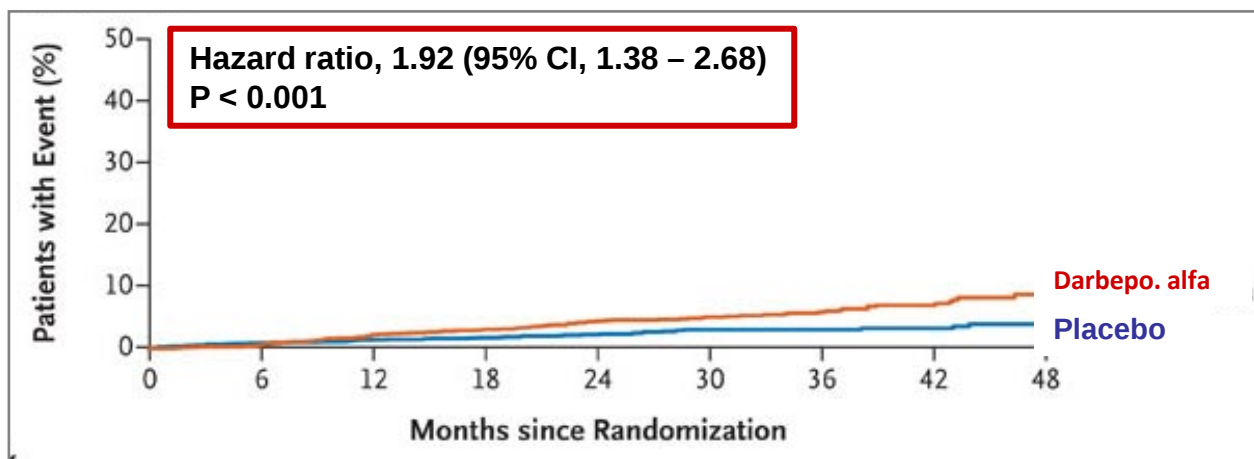
4,044 pts with type 2 diabetes, eGFR 20-60 mL/min/1.73 m², and Hb < 11 g/dL



The TREAT Study: Secondary end-points

Pfeffer MA et al. N Engl J Med 2009; 361:2019-32

Fatal or non fatal stroke



Darbepoetin alfa: 101/2012 (5.0%), 2.1% per 100 patient-years

Placebo: 53/2026 (2.6%), 1.1 per 100 patient-years

Lo studio TREAT

Analisi secondaria sulle neoplasie

Criteri di esclusione:

Pazienti con neoplasia attiva (eccetto basalioma o Ca spinocellulare localizzato)

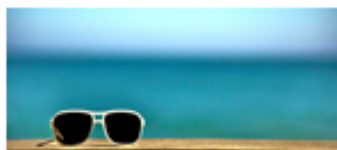
Sottogruppo: 348 pazienti con storia di pregressa neoplasia

Morte per tutte le cause (P=0.13 al log-rank test)

Darbepoetina alfa	Placebo
60 su 188 (31.9%)	37 su 160 (23.1%)
Popolazione globale: 20.5%	Popolazione globale : 19.5%

Morte per neoplasia (P=0.002 al log-rank test)

Darbepoetina alfa	Placebo
14 su 188 (7.4%)	1 su 160 (0.06%)



Agosto, 2012

Kidney Disease: Improving Global Outcomes (KDIGO)

KDIGO CLINICAL PRACTICE GUIDELINE FOR ANEMIA IN CKD

Work Group Co-Chairs: John J V McMurray and Patrick W

Kidney International, 1 August 2012



European Renal Best Practice (ERBP)

March, 2013

**Kidney Disease Improving Global Outcomes (KDIGO) guidelines
on anaemia management in chronic kidney disease.**

A ERBP position statement

Locatelli F, Bárány P, Covic A, De Francisco A, Del Vecchio, Goldsmith D, Hörl W,
London G, Vanholder R, Van Biesen W
on behalf of the ERA-EDTA ERBP Advisory Board

Nephrol Dial Transplant 2013 (28(6)):1346-59

KDIGO CLINICAL PRACTICE GUIDELINE FOR ANEMIA IN CKD



+FERRO
TRASFUSIONI

- ESA
- Hb

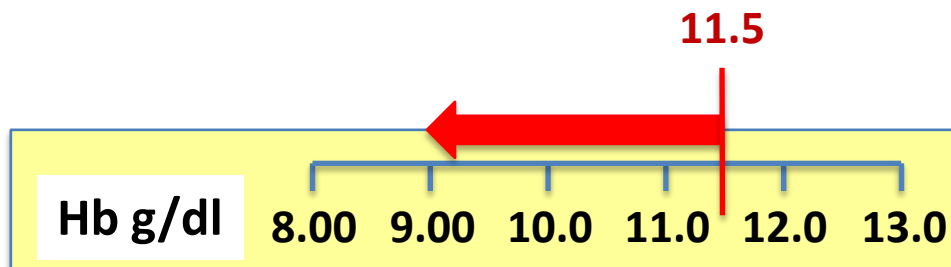


KDIGO CLINICAL PRACTICE GUIDELINE FOR ANEMIA IN CKD

USE OF ESAs AND OTHER AGENTS TO TREAT ANEMIA IN CKD

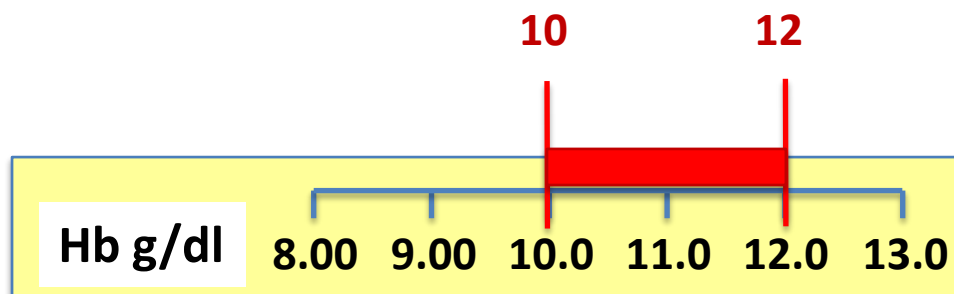
ESA MAINTENANCE THERAPY

- In general, we suggest that **ESAs not be used** to maintain Hb concentration **above 11.5 g/dl (2C)**



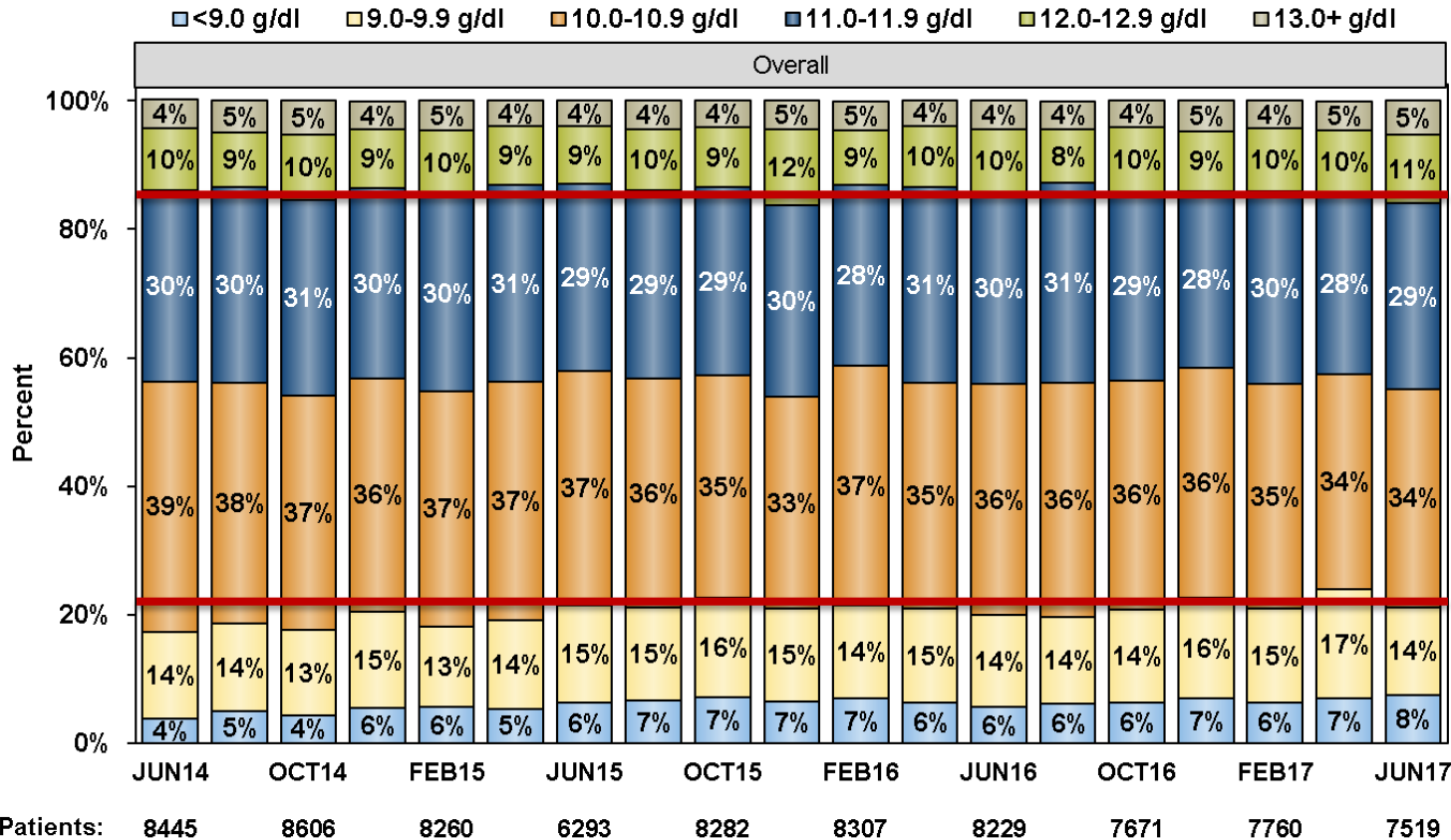
The ERBP position statement about KDIGO guidelines on anaemia

ESA MAINTENANCE THERAPY



Hemoglobin (most recent)

National sample



N Patients:

8445

8606

8260

6293

8282

8307

8229

7671

7760

7519

Most recent (single) monthly value

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, August 2017; <http://www.dopps.org/DPM>

choices
&
sequences

64%

63%%

Da 6,2% a 18.8%

22%

ADVERTISEMENT



**Need a way to stay informed
on-the-go?**

Access information from industry
from your mobile device

**ACCESS
NOW**

From Medscape Nephrology > Viewpoints

A Transfusion Epidemic in Dialysis Patients? Time to Reassess

Lynda A. Szczech, MD, MSCE

Authors and Disclosures

Posted: 07/25/2012

Print This Email this Share

The Policy Changes Leading to Increases in Transfusions

"According to the United States Renal Data System, in each of the first 9 months of 2011, the share of dialysis patients covered by Medicare who received blood transfusions increased by 9 to 22 percent over the corresponding months in 2010. Last September, for instance, there were 10,041 transfusions for dialysis patients, compared with 8,259 for the same month in 2010. There had been virtually no change in transfusion rates between 2009 and 2010."^[1]

The Policy Changes Leading to Increases in Transfusions

Transfusions and the Evidence

Conclusion

References

Read daily medical news on-the-go
with Medscape's free app.

RELATED ARTICLES

[Lowering the Hb Target in CKD: Pro and Con](#)

[Good, Bad, and Different: Highlights From Kidney Week](#)

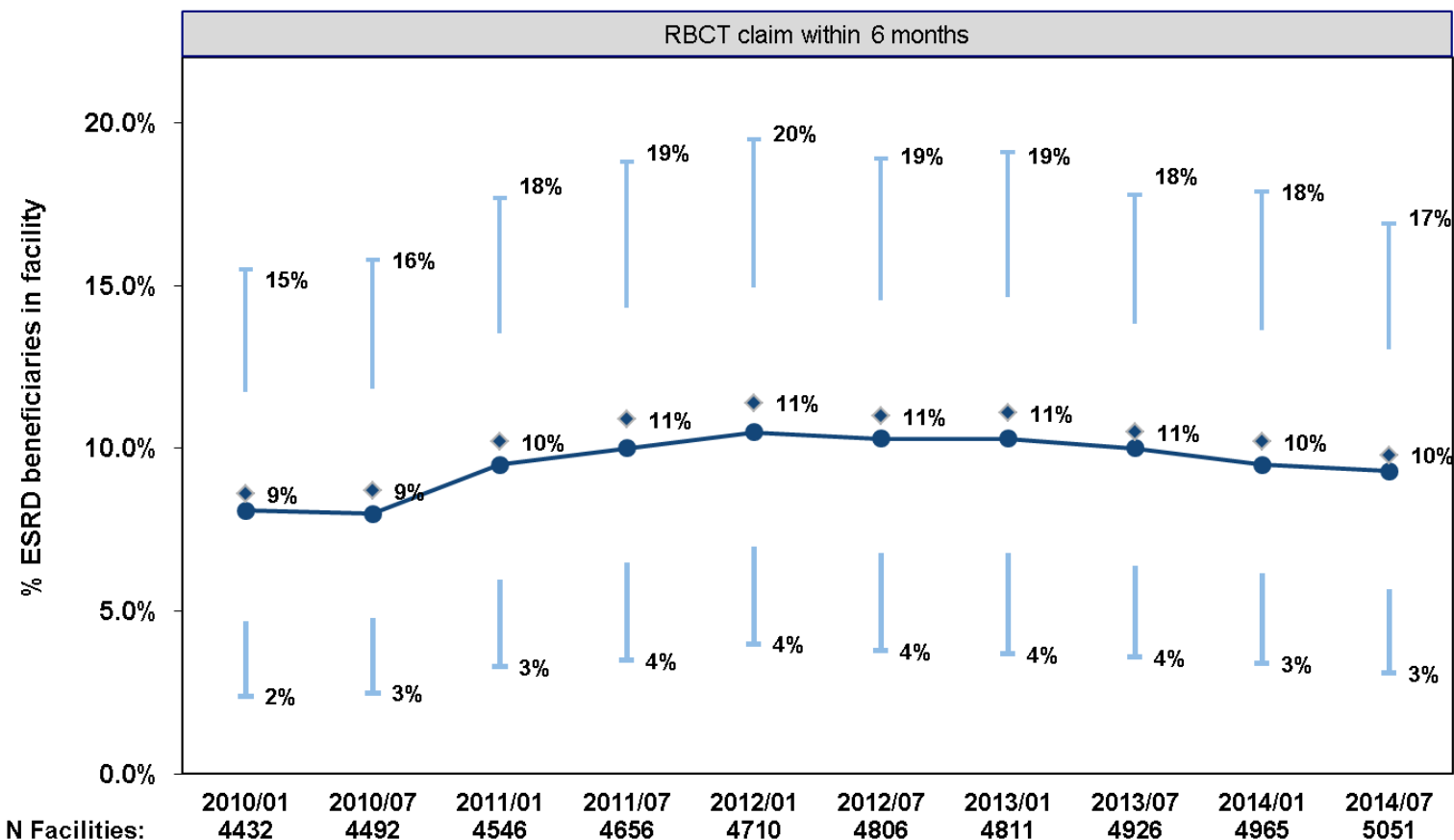
ADVERTISEMENT



Have 2 minutes?

Stay up-to-date on the
latest product information
from Industry

Facility percent ESRD beneficiaries with RBCT claim



Values for each month reflect distribution of facility percent of Medicare ESRD beneficiaries with a red blood cell transfusion (RBCT) claim, among facilities with 20+ patients.

The diamond marker indicates the mean value and the circle marker indicates the median value. The maximum number of procedures per inpatient claim in this Medicare dataset increased from 6 to 25 starting in January 2011.

Source: Medicare Claims, 2010-2014; US-DOPPS Practice Monitor, <http://www.dopps.org/DPM>

2009

TREAT Study

Grande spinta alla terapia marziale



The ERBP position statement about KDIGO guidelines on anaemia management in chronic kidney disease

IRON THERAPY

A trial with iron therapy (either IV or when tolerated orally as a first step in ND-CKD patients, especially in CKD II to III, or in PD patients) is suggested if:

☀ There is absolute iron deficiency (**TSAT < 20% and serum ferritin < 100 ng/ml**)

OR

☀ An increase in Hb concentration or a decrease in ESA dose are desired

AND

☀ **TSAT is < 25% (<30% for ESA treated) and ferritin is <300 ng/ml in dialysis patients**

☀ **Following iron treatment the limit of TSAT of 30% and serum ferritin of 500 should not be intentionally exceeded in both ND-CKD and dialysis patients**

IV iron and ESA in haemodialysis: A systematic review and meta-analysis

Of the 28 RCTs identified, 7 met the criteria for inclusion

Intervention arms:

Optimal → 100-200 mg IV iron per week

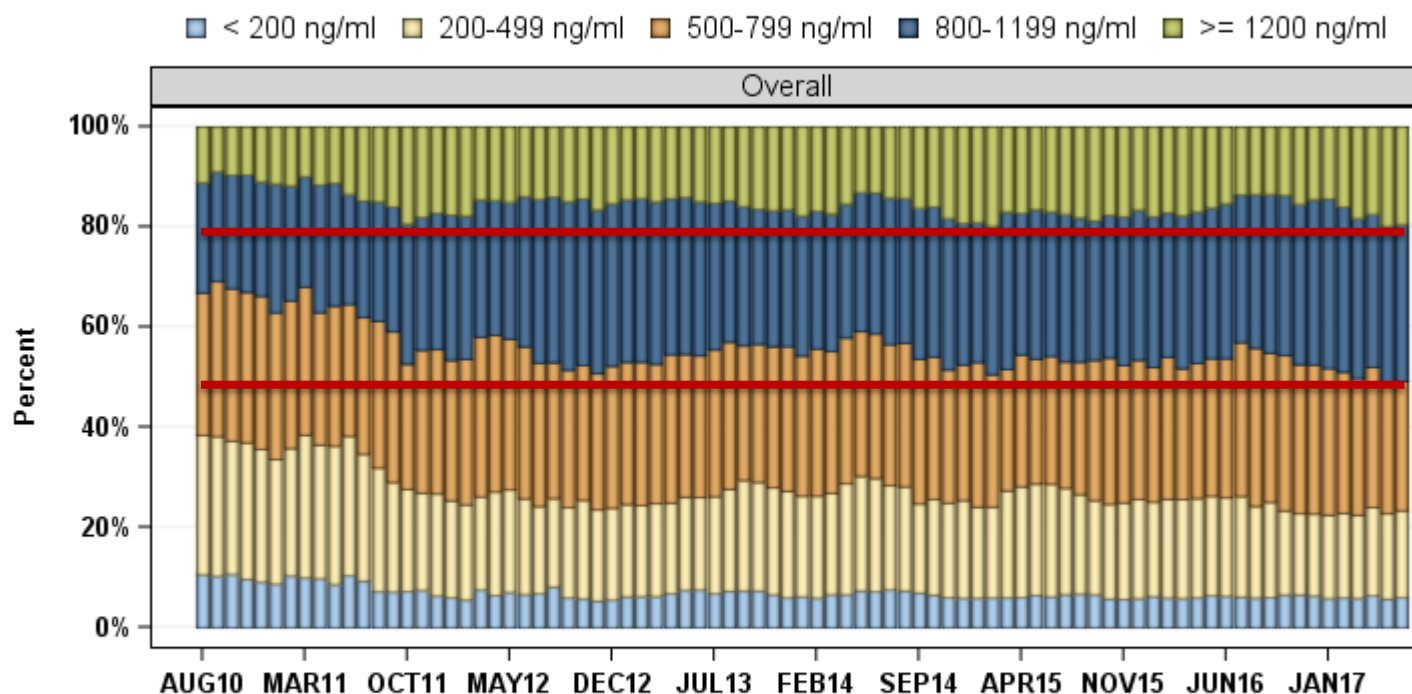
Suboptimal → < 100 mg per week

Weighted average percentage reduction in ESA dose/week

-23% OVERALL
range -7% to -55%

Serum ferritin (most recent), categories

National sample



50% con
ferritina ≥
800 ng/ml

Values at each month are based on the most recent measurement obtained within the prior 3 months

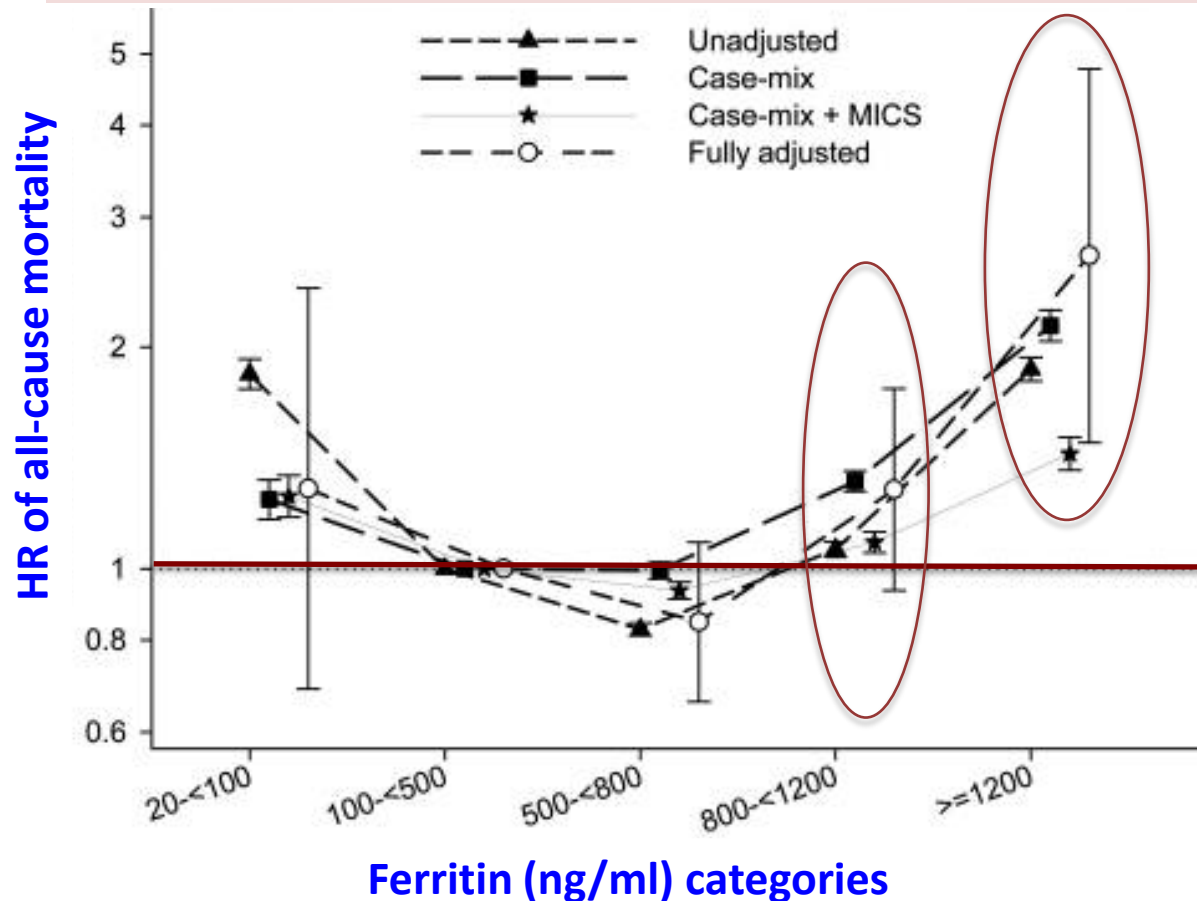
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods").

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

Source: US-DOPPS Practice Monitor, August 2017; <http://www.dopps.org/DPM>

Iron indices and survival in maintenance HD patients with and without polycystic kidney disease

2969 MHD patients with and 128 054 without PKD from 580 outpatient HD facilities between July 2001 and June 2006.

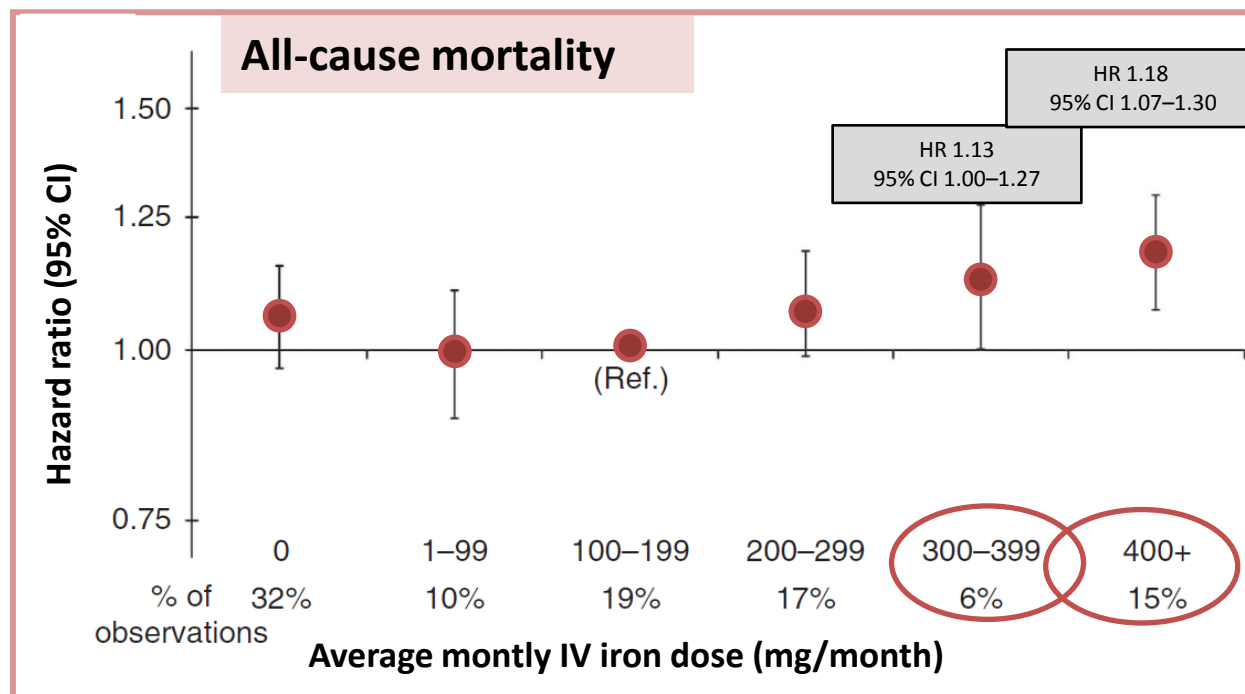


Hazard ratio (95% CI) of mortality across the ferritin categories using time-averaged cox regression analyses in MHD patients without polycystic kidney disease.

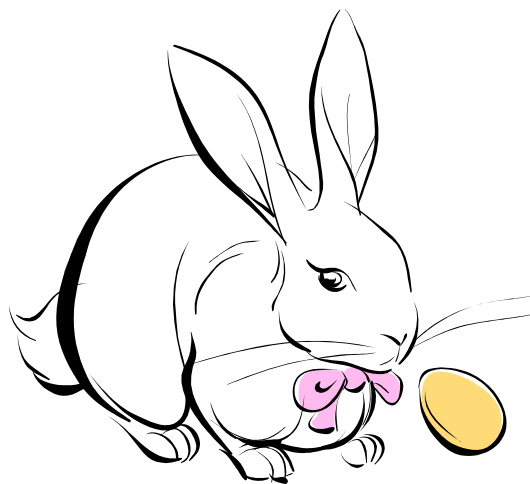
Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality

George R. Bailie¹, Maria Larkina², David A. Goodkin², Yun Li^{2,3}, Ronald L. Pisoni², Brian Bieber², Nancy Mason⁴, Lin Tong², Francesco Locatelli⁵, Mark R. Marshall⁶, Masaaki Inaba⁷ and Bruce M. Robinson^{2,3}

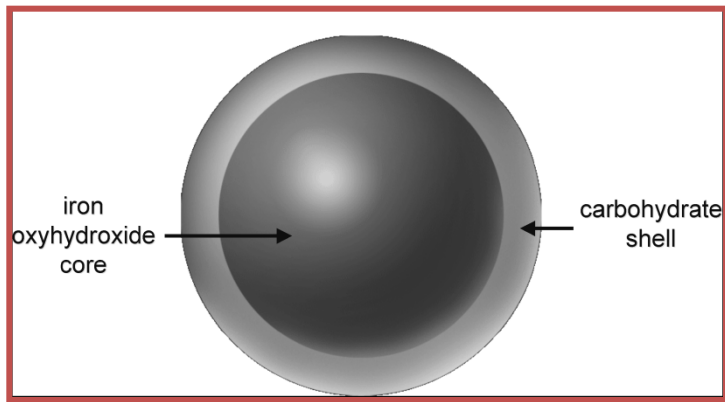
Associations between IV iron dose and clinical outcomes in 32,435 HD patients in 12 countries from 2002 to 2011 in the DOPPS Study



IV iron therapy



Traditional iron molecules



Parenteral Iron Therapy

Traditional molecules

~~HMV iron dextran~~

~~LMV iron dextran~~

Iron sucrose

Iron gluconate



Hypersensitivity reactions
Need of resuscitation Team and medications



Hypotension
Low doses
Repeated administration

New iron molecules



✖ Ferric carboxymaltose

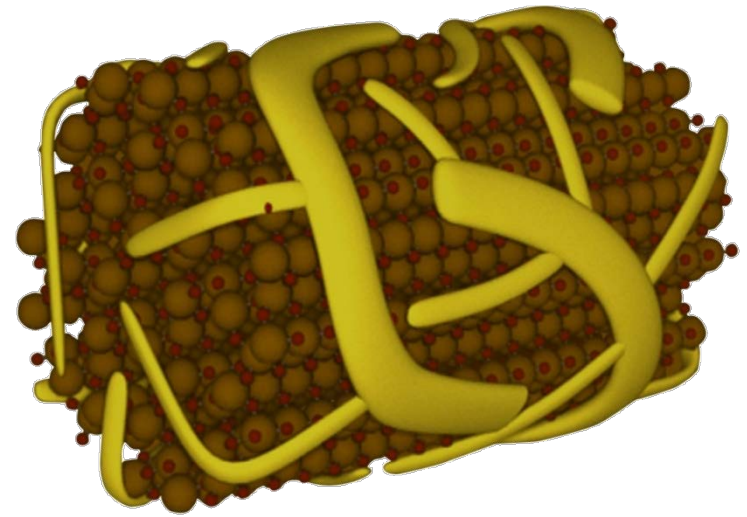
✖ Ferumoxytol

✖ Iron Isomaltoside

Ferric carboxymaltose

● Possible advantages:

- ✗ No free iron
- ✗ Large dose, rapid infusion
- ✗ Lower number of administrations
- ✗ Good safety



- Ferric hydroxide molecules
- Ribbon-like carboxymaltose

**IN DIALISI DOSE MASSIMA DA
SCHEDA TECNICA 200 MG**

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

2584 ND-CKD patients

FCM 750 mg
2 doses in one week

Iron sucrose 200 mg
up to five inf. in 14 days

Primary efficacy endpoint

Mean change to highest Hb from baseline to Day 56

Primary composite safety endpoint

All-cause mortality, nonfatal MI, nonfatal stroke, unstable angina, CHF, arrhythmias and hyper- and hypotensive events

The REPAIR-IDA trial

Proportion of subjects with an increase in Hb ≥ 1.0 g/dL between baseline and Day 56 or time of intervention (modified intent-to-treat population)

FCM (n = 1249)

607/1249 (48.60%)

Iron sucrose (n = 1244)

510/1244 (41.00%)

Treatment difference (95% CI)

7.60% (3.63 to 11.57%)

The REPAIR-IDA trial

Components of the primary composite safety endpoint (safety population)

	FCM (<i>n</i> = 1276) <i>n</i> (%)	Iron sucrose (<i>n</i> = 1285) <i>n</i> (%)	Difference (95% CI) ^a
Any composite safety endpoint component	175 (13.71%)	156 (12.14%)	1.57% (−1.10 to 4.25%)
Components of the composite endpoint			
Death due to any cause	15 (1.18%)	18 (1.40%)	−0.23% (−1.18 to 0.73%)
Nonfatal myocardial infarction	8 (0.63%)	14 (1.09%)	−0.46% (−1.25 to 0.33%)
Nonfatal stroke	3 (0.24%)	3 (0.23%)	0.00% (−0.45 to 0.45%)
Unstable angina requiring hospitalization	11 (0.86%)	3 (0.23%)	0.63% (−0.02 to 1.28%)
CHF requiring hosp./medical intervention	38 (2.98%)	34 (2.65%)	0.33% (−1.03 to 1.69%)
Arrhythmias	18 (1.41%)	13 (1.01%)	0.40% (−0.53 to 1.32%)
Protocol-defined hypertensive events ^b	95 (7.45%)	56 (4.36%)	3.09% (1.19 to 4.99%)
Protocol-defined hypotensive events ^c	23 (1.80%)	41 (3.19%)	−1.39% (−2.67 to −0.10%)



Troppo basso a volte non funziona!!

Grazie per l'attenzione