King's College Hospital NHS
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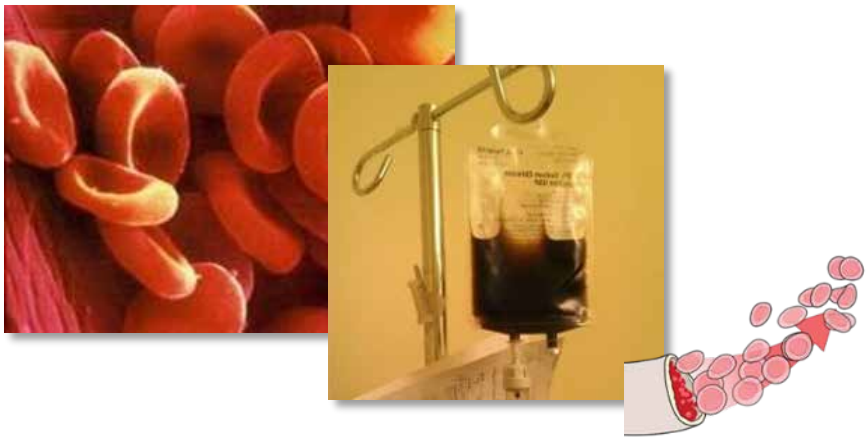
KING'S College LONDON

Novel aspects of anemia and iron management in renal patients with or without cardiorenal syndrome

Iain C. Macdougall

Consultant Nephrologist & Professor of Clinical Nephrology



Renal Unit,
King's College Hospital,
London, UK

Ioannina
Ιωάννινα
Trikala
Τρίκαλα
Larissa
Λάρισα
Balikesir
Corfu
Κέρκυρα
2002
Greece
Ayvalık

Lamia
Λαμία
E7

Akhisar
Manisa
Izmir
Patras
Πάτρα
O-32
2012
Athens
Αθήνα
Planos
Archea
Killini 2012
2008
2018

E65

Kalamata
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2000
2010


2004
Lindos
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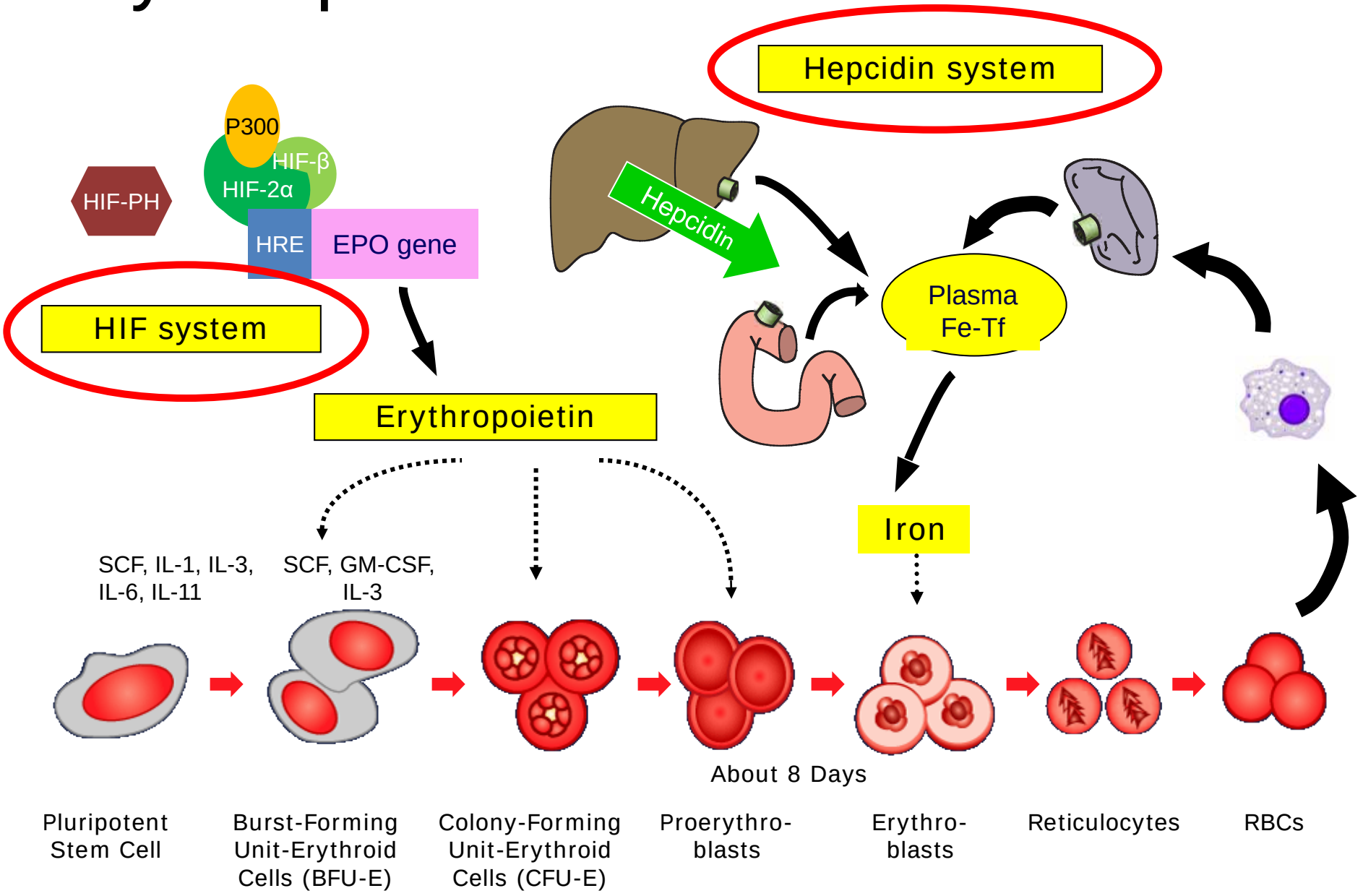
Erythropoiesis

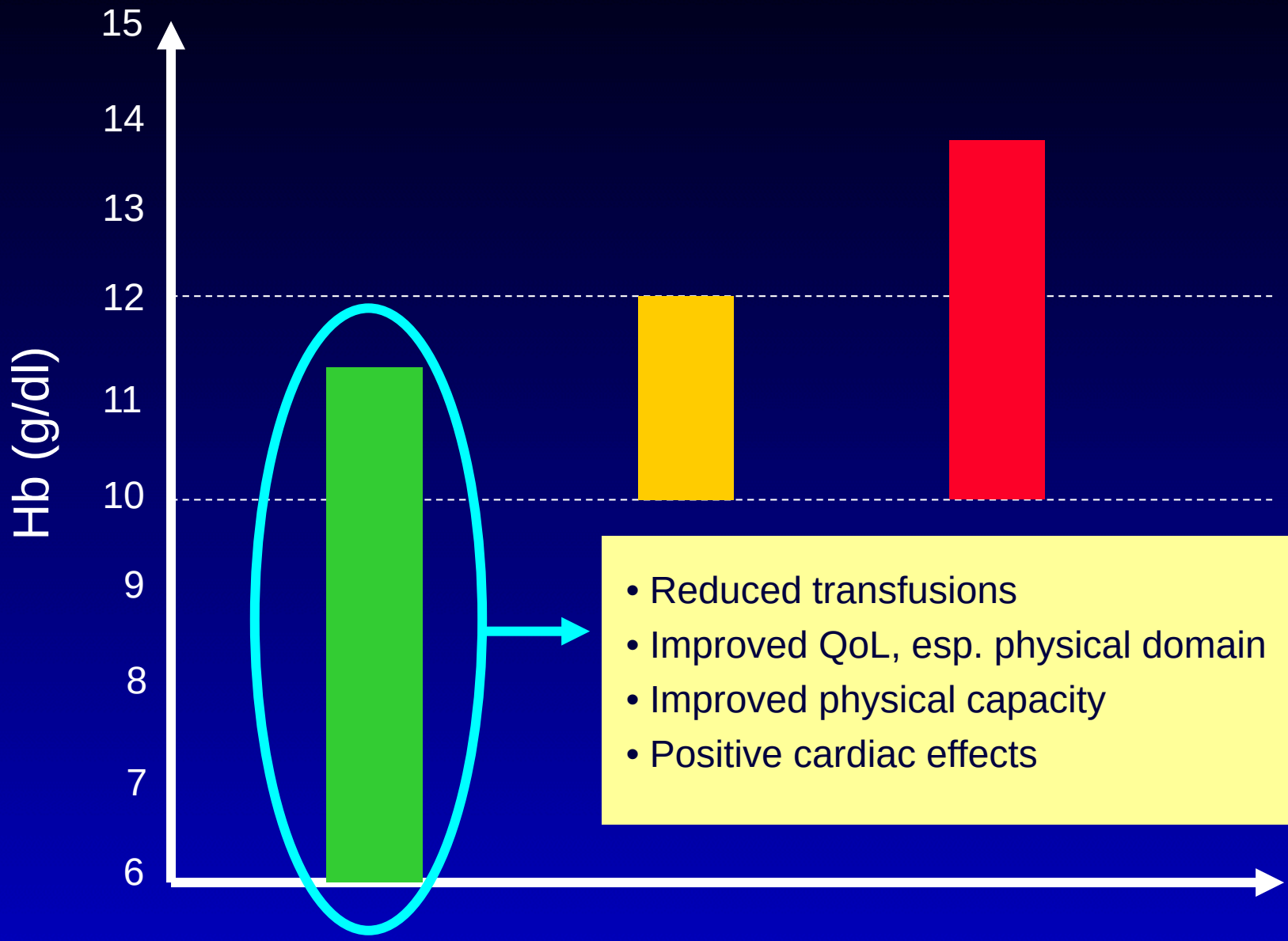


Outline of lecture

- What‘s new in anemia management?
- What‘s new in iron management?
- What‘s new in patients with cardiorenal syndrome?

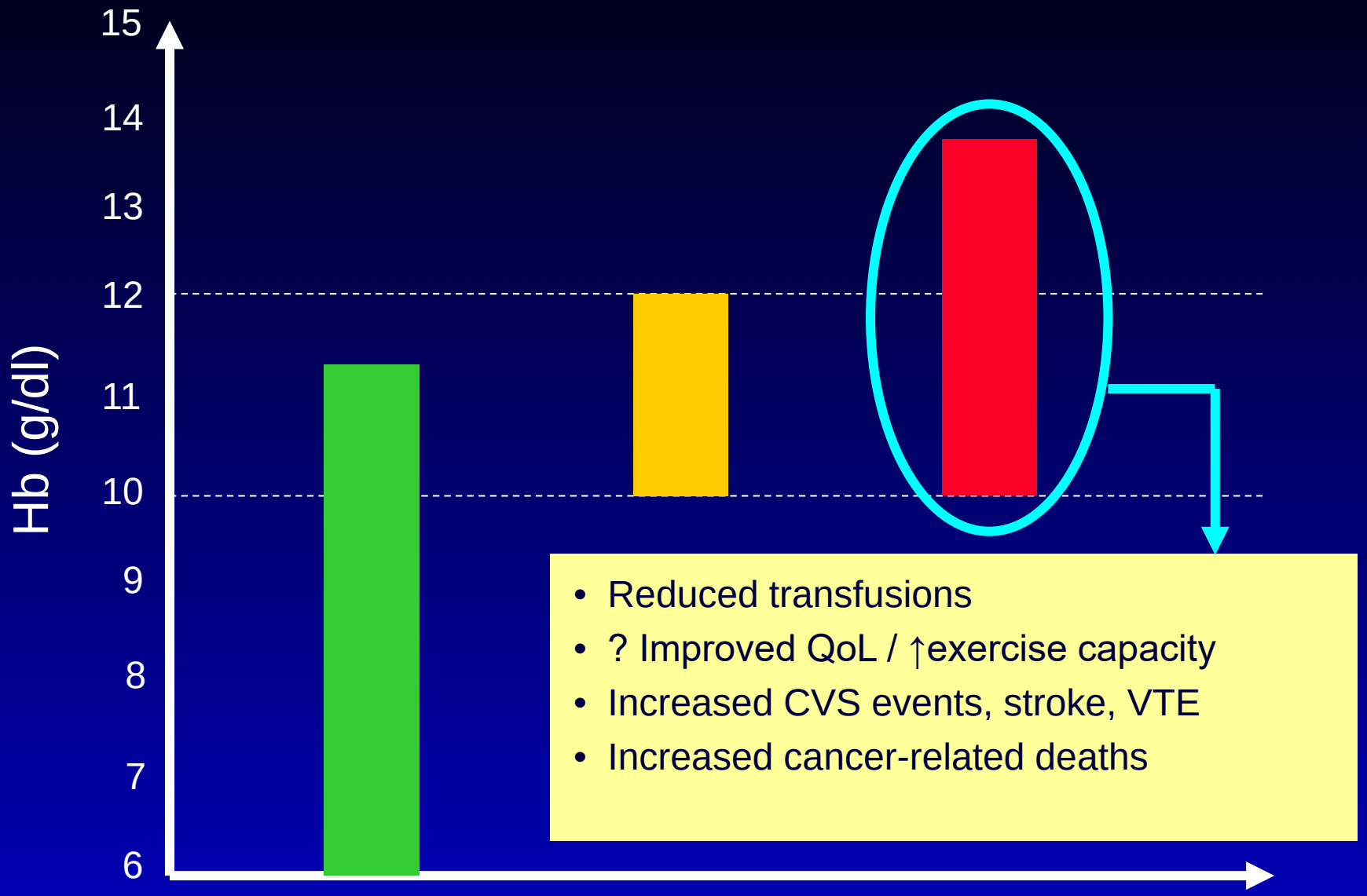
Is there anything new in relation to target haemoglobin?

Hb correction with ESA therapy



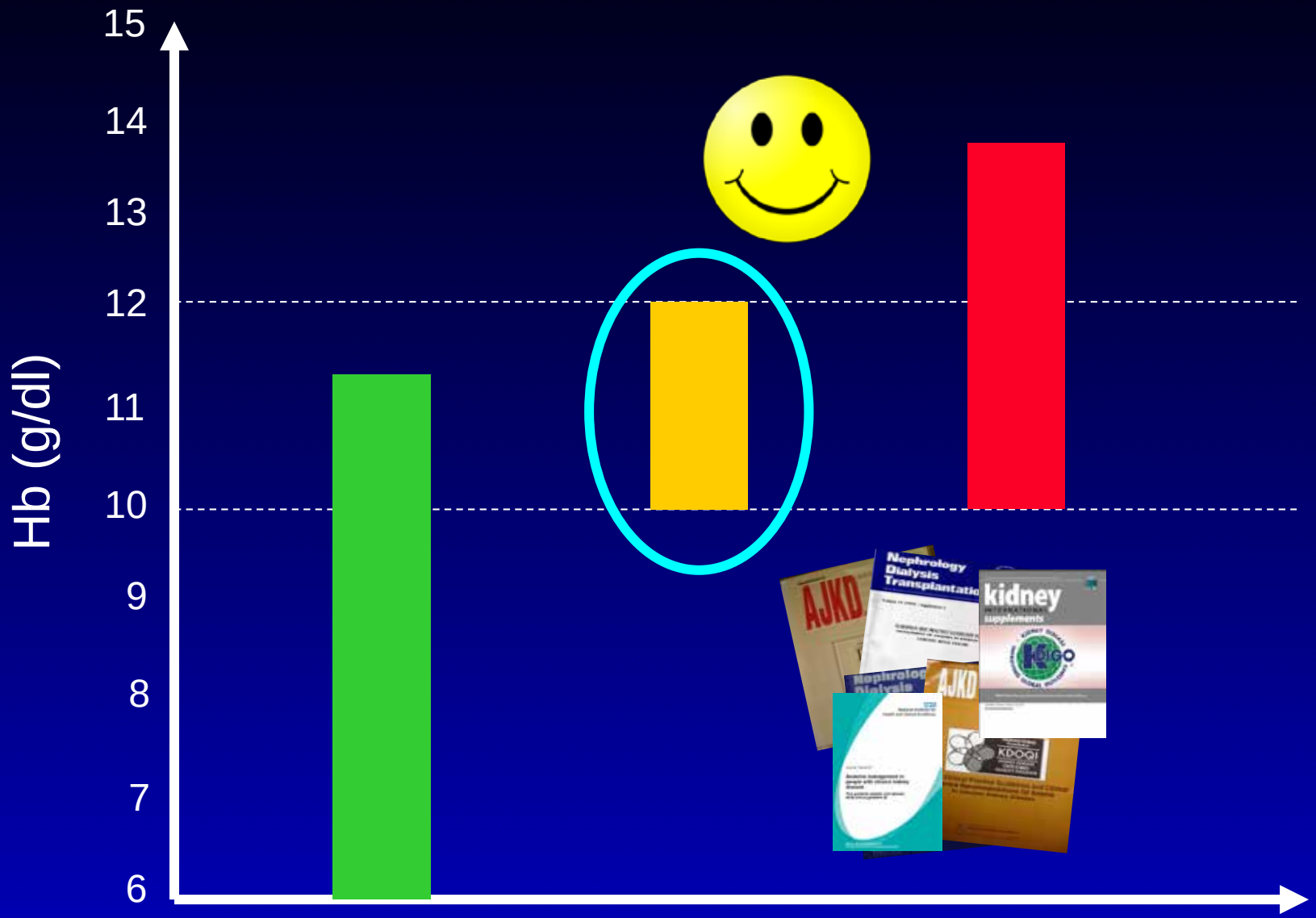
- Reduced transfusions
- Improved QoL, esp. physical domain
- Improved physical capacity
- Positive cardiac effects

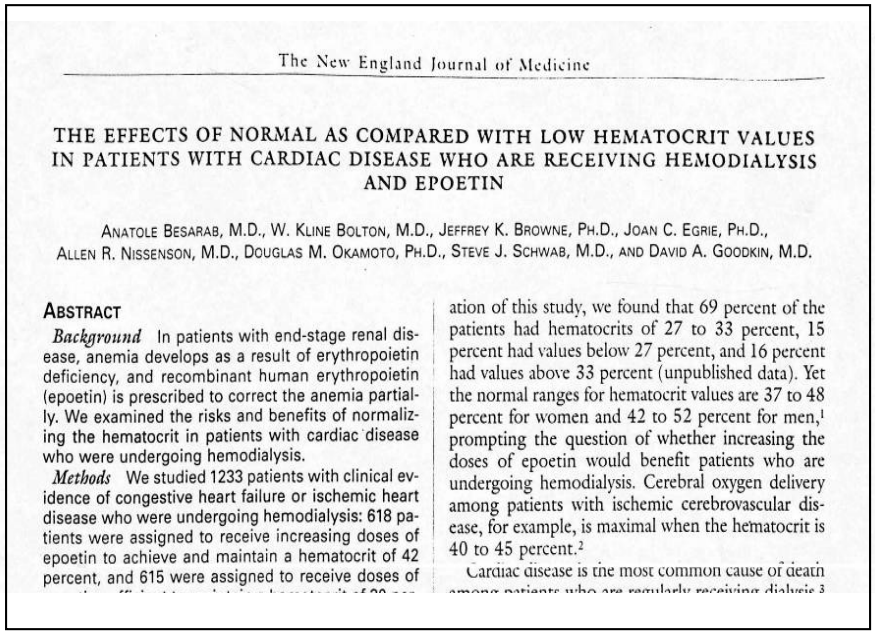
Hb correction with ESA therapy



- Reduced transfusions
- ? Improved QoL / ↑exercise capacity
- Increased CVS events, stroke, VTE
- Increased cancer-related deaths

Hb correction with ESA therapy





The New England Journal of Medicine

THE EFFECTS OF NORMAL AS COMPARED WITH LOW HEMATOCRIT VALUES IN PATIENTS WITH CARDIAC DISEASE WHO ARE RECEIVING HEMODIALYSIS AND EPOETIN

ANATOLE BESARAB, M.D., W. KLINE BOLTON, M.D., JEFFREY K. BROWNE, PH.D., JOAN C. EGRIE, PH.D., ALLEN R. NISSENSON, M.D., DOUGLAS M. OKAMOTO, PH.D., STEVE J. SCHWAB, M.D., AND DAVID A. GOODKIN, M.D.

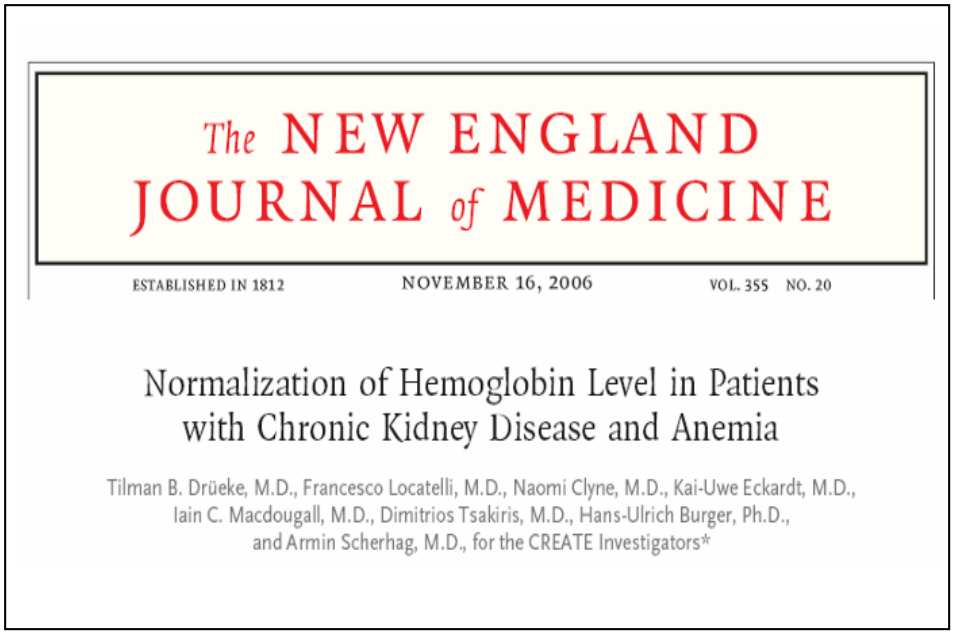
ABSTRACT

Background In patients with end-stage renal disease, anemia develops as a result of erythropoietin deficiency, and recombinant human erythropoietin (epoetin) is prescribed to correct the anemia partially. We examined the risks and benefits of normalizing the hematocrit in patients with cardiac disease who were undergoing hemodialysis.

Methods We studied 1233 patients with clinical evidence of congestive heart failure or ischemic heart disease who were undergoing hemodialysis: 618 patients were assigned to receive increasing doses of epoetin to achieve and maintain a hematocrit of 42 percent, and 615 were assigned to receive doses of

ation of this study, we found that 69 percent of the patients had hematocrits of 27 to 33 percent, 15 percent had values below 27 percent, and 16 percent had values above 33 percent (unpublished data). Yet the normal ranges for hematocrit values are 37 to 48 percent for women and 42 to 52 percent for men,[1] prompting the question of whether increasing the doses of epoetin would benefit patients who are undergoing hemodialysis. Cerebral oxygen delivery among patients with ischemic cerebrovascular disease, for example, is maximal when the hematocrit is 40 to 45 percent.[2]

Cardiac disease is the most common cause of death

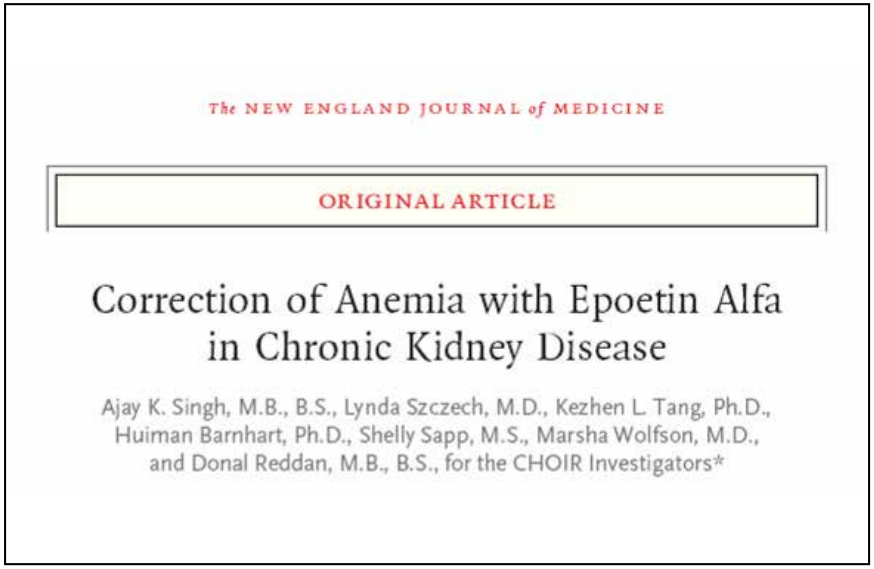


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2006 VOL. 355 NO. 20

Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

Tilman B. Drüeke, M.D., Francesco Locatelli, M.D., Naomi Clyne, M.D., Kai-Uwe Eckardt, M.D., Iain C. Macdougall, M.D., Dimitrios Tsakiris, M.D., Hans-Ulrich Burger, Ph.D., and Armin Scherhag, M.D., for the CREATE Investigators*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D., Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D., and Donal Reddan, M.B., B.S., for the CHOIR Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

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*

ABSTRACT

BACKGROUND

Anemia is associated with an increased risk of cardiovascular and renal events among patients with type 2 diabetes and chronic kidney disease. Although darbepoetin alfa can effectively increase hemoglobin levels, its effect on clinical outcomes in these patients has not been adequately tested.

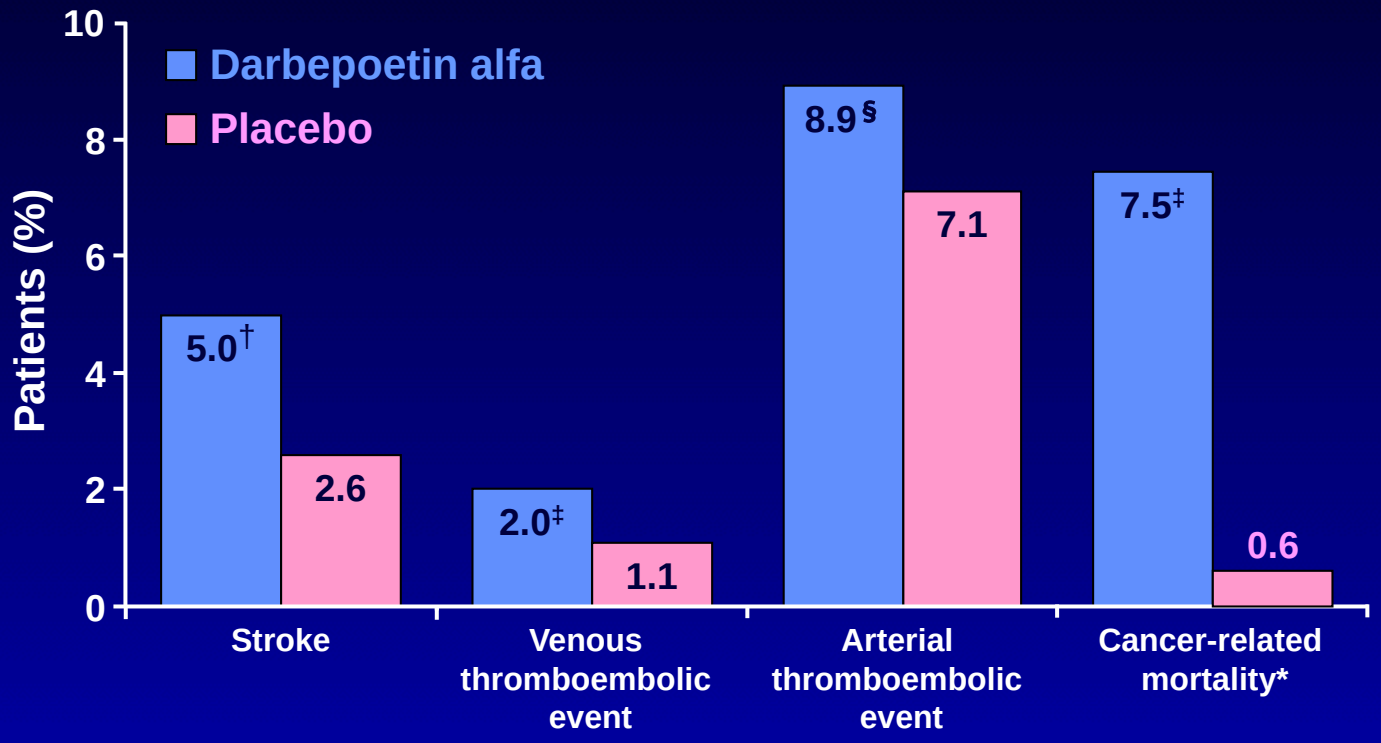
METHODS

In this study involving 4038 patients with diabetes, chronic kidney disease, and anemia, we randomly assigned 2012 patients to darbepoetin alfa to achieve a hemoglobin level of approximately 13 g per deciliter and 2026 patients to placebo, with

The affiliations of the authors are listed in the Appendix. Address reprint requests to Dr. Pfeffer at the Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at mpfeffer@rics.bwh.harvard.edu.

*The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) committees and teams are listed in the Appendix, and investigators and individuals

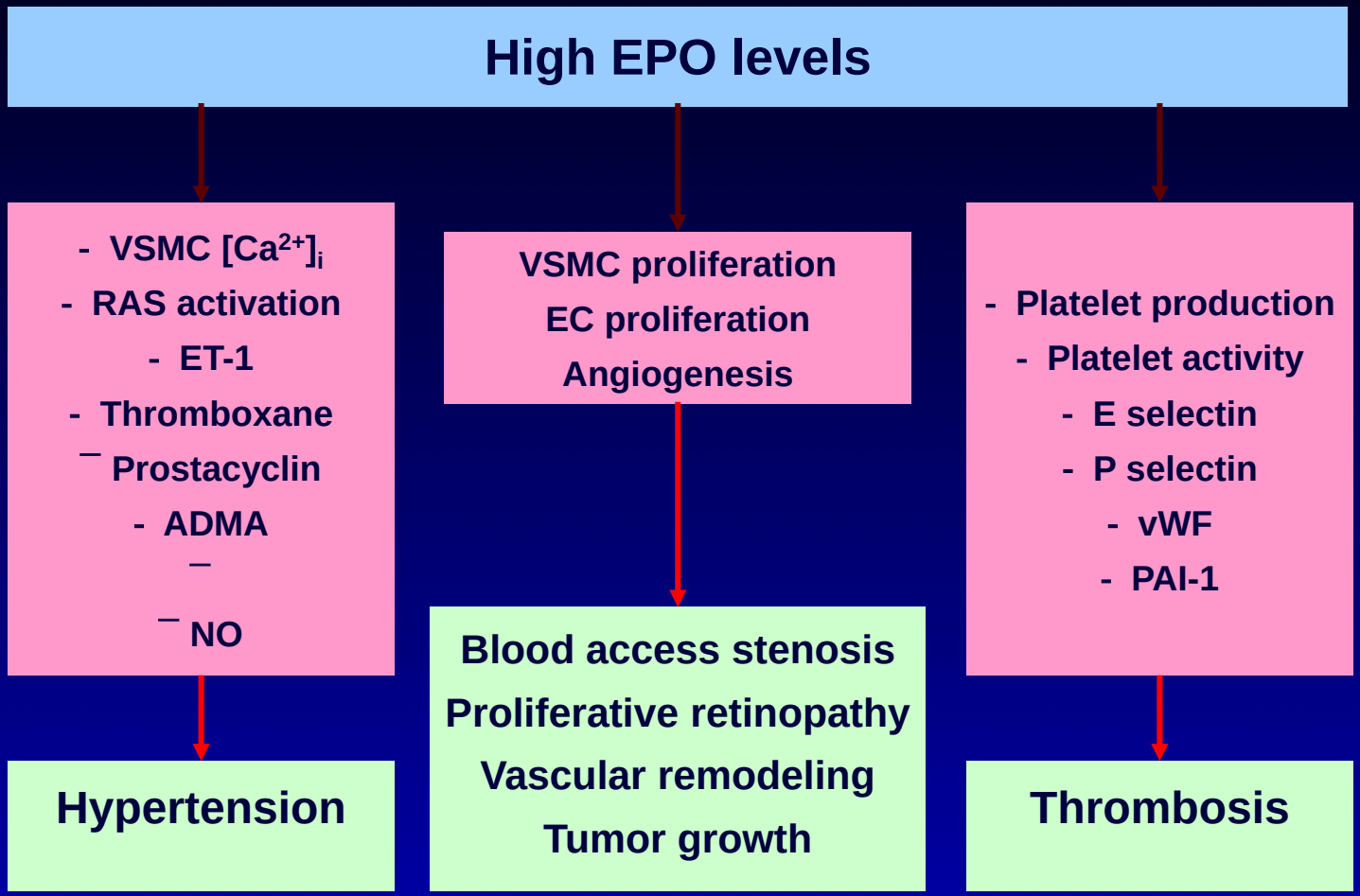
Safety Concerns in the TREAT Study



†, p<0.001 versus placebo
‡, p=0.02 versus placebo
§, p=0.04 versus placebo
*Amongst patients with a history of malignancy at baseline

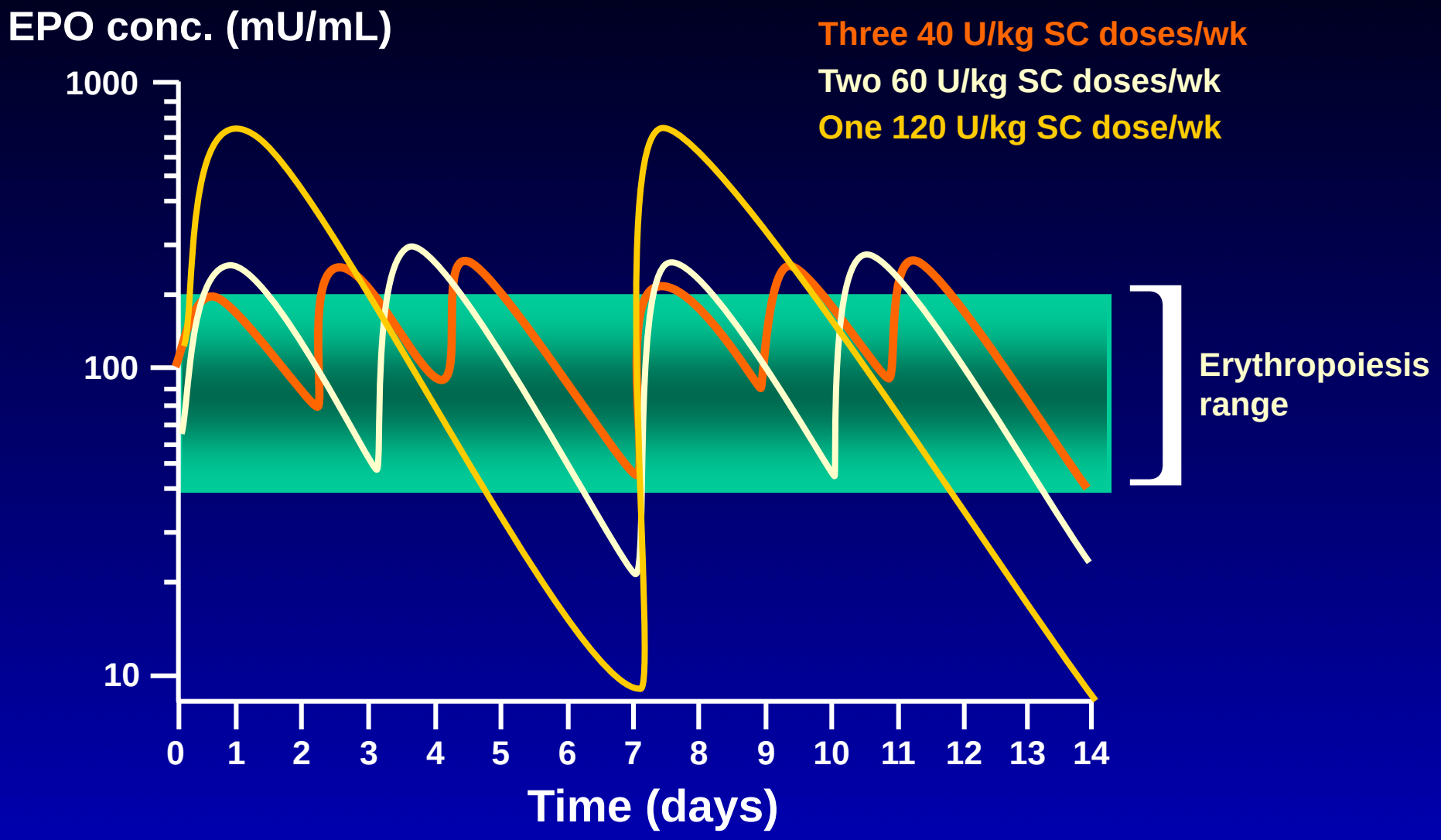
Pfeffer MA et al. *N Engl J Med* 2009;361:2019–2032.

EPO has non-erythropoietic actions



Vaziri ND & Zhou X. Nephrol Dial Transplant 2009; 24: 1082–1088.

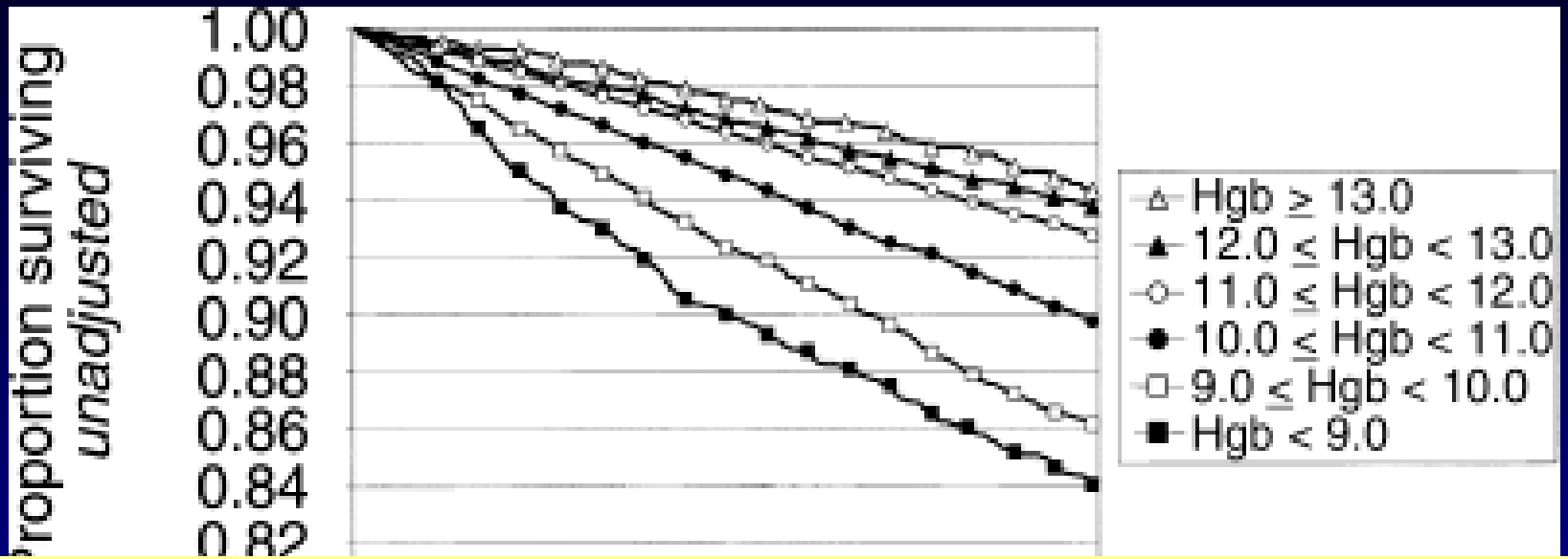
Erythropoietin concentration-time profiles



Besarab et al, J Am Soc Nephrol 1992.

Hb predicts survival in observational studies

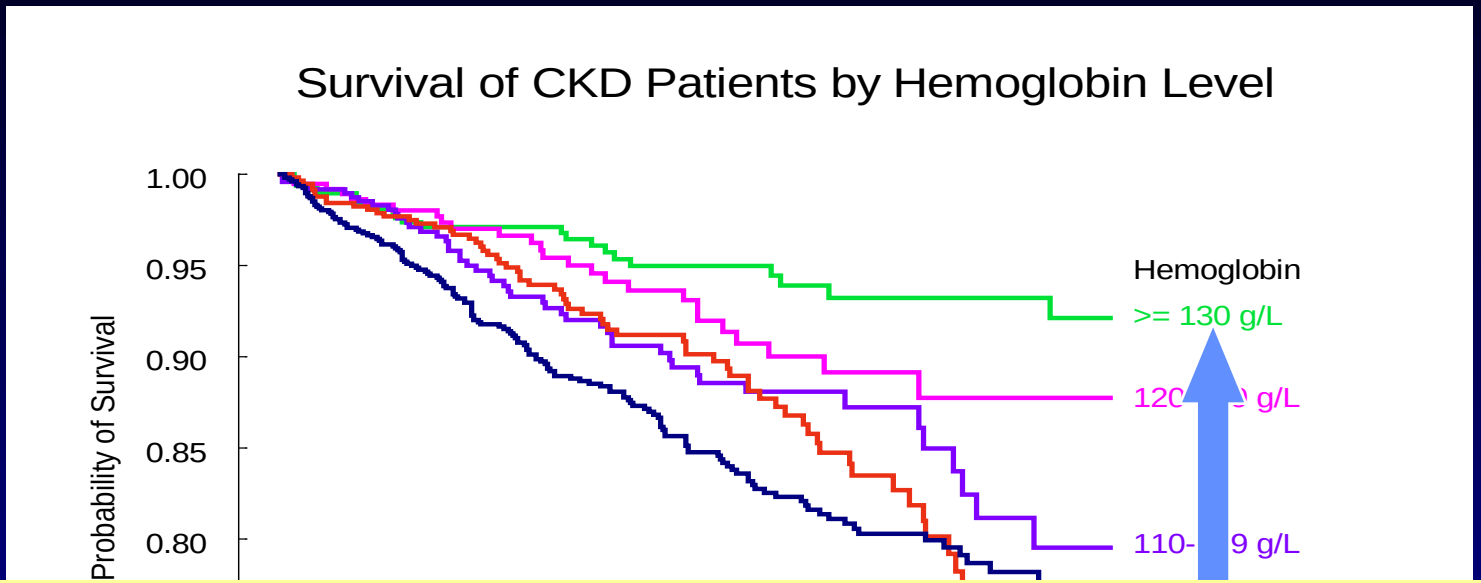
HD patients



If a patient is NOT on ESA therapy and has a high Hb, is there a need to venesect / lose circuits?

Hb predicts survival in observational studies

ND-CKD patients

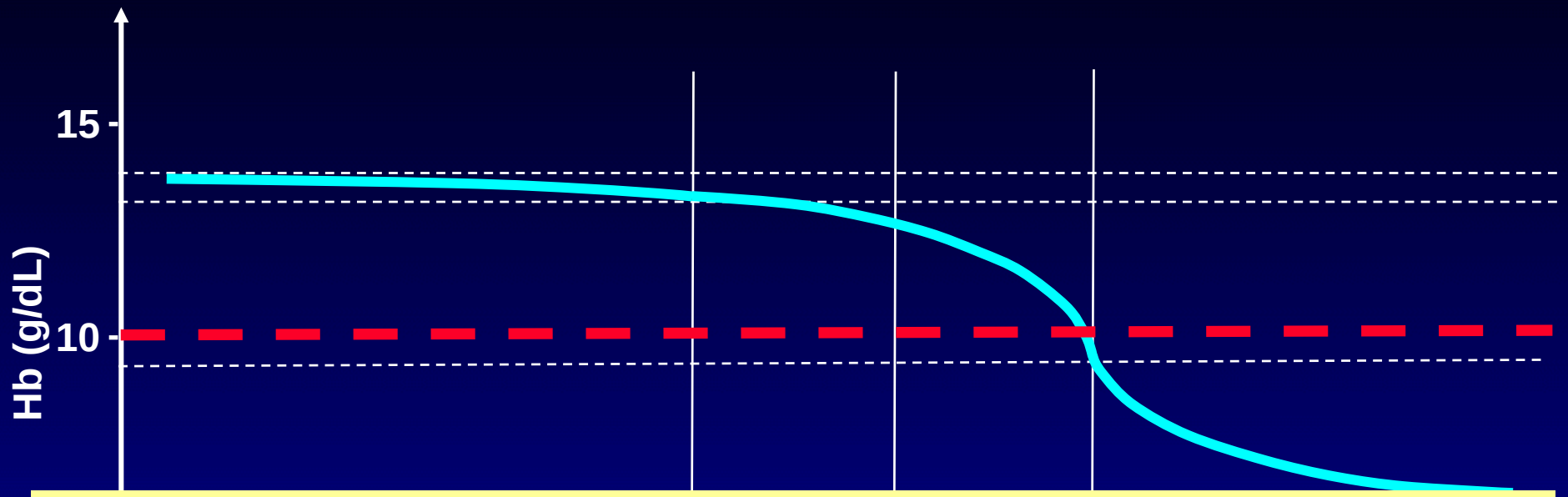


If a patient is NOT on ESA therapy and has a high Hb, is there a need to venesect?

ABSOLUTELY NOT!

What about the trigger haemoglobin to initiate ESA therapy?

When to initiate Hb therapy?



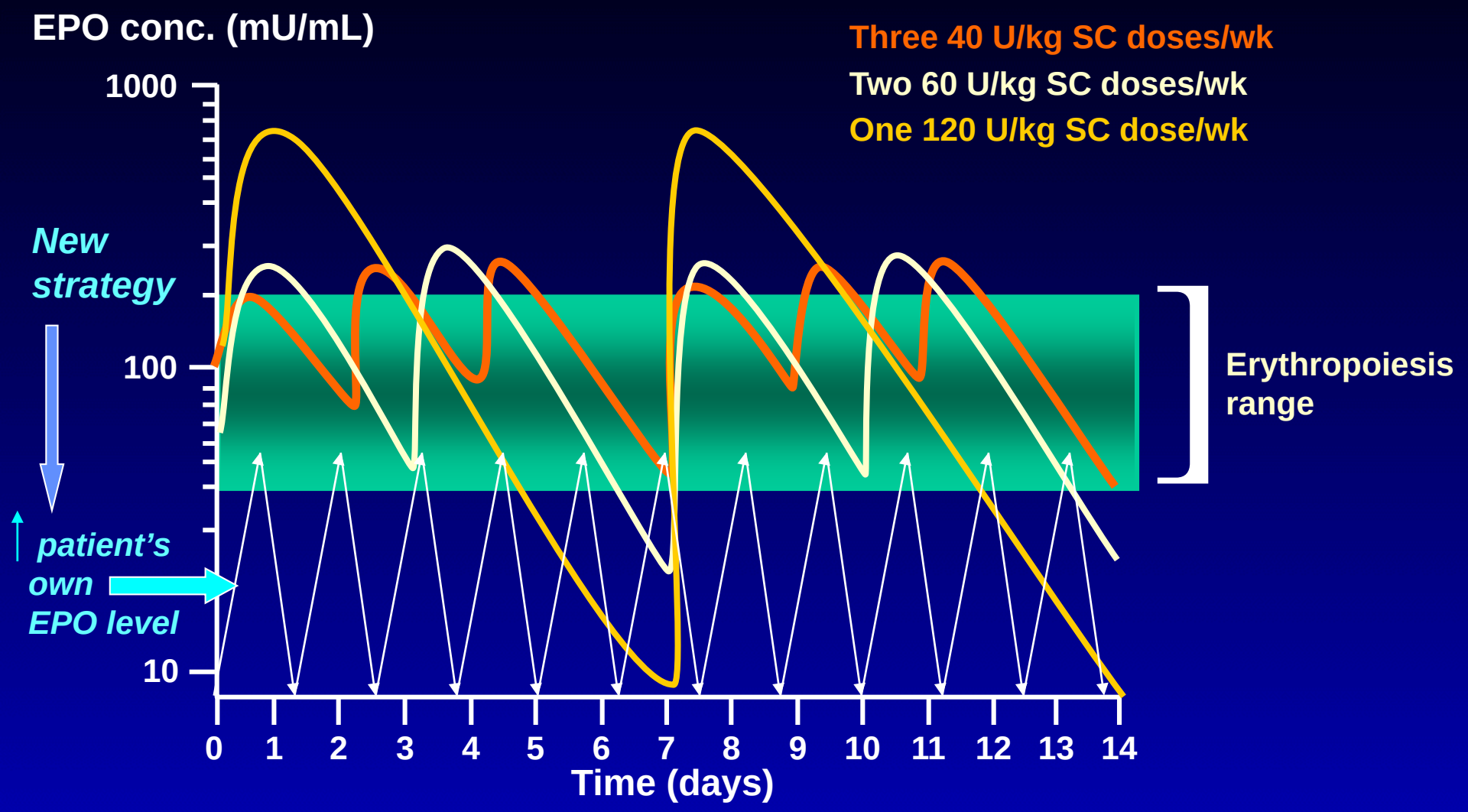
Caveats?

- *Hb < 11 g/dL plus symptoms*
- *Individualisation*

NHANES 3 data.

What about the future of anaemia management in CKD?

Erythropoietin concentration-time profiles



Besarab et al, J Am Soc Nephrol 1992.

Evolution of CKD Anaemia Treatment

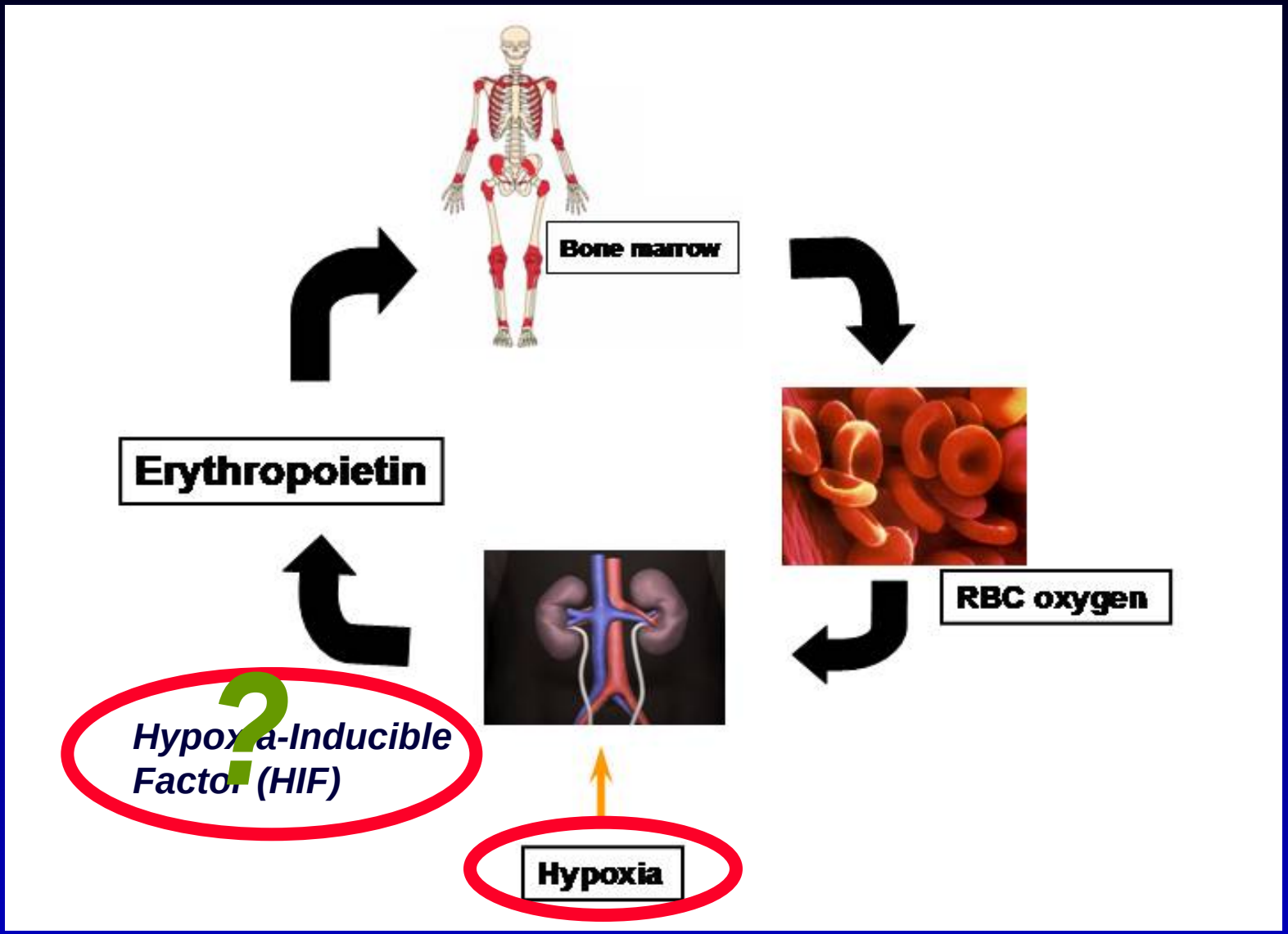
Transfusions

ESAs

HIF stabilisers

HIF stabilisers
– prolyl hydroxylase inhibitors

Regulation of erythropoietin



MOLECULAR AND CELLULAR BIOLOGY, Dec. 1992, p. 5447–5454 Vol. 12, No. 12
0270-7306/92/125447-08$02.00/0

A Nuclear Factor Induced by Hypoxia via De Novo Protein Synthesis Binds to the Human Erythropoietin Gene Enhancer at a Site Required for Transcriptional Activation

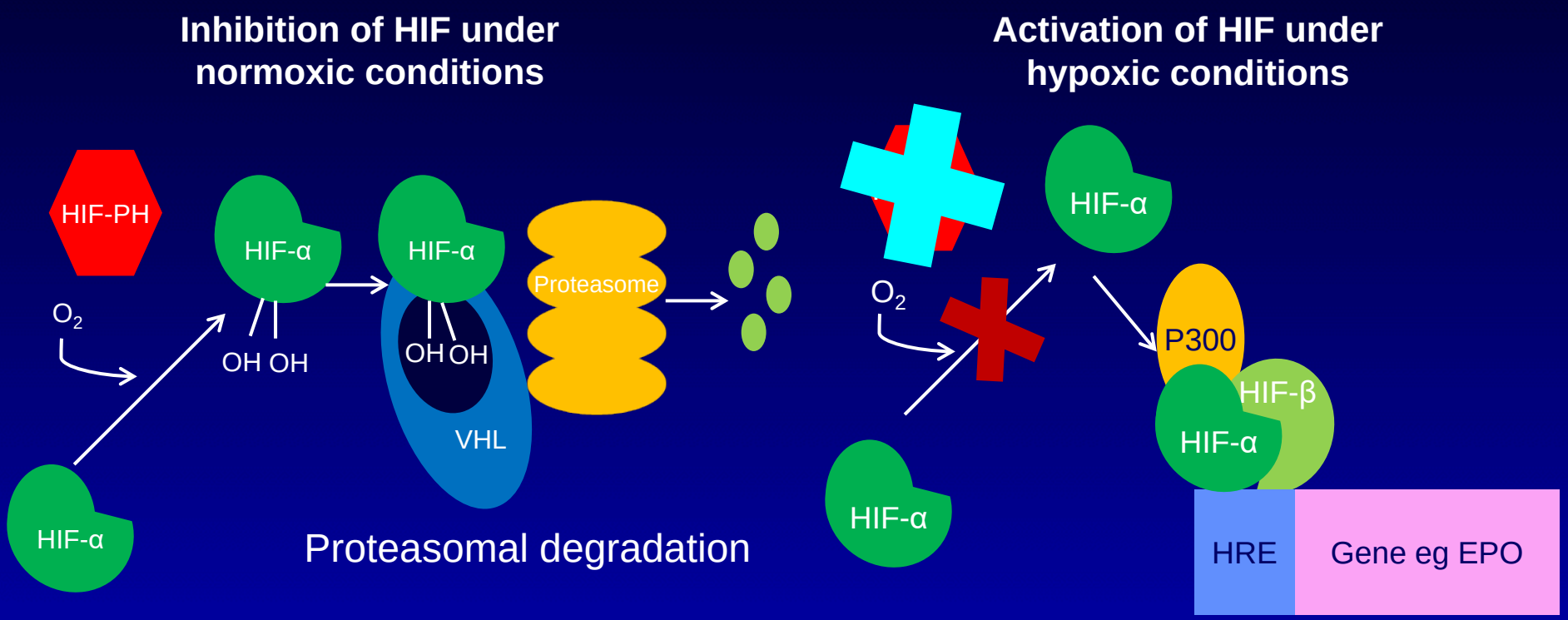
GREGG L. SEMENZA* AND GUANG L. WANG

Center for Medical Genetics, Departments of Pediatrics and Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Received 17 July 1992/Returned for modification 25 August 1992/Accepted 2 September 1992

We have identified a 50-nucleotide enhancer from the human erythropoietin gene 3′-flanking sequence which can mediate a sevenfold transcriptional induction in response to hypoxia when cloned 3′ to a simian virus 40 promoter-chloramphenicol acetyltransferase reporter gene and transiently expressed in Hep3B cells. Nucleotides (nt) 1 to 33 of this sequence mediate sevenfold induction of reporter gene expression when present in two tandem copies compared with threefold induction when present in a single copy, suggesting that nt 34 to 50 bind a factor which amplifies the induction signal. DNase I footprinting demonstrated binding of a constitutive nuclear factor to nt 26 to 48. Mutagenesis studies revealed that nt 4 to 12 and 19 to 23 are essential for induction, as substitutions at either site eliminated hypoxia-induced expression. Electrophoretic mobility shift assays identified a nuclear factor which bound to a probe spanning nt 1 to 18 but not to a probe containing a

Regulation of HIF activity



HIF stabilisers

- HIF is degraded by a prolyl hydroxylase enzyme
- Orally-active inhibitors of PH have been synthesised
- These drugs cause HIF levels to increase
- More HIF leads to more EPO

HIF PHIs in development

Company	Molecule	Drug name	Phase of development
FibroGen Astellas Astra Zeneca	FG-4592	Roxadustat	Phase 3
GSK	GSK 1278863	Daprodustat	Phase 3
Akebia Mitsubishi Otsuka Vifor Fresenius	AKB-6548	Vadadustat	Phase 3
Bayer	BAY 85-3934	Molidustat	Phase 2/3
Japan Tobacco Inc	JTZ-951		Phase 1

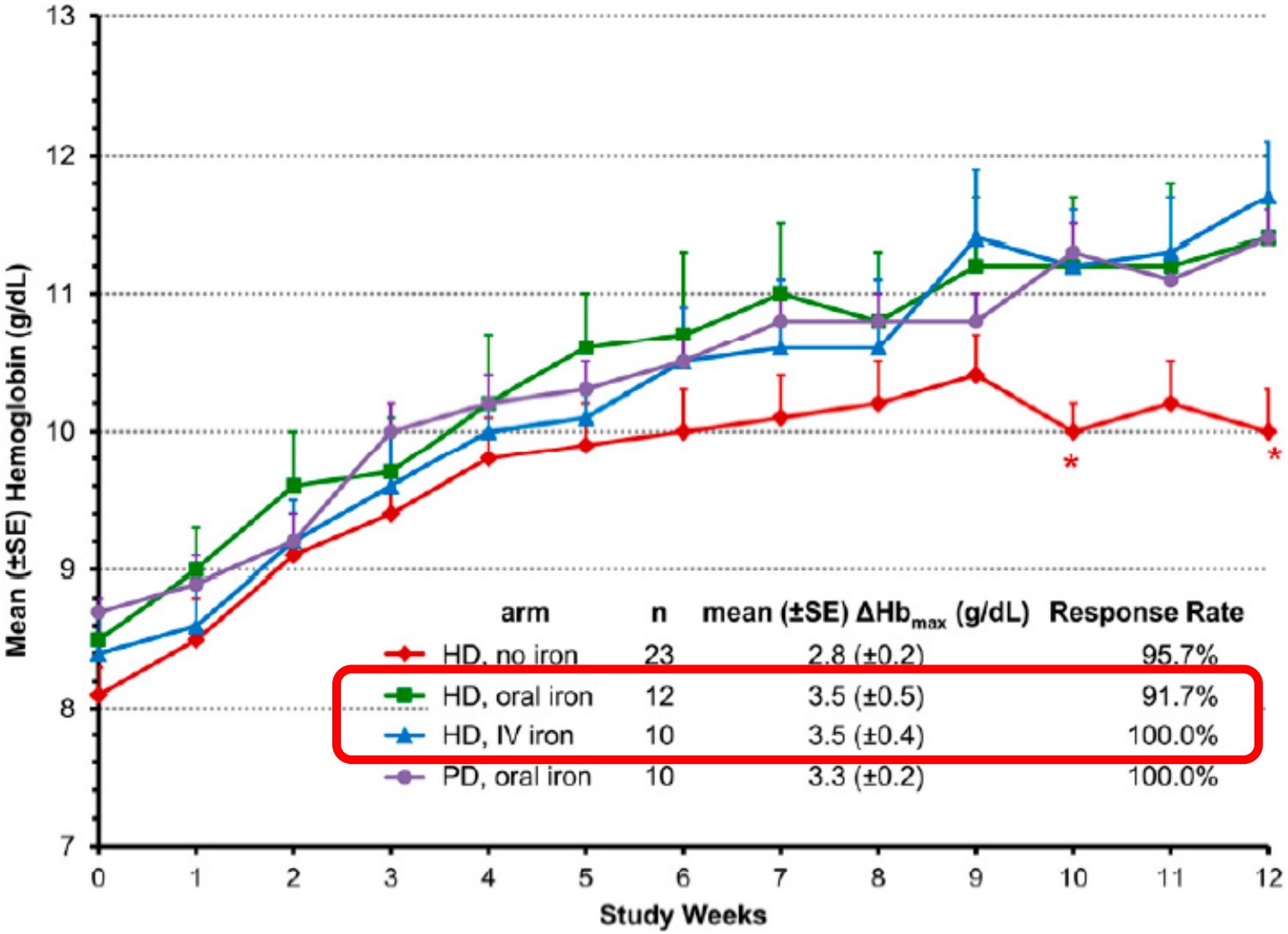
Roxadustat (FG-4592): Correction of Anemia in Incident Dialysis Patients

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*

*FibroGen, Inc., San Francisco, California; †Budgetary Healthcare Institution of Omsk Region, City Clinical Hospital #1, Omsk, Russia; ‡City Hospital #33, Nizhny Novgorod, Russia; §State Budgetary Healthcare Institution of Moscow, City Clinical Hospital, Moscow, Russia; ‖Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan; ¶Fresenius Medical Care, St. Petersburg, Russia; and **Division of Nephrology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong

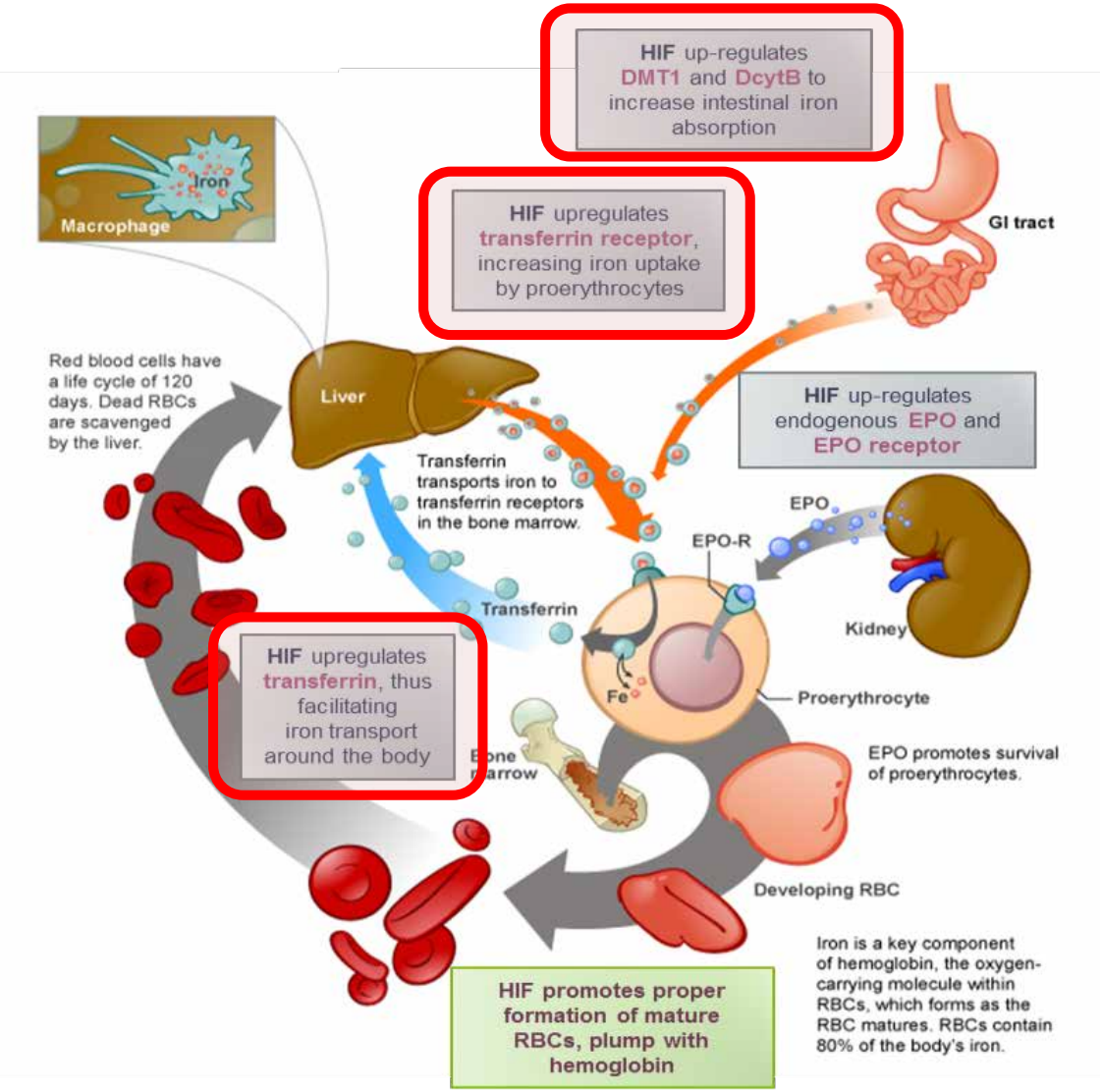
J Am Soc Nephrol 2016 Apr;27(4):1225-33.

Roxadustat increases haemoglobin levels

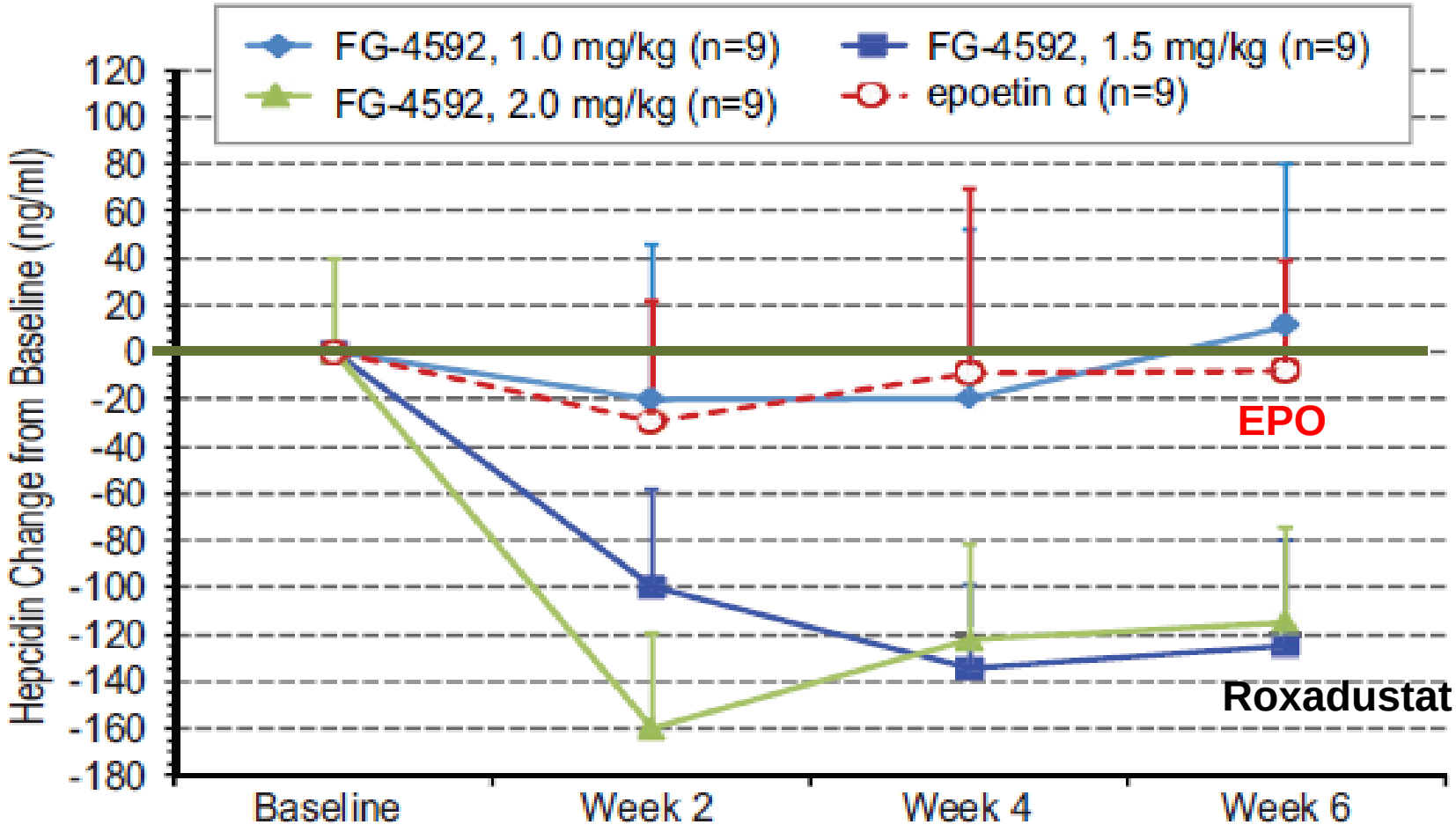


Besarab et al. J Am Soc Nephrol 2016 Apr;27(4):1225-33.

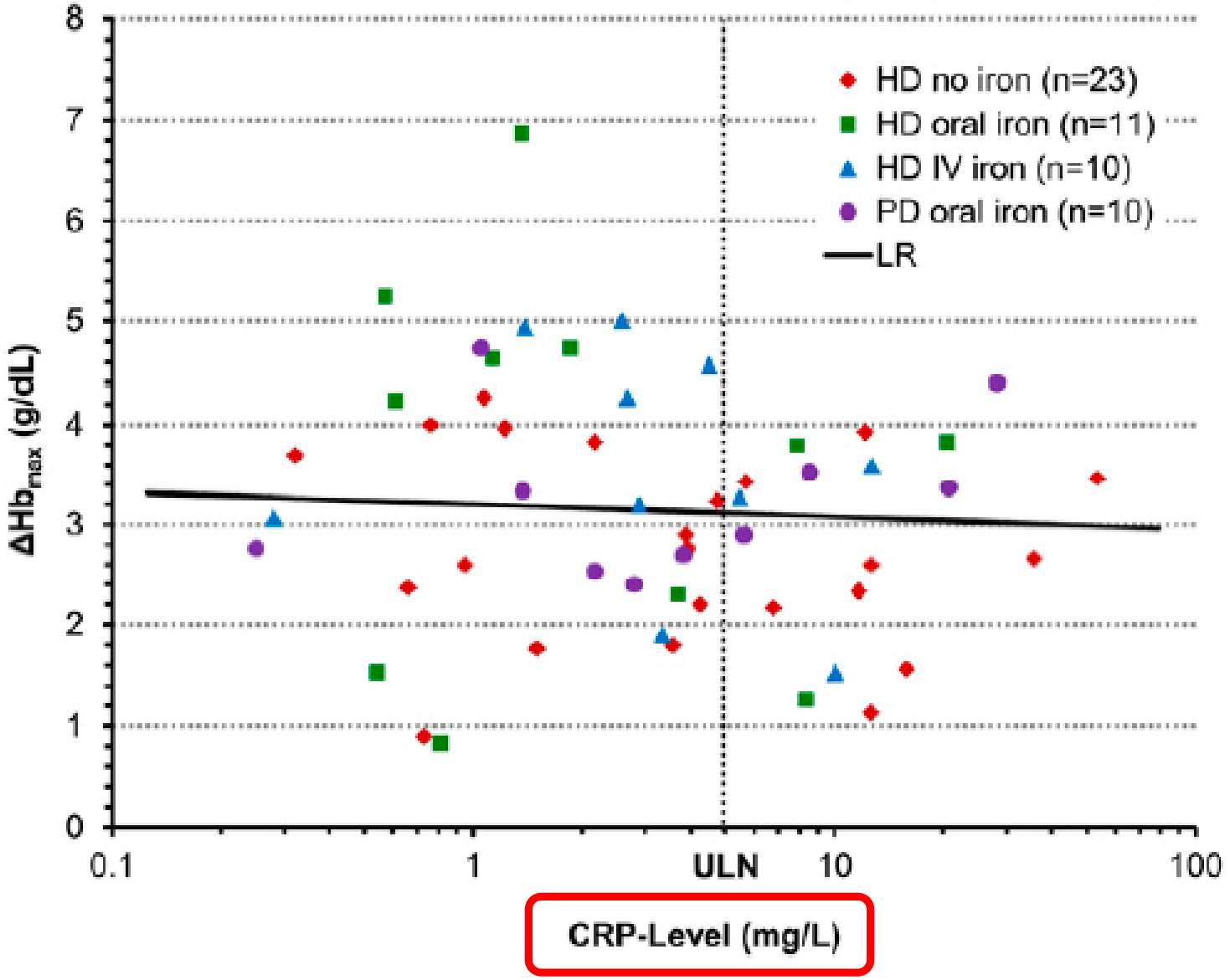
The Erythropoietic Response mediated by HIF



Roxadustat lowers hepcidin levels

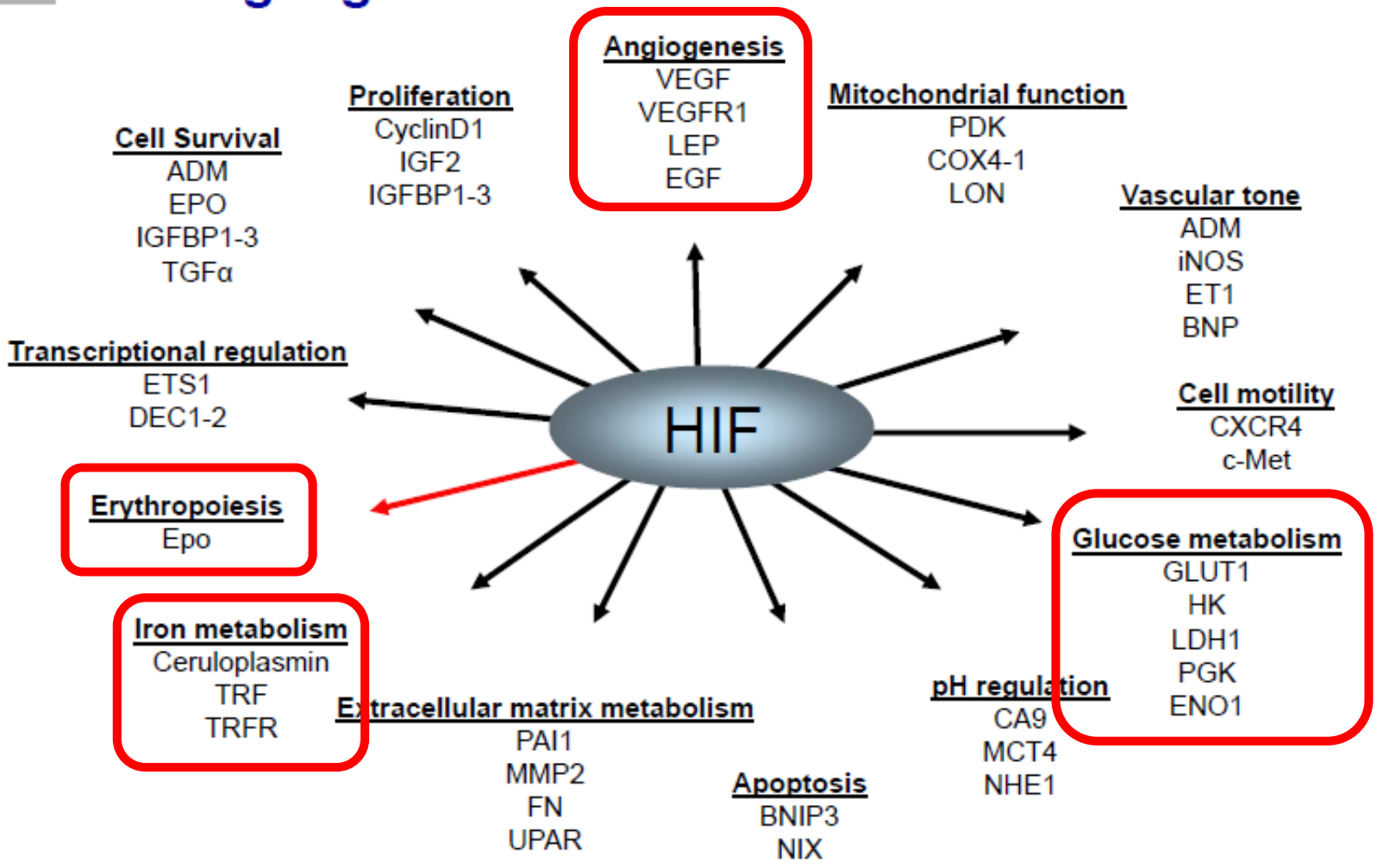


Provenzano *et al*. ASN 2012 Abstract



Besarab et al. J Am Soc Nephrol 2016 Apr;27(4):1225-33.

HIF target genes



Adapted from Schofield & Ratcliffe, *Nat Rev Mol Cell Biol 2004*

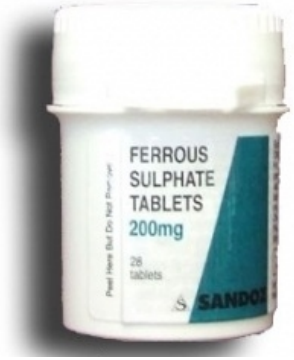
Outline of lecture

- What‘s new in anemia management?
- What‘s new in iron management?
- What‘s new in patients with cardiorenal syndrome?

Iron supplementation

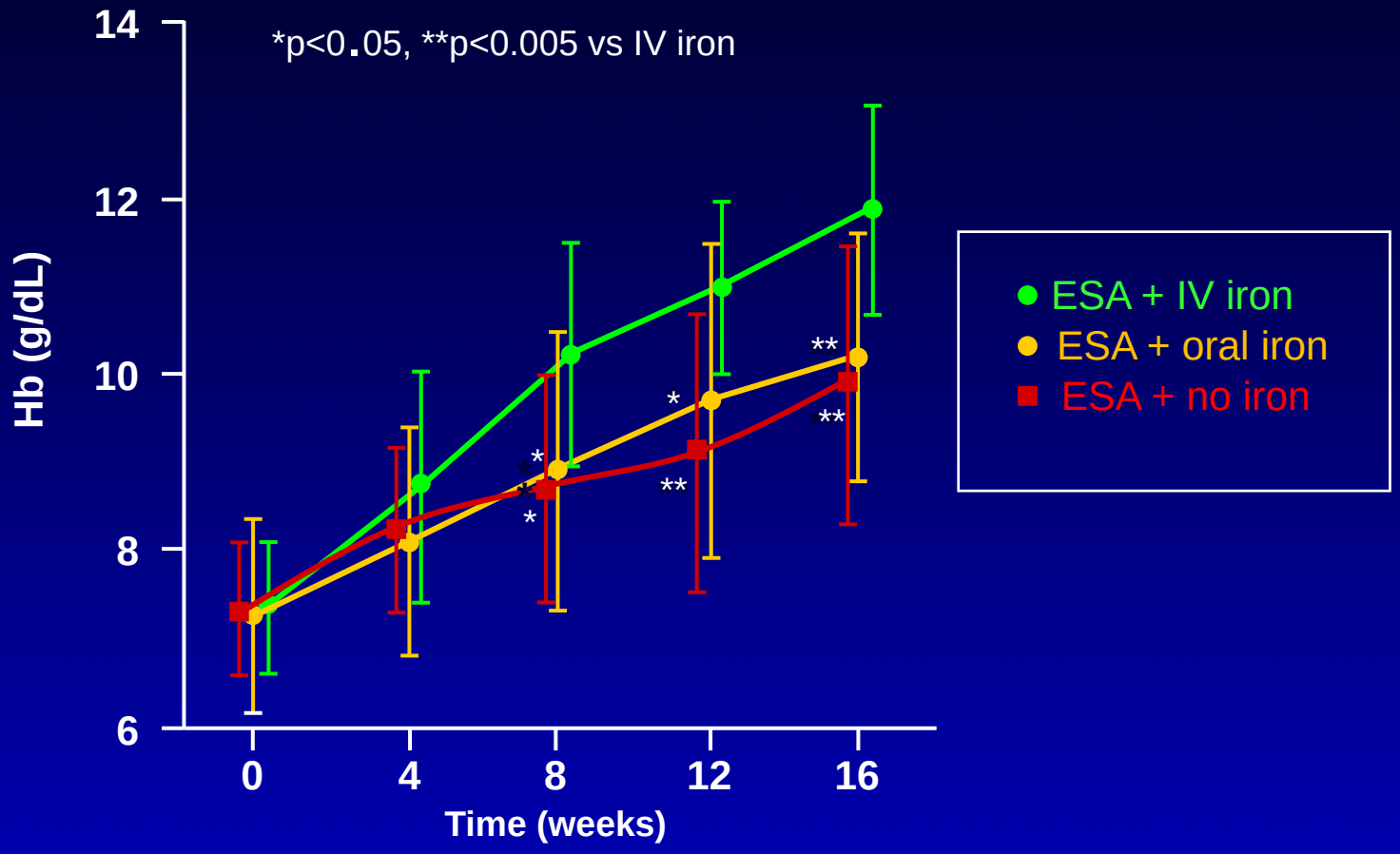
Dietary iron

Oral iron



IV iron

Better Hb response with IV iron compared to oral or no iron



Macdougall et al, *Kidney Int* 1996.

Intravenous Versus Oral Iron Supplementation for the Treatment of Anemia in CKD: Systematic Review and Meta-analysis

Benaya Rozen-Zvi, MD,[1] Anat Gafter-Gvili, MD,[2] Mical Paul, MD,[3] Leonard Leibovici, MD,[4] Ofer Shpilberg, MD,[2] and Uzi Gafter, MD, PhD[1]

Background: Iron supplementation is essential for the treatment of patients with anemia of chronic kidney disease (CKD). It is not clear which is the best method of iron administration.

Study Design: Systematic review and meta-analysis. A search was performed until January 2008 of MEDLINE, Cochrane Central Register of Controlled Trials, conference proceedings in nephrology, and reference lists of included trials.

Setting & Population: Patients with CKD (stages III to V). We included dialysis patients and patients with CKD not on dialysis therapy (hereafter referred to as patients with CKD).

Selection Criteria for Studies: We included all randomized controlled trials regardless of publication status or language.

Intervention: Intravenous (IV) versus oral iron supplementation.

Outcomes Measures: Primary outcomes assessed: absolute hemoglobin (Hb) level or change in Hb level from baseline. We also assessed all-cause mortality, erythropoiesis-stimulating agent requirement, adverse events, ferritin level, and need for renal replacement therapy in patients with CKD.

Results: 13 trials were identified, 6 including patients with CKD and 7 including dialysis patients. Compared with oral iron, there was a significantly greater Hb level in dialysis patients treated with IV iron (weighted mean difference, 0.83 g/dL; 95% confidence interval, 0.09 to 1.57). Meta-regression showed a positive association between Hb level increase and IV iron dose administered and a negative association with baseline Hb level. For patients with CKD, there was a small but significant difference in Hb level favoring the IV iron group (weighted mean difference, 0. 31 g/dL; 95% confidence interval, 0.09 to 0. 53). Data for all-cause mortality were sparse, and there was no difference in adverse events

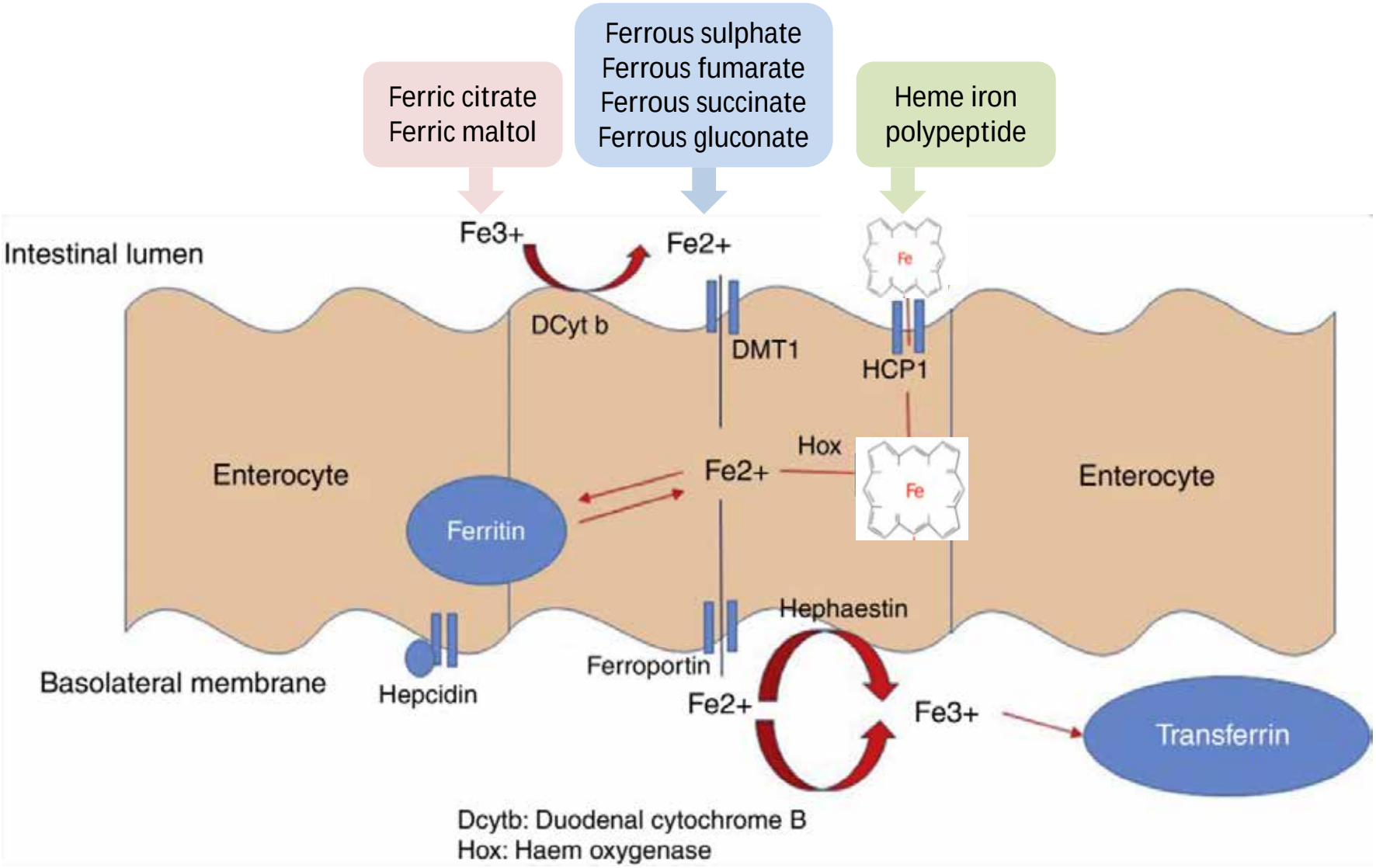
Rozen-Zvi et al. Am J Kidney Dis 2008;52:897–906.

Oral iron – anything new?

Newer oral iron preparations

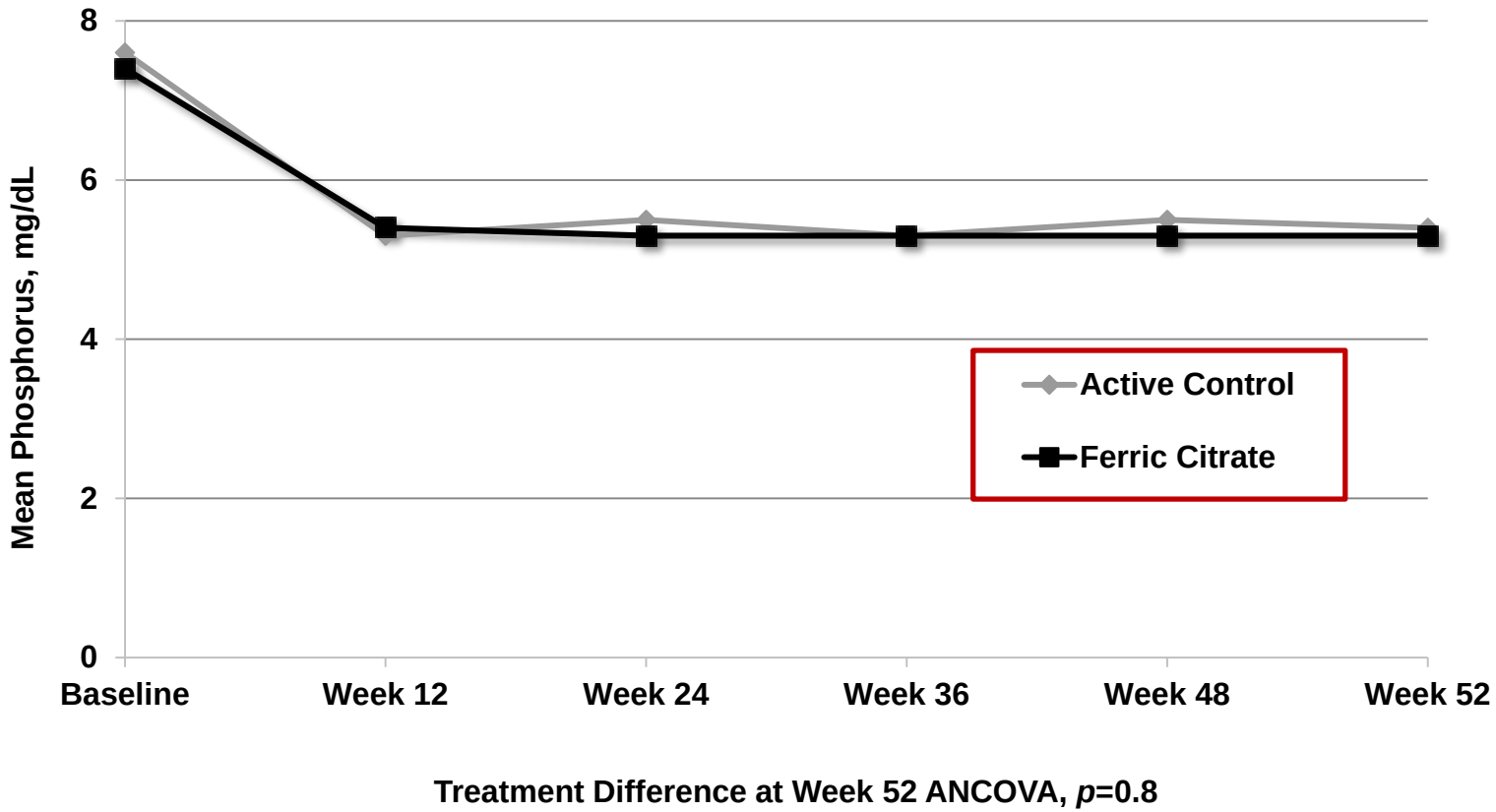
- Ferric citrate
- Ferric maltol
- Liposomal (sucrosomial) iron
- Heme iron polypeptide

Intestinal absorption of iron



Adapted from G. Barragán-Ibañez et al. Rev Med Hosp Gen Mex 2016;79:88-97.

Ferric citrate as a phosphate-binder



Treatment Difference at Week 52 ANCOVA, *p*=0.8

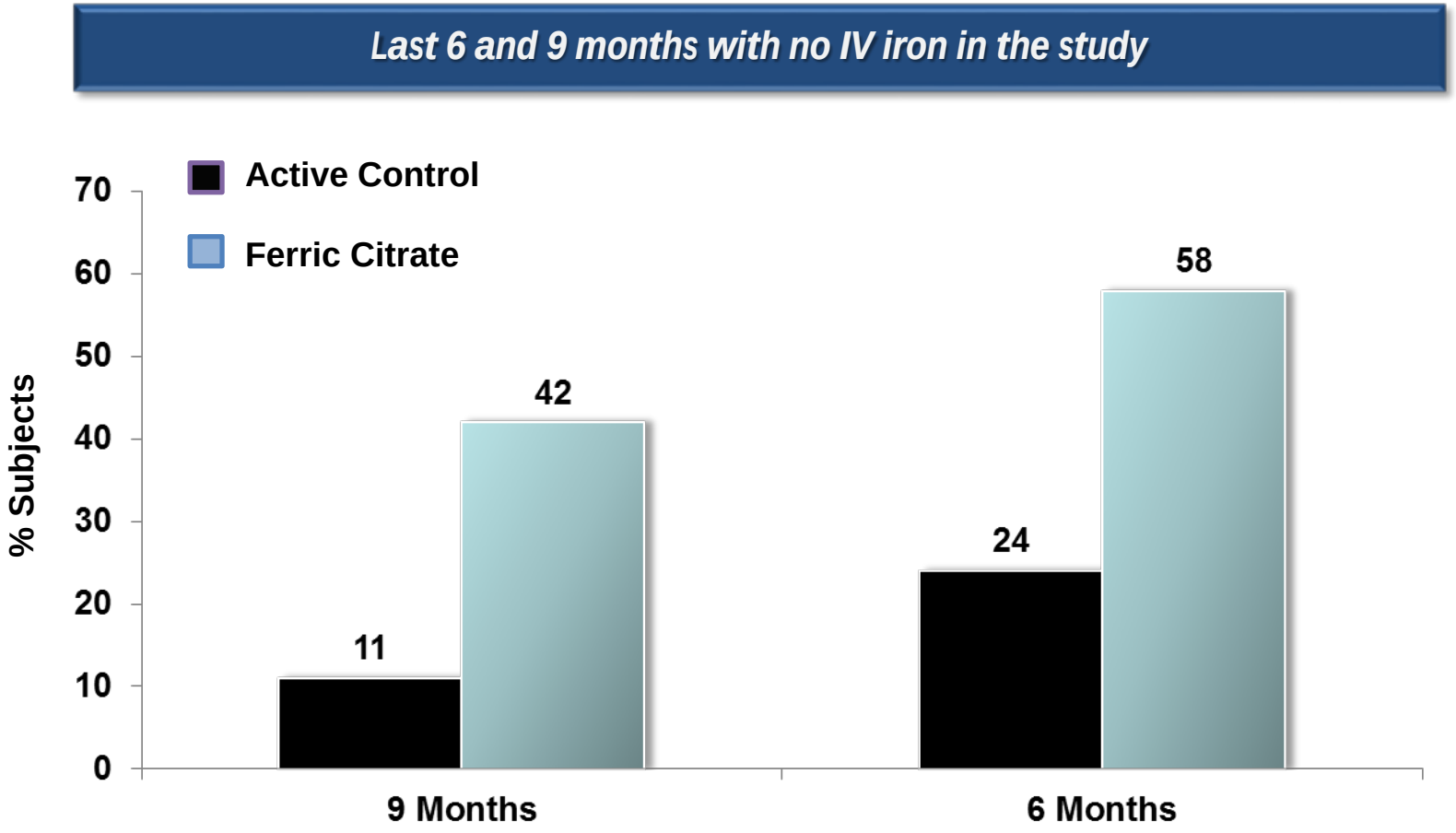
Effect of phosphate-binders on ferritin

Mean Ferritin (ng/mL)	Active Control (n=135)	Ferric Citrate (n=252)
Baseline (Day 0)	609	593
Week 12	649	751
Week 24	652	846
Week 36	631	862
Week 48	619	881
Week 52	624	898
Change from Baseline at Week 52 *% Change from Baseline*	15 *2.5%*	305 *51.4%*
Least Squares Mean Difference at Week 52 P-value		285 <0.0001

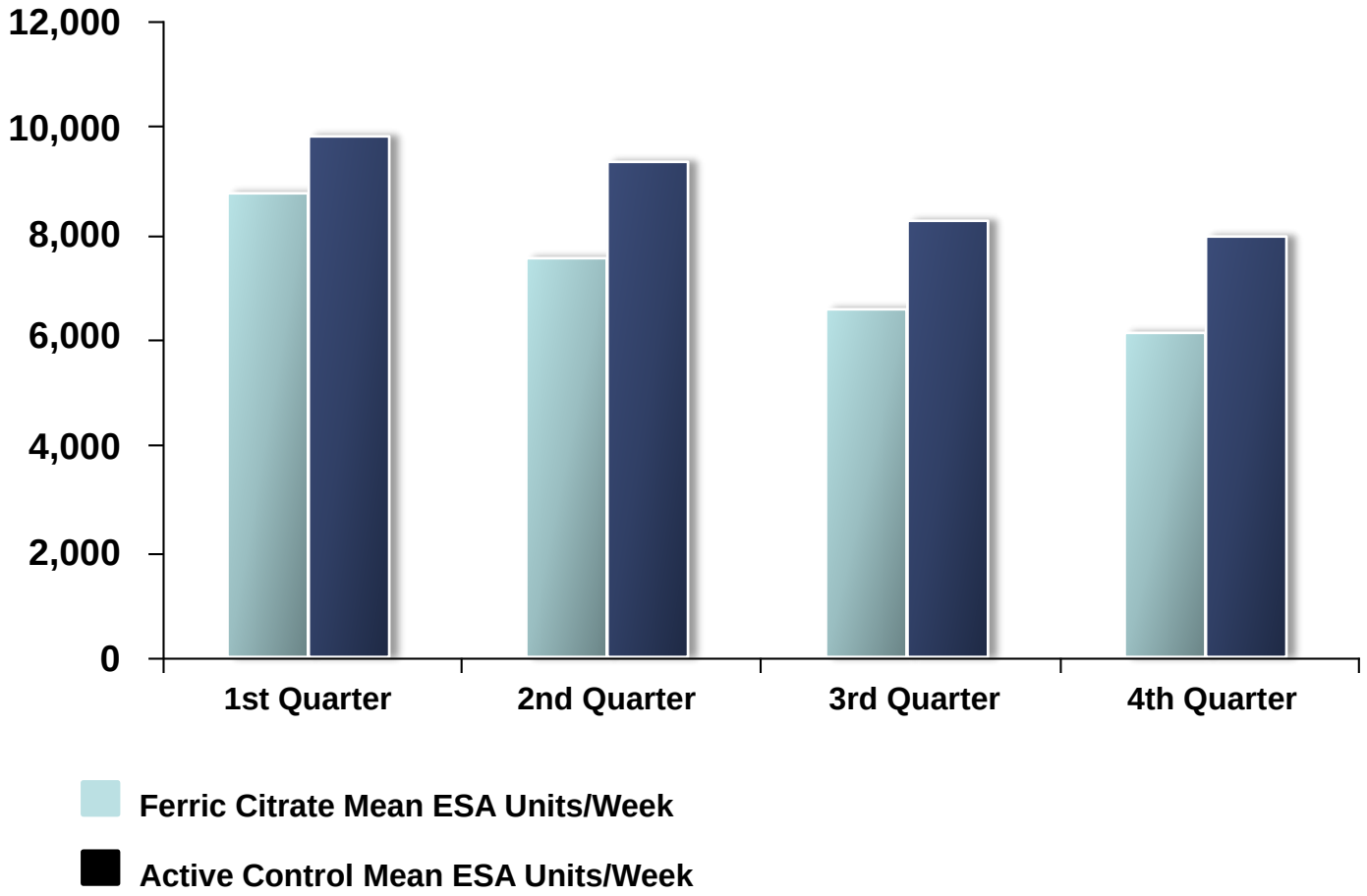
Effect of phosphate-binders on TSAT

Mean TSAT (%)	Active Control (n=135)	Ferric Citrate (n=252)
Baseline (Day 0)	31	31
Week 12	31	40
Week 24	31	40
Week 36	31	40
Week 48	29	41
Week 52	30	39
Change from Baseline at Week 52 *% Change from Baseline*	-1 *-3.2%*	8 *25.8%*
Least Squares Mean Difference at Week 52 P-value		9 <0.0001

Effect of phosphate-binders on IV iron use



Effect of phosphate-binders on ESA dose



OPEN

Ferric Maltol Is Effective in Correcting Iron Deficiency Anemia in Patients with Inflammatory Bowel Disease: Results from a Phase-3 Clinical Trial Program

Christoph Gasche, MD, Tariq Ahmad, MD,† Zsolt Tulassay, MD,‡ Daniel C. Baumgart, MD,§ Bernd Bokemeyer, MD,‖ Carsten Büning, MD,¶ Stefanie Howaldt, MD,** and Andreas Stallmach, MD††on behalf of the AEGIS Study Group*

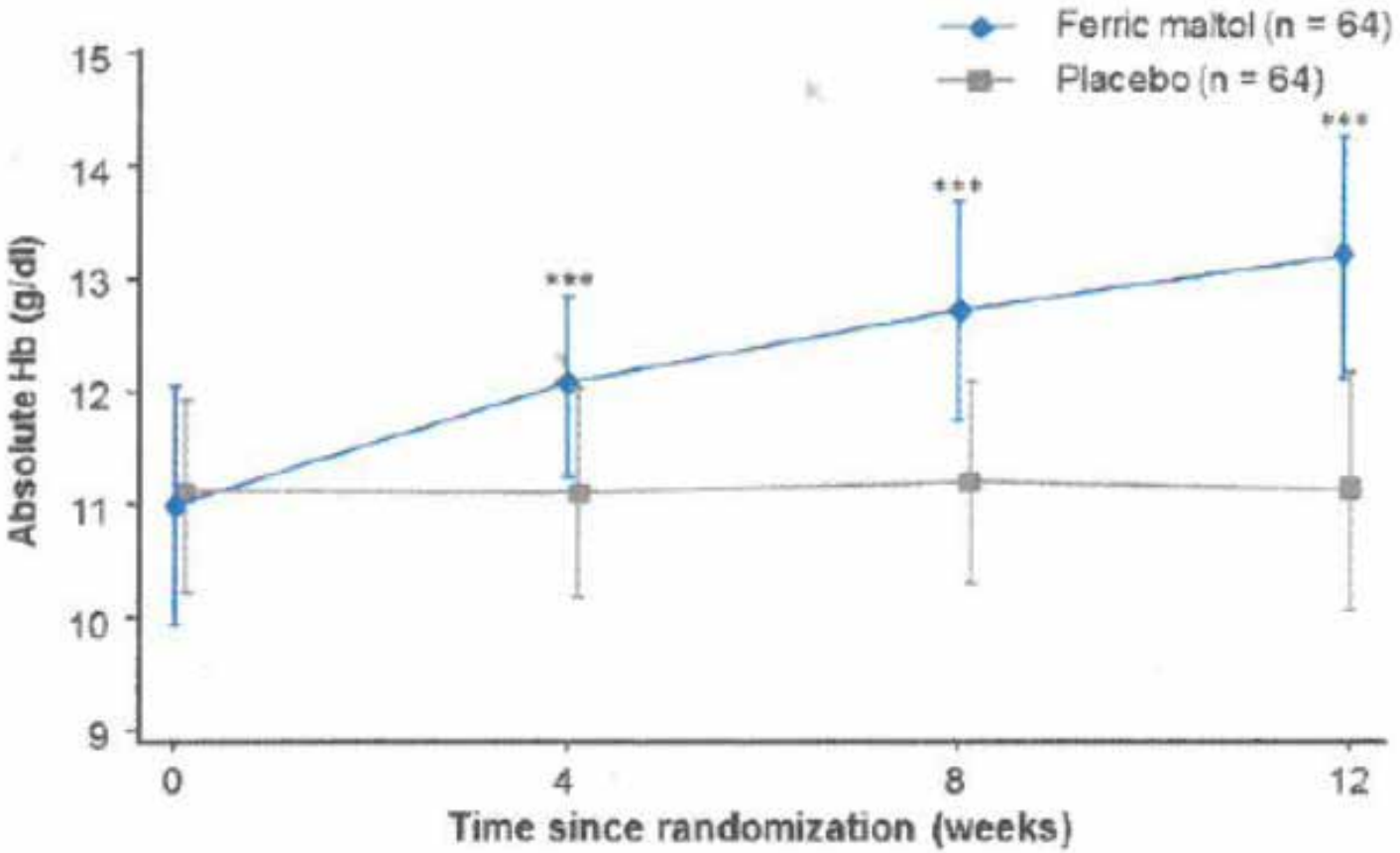
Background: Iron deficiency anemia (IDA) is frequently seen in inflammatory bowel disease. Traditionally, oral iron supplementation is linked to extensive gastrointestinal side effects and possible disease exacerbation. This multicenter phase-3 study tested the efficacy and safety of ferric maltol, a complex of ferric (Fe^{3+}) iron with maltol (3-hydroxy-2-methyl-4-pyrone), as a novel oral iron therapy for IDA.

Methods: Adult patients with quiescent or mild-to-moderate ulcerative colitis or Crohn's disease, mild-to-moderate IDA (9.5–12.0 g/dL and 9.5–13.0 g/dL in females and males, respectively), and documented failure on previous oral ferrous products received oral ferric maltol capsules (30 mg twice a day) or identical placebo for 12 weeks according to a randomized, double-blind, placebo-controlled study design. The primary efficacy endpoint was change in hemoglobin (Hb) from baseline to week 12. Safety and tolerability were assessed.

Results: Of 329 patients screened, 128 received randomized therapy (64 ferric maltol-treated and 64 placebo-treated patients) and comprised the intent-to-treat efficacy analysis: 55 ferric maltol patients (86%) and 53 placebo patients (83%) completed the trial. Significant improvements in Hb were observed with ferric maltol versus placebo at weeks 4, 8, and 12: mean (SE) 1.04 (0.11) g/dL, 1.76 (0.15) g/dL, and 2.25 (0.19) g/dL, respectively ($P < 0.0001$ at all time-points; analysis of covariance). Hb was normalized in two-thirds of patients by week 12. The safety profile of ferric maltol was comparable with placebo, with no impact on inflammatory bowel disease severity.

Conclusions: Ferric maltol provided rapid clinically meaningful improvements in Hb and showed a favorable safety profile, suggesting its possible use as an alternative to intravenous iron in IDA inflammatory bowel disease.

(Inflamm Bowel Dis 2015;21:579–588)



Patients, n				
Ferric maltol	n = 64	n = 59	n = 59	n = 58
Placebo	n = 64	n = 61	n = 56	n = 53

FIGURE 2. Hb concentration from baseline to week 12 (ITT FAS). Data are mean ± SD; ***$P < 0.0001$ (ferric maltol versus placebo based on ANCOVA).

Nephrol Dial Transplant. 2015 Apr;30(4):645-52. doi: 10.1093/ndt/gfu357. Epub 2014 Nov 13.

Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: a randomized trial.

Pisani A[1], Riccio E[1], Sabbatini M[1], Andreucci M[2], Del Rio A[3], Visciano B[1].

Author information

Abstract

INTRODUCTION: Iron deficiency is a common cause of anaemia in non-dialysis chronic kidney disease (ND-CKD). Controversies exist about the optimal route of administration for iron therapy. Liposomal iron, a new generation oral iron with high gastrointestinal absorption and bioavailability and a low incidence of side effects, seems to be a promising new strategy of iron replacement. Therefore, we conducted a study to determine whether liposomal iron, compared with intravenous (IV) iron, improves anaemia in ND-CKD patients.

METHODS: In this randomized, open-label trial, 99 patients with CKD (stage 3-5, not on dialysis) and iron deficiency anaemia [haemoglobin (Hb) ≤12 g/dL, ferritin ≤100 ng/mL, transferrin saturation ≤25%] were assigned (2:1) to receive oral liposomal iron (30 mg/day, Group OS) or a total dose of 1000 mg of IV iron gluconate (125 mg infused weekly) (Group IV) for 3 months. The patients were followed-up for the treatment period and 1 month after drug withdrawal. The primary end point was to evaluate the effects of the two treatments on Hb levels; the iron status, compliance and adverse effects were also evaluated.

RESULTS: The short-term therapy with IV iron produced a more rapid Hb increase compared with liposomal iron, although the final increase in Hb was similar with either treatment; the difference between the groups was statistically significant at the first month and such difference disappeared at the end of treatment. After iron withdrawal, Hb concentrations remained stable in Group IV, while recovered to baseline in the OS group. The replenishment of iron stores was greater in the IV group. The incidence of adverse event was significantly lower in the oral group ($P \leq 0.001$), and the adherence was similar in the two groups.

CONCLUSIONS: Our study shows that oral liposomal iron is a safe and efficacious alternative to IV iron gluconate to correct anaemia in ND-CKD patients, although its effects on repletion of iron stores and on stability of Hb after drug discontinuation are lower.

J Clin Pharm Ther. 2015 Aug;40(4):386-90. doi: 10.1111/jcpt.12281. Epub 2015 May 8.

Heme iron polypeptide for the management of anaemia of chronic kidney disease.

Dull RB[1], Davis E[1].

Author information

Abstract

WHAT IS KNOWN AND OBJECTIVE: Anaemia is a common clinical finding among patients with chronic kidney disease (CKD) and is associated with significant morbidity and healthcare costs. Iron deficiency is an important contributing factor, and adequate iron supplementation is essential to optimize the management of anaemia of CKD. Oral iron is convenient and inexpensive but is poorly absorbed and associated with gastrointestinal distress. Intravenous iron overcomes these limitations but is more expensive, requires additional clinical visits for administration and is associated with serious adverse events. Oral heme iron polypeptide (HIP) is a newer dosage form that has been reported to have higher bioavailability and fewer side effects when compared with non-heme iron in healthy subjects, but data in patients with CKD are limited. The purpose of this review is to evaluate the safety and effectiveness of HIP for the management of CKD.

METHODS: Searches for PubMed (1947-2015) and International Pharmaceutical Abstracts (1970-2015) were conducted using the following terms: heme iron, heme iron polypeptide, oral iron, anaemia and chronic kidney disease. The bibliography of each relevant article was evaluated for additional studies. Articles were selected for review if they were published in the English language and were randomized controlled trials evaluating the bioavailability, tolerability or efficacy of oral HIP in human subjects with CKD.

RESULTS AND DISCUSSION: This search yielded three clinical studies. The safety and efficacy of HIP was evaluated in a total of 161 subjects with anaemia and various stages of CKD. HIP was consistently associated with lower ferritin values when compared with traditional iron supplementation. With few exceptions, the effect of HIP on haemoglobin, haematocrit, transferrin saturation and recombinant human erythropoietin dose, and adverse effects appeared similar to intravenous and oral non-heme iron supplementation. The cost of HIP is substantially more than non-heme iron and comparable to intravenous iron.

WHAT IS NEW AND CONCLUSION: Heme iron polypeptide does not appear to confer benefit over traditional iron supplementation among patients with anaemia of CKD and is more expensive.

What’s new with IV iron?

CJASN ePress. Published on February 20, 2018 as doi: 10.2215/CJN.05390517

Article

Safety of Intravenous Iron in Dialysis

A Systematic Review and Meta-Analysis

Ingrid Hougen,[1] David Collister,[1,2] Mathieu Bourrier,[1] Thomas Ferguson,[1,2] Laura Hochheim,[1] Paul Komenda,[1,2] Claudio Rigatto,[1,2] and Navdeep Tangri[1,2]

Included 7 RCTs comparing higher-dose IV iron with lower-dose intravenous iron, oral iron, or no iron in patients treated with dialysis that had all-cause mortality, infection, cardiovascular events, or hospitalizations as outcomes

Conclusions Higher-dose intravenous iron does not seem to be associated with higher risk of mortality, infection, cardiovascular events, or hospitalizations in adult patients on dialysis. Strength of this finding is limited by small numbers of participants and events in the randomized, controlled trials and statistical heterogeneity in observational studies.

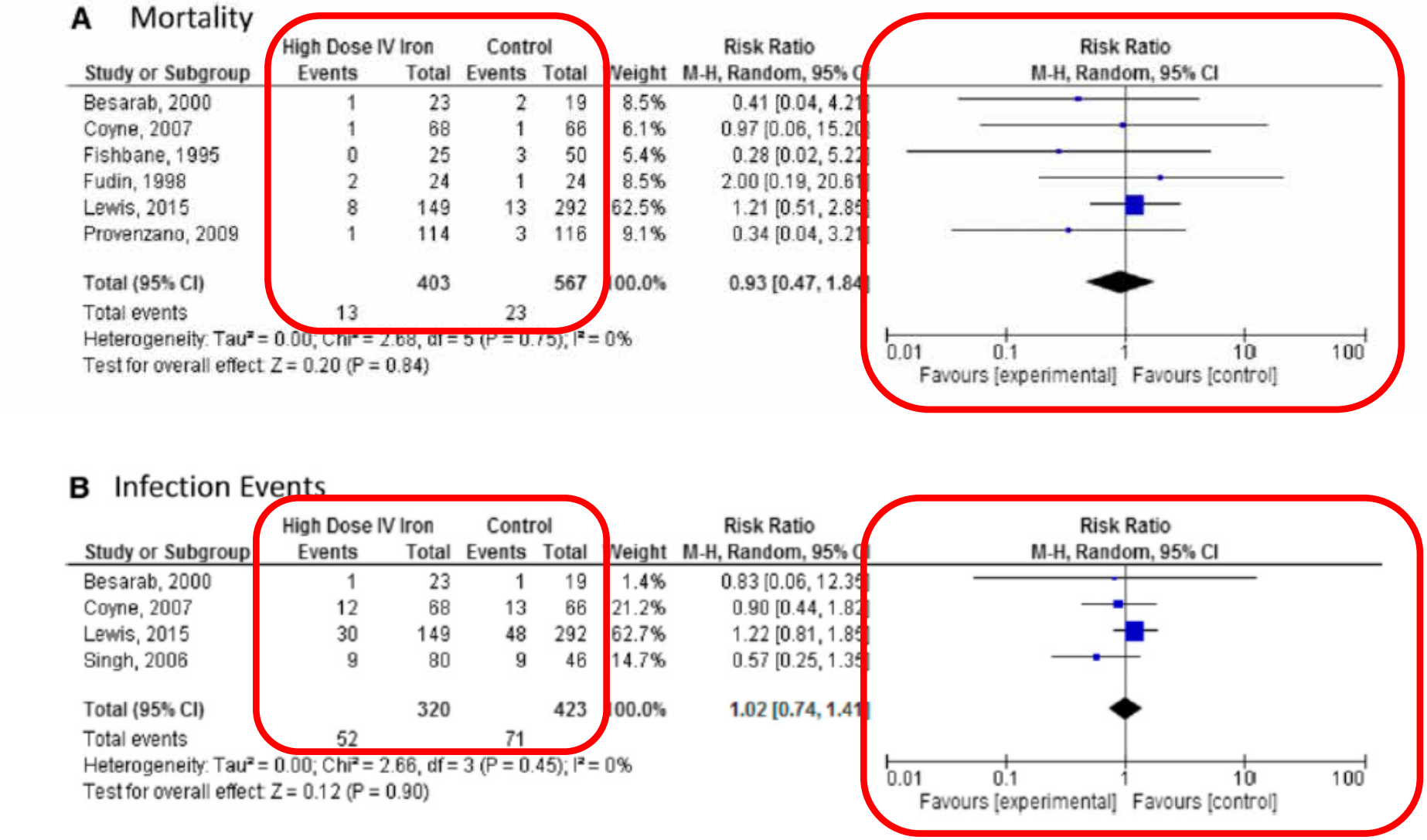


Figure 1. | No statistically significant difference in either mortality or infection events in meta-analyses of randomized controlled trials. Meta-analysis comparing the safety of high-dose intravenous (IV) iron versus control in randomized, controlled trials. (A) Mortality. (B) Infection events. 95% CI, 95% confidence interval; M-H, Mantel-Haenszel.


Optimization of Epoetin Therapy with Intravenous Iron Therapy in Hemodialysis Patients

ANATOLE BESARAB,* NEETA AMIN,† MUHAMMAD AHSAN,* SUSAN E. VOGEL,* GARY ZAZUWA,* STANLEY FINAK,* JAMES I. ZAZRA,‡ I. V. ANANDAN,† and AJAY GUPTA*

Besarab et al, 2002

Single-center (US), open-label, randomized, prospective 6-month study in HD patients

N = 42

R

IV iron dextran (25-150 mg/wk to maintain TSAT 20-30%)

(n=19 -- 15 completed)

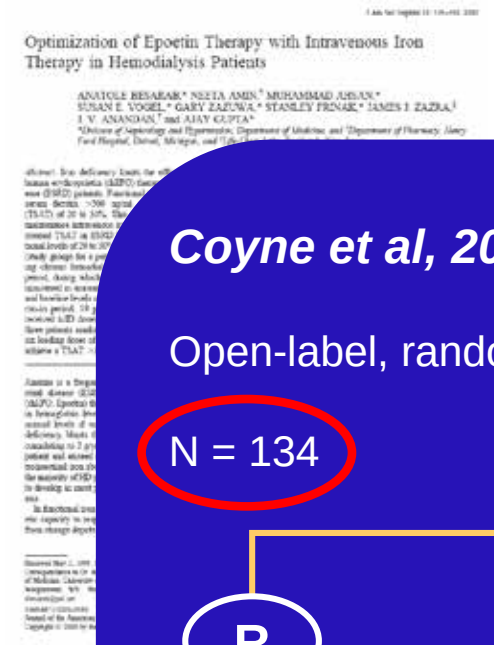
IV iron dextran 4-6 x 100 mg doses to increase TSAT >30%
and thereafter to maintain TSAT at 30-50%

(n=23 -- 17 completed)

Primary outcome: EPO dose (40% lower)

No differences in hospitalizations or infection rate were noted

Each group had 1 admission for an infectious etiology
(pneumonia in the control group, line-related sepsis in the study group)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Coyne et al, 2007 ("DRIVE")

Open-label, randomized, controlled, multicenter trial (37 US centers)

N = 134

R

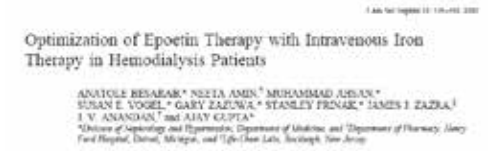
1 g of ferric gluconate (Ferrlecit) administered in 8 consecutive 125-mg doses

No iron

6-weeks follow-up

Better Hb response ($p<0.03$)

13 infection episodes in 10 patients occurred in the control arm, and 12 infection episodes occurred in 8 patients in the IV iron arm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Lewis et al, 2015

Phase 3, sequential, randomized, open-label trial (60 sites in the US and Israel)

N = 441

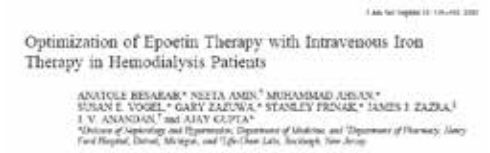
R

- Ferric citrate 1 g (210 mg ferric iron)
- Calcium acetate (667 mg) or sevelamer (800 mg)

52-weeks follow-up

Primary outcome – phosphate level

12.5% of patients in the ferric citrate and 18.5% of patients in the control groups reported infection SAEs


Optimization of Epoetin Therapy with Intravenous Iron Therapy in Hemodialysis Patients

ANATOLE BESARAB,* NEETA AMIN,† MUHAMMAD AHSAN,* SUSAN E. VOGEL,* GARY ZAZUWA,* STANLEY FINAK,* JAMES I. ZAZRA,‡ I. V. ANANDAN,† and AJAY GUPTA*

Singh et al, 2006

Open-label, phase 3, randomized, multicenter trial (21 sites in the US and Mexico)

N = 188

PD patients

R

1000 mg of iron sucrose IV as a 300-mg infusion on days 1 and 15 and a 400-mg infusion on day 28

No iron

8-weeks follow-up

11 episodes of peritonitis: 6 (8.0%) in iron group and 5 (10.9%) in control group
2 in each group were considered serious (no episode related to study drug)
7 episodes of exit-site infection: 3 (4.0%) in iron group and 4 (8.7%) in control group

CJASN ePress. Published on February 20, 2018 as doi: 10.2215/CJN.00930118

Editorial

Rest Easy with Intravenous Iron for Dialysis Patients?
High Dose IV Iron Safety

Xiaojuan Li[1] *and Abhijit V. Kshirsagar*[2]

Clin J Am Soc Nephrol 13: ●●●–●●●, 2018. doi: https://doi.org/10.2215/CJN.00930118

Most in the nephrology community would agree on the necessity of intravenous iron to treat anemia for patients receiving dialysis. The cumulative average yearly blood loss is high among individuals receiving hemodialysis and leads to an estimated loss of over 2 g of iron per annum (1). Functional iron deficiency results from enhanced iron utilization from erythropoiesis stimulating agents (ESAs). Administration of oral iron cannot reliably replete stores to match ongoing demands because of impaired intestinal absorption meanalyzing seven randomized, controlled trials and 15 observational studies, the authors find that high-dose intravenous iron (defined as >400 mg/mo for the clinical trials and >200 mg/mo in the observational studies) does not show an adverse safety signal compared with low-dose intravenous iron with respect to all-cause mortality, infection, cardiovascular disease, or hospitalizations. The study duly notes the common limitations of meta-analysis and takes the appropriate steps to assess statistical heterogeneity, quality of

[1]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts; and [2]University of North Carolina Kidney Center and Division of Nephrology and Hypertension.

PIVOTAL

Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

§ UK multicentre prospective open-label 2-arm RCT of IV iron therapy in incident HD patients

- § Lead investigator: Iain Macdougall
- § Clinical Trial Manager: Claire White
- § No of sites: 50
- § No. of patients: 2080
- § Commenced: November 2013
- § Trial oversight: Glasgow Clinical Trials Unit
- § Funder : Kidney Research UK

This investigator-led clinical trial is supported through an unrestricted grant from
Vifor Fresenius Medical Care Renal Pharma

University of Glasgow

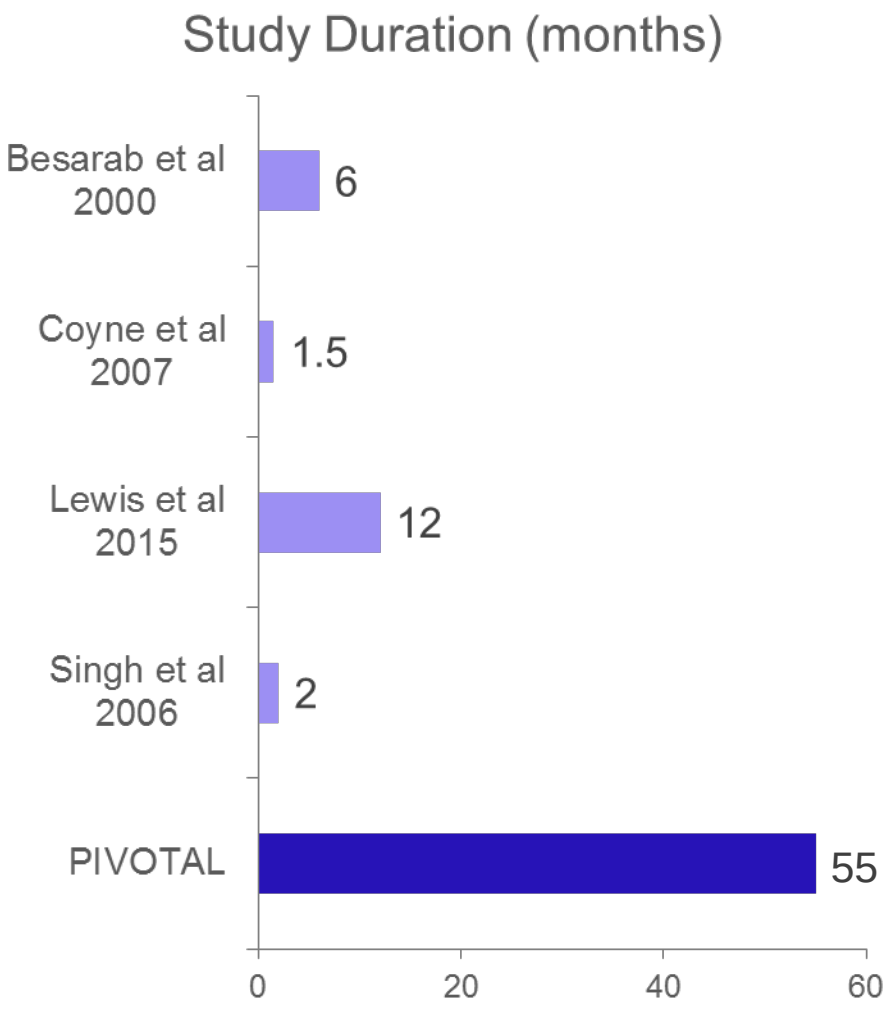
NHS Greater Glasgow and Clyde

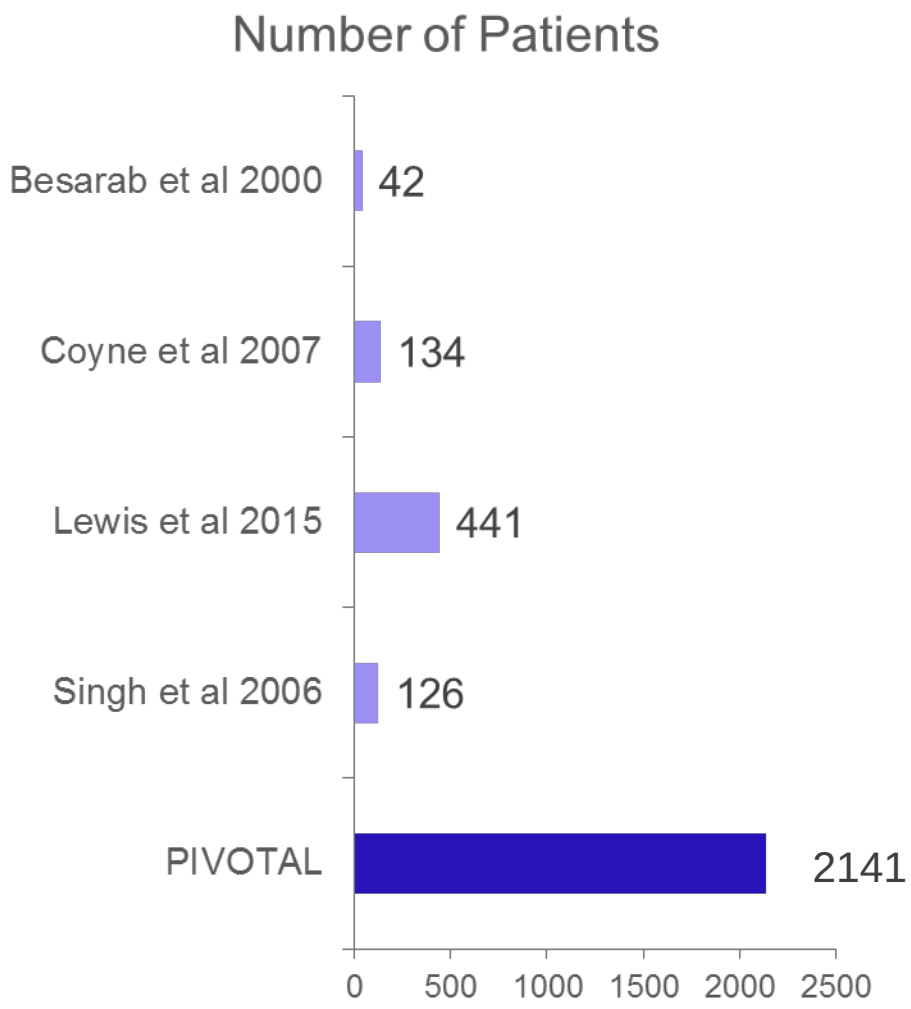
THE RENAL ASSOCIATION founded 1950
UK Kidney Research Consortium : Renal Anaemia CSG

Kidney Research UK
Funding research to save lives

www.kidneyresearchuk.org

PIVOTAL will be the largest, and longest duration RCT examining the safety of IV iron in HD patients





PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

Study design

Proactive IV iron arm – IV iron 400mg/month

(withhold if ferritin>700 ug/l; TSAT>40%)

Incident new HD patients (0-12 mths)

On ESA

R

Reactive – minimalistic IV iron arm
(give IV iron if ferritin<200 ug/l; TSAT<20%)

Primary endpoint

Time to all-cause mortality or composite of MI, stroke, HF hosp

Up to 4 weeks screening

Total study period approximately 4 years *(event-driven)* – 2 years recruitment; 2-4 years follow-up per patient

Sample size: 2080 patients

Kidney Research UK
Funding research to save lives

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

Primary endpoint

- Time to all-cause death or a composite of non-fatal cardiovascular events (MI, stroke, and HF hospitalisation)
  -- adjudicated by a blinded Endpoint Adjudication Committee

Secondary endpoints

- Incidence of all-cause death and a composite of myocardial infarction, stroke, and hospitalisation for heart failure as recurrent events.
- Time to (and incidence of) all-cause death
- Time to (and incidence of) composite cardiovascular event
- Time to (and incidence of) myocardial infarction
- Time to (and incidence of) stroke
- Time to (and incidence of) hospitalisation for heart failure
- ESA dose requirements
- Transfusion requirements
- EQ-5D QOL and KDQOL
- Vascular access thrombosis
- All-cause hospitalisation
- Infections; hospitalisation for infection

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

NETWORK OF SITES

King's College Hospital NHS
NHS Foundation Trust

England
Queen Elizabeth Hospital, Birmingham; Heartlands Hospital, Birmingham; Royal Free, London, King's College Hospital, London; Guy's & St Thomas', London; St Helier, Surrey; St George's, London; Royal Liverpool Hospital, University Hospital Aintree; Sheffield Teaching Hospital; Lister Hospital, Stevenage; Salford Royal Hospital, Manchester; Manchester Royal Hospital; Queen Alexandra Hospital, Portsmouth; Kent & Canterbury Hospital, Leicester General Hospital, Hull Royal Infirmary; Freeman Hospital, Newcastle; Churchill Hospital, Oxford; University Hospital of North Staffordshire, Stoke-on-Trent; Southmead Hospital, Bristol; Royal Cornwall Hospital; Nottingham City Hospital; Norfolk & Norwich Hospital; New Cross Hospital, Wolverhampton; Royal London Hospital; Wirral University Teaching Hospital; Royal Shrewsbury Hospital, Royal Devon & Exeter Hospital, Royal Preston Hospital, St James' Hospital, Leeds; Hammersmith Hospital, London; Royal Sussex Hospital, Brighton; Bradford Teaching Hospital; Coventry University Hospital; Southend University Hospital; Gloucestershire Royal Hospital; Derriford Hospital, Plymouth; Royal Berkshire, Reading

Wales
Morriston Hospital, Swansea; University Hospital, Cardiff

Scotland
Western Infirmary, Glasgow; Victoria Hospital, Kirkcaldy; Ninewells Hospital, Dundee; Royal Edinburgh Hospital

N. Ireland
Belfast City Hospital, **Antrim** Area Hospital;
Daisy Hill Hospital,**Newry;** Altnagelvin Hospital, **Derry**

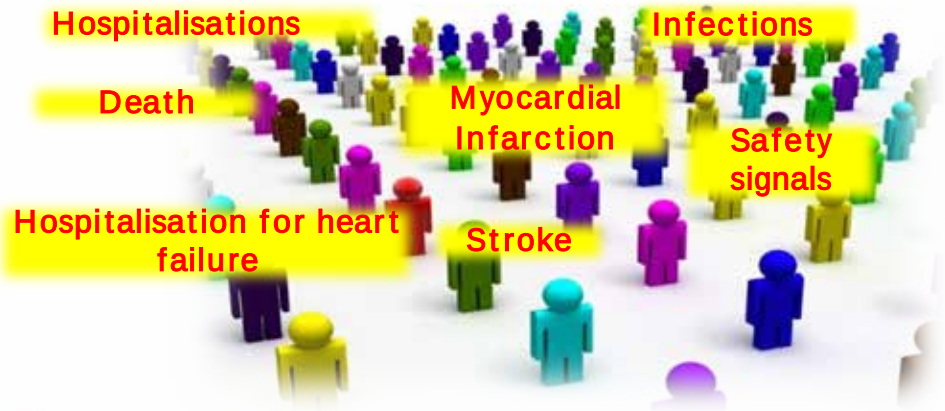
Kidney Research UK
Funding research to save lives

PIVOTAL
Proactive IV irOn Therapy in haemodiALysis patients

King's College Hospital NHS
NHS Foundation Trust

Where we are now

- 2141 patients randomized – (first patient recruited November 2013)
- Follow-up: 0 – 54.4 months (median 26.9 months)
- 478 deaths
- 6035 SAEs
- 631 primary endpoints to accrue (estimated to reach this June 2018)



Kidney Research UK
Funding research to save lives

Outline of lecture

- What‘s new in anemia management?
- What‘s new in iron management?
- What‘s new in patients with cardiorenal syndrome?

ESC Guidelines on Heart Failure 2016

Recommendation	Class	Level
Iron deficiency		
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to **alleviate HF symptoms**, and **improve exercise capacity and quality of life**	IIa	A

Recommendation based on:

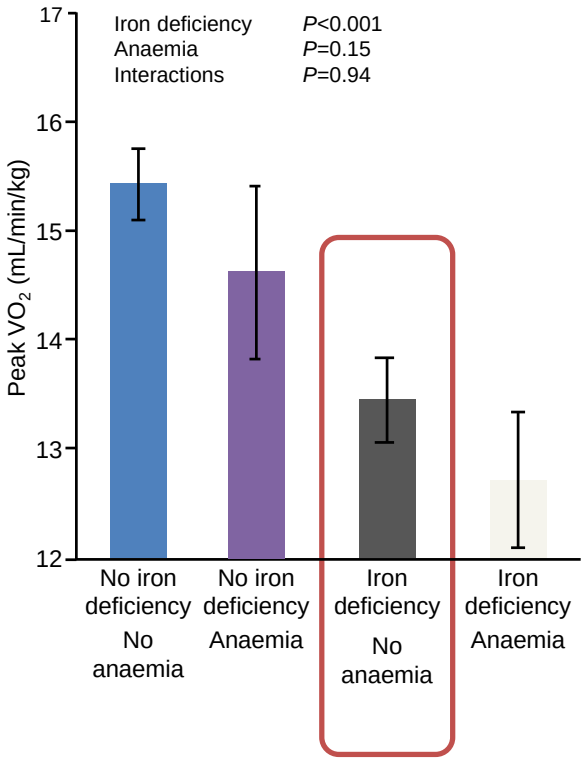
FAIR-HF & CONFIRM-HF

Ponikowski P, et *al.* Eur J Heart Fail 2016 & EHJ 2016

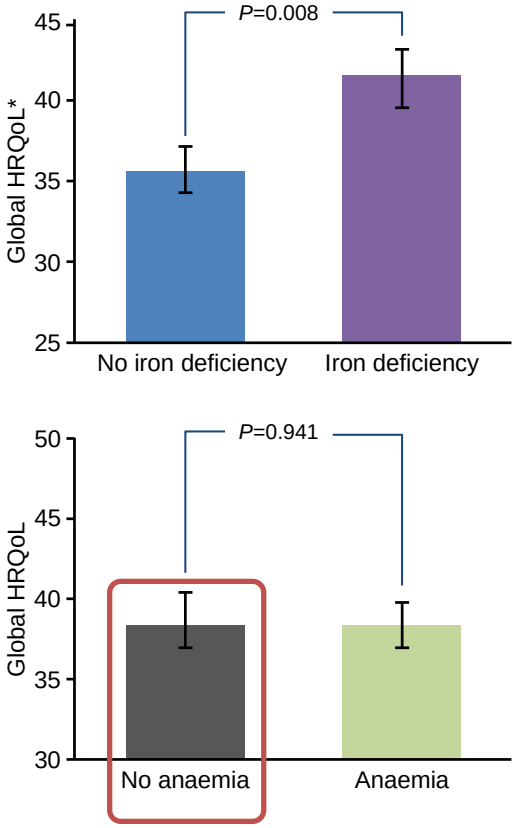
The shift in the cardiology field

Iron deficiency **but not anaemia** is associated with:

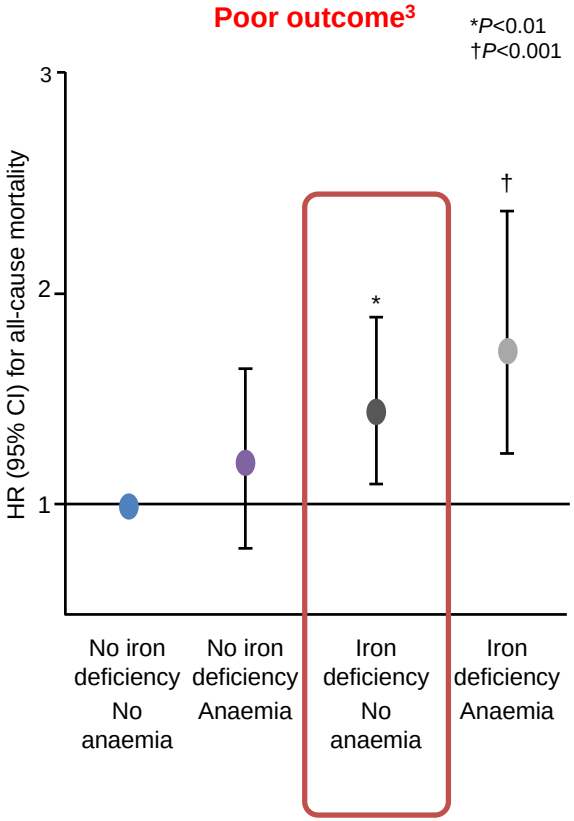
Reduced exercise capacity[1]



Reduced QoL[2]



Poor outcome[3]



*Minnesota Living with Heart Failure Questionnaire (MLHFQ): higher scores reflect worse HRQoL

1. Jankowska EA *et al. J Card Fail* 2011;17:899–906;
2. Comin-Colet J *et al. Eur J Heart Fail* 2013;15:1164–72;
3. Klip IT *et al. Am Heart J* 2013;165:575–82

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D.,
Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D.,
Kenneth Dickstein, M
Thomas F. Lüscher, M.D., Boris
Joanna Niegowska, M.D., Bric
Barbara von Eisenhart
Philip A. Poole-Wilson, M
for the FAI

European Heart Journal (2015) **36**, 657–668
doi:10.1093/eurheartj/ehu385

FASTTRACK ESC HOT LINE
Heart failure/cardiomyopathy

Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†

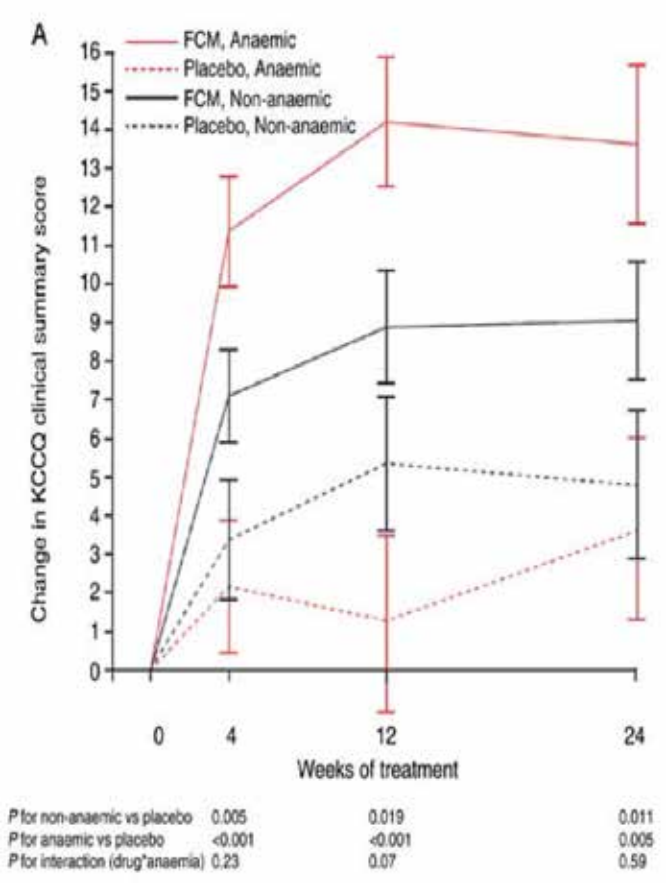
Piotr Ponikowski[1,2]*, Dirk J. van Veldhuisen[3], Josep Comin-Colet[4], Georg Ertl[5,6], Michel Komajda[7], Viacheslav Mareev[8], Theresa McDonagh[9], Alexander Parkhomenko[10], Luigi Tavazzi[11], Victoria Levesque[12], Claudio Mori[12], Bernard Roubert[12], Gerasimos Filippatos[13], Frank Ruschitzka[14], and Stefan D. Anker[15], for the CONFIRM-HF Investigators

[1]Department of Heart Diseases, Medical University, Wroclaw, Poland; [2]Department of Cardiology, Center for Heart Diseases, Clinical Military Hospital, Weigla 5 53-114, Wroclaw, Poland; [3]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [4]Heart Diseases Biomedical Research Group, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain; [5]Department of Internal Medicine I, University Hospital Würzburg, Würzburg, Germany; [6]Comprehensive Heart Failure Center, University of Würzburg, Würzburg, Germany; [7]CHU Pitié-Salpêtrière, Institut de Cardiologie, Paris, France; [8]Lomonosov Moscow State University, Moscow, Russia; [9]Department of Cardiology, King's College Hospital, Denmark Hill, London SE5 9RS, UK; [10]Ukranian Strazhesko Institute of Cardiology, 5, Narodnoko Opolchenia St, Kiev 03151, Ukraine; [11]Maria Cecilia Hospital, GVM Care&Research—E.S. Health Science Foundation, Cotignola, Italy; [12]Vifor Pharma, Glattbrugg, Switzerland; [13]Athens University Hospital Attikon, Athens, Greece; [14]Department of Cardiology, University Hospital Zurich, Switzerland; and [15]Department of Innovative Clinical Trials, University Medical Centre Göttingen, Göttingen, Germany

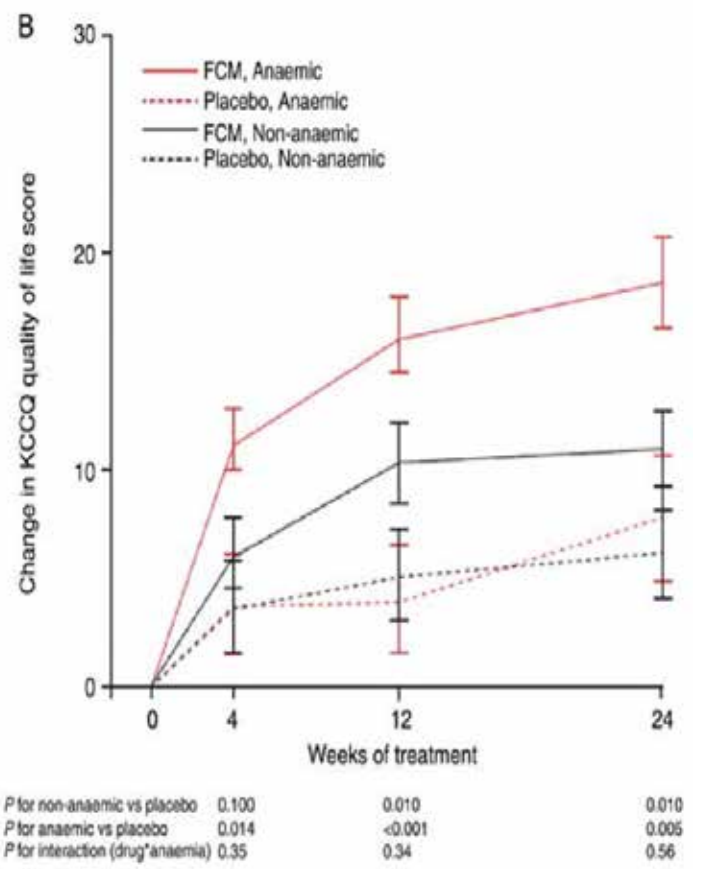
Received 5 August 2014; revised 16 August 2014; accepted 21 August 2014; online publish-ahead-of-print 31 August 2014

FAIR-HF: Ferric carboxymaltose significantly improved QoL in iron-deficient patients

KCCQ clinical summary score (total symptom score and physical limitations)



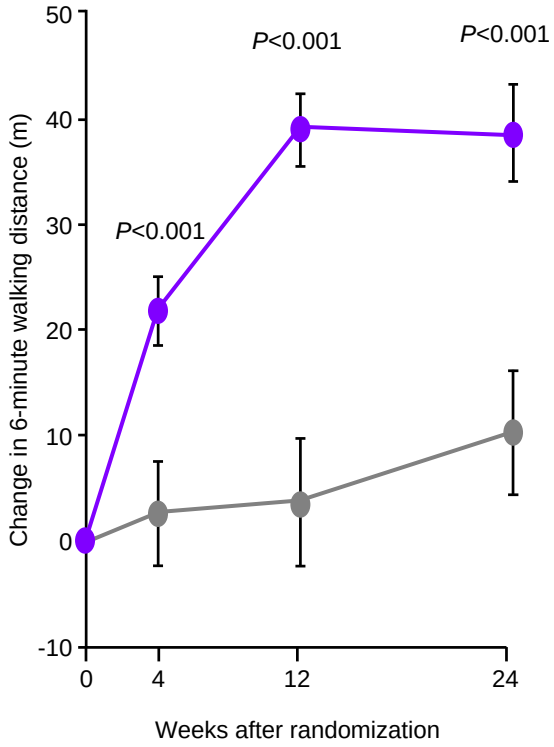
KCCQ QoL score



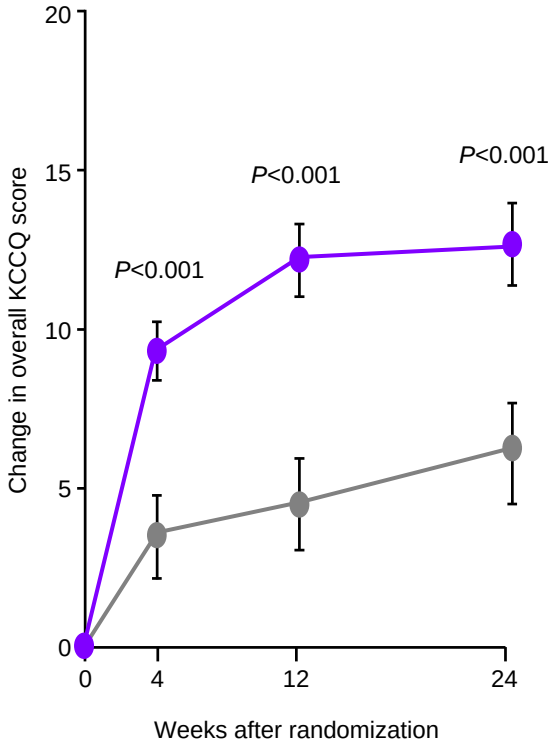
Comin-Colet J *et al. Eur Heart J* 2013;34:30–8

FAIR-HF: Ferric carboxymaltose significantly improved QoL in iron-deficient patients

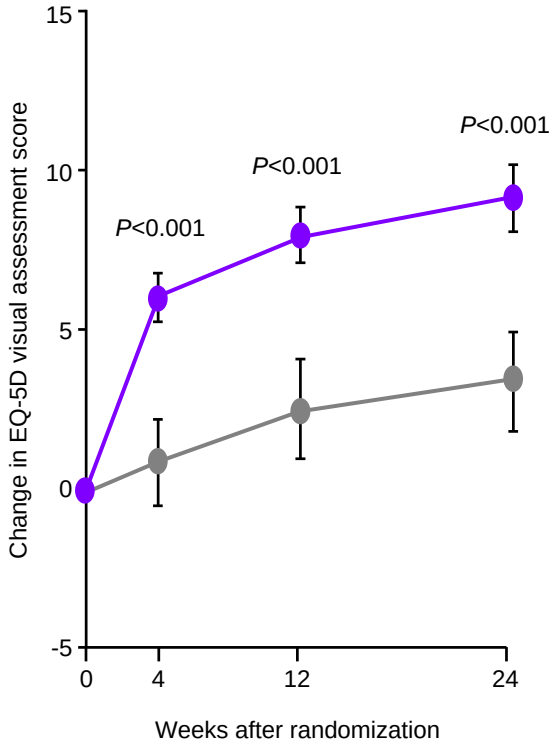
6-minute walk test



KCCQ overall score



EQ-5D VAS score



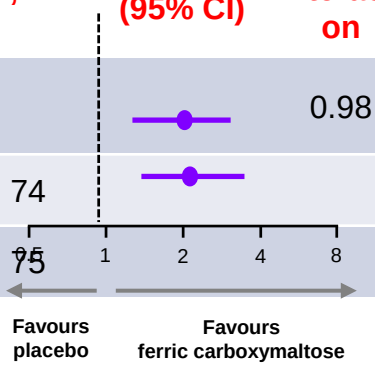
Ferric carboxymaltose

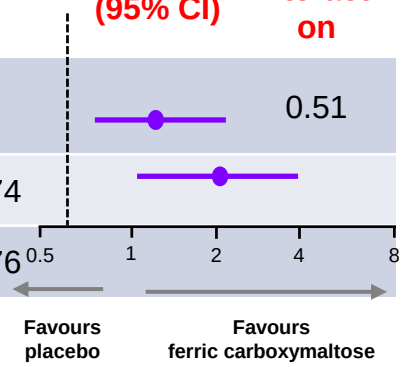
Placebo

Comin-Colet J *et al. Eur Heart J* 2013;34:30–8

… and these improvements were evident in CHF patients with and without anaemia

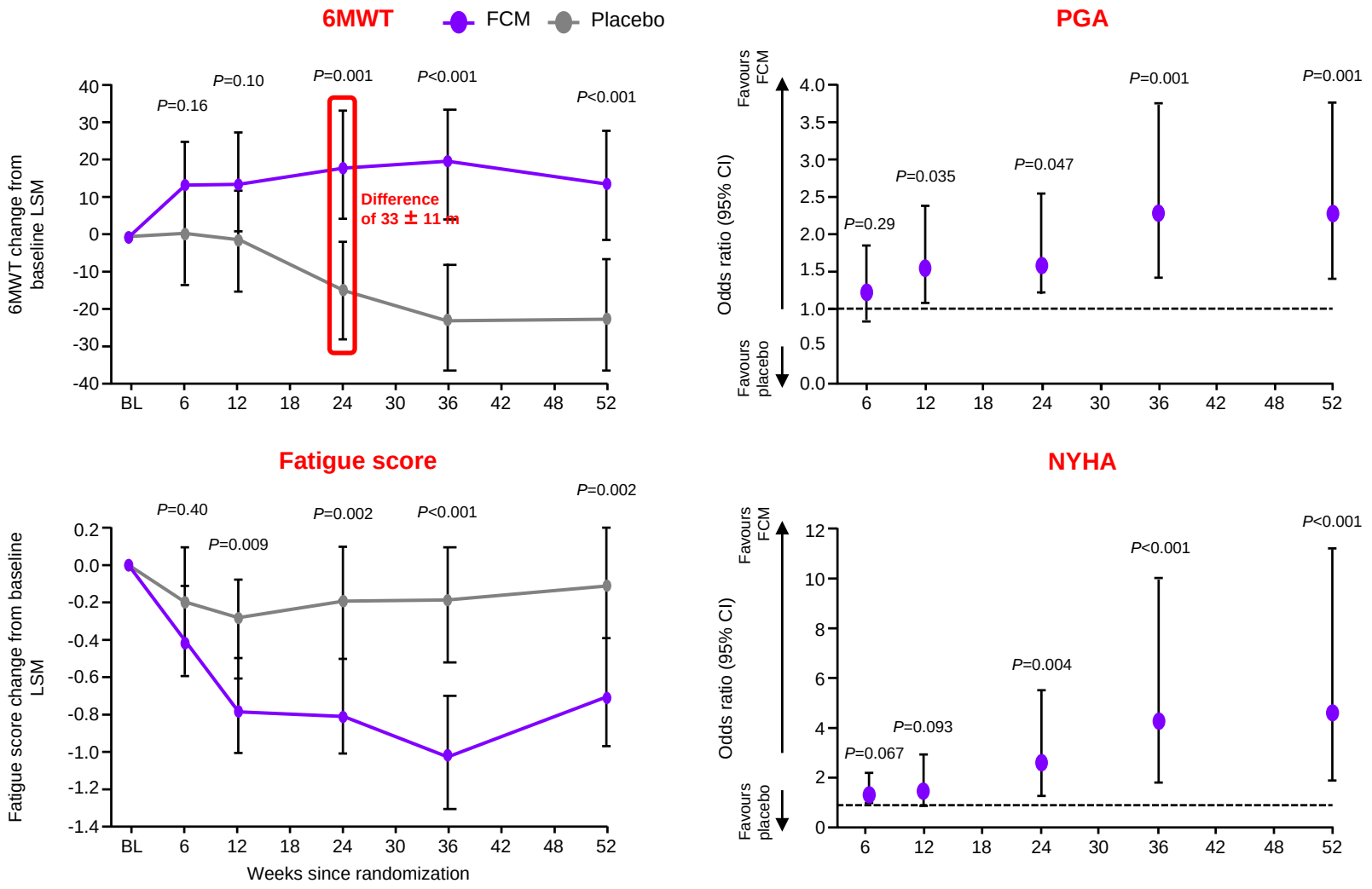
	Self-reported patient global assessment				NYHA functional class			
Subgroup	Ferric carboxymaltose, n	Placebo, n	Odds ratio (95% CI)	*P* value for interaction	Ferric carboxymaltose, n	Placebo, n	Odds ratio (95% CI)	*P* value for interaction
Haemoglobin				0.98				0.51
≤12.0 g/dL	146	74			148	74		
>12.0 g/dL	146	75			146	76		





Anker S *et al*. *N Engl J Med* 2009;361:2436–48

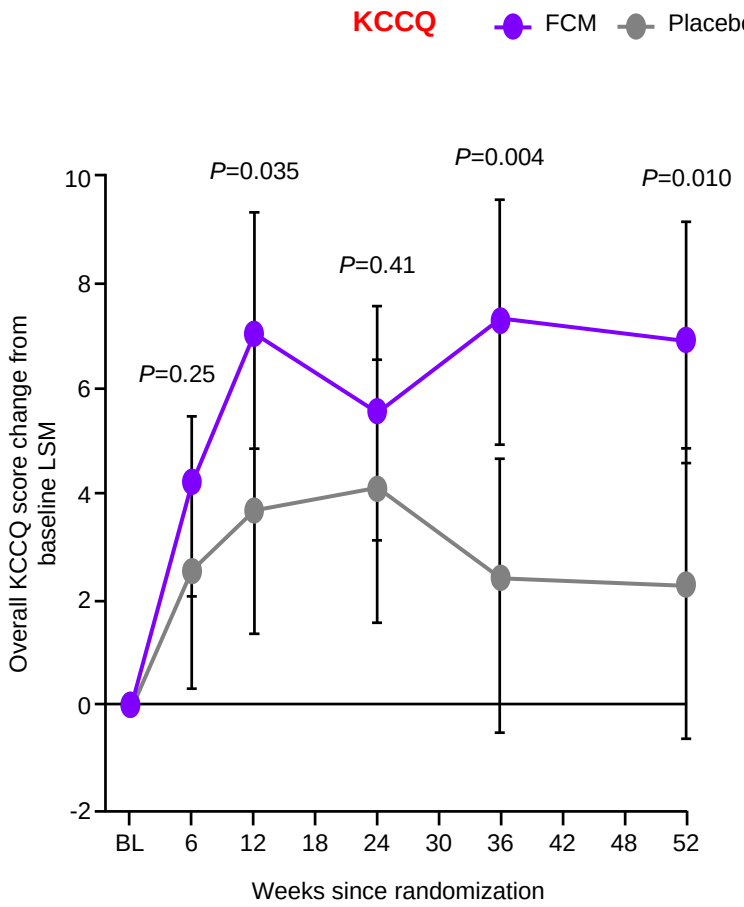
CONFIRM-HF: Ferric carboxymaltose treatment leads to sustained improvements in 6MWT, fatigue, PGA and NYHA



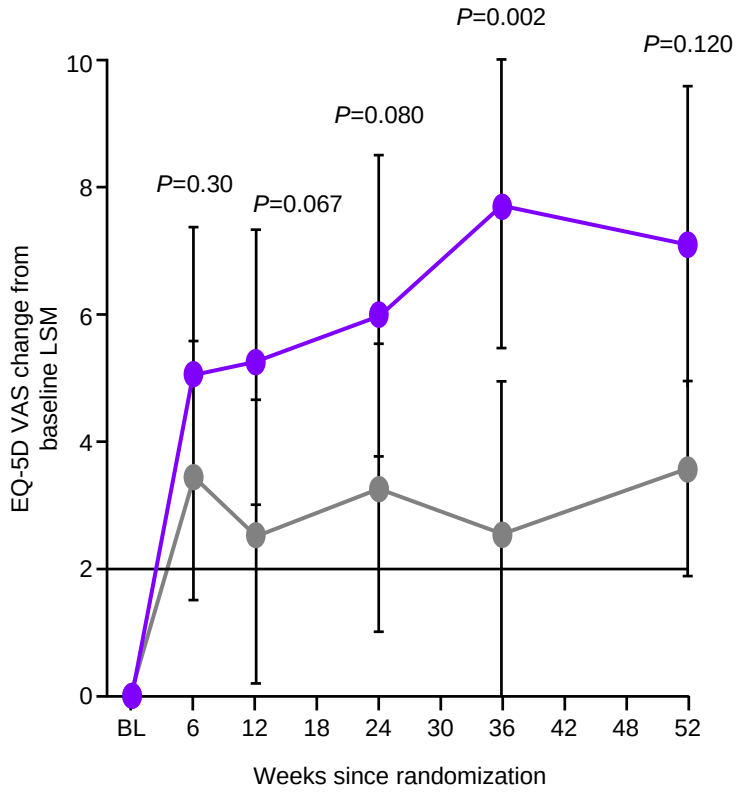
6MWT, 6 minute walk test; FCM, ferric carboxymaltose; LSM, least squares mean; SE, standard error

Ponikowski P *et al. Eur Heart J* 2015;36:657–68

… with improved quality of life over time



FCM vs placebo LSM (95% CI)	1.8 (–1.2, 4.8)	3.3 (0.2, 6.4)	1.3 (–1.9, 4.6)	5.0 (1.6, 8.3)	4.5 (1.1, 7.9)

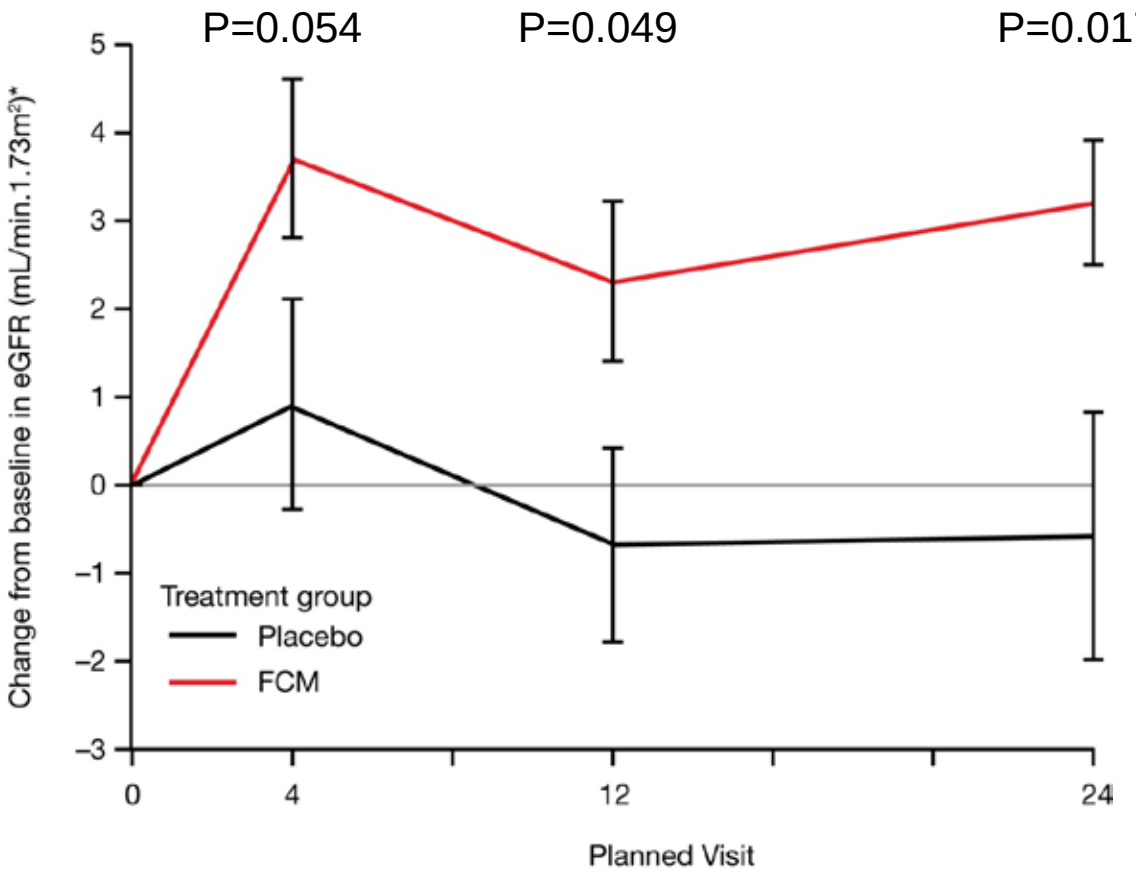


FCM vs placebo LSM (95% CI)	1.5 (–1.4, 4.4)	2.8 (–0.2, 5.8)	2.8 (–0.3, 5.9)	5.2 (2.0, 8.5)	2.6 (–0.7, 5.9)

Ponikowski P *et al. Eur Heart J* 2015;36:657–68

Effect of iv-iron on kidney function

Change in eGFR from baseline (mL/min.1.73m^2)

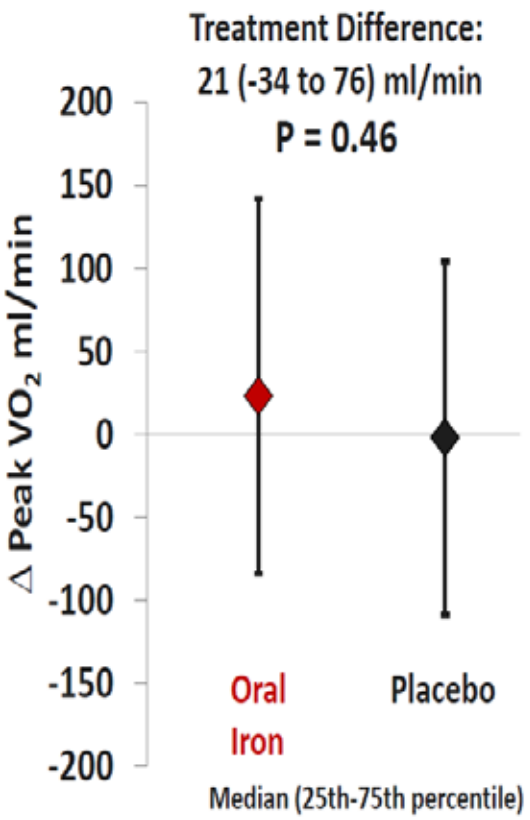


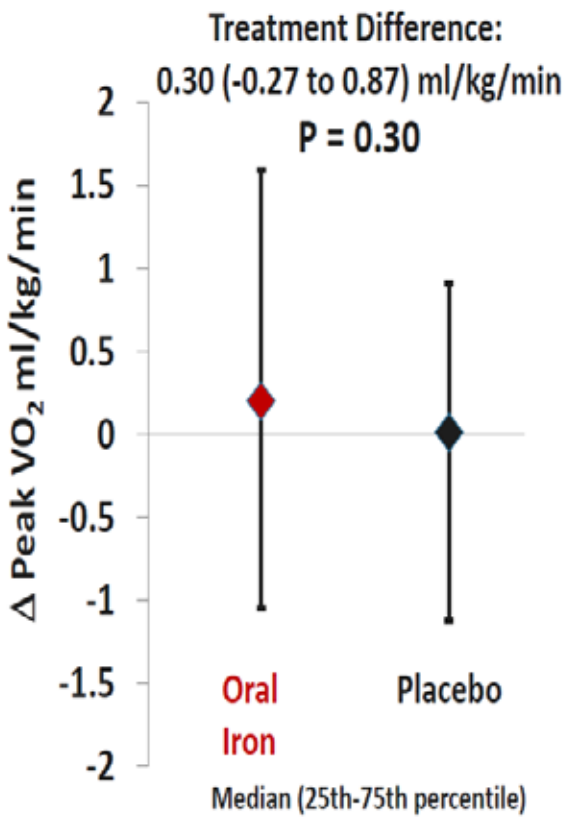
weeks after randomization

Treatment effect (mL/min/1.73m^2):*	2.8 ± 1.5	3.0 ± 1.5	4.0 ± 1.7

Ponikowski *et al. 2015.*

IRONOUT:
No improvements in exercise capacity with oral iron





Lewis GD *et al. JAMA* 2017;317:1958–66

Note: BACK-UP slide
(this slide is animated)

Prevalence of CKD in CHF

FIND-CKD

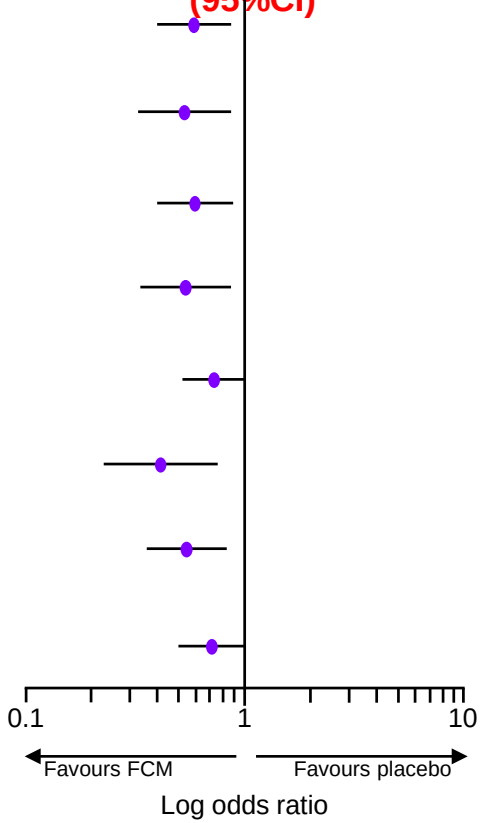
Study	Year	Number of patients	NYHA	Age, years	Male, %	EF, %	eGFR <60, %	Outcome	Adjusted hazard comparing with pts without CKD for the outcome
SOLVD-T	2000	2161	I–IV	60.7	81.5	24.7	**35.7**	All-cause mortality	1.41 for eGFR <60[a]
PRIME-II	2000	1906	III–IV	64.7	80.4	26.2	**49 (eGFR ≤58)**	All-cause mortality	1.91 for eGFR 44–58 2.85 for eGFR <44
DIG	2002	585	II/III: 85%	65	73.9	35	**50 (eGFR ≤63.8)**	All-cause mortality	1.6 for eGFR 47–64[a] 2.1 for eGFR 18–48[a]
McClellan	2002	665	–	75.7	40	38.4	**38[b]**	All-cause mortality	1.24 at 1-year mortality[b]
UK-HEART	2002	553	II/III: 98%	62.7	76	42	**–**	All-cause mortality	1.09 in each 10 µmol/L increase of creatinine
CHARM	2006	2680	II–IV	65.3	66.6	38.5	**36**	CV death + HF hospitalization	1.54 for eGFR 45–59.9 1.86 for eGFR <45
ANCHOR	2006	59,772	–	71.8	54.2	NA	**39.2**	All-cause mortality + HF hospitalization	1.39 for eGFR 30–44 2.28 for eGFR 15-29
CHART	2008	920	II–IV	68.3	65.1	49.3[c]	**42.7**	All-cause mortality + HF hospitalization	1.31 for eGFR 30–59 1.56 for eGFR <30
JCARE-CARE	2009	2013	1.8 (mean)	71.5	58.7	44.8	**70.3**	All-cause mortality	1.26 for eGFR 30–59 2.48 for eGFR <30

[a] mL/min; [b] CKD was defined by serum creatinine of ≥1.4mg/dL for women and ≥1.5 mg/dL for men; [c] Data were retrieved from the previous study that included 1154 patients

Meta-analysis* on individual patient data: Significant improvements on patient outcomes

FIND-CKD

n (%)	FCM (n=504)	Placebo (n=335)	Rate ratio (95%CI)	P
eGFR <60 mL/min per 1.73 m^2	216 (43)	156 (47)		
CV hospitalization and CV death	69 (23.0)	92 (40.9)		0.009
HF hospitalization and CV death	39 (13.0)	60 (26.7)		0.011
CV hospitalization and all-cause death	71 (23.7)	94 (41.8)		0.009
HF hospitalization and all-cause death	41 (13.7)	62 (27.6)		0.011
All-cause hospitalization and all-cause death	108 (36.1)	118 (52.5)		0.060
HF hospitalization	22 (7.3)	43 (19.1)		0.003
CV hospitalization	52 (17.4)	75 (33.3)		0.004
All-cause hospitalization	89 (29.7)	99 (44.0)		0.056



Four studies were included: FER-CARS-01, FAIR-HF, EFFICACY-HF, CONFIRM-HF

Anker SD *et al. Eur J Heart Fail* 2017.

In conclusion

1. No huge changes in anaemia management within the last few years
2. HIF stabilisers represent the new ‘kid on the block’ for anaemia management in CKD
3. Despite a recent meta-analysis we still do not know how much IV iron to give patients
4. The PIVOTAL study should address some of the gaps in the evidence base for IV iron
5. For many CKD patients the latest ESC guidelines on the use of IV iron in heart failure may be relevant