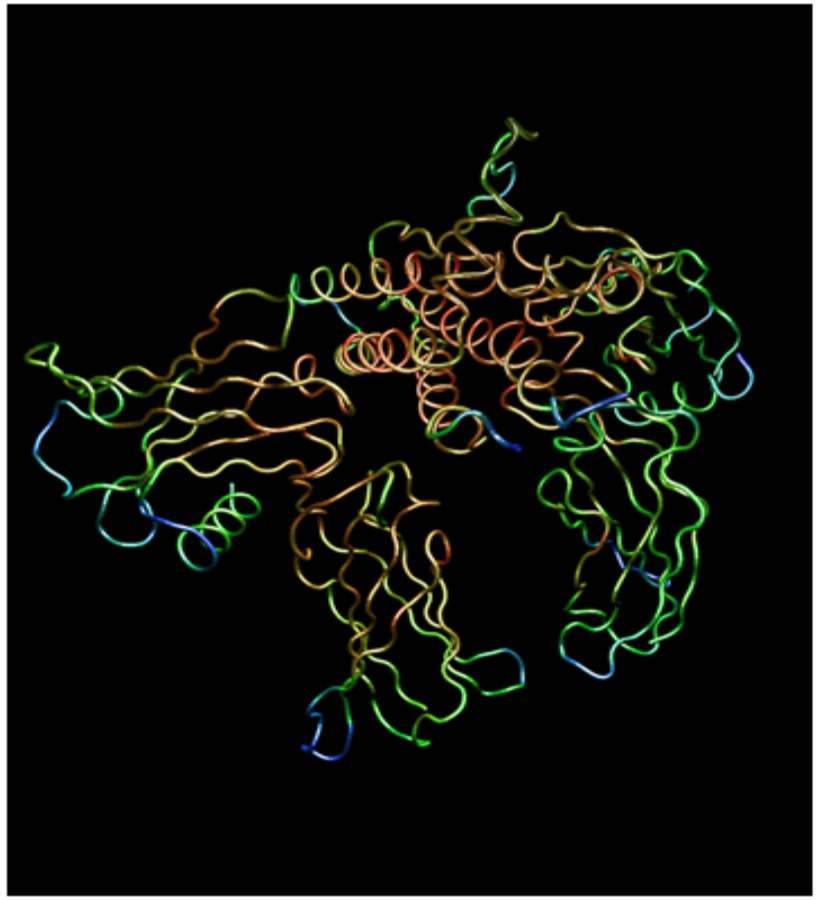
What is new in anemia treatment in CKD since 2010?

Pr. J-M Krzesinski
CHU Liège

5th Belgian Dialysis Symposium
Château Jemeppe, Hargimont (B), April 2012

Erythropoietin

- Hormone produced in peritubular fibroblast-like cells; 165 amino acid glycoprotein with 4 carbohydrate chains
- Anti-apoptotic
- Erythropoietin levels increase with decrease in hemoglobin

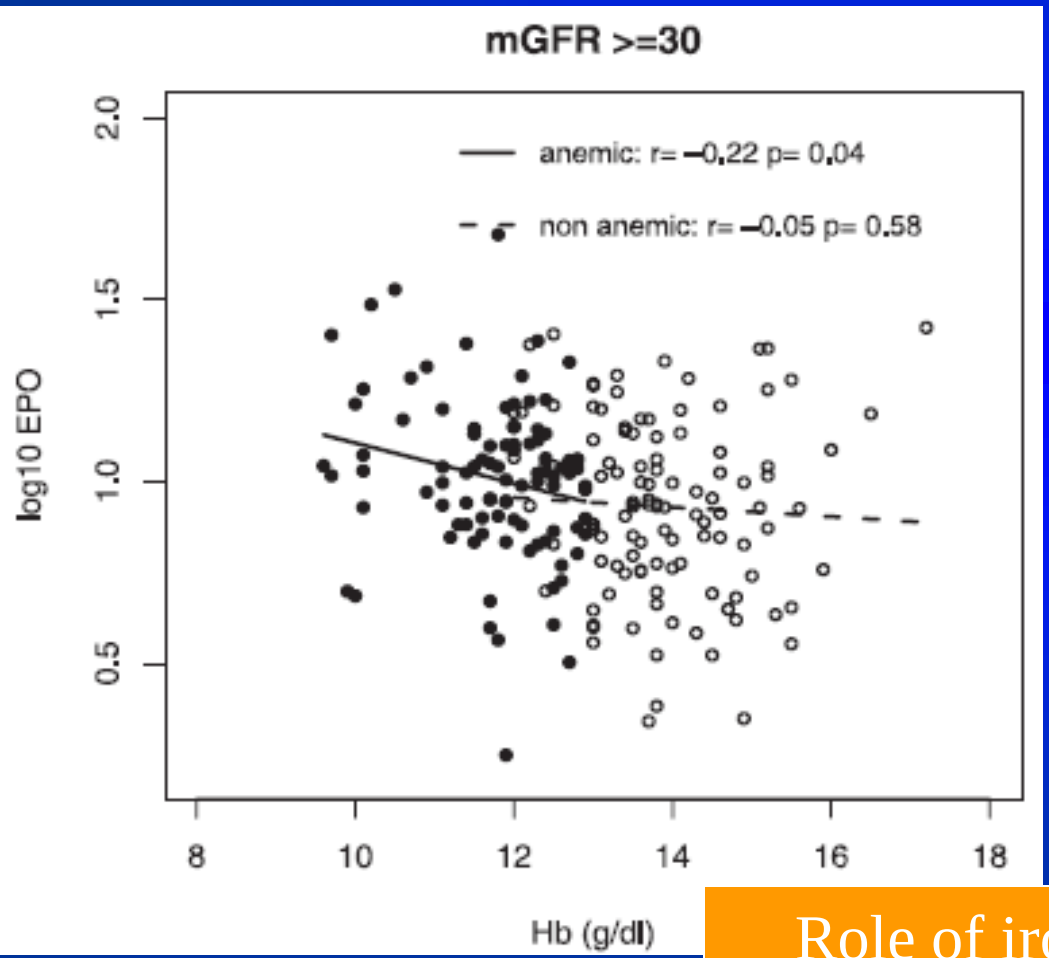


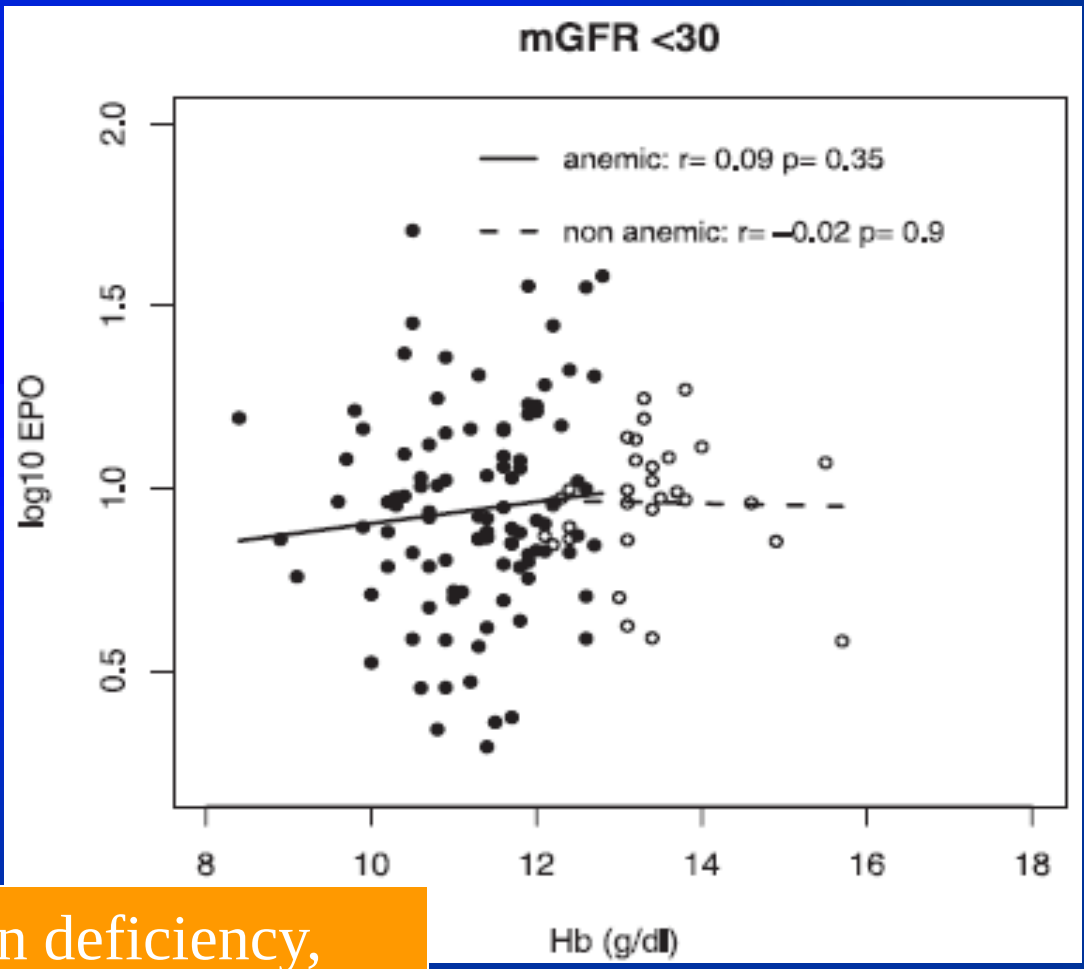
Fishbane S. *Curr Opin Nephrol Hypertens*. 2009;18:112-115.
Brines M, Cerami A. *Nat Rev Neurosci*. 2005;6:484-494.

Timing and Determinants of Erythropoietin Deficiency in Chronic Kidney Disease

Lucile Mercadal,[†] Marie Metzger,[*†] Nicole Casadevall,[‡§] Jean Philippe Haymann,[‖¶] Alexandre Karras,[**] Jean-Jacques Boffa,[¶††] Martin Flamant,[‡‡§§] François Vrtovsnik,[§§‖‖] Bénédicte Stengel,[*†] and Marc Froissart,[*¶¶] on behalf of the NephroTest Study Group*

www.cjasn.org Vol 7 January, 2012





Role of iron deficiency, Inflammation, obesity and DN

New Anemia Therapies: Translating Novel Strategies From Bench to Bedside

Am J Kidney Dis. xx(x):xxx. © 2012

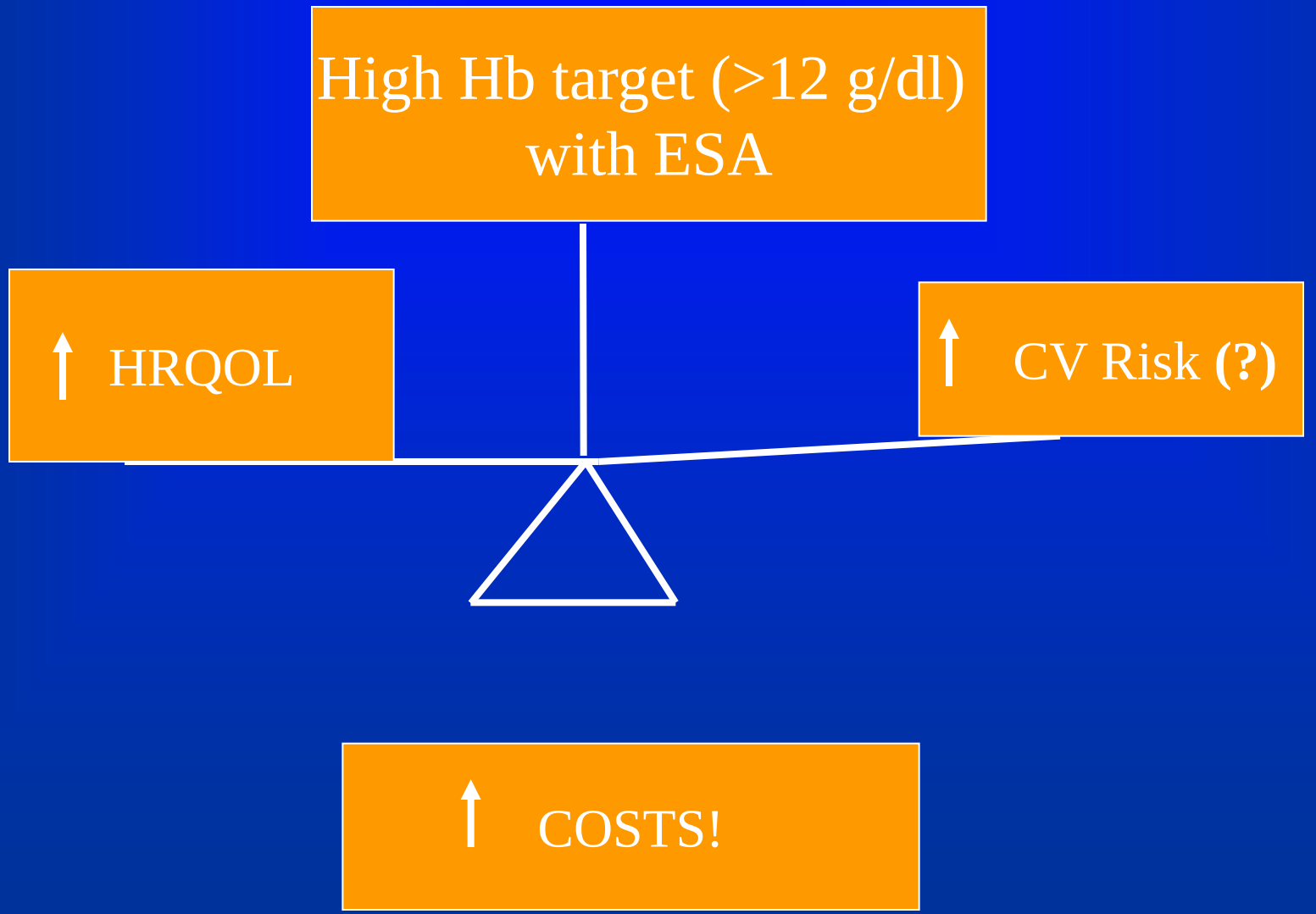
Iain C. Macdougall, BSc, MD, FRCP

Table 1. Currently Available Erythropoiesis-Stimulating Agents

Agent	Active Compound	Manufacturing Process	Year Licensed
Epoetin alfa/beta (Epogen, Eprex, Erypo, NeoRecormon)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected CHO cells	1989 (Epogen, in US); 1990 (Eprex/ Erypo/NeoRecormon, in Europe)
Epoetin delta (Dynepo)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected human cells	2006 (outside of US); product withdrawn by Shire in 2009
"Biosimilar" epoetins (Binocrit, Hexal, Retacrit, Silapo, Eporatio)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected CHO cells	2009 onward
Nonapproved or locally approved "copy" epoetins	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene-transfected human cells	Available in many countries outside of US and Europe, eg, India, China, Thailand, Argentina, Brazil
Darbepoetin alfa (Aranesp)	Hyperglycosylated recombinant human EPO analogue	Recombinant DNA technology; mutated EPO cDNA–transfected CHO cells	2001 (both US and Europe)
C.E.R.A. (Mircera)	Pegylated recombinant human EPO analogue		2009 (outside of US only)

Abbreviations: EPO, erythropoietin; cDNA, complementary DNA; C.E.R.A., continuous erythropoietin receptor activator; CHO, Chinese hamster ovary; US, United States.

What is the dilemma for Hb correction?



An Update on the Controversies in Anemia Management in Chronic Kidney Disease: Lessons Learned and Lost

Geoffrey Teehan[1] and Robert L. Benz[1,2]

Hindawi Publishing Corporation
Anemia
Volume 2011, Article ID 623673, 5 pages
doi:10.1155/2011/623673

Table 2: Study characteristics.

Study	*N* (pts)	HB target (g/dL)	ESA	GFR range (mL/min/1.73 m²)	Primary endpoint	*P* value for primary endpoints
CHOIR (2006) [10]	603	13.5 versus 11.3	Epoetin Alfa	15–50	Death, MI, CHF, CVA	0.03 for composite favoring lower Hb
CREATE (2006) [22]	1432	13–15 versus 10.5–11.5	Epoetin Beta	15–35	Composite of 8 CV events, CKD progression	NS for CV events. 0.03 for ESRD favoring lower Hb group
TREAT (2009) [23]	4038	13 versus 9	Darbepoetin Alfa	20–60	Death, CV Event, ESRD	NS ↑ stroke

AR 1.9

Naturally Occurring Higher Hemoglobin Concentration Does Not Increase Mortality among Hemodialysis Patients

DOPPS

David A. Goodkin,* Douglas S. Fuller,* Bruce M. Robinson,* Christian Combe,† Richard Fluck,‡ David Mendelssohn,§ Tadao Akizawa,‖ Ronald L. Pisoni,* and Friedrich K. Port*

Unadjusted mortality risk for patients with hemoglobin >12 g/dl and no erythropoietic therapy was lower than for the other patients, but after thorough adjustment for case mix, there was no difference between groups (relative risk, 0.98; 95% CI 0.80 to 1.19). These data show that naturally occurring hemoglobin concentration >12 g/dl does not associate with increased mortality among hemodialysis patients.

J Am Soc Nephrol 22: 358–365, 2011. doi: 10.1681/ASN.2010020173

Male
AVF
Cystic disease
Smoking
Lung disease

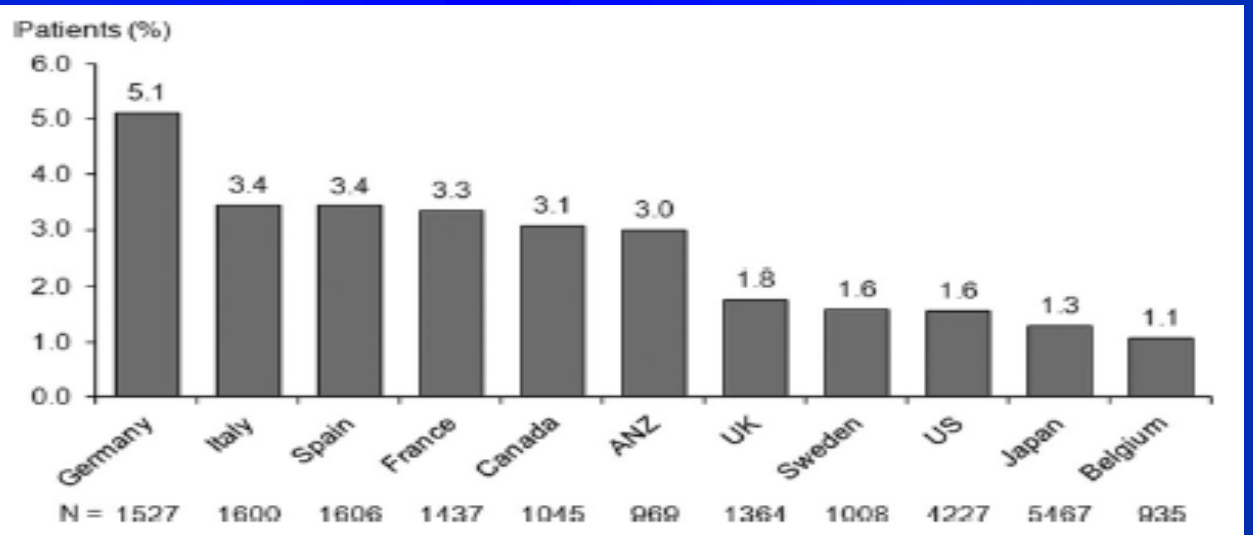


Figure 1. The prevalence of Endogenous EPO patients among the initial study phase samples varies by country (see text). ANZ, Australia/New Zealand. The numbers below figure indicate total denominator for each nation.

N ENGL J MED 363;12 NEJM.ORG SEPTEMBER 16, 2010

Erythropoietic Response and Outcomes in Kidney Disease and Type 2 Diabetes

Scott D. Solomon, M.D., Hajime Uno, Ph.D., Eldrin F. Lewis, M.D., M.P.H., Kai-Uwe Eckardt, M.D., Julie Lin, M.D., M.P.H., Emmanuel A. Burdmann, M.D., Ph.D., Dick de Zeeuw, M.D., Ph.D., Peter Ivanovich, M.D., Andrew S. Levey, M.D., Patrick Parfrey, M.D., Giuseppe Remuzzi, M.D., Ajay K. Singh, M.D., Robert Toto, M.D., Fannie Huang, M.S., Jerome Rossert, M.D., Ph.D., John J.V. McMurray, M.D., and Marc A. Pfeffer, M.D., Ph.D., for the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) Investigators

Table 2. Rate of End Points and Adjusted Hazard Ratios.*

	Placebo (N=1889)	Poor Response (N=471)	Better Response (N=1401)	Adjusted Hazard Ratio (95% CI)†
	rate per 100 patient-yr (95% CI)			
Cardiovascular composite	12.3 (11.3–13.4)	16.3 (14.0–18.9)	12.4 (11.2–13.6)	1.31 (1.09–1.59)
Death from any cause	7.5 (6.8–8.3)	9.9 (8.3–11.9)	7.5 (6.7–8.5)	1.41 (1.12–1.78)
Stroke	1.0 (0.8–1.4)	2.3 (1.6–3.4)	2.0 (1.6–2.6)	1.26 (0.78–2.02)

Initial hemoglobin response to darbepoetin alfa determines outcome in patients with CKD and type 2 diabetes

In response to data from trials showing an increase in clinical events with the use of erythropoiesis-stimulating agents (ESAs), Seliger *et al.* carried out an observational case–control study and have found that high doses of ESAs are associated with an increased risk of stroke.

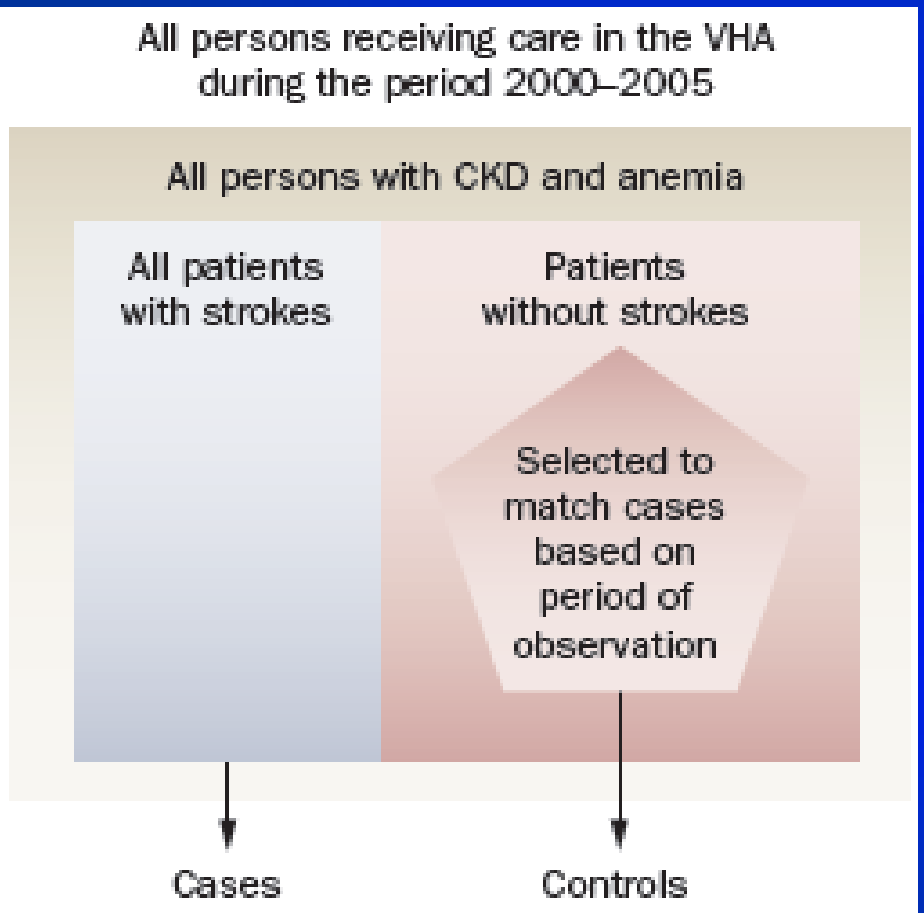


Figure 1 | Patient selection process from the VHA cohort in the Seliger *et al.* study.[3]

the OR between ESA use and stroke was 1.38 (95% CI 1.14–1.68, $P=0.001$).

The association between ESA use and stroke was also stronger in subgroups of patients who had no history of stroke and those who did not have atrial fibrillation (OR 1.41, 95% CI 1.14–1.75 and OR 1.44, 95% CI 1.16–1.78, respectively). By contrast, subgroups with a history of stroke or those who had atrial fibrillation showed no associations between the risk of stroke and ESA use (OR 0.76 and 0.80, respectively).

KI 2011

Black Box Warning

- "In controlled trials, patients experienced greater risks for death, serious adverse CV reactions, and stroke when administered ESAs to a target hemoglobin > 11 g/dL"

a. Epogen® (epoetin alfa) prescribing information. Amgen. 2011.
b. Aranesp® (darbepoetin alfa) prescribing information. Amgen. 2011.
c. Procrit® (epoetin alfa) prescribing information. Amgen. 2011.

Black Box Warning (cont)

- "No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks"

- Use the lowest epoetin alfa or darbepoetin alfa dose sufficient to reduce the need for red blood cell transfusions

a. Epogen® (epoetin alfa) prescribing information. Amgen. 2011.
b. Aranesp® (darbepoetin alfa) prescribing information. Amgen. 2011.
c. Procrit® (epoetin alfa) prescribing information. Amgen. 2011.

TRENDS IN HEMOGLOBIN PRE- AND POST-BUNDLE IN HOSPITAL-BASED DIALYSIS CLINICS

Anjali Acharya[1], Nathan Thompson[1], Gregory A. Maglinte[2], Chun-Lan Chang[3], Jerrold Hill[3], David J. Harrison[2], Akhtar Ashfaq[2], Jeffrey Petersen[2], George N. Coritsidis[1]

[1]NYC Health and Hospitals Corporation, New York, NY; [2]Amgen, Thousand Oaks, CA; [3]IMS Health, Plymouth Meeting, PA

	Mean (SD) Monthly Hb (g/dL)	Mean Monthly Hb Distribution (% of pts) <10 g/dL	>12 g/dL
Mar 2010	11.4 (1.2)	11.1%	29.6%
Jun 2010	11.3 (1.2)	12.3%	27.0%
Sep 2010	11.3 (1.2)	12.6%	29.4%
Dec 2010	11.3 (1.2)	13.4%	26.2%
Mar 2011	11.1 (1.2)	15.1%	21.5%
Jun 2011	11.1 (1.2)	15.7%	20.2%
Sep 2011	11.0 (1.2)	18.0%	17.3%

NKF 2012 Spring Clinical Meetings Abstracts

Am J Kidney Dis. 2012;59(4):A1-A92

IMPACT OF FREQUENT HEMOGLOBIN (HB) MEASUREMENT AND ESA DOSE TITRATION ON HB STABILITY IN DIALYSIS

Lynda Szczech[1], David Gilbertson[2], Ali Hariri[3], Pratyush Kumar[4], Alex Yang[5]

[1]Duke Nephrology, Durham, NC; [2]Chronic Disease Research Group, MMRF, Minneapolis, MN; [3]Takeda, Deerfield, IL; [4]ZS Associates, San Francisco, CA; [5]Affymax, Inc., Palo Alto, CA

	Hb Measurement Frequency (per pt-month)		
	<2	≥2 to <3	≥3
Number of facilities, n	94	954	582
Mean Hb Measurements/pt-month	1.8	2.5	3.6
Mean Dose Titrations/pt-month	0.8	1.0	1.2
Mean Epoetin Use (U/pt-month)	57813	68921	72023
Hb Stability (% pts, 10-12 g/dL)	59.9	61.8	60.9
Hb Variability (mean SD w/in Hb unit)	0.72	0.73	0.72

NKF 2012 Spring Clinical Meetings Abstracts

Am J Kidney Dis. 2012;59(4):A1-A92

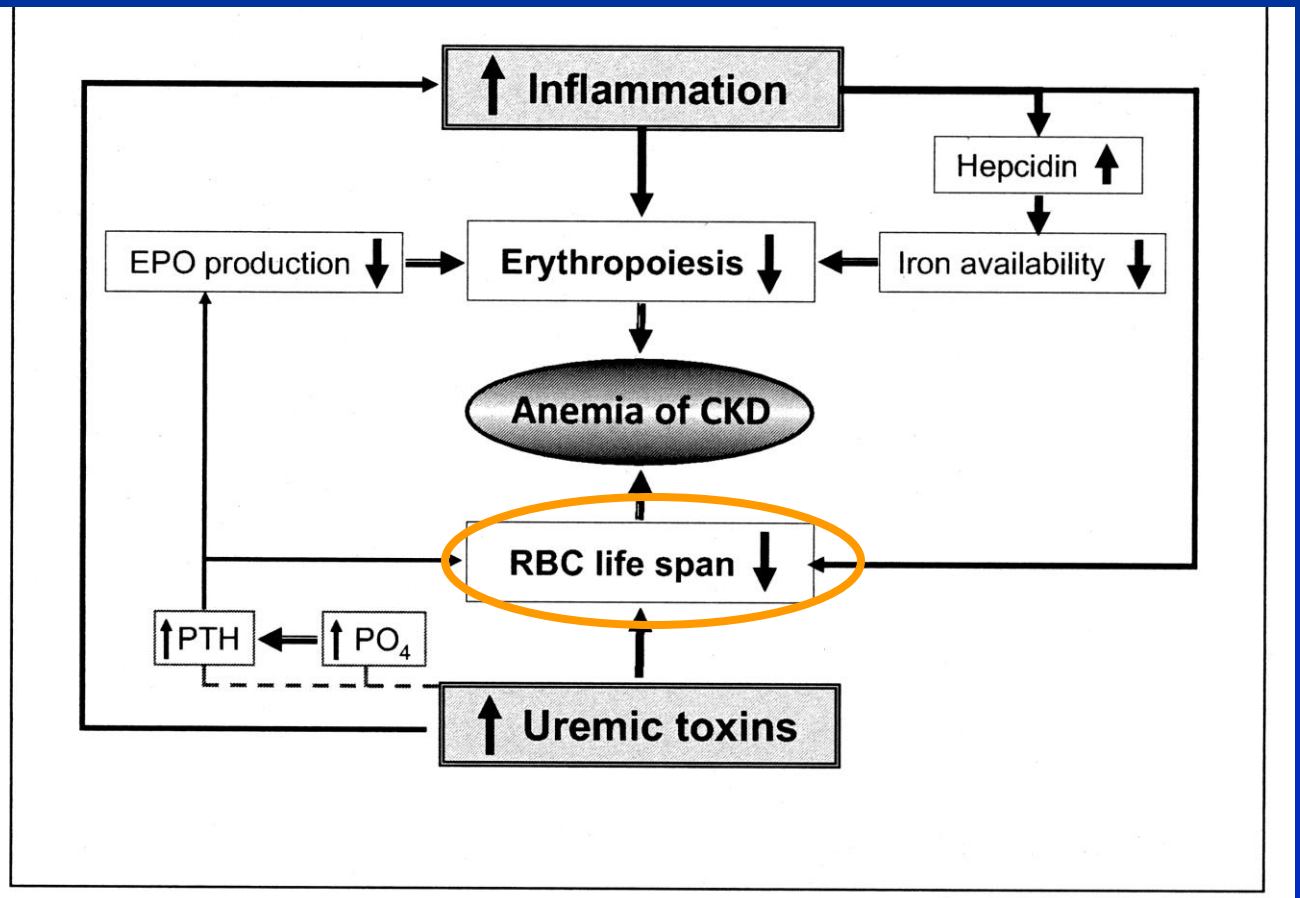


Fig. 1. Uremic toxicity and inflammation both exacerbate anemia of CKD, affecting bone marrow erythropoiesis and erythrocyte survival. Dialysis therapies that curb the effects of both uremic toxins and inflammatory mediators enable anemia correction.

Bowry S. and Gatti E., *Blood Purification*, 2011, **32**, 210-219.

Red Blood Cell Survival in Long-term Dialysis Patients

Frederiek E. Vos, MD,[1] John B. Schollum, MBChB, FRACP,[1] Carolyn V. Coulter, PhD,[2] Terrence C.A. Doyle, MBChB, MD, FRACR,[3] Stephen B. Duffull, PhD,[2] and Robert J. Walker, MBChB, MD, FRACP[1]

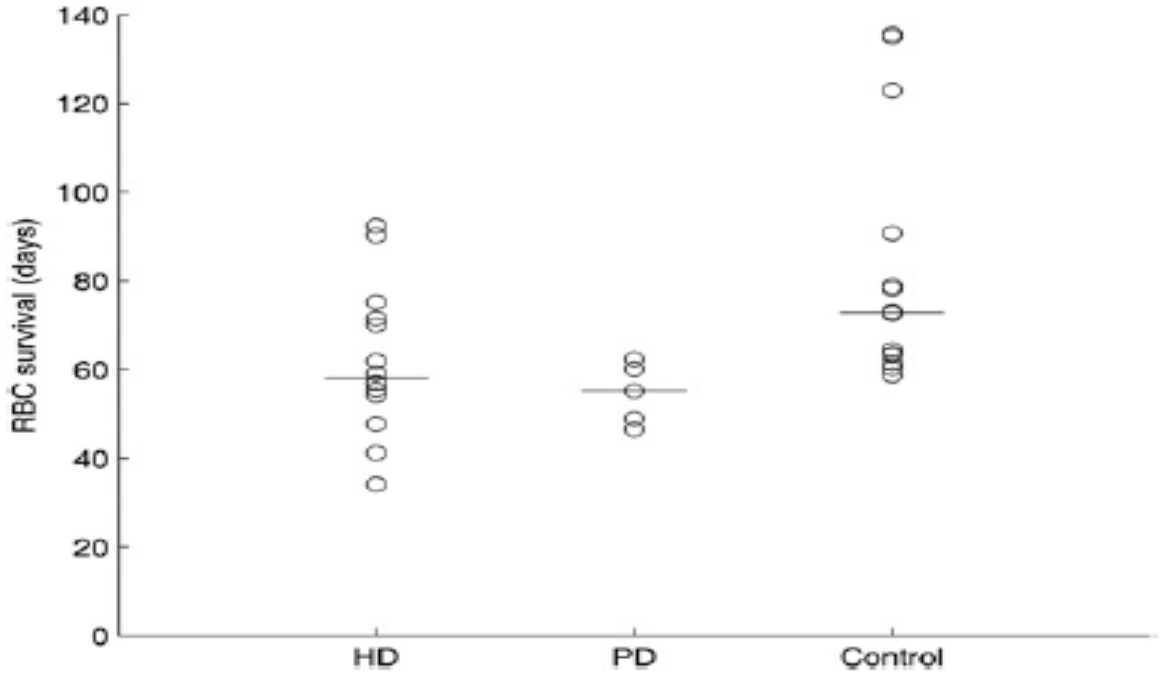


Figure 2. Scatter plot shows red blood cell (RBC) survival in days in hemodialysis (HD) patients, peritoneal dialysis (PD) patients, and controls determined using chromium 51 (^{51}Cr) labeling. Group median values are represented by a full horizontal line. RBC survival is significantly different between HD patients and controls ($P < 0.05$).

Conclusions: Despite current ESA therapy, decreased RBC survival contributes to chronic kidney disease–related anemia, although the reduction is less than previously reported. There does not appear to be net mechanical damage associated with HD therapy resulting in decreased RBC life span.

Am J Kidney Dis. 58(4):591-598.

Erythropoiesis-Stimulating Agent Responsiveness and Mortality in Hemodialysis Patients: Results from a Cohort Study From the Dialysis Registry in Japan

Conclusions: Mortality can be affected by ESA responsiveness, which may include independent and interactive effects of ESA dose and hemoglobin level. Responsiveness category has prognostic importance and clinical relevance in anemia management.

Am J Kidney Dis. 59(1):108-116.

Table 2. Exploratory Logistic Regression Analysis to Determine Predictors of ESA Hyporesponsiveness

Variable	OR (95% CI)
Age (/10-y increase)	1.02 (1.00-1.03)
Man (vs woman)	0.93 (0.90-0.97)
Time on dialysis (/1-y increase)	1.00 (1.00-1.01)
History of CVD	1.04 (1.00-1.09)
Diabetes	1.02 (0.98-1.06)
Transferrin saturation	
<20%	1.90 (1.82-1.98)
20%-49.9%	1.00 (reference)
≥50%	1.03 (0.94-1.14)
C-Reactive protein	
First quartile	1.00 (reference)
Second quartile	1.03 (0.98-1.09)
Third quartile	1.20 (1.14-1.27)
Fourth quartile	1.74 (1.65-1.83)
Serum albumin (/1-g/dL increase)	0.38 (0.37-0.40)
Postdialysis body weight (/10-kg increase)	1.00 (0.98-1.02)

Note: N = 95,460. ESA hyporesponsiveness was defined as having a hemoglobin level <10 g/dL while receiving an ESA dosage ≥6,000 U/wk.

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; ESA, erythropoiesis-stimulating agent; OR, odds ratio.

Retrospective
95000 pts
HD
Japan

Erythropoiesis-Stimulating Agent Responsiveness and Mortality in Hemodialysis Patients: Results from a Cohort Study From the Dialysis Registry in Japan

Shingo Fukuma, MD,[1] Takuhiro Yamaguchi, PhD,[2] Seiji Hashimoto, MD, PhD,[3] Shigeru Nakai, MD, PhD,[3] Kunitoshi Iseki, MD, PhD,[3] Yoshiharu Tsubakihara, MD, PhD,[3] and Shunichi Fukuhara, MD[1]

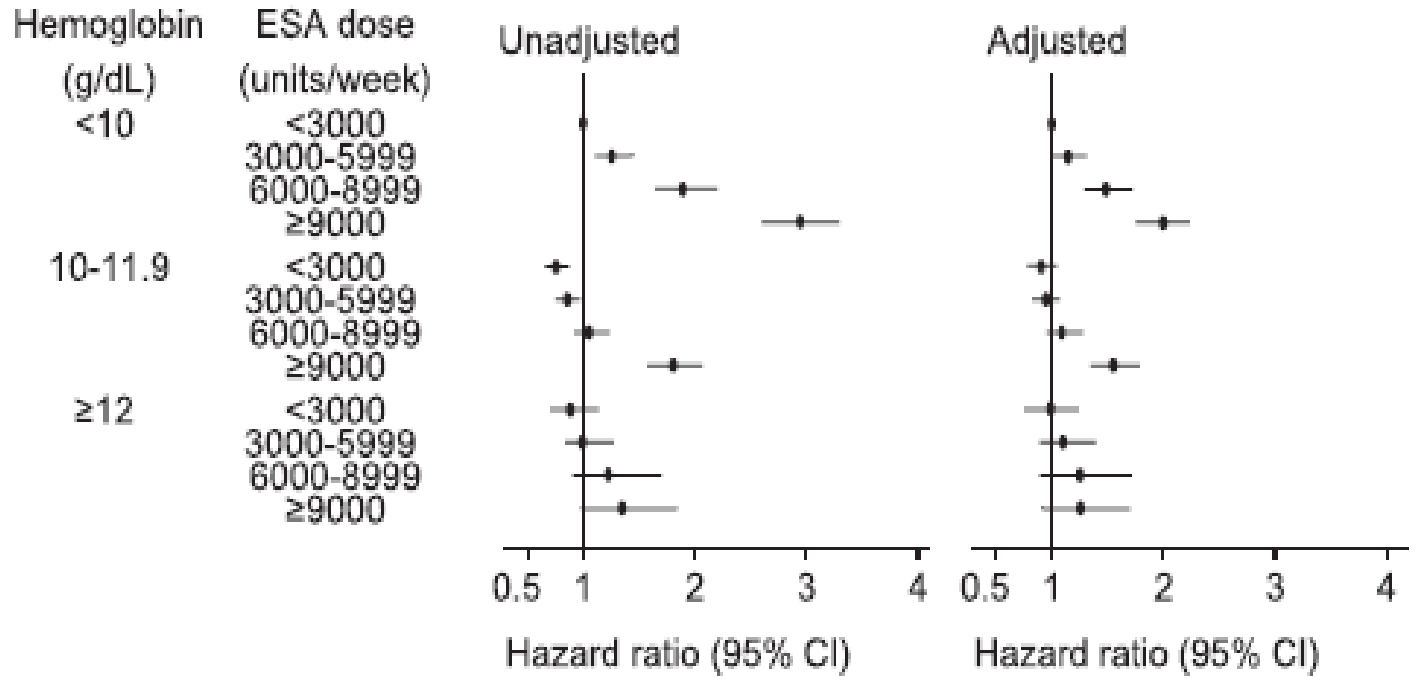


Figure 2. Association between 12 categories of erythropoiesis-stimulating agent (ESA) responsiveness and mortality for all-cause and cardiovascular disease. Categories of ESA responsiveness were defined by combination of ESA dosage (<3,000, 3,000-5,999, 6,000-8,999, and ≥9,000 U/wk) and hemoglobin level (<10, 10-11.9, and ≥12 g/dL). Adjusted model included age, sex, time on dialysis therapy, postdialysis body weight, diabetes, history of cardiovascular disease, serum albumin level, and transferrin saturation. Abbreviation: CI, confidence interval.

Am J Kidney Dis. 2012;59(1):108-116

Worse effect of ESA high dosage and ESA hyporesponsiveness

Table 1. Potentially correctable versus non correctable factors involved in the anemia of CKD, in addition to ESA deficiency

Easily correctable	Potentially correctable	Impossible to correct
Absolute iron deficiency	Infection / inflammation	Hemoglobinopathies
B_{12} / folate deficiency	Underdialysis	Bone marrow disorders
Hypothyroidism	Hemolysis	
ACEi	Bleeding	
	Hyperparathyroidism	
Testosterone deficiency	PRCA	
	Malignancy	
	Malnutrition	

NDT 2011 Carrero et al : hypogonadism as a cause of anemia and ESA resistance in men with CKD

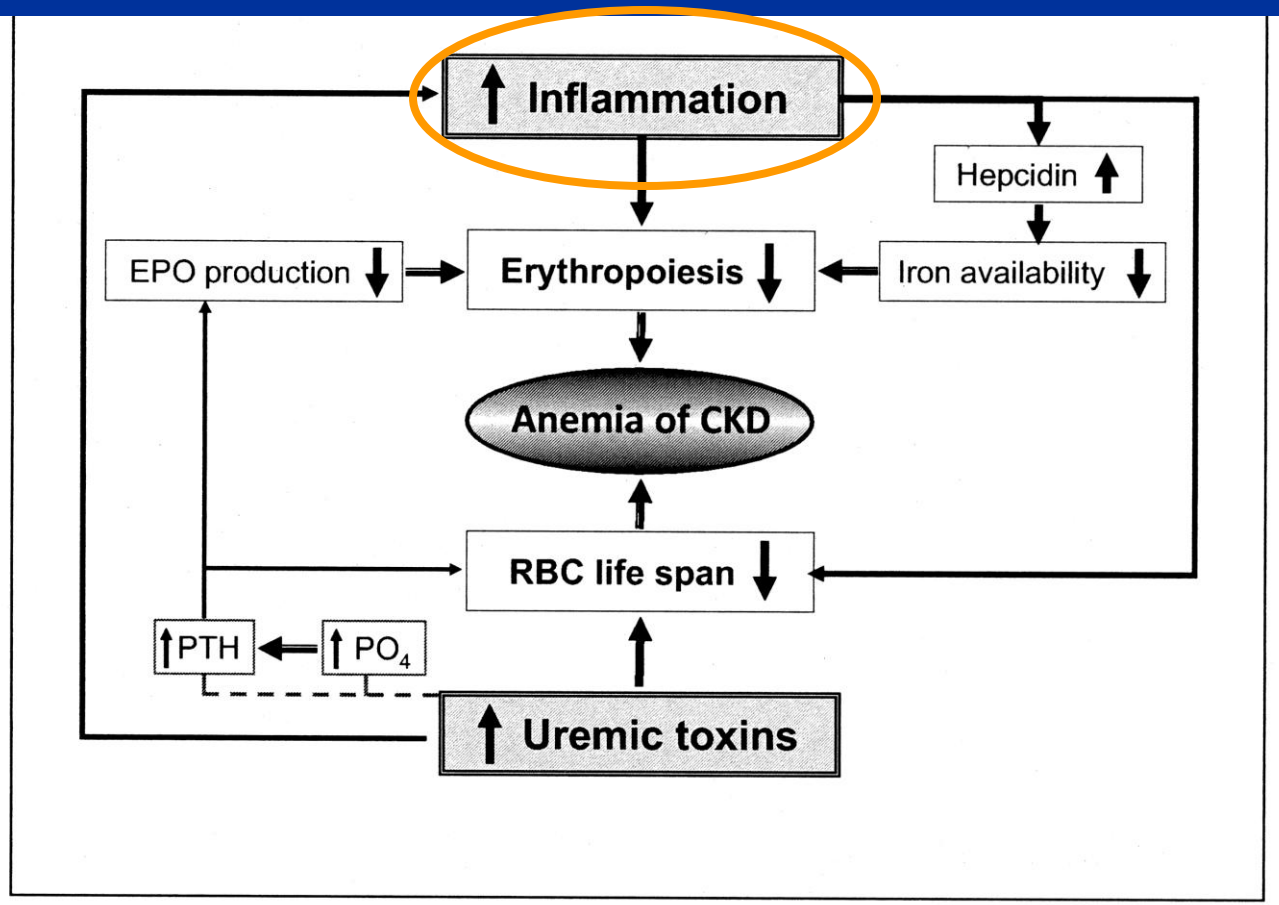


Fig. 1. Uremic toxicity and inflammation both exacerbate anemia of CKD, affecting bone marrow erythropoiesis and erythrocyte survival. Dialysis therapies that curb the effects of both uremic toxins and inflammatory mediators enable anemia correction.

Bowry S. and Gatti E., *Blood Purification*, 2011, **32**, 210-219.

Hepcidin: clinical utility as a diagnostic tool and therapeutic target

Kidney International (2011) **80,** 240–244;

Daniel W. Coyne[1]

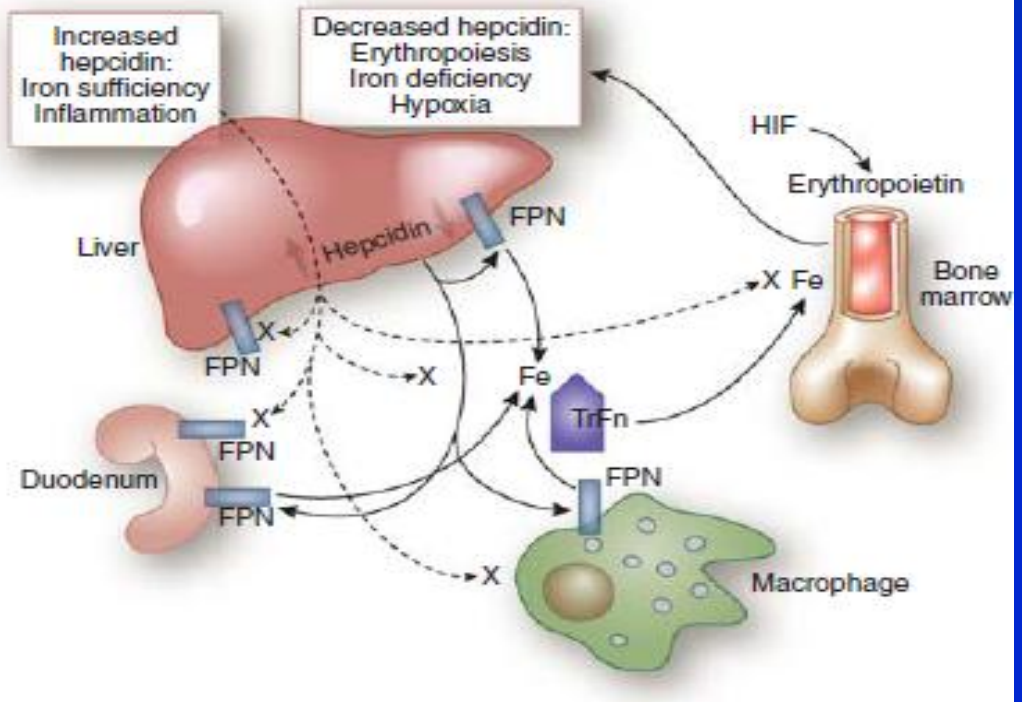


Figure 1 | Iron (Fe) sufficiency and inflammation enhance hepcidin production in the liver. Hepcidin in turn downregulates surface expression of the ferroportin (FPN) in the duodenum and reticuloendothelial stores, resulting in diminished intestinal iron absorption, reduced iron release from iron stores, and lower transferrin (TrFn) saturation. In contrast, stimulation of erythropoiesis via exogenous epoetin or stabilization of hypoxia-inducible factor (HIF), and iron deficiency suppresses hepatic hepcidin production, resulting in intestinal iron absorption, release of iron from stores, and higher transferrin saturation. Iron is then cycled more efficiently to the bone marrow to support erythropoiesis.

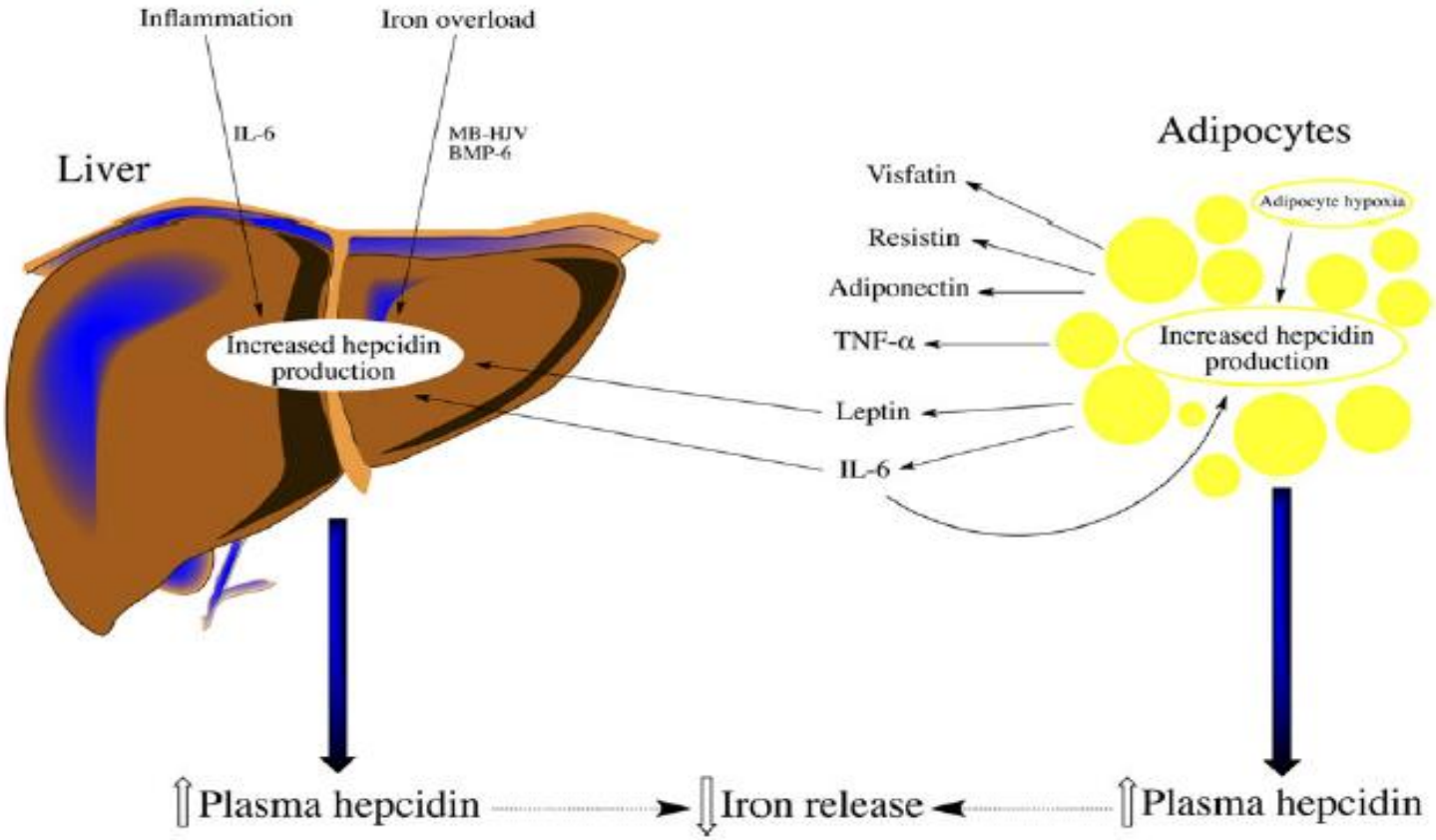


Fig. 2. Hepcidin production in liver and adipose tissue. Accumulating data indicate that apart from hepatocytes, hepcidin can be also produced by adipose tissue cells. The latter hepcidin production seems to be mainly regulated by inflammatory stimuli, such as increased IL-6, but other factors, e.g. adipocyte hypoxia, may also participate. Furthermore, peptide mediators and pro-inflammatory substances produced by adipocytes, such as leptin and IL-6 appear to upregulate hepcidin secretion from hepatocytes, the main production site of hepcidin. Thus, inflammation-induced hepcidin elevation is possibly a major mechanism for iron-deficiency and anaemia in obese individuals. MB-HJV, membrane-bound haemojuvelin; BMP-6, bone morphogenetic protein-6.

Iron supplementation to treat anemia in patients with chronic kidney disease

Besarab, A. & Coyne, D. W. *Nat. Rev. Nephrol.* 6, 699–710 (2010);

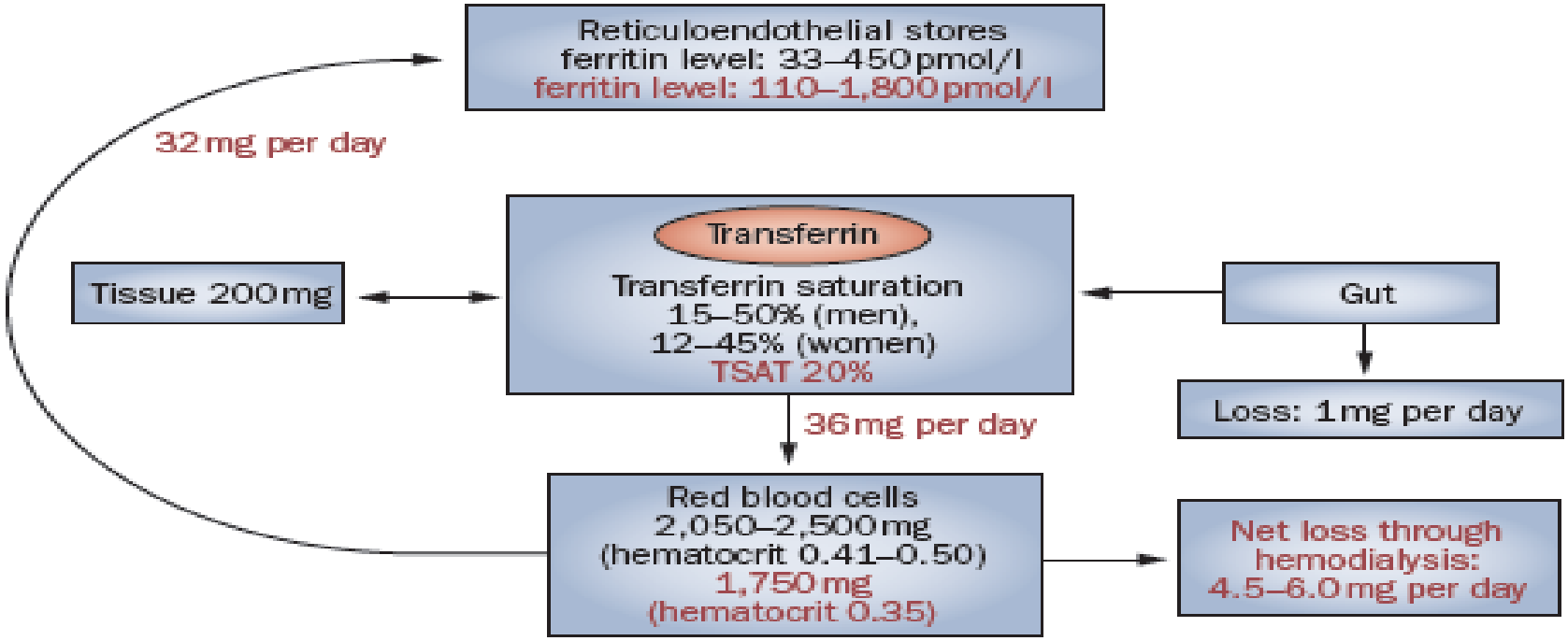


Figure 1 | Iron distribution in the average adult. Values for healthy individuals are shown in black print whereas those for patients with end-stage renal disease (ESRD) on hemodialysis are shown in red print. The overall balance of iron in patients on chronic maintenance hemodialysis is impaired. Transport of iron is decreased by a reduction in circulating transferrin levels. At the same time, dialysis-associated blood losses lead to loss of iron from the body. Daily incorporation of iron into red blood cell hemoglobin and its release from senescent cells is actually increased in patients with ESRD on hemodialysis compared with healthy individuals. Note that both occult blood loss in stool and loss of red blood cells in tubing increase the daily loss of iron in patients with ESRD on hemodialysis.[90]

Superparamagnetic iron oxide coated with CH shell

DIFFERENTIAL HEMOGLOBIN RESPONSE FOLLOWING TREATMENT WITH TWO IV IRONS IN PATIENTS ON HEMODIALYSIS OR WITH MORE SEVERE ANEMIA: RESULTS FROM THE FERUMOXYTOL COMPARED TO IRON SUCROSE TRIAL (FIRST)

William Strauss, Joe Li, Justin McLaughlin, Susan Farkas, Joachim Hertel, Diogo Belo
AMAG Pharmaceuticals Inc., Lexington MA

Efficacy Results from the Intent-to-Treat (ITT) Population

g IV Fer 2X500 vs IS 10X100 mg

	FER	IS
Mean Δ Hgb from Baseline to Day 35 (g/dL)		
ITT Population (FER n=80; IS n=82)	0.89	0.80
Subjects on HD (FER n=34; IS n=36)	1.02	0.54
Subjects with Baseline Hgb 7-9g/dL (FER n=10; IS n=11)	1.39	0.63
Percent achieving ≥1 g increase in Hgb from Baseline to Day 35		
ITT Population	50%	42%
Subjects on HD	56%	39%
Subjects with Baseline Hgb 7-9g/dL	70%	46%

NKF 2012 Spring Clinical Meetings Abstracts

Am J Kidney Dis. 2012;59(4):A1-A92

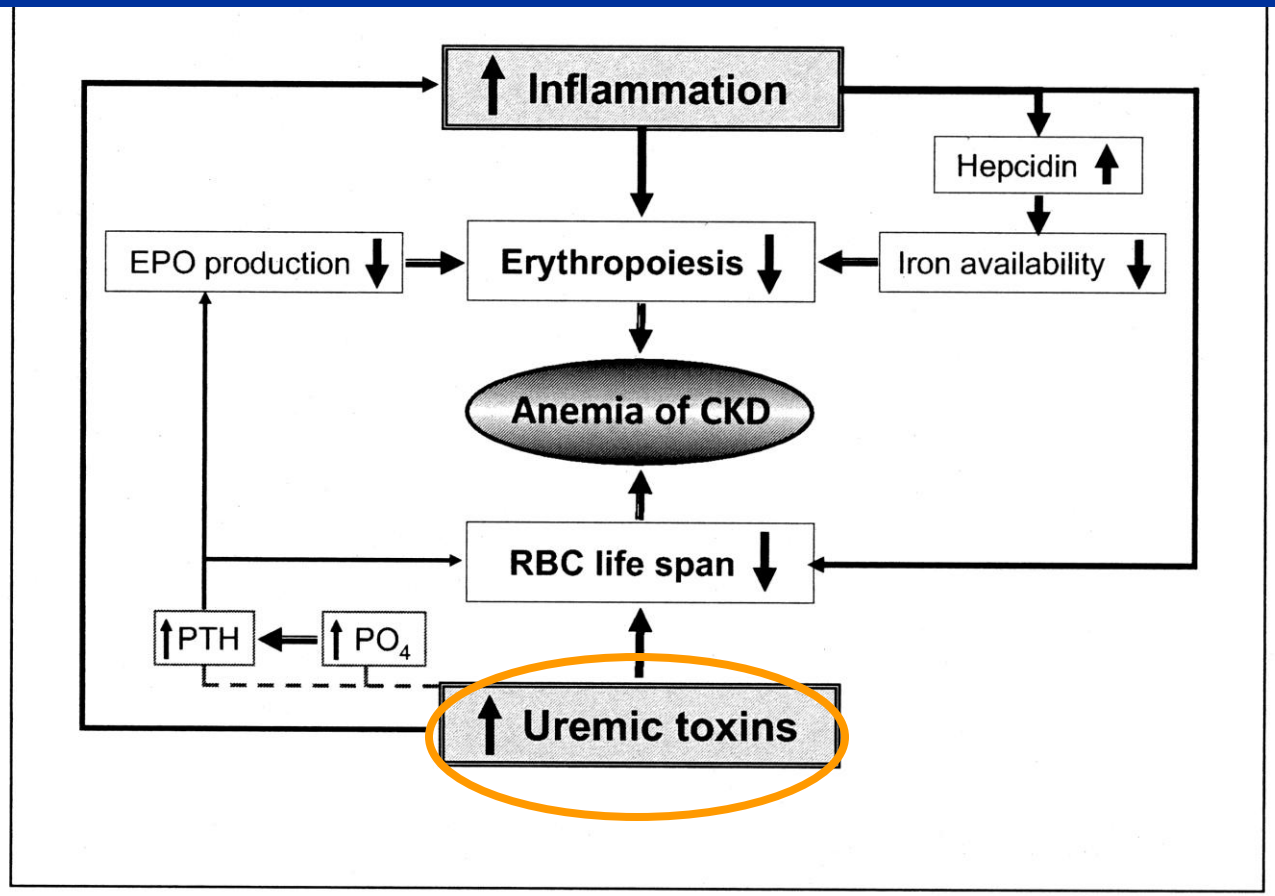


Fig. 1. Uremic toxicity and inflammation both exacerbate anemia of CKD, affecting bone marrow erythropoiesis and erythrocyte survival. Dialysis therapies that curb the effects of both uremic toxins and inflammatory mediators enable anemia correction.

Bowry S. and Gatti E., *Blood Purification*, 2011, **32**, 210-219.

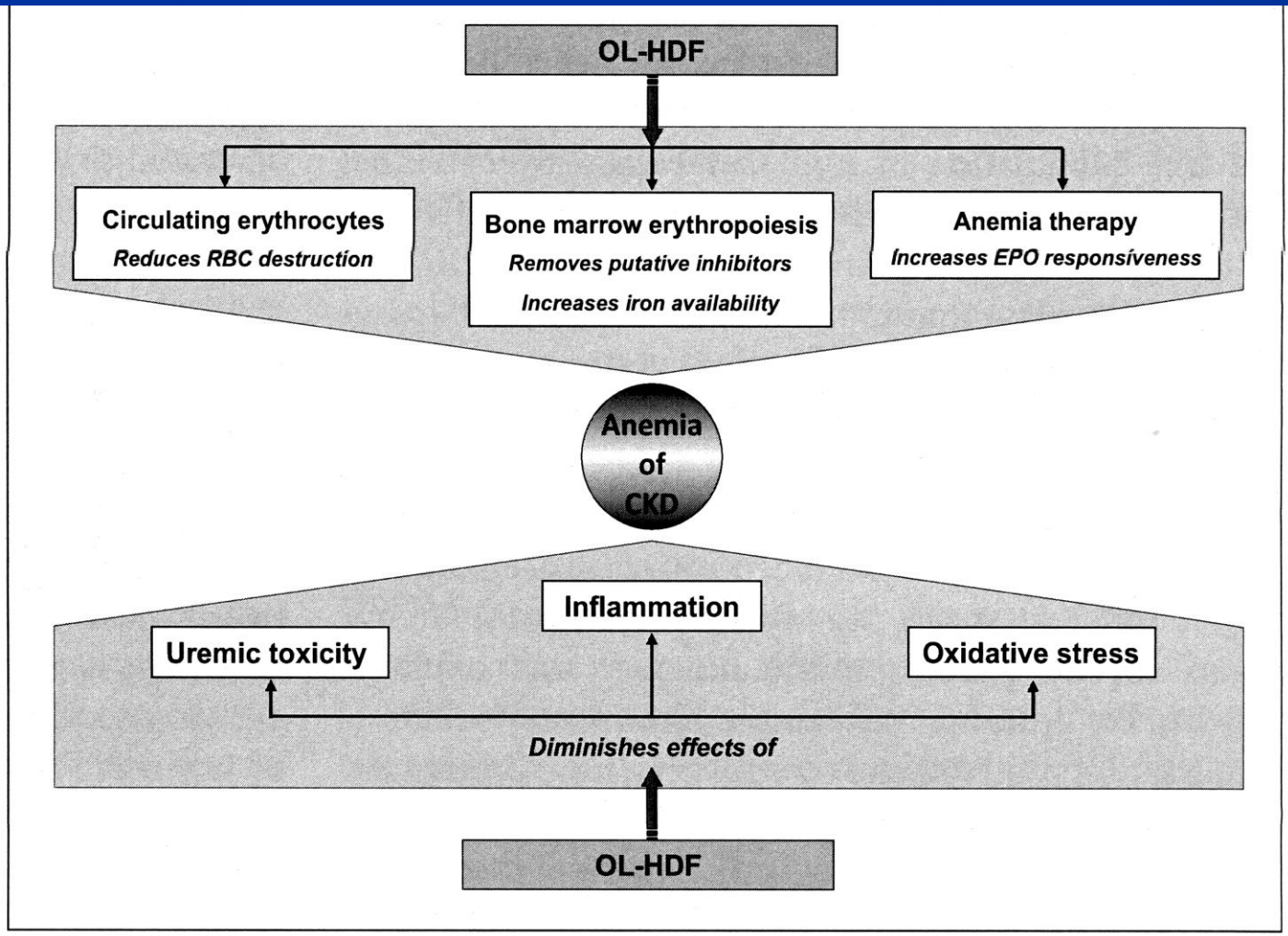


Fig. 2. Mechanisms by which OL-HDF could provide benefits in terms of anemia control. Published data show that OL-HDF favorably impacts anemia of CKD by not only removing putative inhibitors that suppress erythropoiesis, reducing red cell destruction and increasing iron availability, but also by restricting underlying conditions affecting anemia therapy.

Bowry S. and Gatti E., *Blood Purification*, 2011, **32**, 210-219.

Role of Residual Renal Function in Phosphate Control and Anemia Management in Chronic Hemodialysis Patients

E. Lars Penne,† Neelke C. van der Weerd,*† Muriel P.C. Grooteman,†‡ Albert H.A. Mazairac,* Marinus A. van den Dorpel,§ Menso J. Nubé,†‡ Michiel L. Bots,‖ Renée Lévesque,¶ Piet M. ter Wee,†‡ and Peter J. Blankestijn,* on behalf of the CONTRAST investigators*

CJASN 2011; 6

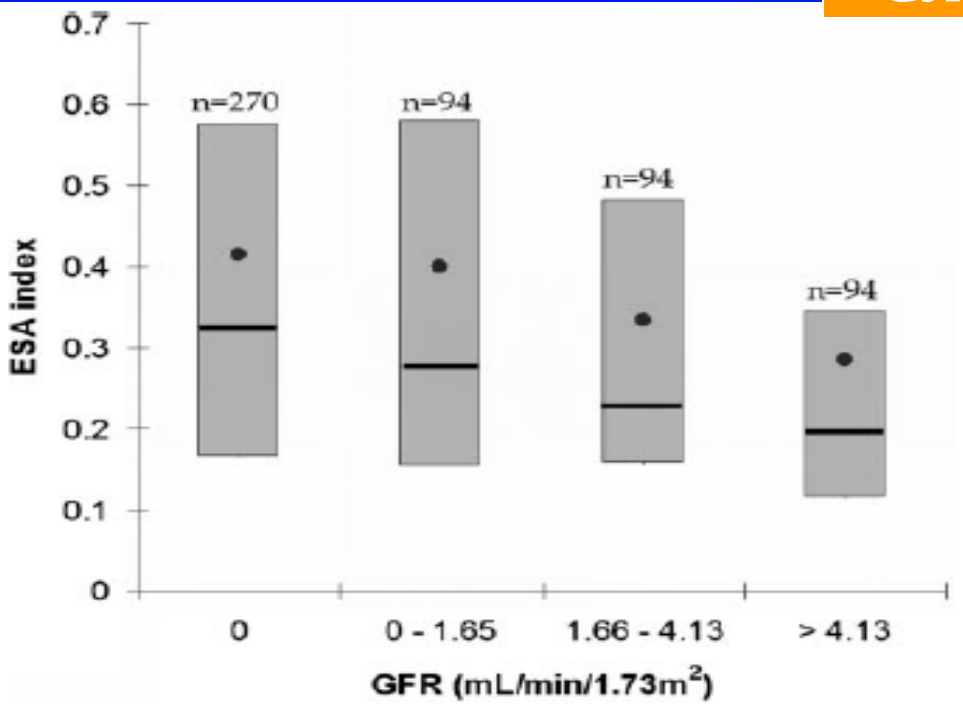


Figure 3. | Relationship between residual renal function and ESA index. Each box shows the distribution of ESA index, defined as the ESA dose per week (in DDD) per kilogram of body weight per percent hematocrit, for the range of RRF as indicated on the horizontal axis. The mean dose for each group is shown by the black circles, the median by the middle horizontal line, and the 25th and 75th percentiles by the bottom and top of the box, respectively. *P* for univariable linear trend = 0.001.

Intravenous Erythropoietin in Patients With ST-Segment Elevation Myocardial Infarction

REVEAL: A Randomized Controlled Trial

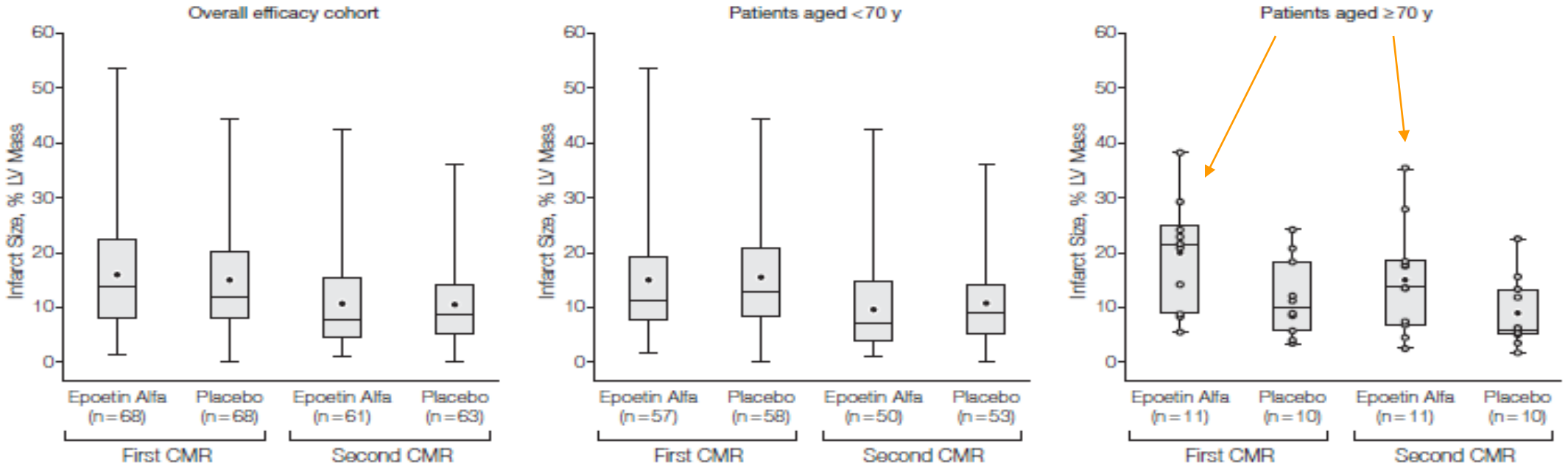
Conclusions In patients with STEMI who had successful reperfusion with primary or rescue PCI, a single intravenous bolus of epoetin alfa within 4 hours of PCI did not reduce infarct size and was associated with higher rates of adverse cardiovascular events. Subgroup analyses raised concerns about an increase in infarct size among older patients.

Trial Registration clinicaltrials.gov Identifier: NCT00378352

JAMA. 2011;305(18):1863-1872 www.jama.com

60000 u IV EPO alpha

Figure 2. Comparison of Infarct Size Between Epoetin Alfa and Placebo Groups



Boxes represent interquartile range, black-filled circles represent means, whiskers represent the minimum and maximum, and horizontal lines represent the median. Individual data points (open circles) are provided for the graph for patients aged 70 years or older due to the low sample sizes. For patients aged 70 years or older, the *P* value is equal to .03 for the comparison of epoetin alfa with placebo for the first cardiac magnetic resonance (CMR) imaging. LV indicates left ventricular.

Single high dose Epoietin bêta after reperfusion in STEMI (Prunier et al Am H J 2012) (EPOMI study)

- 110 patients
- 1000 u/Kg IV EPOETIN beta immediately after reperfusion
- Cardiac magnetic resonance
- Transient favorable effects on LV volume (at 5d)
- No reduction in infact size at 3 months

EPO: Good or Bad for Cancer?

- EPO binds its receptor EPO R surface of RBC progenitors in the bone marrow.
- EPO binds EPO R expressed on the surface of cancer cells and may elicit tumor growth.

- Moreover, increase risk of venous thromboembolism (Bennett et al JAMA 2008)

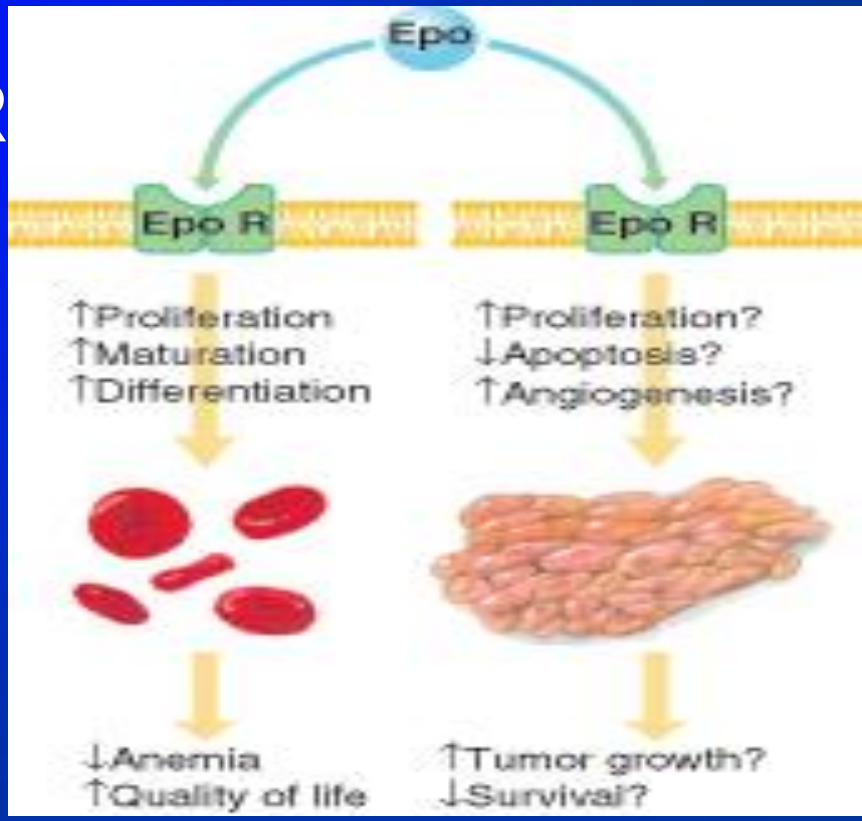


Fig: Brower Nat Med 2003

ESA and cancer risk?

- **2009: (Cochrane database syst rev)** ESA treatment in cancer patients increased on study mortality and worsened overall survival.
- This was less pronounced for patients undergoing chemotherapy.
- There is also a risk for venous thromboembolic events, particularly when ESA are used off label.
- **2012: (Br J Cancer)** ESAs may have little effect on disease progression in chemotherapy patients. Preclinical data indicate an effect of ESAs on tumour growth is not strongly supported.
- **KI 2011**: higher risk of stroke in cancer patients treated by ESA

Biosimilar Epoetins in Nephrology – Where are We Now?

David Goldsmith[1] and Loreto Gesualdo[2]

European Nephrology, 2012;6(1):21–4

Table 1: Biosimilar Epoetins Currently Approved by the European Medicines Agency

Biosimilar	INN	Brand Name	Marketing Authorisation Holder
SB309	Epoetin zeta	Retacrit®	Hospira
		Silapo®	STADA
HX575	Epoetin alfa	Binocrit®	Sandoz
		Epoetin alfa HEXAL®	Hexal
		Abseamed®	Medice Arzneimittel

INN = international non-proprietary name.

Table 2: Biosimilar Share (by Value) of the Short-acting Erythropoiesis-stimulating Agent Market in the EU G5 Countries

Country	Market Share of Biosimilar ESAs
France	7 %
Germany	52 %
Italy	8 %
Spain	14 %
UK	4 %

ESA = erythropoiesis-stimulating agent. Source: IMS, 2011.[3]

Table 2. Future Erythropoiesis-Stimulating Agents

Agent	Active Compound	Manufacturing Process	Stage of Development
Peginesatide (Hematide)	Dimeric pegylated peptide	Synthetic peptide chemistry	Completed Phase 3
HIF stabilizers	Prolyl hydroxylase inhibitor	Chemical synthesis	Phase 1-2
Hepcidin modulation	Various	Various	Planning phase 1
GATA-2 inhibitors	Small molecule	Chemical synthesis	??
EPO gene therapy (EPODURE)	Skin cells (microdermis) transfected with the *EPO* gene	Biopump technology, harvesting skin biopsies and using adenovirus as vector	Phase 2

Abbreviations: EPO, erythropoietin; GATA-2, GATA-binding protein 2; HIF, hypoxia inducible factor.

Peginesatide:* A Novel ESA

- Synthetic, peptide-based ESA; molecular structure unrelated to erythropoietin
- Half life: 60-70 hours IV or subcutaneous

End of March 2012

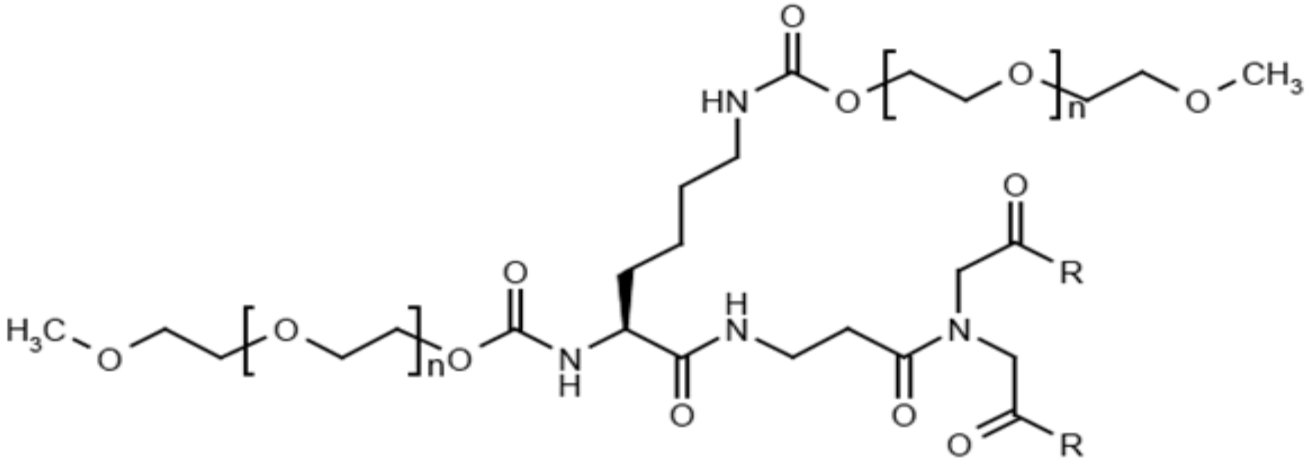
*The FDA has just approved this medication for use.

Del Vecchio L, et al. *Curr Opin Investig Drugs*. 2010;11:1030-1038.

Peginesatide*: Molecular Structure

- Binds to erythropoietin receptor and activated like erythropoietin
- Once-monthly dosing

IV or SC



End March 2012

*The FDA has just approved this medication for use.

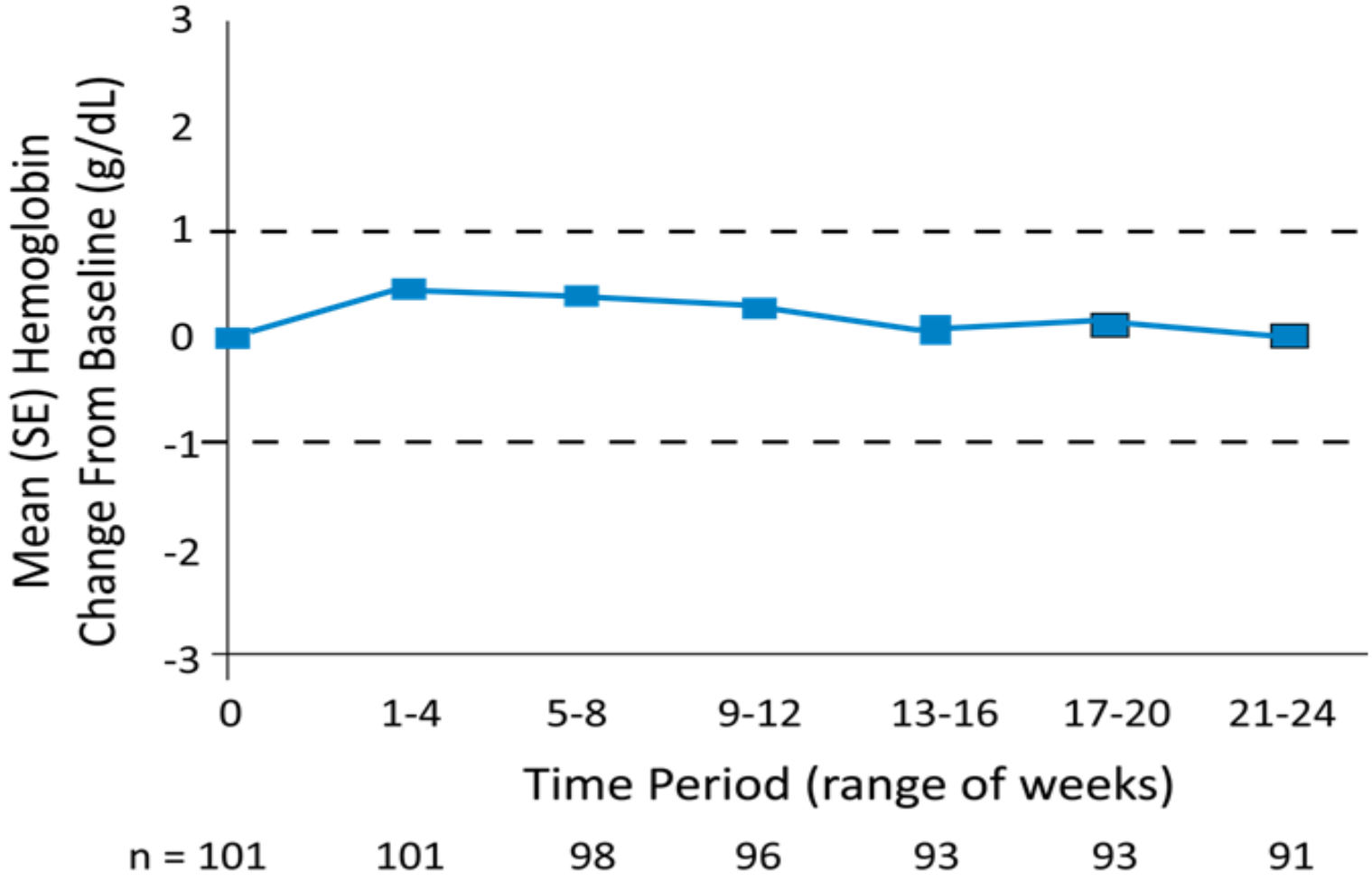
From Del Vecchio L, Cavalli A, Tucci B, et al. Chronic kidney disease-associated anemia: new remedies. *Curr Opin Investig Drugs*. 2010;11:1030-1038. Republished with permission.

Phase 2 Study of the Safety and Effectiveness of Hematide™/Peginesatide for the Maintenance Treatment of Anemia in Patients Who Were Previously Treated With DA

- Objective: To demonstrate that once-monthly peginesatide can maintain Hgb levels in patients after conversion from DA

Fishbane S, et al. ASN Renal Week 2010. Poster F-FC271.

Phase 2 Study of the Safety and Effectiveness of Hematide™/Peginesatide for the Maintenance Treatment of Anemia in Patients Who Were Previously Treated With DA (cont)



Fishbane S, et al. ASN Renal Week 2010. Poster F-FC271.

Table 3. Peginesatide Phase 3 Clinical Trials Overview

Study	Description	Sample Size (region)	Outcomes
PEARL 1	Correction study: peginesatide vs darbepoetin alfa in nondialysis patients (SC)	~330 vs 165 (US)	Efficacy of peginesatide noninferior to darbepoetin; increased HR for composite safety end point at 1.32 for peginesatide vs darbepoetin alfa
PEARL 2	Correction study: peginesatide vs darbepoetin alfa in nondialysis patients (SC)	~330 vs 165 (US and Europe)	
EMERALD 1	Maintenance study: peginesatide vs epoetin alfa in dialysis patients (IV)	~540 vs 270 (US)	Efficacy and safety of peginesatide noninferior to epoetin
EMERALD 2	Maintenance study: peginesatide vs epoetin alfa or beta in dialysis patients (IV/SC)	~540 vs 270 (US and Europe)	

Abbreviations: EMERALD, Hematide Injection for Anemia in Chronic Hemodialysis Patients; HR, hazard ratio; IV, intravenous; PEARL, Safety and Efficacy of Hematide for the Correction of Anemia in Patients With Chronic Renal Failure; SC, subcutaneous; US, United States.

Transfusion, CV events, mortality

Pure Red Cell Aplasia and Antibodies

- Peginesatide has been used in erythropoietin antibody-mediated pure red cell aplasia[a]
- "Biosimilar" erythropoietins and pure red blood cell aplasia[b,c]
- Antibodies to peginesatide* seen in clinical trials but rare occurrence; do not cross react with erythropoietin molecule[d,e]

*The FDA has not approved this medication for use.

a. Macdougall IC, et al. *N Engl J Med*. 2009;361:1848-1855.
b. Locatelli F, et al. *Oncologist*. 2009;14:16-21.
c. Wish JB. *Kidney Int*. 2011;80:11-13.
d. Macdougall IC, et al. *Clin J Am Soc Nephrol*. 2011;6:2579-2586.
e. Locatelli F, et al. *Expert Rev Heamtol*. 2009;2:377-383.

HIF stabilizers

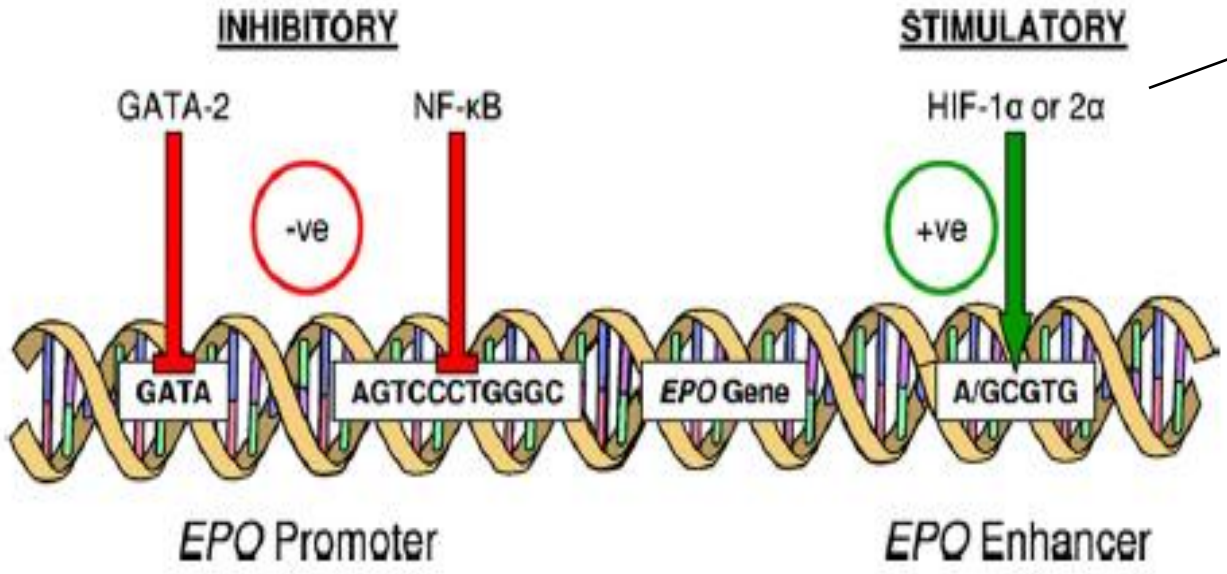


Figure 2. Regulation of *EPO* (erythropoietin) gene expression, showing transcriptional factors that suppress the *EPO* promoter or activate the *EPO* enhancer. Abbreviations: -ve, negative; +ve, positive; HIF, hypoxia inducible factor; NF-κB, nuclear factor κB.

The Role of HIF, a Transcription Factor in Anemia

- HIF: key regulator of erythropoietin (and other) gene transcription
- HIF is rapidly degraded in absence of hypoxia by prolyl hydroxylase, which "senses" oxygen; erythropoietin synthesis is reduced
- With hypoxia, prolyl hydroxylase enzymes are inhibited and HIF stabilized, leading to erythropoietin gene transcription

HIF = hypoxia-inducible factor

Muchnik E, Kaplan J. *Expert Opin Investig Drugs*. 2011;20:645-656.

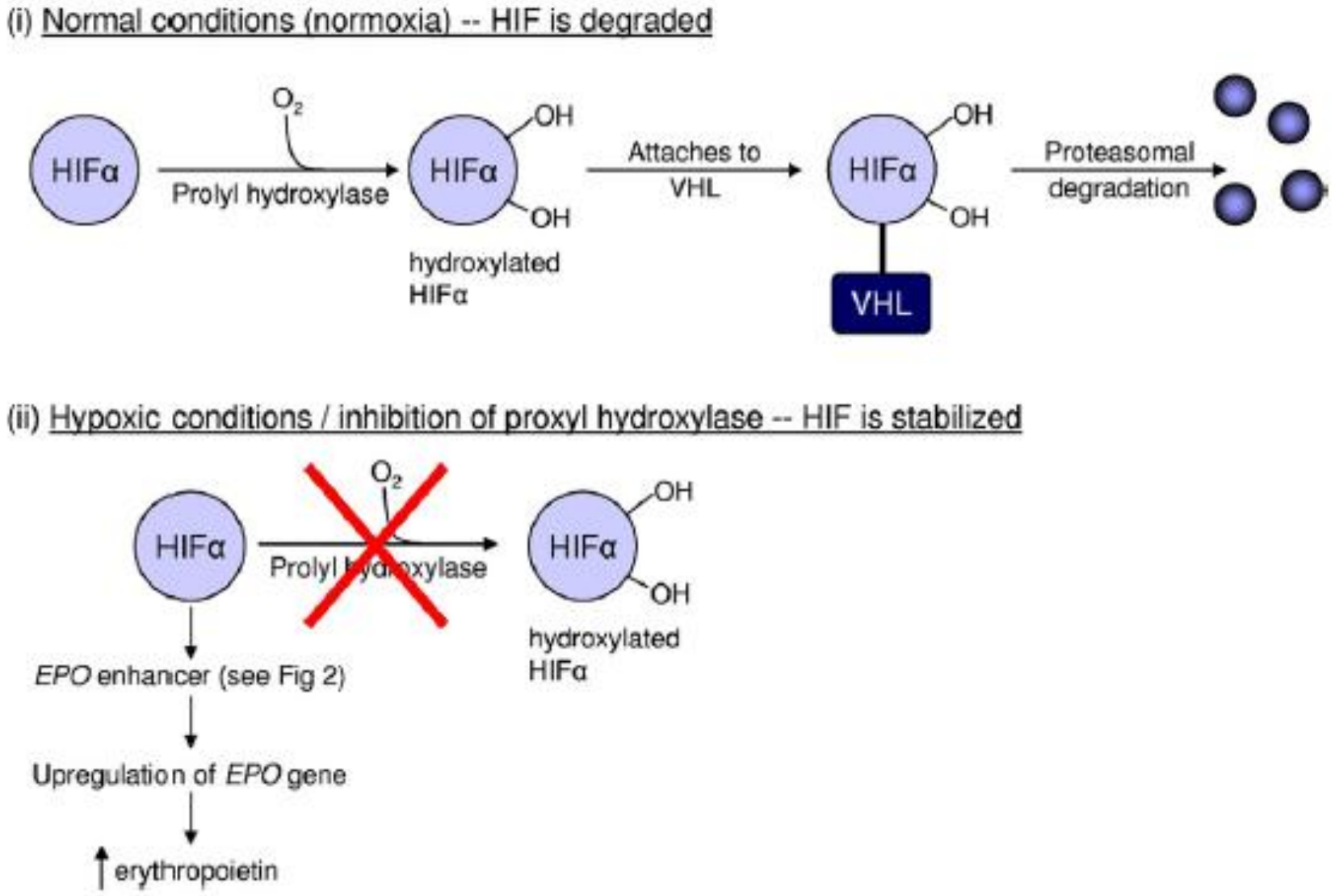


Figure 3. Regulation of hypoxia inducible factor (HIF) activity. Abbreviations: EPO, erythropoietin; VHL, von Hippel Lindau protein.

Clinical Trials: FG-4592*

- HIF down-regulates hepcidin synthesis resulting in improved iron absorption and utilization of iron stores. Potential role in patients with inflammation (eg, anemia of chronic disease); reduce need for supplemental iron
- HIF and related gene regulation pathways are systemic
- Phase 2b agent

*The FDA has not approved this medication for use.

Besarab A, et al. ASN Kidney Week 2011. Abstract TH-PO364.

FG-4592, a Novel Oral HIF PHI, Elevates Hgb Level in Patients With Anemia and Stage 3/4 CKD

- Objective: randomized, single-blind, placebo-controlled phase 2 study; 117 subjects randomly assigned (88 to FG-4592 and 28 to placebo) in 4 dose cohorts

Mean ± Standard Deviation Maximal ΔHgb g/dL (%Hgb Responders)

Cohort	2x/wk [N]	3x/wk [N]
0.7 mg/kg	0.90.8 (33) [9]	1.00.9 (62) [13]
1.0 mg/kg	0.90.8 (60) [5]	1.00.9 (60) [5]
1.5 mg/kg	1.71.0 (80) [10]	2.00.9 (91) [11]
2.0 mg/kg	1.90.6 (100) [9]	2.20.8 (100) [11]
Placebo	0.40.5 (8) [24]	

Besarab A. ASN Renal Week 2010. Poster SA-FC416.

FG-4592, a Novel Oral HIF PHI, Elevates Hgb Level in Patients With Anemia and Stage 3/4 CKD (cont)

- Results:
  - Median time to Hgb response was 22-43 days for the 2x/wk group and 15-22 days for the 3x/wk group and was generally faster than observed with ESA
  - FG-4592 administered for 4 weeks was well tolerated and led to dose-dependent Hgb correction with observed peak estimated EPO levels 1-2 orders of magnitude lower than values reported for ESA
  - No significant blood pressure change was observed across cohorts despite the rapid rate of Hgb rise with higher doses
  - No reports of thrombosis, sustained liver enzyme abnormality, or study drug-related serious adverse events
- Conclusions:
  - Data demonstrate a potentially unique mechanism of action permitting safer Hgb increase and maintenance and avoiding thrombotic or hypertensive responses commonly observed with ESA

Besarab A. ASN Renal Week 2010. Poster SA-FC416.

HIF Stabilizers*

- Experimental oral inhibitors of prolyl hydroxylase[a]
- Stabilize HIF independently of oxygen availability[a]
- Increase endogenous erythropoietin production in ESRD patients, even if anephric[b]

So, in CKD, there is a problem of abnormal oxygen sensing

*The FDA has not approved these medications for use.

a. Muchnik E, Kaplan J. *Expert Opin Investig Drugs*. 2011;20:645-656.
b. Bernhardt WM, et al. *J Am Soc Nephrol*. 2010;21:2151-2156.

Conclusions

- Partial correction (Hb in the range of 10-11.5 g/dL) of CKD-related anemia appears a safer strategy during the last 5y. So recommendation is to start ESA only when Hb <10 and to avoid too high ESA dose (CE DOSE study ongoing in HD)!
- Identify resistant patients and try to improve it.
- Importance of adequate iron management and of hepcidin role in the all-mortality risk in CKD.
- Newer strategies for correcting anemia are currently explored.

KDIGO CLINICAL PRACTICE GUIDELINE FOR ANEMIA IN CKD

CONFIDENTIAL: DO NOT DISTRIBUTE

KDIGO Public Review Draft
September 2011