



# The 18th Budapest Nephrology School (Nephrology, Hypertension, Dialysis, Transplantation)

26-31 August 2011



## Update on renal anemia

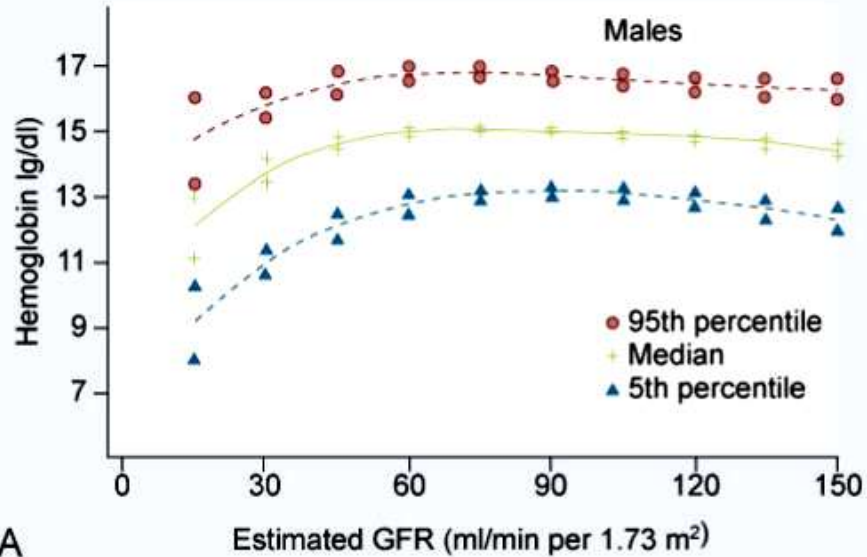
**Prof. Andrzej Więcek**

Department of Nephrology, Endocrinology and Metabolic Diseases

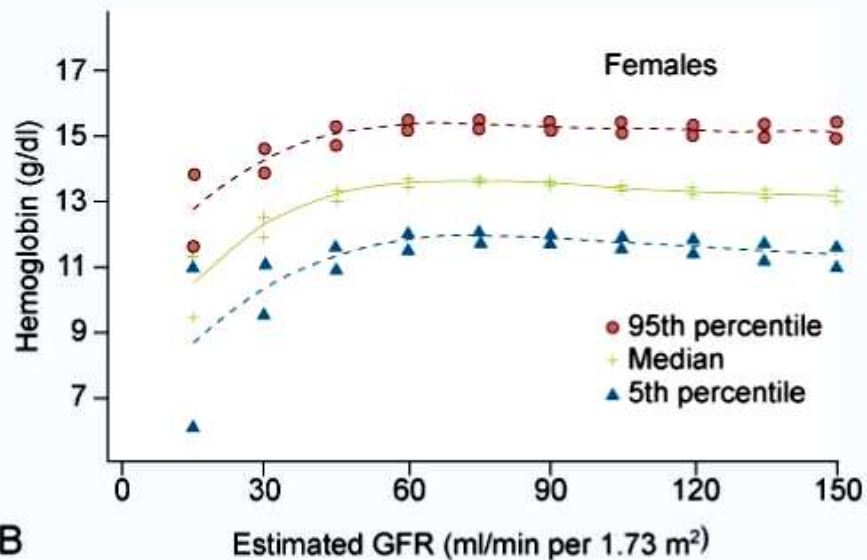
Medical University of Silesia, Katowice, Poland

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# Relationship Between Hb and Estimated GFR



A



B

McClellan et al., Curr. Med. Res. Opin.  
2004, 20, 501-510

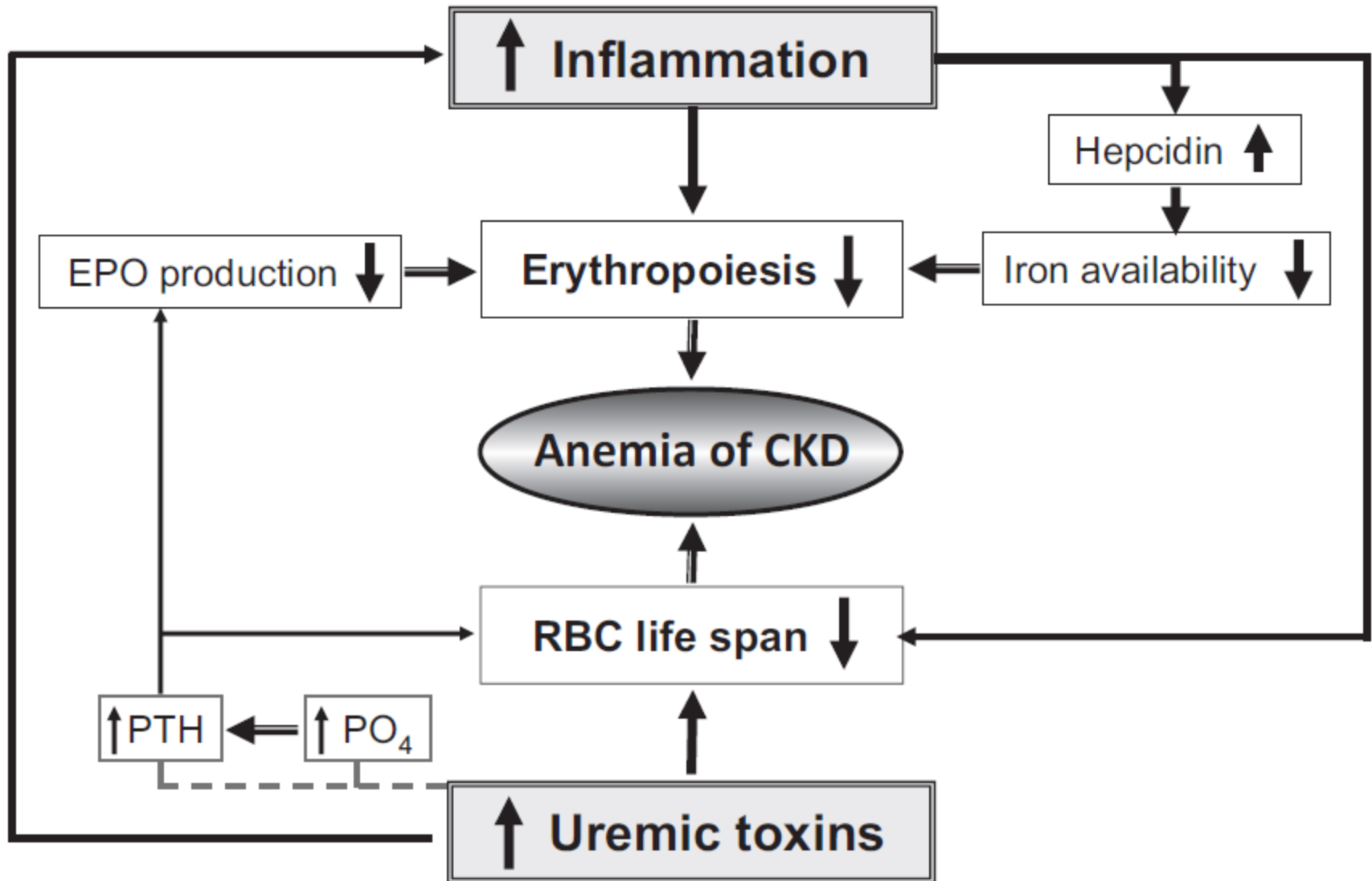
# Causes of anemia secondary to chronic kidney disease

- ❖ Decreased red cell survival
  - External blood loss
  - Decreased red cell survival within the circulation
- ❖ Decreased bone marrow stimulation
  - Decreased (inadequate) erythropoietin production by failure kidneys
- ❖ Decreased bone marrow response

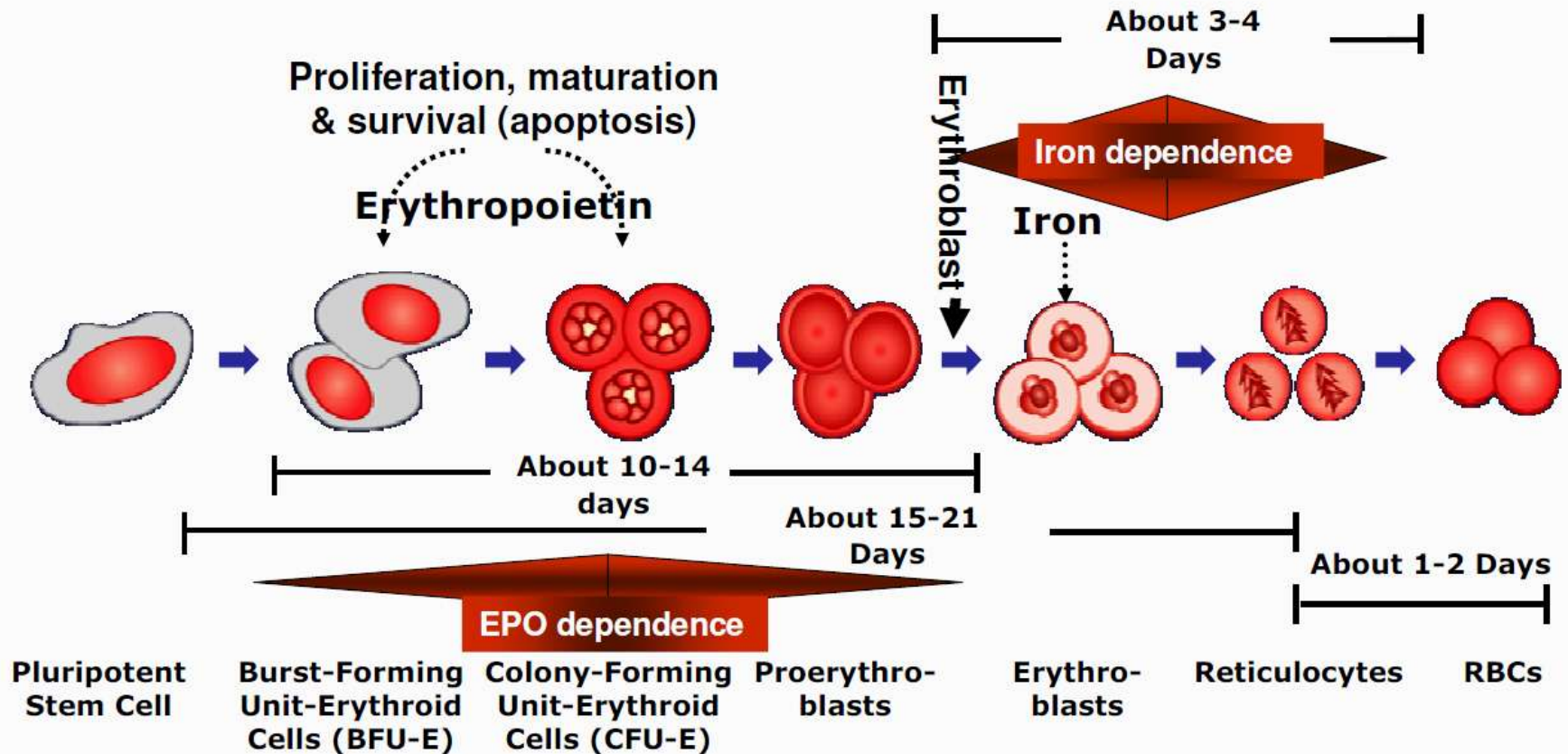
# Decreased bone marrow response to EPO stimulation in CKD patients

- ❖ uraemic inhibitors („middle molecules“, polyamines, PTH, ribonuclease)
- ❖ iron deficiency
- ❖ inflammatory iron block (sepsis, inflammatory diseases, surgery and trauma- proinflammatory cytokines, hepcidine)
- ❖ aluminium excess/intoxication
- ❖ folate deficiency
- ❖ severe secondary hyperparathyroidism (osteitis fibrosa leads to decrease mass of erythropoietic marrow or myelofibrosis)
- ❖ physical inactivity

# Uremic toxicity and inflammation both exacerbate anemia of CKD



# Erythropoiesis – role of erythropoietin and iron

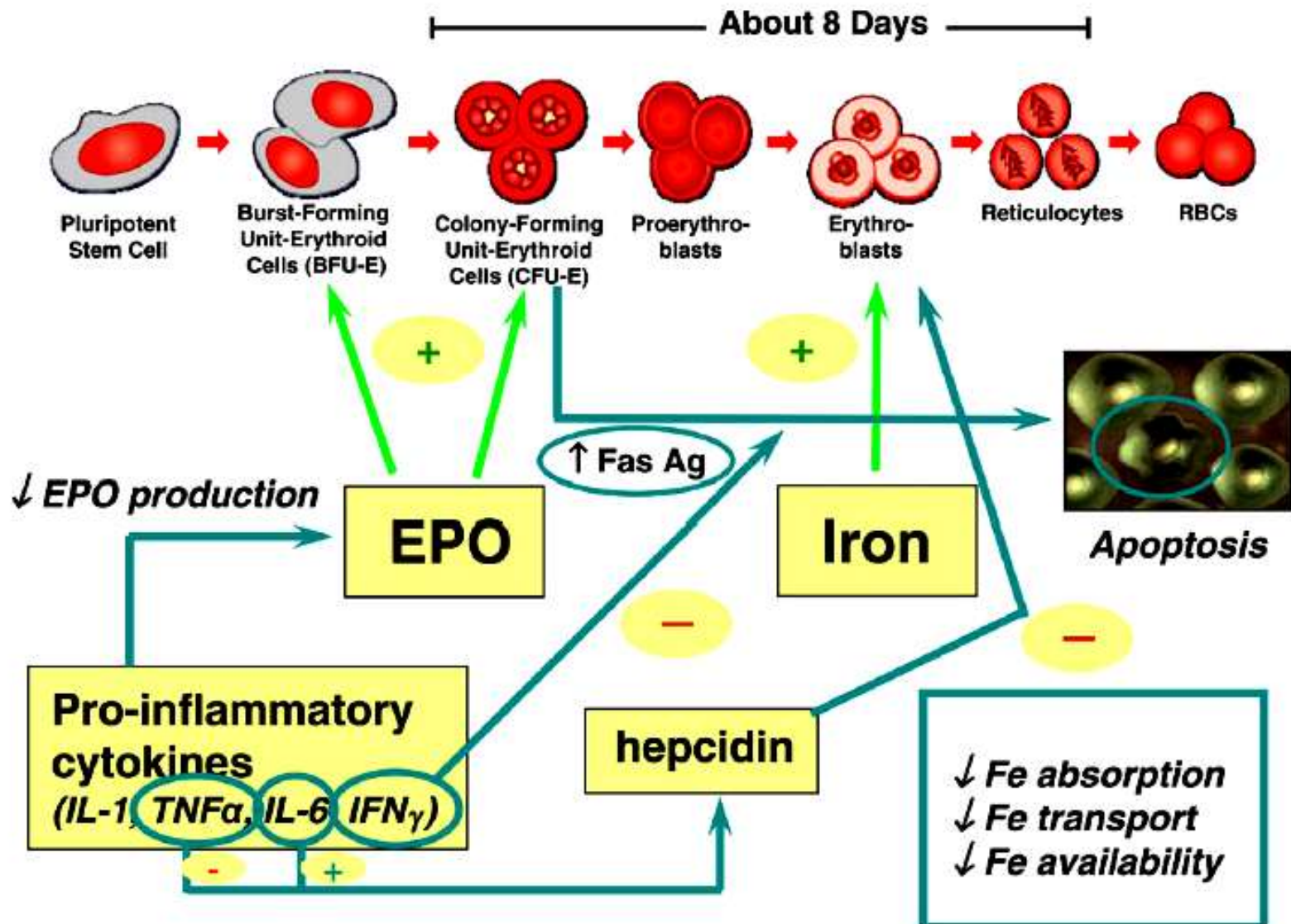


Hillman RS, et al. Red Cell Manual, 7th ed. Philadelphia, PA: F.A. Davis Company;1996:chap 1.

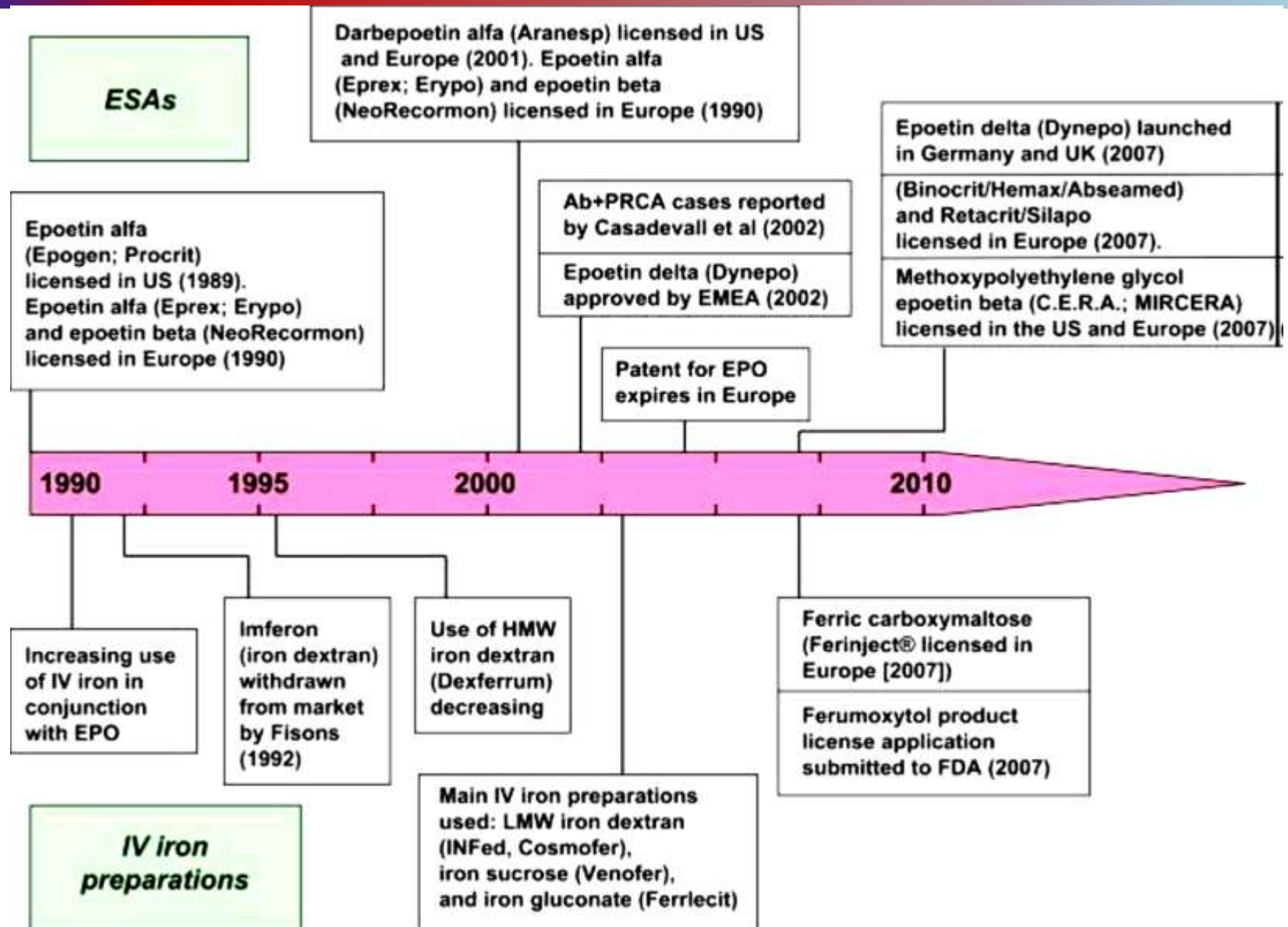
Papayannopoulou T, et al. In: Hoffman R, et al. eds. Hematology: Basic Principles and Practice, 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone;2005:chap 20.

Brock. Iron Metabolism in Health and Disease. W.B. Saunders Co; 1994

# Erythropoiesis in chronic kidney disease



# The development of ESAs and IV iron preparations over the last 20 years



# Anemia treatment in CKD patients



# What we know about anemia treatment in CKD

- ❖ Generally well tolerated
- ❖ Treatment reduces need for blood transfusions
- ❖ Probably improves patients' quality of life
  - Relationships for most subscales particularly vitality, exercise capacity is sigmoid
    - ✓ Major increases occur between 7 to 9-10 g/dl Hb
    - ✓ Effects of Hb levels off at 9-11 g/dL Hb
    - ✓ In most studies no added benefit at higher Hb except for “vitality” or “fatigue” that are measurable up to 13 g/dl

# Safety of anemia treatment

- ❖ Studies of higher Hb targets (NHCT, CCT CREATE, CHOIR, TREAT)
  - Increased cardiovascular risk
  - Increased thrombotic risk
  - Possible effect on cancer
  - Possible increased death risk
- ❖ Etiology of risk unclear
  - Relative/absolute iron deficiency increases platelet counts and makes platelets more reactive
  - High ESA dose may release endothelin 1
  - High dose ESA may produce “non bone marrow” effects in other tissues (vessels, heart)

# Dominant use of ESA treatment without adequate iron

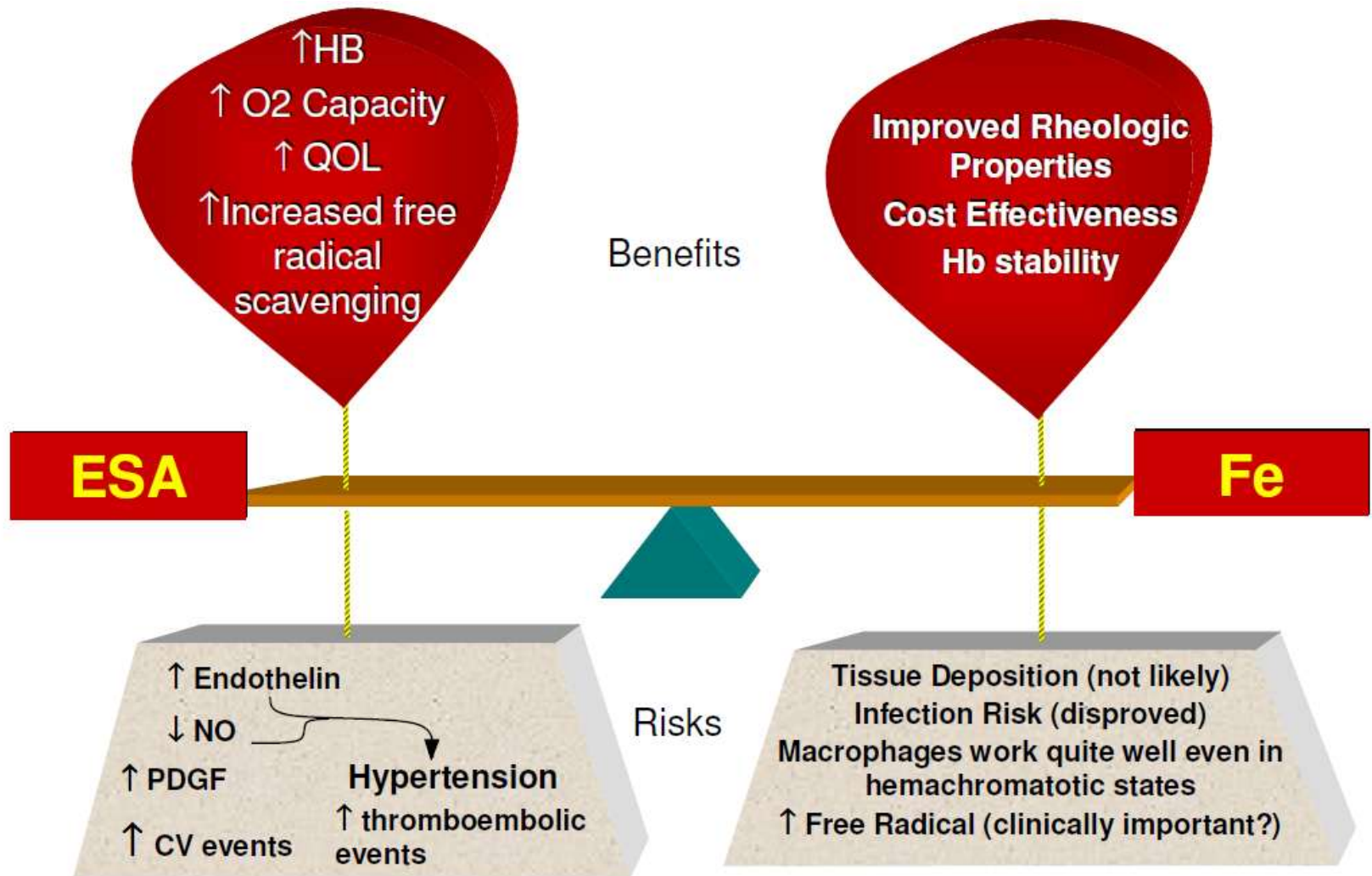
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- ❖ In studies of higher Hb targets with inadequate provision of iron, overt or functional iron deficiency may have contributed to
  - Increased cardiovascular risk
  - Increased thrombotic risk
- ❖ Iron steps forward into the sunshine

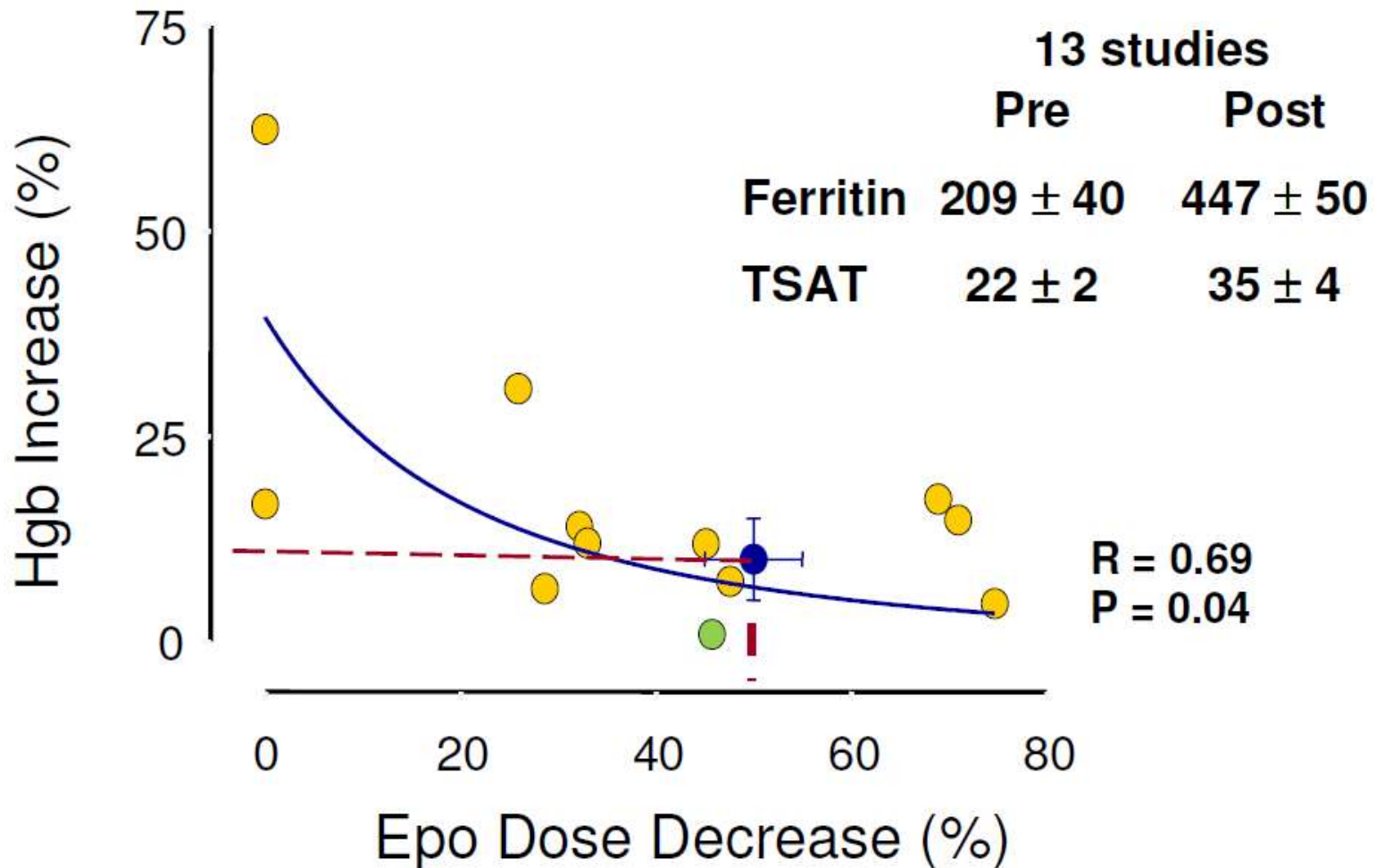
# Why is there a need for new approaches to iron ?

- ❖ Failure to achieve optimal benefits
- ❖ High cost of ESAs
- ❖ Need to reduce Hb variation
  - Maybe be influenced by the pharmacokinetic duration of action of the ESA
  - Coordinating the sequential steps of erythrocyte production; Avoidance of functional iron deficiency
- ❖ Overcoming fear of iron overload
  - Decreased as we have increased maintenance levels
  - Ferritins now commonly average 600 ng/mL as opposed to 300-400 a decade ago
  - Where is the limit?

# Clinical Dilemma: Balancing the roles of ESAs and iron

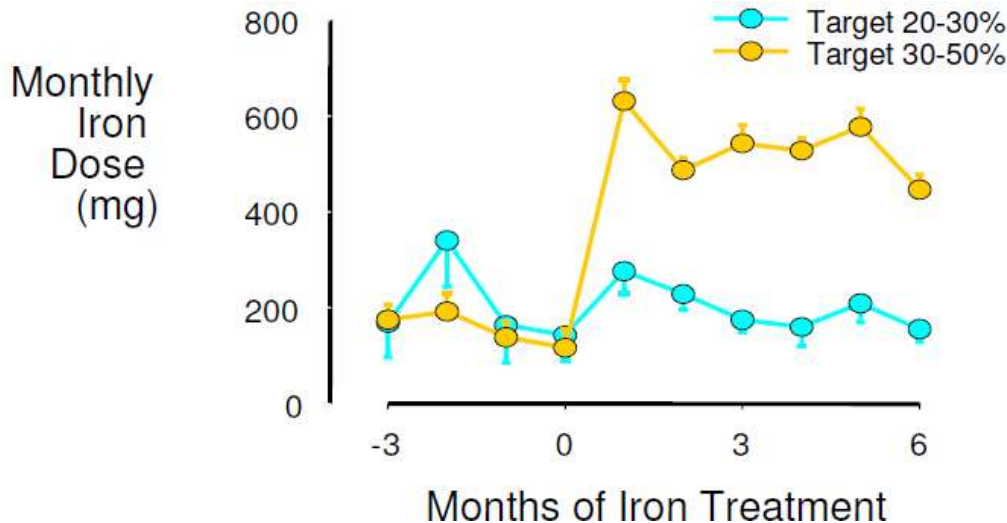
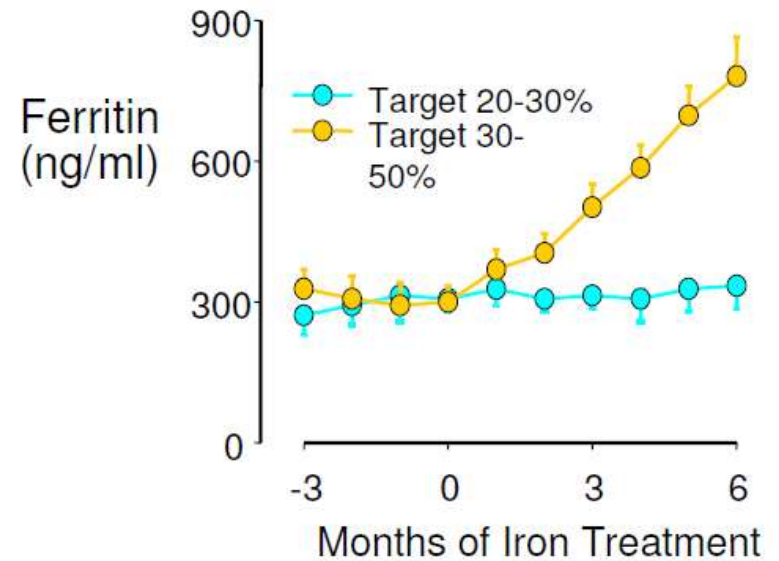
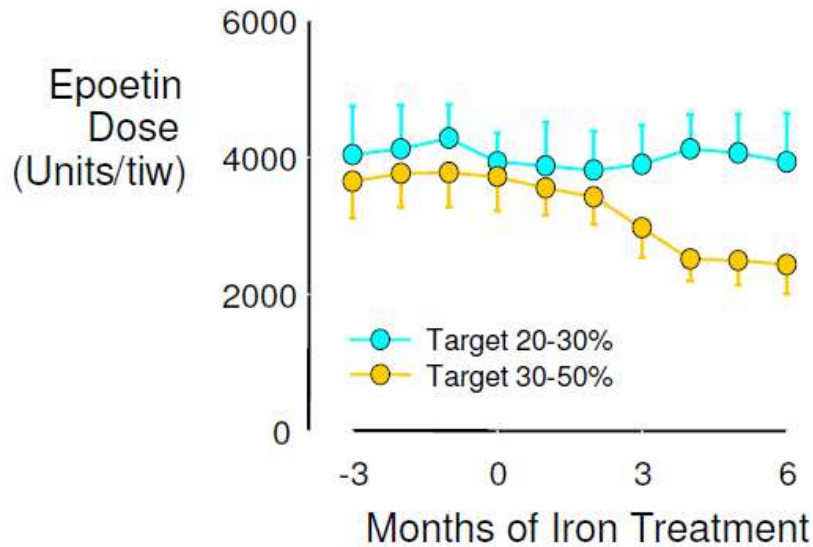


# Maintenance iron efficacy: potential for dose reduction of ESA



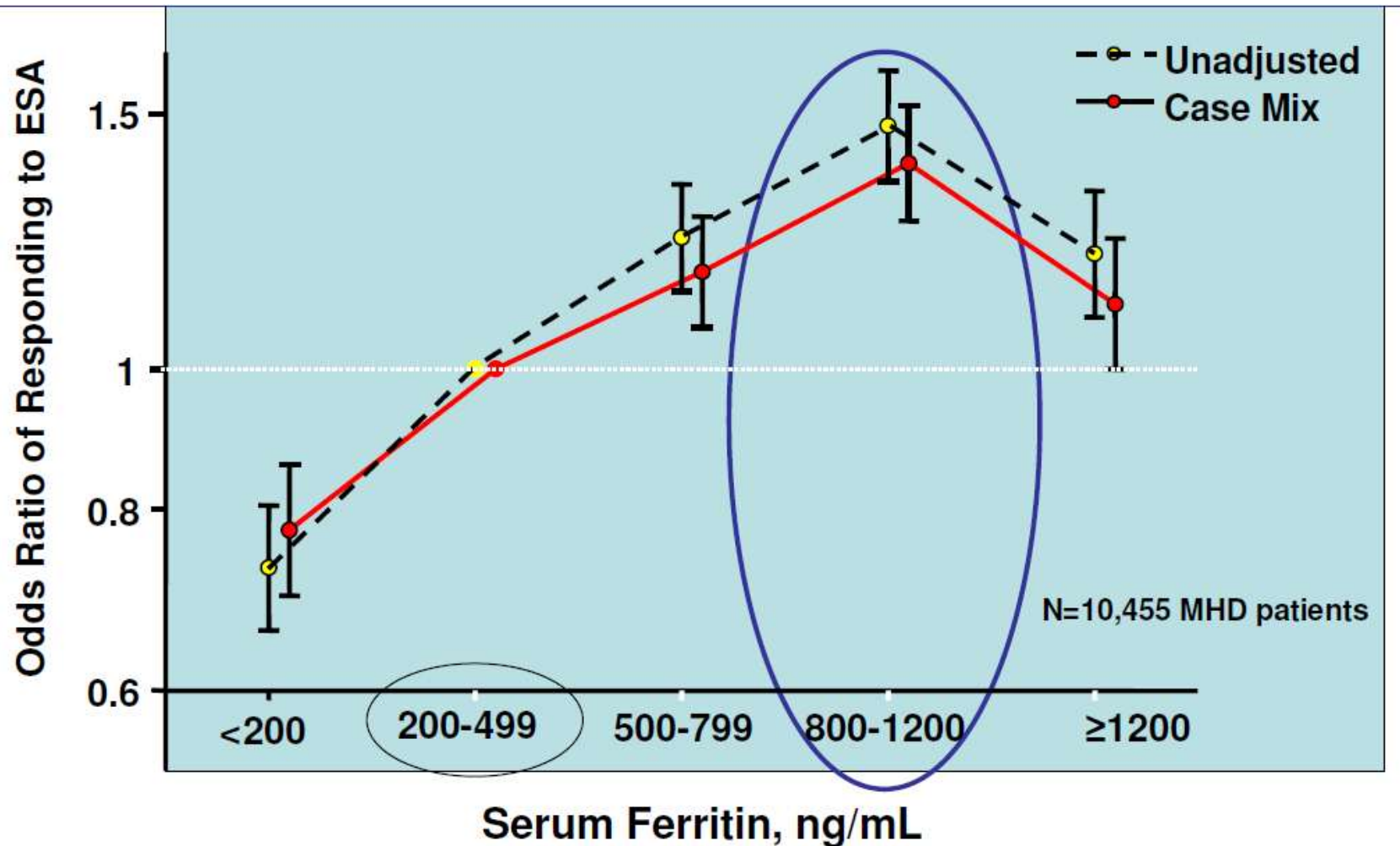
Source: Each point is a separate citation

# Effects of TSAT 30-50% vs 20-30% by continual maintenance iron

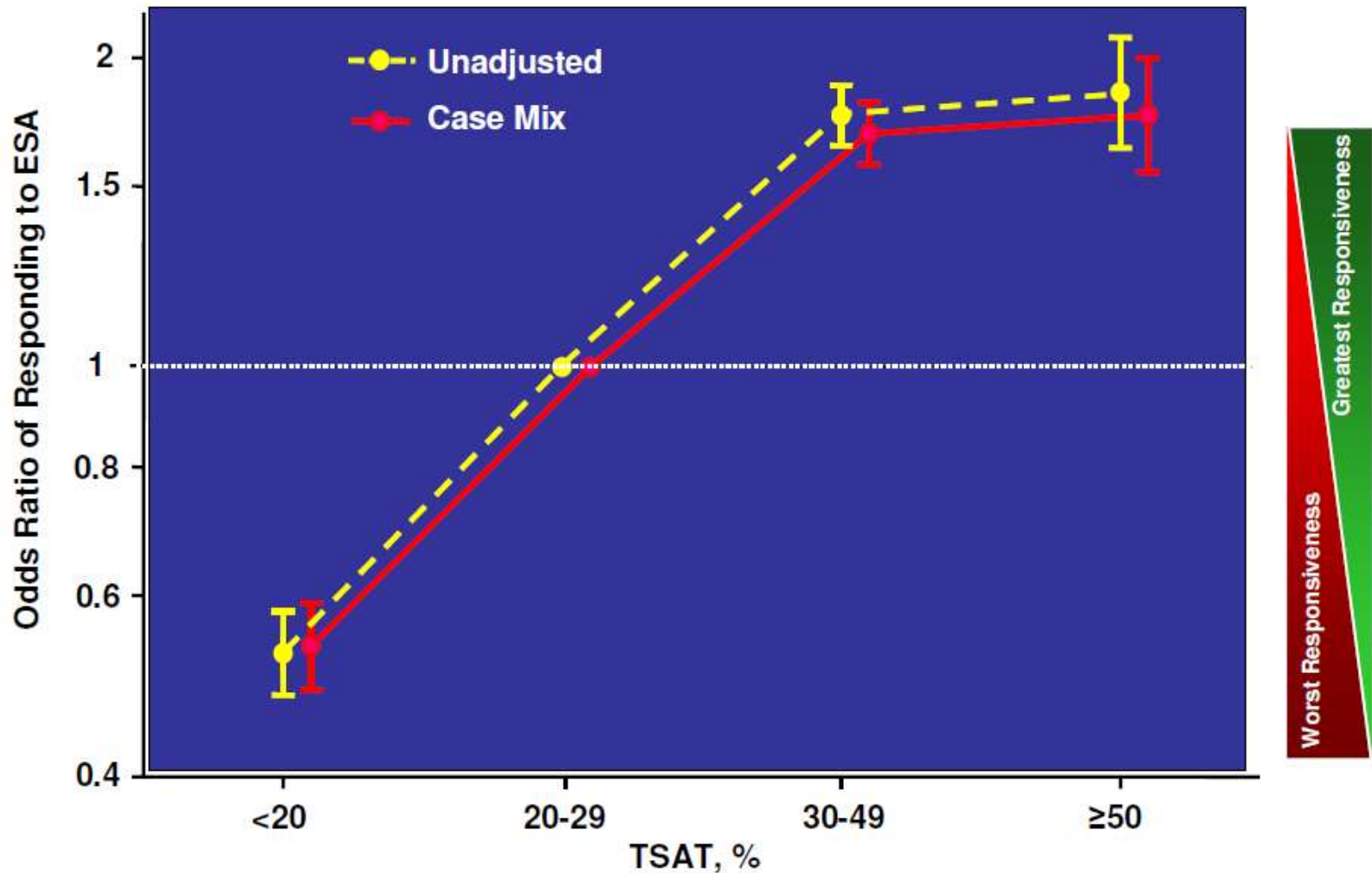


In long term studies, the additional amount of iron is only 30 mg/month<sup>250</sup> vs 220 mg/mo

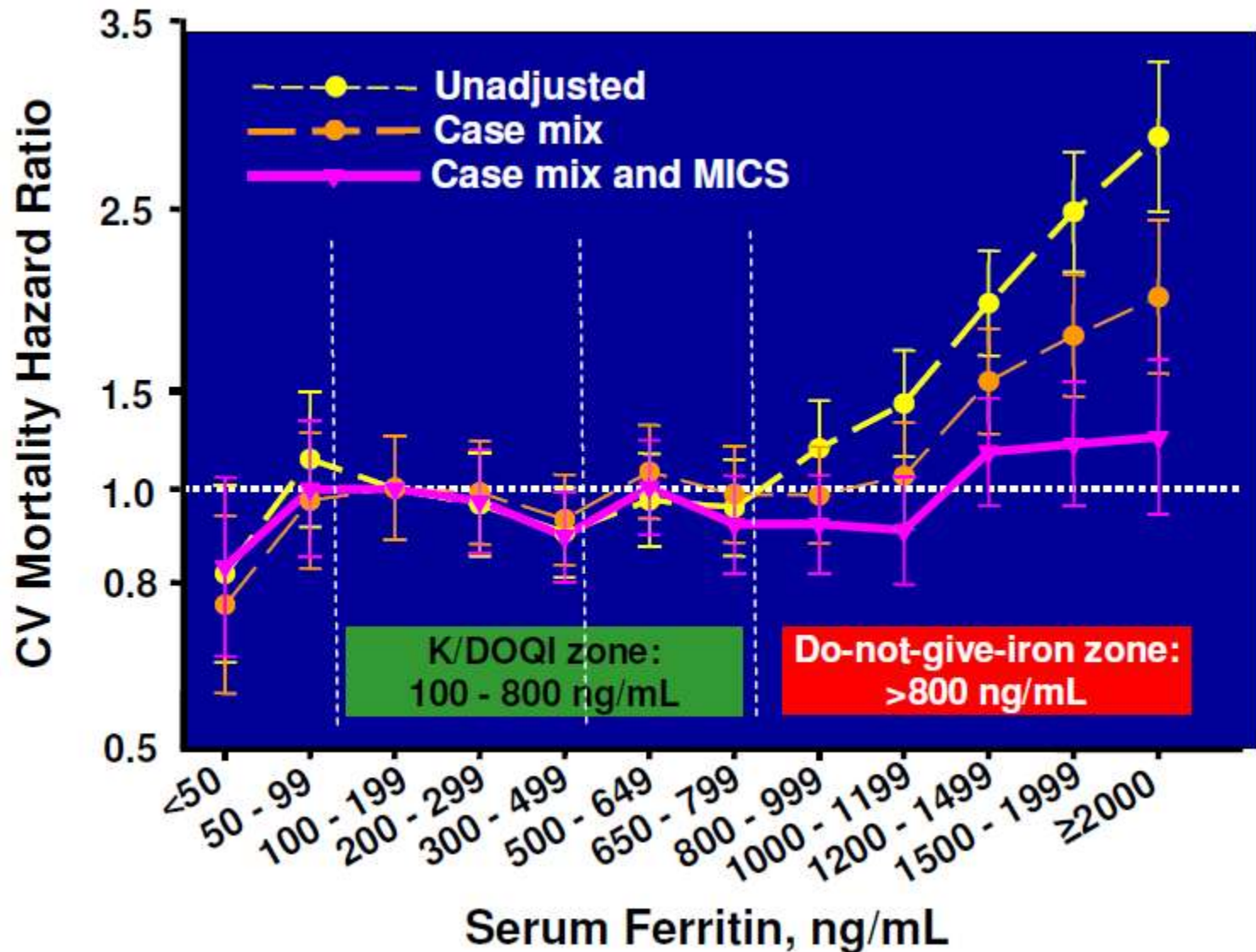
# Serum ferritin and Odds Ratio of responding to ESA



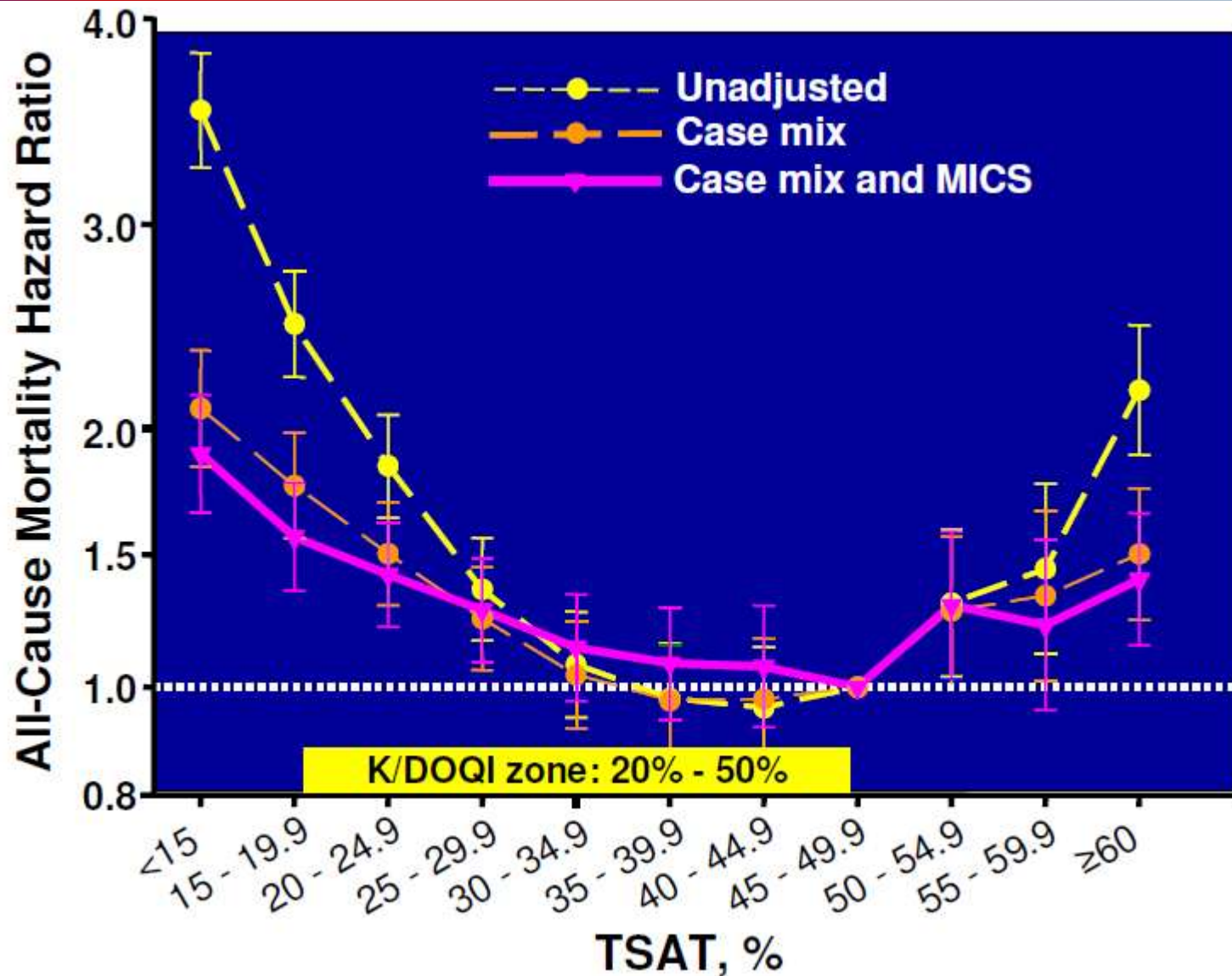
# Greatest ESA response was observed with TSAT >30%



# Risk of death by serum ferritin level (time-dependent Cox model)



# Risk of death by TSAT (time-dependent Cox model)



## TSAT and serum ferritin – ESA response

- ❖ TSAT <20% was associated with almost 50% lower ESA responsiveness ( $P<.0001$ )
  - Unadjusted OR: 0.53 (95% CI, 0.48-0.58)
  - Adjusted OR: 0.54 (95% CI, 0.49-0.59)
- ❖ Serum ferritin <200 ng/mL was associated with 23% lower ESA responsiveness
  - Adjusted OR: 0.77 (95% CI, 0.70-0.86);  $P<.0001$

# New perspective of iron treatment

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## ❖ Parenteral

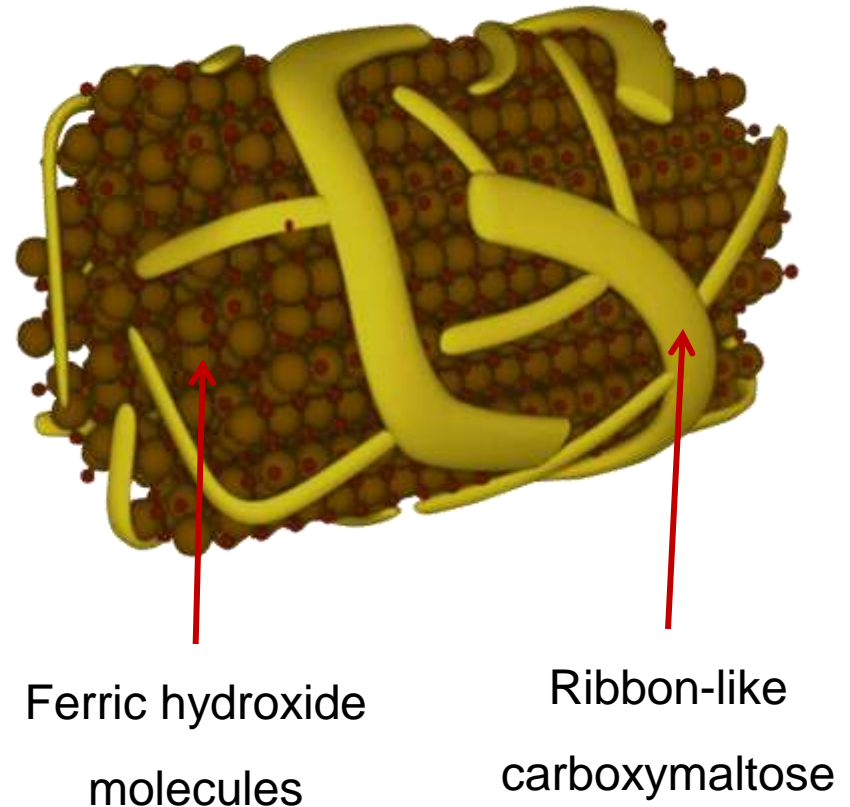
- Ferric carboxymaltose
- Iron isomaltoside 1000

## ❖ Non-conventional

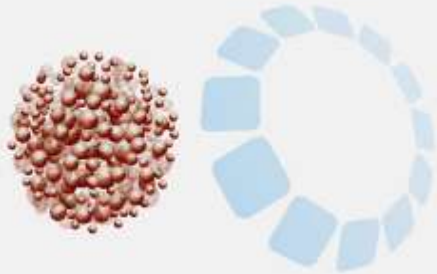
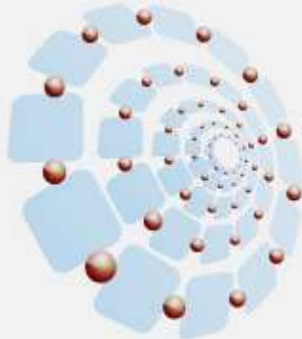
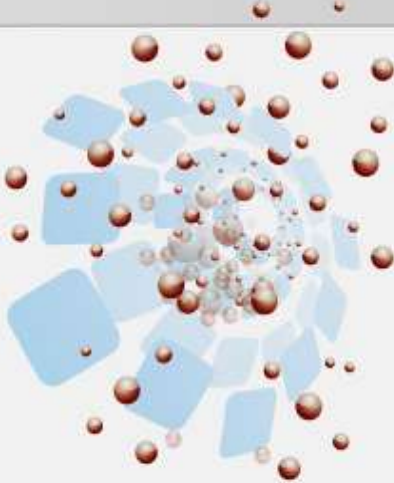
- Dialysate: Sodium Ferric Pyrophosphate

# What it is Ferric Carboxymaltose?

- Stable polynuclear iron complex
- Essentially no release of ionic iron in the circulation
- Dextran-free carbohydrate shell (low immunogenic potential)
- No test dose
- Physiological pH and osmolality
- Rapid administration of up to 1000 mg iron



# iMatrix™ technology

Iron isomaltoside 1000		
 <p><b>Components</b></p>	 <p><b>Delivery System</b></p>	 <p><b>Release</b></p>
<p>Ultra-pure iron Nonanaphylactic isomaltoside 1000</p>	<p>Strong iron binding Low free iron US patented</p>	<ul style="list-style-type: none"><li>▶ Widest dose range</li><li>▶ No test dose</li><li>▶ Controlled release</li></ul>

# A new way of administering iron to HD patients?

*Kidney International, Vol. 55 (1999), pp. 1891–1898*

## Dialysate iron therapy: Infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis

**AJAY GUPTA, NEETA B. AMIN, ANATOLE BESARAB, SUSAN E. VOGEL, GEORGE W. DIVINE, JERRY YEE, and J. V. ANANDAN**

*Division of Nephrology, Department of Pharmacy Services, and Department of Biostatistics, Henry Ford Hospital, Detroit, Michigan, USA*

### **Dialysate iron therapy: Infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis.**

*Background.* Soluble iron salts are toxic for parenteral administration because free iron catalyzes free radical generation. Pyrophosphate strongly complexes iron and enhances iron transport between transferrin, ferritin, and tissues. Hemodialysis patients need iron to replenish ongoing losses. We evaluated the short-term safety and efficacy of infusing soluble ferric pyrophosphate by dialysate.

*Methods.* Maintenance hemodialysis patients receiving ery-

with prematurity and low birth weight during pregnancy, defects in cognitive and psychomotor development during childhood, and impaired work capacity in adulthood [3–8]. Oral iron supplementation programs have failed primarily because of noncompliance in addition to gastrointestinal adverse effects [9]. As an adjunct or alternative to the oral route, iron has been administered parenterally for more than 100 years [10]. Soluble iron

# New erythropoiesis stimulating agents

- Biosimilar erythropoietins
- Hepcidin inhibitors
- EPO-mimetics (Hematide, CNTO 530, Fab-EPO receptor complex)
- HIF stabilizers (FG 2216, FG 4592)
- GATA inhibitors (K-11706, K-7174)
- Fusion proteins (EPO-EPO, GS-CSF-EPO, EPO-CGC, EPO-TpC)
- HCP inhibitors

# Benefits and Problems with Biosimilars

**TABLE II. Benefits and Problems Related to the Use of Biosimilars**

Benefits	Problems
Lower pricing than originator medicines	Lack of long-term experience (efficacy, safety, immunogenicity?)
Pressure on innovator companies to reduce prices of originator medicines	Product-specific administration routes (s.c. and/or i.v. authorization?)
Pressure on innovator companies to develop "second-generation products" with improved pharmacodynamic and/or pharmacokinetic properties (e.g. darbepoetin alfa, methoxy-PEG-epoetin beta, pegfilgrastim)	Product-specific indications Product-specific storage and handling → Instruction of medical staff required Confusing naming (some identical INN, some different INN, different brand names for identical substances) → Difficulties in pharmacovigilance recording

**TABLE I. Primary Biosimilar Recombinant Medicines Candidates**

Active substance (INN)	Main indication	Biosimilar marketing authorization		
		EU	USA	Japan
Epoetin alfa	Anemia in association with CKD, anemia in association with chemotherapy for cancer	+	-	+ (CKD only)
Epoetin beta	Anemia in association with CKD, anemia in association with chemotherapy for cancer	-	-	-
Filgrastim (G-CSF)	Neutropenia in association with cancer	+	-	-
Somatropin	Growth hormone deficiency	+	+	+
Insulin	Diabetes mellitus	-	-	-
Interferon alfa	Cancer, hepatitis B/C	-	-	-
Interferon beta	Multiple sclerosis	-	-	-

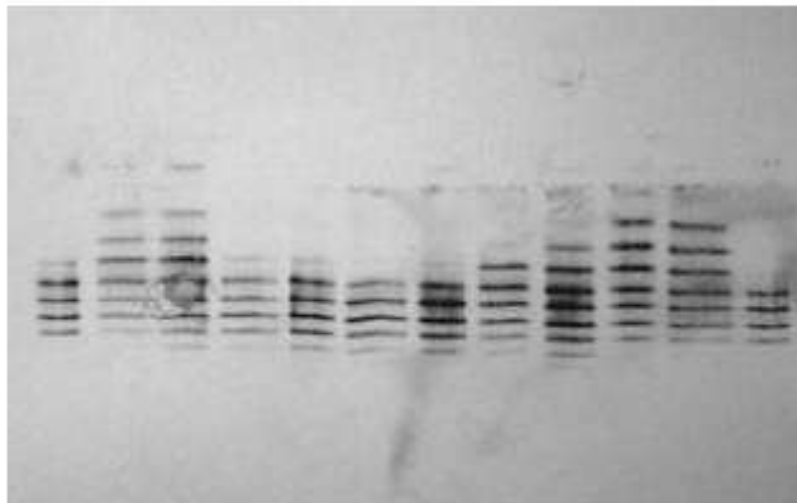
## .....What do we currently have?

INN Reference product	Marketing Authorisation Holder	Date of EC Approval	Brand Name
Somatotropin	Sandoz GmbH	12 April 2006	Omnitrope®
	Biopartners GmbH	24 April 2006	Valtropin
Epoetin alfa	Sandoz GmbH	28 Aug 2007	Binocrit
	Hexal GmbH	28 Aug 2007	Epoetin alfa HEXAL
	Medice Arzneimittel	28 Aug 2007	Abseamed
	Hospira UK	18 Dec 2007	Retacrit
	STADA Arzneimittel GmbH	18 Dec 2007	Silapo
Filgrastim	Ratiopharm GmbH	15 Sept 2008	Ratiograstim
	Teva Generics GmbH	15 Sept 2008	TevaGrastim
	CT Arzneimittel GmbH	15 Sept 2008	Biograstim
	Sandoz GmbH	15 Sept 2008	Zarzio
	Hexal GmbH	6 Feb 2009	Filgrastim HEXAL
	Hospira UK	8 June 2010	Nivestim

# Alternative biologics not approved in regulated markets such as EU – are not “Biosimilars”

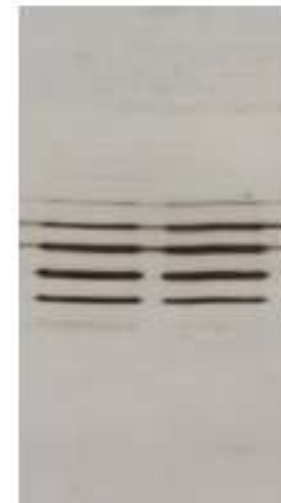
## Isoelectric focusing gels

Alternative biologics ≠ biosimilar  
**NOT** similar to Reference E

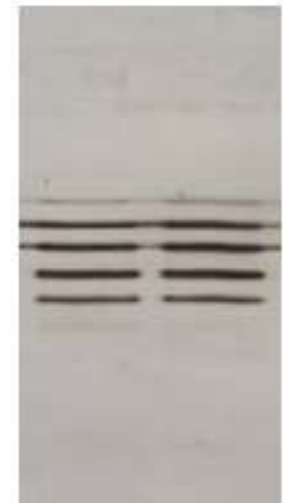


Sample E IA IB IIA IIB IIIA IIIB IV V VII VIII E

Approved biosimilar in EU  
**NO** difference to originator



Sample 1 2



Sample 3 4

# Biosimilar recombinant human erythropoietin (r-HuEPO) induces the production of neutralizing antibodies – a pilot study in Thailand

❖ 30 CKD patients who received subcutaneous injections of biosimilar r-HuEpo and had loss of efficacy

**Table 1 | Patients' characteristics and issues related to the use of biosimilar r-HuEpo and laboratory results**

	Anti-r-HuEpo positive	Anti-r-HuEpo negative	P
Numbers of patients (cases)	23	7	—
Gender, male/female (case/case)	13/10	3/4	0.526
Age, years ± s.d.	61.1 ± 21.4	52.8 ± 4.8	0.784
<i>CKD status, cases (%)</i>			0.647
Predialysis	8 (34.8)	2 (28.6)	
Hemodialysis	14 (60.9)	4 (57.1)	
Peritoneal dialysis	1 (4.3)	1 (14.3)	
<i>Etiology of CKD, cases (%)</i>			0.393
Diabetic nephropathy	5 (26.1)	3 (42.9)	
Chronic glomerulonephritis	3 (13.0)	0	
Unknown	14 (60.9)	4 (57.1)	
r-HuEpo exposure duration, months ± s.d. (range in months)	12.1 ± 7.8 (3–36)	22.3 ± 19.8 (6–60)	0.001*
r-HuEpo dose, U/kg/week ± s.d.	149 ± 82	171 ± 91	0.991
Hb before LOE, g/dl ± s.d.	10.8 ± 1.6	11.4 ± 0.7	0.458
Hemoglobin by the time of LOE, g/dl ± s.d.	5.6 ± 0.9	7.3 ± 0.7	<0.001*
Reticulocytes, cell/mm <sup>3</sup> ± s.d.	5978 ± 1217	13,128 ± 3,456	<0.001*
Serum ferritin, ng/ml ± s.d.	368.6 ± 83.1	370.3 ± 93.7	0.967
Transferring saturation, % ± s.d.	28.3 ± 6.6	28.8 ± 5.2	0.821
Serum folate, pg/ml ± s.d.	12.8 ± 4.5	12.5 ± 4.3	0.526
Serum B <sub>12</sub> , pg/ml ± s.d.	258.2 ± 189.2	177.1 ± 84.4	0.123
CRP, mg/l ± s.d.	4.22 ± 2.98	3.62 ± 3.56	0.692
iPTH, pg/ml ± s.d.	241.4 ± 127.1	284.0 ± 151.6	0.518

Abbreviations: CKD, chronic kidney disease; CRP, C-reactive protein; Hb, hemoglobin; iPTH, intact parathyroid hormone; LOE, loss of efficacy; r-HuEpo, recombinant human erythropoietin.

\*P < 0.05.

# Biosimilar recombinant human erythropoietin (r-HuEPO) induces the production of neutralizing antibodies – a pilot study in Thailand

## Detection of anti-r-HuEpo-associated PRCA cases in patients using subcutaneous biosimilar r-HuEpo

	Mean of percent c.p.m. ± s.d.					
	1:20 dilution	1:50 dilution	1:100 dilution	1:1000 dilution	1:10,000 dilution	1:20,000 dilution
Anti-r-HuEpo-positive cases (N=23)	18.2 ± 8.8	12.7 ± 9.7	10.5 ± 9.2	3.5 ± 5.0	1.0 ± 1.0	0.3 ± 0.8
Anti-r-HuEpo-negative cases (N=7)	0.2 ± 0.1	NA	NA	NA	NA	NA
Negative control (N=30)	0.2 ± 0.1	NA	NA	NA	NA	NA
Pure negative control (N=30)	0.2 ± 0.1	NA	NA	NA	NA	NA

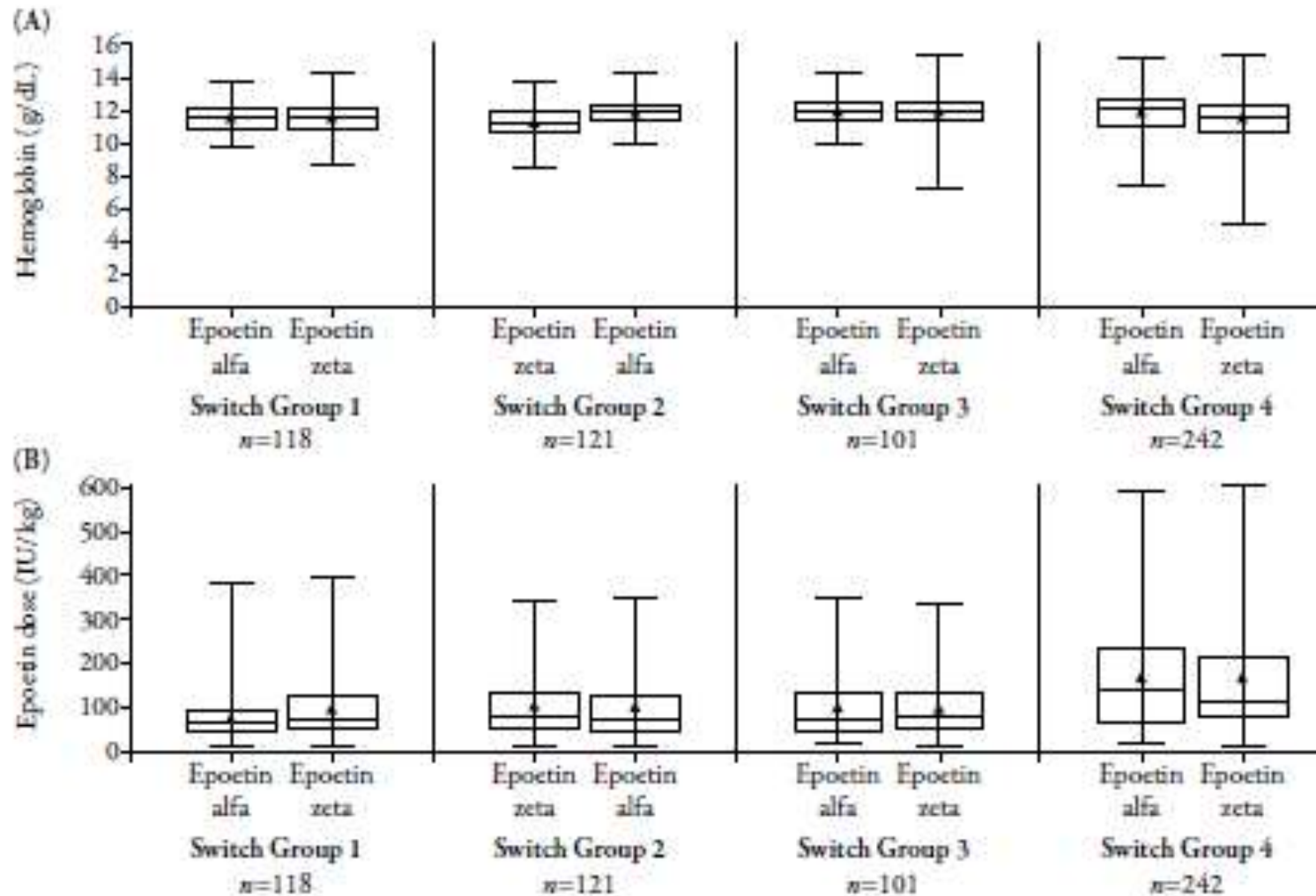
Abbreviations: c.p.m., counts per minute; NA, not applicable; PRCA, pure red-cell aplasia; r-HuEpo, recombinant human erythropoietin.

- General estimated risk for anti-r-HuEpo-associated PRCA in Thailand before this study was 23:59990.
- The actual risk for anti-r-HuEpo-associated PRCA (during using biosimilar r-HuEpo ) is 1:2608.

# Chemical formulation is closely matched: Comparison of Retacrit with other epoetins

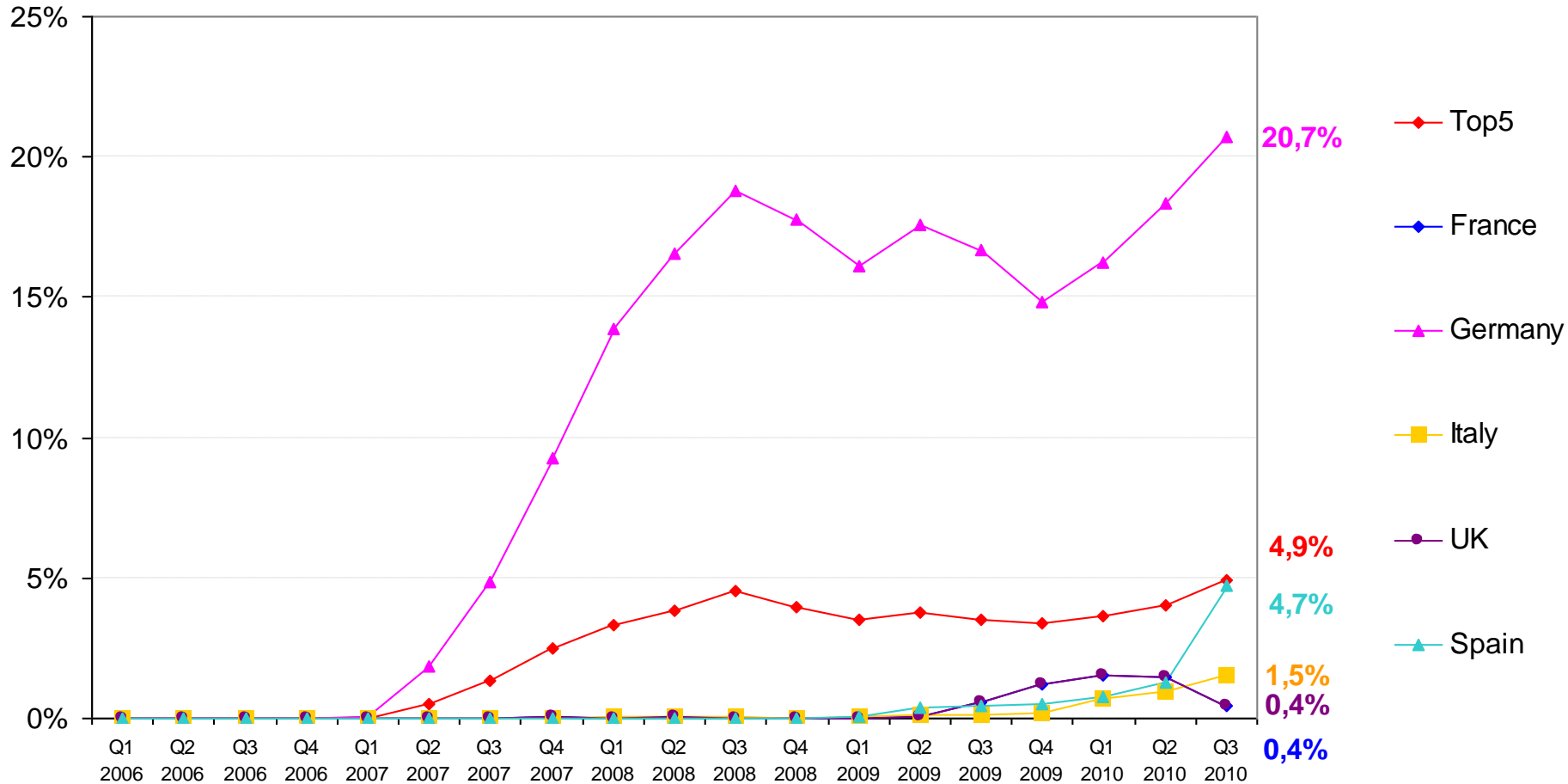
Trade name	Retacrit®	NeoRecormon®	Eprex®	Binocrit®
<b>Active</b>	Epoetin zeta	Epoetin beta	Epoetin alfa	Epoetin alfa
<b>Surfactant</b>	Polysorbate 20	Polysorbate 20	Polysorbate 80	Polysorbate 80
<b>Stabilisers</b>	Amino acids: Glycine Leucine Isoleucine Threonine Glutamic acid Phenylalanine	Amino acids: Glycine Leucine Isoleucine Threonine Glutamic acid Phenylalanine Urea	Amino acid: Glycine	Amino acid: Glycine
<b>Buffer</b>	Na phosphate	Na phosphate	Na phosphate	Na phosphate
<b>Salts</b>	NaCl CaCl <sub>2</sub>	NaCl CaCl <sub>2</sub>	NaCl	NaCl

Mean Hb concentrations were maintained at target levels (Hb 10.5-12.5 g/dL) in all 4 patient groups throughout the treatment switch



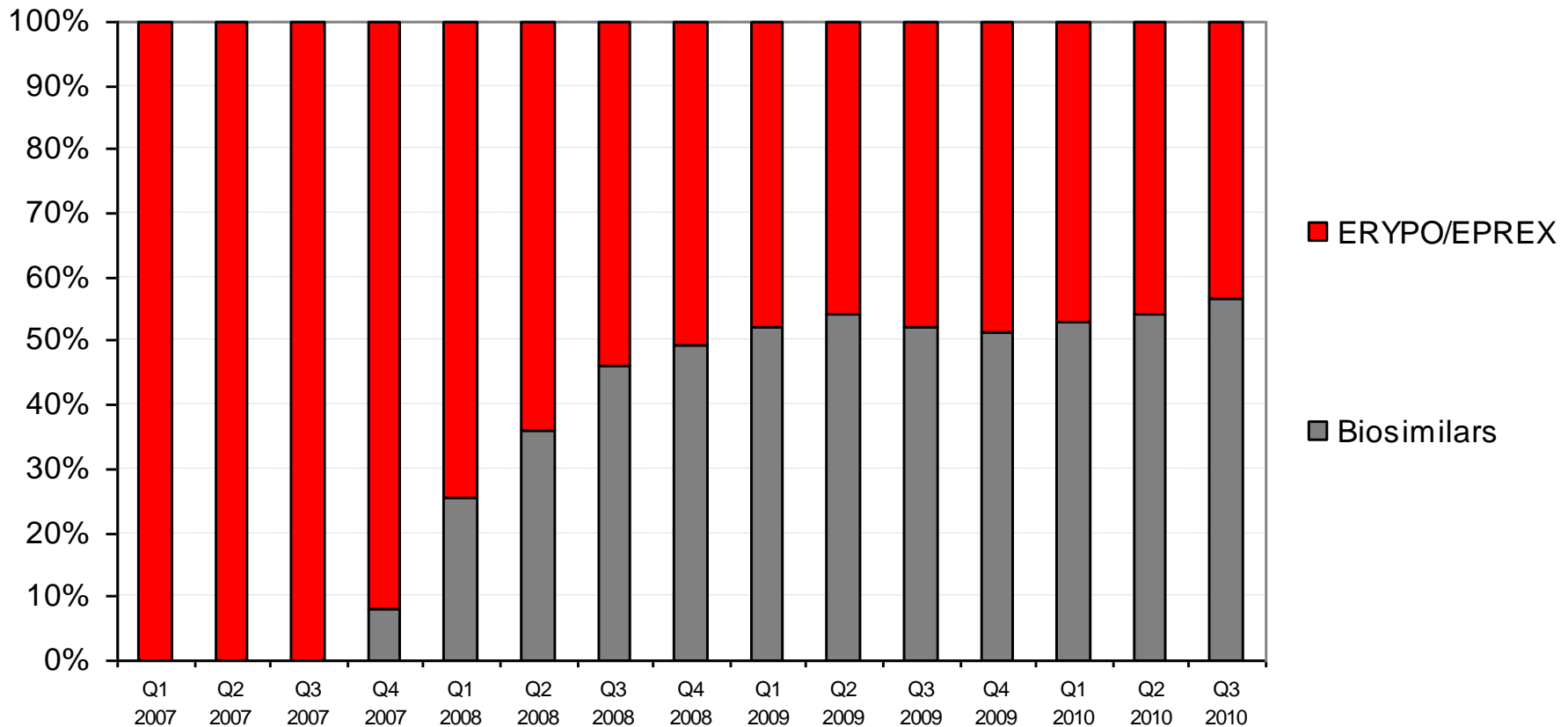
# Biosimilars penetration differs a lot by country, lead by Germany with 21% market share in value

Penetration of Biosimilars in ESA Sales in value by country (CHF)

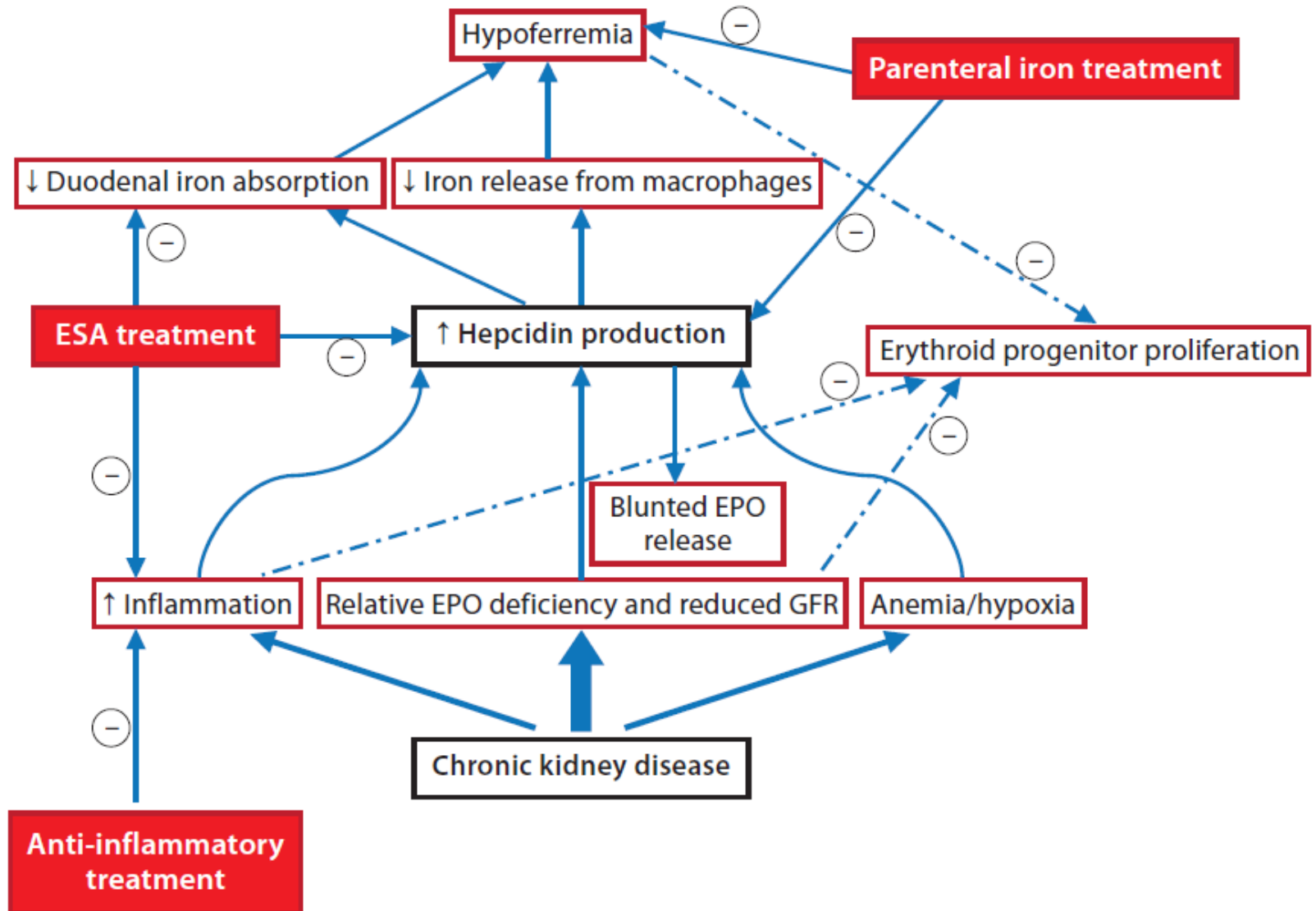


# Fast and strong penetration of Biosimilars within EPOETIN ALFA in Germany:

Germany EPOETIN ALFA biosimilars penetration in value within total molecule sales

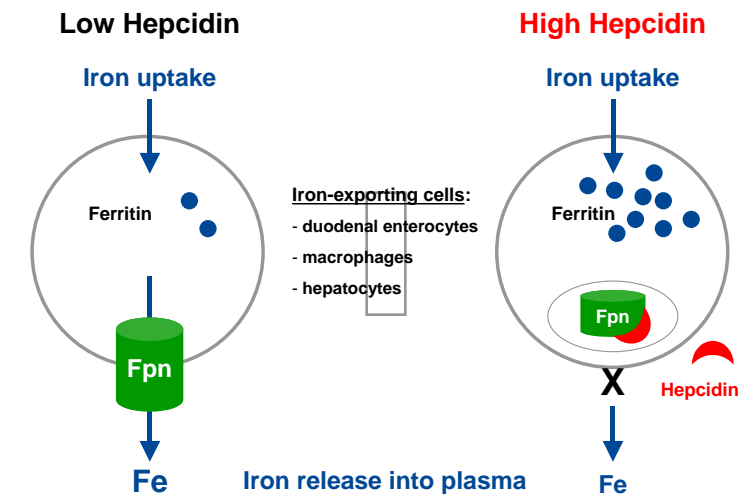


# Renal anemia of inflammation- role of hepcidin



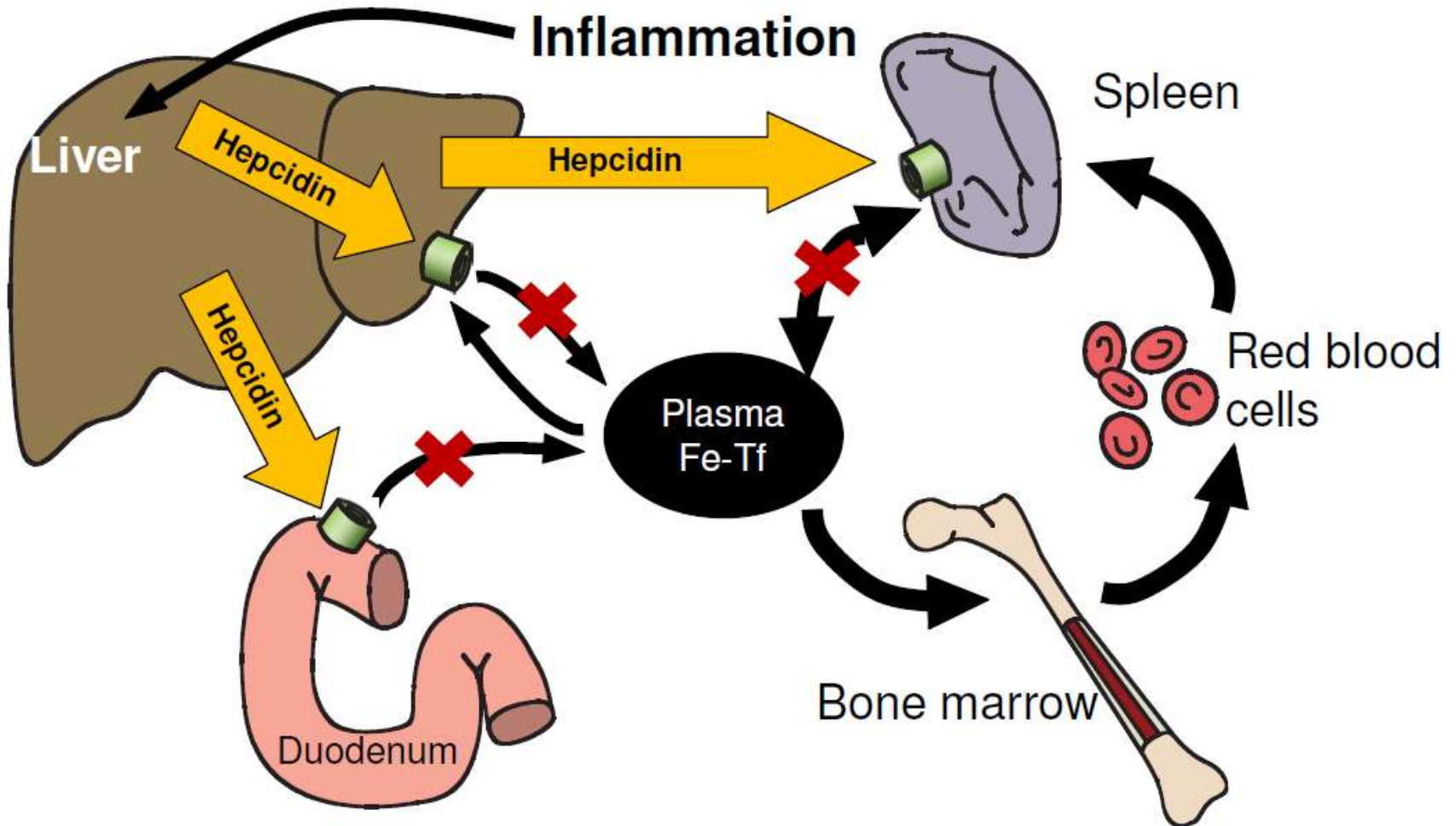
# Background – Hepcidin in Anemia of Inflammation

- Hepcidin is the master regulator of iron homeostasis via its effect on ferroportin, the only known iron export protein
- Cytokine-induced synthesis of hepcidin plays a crucial role in macrophage iron retention, which underlies the anemia of inflammation by limiting the availability of iron for erythroid progenitor cells, “functional iron deficiency”
- Patients with anemia of inflammation display an impaired response to erythropoietin (EPO)



modified from: T. Ganz (2006) *Hematology Am. Soc. Hematol. Educ. Program.* 507, 29-35.

# Regulation of hepcidin by inflammation



# Hepcidin – a potential target for future anaemia therapies ?

RED CELLS, IRON, AND ERYTHROPOIESIS

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## Antihepcidin antibody treatment modulates iron metabolism and is effective in a mouse model of inflammation-induced anemia

Barbra J. Sasu,<sup>1</sup> Keegan S. Cooke,<sup>1</sup> Tara L. Arvedson,<sup>1</sup> Cherylene Plewa,<sup>2</sup> Aaron R. Ellison,<sup>2</sup> Jackie Sheng,<sup>2</sup> Aaron Winters,<sup>2</sup> Todd Juan,<sup>2</sup> Hongyan Li,<sup>3</sup> C. Glenn Begley,<sup>1</sup> and Graham Molineux<sup>1</sup>

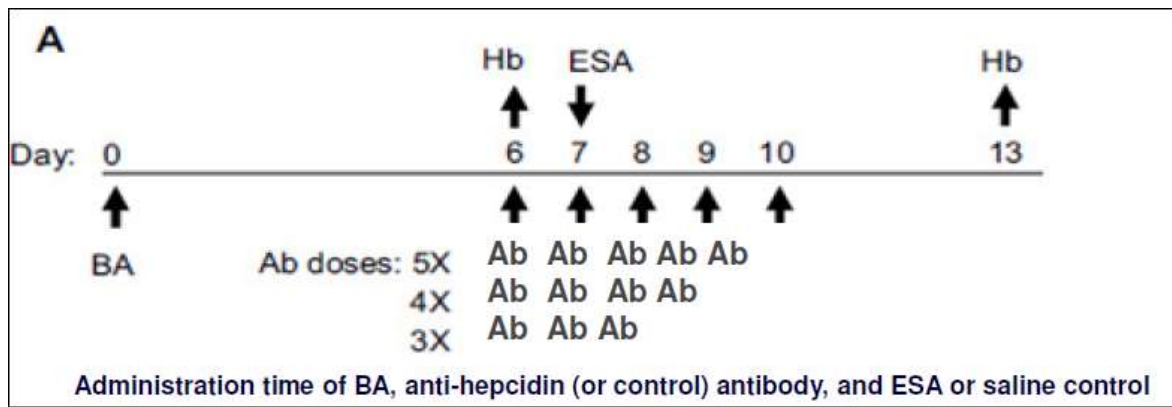
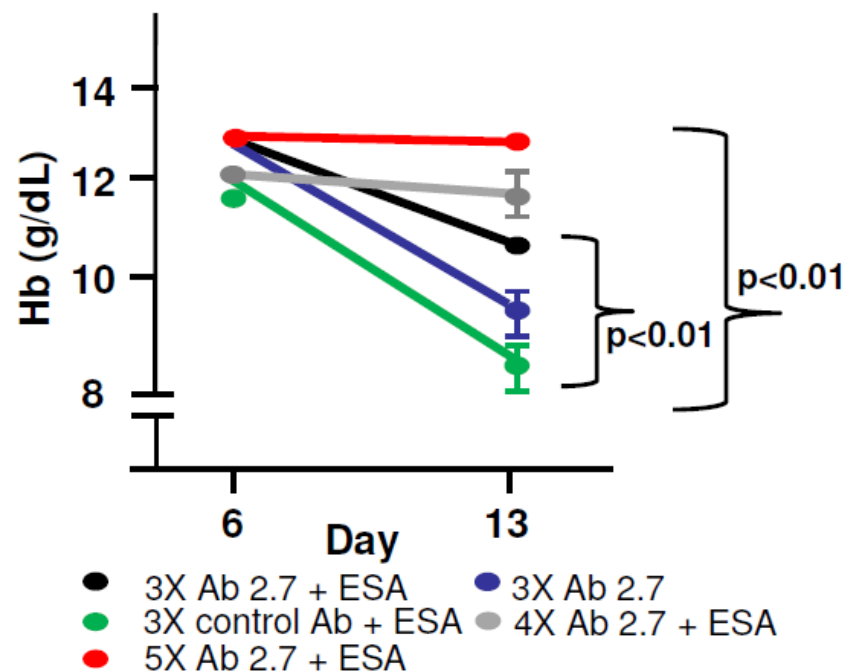
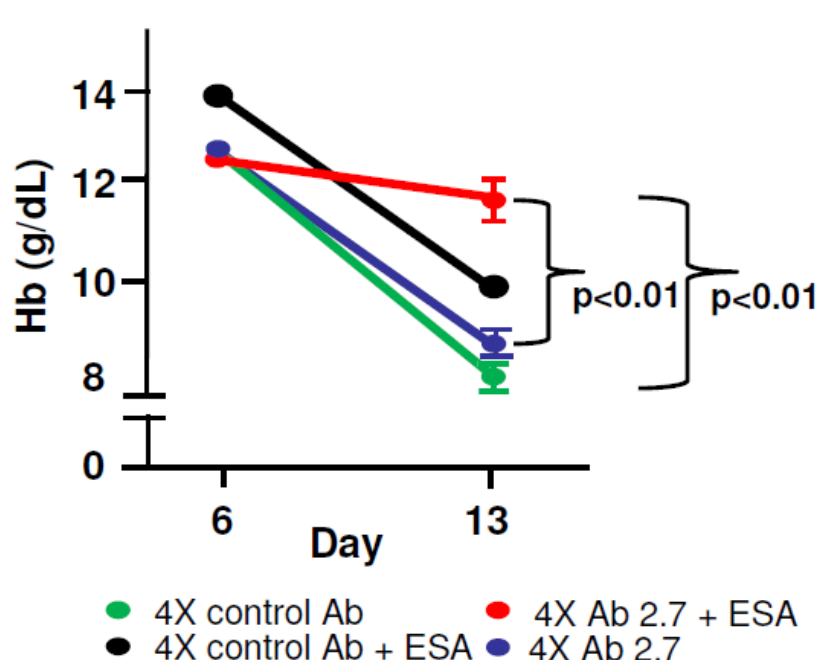
Departments of <sup>1</sup>Hematology/Oncology, <sup>2</sup>Protein Sciences, and <sup>3</sup>Pharmacokinetics and Drug Metabolism, Amgen Inc, Thousand Oaks, CA

Iron maldistribution has been implicated in multiple diseases, including the anemia of inflammation (AI), atherosclerosis, diabetes, and neurodegenerative disorders. Iron metabolism is controlled by hepcidin, a 25-amino acid peptide. Hepcidin is induced by inflammation, causes iron to be sequestered, and thus, potentially contributes to AI. Human hepcidin (hHepc) overexpression in mice caused an iron-deficient phenotype, including stunted growth, hair loss, and iron-deficient erythropoiesis. It also caused

resistance to supraphysiologic levels of erythropoiesis-stimulating agent, supporting the hypothesis that hepcidin may influence response to treatment in AI. To explore the role of hepcidin in inflammatory anemia, a mouse AI model was developed with heat-killed *Brucella abortus* treatment. Suppression of hepcidin mRNA was a successful anemia treatment in this model. High-affinity antibodies specific for hHepc were generated, and hHepc knock-in mice were produced to enable

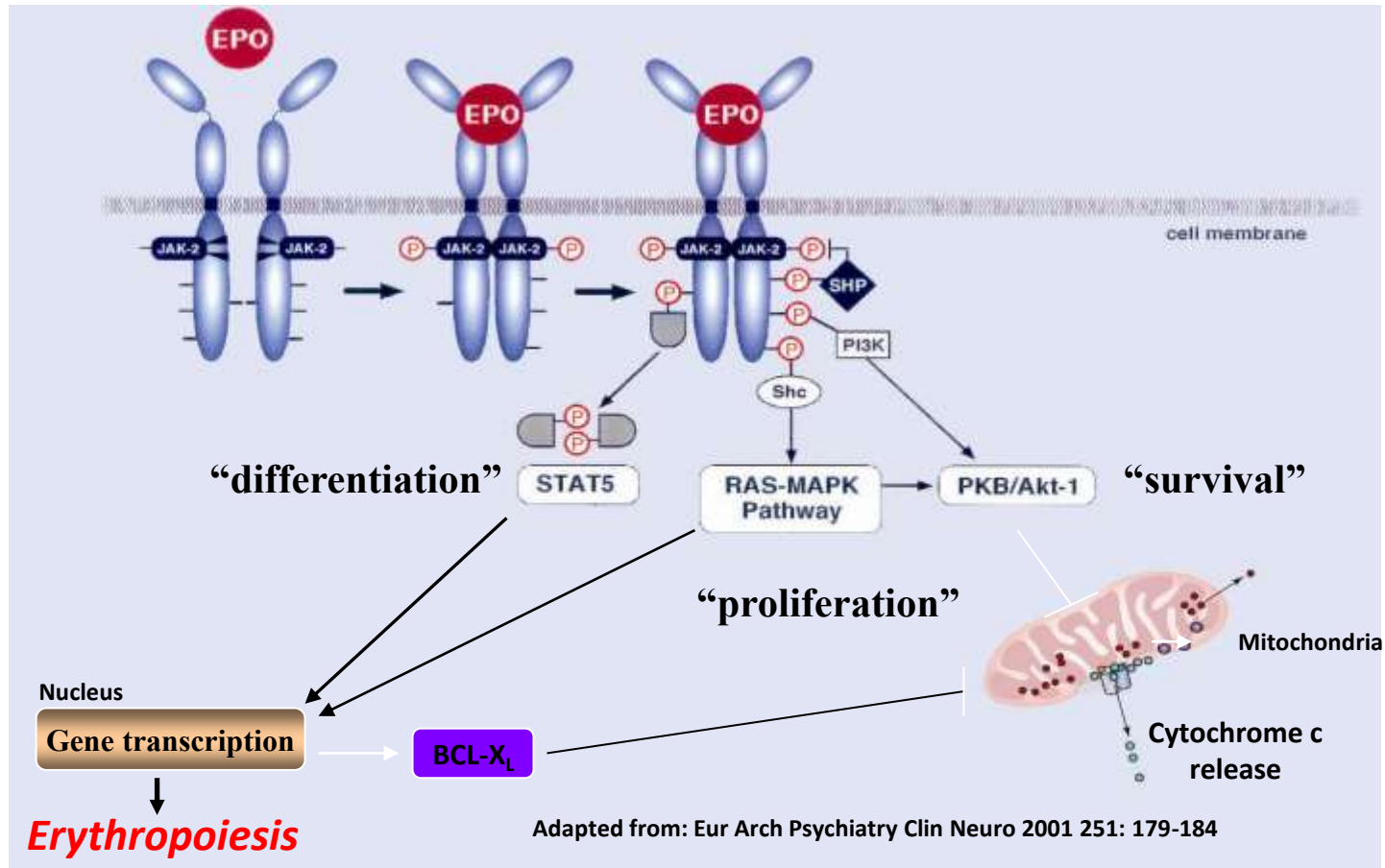
antibody testing. Antibody treatment neutralized hHepc in vitro and in vivo and facilitated anemia treatment in hHepc knock-in mice with AI. These data indicate that antihepcidin antibodies may be an effective treatment for patients with inflammatory anemia. The ability to manipulate iron metabolism in vivo may also allow investigation of the role of iron in a number of other pathologic conditions. (*Blood*. 2010;115(17):3616-3624)

# MAb against hepcidin was effective in combination therapy for anaemia of inflammation



Ab 2.7 restored response to ESA treatment in hHepc knock in AI mice

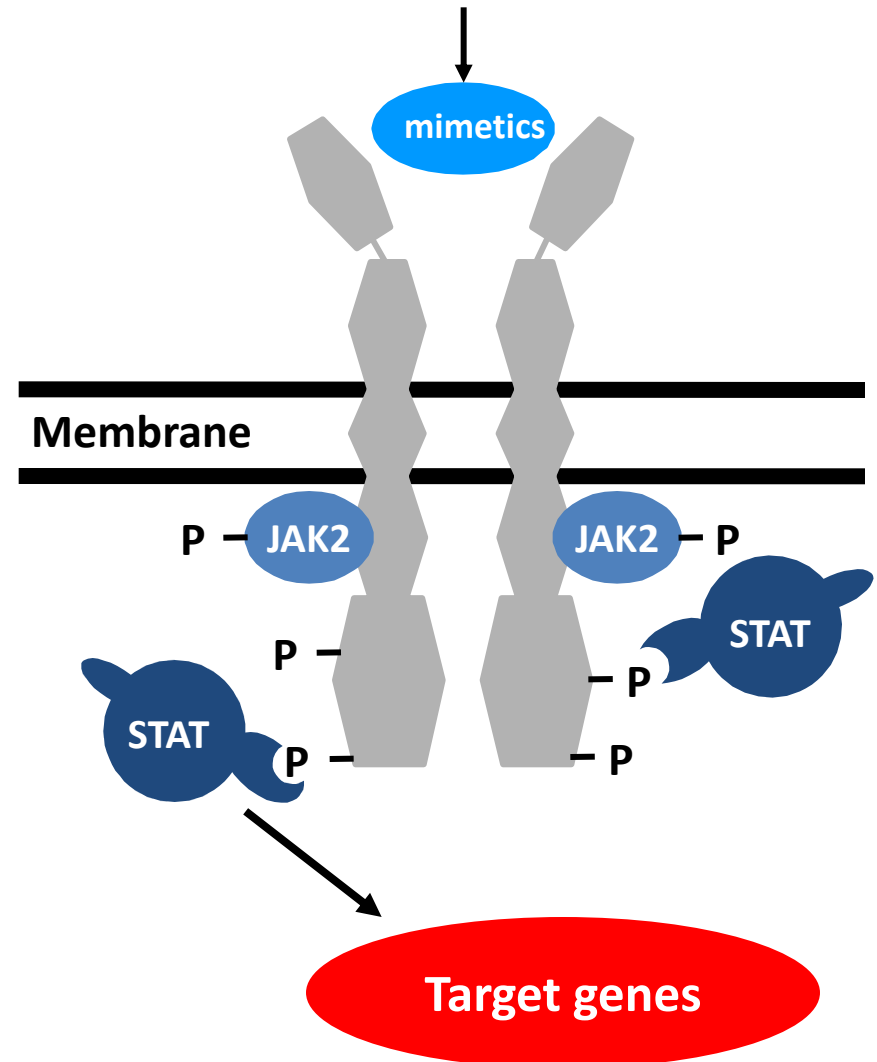
# Dimeric EPO Receptor: both EPO and Hematide activate signal transduction cascade



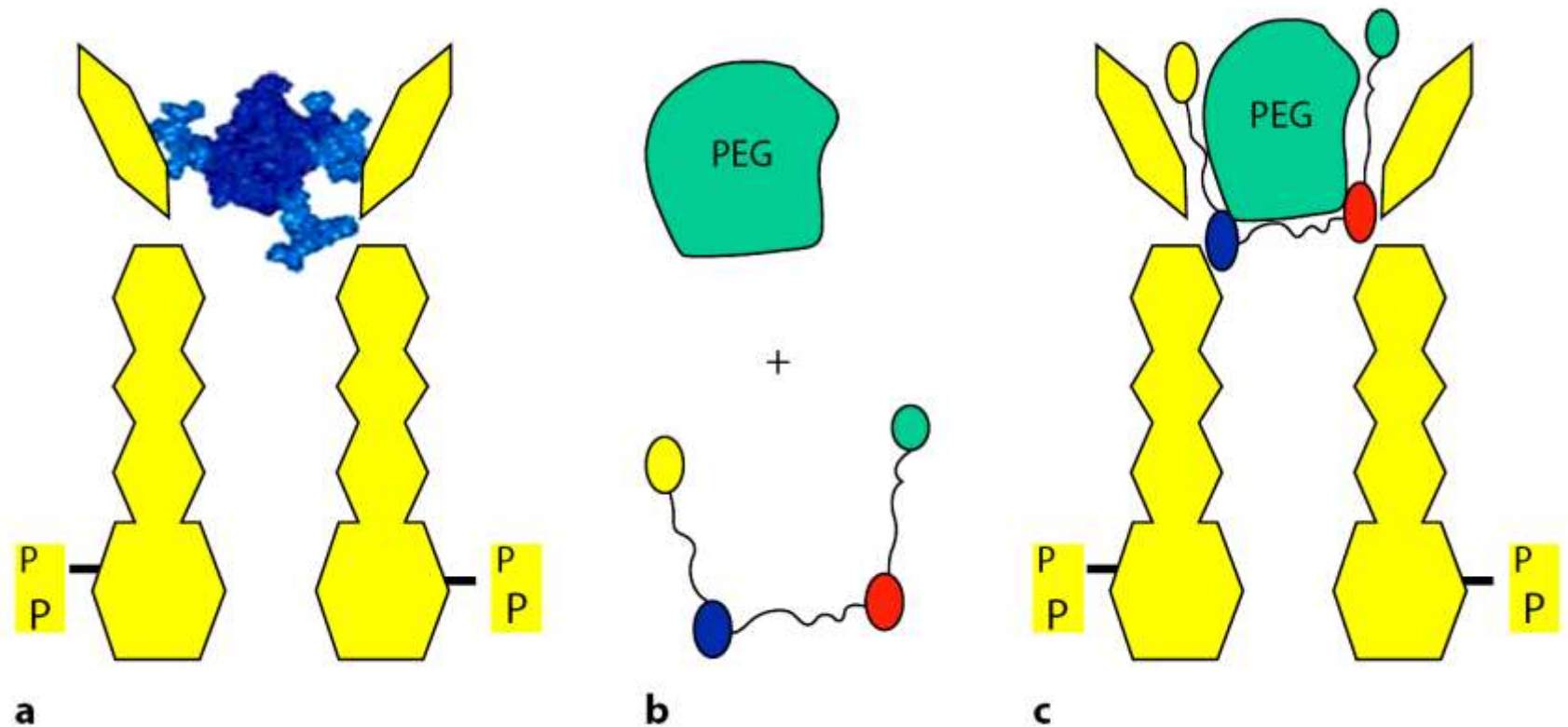
# EPO mimetics

## Rationale and strategy

- Both chains of the EPO receptor are needed
- Conformation of the EPO receptor in the dimer complex is flexible
  - suggests that a variety of molecules capable of dimerising the receptor may be able to act as EPO mimetics



# Erythropoietin mimicry

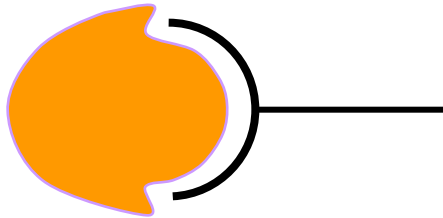


# Hematide™: A Novel Investigational Erythropoiesis Stimulating Agent (ESA)

- Hematide (**Peginesatide**) is a PEGylated synthetic peptide based compound with no sequence homology to EPO
- Hematide binds to and acts through the EPO receptor: potent *in vitro* and *in vivo* activity demonstrated in multiple species
- PEGylated for increased stability and extended half-life
- Hematide is developed by Affymax Inc., a U.S. based public biopharmaceutical company, in partnership with Takeda, for the indication of anemia of chronic kidney disease.

# Peptide Drug: Advantages Over Proteins

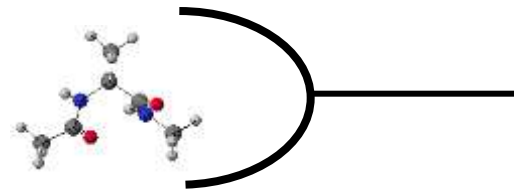
## PROTEINS



## DISADVANTAGES

- Require Cold Storage
- Expensive to Manufacture
- Immunogenic

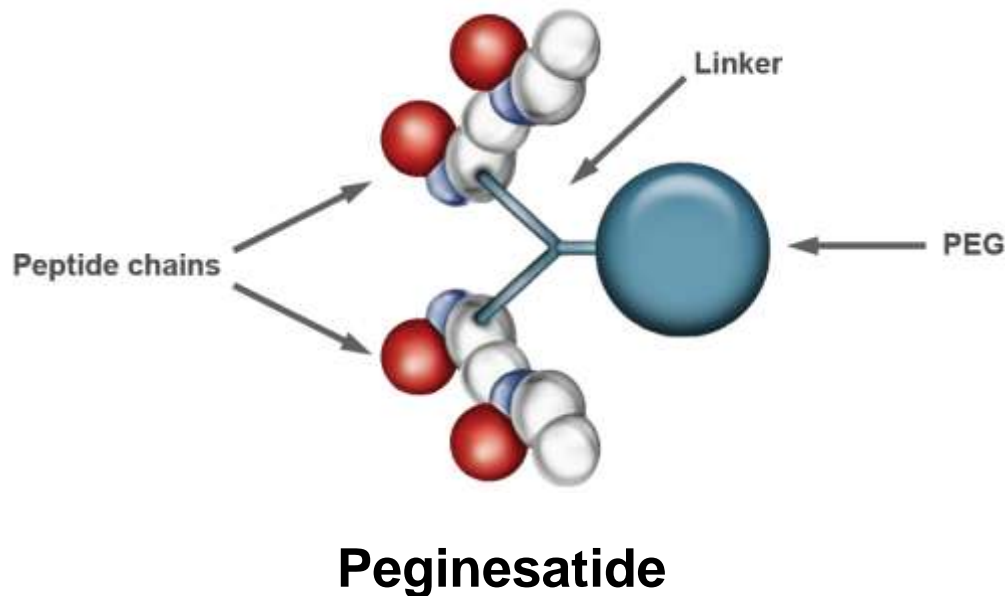
## AFFYMAX PEPTIDES



## ADVANTAGES

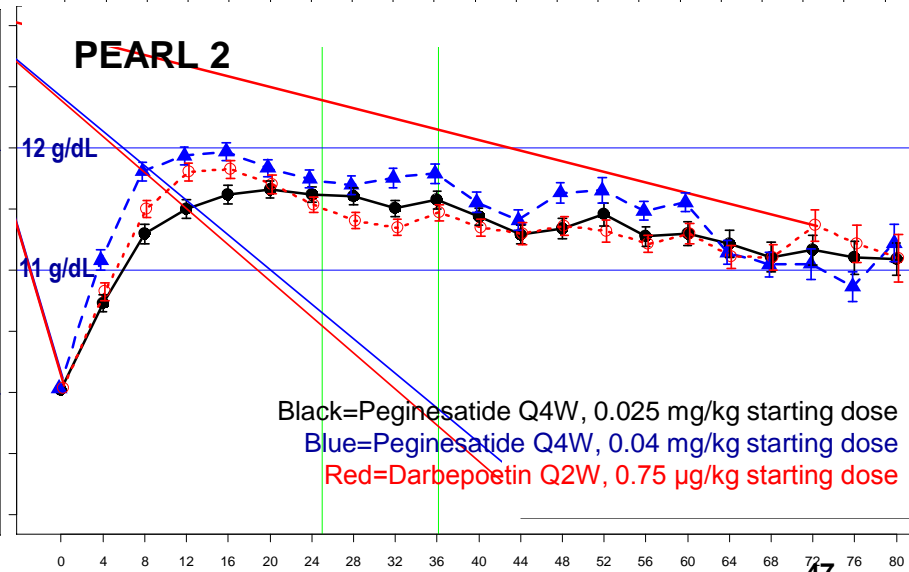
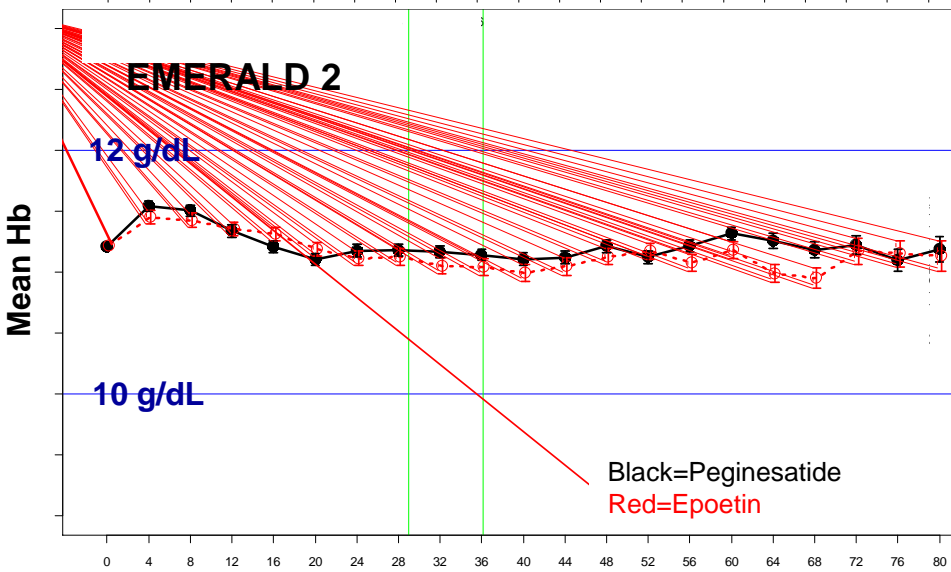
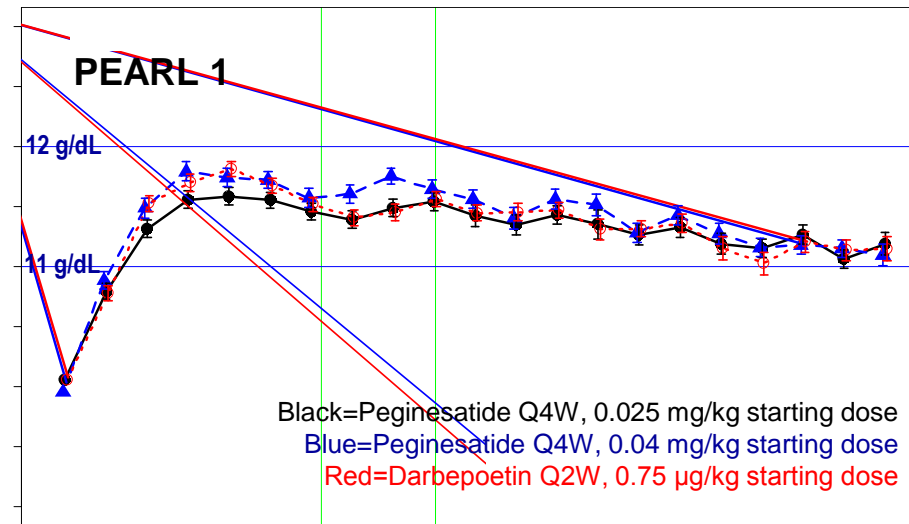
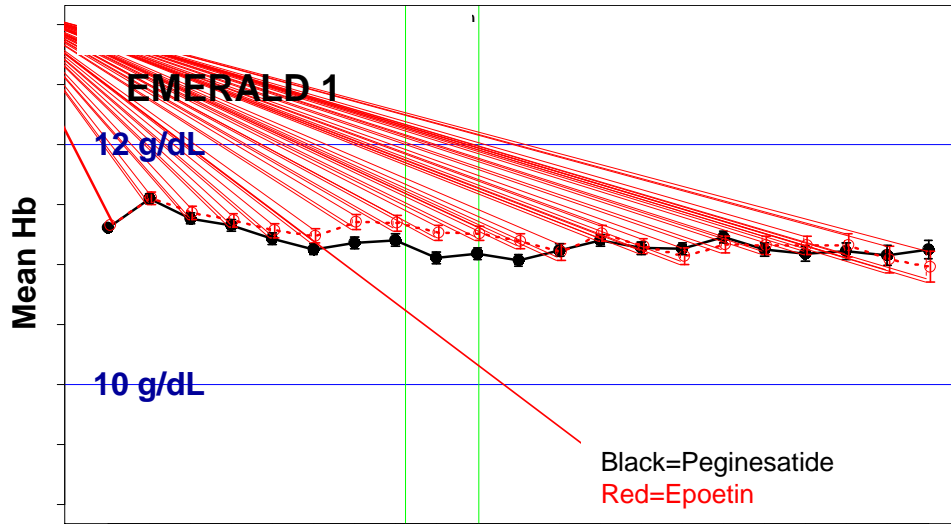
- Improved Stability
- Less Expensive to Manufacture
- Low Immunogenicity Potential
- Flexible Formulations and Delivery
- Equivalent Potency/Efficacy
- Improved PK/PD Profile

# Background – Peginesatide (Hematide™)



- Synthetic peptide-based ESA (dimeric, PEGylated)
- No structural homology with EPO
- Binds to and stimulates the EPO receptor
- Completed Phase 3 clinical trials program

# Efficacy: Maintenance and Correction of Hb Levels



# Composite Safety Endpoint (CSE): Definitions and Methods

## CSE Events:

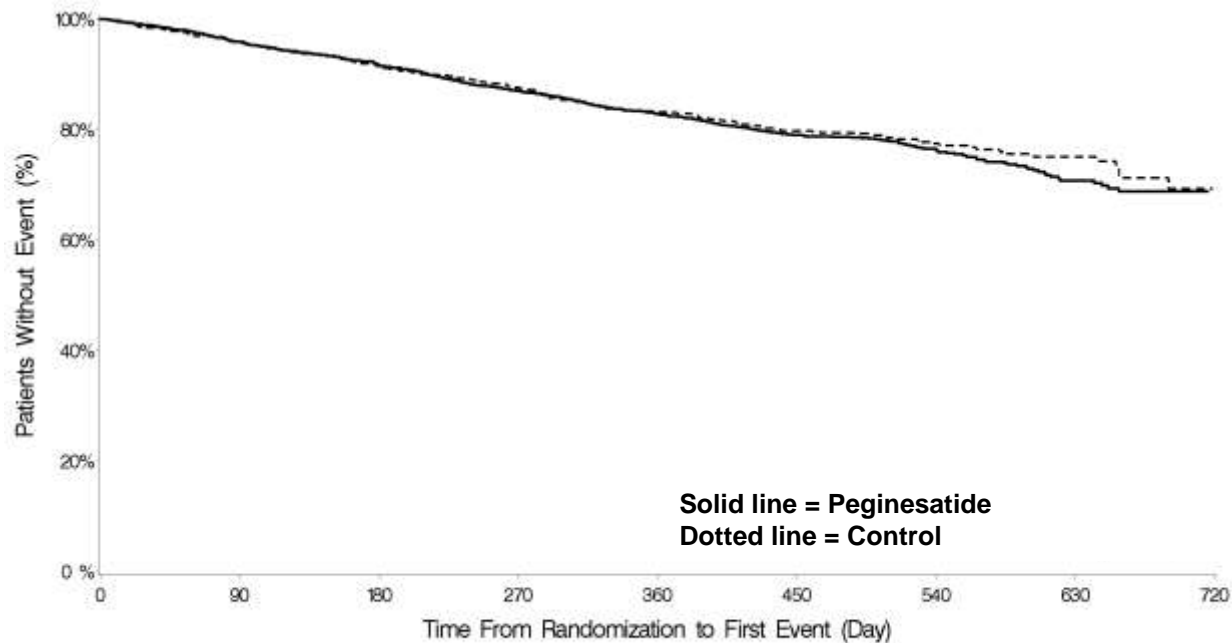
1. Death (All Causes)
2. Stroke
3. Myocardial Infarction
4. Congestive Heart Failure (SAE)
5. Unstable Angina (SAE)
6. Arrhythmia (SAE)

- Adjudicated by blinded, independent Event Review Committee (ERC)
  - CSE endpoint: Time from randomization to first CSE event
- Non-inferiority criterion (overall CSE):
  - Upper limit of two-sided 90% CI for Hazard Ratio  $<1.3$
  - 553 patients with CSE events required for 89% power to exclude hazard ratio  $>1.3$
- 581 patients with CSE events observed

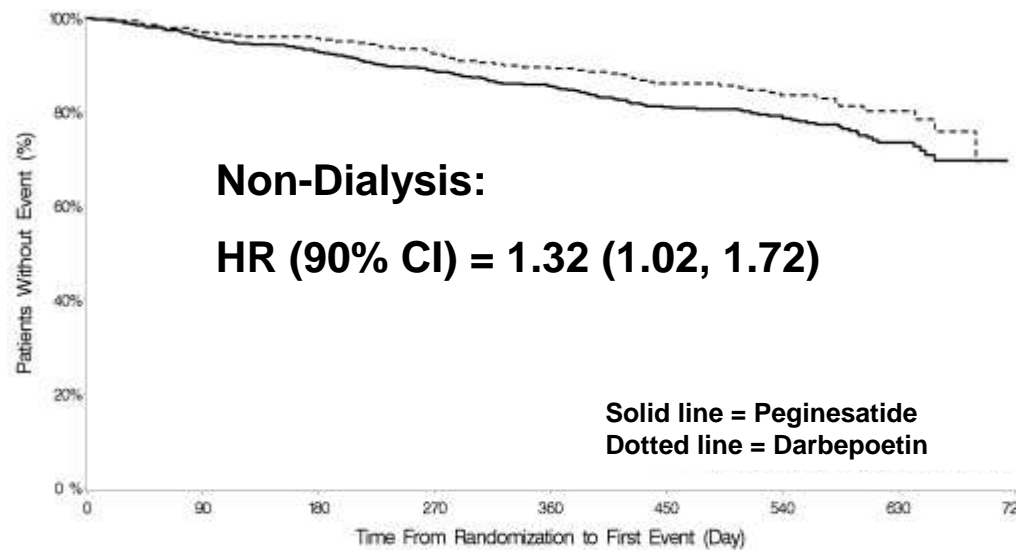
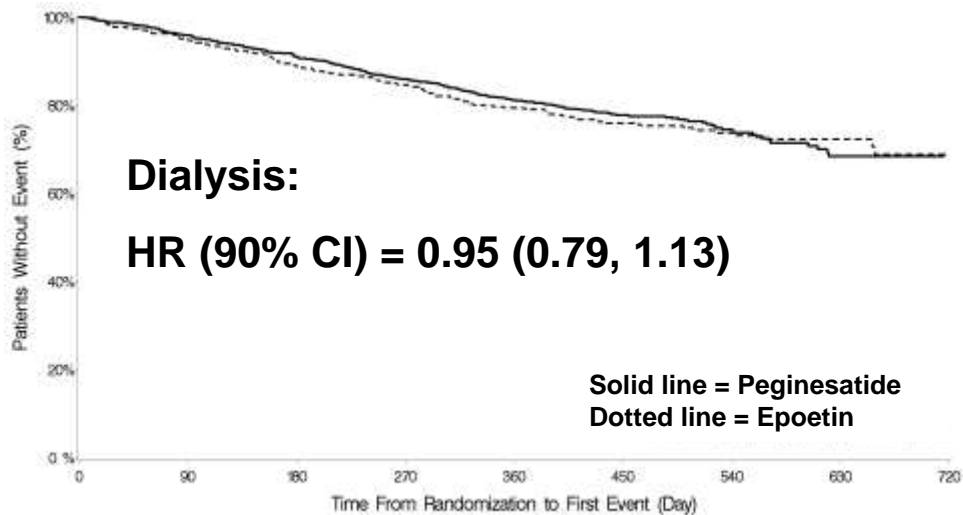
# Composite Safety Endpoint (CSE): Event-Free Rate (Kaplan-Meier Survival)

Total Events Adjudicated: 1625 Events in 734 Patients

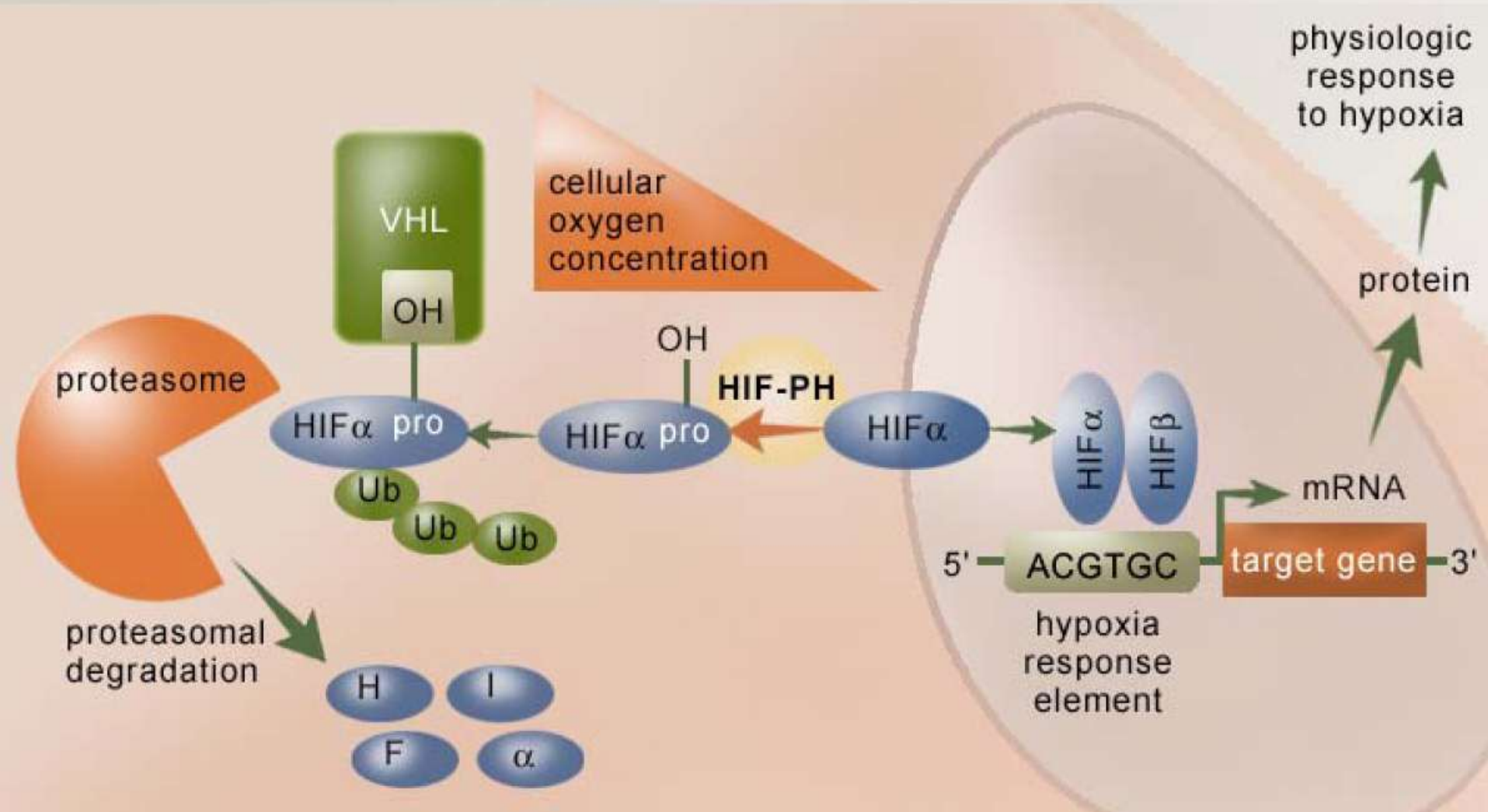
	Dialysis+Non-Dialysis	
	<b>Peginesatide (N=1722)</b>	<b>Control (N=869)</b>
<b>Patients with CSE Events</b>	385 (22%)	188 (22%)
<b>Hazard Ratio</b>	1.06	
<b>90% CI/ 95% CI</b>	(0.91, 1.22) / (0.89, 1.26)	



# Composite Safety Endpoint (CSE): Event-Free Rate (Kaplan-Meier Survival)

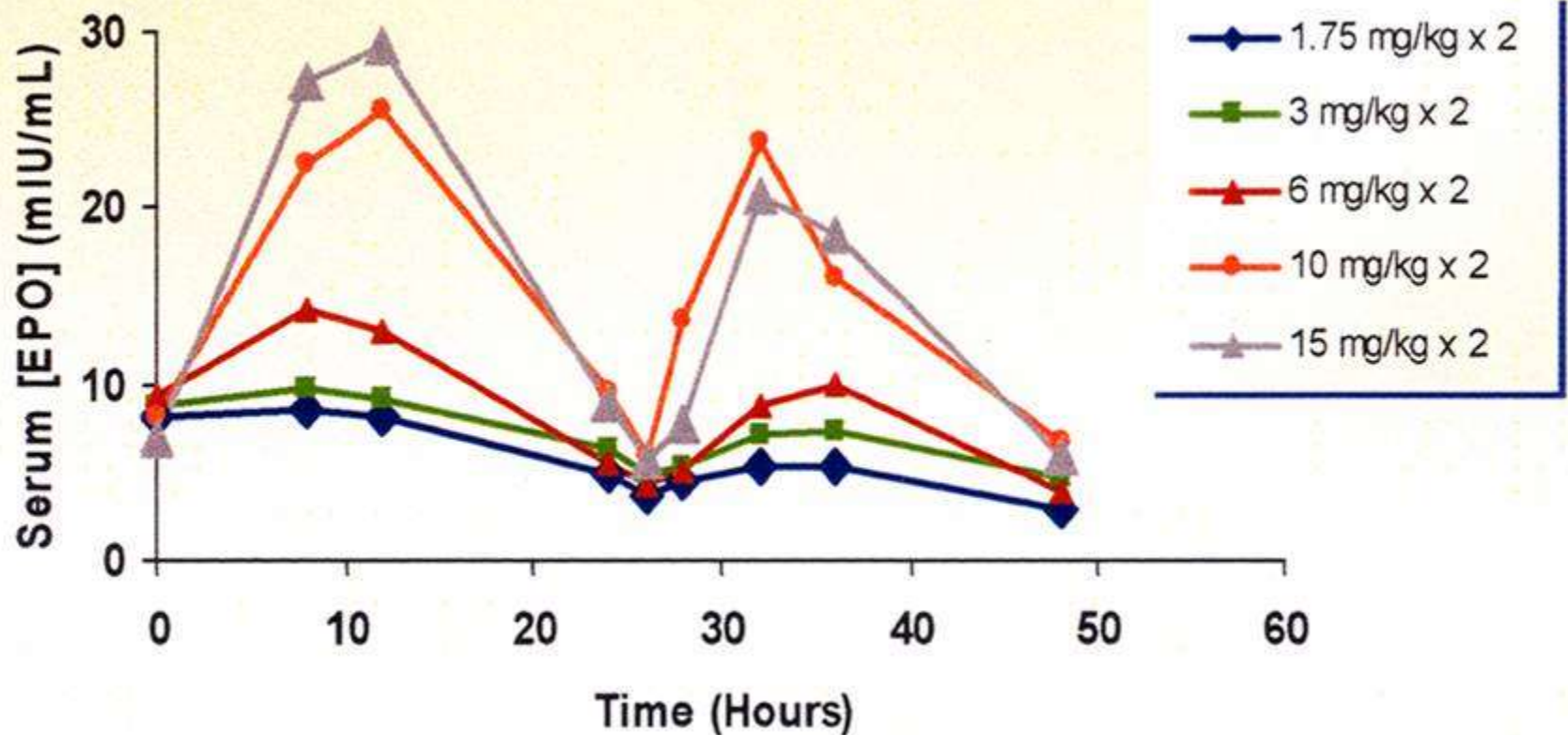


# Cellular Oxygen Sensing Mechanism



# FG-2216 Dose-Related Induction of Endogenous Serum EPO

No Desensitization in EPO Response Following repeated Dosing with FG-2216

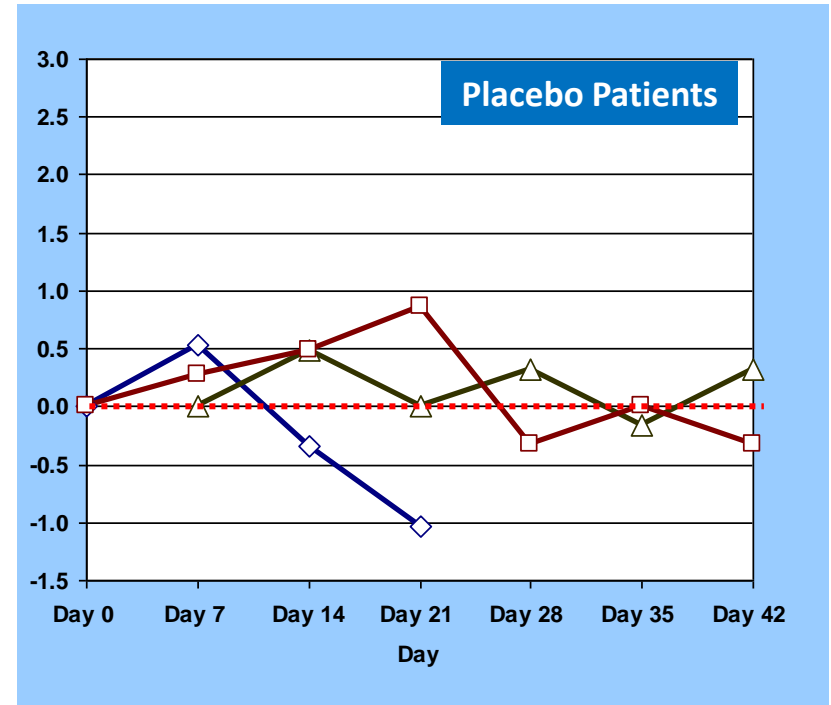
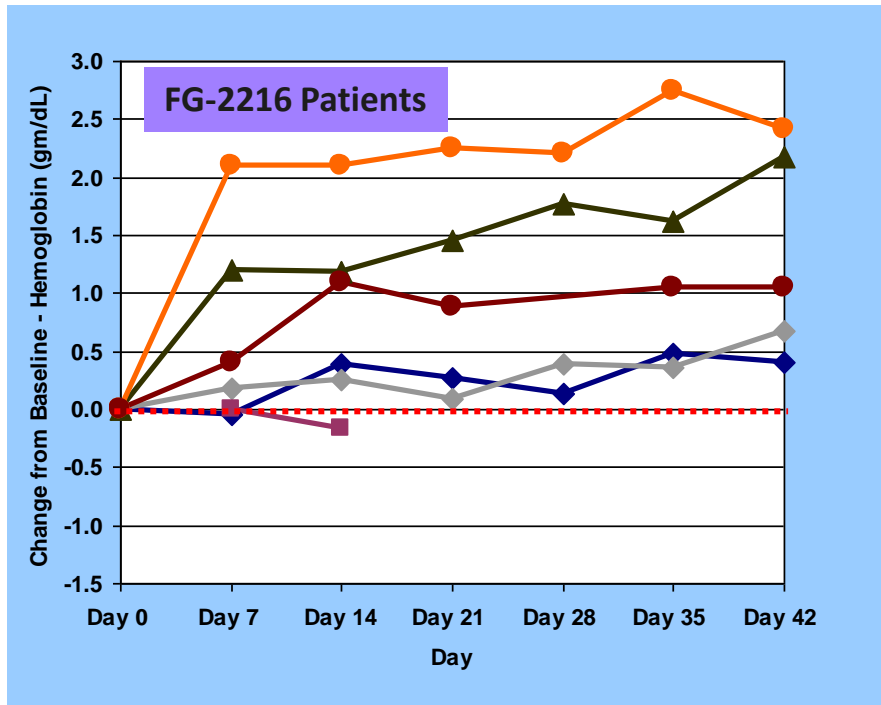


# Phase 2a (rHuEPO- naïve): Individual Hemoglobin Response to FG-2216 vs. Placebo – Change from Baseline

6 mg/kg group (first cohort, rHuEPO-naïve, predialysis patients)

Treatment Group	Mean Baseline Hb (g/dL)	Mean change from Baseline Hb (g/dL) Day 42* (or last value carried forward)
FG-2216 (n=5)	9.6	1.9
Placebo (n=3)	9.8	-0.35

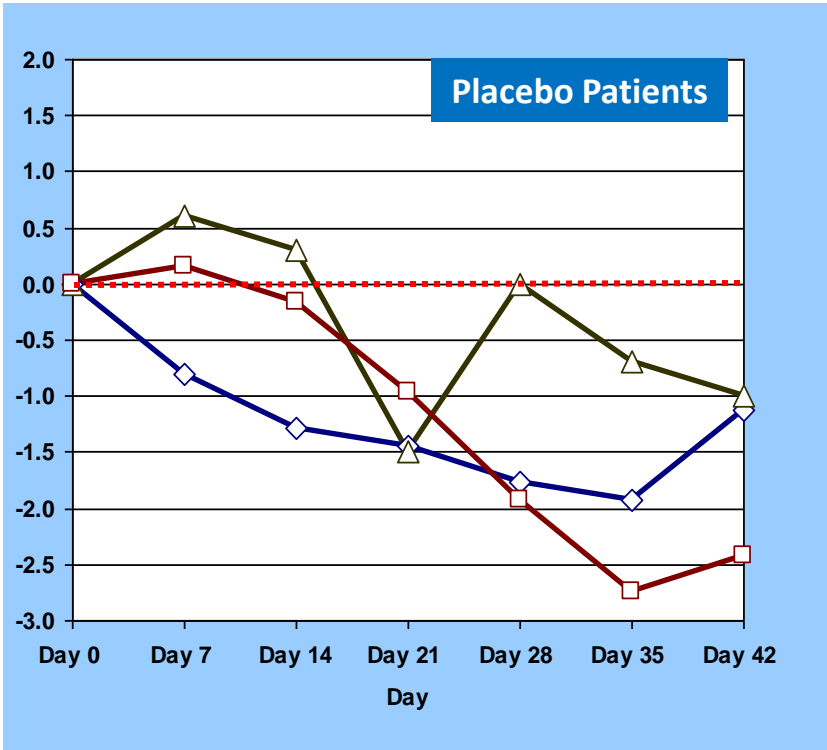
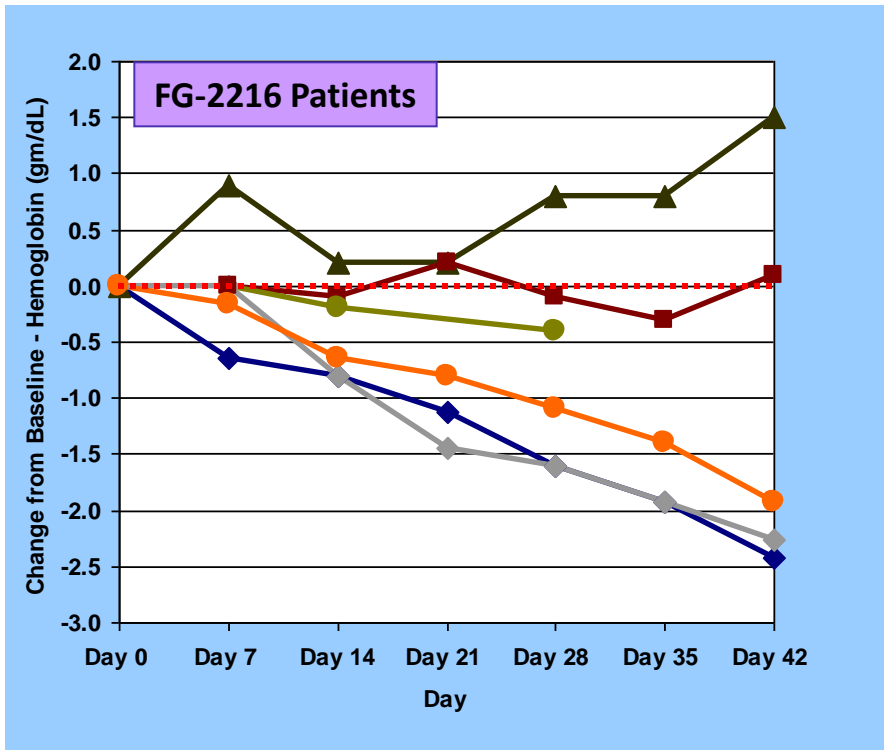
\*Difference between treatment and placebo group is statistically significant (Mann – Whitney rank sum test), p = 0.036



# Phase 2a (rHuEPO-treated): Individual Hemoglobin Response to FG-2216 vs Placebo – Change from Baseline

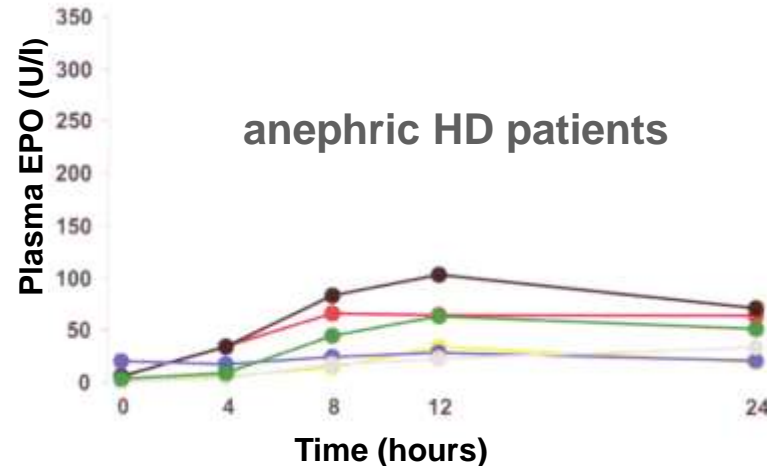
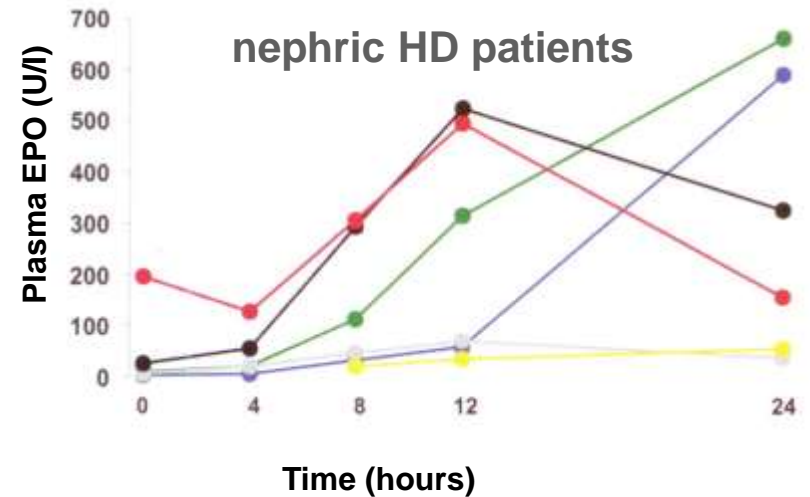
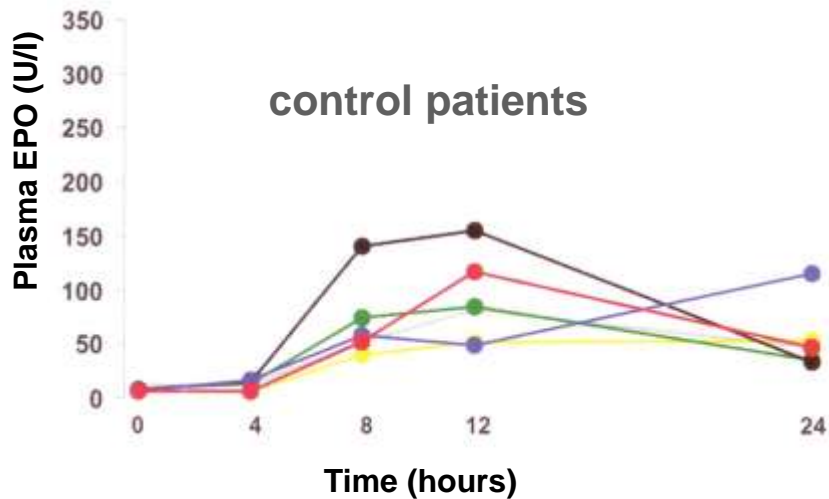
6 mg/kg group (first cohort, rHuEPO-treated, predialysis patients)

Treatment Group	Mean Baseline Hb (g/dL)	Mean change from Baseline Hb (g/dL) Day 42* (or last value carried forward)
FG-2216 (n=6)	11.7	-0.9
Placebo (n=3)	11.5	-1.5



# FG-2216 increases plasma-EPO levels in healthy controls and in HD patients with and without remaining renal tissue

## 24-hour kinetics of plasma EPO levels after a single dose of FG-2216



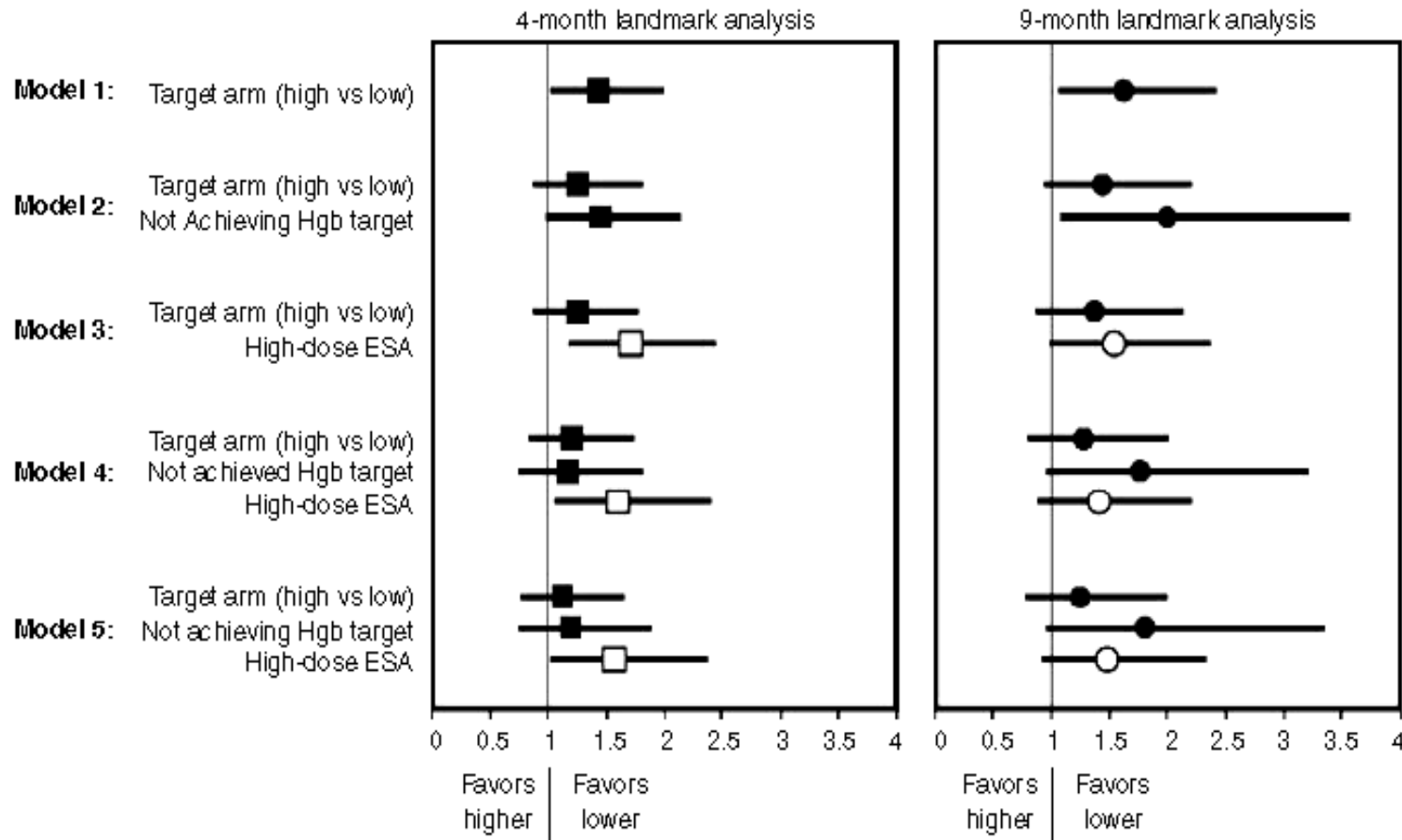
# Medical need for HIF-stabilizers - *pro*

- **HIF inhibitors are orally - active** (could provide in the future a more convenient and cost-effective therapy for anemia of chronic kidney disease than protein - based therapeutics)
- **They may stimulate erythropoiesis with much lower EPO levels** (given some concerns about clinical outcomes arising from use of ESAs that cause supraphysiologic circulating EPO levels, use of agents producing transient, more physiologic increases in endogenous EPO may have significant benefit in the treatment anemia in patients with CKD)

# Medical need for HIF-stabilizers - *contra*

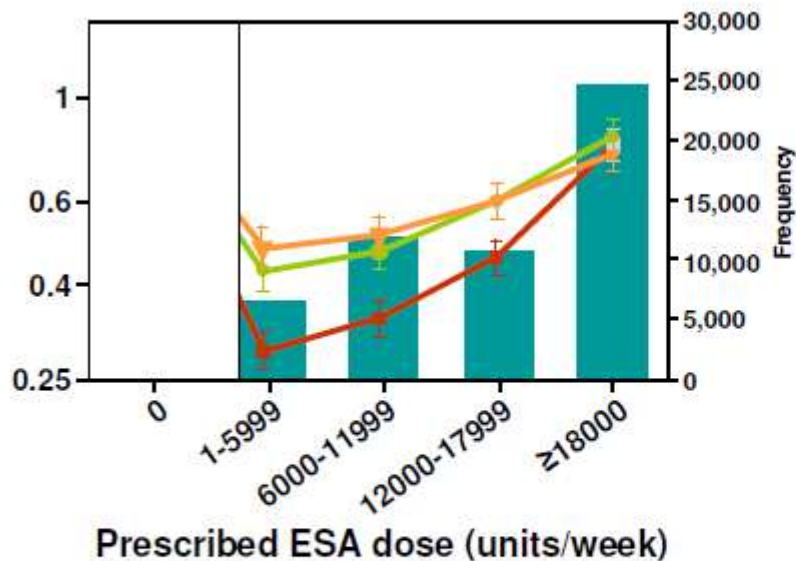
- **Potential and unpredictable adverse effects** (rare development of severe liver toxicity)
- **Several other (hundreds?) genes are also activated** (e.g. VEGF)
- **Larger and long - term clinical trials are needed** (in order to document the safety profile and final clinical benefits of these new compounds)

# Post-hoc analysis of the CHOIR study - high EPO doses were related to the higher risk of the cardiovascular complications

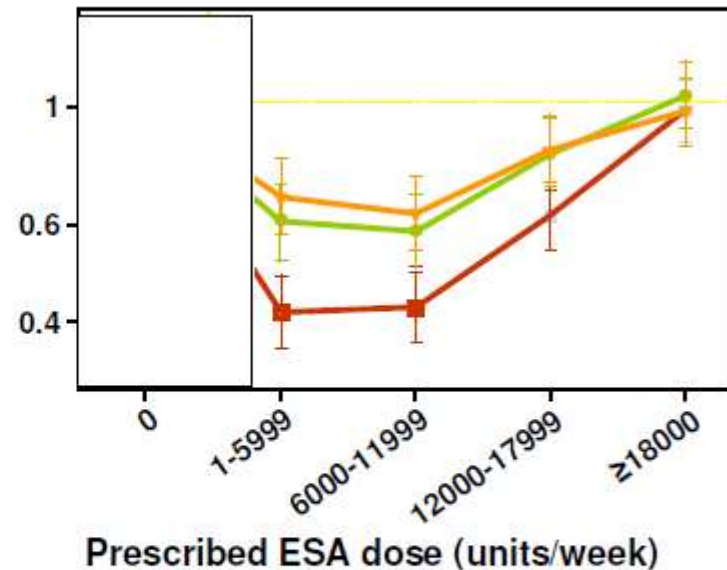


# Greater ESA doses associated with higher mortality

All Cause Mortality Hazard Ratio



Cardiovascular Mortality Hazard Ratio



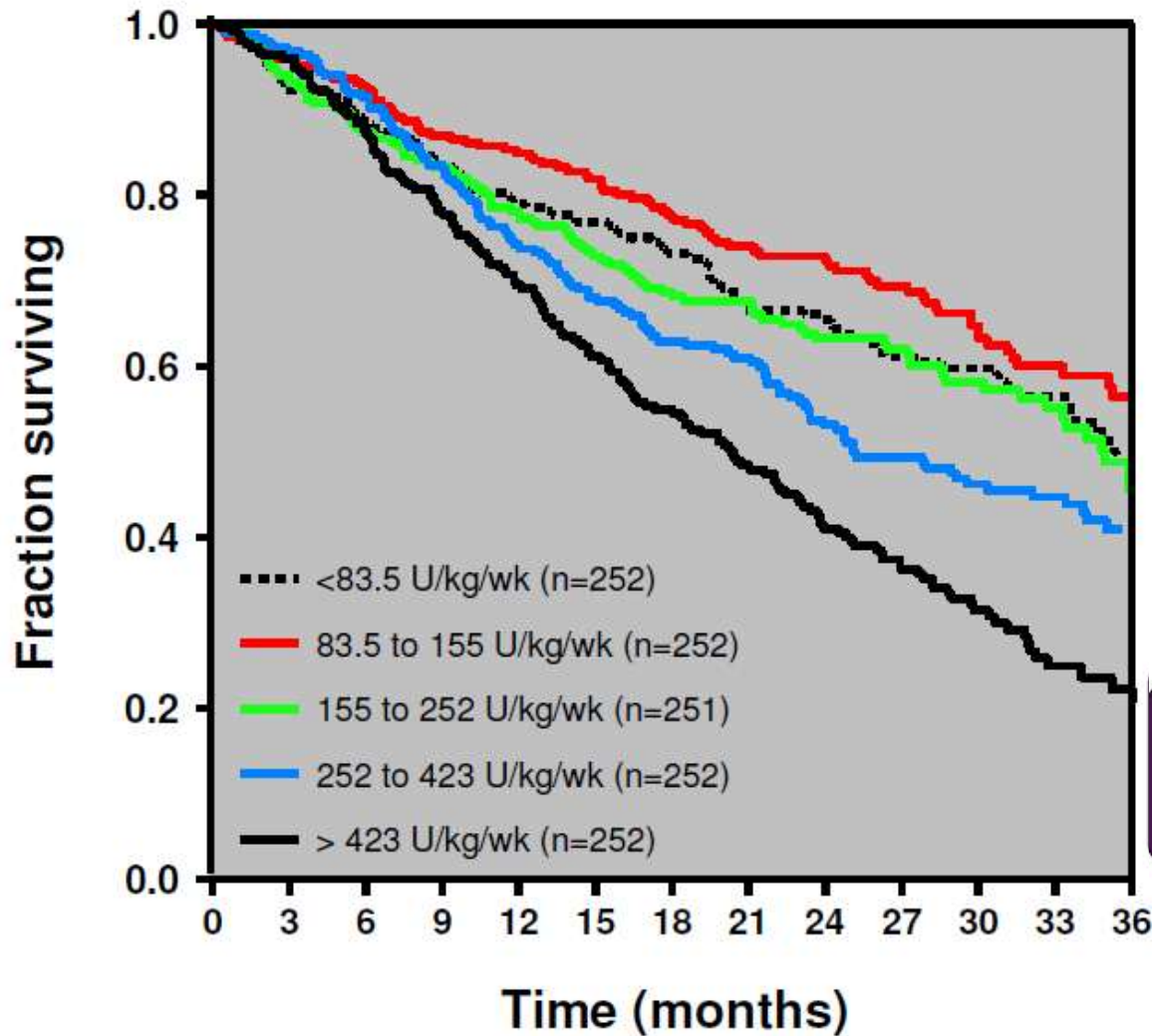
Unadjusted

Case-mix

Case-mix & MICS

n=58,058 dialysis patients

# ESA hyporesponsiveness associated with poor survival



FDA analysis  
Dose and  
responsiveness are  
inversely related

← Higher ESA dose  
Less ESA-responsive  
Poor survival

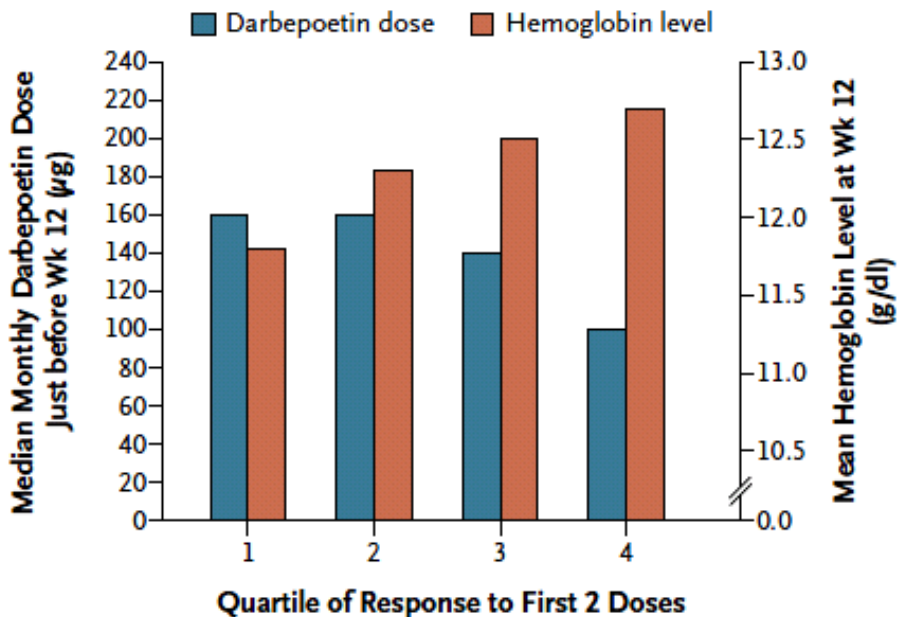
ORIGINAL ARTICLE

# Erythropoietic Response and Outcomes in Kidney Disease and Type 2 Diabetes

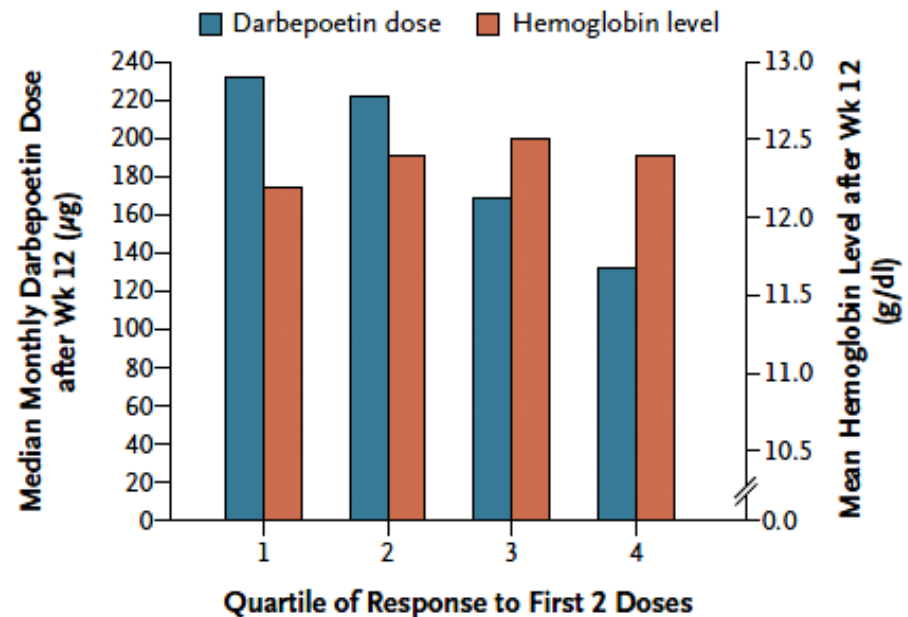
Scott D. Solomon, M.D., Hajime Uno, Ph.D., Eldrin F. Lewis, M.D., M.P.H.,  
Kai-Uwe Eckardt, M.D., Julie Lin, M.D., M.P.H.,  
Emmanuel A. Burdmann, M.D., Ph.D., Dick de Zeeuw, M.D., Ph.D.,  
Peter Ivanovich, M.D., Andrew S. Levey, M.D., Patrick Parfrey, M.D.,  
Giuseppe Remuzzi, M.D., Ajay K. Singh, 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

# Association between hemoglobin level and dose of darbepoetin alfa, according to the level of response to the first two doses in patients from the TREAT Study

**A Early Phase**



**B Late Phase**



# Rate of end points and adjusted hazard ratios in patients from the TREAT Study

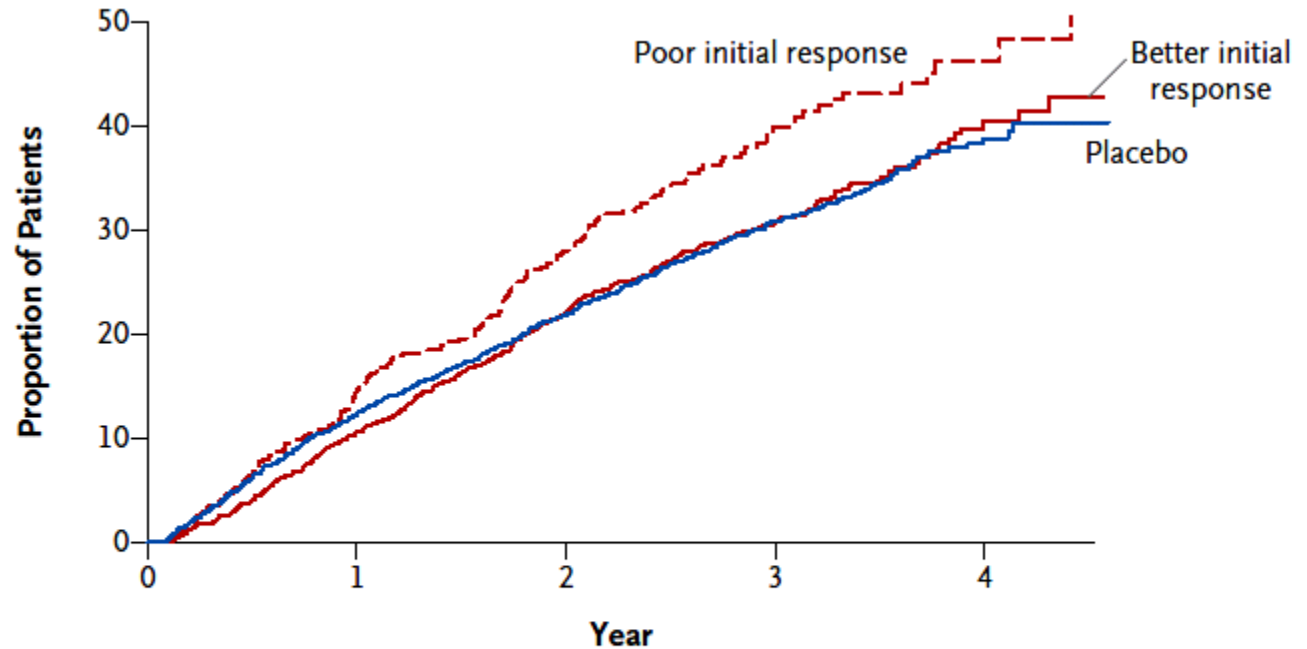
	<b>Placebo (N=1889)</b>	<b>Poor Response (N=471)</b>	<b>Better Response (N=1401)</b>	<b>Adjusted Hazard Ratio (95% CI)<sup>†</sup></b>
	<i>rate per 100 patient-yr (95% CI)</i>			
Cardiovascular composite	12.3 (11.3–13.4)	16.3 (14.0–18.9)	12.4 (11.2–13.6)	1.31 (1.09–1.59)
Death from any cause	7.5 (6.8–8.3)	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)

\* Event rates are shown for patients who survived the first 5 weeks without an event. CI denotes confidence interval.

<sup>†</sup> Hazard ratios are for patients with a poor initial response as compared with those with a better initial response. Hazard ratios have been adjusted for 12 baseline covariates, including age, sex, race, history of cardiovascular disease, urinary protein-to-creatinine ratio, baseline estimated glomerular filtration rate, baseline albumin level, history of cardiac arrhythmia, glycated hemoglobin level, baseline hemoglobin level, history of diabetic neuropathy, and baseline C-reactive protein level.

The rates of the study's primary end points among patients from the TREAT Study with a poor initial response to darbepoetin alfa, those with a better initial response and those in the original placebo group for the cardiovascular composite outcome

**A** Death, Myocardial Infarction, Stroke, Heart Failure, or Hospitalization for Myocardial Ischemia

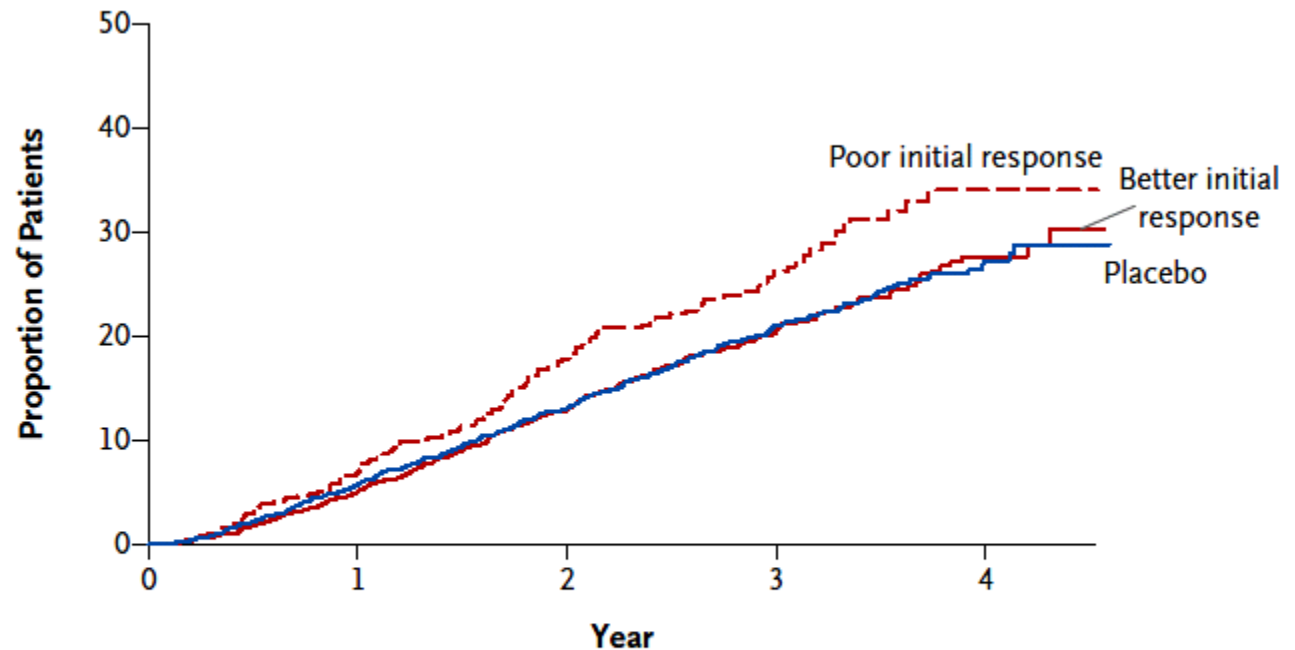


**No. at Risk**

Poor initial response	471	394	272	125	30
Better initial response	1401	1234	854	408	94
Placebo	1889	1611	1138	514	117

The rates of the study's primary end points among patients from the TREAT Study with a poor initial response to darbepoetin alfa, those with a better initial response and those in the original placebo group for the death from any cause

**B Death from Any Cause**

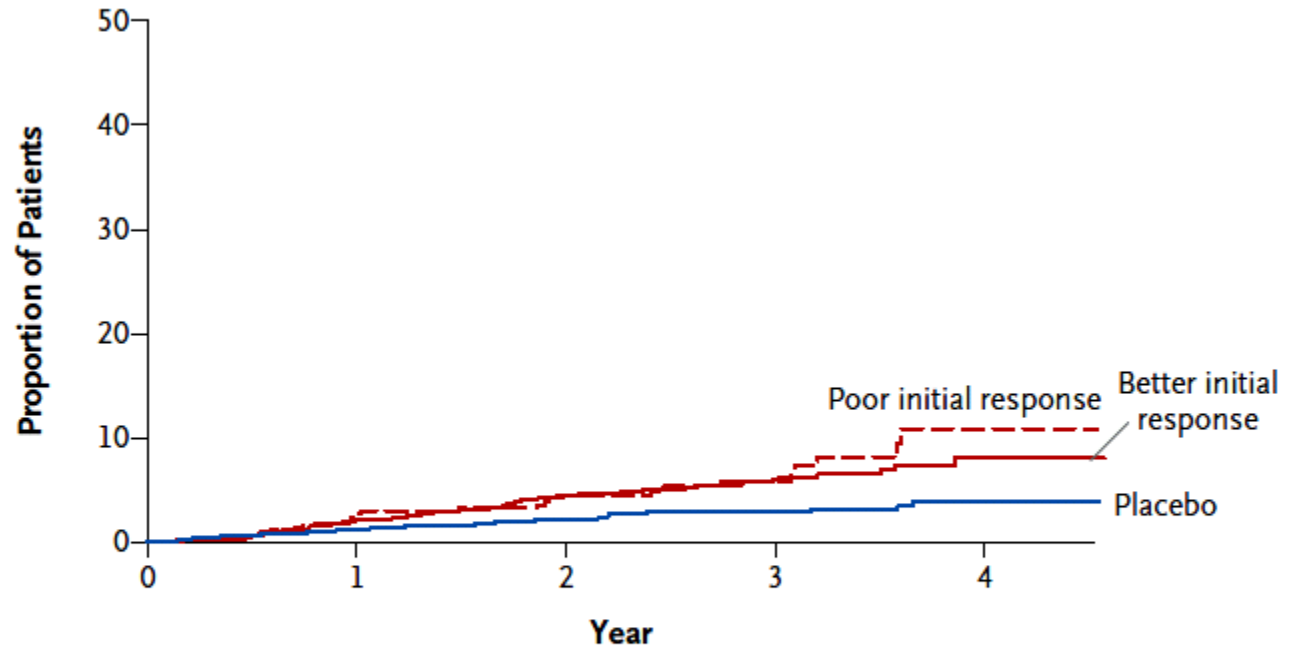


**No. at Risk**

Poor initial response	471	428	312	158	38
Better initial response	1401	1307	952	469	119
Placebo	1889	1732	1274	607	149

The rates of the study's primary end points among patients from the TREAT Study with a poor initial response to darbepoetin alfa, those with a better initial response and those in the original placebo group for the fetal and nonfatal stroke

**C Fatal or Nonfatal Stroke**



**No. at Risk**

Poor initial response	471	415	299	142	30
Better initial response	1401	1271	887	423	104
Placebo	1889	1687	1197	537	125

## ORIGINAL ARTICLE

## 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

N Engl J Med 2010;363:1146-55

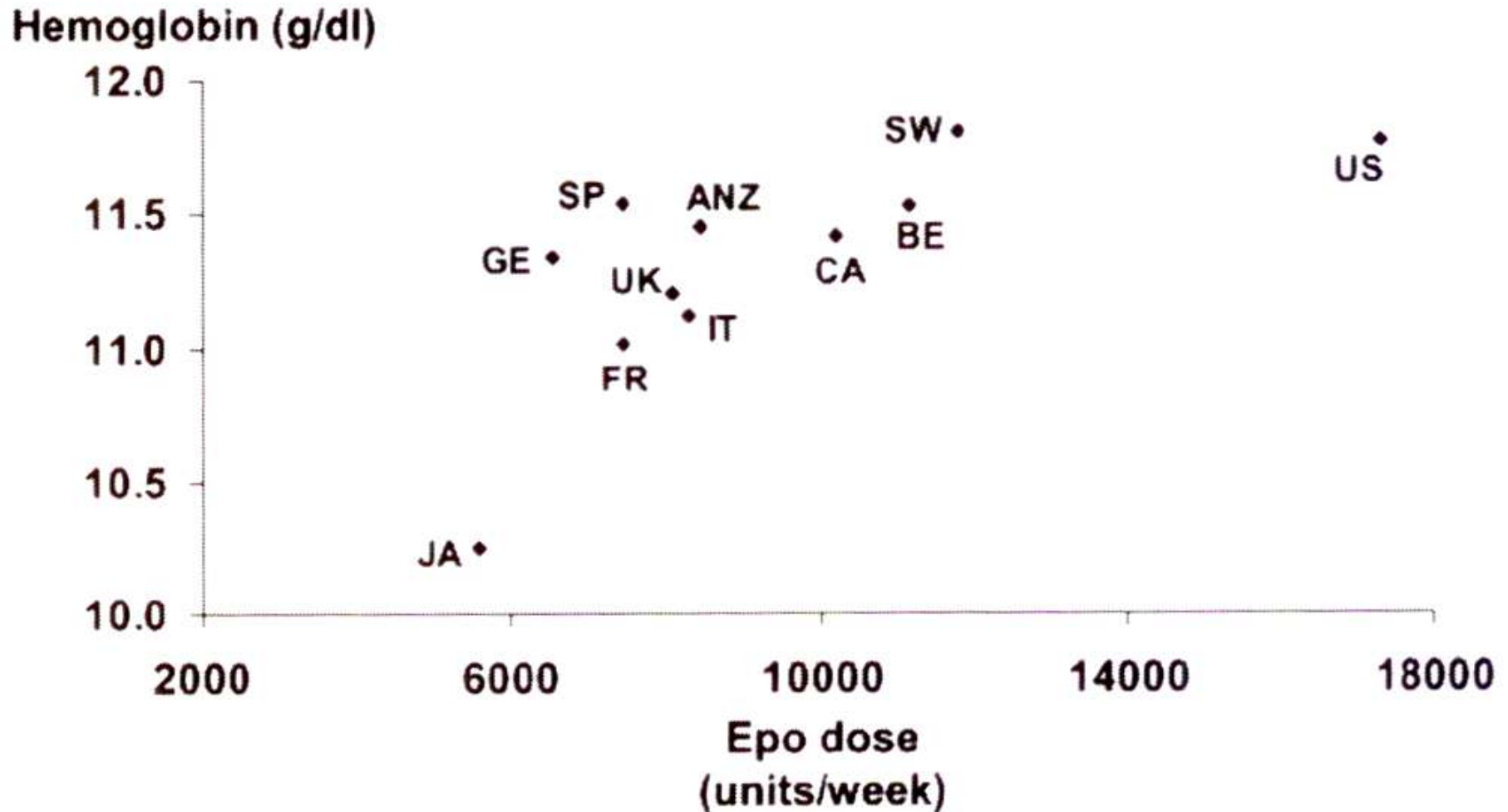
### RESULTS

Patients who had a poor initial response to darbepoetin alfa had a lower average hemoglobin level at 12 weeks and during follow-up than did patients with a better hemoglobin response (a change in hemoglobin level ranging from 2 to 15% or more) ( $P < 0.001$  for both comparisons), despite receiving higher doses of darbepoetin alfa (median dose, 232  $\mu\text{g}$  vs. 167  $\mu\text{g}$ ;  $P < 0.001$ ). Patients with a poor response, as compared with those with a better response, had higher rates of the composite cardiovascular end point (adjusted hazard ratio, 1.31; 95% confidence interval [CI], 1.09 to 1.59) or death (adjusted hazard ratio, 1.41; 95% CI, 1.12 to 1.78).

### CONCLUSIONS

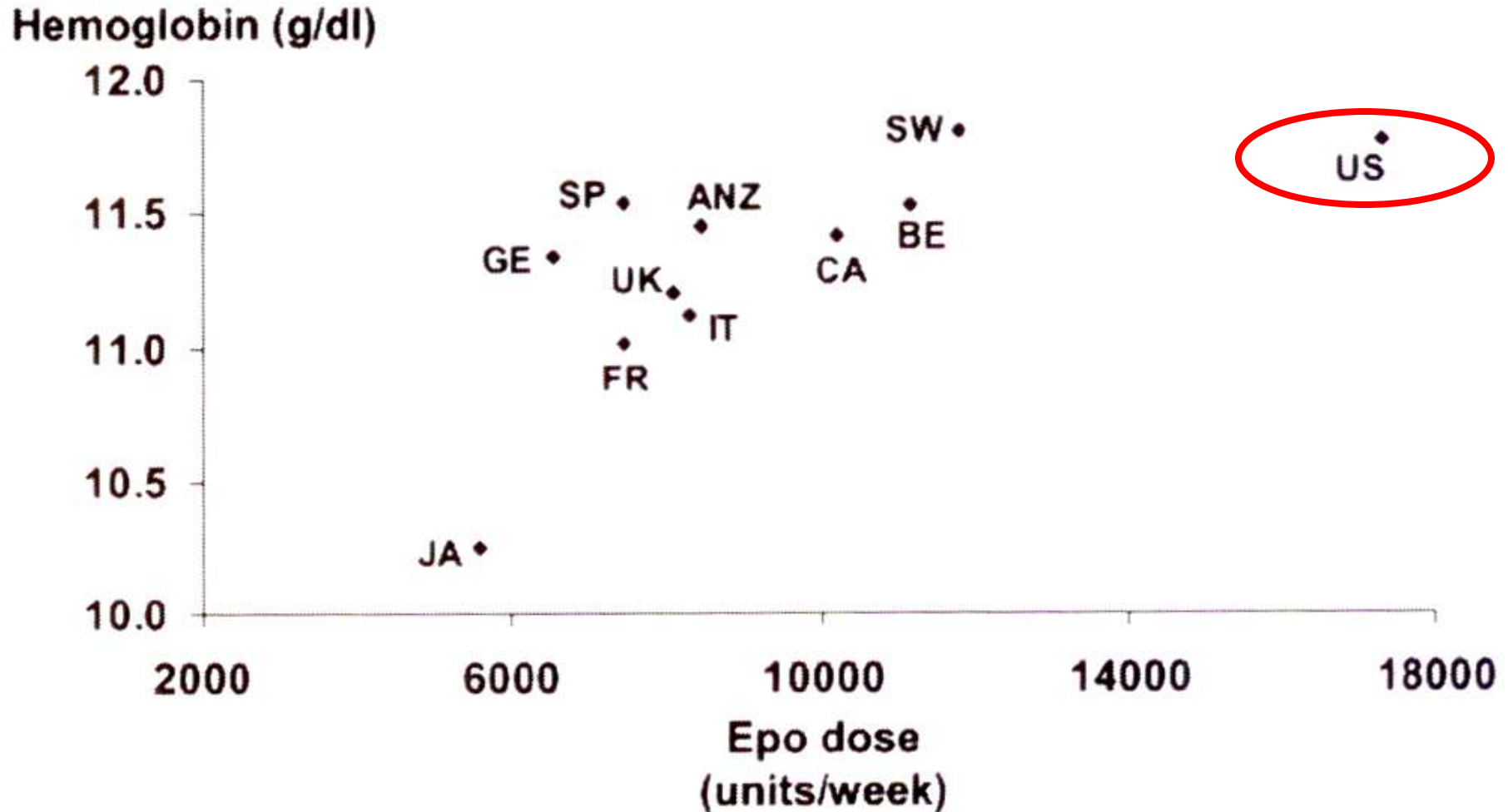
A poor initial hematopoietic response to darbepoetin alfa was associated with an increased subsequent risk of death or cardiovascular events as doses were escalated to meet target hemoglobin levels. Although the mechanism of this differential effect is not known, these findings raise concern about current target-based strategies for treating anemia in patients with chronic kidney disease. (Funded by Amgen; ClinicalTrials.gov number, NCT00093015.)

# Dose of EPO and mean hemoglobin concentration in different countries from the DOPPS II Study



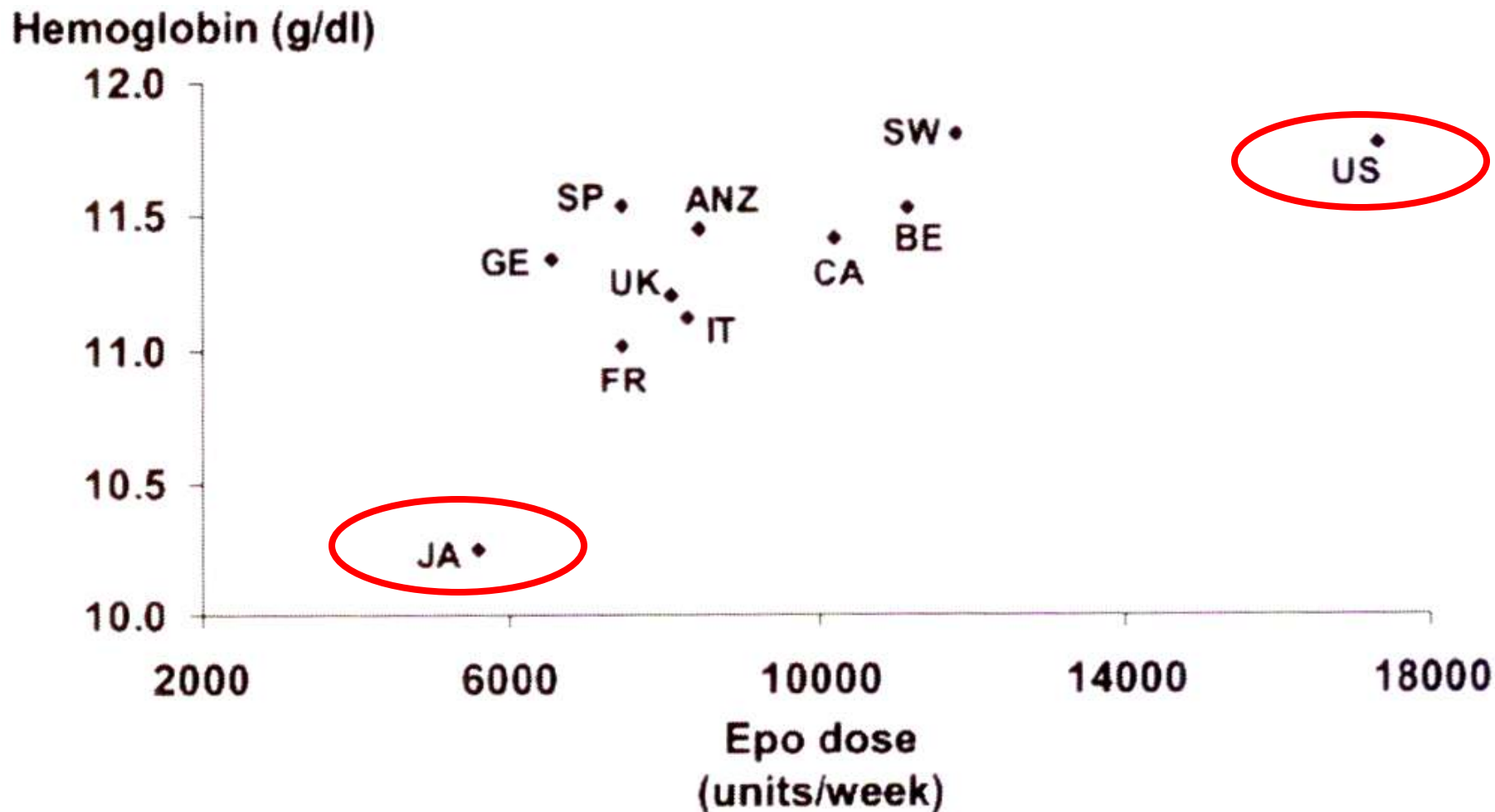
Singh A.J. Clin. J. Am. Soc. Nephrol., 2010, 5, 1355-1358

# Dose of EPO and mean hemoglobin concentration in different countries from the DOPPS II Study

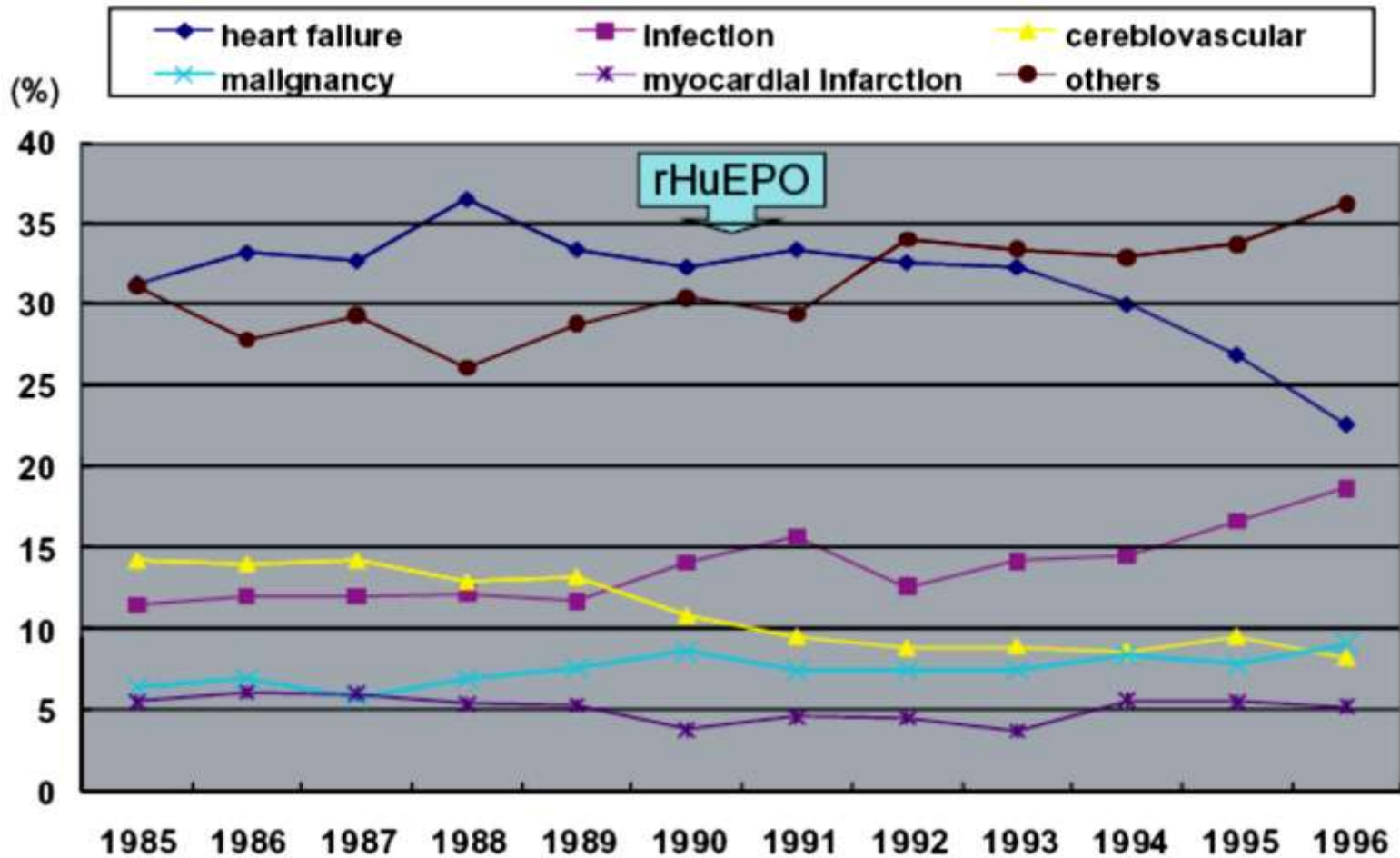


Singh A.J. Clin. J. Am. Soc. Nephrol., 2010, 5, 1355-1358

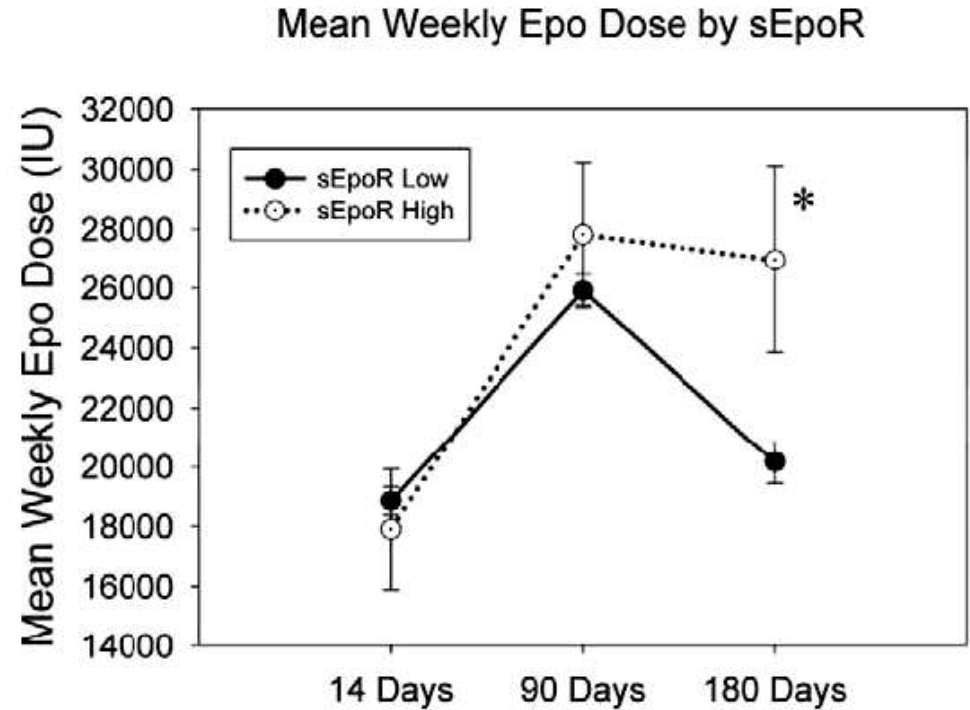
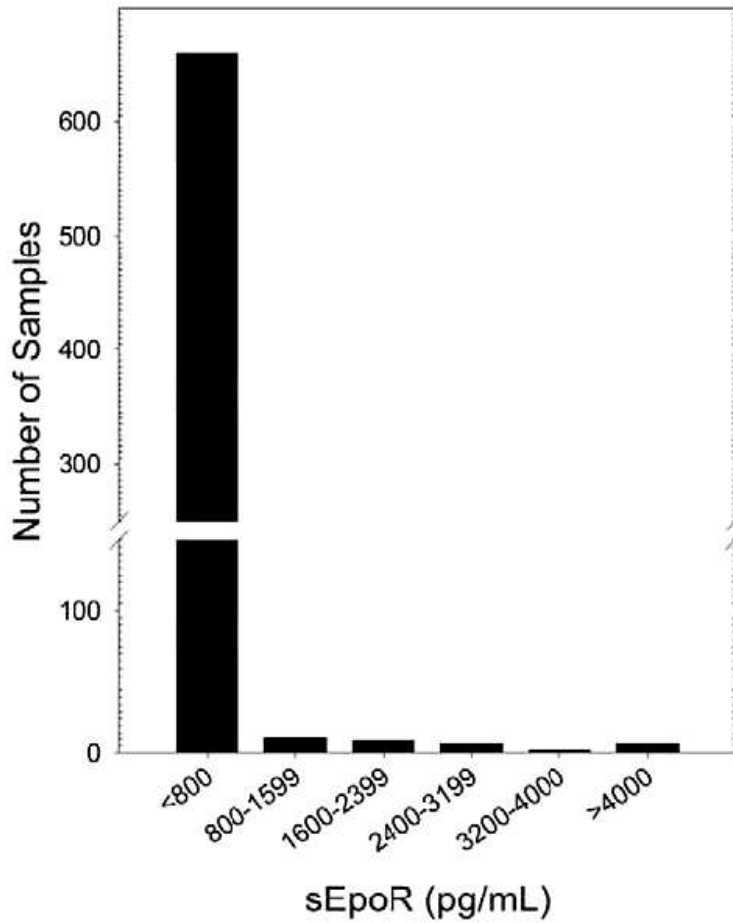
## Dose of EPO and mean hemoglobin concentration in different countries from the DOPPS II Study



# Causes of death in hemodialysis patients, before and after introduction of ESAs into the therapy of anemia in Japan



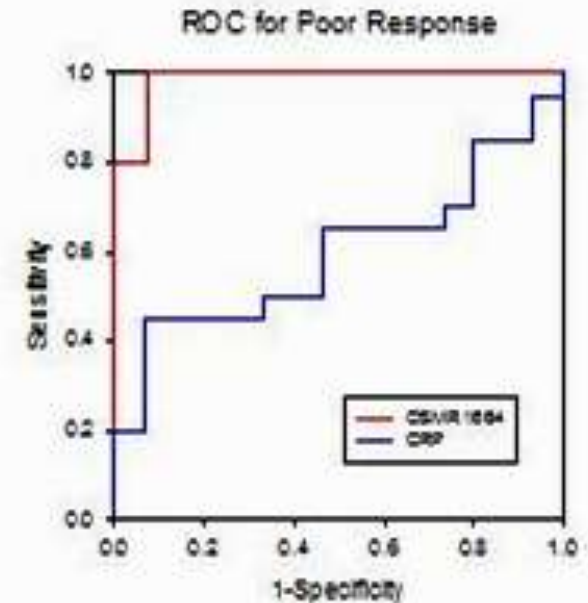
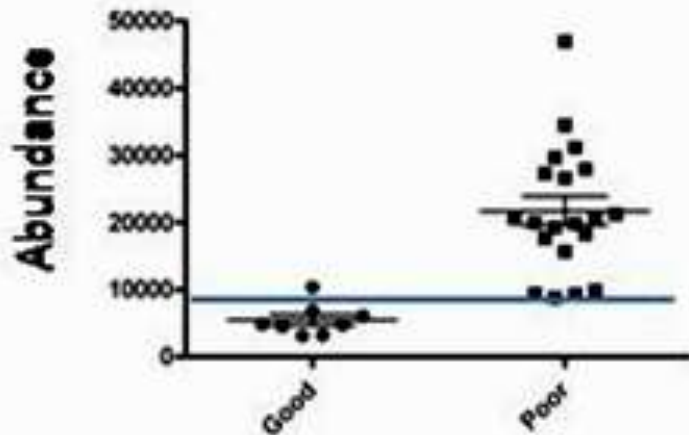
# Biomarkers of ESA response- soluble Epo Receptor



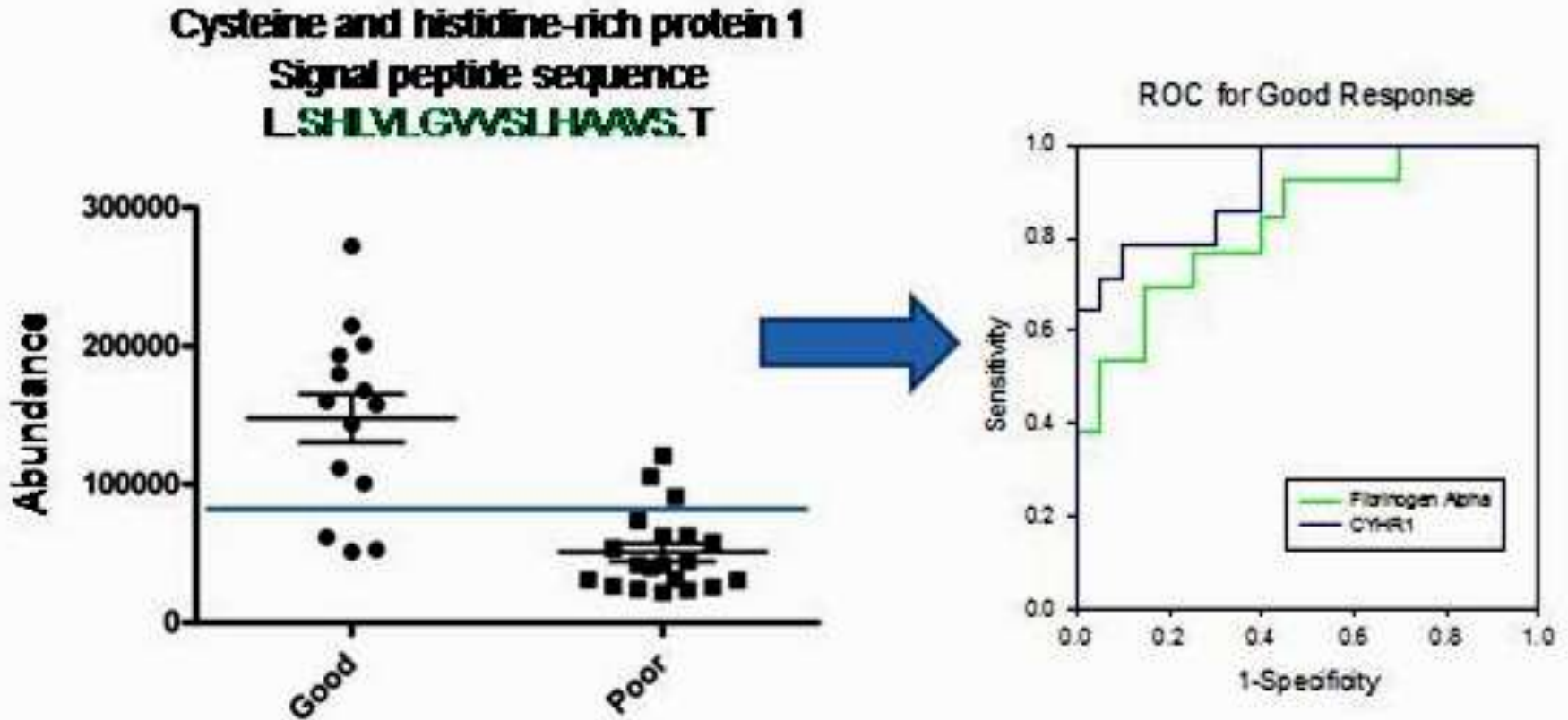
# Oncostatin M Receptor Beta (OSM $\beta$ ) fragment associate with poor response

## Oncostatin M Receptor Beta

E.NDEVEEERIAG.T  
E.NDEVEEERIAGT.E.G  
E.NDEVEEERIAGT.E.G



# Cysteine/histidine-rich 1 (CYHR1) fragment associated with good response



# KDIGO clinical practice guidelines for anemia in CKD

## ESA initiation- treatment



- ❖ We recommend that prior to initiation of ESA therapy all correctable causes of anemia be addressed (including iron deficiency and inflammatory states, if possible). (1A)
- ❖ In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). (1B)
- ❖ We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—a history of malignancy, or a history of stroke. (1C)

**Document in preparation, updated version 19 July 2011**

# KDIGO clinical practice guidelines for anemia in CKD

## ESA initiation- treatment



- ❖ For **CKD ND** patients with **Hb  $\geq 10.0$  g/dL**, we suggest that **ESA therapy not be initiated**. (2D)
- ❖ For **CKD ND** patients with **Hb  $< 10.0$  g/dL** we suggest that the decision whether to initiate **ESA therapy be individualized** based on the rate of fall of Hb, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia. (2C)
- ❖ For **CKD 5D** patients, we suggest that **ESA therapy be used to avoid** having the **Hb concentration fall below 9.0 g/dL**. (2B)
- ❖ In general, we suggest that ESAs **not be used to maintain Hb concentration above 11.5 g/dL**. (2C)

# KDIGO clinical practice guidelines for anemia in CKD



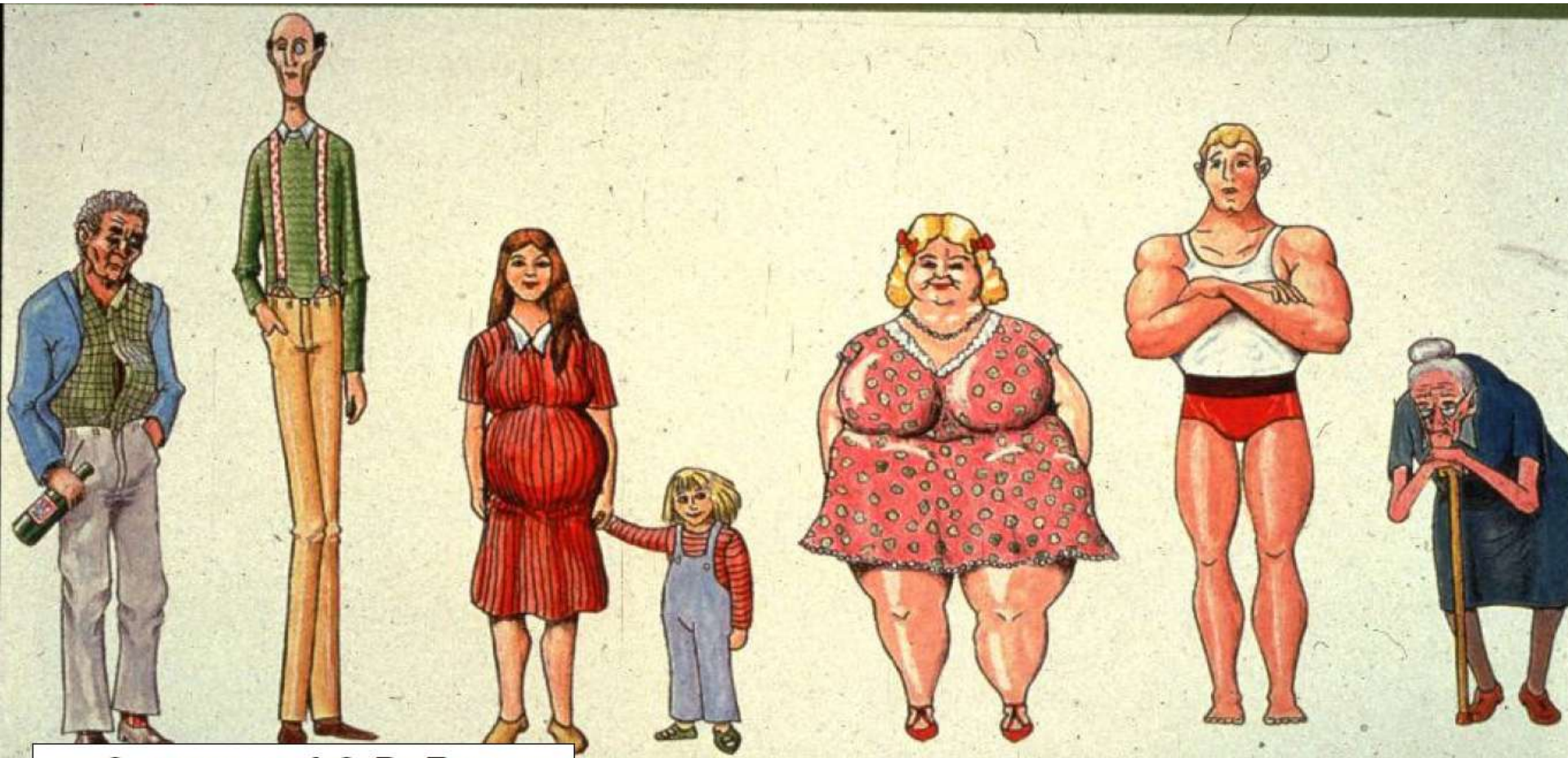
## ESA initiation- treatment

- ❖ Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dL and will be prepared to accept the risks. (Not Graded)
- ❖ In **all patients**, we recommend that **ESAs not be used** to intentionally **increase the Hb above 13 g/dL**. (1A)
- ❖ For all pediatric CKD patients, we suggest that the selection of Hb concentration at which ESA therapy is initiated in the individual patient include consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (2D)
- ❖ In all pediatric CKD patients receiving ESA therapy, we suggest that the selected Hb target be in the range of 11.0 to 12.0 g/dL. (2D)

**We know we must individualize**

**One size does not fit all!!!!**

**Practice Guidelines with patient specific recommendations needed**



Courtesy of G DeRay

# Finding the magic formula for anemia treatment

- ❖ A pinch of ESA...
- ❖ A pinch of iron..



- ❖ And mix everything with wisdom

**Thank you for your attention!**

**Andrzej Więcek**

***Katowice***

