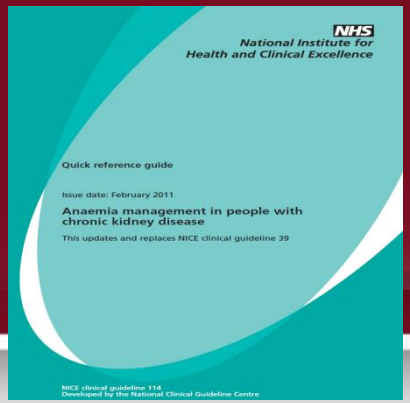
Ερυθροποιητίνες και νέοι αιμοποιητικοί παράγοντες

Ιωάννης Γ. Γριβέας, MD, PhD
Νεφρολόγος

athens-NEPHROLOGY



- **Anaemia** is a state in which the quality and/or quantity of circulating red blood cells are below normal; it is associated with progression of CKD.

- Hb levels fall as kidney function declines.

- Adverse effects associated with anaemia include:
  - tiredness
  - shortness of breath
  - lethargy
  - palpitations
  - increased sensitivity to the cold
  - reduced cognition and concentration.

Anemia in CKD

- Prevalence
  - Stages 1-2: <10%
  - Stage 3: 20-40%
  - Stage 4: 50-60%
  - Stage 5: >70%
- Mechanisms
  - EPO deficiency
  - Iron deficiency and mobilization disorders
  - Shortened RBC lifespan
  - Hyperparathyroidism
  - Vitamin deficiencies

Current Treatment Paradigm / Options for Anemia

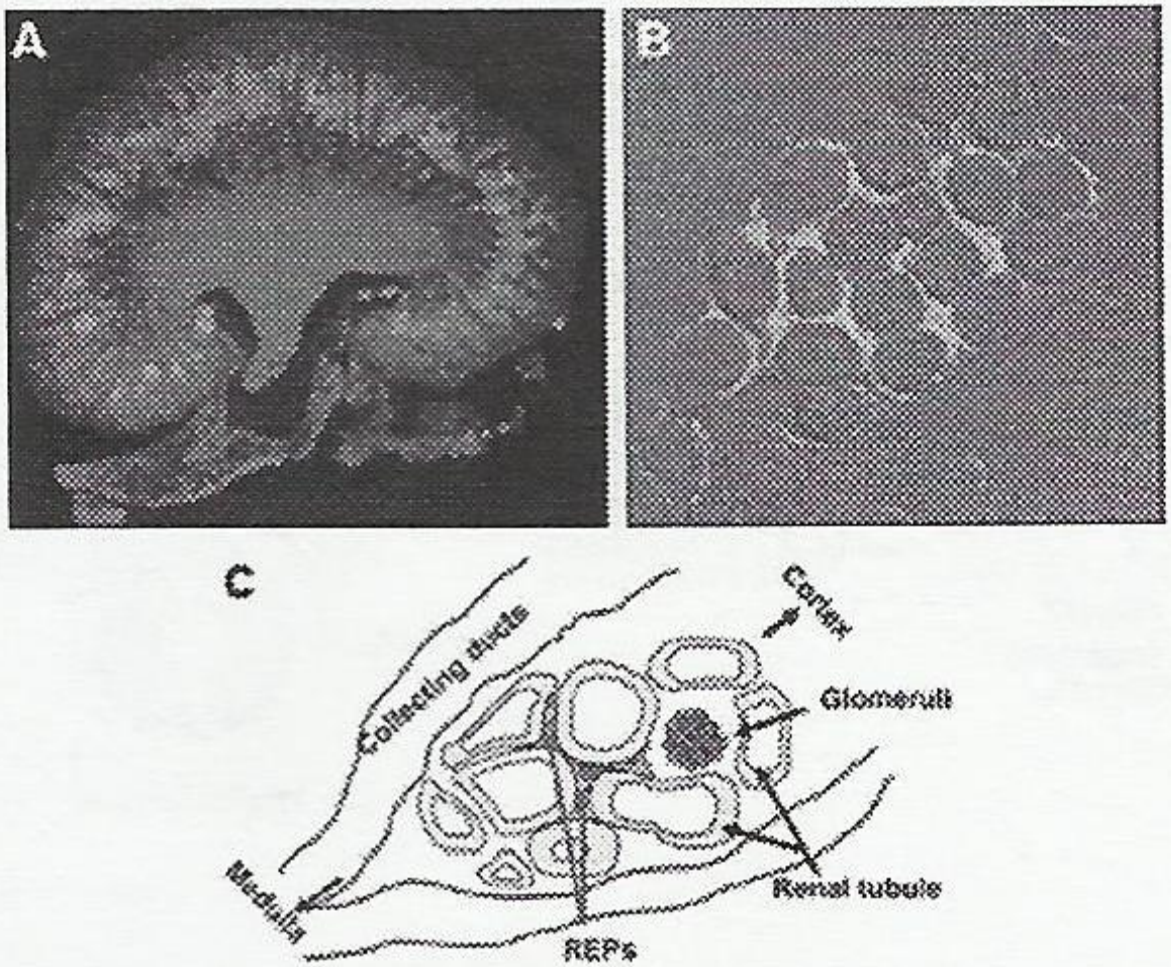
- Transfusion
- Erythropoesis stimulating agents (ESAs)
  (epoeitin alpha & beta, darbepoetin, methoxy polyethylene glycol epoetin beta)
- Iron
  (iron sucrose, ferric gluconate, iron dextran, ferumoxytol, ferrous sulfate)

Endogenous Erythropoietin

- Endogenous erythropoietin production primarily kidney & liver
- Physiologic concentrations
  - 5 to 20 mU/ml
  - Diurnal variation with higher afternoon & lower night-time levels
- Tissue hypoxia is main stimulus for modulating production
  - Erythropoietin levels in various conditions

• High altitude training	3-5 fold increase over baseline
• Acute blood loss (0.5L)	2-4 fold increase over baseline
• Aplastic Anemia	500-20,000 mU/ml
• Polycythemia V	2-5 mU/ml

EPO-producing cells in the kidney



Pan X, Suzuki N, Hirano I, Yamazaki S, Minegishi N, Yamamoto M (2011) Isolation and Characterization of Renal Erythropoietin-Producing Cells from Genetically Produced Anemia Mice. *PLoS ONE* 6(10): e25839. doi:10.1371/journal.pone.0025839

Transfusion Medicine and Hemotherapy

Review Article

Transfus Med Hemother 2013;40:302–309
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Physiology and Pharmacology of Erythropoietin

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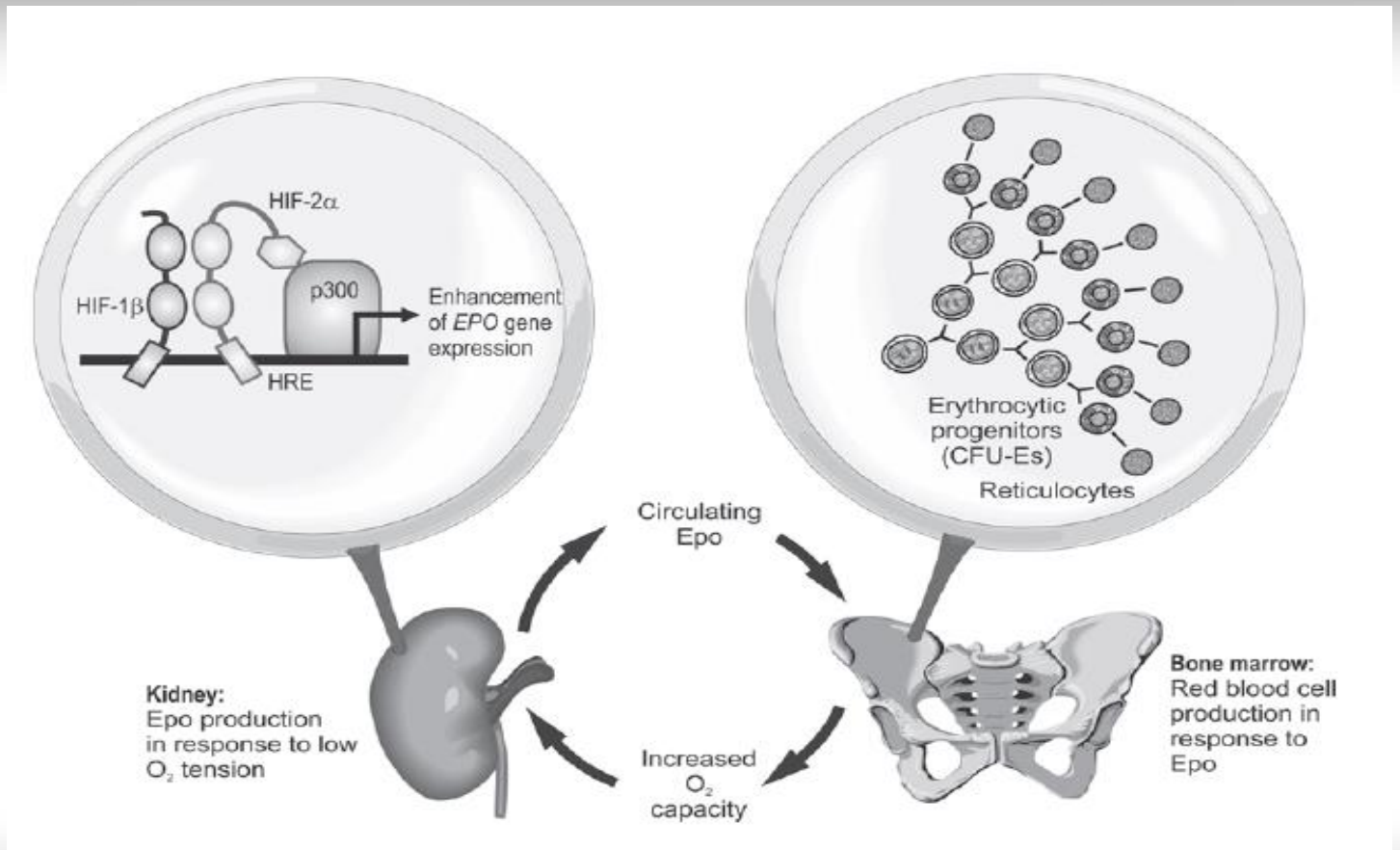
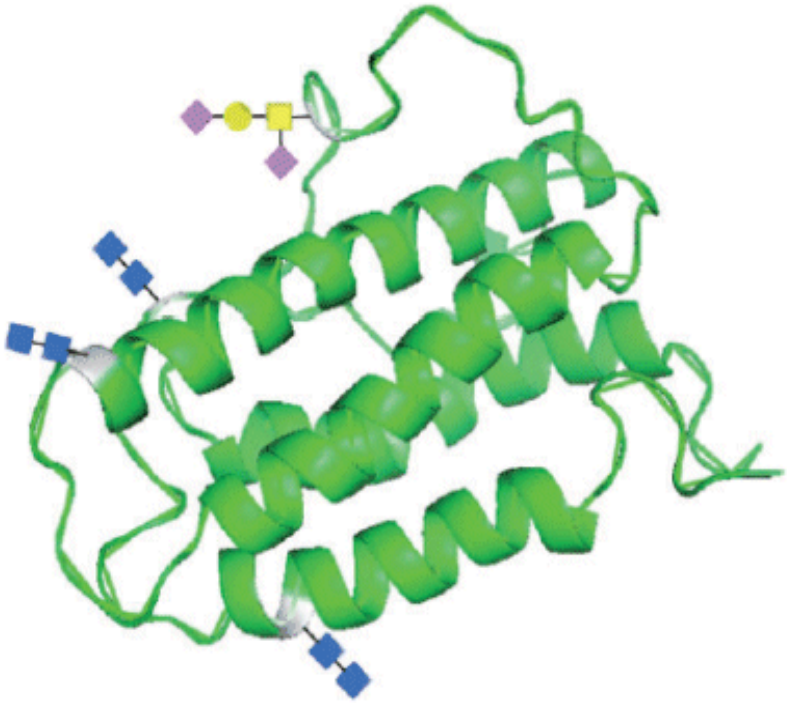
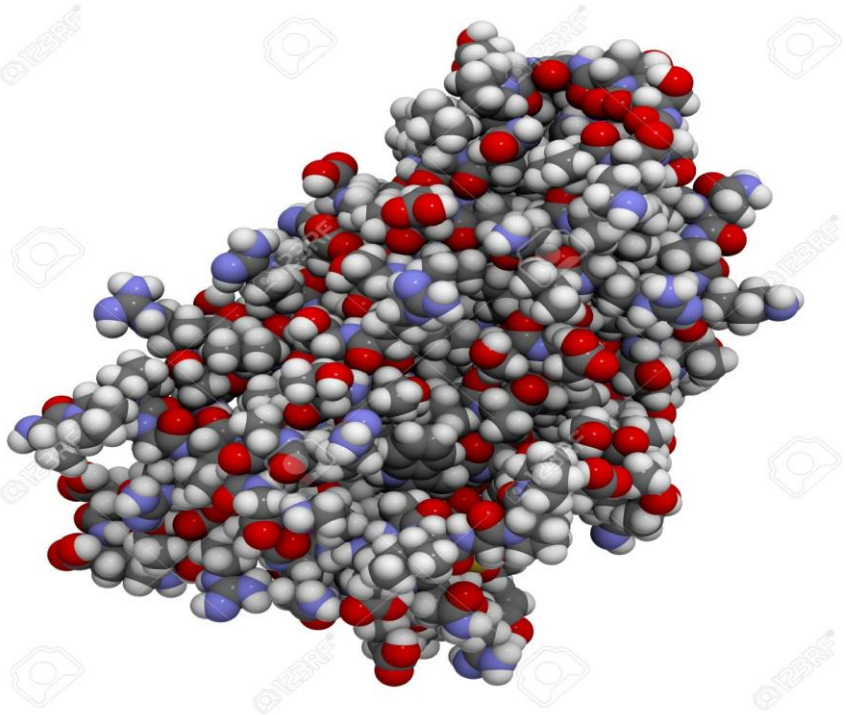




Erythropoietin



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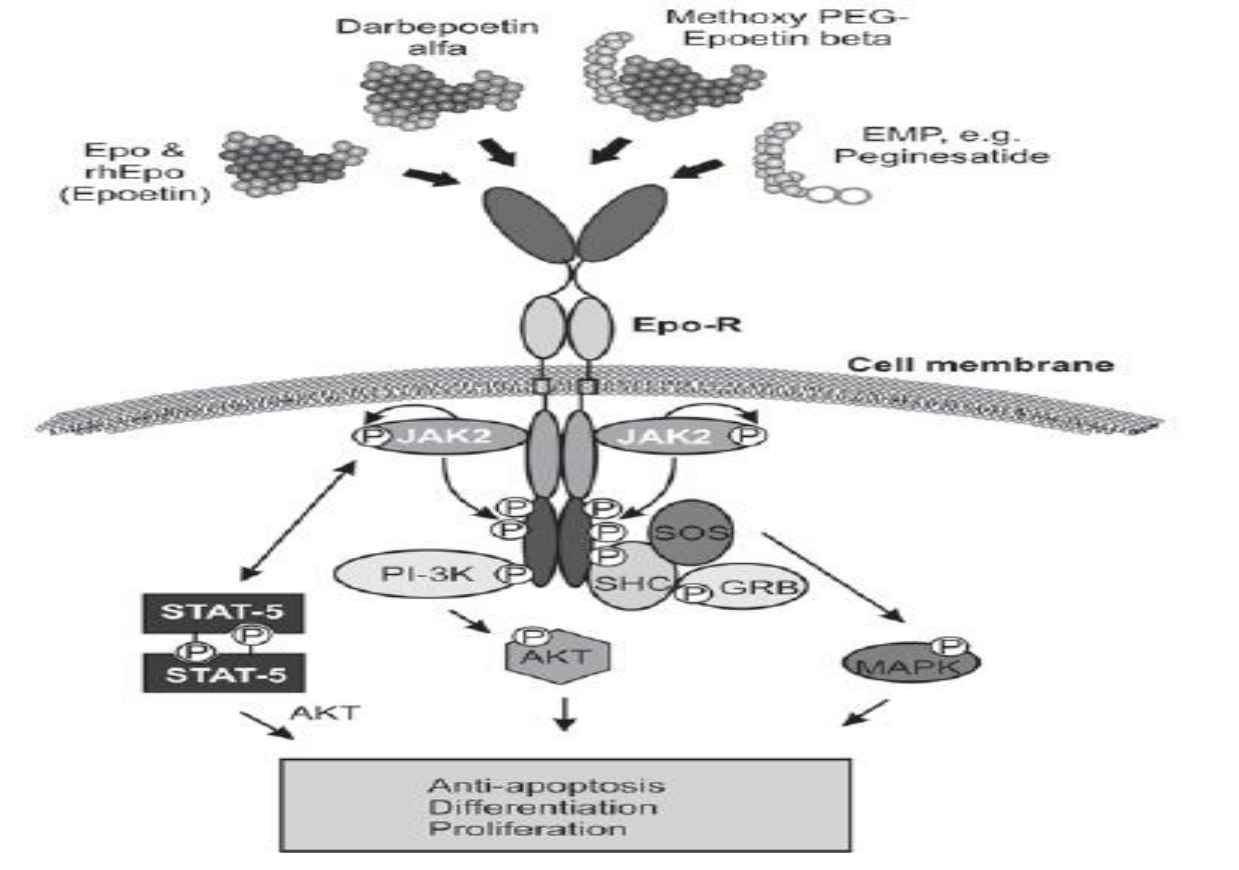


Recombinant EPO preparations

'Epoetin' is the international non-proprietary drug name (INN) for eucaryotic cell-derived rhEpo, whose amino acid sequence is identical with that of endogenous human Epo. Differences in the amino acid residues chain are indicated by a random prefix (e.g. 'darbepoetin'). The glycosylation pattern is indicated by a Greek letter (alfa, beta, etc.). Two brands of innovator CHO cell-derived rhEpo, namely epoetin alfa and epoetin beta, were launched as anti-anemic agents

Recombinant EPO preparations

about 25 years ago. Epoetin alfa has been marketed in the USA as Epogen® (Amgen) for the treatment of CKD patients on hemodialysis and as Procrit® (Johnson and Johnson) for other indications through an agreement with Amgen, and outside the USA mainly as Eprex® or Erypo® (Johnson and Johnson subsidiary Ortho Biotech), and Espo® (Kirin). Epoetin beta has been mainly marketed as NeoRecormon® (F. Hoffmann-LaRoche) and Epogin® (Chugai/F. Hoffmann-LaRoche). The originator epoetins alfa and beta are used for the same major indications (anemias associated with CKD or myelosuppressive chemotherapy treated cancer). In 2009, epoetin theta has been launched as another stand-alone CHO cell-derived rhEpo (Eporatio®, Ratiopharm; Biopoin®, CT Arzneimittel) in the European Union (EU). In some parts of the world, CKD patients have been treated with epoetin omega, which is expressed in EPO cDNA-tranfected baby hamster kidney (BHK, from Syrian hamster) cells, but apparently this product is not widely used.

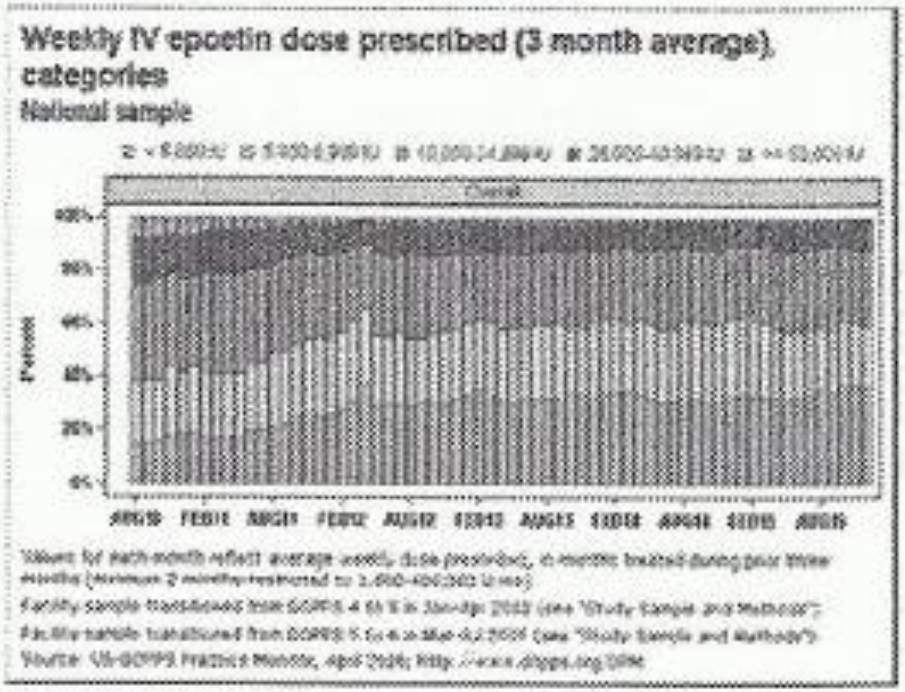
Recombinant EPO preparations

indications of the reference product, Eprex/Erypo. One of the biosimilars has received the INN epoetin alfa (Binocrit®, Sandoz; Epoetin alfa Hexal®, Hexal Biotech; Abseamed®, Medice Arzneimittel Putter) and the other epoetin zeta (Silapo®, Stada; Retacrit®, Hospira). The several brand names are ac-

There are recombinant ESAs with prolonged survival in circulation ('biobetter'). First darbepoetin alfa (Aranesp®; Amgen) has come, a hyperglycosylated analog (37.1 kDa) of rhEpo, which contains two additional N-glycans in association with an exchange of five amino acids [7]. Compared with the terminal half-life of IV administered epoetin (6–9 h), the half-life of darbepoetin alfa is three- to fourfold longer (25 h), which allows for less frequent application [39]. Another biobetter is methoxy polyethylene glycol-epoetin beta (methoxy PEG-epoetin beta; Mircera®, F. Hoffmann-LaRoche). The half-life of methoxy PEG-epoetin beta (60 kDa) amounts to 130–140 h on IV injection. The prolonged in vivo survival of darbepoetin alfa and methoxy PEG-epoetin beta is in part due to a reduced EpoR binding affinity. 1 µg of darbepoetin alfa or of methoxy PEG-epoetin beta peptide corresponds biophysically to 200 IU rhEpo peptide. Clinically, however, the long-acting products may allow for dose reductions below the predicted 1: 200 ratio [39].

ESA Use in Anemia of CKD

- Erythropoesis stimulating agents are typically given in large, pulsatile doses
- The majority of dialysis patients receive less than 10,000 units per week
- A significant minority of patients receive very high doses > 25,000 units per week



ESAs Pros and Cons

- Pros
  - Reproduces deficient native hormone
  - Effective in most patients
  - Well tolerated in most patients
  - >25 years experience
  - IV administration invisible to HD patients
- Cons
  - SC administration in non-HD patients
  - Long-term cardiovascular events
  - ESA resistance
  - Do not address iron mobilization disorders

	Normal HCT (Besarab et al 1998, NEJM)	CHOIR (Singh et al 2006, NEJM)	CREATE (Drueke et al 2006, NEJM)
Πλήθος ασθενών	1.233	1.432	603
Στάδιο νόσου	ΧΝΝ – 5 με καρδιολογικό νόσημα	ΧΝΝ 3 – 4	ΧΝΝ 3 – 4
Στόχος μελέτης	Ποιες είναι οι επιπτώσεις της φυσιολογικοποίησης των τιμών Hb σε ασθενείς με ΧΝΝ και καρδιά	Ποιά είναι τα βέλτιστα επίπεδα Hb;	Αν θα υπάρξει βελτίωση της καρδιακής λειτουργίας με τη διόρθωση της αναιμίας
Στόχοι Hb			
Χαμηλό όριο	10 g/dl	11.3 g/dl	10.5 – 11.5 g/dl
Υψηλό όριο	14 g/dl	13.5 g/dl	13 – 15 g/dl
Follow up	30 μήνες	16 μήνες	35 μήνες
Αποτέλεσμα	Σε ασθενείς με ΧΝΝ-5 και συμφορητική καρδιακή ανεπάρκεια ή ισχαιμικό επεισόδιο, η πλήρης διόρθωση της αναιμίας δεν συστήνεται	Ο υψηλός στόχος οδήγησε σε αύξηση των κινδύνων σε σχέση με τον χαμηλό, χωρίς βελτίωση της QoL	Η διόρθωση της αναιμίας δεν φαίνεται να διορθώνει τον κίνδυνο εμφάνισης καρδιαγγειακών συμβαμάτων

The NEW ENGLAND JOURNAL of MEDICINE

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

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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 rescue darbepoetin alfa when the hemoglobin level was less than 9.0 g per deciliter. The primary end points were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease.

RESULTS

Death or a cardiovascular event occurred in 632 patients assigned to darbepoetin alfa and 602 patients assigned to placebo (hazard ratio for darbepoetin alfa vs. placebo, 1.05; 95% confidence interval [CI], 0.94 to 1.17; P=0.41). Death or end-stage renal disease occurred in 652 patients assigned to darbepoetin alfa and 618 patients assigned to placebo (hazard ratio, 1.06; 95% CI, 0.95 to 1.19; P=0.29). Fatal or nonfatal stroke occurred in 101 patients assigned to darbepoetin alfa and 53 patients assigned to placebo (hazard ratio, 1.92; 95% CI, 1.38 to 2.68; P<0.001). Red-cell transfusions were administered to 297 patients assigned to darbepoetin alfa and 496 patients assigned to placebo (P<0.001). There was only a modest improvement in patient-reported fatigue in the darbepoetin alfa group as compared with the placebo group.

CONCLUSIONS

The use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who were not undergoing dialysis did not reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event or death or a renal event) and was associated with an increased risk of stroke. For many persons involved in clinical decision making, this risk will outweigh the potential benefits. (ClinicalTrials.gov number, NCT00093015.)

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 individual sites are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

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N Engl J Med 2009;361.

Οδηγίες – Guidelines

ERBP Position Paper 2010

Haemoglobin target

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NDT Advance Access published June 29, 2010

Nephrol Dial Transplant (2010) 1 of 5
doi: 10.1093/ndt/gfq336

NDT Nephrology Dialysis Transplantation

Editorial Review

Target haemoglobin to aim for with erythropoiesis-stimulating agents: a position statement by ERBP following publication of the Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) Study

Francesco Locatelli[1], Pedro Aljama[2], Bernard Canaud[3], Adrian Covic[4], Angel De Francisco[5], Iain C. Macdougall[6], Andrzej Wiecek[7], Raymond Vanholder[8] and On behalf of the Anaemia Working Group of European Renal Best Practice (ERBP)

[1]Department of Nephrology, Dialysis and Renal Transplant, "Alessandro Manzoni" Hospital, Lecco, Italy, [2]Department of Nephrology, University Hospital Reina Sofia, Cordoba, Spain, [3]Nephrology, Dialysis and Intensive Care Department. Lapeyronie University Hospital, Montpellier, France, [4]University "Gr. T. Popa" Iasi and Hospital "C. I. Parhon" Iasi, Romania, [5]Department of Nephrology Hospital Universitario Valdecilla, Santander, Spain, [6]Department of Renal Medicine, King's College Hospital, London, UK, [7]Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia, Katowice, Poland and [8]Nephrology Section, Department of Internal Medicine, University Hospital, Ghent, Belgium

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Abstract

The European Renal Best Practice (ERBP), which are issued by ERA–EDTA, are suggestions for clinical practice in areas in which evidence is lacking or weak, together with position statements on recently published randomized controlled trials, or on existing guidelines and recommendations. In 2009, the Anaemia Working Group of ERBP published its first position statement about the haemoglobin target to aim for with erythropoietin-stimulating agents (ESA) and on issues that were not covered by K-DOQI in 2006–07. This second position paper of the group follows the publication of the Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) Study. This multi-centre, placebo-controlled trial compared cardiovascular and renal outcomes in 4038 patients with type 2 diabetes, chronic kidney disease not on dialysis, and anaemia who were randomized to complete anaemia correction (haemoglobin target of 13 g/dL using darbepoetin alfa) or placebo (with a haemoglobin rescue value of 9 g/dL).
Following the findings of the TREAT study, the Anaemia Working Group of ERBP maintains its view that 'Hb values of 11–12 g/dL should be generally sought in the CKD population without intentionally exceeding 13 g/dL' and that the doses of ESA therapy to achieve the target haemoglobin should also be considered. More caution is suggested when treating anaemia with ESA therapy in patients with type 2 diabetes not undergoing dialysis (and probably in diabetics at all CKD stages). In those with ischaemic heart disease or with a previous history of stroke, possible benefits should be weighed up against an increased risk of stroke recurrence, when deciding which Hb level to aim for.
These recommendations are not intended to represent a new guideline as they are not the result of a systematic review of the evidence.

Keyword: anemia; chronic kidney disease; diabetes; erythropoiesis stimulating agents; stroke

Introduction (aim and scope)

Some years ago, the nephrological community planned a single set of international guidelines under the aegis of Kidney Disease Improving Global Outcomes (KDIGO) [1]. Consequently, the ERA–EDTA agreed to issue afterwards only suggestions for clinical practice in areas in which evidence is lacking or weak, together with position statements on recently published randomized controlled trials (RCTs), or on existing guidelines and recommendations issued by other bodies or previous European Best Practice Guidelines (EBPG) [2]. Following the publication of KDOQI guidelines about anaemia in 2006/2007 [3,4], the Anaemia Working Group of European Renal Best Practice (ERBP) published its first position statement [5], giving its opinion on the 'hot' topic of haemoglobin (Hb) targets and on recently raised issues that were not covered by KDOQI in 2006 [3].
The aim of this second position statement on anaemia is to give guidance on the interpretation of the recently published Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) Study [6], and its possible relevance to recommended treatments and Hb targets to be used when treating chronic kidney disease (CKD) patients with erythropoiesis-stimulating agents (ESA) therapy, while

The ERBP group also feels that it is reasonable to suggest that:

(i) In patients with type 2 diabetes not undergoing dialysis (and probably in diabetics at all CKD stages), more caution is needed when treating anaemia with ESA therapy. In diabetic patients with a history of stroke, a lower target is more sensible (10–12 g/dL), balancing the risk–benefit of treatment and the desired Hb target in the individual patient. It is also of paramount importance to involve the patient in the decision making, and seek their personal views after a discussion about the benefits/risks of treatment. On this respect, the patient's opinion should be carefully taken into consideration.

(ii) The risk–benefit of increased transfusions should also be considered carefully, especially for patients eligible for transplantation."

 Locatelli F, et al. Nephrol Dial Transplant 2010;25(9):2846-2850

Οδηγίες – Guidelines

ERBP Position Paper 2010

Continue…

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Following the findings of the TREAT study, the Anaemia Working Group of ERBP maintains its view that 'Hb values of 11–12 g/dL should be generally sought in the CKD population without intentionally exceeding 13 g/dL' and that the doses of ESA therapy to achieve the target haemoglobin should also be considered. More caution is suggested when treating anaemia with ESA therapy in patients with type 2 diabetes not undergoing dialysis (and probably in diabetics at all CKD stages). In those with ischaemic heart disease or with a previous history of stroke, possible benefits should be weighed up against an increased risk of stroke recurrence, when deciding which Hb level to aim for.

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"(iii) In diabetic patients with ischaemic heart disease or with a previous history of stroke, possible benefits of reduced need for coronary revascularization procedures and transfusions should be weighed up against an increased risk of stroke recurrence, when deciding which Hb level to aim for, and use of the lowest possible doses of ESA appears reasonable.

(iv) In patients with CKD and a previous history of cancer, the risk of tumour recurrence and related death should be considered when deciding whether or not to start ESA treatment. Again, in these patients, the lowest possible doses of ESA should be used."

Locatelli F, et al. Nephrol Dial Transplant 2010;25(9):2846-2850

Οδηγίες - Guidelines

ERBP Position Paper 2010

"Treatment of renal anemia

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Following the findings of the TREAT study, the Anaemia Working Group of ERBP maintains its view that Hb values of 11–12 g/dL should be generally sought in the CKD population without intentionally exceeding 13 g/dL and that the doses of ESA therapy to achieve the target haemoglobin should also be considered. More caution is suggested when treating anaemia with ESA therapy in patients with type 2 diabetes not undergoing dialysis (and probably in diabetics at all CKD stages). In those with ischaemic heart disease or with a previous history of stroke, possible benefits should be weighed up against an increased risk of stroke recurrence, when deciding which Hb level to aim for.

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(i) Iron administration is an important factor for the successful treatment with any kind of ESA, in order to use the lowest dose for reaching and maintaining the desired Hb target

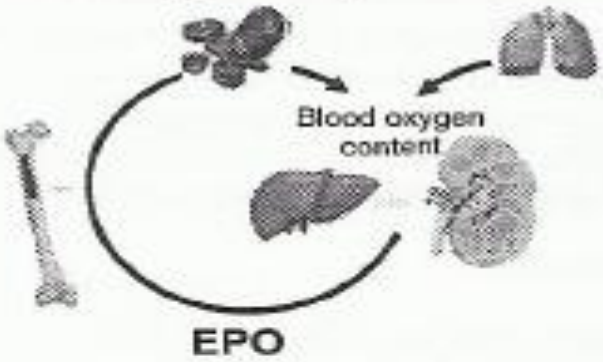
(ii) ESA treatment should not be started in patients who are iron-deficient

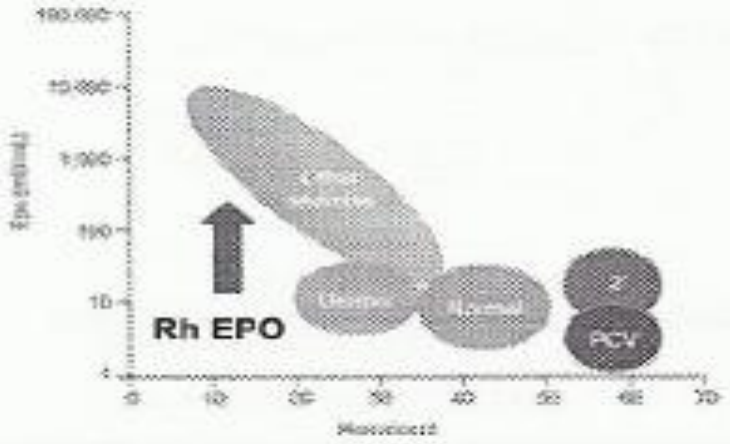
(iii) Iron replacement should be used first in any CKD patient who is proven or likely to be iron-deficient, and only once the iron stores are replete should ESA therapy be initiated

(iv)In CKD patients, ESA treatment should be considered when Hb levels are consistently below 11 g/dL (possibly < 10 g/dL in patients with type 2 diabetes and with a history of strokes), and all other causes of anaemia have been excluded; the threshold for treatment should be decided according to patient characteristics and symptoms, and the desired Hb target"

Locatelli F, et al. Nephrol Dial Transplant 2010;25(9):2846-2850

Inadequately low EPO as cause of renal anemia





Rh EPO

- effective in almost all patients
- overall safe
- with relatively few limitations:
  - biological: high costs, limited stability
  - parenteral dosing required
  - occasionally immunogenic → PRCA
  - efficacy limited by iron availability
  - risks when targeting normal Hb levels

- Rational for new therapies
- Interest in market participation

→ Stimulation of endogenous EPO

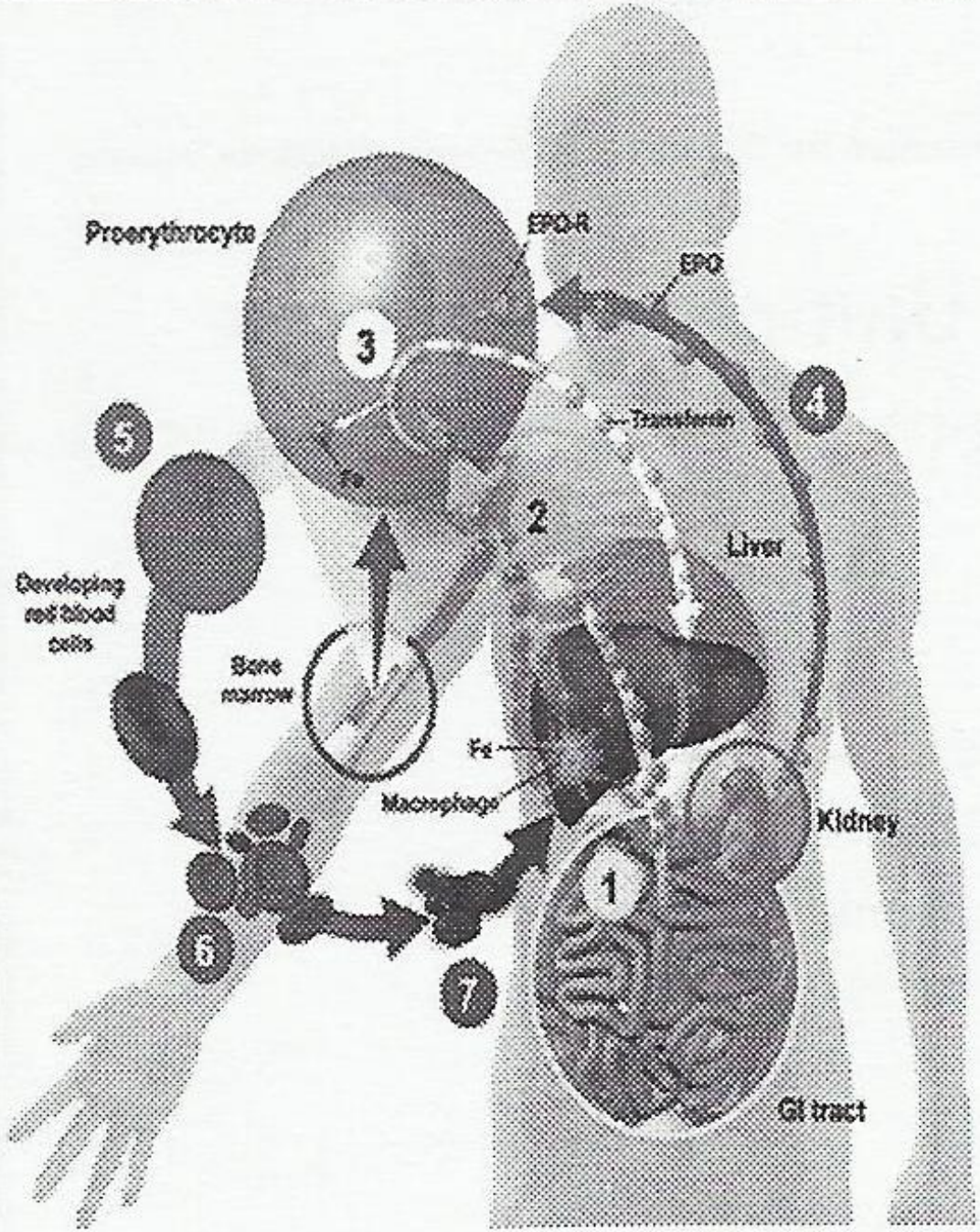
Hypoxia-inducible transcription factors (**HIFs**) bind hypoxia-response sequences of genes related to tissue oxygenation

1. HIFs are transcription factors composed of 2 subunits: HIF-α and HIF-β (ARNT).

2. HIF-β (ARNT) is stable under all levels of oxygenation. HIF-α is continually produced, but undergoes rapid proteasomal degradation during normoxia.

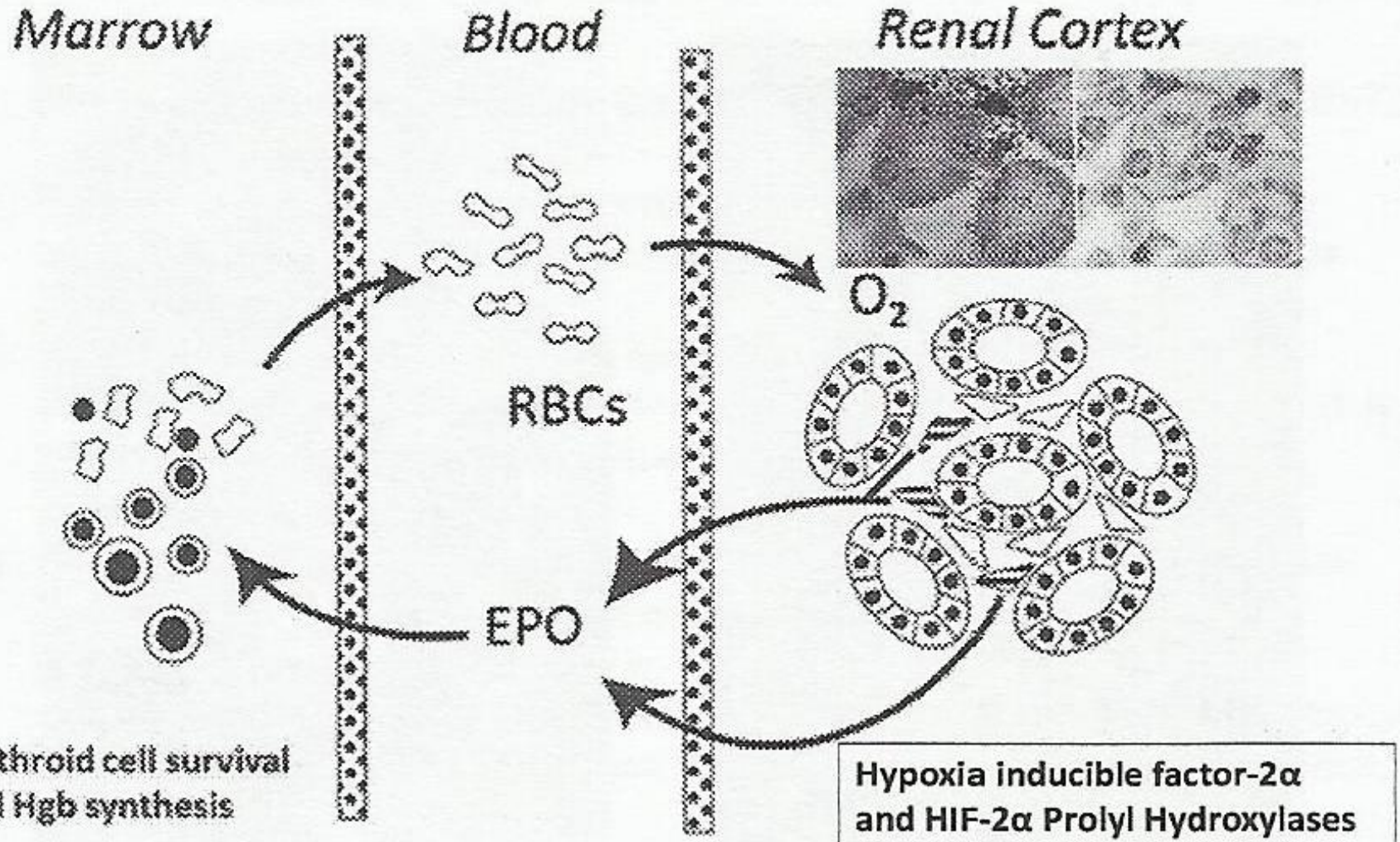
3. Hypoxia stabilizes HIF-α, allowing formation of transcriptionally active HIF-α/HIF-β dimers. The rate limiting step in formation of active HIF-α/HIF-β is stabilization of HIF-α, which is due to decreased prolyl hydroxylation.

4. Genes containing hypoxia responsive elements encode proteins involved in tissue oxygen delivery and utilization:
   a. Eyrthropoiesis: *EPO, Transferrin*
   b. Vascular growth/regulation: *VEGF, VEGF-R/FLT-1, Endothelin1, PAI-1, NOS2*
   c. Glucose transport + metabolism: *GLUT1, Hexokinase, PFK, G3PD, aldolase, PK, LDH*



1. HIF upregulates DMT1 and DcytB to increase intestinal iron absorption
2. Transferrin transports iron to transferrin receptors in the bone marrow
3. Iron is released from transferrin into the developing erythrocyte
4. HIF upregulates the erythropoietin receptor and endogenous erythropoietin production
5. HIF upregulates transferrin receptor increasing iron uptake by proerythrocytes
6. HIF promotes formation of fully functional mature erythrocytes replete with Hb
7. After a lifespan averaging approximately 120 days, exhausted erythrocytes are scavenged in the liver and the iron returned for reuse.

Hypoxia – EPO feedback cycle



Modified from Koury, MJ, Red blood cell production and kinetics, in *Rossi's Principles of Transfusion Medicine, 6th Ed.* (2016), p. 90.

HIF stabilizers and anemia – 5 main questions

- Are HIF stabilizers effective in raising the Hb level in CKD ?
- Do they allow a "fine-tuned", stable increase in Hb levels ?
- Are there clinically relevant side-effects ?
- Are such side-effects "neutral", "beneficial" or "harmful" ?
- Does anemia management with HIF-stabilizers impact on patient outcomes ?

→ *So far partial answers only available to the first three questions*

Dosing

Currently available agents

- Chronic kidney disease patients
  - ESAs: epoietin-α & -β, darbepoeitin administered subcutaneously every 1 to 4 weeks
  - Iron: iron sucrose, ferric gluconate, ferumoxytol, ferric carboxymaltose, iron dextran
    - IV administered monthly or as needed
    - (Oral iron agents)
- Dialysis patients
  - ESA's: epoietin-α & -β, darbepoeitin, epoetin-β & methoxy polyethylene glycol: administered intravenously with hemodialysis & SQ for PD patients
  - Iron: iron sucrose, ferric gluconate, iron dextran
    - IV administration weekly or bolus

HIF activators

Compound	*Oral Doses
AKB-6548	300 QD, 450 QD, 450 mg TIW
BAY85-3934	15, 25, 50, 75, 100, 150 mg QD
GSK1278863	5, 10, 25, 50 mg QD
DS-1093	7.5-50 mg at unspecified frequency
FG-4592	70, 100, 150, 200 mg BIW TIW
JTZ-951	Dose / Frequency to be determined

* From ClinicalTrials.gov, accessed August 31, 2016

Phase 2 studies with PHD-I in CKD patients

Author	Journal	PHD-I	Patients	n	Control	Dosing		Duration
Besarab	NDT	FG-4592	NDD-CKD	116	pl: 1:3	four dose cohorts	BIW or TIW	4 wks
	2015					0.7-2.0 mg/kg		
Provenzano	CJASN	FG-4592	NDD-CKD	145	no	six cohorts	BIW or TIW	16-24 wks
	2016					starting doses	(QW)	
						(tiered weight or fixed)		
Besarab	JASN	FG-4592	incident HD or PD	60	no	titration	TIW	12 wks
	2016		(ESA naive)			1.0 -1.7, up to 2.x mg/kg		
Provenzano	AJKD	FG-4592	HD-CKD (on ESA)	54	ESA: 1:1	1, 1.x, 1.x, 2.0 mg/kg	TIW	6 wks
	2016							
			HD-CKD (on ESA)	90	ESA: 1:3	six cohorts	TIW	19 wks
						diff. start. doses		
Holdstock	JASN	GSK	NDD-CKD	73	pl: 1:3	0.5, 2, 5 mg	once daily	4 wks
	2016	1278863						
			HD-CKD (on ESA)	83	ESA	0.5, 2, 5 mg	once daily	4 wks
Brigandi	AJKD	GSK	NDD-CKD	70	pl	10, 25, 50, 100 mg	once daily	4 wks
	2016	1278863						
			HD-CKD (ESA naive or paused)	97	pl	10, 25 mg	once daily	4 wks
Pergola	Kid Int	AKB-6548	NDD-CKD	210	Pl: 1:2	450 mg; adjusted	once daily	20 wks
	2016		(ESA naive or paused)					

Common endpoint of all studies: Hb response

Efficacy in Raising Hemoglobin

- 26 registered phase II trials on ClinicalTrials.gov*
  - 24 are listed as completed
  - **6 are published in peer-reviewed journals (see adjacent table)**
  - Other trial results can be found in abstract proceedings from ASN, NKF, and ERA-EDTA meetings (2010-2015) but not presented in this talk

Compound	Patient Type	N Comparator	Duration	**Journal / Year
FG-4592	CKD (non-dialysis)	116 placebo	4 weeks	NDT 30:1665 / 2015
FG-4592	Incident dialysis (HD & PD)	60 (Iron)	12 weeks	JASN 27:1225 / 2016
FG-4592	CKD (non dialysis)	145 Dose Titration	16 to 24 weeks	CJASN 11:982 / 2016
FG-4592	Dialysis	144 ESA	6 to 19 weeks	AJKD 67: 912 / 2016
GSK1278863	CKD & Dialysis	156 ESA	4 weeks	JASN 27:1234 /2016
GSK1278863	CKD & Dialysis	107 ESA	4 weeks	AJKD 67: 861 / 2016

**Journal Abbreviations
AJKD: Am J Kidney Dis
CJASN: Clin J Am Soc Nephrol
JASN: J Am Soc Nephrol
NDT: Nephrol Dial Transplant

* https://clinicaltrials.gov, accessed August 31, 2016

AJKD

Original Investigation

Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study

Robert Provenzano, MD,[1] Anatole Besarab, MD,[2] Steven Wright, MD,[3] Sohan Dua, MD,[4] Steven Zeig, MD,[5] Peter Nguyen, MD,[6] Lona Poole, MD,[2] Khalil G. Saikali, PhD, Exec MBA,[2] Gopal Saha, MBBS,[2] Stefan Hemmerich, PhD, RAC,[2] Lynda Szczech, MD, MSCE,[2] K.H. Peony Yu, MD,[2,] and Thomas B. Neff, MD (hc)[2,*]*

Am J Kidney Dis. 2016;67(6):912-924

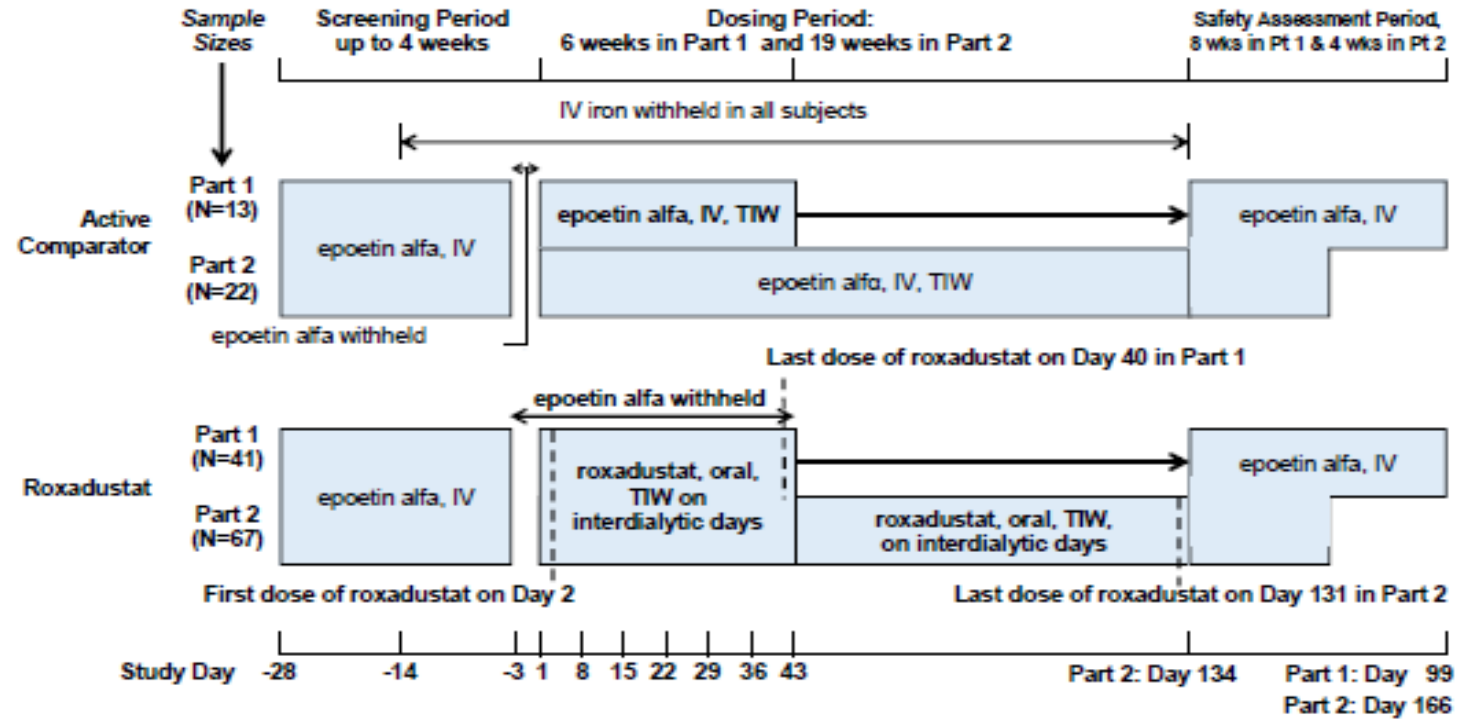


Figure 1. Study scheme. Abbreviations: IV, intravenous; pt, patient; TIW, thrice weekly.

Table 1. Roxadustat Starting Doses

Treatment Cohort	Treatment Duration, wk	Criterion for Epoetin alfa Dose Preceding Study Drug Treatment, IU/kg/dose	Weight-Based Starting Dose of Roxadustat[a]	Fixed Period for Initial Dosing, wk
A-1	6	25-85	1.0 mg/kg	3
A-2	6	25-85	1.5 mg/kg	3
A-3	6	25-85	2.0 mg/kg	3
A-4	6	25-85	1.8 mg/kg	3
A-5	19	85-115	1.8 mg/kg	6 (amendment 2[b]) then 4 (start amendment 3[c])
A-6	19	25-115	1.3 mg/kg	6
A-7	19	25-115	Weight tiered: 70-100-150 mg[d]	6 then 4 (start amendment 3[c])
A-8	19	25-115	Weight tiered: 70-120-200 mg[d]	4
A-9	19	85-150	2.0 mg/kg	4
A-10	19	25-115	Weight tiered: 70-120-200 mg[d]	4

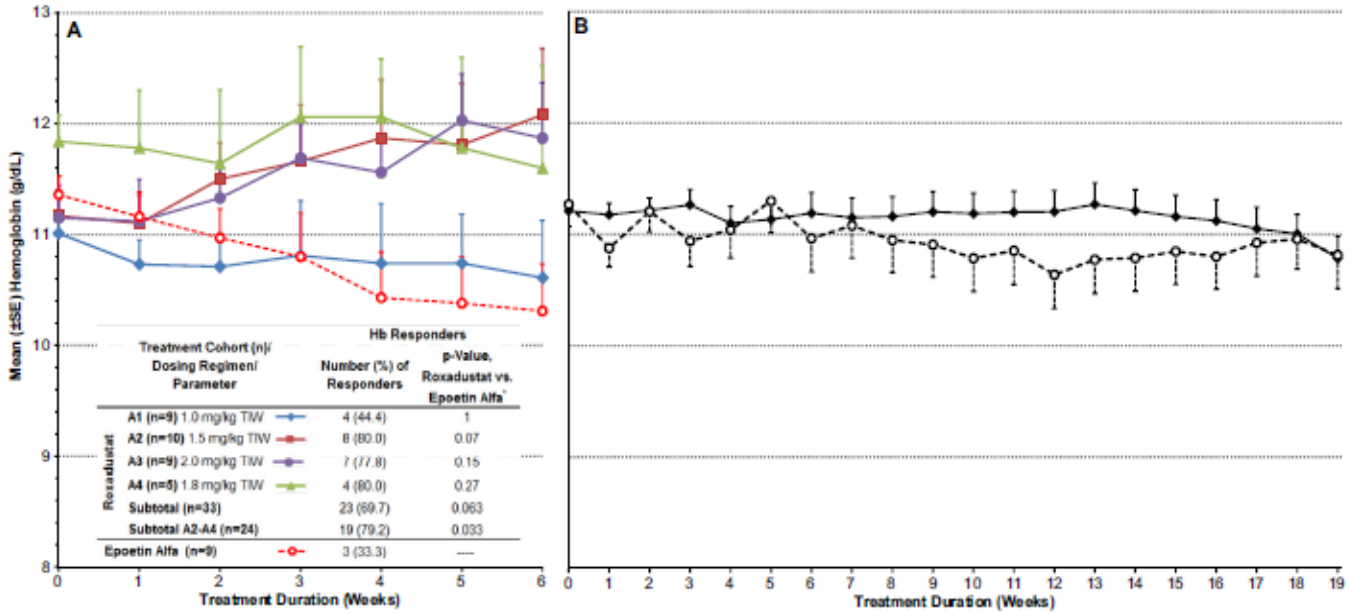


Figure 2. Hemoglobin levels over time (6 weeks) by treatment group. (A) Hb levels over time by dose cohort for participants randomly assigned to 6 weeks of treatment in part 1. Hb level responders are defined as the number (percent) of patients whose Hb levels did not decrease by >0.5 g/dL from their baseline (primary efficacy end point in part 1). (B) Least squares mean Hb levels over time (19 weeks), roxadustat-treated versus epoetin alfa–treated patients. Closed diamonds are roxadustat (n = 61); open circles are epoetin alfa (n = 22). **P* values are from Fisher exact test (2 sided) comparing roxadustat with epoetin alfa. Error bars signify standard error (SE) of the mean.

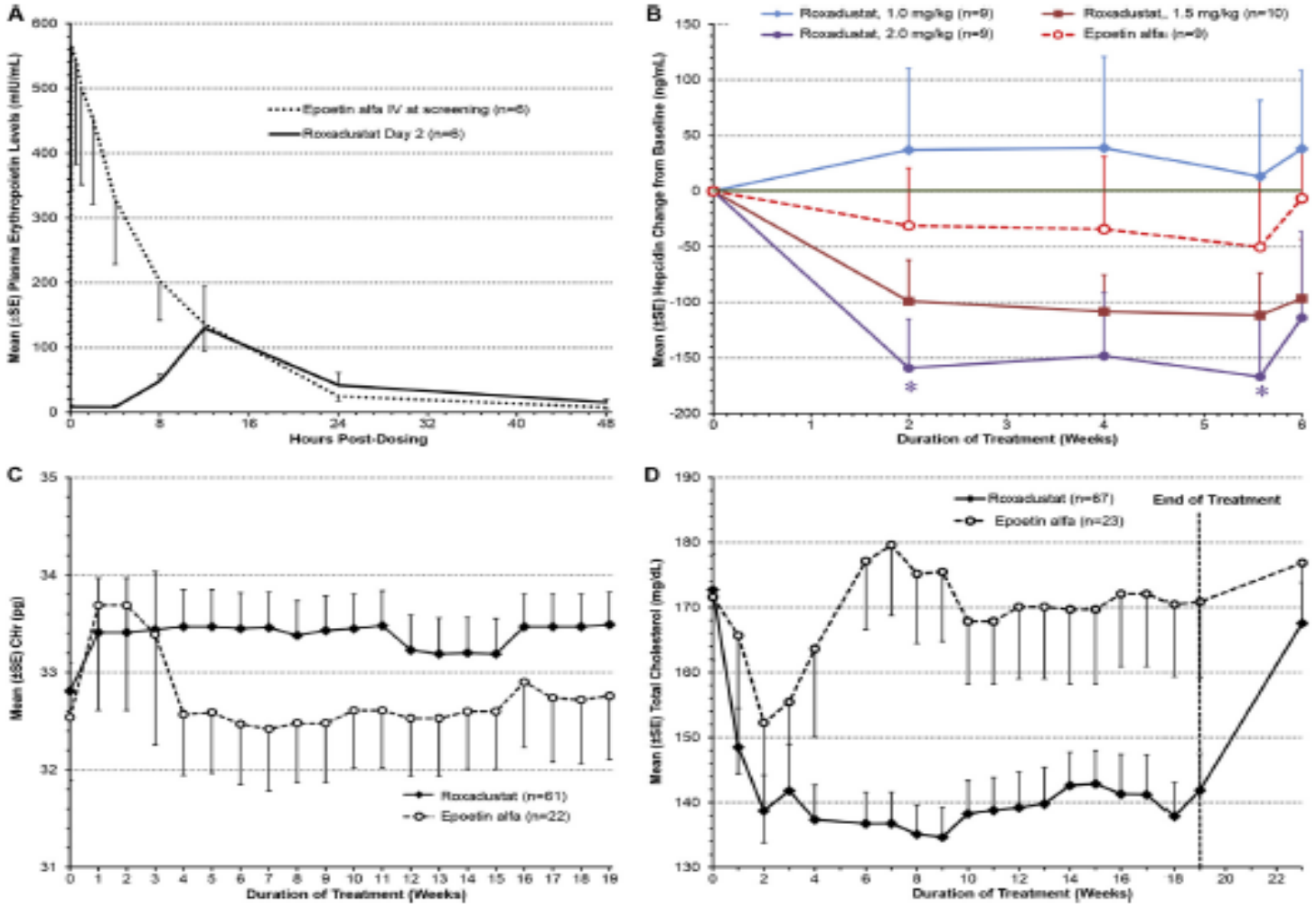


Figure 4. Pharmacodynamic effects of roxadustat compared to epoetin alfa. Error bars signify standard error of the mean. (A) Mean plasma erythropoietin levels during treatment with roxadustat compared to prior epoetin alfa dosing in the same patients (n = 6). (B) Change in hepcidin level (ng/mL) from baseline during 6 weeks of treatment in the 6-week cohorts with the largest sample sizes (n > 5). *$P < 0.05$ (comparing hepcidin change from baseline between the 2.0-mg/kg roxadustat group and the epoetin alfa group). (C) Mean reticulocyte hemoglobin content (CHr) over time in roxadustat- versus epoetin alfa–treated participants randomly assigned to 19 weeks of treatment (last observation carried forward [LOCF], efficacy-evaluable population). (D) Total cholesterol levels over time in roxadustat- versus epoetin alfa–treated participants randomly assigned to 19 weeks of treatment (LOCF, safety population).

www.kidney-international.org

clinical trial

Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease

CrossMark

OPEN

Pablo E. Pergola[1], Bruce S. Spinowitz[2], Charlotte S. Hartman[3], Bradley J. Maroni[3] and Volker H. Haase[4,5,6]

[1]Renal Associates, San Antonio, Texas, USA; [2]Division of Nephrology, New York-Presbyterian/Queens, Flushing, New York, USA; [3]Akebia Therapeutics, Inc., Cambridge, Massachusetts, USA; [4]Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; [5]Department of Cancer Biology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; and [6]Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

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Kidney International (2016) **90,** 1115–1122

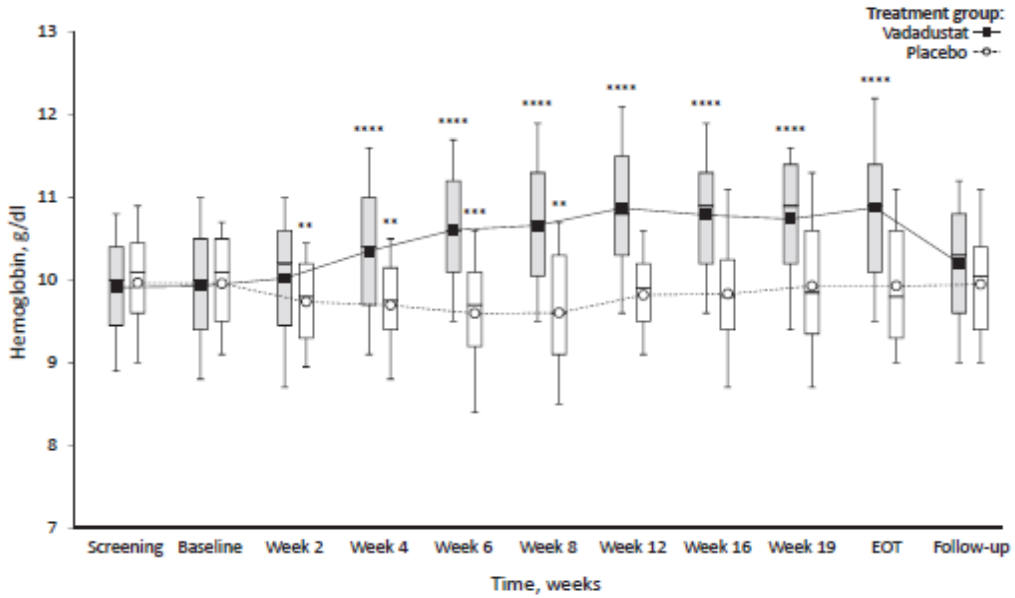
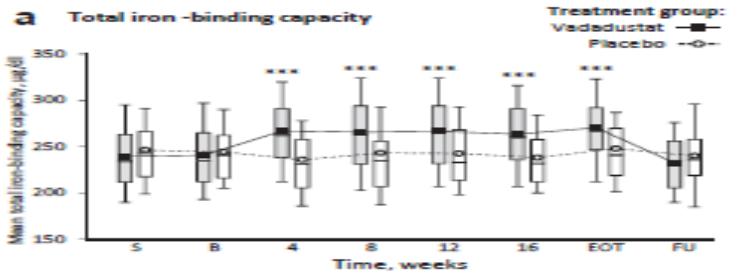
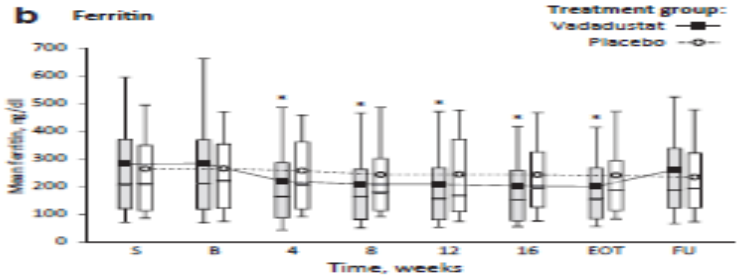
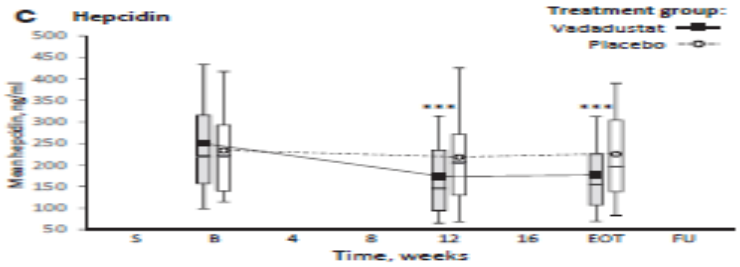


Figure 1 | Mean hemoglobin level over time (modified intent-to-treat population). Box-and-whiskers plot represents 10th, 25th, 75th, and 90th percentiles. The medians are indicated by the line within the boxes, and the means are indicated by the symbol within the boxes. Comparison of baseline to weekly and end of treatment (EOT) means for vadadustat or placebo groups was performed with a 2-sided Student *t*-test at $\alpha = 0.05$: $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$.







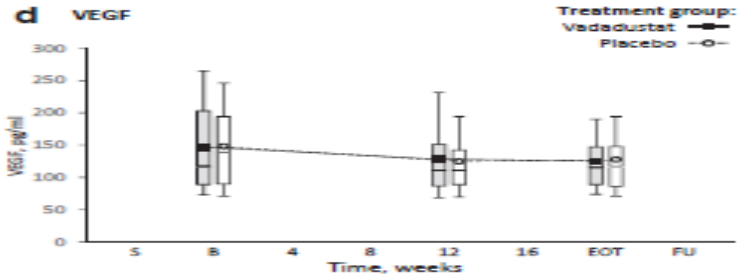


Figure 3 | (a) Total iron-binding capacity, (b) ferritin, (c) hepcidin, and (d) vascular endothelial growth factor (VEGF) over time (modified intent-to-treat [MITT] population). Box-and-whisker plots represent the 10th, 25th, 75th, and 90th percentiles. The medians are represented by a line within the boxes, and the means are the symbol within the boxes. Comparison of vadadustat with

Reported Adverse Events in Published Studies

Compound	Patient Type	Total Study Size	Patients with Any Reported Adverse Events, Treatment Group, N (%)	Patients with Any Reported Adverse Events, Placebo Group N (%)	Patients with Serious Adverse Events	
					Treatment N (%)	Placebo N (%)
[a]FG-4592	CKD (non-dialysis)	116	52 (59.1%)	13 (46.4%)	4 (5%)	1(4%)
[b]FG-4592	Incident Dialysis (Hemo & PD)	60	30 (50.0%)	No placebo group	6 (10%)	--
[c]FG-4592	CKD (non-dialysis)	145	116 (80%)	No placebo group	35(24.1%)	--
[d]FG-4592	Dialysis	144	69 (63.9%)	22 (61%)	26 (24.1%)	6 (17%)
[e]GSK1278863	CKD & Dialysis (Dial)	156	5 (4.5%) For all CKD & Dialysis Patients	Not available	CKD 4 (7.6%) Dial 4 (6.7%)	1 (5%) 2 (10%)
[f]GSK1278863	CKD & Dialysis	107	CKD: 35(57%) Dialysis: 15 (48%)	Not available	CKD 6 (10%) Dial 3 (9.6%)	1 (11%) 0

a: NDT 30: 1665, 2015; b: JASN 27:1225, 2016; c: CJASN 11: 982, 2016;
d: AJKD 67:912, 2016; e: JASN 27: 1234, 2016, f: AJKD 67: 861, 2016

Cardiovascular Safety

- High burden of proof given previous studies targeting normal hemoglobin have demonstrated either no benefit or harm
  - Normal hematocrit study
  - CHOIR
  - CREATE
  - TREAT
- Underlying reason remains unknown
  - Inflammation
  - High hemoglobin
  - ESAs
- We must wait for this answer...

Pending Phase III Clinical Trials from Clinicaltrials.gov*

Compound	Trial Number	Patient Population	Planned Enrollment	Comparator	Main Outcomes (others of interest)	Estimated Date of completion
AKB-6548	NCT02865850	Dialysis	400	Darbepoeitin	Hgb, MACE**	September 2019
AKB-6548	NCT02680574	CKD non dialysis	400	Darbepoeitin	Hgb, MACE	November 2018
AKB-6548	NCT02648347	CKD non dialysis	1000	Darbepoeitin	Hgb, MACE	November 2018
ASP1517	NCT02780141	CKD non dialysis	70	Dose titration	Hgb	September 2017
ASP1517	NCT02779764	Dialysis (ESA conversion)	160	Dose titration	Hgb	December 2017
ASP1517	NCT02278341	Dialysis	828	Epoeitin, Darbepoeitin	Hbg	July 2018
FG-4592/ASP1517	NCT02021318	CKD non dialysis	570	Darbepoeitin	Hgb (QoL, lipids)	July 2017
FG-4592/ASP1517	NCT01887600	CKD non dialysis	600	Placebo	Hgb (QoL, lipids)	June 2016
FG-4592	NCT02174627	CKD non dialysis	2600	Placebo	Hgb, MACE	March 2017
FG-4592	NCT02174731	Dialysis	1425	Epoeitin-alpha	Hgb, MACE	February 2017
FG-4592	NCT01750190	CKD non dialysis	600	Darbepoeitin	Hgb	June 2017
FG-4592	NCT02652819	CKD non dialysis	150	Placebo	Hgb	April 2017
FG-4592	NCT02052310	Incident dialysis	750	Epoeitin-alpha	Hgb (BP, lipids)	June 2017
FG-4592	NCT02273726	Prevalent dialysis	600	Epoeitin-alpha	Hgb (QoL)	June 2017
GSK1278863	NCT02791763	CKD & Peritoneal	320	Epoeitin-beta	Hgb	July 2018
GSK1278863	NCT02829320	CKD non dialysis	22	Iron	Hgb	January 2018
GSK1278863	NCT02879305	Dialysis	3000	Epo, Iron, Placebo	Hgb, MACE	April 2020
GSK1278863	NCT02876835	CKD non dialysis	4500	Epo, Iron, Placebo	Hgb, MACE	January 2021

*Accessed on September 7, 2016

** MACE= Major Adverse Cardiovascular Events

HIF stabilizers and anemia – 5 main questions

- √ **Are HIF stabilizers effective in raising the Hgb level in CKD ?**
- √ **Do they allow a "fine-tuned", stable increase in Hgb levels ?**
- **Are there clinically relevant side-effects ?**
- Are such side-effects "neutral", "beneficial" or "harmful" ?
- Does anemia management with HIF-stabilizers impact on patient outcomes ?

Summary

- Dosing Frequency / Ease of Administration
  - ✓ HIF Activators are all oral agents with either daily or three times per week dosing
    - The optimal dose and frequency has yet to be determined
- Efficacy in Raising Hemoglobin
  - ✓ HIF Activators raise hemoglobin comparably to ESAs and to placebo
  - ✓ HIF Activators demonstrate changes in measures of iron metabolism (TSAT, TIBC)
    - They may obviate the need for IV iron
- Other (Beneficial) Effects of HIF Activators
  - ✓May lower serum cholesterol (both LDL & HDL)
  - ✓Lower markers of inflammation- Hepcidin
- Safety
  - ✓ Adverse events reported with HIF Activators appear to be similar to placebo or ESA
  - ± Little available information on downstream effects of modulating the HIF pathway
  - ? Unknown cardiovascular safety profile
- Intra-class differences among HIF Activators are not (yet) known

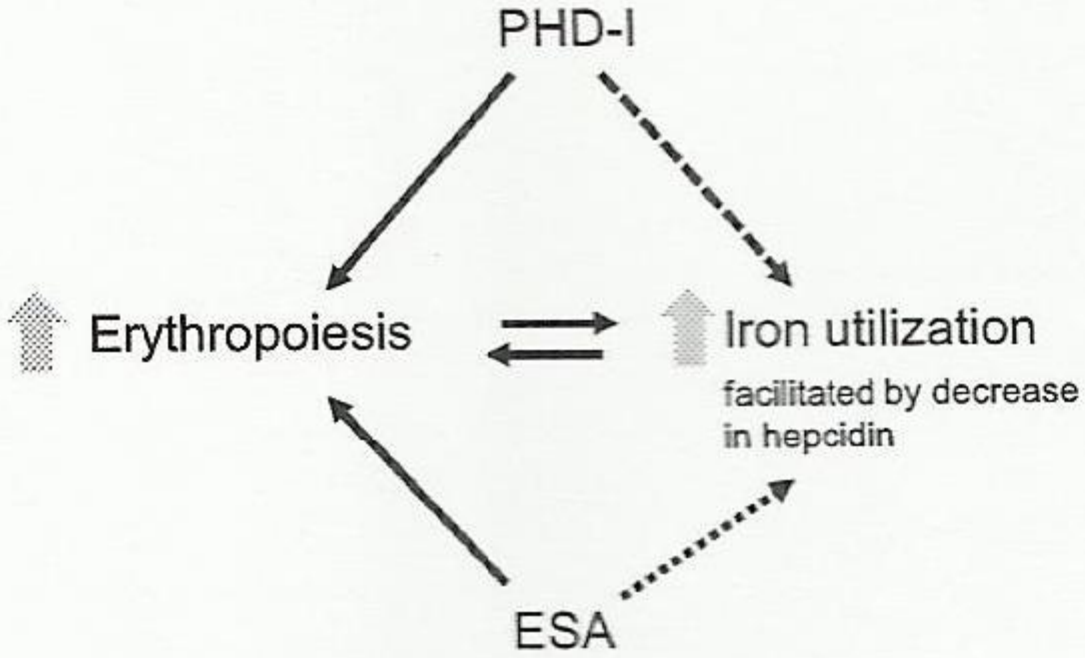
Conclusions

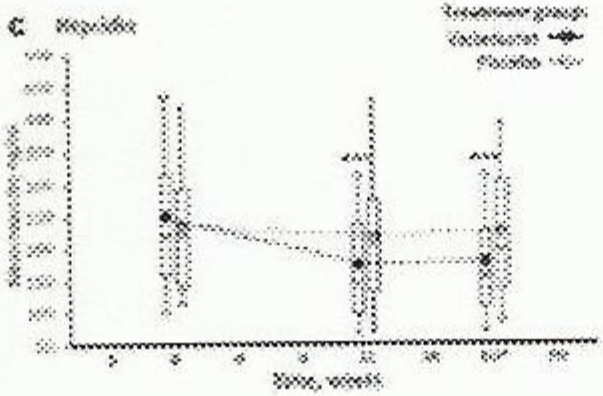
- HIF Activators are an interesting and physiologic alternative to current treatment options for anemia
- The available clinical data appear promising
- No obvious safety signal YET
- Pending phase III clinical trials will help determine whether HIF Activators will one day replace ESAs and iron– ***STAY TUNED***

PHD-I – effects on iron metabolism

Hypoxia / HIF are involved in iron reabsorption and metabolism
(Mastrogiannaki et al. JCI 2009; Shah et al. Cell Metab 2009; Anderson et al. JBC 2011)

PHD-I trials have shown a decrease of plasma hepcidin levels, but unclear to which extent this is independent of EPO



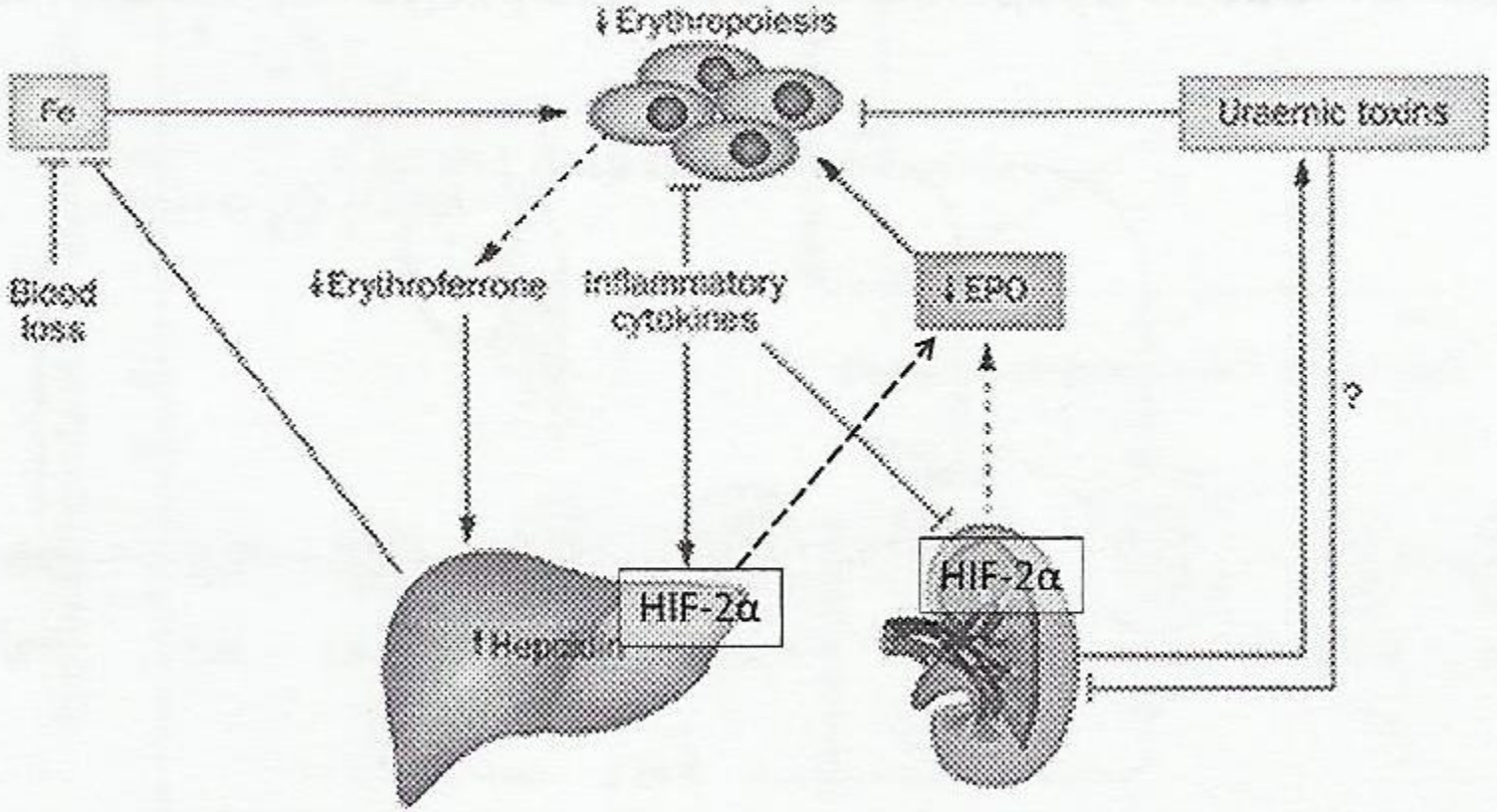


Pergola PE et al., *Kid Int 2016*

Potential risks and benefits of PHD-I in the treatment of anemia in CKD

- PHD-I (HIF stabilizers) are effective in raising EPO and Hb in NDD-CKD and DD-CKD patients.
- No acute or medium-term toxicity has been reported.
- There is evidence for side-effects (which could be "on-target" (HIF-mediated) or "off-target" (HIF-independent), but their clinical implications are yet unclear.
- Potential advantages compared to ESA:
  ease of application (po), better stability, lower costs, possible avoidance of "supraphysiological" EPO and iron concentrations.
- Long-term studies are needed with "hard" outcomes; in DD-CKD vs ESA and in NDD-CKD vs placebo.

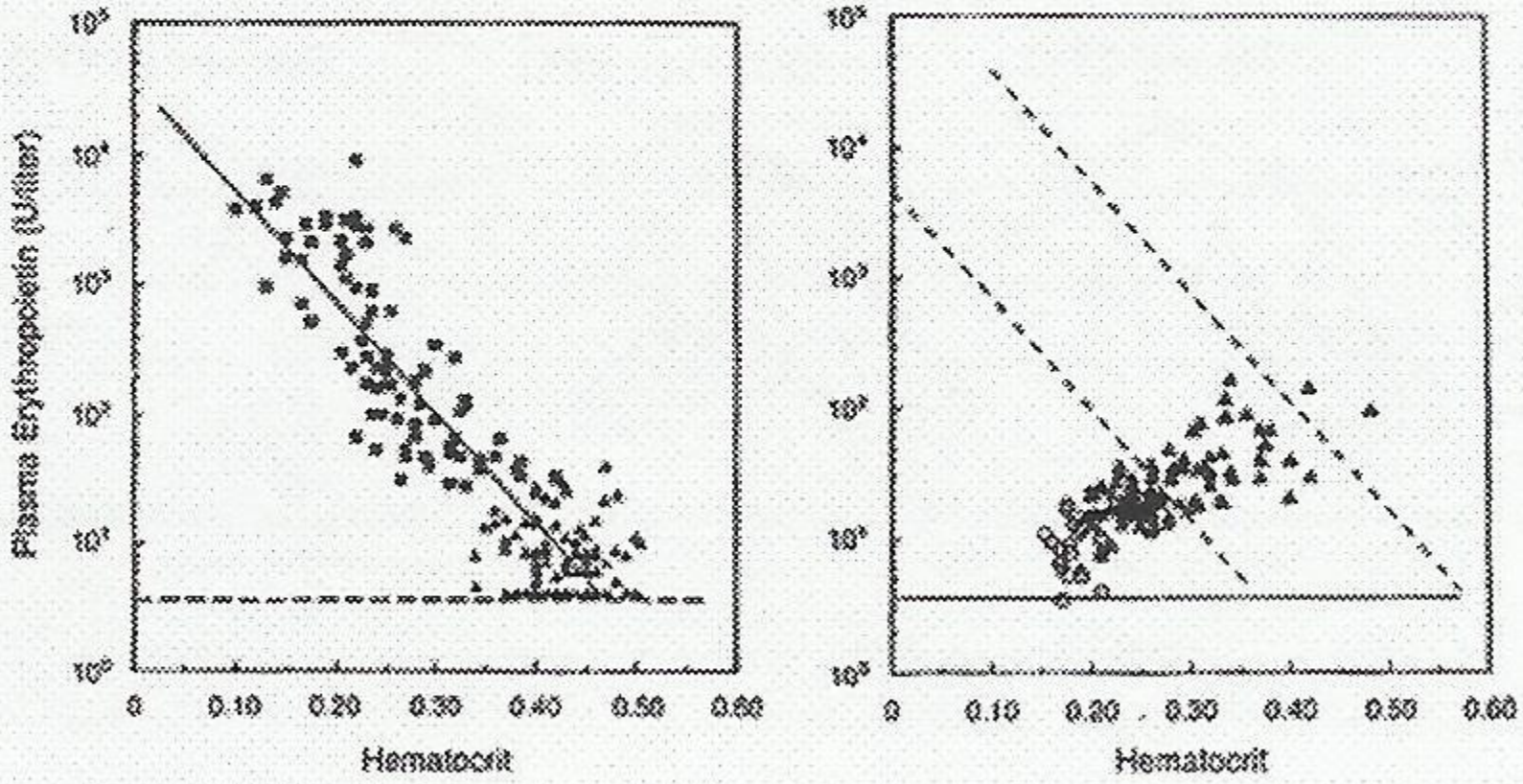
Overview of the anemia of kidney disease



Modified from Koury, M. J. & Haase, V. H. (2015) Anaemia in kidney disease: harnessing hypoxia responses for therapy. *Nat. Rev. Nephrol.* 11:394-410, doi:10.1038/nrneph.2015.82

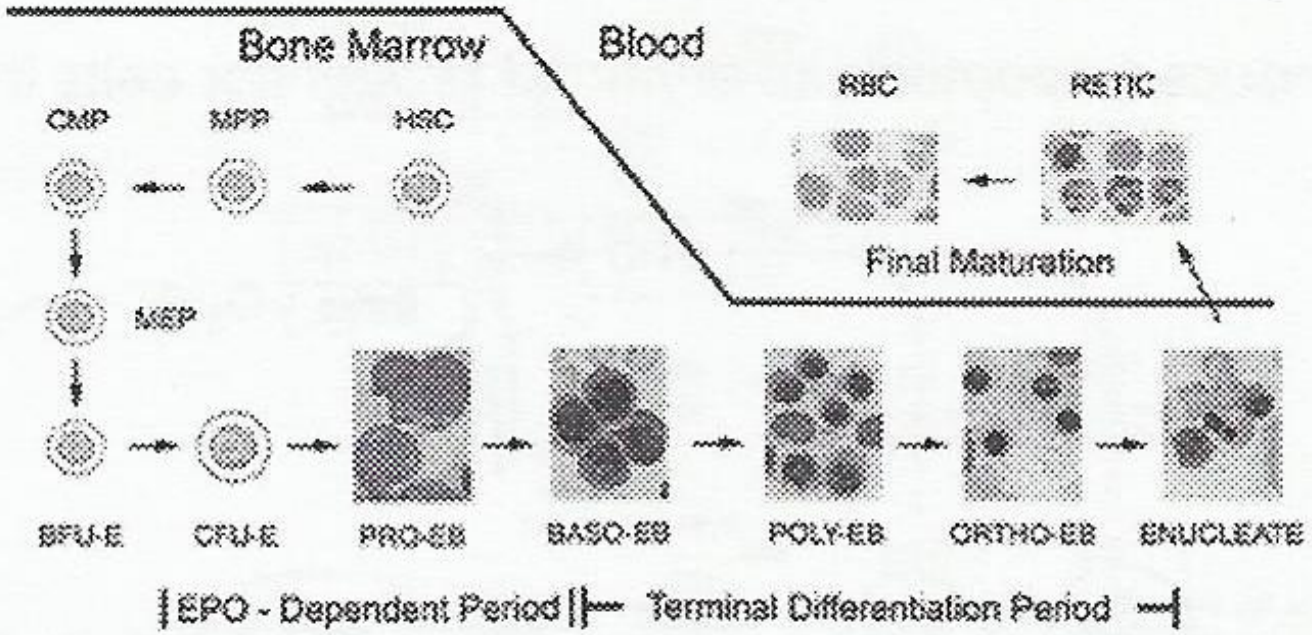
Kidney disease is an EPO deficiency state.

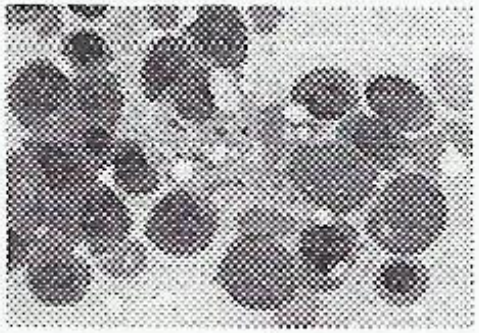
The anemia of kidney disease is largely due to insufficient EPO to maintain normal RBC production rates.



Erslev, AJ, Erythropoietin. *New Engl J Med* 1991;324:1339-1344. Left panel originally published in Erslev AJ, Caro J, Miller O, Silver R. Plasma erythropoietin in health and disease. *Ann Clin Lab Sci* 1980;10:250–257, and right panel courtesy of Dr. A Besarab.

Erythropoietic stages and organization

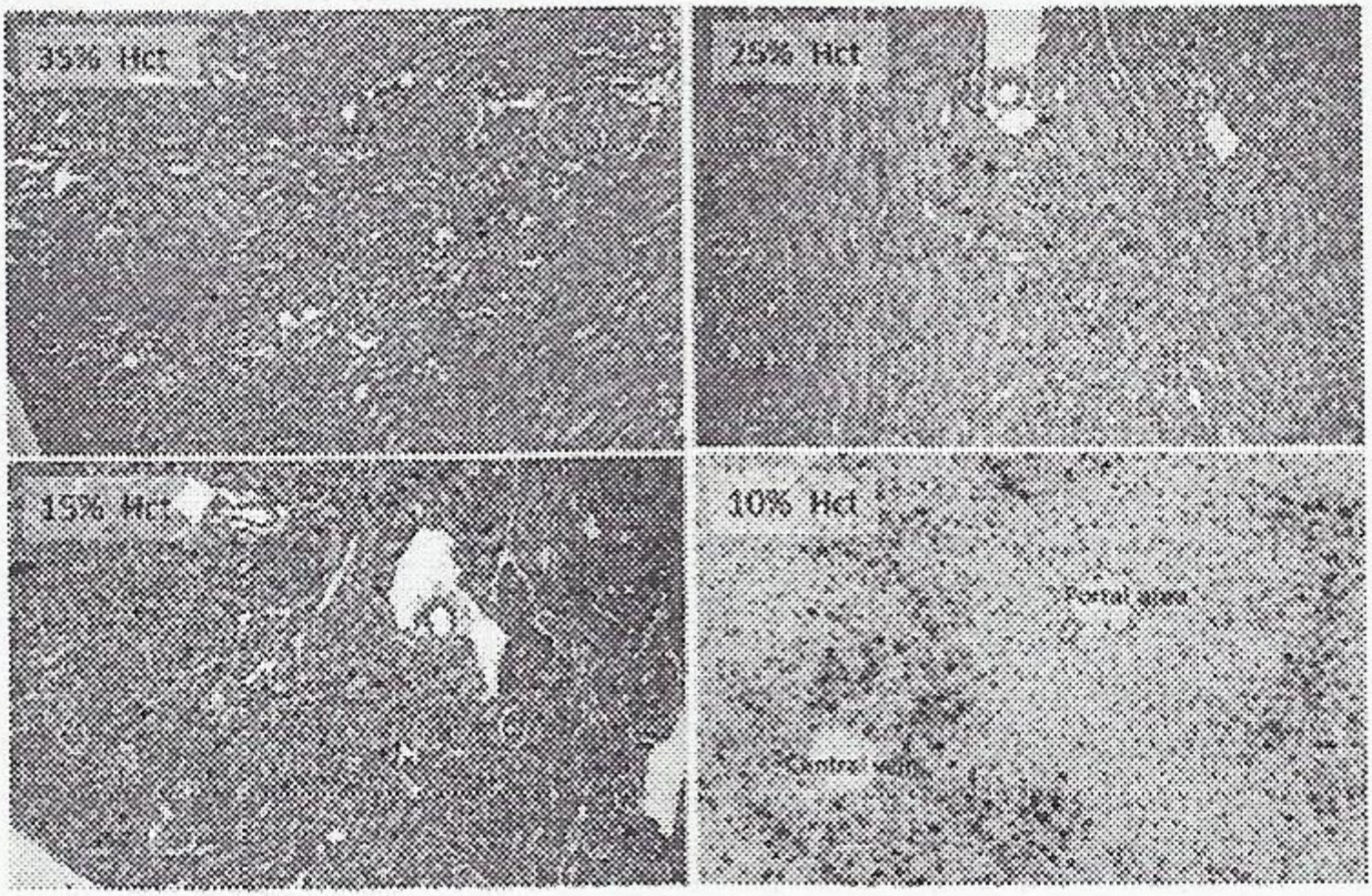




Erythroblastic islands (EBIs):
Marrow niches of terminal erythroid differentiation

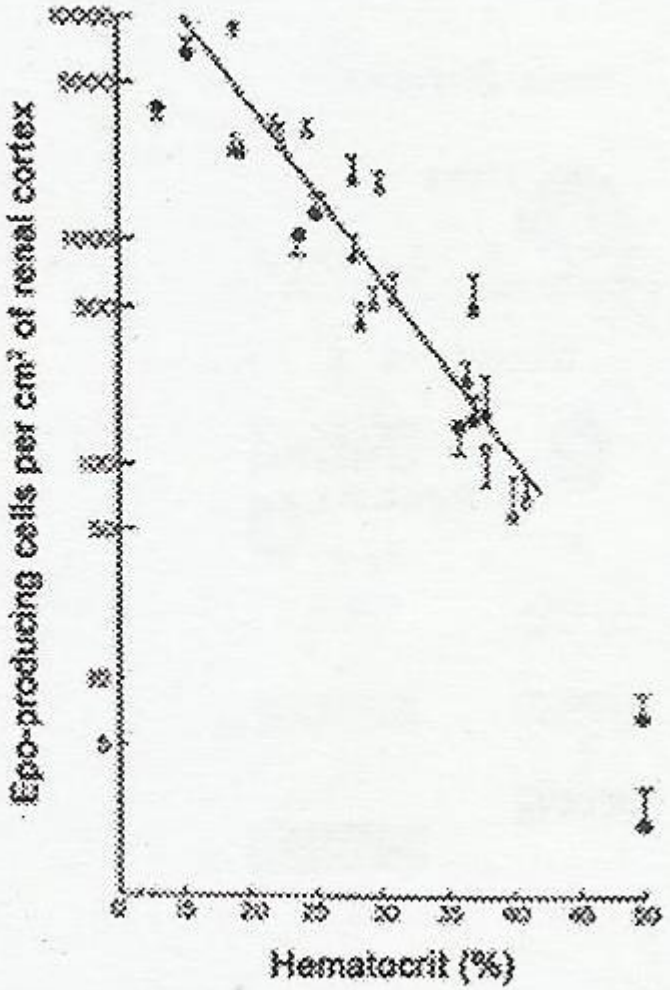
Modified from Ponka, P, Koury, MJ and Sheftel, AD (2013) Erythropoiesis, Hemoglobin Synthesis, and Erythroid Mitochondrial Iron Homeostasis, in Handbook of Porphyrin Science: Volume 27, Erythropoiesis, Heme, and Applications to Biomedicine, Ferreira, G., ed.,Hackensack, NJ, World Scientic Publishing, pp. 41-84, and Koury MJ, Abnormal erythropoiesis and the pathophysiology of chronic anemia. *Blood Reviews*, 2014;28:49–66.

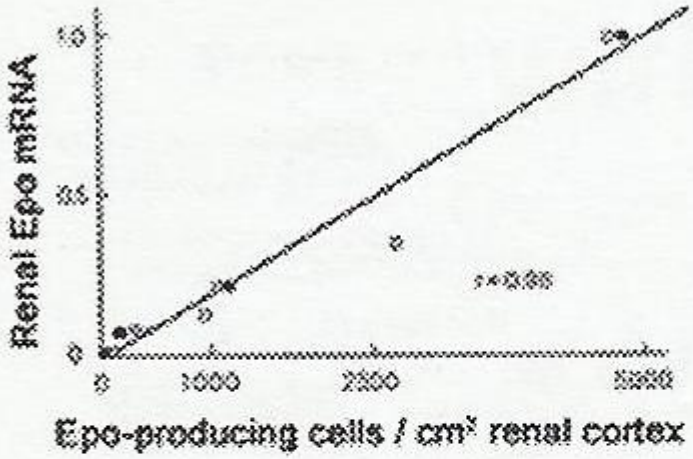
Increasing hypoxia induces EPO production in progressively larger areas of the kidney and the liver

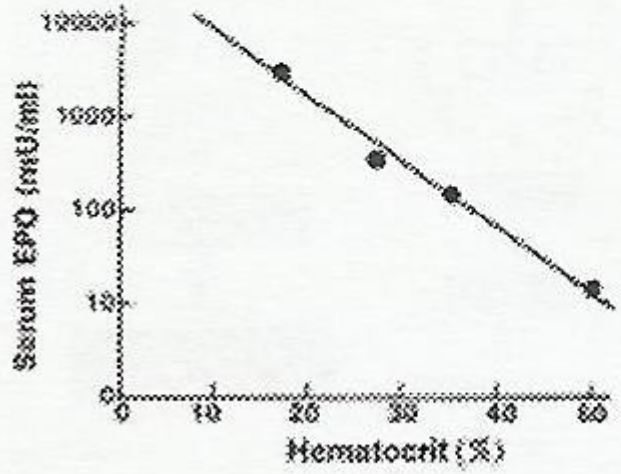


Photomicrographs from: Koury ST, Koury MJ, Bondurant MC, Caro J, Graber SE. Quantitation of erythropoietin producing cells in kidneys of mice by *in situ* hybridization: correlation with hematocrit, renal erythropoietin mRNA, and serum erythropoietin concentration. *Blood* 1989;74:645-651, and Koury ST, Bondurant MC, Koury MJ, Semenza G. Localization of cells producing erythropoietin in murine liver by in situ hybridization. *Blood* 1991;77:2497-2503.

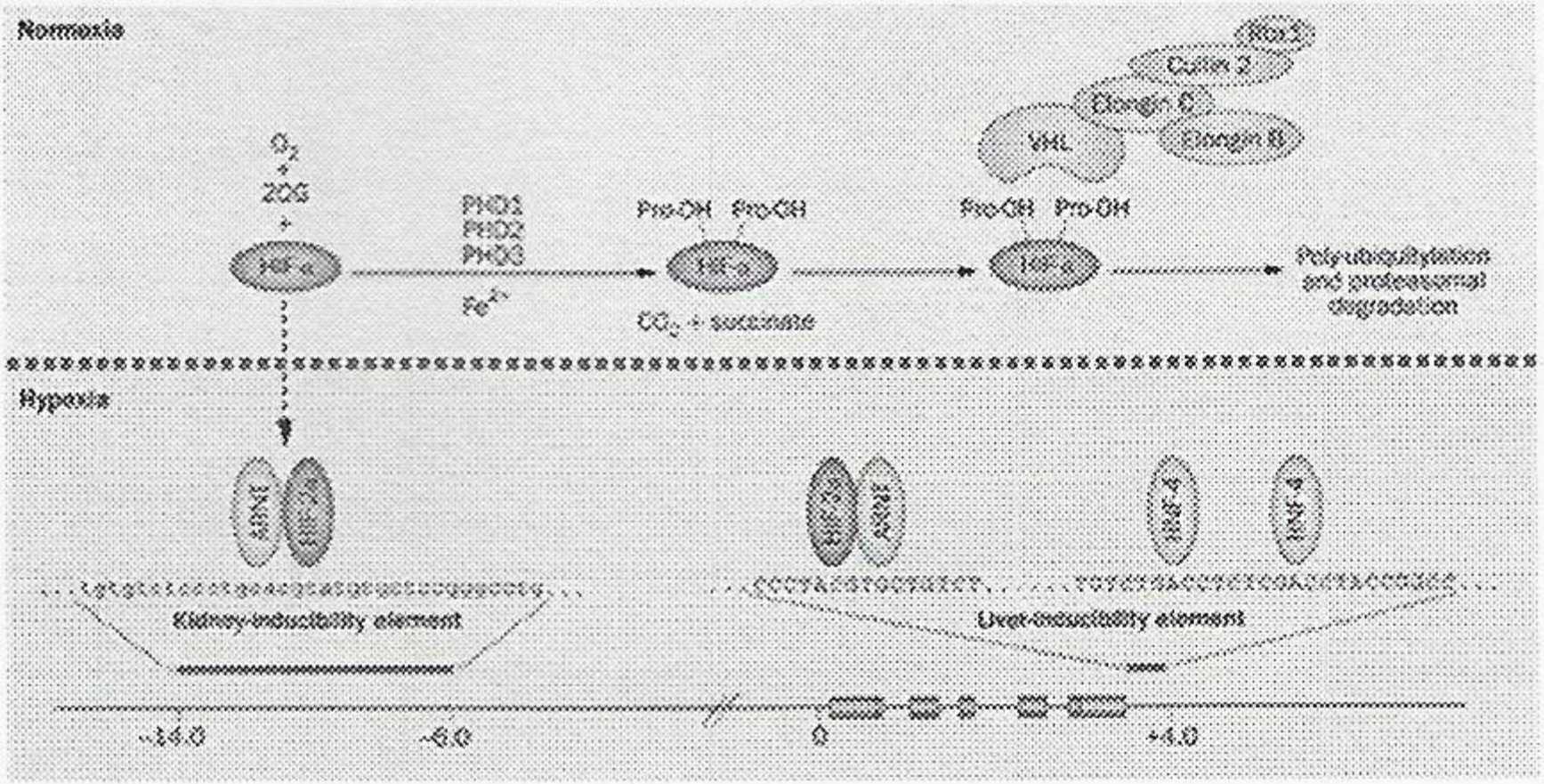
Linear decline in Hct increases EPO-producing cells exponentially. EPO-producing cells are induced in an all-or-none manner.





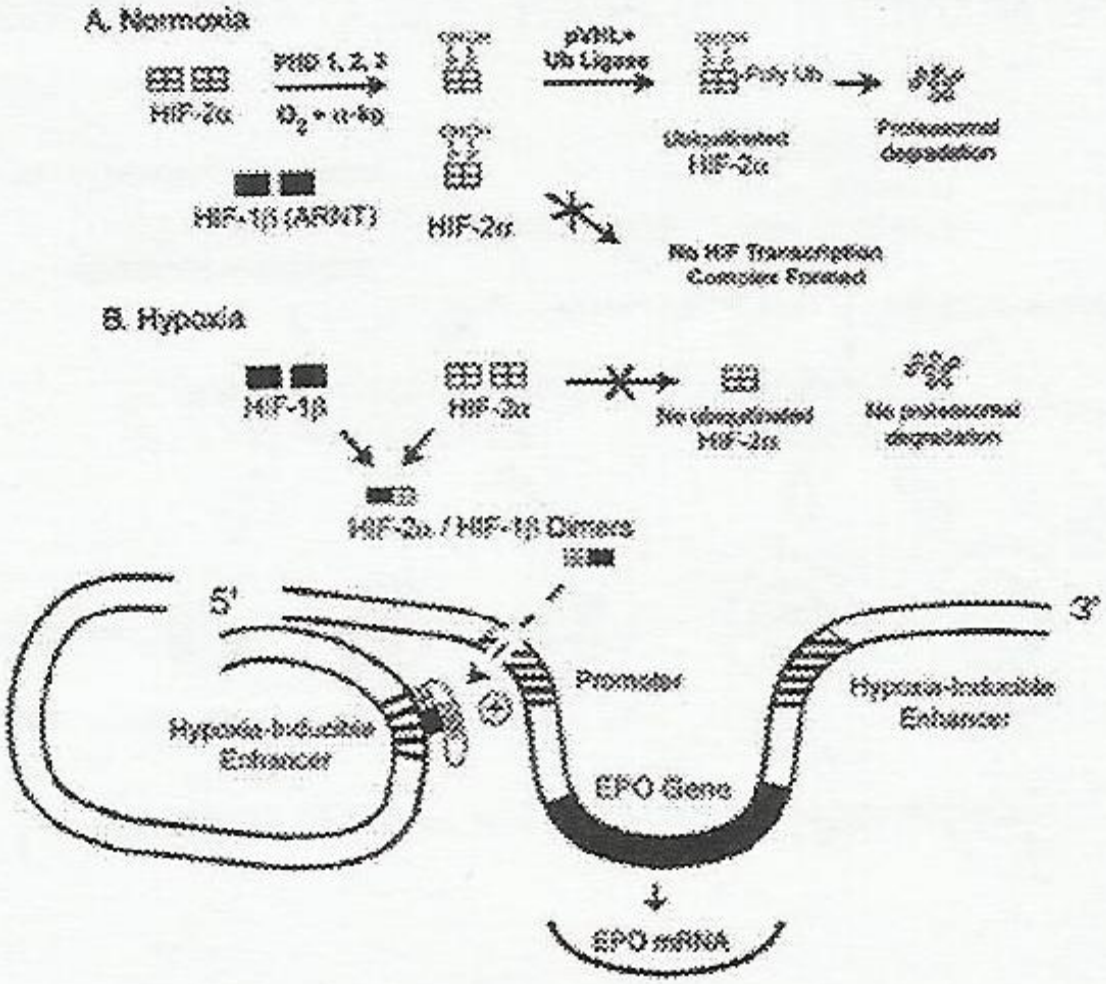


Regulation of HIF-α degradation by PHDs and hypoxic induction of *EPO* transcription by HIF-2α/HIF-β(ARNT) dimers.



Koury, M. J. & Haase, V. H. (2015) Anaemia in kidney disease: harnessing hypoxia responses for therapy. *Nat. Rev. Nephrol.* 11:394-410, doi:10.1038/nrneph.2015.82

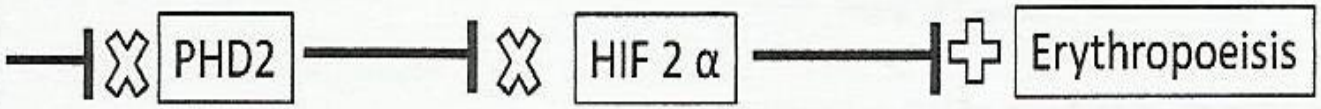
Renal induction of *EPO* transcription by hypoxic stabilization of HIF-2α



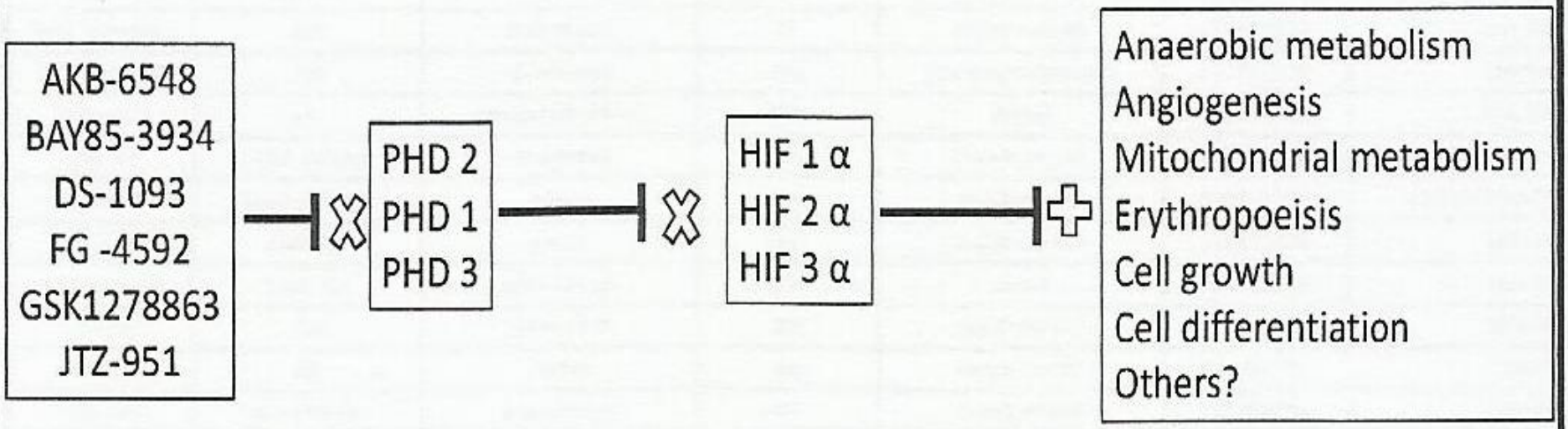
Modified from Koury, MJ, Red blood cell production and kinetics, in *Rossi's Principles of Transfusion Medicine, 6th Ed.*,(2016), p.90.

The Desired Selectivity of HIF Activators

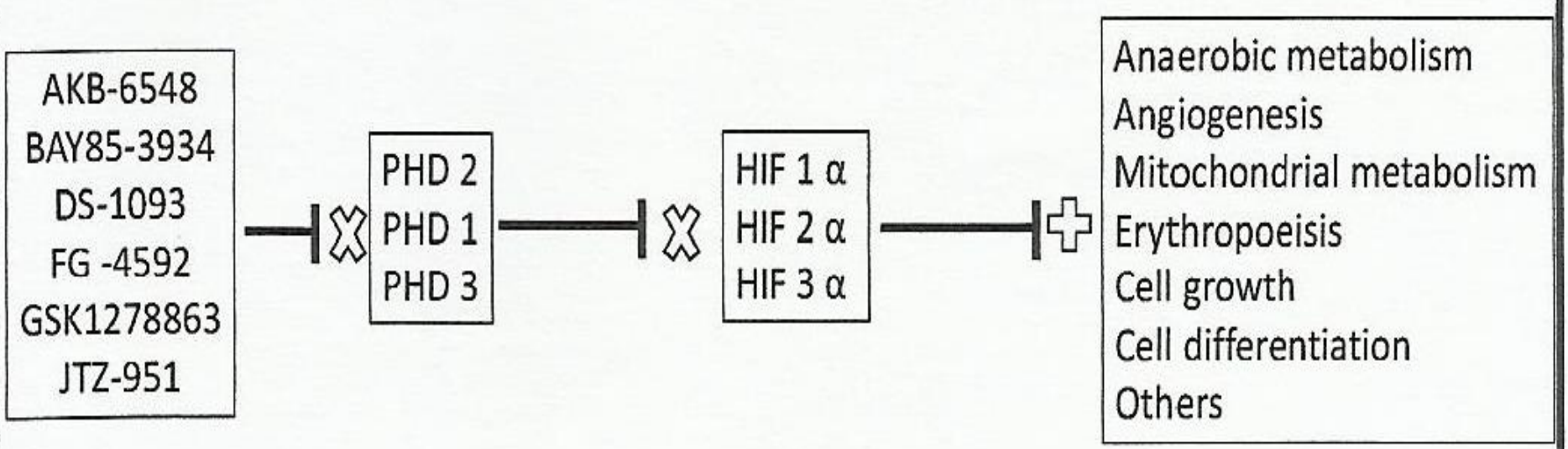
AKB-6548
BAY85-3934
DS-1093
FG -4592
GSK1278863
JTZ-951



The Known Complexity of the HIF Pathway



Potential Consequences of Modulating HIF



HIF 1 α– intra-tumor hypoxia, mediated via vascular endothelial growth factor (VEGF)
HIF 1 α– tumor metastasis, mediated by transforming growth factor (TGF)
HIF 2 α– over expression may lead to pulmonary hypertension

Reported Changes in VEGF in Published Studies

	Placebo	0.5 mg	2 mg	5mg	rhEPO	0.5 mg	2 mg	5 mg
	Non dialysis study				Hemodialysis study			
Baseline (ng/L)	90.4± 123.3	76.1±55.7	82.5±89.2	63.6±32.4	87.5±46.7	124.7±55.4	113.7±67.3	116.7±82.6
Change at 4 weeks (ng/L)	-43.3± 136	0.8±37.9	-3.9±36.5	5.6±41.4	1.2±40.3	-21.4±50.1	-4.6±60.8	19.9±79.6

- **Thus far, data are available only for GSK1278863 (Daprodustat).**
- **Changes in VEGF appear to be variable.**

(Table adapted from Holdstock L et al, J Am Soc Nephrol, 27: 1234, 2016)

GSK1278863 (Daprodustat) and VEGF