Ερυθροποιητίνη και Χρόνια Νεφρική Νόσος

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athens-NEPHROLOGY

Ορισμός αναιμίας

- **Αναιμία είναι η κατάσταση κατά την οποία ανευρίσκεται ελάττωση της αιμοσφαιρίνης, του αιματοκρίτη, ή και του αριθμού των ερυθρών, στη μονάδα του όγκου του αίματος, κάτω από τα φυσιολογικά όρια, για το φύλο και την ηλικία του ατόμου**

Κριτήρια αναιμίας

- **Οι "φυσιολογικές τιμές" εξαρτώνται από :**
  - Το φύλο
  - Την ηλικία
  - Την γεωγραφική περιοχή

Αναιμία (Επίπεδα Hb)

Ηλικία ή φύλο	Hb (g/dl)	Hb (mmol/l)	Hct
Παιδιά (5 μηνών – 5 ετών)	< 11	< 6.83	33%
Παιδιά (5-12 ετών)	< 11,5	< 7.14	34%
Παιδιά (12-15 ετών)	< 12	< 7.45	36%
Μη-έγκυες γυναίκες (>15 ετών)	< 12	< 7.45	36%
Έγκυες γυναίκες	< 11	< 6.83	33%
Άνδρες (>15 ετών)	<13	< 8.07	39%

World Health Organization. Worldwide prevalence of anaemia 1993-2005: WHO global database on anaemia 2008. Available at http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency

WHO Classification of Anaemia

Πίνακας Ι.

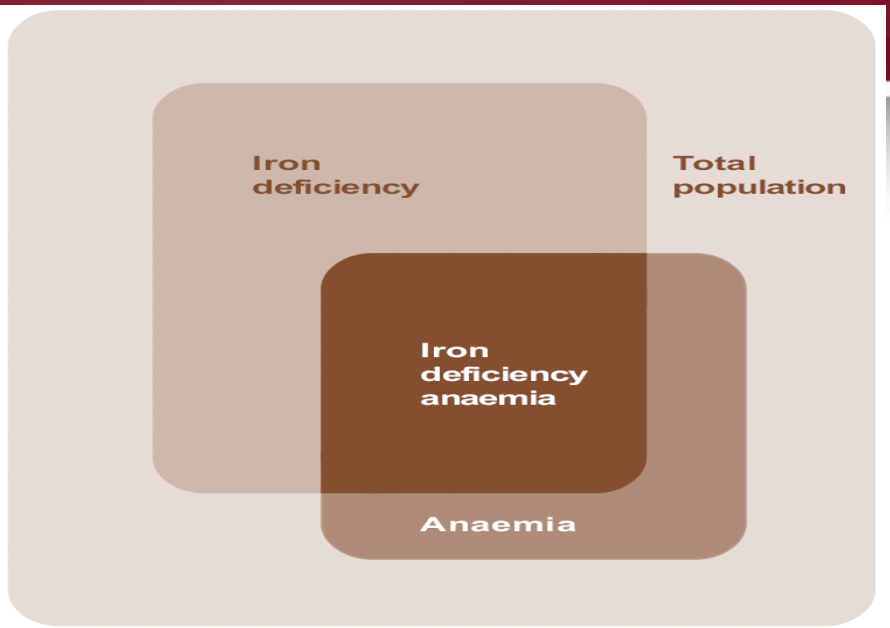
Κατάταξη της αναιμίας ανάλογα με τη βαρύτητά της.

Σοβαρότης	WHO (g/dl)	NCI (g/dl)
Βαθμός 0 (φυσιολ.)	≥ 11	Φυσιολογική
Βαθμός 1 (ηπία)	9,5-10,9	10,0-φυσιολογική
Βαθμός 2 (μετρία)	8,0-9,4	8,0-10,0
Βαθμός 4 (σοβαρά)	6,5-7,9	6,5-7,9
Βαθμός 5 (απειλητική)	< 6,5	< 6,5

Αναιμία και Σιδηροπενική Αναιμία (ΣΑ)

Worldwide prevalence of anaemia 1993–2005

WHO Global Database on Anaemia



- **Η αναιμία παγκοσμίως συναντάται στο 24.8% του γενικού πληθυσμού, ενώ η σιδηροπενία αποτελεί το βασικότερο αίτιο**

World Health Organization

Centers for Disease Control and Prevention Atlanta

Ο επιπολασμός της Αναιμίας WHO(1993-2005)

Table 3.2 ***Global anaemia prevalence and number of individuals affected***

Population group	Prevalence of anaemia		Population affected	
	Percent	95% CI	Number (million)	95% CI
Preschool-age children	47.4	45.7–49.1	293	283–303
School-age children	25.4	19.9–30.9	305	238–371
Pregnant women	41.8	39.9–43.8	56	54–59
Non-pregnant women	30.2	28.7–31.6	468	446–491
Men	12.7	8.6–16.9	260	175–345
Elderly	23.9	18.3–29.4	164	126–202
Total population	**24.8**	**22.9–26.7**	**1620**	**1500–1740**

World Health Organization. Worldwide prevalence of anaemia 1993-2005: WHO global database on anaemia 2008. Available at http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency

Τι αναφέρουν τα στοιχεία για την Αναιμία στην Ευρώπη

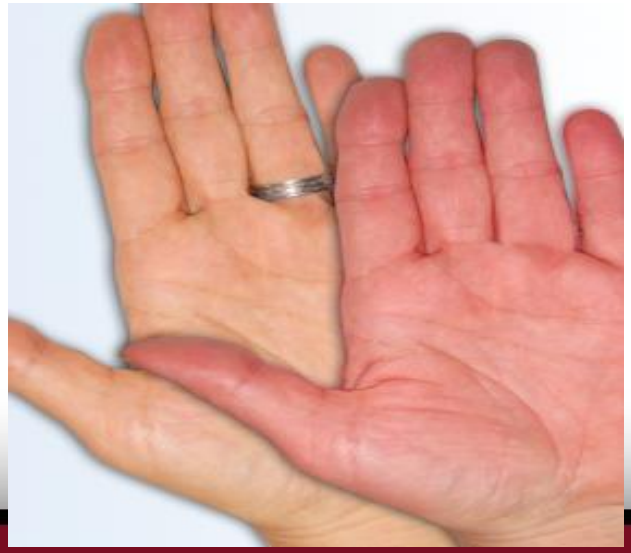
Table 3.3 ***Anaemia prevalence and number of individuals affected in preschool-age children, pregnant women, and non-pregnant women in each WHO region***

WHO region	Preschool-age children[a]		Pregnant women		Non-pregnant women	
	Prevalence (%)	# affected (millions)	Prevalence (%)	# affected (millions)	Prevalence (%)	# affected (millions)
Africa	67.6 (64.3–71.0)[b]	83.5 (79.4–87.6)	57.1 (52.8–61.3)	17.2 (15.9–18.5)	47.5 (43.4–51.6)	69.9 (63.9–75.9)
Americas	29.3 (26.8–31.9)	23.1 (21.1–25.1)	24.1 (17.3–30.8)	3.9 (2.8–5.0)	17.8 (12.9–22.7)	39.0 (28.3–49.7)
South-East Asia	65.5 (61.0–70.0)	115.3 (107.3–123.2)	48.2 (43.9–52.5)	18.1 (16.4–19.7)	45.7 (41.9–49.4)	182.0 (166.9–197.1)
Europe	21.7 (15.4–28.0)	11.1 (7.9–14.4)	25.1 (18.6–31.6)	2.6 (2.0–3.3)	19.0 (14.7–23.3)	40.8 (31.5–50.1)
Eastern Mediterranean	46.7 (42.2–51.2)	0.8 (0.4–1.1)	44.2 (38.2–50.3)	7.1 (6.1–8.0)	32.4 (29.2–35.6)	39.8 (35.8–43.8)
Western Pacific	23.1 (21.9–24.4)	27.4 (25.9–28.9)	30.7 (28.8–32.7)	7.6 (7.1–8.1)	21.5 (20.8–22.2)	97.0 (94.0–100.0)
Global	**47.4 (45.7–49.1)**	**293.1 (282.8–303.5)**	**41.8 (39.9–43.8)**	**56.4 (53.8–59.1)**	**30.2 (28.7–31.6)**	**468.4 (446.2–490.6)**

[a] Population subgroups: Preschool-age children (0.00–4.99 yrs); Pregnant women (no age range defined); Non-pregnant women (15.00–49.99 yrs).
[b] 95% Confidence Intervals.

Αναιμία: κλινικές εκδηλώσεις

- Καταβολή
- Ζάλη
- Κεφαλαλγία
- Διαταραχές του ύπνου
- Ψυχρά άκρα
- Ανορεξία
- Αδυναμία συγκέντρωσης
- Αίσθημα παλμών και δύσπνοια μετά από μικρή κόπωση
- Κατάθλιψη



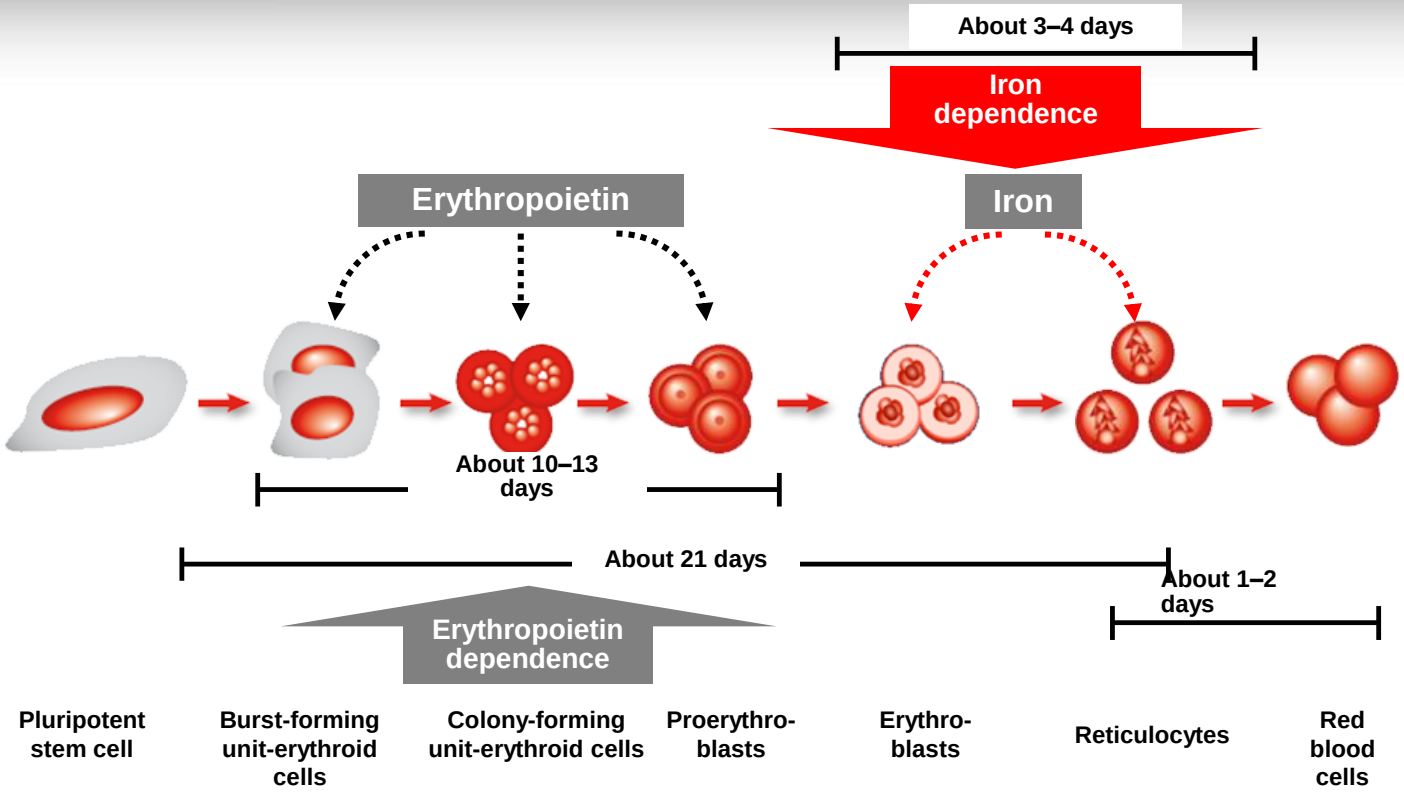
Αναιμία: βασικά σημεία (1)

- Η Αναιμία αποτελεί σοβαρό ιατροκοινωνικό πρόβλημα
- Προσβάλλει περίπου το 25% του πληθυσμού σε παγκόσμιο επίπεδο
- Έχει άμεση σχέση με το βιοτικό επίπεδο του πληθυσμού
- Η συχνότητά της είναι αυξημένη στα ηλικιωμένα άτομα
- 25 – 35 % των παθολογικών εισαγωγών σε νοσοκομείο είναι δυνατόν να παρουσιάζει αναιμία
- Αποτελεί δυσμενή προγνωστικό παράγοντα όταν συνυπάρχει με άλλα νοσήματα

Αναιμία: βασικά σημεία (2)

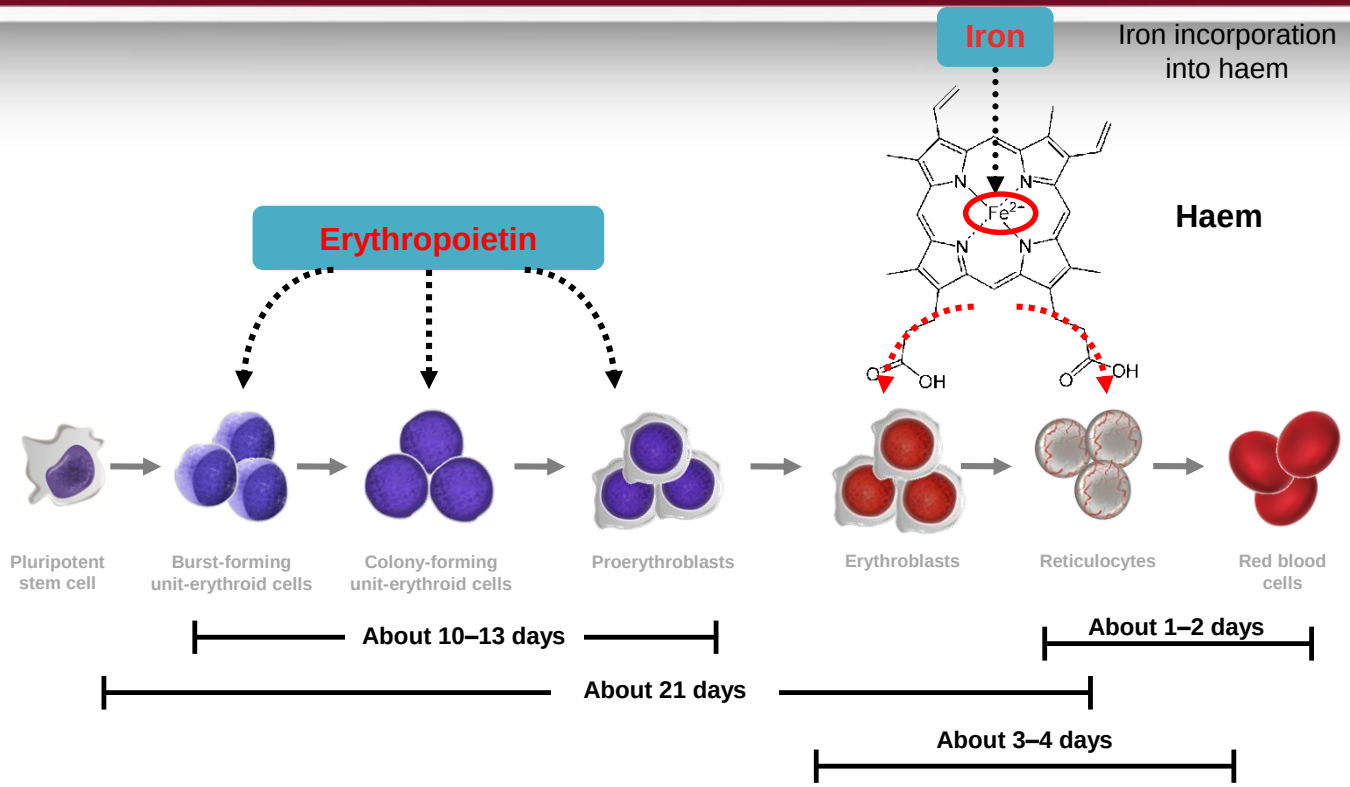
- Η αναιμία στις πιο πολλές περιπτώσεις είναι σύμπτωμα υποκείμενης νόσου και η θεραπευτική παρέμβαση θα πρέπει να έχει ως στόχο την ανάταξη μεν της αναιμίας, αλλά συγχρόνως την αντιμετώπιση της υποκείμενης νόσου, που είναι ο αιτιολογικός παράγοντας
- Τα συμπτώματα ποικίλουν, καθώς εξαρτώνται από την αιτία της αναιμίας, τη σοβαρότητα της, το χρόνο έναρξης της, καθώς και τη δυνατότητα προσαρμογής του οργανισμού στα χαμηλά επίπεδα

Ο σίδηρος είναι καθοριστικός στη διαδικασία της ερυθροποίησης



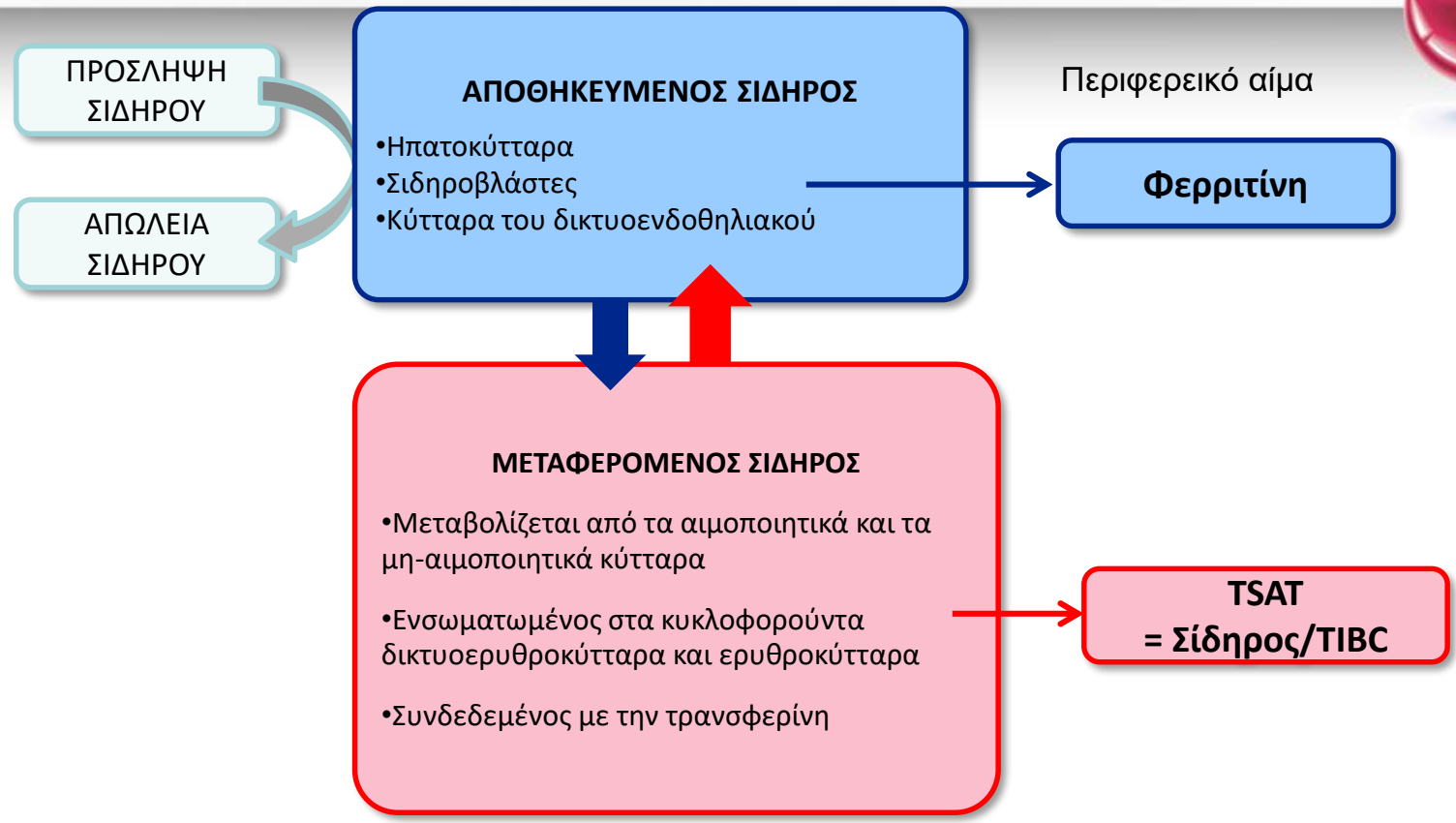
Adapted from: Besarab A, et al. *Oncologist* 2009;14(Suppl 1):22–33

Ο σίδηρος και η ερυθροποιητίνη παίζουν ζωτικό ρόλο στην παραγωγή των ερυθρών κυττάρων



1. Besarab A, *et al*. *Oncologist* 2009;14(Suppl 1):22–33. 2. Jankowska EA, *et al*. *Eur Heart J* 2013;34:816–29
3. Pittman RN. Regulation of Tissue Oxygenation (2011). San Rafael (CA): Morgan & Claypool Life Sciences

Ορισμός της σιδηροπενίας: Δείκτες αποθήκευσης και αξιοποίησης του σιδήρου



Jankowska EA, et al. *Eur. Heart J* 2013;34:816-29

Φερριτίνη ορού – Αποθήκες σιδήρου

Μετρούμενη παράμετρος	Πλεονεκτήματα	Περιορισμοί
• Αποθήκες σιδήρου[1]  Φερριτίνη	• Ο πιο χρήσιμος δείκτης για την αξιολόγηση των αποθηκών σιδήρου[2] • Στα υγιή άτομα, η φερριτίνη ορού σχετίζεται με τα αποθέματα σιδήρου στον οργανισμό[2]	• Τα φυσιολογικά ή αυξημένα επίπεδα φερριτίνης δεν αποκλείουν απόλυτη ή λειτουργική σιδηροπενία[3] • Διαφορές ανάλογα με το φύλο (φυσιολογικά χαμηλότερη στις γυναίκες)[1] • Αντιδραστήριο οξείας φάσης[1] • Τα επίπεδα της φερριτίνης μπορεί να είναι αυξημένα σε άτομα με συνυπάρχοντα φλεγμονώδη νοσήματα, λοίμωξη, κακοήθεια ή ηπατική νόσο[2,3]

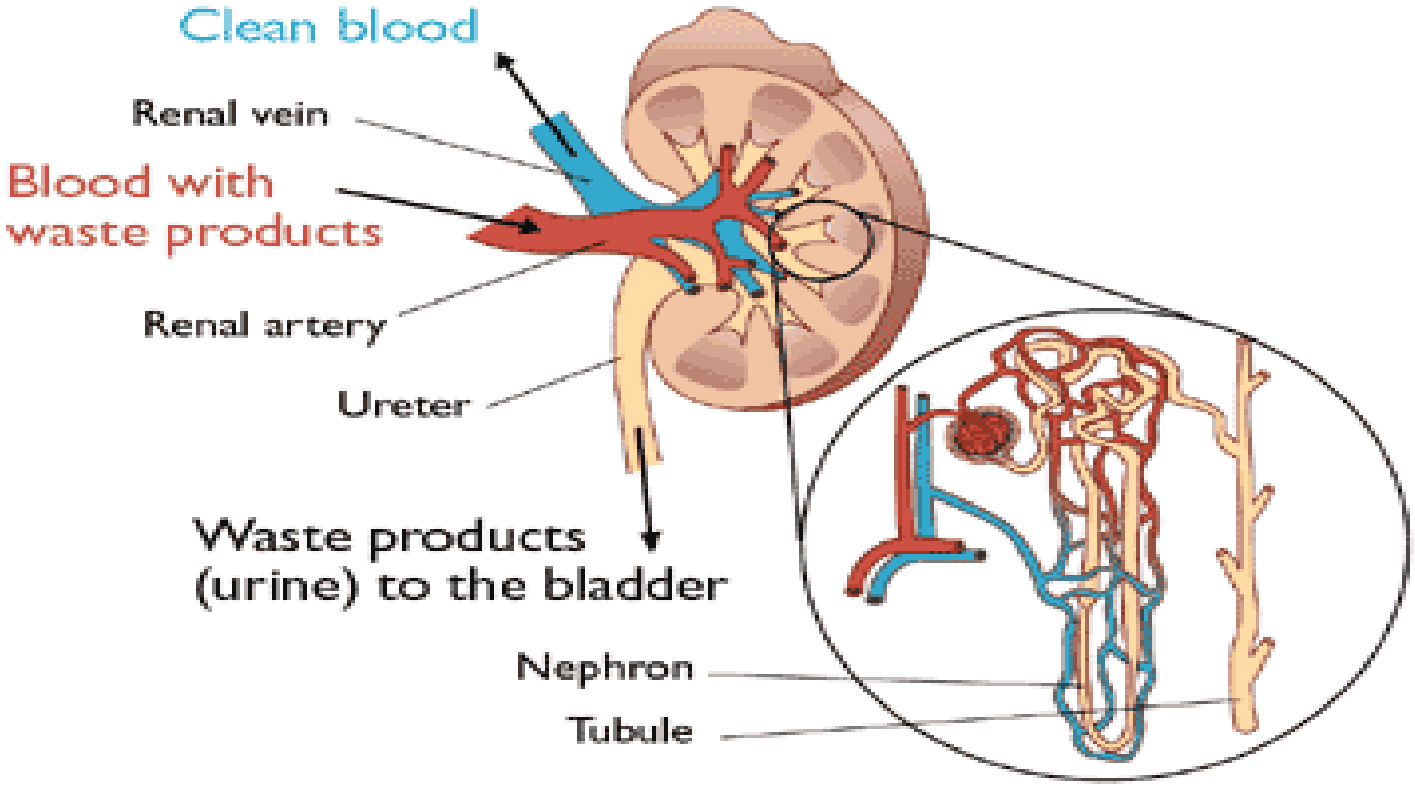
1. Wish JB. *Clin J Am Soc Nephrol* 2006;1:S4–8
2. Crichton RR, et al. Iron therapy with special emphasis on intravenous administration (4th edition). UNI-MED Verlag AG, Bremen
3. Macdougall IC. *Curr Opin Nephrol Hyperten* 1994;3:620–5

Η φερριτίνη είναι μια σημαντική παράμετρος για την αξιολόγηση της σιδηροπενίας

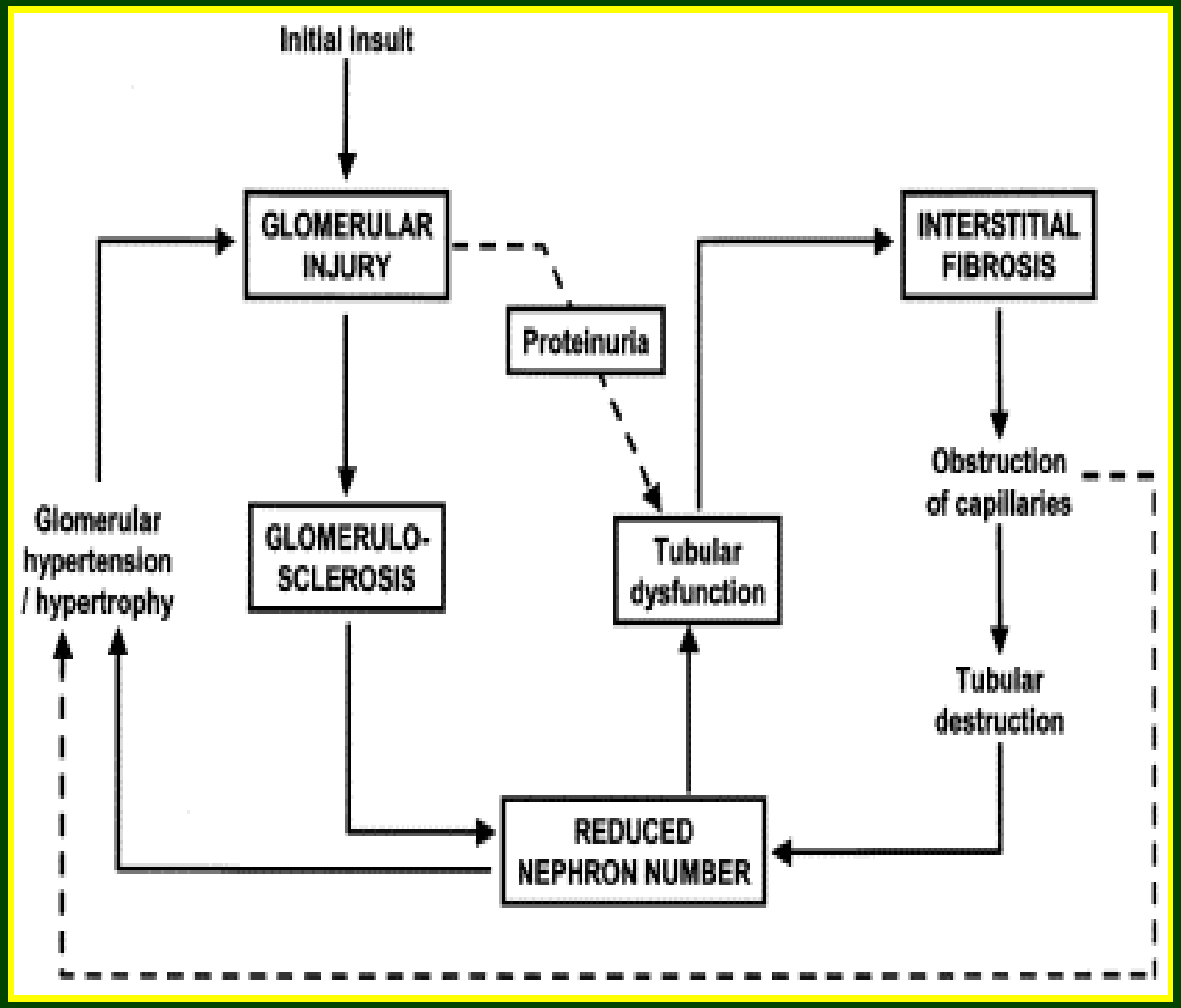
Εργαστηριακή Παράμετρος	Τι μετράει	Πλεονεκτήματα	Περιορισμοί
Φερριτίνη ορού  *Φερριτίνη*	Αποθήκες σιδήρου[2]	• Ο πιο χρήσιμος δείκτης για την αξιολόγηση των αποθηκών σιδήρου[4] • Τα χαμηλά επίπεδα είναι εξαιρετικά ειδικά για ύπαρξη σιδηροπενίας[3] • Στα υγιή άτομα σχετίζεται με τα αποθέματα σιδήρου στον οργανισμό[4] • Εύκολη και ευρέως διαθέσιμη μέτρηση, με μέτριο κόστος	Αντιδραστήριο οξείας φάσης[2] π.χ. μπορεί να αυξηθεί από συνυπάρχοντα φλεγμονώδη νοσήματα, λοίμωξη, κακοήθεια ή ηπατική νόσο[1,4] Τα φυσιολογικά ή αυξημένα επίπεδα φερριτίνης δεν αποκλείουν λειτουργική σιδηροπενία[1] Διαφορές ανάλογα με το φύλο (φυσιολογικά χαμηλότερη στις γυναίκες)[2]

1. Macdougall IC. *Curr Opin Nephrol Hyperten* 1994;3:620–5. 2. Wish JB. *Clin J Am Soc Nephrol* 2006;1:S4–8
3. Kalantar-Zadeh K, *et al*. *Clin J Am Soc Nephrol* 2006;1:S9–S18. 4. Crichton RR, *et al*. UNI-MED Verlag AG, Bremen 2006

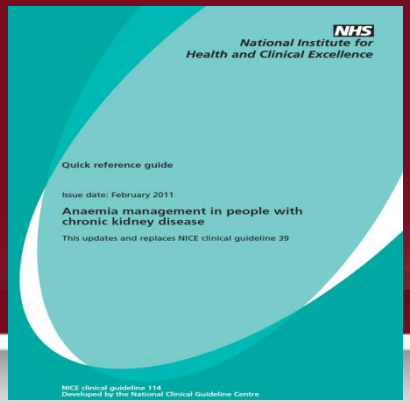
How the kidney works



Mechanism of Progressive CKD



Source: Rossert, JA, et al, *JASN* 14:S173-177, 2003



- **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

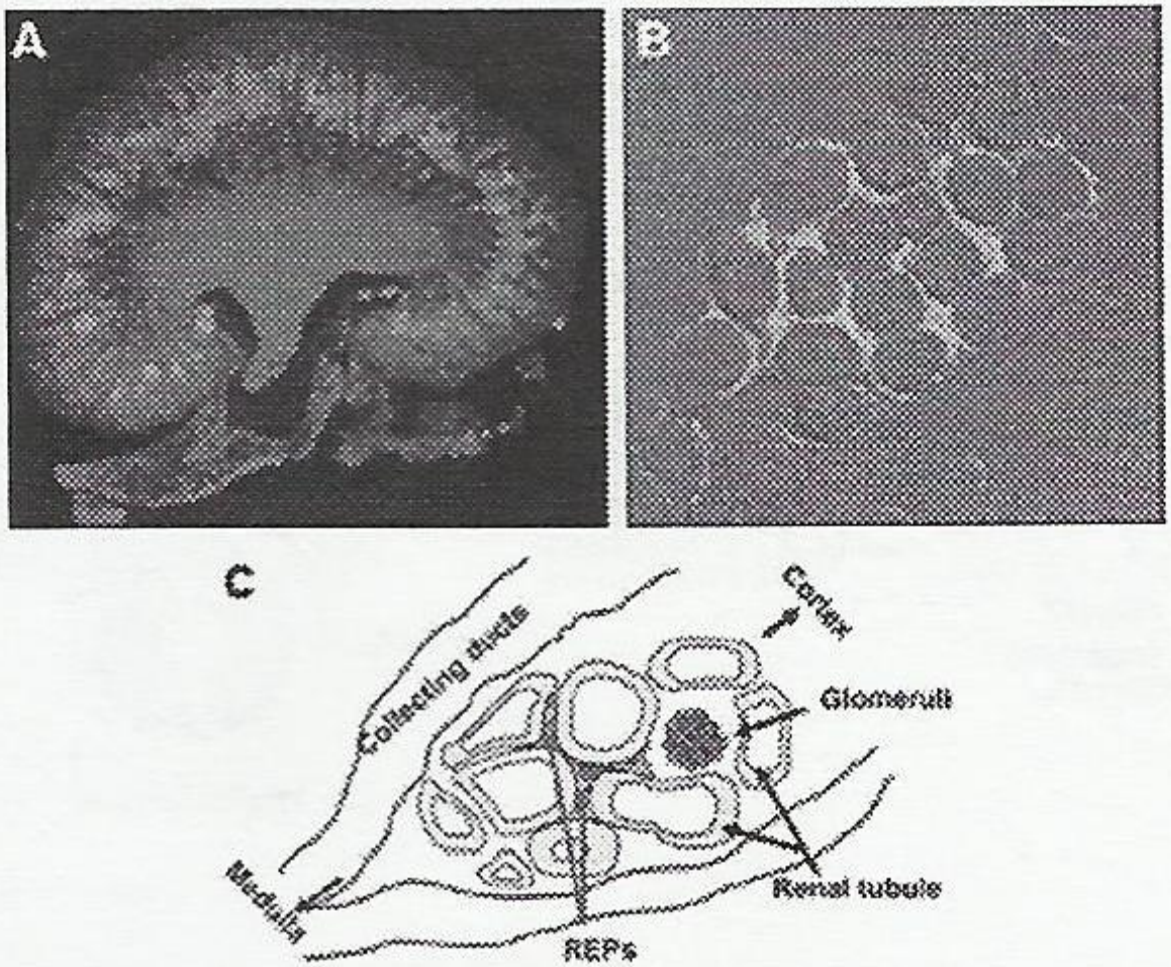
- Transfusion
- Erythropoesis stimulating agents (ESAs)
  (epoeitin alpha & beta, darbepoetin, methoxy polyethylene glycol epoetin beta)
- Iron
  (iron sucrose, ferric gluconate, iron dextran, ferumoxytol, ferrous sulfate)

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

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Physiology and Pharmacology of Erythropoietin

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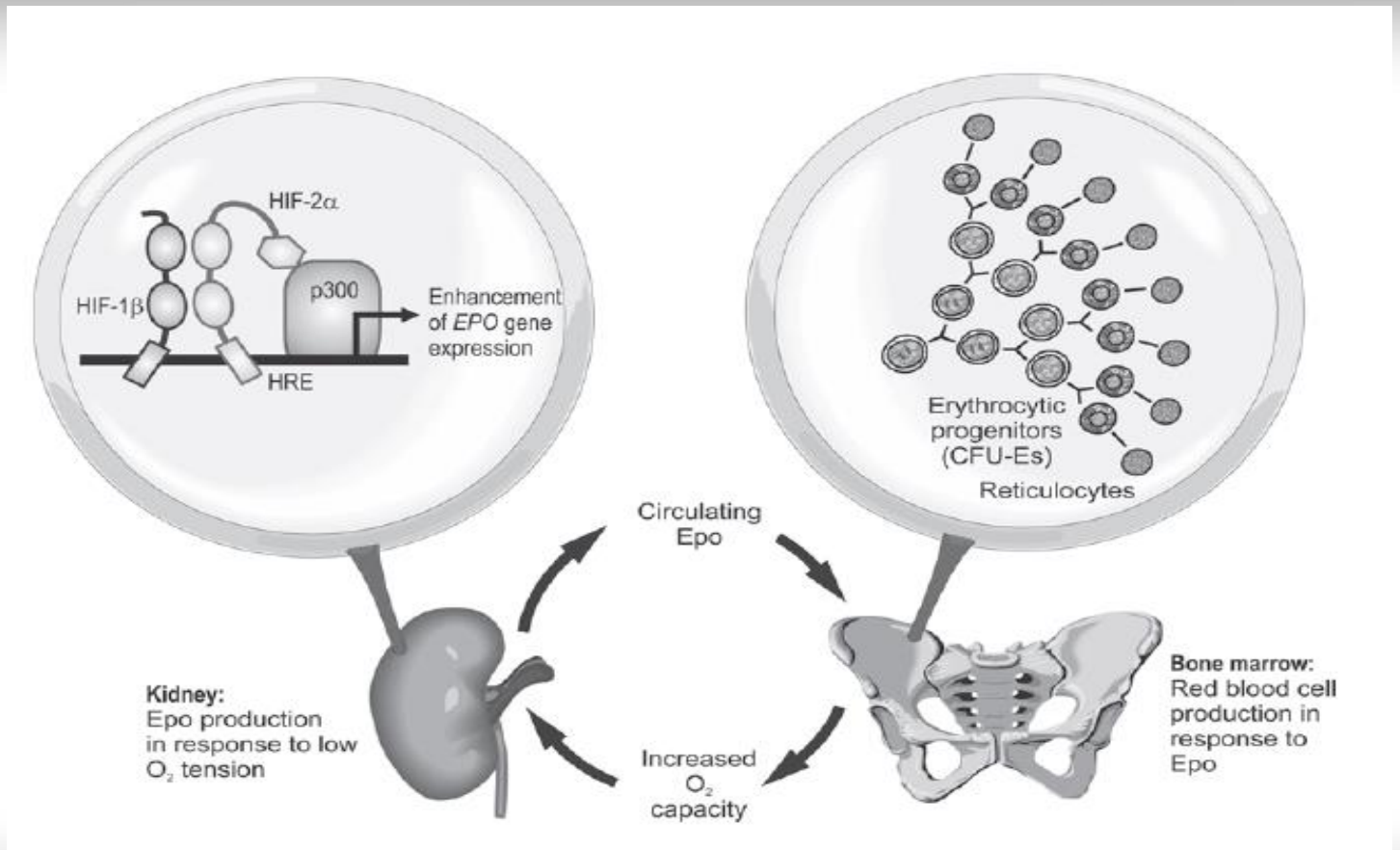
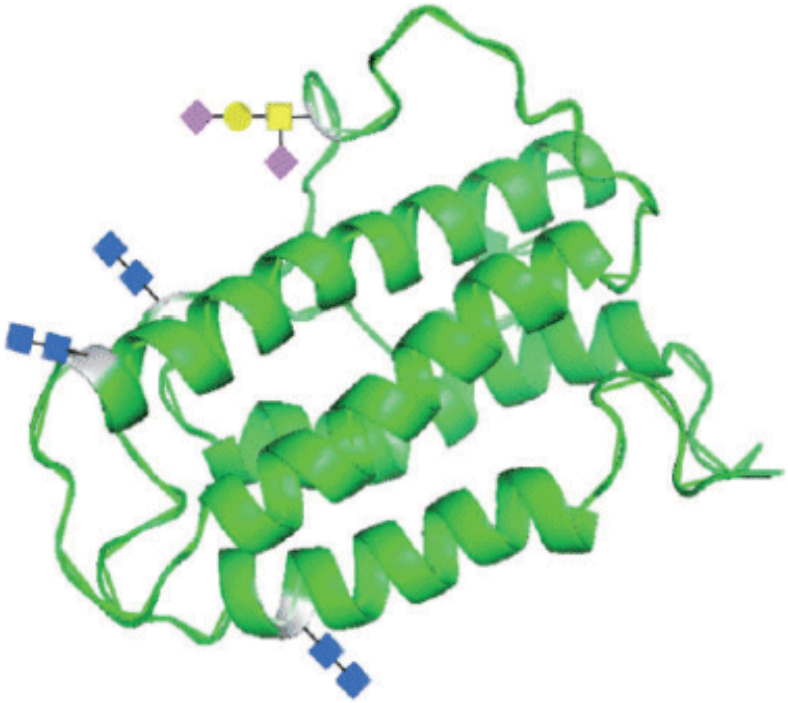
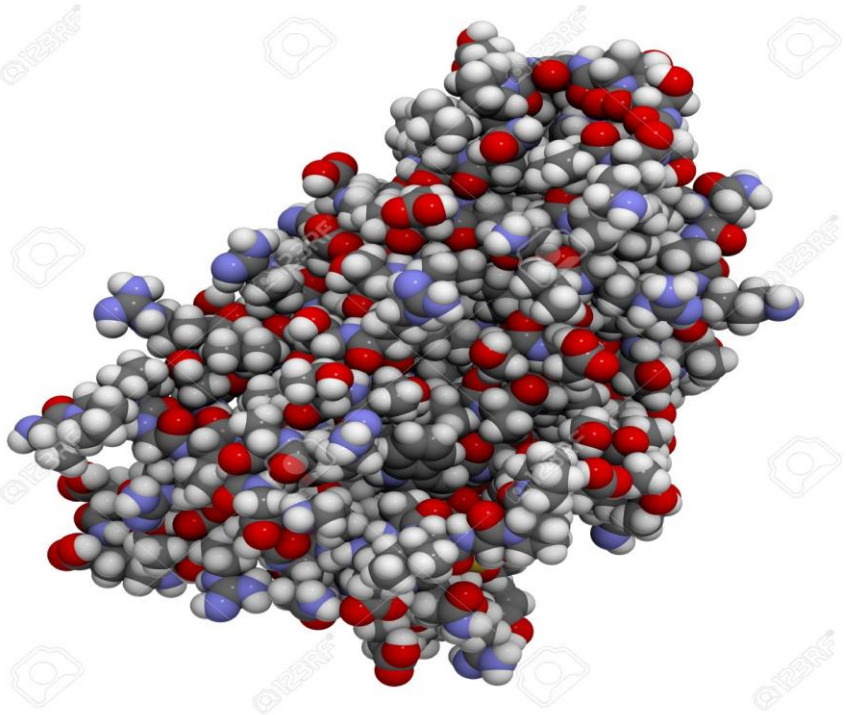




Erythropoietin



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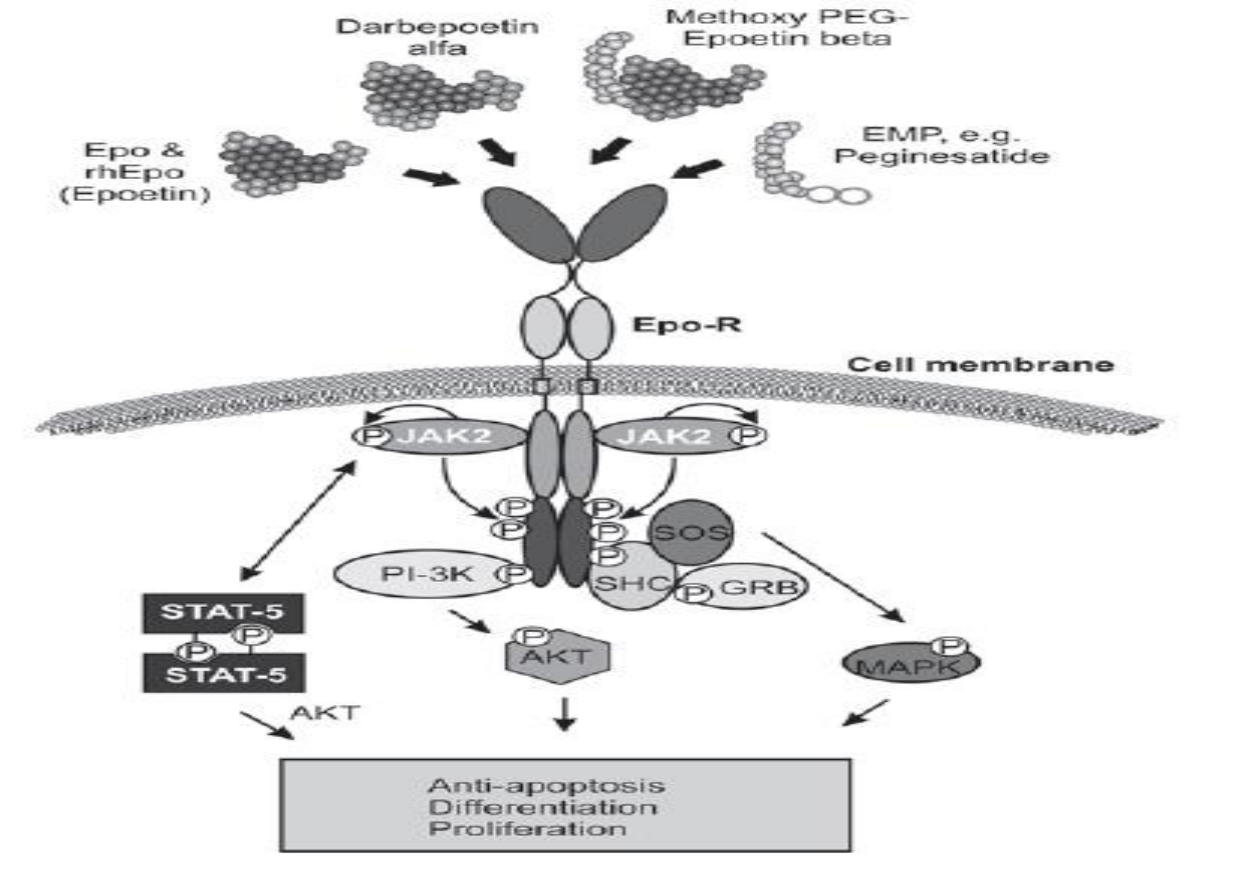


Recombinant EPO preparations

'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.

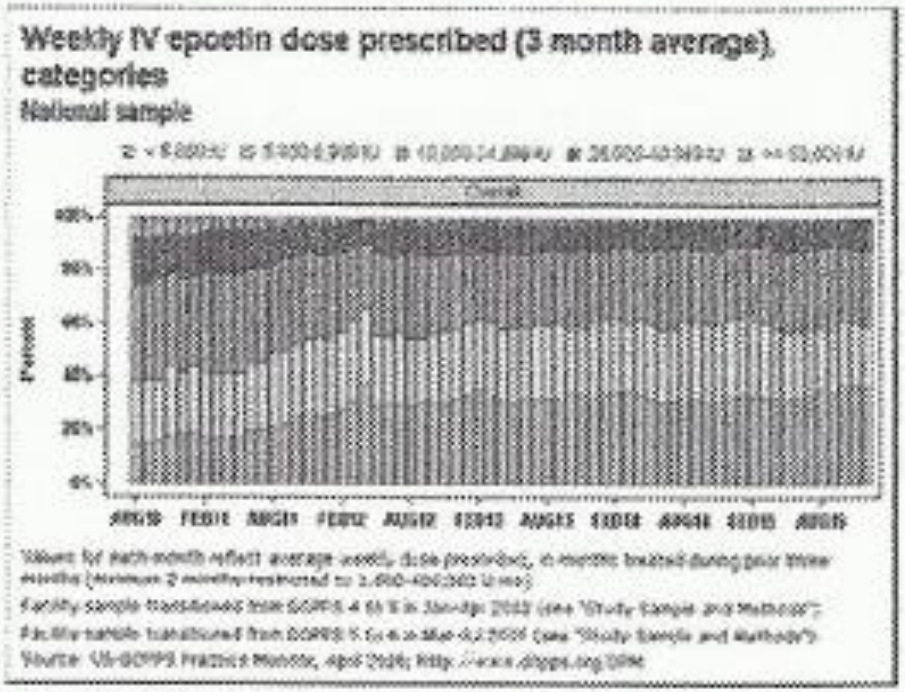
Recombinant EPO preparations

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

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D., Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D., John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D., Ajay K. Singh, M.D., Scott D. Solomon, M.D., and Robert Toto, M.D., for the TREAT Investigators*

ABSTRACT

BACKGROUND

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

METHODS

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

This article (10.1056/NEJMoa0907845) was published on October 30, 2009, at NEJM.org.

N Engl J Med 2009;361.

Οδηγίες – Guidelines

ERBP Position Paper 2010

Haemoglobin target

"

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)

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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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(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

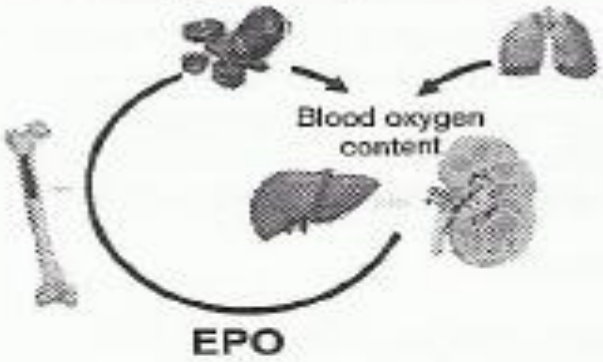
(ii) ESA treatment should not be started in patients who are iron-deficient

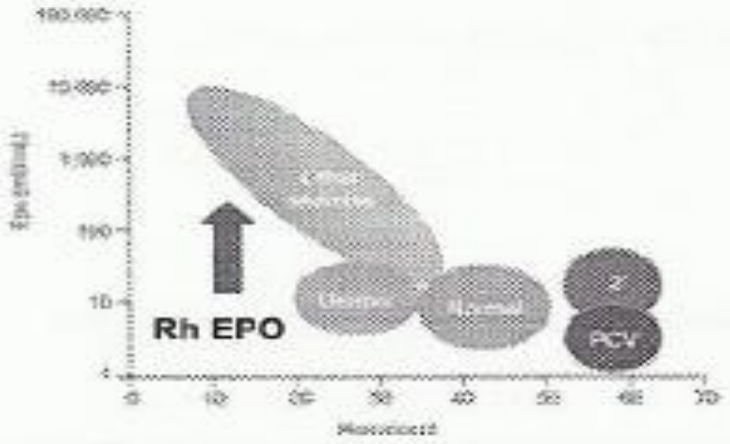
(iii) Iron replacement should be used first in any CKD patient who is proven or likely to be iron-deficient, and only once the iron stores are replete should ESA therapy be initiated

(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

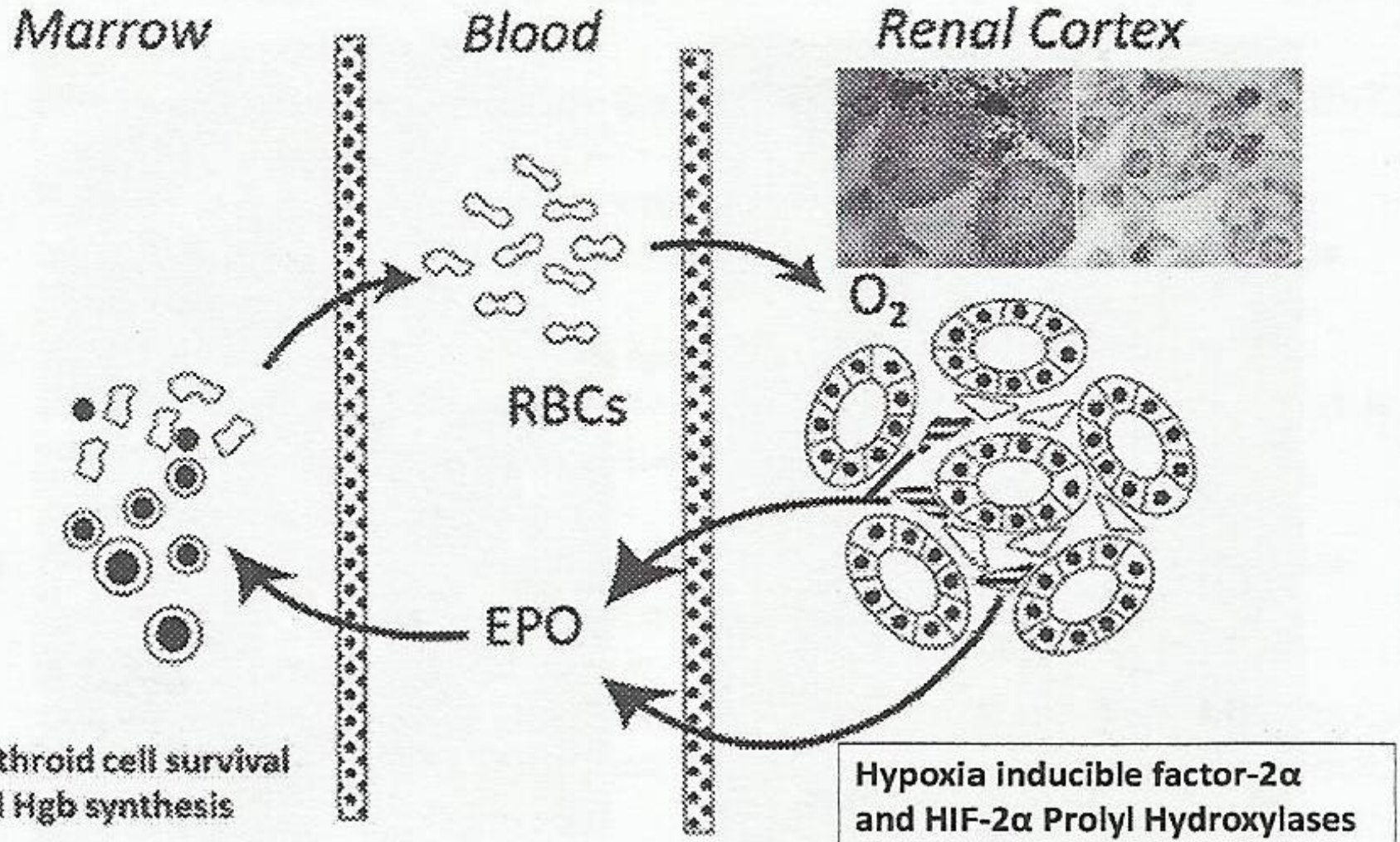
1. HIFs are transcription factors composed of 2 subunits: HIF-α and HIF-β (ARNT).

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*

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.

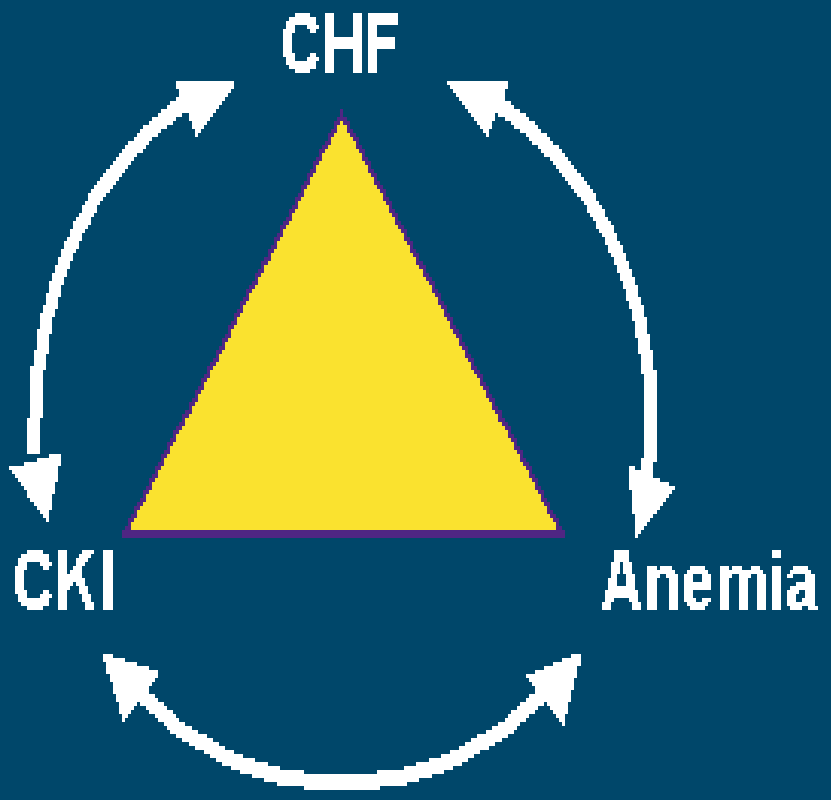
Cardiovascular Safety

- 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...

Conclusions

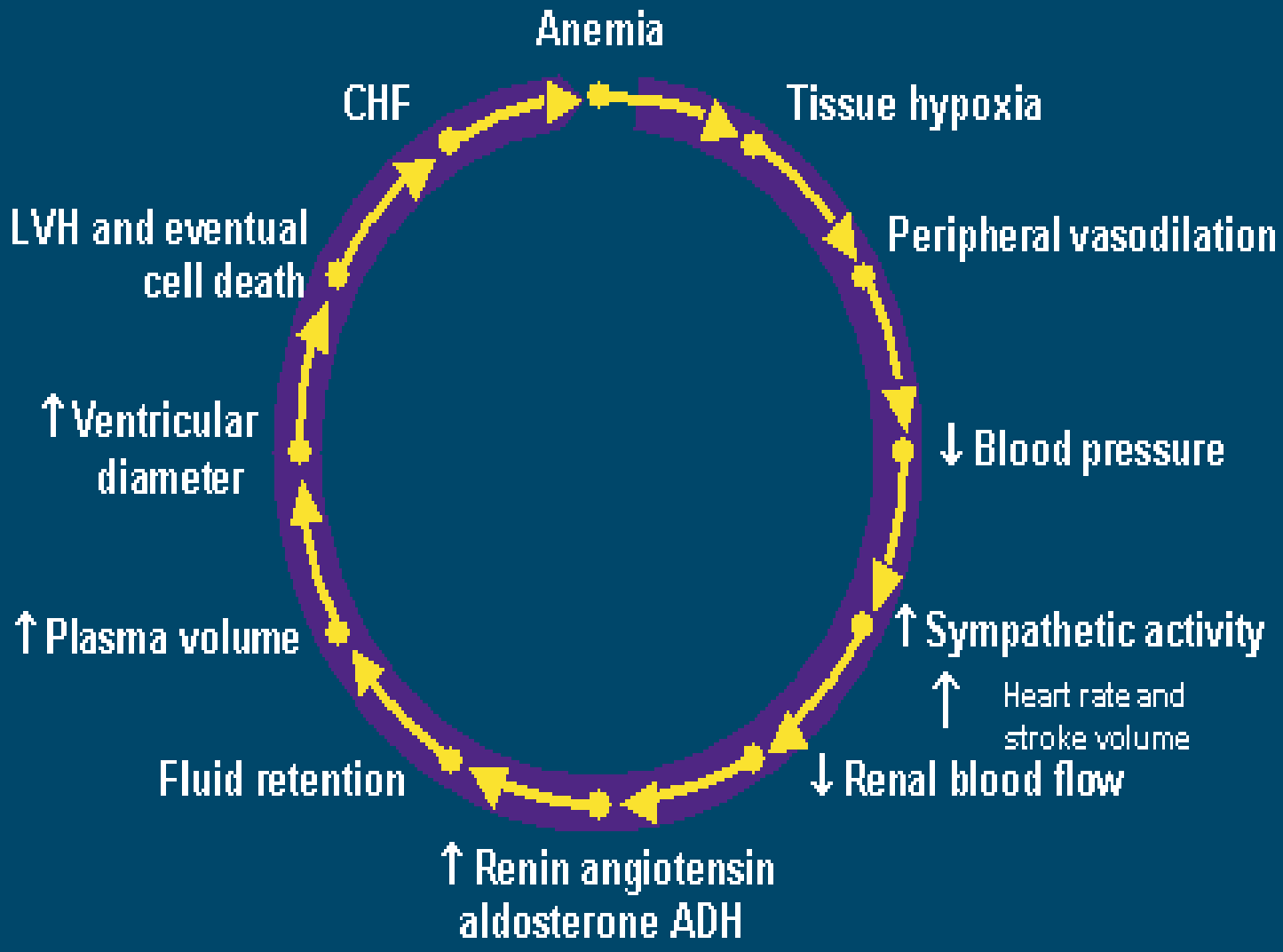
- HIF Activators are an interesting and physiologic alternative to current treatment options for anemia
- The available clinical data appear promising
- No obvious safety signal YET
- Pending phase III clinical trials will help determine whether HIF Activators will one day replace ESAs and iron– ***STAY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

Cardiorenal anemia syndrome: a vicious circle of destruction



Anemia as a cause of heart failure

Anemia and cardiovascular disease



Anand et al Brit Ht J 1993; 70:357

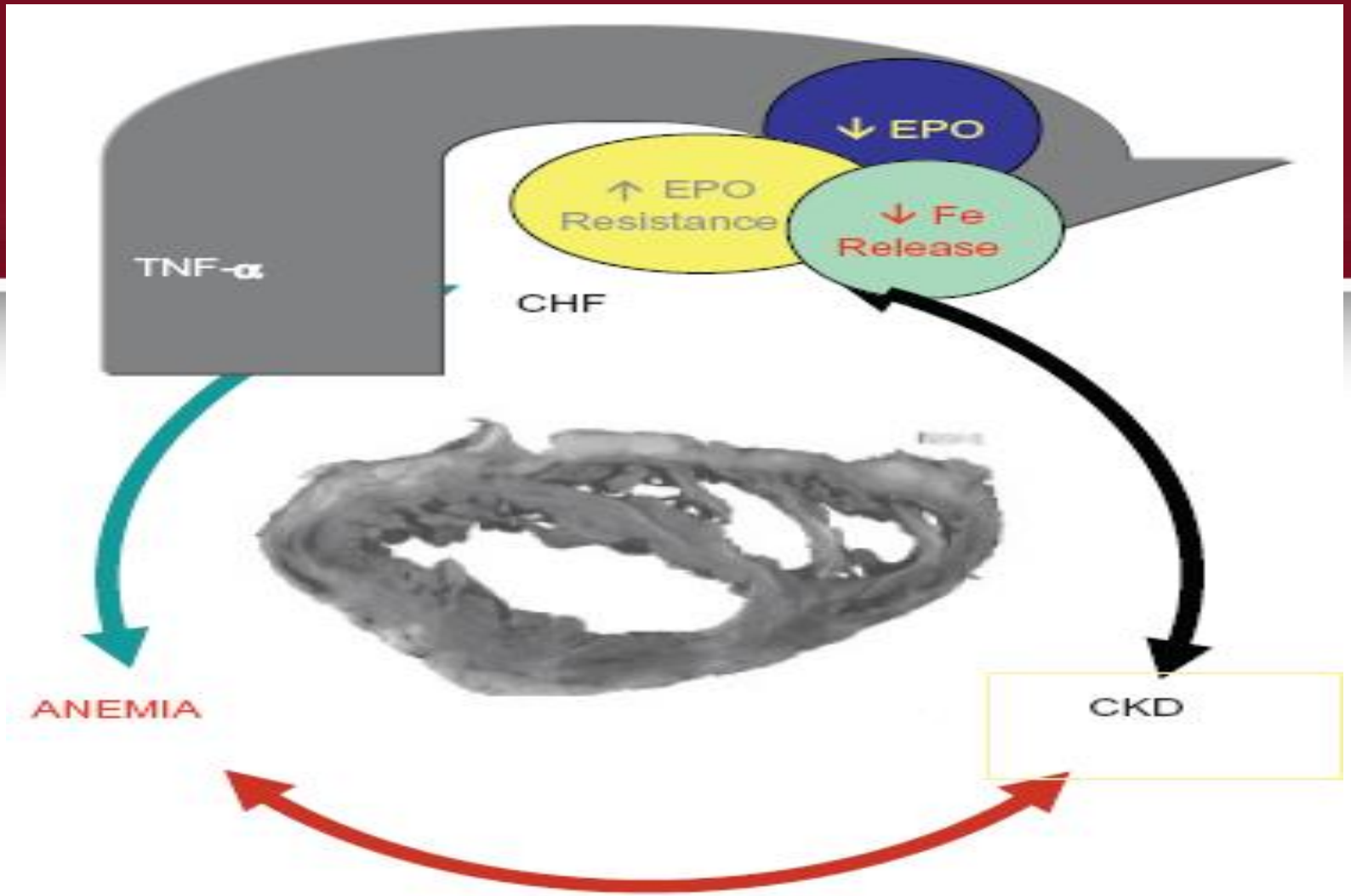
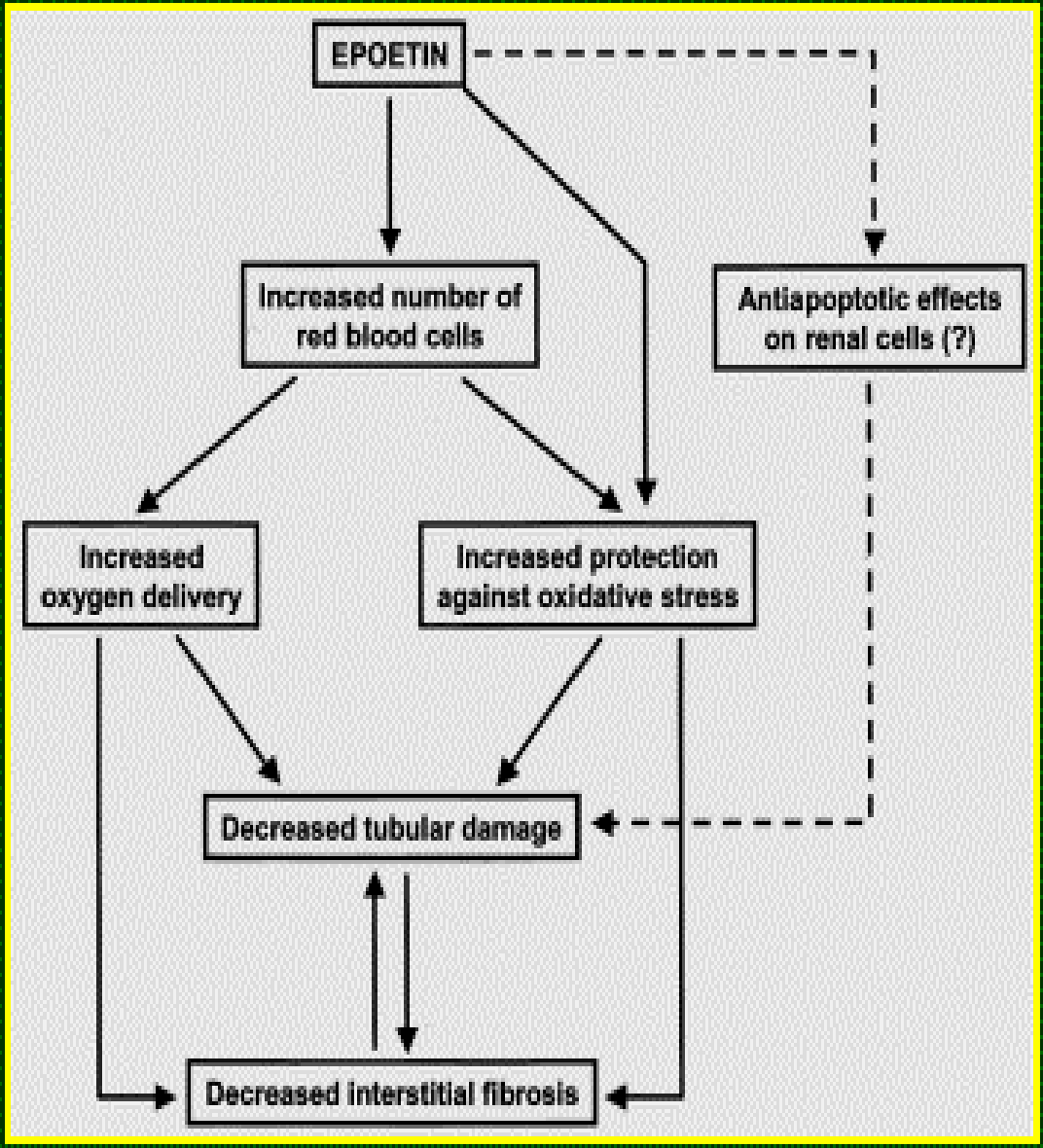
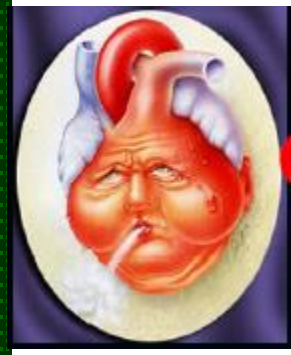


Figure 4 The influence of cytokines in the development of anemia in the cardio-renal anemia syndrome. TNF-α and other cytokines have an inhibitory effect on erythropoietin-stimulating agent-dependent erythropoietic processes in the bone marrow (EPO resistance), inhibit remobilization for hemoglobin synthesis through hepcidin production, and decrease endogenous EPO production in the kidney. Anemia worsens heart failure, decreases renal perfusion, and leads to a circular cycle.
Abbreviation: CKD, chronic kidney disease.

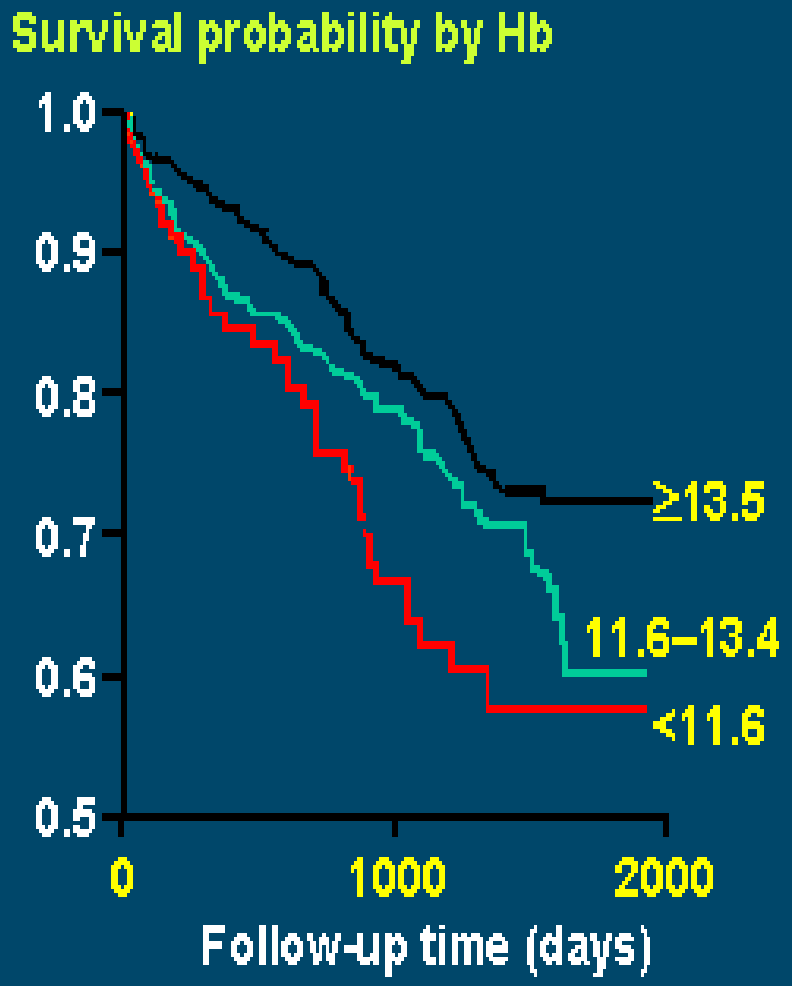
Role of EPO in Preventing Progressive CKD

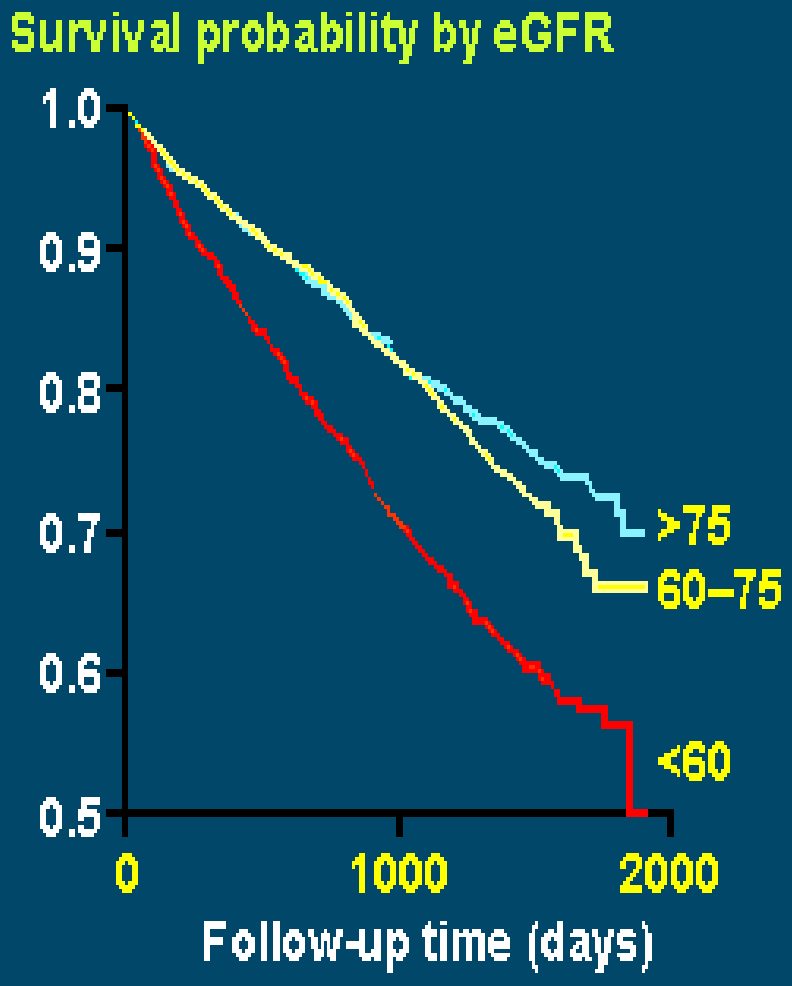




Source: Rossert, JA, et al, *JASN* 14:S173-177, 2003

Hb and GFR as risk factors in CHF patients (SOLVD Study)





From Al Ahmad JACC 2001;38:955

Epoetin and IV Iron for Anemia in Patients with CHF

Prospective uncontrolled intervention study

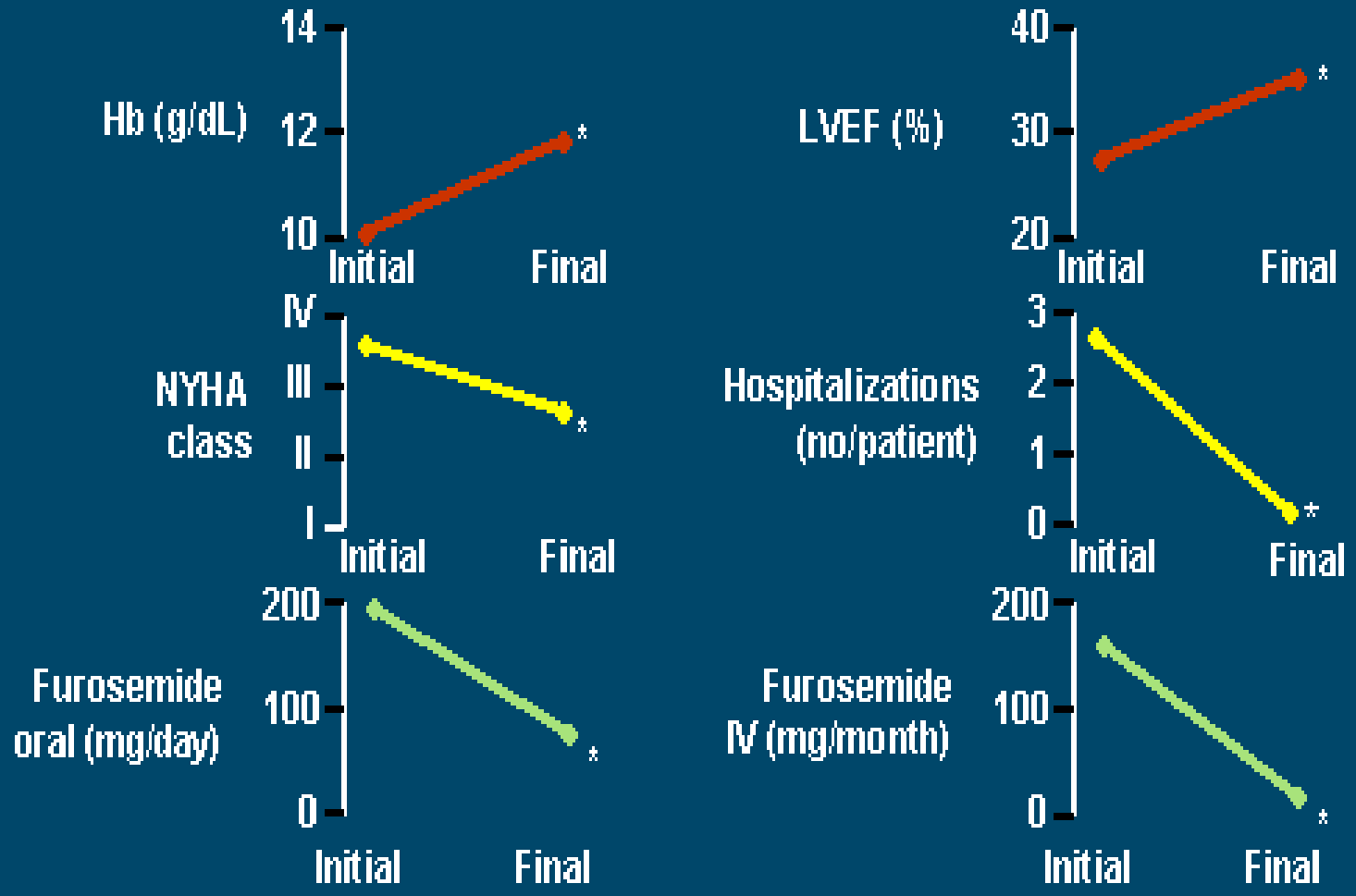
26 anemic patients (Hb 10-11.9g%) with severe CHF despite being treated with maximally tolerated medications for > 6 mo had their anemia corrected

Intervention: Epoetin SC and Iron sucrose IV (Venofer)

Goal: To raise the Hb to above 12g%

Silverberg DS, Wexler D, *et al. JACC* 2000;35:1737

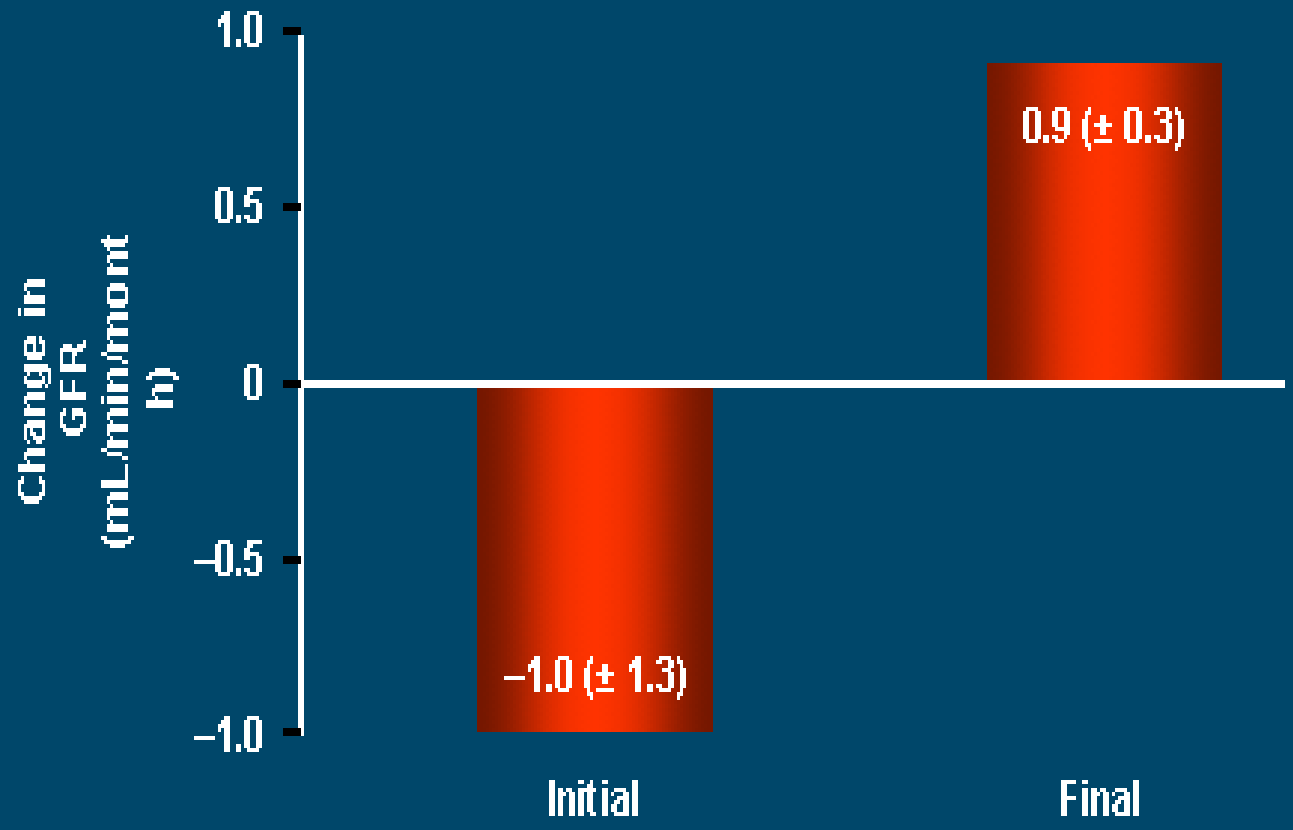
Response of anemic CHF patients to EPO and IV iron



*$P < 0.05$ initial *versus* final

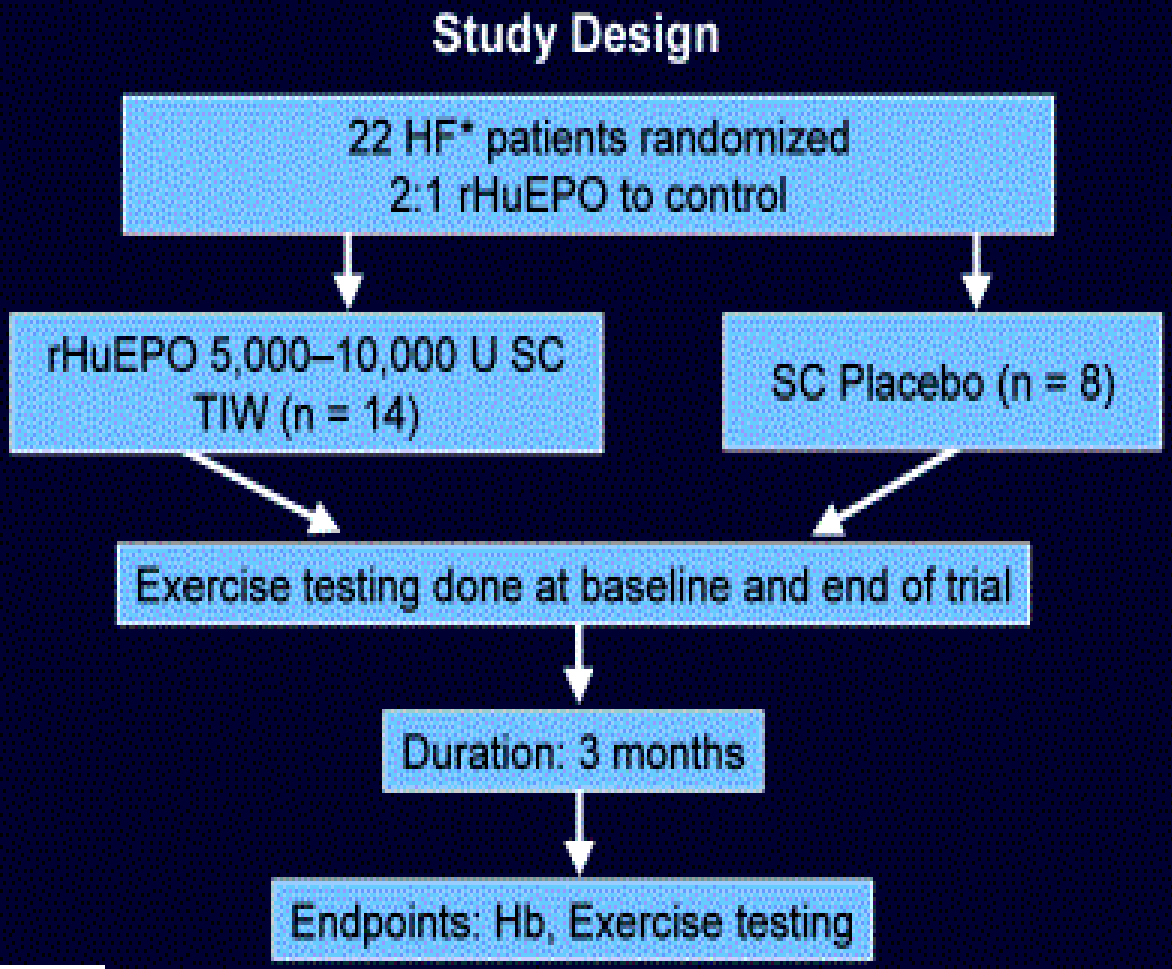
Silverberg DS, Wexler D, *et al. JACC* 2000;35:1737

Prospective intervention study of anemia treatment in CHF: Impact of anemia correction on GFR



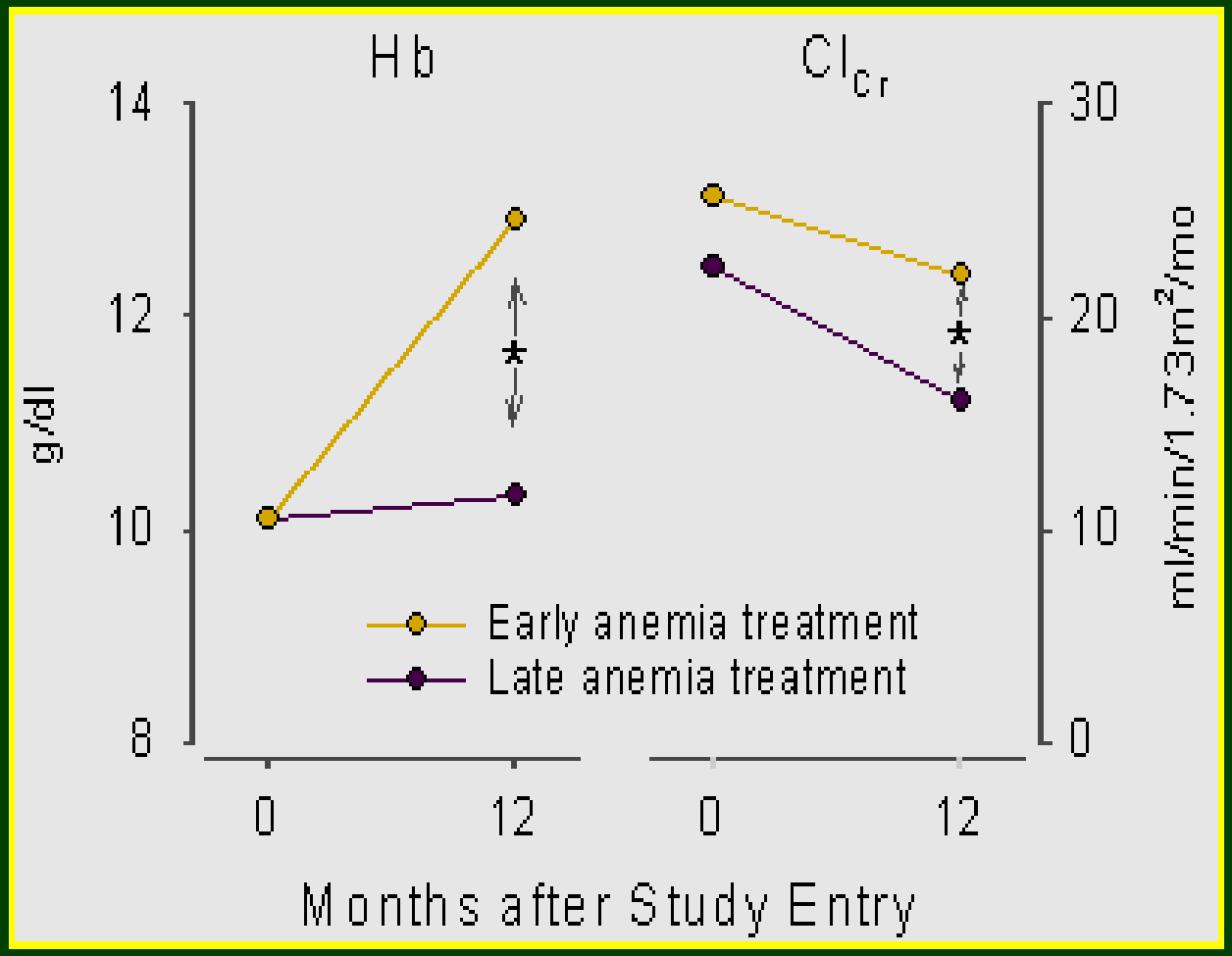
Silverberg DS,Wexler D,*et al. JACC* 2000;35:1737

rHuEPO Impact On Exercise Capacity in HF Patients



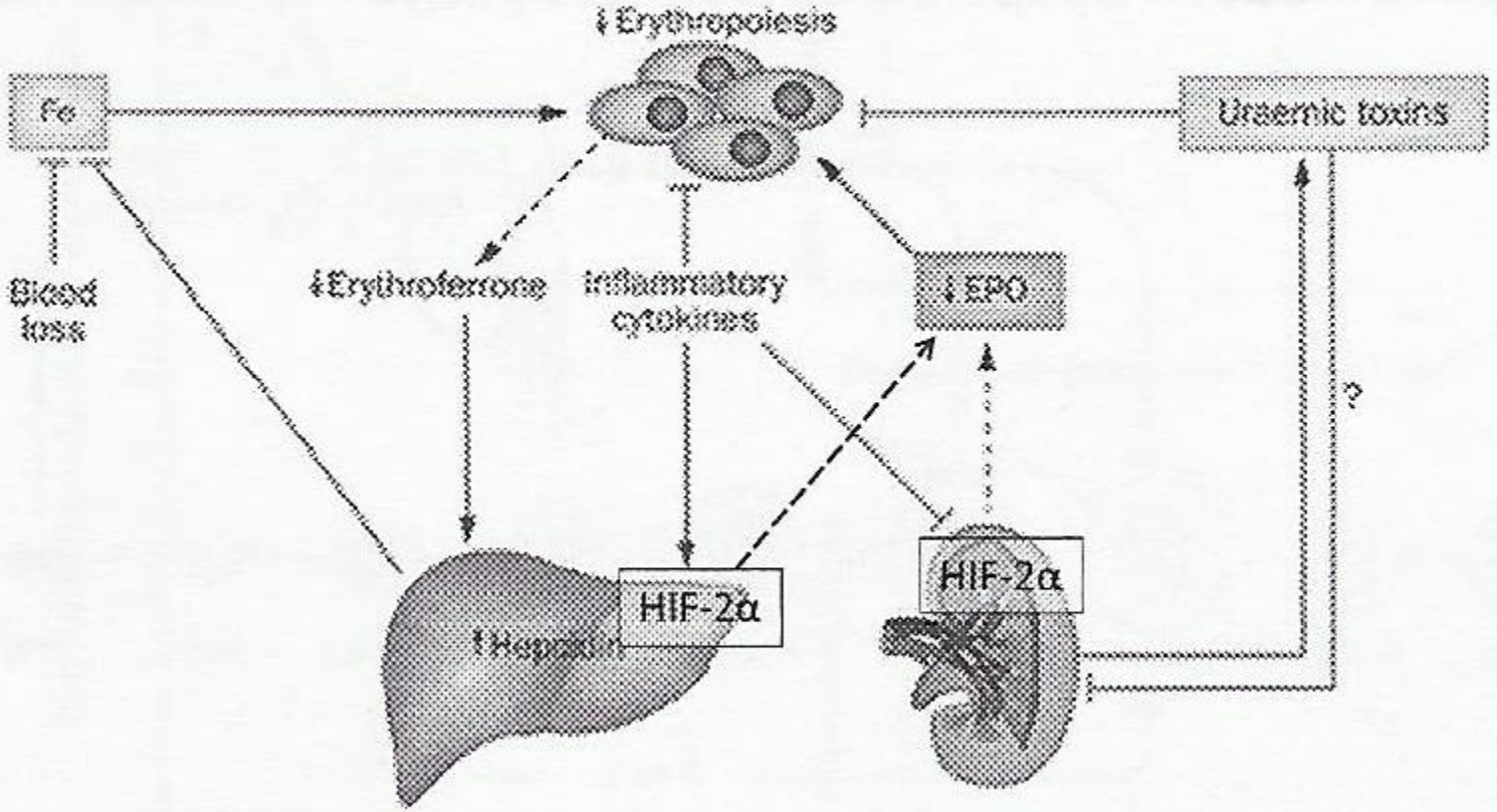
Mancini et al, Circulation 2003:107,294

Early treatment of anemia is associated with slower CKD progression



Source: Gouva C, et al. *Kidney Int* 66:753-760, 2004 (*P < 0.001)

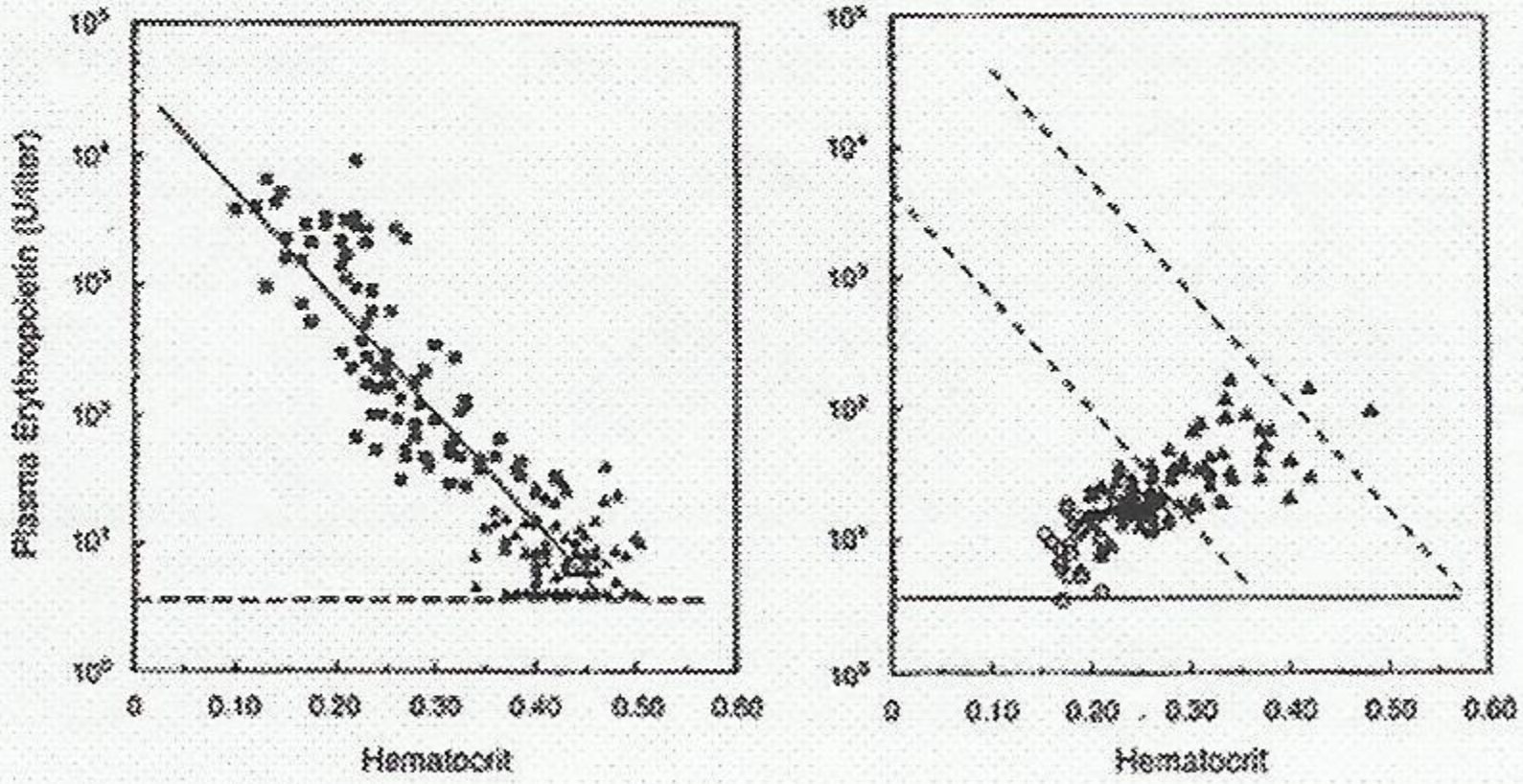
Overview of the anemia of kidney disease



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

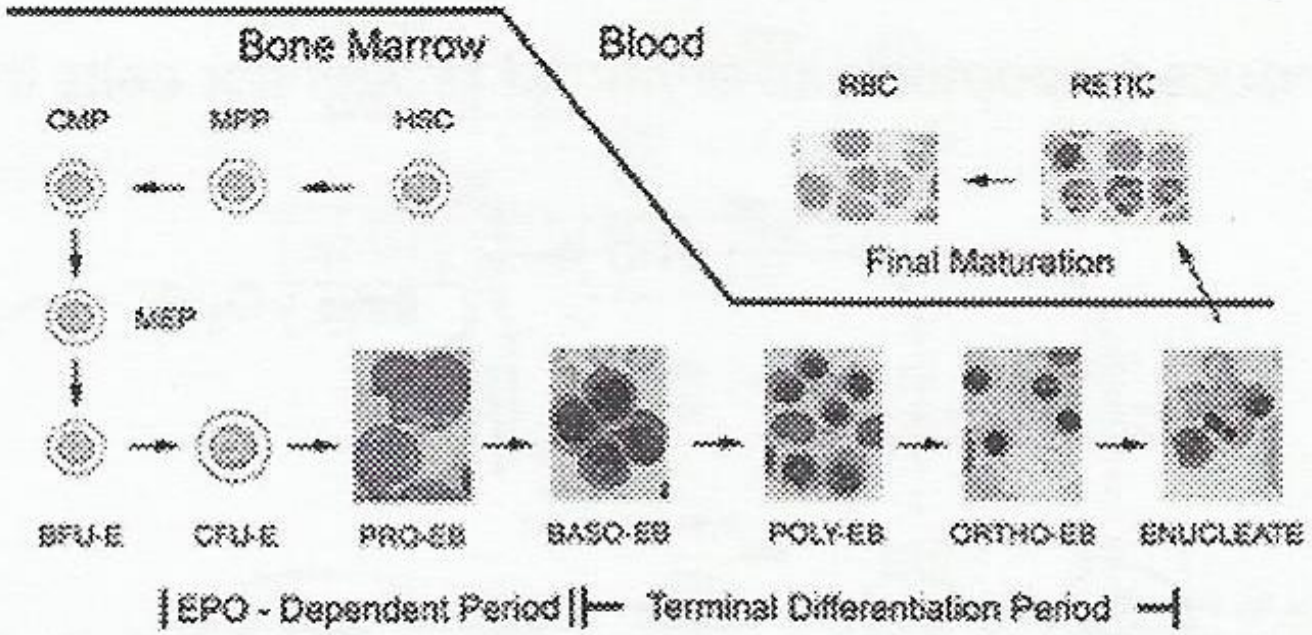
Kidney disease is an EPO deficiency state.

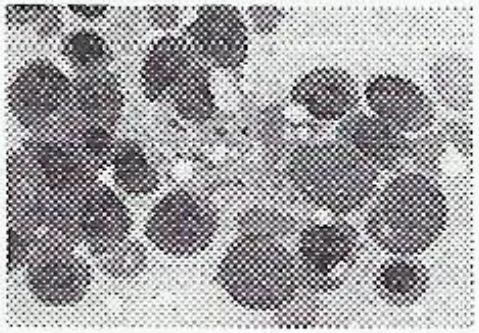
The anemia of kidney disease is largely due to insufficient EPO to maintain normal RBC production rates.



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

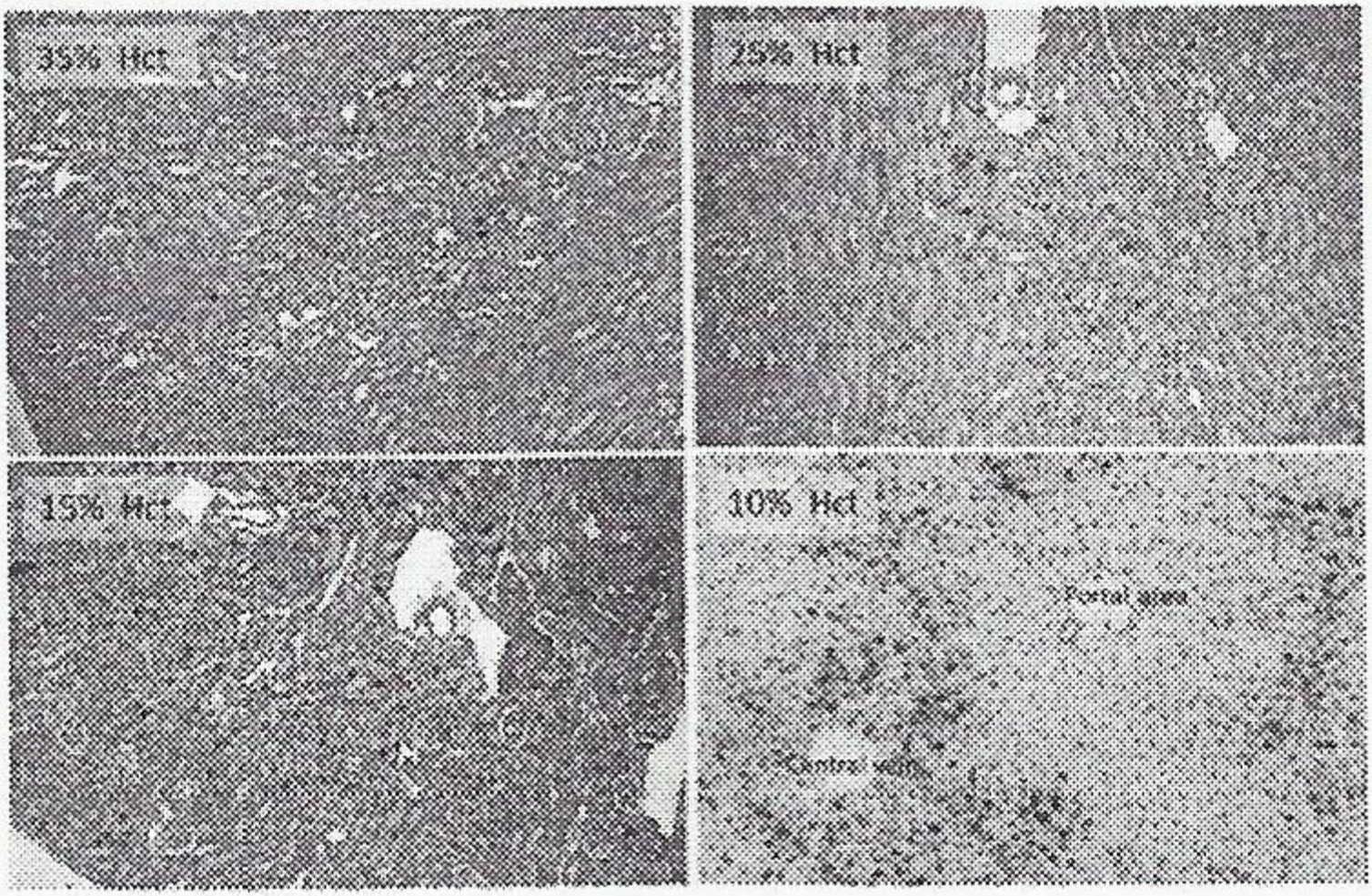




Erythroblastic islands (EBIs):
Marrow niches of terminal erythroid differentiation

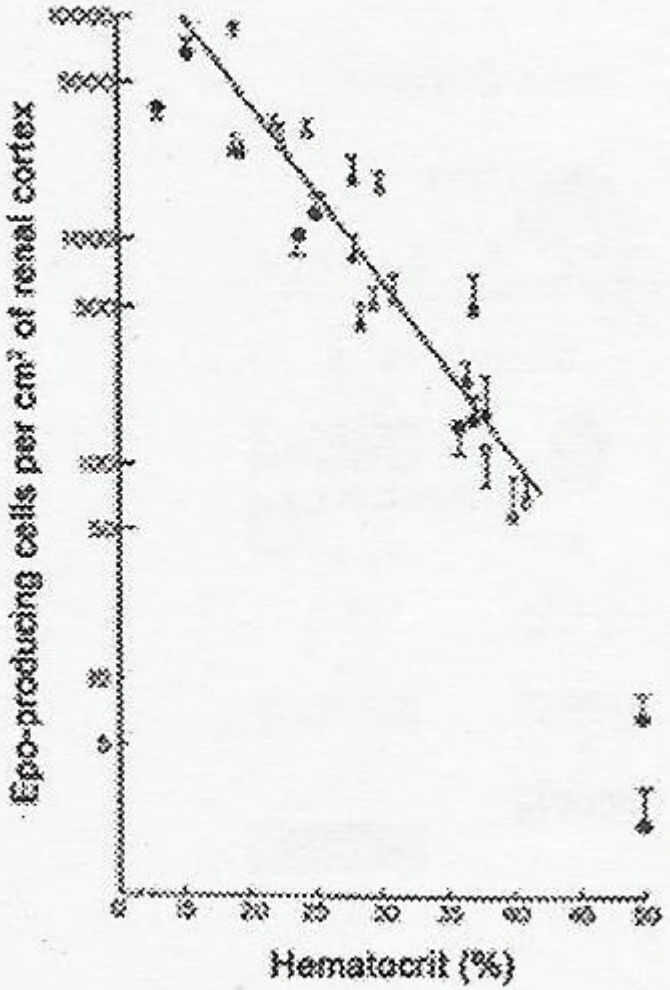
Modified from Ponka, P, Koury, MJ and Sheftel, AD (2013) Erythropoiesis, Hemoglobin Synthesis, and Erythroid Mitochondrial Iron Homeostasis, in Handbook of Porphyrin Science: Volume 27, Erythropoiesis, Heme, and Applications to Biomedicine, Ferreira, G., ed.,Hackensack, NJ, World Scientic Publishing,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

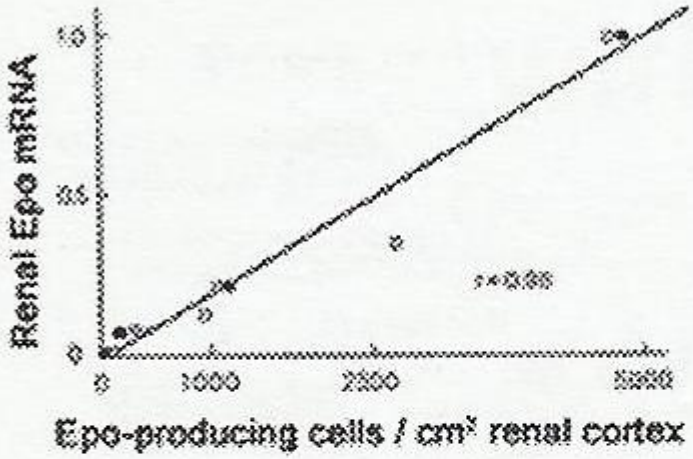
Increasing hypoxia induces EPO production in progressively larger areas of the kidney and the liver

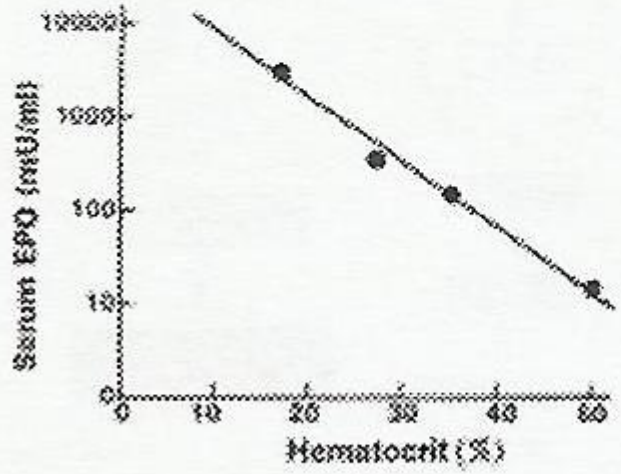


Photomicrographs from: Koury ST, Koury MJ, Bondurant MC, Caro J, Graber SE. Quantitation of erythropoietin producing cells in kidneys of mice by *in situ* hybridization: correlation with hematocrit, renal erythropoietin mRNA, and serum erythropoietin concentration. *Blood* 1989;74:645-651, and Koury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







CKD Clinic: Anemia Management

- Based on KDOQI, 2006
- Maintain Hb values between 11-13 g/dl using ESA agents
- Begin testing at all stages of CKD

CKD Clinic: Anemia Management

- Monthly monitoring of Hgb in ESA treated patients

- ESA doses should be decreased, not necessarily held when a downward trend in Hb is needed

CKD Clinic: Anemia Management

- Iron testing every month at initiation of ESA treatment
- Iron testing every 3 months during stable ESA treatment
- Sufficient iron should be administered to maintain the following indices of Fe status

  -Serum ferritin > 100 ng/ml

  -TSAT > 20 %

  -Discontinue IV Fe is ferritin > 500 ng/ml

Questions?