6TH INTERNATIONAL MULTIDISCIPLINARY COURSE ON IRON DEFICIENCY

SUCROSOMIAL® IRON, UPDATE AND RECENT NEW EVIDENCES TO TREAT IRON DEFICIENCY

2018 • APRIL FRI 13th, SAT 14th
LISBON, PORTUGAL
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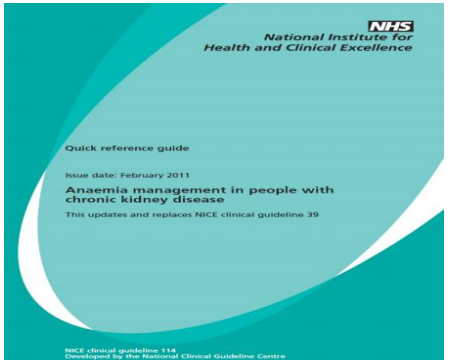
Efficacy and tolerability of oral Sucrosomial® Iron in CKD patients with anemia and its association with CKD progression parameters

Ioannis Griveas, MD, PhD

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.

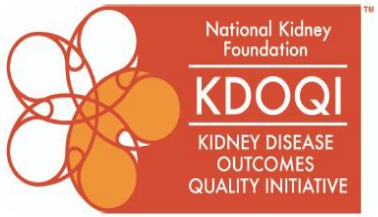
Stage	Description	Classification by Severity	Classification by Treatment
1	Kidney damage with normal or increased GFR	GFR ≥ 90	
2	Kidney damage with mild decrease in GFR	GFR of 60-89	T if kidney transplant
3	Moderate decrease in GFR	GFR of 30-59	recipient
4	Severe decrease in GFR	GFR of 15-29	D if dialysis
5	Kidney failure	GFR < 15	D if dialysis

Note: GFR is given in mL/min/1.73^2

National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Am J Kidney Dis 2002;39(suppl 1):S1-S266

KDIGO, Kidney Disease: Increasing Global Outcomes

KDOQI Guidelines 2006\7



KDOQI CLINICAL PRACTICE GUIDELINE AND CLINICAL PRACTICE RECOMMENDATIONS FOR ANEMIA IN CHRONIC KIDNEY DISEASE:

2007 UPDATE OF HEMOGLOBIN TARGET

"3.2.3 Targets of iron therapy:
In the opinion of the Work Group, sufficient iron should be administered to generally maintain the following indices of iron status during ESA treatment:

3.2.3.1 HD-CKD:

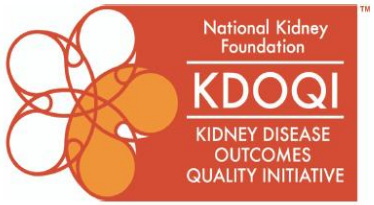
- Serum ferritin>200 ng/mL *AND* TSAT >20%, or CHr >29 pg/cell.

3.2.3.2 ND-CKD and PD-CKD:

- Serum ferritin>100 ng/mL *AND* TSAT >20%.

3.2.4 Upper level of ferritin:
In the opinion of the Work Group, there is insufficient evidence to recommend routine administration of IV iron if serum ferritin level is greater than 500 ng/mL. When ferritin level is greater than 500 ng/mL, decisions regarding IV iron administration should weigh ESA responsiveness, Hb and TSAT level, and the patient's clinical status".

KDOQI Guidelines 2006\7



KDOQI CLINICAL PRACTICE GUIDELINE AND CLINICAL PRACTICE RECOMMENDATIONS FOR ANEMIA IN CHRONIC KIDNEY DISEASE:

2007 UPDATE OF HEMOGLOBIN TARGET

"3.2.5 Route of administration:

3.2.5.1 The preferred route of administration is IV in patients with HD-CKD. (*STRONG RECOMMENDATION)*

3.2.5.2 In the opinion of the Work Group, the route of iron administration can be either IV or oral in patients with ND-CKD or PD-CKD".

KDOQI Guidelines. *Am J Kidney Dis 2006*;47(5):S58-S70
KDOQI Guidelines. *Am J Kidney Dis* 2006;47(5):S33-S53
KDOQI Guidelines. *Am J Kidney Dis* 2007;50(3):474-530

ERBP Position Paper 2010

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

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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

"Treatment of renal anemia

(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

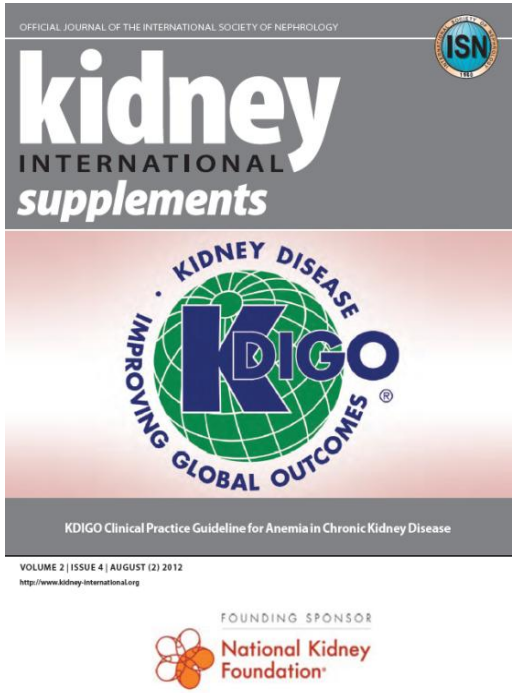
(ii) ESA treatment should not be started in patients who are iron-deficient

(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

KDIGO 2012



"*ESA INITIATION*

3.1: Address all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy. (Not Graded)

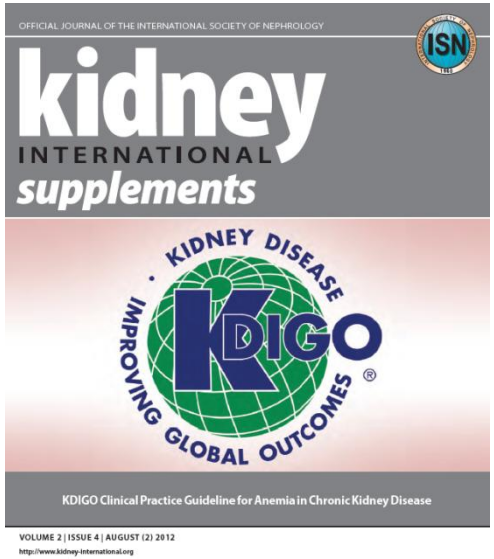
3.2: In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). (1B)

3.3: 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—(1B), a history of stroke (1B), or a history of malignancy (2C).

3.4.1: For adult CKD-ND patients with Hb concentration >10.0 g/dl (>100 g/l), we suggest that ESA therapy not be initiated. (2D)."

KDIGO Guidelines. *Kidney Int* 2012;2(4):279-335

KDIGO 2012



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"***continue…***

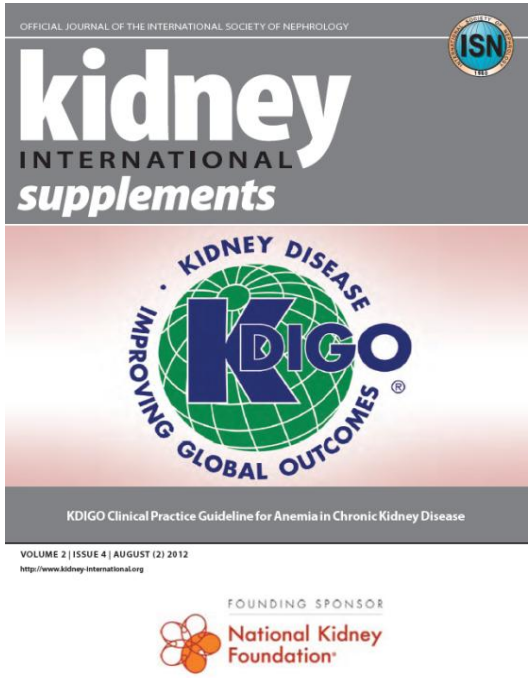
3.4.2: For adult CKD-ND patients with Hb concentration <10.0 g/dl (<100 g/l) we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia. (2C)

3.4.3: For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0–10.0 g/dl (90–100 g/l). (2B)

3.4.4: Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/l). (Not Graded)"

KDIGO Guidelines. *Kidney Int* 2012;2(4):279-335

KDIGO 2012



"***Treatment with iron agents***

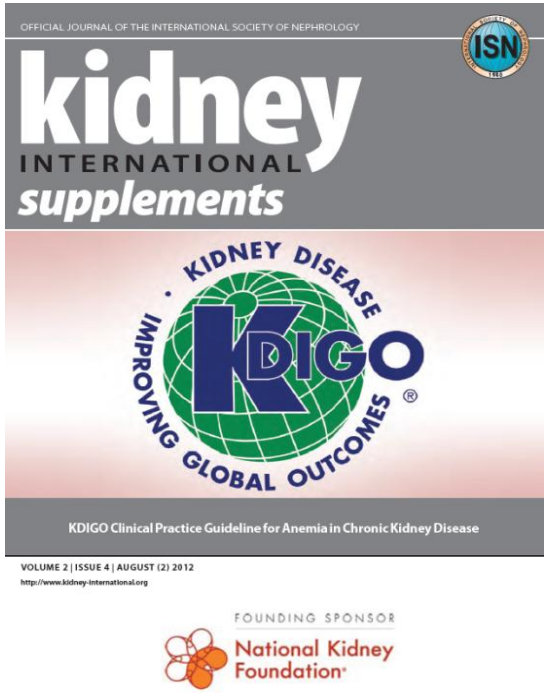
2.1.1: When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). (Not Graded)

2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD-ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):

- an increase in Hb concentration without starting ESA treatment is desired and
- TSAT is <30% and ferritin is <500 ng/ml (<500 mg/l)"

KDIGO Guidelines. *Kidney Int* 2012;2(4):279-335

KDIGO 2012



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"***Treatment with iron agents***

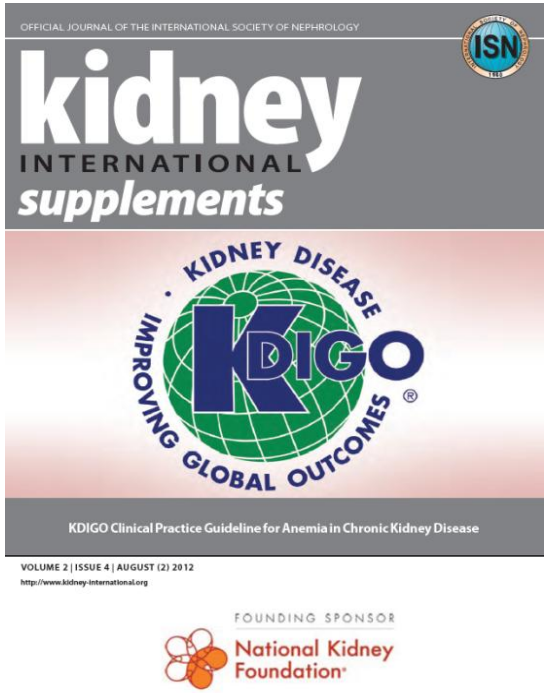
2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD-ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):

- an increase in Hb concentration or a decrease in ESA dose is desired and
- TSAT is <30% and ferritin is <500 ng/ml (<500 mg/l)

2.1.4: For CKD-ND patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost. (Not Graded)."

KDIGO Guidelines. *Kidney Int* 2012;2(4):279-335

KDIGO 2012

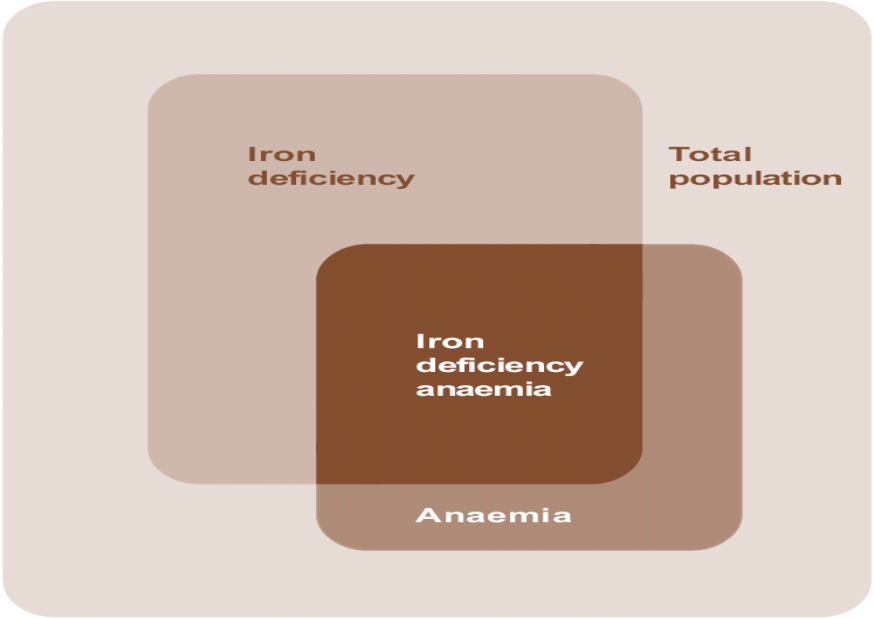


"In patients with CKD-ND, the available evidence supports an efficacy advantage of IV compared with oral administration of iron although the effect is rather small, with a weighted mean Hb difference of 0.31 g/dl (3.1 g/l). Whether the small Hb benefit of IV iron in CKD-ND patients is clinically meaningful or justifies the small risk of serious adverse events and unknown long-term risks is uncertain."

KDIGO Guidelines. *Kidney Int* 2012;2(4):279-335

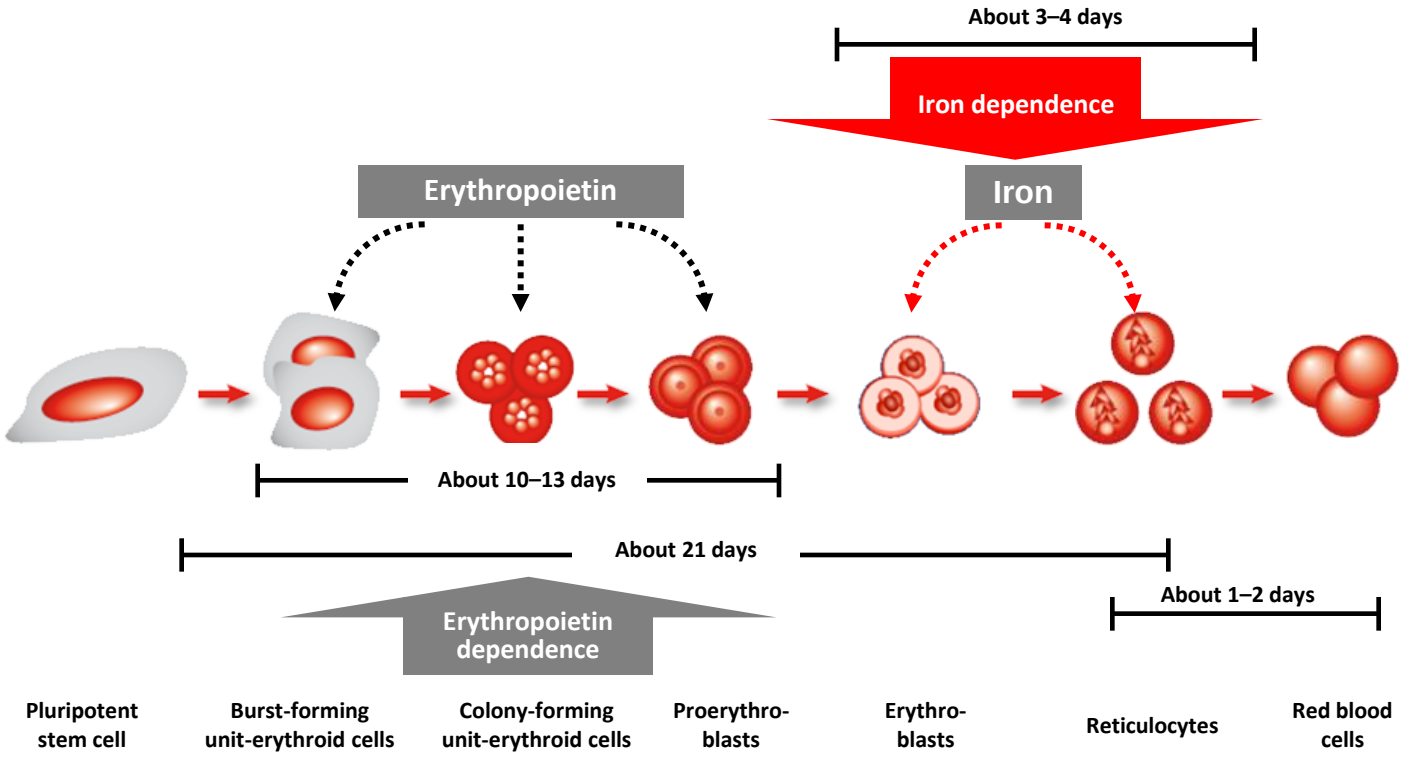
Worldwide prevalence of anaemia 1993–2005

WHO Global Database on Anaemia

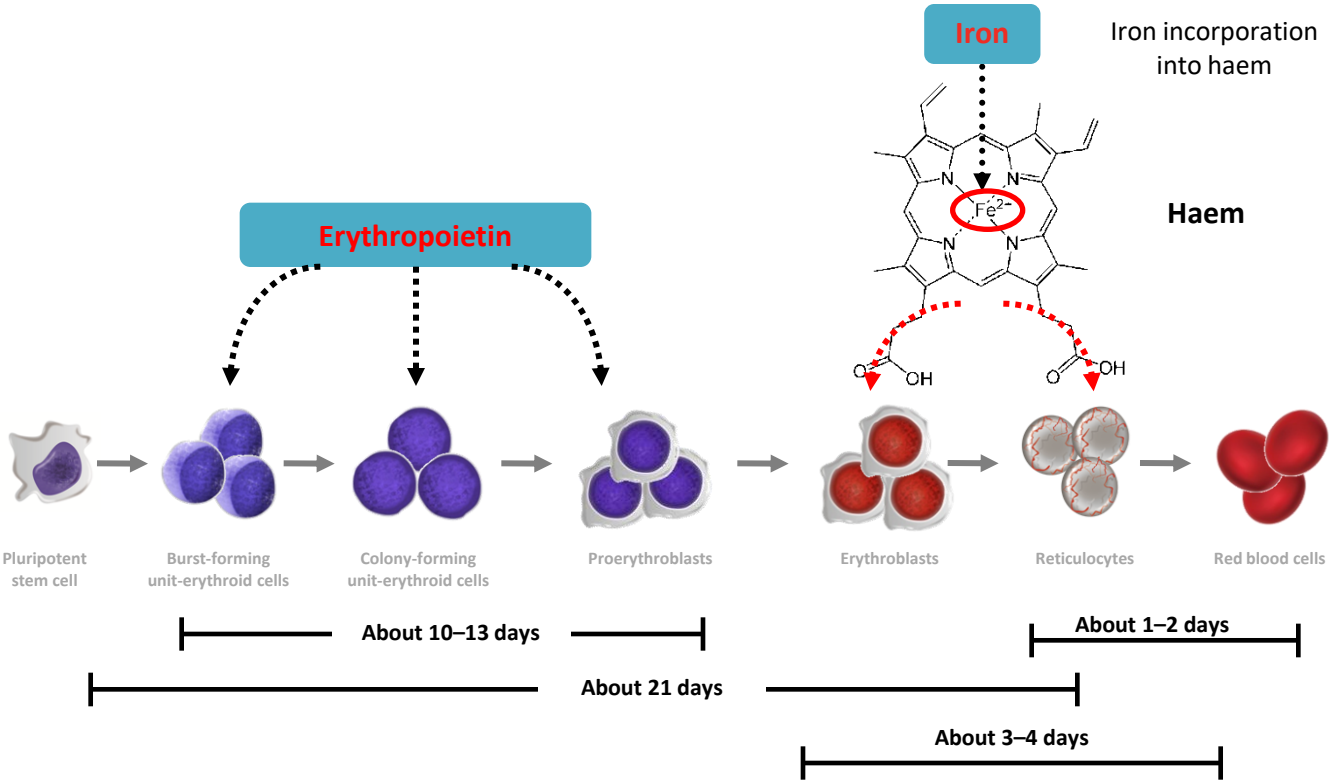


World Health Organization

Centers for Disease Control and Prevention
Atlanta

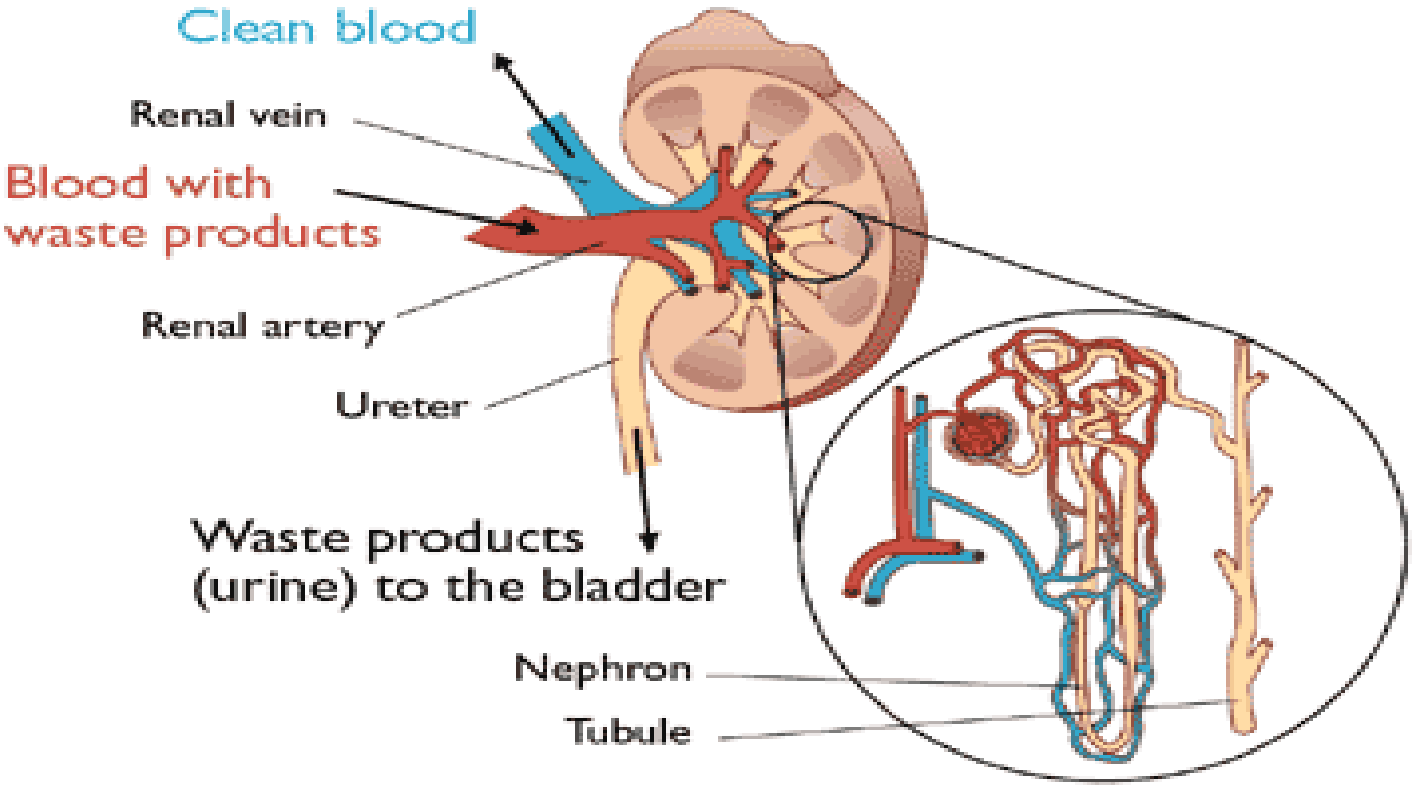


Adapted from: Besarab A, et al. *Oncologist* 2009;14(Suppl 1):22–33

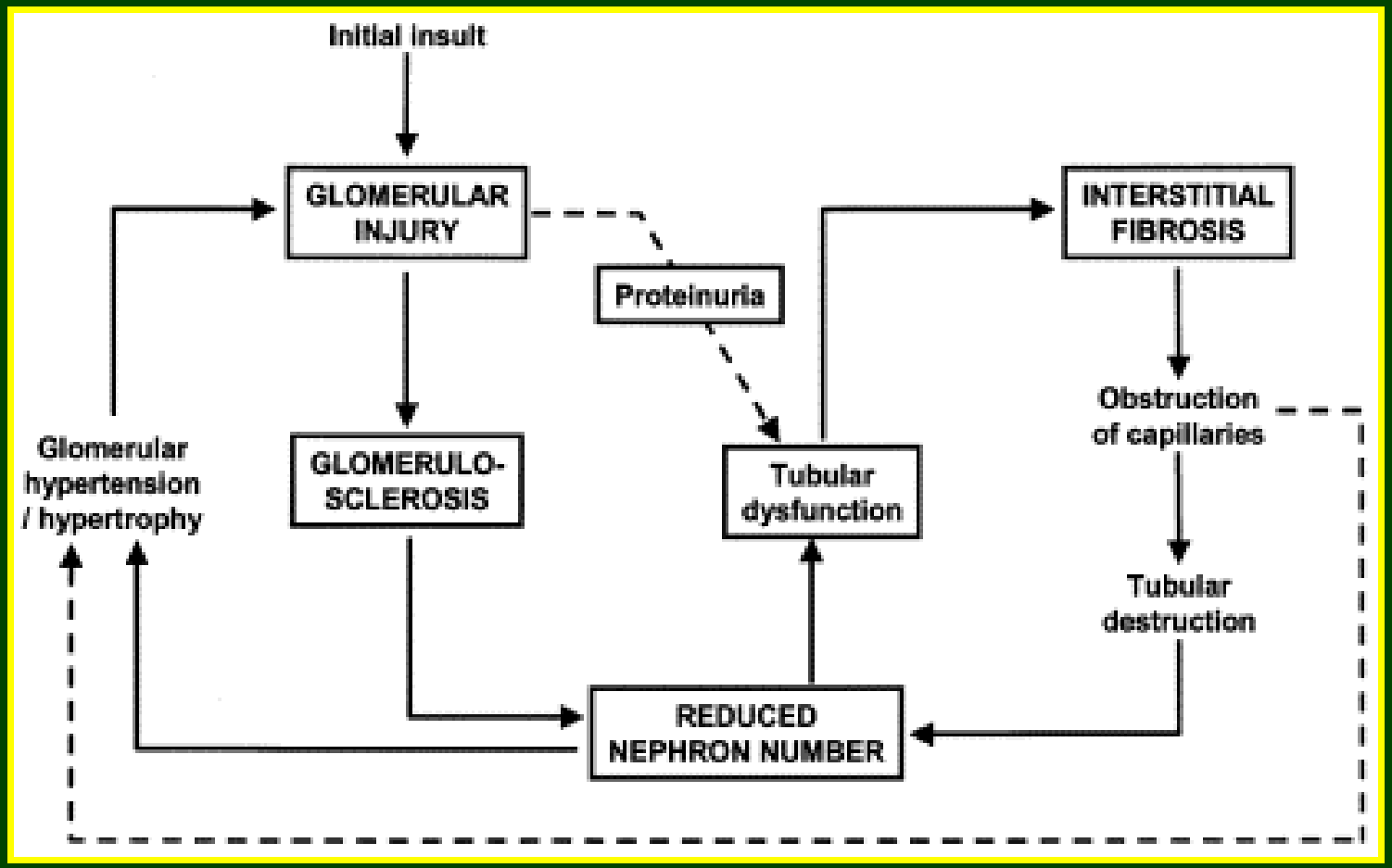


1. Besarab A, *et al. Oncologist* 2009;14(Suppl 1):22–33. 2. Jankowska EA, *et al. Eur Heart J* 2013;34:816–29
3. Pittman RN. Regulation of Tissue Oxygenation (2011). San Rafael (CA): Morgan & Claypool Life Sciences

How the kidney works



Mechanism of Progressive CKD



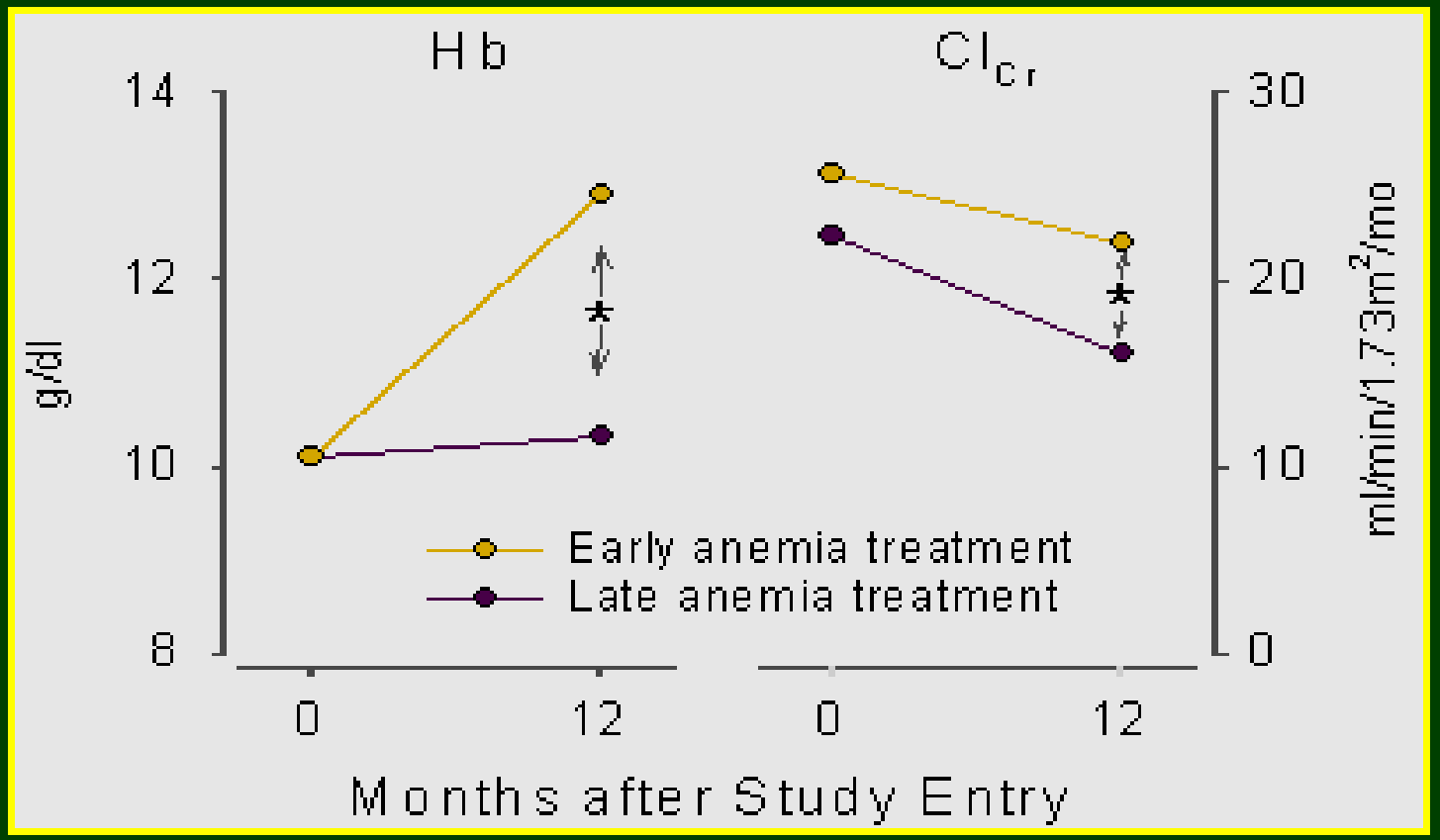
Source: Rossert, JA, et al, *JASN* 14:S173-177, 2003

Anemia in CKD

- Prevalence
  - Stages 1-2: <10%
  - Stage 3: 20-40%
  - Stage 4: 50-60%
  - Stage 5: >70%

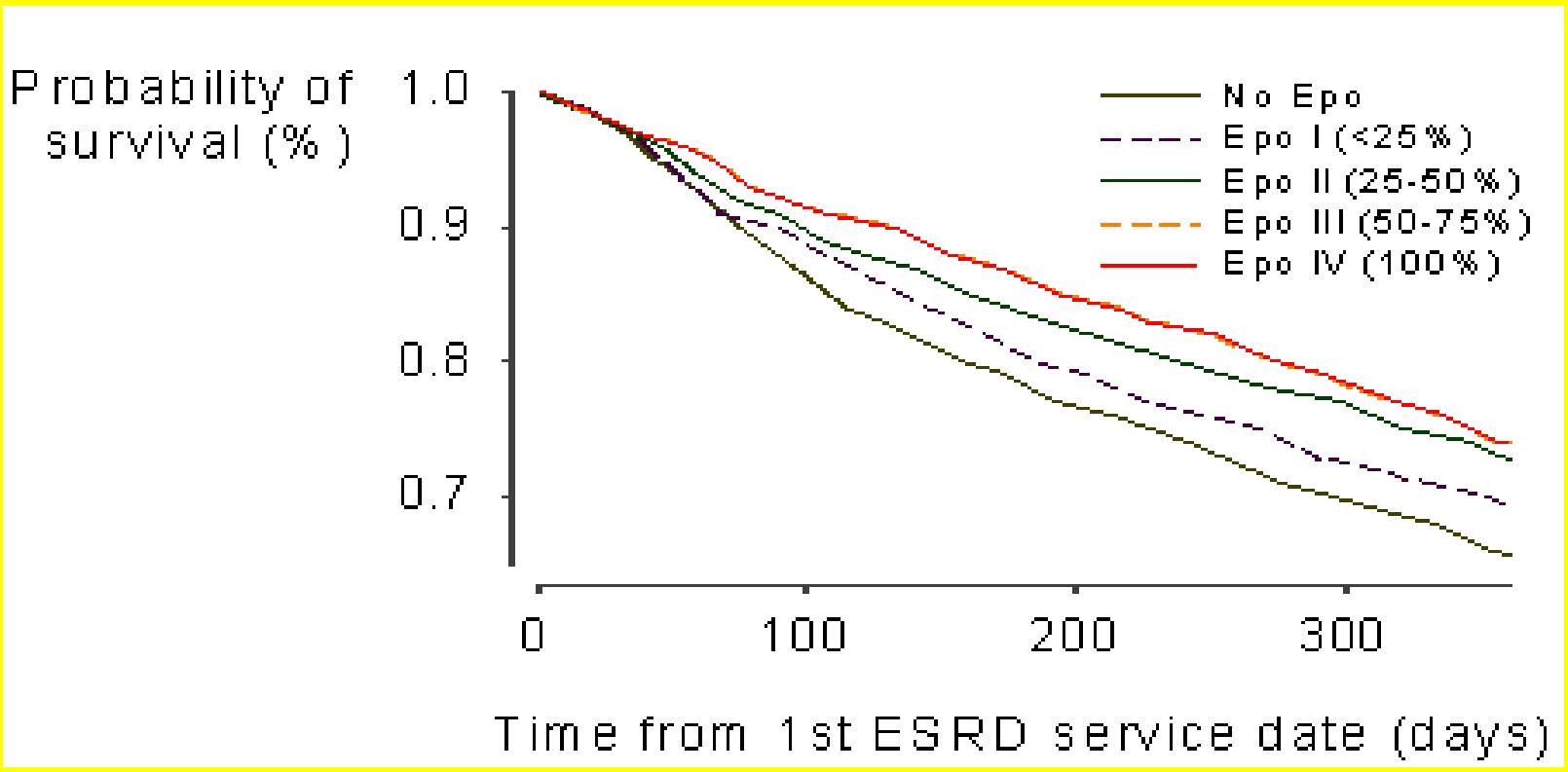
- Mechanisms
  - EPO deficiency
  - Iron deficiency and mobilization disorders
  - Shortened RBC lifespan
  - Hyperparathyroidism
  - Vitamin deficiencies

Early treatment of anemia is associated with slower CKD progression



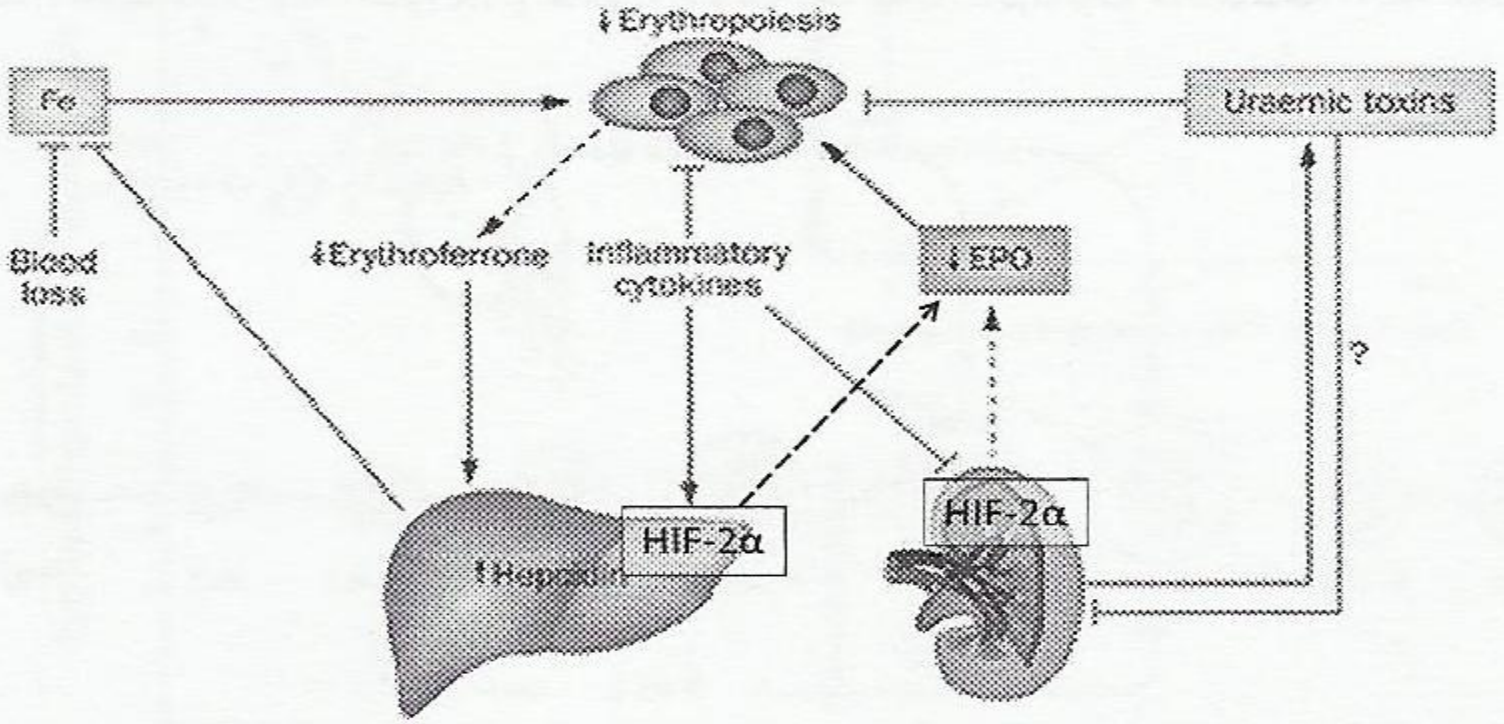
Source: Gouva C, et al. *Kidney Int* 66:753-760, 2004 (*P < 0.001)

In geriatric patients, improved survival is associated with intensity of anemia treatment



Source: Xue JL et al, *Am J Kidney Dis* 40:1153-1161 2002;
Medicare patients > 66 years (n = 89,193), 1995-1997

Overview of the anemia of kidney disease

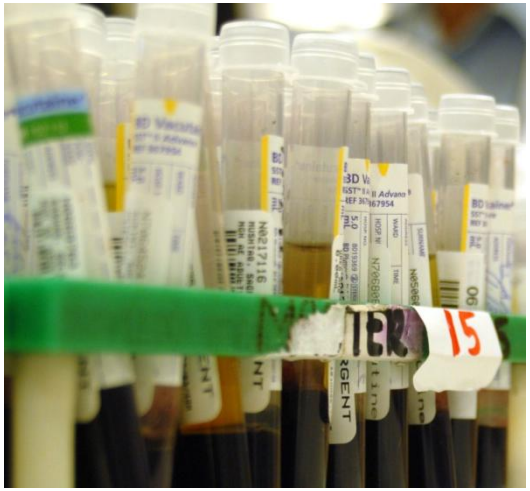


Modified from Koury, M. J. & Haase, V. H. (2015) Anaemia in kidney disease: harnessing hypoxia responses for therapy. *Nat. Rev. Nephrol.* 11:394-410, doi:10.1038/nrneph.2015.82

Assessment and optimisation of erythropoiesis – optimal Hb levels

When determining individual aspirational Hb ranges for people with anaemia of CKD, take into account:

- patient preferences
- symptoms and comorbidities
- the required treatment



EUROPEAN MEDICINES AGENCY
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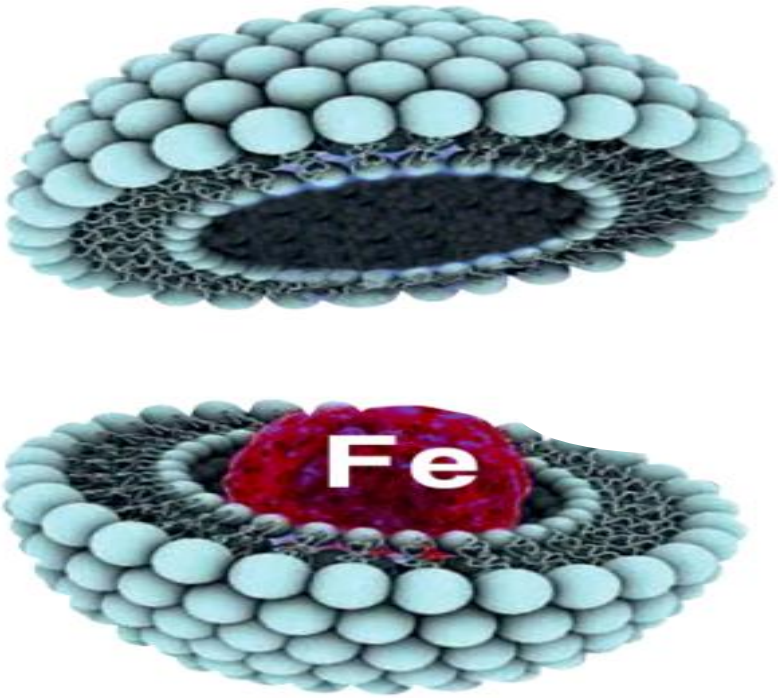
[18–25]; a recent report by Europena Medicines Agency (EMA) (September 2013) clearly points out that IV iron should be prescribed when oral iron cannot be given or does not work, and that should be administered in environments in which resuscitation facilities are present by personnel specifically trained to treat allergic reactions (EMA/579491/2013).



Oral sucrosomial iron

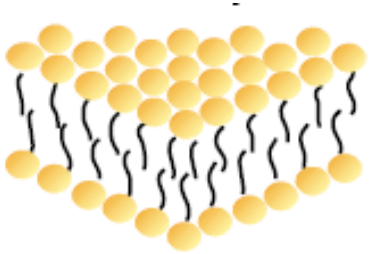
Sucrosome

- Phospolipid

hydrophilic head

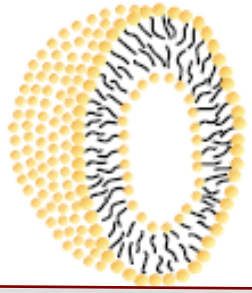
hydrophobic tail

Arrangement of phospholipids in aqueous environment



Phospholipid bilayer

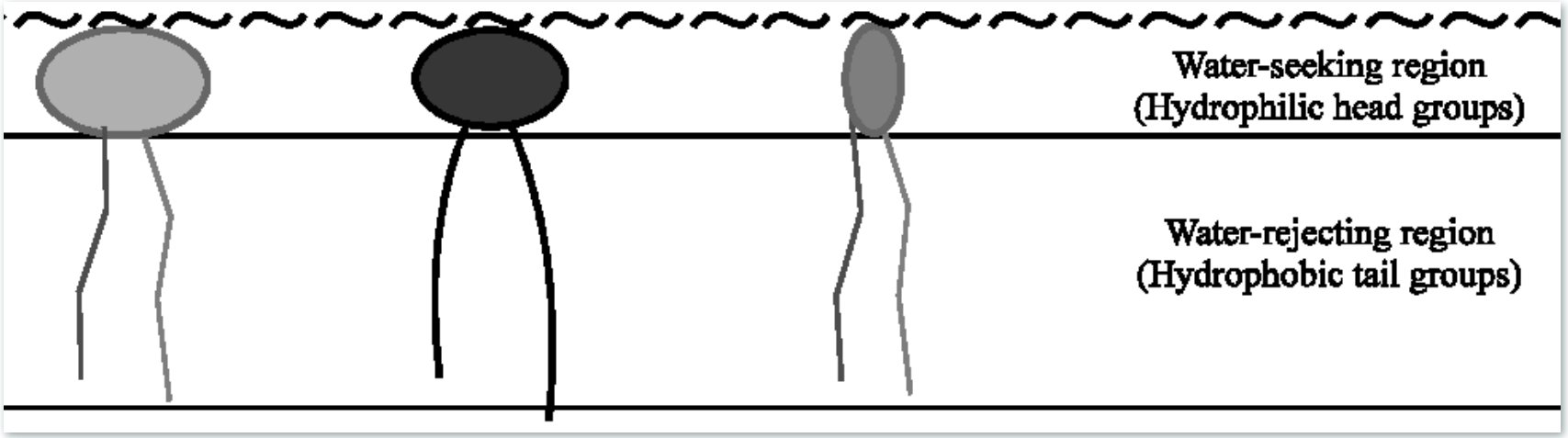
- Longitudinal Section



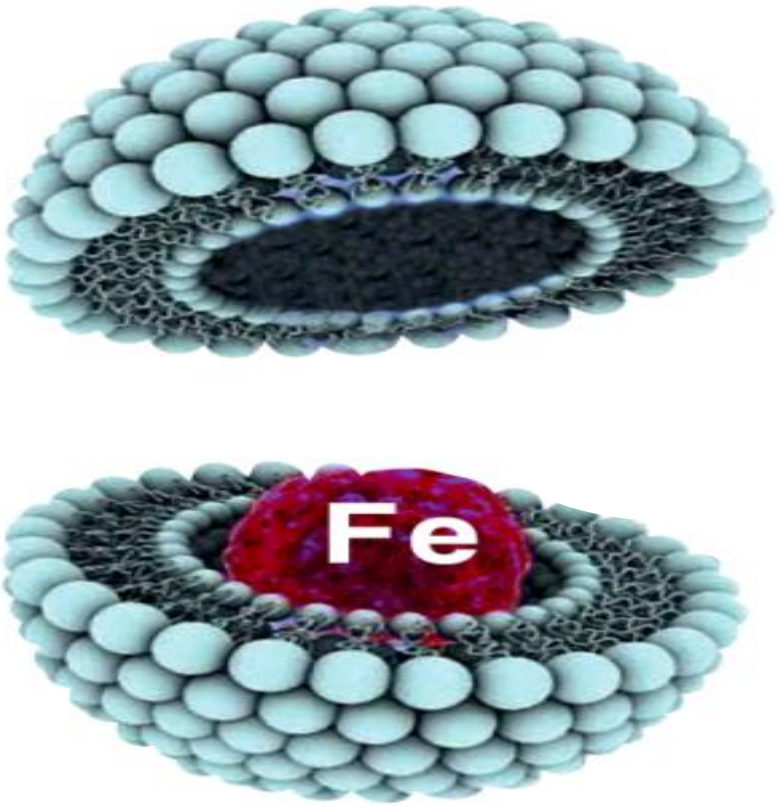
aqueous environment

- Sucrosomes are formed by self-aggregation of the phospholipids in an aqueous phase
- The lipid bilayer is similar to cell membranes

SUCROSOME STRUCTURE



PHOSPHOLIPIDS → Main constituents of the Sucrosome (and of cellular membranes)



Objectives:

The purpose of this study was to investigate the efficacy and tolerability of oral sucrosomial iron in CKD patients with anemia **and its association with CKD progression parameters.**

Methods

- 40 patients with CKD stage 3-5 (e GFR <60 mils/min, range: 12-48) and anemia (Hb<12 gr/dl, ferritin<200 ng/ml) were enrolled in our study.
- During the 24 months study period, all of the patients were stable, did not need to be transfused or admitted to the hospital for any reason and received oral sucrosomial iron (sideral) once daily.
- Hematological profile and renal function were recorded at the beginning of the study, every 2 months and in the end of the study protocol.

- The primary efficacy end points of the study included the change in Hb values from baseline to end of treatment.

- Secondary endpoints were the change in the slopes of estimated glomerular filtration rate (eGFR) over 2 years, estimation of iron repletion, and bone –mineral parametersAdverse effects and compliance data were reported from the day of initial treatment to the end of treatment.

Results

- Hct levels increased from 35.18±3.77% at the beginning of the protocol to 37.12±3.86 in the end ($p<0.05$).
- Hemoglobin levels were 11.62±1.58 g/dl at the beginning of the study and ended to be 12.04±0.99 (p=NS).
- Ferritin levels which is one index of iron stores did not significantly changed over the study period 74.34±43.01 to 65.65±53.93 (p=NS).

Results

- Renal function (e GFR) of our patients slightly improved during the 24th month period of the study (31.76±11.77 mils/min at the beginning to 32.11±16.79 mils/min in the end of the protocol).

Results

PTH levels declined over the study period from 104.95±34.16 pg/ml to 94.9±10.81 pg/ml (p=NS).

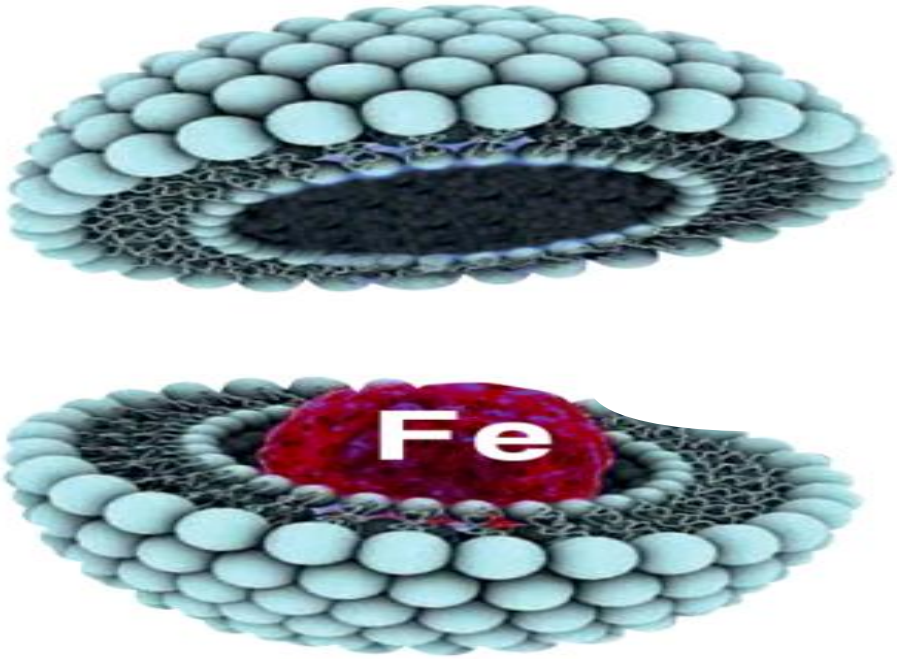
Ca, K, Na levels remained stable without also significant changes.

Results

Oral iron was well tolerated and no significant adverse effects were recorded.

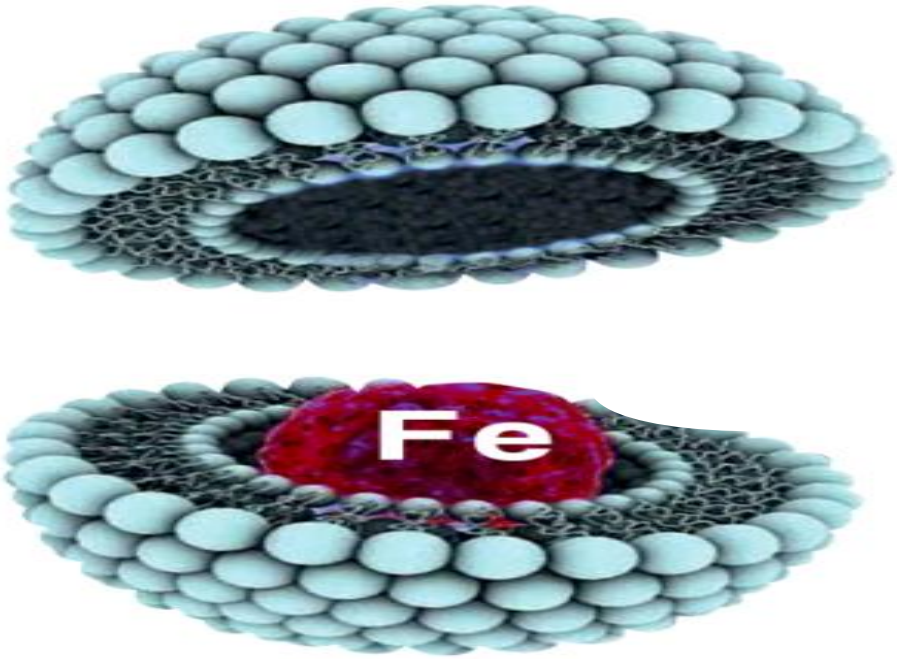
None of our patients dropped out from the study for any reason. It is noticeable that its behavior relating GI effects seems to differ favorably concerning other iron compounds.

Additionally, no serious cardiovascular events and infections were recorded.



Oral sucrosomial iron seems to be a safe and efficacious alternative in managing CKD patients with anemia.

Despite the small amount of patients in our study protocol, the low rate of adverse events with sucrosomial iron and its practicality suggest that this formulation has all the potential to be the first step to correct anemia in stable CKD patients.



It seems also that early treatment of anemia is associated with slower CKD progression.

Further larger studies are needed to investigate iron sucrosomial effects in complicated CKD patients and help scientific community to reach more solid conclusions. Whether oral iron should be preferred to intravenous iron in patients with CKD not on dialysis is another issue that needs a convincing answer.