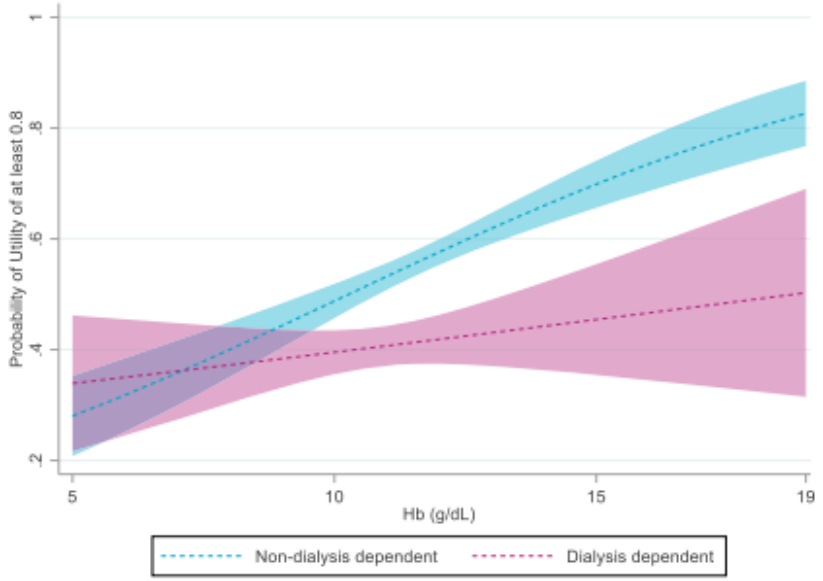
HELLENIC SOCIETY OF NEPHROLOGY
MEETING & SEMINAR
Combined with:
18th BANTAO CONGRESS
October 19-22, 2023
Makedonia Palace Hotel THESSALONIKI, GREECE

Anemia in CKD

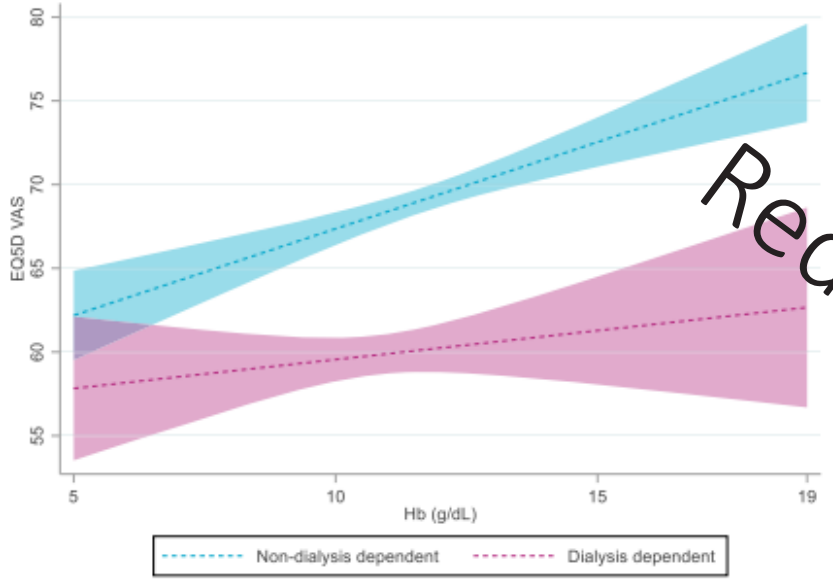
Kantartzi Konstantia

Ass. Prof. of Nephrology D.U.TH.

(a) EQ-5D-3L utility index with Hb level[b]

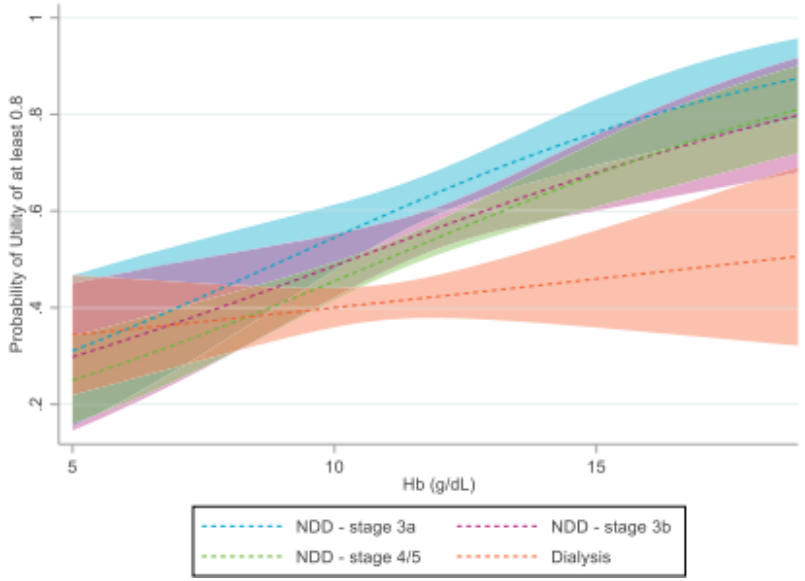


(b) EQ-5D-3L VAS scores with Hb level[b]

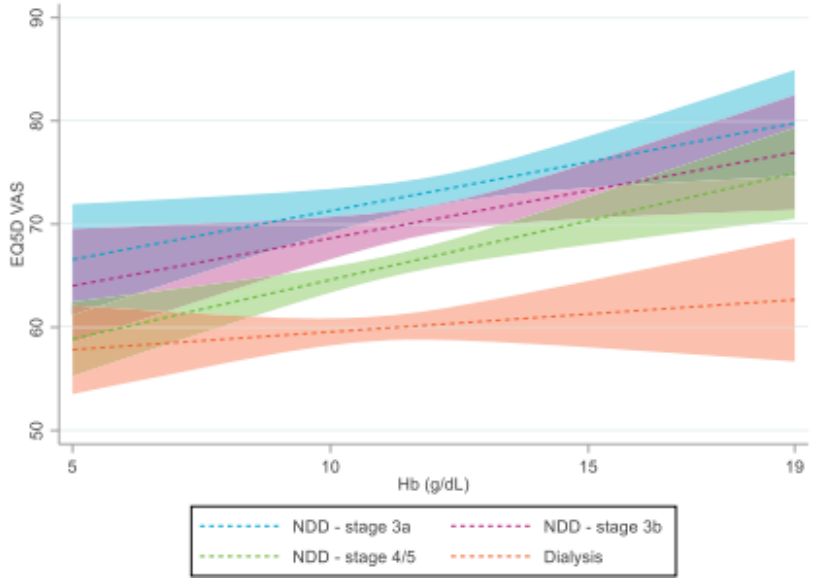


Reduced quality of life

(c) EQ-5D-3L utility index with Hb level and CKD stage[c]

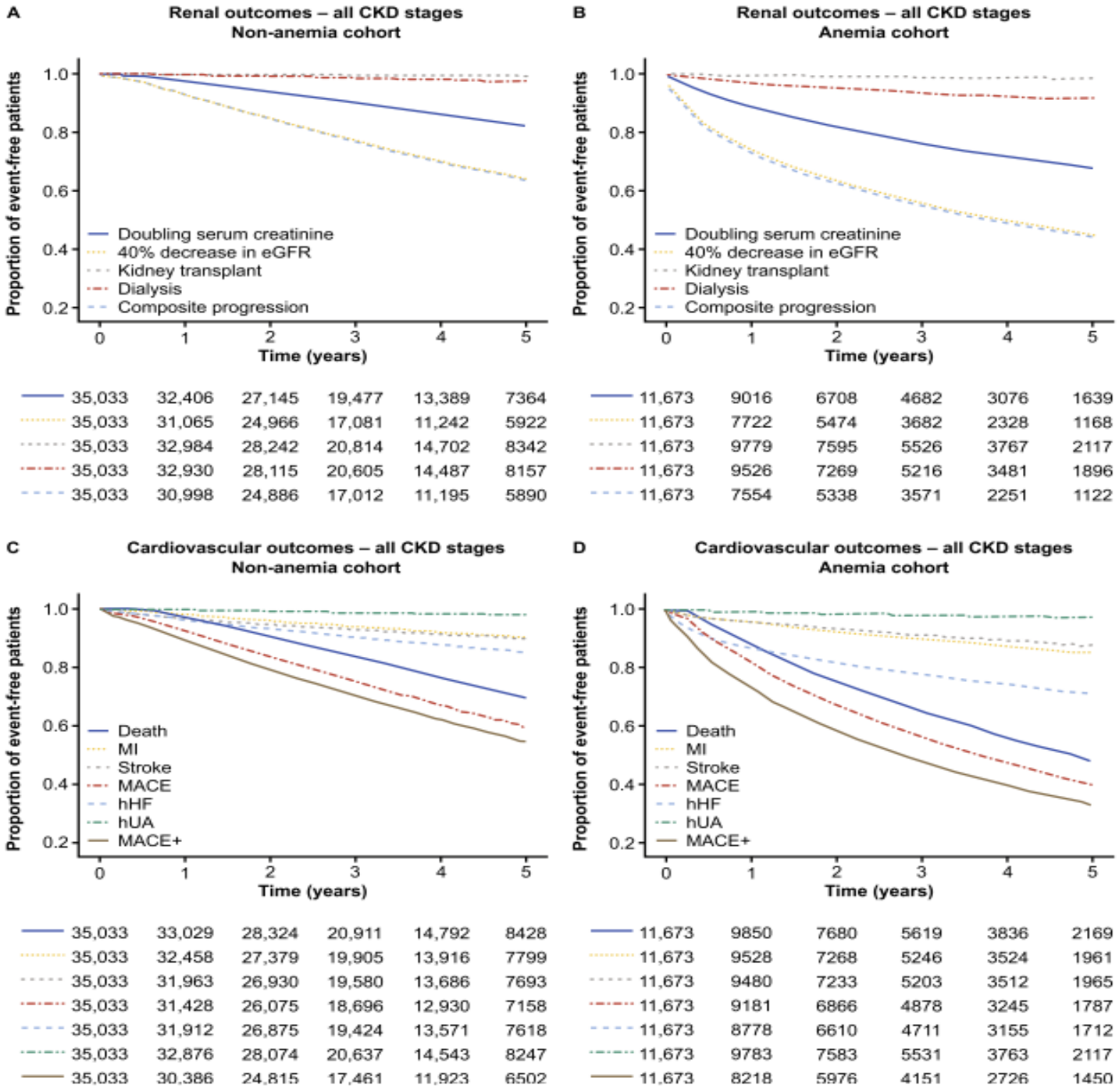


(d) EQ-5D-3L VAS scores with Hb level and CKD stage[c]

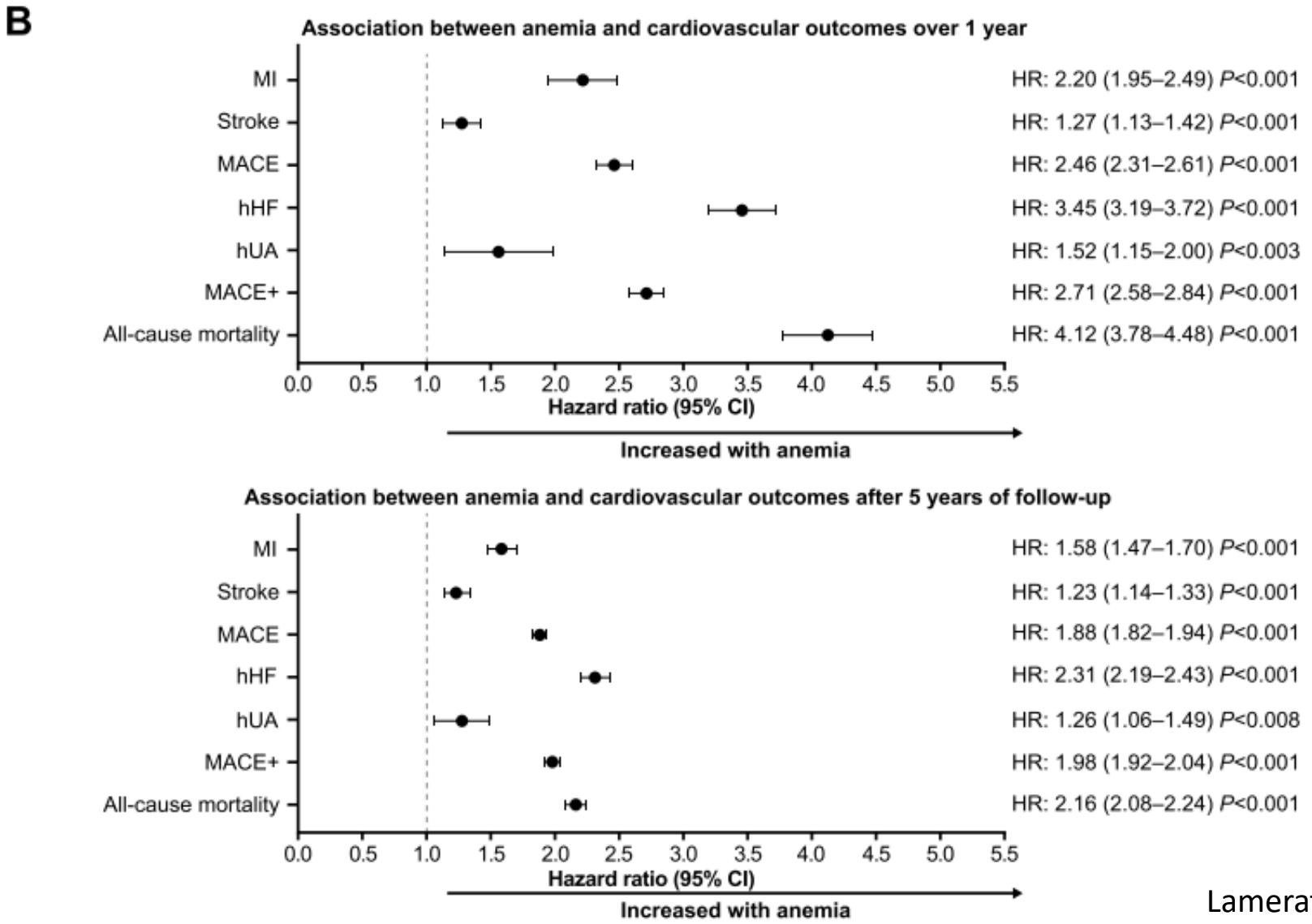


van Haalen et al. BMC Nephrology 2020

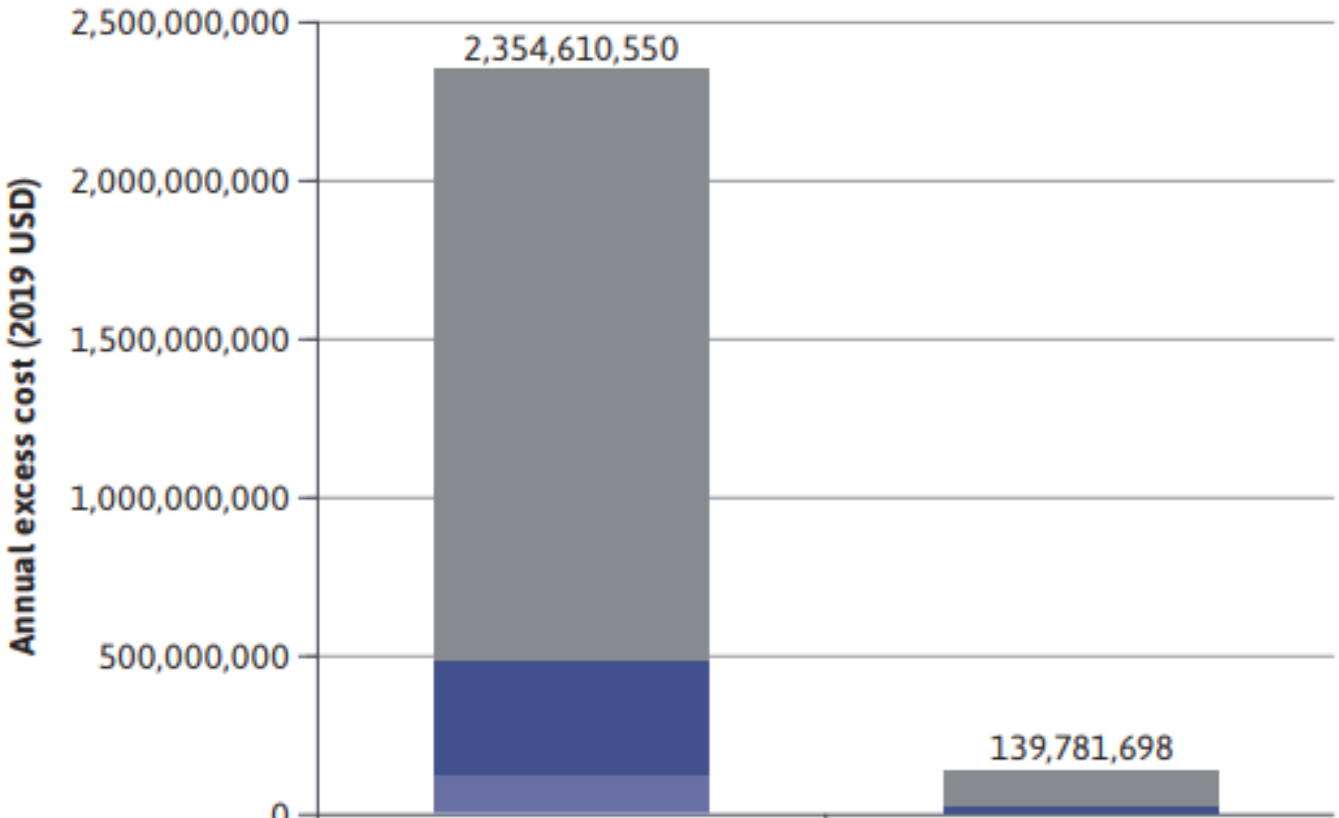
Worse renal survival



Increase in morbidity and mortality



Lamerato et al. BMC Nephrology 2022



	In clinic (USD)	At home (USD)
Medicare	1,869,427,783	110,978,773
Commercial	361,635,896	21,468,552
Medicaid	111,420,235	6,614,474
VA	8,298,255	492,627
Uninsured	3,828,382	22,272

[a]*Based on 2019 US population.*

ESA = erythropoiesis-stimulating agent; NDD-CKD = non-dialysis-dependent chronic kidney disease; USD = US dollars; VA = United States Department of Veterans Affairs.

Higher costs

J Manag Care Spec Pharm. 2021

Anemia in CKD

GFR categories in CKD			
Category	**GFR**	**Terms**	**Clinical Presentations**
G1	≥ 90	Normal or high	Markers of kidney damage (nephrotic syndrome, nephritic syndrome, tubular syndromes, urinary tract symptoms, asymptomatic urinalysis abnormalities, asymptomatic radiologic abnormalities, hypertension due to kidney disease)
G2	60-89	Mildly decreased*	
G3a	45-59	Mildly to moderately decreased	• Mild to severe complications: ○ Anemia ○ Mineral and bone disorder ▪ Elevated parathyroid hormone ○ Cardiovascular disease ▪ Hypertension ▪ Lipid abnormalities ▪ Low serum albumin
G3b	30-44	Moderately to severely decreased	
G4	15-29	Severely decreased	
G5	< 15	Kidney failure	• Includes all of the above in addition • Uremia

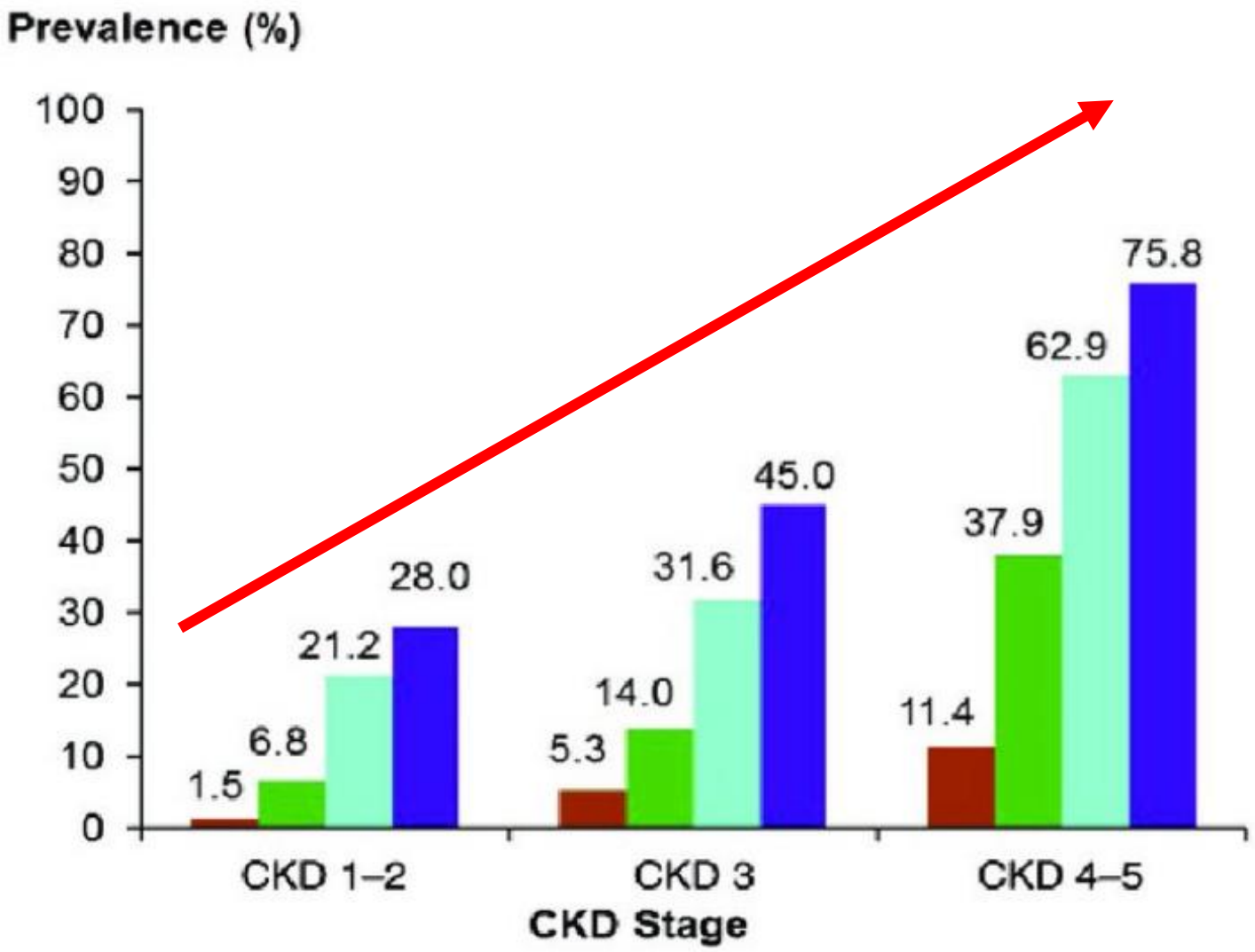
GFR = mL/min/1.73 m^2

*Relative to young adult level

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Refer to a nephrologist and prepare for kidney replacement therapy when GFR <30 mL/min/1.73m^2.

The prevalence of anemia raises with the progression of CKD



Several studies report the prevalence of anemia in non-dialysis dependent (NDD) CKD up to 60%

Hb < 10	P<0.01
Hb < 11	P<0.001
Hb <12	P<0.001
WHO Criteria	P<0.001

Clinical Kidney Journal., 2017

Diagnosis and evaluation of anemia in CKD

Diagnosis of anemia

1.2.1: Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females. (*Not Graded*)

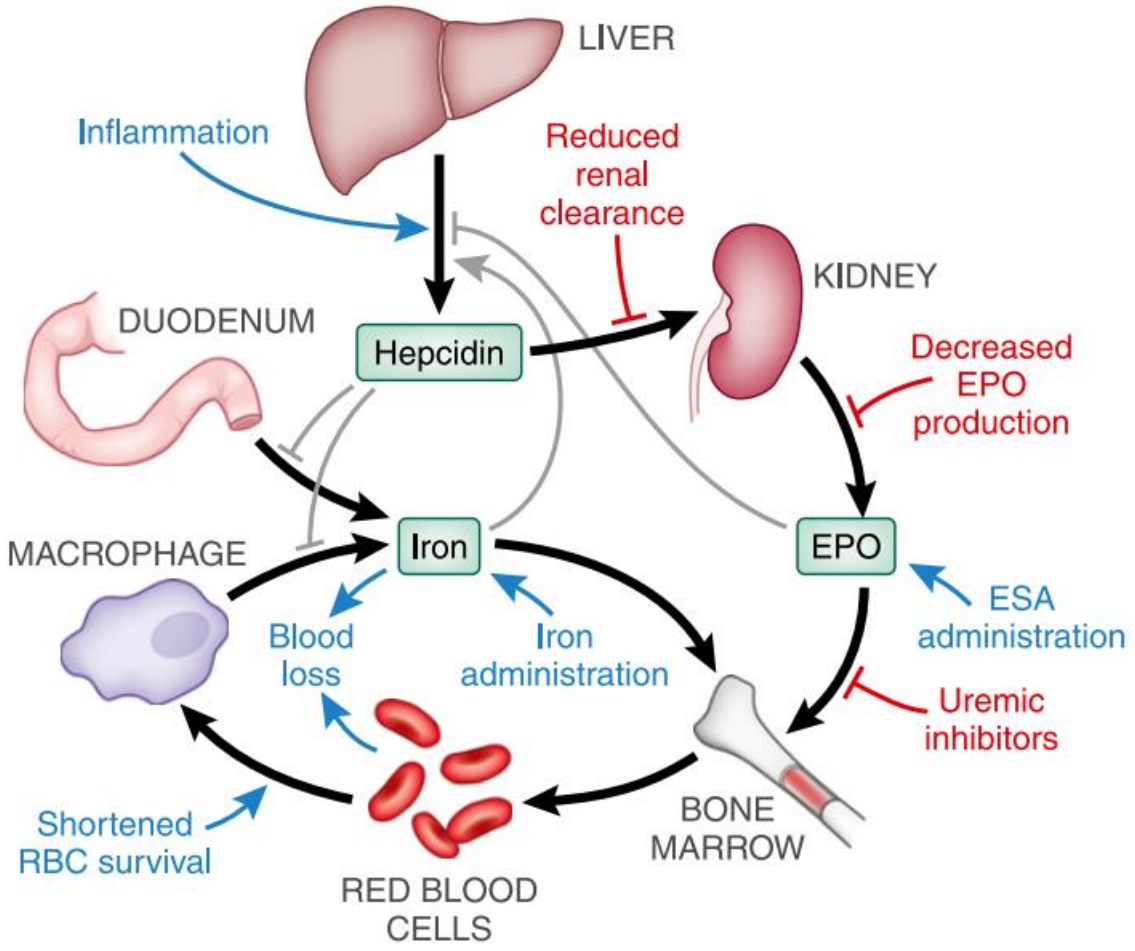
Investigation of anemia

1.3: In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia (*Not Graded*):

- **Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count**
- **Absolute reticulocyte count**
- **Serum ferritin level**
- **Serum transferrin saturation (TSAT)**
- **Serum vitamin B_{12} and folate levels**

KDIGO 2012

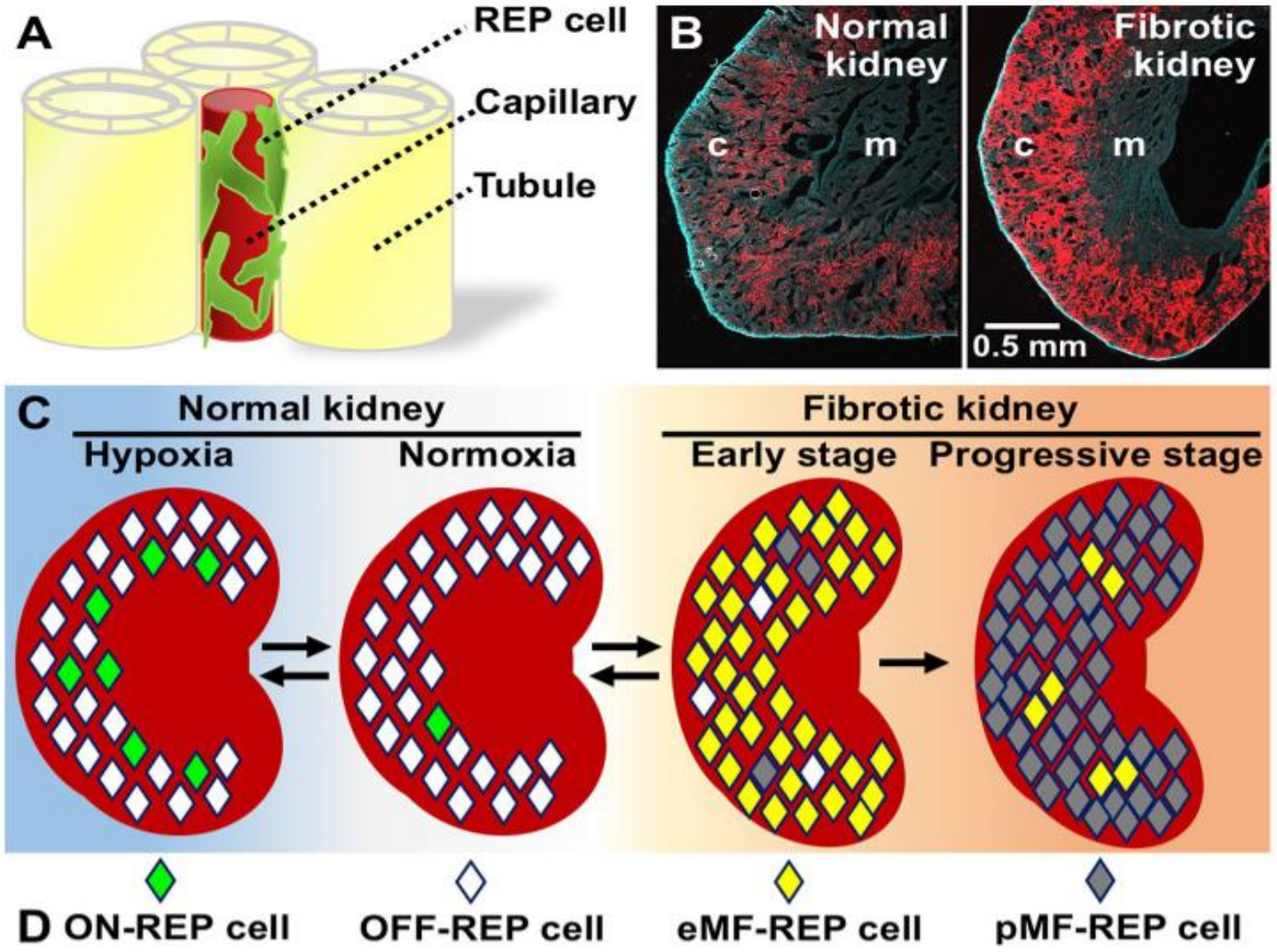
Pathophysiology of anemia in CKD



- Progressive reduction of endogenous erythropoietin (EPO) levels has classically been considered to play a preeminent role
- Absolute iron deficiency due to blood losses or an impaired iron absorption
- Ineffective use of iron stores due to increased hepcidin levels
- Systemic inflammation due to CKD and associated comorbidities
- Reduced bone marrow response to EPO due to uremic toxins
- Reduced red cell life span
- Vitamin B12 or folic acid deficiencies

KDIGO Anemia Working Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int*. 2012

Erythropoietin (EPO), a glycoprotein hormone, is the master regulator of erythropoiesis



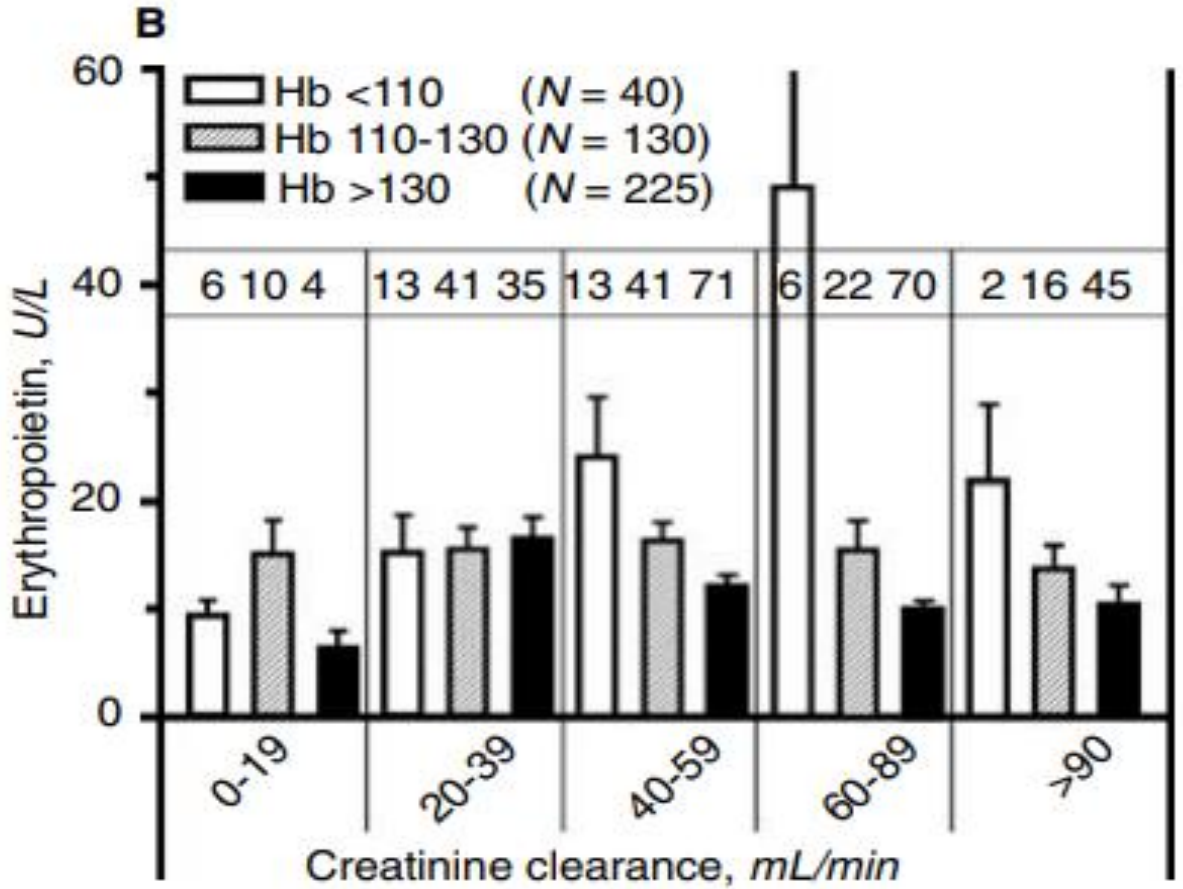
Fibroblast-like interstitial peritubular cells of the kidneys

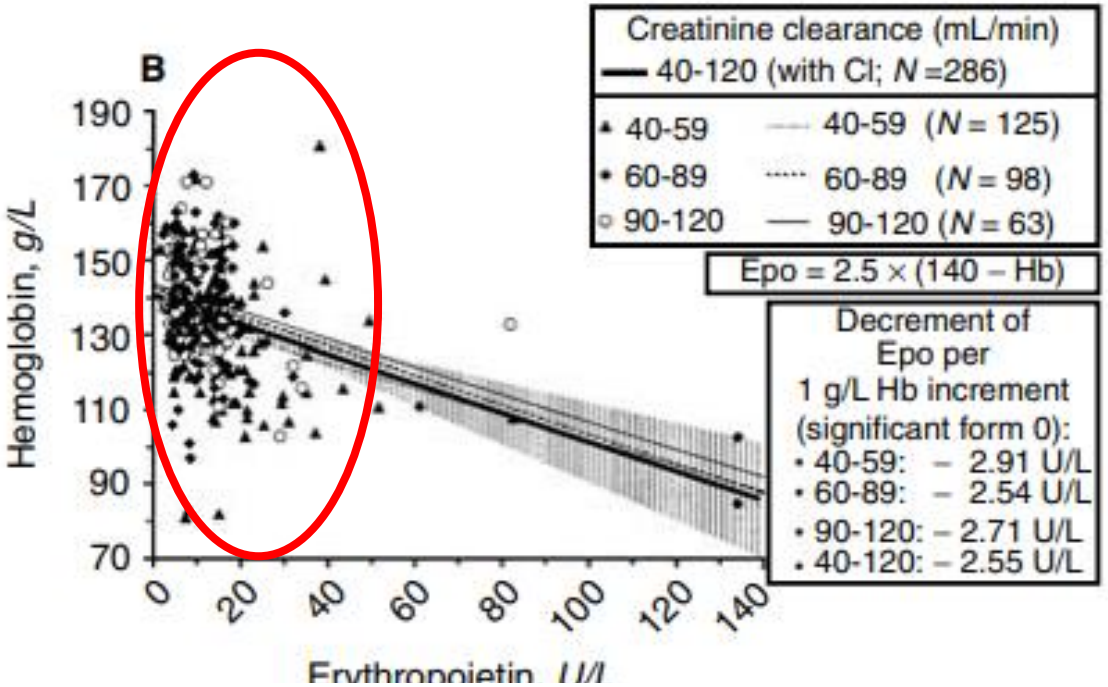
In CKD:

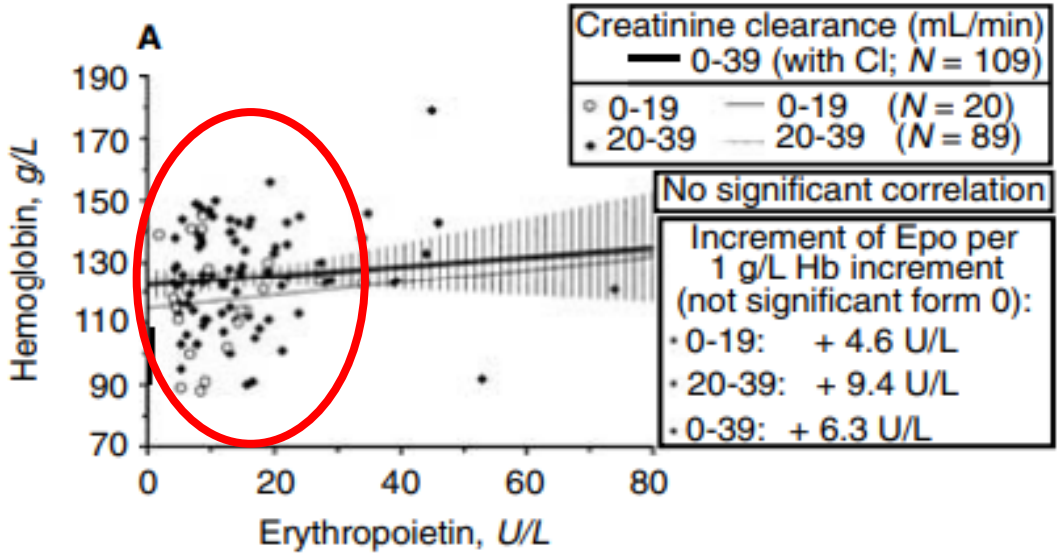
- Decrease in the EPO production due to fibrosis
- Errors in EPO-sensing

Sato et al., Frontiers in Genetics, 2019

In CKD patients, EPO levels are inadequately low with respect to the degree of anemia



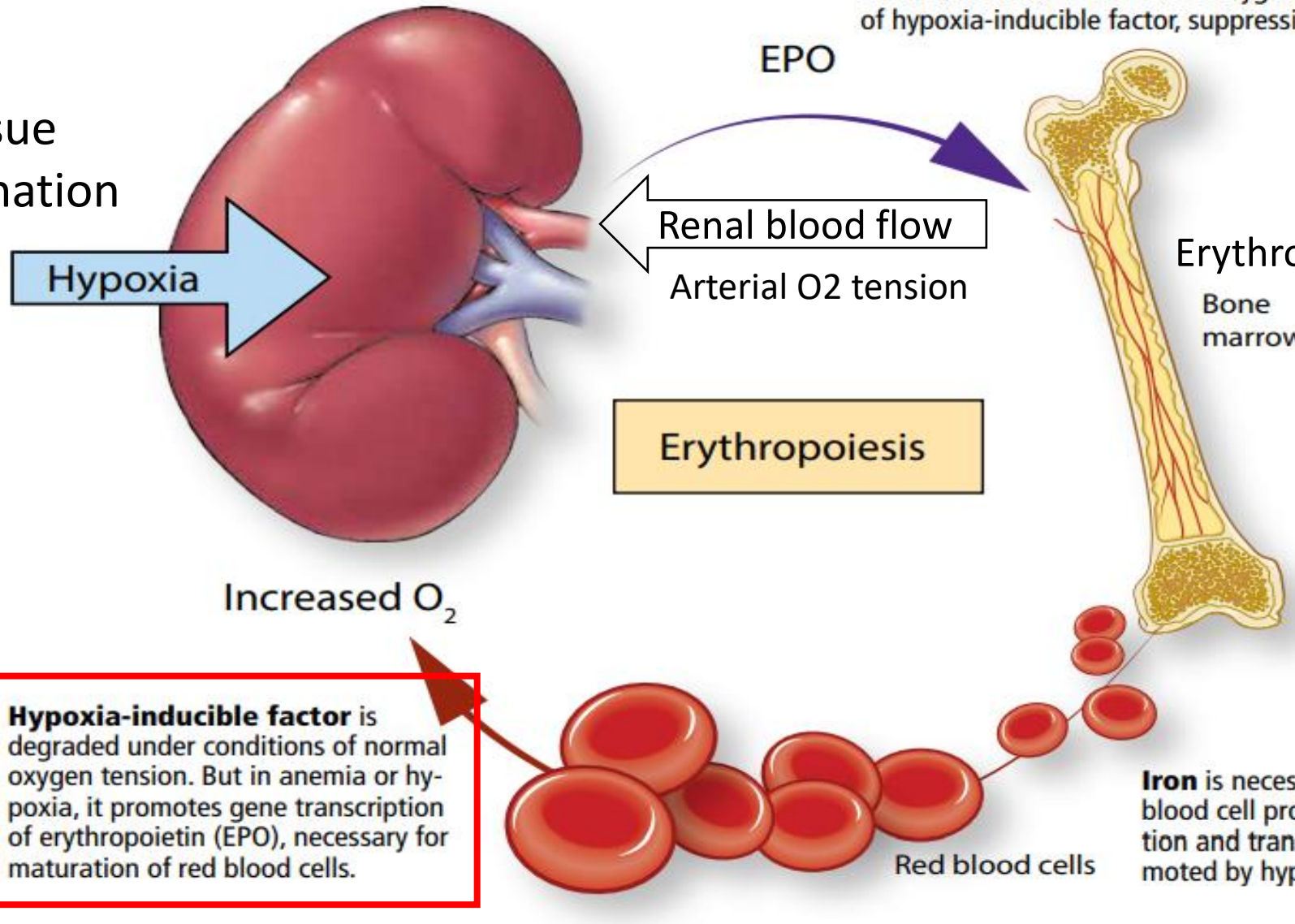




Fehr et al., Kidney International 2004

Erythropoiesis: A homeostatic system

Erythropoietin (EPO) promotes production of mature red blood cells in the bone marrow. More red blood cells in the circulation leads to increased oxygenation and lower levels of hypoxia-inducible factor, suppressing EPO production.



Red blood cells
- Survival
- Proliferation
- Differentiation

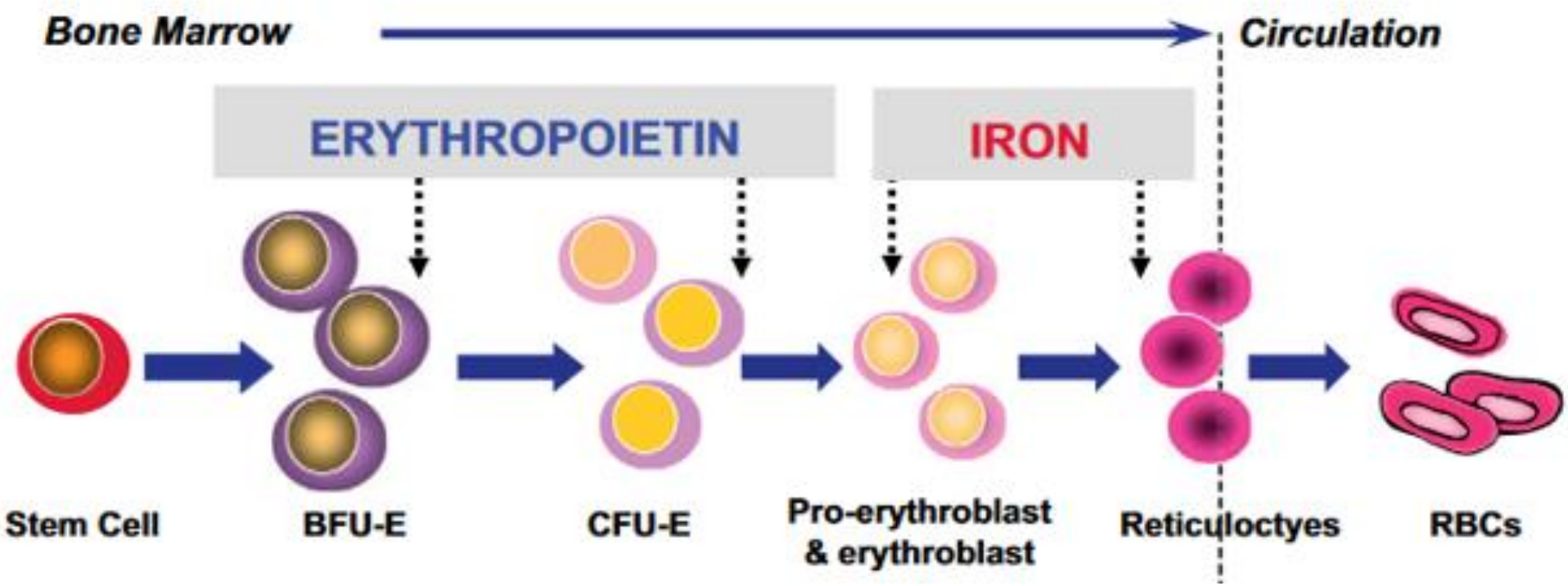
Hypoxia-inducible factor is degraded under conditions of normal oxygen tension. But in anemia or hypoxia, it promotes gene transcription of erythropoietin (EPO), necessary for maturation of red blood cells.

Iron is necessary as well for red blood cell production. Its absorption and transport are also promoted by hypoxia-inducible factor

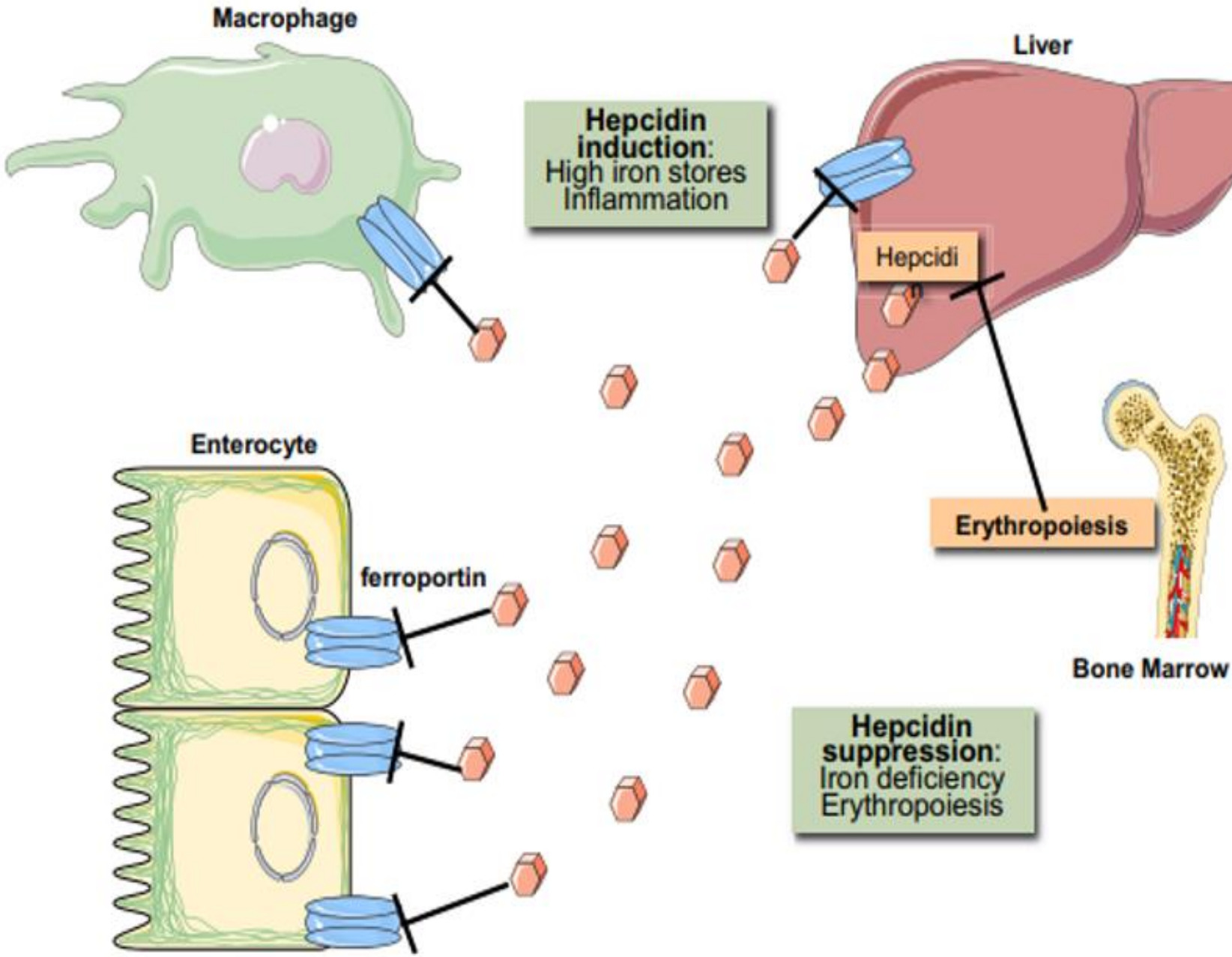
Hypoxia Inducible Factor 1

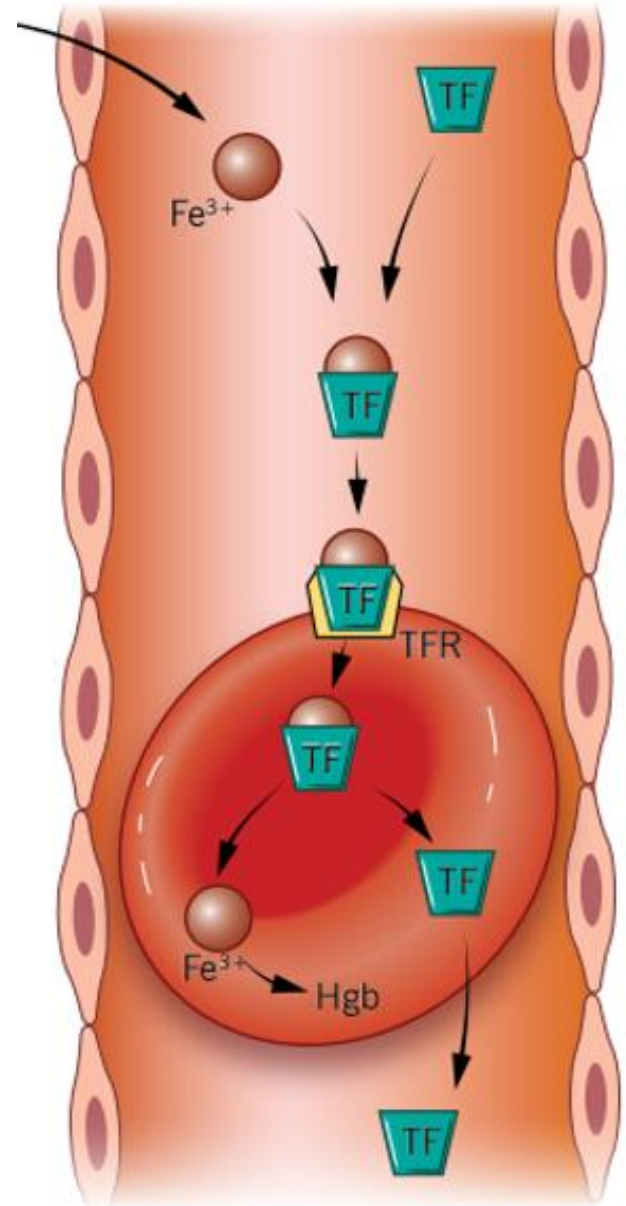
HIF-1

Iron is essential for adequate erythropoietic response to EPO



Kalantar-Zadeh et al., Advances in Chronic Kidney Disease 2009


Macrophage
Liver
Hepcidin induction:
High iron stores
Inflammation
Hepcidi
Erythropoiesis
Bone Marrow
Enterocyte
ferroportin
Hepcidin suppression:
Iron deficiency
Erythropoiesis


TF
Fe3+
TF
TF
TFR
TF
TF
Fe3+
Hgb
TF

Iron deficiency is common in CKD
Depending on its cause, iron deficiency can be categorized as absolute or functional

Absolute Iron Deficiency

Refers to low total iron levels due to blood loss, lack of absorption from the GI tract, and depletion of iron stores in the body.

Contributing Factors

Blood Loss

When the kidneys are damaged, blood may leak into urine (hematuria), resulting in a constant loss of RBCs and hemoglobin. Dialysis patients also lose a significant amount of blood due to the dialysis procedure

Depletion of Iron Stores

Iron reserves may be depleted faster than they are replenished if there is constant blood loss and/or lack of iron absorption from the gut

Lack of Absorption

Absorption of dietary iron from the gut may be impaired, or ingested food may not contain enough iron

Functional Iron Deficiency

Does not stem from total lack of iron in the body; rather, the circulating supply of iron is low due to poor iron mobilization

Contributing Factors

Elevated Hepcidin

Conditions such as chronic inflammation, result in hepcidin release and poor clearance of hepcidin by the kidneys. Hepcidin blocks release of iron from the body's stores

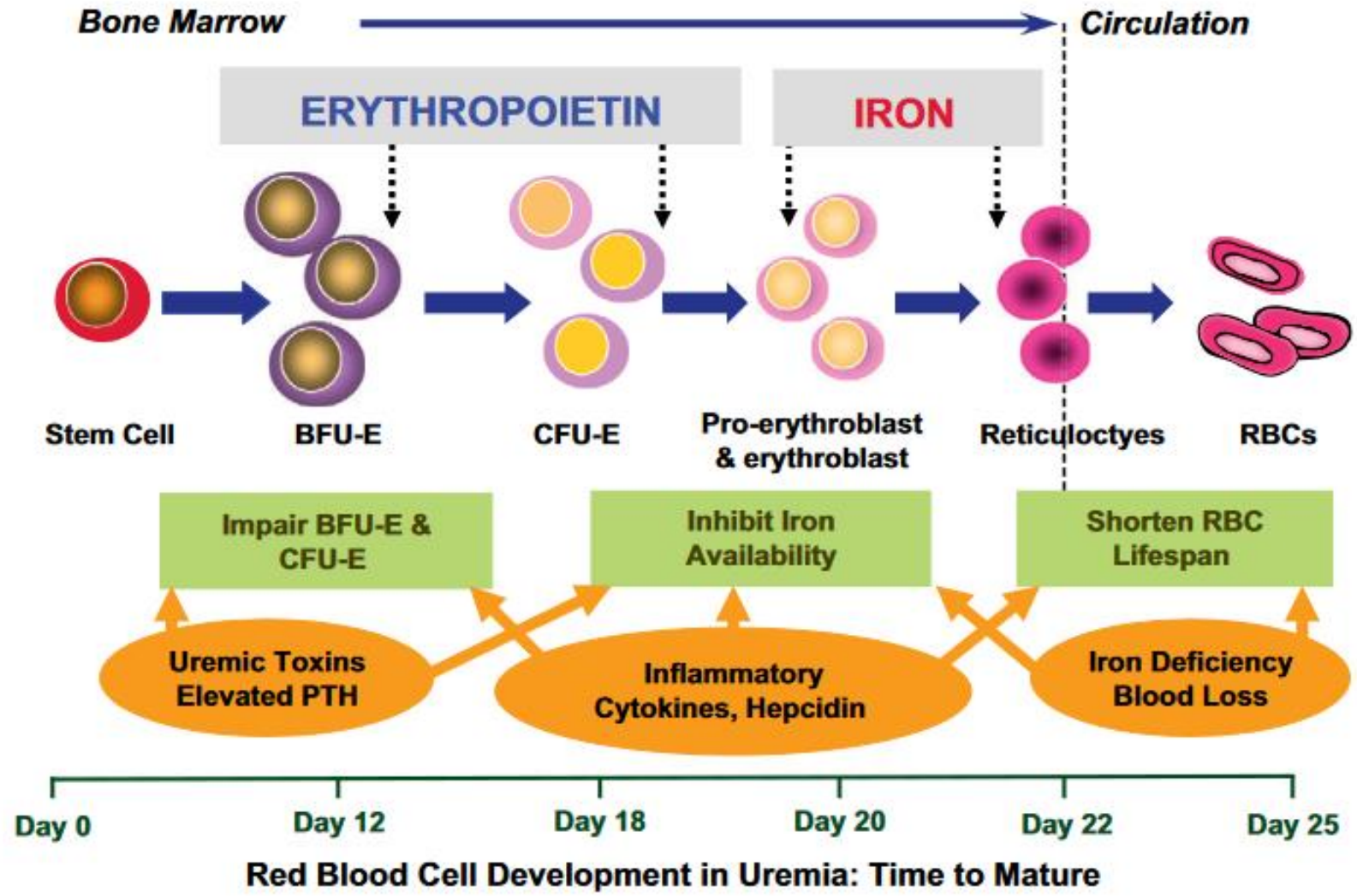
↑Ferritin ↓TSAT

Ferritin levels are normal, or elevated, but stored iron may be inaccessible. This may lead to a below-normal TSAT level and lower RBC production

ESA Treatment

ESA treatment, which stimulates rapid RBC production, quickly depletes the available pool of iron

CKD correlates with impaired iron availability, due to uremic toxins, inflammatory cytokines, hepsidin, malnutrition, malabsorption or blood losses



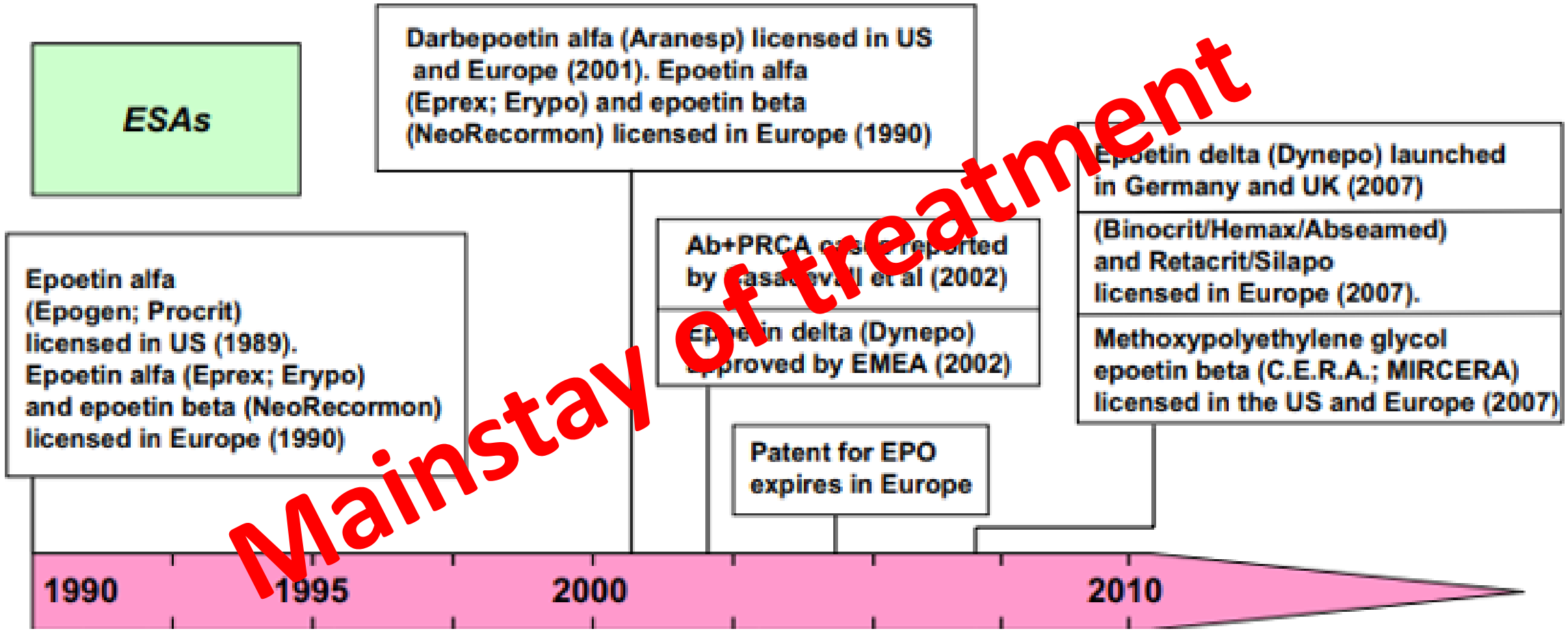
Kalantar-Zadeh et al., Advances in Chronic Kidney Disease 2009

Anemia treatment in CKD

- First oral iron supplements introduced in 1830s
- The use of red blood cell transfusions along the 20th century
- The appearance of the first rhuEPO use in late 1980s followed by longacting ESAs
- The widespread use of intravenous iron supplements in recent years
- The use of Hypoxia Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PHIs) the last few years

	Diagnosis of iron deficiency	Treatment initiation	Hb target under treatment with ESAs	SF and TSAT objectives in patients under treatment	FE oral vs. IV
NICE (2015)	**Test every 3 months (1–3 m in HD)** - Use %HRC > 6%, only if blood processing within 6 h. - if not possible, use CHr < 29 pg - If not, use a combi-nation SF < 100 ng/mL and TSAT < 20%	**Correct iron deficiency before ESA therapy.** - Patient-centered: discuss risks benefits of treatment options. Take into account the person's choice. Avoid Hb < 10 g/dL.	**Hb 10–12 g/dl**	**Avoid SF > 800 ng/mL** To prevent this, review iron dose if SF > 500 ng/mL	**ND-CKD with anemia and iron deficiency:** - offer a 3 months trial of oral iron therapy. - If it fails, offer IV iron therapy. **- DD-CKD:** Preference for IV iron **- If IV iron, consider high dose, low frequency** formulations for ND and DD-CKD patients.
KDIGO (2012)	**SF ≤ 100 ng/mL and TSAT ≤ 20%.**	**A trial with IV iron** if Hb increase or ESA dose reduction is desired and SF ≤ 500 ng/mL and TSAT < 30% **ND-CKD: When Hb < 10 g/dL:** Individualize decision based on the rate of fall of Hb, risks and symptoms. **DD-CKD:** When Hb 9-10 g/dL. Avoid Hb < 9 g/dl.	**Hb ≤ 11.5 g/dl target to Hb > 11.5 g/dl if QoL improve** is foreseen and patient accepts risks. Avoid Hb >13 g/dL	**Stop iron supplements** if SF > 500 ng/mL	**ND-CKD: Select route based on severity of ID, prior response, side effects, costs**, A trial of iv iron, or a 1–3 month trial of oral iron therapy. **- DD- CKD**: Preference for IV iron
ERBP (2009)	**SF < 100 ng/ml and TSAT <20% in ESA naive. SF ≤ 200 ng/mL and TSAT ≤ 30% if ESA treated**	**Avoid Hb < 10 g/dL.** - If low risk patients or a benefit in QoL foreseen ESA could start at ↑ Hb (avoid Hb >12 g/dL) - In high risk patients with worsening heart disease, treatment initiation at Hb9-10 g/dL.	**Hb 10–12 g/dl** - High risk patients with asymptomatic disease: target Hb around 10 g/dL	**Avoid SF > 500 ng/ml and TSAT > 30%.**	**ND-CKD and mild-moderate anemia:** Oral iron as first line therapy for > 3 months. **ND-CKD and severe anemia or when oral iron ineffective:** IV iron as first choice.

Erythropoiesis-Stimulating Agents (ESAs)



Macdougall and Ashenden., Advances in Chronic Kidney Disease, 2009

Erythropoiesis-Stimulating Agents (ESAs)

Not all ESAs are the same
They have different pharmacokinetic and pharmacodynamic properties, such as different half-lives and EPO receptor affinity

Table 1: Comparison of various types of erythropoietin

Parameter	EPO-alpha	EPO-beta	Darbepoetin alpha	CERA
MW (Daltons)	30,000	30,000	37,000	60,000
Polyethylene glycol conjugation	Absent	Absent	Absent	Present
Glycosylation sites	3	3	5	-
Routes of administration	SC, IV, IP	SC, IV, IP	SC, IV	SC, IV
Half-life (SC admn; hours)	19	20	73	139
Bioavailability after SC administration (%)	20	23-42	37	62
Dose	50-150 IU/kg	20-80 IU/kg	0.45 mcg/kg	0.6-1.2 mcg/kg
Dosing schedule	1-3 times/week	1-3 times/week	Once a week or once in 2 weeks	Once in 2 weeks to once a month

First generation	
Epoetin alfa	Epogen® Eprex® Procrit®
Epoetin beta	Recormon®
Epoetin omega	Epomax® Hemax®
Second generation	
Epoetin beta	NeoRecormon®
Darbepoetin alfa	Aranesp®
Third generation	
Epoetin delta	Dynepo®
Methoxy polyethylene glycol epoetin beta	Mircera®
Epoetin alfa (biosimilar)	Binocrit® Abseamed® Epoetin Alfa Hexal®
Epoetin zeta (biosimilar)	Retacrit™ Silapo™
Epoetin theta	Biopoin® Eporatio®

Cochrane Database of Systematic Reviews | Review - Intervention

New search

Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis

Edmund YM Chung, Suetonia C Palmer, Valeria M Saglimbene, Jonathan C Craig, Marcello Tonelli, Giovanni FM Strippoli

Authors' declarations of interest

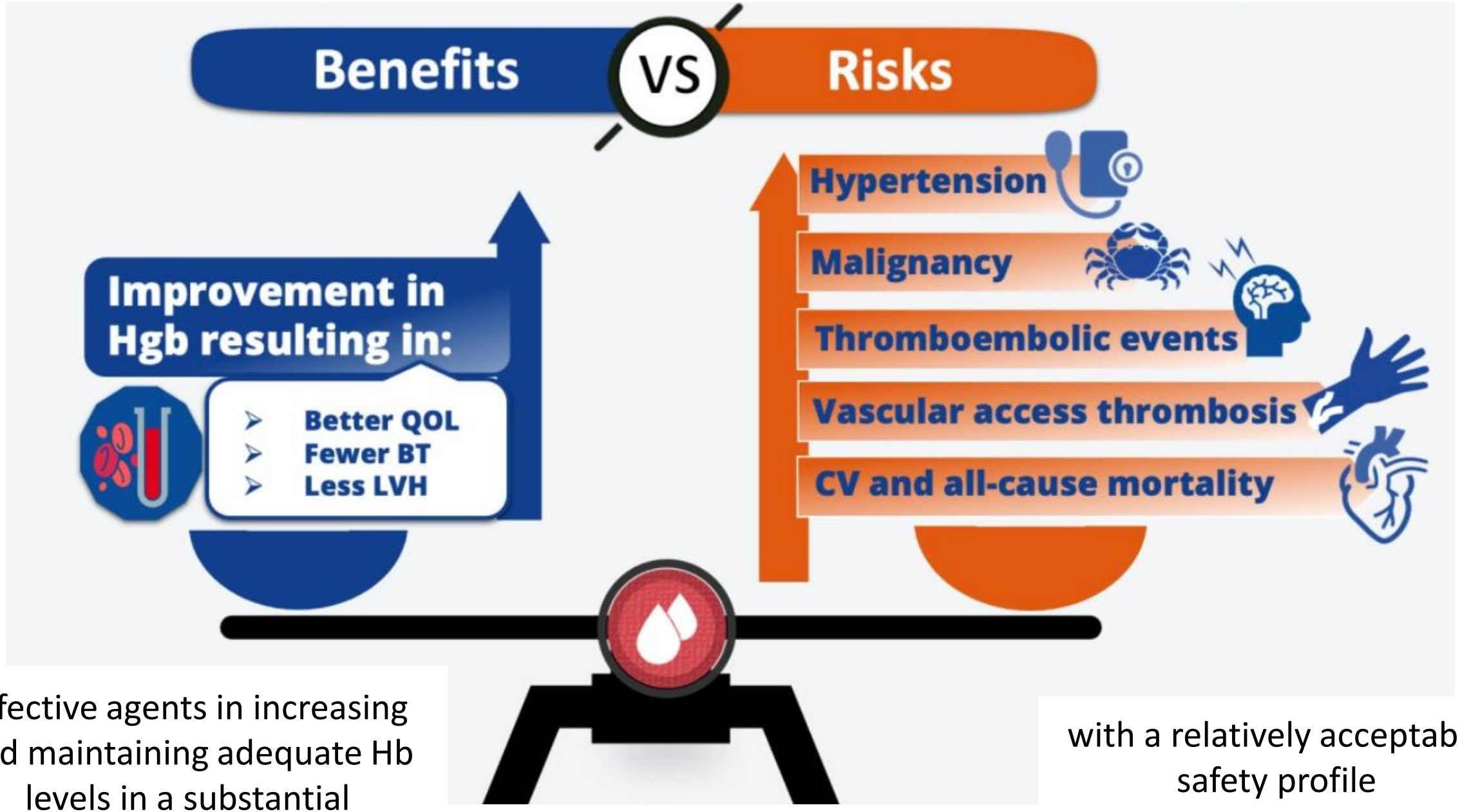
Version published: 13 February 2023 Version history

Sixty-two new studies (9237 participants) were included in this update, so the review now includes 117 studies with 25,237 participants. Most studies were at high or unclear risk of bias in most methodological domains. Overall, results remain similar in this update compared to our previous review in 2014.

Authors' conclusions

The comparative effects of different ESAs on blood transfusions, death (any cause and cardiovascular), major cardiovascular events, myocardial infarction, stroke, vascular access thrombosis, kidney failure, fatigue and breathlessness were uncertain.

Administration convenience, CKD phase, administration route, and costs



Effective agents in increasing and maintaining adequate Hb levels in a substantial proportion of CKD patients

with a relatively acceptable safety profile

Target Hb concentration

At the very beginning, the rationale for their use was quite simple …..

Nephrology:		
NKF-DOQI	1997	Target Hb level of 11–12 g/dL
FDA	2007	Black box warning recommending maintenance of Hb levels within the range of 10–12 g/dL for anemic patients with CKD
ERBP	2010	Target Hb level of 11–12 g/dL in CKD patients, do not intentionally exceed 13 g/dL
FDA	2011	Removed target Hb range of 10–12 g/dL; recommended use of the lowest ESA dose to reduce the need for transfusions
KDIGO	2012	For CKD patients with Hb concentration ≥ 10.0 g/dL, ESA therapy should not be initiated. Upper target limit of 11.5 g/dL. Individualization of therapy will be necessary because some patients may have improvements in QoL at Hb concentrations above 11.5 g/dL and will be prepared to accept the risks
NICE	2015	Target Hb range of 10–12 g/dL
Renal Association	2017	Target Hb range of 10–12 g/dL

The target Hb concentration during ESA therapy is still controversial

Aapro et al., Frontiers in Pharmacology 2019

Therapeutic goals

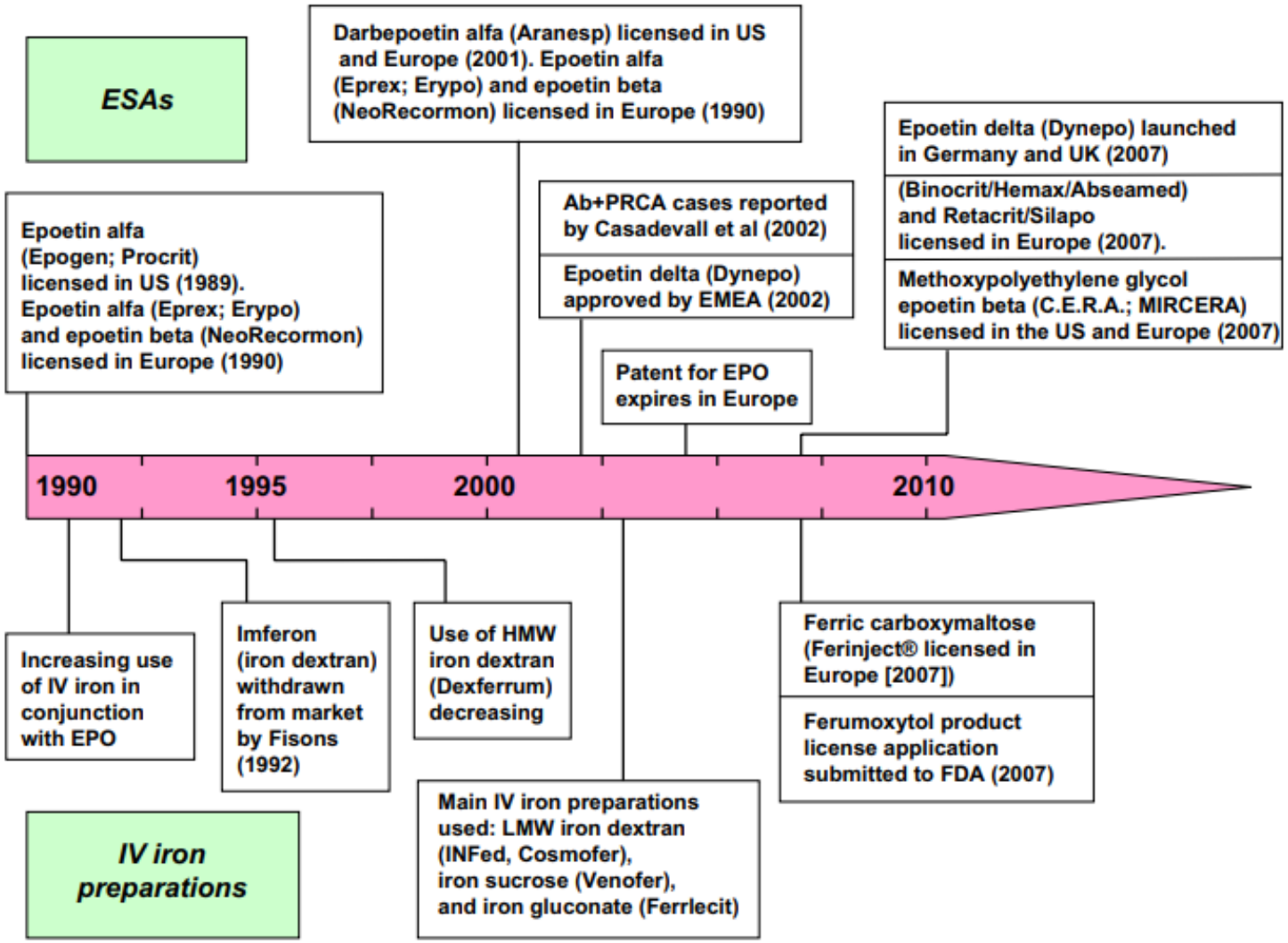
Study	ESA	Target Hb	Clinical outcomes
"Normal Hematocrit Trial" 1998	Epoetin alfa	Hct: 42% vs 30%	Halted early, due to a higher number of deaths and acute myocardial infarction in the group randomized to the higher hematocrit group
CHOIR 2006	Epoetin alfa	13.5g/dl vs 11.3g/dl	Increased risk of a composite of death, myocardial infarction, hospitalization for congestive heart failure and stroke, and no incremental improvement in the quality of life
CREATE 2006	Epoetin alfa	Early therapy 13-15g/dl vs 'salvage' 10.5-11.5g/dl	Increase the necessity of dialysis, more hypertensive episodes, improved QoL in 13-15g/dl
TREAT 2009	Darbepoetin alfa	13g/dl vs placebo rescue (below 9g/dl)	Did not reduce the risk of either of the two primary composite outcomes (either death or a cardiovascular event, death or a renal event), and was associated with an increased risk of stroke

Target Hb concentration

- Correcting Hb levels if they are below 10 g/dL
- Avoiding exceeding Hb 13 g/dl
- The Hb target appears to be somewhere in between 10 and 12 g/dl
- It is advisable individualizing the Hb target relative to the patient's basal conditions, preferences and risks:
  - Cancer
  - Diabetes
  - Symptomatic limb arteriopathy
  - Stroke
  - Non-symptomatic ischemic heart disease

JL Babitt et al.: Optimal anemia management: a KDIGO conference report., Kidney International 2021

Iron Supplementation for Anemia in CKD



Macdougall and Ashenden., Advances in Chronic Kidney Disease, 2009

Evidence for clinical benefits of iron administration

	Patients with CKD not on dialysis	Patients on dialysis
Reduction of congestive heart failure	Limited[60,61]	Yes[62]
Reduced occurrence of myocardial infarction	Limited[63]	Yes[62]
Improved quality of life	Not studied	Limited[64]
Reduced occurrence of fatigue	Not studied	Limited[64]
Improved cognitive function	Not studied	Limited[64]
ESA dose reduction	Yes[65]	Yes[65]
Reduced blood transfusions	Not studied	Yes[62]

Several large studies have reported that correction of iron deficiency may be related with a reduction of congestive heart failure

JL Babitt et al., Kidney International 2021

Concerns about iron supplementation

IV Fe

- Enhanced oxidative stress
- Endothelial dysfunction
- Potential role in favoring infection
- IV iron administration has been associated with an increased risk of hypotension, headaches or hypersensitivity reactions

Oral Fe

- Gastrointestinal intolerance
- Constipation
- effect on gut microbiota
- Increases uremic toxins production ????
- Increases inflammation in CKD ???????

Iron types

Characteristic	Ferrous Sulfate	Ferrous Fumarate	Ferrous Gluconate	Ferric Citrate	Ferric Maltol	Sucrosomial Iron
Side effect						
Dyspepsia	++	++	++	+	+	+
Constipation	+	+	+	+	+	+
Available over the counter	Yes	Yes	Yes	No	No	Yes
Phosphate binder	No	No	No	Yes	No	No
Approximate minimum annual cost, USD	$10.80[a]	$237.60[a]	$37.60[a]	$8,294.40[b]	$7,200.00[b]	$720.00[b]

Agent	Pros	Cons
Iron dextran	Lowest cost, can give 1,000 mg in 1 dose (off label), low risk of 6H syndrome	High rate of hypersensitivity, requires test dose, requires 1.5 h of infusion and observation
Ferric gluconate	Low risk of severe hypersensitivity, low cost, low risk of 6H syndrome	Takes 4-8 doses to administer 1,000 mg, administered over 1 h, risk of hypotension
Iron sucrose	Low risk of severe hypersensitivity, low cost, low risk of 6H syndrome	Takes 3-5 doses to administer 1,000 mg
Ferumoxytol	Low incidence of 6H syndrome, takes 2 doses to administer 1,000 mg	Has black box warning for hypersensitivity, higher cost
Ferric carboxymaltose	Highest total US approved dose (1,500 mg in 2 doses), 1,000 mg in 1 dose also US approved, low risk of severe hypersensitivity	Highest incidence of 6H syndrome/ hypophosphatemia, higher cost
Ferric derisomaltose	1,000 mg in 1 dose is US approved, low risk of severe hypersensitivity	Hypophosphatemia (4%), higher cost, limited availability (?)
Ferric pyrophosphate citrate	Low risk of severe hypersensitivity, given through dialysate, low risk of 6H syndrome	In-center hemodialysis patients only; for iron maintenance, not repletion; risk of hypotension

- ✓ 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

KDIGO 2012

Iron guideline KDIGO

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 μg/l)**

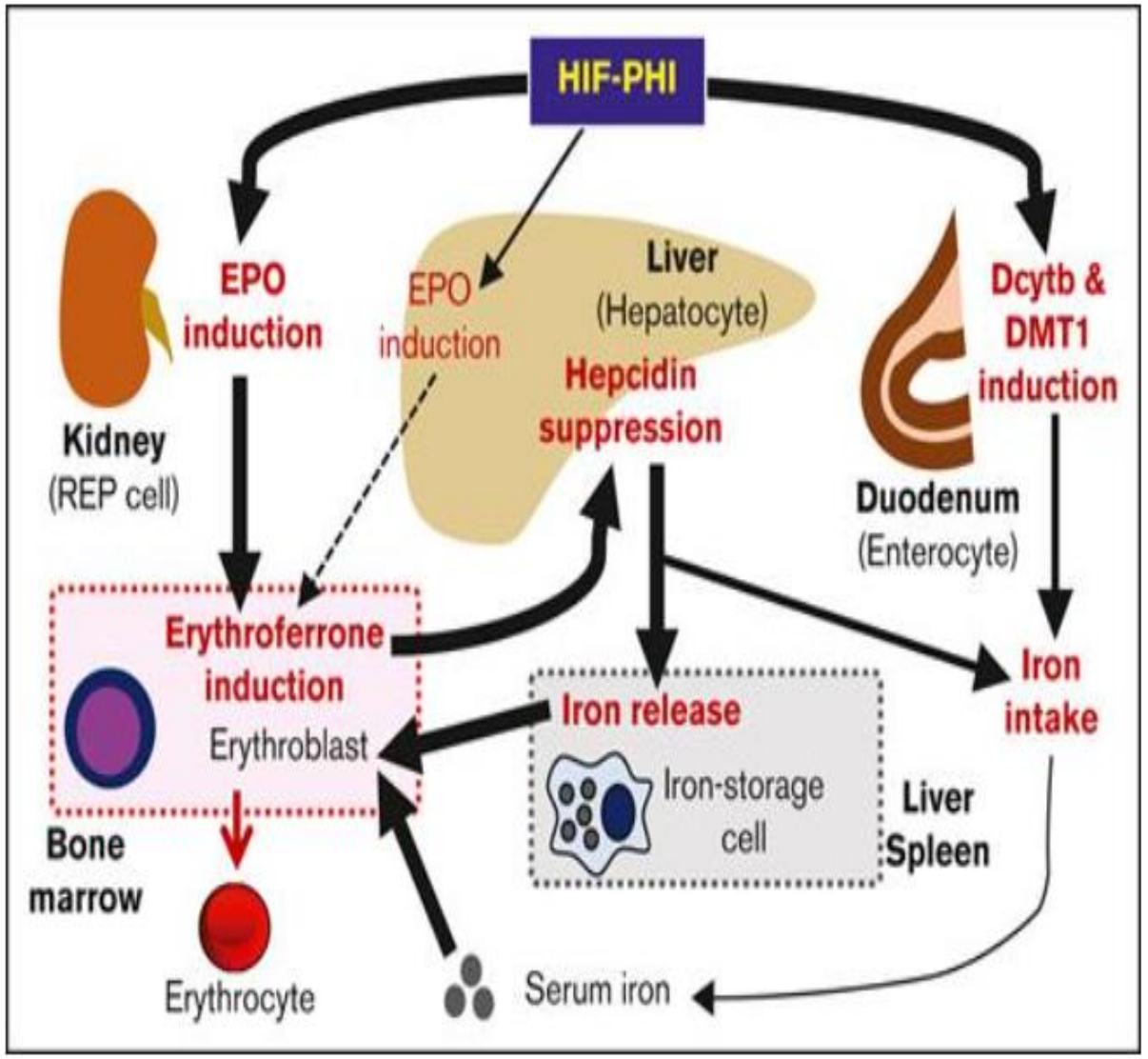
2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):

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

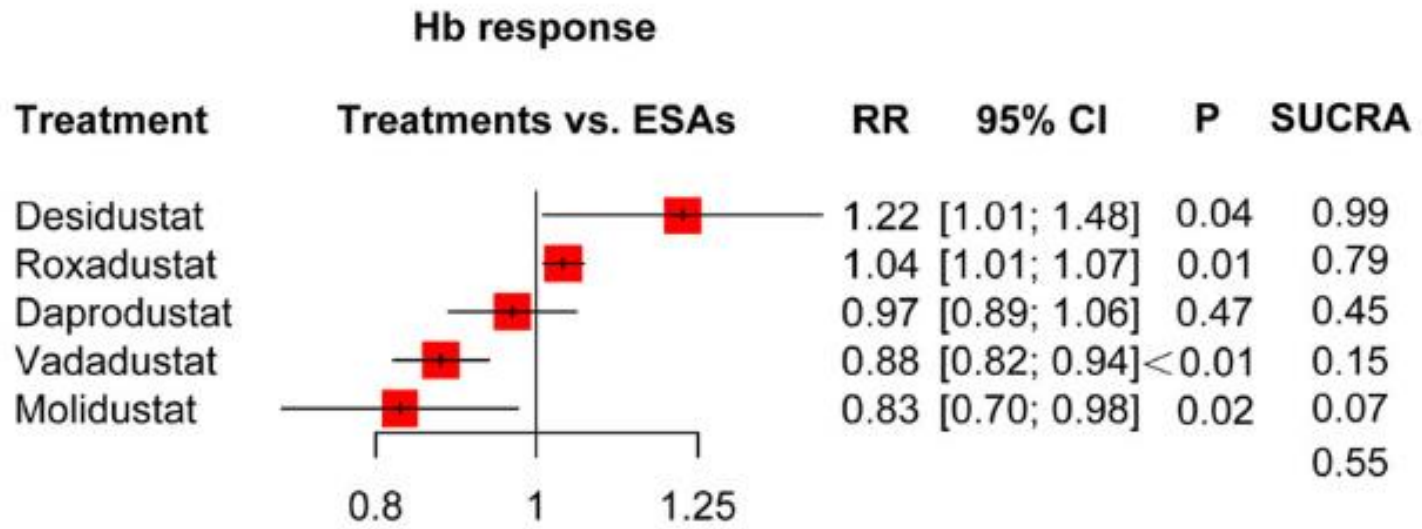
KDIGO 2012

Prolyl hydroxylase domain (PHD) inhibitors

- Prolyl hydroxylase domain (PHD) inhibitors are a new class of drugs for the treatment of anemia
- They differentiate from ESAs, since they do not directly activate the erythropoietin receptor, but rather stimulate the production of endogenous erythropoietin from the kidneys
- Induce the expression of genes related to iron transport
- They are administered orally



Forest plots for the efficacy of Hb response



Quantifying heterogeneity / inconsistency:
$tau^2 = 0$; $tau = 0$; $I^2 = 0\%$ [0.0%; 70.8%]

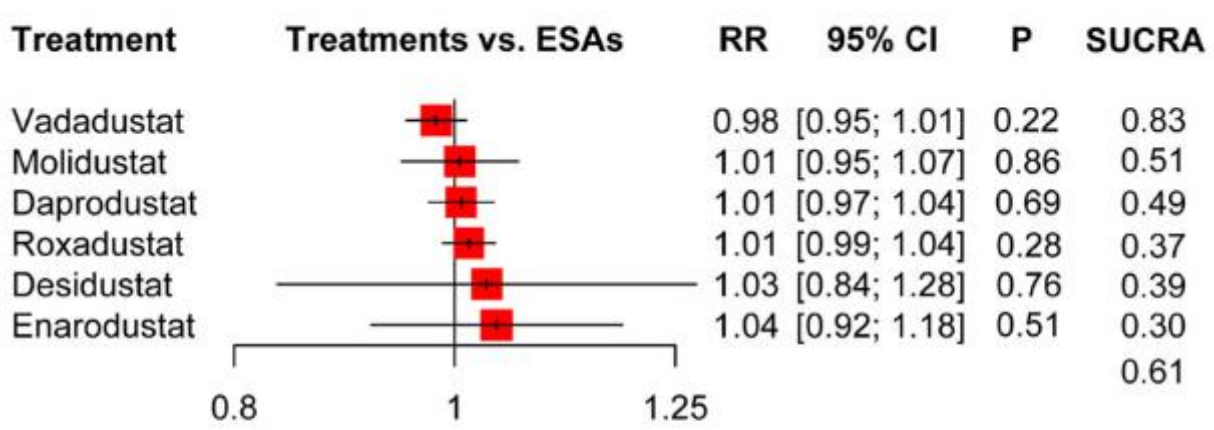
Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value
Total	4.12	6	0.6603
Within designs	4.12	6	0.6603
Between designs	0.00	0	--

Chen et al., Frontiers in Pharmacology 2023

Forest plots for the safety of the treatment-emergent adverse events

Any adverse event

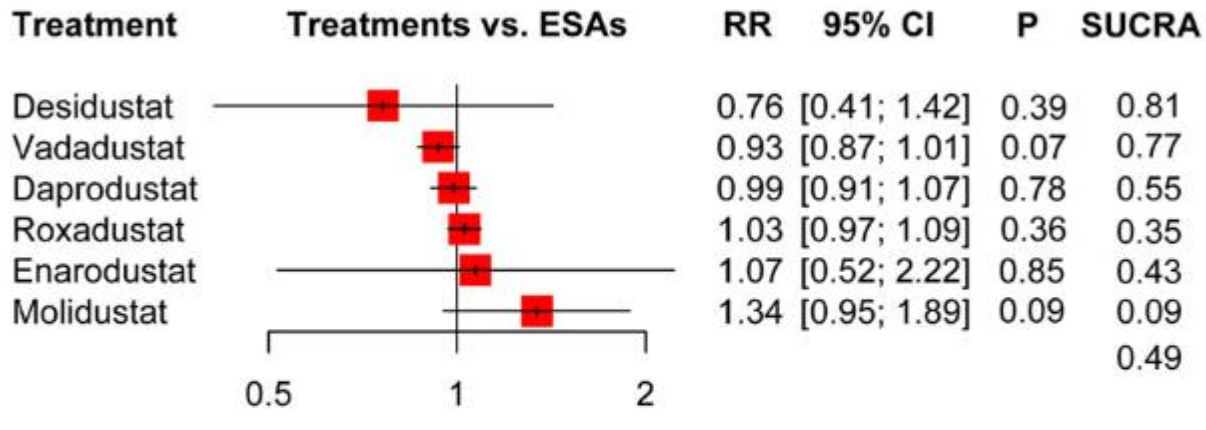


Quantifying heterogeneity / inconsistency:
$\tau^2 = 0.0003$; $\tau = 0.0167$; $I^2 = 21.8\%$ [0.0%; 57.6%]

Tests of heterogeneity (within designs) and inconsistency (between designs):

	Q	d.f.	p-value
Total	17.91	14	0.2109
Within designs	17.91	14	0.2109
Between designs	0.00	0	--

Any serious adverse event

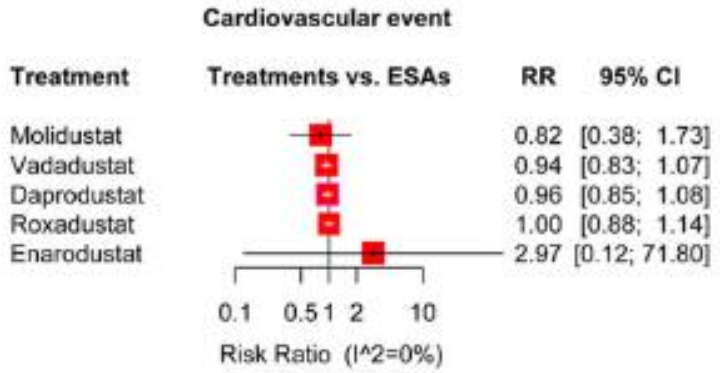


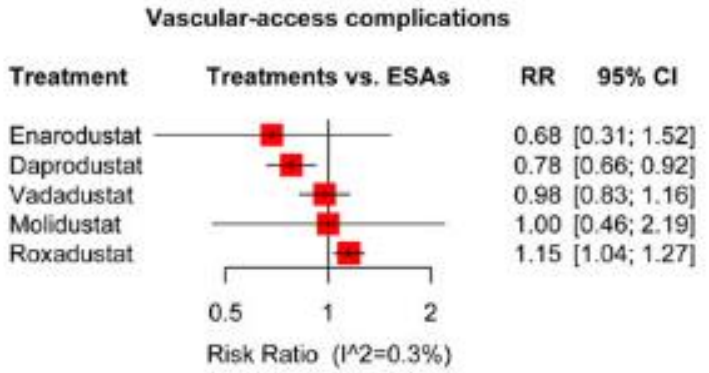
Quantifying heterogeneity / inconsistency:
$\tau^2 = 0.0009$; $\tau = 0.0299$; $I^2 = 8.5\%$ [0.0%; 45.6%]

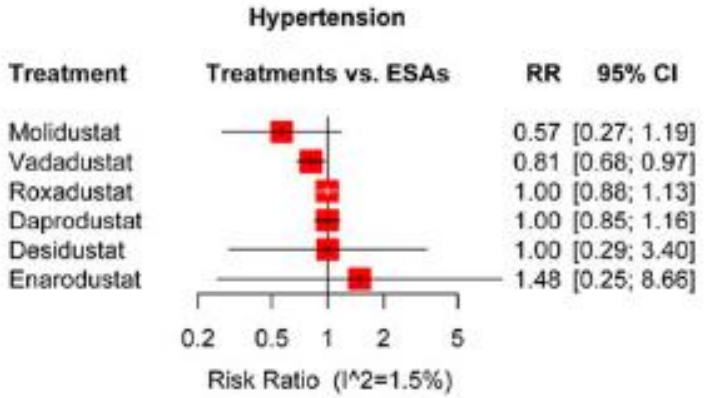
Tests of heterogeneity (within designs) and inconsistency (between designs):

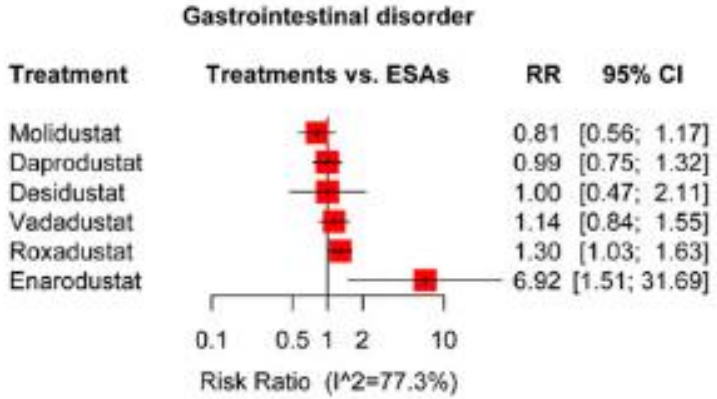
	Q	d.f.	p-value
Total	15.31	14	0.3574
Within designs	15.31	14	0.3574
Between designs	0.00	0	--

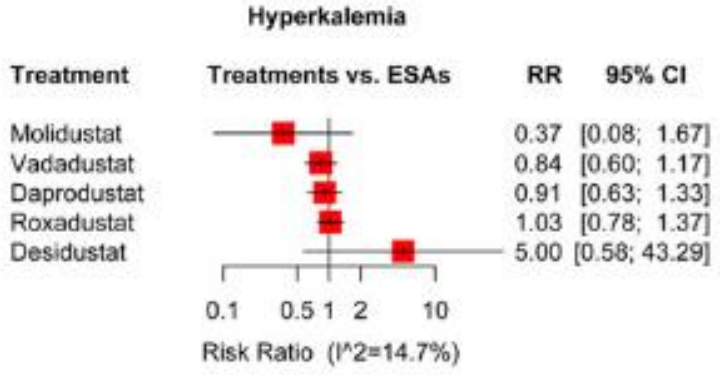
Chen et al., Frontiers in Pharmacology 2023

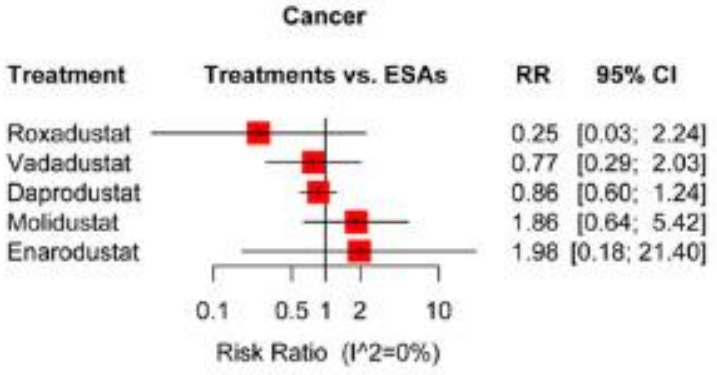












Forest plots for the safety of the treatment-emergent adverse events

Chen et al., Frontiers in Pharmacology 2023

Pleiotropic effects of PHDi

Activation of multiple genes regulating:

- Erythropoiesis
- Iron metabolism
- Angiogenesis
- Lipid and glucose metabolism
- Glycolysis
- Mitochondrial function
- Inflammation and immunity
- Cell growth and survival
- Vasodilation
- Cell migration

Nava Yugavathy., et al., Curr. Issues Mol. Biol. 2023

Anemia in CKD is a significant and frequent complication with multifactorial pathophysiology

- Anemia guidelines are old
- Does not include recent studies assessing the:
  - Efficacy and safety of IV iron
  - Different strategies of iron repletion
  - Current and upcoming erythropoiesis stimulating agents

Kidney International 2021

Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference

Jodie L. Babitt[1], Michele F. Eisenga[2], Volker H. Haase[3,4,5], Abhijit V. Kshirsagar[6], Adeera Levin[7], Francesco Locatelli[8], Jolanta Małyszko[9], Dorine W. Swinkels[10], Der-Cherng Tarng[11], Michael Cheung[12], Michel Jadoul[13], Wolfgang C. Winkelmayer[14] and Tilman B. Drüeke[15,16]; for Conference Participants[17]

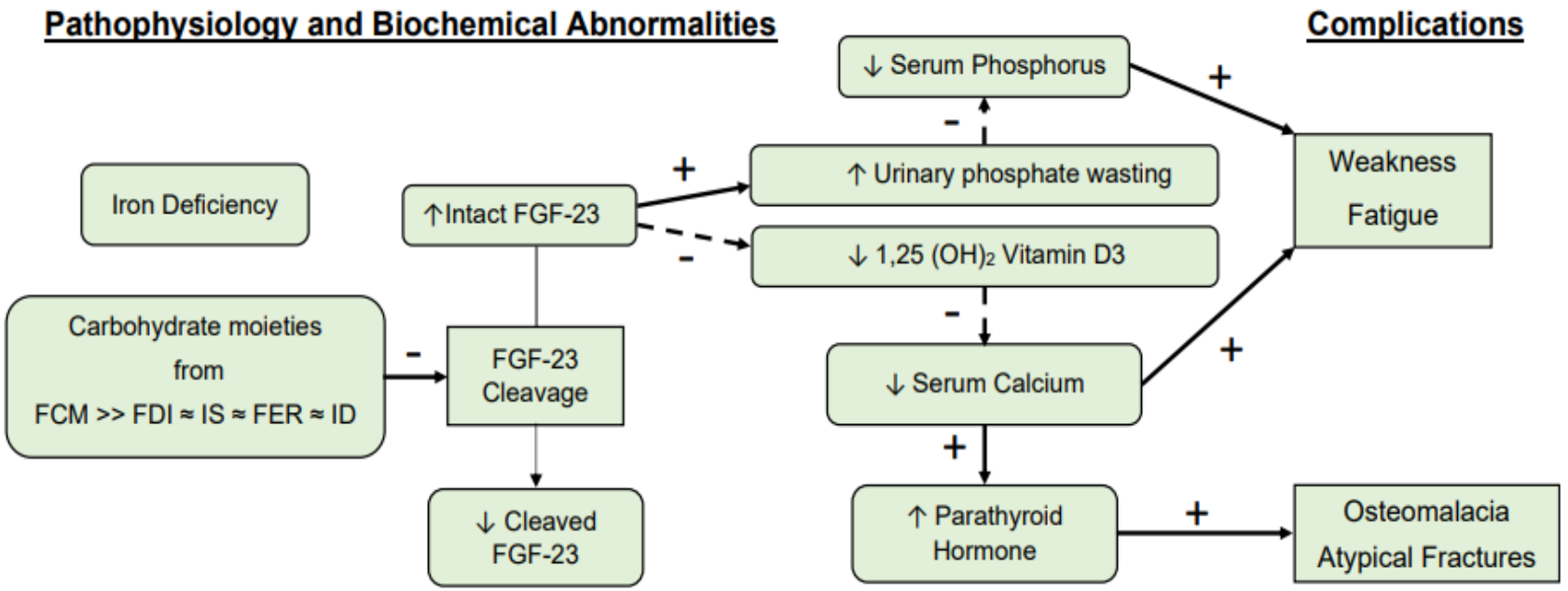
1. Revise anemia guideline
2. With optimal thresholds and targets
3. Individualized diagnosis and therapy
4. There are many areas where more research is needed

CONCLUSIONS

The conference participants agreed that sufficient data are available from new prospective RCTs and novel therapies to warrant convening a new workgroup to revise the KDIGO 2012 anemia guideline. There was also consensus that there are many areas where significantly more research is needed. In particular, the presently used parameters of Hb, serum TSAT, and serum ferritin are not reliable for estimating body iron stores or predicting response to therapy. Moreover, optimal thresholds, targets, and treatment strategies for anemia remain unknown, and have not been customized for specific disease states, age, sex, or within the context of other comorbidities. The need for increasing the complexity and specificity of treatment goals for patients is in keeping with trends to individualize therapy in all specialties. Important for future studies are developing and validating improved tools for determining optimal, individualized anemia correction targets, measuring patient-reported quality of life, and evaluating hard clinical outcomes. Although the class of HIF-PHI agents are predicted to benefit iron metabolism, clinical study data corroborating their predicted ferrokinetic properties in patients with CKD are not yet clearly established and are a high priority.


That's all

6H syndrome



1. High Fibroblast Growth Factor 23
2. Hyperphosphaturia
3. Hypophosphatemia
4. Hypovitaminosis D
5. Hypocalcemia
6. Hyperparathyroidism secondary

Reported clinical manifestations of the 6H syndrome include:

- Osteomalacia
- Bone fractures
- Muscular weakness and
- Respiratory failure

Jonathan W. Bazeley., Jay B. Wish., AJKD 2022