Iron Deficiency Anemia in CKD

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Review

Kidney Medicine

Iron-Deficiency Anemia in CKD: A Narrative Review for the Kidney Care Team

Kidney Med. 5(8):100677. Published online May 25, 2023.

AJKD

Review

Recent and Emerging Therapies for Iron Deficiency in Anemia of CKD: A Review

Jonathan W. Bazeley and Jay B. Wish

Am J Kidney Dis. 79(6):868-876. Published online November 7, 2021.

Core Curriculum

AJKD

Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018

Steven Fishbane and Bruce Spinowitz

Am J Kidney Dis. 71(3): 423-435. Published online January 11, 2018.

Introduction

Many CKD patient with anemia experience **poor health-related quality of life** (QoL: eg, fatigue and reduced productivity) and debilitating symptoms, such as cognitive impairment, shortness of breath, dizziness, headaches, loss of appetite, and depression.

The **overall prevalence of anemia in CKD** was estimated to be **15.4%**, with the prevalence of anemia increasing as the disease advances.

In particular, the **Kidney Disease: Improving Global Outcomes (KDIGO)** anemia work group guidelines define anemia in CKD as a hemoglobin concentration of **<13.0 g/dL in men** and **<12.0 g/dL in women** (hemoglobin concentrations are >13.5-17.5 g/dL in healthy men and >12.0-15.5 g/dL in healthy women).

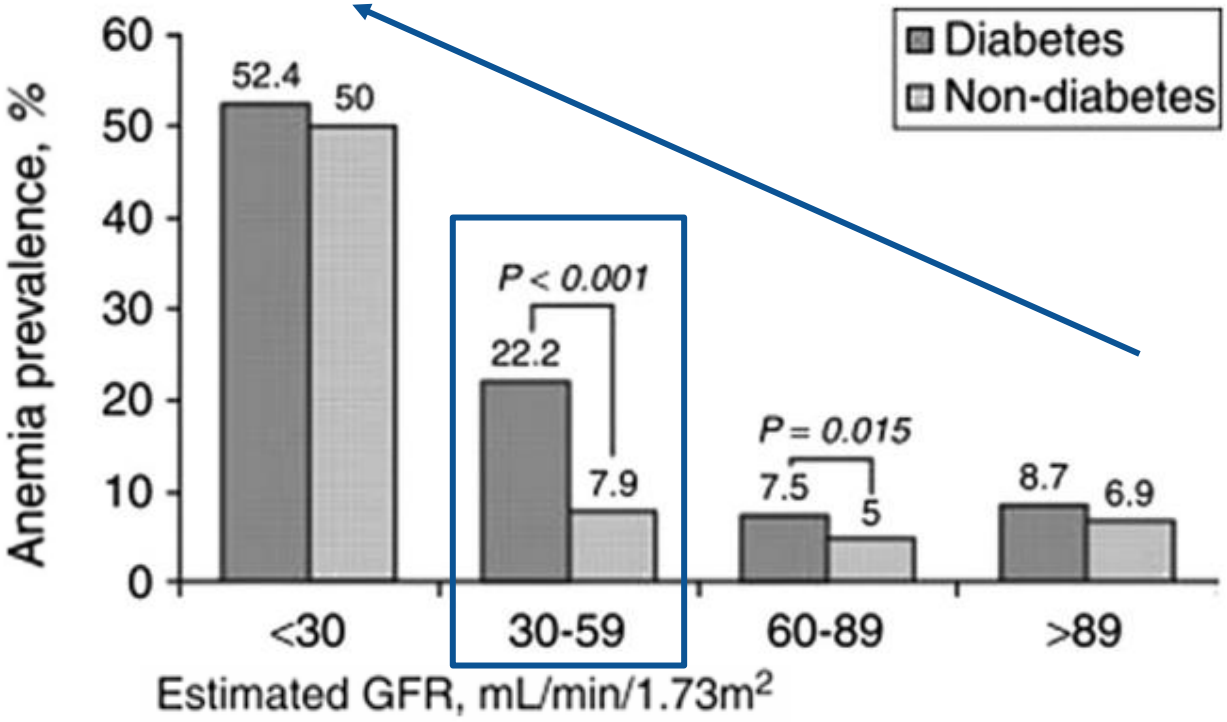


Figure 1. Prevalence of anemia (hemoglobin < 12 g/dL in men and <11 g/dL in women) in patients with or without diabetes. Abbreviation: GFR, glomerular filtration rate. Reproduced from El-Achkar et al (*Kidney Int.* 2015;67:1483-1488) with permission of the copyright holder (International Society of Nephrology).

Anemia in individuals with CKD is considerably undertreated, particularly in those with non–dialysisdependent (NDD) CKD.

In a survey of **410 individuals** with **NDD-CKD anemia** in the United States, **only 22.8%** reported being **treated for anemia**, with the **most being treated** for anemia in **later stages** of CKD (stage 1, 12.1%; stage 2, 16.2%; stage 3, 26.5%; stage 4, 20.7%; and **stage 5**, **43.0%**). The undertreatment of anemia in individuals with NDD-CKD also **increases** the need for **blood transfusions**

Among **kidney transplant candidates**, **transfusions increase the possibility o**f **allosensitization** (ie, the development of antibodies), which may preclude candidates from being able to receive the transplant or may cause transplant rejection altogether.

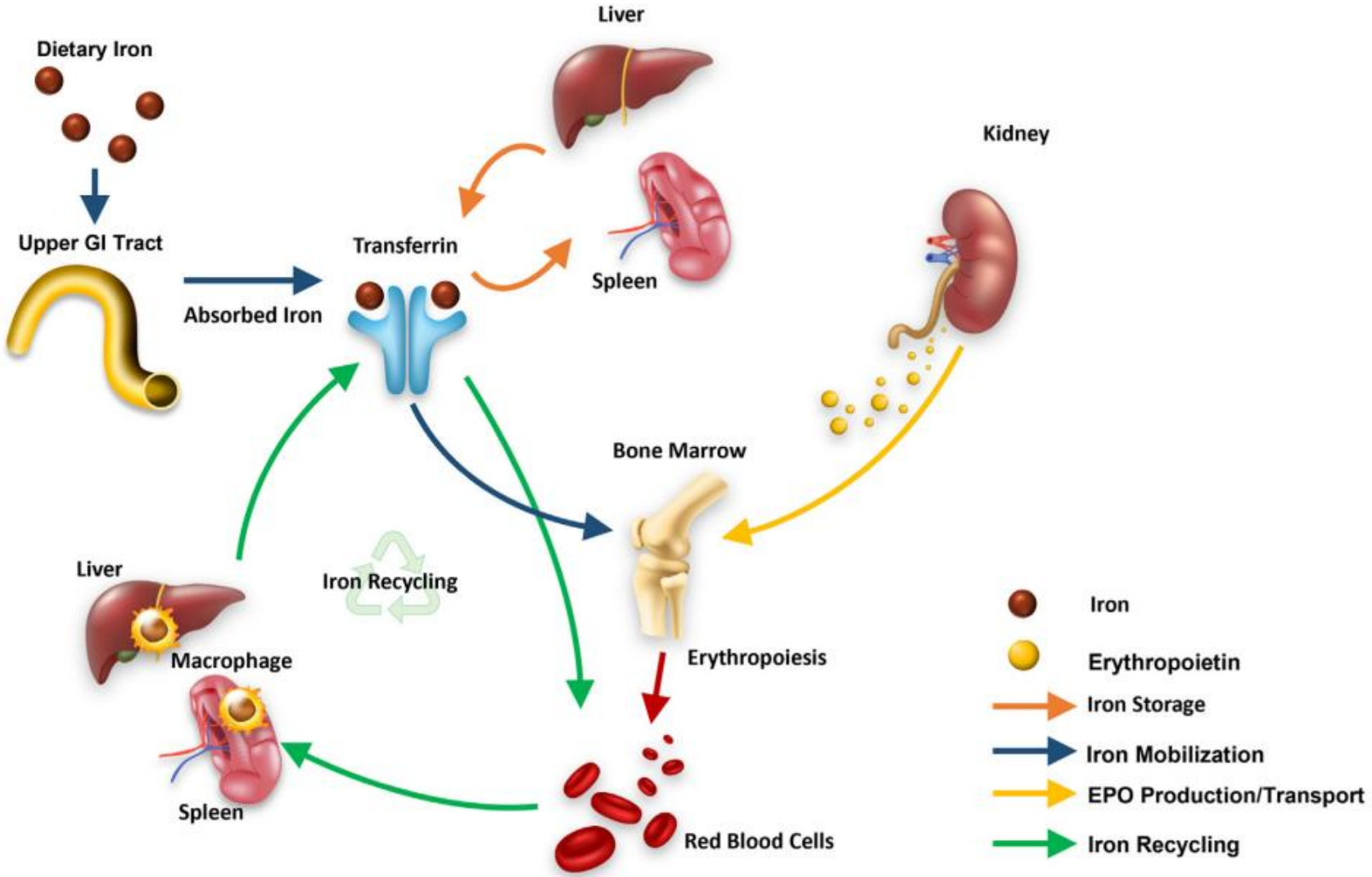
Overview of normal iron homeostasis

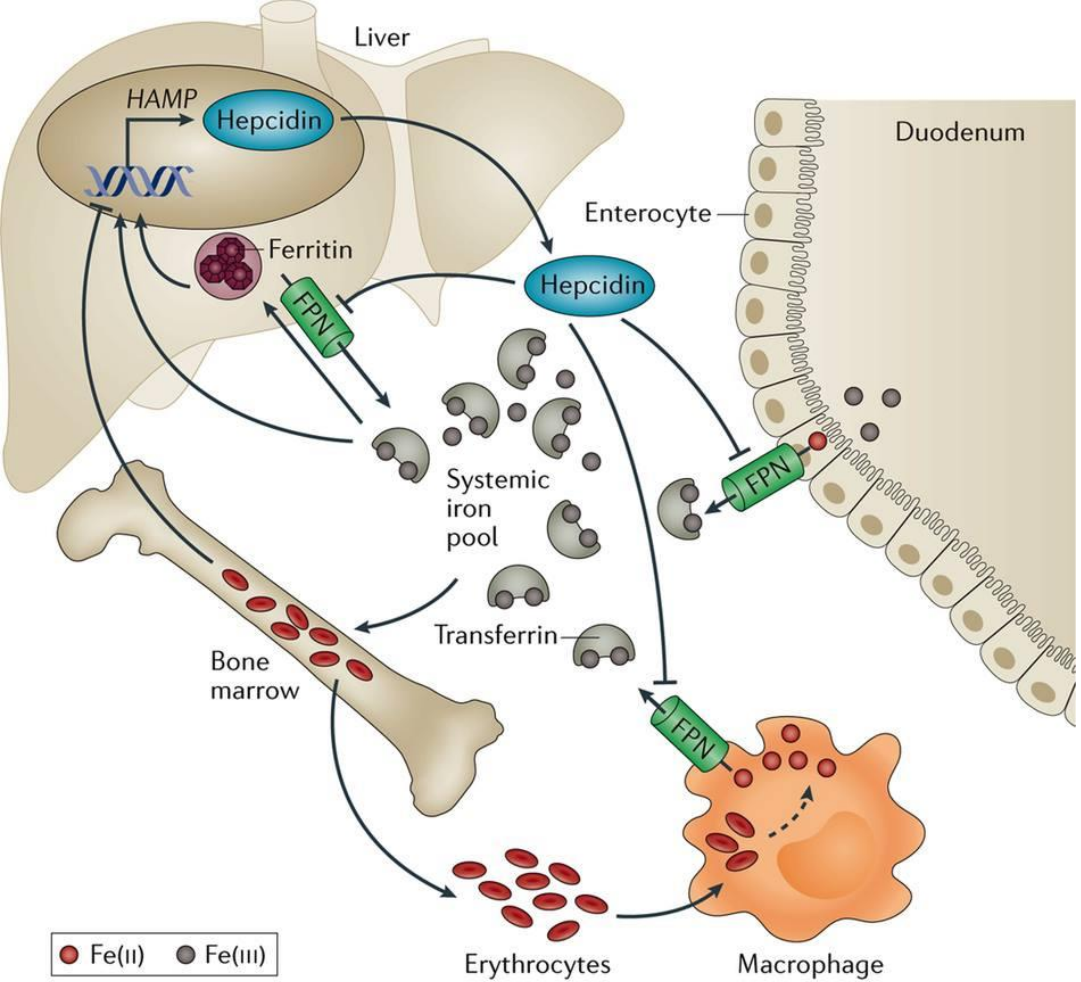
Dietary iron, in the form of either **heme** (ie, found only in **meat**, **poultry**, **seafood**, and **fish**) or **nonheme iron** (ie, found in **plant-based foods** such as grains, beans, vegetables, fruits, nuts, and seeds), is absorbed by the duodenal enterocytes and exported into the circulation, where it is bound to transferrin (an iron transport protein).

Iron is then transported to the **liver and spleen**, where it is bound to **ferritin** (an **iron-storage protein** found in macrophages) or to the **bone marrow**, where it is used for **erythropoiesis**.

Iron stores are replenished when macrophages in the spleen and liver engulf and consume old RBCs, a process known as phagocytosis, ultimately recycling their iron content, which is used either for the production of new RBCs or stored for future use.

The recycling of RBCs in the spleen and liver provides **most of the body's iron (20-25 mg/d)**, whereas **dietary absorption** provides only **1- 2 mg/d of iron.**


Liver
Dietary Iron
Kidney
Upper GI Tract
Transferrin
Spleen
Absorbed Iron
Bone Marrow
Liver
Iron Recycling
Macrophage
Erythropoiesis
Spleen
Red Blood Cells
Iron
Erythropoietin
Iron Storage
Iron Mobilization
EPO Production/Transport
Iron Recycling

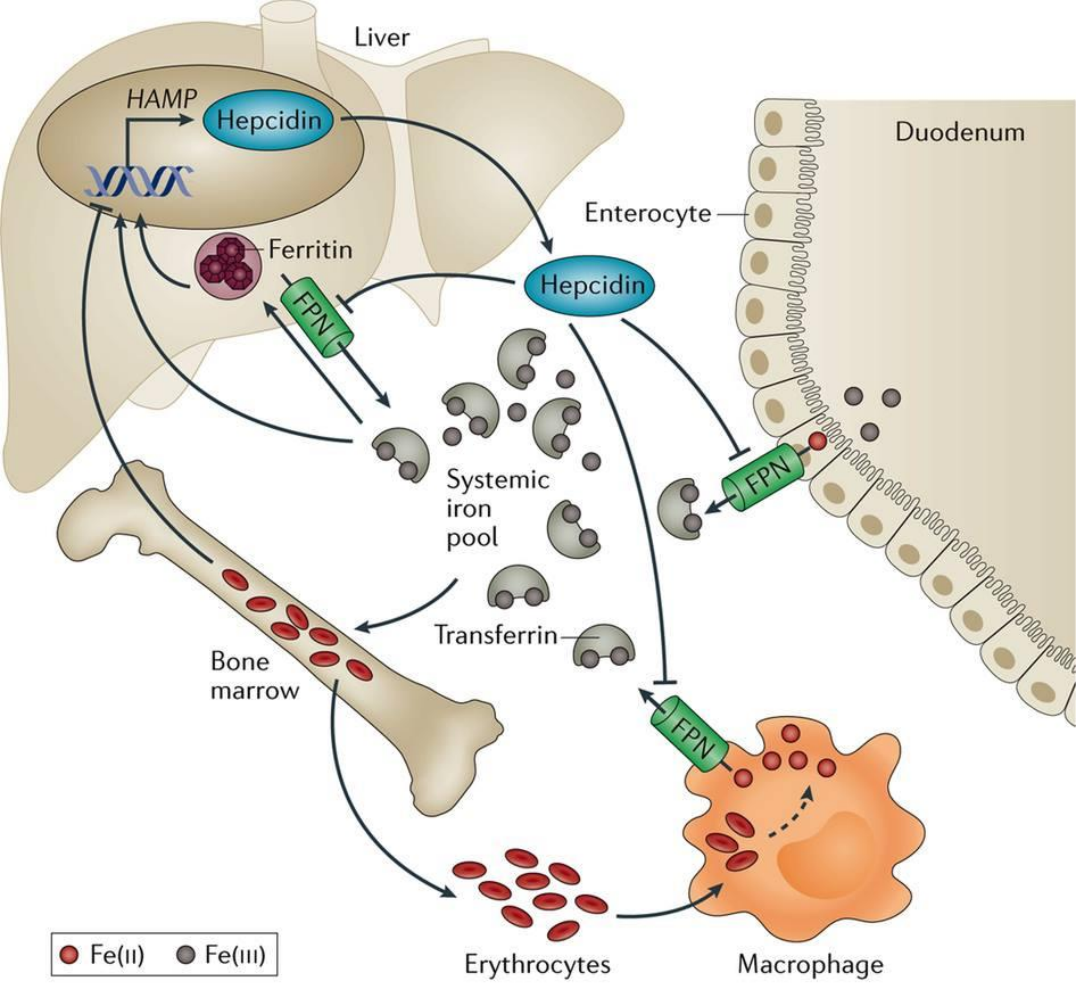


Hepcidin as a key regulator of iron homeostasis

Hepcidin is released from the **liver cells** into the circulation and binds to the **iron exporter ferroportin** that is located on the membranes of the **small intestine**, **macrophages**, and **liver cells**.

This **binding** ultimately causes the **degradation of ferroportin**, preventing iron export into the plasma and, in turn, sequestering iron in iron-storage sites (liver cells and macrophages).

Nature Reviews | Drug Discovery

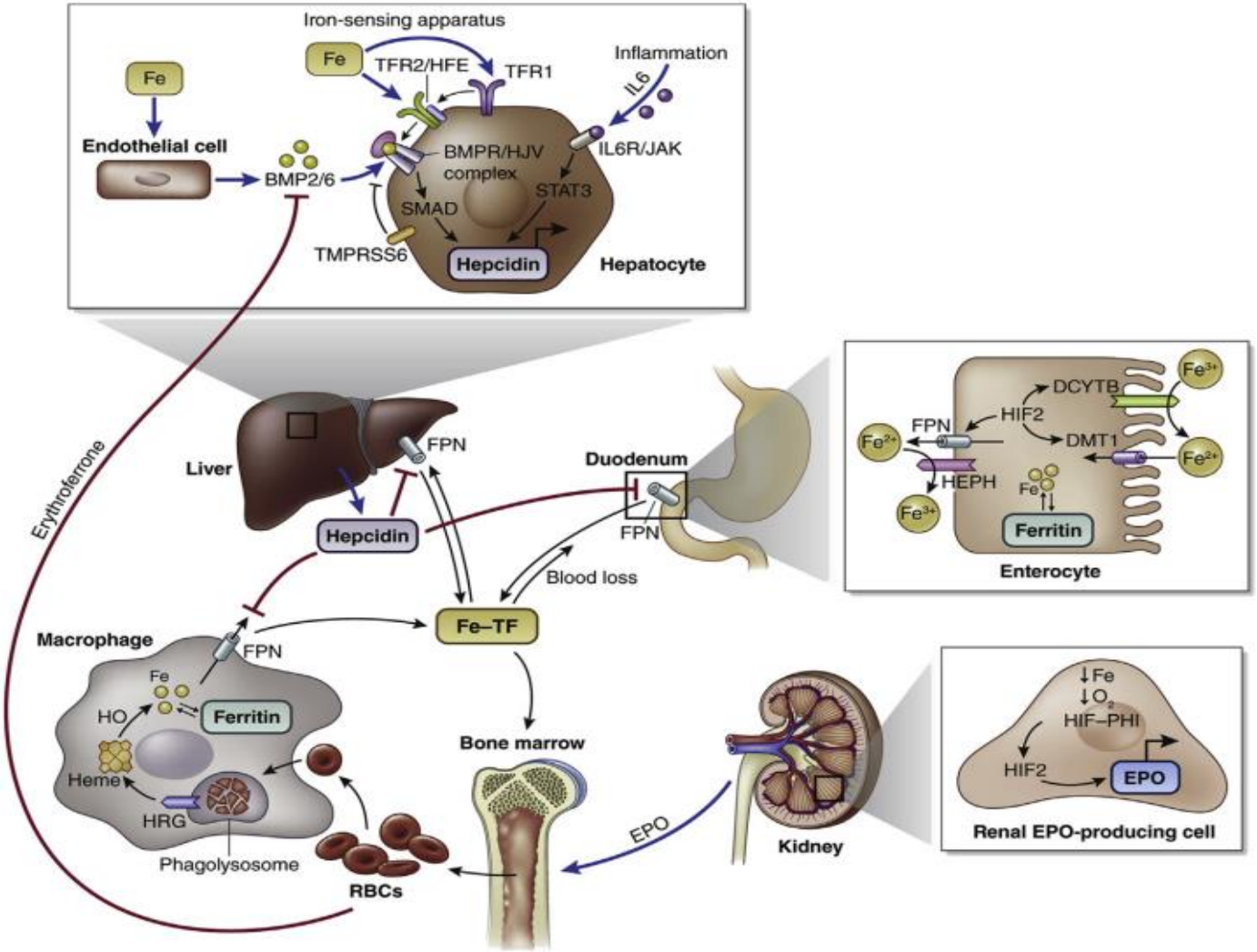


Hepcidin controls the **uptake of iron from the gut** and **its release from the iron stores**.

Hepcidin production ↑ : increased iron uptake, inflammation, and infection

Hepcidin production ↓ : iron deficiency and hypoxia

Nature Reviews | Drug Discovery


Iron-sensing apparatus
Fe
TFR2/HFE
TFR1
Inflammation
IL6
Fe
Endothelial cell
BMP2/6
BMPR/HJV complex
IL6R/JAK
STAT3
SMAD
TMPRSS6
Hepcidin
Hepatocyte
Liver
FPN
Hepcidin
Duodenum
FPN
Blood loss
Erythroferrone
Fe–TF
Macrophage
FPN
Fe
HO
Ferritin
Heme
HRG
Phagolysosome
RBCs
Bone marrow
EPO
Kidney
DCYTB
HIF2
FPN
DMT1
HEPH
Ferritin
Enterocyte
↓Fe
↓O2
HIF–PHI
HIF2
EPO
Renal EPO-producing cell

Absolute Iron Deficiency

In patients with chronic kidney disease (CKD), the unavailability of iron for hematopoiesis can be **absolute** or **functional**.

Absolute iron deficiency occurs when the amount of **storage iron** in the liver, spleen, and marrow is **minimal**
> blood losses related to the dialysis procedure, gastrointestinal bleeding, or poor oral iron intake.

Absolute iron deficiency in individuals with CKD is defined by low circulating and stored iron, particularly **TSAT of ≤20.0% and ferritin of ≤100 ng/mL**

Functional Iron Deficiency

Functional iron deficiency is characterized by adequate iron stores, the **gold standard** for which is **presence of stainable iron in bone marrow**, but usually diagnosed in the clinical setting by blood tests.

Functional iron deficiency represents a **supply/demand mismatch** for iron to support erythropoiesis.

On the **supply side**, **inflammation** leads to decreased iron availability primarily due to **increased hepcidin** concentration in plasma.

On the **demand side**, **erythropoiesis-stimulating agents (ESAs)** used in patients with CKD accelerate red blood cell production and **exceed the ability to sufficiently mobilize iron from stores**.

Functional iron deficiency due to ESA therapy can often be **overcome with therapeutic iron supplementation**, whereas **anemia of inflammation may be more resistant** to this intervention,

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

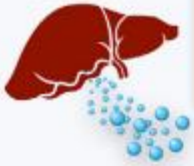
Absorption of dietary iron from the gut may be impaired, or ingested food may not contain enough iron

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

Iron-Deficiency Anemia and Morbidity and Mortality

A longitudinal study of a large population (w28,000) with CKD found that over a 5-year period, **congestive heart failure**, **coronary artery disease**, and **diabetes were** more prevalent in those who died and that these individuals also showed a **high baseline prevalence of anemia**.

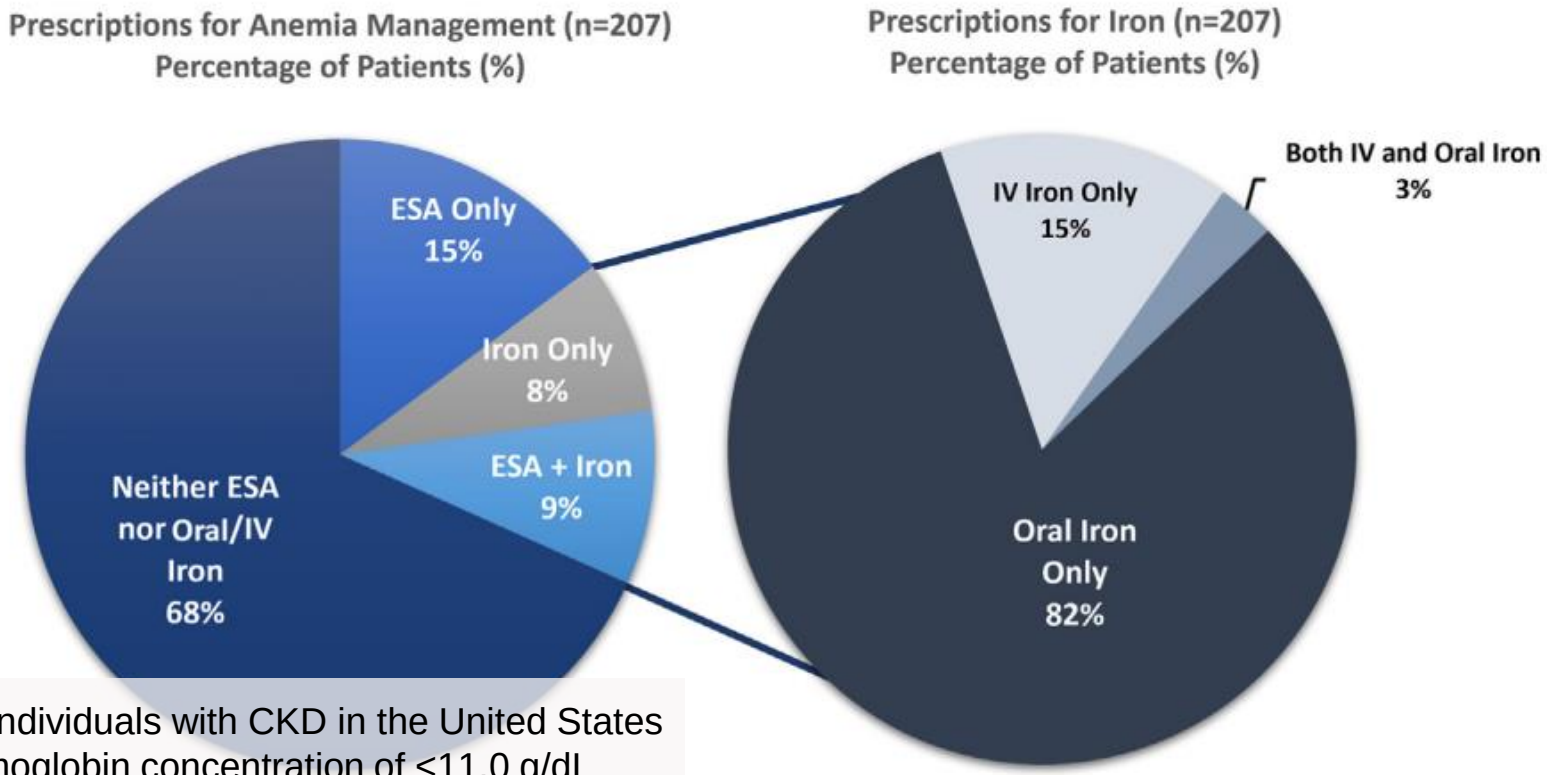
A separate study in men with moderate and severe CKD who were **not yet treated with dialysis (N=853)** found that a **lower hemoglobin level** was significantly associated with **higher non–dialysis-dependent mortality** and **higher risk of kidney failure**.

Anemia in CKD may also contribute to **reduced QoL**.

In an example from a study in the United States and Canada, higher hemoglobin levels were associated with improved QoL domains of the Kidney Disease Quality of Life questionnaire in 1186 individuals with NDD-CKD stages 3-5.

Because hemoglobin concentration increased from **<11** to **13 g/dL**, significant improvements in varied QoL domains were observed, suggesting a relationship between hemoglobin level and QoL. However, **the most dramatic improvements** in QoL domains occurred when hemoglobin levels increased in the groups with a **baseline hemoglobin concentration of <11 g/dL** and **hemoglobin concentration of 11-12 g/dL.**

Prescriptions for anemia management in US individuals with NDD-CKD with hemoglobin concentration of <11.0 g/d



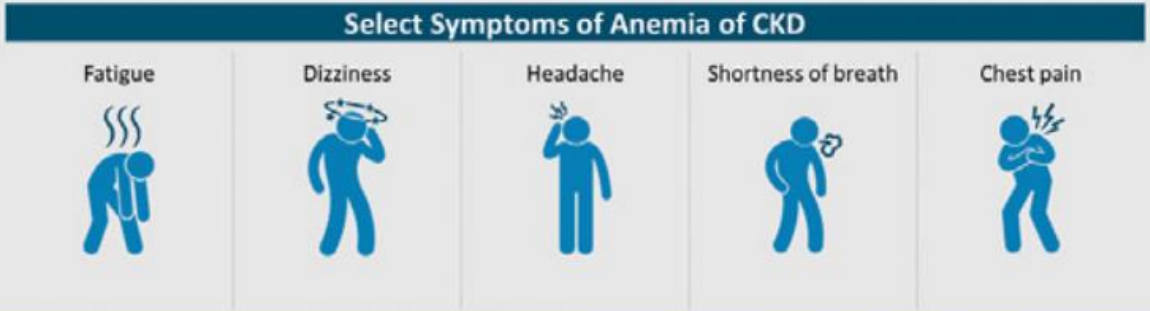
68.0% of individuals with CKD in the United States with a hemoglobin concentration of <11.0 g/dL were not treated with iron or ESAs

Assessment of anemia and iron status

The diagnosis of iron-deficiency anemia is essential to ensure prompt treatment to correct the deficiency and improve the accompanying anemia.

All individuals with CKD, particularly those with an estimated glomerular filtration rate **(eGFR) of <60 mL/min/1.73 m2 (stage ≥3 CKD)**, should be **screened for anemia** as part of their initial evaluation after CKD diagnosis

Step 1: **Anemia Awareness.** Each member of the multidisciplinary care team should maintain careful observation of the symptoms of anemia and be familiar with the diagnostic tests used to assess anemia status.



Test	Detail and Purpose
Complete blood count	Includes hemoglobin, red blood cell indices, white blood cell count and differential, and platelet count. Provides information about anemia severity and adequacy of bone marrow function
Absolute reticulocyte count	Provides an understanding of effective erythropoietic proliferative activity
Serum ferritin level	Provide information about persistence or absence of iron storage and the availability of iron to support ongoing erythropoiesis
Serum TSAT	
Vitamin B_{12}	May indicate underlying disease processes and is easily corrected. Part of the standard workup
Folate	Easily corrected, therefore part of the standard workup

Dietitians

Assess for changes in symptoms, diet or appetite, energy levels, use of supplements, and nutritional and functional status; any findings may prompt an assessment of iron deficiency.

Assessment may be performed by using validated, evidence-based tools, and dietitians should reassess nutritional status after the initial consultation as part of an ongoing, dynamic aspect of care.

Social workers

take note of changes in appetite or food access that can affect nutrition and potentially trigger or worsen iron deficiency. Social workers can also leverage their training and tools to assess for depression, which may be associated with anemia.

For anyone involved in the care of individuals with CKD, a physical examination of the individual, such as looking for specific changes in **nails, hair, conjunctiva**, and **oral mucosa**, may aid in the diagnosis of deficiency of **iron, folate**, or **vitamin B12.**

Pica behavior (craving and consuming substances that have no nutritional value, such as ice, clay, soil, chalk, or paper) has also been associated with iron-deficiency anemia, and evaluation for pica behaviors should be routinely included as part of the overall assessment.

***Step 2:* Diagnosing anemia.** The assessment of serum ferritin, TSAT, and hemoglobin levels is key to diagnosing anemia. The timing and frequency of testing should be guided by symptoms, baseline hemoglobin, rate of hemoglobin decline, target hemoglobin level, and CKD stage.

Parameter	Normal Renal Function	Chronic Kidney Disease	
		Absolute Iron Deficiency	Functional Iron Deficiency
Ferritin	>100 ng/mL	• Non-dialysis: ≤100 ng/mL • Peritoneal dialysis: ≤100 ng/mL • Hemodialysis: ≤200 ng/mL	>100 ng/mL (no consensus on how high levels may reach)
TSAT	20%-50%	≤20%	
Hemoglobin	Normal ranges for adults vary, but in general are: • Women: 12-15 g/dL • Men: 13-17 g/dL	Non-dialysis • Women: <12 g/dL • Men: <13 g/dL	
		Dialysis • Women: <12 g/dL • Men: <13 g/dL	

Treatment Options for Iron-Deficiency Anemia in CKD

Iron supplementation (either oral or intravenous) and/or **ESA therapy** are generally accepted as the standard of care for iron-deficiency anemia in CKD (**correctable causes of anemia**, such as iron deficiency, **should be addressed before ESA initiation**)

Of importance, evidence from clinical trials does not support normalizing hemoglobin level with ESA treatment based on reported worse outcomes compared with lower targets, such as mortality and cardiovascular events. Therefore, most guidelines recommend a **hemoglobin target range of 10-12 g/dL** when **treating with ESAs** and **avoidance of hemoglobin concentrations >13 g/dL** for all adults.

For iron supplementation with ESA therapy, the **KDIGO guidelines** recommend that supplemental iron should be administered to maintain **serum ferritin levels >200 ng/mL** in individuals with **CKD stage 5 treated with hemodialysis** and **>100 ng/mL** in those with **NDDCKD stage 5 treated with peritoneal dialysis** with TSAT of >20% in all individuals with CKD

KDIGO guidelines do **not recommend** routine use of **iron supplementation** in patients with **TSAT >30%** or **serum ferritin >500 ng/mL** (>500 mg/L)

Since this 2012 guidelines, there has been recognition that many individuals who are in an **inflamed state** and exhibit a **hepcidin-induced blockade to iron** may have altered iron metabolism that results in seemingly **high serum ferritin (eg, >500 ng/mL)** but **low TSAT (eg, <15%)**, and thus, some guidelines suggest a **maximum serum ferritin level of 800 ng/mL**

When initiating treatment for iron deficiency, the multidisciplinary care team can help advise individuals and caregivers on the most appropriate **iron formulation**, **dosing**, and **administration schedule** based on the patient's needs and **dietary preferences** and address other comorbidities that may be present.

Oral agents are generally **ineffective for hemodialysis patients** and only **modestly effective in non–dialysis-dependent CKD**.

One exception is the **oral iron phosphate binder ferric citrate**, which is highly efficacious as an iron supplement in both patient populations. It is unclear why this oral iron agent is able to deliver iron to a greater extent than other forms of oral iron and without an apparently greater burden of side effects. **In dialysis patients**, when used as a phosphate binder, the drug will result in **significant increases in iron parameters** and **potentially improves ESA response**.

IV iron is generally **highly efficacious**. It is a **standard-of-care treatment for hemodialysis patients**.

Among these patients, the **most commonly used agent** in the United States is **iron sucrose**, usually administered at **50 to 100 mg/wk** as needed.

Other forms of IV iron are available, including iron dextran, ferric gluconate, ferumoxytol, ferric carboxymaltose, and iron isomaltoside. All these drugs are effective, and all probably carry some **minor risk for hypotension** or **hypersensitivity reactions**.

The major difference is that a larger amount of iron can be administered at a single administration with iron dextran, ferumoxytol, ferric carboxymaltose, and iron isomaltoside compared with iron sucrose and ferric gluconate.

In hemodialysis, access to the circulation is simple, by patients' dialysis lines, and the available drugs are well tolerated. There are 2 strategies for IV iron administration in these patients.

The first strategy is a **repletion approach**. **Testing** is performed for iron deficiency **every 1 to 3 months**. If iron deficiency is detected, a short course of IV iron is administered. **A typical course** would be **1,000 mg** of **iron sucrose** or **ferric gluconate** over **10 to 12 dialysis treatments**.

A second approach might be termed **maintenance therapy**. In anticipation of blood loss, a **weekly dose of IV iron** is administered.

There is **no great evidence to support one IV iron method over the other**. Given the marked difference between the mentioned uses of IV iron, other strategies could be used as well

In patients with **non–dialysis-dependent CKD** or those treated with **peritoneal dialysis**, *IV iron use is complicated by the need to establish IV access*.

Because of this, patients **may be initiated on oral iron agents** instead of or before treatment with IV iron. When IV iron is used in these patients, there should be appropriate observation for the development of hypotension or hypersensitivity reactions. In addition, in both these patient populations, *care should be taken to preserve veins* that may later be needed to create vascular access for hemodialysis.

One safety concern has been the possibility that **IV iron could make iron more available to bacteria and other microorganisms**. Because of this, we would suggest that IV iron **not** be administered **during acute infections**, especially when bacteremia is present.

Treatment of iron deficiency can always be safely postponed until after an infection is fully treated.

ESA Treatment

The first available was **epoetin alfa**, approved by the US Food and Drug Administration (FDA) in **1989** (only 5 years after cloning of the erythropoietin gene). Epoetin alfa is **similar to native erythropoietin** and is produced by recombinant DNA technology in massive cell cultures.

The second ESA developed was **darbepoetin alfa**, which differs from native erythropoietin by **5 amino acids** and by **additional carbohydrate content** that changes the pharmacokinetics, resulting in an **extended serum halflife** (approximately 2-3 times longer than epoetin alfa).

A third ESA is **methoxypolyethylene glycol-epoetin beta**, which has a **significantly increased serum halflife**. Less-frequent dosing is the expected advantage of an ESA with a longer half-life.

Table 1. Plasma Half-Lives of Erythropoietin Analogues

	Half-Life, h	
	Intravenous Administration	Subcutaneous Administration
Epoetin alfa	6.8	19.4
Darbepoetin alfa	25.3	48.8
Methoxy polyethylene glycol-epoetin beta	130	133

After initiating treatment with an ESA, Hb concentration should be **measured weekly** *until Hb stability and goals are achieved*.

A reasonable goal is an **increase of 1 g/dL** in Hb concentration **within the first month** of treatment. If the increase in Hb concentration is **excessive** (**>1 g/dL over 2 weeks**), the **ESA dose** should be **reduced by 25% to 50%**.

As Hb concentration increases, **blood pressure** response should be **monitored** because blood pressure will increase during treatment in some patients.

We recommend **checking iron status monthly** during initial ESA treatment. *As the Hb concentration increases, a large amount of iron is transferred from storage tissues to the developing erythron, and iron deficiency is frequently induced*. This may limit the effectiveness of ESA treatment.

The benefits of ESA treatment are clear; **avoidance of blood transfusions** and **improvement in anemia-related symptoms**. Before the availability of ESAs, blood transfusions were frequently required by dialysis patients. Before the availability of ESAs, Hb concentrations of hemodialysis patients were often <8 g/dL.

Frequent blood transfusion may lead to immune sensitization, which limit the ability of patients to undergo eventual kidney transplantation.

Case Reports > Am J Kidney Dis. 1989 Aug 14(2 Suppl 1):14-8.

Improvements in quality of life following treatment with r-HuEPO in anemic hemodialysis patients

Delano et al studied 37 hemodialysis patients treated with ESAs, with the mean Hct increasing from 19.8% to 31.5%. Eighty-four percent of patients experienced an improved sense of well-being. In addition, **improvements** were found in **appetite (81%)**, **sexual function (62%)**, **socializing (70%)**, and **sleep (68%).**

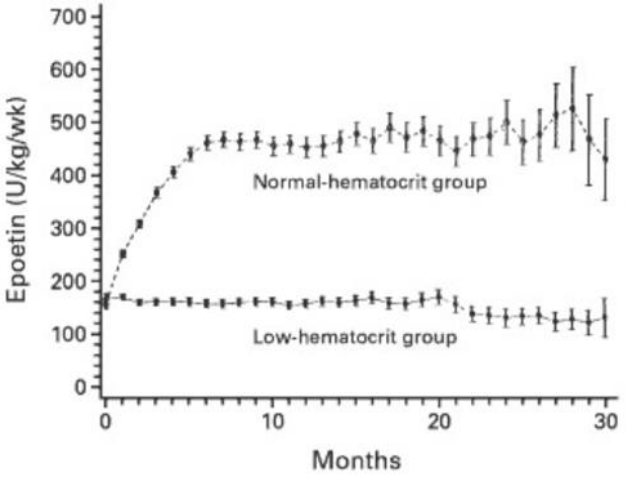
There are **4 major studies** that have helped definitively demonstrate the general lack of benefit and increased risk with full Hb concentration normalization.

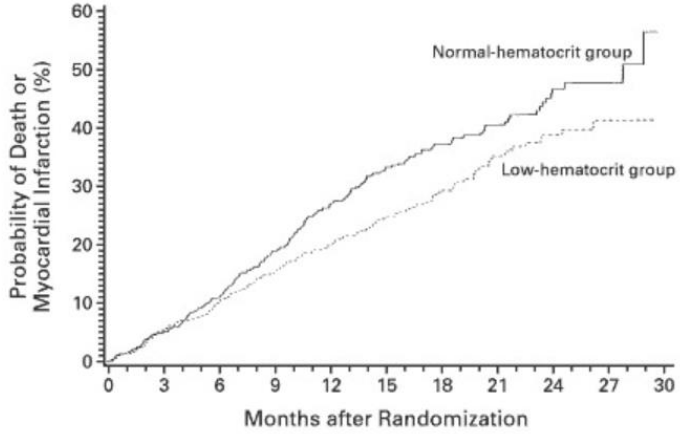
ORIGINAL ARTICLE

August 27, 1998
N Engl J Med 1998; 339:584-590
DOI: 10.1056/NEJM199808273390903

The Effects of Normal as Compared with Low Hematocrit Values in Patients with Cardiac Disease Who Are Receiving Hemodialysis and Epoetin

Besarab et al performed a randomized controlled trial of **1,233 hemodialysis patients**. **Epoetin alfa** was used in both groups to target an **Hct of 30%** or **42%** for **29 months**. At the end of the study, there was **no clear benefit of the higher Hct target**. However, there was a **strong trend toward increased mortality risk**



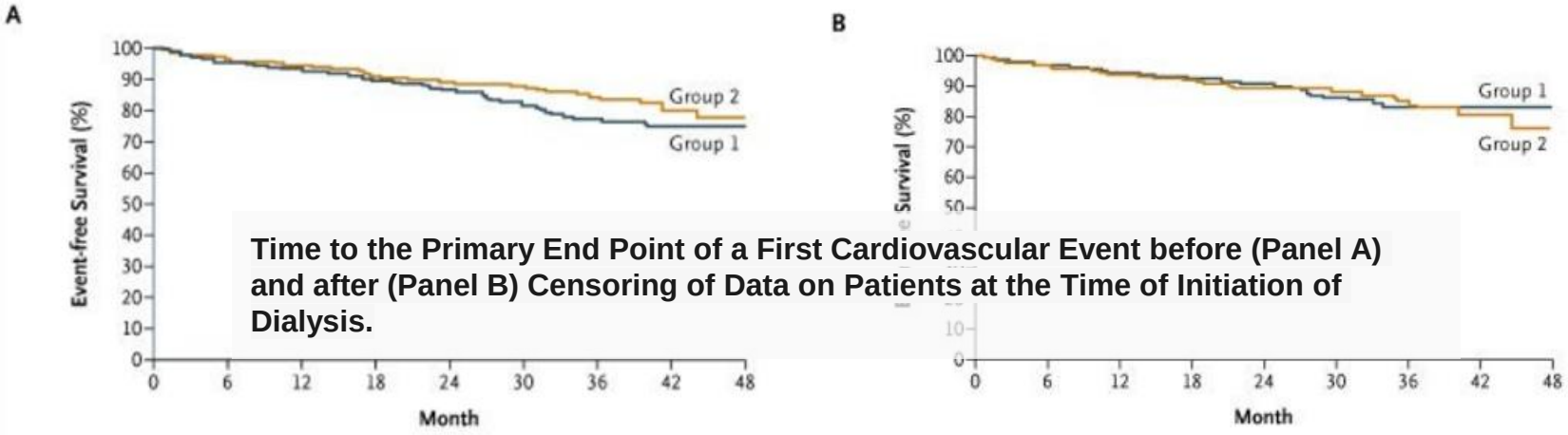


No. at Risk										
Normal hematocrit	618	540	476	415	353	259	186	124	69	26
Low hematocrit	615	537	485	434	391	292	216	131	80	20

Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

November 16, 2006

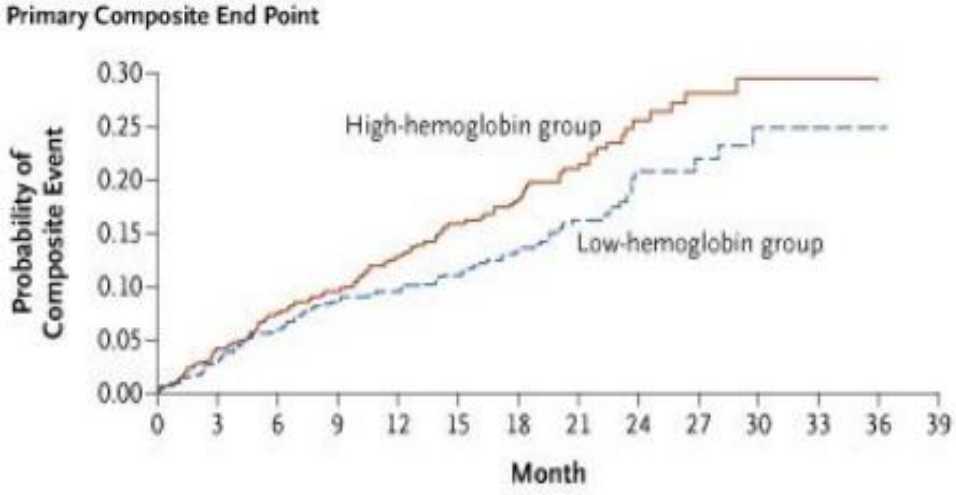
Drueke et al randomly assigned **603 patients** with **non–dialysis-dependent CKD** to ESA treatment to an **Hb goal** of **10.5 to 11.5 g/dL** or **13.0 to 15.0 g/dL** with **3 years** of follow-up. In this study, there was a finding of a **positive quality-of-life benefit**. Patients randomly assigned to the higher Hb target experienced improved general health and physical function scores. However, as in the Besarab et al study, there was a **non–statistically significant trend** to **increased risk for death** in the higher Hb target group

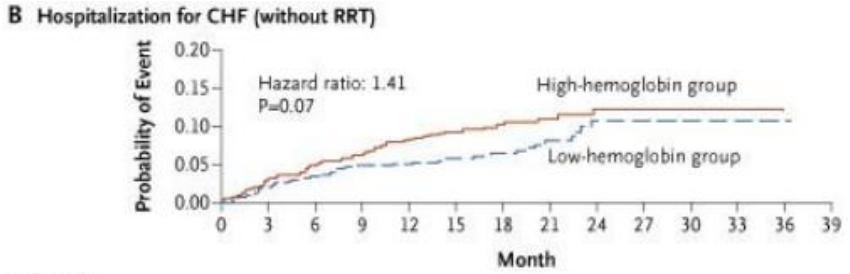


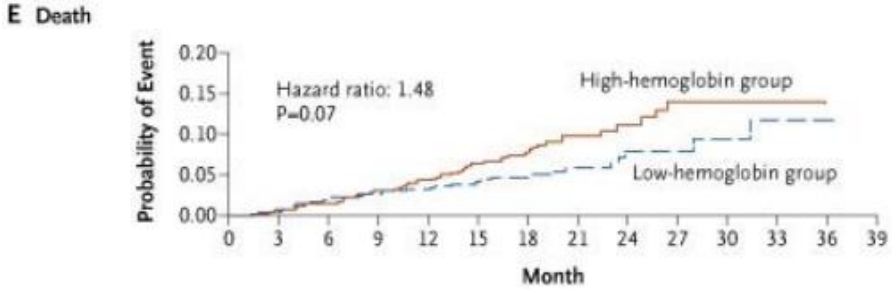
Time to the Primary End Point of a First Cardiovascular Event before (Panel A) and after (Panel B) Censoring of Data on Patients at the Time of Initiation of Dialysis.

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

Singh et al studied **1,432 patients** with **non–dialysisdependent CKD**, treated with **epoetin alfa** to a target Hb concentration of **13.5 g/dL** or **11.3 g/dL**. **Median** patient exposure was **16 months**. **No clinical benefits were demonstrable for the higher Hb group**. However, there were **significant safety signals**, including **increased risk for cardiovascular events** in a composite end point in the higher Hb group. The adverse result was driven by **increased risk for death** and **increased risk for hospitalizations for congestive heart failure.**



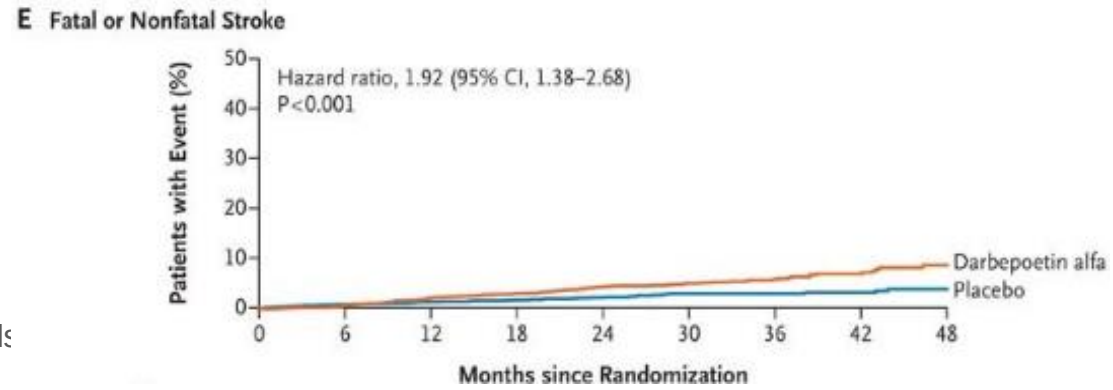




A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

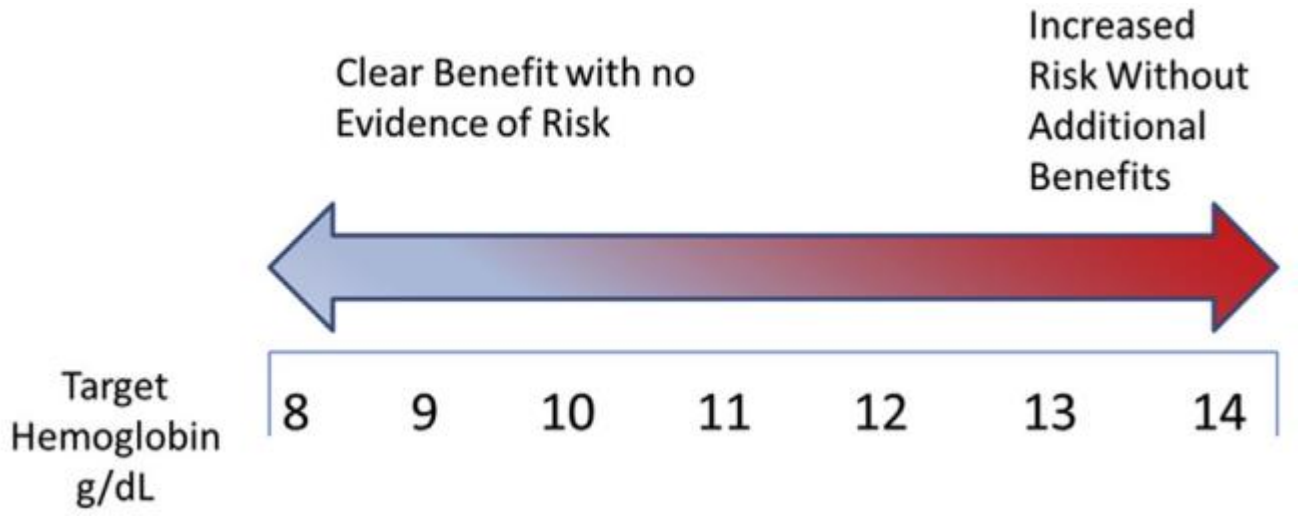
Pfeffer et al reported on a study of **4,038 patients** with **type 2 diabetes mellitus** and **non–dialysis-dependent CKD**. Participants were randomly assigned to **darbepoetin alfa** treatment to an **Hb target of 13 g/dL** (actual achieved median Hb was 12.5 g/dL) or placebo, with rescue darbepoetin treatment only as required. With a mean of **29.1 months** of follow-up, no substantial benefit of the treated group was found for any end point. The major safety risk identified was **increased risk for stroke** in the darbepoetintreated group (hazard ratio, 1.92; 95% confidence interval, 1.38-2.68).

The FDA recommends



Taken together, all acquired knowledge on ESA treatment in patients with CKD indicates clear benefits for patients with baseline Hb concentrations < 10 g/dL and moderate treatment goals.

In contrast, **risks** are present with extended treatment to **Hb targets > 13 g/dL**. It is less clear regarding the relative balance of benefit and risk in patients treated to Hb targets between 10 and 13 g/dL



It is probably true that as *Hb concentration exceeds 11 g/dL and approaches 13 g/dL, the potential benefits of treatment diminish and risks increase*.

Our recommendation is to target an **Hb concentration of 10 to 11.5 g/dL**, seeking to provide patients with the benefits of therapy while diminishing potential risks.

As in all medical treatment, **clinical judgment is needed**. Individualization of the Hb target may be considered based on patient characteristics.

For example, if a patient is asymptomatic with an active life and ESAtreated Hb concentration is 10 g/dL, there is little reason to increase the Hb concentration further. In contrast, for a younger active patient experiencing continued fatigue with an Hb concentration of 10.5 g/dL, treatment to a higher Hb concentration may be tried.

Table 2. Suggested Starting Dose for ESAs

	Hemodialysis	NDD-CKD
Epoetin alfa	50-100 U/kg, 3×/wk	50-100 U/kg every 1-2 wk
Darbepoetin alfa	0.45 μg/kg every wk	0.45 μg/kg every 2- 4 wk
Methoxy polyethylene glycol-epoetin beta	0.6 μg/kg, every 2 wk	0.6 μg/kg every 2-4 wk

Note: Epoetin alfa, US trademarks, Epogen, Procrit; darbepoetin alfa, US trademark, Aranesp; and methoxy polyethylene glycol-epoetin beta, US trademark, Mircera.

Box 4. KDIGO Guideline Recommendations for Initiation and Maintenance of ESAs

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*)

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*)

3.4.5: For all pediatric CKD patients, we suggest that the selection of Hb concentration at which ESA therapy is initiated in the individual patient includes consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (*2D*)

ESA MAINTENANCE THERAPY

3.5.1: In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD. (*2C*)

3.5.2: Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks. (*Not Graded*)

3.6: In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l). (*1A*)

3.7: In all pediatric CKD patients receiving ESA therapy, we suggest that the selected Hb concentration be in the range of 11.0 to 12.0 g/dl (110 to 120 g/l). (*2D*)

Step 3: **Management of anemia.** Once the status of iron deficiency has been assessed, the care team should help advise patients and caregivers on the most appropriate treatment regimen.

KDIGO Clinical Guidelines for the use of iron to treat iron deficiency anemia.

Patient Population	Threshold for Iron Therapy	Recommended Therapy
CKD with anemia not on ESA or iron	• An increase in Hb concentration without starting ESA treatment is desired • TSAT ≤30% and ferritin ≤500 ng/mL	• Trial of IV iron • Alternatively, non–dialysis-dependent CKD patients are recommended to initiate a 1-3 month trial of oral iron therapy
CKD with anemia on ESA but not iron	• An increase in Hb concentration* or decrease in ESA dose† is desired • TSAT ≤30% and ferritin ≤500 ng/mL	

Box 3. KDIGO Guideline Recommendations for When to Treat With Iron in CKD

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)

*Based on patient symptoms and overall clinical goals, including avoidance of transfusion, improvement in anemia-related symptoms, and after exclusion of active infection.

**Consistent with Recommendations #3.4.2 and 3.4.3.

***Based on patient symptoms and overall clinical goals including avoidance of transfusion and improvement in anemia-related symptoms, and after exclusion of active infection and other causes of ESA hyporesponsiveness.

Abbreviations: CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; IV, intravenous; Hb, hemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; ND, nondialysis; TSAT, transferrin saturation.

Choosing a Route of Administration for Iron Therapy‡

The choice of iron therapy should be based on severity of iron deficiency, availability of venous access, response and side effects from prior iron therapy, patient compliance, and cost.

	Oral Iron Therapy	Intravenous Iron Therapy
Select Advantages	• Most are available over the counter although some require a prescription • Convenient • Inexpensive • Effective when intestinal absorption is not impaired	• Fast repletion of iron stores • Effective even when intestinal absorption is impaired
Select Disadvantages	• Slower iron repletion due to limited daily absorption • Dose-dependent gastrointestinal side effects (nausea, vomiting, abdominal pain, constipation) • Uptake impaired in the setting of disease**	• Requires HCP administration, with associated increased costs • Potential for iron overload and oxidative stress • Potential for anaphylactic reactions with dextran-containing formulations

Newer Oral Iron Agents

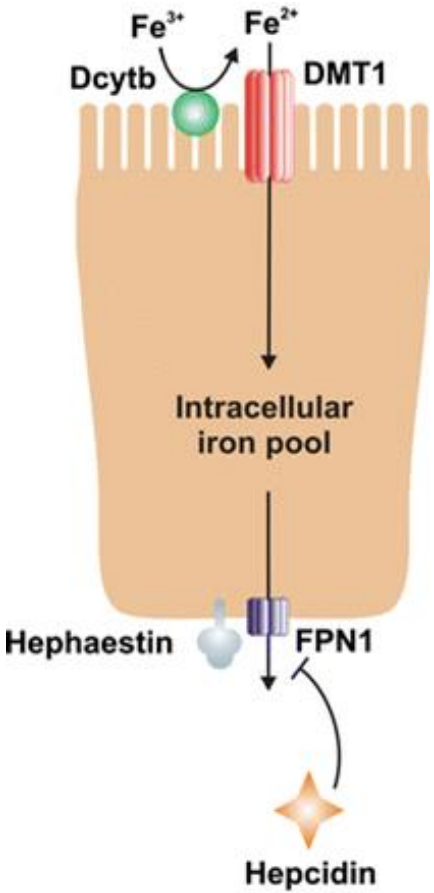
Although oral iron has been available for many years, its use has been limited in part by **gastrointestinal side effects**, including dyspepsia and constipation

Some of the **dyspepsia** is thought to arise from gastric acid interacting with the **ferrous form (ie, Fe2+)**, which is more basic than **ferric iron (Fe3+)**.

Conversion of Fe2+ to Fe3+ by gastric acid facilitates its absorption even though the **Fe3+ must be reduced back to Fe2+ by ferrireductase** (duodenal cytochrome B [DCYTB]) before absorption by the **divalent metal transporter 1 (DMT1) channel** in the **small bowel**

That is the rationale for administering Fe2+ supplements on an empty stomach when gastric acid will not be buffered by food.

Novel iron formulations use Fe3+ , which does not require administration on an empty stomach and causes less dyspepsia, and the bioavailability of which is not decreased by agents that decrease stomach acidity such as H2 blockers and proton pump inhibitors.



Ferric Citrate

Ferric citrate is a novel oral iron preparation in which **Fe3+** is complexed to a polymer of tricarboxylic acid (citrate) and water.

Originally introduced as a **phosphate binder**, ferric citrate subsequently obtained US Food and Drug Administration (FDA) approval as a treatment for **irondeficiency anemia in patients with CKD without KRT.**

Ferric citrate was compared with placebo in 232 patients with CKD and iron-deficiency anemia who were not receiving KRT in whom therapy with iron salts such as ferrous sulfate had failed. A substantially higher percentage of those treated with ferric citrate (**52.1%**) versus placebo (**19.1%**; $P < 0.001$) exhibited the **primary endpoint of a 1-g/dL increase in Hb** level at any time during the **16-week randomization period**.

A randomized trial of **60 patients with CKD who were not receiving KRT** found ferric citrate to be more effective in increasing **TSAT and ferritin level** at **12 weeks**. However, the ferric citrate group was prescribed 1,260 mg of elemental iron per day, compared with 195 mg/d in the ferrous sulfate group, so the differences may not be surprising even accounting for the 3- to 4-fold lower bioavailability of ferric iron.

Hb levels, as well as a number of other parameters (fibroblast growth factor 23 [FGF-23], intact parathyroid hormone, and erythroferrone), were not significantly different between the 2 groups

In patients with **CKD undergoing dialysis**, ferric citrate is indicated for phosphate binding but is used on an offlabel basis as an iron supplement. A phase 3 randomized controlled trial of **ferric citrate** versus **sevelamer carbonate** and/or **calcium acetate** in 441 prevalent HD recipients over 1 year demonstrated **higher median ferritin levels in the ferric citrate arm**, with an average mean difference of 282 ng/mL ($P < 0.001$). **TSAT increased** in the ferric citrate arm by 9.5% ($P < 0.001$). **ESA dose, IV iron requirements, and Hb level were all favorably** affected in the ferric citrate arm to a statistically significant degree, with no increase in adverse events.

Ferric citrate reduced serum phosphate levels among patients with CKD without KRT who had increased baseline serum phosphate concentrations (≥4.5 mg/dL), but **did not reduce serum phosphate levels** among patients with baseline serum **phosphate concentrations within the population reference range**. Ferric citrate **reduced FGF-23 concentrations** to a statistically significant degree ($P < 0.001$) versus placebo.

Ferric Maltol

Ferric maltol consists of one Fe^{3+} ion complexed to 3 maltol moieties. This structure protects the Fe^{3+} ion while passing through the stomach and provides high bioavailability when the complex is dissociated at the enterocyte, where Fe^{3+} is reduced to Fe^{2+} and then absorbed via DMT1. As such, a lower dose of iron has been shown to be efficacious with this agent: 30 mg twice daily.

In a placebo-controlled study of 168 patients with CKD without KRT studied for 16 weeks, ferric maltol increased Hb level by 0.5 ± 0.122 g/dL, compared with a change of -0.02 ± 0.165 g/dL in the placebo arm ($P = 0.0149$)

Table 1. Oral Therapies for Iron Repletion in CKD

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]

Based on information from Lexicomp.[63] Abbreviation: CKD, chronic kidney disease.
[a]Based on daily iron repletion dose.
[b]Based on recommended dose.

Newer IV Iron Agents

The number of IV iron agents has increased steadily in the past few years. Older agents such as iron dextran (1974), **sodium ferric gluconate** (1999), and **iron sucrose** (2000) have been joined by ferumoxytol in 2009 and, more recently, ferric carboxymaltose and ferric derisomaltose (also known as iron isomaltoside). Concerns about oxidative stress induced by rapid iron release, manifested by adverse reactions including cardiovascular events, motivated the development of newer compounds

Modern formulations contain iron **enveloped by a carbohydrate moiety** that **minimizes iron release within the circulation**. The newer agents have **reduced rates of anaphylaxis** compared with **iron dextran**, but ongoing concerns remain surrounding **hypersensitivity reactions, cardiovascular events**.

Thank you for listening