KDIGO 2025 CLINICAL PRACTICE GUIDELINE FOR ANEMIA IN CHRONIC KIDNEY DISEASE (CKD)

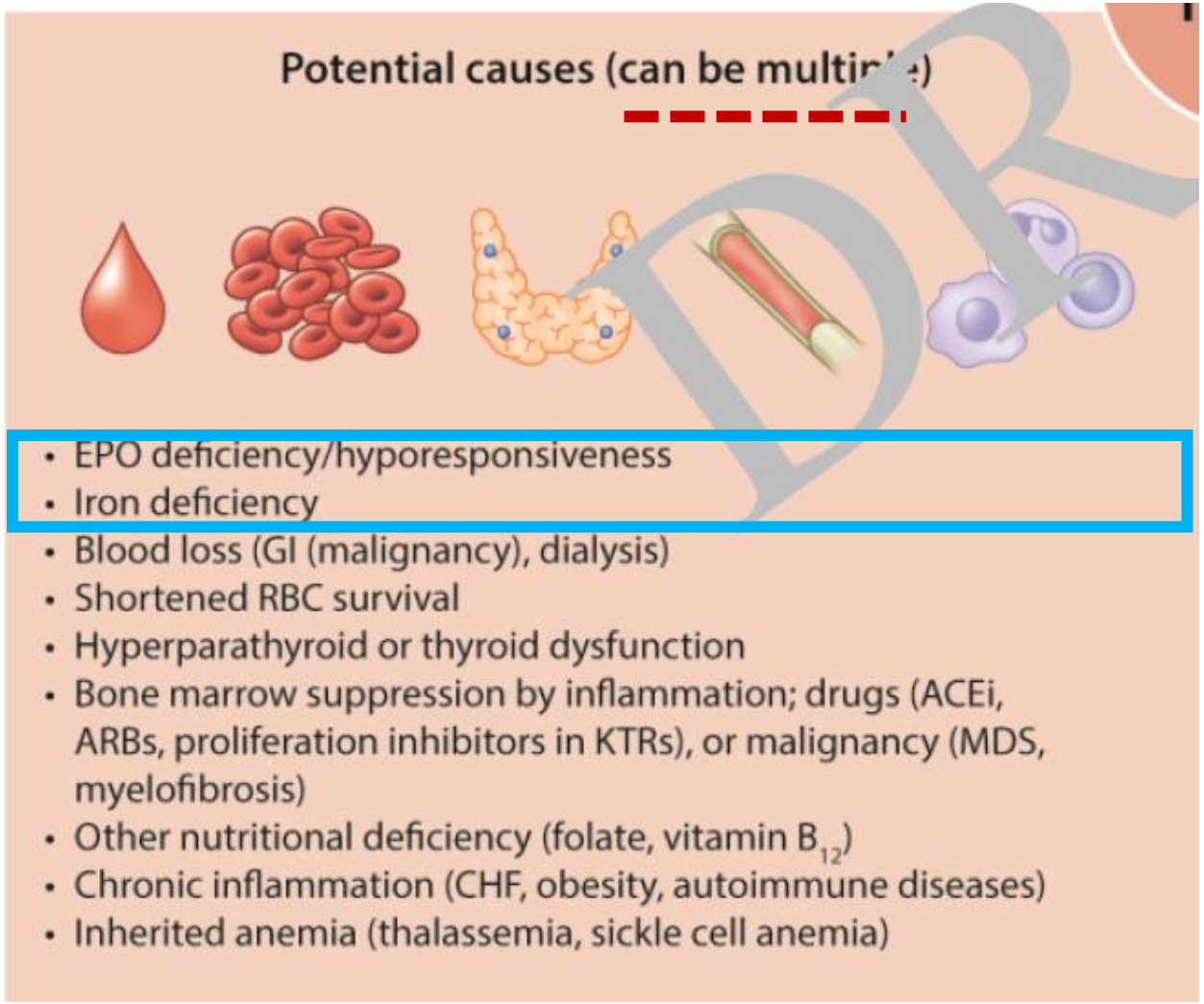
PUBLIC REVIEW DRAFT
NOVEMBER 2024

เนื้อหา : เน้น ผู้ป่วย HD

- การประเมินผู้ป่วย เน้น TSAT, Serum Ferritin (SF)
- การให้ IV iron เน้น iron sucrose (Venofer)
- การให้ ESA เน้น ESA-α

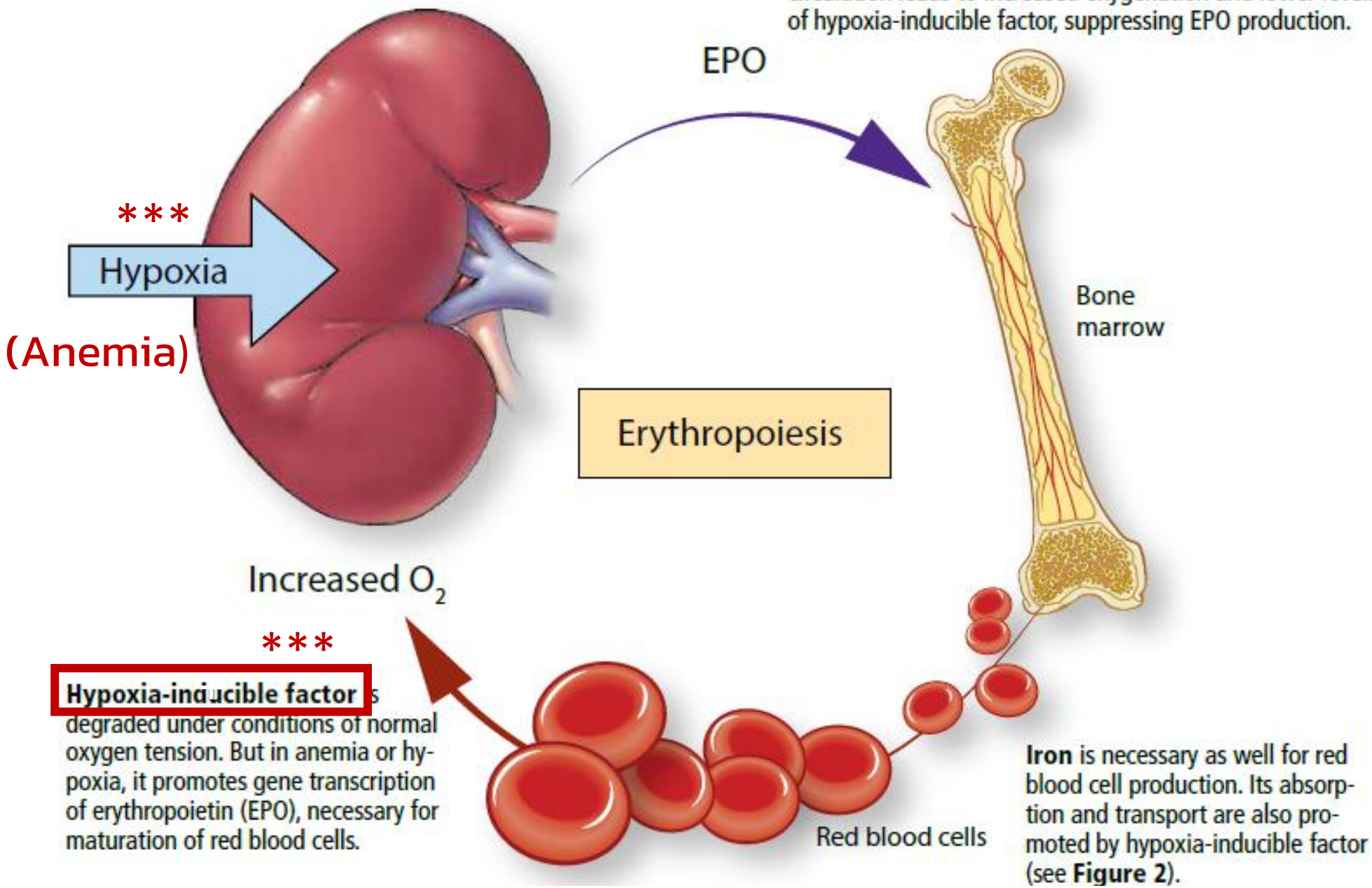
Chapter 1. Diagnosis and Evaluation of Anemia in CKD

1.1 anemia in CKD



Erythropoiesis: A homeostatic system

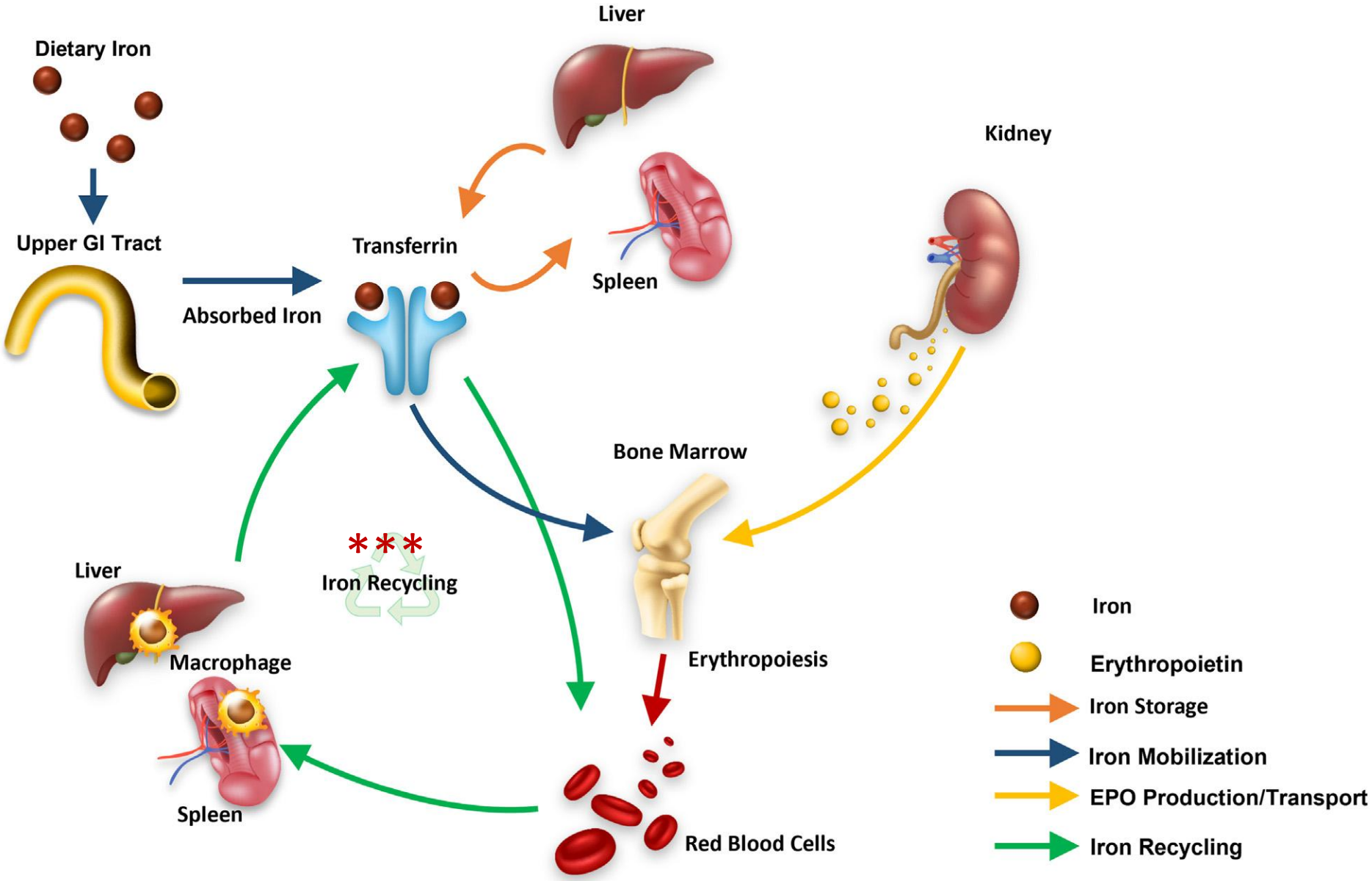
Erythropoietin (EPO) promotes production of mature red blood cells in the bone marrow. More red blood cells in the circulation leads to increased oxygenation and lower levels of hypoxia-inducible factor, suppressing EPO production.



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 (see **Figure 2**).

Overview of normal iron homeostasis



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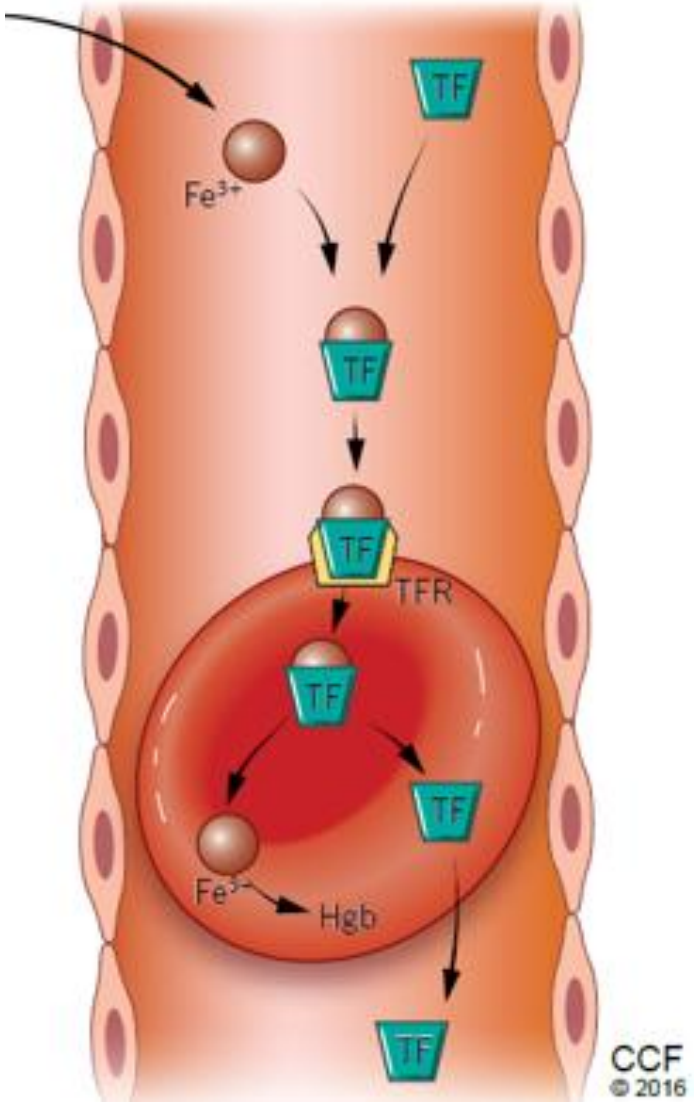
Transferrin (TF) vs Serum Ferritin (SF)



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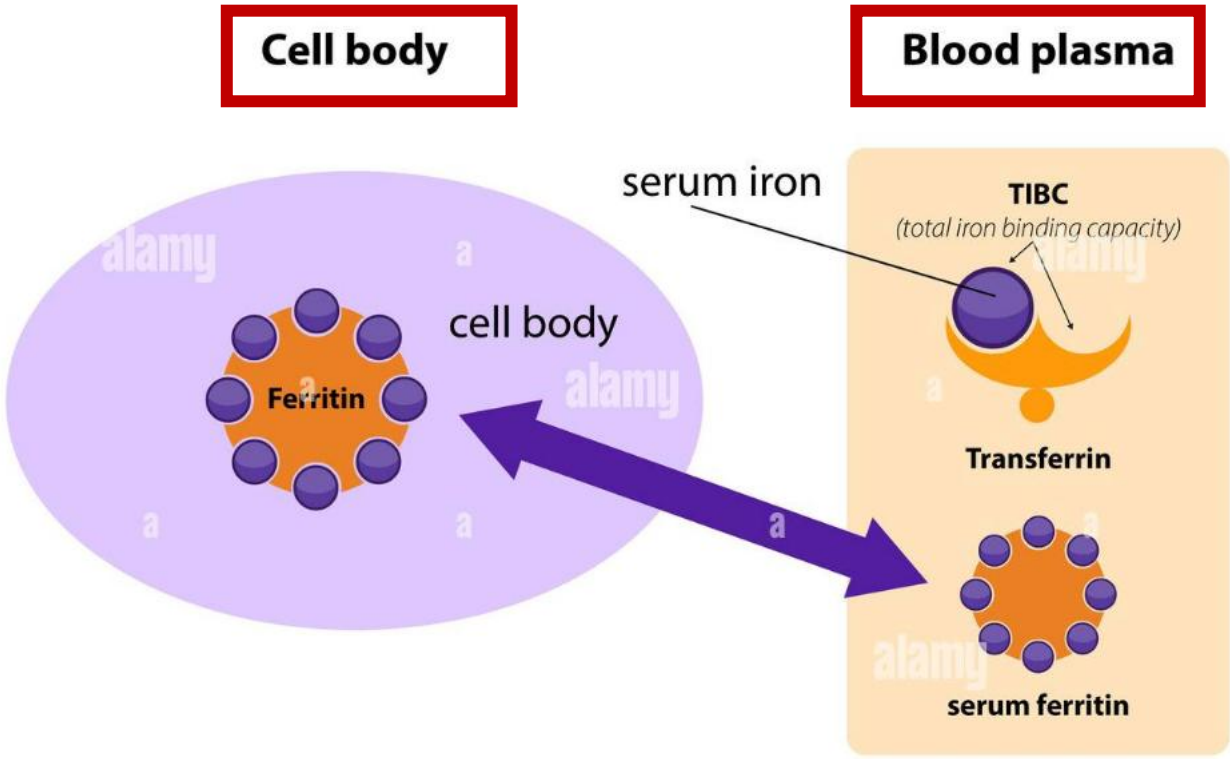


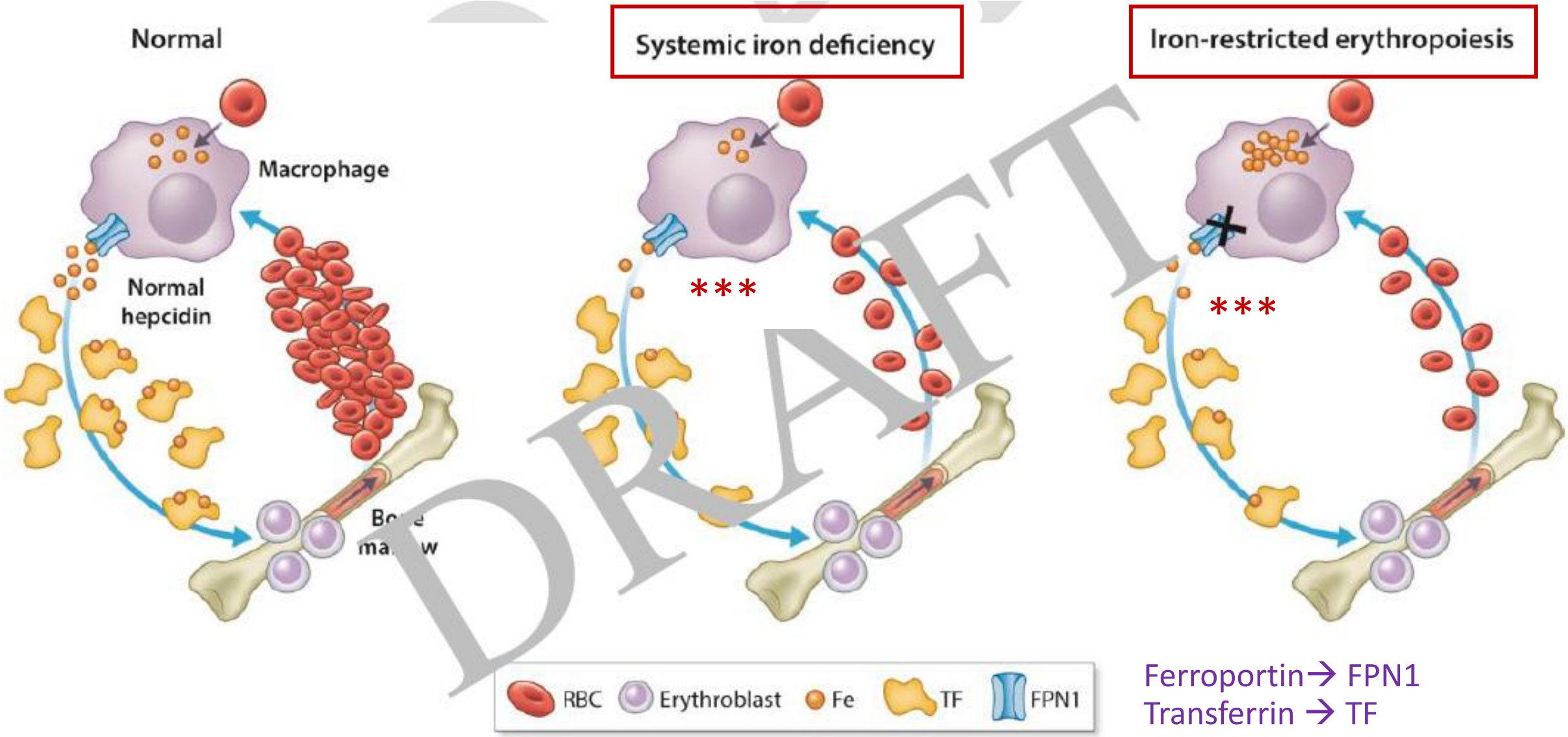
2 Indices of Iron Status

- Transferrin saturation (TSAT) : reflecting iron availability in the circulation
- SF : reflecting iron storage.

2 States of ID

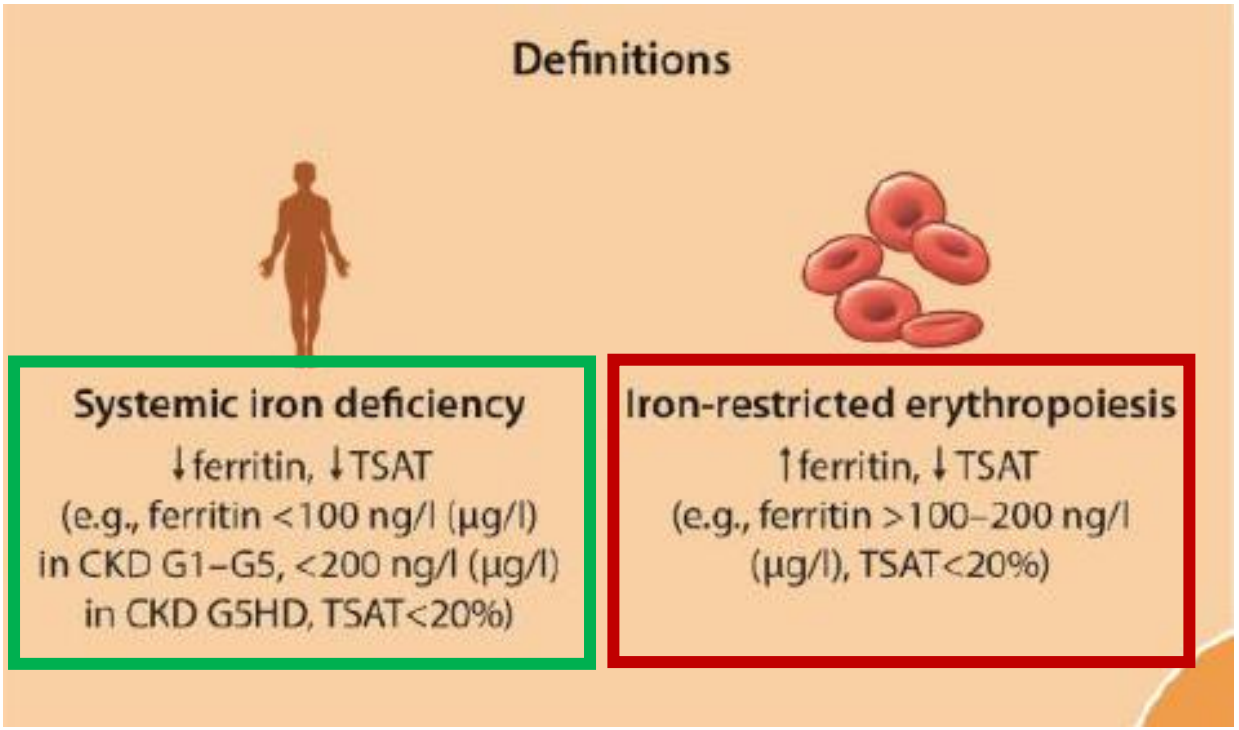
- systemic (or absolute) ID: a low TSAT and low SF : reflecting decreased iron both in the circulation and in tissue stores.
- iron-restricted erythropoiesis or functional ID: a low TSAT and high SF : reflecting limited available iron for erythropoiesis despite adequate iron stores.

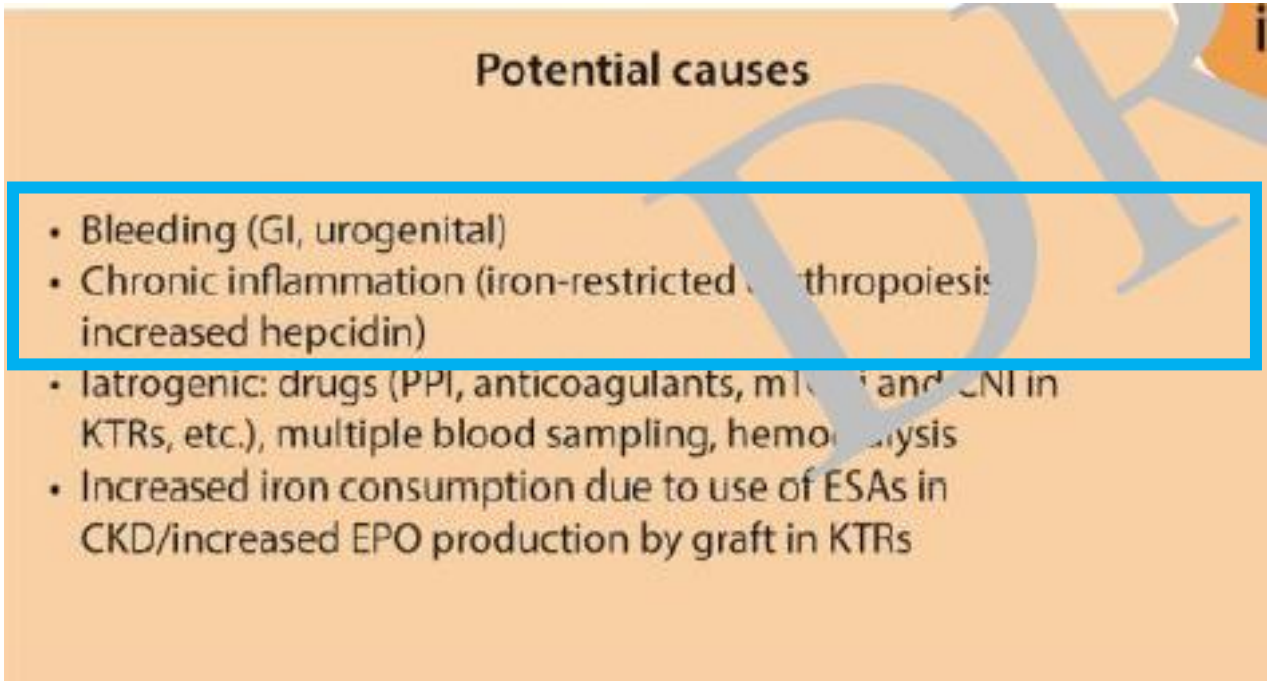
Systemic movement of iron in different iron-related states



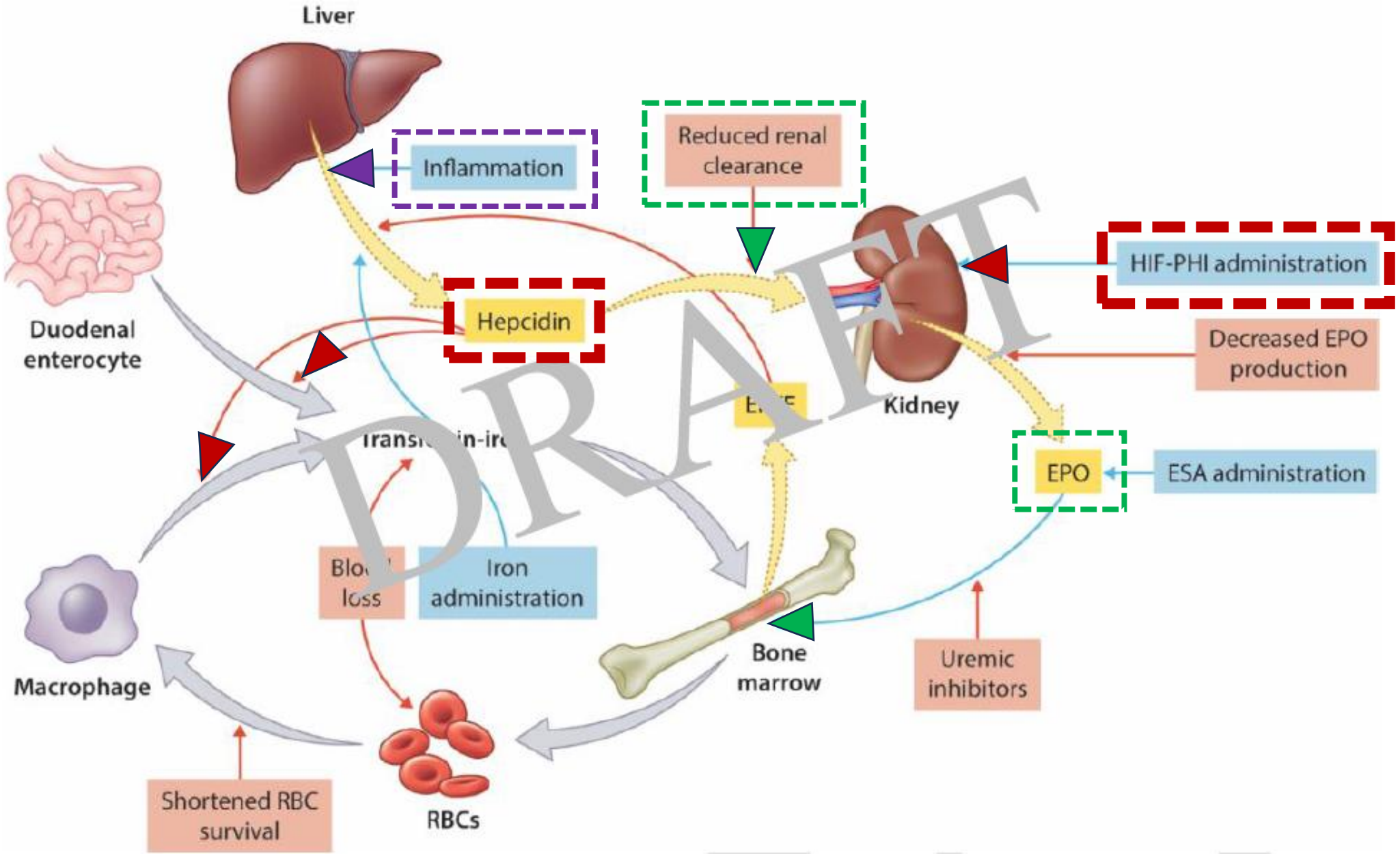
Ferroportin→ FPN1
Transferrin → TF

1.2. Iron deficiency in CKD (absolute & functional)





Mechanisms underlying anemia of CKD



Hepcidin: increased due to

- Inflammatory state (mainly through IL-6)
- Reduced kidney clearance
- reduced EPO and erythroferrone (ERFE) levels

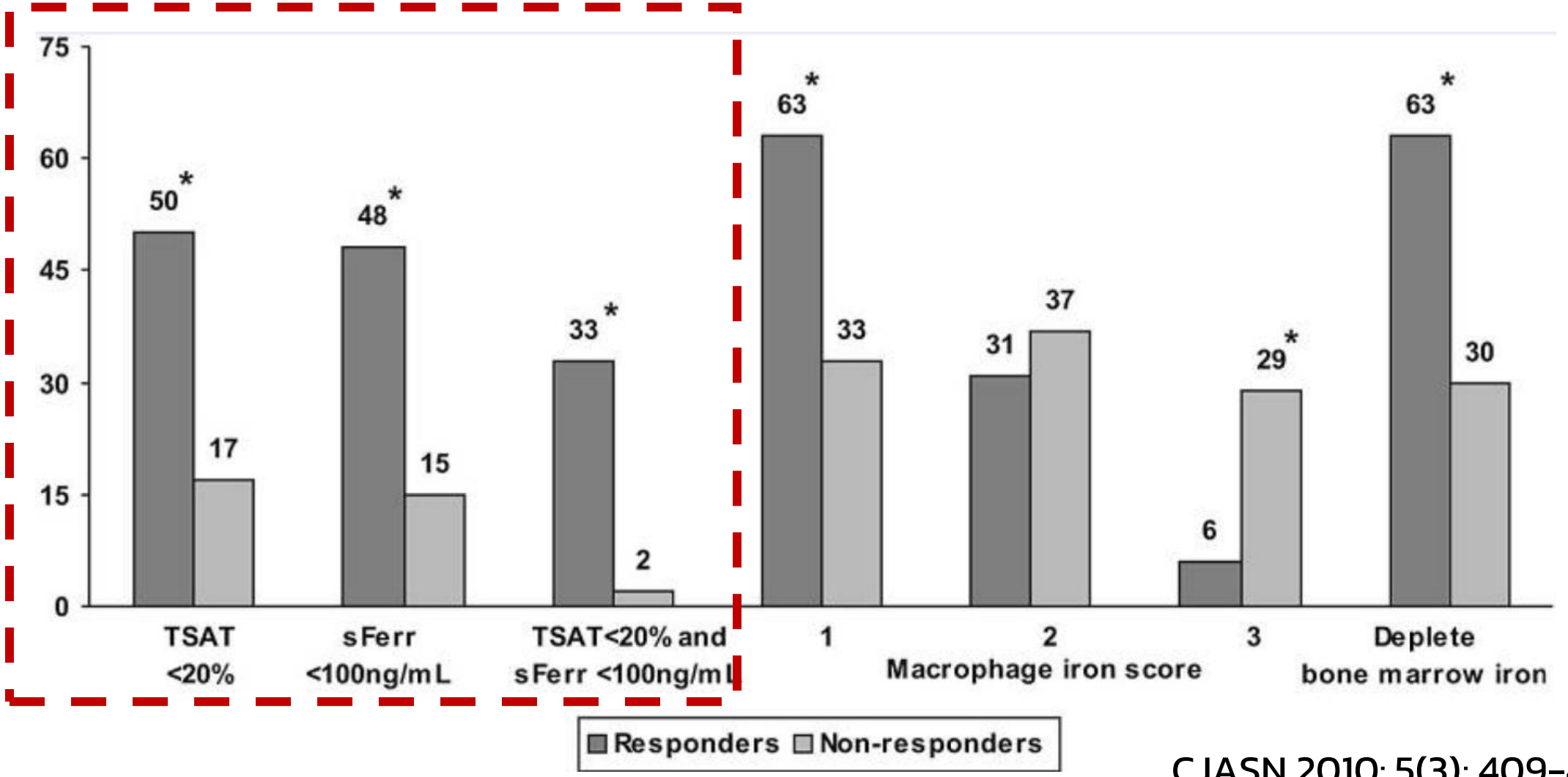
  NB: ERFE is produced by erythroblasts in response to EPO and decreases hepatic expression of hepcidin.

TSAT & Serum Ferritin

- SF <100–200 µg/l or TSAT<20% do not correlate well with BM iron or Hb response to iron in people with CKD.
- In recent years, more focus has been placed on TSAT rather than SF, as the latter only indicates systemic iron deficiency when levels are extremely low.

- Practice Point 1.2.3: In people with CKD, anemia, and SF <45 µg/l, consider referral to gastroenterologists/ gynecologists/ urologists to identify the cause of blood loss

% of BM iron deficit, according to the response to 1000 mg of iv iron (≥1-g/dl increase in Hb) in 100 non-dialysis patients with CKD



CJASN 2010: 5(3); 409-416

Chapter 2. Use of Iron to Treat ID and Anemia in CKD

- Recommendation 2.1: In people with anemia and CKD treated with HD, we suggest initiating iron therapy if SF ≤500 ng/ml and TSAT ≤30% (2D).
- Recommendation 2.2: In people with anemia and CKD G5HD in whom iron therapy is being initiated, we suggest using iv iron rather than oral iron (2D).

- Practice Point 2.1: In people with CKD G5HD in whom iron therapy is being initiated, administer iv iron using a proactive approach to maintain stable iron status.
- Practice Point 2.2: In people with CKD treated with iron, it is reasonable to withhold iron if SF ≥700 ng/ml or TSAT ≥40%.
- Practice Point 2.4: In people with CKD treated with iv iron, the choice between different formulations is guided by cost, individual preference, and recommended dosing schedules.

IV Iron in Patients with HD: PIVOTAL Trial (1)

We conducted this prospective, randomized, open label, blinded end-point,14 controlled trial at 50 sites in the UK

Adults with HD had been initiated no < 12 mo before the initial screening visit, who had a SF < 400 µg/l and a TSAT < 30%, and who were receiving an ESA were eligible to participate.

IV Iron in Patients with HD: PIVOTAL Trial (2)

- high-dose group, 400 mg of iron sucrose / mo, to be administered IV, cutoff limits (SF of 700 µg/l or a TSAT of 40%)
- low-dose group received a monthly dose of 0 mg to 400 mg of iron sucrose as required to maintain a minimum target SF of 200 µg/ l and a TSAT of 20%,
- Clinicians selected the dose of ESA that would be sufficient to maintain a Hb of 10 to 12 g/dL

IV Iron in Patients with HD: PIVOTAL Trial (3)

- Trial End Points The primary end point was the composite of non-fatal MI, non-fatal stroke, hospitalization for HF, or death from any cause, assessed in a time-to-first-event analysis;
- The first secondary end point consisted of the components of the primary end point, including first and repeat events, which were analyzed as recurrent events.
- Other secondary efficacy end points included death from any cause;

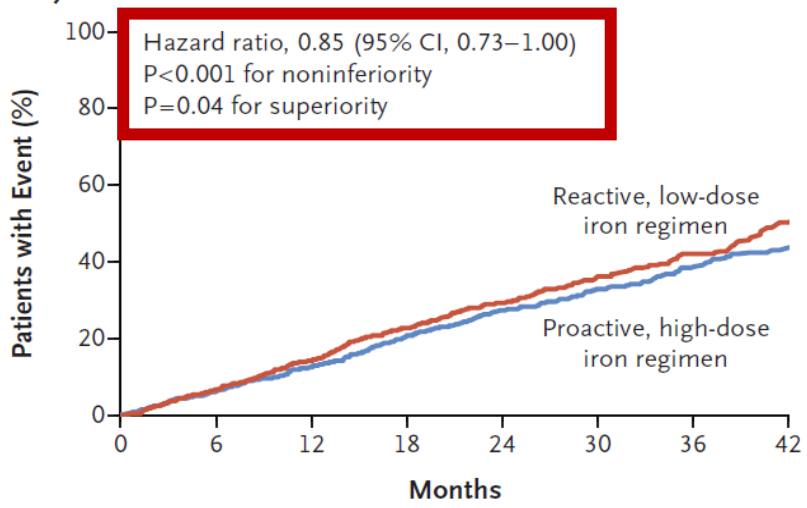
PIVOTAL Trial : Results (1)

The median monthly dose of iron was 264 mg in the high-dose group and 145 mg in the low-dose group;

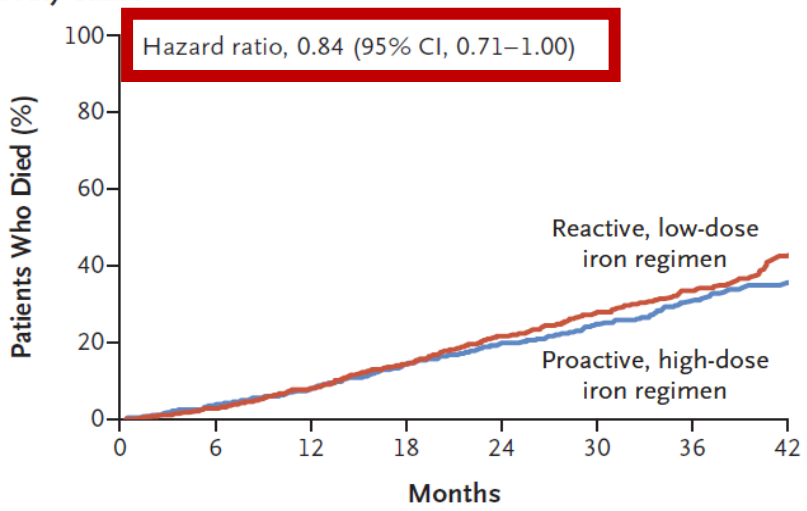
The median monthly dose of ESA was 19.4% lower in patients receiving the high-dose regimen (29,757 IU / mo) than in patients receiving the low-dose regimen (38,805 IU / mo)

PIVOTAL Trial : Results (2)

A Primary Efficacy End Point



B Death from Any Cause



C Primary End-Point Components as Recurrent Events

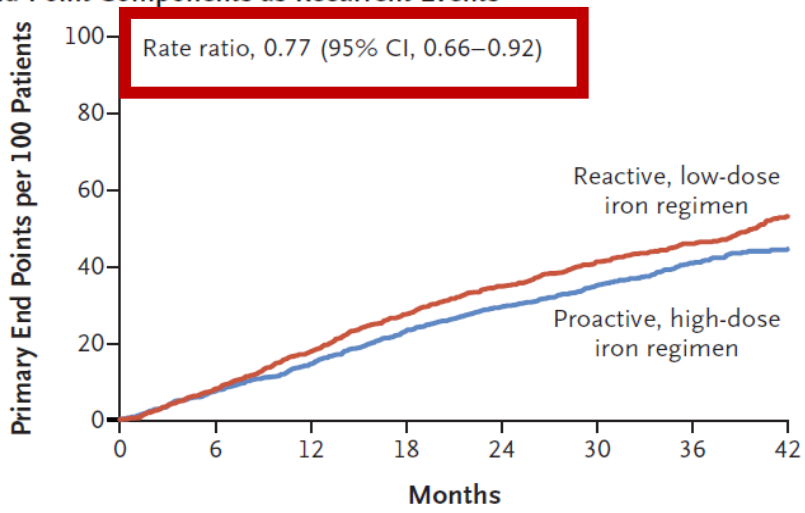


Table 3. Serious Adverse Events.*

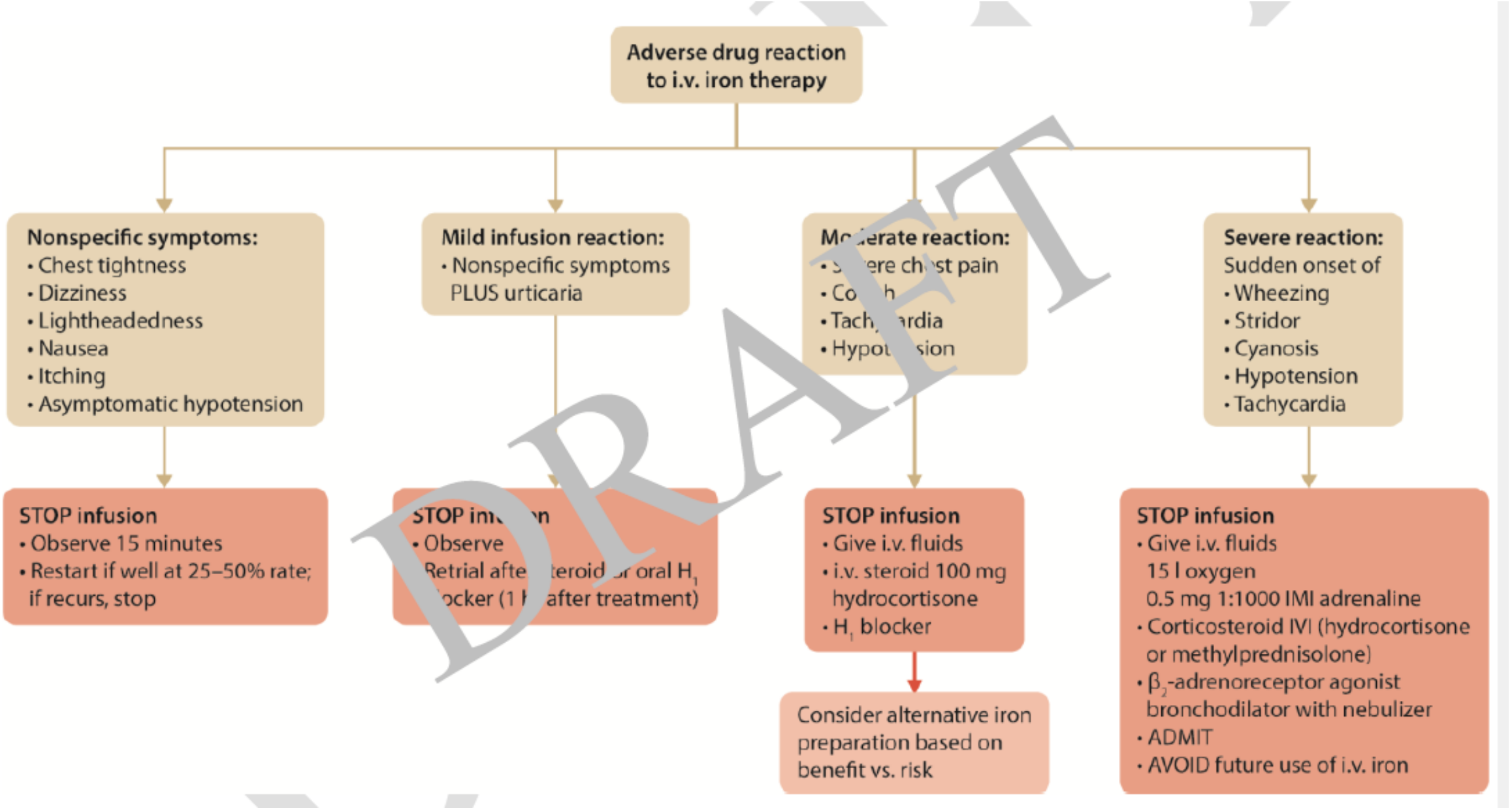
Event	Proactive, High-Dose Iron Regimen (N=1093)	Reactive, Low-Dose Iron Regimen (N=1048)
	no. of patients with event (%)	
Any serious adverse event	709 (64.9)	671 (64.0)
Infection or infestation	341 (31.2)	327 (31.2)
Injury, poisoning, or procedural complication	220 (20.1)	224 (21.4)
Cardiac disorder	154 (14.1)	165 (15.7)
General disorder or administration-site condition	159 (14.5)	129 (12.3)
Respiratory, thoracic, or mediastinal disorder	107 (9.8)	121 (11.5)
Gastrointestinal disorder	111 (10.2)	110 (10.5)
Surgical or medical procedure	117 (10.7)	102 (9.7)
Metabolism or nutrition disorder	95 (8.7)	116 (11.1)
Vascular disorder	90 (8.2)	104 (9.9)
Nervous system disorder	98 (9.0)	82 (7.8)
Renal or urinary disorder	34 (3.1)	48 (4.6)
Investigation†	33 (3.0)	44 (4.2)
Musculoskeletal or connective-tissue disorder	28 (2.6)	37 (3.5)
Neoplasm, benign, malignant, or unspecified, including cysts and polyps	27 (2.5)	27 (2.6)
Psychiatric disorder	21 (1.9)	26 (2.5)
Hepatobiliary disorder	23 (2.1)	18 (1.7)
Skin or subcutaneous-tissue disorder	22 (2.0)	14 (1.3)
Blood or lymphatic system disorder	14 (1.3)	17 (1.6)

Practice Point 2.8: In people with CKD treated with iron, consider temporarily suspending iron therapy during systemic infection.

Practice Point 2.9: In people with CKD treated with iv iron, considerations pertaining to hypersensitivity reactions to iv iron include the following:

- IV iron should only be administered if there is capability to manage acute hypersensitivity and hypotensive reactions,
- Test doses of iv iron are not usually required, because lack of response does not predict the risk of hypersensitivity.

Practice Point 2.10: The suggested management of reactions to iv iron



Iron Sucrose IV: dosage

- Loading dose: 100 mg iv ทุกสัปดาห์ รวม 10 ครั้ง และไม่แนะนำให้ติดต่อกันเกิน 2 ครั้งต่อเนื่องกัน
- Maintenance dose: 100–200 mg iv ต่อเดือน หาก serum ferritin < 500 ng/ml
- หยุดการให้เหล็ก เมื่อ TSAT > 40% หรือ SF > 800 ng/ml

Chapter 3. Use of ESAs

Recommendation 3.1.1: In people with anemia and CKD in whom correctable causes of anemia have been addressed, we suggest using an ESA rather than a HIF-PHI as first-line therapy for treatment of anemia

Recommendation 3.2.1: In people with anemia and CKD G5D treated with HD or PD, we suggest initiation of ESA therapy when the Hb is ≤9.0–10.0 g/dl (2D)

- People who are at higher risk for adverse events from ESA treatment, such as those with a recent stroke or recurrent HD access thrombosis, may be more likely to prefer ESA initiation when Hb is closer to 9.0 g/dl , thus delaying or potentially avoiding ESA treatment
- Recommendation 3.3.1: In adults with anemia and CKD treated with an ESA, we recommend targeting a Hb level below 11.5 g/dl (1D).

Four randomized controlled trials of hemoglobin-raising in chronic kidney disease

	NHCT[52]	CHOIR[53]	CREATE[54]	TREAT[55]
Population	Patients with chronic heart failure and end-stage renal disease on dialysis	Chronic kidney disease	Chronic kidney disease	Chronic kidney disease with diabetes
Hemoglobin target	10 vs 14 g/dL	13.5 vs 11.3 g/dL	> 13 vs 11 g/dL	> 13 vs 9 g/dL
Target achieved?	No	No	Yes	No
Primary outcomes	Time to death or first myocardial infarction	Composite of death, myocardial infarction, hospitalization for chronic heart failure, stroke	Time to first cardiovascular event	Composite of death or a cardiovascular event and death or end-stage renal disease
Risks with higher hemoglobin level	Trend toward increased risk of primary outcome resulted in early study interruption	Increased risk of primary outcome	Trend toward risk increase that was nonsignificant: no benefits	No risk increase or reduction
Other results	Higher rate of thrombosis in high-target group		Improved quality of life	Higher rate of stroke

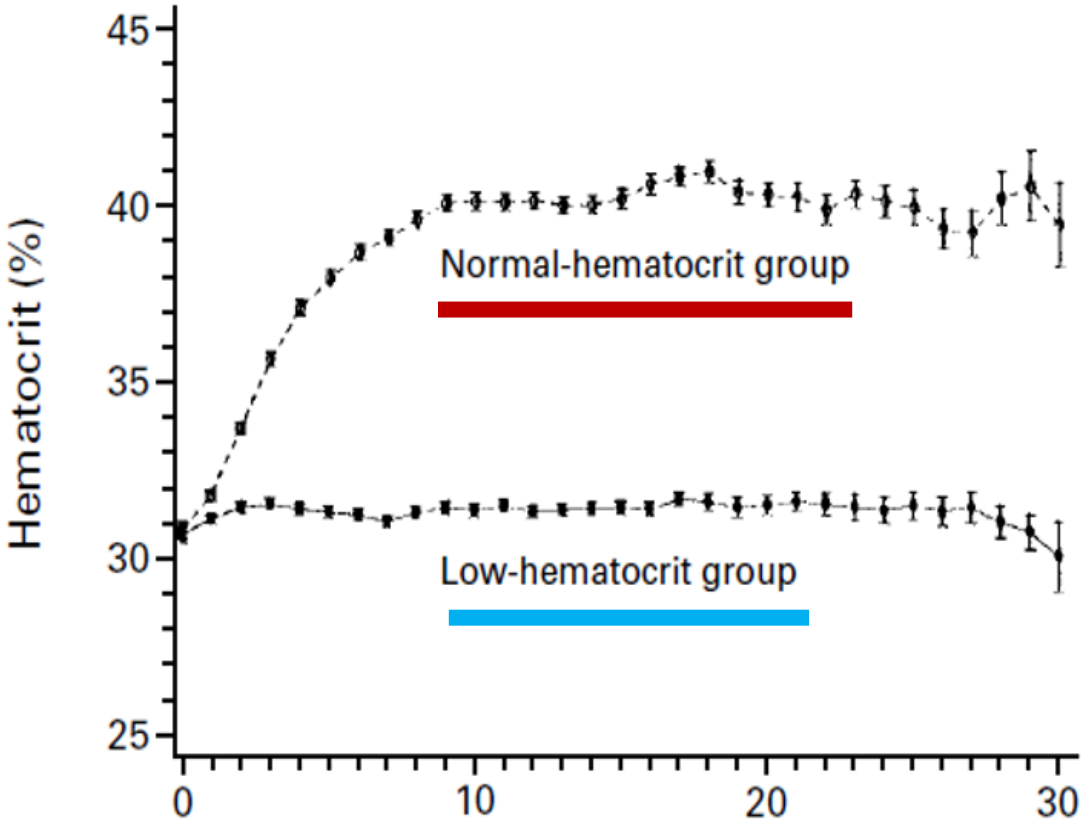
NHCT = Normal Hematocrit Study,[52] CHOIR = Correction of Hemoglobin and Outcomes in Renal Insufficiency trial,[53] CREATE = Cardiovascular Risk Reduction by Early Anemia Treatment trial,[54] TREAT = Trial to Reduce Cardiovascular Events With Aranesp Therapy[55]

NHCT: Methos

We studied 1,233 patients with clinical evidence of CHF or IHD who were undergoing HD: 618 patients were assigned to receive increasing doses of epoetin to achieve and maintain a hct of 42% , and 615 were assigned to receive doses of epoetin sufficient to maintain a hct of 30% throughout the study. The primary end point was the length of time to death or a first nonfatal MI.

(N Engl J Med 1998;339:584-90.)

NHCT: Results



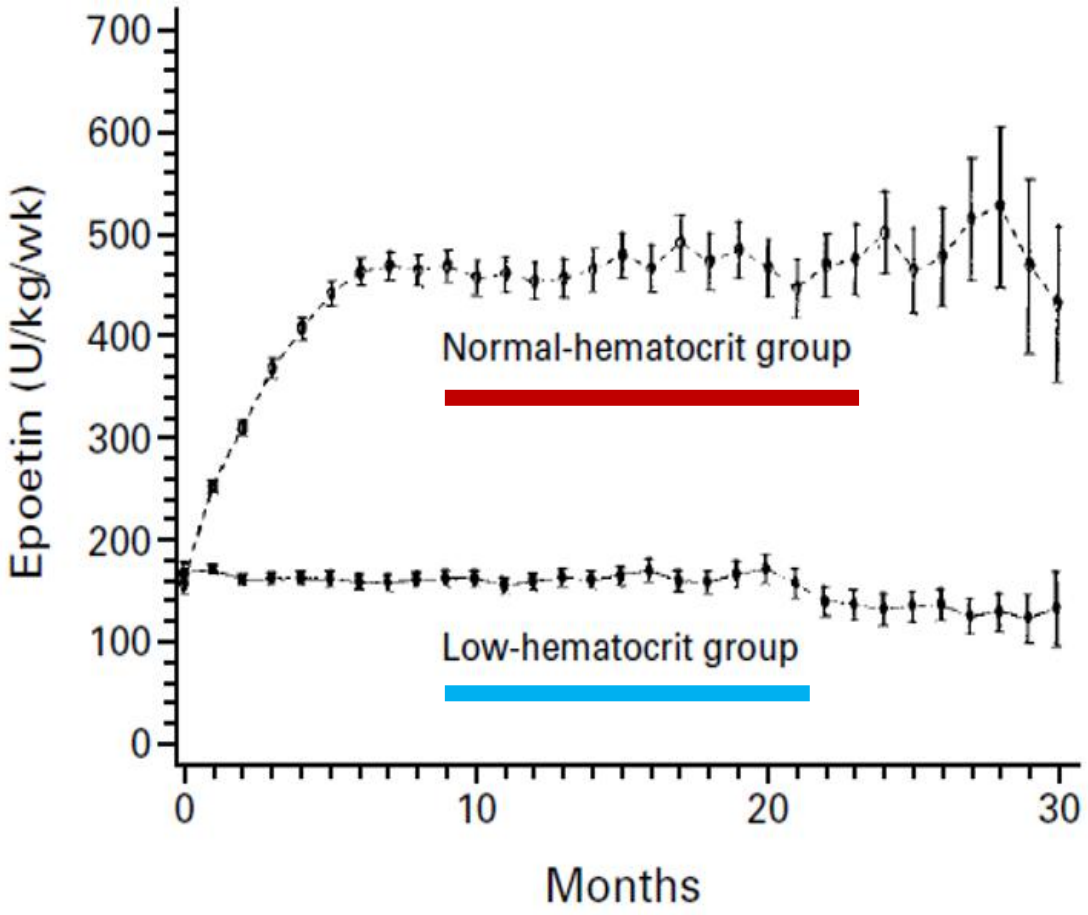
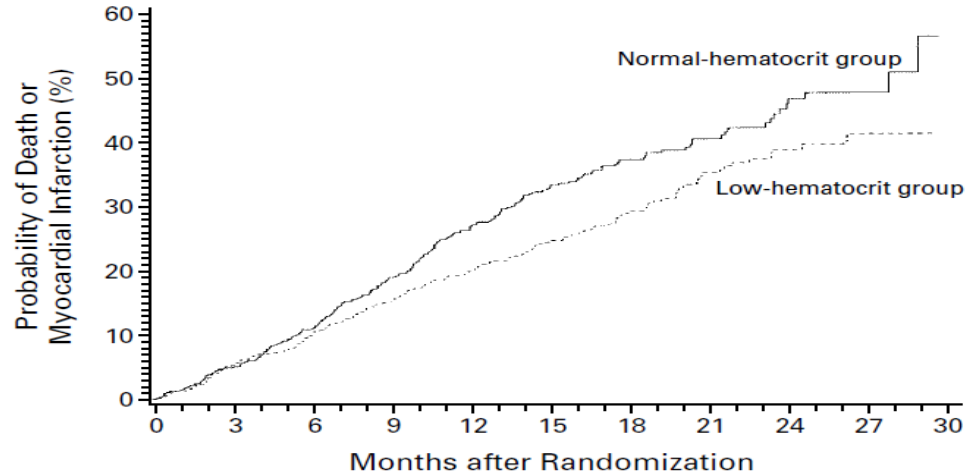
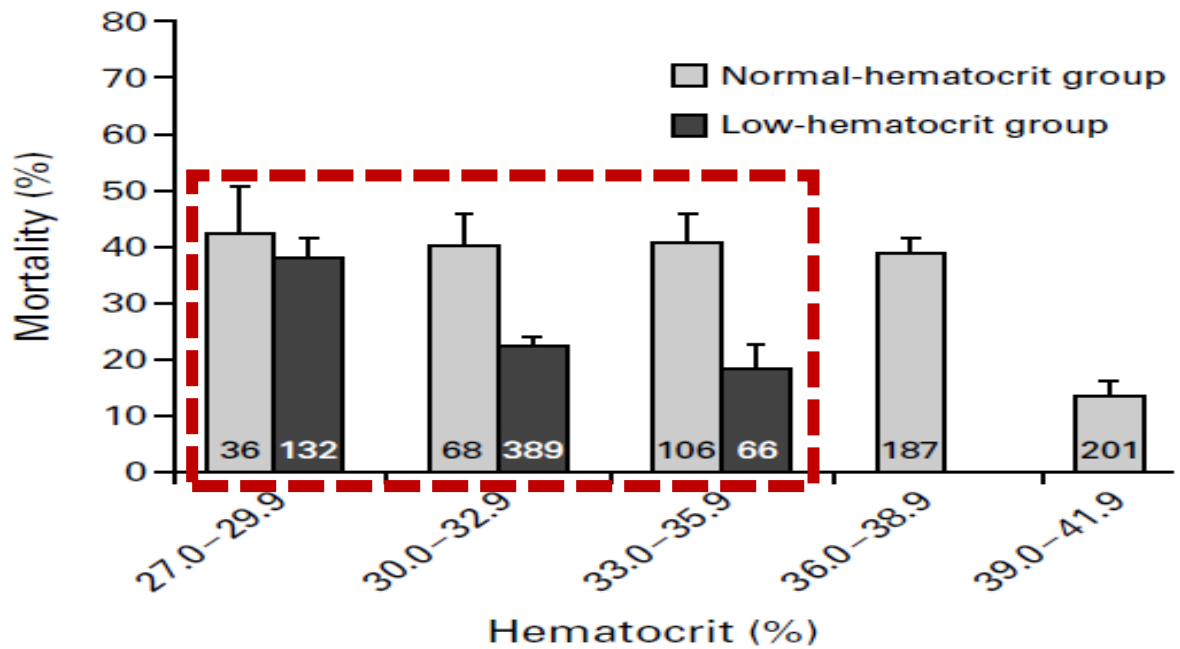


TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	NORMAL-HEMATOCRIT GROUP (N=618)	LOW-HEMATOCRIT GROUP (N=615)
Age (yr)	65±12	64±12
Female sex (%)	50	52
Race or ethnic group (%)		
White	45	42
Black	41	44
Hispanic	8	9
Other	6	5
Duration of dialysis (yr)	3.2±3.6	3.1±3.3
Cause of renal failure (%)		
Diabetes mellitus	42	46
Hypertension	28	27
Glomerulonephritis	7	8
Other	23	19
Type of vascular access (%)		
Graft	66	67
Natural fistula	23	23
Catheter	10	10
Not specified	2	0
Hypertension (%)	71	69
Diabetes mellitus (%)	54	58
Peripheral vascular disease (%)	39	38
Cardiac-related hospitalization (%)		
Angina pectoris	32	28†
Congestive heart failure	44	47
Myocardial infarction	25	23
Coronary-artery bypass graft	20	19
Percutaneous transluminal coronary angioplasty	10	9
New York Heart Association class (%)		
I	29	31
II	51	52
III	19	15
Hematocrit (%)	30.5±3.0	30.5±2.9
Epoetin dose (U/kg/wk)	146±103	153±119



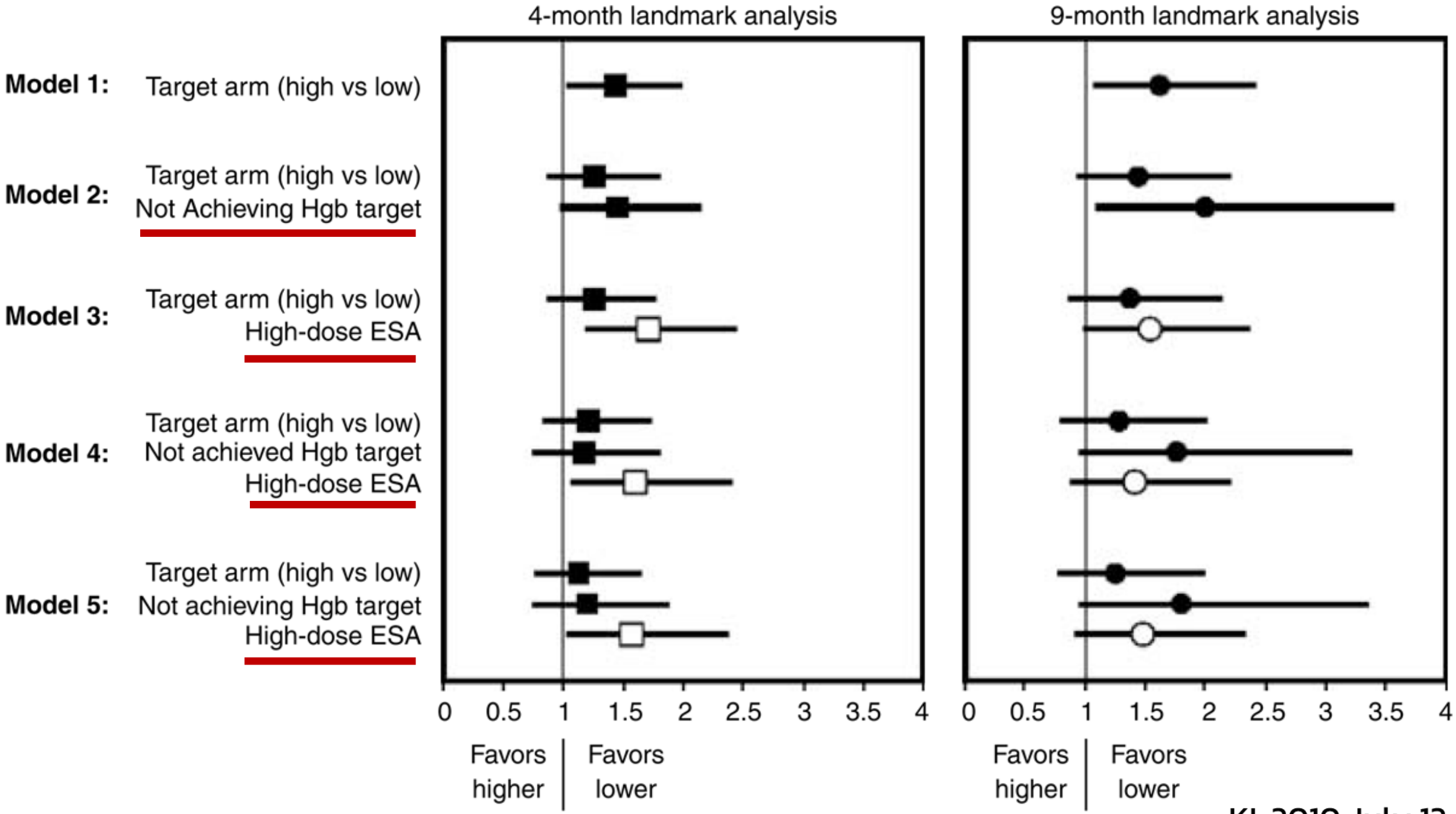
NO. AT RISK										
Normal hematocrit	618	540	476	415	353	259	186	124	69	26
Low hematocrit	615	537	485	434	391	292	216	131	80	20



Secondary analysis of the CHOIR trial epoetin dose and achieved Hb outcomes

- In the 4 mo analysis, significantly more patients in the high-Hb compared to the low Hb arm were unable to achieve target Hb and required high-dose epoetin-α.
- In unadjusted analyses, the inability to achieve a target Hb and high-dose epoetin-α were each significantly associated with increased risk of a primary endpoint (death, MI, CHF or stroke).
- In adjusted models, high-dose epoetin-α was associated with a significant increased hazard of a primary endpoint but the risk associated with randomization to the high Hb arm did not suggest a possible mediating effect of higher target via dose.

KI. 2010 July 12.



KI. 2010 July 12.

Epoetin alfa: dosage

Initial dose: CKD G5D: 50-100 units/kg, 3 times weekly

eg 60 kg: 3000-6000 u x 3/wk

Dose adjustment: CKD G5D:

- Increase by 25 u/kg/dose if Hb rise is <1.0 g/dl after 4 weeks.
- Reduce by 10–25 u/dose if Hb rise is >2 g/dl in 4 weeks

สรุป: ผู้ป่วย HD

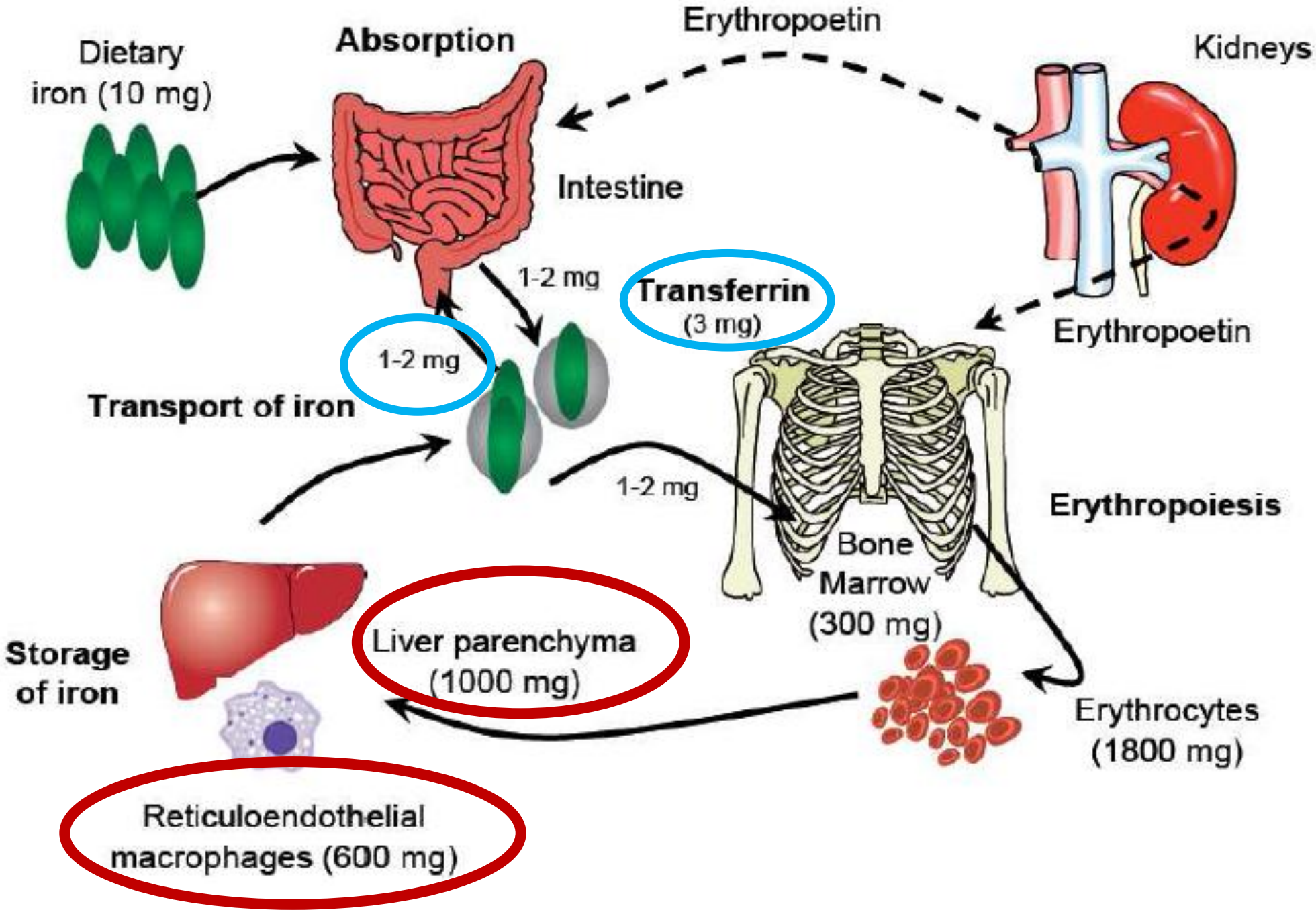
- เข้าใจการประเมินผู้ป่วยด้วย TSAT, SF มากขึ้น
- การให้ IV Venofer อย่างเหมาะสม
- การให้ EPIAO อย่างเหมาะสม

THANK YOU

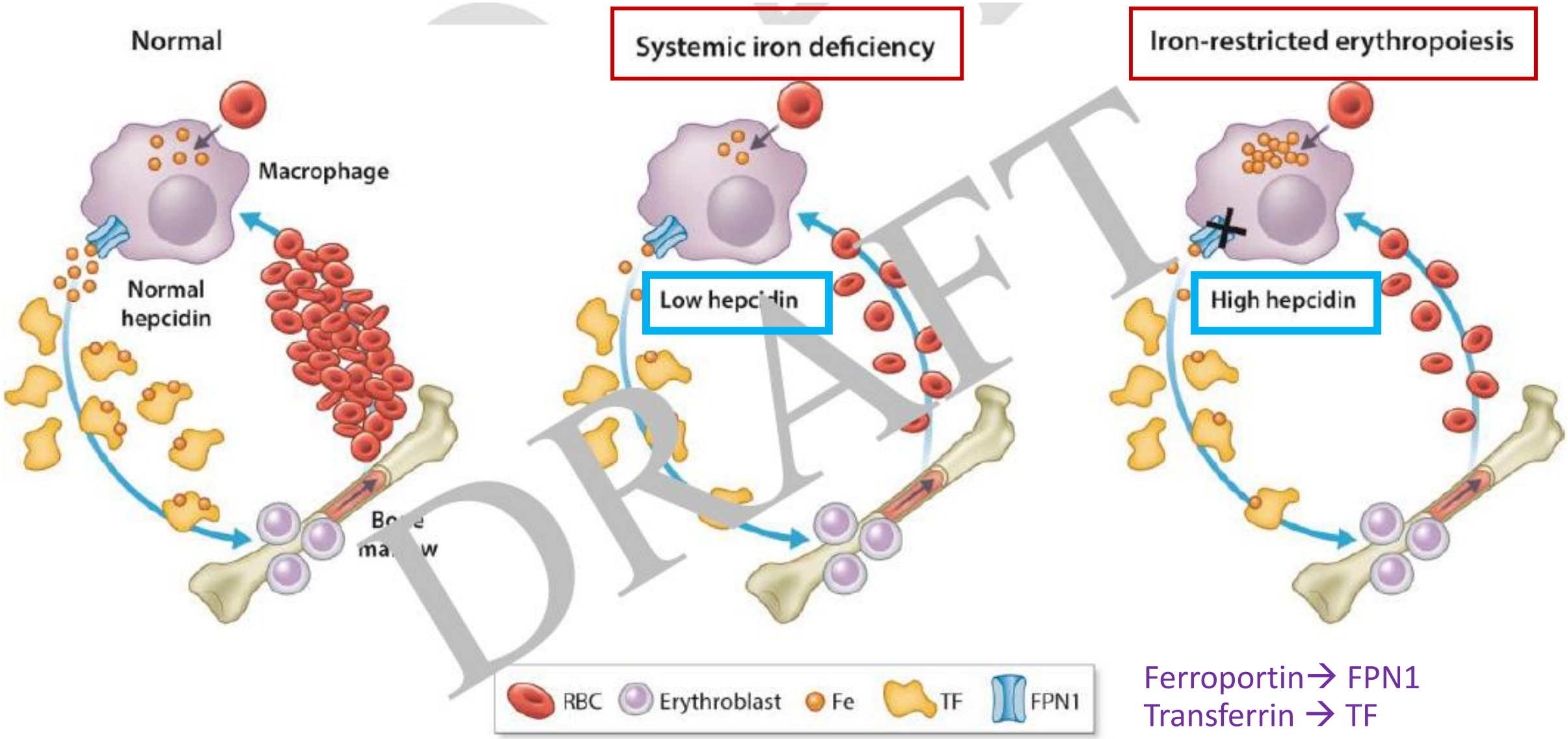
Iron Status Index with ID & inflammation

Variable	Inflammation	Iron deficiency	Inflammation + iron deficiency
Serum iron	Reduced	Reduced	Reduced
Transferrin	Reduced/normal	Increased	Reduced/normal
TSAT	Reduced	Reduced	Reduced
Ferritin	Increased	Reduced	Reduced/normal

Nephrol Dial Transplant (2020) 1–6

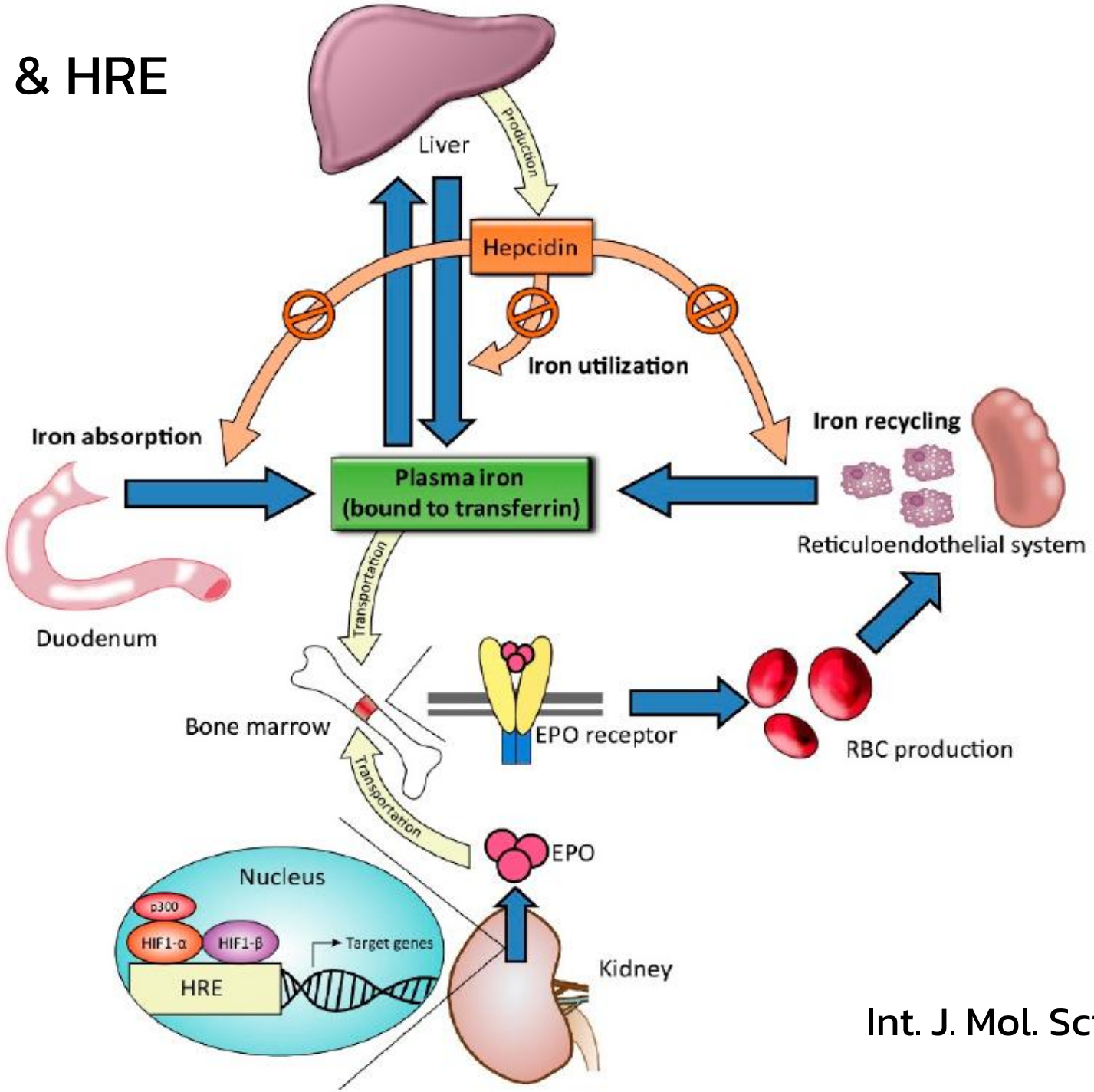

Dietary
iron (10 mg)
Absorption
Intestine
Erythropoetin
Kidneys
1-2 mg
Transferrin
(3 mg)
1-2 mg
Transport of iron
Erythropoetin
1-2 mg
Erythropoiesis
Bone
Marrow
(300 mg)
Storage
of iron
Liver parenchyma
(1000 mg)
Erythrocytes
(1800 mg)
Reticuloendothelial
macrophages (600 mg)

Systemic movement of iron in different iron-related states



Ferroportin→ FPN1
Transferrin → TF

Fe vs Hepcidin & HRE



Int. J. Mol. Sci. 2021, 22, 1008

Oral iron formulations: sulfate vs fumarate

	Dose per tablet	Elemental iron per tablet	Starting dose
Ferrous sulphate	325 mg	65 mg	1 tablet, 3 times daily
Ferrous fumarate	325 mg 200 mg (Thai)	106 mg 65 mg	1 tablet, 2 times daily 1 tablet, 3 times daily

IV iron sucrose treatment regimen

Element iron con: 20 mg/ml

Max single dose: 200 mg

Min infusion time for max dose: 15 min

Min injection time: 5 min

IV iron may cause harm by increasing the risks of

infection,

oxidative stress,

vascular calcification, and

atherothrombosis.

Practice Point 2.8: In people with CKD treated with iron, consider temporarily suspending iron therapy during systemic infection.

- Iron is essential for the growth and proliferation of most pathogens including many bacteria, viruses, fungi, parasites, and helminths. Iron also exerts subtle effects on immune function and host responses towards microbes

Practice Point 2.9: In people with CKD treated with iv iron, considerations pertaining to hypersensitivity reactions to intravenous iron include the following:

- IV iron should only be administered if there is capability to manage acute hypersensitivity and hypotensive reactions,
- IV doses of iron should not exceed the maximum dose/administration for the compound
- Pretreatment with corticosteroids or antihistamines is not routinely necessary (type 1 histamine [H1]–channel blockers), and
- Test doses of iv iron are not usually required, because lack of response does not predict the risk of hypersensitivity.

- IV iron is rarely associated with acute hypersensitivity, hypotensive, and even anaphylactoid-type reactions.
- People may present with a variety of symptoms ranging from flushing, itching, shortness of breath, and hypotension.
- In older studies, such reactions were found to occur in 0.6%–0.7% of treated people. The frequency of reactions is probably significantly lower with newer iron preparations.

Practice Point 2.11: In people with CKD and profound iron deficiency (ferritin <30 µg/l and TSAT<20%) but no anemia, consider treatment with oral or intravenous iron.

- If profound iron deficiency (e.g., ferritin <30 µg/l and TSAT<20%) is present even in the absence of anemia, treatment with oral or i.v. iron could be considered in shared-decision-making, especially in symptomatic people with advanced CKD (CKD G4–G5).
- Observational data in people with CKD and KTRs underscores this, as iron deficiency, independent of anemia, is associated with higher risk of all-cause mortality, MACE, and worse patient-reported outcomes

Practice Point 3.4.1.2: In people with anemia and CKD treated with ESA, avoid adjusting the dose of ESA more frequently than once every 4 weeks. The exception is when Hb increases by more than 1.0 g/dl (10 g/l) in 2–4 weeks after initiation of therapy, at which time the dose should be reduced by 25%–50%.

Practice Point 3.4.3.4: In people with anemia and CKD treated with ESA, it is reasonable to suspend ESA during hospitalization for acute stroke, vascular access thrombosis, or thromboembolic events.

Practice Point 3.4.3.5: In people with CKD, anemia, and active cancer or a history of cancer, use shared decision-making regarding continuation or discontinuation of ESA therapy based on patient preferences and anticipated outcomes, especially when treatment is aimed at cure.