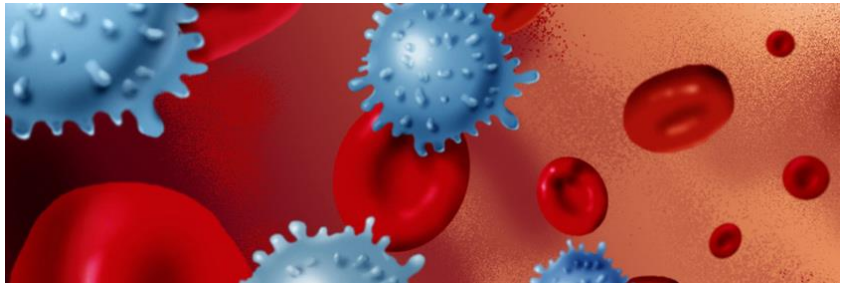


ANEMIA IN CHRONIC KIDNEY DISEASE PATIENTS

Dr Heba Al Rajab

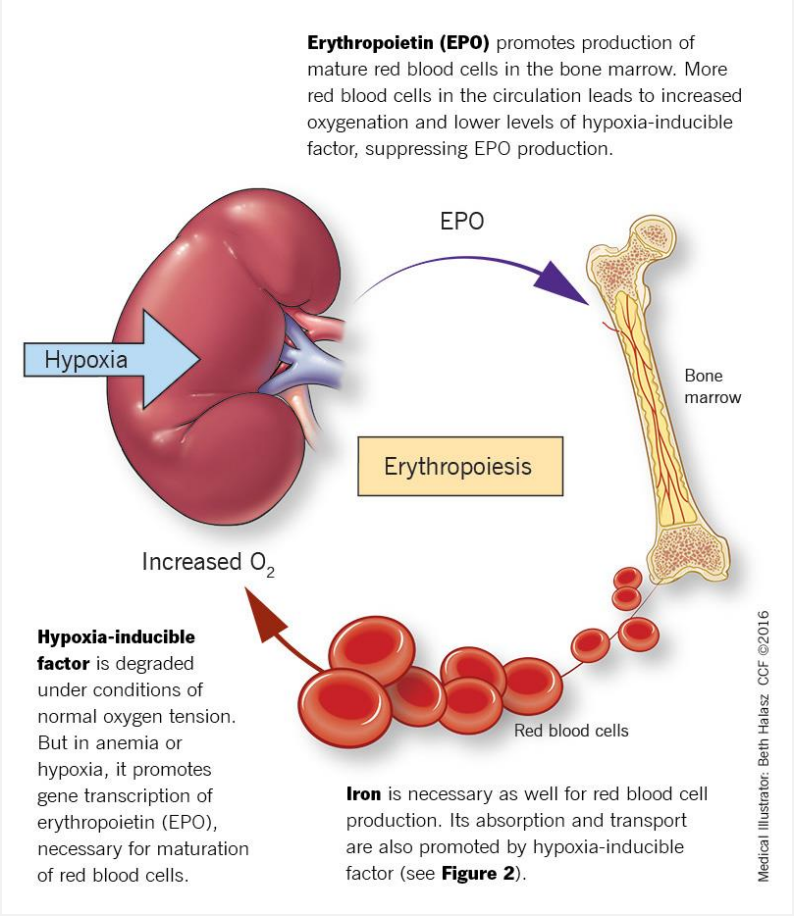
Head of Nephrology & Dialysis centre

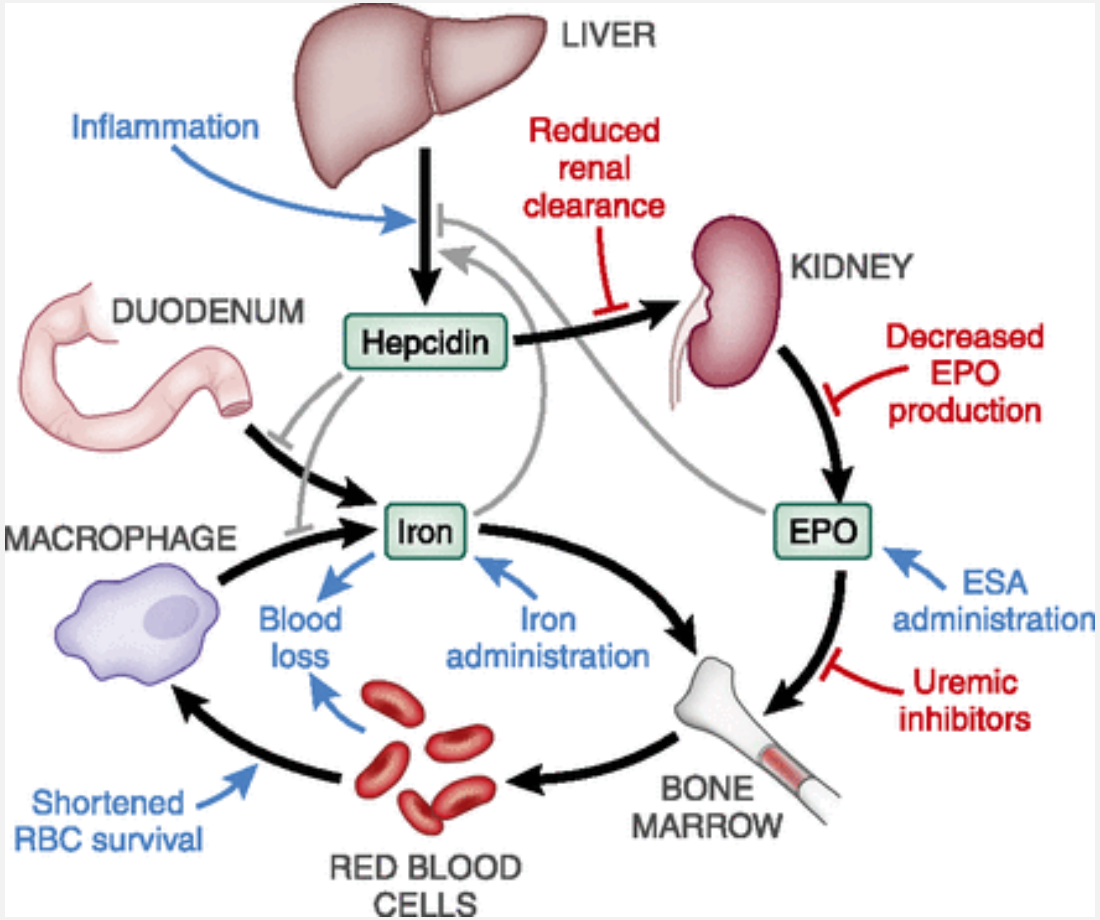
Farwaniya Hospital

AGENDA

- Introduction
- Pathophysiology of anemia in CKD
- Etiology of anemia in CKD
- Diagnosis and evaluation of anemia in CKD
- Use of iron to treat anemia in CKD
- Use of ESAs and other agents to treat anemia in CKD
- Red cell transfusion to treat anemia in CKD
- Land marks trials

WHY ANEMIA IS SO IMPORTANT IN CKD?





J Am Soc Nephrol 23: 1631–1634, 2012.

Key Points: Anemia of Chronic Kidney Disease

Causes and Effects

- ↓ **EPO production**
- ↑ **hepcidin**
  - Due to ↓ renal clearance and ↑ IL-6
  - Leads to:
    - iron sequestration in macrophages
    - iron-restricted erythropoiesis, resistance to EPO
- **True iron deficiency**
  - Due to increased blood loss and hepcidin-mediated decrease in intestinal iron absorption)
- **Suppression of erythropoiesis by inflammatory cytokines** (important in acute inflammation)
- **Shortened erythrocyte lifespan**
  - Due to inflammation and uremia

Treatments and Modulators

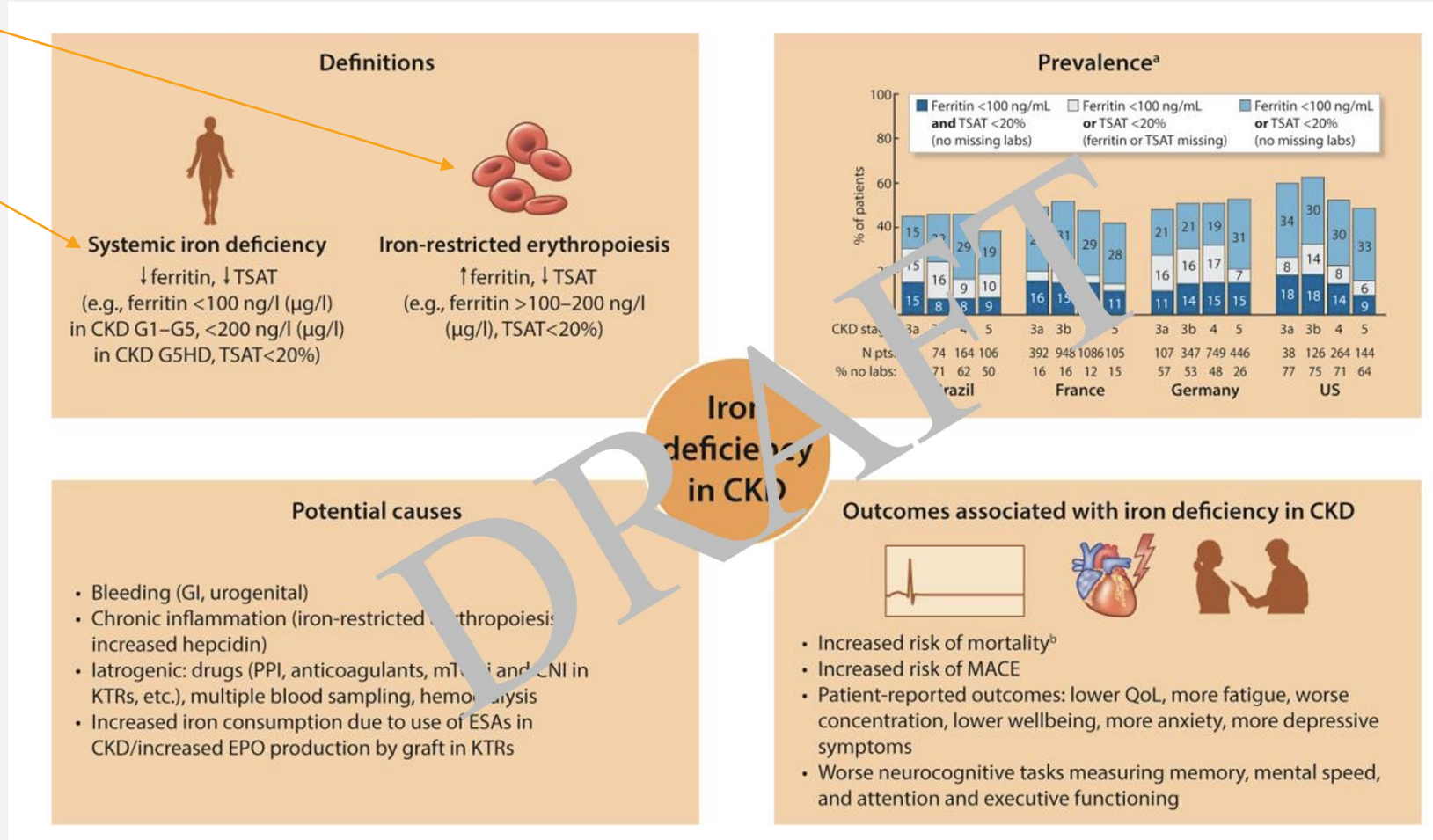
- **Exogenous EPO/Erythropoietin Stimulating Agents (ESAs)**
  - Causes pulsatile erythropoiesis and transient high demand for iron
  - High doses ↓hepcidin but at the cost of side effects
- **Iron**
  - Overcomes hepcidin-induced blockade of iron release from macrophages
  - Decreases resistance to EPO
- **HIF-PHD Inhibitors**
  - Increases uptake of iron
  - Increases endogenous EPO release, leads to:
    - Inhibition of downstream effects of hepcidin

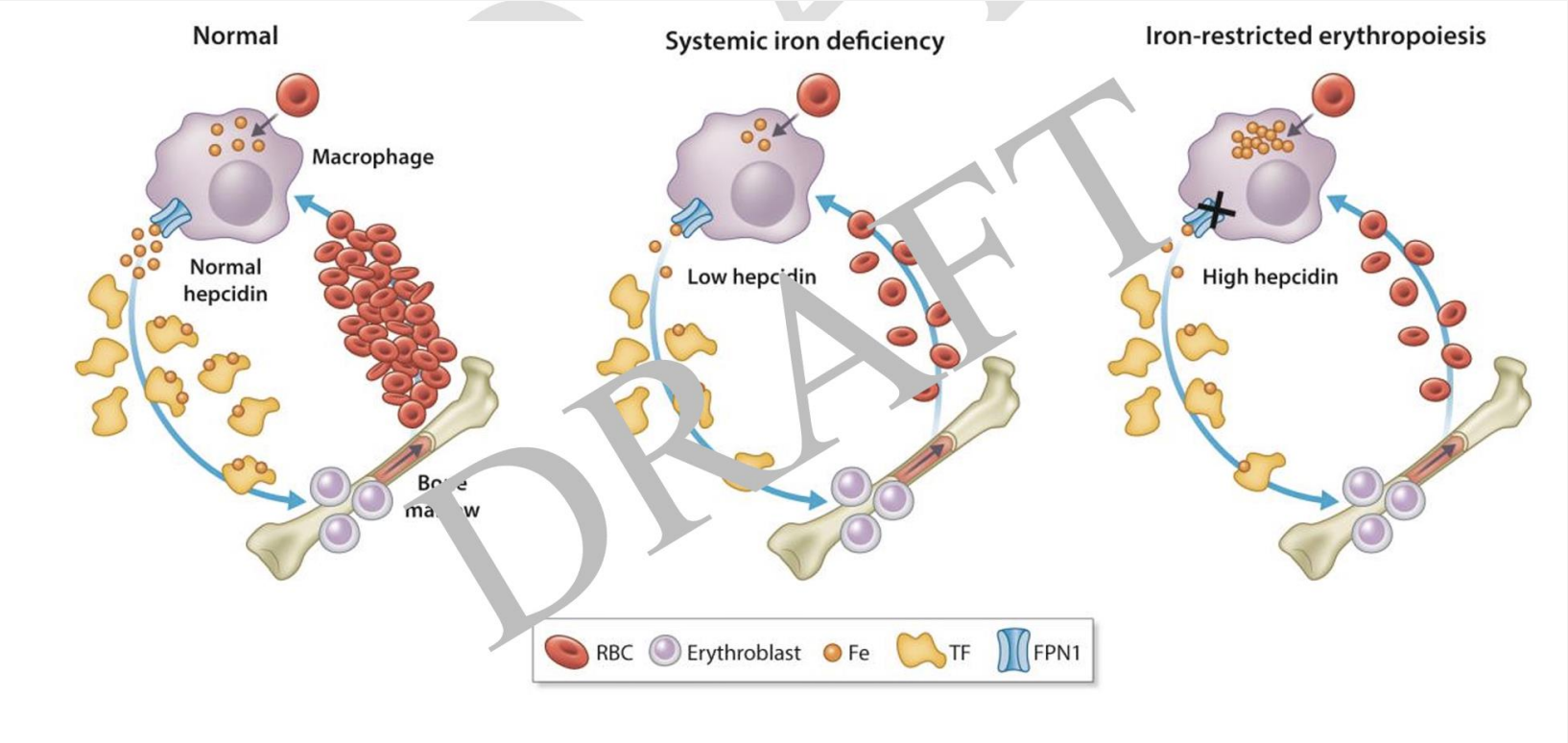
JASN 31: 456–468, 2020

IRON DEFICIENCY ANEMIA

functional

absolute




Normal
Macrophage
Normal hepcidin
Systemic iron deficiency
Low hepcidin
Iron-restricted erythropoiesis
High hepcidin
RBC
Erythroblast
Fe
TF
FPN1

Prevalence of Anemia in Chronic Kidney Disease in the United States

Melissa E. Stauffer[1]*, Tao Fan[2]

1 SCRIBCO, Effort, Pennsylvania, United States of America, 2 Merck & Co., Inc., Whitehouse Station, New Jersey, United States of America

	N	Weighted percentage	95% CI
With CKD	410	15.4	13.1–18.2
Stage 1	57	8.4	5.5–12.4
Stage 2	68	12.2	9.2–16.0
Stage 3	231	17.4	13.7–21.8
Stage 4	37	50.3	37.2–63.4
Stage 5	17	53.4	34.1–71.7
Without CKD	729	6.3	5.3–7.4

- **A total of 12,077 adults**
- **National Health and Nutrition Examination Survey (NHANES) interview and examination components of the surveys in 2007–2008 and 2009–2010.**

January 2014 | Volume 9 | Issue 1 | e84943

Hemoglobin Levels in Patients Undergoing Dialysis

About 50% of patients starting dialysis have hemoglobin < 10 g/dL

	Serum albumin	Hemoglobin < 10 g/dL
Age		
20-44	56.6	57.0
45-64	58.1	54.0
65-74	56.3	51.8
75+	57.9	48.2
Gender		
Male	56.2	50.8
Female	58.6	54.5
Race		
White	56.5	49.5
African American	59.6	59.9
Native American	68.2	55.0
Asian	51.3	47.3
Hispanic	60.6	55.3
Primary diagnosis		
Diabetes	61.8	53.7
Hypertension	52.8	51.3
Glomerulonephritis	51.7	49.3
Cystic kidney disease	23.2	31.4
All	57.2	52.4

U.S. Renal Data System, USRDS 2011 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2011.

Key Points: Anemia of Chronic Kidney Disease

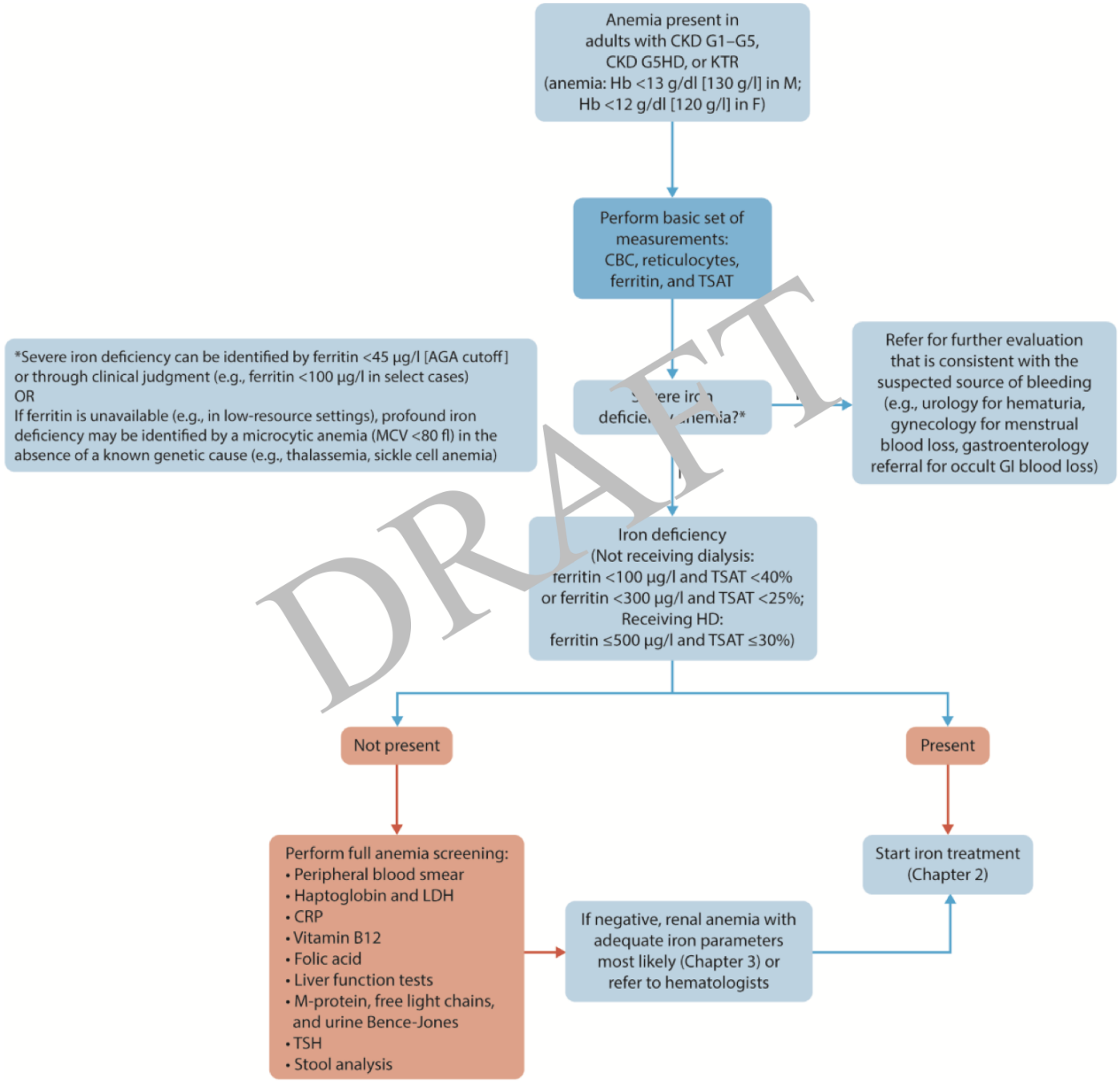
Causes and Effects

- ↓ **EPO production**
- ↑ **hepcidin**
  - Due to ↓ renal clearance and ↑ IL-6
  - Leads to:
    - iron sequestration in macrophages
    - iron-restricted erythropoiesis, resistance to EP
- **True iron deficiency**
  - Due to increased blood loss and hepcidin-med ted decrease in intestinal iron absorption)
- **Suppression of erythropoiesis by inflamm tory cytokines** (important in acute inflammation)
- **Shortened erythrocyte lifespan**
  - Due to inflammation and uremia

Treatments and Modulators

- **Exogenous EPO/Erythropoietin Stimulating Agents (ESAs)**
  - Causes pulsatile erythropoiesis and transient high demand for iron
  - High doses ↓hepcidin but at the cost of side effects
- **Iron**
  - Overcomes hepcidin-induced blockade of iron release from macrophages
  - Decreases resistance to EPO
- **HIF-PHD Inhibitors**
  - Increases uptake of iron
  - Increases endogenous EPO release, leads to:
    - Inhibition of downstream effects of hepcidin

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


Anemia present in adults with CKD G1–G5, CKD G5HD, or KTR (anemia: Hb <13 g/dl [130 g/l] in M; Hb <12 g/dl [120 g/l] in F)
Perform basic set of measurements: CBC, reticulocytes, ferritin, and TSAT
*Severe iron deficiency can be identified by ferritin <45 µg/l [AGA cutoff] or through clinical judgment (e.g., ferritin <100 µg/l in select cases)
OR
If ferritin is unavailable (e.g., in low-resource settings), profound iron deficiency may be identified by a microcytic anemia (MCV <80 fl) in the absence of a known genetic cause (e.g., thalassemia, sickle cell anemia)
Refer for further evaluation that is consistent with the suspected source of bleeding (e.g., urology for hematuria, gynecology for menstrual blood loss, gastroenterology referral for occult GI blood loss)
Iron deficiency (Not receiving dialysis: ferritin <100 µg/l and TSAT <40% or ferritin <300 µg/l and TSAT <25%; Receiving HD: ferritin ≤500 µg/l and TSAT ≤30%)
Not present
Present
Perform full anemia screening:
• Peripheral blood smear
• Haptoglobin and LDH
• CRP
• Vitamin B12
• Folic acid
• Liver function tests
• M-protein, free light chains, and urine Bence-Jones
• TSH
• Stool analysis
If negative, renal anemia with adequate iron parameters most likely (Chapter 3) or refer to hematologists
Start iron treatment (Chapter 2)

USE OF IRON TO TREAT IRON DEFICINCY AND ANEMIA IN CKD

- **Recommendation 2.1: In people with anemia and CKD treated with hemodialysis (CKD G5HD), we suggest initiating iron therapy if ferritin ≤500 ng/ml (≤500 µg/l) and TSAT ≤30% (*2D*).**
- **Recommendation 2.3: In people with anemia and CKD not receiving dialysis or treated with peritoneal dialysis (CKD G5PD), we suggest initiating iron if (2D):**
  - **ferritin <100 ng/ml (<100 µg/l) and transferrin saturation (TSAT) <40%,**
  - **or ferritin ≥100 ng/ml (≥100 µg/l) and <300 ng/ml (<300 µg/l), and TSAT <25%.**
- **Practice Point 2.2: In people with CKD treated with iron, it is reasonable to withhold iron if ferritin ≥ 700 ng/ml (≥700 µg/l) or TSAT ≥40%**

- **Practice Point 2.5: In people with CKD treated with iron, it is reasonable to test hemoglobin, ferritin, and TSAT every 1 month for those with CKD G5HD.**

- **Practice Point 2.6: In people with CKD treated with iron, certain circumstances may warrant more frequent iron testing:**
  - **Initiation of or increase in dose of ESA of HIF-PHI**
  - **Episodes of known blood loss**
  - **Recent hospitalization**
  - **Important increase in ferritin or TSAT or overshooting target limit**

USE OF ESA, HIF-PHI TO TREAT ANEMIA IN CKD

- 3.1. Treatment initiation

  Practice Point 3.1.1: In people with anemia and CKD (whether treated with dialysis or not), the decision to use erythropoietin- stimulating agents (ESAs) or hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) to raise the hemoglobin (Hb) should be made together with patients and consider each individual's symptoms, potential for harm from red blood cell (RBC) transfusions, and potential risk of adverse events (e.g. stroke, cardiovascular event, cancer).

- 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 (2D)

- 3.2. ESA initiation

  Recommendation 3.2.1: In people with anemia and CKD G5D treated with hemodialysis (HD) or peritoneal dialysis (PD), we suggest initiation of ESA therapy when the Hb concentration is ≤9.0–10.0 g/dl (90–100 g/l) (2D).

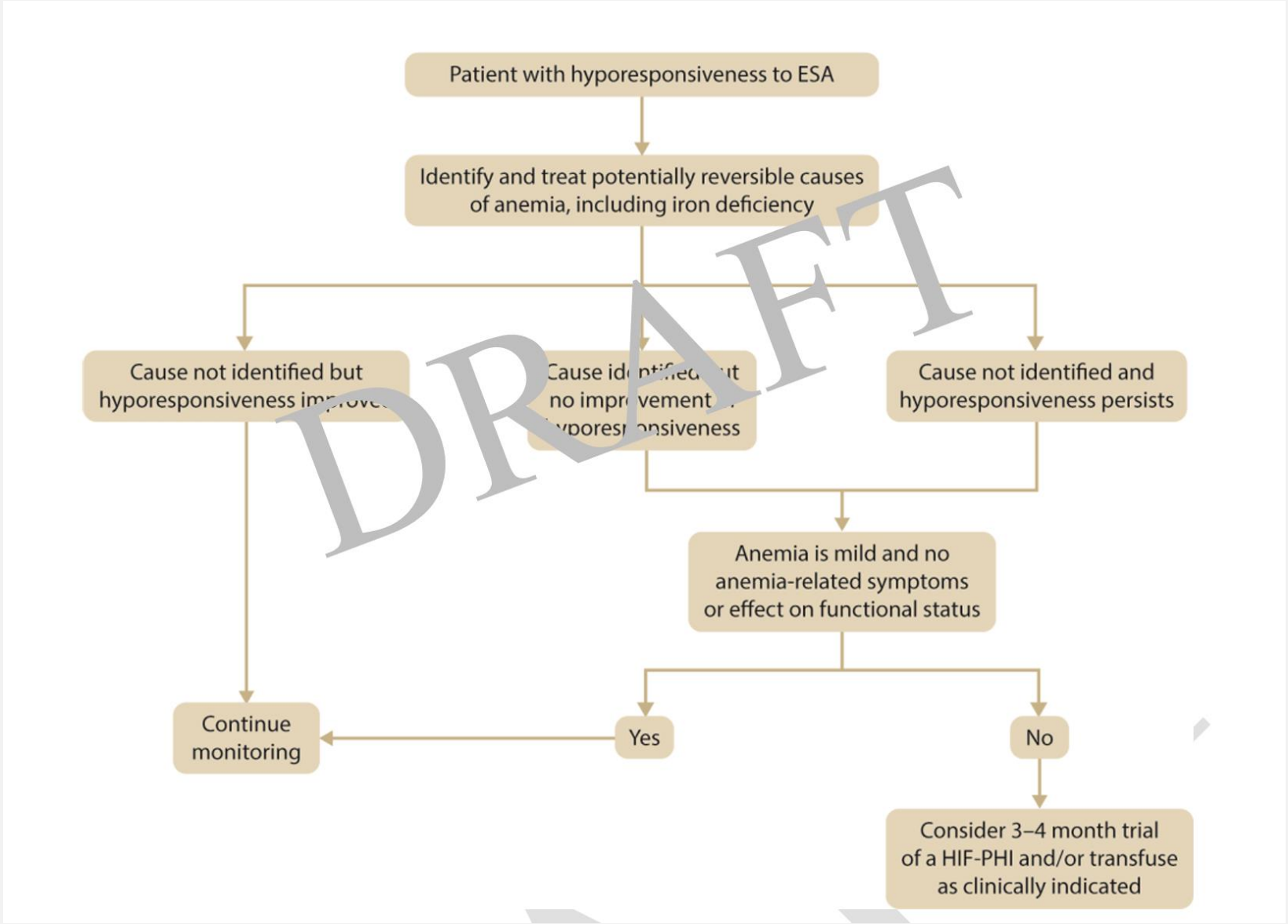
- Recommendation 3.3.1: In adults with anemia and CKD treated with an ESA, we recommend targeting a Hb level below 11.5 g/dl (115 g/l) (1D).

- 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 3.4.3.2: In people with anemia and CKD, following the initiation of ESA therapy or change in dose, monitor Hb every 2–4 weeks and adjust the dose accordingly to avoid a rapid rise of >1.0 g/dl (10 g/l) during that interval.

- 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. Individualize consideration for ESA reinitiation based on patient characteristics, Hb level, and preferences regarding risks and benefits of ESA treatment.

- 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.


Patient with hyporesponsiveness to ESA
Identify and treat potentially reversible causes of anemia, including iron deficiency
Cause not identified but hyporesponsiveness improves
Cause identified but no improvement in hyporesponsiveness
Cause not identified and hyporesponsiveness persists
Anemia is mild and no anemia-related symptoms or effect on functional status
Continue monitoring
Yes
No
Consider 3–4 month trial of a HIF-PHI and/or transfuse as clinically indicated

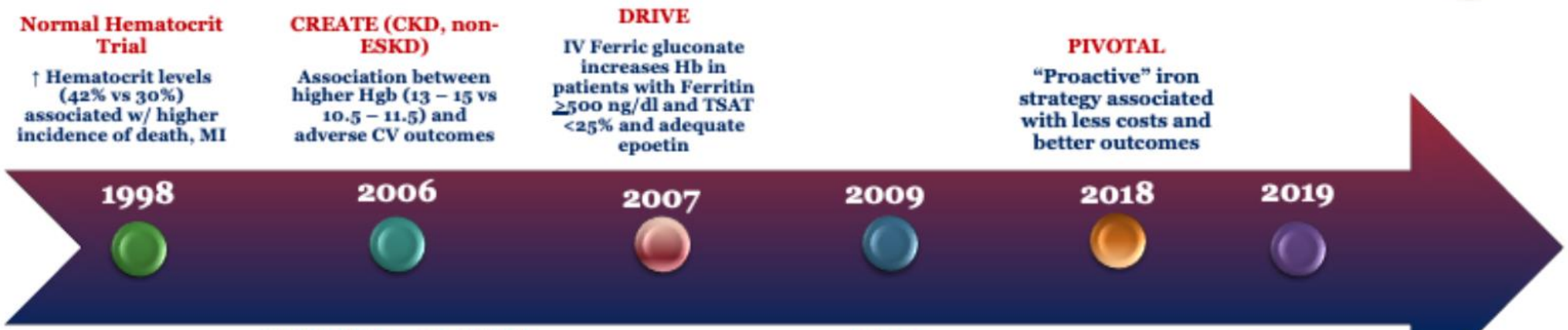
RED BLOOD CELL TRASNFUSION

- Practice Point 4.3: In people with CKD and chronic anemia, consider that the benefits of RBC transfusions may outweigh its harms in people in whom:
  - ESA or HIF-PHI therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA or HIF-PHI resistance)
  - ESA or HIF-PHI therapy is harmful (e.g., previous or current malignancy, previous stroke)

WHAT DO WE KNOW?

- Is too much iron is too much?
- Will it lead to iron overload?
- Is there a risk for CVS disease?
- How about risk of infection?
- How about the hypersensitivity to iron?
- Is there anything else than we can use?

Landmark Trials in Anemia & Kidney Disease



- MI: myocardial infarction
- CKD: chronic kidney disease
- ESKD: end-stage kidney disease
- Hgb: hemoglobin (g/dL)
- HF: heart failure
- DM: Diabetes mellitus
- VTE: venous thromboembolism
- HD: hemodialysis
- IV: intravenous

@xaviervel @landmark_neph

CREATE TRIAL

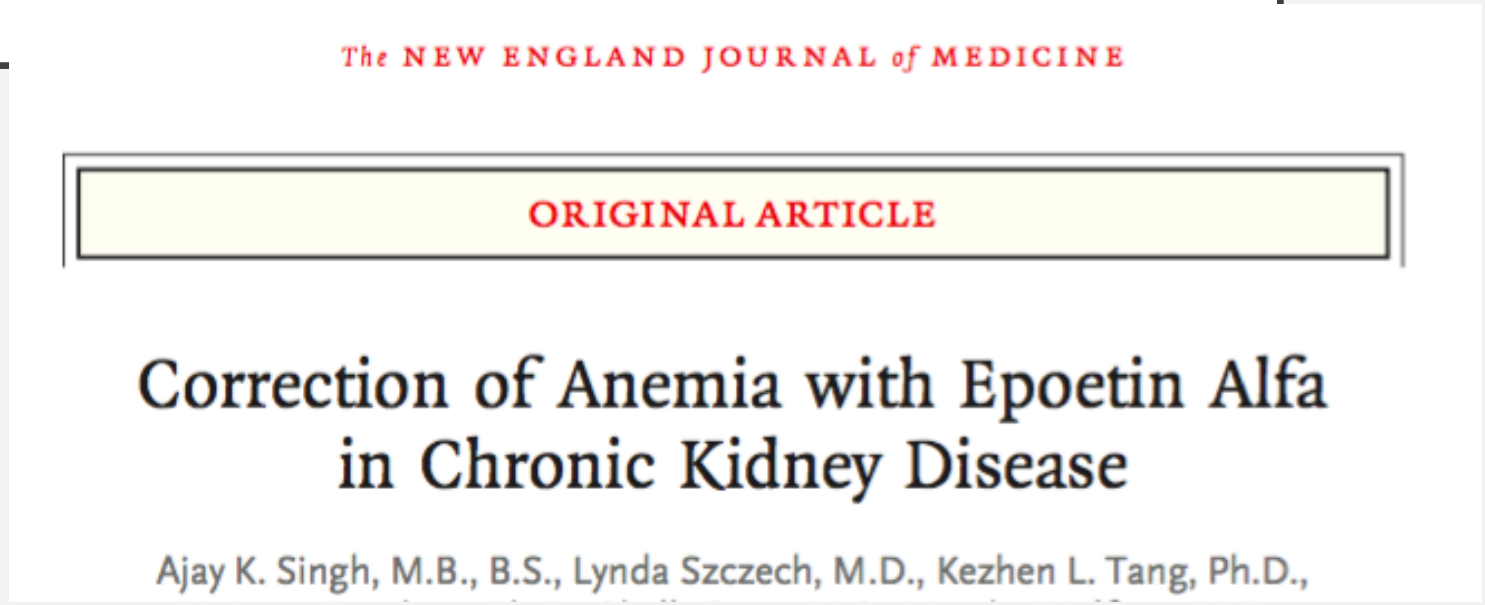
Nephrol Dial Transplant. 2001;16 Suppl 2:16-8.

The CREATE trial--building the evidence.

Eckardt KU[1]; Cardiovascular risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) Trial.

- 603 patients in 22 countries with stage 3 to 4 CKD and mild to moderate anemia (hemoglobin 11 to 12.5 g/dL) were randomized to treatment with epoetin beta to a target hemoglobin of either 13 to 15 g/dL or 10.5 to11.5 g/dL.
- The primary outcome was a composite of 8 cardiovascular events. In a 3-year follow-up, investigators found no significant difference in cardiovascular-event rates or in all-cause mortality between the 2 treatment groups, **but patients in the high-hemoglobin group achieved significantly better quality-of-life outcomes.**

CHOIR TRIAL



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

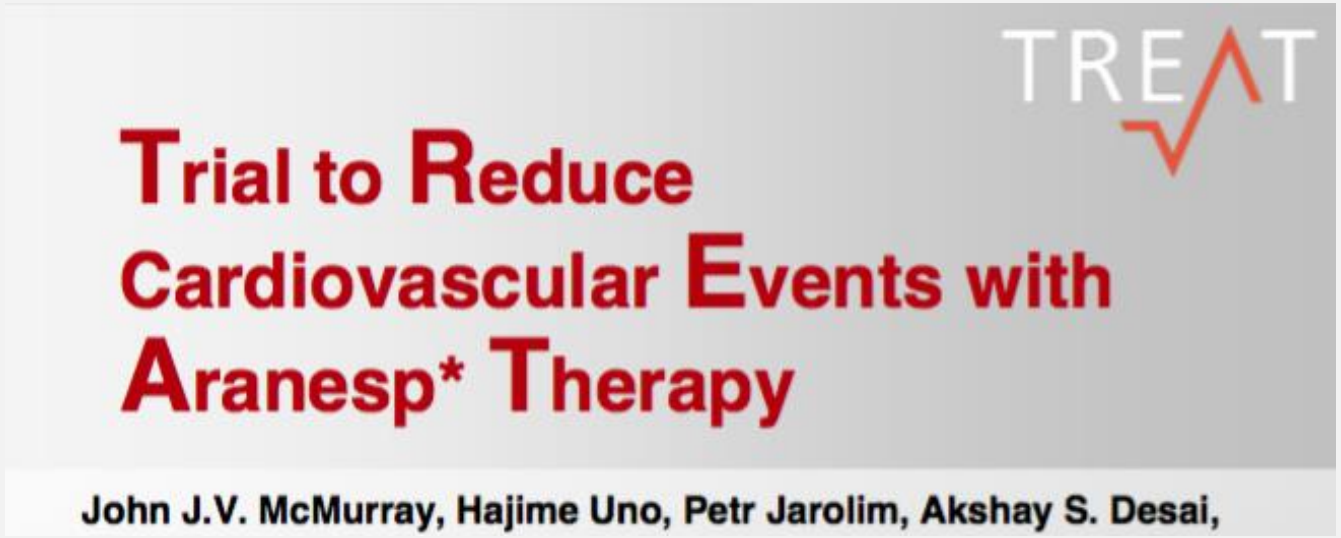
Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D.,

N Engl J Med 2006; 355:2085-2098

Conclusion: treating anemia in patients with chronic kidney disease using epoetin alfa to a lower hemoglobin target (i.e., ≥11.3 g/dL) was associated with a significantly lower risk of composite events compared to a high target (i.e., ≥13.5 g/dL).

TREAT TRIAL



Am Heart J. 2005 Mar;149(3):408-13

- Conclusion: The routine use of ESAs in patients with diabetes and CKD not on dialysis (who are at a high risk for renal and CV events) is not associated with a reduction in renal and CV events over an intermediate period of follow-up
- There is a reduction in the need for packed red blood cell transfusion with darbepoetin alfa,

FIND CKD STUDY

Nephrol Dial Transplant (2014) 29: 2075–2084
doi: 10.1093/ndt/gfu201
Advance Access publication 2 June 2014

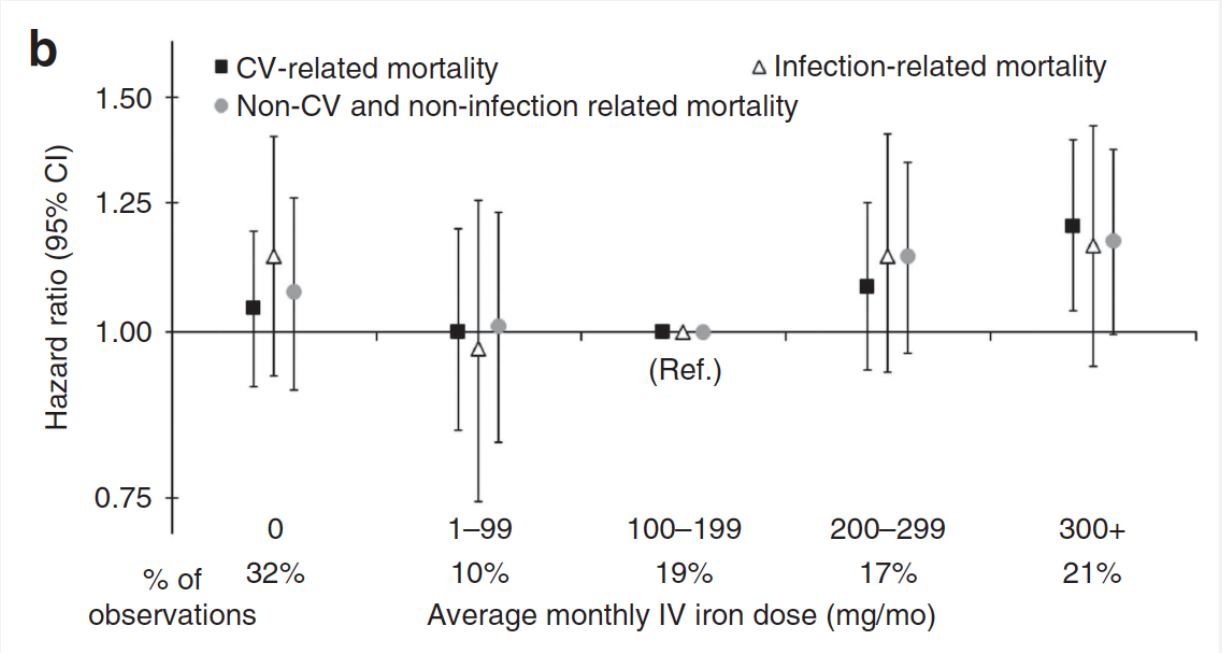
FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia

Iain C. Macdougall[1], Andreas H. Bock[2], Fernando Carrera[3], Kai-Uwe Eckardt[4], Carlo Gaillard[5],

- Study results indicated that **IV iron dosed to a target ferritin of 400-600 µg/l was superior to IV iron dosed to a target ferritin of 100-200 µg/l or oral ferrous sulphate**, for achieving an Hb increase ≥1 g/dl
- IV iron with a higher ferritin target was also superior to oral ferrous sulphate in delaying or reducing the need for other anemia management

IV IRON IN HD: INFECTION-RELATED OUTCOMES

Association of IV iron dose and cause-specific mortality in HD.[1]



IV iron dose is the total 4-month dose, expressed as average mg/month.

Bailie G, et al. Kidney Int. 2015;87:162–168.

REVOKE TRIAL

Kidney Int. 2015 October ; 88(4): 905–914. doi:10.1038/ki.2015.163.

A randomized trial of intravenous and oral iron in chronic kidney disease

Rajiv Agarwal, MD[1], **John W. Kusek, PhD**[2], and **Maria K. Pappas, BA**[1]

A single-center RCT (REVOKE) also showed IV iron was associated with higher rate of adverse events; however, the findings are controversial

PIVOTAL TRIAL

Original Report: Patient-Oriented, Translational Research

American Journal of Nephrology

Am J Nephrol 2018;48:260–268
DOI: 10.1159/000493551

Received: August 11, 2018
Accepted: September 6, 2018
Published online: October 10, 2018

Randomized Trial Comparing Proactive, High-Dose versus Reactive, Low-Dose Intravenous Iron Supplementation in Hemodialysis (PIVOTAL): Study Design and Baseline Data

Iain C. Macdougall[a] Claire White[a] Stefan D. Anker[b] Sunil Bhandari[c]

- The study demonstrated that a **proactive high-dose IV iron (ferric carboxymaltose) regimen was superior to a reactive low-dose strategy**
- The proactive high-dose IV iron regimen was associated with a significantly reduced risk of: death or non-fatal CV events, MI or HF hospitalization, or recurrent CV events

ARCTOS TRIAL

Clinical Trial > Clin J Am Soc Nephrol. 2008 Mar;3(2):337-47. doi: 10.2215/CJN.00480107. Epub 2008 Feb 20.

C.E.R.A. corrects anemia in patients with chronic kidney disease not on dialysis: results of a randomized clinical trial

Iain C Macdougall [1], Rowan Walker, Robert Provenzano, Fernando de Alvaro, Harold R Locay,

- Subcutaneous C.E.R.A. once every 2 wk corrects anemia in ESA-naïve patients who are not on dialysis.
- Subcutaneous C.E.R.A. Q4W is safe and effective in maintaining stable Hb levels in patients with CKD not on dialysis following correction with subcutaneous C.E.R.A. Q2W. **”in the ARCTOS extension study”**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

FREE PREVIEW

Intravenous Iron in Patients Undergoing Maintenance Hemodialysis

Iain C. Macdougall, M.D., Claire White, B.Sc., Stefan D. Anker, M.D., Sunil Bhandari, Ph.D., F.R.C.P.,

N Engl J Med 2019; 380:447-458

- Conclusion: high-dose IV iron regimen administered proactively was superior to a low-dose regimen administered reactively and resulted in lower doses of ESAs being administered

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 12, 2019 VOL. 381 NO. 11

Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis

N. Chen, C. Hao, X. Peng, H. Lin, A. Yin, L. Hao, Y. Tao, X. Liang, Z. Liu, C. Xing, J. Chen, L. Luo, L. Zuo, Y. Liao, B.-C. Liu, R. Leong, C. Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu

- patients were randomly assigned (2:1) to receive **Roxadustat** or placebo in a double-blinded fashion. The group that received the HIF inhibitor saw a change from baseline in the hemoglobin level, with an average increase of 1.9 g/dL versus a decrease of 0.4 g/dL in the placebo group ($P < 0.001$)

- HIF stabilizers represent a novel therapeutic intervention in the future management of anemia

- Resulting in the upregulation of EPO gene expression, and in an increase in both hemoglobin concentration and iron transport proteins.

Table 8 | Overview of hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) approved for marketing as of October 2024

HIF-PHI	Recommended dosing for treatment initiation	Maximum daily dose	Dose frequency	Drug metabolism and transport	Approved for marketing in (as of May 2024):
Daprodustat	CKD not receiving dialysis: 2–~4 mg (ESA-naïve), 4 mg (switch from ESA) CKD G5D: [Japan] 4 mg, [U.S.] 1–~4 mg (ESA-naïve), 4–12 mg (switch from ESA)	24 mg	daily	CYP2C8[254]	Japan, U.S.*
Desidustat	CKD not receiving dialysis: 100 mg (ESA-naïve), 100, 125, or 150 mg (switch from ESA) CKD G5D: 100 mg (ESA-naïve), 100, 125, or 150 mg (switch from ESA)	150 mg	3 times per week	Not inhibitor of: CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4/5[255] Not inducer of: CYP1A2 or CYP3A4/5[255]	India
Enarodustat	CKD not receiving dialysis and CKD G5PD: 2 mg (ESA-naïve and switch from ESA) CKD G5HD: 4 mg (ESA-naïve and switch from ESA)	8 mg	daily	CYP2C8, CYP2C9, CYP3A4[256]	China, Japan, Korea
Molidustat	CKD not receiving dialysis: 25 mg (ESA-naïve), 25–~50 mg (switch from ESA) CKD G5D: 75 mg (ESA-naïve and switch from ESA)	200 mg	daily	UGT1A1, UGT1A9[257]	Japan
Roxadustat	CKD not receiving dialysis and CKD G5D (ESA-naïve): [EU] 70 mg for body weight <100 kg, 100 mg for body weight ≥100 kg CKD not receiving dialysis (switch from ESA): [EU] 70–200 mg, [Japan] 50 mg (ESA-naïve), 70–100 mg (switch from ESA)	3.0 mg/kg body weight	3 times per week	CYP2C8, UGT1A9, BCRP, OATP1B1, OAT1, OAT3[230] inhibitor of: CYP2C8, BCRP, OATP1B1, OAT3[230, 258]	China, Chile, Egypt, EU, Iceland, Japan, Kuwait, Lichtenstein, Mexico, Norway, Russia, Saudi Arabia, South Africa, South, Korea, Turkey, UAE, UK
Vadadustat	300 mg (ESA-naïve and switch from ESA)	600 mg	daily	UGT1A1, 1A7, 1A8, 1A9, BCRP, OAT3[259] inhibitor of CYP2C8 (in vitro), BCRP, OAT3 and inducer of CYP2B6 (in vitro)[259, 260]	Australia, EU, Japan, Korea, Taiwan, U.S.†

- Practice Point 3.5.1: In people with anemia and CKD, including those with ESA hyporesponsiveness, do not use ESAs and HIF-PHIs in combination.

- Practice Point 3.5.2: In people with anemia and CKD, the Hb thresholds for the initiation and maintenance of HIF-PHIs are unknown, but it is reasonable to use the same Hb thresholds as those recommended or suggested for ESA therapy (Recommendations 3.2.1, 3.2.2, 3.3.1).

- Practice Point 3.5.4: In people with anemia and CKD, administer HIF-PHIs at the lowest dose needed to improve symptoms attributable to anemia and to avoid RBC transfusions

- Practice Point 3.6.1: In people with anemia and CKD, when dosing HIF-PHIs, monitor the Hb levels 2–4 weeks after initiation or dose changes and subsequently, every 4 weeks during therapy.

CONSIDERATION !

- Practice Point 3.6.2.: In people with anemia and CKD treated with roxadustat, monitor thyroid stimulating hormone and free T3 and T4 after 4 weeks of therapy initiation.

- Practice Point 3.6.3: In people with anemia and CKD, discontinue HIF-PHI after 3–4 months if a desired erythropoietic response has not been achieved.

- Practice Point 3.6.4: In people with anemia and CKD, suspend treatment with HIF-PHIs in those who experience cardiovascular events (e.g., stroke, myocardial infarction); thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism); vascular access thrombosis; or newly diagnosed cancer.

WHAT'S AVAILABLE HERE IN KUWAIT ?

- IV IRON (IV ferosac and IV ferinject)
- Darbepoetin alfa (Aranesp)
- Methoxy polyethylene glycol-epoetin beta (Mircera)

CONCLUSION

- In summary, the field of anemia therapy in CKD and ESRD has progressed from one with very limited options in the pre-ESA era to one in which novel agents are developed to induce therapeutic effects that more closely mimic the body's own responses to hypoxia

- HIF stabilizers increase hemoglobin with much lower levels of circulating EPO, thus eliminating the risk of patient exposure to such high levels

- But because these agents may upregulate other hypoxia-sensitive genes that are involved in angiogenesis and tumor growth, their long-term safety will need to be proven ??

? QUESTIONS