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Anemia Management: Update and Best Practices

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- Critical Care Training in Adelaide, Australia
- MGB Clinical & Research Nephrology Fellowship
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- Attending Nephrologist at BWH
- Research interests: Autonomic Dysfunction, inflammation & adverse cardio-kidney metabolic outcomes in CKD, ESKD & Transplant

Disclosures

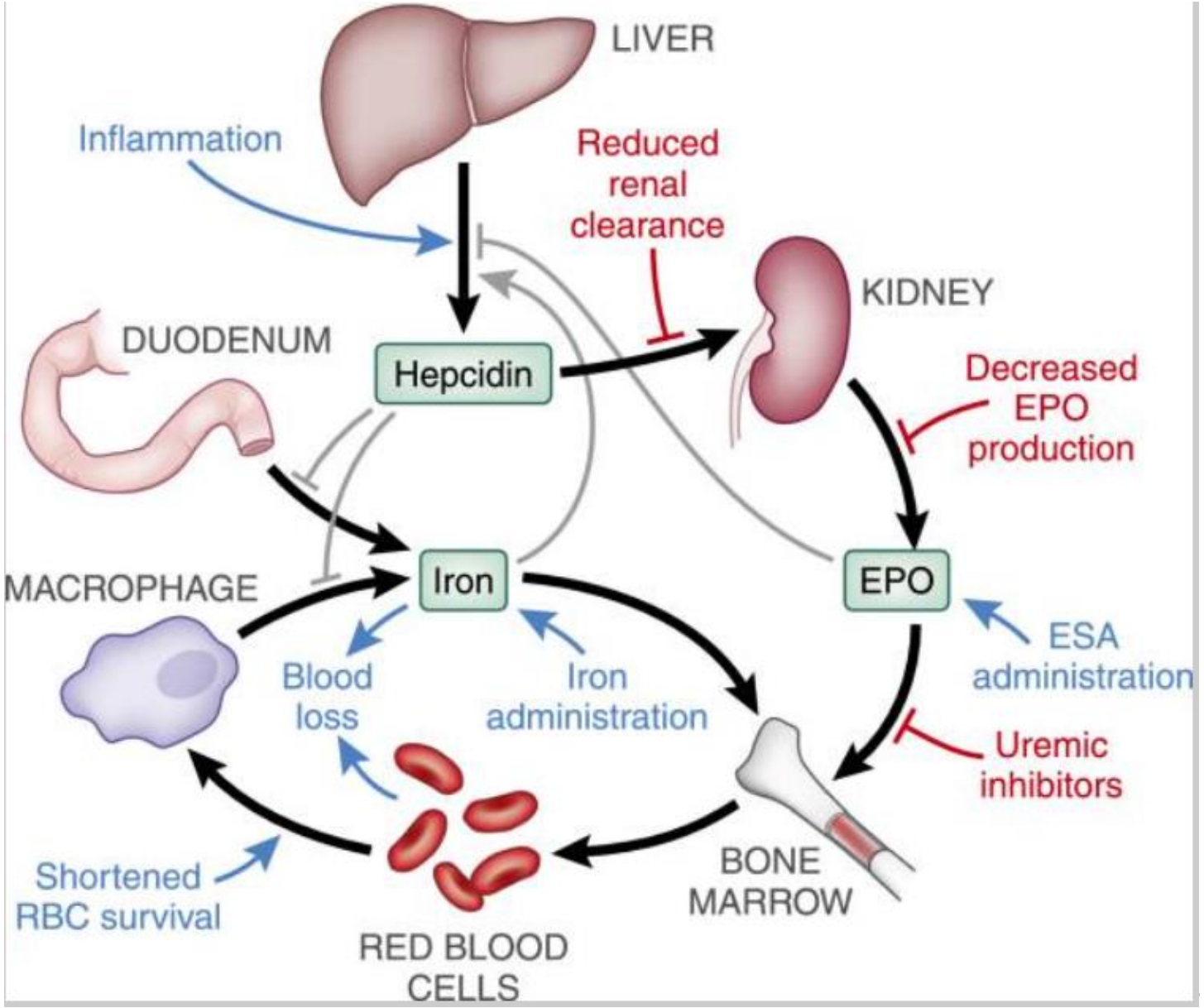
- None relevant to this presentation
- Special thanks to Finnian Mc Causland & Gearoid McMahon for use of some of their slides

Objectives

- Review current understanding of anemia pathophysiology in CKD/dialysis
- Updated guidelines and evidence
- Compare therapeutic options including novel agents
- Share practical approaches illustrated with clinical vignettes

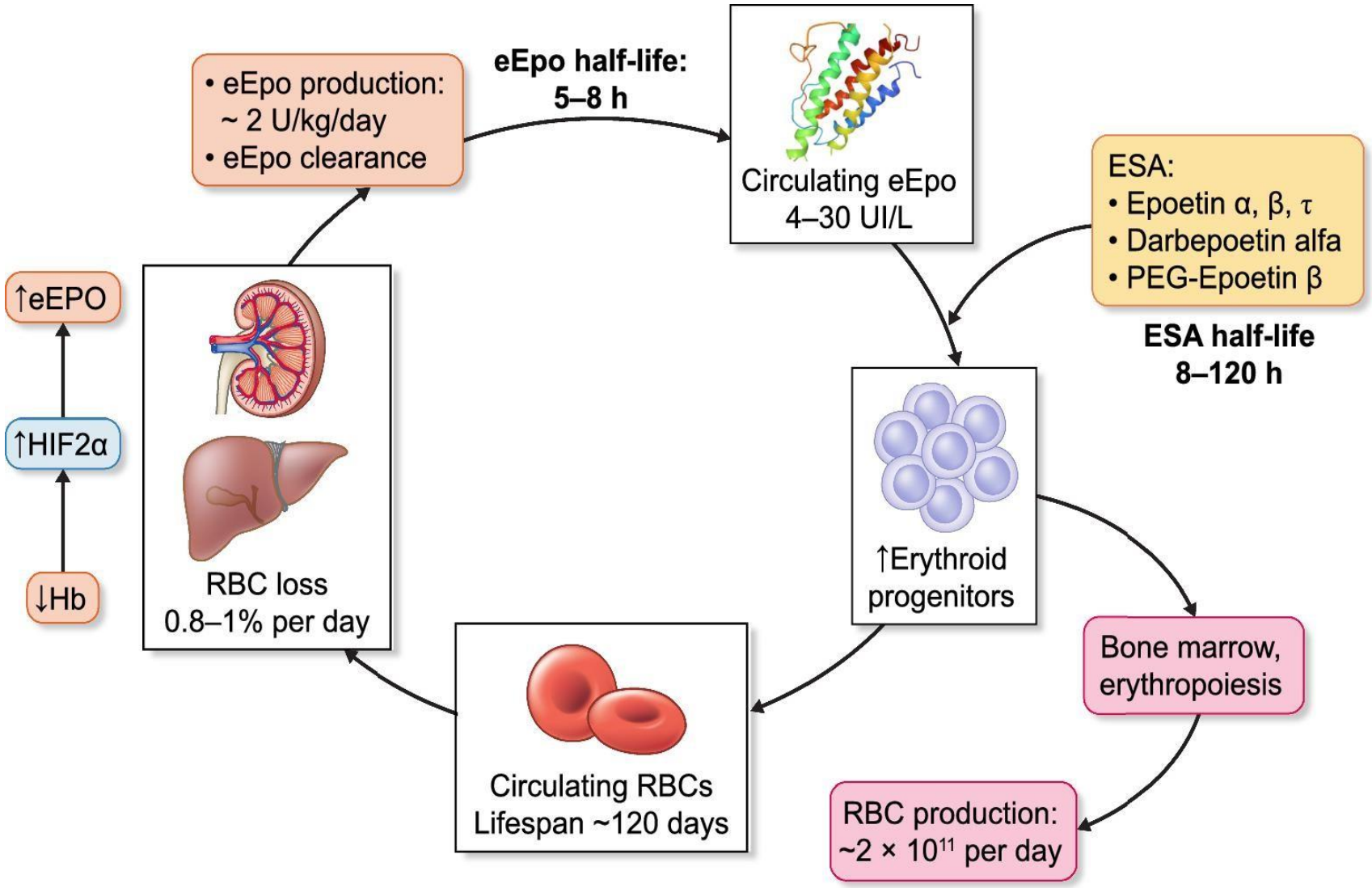
Pathophysiology of Anemia in CKD/Dialysis

- Iron-restricted erythropoiesis (↑ hepcidin)
- Inhibition of EPO production
- Uremic-inhibitors of erythropoiesis?
- Shortened RBC lifespan
- Increased blood loss (e.g. dialysis procedure)

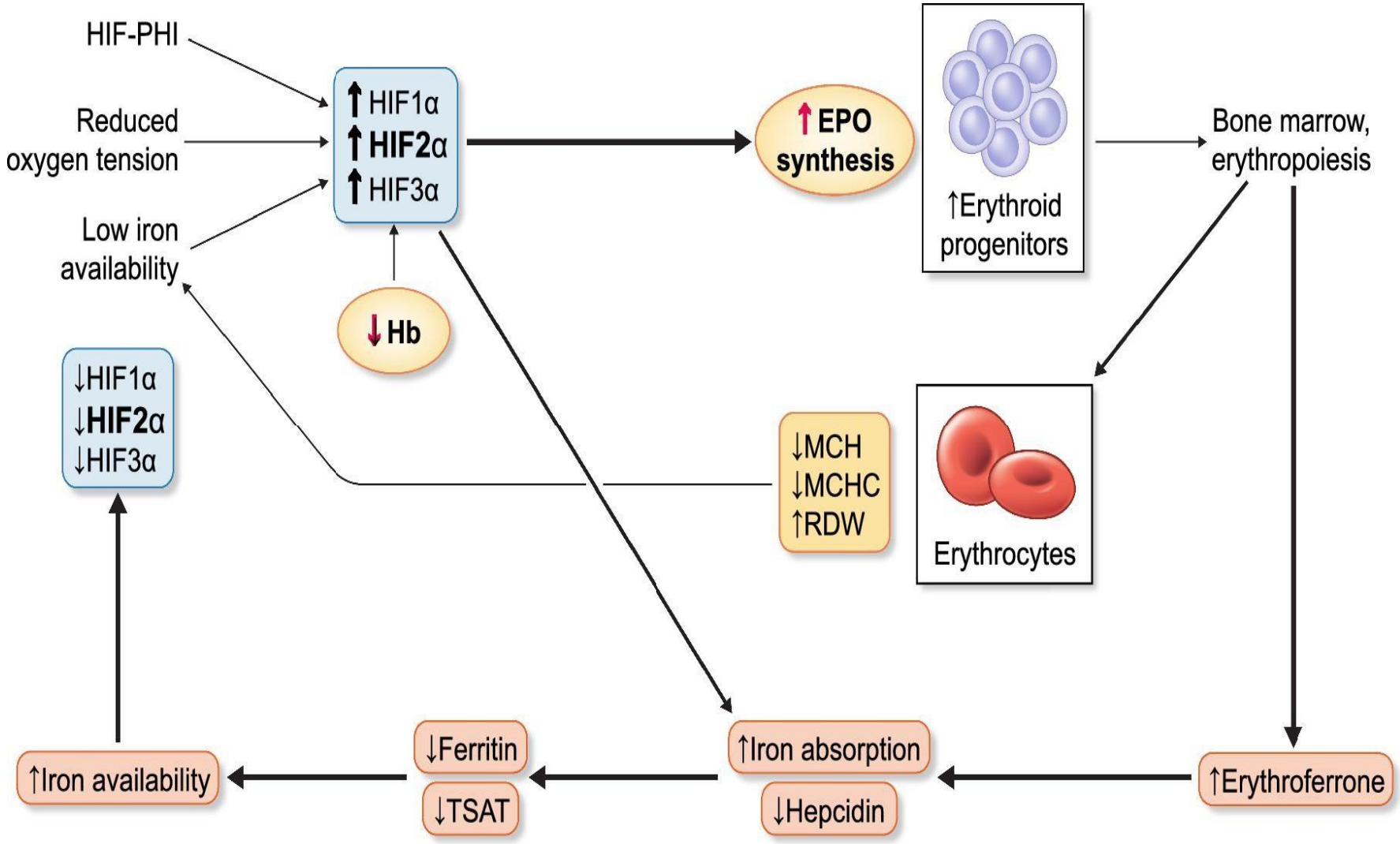


Babitt J. et al, JASN 2012

Stimulation of HIF System leads to EPO-stimulated Erythropoiesis

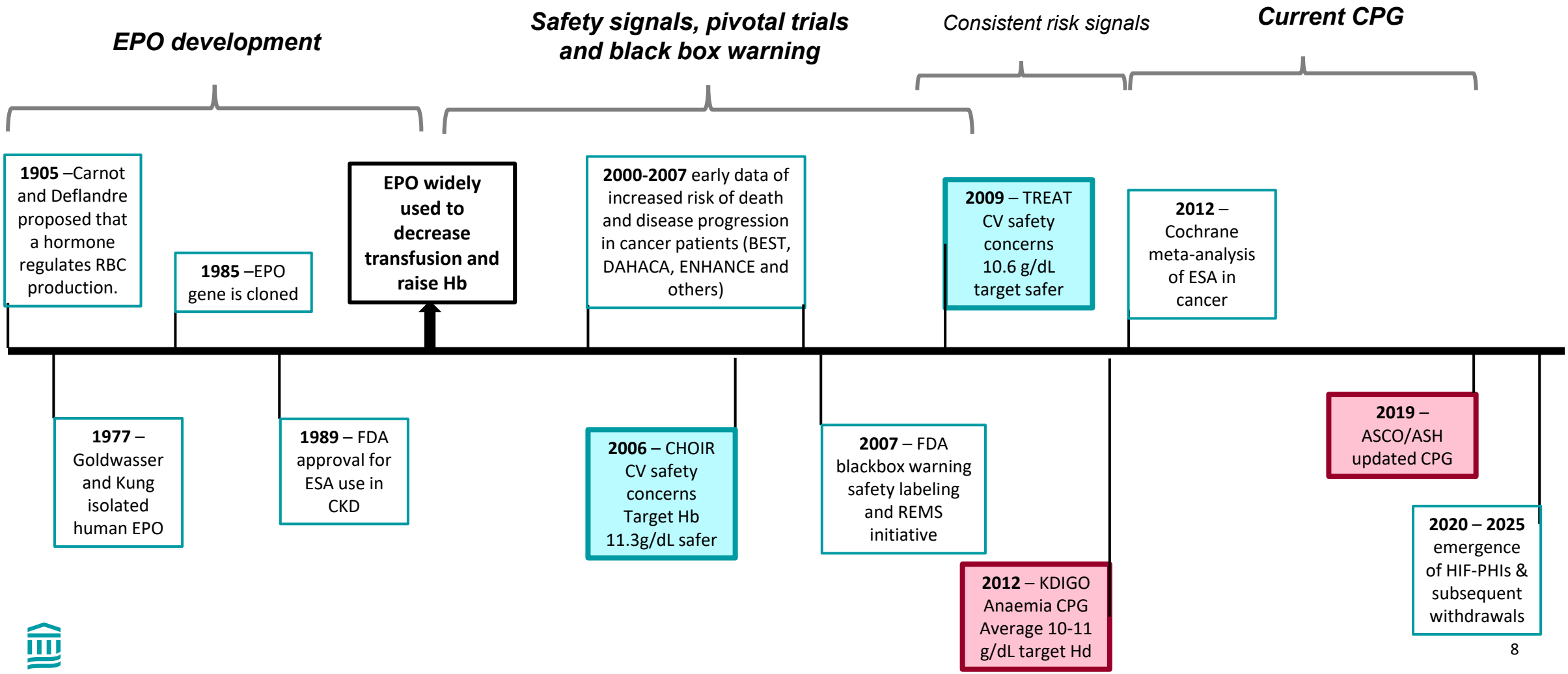


Relationship between Iron Metabolism, HIF Pathways and Erythropoiesis



Locatelli et al CKJ, 2023

ESAs: An Ever-Evolving Story



KDIGO Guidelines for Anemia 2026

Testing for Anemia *(not graded)*

- At least annually in CKD 3
- At least twice per year in CKD 4
- At least every 3 months in CKD 5 or G5D

Diagnosis

- Hb <13 g/dl males, <12g/dl females

Evaluation

Peripheral Blood smear
Hapto and LDH
Retics
CRP
B12
Folic acid
LFTs
SPEP/SFLC
TSH
PTH
Stool analysis
Parasites

KDIGO 2026: Treatment of Anemia in CKD- Iron Deficiency

CKD Non-Dialysis or CKD G5 on Peritoneal Dialysis

Indication? (2D)

- TSAT < 40% & ferritin < 100µg/L

  Or

  TSAT <25% & ferritin ≥ 100µg/L and <300µg/L

What preparation?

- 1-3 month trial of oral iron therapy or IV iron

Monitoring?

- Further doses guided by Hb response, TSAT, ferritin, ESA responsiveness/dose
- Evaluate iron status every 3 months

KDIGO 2026: Treatment of Anemia in CKD- Iron Deficiency

CKD on Hemodialysis (CKD 5HD)

Indication?

- TSAT ≤ 30% & ferritin ≤ 500µg/L

What preparation?

- Preference for IV iron in CKD 5HD

Monitoring?

- Further doses guided by Hb response, TSAT, ferritin, ESA responsiveness/dose
- Evaluate iron status every 1-3 months

KDIGO 2026: Treatment of Anemia in CKD-iron deficiency

Withhold?

- Ferritin >700µg/L **OR** TSAT ≥40%

Practice Points

- Switch from PO Iron to IV iron if insufficient effect on optimal oral regimen after 1-3 months or if poor tolerability
- Consider temporarily suspending iron therapy during systemic infections
- CKD & iron deficiency without anemia, consider treatment if ferritin <30µg/L & TSAT <20%

Domain	KDIGO 2012	KDIGO 2026	Change
CKD G5 PD — ferritin threshold	≤500 µg/L and TSAT ≤30% (same as HD)	TSAT <40% and ferritin <100 µg/L *or* TSAT <25% and ferritin 100–<300 µg/L (2D)	Two-tier threshold; lowered
CKD non-HD — ferritin threshold	≤500 µg/L and TSAT ≤30% (same as HD)	TSAT <40% and ferritin <100 µg/L *or* TSAT <25% and ferritin 100–<300 µg/L (2D)	Two-tier threshold; lowered
CKD G5 HD — route	IV preferred (2C)	IV preferred; proactive higher-dose approach endorsed (2D)	Grade 2C→2D; PIVOTAL cited
PD & non-HD — route	1–3 month oral trial; IV as alternative	Oral or IV; individualized by preference, severity, efficacy, tolerability, and cost. Switch to IV if oral fails at 1–3 months	More individualized
Upper safety stop	No formal ceiling; consensus against IV if ferritin >500 ng/mL	Withhold if ferritin >700 ng/mL or TSAT ≥40%; suspend during active infection	New in 2026
Evidence grade (initiation)	2C across most recommendations	2D — uncertainty in initiation thresholds explicitly acknowledged	Downgraded

IV Iron Preparations

Drug	Formulation
ferric carboxymaltose (Injectafer)	Colloidal iron hydroxide in complex with carboxymaltose
ferric pyrophosphate citrate (Triferic)	Mixed-ligand iron complex in which iron is bound to pyrophosphate and citrate
ferumoxytol (Feraheme)	Carbohydrate-coated iron oxide
iron dextran (Infed)	Complex of ferric oxyhydroxide and a polyglucose
iron sucrose (Venofer)	Aqueous complex of poly-nuclear iron hydroxide in sucrose
sodium ferric gluconate complex (generic Ferrlecit)	Iron oxide hydrate directly bonded to sucrose with a chelating gluconate

All preparations are colloids that have an iron-oxyhydroxide core that varies in size and density

The iron-oxyhydroxide core is surrounded by a carbohydrate shell to stabilize the core and slow the release of iron

Case

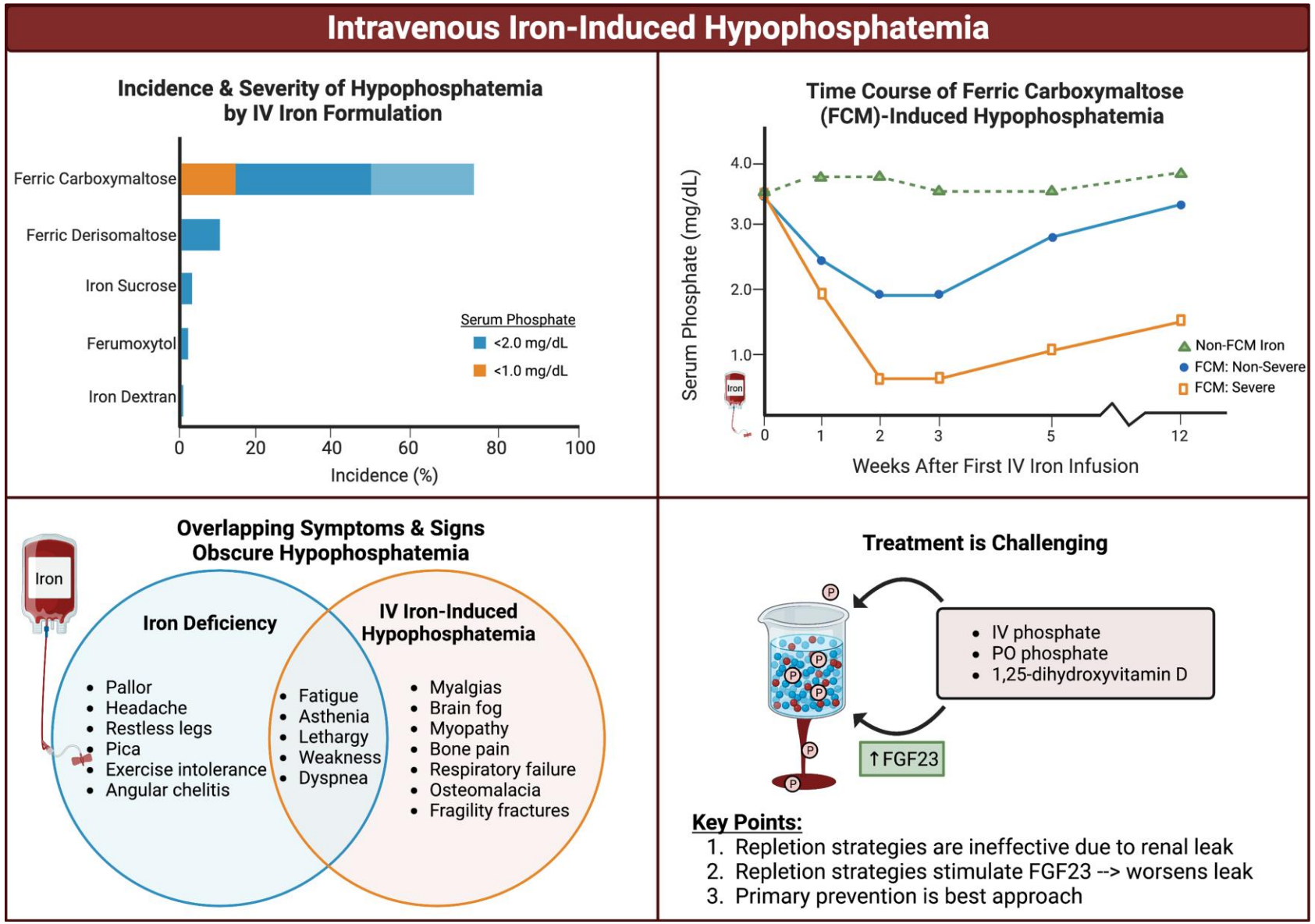
A patient with iron deficiency anemia receives IV iron therapy and subsequently develops severe hypophosphatemia with symptoms of muscle weakness and fatigue.

Which of the following IV iron formulations is most likely to cause this patient's hypophosphatemia, and what is the underlying mechanism?

(A) Iron Dextran; inhibition of sodium-phosphate co-transporters in the kidney.
(B) Ferric Carboxymaltose (FCM); increased levels of fibroblast growth factor 23 (FGF23).
(C) Iron Sucrose; decreased parathyroid hormone (PTH) secretion.
(D) Ferumoxytol (FER); decreased intestinal phosphate absorption.

Answer: B

Incidence, Mechanisms & Consequences of IV Iron induced hypophosphatemia



Martens et al, Hematology Am Soc Hematol Educ Program, 2023,

KDIGO 2026: Practice Points for ESAs

- Address all correctable causes of anemia prior to treatment initiation
- In anemia & CKD, in whom correctable causes of anemia addressed, ESA rather than HIF-PHI as first line

CKD Non-Dialysis/Kidney transplant/Pediatrics

- Initiate ESA if Hb ≤ 8.5-10 g/dl
- Hb concentration at which initiated individualized-symptoms, benefits vs risks (transfusions) (2D)
- Target the Hb level to below 11.5 g/dl

CKD Hemodialysis/PD

- Initiate ESA if Hb ≤ 9-10g/dl, avoid Hb falling below 9g/dl
- Individualization is reasonable- ESA may be started above 10g/dL
- Target Hb level to below 11.5 g/dl

KDIGO 2026: Practice Points for ESAs

- Avoid adjusting the dose of ESA more frequently than once every 4 weeks
- Exception: Hb increase by >1g/dl in 2-4 weeks after ESA initiation, reduce dose by 25-50%

- Use lowest dose possible that achieves & maintains treatment goals

- Reduce ESA dose rather than hold to avoid rapid Hb decline (unless Hb >11.5g/dl)

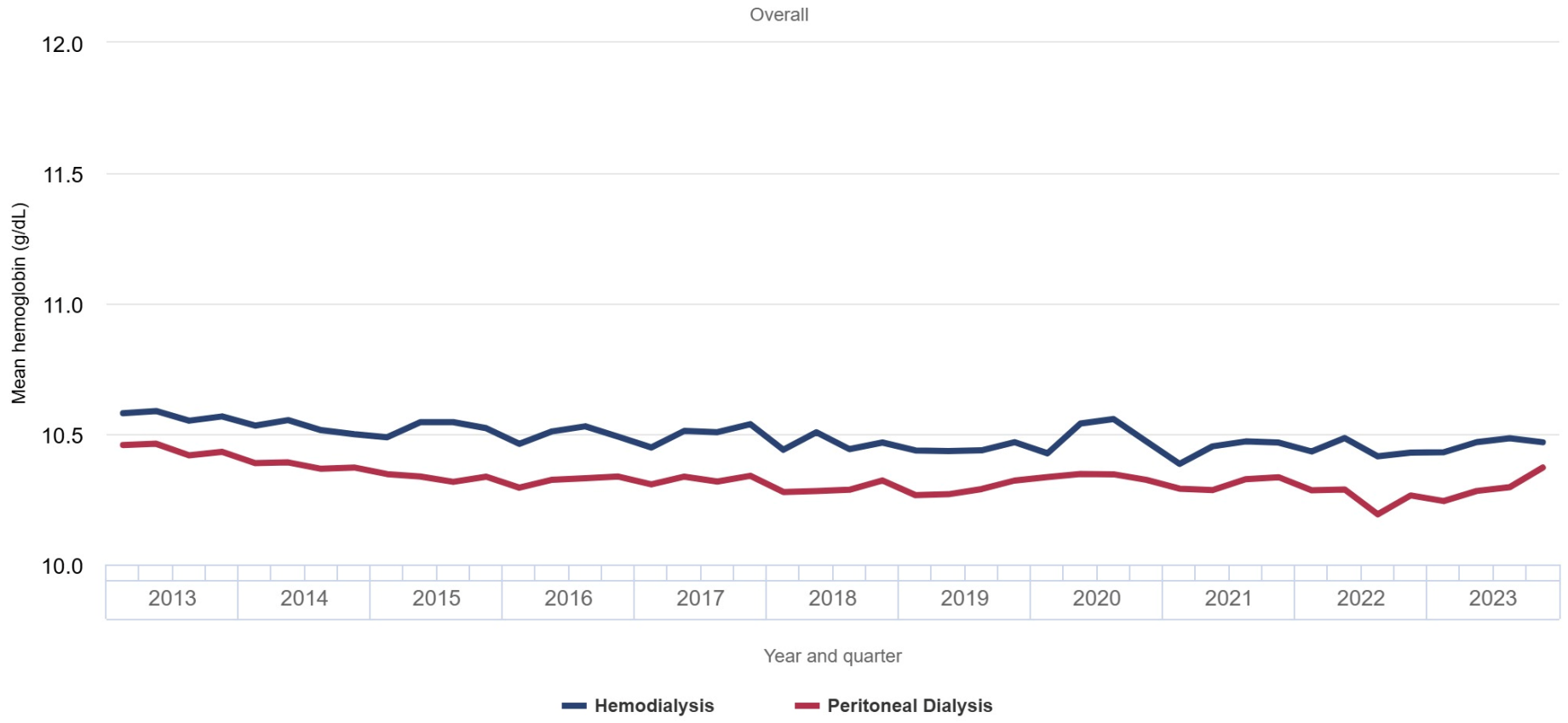
- Reasonable to suspend ESA during hospitalization for acute stroke, vascular access thrombosis, or thromboembolic events

- Active cancer or a history of cancer necessitate shared-decision making

	Normal Hematocrit Study (N=1233)	CHOIR (N=1432)	CREATE (N=603)	TREAT (N=4038)
Population	CHF & ESKD on dialysis	CKD	CKD	CKD with diabetes
Intervention	Epoetin alfa Hct 42% vs. 30%	Epoetin alfa 13.5 vs. 11.3 g/dL	Epoetin beta > 13 vs. 11g/dL	Darbepoetin alfa vs. placebo >13 vs. 9g/dL
Target Achieved?	No	No	Yes	No
Primary Endpoints	Time to death or first MI	Composite death, MI, HF Hospitalization, stroke	Time to first CV event	Composite of death or CV event Composite of death or ESKD
Results with higher Hb target	Trend towards increased risk Primary Outcome-stopped early RR 1.3 (0.92, 1.85)	Increased risk primary outcome HR 1.34 (1.03, 1.74)	Trend towards an increased risk primary outcome but non-significant HR 0.78 (0.53, 1.14)	No increase or reduction in the primary outcome HR 1.05 (0.94, 1.17) HR 1.06 (0.95, 1.19)
Additional Notes/Concerns	Follow up analysis: Higher rate thrombosis Increased events with higher EPO doses			Higher rates stroke HR 1.92 (1.38, 2.68) & malignancy assoc. mortality; less blood transfusions

Decline in mean Hb level and ESA dose since CHOIR & TREAT

Figure 3.5 Mean hemoglobin in patients receiving dialysis and using erythropoiesis-stimulating agents, 2013-2023



USRDS, 2017 & 2024

KDIGO 2026: ESA Use & Caution- Malignancy

"Active cancer or a history of cancer necessitate shared-decision making based on patient preferences, anticipated outcomes, esp. when cancer treatment is aimed at cure, with a target Hb that minimizes transfusion risk."

ASCO/ASH 2019
Management of cancer-associated anemia with ESA

Recommendation 1.1

Depending on clinical circumstances, ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose HgB has declined to < 10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Case

A 59-year-old man with **ESRD on thrice-weekly hemodialysis** has persistent anemia despite **high-dose ESA therapy**.

Current meds: epoetin alfa 15,000 units

Recent labs:

Hemoglobin: 8.8 g/dL (stable for 2 months)
Ferritin: 950 ng/mL
TSAT: 19%
CRP: 24 mg/L (↑)
Reticulocyte count: Low
PTH: 1400 pg/mL
Albumin: 2.9 g/dL
Stool guaiac: Negative
Peripheral smear: Normocytic, no schistocytes
Dialysis adequacy: Kt/V 1.5
Hepatitis B/C, HIV: Negative

Table 4 | Practical approach in presence of ESA hyporesponsiveness

Tests	Finding and action
1. Check adherence	If poor, attempt to improve (if self-injection)
2. Reticulocyte count	If >130,000/µl, look for blood loss or hemolysis: endoscopy, colonoscopy, hemolysis screen
Serum vitamin B_{12}, folate	If low, replenish
Iron status	If low, replenish iron
Serum PTH	If elevated, manage hyperparathyroidism
Serum CRP	If elevated, check for and treat infection or inflammation
Underdialysis	If underdialyzed, improve dialysis efficiency
ACEi/ARB use	If yes, consider reducing dose or discontinuing drug
3. Bone marrow biopsy	Manage condition diagnosed e.g., dyscrasia, infiltration, fibrosis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CRP, C-reactive protein; PTH, parathyroid hormone.

y.

KDIGO 2026: ESA Monitoring

- Monitor Hb every 2-4 weeks following ESA initiation or dose change
- Monitor Hb at least once every 3 months during maintenance phase

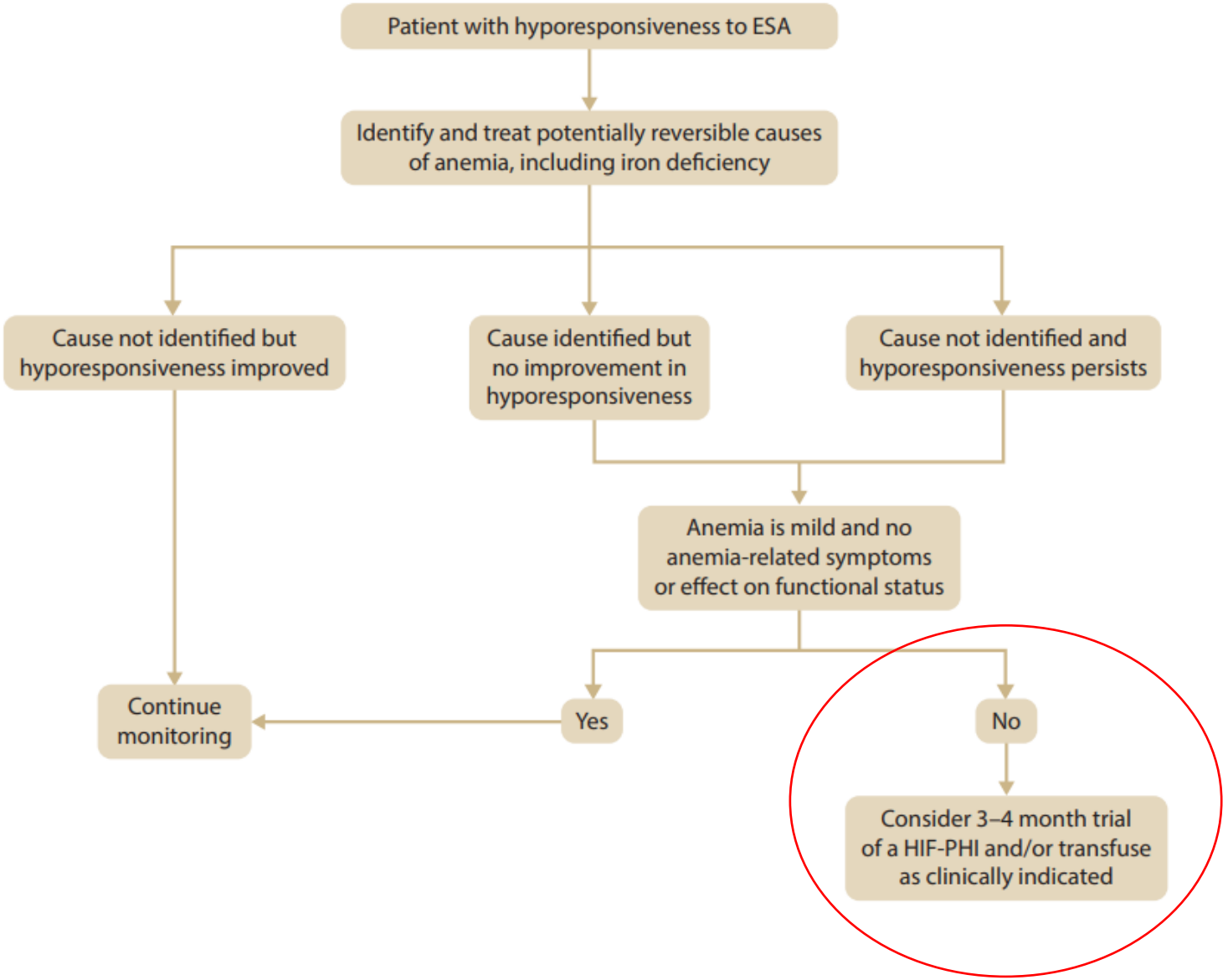
CLINICAL RESEARCH: DIALYSIS

Association of Different Definitions of Erythropoiesis-Stimulating Agent Hyporesponsiveness with Major Adverse Cardiovascular Events

Insights From ASCEND-D

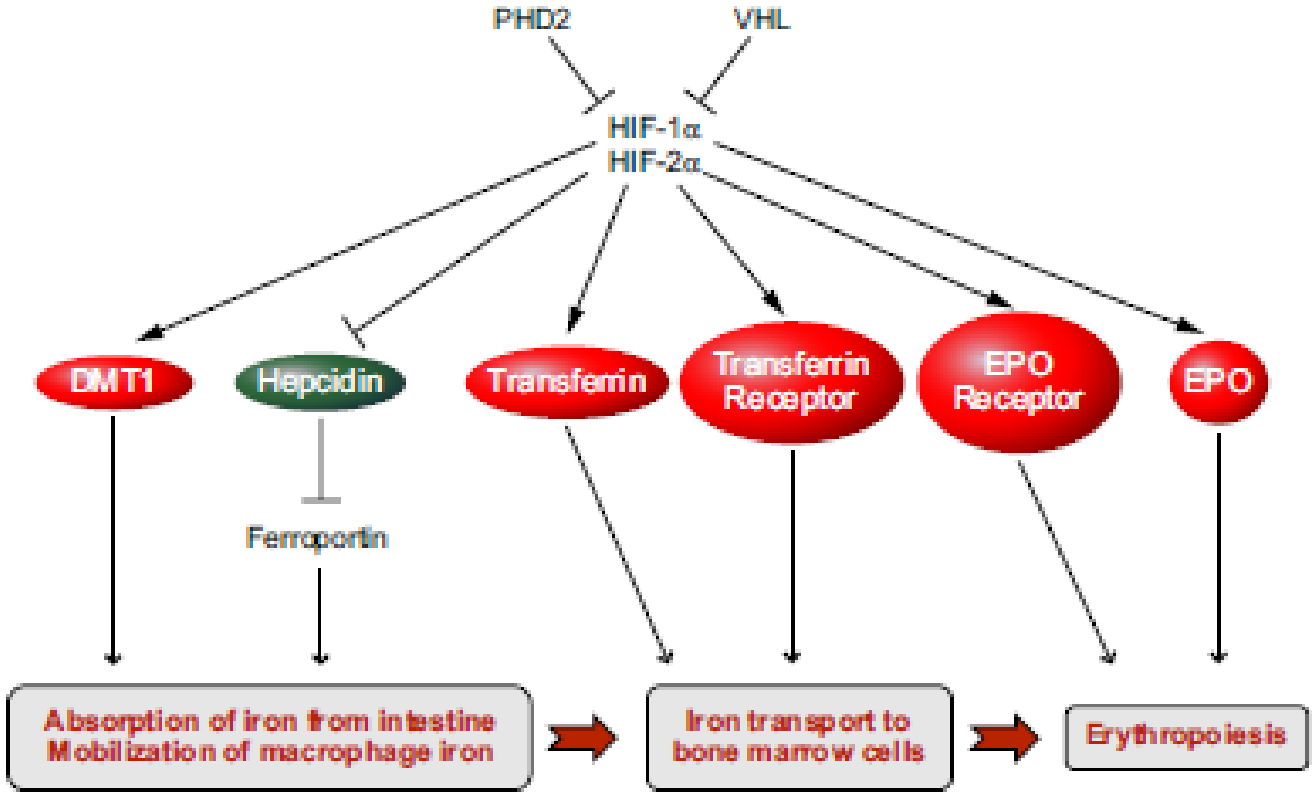
All 3 definitions were associated with higher risk of composite MACE outcome

KDIGO 2026: ESA Hyporesponsiveness & HIF-PHIs

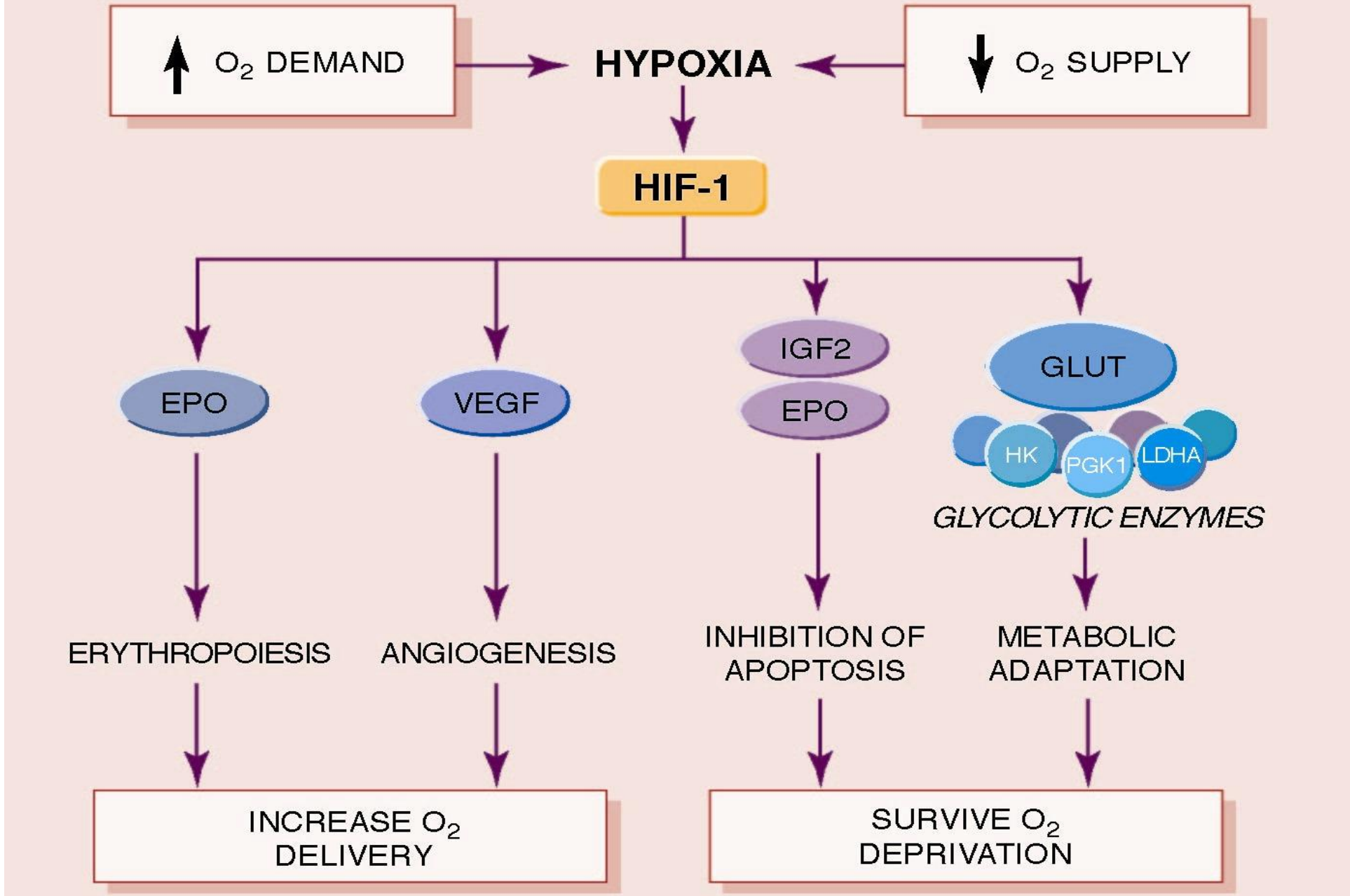


Hypoxia Inducible Factor

- Regulates multiple genes as a response to hypoxia via
  - Transcriptional effects
  - Regulating RNA expression
  - Enhancing the function of other transcription regulators
- Regulates iron metabolism through effects on absorption, transport and utilization
- Regulates immune response pathways (via NF-κβ)
- Overall effect is to improve efficiency of tissue oxygen utilization

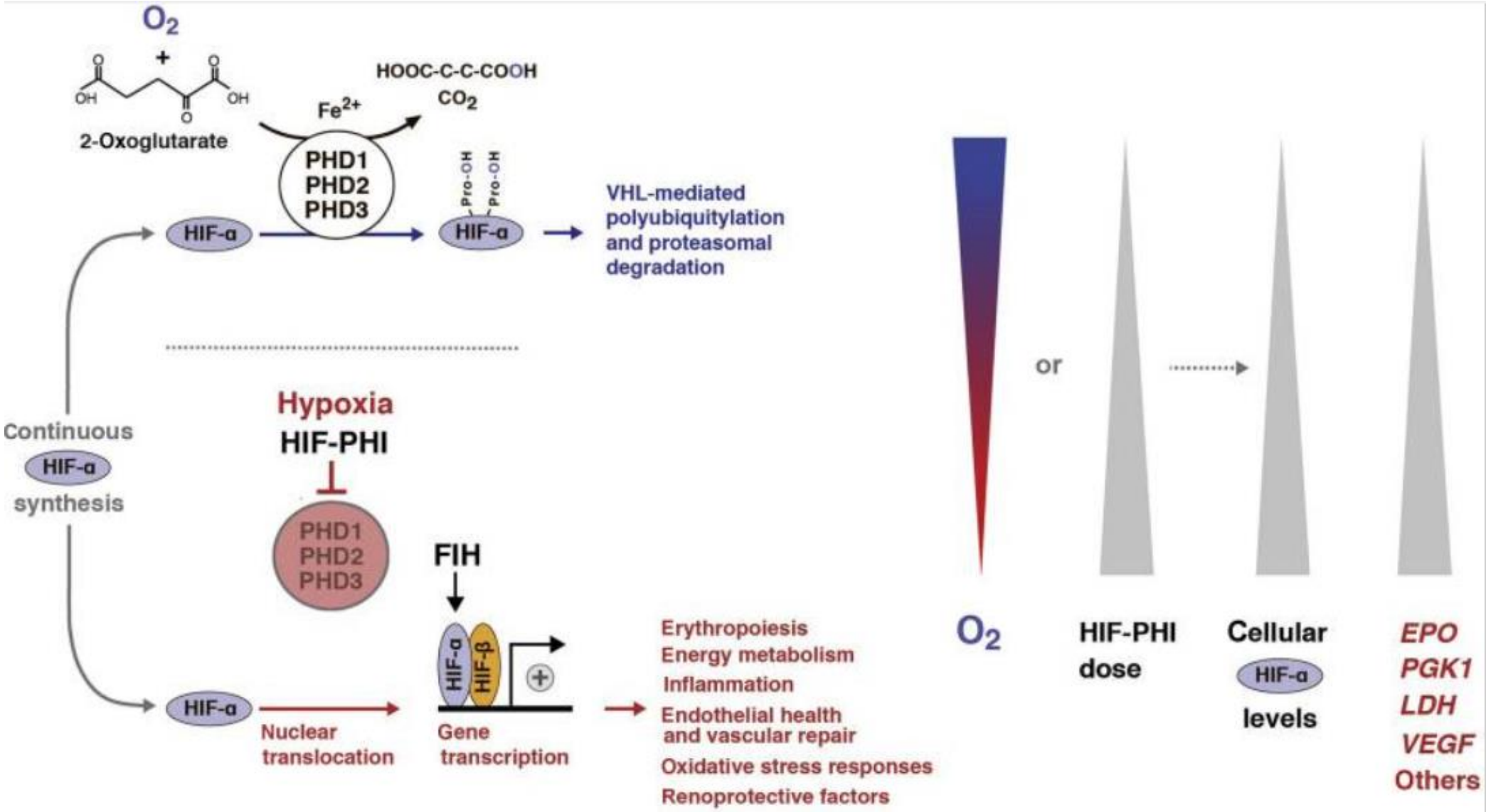


Prabhakar, Physiol Rev 2012



(Modified from Semenza et al)

- Three enzymes responsible for HIF degradation: PHD1, PHD2 and PHD3
- Part of family of iron and 2-oxoglutarate dependent oxygenases
- Require oxygen as a substrate and so act as oxygen-sensitive regulators of HIF activation



Haase, KI Supplements,,2021

Study	Comparator	Patients, *n*	CKD stage	Treatment period (weeks)	Target Hb (g/dl)	Efficacy endpoints	Safety endpoints
Roxadustat (vs placebo)							
ALPS [56] (Europe)	Placebo	594	3–5	52–104	10–12	Mean Hb change at 28–52 weeks: 1.99 vs 0.30 g/dl Patients with Hb response at 24 weeks: 79.2% vs 9.9%	Hypertension: 22.3% vs 13.8% Nausea: 9.5% vs 3.0% Diarrhoea: 8.4% vs 3.4%
ANDES [54] (glob							vs % vs vs
OLYMPUS [55] (global)							vs % vs
Chen *et al*. [57] (China)						6% Rescue therapy: 3% vs 12% Mean hepcidin change at 9 weeks: −56.1 vs −15.1 ng/ml	vs 8% 2% vs 2%
Daprodustat (vs placebo)							
ASCEND-NHQ [58] (global)	Placebo	614	3–5	28 weeks	11–12	Mean Hb change at 24–28 weeks: 1.58 vs 0.19 g/dl Patients with Hb increase ≥1 g/dl at 28 weeks: 77% vs 18% Rescue therapy: <1% vs 10% Change in the SF-36 vitality (fatigue) score at 28 weeks: 7.3 vs 1.9 points	Hypertension: 7% vs 5% Retinal disorder: <1% vs 3.0%

HIF-PHIs vs. Placebo

What did we learn?

Their physiological mechanisms translate into a measurable improvement in Hb among patients with CKD

Stoumpos et al, NDT 2024

Study	Comparator	Patients, *n*	CKD stage	Treatment period (weeks)	Target Hb (g/dl)	Efficacy endpoints	Safety endpoints
Enarodustat (vs ESAs)							
SYMPHONY-ND [67] (Japan)	Darbepoetin alfa	216	3–5	24	10–12	Mean Hb level at 20–24 weeks: 10.96 vs 10.87 g/dl Patients with target Hb at 24 weeks: 88.6% vs 87.9%	Retinal disorders: 3.7% vs 0.9% Upper respiratory tract infection: 17.8% vs 22.9% Hypertension: 4.7% vs 4.6%
Molidustat vs ESA							
MIYABI ND-C [66]							
MIYABI ND-M [68]							
Desidustat (vs ESA							
DREAM-ND [69] (I Sri Lanka)							

HIF-PHIs vs. ESAs

What did we learn?

In non-inferiority designed studies, HIF-PHIs were as effective as ESAs in increasing Hb

Vadadustat Trials

	PROTECT (N= 3476)	INNO2VATE (N=3923)
Population	**ESA-untreated** ND-CKD: Hb <10 g/dL **ESA-treated** ND-CKD: Hb 8-12 g/dL	**Incident** DD-CKD: Hb <10 g/dL **Prevalent** DD-CKD: Hb 8-12 g/dL
Intervention	1:1 randomization; ESA or Vadadustat	
Key Inclusion Criteria	≥ 18yrs, ferritin >99, tsat >19%	
Key Exclusion Criteria	Recent CV event, uncontrolled HTN	
Primary Safety Endpoint	MACE **HR 1.17 (1.01, 1.36)** **Did not meet the non-inferiority margin for CV safety**	MACE **HR 0.96 (0.83, 1.11)** **Vadadustat non-inferior to ESA for CV safety**
Primary Efficacy Endpoint	Mean change in Hb from baseline **Met non-inferiority criterion at weeks 24 for both ESA-untreated and ESA-treated**	Mean change in Hb from baseline **Met non-inferiority criterion at weeks 24 and weeks 40 in both incident and prevalent DD-CKD**

Chertow et al, NEJM 2021
Eckardt et al, NEJM, 2021

Daprodustat Trials

	ASCEND-ND (N= 3872)	ASCEND-D (N=2964)
Population	Within 6/52 of planned dialysis initiation or initiated within 90 days of randomization & Hb 8-11 g/Dl	Prevalent DD-CKD Hb 8-10 g/dL
Intervention	1:1 randomization; ESA or Daprodustat	
Key Inclusion Criteria	≥ 18yrs, ferritin >99, tsat >19%	
Key Exclusion Criteria	ESA treatment within 8/52 of screening	Recent CV event, recurrent or recent cancer
Primary Safety Endpoint	MACE **HR 1.03 (0.89, 1.19)** **Met the non-inferiority margin for CV safety**	MACE **HR 0.93 (0.81,1.07)** **Met the non-inferiority margin for CV safety**
Primary Efficacy Endpoint	Mean change in Hb from baseline **Met pre-specified non-inferiority criterion**	Mean change in Hb from baseline to average follow **Met non-inferiority criterion**

Singh et al, NEJM 2021
Singh et al, NEJM, 2021

KDIGO 2026: HIF-PHIs

- Do not use ESAs & HIF-PHIs in combination
- Hb thresholds for initiation and maintenance of HIF-PHIs unknown
- Monitor Hb levels 2-4 weeks after initiation or dose adjustments; every 4 weeks during maintenance
- Discontinue after 3-4 months if desired response has not been achieved
- Do not use in active malignancy, recent CV event, thromboembolic events or vascular thrombosis

KDIGO 2026: Anemia & CKD at risk for adverse events with HIF-PHIs

Theoretical or Experimental Risk

- Active cancer/not in remission for at least 2-5 years
- Polycystic Kidney Disease
- Proliferative Retinal Disease
- Pulmonary Arterial Hypertension
- Pregnancy

Concern for Risk

- Hx cardiovascular events
- Hx of thromboembolic events
- Hx access thrombosis
- Hepatic impairment
- Seizures, exfoliative dermatitis, hypothyroidism, bacterial sepsis

Insufficient Data

- Post-transplant anemia
- Pediatrics

ESA HIF-PHI

Area	Domain	KDIGO 2012	KDIGO 2026	Change
ESA	**First-line agent**	ESA (HIF-PHIs not yet available)	ESA preferred over HIF-PHI as first-line after correctable causes addressed (2D)	New in 2026
ESA	**CKD G5D initiation**	Hb 9–10 g/dL to avoid Hb falling <9 g/dL (2B)	Hb ≤9–10 g/dL; lower end for high ESA risk; higher end for transplant candidates (2D)	More stratified; grade 2B→2D
ESA	**CKD non-dialysis initiation**	Hb <10 g/dL; individualize based on rate of fall, transfusion risk, symptoms (2C)	Hb 8.5–10 g/dL; symptom-driven; stratified by comorbidity and transplant status (2D)	Threshold narrowed; grade downgraded
ESA	**Suspension triggers**	Not specified	Suspend during hospitalization for acute stroke, vascular access thrombosis, or thromboembolic events	New in 2026
ESA	**Hyporesponsiveness**	Avoid escalation beyond 2× initial weight-based dose (2D)	Confirmed; reassess indication if no reversible cause; consider HIF-PHI in selected cases	HIF-PHI as rescue added
HIF-PHI	**Role vs ESA**	Not addressed	Second-line to ESA; do not combine with ESA	New in 2026
HIF-PHI	**Safety contraindications**	Not addressed	Avoid in active malignancy, high thrombosis or cardiovascular risk	New in 2026
HIF-PHI	**Hb initiation & target**	Not addressed	Use same Hb thresholds as ESA; lowest effective dose; insufficient data for different targets	New in 2026

ESA = erythropoiesis-stimulating agent; HIF-PHI = hypoxia-inducible factor prolyl hydroxylase inhibitor; Hb = haemoglobin

KDIGO 2026 Anemia Guideline — Kidney International, Jan 2026

Summary

- Iron deficiency should be corrected across the spectrum of kidney disease, even in the absence of overt anemia
- ESA use should be guided by evidence from placebo-controlled trials
- ESA hyporesponsiveness is important to recognize & work-up
- Although HIF-PHIs show promise, their approval and use has been limited by safety concerns
- Specific guidelines on Hb thresholds/maintenance with HIF-PHIs extrapolated from ESA literature
- Guidelines are guidelines- as such should be thoughtfully integrated into patient-physician discussions