Brigham and Women's Hospital
Founding Member, Mass General Brigham

Anemia Management: Update and Best Practices

Brona M. Moloney MB BCh BAO, MMSc
Associate Physician MGB Nephrology Division

Brona M. Moloney, MB BCh BAO, MMSc

- Residency in Internal Medicine with RCPI
- Higher Specialist Training Nephrology & Internal Medicine RCPI with CSCST
- Critical Care Training in Adelaide, Australia
- MGB Clinical Research Nephrology Fellowship
- MMSc from HMS
- Attending Nephrologist at BWH
- Research interests: Autonomic Dysfunction and adverse cardio-kidney metabolic outcomes in CKD and ESKD
- Clinical Interests: Everything!

Disclosures

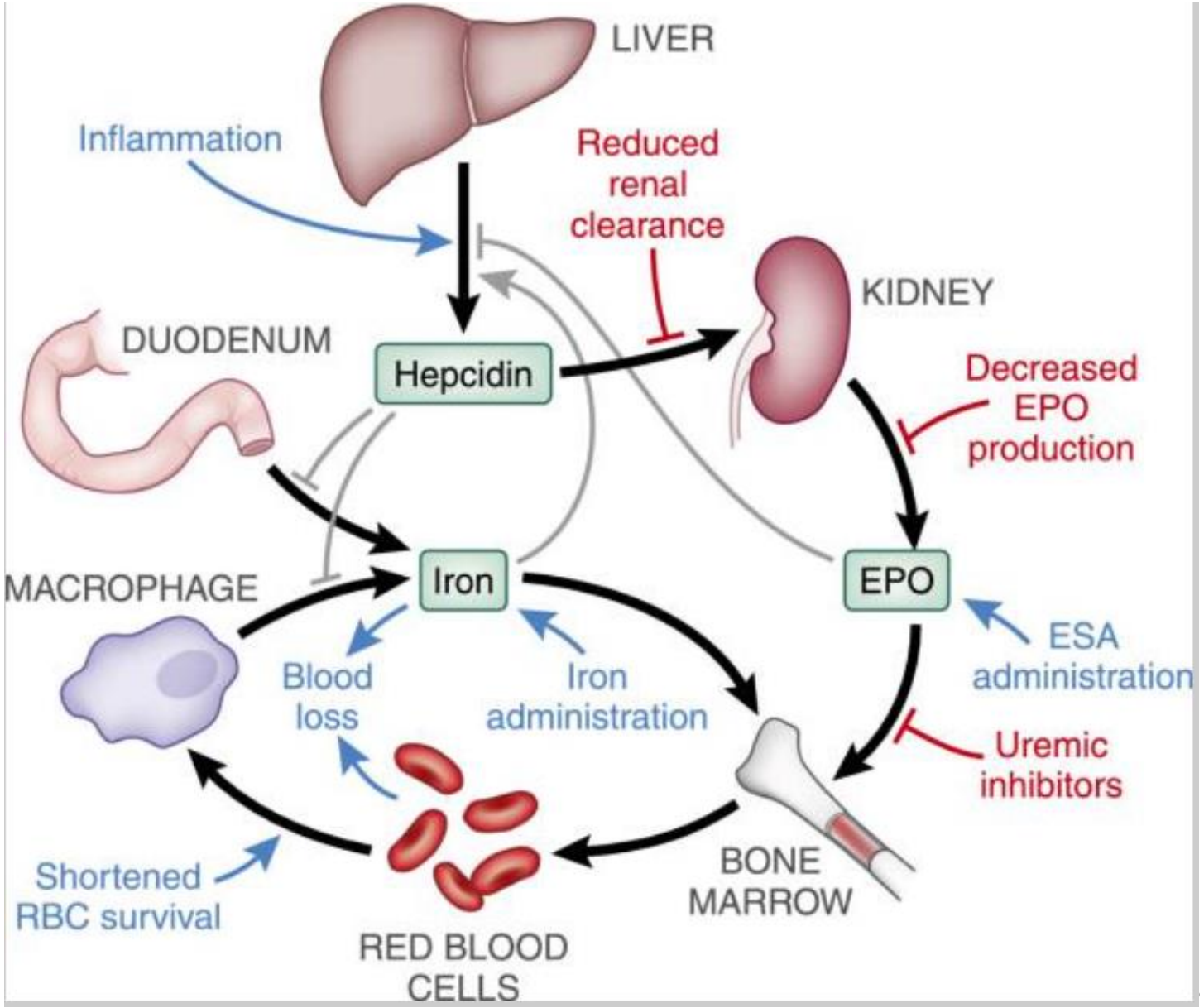
- None relevant to this presentation
- Special thanks to Finnian Mc Causland & Gearoid McMahon for use of some of their slides

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

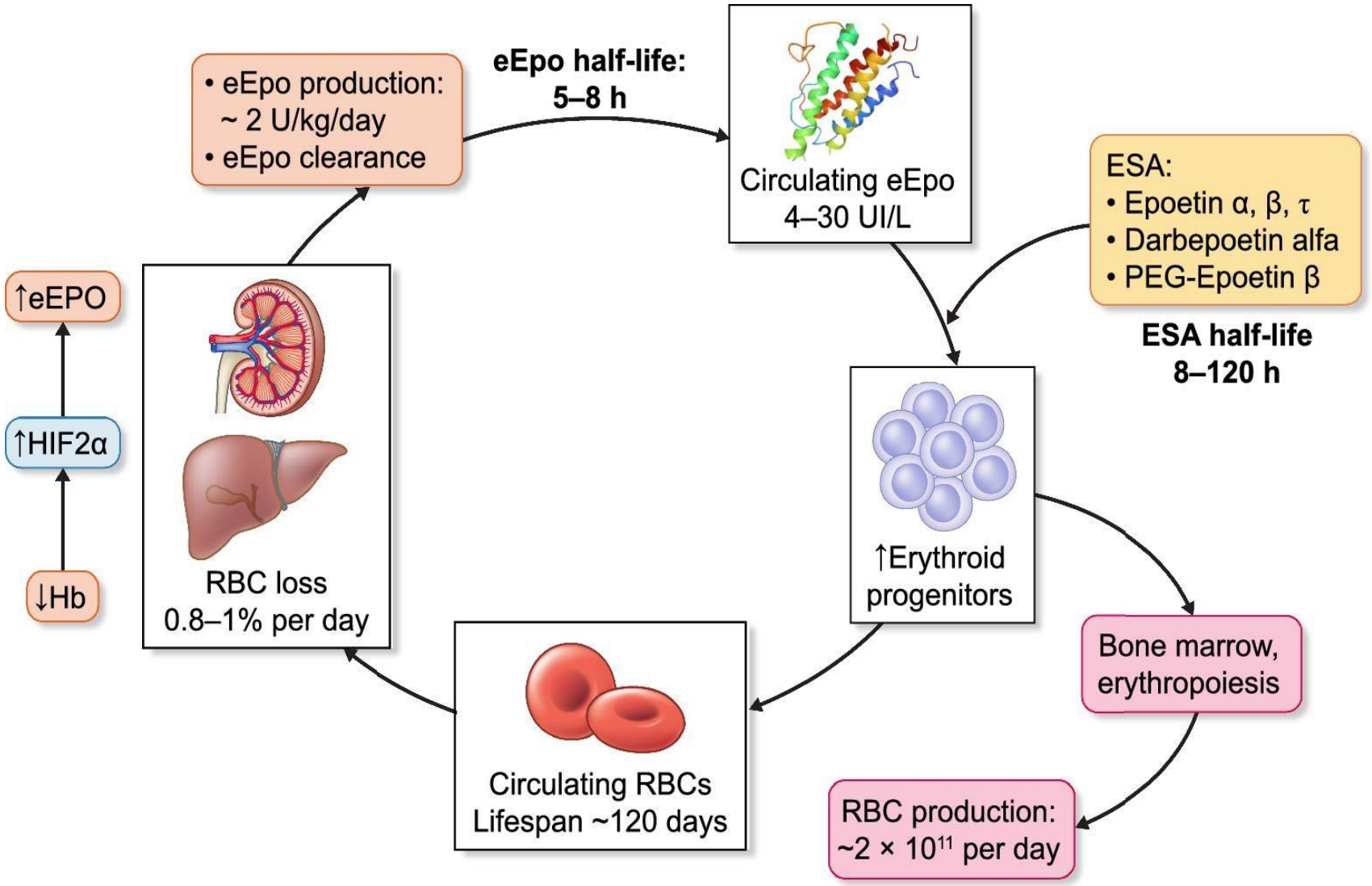
Pathophysiology of Anemia in CKD/Dialysis

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

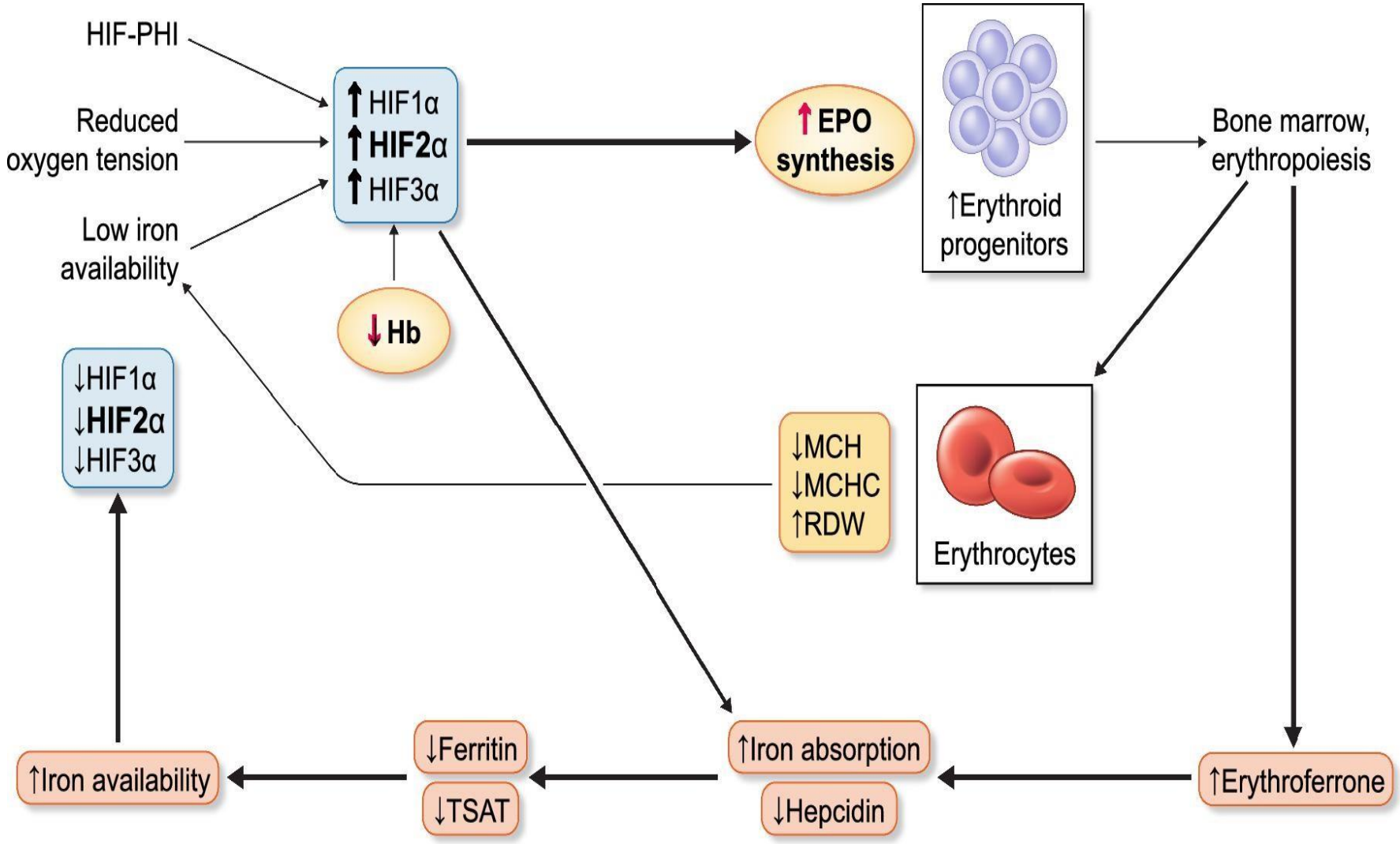


Babitt J. et al, JASN 2012

Stimulation of HIF System leads to EPO-stimulated Erythropoiesis

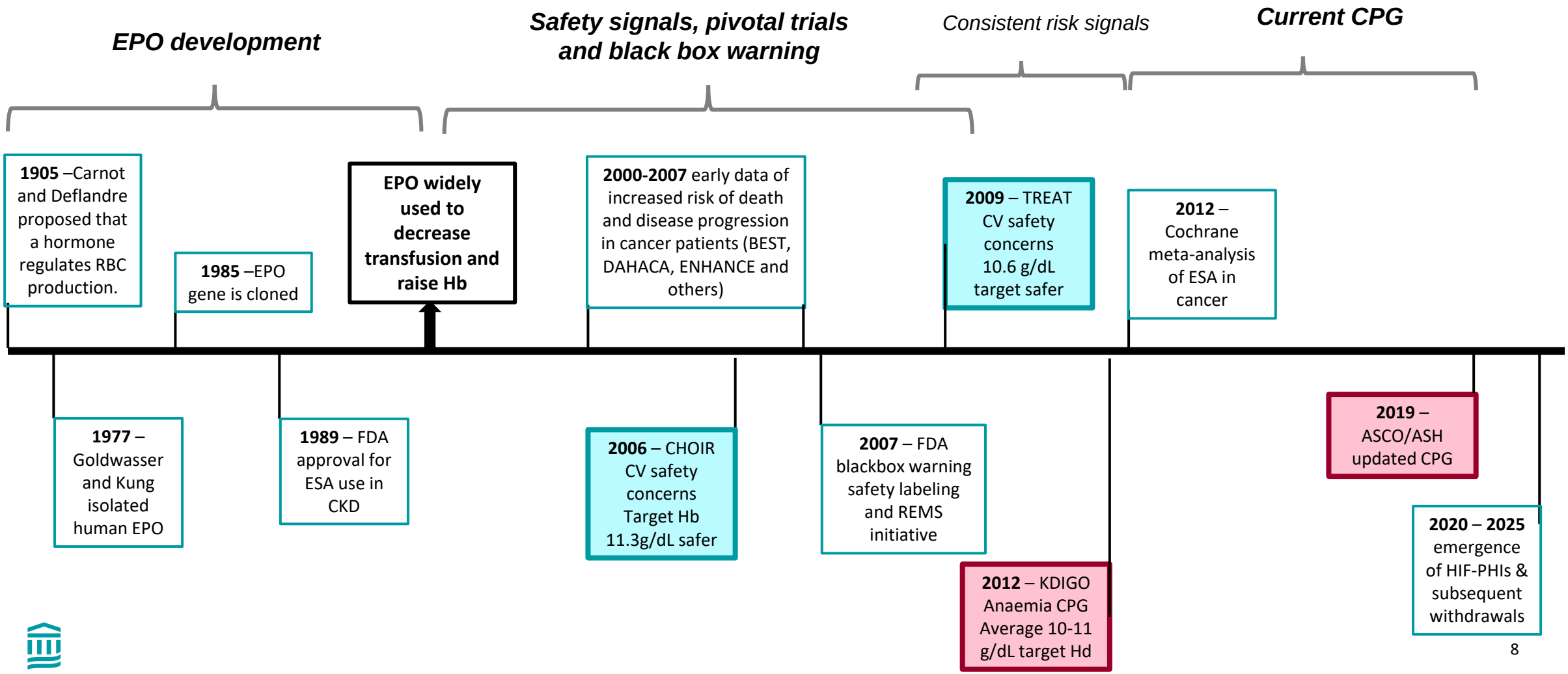


Relationship between Iron Metabolism, HIF Pathways and Erythropoiesis



Locatelli et al CKJ, 2023

ESAs: An Ever-Evolving Story



KDIGO Guidelines for Anemia 2012 (2025 coming soon…)

Testing for Anemia *(not graded)*

- At least annually in CKD 3
- At least twice per year in CKD 4-5ND
- At least every 3 months in CKD 5HD and CKD 5PD

Diagnosis

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

CKD with known anemia, not on ESA *(not graded)*

- At least every 3 months in CKD 3-5ND and CKD 5PD
- At least monthly in CKD 5HD

Evaluation*

- CBC and differential
- Absolute reticulocyte count
- Serum ferritin
- Serum transferrin saturation (TSAT)
- Serum vitamin B12 and folate levels

*2025 guidelines will suggest an expanded evaluation

KIDGO 2012: Treatment of Anemia in CKD- Iron agents

CKD Non-Dialysis

What preparation?

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

Indication?

- TSAT ≤ 30%, ferritin ≤ 500µg/L**
- ↑ Hb desired without starting ESA/ decrease in ESA dose required

Monitoring?

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

*200mg elemental iron daily e.g. ferrous sulphate 325mg TID (65mg elemental iron in each pill)

Vs. KDOQI 2006

- Ferritin: >200 µg/L in CKD 5HD &
- >100 µg/L in CKD ND and CKD5PD
- TSAT >20%

**2025 guidelines will be even more prescriptive

KDIGO 2012: Treatment of Anemia in CKD- Iron agents

CKD on Dialysis

What preparation?

- Preference for IV iron in CKD 5HD/PD

Indication?

- TSAT ≤ 30%, ferritin ≤ 500 µg/L
- ↑ Hb desired without starting ESA/decrease in ESA dose required

Monitoring?

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

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

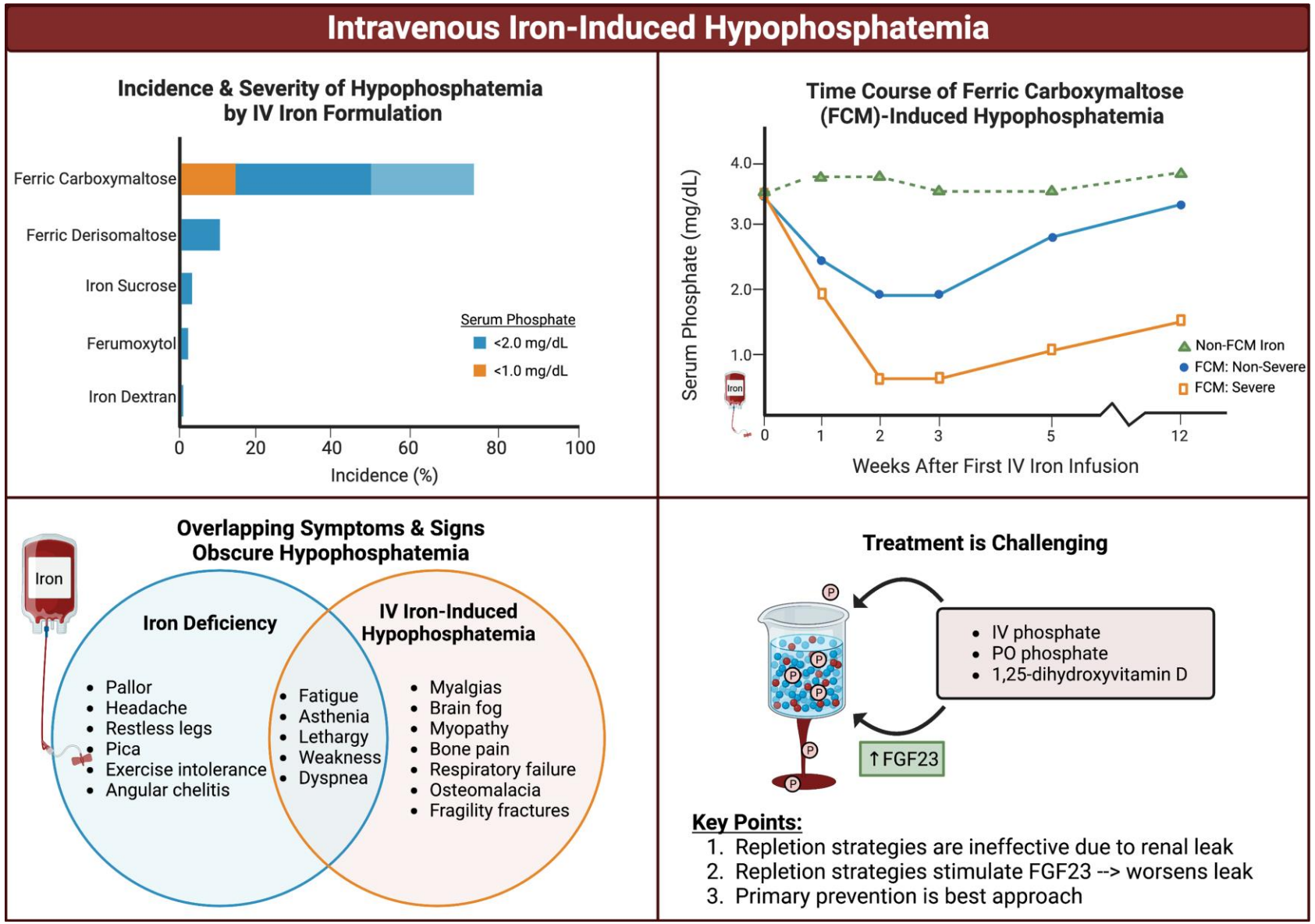
A patient with iron deficiency anemia receives IV iron therapy and subsequently develops severe hypophosphatemia with symptoms of muscle weakness and fatigue.

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,

Practice Points for ESAs

- Address all correctable causes of anemia prior to initiation
- **Current guidelines (KIDGO 2012)**

  CKD-ND

  - Initiate ESA if Hb<10g/dL
  - Individualized decision based on rate fall, prior response to iron, risk transfusion, risks related to ESA and anemia symptoms

  CKD-5/HD

  - Initiate ESA if Hb is between 9-10g/dL, avoid Hb falling below 9g/dL
  - Individualization is reasonable- and ESA may be started above 10g/dL
  - It is suggested that ESAs not be used to maintain doses >11.5g/dL

In all patients, ESAs should not be used to intentionally increase the Hb >13g/dL

KDIGO 2012, KI Supplements, 212

	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

TREAT Trial
What came before: The perils of non-placebo-controlled trials

- The long-standing presumption of a benefit of ESAs in this patient population led to **non–placebo-controlled trials**, which, by design, cannot provide a reliable assessment of risk and benefit

- TREAT was the only placebo-controlled trial

- Following TREAT, “it is reasonable to conclude that among patients with diabetes, chronic kidney disease, and moderate anemia who are not undergoing dialysis, the increased risk of stroke, and possibly death among patients with a history of a malignant condition, outweighs any potential benefit of an ESA”.

KDIGO 2012: ESA Use & Caution- Malignancy

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*).

Limitation:

- Patients with cancer are often excluded from CKD trials
- Patients with CKD are often excluded from cancer trials

Lack of well-designed studies to examine the relationship between ESA exposure in patients with CKD and the risk for incident or recurrent malignancy

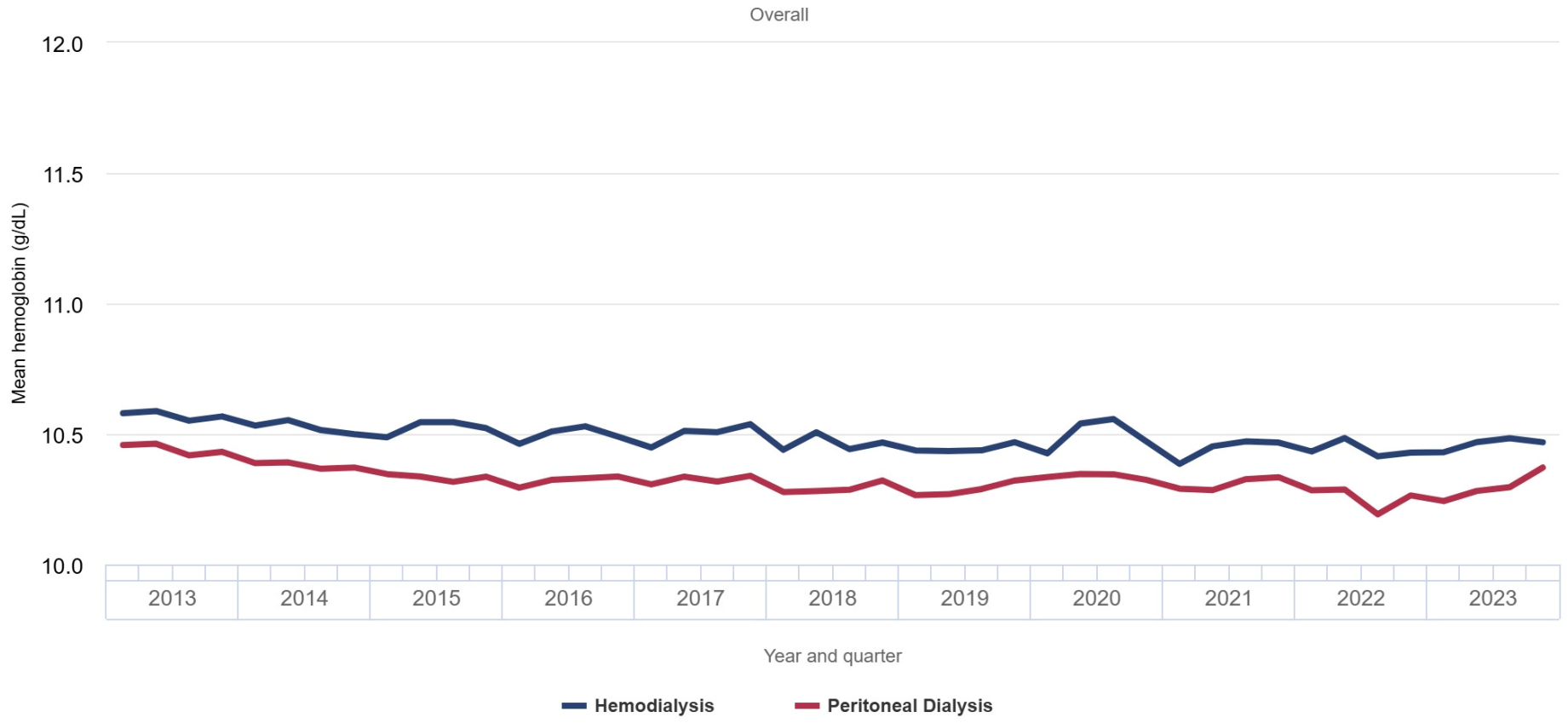
ASCO/ASH 2019
Management of cancer-associated anemia with ESA

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).

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 2012
ESA Monitoring

- Monthly Hb check at initiation
- CKD non-HD: 3 monthly check
- CKD 5D: Monthly check

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

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 y.

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

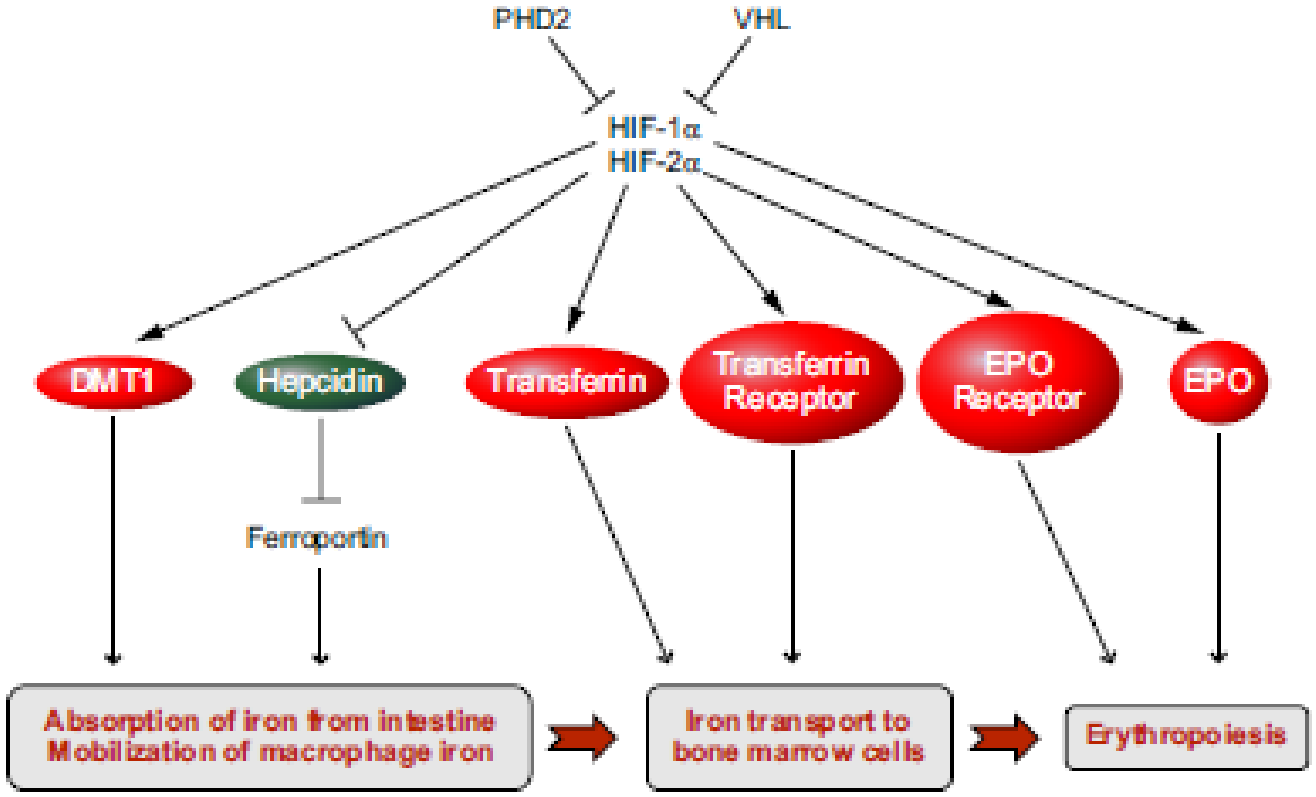
Table 4 | Practical approach in presence of ESA hyporesponsiveness

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

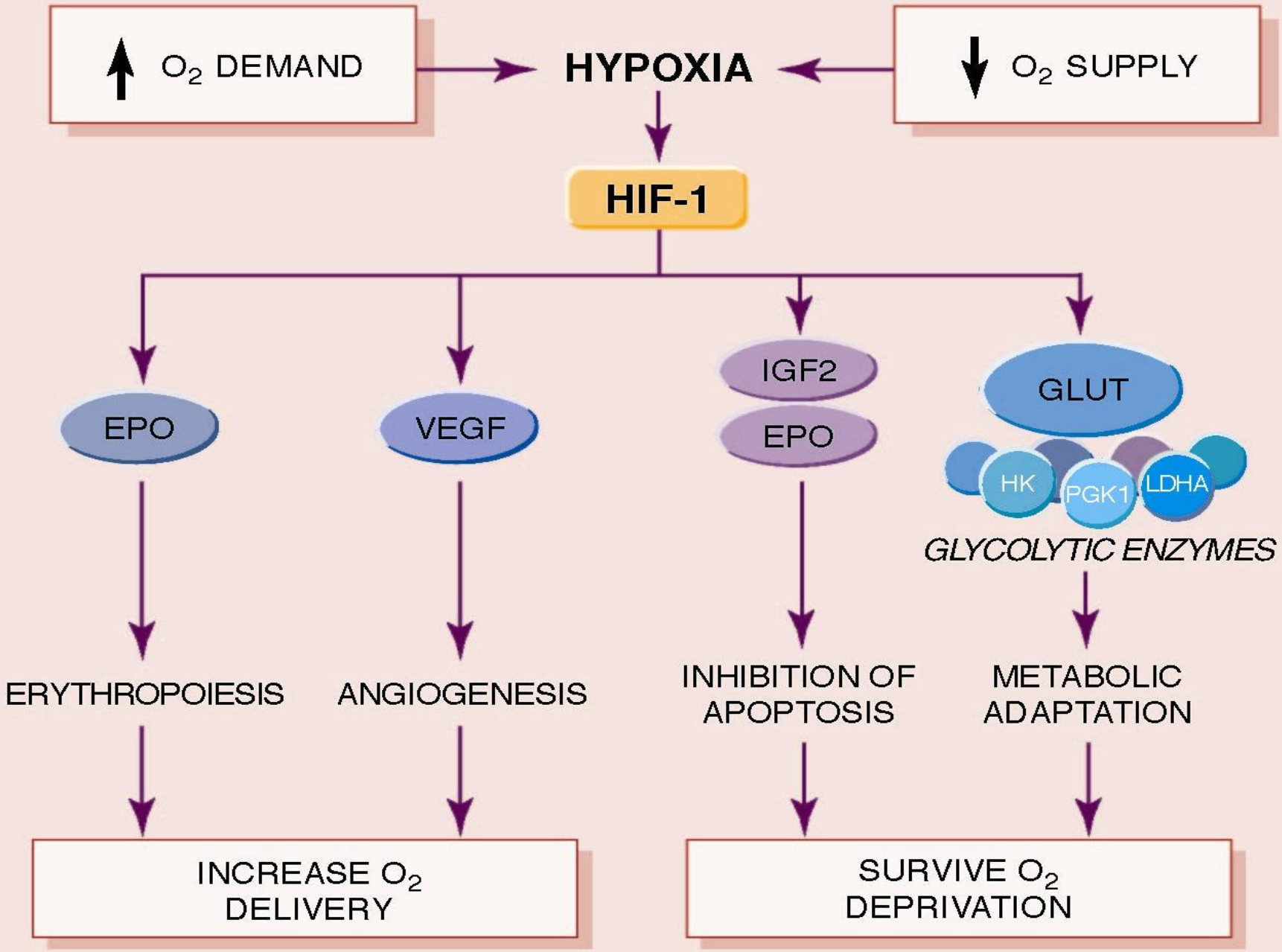
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CRP, C-reactive protein; PTH, parathyroid hormone.

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

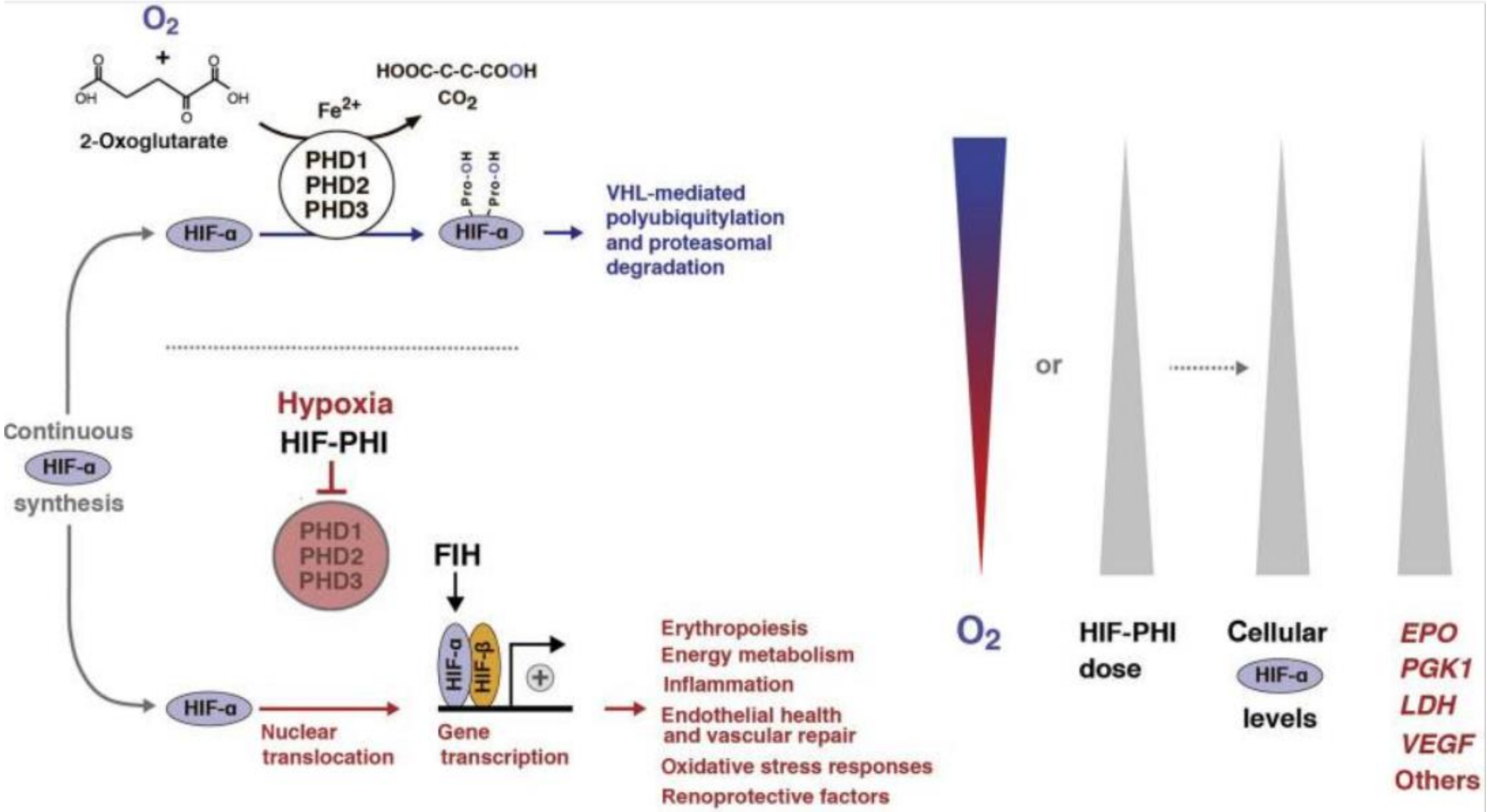


Prabhakar, Physiol Rev 2012



(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

Approved HIF-PHI by different regulatory authorities in Europe, US and other countries

	Europe		US		Other countries	
	NDD-CKD	DD-CKD	NDD-CKD	DD-CKD	NDD-CKD	DD-CKD
Roxadustat	**Approved by EMA (2021)**	**Approved by EMA (2021) avoid switching from ESAs**	Rejected by FDA (2021) thrombotic events and MACE	Rejected by FDA (2021) thrombotic events and MACE	**Approved in Japan, China, Chile, South Korea, South Africa, Turkey, Middle East**	**Approved in Japan, China, Chile, South Korea, South Africa, Turkey, Middle East**
Vadadustat	Rejected by EMA (2023) increased risk of MACE	**Approved by EMA (2023) risk of thromboembolic events**	Rejected by FDA due to concerns of thromboembolic events and drug-induced liver injury	**Approved in Dec 2024 (following initial rejection 2 years prior for thromboembolic events/DILI)**	**Approved by PMDA in Japan (2020)**	**Approved by PMDA in Japan (2020), authorisation pending in Australia**
Daprodustat	Rejected by EMA (2023) insufficient safety data	Received marketing authorisation (2023) but withdrawn by the pharmaceutical company	Rejected by FDA insufficient safety data	Withdrawn in 2024 after initial approval in 2023	**Approved by PMDA in Japan (2020)**	**Approved by PMDA in Japan (2020)**
Molidustat	Not marketed in Europe	Not marketed in Europe	Not marketed in US	Not marketed in US	**Approved by PMDA in Japan (2021)**	**Approved by PMDA in Japan (2021)**
Desidustat	Not marketed in Europe	Not marketed in Europe	Not marketed in US	Not marketed in US	**Approved in India (2022)**	**Approved in India (2022)**
Enarodustat	Not marketed in Europe	Not marketed in Europe	Not marketed in US	Not marketed in US	**Approved by PMDA in India (2020)**	**Approved by PMDA in India (2020)**

Modiified from Stoumpos et al, NDT, 2024

Guidelines…. Pending KDIGO 2025
Groups at risk & Special Considerations

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

Practice Points... Coming in KDIGO 2025

- ESAs and HIF-PHIs not to be used in combination
- Hb thresholds for initiation and maintenance unknown but reasonable to use same Hb thresholds for existing ESA therapy
- Use lowest dose possible needed to improve symptoms and avoid RBC transfusion
- If ESA hyporesponsive and wish to avoid RBC transfusion, trial of HIF-PHI may be considered

Monitoring

- Check Hb 2-4 weeks post initiation or dose changes and then every 4 weeks
- Check TFTs 4 weeks following initiation of Roxadustat
- Discontinue after 3-4 months if desired response not achieved
- Suspend treatment if MACE, VTE, vascular access thrombosis or new diagnosis malignancy
- Do not use in CKD-ND or CKD-DD if active malignancy, recent CV event, or vascular thrombosis

Summary

- ESA therapy has revolutionized the treatment of anemia in patients with CKD
- ESA use and patient selection should be guided by the evidence from placebo-controlled trials
- Publication of KIDGO 2025 anemia guidelines pending with more prescriptive recommendations
- 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