Erythropoiesis-stimulating agents (ESAs) and Hypoxia-inducible factor–prolyl hydroxylase inhibitors(HIF-PHIs) in Anemia Treatment of CKD

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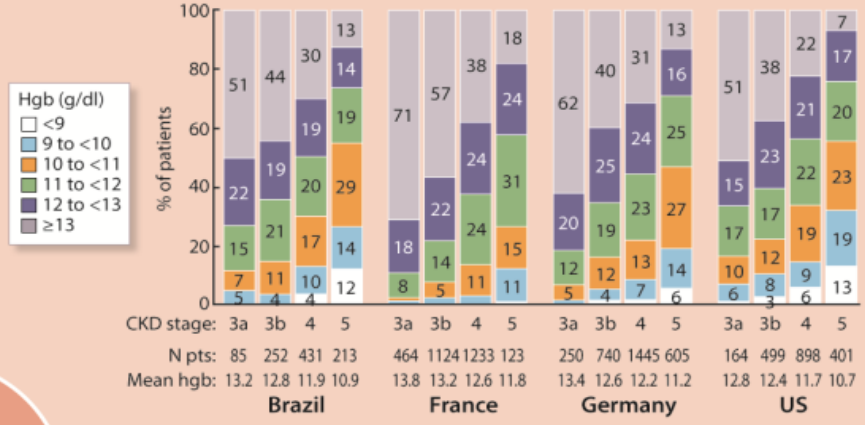
Anemia in CKD

Definitions

0.5–4 years <11.0g/dl | 5–11 years <11.5 g/dl | 12–14 years <12.0 g/dl | Males <13.0 g/dl* | Females <12.0 g/dl*

Age <15 years | **Age ≥15 years**

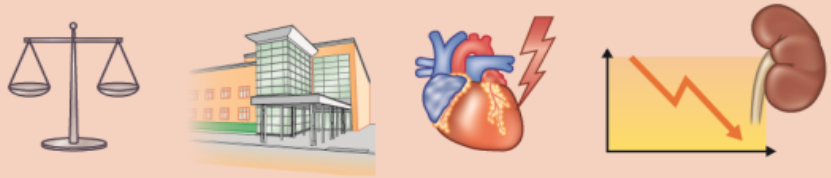
Prevalence[a]



Potential causes (can be multiple)

- EPO deficiency/hyporesponsiveness
- Iron deficiency
- Blood loss (GI (malignancy), dialysis)
- Shortened RBC survival
- Hyperparathyroid or thyroid dysfunction
- Bone marrow suppression by inflammation; drugs (ACEi, ARBs, proliferation inhibitors in KTRs), or malignancy (MDS, myelofibrosis)
- Other nutritional deficiency (folate, vitamin B_{12})
- Chronic inflammation (CHF, obesity, autoimmune diseases)
- Inherited anemia (thalassemia, sickle cell anemia)

Outcomes associated with anemia in CKD

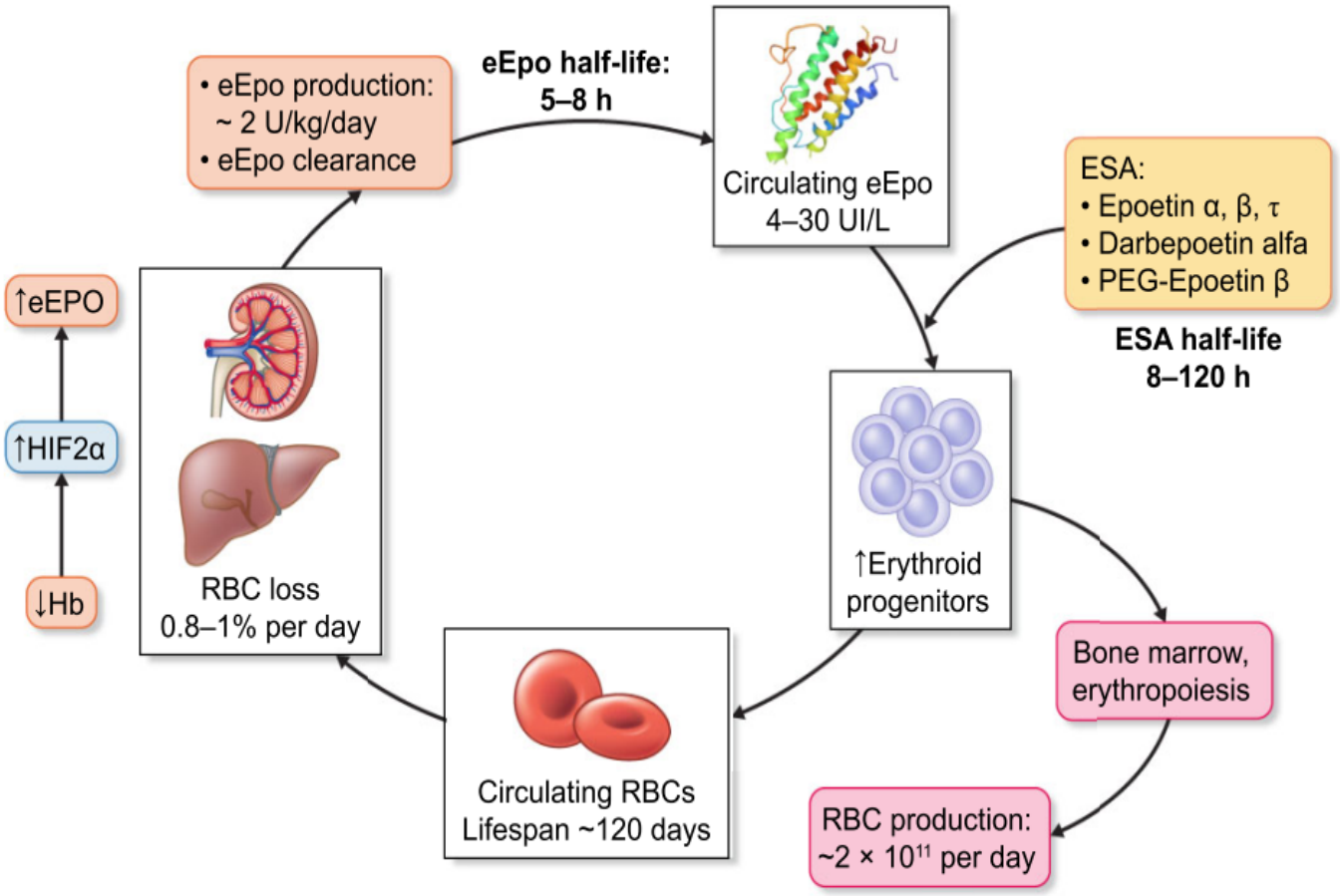


- Higher mortality[d,f,g,h]
- Increased risk of kidney failure[g,h]/CKD progression[e]
- Higher risk of coronary heart disease/MACE[e]
- More left ventricular hypertrophy[j]
- Increased risk of heart failure[m]
- Lower QoL[b,c]
- Decreased muscle mass and strength in KTRs as measured by lower 24-urinary creatinine excretion, BIA-derived skeletal muscle mass, handgrip strength, and worse FTSTS test scores[n]
- Lower work productivity[c]
- More cognitive impairment[k]
- Increased risk of dementia[l]
- Higher transfusion requirements[e]
- More hospitalizations (all-cause, cardiovascular, and bleeding)[e]
- Higher medical costs[i]

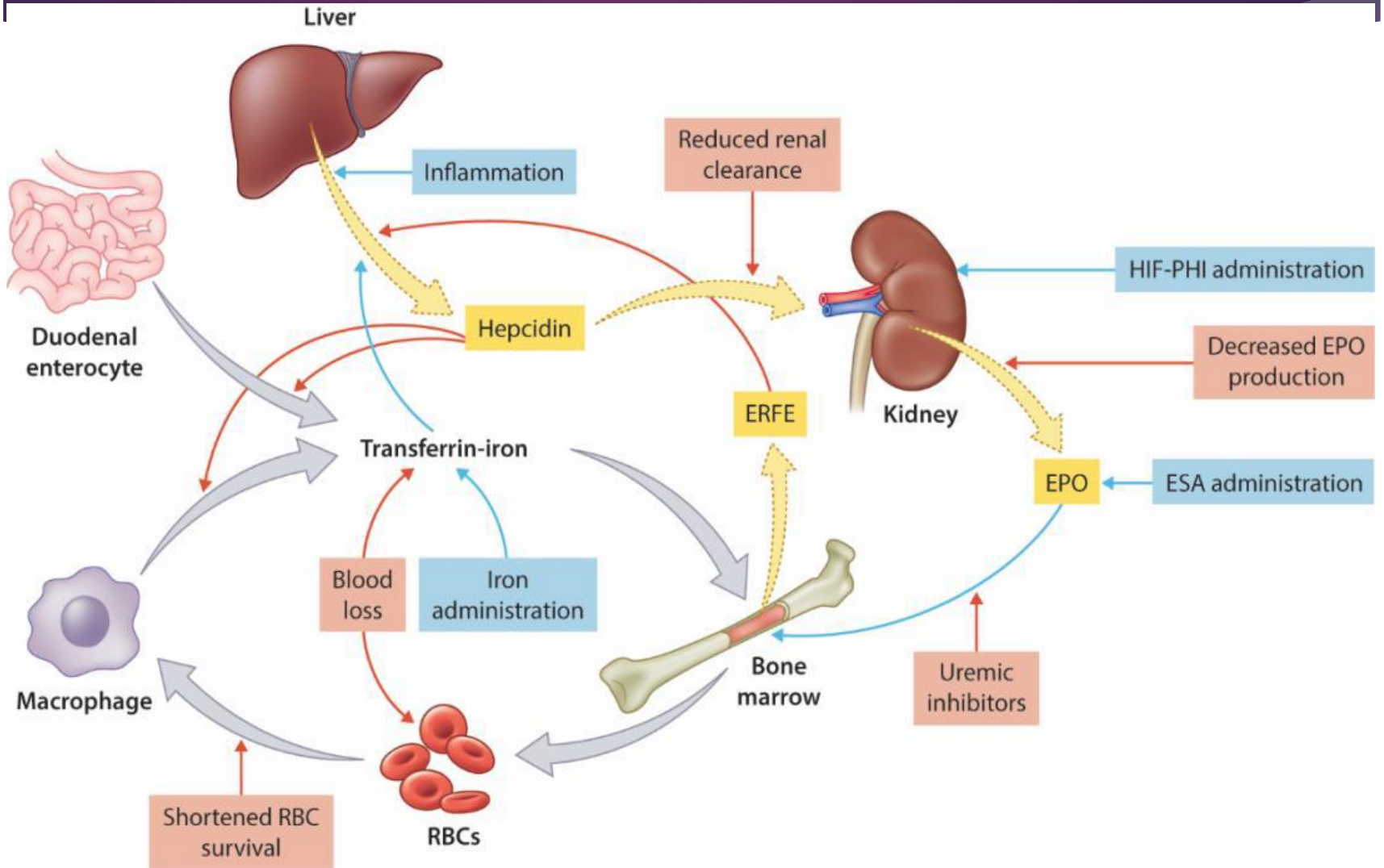
Prevalence of anemia across CKD stages in different countries

CKD stage	Prevalence (%)				
	USA[1]	Italy[19]	Japan[20]	Mexico[21]	South Africa[22]
3a	49.0	28.2	3.8	35.3	21.9
3b	62.0	44.6	11.9	52.1	25.0
4	78.0	63.1	47.5	73.7	52.5
5	93.0	78.9	81.3	97.5	91.4

RBC homeostasis and Epo-stimulated erythropoiesis



Pathophysiology of anemia in CKD



Milestone in the Use of ESAs in CKD

1836	Bright described anemia as a complication of renal failure[51]
1957	Jacobson et al established that the kidney produces EPO[52]
1977	Miyake et al purified human EPO from the urine of patients with aplastic anemia[7]
1983	Lin et al cloned and expressed the human EPO gene[8]
1986	Winearls et al reported the first use of rHuEPO for anemia in patients on chronic hemodialysis[14]
1987	Eschbach et al reported the correction of anemia of end-stage renal disease with rHuEPO. Results of a combined phase I and II clinical trial[1]
1989	FDA approval of the first rHuEPO for the treatment of renal anemia
1996	PRCA reported[9]
1998	Normal Hematocrit Trial[15]
2001	FDA approval of Aranesp (darbepoetin α)
2006	KDOQI guideline for anemia in CKD[53]
2006	CREATE and CHOIR studies[16,17]
2007	FDA approval of MIRCERA

ESAs

Available types of ESAs :

- Erythropoietin (Epo)
- Epoetin alfa (Procrit, Epogen)
- Epoetin beta (NeoRecormon)
- Epoetin zeta (Silapo, Retacrit)
- Darbepoetin alfa (Aranesp)
- Methoxy polyethylene glycol-epoetin beta (Mircera)

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Hypoxia-Inducible Factor–Prolyl Hydroxyl Domain Inhibitors: From Theoretical Superiority to Clinical Noninferiority Compared with Current ESAs?

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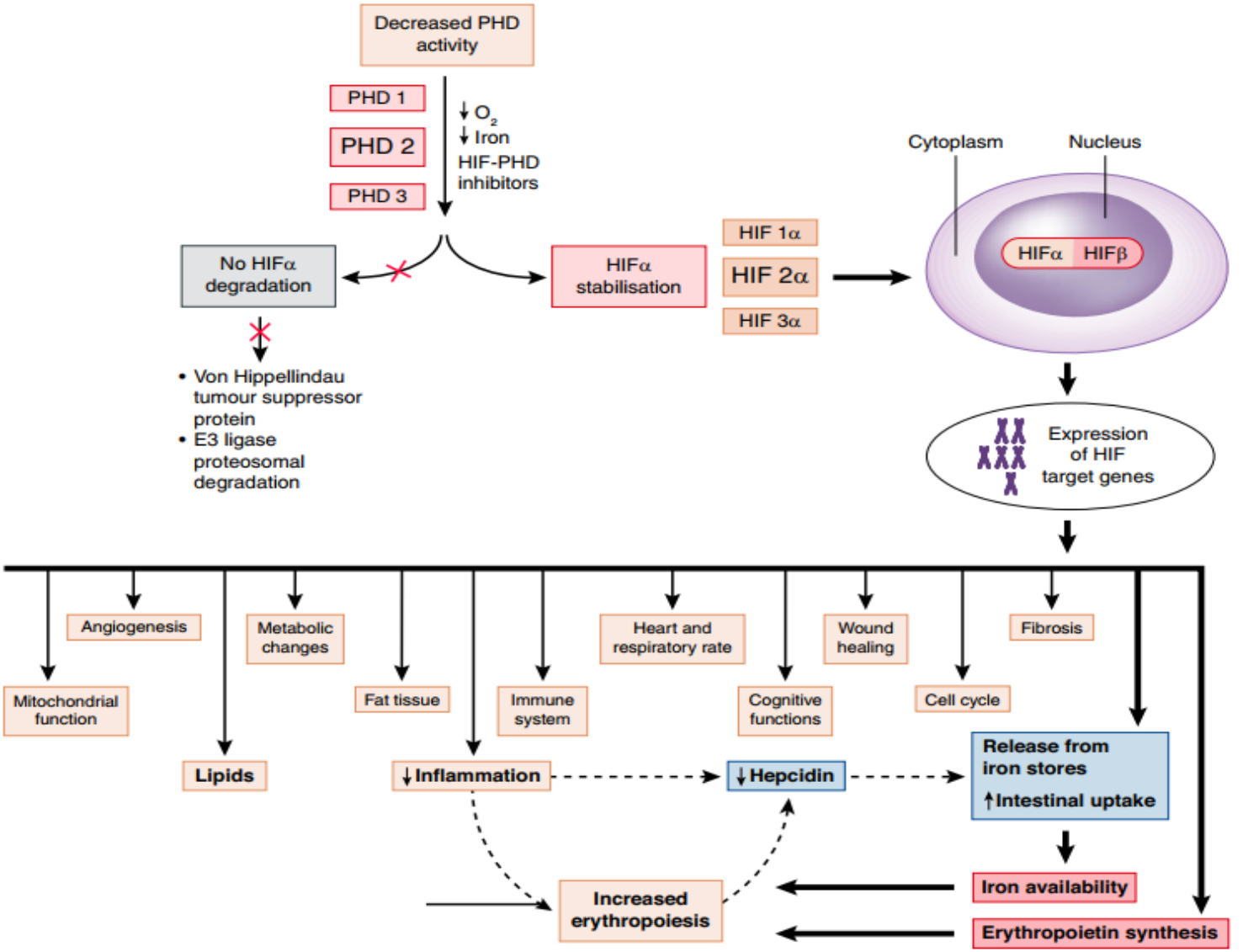
Mechanisms of HIF-PHI



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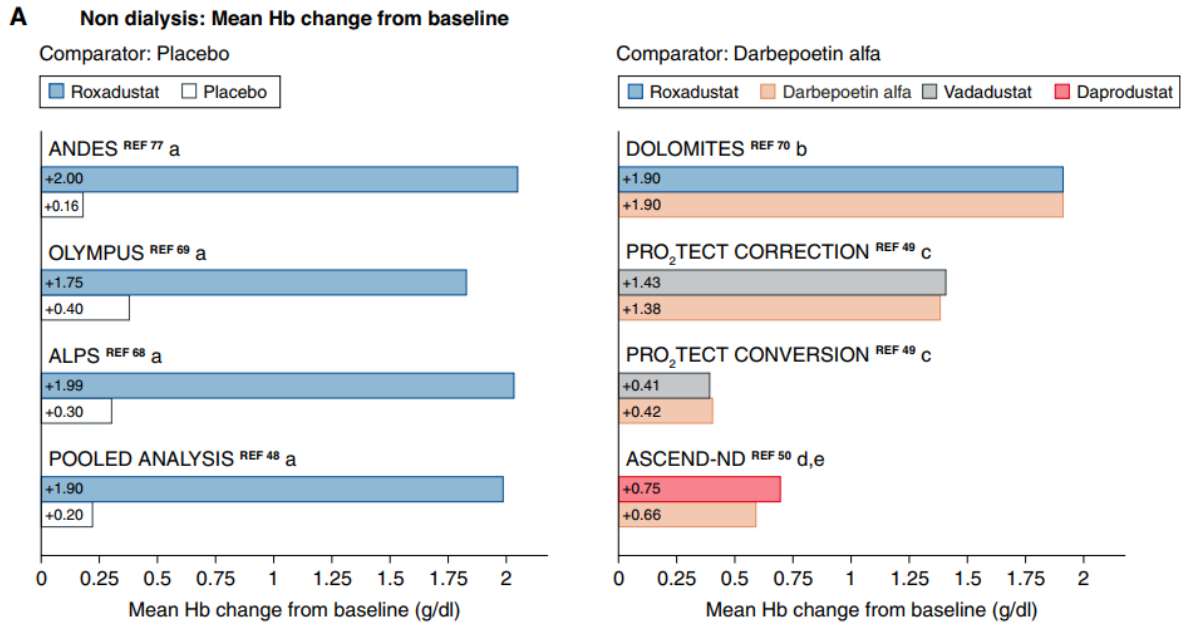
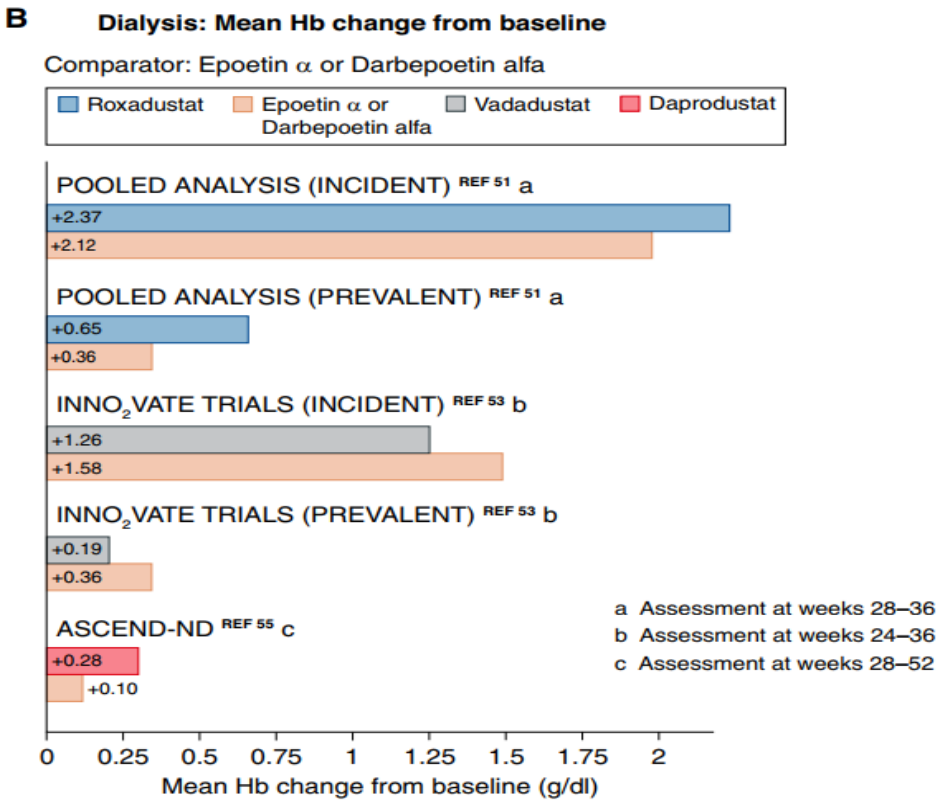
HIF-PHIs vs. ESAs



a Assessment at weeks 28–52
b Estimated from Figure 3 at week 28
c Assessment at weeks 24–36
d Assessment at weeks 28–52
e No separate information for ESA treated and ESA naive at baseline

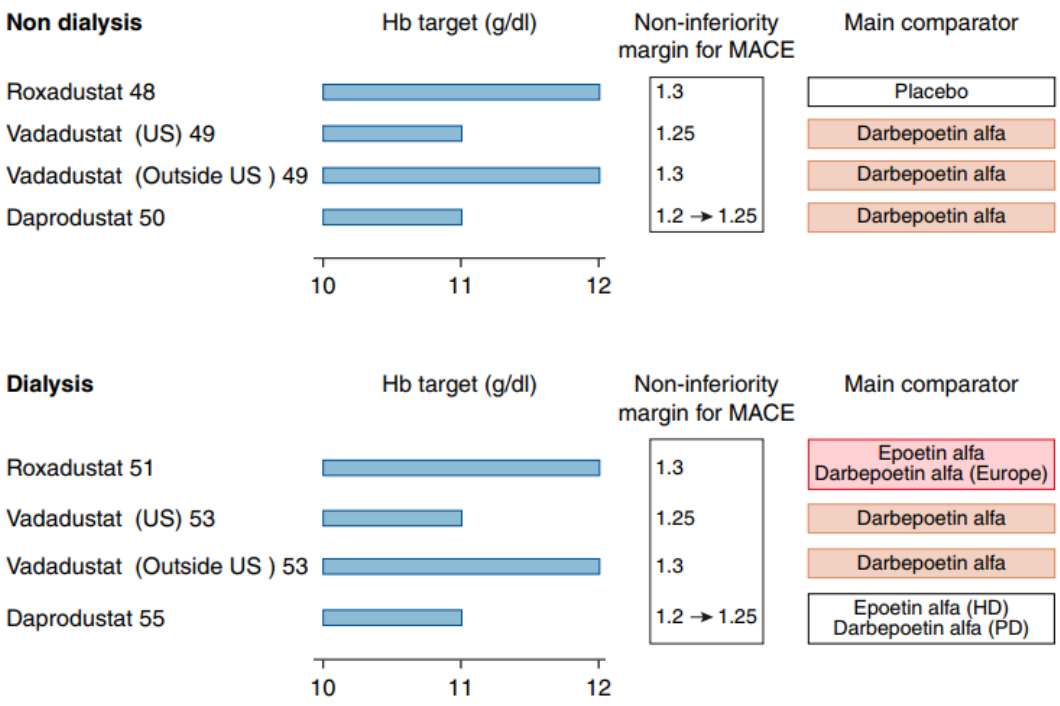
JASN **33:** 1966–1979, 2022

HIF-PHIs vs. ESAs



JASN **33:** 1966–1979, 2022

HIF-PHIs vs. ESAs



HIF-PHIs vs. ESAs

- RCTs have **not demonstrated** a lower cardiovascular burden with HIF-PHIs
- **Oral administration**, could be perceived as an improvement in quality of life by many nondialysis patients
- the likely benefit in inflamed patients suggests that HIF-PHIs could be the treatment of choice for anemia in hyporesponsive inflamed patients
- RCTs comparing HIF-PHIs with ESAs are still needed to evaluate safety

HIF-PHI	Recommended dosing for treatment initiation	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)	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)	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)	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)	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)	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)	Australia, EU, Japan, Korea, Taiwan, U.S.

people with anemia and CKD at risk for adverse events with HIF-PHI therapy

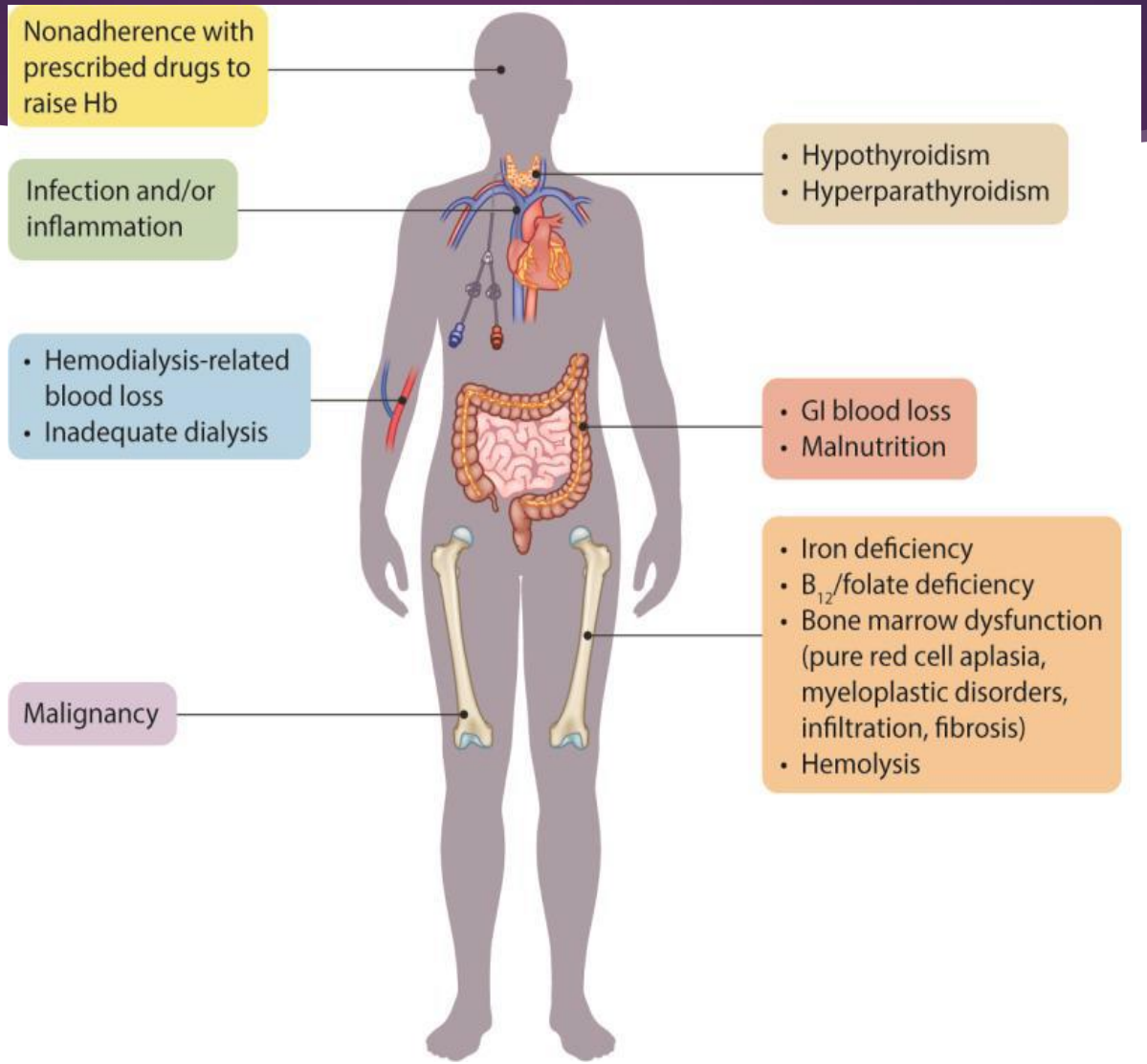
Theoretical risk or experimental evidence of risk for disease development or progression	Concern for risk based on adverse event profiles in clinical trials	Insufficient data for risk assessment; dedicated studies needed
Active cancer or with a history of cancer not in complete remission for at least 2–5 years (based on trial exclusion criteria) Polycystic kidney disease Proliferative retinal disease Pulmonary arterial hypertension Pregnancy*	Prior cardiovascular events (i.e., stroke, myocardial infarction) Prior thromboembolic events (i.e., deep venous thrombosis, pulmonary embolism) Prior vascular access thrombosis Hepatic impairment† Seizures, exfoliative dermatitis, hypothyroidism, bacterial infections/sepsis (roxadustat	Post-kidney transplant anemia Children

Treatment of Anemia

In people with anemia and CKD

address all correctable causes of anemia prior to initiation of treatment with an ESA or a HIF-PHI

Potentially reversible causes of anemia in CKD in addition to decreased erythropoietin production



Suggested testing frequency for anemia by CKD stage

- at referral, regularly during follow-up, and when anemia is suspected based on symptoms
- Tests for anemia: CBC, reticulocytes, ferritin, transferrin saturation (TSAT)

Suggested testing frequency for anemia by CKD stage

Population	Frequency (at least)
CKD G3	Annually
CKD G4	Twice a year
CKD G5 or G5D	Every 3 months

Treatment o Anemia

In people with CKD, anemia, and ferritin <45 µg/l, consider referral to

gastroenterologists/gynecologists/urologists to identify the cause of blood loss

USE OF ESAs, HIF-PHIs AGENTS

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).

USE OF ESAs, HIF-PHIs AGENTS

Recommendation:

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*)

USE OF ESAs, HIF-PHIs AGENTS

- Head-to-head studies of HIF-PHIs compared to ESAs show generally **similar efficacy** in people with CKD G5HD and CKD not receiving dialysis
- Among people with CKD G5D, there may be little or no difference in mortality, MACE, and other important clinical outcomes for HIF-PHI versus ESA
- Among people with CKD not receiving dialysis, there is even more uncertainty about comparative safety, with some HIF-PHIs possibly associated with a higher risk of MACE and vascular access thrombosis than ESAs

ESA Initiation

Recommendation

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** (2D)

ESA Initiation

- *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*

- *People with* ***lower cardiovascular risk*** *and symptoms or* ***reduced exercise capacity attributable to anemia****, and people who especially prefer* ***to avoid RBC transfusions*** *may be more likely to prefer ESA initiation* ***when Hb is closer to 10.0***

ESA Initiation

The Hb concentration for ESA initiation should be individualized and for most people should be 8.5–10.0 g/dl

CKD Pt.s with:

- ***Cardiovascular disease***
- ***thromboembolic disease***
- ***Malignancy (especially with active malignancy when the expected treatment outcome is cure)***

the risk versus benefits of ESA treatment should be discussed with patients, and ***a lower Hb threshold or ESA avoidance may be considered***

- *For children, kidney transplant candidates, and those with symptoms attributable to anemia, a higher Hb threshold may be considered*

ESA Maintenance Therapy

Recommendation:

- **In adults with anemia and CKD treated with an ESA, we recommend targeting a Hb level below 11.5 g/dl (*1D*)**
  This recommendation places a high value on avoiding the critically important risk of stroke and thromboembolic events and the important risk of high blood pressure reported when ESAs are used to target or achieve Hb levels of 11.5 g/dl or greater in RCTs.

ESA dosing

ESA agent	Initial dose	Dose adjustment
Epoetin alfa and beta	CKD not receiving dialysis: 4,000 or 10,000 units weekly or every 2 weeks CKD G5D: 50-100 units/kg, 3 times weekly (may round to convenient dose in units)	CKD not receiving dialysis: Increase or decrease dose and/or dosing frequency as needed (generally not given more than once per week) CKD G5D: Increase by 25 units/kg/dose if Hb rise is <1.0 g/dl (<10 g/l) after 4 weeks. Reduce by 10–25 units/dose if Hb rise is >2 g/dl (20 g/l) in 4 weeks

ESA dosing

ESA agent	Initial dose	Dose adjustmen
Darbepoetin	CKD not receiving dialysis: 40-100 µg every 2–4 weeks CKD G5D: 0.45 µg/kg weekly or 0.75 µg/kg every 2 weeks (may round to convenient dose: 25, 40, 60, 100, 150, or 200 µg (300 µg and 500 mcg also available)	CKD not receiving dialysis: Increase or decrease dose and/or dosing frequency as needed (generally not given more than once per week) CKD G5D: Increase by 25% if Hb rise is <1.0 g/dl (<10 g/l) after 4 weeks. Decrease dose by 25% if Hb rise is >2 g/dl (20 g/l) in 4 weeks.
Methyl polyethylene glycol-epoetin beta Continuous erythropoiesis receptor activator (CERA)	CKD not receiving dialysis: 50-120 µg every two weeks or 120–200 µg every month CKD G5D: 0.6 µg/kg every 2 weeks (may round to convenient dose)	CKD not receiving dialysis: Increase or decrease dose and/or dosing frequency as needed (generally not given more than once every 2 weeks) CKD G5D: Increase by 30-50 µg/dose if Hb rise is <1.0 g/dl (<10 g/l) in 4 weeks. Reduce by 30–50 µg/dose if Hb rise is >2 g/dl (20 g/l) in 4 weeks

ESA Therapy

ESA route of administration

- In adults and children with anemia and CKD G5HD treated with ESA, choose the ESA administration route (i.v. vs. subcutaneous) based on patient preferences, local practices, and costs

- In adults and children with anemia and CKD not receiving dialysis, CKD G5PD, or kidney transplant recipients receiving ESA therapy,

administer ESA by the subcutaneous route

ESA Maintenance Therapy

In people with anemia and CKD treated with ESA, it is reasonable to suspend ESA during hospitalization for

- Acute stroke
- Vascular access thrombosis
- Thromboembolic events

Monitoring of treatment

Resistance to ESA therapy

We recommend that inadequate response ('resistance') to ESA therapy is defined as failure to reach the target Hb level despite

SC epoetin dose >300 IU/kg/week (450 IU/kg/week IV epoetin), or

darbepoetin dose >1.5 microgram/kg/week.

Hyporesponsive patients who are iron replete should be screened clinically and by investigations for other common causes of anaemia. (1A)

ESA Therapy

ESA hyporesponsiveness

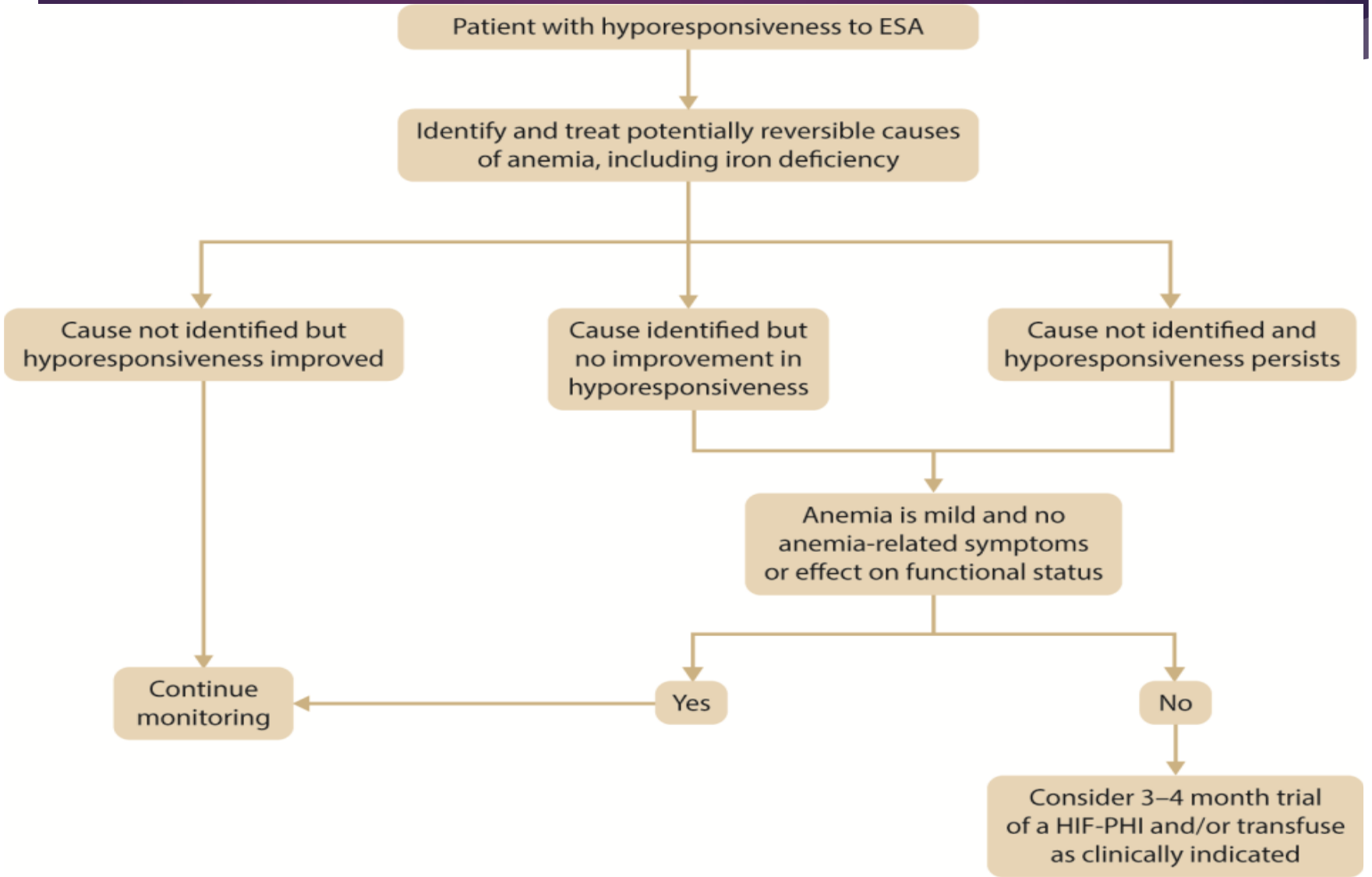
- **In people with anemia and CKD G5D and CKD not receiving dialysis with initial or subsequent ESA hyporesponsiveness,**

identify and treat the underlying causes of ESA hyporesponsiveness, if possible

- **In people with CKD, anemia, and ESA hyporesponsiveness**

a trial of HIF-PHI may be considered after discussion of potential risks and benefits prior to treatment

ESA hyporesponsiveness



Maintenance Therapy

Recommendation : 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*)

Maintenance Therapy

Recommendation : 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%,**

- **ferritin ≥100 ng/ml (≥100 µg/l) and <300 ng/ml (<300 µg/l), and TSAT <25%.**

Maintenance Therapy

- In people with CKD treated with iron, it is reasonable to withhold iron if ferritin ≥700 ng/ml (≥700 µg/l) or TSAT ≥40%

Maintenance Therapy

- Switch from oral to intravenous iron if there is an insufficient effect of an optimal oral regimen after 1 to 3 months

- In people with CKD treated with iron, consider temporarily suspending iron therapy during systemic infection.

Maintenance Therapy

In people with CKD treated with iron, it is reasonable to

<u>test hemoglobin, ferritin, and TSAT</u>

- **every 3 months for those not receiving dialysis or CKD G5PD**
- **every month for those with CKD G5HD**

HIF-PHIs Therapy

HIF-PHI treatment initiation and maintenance

- **In people with anemia and CKD, including those with ESA hyporesponsiveness**

do not use ESAs and HIF-PHIs in combination

HIF-PHIs Therapy

In patients with CKD, anemia, and ESA hyporesponsiveness

if a desired erythropoietic response has not been achieved after 3–4 months of initiating a trial of HIF-PHI, <u>discontinue treatment</u>

Pure Red Cell Aplasia (PRCA)

Evaluation for ESA Induced Pure Red Cell Aplasia (PRCA)

We do not recommend routine screening for anti-erythropoietin antibodies among CKD patients regularly treated with erythropoiesis stimulating agents. (2A)

Pure Red Cell Aplasia (PRCA)

Diagnosis of ESA induced PRCA should be considered whenever

- **a patient receiving long term ESA therapy (more than 8 weeks) develops all the following (2A):**
- **a sudden decrease in Hb concentration at the rate of 5 to 10g/L per week OR requirement of transfusions at the rate of approximately 1 to 2 per week**
- **normal platelet and white cell counts**
- **absolute reticulocyte count less than 10,000/µl**

Pure Red Cell Aplasia (PRCA)

- We recommend that all ESA therapy should be stopped in patients who develop ESA induced PRCA. (2A)

- We recommend that patients who remain transfusion dependent after withdrawing ESA therapy should be
treated with immunosuppressant medications guided by the level of anti EPO antibodies. (2A)