
بسم الله الرحمن الرحيم

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

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دانشگاه علوم پزشکی اصفهان

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➢ DIAGNOSIS AND EVALUATION OF ANEMIA IN CKD

❖ Potential causes of anemia in CKD patient:

- EPO deficiency/ hyporesponsiveness
- Iron deficiency
- Blood loss
- Shortened RBC survival
- Hyperparathyroid or thyroid dysfunction
- Bone marrow suppression by inflammation, drugs or malignancy
- Other nutritional deficiency
- Chronic inflammation
- Inherited anemia

TEST FOR ANEMIA

- Complete blood count (CBC)
- Reticulocytes
- Ferritin
- Transferrin saturation (TSAT)

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

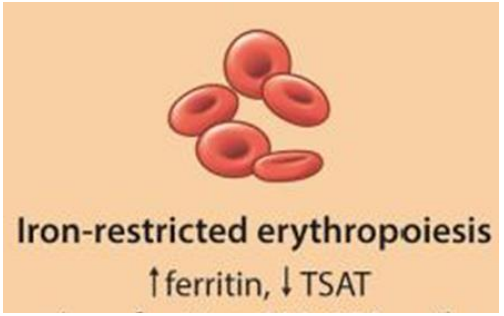
IRON DEFICIENCY IN CKD

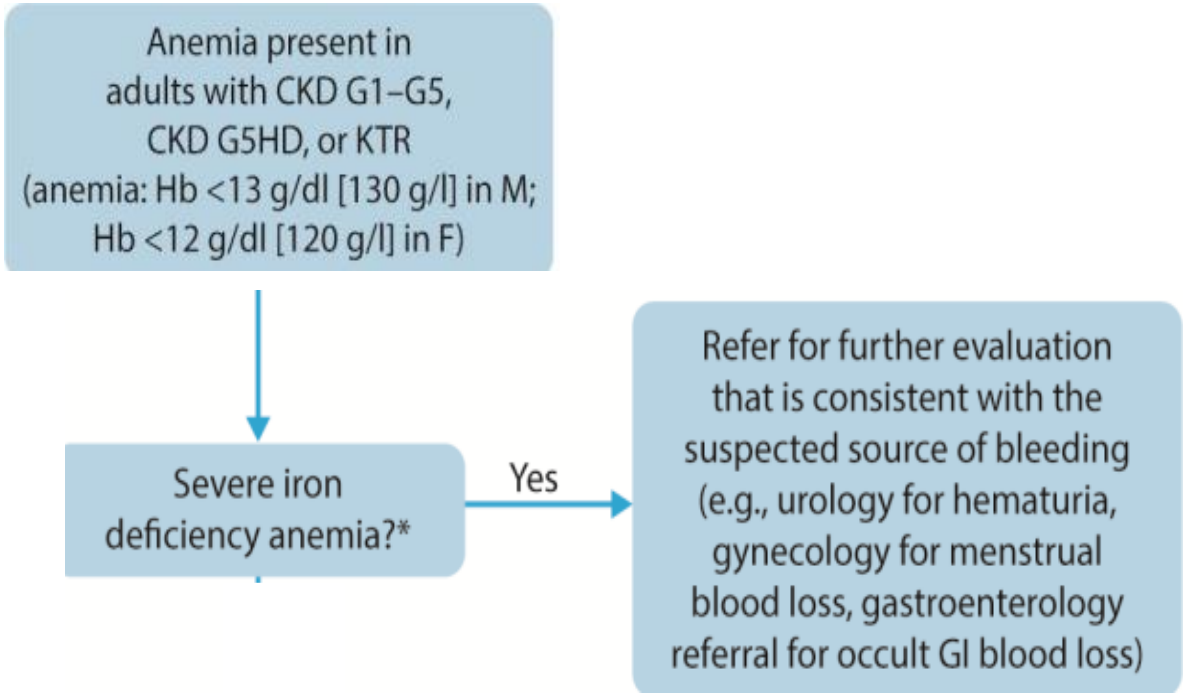
- **Systemic iron deficiency**:

  TSAT<20% and ferritin <100 μg/l in CKD not receiving dialysis
  or
  ferritin <200 μg/l in CKD G5HD

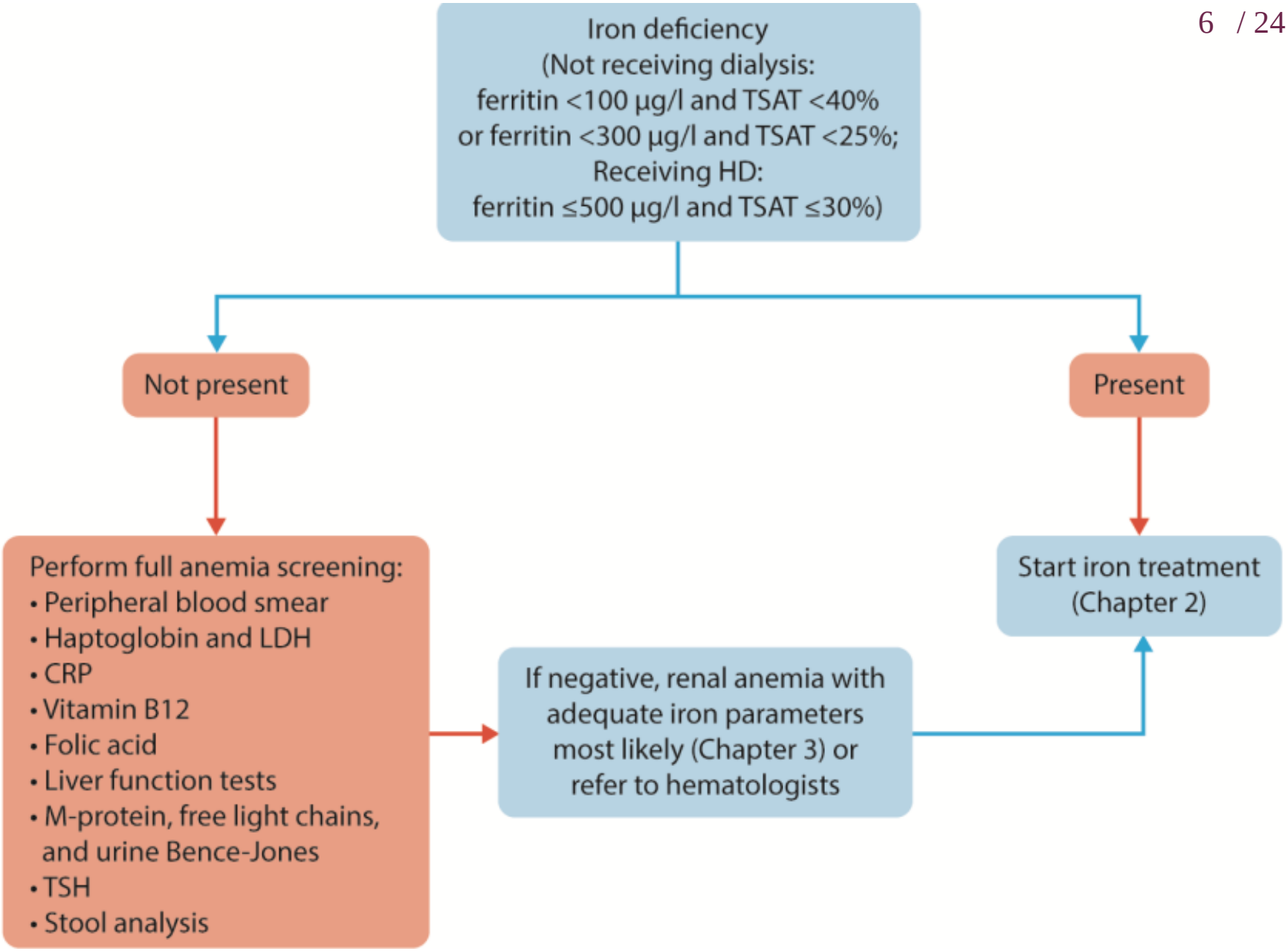
- **Iron-restricted erythropoiesis:**

  TSAT<20% with ferritin >100–200 μg/l





*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)


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 DEFICIENCY AND ANEMIA IN CKD**

❖ In people with anemia and **CKD treated with hemodialysis** (CKD G5HD), we suggest initiating iron therapy if:

- **Ferritin ≤500 ng/ml and TSAT ≤30%**

❑ suggest using intravenous iron rather than oral iron.
❑ using a proactive approach to maintain stable iron status.

❖ In people with anemia and **CKD not receiving dialysis or treated with peritoneal dialysis** (CKD G5PD), we suggest initiating iron if :

- **Ferritin <100 ng/ml and TSAT <40%, or**
- **Ferritin ≥100 ng/ml and <300 ng/ml , and TSAT <25%.**

suggest using either oral or intravenous iron based on the person's values and preferences

Table 3 | Oral iron formulations, treatment regimen, and factors influencing the choice between different formulations

	Dose per tablet	Elemental iron per tablet	Starting dose	Considerations
Ferric citrate	1 g	210 mg	CKD not receiving dialysis: 1 tablet, 3 times daily	In CKD not receiving dialysis, it will help with phosphate-binding as a secondary effect
			CKD G5D: 2 tablets, 3 times daily	In CKD G5D, indicated as a phosphate binder with iron supplementation being an additional effect
Ferric maltol	30 mg	30 mg	1 tablet, 2 times daily	Taken between meals
Ferrous sulphate	325 mg	65 mg	1 tablet, 3 times daily	Taken between meals
Ferrous fumarate	325 mg	106 mg	1 tablet, 2 times daily	Gastrointestinal side effects, dark green stools
Ferrous gluconate	300 mg	35 mg	4–6 tablets, daily	Less gastrointestinal side effects and better bioavailability
Liposomal iron	30 mg	30 mg	1 tablet, daily	Less gastrointestinal side effects and better bioavailability
Heme iron polypeptide	12 mg	12 mg	1 tablet, 3–4 times daily	Less gastrointestinal side effects and better bioavailability

Table 4 | Intravenous iron formulations and treatment regimen

	Elemental iron concentration	Maximum single dose	Minimum infusion time for maximum dose	Minimum injection time	Considerations
Low-molecular weight iron dextran	50 mg/ml	20 mg/kg	15 min for 50 mg, 100 mg/min 4–6 hours	>60 min	Hypersensitivity lower than high-molecular weight dextran
Iron sucrose	20 mg/ml	200 mg	15 min	5 min	For people with CKD G1–G5 not receiving HD, requires multiple patient visits as 1000 mg cannot be given at a single sitting. (5 doses of 200 mg over 5 weeks)
Ferric gluconate	12.5 mg/ml	125 mg	60 min	10 min	Ferric gluconate in sucrose complex (250 mg 4 doses weekly)
Ferric carboxymaltose	50 mg/ml	750 mg (FDA) 1000 mg (EMA)	15 min	7.5 min (FDA) 15 min (EMA)	Full dose can be given in 1 or 2 sittings (750 mg 2 doses 1 week apart) May cause hypophosphatemia, especially in people with early CKD and kidney transplant recipients
Ferric derisomaltose / iron isomaltoside	100 mg/ml	1000 mg (FDA) 20 mg/kg (EMA)	20 min	250 mg/min (max. 500 mg) (EMA)	Full dose can be given in single sitting
Ferumoxytol	30 mg/ml	510 mg	15 min	15 min	Full dose can be given in single sitting

- 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.

In people with CKD treated with iron, it is reasonable to **withhold iron** if:

- **Ferritin ≥700 ng/ml or TSAT ≥40%.**

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

- In people with CKD treated with iron, it is reasonable to **test hemoglobin, ferritin, and TSAT**:
  - **every 3 months** for those not receiving dialysis or CKD G5PD
  - **every month** for those with CKD G5HD

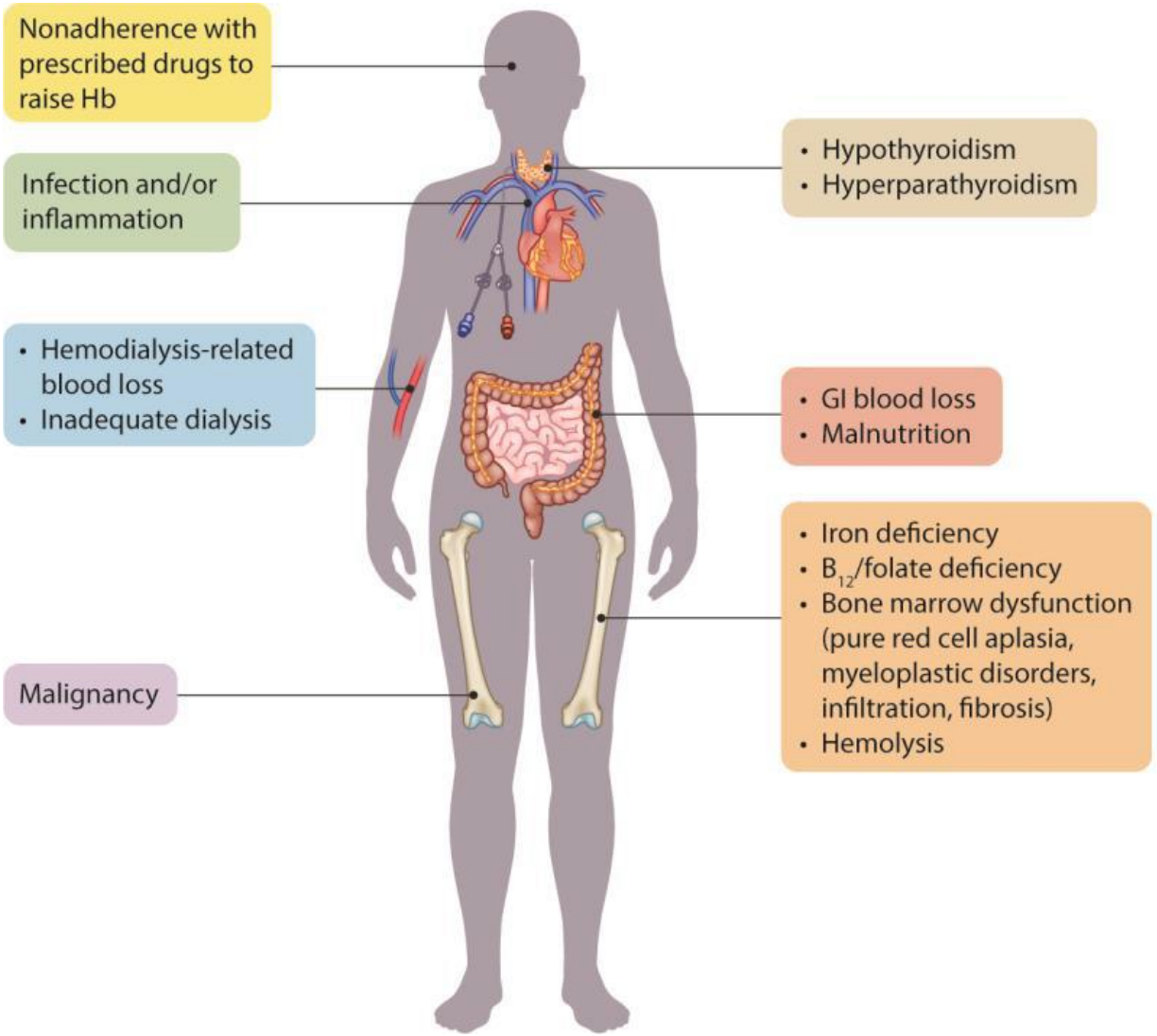
Table 5 | Circumstances warranting more frequent iron testing

- Initiation of or increase in dose of ESAs or HIF-PHIs
- Episodes of known blood loss
- Recent hospitalization
- Important increase in ferritin or TSAT or overshooting target limit

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

- **USE OF ESAS, HIF-PHIS, AND OTHER AGENTS TO TREAT ANEMIA IN CKD**

- Potentially reversible causes of anemia in chronic kidney disease (CKD) in addition to decreased erythropoietin production.



- In people with anemia and **CKD G5D** treated with hemodialysis or peritoneal dialysis , we suggest **initiation of ESA therapy** when the Hb concentration is ≤9.0–10.0 g/dl

- In adults with anemia and CKD treated with an ESA, we recommend **targeting** a **Hb level below 11.5 g/dl .**

- In people with **CKD not receiving dialysis**, including kidney transplant recipients and children, the selection of Hb concentration at which ESA therapy is initiated should consider the **presence of symptoms** attributable to anemia, the potential **benefits** of higher Hb concentration, and the potential **harms** of RBC transfusion or receiving ESA therapy

Table 7 | Dosing of erythropoietin-stimulating agents (ESAs)

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

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	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

- 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.

- In people with anemia and CKD, and **during the maintenance phase** of ESA therapy, monitor Hb level at least once every 3 months

- 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%.

- 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.

- 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.

- ESA hyporesponsiveness

  Definitions:

  Failure to achieve target Hb levels with epoetin doses greater than:

  - i.v. EPO 450 IU/kg/week,
  - **s.c. EPO: 300 IU/kg/week**,
  - darbepoetin dose >1.5 µg/kg/week

Table 9 | Causes of erythropoiesis-stimulating agents (ESA) hyporesponsiveness

- Iron deficiency
- Inflammation (infections, dialysis catheter use, autoimmune disease)
- Hyperparathyroidism
- Blood loss (GI tract, dialysis procedure, menses)
- Inadequate dialysis
- Malignancy
- Hematologic disorders (hemoglobinopathies, multiple myeloma, hemolysis, antibody-mediated pure red cell aplasia)
- Nutritional deficiencies (copper, zinc, folate, vitamin B12, carnitine, vitamin E)
- Medications (RAS inhibition)
- Unexplained (~30%)

- In people with CKD, anemia, and ESA hyporesponsiveness, if there is a desire to raise the Hb to avoid a transfusion or improve symptoms attributable to anemia, a trial of HIF-PHI may be considered after discussion of potential risks and benefits prior to treatment

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

- In people with anemia and CKD not receiving dialysis or with CKD G5D who have active malignancy, a recent cardiovascular event, or recent vascular thrombosis do not use HIF-PHI.

Table 6 | Considerations for people with anemia and CKD at risk for adverse events with hypoxia-inducible factor-prolyl hydroxylase inhibitors (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)[223] • Polycystic kidney disease[224] • Proliferative retinal disease[225, 226] • Pulmonary arterial hypertension[227-229] • Pregnancy*	• Prior cardiovascular events (i.e., stroke, myocardial infarction)[223] • Prior thromboembolic events (i.e., deep venous thrombosis, pulmonary embolism)[223] • Prior vascular access thrombosis[223] • Hepatic impairment† • Seizures, exfoliative dermatitis, hypothyroidism, bacterial infections/sepsis (roxadustat)[230]	• Post-kidney transplant anemia[223] • Children[231]

- **RED BLOOD CELL TRANSFUSION TO TREAT ANEMIA IN PEOPLE WITH CKD**

- 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)
  - When rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage, unstable coronary artery disease)
  - When rapid preoperative Hb correction is required.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