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

**PUBLIC REVIEW DRAFT**
**NOVEMBER 2024**

**This is a draft document shared for public review and feedback only. The content of this draft will change based on the feedback received, and should not be used for any other purpose beyond its original intent.**

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## SUPPLEMENTARY MATERIAL

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## NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1** or **Level 2**, and the certainty of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

| Grade | Implications | | |
|---|---|---|---|
| | **Patients** | **Clinicians** | **Policy** |
| **Level 1** "We recommend" | Most people in your situation would want the recommended course of action, and only a small proportion would not. | Most patients should receive the recommended course of action. | The recommendation can be evaluated as a candidate for developing a policy or a performance measure. |
| **Level 2** "We suggest" | The majority of people in your situation would want the recommended course of action, but many would not. | Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences. | The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined. |

| Grade | Certainty of evidence | Meaning |
|---|---|---|
| **A** | High | We are confident that the true effect is close to the estimate of the effect. |
| **B** | Moderate | The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| **C** | Low | The true effect may be substantially different from the estimate of the effect. |
| **D** | Very low | The estimate of the effect is very uncertain, and often it will be far from the true effect. |

***Practice points*** are consensus-based statements representing the expert judgment of the Work Group and are not graded. They are issued when a clinical question did not have a systematic review performed, to help readers implement the guidance from graded recommendation (e.g., frequency of monitoring, provision of standard care [such as regular clinic visits], referral to specialist care, etc.), or for issuing "good practice statements" when the alternative is considered to be absurd. Users should consider the practice point as expert guidance and use it as they see fit to inform the care of patients. Although these statements are developed based on a different methodology, they should not be seen as "less important" or a "downgrade" from graded recommendations.

## CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

***CKD is <u>defined</u> as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is <u>classified</u> based on <u>C</u>ause, <u>G</u>FR category (G1-G5), and <u>A</u>lbuminuria category (A1-A3), abbreviated as CGA.***

**KDIGO: Prognosis of CKD by GFR and albuminuria categories**

| GFR categories (ml/min/1.73 m²) Description and range | | | | Persistent albuminuria categories Description and range | | |
|---|---|---|---|---|---|---|
| | | | | **A1** | **A2** | **A3** |
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | <30 mg/g <3 mg/mmol | 30–300 mg/g 3–30 mg/mmol | >300 mg/g >30 mg/mmol |
| | **G1** | Normal or high | ≥90 | | | |
| | **G2** | Mildly decreased | 60–89 | | | |
| | **G3a** | Mildly to moderately decreased | 45–59 | | | |
| | **G3b** | Moderately to severely decreased | 30–44 | | | |
| | **G4** | Severely decreased | 15–29 | | | |
| | **G5** | Kidney failure | <15 | | | |

**Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.**

GFR, glomerular filtration rate

## CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

| | Conventional unit | Conversion factor | SI Unit |
|---|---|---|---|
| Creatinine | mg/dl | 88.4 | µmol/l |
| Ferritin | ng/ml | 1 | µg/l |
| Hemoglobin | g/dl | 10 | g/l |

PCR, protein-to-creatinine ratio; SI, International System of Units

Note: Conventional unit x conversion factor = SI unit

## EQUIVALENT ALBUMINURIA CATEGORIES IN CKD

| Category | AER (mg/24 hours) | ACR (approximate equivalent) (mg/mmol) | ACR (approximate equivalent) (mg/g) | Terms |
|---|---|---|---|---|
| **A1** | <30 | <3 | <30 | Normal to mildly increased |
| **A2** | 30-300 | 3-30 | 30-300 | Moderately increased* |
| **A3** | >300 | >30 | >300 | Severely increased |

*Relative to young adult level

ACR, albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease

# ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| AABB | Association for the Advancement of Blood & Biotherapies |
| ACEi | angiotensin-converting enzyme inhibitor |
| AGA | American Gastroenterological Association |
| ARB | angiotensin II receptor blocker |
| BIA | bioimpedance analysis |
| CBC | complete blood count |
| CKD | chronic kidney disease |
| CHOIR | Correction of Hemoglobin and Outcomes in Renal Insufficiency |
| CKD G5HD | chronic kidney disease stage G5 receiving hemodialysis |
| CKD G5PD | chronic kidney disease stage G5 receiving peritoneal dialysis |
| CI | confidence interval |
| CRP | C-reactive protein |
| DRIVE | Dialysis Patients Response to IV Iron with Elevated Ferritin |
| DSA | donor-specific antibodies |
| eGFR | estimated glomerular filtration rate |
| EMA | European Medicines Association |
| EPO | erythropoietin |
| ERT | Evidence Review Team |
| ESA | erythropoiesis-stimulating agents |
| EU | European Union |
| FDA | Food and Drug Administration |
| FGF23 | fibroblast growth factor 23 |
| FIND-CKD | Ferinject® assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent Chronic Kidney Disease |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| GFR | glomerular filtration rate |
| Hb | hemoglobin |
| HD | hemodialysis |
| HIF | hypoxia-inducible factor |
| HIF-PHI | hypoxia-inducible factor–prolyl hydroxylase inhibitors |
| HLA | human leukocyte antigen |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| i.v. | intravenous |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| KRT | kidney replacement therapy |
| KTR | kidney transplant recipient |
| LDH | lactate dehydrogenase |
| LVH | left ventricular hypertrophy |
| MACE | major adverse cardiovascular events |
| MCV | mean corpuscular volume |
| mTOR | mammalian target of rapamycin inhibitors |
| NHANES | National Health and Nutrition Examination Survey |
| OR | odds ration |
| QoL | quality of life |
| PD | peritoneal dialysis |

| | |
|---|---|
| PICOS | population, intervention, comparator, outcomes, and study design |
| PIVOTAL | Proactive IV irOn Therapy in hemodiALysis patients |
| PRA | panel reactive antibody |
| PTA | post-transplant anemia |
| RASi | renin-angiotensin system inhibitor |
| RBC | red blood cell |
| RCT | randomized controlled trial |
| RENAAL | Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan |
| RR | risk ratio |
| SCr | serum creatinine |
| TIBC | total iron binding capacity |
| TREAT | Trial to Reduce Cardiovascular Events with Aranesp Therapy |
| TSAT | transferrin saturation |
| U.S. | United States |
| USRDS | United States Renal Data System |
| WHO | World Health Organization |

# NOTICE

## SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in April 2023. It is designed to assist decision-making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

## SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually, and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Disclosure section and is kept on file at KDIGO.

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# ABSTRACT

The Kidney Disease: Improving Global Outcomes (KDIGO) 2025 Clinical Practice Guideline for Anemia in Chronic Kidney Disease (CKD) is an update of the KDIGO 2012 guideline on the topic. The guideline informs the care of adults and children with anemia and CKD, whether treated with kidney replacement or not. The guideline includes chapters dedicated to diagnosis and evaluation of iron deficiency and anemia in CKD, use of iron to treat iron deficiency and anemia in CKD, use of erythropoiesis-stimulating agents (ESAs), hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs), and other agents to treat anemia in CKD, and red cell transfusion to treat anemia. The update considers evidence from randomized controlled trials published through April 2023. The guideline provides actionable recommendations based on a rigorous formal evidence review, practice points that were not based on a systematic review, and supporting infographics. The target audiences for the guideline are providers involved in the care of people with anemia and CKD as well as people with anemia and CKD themselves; recommendations also consider implications for policy. Development of the guideline followed an explicit process of evidence review and appraisal. The guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the certainty of evidence and of the strength of recommendations following the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach. Limitations of the evidence are discussed and suggested areas for future research are also presented.

**Keywords**: anemia, chronic kidney disease, evidence-based; guideline; KDIGO; systematic review; GRADE

# SUMMARY OF RECOMMENDATION STATEMENTS AND PRACTICE POINTS

## CHAPTER 1. DIAGNOSIS AND EVALUATION OF ANEMIA IN CKD

**Practice Point 1.2.1: In people with CKD, test for anemia at referral, regularly during follow-up, and when anemia is suspected based on symptoms (Figure 5). Test for anemia with the following set: complete blood count (CBC), reticulocytes, ferritin, transferrin saturation (TSAT) (Figure 6).**

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

**Figure 5 | Suggested testing frequency for anemia by chronic kidney disease (CKD) stage**

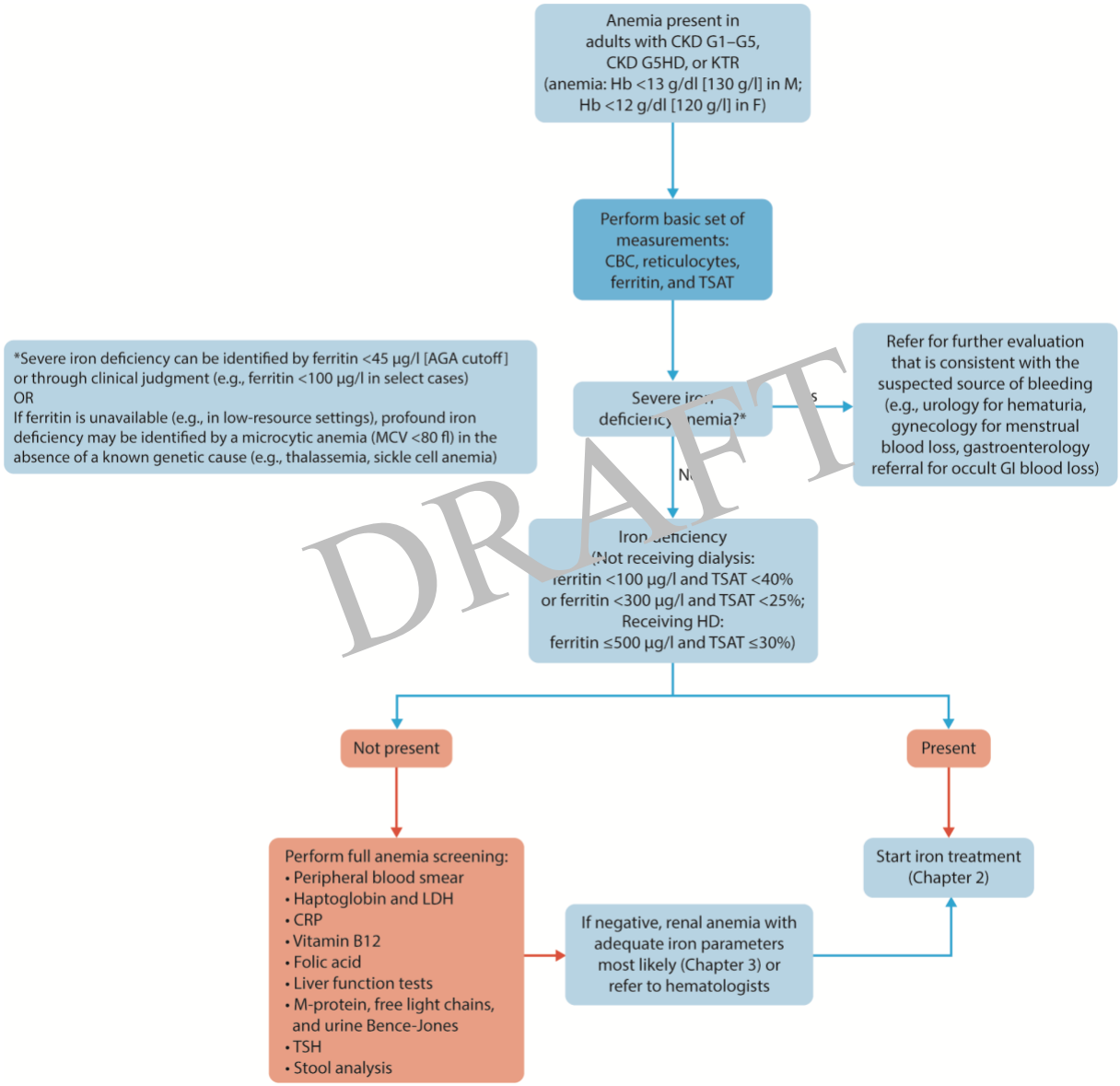


**Figure 6 | Flowchart of the different steps to follow when people with chronic kidney disease (CKD) who have anemia.** AGA, American Gastroenterological Association; CBC, complete blood count; CKD G5HD, CKD receiving hemodialysis; CKD G1-G5, CKD not receiving dialysis; CRP, C-reactive protein; F, female; GI, gastrointestinal; KTR, kidney transplant recipients; LDH, lactate dehydrogenase; M, male; MCV, mean corpuscular volume; TSAT, transferrin saturation; TSH, thyroid-stimulating hormone

**Practice Point 1.2.2: In people with anemia and CKD, and in whom the initial tests do not reveal the cause, consider this expanded panel to identify potential underlying causes:**

- **Blood smear review,**
- **Haptoglobin,**
- **Lactate dehydrogenase (LDH),**
- **C-reactive protein (CRP),**
- **Vitamin $B_{12}$,**
- **Folate,**
- **Liver enzymes,**
- **Serum protein electrophoresis (SPEP) with immunofixation, serum free light chains, urinary Bence-Jones protein,**
- **Thyroid-stimulating hormone (TSH) and,**
- **Stool analysis.**

**Practice Point 1.2.3: In people with CKD, anemia, and ferritin <45 µg/l, consider referral to gastroenterologists/gynecologists/urologists to identify the cause of blood loss.**

# CHAPTER 2. USE OF IRON TO TREAT IRON DEFICIENCY 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 2.2: In people with anemia and CKD G5HD in whom iron therapy is being initiated, we suggest using intravenous iron rather than oral iron (*2D*).**

**Practice Point 2.1: In people with CKD G5HD in whom iron therapy is being initiated, administer intravenous iron using a proactive approach to maintain stable iron status.**

**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%.**

**Recommendation 2.4: In people with anemia and CKD not receiving hemodialysis in whom iron is initiated, we suggest using either oral or intravenous iron based on the person's values and preferences (*2D*).**

**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 2.3: In people with CKD treated with oral iron, the choice between different formulations and dosing schedules is guided by cost, individual patient preference, tolerability, and efficacy.**

**Practice Point 2.4: In people with CKD treated with intravenous iron, the choice between different formulations is guided by cost, individual preference, and recommended dosing schedules.**

**Practice Point 2.5: 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 and every 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 as shown in Table 5.**

**Table 5 | Circumstances warranting more frequent iron testing**

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

ESA, erythropoietin-stimulating agents, HIF-PHI, hypoxia-inducible factor-prolyl hydroxylase inhibitors; TSAT, transferrin saturation

**Practice Point 2.7: Switch from oral to intravenous iron if there is an insufficient effect of an optimal oral regimen after 1 to 3 months.**

**Practice Point 2.8: In people with CKD treated with iron, consider temporarily suspending iron therapy during systemic infection.**

**Practice Point 2.9: In people with CKD treated with intravenous iron, considerations pertaining to hypersensitivity reactions to intravenous iron include the following:**

- **Intravenous iron should only be administered if there is capability to manage acute hypersensitivity and hypotensive reactions,**
- **Intravenous doses of iron should not exceed the maximum dose/administration for the compound (Table 4),**
- **Pretreatment with corticosteroids or antihistamines is not routinely necessary (type 1 histamine [H1]-channel blockers), and**
- **Test doses of intravenous iron are not usually required, because lack of response does not predict the risk of hypersensitivity.**

**Practice Point 2.10: The suggested management of reactions to intravenous iron is presented in Figure 7.**

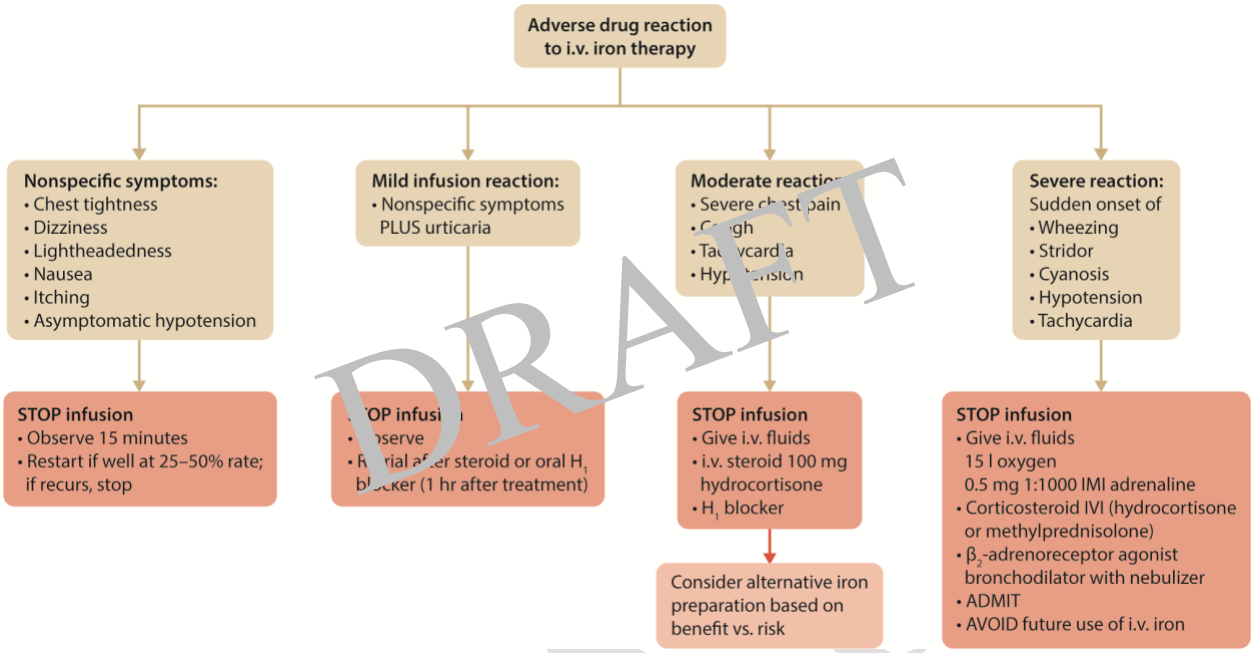


**Figure 7 | Suggested management of reactions to intravenous (i.v.) iron.** H1, type 1 histamine

**Practice Point 2.11: 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.**

# CHAPTER 3. USE OF ESAs, HIF-PHIs, AND OTHER AGENTS 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).**

**Practice Point 3.1.2.: In people with anemia and CKD, address all correctable causes of anemia prior to initiation of treatment with an ESA or a HIF-PHI (Figure 8).**

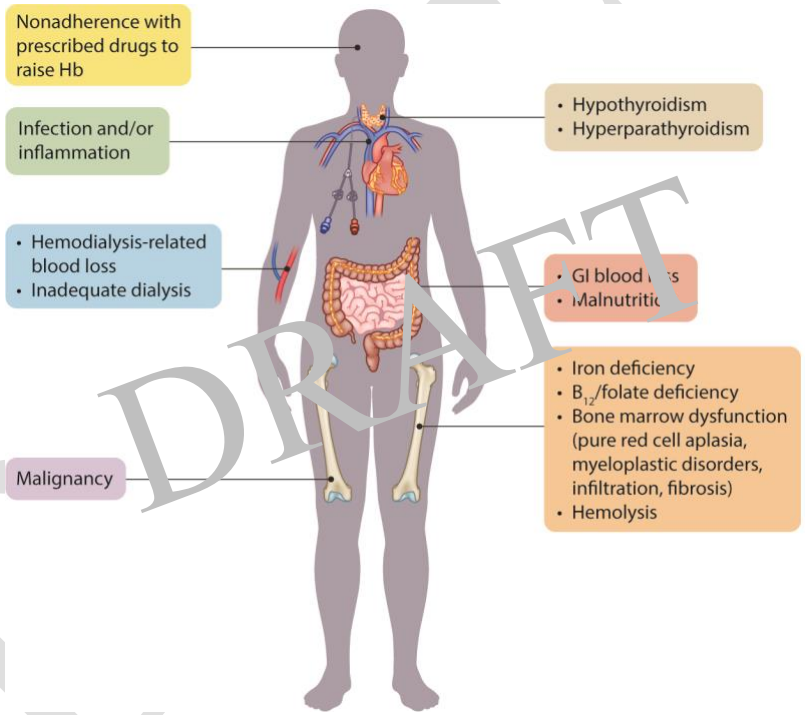


**Figure 8 | Potentially reversible causes of anemia in chronic kidney disease (CKD) in addition to decreased erythropoietin production.** ACEi, angiotensin-converting enzyme inhibitor(s); ARB, angiotensin II receptor blocker; GI, gastrointestinal

**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*).**

**Practice Point 3.1.3: In people with anemia and CKD, HIF-PHIs should be avoided in those at increased risk of adverse events (Table 6).**

**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]<br>• Polycystic kidney disease[224]<br>• Proliferative retinal disease[225, 226]<br>• Pulmonary arterial hypertension[227-229]<br>• Pregnancy[*] | • Prior cardiovascular events (i.e., stroke, myocardial infarction)[223]<br>• Prior thromboembolic events (i.e., deep venous thrombosis, pulmonary embolism)[223]<br>• Prior vascular access thrombosis[223]<br>• Hepatic impairment[†]<br>• Seizures, exfoliative dermatitis, hypothyroidism, bacterial infections/sepsis (roxadustat)[230] | • Post-kidney transplant anemia[223]<br>• Children[231] |

[*]HIF-PHIs are contraindicated in pregnancy, please refer to package inserts for individual compounds.
[†]Caution is advised in patients with hepatic impairment. HIF-PHIs are not recommended for patients with significant hepatic impairment. Please refer to package inserts of individual compounds for specific guidance.

## 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 3.2.2: 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 (*2D*).**

## 3.3. ESA maintenance therapy

**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 3.3.1: For children with anemia and CKD, the selection of Hb target for ESA maintenance therapy should be individualized, considering potential benefits (e.g., improvement in QoL, school attendance/performance, and avoidance of RBC transfusion) and potential harms.**

## 3.4. ESA dosing, frequency, route of administration, and monitoring

### 3.4.1. ESA dosing

**Practice Point 3.4.1.1: In people with anemia and CKD treated with ESA, the initial dose of ESA should be determined by the Hb concentration of the person, their body weight, and clinical circumstances (Table 7).**

**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<br><br>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)<br><br>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 |
| **Erythropoietin biosimilars** | *Product names and doses vary by region - Refer to individual product information* | |
| **Darbepoetin** | CKD not receiving dialysis: 40-100 µg every 2–4 weeks<br><br>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)<br><br>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<br><br>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)<br><br>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 |

CKD, chronic kidney disease; Hb, hemoglobin; i.v., intravenous; KRT, kidney replacement therapy; s.c., subcutaneous

**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 3.4.1.3: In people with anemia and CKD treated with ESA, administer ESAs with the lowest dose possible which achieves and maintain treatment goals.**

### 3.4.2. ESA route of administration

**Practice Point 3.4.2.1: 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.**

**Practice Point 3.4.2.2: 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.**

### 3.4.3. Frequency of administration and monitoring of ESAs

**Practice Point 3.4.3.1: In people with CKD G5 or CKD not receiving dialysis, individualize the frequency of administration of ESA based on patient preferences and type of ESA administered (Table 7).**

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

**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.**

### 3.5. HIF-PHI treatment initiation and maintenance

**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 3.5.3: In people with anemia and CKD, dose HIF-PHIs according to the recommended starting doses (Table 8).**

**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)<br><br>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)<br><br>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]<br>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)<br><br>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)<br><br>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<br><br>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]<br>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]<br>inhibitor of CYP2C8 (in vitro), BCRP, OAT3 and inducer of CYP2B6 (in vitro)[259, 260] | Australia, EU, Japan, Korea, Taiwan, U.S.[†] |

More detailed information about drug-drug interactions between individual HIF-PHIs and other drugs can be found in package inserts and product information documents issued by regulatory agencies. *Daprodustat is only approved for chronic kidney disease (CKD) receiving dialysis only in the United States (U.S.) and for both CKD receiving and not receiving dialysis in Japan. [†]Vadadustat is only approved for CKD receiving dialysis in the Australia, Europe (EU), Korea, Taiwan, and the U.S. and for both CKD receiving and not receiving dialysis in Japan. BRCP, Breast cancer resistance protein [ATP-binding cassette (ABC) transporter family member]; CYP, Cytochromes P450; ESA, erythropoietin-stimulating agent(s); OAT, Organic ion transporter; UAE, United Arab Emirates; UGT, uridine 5'-diphospho-glucuronosyltransferase; UK, United Kingdom

**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 (Table 8).**

**Practice Point 3.5.5: In people with anemia and CKD, do not escalate HIF-PHI doses beyond the recommended maximum dose.**

**3.6. HIF-PHI monitoring**

**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.**

**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.**

**3.7. ESA hyporesponsiveness**

**Practice Point 3.7.1: 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.**

**Practice Point 3.7.2: 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 (Figure 10).**

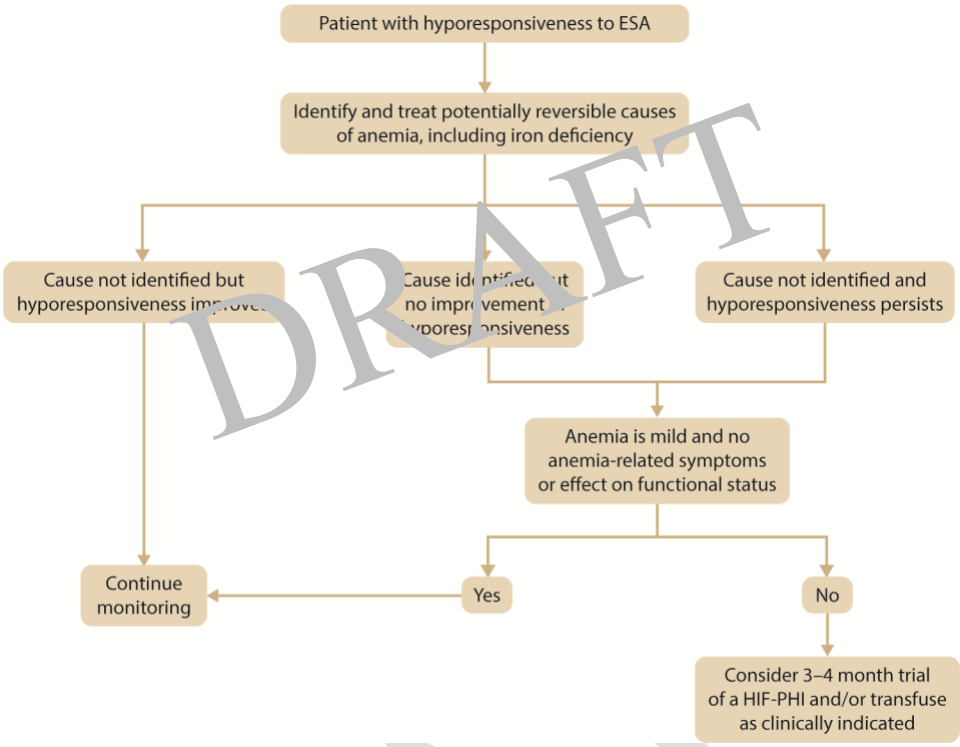


**Figure 10 | Treatment algorithm for sustained ESA hyporesponsiveness**. For definition of hyporesponsiveness, refer to Table 10. See Figure 8 for potentially reversible causes of anemia in CKD.

**Practice Point 3.7.3: In patients with anemia and CKD, if a decision is made to use HIF-PHI for the treatment of ESA hyporesponsiveness, the Hb should be raised to the lowest level that alleviates anemia-related symptoms or which reduces the risk of requiring an RBC transfusion to an acceptable level.**

**Practice Point 3.7.4: 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, discontinue treatment.**

**Practice Point 3.7.5: 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.**

# CHAPTER 4. RED BLOOD CELL TRANSFUSION TO TREAT ANEMIA IN PEOPLE WITH CKD

**Practice Point 4.1: In people with anemia and CKD, use red blood cell (RBC) transfusion as part of a comprehensive treatment strategy, carefully weighing risks and benefits in a shared decision-making process.**

**Practice Point 4.2: In people with anemia and CKD eligible for organ transplantation, avoid, when possible, RBC transfusions to minimize the risk of allosensitization.**

**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)**

**Practice Point 4.4: In people with anemia and CKD, base the decision to transfuse a person with CKD and chronic anemia on symptoms and signs caused by anemia rather than an arbitrary Hb threshold.**

**Practice Point 4.5: In people with CKD and acute anemia consider RBC transfusion when the benefits outweigh the risks, including:**

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

**Practice Point 4.6: Consider implementing strategies at the individual, organizational, and public health policy levels to reduce RBC transfusions in people with CKD (Table 11).**

**Table 11 | Strategies to reduce red blood cells (RBC) transfusions in people with chronic kidney disease (CKD)**

- Opt for less invasive procedures in hospitalized patients whenever possible.
- Limit phlebotomy when medically appropriate.
- Continue ESA/HIF-PHI/iron therapy in hospitalized patients unless clinically contraindicated.
- Consider Hb trend over time rather than absolute Hb values, in people using ESA/HIF-PHI/iron therapy.
- Avoid RBC transfusion in patients with chronic anemia who are asymptomatic.
- Individualize transfusion need based on the clinical situation.
- In every person with CKD patient, triage the decision for RBC transfusion on whether the person is a potential future transplant candidate.

ESA, erythropoiesis-stimulating agent [10,11] Adapted with permission from Brenner et al. Red cell transfusion in chronic kidney disease in the United States in the current era of erythropoiesis stimulating agents. Journal of Nephrology. 2022;33: 267-275.

# CHAPTER 1. DIAGNOSIS AND EVALUATION OF ANEMIA IN CKD

Anemia is a common complication in people with chronic kidney disease (CKD) and is associated with adverse clinical outcomes. The onset or progression of anemia in CKD may herald a new problem that is causing blood loss or interfering with red blood cell (RBC) production. The anemia should be evaluated independently of CKD stage in order to identify any additional underlying processes contributing to anemia beyond CKD per se. A comprehensive list of causes and the approach to diagnosis can be found in standard medical textbooks. This guideline focuses on anemia in people with CKD specifically, as well as one of its common causes, namely iron deficiency.

## 1.1. Anemia in CKD

An overview of anemia in CKD populations can be found in Figure 1, including its definition, prevalence, pathophysiology, and association with clinical outcomes. Each of these topics is discussed below.

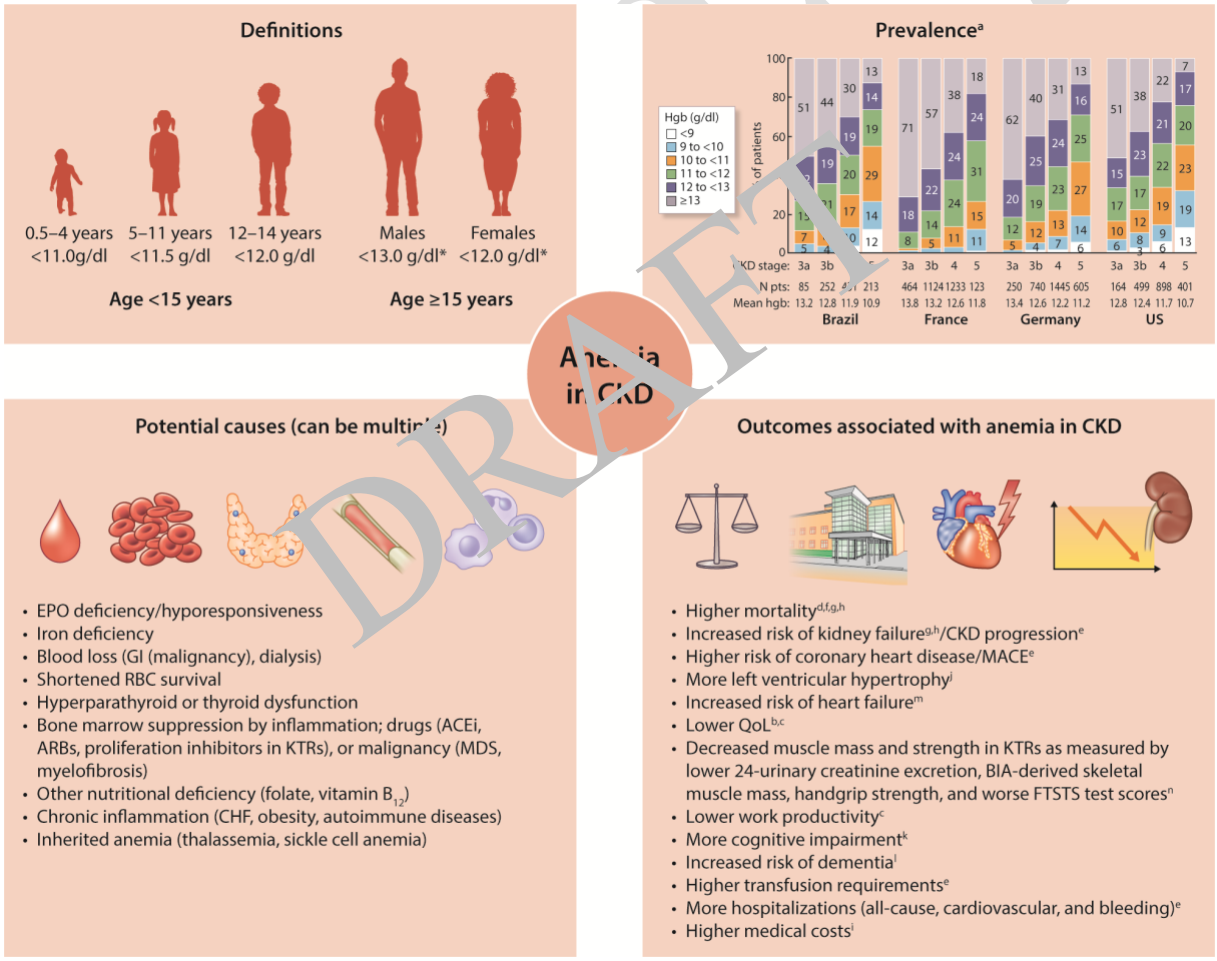


**Figure 1 | Overview of anemia in chronic kidney disease (CKD) with its definition, prevalence across CKD stages, potential causes, and associated outcomes.** *Specific cut-offs for age and sex are provided. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BIA, bioimpedance analysis; CHF, congestive heart failure; EPO, erythropoietin; FTSTS, 5 Times Sit to Stand; GI, gastrointestinal; KTR, kidney transplant recipient; MACE, major

adverse cardiovascular events; MDS, myelodysplastic syndrome; QoL, quality of life; PTH, parathyroid hormone; RBC, red blood cell; RCT, randomized controlled trial. [a]Wong et al. CKJ 2020;[1] [b]Moreno *et al.* NDT 1996;[2] [c]Van Haalen *et al.* BMC Nephrology 2020;[3] [d]Astor *et al.* American Heart Journal 2006;[4] [e]Lamerato *et al.* BMC Nephrology 2022;[5] [f]Al-Ahmed *et al.* JACC 2001;[6] [g]Kovesdy *et al.* Kidney Int 2006;[7] [h]Thorp *et al.* Nephrology 2009;[8] [i]Nissenson *et al.* J Manag Pharm Care;[9] [j]Levin *et al.* AJKD 1999;[10] [k]Kurella Tamura *et al.* CJASN 2011;[11] [l]Koyama *et al.* AJKD 2023;[12] [m]He *et al.* JAHA 2017;[13] [n]Vinke *et al.* J Cachexia Sarcopenia Muscle 2022[14]

*Definition of anemia in CKD*

Anemia in adults is typically defined according to the thresholds from the World Health Organization (WHO): hemoglobin (Hb) <12 g/dl (120 g/l) for women, and <13 g/dl (130 g/l) for men[15] (Figure 1). Other thresholds have been proposed (including those that vary based on ethnicity, age and sex), but the WHO thresholds have been consistently used in studies of anemia in people with CKD. Anemia in children is defined using age-specific thresholds, namely for 0.5 to 4 years, a Hb <11 g/dl (110 g/d); for 5 to 11 years, a Hb <11.5 g/dl (115 g/l); and for 12 to 14 years, a Hb <12 g/dl (120 g/l).[15] Identification of anemia should prompt an evaluation for potential causes as outlined below.

*Prevalence of anemia in CKD*

The prevalence of anemia in CKD increases at lower levels of estimated glomerular filtration rate (eGFR), reaching a prevalence of >50% at the advanced CKD (CKD G4-G5).4 The prevalence is disproportionately higher in women compared to men.16 A recent analysis of United States (U.S.) National Health and Nutrition Examination Survey (NHANES) data from 1999–2000 to 2017–18 suggests that among other factors (increased age ≥75 years, female sex, CKD ≥G3b, and concurrent diabetes), anemia is also significantly more likely to occur in Blacks compared to other racial groups.17 In children, anemia in CKD ranges from 18.5% in G2 to 93% in G4 and G5.18 Table 1 provides an overview of the prevalence of anemia across CKD stages in different countries..

**Table 1 | 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 |

Multiple studies showed that 21%–62% of people with CKD not receiving dialysis have anemia, defined as Hb <12 g/dl in females and <13.5 g/dl in males, with increasing prevalence in more advanced CKD (Figure 1).[1, 23, 24] For people with CKD receiving hemodialysis (CKD G5HD), data from the United States Renal Data System (USRDS) showed that 64.5%, 14.4%, and 6.6% have Hb levels between 10–12 g/dl (100-120 g/l), 9–10 g/dl (90-100 g/l), or <9 g/dl (90 g/l), respectively.[25] A systematic review of studies from sub-Saharan Africa found a pooled prevalence of anemia in 50.2% in people with CKD regardless of kidney replacement therapy (KRT).[26] Similarly, data from the Japan Chronic Kidney

Disease Database (J-CKD-DB) have shown a prevalence of anemia in people with CKD G4 and G5 as 40.1% and 60.3%, respectively.[27] In kidney transplant recipients (KTRs), the prevalence of anemia ranges between 20%–51% and varies with time since transplantation.[28]

*Pathophysiology of anemia in CKD*

Anemia in CKD is frequently multifactorial. Common causes include relative erythropoietin (EPO) deficiency, shortened RBC survival, iron and other nutritional deficiencies (folate and vitamin $B_{12}$), blood loss during hemodialysis, uremic toxin-induced inhibition of bone marrow response to EPO, systemic inflammation related to the specific cause of CKD, and other comorbidities (Figure 1). Of these factors, EPO and iron are pivotal in stimulating bone marrow RBC production (Figure 2).[29] Hepcidin, a liver-derived 25-amino acid hormone, is a critical regulator of iron homeostasis, or how one's body regulates iron levels and metabolism. It is responsible for regulating the absorption of dietary iron and macrophage recycling of iron for delivery to RBC precursors. Increased hepcidin levels in CKD contribute to dysregulated iron homeostasis, or an imbalance in the body's regulation of iron levels. Increased hepcidin levels also causes the degradation of the cellular iron transporter protein called ferroportin, the sole known iron exporter, which inhibits iron release into the bloodstream by macrophages, hepatocytes and duodenal enterocytes. A key factor that regulates EPO expression is the hypoxia-inducible factor (HIF) system, the activity of which is driven by tissue oxygen levels. This hypoxia-mediated transcription factor pathway, which helps cells survive and function in low-oxygen environments, leads to several effects in addition to the stimulation of renal and hepatic EPO synthesis, including iron absorption and utilization, proliferation and differentiation of bone marrow stem cells, and lineage differentiation.[30]

After kidney transplantation, renewed EPO production promotes erythropoiesis, which leads to increased iron utilization and thereby iron deficiency, a major cause of post-transplantation anemia. Other important causes for post-transplantation anemia are inflammation and infection, immunosuppressive medication (especially mycophenolate mofetil, mycofenolic acid, and azathioprine), medications affecting the renin-angiotensin system (RAS) such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), antimicrobial agents such as trimethoprim-sulfamethoxazole, and antiviral agents such as ganciclovir.[31]

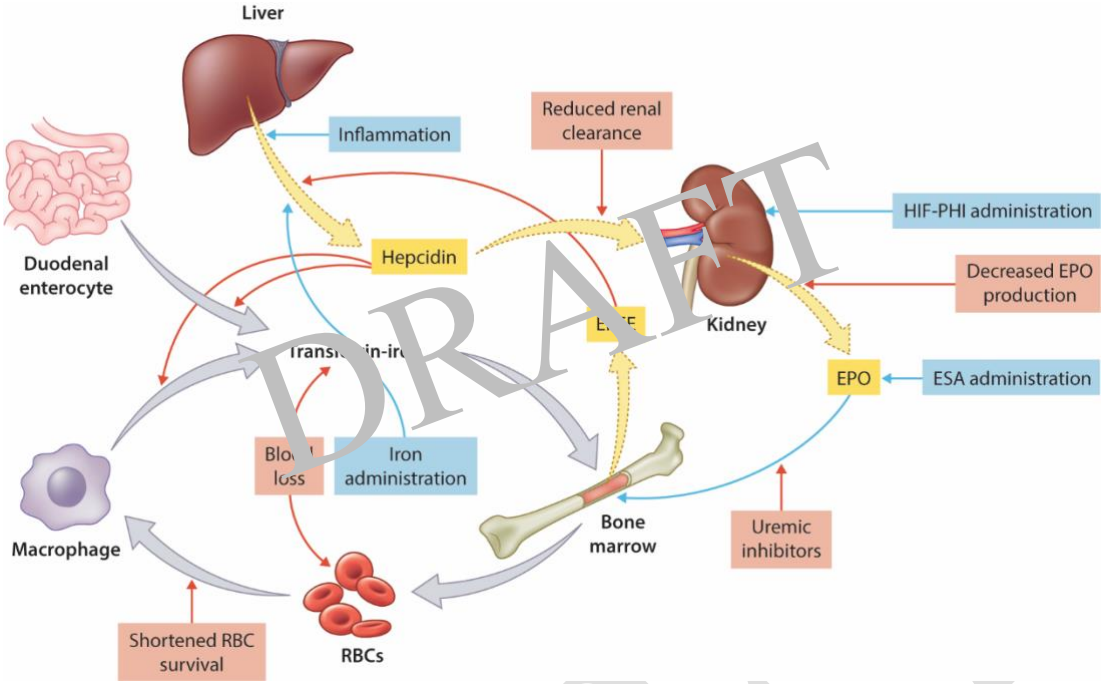


**Figure 2 | Mechanisms underlying anemia of CKD.** Red color arrows are inhibitory and the blue arrows are stimulatory. EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; ERFE, erythroferrone; ESA, erythropoiesis-stimulating agents; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitors; RBC, red blood cell. Modified from Babitt *et al.*[29]

*Outcomes associated with anemia in CKD*

Anemia in CKD is associated with several adverse cardiovascular, functional, and kidney outcomes. Studies have shown that anemia is associated with higher risks of coronary artery disease, heart failure, left ventricular hypertrophy (LVH), cardiovascular hospitalizations, and mortality.[4-8, 10, 13] Functional outcomes such as lower quality of life (QoL), lower work productivity, more cognitive impairment, and increased risk of dementia have also been reported.[2, 3, 11, 12] Moreover, anemia symptoms such as fatigue, shortness of breath, poor sleep, headaches, and reduced mental acuity ("brain fog") are common and may contribute to the lower health-related quality of life (HRQoL) commonly seen in kidney disease populations.[32] Additionally, anemia in CKD is associated with an increased need for RBC transfusion.[5] In children, anemia in CKD is also associated with impaired linear growth and neurocognitive impairments.[33, 34] Whether anemia accelerates the progression of CKD is uncertain.[35-38] Some studies have shown an increased risk of worsening kidney function, including a doubling of serum creatinine (SCr), progression to kidney failure, or progression to KRT.[5, 7, 8] For example, a *post hoc* analysis of a subset of 1513 participants in the RENAAL (Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan) study found that Hb at initiation of hemodialysis significantly predicted time to start of hemodialysis and doubling of SCr levels.[38]

After kidney transplantation, post-transplant anemia (PTA) is associated with increased mortality, reduced graft survival, and a decline in GFR. The association with mortality is related to the severity of the anemia and to specific causes of anemia.[31] In addition, PTA is associated with reduction in exercise capacity, decline in cognitive functions,

and impaired HRQoL.[39, 40] In addition, low hemoglobin levels in KTRs have been found to be associated with lower muscle mass and strength, as measured by 24-hour urinary creatinine excretion rate, bioelectrical impedance analysis (BIA)-derived skeletal muscle mass, handgrip strength, and 5-time-sit-to-stand test score.[14]

Although anemia is associated with myriad adverse outcomes in people with CKD (Figure 1), normalization of hemoglobin levels by treatment with erythropoietin stimulating agents (ESAs) failed to improve most adverse outcomes associated with anemia. Benefits included a modest improvement in HRQoL and receipt of fewer blood transfusions,[41] whereas clinically relevant harms were also noted. Accordingly, it remains uncertain whether anemia plays a causal role in adverse outcomes associated with anemia beyond HRQoL or transfusion requirements, or whether the harms of ESA therapy outweigh other potential benefits of anemia correction. The consequences of treatment of anemia will be thoroughly discussed in Chapter 2 and 3.

## 1.2. Iron deficiency in CKD

An overview of iron deficiency in CKD populations can be found in Figure 3, including its definition, prevalence, pathophysiology, and association with clinical outcomes. Each of these topics are discussed below.

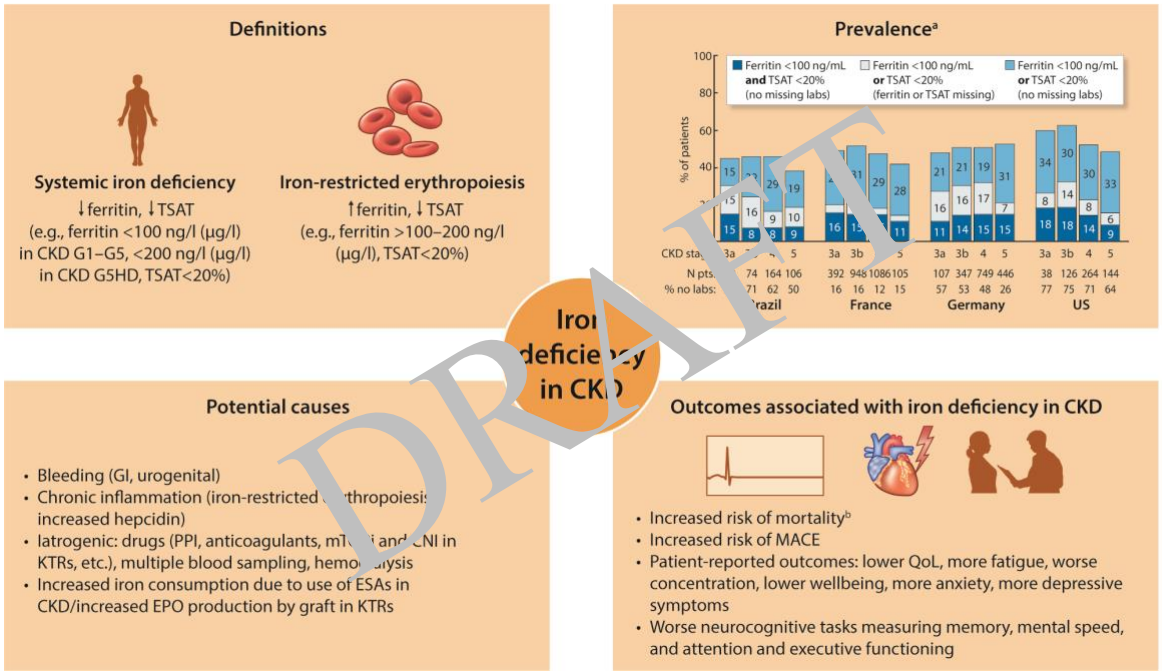


**Figure 3 | Overview of iron deficiency in CKD with its definitions, prevalence across CKD stages, potential causes, and associated outcomes.** CKD, chronic kidney disease; CNI, calcineurin inhibitors; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; GI, gastrointestinal; HD, hemodialysis; KTR, kidney transplant recipient; MACE, major adverse cardiovascular events; mTORi, mammalian target of rapamycin inhibitors; PPI, proton-pump inhibitors; QoL, quality of life; TSAT, transferrin saturation. [a]Wong *et al*. CKJ 2020;[1] [b]Guedes *et al*. JASN 2021 and Eisenga *et al*. Transplant Int 2016.[42, 43]

*Definition of iron deficiency in CKD*

Iron deficiency is typically defined based on 2 conventional indices, namely transferrin saturation (TSAT), reflecting iron availability in the circulation, and ferritin, reflecting iron storage. In people with CKD, two states of iron deficiency can exist (Figure 3). One form is characterized by a low TSAT and low ferritin level (e.g., TSAT<20% and ferritin <100 µg/l in CKD not receiving dialysis or ferritin <200 µg/l in CKD G5HD), reflecting decreased iron levels both in the circulation and in tissue stores. Although this has historically been labeled "absolute iron deficiency", we propose a change in nomenclature to "systemic iron deficiency" to more accurately reflect the physiological state. The second form of iron deficiency is characterized by a low TSAT and high ferritin level (generally ferritin >100–200 µg/l with TSAT<20%), reflecting limited available iron for erythropoiesis despite adequate iron stores. Although this has historically been termed "functional iron deficiency", we propose a change in nomenclature to "iron-restricted erythropoiesis" to provide a more physiological representation for why treating people with iron may result in increased erythropoiesis and Hb concentration. Specifically, a decrease in TSAT leads to less Hb produced per cell and fewer RBCs in circulation. This occurs as a consequence of suppressed erythroblast proliferation and differentiation together with decreased EPO responsiveness, collectively called the "iron restriction erythropoiesis response".[44-48] Applying this to CKD, where EPO production is relatively limited, the term "iron-restricted erythropoiesis" is in part intended to explain why iron administration may reduce the dose of ESA needed. See Figure 4 for the visual distinction between these entities (i.e., systemic iron deficiency and iron-restricted erythropoiesis).

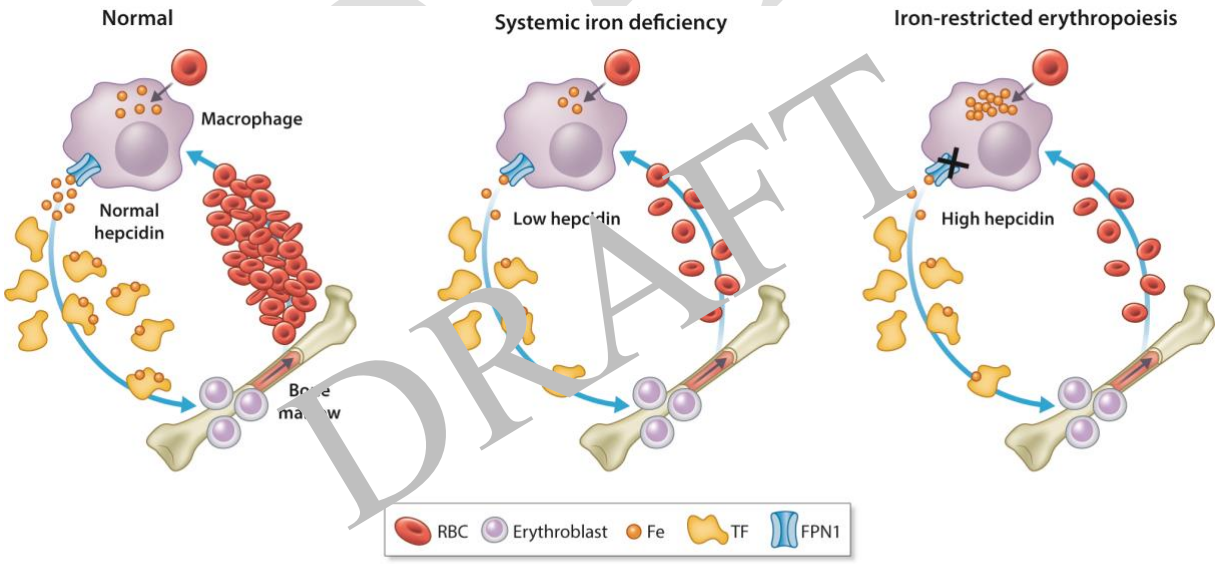


**Figure 4 | Systemic movement of iron in different iron-related states.** a) In normal circumstances, splenic macrophages recycle iron (Fe) from senescent red blood cells (RBCs) via erythrophagocytosis and release of iron via the ferroportin (FPN1) export channel. This enables recycled iron to be loaded onto transferrin (TF) in circulation and delivered to the bone marrow for erythropoiesis to replace senescent erythrocytes. b) In systemic iron deficiency, insufficient amounts of iron are available to sustain erythropoiesis, resulting in anemia with low cellular hemoglobin;

decreased systemic iron also results in hepcidin suppression, enabling the release of all macrophage iron. c) In conditions of iron restricted erythropoiesis, while erythrophagocytosis results in ample recycled iron, inflammation-induced elevation in hepcidin levels leads to iron sequestration in macrophages, preventing its release into circulation, resulting in low TF saturation and anemia with normal cellular hemoglobin.

Commonly used diagnostic thresholds for these parameters, such as ferritin <100–200 µg/l or TSAT<20% do not correlate well with bone marrow iron or Hb response to iron in people with CKD.[49] In recent years, more focus has been placed on TSAT rather than ferritin levels, as the latter only indicates systemic iron deficiency when levels are extremely low. For example, in the general population, ferritin levels <30 µg/l has a high sensitivity and specificity to define iron deficiency.[50] However, in settings where inflammation is common (as in people with CKD), higher cut-offs are chosen as ferritin is an acute phase reactant that increases due to cellular damage and inflammation.[51] In several observational analyses, low TSAT was associated with an increased risk of adverse outcomes in people with CKD, irrespective of the serum ferritin level.[43, 52, 53] Additionally, in people with chronic heart failure, many of whom have CKD, TSAT ≤19.8% or serum iron ≤13 µmol/l showed the best performance in identifying iron deficiency based on the gold standard of bone marrow iron staining. Moreover, these thresholds identified people with the highest risk of death, suggesting that TSAT or serum iron may have the strongest diagnostic value for defining iron deficiency in this setting.[54] However, using TSAT as an isolated marker of iron status has its drawbacks, since the efficacy and safety of using iron therapy in people with low TSAT and elevated ferritin levels is uncertain. It is clear that more investigation is needed into these and other diagnostic markers, which might be able to better identify people with iron deficiency and those who will benefit most from treatment (see Research Recommendations).[55] Nonetheless, because TSAT and ferritin levels are the most commonly used parameters worldwide, are readily available, and are the main parameters utilized in clinical outcome trials to date, they are still recommended to guide diagnosis and management of iron deficiency and anemia in people with CKD. Recommendations and indications for iron treatment are given in Chapter 2.

*Prevalence of iron deficiency in CKD*

Iron deficiency is highly prevalent in people with CKD. The high prevalence is present in people with CKD not receiving dialysis, CKD G5HD, people receiving peritoneal dialysis (CKD G5PD), and KTRs. In people with CKD not receiving dialysis, 15%–78% of people have either ferritin <100 µg/l or TSAT<20%, and 8%–20% have both parameters below these thresholds.[1, 24, 56, 57] For people with CKD G5HD, data from the USRDS shows that 16% have TSAT<20% and 5% have ferritin <200 µg/l,[58] and Japanese registry data show that 36%, 60%, and 28% have TSAT<20%, ferritin <100 µg/l, or both, respectively.[59] In stable KTRs, the prevalence of iron deficiency, defined as TSAT<20% with ferritin<300 µg/l is estimated at around 30%,[28, 42] with a range between 6% and 47%.[18-20] The high prevalence of iron deficiency is likely due to the multifactorial causes of iron deficiency in these populations,[60-62] as well as to poor adherence to oral iron and therapeutic inertia among prescribers.[1] Besides the failure to initiate or change iron therapy promptly, poor adherence to

oral iron can be due to multiple factors including lack of knowledge regarding the importance of dosing consistency, affordability issues, or forgetfulness in taking medication.

*Pathophysiology of iron deficiency in CKD*

Systemic iron deficiency implies a lack of adequate iron stores, which is mainly present due to blood loss, especially in the hemodialysis setting.[29] The frequent phlebotomies, blood remaining in the artificial kidney and dialysis tubing and accidental blood losses all contribute.[63, 64] The high rate of iron loss is also due to gastrointestinal bleeding from the combination of gastritis and platelet dysfunction.[31] In addition, people with CKD have angiodysplasia, frequent use of anticoagulants or antiplatelet therapy, and use of proton pump inhibitors that hamper iron absorption.[65, 66] Finally, all the typical causes of blood loss in the general population (e.g., heavy menstrual blood loss, colonic polyps, hemorrhoids) continue to occur in people with CKD.

Iron-restricted erythropoiesis can also occur in the setting of CKD, leading to anemia. Iron-restricted erythropoiesis occurs when there are normal or increased total body iron stores (including evidence of iron staining in the bone marrow), which are unavailable for incorporation into erythroid precursors. Iron-restricted erythropoiesis mainly occurs due to increased hepcidin levels.[67] Hepcidin levels are increased in people with CKD due to the higher inflammatory state (mainly through interleukin-6 [IL-6]), reduced kidney clearance, and reduced EPO and erythroferrone (ERFE) levels.[68, 69] ERFE is produced by erythroblasts in response to EPO and decreases hepatic expression of hepcidin.

For KTRs, there are numerous reasons for iron deficiency. The most important reason is the upregulated levels of hepcidin due to the inflammatory state and the possible use of mammalian target of rapamycin (mTOR) inhibitors.[70] In addition, bleeding is common due to higher incidence of gastrointestinal and urologic malignancies after transplantation and return of the menstrual cycle in females of reproductive age (which were generally amenorrhoeic during kidney failure). Finally, after kidney transplantation, renewed EPO production will increase iron utilization to promote erythropoiesis.[62]

*Outcomes associated with iron deficiency in CKD*

Many observational studies show that iron deficiency is associated with an increased risk of mortality and cardiovascular hospitalization in people with CKD.[28-30] In particular, iron deficiency, as captured by low TSAT, is associated with higher risk of all-cause mortality and major adverse cardiovascular events (MACE) in people with CKD not receiving dialysis, regardless of ferritin levels or the presence of anemia.[43, 52, 53] Additionally, low TSAT levels (≤15%), irrespective of ferritin levels, are associated with worse physical HRQoL compared to higher TSAT levels in people with CKD not receiving dialysis, even after accounting for Hb level.[71] In people with CKD G5HD, normal iron status (i.e., TSAT>20% and ferritin ≤800 µg/l) was associated with better survival as compared to iron deficiency (systemic iron deficiency defined as TSAT ≤20% and serum ferritin ≤200 ng/ml or iron-restricted erythropoiesis defined as TSAT ≤20% and serum ferritin 200–800 ng/ml) or high iron status (i.e., ferritin>800 µg/l).[72] In Japanese hemodialysis patients, a TSAT ≤20% was a significant

independent risk factor for all-cause mortality.[73] Similarly, in Korean anemic incident dialysis patients, a low TSAT of ≤20% was associated with an increased risk of mortality and the cardiovascular composite endpoint consisting of death or hospitalization from myocardial infarction/ischemia, congestive heart failure, pulmonary edema, or cerebrovascular disorder.[74] In KTRs, iron deficiency, independent of anemia, has been found to be associated with an increased risk of death.[42] Similarly, an independent association of percent hypochromic RBCs >10% (an indicator of iron-restricted erythropoiesis) was associated with an increased risk of death in this setting.[75] Iron-deficient KTRs also performed worse on neurocognitive tasks measuring memory, mental speed and attention, and executive functioning.[76] Finally, in KTRs, iron deficiency, independent of anemia, was associated with more fatigue, worse concentration, more anxiety, higher risks of major depressive symptoms and sick leave, and lower physical and mental component scores of HRQoL as patient-reported outcomes.[77]

The strongest evidence of a causal effect of iron deficiency on outcomes, however, comes from the Proactive IV irOn Therapy in hemodiALysis patients (PIVOTAL) study, which involves treatment strategies, rather than defining iron deficiency and assessing the association with outcomes. This study will be thoroughly discussed in Chapter 2.

*How to approach the diagnosis and evaluation of anemia and iron deficiency in CKD*

**Practice Point 1.2.1: In people with CKD, test for anemia at referral, regularly during follow-up, and when anemia is suspected based on symptoms (Figure 5). Test for anemia with the following set: complete blood count (CBC), reticulocytes, ferritin, transferrin saturation (TSAT) (Figure 6).**

The age of the person, degree of anemia (i.e., Hb concentration), RBC volume (i.e., mean corpuscular volume [MCV]), attributable symptoms, severity of CKD, use of dialysis, comorbid diseases, and RBC transfusion risk may all influence the need for and frequency of testing for anemia and its underlying causes. This drive for screening must be counterbalanced by attempts to minimize unnecessary blood draws.

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

**Figure 5 | Suggested testing frequency for anemia by chronic kidney disease (CKD) stage**

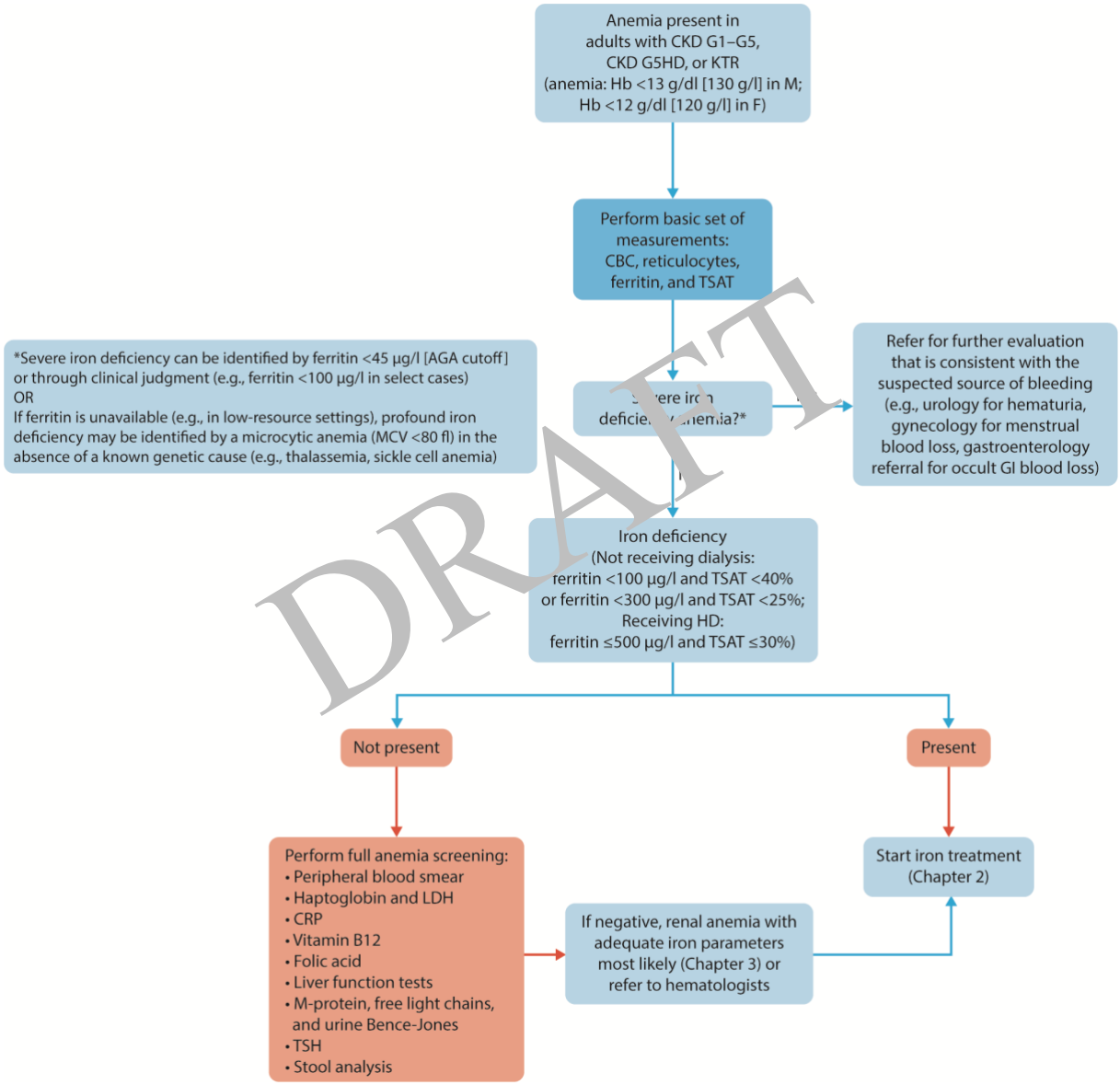


**Figure 6 | Flowchart of the different steps to follow when people with chronic kidney disease (CKD) who have anemia.** AGA, American Gastroenterological Association; CBC, complete blood count; CKD G5HD, CKD receiving hemodialysis; CKD G1-G5, CKD not receiving dialysis; CRP, C-reactive protein; F, female; GI, gastrointestinal; KTR, kidney transplant recipients; LDH, lactate dehydrogenase; M, male; MCV, mean corpuscular volume; TSAT, transferrin saturation; TSH, thyroid-stimulating hormone

**Practice Point 1.2.2: In people with anemia and CKD, and in whom the initial tests do not reveal the cause, consider this expanded panel to identify potential underlying causes:**

- **Blood smear review,**
- **Haptoglobin,**
- **Lactate dehydrogenase (LDH),**
- **C-reactive protein (CRP),**
- **Vitamin $B_{12}$,**
- **Folate,**
- **Liver enzymes,**
- **Serum protein electrophoresis (SPEP) with immunofixation, serum free light chains, urinary Bence-Jones protein,**
- **Thyroid-stimulating hormone (TSH) and,**
- **Stool analysis.**

In addition to iron deficiency, anemia may be the consequence of inflammation, hemolysis, liver insufficiency, vitamin $B_{12}$ or folate deficiencies, endocrine disorders (e.g., hypothyroidism), malignancy (plasma cell disorders such as multiple myeloma), or other causes for which no diagnostic testing is available (e.g., medications). In people with persistent or progressive anemia with associated symptoms, if the initial diagnosis and management of the anemia does not yield resolution of anemia, consider intermittently repeating assessment of alternative causes for anemia.

**Practice Point 1.2.3: In people with CKD, anemia, and ferritin <45 µg/l, consider referral to gastroenterologists/gynecologists/urologists to identify the cause of blood loss.**

When a medical care provider identifies severe iron deficiency, defined by the American Gastroenterological Association (AGA) as ferritin <45 µg/l, or microcytic anemia (MCV <80 fl) in the absence of measured ferritin or known genetic cause, determine potential sources of blood loss. Since unrecognized possible blood loss typically occurs in the gastrointestinal or genitourinary tract, iron deficiency without an obvious cause (e.g., recent surgery, blood donation or cumulative large volume phlebotomy) warrants referral to identify the cause of blood loss.

**Research recommendations:**

1. Investigate the prevalence and health outcomes of iron deficiency in the absence of anemia. Important outcomes to assess include hard clinical endpoints such as mortality and MACE, patient-reported outcomes, and exercise capacity, as well as cardiac function, skeletal muscle function, gut microbiome, and the immune system.
2. Investigate the use of other iron status parameters (e.g., soluble transferrin receptor levels, hepcidin, reticulocyte hemoglobin content, percentage hypochromic RBCs, or other novel parameters) for diagnosis iron deficiency in people with CKD. An important aspect is the need for standardization of the test performed.

3. In pregnant women with anemia and CKD, describe the variability in hemoglobin and iron parameters across eGFR strata, investigate cut-off levels of Hb and iron parameters and relate them to maternal and fetal outcomes.

# CHAPTER 2. USE OF IRON TO TREAT IRON DEFICIENCY 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*).**

*This recommendation places high value on the potential benefits of iron for improving life expectancy and symptoms, reducing the required dose of ESAs, and reducing the need for RBC transfusion, and a relatively lower value on the potential side effects of iron. The recommendation applies to both adults and children regardless of treatment with ESAs, hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs), or neither. People who are not treated with ESAs or HIF-PHIs and do not have symptoms attributable to anemia may opt for lower ferritin and TSAT initiation thresholds, particularly if they are concerned about potential side effects of iron. The recommendation may not apply to people with active infection.*

**Key information**

*Balance of benefits and harms*

Oral or intravenous (i.v.) iron versus no iron

Nineteen studies have compared oral (8 RCTs[78-85]) or i.v. iron (13 RCTs[78, 79, 86-97], including 2 RCTs investigating dialysate iron[90, 91]) versus placebo in people with CKD G5HD treated with ESAs or HIF-PHIs. Overall, critical outcomes were assessed in a small number of studies with relatively few participants, so the effects of iron on critical outcomes including all-cause death, cardiovascular events, stroke, myocardial infarction, serious adverse effects, serious gastrointestinal adverse events, serious hypersensitivity reactions, and infections are very uncertain (Supplementary Table S4). QoL was assessed in a single, small RCT including 32 participants.

When compared to placebo, iron dosing agents seem to increase Hb values by about 0.5 g/dl (5 g/l). Iron treatment may allow fewer RBC transfusions and probably also lowers ESA doses, while the impact on HIF-PHI dosing has not been assessed. Iron administration also increases TSAT and ferritin levels. Evidence for the effect of iron on cancer was very uncertain (Supplementary Table S5).

Iron status thresholds to initiate iron therapy and treatment targets

Seven RCTs (11 reports) evaluated cut-off values of ferritin and TSAT at which to initiate iron therapy or to achieve as targets for iron therapy.[98-108] However, studies on long-term safety, cost-effectiveness, and risk-benefit of using different ferritin and TSAT targets are limited. Healthcare providers selected the dose of ESA that would be sufficient to maintain a Hb level of 10–12 g/dl (100-120 g/l), and studies were mostly designed to assess ESA requirements. Only 3 studies assessed critical outcomes.

One small trial randomized 42 participants to receive i.v. iron dextran to maintain TSAT either at 30%–50% or at 20%–30%.[98] At 24 weeks, 2 of 19 participants died in the low target group, versus 1 of 23 participants in the high target group. There was no evidence that the TSAT target influenced the risk of cardiovascular events, hospital admission, or other adverse events.

The PIVOTAL trial randomized 2141 participants to receive either high-dose iron sucrose, administered intravenously in a proactive fashion (400 mg monthly, unless the ferritin concentration was >700 µg/l or the TSAT ≥40%), or low-dose iron sucrose, administered intravenously in a reactive fashion (0–400 mg monthly, with a ferritin concentration of <200 µg/l or a TSAT <20% being a trigger for iron administration).[104] The rate of the composite of fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure after a median of 2.1 years appeared lower in the proactive group than in the reactive group (hazard ratio [HR]: 0.80; 95% confidence interval [CI]: 0.64–1.00). Similarly, the rates of the individual components of fatal or nonfatal myocardial infarction and hospitalization for heart failure appeared lower among people receiving proactive iron than among those receiving reactive iron, as did the risk of death. Rates of stroke, hospitalization and infection were similar in the 2 treatment groups. Investigators found no apparent differences in either the Euro-QoL-5D (EQ-5D) QoL health index or the Kidney Disease Quality of Life (KDQOL) score. Adverse events were generally similar in type and number in both groups (risk ratio [RR]: 1.01; 95% CI: 0.95–1.08). Fewer (3.5%) people required a blood transfusion and ESA requirements were generally lower in the proactive group than the reactive group.

A third study randomized 200 participants to receive i.v. iron sucrose to maintain ferritin concentrations between 600–700 ng/ml (600–700 µg/l) or 200–400 ng/ml (200–400 µg/l) for a period of 6 months.[108] Rate of death was similar between the 2 groups. No other critical outcome was reported.

Overall, the Work Group felt that available data supported higher rather than lower iron status targets to reduce ESA requirements and improve clinical outcomes.

*Certainty of the evidence*

The overall certainty of the evidence for iron therapy among people with CKD G5HD is very low (Supplementary Tables S4 and S5). The certainty of the evidence was graded to be very low for several critical outcomes due to concerns with risk of bias and very serious or extremely serious concerns regarding imprecision.

*Values and preferences*

Although there has not been a formal assessment of patient values and preferences regarding iron, the Work Group believes most people with CKD G5HD would want iron if it prolonged life, reduced the risk of cardiovascular events, or improved QoL.[109]

*Resource use and costs*

Iron supplementation seems to reduce the requirement for ESA therapy. Given the high cost of ESAs, appropriate use of iron in people with CKD would be expected to reduce overall costs.

*Considerations for implementation*

It is difficult to precisely predict the effect iron will have on both Hb and iron status, the assessment of which requires repeated testing. This is particularly important given that results will drive dose adjustments and formulation switch in case of insufficient effect. In the absence of clinical trials that specifically inform the optimal frequency for testing of iron status, and consistent with prior guidelines, it seems reasonable to test iron status each month for those treated with CKD G5HD. Additionally, treatment thresholds and treatment targets may vary across populations (e.g., in Japan where lower ferritin levels are often targeted).

Some dialysis units have developed and/or are using protocols to guide dosing and dosing adjustments based on repeated measures. Such protocols could help implement the above.

**Rationale**

Several recent trials evaluated the benefits and harms of various treatment targets. By far the largest of those studies, PIVOTAL, found that compared with a reactive low-dose i.v. iron strategy, a proactive high-dose i.v. iron regime moderately decreased the risk of death and important cardiovascular events without increasing the risk of infection or serious adverse events.[104] In addition, there was no evidence for effect modification by vascular access type.

Several issues arise when interpreting PIVOTAL.[104] First, the trial had 2 arms comparing discrete iron treatment regimens. Compared to a reactive low-dose strategy, the proactive higher-dose regimen resulted in better outcomes. This does not imply, however, that the proactive high-dose regimen is the optimal strategy. It is simply better compared with the reactive low-dose regimen. Optimal doses may be somewhere between the 2 regimens, or higher still, although retrospective, observational data suggest that more intensive i.v. iron regimens (greater than in PIVOTAL) are associated with an increased risk of mortality and infections.[110] Optimal dose-finding would require a multi-arm trial that includes different ferritin and TSAT targets, using different ESA doses, which may not be feasible in a randomized trial.

The KDIGO 2012 guideline highlighted the difficulty of trying to specify treatment initiation thresholds. PIVOTAL may have indicated that in people with CKD G5HD treated with ESA, higher iron dosing leads to improved outcomes, but it is not entirely clear what is driving these outcomes. Possibilities include the lower ESA doses required to maintain Hb within the target range, the correction of iron deficiency *per se*, a combination of these mechanisms, or other mechanisms yet unknown. For any individual, the optimal balance of Hb, ESA, and iron dose at which clinical benefit is maximized is still not known. All of this is

complicated by the relatively poor diagnostic accuracy of serum ferritin and TSAT to estimate body iron stores or to predict the Hb response to iron supplementation.

The Work Group aimed to propose a treatment initiation threshold that would balance the benefits seen with higher iron dosing against the uncertainty about the optimal treatment targets. No studies have truly randomized different initiation thresholds. The inclusion criteria in terms of ferritin and TSAT were highly variable, preventing the identification of a clear initiation threshold. Similarly, target studies do not provide a definitive threshold for initiation. The 2012 threshold remains broad, encompassing most of the inclusion thresholds used in various studies. This includes the PIVOTAL study, which included participants with ferritin <400 ng/l (400 µg/l) and TSAT <30%. Given that establishing an actual target based on the PIVOTAL data is still problematic, the Work Group felt it was reasonable to maintain the previous initiation threshold. However, we acknowledge that these numbers are somewhat arbitrary and that future research may lead to revised conclusions. For example, the Dialysis Patients Response to IV Iron with Elevated Ferritin (DRIVE) I and II trials investigated the effect of iron administration in people with CKD G5HD with ferritin levels ranging from 500–1200 ng/ml (500–1200 µg/l) and with TSAT ≤25%.[88] During a 6-week follow-up, people who had received ferric gluconate had achieved a Hb concentration which was ±0.5 g/dl higher than those who did not, without appreciable differences in serious adverse effects. After another 6-week observational extension, people who had received ferric gluconate required significantly lower ESA doses than controls, with fewer serious adverse events. These data support the use of iron supplementation as an ESA-sparing strategy, even in people with elevated serum ferritin levels, but they would require confirmation on the longer term.

There are no studies in people with CKD G5HD not yet treated with ESAs or HIF-PHIs. For those people, the balance of benefits to harms may be different from that among people treated with ESA, especially if improved outcomes in higher iron dosing strategies primarily stem from reductions in ESA dosage. Concurrently, the threshold for initiating treatment may be lower. There are also no studies in people with CKD G5HD treated with HIF-PHI, where optimal iron dosing strategies are unknown. It has been postulated that HIF-PHIs may improve iron availability and reduce iron treatment needs over ESAs, but this has not yet been demonstrated in RCTs. Additionally, it is possible that higher iron strategies could lower HIF-PHI dosage as it does for ESAs. Since HIF-PHIs have not shown improved safety over ESAs in RCTs (see Chapter 3), lower HIF-PHI dosing could also be beneficial. At present, we found no compelling evidence or rationale to propose an alternative threshold for people not yet treated with ESA or people treated with HIF-PHI. We also recognized the advantage of maintaining uniformity for the sake of simplicity.

Observational studies in children with CKD G5HD have illustrated that iron reduces the dose of ESA required to maintain target Hb concentrations.[111, 112] Initiation targets for iron therapy in children with CKD G5HD are unclear; however, one RCT illustrated a benefit on Hb in the use of iron therapy in children with CKD G5HD who are iron deplete as defined as TSAT <20% and or serum ferritin <100 ng/ml (<100 µg/l).[113] Another trial on the optimum

iron dose conducted in children with CKD G5HD with ferritin ≤800 mg/ml and TSAT 20%–50% suggested that a similar broad threshold to adults for initiation of iron therapy is appropriate.[114]

**Recommendation 2.2: In people with anemia and CKD G5HD in whom iron therapy is being initiated, we suggest using intravenous iron rather than oral iron (*2D*).**

*This recommendation places a high value on the benefits associated with more intensive administration of supplemental iron and the reduction in pill burden associated with i.v. iron. Most people receiving HD are likely to prefer i.v. iron, but those at risk of hypersensitivity reactions may prefer oral treatment. This recommendation is also applicable in children.*

**Key information**

*Balance of benefits and harms*

Eleven studies compared i.v. versus oral iron in 844 people with CKD G5HD treated with ESAs (Supplementary Table S6 and S7).[78, 79, 113, 115-123] Most were designed to examine increases in Hb concentrations. Studies assessed different oral and i.v. iron preparations, and inclusion criteria for ferritin concentrations and TSAT varied substantially. We did not find any head-to-head RCTs comparing the effect of different i.v. iron compounds on important health outcomes in people with CKD G5HD.

When compared with oral iron, i.v. iron may have lowered the risk of death, but numbers were small and event rates low (Supplementary Table S6). Evidence for cardiovascular events, stroke, myocardial infarction, all-cause hospital admission, infections, serious adverse events, serious gastrointestinal events, blood transfusions, and cancer was mostly limited to single and small trials. Heart failure, QoL, and functional status were not reported.

Intravenous iron had variable effects on ESA dose, with 4 in 6 studies indicating an average reduction in comparison with oral iron, and average effects on Hb values were variable. Intravenous iron seemed to increase ferritin concentrations and TSAT to a greater extent than oral iron, regardless of the total dose of iron given.

Ferric pyrophosphate citrate is a water-soluble iron salt administered intravenously or via dialysate. In contrast to other i.v. iron preparations that are taken up by reticuloendothelial macrophages to liberalize iron, ferric pyrophosphate citrate delivers iron directly to circulating transferrin. Phase 2 and 3 RCTs have demonstrated that dialysate ferric pyrophosphate citrate maintains Hb levels without an excessive increase in iron stores,[90, 91] together with decreasing ESA and i.v. iron needs. However, no studies have directly compared the efficacy or safety of dialysate iron with i.v. or oral iron. Additionally, ferric pyrophosphate citrate is not available in most countries, limiting its use.

Two studies were conducted in children comparing i.v. versus oral administration of iron (Supplementary Table S7). A first study compared i.v. iron sucrose to oral iron

gluconate, and found i.v. iron resulted in a greater Hb response and higher ferritin and TSAT.[124] A second study found ferritin concentrations were higher in children given i.v. iron dextran compared to those receiving oral ferrous fumarate. Serious adverse events, serious gastrointestinal adverse events, serious hypersensitivity reactions, and risk of RBC transfusion were not different between the oral and i.v. arms.[113] Other trials comparing dosing of i.v. versus oral iron in children with CKD G5HD have also reported low rates of adverse events, which further supports the recommendation of i.v. iron over oral iron in children with CKD G5HD.[114, 125]

*Certainty of evidence*

The overall certainty of the evidence for i.v. iron therapy compared with oral iron therapy among people with CKD G5HD is very low for all critical outcomes (Supplementary Table S6 and S7). The certainty of the evidence for these outcomes was often downgraded due to concerns with risk of bias and extremely serious concerns regarding imprecision.

*Values and preferences*

The Work Group believes most people with CKD G5HD would prefer i.v. iron over oral iron as it can be administered during dialysis. Those at risk of or particularly worried about hypersensitivity reactions may prefer oral treatment (Table 2). Dialysate iron is not presented in the Table given its limited availability.

**Table 2 | Factors to consider when choosing between oral and intravenous iron**

| Oral iron | Intravenous iron |
|---|---|
| Slower increase in Hb, ferritin, TSAT | More rapid increase in Hb, ferritin, TSAT<br>Delayed and reduced ESA use<br>Possibly faster increase in QoL |
| Side effects<br>• More frequent<br>• Less severe<br><br>Constipation and other gastrointestinal symptoms are frequent. If the patient suffers from these symptoms at baseline, then i.v. iron may be preferred | Side effects<br>• Less frequent<br>• More severe<br><br>Hypotension and immediate hypersensitivity reactions are uncommon but can occur with any i.v. iron agent, especially in people with a history of drug allergies |
| Less expensive<br>More convenient | More expensive<br>Requires trained healthcare providers |
| Accessibility<br>• Appealing to people who want to limit hospital visits.<br>• Addresses mobility inequality for people with CKD | |
| Preserve veins for hemodialysis vascular access | Consider possible effect on preserving veins for hemodialysis vascular access |
| Inconsistent adherence | Assured administration |
| Avoid if intestinal absorption impaired | |

CKD, chronic kidney disease; ESA, erythropoietin-stimulating agents; Hb, hemoglobin; QoL, quality of life; TSAT, transferrin saturation

*Resource use and costs*

Iron supplementation seems to reduce the requirement for ESA therapy. Given the high cost of ESAs, appropriate use of iron in people with CKD would be expected to reduce overall costs.

*Considerations for implementation*

Oral iron is inexpensive and readily available in most parts of the world, which may not necessarily be the case for i.v. iron. Tables 3 and 4 outline the available oral and i.v. iron formulations, respectively, their recommended doses, and considerations for their use.

**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 |

CKD, chronic kidney disease

**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)<br>1000 mg (EMA) | 15 min | 7.5 min (FDA)<br>15 min (EMA) | Full dose can be given in 1 or 2 sittings (750 mg 2 doses 1 week apart)<br>May cause hypophosphatemia, especially in people with early CKD and kidney transplant recipients |
| **Ferric derisomaltose / iron isomaltoside** | 100 mg/ml | 1000 mg (FDA)<br>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 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Hypersensitivity (due to bolus dosing) rarely occurs |

CKD, chronic kidney disease; EMA, European Medicines Association; FDA, Food and Drug Association; HD, hemodialysis.

**Rationale**

The Work Group felt that available data support the administration of i.v. iron to people with CKD treated with in-center HD, aiming to increase iron stores and probably reduce the ESA dose required and associated cost. Given the initiation threshold suggested in Recommendation 2.1 (and its implicit lower limit of the target interval), it seems much less likely that this could be achieved with oral iron than with i.v. iron. Additionally, the strongest evidence for benefit from iron therapy comes from the PIVOTAL trial, which utilized an i.v. iron replacement strategy. To our knowledge, there is no published data on patient preference, but the Work Group, which included patient partners, believed most people receiving dialysis would prefer i.v. iron over oral iron as it can be administered during dialysis. We also recognized that some people, particularly those at risk of or worried about hypersensitivity reactions, might prefer oral treatment. Additionally, we are aware that i.v. iron may not be widely available or economically viable in all countries.

**Practice Point 2.1: In people with CKD G5HD in whom iron therapy is being initiated, administer intravenous iron using a proactive approach to maintain stable iron status.**

Intravenous iron can be administered either proactively at regular intervals to maintain stable iron status or reactively when iron status test values fall below certain thresholds. The Work Group believes that a proactive approach has advantages over a reactive one based on the benefits demonstrated in the PIVOTAL trial.[104] Proactive administration likely helps prevent periods of iron restriction, leading to more consistent and optimal management of anemia.

Repeated doses of i.v. iron may be required, depending on the specific i.v. iron preparation used. The maximum single dose varies by formulation, with some preparations allowing higher doses in one session than others. This is typically determined by the degree of labile iron release into the circulation, which limits the maximal dose.[126] For example, ferric gluconate and iron sucrose typically allow a maximum single dose of 125 mg or 200 mg, respectively, whereas other formulations like ferumoxytal, ferric carboxymaltose, and iron isomaltoside have higher dosing limits of 510–1000 mg (Table 4).

**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%.**

*This recommendation places a high value on increasing iron availability as a means of increasing Hb, which may improve symptoms and QoL and reduce transfusions. Our recommended thresholds for starting iron are based on the most liberal inclusion criteria of the*

*randomized controlled trials (RCTs) that informed the recommendation. The recommendation applies to KTRs and to both adults and children.*

**Key information**

*Balance of benefits and harms*

Iron versus no iron

Among people with CKD not receiving dialysis, ESAs or HIF-PHIs, 16 studies (22 publications) of 1768 participants compared either oral iron or i.v. iron to placebo.[127-146] Studies set different thresholds of Hb (8.0–15.0 g/dl [80–150 g/l]), ferritin (<100–<300 ng/ml [<100–<300 µg/l]), and TSAT (<20% to ≤30%) as inclusion criteria. None compared iron with placebo in those treated with ESA. Two studies included KTRs and none were conducted in children.

Overall, iron may have reduced all-cause mortality and all-cause hospitalization, but results were very uncertain; as were effects on cardiovascular events, stroke, heart failure, myocardial infarction, serious gastrointestinal adverse events, QoL, functional status, or cancer. Individual studies were small, and only a handful reported on these outcomes altogether. The available evidence does not suggest an important increase in serious adverse events or infections with iron compared to placebo. Iron probably increases the Hb concentration on average by about 0.65–1.0 g/dl compared to no iron. Studies reported no hypersensitivity reactions (Supplementary Table S8 and S9).

Three studies assessed the effects of oral or i.v. iron versus placebo in 294 adults with CKD G5PD (Supplementary Table S10 and S11).[147-149] None reported on all-cause death, cardiovascular events, stroke, heart failure, myocardial infarction, QoL, functional status, all-cause hospitalization, hypersensitivity reactions, RBC transfusions, or cancer risk. Effects were unclear on serious adverse events, serious gastrointestinal adverse events, infections notably peritonitis, hemoglobin values, or ESA dose.

Different iron status targets

No RCTs assess the benefits and harms for critical outcomes of different treatment targets (Hb or iron indices) among people with CKD not receiving dialysis or CKD G5PD. The Ferinject® assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent Chronic Kidney Disease (FIND-CKD) trial compared i.v. ferric carboxymaltose targeted to ferritin concentrations of 400–600 ng/ml (400–600 µg/l) versus 100–200 ng/ml (100–200 µg/l) in 305 participants. The primary endpoint for time to initiation of another anemia treatment (i.e., ESA, another iron treatment or blood transfusion) was not statistically different between the 2 groups.[150]

*Certainty of the evidence*

CKD not receiving dialysis

The overall certainty of the evidence for iron therapy among people with CKD not receiving HD is very low (see Supplementary Table S8 and S9). The certainty of the evidence was determined to be very low due to very serious or extremely serious concerns regarding imprecision due to few events and/or wide confidence intervals that included both significant benefits and significant harms. Certain outcomes were downgraded for concerns with indirectness because studies addressed only one of the relevant comparisons (i.e., oral iron vs. placebo or i.v. iron vs. placebo).

CKD G5PD

The overall certainty of the evidence for iron therapy among people with CKD G5PD is very low (Supplementary Table S10 and S11). No trials among people with CKD G5PD reported on critical outcomes, and only one study addressed total serious adverse events and infections.[149] The certainty of the evidence for these critical outcomes is very low due to serious concerns with the risk of bias and indirectness and extremely serious concerns with the imprecision.

*Values and preferences*

Although there has not been a formal assessment of published evidence concerning values and preferences of people with CKD not receiving dialysis regarding iron, the Work Group believes that most would want iron if it prolonged life, reduced the risk of cardiovascular events, or improved QoL.[109] The threshold Hb at which anemia causes symptoms that can be improved is likely to vary according to the person's activities and the ability to compensate for the reduced oxygen delivery that anemia causes, and will likely influence the willingness to add another treatment to their regimen. Likewise, the iron status threshold at which people can expect symptom improvement and are willing to start treatment is likely to differ. People with relatively more symptoms attributable to anemia, a higher likelihood of responding to iron, and/or who are less concerned about side effects may be more inclined to choose iron treatment.

*Resource use and costs*

Iron supplementation is likely to reduce the requirement for ESA therapy. Given the high cost of ESAs, appropriate use of oral iron in people with anemia and CKD would be expected to reduce overall costs by lowering ESA use. For people not treated with dialysis, administration of i.v. iron requires additional facilities and personnel, the relative costs of which are uncertain as compared to ESA treatment.

*Considerations for implementation*

It is difficult to predict the effect that iron will have on Hb and iron status, the assessment of which requires repeated testing. This is particularly important given that results will drive dose adjustments and formulation switch in case of insufficient effect. In the absence of clinical trials that specifically inform the optimal frequency for testing of iron status, and consistent with

prior guidelines, it seems reasonable to test iron status every 3 months among those not treated with HD.

**Rationale**

For people with anemia and CKD, iron supplementation is aimed at maintaining adequate iron reserves for erythropoiesis or stimulating an erythropoietic response, even in the absence of systemic iron deficiency. This, in turn, may allow for reduced ESA doses, thereby mitigating ESA-related risks. Nonetheless, the ideal balance of Hb concentration, ESA dosage, and iron supplementation for maximizing clinical benefits while minimizing potential risks remains uncertain for each individual person.

No RCTs assess the benefits and harms of iron at different starting thresholds of Hb or indices of iron status. None have assessed different treatment targets looking at critical outcomes. Mostly studies compare either oral or i.v. iron versus placebo, or i.v. iron versus oral iron, and set different thresholds of Hb, ferritin, and TSAT as inclusion criteria. In addition, studies comparing iron to placebo did not include people treated with ESAs or HIF-PHIs so it is difficult to extrapolate data to those people.

Systematic review of the evidence indicated that compared with placebo, iron increased Hb concentrations on average by about 0.65–1 g/dl (6.5–10 g/l). The effect appeared similar for people with CKD, KTRs, and those treated with PD. What the increase in Hb or iron status parameters means, however, for critical, patient-important outcomes such as death, cardiovascular risk, QoL, or functional status remains unclear. Such outcomes were not systematically reported, and total numbers in meta-analyses were relatively small, which resulted in wide confidence intervals and low certainty of evidence. Hence, any suggestion to treat with iron hinges on the belief that if the Hb drops below a certain threshold, the benefits of iron outweigh its risks; that a likely reduction in need and/or dosage of ESA is beneficial; and that data generated for CKD G5HD can be extrapolated to those considered here. The threshold for anticipated benefits at higher Hb concentrations likely depends on multiple factors, including age, level of physical activity, and underlying comorbidities. Consequently, some people may be more inclined than others to receive anemia treatment at any specific Hb level, and shared decision-making is required.

Evidence is limited to support a recommendation for specific ferritin concentrations and TSAT values at which to initiate iron therapy. The Work Group chose the suggested thresholds compatible with the inclusion criteria of most contemporary trials, including trials in KTRs and those treated with PD. The trials mostly defined either a combination of ferritin ≥100 ng/ml (≥100 µg/l) to <300 ng/ml (<300 µg/l) and TSAT <25%, or ferritin <100 ng/ml (<100 µg/l) without the TSAT threshold. The Work Group decided to provide an upper limit for TSAT

driven by concerns about the risk of potential toxic effects of non-transferrin-bound iron that appears at higher TSAT values.

Studies conducted in people already treated with ESAs or HIF-PHIs generally had more liberal TSAT thresholds (<25%) for inclusion than those conducted in ESA-naïve patients (<20%). Given the measurement error that exists in TSAT measurements, we opted for a single threshold to include both, reasoning that this simpler approach should facilitate implementation. The current recommendation represents a change from the previous guideline,[151] in which a single initiation threshold was selected for those with CKD not receiving dialysis and those with CKD G5HD. We felt the publication of several larger studies in CKD G5HD comparing different and much higher targets warranted a separate recommendation at the present time. Moreover, it is important to consider that all people enrolled in the CKD G5HD trials were already treated with ESA. In this context, the balance between benefits and harms of iron treatment may differ from those who are ESA-naïve.

In children with CKD not receiving dialysis and CKD G5PD, RCTs have had liberal iron targets. One study in children across all CKD stages comparing differing doses of i.v. iron included children with ferritin ≤800 ng/ml and TSAT between 20%–50%. Accordingly, similar initiation thresholds appear appropriate in children.

**Recommendation 2.4: In people with anemia and CKD not receiving hemodialysis in whom iron is initiated, we suggest using either oral or intravenous iron based on the person's values and preferences (*2D*).**

*People with anemia and CKD should choose whether to receive oral or i.v. iron based on their values and preferences. For some, affordability and ease of use are key factors when considering iron supplementation. Others may prioritize a quicker rise in hemoglobin levels and potentially a better quality of life. This recommendation places a lower value on the very low certainty evidence for critical outcomes and potential side effects. This recommendation is also applicable to CKD G5PD, kidney transplant recipients, and children.*

**Key information**

*Balance of benefits and harms*

Ten studies compared i.v. iron versus oral iron head-to-head in 1868 adults with CKD not receiving dialysis , ESAs, or HIF-PHIs;[150, 152-163] 5 RCTs did so in in 800 adults who were already treated with ESAs.[164-168] The studies compared different oral and i.v. iron preparations and varied substantially in the dose and duration of i.v. and oral treatments prescribed. One study was conducted in kidney transplant recipients.[160] None was conducted children.

For i.v. versus oral iron, studies did not indicate a clear effect on all-cause mortality, cardiovascular events, stroke, myocardial infarction, serious adverse events, serious gastrointestinal events, infections, blood transfusions, ESA use, or cancer, but the evidence was very uncertain (Supplementary Table S12). These findings are compatible with minimal to no statistical heterogeneity in effect for death, cardiovascular events, serious adverse events, and infections when i.v. or oral iron were tested versus placebo. Studies offered no data on all-cause hospitalization.

Serious hypersensitivity reactions did not seem to be more frequent with i.v. iron compared to oral iron. Probably more people reached a preset Hb target - usually 11.0 g/dl (110 g/l) or an increase of 1.0 g/dl (10 g/l) with i.v. iron, corresponding to a 0.3–0.5 g/dl (30–50 g/l) higher average Hb concentration with i.v. iron versus oral iron. This seems consistent with the effects found on average Hb concentrations when i.v. or oral iron were tested versus placebo. TSAT seemed to increase faster and ferritin appeared to be higher with i.v. iron.

Two studies (3 publications) compared i.v. versus oral iron in 231 adults with CKD G5PD, testing different i.v. compounds for a maximum of 4 months, with doses per month of iron ranging from 500–1000 mg for i.v. iron and 5400–6000 mg for elemental oral iron (Supplementary Table S13).[118, 119, 147, 160] None reported critical outcomes, but more people reached higher Hb values with i.v. iron. This seems consistent with the analyses of i.v. or oral iron versus placebo where i.v. iron use led to attainment of higher Hb concentrations versus placebo than oral iron did.

*Certainty of the evidence*

The overall certainty of the evidence for i.v. iron therapy compared with oral iron therapy among people with CKD not receiving HD is very low (Supplementary Table S12 and S13). The certainty of the evidence was determined to be very low for all critical outcomes and was often downgraded due to concerns with risk of bias, including selection bias, lack of blinding, and/or attrition bias. Additionally, there were extremely serious concerns regarding imprecision due to few events and/or wide confidence intervals that included both significant benefits and significant harms.

*Values and preferences*

The Work Group believes that patients will have varying preferences for i.v. or oral iron based on their health and mobility status. Oral options may be favored for their convenience, as they eliminate the need for additional hospital visits for i.v. administration, which can be especially desirable in cases where access to transportation or patient mobility is limited. Additionally, factors such as the cost of i.v. iron compared to oral iron and the accessibility of medication may also influence an individual's choice. On the other hand, some people may prefer i.v. iron to reduce pill intake, to avoid certain side effects such as gastrointestinal

discomfort, or to experience a quicker improvement in their QoL through a more rapid increase in Hb levels.[169]

*Resource use and costs*

Oral iron is inexpensive and readily available in most parts of the world. Intravenous iron requires facilities and personnel to allow administration which may be more costly to both the person with anemia and CKD as well as the healthcare system.

*Considerations for implementation*

While oral iron is the more convenient option, adherence to oral iron may be lower. Several oral iron and i.v. formulations exist. Tables 4 and 5 outline the available and the recommended starting and maximum doses and specific regimens for oral and i.v. iron, respectively.

**Rationale**

When compared with oral iron therapy, i.v. iron provided a small additional increase in Hb of about 0.3–0.5 g/dl (30–50 g/l), and increased ferritin and TSAT. However, i.v. iron may cause serious hypersensitivity reactions, and although rare, these may be life-threatening, dependent on the compound. Oral iron, on the other hand, causes more gastrointestinal side effects, which may limit adherence, but severe events are very rare. Whether the small Hb benefit of i.v. iron is clinically meaningful, especially in those not yet treated with ESA, or justifies the tiny risk of serious adverse events is uncertain. Oral iron is inexpensive, readily available, does not require i.v. access, and does not require additional hospital visits. Overall, the Work Group felt the balance between benefits and harms and the influence of patient preference did not allow a systematic preference for one route over another.

**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%.**

There is little doubt that iron treatment results in higher Hb in people with CKD. However, it is unknown at what levels of iron tests this erythropoietic effect is optimized. The KDIGO 2012 guideline proposed an initiation threshold of ferritin ≤500 ng/ml (≤500 µg/l) and TSAT ≤30%, but did not clearly differentiate between the initiation threshold and the treatment target. Evidence is lacking to propose a treatment target. The Work Group has chosen to provide guidance on when to initiate iron (Recommendations 2.1 and 2.3) as well as when to withhold it (Practice Point 2.2).

The PIVOTAL Trial, discussed in depth elsewhere, found that cardiovascular outcomes were improved with a proactive iron treatment strategy to higher iron targets (treatment until serum ferritin ≥700 ng/ml [≥700 µg/l] or TSAT ≥40%).[104] These results do not necessarily

indicate that these higher iron test levels should be targeted in clinical treatment. An alternative interpretation of the study results was that this intensive iron strategy yielded improved cardiovascular outcomes, but specifically in comparison to a very conservative iron strategy that may have resulted in impaired health due to iron deficiency. PIVOTAL indicates that iron deficiency should be avoided, but PIVOTAL leaves open the possibility that intermediate iron targets could have been equally effective as the 700 ng/ml (700 µg/l) ferritin and 40% TSAT limits employed.[104] Although a recent meta-analysis did not identify safety concerns with higher dose i.v. iron,[170] it is uncertain whether giving iron when ferritin ≥700 ng/ml (≥700 µg/l) or TSAT ≥40% yields additional benefit or perhaps causes harm. The DRIVE studies found that in people with CKD G5HD, i.v. iron resulted in higher Hb concentrations and lower ESA usage even when the iron initiation threshold included serum ferritin concentrations >800 ng/ml (>800 µg/l).[88] However, whether this improved health outcomes or even provided incremental QoL benefits is unknown. Some retrospective observational data suggests that more intensive i.v. iron administration may be associated with increased risk of mortality and infections.[110] There is a theoretical concern that iron could be deposited in tissues or that non-transferrin-bound iron could have direct toxic effects, although this has not been well-studied in people with CKD. In light of the above, the Work Group felt it would be reasonable to withhold iron if ferritin ≥700 ng/ml (≥700 µg/l) or TSAT ≥40%.

**Practice Point 2.3: In people with CKD treated with oral iron, the choice between different formulations and dosing schedules is guided by cost, individual patient preference, tolerability, and efficacy.**

The various oral iron preparations have different bioavailability, dosing strategies, and gastrointestinal side effects (Table 3). If two or three times daily dosing causes gastrointestinal side effects, then reducing dosing to once daily may be reasonable. Although not well-studied in people with CKD, there is some evidence in other populations, such as those with gastrointestinal disease, that less frequent dosing is effective. Alternate-day oral supplementation with 60 mg iron resulted in 34% higher iron absorption than with consecutive-day supplementation.[171-173] Also, splitting a single oral dose of 120 mg iron into 2 daily doses of 60 mg iron does not improve iron absorption as shown in 2 open-label RCTs.[172]

Some newer oral iron preparations may have improved efficacy and/or tolerability, but head-to-head RCT data is minimal. Ferric citrate is an oral iron repletion agent approved to treat iron deficiency anemia in people with CKD not receiving dialysis. It has a favorable safety and efficacy profile and may spare i.v. iron and ESA use, and possibly delay the transition to dialysis. Ferric citrate also improves iron parameters and reduces ESA and i.v. iron exposure in people with CKD G5HD;[174] however, its role as an iron-repletion agent in this population remains to be clarified. Ferric maltol demonstrated improvements in Hb versus placebo with a favorable tolerability profile in a phase 3 trial in people with CKD not receiving dialysis.[174] Sucrosomial

iron, which has been evaluated in iron deficiency anemia associated with CKD and several other clinical settings, demonstrated improved tolerability over i.v. iron.[174]

**Practice Point 2.4: In people with CKD treated with intravenous iron, the choice between different formulations is guided by cost, individual preference, and recommended dosing schedules.**

Different formulations of i.v. iron differ in the maximum dose which can be administered at a single sitting and the rate of infusion (Table 4).[175] Some i.v. iron preparations, including ferric carboxymaltose, saccharated iron oxide, and iron polymaltose, increase intact fibroblast growth factor 23 (FGF23) through mechanisms that appear to be related to the carbohydrate shell. As a consequence of their effect on FGF23, these i.v. iron preparations are associated with hypophosphatemia, which should be monitored, particularly in KTR, people with earlier stage CKD, and people receiving repeated dosing.[176] There are no head-to-head RCTs comparing the effect of different i.v. iron compounds on critical outcomes (Table 12) in people with CKD.

Ferric pyrophosphate citrate is a water-soluble iron salt administered intravenously or via dialysate. In contrast to other i.v. iron preparations that are taken up by reticuloendothelial macrophages to liberalize iron, ferric pyrophosphate citrate delivers iron directly to circulating transferrin. Phase 2 and 3 RCTs have demonstrated that ferric pyrophosphate citrate maintains Hb levels without an excessive increase in iron stores, together with decreasing ESA and i.v. iron needs. However, no studies have directly compared efficacy or safety of dialysate iron with other i.v. iron formulations or oral iron, and its long-term safety has not been established.[177]. Additionally, ferric pyrophosphate citrate is not available in most countries.

**Practice Point 2.5: 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 and every month for those with CKD G5HD.**

No clinical trials specifically determine the optimal frequency for testing iron status during iron treatment. Consequently, in line with previous guidelines, the Work Group agrees that it is reasonable to test iron status at least every three months for people with CKD not receiving HD, and every month for those with CKD G5HD.

Falling ferritin and/or TSAT levels are likely to reflect ongoing blood loss and can be used as an indication for additional iron supplementation. In people on oral iron, iron status testing can also be used to assess adherence with iron treatment. Conversely, increasing ferritin and/or TSAT levels may indicate that iron treatment is excessive and can be stopped or reduced.

**Practice Point 2.6: In people with CKD treated with iron, certain circumstances may warrant more frequent iron testing as shown in Table 5.**

**Table 5 | Circumstances warranting more frequent iron testing**

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

ESA, erythropoietin-stimulating agents, HIF-PHI, hypoxia-inducible factor-prolyl hydroxylase inhibitors; TSAT, transferrin saturation

Certain situations may warrant more frequent testing than what is proposed in Practice Point 2.4. Initiating or increasing the ESA dose may rapidly deplete iron stores as RBC production increases. Development of iron deficiency or onset of ESA hyporesponsiveness may be averted if Hb, ferritin, and TSAT are tested more often, and treatment is adjusted accordingly. In addition, there is the potential for spuriously elevated values if iron status is checked soon after administration of i.v. iron administration or packed red blood cells.

Accidental blood loss, as can occur through needle dislodgements or gastrointestinal bleeding, may lead to significant loss of iron. It may be reasonable to retest the iron status immediately and a week after any such event.

The iron status can change substantially during hospitalization due to increased phlebotomy for blood testing and other sources of blood loss. It may be reasonable for iron tests to be performed more frequently after most hospitalizations, especially when it is known that blood loss may have occurred.

As opposed to clinical circumstances where iron stores may be depleted, more frequent testing may also be needed if there is a major rise in iron status test results or if they are well above targets. More frequent testing may be considered until normalization occurs.

**Practice Point 2.7: Switch from oral to intravenous iron if there is an insufficient effect of an optimal oral regimen after 1 to 3 months.**

Oral iron is typically prescribed to provide approximately 200 mg of elemental iron daily, with most studies showing its effect on Hb concentration within 1 to 3 months. However, the desired effect may not be achieved for several reasons, justifying a switch in administration route. In people with CKD, gastrointestinal absorption of oral iron can be impaired by factors such as inflammation, reduced gastric acid production, or interactions with other medications. Intravenous iron bypasses the gastrointestinal tract, ensuring better and more consistent iron delivery to the body. Additionally, oral iron may cause gastrointestinal side effects like

constipation, nausea, and abdominal discomfort, leading to poor adherence, while i.v. iron avoids these issues and improves patient compliance.

**Practice Point 2.8: In people with CKD treated with iron, consider temporarily suspending iron therapy during systemic infection.**

Iron is essential for the growth and proliferation of most pathogens including many bacteria, viruses, fungi, parasites, and helminths. Iron also exerts subtle effects on immune function and host responses towards microbes.[178] There is theoretical and experimental evidence to suggest that iron administration may worsen an existing infection, but clinical evidence is lacking. Briefly suspending iron therapy until the infection is cleared is unlikely to significantly affect the progress of iron replenishment or the correction of anemia. Therefore, i.v. iron is usually not administered when people have an active systemic infection such as pneumonia or a catheter related blood stream infection. Clinical judgment is necessary with milder infections to balance the risks of continued use of i.v. iron as opposed to delaying further iron administration until infection resolves.

**Practice Point 2.9: In people with CKD treated with intravenous iron, considerations pertaining to hypersensitivity reactions to intravenous iron include the following:**

- **Intravenous iron should only be administered if there is capability to manage acute hypersensitivity and hypotensive reactions,**
- **Intravenous doses of iron should not exceed the maximum dose/administration for the compound (Table 4),**
- **Pretreatment with corticosteroids or antihistamines is not routinely necessary (type 1 histamine [H1]-channel blockers), and**
- **Test doses of intravenous iron are not usually required, because lack of response does not predict the risk of hypersensitivity.**

Intravenous iron is rarely associated with acute hypersensitivity, hypotensive, and even anaphylactoid-type reactions. People may present with a variety of symptoms ranging from flushing, itching, shortness of breath, and hypotension. In older studies, such reactions were found to occur in 0.6%–0.7% of treated people. The frequency of reactions is probably significantly lower with newer iron preparations. Although these reactions are uncommon, we believe that whenever i.v. iron is administered, suitable preparations should be in place for emergency treatment.

Some formulations of i.v. iron can be administered at doses of 750–1000 mg (or higher) at a time. In contrast, doses of i.v. iron sucrose should not exceed 200 mg per administration and iron gluconate should not exceed 125 mg because of the risk for the release of labile iron and associated hypotension at higher doses.[179]

There is no physiological basis to advise that people should be observed for 30 minutes after an infusion of iron is completed, since i.v. iron delivery should not be associated with a severe delayed reaction. There is no evidence that pretreatment with corticosteroids or antihistamines (H1-channel blockers) reduces the risk of severe reactions to i.v. iron. Paradoxically, i.v. antihistamines may be associated with unwanted side effects, particularly drowsiness or flushing upon rapid infusion. Hence, pretreatment with corticosteroids or antihistamines is not advised in people identified as being at potential risk of a hypersensitivity reaction. Desensitization protocols to limit hypersensitivity reactions are not established and, therefore, not advised either. In the past, test doses were commonly given prior to i.v. iron. This practice has greatly fallen out of favor, and we agree that test doses are not clinically useful.[180]

**Practice Point 2.10: The suggested management of reactions to intravenous iron is presented in Figure 7.**

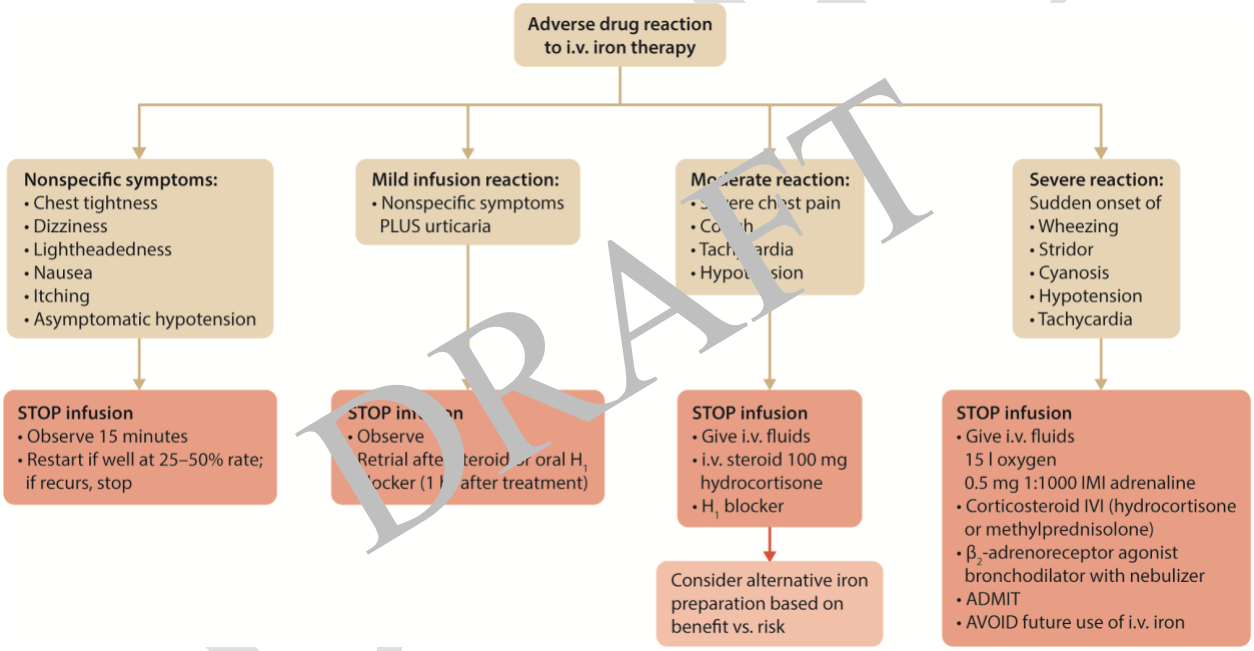


**Figure 7 | Suggested management of reactions to intravenous (i.v.) iron.** H1, type 1 histamine

Optimal clinical treatment of severe anaphylaxis includes adrenaline as an essential anti-anaphylactic drug given by intramuscular injection of 0.5 mg in 1:1000 solution. This should be repeated after 5–10 minutes if needed. Additional supportive oxygen should be given at a high rate (>15 l/min) by face mask. Volume loading should be given using one liter of crystalloid solution in addition to an antihistamine (H1-channel blocker) and corticosteroids to prevent a protracted or biphasic course of anaphylaxis. For nonspecific reactions (e.g., hot flushes), stopping the infusion for at least 15 minutes and monitoring the response (i.e., pulse, blood pressure, respiratory rate, and oxygen saturation) may be sufficient. If the patient improves, then

the iron infusion can be resumed at 25%–50% of the initial infusion rate with monitoring. For mild reactions, if treatment is restarted, i.v. H1-channel blockers and corticosteroids should be considered and monitoring after therapy should be continued for one hour. If the infusion is discontinued and the reaction subsides, then rechallenge with the same or a different iron preparation may be undertaken in an environment where monitoring is available. A much lower dose of the iron preparation or slower infusion rate should be considered to gain reassurance that this reaction is likely to be dose-related and possibly due to labile iron release.[180]

**Practice Point 2.11: 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.**

If profound iron deficiency (e.g., ferritin <30 µg/l and TSAT<20%) is present even in the absence of anemia, treatment with oral or i.v. iron could be considered in shared-decision-making, especially in symptomatic people with advanced CKD (CKD G4–G5).

The rationale is that iron fulfills many more functions besides being the fuel for erythropoiesis, including deoxyribonucleic acid (DNA) synthesis, electron transport, and cellular proliferation and differentiation.[181] Iron deficiency impairs myoblast proliferation[182] and impairs cardiomyocyte function. [183] Anemia is the end-phase of depleted iron stores and hence, correcting iron deficiency prior to the occurrence of anemia would make sense. Observational data in people with CKD and KTRs underscores this, as iron deficiency, independent of anemia, is associated with higher risk of all-cause mortality, MACE, and worse patient-reported outcomes.[43,59,32,77] In addition, ample evidence from the field of chronic heart failure, including the subset of people with CKD, suggest benefit of iron therapy independent of anemia to improve functional status and hospitalizations.[127, 184-186] Nevertheless, prospective randomized controlled trial (RCT) data are lacking in people with CKD, and the only small RCT involving 75 people with CKD not receiving dialysis found no benefit of i.v. iron therapy capacity at 4 weeks,[133] making this an important research recommendation.

**Research recommendations**

- Adequately powered pragmatic RCTs are needed to assess the benefits, harms and costs of:
  - a proactive high dose i.v. iron regimen - such as used in the PIVOTAL trial – in people with CKD not receiving dialysis.
  - different protocolized iron dosing regimens with a higher iron dose comparator than the reactive arm used in the PIVOTAL trial in people with CKD G5D. For example, randomization of participants to withholding iron if ferritin ≥700 ng/ml (≥700 µg/l) or TSAT ≥40% versus withholding iron if ferritin ≥500 ng/ml (≥500 µg/l) or TSAT ≥30%.

  - even higher ferritin and TSAT concentrations targets in both CKD not receiving dialysis and CKD G5D.
  - iron treatment in people with CKD with iron deficiency in the absence of anemia.
  - newly available oral iron compounds compared to traditional oral and i.v. iron compounds in people with CKD not receiving dialysis.
  - alternate day versus once-daily oral iron administration in people with CKD not receiving dialysis.
- Trials should assess at least a core outcome set considered critical for decision-making such as mortality, MACE, vascular access outcome, patient-reported outcomes, and exercise capacity).[187] Additional outcomes of interest include cardiac function, skeletal muscle function, gut microbiome, and the immune system.
- Future studies should also prioritize patient-focused therapy to better tailor treatment decisions based on individual patient characteristics (e.g., phenotype and genotype) rather than population Hb and TSAT values only.[188]
- Studies are needed to evaluate the prevalence of iron overload in people with CKD on iron therapy, how it should be detected, and what thresholds are associated with toxicity. They should consider novel biomarkers or imaging techniques.
- In pregnant women with anemia and CKD, future studies should investigate the effectiveness of different dosing schedules of oral and i.v. iron formulations.

# CHAPTER 3. USE OF ESAs, HIF-PHIs, AND OTHER AGENTS 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).**

Treatment of anemia with ESAs or HIF-PHIs improves symptoms and reduces RBC transfusions as compared to no treatment. However, there is no evidence that such treatment improves mortality or cardiovascular outcomes in people with CKD with or without receiving dialysis. Moreover, the use of ESAs to target higher Hb levels has been associated with harm, and HIF-PHIs have not been shown to be safer than ESA. Therefore, patients should be informed about the risks and benefits of such treatment, aiming to facilitate a decision that is consistent with their values and preferences. This shared decision-making should occur at the time of treatment initiation and periodically thereafter (e.g., after major health-related events such as hospitalization, vascular access thrombosis, cardiovascular or thromboembolic event, or new malignancy).

**Practice Point 3.1.2.: In people with anemia and CKD, address all correctable causes of anemia prior to initiation of treatment with an ESA or a HIF-PHI (Figure 8).**

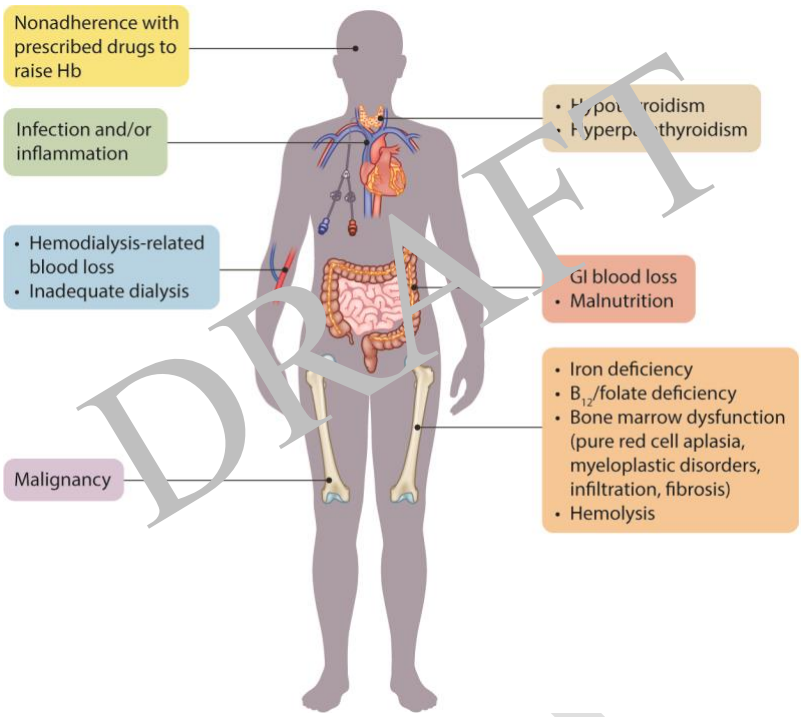


**Figure 8 | Potentially reversible causes of anemia in chronic kidney disease (CKD) in addition to decreased erythropoietin production.** ACEi, angiotensin-converting enzyme inhibitor(s); ARB, angiotensin II receptor blocker; GI, gastrointestinal

**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*).**

*This recommendation places a higher value on the well-documented benefits and risks of ESA treatment and a lower value on the putative advantages of HIF-PHIs, such as oral route of administration. Although head-to-head RCTs revealed noninferiority of HIF-PHIs versus ESAs for efficacy as treatment for anemia, some studies suggested a higher risk of MACE and vascular access thrombosis with HIF-PHIs compared to ESAs, at least in some CKD populations and for some HIF-PHI agents. Also, the long-term risks and benefits of HIF-PHIs in the broader population of patients treated outside of clinical trials are unknown.*

**Key information**

*Balance of benefits and harms*

ESA increases Hb compared to placebo in people with anemia and CKD regardless of dialysis status. HIF-PHIs increase Hb compared to placebo in people with anemia and CKD G5D[189-193] and CKD not receiving dialysis.[194-203] Head-to-head studies of HIF-PHIs compared to ESAs show generally similar efficacy in people with CKD G5HD[204-211] and CKD not receiving dialysis.[210, 212-216] 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, but there

remains a high degree of uncertainty about the comparative side effect profiles (Supplementary Tables S18–S28). 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.[210, 215, 217] Individual studies and meta-analyses have not detected superiority of HIF-PHIs as compared with ESAs for any clinically important outcome, and the long-term risks and benefits of HIF-PHIs are uncertain in the broader population of people treated outside of clinical trials.[218-222] On balance, these studies do not demonstrate that HIF-PHIs are safer than ESAs, and some HIF-PHIs may be associated with more MACE and other adverse events as compared to ESAs, particularly in people with CKD not receiving dialysis. Furthermore, the long-term risks and benefits of HIF-PHIs in any CKD population are not yet known. Daprodustat and vadadustat were rejected by the U.S. Food and Drug Administration (FDA) for use in CKD not receiving dialysis, with approval granted for CKD-G5D after 3 or 4 months on dialysis with a boxed warning regarding the increased risk of thrombotic and other cardiovascular events. Roxadustat was approved by the European Union (EU) European Medicines Agency (EMA) for both CKD not receiving dialysis and CKD G5D but was rejected due to safety concerns by the U.S. FDA. These and other HIF-PHIs have been approved by other regulatory agencies for use in both populations.

*Certainty of evidence*

The overall certainty of evidence comparing ESAs with HIF-PHIs in people with anemia and CKD not receiving dialysis is very low (Supplementary Tables S29–S37) for all of the critical outcomes reported. Evidence for all outcomes had very serious concerns about risk of bias, serious or very serious concerns about imprecision, and a strong suspicion with regard to publication bias for many outcomes.

The overall certainty of evidence comparing ESAs with HIF-PHIs in people with anemia and CKD G5D is very low (Supplementary Tables S18–S28). The certainty of evidence is very low for all of the critical outcomes and low for QoL. Risk of bias was rated as serious to very serious across all reported outcomes, serious inconsistency or very serious inconsistency was noted, and there were very serious concerns about precision for many outcomes. Publication bias was also strongly suspected for many outcomes.

*Values and preferences*

In the opinion of the Work Group, most well-informed people with anemia and CKD would choose to receive ESAs as first-line treatment for anemia, based on the long clinical experience with these agents, their efficacy for increasing Hb concentration, and the extensive data demonstrating the balance of risks and benefits associated with their use. People with ESA hyporesponsiveness and those in whom an oral treatment is preferred to i.v. or subcutaneous administration of ESA may consider a trial of HIF-PHI treatment.

*Resource use and costs*

Direct costs of HIF-PHIs are evolving as these agents enter global markets, and the Work Group did not consider their costs or the relative costs of ESAs compared to HIF-PHIs or their administration when formulating this recommendation. In the U.S. and perhaps other countries, the costs of HIF-PHIs will be borne by dialysis facilities, so relative costs of these classes of agent may influence practices at each facility.

*Considerations for implementation*

This recommendation applies to adults of both sexes and all ethnicities with CKD G5D or CKD not receiving dialysis. There are insufficient data for efficacy and safety regarding the use of HIF-PHIs for the treatment of children with anemia and CKD G5D or CKD not receiving dialysis. Weight-based dosing is appropriate in people treated with ESAs. Suggestions for ESA administration, dosing, and monitoring are discussed in the practice points below.

**Rationale**

ESAs and HIF-PHIs are both effective for treatment of anemia in adults with CKD G5D or CKD not receiving dialysis. ESAs are effective in children while HIF-PHIs have not been studied in children. Although the overall analyses suggest noninferiority of HIF-PHIs to ESAs for MACE and other critical outcomes, some studies suggest that at least some HIF-PHIs may have more MACE and other vascular events than ESAs, particularly in CKD not receiving dialysis. Additionally, there are limited long-term head-to-head studies demonstrating the risks and benefits of HIF-PHIs as compared with ESAs, whereas ESAs have been used for decades and their risks and benefits are well understood. Whether HIF-PHIs may have increased efficacy over ESAs in some clinical contexts (e.g., ESA hyporesponsiveness) or may reduce iron requirements compared with ESAs has not been demonstrated in RCTs. If HIF-PHIs are shown to have comparable long-term safety to ESA, direct medication costs and patient preferences may become key determinants as to which class of drug is used for anemia management in people with CKD. In the absence of such long-term safety data, ESAs are preferred to HIF-PHI for most patients with CKD (with or without KRT).

**Practice Point 3.1.3: In people with anemia and CKD, HIF-PHIs should be avoided in those at increased risk of adverse events (Table 6).**

This practice point is based on theoretical concerns based on mechanism of action, preclinical experimental data, adverse event profiles from clinical trials with HIF-PHIs, and data from people with genetic mutations in the HIF oxygen-sensing pathway.

**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]<br>• Polycystic kidney disease[224]<br>• Proliferative retinal disease[225, 226]<br>• Pulmonary arterial hypertension[227-229]<br>• Pregnancy[*] | • Prior cardiovascular events (i.e., stroke, myocardial infarction)[223]<br>• Prior thromboembolic events (i.e., deep venous thrombosis, pulmonary embolism)[223]<br>• Prior vascular access thrombosis[223]<br>• Hepatic impairment[†]<br>• Seizures, exfoliative dermatitis, hypothyroidism, bacterial infections/sepsis (roxadustat)[230] | • Post-kidney transplant anemia[223]<br>• Children[231] |

[*]HIF-PHIs are contraindicated in pregnancy, please refer to package inserts for individual compounds.
[†]Caution is advised in patients with hepatic impairment. HIF-PHIs are not recommended for patients with significant hepatic impairment. Please refer to package inserts of individual compounds for specific guidance.

## 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).**

*This recommendation places a relatively high value on the risk of RBC transfusions and poor functional status associated with Hb concentrations <9.0 g/dl (90 g/l) in people with CKD G5D. 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 (90 g/l), 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 (e.g., those being considered for*

*kidney transplantation) may be more likely to prefer ESA initiation when Hb is closer to 10.0 g/dl (100 g/l).*

**Key information**

*Balance of benefits and harms*

As compared to placebo or standard of care, ESA therapy may reduce the risk of requiring RBC transfusions and increase QoL, especially when the pre-treatment Hb concentration is <9.0 g/dl (90 g/l).[232-235] In the judgement of the Work Group, both outcomes are important to people with anemia and CKD G5D. When comparing the same ESA administered to reach a specific Hb target, pooled analysis revealed that a higher Hb target as compared with a lower Hb target may reduce RBC transfusion (Supplementary Tables S38–S41). In a double-blind RCT, 118 people with CKD G5HD and Hb levels of <9.0 g/dl (<90 g/l) were randomly assigned to receive placebo, ESA for a Hb target of 9.5–11.0 g/dl [95–110 g/l], or ESA for a higher Hb target of >11.0 g/dl (>110 g/l]. After 8 weeks, a higher proportion of participants was transfused in the placebo group versus the group with the Hb target of 9.5–11.0 g/dl (95–110 g/l) and a target Hb >11.0 g/dl (>110 g/l) (Supplementary Tables S38–S41).[232, 236] In addition, improvements in fatigue, physical function, and 6-minute walk tests were observed for the group with the Hb target of 9.5–11.0 g/dl (95–110 g/l) as compared with placebo. However, there were no improvements for the group with a target Hb >11.0 g/dl (>110 g/l) versus 9.5–11.0 g/dl (95–110 g/l). In addition, the risks of increased blood pressure or vascular access loss were higher in the groups treated with ESA with higher Hb target (Supplementary Tables S38–S41). There were no data available with regard to malignancy.

People with cardiovascular disease or congestive heart failure may be at the lower end of the Hb range and treatment initiation if ESA therapy may be contemplated. In a study of 1233 people with CKD G5HD and congestive heart failure or ischemic heart disease where people were randomly assigned to receive epoetin alfa to maintain a Hb of 14.0 g/dl [140 g/l] versus 10.0 g/dl [100 g/l], people in the high Hb arm had a lower risk of RBC transfusions and higher physical functioning as compared with the low Hb arm (Supplementary Table S42).[237] However, the number of deaths, nonfatal myocardial infarctions, and vascular access thromboses were higher in the high Hb arm as compared to the low Hb arm. Although the difference in event-free survival did not reach the prespecified statistical stopping threshold, the trial was stopped.

Data on the risks and benefits of ESA therapy among people treated with maintenance PD are scarce. However, in the judgment of the Work Group and in the absence of evidence to the contrary, it is reasonable to extrapolate findings from studies of people treated with HD to those treated with PD. Therefore, this recommendation applies to people treated with either HD or PD.

*Certainty of evidence*

The overall certainty of evidence comparing the use of ESAs to reach a higher Hb target versus a lower Hb target in a CKD G5D population is very low (Supplementary Tables S40 and S41). The certainty of evidence is very low for critical outcomes due to serious concerns about inconsistency and extremely serious concerns about precision. The certainty of evidence is low for the following outcomes: mortality, heart failure, and vascular access thrombosis; moderate for QoL; and high for functional status. No studies reported on total serious adverse events.

The overall certainty of the evidence comparing ESAs to placebo is very low in adults with CKD G5D (Supplementary Tables S38 and S39). The certainty of evidence is very low for the critical outcomes due to serious concerns about risk of bias and extremely serious concerns about precision. The certainty of evidence is moderate for both QoL and functional status. No studies reported on total cardiovascular events, thrombosis, and all-cause hospitalization.

*Values and preferences*

The decision to initiate ESA therapy should balance the potential benefits of reducing anemia-related symptoms and RBC transfusions against the potential risks of harm. The increased risks of mortality, cardiovascular events, and vascular access thrombosis associated with ESA therapy to target higher Hb levels were judged to be critically important, particularly in people with congestive heart failure or ischemic heart disease. The increased risk of hypertension was judged to be important to people with anemia and CKD. The potential risks associated with ESA therapy in people with active malignancy, especially when cure is the anticipated outcome, should also be considered and discussed. Therefore, people at higher risk for adverse events from ESA may choose to initiate ESA at the lower end of the Hb range. However, people with lower cardiovascular risk who are being considered for kidney transplantation listing may choose to initiate ESA at the higher end of the range of Hb to avoid the risk of allosensitization associated with RBC transfusions. Although QoL is important to patients, the Work Group judged that most, if not all well-informed people with CKD would prefer to avoid the risk of serious adverse outcomes associated with higher Hb targets as compared with an uncertain and clinically modest potential improvement in QoL.

*Resource use and costs*

Initiating treatment with ESA at the higher end of the range of Hb levels may lead to greater treatment-related costs and resource utilization, including costs for managing adverse events (e.g., vascular access thrombosis or acute coronary syndrome). Initiating ESA at the lower end of the Hb range may lead to more RBC transfusions and their associated costs, including the emergency department visits and/or hospital admissions, as well as complications such as alloimmunization.

*Considerations for implementation*

Hb and blood pressure levels should be monitored in people who are treated with ESA or whenever there is a change in the dose of ESAs. The increase in Hb and blood pressure are generally reversible if ESA is stopped or doses are reduced. In people who are at a risk for rapid drop in Hb when ESA therapy is delayed until the Hb level reaches the threshold for ESA initiation, more frequent Hb monitoring may be required. People with anemia and CKD should be informed about risks and benefits associated with ESA prior to initiation of therapy.

**Rationale**

ESAs effectively raise Hb, which reduces the risk of RBC transfusions and increases QoL for people with CKD G5D and CKD not receiving dialysis and Hb concentrations <9.0 g/dl (<90 g/l). However, the risk of harms such as cardiovascular events and vascular access thrombosis may be increased with ESA therapy to target higher Hb concentrations >10–11 g/d1 (100–110 g/l) and, thus, may outweigh the potential benefits. This recommendation attempts to balance the benefits of ESA treatment against its harms.

**Recommendation 3.2.2: 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 (*2D*).**

*This recommendation places a high value on balancing the increased risks of stroke, other MACE outcomes, and high blood pressure against the potential benefit of a modest improvement in QoL and reduced need for RBC transfusions when a higher versus lower Hb threshold and target are used for ESA therapy. The Hb concentration for ESA initiation should be individualized and for most people should be 8.5–10.0 g/dl (85–100 g/l). For people with cardiovascular disease, thromboembolic disease, and 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.*

**Key information**

*Balance of benefits and harms*

RCTs of ESA treatment among in people with CKD not receiving dialysis did not reveal a survival benefit or improvement in cardiovascular outcomes for higher versus lower Hb targets (Supplementary Tables S43–S45).[41, 238, 239] People with anemia and CKD not receiving dialysis experienced a greater risk of a composite of death or serious cardiovascular events when administered ESAs to target higher versus lower Hb levels (13.5 g/dl vs. 11.3 g/d [135 g/l vs.

113 g/l]), without an incremental improvement in the QoL.[239] The risk of stroke, prespecified as a secondary outcome, was significantly higher in people with diabetes and CKD not receiving dialysis treated with ESA to target a Hb level of 13.0 g/dl [130 g/l] versus treatment with placebo and rescue ESA administered when the Hb level was <9.0 g/dl [90 g/l].[41] Cancer-related events were reported in one study where the risk ratio was 1.08 (95% CI, 0.85 to 1.36) when comparing a higher hemoglobin target to a lower target, and one study reporting on malignant neoplasms where the risk ratio was 1.00 (95% CI 0.25 to 3.97) when comparing a higher hemoglobin target to a lower target.[41, 240-243] The systemic review from the ERT also concluded that there was evidence from clinical trials with ESAs to indicate that higher Hb targets increased functional status but made little or no difference in QoL and were associated with an increased risk of hypertension (Supplementary Tables S43–S45).[41, 238, 241-247] Finally, in clinical trials comparing specific Hb targets, ESA regimens used to target higher Hb were associated with a lower risk of RBC transfusions.[41, 238, 241-243]

In the judgment of the Work Group, it is reasonable to extrapolate findings from studies of people with CKD not receiving dialysis to kidney transplant recipients, given the paucity of trials done in kidney transplant recipients specifically.

No RCTs have investigated the effects of ESA treatment on mortality or MACE in children with CKD not receiving dialysis. Observational data suggest that children with a Hb <10.0 g/dl (100 g/l) when starting dialysis have higher cardiovascular and all-cause hospitalizations compared to those with Hb between 10.0–12.0 g/dl (100–120 g/l). We advise considering this data as well as patient symptoms, QoL, growth and development, and the need to limit allosensitization from RBC transfusion when deciding when to initiate ESA therapy in children.[248]

*Certainty of evidence*

The overall certainty of evidence comparing the use of ESAs to reach a higher Hb target versus a lower Hb target in adults with CKD not receiving dialysis is very low (Supplementary Tables S43–S45). There are serious concerns about risk of bias, serious concerns about inconsistency, and serious to very serious concerns about imprecision. The certainty of evidence is low for mortality, and acute coronary syndrome; and moderate for QoL and functional status. No studies reported on thromboembolism or all-cause hospitalization.

The overall certainty of the evidence comparing ESAs to placebo is very low in adults with not receiving dialysis (Supplementary Tables S46 and S47). There were serious concerns about risk of bias for thromboembolism and very serious for mortality and serious adverse events, and very serious concerns about precision. No studies reported on total cardiovascular events, vascular access thrombosis, and all-cause hospitalization.

*Values and preferences*

Choosing the Hb at which ESA should be initiated in this population must balance the critically important potential risks of stroke, other MACE outcomes , and worsening hypertension against the potential benefits of fewer RBC transfusions and perhaps a clinically modest improvement in QoL. In younger people, those with lower cardiovascular risk, and those who are being considered for kidney transplant listing, a higher Hb threshold may be considered for initiation of ESA therapy given the risk of allosensitization with RBC transfusions. People with a higher burden of anemia-related symptoms may be more inclined to initiate ESA at a relatively higher Hb concentration. In contrast, ESA may be initiated at a lower Hb (or avoided altogether) in those with a history of or major risk for cardiovascular events or thromboembolism, and in those with active malignancy (especially when the treatment expectation is to cure).

*Resource use and costs*

ESA treatment-related costs and resource utilization, including costs for managing adverse cardiovascular events (e.g., stroke) may be higher with initiating ESA at higher Hb levels. However, the cost of RBC transfusions and associated healthcare resource utilization costs may be also higher if initiating ESA at lower Hb concentrations for some people.

*Considerations for implementation*

People with anemia and CKD should be informed about risks and benefits associated with ESA prior to initiation of therapy. If a lower Hb threshold is chosen for ESA initiation, Hb may need to be monitored more frequently. Hb levels and blood pressure should be monitored regularly in people who are treated with ESA or whenever there is a change in the dose of ESAs.

**Rationale**

The Hb concentration at which ESA therapy is initiated in people with CKD not receiving dialysis should be individualized to balance the potential QoL benefits of ESA treatment among people with anemia-related symptoms against potential harms of stroke and other MACE in high-risk groups. The increased risk of RBC transfusions associated with initiating ESA at lower Hb concentrations should be considered in younger people and those being considered for kidney transplantation.

## 3.3. ESA maintenance therapy

**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*).**

*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.*

**Key information**

*Balance of benefits and harms*

Although the systematic review from the ERT did not find a difference in mortality in people with CKD not receiving dialysis treated with ESA to target a high versus a low Hb, several adverse events and/or adverse composite outcomes were reported in individual trials (Supplementary Tables S43–S47). The risk of a primary composite endpoint of death, nonfatal myocardial infarction, or hospitalization for congestive heart failure was higher in a study of 1432 people with anemia and CKD not receiving dialysis randomized to receive epoetin alfa dosed to target a Hb level of 13.5 g/dl (135 g/l) versus those receiving epoetin alfa to target a Hb level of 11.3 g/dl (113 g/l), with no incremental improvement in the QoL.[239] Importantly, although a Hb target of 13.5 g/dl (135 g/l) was used for the high Hb group, only a mean Hb level of 12.6 g/dl (126 g/l) was achieved in the trial.[41, 239]

In another RCT of 603 participants with CKD not receiving dialysis randomized to a Hb target of 13.0–15.0 g/dl (130–150 g/l) as compared with a target of 10.5–11.5 g/dl (105–115 g/l), there was no difference in the primary composite cardiovascular endpoint (Supplementary Tables S43–S45).[238] Although general health and physical function improved in people randomized to the higher Hb target, hypertensive episodes were more prevalent in the higher Hb target group.[238]

Finally, in a study of 4038 people with anemia, CKD not receiving dialysis,, and diabetes, participants were randomized to ESA to achieve a Hb level of 13.0 g/dl (130 g/l) or to placebo, with rescue ESA when the Hb level was <9.0 g/dl (90 g/l) (Supplementary Tables S46 and S47). Although a difference was not observed for the primary composite outcome of death or a cardiovascular event, the risk of fatal or nonfatal stroke was higher in people randomized to ESA versus placebo.[41] People in the ESA arm did have fewer RBC transfusions and a modest improvement in patient-reported fatigue compared with those in the placebo arm, but this QoL improvement was not considered clinically meaningful (<5 point increase in the QoL score).[41]

Fewer data describe the benefits and risks of ESA used to achieve different Hb targets in people with CKD G5D. The systemic review from the ERT concluded that when comparing the same ESA to reach a specific Hb target in people with CKD G5D, higher Hb targets have a similar effect on mortality as compared to lower Hb targets, and also have similar effects on QoL, functional status, and RBC transfusion rates (Supplementary Tables S40–S42). However, the largest RCT of 1233 participants with CKD G5HD and congestive heart failure or ischemic heart disease did reveal that the incidence of deaths, non-fatal myocardial infarctions, and vascular access thromboses were higher in people in the high Hb arm (14.0 g/dl [140 g/l]) versus the low Hb arm (10.0 g/dl [100 g/l]), although there were a lower number of RBC transfusions and higher reports of physical functioning in the high Hb arm.[237]

In people with CKD G5D receiving maintenance PD, there are no RCTs comparing ESA to reach a specific Hb target or comparing ESA with placebo or usual care for critical or important outcomes. In the opinion of the Work Group, it is reasonable to extrapolate findings from studies in people with CKD G5HD and CKD not receiving dialysis to people with CKD G5PD.

The evidence for Hb target and risks and benefits of ESA therapy are scarce in kidney transplant recipients. Therefore, in the judgment of the Work Group, it is reasonable to extrapolate findings from studies of people with anemia and CKD not receiving dialysis without a kidney transplant to kidney transplant recipients with anemia.

*Certainty of evidence*

The overall certainty of evidence comparing the use of ESAs to maintain a higher Hb target versus a lower Hb target in adults with CKD not receiving dialysis is very low (Supplementary Tables S43–S47). The certainty of evidence is very low for total cardiovascular events, stroke, heart failure, MACE, vascular access thrombosis, and serious adverse events. There are serious concerns about risk of bias, serious concerns about inconsistencies, and serious to very serious concerns about imprecision. The certainty of evidence is low for the following outcomes: mortality and acute coronary syndrome; and moderate for QoL and functional status. No studies reported on thromboembolism or all-cause hospitalization.

The overall certainty of evidence comparing the use of ESAs to maintain a higher Hb target versus a lower Hb target in a CKD G5D population is very low (Supplementary Tables S38–S42). There are serious concerns about inconsistency and extremely serious concerns about precision. No studies reported on total serious adverse events.

*Values and preferences*

In the opinion of the Work Group, most well-informed people with anemia and CKD not receiving dialysis or CKD G5D would choose not to receive ESA to maintain a Hb level of 11.5 g/dl [115 g/dl] or higher, given the data regarding the risks, such as the increased risk of stroke and other cardiovascular events, which the Work Group judged to be critically important to people with anemia and CKD. Although QoL was judged to also be important to people with anemia and CKD not receiving dialysis or CKD G5D, the Work Group decided that most, if not all, people would value avoiding the potential critical risks associated with higher Hb levels relative to a potential modest improvement in QoL.

*Resource use and costs*

Maintaining a higher Hb would result in higher healthcare costs related to the cost of ESA drug, drug administration, and hospitalization for stroke and other adverse cardiovascular events without potential cost-savings realized by avoiding hard clinical outcomes.

*Considerations for implementation*

This recommendation applies to adults of both sexes and all ethnicities with CKD G5D or CKD not receiving dialysis with or without a kidney transplant.

**Rationale**

Maintaining a Hb higher than 11.5 g/dl (115 g/l) with ESA therapy does not improve survival in people with anemia and CKD G5D or CKD not receiving dialysis and may result in adverse cardiovascular outcomes such as stroke. The potential for further improvement in QoL when Hb levels are maintained above 11.5 g/dl (115 g/l) is uncertain and, in some trials, was not considered clinically significant. This recommendation attempts to balance the benefits of ESA treatment to maintain a higher Hb target against its harms**.**

**Practice Point 3.3.1: For children with anemia and CKD, the selection of Hb target for ESA maintenance therapy should be individualized, considering potential benefits (e.g., improvement in QoL, school attendance/performance, and avoidance of RBC transfusion) and potential harms.**

In children with anemia and CKD, there are no RCTs examining the effects of ESA administration on mortality or cardiovascular events. Therefore, any suggestion for Hb targets in this subgroup must rely on results obtained in adults with CKD and on clinical experience in the pediatric setting. Observational data suggests that Hb concentrations >12.0 g/dl [120 g/l] are not associated with increased all-cause mortality or cardiovascular-related hospitalization in children on HD.[248] Other cohort studies involving children treated with PD have found positive correlation between Hb concentration and patient survival, but lower survival with increasing ESA dose.[249] However, caution is advised given the discrepancy between the data from observational studies and RCTs seen in adults. Factors unique to children, which mean that data from adults may not apply, include developmental and psychological factors, lower risk of cardiovascular events, and potentially greater importance of avoiding allosensitization to facilitate kidney transplantation. For these reasons, the Work Group cannot provide certainty about the optimal maintenance Hb target in children and suggests that clinicians consider both the rationale for the recommended adult upper target of 11.5 g/dl [115 g/l] and individualization to the child with CKD and their clinical priorities and patient's and family's values and preferences.

## 3.4. ESA dosing, frequency, route of administration, and monitoring

### 3.4.1. ESA dosing

**Practice Point 3.4.1.1: In people with anemia and CKD treated with ESA, the initial dose of ESA should be determined by the Hb concentration of the person, their body weight, and clinical circumstances (Table 7).**

**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<br><br>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)<br><br>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 |
| **Erythropoietin biosimilars** | *Product names and doses vary by region - Refer to individual product information* | |
| **Darbepoetin** | CKD not receiving dialysis: 40-100 µg every 2–4 weeks<br><br>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)<br><br>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<br><br>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)<br><br>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 |

CKD, chronic kidney disease; Hb, hemoglobin; i.v., intravenous; KRT, kidney replacement therapy; s.c., subcutaneous

**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%.**

Initial therapy with ESA aims to increase the Hb concentration by 1.0 g/dl (10 g/l) per month, which is consistent with the findings in clinical trials that used ESA to treat anemia in people with CKD G5D and CKD not receiving dialysis. Initial rates of Hb concentration increase were 0.7–2.5 g/dl (7–25 g/l) in the first 4 weeks. However, a rise in Hb of >2.0 g/dl (20 g/l) over a period of 4 weeks should be avoided to reduce the likelihood that concentrations will exceed 11.5 g/dl (115 g/l), which may increase the risk of hypertension and/or stroke.[41, 239]

**Practice Point 3.4.1.3: In people with anemia and CKD treated with ESA, administer ESAs with the lowest dose possible which achieves and maintain treatment goals.**

High doses of ESA may contribute to the higher risk of stroke and other cardiovascular events associated with higher Hb targets in people with anemia and CKD treated with ESA. This was shown in the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study in which the use of darbepoetin to maintain a Hb level at approximately 13.0 g/dl (130 g/l) (achieved median Hb, 12.5 g/dl [120 g/l]) in people with anemia and CKD not receiving dialysis did not reduce the risk of 2 primary composite outcomes (either death or a cardiovascular event, or death or a kidney event) as compared to placebo, but was associated with an increased risk of stroke.[41] Another RCT, the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study, showed a higher hazard ratio for the primary composite outcome of death, myocardial infarction, hospitalization for congestive heart failure, or stroke in people with CKD not receiving dialysis randomized to receive epoetin alfa dosed to target a higher Hb 13.5 g/dl (135 g/l) (achieved mean Hb 12.6 g/dl (126 g/l)) versus lower Hb 11.3 g/dl (113 g/l).[239] Similarly, an RCT in people with CKD G5HD with background ischemic heart disease or heart failure revealed that treatment with ESA to maintain a Hb of 14.0 g/dl (140 g/l) as compared with 10.0 g/dl (100 g/l) may increase risk of adverse events (death or myocardial infarction). Although the difference in event-free survival did not reach the prespecified statistical significance, the trial was stopped early.[237] Secondary analyses of these studies suggested that higher doses of ESAs may have contributed to the increased adverse outcomes in the high Hb target groups.[250]

### 3.4.2. ESA route of administration

**Practice Point 3.4.2.1: 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.**

Higher doses of epoetin are required when administered via i.v. as compared with s.c., which in turn will increase costs. However, people with CKD G5HD may prefer an i.v. route to reduce injection pain.

**Practice Point 3.4.2.2: 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.**

Subcutaneous administration avoids the need for i.v. access and allows for self-administration at home.

### 3.4.3. Frequency of administration and monitoring of ESAs

**Practice Point 3.4.3.1: In people with CKD G5 or CKD not receiving dialysis, individualize the frequency of administration of ESA based on patient preferences and type of ESA administered (Table 7).**

Patient preferences and local practice patterns often determine the choice of ESA and the frequency of ESA administration.

**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.**

This practice point emphasizes the need to detect rapid rises in Hb to prevent overshooting Hb targets where RCT data indicate an increased risk of adverse events such as hypertension and cardiovascular events.[41, 239] In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study, people with CKD randomized to a Hb target of 13.5 g/dl (135 g/l, achieved mean Hb level of 12.6 g/dl [126 g/l]) had a higher risk of a composite of death and cardiovascular events as compared with a Hb targets of 11.3 g/dl (113 g/l).[239] In the TREAT study, the risk of stroke was higher in people with CKD randomized to darbepoetin to maintain a Hb level at approximately 13.0 g/dl (130 g/l) (achieved median Hb, 12.5 g/dl or 120 g/l) vs. randomized to placebo.[41]

**Practice Point 3.4.3.3: In people with anemia and CKD, and during the maintenance phase of ESA therapy, monitor Hb level at least once every 3 months.**

Ongoing monitoring of Hb is desirable in all people with anemia and CKD who are maintained on ESA therapy to avoid overshooting the Hb beyond target, as well as being able to identify ESA hyporesponsiveness. A minimum frequency of 1–3 months is suggested, with more frequent monitoring suggested among people with CKD G5HD where trial data shows dose

adjustments were required in 40%–50% of people during the maintenance phase of ESA therapy.[9]

**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.**

Clinical trials of ESA therapy revealed an increased risk of stroke, vascular access thrombosis, and nonfatal myocardial infarction.[41, 237] One in 4 stroke survivors will have another stroke.[237] In addition, the risk of vascular access thrombosis and future thromboembolic events is increased in people with a prior history of these events. For these reasons, suspension of ESA treatment should be considered in people with a history of these events. Reinitiation of ESA therapy should be based on shared decision-making after discussion of benefits and risks.

**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.**

Studies in people with cancer have shown that using ESAs to treat anemia of some cancers may lead to increased cancer progression and death.[251] The American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) clinical practice guideline for the use of ESAs in adults with cancer and anemia recommend that treatment with ESA may be considered in people with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose Hb has declined to <10 g/dl (<100 g/l).[252] According to this guideline, ESAs should not be offered to most people with nonchemotherapy-associated anemia, except for selected people with lower risk myelodysplastic syndromes. In addition, Hb may be increased to the lowest concentration needed to avoid RBC transfusions. Although this guideline does not specifically consider the use of ESAs to treat anemia in people with CKD who have a history of cancer or who are subsequently diagnosed with cancer, caution is warranted based a *post hoc* analysis of the TREAT study. In TREAT, where people with anemia and CKD not receiving dialysis were randomized to ESA to achieve a Hb level of 13.0 g/dl (130 g/l) or to placebo, with rescue ESA when the Hb level was <9.0 g/dl (90 g/l), among people with a history of cancer at baseline, 14 of the 188 people assigned to darbepoetin alfa died from cancer, as compared with 1 of the 160 people assigned to placebo ($P$=0.002 by the log-rank test).[41]

## 3.5. HIF-PHI treatment initiation and maintenance

**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.**

No RCTs have investigated the efficacy or safety of combining ESA with HIF-PHIs. While in one small, open-label study of 9 patients on PD diagnosed with ESA hyporesponsiveness, roxadustat added to continued ESA therapy led to ESA dose reductions in 6 patients, the Work Group did not believe that there was a sufficiently reasonable rationale for using ESA and HIF-PHI in combination to justify this treatment approach.[253]

**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).**

Clinical trials of HIF-PHI were based on established Hb thresholds/targets for ESA therapy. No RCTs have been performed to date to establish new thresholds/targets for HIF-PHI therapy.

**Practice Point 3.5.3: In people with anemia and CKD, dose HIF-PHIs according to the recommended starting doses (Table 8).**

**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)<br><br>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)<br><br>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]<br>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)<br><br>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)<br><br>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<br><br>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]<br>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]<br>inhibitor of CYP2C8 (in vitro), BCRP, OAT3 and inducer of CYP2B6 (in vitro)[259, 260] | Australia, EU, Japan, Korea, Taiwan, U.S.† |

More detailed information about drug-drug interactions between individual HIF-PHIs and other drugs can be found in package inserts and product information documents issued by regulatory agencies. *Daprodustat is only approved for chronic kidney disease (CKD) receiving dialysis only in the United States (U.S.) and for both CKD receiving and not receiving dialysis in Japan. †Vadadustat is only approved for CKD receiving dialysis in the Australia, Europe (EU), Korea, Taiwan, and the U.S. and for both CKD receiving and not receiving dialysis in Japan. BRCP, Breast cancer resistance protein [ATP-binding cassette (ABC) transporter family member]; CYP, Cytochromes P450; ESA, erythropoietin-stimulating agent(s); OAT, Organic ion transporter; UAE, United Arab Emirates; UGT, uridine 5'-diphospho-glucuronosyltransferase; UK, United Kingdom

**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 (Table 8).**

This practice point considers the possibility that, based on mechanism of action, higher HIF-PHI doses may result in adverse events.

**Practice Point 3.5.5: In people with anemia and CKD, do not escalate HIF-PHI doses beyond the recommended maximum dose.**

This practice point considers the possibility that, based on mechanism of action, higher HIF-PHI doses may result in adverse events.

### 3.6. HIF-PHI monitoring

**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.**

This practice point refers to an effort to reduce the risk of overshooting the Hb target, undesirable on-target effects at higher doses, and adverse events. The ideal frequency of monitoring is uncertain, but one study of vadadustat in CKD not receiving dialysis, for example, required dose adjustments in 12.5%–54.4% (0–8 weeks) and in 11.5%–38.5% (8–24 weeks) on biweekly monitoring, to increase or maintain Hb, respectively.[261] This practice point may change as more experience is gained with this new class of drugs.

**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.**

This appears to be a drug-specific effect for roxadustat and not a class effect. Post-marketing surveillance of roxadustat in Japan and a retrospective cohort study in China reported cases of central hypothyroidism during treatment.[262] Abnormal laboratory findings became apparent at 2 weeks in the earliest case. Although detailed clinical information, such as frequency and demographics of affected patients, are limited, biochemical and crystallographic assays suggest that roxadustat has affinity to thyroid hormone receptor β (THRβ) and affects the negative feedback loop in the hypothalamic-pituitary-thyroid axis.[223, 263]

**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.**

Factors affecting hyporesponsiveness to HIF-PHIs are not clearly defined. In the majority of clinical trials of HIF-PHIs, increases and stabilization of Hb are achieved within 6–16 weeks after initiation of therapy, both in people who are ESA-naïve or after conversion from ESA to HIF-PHI. Due to insufficient clinical information on the long-term safety of HIF-PHIs, other therapeutic options, such as ESAs, may be prudently considered in cases of insufficient erythropoietic response to HIF-PHIs.

**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.**

This practice point is based on insufficient clinical information regarding the long-term safety of HIF-PHIs, which include risks of cardiovascular, thromboembolic events and malignancy (Table 6).

## 3.7. ESA hyporesponsiveness

**Practice Point 3.7.1: 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.**

*Hyporesponsiveness to ESA in anemia of CKD*

People with CKD receiving or not receiving dialysis, who do not achieve target Hb levels despite a significant increase in ESA doses or continue to require high doses to maintain the target are considered ESA hyporesponders. People with ESA hyporesponsiveness are at increased risk for cardiovascular events, kidney failure, and death.[250, 264-274] ESA hyporesponsiveness can be acute or chronic (>4 months) and is a difficult-to-treat dynamic condition that is frequently transient.[272, 275] Its prevalence varies by geographical region ranging from 12.5% to 30.3% as reported in recent studies.[267, 269, 276, 277] Whereas the etiology of ESA hyporesponsiveness is complex, involving multiple risk factors, evident causes cannot be identified in approximately 30% of cases (Table 9).[278]

**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%)

GI, gastrointestinal; RAS, renin-angiotensin system

The definitions of hyporesponsiveness vary by geographical region and numerical values of ESA thresholds in guidelines (Table 10). Although based on clinical experience, these definitions are not derived from randomized controlled studies evaluating patient prognosis in relation to ESA response.

**Table 10 | Definitions of hyporesponsiveness to erythropoiesis-stimulating agents (ESA)**

| Definitions of ESA hyporesponsiveness | Organization or study |
|---|---|
| Failure to achieve target Hb levels with epoetin doses greater than<br>- i.v. EPO: 450 IU/kg/week<br>- s.c. EPO: 300 IU/kg/week | NKF-KDOQI, 2000[279] |
| Failure to attain the target Hb concentration while receiving greater than 300 IU/kg/week (20,000 IU/week) of epoetin or 1.5 μg/kg of darbepoetin alfa (100 μg/week), or a continued need for such high dosages to maintain the target | Revised EBPG, ERA-EDTA2004[280] |
| *Initial ESA hyporesponsiveness:*<br>- If no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing.<br>- In people with ESA hyporesponsiveness, avoid repeated escalations in ESA dose beyond double the initial weight-based dose.<br><br>*Subsequent ESA hyporesponsiveness:*<br>- Classify people as having acquired ESA hyporesponsiveness if after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable Hb concentration.<br>- In people with acquired ESA hyporesponsiveness, avoid repeated escalations in ESA dose beyond double the dose at which they had been stable. | KDIGO 2012[151] |

| | |
|---|---|
| Weight-adjusted ESA resistance index (ERI) [weekly ESA dose/(body weight x Hb) > 15.4 IU/kg x g/dl (quartile IV)* | Panichi et al. RISCAVID study, 2011[271] |
| Failure to achieve target Hb levels with epoetin doses greater than:<br>- i.v. EPO 450 IU/kg/week,<br>- s.c. EPO: 300 IU/kg/week,<br>- darbepoetin dose >1.5 μg/kg/week | The Renal Association, UK,<br>2017, 2020[281] |
| Failure to achieve Hb target:<br>People receiving HD: Despite 3000 IU/dose of i.v. rHuEPO 3x/ week (9000 IU/week) or 60 μg/week of i.v. darbepoetin alfa once per week<br><br>People receiving PD: Despite 6000 IU/dose of s.c. rHuEPO once per week (6000 IU/week) or 60 μg/week of i.v. darbepoetin alfa once per week<br><br>Predialysis people with CKD: Despite 6000 IU/dose of s.c. rHuEPO once per week (6000 IU/week) | Japanese Society for Dialysis Therapy, 2015[282] |

*ESA thresholds vary between studies. CKD, chronic kidney disease; EBPG, European Best Practice Guideline; ERA-EDTA, European Renal Association-European Dialysis and Transplant Association; ESA, erythropoiesis-stimulating agents; IU, international units; Hb, hemoglobin; i.v. intravenous; KDOQI, Kidney Disease Outcomes Quality Initiative; NKF: National Kidney Foundation; rHuEPO, recombinant human erythropoietin; RISCAVID, RISchio CArdiovascolare nei pazienti afferenti all' Area Vasta In Dialisi, s.c., subcutaneous

The most common causes of ESA hyporesponsiveness are inflammation and iron deficiency. Inflammation suppresses erythropoiesis via cytokine-mediated effects on bone marrow, EPO-responsiveness and synthesis, iron restriction (as a consequence of elevated serum hepcidin levels), and other mechanisms (Figure 9).[283] These mechanistic concepts are supported by clinical studies, which demonstrated that higher serum levels of inflammatory markers, such as CRP and IL-6, as well as iron-regulatory peptide hepcidin were associated with and/or predict increased ESA requirements in people receiving or not receiving dialysis.[271, 284-291]

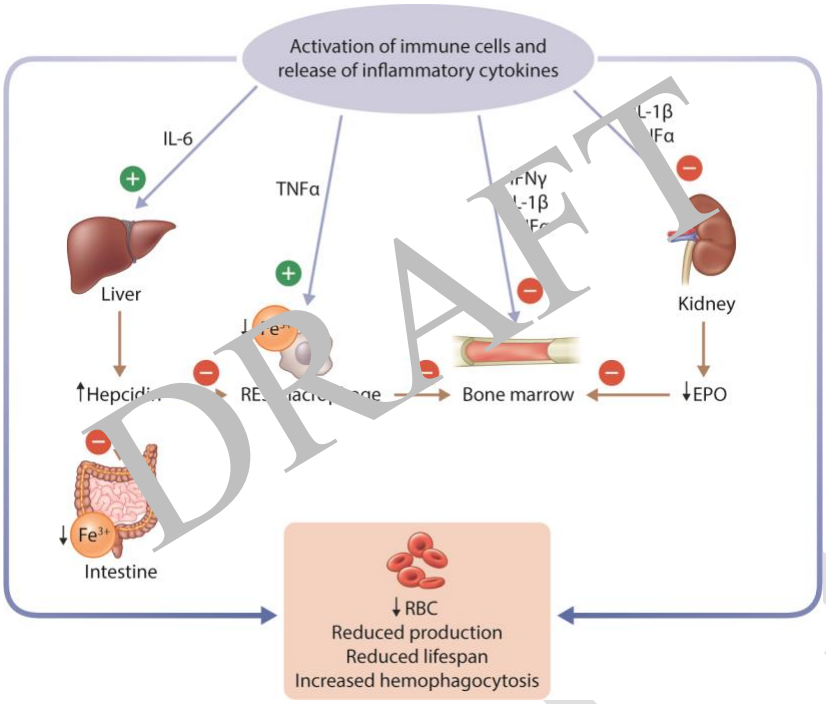


**Figure 9 | Pathophysiological mechanisms of the anemia of inflammation.** During inflammation, activated immune cells release cytokines that reduce hemoglobin levels through multiple pathophysiological mechanisms: hepatic production of hepcidin is increased that prevents iron (Fe3þ) egress from macrophages and inhibits dietary iron absorption leading to sequestration of stored iron; erythropoietin (EPO) release from the kidneys is inhibited, which decreases erythropoietic stimulation of the bone marrow; at the same time, bone marrow erythroid proliferation is directly inhibited; hemophagocytosis of RBC by reticuloendothelial system (RES) macrophages is increased, leading to further RBC loss. IFN, interferon; IL, interleukin; TNF, tumor necrosis factor. Reproduced with permission from Raichoudhury et al.[283]

Recent studies have suggested that causes of ESA hyporesponsiveness cannot be identified in approximately 30% of people with anemia and CKD.[278] ESA hyporesponsiveness is also often transient and sustained ESA hyporesponsiveness in people with CKD not receiving dialysis is rare in the absence of iron deficiency, hemoglobinopathies, myelofibrosis and other hematological diseases.[275]

**Practice Point 3.7.2: 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 (Figure 10).**

The safety and benefits of HIF-PHI in people with ESA-hyporesponsiveness have not been established; few, if any, data support their use. People with ESA hyporesponsiveness are at

increased risk for cardiovascular events, kidney failure, and death.[250, 264-274] Given the cardiovascular safety concerns raised in large global cardiovascular safety trials[223], HIF-PHI use in people with CKD and ESA hyporesponsiveness may further increase their pre-existing risk for serious cardiovascular events.

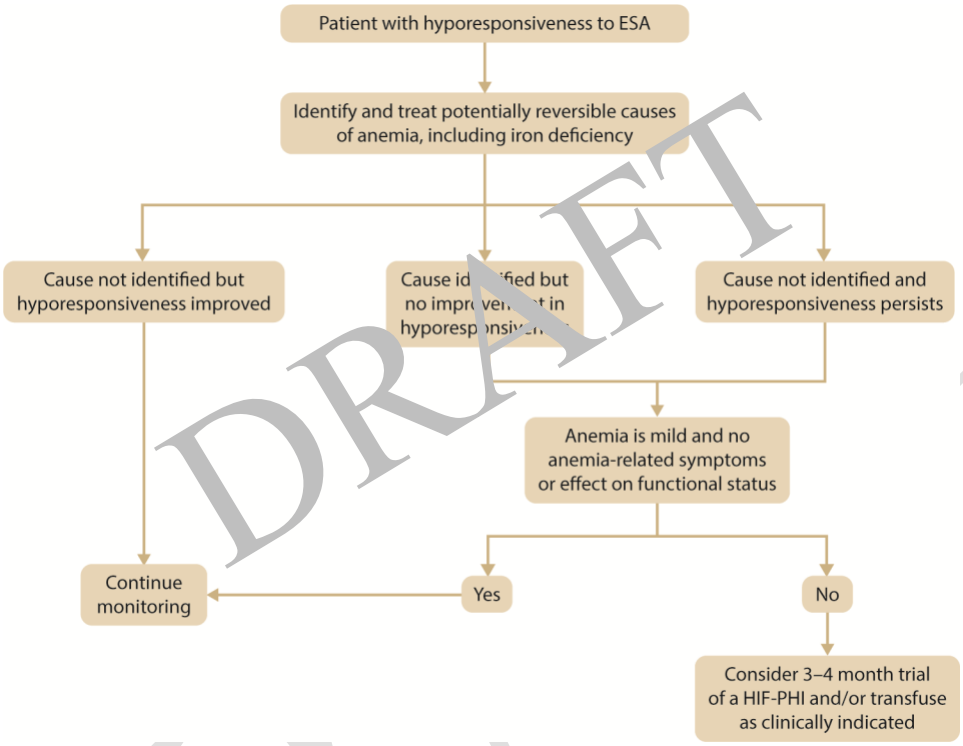


**Figure 10 | Treatment algorithm for sustained ESA hyporesponsiveness**. For definition of hyporesponsiveness, refer to Table 10. See Figure 8 for potentially reversible causes of anemia in CKD.

**Practice Point 3.7.3: In patients with anemia and CKD, if a decision is made to use HIF-PHI for the treatment of ESA hyporesponsiveness, the Hb should be raised to the lowest level that alleviates anemia-related symptoms or which reduces the risk of requiring an RBC transfusion to an acceptable level.**

Few studies examine the effects of a HIF-PHI on Hb levels in people with anemia and CKD G5D and ESA hyporesponsiveness, none have meaningfully examined other important clinical or patient-centered outcomes and all have been very short-term.[253, 292, 293] Some, but not all such people will have an increase in Hb level with HIF-PHI treatment but many do not achieve the desired Hb goal. Additionally, the HIF-PHI doses required tend to be higher than the mean doses used in clinical trials. In the absence of evidence that treatment improves clinically relevant outcomes and with limited data about the risks of HIF-PHI treatment in this patient population, the lowest possible dose should be used to alleviate symptoms due to anemia and/or to achieve a Hb level that might reduce the need for RBC transfusion rather than using HIF-PHI

to try attaining the same Hb level that might be targeted in people with CKD G5D who are not ESA hyporesponsive.

**Practice Point 3.7.4: 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, discontinue treatment.**

No long-term studies evaluate the risks and benefits of HIF-PHI use in people with ESA hyporesponsiveness. The doses of HIF-PHI used in available studies done in this population tended to be higher than was typically used in clinical trials of people without ESA hyporesponsiveness. In the absence of evidence that HIF-PHI treatment in these people confers any benefit other than a small increase in Hb in some people, and given the uncertainty as to the risks of such treatment, it seems prudent to use the lowest possible HIF-PHI dose and discontinue treatment after 4 months if there has not been a meaningful increase in Hb. As noted in Practice Point 3.7.5, even among people with ESA-hyporesponsive and CKD G5D who experience a Hb increase with a HIF-PHI, many do not achieve the goal Hb level used for ESA dosing (Figure 10).

**Practice Point 3.7.5: 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.**

HIF PHIs are associated with an increased risk of death, myocardial infarction, stroke, venous thromboembolism, and vascular assess thrombosis. There is theoretical risk that they may exacerbate or enhance growth of some malignant tumors. There is no evidence to indicate safety of HIF-PHIs in people with an active malignancy. For these reasons, it is prudent to avoid their use in these clinical circumstances.

**Research recommendations:**

- Conduct RCTs to investigate the use of ESA to reach a specific Hb target or compare ESA with placebo for critical (all-cause mortality, MACE) and important outcomes (QoL, fatigue, vascular access thrombosis) in people with CKD G5PD.
- Conduct RCTs to investigate the use of ESA to reach specific Hb targets for critical (all-cause mortality, MACE) and important outcomes (QoL, fatigue, vascular access thrombosis) in children with CKD G5D and CKD not receiving dialysis.
- Investigate the long-term risks and benefits of treatment with HIF-PHI versus ESA in adults and children with CKD5D and CKD not receiving dialysis.
- Examine the effects of HIF-PHI in people with CKD G5D and CKD not receiving dialysis and ESA hyporesponsiveness on critical (all-cause mortality, MACE) and important outcomes (QoL, fatigue, vascular access thrombosis).

# CHAPTER 4. RED BLOOD CELL TRANSFUSION TO TREAT ANEMIA IN PEOPLE WITH CKD

Red blood cell transfusions are a treatment option for anemia in people with CKD. The choice between RBC transfusions and other anemia therapies depends on their relative benefits and harms, which vary between people. In this Chapter, we present an overview of the advantages and disadvantages of RBC transfusions in people with CKD, including a specific focus on those who are or may become KTRs.

**Practice Point 4.1: In people with anemia and CKD, use red blood cell (RBC) transfusion as part of a comprehensive treatment strategy, carefully weighing risks and benefits in a shared decision-making process.**

The decision to transfuse RBCs to people with anemia and CKD is often challenging. Healthcare providers must carefully balance the potential benefits and harms on a case-by-case basis, involving people with anemia and CKD and their families in a shared decision-making process. While some earlier guidelines aimed to establish Hb thresholds, the National Institutes of Health Consensus Conference on Perioperative Red Blood Cell Transfusions in 1988 proposed that the Hb level should not be the exclusive basis for the decision to transfuse or not.[294]

The primary benefits of RBC transfusion are maintaining sufficient oxygen-carrying capacity and improving anemia-related symptoms.[295] The harms are discussed further below. The benefits and harms of RBC transfusion must also be considered in light of the benefits and harms of other anemia therapies (ESA or HIF-PHI), which in most settings are a preferred alternative to RBC transfusion. The benefits and harms of ESA and HIF-PHIs are discussed in detail in Chapter 3. Benefits include improvement in anemia-related symptoms and reduced need for transfusion, whereas the most important harms are increased risk of stroke, thromboembolic events, and cancer progression or recurrence. When choosing between RBC transfusion and ESA or HIF-PHI in an individual, personal characteristics that influence the balance between benefits and harms for each treatment should be considered. For example, a history of stroke and previous or current cancer place individuals receiving ESA at a much higher absolute risk of these complications. Conversely, patients potentially eligible for kidney transplantation, especially those with a prior kidney transplant and multiparous women, have the greatest risk of allosensitization.[296-300] [296, 301]

*Potential harms of RBC transfusions*

Potential harms of RBC transfusions are infrequent and encompass transfusion errors, infections, transfusion-related acute lung injury [TRALI], transfusion-associated circulatory overload [TACO], hemolytic transfusion reactions, febrile nonhemolytic transfusion reactions,

iron overload (with chronic transfusion dependence), volume overload, citrate toxicity (leading to metabolic alkalosis and hypocalcemia), coagulopathy, allosensitization, allergy, hypothermia, hyperkalemia, and health-related errors.[302, 303] Most of these potential harms are uncommon (Figure 11).

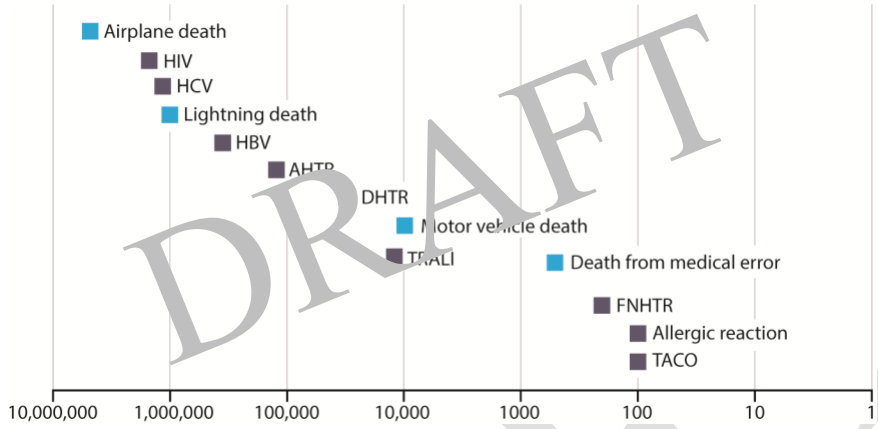


**Figure 11 | Infectious and noninfectious adverse effects of red blood cell (RBC) transfusions as compared with other, unrelated risks.** AHTR, acute hemolytic transfusion reaction; DHTR, delayed hemolytic transfusion reaction; FNHTR, febrile non-hemolytic transfusion rection; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; TACO, transfusion-related cardiac overload; TRALI, transfusion-acute lung injury. Reproduced with permission from Carson et al. Indications for and Adverse Effects of Red-Cell Transfusion. NEJM. 2017; 377: 1261-1272.[302]

Infection transmission is uncommon; the risk of acquiring HIV or hepatitis C virus (HCV) due to RBC transfusion is <1 in a million. However, certain other viruses, parasites, and bacteria may potentially be transmitted if present in donor blood. It is noteworthy that this risk may vary between countries.[304-307] Nevertheless, a meta-analysis of RCTs with data from 17,104 participants did not find an increased risk of all infections defined as sepsis/bacteremia, pneumonia, and wound infection for a restrictive versus liberal transfusion strategy (relative risk [RR]: 0.97; 95% CI: 0.88–1.07).[308] Immunologic reactions (including allergic and hemolytic reactions), are more likely to occur in people with multiple transfusions. Volume overload is a concern in CKD populations, especially the elderly, small children, those with heart failure, and patients with severely compromised kidney function. Iron overload can become a concern in the long term after numerous transfusions for chronic anemia.[309] Approximately 200–250 mg of iron are delivered per unit of RBCs; this iron is released when Hb from the transfused red cells is metabolized after RBC death. It is assumed that hemosiderosis can produce organ damage when the total iron delivered approaches 15–20 grams, the amount of iron in 75–100 units of RBCs. Hyperkalemia, resulting from potassium release during RBC storage may be clinically significant in cases of massive transfusion, especially in people with lower residual kidney function, and infants.

There is no consensus for a universally applicable Hb threshold for RBC transfusion. Medical assessments should encompass clinical conditions, eligibility for kidney transplantation, patient beliefs and preferences, costs, and the availability of alternative therapies. As a framework for the decision to transfuse RBC or not, below we discuss the recommendations by the Association for the Advancement of Blood & Biotherapies (AABB) in their 2023 guideline on RBC transfusions for the general population.[2] We will now highlight the importance of a more restrictive approach for people with CKD eligible for kidney transplantation or for KTRs, due to the risk of allosensitization.

**Practice Point 4.2: In people with anemia and CKD eligible for organ transplantation, avoid, when possible, RBC transfusions to minimize the risk of allosensitization.**

The risk of sensitization after RBC transfusion has probably decreased over time, at least partly due to changes in blood transfusion practices and the use of more precise methods to measure allosensitization.

In the early 1980s, Opelz *et al.* examined the risk of sensitization in 737 people with CKD G5HD (Figures 12a and 12b), of whom 331 were followed prospectively (Figure 12c).[301] Approximately 90% of all RBC transfusions were given in the form of "packed cells" and antibodies were measured by the lymphocyte cytotoxicity test. Overall, 28% of those followed prospectively developed human leukocyte antigen (HLA) antibodies. Of these, 18% developed reactivity to 10%–50% of the panel, 7% to 50%–90% of the panel, and <3% to >90% of the panel after up to 20 transfusions (Figure 12c). Among men, 90% remained "unresponsive" (<10% antibody reactivity against the panel) and 10% developed reactivity to 10%–50% of the panel (Figure 12c). In contrast, after 10 transfusions, only 60% of the women were "unresponsive", 11% demonstrated 10%–50% reactivity, 23% demonstrated 51%–90% reactivity, and 6% demonstrated >90% reactivity (Figure 12c). These data suggest that the main drivers of HLA sensitization following RBC transfusion are a history of pregnancies and a history of transplantation. Women with multiple pregnancies have a much greater risk of HLA sensitization than nulliparous women.

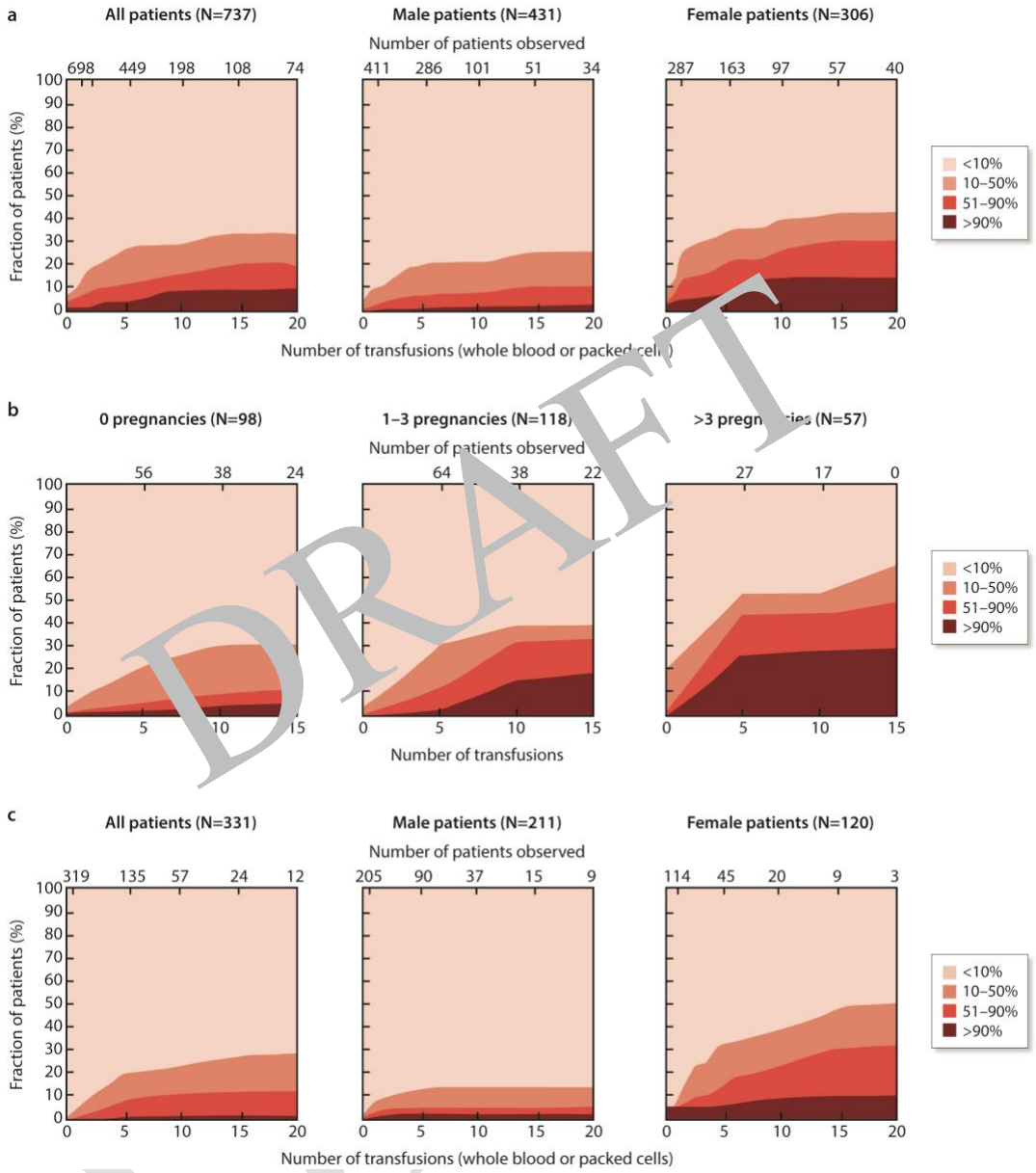


**Figure 12 | Lymphocytotoxic antibody reactivity against random donor test panel in relation to the number of red blood cell (RBC) transfusions.** Fractions of patients reacting against <10%, 10 to 50%, 51 to 90% and >90% of the panel donors are plotted. All 737 patients were on chronic hemodialysis, waiting for a first kidney transplant. Numbers of patients after 2, 5, 10, 15, and 20 transfusions are indicated at top of graphs. a) Male and female patients. b) Females patients separated by the number of previous pregnancies. c) Lymphocytotoxic antibodies in people who were studied prospectively throughout the course of treatment. Reproduced from Opelz G, Graver B, Mickey MR et al. Lymphocytotoxic antibody responses to transfusions in potential kidney transplant recipients. Transplantation 1981; 32(3): 177–183.[301]

The risk of allosensitization with RBC transfusion is not exactly known, but generally, an overall response rate ranging from 2%–21% has been reported.[310-312] The 2010 Annual report

of the USRDS showed that the risk of allosensitization with RBC transfusion is substantial; people who received transfusions have an odds ratio (OR) of 2.38 for having panel reactive antibody (PRA) >80%.[296] Other tentative conclusions from previous studies include the following: a) washed RBC do not appear to be less immunogenic than nonwashed RBCs;[301] b) no consistent reduction in sensitization has been demonstrated with donor-specific[311] and HLA-DR matched transfusions;[313] c) higher numbers of RBC transfusions have been associated with an increased risk of sensitization in some studies,[314, 315] but not in others.[301, 316]

A systematic review by Scornik *et al*. identified 180 eligible studies from 1984 to 2011. The findings indicated that alloimmunization was significantly more common in people with CKD receiving a pretransplant RBC transfusion compared with people with CKD not being transfused.[317] In addition, the risk of allosensitization was also determined by the number of RBC transfusions, with an increased number of RBC transfusions increasing the risk of allosensitization.

*Effect of leukocyte-reduced RBC transfusions on allosensitization*

Many countries and institutions have introduced universal pre- or post-storage leukocyte filtration. Leukocytes may be a contributor to, if not the cause of, a number of adverse consequences of RBC transfusion, including immunologically-mediated effects, infectious disease transmission, and reperfusion injury. However, leukoreduction of blood products does not decrease the risk of allosensitization in previously transplanted or in potential future kidney transplant candidates.[216, 318, 319] Also, in the post-leukodepletion era, male patients awaiting their first organ transplant had a 4-fold increased risk of developing HLA antibody if they had been previously transfused when compared with those who did not have a history of a transfusion.[320] A possible reason for this finding is that the number of HLA molecules contributed by the RBCs is comparable to that of leukocytes.[321]

*Effect of allosensitization on time to transplantation and outcomes*

Previously, allosensitization has been linked with longer wait times compared to non-allosensitized patients.[317] Data from the 2010 USRDS Annual Report suggested an increase in median wait time to transplantation (2 months longer) for people who are transfused versus nontransfused in the United States.[296] In addition, wait time to transplantation was increased with increasing levels of allosensitization (PRA levels of 0%: 1.86 years; 1%–9%: 1.84 years; 10%–79%: 2.09 years; ≥80%: 2.88 years) in that era. In contrast, the 2023 USRDS Annual Report[322] reported little difference in the 3-year probability of receiving a transplant among people with PRA levels <80% (i.e., no difference between the patients with PRA level <1%, 1%–19%, or 20%–79%). In fact, the 3-year probability of receiving a deceased kidney transplant substantially increased for people with PRA ≥80% (with the highest chance of receiving a transplant in people with PRA 98%–100%). This higher likelihood of deceased

donor transplantation was accompanied by a lower chance of receiving a living donor transplant for people with PRA≥80% compared to those with PRA<80%.

In people with transplants, the presence of preformed HLA antibodies is associated with an increased risk of early and late graft loss.[297, 298, 323, 324] In the systematic review by Scornik *et al.*, allosensitization was linked with higher rates of graft rejection and lower rates of graft survival compared to people who are nonsensitized.[317] Data from the USRDS 2010 annual report also showed that the risk of graft failure was higher in people who are allosensitized compared to those who are nonallosensitized (HR: 1.41 for PRA levels ≥80% compared to PRA levels of 0%).[296] It is potentially useful to know that calculated PRA is poorly associated with post-transplant immune reactivity to the allograft in the absence of donor-specific antibodies (DSA).[325]

Most but not all studies found the presence of DSAs to be associated with more acute graft rejections and lower graft survival.[317] A systematic review of 7 retrospective cohort studies involving 1119 people with CKD identified that the presence of DSAs doubled the risk of antibody-mediated rejection and increased the risk of graft failure with 76%.[326] A recent study from the Swiss transplant cohort study confirmed that pretransplant DSA were associated with a significantly increased risk of antibody-mediated rejection, graft loss, and accelerated eGFR decline.[327]

A recent systematic review and meta-analysis among 32,817 KTRs included in 10 studies from 2000–2022 found that RBC transfusion post-kidney transplantation was significantly associated with inferior patient survival (OR: 6.00; 95% CI: 1.70–21.17), allograft loss (OR: 2.11; 95% CI: 1.69–2.64), rejection (OR: 1.42; 95% CI: 1.04–1.94), and the formation of DSAs (OR: 1.73; 95% CI: 1.24–2.41).[328] RBC transfusion could be given intraoperatively, perioperatively, or postoperatively up to 1 year post-transplant. Although there was considerable heterogeneity between studies, the systematic review finding marks the need for high-quality, prospective evidence of the effect of RBC transfusions on transplant outcomes.

**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)**

For people with CKD and chronic anemia, RBC transfusion can be considered in states of ESA or HIF-PHI hyporesponsiveness, such as in bone marrow failure, hemoglobinopathies, and ESA or HIF-PHI resistance settings, or if the potential risks of ESA or HIF-PHIs outweigh

the benefits, such as people with current or previous malignancy. This decision is subtly different for the types of treatment as ESAs and HIF-PHIs may be used to avoid transfusion and therefore before the need for transfusion has arisen. Furthermore, the magnitude of the potential harms of transfusion (e.g., from infection) and some of the benefits from ESAs and HIF-PHIs (e.g., transfusion avoidance) are dependent on the threshold for transfusion. If that threshold is high (i.e., transfusion is reserved until symptoms become severe or the Hb reaches a very low level) the risks related to transfusion will be low and the benefit of ESA or HIF-PHI therapy in avoiding transfusions will be small.

In the TREAT study, published in 2009, 4038 people with diabetes, CKD G5, and anemia (Hb ≤11.0 g/dl [≤110 g/l]) were randomized to darbepoetin alfa with target Hb 13 g/dl (130 g/l) or to placebo with "rescue" darbepoetin alfa when Hb fell below 9.0 g/dl (90 g/l).[41] Over a median follow-up of 29 months, 297/2012 (15%) patients randomized to darbepoetin alfa and 496/2026 (25%) assigned to placebo received RBC transfusions (HR: 0.56; 95% CI: 0.49–0.65; *P*<0.001). It is known that RBC transfusion use has been increased during the post-TREAT study and post-FDA warning period with 14% and 31%, respectively, as compared to the pre-TREAT period.[329]

According to the 2023 Annual Report of the USRDS,[322] the mean Hb among people with incident kidney failure was 9.4 g/dl (94 g/l), and the percentage of patients with Hb <9/dl (90 g/l) at onset of kidney failure was >30%. Fewer than 1 of 6 people with incident kidney failure had received ESAs prior to initiating dialysis, despite the large percentage of people with CKD having a low Hb level. Those with Hb <9 g/dl (90 g/l) were 4 times more likely to have received an RBC transfusion than those with Hb 9–<10 g/dl (90–<100 g/l). RBC transfusions were more common than ESA use in Medicare beneficiaries with CKD G4 and were almost as common as ESA use in people with CKD G5.

The above findings underscore that anemia is undertreated prior to the onset of kidney failure, and undertreatment may lead to high rates of RBC transfusion, which in turn has negative consequences, especially for people who are eligible for kidney transplantation. Black people were more likely to receive RBC transfusions than members of any other race group, particularly those with CKD G5. These data underscore the necessity to adequately treat anemia of CKD with iron and ESA or HIF-PHI, and only use RBC transfusions in case of ESA or HIF-PHI hyporesponsiveness or when risks of ESA or HIF-PHI therapy are considered to outweigh benefits.

**Practice Point 4.4: In people with anemia and CKD, base the decision to transfuse a person with CKD and chronic anemia on symptoms and signs caused by anemia rather than an arbitrary Hb threshold.**

We recognize that symptoms such as dyspnea and fatigue are nonspecific, and that anemia-related symptoms may occur at different Hb levels in different people. In fact, we know that current daily practice is that RBC transfusion in CKD is performed as a target Hb-driven approach or during acute illnesses.[303] The latter was shown in a Canadian study involving people receiving outpatient dialysis in which a low Hb value was the reason for RBC transfusion (92%), whereas only 4.5% of patients had symptoms of severe anemia necessitating RBC transfusion.[330] In a choice-based survey in the Veteran Administration System on the decision to transfuse people with anemia receiving dialysis, absolute Hb level was the most important consideration (29%), followed by patient functional status (16%).[303, 331] However, there is a paucity of RCT data evaluating transfusion thresholds in people with CKD and chronic anemia. Notably, meta-analyses of RBC transfusions in acute settings in the general population have failed to show benefits of more liberal transfusion strategies (generally a Hb threshold of 9–10 g/dl [90–100 g/l]) compared with a more restrictive strategy (generally a Hb threshold of 7–8 g/dl [70–80 g/l])[308] as discussed further below. We recognize that anemia-related symptoms such as dyspnea and fatigue are nonspecific and may occur at different Hb levels in different people. We therefore suggest that anemia-related signs and symptoms be the primary trigger for deciding when to give RBC transfusions rather than an arbitrary Hb threshold.

**Practice Point 4.5: In people with CKD and acute anemia consider RBC transfusion when the benefits outweigh the risks, including:**

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

In certain urgent clinical situations, RBC transfusion may be needed for the immediate correction of anemia. These include acute severe hemorrhage and other clinical problems caused by, or exacerbated by, anemia, such as acute myocardial ischemia. When urgent surgery is required, transfusion may also be given to achieve rapid preoperative correction of Hb. The Hb threshold for transfusion in this situation is uncertain especially as there is a paucity of randomized studies evaluating thresholds for RBC transfusions specifically in people with CKD.

A Cochrane review involving 48 RCTs with 21,433 people across different clinical settings showed that a restrictive transfusion strategy (using a Hb threshold of most commonly 7.0–8.0 g/dl [70–80 g/l]) decreased the proportion of people exposed to RBC transfusion to 41% compared to the liberal transfusion strategy (using generally a Hb threshold of 9–10 g/dl [90-100 g/l]).[308] Importantly, the restrictive RBC transfusion strategy did not impact 30-day mortality, mortality at other timepoints, or morbidity (i.e., cardiac events, myocardial infarction, stroke, pneumonia, thromboembolism, infection) compared with a liberal transfusion strategy.

The results of this Cochrane library review is also applicable for people with CKD as none of the individual studies excluded people with CKD. In fact, one of the included studies specifically included people with CKD.[332]

In 2023, the Association for the AABB International guidelines were published using evidence of systematic reviews of RCTs using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods, managing conflicts of interest, and making values and preferences explicit. The thresholds are applicable to all people, and can provide guidance for clinicians when to consider RBC transfusions. For hemodynamically stable adult inpatients (including patients with hematologic and oncologic disorders), a restrictive transfusion strategy can be used when hemoglobin level is less than 7 g/dl, less than 7.5 g/dL for patients undergoing cardiac surgery, less than 8 g/dl for those undergoing orthopedic surgery or those with preexisting cardiovascular disease. We consider these thresholds reasonable guides to consider RBC transfusion, but symptoms and signs caused by anemia should also be considered when transfusing people with CKD.

In summary, Figure 13 outlines key clinical scenarios that can guide decisions regarding RBC transfusion in people with CKD, as well as potential risks. RBC transfusion should be considered in acute clinical situations where delaying anemia correction may lead to serious outcomes, including the imminent risk of death. These acute clinical situations include, but are not limited to, severe acute hemorrhage from gastrointestinal, genitourinary disorders, or other causes, unstable coronary artery disease, and preoperative situations necessitating rapid Hb correction. In addition, a flowchart specifically for special chronic clinical situations, including KTRs, is included.

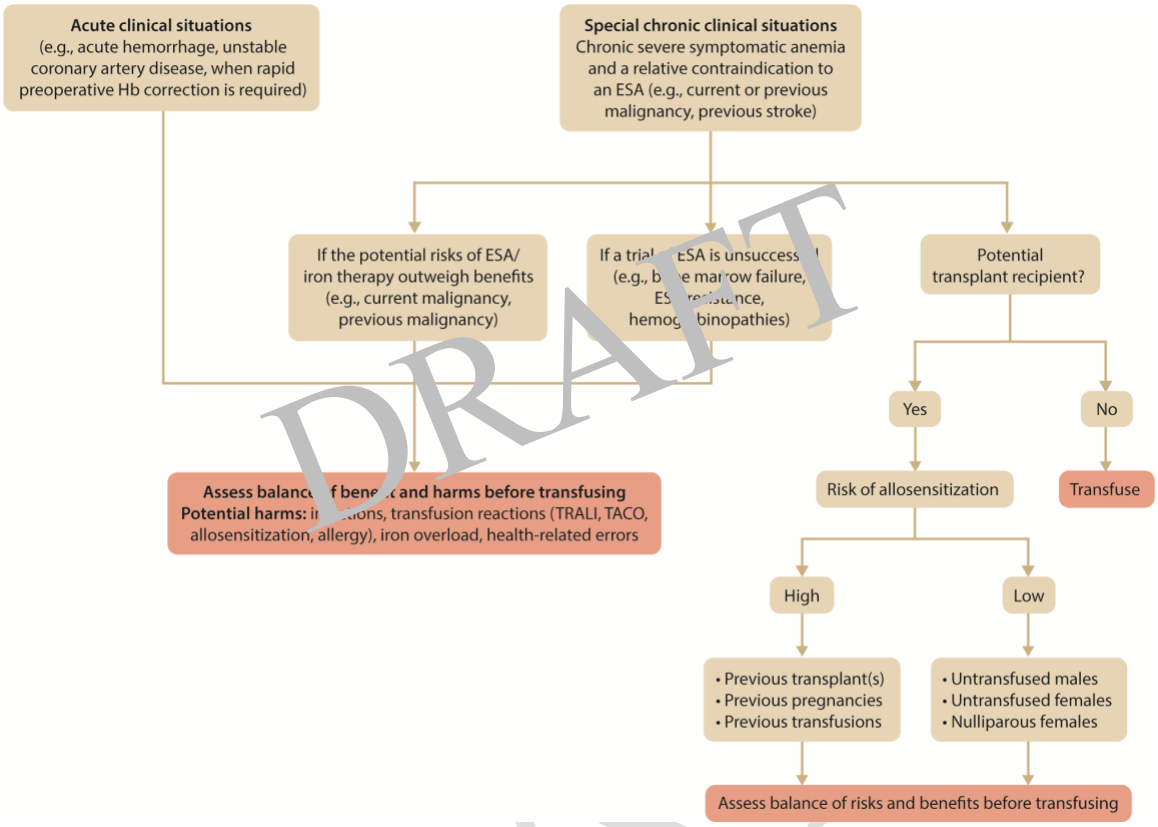


**Figure 13 | Algorithm for guiding the use of red blood cell (RBC) transfusion to treat anemia in people with chronic kidney disease.** ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; TACO, transfusion-associated circulatory overload; TRALi, transfusion-related acute lung injury.

**Practice Point 4.6: Consider implementing strategies at the individual, organizational, and public health policy levels to reduce RBC transfusions in people with CKD (Table 11).**

We provide different strategies in Table 11 in order to reduce the use of RBC transfusions in people with CKD:

**Table 11 | Strategies to reduce red blood cells (RBC) transfusions in people with chronic kidney disease (CKD)**

- Opt for less invasive procedures in hospitalized patients whenever possible.
- Limit phlebotomy when medically appropriate.
- Continue ESA/HIF-PHI/iron therapy in hospitalized patients unless clinically contraindicated.
- Consider Hb trend over time rather than absolute Hb values, in people using ESA/HIF-PHI/iron therapy.
- Avoid RBC transfusion in patients with chronic anemia who are asymptomatic.
- Individualize transfusion need based on the clinical situation.
- In every person with CKD patient, triage the decision for RBC transfusion on whether the person is a potential future transplant candidate.

ESA, erythropoiesis-stimulating agent [10,11] Adapted with permission from Brenner et al. Red cell transfusion in chronic kidney disease in the United States in the current era of erythropoiesis stimulating agents. Journal of Nephrology. 2022;33: 267-275.

**Research recommendations**

There is a lack of RCTs on the use of RBC transfusions as a primary intervention in people with anemia and CKD. Given the logistical difficulties in conducting such trials, it is likely that observational data will continue to predominate in this therapeutic area.

Future research should include:

- Prospective observational data collection on the use of RBC transfusions in people with CKD, particularly those receiving dialysis, including the reason(s) for transfusion, intent to list for future kidney transplantation, likelihood of receiving a kidney transplant, and graft outcomes.
- Prospective, observational evaluation of the impact of RBC transfusions on the level of HLA sensitization.
- Investigate different practices for RBC transfusions between different cities, countries, and continents to assess which factors most strongly predispose to the suboptimal treatment of anemia in CKD, thereby leading to higher need for RBC transfusions.
- Further investigation is needed into the optimal duration of RBC storage and the occurrence of thrombosis due to RBC transfusion. The optimal duration of RBC storage could be evaluated in a randomized trial to assess whether longer storage provides a clinical benefit to KTRs.

# METHODS FOR GUIDELINE DEVELOPMENT

## Aim

The aim of this project was to update the *KDIGO 2012 Clinical Practice Guideline for Anemia in Chronic Kidney Disease*.[151] The guideline development methods are described below.

## Overview of the Process

This guideline adhered to international best practices for guideline development (Appendix B: Supplementary Table S2 and Table S3)[333, 334] and have been reported in accordance with the AGREE II reporting checklist.[335] The processes undertaken for the development of the KDIGO 2025 Clinical Practice Guideline for Anemia in CKD are described below.

- Appointing Work Group members and the ERT
- Finalizing guideline development methodology
- Defining scope of the guideline
- Developing and registering protocols for systematic reviews
- Implementing literature search strategies to identify the evidence base for the guideline
- Selecting studies according to predefined inclusion criteria
- Conducting data extraction and risk of bias assessment of included studies
- Conducting evidence syntheses, including meta-analysis where appropriate
- Assessing the certainty of the evidence for each critical outcome
- Finalizing guideline recommendations and supporting rationale
- Grading the strength of the recommendations, based on the overall certainty of the evidence and other considerations
- Convening a public review of the guideline draft in November 2024
- Updating systematic reviews
- Amending the guideline based on the external review feedback and updated systematic reviews
- Finalizing and publishing the guideline

### *Commissioning of Work Group and ERT*

KDIGO and the Co-Chairs assembled and engaged a Work Group with expertise in pediatric and adult nephrology, including both dialysis and transplant specialists; cardiology; hematology; clinical trials; epidemiology; as well as people living with anemia and CKD. Johns Hopkins University with expertise in nephrology, evidence synthesis, and guideline development was contracted as the ERT and was tasked with conducting the evidence reviews. The ERT coordinated the methodological and analytical processes of guideline development, including literature searching, data

extraction, risk of bias assessment, evidence synthesis and meta-analysis, grading the certainty of the evidence of each critical and important outcome, and grading the overall certainty of the evidence for each recommendation. The Work Group was responsible for writing the recommendations and the underlying rationale, grading the strength of the recommendations, and developing practice points.

***Defining scope and topics and formulating key clinical questions***

The KDIGO 2012 Anemia guideline was reviewed by the Co-Chairs to identify topics to be included in the 2025 guideline. Scoping reviews of these topics were conducted by the ERT to provide an overview of the available evidence and to identify existing relevant systematic reviews.

Protocols for all review were developed by the ERT and reviewed by the Work Group. Protocols were registered on PROSPERO (https://www.crd.york.ac.uk/prospero/). Systematic reviews were conducted in accordance with current standards, including those from the Cochrane Handbook.[336]

Details of the Population, Intervention, Comparator, Outcome and Study design (PICOS) of the review questions are provided in Table 12. Information about any existing reviews used is included in these tables.

**Table 12 | Clinical questions and systematic review topics in PICOS format**

| **Chapter 2** | **Use of iron in CKD** |
|---|---|
| **Review question** | **What are the benefits and harms of iron dosing agents (oral, i.v., and dialysate) in adults and children with CKD?** |
| Population | Adults and children with CKD; on or not on ESA/HIF-PHI therapy<br><br>Subpopulations:<br>• Not treated with dialysis<br>• Treated with hemodialysis<br>• Treated with peritoneal dialysis<br>• Heart failure<br>• Children |
| Intervention (index test) | Iron therapy: oral, i.v., or dialysate |
| Comparator | Other iron dosing modalities, placebo, or no iron therapy |
| Outcomes | • Critical outcomes: Mortality; cardiovascular events, including stroke, heart failure, and myocardial infarction; quality of life; functional status, all-cause hospitalization, serious adverse events (gastrointestinal, hypersensitivity reaction, other serious adverse events as defined by study authors); infections<br>• Important outcomes: Growth, height, weight, and cognitive development in pediatric studies; blood transfusion; cancer; ESA/HIF-PHI use and dose; hemoglobin values, and percent of patients reaching a hemoglobin target<br>• Other outcomes: Iron use and dose, transferrin saturation, serum ferritin |
| Study design | RCTs |
| Existing systematic review used for hand-searching | O'Lone EL, Hodson EM, Nistor I, et al. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. The Cochrane database of systematic reviews. 2019 Feb 21;**2:**Cd007857.[337] |
| SoF tables | Appendix C: Supplementary Tables S4–S13 |
| Search date | April 2023 |
| Citations screened/included studies | Supplemental Figure S1<br>• Iron dosing agent versus placebo in people with CKD not receiving dialysis or ESAs/HIF-PHIs: 13,177/24 |

| | |
|---|---|
| | • Iron dosing agent versus placebo in people with CKD not receiving dialysis but receiving ESAs/HIF-PHIs: 13,177/5 (no critical or important outcomes recorded)<br>• Iron dosing agent versus placebo in people with CKD treated with dialysis and ESAs/HIF-PHIs, evaluation iron dosing agents: 13,177/28<br>• Iron dosing agent versus placebo in people with CKD treated with dialysis and ESAs/HIF-PHIs, evaluating different targets/thresholds: 13,177/7 (not identified as a comparison for grading)<br>• Iron dosing agent versus placebo in people with CKD treated with peritoneal dialysis: 13,177/4<br>• Iron dosing agents versus placebo in children with CKD: 13,177/2 (no critical or important outcomes recorded)<br>• Iron dosing agents versus placebo in people with CKD and heart failure: 13,177/4 |
| **Chapter 3** | **Use of ESAs, HIF-PHIs, and other agents to treat anemia in CKD** |
| **Review question** | **What are the benefits and harms of ESAs in adults and children with CKD?** |
| Population | Adults and children with CKD<br><br>Subpopulations:<br>• Not treated with dialysis<br>• Treated with hemodialysis<br>• Treated with peritoneal dialysis<br>• Heart failure<br>• Children |
| Intervention | ESA therapy: Erythropoietin (EPO), epoetin alfa (Procrit, Epogen, Eprex), epoetin beta (NeoRecormon, Recormon), epoetin delta (Dynepo); epoetin omega (Epomax, Hemax), epoetin zeta (Silapo, Retacrit), darbepoetin alfa (Aranesp), methoxy polyethylene glycol-epoetin beta (Mircera) |
| Comparator | Other ESA, other doses and routes of ESA, other hemoglobin thresholds/targets for ESA therapy, placebo, or no ESA therapy |
| Outcomes | • Critical outcomes: Mortality; cardiovascular events: stroke, heart failure, and myocardial infarction; thromboembolism, deep vein thrombosis, pulmonary embolism; vascular access thrombosis; all-cause hospitalization; serious adverse events: gastrointestinal, infections, hypersensitivity reaction; quality of life; functional status |

| | |
|---|---|
| | • Important outcomes: Growth, height, weight, and cognitive development in pediatric studies; blood transfusion; hypertension or change in blood pressure; cancer; Hb: change in Hb, % patients reaching target Hb, mean Hb; iron use and dose |
| Study design | RCTs |
| Existing systematic review data included | KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease Kidney Int Suppl (2011). 2012 Aug;**2:** 279[151]<br><br>Chung EYM, Palmer SC, Saglimbene VM, Craig JC, Tonelli M, Strippoli GFM. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. Cochrane Database of Systematic Reviews. 2023; **2:** CD010590.[338] |
| SoF tables | Appendix C: Supplementary Tables S38–S49; Appendix D: Supplementary Tables 54-58 |
| Search date | April 2023 |
| Citations screened/included studies | Supplemental Figure S2<br>• ESA use in adults with CKD not receiving dialysis: 4992/38(no critical outcomes were recorded in the graded comparison of ESA dose versus dose)<br>• ESA use in adults with CKD treated with dialysis*: 4992/66<br>• ESA use in adults treated with peritoneal dialysis: 4992/1 (no critical or important outcomes were recorded for) the graded comparisons of ESA treating to a high hemoglobin target versus low hemoglobin target, ESA dose verse dose, or ESA versus placebo)<br>• ESA use in children: 4992/4 (no critical or important outcomes were recorded for the graded comparison of ESA treating to a high hemoglobin target versus low hemoglobin target<br>• ESA use in people with heart failure: 4992/0 |
| **Review question** | **What are the benefits and harms of HIF-PHIs in adults and children with CKD?** |
| Population | Adults and children with CKD<br><br>Subpopulations:<br>• Not treated with dialysis<br>• Treated with hemodialysis<br>• Treated with peritoneal dialysis |

| | |
|---|---|
| | • Heart failure<br>• Children |
| Intervention | HIF-PHI therapy: Daprodustat (Duvroq), desidustat (Oxemia), enarodustat (Enaroy), molidustat, roxadustat (Evrenzo), vadadustat |
| Comparator | Other HIF-PHI, other HIF-PHI doses, other Hb thresholds/targets, placebo, or no HIF-PHI therapy |
| Outcomes | • Critical outcomes: Mortality; cardiovascular events: stroke, heart failure, and myocardial infarction; thromboembolism, deep vein thrombosis, pulmonary embolism; vascular access thrombosis; all-cause hospitalization; serious adverse events as defined by study authors; quality of life; functional status<br>• Important outcomes: Blood transfusion; hypertension or change in blood pressure; cancer; Hb: change in Hb, % patients reaching target Hb, mean Hb; iron use and dose; CKD related measures: SCr doubling, progression to kidney failure, 50% decline in GFR |
| Study design | RCTs |
| Existing systematic review used for data or hand-searching | None |
| SoF tables | Appendix C: Supplementary Tables S14-S17; Appendix D: Supplementary Tables S50-53 |
| Search date | April 2023 |
| Citations screened/included studies | Supplemental Figure S3<br>• HIF-PHI versus placebo in people with CKD not receiving dialysis: 1040/14<br>• HIF-PHI versus placebo in people with CKD treated with dialysis*: 1040/6<br>• HIF-PHI versus HIF-PHI in people with CKD not treated with dialysis: 1040/1<br>• HIF-PHI versus HIF-PHI in people with CKD treated with peritoneal or hemodialysis: 1040/3 |
| **Review question** | **What are the benefits and harms of ESAs versus HIF-PHIs in adults and children with CKD?** |
| Population | Adults and children with CKD<br><br>Subpopulations:<br>• Not treated with dialysis<br>• Treated with hemodialysis<br>• Treated with peritoneal dialysis |

| | |
|---|---|
| | • Heart failure<br>• Children |
| Intervention | ESA therapy: Erythropoietin (Epo), epoetin alfa (Procrit, Epogen, Eprex), epoetin beta (NeoRecormon, Recormon), epoetin delta (Dynepo), epoetin omega (Epomax, Hemax), epoetin zeta (Silapo, Retacrit), darbepoetin alfa (Aranesp), methoxy polyethylene glycol-epoetin beta (Mircera)<br><br>HIF-PHI therapy: Daprodustat (Duvroq), desidustat (Oxemia), enarodustat (Enaroy), molidustat, roxadustat (Evrenzo), vadadustat |
| Comparator | ESA or HIF-PHI |
| Outcomes | • Critical outcomes: Mortality; cardiovascular events: stroke, heart failure, and myocardial infarction; thromboembolism, deep vein thrombosis, pulmonary embolism; vascular access thrombosis; all-cause hospitalization; serious adverse events: as defined by the study authors; quality of life; functional status<br>• Important outcomes: Growth, height,3 weight, and cognitive development in pediatric studies; blood transfusion; hypertension or change in blood pressure; cancer; Hb: change in Hb, % patients reaching target Hb, mean Hb; iron markers: transferrin saturation, serum iron, transferrin/total iron binding capacity, ferritin, hepcidin; iron use and dose; CKD related measures: SCr doubling, progression to kidney failure, 50% decline in GFR |
| Study design | RCTs |
| Existing systematic review used for data or hand-searching | None |
| SoF tables | Appendix C: Supplementary Tables S18–S37 |
| Search date | April 2023 |
| Citations screened/included studies | Supplemental Figure S4<br>• ESA versus HIF-PHIs in people with CKD not receiving dialysis: 5989/14<br>• ESA versus HIF-PHIs in people with CKD treated with peritoneal or hemodialysis: 5989/23 |

*It was anticipated that separate reports would be completed for people with CKD treated with hemodialysis and those treated with peritoneal dialysis. However, due to the number of studies not reporting results separately by dialysis modality, reports that combined modalities were completed. CKD, chronic kidney disease; ESA, erythropoietin stimulating agent; GFR, glomerular filtration rate, Hb, hemoglobin; HIF-PHI,

hypoxia inducible factor-propyl hydroxylase inhibitor; i.v., intravenous; KDIGO, Kidney Disease: Improving Global Outcomes; PICOS, Population, Intervention, Comparator, Outcomes, Study design; RCT, randomized controlled trial; SoF, summary of findings; SCr, serum creatinine.

***Literature searches and article selection***

Searches for RCTs were conducted on PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategies are provided in Appendix A: Supplementary Table Sl. Because of the relative newness of HIF-PHIs, additional information from the FDA and the EMA was reviewed.

For the question on benefits and harms of ESAs in adults and children with anemia and CKD, we updated the KDIGO 2012 Anemia guideline using a search strategy comparable to this guideline.[151] A review by Chung, 2023 on the use of ESAs in adults with CKD partially aligned with one of our review questions;[338] we hand-searched the articles analyzed in this study and included those not captured in our search.

To improve efficiency and accuracy in the title/abstract screening process and to manage the process, search results were uploaded to a web-based screening tool, PICO Portal (www.picoportal.net). PICO Portal uses machine learning to sort and present first those citations most likely to be promoted to full-text screening. The titles and abstracts resulting from the searches were initially screened independently by 2 members of the ERT. Two people screened articles identified in the searches for studies evaluating iron dosing agents and ESAs, and when the recall rate of citations promoted to full text was at least 95% screening was stopped. Because of the small search yield, all uploaded abstracts identified for studies evaluating HIF-PHIs were screened by 2 reviewers. Citations deemed potentially eligible at the title and abstract stage were screened independently by 2 ERT members at the full-text level. At both title/abstract and full-text screening disagreements about eligibility were resolved by consensus, and, as necessary through discussion amongst the ERT members.

Search dates, number of citations screened, and number of eligible studies are reported in Figure 14. Supplemental Figures S1 through S21 include PRISMA diagrams for each systematic review. A total of 19,343 citations were screened. Of these, 269 RCTs were included in the evidence review (Figure 14).

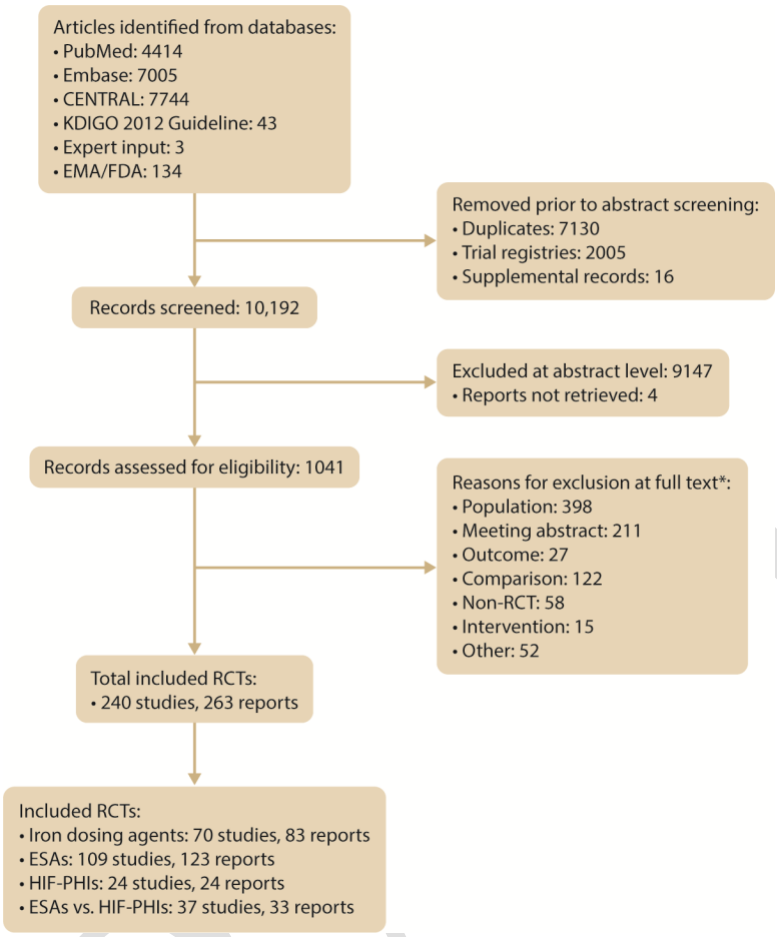


**Figure 14 | Search yield and study flow diagram.** *Number of reasons for exclusion exceeds 778 because articles could be excluded for more than one reason.

***Data extraction***

Data extraction, from studies and existing systematic reviews, was performed by a member and confirmed by a second member of the ERT. Any differences among members of the ERT were resolved through discussion. A third reviewer was included if consensus could not be achieved.

***Risk of bias of studies and systematic reviews***

The Cochrane Risk of Bias tool was used to assess risk of bias for RCTs based on the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results.[339]

All risk of bias assessments were conducted independently by 2 members of the ERT, with disagreements resolved by internal discussion and consultation with a third ERT member, as needed.

***Evidence synthesis and meta-analysis***

*Measures of treatment effect* – For dichotomous outcomes, a pooled effect estimate was calculated of the relative risk between the trial arms of RCTs, with each study weighted by the inverse variance, by using a random-effects model with the DerSimonian and Laird formula for calculating between-study variance.[340] We also extracted unadjusted HRs and their CIs and weighted them using the same method. For continuous outcomes, a standardized mean difference was calculated by using a random-effects model with the DerSimonian and Laird formula.[340]

*Data synthesis* – Meta-analysis was conducted if there were 2 or more studies that were sufficiently similar with respect to key variables (population characteristics, study duration, comparisons).

We combined studies of interventions in the same class when reporting outcomes. If there was substantial heterogeneity ($I^2$ >50%) in pooled estimates for any outcome, we stratified by the type of intervention, population, length of follow-up before conducting the pooled analyses, where practical.

*Assessment of heterogeneity* – Statistical heterogeneity among the trials for each outcome was tested using a standard $\chi^2$ test using a significance level of $\alpha \leq 0.10$. Heterogeneity was also assessed with an $I^2$ statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance. A value greater than 50% was considered to indicate substantial heterogeneity.[341] Summary estimates were not provided if the $I^2$ was above 75%.

***Grading the certainty of the evidence and the strength of a guideline recommendation***

The certainty of evidence for each critical and important outcome was assessed by the ERT using the GRADE approach.[342, 343] For RCTs, the initial grade for the certainty of the evidence is considered to be high. The certainty of the evidence is lowered in the event of study limitations; important inconsistencies in results across studies; indirectness of the results, including uncertainty about the population, intervention, outcomes measured in trials, and their applicability to the clinical question of interest; imprecision in the evidence review results; and concerns about publication bias. For imprecision, data were benchmarked against optimal information size,[344] low event rates in either arm, CIs that indicate appreciable benefit and harm (25% decrease and 25% increase in the outcome of interest), and sparse data (only 1 study), all indicating concerns about the precision of the results.[344] The final grade for the certainty of the evidence for an outcome could be high (A), moderate (B), low (C), or very low (D) (Tables 13 and 14).

**Table 13 | Classification for certainty of the evidence**

| Grade | Certainty of evidence | Meaning |
|---|---|---|
| A | High | We are confident that the true effect is close to the estimate of the effect. |
| B | Moderate | The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| C | Low | The true effect may be substantially different from the estimate of the effect. |
| D | Very low | The estimate of the effect is very uncertain, and often it will be far from the true effect. |

**Table 14 | GRADE system for grading the certainty of evidence**

| Study design | Step 1–Starting grade for the certainty of evidence | Step 2—Lower grade | Step 3—Raise grade for observational evidence |
|---|---|---|---|
| RCT | High | Study limitations:<br>–1, serious<br>–2, very serious | Strength of association<br>+1, large effect size (e.g., <0.5 or >2)<br>+2, very large effect size (e.g., <0.2 or >5) |
| | Moderate | Inconsistency:<br>–1, serious<br>–2, very serious | Evidence of a dose–response gradient |
| Observational | Low | Indirectness:<br>–1, serious<br>–2, very serious | All plausible confounding would reduce the demonstrated effect |
| | Very low | Imprecision:<br>–1, serious<br>–2, very serious<br>-3, extremely serious<br>Publication bias:<br>–1, strongly suspected | |

RCT, randomized controlled trial; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

***Summary of findings (SoF) tables***

Summary of findings tables were developed using GRADEpro (https://www.gradepro.org/). The SoF tables include a description of the population, intervention, and comparator and, where applicable, the results from the data synthesis as

relative and absolute effect estimates. The grading of the certainty of the evidence for each critical and important outcome is also provided in these tables. The SoF tables are available in the Appendix C of the Data Supplement published alongside the guideline or at https://kdigo.org/guidelines/ckd-evaluation-and-management/.

***Updating and developing the recommendations***

Recommendations from the *KDIGO 2012 Clinical Practice Guideline for Anemia in Chronic Kidney Disease* were considered in the context of new evidence by the Work Group Co-Chairs and Work Group members, and updated as appropriate.[151] Practice points were not yet proposed as a separate category in 2012, so the KDIGO 2025 Work Group considered the following options: where new evidence did not suggest a change to graded recommendations, the statements were retained as graded recommendations; graded recommendations were updated where appropriate based on new evidence; existing recommendations that fit the criteria for practice points were rewritten as practice points, and new guideline statements (both recommendations and practice points) were generated for new clinical questions from the 2025 update.

***Grading the strength of the recommendations***

The strength of a recommendation was classified by the Work Group as Level 1 or Level 2 (Table 15). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall certainty of the evidence, patient values and preferences, resource use and costs, and other considerations (Table 16).

**Table 15 | KDIGO nomenclature and description for grading of recommendations**

| Grade | Implications | | |
|---|---|---|---|
| | **Patients** | **Clinicians** | **Policy** |
| Level 1, "We recommend" | Most people in your situation would want the recommended course of action, and only a small proportion would not. | Most patients should receive the recommended course of action. | The recommendation can be evaluated as a candidate for developing a policy or a performance measure. |
| Level 2, "We suggest" | The majority of people in your situation would want the recommended course of action, but many would not. | Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences. | The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined. |

**Table 16 | Determinants of the strength of recommendation**

| Factors | Comment |
|---|---|
| Balance of benefits and harms | The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is provided. The narrower the gradient, the more likely a weak recommendation is warranted. |
| Certainty of evidence | The higher the certainty of evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low certainty of the evidence will warrant a strong recommendation. |
| Values and preferences | The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed by the judgment of the Work Group when robust evidence was not identified. |
| Resource use and costs | The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted. |

*Balance of benefits and harms* – The Work Group determined the anticipated net health benefit on the basis of expected benefits and harms across all critical outcomes from the underlying evidence review.

*The overall certainty of the evidence* – The overall certainty of the evidence for each recommendation is determined by the certainty of evidence for critical outcomes. In general, the overall certainty of evidence is dictated by the critical outcome with the lowest certainty of evidence.[344] This could be modified based on the relative importance of each outcome to the population of interest. The overall certainty of the evidence was graded high (A), moderate (B), low (C), or very low (D) (Table 13).

*Patient values and preferences* – The Work Group included 2 people living with anemia and CKD. These members' unique perspectives and lived experience, in addition to the Work Group understanding of patient preferences and priorities, informed decisions about the strength of the recommendations. A systematic review of qualitative studies on patient priorities and preferences was not undertaken for this guideline.

*Resources and other costs* – Healthcare and non-healthcare resources, including all inputs in the treatment management pathway, were considered in grading the strength of a recommendation.[345] The following resources were considered: direct healthcare costs, non-healthcare resources (such as transportation and social services), informal

caregiver resources, such as time of family and caregivers, and changes in productivity. No formal economic evaluations, including cost-effectiveness analysis, were conducted.

***Practice points***

In addition to graded recommendations, KDIGO guidelines now include "practice points" to help healthcare providers better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care and supplement recommendations. These were developed when no formal systematic evidence review was undertaken or there was deemed to be insufficient evidence to provide a graded recommendation. Practice points represent the expert judgment of the guideline Work Group, and they may be based on limited evidence. Practice points were sometimes formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

***Format for guideline recommendations***

Each guideline recommendation provides an assessment of the strength of the recommendation (Level 1, "we recommend" or Level 2, "we suggest") and the overall certainty of the evidence (A, B, C, D). The recommendation statements are followed by Key information (Balance of benefits and harms, Certainty of the evidence, Values and preferences, Resource use and costs, Considerations for implementation), and Rationale. Each recommendation is linked to relevant SoF tables. An underlying rationale may also support a practice point.

***Limitations of the guideline development process***

Each guideline recommendation provides an assessment of the strength of the recommendation (Level 1, "we recommend" or Level 2, "we suggest") and the overall certainty of the evidence (A, B, C, D). The recommendation statements are followed by Key information (Balance of benefits and harms, Certainty of the evidence, Values and preferences, Resource use and costs, Considerations for implementation), and Rationale. Each recommendation is linked to relevant SoF tables. An underlying rationale may also support a practice point.

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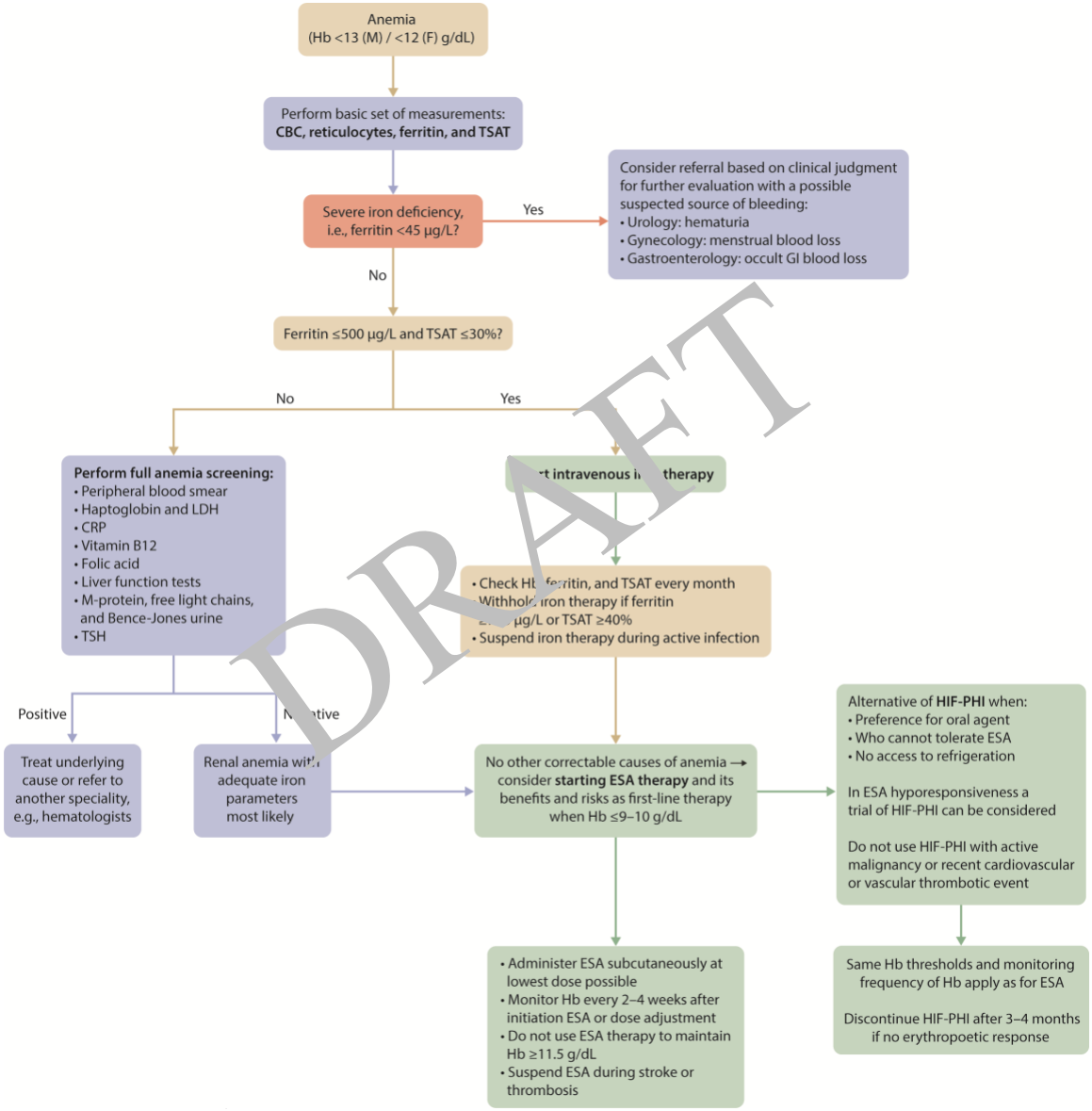
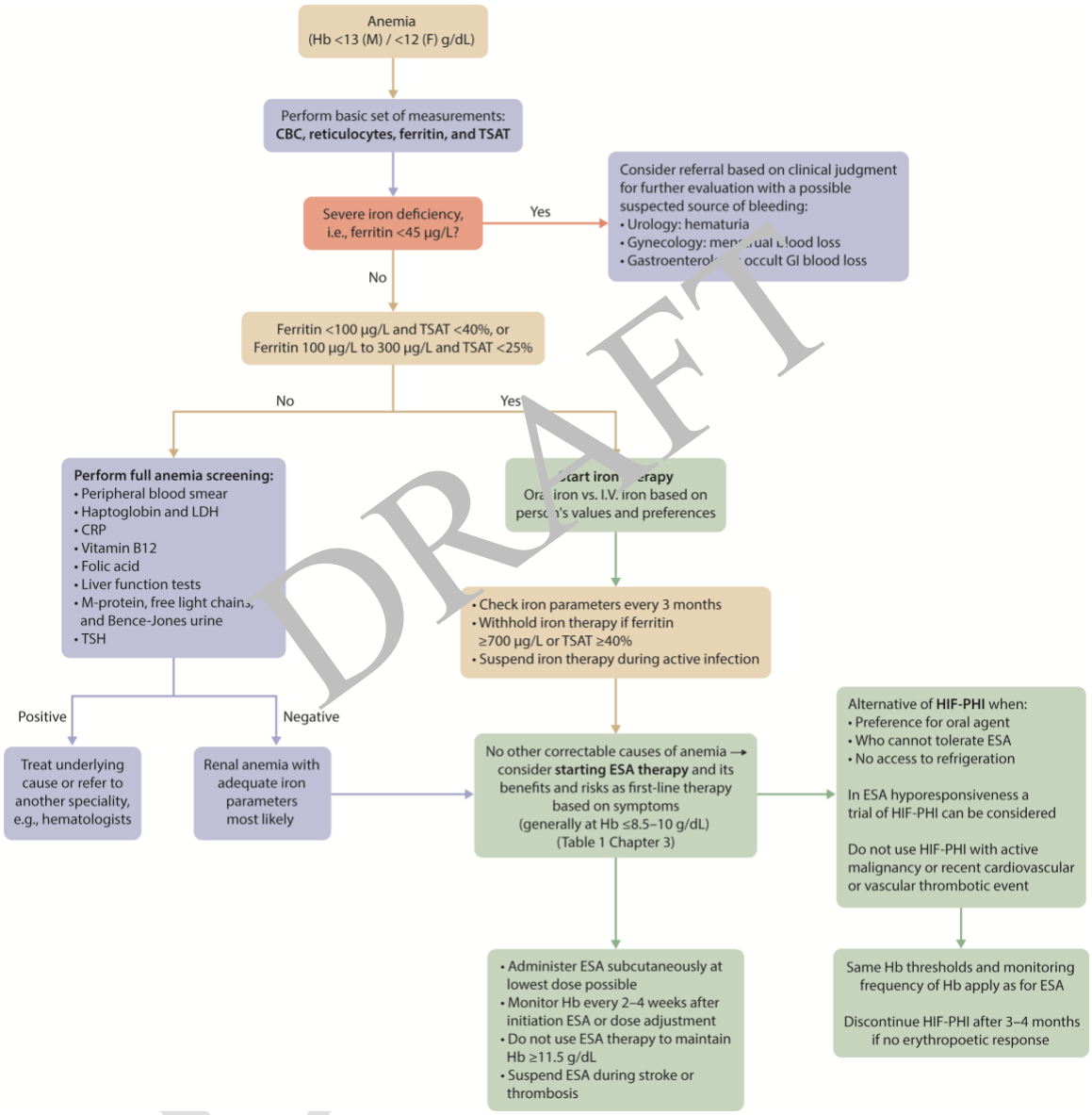
# APPENDIX A. POPULATION-BASED ALGORITHMS FOR THE MANAGEMENT OF ANEMIA IN CKD

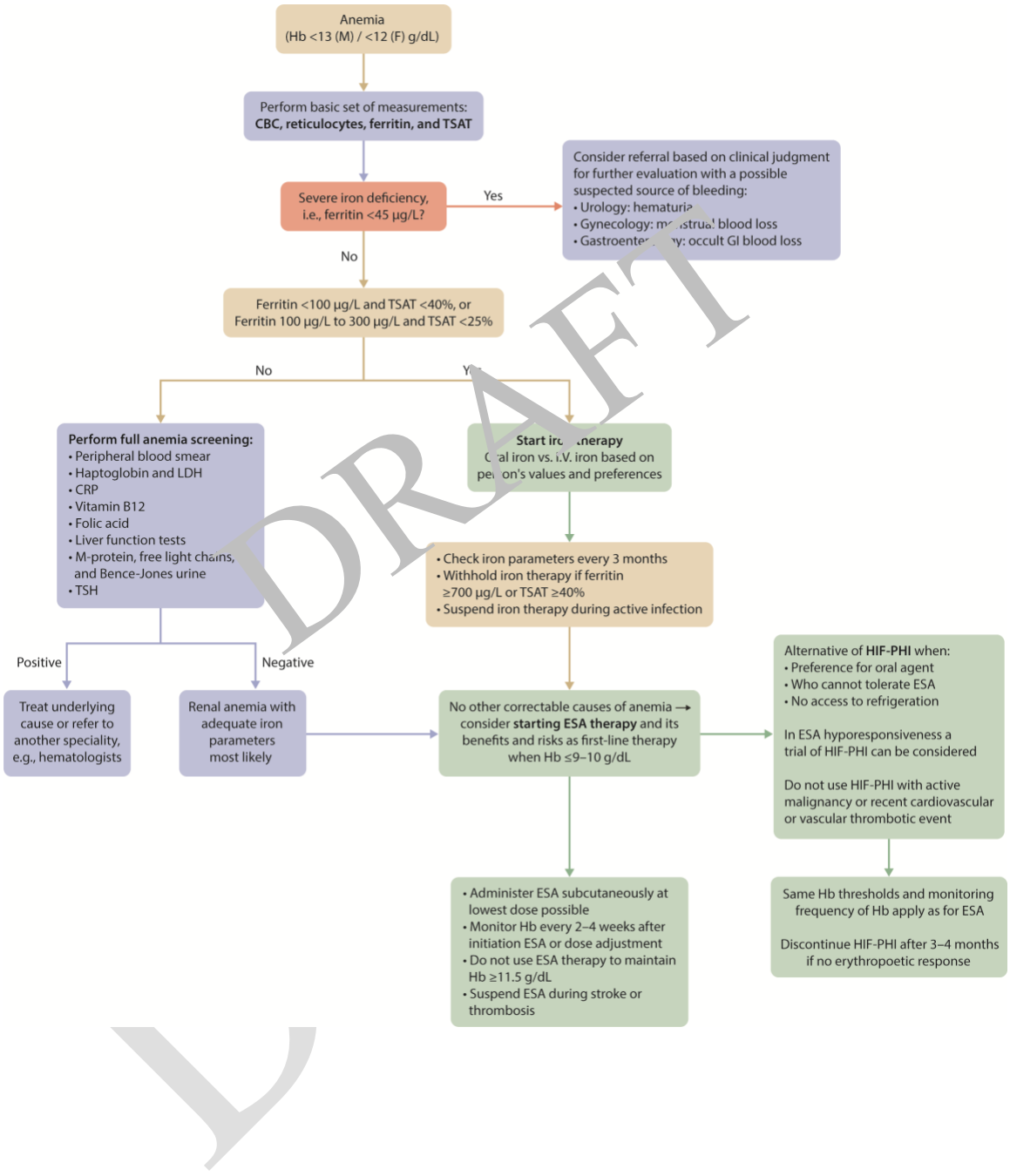
## *Appendix Figure 1. Management of anemia in CKD G5HD*



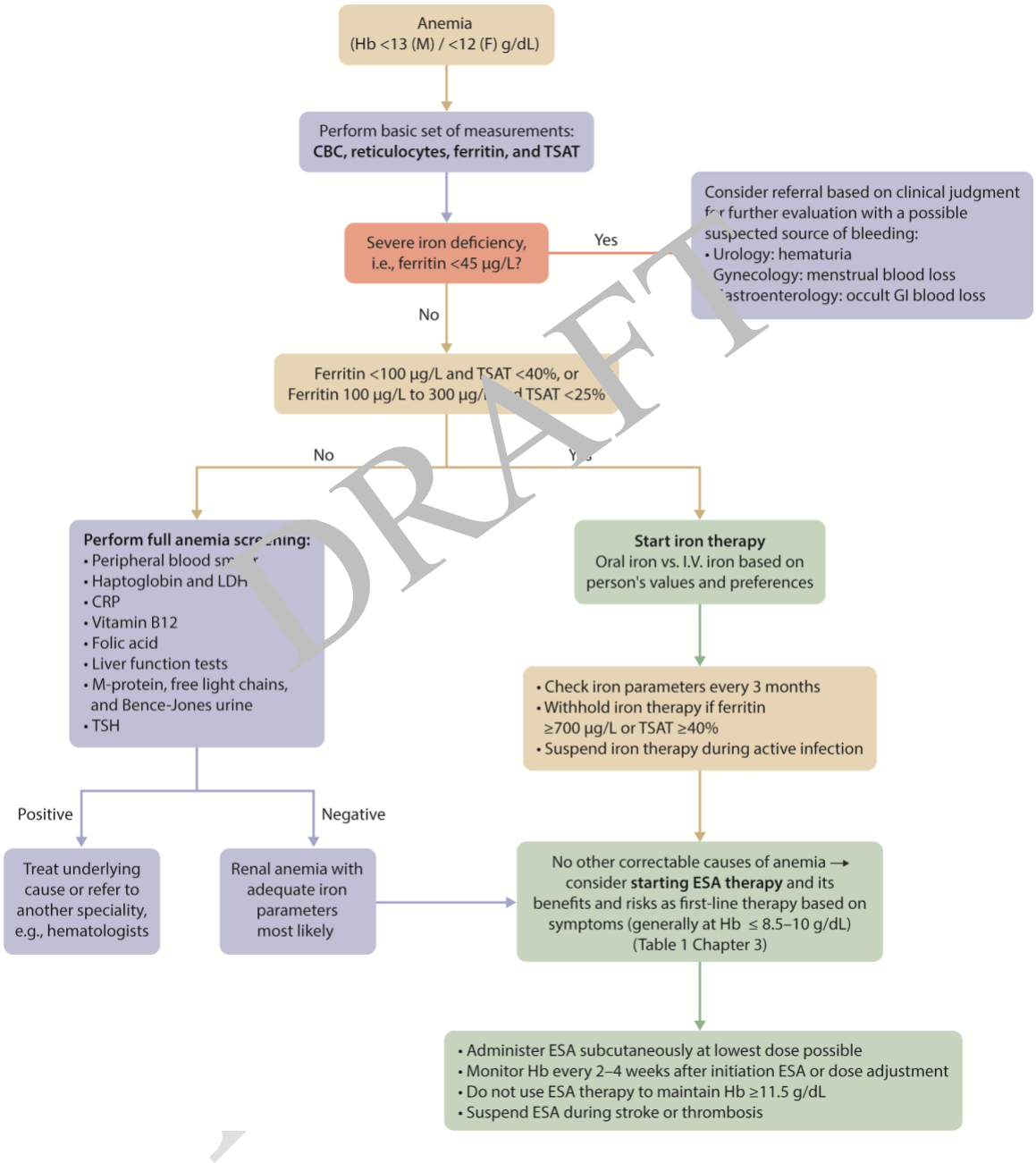
## *Appendix Figure 2. Management of anemia in CKD G1-G5 not receiving dialysis*



## *Appendix Figure 3. Management of anemia in CKD G5PD*



***Appendix Figure 4. Management of anemia and CKD in kidney transplant recipients***



## *Appendix Figure 5. Management of anemia and CKD in children*