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KDIGO 2026 Clinical Practice Guideline for the Management of Anemia in Chronic Kidney Disease (CKD)

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KDIGO 2026 Clinical Practice Guideline for the Management of Anemia in Chronic Kidney Disease (CKD)

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KDIGO EXECUTIVE COMMITTEE

Reference keys

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

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

	Implications		
Grade	**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 recommendations (e.g., frequency of monitoring, provision of standard care [such as regular clinic visits], and referral to specialist care), or to issue "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 defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1–G5), and Albuminuria 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

SI, International System of Units.
Note: Conventional unit × conversion factor = SI unit.

EQUIVALENT ALBUMINURIA CATEGORIES IN CKD

Category	AER (mg/24 h)	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

ACR, albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease.
*Relative to young adult level.

Abbreviations and acronyms

AABB	Association for the Advancement of Blood & Biotherapies
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency
CI	confidence interval
CKD	chronic kidney disease
CKD G5D	chronic kidney disease receiving dialysis
CKD G5HD	chronic kidney disease G5 receiving hemodialysis
CKD G5PD	chronic kidney disease G5 receiving peritoneal dialysis
CRP	C-reactive protein
DRIVE	Dialysis Patients Response to IV Iron with Elevated Ferritin
DSA	donor-specific antibody
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPO	erythropoietin
ERFE	erythroferrone
ERT	Evidence Review Team
ESA	erythropoiesis-stimulating agent
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
GRADE	Grading of Recommendations Assessment, Development and Evaluation
H_1	histamine type 1
Hb	hemoglobin
HD	hemodialysis
HIF-PHI	hypoxia-inducible factor–prolyl hydroxylase inhibitor
HLA	human leukocyte antigen
HR	hazard ratio
HRQoL	health-related quality of life
IL-6	interleukin-6
i.v.	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KRT	kidney replacement therapy
KTR	kidney transplant recipient
LVH	left ventricular hypertrophy
MACE	major adverse cardiovascular event(s)
MCV	mean corpuscular volume
OR	odds ratio
PD	peritoneal dialysis
PICOS	Population, Intervention, Comparator, Outcomes, and Study design
PIVOTAL	Proactive IV irOn Therapy in hemodiALysis patients
PRA	panel reactive antibody
PRCA	pure red cell aplasia
PTA	post-transplant anemia
QoL	quality of life
RBC	red blood cell
RCT	randomized controlled trial
RR	risk ratio
SCr	serum creatinine
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TSAT	transferrin saturation
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 on literature searches last conducted in October 2024. 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.

Foreword

Kidney International (2026) **109** (Suppl 1S), S1–S99; https://doi.org/10.1016/j.kint.2025.06.006

Anemia is a common and serious complication of chronic kidney disease (CKD), affecting patient outcomes and quality of life worldwide. As the understanding of anemia in CKD continues to evolve, so too must our clinical approaches. With this in mind, Kidney Disease: Improving Global Outcomes (KDIGO) is proud to present the updated Clinical Practice Guideline for the Management of Anemia in Chronic Kidney Disease.

This guideline represents a comprehensive and evidence-based update aimed at supporting healthcare providers in the optimal evaluation and management of anemia across all stages of CKD. It reflects not only the latest scientific advancements and emerging therapies but also a commitment to individualized patient care and global applicability. The guideline addresses critical areas including diagnosis, iron management, use of erythropoiesis-stimulating agents, and novel therapeutic strategies, always with an emphasis on balancing benefit, risk, and patient values and preferences.

KDIGO continuously strives to maintain the highest standards of excellence and to provide healthcare providers with the most relevant, evidence-based guidance, incorporating both recent advancements and widely accepted clinical standards through a systematic process. As such, the guideline includes a combination of both graded recommendations and practice points, as put forth in the KDIGO Methods Manual. Graded recommendations are based on a systematic review of the evidence and are graded for the strength of the recommendation (Level 1 or Level 2) and certainty of evidence (A, "high"; B, "moderate"; C, "low"; or D, "very low"). Practice points are ungraded, consensus-based statements representing the expert judgment of the Work Group. Although practice points are issued when there has not been a systematic review, most practice points aim to inform the implementation of graded recommendations; they are often provided in a graphical format. Readers should consider practice points to be expert guidance or "good practice statements" and use them as they see fit to inform the care of patients.

To ensure transparency during guideline development, the draft guideline update was made publicly available for comment as per KDIGO policy. We very much appreciate the valuable feedback received from the scientific community, contributing to the clinical relevance and global applicability of the guideline. All Work Group members have revised and approved the update for formal release.

The development of this guideline would not have been possible without the tireless efforts of the dedicated individuals who contributed their time, expertise, and insight. We extend our sincere thanks to the Co-Chairs of the guideline—Jodie L. Babitt, MD, and Marcello Tonelli, MD, SM, MSc, FRCPC—for their outstanding leadership and vision throughout the process. We are equally grateful to the members of the Work Group, Evidence Review Team, and KDIGO staff for their collaboration, rigor, and consistent commitment to excellence.

We hope that this guideline will be a valuable tool in improving the care and outcomes of patients with CKD-related anemia, and we invite clinicians, researchers, and policymakers to use it as a foundation for best practices and continued innovation.

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Abstract

The Kidney Disease: Improving Global Outcomes (KDIGO) 2026 Clinical Practice Guideline for the Management of 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 receiving kidney replacement therapy or not. The guideline includes chapters dedicated to diagnosis and evaluation of anemia in CKD, use of iron to treat iron deficiency and anemia in people with CKD, use of erythropoiesis-stimulating agents, hypoxia-inducible factor–prolyl hydroxylase inhibitors, and other agents to treat anemia in people with CKD, and red blood cell transfusions to treat anemia in people with CKD. New nomenclature is proposed to define different states of iron deficiency, replacing "absolute iron deficiency" with "systemic iron deficiency" and "functional iron deficiency" with "iron-restricted erythropoiesis" to more accurately reflect the pathophysiological state. The update considers evidence from randomized controlled trials published through October 2024. The guideline provides actionable recommendations based on a rigorous formal evidence review with practice points and supporting infographics to aid in the implementation of guideline recommendations. The target audience for the guideline includes providers involved in the care of people with anemia and CKD as well as people with anemia and CKD themselves. Development of this 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 strength of the 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; GRADE; guideline; KDIGO; systematic review

CITATION

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Introduction from the Guideline Co-Chairs

Anemia is a common complication of chronic kidney disease (CKD) and is increasingly prevalent in people with lower glomerular filtration rate. Anemia is associated with a substantial burden of morbidity and mortality, including reduced functional capacity, poor quality of life, and increased risks of cardiovascular disease and death. Accordingly, management of anemia is an essential element of contemporary nephrology practice.

There have been several relevant new developments since the publication of the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Anemia in CKD. A better understanding of the mechanisms causing anemia in this population, new evidence on strategies for iron supplementation, and novel agents such as hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs) have all emerged in recent years. However, there is continued uncertainty regarding the indications to start treatment, the optimal treatment targets, and how best to reduce the risk of medication-related adverse events.

The KDIGO 2026 Clinical Practice Guideline for the Management of Anemia in CKD uses the latest available evidence to update the 2012 guideline. The guideline aims to help healthcare providers and patients make informed decisions across the spectrum of kidney disease, including CKD populations not receiving dialysis to those receiving hemodialysis or peritoneal dialysis or having a kidney transplant — for both adults and children.

The Work Group commissioned a rigorous systematic review of available evidence from the expert Evidence Review Team. Particular attention was given to new clinical trial data evaluating iron supplementation strategies, erythropoiesis-stimulating agents (ESAs), HIF-PHIs, and the role of red blood cell transfusions. The recommendations aim to balance efficacy, safety, patient preferences, considerations for implementation, and resource considerations. The Work Group did its best to indicate where evidence was lacking and to explain the factors that influenced the strength and direction of each recommendation. As in recent KDIGO guidelines, a selection of practice points is presented to advise clinicians on practical aspects of care for which a systematic review was not performed.

The guideline is organized into 4 chapters. Chapter 1 discusses the evaluation and diagnosis of anemia in CKD. Chapter 2 focuses on iron management, including indications for iron supplementation and factors that could influence its route of administration. Chapter 3 presents guidance on the initiation and monitoring of ESAs and HIF-PHIs. Chapter 4 discusses the role of red blood cell transfusions. Each chapter includes recommendations and/or practice points. Where recommendations are issued, supporting rationale and considerations for implementation are provided. Where possible, Level 2 recommendations are accompanied by a discussion of the factors that might lead healthcare providers to follow (or not follow) that recommendation in a specific patient. The guideline also identifies areas where additional research is needed to guide future practice and provides comprehensive population-based algorithms that summarize the guidance for the management of anemia (Appendix A).

As with all KDIGO guidance, the anemia guideline is intended to inform but not dictate practice; individual patient circumstances, preferences, and clinical judgment remain critical for decision-making. The guideline was developed using internationally accepted processes for guideline development, acknowledging that recommendations will evolve as new evidence emerges.

Throughout the guideline, emphasis is placed on patient-centered care and individualized treatment decisions based on each patient's values and preferences. The Work Group has attempted to ensure that the guidance is relevant for a global audience practicing in a wide range of clinical settings.

We thank the members of the Work Group, the Evidence Review Team, the external reviewers, and above all the dedicated KDIGO staff for their contributions to this guideline.

Jodie L. Babitt, MD
Marcello Tonelli, MD, SM, MSc, FRCPC
Anemia Guideline Co-Chairs

Summary of recommendation statements and practice points

Chapter 1: Diagnosis and evaluation of anemia in people with chronic kidney disease

1.1 Anemia in CKD

Definition of anemia in CKD

[No recommendations or practice points]

Prevalence of anemia in CKD

[No recommendations or practice points]

Pathophysiology of anemia in CKD

[No recommendations or practice points]

Outcomes associated with anemia in CKD

[No recommendations or practice points]

1.2 Iron deficiency in CKD

Definition of iron deficiency in CKD

[No recommendations or practice points]

Prevalence of iron deficiency in CKD

[No recommendations or practice points]

Pathophysiology of iron deficiency in CKD

[No recommendations or practice points]

Outcomes associated with iron deficiency in CKD

[No recommendations or practice points]

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

Practice Point 1.2.1: **In people with chronic kidney disease (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, reticulocytes (reticulocyte production index), ferritin, and 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) population. The suggested intervals are minimum frequencies to measure hemoglobin levels. In patients using erythropoiesis-stimulating agents or hypoxia-inducible factor-prolyl hydroxylase inhibitors, those with hemoglobin levels below the target range, or those experiencing a rapid progression of CKD, a higher testing frequency is advised. CKD G5D, CKD G5 receiving dialysis.

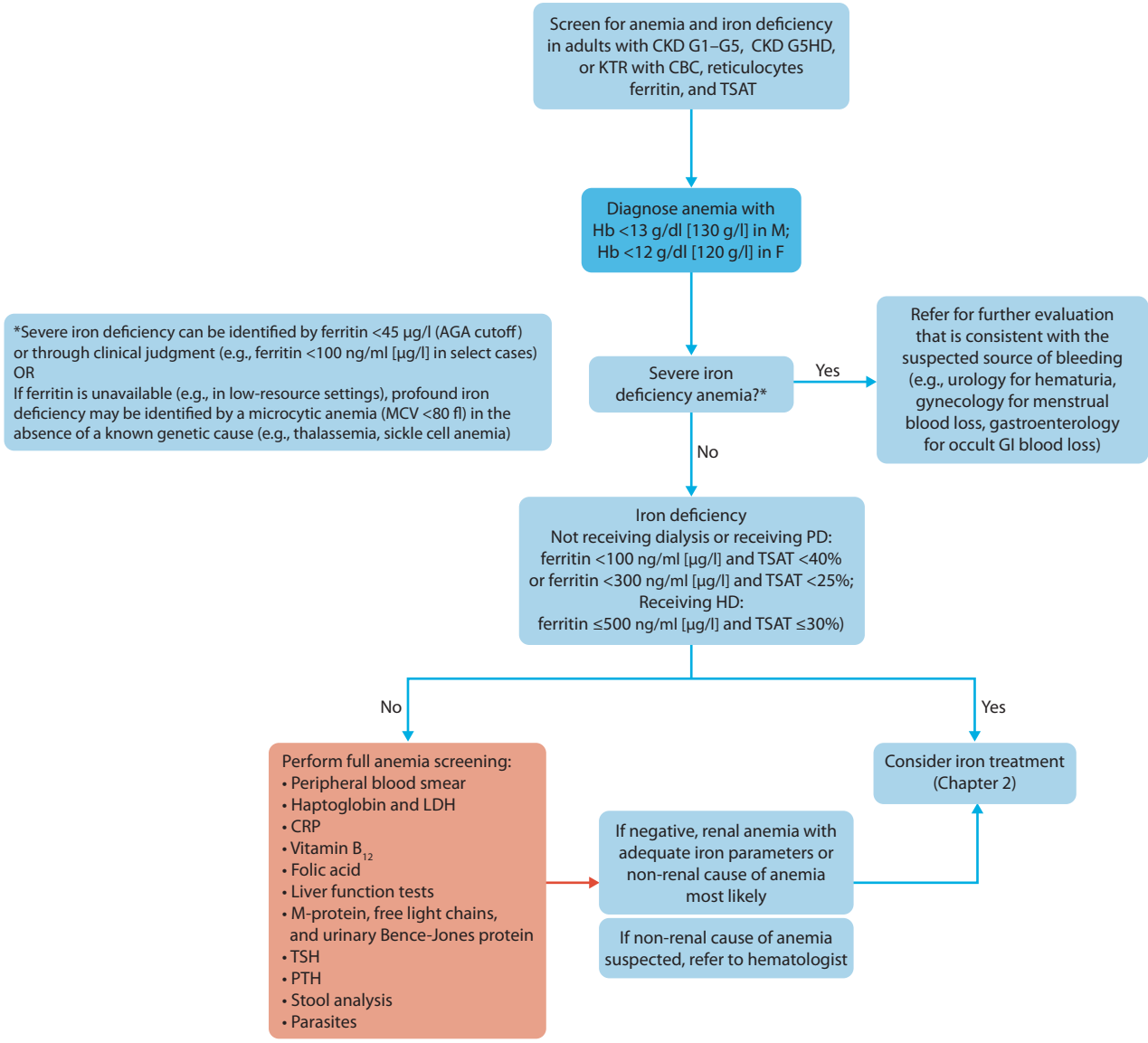


Figure 6 | Flowchart of the different steps to follow when people with chronic kidney disease (CKD) have anemia. AGA, American Gastroenterological Association; CBC, complete blood count; CKD G1–G5, chronic kidney disease not receiving dialysis; CKD G5HD, chronic kidney disease G5 receiving hemodialysis;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

Practice Point 1.2.2: In people with anemia and CKD in whom the initial tests do not reveal the cause, consider an expanded panel to identify potential underlying causes as warranted based on the clinical scenario:

- Blood smear review
- Haptoglobin
- Lactate dehydrogenase
- C-reactive protein
- Vitamin B_{12}
- Folate
- Liver function tests
- Serum protein electrophoresis with immunofixation, serum free light chains, and urinary Bence-Jones protein
- Thyroid-stimulating hormone
- Parathyroid hormone
- Fecal occult blood test.

Practice Point 1.2.3: In people with anemia and CKD who have ferritin <45 ng/ml (<45 μg/l) or microcytic anemia (mean corpuscular volume <80 fl) in the absence of measured ferritin or known genetic cause, and where the cause of iron deficiency is uncertain, consider clinical evaluation for blood loss. Referral to gastroenterologists/gynecologists/urologists may be appropriate to identify the cause.

Chapter 2: Use of iron to treat iron deficiency and anemia in people with chronic kidney disease

Recommendation 2.1: In people with anemia and CKD G5 receiving 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 who are initiating iron therapy, we suggest using intravenous (i.v.) iron rather than oral iron (*2D*).

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

Recommendation 2.3: In people with anemia and CKD not receiving dialysis or CKD G5 receiving peritoneal dialysis (CKD G5PD), we suggest initiating iron if (*2D*):

- **Ferritin <100 ng/ml (<100 μg/l) and 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 (HD) in whom iron is initiated, we suggest using either oral iron or i.v. iron based on the person's values and preferences, the degree of anemia and iron deficiency, and the relative efficacy, tolerability, availability, and cost of each (*2D*).

Practice Point 2.2: In people with CKD treated with iron, it is reasonable to withhold routine 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 i.v. iron, the choice between different formulations is guided by cost, individual patient preference, safety, tolerability, and recommended dosing schedules.

Practice Point 2.5: In people with CKD treated with iron, it is reasonable to test hemoglobin (Hb), ferritin, and TSAT every 3 months for those with CKD not receiving dialysis or CKD G5PD and every 1–3 months 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 testings

- Initiation of or increase in the dose of erythropoiesis-stimulating agents (ESAs) or hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs)
- Episodes of known blood loss
- Recent hospitalization
- Important increase in ferritin or transferrin saturation (TSAT) or overshooting target limit

Practice Point 2.7: **Switch from oral to i.v. iron if there is an insufficient effect of an optimal oral regimen after 1–3 months or if tolerability is poor.**

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 i.v. iron, considerations pertaining to hypersensitivity reactions to i.v. iron include the following:**

- **Intravenous iron should be administered only 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 (i.e., histamine type 1 channel blockers)**
- **Test doses of i.v. iron are not usually required, because lack of response does not predict the risk of hypersensitivity.**

Table 4 | Intravenous iron formulations and treatment regimens

Iron formulation	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 h	>60 min	Hypersensitivity lower than with high-molecular-weight dextran
Iron sucrose	20 mg/ml	CKD: 200 mg PD: 400 mg	15 min 2.5 h	5 min	For people with CKD G1–G5 not receiving HD, multiple patient visits are required because 1000 mg cannot be given in a single sitting: CKD: 5 doses of 200 mg over 5 wk PD: 2 infusions of 300 mg over 1.5 h 14 d apart followed by one 400 mg infusion over 2.5 h 14 d later
Ferric gluconate	12.5 mg/ml	125 mg	60 min	10 min	Ferric gluconate in sucrose complex (250 mg 4 doses weekly)
Ferric carboxymaltose	50 mg/ml	750 mg (FDA) 1000 mg (EMA)	15 min	7.5 min (FDA) 15 min (EMA)	Full dose can be given in 1 or 2 sittings (750 mg 2 doses 1 wk apart) May cause hypophosphatemia, especially in people with early CKD and kidney transplant recipients
Ferric derisomaltose/ iron isomaltoside	100 mg/ml	1000 mg (FDA) 20 mg/kg (EMA)	20 min (FDA) >15 min if ≤1000 mg; >30 min if >1000 mg (EMA)	250 mg/min (maximum 500 mg) (EMA)	Full dose can be given in a single sitting
Ferumoxytol	30 mg/ml	510 mg	15 min	15 min	Full dose can be given in a single sitting Hypersensitivity (due to bolus dosing) rarely occurs

CKD, chronic kidney disease; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD, hemodialysis; i.v., intravenous; PD, peritoneal dialysis.

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

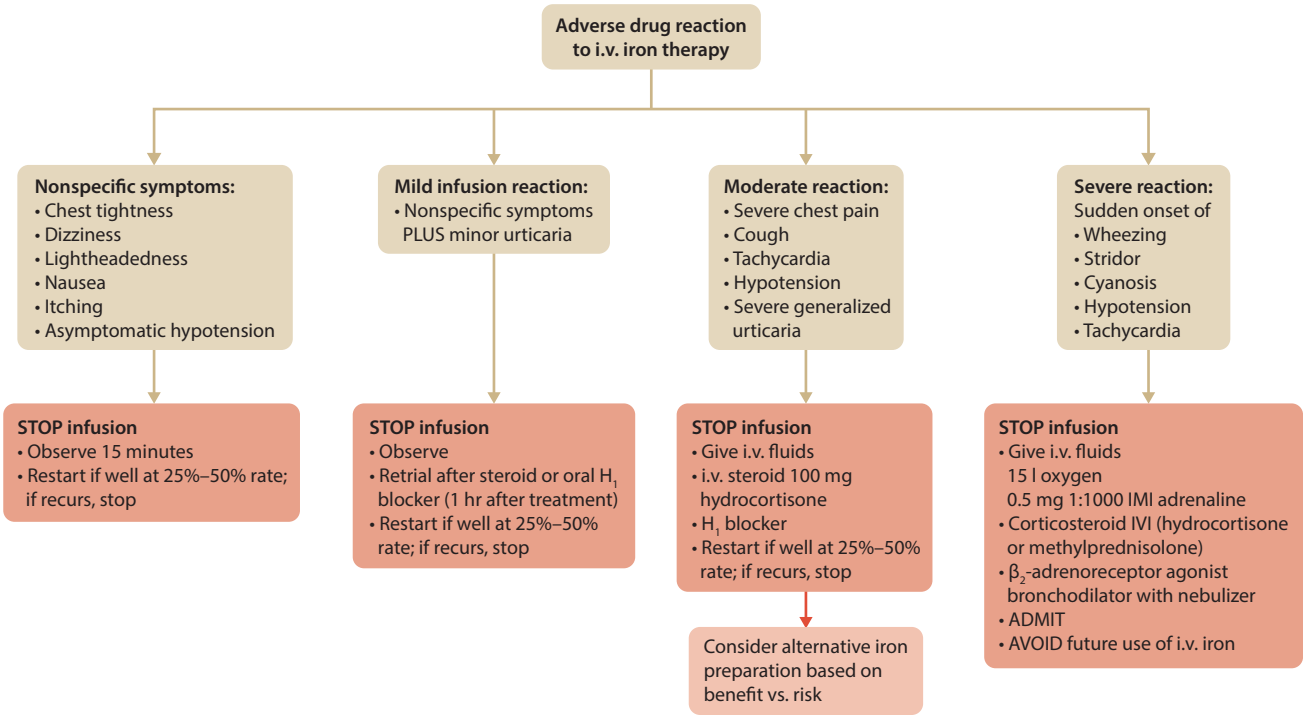


Figure 7 | Suggested management of reactions to intravenous (i.v.) iron. H_1, histamine type 1; IMI, intramuscular injection; IVI, intravenous infusion.

Practice Point 2.11: **In people with CKD and profound iron deficiency (ferritin <30 ng/ml [<30 μg/l] and TSAT <20%) but no anemia, consider treatment with oral or i.v. iron.**

Chapter 3: Use of erythropoiesis-stimulating agents, hypoxia-inducible factor–prolyl hydroxylase inhibitors, and other agents to treat anemia in people with chronic kidney disease

3.1 Treatment initiation

Practice Point 3.1.1: **In people with anemia and CKD (whether receiving dialysis or not), the decision to use erythropoiesis-stimulating agents (ESAs) or hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs) to raise Hb should be made through a shared decision-making process, considering each individual's symptoms, potential for harm from red blood cell (RBC) transfusions, and potential risk of adverse events (e.g., stroke, cardiovascular event, and cancer).**

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

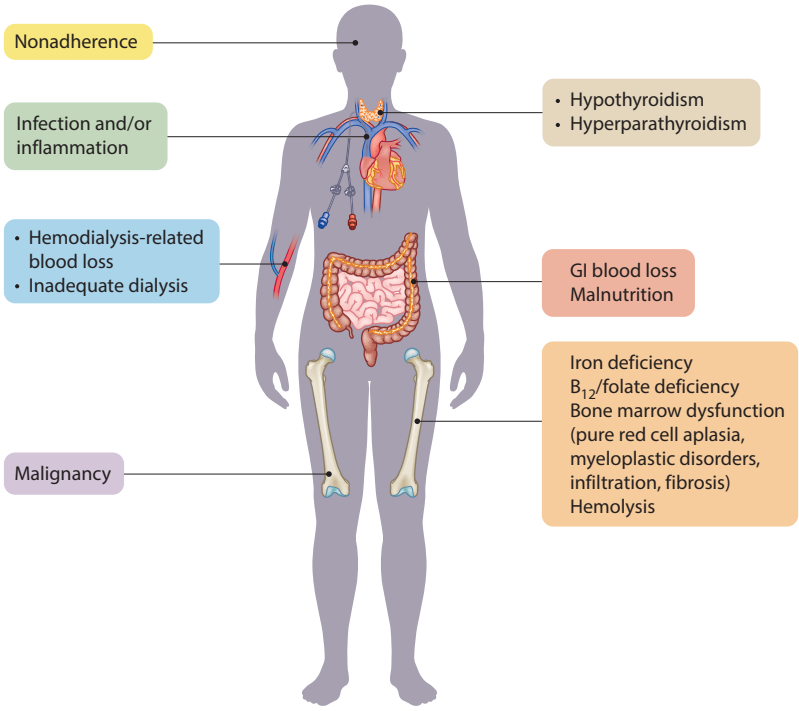


Figure 8 | Potentially reversible causes of anemia in chronic kidney disease in addition to decreased erythropoietin production. GI, gastrointestinal.

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 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 for adverse events (Table 6).**

Table 6 | Considerations for people with anemia and CKD at risk for adverse events with HIF-PHIs

Theoretical risk or experimental evidence of disease development or progression	Concern about risk based on adverse event profiles in clinical trials	Insufficient data to assess risk; dedicated studies needed
• Active cancer or with a history of cancer not in complete remission for at least 2–5 yr (based on trial exclusion criteria)[231] • Polycystic kidney disease[232] • Proliferative retinal disease[233,234] • Pulmonary arterial hypertension[235–237] • Pregnancy[a]	• Prior cardiovascular events (i.e., stroke and myocardial infarction)[231] • Prior thromboembolic events (i.e., deep venous thrombosis and pulmonary embolism)[231] • Prior vascular access thrombosis[231] • Hepatic impairment[b] • Seizures, exfoliative dermatitis, hypothyroidism, and bacterial infections/sepsis (roxadustat)[238]	• Post–kidney transplant anemia[231] • Children[239]

CKD, chronic kidney disease; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor.
[a]HIF-PHIs are contraindicated in pregnancy. Please refer to the package inserts for individual compounds for specific guidance.
[b]Caution is advised in patients with hepatic impairment. HIF-PHIs are not recommended for patients with significant hepatic impairment. Please refer to the package inserts for individual compounds for specific guidance.

3.2 ESA initiation

Recommendation 3.2.1: In people with anemia and CKD G5D receiving HD or peritoneal dialysis, 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 transfusions or ESA therapy (*2D*).

3.3 ESA maintenance therapy

Recommendation 3.3.1: In adults with anemia and CKD treated with ESAs, we recommend targeting the Hb level to below 11.5 g/dl (115 g/l) (*1D*).

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

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

3.4.1 ESA dosing

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

Table 7 | Dosing of ESAs

ESA	Initial dose	Dose adjustment[a]
Epoetin alfa and beta	CKD not receiving dialysis: ∼50 U/kg once or twice weekly (some use up to 100 U/kg once every 2 wk) (may also round to a convenient dose in units, such as 4000 or 10,000 U, using the lower dose range once or twice weekly and a higher dose range every 2 wk)	CKD not receiving dialysis: Increase or decrease the dose and/or dosing frequency as needed (generally not given more than once weekly)
	CKD G5D: 50–100 U/kg 3 times weekly (may round to a convenient dose in units)	CKD G5D: Increase the dose by 25 U/kg/dose if Hb rise is <1.0 g/dl (<10 g/l) after 4 wk. Decrease the dose by 10–25 U/kg/dose if Hb rise is >2 g/dl (>20 g/l) in 4 wk
Erythropoietin biosimilars	*Product names and doses vary by region (refer to individual product information)*	
Darbepoetin	CKD not receiving dialysis: 0.45 μg/kg weekly or 40–100 μg every 2–4 wk	CKD not receiving dialysis: Increase or decrease the dose and/or dosing frequency as needed (generally not given more than once weekly)
	CKD G5D: 0.45 μg/kg weekly or 0.75 μg/kg every 2 wk (may round to convenient dose: 25, 40, 60, 100, 150, or 200 μg; 300 and 500 μg also available)	CKD G5D: Increase the dose by 25% if Hb rise is <1.0 g/dl (<10 g/l) after 4 wk. Decrease the dose by 25% if Hb rise is >2 g/dl (>20 g/l) in 4 wk
Methyl polyethylene glycol–epoetin beta	CKD not receiving dialysis: 0.6 μg/kg or 50–120 μg every 2 wk, or 1.5 mg/kg or 120–200 μg/kg every month	CKD not receiving dialysis: Increase or decrease the dose and/or dosing frequency as needed (generally not given more than once every 2 wk)
	CKD G5D: 0.6 μg/kg every 2 wk (may round to a convenient dose)	CKD G5D: Increase the dose by 30–50 μg/dose if Hb rise is <1.0 g/dl (<10 g/l) in 4 wk. Decrease the dose by 30–50 μg/dose if Hb rise is >2 g/dl (>20 g/l) in 4 wk

CKD, chronic kidney disease; CKD G5D, CKD G5 receiving dialysis; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.
[a]Refer to product labeling or dialysis facility protocols for other details of dosing and conversion from an ESA. In general, weight-based dosing is used for children.

Practice Point 3.4.1.2: In people with anemia and CKD treated with ESAs, avoid adjusting the dose of the ESA more frequently than once every 4 weeks. The exception is when Hb increases by >1.0 g/dl (>10 g/l) in 2–4 weeks after the 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 ESAs, administer ESAs with the lowest dose possible that achieves and maintains 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 ESAs, 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, those with CKD G5PD, or kidney transplant recipients receiving ESA therapy, administer ESA via the subcutaneous route.

3.4.3 Frequency of administration and monitoring of ESAs

Practice Point 3.4.3.1: In people with CKD G5D or CKD not receiving dialysis, individualize the frequency of ESA administration 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 a 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. To avoid a rapid decline in Hb, consider reducing the ESA dose rather than holding ESA therapy, as long as the Hb does not exceed 11.5 g/dl (115 g/l).

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

Practice Point 3.4.3.4: In people with anemia and CKD treated with ESAs, it is reasonable to suspend the 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 cancer treatment is aimed at cure, with a target Hb that minimizes transfusion needs.

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, and 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 HIF-PHIs approved for marketing as of October 2024

HIF-PHI[a]	Recommended dosing for treatment initiation	Maximum daily dose	Dose frequency	Drug metabolism and transport
Daprodustat	CKD not receiving dialysis: 2–∼4 mg (ESA-naive), 4 mg (switch from ESA) CKD G5D: Japan, 4 mg; the United States, 1–∼4 mg (ESA-naive), 4–12 mg (switch from ESA)	24 mg	Daily	CYP2C8[265]
Desidustat	CKD not receiving dialysis: 100 mg (ESA-naive), 100, 125, or 150 mg (switch from ESA) CKD G5D: 100 mg (ESA-naive), 100, 125, or 150 mg (switch from ESA)	150 mg	3 times weekly	Not inhibitor of CYP1A2, 2C8, 2C9, 2C19, 2D6, or 3A4/5[266] Not inducer of CYP1A2 or CYP3A4/5[266]
Enarodustat	CKD not receiving dialysis and CKD G5PD: 2 mg (ESA-naive and switch from ESA) CKD G5HD: 4 mg (ESA-naive and switch from ESA)	8 mg	Daily	CYP2C8, CYP2C9, or CYP3A4[267]
Molidustat	CKD not receiving dialysis: 25 mg (ESA-naive), 25–∼50 mg (switch from ESA) CKD G5D: 75 mg (ESA-naive and switch from ESA)	200 mg	Daily	UGT1A1 or UGT1A9[268]
Roxadustat	CKD not receiving dialysis and CKD G5D (ESA-naive): European Union, 70 mg for body weight <100 kg, 100 mg for body weight ≥100 kg; Japan, 50 mg CKD not receiving dialysis (switch from ESA): European Union, 70–200 mg; Japan, 70–100 mg	3.0 mg/kg body weight	3 times weekly	CYP2C8, UGT1A9, BCRP, OATP1B1, OAT1, or OAT3[238] Inhibitor of CYP2C8, BCRP, OATP1B1, or OAT3[238,269]
Vadadustat	300 mg (ESA-naive and switch from ESA)	600 mg	Daily	UGT1A1, 1A7, 1A8, 1A9, BCRP, and OAT3[270] Inhibitor of CYP2C8 (*in vitro*), BCRP, or OAT3 and inducer of CYP2B6 (*in vitro*)[270,271]

BCRP, breast cancer resistance protein (adenosine triphosphate–binding cassette transporter family member); CKD, chronic kidney disease; CKD G5D, CKD G5 receiving dialysis; CKD G5HD, chronic kidney disease G5 receiving hemodialysis; CKD G5PD, chronic kidney disease G5 receiving peritoneal dialysis; CYP, cytochrome P450; ESA, erythropoiesis-stimulating agent; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; OAT, organic ion transporter; UGT, uridine 5'-diphospho-glucuronosyltransferase.
[a]Approval for use in specific patient populations varies by country.
More detailed information about drug-drug interactions between individual HIF-PHIs and other drugs can be found in the package inserts and product information documents issued by regulatory agencies. This table was based on information available in early 2024; labeling information may change over time. Use of a lower starting dose of any of the HIF-PHIs is reasonable.

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 administering HIF-PHIs, monitor Hb levels 2–4 weeks after initiation or dose adjustments and subsequently every 4 weeks during therapy.

Practice Point 3.6.2: In people with anemia and CKD treated with roxadustat, periodic monitoring of thyroid function is recommended during the first 3 months of treatment and as clinically indicated subsequently.

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 or myocardial infarction), thromboembolic events (e.g., deep vein thrombosis or pulmonary embolism), vascular access thrombosis, or newly diagnosed cancer. Individualize consideration for HIF-PHI reinitiation or ESA initiation based on Hb levels and patient characteristics and preferences after discussion of risks and benefits of treatment.

3.7 ESA hyporesponsiveness

Practice Point 3.7.1: **In people with anemia and CKD G5D or 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 Hb to avoid transfusion or improve symptoms attributable to anemia, a trial course of HIF-PHI may be considered after discussion of potential risks and benefits (Figure 10).**

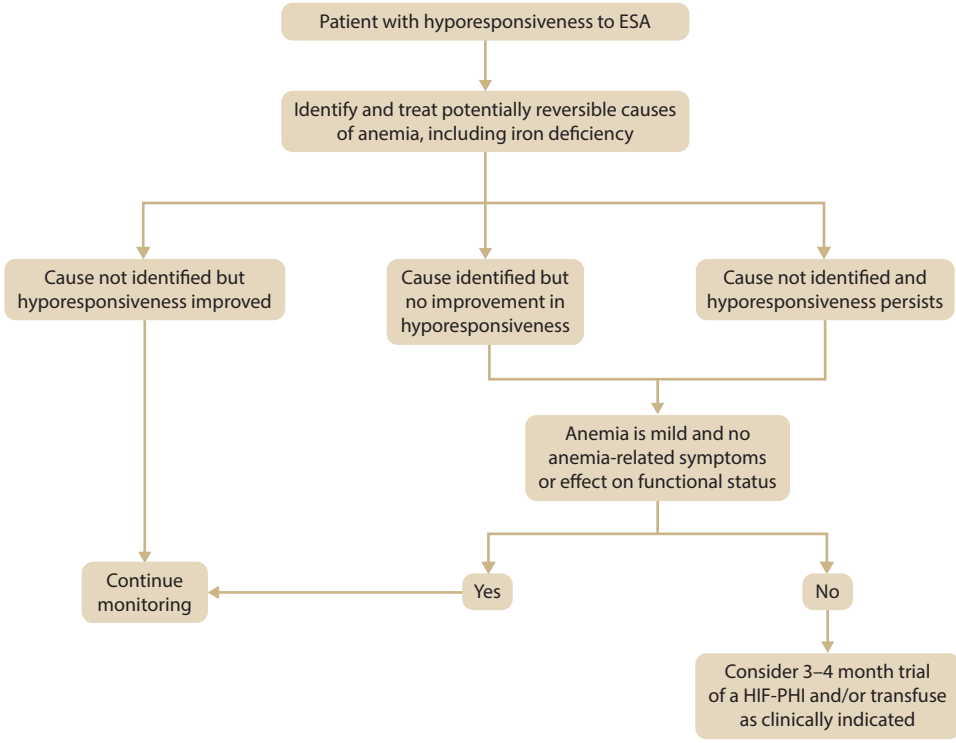


Figure 10 | Treatment algorithm for sustained erythropoiesis-stimulating agent (ESA) hyporesponsiveness. For definition of hyporesponsiveness, refer to Table 10. See Figure 8 for potentially reversible causes of anemia in chronic kidney disease. HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor.

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

Practice Point 3.7.4: **In people with CKD, anemia, and ESA hyporesponsiveness, if a desired erythropoietic response has not been achieved after 3–4 months of initiating HIF-PHIs, 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-PHIs.**

Practice Point 3.7.6: **In people with suspected ESA-related pure red cell aplasia, discontinue the ESA, transfuse as clinically appropriate, and consider referral to a hematologist, use of immunosuppressive medications, and use of a HIF-PHI for subsequent treatment of anemia based on patient preferences after consideration of risks and benefits.**

Chapter 4: Red blood cell transfusions to treat anemia in people with chronic kidney disease

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

Potential harms of RBC transfusions

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.**

Effect of leukocyte-reduced RBC transfusions on allosensitization

[No recommendations or practice points]

Effect of allosensitization on time to transplantation and outcomes

Practice Point 4.3: **In people with CKD and chronic anemia, consider that the benefits of RBC transfusion may outweigh its harms in people in whom**
- **ESA or HIF-PHI therapy is ineffective (e.g., those with hemoglobinopathies, bone marrow failure, or ESA or HIF-PHI resistance)**
- **ESA or HIF-PHI therapy may be harmful (e.g., those with previous or current malignancy or previous stroke).**

Practice Point 4.4: **In people with anemia and CKD, base the decision to transfuse 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 or unstable coronary artery disease)**
- **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 RBC transfusions in people with 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, base the decision for RBC transfusion on whether the person is a potential transplant candidate.

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; RBC, red blood cell.
Adapted with permission from Brenner N, Kommalapati A, Ahsan M, et al. Red cell transfusion in chronic kidney disease in the United States in the current era of erythropoiesis stimulating agents. *J Nephrol.* 2022;33:267–275.[313]

Chapter 1: Diagnosis and evaluation of anemia in people with chronic kidney disease

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. Anemia should be evaluated independently of CKD stage to identify any additional underlying processes contributing to anemia beyond CKD *per se*, which is uncommon in earlier stages (CKD G1–G2). A comprehensive list of causes and the approach to diagnosis can be found in standard medical textbooks. This guideline focuses specifically on anemia in people with CKD, as well as one of its common causes: 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.

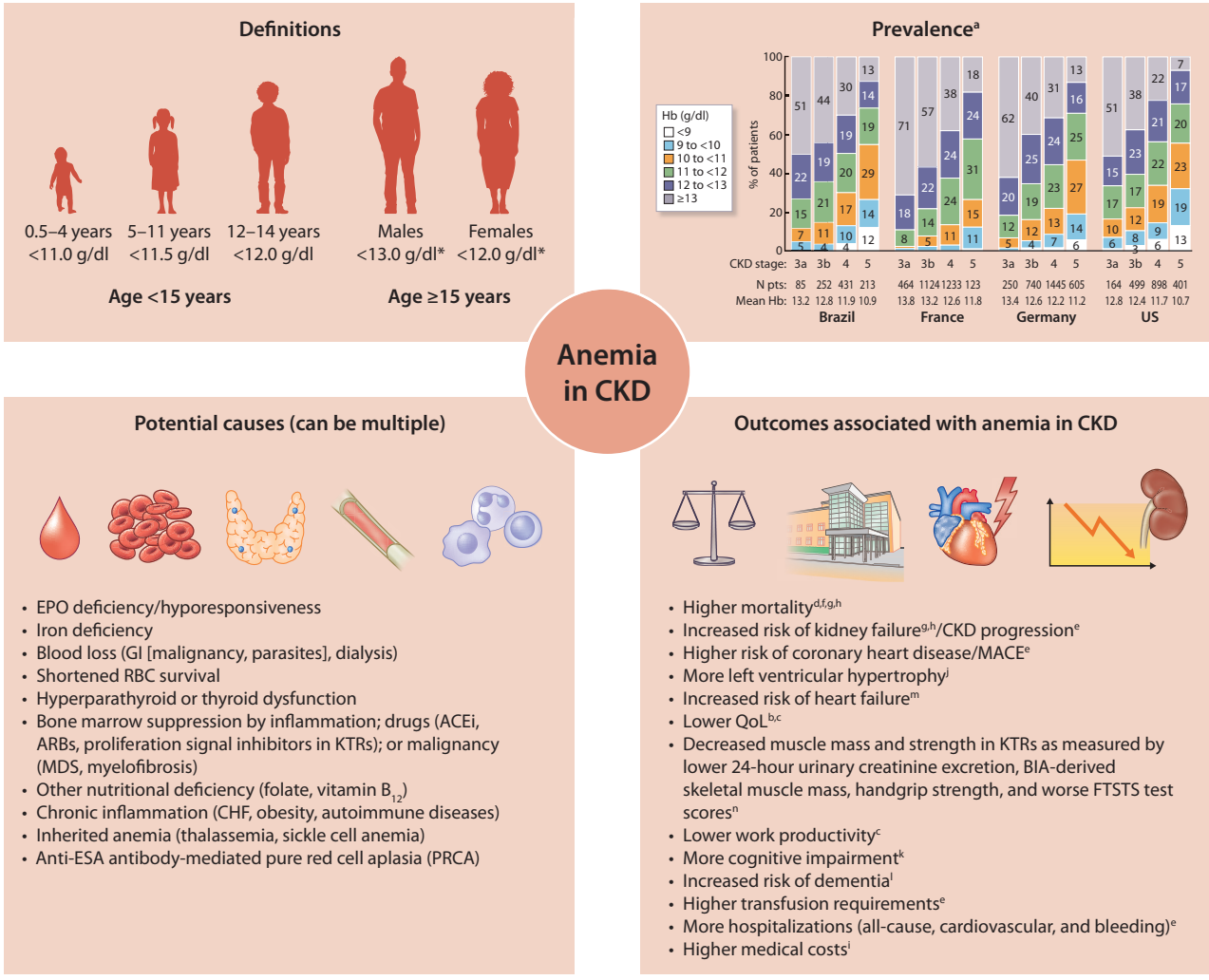


Figure 1 | Overview of anemia in chronic kidney disease (CKD) with its definition, prevalence across CKD stages, potential causes, and associated outcomes. *Specific cutoffs for age and sex are provided. ACEi, angiotensin-converting enzyme inhibitor(s); ARB, angiotensin II receptor blocker; BIA, bioelectrical impedance analysis; CHF, congestive heart failure; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FTSTS, Five Times Sit-to-Stand; GI, gastrointestinal; Hb, hemoglobin; KTR, kidney transplant recipient; MACE, major adverse cardiovascular events; MDS, myelodysplastic syndrome; QoL, quality of life; RBC, red blood cell. [a]Wong *et al.*,[1] *Clin Kidney J.* (2020); [b]Moreno *et al.*,[2] *Nephrol Dial Transplant*. (1996); [c]van Haalen *et al.*,[3] *BMC Nephrol*. (2020); [d]Astor *et al.*,[4] *Am Heart J.* (2006); [e]Lamerato *et al.*,[5] *BMC Nephrol*. (2022); [f]Al-Ahmad *et al.*,[6] *J Am Coll Cardiol.* (2001); [g]Kovesdy *et al.*,[7] *Kidney Int*. (2006); [h]Thorp *et al*,[8] *Nephrology (Carlton)*. (2009); [i]Nissenson *et al.*,[9] *J Manag Care Pharm.*; [j]Levin *et al.*,[10] *Am J Kidney Dis*. (1999); [k]Kurella Tamura *et al.*,[11] *BMC Nephrol.* (2011); [l]Koyama *et al.*,[12] *Am J Kidney Dis.* (2023); [m]He *et al.*,[13] *J Am Heart Assoc.* (2017); [n]Vinke *et al.*,[14] *J Cachexia Sarcopenia Muscle.* (2022).

Definition of anemia in CKD

Anemia in adults is typically defined according to the thresholds of 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 [biological attributes]), 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: for 0.5–4 years, Hb <11 g/dl (<110 g/d); for 5–11 years, Hb <11.5 g/dl (<115 g/l); and for 12–14 years, 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), uncommonly occurring in CKD G1–G2 and reaching a prevalence of >50% in advanced CKD (CKD G4–G5).[4] The prevalence is disproportionately higher in women than in men.[16] A recent analysis of United States (U.S.) National Health and Nutrition Examination Survey data from 1999–2000 to 2017–2018 suggests that among other factors (age ≥75 years, female sex, CKD ≥G3b, and concurrent diabetes), anemia is significantly more likely to occur in Black populations than in other races.[17] In children, anemia in CKD ranges from 18.5% in CKD G2 to 93% in CKD G4 and G5.[18] Table 1 provides an overview of the prevalence of anemia across CKD stages in different countries.

Multiple studies showed that 21%–62% of people with CKD not receiving dialysis have anemia, defined as Hb <12 g/dl (120 g/l) in females and <13 g/dl (130 g/l) in males, with increasing prevalence in more advanced CKD (Figure 1).[1,23,24] For people with CKD G5 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 and 12 g/dl (between 100 and 120 g/l), between 9 and 10 g/dl (between 90 and 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), with a 5-fold higher odds ratio (OR) of anemia in CKD G4–G5 compared with CKD G1–G3.[26] Similarly, data from the Japan Chronic Kidney Disease Database 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% and 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 HD, 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 cause 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 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 medications (especially mycophenolate mofetil, mycophenolic acid, and azathioprine), medications affecting the renin-angiotensin system such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, antimicrobial agents such as trimethoprim-sulfamethoxazole, and antiviral agents such as ganciclovir.[31]

Table 1 | Prevalence of anemia across CKD stages in different countries

CKD stage	Prevalence (%)				
	United States[1]	Italy[19]	Japan[20]	Spain[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

CKD, chronic kidney disease.

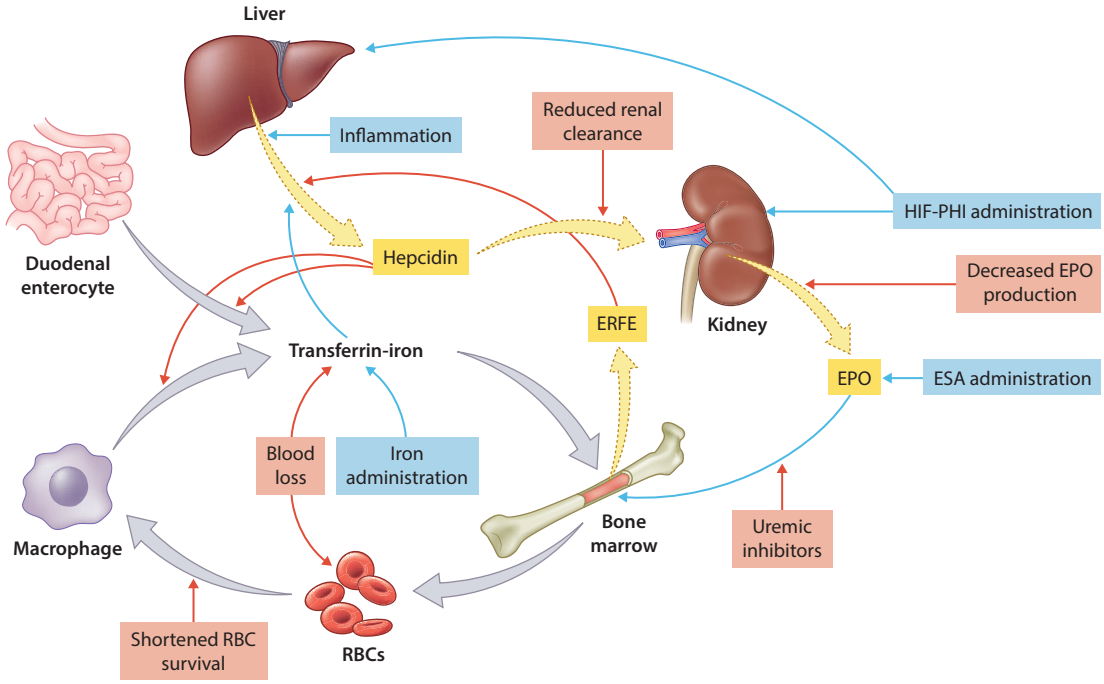


Figure 2 | Mechanisms underlying anemia of chronic kidney disease. The red color arrows indicate inhibitory effects, and the blue arrows indicate stimulatory effects. EPO, erythropoietin; ERFE, erythroferrone; ESA, erythropoiesis-stimulating agent; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; RBC, red blood cell. Modified from Babitt and Lin.[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, 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 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 baseline Hb at the initiation of hemodialysis significantly predicted time to the start of HD and the doubling of SCr levels.[38]

After kidney transplantation, post-transplant anemia (PTA) is associated with increased mortality, reduced graft survival, and a decline in glomerular filtration rate. The association with mortality is related to the severity of anemia and to specific causes of anemia.[31] In addition, PTA is associated with reduction in exercise capacity, decline in cognitive functions, and lower HRQoL.[39,40] Low Hb 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–derived skeletal muscle mass, handgrip strength, and Five Times Sit-to-Stand Test score.[14]

Although anemia is associated with a myriad of adverse outcomes in people with CKD (Figure 1), raising Hb levels by treatment with erythropoiesis-stimulating agents (ESAs) fails to improve most adverse outcomes associated with anemia. Benefits included a modest improvement in HRQoL and receipt of fewer blood transfusions,[41] although clinically relevant harms have also been noted, in particular when targeting the normal Hb range. 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 the other potential benefits of anemia correction. The consequences of treatment of anemia are thoroughly discussed in Chapters 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 is discussed below.

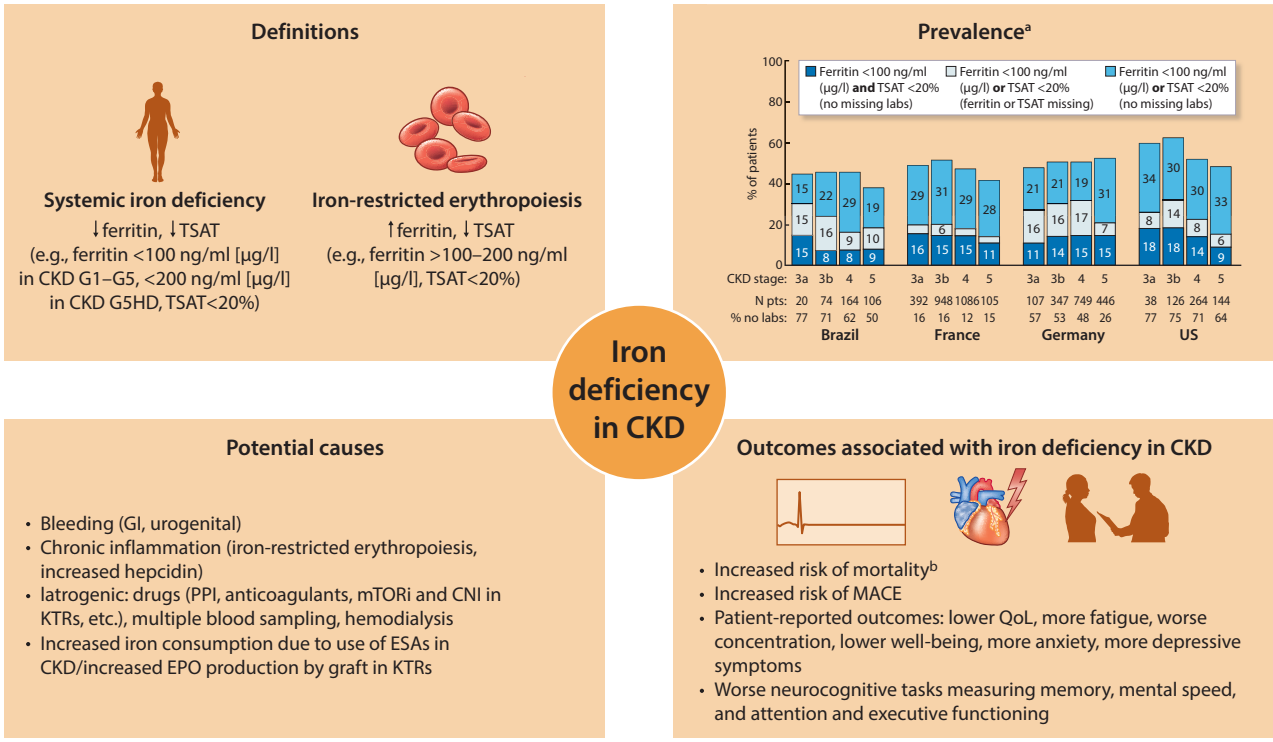


Figure 3 | Overview of iron deficiency in chronic kidney disease (CKD) with its definitions, prevalence across CKD stages, potential causes, and associated outcomes. CKD G5HD, chronic kidney disease G5 receiving hemodialysis; CNI, calcineurin inhibitor; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; GI, gastrointestinal; KTR, kidney transplant recipient; MACE, major adverse cardiovascular events; mTORi, mammalian target of rapamycin inhibitor; PPI, proton-pump inhibitor; QoL, quality of life; TSAT, transferrin saturation. [a]Wong *et al.*,[1] *Clin Kidney J.* (2020); [b]Guedes *et al.*,[43] *J Am Soc Nephrol.* (2021); and Eisenga *et al.*,[42] *Transpl Int.* (2016).

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, 2 states of iron deficiency can exist (Figure 3). One form is characterized by low TSAT and a low ferritin level (e.g., TSAT <20% and ferritin <100 ng/ml [<100 µg/l] in CKD not receiving dialysis or ferritin <200 ng/ml [<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 reflect the state more accurately. The second form of iron deficiency is characterized by low TSAT and a high ferritin level (generally ferritin >100–200 ng/ml [>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 systemic iron deficiency and iron-restricted erythropoiesis.

Commonly used diagnostic thresholds for these parameters, such as ferritin <100–200 ng/ml (<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 <30 ng/ml (<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 cutoffs 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,

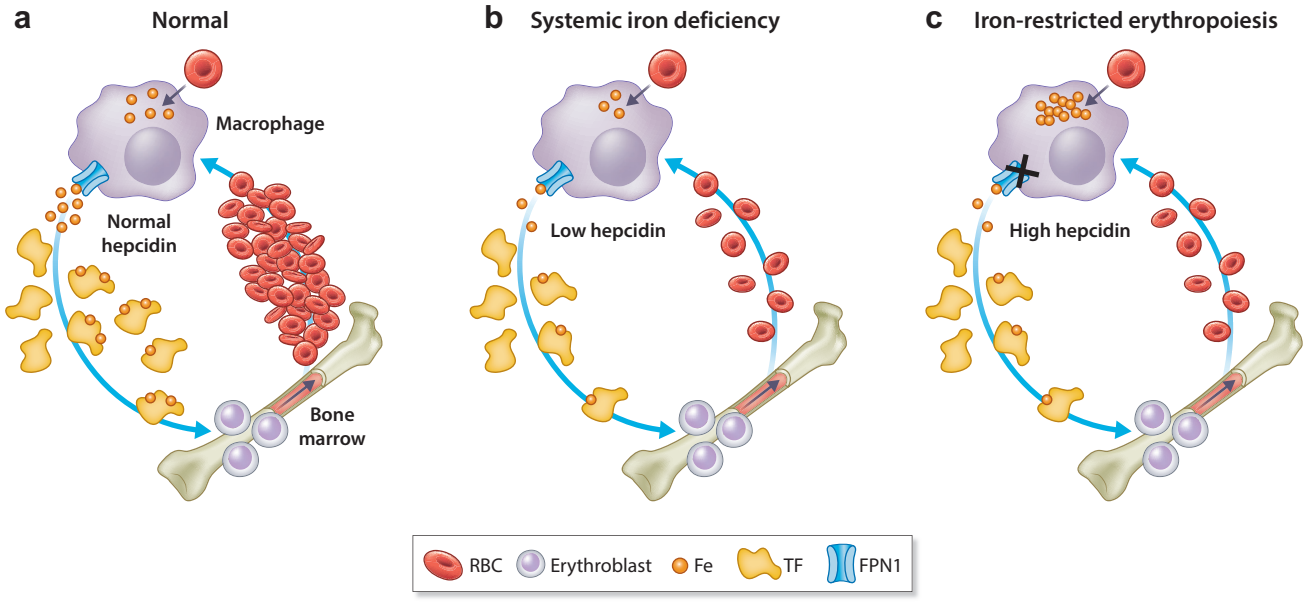


Figure 4 | Systemic movement of iron in different iron-related states. (**a**) In normal circumstances, splenic macrophages recycle iron (Fe) from senescent red blood cells (RBCs) via erythrophagocytosis and release of iron via the ferroportin (FPN1) export channel. This enables recycled iron to be loaded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

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. The Work Group did not explicitly consider serum iron (a component of TSAT) as an independent marker of iron status, since it was not used in clinical outcome trials. It is clear that more investigation is needed into these and other diagnostic markers possibly 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, those with CKD G5HD, those with CKD G5 receiving peritoneal dialysis (CKD G5PD), and KTRs. Among people with CKD G3–G5 not receiving dialysis, 15%–78% have either ferritin <100 ng/ml (<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 show that 16% have TSAT <20% and 5% have ferritin <200 ng/ml (<200 μg/l),[58] and Japanese registry data show that 36%, 60%, and 28% have TSAT <20%, ferritin <100 ng/ml (<100 μg/l), or both, respectively.[59] In stable KTRs, the prevalence of iron deficiency, defined as TSAT <20% with ferritin <300 ng/ml (<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 multitude of causes of iron deficiency in CKD populations[60–62] as well as poor adherence to oral iron and therapeutic inertia among prescribers.[1] In addition to 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 that is mainly due to blood loss, especially in the HD 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, and 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 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 (who were generally amenorrhoeic during kidney failure). Finally, after kidney transplantation, renewed EPO production increases iron utilization to promote erythropoiesis.[62]

Outcomes associated with iron deficiency in CKD

Many observational studies have shown that iron deficiency is associated with increased risks of mortality and cardiovascular hospitalization in people with CKD.[28–30] In particular, iron deficiency, as indicated by low TSAT, has been associated with a 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, were associated with worse physical component scores of HRQoL compared with 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 ng/ml [≤800 μg/l]) was associated with better survival as compared with either iron deficiency (systemic iron deficiency defined as TSAT ≤20% and serum ferritin ≤200 ng/ml [≤200 μg/l] or iron-restricted erythropoiesis defined as TSAT ≤20% and serum ferritin 200–800 ng/ml [200–800 μg/l]) or high iron status (i.e., ferritin >800 ng/ml [>800 μg/l]).[72] In Japanese HD patients, TSAT ≤20% was a significant independent risk factor for all-cause mortality.[73] Similarly, in Korean incident dialysis patients with anemia, TSAT ≤20% was associated with increased risks of mortality and the cardiovascular composite endpoint consisting of death or hospitalization due to 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 for 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 involved treatment strategies, rather than defining iron deficiency and assessing the association with outcomes. This study is 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 chronic kidney disease (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, reticulocytes (reticulocyte production index), ferritin, and 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) population. The suggested intervals are minimum frequencies to measure hemoglobin levels. In patients using erythropoiesis-stimulating agents or hypoxia-inducible factor-prolyl hydroxylase inhibitors, those with hemoglobin levels below the target range, or those experiencing a rapid progression of CKD, a higher testing frequency is advised. CKD G5D, CKD G5 receiving dialysis.

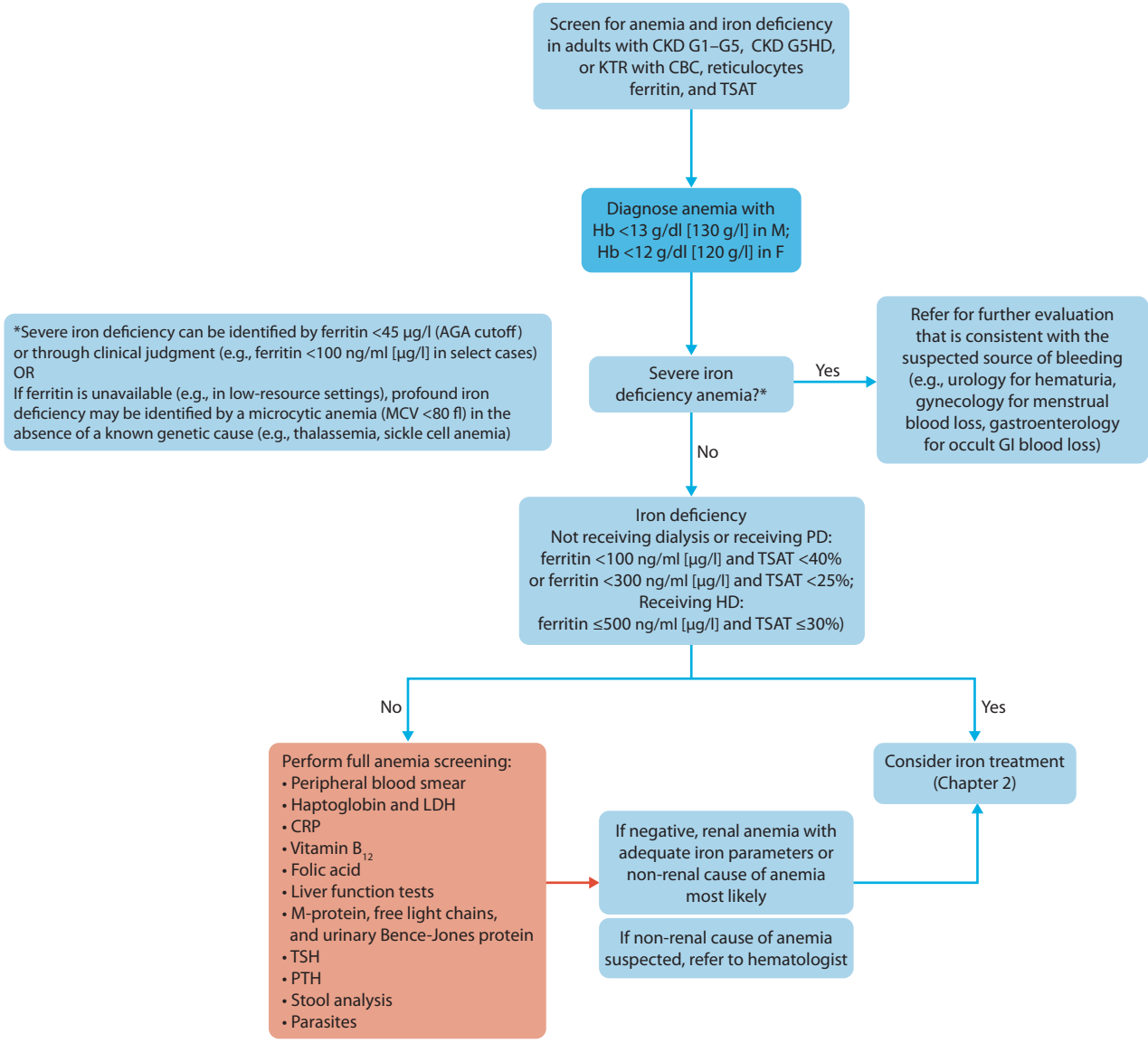


Figure 6 | Flowchart of the different steps to follow when people with chronic kidney disease (CKD) have anemia. AGA, American Gastroenterological Association; CBC, complete blood count; CKD G1–G5, chronic kidney disease not receiving dialysis; CKD G5HD, chronic kidney disease G5 receiving hemodialysis;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

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.

Practice Point 1.2.2: In people with anemia and CKD in whom the initial tests do not reveal the cause, consider an expanded panel to identify potential underlying causes as warranted based on the clinical scenario:

- **Blood smear review**
- **Haptoglobin**
- **Lactate dehydrogenase**
- **C-reactive protein**
- **Vitamin B_{12}**
- **Folate**
- **Liver function tests**
- **Serum protein electrophoresis with immunofixation, serum free light chains, and urinary Bence-Jones protein**
- **Thyroid-stimulating hormone**
- **Parathyroid hormone**
- **Fecal occult blood test.**

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 and hyperparathyroidism), 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 anemia does not yield resolution of anemia, consider intermittently repeating assessment of alternative causes for anemia and hematology referral.

Practice Point 1.2.3: In people with anemia and CKD who have ferritin <45 ng/ml (<45 μg/l) or microcytic anemia (mean corpuscular volume <80 fl) in the absence of measured ferritin or known genetic cause, and where the cause of iron deficiency is uncertain, consider clinical evaluation for blood loss. Referral to gastroenterologists/gynecologists/urologists may be appropriate to identify the cause.

When a medical care provider identifies severe iron deficiency, defined by the American Gastroenterological Association as ferritin <45 ng/ml (<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.[78] Since unrecognized 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) may warrant referral to identify the cause of blood loss.

Research recommendations

- 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.
- Investigate the use of other iron status parameters (e.g., soluble transferrin receptor levels, hepcidin, reticulocyte Hb content, percent hypochromic RBCs, or other novel parameters) for diagnosing iron deficiency in people with CKD. Also important is standardization of these measures.
- In pregnant women with anemia and CKD, describe the variability in Hb and iron parameters across eGFR strata, investigate cutoff 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 people with chronic kidney disease

Recommendation 2.1: In people with anemia and CKD G5 receiving 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 it places 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 iron (8 randomized controlled trials [RCTs][79–86]) or i.v. iron (14 RCTs,[79,80,87–98] including 2 RCTs investigating dialysate iron[91,92]) with 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.

Compared with placebo, iron supplementation agents seem to increase Hb values by an average of ∼0.5 g/dl (∼5 g/l) in people with CKD G5HD (Supplementary Table S5). Iron treatment may result in fewer RBC transfusions and probably also lowers ESA doses; its 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 outcomes is very uncertain (Supplementary Table S5).

Iron status thresholds to initiate iron therapy and treatment targets. Seven RCTs (11 reports) evaluated cutoff values of ferritin and TSAT for initiating iron therapy or for targeting therapy.[99–109] 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 of 10–12 g/dl (100–120 g/l), and studies were mostly designed to assess ESA requirements. Only 3 studies assessed outcomes considered critical for decision-making.

One small trial randomized 42 participants with CKD G5HD to receive i.v. iron dextran to maintain TSAT either at 30%–50% or at 20%–30%.[99] 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 with CKD G5HD to receive either high-dose iron sucrose, administered intravenously in a proactive fashion (400 mg monthly, unless the ferritin concentration was >700 ng/ml [>700 μg/l] or TSAT ≥40%), or low-dose iron sucrose, administered intravenously in a reactive fashion (0–400 mg monthly, with a ferritin concentration of <200 ng/ml [<200 μg/l] or TSAT <20% being a trigger for iron administration).[105] The rate of the composite outcome of fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure after a median of 2.1 years was lower in the group receiving proactive versus reactive treatment (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 were lower among people receiving proactive iron than among those receiving reactive iron, as was 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 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: 1.01; 95% CI: 0.95–1.08). Fewer (3.5%) people required a blood transfusion, and ESA requirements were generally lower in the group receiving proactive versus reactive treatment.

A third study randomized 200 participants with CKD G5HD 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.[109] The 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 evidence. The overall certainty of evidence for iron therapy among people with CKD G5HD is very low (Supplementary Tables S4 and S5). The certainty of evidence was graded to be very low for several critical outcomes due to concerns about 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 supplementation, the Work Group believes that most people with CKD G5HD would want iron supplementation if it prolonged life, reduced the risk of cardiovascular events, or improved QoL.[110]

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 the status of Hb and iron, which requires repeated testing to assess. This is particularly important given that results will drive dose adjustments and formulation switch in the 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 1–3 months for those 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 strategy with low-dose i.v. iron, a proactive strategy with high-dose i.v. iron moderately decreased the risk of death and important cardiovascular events without increasing the risk of infection or serious adverse events.[105] In addition, there was no evidence for effect modification by vascular access type.

Several issues arise when interpreting PIVOTAL.[105] First, the trial had 2 arms comparing discrete iron treatment regimens. Compared with a reactive low-dose regimen, the proactive higher-dose regimen resulted in better outcomes. However, this does not imply 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) may be associated with increased risks of mortality and infections.[111] Optimal dose finding would require a multiarm trial that includes different ferritin and TSAT targets, using different ESA doses, which may not be feasible in a randomized design.

The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guideline highlighted the difficulty in trying to specify treatment initiation thresholds. PIVOTAL may have indicated that in people with CKD G5HD treated with ESAs, 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 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 evaluated different initiation thresholds using a truly randomized design. The inclusion criteria in terms of ferritin and TSAT have been 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 $<$400 ng/ml ($<$400 μg/l) and TSAT $<$30%. Given that establishing an actual target based on the PIVOTAL data is still problematic, the Work Group felt that 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 ranging from 500 to 1200 ng/ml (500 to 1200 μg/l) and TSAT $\leq$25%.[89] During a 6-week follow-up, people who had received ferric gluconate had achieved a Hb concentration that was $\pm$0.5 g/dl ($\pm$50 g/l) higher than those who did not, without appreciable differences in serious adverse effects. After an additional observation period of 6 weeks, people who had received ferric gluconate required significantly lower ESA doses than those in the control group, 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 longer-term confirmation.

There are no studies of initiation thresholds 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 ESAs, especially if improved outcomes seen with 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-PHIs, where optimal iron dosing strategies are unknown. It has been postulated that HIF-PHIs may improve iron availability and reduce iron treatment needs compared with ESAs, but this has not yet been demonstrated in RCTs. Additionally, it is possible that higher iron strategies could lower HIF-PHI dosage as seen with 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 ESAs or people treated with HIF-PHIs. 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.[112,113] Initiation targets for iron therapy in children with CKD G5HD are unclear; however, 1 RCT showed improved Hb levels with iron therapy in children with CKD G5HD who are iron deplete, defined as TSAT <20% and/or serum ferritin <100 ng/ml (<100 μg/l).[114] Another trial on the optimum iron dose conducted in children with CKD G5HD with ferritin ≤800 ng/ml (≤800 μg/l) and TSAT 20%–50% suggested that a broad threshold similar to what is used for adults for initiating iron therapy is appropriate.[115]

Recommendation 2.2: In people with anemia and CKD G5HD who are initiaing iron therapy, we suggest using intravenous (i.v.) 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 to children.

Key information

Balance of benefits and harms. Eleven studies compared i.v. iron with oral iron in a total of 844 people with CKD G5HD treated with an ESA (Supplementary Tables S6 and S7).[79,80,114,116–124] Most of the studies 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.

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 adverse 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; 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,[91,92] and decreases 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. Ferric pyrophosphate citrate is not available in most countries.

Two studies conducted in children compared i.v. versus oral administration of iron (Supplementary Table S7). A first study compared i.v. iron sucrose with oral iron gluconate and found that i.v. iron resulted in a greater Hb response and higher ferritin and TSAT.[125] A second study found that ferritin concentrations were higher in children given i.v. iron dextran than in those receiving oral ferrous fumarate. Serious adverse events, serious gastrointestinal adverse events, serious hypersensitivity reactions, and the risk of RBC transfusion were not different between the oral and i.v. arms.[114] Other trials comparing dosing of i.v. iron with 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.[115,126]

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

Values and preferences. The Work Group believes that 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

Table 2 | Factors to consider when choosing between oral and i.v. iron

Oral iron	Intravenous iron
Slower increase in Hb, ferritin, or TSAT	More rapid increase in Hb, ferritin, or TSAT Delayed and reduced ESA use Possibly faster increase in QoL
Side effects • More frequent • Less severe 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 • Less frequent • More severe 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	More expensive
More convenient	Requires trained healthcare providers
Accessibility • Appealing to people who want to limit hospital visits • 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, erythropoiesis-stimulating agent; Hb, hemoglobin; i.v., intravenous; QoL, quality of life; TSAT, transferrin saturation.

prefer oral treatment (Table 2). Given its limited availability, dialysate iron is not presented in the table.

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 regimens, and factors influencing the choice between different formulations

Iron formulation	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 patients with CKD not receiving dialysis, it will help with phosphate binding as a secondary effect
			CKD G5D: 2 tablets, 3 times daily	In patients with CKD G5D, it is 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 sulfate	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 G5D, CKD G5 receiving dialysis.

Table 4 | Intravenous iron formulations and treatment regimens

Iron formulation	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 h	>60 min	Hypersensitivity lower than with high-molecular-weight dextran
Iron sucrose	20 mg/ml	CKD: 200 mg PD: 400 mg	15 min 2.5 h	5 min	For people with CKD G1–G5 not receiving HD, multiple patient visits are required because 1000 mg cannot be given in a single sitting: CKD: 5 doses of 200 mg over 5 wk PD: 2 infusions of 300 mg over 1.5 h 14 d apart followed by one 400 mg infusion over 2.5 h 14 d later
Ferric gluconate	12.5 mg/ml	125 mg	60 min	10 min	Ferric gluconate in sucrose complex (250 mg 4 doses weekly)
Ferric carboxymaltose	50 mg/ml	750 mg (FDA) 1000 mg (EMA)	15 min	7.5 min (FDA) 15 min (EMA)	Full dose can be given in 1 or 2 sittings (750 mg 2 doses 1 wk apart) May cause hypophosphatemia, especially in people with early CKD and kidney transplant recipients
Ferric derisomaltose/ iron isomaltoside	100 mg/ml	1000 mg (FDA) 20 mg/kg (EMA)	20 min (FDA) >15 min if ≤1000 mg; >30 min if >1000 mg (EMA)	250 mg/min (maximum 500 mg) (EMA)	Full dose can be given in a single sitting
Ferumoxytol	30 mg/ml	510 mg	15 min	15 min	Full dose can be given in a single sitting Hypersensitivity (due to bolus dosing) rarely occurs

CKD, chronic kidney disease; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD, hemodialysis; i.v., intravenous; PD, peritoneal dialysis.

Rationale

The Work Group felt that available data support the administration of i.v. iron to people with CKD receiving 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 are no published data on patient preference, but the Work Group, which included patient partners, believed that 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 particularly 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 i.v. 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.[105] 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 maximum dose.[127] For example, ferric gluconate and iron sucrose typically allow a maximum single dose of 125 or 200 mg, respectively, whereas other formulations such as ferumoxytol, ferric carboxymaltose, and ferric derisomaltose have higher dosing limits of 510–2000 mg (Table 4).

Recommendation 2.3: In people with anemia and CKD not receiving dialysis or CKD G5 receiving peritoneal dialysis (CKD G5PD), we suggest initiating iron if (*2D*):

- **Ferritin <100 ng/ml (<100 μg/l) and 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 RCTs that informed the recommendation. The recommendation applies to KTRs and to both adults and

children regardless of treatment with ESAs, 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.

Key information

Balance of benefits and harms. *Iron versus no iron.* Among people with CKD not receiving dialysis, ESAs, or HIF-PHIs, 18 studies (25 publications) compared either oral iron or i.v. iron with placebo.[128–152] 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%–≤30%) as inclusion criteria. None compared iron with placebo in those treated with ESAs or HIF-PHIs. Three 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 with placebo. Iron probably increases the Hb concentration on average by ∼0.65–1.0 g/dl (∼6.5–10 g/l) compared with no iron. Studies reported no hypersensitivity reactions (Supplementary Tables S8 and S9).

Three studies assessed the effects of oral or i.v. iron versus placebo in 294 adults with CKD G5PD (Supplementary Tables S8 and S9).[153–155] No trials among people with CKD G5PD reported on critical outcomes, and only 1 study addressed total serious adverse events and infections. Effects were unclear on serious adverse events, serious gastrointestinal adverse events, infections (notably peritonitis), Hb values, or ESA dose.

Different iron status targets. No RCTs have assessed the 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 evaluated i.v. ferric carboxymaltose to target ferritin concentrations of 400–600 ng/ml (400–600 μg/l) and compared it with oral iron to target ferritin concentrations of 100–200 ng/ml (100–200 μg/l). Targeting a ferritin of 400–600 ng/ml (400–600 μg/l) with i.v. iron was significantly more effective than with oral iron, reducing the absolute risk of requiring ESA therapy, additional anemia treatments, or the occurrence of 2 consecutive Hb levels below 10 g/dl (100 g/l) by ∼8% at 1 year. It led to a similar absolute risk reduction when compared with the lower ferritin target, though this difference was not statistically significant.[156]

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

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.[110] 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, with 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 receiving dialysis, administration of i.v. iron requires additional facilities and personnel, the relative costs of which are uncertain as compared with ESA treatment.

Considerations for implementation. It is difficult to predict the effect that iron will have on Hb and iron status because assessment requires repeated testing. This is particularly important, given that results will drive dose adjustments and formulation switch in cases 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 receiving 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 have assessed 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 compared either oral iron 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 with placebo did not include people treated with ESAs or HIF-PHIs, so it is difficult to extrapolate data to those people.

In a systematic review of the evidence by the Evidence Review Team (ERT), compared with placebo, iron increased Hb concentrations on average by ~0.65–1.0 g/dl (~6.5–10 g/l). The effect appeared similar for people with CKD, KTRs, and those receiving PD. However, what the increase in Hb or iron status parameters means 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 CIs 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 people with 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 receiving PD. The trials mostly defined either a combination of ferritin ≥100–<300 ng/ml (≥100–<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 people who were ESA-naive (<20%). Given the measurement error that exists in TSAT measurements, we opted for a single threshold to include both, reasoning that this simpler approach would facilitate implementation. The current recommendation represents a change from the previous guideline,[157] in which the same threshold was selected for those with CKD not receiving dialysis and those with CKD G5HD. We felt that 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 ESAs. In this context, the balance between benefits and harms of iron treatment may differ from that in people who are ESA-naive.

In children with CKD not receiving dialysis and those with 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 (≤800 μg/l) and TSAT between 20% and 50%. Accordingly, similar initiation thresholds appear appropriate in children.

Recommendation 2.4: In people with anemia and CKD not receiving hemodialysis (HD) in whom iron is initiated, we suggest using either oral iron or i.v. iron based on the person's values and preferences, the degree of anemia and iron deficiency, and the relative efficacy, tolerability, availability, and cost of each (*2D*).

People with anemia and CKD should choose whether to receive oral or i.v. iron based on their values and preferences. For some, ease of use and tolerability are key factors when considering iron supplementation (Table 2). Others may prioritize a rapid rise in Hb levels and potentially better QoL. This recommendation places a lower value on very low certainty evidence for critical outcomes and potential side effects. This recommendation is also applicable to people with CKD G5PD, KTRs, and children.

Key information

Balance of benefits and harms. Thirteen studies compared i.v. iron with oral iron head-to-head in 1868 adults with CKD not receiving dialysis, ESAs, or HIF-PHIs[156,158–169]; 5 RCTs did so in 800 adults who were already treated with ESAs.[170–174] 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 KTRs.[166] None was conducted in 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 adverse events, infections, blood transfusions, ESA use, or cancer outcomes, but the evidence was very uncertain (Supplementary Tables S10 and S11). 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 was 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 than with oral iron. 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 (3–5 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 was 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. iron with 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.[153,155] 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 the attainment of higher Hb concentrations compared with placebo than oral iron use did.

Certainty of evidence. The overall certainty of evidence for i.v. iron therapy compared with oral iron therapy among people with CKD not receiving HD is very low (Supplementary Tables S10 and S11). The certainty of evidence was determined to be very low for all critical outcomes and was often downgraded due to concerns about 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 CIs, which 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 with oral iron and the accessibility of medication may influence an individual's choice. On the contrary, 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.[175]

Resource use and costs. Oral iron is inexpensive and readily available in most parts of the world. Intravenous iron requires facilities and personnel for administration, which may be more costly to both people 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 3 and 4 outline the available doses, the recommended starting doses, and maximum doses and specific regimens for oral and i.v. iron, respectively. The use of shared decision-making tools or patient education may help support informed choices.

Table 5 | Circumstances warranting more frequent iron testings

• Initiation of or increase in the dose of erythropoiesis-stimulating agents (ESAs) or hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs)
• Episodes of known blood loss
• Recent hospitalization
• Important increase in ferritin or transferrin saturation (TSAT) or overshooting target limit

Rationale

Compared with oral iron therapy, i.v. iron provided a small additional increase in Hb of ∼0.3–0.5 g/dl (∼3–5 g/l) and increased ferritin and TSAT. Intravenous iron likely also increased Hb more rapidly. However, i.v. iron may cause serious hypersensitivity reactions, and although rare, these may be life-threatening, depending on the compound. Oral iron, in contrast, 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 an ESA, or justifies the minor risk of serious adverse events is uncertain. Oral iron is inexpensive, readily available, does not require i.v. access, which may preserve venous capital for arteriovenous access creation, and does not require additional hospital visits. Overall, the Work Group felt that 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 routine 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 what levels of iron are optimal for the erythropoietic effect. 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 above, 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%).[105] These results do not necessarily indicate that these higher iron levels should be targeted in clinical treatment. An alternative interpretation of the study results was that this intensive iron strategy did yield improved cardiovascular outcomes, but they did so specifically in comparison with 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.[105] Although a recent meta-analysis did not identify safety concerns with higher-dose i.v. iron,[176] 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 trials found that in people with CKD G5HD, i.v. iron resulted in higher Hb concentrations and lower ESA use even when the iron initiation threshold included serum ferritin concentrations >800 ng/ml (>800 μg/l).[89] However, whether this improved health outcomes or even provided incremental QoL benefits is unknown. Some retrospective observational

data suggest that more intensive i.v. iron administration may be associated with increased risks of mortality and infections.[111] 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 that it would be reasonable to start thinking about withholding routine iron if ferritin >700 ng/ml (>700 μg/l) or TSAT ≥40%. However, a trial course of i.v. iron could be considered for some people with low TSAT (e.g., <20%) and elevated ferritin (>700 ng/ml [>700 μg/l]) if they have refractory anemia or high ESA requirements. Clearly more research is needed here before a recommendation—rather than a practice point—can be made.

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 2 or 3 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 results in 34% higher iron absorption than with consecutive-day supplementation.[177–179] Also, splitting a single oral dose of 120 mg of iron into 2 daily doses of 60 mg of iron does not improve iron absorption, as shown in 2 open-label RCTs.[178]

Some newer oral iron preparations may have improved efficacy and/or tolerability, but head-to-head RCT data are 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[180]; however, its role as an iron-repletion agent in this population remains to be clarified. In a phase 3 trial in people with CKD not receiving dialysis, ferric maltol demonstrated improvements in Hb versus placebo, with a favorable tolerability profile.[180] Sucrosomial iron, which has been evaluated in iron deficiency anemia associated with CKD and several other clinical settings, has demonstrated improved tolerability over i.v. iron.[180]

Practice Point 2.4: In people with CKD treated with i.v. iron, the choice between different formulations is guided by cost, individual patient preference, safety, tolerability, and recommended dosing schedules.

There are no head-to-head RCTs comparing the effect of different i.v. iron compounds on critical outcomes in people with CKD. Although PIVOTAL used iron sucrose specifically, in the judgment of the Work Group, the benefits of the proactive regimen likely extend to other i.v. iron formulations. Different formulations of i.v. iron differ in the maximum dose that can be administered at a single sitting and the rate of infusion (Table 4).[181] 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 KTRs, people with earlier stage CKD, and people receiving repeated dosing.[182]

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 the efficacy or safety of dialysate iron with other i.v. iron formulations or oral iron, and its long-term safety has not been established.[183] 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 (Hb), ferritin, and TSAT every 3 months for those with CKD not receiving dialysis or CKD G5PD and every 1–3 months 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 3 months for people with CKD not receiving HD and every 1–3 months 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 to iron treatment. Conversely, increasing ferritin and/or TSAT levels may indicate that iron treatment is excessive and can be stopped or reduced. While not necessary for oral iron, healthcare providers should delay TSAT testing for 2–4 weeks after i.v. iron administration.[104,184]

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

Certain situations may warrant more frequent testing than what is proposed in Practice Point 2.5. 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 potential for spuriously elevated values if iron status is checked soon after administration of i.v. iron or packed RBCs.

Accidental blood loss, as can occur through needle dislodgments or gastrointestinal bleeding, may lead to a 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 increase in iron status test results or if results are well above targets. More frequent testing may be considered until normalization occurs.

Practice Point 2.7: Switch from oral to i.v. iron if there is an insufficient effect of an optimal oral regimen after 1–3 months or if tolerability is poor.

Oral iron is typically prescribed to provide ∼200 mg of elemental iron daily, with most studies showing its effect on Hb concentration within 1–3 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 such as constipation, nausea, and abdominal discomfort, leading to poor adherence, while i.v. iron avoids these issues and improves consistency in dosing.

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 toward microbes.[185] There is theoretical and experimental evidence to suggest that iron administration may worsen an existing infection, but clinical evidence for this is lacking.

Our systematic review did not find a statistically significant increase in infection risk when comparing iron with placebo or i.v. iron with oral iron. However, the trend in the data suggests a potential difference. In people with CKD not receiving HD, the risk estimate for i.v. iron compared with placebo was slightly above 1, as was the estimate for i.v. iron compared with oral iron—though neither reached statistical significance. This aligns with previous research on i.v. versus oral iron in various other populations, where a subgroup analysis in people with CKD showed similar findings.[186] The event rate in the HD trials was too low to support any inference here. One potential explanation for why there could be a difference between oral and i.v. iron is that during infection, rising hepcidin levels may reduce the absorption of oral iron, leading to lower exposure compared with i.v. iron. While we certainly cannot confirm a direct harmful effect of iron on infection risk, it remains a possibility. Taken together, it may be prudent to withhold both oral and i.v. iron in situations where active infection is present.

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 bloodstream infection. Clinical judgment is necessary for milder infections to balance the risks of continued use of i.v. iron as opposed to delaying further iron administration until the infection resolves.

Practice Point 2.9: In people with CKD treated with i.v. iron, considerations pertaining to hypersensitivity reactions to i.v. iron include the following:

- **Intravenous iron should be administered only 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 (i.e., histamine type 1 channel blockers)**
- **Test doses of i.v. 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, or 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 the first dose of 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 200–400 mg per administration, and iron gluconate should not exceed 125–250 mg because of the risk of the release of labile iron and associated hypotension at higher doses.[187]

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 (histamine type 1 [H_1] 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.[188]

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

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 a face mask. Volume loading should be given using 1 l of crystalloid solution in addition to an antihistamine (H_1 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. H_1 channel blockers and corticosteroids should be considered, and monitoring after therapy should be continued for 1 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.[188]

Practice Point 2.11: In people with CKD and profound iron deficiency (ferritin <30 ng/ml [<30 μg/l] and TSAT <20%) but no anemia, consider treatment with oral or i.v. iron.

If profound iron deficiency (e.g., ferritin <30 ng/ml [<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 DNA synthesis, electron transport, and cellular proliferation and differentiation.[189] Iron deficiency impairs myoblast proliferation[190] and impairs cardiomyocyte function.[191] 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 underscore this, as iron deficiency, independent of anemia, is associated with a higher risk of all-cause mortality, MACE, and worse patient-reported outcomes.[32,43,59,77] In addition, ample evidence from the field of chronic heart failure, including the subset of people with CKD, suggests benefit of iron therapy independent of anemia to improve functional status and hospitalizations.[128,192–194] Nevertheless, prospective 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 on exercise capacity at 4 weeks,[134] making this an important research recommendation.

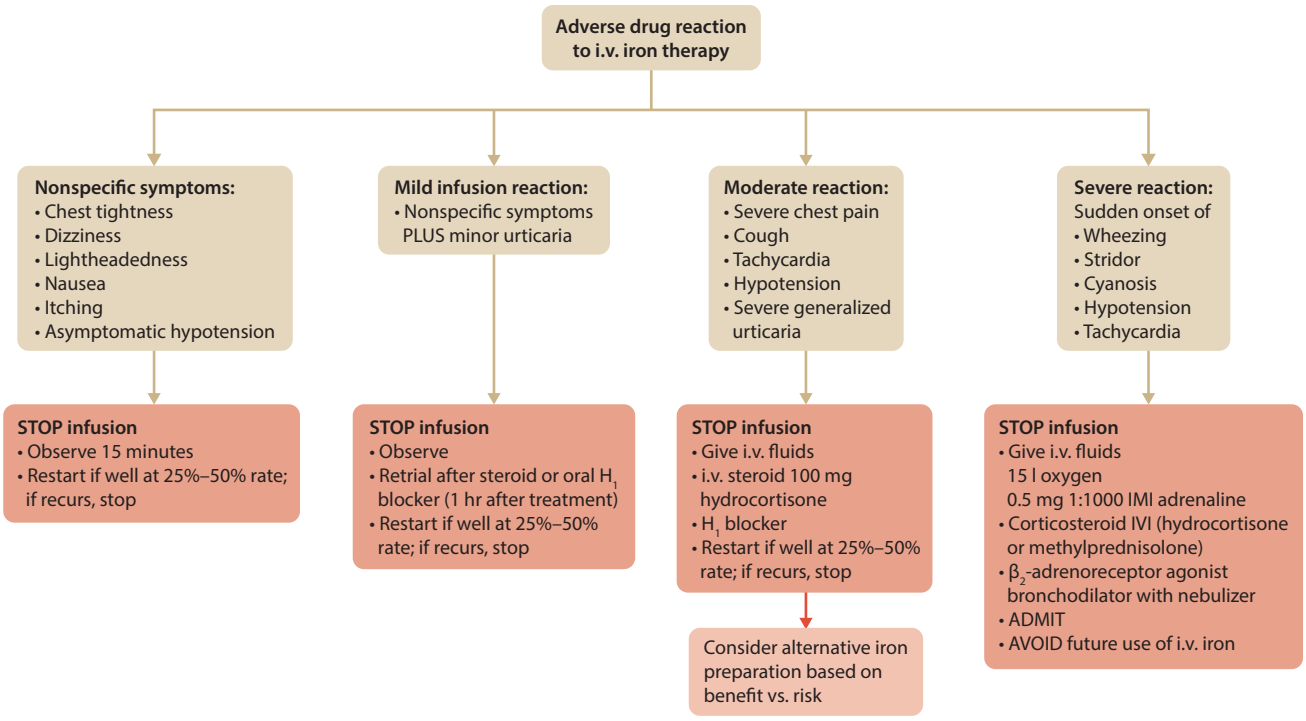


Figure 7 | Suggested management of reactions to intravenous (i.v.) iron. H_1, histamine type 1; IMI, intramuscular injection; IVI, intravenous infusion.

Research recommendations

- Adequately powered pragmatic RCTs are needed to assess the benefits, harms, and costs of the following:
  - A proactive high-dose i.v. iron regimen, such as used in the PIVOTAL trial, in people with CKD not receiving HD.
  - Different protocolized iron dosing regimens with a higher iron dose comparator than the reactive arm used in the PIVOTAL trial in people with CKD G5HD. 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 concentrations and TSAT targets in both people with CKD not receiving HD and those with CKD G5HD.
  - Iron treatment in people with CKD treated with HIF-PHIs.
  - Iron treatment in people with CKD with iron deficiency in the absence of anemia.
  - Newly available oral iron compounds compared with 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.[195] 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 only on population Hb and TSAT values.[196]
- 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.
- Future studies should investigate the effectiveness of different dosing schedules of oral and i.v. iron formulations in pregnant women with anemia and CKD.

Chapter 3: Use of erythropoiesis-stimulating agents, hypoxia-inducible factor–prolyl hydroxylase inhibitors, and other agents to treat anemia in people with chronic kidney disease

3.1 Treatment initiation

Practice Point 3.1.1: In people with anemia and CKD (whether receiving dialysis or not), the decision to use erythropoiesis-stimulating agents (ESAs) or hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs) to raise Hb should be made through a shared decision-making process, considering each individual's symptoms, potential for harm from red blood cell (RBC) transfusions, and potential risk of adverse events (e.g., stroke, cardiovascular event, and cancer).

Treatment of anemia with ESAs or HIF-PHIs improves symptoms and reduces RBC transfusions as compared with 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 ESAs. Therefore, people with anemia and CKD 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, including iron deficiency, prior to the initiation of treatment with an ESA or a HIF-PHI (Figure 8).

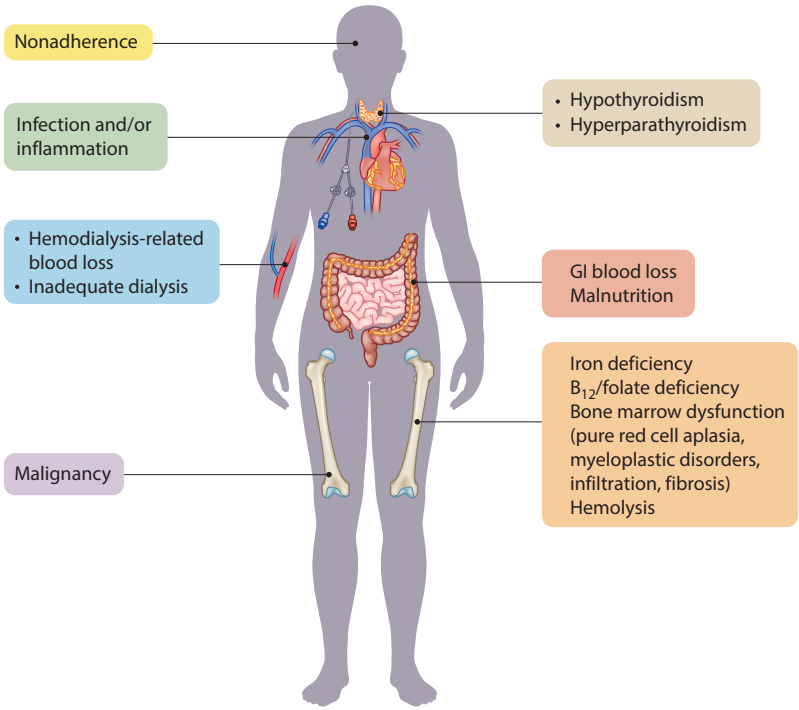


Figure 8 | Potentially reversible causes of anemia in chronic kidney disease in addition to decreased erythropoietin production. GI, gastrointestinal.

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 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 treating anemia, some studies suggested a higher risk of MACE and vascular access thrombosis with HIF-PHIs compared with 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 people treated outside clinical trials are unknown.

Key information

Balance of benefits and harms. ESAs increase Hb compared with placebo in people with anemia and CKD regardless of dialysis status. HIF-PHIs increase Hb compared with placebo in people with anemia and CKD G5 receiving dialysis (G5D)[197–201] and those with CKD not receiving dialysis.[202–211] Head-to-head studies of HIF-PHIs compared with ESAs show generally similar efficacy in people with CKD G5HD[212–219] and with CKD not receiving dialysis.[218,220–224] Among people with CKD G5D, there may be little or no difference in mortality, MACE, and other important clinical outcomes for HIF-PHIs versus ESAs, but there remains a high degree of uncertainty about the comparative side-effect profiles (Supplementary Tables S12–S22). 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 (Supplementary Tables S23–S31).[218,223,225] 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 clinical trials.[226–230] For 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 with 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 people with CKD not receiving dialysis, with approval granted for those with CKD G5D after 3 or 4 months on dialysis, with a boxed warning regarding the increased risks of thrombotic and other cardiovascular events. Daprodustat was later withdrawn from the U.S. market by the manufacturer. Roxadustat was approved by the European Medicines Agency (EMA) for people with CKD not receiving dialysis and those with CKD G5D, but it was rejected by the U.S. FDA due to safety concerns. These and other HIF-PHIs have been approved by other countries' regulatory agencies, including China and Japan, for use in one or both of these 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 for all the critical outcomes reported. Considering evidence regarding all outcomes, there were 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 (Supplementary Tables S23–S31).

The overall certainty of evidence comparing ESAs with HIF-PHIs in people with anemia and CKD G5D is very low (Supplementary Tables S12–S22). The certainty of evidence is very low for all the critical outcomes and low for QoL. The 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 of 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. However, those who prefer an oral treatment to parenteral treatment may consider initiating first-line treatment with HIF-PHIs after being informed of the potential risks. Additionally, people with ESA hyporesponsiveness may consider a trial course of HIF-PHI treatment, although the evidence for efficacy of HIF-PHIs in this setting is weak.

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 with HIF-PHIs or their administration when formulating this recommendation. In the United States and perhaps other countries, the costs of HIF-PHIs will be borne by dialysis facilities, so relative costs of these classes of agents 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 the 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

Table 6 | Considerations for people with anemia and CKD at risk for adverse events with HIF-PHIs

Theoretical risk or experimental evidence of disease development or progression	Concern about risk based on adverse event profiles in clinical trials	Insufficient data to assess risk; dedicated studies needed
• Active cancer or with a history of cancer not in complete remission for at least 2–5 yr (based on trial exclusion criteria)[231] • Polycystic kidney disease[232] • Proliferative retinal disease[233,234] • Pulmonary arterial hypertension[235–237] • Pregnancy[a]	• Prior cardiovascular events (i.e., stroke and myocardial infarction)[231] • Prior thromboembolic events (i.e., deep venous thrombosis and pulmonary embolism)[231] • Prior vascular access thrombosis[231] • Hepatic impairment[b] • Seizures, exfoliative dermatitis, hypothyroidism, and bacterial infections/sepsis (roxadustat)[238]	• Post–kidney transplant anemia[231] • Children[239]

CKD, chronic kidney disease; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor.
[a]HIF-PHIs are contraindicated in pregnancy. Please refer to the package inserts for individual compounds for specific guidance.
[b]Caution is advised in patients with hepatic impairment. HIF-PHIs are not recommended for patients with significant hepatic impairment. Please refer to the package inserts for individual compounds for specific guidance.

other critical outcomes, some studies suggest that at least some HIF-PHIs may have more MACE and other vascular events than ESAs, particularly in people with 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 better understood. Whether HIF-PHIs may have increased efficacy compared with 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 long-term safety comparable to ESAs, 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-PHIs for most people 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 for adverse events (Table 6).

This practice point is based on theoretical concerns based on the 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.

3.2 ESA initiation

Recommendation 3.2.1: In people with anemia and CKD G5D receiving HD or peritoneal dialysis, 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 due to 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) or even lower, 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. Compared with placebo or standard of care, ESA therapy may reduce the risk of requiring RBC transfusions and improve QoL, especially when the pretreatment Hb concentration is <9.0 g/dl (<90 g/l).[240–243] In the judgment 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 the occurrence of RBC transfusions (Supplementary Tables S38–S41). In a double-blind RCT, 118 people with CKD G5HD and Hb <9.0 g/dl (<90 g/l) were randomly assigned to receive placebo, an ESA for a Hb target of 9.5–11.0 g/dl (95–110 g/l), or an 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 the group with target Hb >11.0 g/dl (>110 g/l) (Supplementary Tables S38–S41).[240,244] 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 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 and vascular access loss were higher in the group treated with ESAs for a higher Hb target (Supplementary Tables S38–S41). No data were available with regard to malignancy.

The use of ESAs to target normal Hb levels may be associated with an increased risk of harm, particularly in people with cardiovascular disease or congestive heart failure, and therefore a Hb initiation threshold in the lower range may be

warranted. 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 than those in the low Hb arm (Supplementary Table S36).[245] However, the number of deaths, nonfatal myocardial infarctions, and vascular access thromboses were higher in the high Hb arm than in 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 receiving 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 in people receiving HD to those receiving PD. Therefore, this recommendation applies to people receiving 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 S34 and S35). 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 outcome of 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 evidence comparing ESAs to placebo is very low in adults with CKD G5D (Supplementary Tables S32 and S33). 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 targeting 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 therapy may choose to initiate the 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 the ESA at the higher end of the Hb range 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 ESAs at the higher end of the Hb range 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 ESAs at the lower end of the Hb range may lead to more RBC transfusions and their associated costs, including 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 ESAs or whenever there is a change in the dose of ESAs. The increases in Hb and blood pressure are generally reversible if ESA is stopped or doses are reduced. Given the variability in Hb measurements, more than 1 Hb measurement and the Hb trend should be used to guide the initiation of ESA therapy. In people who are at 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 ESAs prior to initiation of therapy.

Rationale

ESAs effectively raise Hb, which reduces the risk of RBC transfusions and improves QoL for people with CKD G5D or 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/dl (>100–110 g/l) and, thus, may outweigh the potential benefits. This recommendation attempts to balance the benefits of ESA treatment against its potential 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 transfusions or 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 with ESA therapy. The Hb concentration for ESA initiation should be

individualized, and for most people, it 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 risks versus benefits of ESA treatment should be discussed, 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 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 S37–S39).[41,246,247] People with anemia and CKD not receiving dialysis experienced a higher 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 QoL.[247] The risk of stroke, prespecified as a secondary outcome, was significantly higher in people with diabetes and CKD not receiving dialysis treated with ESAs to target a Hb of 13.0 g/dl (130 g/l) versus those treated with placebo and rescue ESA administered when the Hb was <9.0 g/dl (<90 g/l).[41] Cancer-related events were reported in 1 study where the RR was 1.08 (95% CI: 0.85–1.36) when comparing a higher Hb target to a lower target and in 1 study reporting on malignant neoplasms where the RR was 1.00 (95% CI: 0.25–3.97) when comparing a higher Hb target to a lower target.[41,248–251] The systematic review from the ERT also concluded that there was evidence from clinical trials of ESAs that indicated 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 S37–S39).[41,246,249–255] Finally, in clinical trials comparing specific Hb targets, ESA regimens with higher Hb targets were associated with a lower risk of RBC transfusions.[41,246,249–251]

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

No RCTs have investigated the effects of ESA treatment on mortality or MACE in children with CKD not receiving dialysis (Supplementary Tables S42 and S43). Observational data suggest that children with Hb <10.0 g/dl (<100 g/l) when starting dialysis have higher cardiovascular and all-cause hospitalizations than those with Hb between 10.0–12.0 g/dl (100–120 g/l). We advise considering these 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.[256]

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 S37–S39). 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 evidence comparing ESAs to placebo is very low in adults with CKD not receiving dialysis (Supplementary Tables S40 and S41). There were serious concerns about risk of bias for thromboembolism, very serious concerns about risk of bias 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. Choice of Hb concentration 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 the 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 ESAs at a relatively higher Hb concentration. In contrast, ESAs may be initiated at a lower Hb threshold (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 cure).

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

Considerations for implementation. People with anemia and CKD should be informed about risks and benefits associated with ESAs 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 ESAs 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 outcomes in high-risk groups. The increased risk of RBC transfusions associated with initiating ESAs 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 ESAs, we recommend targeting the Hb level to 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 ≥11.5 g/dl (≥115 g/l) 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 ESAs to target a high versus a low Hb, several adverse events and/or adverse composite outcomes were reported in individual trials (Supplementary Tables S37–S39). 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 of 13.5 g/dl (135 g/l) versus those receiving epoetin alfa to target a Hb of 11.3 g/dl (113 g/l), with no incremental improvement in QoL.[247] Importantly, although a Hb target of 13.5 g/dl (135 g/l) was used for the high Hb group, only a mean Hb of 12.6 g/dl (126 g/l) was achieved in the trial.[41,247]

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 S37–S39).[246] 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.[246]

Finally, in a study of 4038 people with anemia, CKD not receiving dialysis, and diabetes, participants were randomized to an ESA to achieve a Hb of 13.0 g/dl (130 g/l) or to placebo, with a rescue ESA when the Hb was <9.0 g/dl (<90 g/l) (Supplementary Tables S40 and S41). 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 an 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 QoL score).[41]

Fewer data describe the benefits and risks of ESAs used to achieve different Hb targets in people with CKD G5D. The systematic review from the ERT concluded that when comparing the same ESA to reach specific Hb targets in people with CKD G5D, higher Hb targets have a similar effect on mortality as compared with lower Hb targets and also have similar effects on QoL, functional status, and RBC transfusion rates (Supplementary Tables S34 and S35). 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, nonfatal myocardial infarctions, and vascular access thromboses was 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 reports of higher physical functioning in the high Hb arm.[245]

In people with CKD G5D receiving maintenance PD, there are no RCTs comparing ESAs to reach a specific Hb target or comparing ESAs with placebo or usual care for critical or important outcomes. In the judgment 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 KTRs. Therefore, in the judgment of the Work Group, it is reasonable to extrapolate findings from studies in people with anemia and CKD not receiving dialysis without a kidney transplant to KTRs 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 hemodialysis is very low (Supplementary Tables S37–S39). 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 mortality and acute coronary syndrome and moderate for QoL and functional status. No studies reported on thromboembolism or all-cause hospitalization.

Values and preferences. In the judgment of the Work Group, most well-informed people with anemia and CKD not receiving dialysis or CKD G5D would choose not to receive an ESA to maintain Hb ≥11.5 g/dl (≥115 g/l), given the data on the risks, such as increased risks of stroke and other cardiovascular events, which the Work Group judged to be critically important to people with anemia and CKD. Although QoL was also judged to 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 level would result in higher healthcare costs related to the cost of the ESA, ESA 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 above 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 adults and children with anemia and CKD, selection of the Hb target for ESA maintenance therapy should be individualized, considering potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of RBC transfusion) and potential harms.

Since optimal Hb treatment targets for ESA therapy are likely to differ for each individual based on the balance of potential benefits and harms, the Work Group has chosen to provide guidance on when to initiate ESAs (Recommendations 3.2.1 and 3.2.2) as well as the upper Hb limit for maintenance therapy (Recommendation 3.3.1). In general, Hb levels should be maintained at the lowest target level that achieves and maintains treatment goals (i.e., reduce the risk of transfusion).

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 suggest 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.[256] Other cohort studies involving children receiving PD have found positive correlation between Hb concentration and patient survival but lower survival with increasing ESA dose.[257] However, caution is advised, given the discrepancy between data from observational studies and RCTs seen in adults. Data from adults may not apply to children because of 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 personal and family values and preferences.

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

3.4.1 ESA dosing

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

Table 7 | Dosing of ESAs

ESA	Initial dose	Dose adjustment[a]
Epoetin alfa and beta	CKD not receiving dialysis: ~50 U/kg once or twice weekly (some use up to 100 U/kg once every 2 wk) (may also round to a convenient dose in units, such as 4000 or 10,000 U, using the lower dose range once or twice weekly and a higher dose range every 2 wk)	CKD not receiving dialysis: Increase or decrease the dose and/or dosing frequency as needed (generally not given more than once weekly)
	CKD G5D: 50–100 U/kg 3 times weekly (may round to a convenient dose in units)	CKD G5D: Increase the dose by 25 U/kg/dose if Hb rise is <1.0 g/dl (<10 g/l) after 4 wk. Decrease the dose by 10–25 U/kg/dose if Hb rise is >2 g/dl (>20 g/l) in 4 wk
Erythropoietin biosimilars	*Product names and doses vary by region (refer to individual product information)*	
Darbepoetin	CKD not receiving dialysis: 0.45 μg/kg weekly or 40–100 μg every 2–4 wk	CKD not receiving dialysis: Increase or decrease the dose and/or dosing frequency as needed (generally not given more than once weekly)
	CKD G5D: 0.45 μg/kg weekly or 0.75 μg/kg every 2 wk (may round to convenient dose: 25, 40, 60, 100, 150, or 200 μg; 300 and 500 μg also available)	CKD G5D: Increase the dose by 25% if Hb rise is <1.0 g/dl (<10 g/l) after 4 wk. Decrease the dose by 25% if Hb rise is >2 g/dl (>20 g/l) in 4 wk
Methyl polyethylene glycol–epoetin beta	CKD not receiving dialysis: 0.6 μg/kg or 50–120 μg every 2 wk, or 1.5 mg/kg or 120–200 μg/kg every month	CKD not receiving dialysis: Increase or decrease the dose and/or dosing frequency as needed (generally not given more than once every 2 wk)
	CKD G5D: 0.6 μg/kg every 2 wk (may round to a convenient dose)	CKD G5D: Increase the dose by 30–50 μg/dose if Hb rise is <1.0 g/dl (<10 g/l) in 4 wk. Decrease the dose by 30–50 μg/dose if Hb rise is >2 g/dl (>20 g/l) in 4 wk

CKD, chronic kidney disease; CKD G5D, CKD G5 receiving dialysis; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.
[a]Refer to product labeling or dialysis facility protocols for other details of dosing and conversion from an ESA. In general, weight-based dosing is used for children.

Practice Point 3.4.1.2: In people with anemia and CKD treated with ESAs, avoid adjusting the dose of the ESA more frequently than once every 4 weeks. The exception is when Hb increases by >1.0 g/dl (>10 g/l) in 2–4 weeks after the initiation of therapy, at which time the dose should be reduced by 25%–50%.

Initial therapy with an 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 an ESA to treat anemia in people with CKD G5D and CKD not receiving dialysis. The 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.[41,247]

Practice Point 3.4.1.3: In people with anemia and CKD treated with ESAs, administer ESAs with the lowest dose possible that achieves and maintains treatment goals.

High doses of ESAs 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 ESAs. This was shown in the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), in which the use of darbepoetin to maintain a Hb level at ∼13.0 g/dl (∼130 g/l) (achieved median Hb of 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 with 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 HR 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 Hb of 13.5 g/dl (135 g/l) (achieved mean Hb: 12.6 g/dl [126 g/l]) vs. Hb: 11.3 g/dl [113 g/l]).[247] Similarly, an RCT in people with CKD G5HD and background ischemic heart disease or heart failure revealed that treatment with an 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 the 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.[245] Secondary analyses of these studies suggested that higher doses of ESAs may have contributed to the increased adverse outcomes in the groups targeting a higher Hb target.[258]

3.4.2 ESA route of administration

Practice Point 3.4.2.1: In adults and children with anemia and CKD G5HD treated with ESAs, 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. versus subcutaneous routes, which in turn will increase costs.[259–261] In contrast, there are no differences in dose recommendations for i.v. versus subcutaneous darbepoetin alfa. 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, those with CKD G5PD, or kidney transplant recipients receiving ESA therapy, administer ESA via the subcutaneous route.

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

3.4.3 Frequency of administration and monitoring of ESAs

Practice Point 3.4.3.1: In people with CKD G5D or CKD not receiving dialysis, individualize the frequency of ESA administration 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 a 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. To avoid a rapid decline in Hb, consider reducing the ESA dose rather than holding ESA therapy, as long as the Hb does not exceed 11.5 g/dl (115 g/l).

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.[41,247] In the CHOIR study, people with CKD randomized to a Hb target of 13.5 g/dl (135 g/l) (achieved mean Hb: 12.6 g/dl [126 g/l]) had a higher risk of a composite of death and cardiovascular events as compared with participants with a Hb target of 11.3 g/dl (113 g/l).[247] In TREAT, the risk of stroke was higher in people with CKD randomized to darbepoetin to maintain a Hb level of ∼13.0 g/dl (∼130 g/l) (achieved median Hb: 12.5 g/dl [120 g/l]) than in those 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 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 the target and to identify ESA hyporesponsiveness. A minimum frequency of 1–3 months is suggested, with more frequent monitoring suggested for people with CKD G5HD, in whom there are trial data showing that 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 ESAs, it is reasonable to suspend the 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 have revealed increased risks of stroke, vascular access thrombosis, and nonfatal myocardial infarction.[41,245] One in 4 stroke survivors will have another stroke.[245] In addition, the risk of vascular access thrombosis and future thromboembolic events is increased in people with a 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 cancer treatment is aimed at cure, with a target Hb that minimizes transfusion needs.

Studies have shown that using ESAs to treat anemia in some cancers may lead to increased cancer progression and death.[262] The American Society of Clinical Oncology/American Society of Hematology clinical practice guideline for the use of ESAs in adults with cancer and anemia recommends that treatment with an 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).[263] 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 on a *post hoc* analysis of TREAT. In TREAT, where people with anemia and CKD not receiving dialysis were randomized to an ESA to achieve a Hb of 13.0 g/dl (130 g/l) or to placebo, with rescue ESA when the Hb 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 of 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 ESAs with HIF-PHIs. In 1 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. However, the Work Group did not believe that there was a sufficiently reasonable rationale for using ESAs and HIF-PHIs in combination to justify this treatment approach.[264]

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, and 3.3.1).

Clinical trials of HIF-PHIs 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 HIF-PHIs approved for marketing as of October 2024

HIF-PHI[a]	Recommended dosing for treatment initiation	Maximum daily dose	Dose frequency	Drug metabolism and transport
Daprodustat	CKD not receiving dialysis: 2–∼4 mg (ESA-naive), 4 mg (switch from ESA) CKD G5D: Japan, 4 mg; the United States, 1–∼4 mg (ESA-naive), 4–12 mg (switch from ESA)	24 mg	Daily	CYP2C8[265]
Desidustat	CKD not receiving dialysis: 100 mg (ESA-naive), 100, 125, or 150 mg (switch from ESA) CKD G5D: 100 mg (ESA-naive), 100, 125, or 150 mg (switch from ESA)	150 mg	3 times weekly	Not inhibitor of CYP1A2, 2C8, 2C9, 2C19, 2D6, or 3A4/5[266] Not inducer of CYP1A2 or CYP3A4/5[266]
Enarodustat	CKD not receiving dialysis and CKD G5PD: 2 mg (ESA-naive and switch from ESA) CKD G5HD: 4 mg (ESA-naive and switch from ESA)	8 mg	Daily	CYP2C8, CYP2C9, or CYP3A4[267]
Molidustat	CKD not receiving dialysis: 25 mg (ESA-naive), 25–∼50 mg (switch from ESA) CKD G5D: 75 mg (ESA-naive and switch from ESA)	200 mg	Daily	UGT1A1 or UGT1A9[268]
Roxadustat	CKD not receiving dialysis and CKD G5D (ESA-naive): European Union, 70 mg for body weight <100 kg, 100 mg for body weight ≥100 kg; Japan, 50 mg CKD not receiving dialysis (switch from ESA): European Union, 70–200 mg; Japan, 70–100 mg	3.0 mg/kg body weight	3 times weekly	CYP2C8, UGT1A9, BCRP, OATP1B1, OAT1, or OAT3[238] Inhibitor of CYP2C8, BCRP, OATP1B1, or OAT3[238,269]
Vadadustat	300 mg (ESA-naive and switch from ESA)	600 mg	Daily	UGT1A1, 1A7, 1A8, 1A9, BCRP, and OAT3[270] Inhibitor of CYP2C8 (*in vitro*), BCRP, or OAT3 and inducer of CYP2B6 (*in vitro*)[270,271]

BCRP, breast cancer resistance protein (adenosine triphosphate–binding cassette transporter family member); CKD, chronic kidney disease; CKD G5D, CKD G5 receiving dialysis; CKD G5HD, chronic kidney disease G5 receiving hemodialysis; CKD G5PD, chronic kidney disease G5 receiving peritoneal dialysis; CYP, cytochrome P450; ESA, erythropoiesis-stimulating agent; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; OAT, organic ion transporter; UGT, uridine 5'-diphospho-glucuronosyltransferase.

[a]Approval for use in specific patient populations varies by country.

More detailed information about drug-drug interactions between individual HIF-PHIs and other drugs can be found in the package inserts and product information documents issued by regulatory agencies. This table was based on information available in early 2024; labeling information may change over time. Use of a lower starting dose of any of the HIF-PHIs is reasonable.

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.

These practice points considers the possibility that, based on the 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 administering HIF-PHIs, monitor Hb levels 2–4 weeks after initiation or dose adjustments 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 1 study of vadadustat in people with CKD not receiving dialysis, for example, required dose adjustments in 12.5%–54.4% of participants during 0–8 weeks and in 11.5%–38.5% of participants during 8–24 weeks with biweekly monitoring to increase or maintain Hb.[272] 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, periodic monitoring of thyroid function is recommended during the first 3 months of treatment and as clinically indicated subsequently.

This appears to be a drug-specific effect for roxadustat and not a class effect. Postmarketing surveillance of roxadustat in Japan and a retrospective cohort study in China reported cases of central hypothyroidism during treatment, primarily during the first 3 months of treatment, but also later.[273] In the earliest case, abnormal laboratory findings became apparent at 2 weeks. 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 and affects the negative feedback loop in the hypothalamic-pituitary-thyroid axis.[231,274]

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 of the initiation of therapy, both in people who are ESA-naive and in those who have conversion from an ESA to a 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 or myocardial infarction), thromboembolic events (e.g., deep vein thrombosis or pulmonary embolism), vascular access thrombosis, or newly diagnosed cancer. Individualize consideration for HIF-PHI reinitiation or ESA initiation based on Hb levels and patient characteristics and preferences after discussion of risks and benefits of treatment.

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

3.7 ESA hyporesponsiveness

Practice Point 3.7.1: In people with anemia and CKD G5D or 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 risks for cardiovascular events, kidney failure, and death.[258,275–285] ESA hyporesponsiveness can be acute or chronic (>4 months) and is dynamic, frequently transient, and difficult-to-treat.[283,286] Its prevalence varies by geographic region, ranging from 12.5% to 30.3% as reported in recent studies.[278,280,287,288] Whereas the etiology of ESA hyporesponsiveness is complex, involving multiple risk factors, evident causes cannot be identified in ~30% of cases (Table 9).[289]

The definitions of hyporesponsiveness vary by geographic 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 9 | Causes of hyporesponsiveness to erythropoiesis-stimulating agents

• Iron deficiency
• Inflammation (infections, dialysis catheter use, and autoimmune disease)
• Hyperparathyroidism
• Blood loss (GI tract, dialysis procedure, and menses)
• Inadequate dialysis
• Malignancy
• Hematologic disorders (hemoglobinopathies, multiple myeloma, hemolysis, and antibody-mediated pure red cell aplasia)
• Nutritional deficiencies (copper, zinc, folate, vitamin B_{12}, carnitine, and vitamin E)
• Medications (RAS inhibition)
• Unexplained (~30%)

GI, gastrointestinal; RAS, renin-angiotensin system.

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).[294] These mechanistic concepts are supported by clinical studies, which demonstrated that higher serum levels of inflammatory markers such as C-reactive protein and IL-6, as well as the iron-regulatory peptide hepcidin, were associated with and/or predicted increased ESA requirements in people receiving or not receiving dialysis.[282,295–302]

Recent studies have suggested that causes of ESA hyporesponsiveness cannot be identified in ~30% of people with anemia and CKD.[289] 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 hematologic diseases.[286]

Table 10 | Definitions of hyporesponsiveness to ESAs

Definitions of ESA hyporesponsiveness	Organization or study
Failure to achieve target Hb levels with epoetin doses greater than: • i.v. EPO: 450 IU/kg/wk • s.c. EPO: 300 IU/kg/wk	NKF-KDOQI, 2001[290]
Failure to attain the target Hb concentration while receiving >300 IU/kg/wk (20,000 IU/wk) of epoetin or 1.5 μg/kg of darbepoetin alfa (100 μg/wk), or a continued need for such high dosages to maintain the target	Revised EBPG, ERA-EDTA, 2004[291]
Initial ESA hyporesponsiveness: • If no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing • In people with ESA hyporesponsiveness, avoid repeated escalations in ESA dose beyond double the initial weight-based dose *Subsequent ESA hyporesponsiveness:* • 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 • In people with acquired ESA hyporesponsiveness, avoid repeated escalations in ESA dose beyond double the dose at which they had been stable	KDIGO, 2012[157]
Weight-adjusted ESA resistance index (weekly ESA dose/[body weight × Hb]) > 15.4 IU/kg × g/dl (quartile IV)[a]	RISCAVID study, 2011[282]
Failure to achieve target Hb levels with epoetin doses greater than: • i.v. EPO 450 IU/kg/wk • s.c. EPO: 300 IU/kg/wk • Darbepoetin dose >1.5 μg/kg/wk	The UK Kidney Association (formerly the Renal Association), 2017, 2020, 2025[292]
Failure to achieve Hb target: • People receiving HD: Despite 3000 IU/dose of i.v. rHuEPO 3 times weekly (9000 IU/wk) or 60 μg/wk of i.v. darbepoetin alfa once weekly • People receiving PD: Despite 6000 IU/dose of s.c. rHuEPO once weekly (6000 IU/wk) or 60 μg/wk of i.v. darbepoetin alfa once weekly • People with CKD not receiving dialysis: Despite 6000 IU/dose of s.c. rHuEPO once weekly (6000 IU/wk)	Japanese Society for Dialysis Therapy, 2017[293]

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

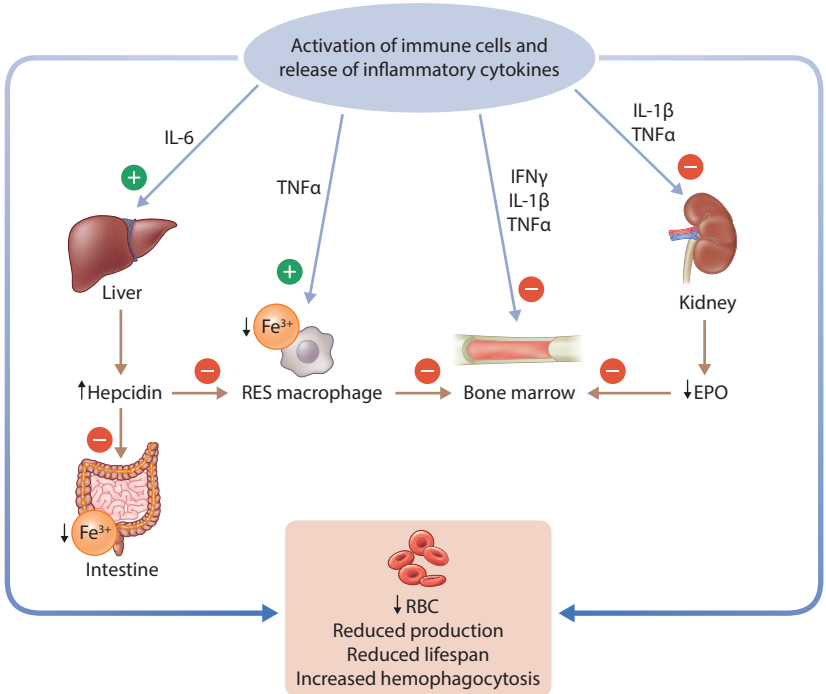


Figure 9 | Pathophysiological mechanisms of the anemia of inflammation. During inflammation, activated immune cells release cytokines that reduce hemoglobin levels through multiple pathophysiological mechanisms: hepatic production of hepcidin is increased, which prevents iron (Fe^{3+}) egress from macrophages 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; and hemophagocytosis of red blood cells (RBCs) 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 and Spinowitz.[294]

Practice Point 3.7.2: In people with CKD, anemia, and ESA hyporesponsiveness, if there is a desire to raise Hb to avoid transfusion or improve symptoms attributable to anemia, a trial course of HIF-PHI may be considered after discussion of potential risks and benefits (Figure 10).

The safety and benefits of HIF-PHIs in people with ESA hyporesponsiveness have not been established; few, if any, data support their use. People with ESA hyporesponsiveness are at increased risks for cardiovascular events, kidney failure, and death.[258,275–285] Given the cardiovascular safety concerns raised in large global cardiovascular safety trials,[231] HIF-PHI use in people with CKD and ESA hyporesponsiveness may further increase their preexisting risk of serious cardiovascular events.

Practice Point 3.7.3: In people with anemia and CKD, if a decision is made to use HIF-PHIs for the treatment of ESA hyporesponsiveness, use the lowest dose that alleviates anemia-related symptoms or reduces the risk of requiring an RBC transfusion.

A few studies have examined the effects of HIF-PHIs on Hb levels in people with anemia, CKD G5D, and ESA hyporesponsiveness; none has meaningfully examined other important clinical or patient-centered outcomes; and all have been very short term.[264,303,304] 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

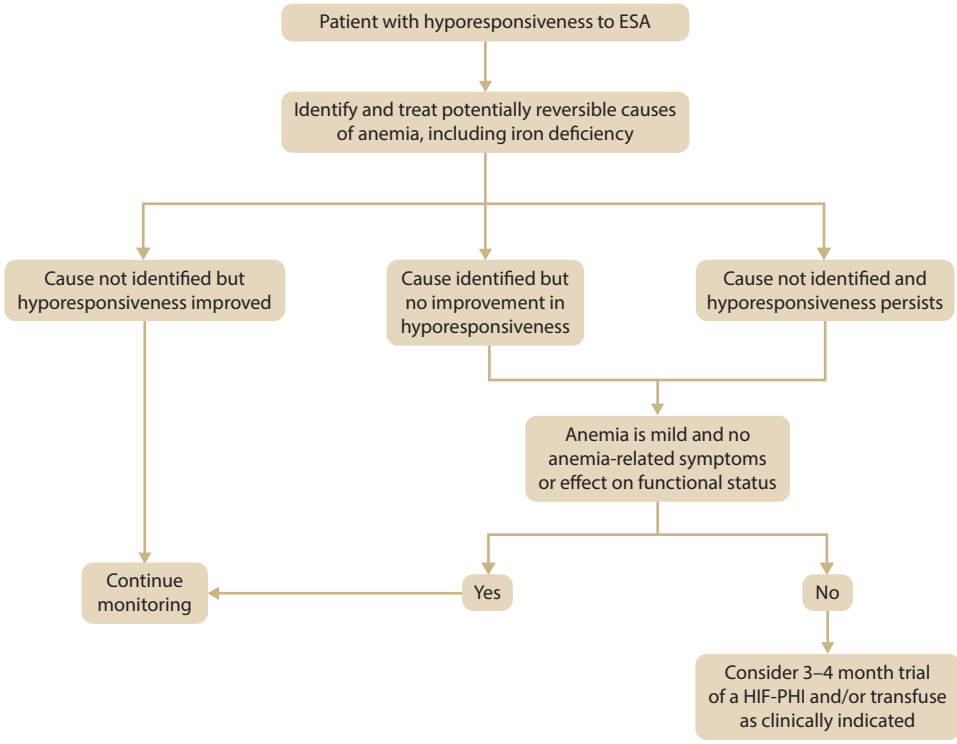


Figure 10 | Treatment algorithm for sustained erythropoiesis-stimulating agent (ESA) hyporesponsiveness. For definition of hyporesponsiveness, refer to Table 10. See Figure 8 for potentially reversible causes of anemia in chronic kidney disease. HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor.

improves clinically relevant outcomes and with limited data on 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-PHIs to try to attain the same Hb level that might be targeted in people with CKD G5D who are not ESA hyporesponsive.

Practice Point 3.7.4: In people with CKD, anemia, and ESA hyporesponsiveness, if a desired erythropoietic response has not been achieved after 3–4 months of initiating HIF-PHIs, 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 those 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 3.7.3, even among people with ESA hyporesponsive and CKD G5D who experience a Hb increase with HIF-PHIs, many do not achieve the target 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-PHIs.

HIF-PHIs are associated with increased risks of death, myocardial infarction, stroke, venous thromboembolism, and vascular access thrombosis. There is a 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.

Practice Point 3.7.6: In people with suspected ESA-related pure red cell aplasia, discontinue the ESA, transfuse as clinically appropriate, and consider referral to a hematologist, use of immunosuppressive medications, and use of a HIF-PHI for subsequent treatment of anemia based on patient preferences after consideration of risks and benefits.

ESA-related pure red cell aplasia (PRCA) is very rare but should be considered in people with a sudden decline in Hb levels despite continued use of ESAs, reduced reticulocyte count, and normal white blood cell and platelet counts. Bone marrow aspiration showing severe erythroid hypoplasia and presence of neutralizing anti-EPO antibodies are needed for a definitive diagnosis. Given that spontaneous remission after ESA cessation is rare, the administration of immunosuppressive therapy may be considered in most patients. For the subsequent treatment of anemia, alternative treatment with HIF-PHI may be considered for selected patients, with subsequent close monitoring of Hb, reticulocyte count, and anti-EPO antibody levels.

Research recommendations

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

Chapter 4: Red blood cell transfusions to treat anemia in people with chronic kidney disease

RBC 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 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 1988 National Institutes of Health Consensus Conference on Perioperative Red Blood Cell Transfusions proposed that the Hb level should not be the exclusive basis for the decision to transfuse.[305]

The primary benefits of RBC transfusions are maintaining sufficient oxygen-carrying capacity and improving anemia-related symptoms.[306] The harms are discussed further below. The benefits and harms of RBC transfusions must also be considered in light of the benefits and harms of other anemia therapies (ESAs or HIF-PHIs), which in most settings are a preferred alternative to RBC transfusion. The benefits and harms of ESAs and HIF-PHIs are discussed in detail in Chapter 3. Benefits include improvement in anemia-related symptoms and reduced need for transfusion. The most important harms are increased risks of stroke, thromboembolic events, and cancer progression or recurrence. When choosing between RBC transfusion and an ESA or HIF-PHI in an individual, personal characteristics that influence the balance between benefits and harms of each treatment should be considered. For example, a history of stroke and previous or current cancer place individuals receiving ESA therapy 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 highest risk of allosensitization.[307–311]

Potential harms of RBC transfusions

Potential harms of RBC transfusions are infrequent and encompass transfusion errors, infections, transfusion-related acute lung injury, transfusion-associated circulatory overload, 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 medical errors.[312,313] Most of these potential harms are uncommon (Figure 11).

Infection transmission is uncommon; the risk of acquiring human immunodeficiency virus or hepatitis C virus due to

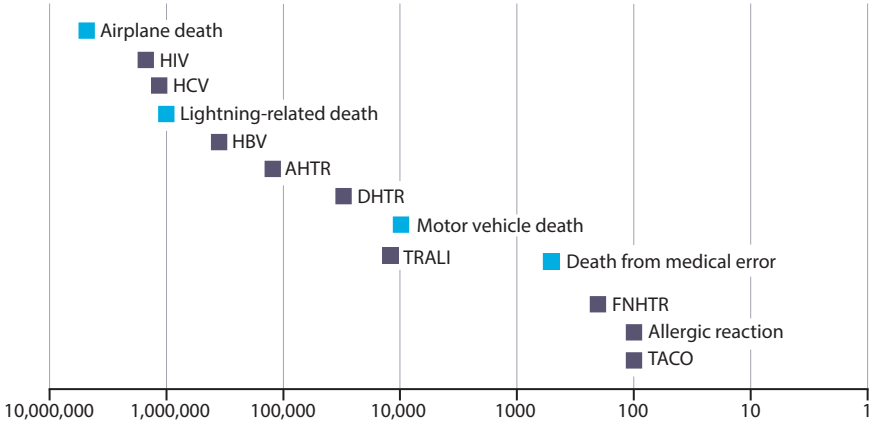


Figure 11 | Infectious and noninfectious adverse effects of red blood cell transfusions as compared with other, unrelated risks. Adverse effects of transfusions (black boxes) are shown per transfused unit of red cells, except for transfusion-associated circulatory overload (TACO), which is per transfusion episode. For unrelated risks (blue boxes), the risk of an airplane death is per flight, the risk of death from lightning is per year, the risk of death from a motor vehicle accident is per 10,000 persons, and the risk of death from medical error is per hospital admission. AHTR, acute hemolytic transfusion reaction; DHTR, delayed hemolytic transfusion reaction; FNHTR, febrile nonhemolytic transfusion reaction; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; TRALI, transfusion-related acute lung injury. Reproduced with permission from Carson *et al.* Indications for and adverse effects of red-cell transfusion. *N Engl J Med.* 2017;377:1261–1272.[312]

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.[314–317] 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: 0.97; 95% CI: 0.88–1.07).[318] 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.[319] 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 dose of iron delivered approaches 15–20 g, the amount of iron in 75–100 U 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 RBCs, we discuss below the recommendations from the 2023 Association for the Advancement of Blood & Biotherapies (AABB) guideline on RBC transfusions for the general population.[319a] 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 (Figure 12a and b), of whom 331 were followed prospectively (Figure 12c).[320] 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 prospectively developed human leukocyte antigen (HLA) antibodies. After up to 20 transfusions, 18% of those who developed HLA antibodies developed reactivity to 10%–50% of the panel, 7% developed reactivity to 50%–90% of the panel, and <3% developed reactivity to >90% of the panel (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 higher risk of HLA sensitization than nulliparous women.

The risk of allosensitization with RBC transfusion is not exactly known, but generally, an overall response rate ranging from 2% to 21% has been reported.[321–323] The 2010 USRDS Annual Report showed that the risk of allosensitization with RBC transfusion is substantial; among people who received transfusions, the OR for having panel reactive antibody (PRA) levels >80% was 2.38.[307] Other tentative conclusions from previous studies include the following: (i) washed RBCs do not appear to be less immunogenic than nonwashed RBCs[320]; (ii) no consistent reduction in sensitization has been demonstrated with donor-specific[322] and HLA-DR–matched transfusions[324]; (iii) higher numbers of RBC transfusions have been associated with an increased risk of sensitization in some studies,[325,326] but not in others.[320,327]

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.[328] In addition, the risk of allosensitization increased with increasing numbers of RBC transfusions.

Irradiated RBC transfusion is generally not advised for people with anemia and CKD who are eligible for kidney transplantation, nor for solid organ transplant recipients who have received alemtuzumab or antithymocyte globulin as induction or graft rejection therapy. The risk of transfusion-associated graft-versus-host disease in these patients is considered low.[329] While standard practice does not advocate routine RBC irradiation, exceptions may be justified based on local guidelines or specific clinical circumstances.

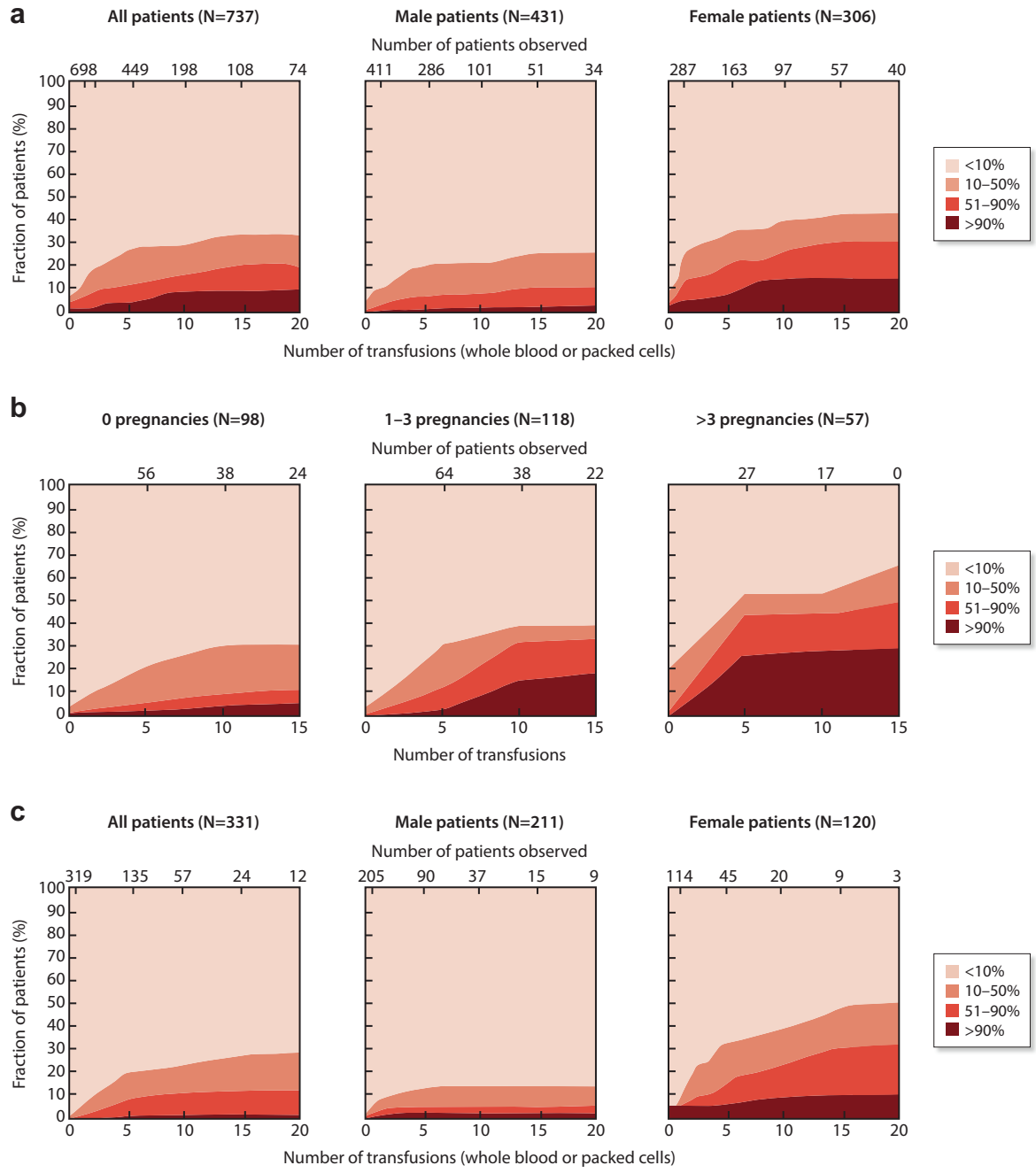


Figure 12 | Lymphocytotoxic antibody reactivity against random donor test panel in relation to the number of red blood cell transfusions. Fractions of patients reacting against <10%, 10%–50%, 51%–90%, and >90% of the panel donors are plotted. All 737 patients were on chronic hemodialysis, waiting for a first kidney transplant. Numbers of patients after 2, 5, 10, 15, and 20 transfusions are indicated at the top of graphs. (**a**) Male and female patients. (**b**) Female 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;32:177–183.[320]

Effect of leukocyte-reduced RBC transfusions on allosensitization

Many countries and institutions have introduced universal pre- or poststorage 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.[224,330,331] Also, in the post-leukodepletion era, there is evidence male patients awaiting their first organ transplant have 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 transfusion.[332] A possible reason for this finding is that the number of HLA

molecules contributed by the RBCs is comparable to that of leukocytes.[333]

Effect of allosensitization on time to transplantation and outcomes

Previously, allosensitization has been linked with longer wait times compared with nonallosensitization.[328] 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.[307] 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[334] reported little difference in the 3-year probability of receiving a transplant among people with PRA levels <80% (i.e., no difference between patients with PRA levels <1%, 1%–19%, or 20%–79%). In fact, the 3-year probability of receiving a deceased kidney transplant substantially increased for people with PRA levels ≥80% (with the highest chance of receiving a transplant in people with PRA levels 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 levels ≥80% compared with those with PRA levels <80%.

In people with transplants, the presence of preformed HLA antibodies is associated with an increased risk of early and late graft loss.[308,309,335,336] In a systematic review by Scornik *et al.*, allosensitization was linked with higher rates of graft rejection and lower rates of graft survival compared with nonsensitization.[328] Data from the 2010 USRDS Annual Report also showed that the risk of graft failure was higher in people who are allosensitized than in those who are nonallosensitized (HR: 1.41 for PRA levels ≥80% compared with PRA levels 0%).[307] It is potentially useful to know that calculated PRA level is poorly associated with post-transplant immune reactivity to the allograft in the absence of donor-specific antibodies (DSAs).[337]

Most, but not all, relevant studies found the presence of DSAs to be associated with more acute graft rejections and lower graft survival.[328] In a systematic review of 7 retrospective cohort studies involving 1119 people with CKD, presence of DSAs doubled the risk of antibody-mediated rejection and increased the risk of graft failure for 76%.[338] A recent study from the Swiss transplant cohort study confirmed that pretransplant DSAs were associated with significantly increased risks of antibody-mediated rejection, graft loss, and accelerated eGFR decline.[339]

In a recent systematic review and meta-analysis among 32,817 KTRs within 10 studies from 2000–2022, RBC transfusion after kidney transplantation was significantly associated with lower 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).[340] 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 underscores 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 transfusion may outweigh its harms in people in whom

- **ESA or HIF-PHI therapy is ineffective (e.g., those with hemoglobinopathies, bone marrow failure, or ESA or HIF-PHI resistance)**
- **ESA or HIF-PHI therapy may be harmful (e.g., those with previous or current malignancy or 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, or if the potential risks of ESAs or HIF-PHIs outweigh the benefits, such as in 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 of 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 Hb reaches a very low level), the risks related to transfusion will be low, and the benefits of ESA or HIF-PHI therapy in avoiding transfusions will be small.

In TREAT, 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 of 2012 (15%) patients randomized to darbepoetin alfa and 496 of 2026 (25%) assigned to placebo received RBC transfusions (HR: 0.56; 95% CI: 0.49–0.65; $P < 0.001$). RBC transfusion use increased during the post-TREAT and post-FDA warning periods, by 14% and 31%, respectively, compared with the pre-TREAT period.[341]

In the 2023 USRDS Annual Report,[334] the mean Hb level among people with incident kidney failure was 9.4 g/dl (94 g/l), and the percentage of patients with Hb <9 g/dl (<90 g/l) at the 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 populations had higher rates of RBC transfusions than other racial groups, particularly those with CKD G5. These data underscore the necessity of adequately treating anemia in CKD with iron and ESAs or HIF-PHIs, and only using RBC transfusions in cases of ESA or HIF-PHI hyporesponsiveness or when the risks of ESA or HIF-PHI therapy are considered to outweigh the benefits.

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

In current practice, RBC transfusion in CKD is performed as a Hb target-driven approach or during acute illnesses.[313] 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%), yet only 4.5% of patients had symptoms of severe anemia necessitating RBC transfusion.[342] In a choice-based survey in the Veteran Administration system on the decision to transfuse people with anemia receiving dialysis, the absolute Hb level was the most important consideration (29%), followed by patient functional status (16%).[313,343] 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 more restrictive strategies (generally a Hb threshold of 7–8 g/dl [70–80 g/l]),[318] 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 or unstable coronary artery disease)**
- **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, 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 (most commonly using a Hb threshold of 7.0–8.0 g/dl [70–80 g/l]) decreased the proportion of people exposed to RBC transfusion to 41% compared with a liberal transfusion strategy (generally using a Hb threshold of 9–10 g/dl [90–100 g/l]).[318] Importantly, the restrictive RBC transfusion strategy did not impact 30-day mortality, mortality at other time points, or morbidity (i.e., cardiac events, myocardial infarction, stroke, pneumonia, thromboembolism, or infection) compared with the liberal transfusion strategy. The results of this Cochrane library review are 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.[344]

In 2023, the AABB international guidelines were published evaluating evidence from 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.[319a] The thresholds are applicable to all people and can provide guidance for clinicians as to 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 Hb is <7 g/dl (<70 g/l), <7.5 g/dl (<75 g/l) for patients undergoing cardiac surgery, and <8 g/dl (<80 g/l) for those undergoing orthopedic surgery or those with clinically significant cardiovascular disease. We consider these thresholds reasonable guides in considering 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 the gastrointestinal tract, 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.

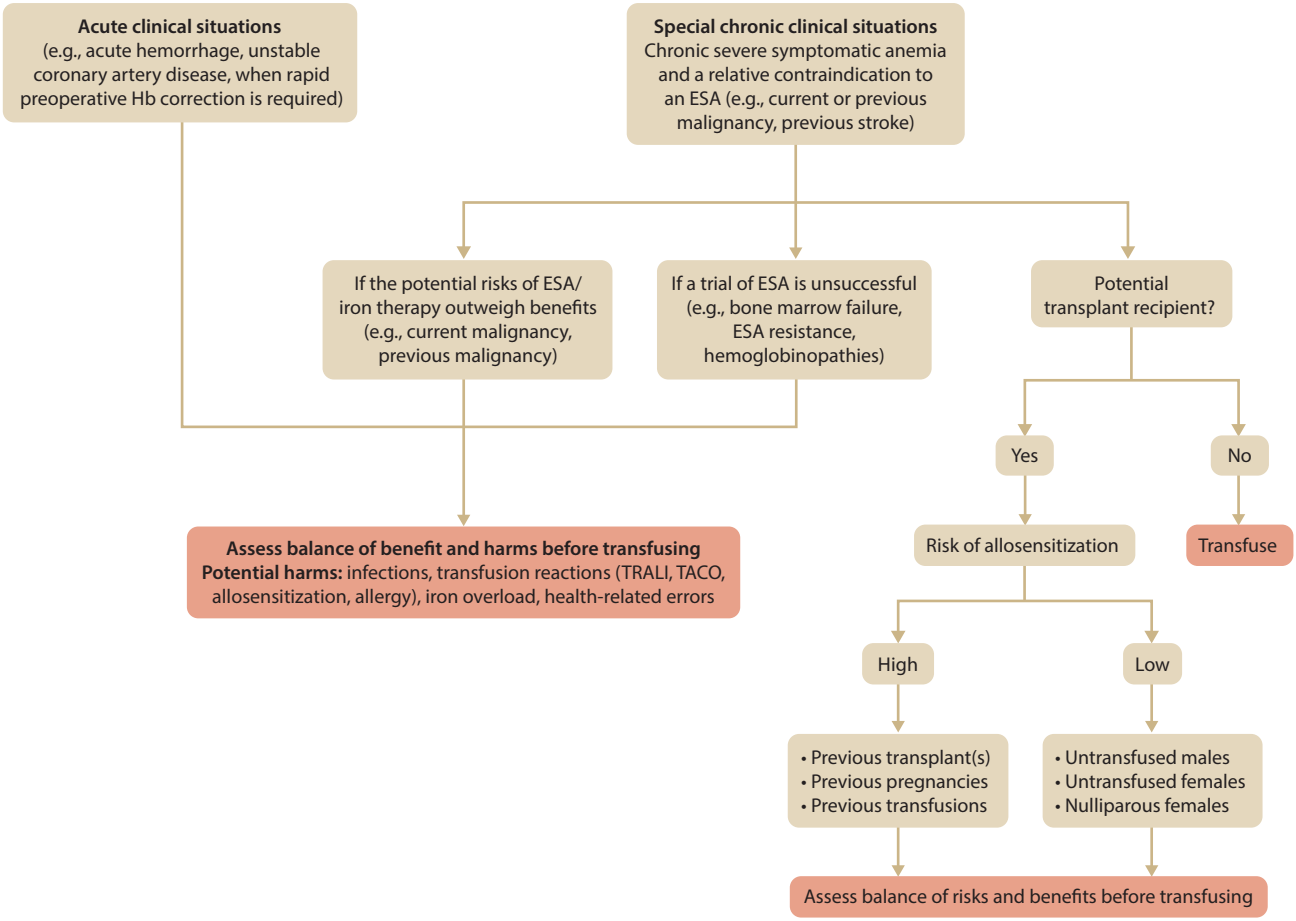


Figure 13 | Algorithm for guiding the use of red blood cell transfusion to treat anemia in people with chronic kidney disease. ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

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 to reduce the use of RBC transfusions in people with CKD.

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 the following:

- 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.

Table 11 | Strategies to reduce RBC transfusions in people with 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, base the decision for RBC transfusion on whether the person is a potential transplant candidate.

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; RBC, red blood cell.
Adapted with permission from Brenner N, Kommalapati A, Ahsan M, et al. Red cell transfusion in chronic kidney disease in the United States in the current era of erythropoiesis stimulating agents. *J Nephrol.* 2022;33:267–275.[313]

- Investigation of 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 greater need for RBC transfusions.
- Further investigation 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*.[157] The guideline development methods are described below.

Overview of the process

This guideline adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2 and S3)[345,346] and have been reported in accordance with the Appraisal of Guidelines for Research and Evaluation II reporting checklist.[347] The processes undertaken for the development of the KDIGO 2026 Clinical Practice Guideline for the Management of Anemia in CKD are described as follows:

- 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 the risk of bias assessment of the included studies
- Conducting evidence syntheses, including meta-analysis, where appropriate
- Assessing the certainty of evidence for each critical outcome
- Finalizing guideline recommendations and supporting rationale
- Grading the strength of the recommendations based on the overall certainty of 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 the Work Group and ERT. The 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 evidence of each critical and important outcome, and grading the overall certainty of evidence for each recommendation. The Work Group was responsible for writing the recommendations, practice points, and the underlying supporting text, grading the strength of the recommendations, and developing practice points.

Defining the 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 2026 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 reviews 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*.[348]

Details of the Population, Intervention, Comparator, Outcomes, 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 to treat iron deficiency and anemia in people with chronic kidney disease**
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 Subpopulations: • Not receiving dialysis • Receiving hemodialysis • Receiving peritoneal dialysis • Heart failure • 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 • Important outcomes: Growth, height, weight, and cognitive development in pediatric studies; blood transfusion; cancer; ESA/HIF-PHI use and dose; Hb values, and percentage of patients reaching target Hb • 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. *Cochrane Database Syst Rev*. 2019;2:CD007857.[349]
SoF tables	Appendix C: Supplementary Tables S4–S11
Search date	April 2023
Citations screened/ included studies	Supplementary Figure S1 • 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) • Iron dosing agent versus placebo in people with CKD receiving dialysis and ESAs/HIF-PHIs, evaluation iron dosing agents: 13,177/28 • Iron dosing agent versus placebo in people with CKD receiving dialysis and ESAs/HIF-PHIs, evaluating different targets/thresholds: 13,177/7 (not identified as a comparison for grading) • Iron dosing agent versus placebo in people with CKD receiving peritoneal dialysis: 13,177/4 • Iron dosing agents versus placebo in children with CKD: 13,177/2 (no critical or important outcomes recorded) • Iron dosing agents versus placebo in people with CKD and heart failure: 13,177/4
Chapter 3	**Use of erythropoiesis-stimulating agents, hypoxia-inducible factor–prolyl hydroxylase inhibitors, and other agents to treat anemia in people with chronic kidney disease**
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 Subpopulations: • Not receiving dialysis • Receiving hemodialysis • Receiving peritoneal dialysis • Heart failure • 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) 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 • Important outcomes: Growth, height, weight, and cognitive development in pediatric studies; blood transfusion; hypertension or change in blood pressure; cancer; Hb: change in Hb, percentage of 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 hand searching	None
SoF tables	Supplementary Tables S12–S31

(*Continued on following page*)

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

Search date	October 7, 2024
Citations screened/included studies	Supplementary Figure S2 • ESA versus HIF-PHIs in people with CKD not receiving dialysis: 5989/12 • ESA versus HIF-PHIs in people with CKD receiving peritoneal or hemodialysis: 5989/24
Review question	**What are the benefits and harms of ESAs in adults and children with CKD?**
Population	Adults and children with CKD Subpopulations: • Not receiving dialysis • Receiving hemodialysis • Receiving peritoneal dialysis • Heart failure • 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 Hb 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, percentage of patients reaching target Hb, mean Hb; iron use and dose
Study design	RCTs
Existing systematic review used for data or hand searching	Kidney Disease: Improving Global Outcomes Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl (2011)*. 2012;2:279–335.[157] Chung EY, Palmer SC, Saglimbene VM, et al. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. *Cochrane Database Syst Rev*. 2023;2:CD010590.[350]
SoF tables	Supplementary Tables S32–S48
Search date	October 7, 2024
Citations screened/included studies	Supplementary Figure S3 • ESA use in adults with CKD not receiving dialysis: 6127/44 (no critical outcomes were recorded in the graded comparison of ESA high dose versus low dose) • ESA use in adults with CKD receiving dialysis[a]: 6127/70 • ESA use in adults receiving peritoneal dialysis: 6127/3 (no critical or important outcomes were recorded for the graded comparisons of ESA treating to a high Hb target versus a low Hb target or ESA versus placebo; no critical outcomes were reported for the graded comparison of ESA high dose versus ESA low dose) • ESA use in children: 6127/6 (no critical or important outcomes were recorded for the graded comparison of ESA treating to a high Hb target versus a low Hb target) • ESA use in people with heart failure: 6127/2 (no critical or important outcomes were recorded for the graded comparison of ESA dose versus ESA dose)
Review question	**What are the benefits and harms of HIF-PHIs in adults and children with CKD?**
Population	Adults and children with CKD Subpopulations: • Not receiving dialysis • Receiving hemodialysis • Receiving peritoneal dialysis • Heart failure • 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 • Important outcomes: Blood transfusion; hypertension or change in blood pressure; cancer; Hb: change in Hb, percentage of 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

(*Continued on following page*)

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

SoF tables	Supplementary Tables S49–S52
Search date	October 7, 2024
Citations screened/ included studies	Supplementary Figure S4 • HIF-PHI versus placebo in people with CKD not receiving dialysis: 1566/16 • HIF-PHI versus placebo in people with CKD receiving dialysis[a]: 1566/6 • HIF-PHI versus HIF-PHI in people with CKD not receiving dialysis: 1566/2 • HIF-PHI versus HIF-PHI in people with CKD receiving peritoneal dialysis or hemodialysis: 1566/3

CKD, chronic kidney disease; ESA, erythropoiesis-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, and Study design; RCT, randomized controlled trial; SoF, summary of findings; SCr, serum creatinine.
[a]It was anticipated that separate reports would be completed for people with CKD G5 receiving hemodialysis and those receiving peritoneal dialysis. However, due to the number of studies not reporting results separately by dialysis modality, reports that combined modalities were completed.

Literature searches and article selection. Searches for RCTs were conducted in PubMed, Embase, and the Cochrane Central Register of Controlled Trials. The search strategies are provided in Appendix A: Supplementary Table Sl of the Data Supplement. 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 that of this guideline.[157] A review by Chung *et al.* on the use of ESAs in adults with CKD partially aligned with one of our review questions[350]; 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 the 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 reviewers screened articles identified in the searches for studies evaluating iron dosing agents and ESAs, and screening was stopped when the recall rate of citations promoted to full text was at least 95%. 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 the title/abstract and full-text screening stages, disagreements about eligibility were resolved by consensus or, if necessary, through discussion among the ERT members.

Search dates, number of citations screened, and number of eligible studies are reported in Table 12. Appendix E: Supplementary Figures S1–S4 include Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams for each systematic review.

A total of 11,094 citations were screened. Of these, 261 RCTs from 293 reports were included in the evidence review (Figure 14).

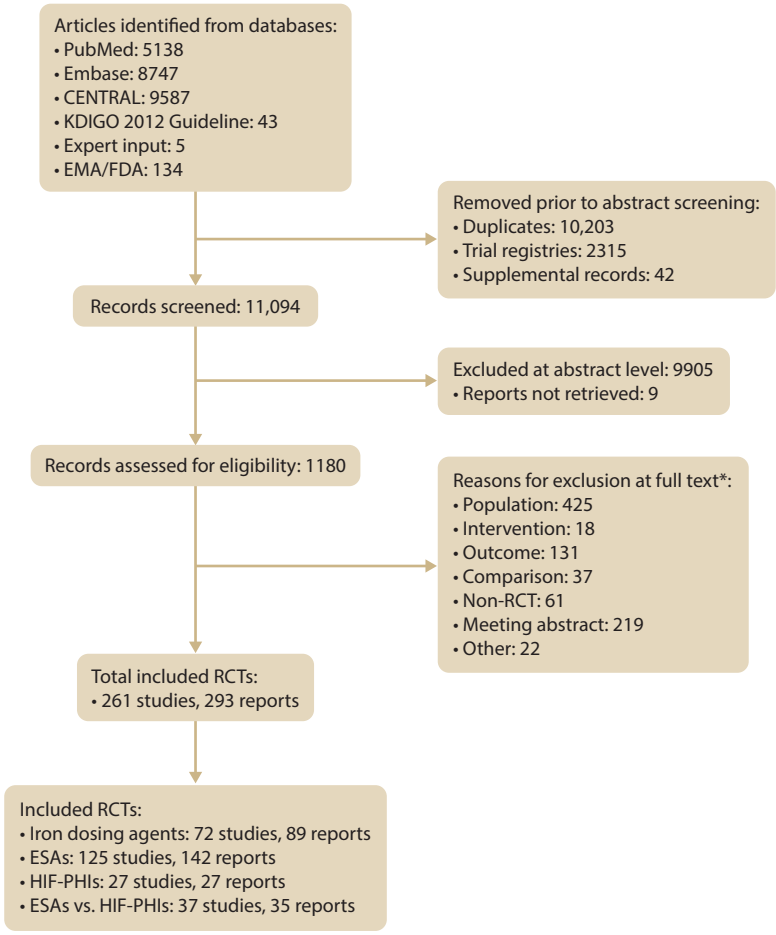


Figure 14 | Search yield and study flow diagram. EMA, European Medicines Agency; ESA, erythropoiesis-stimulating agent; FDA, Food and Drug Administration; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; KDIGO, Kidney Disease: Improving Global Outcomes; RCT, randomized controlled trial. *Number of reasons for exclusion exceeds 887 because articles could be excluded for >1 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 in extraction 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.[351]

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 as the relative risk between the trial arms of RCTs, with each study weighted by the inverse variance, using a random effects model with the DerSimonian and Laird formula for calculating between-study variance.[352] 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.[352]

Data synthesis. Meta-analysis was conducted if there were ≥2 studies that were sufficiently similar with respect to key variables (population characteristics, study duration, and 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 χ^2 test with a significance level of $\alpha \leq 0.10$. Heterogeneity was also assessed using 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.[353] Summary estimates were not provided if the I^2 was above 75%.

Grading the certainty of evidence and the strength of the guideline recommendation. The certainty of evidence for each critical and important outcome was assessed by the ERT using the GRADE approach.[354,355] For RCTs, the initial grade of the

certainty of evidence is considered to be high. The certainty of 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,[356] low event rates in either arm, CIs that indicate appreciable benefits and harms (a 25% decrease and a 25% increase in the outcome of interest), and sparse data (only 1 study)—all indicating concerns about the precision of the results.[356] The final grade of the certainty of evidence for an outcome could be high (A), moderate (B), low (C), or very low (D) (Tables 13 and 14).

Summary of findings (SoF) tables. SoF 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 evidence for each critical and important outcome is also provided in these tables. The SoF tables are available in Appendices C and D of the Data Supplement published alongside the guideline or at https://kdigo.org/guidelines/anemia-in-ckd/.

Updating and developing the recommendations. Recommendations from the *KDIGO 2012 Clinical Practice Guideline for the Management of 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.[157] Practice points were not yet proposed as a separate category in 2012, so the KDIGO 2026 Work Group considered the following options: (i) where new evidence did not suggest a change to graded recommendations, the statements were retained as graded recommendations; (ii) graded recommendations were updated, where appropriate, based on new evidence; (iii) existing recommendations that fit the criteria for practice points were rewritten as practice points; and (iv) new guideline statements (both recommendations and practice points) were generated for new clinical questions in the 2026 update.

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

Balance of benefits and harms. The Work Group determined the anticipated net health benefit on the basis of expected

Table 13 | Classification for the grade of the certainty of 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 of the certainty of evidence	Step 2—lower the grade	Step 3—raise the grade for observational studies
RCT	High	Study limitations: −1, serious −2, very serious	Strength of association: +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: −1, serious −2, very serious	Evidence of a dose-response gradient
Observational	Low	Indirectness: −1, serious −2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: −1, serious −2, very serious −3, extremely serious	
		Publication bias: −1, strongly suspected	

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

Table 15 | KDIGO nomenclature and description for grading 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.

KDIGO, Kidney Disease: Improving Global Outcomes.

Table 16 | Determinants of the strength of a recommendation

Factors	Comment
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the more likely a Level 1 recommendation is provided. The narrower the gradient, the more likely a Level 2 recommendation is warranted.
Certainty of evidence	The higher the certainty of evidence, the more likely a Level 1 recommendation is warranted. However, there are exceptions for which low or very low certainty of evidence will warrant a Level 1 recommendation.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a Level 2 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 Level 1 recommendation is warranted.

benefits and harms across all critical outcomes from the underlying evidence review.

Overall certainty of evidence. The overall certainty of 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.[356] This could be modified based on the relative importance of each outcome to the population of interest. The overall certainty of evidence was graded as 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 costs. Healthcare and non-healthcare resources, including all inputs in the treatment management pathway, were considered in grading the strength of the recommendation.[357] The following resources were considered: direct healthcare costs, non-healthcare resources (such as transportation and social services), informal caregiver resources (e.g., 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. Although systematic reviews are not performed for clinical questions underlying practice points, they are often crafted to help readers implement the guidance from graded recommendations. 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 evidence (high (A), moderate (B), low (C), or very low (D)). The recommendation statements are followed by Key information (Balance of benefits and harms, Certainty of evidence, Values and preferences, Resource use and costs, and 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

Two people living with anemia and CKD were members of the Work Group and provided invaluable perspectives and lived experiences for the development of this guideline. However, no scoping exercise with patients, searches of the qualitative literature, or formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, although resource implications were considered in the formulation of recommendations, no formal economic evaluations were undertaken.

Biographic and disclosure information

Jodie L. Babitt, MD (Work Group Co-Chair), is Professor of Medicine at Harvard Medical School and Director of Translational Research in the Division of Nephrology at Massachusetts General Hospital, Boston, Massachusetts, USA. She earned her MD at the Harvard–MIT Program in Health Sciences and Technology, completed her internal medicine residency at Beth Israel Deaconess Medical Center, and pursued a nephrology fellowship at Massachusetts General Hospital and Brigham and Women's Hospital.

Continuously funded by the National Institutes of Health (NIH) for more than 20 years, Dr. Babitt's laboratory focuses on elucidating the mechanisms regulating systemic iron homeostasis and developing new treatments for iron disorders. She has authored more than 80 publications and has received numerous awards, including the Marcel Simon Award from the International BioIron Society for excellence in research on genetic hemochromatosis and the American Society of Nephrology Distinguished Researcher Award. Dr. Babitt was inducted into the American Society for Clinical Investigation and has served on the Board of Directors of the International BioIron Society and the American Society of Hematology Committee on Iron and Heme.

JLB reports receiving support from the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases*.*

**Monies paid to institution.*

Marcello Tonelli, MD, SM, MSc, FRCPC (Work Group Co-Chair), received a medical degree from the University of Western Ontario, London, Ontario, Canada; a Master of Science in Epidemiology from Harvard University, Cambridge, Massachusetts, USA; and a Master of Science in Health Policy from Imperial College London, London, UK. He is a nephrologist and professor at the University of Calgary. Dr. Tonelli is a past president of the Canadian Society of Nephrology, a former member of the Kidney Disease: Improving Global Outcomes (KDIGO) Executive Committee, and is currently President of the International Society of Nephrology.

MT declared no competing interests.

Jeffrey S. Berns, MD, FASN, is Professor of Medicine and Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA. He earned his MD from Case Western Reserve University in Cleveland, Ohio, USA; completed his internal medicine residency at University Hospitals of Cleveland and pursued a nephrology fellowship and served as Associate Research Scientist at Yale University, New Haven, Connecticut, USA. He was until recently Vice President and Associate Dean for Graduate Medical Education for the University of Pennsylvania Health System. He also serves as Associate Chief of the Renal, Electrolyte, and Hypertension Division at the Hospital of the University of Pennsylvania, where he is a practicing clinical nephrologist.

Dr. Berns has a long-standing interest in clinical nephrology, chronic kidney disease, and particularly the anemia of chronic kidney disease. He has published more than 160 original articles, chapters, and books and is both a contributing author and editor of *UpToDate*. His publications span the fields of clinical nephrology, nephrology fellow training and assessment, public policy, and graduate medical education. He has been involved in anemia guideline development for more than 20 years. He is currently Councilor-at-Large for the American Society of Nephrology.

JSB reports receiving royalties or licenses from UpToDate.

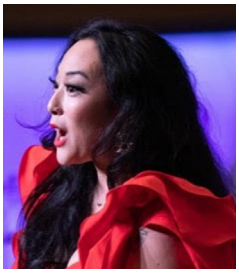
Biykem Bozkurt, MD, PhD, FHFSA, FAHA, FACC, FESC, FACP, is the Senior Dean of Faculty, the Mary and Gordon Cain Chair, and Professor of Medicine; Director of the Winters Center for Heart Failure; Associate Director of the Cardiovascular Research Institute at the Baylor College of Medicine, and Medicine Chief at the Michael E. DeBakey VA Medical Center in Houston, Texas, USA.

Throughout her career, Dr. Bozkurt has been recognized for excellence in clinical care, education, and research. She was the recipient of the VA career development grant and MERIT research awards, the American College of Cardiology Proctor Harvey MD Young Teacher Award, the American College of Cardiology Gifted Educator Award, and Baylor College of Medicine presidential awards in education, lifetime master clinician, and professionalism. In 2024, she received the

Distinguished Leadership Award from the Heart Failure Society of America and the American College of Cardiology 2024 Bahr Award of Excellence. In 2025, she was awarded the American College of Cardiology Distinguished Fellow Award. She has been listed among Clarivate World's Highly Cited Researchers (top 1% in Web of Science) in 2018, 2019, 2020, 2023, and 2024.

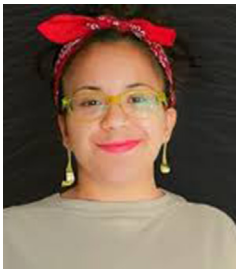
Dr. Bozkurt is Editor-in-Chief of *JACC: Heart Failure*. She served as President of the Heart Failure Society of America in 2019–2020, led the Universal Definition and Classification of Heart Failure as Chair in 2021, and is Vice-Chair of the 2022 AHA/ACC Heart Failure Guidelines Writing Committee. Dr. Bozkurt actively participates in clinical and translational research, provides advanced heart failure patient care, presents at national and international scientific meetings, and mentors trainees and faculty.

BB reports receiving consultancy fees and travel support from Abbott, Abiomed/Johnson & Johnson, Bayer, Boehringer Ingelheim, Cardurion, Cytokinetics, Eli Lilly, Idorsia, Medtronic, Merck, Novo Nordisk, Regeneron, Renovacor, Roche, SalubrisBio, Sanofi-Aventis, scPharmaceuticals, Vifor, and Respicardia/Zoll and serving as an advisory board member for Abbott, LivaNova, and Novo Nordisk.



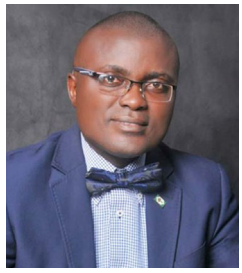
Rebecca S. Cheung Khedairy, LLM, MA, is a seasoned fundraiser with 14 years of experience in human rights, higher education, and medicine. She has successfully consulted on campaigns and established foundations in Seattle, Los Angeles, Washington, DC, and Sydney, Australia. Diagnosed with kidney failure at age 26, Ms Khedairy underwent a successful kidney transplant, thanks to an altruistic donor. She holds a master's degree in human rights law from the University of New South Wales. Currently, she serves as Director of Corporate and Foundation Relations at the University of Washington (UW), UW Medicine, Seattle, Washington, USA giving back to the institution where she received her transplant. Since 2016, Ms Khedairy has actively contributed to the Northwest Kidney Centers (NKC) as a former member of the Young Professionals Advisory Forum, Co-Chair of the NKC Gala Committee, and a member of the Kidney Research Institute's Patient Advisory Board. She is a dedicated patient advocate, committed to incorporating an equity lens in her healthcare and volunteer efforts.

RSCK declared no competing interests.



Yarieli Cuevas was born in Puerto Rico and was diagnosed with nephrotic syndrome at the age of 3. Since her diagnosis, she has been hospitalized multiple times, undergone many operations, experienced different forms of dialysis, and received a transplant. Ms. Cuevas is currently on dialysis for a second time after losing her transplant. During her first experience with dialysis, she realized the importance of having a support team that is always present. Thankfully, she had support of her family, but she noticed that this was not the case for every patient on dialysis. She decided to make it her life's goal to be that support for patients without it. She has been active and vocal, voicing her support for these patients. Yarieli advocates for the needs and preferences of people in the community who are living with kidney disease and undergoing dialysis, particularly those who may feel they do not have a voice.

YC declared no competing interests,



Emmanuel E. Effa, MBBCh, MSc (Clin. Epi), FMCP, earned his medical degree from the University of Calabar, Calabar, Nigeria where he is Associate Professor of Medicine and serves as an Honorary Consultant Nephrologist at the University of Calabar Teaching Hospital, Nigeria, where he pioneered kidney care services. He was trained in Nephrology at the University College Hospital, Ibadan, Nigeria, and earned the Fellowship of Medical College of Physique (FMCP) from the National Postgraduate Medical College of Nigeria. He also earned a master's degree in Clinical Epidemiology from Stellenbosch University, Stellenbosch, South Africa. He is also an International Society of Nephrology (ISN) scholar, following a clinical nephrology fellowship at the Division of Nephrology and Hypertension, Groote Schuur Hospital, Cape Town, South Africa. He was awarded a Clinical Research Program grant by the ISN for an early kidney evaluation and prevention study in Cross River State, Nigeria.

As a clinician-scientist, his interests include acute kidney injury, chronic kidney disease epidemiology, priority setting, systematic reviews, and clinical practice guideline development and adaptation. He is currently Deputy Director of Cochrane Nigeria, Co-Lead of West African Hub of Cochrane Africa, and a member of the Cochrane Library's Central Editorial Board. He has authored more than 70 peer-reviewed publications and serves as a peer reviewer for several journals.

EEE declared no competing interests.

Michele F. Eisenga, MD, PhD, is Assistant Professor in the Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, Groningen, The Netherlands. He earned his MD and PhD (cum laude) from the University of Groningen, which included a research clerkship at the Transplant Research Program at Children's Hospital in Boston, Massachusetts. Dr. Eisenga completed his internal medicine training

at Medisch Spectrum Twente, Enschede, The Netherlands, and University Medical Center Groningen, followed by nephrology training at University Medical Center Groningen.

His research focuses on anemia and iron homeostasis disorders in patients with chronic kidney disease and kidney transplant recipients. Dr. Eisenga has made significant contributions to the understanding of iron deficiency, the role of iron deficiency beyond anemia, and its interactions with other conditions such as CKD–mineral bone disorder and heavy metal toxicity. He has authored more than 110 peer-reviewed publications.

Dr. Eisenga has received several prestigious grants and awards, including from the Dutch Kidney Foundation. He served as a member of the Steering Committee for the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on Optimal Anemia Management in CKD. He is also a board member of the TransplantLines Biobank and Cohort study, an associate editor for *Scientific Reports* and *Frontiers in Nephrology*, and a board member of the European Renal Association Young Nephrologists' Platform.

MFE reports receiving grants or contracts from Astellas and Cablon Medical; speaker honoraria from Astellas, Cablon Medical*, GlaxoSmithKline*, Medice*, and Pharmacosmos*; and serving as an advisory board member for GlaxoSmithKline and Medice.*

**Monies paid to institution.*

Steven Fishbane, MD, is Chief of the Division of Kidney Diseases and Hypertension at Northwell Health in Great Neck, New York, USA. He also serves as Vice President and Managing Director of Kidney Disease Services for Northwell Health. Additionally, he is Chief Medical Officer for the True North Dialysis Centers, a joint venture of Northwell Health and DaVita Inc. He is Medical Director of Healthy Transitions in Late-Stage Kidney Disease, a program focused on improving kidney disease education, preparation, and transition for end-stage kidney disease. Dr. Fishbane is Chair of the Northwell Health's Department of Medicine Promotions Committee. He has also worked with the National Kidney Foundation Serving Greater New York for 18 years on educational programs.

Dr. Fishbane is Professor of Medicine at the Zucker School of Medicine at Hofstra and Northwell Health. After receiving his medical degree from the Albert Einstein College of Medicine, Dr. Fishbane trained in internal medicine and nephrology at Montefiore Medical Center in Bronx, New York, USA. He became involved in anemia- and iron deficiency–related research during his nephrology fellowship. Early in his career, this led to a series of studies on various aspects of iron deficiency diagnosis and treatment in patients with kidney disease. He was part of the 2007 KDOQI (Kidney Disease Outcomes Quality Initiative) Anemia Guideline Panel and the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Guideline Group. He was also a member of the 2019 KDIGO Controversies Conference on Optimal Anemia Management in CKD, the 2021 KDIGO Controversies Conference on Novel Anemia Therapies in CKD, and the KDIGO 2026 Clinical Practice Guideline for Management of Anemia in CKD. His research interests cover a wide variety of fields in kidney disease but with a continuing interest in anemia and iron management.

SF reports receiving consultancy fees from Akebia Therapeutics and GlaxoSmithKline; speaker honoraria from Akebia Therapeutics; and serving as an advisory board member for AstraZeneca.

Yelena Z. Ginzburg, MD, is a physician-scientist and professor at the Tisch Cancer Institute and in the Division of Hematology and Medical Oncology at the Icahn School of Medicine at Mount Sinai, New York, New York, USA. She is a board-certified hematologist, and her research focuses on translational discovery to mitigate disease in a variety of hematologic disorders, including iron deficiency anemia, primary and secondary iron overload, myelodysplastic syndromes, and polycythemia vera. Her laboratory continues to make important translational discoveries that both contribute significantly to our understanding of how crosstalk between erythropoiesis and iron metabolism impacts regulation of a variety of organ systems in health and disease and galvanize their translation for therapeutic purposes. This work has resulted in peer-reviewed publications in high impact journals, including *New England Journal of Medicine*, *Nature Medicine*, *eLife*, and *Blood*, and successful competition for numerous government, foundation, and industry grants.

Dr. Ginzburg earned her MD from Tel Aviv University, Israel and completed her internal medicine residency and hematology-oncology fellowship at the Albert Einstein College of Medicine, New York, New York, USA. As a postdoctoral fellow with Dr. Ronald Nagel, she began her studies on β-thalassemia mouse models, started her own laboratory at New York Blood Center in 2007 while serving as Medical Director of Blood Donor Services, and moved to Mount Sinai in 2016.

YZG reports receiving consultancy fees from Denali Therapeutics, Disc Medicine, Ionis Pharmaceuticals, Protagonist Therapeutics, and Takeda and speaker honoraria from Pharmacosmos.

Volker H. Haase, MD, holds the Krick-Brooks Chair in Nephrology at the Vanderbilt University School of Medicine, Nashville, Tennessee, where he serves as Professor of Medicine and Professor of Molecular Physiology and Biophysics. He received his medical degree from the Johann Wolfgang Goethe University, Frankfurt am Main, Germany; completed his medical internship and residency at Emory University, Atlanta, Georgia, USA; and trained in renal medicine at the Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts, USA. Dr. Haase practices internal medicine and nephrology at the Nashville Veterans Affairs Hospital.

Dr. Haase is a physician-scientist with postdoctoral training in molecular genetics at Massachusetts General Hospital, Boston, Massachusetts, and the Whitehead Institute for Biomedical Research, Cambridge, Massachusetts. He is internationally recognized for his research on hypoxia-inducible factor oxygen sensing and mitochondrial metabolism in kidney physiology and disease. A major focus of his research group is on the mechanisms and treatment of anemia in chronic kidney disease, with a particular emphasis on hypoxia-inducible factor–prolyl hydroxylase inhibitors. In recognition of his contributions to biomedical science, Dr. Haase received the 2006 Sir William Osler Young Investigator Award from the Interurban Clinical Club, was elected to the American Society for Clinical Investigation and the Association of American Physicians, and was recently named a Fellow of the American Association for the Advancement of Science.

VHH reports receiving consultancy fees from Akebia Therapeutics and speaker honoraria from the American Society of Hematology, MJH Life Sciences, Medscape, and the National Kidney Foundation.

S. Susan Hedayati, MD, MSc, FASN, FACP, is Professor of Medicine in the Division of Nephrology and holds the Lina Obeid Endowed Chair in Biomedical Sciences at the Stony Brook University School of Medicine, Stony Brook, New York, USA, where she serves as Vice Dean for Research and Director of the Office of Scientific Affairs. Prior to that, she was Professor of Medicine in the Division of Nephrology at the University of Texas (UT) Southwestern in Dallas, Texas, where she was Associate Vice Chair for Research and Director for Clinical and Translational Research in Nephrology. She earned her MD from the George Washington University School of Medicine, Washington, DC, USA and MSc in Clinical Sciences from Duke University, Durham, North Carolina, USA, where she completed her internal medicine residency and fellowship in nephrology.

Dr. Hedayati is a National Institutes of Health R01–funded physician-scientist, and her research focuses on elucidating nontraditional cardiovascular risk factors in people with chronic kidney disease (CKD) and cardiorenal syndrome, as well as on investigating the efficacy and tolerability of treatments for major depression in people with CKD, which led to 3 investigator-initiated, federally funded, multicenter randomized controlled trials. In 2023, she received the Shaul G. Massry Distinguished Lecture Award from the National Kidney Foundation to recognize her outstanding achievements in kidney disease research and contributions to kidney healthcare.

In addition to her research, Dr. Hedayati is a nationally renowned mentor and educator who has served as a Training Program Director of the Nephrology Fellowship and has personally mentored a broad range of more than 20 trainees in a broad range of research funded by R25, T32, and KL2 training grants. As the recipient of the first institutional R38 grant funded by the National Institute of Heart, Lung, and Blood, she created the UT-STARR residency research training program while at UT Southwestern, as well as the Funds to Retain Clinical Scientists Affected by COVID-19 (UT-FOCUS) program awarded by the Doris Duke Foundation and American Heart Association. As testament to her years of effective mentoring of numerous medical students, residents, nephrology fellows, and junior faculty, she received the Leaders in Clinical Excellence Mentoring Award while at UT Southwestern. She has been involved in graduate medical education at the national level on the American College of Physicians MKSAP (Medical Knowledge Self-Assessment Program) Nephrology Writing Committee, as well as the board review course offered by the American Society of Nephrology.

SSH reports receiving speaker honoraria from the American College of Physicians Nephrology and MKSAP Faculty.

Siah Kim, BSc(Hons), MBBS, FRACP, MMed(ClinEpi), PhD, is a clinician-researcher, a consultant pediatric nephrologist at the Children's Hospital at Westmead, Australia and a senior lecturer in clinical epidemiology at the Sydney School of Public Health, Sydney, New South Wales, Australia. Dr. Kim completed her PhD at the Centre for Kidney Research, focusing on early markers of kidney disease among Aboriginal children and adolescents.

Dr. Kim's current research interests focuses on minimizing the burden of chronic kidney disease on the lives of children and their families. Her leadership in pediatric nephrology research is demonstrated through her roles in national and international guideline development. Dr. Kim has continued to support the growth of pediatric nephrology worldwide through her establishment of the International Pediatric Nephrology Association mentorship program, teaching across outreach programs across Southeast Asia and supporting the ISN-The Transplant Society Sister Transplant Center in Vietnam.

SK declares no competing interests.

José A. Moura-Neto, MD, PhD, MBA, FASN, FACP, FRCP (Lon), is a consultant nephrologist and Professor of Internal Medicine at the Bahiana School of Medicine and Public Health, Salvador, Bahia, Brazil. He brings together expertise in nephrology, internal medicine, and health management, with clinical and academic work focused on chronic kidney disease and kidney replacement therapy.

He earned his MD from the Bahiana School of Medicine and Public Health, Salvador, Brazil in 2011. He completed residencies in internal medicine (Hospital Federal do Andaraí, 2012–2014), nephrology (Universidade do Estado do Rio de Janeiro, 2014–2016), and kidney transplantation (Universidade do Estado do Rio de Janeiro, 2016–2017). In 2017, he became a board-certified nephrologist by examination through the Brazilian Society of Nephrology. He also holds an MBA in health management and a master's degree in administration, both from Fundação Getulio Vargas (2014–2017), and a PhD in medicine from the Bahiana School of Medicine and Public Health (2022–2025).

Dr. Moura-Neto is currently serving 2 terms as President of the Brazilian Society of Nephrology (2023–2024 and 2025–2026). He is a board member of the ISN Latin America Regional Board (2023–2025) and the International Society for Hemodialysis (2022–2025).

He has edited 8 books, including *Nephrology Worldwide* and *Complications in Dialysis*, and authored more than 70 peer-reviewed articles and book chapters, with more than 1100 citations. He is Associate Editor of *Blood Purification* and Visual Abstract Editor for *Clinical Journal of the American Society of Nephrology*, *Journal of the American Society of Nephrology*, and *Kidney360*.

He lives in Salvador, Brazil, with his wife and 3 children.

JAM-N declares no competing interests.

Evi V. Nagler, MD, PhD, is a clinical nephrologist at Ghent University Hospital, Ghent, Belgium, where she primarily focuses on transplant medicine. She has dedicated her research career to guideline development and systematic review methodology. From 2009 to 2020, Dr. Nagler served as Senior Methodologist and later as Vice-Chair for the European Renal Association's guideline development body, European Renal Best Practice. During her tenure, she actively participated in the creation of numerous clinical practice guidelines, offering methodological support to development teams and ensuring the quality and integrity of the production process. In 2025, she joined the Kidney Disease: Improving Global Outcomes (KDIGO) Methods Committee, contributing to enhancing the rigor and transparency of KDIGO Guidelines.

EVN declares no competing interests.

Patrick Rossignol, MD, PhD, is a nephrologist and vascular medicine specialist, a European Society of Hypertension–certified hypertension specialist, and formerly a Professor of Therapeutics at the University of Lorraine, Nancy, France.

Since 2022, he has headed the Department of Medicine Specialties and Nephrology-Hemodialysis at Princess Grace Hospital, Monaco. He is also Medical Director of a private hemodialysis center in Monaco. He has chaired the Monaco Clinical Research Infrastructure Network since its creation in 2025.

He is Coordinator of the French Clinical Research Infrastructure Network Cardiovascular and Renal Clinical Trialists Network of Excellence since its creation in 2014.

From 2018 to 2022, he served as Director of the Nancy University Hospital INSERM Clinical Investigation Centre, after serving as its Deputy Director for 10 years. He is now an associate researcher.

He is also Course Director of the Kidney Disease Clinical Trialists (KDCT) Workshop.

Dr. Rossignol has been involved in numerous clinical trials in the settings of heart failure, hypertension, and chronic kidney disease as well as in translational basic research studies on cardiorenal syndrome.

He has published more than 600 peer-reviewed publications and is a coinventor of 9 biomarker international patents in the cardiorenal syndrome setting.

PR reports receiving consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, Vera Therapeutics, and Vifor; travel support from Bayer, Vera Therapeutics, and Vifor; and serving as an advisory board member for Bayer and Novartis.

Manisha Sahay, MD, DNB, FAMS, FRCP, is Professor and Head of Nephrology at Osmania Medical College and Hospital, Hyderabad, India. She is the recipient of 13 gold medals, including the National Gold Medal in Nephrology, 2003. She has 250 publications to her credit in peer-reviewed journals and has trained 50 nephrology fellows.

She is Emeritus Editor of the *Indian Journal of Transplantation* and Associate Editor of the *Indian Journal of*

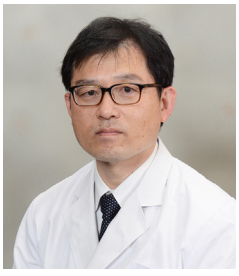
Nephrology and serves as a reviewer for several international and national journals.

She has held several positions in the International Society of Nephrology (ISN), including council member, Chair of the South Asia Regional Board, Chair of the CME Committee, and executive member of the American Nephrologists of Indian Origin; executive member of the Sister Renal Center Committee; and executive committee member of the Young Nephrologists' Committee; as well as in the Transplantation Society.

She is currently President of Women in Nephrology (WIN-India) and has served as Vice President of ISN and a scientific committee member and an executive member of the Indian Society of Organ Transplant. She is involved in several global clinical trials and has served as a national leader for some of them.

She is in charge of the hub-and-spoke model of dialysis at the Osmania hub center, which provides dialysis to patients in several districts around Telangana, India. She played a key role in the initiation of deceased donor transplant, multiorgan transplants, and continuous ambulatory peritoneal dialysis in the government sector in Telangana and is actively involved in screening and prevention of chronic kidney disease programs in low- and middle-income countries.

MS declared no competing interests



Tetsuhiro Tanaka, MD, PhD, FASN, is Professor of Nephrology at the Tohoku University Graduate School of Medicine, Miyagi, Japan. He graduated from the University of Tokyo Faculty of Medicine in 1997 and completed graduate studies at the University of Tokyo Graduate School of Medicine in 2005. He continued his research in experimental chronic kidney disease, hypoxia, and anemia at the University of Erlangen, Germany, and the University of Tokyo, Tokyo, Japan, with a particular focus on the role of hypoxia in tubulointerstitial injury of the kidney. He was awarded a Young Investigator's Award by the Japanese Society of Nephrology in 2014.

As a physician scientist in nephrology, he has served in the Division for Health Service Promotion at the University of Tokyo and the Department of Nephrology and Endocrinology at the University of Tokyo Hospital. Since 2022, he has been a professor in the Department of Nephrology at the Tohoku University Graduate School of Medicine. He is currently an editorial board member for *Kidney International*, *Nephrology (Carlton)*, and *Clinical and Experimental Nephrology*.

TT reports receiving consultancy fees from Torii Pharmaceutical and speaker honoraria from Astellas, Bayer, Kyowa Kirin, Mitsubishi Tanabe, and Torii Pharmaceutical.

Angela Yee-Moon Wang, MD (UNSW), PhD (HKU), FRCP (Edin/Lond), is Clinical Professor at the Duke–National University of Singapore (NUS) and Senior Consultant at the Department of Renal Medicine, Singapore General Hospital, Singapore. Dr. Wang is recognized for her research in peritoneal dialysis, cardiovascular-kidney-metabolic (CKM) complications, chronic kidney disease–mineral bone disease (CKD-MBD), and renal nutrition. Her latest research endeavors are in clinical trials and innovations to improve the outcomes of patients with kidney diseases, precision medicine in CKM complications, and preventive kidney medicine.

Dr. Wang has received several prestigious international awards, including Thomas Addis Award, a lifetime award of the International Society of Renal Nutrition and Metabolism (ISRNM) (2022); Joel D. Kopple Award from the United States National Kidney Foundation (2018); Travelling Lecturer Award of the Asia Pacific Federation of Clinical Biochemistry (2011/2012); and International Society of Peritoneal Dialysis (ISPD) John F. Maher Award (2006). She served as International Society of Nephrology (ISN) Councilor (2021–2025), Chair of the ISN Education Working Group (2023–2025), and Chair of the ISN North and East Asia Regional Board (2023–2025). She is a past president of the ISRNM, a previous executive committee member of Kidney Disease: Improving Global Outcomes (KDIGO) (2015–2017), and a council member of the International Society for Peritoneal Dialysis (ISPD) (2016–2024).

She has contributed to various international clinical practice guidelines, including KDOQI (Kidney Disease Outcomes Quality Initiative) Clinical Practice Guideline for Nutrition in Chronic Kidney Disease 2020, ISPD Prescribing High-Quality Goal-Directed Peritoneal Dialysis: 2020 Update of ISPD Peritoneal Dialysis Prescription and Adequacy Guidelines, and KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) 2009. She chairs the First Joint ISRNM and ISPD Practice Recommendations on Nutrition Management in Peritoneal Dialysis Patients 2023–2025 and previously chaired ISPD Cardiovascular and Metabolic Guidelines for Adult Peritoneal Dialysis Patients 2015. She serves on the editorial boards of *Kidney International*, *Journal of the American Society of Nephrology*, *Clinical Journal of the American Society of Nephrology*, *Nephrology Dialysis Transplantation*, *Nephron Clinical Practice* (Associate Editor), *Journal of Renal Nutrition*, *Journal of Diabetes*, and so on. She is Editor-in-Chief of *EMJ-Nephrology*. She has also served as Associate Editor of *American Journal of Kidney Diseases* and International Editor of *Clinical Journal of the American Society of Nephrology*. She has published more than 250 papers and 15 book chapters and

delivered more than 250 invited lectures at international, regional, and national conferences.

AY-MW reports receiving consultancy fees from CSL Behring and Fresenius Kabi; speaker honoraria from AstraZeneca, Bayer, and Fresenius Kabi; and travel support from Bayer, CSL Behring, and Fresenius Kabi.

David C. Wheeler, MD, FRCP, is Professor of Kidney Medicine at the University College London and Honorary Consultant Nephrologist at the Royal Free Hospital, London, UK. He has contributed to the development and operationalization of several large-scale clinical trials testing therapeutic interventions in patients with chronic kidney disease. He was a coprincipal investigator of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trial, which has led to the broader use of sodium-glucose cotransporter-2 inhibitors to slow progression of kidney disease. His previous roles include President of the UK Renal Association and Kidney Disease: Improving Global Outcomes (KDIGO) Co-Chair. He has recently completed a term as Chair of the International Society of Nephrology Advancing Clinical Trials (ISN-ACTs) Committee and is currently the ISN's Deputy Chair for Western Europe. In England, he is National Institute for Health Research National Specialty Lead for Renal Disorders.

DCW reports receiving support for manuscript development from Astellas, GlaxoSmithKline, Medici, and Vifor; grants or contracts from AstraZeneca, Bayer, Boehringer Ingelheim, CSL, Eledon Pharmaceuticals, Galderma, Merck, Menarini, and ProKidney; consultancy fees from AstraZeneca; travel support from AstraZeneca and Boehringer Ingelheim; and speaker honoraria from AstraZeneca, Boehringer Ingelheim, and Menarini as well as serving as an advisory board member for Dimerix, Eledon Pharmaceuticals, Pathalys Pharma, ProKidney, and Vertex Pharmaceuticals.*

**Monies paid to institution.*

KDIGO Chairs

Michel Jadoul, MD, chaired the Division of Nephrology of the Cliniques universitaires Saint-Luc for 20 years (2003–2023) and is now a young emeritus full clinical professor at UCLouvain, both in Brussels, Belgium. His clinical activities still include follow-up of patients with chronic kidney disease undergoing hemodialysis.

His research interests encompass various complications of hemodialysis, including hepatitis C, cardiovascular complications after kidney transplantation, various causes of drug nephrotoxicity, and the epidemiology of CKD in sub-Saharan Africa.

Professor Jadoul has (co-)authored more than 360 scientific papers, most of them published in major nephrology journals. He is an associate editor of *Nephrology Dialysis Transplantation*. In 2008, he received the International Distinguished Medal of the National Kidney Foundation and was a member of the European Renal Association Council (2013–2016). Professor Jadoul co-chaired development of the 2008, 2018 and 2022 versions of the Kidney Disease: Improving Global Outcomes (KDIGO) Hepatitis C Virus in Chronic Kidney Disease Guideline and served as KDIGO Co-Chair since January 1, 2019.

MJ reports receiving consultancy fees from Astellas, AstraZeneca, Bayer*, and Boehringer Ingelheim*; speaker honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Menarini, and STADA Eurogenerics; funding for expert testimony from STADA-Eurogenerics*; travel support from AstraZeneca and Boehringer Ingelheim*; and serving as an advisory board member for Boehringer Ingelheim, CSL Vifor, and Novo Nordisk.*

**Monies paid to institution.*

Morgan E. Grams, MD, PhD, MHS, is a nephrologist, PhD-trained epidemiologist, and the Susan and Morris Mark Professor of Medicine and Population Health at New York University, New York, USA, where she helps lead the Division of Precision Medicine, a multidisciplinary research unit. Dr. Grams is Co-Principal Investigator of the Chronic Kidney Disease Prognosis Consortium, a consortium of more than 30 million participants, 100 cohorts, and 250 investigators from around the globe. Her research encompasses the epidemiology of chronic kidney disease, pharmacoepidemiology, and analysis of real-world evidence as well as the integration of multimodal omics, histology, and imaging data. She was the winner of the Young Investigator Award in 2018 given by the American Society of Nephrology (ASN)/American Heart Association Kidney Council, the highest award for investigators under the age of 45 years, and she is a member of the American Society of Clinical Investigation. Her formal training was completed at Yale, Columbia, and Johns Hopkins universities. She is presently a Kidney Disease: Improving Global Outcomes (KDIGO) Co-Chair.

MEG reports receiving grants or contracts from the National Institutes of Health and National Kidney Foundation (NKF)*; speaker honoraria from the University of Washington; and travel support from ASN, KDIGO, and NKF; and serving as an advisory board member for Kidney Research Institute, Optimal Aging Institute, and United States Renal Disease System.*

**Monies paid to institution.*

Methods Committee Representative

Elie A. Akl, MD, MPH, PhD, is a tenured professor of medicine and Vice Provost for Research at the American University of Beirut (AUB), Lebanon. He is Founding Head of the Division of General Internal Medicine and Geriatrics and Founding Director of the AUB GRADE Center. He is internationally recognized for his expertise in evidence synthesis, development of practice guidelines, and management of conflicts of interest. He has published more than 550 peer-reviewed papers and has been listed by Clarivate as one of the "Highly Cited Researchers" annually since 2015 (top 0.1% of scientists globally). He serves as a guideline methodologist for many guideline development groups, including at the World Health Organization (WHO). At the WHO, he is Co-Chair of the Expert Advisory Panel on Drug Evaluation (Essential Medicines List) and a member of the Advisory Panel on the International Clinical Trials Registry Platform. He is a member the GRADE Executive Committee and of the Guidelines International Network Board of Trustees.

EAA declared no competing interests.

Evidence Review Team

Karen A. Robinson, PhD, is Professor of Medicine in the Department of Medicine at the Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, with joint appointments in the Department of Epidemiology and the Department of Health Policy and Management at the university's Bloomberg School of Public Health.

Dr. Robinson conducts systematic reviews and research on the use of evidence in clinical decision-making. She is Director of the Johns Hopkins University Evidence-Based Practice Center (EPC) and, within the EPC Program, serves as Associate Editor and on the Methods Steering Committee. For more than 20 years, she has been an active member of Cochrane, where she has served as a systematic review author, methods researcher, and editor for 2 review groups (including the Methodology Review Group). Within the Guidelines International Network, she served on the steering committees for 2 groups: Tech and North America. She has also served on 6 National Academy of Sciences panels reviewing evidence synthesis methods for decision-making used by US agencies such as the Environmental Protection Agency and Department of Defense. Dr. Robinson is a founding steering group member and current Chair of the Evidence-Based Research Network.

KAR reports receiving travel support from Kidney Disease: Improving Global Outcomes (KDIGO).

Lisa M. Wilson, ScM, is Senior Research Associate in Health Policy and Management in the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. She has been with the Johns Hopkins University Evidence-Based Practice Center since 2004 and has managed more than 25 systematic reviews and several methods projects. As a coinvestigator of the Evidence Review Team, she participated in all aspects of the review and took the lead in drafting synthesis sections, performing meta-analyses, and drafting evidence profiles.

LMW reports receiving travel support from Kidney Disease: Improving Global Outcomes (KDIGO).

Renee F. Wilson, MS, is Senior Research Associate with the Johns Hopkins University Evidence-Based Practice Center, Baltimore, Maryland, USA. She has extensive experience in systematic review methods and in the development of comprehensive literature search strategies using multiple databases. She has managed and participated in a number of large multidisciplinary collaborative projects. In addition to her work with the Evidence-Based Practice Center, she has worked on a project sponsored by the Patient-Centered Outcomes Research Institute to develop methods for guideline developers writing guidelines for individuals with multiple chronic conditions; worked at the University of Maryland School of Nursing to assess the effectiveness of nurse-led care compared with physician-led care; assisted in the creation of an effectiveness guidance document for the Center for Medical Technology Workgroup; collaborated with the World Health Organization on a project centered on patient safety during the coronavirus disease 2019 pandemic; and worked on the evidence review team for 2 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

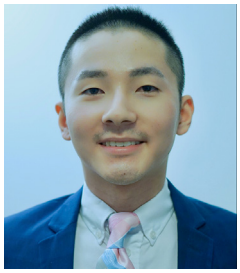
RFW declared no competing interests.

Dipal M. Patel, MD, PhD, is Assistant Professor of Medicine in the Division of Nephrology at Johns Hopkins University, Baltimore, Maryland, USA. She is a practicing nephrologist dedicated to improving care for people with kidney disease, including the implementation of patient-reported outcome measures and person-centered practices in nephrology care. She served as an internal advisor to the Evidence Review Team.

DMP declared no competing interests.

Troy Gharibani, BS, BA, is Research Assistant at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. He has worked with the Johns Hopkins Evidence-Based Practice Center since 2022, where he has gained experience in various aspects of systematic reviews, including development of search strategies in multiple databases, screening and data extraction, quality assessment, and data synthesis. He studied neurobiology and English at the University of Maryland, College Park, Maryland, USA. He served as a research assistant on the Evidence Review Team.

TG declared no competing interests.



Xuhao Yang, MSPH, is Research Assistant at the Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. He completed a Master of Science in Public Health degree at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, focusing on social and behavioral interventions. Mr. Yang has been involved with Kidney Disease: Improving Global Outcomes (KDIGO) Anemia systematic review and guideline development projects since 2022. He is also employed at Kennedy Krieger Institute, where he provides statistical solutions and research mentorship on evidence-based health policies and interventions to improve life-course health outcomes for diverse communities.

XY declared no competing interests.

Yuanxi Jia, PhD, earned his PhD in epidemiology from the Johns Hopkins Bloomberg School of Public Health and completed a postdoctoral fellowship at the Johns Hopkins School of Medicine, Baltimore, Maryland, USA. He is currently a senior research fellow at the School of Medicine, National University of Singapore. His research interests include meta-research aimed at improving the quality of randomized clinical trials and reducing bias in clinical evidence, with publications in leading journals such as *The BMJ*, *JAMA Network Open*, and *BMC Medicine*.

YJ declared no competing interests.

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A special debt of gratitude is owed to the KDIGO Co-Chairs Morgan E. Grams and Michel Jadoul and immediate past Co-Chair Wolfgang C. Winkelmayer, for their invaluable oversight throughout the development of this guideline. In particular, we thank Melissa Thompson, Michael Cheung, Jennifer King, and Karen A. Robinson, Lisa M. Wilson, Renee F. Wilson, Dipal M. Patel, Troy Gharibani, Xuhao Yang, Yuanxi Jia for their substantial contribution to the rigorous assessment of the available evidence. We also acknowledge Debbie Maizels for her vital contributions to the artwork presented in this guideline.

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Participation in the public review does not necessarily constitute endorsement of the content of this report by the above individuals or the organizations or institutions they represent.

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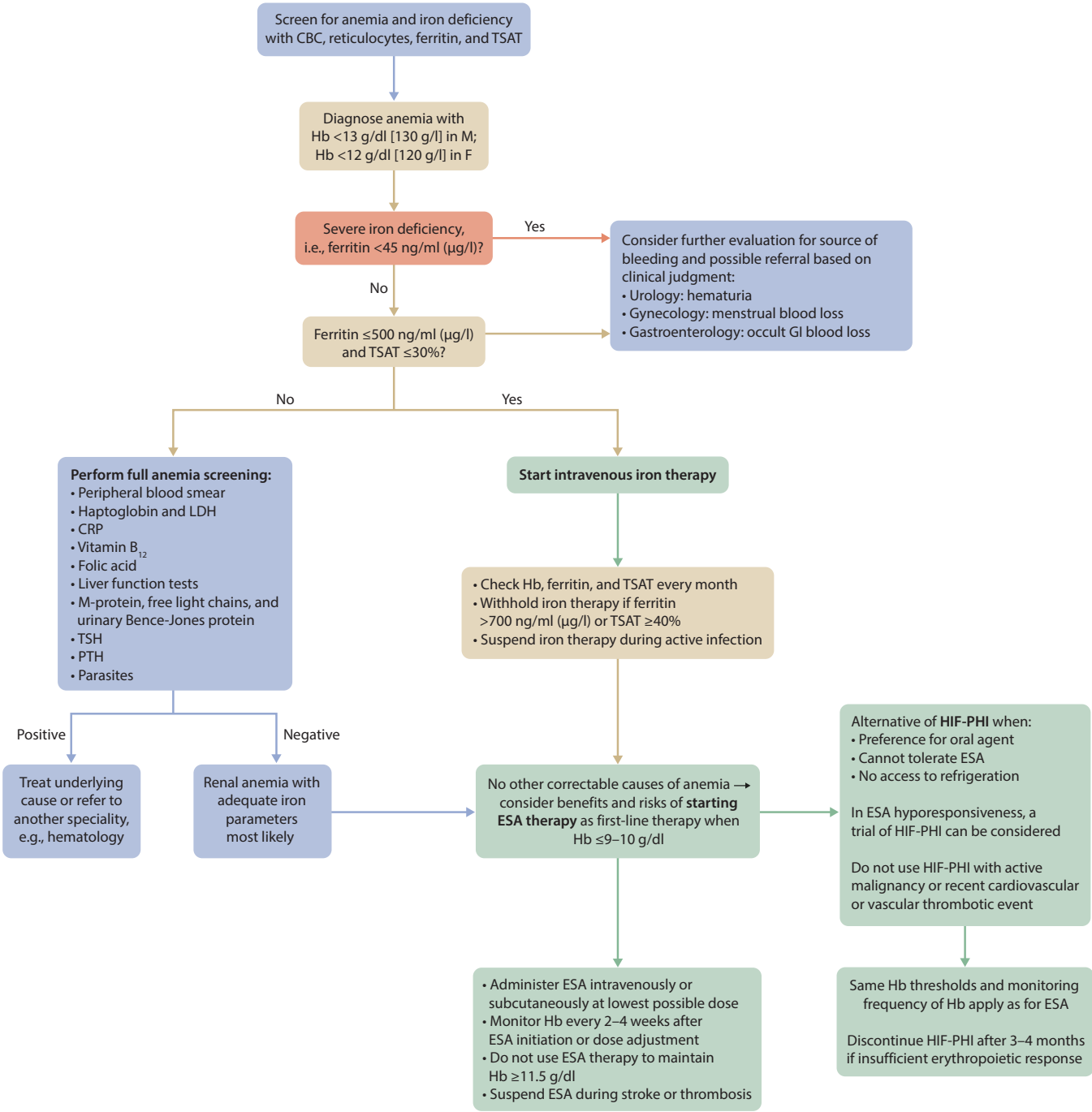
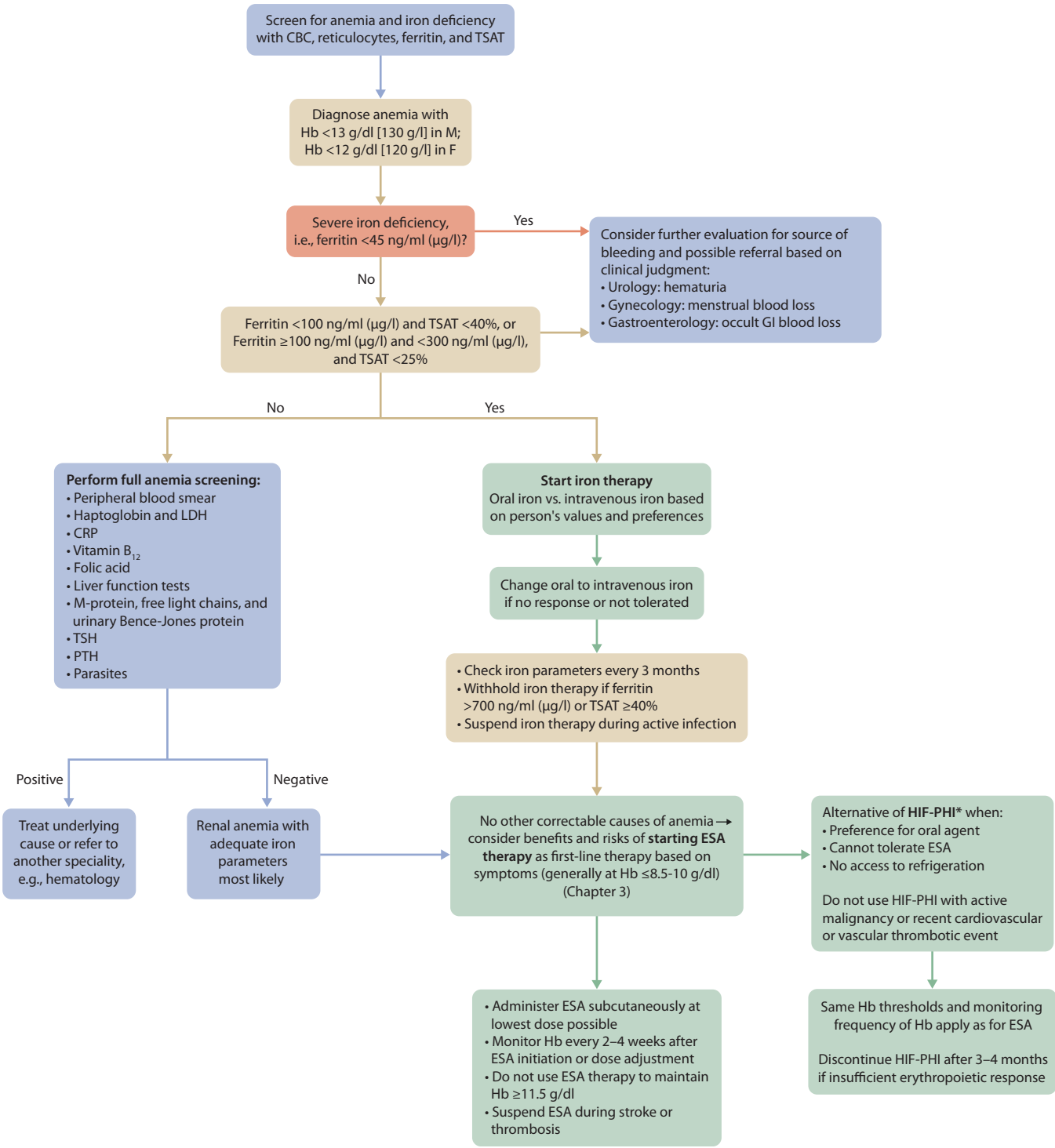
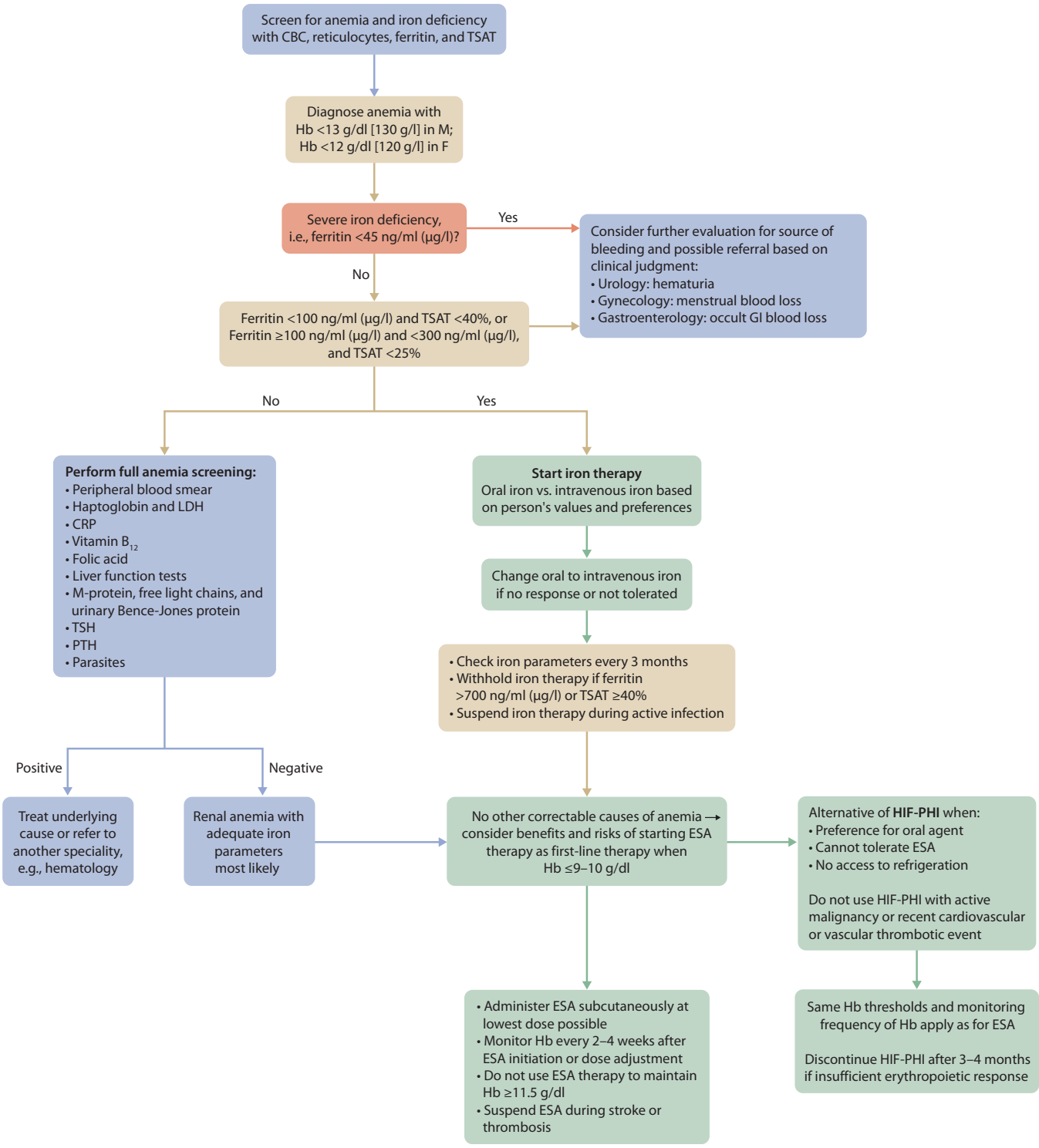
Appendix A: Population-based algorithms for the management of anemia in chronic kidney disease



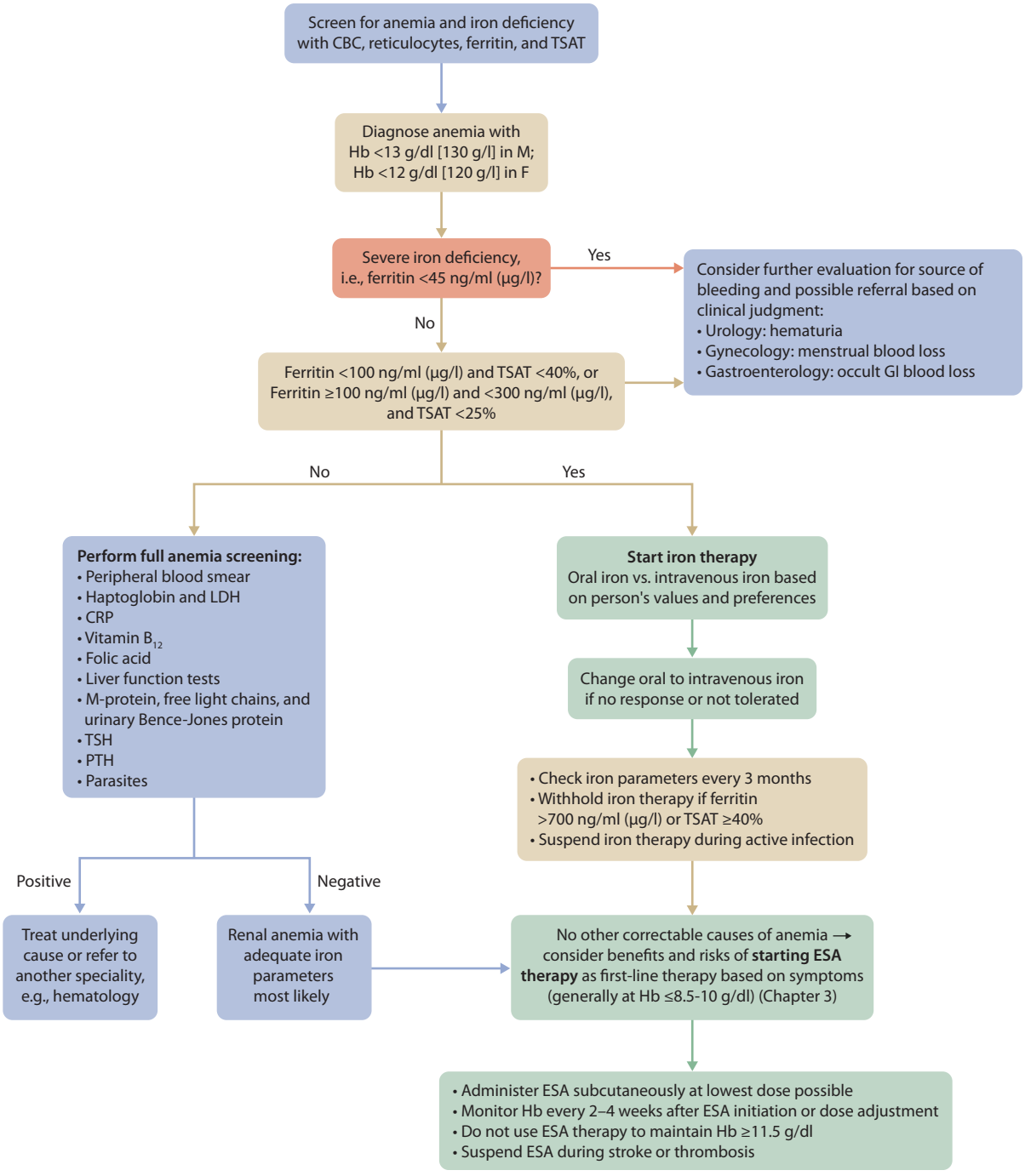
Appendix Figure 1 | Management of anemia in chronic kidney disease G5 receiving hemodialysis. CBC, complete blood count; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; F, female; GI, gastrointestinal; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; LDH, lactate dehydrogenase; M, male; PTH, parathyroid hormone; TSAT, transferrin saturation; TSH, thyroid-stimulating hormone.



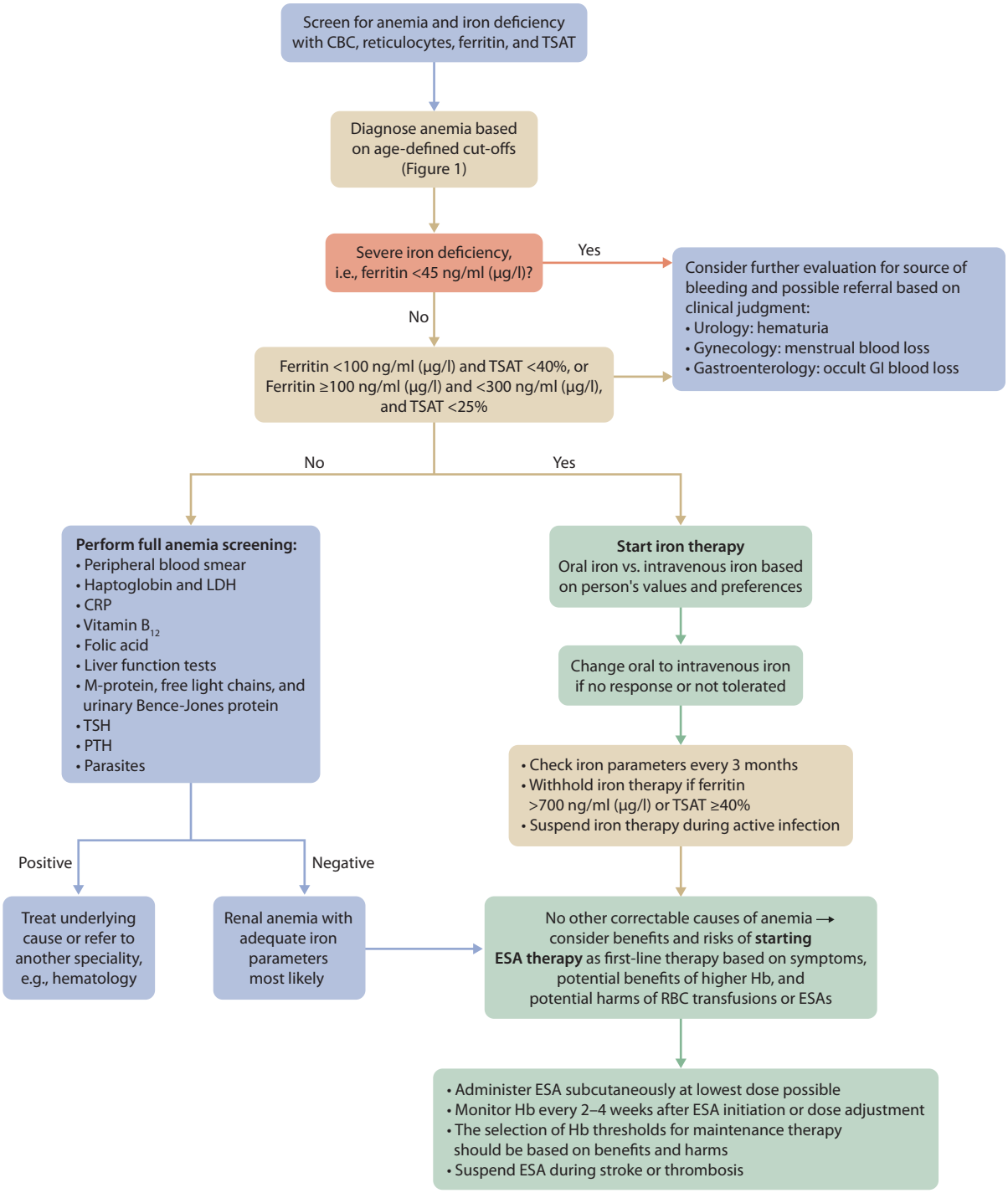
Appendix Figure 2 | Management of anemia in chronic kidney disease not receiving dialysis. CBC, complete blood count; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; F, female; GI, gastrointestinal; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; LDH, lactate dehydrogenase; M, male; PTH, parathyroid hormone; TSAT, transferrin saturation; TSH, thyroid-stimulating hormone. *While not U.S. Food and Drug Administration approved for this patient population, HIF-PHIs have been approved by other regulatory agencies.



Appendix Figure 3 | Management of anemia in chronic kidney disease G5 receiving peritoneal dialysis. CBC, complete blood count; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; F, female; GI, gastrointestinal; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; LDH, lactate dehydrogenase; M, male; PTH, parathyroid hormone; TSAT, transferrin saturation; TSH, thyroid-stimulating hormone.



Appendix Figure 4 | Management of anemia and chronic kidney disease in kidney transplant recipients. CBC, complete blood count; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; F, female; GI, gastrointestinal; Hb, hemoglobin; LDH, lactate dehydrogenase; M, male; PTH, parathyroid hormone; TSAT, transferrin saturation; TSH, thyroid-stimulating hormone.



Appendix Figure 5 | Management of anemia and chronic kidney disease in children. CBC, complete blood count; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; F, female; GI, gastrointestinal; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; LDH, lactate dehydrogenase; M, male; PTH, parathyroid hormone; TSAT, transferrin saturation; TSH, thyroid-stimulating hormone.