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

OPEN

Jodie L. Babitt[1], Jeffrey S. Berns[2], Biykem Bozkurt[3], Rebecca S. Cheung Khedairy[4], Yarieli Cuevas[5], Emmanuel E. Effa[6], Michele F. Eisenga[7], Steven Fishbane[8,9], Yelena Z. Ginzburg[10], Volker H. Haase[11,12], S. Susan Hedayati[13,14], Siah Kim[15], José A. Moura-Neto[16], Evi V. Nagler[17], Patrick Rossignol[18,19], Manisha Sahay[20], Tetsuhiro Tanaka[21], Angela Yee-Moon Wang[22,23], David C. Wheeler[24], Karen A. Robinson[25], Lisa M. Wilson[25], Renee F. Wilson[25], Amy Earley[26], Elie A. Akl[27,28] and Marcello Tonelli[29]

[1]Department of Nephrology, Massachusetts General Hospital, Boston, Massachusetts, USA; [2]Renal Electrolyte and Hypertension Division, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [3]Winters Center for Heart Failure, Cardiology Section, Baylor College of Medicine, Houston, Texas, USA; [4]Corporate and Foundation Relations, University of Washington Medicine, Seattle, Washington, USA; [5]Kidney Research Institute, Louisville, Kentucky, USA; [6]Department of Internal Medicine, University of Calabar, Calabar, Cross River State, Nigeria; [7]Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [8]Department of Medicine, Zucker School of Medicine at Hofstra, Great Neck, New York, USA; [9]Department of Nephrology, Northwell Health, Great Neck, New York, USA; [10]Department of Hematology and Medical Oncology, Mount Sinai Hospital, New York, New York, USA; [11]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [12]Vanderbilt University School of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [13]Division of Nephrology, Stony Brook University School of Medicine, Stony Brook, New York, USA; [14]Division of Nephrology, University of Texas Southwestern Medical Center, Dallas, Texas, USA; [15]Department of Medicine, The Children's Hospital at Westmead, Sydney, New South Wales, Australia; [16]Department of Medicine, Bahiana School of Medicine and Public Health, Salvador, Bahia, Brazil; [17]Renal Division, Ghent University Hospital, Ghent, Belgium; [18]Université de Lorraine, INSERM, Centre d'Investigations Cliniques-Plurithématique 1433, INSERM Unit 1116, Centre Hospitalier Régional Universitaire (CHRU) de Nancy, and F-CRIN INI-CRCT, Nancy, France; [19]Medical specialties and nephrology departments, Princess Grace Hospital, Monaco Private Hemodialysis Centre, and Monaco Clinical Research Infrastructure Network (M-CRIN), Monaco; [20]Department of Nephrology, Osmania Medical College and Hospital, Hyderabad, Telangana, India; [21]Department of Nephrology, Tohoku University, Sendai, Miyagi, Japan; [22]Department of Renal Medicine, Singapore General Hospital, Singapore; [23]Duke–National University of Singapore (NUS), Singapore; [24]Department of Renal Medicine, University College London, London, United Kingdom; [25]The Johns Hopkins University Evidence-Based Practice Center, Johns Hopkins University, Baltimore, Maryland, USA; [26]KDIGO, Brussels, Belgium; [27]Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon; [28]Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, Ontario, Canada; and [29]Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

The *Kidney Disease: Improving Global Outcomes (KDIGO) 2026 Clinical Practice Guideline for the Management of Anemia in Chronic Kidney Disease (CKD)* represents an update to the guideline published in 2012. Its scope includes diagnosis and evaluation of anemia; use of iron to treat iron deficiency and anemia in CKD; use of erythropoiesis-stimulating agents and hypoxia-inducible factor–prolyl hydroxylase inhibitors to treat anemia in CKD; and red blood cell transfusions to treat anemia in CKD. The guideline has been developed with patient partners, healthcare providers, and researchers around the world, with the goal to generate a useful resource for healthcare providers and patients by providing actionable recommendations. The development of this guideline followed an explicit process of evidence review and appraisal based on systematic reviews. The certainty of evidence and strength of recommendations follows the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. The guideline also provides practice points that provide clinical advice but are not supported by a systematic review. Limitations of the evidence are discussed. Research recommendations to address gaps in knowledge, and implications for policy and payment, are provided. The guideline targets a broad audience of healthcare providers, affected individuals, and stakeholders involved in the various aspects of anemia and CKD care.

Correspondence: *Jodie L. Babitt, Department of Nephrology, Massachusetts General Hospital, Thier Research Building, 1123A, 50 Blossom Street, Boston, Massachusetts 02114, USA. E-mail: Babitt.Jodie@mgh.harvard.edu; or Marcello Tonelli, Department of Medicine, Cumming School of Medicine, University of Calgary, TRW Building, 3280 Hospital Drive NW, Calgary, Alberta, Canada T2N 4Z6. E-mail: cello@ucalgary.ca*

The complete *KDIGO 2026 Clinical Practice Guideline for the Management of Anemia in Chronic Kidney Disease (CKD)* is published in *Kidney International*, volume 109, issue 1, 2026, which is available online at www.kidney-international.org.

Received 15 May 2025; revised 14 June 2025; accepted 20 June 2025

Kidney International (2026) **109,** 44–56; https://doi.org/10.1016/j.kint.2025.06.005

KEYWORDS: anemia; chronic kidney disease; dialysis; evidence-based; guideline; nondialysis

Anemia is a common complication of chronic kidney disease (CKD), and anemia management is a key element of contemporary nephrology practice. The last Kidney Disease: Improving Global Outcomes (KDIGO) guideline on the management of anemia in CKD was published in 2012.[1] Since the prior guideline was released, a more robust consensus has emerged about the risks and limited benefits of erythropoiesis-stimulating agents (ESAs), as has additional evidence to guide the optimal use of intravenous (i.v.) iron. More recently, hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs) have been introduced as an alternative to ESAs for anemia correction in people with CKD. However, uncertainties remain about the long-term risks and benefits of HIF-PHIs as compared with ESAs.

Since the publication of the 2012 guideline, KDIGO held 2 Controversies Conferences on anemia management in kidney disease populations.[2,3] The first (in December 2019) was on optimal anemia management in CKD and covered aspects such as iron, anemia, and outcomes; pathogenesis and diagnosis of iron deficiency and anemia in CKD; use of iron agents in CKD anemia management; and impact of ESAs and novel therapeutic agents in relation to hemoglobin (Hb) control, iron status, and iron supplementation needs. The second (in December 2021) was on novel anemia therapies in CKD, with a special focus on HIF-PHIs. Participants agreed that an update to the 2012 guideline was warranted and timely.

The KDIGO 2026 Clinical Practice Guideline for the Management of Anemia in CKD was developed by an international, multidisciplinary Work Group with expertise in CKD, a dedicated Evidence Review Team, and the KDIGO staff. The guideline includes 4 chapters addressing the diagnosis and management of anemia and iron deficiency, based on high-quality scientific evidence collected by the Evidence Review Team. The guideline includes graded recommendations, based on the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) criteria and supported by systematic reviews, and ungraded practice points that direct clinical activities and are based on expert opinion without a systematic review. Both recommendations and practice points are intended to help guide clinical practice and to aid in decision-making. The KDIGO 2026 Clinical Practice Guideline for the Management of Anemia in CKD aims to be relevant to a global audience practicing in a wide range of clinical settings.

This report summarizes the main recommendations and practice points of the guideline (Supplementary Table S1). For more details, the reader is referred to the full guideline, including grading details, a complete reference list, and a research agenda (Supplementary Table S2), available at https://kdigo.org/guidelines/anemia-in-ckd/.

Chapter 1: Diagnosis and evaluation of anemia in people with CKD

This chapter summarizes current knowledge regarding the definition, prevalence, and pathophysiology of anemia in CKD and its associated outcomes. Recognizing that iron deficiency is a major cause of anemia in CKD as well as a therapeutic target in anemia management, the chapter also describes the definition, prevalence, pathophysiology, diagnosis, and evaluation of this condition.

Rationale for anemia management in CKD. Consistent with the KDIGO 2012 guideline, anemia is defined according to World Health Organization guidelines as Hb <12 g/dl (<120 g/l) for women and <13 g/dl (<130 g/l) for men, with age-specific thresholds in children (Figure 1).[4] Anemia is highly prevalent in people with CKD and increases as CKD advances, impacting more than half of people with CKD G4 and G5 (Figure 1).[5] The pathophysiology of anemia in CKD is multifactorial, including relative erythropoietin (EPO) deficiency and bone marrow EPO resistance, iron and other nutritional deficiencies, blood loss, systemic inflammation, and shortened red blood cell (RBC) survival (Figure 1). Anemia is associated with numerous adverse outcomes, including increased mortality, cardiovascular disease, heart failure, kidney disease progression, cognitive impairment, hospitalizations, and transfusion requirements, as well as reduced health-related quality of life (QoL), providing a rationale for anemia management (Figure 1).[5–11] Notably, association does not prove causation, and although treatment of anemia with ESAs modestly improves QoL and reduces transfusion requirements, other benefits have not been demonstrated in randomized controlled trials (RCTs). Thus, it is uncertain whether anemia plays a causal role in other adverse outcomes or whether the harms of ESA therapy outweigh other potential benefits of anemia correction.

New terminology for iron deficiency in CKD. A major cause of anemia in people with CKD is the limitation of available iron to support RBC production. The etiology is multifactorial due to increased blood loss, nutritional deficiencies, medications that interfere with dietary iron absorption, excess levels of the iron hormone hepcidin, which inhibits dietary iron absorption and iron release from body stores, and enhanced iron utilization due to ESA use. The combination of these factors causes 2 major states of iron deficiency in CKD, which were previously termed "absolute iron deficiency" and "functional iron deficiency." The KDIGO Work Group has renamed these "systemic iron deficiency" and "iron-restricted erythropoiesis," respectively, to more accurately reflect the physiological state (Figure 2). The term iron-restricted erythropoiesis provides a rationale for why treating people with iron may increase Hb concentration and reduce ESA requirements, even when iron levels are above those typically associated with deficiency.[19–23]

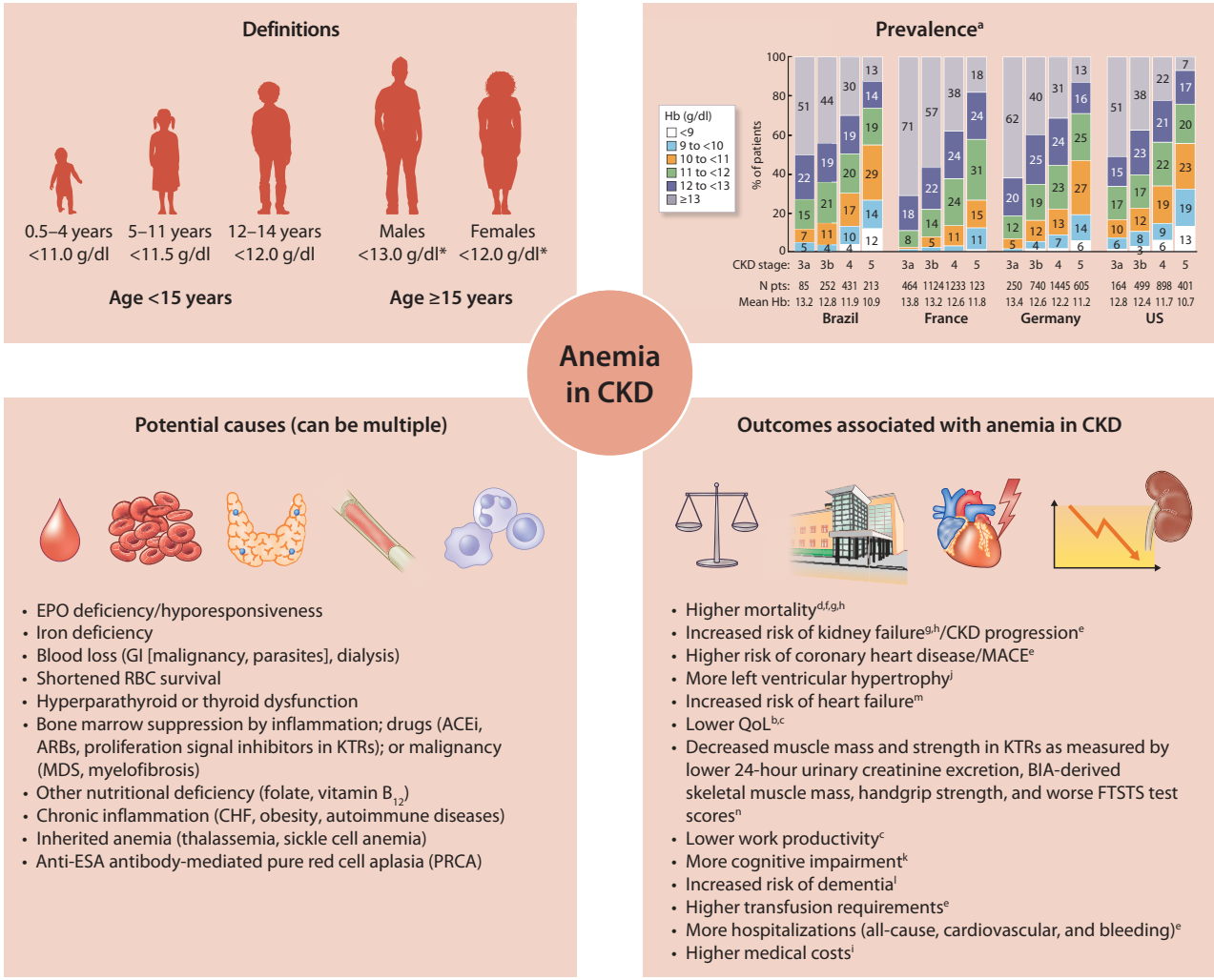

Figure 1 | Overview of anemia in chronic kidney disease (CKD) with its definition, prevalence across CKD stages, potential causes, and associated outcomes. ACEi, angiotensin-converting enzyme inhibitor(s); ARB, angiotensin II receptor blocker; BIA, bioelectrical impedance analysis; CHF, congestive heart failure; EPO, erythropoietin; 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. *Specific cutoffs for age and sex are provided. [a]Wong *et al.*,[12] [b]Moreno *et al.*,[13] [c]van Haalen *et al.*,[14] [d]Astor *et al.*,[5] [e]Lamerato *et al.*,[9] [f]Al-Ahmad *et al.*,[6] [g]Kovesdy *et al.*,[8] [h]Thorp *et al.*,[11] [i]Nissenson *et al.*,[15] [j]Levin *et al.*,[10] [k]Kurella Tamura *et al.*,[16] [l]Koyama *et al.*,[17] [m]He *et al.*,[7] and [n]Vinke *et al.*,[18]

Measures of transferrin saturation (TSAT) and ferritin have limitations as markers of iron status. However, they remain the gold standard tests for defining and managing iron deficiency and anemia in people with CKD because they are commonly used, are readily available, and are the main parameters utilized in clinical outcome trials to date. The KDIGO Work Group did not explicitly consider serum iron (a component of TSAT) as an independent marker of iron status.

Rationale for iron management in CKD. Many observational studies have reported that iron deficiency is associated with an increased risk of mortality, major adverse cardiovascular events, lower health-related QoL, and impaired neurocognitive tasks (Figure 3).[24–26] In several of these studies, the association of iron deficiency with adverse outcomes is independent of the presence of anemia. The strongest evidence supporting a causal effect of iron deficiency on outcomes arises from the Proactive IV irOn Therapy in hemodiALysis patients (PIVOTAL) trial, which evaluated different treatment strategies for i.v. iron in people with CKD G5 receiving hemodialysis (CKD G5HD) treated with ESAs.[27] PIVOTAL demonstrated an improvement in cardiovascular outcomes and mortality with a higher-dose proactive iron strategy compared with a lower-dose reactive strategy (described more in Chapter 2). These data provide the rationale for diagnosing and treating iron deficiency in people with CKD.

Approach to diagnosis and evaluation of anemia and iron deficiency. People with CKD should be tested for anemia and iron deficiency at referral, when anemia is suspected based on symptoms, and regularly during follow-up. Reasonable testing intervals are at least annually for CKD G3, twice a year for CKD G4, and every 3 months for CKD G5 or G5 receiving dialysis (G5D). Anemia should be evaluated with complete blood count, reticulocytes, ferritin, and

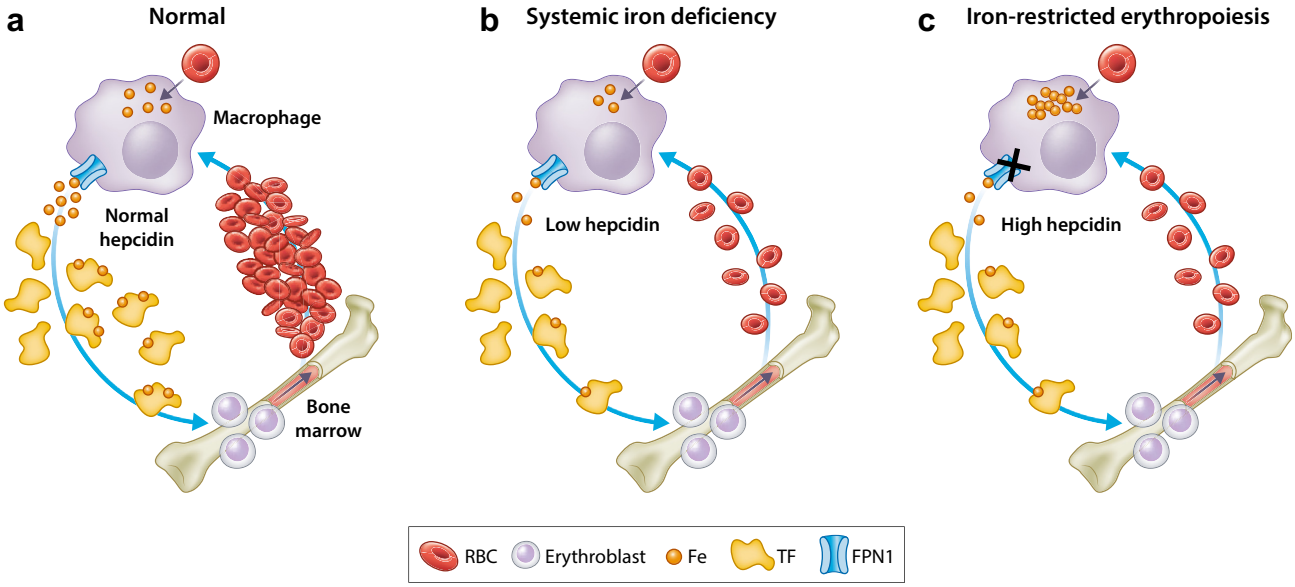

Figure 2 | Systemic movement of iron in different iron-related states. (**a**) In normal circumstances, splenic macrophages recycle iron (Fe) from senescent red blood cells (RBCs) via erythrophagocytosis and release of iron via the ferroportin (FPN1) export channel. This enables recycled iron to be loaded onto transferrin (TF) in circulation and delivered to the bone marrow for erythropoiesis, replacing senescent erythrocytes. (**b**) Systemic iron deficiency is characterized by reduced levels of both circulating and stored iron, generally defined as TF saturation (TSAT) <20% and ferritin <100 ng/ml (<100 μg/l) in people with chronic kidney disease (CKD) not receiving dialysis or ferritin <200 ng/ml (<200 μg/l) in people with CKD G5 receiving hemodialysis. 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**) Iron-restricted erythropoiesis is characterized by reduced levels of circulating iron that limit RBC production despite adequate iron stores, generally defined as ferritin >100–200 ng/ml (>100–200 μg/l) with TSAT <20%. 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.

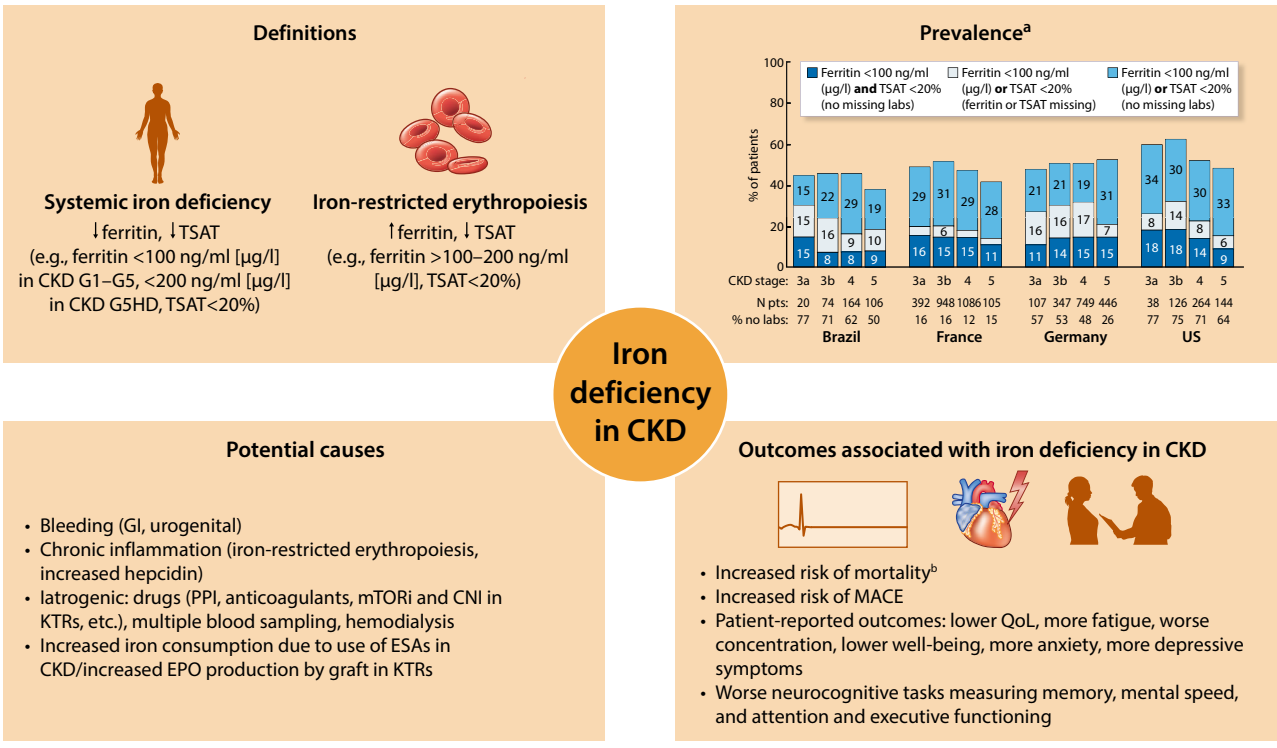

Figure 3 | Overview of iron deficiency in chronic kidney disease (CKD) with its definitions, prevalence across CKD stages, potential causes, and associated outcomes. CKD G5HD, chronic kidney disease stage G5 receiving hemodialysis; CNI, calcineurin inhibitor; EPO, erythropoietin; ESA, erythropoiesis-stimulating 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.*,[12] [b]Guedes *et al.*,[29] and Eisenga *et al.*[28]

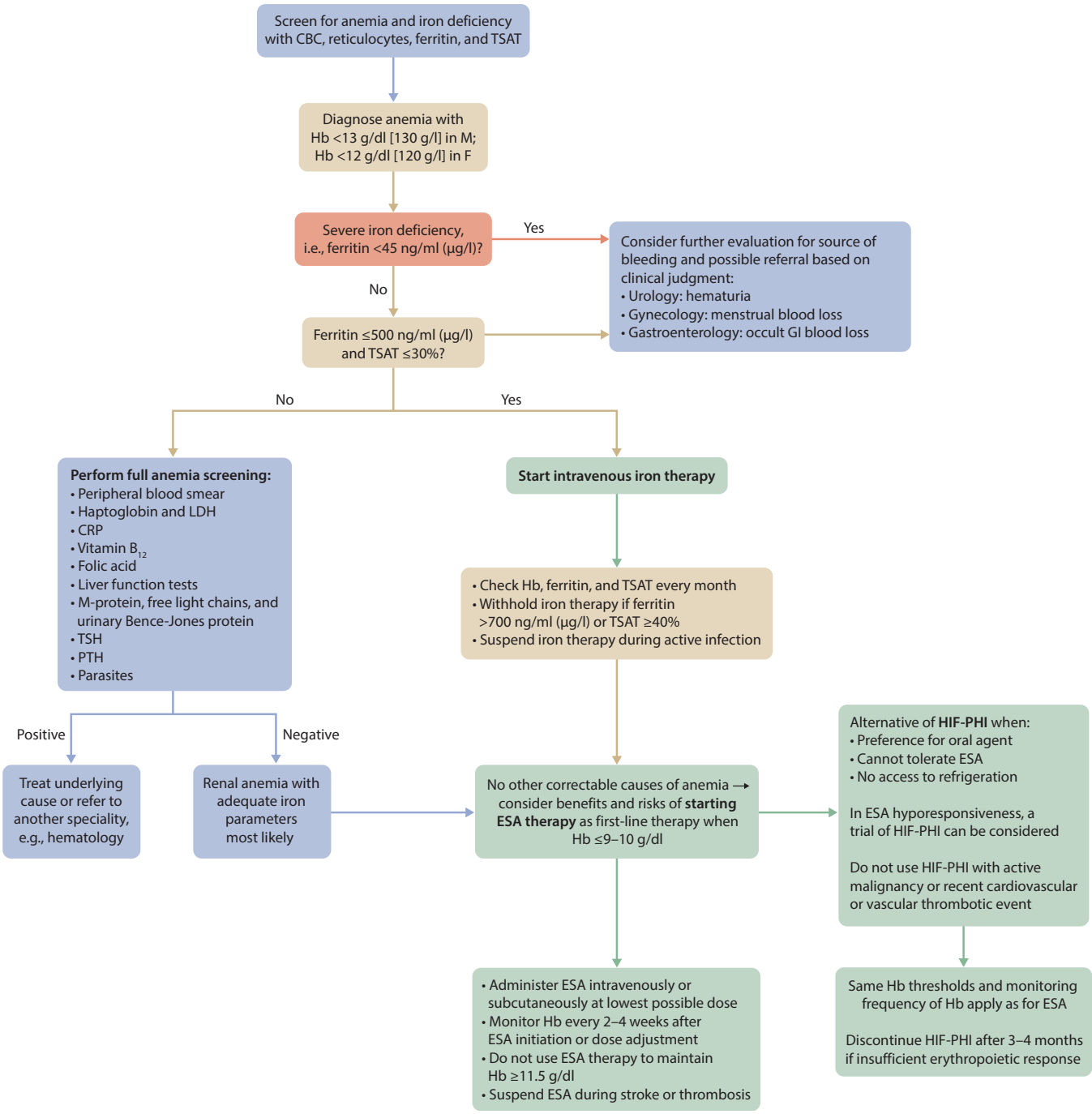

Figure 4 | Management of anemia in chronic kidney disease G5 receiving hemodialysis. CBC, complete blood count; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; F, female; GI, gastrointestinal; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; LDH, lactate dehydrogenase; M, male; PTH, parathyroid hormone; TSAT, transferrin saturation; TSH, thyroid-stimulating hormone.

TSAT. If initial tests do not reveal the cause, healthcare providers should consider an expanded panel as warranted, including 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, urinary Bence-Jones protein, thyroid-stimulating hormone, and fecal occult blood test. Parathyroid hormone could also be measured if clinically indicated and with reference to the KDIGO 2024 CKD guideline.[30] In people with iron deficiency of uncertain cause, particularly with ferritin <45 ng/ml (<45 µg/l) or microcytic anemia (mean cell volume <80 fl), healthcare providers should consider evaluation for blood loss and referral to specialists (e.g., gastroenterologist), as needed (Figures 4 and 5).[31]

Research recommendations. Additional studies are needed to understand the prevalence and health outcomes of iron deficiency in the absence of anemia, investigate the use of

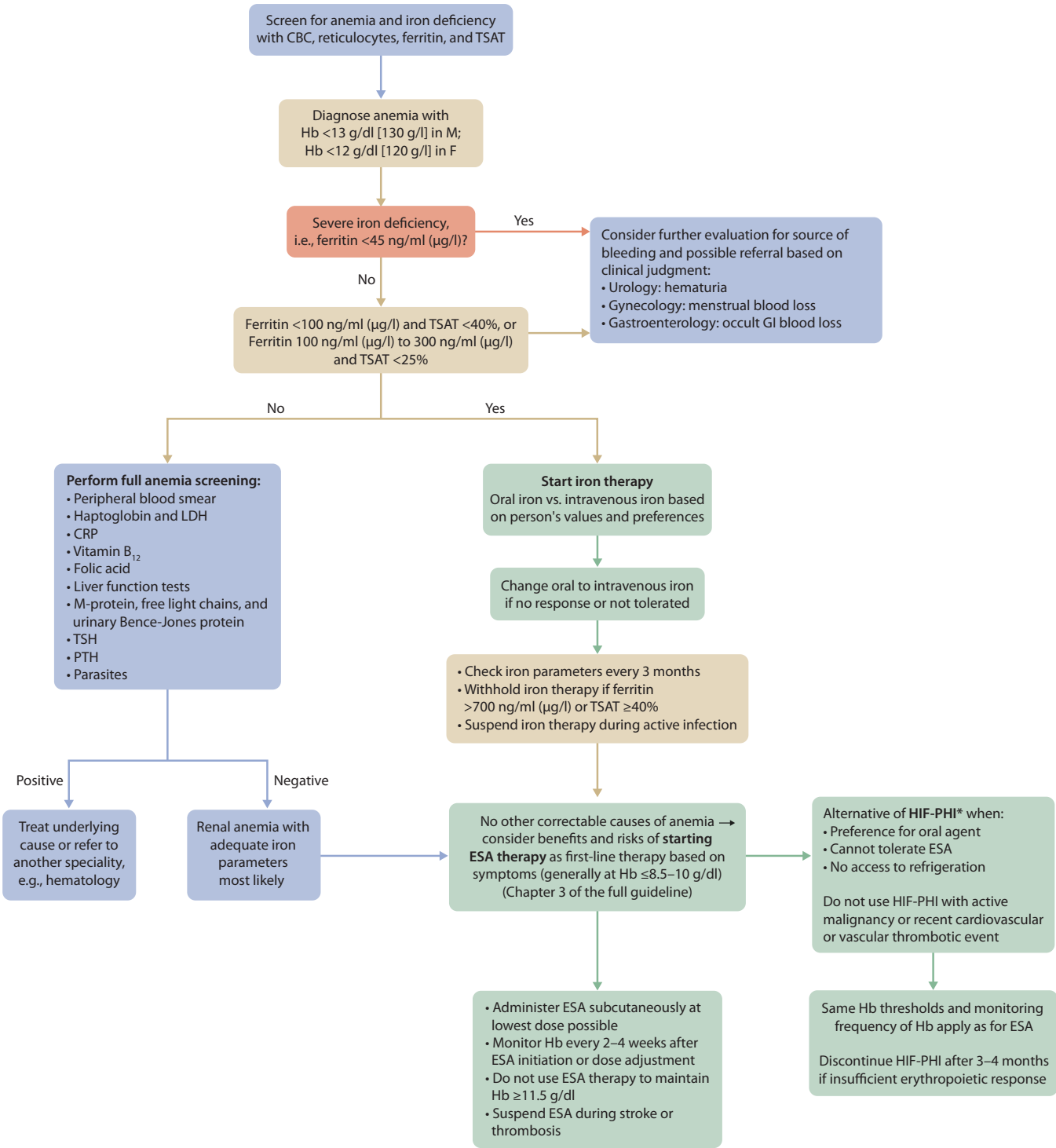

Figure 5 | Management of anemia in chronic kidney disease not receiving dialysis. CBC, complete blood count; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; F, female; GI, gastrointestinal; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; LDH, lactate dehydrogenase; 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.

other iron status parameters (e.g., reticulocyte Hb content and percentage of hypochromic RBCs) including test standardization, and evaluate Hb levels and iron parameters in pregnant women with CKD and their association with maternal and fetal outcomes.

Chapter 2: Use of iron to treat iron deficiency and anemia in people with CKD

This chapter highlights when and how to use iron supplementation to treat iron deficiency and anemia in people with CKD. This includes the goal and rationale for iron use, iron

status parameters for initiating and withholding iron therapy, choice of iron formulation and route of administration, and frequency of monitoring. Approaches for mitigating and managing potential adverse consequences of iron are also discussed, including infection, hypersensitivity, and labile iron reactions. Key guidance for iron management is summarized in Figures 4 and 5.

Iron supplementation initiation thresholds and treatment targets. The goal of iron supplementation is to maintain sufficient iron reserves to support RBC production or stimulate an erythropoietic response while minimizing the potential risks of excess iron, including infection and oxidant-mediated tissue injury. Evidence from RCTs demonstrates that iron supplementation can increase iron stores and modestly improve Hb values, which may allow fewer RBC transfusions and lower ESA doses, thereby potentially mitigating their associated risks (see Chapters 3 and 4). However, there are limited data from RCTs on critical clinical outcomes, particularly in people with CKD not receiving hemodialysis (HD) or ESAs, including those treated with HIF-PHIs. Moreover, no RCTs have assessed the benefits and harms of iron through evaluating critical outcomes at different starting thresholds of Hb, indices of iron status, or treatment targets. Thus, uncertainties remain regarding the ideal balance of Hb concentration, ESA or HIF-PHI dose, and iron supplementation, as well as optimal thresholds for initiating iron and treatment targets.

In PIVOTAL, for people with CKD G5HD treated with ESAs, high-dose i.v. iron sucrose (400 mg/mo) administered in a proactive fashion unless ferritin was >700 ng/ml (>700 μg/l) or TSAT ≥40% resulted in a moderately reduced risk of death and important cardiovascular events compared with reactive low-dose iron (0–400 mg/mo) administered only when ferritin was <200 ng/ml (<200 μg/l) or TSAT <20%, without increasing the risk of infections or other adverse events.[27] Transfusion and ESA requirements were also lower in the proactive high-dose arm. Notably, it remains uncertain what drove these outcomes: correction of iron deficiency *per se*, lower ESA doses, a combination of these, or another mechanism. It is also uncertain whether the proactive high-dose iron regimen is the optimal strategy or whether a regimen between the 2 tested in PIVOTAL (or more intensive than either) is even better. However, preclinical studies and observational data suggest that more intensive iron regimens may be associated with an increased risk of mortality and infections.

To balance the benefits seen with higher iron doses in PIVOTAL against the uncertainty about optimal treatment targets, the KDIGO Work Group has provided guidance on when to initiate iron and when to withhold it. In people with anemia and CKD G5HD, initiation of iron supplementation is suggested when ferritin ≤500 ng/ml (≤500 μg/l) and TSAT ≤30%, consistent with the KDIGO 2012 Anemia guideline and the inclusion thresholds from key studies in this population, including PIVOTAL. For people with anemia and CKD not receiving HD, iron initiation is suggested when either ferritin <100 ng/ml (<100 μg/l) and TSAT <40% or ferritin is between 100 and 300 ng/ml (between 100 and 300 μg/l) with TSAT <25%. For all people with CKD treated with iron, it is reasonable to withhold routine iron if ferritin >700 ng/ml (>700 μg/l) or TSAT ≥40%. Although HIF-PHIs have been postulated to improve iron availability and reduce iron treatment needs, there are insufficient data to recommend different thresholds in people treated with HIF-PHIs compared with ESAs.

The KDIGO Work Group acknowledged that these criteria for initiating and withholding iron are somewhat arbitrary, and individualization may be warranted. For example, smaller, shorter-term studies, including the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) I and II trials, suggest that iron may lower ESA doses without increasing adverse effects when ferritin is from 500 to 1200 ng/ml (from 500 to 1200 μg/l) in people with CKD G5HD, anemia, and TSAT ≤25%.[32] Thus, a trial course of iron administration could be considered in people with low TSAT and elevated ferritin if they have refractory anemia or high ESA requirements.

Iron treatment may also be considered in people with CKD and profound iron deficiency (ferritin <30 ng/ml [<30 μg/l] and TSAT <20%) in the absence of anemia, especially in the presence of symptoms. This is based on the notion that iron fulfills many additional biological functions in addition to Hb synthesis, including energy generation by the electron transport chain, DNA synthesis, and cellular proliferation and differentiation.[33] Moreover, iron deficiency is associated with adverse outcomes in people with CKD, independent of anemia.[29,34–36] Finally, there is evidence from several RCTs in people with heart failure, including the subset of people with CKD, that iron therapy independent of anemia improves functional status and hospitalizations.[37–40]

Personalizing route of administration, iron formulation, and treatment strategy. In people with anemia and CKD G5HD in whom iron therapy is initiated, i.v. iron is suggested rather than oral iron. This is based on the greater effectiveness of i.v. iron versus oral iron to increase iron stores and the fact that the strongest evidence for benefit from iron therapy comes from PIVOTAL, which utilized i.v. iron.[27] Additional factors include the ease of administering i.v. iron during in-center HD and reduction in pill burden. However, oral iron may be utilized in people concerned about hypersensitivity reactions or where availability and/or cost limit i.v. iron. In people with CKD G5HD receiving i.v. iron, a proactive approach similar to that used in PIVOTAL is reasonable, with monitoring of TSAT, ferritin, and Hb every 1–3 months or more frequently where indicated (e.g., initiation of or increase in ESA or HIF-PHI, episode of known blood loss, recent hospitalization, important increase in TSAT or ferritin, or overshooting target limits).

In people with anemia and CKD not receiving HD, either oral iron or i.v. iron is suggested 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. Intravenous iron appears to have a small benefit in increasing iron parameters and Hb levels higher and more

rapidly than oral iron, but it is uncertain whether this is clinically meaningful. Oral iron may be favored for some people as it is inexpensive, readily available, and does not require i.v. access or hospital visits and may preserve venous capital for arteriovenous access creation. Tolerability may also influence the choice between oral and i.v. iron; gastrointestinal side effects frequently limit oral iron dosing, and hypersensitivity reactions are uncommon but potentially severe complications of i.v. iron. In people with CKD not receiving HD treated with iron, it is reasonable to monitor TSAT, ferritin, and Hb at least every 3 months (or more frequently where indicated, as above). In people who are treated with oral iron, if there is insufficient effect after 1–3 months or if tolerability is poor, switching to i.v. iron is advised.

The choice among different formulations of oral iron or i.v. iron is guided by cost/availability, individual patient preference, tolerability, efficacy, and recommended dosing schedules; head-to-head RCT data are minimal to support recommending certain formulations over others. Various oral and i.v. iron formulations have different bioavailability, dosing strategies, and side-effect profiles that may influence the choice of agent used. A key difference between i.v. formulations is the amount of labile iron released, which affects the maximum dose that can be administered in a single setting. Although PIVOTAL used iron sucrose specifically, in the judgment of the KDIGO Work Group, the benefits of the proactive regimen likely extend to other i.v. iron formulations. Certain i.v. iron preparations (ferric carboxymaltose, saccharated iron oxide, and iron polymaltose) raise intact fibroblast growth factor 23 through unknown mechanisms related to the carbohydrate carrier and can thus cause hypophosphatemia and bone complications.[41] Phosphate levels should therefore be monitored in people receiving these agents, particularly in earlier stages of CKD, kidney transplant recipients, and people receiving repeated doses.

Improving the safety of iron treatment. Iron is essential for growth of many pathogens, and preclinical data have demonstrated that iron may worsen outcomes in certain infections. Although there is no conclusive evidence from RCTs that iron increases infection risk in people with CKD, given the limited clinical trial data and theoretical and experimental support for potential harm, temporarily holding iron therapy should be considered during systemic infections. It is unlikely that briefly holding iron therapy until the infection resolves will significantly impact anemia management over the longer term.

Hypersensitivity reactions are a rare complication of i.v. iron. Less severe reactions can also be caused by the release of labile iron. The first dose of i.v. iron should therefore be administered only if there is a capability to manage acute hypersensitivity and hypotensive reactions, and the dose of iron administered should not exceed the maximum recommended. Test doses of iron and routine pretreatment with corticosteroids or antihistamines are not necessary because they do not predict or reduce the risk of hypersensitivity. If there is a mild or moderate reaction, the infusion should be stopped temporarily without (for nonspecific symptoms) or with (for mild or moderate infusion reactions) administration of corticosteroids or antihistamines, with or without i.v. fluids. If symptoms improve, iron can be restarted at a 25%–50% lower rate, given that these reactions are often related to labile iron release, which may be ameliorated with slower infusions. Alternative iron preparations can also be considered for stronger reactions. Severe anaphylactoid reactions necessitate appropriate treatment, and future i.v. iron use should be avoided.

Research recommendations. Additional studies are needed to assess the benefits and harms of different iron dosing regimens in people with CKD not receiving HD and people with CKD G5HD targeting intermediate ferritin and TSAT levels as well as higher ferritin levels than those studied in PIVOTAL. Studies are also needed to evaluate optimal iron regimens in people with CKD and anemia treated with HIF-PHIs, people with CKD and iron deficiency without anemia, and pregnant women with CKD. Newly available oral iron compounds should be compared with traditional oral and i.v. iron compounds, and alternate day versus once daily oral iron administration should be compared. Studies are also needed to evaluate the prevalence of iron overload in people with CKD on iron therapy, including novel biomarkers and imaging techniques, as well as what thresholds are associated with toxicity.

Chapter 3: Use of ESAs, HIF-PHIs, and other agents to treat anemia in people with CKD

This chapter highlights how and when to initiate ESAs, including recommended investigations for identifying correctable causes before starting therapy, the goal and rationale for ESA use, Hb targets for people receiving an ESA, how to titrate ESA dose to avoid a rapid rise of Hb, and how to investigate and manage hyporesponsiveness. The chapter also discusses how HIF-PHIs could be used in clinical practice, primarily in those who cannot tolerate or do not adequately respond to ESAs. Key recommendations for ESA and HIF-PHI usage are summarized in Figures 4 and 5.

Personalizing Hb levels for ESA initiation. ESAs improve anemia-related fatigue and reduce the risk of RBC transfusions, although they do not reduce the risk of adverse cardiovascular outcomes or have a major effect on QoL in people with CKD-related anemia. In people receiving maintenance HD, evidence clearly shows that using ESAs to target higher Hb levels (e.g., ≥13 g/dl [≥130 g/l]) increases the risk of cardiovascular events, such as stroke and vascular access loss.

Before initiating ESA treatment, healthcare providers should ensure that patients are iron replete and that other reversible causes of anemia have been investigated and addressed (see Chapter 1). For some patients, addressing reversible causes of anemia (including iron deficiency) may obviate the need for ESA treatment.

If ESAs are desired, a Hb of ≤9–10 g/dl (≤90–100 g/l) is a reasonable threshold for initiation among people receiving maintenance dialysis. The guideline also advises consideration of each individual's overall health, comorbidities, and personal preferences when deciding whether to initiate ESAs. People who are at higher risk for adverse events from ESA

treatment, such as those with a recent stroke or recurrent HD access thrombosis, may be more likely to prefer ESA initiation when Hb is closer to 9.0 g/dl (90 g/l) or even lower, thus delaying or potentially avoiding ESA treatment. People with lower cardiovascular risk and reduced exercise capacity or symptoms attributable to anemia and people who place a high value on avoiding 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).

For people with CKD not receiving dialysis, the Hb threshold for the initiation of ESAs should be individualized based on the presence of symptoms attributable to anemia, the potential benefits of higher Hb concentration, and the potential harms of RBC transfusion or ESA therapy. For most people, the Hb threshold for initiation should be 8.5–10.0 g/dl (85–100 g/l). However, a lower Hb threshold could be considered in people with cardiovascular disease, thromboembolic disease, and malignancy (especially with active malignancy when the expected treatment outcome is cure). In contrast, for children, kidney transplant candidates, and those with symptoms attributable to anemia, a higher Hb threshold may be considered.

Personalizing Hb targets for people receiving ESAs. For adults receiving ESAs, the guideline recommends a target Hb ≤11.5 g/dl (≤115 g/l) and typically between 10 and 11.5 g/dl (between 100 and 115 g/l). The target range was selected to balance the potential benefits of higher Hb against its potential harms, including the excess risk of hypertension at Hb targets >11.5 g/dl (>115 g/l) and the risks of vascular events at even higher targets.[42–44]

For children receiving ESAs, the Hb target should be individualized. Clinical factors that are unique to children include developmental and psychological factors, lower risk of cardiovascular events, and potentially greater importance of avoiding allosensitization to facilitate kidney transplantation. Therefore, the optimal Hb target for children is unknown, and healthcare providers must consider how the recommendation for adults could be adapted to children with kidney disease.

ESAs may be administered subcutaneously or intravenously in people receiving maintenance HD, whereas the subcutaneous route is preferred for ESA recipients with other forms of CKD. For epoetin, the subcutaneous route is more efficient, but for darbepoetin alfa, there is no difference in dose requirements between routes.

Improving the safety of ESA treatment. For both adults and children, the guideline advises that healthcare providers aim to increase Hb gradually, with ESA dose adjusted to avoid rapid increases of more than about 1 g/dl (10 g/l) every 2 weeks. If rapid rises of this magnitude occur, the dose should be reduced by 25%–50%. If Hb exceeds 11.5 g/dl (115 g/l), reducing the dose of ESA may be preferable to temporary discontinuation.

Consideration should be given to suspending ESAs during hospitalization for acute stroke, vascular access thrombosis, or thromboembolic events. Reinitiation of ESA therapy after hospitalization should be based on shared decision-making after discussion of benefits and risks.

Studies in people with certain cancers show that using ESAs to treat anemia may lead to increased risk of cancer progression and death.[45] Therefore, in people with CKD, anemia, and active cancer (or a history of cancer), healthcare providers should consider whether to initiate or continue ESAs based on patient preferences and anticipated clinical outcomes, especially when cancer treatment is aimed at cure.

ESA hyporesponsiveness. The guideline defines people who have CKD and ESA hyporesponsiveness as those who "do not achieve target Hb levels despite a significant increase in ESA doses or continue to require high doses to maintain the target." It advises healthcare providers to identify and treat possible causes, including iron deficiency, iron sequestration from chronic inflammation, suboptimal dialysis adequacy, and occult blood loss.

Role of HIF-PHIs. HIF-PHIs are oral agents that stimulate endogenous EPO production by stabilizing HIF transcription factors. Available evidence suggests that HIF-PHI treatment can achieve comparable Hb levels among people with CKD-related anemia as compared with ESA treatment.[46–60] The guideline suggests using an ESA rather than a HIF-PHI to treat anemia in people for whom a further increase in Hb is desired despite addressing potentially correctable causes. This recommendation is based on the long clinical experience with ESAs and their efficacy for increasing Hb. In particular, the extensive long-term data demonstrating the balance of risks and benefits associated with ESA use were felt to be a substantial advantage compared with the lack of such data from HIF-PHI recipients outside clinical trials.[61–63] Additionally, although the overall analyses of RCTs suggest that HIF-PHIs are noninferior to ESAs for critical adverse outcomes, some studies suggest that at least some HIF-PHIs may have a higher risk of major adverse cardiovascular events and other vascular events than ESAs, particularly in CKD populations not receiving dialysis.[61–63]

The guideline highlights 2 clinical scenarios where HIF-PHIs may be considered: (i) ESA hyporesponsiveness or intolerance and (ii) circumstances where ESA use is impractical (e.g., if there are barriers to parenteral administration). However, healthcare providers should be aware that although a few studies have suggested that HIF-PHIs may require less dose escalation than ESAs in people with elevated inflammatory markers,[51,64] the safety and benefit of HIF-PHIs in people with ESA hyporesponsiveness have not been established. Very limited studies have been conducted in people with ESA hyporesponsiveness, and none have meaningfully examined important clinical or patient-centered outcomes beyond Hb levels.[65–67] In either case, healthcare providers should discuss the risks and benefits of HIF-PHIs with individuals in whom treatment is considered and aim to identify conditions where the theoretical risk of adverse events may be higher than average, such as polycystic kidney disease, proliferative retinal disease, pulmonary arterial hypertension, and pregnancy.[68–73]

For people who elect a trial of HIF-PHIs, the principles for the use of these medications are generally similar to those

advised for ESAs. The guideline advises against the use of ESA and HIF-PHI therapies in combination, given the lack of clinical data on safety and efficacy.

Research recommendations. Additional studies are needed to inform optimal ESA use in people receiving maintenance peritoneal dialysis, in kidney transplant recipients, and in children across all severities of CKD. Studies comparing the long-term risks and benefits of HIF-PHI treatment with those of ESA treatment are needed in adults and children with CKD G5D and CKD not receiving dialysis.

Chapter 4: Red blood cell transfusions to treat anemia in people with CKD

Supplemental iron and ESAs both reduce the risk of RBC transfusion in people with CKD. However, RBC transfusions remain essential for the management of severe or refractory anemia in this population. This chapter highlights situations where RBC transfusion should be used and strategies that can minimize complications such as alloimmunization.

Rationale for a restrictive transfusion strategy in CKD populations. RBC transfusion has well-documented adverse effects in the general population, including transfusion-associated circulatory overload, transfusion-related acute lung injury, immunologic sensitization, and hemolytic transfusion reactions. An additional consideration in people with CKD is that alloimmunization following RBC transfusion may reduce future suitability for kidney transplantation.[74–79] However, many of these harms are relatively uncommon and must be considered against the risks of severe untreated anemia, such as myocardial ischemia, decompensated heart failure, or death.

Indications for RBC transfusion. For people with CKD and acute life-threatening anemia, the guideline advises RBC transfusion whenever rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage and unstable coronary artery disease). The guideline also advises that RBC transfusion should be considered for preoperative correction of Hb in people with severe anemia who are undergoing surgery in which clinically relevant intraoperative blood loss is anticipated.

For people with CKD and chronic anemia, the guideline advises that the benefits of RBC transfusion may outweigh its harms in 2 groups: (i) those in whom ESA or HIF-PHI therapy is ineffective (e.g., those with hemoglobinopathies, bone marrow failure, and ESA or HIF-PHI hyporesponsiveness) and (ii) those in whom ESA or HIF-PHI therapy may be harmful (e.g., those with previous or current malignancy and previous stroke).

Hb threshold for RBC transfusion. RBC transfusion should be considered in any acute clinical situation where delaying anemia correction may lead to adverse outcomes or death, such as severe acute hemorrhage, unstable coronary artery disease, or imminent surgery where substantial blood loss is expected.

For less acute situations, the guideline emphasizes that anemia-related signs and symptoms should be the primary trigger for deciding when to give RBC transfusions in people with CKD rather than an arbitrary Hb threshold. However, transfusions could be given when the Hb level is <7 g/dl (<70 g/l) for asymptomatic and hemodynamically stable adult inpatients, <7.5 g/dl (<75 g/l) for people undergoing cardiac surgery, or <8 g/dl (<80 g/l) for those undergoing orthopedic surgery or those with clinically significant cardiovascular disease.[80]

Reducing the need for RBC transfusions. The guideline highlights strategies that may reduce the need for RBC transfusions among people with CKD, if applied broadly at the level of the healthcare system as well as in individual patients. Exemplar strategies include implementing standardized protocols for early detection and correction of iron deficiency; guideline-concordant use of i.v. iron and ESAs; patient education about options for anemia management; and decision aids to help individual patients make informed decisions about the use of RBC transfusions in a manner that is consistent with their values and preferences.

Research recommendations. In CKD populations, prospective observational studies are needed to examine the contemporary use of RBC transfusions, including the indication for transfusion, the subsequent risk of alloimmunization, and uptake of kidney transplantation among transfusion recipients. Comparisons between regions may help to identify best practices for managing anemia among people with CKD, which in turn may determine how to reduce the risk for RBC transfusion. Further studies are needed on the optimal methods for RBC processing and storage and how these methods may affect clinical outcomes including alloimmunization and post-transplant outcomes.

Conclusion

The KDIGO 2026 Clinical Practice Guideline for the Management of Anemia in CKD updates the 2012 guideline. Recent developments impacting the management of anemia in CKD, and the emergence of new evidence for iron management and novel therapies such as HIF-PHIs, justified the need for a global guideline document. The guideline summarizes the diagnosis, management, and treatment of anemia in people with CKD and aims to be relevant to a global audience. Our systematic reviews identified gaps in the knowledge base and remaining controversies, which are integrated into a comprehensive research agenda. Together, these recommendations and practice points offer a strong basis for the management of anemia in people with CKD.

DISCLOSURE

The development and publication of this guideline were supported by Kidney Disease: Improving Global Outcomes (KDIGO). The opinions or views expressed in this summary are those of the authors and do not necessarily reflect the opinions or recommendations of the International Society of Nephrology or Elsevier. Dosages, indications, and methods of use for products that are referred to in the supplement by the authors may reflect their clinical experience or may be derived from the professional literature or other clinical sources. Because of the differences between *in vitro* and *in vivo* systems and between laboratory animal models and clinical data in

humans, *in vitro* and animal data do not necessarily correlate with clinical results.

JLB reports receiving support from the National Institutes of Health*, and the National Institute of Diabetes and Digestive and Kidney Diseases*. JSB reports receiving royalties or licenses from *UpToDate*. 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. 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. SF reports receiving consultancy fees from Akebia Therapeutics and GlaxoSmithKline; speaker honoraria from Akebia Therapeutics; and serving as an advisory board member for AstraZeneca. YZG reports receiving consultancy fees from Denali Therapeutics, Disc Medicine, Ionis Pharmaceuticals, Protagonist Therapeutics, and Takeda and speaker honoraria from Pharmacosmos. 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. SSH reports receiving speaker honoraria from the American College of Physicians Nephrology and MKSAP Faculty. 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. TT reports receiving consultancy fees from Torii Pharmaceutical and speaker honoraria from Astellas, Bayer, Kyowa Kirin, Mitsubishi Tanabe, and Torii Pharmaceutical. AY-MW reports receiving consultancy fees from CSL Behring and Fresenius Kabi; speaker honoraria from AstraZeneca, Bayer, and Fresenius Kabi; and travel support from AstraZeneca, Bayer, CSL Behring, and Fresenius Kabi. DCW reports receiving support for manuscript development from Astellas, GlaxoSmithKline, Medice, 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. All the other authors declared no competing interests.

**Monies paid to institution.*

ACKNOWLEDGMENTS

A special debt of gratitude is owed to the following people for their contribution to this important guideline effort: Michael Cheung, Melissa Thompson, Debbie Maizels, Jennifer King, Dipal M. Patel, Troy Gharibani, Xuhao Yang, Yuanxi Jia, Morgan E. Grams, and Michel Jadoul. We are also thankful to all those who provided helpful comments and suggestions during the public review of the guideline.

Supplementary material is available online at www.kidney-international.org.

REFERENCES

1. Kidney Disease: Improving Global Outcomes Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl*. 2012;2:279–335.
2. Babitt JL, Eisenga MF, Haase VH, et al. Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. *Kidney Int*. 2021;99:1280–1295.
3. Ku E, Del Vecchio L, Eckardt KU, et al. Novel anemia therapies in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2023;104:655–680.
4. Nutritional anaemias: report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5–37.
5. Astor BC, Coresh J, Heiss G, et al. Kidney function and anemia as risk factors for coronary heart disease and mortality: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J*. 2006;151:492–500.
6. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol*. 2001;38:955–962.
7. He J, Shlipak M, Anderson A, et al. Risk factors for heart failure in patients with chronic kidney disease: the CRIC (Chronic Renal Insufficiency Cohort) Study. *J Am Heart Assoc*. 2017;6:e005336.
8. Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, et al. Association of anemia with outcomes in men with moderate and severe chronic kidney disease. *Kidney Int*. 2006;69:560–564.
9. Lamerato L, James G, van Haalen H, et al. Epidemiology and outcomes in patients with anemia of CKD not on dialysis from a large US healthcare system database: a retrospective observational study. *BMC Nephrol*. 2022;23:166.
10. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis*. 1999;34:125–134.
11. Thorp ML, Johnson ES, Yang X, et al. Effect of anaemia on mortality, cardiovascular hospitalizations and end-stage renal disease among patients with chronic kidney disease. *Nephrology (Carlton)*. 2009;14:240–246.
12. Wong MMY, Tu C, Li Y, et al. Anemia and iron deficiency among chronic kidney disease stages 3-5ND patients in the Chronic Kidney Disease Outcomes and Practice Patterns Study: often unmeasured, variably treated. *Clin Kidney J*. 2020;13:613–624.
13. Moreno F, Lopez Gomez JM, Sanz-Guajardo D, et al., Spanish Cooperative Renal Patients Quality of Life Study Group. Quality of life in dialysis patients: a Spanish multicentre study. *Nephrol Dial Transplant*. 1996;11(suppl 2):125–129.
14. van Haalen H, Jackson J, Spinowitz B, et al. Impact of chronic kidney disease and anemia on health-related quality of life and work productivity: analysis of multinational real-world data. *BMC Nephrol*. 2020;21:88.
15. Nissenson AR, Wade S, Goodnough T, et al. Economic burden of anemia in an insured population. *J Manag Care Pharm*. 2005;11:565–574.
16. Kurella Tamura M, Vittinghoff E, Yang J, et al. Anemia and risk for cognitive decline in chronic kidney disease. *BMC Nephrol*. 2016;17:13.
17. Koyama AK, Nee R, Yu W, et al. Role of anemia in dementia risk among veterans with incident CKD. *Am J Kidney Dis*. 2023;82:706–714.
18. Vinke JSJ, Wouters H, Stam SP, et al. Decreased haemoglobin levels are associated with lower muscle mass and strength in kidney transplant recipients. *J Cachexia Sarcopenia Muscle*. 2022;13:2044–2053.
19. Bullock GC, Delehanty LL, Talbot AL, et al. Iron control of erythroid development by a novel aconitase-associated regulatory pathway. *Blood*. 2010;116:97–108.
20. Khalil S, Delehanty L, Grado S, et al. Iron modulation of erythropoiesis is associated with Scribble-mediated control of the erythropoietin receptor. *J Exp Med*. 2018;215:661–679.
21. Khalil S, Holy M, Grado S, et al. A specialized pathway for erythroid iron delivery through lysosomal trafficking of transferrin receptor 2. *Blood Adv*. 2017;1:1181–1194.
22. Richardson CL, Delehanty LL, Bullock GC, et al. Isocitrate ameliorates anemia by suppressing the erythroid iron restriction response. *J Clin Invest*. 2013;123:3614–3623.
23. Talbot AL, Bullock GC, Delehanty LL, et al. Aconitase regulation of erythropoiesis correlates with a novel licensing function in erythropoietin-induced ERK signaling. *PLoS One*. 2011;6:e23850.
24. Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am Soc Nephrol*. 2012;23:1631–1634.
25. Koury MJ, Haase VH. Anaemia in kidney disease: harnessing hypoxia responses for therapy. *Nat Rev Nephrol*. 2015;11:39–410.
26. Schechter A, Gafter-Gvili A, Shepshelovich D, et al. Post renal transplant anemia: severity, causes and their association with graft and patient survival. *BMC Nephrol*. 2019;20:51.

27. Macdougall IC, White C, Anker SD, et al. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med*. 2019;380:447–458.
28. Eisenga MF, Minovic I, Berger SP, et al. Iron deficiency, anemia, and mortality in renal transplant recipients. *Transpl Int*. 2016;29:1176–1183.
29. Guedes M, Muenz DG, Zee J, et al. Serum biomarkers of iron stores are associated with increased risk of all-cause mortality and cardiovascular events in nondialysis CKD patients, with or without anemia. *J Am Soc Nephrol*. 2021;32:2020–2030.
30. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2024;105(4S):S117–S314.
31. Ko CW, Siddique SM, Patel A, et al. AGA Clinical Practice Guidelines on the Gastrointestinal Evaluation of Iron Deficiency Anemia. *Gastroenterology*. 2020;159:1085–1094.
32. Coyne DW, Kapoian T, Suki W, et al. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. *J Am Soc Nephrol*. 2007;18:975–984.
33. Sangkhae V, Nemeth E. Regulation of the iron homeostatic hormone hepcidin. *Adv Nutr*. 2017;8:126–136.
34. Hamano T, Fujii N, Hayashi T, et al. Thresholds of iron markers for iron deficiency erythropoiesis-finding of the Japanese nationwide dialysis registry. *Kidney Int Suppl (2011)*. 2015;(5):23–32.
35. Kremer D, Knobbe TJ, Vinke JSJ, et al. Iron deficiency, anemia, and patient-reported outcomes in kidney transplant recipients. *Am J Transplant*. 2024;24:1456–1466.
36. Spinowitz B, Pecoits-Filho R, Winkelmayer WC, et al. Economic and quality of life burden of anemia on patients with CKD on dialysis: a systematic review. *J Med Econ*. 2019;22:593–604.
37. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009;361:2436–2448.
38. Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure. *J Card Fail*. 2011;17:899–906.
39. Okonko DO, Grzeslo A, Witkowski T, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol*. 2008;51:103–112.
40. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18:891–975.
41. Wolf M, Chertow GM, Macdougall IC, et al. Randomized trial of intravenous iron-induced hypophosphatemia. *JCI Insight*. 2018;3:e124486.
42. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006;355:2071–2084.
43. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. 2009;361:2019–2032.
44. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006;355:2085–2098.
45. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol*. 2005;23:5960–5972.
46. Akizawa T, Nangaku M, Yamaguchi T, et al. Enarodustat, conversion and maintenance therapy for anemia in hemodialysis patients: a randomized, placebo-controlled phase 2b trial followed by long-term trial. *Nephron*. 2019;143:77–85.
47. Akizawa T, Tsubakihara Y, Nangaku M, et al. Effects of daprodustat, a novel hypoxia-inducible factor prolyl hydroxylase inhibitor on anemia management in Japanese hemodialysis subjects. *Am J Nephrol*. 2017;45:127–135.
48. Bailey CK, Caltabiano S, Cobitz AR, et al. A randomized, 29-day, dose-ranging, efficacy and safety study of daprodustat, administered three times weekly in patients with anemia on hemodialysis. *BMC Nephrol*. 2019;20:372.
49. Besarab A, Provenzano R, Hertel J, et al. Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients. *Nephrol Dial Transplant*. 2015;30:1665–1673.
50. Brigandi RA, Johnson B, Oei C, et al. A novel hypoxia-inducible factor-prolyl hydroxylase inhibitor (GSK1278863) for anemia in CKD: a 28-day, phase 2a randomized trial. *Am J Kidney Dis*. 2016;67:861–871.
51. Chen N, Hao C, Peng X, et al. Roxadustat for anemia in patients with kidney disease not receiving dialysis. *N Engl J Med*. 2019;381:1001–1010.
52. Chen N, Qian J, Chen J, et al. Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. *Nephrol Dial Transplant*. 2017;32:1373–1386.
53. Coyne DW, Roger SD, Shin SK, et al. Roxadustat for CKD-related anemia in non-dialysis patients. *Kidney Int Rep*. 2021;6:624–635.
54. Fishbane S, El-Shahawy MA, Pecoits-Filho R, et al. Roxadustat for treating anemia in patients with CKD not on dialysis: results from a randomized phase 3 study. *J Am Soc Nephrol*. 2021;32:737–755.
55. Holdstock L, Meadowcroft AM, Maier R, et al. Four-week studies of oral hypoxia-inducible factor-prolyl hydroxylase inhibitor GSK1278863 for treatment of anemia. *J Am Soc Nephrol*. 2016;27:1234–1244.
56. Martin ER, Smith MT, Maroni BJ, et al. Clinical trial of vadadustat in patients with anemia secondary to stage 3 or 4 chronic kidney disease. *Am J Nephrol*. 2017;45:380–388.
57. Nangaku M, Farag YMK, deGoma E, et al. Vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, for treatment of anemia of chronic kidney disease: two randomized Phase 2 trials in Japanese patients. *Nephrol Dial Transplant*. 2021;36:1244–1252.
58. Parmar DV, Kansagra KA, Patel JC, et al. Outcomes of desidustat treatment in people with anemia and chronic kidney disease: a phase 2 study. *Am J Nephrol*. 2019;49:470–478.
59. Pergola PE, Spinowitz BS, Hartman CS, et al. Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. *Kidney Int*. 2016;90:1115–1122.
60. Shutov E, Sulowicz W, Esposito C, et al. Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, double-blind, placebo-controlled study (ALPS). *Nephrol Dial Transplant*. 2021;36:1629–1639.
61. Chertow GM, Pergola PE, Farag YMK, et al. Vadadustat in patients with anemia and non-dialysis-dependent CKD. *N Engl J Med*. 2021;384:1589–1600.
62. Cunningham JW, Claggett BL, Lopes RD, et al. Daprodustat and heart failure in CKD. *J Am Soc Nephrol*. 2024;35:607–617.
63. Singh AK, Carroll K, McMurray JJV, et al. Daprodustat for the treatment of anemia in patients not undergoing dialysis. *N Engl J Med*. 2021;385:2313–2324.
64. Provenzano R, Besarab A, Wright S, et al. Roxadustat (FG-4592) versus epoetin alfa for anemia in patients receiving maintenance hemodialysis: a phase 2, randomized, 6- to 19-week, open-label, active-comparator, dose-ranging, safety and exploratory efficacy study. *Am J Kidney Dis*. 2016;67:912–924.
65. Cizman B, Sykes AP, Paul G, et al. An exploratory study of daprodustat in erythropoietin-hyporesponsive subjects. *Kidney Int Rep*. 2018;3:841–850.
66. Dai S, Chen Y, Hao C, et al. Addition of roxadustat to erythropoiesis-stimulating agent (ESA) effectively corrects ESA-hyporesponsive anaemia in patients on peritoneal dialysis. *J Clin Pharm Ther*. 2022;47:1525–1530.
67. Zhou Y, Chen XX, Zhang YF, et al. Roxadustat for dialysis patients with erythropoietin hypo-responsiveness: a single-center, prospective investigation. *Intern Emerg Med*. 2021;16:2193–2199.
68. Barben M, Samardzija M, Grimm C. The role of hypoxia, hypoxia-inducible factor (HIF), and VEGF in retinal angiomatous proliferation. *Adv Exp Med Biol*. 2018;1074:177–183.
69. Cowburn AS, Crosby A, Macias D, et al. HIF2α-arginase axis is essential for the development of pulmonary hypertension. *Proc Natl Acad Sci U S A*. 2016;113:8801–8806.
70. Kapitsinou PP, Rajendran G, Astleford L, et al. The endothelial prolyl-4-hydroxylase domain 2/hypoxia-inducible factor 2 axis regulates pulmonary artery pressure in mice. *Mol Cell Biol*. 2016;36:1584–1594.
71. Kraus A, Peters DJM, Klanke B, et al. HIF-1α promotes cyst progression in a mouse model of autosomal dominant polycystic kidney disease. *Kidney Int*. 2018;94:887–899.
72. Lin M, Chen Y, Jin J, et al. Ischaemia-induced retinal neovascularisation and diabetic retinopathy in mice with conditional knockout of hypoxia-inducible factor-1 in retinal Muller cells. *Diabetologia*. 2011;54:1554–1566.

73. Shimoda LA, Yun X, Sikka G. Revisiting the role of hypoxia-inducible factors in pulmonary hypertension. *Curr Opin Physiol*. 2019;7:33–40.
74. Leffell MS, Kim D, Vega RM, et al. Red blood cell transfusions and the risk of allosensitization in patients awaiting primary kidney transplantation. *Transplantation*. 2014;97:525–533.
75. Opelz G, Graver B, Mickey MR, et al. Lymphocytotoxic antibody responses to transfusions in potential kidney transplant recipients. *Transplantation*. 1981;32:177–183.
76. United States Renal Data System. *2010 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2010.
77. Terasaki PI, Ozawa M. Predicting kidney graft failure by HLA antibodies: a prospective trial. *Am J Transplant*. 2004;4:438–443.
78. Terasaki PI, Ozawa M. Predictive value of HLA antibodies and serum creatinine in chronic rejection: results of a 2-year prospective trial. *Transplantation*. 2005;80:119–1197.
79. Yabu JM, Anderson MW, Kim D, et al. Sensitization from transfusion in patients awaiting primary kidney transplant. *Nephrol Dial Transplant*. 2013;28:2908–2918.
80. Carson JL, Stanworth SJ, Guyatt G, et al. Red Blood Cell Transfusion: 2023 AABB International Guidelines. *JAMA*. 2023;330:1892–1902.