



**HAL**  
open science

## **Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference**

Jodie L. Babitt, Michele F. Eisenga, Volker H. Haase, Abhijit V. Kshirsagar, Adeera I. Levin, Francesco Locatelli, Jolanta Malyszko, Dorine W. Swinkels, Der Cherng Tarnng, Michael Cheung, et al.

### **► To cite this version:**

Jodie L. Babitt, Michele F. Eisenga, Volker H. Haase, Abhijit V. Kshirsagar, Adeera I. Levin, et al.. Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. unknow, 2021, unknow, France. pp.1280-1295, 10.1016/j.kint.2021.03.020 . hal-03287346

**HAL Id: hal-03287346**

**<https://hal.science/hal-03287346>**

Submitted on 7 Jun 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

# Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference



OPEN

Jodie L. Babitt<sup>1</sup>, Michele F. Eisenga<sup>2</sup>, Volker H. Haase<sup>3,4,5</sup>, Abhijit V. Kshirsagar<sup>6</sup>, Adeera Levin<sup>7</sup>, Francesco Locatelli<sup>8</sup>, Jolanta Malyszko<sup>9</sup>, Dorine W. Swinkels<sup>10</sup>, Der-Cherng Tarng<sup>11</sup>, Michael Cheung<sup>12</sup>, Michel Jadoul<sup>13</sup>, Wolfgang C. Winkelmayer<sup>14</sup> and Tilman B. Drüeke<sup>15,16</sup>; for Conference Participants<sup>17</sup>

<sup>1</sup>Nephrology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; <sup>2</sup>Department of Internal Medicine, Division of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; <sup>3</sup>Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; <sup>4</sup>Department of Molecular Physiology and Biophysics and Program in Cancer Biology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; <sup>5</sup>Department of Medical Cell Biology, Division of Integrative Physiology, Uppsala University, Uppsala, Sweden; <sup>6</sup>UNC Kidney Center and Division of Nephrology & Hypertension, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; <sup>7</sup>Department of Medicine, Division of Nephrology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; <sup>8</sup>Department of Nephrology and Dialysis, Alessandro Manzoni Hospital, ASST Lecco, Lecco, Italy; <sup>9</sup>Department of Nephrology, Dialysis, and Internal Medicine, Medical University of Warsaw, Warsaw, Poland; <sup>10</sup>Translational Metabolic Laboratory, Department of Laboratory Medicine, Radboud University Medical Center, Nijmegen, the Netherlands; <sup>11</sup>Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; <sup>12</sup>KDIGO, Brussels, Belgium; <sup>13</sup>Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium; <sup>14</sup>Department of Medicine, Section of Nephrology, Selzman Institute for Kidney Health, Baylor College of Medicine, Houston, Texas, USA; <sup>15</sup>Inserm Unit 1018, Team 5, CESP, Hôpital Paul Brousse, Paris-Sud University (UPS), Villejuif, France; and <sup>16</sup>Versailles Saint-Quentin-en-Yvelines University (Paris-Ile-de-France-Ouest University, UVSQ), Villejuif, France

In chronic kidney disease, anemia and disordered iron homeostasis are prevalent and associated with significant adverse consequences. In 2012, Kidney Disease: Improving Global Outcomes (KDIGO) issued an anemia guideline for managing the diagnosis, evaluation, and treatment of anemia in chronic kidney disease. Since then, new data have accrued from basic research, epidemiological studies, and randomized trials that warrant a re-examination of previous recommendations. Therefore, in 2019, KDIGO decided to convene 2 Controversies Conferences to review the latest evidence, explore new and ongoing controversies, assess change implications for the current KDIGO anemia guideline, and propose a research agenda. The first conference, described here, focused mainly on iron-related issues, including the contribution of disordered iron homeostasis to the anemia of chronic kidney disease, diagnostic challenges, available and emerging iron therapies, treatment targets, and patient outcomes. The second conference will discuss issues more specifically related to erythropoiesis-stimulating agents, including epoetins, and hypoxia-inducible factor-prolyl hydroxylase inhibitors. Here we provide a concise overview of the consensus points and controversies resulting from

the first conference and prioritize key questions that need to be answered by future research.

*Kidney International* (2021) **99**, 1280–1295; <https://doi.org/10.1016/j.kint.2021.03.020>

KEYWORDS: anemia; chronic kidney disease; dialysis; erythropoiesis stimulating agents; erythropoietin; hepcidin; hypoxia-inducible factor-prolyl hydroxylase inhibitor; iron; iron deficiency

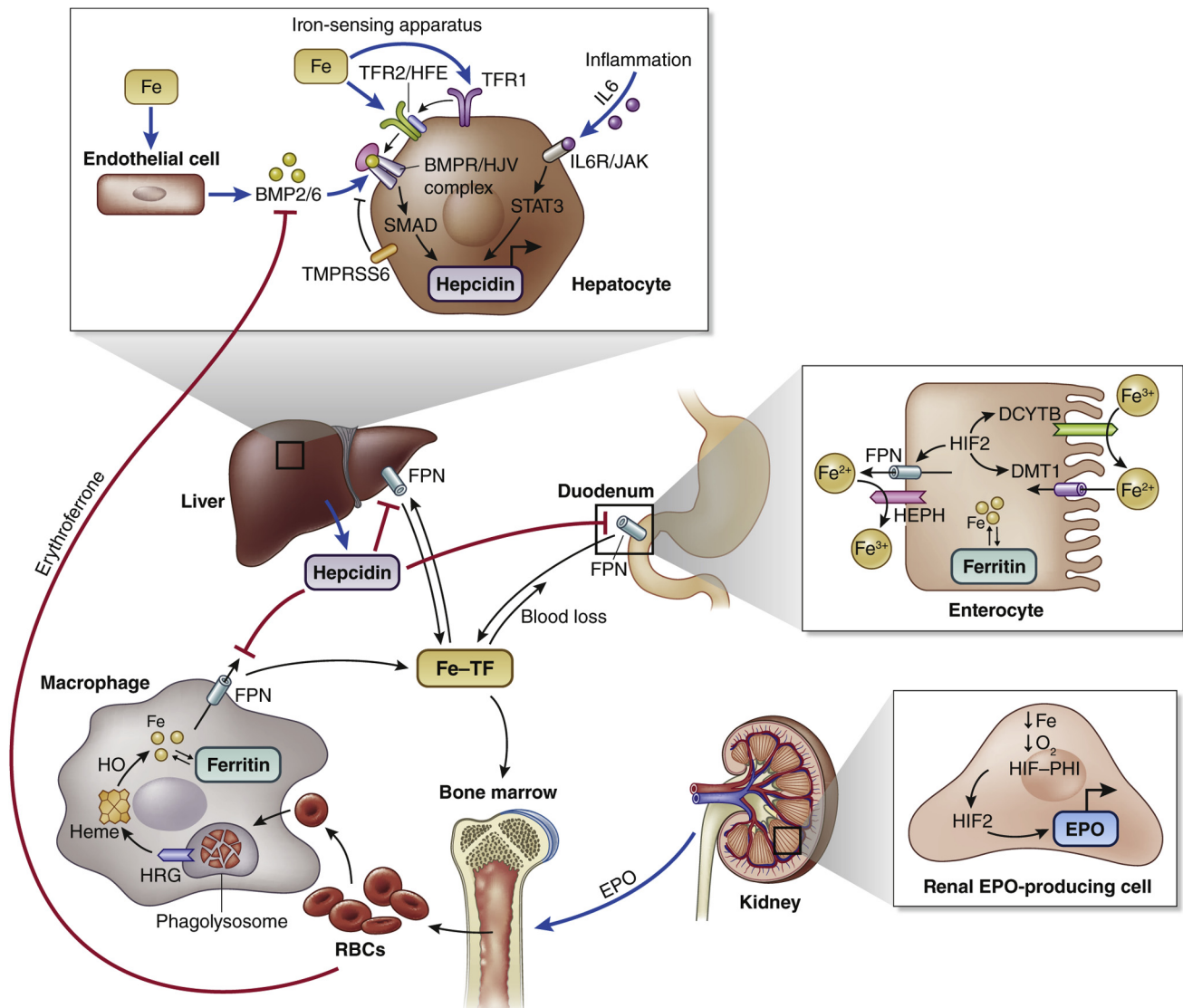
Copyright © 2021, Kidney Disease: Improving Global Outcomes (KDIGO). Published by Elsevier, Inc., on behalf of the International Society of Nephrology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Anemia and iron deficiency are prevalent in patients with chronic kidney disease (CKD)<sup>1–6</sup> and associated with poor outcomes.<sup>7–15</sup> The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) anemia guideline provides recommendations on the diagnosis and treatment of anemia in CKD, including the use of iron agents, erythropoiesis-stimulating agents (ESAs), and red cell transfusions.<sup>16</sup> Subsequently, based on evidence that full anemia correction with ESAs is associated with adverse outcomes,<sup>17–20</sup> and consequent regulatory and reimbursement changes in many countries, practice patterns have shifted toward reduced ESA use and increased iron supplementation.<sup>21–26</sup> The ensuing 8 years have yielded a plethora of new biological and clinical trial data, including the emergence of new iron agents and other novel anemia therapies, that merit a reevaluation of the 2012 guideline. In December 2019, KDIGO held its first of 2 Controversies Conferences on Optimal Management of Anemia focused on iron, to critically assess the latest evidence, to evaluate

Correspondence: Jodie L. Babitt, Massachusetts General Hospital, 185 Cambridge St., CPZN-8208, Boston, Massachusetts 02114, USA. E-mail: [Babitt.jodie@mgh.harvard.edu](mailto:Babitt.jodie@mgh.harvard.edu); or Tilman B. Drüeke, Inserm Unit 1018, Team 5, CESP, Hôpital Paul Brousse, 16 Avenue Paul Vaillant, Couturier, 94807 Villejuif Cedex, France. E-mail: [tilman.drueke@inserm.fr](mailto:tilman.drueke@inserm.fr)

<sup>17</sup>See [Appendix](#) for list of other Conference Participants.

Received 30 December 2020; revised 2 March 2021; accepted 9 March 2021; published online 8 April 2021



**Figure 1 | Direct and indirect regulation of systemic iron homeostasis.** Iron (Fe) is provided mainly by reticuloendothelial macrophages that recycle iron from senescent red blood cells (RBCs), with a lesser contribution from dietary absorption and other body stores. Iron circulates in the plasma predominantly bound to transferrin (TF) and is stored in cells in the form of ferritin. The liver hormone hepcidin controls systemic iron homeostasis by inducing degradation of the iron exporter ferroportin (FPN) to reduce iron entry into plasma from dietary sources and body stores. Iron deficiency and erythropoietic drive suppress hepcidin production to provide adequate iron for erythropoiesis and other essential functions. Iron and inflammation induce hepcidin to prevent iron overload and limit iron availability to pathogens. Iron induces hepcidin transcription by stimulating liver endothelial cells to produce bone morphogenetic proteins BMP2 and BMP6, which bind to the hepatocyte BMP receptor complex and coreceptor hemojuvelin (HJV) to activate SMAD transcription factors. Iron also induces hepcidin via the hepatocyte iron-sensing apparatus involving transferrin receptor 2 (TFR2), transferrin receptor 1 (TFR1), and homeostatic iron regulator protein (HFE).<sup>27</sup> These pathways are all inhibited by iron deficiency, which also increases the activity of transmembrane serine protease 6 (TMPRSS6) to cleave HJV and further suppress hepcidin.<sup>27</sup> Under conditions of accelerated erythropoietic activity, erythropoietin (EPO) induces erythroid progenitor cells to produce erythroferrone (ERFE), which suppresses hepcidin by functioning as a ligand trap to block the BMP signaling pathway.<sup>28</sup> During inflammation, IL-6 and other inflammatory cytokines induce hepcidin transcription directly via a (STAT)-3 binding element in the hepcidin promoter.<sup>29,30</sup> Hypoxia-inducible factors (HIFs), which are stabilized by low oxygen (O<sub>2</sub>) and low iron conditions, contribute to iron homeostasis and erythropoiesis by regulating the production of EPO in the kidney; ferriductase DCYTB and iron transporters FPN and divalent metal transporter 1 (DMT1) in the intestine; and the plasma iron carrier TF. HEPH, hephaestin; HO, heme oxygenase; HRG, heme transporter HRG1.

the need for guideline updates, and to identify key knowledge gaps for future research. The second conference, scheduled in 2021, will address ESAs and novel anemia therapies, including hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs), after data from ongoing long-term outcome studies become available.

**ETIOLOGY, DIAGNOSIS, AND PREVALENCE OF IRON DEFICIENCY AND ANEMIA IN CKD**

**Novel insights into iron homeostasis and the anemia of CKD**

Iron is an essential component of hemoglobin for erythropoiesis. CKD is associated with several disturbances in systemic iron homeostasis resulting in an inadequate iron

**Table 1 | Research priorities for managing anemia in CKD****Etiology and diagnosis of iron deficiency and anemia in CKD**

1. Describe the variability in Hb and iron parameters by levels of eGFR, disease states, age, and sex around the world to more accurately characterize “expected” Hb values for populations
2. Define and implement optimal preanalysis and standardized assays on the various hematological platforms for RBC parameters (e.g., RetHb and % hypochromic cells) to allow uniform use of clinical decision limits and avoid reliance on ferritin and TSAT alone. Educate clinicians on the adoption of these tools to clinical practice
3. Develop and validate novel diagnostic laboratory tools, possibly in partnership with industry
4. Develop and validate tools to capture symptoms of anemia that are easy to administer and have clinical utility, such as wearable health devices (phone trackers, Fitbits), fatigue scales, and 6-min walk test. Use these patient-derived data to assess optimal quality of life information in relationship to improvement of Hb or iron parameters in clinical trials
5. Determine the feasibility of redefining functional iron deficiency to more precisely describe specific etiologies (due to inflammation/hepcidin-mediated RES iron sequestration vs. kinetic iron deficiency due to bursts of erythropoiesis stimulated by ESAs) and the utility of this distinction for guiding clinical care. This would require validating additional diagnostic tests to discriminate between the 2 entities

**Iron, anemia, and outcomes in CKD**

1. Conduct an RCT to evaluate the impact of different iron preparations (traditional oral iron preparations, ferric citrate, and i.v.) on hard clinical outcomes (major adverse cardiovascular events, mortality, infection) and patient-reported outcomes in patients with CKD with iron deficiency without anemia
2. Conduct a large, pragmatic trial in hemodialysis patients examining the harms, benefits, and costs of protocolized iron therapy strategy (such as in PIVOTAL). Randomize patients to holding of iron if ferritin is 400 versus 700 versus 1200 µg/l (ng/ml). Compare hard clinical outcomes (major adverse cardiovascular events, infections, mortality), patient-reported outcomes, ESA use, and transfusions
3. Conduct clinical trials to evaluate whether giving iron or ESAs to reach Hb targets leads to better clinical outcomes (and prevents transfusions). Data are needed for determining the optimal relative amount of iron and ESAs to reach Hb targets

**Use of iron agents in CKD anemia management**

1. Conduct clinical trials to define optimal targets and treatment strategies for use of iron agents in patients with CKD at different eGFR values or etiologies of CKD, informed by epidemiology data above. Future studies should aim to more completely phenotype and genotype patients to enable the development of more personalized approaches
2. Conduct clinical trials to compare newly available oral iron compounds to traditional oral and i.v. iron compounds in patients with CKD; investigate the appropriateness of an alternate day, single-dose administration of oral iron in patients with CKD; and investigate the proactive versus reactive oral iron therapy strategy in CKD (i.e., equivalent of PIVOTAL trial for oral iron therapy)
3. Conduct head-to-head trials of different i.v. iron formulations, including iron similars, to evaluate relative efficacy and safety
4. Conduct dedicated studies on biodistribution and bioavailability of iron compounds

**ESAs and novel therapies**

1. Determine the ferrokinetic properties of HIF-PHIs and optimal iron management for HIF-PHI therapy, including:
  - a. Optimal diagnostic parameters for initiating, monitoring, and optimizing HIF-PHI therapy, including novel diagnostic parameters such as retHb and % hypochromic RBC
  - b. Upper limits of i.v. iron therapy (i.e., ferritin, TSAT, iron dose)
  - c. Iron needs for successful therapy, e.g., oral versus i.v. preparation and i.v. iron dosing levels
  - d. Effects of HIF-PHI therapy on erythroferrone/hepcidin axis
  - e. Impact of HIF-PHIs on intestinal iron absorption using Fe-isotope labeling studies
  - f. Impact of HIF-PHIs on monoferric and diferric transferrin and how this affects hepcidin regulatory pathways and erythropoiesis
2. Conduct studies dedicated to specific populations to define the CKD populations that are suitable for HIF-PHI therapy and those that should be excluded from HIF-PHI therapy:
  - a. Patients with diabetic nephropathy and retinopathy
  - b. Patients with autosomal dominant polycystic kidney disease
  - c. Inflamed patients and ESA hyporesponders
  - d. Pediatric patients with CKD
  - e. Patients with vascular calcifications
  - f. Patients with pulmonary arterial hypertension
3. Explore the potential of combination therapies targeting the different pathogenetic mechanisms underlying CKD anemia development—take advantage of drugs, agents, or treatment that are being studied in other clinical settings

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor-prolyl hydroxylase inhibitor; i.v., intravenous; PIVOTAL, Proactive IV Iron Therapy in Haemodialysis Patients; RCT, randomized controlled trial; RES, reticuloendothelial system; retHb, reticulocyte hemoglobin; TSAT, transferrin saturation.

supply, broadly categorized as absolute iron deficiency and functional iron deficiency. Absolute iron deficiency is a deficit of total body iron manifest as reduced levels of both circulating and stored iron. Functional iron deficiency has been defined as a deficiency of circulating iron that limits erythropoiesis despite normal or elevated body iron stores. The distinction between absolute and functional iron deficiency is important for determining the etiology of anemia and the optimal therapeutic approach.

In the last 2 decades, there have been new insights into the regulation of systemic iron homeostasis and the

pathophysiology of both absolute and functional iron deficiency in CKD, including the discoveries of the hepcidin-ferroportin axis, erythroferrone, and the role of HIFs (Figure 1<sup>27–30</sup>). Advanced CKD is associated with a negative iron balance due to reduced dietary intake, impaired enteral absorption, and increased losses.<sup>31</sup> Functional iron deficiency is multifactorial, due in part to hepcidin excess (as a consequence of inflammation, decreased renal clearance, and reduced erythropoietin [EPO] production), leading to iron sequestration in macrophage stores.<sup>32</sup> ESAs may also contribute to functional iron deficiency by causing a brisk

**Table 2 | Evidence for clinical benefits of iron administration**

	Patients with CKD not on dialysis	Patients on dialysis
Reduction of congestive heart failure	Limited <sup>60,61</sup>	Yes <sup>62</sup>
Reduced occurrence of myocardial infarction	Limited <sup>63</sup>	Yes <sup>62</sup>
Improved quality of life	Not studied	Limited <sup>64</sup>
Reduced occurrence of fatigue	Not studied	Limited <sup>64</sup>
Improved cognitive function	Not studied	Limited <sup>64</sup>
ESA dose reduction	Yes <sup>65</sup>	Yes <sup>65</sup>
Reduced blood transfusions	Not studied	Yes <sup>62</sup>

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agents; RCT, randomized controlled trial.

Limited: data from retrospective, observational studies. Yes: supported by RCT data.

iron demand that kinetically exceeds the iron supply. Other factors contributing to the anemia of CKD include reduced EPO production, poor bone marrow responsiveness, shortened red blood cell (RBC) survival, and direct bone marrow suppression.

**Definitions and diagnosis of iron deficiency and anemia: toward increasing precision**

The definitions and diagnosis of iron deficiency and anemia in CKD are historically based on 3 parameters: hemoglobin (Hb); serum transferrin saturation (TSAT), an indicator of circulating iron; and serum ferritin, an indicator of stored iron. In CKD, absolute iron deficiency has been defined as TSAT <20% and ferritin <100 µg/l in patients not on hemodialysis therapy or <200 µg/l in hemodialysis (HDCKD) patients. Functional iron deficiency has been defined as TSAT <20% and ferritin >100 µg/l in patients not on dialysis therapy (NDCKD) or >200 µg/l in HDCKD patients.<sup>16,33–36</sup> However, these terms and definitions have come under scrutiny and discussion.<sup>37,38</sup> The conference participants agreed that the presently used parameters are not reliable for estimating body iron stores or predicting response to therapy. Furthermore, there may be clinical utility in more precisely distinguishing subgroups of “functional iron deficiency” due to inflammation/hepcidin-mediated iron sequestration versus kinetic iron deficiency from ESA-stimulated bursts of erythropoiesis, to inform optimal treatment. These areas were identified as high priority for future research (Table 1).

The development and adoption of new tests to more accurately diagnose both absolute and functional iron deficiency, and to monitor response to therapy, is another high-priority research area. Several RBC parameters have been developed that are now more widely available in multiple hematology analyzers, including reticulocyte Hb content and percentage of hypochromic RBC.<sup>39,40</sup> Reticulocyte Hb indicates whether iron is incorporated into reticulocytes within 3–4 days after starting iron administration and thus serves as a functional parameter that may be useful in guiding iron and ESA therapy.<sup>41–45</sup> Percentage of hypochromic RBC reflects iron availability in the preceding 2–3 months, making it a sensitive long-term time-averaged functional parameter.

However, widespread clinical use of both of these parameters is constrained by the absence of universal clinical decision limits. The requirement for fresh blood samples also limits the use of percentage of hypochromic RBC.<sup>46</sup> Parameters to assess other functional consequences of iron deficiency or its correction, for example, in skeletal muscle and heart, may also be useful, but are not available. Heparin has not proved to be a consistent marker to distinguish absolute from functional iron deficiency or determine ESA responsiveness in patients with CKD.<sup>32</sup> Other diagnostics related to novel mechanistic insights, for example, erythroferrone levels, are still under investigation.

**Iron deficiency and anemia in CKD**

Data from multiple countries show that anemia and iron deficiency remain highly prevalent in patients with CKD. In NDCKD patients, the US Veteran study, REport of COMorbidities in non-Dialysis Renal Disease Population in Italy (RECORD-IT), and Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDoppS) report that 21%–62% of patients have anemia, defined as Hb <12 g/dl or <12 g/dl in females and <13.5 g/dl in males, with increasing prevalence in more advanced CKD.<sup>47–49</sup> Moreover, 15%–72.8% have either ferritin <100 µg/l or TSAT <20%, and 8%–20% have both parameters below the threshold.<sup>3,47,48,50,51</sup> For HDCKD patients, data from United States Renal Data System<sup>52</sup> show that 64.5%, 14.4%, and 6.6% have Hb levels between 10–12 g/dl, 9 and 10 g/dl, or below 9 g/dl, respectively. Moreover, 15.8% have TSAT <20%, and 4.9% have ferritin <200 µg/l.<sup>53</sup> Data from a Japanese registry show that 36.3%, 60.2%, and 28.0% of HDCKD patients have TSAT <20%, ferritin <100 µg/l, or both, respectively.<sup>54</sup> In peritoneal dialysis patients, the prevalence of iron deficiency anemia is reported in the range of 16%–23%.<sup>55</sup> These observations may reflect poor adherence with oral iron prescriptions in NDCKD and peritoneal dialysis patients, as well as therapeutic inertia, that is, lack of adequate iron or ESA prescriptions despite low Hb and/or iron deficiency.

**IRON, ANEMIA, AND OUTCOMES IN CKD**

Observational data indicate that anemia is associated with adverse outcomes in all disease states, including CKD<sup>7–15,56</sup> and congestive heart failure.<sup>57</sup> In CKD, anemia is associated with an increased risk of hospitalizations, cardiovascular disease, cognitive impairment, and mortality.<sup>58</sup> Moreover, TSAT <20% is also associated with cardiovascular hospitalizations and mortality.<sup>49,54,59</sup> However, given the association of anemia and iron deficiency with other comorbidities, the truly independent risk of abnormal Hb and/or iron levels remains uncertain.

**Benefits of iron administration in CKD**

In patients with CKD, data on the benefits of iron administration are limited (Table 2<sup>60–65</sup>). Results from PIVOTAL (Proactive IV Iron Therapy in Haemodialysis Patients), a randomized controlled trial (RCT) of more than 2000

**Table 3 | Evidence for increased risk of clinical harm with iron administration**

	Patients with CKD not on dialysis	Patients on dialysis
Infections	Limited <sup>78,79</sup>	No <sup>80,81</sup>
Cardiovascular events	Limited <sup>78,79,82</sup>	No <sup>62</sup>
Diabetes	Limited <sup>83</sup>	Limited <sup>83</sup>
CKD progression	Limited <sup>78,79</sup>	Not applicable
Anaphylaxis	Minimal <sup>84</sup>	Minimal <sup>84</sup>

CKD, chronic kidney disease; i.v., intravenous; RCT, randomized controlled trial. No: supported by RCT data. Limited: data from retrospective, observational trials only. Minimal: overall minimal risk for contemporary i.v. iron formulations.

HDCKD patients, indicate that proactive monthly administration of 400 mg intravenous (i.v.) iron in patients with serum ferritin <700 µg/l and TSAT ≤40% decreases ESA use and lowers the composite risk of all-cause death, nonfatal myocardial infarction, nonfatal stroke, and heart failure hospitalization compared with low-dose i.v. iron administered in a reactive fashion for ferritin <200 µg/l or TSAT <20%.<sup>62</sup>

In patients with heart failure with reduced ejection fraction and iron deficiency, multiple RCTs show that i.v. iron has benefits in terms of intermediate endpoints (6-minute walk test, quality of life, New York Heart Association class) and hospitalization.<sup>60,61,66</sup> Within the heart failure studies, those with CKD had similar benefits in subgroup analyses.<sup>60,61</sup> Meta-analysis results also suggest that i.v. iron lowers the composite risk of recurrent cardiovascular or heart failure hospitalizations and mortality in heart failure patients.<sup>67</sup> Notably, the benefits of iron administration in heart failure patients appears to be independent of Hb.<sup>60,61</sup> Moreover, iron deficiency without anemia may be clinically relevant in other contexts,<sup>68,69</sup> although limited data are available in CKD.<sup>14</sup> Understanding the clinical impact of iron deficiency and its correction, independent of anemia, is a high-priority research area for future studies in patients with CKD (Table 1).

**Risks of iron administration in CKD**

Because iron is essential for nearly all infectious microorganisms, there is concern that iron administration may increase infection risk.<sup>70-72</sup> Iron may also promote oxidative stress by participating in the Fenton reaction.<sup>73</sup> This has been suggested to potentially contribute to cardiovascular disease risk, CKD progression, and other organ damage in patients with CKD.<sup>31</sup> Non-transferrin-bound iron may be particularly important as a risk factor for certain pathogens, particularly gram-negative and other siderophilic bacteria.<sup>70,71</sup> The level of labile plasma iron, a component of non-transferrin-bound iron, may also be indicative of impending, clinically significant iron overload.<sup>74</sup> However, validated non-transferrin-bound iron and labile plasma iron assays are not widely available, and would require assay standardization, consensus on results reporting, and clinical outcome studies to

**Table 4 | Iron and chronic kidney disease—mineral and bone disorder**

	Expected effect on plasma C-terminal FGF23	Expected effect on plasma intact FGF23
Oral ferrous sulfate	?	↔
Oral ferric citrate	↓	↓
I.v. FCM, saccharated iron oxide, or iron polymaltose <sup>90-93</sup>	↓	↑
I.v. iron other than FCM, saccharated iron oxide, or iron polymaltose <sup>90-93</sup>	↓	↔
EPO <sup>84-97</sup>	↑	↔

EPO, erythropoietin; FCM, ferric carboxymaltose; FGF23, fibroblast growth factor-23, i.v., intravenous.

The C-terminal FGF23 immunometric assay uses 2 antibodies directed against different epitopes within the C-terminal part of the molecule, which therefore detects both the intact hormone and C-terminal cleavage products. The iFGF23 assay detects only the intact molecule.

determine clinically relevant assay formats and toxic thresholds before introduction into clinical practice.<sup>75,76</sup> In addition, data in hereditary hemochromatosis patients suggest that organ damage requires long-term exposure to high TSAT and labile plasma iron levels.<sup>77</sup>

Clinical trial data are now accruing to better evaluate the risks of iron administration in patients with CKD (Table 3<sup>78-84</sup>). In HDCKD patients, the high-dose i.v. arm in PIVOTAL had a reduced incidence of a composite outcome including cardiovascular events and mortality compared with the low-dose i.v. iron arm.<sup>62</sup> Moreover, infection rates were similar in both arms.<sup>81</sup> In addition, although patients dialyzing via a catheter had higher infection rates than those dialyzing via a fistula, i.v. iron did not influence this outcome.<sup>81</sup> A meta-analysis of prior epidemiological studies and RCTs also does not support a higher risk of infection or cardiovascular events from i.v. iron,<sup>80</sup> although this conclusion is limited by small participant and event numbers and statistical heterogeneity.<sup>85</sup> Overall, these data are reassuring regarding the safety of i.v. iron administered at levels in the high-dose arm of PIVOTAL.

However, retrospective, observational data suggest that more intensive i.v. iron administration (greater than in PIVOTAL) may be associated with increased risk of mortality and infections.<sup>86</sup> Increased risk of infection-related mortality with bolus versus maintenance dosing has also been reported in HDCKD patients with a catheter.<sup>87</sup> In NDCKD patients, data are mixed regarding whether high-dose iron administration increases risks of infections or cardiovascular events.<sup>78,79,82</sup> Thus, until more RCT data are available, caution is still warranted regarding high-dose i.v. iron strategies that are more aggressive than in PIVOTAL. Moreover, the conference participants continue to recommend withholding i.v. iron during active infections because these patients were excluded from currently available RCTs. Trials examining the effects of high-dose i.v. iron on infections, including specific types of infections (e.g., gram-negative

**Table 5 | Oral iron agents for treating anemia in CKD**

Preparation (brand name)	Elemental iron per tablet	Total salt content per tablet	Recommended dosage
Ferric citrate			
Auryxia (USA)	210 mg	1 g	1 tablet 3 times a day with meals for IDA in CKD not on dialysis; 2 tablets, 3 times a day for those on dialysis
Riona (ferric citrate hydrate [Japan])	45 mg	250 mg	500 mg, 3 times a day for hyperphosphatemia in CKD
Nephoxil (Taiwan)	105 mg	500 mg	Starting dose: 4 g a day with meals
Ferric maltol (Feracru [Europe]; Accrufer [USA])	30 mg	30 mg	1 tablet, twice daily
Ferrous sulfate (generic)	65 mg	325 mg	1000 mg/d for IDA in CKD
Ferrous fumarate (Ferro-Sequels, Ferretts, Ferrimin, Hemocyte, etc. [USA])	106 mg	325 mg	600 mg/d for IDA in CKD
Ferrous gluconate (Fergon, Ferate [USA])	38 mg	325 mg	1600 mg/d for IDA in CKD
Liposomal iron			
Ferrolip (Europe)	30 mg	30 mg	30 mg/d for IDA
SiderAL Forte (Europe)	30 mg	30 mg	30 mg/d for IDA
Heme iron polypeptide (Proferrin [USA])	12 mg	12 mg	3 or 4 tablets a day for IDA in CKD

CKD, chronic kidney disease; IDA, iron deficiency anemia. Sucroferric oxyhydroxide is not included on this list as it is poorly absorbed. Adapted with permission from Pergola PE, Fishbane S, Ganz T. Novel oral iron therapies for iron deficiency anemia in chronic kidney disease. *Adv Chronic Kidney Dis.* 2019;26:272–291.<sup>113</sup> © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0>).

bacteria), and associated mortality are another priority research area for future studies (Table 1).

**Iron, anemia, and CKD-associated mineral and bone disorder (CKD-MBD)**

Iron, inflammation, and erythropoiesis play a critical role in regulating fibroblast growth factor 23 (FGF23), which is an important contributor to CKD-MBD.<sup>88,89</sup> In the absence of CKD, iron deficiency, ESA administration, and inflammation increase c-terminal FGF23 (cFGF23) levels by simultaneously increasing FGF23 transcription and cleavage, whereas the biologically active intact FGF23 (iFGF23) levels remain largely unchanged. However, in CKD, where FGF23 cleavage is impaired, iron deficiency, ESAs, and inflammation increase iFGF23. The relative amounts of circulating iFGF23 and cFGF23 are impacted not only by iron status, inflammation, ESA use, and the presence of CKD, but also by the iron formulation administered (Table 4<sup>90–97</sup>).

Indeed, certain i.v. iron preparations increase iFGF23 through mechanisms that appear to be related to the carbohydrate shell.<sup>91,98</sup> In contrast, ferric citrate, by functioning as a phosphate binder, can lower both cFGF23 and iFGF23

levels.<sup>99,100</sup> These effects may be important not only for CKD-MBD, but also for cardiovascular and mortality outcomes that are strongly associated with excess FGF23,<sup>101–103</sup> although the causative role for excess FGF23 *per se* in cardiovascular disease is still a matter of debate.<sup>104</sup> Future studies are needed to better define the impacts of iron deficiency, anemia, iron therapy, and ESAs on CKD-MBD and its associated adverse outcomes. These studies should also take into account the bidirectional nature of these relationships, as FGF23 is also implicated as a regulator of erythropoiesis, iron metabolism, and systemic inflammation.<sup>105–108</sup>

**Iron, immune response, and the microbiome**

Iron is increasingly recognized to impact host immunity by altering immune cell proliferation and differentiation and by directly regulating cytokine formation and antimicrobial immune effector mechanisms.<sup>109</sup> These effects may not only influence infection risk as discussed above, but may also have other health consequences, including a potentially diminished response to vaccination in iron deficiency.<sup>110–112</sup> In addition, oral iron supplementation may alter gut microbiota and the gut and systemic metabolome, which may impact intestinal health, host immunity, and have other systemic health consequences.<sup>109</sup> Future studies are needed to address these issues in a more detailed fashion in patients with CKD.

**Designing future outcomes trials**

At present, only PIVOTAL has been of sufficient sample size and duration to allow statistically valid conclusions regarding the effects of iron administration on hard clinical outcomes in HDCKD patients. Similar studies in NDCKD patients and studies with different treatment targets and iron preparations in both NDCKD and HDCKD patients are needed (Table 1). Future RCTs will benefit from the development of improved, validated tools for determining optimal, individualized anemia correction targets, measuring patient-reported quality of life, and evaluating hard clinical outcomes (Table 1). Such tools should be easy to administer in trials and useful in clinical practice. They could include wearable health devices (phone trackers, Fitbits), fatigue scales, and walk tests aimed at examining improvements in general well-being. Many questions could be addressed through adaptive clinical trials that allow for planned design modifications based on collected trial data. Adaptive approaches could have several advantages: (i) statistical efficiency, especially with sequential design and adaptive modification of sample size; (ii) a process for early study termination, thus reducing patient exposure to intervention-associated risk; (iii) improved understanding of drug effects in targeted subgroups; and (iv) stakeholder receptiveness for both sponsors and patients.

**USE OF IRON AGENTS IN CKD ANEMIA MANAGEMENT**

**Oral iron**

Currently available oral iron compounds (Table 5<sup>113</sup>) have variable effectiveness in increasing Hb, ferritin, and TSAT, and in reducing ESA use or blood transfusions.<sup>65,114,115</sup> The main

**Table 6 | I.v. iron formulations for treating anemia in CKD**

Preparation (brand name) <sup>a,b</sup>	Concentration of elemental iron (mg/ml)	Max. single dose	Max. weekly dose	Min. infusion time for max. dose	Min. injection time for max. dose
Iron sucrose (Venofer); Iron sucrose similars (FerMed)	20	200 mg	500 mg	30 min (EMA) 15 min (FDA)	10 min (EMA) 2–5 min (FDA)
Sodium ferric gluconate (Ferrlecit)	12.5	125 mg	Not stated	60 min (FDA)	10 min (FDA)
LMW iron dextran (Cosmofer [Europe]; INFeD [USA])	50	20 mg/kg	Not stated	15 min, then 100 mg/15 min (EMA) Total infusion: 4–6 h	Approx. 20 min (EMA) >60 min (FDA)
Ferric carboxymaltose (Ferinject [Europe]; Injectafer [USA])	50	1000 mg (EMA) 750 mg (FDA)	1000 mg (EMA) 750 mg (FDA)	15 min	15 min (EMA) 7.5 min (FDA)
Iron isomaltoside/ferric derisomaltose (Monofer [Europe], Monoferric [USA])	100	20 mg/kg (EMA) 1000 mg (FDA)	20 mg/kg (EMA) Not stated (FDA)	More than 15 min (≤1000 mg) (EMC) 30 min or more (>1000 mg) (EMC) 20 min for ≤1000 mg (FDA)	250 mg/min (max. 500 mg) (EMA)
Ferumoxytol (Rienso [Europe] <sup>c</sup> , Feraheme [USA])	30	510 mg	1020 mg	15 min (EMA)	15 min (FDA)

CKD, chronic kidney disease; EMA, European Medicines Agency; EMC, electronic medicines compendium; FDA, Food and Drug Administration; LMW, low molecular weight; Max., maximum; Min., minimum.

<sup>a</sup>Listing of iron sucrose similars and other intravenous iron-containing medicinal products in the European Union can be found here: [https://www.ema.europa.eu/en/documents/additional-monitoring/annex-iii-list-intravenous-iron-containing-medicinal-products-european-union\\_en-0.pdf](https://www.ema.europa.eu/en/documents/additional-monitoring/annex-iii-list-intravenous-iron-containing-medicinal-products-european-union_en-0.pdf).

<sup>b</sup>I.v. ferric pyrophosphate citrate has just been approved by the FDA at the writing of this report.

<sup>c</sup>Has since been withdrawn from the EU.

Adapted with permission from Schaefer B, Meindl E, Wagner S, et al. Intravenous iron supplementation therapy. *Mol Aspects Med.* 2020;75:100862.<sup>118</sup>

© 2020 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

drawbacks of oral iron include reduced effectiveness compared with i.v. iron,<sup>65,115</sup> poor gastrointestinal tolerance, poor absorption due to elevated hepcidin, and possible microbiome changes (see above).<sup>109</sup> However, oral iron administration is noninvasive, avoids injection-site complications, does not jeopardize venous capital for arteriovenous fistulae creation, has not been associated with hypersensitivity reactions or increased infection rates, and has no direct effects to induce FGF23.

Newer oral iron preparations may offer some advantages over previously available oral iron preparations in terms of efficacy and tolerability, but this is an understudied area. In NDCKD patients, ferric citrate was shown to increase TSAT, ferritin, and Hb, together with lowering serum phosphate, FGF23 levels, i.v. iron needs, and ESA needs.<sup>82,100</sup> Preliminary evidence from a single trial suggested that ferric citrate reduced hospitalization rates and death compared with usual care.<sup>100</sup> Liposomal iron avoids direct contact of iron with intestinal mucosa and bypasses the intestinal hepcidin-ferroportin block via a different uptake mechanism into intestinal M cells.<sup>113,116</sup> In a small trial, liposomal iron increased Hb in NDCKD patients,<sup>116</sup> although larger confirmatory trials are needed. Future RCTs investigating the benefits and risks of newer oral iron compounds compared with established oral iron compounds or i.v. iron preparations, and

optimal dosing strategies were designated as high-priority research areas (Table 1). In patients without CKD, single-dose oral iron administration on alternate days versus every day increases fractional iron absorption by limiting the impact of iron-mediated hepcidin induction.<sup>117</sup> Similar trials should be conducted in patients with CKD (Table 1).

### I.v. iron

I.v. iron (nanoparticle) preparations (Table 6<sup>118</sup>) have an Fe<sup>3+</sup> oxyhydroxide/oxide core, with a carbohydrate shell that determines specific functionalities.<sup>119</sup> Available clinical trial data<sup>63,113,120–122</sup> suggest that i.v. iron formulations have largely comparable efficacy in improving Hb, ferritin, and TSAT, and reducing ESA use or blood transfusions, although iron sucrose similars may have reduced efficacy and safety relative to parent iron sucrose.<sup>123–125</sup> However, such data are limited. I.v. iron has a good overall safety profile,<sup>65,80,115</sup> yet there are some safety differences among formulations. In particular, an increased risk of hypophosphatemia is conferred by certain i.v. iron preparations, including ferric carboxymaltose,<sup>90,98,126–128</sup> saccharated iron oxide,<sup>92</sup> and iron polymaltose,<sup>93</sup> due to their ability to induce FGF23 (see above). Although this risk is attenuated in patients with more advanced CKD, caution is advised in



kidney transplant recipients, and in NDCKD, measurement of serum phosphate prior to repeated doses or in symptomatic patients receiving the relevant i.v. iron preparations is warranted. Overall, anaphylaxis is very rare, but varying levels of risk have been reported for different IV iron formulations.<sup>84</sup> Risk of proteinuria<sup>129</sup> or surrogate markers of nephrotoxicity may vary based on i.v. iron formulation, but available data in NDCKD patients suggest that i.v. iron does not negatively impact kidney function (Table 3).<sup>78,130</sup> Future research priority areas include more head-to-head RCTs to confirm comparable efficacy and better understand safety differences between i.v. iron formulations, as well as dedicated biodistribution and bioavailability studies (Table 1).

#### Iron administration via dialysate

Ferric pyrophosphate citrate is a water-soluble iron salt administered via dialysate or i.v.<sup>131,132</sup> 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.<sup>133</sup> 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.<sup>134,135</sup> However, whether ferric pyrophosphate citrate has a superior safety profile relative to oral or i.v. iron has not been determined.

#### Optimal treatment targets and strategies

One of the primary strategies for managing anemia is maintaining appropriate TSAT and ferritin levels. The KDIGO 2012 Anemia guideline recommends a trial of i.v. iron in HDCKD patients (or a 1- to 3-month trial of oral iron for NDCKD patients) if an increase in Hb or a decrease in ESA dose is desired and TSAT is  $\leq 30\%$  and ferritin is  $\leq 500$   $\mu\text{g/l}$ .<sup>16</sup> Continued iron therapy should be based on an integrated assessment of Hb responses, iron status tests, ESA dose/responsiveness, ongoing blood losses, and clinical status, although available data were considered insufficient to recommend long-term i.v. dosing strategies. Importantly, these treatment target recommendations were largely based on observational data.

New data are now available from prospective RCTs to provide more firm evidence and further refinement to the 2012 guideline. For NDCKD patients, the FIND-CKD study indicated that i.v. iron dosed to a target ferritin of 400 to 600  $\mu\text{g/l}$  was superior to i.v. iron dosed to a target ferritin of 100 to 200  $\mu\text{g/l}$  or oral iron for achieving an Hb increase  $\geq 1$  g/dl.<sup>136</sup> I.v. iron to the higher ferritin target was also superior to oral iron in delaying or reducing the need for other anemia management.<sup>136</sup> However, no hard patient outcomes were assessed specifically.<sup>136</sup> For HDCKD patients, PIVOTAL showed that proactive i.v. iron administered unless serum ferritin  $>700$   $\mu\text{g/l}$  or TSAT  $>40\%$  was superior to a reactive strategy triggered only for TSAT  $<20\%$  and ferritin  $<200$   $\mu\text{g/l}$ ,

indicating that the latter strategy should be avoided.<sup>62</sup> However, it remains uncertain whether intermediate target strategies might be sufficient, or even optimal. Moreover, the upper limit of TSAT and ferritin in terms of safety, ESA dose reduction, and patient outcomes is unknown. These questions should be addressed in future RCTs in both NDCKD and HDCKD patients (Table 1).

Additional understudied areas include the optimal treatment algorithm for the use of iron therapy relative to ESAs.<sup>137</sup> There is evidence that optimal treatment targets may differ worldwide. For example, Japanese HDCKD patients achieve similar outcomes with much lower median ferritin levels than HDCKD patients in the United States and Europe, possibly related to lower C-reactive protein levels.<sup>138,139</sup> Hence, another high-priority research area is patient-focused therapy to better tailor treatment decisions based on individual patient characteristics (e.g., phenotype and genotype) and not only on population Hb and TSAT values (Table 1).

### THE IMPACT OF ESAs AND NOVEL THERAPEUTIC AGENTS ON HEMOGLOBIN CONTROL, IRON STATUS, AND IRON SUPPLEMENTATION NEEDS

#### Iron in current ESA therapy

ESAs increase iron utilization and decrease several iron parameters, including serum iron, TSAT, and ferritin. ESAs also suppress hepcidin by inducing erythropoiesis and erythroferrone, thereby increasing the iron supply from macrophage stores and dietary sources (Figure 1). Intense ESA stimulation can unmask or contribute to iron deficiency by causing a strong iron demand that outstrips the iron supply. This can occur even if there are adequate iron stores, particularly in the setting of inflammation, which induces hepcidin and limits the release of stored iron. Response to ESAs is therefore affected by iron status and extent of inflammation, which also inhibits erythropoiesis via other mechanisms.<sup>140–142</sup>

#### New upcoming therapies: HIF-PHIs

HIF-PHIs are small molecule inhibitors of prolyl-4-hydroxylase domain (PHD) dioxygenases (PHD1, PHD2, and PHD3) that sense oxygen and iron and control the activity of HIFs.<sup>143</sup> HIFs are heterodimeric transcription factors that consist of a constitutively expressed  $\beta$ -subunit and an oxygen- and iron-regulated  $\alpha$ -subunit (either HIF-1 $\alpha$ , HIF-2 $\alpha$ , or HIF-3 $\alpha$ ). In the presence of oxygen and iron, HIF  $\alpha$ -subunits are rapidly hydroxylated by PHDs, leading to degradation. When oxygen and iron are limited, HIFs are stabilized to regulate biological processes that facilitate oxygen and iron transport and delivery to enhance cell survival, including genes involved in angiogenesis, anaerobic glycolysis, fatty acid and mitochondrial metabolism, cellular differentiation and motility, erythropoiesis, and iron metabolism.<sup>144</sup> HIF-PHIs inhibit the degradation of HIF  $\alpha$ -subunits irrespective of oxygen and iron levels, resulting in the increased expression of HIF-regulated genes, such as *EPO* and genes involved in iron uptake and transport, for example, divalent

**Table 7 | Summary of peer-reviewed phase 3 studies of HIF-PHIs in patients on dialysis and in patients with CKD not on dialysis**

Compound	Study	N	Duration (wk)	Comp	Ferritin	TSAT	TIBC or transferrin	Hepcidin	Cholesterol (total or LDL)
<b>Patients on dialysis (no comparator or placebo)</b>									
Daprodustat	Tsubakihara <i>et al.</i> <sup>162</sup>	28	24	None	↓	a	↑	↓	a
Roxadustat	Akizawa <i>et al.</i> <sup>163</sup> (PD)	13 (corr.)	24	None	a	a	b	a	No chg.
		43 (conv.)							
	Akizawa <i>et al.</i> <sup>164</sup>	74 (corr.)	24–52	None	a	a	b	a	n.r.
		163 (conv.)							
Vadadustat	Nangaku <i>et al.</i> <sup>166</sup> (PD)	42	24	None	↓	↓	↑	↓	n.r.
<b>Patients with CKD not on dialysis (no comparator or placebo)</b>									
Roxadustat	Chen <i>et al.</i> <sup>169</sup>	152	8 db 18 ol	pbo (8 wk)	↓	↓	↑	↓	↓
	Akizawa <i>et al.</i> <sup>170</sup>	99	24	None	a	No chg.	b	a	n.r.
	Coyne <i>et al.</i> <sup>171</sup> (ANDES)	922	52	pbo	↓	No chg.	↑	↓	↓
	Fishbane <i>et al.</i> <sup>172</sup> (OLYMPUS)	2781	52	pbo	↓	No chg.	↑	↓	↓
	Shutov <i>et al.</i> <sup>173</sup> (ALPS)	594	52–104	pbo	a	No chg.	n.r.	a	↓
<b>Patients on dialysis (ESA comparator)</b>									
Daprodustat	Akizawa <i>et al.</i> <sup>160</sup>	271	52	darbe	No chg.	No chg.	↑	↓	n.r.
Roxadustat	Chen <i>et al.</i> <sup>150</sup> (HD and PD)	304	26	epoetin-alfa	b	↑	↑	a	↓
	Akizawa <i>et al.</i> <sup>161</sup>	303	24	darbe	No chg.	No chg.	b	No chg.	n.r.
	Provenzano <i>et al.</i> <sup>165</sup>	1043	52	epoetin-alfa	↓	No chg.	↑	a	↓
	Incident HD and PD (HIMAYALAS)								
Vadadustat	Nangaku <i>et al.</i> <sup>167</sup>	323	52	darbe	No chg.	No chg.	↑	a	n.r.
<b>Patients with CKD not on dialysis (ESA comparator)</b>									
Daprodustat	Nangaku <i>et al.</i> <sup>168</sup>	299	52	epoetin-beta pegol	a	a	b	a	a

CKD, chronic kidney disease; comp, active comparator group; conv., conversion from ESA; corr., correction (EPO-naïve patients); darbe, darbepoetin alfa; db, double-blind; ESA, erythropoiesis stimulating agent; HIF-PHI, hypoxia-inducible factor-prolyl hydroxylase inhibitor; n, number of patients; No chg., no change; n.r., not reported; ol, open label (all patients eligible for roxadustat); pbo, placebo; PD, peritoneal dialysis; TIBC, total iron-binding capacity; wk, weeks.

<sup>a</sup>Denotes that a numerical decrease in mean compared with baseline (no comparator), a greater numerical decrease in mean compared with placebo or ESA comparator, or a lesser numerical increase in mean compared with placebo or ESA was reported; statistical significance was not reached or not reported.

<sup>b</sup>Denotes that a numerical increase in mean compared with baseline (no comparator), a greater numerical increase in mean compared with placebo or ESA comparator, or a lesser numerical decrease in mean compared with placebo or ESA comparator was reported; statistical significance was not reached or not reported.

↓ Denotes that a statistically significant decrease in mean compared with baseline (no comparator), a greater decrease in mean compared with placebo or ESA comparator, or a lesser increase in mean compared with placebo or ESA comparator was reported in 1 or several dose cohorts or for the combined analysis of all dosing groups.

↑ Denotes that a statistically significant increase in mean compared with baseline (no comparator), a greater increase in mean compared with placebo or ESA comparator, or a lesser decrease in mean compared with placebo or ESA comparator was reported in 1 or several dose cohorts or for the combined analysis of all dosing groups.

metal transporter 1, duodenal cytochrome B, ferroportin, and transferrin.<sup>145,146</sup> HIF-2 is particularly important for regulating erythropoiesis and iron metabolism genes (Figure 1).

**Effects on erythropoiesis.** HIF-PHIs stimulate the endogenous production of EPO in the kidney and liver and may have other erythropoiesis-promoting effects in the bone marrow.<sup>147</sup> Phase 2 and 3 clinical trials in patients with CKD have shown that HIF-PHIs are efficacious in correcting and maintaining Hb in a titratable manner.<sup>148–156</sup> In addition, efficacious treatment with HIF-PHIs was associated with much lower increases in plasma EPO levels compared with traditional ESAs administered i.v.<sup>151,157</sup> Achievement of lower plasma EPO levels may be of clinical benefit as high ESA doses in CKD patients have been associated with increased cardiovascular risk and mortality.<sup>158,159</sup> Several recent phase 3 studies in HDCKD patients from Asia indicated noninferiority of HIF-PHIs compared with traditional ESAs,<sup>150,160,161</sup> but peer-reviewed publications from global efficacy and cardiovascular safety trials are still awaited. It is anticipated that these data will be reviewed in the KDIGO Controversies Conference on Novel Anemia Therapies scheduled in 2021.

**Impact on iron metabolism.** HIF-PHIs are predicted to impact iron homeostasis by 2 major mechanisms: (i) decreased hepcidin production in the liver and (ii) increased transcription of genes that promote the dietary uptake and transport of iron (Figure 1).<sup>145</sup> Oral administration of HIF-PHIs to patients with CKD was associated with decreased plasma hepcidin levels compared with placebo in the majority of phase 2 and 3 clinical trials (Table 7<sup>150,160–173</sup>). Genetic and cell culture-based studies as well as studies with EPO-neutralizing antibodies have provided convincing evidence that hepcidin is not a direct transcriptional target of HIF. Instead, systemic or liver-specific HIF activation suppresses hepcidin indirectly through EPO-dependent effects on erythropoiesis,<sup>174–176</sup> which is the same mechanism of action for hepcidin suppression by traditional ESAs. The smaller number of published trials comparing HIF-PHIs with traditional ESAs have reported more variable effects on plasma hepcidin than placebo-controlled trials (Table 7), and these studies have several limitations requiring interpretation with caution. More clinical trial data are needed to address whether HIF-PHIs and ESAs are differentially effective in suppressing hepcidin, and if so, the molecular mechanisms responsible.

Clinical trial data corroborating the predicted ferrokinetic properties of HIF-PHIs in patients with CKD are still too limited to provide meaningful conclusions (Table 7) and are a high priority (Table 1). Although data from phase 2 and phase 3 studies have suggested that HIF-PHIs may reduce the need for i.v. iron supplementation,<sup>150,162,169,177–180</sup> the degree to which this occurs, especially in patients who are inflamed, remains unclear and will need to be established in future studies. It remains to be established what degree of iron repletion is needed and which laboratory parameters should be met before HIF-PHI treatment can be safely initiated. Recent recommendations by the Asian Pacific Society of Nephrology emphasized the importance of avoiding excessive

serum iron lowering by HIF-PHIs to minimize the risk of associated adverse effects.<sup>181</sup>

**Additional areas of uncertainty.** Several mechanistic knowledge gaps and high-priority research areas regarding HIF-PHIs were identified (Table 1). In particular, because HIFs regulate a large number of genes, nonerythropoietic effects could be beneficial or concerning.<sup>182</sup> At least a subset of HIF-PHIs are reported to reduce serum triglyceride, total cholesterol, and low-density lipoprotein levels, in part due to HIF-mediated increases in HMG-CoA reductase degradation.<sup>183,184</sup> Preclinical studies suggest that HIF-PHIs lower blood pressure in animal models of CKD,<sup>185</sup> but this has not been corroborated in clinical trials. Other benefits predicted from animal models are potential HIF-mediated anti-inflammatory effects,<sup>186,187</sup> protection from ischemic injuries, and reduced CKD progression.<sup>188</sup> Although phase 2 and 3 clinical studies have suggested that HIF-PHIs may be efficacious in patients with CKD irrespective of baseline C-reactive protein levels (Table 7),<sup>150,157,177,178,189</sup> overtly inflamed patients were excluded from most trials. Areas of concern regarding HIF-PHIs include potential tumor-promoting effects, risk for pulmonary arterial hypertension,<sup>190–194</sup> cyst growth-promoting effects in patients with polycystic kidney disease,<sup>195</sup> proangiogenic effects in patients with vascular retinopathies,<sup>196</sup> enhancement of vascular calcifications,<sup>197</sup> and risk for abnormal embryonic and fetal development. Notably, many HIF-PHIs are in advanced clinical development (daprodustat, desidustat, enarodustat, molidustat, roxadustat, vadadustat), with several compounds now being marketed in Asia. Although all compounds are strong inhibitors of PHD1, PHD2, and PHD3 and stabilize both HIF-1 $\alpha$  and HIF-2 $\alpha$ ,<sup>198</sup> differences in pharmacokinetic and pharmacodynamic profiles, such as dosing regimen, drug half-life, and differences in the degree, range and kinetics of HIF-regulated gene activation, are ill-defined. These areas will be explored further in the next KDIGO Controversies Conference scheduled for 2021.

### Other new therapeutic strategies

Investigational strategies for renal anemia therapy were discussed. These include inhibitors of hepcidin production or action, which are in development at preclinical and clinical stages (Supplementary Table S1), and therapies currently used or being investigated in other disease states, for example, interleukin-6 specific antibodies, other anti-inflammatory biologicals, and activin receptor ligand traps.<sup>199–202</sup> The combination of multiple therapeutic approaches and the development of individualized treatment options for renal anemia were recognized as important areas of investigation (Table 1). By targeting multiple underlying pathogenic disease processes simultaneously, combination therapies would have potential for creating individualized therapies, minimizing costs and side effects, and enhancing quality of life. However, combination therapy could also increase pill burden and the risks of adverse events. It was emphasized that novel therapeutic strategies for renal anemia necessitate a reassessment of iron supplementation

strategies and re-evaluation of laboratory and clinical parameters for treatment initiation and monitoring.

### Special populations with CKD

In several populations, iron treatment deserves specific considerations (Supplementary Table S2). The safety and effectiveness of anemia treatments in children with CKD is an understudied area. The absence of RCTs examining the effects of ESA and iron on hard clinical outcomes in anemic pediatric patients with CKD raises concerns whether current pediatric anemia/iron management is appropriate. Results from small open-label and retrospective studies suggest that newer iron agents, including ferric pyrophosphate and ferric citrate, may be efficacious in children,<sup>131,203</sup> but more data are needed. Clinical investigations of HIF-PHIs in pediatric patients with CKD are not yet available, but are planned.<sup>204</sup> Concerns were raised with regard to potential adverse effects of systemic HIF activation on embryonic and fetal development, and growth and development in children. In particular, the cholesterol-lowering effects reported for some HIF-PHIs may impair nervous system development and myelination. In addition, mouse models have shown adverse impacts of genetic HIF activation on bone and cartilage growth and development.<sup>205,206</sup> However, it is difficult to extrapolate findings from genetic mouse models and make predictions regarding the effects of pharmacologic HIF stabilization in children with CKD.

### CONCLUSIONS

The conference participants agreed that sufficient data are available from new prospective RCTs and novel therapies to warrant convening a new workgroup to revise the KDIGO 2012 anemia guideline. There was also consensus that there are many areas where significantly more research is needed. In particular, the presently used parameters of Hb, serum TSAT, and serum ferritin are not reliable for estimating body iron stores or predicting response to therapy. Moreover, optimal thresholds, targets, and treatment strategies for anemia remain unknown, and have not been customized for specific disease states, age, sex, or within the context of other comorbidities. The need for increasing the complexity and specificity of treatment goals for patients is in keeping with trends to individualize therapy in all specialties. Important for future studies are developing and validating improved tools for determining optimal, individualized anemia correction targets, measuring patient-reported quality of life, and evaluating hard clinical outcomes. Although the class of HIF-PHI agents are predicted to benefit iron metabolism, clinical study data corroborating their predicted ferrokinetic properties in patients with CKD are not yet clearly established and are a high priority.

### APPENDIX

#### Other Conference Participants

Ali K. Abu-Alfa, Lebanon; Baris Afsar, Turkey; Amy Barton Pai, USA; Anatole Besarab, USA; Geraldine Biddle Moore, USA; Nicole Casadevall, France; Aleix Cases, Spain; Angel de Francisco, Spain; Kai-Uwe Eckardt, Germany; Steven Fishbane, USA; Linda F. Fried, USA; Tomas Ganz, USA; Yelena Z. Ginzburg, USA;

Rafael Gómez, Colombia; Lawrence T. Goodnough, USA; Takayuki Hamano, Japan; Mark R. Hanudel, USA; Chuan-Ming Hao, China; Kunitoshi Iseki, Japan; Joachim H. Ix, USA; Kirsten L. Johansen, USA; Markus Ketteler, Germany; Csaba P. Kovcsy, USA; David E. Leaf, USA; Iain C. Macdougall, UK; Ziad A. Massy, France; Lawrence P. McMahon, Australia; Roberto Minutolo, Italy; Takeshi Nakanishi, Japan; Elizabeta Nemeth, USA; Gregorio T. Obrador, Mexico; Patrick S. Parfrey, Canada; Hyeong-Cheon Park, Korea; Roberto Pecoits-Filho, USA; Bruce M. Robinson, USA; Simon D. Roger, Australia; Yatrik M. Shah, USA; Bruce S. Spinowitz, USA; Tetsuhiro Tanaka, Japan; Yusuke Tsukamoto, Japan; Kriang Tungsanga, Thailand; Carl P. Walthers, USA; Angela Yee-Moon Wang, Hong Kong, SAR, China; and Myles Wolf, USA.

### DISCLOSURE

JLB has declared receiving consulting fees from Disc Medicine and Incyte Corporation; equity ownership from Ferrumax Pharmaceuticals; research support from the National Institutes of Health (grant RO1-DK087727) and the Patricia and Scott Eston Massachusetts General Hospital Research Scholar Award; and patent royalties for intellectual property owned by Massachusetts General Hospital that is licensed to Ferrumax Pharmaceuticals on BMP and HJV targeted therapies for iron disorders. MFE has declared receiving consultant fees from Vifor Pharma; serving on the Advisory Board for Cablon Medical; and receiving speakers bureaus from Vifor Pharma. VHH has declared receiving consultant fees from Akebia Therapeutics, AstraZeneca, FibroGen, Incyte Corporation, and Rockwell Medical. AVK has declared receiving consultant fees from Rockwell Medical. AL has declared receiving consultant fees from AstraZeneca and research support from AstraZeneca. FL has declared receiving consultant fees from Amgen and AstraZeneca, and speakers bureaus from Amgen, AstraZeneca, and Roche. JM has declared receiving consultant fees from AstraZeneca and speakers bureaus from Bayer Healthcare. DWS has declared receiving consultant fees from Silence Therapeutics. MJ has declared receiving consultant fees from Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius Medical Care Asia Pacific, Mundipharma, and Vifor Fresenius Medical Care; serving on speakers bureaus from Astellas, AstraZeneca, Mundipharma, and Vifor Fresenius Medical Care; and receiving research support from Amgen and future research support from AstraZeneca. WCW has declared receiving consultant fees from Akebia/Otsuka, AstraZeneca, Bayer Healthcare, Janssen, Merck, Reata, and Relypsa; future consultant fees from Boehringer Ingelheim; and research support from the National Institutes of Health. TBD has declared receiving consultancy fees from Astellas, GlaxoSmithKline, and KfH Stiftung; and future consultant fees from Astellas. All the other authors declared no competing interests.

### ACKNOWLEDGMENTS

This conference was sponsored by KDIGO and supported in part by unrestricted educational grants from Akebia Therapeutics, AMAG Pharmaceuticals, Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, FibroGen, GlaxoSmithKline, Mitsubishi Tanabe Pharma Group, Pharmacosmos, Roche, Rockwell Medical, Torii Pharmaceutical, and Vifor Fresenius Medical Care Renal Pharma.

### SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Table S1.** Inhibitors of hepcidin in development.

**Table S2.** Special considerations in specific populations with CKD.

#### Supplementary References.

The conference agenda, discussion questions, and plenary session presentations are available on the KDIGO website: <https://kdigo.org/conferences/controversies-conference-on-optimal-anemia-management-in-ckd/>.

### REFERENCES

1. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One*. 2014;9:e84943.
2. St Peter WL, Guo H, Kabadi S, et al. Prevalence, treatment patterns, and healthcare resource utilization in Medicare and commercially insured non-dialysis-dependent chronic kidney disease patients with and without anemia in the United States. *BMC Nephrol*. 2018;19:67.
3. Ryu SR, Park SK, Jung JY, et al. The prevalence and management of anemia in chronic kidney disease patients: result from the Korean

- Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). *J Korean Med Sci.* 2017;32:249–256.
4. Akizawa T, Okumura H, Alexandre AF, et al. Burden of anemia in chronic kidney disease patients in Japan: a literature review. *Ther Apher Dial.* 2018;22:444–456.
  5. Li Y, Shi H, Wang WM, et al. Prevalence, awareness, and treatment of anemia in Chinese patients with nondialysis chronic kidney disease: first multicenter, cross-sectional study. *Medicine.* 2016;95:e3872.
  6. Iyawe IO, Adejumo OA, Iyawe LI, et al. Assessment of iron status in predialysis chronic kidney disease patients in a Nigerian Tertiary Hospital. *Saudi J Kidney Dis Transpl.* 2018;29:1431–1440.
  7. Hayashi T, Tanaka Y, Iwasaki M, et al. Association of circulatory iron deficiency with an enlarged heart in patients with end-stage kidney disease. *J Ren Nutr.* 2019;29:39–47.
  8. Eisenga MF, Nolte IM, van der Meer P, et al. Association of different iron deficiency cutoffs with adverse outcomes in chronic kidney disease. *BMC Nephrol.* 2018;19:225.
  9. Sato Y, Fujimoto S, Konta T, et al. Anemia as a risk factor for all-cause mortality: obscure synergic effect of chronic kidney disease. *Clin Exp Nephrol.* 2018;22:388–394.
  10. Eriksson D, Goldsmith D, Teitsson S, et al. Cross-sectional survey in CKD patients across Europe describing the association between quality of life and anaemia. *BMC Nephrol.* 2016;17:97.
  11. Shaker AM, Mohamed OM, Mohamed MF, et al. Impact of correction of anemia in end-stage renal disease patients on cerebral circulation and cognitive functions. *Saudi J Kidney Dis Transpl.* 2018;29:1333–1341.
  12. Majernikova M, Rosenberger J, Prihodova L, et al. Posttransplant anemia as a prognostic factor of mortality in kidney-transplant recipients. *Biomed Res Int.* 2017;6987240.
  13. Yi SW, Moon SJ, Yi JJ. Low-normal hemoglobin levels and anemia are associated with increased risk of end-stage renal disease in general populations: a prospective cohort study. *PLoS One.* 2019;14:e0215920.
  14. Eisenga MF, Minovic I, Berger SP, et al. Iron deficiency, anemia, and mortality in renal transplant recipients. *Transpl Int.* 2016;29:1176–1183.
  15. van Swelm RPL, Wetzels JFM, Swinkels DW. The multifaceted role of iron in renal health and disease. *Nat Rev Nephrol.* 2020;16:77–98.
  16. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl.* 2012;2:279–335.
  17. Pfeffer MA, Burdman 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.
  18. Druke 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.
  19. 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.
  20. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med.* 1998;339:584–590.
  21. Gardiner R, Roshan D, Brennan A, et al. Trends in the treatment of chronic kidney disease-associated anaemia in a cohort of haemodialysis patients: the Irish experience. *Ir J Med Sci.* 2019;188:223–230.
  22. Evans M, Suttrop MM, Bellocco R, et al. Trends in haemoglobin, erythropoietin-stimulating agents and iron use in Swedish chronic kidney disease patients between 2008 and 2013. *Nephrol Dial Transplant.* 2016;31:628–635.
  23. Charytan DM, Pai AB, Chan CT, et al. Considerations and challenges in defining optimal iron utilization in hemodialysis. *J Am Soc Nephrol.* 2015;26:1238–1247.
  24. Park H, Liu X, Henry L, et al. Trends in anemia care in non-dialysis-dependent chronic kidney disease (CKD) patients in the United States (2006–2015). *BMC Nephrol.* 2018;19:318.
  25. Fuller DS, Bieber BA, Pisoni RL, et al. International comparisons to assess effects of payment and regulatory changes in the United States on anemia practice in patients on hemodialysis: The Dialysis Outcomes and Practice Patterns Study. *J Am Soc Nephrol.* 2016;27:2205–2215.
  26. Thamer M, Zhang Y, Kaufman J, et al. Major declines in epoetin dosing after prospective payment system based on dialysis facility organizational status. *Am J Nephrol.* 2014;40:554–560.
  27. Wang CY, Babitt JL. Liver iron sensing and body iron homeostasis. *Blood.* 2019;133:18–29.
  28. Arezes J, Foy N, McHugh K, et al. Erythroferrone inhibits the induction of hepcidin by BMP6. *Blood.* 2018;132:1473–1477.
  29. Wrighting DM, Andrews NC. Interleukin-6 induces hepcidin expression through STAT3. *Blood.* 2006;108:3204–3209.
  30. Lee P, Peng H, Gelbart T, et al. Regulation of hepcidin transcription by interleukin-1 and interleukin-6. *Proc Natl Acad Sci U S A.* 2005;102:1906–1910.
  31. Macdougall IC, Bircher AJ, Eckardt KU, et al. Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int.* 2016;89:28–39.
  32. van der Weerd NC, Grooteman MP, Nube MJ, et al. Hepcidin in chronic kidney disease: not an anaemia management tool, but promising as a cardiovascular biomarker. *Neth J Med.* 2015;73:108–118.
  33. Fishbane S, Kowalski EA, Imbriano LJ, et al. The evaluation of iron status in hemodialysis patients. *J Am Soc Nephrol.* 1996;7:2654–2657.
  34. Kalantar-Zadeh K, Hoffken B, Wunsch H, et al. Diagnosis of iron deficiency anemia in renal failure patients during the post-erythropoietin era. *Am J Kidney Dis.* 1995;26:292–299.
  35. Tessitore N, Solero GP, Lippi G, et al. The role of iron status markers in predicting response to intravenous iron in haemodialysis patients on maintenance erythropoietin. *Nephrol Dial Transplant.* 2001;16:1416–1423.
  36. Stancu S, Barsan L, Stanciu A, et al. Can the response to iron therapy be predicted in anemic nondialysis patients with chronic kidney disease? *Clin J Am Soc Nephrol.* 2010;5:409–416.
  37. Batchelor EK, Kapitsinou P, Pergola PE, et al. Iron deficiency in chronic kidney disease: updates on pathophysiology, diagnosis, and treatment. *J Am Soc Nephrol.* 2020;31:456–468.
  38. Besarab A, Druke TB. The problem with transferrin saturation as an indicator of iron 'sufficiency' in chronic kidney disease [e-pub ahead of print]. *Nephrol Dial Transplant.* <https://doi.org/10.1093/ndt/gfaa048>. Accessed April 18, 2021.
  39. Ullrich C, Wu A, Armsby C, et al. Screening healthy infants for iron deficiency using reticulocyte hemoglobin content. *JAMA.* 2005;294:924–930.
  40. Urrechaga E, Hoffmann J. Assessment of iron-restricted erythropoiesis in chronic renal disease: evaluation of Abbott CELL-DYN Sapphire mean reticulocyte hemoglobin content (MCHr). *Scand J Clin Lab Invest.* 2019;79:363–367.
  41. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. *Blood.* 2010;116:4754–4761.
  42. Piva E, Brugnara C, Spolaore F, et al. Clinical utility of reticulocyte parameters. *Clin Lab Med.* 2015;35:133–163.
  43. Fishbane S, Shapiro W, Dutka P, et al. A randomized trial of iron deficiency testing strategies in hemodialysis patients. *Kidney Int.* 2001;60:2406–2411.
  44. Mittman N, Sreedhara R, Mushnick R, et al. Reticulocyte hemoglobin content predicts functional iron deficiency in hemodialysis patients receiving rHuEPO. *Am J Kidney Dis.* 1997;30:912–922.
  45. Brugnara C, Laufer MR, Friedman AJ, et al. Reticulocyte hemoglobin content (CHr): early indicator of iron deficiency and response to therapy. *Blood.* 1994;83:3100–3101.
  46. Brugnara C, Mohandas N. Red cell indices in classification and treatment of anemias: from M.M. Wintrob's original 1934 classification to the third millennium. *Curr Opin Hematol.* 2013;20:222–230.
  47. Minutolo R, Locatelli F, Gallieni M, et al. Anaemia management in non-dialysis chronic kidney disease (CKD) patients: a multicentre prospective study in renal clinics. *Nephrol Dial Transplant.* 2013;28:3035–3045.
  48. 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.
  49. Awan AA, Walthers CP, Richardson PA, et al. Prevalence, correlates and outcomes of absolute and functional iron deficiency anemia in nondialysis-dependent chronic kidney disease. *Nephrol Dial Transplant.* 2019;36:129–136.
  50. Iimori S, Naito S, Noda Y, et al. Anaemia management and mortality risk in newly visiting patients with chronic kidney disease in Japan: The CKD-ROUTE study. *Nephrology.* 2015;20:601–608.

51. Fishbane S, Pollack S, Feldman HI, et al. Iron indices in chronic kidney disease in the National Health and Nutritional Examination Survey 1988-2004. *Clin J Am Soc Nephrol.* 2009;4:57-61.
52. United States Renal Data System. Special analyses, USRDS ESRD Database. Available at: [https://render.usrds.org/2017/view/img\\_v2\\_02.html](https://render.usrds.org/2017/view/img_v2_02.html). Accessed November 2, 2020.
53. United States Renal Data System. Annual Data Report 2018. Available at: <https://www.usrds.org/annual-data-report/previous-adrs/>. Accessed November 2, 2020.
54. 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.* 2015;5:23-32.
55. Perlman RL, Zhao J, Fuller DS, et al. International anemia prevalence and management in peritoneal dialysis patients. *Perit Dial Int.* 2019;39:539-546.
56. Borzych-Duzalka D, Bilginer Y, Ha IS, et al. Management of anemia in children receiving chronic peritoneal dialysis. *J Am Soc Nephrol.* 2013;24:665-676.
57. Lam CSP, Doehner W, Comin-Colet J, et al. Iron deficiency in chronic heart failure: case-based practical guidance. *ESC Heart Fail.* 2018;5:764-771.
58. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis.* 2006;47:511-5145.
59. Cho ME, Hansen JL, Peters CB, et al. An increased mortality risk is associated with abnormal iron status in diabetic and non-diabetic veterans with predialysis chronic kidney disease. *Kidney Int.* 2019;96:750-760.
60. 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.
61. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J.* 2015;36:657-668.
62. Macdougall IC, White C, Anker SD, et al. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med.* 2019;380:447-458.
63. Onken JE, Bregman DB, Harrington RA, et al. Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. *Nephrol Dial Transplant.* 2014;29:833-842.
64. Freburger JK, Ellis AR, Wang L, et al. Comparative effectiveness of iron and erythropoiesis-stimulating agent dosing on health-related quality of life in patients receiving hemodialysis. *Am J Kidney Dis.* 2016;67:271-282.
65. O'Loone 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.
66. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet.* 2020;396:1895-1904.
67. Anker SD, Kirwan BA, van Veldhuisen DJ, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail.* 2018;20:125-133.
68. Houston BL, Hurrie D, Graham J, et al. Efficacy of iron supplementation on fatigue and physical capacity in non-anaemic iron-deficient adults: a systematic review of randomised controlled trials. *BMJ Open.* 2018;8:e019240.
69. Avni T, Reich S, Lev N, et al. Iron supplementation for restless legs syndrome—a systematic review and meta-analysis. *Eur J Intern Med.* 2019;63:34-41.
70. Stefanova D, Raychev A, Arezes J, et al. Endogenous hepcidin and its agonist mediate resistance to selected infections by clearing non-transferrin-bound iron. *Blood.* 2017;130:245-257.
71. Stefanova D, Raychev A, Deville J, et al. Heparin protects against lethal *Escherichia coli* sepsis in mice inoculated with isolates from septic patients. *Infect Immun.* 2018;86:e00253.
72. Sazawal S, Black RE, Ramsan M, et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet.* 2006;367:133-143.
73. Winterbourn CC. Toxicity of iron and hydrogen peroxide: the Fenton reaction. *Toxicol Lett.* 1995;82-83:969-974.
74. Bnaya A, Shavit L, Malyszko JS, et al. Labile plasma iron levels in chronic hemodialysis patients treated by intravenous iron supplementation. *Ther Apher Dial.* 2020;24:416-422.
75. Leaf DE, Swinkels DW. Catalytic iron and acute kidney injury. *Am J Physiol Renal Physiol.* 2016;311:F871-F876.
76. de Swart L, Hendriks JC, van der Vorm LN, et al. Second international round robin for the quantification of serum non-transferrin-bound iron and labile plasma iron in patients with iron-overload disorders. *Haematologica.* 2016;101:38-45.
77. Niederau C. Hereditary hemochromatosis. *Med Klin.* 2009;104:931-946.
78. Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. *Kidney Int.* 2015;88:905-914.
79. Roger SD, Gaillard CA, Bock AH, et al. Safety of intravenous ferric carboxymaltose versus oral iron in patients with nondialysis-dependent CKD: an analysis of the 1-year FIND-CKD trial. *Nephrol Dial Transplant.* 2017;32:1530-1539.
80. Hougen I, Collister D, Bourrier M, et al. Safety of intravenous iron in dialysis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol.* 2018;13:457-467.
81. Macdougall IC, Bhandari S, White C, et al. Intravenous iron dosing and infection risk in patients on hemodialysis: a prespecified secondary analysis of the PIVOTAL trial. *J Am Soc Nephrol.* 2020;31:1118-1127.
82. Fishbane S, Block GA, Loram L, et al. Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. *J Am Soc Nephrol.* 2017;28:1851-1858.
83. Kunutsor SK, Apekey TA, Walley J, et al. Ferritin levels and risk of type 2 diabetes mellitus: an updated systematic review and meta-analysis of prospective evidence. *Diabetes Metab Res Rev.* 2013;29:308-318.
84. Wang C, Graham DJ, Kane RC, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. *JAMA.* 2015;314:2062-2068.
85. Li X, Kshirsagar AV. Rest easy with intravenous iron for dialysis patients? High dose IV iron safety. *Clin J Am Soc Nephrol.* 2018;13:363-365.
86. Li X, Cole SR, Kshirsagar AV, et al. Safety of dynamic intravenous iron administration strategies in hemodialysis patients. *Clin J Am Soc Nephrol.* 2019;14:728-737.
87. Brookhart MA, Freburger JK, Ellis AR, et al. Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. *J Am Soc Nephrol.* 2013;24:1151-1158.
88. Edmonston D, Wolf M. FGF23 at the crossroads of phosphate, iron economy and erythropoiesis. *Nat Rev Nephrol.* 2020;16:7-19.
89. Zoller H, Schaefer B, Glodny B. Iron-induced hypophosphatemia: an emerging complication. *Curr Opin Nephrol Hypertens.* 2017;26:266-275.
90. Wolf M, Chertow GM, Macdougall IC, et al. Randomized trial of intravenous iron-induced hypophosphatemia. *JCI Insight.* 2018;3:e124486.
91. Wolf M, Rubin J, Achebe M, et al. Effects of iron isomaltoside vs ferric carboxymaltose on hypophosphatemia in iron-deficiency anemia: two randomized clinical trials. *JAMA.* 2020;323:432-443.
92. Shimizu Y, Tada Y, Yamauchi M, et al. Hypophosphatemia induced by intravenous administration of saccharated ferric oxide: another form of FGF23-related hypophosphatemia. *Bone.* 2009;45:814-816.
93. Schouten BJ, Doogue MP, Soule SG, et al. Iron polymaltose-induced FGF23 elevation complicated by hypophosphatemic osteomalacia. *Ann Clin Biochem.* 2009;46:167-169.
94. Hanudel MR, Eisenga MF, Rappaport M, et al. Effects of erythropoietin on fibroblast growth factor 23 in mice and humans. *Nephrol Dial Transplant.* 2019;34:2057-2065.
95. Eisenga MF, Emans ME, van der Putten K, et al. Epoetin beta and C-terminal fibroblast growth factor 23 in patients with chronic heart failure and chronic kidney disease. *J Am Heart Assoc.* 2019;8:e011130.
96. Rabadí S, Udo I, Leaf DE, et al. Acute blood loss stimulates fibroblast growth factor 23 production. *Am J Physiol Renal Physiol.* 2018;314:F132-F139.
97. Clinkenbeard EL, Hanudel MR, Stayrook KR, et al. Erythropoietin stimulates murine and human fibroblast growth factor-23, revealing novel roles for bone and bone marrow. *Haematologica.* 2017;102:e427-e430.
98. Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Miner Res.* 2013;28:1793-1803.
99. Francis C, Courbon G, Gerber C, et al. Ferric citrate reduces fibroblast growth factor 23 levels and improves renal and cardiac function in a

- mouse model of chronic kidney disease. *Kidney Int.* 2019;96:1346–1358.
100. Block GA, Block MS, Smits G, et al. A pilot randomized trial of ferric citrate coordination complex for the treatment of advanced CKD. *J Am Soc Nephrol.* 2019;30:1495–1504.
  101. Gutierrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med.* 2008;359:584–592.
  102. Isakova T, Xie H, Yang W, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA.* 2011;305:2432–2439.
  103. Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest.* 2011;121:4393–4408.
  104. Pastor-Arroyo EM, Gehring N, Krudewig C, et al. The elevation of circulating fibroblast growth factor 23 without kidney disease does not increase cardiovascular disease risk. *Kidney Int.* 2018;94:49–59.
  105. van Vuren AJ, Gaillard C, Eisenga MF, et al. The EPO-FGF23 signaling pathway in erythroid progenitor cells: opening a new area of research. *Front Physiol.* 2019;10:304.
  106. Agoro R, Montagna A, Goetz R, et al. Inhibition of fibroblast growth factor 23 (FGF23) signaling rescues renal anemia. *FASEB J.* 2018;32:3752–3764.
  107. Hanudel MR, Laster M, Salusky IB. Non-renal-related mechanisms of FGF23 pathophysiology. *Curr Osteoporos Rep.* 2018;16:724–729.
  108. Czaya B, Faul C. The role of fibroblast growth factor 23 in inflammation and anemia. *Int J Mol Sci.* 2019;20:4195.
  109. Kortman GAM, Reijnders D, Swinkels DW. Oral iron supplementation: potential implications for the gut microbiome and metabolome in patients with CKD. *Hemodial Int.* 2017;21(Suppl 1):S28–S36.
  110. Savy M, Edmond K, Fine PE, et al. Landscape analysis of interactions between nutrition and vaccine responses in children. *J Nutr.* 2009;139:2154S–2218S.
  111. Stoffel NU, Uyoga MA, Mutuku FM, et al. Iron deficiency anemia at time of vaccination predicts decreased vaccine response and iron supplementation at time of vaccination increases humoral vaccine response: a birth cohort study and a randomized trial follow-up study in Kenyan infants. *Front Immunol.* 2020;11:1313.
  112. Jiang Y, Li C, Wu Q, et al. Iron-dependent histone 3 lysine 9 demethylation controls B cell proliferation and humoral immune responses. *Nat Commun.* 2019;10:2935.
  113. Pergola PE, Fishbane S, Ganz T. Novel oral iron therapies for iron deficiency anemia in chronic kidney disease. *Adv Chronic Kidney Dis.* 2019;26:272–291.
  114. Locatelli F, Mazzaferro S, Yee J. Iron therapy challenges for the treatment of nondialysis CKD patients. *Clin J Am Soc Nephrol.* 2016;11:1269–1280.
  115. Shepshelovich D, Rozen-Zvi B, Avni T, et al. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. *Am J Kidney Dis.* 2016;68:677–690.
  116. Pisani A, Riccio E, Sabbatini M, et al. Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: a randomized trial. *Nephrol Dial Transplant.* 2015;30:645–652.
  117. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. *Lancet Haematol.* 2017;4:e524–e533.
  118. Schaefer B, Meindl E, Wagner S, et al. Intravenous iron supplementation therapy. *Mol Aspects Med.* 2020;75:100862.
  119. Girelli D, Ugolini S, Busti F, et al. Modern iron replacement therapy: clinical and pathophysiological insights. *Int J Hematol.* 2018;107:16–30.
  120. Adkinson NF, Strauss WE, Macdougall IC, et al. Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: a randomized trial. *Am J Hematol.* 2018;93:683–690.
  121. Macdougall IC, Strauss WE, McLaughlin J, et al. A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. *Clin J Am Soc Nephrol.* 2014;9:705–712.
  122. Bhandari S, Kalra PA, Berkowitz M, et al. Safety and efficacy of iron isomaltoiside 1000/ferric derisomaltose versus iron sucrose in patients with chronic kidney disease: the FERWON-NEPHRO randomized, open-label, comparative trial. *Nephrol Dial Transplant.* 2021;36:111–120.
  123. Lee ES, Park BR, Kim JS, et al. Comparison of adverse event profile of intravenous iron sucrose and iron sucrose similar in postpartum and gynecologic operative patients. *Curr Med Res Opin.* 2013;29:141–147.
  124. Rottembourg J, Kadri A, Leonard E, et al. Do two intravenous iron sucrose preparations have the same efficacy? *Nephrol Dial Transplant.* 2011;26:3262–3267.
  125. Aguera ML, Martin-Malo A, Alvarez-Lara MA, et al. Efficiency of original versus generic intravenous iron formulations in patients on haemodialysis. *PLoS One.* 2015;10:e0135967.
  126. Prats M, Font R, Garcia C, et al. Effect of ferric carboxymaltose on serum phosphate and C-terminal FGF23 levels in non-dialysis chronic kidney disease patients: post-hoc analysis of a prospective study. *BMC Nephrol.* 2013;14:167.
  127. Bager P, Hvas CL, Dahlerup JF. Drug-specific hypophosphatemia and hypersensitivity reactions following different intravenous iron infusions. *Br J Clin Pharmacol.* 2017;83:1118–1125.
  128. Huang LL, Lee D, Troster SM, et al. A controlled study of the effects of ferric carboxymaltose on bone and haematinic biomarkers in chronic kidney disease and pregnancy. *Nephrol Dial Transplant.* 2018;33:1628–1635.
  129. Agarwal R, Leehey DJ, Olsen SM, et al. Proteinuria induced by parenteral iron in chronic kidney disease—a comparative randomized controlled trial. *Clin J Am Soc Nephrol.* 2011;6:114–121.
  130. Macdougall IC, Bock AH, Carrera F, et al. Renal function in patients with non-dialysis chronic kidney disease receiving intravenous ferric carboxymaltose: an analysis of the randomized FIND-CKD trial. *BMC Nephrol.* 2017;18:24.
  131. Pratt RD, Grimberg S, Zaritsky JJ, et al. Pharmacokinetics of ferric pyrophosphate citrate administered via dialysate and intravenously to pediatric patients on chronic hemodialysis. *Pediatr Nephrol.* 2018;33:2151–2159.
  132. Pratt RD, Swinkels DW, Ikizler TA, et al. Pharmacokinetics of ferric pyrophosphate citrate, a novel iron salt, administered intravenously to healthy volunteers. *J Clin Pharmacol.* 2017;57:312–320.
  133. Pratt R, Handelman GJ, Edwards TE, et al. Ferric pyrophosphate citrate: interactions with transferrin. *Biometals.* 2018;31:1081–1089.
  134. Fishbane SN, Singh AK, Cournoyer SH, et al. Ferric pyrophosphate citrate (Triferic) administration via the dialysate maintains hemoglobin and iron balance in chronic hemodialysis patients. *Nephrol Dial Transplant.* 2015;30:2019–2026.
  135. Gupta A, Lin V, Guss C, et al. Ferric pyrophosphate citrate administered via dialysate reduces erythropoiesis-stimulating agent use and maintains hemoglobin in hemodialysis patients. *Kidney Int.* 2015;88:1187–1194.
  136. Macdougall IC, Bock AH, Carrera F, et al. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. *Nephrol Dial Transplant.* 2014;29:2075–2084.
  137. Drozd M, Weigert A, Silva F, et al. Achievement of renal anemia KDIGO targets by two different clinical strategies—a European hemodialysis multicenter analysis. *BMC Nephrol.* 2019;20:5.
  138. Karaboyas A, Morgenstern H, Pisoni RL, et al. Association between serum ferritin and mortality: findings from the USA, Japan and European Dialysis Outcomes and Practice Patterns Study. *Nephrol Dial Transplant.* 2018;33:2234–2244.
  139. Bazeley J, Bieber B, Li Y, et al. C-reactive protein and prediction of 1-year mortality in prevalent hemodialysis patients. *Clin J Am Soc Nephrol.* 2011;6:2452–2461.
  140. Petzer V, Tymoszuk P, Asshoff M, et al. A fully human anti-BMP6 antibody reduces the need for erythropoietin in rodent models of the anemia of chronic disease. *Blood.* 2020;136:1080–1090.
  141. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood.* 2014;123:615–624.
  142. Begum S, Latunde-Dada GO. Anemia of inflammation with an emphasis on chronic kidney disease. *Nutrients.* 2019;11:2424.
  143. Kaelin WG Jr, Ratcliffe PJ. Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. *Mol Cell.* 2008;30:393–402.
  144. Semenza GL. Oxygen sensing, homeostasis, and disease. *N Engl J Med.* 2011;365:537–547.
  145. Sanghani NS, Haase VH. Hypoxia-inducible factor activators in renal anemia: current clinical experience. *Adv Chronic Kidney Dis.* 2019;26:253–266.
  146. Sugahara M, Tanaka T, Nangaku M. Prolyl hydroxylase domain inhibitors as a novel therapeutic approach against anemia in chronic kidney disease. *Kidney Int.* 2017;92:306–312.

147. Koury MJ, Haase VH. Anaemia in kidney disease: harnessing hypoxia responses for therapy. *Nat Rev Nephrol.* 2015;11:394–410.
148. 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.
149. Cizman B, Sykes AP, Paul G, et al. An exploratory study of daprodustat in erythropoietin-hyporesponsive subjects. *Kidney Int Rep.* 2018;3:841–850.
150. Chen N, Hao C, Liu BC, et al. Roxadustat treatment for anemia in patients undergoing long-term dialysis. *N Engl J Med.* 2019;381:1011–1022.
151. 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.
152. 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.
153. 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.
154. Macdougall IC, Akizawa T, Berns JS, et al. Effects of molidustat in the treatment of anemia in CKD. *Clin J Am Soc Nephrol.* 2019;14:28–39.
155. 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.
156. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6:e1000100.
157. 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.
158. McCullough PA, Barnhart HX, Inrig JK, et al. Cardiovascular toxicity of epoetin-alfa in patients with chronic kidney disease. *Am J Nephrol.* 2013;37:549–558.
159. Vaziri ND, Zhou XJ. Potential mechanisms of adverse outcomes in trials of anemia correction with erythropoietin in chronic kidney disease. *Nephrol Dial Transplant.* 2009;24:1082–1088.
160. Akizawa T, Nangaku M, Yonekawa T, et al. Efficacy and safety of daprodustat compared with darbepoetin alfa in Japanese hemodialysis patients with anemia: a randomized, double-blind, Phase 3 trial. *Clin J Am Soc Nephrol.* 2020;15:1155–1165.
161. Akizawa T, Iwasaki M, Yamaguchi Y, et al. Phase 3, randomized, double-blind, active-comparator (darbepoetin alfa) study of oral roxadustat in CKD patients with anemia on hemodialysis in Japan. *J Am Soc Nephrol.* 2020;31:1628–1639.
162. Tsubakihara Y, Akizawa T, Nangaku M, et al. A 24-week anemia correction study of daprodustat in Japanese dialysis patients. *Ther Apher Dial.* 2020;24:108–114.
163. Akizawa T, Otsuka T, Reusch M, et al. Intermittent oral dosing of roxadustat in peritoneal dialysis chronic kidney disease patients with anemia: a randomized, Phase 3, multicenter, open-label study. *Ther Apher Dial.* 2020;24:115–125.
164. Akizawa T, Ueno M, Shiga T, et al. Oral roxadustat three times weekly in ESA-naive and ESA-converted patients with anemia of chronic kidney disease on hemodialysis: results from two phase 3 studies. *Ther Apher Dial.* 2020;24:628–641.
165. Provenzano R, Shutov E, Ereemeeva L, et al. Roxadustat for anemia in patients with end-stage renal disease incident to dialysis [e-pub ahead of print]. *Nephrol Dial Transplant.* <https://doi.org/10.1093/ndt/gfab051>. Accessed April 18, 2021.
166. Nangaku M, Kondo K, Takabe S, et al. Vadadustat for anemia in chronic kidney disease on peritoneal dialysis: a Phase 3 open-label study in Japan [e-pub ahead of print]. *Ther Apher Dial.* <https://doi.org/10.1111/1744-9987.13611>. Accessed April 18, 2021.
167. Nangaku M, Kondo K, Ueta K, et al. Efficacy and safety of vadadustat compared with darbepoetin alfa in Japanese anemic patients on hemodialysis: a phase 3, multicenter, randomized, double-blind study [e-pub ahead of print]. *Nephrol Dial Transplant.* <https://doi.org/10.1093/ndt/gfab055>. Accessed April 18, 2021.
168. Nangaku M, Hamano T, Akizawa T, et al. Daprodustat compared with epoetin beta pegol for anemia in Japanese patients not on dialysis: a 52week randomized open-label Phase 3 trial. *Am J Nephrol.* 2021;52:26–35.
169. 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.
170. Akizawa T, Yamaguchi Y, Otsuka T, et al. A phase 3, multicenter, randomized, two-arm, open-label study of intermittent oral dosing of roxadustat for the treatment of anemia in Japanese erythropoiesis-stimulating agent-naive chronic kidney disease patients not on dialysis. *Nephron.* 2020;144:372–382.
171. Coyne DW, Roger SD, Shin SK, et al. Roxadustat for CKD-related anemia in non-dialysis patients. *Kidney Int Rep.* 2020;6:624–635.
172. 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.
173. Shutov E, Sulowicz W, Esposito C. Roxadustat for the treatment of anemia in chronic kidney disease (CKD) patients not on dialysis: a phase 3, randomized, double-blind, placebo-controlled study (ALPS) [e-pub ahead of print]. *Nephrol Dial Transplant.* <https://doi.org/10.1093/ndt/gfab057>. Accessed April 18, 2021.
174. Volke M, Gale DP, Maegdefrau U, et al. Evidence for a lack of a direct transcriptional suppression of the iron regulatory peptide hepcidin by hypoxia-inducible factors. *PLoS One.* 2009;4:e7875.
175. Liu Q, Davidoff O, Niss K, et al. Hypoxia-inducible factor regulates hepcidin via erythropoietin-induced erythropoiesis. *J Clin Invest.* 2012;122:4635–4644.
176. Mastroianni M, Matak P, Mathieu JR, et al. Hepatic hypoxia-inducible factor-2 down-regulates hepcidin expression in mice through an erythropoietin-mediated increase in erythropoiesis. *Haematologica.* 2012;97:827–834.
177. Besarab A, Chernyavskaya E, Motylev I, et al. Roxadustat (FG-4592): correction of anemia in incident dialysis patients. *J Am Soc Nephrol.* 2016;27:1225–1233.
178. Provenzano R, Besarab A, Sun CH, et al. Oral hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) for the treatment of anemia in patients with CKD. *Clin J Am Soc Nephrol.* 2016;11:982–991.
179. Akizawa T, Macdougall IC, Berns JS, et al. Iron regulation by molidustat, a daily oral hypoxia-inducible factor prolyl hydroxylase inhibitor, in patients with chronic kidney disease. *Nephron.* 2019;143:243–254.
180. Meadowcroft AM, Cizman B, Holdstock L, et al. Daprodustat for anemia: a 24-week, open-label, randomized controlled trial in participants on hemodialysis. *Clin Kidney J.* 2019;12:139–148.
181. Yap DYH, McMahon LP, Hao CM, et al. Recommendations by the Asian Pacific Society of Nephrology (APSN) on the appropriate use of HIF-PH inhibitors. *Nephrology (Carlton).* 2021;26:105–118.
182. Semenza GL. Hypoxia-inducible factor 1: oxygen homeostasis and disease pathophysiology. *Trends Mol Med.* 2001;7:345–350.
183. Shen GM, Zhao YZ, Chen MT, et al. Hypoxia-inducible factor-1 (HIF-1) promotes LDL and VLDL uptake through inducing VLDLR under hypoxia. *Biochem J.* 2012;441:675–683.
184. Hwang S, Nguyen AD, Jo Y, et al. Hypoxia-inducible factor 1 $\alpha$  activates insulin-induced gene 2 (Insig-2) transcription for degradation of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase in the liver. *J Biol Chem.* 2017;292:9382–9393.
185. Flamme I, Oehme F, Ellinghaus P, et al. Mimicking hypoxia to treat anemia: HIF-stabilizer BAY 85-3934 (Molidustat) stimulates erythropoietin production without hypertensive effects. *PLoS One.* 2014;9:e111838.
186. Eltzschig HK, Bratton DL, Colgan SP. Targeting hypoxia signalling for the treatment of ischaemic and inflammatory diseases. *Nat Rev Drug Discov.* 2014;13:852–869.
187. Taylor CT, Doherty G, Fallon PG, et al. Hypoxia-dependent regulation of inflammatory pathways in immune cells. *J Clin Invest.* 2016;126:3716–3724.
188. Schodel J, Ratcliffe PJ. Mechanisms of hypoxia signalling: new implications for nephrology. *Nat Rev Nephrol.* 2019;15:641–659.
189. 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.
190. Simonson TS, McClain DA, Jorde LB, et al. Genetic determinants of Tibetan high-altitude adaptation. *Hum Genet.* 2012;131:527–533.
191. Newman JH, Holt TN, Cogan JD, et al. Increased prevalence of EPAS1 variant in cattle with high-altitude pulmonary hypertension. *Nat Commun.* 2015;6:6863.
192. 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.



193. Cowburn AS, Crosby A, Macias D, et al. HIF2alpha-arginase axis is essential for the development of pulmonary hypertension. *Proc Natl Acad Sci U S A*. 2016;113:8801–8806.
194. Shimoda LA, Yun X, Sikka G. Revisiting the role of hypoxia-inducible factors in pulmonary hypertension. *Curr Opin Physiol*. 2019;7:33–40.
195. Kraus A, Peters DJM, Klanke B, et al. HIF-1alpha promotes cyst progression in a mouse model of autosomal dominant polycystic kidney disease. *Kidney Int*. 2018;94:887–899.
196. Zhang D, Lv FL, Wang GH. Effects of HIF-1alpha on diabetic retinopathy angiogenesis and VEGF expression. *Eur Rev Med Pharmacol Sci*. 2018;22:5071–5076.
197. Mokas S, Lariviere R, Lamalice L, et al. Hypoxia-inducible factor-1 plays a role in phosphate-induced vascular smooth muscle cell calcification. *Kidney Int*. 2016;90:598–609.
198. Yeh TL, Leissing TM, Abboud MI, et al. Molecular and cellular mechanisms of HIF prolyl hydroxylase inhibitors in clinical trials. *Chem Sci*. 2017;8:7651–7668.
199. Casper C, Chaturvedi S, Munshi N, et al. Analysis of inflammatory and anemia-related biomarkers in a randomized, double-blind, placebo-controlled study of siltuximab (anti-IL6 monoclonal antibody) in patients with multicentric Castleman Disease. *Clin Cancer Res*. 2015;21:4294–4304.
200. Massy ZA, Drueke TB. Activin receptor IIA ligand trap in chronic kidney disease: 1 drug to prevent 2 complications—or even more? *Kidney Int*. 2016;89:1180–1182.
201. Crielard BJ, Lammers T, Rivella S. Targeting iron metabolism in drug discovery and delivery. *Nat Rev Drug Discov*. 2017;16:400–423.
202. Jelkmann W. Activin receptor ligand traps in chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2018;27:351–357.
203. Hanudel MR, Laster M, Ramos G, et al. Clinical experience with the use of ferric citrate as a phosphate binder in pediatric dialysis patients. *Pediatr Nephrol*. 2018;33:2137–2142.
204. Kular D, Macdougall IC. HIF stabilizers in the management of renal anemia: from bench to bedside to pediatrics. *Pediatr Nephrol*. 2019;34:365–378.
205. Maes C, Carmeliet G, Schipani E. Hypoxia-driven pathways in bone development, regeneration and disease. *Nat Rev Rheumatol*. 2012;8:358–366.
206. Stegen S, Laperre K, Eelen G, et al. HIF-1alpha metabolically controls collagen synthesis and modification in chondrocytes. *Nature*. 2019;565:511–515.