ABSTRACT

Anemia is a frequent comorbidity of chronic kidney disease (CKD) and is associated with a considerable burden because of decreased patient health-related quality of life and increased healthcare resource utilization. Based on observational data, anemia is associated with an increased risk of CKD progression, cardiovascular events, and all-cause mortality. The current standard of care includes oral or intravenous iron supplementation, erythropoiesis-stimulating agents, and red blood cell transfusion. However, each of these therapies has its own set of population-specific patient concerns, including increased risk of cardiovascular disease, thrombosis, and mortality. Patients receiving dialysis or those who have concurrent diabetes or high blood pressure may be at greater risk of developing these complications. In particular, treatment with high doses of erythropoiesis-stimulating agents has been associated with increased rates of hospitalization, cardiovascular events, and mortality. Resistance to erythropoiesis-stimulating agents remains a therapeutic challenge in a subset of patients. Hypoxia-inducible factor transcription factors, which regulate several genes involved in erythropoiesis and iron metabolism, can be stabilized by a new class of drugs that act as inhibitors of hypoxia-inducible factor prolyl-hydroxylase enzymes to promote erythropoiesis and elevate hemoglobin levels. Here, we review the burden of anemia of chronic kidney disease, the shortcomings of current standard of care, and the potential practical advantages of hypoxia-inducible factor prolyl-hydroxylase inhibitors in the treatment of patients with anemia of CKD.

Keywords: Anemia; Burden; Chronic kidney disease; Erythropoietin; Hypoxia-inducible factor; Iron; Nephrology
Anemia is common in patients with chronic kidney disease and has been associated with increased risk of cardiovascular morbidity and mortality in observational studies as well as decreased patient quality of life and increased healthcare utilization.

The current standard of care includes supplemental iron, erythropoiesis-stimulating agents, and red blood cell transfusions, although each has drawbacks.

High doses of erythropoiesis-stimulating agents have been associated with increased cardiovascular complications and mortality.

Hypoxia-inducible factor-prolyl hydroxylase inhibitors are novel treatments for anemia of chronic kidney disease that prevent degradation of the transcription factor hypoxia-inducible factor, which stimulates erythropoiesis to physiologic levels.

DISEASE BURDEN

Prevalence

The estimated global prevalence of CKD is 11% for patients with CKD stage 3 [estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m²] to stage 5 (eGFR < 15 ml/min/1.73 m²) and 13% for patients with CKD stage 1 (albumin-to-creatine ratio > 30 plus eGFR > 90 ml/min/1.73 m²) to stage 5 [6]. In the US, the prevalence of stage 1–5 CKD was 14.0% (representing ~31.4 million people) according to the 2007–2010 data from the National Health and Nutrition Examination Survey (NHANES) [7]. Similarly, the US Centers for Disease Control and Prevention estimated that the prevalence of
CKD stage 1 to stage 4 (eGFR 15–29 ml/min/1.73 m²) was 15% (~37 million people) in 2013–2016 [8].

Anemia prevalence increases with CKD stage. In the NHANES analysis, 15.4% (~4.8 million people) had anemia of CKD, and anemia prevalence was 17.4%, 50.3%, and 53.4% in stages 3, 4, and 5 CKD, respectively [7]. Anemia of CKD prevalence also increases in patients with comorbidities and with age, from 28.0% in those aged 18–63 years to 50.1% in those aged ≥ 66 years among US patients with non-dialysis-dependent (NDD) CKD [1].

**Cardiovascular Risk and Mortality**

Anemia, fluid overload, and arteriovenous fistulas can lead to volume overload that ultimately results in cardiomyopathy, including increased left ventricular hypertrophy (LVH), and systolic and diastolic dysfunction [9, 10]. This cardiomyopathy may present as ischemic heart disease or heart failure, even when arterial vascular disease is absent [10]. Anemia has been associated with an increased risk of cardiovascular events and all-cause mortality in a number of observational studies [11–18], and the American Heart Association considers anemia to be a nontraditional (non-Framingham) cardiovascular risk factor in patients with CKD [10]. In a US study of > 900,000 patients with NDD-CKD, functional iron deficiency anemia was associated with an increased risk of mortality [hazard ratio (HR) 1.11, 95% CI 1.07–1.14] and an increased relative risk (RR) of cardiovascular hospitalization after 1 year (RR 1.21, 95% CI 1.12–1.30) and 2 years (RR 1.13, 95% CI 1.07–1.21) [11]. Similarly, a Danish study of patients with dialysis-dependent-CKD (DD-CKD) and NDD-CKD found that anemia was associated with increased risks of major adverse cardiovascular events (MACE), acute hospitalization, and all-cause death [12], and a Japanese study of NDD-CKD patients reported that isolated anemia and iron deficiency anemia were associated with increased risks of cardiovascular-related and all-cause mortality [13]. After adjusting for other cardiovascular risk factors (including age, diabetes, hypertension, and dyslipidemia), patients with anemia in the US Atherosclerosis Risk in Communities (ARIC) study had a significantly increased risk of stroke with comorbid CKD versus no CKD (HR 5.43, 95% CI 2.04–14.41), whereas in patients without anemia, the risk of stroke with CKD was not significantly increased (HR 1.41, 95% CI 0.93–2.14) [14]. In patients with diabetes, a pooled analysis of data from the ARIC, Cardiovascular Health, Framingham Heart, and Framingham Offspring studies found an association between anemia and increased risks of the individual and composite outcomes of myocardial infarction (MI), fatal coronary heart disease, stroke, or death, and all-cause mortality among patients with comorbid CKD, but not in those without CKD [15]. An association between low Hb levels and increased risks of cardiovascular and all-cause mortality was also observed in a Korean study of ~300,000 patients without cardiovascular disease [16]. Furthermore, anemia was associated with increased cardiovascular risk among Japanese patients undergoing treatment for hypertension [17] and in an Italian study of patients with diabetes [18].

However, the association between anemia and cardiovascular morbidity and mortality in patients with CKD is primarily based on observational studies, and randomized interventional trials have yet to demonstrate a reduction in mortality risk with correction of anemia [19]. Notably, clinical trials that attempted to raise Hb to high levels (13–13.5 g/dl) with darbepoetin alfa therapy found an increased risk of mortality or cardiovascular- or renal-related complications compared with a near-normal or low Hb target (11.3 g/dl; HR 1.34, 95% CI 1.03–1.74, \( P = 0.03 \)) [20] and also an increased risk of fatal or non-fatal stroke compared with placebo (HR 1.92, 95% CI 1.38–2.68, \( P < 0.001 \)) [21].

**Health-Related Quality of Life**

Anemia of CKD represents an independent risk factor for poor HR-QOL [22]. In patients with CKD anemia, cardiovascular complications are associated with significantly impaired HR-QOL (EQ-5D visual analog scale coefficient −5.68, \( P = 0.028 \)) and work productivity (Work
Productivity and Activity Impairment questionnaire: activity impairment coefficient 8.04, $P = 0.032$) compared with non-anemic CKD patients [23]. The Centers for Medicare and Medicaid Services states that all dialysis units should actively monitor patient HR-QOL, underscoring the need to understand long-term HR-QOL implications when treating anemia and other comorbidities in patients with CKD [24].

**Healthcare Resource Use**

The high prevalence of anemia of CKD represents an important clinical and economic healthcare burden [25]. Patients with moderate CKD and severe anemia (Hb $\leq 9 \text{ g/dl}$) generally require increased hospitalization compared with those without severe anemia [26]. Because patients with CKD and anemia use more overall healthcare resources, their care incurs more costs than those without anemia [1]. In the US, patients with anemia of CKD have estimated total healthcare costs of US$3800–US$4800/patient-month [27]; yearly treatment costs among US patients with CKD are estimated to be more than three-fold higher in patients with anemia than in those without anemia [28].

**CURRENT STANDARD OF CARE**

Current treatment options for anemia include oral or IV iron, ESAs, and RBC transfusion (Table 1). Although raising Hb levels can lead to improved HR-QOL, morbidity, mortality, and reduced hospitalization [29, 30], increasing Hb to “normal” levels has led to adverse outcomes highlighting the issues associated with the current standard of care for anemia of CKD.

**Iron**

Iron deficiency frequently presents in patients with CKD and is mediated by hepcidin, a hepatic peptide that inhibits iron absorption and release from iron stores and macrophages [5]. Iron deficiency is compounded by increased iron demands with ESAs, which can limit their effectiveness [39]. Supplementary iron can improve physical, cognitive, and immune function [40]. Although less expensive and safer than IV iron, oral iron is poorly absorbed and associated with gastrointestinal adverse reactions [3]. IV iron allows for administration of larger doses with better tolerability and is considered to be superior to oral iron in patients with CKD [41].

Although rare, IV iron administration may be associated with an increased risk of iron overload, which could potentially lead to organ dysfunction in patients with or without ESRD, although end-organ damage due to IV iron has not been demonstrated in clinical studies [42]. Iron overload can also increase infection risk and worsen CKD-associated inflammation, while inflammation can exacerbate oxidative stress caused by IV iron [42, 43]. Previous reports of hypersensitivity with IV iron were largely during the use of high-molecular-weight iron dextrans that are no longer commercially available [44, 45]. IV iron is burdensome in patients with NDD-CKD because of the need for IV access and a transfusion clinic [46].

**Erythropoiesis-Stimulating Agents**

ESAs trigger EPO production to increase Hb and improve anemia [3]. Although ESAs reduce the adverse impact of anemia on morbidity and HR-QOL [47], safety concerns regarding the potential increased risk of cardiovascular events with increased ESA doses (due to poor response or a higher Hb target) have led to reductions in the prescribed ESA dose, increased use of RBC transfusion/IV iron, and uncertainty regarding optimal target Hb [4]. Consequently, regulatory authorities increasingly require detailed safety data for ESAs. Other considerations for ESA use include parenteral administration, cold storage, expense, and the generation of neutralizing anti-EPO antibodies, which may cause pure red cell aplasia [4].
Impact of ESA-Mediated Anemia Correction

Hemoglobin normalization in patients with CKD is currently not recommended because of safety concerns related to ESA dosage [48]. Some studies show cardiovascular benefits in treating to a lower Hb target while others describe poor cardiovascular outcomes with a physiologically normal or supraphysiologic Hb target, rendering the optimal target Hb uncertain [3, 4, 30]. Higher ESA dose (rather than higher Hb) may cause adverse effects, as ESRD patients who maintain high Hb (>12 g/dl) without ESA therapy do not show increased mortality compared with other patients on dialysis [49]. Current guidelines recommend a target Hb ≤ 11.5 g/dl [3].

Anemia correction with ESAs may provide improvement in cardiovascular parameters, including ejection fraction, left ventricular (LV) mass index, and LV wall thickness [22, 50]. In patients with NDD-CKD, the risk of renal events (i.e., progression to renal replacement therapy, doubling of serum creatinine, or decline in eGFR to < 6 ml/min/1.73m²) was significantly lower in those with Hb target of ≥ 11 g/dl versus < 11 g/dl [51]. However, the ACORD, CHOIR, and CREATE studies in patients with NDD-CKD showed no advantage with a high (13.0–15.0 g/dl) versus low (10.5–11.5 g/dl) Hb target in the risk for LVH [52] or cardiovascular events (including sudden death, stroke, transient ischemic attack, MI, acute heart failure, hospitalization for angina pectoris, cardiac arrhythmia, or congestive heart failure, or complication of peripheral vascular disease)

### Table 1 Pros and cons of pharmacologic treatment for anemia of chronic kidney disease

| Pros                                      | Long-acting ESAs | HIF-PH inhibitors |
|-------------------------------------------|------------------|-------------------|
| Reduces need for RBC transfusions         | Reduces need for RBC transfusions | Have been shown to be noninferior to ESAs in raising or maintaining Hb [35] |
| May reduce fatigue and improve HR-QOL [29]| May reduce fatigue and improve HR-QOL [29] | Can be administered orally [36] |
| IV administration is preferred in patients on hemodialysis [32] | Can be administered less frequently than short-acting ESAs [33] | May reduce the need for iron supplementation by mobilizing stored iron [37] |
| IV administration is preferred in patients on hemodialysis [32] | | |

| Cons                                      | Long-acting ESAs | HIF-PH inhibitors |
|-------------------------------------------|------------------|-------------------|
| Higher doses required to reach high Hb targets may increase risk of adverse cardiovascular outcomes [20] | Higher doses required to reach high Hb targets may increase risk of adverse cardiovascular outcomes [21] | Additional research needed to evaluate potential effects on tumor growth [36] |
| Often requires supplemental iron administration [3] | Often requires supplemental iron administration [3] | |
| Administered 3 times per week [31]        | May confer increased risk of mortality compared with short-acting ESAs [38] | |

*ESA* erythropoiesis-stimulating agent, *Hb* hemoglobin, *HIF-PH* hypoxia-inducible factor prolyl-hydroxylase, *HR-QOL* health-related quality of life, *IV* intravenous, *RBC* red blood cell
Additionally, in a subanalysis of the TREAT trial, poor initial response to ESA therapy (and consequently higher doses of ESA) in patients with NDD-CKD and type 2 diabetes was associated with increased risks of all-cause death (HR 1.41, 95% CI 1.12–1.78) and adverse cardiovascular events (HR 1.31, 95% CI 1.09–1.59) compared with patients with better response to ESA [54]. Due to greater risks for death, MACE, and stroke with target Hb 13 g/dl [20, 21], the US Food and Drug Administration (FDA) recommends that ESA dosing be individualized to the lowest dose necessary to reduce RBC transfusion requirements rather than to a specific target Hb [48]. Notably, following the FDA communication, there was a 59%–74% decrease in the prescribing of ESAs despite stable anemia prevalence rates [55]. However, there was no corresponding reduction in the rate of mortality or MACE [56].

Impact of ESAs on HR-QOL

Although benefits are reported often, significant improvements in HR-QOL following ESA treatment of anemia in patients with CKD are inconsistent. ESA therapy was associated with significant improvements in fatigue, vitality, mental health/emotional well-being, and overall physical health in patients with NDD-CKD [20]. Correction of anemia to a target Hb of 13–15 g/dl improved HR-QOL in patients with CKD with or without diabetes [52, 53] with improvements in several subscales of the Short Form 36 health survey versus a target Hb of 10.5–11.5 g/dl [53]. In contrast, a meta-analysis showed that ESA therapy to obtain higher Hb targets (10.2–13.6 g/dl) does not improve HR-QOL [57]. In patients with CKD on dialysis, ESA therapy is associated with better overall HR-QOL and lower costs and healthcare resource utilization compared with no ESA therapy, although there appears to be minimal benefit with higher Hb targets [58]. Partial correction of anemia with ESAs in dialysis patients has been shown to reduce fatigue and improve exercise tolerance and general well-being, while high-dose ESA was associated with increased cardiovascular risk that negatively impacted HR-QOL, thereby resulting in only a modest overall improvement [59, 60].

Red Blood Cell Transfusion

Before ESA availability, frequent RBC transfusion was the primary means of correcting CKD anemia [47]. Currently, ~20% of patients with NDD-CKD receive RBC transfusions [61]; however, blood volume overload, hyperkalemia, iron overload, blood-borne infections, fever, or allosensitization may occur [3]. Given the burdens associated with RBC transfusion, clinicians should consider alternative treatments for anemia in CKD [61]. However, RBC transfusion may be the only available option in some patients in whom ESAs are not recommended, for example, cancer patients with non-chemotherapy-associated anemia (except for selected patients with myelodysplastic syndrome) [62].

SPECIAL POPULATIONS

Elderly Patients

The prevalence of cardiovascular conditions increases in elderly patients with anemia of CKD [1]. Indeed, CKD, anemia, and mobility limitation are important prognostic indicators of mortality risk in elderly patients [63]. Older patients with CKD have higher rates of inflammatory conditions, nutritional deficiencies, and cardiovascular comorbidities, as well as increased hepcidin levels [64], potentially complicating iron and/or ESA therapy. In addition, Hb decreases with age because of reduced erythropoiesis, so the optimal target Hb in elderly patients may be lower [64].

Diabetes

Type 2 diabetes frequently contributes to CKD development and may also increase the risk of anemia in CKD [65]. Diabetes is an inflammatory condition exacerbated by hyperglycemia and other inflammatory disorders, including obesity, arterial hypertension, and
dyslipidemia; this increased inflammation is thought to cause EPO deficiency in patients with diabetes [66–68]. Deficiencies in EPO and iron, as well as hyporesponsiveness to EPO, are the main mechanisms for anemia development in patients with diabetic kidney disease [69]. In patients with diabetes, anemia is generally more severe, occurs at an earlier stage of CKD, and is associated with a potentially greater risk of cardiovascular disease [70]. Additionally, diabetic macrovascular complications also contribute to the development of atherosclerosis [71], which can further complicate anemia management. However, despite the increased risk of adverse clinical outcomes in patients with diabetes and anemia, there is often clinical inertia regarding initiating IV iron or ESA therapy in these patients [72]. In patients with comorbid diabetes, treatment with the ESA darbepoetin alfa showed no reduction in the risk of composite outcomes (death or cardiovascular event and death or renal event) and an increased risk of stroke versus placebo [21]. In this study, patients with poor initial response to ESA therapy (who received higher ESA doses to meet Hb targets) had increased risks of all-cause mortality (HR 1.41, 95% CI 1.12–1.78) and cardiovascular events (HR 1.31, 95% CI 1.09–1.59) than those with better initial response [54]. This indicates that some patients with diabetes and anemia may benefit from alternative therapies, eliminating the need for ESA dose escalation in those with poor initial response to ESA therapy.

End-Stage Renal Disease

In patients with stage 3 CKD, those who develop anemia have more rapid progression to stage 4 and 5 CKD [73]. Dialysis plays a key role in ESRD management, but HR-QOL for patients with DD-CKD remains a concern, suggesting the need for a more patient-centric assessment [74]. In addition to blood loss associated with hemodialysis, complications of severe anemia contribute significantly to a decreased HR-QOL and increased dependence on RBC transfusion [75]. Iron overload is another concern and was observed in 84% of patients with DD-CKD treated with ESAs and IV iron [76]. Similar to patients with NDD-CKD, adverse outcomes occur in patients with DD-CKD, with higher mortality rates and no difference in cardiovascular events when epoetin was used to target higher versus lower hematocrit [77]. Notably, attenuation of CKD progression has not been shown with ESA therapy.

Kidney Transplantation

Anemia prevalence decreases following kidney transplant, from 71% pre-transplant to 51% at 6 months and 37% at 2 years post-transplant. However, post-transplant anemia does occur [78]. In kidney transplant recipients, lower Hb is a predictor for a return to dialysis, graft failure, subsequent kidney transplant, reduced LV mass index, or death [78, 79]. ESA use to target high Hb (12.5–13.5 g/dl) appears to attenuate the decline of kidney function compared with low Hb (10.5–11.5 g/dl) after 3 years of follow-up in kidney transplant recipients [80]. Of note, patients with ESA hyporesponsiveness before kidney transplant remained hyporesponsive following transplant [81], indicating a need for new therapies to treat anemia in this subpopulation.

EMERGING ALTERNATIVES

Given the inherent limitations of the current standard of care, new effective and tolerable treatment options for CKD anemia are needed. One particularly promising class of agents in development is hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitors.

HIF-PH Inhibitors

Hypoxia-inducible factor (HIF) regulates gene expression in response to hypoxia, including genes involved in erythropoiesis and iron metabolism, promoting iron absorption, iron transport, and heme synthesis (Fig. 1) [37]. Notably, work on the discovery of HIF and its mechanism of action received the 2019 Nobel Prize in Physiology or Medicine. Under
normoxic conditions, HIF-PH enzymes promote HIF degradation; thus, selective HIF stabilization with HIF-PH inhibitors is an innovative approach for treating anemia of CKD [36, 82]. Several HIF-PH inhibitors are currently under development (Table 2). HIF-PH inhibitors are orally administered, and significantly lower EPO levels are induced compared with the supraphysiologic levels typically attained with ESA therapy (Fig. 2) [82]. Animal studies have shown that HIF-PH inhibitors stimulate EPO expression in the kidneys and liver, increasing Hb levels in models of anemia of CKD, including 5/6th nephrectomized rats [83, 84]. HIF-PH inhibitors have also been shown to decrease hepcidin, which may allow patients to mobilize iron stores and lessen iron supplementation needs. Additionally, HIF stabilization should increase gastrointestinal iron absorption through increased expression of divalent metal transporter-1 and duodenal cytochrome B [85].

**Approved HIF-PH Inhibitors**

Roxadustat (FG-4592) was the first-in-class HIF-PH inhibitor approved in Japan for the treatment of anemia in patients with DD-CKD [121] and in China for patients with DD-CKD or NDD-CKD [122]. Daprodustat (GSK1278863) and vadadustat (AKB-6548) are also now approved in Japan for the treatment of anemia in patients with DD-CKD or NDD-CKD [123, 124]. All three HIF-PH inhibitors effectively stimulate EPO production in patients with anemia of CKD, providing dose-dependent increases in Hb and reductions in hepcidin levels, and thus improving total iron binding capacity (TIBC) [35, 90–93, 96–98, 103, 125–127].

In NDD-CKD patients, roxadustat was associated with superior and/or statistically significant Hb response rates and changes from baseline compared with placebo in a Chinese
Table 2 Phase 2 and 3 clinical trials of hypoxia-inducible factor prolyl-hydroxylase inhibitors

| Trial identifier | Participants                                                                 | N   | Study design       | Comparator      | Location                  | Treatment duration |
|------------------|-------------------------------------------------------------------------------|-----|--------------------|-----------------|----------------------------|--------------------|
| Roxadustat<sup>a</sup> | Patients with DD-CKD                                                          |     |                    |                 |                            |                    |
| NCT01596855      | ESRD, hemodialysis, Hb 9–12 g/dl, stable epoetin 7 weeks                      | 87  | Phase 2 RCT OL     | Epoetin alfa    | China                      | 6 weeks            |
| NCT01147666      | ESRD, maintenance hemodialysis ≥ 4 months, Hb 9.0–13.5 g/dl for 8 weeks, epoetin alfa and intravenous iron 4 weeks | 144 | Phase 2 RCT OL     | Epoetin alfa    | US                         | 6 weeks            |
| NCT01414075      | Incident dialysis (2 weeks–4 months), Hb ≤ 10 g/dl, ferritin 50–300 ng/mL, TSAT 10%–30%, ESA-naive, no intravenous iron ≥ 4 weeks | 60  | Phase 2b RCT OL    | None            | US, Russia, Hong Kong      | 12 weeks           |
| NCT02652806      | ESRD, dialysis ≥ 16 weeks, Hb 9.0–12.0 g/dl, stable epoetin alfa ≥ 6 weeks    | 305 | Phase 3 RCT OL     | Epoetin alfa    | China                      | 26 weeks           |
| NCT02779764      | Hemodialysis 3 times/weeks for ≥ 12 weeks, ESA ≥ 8 weeks, mean of 2 latest Hb levels 10–12 g/dl, TSAT ≥ 20% or ferritin ≥ 100 ng/ml | 164 | Phase 3            | None            | Japan                      | 52 weeks           |
| NCT02780141      | Hemodialysis ≥ 1 time/weeks, ESA-naive, mean of 2 latest Hb levels ≤ 10 g/dl, TSAT ≥ 5% or ferritin ≥ 30 ng/ml | 75  | Phase 3 RCT OL     | None            | Japan                      | 24 weeks           |
| NCT02273726      | ESRD, dialysis ≥ 3 months, Hb 8.5–12.0 g/dl, ferritin ≥ 100 ng/mL, TSAT ≥ 20%, ESA ≥ 4 weeks | 741 | Phase 3 RCT OL     | Epoetin alfa    | US                         | 52 weeks to 3 years|
| NCT02174731      | Hemodialysis or peritoneal dialysis; Hb < 12.0 g/dl in those on ESA, < 10 g/dl in those not on ESA; ferritin ≥ 100 ng/mL TSAT ≥ 20% | 2133| Phase 3 RCT OL     | Epoetin alfa    | North America, Asia, Australia, EU, India, South America | 52 weeks to 4 years|
| Trial identifier   | Participants                                                                 | N   | Study design   | Comparator  | Treatment duration |
|--------------------|------------------------------------------------------------------------------|-----|----------------|-------------|--------------------|
| NCT0278341         | Stable hemodialysis or peritoneal dialysis, Hb 9.5–12 g/dl, epoetin alfa or | 836 | Phase 3 RCT    | ESA (epoetin alfa or darbepoetin alfa) | 8 weeks |
|                    | darbepoetin alfa                                                           |     |                | U.S. Asia, E.U., South America         |        |
| NCT02052310        | ESRD, incident dialysis (2 weeks–4 months)                                  | 1043| Phase 3 RCT    | Epoetin alfa                           | 52 weeks to 3 years |
|                    |                                                                              |     |                | None                                    |        |
| NCT01599507        | Patients with NDD-CKD                                                       | 91  | Phase 2 RCT    | Epoetin alfa                           | 8 weeks |
|                    |                                                                              |     |                | None                                    |        |
| NCT01244763        | NDD-CKD (eGFR < 60 ml/min/1.73 m²), Hb < 10 g/dl                            | 145 | Phase 2 RCT    | Epoetin alfa                           | 16 or 24 weeks |
|                    |                                                                              |     |                | None                                    |        |
| NCT00761657        | NDD-CKD stage 3–5, Hb ≤ 10.5 g/dl, ferritin ≤ 30 ng/ml, TSAT ≤ 5% no ESA    | 117 | Phase 2a RCT   | None                                    | 4 weeks |
|                    |                                                                              |     |                | U.S. Asia, South America                |        |
| NCT02652819        | NDD-CKD stage 3–5, Hb 7–< 10 g/dl, no ESA                                    | 154 | Phase 3 RCT    | DB followed by OL by OL extension      | 8 weeks |
|                    |                                                                              |     |                | U.S. Asia, Australia, South America     |        |
| NCT00761657        | NDD-CKD stage 3–5, Hb ≤ 10.5 g/dl, ferritin ≤ 30 ng/ml, TSAT ≤ 5% no ESA    | 117 | Phase 2a RCT   | None                                    | 4 weeks |
|                    |                                                                              |     |                | U.S. Asia, South America                |        |
| NCT01750190        | NDD-CKD stage 3–5, Hb < 10 g/dl, ferritin ≤ 50 ng/ml, TSAT ≥ 15%, ESA-naive | 922 | Phase 3 RCT    | DB                                      | 2781 weeks |
|                    |                                                                              |     |                | North America, Asia, E.U., India, South America |        |
| NCT01887600        | NDD-CKD stage 3–5, Hb ≤ 10 g/dl, ferritin ≤ 50 ng/ml, TSAT ≥ 15%, ESA-naive | 594 | Phase 3 RCT    | DB                                      | 52 weeks |
|                    |                                                                              |     |                | North America, Asia, E.U., India, South America |        |
| Trial identifier     | Participants                                                                 | N<sup>b</sup> | Study design | Comparator | Location                      | Treatment duration |
|---------------------|------------------------------------------------------------------------------|--------------|--------------|------------|-------------------------------|-------------------|
| **Daprodustat**     |                                                                              |              |              |            |                               |                   |
| **Patients with DD-CKD** |                                                                              |              |              |            |                               |                   |
| NCT02019719 [99]    | Hemodialysis ≥ 8 weeks, Hb 9.5–12.0 g/dl, ferritin ≥ 100 µg/l, TSAT ≥ 20%, stable ESA use ≥ 4 weeks | 97           | Phase 2, RCT | DB         | Japan                         | 4 weeks           |
| NCT01587924 [100]   | Hemodialysis ≥ 8 weeks, Hb 9.5–12.0 g/dl, ferritin ≥ 40 ng/ml, stable ESA use ≥ 4 weeks | 83           | Phase 2a RCT| DB         | US, Canada, EU                | 4 weeks           |
| NCT02075463 [101]   | Stable hemodialysis ≥ 12 weeks, ESA hyporesponsiveness, ferritin ≥ 100 ng/ml, TSAT ≥ 20% | 15           | Phase 2a OL  | None       | US                            | 16 weeks          |
| NCT01977482 [102]   | Adequate hemodialysis, Hb 9–11.5 g/dl, ferritin < 100 ng/ml, TSAT < 12%–20%, stable ESA use ≥ 4 weeks | 177          | Phase 2b RCT| DB         | US, Australia, EU, Canada, Asia| 24 weeks          |
| NCT02829320 [103]   | Hemodialysis (newly initiated < 12 weeks and ESA-naïve) or maintenance ≥ 12 weeks and no ESA use ≥ 8 weeks, Hb ≥ 8–10 g/dl, ferritin ≥ 100 ng/ml | 28           | Phase 3 RCT | OL         | Japan                         | 24 weeks          |
| **Patients with NDD-CKD** |                                                                              |              |              |            |                               |                   |
| NCT01977573 [104]   | NDD-CKD stage 3–5; Hb 8–11 g/dl (ESA-naïve), 9–11.5 g/dl (ESA users); for ESA users, stable ESA use ≥ 4 weeks | 252          | Phase 2 RCT  | ESA        | US, Australia, EU, Canada, Asia| 24 weeks          |
| NCT01587898 [100]   | NDD-CKD stage 3–5, Hb 8.5–11.0 g/dl, ferritin ≥ 40 ng/ml or TSAT in reference range, no ESA use ≥ 7 weeks | 73           | Phase 2a RCT| DB         | US, Canada, EU                | 4 weeks           |

**Notes:**

- ESA: Erythropoiesis-stimulating agent
- DD-CKD: Dialysis-dependent chronic kidney disease
- NDD-CKD: Non-dialysis-dependent chronic kidney disease

<sup>b</sup> Number of patients in the study.
| Trial identifier  | Participants                                                                 | N  | Study design       | Comparator | Location            | Treatment duration |
|------------------|------------------------------------------------------------------------------|----|--------------------|------------|---------------------|--------------------|
| NCT01047397 [105] | CKD stage 3–4 (eGFR 15–59 ml/min/1.73 m²), CKD stage 5 (eGFR 10–15 ml/min/1.73 m²), or CKD stage 5d (eGFR 10–15 ml/min/1.73 m² and hemodialysis); ESA-naive with Hb ≤ 11 g/dl or no ESA use ≥ 7 days | 107 | Phase 2a RCT       | Australia, India, Russia | 28 days |
| NCT02260193 [106] | Maintenance hemodialysis thrice weekly ≥ 3 months, epoetin alfa and intravenous iron ≥ 3 months | 94  | Phase 2 OL         | None       | US                  | 16 weeks |
| NCT01906489 [107] | NDD-CKD stage 3a–5, ferritin level ≥ 50 ng/ml with TSAT ≥ 18% or a ferritin level ≥ 100 ng/ml regardless of TSAT | 210 | Phase 2 RCT DB    | US         | 20 weeks |
| NCT01381094 [108] | CKD stage 3 or 4 (eGFR 30–59 or 15–29 ml/min/1.73 m²), no ESA ≥ 11 weeks, Hb ≤ 10.5 g/dl, ferritin ≥ 50 ng/ml, TSAT ≥ 20% | 93  | Phase 2a, RCT DB  | US         | 6 weeks  |
| NCT01975818 (DIALOGUE 4) [109] | DD-CKD, Hb 9.0–11.5 g/dl, stable epoetin use ≥ 8 weeks | 199 | Phase 2b RCT OL   | Epoetin alfa/beta | US, Japan | 16 weeks |
| NCT02064426 (DIALOGUE 5) [110] | DD-CKD (from DIALOGUE 4) | 88  | OL extension of DIALOGUE 4 | Epoetin alfa/beta | US, Japan | ≤ 36 months |

Vadadustat³

Patients with DD-CKD

Molidustat³

Patients with DD-CKD

Patients with NDD-CKD
### Table 2 continued

| Trial identifier | Participants | N\(^{b}\) | Study design | Comparator | Location | Treatment duration |
|------------------|--------------|-----------|--------------|------------|----------|--------------------|
| NCT02021370 (DIALOGUE 1) [109] | NDD-CKD (ESA-naïve eGFR < 60 ml/min/1.73 m\(^2\)), Hb < 10.5 g/dl, ESA-naïve or no ESA use ≥ 8 weeks | 121 | Phase 2b RCT DB | Darbepoetin | EU, Asia–Pacific | 16 weeks |
| NCT02021409 (DIALOGUE 2) [109] | NDD-CKD (eGFR < 60 ml/min/1.73 m\(^2\)), Hb 9–12 g/dl, stable darbepoetin use ≥ 8 weeks | 124 | Phase 2b RCT OL | Darbepoetin | EU, Asia–Pacific | 16 weeks |
| NCT02055482 (DIALOGUE 3) [110] | NDD-CKD (from DIALOGUE 1 and 2) | 164 | OL extension of DIALOGUE 1 and 2 | Darbepoetin | EU, Asia–Pacific | ≤ 36 months |

**Enarodustat**

| Participants with DD-CKD |
|--------------------------|
| JapicCTI-152892 [111] | Hemodialysis or hemodiafiltration 3 times per weeks ≥ 12 weeks, ESA therapy ≥ 4 weeks, mean Hb at screening and 2 weeks later 9.5–12.0 g/dl with absolute difference of ≤ 1.0 g/dl, TSAT > 20% or ferritin > 75 ng/ml | 85 | Phase 2b RCT DB followed by OL extension | Japan | 6 weeks (RCT); 24 weeks (OL) |

| Participants with NDD-CKD |
|--------------------------|
| JapicCTI-152881 [112] | CKD not on dialysis (eGFR < 60 ml/min/1.73 m\(^2\)), mean Hb 8.0–10.5 g/dl for correction group (ESA-naïve: no ESA ≥ 12 weeks) and 9.5–12.0 g/dl for conversion group (ESA-treated: stable ESA ≥ 8 weeks) | 201 | Phase 2b RCT DB followed by OL extension | Japan | 6 weeks (RCT); 24 weeks (OL) |

**Desidustat**

| Participants with NDD-CKD |

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\(^{a}\) Patients with DD-CKD

\(^{b}\) Patients with NDD-CKD
In these studies, roxadustat was also associated with a reduced risk of rescue therapy (ESA or IV iron) and RBC transfusion [98] and reduced hepcidin levels compared with placebo (between group difference -50 ng/ml) [96]. Interim data from a phase 3 study showed that roxadustat was noninferior to darbepoetin alfa regarding Hb response in NDD-CKD patients [125]. Preliminary data from a Japanese phase 3 study showed that vadadustat was as effective as darbepoetin alfa in maintaining Hb levels in both ESA-naïve and ESA-converted NDD-CKD patients with anemia [126].

In both ESA-naïve and -experienced DD-CKD patients with anemia, roxadustat demonstrated non-inferiority or superiority in increasing Hb from baseline versus epoetin alfa or darbepoetin alfa in a Chinese phase 3 study [35] and in preliminary data from four international phase three studies [90–93]. Greater decreases in hepcidin from baseline were also observed with roxadustat versus epoetin alfa [35]. In a phase 3 Japanese study in ESA-naïve hemodialysis patients, daprodustat effectively corrected and maintained Hb levels within the target range (10–12 g/dl), decreased hepcidin levels, and increased TIBC [103]. Similarly, preliminary data demonstrated that vadadustat was as effective as darbepoetin alfa in maintaining Hb levels within the target range in Japanese patients on maintenance hemodialysis and resulted in reduced hepcidin levels and increased TIBC over 24 weeks, which was not observed in the darbepoetin alfa group [127].

HIF-PH inhibitors were well tolerated in phase 3 clinical studies, and adverse events (AEs) were consistent with those expected in a CKD population [35, 92, 96, 126, 127]. The most common AEs with roxadustat were hyperkalemia and metabolic acidosis in NDD-CKD patients [96] and hyperkalemia in DD-CKD patients [35]. Additionally, preliminary data from two further international phase 3 studies reported the most common AEs with roxadustat to be ESRD, urinary tract infection, pneumonia, and hypertension in NDD-CKD patients [128] and diarrhea in DD-CKD patients [129]. The most commonly reported AE with

### Table 2 continued

| Trial identifier | Participants | N \(^b\) | Study design | Comparator Location | Treatment duration |
|------------------|--------------|---------|--------------|---------------------|-------------------|
| CTRI/2017/05/00534 | NDD-CKD stage 1–4, Hb 6.5–11 g/dl, ferritin 100–1000 μg/l or TSAT ≥20%, body weight ≥45 kg | 117 | Phase 2 RCT | DB | 6 weeks |
| C2017/05/008534 | CKD (chronic kidney disease), DB (double blind), DD (dialysis-dependent), eGFR (estimated glomerular filtration rate), ESA (erythropoiesis-stimulating agent), ESRD (end-stage renal disease), EU (European Union), Hb (hemoglobin), NDD (non-dialysis-dependent), OL (open-label), RCT (randomized controlled trial), TSAT (transferrin saturation) | 120 | DB | 6 weeks |

\(^a\) Half-life for roxadustat: 11.4–14.7 h [114–116]; daprodustat: 0.9–2.3 h [117]; vadadustat: 4.7–9.1 h [118]; molidustat: mean, 4.6–10.4 h [119]; esidustat: not available;

\(^b\) Number randomized
daprodustat in DD-CKD patients was nasopharyngitis [103]. For vadadustat, these were nasopharyngitis, diarrhea, and constipation in NDD-CKD patients [126] and nasopharyngitis, constipation, and shunt stenosis in DD-CKD patients [127].

Preliminary results from a pooled safety analysis of NDD-CKD or stable DD-CKD patients with anemia indicated a similar or reduced risk of MACE and MACE plus heart failure or unstable angina requiring hospitalization (MACE+ with roxadustat versus placebo and epoetin alfa, respectively [130]. In incident DD-CKD patients with anemia, the HRs for MACE and MACE+ were 0.70 (95% CI 0.51–0.97, \( P = 0.03 \)) and 0.66 (95% CI 0.50–0.89, \( P = 0.005 \)), respectively, with roxadustat versus epoetin alfa [130]. Further analyses are needed to confirm these initial safety findings.

HIF-PH Inhibitors in Development

Several other HIF-PH inhibitors are in development, with data available for molidustat (BAY 85-3934), enarodustat (JTZ-951), and desidustat (Zyan1) (Table 2). These studies show dose-dependent Hb increases and maintenance of Hb (in NDD-CKD) and maintenance of Hb (in DD-CKD) for molidustat [109], enarodustat [111, 112], and desidustat [113]. However, high Hb or a rapid rate of increase led to high incidences of early discontinuation from some studies of molidustat [109]. In the long-term extension studies DIALOGUE 3 and DIALOGUE 5, Hb was maintained in the target range (10–12 g/dl) for up to 36 months with molidustat, with a similar effect to darbepoetin or epoetin [110]. Increased TIBC and/or decreased hepcidin and/or ferritin was observed with these agents, which were generally well tolerated [109, 112, 113]. Furthermore, animal
studies have indicated that prolonged exposure to roxadustat is not associated with pro-oncogenic activity [131, 132]. However, long-term clinical data are needed to confirm the safety of HIF-PH inhibitors regarding to cardiovascular events and carcinogenesis.

Potential for Clinical Use of HIF-PH Inhibitors

HIF-PH inhibitors may present several practical advantages for patients with anemia of CKD. In addition to their oral route of administration, HIF-PH inhibitors may provide closer to physiologic EPO levels than the intermittent high levels attained with ESA therapy [87, 95]. Beyond erythropoiesis stimulation, HIF-PH inhibitors may improve iron homeostasis [133] and therefore reduce patients’ iron supplementation needs, thus potentially reducing costs and medication burden. Although data on the cost effectiveness of HIF-PH inhibitors are limited, a meta-analysis conducted to evaluate the cost effectiveness of roxadustat in Chinese patients with NDD-CKD confirmed that roxadustat was cost effective compared with placebo [134].

Evidence suggests that HIF-PH inhibitors may be efficacious without increasing inflammatory status [88], which could benefit patients with inflammation, associated with diabetic and non-diabetic kidney disease as well as those with acute inflammation (e.g., associated with infection). Although clinical data in patients who are ESA hyporesponsive are limited, key studies included patients with moderate inflammation, which is associated with reduced responsiveness to ESA therapy [135]. In the Chinese phase 3 study of roxadustat in patients with DD-CKD, similar increases in Hb levels were observed in patients with normal and elevated C-reactive protein levels (≤ 4 and > 4 mg/l) [35]. In addition, preliminary phase 3 data showed greater mean changes in Hb in patients with elevated high-sensitivity C-reactive protein levels receiving roxadustat versus epoetin alfa (DD-CKD) [91] or placebo (NDD-CKD) [98]. In these patients with moderate inflammation, who are potentially hyporesponsive to ESA therapy, HIF-PH inhibitors may be an effective alternative that avoids the need for high-dose ESA therapy. Further studies are needed to confirm the efficacy of HIF-PH inhibitors in patients who are ESA hyporesponsive. Finally, HIF-PH inhibitors may confer a reduced risk of cardiovascular events compared with ESAs in incident dialysis patients as a preliminary phase 3 pooled analysis showed a lower risk of MACE and MACE+ with roxadustat versus epoetin alfa [130]. Further studies are needed to confirm the practical benefits of HIF-PH inhibitors in patients with anemia of CKD.

Because HIF transcription factors regulate many biologic processes, there was concern that HIF-PH inhibitors may adversely affect cholesterol metabolism [136]. Based on animal studies, constitutive HIF-2 activation may theoretically suppress hepatic fatty acid β-oxidation and lipid synthesis and increase lipid storage capacity [136]. However, clinical studies showed reductions in total and low-density lipoprotein cholesterol (LDL-C) with roxadustat over 19–24 weeks [87, 94] and daprodustat over 24 weeks [103] as well as no changes in serum lipids with vadadustat over 16 or 20 weeks [106, 107] and only small changes in LDL-C with molidustat over 16 weeks [109]. Roxadustat phase 3 data showed decreases in low-density lipoprotein cholesterol versus placebo (NDD-CKD patients) [96] or versus ESA (DD-CKD patients) [35]. One potential mechanism for this reduction in serum cholesterol with roxadustat is thought to be a HIF-dependent decrease in 3-hydroxy-3-methylglutaryl coenzyme A reductase levels, a rate-limiting enzyme in the cholesterol biosynthesis pathway [137].

At-Home Anemia Management

At-home care of CKD is one of the goals outlined in the recent Executive Order, Advancing American Kidney Health, which aims to improve the diagnosis and treatment of CKD [138]. Compared with conventional hemodialysis, at-home hemodialysis benefits include reductions in LV mass and hypertension and increased HR-QOL, although there are no
observed differences in anemia management [139, 140].

Because they are orally administered, HIF-PH inhibitors may confer advantages for at-home CKD care. In ESRD patients receiving peritoneal dialysis, the more common modality for at-home dialysis, roxadustat increased Hb to within the target range [141], and daprodustat pharmacokinetics were similar in patients receiving peritoneal dialysis or in-center hemodialysis, while Hb was maintained in those receiving peritoneal dialysis [142].

CONCLUSIONS

Anemia of CKD represents a considerable burden to both patients and the healthcare system. Although effective, the current standard of care is associated with inherent practical difficulties and safety concerns, including the increased risk of cardiovascular events and mortality. HIF-PH inhibitors may offer advantages over ESAs through more physiologic and effective means of treating anemia of CKD.

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