



REVIEW

Burden of Anemia in Chronic Kidney Disease: Beyond Erythropoietin

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Received: June 24, 2020 / Accepted: October 3, 2020 / Published online: October 29, 2020
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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 health-care 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

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Key Summary Points

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.

hemoglobin (Hb) < 13.0 g/dl for men and < 12.0 g/dl for nonpregnant women [3] and largely results from decreased erythropoietin (EPO) production by the failing kidney and/or altered iron homeostasis [4, 5]. The current standard of care for anemia of CKD includes oral or intravenous (IV) iron, erythropoiesis-stimulating agents (ESAs), and red blood cell (RBC) transfusion, each of which has potential problems and variable effectiveness [2, 3]. The impact of anemia correction on patient health-related quality of life (HR-QOL) is unknown, and persistent safety issues contribute to uncertainty regarding the optimal target Hb. This article reviews the burden of anemia of CKD, including its impact on mortality and cardiovascular risk, HR-QOL, hospitalization and transfusion needs, iron supplementation needs, the conservative management of CKD to delay dialysis, end-stage renal disease (ESRD) transition outcomes, anemia management at home, and anemia management in transplant recipients. An assessment of the risk to the benefit profile associated with current standard of care and discussion surrounding novel agents in development based on alternative erythropoietic mechanisms are also provided. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13035146>.

INTRODUCTION

Anemia is a common complication of chronic kidney disease (CKD), representing a significant burden to patients and healthcare systems [1, 2]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines, anemia of CKD is defined as

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-creatinine 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 ($Hb \leq 9$ 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].

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

	Short-acting ESAs	Long-acting ESAs	HIF-PH inhibitors
Pros	Reduces need for RBC transfusions [31] May reduce fatigue and improve HR-QOL [29] IV administration is preferred in patients on hemodialysis [32]	Reduces need for RBC transfusions [21] May reduce fatigue and improve HR-QOL [29] Can be administered less frequently than short-acting ESAs [33] May be cheaper than short-acting ESAs [34] IV administration is preferred in patients on hemodialysis [32]	Have been shown to be noninferior to ESAs in raising or maintaining Hb [35] Can be administered orally [36] May reduce the need for iron supplementation by mobilizing stored iron [37]
Cons	Higher doses required to reach high Hb targets may increase risk of adverse cardiovascular outcomes [20] Often requires supplemental iron administration [3] Administered 3 times per week [31]	Higher doses required to reach high Hb targets may increase risk of adverse cardiovascular outcomes [21] Often requires supplemental iron administration [3] May confer increased risk of mortality compared with short-acting ESAs [38]	Additional research needed to evaluate potential effects on tumor growth [36]

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

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 \leq 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)

[20, 53]. 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 \geq 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

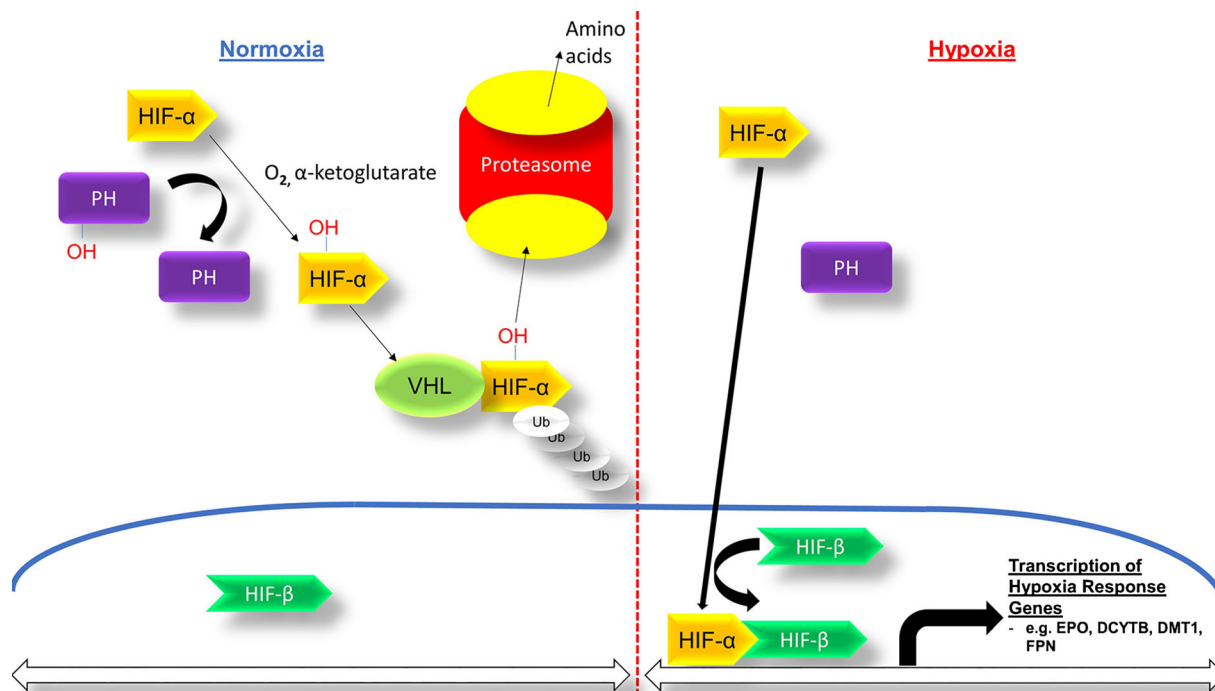


Fig. 1 Hypoxia-inducible factor (HIF) pathway biology. Under normoxic conditions, the HIF- α transcription factor subunit undergoes ubiquitination and proteasome degradation after prolyl hydroxylation (left side of figure). Under hypoxic conditions or pharmacologic HIF prolyl-hydroxylase inhibition, HIF- α is stabilized and, after heterodimerization with HIF- β , increases transcription of

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].

hypoxia-responsive genes, including those encoding erythropoietin (EPO) and iron metabolism (right side of figure). *DCYTb* duodenal cytochrome B, *DMT1* divalent metal transporter 1, *EPO* erythropoietin, *FPN* ferroportin, *OH* hydroxide, *PH* prolyl hydroxylase, *Ub* ubiquitin, *VHL* von Hippel-Lindau protein

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 ^b	Study design	Comparator	Location	Treatment duration
Roxadustat ^a						
Patients with DD-CKD						
NCT01596855 [86]	ESRD, hemodialysis, Hb 9–12 g/dl, stable epoetin 7 weeks	87	Phase 2 RCT OL	Epoetin alfa	China	6 weeks
NCT01147666 [87]	ESRD, maintenance hemodialysis \geq 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 [88]	Incident dialysis (2 weeks–4 months), Hb \leq 10 g/dl, ferritin 50–300 ng/ml, TSAT 10%–30%, ESA-naïve, no intravenous iron \geq 4 weeks	60	Phase 2b RCT OL	None	US, Russia, Hong Kong	12 weeks
NCT02652806 [35]	ESRD, dialysis \geq 16 week, Hb 9.0–12.0 g/dl, stable epoetin alfa \geq 6 weeks	305	Phase 3 RCT OL	Epoetin alfa	China	26 weeks
NCT02779764 [89]	Hemodialysis 3 times/weeks for \geq 12 weeks, ESA \geq 8 weeks, mean of 2 latest Hb levels 10–12 g/dl, TSAT \geq 20% or ferritin \geq 100 ng/ml	164	Phase 3 OL	None	Japan	52 weeks
NCT02780141 [89]	Hemodialysis \geq 1 time/weeks, ESA-naïve, mean of 2 latest Hb levels \leq 10 g/dl, TSAT \geq 5% or ferritin \geq 30 ng/ml	75	Phase 3 RCT OL	None	Japan	24 weeks
NCT02273726 (SIERRAS) [90]	ESRD, dialysis \geq 3 months, Hb 8.5–12.0 g/dl, ferritin \geq 100 ng/ml, TSAT \geq 20%, ESA \geq 4 weeks	741	Phase 3 RCT OL	Epoetin alfa	US	52 weeks to 3 years
NCT02174731 (ROCKIES) [91]	Hemodialysis or peritoneal dialysis; Hb $<$ 12.0 g/dl in those on ESA, $<$ 10 g/dl in those not on ESA; ferritin \geq 100 ng/ml; TSAT \geq 20%	2133	Phase 3 RCT OL	Epoetin alfa	North America, Asia, Australia, EU, India, South America	52 weeks to 4 years

Table 2 continued

Trial identifier	Participants	N ^b	Study design	Comparator	Location	Treatment duration
NCT02278341 (PYRENEES) [92]	Stable hemodialysis or peritoneal dialysis, Hb 9.5–12 g/dl, epoetin alfa or darbepoetin alfa ≥ 8 weeks	836	Phase 3 RCT OL	ESA (epoetin alfa or darbepoetin alfa)	EU	52–104 weeks
NCT02052310 (HIMALAYAS) [93] Patients with NDD-CKD	ESRD, incident dialysis (2 weeks–4 months)	1043	Phase 3 RCT OL	Epoetin alfa	US, Asia, EU, South America	52 weeks to 3 years
NCT01599507 [86]	NDD-CKD (eGFR < 60 ml/min/1.73 m ²), Hb < 10 g/dl	91	Phase 2 RCT DB		China	8 weeks
NCT01244763 [94]	NDD-CKD (eGFR 15–59 ml/min/1.73 m ²), Hb < 10.5 g/dl, ferritin > 30 ng/ml, TSAT ≥ 5%, no ESA use ≤ 12 weeks	145	Phase 2 RCT OL	None	US	16 or 24 weeks
NCT00761657 [95]	NDD-CKD stage 3–4 (eGFR 15–59 ml/min/1.73 m ²), Hb < 11 g/dl	117	Phase 2a RCT		US	4 weeks
NCT02652819 [96]	NDD-CKD stage 3–5, Hb 7– < 10 g/dl, no ESA use ≤ 5 weeks	154	Phase 3 RCT DB followed by OL extension		China	8 weeks (RCT); 18 weeks (OL)
NCT01750190 (ANDES) [97]	NDD-CKD stage 3–5	922	Phase 3 RCT DB		US, Asia, Australia, South America	< 52 weeks to 3 years
NCT01887600 (ALPS) [92]	NDD-CKD stage 3–5 (eGFR < 60 ml/min/1.73 m ²), Hb ≤ 10 g/dl, ferritin ≥ 30 ng/ml, TSAT ≥ 5%, ESA-naïve	594	Phase 3 RCT DB		EU	52–104 weeks
NCT02174627 (OLYMPUS) [98]	NDD-CKD stage 3–5 (eGFR < 60 ml/min/1.73 m ²), Hb ≤ 10 g/dl, ferritin ≥ 50 ng/ml, TSAT ≥ 15%, ESA-naïve	2781	Phase 3 RCT DB		North America, Asia, EU, India, South America	52 weeks

Table 2 continued

Trial identifier	Participants	N ^b	Study design	Comparator	Location	Treatment duration
Daprodustat ^a						
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	ESA	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	ESA	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%–> 57%, stable ESA use ≥ 4 weeks	177	Phase 2b RCT DB	ESA	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	None	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	None	US, Canada, EU	4 weeks
Patients with NDD-CKD or DD-CKD						

Table 2 continued

Trials identifier	Participants	N ^b	Study design	Comparator	Location	Treatment duration
NCT01047397 [105]	CKD stage 3–4 (eGFR 15–59 ml/min/1.73 m ²), CKD stage 5 (eGFR 10– < 15 ml/min/1.73 m ²), or CKD stage 5d (eGFR 10– < 15 ml/min/1.73 m ² and hemodialysis); ESA-naïve with Hb ≤ 11 g/dl or no ESA use ≥ 7 days	107	Phase 2a RCT		Australia, India, Russia	28 days
Vadadustat ^a						
Patients with DD-CKD						
NCT02260193 [106]	Maintenance hemodialysis thrice weekly ≥ 3 months, epoetin alfa and intravenous iron ≥ 3 months	94	Phase 2 OL	None	US	16 weeks
Patients with NDD-CKD						
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 m ²), no ESA ≥ 11 weeks, Hb ≤ 10.5 g/dl, ferritin ≥ 50 ng/ml, TSAT ≥ 20%	93	Phase 2a, RCT		US	6 weeks
Molidustat ^a						
Patients with DD-CKD						
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
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		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 ^a Patients 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)
Patients 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 ^a Patients with NDD-CKD						

Table 2 continued

Trial identifier	Participants	N ^b	Study design	Comparator	Location	Treatment duration
CTRU/2017/05/008534 [113]	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		India	6 weeks

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

^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]; enarodustat: not available; desidustat: mean, 6.9–11.4 h [120]

^b Number randomized

phase 3 randomized study [96] and in preliminary results from three international phase 3 studies [92, 97, 98]. 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

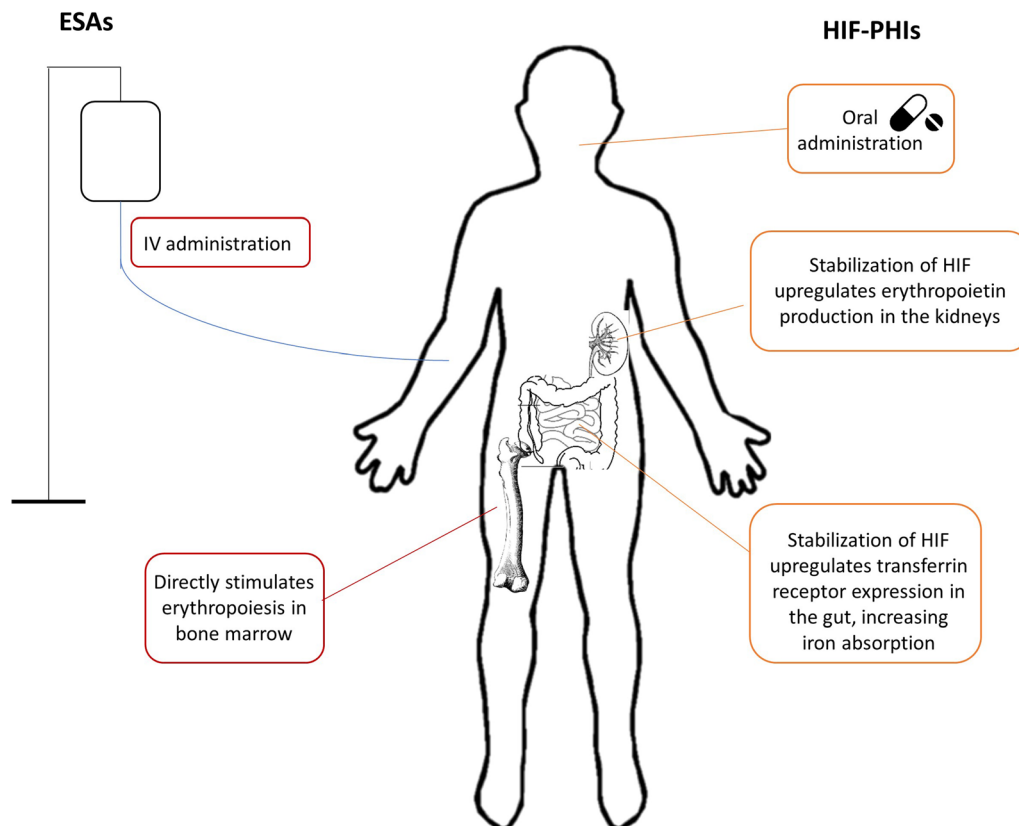


Fig. 2 Actions of erythropoiesis-stimulating agents (ESAs) and hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs). *IV* intravenous

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 0.5–0.89, $P = 0.005$), 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.

ACKNOWLEDGEMENTS

Funding. This review, the Rapid Service, and Open Access Fees were funded by AstraZeneca.

Editorial Assistance. Sarah Greig, PhD (Auckland, NZ), and Meri D. Pozo, PhD, CMPP (New York, NY, USA), of inScience Communications, Springer Healthcare provided editorial support, which was funded by AstraZeneca.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. All authors wrote the first draft of the manuscript and participated in subsequent drafts, approved the

submission of the manuscript, and are fully accountable for all aspects of the work.

Disclosures. Ramy M. Hanna and Elani Streja have nothing to disclose. Kamyar Kalantar-Zadeh reports personal fees from Abbott, AbbVie, Alexion, AMAG Pharma, Amgen, AstraZeneca, AVEO, Baxter, Chugai, Fresenius Medical Services, Genentech, Haymarket, Hospira, Fresenius Kabi USA, Keryx, Novartis, PCORI, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and grants and personal fees from National Institutes of Health. None of the authors received honoraria for this work.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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