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# The role and clinical implications of HIF-PHI daprodustat in dialysis-dependent and non-dialysis-dependent chronic kidney disease anemic patients: a general review

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Chronic kidney disease (CKD) patients often suffer from complications such as anemia as the kidney function declines. More than 25% of CKD hemodialysis patients in China are complicated with renal anemia due to renal and hepatic impairment in the production of erythropoietin (EPO). In recent years, prolyl hydroxylase domain (PHD) inhibitors have been approved in China and Japan for the treatment of CKD patients complicated with anemia. Daprodustat is a novel orally administrated active hypoxia-induced factor-prolyl hydroxylase inhibitor (HIF-PHI) that may improve quality of life and ischemic conditions such as peripheral arterial disease (PAD), stimulate the synthesis of endogenous EPO, and can effectively induce the production of red blood cells. It has been shown to increase EPO levels, which can lead to an increase in hemoglobin (Hgb), hematocrit, and red blood cell counts. Clinical studies have shown its effectiveness in dialysis and non-dialysis CKD anemic patients. In this literature review, we will focus on the mechanism and metabolism of the drug as well as its clinical applications in dialysis and non-dialysis CKD patients and summarize the adverse reactions.

## KEYWORDS

daprodustat, anemia, chronic kidney disease, erythropoietin, dialysis, hypoxia-induced factor-prolyl hydroxylase inhibitor

## 1 Introduction

The number of chronic kidney disease (CKD) patients is growing worldwide and is expected to exceed 850 million (1). As kidney function worsens and CKD progresses, pathological conditions tend to become more severe due to the accumulation of uremic toxins, inflammation, and other factors (2). Patients with CKD often develop complications including anemia and cardiovascular disease (CVD). Anemia, a well-known comorbidity in patients with CKD, is associated with several factors including inflammation; deficiency in iron, vitamin D, and other factors; and resistance to erythropoietin (EPO) (3–6). As EPO is synthesized mainly in kidney tissue, the diseased kidney cannot produce the required amount of EPO. It is well known that serum EPO production is suppressed due to a feedback system according to the change in the oxygen tension of the tissues. The production of EPO is known to be regulated by the hypoxia-inducible factors HIF-1 $\alpha$  and HIF-2 $\alpha$ , which bind to the hypoxia response element (HRE) on the EPO gene, thus preventing it from degrading (7). HIFs are heterodimeric transcription factors that are expressed in many cell types and allow tissues to adapt to hypoxia. In the liver, when hypoxia is sensed, EPO expression and the liver's capacity to transport iron are increased, and the liver can induce an erythropoietic response (8). In the field of EPO production, the main driver of hypoxic EPO production is HIF- $\alpha$ , especially HIF-2 $\alpha$  (9). Nevertheless, when there is plenty of oxygen, protein HIF-1 $\alpha$  is generated from mRNA and the proline residues are hydroxylated by prolyl hydroxylases (PHDs), also called HIF-PHDs under a different nomenclature system, before being transported to the proteasome in a hydroxylated proline residue-dependent manner. The development of HIF-PHI is targeting the treatment of anemia in chronic kidney disease patients. Members of the HIF-PHD family are the most studied prolyl hydroxylases that regulate the HIF- $\alpha$  level and ensure the symbiotic balance of oxygen levels and HIF's activity (10).

In recent decades, the main treatment for renal anemia has been the use of ESAs combined with iron therapy (11). Studies have shown that ESA can significantly increase Hgb levels in patients and improve their quality of life (12, 13). In addition, the use of ESA is also associated with a reduction of the requirement for the number of blood transfusions (14). However, the use of ESA has several side effects, such as accelerating atherosclerosis, increasing the risk of myocardial infarction and stroke, and promoting a high level of blood pressure to meet the Hgb level, which can occur with the rapid increase of Hgb above the recommended targets (15–17). The mechanism by which the rate of increase in Hgb level is directly proportional to the dose of ESAs is not well understood. It is well known that hyporesponsiveness to ESAs is multifactorial including inflammation, malnutrition, and iron maldistribution, just to list a few (18). Conversely, some patients may need a high dose of ESAs to meet the target Hgb level, but high doses of ESAs are also linked to increased morbidity and mortality (19).

HIF-PHIs are revolutionary oral drugs to treat anemia in patients with CKD (20). In 2020, the Asian Pacific Society of Nephrology (APSN) recommended HIF-PHIs as alternatives to ESAs to maintain Hgb levels in anemic patients with CKD, both on and not on dialysis (21). These medications work by preserving the functions of HIF-1 $\alpha$  and HIF-2 $\alpha$  through inhibition of intracellular HIF degradation, leading to the activation of HIF-

regulated genes such as EPO and genes involved in iron absorption and utilization, thereby stimulating EPO synthesis (22). Additionally, they have been found to enhance iron availability by increasing mobilization and indirectly reducing serum hepcidin levels in CKD patients (23, 24).

At present, there are five recognized varieties of HIF-PHIs that have been verified and implemented in China's medical institutions for patients with anemia (6, 25–27), namely, roxadustat, daprodustat, vadadustat, molidustat, and enarodustat. Among these HIF-PHIs, daprodustat has recently been scrutinized, with multiple phase 2 investigations indicating its potential to ameliorate renal anemia in both dialysis and non-dialysis CKD patients, as well as enhance iron utilization. Following phase 3 clinical trials, daprodustat demonstrated satisfactory tolerance among CKD anemic patients in enhancing Hgb levels, resulting in its endorsement by GlaxoSmithKline.

HIF-PHIs can prevent the degradation of intracellular HIF, leading to the activation of genes regulated by HIF, including those involved in EPO production and iron reabsorption (22). Roxadustat has been approved for use in China, Japan, and Europe. Previous research has shown that roxadustat is non-inferior to ESAs in patients undergoing dialysis (28). Other HIF-PHIs, such as vadadustat and enrodustat, have also been indicated for the treatment of renal anemia in hemodialysis patients in China and Japan. While most of these drugs have been well tolerated by patients and have improved renal anemia, some effects vary among this class of medications. Haase et al. (29) have detailed some of these variations, particularly regarding iron metabolism and its impact on iron utilization, which has been regarded as a class effect of HIF-PHIs. Notably, Roxadustat has been associated with cholesterol-lowering effects (28), while changes in cystatin C levels have been observed in non-dialysis-dependent CKD patients receiving vadadustat (30). In contrast, the pharmacological properties of HIF-PHD inhibitors differ from one another, and their varying potencies to stabilize HIF suggest that the rate at which Hgb levels increase may also vary (31). Furthermore, the structural differences and metabolic profiles among these medications are not fully understood. Consequently, more clinical trials are necessary to compare these drugs against each other. So far, daprodustat has shown efficacy in treating renal anemia in both hemodialysis and non-hemodialysis-dependent CKD patients. If future studies report positive outcomes, daprodustat could become another valuable treatment option for anemia in other countries.

This review will focus on the mechanism and metabolism of daprodustat and its impact on renal anemia. Additionally, we will explore the clinical applications of daprodustat in both dialysis and non-dialysis CKD patients. Lastly, an overview of the adverse reactions associated with daprodustat will be provided.

## 2 Mechanism of action

### 2.1 Mechanism of renal anemia

CKD can often cause renal anemia, a significant complication that is related to a poor prognosis. The association between CKD

and renal anemia was initially established by Richard Bright et al. (32). Furthermore, research has shown that the prevalence of anemia tends to increase as CKD progresses to more advanced stages (33). In CKD patients, anemia is typically characterized by hypoproliferative and normocytic features. The production of EPO, a hormone crucial for red blood cell production, is primarily stimulated by the circulation factor, and the kidneys play a vital role as the main source of EPO in the body (34). Understanding the relationship between CKD and renal anemia is essential for effective management and treatment strategies. By recognizing the role of EPO and the kidneys in the development of anemia in CKD patients, healthcare providers can better understand this complication and improve patient outcomes. Further research in this area may lead to advancements in the management of renal anemia in CKD patients.

The development of renal anemia involves multiple elements, one of which is chronic inflammation. Additionally, iron deficiency can manifest due to either blood losses or impaired iron absorption. Nevertheless, the primary factor responsible for renal anemia is the deficiency and progressive reduction of endogenous EPO. A study (35) highlights that those individuals with CKD exhibit EPO levels within the normal range. However, when faced with decreased Hgb levels, the expected increase in EPO is absent, unlike what is observed in cases of non-renal anemia. The synthesis of EPO within the kidneys is a critical function performed by the fibroblast-like interstitial peritubular cells. These cells, along with the perisinusoidal cells in the liver, contribute to EPO production, although the liver cells produce smaller quantities. The production of EPO is influenced by any changes in the oxygen levels within the tissues (36). The regulation of EPO expression is primarily controlled by the transcription of the EPO gene. The activation of the HIF system depends on the oxygen levels in the tissues, which is the key factor in regulating EPO expression. In cases of hypoxia, the HIF-1 protein binds to the EPO gene and triggers its expression mechanism. The HIF-1 protein consists of two subunits: HIF-1 $\alpha$  and HIF-1 $\beta$ . HIF-1 $\alpha$  is typically absent under normal oxygen conditions, while HIF-1 $\beta$  is usually present and expressed even under normal oxygen conditions.

In instances of low oxygen levels, HIF-1 $\alpha$  tends to accumulate and translocate to the nucleus, where it forms a complex with HIF-1 $\beta$ , resulting in the formation of a HIF-1 $\alpha$ - $\beta$  heterodimer. This heterodimer then binds to the DNA sequence known as hypoxia response element (HRE), which plays a crucial role in regulating the expression of hypoxia-sensitive genes by either upregulating or downregulating them. This rapid process is essential for cellular protection, ensuring adequate oxygen delivery while reducing oxygen consumption. Among the hypoxia-sensitive genes is the EPO gene, which, when activated, leads to EPO production. Additionally, the HIF subunits are involved in upregulating other genes such as vascular endothelial growth factor (VEGF) and transferrin receptors (37). Previous studies have highlighted the significant role of HIF transcription factors in governing cellular mechanisms and functions (38–40). In normoxic conditions, HIF-1 $\alpha$  undergoes degradation and experiences hydroxylation at two proline residues. This hydroxylation process is mediated by a specific enzyme known as the prolyl hydroxylase domain (PHD)

enzyme, which necessitates the presence of oxygen, 2-oxoglutarate, and iron. Previous studies have identified three PHDs, with PHD-2 playing a pivotal role in regulating HIF activity (41). However, when hypoxia occurs, the action of PHDs is hindered, enabling HIF-1 $\alpha$  to stabilize and translocate to the nucleus (42, 43). Additionally, factor-inhibiting HIF (FIH) is another regulatory factor involved in modulating HIF activities (44).

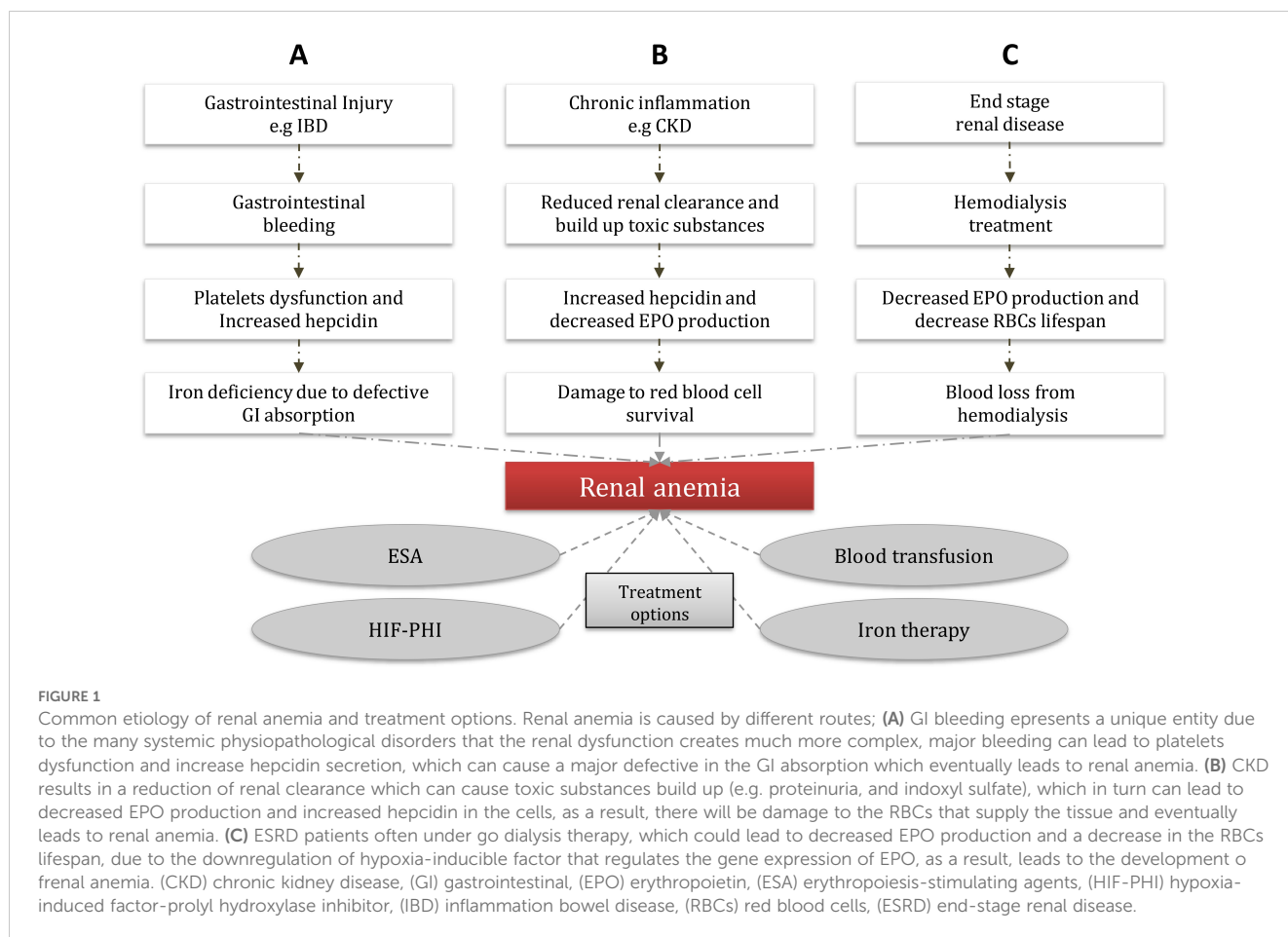
When oxygen levels are within the normal range, the hydroxylation process of HIF-1 $\alpha$  is activated, resulting in a decline in its transcriptional capabilities. Furthermore, under no hypoxic conditions, there is a consistent increase in angiotensin II levels, leading to the generation of reactive oxygen species that inhibit the activity of PHD enzymes, which leads to a rise in EPO levels (45–47). All subunits of the HIF- $\alpha$  component have the capacity to bind with HIF- $\beta$  and perform similar functions that are crucial within the HIF system. However, there are differences among them; HIF-1 $\alpha$  and HIF-2 $\alpha$  are more inclined toward stimulating gene transcriptions, while HIF-3 $\alpha$  tends to suppress the activities of HIF-1 $\alpha$  and HIF-2 $\alpha$ . Additionally, variations in their gene expressions may also be observed. Importantly, HIF-2 $\alpha$  plays a pivotal role in regulating EPO production compared to HIF-1 $\alpha$ , especially in the context of EPO synthesis in the kidneys.

In individuals suffering from CKD, the levels of EPO are contingent upon the extent of anemia present. The root cause of CKD contributes to the insufficiency of EPO. Previous research has demonstrated that once the estimated glomerular filtration rate (eGFR) falls below 30 ml/min per 1.73 m<sup>2</sup>, the deficiency in EPO becomes more pronounced (48). This deficiency arises from a decline in EPO synthesis. The diminished blood flow to the kidneys due to CKD-induced alterations in oxygen delivery leads to decreased oxygen consumption by the kidney tissue, disrupting the normal tissue oxygen gradient and causing the PHD enzymes to remain active. Consequently, the formation of the HIF heterodimer is obstructed, ultimately deactivating the EPO gene (49). Furthermore, it is widely recognized that CKD triggers heightened inflammation and the activation of immune molecules, which hinder EPO production (50). An overview of the etiology of renal anemia is shown in Figure 1.

## 2.2 Mechanism and metabolism of the HIF-PHI daprodustat

HIF-PHIs imitate the effects of moderate hypoxia on the body by reversibly inhibiting the enzymatic activity of PHD, thereby extending the half-life of HIF- $\alpha$ . While all members of this class of molecules exhibit similar actions, they possess unique molecular structures and display variations in potency and kinetics of inhibition across different PHD isoforms (51). Agents with prolonged half-lives may exhibit increased cellular or *in-vivo* effectiveness, but they also tend to have more unintended off-target effects (52). Presently, there is insufficient evidence to suggest that these molecular distinctions result in variations in efficacy or safety.

Under hypoxic conditions, the transcription factors of HIF play a critical role in cellular survival and the regulation of biological



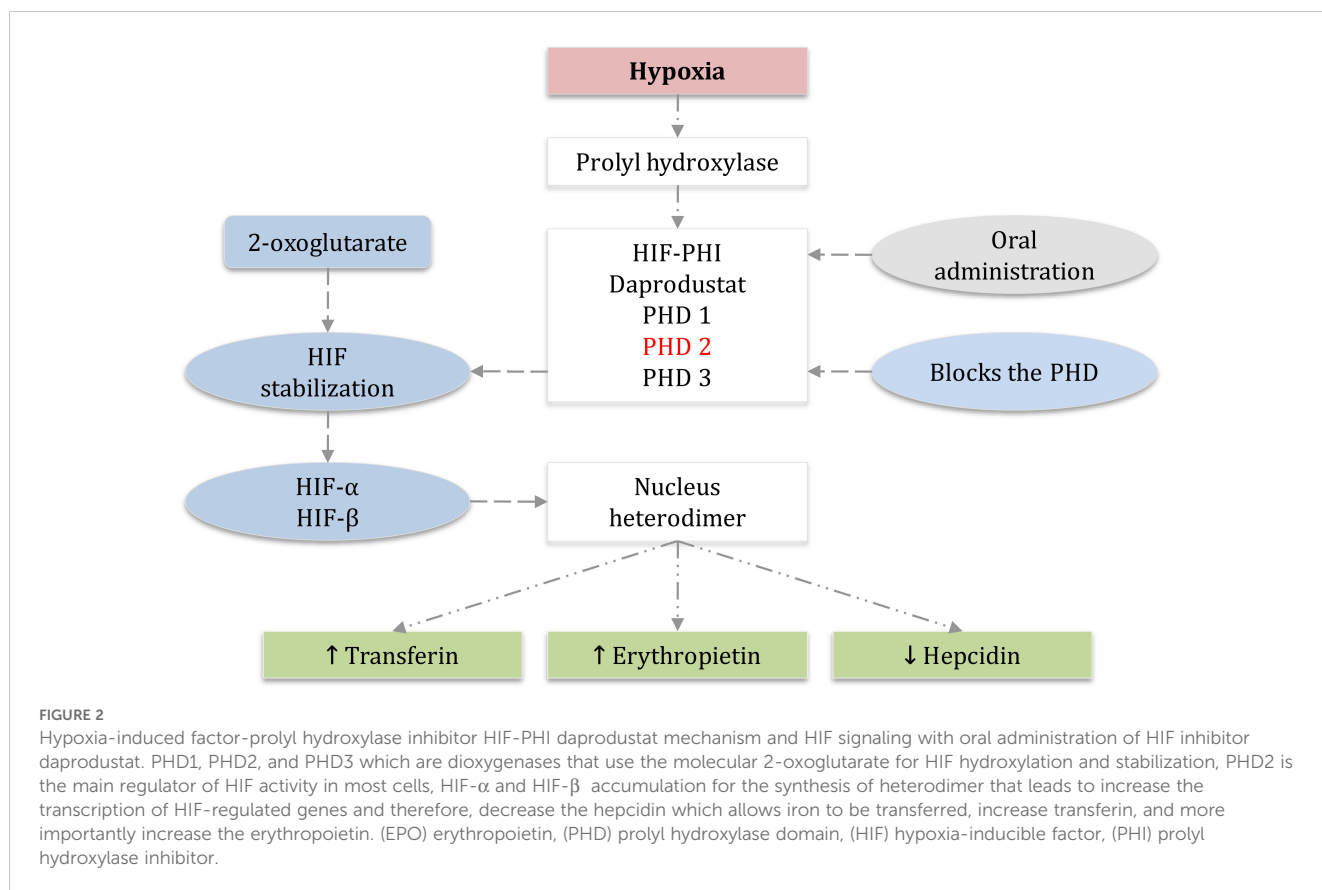
processes like cell growth, angiogenesis, metabolism, and erythropoiesis to restore the oxygen balance (53–55). Daprodustat, an inhibitor of PHDs 1–3, stabilizes HIF-1 $\alpha$  and HIF-2 $\alpha$ , leading to increased EPO production and the initiation of erythropoiesis. *In-vivo* studies have shown that this class of HIF-PHD inhibitors has a high selectivity of 1,000-fold, suggesting potential benefits in treating renal anemia by enhancing iron absorption and reducing hepcidin levels (10).

The elimination half-life of daprodustat is approximately 1 to 2 h in individuals with normal kidney function. However, in patients with CKD who also suffer from anemia, the half-life is prolonged to around 7 h when a daily dose of 10 mg is administered (56, 57). During hemodialysis (HD) treatment, daprodustat primarily binds to proteins, particularly albumin, which prevents the significant removal of the drug (3). Daprodustat is classified as a novel oral HIF-PHI and is specifically developed for the management of anemia associated with CKD in both non-dialysis-dependent (NDD) and dialysis-dependent (DD) patients. The metabolism of daprodustat involves the enzyme CYP2C8, and the concomitant use of CYP2C8 inhibitors can potentially increase the plasma concentration of the drug (58). Therefore, it is recommended to avoid the simultaneous administration of these inhibitors with daprodustat. The induction of EPO gene expression has the potential to stimulate a response in erythropoiesis and upregulate the transport of iron. Hepcidin, a hormone responsible

for regulating iron levels, indirectly affects iron by facilitating the transfer of iron stored in the liver through a protein known as transferrin. Daprodustat, by inhibiting the activity of HIF-PHI, can increase EPO levels and decrease hepcidin levels, thereby enabling a greater transfer of iron from the liver (refer to Figure 2).

### 3 Daprodustat and clinical applications (advantages of HIF-PHI)

Before discussing the clinical trials involving daprodustat, it is important to outline the benefits of using HIF-PHI in anemic patients with CKD. Managing anemia in CKD patients presents various clinical obstacles and raises concerns about patient’s safety, including the heightened risk of CVD linked to ESA plasma levels, EPO resistance due to chronic inflammation, hypertension, iron supplementation due to iron deficiency, and iron administration due to the lack of iron and deficiency in CKD anemic patients (59–61). Conventional ESA therapy has been extensively utilized to address anemia in NDD-CKD and DD-CKD patients, demonstrating significant efficacy in Hgb control and elevation. Previous studies on the use of the HIF-PHI daprodustat have shown promising outcomes in increasing Hgb levels with comparable targets to ESA therapy. However, the absence of long-term trials with daprodustat poses challenges for physicians considering transitioning their patients



from ESA therapy to this novel oral HIF-PHI. Extensive research on the long-term use of daprodustat is necessary to assess any adverse reactions and the potential for CVD development or deficiencies in order to assure its safety as a substitute for ESA therapy.

Recent research has highlighted a key benefit of HIF-PHI therapy over ESA, as it helps achieve Hgb targets with significantly lower plasma EPO levels. Patients with CKD receiving HIF-PHI have been found to have 5–15 times lower plasma EPO compared to those receiving epoetin alfa (62, 63). While ESA treatment has been associated with increased CVD events, HIF-PHI therapy may mitigate these risks and enhance cardiovascular outcomes in the long run. However, there is currently a lack of clinical evidence to substantiate this hypothesis.

An additional advantage of utilizing HIF-PHI therapy is its ability to suppress serum hepatic hepcidin production, a crucial factor in the development of iron deficiency. Hepcidin inhibits gastrointestinal iron absorption and iron release by downregulating the surface expression of ferroportin, a cellular iron exporter. Clinical studies have demonstrated positive outcomes in iron metabolism with HIF-PHI treatment, leading to reduced plasma ferritin and serum hepcidin levels, as well as increased plasma transferrin levels (64, 65). Animal experiments have also shown similar results in regulating iron metabolism through the modulation of genes involved in iron transport and release (22). In individuals with CKD who are receiving HIF-PHI therapy, the impact of plasma hepcidin is not direct. This is due to the fact that hepcidin is not directly regulated at the transcriptional level by HIF (66, 67). Instead, the suppression of hepcidin transcription is

dependent on the erythropoietic activity facilitated by a factor derived from the bone marrow, known as erythroferrone (68, 69).

The preclinical studies of using HIF-PHI in managing CKD rodent models have demonstrated effectiveness in lowering blood pressure, as evidenced by recent research (70). Nevertheless, further investigations and prolonged trials are required to substantiate this advantage in clinical studies to establish a better understanding regarding this case. Furthermore, treatment with HIF-PHI has the potential to modulate lipid metabolism, resulting in decreased triglyceride and cholesterol levels. The activation of HIF can enhance lipoprotein uptake, leading to the degradation of 3-hydroxy-3-methyl-glutaryl-coenzyme-A and a subsequent reduction in cholesterol synthesis (71, 72). Given that CKD patients are at high risk of developing dyslipidemia associated with cardiovascular disease (73), the impact of HIF-PHI therapy on its management remains uncertain, necessitating additional studies to confirm its potential (refer to Table 1 for the mechanisms of daprodustat and ESAs).

### 3.1 Daprodustat in dialysis chronic kidney disease patients

Daprodustat is administered orally to inhibit all the PHDs and stabilize HIF-1 and HIF-2. Its half-life is approximately 1 h in healthy individuals and approximately 7 h in subjects with CKD (10, 56). Due to its high protein binding, daprodustat is not readily eliminated in patients undergoing HD therapy. In the following



**TABLE 1** Mechanisms, advantages, and general overview of daprodustat and ESAs in CKD anemic patients.

Index	HIF-PHI daprodustat	ESAs
<b>Mechanism</b>	HIF prolyl hydroxylase inhibitor	Acts directly on erythroid progenitor cells
<b>Administration method</b>	Oral	IV, SC injections
<b>Treatment effect</b>	Reduces hepcidin levels and improves renal anemia	Improves renal anemia
<b>Advantages</b>	<ul style="list-style-type: none"> <li>Controls and maintains hemoglobin levels</li> <li>Decreases hepcidin levels and improves iron metabolism</li> </ul>	Controls and increases the levels of hemoglobin
<b>Potentials</b>	<ul style="list-style-type: none"> <li>Lowers the blood pressure</li> <li>Alteration of lipid metabolism</li> <li>Anti-inflammation effects</li> <li>Benefits ESA-hyporesponsive patients</li> </ul>	A high dose lowers hepcidin but could cause side effects
<b>Adverse reactions</b>	Increases thromboembolism, hemorrhage, hypersensitivity, and hypertension	<ul style="list-style-type: none"> <li>Increases the risk for cardiovascular events such as stroke</li> <li>Increases the risk of thromboembolic events when given at a higher dose than recommended</li> </ul>
<b>Limitation</b>	Too expensive for most CKD patients to obtain	The effects are reduced in patients suffering from inflammation

HIF, hypoxia-inducible factor; ESA, erythropoiesis-stimulating agents; IV, intravenous; SC, subcutaneous; CKD, chronic kidney disease.

section, we will discuss several recently published trials pertaining to this issue.

An open-label control trial was conducted with 216 HD-CKD anemic patients having a baseline Hgb level of 9–11.5 g/dL, who were previously administered stable doses of rhEPO. These patients were then randomized to different doses of daprodustat over a 24-week period to investigate the dose–response relationship of Hgb and the safety of daprodustat. The study findings demonstrated that Hgb targets were dependent on the dose of daprodustat after 4 weeks of treatment, with the mean Hgb levels changing from –0.29 g/dL for daprodustat 4 mg to 0.69 g/dL for daprodustat 10 mg and 12 mg. Furthermore, these changes were linked to a decrease in hepcidin levels and transferring saturation (74). In a different study, 82 HD-CKD anemic subjects who had been treated with rhEPO doses were transitioned to daprodustat (0.5, 2, and 5 mg). The investigation showed that daprodustat 5 mg resulted in higher EPO plasma levels and Hgb levels compared to the control group. Moreover, there was a decrease in ferritin level and a 10% increase in total iron binding capacity (TIBC) (62).

A phase II, placebo-controlled trial with 97 Japanese HD-CKD anemic patients who had been on dialysis for more than 8 weeks and were previously receiving ESAs was conducted to evaluate the Hgb dose and safety of daprodustat. The study revealed that the

mean changes of Hgb were –0.28, –0.01, 0.54, and 0.97 g/dL in the 4, 6, 8, and 10 mg daprodustat groups, respectively; daprodustat 4–10 mg increased the Hgb level and EPO and had no changes on the VEGF levels (64).

A previous study conducted to study the safety of higher doses of daprodustat with 10 and 25 mg doses, in HD-CKD and NDD-CKD patients previously receiving rhEPO therapy, showed a significant dose-dependent increase in Hgb levels, and there was a decrease in the hepcidin level; however, 50% of the subjects withdrew from the 25-mg dose after 2 weeks due to a significant increase in Hgb levels more than 1 g/dL (56). These results were consistent with the findings of Akizawa et al. (64), who studied Japanese HD-CKD patients; daprodustat 8 and 10 mg daily significantly increased Hgb levels after 4 weeks of treatment.

Coyne et al. (75) conducted a three-times weekly dose of daprodustat versus epoetin alfa therapy, involving 407 HD-CKD patients switched from ESA treatment. The study aimed to compare the efficacy of daprodustat and epoetin alfa therapies in terms of their impact on Hgb levels. The participants received a three-times weekly dose of either daprodustat or epoetin alfa. The baseline Hgb levels ranged from 8 to 11.5 g/dL. The results indicated that daprodustat was non-inferior to epoetin alfa in terms of the mean change in Hgb levels. The model-adjusted mean treatment difference between daprodustat and epoetin alfa was –0.05, with a 95% confidence interval of –0.21 to 0.10. The mean Hgb values at the end of the study were 10.45 g/dL for daprodustat and 10.51 g/dL for epoetin alfa.

Most of these trials are consistent regarding increasing the level of Hgb and the production of EPO associated with decreasing the hepcidin and ferritin levels. However, long-term studies are required to assess the long-term safety of daprodustat in low or higher doses (refer to Table 2).

### 3.2 Daprodustat in non-dialysis chronic kidney disease patients

Holdstock and colleagues (62) conducted a randomized control trial to study the safety and efficacy of daprodustat in 73 participants with NDD-CKD stages 3–5. These patients had not been treated with rhEPO therapy for the past 7 weeks and were enrolled and received oral doses of 0.5, 2, and 5 mg of daprodustat versus a control group. The treatment with daprodustat 5 mg showed a significant improvement in Hgb levels after 4 weeks of treatment with an estimated increase of 1.01 g/dL when compared to the control group which showed a decrease in Hgb levels of –0.15 g/dL. Moreover, other indicators such as ferritin and hepcidin significantly decreased, and the TIBC improved in the daprodustat 5 mg group, which means that treatment with daprodustat is dose-dependent. In addition, treatment with daprodustat led to a significant decrease in the level of total cholesterol, high-density lipoproteins (–15.6%), and low-density lipoproteins (–13.9%).

In a phase 3 trial conducted by Ajay K et al. (76), a total of 3,872 NDD-CKD participants were randomly assigned to daprodustat or darbepoetin alfa. The purpose of this investigation was to evaluate

TABLE 2 Previously conducted trials on daprodustat in DD-CKD and NDD-CKD patients.

Study	No. of patients	Trial type	Population	Duration	Findings
Meadowcroft et al. (74)	216	Open-label, randomized controlled study	HD-CKD	24 weeks	Daprodustat had dose-dependent changes in Hgb over the first 4 weeks after switching from a stable dose of rhEPO and maintained Hgb target levels after 24 weeks.
Holdstock et al. (62)	82	Randomized control study	HD-CKD	4 weeks	Increases in the EPO plasma level and Hgb level in daprodustat 5 mg compared to the control group. There were a decrease in the ferritin level and an increase in TIBC by approximately 10%.
Akiwaza et al. (64)	97	Double-blind, placebo-controlled study	HD-CKD	4 weeks	Daprodustat 4–10 mg once daily produced a dose-dependent increase in Hgb relative to placebo in HD subjects and had no changes on the VEGF levels.
Coyne et al. (75)	407	Double-blind randomized non-inferiority study	HD-CKD	52 weeks	Daprodustat treatment was non-inferior to epoetin alfa in Hgb response and was generally well tolerated.
Brigandi et al. (56)	107	Randomized trial	HD-CKD and NDD-CKD	28 days	Daprodustat induced an effective EPO response and stimulated non-EPO mechanisms for erythropoiesis in anemic NDD-CKD and HD-CKD.
Holdstock et al. (62)	73	Randomized control study	NDD-CKD	4 weeks	The treatment with daprodustat 5 mg showed a significant improvement in Hgb levels after 4 weeks of treatment with an estimated increase of 1.01 g/dL when compared to the control group, which showed a decrease in Hgb levels of -0.15 g/dL, and other indicators such as ferritin and hepcidin significantly decreased. The TIBC improved in the daprodustat 5 mg group.
Ajay K et al. (76)	3872	Randomized open-label phase 3 study	NDD-CKD	28–52 weeks	Daprodustat was non-inferior to darbepoetin alfa in terms of changes in the Hgb level from baseline; these results were also associated with a decrease in the hepcidin and transferrin levels, and the TIBC significantly improved in the daprodustat group compared to darbepoetin.
Richard A et al. (56)	107	Multicenter single-blind randomized placebo-controlled parallel-group study	HD-CKD and NDD-CKD	28 days	Treatment with daprodustat showed a dose-dependent increase in EPO and Hgb levels. The mean change of Hgb increased by 1.0 g/dL in CKD stages 3–5 and >0.5 g/dL in CKD-5D. These results were also associated with a decrease in hepcidin levels and an increase in the TIBC.

HD-CKD, hemodialysis chronic kidney disease; Hgb, hemoglobin; rhEPO, recombinant human erythropoietin; EPO, erythropoietin; TIBC, total iron binding capacity; NDD-CKD, non-dialysis-dependent CKD.

the efficacy and safety of daprodustat. The results showed that the mean difference in Hgb levels between the initial measurement and the 28–52-week period was changed to 0.74 g/dL in the daprodustat group, whereas it was 0.66 g/dL in the darbepoetin alfa group. The 95% confidence interval (CI) for this change ranged from 0.03 to 0.13. Daprodustat exhibited non-inferiority to darbepoetin alfa in terms of alterations in Hgb levels from baseline. Furthermore, these outcomes were accompanied by a decrease in hepcidin and transferrin levels. Moreover, the TIBC significantly improved in the daprodustat group compared to darbepoetin.

Richard et al. (56) conducted a single-blind randomized control study, involving 107 (NDD-CKD, *n* = 70; DD-CKD, *n* = 37) stage 3–5 anemic patients. Treatment with daprodustat showed a dose-dependent increase in the EPO and Hgb levels. The mean change of Hgb increased by 1.0 g/dL in CKD stages 3–5 and >0.5 g/dL in CKD-5D. These results were also associated with a decrease in hepcidin levels and an increase in the TIBC. In contrast, daprodustat induced an effective EPO response and improved the stimulation of non-EPO mechanisms for erythropoiesis in anemic NDD-CKD and DD-CKD patients.

The majority of these trials have consistent findings regarding improving the quality of life and the level of Hgb in anemic patients. Additionally, decreasing hepcidin and transferrin levels led to effective EPO responses. However, more trials are necessary to study the long-term safety of daprodustat (refer to Table 2).

### 4 Daprodustat and adverse reactions

So far, the recent phase III trials showed encouraging and positive results regarding the use of daprodustat, and it was well tolerated in both DD-CKD and NDD-CKD patients (77, 78). Nevertheless, there are several undesirable on-target biological effects of inhibiting PHDs, such as alterations in fat levels, glucose levels, metabolism processes, inflammation, cellular differentiation, and cell growth, which are controlled by HIF-1 and HIF-2 that regulate gene expression and EPO production (20). However, long-term trials and patient safety regarding the use of the HIP-PHI daprodustat still need to be carefully investigated. Some adverse reactions have been reported such as hypersensitivity and high

blood pressure. Nonetheless, the long-term cardiovascular and malignant events are yet to be discovered in the near future.

Long-term safety concerns associated with a particular treatment encompass several potential risks: a potential oncogenic risk, certain cardiovascular risks such as tendency to a thromboembolic disease and pulmonary arterial hypertension, the possibility of metabolic changes and acceleration and formation of new blood vessels (angiogenesis) that could expedite the progression of diabetic retinopathy, and the potential harmful effects on the advancement of renal cysts and CKD.

Numerous unfavorable reactions to systemic HIF-PHI administration have been projected based on animal genetic studies or clinical observations of individuals with genetic defects that cause the HIF pathway to be activated, such as Chuvash polycythemia, which is brought on by particular non-tumorigenic mutations in the VHL gene (79–81). Clinical predictions, however, are challenging to derive from these genetic circumstances since HIF-PHI treatment induces restricted low-level bursts of reversible HIF- $\alpha$  stabilization and HIF target gene activation, rather than sustained and irreversible HIF activation.

The undesirable HIF responses in patients with CKD are influenced by the extent, duration, and distribution of cellular HIF stabilization, and these factors are determined by pharmacokinetics and the dosing of PHIs. An example of this can be seen in healthy individuals who received relatively high doses of daprodustat (50–100 mg). Significant increases in plasma VEGF levels were noted (57). However, lower doses of daprodustat, sufficient to maintain Hgb levels in patients with CKD, did not show any observed effects. On the other hand, higher doses of daprodustat (50–100 mg) were associated with increases in blood glucose levels, although these increases were not statistically significant, in NDD-CKD patients. Therefore, it can be concluded that HIF-PHI therapy may produce favorable pro-erythropoietic effects at doses that are not adequate to induce a wider range of HIF responses in CKD patients (56).

Among the numerous eye diseases that can affect individuals, diabetic retinopathy and macular degeneration are notable examples that have been linked to the involvement of VEGF in their pathogenesis. However, during randomized controlled trials involving HIF-PHIs, routine eye examinations were not regularly conducted, except for a small trial that specifically included blinded ophthalmologic visits at the beginning and end of the study (78). For 48 weeks, the utilization of daprodustat did not exhibit an elevated risk, as only a limited number of cases were observed in both treatment cohorts. Conversely, in the ASCEND-ND trial, a slightly higher occurrence of proliferative retinopathy, macular edema, or choroidal neovascularization was noted in the daprodustat group ( $n = 554$ ; 2.8%) in comparison to the darbepoetin alfa group ( $n = 546$ ; 2.4%; HR = 1.22; 95% CI, 0.83 to 1.81) (82).

During the 52-week therapy period of HD patients with anemia due to CKD who were administered ESAs, the most frequently observed treatment-emergent adverse events (with an incidence of 10% or higher) with daprodustat or darbepoetin alfa were nasopharyngitis, diarrhea, shunt stenosis, contusion, and vomiting (78). The majority of these adverse events were of mild or moderate

severity, and no deaths were recorded during the study. Additionally, the occurrence of ocular adverse events, including proliferative retinopathy, macular edema, and choroidal neovascularization, was similar between the two treatment groups.

Among the peritoneal dialysis patients who were diagnosed with anemia caused by CKD, a study revealed that 14% (8 out of 56) of them experienced treatment-related adverse events associated with daprodustat. These adverse events encompassed various symptoms, including nausea, which affected 4% (2 out of 56) of the patients. Furthermore, other adverse events such as diarrhea, cough, pulmonary embolism, pulmonary hypertension, retinal hemorrhage, liver function abnormality, decreased Hgb, acne-like dermatitis, and deep vein thrombosis were each reported by 2% (1 out of 56) of the patients (83). On the other hand, the administration of daprodustat to NDD-CKD patients with anemia resulted in treatment-related adverse events in 6% (9/149) of the patients. These adverse events encompassed various conditions such as elevated Hgb levels, increased blood pressure, and elevated levels of eosinophils, along with hypertension, abdominal distension, epigastric pain, gastroesophageal reflux disease, retinal hemorrhage, and cerebral infarction. It is noteworthy that the incidence of each of these adverse events was less than 1% (1/149). Due to the uncertain role of HIF-PHIs to treat anemia in patients with CKD who are not on dialysis, the safety of these medications in this type of population has not been fully established.

Morbidity and mortality in CKD patients are considerably linked to vascular calcification (VC), a process that is actively regulated—how it involves the transdifferentiation of vascular smooth muscle cells (VSMCs) into osteocyte- or chondrocyte-like cell types. In both normoxic and hypoxic conditions, the HIF-1 pathway mediates the cellular and systemic responses to hypoxia. Recent research demonstrated that activation of the HIF-1 does promote the transdifferentiation of VSMCs into osteogenic cells via upregulation of osteo- and chondrogenic genes. Furthermore, inhibition of the HIF-1 pathway effectively blunts the osteochondrogenic differentiation of VSMCs. The osteogenic transdifferentiation and calcification of VSMCs that are induced by elevated phosphate concentrations are significantly magnified by hypoxia. HIF-1 is vital for VSMC calcification due to high phosphate levels. PHD enzymes initiate the oxygen-dependent degradation of HIF-1. Daprodustat has been seen to increase VC in VSMCs under high phosphate concentrations due to the stabilization of HIF-1 $\alpha$  and activation of the HIF-1 pathway. However, the potential effect of PHD inhibitors on vascular calcification when used for CKD-related anemia treatment remains to be explored further. In their research, Tóth et al. (84) have explored how daprodustat can alleviate the VC elicited through high phosphate levels in primary human aortic VSMCs, mouse aorta rings, and a murine model of CKD induced by adenine and high phosphate. The study suggested that daprodustat not only stabilized HIF-1 $\alpha$  and HIF-2 $\alpha$  but also activated the HIF-1 pathway in VSMCs. Notably, daprodustat treatment further exacerbated phosphate-induced calcification in cultured VSMCs and mouse aorta rings. Daprodustat orally administered to CKD mice effectively corrected anemia; however, this increased the VC of



the aortic wall. The effects of daprodustat on VSMC calcification were ameliorated when HIF-1 transcriptional activity was inhibited by chetomin or HIF-1 $\alpha$  silencing.

The results obtained from preclinical *in-vitro* and *in-vivo* studies indicated that hypoxia activates VC primarily through the HIF-1 $\alpha$  pathway. However, it is unclear at present whether using PHD inhibitors to address anemia in CKD patients can increase the risk of developing and advancing VC. These are topics that we need to investigate further in future studies.

## 5 Conclusions

Daprodustat, a potent blocker of PHD enzymes, has the potential to improve the production of red blood cells in advanced CKD patients. The impacts of daprodustat on cells may vary from other HIF-PHIs; it is anticipated that these distinctions may also be noticeable in their non-red blood cell functions, which are still not fully understood in CKD patients. So far, data and literature indicate that daprodustat could be an effective option for managing anemia in dialysis CKD patients. Moreover, daprodustat has also revealed dose-dependent mechanisms for erythropoietin and non-erythropoietin responses, effectively boosting and maintaining hemoglobin levels. Notably, daprodustat did not lead to significant increases in VEGF compared to placebo groups, suggesting that the control of VEGF by EPO might not be affected by HIF-PHIs. Common side effects such as nausea and dyspepsia were generally well tolerated and mostly mild. However, more extensive trials are needed to examine further the effects of daprodustat.

## Author contributions

YW: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. LJ: Investigation, Writing – review & editing. SA: Writing – review & editing. DS: Funding acquisition, Investigation, Project administration, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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