Frontiers in Bioscience Landmark

*Front. Biosci. (Landmark Ed)* **2026**; 31(4): 47718
https://doi.org/10.31083/FBL47718

*Review*

# Potential Application of HIF-PH Inhibitors to Treat Kidney Diseases

Yuichiro Izumi[1], Yukiko Yasuoka[2], Masayoshi Nanami[3], Katsumasa Kawahara[2], Hiroshi Nonoguchi[4,*]

[1]Department of Nephrology, Kumamoto University Graduate School of Medical Sciences, 860-8556 Kumamoto, Kumamoto, Japan
[2]Department of Physiology, Kitasato University School of Medicine, 252-0374 Sagamihara, Kanagawa, Japan
[3]Department of Cardiovascular and Renal Medicine, Hyogo Medical University, 663-8501 Nishinomiya, Hyogo, Japan
[4]Nephrology, Internal Medicine, Sagamihara Red-Cross Hospital, 252-0157 Sagamihara, Kanagawa, Japan
*Correspondence: nono@insti.kitasato-u.ac.jp (Hiroshi Nonoguchi)
Academic Editor: Guoping Zheng
Submitted: 27 October 2025 Revised: 17 December 2025 Accepted: 31 December 2025 Published: 21 April 2026

**Abstract**

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors have recently been approved for clinical use in the treatment of renal anemia. HIF-PH inhibitors were developed following studies investigating the role of HIFs and their molecular mechanisms. Unlike erythropoiesis-stimulating agents, these orally administered agents improve renal anemia in patients with chronic kidney disease (CKD) and chronic inflammation. HIF-PH inhibitors improve renal anemia by stabilizing HIF-2$\alpha$, which increases erythropoietin production. They also improve iron metabolism by suppressing hepcidin and inducing the expression of iron transport-related genes. The renoprotective effects of HIF-PH inhibitors are controversial, owing to the opposing effects of hypoxia-inducible factor 1-alpha (HIF-1$\alpha$) and hypoxia-inducible factor 2-alpha (HIF-2$\alpha$) on kidney injury. They induce the expression of both HIF-1$\alpha$ and HIF-2$\alpha$. HIF-2$\alpha$ plays a key role in erythropoietin production and mitigates CKD. Although HIF-1$\alpha$ contributes to cell survival under hypoxic conditions, its overexpression is suspected to exacerbate kidney injury in CKD. This review summarizes the development of HIF and HIF-PH, from their discovery to the elucidation of their regulatory mechanisms and the development of HIF-PH inhibitors. We reviewed basic research and recently published clinical studies investigating the effects of HIF-PH inhibitors on renal injury, focusing on their clinical use in treating renal injury rather than renal anemia. We discuss the possible benefits of HIF-PH inhibitors used clinically for acute and chronic kidney injury, especially in the advanced stages of CKD.

**Keywords:** HIF-PH inhibitors; chronic kidney disease; acute kidney injury; diabetic kidney disease; renal anemia

## 1. Introduction

It has been 6 years since hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors were approved for the treatment of renal anemia in Japan. Erythropoiesis-stimulating agents (ESAs) is used for the treatment of renal anemia in patients with chronic kidney disease (CKD). Given that the production of erythropoietin decreases as CKD progresses, patients with CKD exhibit anemia. Endogenous erythropoietin is produced by HIF-2$\alpha$, which is a member of the HIF family. The HIF family comprises three $\alpha$-subunits (HIF-1$\alpha$, HIF-2$\alpha$, and HIF-3$\alpha$) and one $\beta$-subunit (HIF-1$\beta$) [1]. Although HIF-2$\alpha$ is mainly expressed in the kidney, liver, and vascular endothelial cells under basal conditions, HIF-1$\alpha$ and HIF-3$\alpha$ are broadly expressed in many organs, including the kidney [2,3]. The roles of HIF-1$\alpha$ and HIF-2$\alpha$ in the kidney are well investigated, whereas the role of HIF-3$\alpha$ remains largely unknown. HIF-3$\alpha$ has several variants and seems to modulate the functions of HIF-1$\alpha$ and HIF-2$\alpha$ [4,5]. In the kidney, HIF-1$\alpha$ is mainly expressed in glomerular epithelial cells, renal tubules, and papillary interstitial cells, whereas HIF-2$\alpha$ is mainly expressed in endothelial cells and interstitial fibroblast cells. HIF-1$\alpha$ promotes glycolysis, angiogenesis, and the optimization of oxygen delivery. Given that HIF-1$\alpha$ induces vascular endothelial growth factor (VEGF), HIF-PH inhibitor theoretically induces malignant tumor, diabetic retinopathy, and progression of polycystic kidney disease [1,6,7]. The activation of HIF-1$\alpha$ worsens renal fibrosis in CKD while improving acute kidney injury (AKI). The activation of HIF-2$\alpha$ improves chronic kidney injury. Given that HIF-PH inhibitors induce both expressions of HIF-1$\alpha$ and HIF-2$\alpha$, the effects on kidney injury are controversial. In our review, we first reviewed papers on the mechanisms of HIF-dependent hematopoiesis, the history of the development of HIF-PH inhibitors, and their current clinical application in the treatment of renal anemia. We examined basic research studies investigating the effects of HIF-PH inhibitors on AKI, CKD, and diabetic kidney disease models, which involve the activation of HIF-1$\alpha$ and HIF-2$\alpha$. We also reviewed recent studies evaluating the effect of HIF-PH inhibitors for efficacy and safety on patients with renal anemia. Finally, we discussed their potential clinical applications in the treatment for CKD progression.

## 2. Literature Review

### *2.1 History of HIF-Dependent Hematopoiesis From Elucidation of Its Mechanism to the Development of HIF-PH Inhibitors*

HIF-1$\alpha$ was first discovered by Semenza *et al*. [8,9], who in their study identified a transcription factor that binds to the enhancer region of the erythropoietin gene in response to hypoxic conditions. They named this factor HIF-1 and later discovered that it was composed of HIF-1$\alpha$ and HIF-1$\beta$ [10]. HIF-2$\alpha$ was discovered by Tian *et al*. [11]. By cloning and characterization, they found that HIF-2$\alpha$ shares 48% sequence identity with HIF-1$\alpha$ and dimerizes with HIF-1$\beta$ to activate the transcription of the erythropoietin gene [11]. Although both HIF-1$\alpha$ and HIF-2$\alpha$ bind to the hypoxia-responsive element of the erythropoietin gene, HIF-2$\alpha$ primarily regulates erythropoietin transcription in adults owing to differences in cell specificity and target genes between HIF-1$\alpha$ and HIF-2$\alpha$ [12,13].

Several research groups contributed to the discovery of HIF degeneration through the von Hippel-Lindau tumor suppressor protein (pVHL). Kaelin Jr.'s group discovered that various hypoxia-inducible mRNAs were insensitive to oxygen and were overexpressed in renal cancer cell lines lacking functional pVHL [14]. Concurrently, Salceda and Caro [15] reported that HIF-1$\alpha$ undergoes rapid ubiquitination and subsequent proteasomal degradation under normoxic conditions. Ratcliffe's group demonstrated that cells lacking pVHL did not target HIF-1$\alpha$ for oxygen-dependent proteolysis [16]. Kaelin's group [17] revealed the mechanism of ubiquitination of HIF-1$\alpha$ by pVHL. pVHL-elongin B/C-CUL2 complex binds directly to the oxygen-dependent degradation domain of HIF-1$\alpha$, resulting in its polyubiquitination [17]. They further reported that pVHL binds to HIF when a conserved proline residue in HIF is hydroxylated, which requires molecular oxygen and ferrous ion [18]. Studies by Kaelin's group and Ratcliffe's group finally revealed that hypoxia sensing and pVHL-dependent degradation of HIFs are primarily regulated by HIF-PH [19,20].

William G. Kaelin Jr., Peter J. Ratcliffe, and Greg L. Semenza were awarded the Albert Lasker Basic Medical Research Award in 2016 and were subsequently awarded the Nobel Prize in 2019 for their contributions to the discovery of HIF and pVHL-mediated oxygen-sensing regulation of HIF [21,22]. The first orally active HIF-PH inhibitor, roxadustat, was developed by FibroGen [23,24] and was approved in China in 2018 for the treatment of renal anemia in patients with dialysis-dependent CKD [25]. There are five HIF-PH inhibitors currently approved for the treatment of renal anemia in patients with CKD: roxadustat, daprodustat, vadadustat, enarodustat, and molidustat [26–29].

### *2.2 Current Clinical Application of ESAs and HIF-PH Inhibitors in the Treatment of Renal Anemia*

Both ESAs and HIF-PH inhibitors are currently used for the treatment of renal anemia. ESAs are synthesized from human endogenous erythropoietin and possess additional glycosylation or polyethylene glycol residue to extend their half-life, allowing them to remain in the body and exert a hematopoietic effect for several days [30–32]. Consequently, ESAs are administered to patients every 2 to 4 weeks. Although their half-life is extended, they are degraded in approximately 1 week, which may cause a wide variation in hemoglobin levels between pre- and post-injections. HIF expression is induced under hypoxic conditions and further induces the transcription of hypoxia-inducible genes, including erythropoietin and iron metabolism-related genes. Once hypoxic conditions are corrected to normoxic conditions, HIFs are hydroxylated by HIF-PHs and promptly degraded by the ubiquitin-proteasome pathway. HIF-PH inhibitors stabilize HIFs regardless of the oxygen level by inhibiting the hydroxylation of HIF-PHs, which maintains the transcription of hypoxia-inducible genes. In contrast to ESAs, they are administered to patients every day or thrice a week, which induces stable erythropoietin production at physiological levels. Given that HIF-PH inhibitors promote iron use by regulating iron metabolism-related genes such as hepcidin, they improve renal anemia even in patients with chronic inflammation [32]. They are better for patients because they are oral medications.

### *2.3 Renoprotective Effects of HIF-PH Inhibitors on AKI*

Several studies have demonstrated the protection of renal tubules under AKI by HIF-PH inhibitors. An overview of the studies introduced in this section is shown in Table 1 (Ref. [33–38]). Ito *et al*. [33] demonstrated that enarodustat offers a protective effect against AKI using a rat model of renal ischemia–reperfusion injury (IRI). Pretreatment with enarodustat reduced plasma creatinine 48 h after ischemia reperfusion, dependent on glycogenesis. Performing an *in vitro* experiment using proximal tubular-derived cell lines, they demonstrated that enarodustat induced the expression of HIF-1$\alpha$ via inhibition of prolyl hydroxylase domain-containing protein (PHD) 2, one of HIF-PHs, leading to an increase in glycogenesis, suppression of reactive oxygen species (ROS), and improvement of cell viability in cells under the deprivation of glucose and oxygen.

Yang *et al*. [34] reported the involvement of absent in melanoma 2 (AIM2) activation and 5'-Nucreotidase Ecto (CD73) expression in the renoprotective effect of roxadustat using an IRI mouse model. They confirmed that the expressions of the AIM2 inflammasome complex and CD73 were induced in the proximal tubular cells of the kidneys of patients with AKI and post-transplant kidneys. In IRI mice, treatment with roxadustat enhanced the expression of HIF-1$\alpha$ and CD73 in the proximal tubular cells and suppressed

**Table 1. An overview of the studies investigated renoprotective effect of HIF-PH inhibitors in AKI.**

| Treatment or genetic modification | Experimental model | Results/Mechanisms | Role of HIF-1$\alpha$ | Role of HIF-2$\alpha$ | Ref. No. |
|---|---|---|---|---|---|
| Enarodustat | IRI | Enarodustat improved IRI. Enarodustat increased glycogenesis and suppressed ROS via HIF-1$\alpha$ in proximal tubular cells. | Protective | Not mentioned | [33] |
| Enarodustat | IRI | Roxadustat enhanced the expression of HIF-1$\alpha$ and 5'-Nucreotidase Ecto (CD73) in the proximal tubular cells and suppressed the expression of AIM2 complex, resulting in the improvement of renal function and tissue injury. | Protective | Not mentioned | [34] |
| Roxadustat | IRI | Roxadustat induced erythropoietin in renal tubular cells and maintained the expression of nephron-specific genes after IRI, suggesting the prolonged renoprotective effects by inducing HIF-2$\alpha$ and erythropoietin in renal tubular cells. | Not mentioned | Protective | [35] |
| Endothelial cell-specific HIF-PH2 KO mice | IRI | The mice exerted protective effects against AKI by inhibiting the infiltration of macrophages and inflammation in the kidney. The renoprotective effect was attributed to the activation of HIF-1$\alpha$ alone. A humoral factor in the anti-inflammatory effects generated by endothelial HIF-PH2/HIF-1 signaling was implicated for renoprotective effects. | Protective | Irrelevant | [36] |
| Endothelial cell-specific HIF-2$\alpha$ KO mice | IRI or ureteral obstruction | Renal injury was exacerbated in the mice, which was reversed by blockade of VCAM1 and VLA4. | Irrelevant | Protective | [37] |
| GSK1002083A, an HIF-PH inhibitor | IRI | Renoprotective effect of an HIF-PH inhibitor was observed only when the kidney was pretreated with it. Treatment after IRI did not exert the renoprotective effect on the kidneys. | Generally protective, not distinguished | | [38] |

HIF-PH, hypoxia-inducible factor prolyl hydroxylase; AKI, acute kidney injury; KO, knockout; AIM2, absent in melanoma 2; IRI, ischemia–reperfusion injury; ROS, reactive oxygen species; VCAM1, vascular cell adhesion molecule-1; VLA4, very late antigen-4.

the expression of AIM2 complex, resulting in the improvement of renal function and tissue injury. Co-administration with a CD73 inhibitor abolished the effect of roxadustat on AIM2 complex expression and improved renal function and tissue injury.

Both the renoprotective and cardioprotective effects of HIF-PH inhibitors have been suggested. Deguchi *et al*. [39] reported the cardioprotective effects of a HIF-PH inhibitor. Pretreatment with roxadustat markedly reduced infarct size and suppressed plasma creatinine kinase activity in the mouse cardio-IRI model. The protective effect was accompanied by an increase in HIF-1$\alpha$ expression, suggesting that HIF-1$\alpha$ plays a key role in the protective effects of HIF-PH inhibitors against ischemic injury.

Both HIF-1$\alpha$ and HIF-2$\alpha$ could be involved in the improvement of AKI. We recently demonstrated that pretreatment with roxadustat improved renal function after renal IRI in Sprague–Dawley (SD) rats, which was accompanied by the production of erythropoietin in renal tubular cells [35]. The expression of nephron-specific genes after IRI was higher in rats pretreated with roxadustat than in rats pretreated with hypoxia, suggesting the protective effect of roxadustat on renal tubules. Pretreatment with roxadustat significantly maintained the increase in plasma erythropoietin levels and erythropoietin expression in the kidney during IRI, whereas the induction of erythropoietin by hypoxic preconditioning was transient before IRI. Immunohistochemical analysis revealed that roxadustat induced the expression of erythropoietin in the proximal and distal tubular cells but not in the interstitial cells of the kidney with IRI. It has been demonstrated that small amounts of HIF-2$\alpha$ are expressed in renal tubular cells and that its expression can be induced [40,41]. Therefore, we hypothesize that pretreatment with HIF-PH inhibitor contributes to prolonged renoprotective effects on AKI by inducing HIF-2$\alpha$ and erythropoietin expressions in renal tubules.

The involvement of hypoxia-inducible factor prolyl hydroxylase 2 (HIF-PH2; also called PHD2) in the renoprotective effects of endothelial cells has been suggested. Tamoxifen-induced endothelial cell-specific deficits in HIF-PH2 in adult mice exerted protective effects against AKI caused by bilateral renal IRI, in which the infiltration of macrophages and expression of inflammation-related genes were significantly inhibited in HIF-PH2 knockout (KO) mice [36]. The renoprotective effect was attributed to the activation of HIF-1$\alpha$ alone. Furthermore, the study implied that a humoral factor, such as vascular cell adhesion molecule-1 and interferon regulatory factor 1, generated by the activation of HIF-1$\alpha$ in extrarenal endothelial cells contributed to the renoprotective effects. The same study reported that in endothelial HIF-2$\alpha$ or HIF-1$\alpha$ KO mice, the loss of HIF-2$\alpha$ alone exacerbated AKI induced by IRI [37]. The loss of HIF-PH2 probably changes both activation of HIF-1$\alpha$ and HIF-2$\alpha$, which may alter the effects of HIF-1$\alpha$ and HIF-2$\alpha$ on renal injury in both studies. Together, these studies suggest that HIF-1$\alpha$ and HIF-2$\alpha$ act cooperatively rather than antagonistically to protect against AKI.

Collectively, the renoprotective effects of HIF-PH inhibitor in AKI are likely exerted in proximal tubular cells via activation of HIF-1$\alpha$, which induces glycogenesis, suppresses inflammation, and enhances erythropoietin production. HIF-PH inhibitor inhibits HIF-PH2 in renal tubular and extrarenal endothelial cells in AKI, leading to the protective effects on AKI through the activation of HIF-1$\alpha$ and HIF-2$\alpha$. The activations of HIF-1$\alpha$ and HIF-2$\alpha$ in extrarenal endothelial cells suppress the secretion of inflammation-inducible humoral factors, possibly contributing to the renoprotective effect against AKI.

Kapitsinou *et al*. [38] reported that the renoprotective effect of an HIF-PH inhibitor was observed only when the kidney was pretreated with an HIF-PH inhibitor. Treatment after ischemic reperfusion did not exert the renoprotective effect on the kidneys. Treatment with GSK1002083A, a structural analog of 2-oxoglutarate, at 48 and 6 h before 20 min of bilateral renal pedicle clamping significantly suppressed the increase in blood urea nitrogen levels. IRI-induced fibrosis and inflammation were significantly improved following treatment with an HIF-PH inhibitor 21 days after IRI [38]. Therefore, HIF-PH inhibitors may be useful for the prevention of AKI due to ischemia, sepsis, and post-transplant kidney injury. In particular, in case of kidney transplantation, the time when renal ischemia occurs is clear. We believe that the use of HIF-PH inhibitors for pretreatment of transplanted kidney before the transplantation is practical. A search of ClinicalTrials.gov (https://clinicaltrials.gov) revealed that there appear to be no clinical studies examining the protective effect of HIF-PH inhibitors on AKI. The clinical studies are warranted to clarify the benefit of HIF-PH inhibitors for AKI.

### *2.4 Renoprotective Effect of HIF-PH Inhibitors in CKD*

Treatment with HIF-PH inhibitors induces the expression of both HIF-1$\alpha$ and HIF-2$\alpha$, and opposing roles of these two factors in chronic renal fibrosis have been suggested. An overview of the studies introduced in this section is shown in Table 2 (Ref. [42–47]).

Higgins *et al*. [42] found that progression of renal fibrosis was HIF-1$\alpha$ dependent. They demonstrated that unilateral ureteral obstruction (UUO) caused hypoxia in renal tissue, which induced epithelial–mesenchymal transition (EMT) accompanied by the expression of HIF1$\alpha$, leading to renal fibrosis. An *in vitro* study revealed that the epithelial tubular cells derived from proximal tubular cell-specific HIF-1$\alpha$ KO mice did not exhibit EMT, consistent with the *in vivo* results that renal fibrosis and macrophage infiltration induced by UUO were mitigated in the HIF-1$\alpha$ KO mice. This suggests that HIF-1$\alpha$ in renal tubular cells could be a therapeutic target for renal fibrosis, although the

**Table 2. An overview of the studies investigated renoprotective effect of HIF-PH inhibitors in CKD.**

| Treatment or genetic modification | Experimental model | Results/Mechanisms | Role of HIF-1$\alpha$ | Role of HIF-2$\alpha$ | Ref. No. |
|---|---|---|---|---|---|
| Proximal tubular cell-specific HIF-1$\alpha$ KO mice | UUO | Renal fibrosis is caused by EMT, which is induced by the activation of HIF-1$\alpha$ in the proximal tubular cells in response to hypoxia in renal tissue. | Harmful | Not mentioned | [42] |
| Systemic HIF-1$\alpha$ and HIF-2$\alpha$ KO mice/Systemic Vhl tumor suppressor KO mice | UUO | Systemic KO and activation of HIFs exacerbated and attenuated renal fibrosis, respectively. The effects were partially due to activation of HIFs in myeloid cells, which regulates the infiltration of macrophages in the kidney. | Generally protective, not distinguished | | [43] |
| Renal epithelial cell-specific HIF-2$\alpha$ transgenic mice | Adenine-induced kidney injury | Activation of renal tubular HIF-2$\alpha$ aggravated and improved renal fibrosis at early stage and at late stage kidney injury, respectively. HIF-2$\alpha$ inhibited TGF-$\beta$1-induced expressions of fibronectin and $\alpha$-smooth muscle actin, confirming the renoprotective role of HIF-2$\alpha$ in renal tubular cells. | Not mentioned | Harmful at early stage and protective at late stage kidney injury | [44] |
| ICA/Roxiadustat | Adenine-induced chronic tubulointerstitial nephritis | Both ICA and Roxiadustat inhibited the progression of renal tubular damage and interstitial fibrosis by activating a regulatory, anti-inflammatory MNP phenotype. | Generally protective, not distinguished | | [45] |
| Endothelial cell-specific HIF-PH2 KO mice | Angiotensin II-induced renal fibrosis | Deficit of HIF-PH2 in endothelial cells inhibited angiotensin II-induced renal fibrosis owing to decreased expression of angiotensin II receptor type 1 with subsequent suppression of ROS production and TGF-$\beta$1 expression. | Generally protective, not distinguished | | [46] |
| L-mimosine, a HIF-PH inhibitor | Subtotal nephrectomy | Administration of L-mimosine at an advanced stage significantly improved renal function, renal fibrosis, and anemia, exacerbating them at the early stage and not having any effects at the end stage. | Harmful at early stage | Protective at advanced stage | [47] |

CKD, chronic kidney disease; ICA, Isoquinoline derivative 2-(1-chloro-4-hydroxyisoquinoline-3-carboxamido) acetate; EMT, epithelial-mesenchymal transition; HIFs, HIF-1$\alpha$ and HIF-2$\alpha$; MNP, mononuclear phagocytes; ROS, reactive oxygen species; TGF-$\beta$1, transforming growth factor-$\beta$1; UUO, unilateral ureteral obstruction.

**Table 3. An overview of the studies investigated renoprotective effect of HIF-PH inhibitors in diabetic kidney disease.**

| Treatment or genetic modification | Experimental model | Results/Mechanisms | Role of HIF-1$\alpha$ | Role of HIF-2$\alpha$ | Ref. No. |
|---|---|---|---|---|---|
| $CoCl_2$ | Streptozotocin-induced diabetes | Treatment with $CoCl_2$ reduced oxygen consumption and improved excessive GFR, proteinuria, and tubulointerstitial injury. The beneficial effects of $CoCl_2$ were related to reduced oxidative stress. | Generally protective, not distinguished | | [53] |
| Proximal tubular cell-specific conditional HIF-1$\alpha$ KO mice | Streptozotocin-induced diabetes | In HIF-1$\alpha$ KO mice, streptozotocin-induced diabetes exacerbated proteinuria and tubular injury due to increased ROS accumulation and apoptosis in the kidney. The study demonstrated that HIF-1$\alpha$ inhibited mitochondrial fragmentation, ROS production, mitochondrial membrane potential loss, and apoptosis under hypoxic ambiance by activating heme oxygenase-1, a target gene of HIF-1$\alpha$. | Protective | Not mentioned | [54] |
| Systemic HIF-1$\alpha$ KO mice | Streptozotocin-induced diabetes | HIF-1$\alpha$ KO mice exhibited exacerbation of streptozotocin-induced diabetic nephropathy. | Protective | Not mentioned | [55] |
| Systemic HIF-1$\alpha$ KO mice | Streptozotocin-induced diabetes | HIF-1$\alpha$ KO mice exhibited exacerbation of streptozotocin-induced diabetic nephropathy and hypertension. | Protective | Not mentioned | [56] |
| YC-1, an HIF-1$\alpha$ inhibitor | OVE26 mice, a type 1 diabetic animal model | The expression of HIF-1$\alpha$ was increased in the kidney of OVE26 mice. YC-1 improved diabetic nephropathy by reducing NADPH oxidase 4 protein expression and NADPH-dependent reactive oxygen species production through the inhibition of HIF-1$\alpha$-induced GLUT-1 expression. | Harmful | Not mentioned | [57] |
| Enarodustat | BTBR ob/ob mice, a type 2 diabetic animal model | Enarodustat improved albuminuria and foot process effacement by suppressing palmitate-induced CCL2/MCP-1 production via HIF-1$\alpha$, resulting in the suppression of macrophage infiltration. | Protective | Not mentioned | [58] |

BTBR, black and tan brachyury; GFR, glomerular filtration rate; CCL2/MCP1, C-C motif chemokine ligand 2/monocyte chemoattractant protein 1; GLUT-1, glucose transporter 1.

study has not explored the role of HIF-2$\alpha$, whose expression was induced by UUO as well as HIF-1$\alpha$.

Kobayashi *et al*. [43] examined the effect of global deletion or activation of HIF-1$\alpha$ and HIF-2$\alpha$ on renal fibrosis using transgenic mice. In conditional global deletion of HIFs in mice, renal fibrosis was exacerbated by UUO compared to control mice with UUO. In contrast, UUO-induced renal fibrosis was mitigated in mice with global activation of HIFs. Renal fibrosis exacerbated by the deletion of HIFs was dependent on macrophage infiltration into the kidneys. They further demonstrated that myeloid-specific deletion and activation of HIFs enhanced and attenuated the infiltration of macrophages in the kidney, respectively, although they did not affect renal fibrosis caused by UUO. This study suggested that HIF-1$\alpha$ and HIF-2$\alpha$ play key roles in renoprotective effect through the regulation of infiltration of macrophages and fibrosis in the kidney. This finding suggests that the activation of HIF-2$\alpha$, rather than the suppression of HIF-1$\alpha$, contributes to the renoprotective effect [43].

The expression of HIF-2$\alpha$ is localized mainly to glomerular mesangial cells, vascular smooth muscle cells, endothelial cells, and interstitial fibroblast cells in the kidney. A small amount of HIF-2$\alpha$ is expressed in glomerular and tubular epithelial cells [40]. The HIF-2$\alpha$ expression in renal tubular cells was inducible with aldosterone and vasopressin, accompanied by erythropoietin expression [41]. Renoprotective role of HIF-2$\alpha$ has been suggested by a study using transgenic mice, in which the expression of HIF-2$\alpha$ was conditionally enhanced in renal epithelial cells [44]. The study examined the effect of renal tubular cell-specific induction of HIF-2$\alpha$ at early-stage or at late-stage kidney injury caused by a 0.2% adenine diet. The induction of HIF-2$\alpha$ at early-stage kidney injury aggravated renal fibrosis by increasing the expression of type I collagen and fibronectin. In contrast, the induction of HIF-2$\alpha$ at late-stage kidney injury restored reduced renal vasculature and improved renal tissue hypoxia, resulting in the improvement of renal fibrosis. The study further demonstrated that the expression of HIF-2$\alpha$ was increased in microdissected renal tubulointerstitium of patients with early-stage immunoglobulin A (IgA) nephropathy, while the expression of HIF-2$\alpha$ was decreased in the subjects with progressed IgA nephropathy [44]. *In vitro* studies showed that the induction of HIF-2$\alpha$ in isolated renal tubular cells inhibited transforming growth factor-$\beta$1 (TGF-$\beta$1)-induced expressions of fibronectin and $\alpha$-smooth muscle actin, confirming the renoprotective role of HIF-2$\alpha$ in renal tubular cells [48]. These findings suggest a possible therapeutic target of HIF-2$\alpha$ for the treatment of late-stage patients with CKD. We demonstrated that treatment of rats with roxadustat stimulated erythropoietin production not only in interstitial cells but also in proximal tubular cells in the kidney, suggesting that HIF-PH inhibitors induce HIF-2$\alpha$ in proximal tubules [49]. These findings suggest that HIF-2$\alpha$ in renal tubular cells, as well as in interstitial cells, is inducible with HIF-PH inhibitor and contributes to the prevention of CKD progression.

Schley *et al*. [45] reported the renoprotective effect of an HIF-PH inhibitor on tubulointerstitial nephritis caused by an adenine-containing diet in mice. In the study, the effects of isoquinoline derivative 2-(1-chloro-4-hydroxyisoquinoline-3-carboxamido) acetate (ICA), an inhibitor for PHD enzymes, and roxadustat were examined. Both ICA and roxadustat inhibited the progression of renal tubular damage and interstitial fibrosis induced by adenine, accompanied by a reduced infiltration of mononuclear phagocytes. Notably, the renoprotective effects of ICA were independent of HIF-1$\alpha$ and HIF-2$\alpha$ in renal tubular and myeloid cells. This study suggests the broad effects of HIF-PH inhibitors, independent of HIFs in kidney epithelial cells.

The roles of HIF-PH2 in chronic kidney injury have been examined. Zhao *et al*. [46] demonstrated that a deficit of HIF-PH2 in endothelial cells inhibited angiotensin II-induced renal fibrosis owing to decreased expression of angiotensin II receptor type 1 with subsequent suppression of ROS production and TGF-$\beta$1 expression. In contrast, another study demonstrated that a congenital deficit of HIF-PH2 in endothelial cells caused renal fibrosis (over 15 months) in endothelial HIF-PH2 KO mice [50]. In the study, a deficit of HIF-PH2 in endothelial cells increased the expression of HIF-1$\alpha$ and HIF-2$\alpha$ in the kidney, which subsequently induced Notch3 and TGF-$\beta$1, resulting in remodeling of arterioles and fibrosis in the kidney. These results suggest that the inhibition of endothelial HIF-PH2 exerts renoprotective effects on CKD through the activation of HIF-1$\alpha$ and HIF-2$\alpha$ in the kidney, while HIF-PH2 is important for normal development of the kidney.

Previous studies suggest that the timing of HIF-PH inhibitor administration is important for exerting the renoprotective effects in CKD. Yu *et al*. [47,51] examined the effect of L-mimosine, a HIF-PH inhibitor, on kidney injury in rats subjected to subtotal nephrectomy. L-mimosine was administered during early, advanced, or end-stage kidney damage. The study demonstrated that the administration of L-mimosine at an advanced stage significantly improved renal function, renal fibrosis, and anemia, exacerbating them at the early stage and not having any effects at the end stage. The study further demonstrated that the renoprotective effect of L-mimosine at the advanced stage of kidney injury was accompanied by significantly increased expression of HIF-2$\alpha$ and erythropoietin. However, HIF-1$\alpha$ expression was induced only at the early stage, with HIF-2$\alpha$ and erythropoietin expressions occurring slightly at the end stage of kidney injury under the L-mimosine administration [47]. In the subtotal nephrectomy model, the expressions of HIF-1$\alpha$ and HIF-2$\alpha$ and their target genes were increased in the early stage, and returned to basal level in the advanced and end stages [51]. The same study suggested mechanisms of

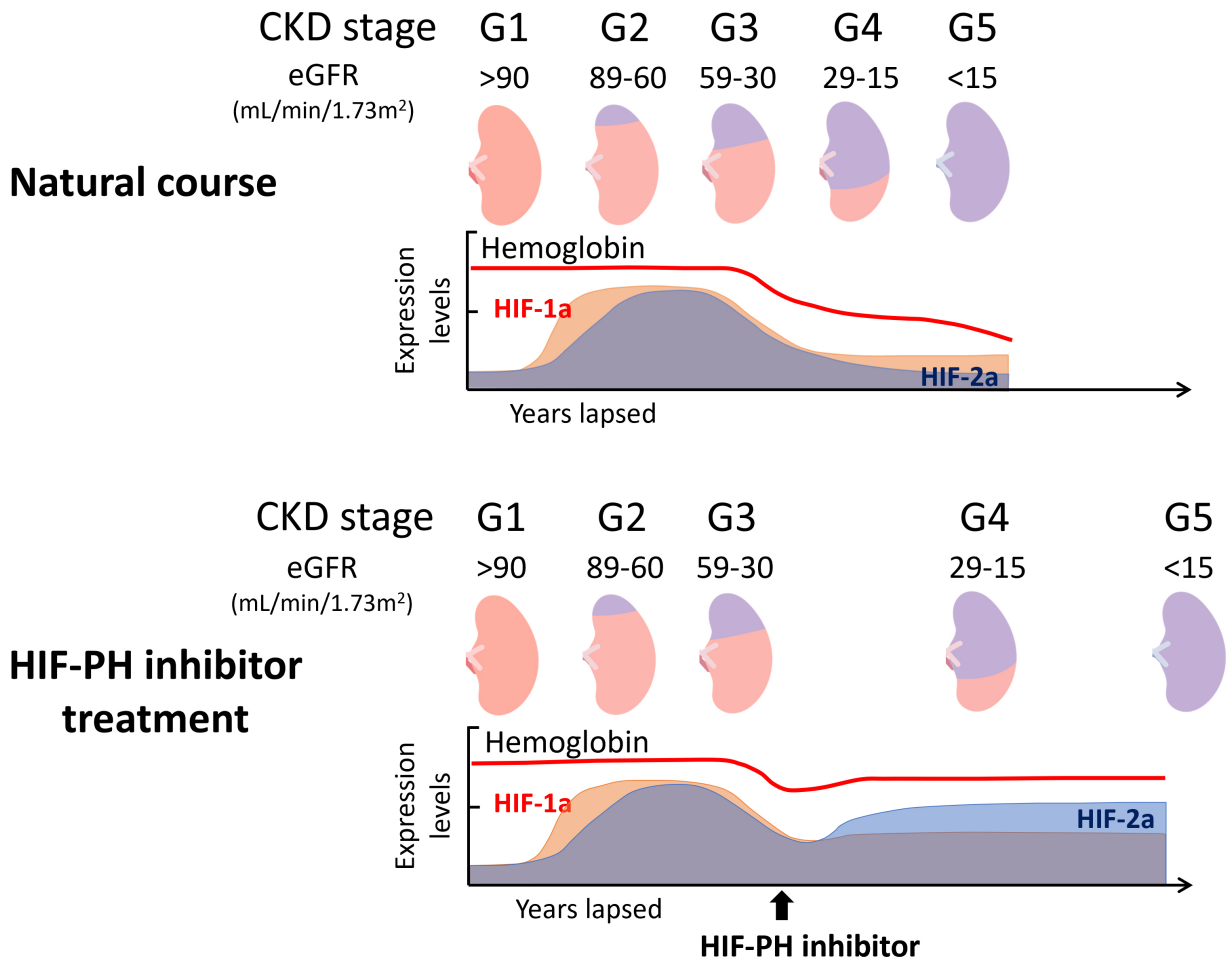


**Fig. 1. Schematic illustration of hemoglobin levels, HIF-1$\alpha$ and HIF-2$\alpha$ expression, and the effects of HIF-PH inhibitors during CKD progression.** Previous studies demonstrated that the expressions of HIF-1$\alpha$ and HIF-2$\alpha$ in the kidney were increased in the early stage, and returned to basal level in the advanced and end stages of CKD [51]. Activation of HIF-1$\alpha$ in renal tubules accelerated renal fibrosis by inducing EMT [42]. The activation of HIF-2$\alpha$ in renal tubules at early-stage kidney injury aggravated renal fibrosis by increasing the expression of type I collagen and fibronectin. In contrast, the induction of HIF-2$\alpha$ at late-stage kidney injury improved renal fibrosis [44]. Treatment with HIF-PH inhibitor at an advanced stage significantly improved renal function, renal fibrosis, and anemia, exacerbating them at the early stage and not having any effects at the end stage [47]. Treatment with HIF-PH inhibitors probably maintains the expression of HIF-2$\alpha$ alone in progressed CKD, leading to renoprotective effect against renal fibrosis. The broad effects of HIF-PH inhibitors (except on HIFs) could also be involved in renoprotective effect. As description of graphs, vertical axis indicates levels of HIF-1$\alpha$ and HIF-2$\alpha$ expression and hemoglobin. Horizontal axis indicates years lapsed. Hemoglobin level is shown with red line. Expressions of HIF-1$\alpha$ and HIF-2$\alpha$ are shown in cumulative graph with orange and blue, respectively.

renoprotective effect by HIF-PH inhibitors, which involve miRNAs. They demonstrated that the expression of miR-29c decreased in subtotal nephrectomized kidneys, whereas treatment with L-mimosine restored its expression. miR-29c targets extracellular matrix genes and reduces their expression. *In vitro* study revealed that the expression of miR-29c was increased by cobalt chloride ($CoCl_2$) and decreased by knockdown of HIF-1$\alpha$ or HIF-2$\alpha$ [52].

These findings suggest the possible use of HIF-PH inhibitors in the treatment of patients with progressive CKD. Treatment with HIF-PH inhibitors probably maintains the expression of HIF-2$\alpha$ alone in progressed CKD, leading to renoprotective effect against renal fibrosis. The broad effects of HIF-PH inhibitors (except on HIFs) could also be involved in renoprotective effect. The appearance of renal anemia, which indicates erythropoietin deficiency due to lack of HIF-2$\alpha$ and advanced progression of CKD, would represent an appropriate timing to start HIF-PH inhibitor, not only for the treatment of anemia but also for the treatment of renal fibrosis. Administration of HIF-PH inhibitors restores HIF-2$\alpha$ expression in renal tissue and contributes to renoprotective effect. In any case, treatment with HIF-PH inhibitor in the early stage of CKD is not appropriate as it may induce increased erythropoiesis and subsequent

risk of polycythemia, as well as inappropriate induction of HIF-1$\alpha$ (Fig. 1, Ref. [42,44,47,51]).

### *2.5 Renoprotective Effect of HIF-PH Inhibitors on Diabetic Kidney Disease*

The pathogenesis of diabetic kidney disease is unique and induced by vascular damage due to hyperglycemia. Once proteinuria occurs, disease progression is rapid and unavoidable. The establishment of a treatment method before the progression to renal fibrosis is necessary. An overview of the studies introduced in this section is shown in Table 3 (Ref. [53–58]). Nordquist *et al*. [53] examined the effects of $CoCl_2$ on kidney injury in rats with streptozotocin-induced diabetes. In diabetic rats, oxygen consumption was significantly increased, accompanied by excessive glomerular filtration rate (GFR), proteinuria, and tubulointerstitial injury. Treatment with $CoCl_2$ reduced oxygen consumption and improved excessive GFR, proteinuria, and tubulointerstitial injury, suggesting the protective effect of HIFs on diabetic kidney injury. The beneficial effects of $CoCl_2$ were related to reduced oxidative stress [53]. In proximal tubule-specific conditional HIF-1$\alpha$ KO mice, diabetes induced by streptozotocin exacerbated proteinuria and tubular injury due to increased ROS accumulation and apoptosis in the kidney. An *in vitro* study demonstrated that HIF-1$\alpha$ inhibited mitochondrial fragmentation, ROS production, mitochondrial membrane potential loss, and apoptosis under hypoxic ambiance by activating heme oxygenase-1, a target gene of HIF-1$\alpha$ [54]. Systemic HIF-1$\alpha$-deficient mice exhibited exacerbation of streptozotocin-induced diabetic nephropathy [55,56]. Notably, the above studies were conducted on streptozotocin-induced diabetic nephropathy, which could be considered as subacute kidney injury rather than chronic kidney injury caused by diabetes.

The opposite effects of HIF-1$\alpha$ on diabetic kidney injury have been suggested. Nayak *et al*. [57] reported the renoprotective effect of HIF-1 inhibitor on diabetic nephropathy. OVE26 mice, a type 1 diabetic animal model, were treated with 3-(5′-hydroxymethyl-2′-furyl)-1-benzyl indazole (YC-1), an HIF-1$\alpha$ inhibitor. The expression of HIF-1$\alpha$ was increased in the kidney of OVE26 mice. Treatment with YC-1 reduced glomerular hypertrophy, mesangial matrix expansion, extracellular matrix accumulation, and urinary albumin excretion, as well as NADPH oxidase 4 protein expression and NADPH-dependent reactive oxygen species production in OVE26 mice, while their blood glucose levels remained unchanged. The study suggests the renoprotective effect of YC-1 through the inhibition of HIF-1$\alpha$-induced glucose transporter 1 (GLUT-1) expression. It should be noted that YC-1 induces cGMP production in a nitric oxide-independent manner, promoting vasodilation and antiplatelet effect, as well as HIF-1$\alpha$ inhibition.

Sugahara *et al*. [58] demonstrated the renoprotective effect of an HIF-PH inhibitor in a diabetic kidney disease model. Diabetic black and tan brachyury (BTBR) ob/ob mice were treated with enarodustat or its vehicle between 4 and 22 weeks of age. BTBR ob/ob mice exhibited albuminuria with foot process effacement, glomerular hypertrophy, mesangial expansion, and interstitial fibrosis. Treatment with enarodustat improved albuminuria and foot process effacement, but did not alter glomerular hypertrophy and interstitial fibrosis. Treatment with enarodustat decreased the expression of C-C motif chemokine ligand 2/monocyte chemoattractant protein 1 (CCL2/MCP1) in the glomeruli of BTBR ob/ob mice, resulting in the suppression of macrophage infiltration. An *in vitro* study revealed that enarodustat suppressed palmitate-induced CCL2/MCP-1 production via HIF-1$\alpha$. Treatment with enarodustat improved hyperglycemia and insulin sensitivity in BTBR ob/ob mice. It also decreased cholesterol levels and increased adiponectin levels. The study concluded that HIF-PH inhibitors may prevent metabolic disorders and have potential renoprotective effects [58].

Generally, few studies have examined the effects of HIF-PH inhibitors in diabetic kidney disease models. Although they may be effective in diabetic kidney disease, activation of HIF-1$\alpha$ may be harmful depending on the stage of disease progression.

### *2.6 HIF-PH Inhibitors in Combination Therapy*

Given that HIF-PH inhibitors are involved in the regulation of various pathways, the effects of combining them with other drugs on CKD should be considered. Sung *et al*. [59] examined the combination therapy of roxadustat and dapagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, for cardiorenal syndrome-induced damage in rats. SD rats were subjected to remnant kidney-induced chronic kidney injury, followed by acute myocardial infarction. The rats were treated with either roxadustat or dapagliflozin, or both, for a month. Combination therapy significantly improved cardiorenal syndrome—both cardiac and renal functions improved by suppressing tissue fibrosis. The study suggested that the combination therapy enhanced HIF-1$\alpha$ production by activating the Nrf2/ARE pathway and stabilizing HIF-1$\alpha$, although the involvement of HIF-2$\alpha$ in the cardiorenal protection has not been examined [59]. A previous study suggests the involvement of HIF-1$\alpha$ suppression in the renoprotective effect of SGLT2 inhibitors for diabetic kidney injury [60]. Treatment of diabetic db/db mice with luseogliflozin decreased the expression of cortical tubular HIF-1$\alpha$, accompanied by attenuation of tubular injury. An *in vitro* study demonstrated that the treatment with luseogliflozin reduced oxygen consumption under hypoxic conditions, resulting in suppression of HIF-1$\alpha$ expression in human renal proximal tubular epithelial cells [60].

The involvement of Zinc (Zn) deficiency in CKD progression and the renoprotective effects of Zn supplementation have been suggested [61]. Zhang *et al*. [62] reported that treatment with Zn inhibited tubular EMT and

attenuated renal tubulointerstitial fibrosis by downregulation of HIF-1$\alpha$ in the kidneys of diabetic streptozotocin-treated mice, which was accompanied by improved hyperglycemia and proteinuria. *In vitro* experiments showed that the supplementation of Zn suppressed the expression of HIF-1$\alpha$ protein and phosphoinositide 3-kinase signaling-related proteins induced by high glucose and hypoxia [62].

The Rho-kinase inhibitor, fasudil, used to treat cerebral vasospasm after subarachnoid hemorrhage, is expected to be approved for other diseases such as pulmonary hypertension and heart failure [63]. Matoba *et al*. [64] demonstrated that fasudil improved kidney injury in db/db mice through the inhibition of HIF-1$\alpha$ expression by increased expression of HIF-PH2.

HIFs are involved in many signaling pathways, such as mitochondrial and glycolytic metabolism, erythropoiesis, ferroptosis, and inflammation [65]. Some of these pathways are thought to be common to other clinically approved drugs. Although the use of HIF-PH inhibitors in combination therapy is expected to have a renoprotective effect, caution is required as they may also inhibit the effects of combined medication.

### *2.7 Safety and Efficacy of HIF-PH Inhibitors*

Clinical trials have examined the safety and efficacy of HIF-PH inhibitors. The effect of vadadustat on renal anemia and major adverse cardiovascular events (MACE) was examined in non-dialysis patients with CKD who either received or did not receive darbepoetin alfa [66]. Treatment with vadadustat improved renal anemia comparably to darbepoetin alfa, demonstrating the non-inferiority of vadadustat to darbepoetin. However, MACE was more in patients with vadadustat than in patients with darbepoetin alfa (22.0% vs. 19.9%; hazard ratio, 1.17). The increased risk of MACE in patients treated with vadadustat was largely due to an excess of nonfatal myocardial infarctions and a higher incidence of death from non-cardiovascular causes. The effects of daprodustat on renal anemia and MACE were examined in non-dialysis patients with stage 3–5 CKD [67]. The control group comprised non-dialysis patients with stage 3–5 CKD who received an injection of darbepoetin alfa. The effect of daprodustat on Hb elevation was not significantly different from that of darbepoetin, confirming the non-inferiority of daprodustat to darbepoetin alfa. The occurrence of MACE in patients treated with daprodustat was not different from that in patients treated with darbepoetin, suggesting the safety of daprodustat in non-dialysis patients with CKD. These two large-scale clinical studies revealed controversial results regarding the safety of HIF-PH inhibitors. The incidence of MACE in different HIF-PH inhibitors including vadadustat and daprodustat is shown in Table 4 (Ref. [66–70]) for reference.

Systematic reviews of meta-analyses examining the efficacy and safety of HIF-PH inhibitors for the treatment of anemia in patients with CKD showed no notable disparities in safety outcomes between the HIF-PH inhibitor and ESA or placebo groups [71,72]. These agents improved anemia as much as ESA by enhancing iron metabolism, decreasing hepcidin levels, and improving iron transport. Potential adverse events (AEs) associated with HIF-PH inhibitors have been suggested, including the development of malignant tumors, diabetic retinopathy, age-related macular degeneration, and progression of polycystic kidney diseases [73,74]. The onset or progression of these diseases has been suggested to be induced by the activation of HIF-1$\alpha$ and the subsequent induction of VEGF. Although there is no clinical evidence that shows the correlation between HIF-PH inhibitors and potential AEs currently, the Japanese Society of Nephrology and the Asian Pacific Society of Nephrology have issued recommendation papers for the proper use of these agents and regular check-ups for low-risk patients [75]. Long-term careful observation of patients treated with HIF-PH inhibitors is required.

**Table 4. The incidence of MACE in different HIF-PH inhibitors.**

| HIF-PH inhibitor | Control | Ref. No. |
|---|---|---|
| Vadadustat (n = 1739)<br>382 (22.0%) | Darbepoetin (n = 1732)<br>344 (19.9%) | [66] |
| Daprodustat (n = 1937)<br>378 (19.5%) | Darbepoetin (n = 1935)<br>371 (19.2%) | [67] |
| Roxadustat (n = 1083)<br>105 (9.7%) | ESA (n =1059)<br>136 (12.8%) | [68] |
| Molidustat (n = 82)<br>3 (3.7%) | Darbepoetin (n = 82)<br>1 (1.2%) | [69] |
| Molidustat (n = 82)<br>6 (7.3%) | Darbepoetin (n = 79)<br>0 (0%) | [70] |

The data was referenced from their representative clinical trials. The number of patients who developed MACE and their incidence rates are shown. The incidence of MACE for enarodustat does not appear to be published. MACE, major adverse cardiovascular events; ESA, erythropoiesis-stimulating agents.

### *2.8 Clinical Application of HIF-PH Inhibitors to Slow CKD Progression*

Two clinical trials described above reported that CKD progression was not delayed in patients treated with HIF-PH inhibitors compared to patients treated with darbepoetin alfa. The effect of the HIF-PH inhibitor on CKD progression has not been examined in comparison to a placebo. A few clinical studies have suggested a renoprotective effect of ESA on CKD progression; however, these studies were small-scale. Recently, we performed a retrospective study to examine the renoprotective effects of daprodustat [76]. The study included patients with stage 3–5 CKD (mean eGFR, 26.0 mL/min/1.73 $m^2$ $\pm$14.0) and revealed that daprodustat significantly attenuated the decline in eGFR compared to the period before the treatment (Fig. 2, Ref. [76]). The decline in eGFR was halted in ap-

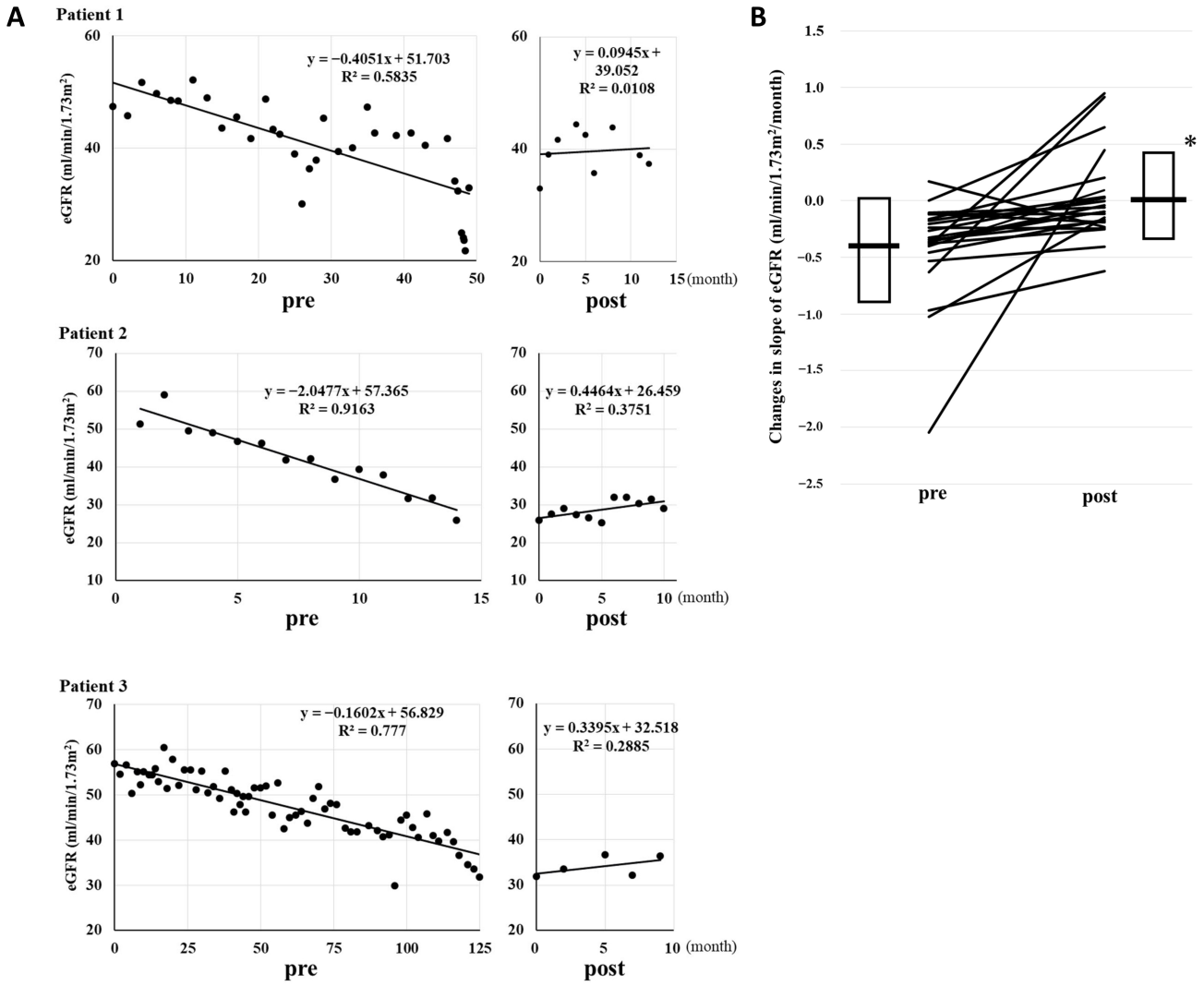


**Fig. 2. Renoprotective effect of daprodustat in patients with CKD.** (A) The changes in the eGFR slope in three patients before and after (pre and post, respectively) the administration of daprodustat. The figures are shown as representative results from a retrospective study to examine renoprotective effect of daprodustat. (B) The changes in the slope of the decline of eGFR (mL/min/1.73 $m^2$/month) by daprodustat. Daprodustat significantly reduced the decline of eGFR slope. Box and bar show mean ± SD. * $p < 0.05$. The original figures were published in Ref. [76].

proximately 90% of patients, although the sample size was small. The effect of daprodustat was not observed in patients who had already progressed to stage 5 CKD, suggesting a CKD stage-dependent effect of HIF-PH inhibitors, as implied by *in vivo* studies [46,47]. The clinical trials described above seem to have included a relatively large number of patients with stage 5 disease. Another clinical study reported a beneficial effect of HIF-PH inhibitors on heart failure-induced CKD progression. The study included 69 patients with a median eGFR of 29.1 mL/min/1.73 $m^2$ (interquartile range: 19.0–35.1 mL/min/1.73 $m^2$) at treatment initiation [77]. Treatment with HIF-PH inhibitors for 6 months resulted in an improvement in hemoglobin levels and eGFR, comparable to those observed 6 months before treatment. This study suggests that an improvement in heart failure results in an improvement in CKD. Our study examined long-term (about 15 months) effects of HIF-PH inhibitors on the progression of CKD. Given that the study was retrospective and included only a small number of patients, prospective studies including a large number of patients with moderately advanced CKD are required.

Due to their pharmacological effects, HIF-PH inhibitors have been developed as drugs to improve anemia. Clinical studies have been conducted on renal anemia, leading to their current practical application for renal anemia. It appears that renoprotective effect of HIF-PH inhibitors was not anticipated. A search on ClinicalTrials.gov revealed that currently, very few clinical studies examining the renoprotective effect of HIF-PH inhibitors as a primary endpoint have registered. It is expected that the large-scale clinical trials will be conducted with renoprotective effects as a primary endpoint.

In the last decade, SGLT2 and nonsteroidal mineralocorticoid receptor (MR) inhibitors have proven their renoprotective effects and have been used as promising new drugs for the treatment of patients with CKD. Although SGLT2 inhibitors are effective in early-stage patients with CKD with proteinuria, their renoprotective effect is not much expected in patients with advanced CKD, in whom proximal tubular function has already been abolished. MR inhibitors have been shown to suppress proteinuria and delay CKD progression; however, an initial dip in eGFR and hyperkalemia limits their use in patients with advanced CKD. Collectively, HIF-PH inhibitors may represent an unmet therapeutic need for delaying the progression of moderately advanced CKD.

## 3. Conclusions

HIF-PH inhibitors hold potential clinical applications in kidney injury treatment. The activation of HIF-1$\alpha$ by HIF-PH inhibitor could induce glycogenesis and suppress inflammation in renal tubular cells in AKI. The activation of HIF-2$\alpha$ by HIF-PH inhibitor possibly contributes to renoprotective effects on AKI by synergizing with HIF-1$\alpha$. Furthermore, HIF-PH inhibitors may protect the kidneys from acute injury in an HIF-independent manner. In particular, their use for transplanted kidney could be practical because the time when renal ischemia occurs is clear. HIF-PH inhibitors may also be effective in treating CKD. In CKD, they could have stage-dependent effects. Although activation of HIF-1$\alpha$ may be detrimental in the early stages, activation of HIF-2$\alpha$ in advanced stages may exert renoprotective actions and improve renal anemia.

In this review, we mainly focused on the renoprotective effects of HIF-PH inhibitors via activation of HIF-1$\alpha$ and HIF-2$\alpha$. The latest research shows that HIF-3$\alpha$ variants may affect the overall efficacy of these agents, including their effects in kidney diseases, which should be considered for further basic research [78,79]. In clinical aspects, currently, very few clinical studies examining the renoprotective effect of HIF-PH inhibitors as a primary endpoint have registered. The clinical studies are warranted to clarify the renoprotective effect of HIF-PH inhibitors in patients with AKI and CKD.

## Abbreviations

AEs, adverse events; AIM2, absent in melanoma 2; AKI, acute kidney injury; BTBR, black and tan brachyury; CCL2/MCP1, C-C motif chemokine ligand 2/monocyte chemoattractant protein 1; CKD, chronic kidney disease; $CoCl_2$, cobalt(II)chloride; EMT, epithelial–mesenchymal transition; ESA, erythropoiesis-stimulating agents; GLUT-1, glucose transporter 1; GFR, glomerular filtration rate; HIF, hypoxia-inducible factor; HIFs, HIF-1$\alpha$ and HIF-2$\alpha$; HIF-PH, hypoxia-inducible factor prolyl-hydroxylase; ICA, isoquinoline derivative 2-(1-chloro-4-hydroxyisoquinoline-3-carboxamido) acetate; IRI, ischemia–reperfusion injury; KO, knockout; MACE, major adverse cardiovascular events; PHD, prolyl hydroxylase domain-containing protein; ROS, reactive oxygen species; SGLT2, sodium glucose co-transporter 2; TGF-$\beta$1, transforming growth factor-1$\beta$; UUO, unilateral ureteral obstruction; pVHL, von Hippel-Lindau tumor suppressor protein; VEGF, vascular endothelial growth factor; YC-1, 3-(5′-hydroxymethyl-2′-furyl)-1-benzyl indazole; Zn, Zinc.

## Author Contributions

YI and HN conceived the study. YI, YY, MN, and KK conducted the literature review from physiological, pathological, and clinical perspectives and interpreted the data. YI and HN contributed to the manuscript writing and editing. YY, MN, and KK reviewed the manuscript and provided critical feedback and suggestions. All authors contributed to editorial changes in the manuscript. All the authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


## Acknowledgment

We would like to thank Editage for English language editing.

## Funding

This research received no external funding.


## Conflict of Interest

The authors declare no conflict of interest.

## Declaration of AI and AI-Assisted Technologies in the Writing Process

ChatGPT-4o was used for minor grammatical refinement during the drafting of this article. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

## References


[1] Shi Y, Gilkes DM. HIF-1 and HIF-2 in cancer: structure, regulation, and therapeutic prospects. Cellular and Molecular Life Sciences: CMLS. 2025; 82: 44. https://doi.org/10.1007/s00018-024-05537-0.

[2] Wiesener MS, Jürgensen JS, Rosenberger C, Scholze CK, Hörstrup JH, Warnecke C, *et al*. Widespread hypoxia-inducible expression of HIF-2alpha in distinct cell populations of different organs. FASEB Journal. 2003; 17: 271–273. https://doi.org/10.1096/fj.02-0445fje.

[3] Heidbreder M, Fröhlich F, Jöhren O, Dendorfer A, Qadri F, Dominiak P. Hypoxia rapidly activates HIF-3alpha mRNA expression. FASEB Journal. 2003; 17: 1541–1543. https://doi.org/10.1096/fj.02-0963fje.

[4] Tanaka T, Wiesener M, Bernhardt W, Eckardt KU, Warnecke C. The human HIF (hypoxia-inducible factor)-3alpha gene is a HIF-1 target gene and may modulate hypoxic gene induction. The Biochemical Journal. 2009; 424: 143–151. https://doi.org/10.1042/BJ20090120.

[5] Heikkilä M, Pasanen A, Kivirikko KI, Myllyharju J. Roles of the human hypoxia-inducible factor (HIF)-3$\alpha$ variants in the hypoxia response. Cellular and Molecular Life Sciences: CMLS. 2011; 68: 3885–3901. https://doi.org/10.1007/s00018-011-0679-5.

[6] Kleibert M, Tkacz K, Winiarska K, Małyszko J, Cudnoch-Jędrzejewska A. The role of hypoxia-inducible factors 1 and 2 in the pathogenesis of diabetic kidney disease. Journal of Nephrology. 2025; 38: 37–47. https://doi.org/10.1007/s40620-024-02152-x.

[7] Buchholz B, Eckardt KU. Role of oxygen and the HIF-pathway in polycystic kidney disease. Cellular Signalling. 2020; 69: 109524. https://doi.org/10.1016/j.cellsig.2020.109524.

[8] Semenza GL, Nejfelt MK, Chi SM, Antonarakis SE. Hypoxia-inducible nuclear factors bind to an enhancer element located 3' to the human erythropoietin gene. Proceedings of the National Academy of Sciences of the United States of America. 1991; 88: 5680–5684. https://doi.org/10.1073/pnas.88.13.5680.

[9] Semenza GL, Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. Molecular and Cellular Biology. 1992; 12: 5447–5454. https://doi.org/10.1128/mcb.12.12.5447-5454.1992.

[10] Wang GL, Semenza GL. Purification and characterization of hypoxia-inducible factor 1. The Journal of Biological Chemistry. 1995; 270: 1230–1237. https://doi.org/10.1074/jbc.270.3.1230.

[11] Tian H, McKnight SL, Russell DW. Endothelial PAS domain protein 1 (EPAS1), a transcription factor selectively expressed in endothelial cells. Genes & Development. 1997; 11: 72–82. https://doi.org/10.1101/gad.11.1.72.

[12] Gruber M, Hu CJ, Johnson RS, Brown EJ, Keith B, Simon MC. Acute postnatal ablation of Hif-2alpha results in anemia. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104: 2301–2306. https://doi.org/10.1073/pnas.0608382104.

[13] Scortegagna M, Ding K, Zhang Q, Oktay Y, Bennett MJ, Bennett M, *et al*. HIF-2alpha regulates murine hematopoietic development in an erythropoietin-dependent manner. Blood. 2005; 105: 3133–3140. https://doi.org/10.1182/blood-2004-05-1695.

[14] Iliopoulos O, Levy AP, Jiang C, Kaelin WG Jr, Goldberg MA. Negative regulation of hypoxia-inducible genes by the von Hippel-Lindau protein. Proceedings of the National Academy of Sciences of the United States of America. 1996; 93: 10595–10599. https://doi.org/10.1073/pnas.93.20.10595.

[15] Salceda S, Caro J. Hypoxia-inducible factor 1alpha (HIF-1alpha) protein is rapidly degraded by the ubiquitin-proteasome system under normoxic conditions. Its stabilization by hypoxia depends on redox-induced changes. The Journal of Biological Chemistry. 1997; 272: 22642–22647. https://doi.org/10.1074/jbc.272.36.22642.

[16] Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, *et al*. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature. 1999; 399: 271–275. https://doi.org/10.1038/20459.

[17] Ohh M, Park CW, Ivan M, Hoffman MA, Kim TY, Huang LE, *et al*. Ubiquitination of hypoxia-inducible factor requires direct binding to the beta-domain of the von Hippel-Lindau protein. Nature Cell Biology. 2000; 2: 423–427. https://doi.org/10.1038/35017054.

[18] Ivan M, Kondo K, Yang H, Kim W, Valiando J, Ohh M, *et al*. HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. Science. 2001; 292: 464–468. https://doi.org/10.1126/science.1059817.

[19] Min JH, Yang H, Ivan M, Gertler F, Kaelin WG Jr, Pavletich NP. Structure of an HIF-1alpha -pVHL complex: hydroxyproline recognition in signaling. Science. 2002; 296: 1886–1889. https://doi.org/10.1126/science.1073440.

[20] Hon WC, Wilson MI, Harlos K, Claridge TDW, Schofield CJ, Pugh CW, *et al*. Structural basis for the recognition of hydroxyproline in HIF-1 alpha by pVHL. Nature. 2002; 417: 975–978. https://doi.org/10.1038/nature00767.

[21] An award to oxygen sensing. Nature Biomedical Engineering. 2019; 3: 843–844. https://doi.org/10.1038/s41551-019-0479-z.

[22] Hurst JH. William Kaelin, Peter Ratcliffe, and Gregg Semenza receive the 2016 Albert Lasker Basic Medical Research Award. The Journal of Clinical Investigation. 2016; 126: 3628–3638. https://doi.org/10.1172/JCI90055.

[23] Besarab A, Provenzano R, Hertel J, Zabaneh R, Klaus SJ, Lee T, *et al*. Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients. Nephrology, Dialysis, Transplantation. 2015; 30: 1665–1673. https://doi.org/10.1093/ndt/gfv302.

[24] Besarab A, Chernyavskaya E, Motylev I, Shutov E, Kumbar LM, Gurevich K, *et al*. Roxadustat (FG-4592): Correction of Anemia in Incident Dialysis Patients. Journal of the American Society of Nephrology: JASN. 2016; 27: 1225–1233. https://doi.org/10.1681/ASN.2015030241.

[25] Dhillon S. Roxadustat: First global approval. Drugs. 2019; 79: 563–572. https://doi.org/10.1007/s40265-019-01077-1.

[26] Akizawa T, Tsubakihara Y, Nangaku M, Endo Y, Nakajima H, Kohno T, *et al*. Effects of Daprodustat, a Novel Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor on Anemia Management in Japanese Hemodialysis Subjects. American Journal of Nephrology. 2017; 45: 127–135. https://doi.org/10.1159/000454818.

[27] Pergola PE, Spinowitz BS, Hartman CS, Maroni BJ, Haase VH. Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. Kidney International. 2016; 90: 1115–1122. https://doi.org/10.1016/j.kint.2016.07.019.

[28] Akizawa T, Nangaku M, Yamaguchi T, Arai M, Koretomo R, Maeda K, *et al*. Enarodustat, Conversion and Maintenance Therapy for Anemia in Hemodialysis Patients: A Randomized, Placebo-Controlled Phase 2b Trial Followed by Long-Term Trial. Nephron. 2019; 143: 77–85. https://doi.org/10.1159/000500487.

[29] Macdougall IC, Akizawa T, Berns JS, Bernhardt T, Krueger T. Effects of Molidustat in the Treatment of Anemia in CKD. Clinical Journal of the American Society of Nephrology: CJASN. 2019; 14: 28–39. https://doi.org/10.2215/CJN.02510218.

[30] Padhi D, Ni L, Cooke B, Marino R, Jang G. An extended terminal half-life for darbepoetin alfa: results from a single-dose pharmacokinetic study in patients with chronic kidney disease not receiving dialysis. Clinical Pharmacokinetics. 2006; 45: 503–510. https://doi.org/10.2165/00003088-200645050-00005.

[31] Locatelli F, Reigner B. C.E.R.A.: pharmacodynamics, pharmacokinetics and efficacy in patients with chronic kidney disease. Expert Opinion on Investigational Drugs. 2007; 16: 1649–1661. https://doi.org/10.1517/13543784.16.10.1649.

[32] Locatelli F, Del Vecchio L, Elliott S. The anaemia treatment journey of CKD patients: from epoetins to hypoxia-inducible factor-prolyl hydroxylase inhibitors. Clinical Kidney Journal. 2023; 16: 1563–1579. https://doi.org/10.1093/ckj/sfad105.

[33] Ito M, Tanaka T, Ishii T, Wakashima T, Fukui K, Nangaku M. Prolyl hydroxylase inhibition protects the kidneys from is-

chemia via upregulation of glycogen storage. Kidney International. 2020; 97: 687–701. https://doi.org/10.1016/j.kint.2019.10.020.

[34] Yang H, Wu Y, Cheng M, Zhang M, Qiu X, Liu S, *et al*. Roxadustat (FG-4592) protects against ischaemia-induced acute kidney injury via improving CD73 and decreasing AIM2 inflammasome activation. Nephrology, Dialysis, Transplantation. 2023; 38: 858–875. https://doi.org/10.1093/ndt/gfac308.

[35] Yasuoka Y, Izumi Y, Fukuyama T, Oshima T, Yamazaki T, Uematsu T, *et al*. Tubular Endogenous Erythropoietin Protects Renal Function against Ischemic Reperfusion Injury. International Journal of Molecular Sciences. 2024; 25: 1223. https://doi.org/10.3390/ijms25021223.

[36] Rajendran G, Schonfeld MP, Tiwari R, Huang S, Torosyan R, Fields T, *et al*. Inhibition of Endothelial PHD2 Suppresses Post-Ischemic Kidney Inflammation through Hypoxia-Inducible Factor-1. Journal of the American Society of Nephrology: JASN. 2020; 31: 501–516. https://doi.org/10.1681/ASN.2019050523.

[37] Kapitsinou PP, Sano H, Michael M, Kobayashi H, Davidoff O, Bian A, *et al*. Endothelial HIF-2 mediates protection and recovery from ischemic kidney injury. The Journal of Clinical Investigation. 2014; 124: 2396–2409. https://doi.org/10.1172/JCI69073.

[38] Kapitsinou PP, Jaffe J, Michael M, Swan CE, Duffy KJ, Erickson-Miller CL, *et al*. Preischemic targeting of HIF prolyl hydroxylation inhibits fibrosis associated with acute kidney injury. American Journal of Physiology. Renal Physiology. 2012; 302: F1172–F1179. https://doi.org/10.1152/ajprenal.00667.2011.

[39] Deguchi H, Ikeda M, Ide T, Tadokoro T, Ikeda S, Okabe K, *et al*. Roxadustat Markedly Reduces Myocardial Ischemia Reperfusion Injury in Mice. Circulation Journal. 2020; 84: 1028–1033. https://doi.org/10.1253/circj.CJ-19-1039.

[40] Steenhard BM, Freeburg PB, Isom K, Stroganova L, Borza DB, Hudson BG, *et al*. Kidney development and gene expression in the HIF2alpha knockout mouse. Developmental Dynamics. 2007; 236: 1115–1125. https://doi.org/10.1002/dvdy.21106.

[41] Yasuoka Y, Izumi Y, Nagai T, Fukuyama T, Nakayama Y, Inoue H, *et al*. Fludrocortisone stimulates erythropoietin production in the intercalated cells of the collecting ducts. Biochemical and Biophysical Research Communications. 2018; 503: 3121–3127. https://doi.org/10.1016/j.bbrc.2018.08.102.

[42] Higgins DF, Kimura K, Bernhardt WM, Shrimanker N, Akai Y, Hohenstein B, *et al*. Hypoxia promotes fibrogenesis in vivo via HIF-1 stimulation of epithelial-to-mesenchymal transition. The Journal of Clinical Investigation. 2007; 117: 3810–3820. https://doi.org/10.1172/JCI30487.

[43] Kobayashi H, Gilbert V, Liu Q, Kapitsinou PP, Unger TL, Rha J, *et al*. Myeloid cell-derived hypoxia-inducible factor attenuates inflammation in unilateral ureteral obstruction-induced kidney injury. Journal of Immunology. 2012; 188: 5106–5115. https://doi.org/10.4049/jimmunol.1103377.

[44] Kong KH, Oh HJ, Lim BJ, Kim M, Han KH, Choi YH, *et al*. Selective tubular activation of hypoxia-inducible factor-2$\alpha$ has dual effects on renal fibrosis. Scientific Reports. 2017; 7: 11351. https://doi.org/10.1038/s41598-017-11829-2.

[45] Schley G, Klanke B, Kalucka J, Schatz V, Daniel C, Mayer M, *et al*. Mononuclear phagocytes orchestrate prolyl hydroxylase inhibition-mediated renoprotection in chronic tubulointerstitial nephritis. Kidney International. 2019; 96: 378–396. https://doi.org/10.1016/j.kint.2019.02.016.

[46] Zhao Y, Zeng H, Liu B, He X, Chen JX. Endothelial prolyl hydroxylase 2 is necessary for angiotensin II-mediated renal fibrosis and injury. American Journal of Physiology. Renal Physiology. 2020; 319: F345–F357. https://doi.org/10.1152/ajprenal.00032.2020.

[47] Yu X, Fang Y, Liu H, Zhu J, Zou J, Xu X, *et al*. The balance of beneficial and deleterious effects of hypoxia-inducible factor activation by prolyl hydroxylase inhibitor in rat remnant kidney depends on the timing of administration. Nephrology, Dialysis, Transplantation. 2012; 27: 3110–3119. https://doi.org/10.1093/ndt/gfr754.

[48] Kim DA, Lee MR, Oh HJ, Kim M, Kong KH. Effects of long-term tubular HIF-2$\alpha$ overexpression on progressive renal fibrosis in a chronic kidney disease model. BMB Reports. 2023; 56: 196–201. https://doi.org/10.5483/BMBRep.2022-0145.

[49] Yasuoka Y, Izumi Y, Fukuyama T, Omiya H, Pham TD, Inoue H, *et al*. Effects of Roxadustat on Erythropoietin Production in the Rat Body. Molecules. 2022; 27: 1119. https://doi.org/10.3390/molecules27031119.

[50] Wang S, Zeng H, Chen ST, Zhou L, Xie XJ, He X, *et al*. Ablation of endothelial prolyl hydroxylase domain protein-2 promotes renal vascular remodelling and fibrosis in mice. Journal of Cellular and Molecular Medicine. 2017; 21: 1967–1978. https://doi.org/10.1111/jcmm.13117.

[51] Yu X, Fang Y, Ding X, Liu H, Zhu J, Zou J, *et al*. Transient hypoxia-inducible factor activation in rat renal ablation and reduced fibrosis with L-mimosine. Nephrology. 2012; 17: 58–67. https://doi.org/10.1111/j.1440-1797.2011.01498.x.

[52] Fang Y, Yu X, Liu Y, Kriegel AJ, Heng Y, Xu X, *et al*. miR-29c is downregulated in renal interstitial fibrosis in humans and rats and restored by HIF-$\alpha$ activation. American Journal of Physiology. Renal Physiology. 2013; 304: F1274–F1282. https://doi.org/10.1152/ajprenal.00287.2012.

[53] Nordquist L, Friederich-Persson M, Fasching A, Liss P, Shoji K, Nangaku M, *et al*. Activation of hypoxia-inducible factors prevents diabetic nephropathy. Journal of the American Society of Nephrology: JASN. 2015; 26: 328–338. https://doi.org/10.1681/ASN.2013090990.

[54] Jiang N, Zhao H, Han Y, Li L, Xiong S, Zeng L, *et al*. HIF-1$\alpha$ ameliorates tubular injury in diabetic nephropathy via HO-1-mediated control of mitochondrial dynamics. Cell Proliferation. 2020; 53: e12909. https://doi.org/10.1111/cpr.12909.

[55] Bohuslavova R, Cerychova R, Nepomucka K, Pavlinkova G. Renal injury is accelerated by global hypoxia-inducible factor 1 alpha deficiency in a mouse model of STZ-induced diabetes. BMC Endocrine Disorders. 2017; 17: 48. https://doi.org/10.1186/s12902-017-0200-8.

[56] Jiao Y, Jiang H, Lu H, Yang Y, Zhang Y, Zhang K, *et al*. Deficiency of hypoxia inducible factor-1$\alpha$ promoted progression of diabetic nephropathy with hypertension. Experimental and Therapeutic Medicine. 2018; 16: 3658–3662. https://doi.org/10.3892/etm.2018.6621.

[57] Nayak BK, Shanmugasundaram K, Friedrichs WE, Cavaglierii RC, Patel M, Barnes J, *et al*. HIF-1 Mediates Renal Fibrosis in OVE26 Type 1 Diabetic Mice. Diabetes. 2016; 65: 1387–1397. https://doi.org/10.2337/db15-0519.

[58] Sugahara M, Tanaka S, Tanaka T, Saito H, Ishimoto Y, Wakashima T, *et al*. Prolyl Hydroxylase Domain Inhibitor Protects against Metabolic Disorders and Associated Kidney Disease in Obese Type 2 Diabetic Mice. Journal of the American Society of Nephrology: JASN. 2020; 31: 560–577. https://doi.org/10.1681/ASN.2019060582.

[59] Sung PH, Yue Y, Chen YL, Chiang JY, Cheng BC, Yang CC, *et al*. Combined dapagliflozin and roxadustat effectively protected heart and kidney against cardiorenal syndrome-induced damage in rodent through activation of cell stress-Nfr2/ARE signalings and stabilizing HIF-1$\alpha$. Biomedicine & Pharmacotherapy. 2024; 180: 117567. https://doi.org/10.1016/j.biopha.2024.117567.

[60] Bessho R, Takiyama Y, Takiyama T, Kitsunai H, Takeda Y, Sakagami H, *et al*. Hypoxia-inducible factor-1$\alpha$ is the ther-

apeutic target of the SGLT2 inhibitor for diabetic nephropathy. Scientific Reports. 2019; 9: 14754. https://doi.org/10.1038/s41598-019-51343-1.

[61] Ume AC, Wenegieme TY, Adams DN, Adesina SE, Williams CR. Zinc Deficiency: A Potential Hidden Driver of the Detrimental Cycle of Chronic Kidney Disease and Hypertension. Kidney360. 2023; 4: 398–404. https://doi.org/10.34067/KID.0007812021.

[62] Zhang X, Liang D, Fan J, Lian X, Zhao Y, Wang X, *et al*. Zinc Attenuates Tubulointerstitial Fibrosis in Diabetic Nephropathy Via Inhibition of HIF Through PI-3K Signaling. Biological Trace Element Research. 2016; 173: 372–383. https://doi.org/10.1007/s12011-016-0661-z.

[63] Shimokawa H, Satoh K. 2015 ATVB Plenary Lecture: translational research on rho-kinase in cardiovascular medicine. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015; 35: 1756–1769. https://doi.org/10.1161/ATVBAHA.115.305353.

[64] Matoba K, Kawanami D, Okada R, Tsukamoto M, Kinoshita J, Ito T, *et al*. Rho-kinase inhibition prevents the progression of diabetic nephropathy by downregulating hypoxia-inducible factor 1$\alpha$. Kidney International. 2013; 84: 545–554. https://doi.org/10.1038/ki.2013.130.

[65] Li QY, Liu F, Tang X, Fu H, Mao J. Renoprotective Role of Hypoxia-Inducible Factors and the Mechanism. Kidney Diseases. 2021; 8: 44–56. https://doi.org/10.1159/000520141.

[66] Chertow GM, Pergola PE, Farag YMK, Agarwal R, Arnold S, Bako G, *et al*. Vadadustat in Patients with Anemia and Non-Dialysis-Dependent CKD. The New England Journal of Medicine. 2021; 384: 1589–1600. https://doi.org/10.1056/NEJMoa2035938.

[67] Singh AK, Carroll K, McMurray JJV, Solomon S, Jha V, Johansen KL, *et al*. Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis. The New England Journal of Medicine. 2021; 385: 2313–2324. https://doi.org/10.1056/NEJMoa2113380.

[68] Barratt J, Dellanna F, Portoles J, Choukroun G, De Nicola L, Young J, *et al*. Safety of Roxadustat Versus Erythropoiesis-Stimulating Agents in Patients with Anemia of Non-dialysis-Dependent or Incident-to-Dialysis Chronic Kidney Disease: Pooled Analysis of Four Phase 3 Studies. Advances in Therapy. 2023; 40: 1546–1559. https://doi.org/10.1007/s12325-023-02433-0.

[69] Yamamoto H, Nobori K, Matsuda Y, Hayashi Y, Hayasaki T, Akizawa T. Molidustat for Renal Anemia in Nondialysis Patients Previously Treated with Erythropoiesis-Stimulating Agents: A Randomized, Open-Label, Phase 3 Study. American Journal of Nephrology. 2021; 52: 884–893. https://doi.org/10.1159/000518072.

[70] Yamamoto H, Nobori K, Matsuda Y, Hayashi Y, Hayasaki T, Akizawa T. Efficacy and Safety of Molidustat for Anemia in ESA-Naive Nondialysis Patients: A Randomized, Phase 3 Trial. American Journal of Nephrology. 2021; 52: 871–883. https://doi.org/10.1159/000518071.

[71] Ha JT, Hiremath S, Jun M, Green SC, Wheeler DC, Coyne DW, *et al*. Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors in Kidney Disease. NEJM Evidence. 2024; 3: EVIDoa2300189. https://doi.org/10.1056/EVIDoa2300189.

[72] Ren S, Yao X, Li Y, Zhang Y, Tong C, Feng Y. Efficacy and safety of hypoxia-inducible factor-prolyl hydroxylase inhibitor treatment for anemia in chronic kidney disease: an umbrella review of meta-analyses. Frontiers in Pharmacology. 2023; 14: 1296702. https://doi.org/10.3389/fphar.2023.1296702.

[73] Stoumpos S, Crowe K, Sarafidis P, Barratt J, Bolignano D, Del Vecchio L, *et al*. Hypoxia-inducible factor prolyl hydroxylase inhibitors for anaemia in chronic kidney disease: a clinical practice document by the European Renal Best Practice board of the European Renal Association. Nephrology, Dialysis, Transplantation. 2024; 39: 1710–1730. https://doi.org/10.1093/ndt/gfae075.

[74] Liu F, Wang J, Ye Q, Fu H, Mao J. Roxadustat for Renal Anemia in ESRD from PKD Patients: Is It Safe Enough? Journal of the American Society of Nephrology: JASN. 2021; 32: 1005. https://doi.org/10.1681/ASN.2020111664.

[75] Yap DYH, McMahon LP, Hao CM, Hu N, Okada H, Suzuki Y, *et al*. Recommendations by the Asian Pacific society of nephrology (APSN) on the appropriate use of HIF-PH inhibitors. Nephrology. 2021; 26: 105–118. https://doi.org/10.1111/nep.13835.

[76] Shimada Y, Izumi Y, Yasuoka Y, Oshima T, Nagaba Y, Nanami M, *et al*. Renoprotective Effects of Daprodustat in Patients with Chronic Kidney Disease and Renal Anemia. International Journal of Molecular Sciences. 2024; 25: 9468. https://doi.org/10.3390/ijms25179468.

[77] Hida Y, Imamura T, Kinugawa K. Clinical Implication of HIF-PH Inhibitor in Patients with Heart Failure, Chronic Kidney Disease, and Renal Anemia. Journal of Clinical Medicine. 2024; 13: 7619. https://doi.org/10.3390/jcm13247619.

[78] Ravenna L, Salvatori L, Russo MA. HIF3$\alpha$: the little we know. The FEBS Journal. 2016; 283: 993–1003. https://doi.org/10.1111/febs.13572.

[79] Duan C. Hypoxia-inducible factor 3 biology: complexities and emerging themes. American Journal of Physiology. Cell Physiology. 2016; 310: C260–C269. https://doi.org/10.1152/ajpcell.00315.2015.