HIF Activation Against CVD in CKD: Novel Treatment Opportunities

Tetsuhiro Tanaka, MD, PhD,[*] and Kai-Uwe Eckardt, MD[†]

Summary: Cardiovascular disease is a common and serious complication in patients with chronic kidney disease (CKD). One of the fundamental functions of the cardiovascular system is oxygen delivery, therefore cardiovascular disease inherently is linked to insufficient tissue oxygenation. Advances in our knowledge of cellular oxygen sensing by a family of prolyl hydroxylases (PHDs) and their role in regulating hypoxia-inducible factors (HIFs) have led to the discovery of PHD inhibitors as HIF stabilizers. Several small-molecule PHD inhibitors are currently in clinical trials for the treatment of anemia in CKD. An additional advantage of PHD inhibition may be found in the potential impact on cardiovascular consequences associated with CKD. Several preclinical studies have suggested a potential benefit of HIF activation in myocardial infarction, cardiac remodeling, atherosclerosis, and peripheral artery disease. Ameliorating glucose and lipid metabolism and lowering blood pressure may also contribute to cardiovascular protection. On the other hand, the broad spectrum of HIF-dependent functions also may include unwanted side effects. Clinical application of PHD inhibitors therefore necessitates careful evaluation of the net systemic effect of HIF activation.
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Cardiovascular disease (CVD) is the leading cause of death among the kidney disease population. In the United States, more than 60% of patients with chronic kidney disease (CKD) suffer from CVD and the risk of cardiovascular events increases as the estimated glomerular filtration rate decreases.[1] Notably, one survey on the natural history of CKD patients showed that the rate of all-cause mortality over the 5-year observation far exceeded that of end-stage kidney disease requiring renal replacement therapy, and cardiac comorbidities such as congestive heart failure and myocardial infarction were more prevalent in the deceased population.[2] Conversely, patients with heart failure have a high prevalence of CKD; 40% to 50% of such patients have CKD stage 3 or higher.

[*]*Division of Nephrology and Endocrinology, University of Tokyo School of Medicine, Tokyo, Japan.*
[†]*Department of Nephrology and Medical Intensive Care, Charité–Universitätsmedizin Berlin, Berlin, Germany.*

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Address reprint requests to Tetsuhiro Tanaka, MD, PhD, Division of Nephrology and Endocrinology, University of Tokyo School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655 Japan. E-mail: tetsu-tky@umin.ac.jp,

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PATHOPHYSIOLOGY OF CVD IN CKD

The pathophysiology of CVD and CKD is complex, with common elements and mutual interferences. It includes factors such as inflammation, hormonal responses, metabolic and nutritional changes, altered hemodynamic and fluid status, acid-base disorders, and others. Together with the frequent comorbidity of anemia, these schemes also are highlighted within the concept of cardio-renal-anemia syndrome.[3] CKD increases oxidative stress and inflammation, activates the renin-angiotensin system, and causes nutritional disorders, which facilitate CVD. CKD may further impact cardiac function through the anemia caused by reduced renal erythropoietin (EPO) production. CVD in turn can aggravate CKD through reduced renal perfusion as a consequence of a reduced cardiac output and increased venous pressure. Inflammation in the CVD state further aggravates anemia, which may aggravate ischemia and oxidative stress. Thus, CKD, CVD, and anemia cause a vicious circle mutually influencing one another (Fig. 1). From a therapeutic point, an effort to disrupt these mutual relations may help to retard the progression of CKD and CVD.

ADAPTIVE RESPONSES BY HIF AND THE PROLYL HYDROXYLASE SYSTEM

Virtually all cells of the body are endowed with a mechanism though which they sense and cope with hypoxia, which is mediated primarily by a family of hypoxia-inducible factors (HIFs). HIF is a heterodimeric transcription factor composed of an oxygen-labile α subunit (HIF-1α, HIF-2α, and HIF-3α) and a constitutively expressed β subunit (also referred to as

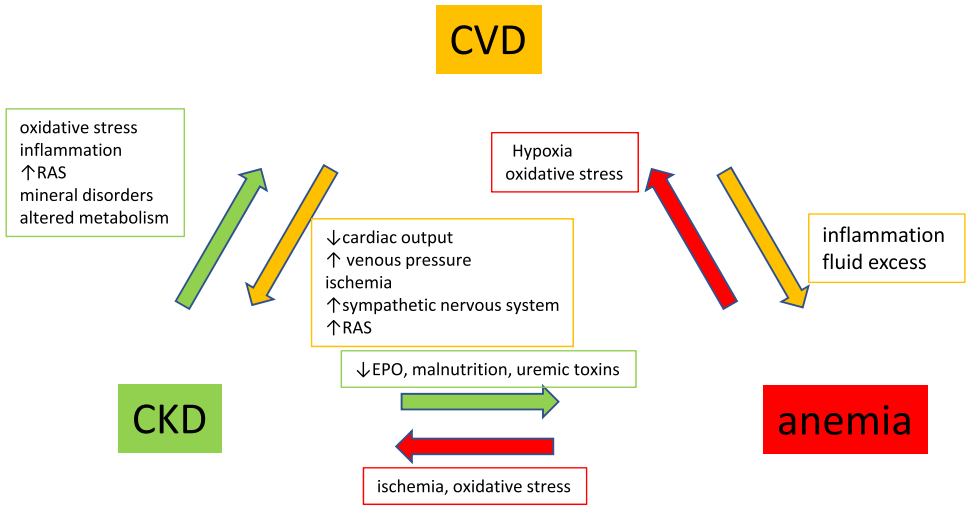

Figure 1. Relationships among CKD, CVD, and anemia. CKD increases oxidative stress and inflammation, activates the renin-angiotensin system (RAS), and causes nutritional disorders, which facilitate CVD. CKD may further impact cardiac function through anemia. CVD in turn can aggravate CKD through reduced renal perfusion as a consequence of a reduced cardiac output and increased venous pressure. Inflammation in the CVD state further aggravates anemia, which may aggravate tissue hypoxia and oxidative stress. Thus, CKD, CVD, and anemia form a vicious circle.

aryl hydrocarbon receptor nuclear translocator). The hypoxia-specific operation of this factor is accomplished by oxygen-dependent hydroxylation of conserved proline residues via prolyl hydroxylases (PHDs). Hydroxylated HIF then is recognized by the von Hippel-Lindau (VHL) tumor-suppressor protein, a component of an E3 ubiquitin ligase, and undergoes subsequent proteasomal degradation.[4] In hypoxia, HIF-α escapes hydroxylation and degradation, translocates to the nucleus, forms a heterodimer with HIF-1β, and transactivates at least 100 to 200 target genes. Many of these target genes play a role in improving oxygen delivery, including angiogenesis and erythropoiesis, or in adaptation to reduced oxygen availability, including anaerobic metabolism and other processes essential to hypoxic adaptation. Of the two major isoforms, HIF-1 is expressed in a broad range of cells and controls global cellular response, whereas the expression of HIF-2 is more spatially restricted. Despite sharing similar domain architecture and the same mode of proteolytic regulation, HIF-2 possesses nonredundant functions as compared with HIF-1.[5]

PHDs (PHD1, PHD2, and PHD3; also referred to as Egl nine homolog [Egln] 2, 1, and 3, respectively) are members of the iron- and 2-oxoglutarate–dependent dioxygenase superfamily, among which PHD2 is the key regulator of HIF-α expression,[6] whereas the relative abundance of PHD1 and PHD3 might determine selectivity for HIF-2α versus HIF-1α expression.[7]

PHD INHIBITORS AS THE NEXT-GENERATION ERYTHROPOIESIS STIMULATING AGENTS

The mechanistic link between the HIF-2–PHD2 axis and the induction of erythropoiesis has been studied extensively in cell-based, animal, and human genetic studies. In vitro, Hep3B and Kelly cells showed the hypoxic induction of EPO messenger RNA (mRNA) in a HIF-2–, but not HIF-1–dependent manner.[8] HIF-2 hypomorphic mice are anemic,[9] whereas somatic inactivation of *Phd2* in mice induced a marked increase in serum EPO and hematocrit levels.[10] In human beings, familial cases of erythrocytosis associated with a gain-of-function mutation in the *HIF2A* gene,[11] or with an inactivating mutation in the *PHD2* gene,[12] have been reported.

Based on the fundamental roles of HIF on EPO production, small-molecule inhibitors of PHDs have been developed for the treatment of anemia in CKD (Fig. 2). There is some expectation that this therapeutic approach also may improve iron utilization. To date, at least 6 compounds are being tested in human clinical settings, and studies successfully completed so far have shown increases in hemoglobin (Hgb) levels without serious adverse effects.[4,13]

The potential advantages of such inhibitors include lower cost, the oral route of administration, improved iron profile, and endogenous EPO production at levels close to the physiological range. The possible relevance of the latter is highlighted by a post hoc analysis showing an increased incidence of cardiovascular events in patients receiving high doses of EPO.[14] Although the EPO therapy in daily clinical settings generally is safe, it has been speculated that a high dose of exogenous EPO may create a prothrombotic state through production of highly reactive platelets and activation of vascular endothelium. PHD inhibitors thus may have the potential to reduce cardiovascular risk by stimulating erythropoiesis in the absence of very high EPO concentrations in the blood stream.