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One Size Doesn't Fit All: Revisiting the Threshold, Target, and Type of Erythropoietin-Stimulating Agent Therapy in Anemia of CKD

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Kidney Int Rep (2024) **9,** 1954–1956; https://doi.org/10.1016/j.ekir.2024.05.023

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Anemia has multisystem effects in patients with chronic kidney disease (CKD). Not only does it affect quality of life but is also associated with cardiovascular morbidity, worsening of kidney function, and mortality.

Anemia and its effects on cardiovascular function have been a topic of contention for years. Anemia increases left ventricular mass index and the risk of heart failure hospitalization. The mechanism by which this occurs is not yet elucidated but may involve oxidative stress, mitochondrial dysfunction, myocyte apoptosis, and sympathetic stimulation.[1–3] Both erythropoietin, via receptors present on cardiac myocytes, and iron have beneficial effects on cardiovascular function.[3,4]

The effect of anemia on kidney function is less well-defined. Animal models demonstrate the beneficial effect of erythropoietin on kidney interstitial fibrosis via amelioration of ischemia, decreased oxidative stress, and tubular antiapoptotic effect. It may help preserve kidney capillary integrity by its effect on endothelial capillary cells.[5] Although observational studies show the benefit of treatment of anemia on kidney end points, the results have been equivocal in clinical trials designed specifically to study the same.[6,7]

In this edition of Kidney International Reports, Kawai *et al.*[8] describe a retrospective cohort to study the outcomes of early (hemoglobin $\geq$ 9 g/dl or 90 g/l) versus delayed (hemoglobin $\leq$ 9 g/dl or 90 g/l) initiation of anemia treatment with long-acting erythropoietin-stimulating agents (ESA) in patients with nondialysis-dependent CKD. The study included data from 2732 patients from 2 databases with a long data extraction period of 7 years (2011–2018) but with a relatively shorter follow-up period of 2 years for each patient. Delayed treatment was not associated with an increased risk of kidney composite outcome but was associated with higher risk of cardiovascular composite outcome, heart failure, and all-cause mortality. Only half of the selected patients reached the composite kidney end point and almost a quarter reached cardiovascular composite end point at the end of the follow-up period. Considering that this was a database study of selected patients, a prospective cohort study with longer follow-up may yield essential results to understand the true effect of early versus delayed anemia treatment, especillay on kidney outcomes.

The Japanese Society of Dialysis Therapy recommends target hemoglobin levels between 11 g/dl and 13 g/dl in patients with predialysis CKD. The recommendation of a higher target hemoglobin compared to guidelines from Western countries was based on a significantly lower incidence of cardiovascular events in the Japanese CKD population on ESA than in those in Western countries.[9] In addition, stroke incidence, which is otherwise high in the Japanese population, was comparable with the incidence of stroke with ESA use in Western countries.[9] More recently, the PREDICT trial randomized patients with advanced nondiabetic CKD to a high versus a low hemoglobin target with long-acting ESA use.[S1] Only a small percentage (8%) of patients reached the cardiovascular end point (cardiovascular death, nonfatal myocardial infarction, angina, stroke, hospitalization for heart failure, and amputation) at 2 years follow-up in the high hemoglobin group. These data support the safety of high hemoglobin

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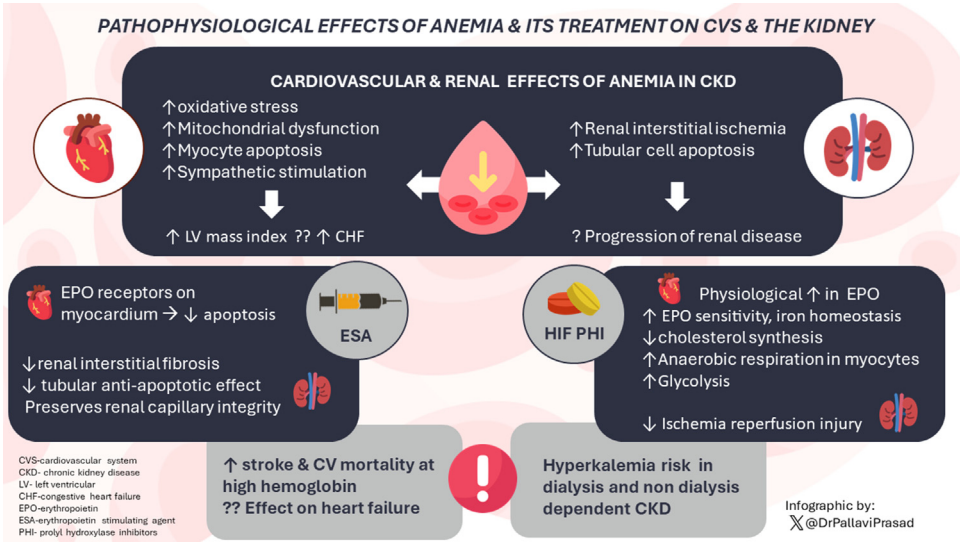

Figure 1. Pathophysiological effects of anemia and its treatment on the cardiovascular system and the kidney.

targets in patients with advanced nondiabetic CKD in Japan.

In contrast to these studies, Kawai *et al*.[8] describe a high rate of cardiovascular events, predominantly contributed by the heart failure component of the end point, in the delayed treatment group.[8,9,S1] The number of patients with heart failure at baseline in the early versus delayed group was not mentioned. In addition, the cause of heart failure is not established in this study,[8] as is the case in most other studies analyzing cardiovascular end points in anemia. Establishing whether the heart failure events were due to pump failure or other primary cardiac pathology versus congestive heart failure due to secondary noncardiac causes would be instrumental in understanding this result. If congestion due to anemia were to be found as the cause of heart failure, it would support the early initiation of treatment of anemia in patients with predialysis CKD. Conversely, if congestion and fluid retention at baseline led to hemodilution and contributed to anemia, it can be assumed that the progression of anemia indicates a precondition for congestive heart failure, and that ESA treatment may have been responsible for the worsening of heart failure and resulted in increased number of admission due to heart failure. Clinical trials in the same domain would be needed to firmly establish this association due to inherent limitations of retrospective database analyses using medical codes.

The use of long-acting versus short-acting erythropoietin adds another layer of complexity to the interpretation of ESA trials. The databases analyzed by Kawai *et al*.[8] included patients on long-acting ESA alone. A nationwide registry of 194,698 hemodialysis patients from Japan had demonstrated a 13% higher all-cause mortality in patients treated with long-acting ESA versus those treated with short-acting ESA.[S2] This effect was particularly pronounced in the subgroup receiving high doses of long-acting ESA and those with a high erythropoietin resistance index. In cause-specific mortality, high dose ESA was associated with a higher cardiovascular mortality and mortality due to malignancies or infections.[S2] The high peak and prolonged effect of high dose ESA on nonerythroid cells (endothelial cells, megakaryocytes, and tumor cells) and their *in vitro* immunosuppressive effects may explain, in part, the increased mortality associated with these agents.[S2] Due to the above issues, a gap has been observed between the guideline recommended level (11 g/dl) and real-world threshold for starting anemia therapy (close to 9 g/l) in Japan.[S3]

In current practice, oral hypoxia-inducible factor-prolyl hydroxylase inhibitors are changing the landscape of anemia treatment in CKD. In patients with nondialysis CKD, hypoxia-inducible factor-prolyl hydroxylase inhibitor may be used as an alternative to long-acting ESA due to their ease of administration. Data regarding cardiovascular and kidney end points in anemia treatment with hypoxia-inducible factor-prolyl hydroxylase inhibitors are not as robust as data with erythropoietin. In a meta-analysis, roxadustat was not observed to have a significant difference in cardiovascular or kidney end points as compared to placebo or

erythropoietin in patients with nondialysis or dialysis dependent CKD.[4] However, the roxadustat arm had a numerically lower number of patients who reached cardiovascular end points. This may be explained by a more physiological increase in erythropoietin with this agent, inhibition of cholesterol synthesis, or via enhancement of anaerobic respiration in cardiac myocytes[S4] (Figure 1). In the future, if hypoxia-inducible factor-prolyl hydroxylase inhibitors replace erythropoietin, target hemoglobin levels will need to be reestablished for these agents with a focus on nonerythroid effects as well as cardiovascular and kidney end points.[S5]

Lastly, data from the ESA trials from Japan underscore the urgent need to promote regional and national level research to formulate local guidelines for defining and treating anemia in CKD. Country- or region-specific definitions of anemia, thresholds for therapy initiation, choice of agent, and target hemoglobin levels in CKD are imperative for optimal kidney care.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplemental References.

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