The burden of anaemia in CKD patients and the unmet needs

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Chronic kidney disease (CKD) typically manifests with a progressive decline of renal function, eventually requiring dialysis or transplantation in its final stages. It presents a global health burden with high economic costs to health systems worldwide. Unfortunately, early diagnosis is frequently missed, and epidemiological data indicate that only 10% of individuals with renal disease are timely identified and treated. According to the Kidney Disease: Improving Global Outcomes (KDIGO) data, the prevalence of CKD stages 1, 2 and 3 in the general population are 3.5%, 3.9% and 7.6% respectively. The prevalences of stages 4 and 5 are dramatically lower (0.4% and 0.1% respectively), mostly due to the high cardiovascular morbidity and premature mortality in stage 3. According to the meta-analysis performed on over one million subjects, CKD is an acknowledged multiplier of cardiovascular risk independent of hypertension, diabetes and age.

CKD-related anaemia

Anaemia is also a common complication among CKD patients and a known risk factor for cardiovascular disease. According to Hanna et al., anaemia in CKD is also associated with diminished quality of life and increased healthcare utilization, causing a significant clinical and economic burden. A prospective multicenter study by Minutolo et al. examined anaemia management in two visits six months apart in 755 prevalent non-dialyzed CKD stage 3b-5 patients at 19 nephrology clinics in Italy. It revealed an extraordinarily high prevalence of anaemia in tertiary nephrology care, which was attributed to chronic clinical inertia in anaemia management, especially related to iron supplementation and, less crucial but still substantial, insufficient application of erythropoiesis-stimulating agents (ESA). An investigation by Covic et al. found that the prevalence of anaemia in a cohort of non-dialysis dependant (NDD)-CKD patients exceeded 60% and was associated with more frequent cardiovascular issues and diminished quality of life and work productivity.

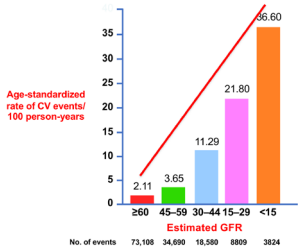

Figure 1.
Rate of cardiovascular events at different eGFR levels

The standard of care for anaemia management in CKD patients involves ESAs to achieve a haemoglobin (HB) target of 11-12 g/dL. To minimize iron overload and reduce HB fluctuation, it is critical to evaluate iron stores, supplement carefully, and individualize the ESA dose. Intravenous iron administration may help to prevent iron deficiency. Nevertheless, caution is advised to avoid reactive thrombocytosis. To reduce the risk of thrombotic events, it is crucial to examine the causes of ESA hyper-responsiveness, including insufficient dialysis, occult bleeding, and inflammation.

Major randomized clinical trials conducted to assess the impact of anaemia therapy on cardiovascular outcomes in CKD patients failed to

demonstrate any survival benefits from normalizing HB levels. Still, ESAs are often prescribed for inpatients with CKD, although there may be potential risks associated with their use. Targeting HB levels at different CKD stages has also been a matter of debate. A study by Del Vecchio et al. found no survival benefits from normalizing HB levels but suggested that the HB target range of 11.5-12 g/dL may be reasonable, especially for older, frail patients. However, the study also noted that there may be potential risks associated with higher doses of ESA which should be carefully considered.

Table 27 | Prevalence of CKD complications by GFR category* derived from CKD cohorts

Complication	GFR category (ml/min/1.73 m^2)					Reference
	≥90	60-89	45-59	30-44	<30	
Anemia[1]	4.0%	4.7%	12.3%	22.7%	51.5%	366
Hypertension[2]	18.3%	41.0%	71.8%	78.3%	82.1%	366
25(OH) Vit D deficiency[3]	14.1%	9.1%	10.7%		27.2%	367
Acidosis[4]	11.2%	8.4%	9.4%	18.1%	31.5%	366
Hyperphosphatemia[5]	7.2%	7.4%	9.2%	9.3%	23.0%	366
Hypoalbuminemia[6]	1.0%	1.3%	2.8%	9.0%	7.5%	366
Hyperparathyroidism[7]	5.5%	9.4%	23.0%	44.0%	72.5%	366

Figure 2.
KDIGO Clinical practice guidelines for Anemia in CKD - Prevalence of CKD complications by GFR category

Novel treatment options for CKD-related anaemia

Anaemia management in CKD patients evolved, from transfusions as the mainstay therapy from the 1950s to the 1980s, to the introduction of the first ESAs in the 1990s. The use of ESAs brought attention to functional iron deficiency, and, although they significantly reduced the need for transfusions, these agents also exhibited potential side effects such as hypertension, fistula thrombosis, and cardiovascular and cerebrovascular events.

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors have been recently developed as a new option for the treatment of CKD-related anaemia. These agents act by inhibiting the enzyme prolyl hydroxylase which promotes the degradation of hypoxia-inducible factors (HIFs). HIFs are a family of oxygen-sensitive proteins that regulate the cell's transcriptional response to hypoxia. The HIF pathway acts as a central regulator of erythropoiesis by coordinating a series of cell-specific responses to hypoxia: indirect hepcidin suppression to increase iron availability for HB synthesis, enhancement of enteric iron absorption and its plasma transport, redistribution of endogenous iron stores and EPO production.

A functional HIF transcription factor consists of two subunits - alpha (α) and beta (β). They combine in the nucleus under hypoxic conditions and bind to DNA sequences, called hypoxia response elements (HREs), to induce the expression of target erythropoietin genes. The HIF-α subunit has 3 isoforms: HIF-1α, HIF-2α, and HIF-3α. Several experiments have demonstrated that HIF-2α is the main subunit involved in upregulating EPO gene expression and iron transport in hypoxia. HIF-1α plays a critical role in the cell-cycle regulation of hematopoietic stem cells, which are found in the hypoxic niches of bone marrow. Therefore, stabilization of HIF-α using HIF-PH inhibitors effectively improve iron mobilization to the bone marrow, stimulate endogenous EPO production and promotes hematopoiesis, even in patients with end-stage renal disease. However, one significant concern regarding the long-term use of these agents is their possible effect on tumours, since HIF activation in hypoxic environments may help already existing tumours survive and grow.

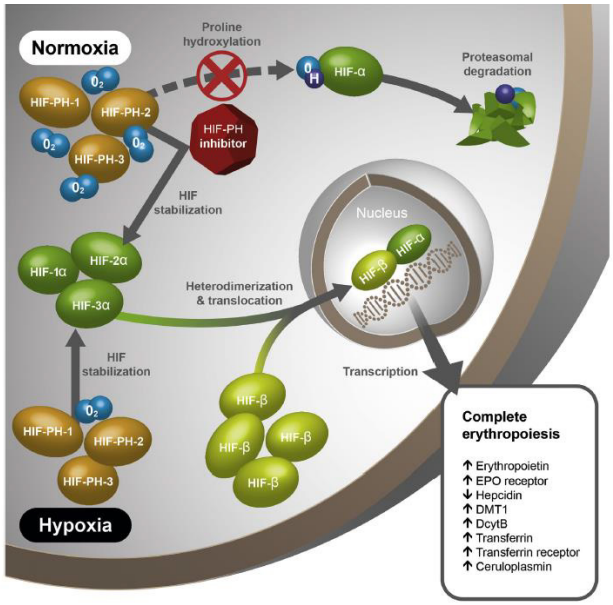

Figure 3.
Mechanism of hypoxia signalling

Several HIF stabilizers, including roxadustat, vadadustat, daprodustat, and molidustat, are currently under clinical evaluation. These agents have different dosing regimens and levels of selectivity for HIF-1α and HIF-2α. Roxadustat, daprodustat, and molidustat have a broader range of activity, while vadadustat exhibits higher selectivity for HIF-2α. Roxadustat has already been approved for use in Japan, while other agents completed phase three clinical trials. Molidustat was specifically developed for use in both dialysis and non-dialysis patients for the correction and maintenance of erythropoietin levels. According to the currently available data, these agents might be promising new therapeutic tools to improve renal anaemia management.

Written by: Jasna Trbojevic-Stankovic .
All the speakers reviewed and approved the content.

KEY POINTS

1. Anaemia commonly accompanies CKD and aggravates as eGFR decreases.
2. ESAs are often prescribed for inpatients with CKD, although their use is associated with potential risks.
3. HIF-PHIs effectively improve iron mobilization to the bone marrow and erythropoietin production, even in later CKD stages.
4. More data is required regarding the long-term safety and possible non-erythropoietic effects of HIF inhibitors.

Further readings

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