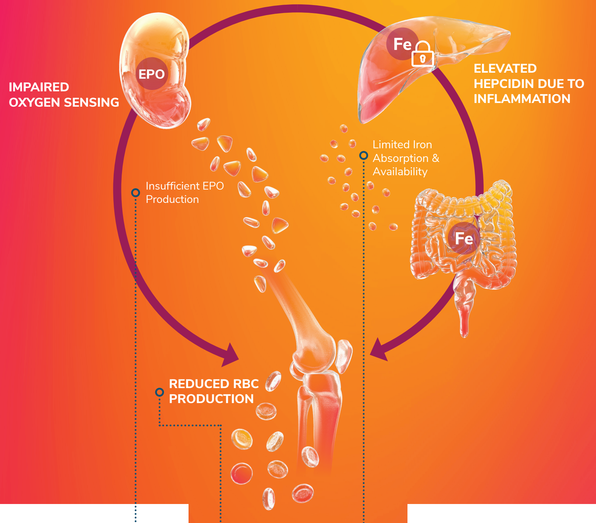
Anemia Due to Chronic Kidney Disease: Therapeutic Landscape & Scientific Discovery

Anemia due to chronic kidney disease (CKD) is multifactorial, primarily arising from insufficient synthesis of EPO, EPO resistance, disordered iron homeostasis, and inflammation.[1,2]

The treatment landscape had remained largely unchanged for 30 years until the arrival of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), which represents the most recent scientific discovery in the treatment of anemia due to CKD.[3,4]

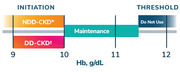
Pathogenesis of Anemia Due to CKD[1,2]



ESA[3]

KDIGO Guideline Recommendations

- Address all correctable causes of anemia
- Balance potential benefits (i.e., reducing RBC transfusion and anemia symptoms) vs. risks of therapy
- Individualize decision to treat



Transfusions[3]

KDIGO Guideline Recommendations

- Benefits may outweigh risks in cases of:
  - Rapid correction of anemia
  - Hyporesponsiveness to ESA therapy
  - Potential risks with ESA therapy
- Avoid when possible to minimize general risks
- Avoid in patients eligible for organ transplantation, when possible

Iron Therapy[3]

KDIGO Guideline Recommendations

- Balance potential benefits (i.e., minimize/reduce RBC transfusion, ESAs, and anemia symptoms) vs. risks of therapy
- DD-CKD: trial of IV iron regardless of ESA therapy
- NDD-CKD: oral or IV iron depends on severity of iron deficiency and experience with prior iron therapy

*Decision to start ESA for NDD-CKD should be individualized based on rate of Hb concentration decline, prior response to iron therapy, risk of needing transfusion, risk related to ESA therapy, and anemia symptoms. †For DD-CKD, ESA should be initiated to prevent a decline in Hb to <9.0 g/dL.

Scientific Discovery[2,4-8]

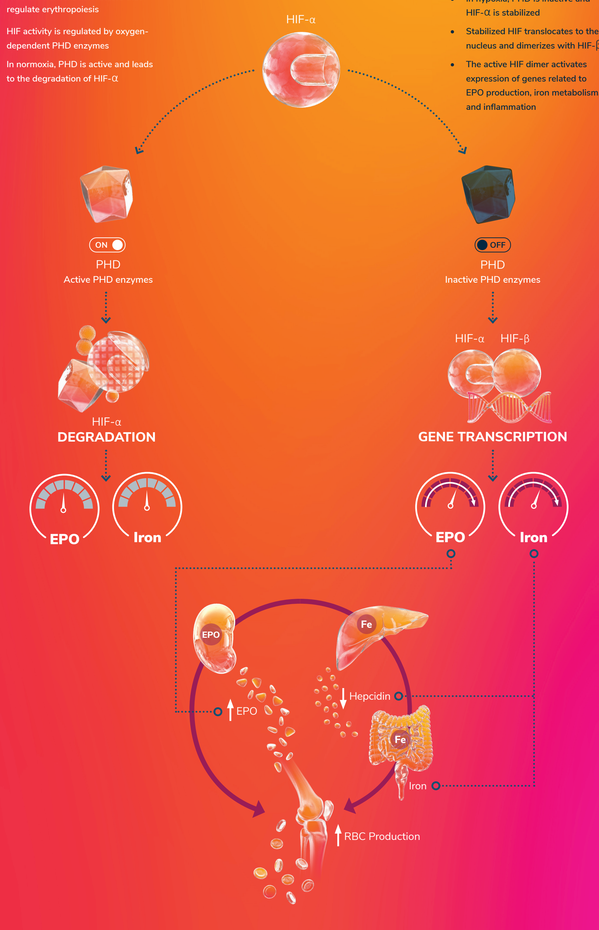
Pharmacological stabilization of hypoxia-inducible factor by HIF-PHIs is a recent scientific discovery that mimics the body's physiological response to hypoxia and addresses the underlying mechanisms of anemia due to CKD.

Normoxia

- HIFs are transcription factors that regulate erythropoiesis
- HIF activity is regulated by oxygen-dependent PHD enzymes
- In normoxia, PHD is active and leads to the degradation of HIF-α

Hypoxia

- In hypoxia, PHD is inactive and HIF-α is stabilized
- Stabilized HIF translocates to the nucleus and dimerizes with HIF-β
- The active HIF dimer activates expression of genes related to EPO production, iron metabolism, and inflammation



Abbreviations List: CKD, chronic kidney disease; DD, dialysis-dependent; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IV, intravenous; KDIGO, Kidney Disease: Improving Global Outcomes; NDD, non–dialysis-dependent; PHD, prolyl hydroxylase domain; RBC, red blood cell.

References: 1. Koury MJ, Haase VH. Nat Rev Nephrol. 2015;11:394-410. 2. Bugnara C, Eckardt KU. Hematologic aspects of kidney disease. In: Taal M, et al, eds. Brenner and Rector's The Kidney, 9th ed. Philadelphia, PA: Saunders; 2012. 3. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int Suppl. 2012;2:279-335. 4. Haase VH. Kidney Int Suppl (2011). 2021 Apr;11(1):8-25 5. Maxwell PH, Eckardt KU. Nat Rev Nephrol. 2016;12:157-168. 6. Kile M, Sudchada P. Int Urol Nephrol. 2020 Aug 8. doi: 10.1007/s11255- 020-02584-x. Online ahead of print. 7. Haase VH. Hemodial Int. 2017;21:S110-S214. 8. Kaplan JM, et al. Int J Mol Sci. 2018;19(2):389.

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