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Novel and Emerging Treatments for Anemia in CKD: HIF- Prolyl Hydroxylase Inhibitors and Beyond

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Abstract: Anemia remains a significant complication of chronic kidney disease (CKD), contributing to cardiovascular morbidity, reduced quality of life, and increased mortality. Conventional therapies, including erythropoiesis-stimulating agents (ESAs), iron supplementation, and blood transfusions, have improved outcomes but are limited by safety concerns, hyporesponsiveness, and incomplete correction of underlying pathophysiology. Advances in molecular understanding of erythropoiesis, iron regulation, and inflammation have catalyzed the development of novel therapeutic strategies. Among these, hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) represent a paradigm shift, offering an oral, physiologically adaptive approach that enhances endogenous erythropoietin production, optimizes iron utilization, and mitigates inflammation-driven erythropoietic suppression. Emerging therapies targeting hepcidin, ferroportin, and inflammatory pathways, as well as gene-editing, stem cell, and small-molecule approaches, further expand the therapeutic landscape. Despite their promise, unresolved issues regarding long-term safety, cardiovascular risk, tumorigenic potential, and cost-effectiveness necessitate ongoing research. This review synthesizes current evidence on HIF-PHIs and other novel agents, explores their clinical integration, and highlights future directions toward a personalized, multimodal approach to CKD anemia management, aiming to transcend the limitations of ESA-based therapy and improve patient outcomes.

Keywords: Chronic kidney disease (CKD), Anemia management, HIF-prolyl hydroxylase inhibitors (HIF-PHIs), Erythropoiesis, Hepcidin and iron metabolism, emerging therapies

1. Introduction

Anemia is one of the most prevalent and debilitating complications of chronic kidney disease (CKD), affecting nearly 30–90% of patients across different stages, with its prevalence increasing as renal function declines. It is a major contributor to reduced quality of life, impaired exercise capacity, progression of cardiovascular disease, and increased mortality. The etiology of anemia in CKD is multifactorial, with the primary driver being reduced erythropoietin (EPO) production by the failing kidneys. Additional mechanisms such as iron dysregulation, chronic inflammation,

and hepcidin upregulation further aggravate erythropoietic failure by limiting iron bioavailability and impairing hemoglobin synthesis [1].

For decades, the mainstay of therapy has relied on erythropoiesis-stimulating agents (ESAs), iron supplementation (oral or intravenous), and red blood cell transfusions. While ESAs revolutionized anemia management in the 1980s, their limitations have become increasingly evident, including ESA hyporesponsiveness in inflammatory states, iron dependency, high treatment costs, and increased risks of hypertension, thrombosis, and cardiovascular events at higher hemoglobin targets. Iron therapy, though essential, is often constrained by gastrointestinal intolerance, oxidative stress, and functional iron deficiency mediated by elevated hepcidin levels. Transfusions, while effective in acute settings, are associated with alloimmunization, infection risk, and increased transplant incompatibility [2].

These challenges underscore the urgent need for novel, safer, and more physiologically adaptive therapies that target underlying molecular pathways of anemia beyond simply replacing EPO. In this context, the discovery of hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs) represents a paradigm shift, offering an oral alternative that stimulates endogenous EPO production and improves iron metabolism. Moreover, other emerging strategies—including hepcidin modulators, novel iron formulations, anti-inflammatory agents, and gene-based therapies—hold promise in redefining anemia management in CKD. This review aims to provide a comprehensive overview of these novel and emerging treatments, with particular focus on HIF-PHIs, their clinical evidence, and the evolving therapeutic landscape that extends ‘‘beyond’’ traditional approaches.

2. Pathophysiological Basis for Novel Therapies

The development of anemia in CKD is tightly linked to the disruption of molecular pathways that regulate erythropoiesis, iron homeostasis, and systemic inflammation. A deeper understanding of these mechanisms has not only clarified why conventional therapies are limited but also unveiled novel therapeutic targets.

2.1 The Role of Hypoxia-Inducible Factor (HIF) Signaling in Oxygen Homeostasis and Erythropoiesis

HIF is a master transcriptional regulator of oxygen sensing and erythropoiesis. Under normoxic conditions, HIF-α subunits are hydroxylated by prolyl hydroxylase domain (PHD) enzymes, targeting them for proteasomal degradation [3]. In hypoxia, or upon inhibition of PHDs, HIF-α stabilizes, translocates to the nucleus, and dimerizes with HIF-β, leading to transcription of genes that regulate erythropoietin (EPO) synthesis, iron absorption, mobilization, and angiogenesis. In CKD, impaired renal oxygen sensing and reduced endogenous EPO production contribute significantly to anemia. Therapeutically, HIF stabilization via PHD inhibition mimics

hypoxic signaling, stimulating endogenous EPO production and enhancing erythropoietic efficiency in a more physiologic manner than exogenous ESAs [4,5].

2.2 Iron Metabolism and Hepcidin Regulation in CKD

Iron deficiency in CKD is often functional rather than absolute, characterized by abundant iron stores but poor availability for erythropoiesis. A central regulator of this process is hepcidin, a peptide hormone produced in the liver that degrades ferroportin, the only known cellular iron exporter [6]. In CKD, hepcidin levels are markedly elevated due to reduced renal clearance, chronic inflammation, and disordered iron regulation, leading to iron sequestration in macrophages and hepatocytes. This functional iron deficiency undermines the efficacy of both oral and intravenous iron supplementation. Novel therapies targeting hepcidin or ferroportin signaling aim to restore iron availability, thereby synergizing with erythropoietic pathways [7].

2.3 Inflammation-Driven Anemia Mechanisms

CKD is a chronic inflammatory state characterized by elevated levels of cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-γ. These cytokines directly suppress erythropoietin production and blunt bone marrow responsiveness. IL-6, in particular, drives hepcidin overexpression through the JAK-STAT3 pathway, further compounding iron-restricted erythropoiesis. Inflammation also induces oxidative stress, shortens red blood cell lifespan, and increases ESA hyporesponsiveness, explaining why conventional treatments often fail in CKD populations with high inflammatory burden [8].

2.4 Therapeutic Targets Emerging from Molecular Understanding

Insights into these interconnected mechanisms have led to the identification of multiple druggable targets:

- HIF-PHDs to enhance endogenous EPO and improve iron handling.
- Hepcidin antagonists and ferroportin agonists to restore iron availability.
- IL-6 inhibitors and JAK-STAT modulators to alleviate inflammation-driven suppression of erythropoiesis.
- Novel oral iron formulations designed to bypass hepcidin-mediated blockade.
- Gene and cell-based therapies that aim to restore physiologic EPO production or enhance erythroid progenitor survival [9].

Together, these advances provide a rational basis for therapies that go beyond simply replacing EPO or iron, instead addressing the molecular drivers of anemia in CKD at their source.

3. HIF-Prolyl Hydroxylase Inhibitors (HIF-PHIs)

3.1 Mechanism of Action

HIF-prolyl hydroxylase inhibitors (HIF-PHIs) represent the most clinically advanced class of novel therapies for anemia in CKD. By reversibly inhibiting prolyl hydroxylase domain (PHD) enzymes, these agents stabilize HIF-α subunits, allowing them to escape oxygen-dependent degradation. Stabilized HIF-α translocates to the nucleus, dimerizes with HIF-β, and activates transcription of multiple genes involved in erythropoietin (EPO) production, iron absorption, heme biosynthesis, and suppression of hepcidin [10]. Unlike exogenous ESAs, which deliver supraphysiological EPO levels, HIF-PHIs induce endogenous EPO production within a physiologic range, while simultaneously improving iron metabolism and mobilization (Fig.1).

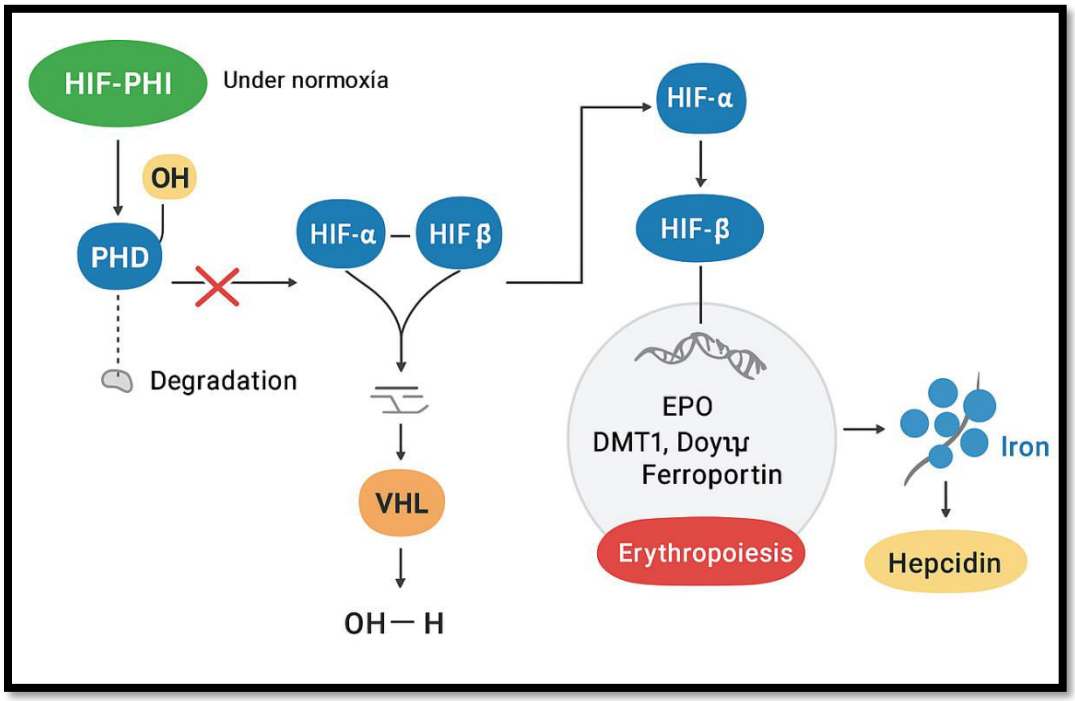

Fig.1. Mechanism of HIF-PHIs in regulating erythropoiesis and iron metabolism

3.2 Key Agents in Clinical Development and Approval

- **Roxadustat (Evrenzo / FG-4592):** Roxadustat received marketing authorization from the European Medicines Agency (EMA) on 18 August 2021 for treatment of anemia of CKD. It was first approved in China (Dec 2018 for dialysis; Aug 2019 expanded to non-dialysis) and has subsequent approvals/registrations in Japan, Chile, and South Korea (company/regulatory press releases) [11].
- **Vadadustat (AKB-6548)** - cardiovascular safety findings: Large global phase-3 trials (the PRO2TECT program for non-dialysis CKD and

INNO2VATE/INNO$_2$VATE for dialysis) showed noninferiority for hematologic efficacy but PRO2TECT did not meet noninferiority for major adverse cardiovascular events (MACE) in non-dialysis CKD (i.e., raised cardiovascular safety concerns in that population) [12].

- **Daprodustat (Jesduvroq / Jesduvroq / Duvroq)**: Approved by the US FDA for treatment of anemia of CKD in adults on dialysis (FDA decision announced in February 2023). It was approved earlier in Japan (brand name Duvroq) [13].
- Across pivotal phase-3 programs for several HIF-PHIs (roxadustat, daprodustat, molidustat, enarodustat, vadadustat), trials have shown ability to correct and maintain hemoglobin in both dialysis and non-dialysis CKD populations and reduced intravenous iron utilization in many studies, effects thought to reflect HIF-mediated hepcidin suppression and improved iron mobilization. Major regulatory and scientific attention remains on cardiovascular safety (MACE), thrombotic risk, and theoretical long-term risks from chronic HIF activation (e.g., tumor, pulmonary hypertension, retinopathy) but long-term outcomes data are still being accrued. Peer reviews and trial safety analyses document ongoing surveillance.

3.3 Clinical Trial Evidence

Large-scale Phase III clinical trials have established the efficacy of HIF-PHIs in anemia management for CKD.

- **Efficacy:**

○ Roxadustat was shown to effectively raise and maintain hemoglobin levels in both dialysis and non-dialysis patients. In a landmark randomized trial, roxadustat was non-inferior to epoetin alfa in dialysis patients and superior to placebo in non-dialysis patients [14]. Roxadustat also reduced the requirement for intravenous iron.

○ Daprodustat demonstrated non-inferiority to ESAs for hemoglobin correction and maintenance in the global ASCEND program, covering both dialysis and non-dialysis CKD populations [15].

○ Vadadustat achieved non-inferiority to darbepoetin alfa in dialysis patients but failed to do so in non-dialysis patients due to higher incidence of major adverse cardiovascular events (MACE) [16].

○ Molidustat and enarodustat, primarily studied in Japan, showed efficacy comparable to ESAs in phase III studies, leading to their national approval [17].

- **Safety:**

Cardiovascular safety remains a central consideration. Daprodustat's ASCEND trials demonstrated non-inferiority to ESAs for MACE, supporting FDA approval.

Roxadustat, despite efficacy, raised safety concerns in U.S. FDA reviews due to inconsistent cardiovascular outcomes across studies. Vadadustat showed an excess of MACE in non-dialysis CKD, limiting its approval outside Japan. Long-term safety monitoring is ongoing, particularly for risks such as thromboembolism, malignancy progression, and retinopathy.

3.4 Comparisons with ESAs in CKD (Dialysis and Non-Dialysis Patients)

Head-to-head comparisons of HIF-PHIs and ESAs have been extensively evaluated in Phase III trials.

- **Dialysis-dependent CKD**:
  Roxadustat demonstrated non-inferiority to epoetin alfa in maintaining hemoglobin levels in long-term dialysis patients [14]. Similarly, vadadustat and daprodustat both achieved hemoglobin targets comparable to darbepoetin alfa and epoetin alfa, respectively, in dialysis populations [15].
- **Non-dialysis-dependent CKD**:
  Roxadustat and daprodustat corrected anemia more effectively than placebo, offering the advantage of oral administration and reducing the need for intravenous iron [18]. However, vadadustat failed to show cardiovascular safety non-inferiority in non-dialysis patients, limiting its broader applicability [19].

Overall, HIF-PHIs provide hemoglobin correction comparable to ESAs, with added benefits of oral delivery, reduced iron dependency, and better efficacy in inflamed states, but cardiovascular safety remains a key differentiator across agents.

4. Beyond HIF-PHIs: Other Emerging Therapies

4.1 Iron-Targeted Therapies

Iron dysregulation is central to anemia in CKD, particularly functional iron deficiency, where iron stores are adequate but not bioavailable due to hepcidin-mediated sequestration. Novel therapies aim to restore iron homeostasis more effectively than conventional supplementation.

i. Hepcidin Antagonists

Hepcidin inhibits ferroportin, limiting iron export from enterocytes and macrophages. Targeting this pathway improves iron availability:

- **PTG-300 (Rusfertide)**: A hepcidin mimetic/antagonist showing promising results in early-phase trials for increasing hemoglobin and reducing iron-restricted erythropoiesis in CKD and other anemias.
- **LY2787106**: A monoclonal antibody against hepcidin; early studies suggest enhanced iron mobilization and potential synergy with ESAs [20].

ii. Ferroportin Agonists

These agents directly activate ferroportin to increase iron export from storage sites to plasma, countering hepcidin's inhibitory effect. Preclinical and early clinical studies indicate potential efficacy in correcting anemia in CKD [21].

iii. BMP-SMAD Pathway Modulators

Bone morphogenetic protein (BMP)–SMAD signaling regulates hepcidin transcription. Pharmacological inhibition reduces hepcidin, improving iron availability. These approaches are mostly in preclinical or early clinical evaluation [22].

iv. Novel Oral Iron Formulations

Improved oral iron formulations aim to enhance absorption and tolerability:

- **Ferric citrate**: Raises hemoglobin while treating hyperphosphatemia in CKD.
- **Ferric maltol**: Demonstrates efficacy in iron-deficiency anemia with improved gastrointestinal tolerability.
- **Sucrosomial iron**: Encapsulated iron with enhanced bioavailability and fewer gastrointestinal adverse events; early CKD studies show positive hematologic responses [23].

These therapies, by targeting the molecular drivers of iron-restricted erythropoiesis, offer potential alternatives or complements to ESAs and HIF-PHIs, particularly in patients with ESA hyporesponsiveness.

4.2 Inflammation-Modulating Therapies

Chronic inflammation is a major contributor to anemia in CKD, often leading to functional iron deficiency and ESA hyporesponsiveness. Therapeutic strategies that modulate inflammatory pathways are emerging as adjuncts or alternatives to conventional erythropoietic therapies

i. IL-6 Inhibitors

Interleukin-6 (IL-6) upregulates hepcidin synthesis, reducing iron availability and suppressing erythropoiesis. IL-6 blockade has been investigated for anemia correction in CKD. Ziltivekimab, a monoclonal antibody targeting IL-6, has demonstrated promising results in early-phase trials. In patients with CKD and elevated inflammatory markers, ziltivekimab reduced hepcidin levels and improved hemoglobin concentrations, highlighting its potential to overcome inflammation-driven anemia [24].

ii. JAK-STAT Pathway Modulators

The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway mediates multiple cytokine signals, including those that induce hepcidin

and suppress erythropoiesis. Pharmacologic inhibition of JAK-STAT signaling has shown efficacy in preclinical and early clinical studies by:

- Reducing hepcidin expression, thereby increasing iron availability.
- Enhancing erythropoietic responses in inflammatory states. Agents targeting this pathway are under early investigation for CKD-associated anemia, particularly in patients who are ESA-resistant or have chronic systemic inflammation [25].

By addressing the inflammatory component of anemia, these therapies may complement existing treatments such as HIF-PHIs and iron-based therapies, potentially improving outcomes in patients with complex CKD anemia profiles.

4.3 Gene and Cell-Based Therapies

Recent advances in molecular medicine have opened avenues for gene and cell-based approaches to treat anemia in CKD, targeting the underlying defects in erythropoiesis rather than symptomatic correction alone.

i. Gene Editing Strategies for EPO Production

Gene therapy approaches aim to restore or enhance endogenous erythropoietin (EPO) synthesis in the kidney or liver. CRISPR/Cas9 and other gene-editing platforms are being explored to modulate EPO gene expression or to downregulate negative regulators such as hepcidin. Preclinical studies in animal models have demonstrated that precise editing can increase EPO production and correct anemia without exogenous ESA administration. These strategies remain largely in preclinical or early-phase experimental stages, with challenges including targeted delivery, long-term expression, and safety monitoring for off-target effects [26].

ii. Stem Cell-Based Erythropoiesis Augmentation

Hematopoietic stem cell (HSC)–based therapies seek to enhance red blood cell production directly. Approaches include ex vivo expansion of HSCs followed by autologous transplantation or pharmacologic stimulation of resident progenitors. Induced pluripotent stem cells (iPSCs) have been investigated to generate erythroid progenitors capable of producing functional red blood cells, offering a potential long-term solution for ESA-resistant anemia. Early experimental models demonstrate feasibility, but clinical translation is still in its infancy, with ongoing studies addressing engraftment efficiency, immune compatibility, and scalability [27].

Collectively, gene and cell-based therapies represent a future direction for CKD anemia management, offering the possibility of durable or curative interventions by targeting the root molecular and cellular defects underlying erythropoietic failure.

4.4 Other Small-Molecule Agents

In addition to HIF-PHIs, iron-targeted, and inflammation-modulating therapies, several small-molecule agents are emerging as potential treatments for anemia in CKD, acting via diverse mechanisms to enhance erythropoiesis or improve red blood cell function [28].

i. Activin Receptor Ligand Traps

Sotatercept and similar agents act as ligand traps for activin and related TGF-β superfamily members, modulating late-stage erythropoiesis in the bone marrow. By sequestering inhibitory ligands, these agents promote maturation of erythroid precursors, improving hemoglobin and red blood cell counts independently of EPO stimulation. Early-phase clinical trials in CKD patients show that sotatercept increases hemoglobin levels and may complement ESA therapy, particularly in patients with ESA hyporesponsiveness [29,30].

ii. Antioxidants and Metabolic Modulators

Oxidative stress and metabolic derangements contribute to impaired erythropoiesis in CKD. Small molecules such as N-acetylcysteine, bardoxolone methyl, and mitochondrial-targeted antioxidants have demonstrated improvement in erythroid precursor survival and red blood cell function in preclinical models and early human studies. These agents may enhance the efficacy of conventional therapies by reducing erythrocyte apoptosis, improving iron utilization, and modulating inflammatory/metabolic stress, although large-scale clinical validation is still pending [31].

Overall, these small-molecule therapies represent adjunctive or alternative strategies for CKD anemia management, particularly in patients who are ESA-resistant, have functional iron deficiency, or are not ideal candidates for HIF-PHIs.

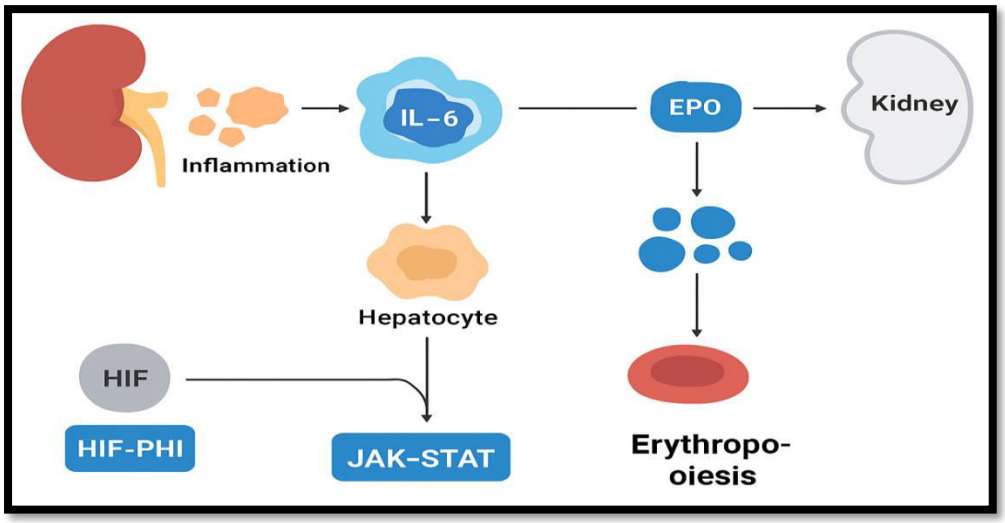

Fig. 2. Emerging therapeutic targets in CKD anemia

Table 1. Comparison of currently available treatments for anemia in CKD [32-36]

Therapy	Mechanism of Action	Route of Administration	Key Advantages	Limitations / Safety Concerns	Clinical Notes
ESAs (Epoetin alfa, Darbepoetin alfa, CERA)	Stimulate erythropoiesis by activating EPO receptors in bone marrow	Subcutaneous / IV	Proven efficacy in raising hemoglobin; widely available	Cardiovascular risk (hypertension, thrombosis, stroke); parenteral only; ESA hyporesponsiveness in inflammation	Requires iron supplementation; dose titration needed to avoid hemoglobin overshoot
HIF-PHIs (Roxadustat, Vadadustat, Daprodustat, Molidustat, Enarodustat)	Stabilize HIF-α → upregulate endogenous EPO and genes regulating iron metabolism	Oral	Effective in dialysis and non-dialysis CKD; reduces iron and ESA requirements; effective in inflammatory states	Cardiovascular risk varies by agent; theoretical tumorigenesis risk; long-term safety data limited	Oral therapy improves adherence; may reduce IV iron use; careful cardiovascular monitoring required
Iron Supplements (Ferric citrate, Ferric maltol, Sucrosomial iron)	Provide bioavailable iron for erythropoiesis	Oral / IV	Well-established; improves hemoglobin and iron stores; oral options improve tolerability	IV iron: risk of overload, hypersensitivity; oral iron: gastrointestinal intolerance, limited absorption	Preferred in iron-deficient patients; monitor ferritin and TSAT
Hepcidin	Block	Subcutaneo	Target	Early-stage;	Particularly

Antagonists (PTG-300, LY2787106)	hepcidin or its activity → mobilize iron from stores	us / IV	functional iron deficiency; synergistic with ESAs	limited long-term data; injection required	useful in ESA-resistant or inflamed patients
Activin Receptor Ligand Traps (Sotatercept)	Sequester TGF-β superfamily ligands → promote late-stage erythropoiesis	Subcutaneous	Enhances erythroid maturation; ESA-independent	Early-phase clinical data; potential off-target effects; cost	May complement ESA therapy in hyporesponsive patients
Inflammation-Modulating Agents (IL-6 inhibitors, JAK-STAT inhibitors)	Reduce cytokine-mediated hepcidin upregulation and erythropoiesis suppression	IV / Oral	Effective in inflammation-driven anemia; may improve ESA responsiveness	Early clinical data; risk of immunosuppression; cost	Best suited for patients with high inflammatory burden
Gene / Cell-Based Therapies (CRISPR/Cas9, HSC, iPSC-based strategies)	Restore endogenous EPO production or enhance erythropoiesis	Ex vivo / targeted gene delivery	Potentially curative; addresses root cause	Experimental; safety, delivery, and ethical considerations; not yet approved	Preclinical/early-phase only; long-term outcomes unknown
Antioxidants / Metabolic Modulators (N-acetylcyst	Reduce oxidative stress, improve erythroid survival	Oral / IV	May enhance erythropoiesis; adjunct to ESA/HIF-	Limited clinical data; long-term efficacy unclear	Potential supportive therapy, especially in oxidative stress-

eine, Bardoxolone methyl)	and iron utilization		PHIs		mediated anemia

5. Safety Concerns and Long-Term Considerations

While novel therapies for CKD-associated anemia offer significant advantages over conventional ESAs, safety and long-term effects remain critical considerations for clinical adoption.

i. Cardiovascular Outcomes and Thrombosis Risks

HIF-PHIs, while effective in correcting hemoglobin, have raised concerns regarding cardiovascular safety. Some trials (e.g., vadadustat in non-dialysis CKD) demonstrated a higher incidence of major adverse cardiovascular events (MACE) compared with ESAs [19]. ESAs are also associated with hypertension, stroke, and thrombosis, particularly at higher hemoglobin targets. Careful dose titration, patient selection, and regular monitoring of hemoglobin and blood pressure are essential to mitigate cardiovascular risk.

ii. Potential Tumorigenesis with HIF Stabilization

HIF stabilization upregulates multiple genes involved in angiogenesis (e.g., VEGF) and metabolism. Preclinical studies suggest a theoretical risk of promoting tumorigenesis or progression of pre-existing malignancies, although clinical evidence in CKD patients remains limited [37]. Long-term pharmacovigilance and registry studies are recommended to monitor malignancy incidence among patients receiving chronic HIF-PHI therapy.

iii. Iron Overload vs. Functional Iron Deficiency

Iron-targeted therapies and chronic ESA use carry a risk of iron overload, particularly with intravenous iron administration. Conversely, inflammation-driven CKD anemia can present as functional iron deficiency, where iron stores are sufficient but not bioavailable. Regular monitoring of ferritin, transferrin saturation (TSAT), and hepcidin is recommended to guide therapy and prevent both iron deficiency and toxicity [33].

iv. Monitoring Strategies and Risk Mitigation

Hemoglobin, hematocrit, iron parameters, blood pressure, and cardiovascular markers should be routinely assessed. Dose adjustments for HIF-PHIs, ESAs, or iron therapies should be guided by these parameters to optimize efficacy while minimizing adverse effects. Special consideration should be given to elderly patients, those with pre-existing cardiovascular disease, or patients with active

malignancy, as these populations may be more susceptible to therapy-related risks [38].

6. Clinical Integration and Real-World Evidence

Translating emerging therapies for CKD-related anemia into routine clinical practice requires consideration of patient characteristics, healthcare resources, and real-world treatment outcomes.

i. Patient Selection

- **Dialysis vs. Non-Dialysis**: HIF-PHIs have demonstrated efficacy in both populations; however, cardiovascular safety profiles differ. For example, vadadustat showed non-inferiority in dialysis-dependent CKD but had increased MACE in non-dialysis patients [19].
- **ESA Hyporesponsiveness**: Patients who exhibit poor response to conventional ESAs, often due to chronic inflammation or iron-restricted erythropoiesis, are prime candidates for HIF-PHIs or iron-targeted therapies.
- **High Inflammatory Burden**: Agents that modulate IL-6 or JAK-STAT signaling may be particularly beneficial in patients with elevated inflammatory markers, where conventional therapies are less effective [39].

ii. Cost-Effectiveness and Access Considerations

Oral HIF-PHIs may reduce the need for intravenous iron and ESA injections, potentially decreasing healthcare resource utilization. However, regional variations in drug pricing, reimbursement, and regulatory approvals influence accessibility. For instance, Japan and China have broader adoption of multiple HIF-PHIs, whereas in the U.S. and EU, restricted approvals and cost considerations limit widespread use. Early economic models suggest that HIF-PHIs may be cost-effective in ESA-hyporesponsive populations, but real-world data remain limited [17].

iii. Real-World Prescribing Trends and Challenges

Real-world registry data indicate that HIF-PHIs are increasingly used in patients with difficult-to-manage anemia, often in combination with conventional therapies to optimize hemoglobin targets. Challenges include monitoring requirements, cardiovascular safety, long-term outcomes, and adherence, particularly with oral agents in elderly or comorbid populations.

iv. Role in Personalized Anemia Management

- Integration of novel therapies enables precision medicine approaches, tailoring treatment based on:
    - Hemoglobin trajectory
    - Iron status and hepcidin levels

- Inflammatory markers
- Comorbid conditions (cardiovascular disease, diabetes, malignancy)

Combining HIF-PHIs, iron-targeted therapies, anti-inflammatory agents, or small-molecule adjuncts allows individualized regimens that optimize efficacy while minimizing adverse events [40].

7. Research Gaps and Future Directions

Despite rapid advancements in CKD-related anemia therapeutics, several critical knowledge gaps remain, highlighting opportunities for future research.

i. Head-to-Head Comparative Studies

Most clinical trials have compared HIF-PHIs or emerging agents against placebo or conventional ESAs, but direct head-to-head comparisons among novel therapies are limited. Comparative studies are needed to determine relative efficacy, safety, and cost-effectiveness of HIF-PHIs, iron-targeted agents, anti-inflammatory therapies, and small-molecule modulators in diverse CKD populations [14].

ii. Biomarkers for Therapy Response and Risk Stratification

Reliable biomarkers could guide personalized therapy selection and predict response. Potential candidates include hepcidin, soluble transferrin receptor, erythroferrone, inflammatory cytokines, and genetic markers. Integrating biomarker-guided algorithms could optimize outcomes, minimize adverse events, and reduce unnecessary therapy exposure [19].

iii. Long-Term Safety Data

Current trials provide up to 2–3 years of follow-up; long-term safety beyond 5–10 years remains largely unknown. Monitoring for cardiovascular events, thromboembolism, malignancy, and retinopathy is essential, particularly for chronic HIF-PHI use. Real-world registries and post-marketing surveillance studies will be crucial for comprehensive safety assessment [17].

iv. Integration into Multi-Pronged Anemia Management

Future research should focus on algorithmic integration of novel therapies with conventional ESAs, iron supplementation, and anti-inflammatory strategies. Combination or sequential therapy strategies could maximize hemoglobin response, address functional iron deficiency, and personalize treatment for CKD patients with complex comorbidities. Modeling studies and pragmatic trials could inform best practices for individualized, mechanism-based anemia management [41].

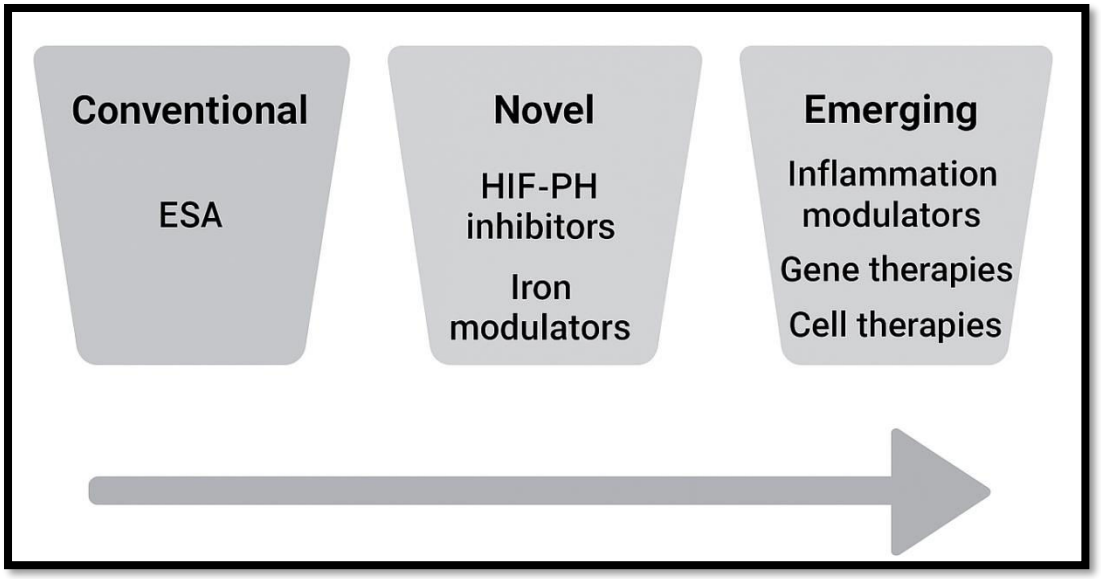

Fig. 3. Future landscape of CKD anemia therapy

8. Conclusion

The landscape of anemia management in CKD is undergoing a transformative shift with the advent of HIF-prolyl hydroxylase inhibitors and other emerging therapies. HIF-PHIs offer an oral, physiologically aligned alternative to conventional ESAs, improving hemoglobin levels, enhancing iron utilization, and demonstrating efficacy in both dialysis and non-dialysis populations. Beyond HIF-PHIs, iron-targeted agents, inflammation-modulating therapies, small-molecule modulators, and gene or cell-based approaches expand the therapeutic arsenal, providing options for ESA-resistant patients, those with functional iron deficiency, or high inflammatory burden. These advances support a movement away from sole dependence on ESAs toward a multi-pronged, mechanism-driven approach. Looking forward, integration of these therapies into personalized anemia management strategies, guided by biomarkers, patient comorbidities, and real-world evidence, holds promise for safer, more effective, and sustainable treatment. Continued research, long-term safety monitoring, and clinical experience will be pivotal in fully realizing the potential of these innovative approaches, ultimately improving outcomes and quality of life for patients with CKD-related anemia.

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Conflicts of Interest: The authors declare no conflicts of interest.

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