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Kidney Updates 2026

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KIDNEY UPDATES 2026

Smarter Anemia Care in Dialysis

Integrating HIF-PHIs, Iron Strategies, and AI-Guided Therapy

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LEARNING OBJECTIVES

- Explain the evolving role, mechanisms of action, and safety profile of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) in anemia management for dialysis patients.
- Apply evidence-based and precision-focused principles of anemia management in dialysis care and incorporate emerging AI-guided decision-support tools to optimize individualized treatment strategies.

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THE BURDEN OF ANEMIA IN DIALYSIS

>90%
HD patients affected by renal anemia

11%
Higher dialysis risk per 1 g/dL ↓ in Hb

50-53%
Anemia prevalence in CKD stage 4–5

Clinical Consequences of Untreated Anemia:

- ↑ Cardiovascular morbidity and mortality
- Reduced exercise tolerance and quality of life
- Higher hospitalization rates and transfusion burden
- Accelerated CKD progression
- Increased risk of left ventricular hypertrophy

Source: NHANES analysis; Int Urol Nephrol 2025; KDIGO 2026

KEY CAUSES

- EPO deficiency/hyporesponsiveness
- Iron deficiency
- Blood loss (GI [malignancy, parasites], dialysis)
- Shortened RBC survival
- Hyperparathyroid or thyroid dysfunction
- Bone marrow suppression by inflammation; drugs (ACEi, ARBs, proliferation signal inhibitors in KTRs); or malignancy (MDS, myelofibrosis)
- Other nutritional deficiency (folate, vitamin B_{12})
- Chronic inflammation (CHF, obesity, autoimmune diseases)
- Inherited anemia (thalassemia, sickle cell anemia)
- Anti-ESA antibody-mediated pure red cell aplasia (PRCA)

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IRON STRATEGIES IN DIALYSIS

KDIGO 2026 NEW NOMENCLATURE: 'Absolute iron deficiency' → Systemic Iron Deficiency | 'Functional iron deficiency' → Iron-Restricted Erythropoiesis

CKD G5HD (Hemodialysis)

Initiate iron when:
Ferritin ≤ 500 ng/mL AND TSAT ≤ 30%

Route of delivery:
IV iron preferred over oral (KDIGO Rec 2.2)
Proactive approach to maintain stable iron status

Withhold if:
Ferritin > 700 ng/mL OR TSAT ≥ 40%
During active systemic infection

CKD Not on HD / Peritoneal Dialysis

Initiate iron when (either criterion):
Ferritin < 100 ng/mL AND TSAT < 40%
OR Ferritin 100–300 ng/mL AND TSAT < 25%

Route of delivery:
Oral or IV based on patient preference, severity, tolerability, and cost (KDIGO Rec 2.4)

Switch oral → IV if:
Insufficient effect after 1–3 months
OR poor oral tolerability

Monitor: Hb, ferritin, TSAT every 1–3 months (HD) or every 3 months (PD/NDD-CKD). Manage hypersensitivity risk with all IV formulations.

Ref: KDIGO 2026 Anemia in CKD Guideline (Kidney Int 2026) | Medscape: New KDIGO Guidelines 2026

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IV IRON FORMULATIONS: PRACTICAL GUIDE

Formulation	Typical HD Dose	Infusion Time	Dose/Session	Key Notes
Iron Sucrose (Venofer)	100 mg × 10 (1000 mg total)	15–30 min per session	100 mg over 2 weeks HD	Well-studied; mild allergy risk
Ferric Gluconate (Ferrlecit)	125 mg × 8 (1000 mg)	60 min infusion	125 mg over 8 sessions	Lower single dose; frequent dosing
Ferric Carboxymaltose (Ferinject/Injectafer)	Up to 1000 mg single dose	15–60 min (high-dose)	Less frequent dosing	Phosphate monitoring needed
Low MW Iron Dextran (INFeD)	Total dose calculated	1–4 hrs test dose req	Infrequent big doses	Test dose required; higher allergy risk
Ferumoxytol (Feraheme)	510 mg × 2 doses	≥15 min per dose	2 doses, 3-8 days apart	MRI interference; black box warning

All IV iron: Administer only where acute hypersensitivity and hypotensive reactions can be managed promptly (KDIGO 2026 Practice Point 2.9)

Ref: KDIGO 2026 Anemia in CKD Guideline Table 4 | Guideline Central KDIGO 2026 Summary

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ESAs IN 2026: PLACE IN THERAPY

ESA First-Line: Key Guidance

- ESAs remain first-line when correctable causes are addressed (KDIGO 3.1.1)
- Initiate ESA in CKD G5D when Hb ≤ 9.0–10.0 g/dL (Rec 3.2.1)
- Target Hb maintenance below 11.5 g/dL to minimize CV risk
- For non-dialysis CKD: individualize initiation based on symptoms, risk of transfusion
- Identify and treat ESA hyporesponsiveness causes before escalating dose

ESA Hyporesponsiveness: Causes

- Iron deficiency (most common — check TSAT, ferritin)
- Chronic inflammation / elevated hepcidin
- Suboptimal dialysis adequacy (↓ Kt/V)
- Secondary hyperparathyroidism
- Folate/B12 deficiency
- Occult blood loss (GI, access site)
- Malnutrition, malignancy, myelodysplasia
- Anti-EPO antibodies (PRCA — rare but important)

HIF-PHIs may overcome inflammation-driven ESA hyporesponsiveness — a key clinical advantage (PMC12180824, 2025)

Ref: KDIGO 2026 Guidelines | Medscape Jan 2026 | Renal & Urology News Feb 2026

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HIF-PHIs: MECHANISM OF ACTION

NORMOXIA
PHD enzymes active

→

HIF-α hydroxylated by PHD1/2/3
VHL-mediated ubiquitination

→

Proteasomal degradation of HIF-α
No EPO transcription

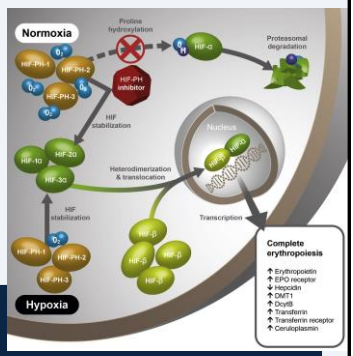
HIF-PHI Administered
Oral agent inhibits PHD enzymes

→

HIF-α Stabilized
Escapes VHL-mediated degradation

→

↑ EPO Production + Iron Mobilization
↓ Hepcidin, ↑ Hb



Key Advantages of HIF-PHIs over ESAs

- Oral administration — no injections required
- Effective under inflammatory conditions (↓ ESA hyporesponsiveness)
- Stimulates physiologic EPO levels (avoids supraphysiologic peaks)
- Lowers hepcidin → improves iron availability for erythropoiesis
- Associated with favorable lipid profile (↓ LDL with roxadustat)

References: Biomedicines 2024;12(8):1884 | Stoumpos et al., NDT 2024;39(10):1710 | PMC12180824

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HIF-PHI CLINICAL TRIAL EVIDENCE

Agent	Trial	Design	Hb Outcome vs ESA	MACE Safety	Approval
Roxadustat	ROCKIES OLYMPUS	RCT vs ESA (DD-CKD)	Non-inferior +0.7 g/dL HD	Non-inferior (MACE)	EU/CN/JP (Not FDA)
Daprodustat	ASCEND-D NEJM 2021	Phase 3 RCT vs EPO/darbe	Non-inferior ΔHb ≥ 0 g/dL	Non-inferior MACE+	FDA 2023 US approved
Vadadustat	INNO2VATE NEJM 2021	Phase 3 RCT vs darbe	Non-inferior DD-CKD	Non-inferior MAP	EU, JP (Not FDA)
Molidustat	MIYABI-HD-M Japan	Phase 3 RCT vs ESA	Non-inferior Hb stable	No significant difference	JP only (2021)

Key take-away: All major HIF-PHIs show non-inferiority to ESAs for Hb correction and MACE endpoints in dialysis populations.

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HIF-PHI vs ESA

Efficacy Evidence

26 Phase 3 RCTs

24,387 patients
2024 Meta-Analysis

✓ NONINFERIOR

Hemoglobin correction confirmed

Primary Efficacy Finding

HIF-PHIs achieved a small but statistically significant Hgb increase vs ESAs (mean difference +0.10 g/dL, 95% CI 0.02–0.17). Effect more pronounced vs short-acting ESAs (+0.21 g/dL) than long-acting (−0.01 g/dL). More pronounced in younger patients.

No Significant Difference in Safety Outcomes

No significant differences found in MACE (RR 1.00, 95% CI 0.94–1.07), MACE+, thrombotic events, AV fistula thrombosis, cancer, or death vs ESAs in the 2024 meta-analysis.

Umbrella Review Confirmation

An umbrella review of 14 meta-analyses confirmed HIF-PHIs effectively increase hemoglobin and improve iron metabolism (↓ hepcidin, ↑ transferrin saturation) with safety profiles generally comparable to ESAs. Network meta-analyses and systematic reviews reach similar noninferiority conclusions.

Minutolo R, Liberti ME, Simeon V, et al. Efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in patients with chronic kidney disease: meta-analysis of phase 3 randomized controlled trials. *Clin Kidney J.* 2023;17(1):sfad143. Published 2023 Jun 22. doi:10.1093/ckj/sfad143

Ren S, Yao X, Li Y, Zhang Y, Tong C, Feng Y. Efficacy and safety of hypoxia-inducible factor-prolyl hydroxylase inhibitor treatment for anemia in chronic kidney disease: an umbrella review of meta-analyses. *Front Pharmacol.* 2023;14:1296702. Published 2023 Nov 30. doi:10.3389/fphar.2023.1296702

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Safety Concerns, Regulatory Status & Clinical Implications

2026 KDIGO Guidelines recommend ESAs over HIF-PHIs as first-line (Grade 2D)

⚠ Critical Safety Concerns

- Vadadustat failed noninferiority for MACE in non-dialysis CKD
- Some HIF-PHIs show signals for ↑ MACE & vascular access thrombosis (non-dialysis)
- Long-term safety data limited vs. decades of ESA experience
- Very low certainty of evidence for comparative safety (dialysis & non-dialysis)

FDA Regulatory Status

FDA Orange Book

Vadadustat (Vafseo): FDA approved Mar 2024 — dialysis ≥3 months only
Daprodustat (Jesduvroq): Approved 2023, withdrawn Dec 2024 (business reasons)
Roxadustat: FDA rejected; approved Europe, China, Japan
Boxed warnings: Thrombotic/cardiovascular events (dialysis patients)

Locatelli F, Del Vecchio L. Hypoxia-Inducible Factor-Prolyl Hydroxyl Domain Inhibitors: From Theoretical Superiority to Clinical Noninferiority Compared with Current ESAs?. *J Am Soc Nephrol*. 2022;33(11):1966-1979. doi:10.1681/ASN.2022040413

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KDIGO 2026: HIF-PHI RECOMMENDATIONS

Guideline 3.1.1: Suggest using an ESA rather than HIF-PHI as FIRST-LINE treatment when correctable causes have been addressed (Evidence 2D)

When to Consider HIF-PHIs (KDIGO 2026):

- ESA hyporesponsiveness or intolerance
- Barriers to parenteral administration (e.g., peritoneal or home dialysis)
- Patient preference for oral therapy

DOSING GUIDANCE

- Start at recommended dose; titrate to lowest effective dose
- Target Hb: 10–11.5 g/dL (avoid >13 g/dL)
- Monitor CBC, iron studies every 1–3 months
- Suspend during active systemic infection

Avoid HIF-PHIs In (KDIGO 2026):

- Children & kidney transplant recipients
- Active cancer or history of malignancy
- History of cardiovascular events / thrombosis
- Polycystic kidney disease
- Pulmonary arterial hypertension
- Proliferative retinal disease
- Hepatic impairment, active seizures
- Pregnancy

Not indicated for:

- Non-dialysis CKD anemia • RBC transfusion substitution
- QoL, fatigue, or well-being improvement

Ref: KDIGO 2026 Anemia in CKD Guideline (Kidney Int, Jan 2026) | Stoumpos et al., NDT 2024;39:1710

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SAFETY: HIF-PHIs & ESAs — WHAT TO WATCH

HIF-PHI Safety Concerns

MACE / Thrombosis	Non-inferior in trials; screen CV history carefully before use
Hypertension	Monitor BP; some reports of worsening hypertension
Tumor growth	HIF pathway activates VEGF; avoid in active/recent cancer
Retinal disease	Theoretical risk of progression; contraindicated in proliferative retinopathy
Pulm. Hypertension	HIF-1α promotes PAH pathways; contraindicated
Drug interactions	CYP2C8/1A2 metabolism — check for gemfibrozil, rifampin co-administration

ESA Safety Monitoring

MACE Risk	Risk increases if target Hb >13 g/dL; keep <11.5 g/dL
Stroke	Elevated risk with supraphysiologic hemoglobin targets (TREAT trial)
Hypertension	Monitor BP at each visit; exacerbated by rapid Hb rise
PRCA	Pure red cell aplasia: rare; suspect if sudden Hb drop + reticulocytopenia
Thrombosis	Vascular access thrombosis; tumor progression in cancer patients
Hb Oscillation	Frequent cycling increases CV risk; AI tools can reduce this

Target Hb: 10–11.5 g/dL for all dialysis patients regardless of agent used. Individualize shared decision-making. (KDIGO 2026)

Ref: KDIGO 2026 Guideline | NDT 2024;39:1710 (Stoumpos) | MDPI Biomedicines 2024;12:1884

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SECTION 3

AI-Guided Anemia Therapy

Machine learning, clinical decision support, and the future of personalized erythropoiesis management

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WHY AI FOR ANEMIA MANAGEMENT?

High Variability

Inter- and intra-patient variability in ESA and iron response makes uniform dosing protocols suboptimal

Complex Data

Each HD patient generates labs, dialysis metrics, medications, and clinical notes every session

Hb Cycling

Maintaining Hb within 10–12 g/dL is difficult; oscillations between anemia and erythrocytosis are common

ESA Cost

ESA overprescribing increases costs and adverse events; under-dosing leads to anemia and transfusions

AI Solution

Machine learning models can process high-dimensional longitudinal data from HD patients to predict Hb trajectories, recommend individualized ESA/iron doses, and alert for transfusion risk — all in real time.

Ref: Barbieri et al., Kidney Int 2016;90:422 | Inoue et al., Ren Replace Ther 2025 | PMC11984408

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THE ANEMIA CONTROL MODEL (ACM)

ACM Architecture:

1. **Artificial Neural Network (ANN)**

   Trained on 170,000 clinical records
   Predicts future Hb concentrations
   Inputs: labs, doses, demographics, dialysis metrics

2. **Dose Selection Algorithm**

   Generates optimal ESA (darbepoetin) and IV iron recommendations per patient
   Targets Hb and ferritin goals

Clinical Results (Barbieri et al.)

Kidney Int. 2016;90:422–429

752 HD patients in 3 pilot clinics	**↓ESA** Reduced ESA use across cohort
↓Hb Swing Minimized Hb fluctuations	**↑Target** Improved %time at Hb target

Updated 2024 validation (Blood Purif 2024;53:405): ACM reduces inappropriate ESA prescribing and severe anemia in dialysis centers.

Ref: Barbieri et al., Kidney Int 2016;90:422 | Garbelli et al., Blood Purif 2024;53:405 | PMID: 38382484

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ADVANCED AI MODELS: RECENT EVIDENCE

GRU-Attention Model (GAM) — Kang et al., Sci Rep 2024

Design: Gated Recurrent Unit + multi-head attention module for sequential HD patient data (252 patients, 6 years, Kangwon Univ. Hospital)
Function: (1) Hb level prediction → ESA dose recommendation (more/similar/less) | (2) Transfusion alert: necessary vs. not necessary
Result: Outperformed conventional rule-based dosing; reduced transfusion events.

Open-Source ML Prediction — Inoue et al., Ren Replace Ther 2025

Design: PyCaret open-source library applied to 67 long-term HD patients (986 data points, Tokyo Women's Medical University)
Inputs: CBC, iron indices (TSAT, ferritin), albumin, CRP, dialysis adequacy, ESA and iron doses
Finding: ML showed potential to predict Hb levels and reduce ESA usage; clinical implementation remains limited but feasible with accessible tools.

AI in CKD Scoping Review — Singh et al., Kidney Medicine 2025;7:100927

41 studies (2014–2024): AI use cases in CKD include early detection (n=6), risk stratification (n=14), treatment recommendations (n=4), NLP/LLMs for patient care (n=17). Anemia management among the most actionable AI targets.

Ref: Kang et al., Sci Rep 2024 (PubMed 39500941) | Inoue et al., Ren Replace Ther 2025 | Singh et al., Kidney Medicine 2025

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KidneyNews Online
Keeping the Kidney Community Informed

From: Neri L, Fuertinger D, Usvyat L. Leveraging Artificial Intelligence to Optimize Anemia Management in Dialysis and Transplantation Populations. *Kidney News. 2026;18(3):20-21. doi:10.62716/kn.002642025*

DOI: https://doi.org/10.62716/kn.002642025

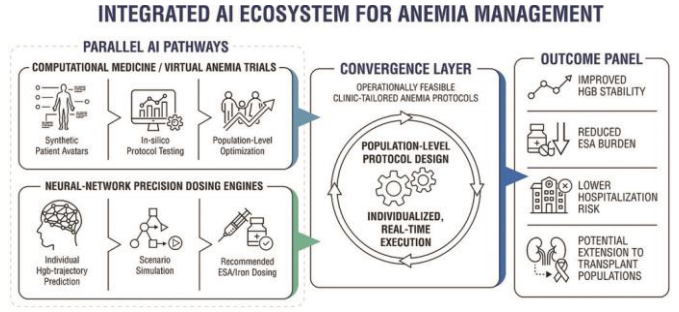

Figure. Unified AI ecosystem supporting strategic protocols and individualized execution of anemia therapy

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AI IN DIALYSIS: OPPORTUNITIES & BARRIERS

Opportunities

- Real-time Hb prediction and proactive ESA/iron dose adjustment
- Transfusion risk alerting — reduce blood product utilization
- Personalized HIF-PHI vs ESA selection using patient profiles
- Identification of ESA hyporesponders early in treatment course
- Integration with digital twin models for therapy simulation
- Large language models for patient communication and adherence
- Population-level quality improvement and benchmark reporting

Barriers to Implementation

- Data quality and accessibility across EHR systems
- Model interpretability — 'black box' concerns for clinical trust
- Regulatory approval requirements (FDA clearance for CDSS)
- Workflow integration — alert fatigue and usability
- Clinician training and adoption challenges
- Privacy and data governance concerns
- Need for prospective validation across diverse populations
- Liability and accountability frameworks

Ref: Singh et al., Kidney Medicine 2025 | Barbieri, Artif. Intell. Kidney Disease 2025 (renalresearch.com)

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INTEGRATED ANEMIA MANAGEMENT ALGORITHM

1 Evaluate Anemia (All HD Patients)

2 Iron First: Correct Iron Deficiency

- HD patients: IV iron if ferritin ≤500 ng/mL and TSAT ≤30%

3 ESA or HIF-PHI? (Decision Points)

- Initiate ESA when Hb ≤9.0–10.0 g/dL; target Hb <11.5 g/dL

4 AI-Augmented Monitoring

- ML-based Hb prediction → proactive dose adjustment
- Transfusion alert system integration
- Ongoing outcome tracking and dose optimization

Algorithm based on KDIGO 2026 Guideline | Barbieri ACM | Kim GRU-Attention Model | Singh et al. AI Review

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CLINICAL CASE: PUTTING IT ALL TOGETHER

Case Vignette

65F with ESKD on HD ×5 years, DM, CAD. Current darbepoetin alfa 100 mcg q2wks. Hb 8.8 g/dL ×3 months despite dose escalation. Ferritin 220 ng/mL, TSAT 18%, CRP 28 mg/L.

Q1: How would you approach her iron status?

TSAT 18% with ferritin 220 = Iron-Restricted Erythropoiesis (functional iron deficiency, KDIGO 2026). Initiate IV iron — ferritin ≤500 & TSAT ≤30%. However, suspend if active infection is contributing to high CRP. Recheck in 4–6 weeks.

Q2: Is she an ESA hyporesponder? What's next?

Yes — CRP elevation suggests inflammation-driven hyporesponsiveness. Optimize dialysis Kt/V, check B12/folate. If persistently unresponsive, she may be a candidate for HIF-PHI trial — she has CAD so requires careful risk/benefit discussion and shared decision-making.

Q3: How could AI tools help manage her?

An ACM-style ML tool, given her longitudinal HD data, would predict her next Hb, flag her as at-risk for further Hb decline, recommend iron dosing, and alert if transfusion becomes necessary — all while optimizing ESA utilization.

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MORE CASES

01 ESA Hyporesponsiveness

58M, HD, DM, HTN · Hb 8.5 despite darbe 150 mcg · High CRP · TSAT 21%

DIAGNOSIS	DECISION	TAKE-HOME
Iron-Restricted Erythropoiesis + Inflammation-Driven ESA Hyporesponsiveness	Switch to daprodustat (HIF-PHI) + IV iron optimization	HIF-PHIs overcome hepcidin-mediated ESA resistance — an ESA alone cannot.

02 Peritoneal Dialysis Iron Management

44F, PD, IgA nephropathy · Hb 10.1 · Ferritin 88 · Oral iron failure · Needle phobia

DIAGNOSIS	DECISION	TAKE-HOME
Systemic Iron Deficiency with oral therapy failure	IV ferric carboxymaltose; consider HIF-PHI as oral alternative to ESA long-term	Patient preference and route of administration shape the iron AND ESA/HIF-PHI choice.

03 Acute Hb Decline + PRCA

71M, HD 7yr · Sudden Hb 11.2 → 7.1 over 6wk · Retic 0.3% · AI alert fired

DIAGNOSIS	DECISION	TAKE-HOME
Pure Red Cell Aplasia (anti-EPO antibodies) — confirmed on antibody assay	STOP ESA immediately · Transfuse · Cyclosporine immunosuppression · Switch to HIF-PHI after recovery	AI detected the declining Hb trend before escalation. Reticulocytopenia = PRCA until proven otherwise.

Iron First · ESA or HIF-PHI? · Monitor with AI · Know when something else is happening

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KEY TAKEAWAYS

1. Iron first, always. In HD patients, IV iron remains the cornerstone — correct iron-restricted erythropoiesis before escalating ESA or HIF-PHI.
2. ESAs remain first-line (KDIGO 2026). HIF-PHIs are a valuable addition for ESA-refractory or parenteral-intolerant patients — not a replacement.
3. HIF-PHIs are non-inferior to ESAs in Hb maintenance and MACE outcomes across Phase 3 trials (n>14,999 patients in meta-analysis).
4. Patient selection for HIF-PHI matters critically. Contraindications include active cancer, history of CV events, proliferative retinopathy, PAH, and pregnancy.
5. AI-guided anemia management (ACM, GRU-attention) demonstrates real-world improvements in Hb stability, ESA efficiency, and transfusion reduction.

THANK YOU!

Questions & Discussion

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