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Review

Position statement of the SEN Anemia Working Group: A critical and contextualized adaptation of the KDIGO 2026 anemia guidelines to the Spanish setting

Documento de posicionamiento del Grupo de Anemia de la SEN: una lectura crítica y adaptada de las guías de anemia KDIGO 2026 a la realidad española

Jose Portolés[a,b], Elisabeth Coll[c,*], M. Jesús Puchades[d], Jose J. Broseta[e,f], Borja Quiroga[g], Diana Rodríguez[h], M. Auxiliadora Bajo[g], Jose Luis Merino[i,j], Raquel Ojeda[k], Patricia de Sequera[l,m], Julio Pascual[n], Aleix Cases[e]

[a] *Servicio de Nefrología, Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, RICORS 2040, Majadahonda, Madrid, Spain*
[b] *Departamento de Medicina, Facultad de Medicina, Universidad Autónoma de Madrid, Madrid, Spain*
[c] *Servicio de Nefrología, Fundació Puigvert, Barcelona, Spain*
[d] *Servicio de Nefrología, Hospital Clínico Universitario de Valencia, INCLIVA, Universitat de Valencia, Valencia, Spain*
[e] *Servicio de Nefrología, Hospital Clínic de Barcelona, RICORS 2040, Barcelona, Spain*
[f] *Departamento de Medicina, Universitat de Barcelona, Barcelona, Spain*
[g] *Servicio de Nefrología, Hospital Universitario de La Princesa, ISS-Princesa-RICORS 2040, Madrid, Spain*
[h] *Servicio de Nefrología y Trasplante Renal, Hospital Clínic de Barcelona, IDIBAPS, Universitat de Barcelona, Barcelona, Spain*
[i] *Sección de Nefrología, Hospital Universitario del Henares, Coslada, Madrid, Spain*
[j] *Departamento de Medicina, Universidad Francisco de Vitoria, Madrid, Spain*
[k] *Servicio de Nefrología, Hospital Universitario Reina Sofía, Córdoba, Spain*
[l] *Servicio de Nefrología, Hospital Universitario Infanta Leonor, Madrid, Spain*
[m] *Departamento de Medicina, Universidad Complutense de Madrid, Madrid, Spain*
[n] *Instituto de Investigación i+12, Hospital Universitario 12 de Octubre, RICORS 2040, Madrid, Spain*

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ABSTRACT

Anemia in chronic kidney disease (CKD) remains highly prevalent and is strongly associated with increased cardiovascular morbidity, mortality, and impaired quality of life. The Anemia Working Group of the Spanish Society of Nephrology reviews the KDIGO 2026 anemia guideline, structured into 4 chapters, integrating national epidemiological data and the regulatory framework of the Spanish National Health System to contextualize its implementation.

The guideline introduces substantial updates, particularly in iron therapy strategies, the role of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), and the systematic assessment of treatment resistance. Iron deficiency is reclassified as 'systemic deficiency' or 'iron-restricted erythropoiesis', reinforcing a proactive intravenous iron approach in hemodialysis, supported by the PIVOTAL trial. Broader thresholds for initiating iron therapy in non-dialysis CKD are proposed, although uncertainties persist regarding upper ferritin and transferrin saturation limits. The guideline emphasizes individualized selection of the administration route and recommends withholding iron during systemic infections. Notably, treatment of marked iron deficiency without anemia is now considered.

Erythropoiesis-stimulating agents remain first-line therapy once alternative causes are excluded and iron deficiency corrected. Hemoglobin targets remain < 11.5 g/dL, with individualized initiation between 8.5 and 10 g/dL depending on cardiovascular risk, symptoms, and transfusion needs, with slightly lower thresholds in dialysis (≥9–10 g/dL). The guideline stresses using the lowest effective erythropoiesis-stimulating agent or HIF-PHI dose, with adjustments every 4 weeks. HIF-PHIs, such as roxadustat, are reserved for non-dialysis CKD when erythropoiesis-stimulating agents are unsuitable, given potential risks and limited long-term data.

* Corresponding author.
E-mail address: ecoll@fundacio-puigvert.es (E. Coll).

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Finally, Patient Blood Management strategies are promoted to reduce transfusions, particularly in kidney transplant candidates.

This position statement underscores the importance of adapting international recommendations to Spanish clinical practice, prioritizing safety, individualized care, and shared decision-making.

Palabras clave:
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RESUMEN

La anemia en la enfermedad renal crónica (ERC) es frecuente, asociada a una mayor morbimortalidad cardiovascular y peor calidad de vida. El Grupo de Anemia de la Sociedad Española de Nefrología analiza la nueva guía KDIGO 2026 de anemia estructurada en 4 capítulos, teniendo en cuenta estudios propios sobre nuestra realidad epidemiológica para adaptarlas a nuestro contexto y normas regulatorias.

Las principales novedades incluyen la redefinición de la estrategia de ferroterapia, el papel de los estabilizadores del HIF (HIF-PHI), y la importancia de la evaluación de la resistencia al tratamiento. Se categoriza el déficit de hierro como 'déficit sistémico' y 'eritropoyesis con restricción de hierro' y se refuerza la estrategia proactiva de hierro intravenoso en hemodiálisis, basada en el ensayo PIVOTAL. Se amplían los umbrales para iniciar ferroterapia en ERC no dependiente de diálisis, aunque persisten dudas sobre límites superiores de ferritina e índice de saturación de transferrina. Se aconseja individualizar la vía de administración y suspender la ferroterapia durante infecciones sistémicas. Como novedad, se contempla tratar el déficit de hierro marcado sin anemia.

Los agentes estimuladores de la eritropoyesis se mantienen como primera línea frente a los HIF-PHI una vez descartadas otras causas y corregido el déficit de hierro. Se mantiene el objetivo de hemoglobina < 11,5 g/dL, con inicio individualizado entre 8,5 y 10 g/dL según riesgo cardiovascular, síntomas y necesidad transfusional en ERC no dependiente de diálisis (≥9–10 g/dL en diálisis). Se enfatiza el uso de la dosis mínima eficaz de agentes estimuladores de la eritropoyesis y HIF-PHI, realizando ajustes cada 4 semanas. Los HIF-PHI, como roxadustat, se reservan para ERC no dependiente de diálisis cuando los agentes estimuladores de la eritropoyesis no son adecuados, con precaución ante riesgos potenciales y ausencia de datos a largo plazo. Finalmente, se promueve el Patient Blood Management para reducir transfusiones, especialmente en trasplante renal.

Este posicionamiento subraya la necesidad de adaptar las recomendaciones internacionales a la práctica española, priorizando seguridad, individualización y decisiones compartidas.

Introduction

Anemia is a common complication of chronic kidney disease (CKD). Its prevalence and severity increase as glomerular filtration rate (eGFR) declines, especially below 30 mL/min/1.73 m^2.[1,2] Anemia is associated with reduced functional capacity, impaired health-related quality of life (HRQoL), increased risk of cardiovascular events, CKD progression, and mortality, as well as higher costs.[3]

The Kidney Disease: Improving Global Outcomes (KDIGO) guideline for the management of anemia in CKD (2026)[4] represents an update to the previous recommendations dating from 2012.[5] This guideline incorporates new evidence generated over the past 13 years, including changes in the nomenclature of iron deficiency (ID), on the safety and efficacy of oral and intravenous (IV) iron therapy, positioning on the use of erythropoiesis-stimulating agents (ESAs) and the new hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs). In addition, the guideline underscores the importance of an individualized approach, weighing the risk/benefit profile and shared decision-making.

This position statement from the Spanish Society of Nephrology Anemia Working Group on the new KDIGO guideline aims to highlight the key updates and their most relevant implications from a Spanish perspective, taking into account publications on anemia management in routine clinical practice derived from registries and observational studies. We will highlight differing interpretations of the available evidence relative to the guideline recommendations, as well as the challenges of their implementation in the Spanish setting and some aspects not resolved by KDIGO.

Diagnosis and evaluation of anemia in CKD

The new KDIGO 2026 guidelines[4] adopt the updated World Health Organization criteria for defining anemia in adults,[6] as a hemoglobin (Hb) < 13 g/dL in men and <12 g/dL in women, unchanged from the previous KDIGO guidelines.[5]

Anemia in CKD is primarily caused by a relative reduction in renal erythropoietin (EPO) synthesis, shortened red blood cell lifespan, ID and other nutrient deficiencies (folate and vitamin B12), blood losses during hemodialysis (HD), and inhibition of the EPO response induced by uremic toxins and systemic inflammation,[3] in addition to disruption of the hepcidin-ferroportin axis as a key mechanism of functional iron restriction in CKD.[7]

The basic anemia workup in CKD in the new guidelines includes: complete blood count, reticulocytes, ferritin, and transferrin saturation index (TSAT).[4] The previous recommendations also included determination of vitamin B12 and folic acid in this initial workup.[5] We consider that the determination of B12 and folic acid should be maintained in the initial analysis, since, although low in the general population, deficiency increases in elderly and polypharmacy patients, which is common in our setting.[8]

Monitoring of iron status in renal patients continues to rely on ferritin levels and TSAT, despite the important limitations of both. In this regard, it should be recalled that ferritin is an acute-phase reactant[9] and TSAT has significant limitations in this population.[10] Indeed, the UK guidelines preferentially recommend other parameters, such as the percentage of hypochromic red blood cells or reticulocyte hemoglobin content,[11] although these also have practical limitations in sample processing.[12]

The criteria for defining ID subtypes are similar to the previous guideline,[5] but their nomenclature has changed: 1) 'Absolute iron deficiency': TSAT < 20% and ferritin <100 μg/L in non-dialysis CKD (NDD-CKD) patients or ferritin < 200 μg/L in HD patients, now designated 'systemic iron deficiency'; and 2) 'Functional iron deficiency': TSAT < 20% but ferritin > 100–200 μg/L, reflecting limited iron availability for erythropoiesis despite adequate reserves, now designated 'iron-restricted erythropoiesis'.

If initial tests do not clarify the cause of anemia and further workup is needed, the parameters summarized in Table 1 are recommended.

Table 1
Approach to the diagnosis and evaluation of anemia in CKD.

Initial parameters in the evaluation of anemia in CKD	Optional parameters in the workup of anemia in CKD
Complete blood count	Blood smear
Reticulocytes (reticulocyte production index)	Haptoglobin
Ferritin	Lactate dehydrogenase
Transferrin saturation index	C-reactive protein
Vitamin B12	Liver function tests
Folic acid	Serum protein electrophoresis with immunofixation, serum free light chains, urine Bence-Jones protein
	Thyrotropin
	Parathyroid hormone
	Fecal occult blood

CKD: chronic kidney disease.

In the case of anemia and severe ID (ferritin < 45 μg/L) or microcytic anemia in the absence of a genetic cause, referral to other specialists for investigation of possible blood losses should be considered.

Iron therapy in the treatment of iron deficiency and anemia in CKD

In HD patients, the recommended thresholds for initiating iron therapy are ferritin ≤ 500 μg/L and TSAT ≤ 30%, recommending preferential IV over oral iron therapy, which we support. In the systematic review performed, iron therapy increases Hb levels by approximately 0.5 g/dL vs. placebo, reduces the risk of transfusions, and likely reduces ESA doses in HD patients (Table 2).

Based on the results of the PIVOTAL trial,[13] proactive IV iron administration is recommended over a reactive approach in this population. This trial demonstrated that proactive iron sucrose administration (maintaining 400 mg/month, unless ferritin was >700 μg/L or TSAT ≥ 40%) was superior to reactive administration (0–400 mg/month, only if ferritin was <200 μg/L or TSAT < 20%) in reducing cardiovascular events, ESA doses, or transfusion requirements, and was safe. This trial demonstrates the superiority of the proactive strategy in incident HD patients (less than one year) treated with ESAs and ID, but does not clarify the optimal iron repletion strategy in this population (e.g., ferritin levels ~400–500 μg/L and TSAT > 30%). Its results cannot be extrapolated to prevalent HD patients or peritoneal dialysis, those with functional ID, those not treated with ESAs, those receiving HIF-PHIs, or other CKD populations.

The guideline proposes initiating iron therapy in NDD-CKD or PD patients when ferritin is <100 μg/L and TSAT < 40%, or with ferritin between 100–299 μg/L and TSAT < 25%. In the systematic review in NDD-CKD patients not treated with ESAs or HIF-PHIs, iron therapy increases Hb by 0.65–1.0 g/dL vs. placebo and could reduce mortality and hospitalization. The FIND-CKD trial demonstrated the superiority of IV ferric carboxymaltose (FCM) targeting serum ferritin 400–600 μg/L (unless TSAT exceeded 40%) over IV FCM targeting ferritin 100–200 μg/L and over oral iron, for increasing Hb levels and reducing ESA requirements in NDD-CKD patients.[13] However, the superiority of IV over oral iron therapy for increasing Hb levels was not confirmed in the REVOKE trial, although its primary endpoint was not Hb increase.[14] Furthermore, the FIND-CKD trial does not provide long-term safety results or data on clinical outcomes beyond hematimetric correction. Additionally, questions arise regarding the proposed upper TSAT limit (40%) when ferritin is <100 μg/L, as the optimal TSAT level to maximize Hb response to ESAs appears to be around 30%–35% in HD patients,[15–17] while more intensive iron therapy could promote tissue iron accumulation.

Evidence shows that TSAT levels of 30%–40% could be associated with cardiovascular morbimortality benefits in observational studies. Hasegawa et al. found that in NDD-CKD patients, low TSAT levels (regardless of ferritin value) were associated with higher risk of cardiovascular events and heart failure (HF), and iron repletion was beneficial in reducing these risks up to TSAT > 30%.[18] Similarly, Guedes et al. demonstrated that ID was associated with higher risk of overall mortality and major adverse cardiovascular events, independently of the presence of anemia in this population.[19] These findings, and those of similar studies, support initiating iron therapy in CKD patients if TSAT < 40%, especially if serum ferritin is low, regardless of the degree of anemia. These associations do not imply causality, but have a pathophysiological basis, as ID has been associated with increased platelet count and activity.[20,21] ID increases fibroblast growth factor 23 levels, which partly mediates the association between ID and higher morbimortality in NDD-CKD and kidney transplant (KT) patients.[22,23] Therefore, randomized controlled trials (RCTs) are required to define target TSAT values both for increasing Hb and for reducing relevant clinical events.

Regarding the recommendation for iron therapy with serum ferritin between 100–299 μg/L and TSAT < 25%, the guideline authors acknowledge that it is based on the inclusion criteria of RCTs in patients treated with ESAs or HIF-PHIs, which used higher TSAT thresholds than in patients not receiving these drugs, questioning its extrapolation to those who do not receive them.

Table 2
Comparison of KDIGO 2012 and KDIGO 2026 recommendations on iron therapy in CKD.

Criterion	KDIGO 2012[5]	KDIGO 2026[4]
Initiation criterion in NDD-CKD	Trial with IV iron (alternatively oral route for 1–3 months) if:	Starting treatment is recommended if:
	TSAT ≤ 30% and ferritin ≤500 μg/L and desire to increase Hb without ESA	Ferritin <100 μg/L and TSAT < 40%, or
	In patients treated with ESA if desire to increase Hb or reduce ESA dose (2C)	Ferritin ≥100–<300 μg/L and TSAT < 25% (2D)
Initiation criterion in HD	Administration of IV iron is recommended if:	IV iron if TSAT ≤ 30% and ferritin ≤500 μg/L (2D)
	TSAT ≤ 30% and ferritin ≤500 μg/L (2C)	A proactive IV iron strategy to correct ID is recommended
Safety limits	Avoid routine iron therapy if ferritin is >500 μg/L	Avoid routine iron therapy if ferritin ≥700 μg/L or TSAT ≥ 40%
Route of administration	NDD-CKD: decide based on the severity of ID, venous access, prior response to oral iron therapy, tolerability, therapeutic adherence, and costs	Oral or IV route based on patient factors (severity of anemia and ID, CKD stage, patient preference, prior response, venous access, costs, and availability of preparations)

ESA: erythropoiesis-stimulating agent; ID: iron deficiency; CKD: chronic kidney disease; NDD-CKD: non-dialysis-dependent CKD; HD: hemodialysis; IV: intravenous; TSAT: transferrin saturation index.

The systematic review on iron therapy on which these recommendations were partly based included HD patients and NDD-CKD patients, with the latter subgroup including a significant proportion of patients from RCTs conducted in populations with heart failure with reduced ejection fraction. A subsequent meta-analysis evaluated the benefit and safety of iron therapy on morbimortality but not on Hb response or ESA dose reduction.[24] The benefit on the primary endpoint (hospitalization for HF or cardiovascular death) in NDD-CKD patients was observed predominantly in RCTs of patients with HF with reduced ejection fraction, but in HF with preserved ejection fraction, more common in CKD, there is limited scientific evidence of benefit.[25] The Spanish Society of Nephrology Anemia Working Group wishes to highlight the aforementioned limitations of the new thresholds proposed by KDIGO and the need for further evidence in the CKD population.

The choice between oral or IV iron in NDD-CKD considers patient preference, the degree of anemia and ID, efficacy, tolerability, availability, and cost. However, if oral iron therapy proves ineffective in increasing Hb levels after 1–3 months or if there is gastrointestinal intolerance, switching to IV iron is recommended, which we endorse.

The guideline recommends withholding iron in CKD patients when ferritin is ≥700 μg/L or TSAT is ≥40%. These thresholds are based on the PIVOTAL trial,[26] which makes them reasonable for the HD population treated with ESAs, but generalizing this approach to non-HD patients appears questionable given the limitations mentioned above. In NDD-CKD, the FIND-CKD trial[26] recommended withholding iron therapy when ferritin was >600 μg/L or TSAT was ≥40%. Therefore, serum ferritin thresholds of 400–600 μg/L appear more reasonable in NDD-CKD, despite the limitations mentioned.

The guideline indicates that in CKD patients treated with IV iron, the choice between different formulations should be based on cost, individual preference, and recommended dosing regimens. However, modern IV iron formulations, such as FCM, allow high doses of iron to be administered safely at each administration. Therefore, in CKD patients not on HD who require IV iron, we recommend a high-dose, low-frequency strategy,[11] also considering indirect costs (staff, saline, lines), increased hospital visits and transport requirements, preservation of the vascular tree for future vascular access, and patients' HRQoL.[8] In high-risk patients, such as recent KT recipients, consider the risk of hypophosphatemia with FCM due to increased fibroblast growth factor 23[27] and monitor phosphorus levels or consider less efficient alternatives (iron sucrose).

Temporary withholding of iron therapy during systemic infection is also recommended.[4] Most RCTs with IV iron in CKD patients[13,26] did not identify a higher risk of infections, although not all did.[14] Furthermore, iron is essential for the proliferation of many pathogens and may also affect immune function, potentially increasing infection virulence.[28,29] Therefore, we support this recommendation.

As a novel recommendation, the present guideline considers treatment with oral or IV iron in patients with marked ID without anemia (ferritin < 30 ng/mL and TSAT < 20%), which represents a profound change from the previous guideline, which only considered iron therapy if ID was present in the presence of anemia, although the clinical benefit of this strategy on clinical events or HRQoL remains to be demonstrated.

Use of ESAs, HIF-PHIs, and other agents for treating anemia in CKD patients

Initiation of treatment

Anemia evaluation and treatment require following 3 consecutive steps: ruling out and treating causes of anemia unrelated to CKD; correcting ID if present; and finally, considering initiation of treatment with specific pharmacological agents, ESAs or HIF-PHIs.[30] Correction of ID and treatable causes of inflammation is a priority, as they worsen hyporesponse to ESAs. Furthermore, administration of ESAs or HIF-PHIs increases iron demand by stimulating erythropoiesis, which may worsen or generate ID with its consequences on the erythropoietic response to ESAs or cardiovascular risk.[31]

The decision to initiate treatment with an ESA or HIF-PHI should be individualized taking into consideration: Hb levels, anemia-related symptoms, transfusion requirements, and the potential adverse effects associated with these drugs, and considering the patient's perspective, providing clear information on risks and benefits, to reach a shared treatment decision (Fig. 1).[32]

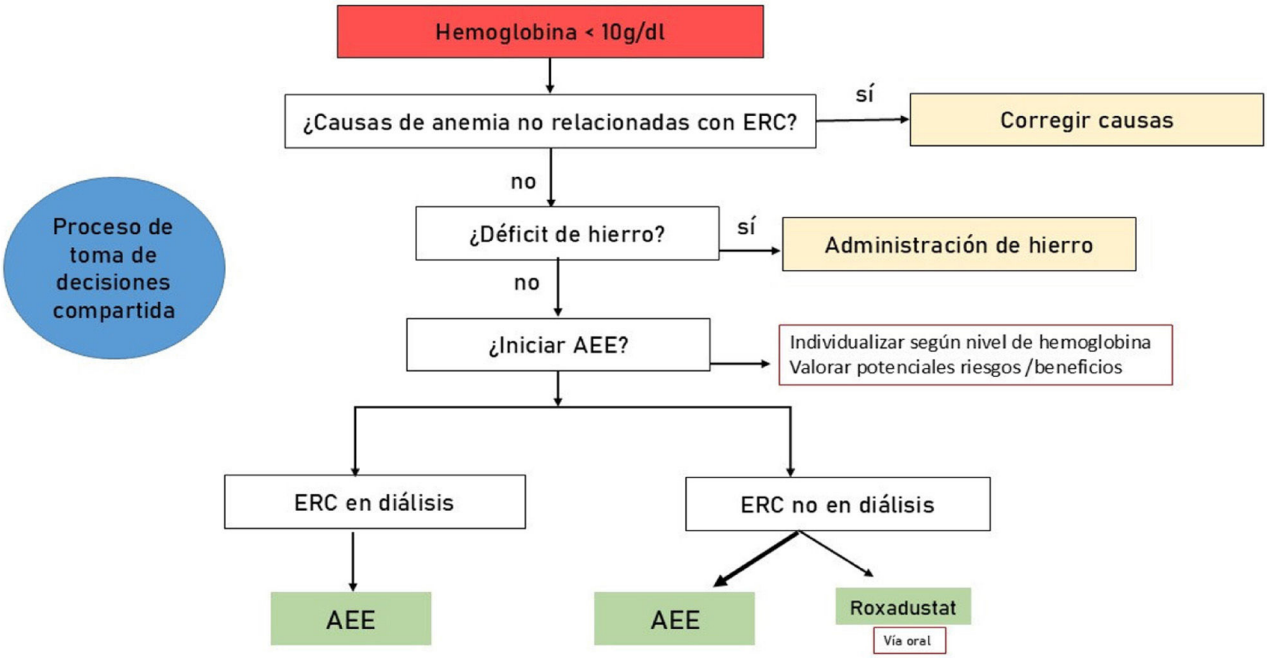


Fig. 1. Algorithm for initiating treatment with erythropoiesis-stimulating agents (ESAs)/hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) in Spain. CKD: chronic kidney disease.

The KDIGO 2026 guidelines recommend initiating treatment preferentially with an ESA due to accumulated clinical experience, demonstrated efficacy, and a well-established risk/benefit balance.[4] In Spain, this is the only option available for patients with dialysis-dependent CKD (DD-CKD), as the only HIF-PHI authorized by the Spanish Agency for Medicines and Medical Devices, roxadustat, limits its indication to NDD-CKD patients.[33]

Initiation of ESA treatment

Initiation of ESA treatment must be individualized considering the clinical situation, the risk of transfusions, and the potential risks associated with treatment: cerebrovascular and cardiovascular events, and cancer.

In dialysis patients, the KDIGO 2026 guidelines recommend adapting the decision to individual risk and initiating treatment with Hb levels ≥9–10 g/dL (≥9 g/dL in patients with higher cardiovascular or thrombosis risk, and Hb < 10 g/dL in patients with lower risk, anemia symptoms, or to avoid transfusion requirements).[4] European Renal Best Practice already proposed risk stratification based on cardiovascular risk and comorbidity, noting that in low-risk patients, initiation could be considered even with Hb > 10 g/dL.[34] Evidence on risks and benefits of ESAs in PD patients is limited and results obtained in HD are often extrapolated, maintaining common indications. However, this approach does not seem appropriate, as PD patients receive a continuous technique, do not present post-HD hemoconcentration, usually require lower ESA doses, and often have lower associated comorbidity.[35]

In NDD-CKD patients, ESA initiation should be individualized. Achieving higher Hb levels improves functional status but increases the risk of hypertension and has little impact on HRQoL. Therefore, KDIGO guidelines recommend initiating therapy with Hb between 8.5–10 g/dL, adjusting the threshold according to potential risks and benefits.[4] However, the presence of Hb < 10 g/dL is associated with a higher left ventricular mass index that improves in patients treated with ESAs,[36] demonstrating that early treatment of anemia, especially in advanced CKD, would be cardiovascular beneficial. We therefore believe that Hb levels should not fall below 10 g/dL in untreated CKD patients. In children, young people, KT candidates, or those with significant anemia symptoms, a higher Hb target may be considered, while in patients with high cardiovascular risk, thromboembolic risk, or active malignancies, initiation of therapy should be evaluated with caution.[4,37] The limited evidence in KT patients necessitates data extrapolation, although their specific characteristics highlight the need for tailored treatment strategies.[38]

Maintenance ESA treatment: Hb targets

The new KDIGO 2026 guidelines continue to recommend a target Hb level < 11.5 g/dL, similar to previous guidelines.[5] We consider it more appropriate to maintain target Hb levels between 10–12 g/dL, in accordance with the 2013 European Renal Best Practice position statement, and to individualize the target considering the patient profile, the dose used, risks, and benefits.[34] In HD patients, the upper limit of 11.5–12 g/dL should not be exceeded due to the added risk from hemoconcentration at the end of the HD session.[39,40] Under no circumstances should Hb > 13 g/dL be intentionally exceeded.[5]

Several studies have shown that greater anemia correction with ESAs after KT is associated with better graft survival and HRQoL, without increasing cardiovascular risk. In the CAPRIT RCT,[41] 125 KT patients were treated with epoetin α and randomized to Hb targets of 13–15 g/dL (full correction) or 10.5–11.5 g/dL (partial correction). The full correction group had a lower decline in eGFR, lower rate of end-stage kidney disease, better graft survival, and significantly improved HRQoL, all without increasing the incidence of cardiovascular events. These results were confirmed in a similar study conducted in Japan with 127 patients followed for 3 years.[42] Another study limited to early anemia (at 3 months post-KT) of only 55 patients randomized to receive epoetin α with a target Hb of 11.5–13.5 g/dL or no treatment showed improvement in HRQoL but not in eGFR or proteinuria.[43] The study designs do not allow conclusions regarding cardiovascular safety. A recent meta-analysis, not included in KDIGO, integrated 652 patients from 4 RCTs comparing a high Hb target vs. conventional (mean Hb 12.6 vs. 11.4 g/dL), with a median follow-up of 2 years. The high-target groups were associated with less eGFR loss (difference of 3.1 mL/min/1.73 m^2 [95% CI: 0.91–5.24], $P = .026$) and lower mortality risk (combined OR 0.36 [95% CI: 0.14–0.89], $P = .040$).[44] Spanish nephrologists tend to maintain targets above 11.5 g/dL, with 43.7% of patients on ESA treatment above this limit.[38] The KDIGO 2026 guidelines do not consider this meta-analysis and maintain the same Hb targets for KT recipients as for other CKD situations, despite recommending individualized targets and minimizing transfusions, which is hardly compatible with a uniform target for KT patients.[45]

These results suggest that the Hb target post-KT should be 12–13 g/dL, to preserve renal graft function and reduce mortality. In summary, we agree that ESA treatment should be individualized according to each patient's characteristics and different clinical situations.

ESA dosing, frequency, route of administration, and monitoring

We consider it relevant to use the lowest possible ESA doses that allow achieving and maintaining target Hb levels, for safety and efficiency.

The KDIGO 2026 guidelines recommend monitoring Hb every 2–4 weeks and adjusting the ESA dose to avoid an increase greater than 1 g/dL in that period. We consider biweekly Hb monitoring excessive, especially in NDD-CKD patients, and frequent dose adjustments promote excessive Hb variability.[46] We consider it more appropriate to monitor every 4 weeks, to make dose adjustments, attempting to maintain an increase of 1–2 g/dL per month until the target is reached. In case of rapid Hb increase (>2 g/dL/month), a dose reduction of 25%–50% is advised, rather than stopping treatment. In the maintenance phase in NDD-CKD, Hb monitoring every 2–3 months seems appropriate.

There is no new evidence regarding the frequency of administration of the different ESAs, and following the technical data sheet is recommended. The new guidelines promote patient-centered care, simplifying treatment regimens in NDD-CKD and promoting ESAs requiring less frequent administration (Table 3). They recommend an initial dose of 0.25 μg/kg weekly or 40–100 μg every 2–4 weeks and adjusting the dose without increasing the frequency to more than once per week. According to some studies, NDD-CKD patients in the maintenance phase could receive epoetin alfa every two weeks or darbepoetin alfa monthly. However, this strategy should be reserved for patients requiring low ESA doses. In the remainder, extending intervals is inadvisable, as it will require higher peak ESA doses to maintain Hb, with the consequent risk of dose-dependent adverse effects.

The KDIGO 2026 guidelines allow both SC and IV routes of administration for HD, and logically, SC for NDD-CKD, PD, or KT. However, it should be noted that higher doses of short-acting ESAs are required IV than SC, in contrast to long-acting ESAs (pegylated epoetin β or darbepoetin alfa), which require equivalent doses by both routes,[47] which may be relevant in HD patients requiring high doses of epoetins (Table 3).

The KDIGO 2026 guidelines recommend discontinuing ESAs during hospitalization for stroke, vascular access thrombosis, or thromboembolic events, and individualizing consideration of subsequent reinitiation. Similarly, for patients with renal anemia and active or prior malignancy, KDIGO 2026 guidelines advise shared decision-making considering: patient preferences and expected disease

Table 3
Initiation and maintenance of ESA treatment, adapted from KDIGO.

ESA type	Initial dose (correction)	Maintenance dose
Epoetin alfa and beta	NDD-CKD: 50–100 units/kg weekly or every 2 weeks CKD G5D: 50–100 units/kg, 3 times per week	NDD-CKD: increase or decrease dose and/or frequency as needed (no more than once per week) CKD G5D: increase 25 units/kg/dose if Hb increase <1 g/dL (<10 g/L) after 4 weeks; decrease 10–25 units/dose if Hb increase >2 g/dL (20 g/L) in 4 weeks
Darbepoetin alfa	NDD-CKD: 0.45 μg/kg weekly, 0.75 μg/kg every 2 weeks SC CKD G5D: 0.45 μg/kg weekly (may be rounded to convenient dose: 25, 40, 60, 100, 150, or 200 μg)	NDD-CKD: increase or decrease dose (25%) and/or frequency as needed (no more than once per week) CKD G5D: increase 25% if Hb increase <1.0 g/dL after 4 weeks; decrease 25% if Hb increase >2 g/dL (20 g/L) in 4 weeks
Pegylated epoetin β	NDD-CKD: 0.6 μg/kg or 50–120 μg every 2 weeks; 1.5 μg/kg or 120–200 μg every month CKD G5D: 0.6 μg/kg every 2 weeks (may be rounded to convenient dose)	NDD-CKD: increase or decrease dose and/or frequency as needed (no more frequently than every 2 weeks) CKD G5D: increase by 30–50 μg/dose if Hb increase <1.0 g/dL (<10 g/L) in 4 weeks; decrease by 30–50 μg/dose if Hb increase >2 g/dL (20 g/L) in 4 weeks
Biosimilars	Names differ by region; refer to the product's technical data sheet	

ESA: erythropoiesis-stimulating agent; CKD: chronic kidney disease; CKD G5D: dialysis-dependent CKD; NDD-CKD: non-dialysis-dependent CKD; Hb: hemoglobin; SC: subcutaneous.

evolution, especially when cancer treatment has curative intent, aiming for an Hb level that minimizes transfusion requirements.[48]

Finally, simultaneous use of ESAs and HIF-PHIs is not advised, including in situations of ESA hyporesponse, due to the lack of studies evaluating safety and efficacy with this combination.

ESA hyporesponse

The new guidelines define ESA hyporesponse as the inability to increase Hb with adequate ESA doses at initiation, or if during follow-up 2 dose adjustments > 50% above the previous stability level are required to maintain the same Hb, similar to the definition in the previous guideline. The guideline emphasizes that hyporesponse is associated with increased cardiovascular risk, end-stage kidney disease, or death. It also notes that hyporesponse can be acute or chronic (≥4 months), is typically dynamic and frequently transient,[49] with an approximate prevalence of 12.5%–30.3% depending on the series.[50]

The etiology can be multifactorial, where several factors often coexist, although in 30% of cases there is no clear cause. The most frequent causes include ID (absolute or functional) and inflammation, as cytokines and elevated hepcidin reduce erythropoiesis, EPO synthesis/response, and iron availability. Other causes to investigate include secondary hyperparathyroidism, blood losses, inadequate dialysis dose, tumor disease, nutritional deficiencies (copper, zinc, folic acid, vitamin B12, carnitine, vitamin E), drugs (e.g., renin-angiotensin system inhibitors), or hematological abnormalities (multiple myeloma, hemoglobinopathies, hemolysis, antibody-mediated pure red cell aplasia).

The guidelines emphasize that in the absence of response to ESAs, treatment should be re-evaluated, causes sought and corrected if possible, before increasing the dose. Hyporesponse definitions and dose thresholds vary between guidelines and regions (Table 4), and are based on clinical experience, not on solid evidence directly linking these definitions to prognosis.

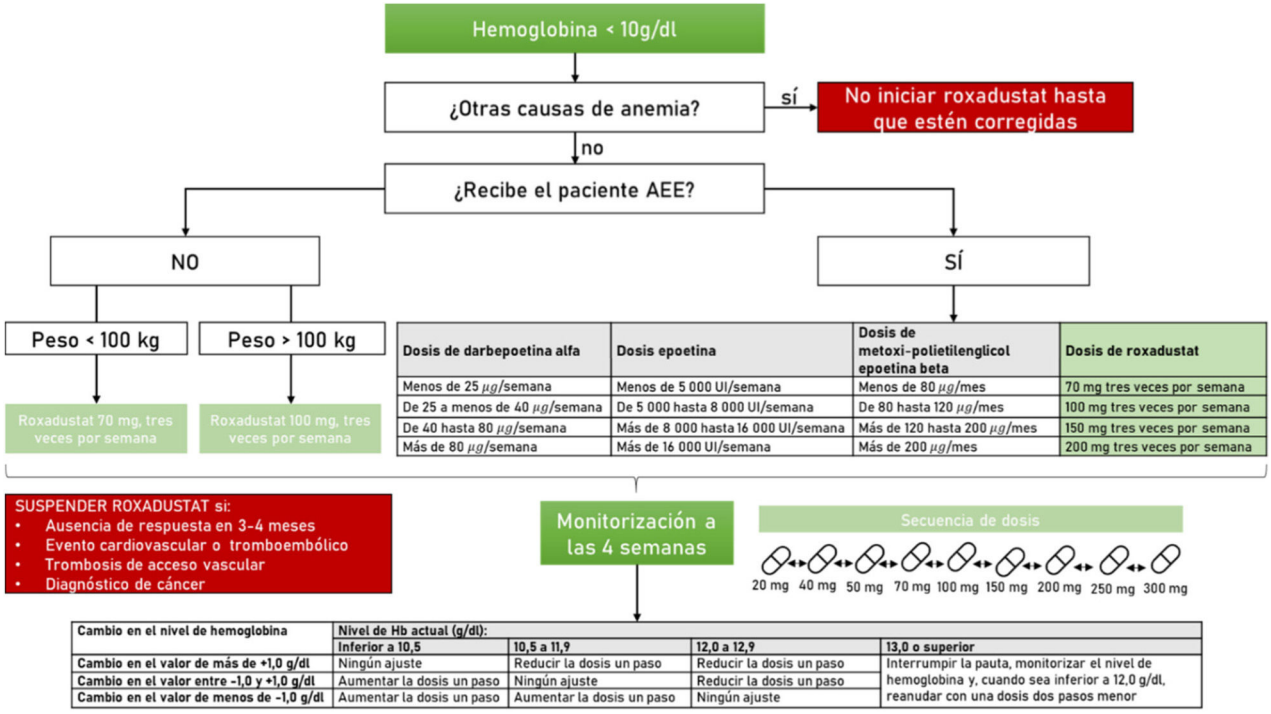
The lowest ESA dose that allows avoiding transfusions and maintaining an acceptable Hb is recommended, avoiding excessive dose increases in the case of hyporesponse due to the risk of cardiovascular events and mortality. If hyporesponse persists with low Hb levels, the risk-benefit of maintaining high ESA doses (with their associated adverse effects) or the possibility of transfusion should be considered, taking into account the risks of transfusion (iron overload, alloimmunization, etc.).

The KDIGO 2026 guideline raises the possibility of initiating an HIF-PHI trial in patients with ESA hyporesponse without identifiable cause. For safety, the lowest necessary HIF-PHI dose is recommended to alleviate anemia symptoms or reduce transfusions, not to achieve the same target as in responders. Additionally, HIF-PHI discontinua-

Table 4
Hyporesponse to erythropoiesis-stimulating agents.

Guideline or study	Definition of hyporesponse	Relevant comment
KDIGO 2012/2026[4,5]	Initial hyporesponse: absence of Hb increase after the 1st month with adequate weight-adjusted doses. Subsequent hyporesponse: need for 2 dose increases to more than 50% above the prior stable dose to maintain the same Hb	Emphasizes that there is no global consensus and that definitions are experience-based, not derived from prognostic trials
The Renal Association, UK, 2025[11]	Failure to achieve the Hb target with ESA dose greater than: EPO IV: 450 UI/kg/week EPO SC: 300 UI/kg/week Darbepoetin more than 1.5 μg/kg/week	
JSN/Japanese Society for Dialysis Therapy (renal anemia guideline 2015)[51]	Uses high ESA dose thresholds relative to weight and Hb to define hyporesponse in national registries; details described as 'high ESA doses relative to Japanese standard'	Links hyporesponse to worse prognosis and the need to review iron, inflammation, and dialysis adequacy
KDOQI/NKF 2006 (CKD anemia)[52]	Failure to achieve Hb >11 g/dL despite doses equivalent to epoetin >500 UI/kg/week In previously stable patients, requiring 2 dose increases to >50% of the previous dose or significant Hb decline with stable dose	Recognizes the lack of a validated quantitative index and mentions the use of the ESA resistance index as an exploratory tool
RISCAVID study[53]	ERI adjusted to patient weight formula: weight adjusted weekly ESA dose/Actual Hb > 15.4 UI/kg × g/dL	
ERI, used in studies and guidelines[54]	ERI = weekly ESA dose (UI/kg/week) divided by Hb; thresholds such as ERI ≥ 1.5 or ≥2 UI/kg/week/g/L, or belonging to the highest quintile of doses to define hyporesponse	Research tool; most guidelines do not recommend ERI as the sole routine clinical criterion

ESA: erythropoiesis-stimulating agent; EPO: erythropoietin; ERI: erythropoietin resistance index; IV: intravenous; Hb: hemoglobin; SC: subcutaneous.
Adapted from KDIGO 2026 guidelines.[5]



Dosis de darbepoetina alfa	Dosis epoetina	Dosis de metoxi-polietilenglicol epoetina beta	Dosis de roxadustat
Menos de 25 μg/semana	Menos de 5 000 UI/semana	Menos de 80 μg/mes	70 mg tres veces por semana
De 25 a menos de 40 μg/semana	De 5 000 hasta 8 000 UI/semana	De 80 hasta 120 μg/mes	100 mg tres veces por semana
De 40 hasta 80 μg/semana	Más de 8 000 hasta 16 000 UI/semana	Más de 120 hasta 200 μg/mes	150 mg tres veces por semana
Más de 80 μg/semana	Más de 16 000 UI/semana	Más de 200 μg/mes	200 mg tres veces por semana

Cambio en el nivel de hemoglobina	Nivel de Hb actual (g/dl):			
	Inferior a 10,5	10,5 a 11,9	12,0 a 12,9	13,0 o superior
Cambio en el valor de más de +1,0 g/dl	Ningún ajuste	Reducir la dosis un paso	Reducir la dosis un paso	Interrumpir la pauta, monitorizar el nivel de hemoglobina y, cuando sea inferior a 12,0 g/dl, reanudar con una dosis dos pasos menor
Cambio en el valor entre -1,0 y +1,0 g/dl	Aumentar la dosis un paso	Ningún ajuste	Reducir la dosis un paso	
Cambio en el valor de menos de -1,0 g/dl	Aumentar la dosis un paso	Aumentar la dosis un paso	Ningún ajuste	

Fig. 2. Proposed algorithm for initiating and maintaining roxadustat according to the technical data sheet. ESA: erythropoiesis-stimulating agent; Hb: hemoglobin.

tion is advised if after 3–4 months no 'significant' erythropoietic response has been achieved, given the absence of long-term safety and efficacy data.

Hypoxia-inducible factor prolyl hydroxylase inhibitors

Introduction to the Spanish setting

In Spain, roxadustat is currently the only available HIF-PHI. The Spanish therapeutic positioning report (TPR) limited its indication to de novo NDD-CKD patients, excluding for safety reasons dialysis patients who were included in the European Medicines Agency authorization.[33] Roxadustat had demonstrated superiority over placebo[55–57] and non-inferiority versus ESAs in NDD-CKD[58] and DD-CKD[59–62] populations, effectively and sustainably correcting anemia.

As with ESAs, treatment with roxadustat should be initiated after shared decision-making considering anemia-related symptoms, transfusion risk, and potential adverse events, and when other factors such as ID have been corrected. Given that HIF-PHIs have not been shown to be safer than ESAs, use of ESAs as a first option is prioritized, and, according to the Spanish TPR, roxadustat may be an alternative for those NDD-CKD patients in whom ESAs are not appropriate, are contraindicated, or for whom the SC route is not feasible.[33]

Initial prescription and HIF-PHI adjustment

Roxadustat prescription should be considered taking into account the risk of adverse events and special situations (prior tumor disease progression, adult hepatorenal polycystic disease, diabetic retinopathy, pulmonary hypertension, or pregnancy). Conversion from ESAs to roxadustat is not formally contraindicated by the European Medicines Agency, but evidence to recommend it systematically is limited, and therefore it should be individualized.

Based on published RCTs, roxadustat should be initiated with Hb levels similar to the indication for ESAs. In NDD-CKD patients in the absence of other causes of anemia, it is reasonable to propose its initiation when Hb falls below 10 g/dL.[57] The recommended starting dose of roxadustat is 70 mg three times per week if the patient weighs less than 100 kg, or 100 mg in case of higher weight. The technical data sheet recommends a dose adjustment algorithm for conversion from ESAs to roxadustat (Fig. 2), although the TPR does not contemplate this change due to the absence of conversion studies in NDD-CKD.[63]

Similar to what has been described for ESAs, we recommend monitoring Hb every 4 weeks, with the possibility of extending this to longer intervals whenever there are no relevant clinical changes or recent dose adjustments, in the maintenance phase with a target range of 10–12 g/dL. Dose adjustment should follow the attached algorithm (Fig. 2). In addition, patients receiving roxadustat should have thyroid function monitored in the first 3 months.[64]

HIF-PHI treatment should be discontinued if after 3–4 months the desired erythropoietic response has not been achieved, cardiovascular, thromboembolic, or vascular access thrombosis events occur, or a recent cancer diagnosis is made. The decision to reinitiate HIF-PHI treatment or switch to ESAs should be individualized based on Hb, comorbidities, and patient preferences, and weighing the risks and benefits of treatment.

Special considerations on risks

Combined analysis of incident NDD-CKD and dialysis-dependent patients showed comparable risk of roxadustat vs. ESAs in terms of cardiovascular safety and mortality[33]; however, in prevalent dialysis-dependent patients, results show a higher risk of cardiovascular events and mortality with roxadustat vs. ESAs, especially in hyporesponders or patients previously treated with high ESA doses.[65] No additional factors associated with higher cardiovascular risk were identified. Long-term safety data are limited.

In CKD patients with anemia and ESA hyporesponse, or suspected ESA-related pure red cell aplasia, a trial treatment with HIF-PHI using the lowest dose that alleviates anemia-related symptoms and reduces the risk of transfusion may be considered.[4]

The pleiotropic effects of HIF-PHIs raised concerns about a higher risk of tumor proliferation,[66] renal cyst growth in polycystic kidney disease,[67] diabetic retinopathy progression,[68] and pulmonary hypertension,[69] but no increased incidence of cases has been demonstrated in phase 3 clinical trials. A higher risk of cardiovascular,[55] thromboembolic,[55] or vascular access thrombosis[55] events has been described. A risk of hepatic impairment, seizures, exfoliative dermatitis, hypothyroidism, or sepsis/bacterial infection has also been described with roxadustat.

There are insufficient data on the risk in post-KT anemia[45] or in children.[70]

Transfusions

The indication for transfusion should be based primarily on the presence of symptoms and the overall clinical situation, rather than strict Hb thresholds. In CKD patients, and especially in KT candidates, transfusions should be avoided whenever possible due to the risk of HLA allosensitization, which can complicate the assignment of a compatible organ. Although the overall immunological risk is relatively low (between 2% and 21%) according to historical series,[71,72] this risk increases notably in prior transplant recipients and in multiparous women.[73–76]

The risk of infectious transmission is very rare. Currently, the probability of acquiring HIV or hepatitis C is estimated at less than 1/million transfusions, and universal leukodepletion has significantly reduced transmission of other viruses, such as cytomegalovirus, although a residual risk remains in immunocompromised populations.[77] In Spain, screening via nucleic acid amplification is performed for the detection of transfusion-transmitted infections, including seasonal surveillance of West Nile virus.[78]

Implementation of Patient Blood Management strategies is recommended, which include ID correction, optimization of ESA treatment, reduction of perioperative blood losses, and adoption of conservative transfusion protocols, preferably one unit at a time, with subsequent clinical reassessment.[79]

Spanish practice is compatible with these recommendations, although there are clear opportunities for improvement. In a recent study, 39% of KT recipients required at least one perioperative transfusion, with a pre-surgery Hb generally below 11.5 g/dL. Significantly higher transfusion risk was observed in patients with TSAT < 30%, deceased donor recipients, those with prolonged cold ischemia times, or those requiring re-intervention. Furthermore, a higher number of transfused units was associated with worse renal function at 6 months, demonstrating that transfusion requirements may reflect both clinical complexity and slower graft recovery.[80] This high frequency of perioperative transfusions in KT in Spain contrasts with the reduction achieved in other high-risk surgeries after implementation of Patient Blood Management programs, and necessitates harmonization of protocols between centers and strengthening their systematic implementation.

All transfusion risks should be considered, in addition to those described, along with the need to avoid serious, albeit infrequent, transfusion complications, such as transfusion-related acute lung injury, transfusion-associated circulatory overload, or hyperkalemia, especially in massive transfusions.[79,81]

Nevertheless, transfusion remains necessary in situations of acute anemia, hemodynamic instability, active bleeding, or need for rapid correction. A Cochrane review including 48 RCTs and 21,433 participants demonstrated that a restrictive transfusion strategy (Hb threshold 7–8 g/dL) reduced transfusions by 41%, without increasing 30-day mortality or major adverse events (myocardial infarction, stroke, pneumonia, thromboembolism, or infections), compared to liberal strategies (Hb 9–10 g/dL).[82]

Overall, the available evidence shows that the optimal strategy in our setting to reduce transfusions is especially relevant for patients on the transplant waiting list and should focus on early correction of anemia, systematic assessment of iron status, application of transfusion thresholds strictly based on symptoms and clinical situation, and strengthening of Patient Blood Management programs.

Relevant topics not addressed in KDIGO 2026

The recent KDIGO guideline update omits some aspects we consider relevant, such as sex differences or the role of new treatments such as SGLT2i and anti-inflammatory therapies.

SGLT2i have demonstrated cardiorenal benefits in type 2 diabetes mellitus, HF, and CKD,[83] to which a sustained increase in Hb is added, initially considered due to hemoconcentration and subsequently attributed to direct stimulation of erythropoiesis.[84,85] They also improve iron utilization through several mechanisms: reduction of hepcidin and ferritin, increase of erythroferrone, and increased total iron-binding capacity.[86,87] These drugs may delay or correct the onset of anemia in this population and, therefore, reduce the need for ESAs. Post hoc analyses of phase 3 studies find a mean Hb increase of 0.6–0.9 g/dL vs. placebo in CKD patients.[88–90]

An infrequent complication with SGLT2i use is erythrocytosis, especially in CKD patients. In a post hoc analysis of the CREDENCE trial, an increased risk of myocardial infarction was observed in males with elevated baseline hematocrit with canagliflozin treatment.[91] Retrospective studies report erythrocytosis in up to 16.9% of patients treated with SGLT2i, with a low incidence of arterial thrombosis (0.5%) and no direct relationship with the drug.[92] Another population-based analysis (>137,000 patients) found no increased cardiovascular or thromboembolic risk.[93]

Low-grade chronic inflammation contributes to renal anemia, ESA resistance, and cardiovascular and CKD progression risk.[94] Several monoclonal antibodies aim to reduce this persistent inflammatory milieu and have been associated with improved erythropoietic response to ESAs in preliminary studies: canakinumab (anti-IL-1β) raised Hb in patients with myocardial infarction,[95] ziltivekimab (anti-IL-6) improved ESA resistance in the RESCUE trial,[96] and clazakizumab (anti-IL-6) was associated with lower ESA requirements in HD.[97] These are promising results, but currently not available for routine clinical use, perhaps for this reason they were not included in KDIGO.

The KDIGO 2026 guideline does not include specific recommendations on sex differences in the diagnosis, management, or therapeutic response to anemia.[4] The lack of specific evidence and tailored designs in RCTs and observational studies justifies this. However, many aspects of CKD-associated anemia are modulated by biological sex, including the WHO definition itself, iron metabolism, and ESA response.[6] Anemia is more prevalent in women with CKD, who present lower Hb levels at all stages, although the difference tends to attenuate with declining eGFR.[98,99] Furthermore, cardiovascular and renal events linked to anemia appear to be more severe in women.[34,100] Clinical data show that women on dialysis require higher ESA doses to achieve comparable Hb levels.[34] Since high ESA doses have been associated with increased cardiovascular risk in RCTs, these differences could have relevant clinical implications. Uncertainty persists as to whether the same Hb targets during ESA or HIF-PHI treatment should apply to both sexes, considering the aforementioned differences. As previously mentioned, we do not have studies specifically designed to resolve this uncertainty.

Authorship

All signatories meet the authorship criteria proposed by the International Committee of Medical Journal Editors (ICMJE), are responsible for the work, and have approved this version.

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Declaration of competing interest

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