

Management of Anemia in Nondialysis Chronic Kidney Disease: Current Recommendations, Real-World Practice, and Patient Perspectives

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Abstract

In nondialysis CKD (ND-CKD), anemia is a multifactorial and complex condition in which several dysfunctions dynamically contribute to a reduction in circulating hemoglobin (Hb) levels in red blood cells. Anemia is common in CKD and represents an important and modifiable risk factor for poor clinical outcomes. Importantly, symptoms related to anemia, including reduced physical functioning and fatigue, have been identified as high priorities by patients with CKD. The current management of anemia in ND-CKD (*i.e.*, parameters to initiate treatment, Hb and iron indexes targets, choice of therapies, and effect of treatment on clinical and patient-reported outcomes) remains controversial. In this review article, we explore the epidemiology of anemia in ND-CKD and revise current recommendations and controversies in its management. Exploring data from real-world clinical practices, particularly from the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps), we highlight the current challenges to translating current recommendations to clinical practice, providing patients' perspectives of anemia and how it affects their quality of life. Finally, we summarize recent advances in the field of anemia that may change the way this condition will be managed in the future.

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Introduction

Anemia is a sign of a disease process rather than a disease itself, and it is defined as a hemoglobin (Hb) level below 13 g/dl in men and 12 g/dl in women (1). In CKD, anemia is caused by decrease in erythropoietin (EPO) synthesis and iron deficiency (ID). Moreover, the assessment and management of anemia in CKD differs profoundly from the anemia that occurs in non-inflammatory states (2). The role of inflammation in the impaired response to erythropoiesis-stimulating agents (ESAs) and a hepcidin-mediated decrease in availability of endogenous and exogenous iron led to a change in the understanding of the mechanisms leading to anemia. Moreover, a derangement in oxygen sensing *via* the hypoxia-inducible factor pathway contributes to CKD anemia development (2), a discovery that has recently led to the first ever Nobel Prize in Medicine awarded to a nephrologist. An overview of the current understanding of mechanisms involved in the anemia of patients with CKD and how they affect the management of patients is displayed in Figure 1.

Treatment with EPO was initially restricted to patients on dialysis with very low Hb, with the aim of reducing red blood cell transfusion rates, but ESAs are currently used more broadly to include patients with nondialysis CKD (ND-CKD). Because serum EPO

levels are not routinely measured, adequate erythropoiesis is indirectly evaluated in CKD by Hb measurements, which define when treatment should be initiated and serve as a basis for treatment targets. Iron storage is clinically assessed by the combination of the percentage of transferrin saturation and ferritin concentrations (3). Most guidelines define ID when Transferrin Saturation Index (TSAT) levels are below 20%–30% and ferritin is below 100 $\mu\text{g/L}$, although a functional ID can be observed in patients with higher ferritin levels, which is commonly observed in inflammatory states.

Anemia and ID are very common in CKD and represent important and modifiable risk factors for poor clinical outcomes and worse health-related quality of life (HRQoL) (4). Importantly, symptoms related to anemia, including reduced physical functioning and fatigue, have been identified as high priorities by patients with CKD (5). In this review article, we explore the epidemiology of anemia in ND-CKD, the current recommendations for its management, how they differ from real-world clinical practice, and recent advances that may change the way CKD anemia is managed in the future. We also include a patient's perspective on CKD anemia treatment and how it affected her life.

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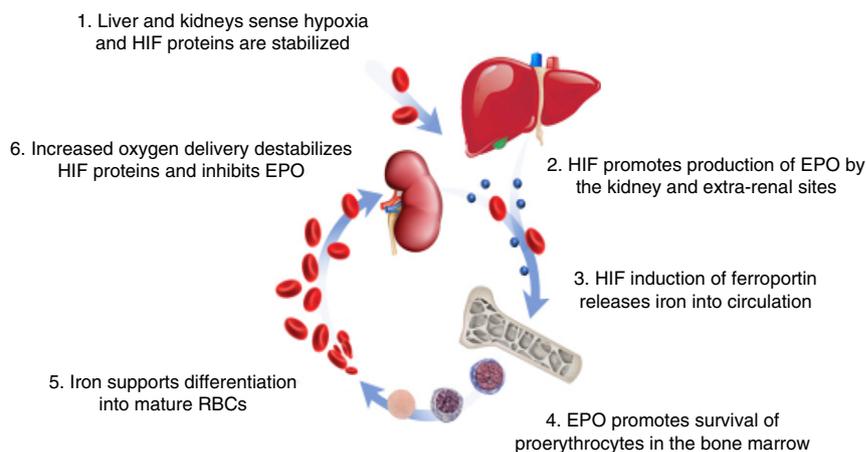


Figure 1. | Treatment strategies targeting the pathophysiology of anemia in CKD and current limitations and challenges. (1) As the oxygen tension reduces in kidneys and liver, (2) the stabilization of hypoxia-inducible factor (HIF) promotes the production of erythropoietin (EPO) and (3) induces the release of iron from enterocytes and macrophages into circulation. (4) EPO stimulates the differentiation of proerythrocytes into mature red blood cells (RBCs) in the blood marrow, whereas (5) iron is incorporated in the hemoglobin synthesis. (6) Finally, the increase in O₂ delivery to the tissues destabilizes HIFs and inhibits EPO production. Current United States–approved treatment strategies target 4 (erythropoiesis-stimulating agents) and 5 (iron supplements). Novel therapies, as HIF prolyl hydroxylase inhibitors, target 2 and 3.

Anemia in ND-CKD: Common and Harmful

The prevalence of CKD anemia increases with the progression of CKD to advanced stages, ranging from 40% in

stage 3 to 70% in stage 5 (6,7). The prevalence of ID is also high in CKD, affecting about half of patients with ND-CKD; however, ID does not seem to vary across CKD stages (6)

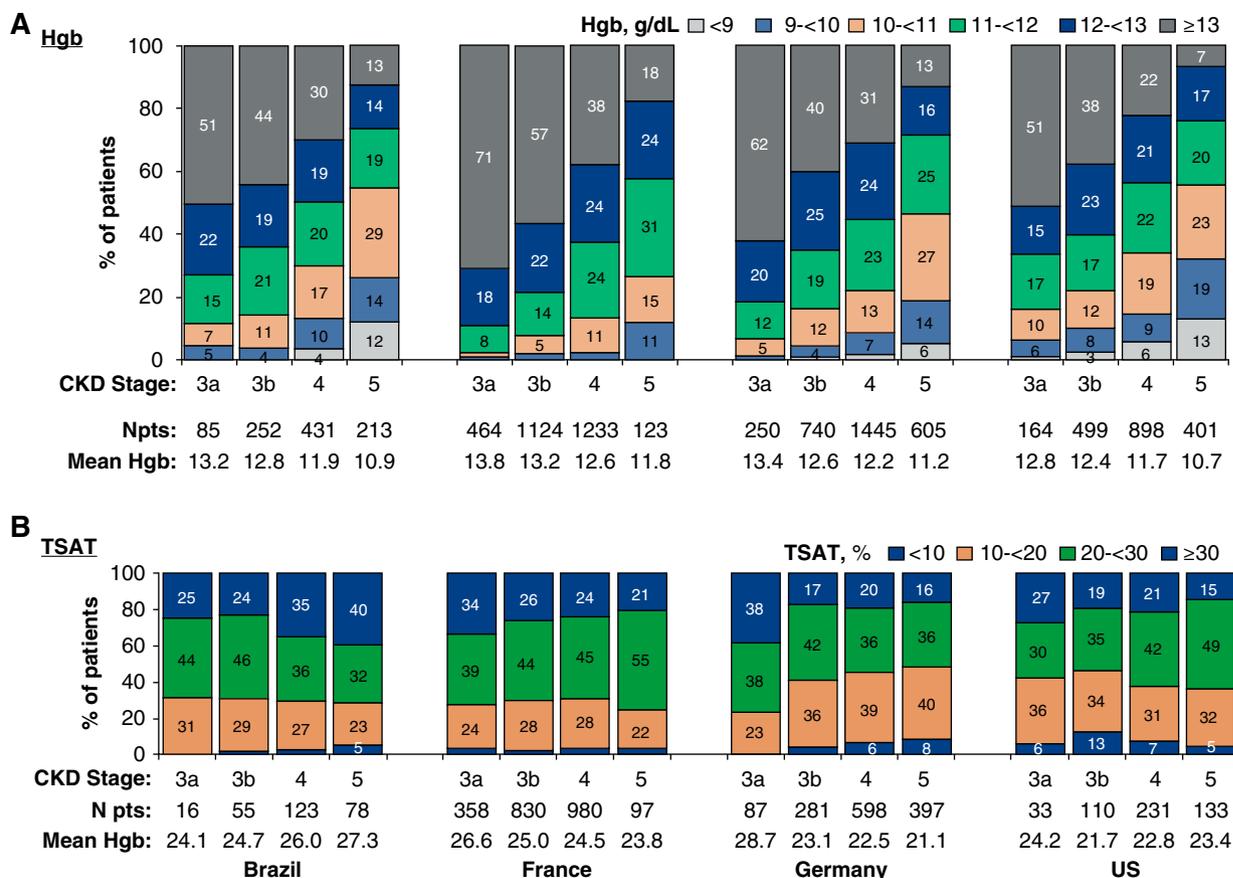


Figure 2. | Hemoglobin (Hgb) and Transferrin Saturation Index (TSAT) distributions according to CKD stage. Data from the Chronic Kidney Disease Outcomes and Practice Patterns Study. (A) Hgb. (B) TSAT. Pts, patients.

(Figures 2 and 3). Because of the progressive increase in inflammation, patients with more advanced CKD tend to have a higher prevalence of the functional ID subtype. Functional ID is characterized by restricted iron availability, commonly due to inflammatory conditions. Inflammation induces the release of hepcidin and therefore, reduces gastrointestinal iron absorption as well as higher mobilization of stores in the reticuloendothelial system (8).

Anemia has been consistently associated with poor outcomes in patients with ND-CKD. In fact, recent reports from the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) (9) showed a negative association of lower Hb with CKD progression and all-cause mortality (10). Indeed, in an analysis of four community-based longitudinal studies, anemia was associated with a 51% increase in the composite of myocardial infarction, stroke, and all-cause mortality (11). Also, anemia is strongly associated with the development of left ventricular hypertrophy (12), a major risk factor for hospitalization and mortality in patients with CKD.

Anemia has also been associated with worse HRQoL in CKD. In an analysis of patients with ND-CKD in The Netherlands, individuals with Hb < 11 g/dl had considerably worse HRQoL for both physical and mental components of the Short-Form 36 (SF-36) than those with Hb above 11 g/dl (13). An analysis of data from 2121 individuals included in the CKDopps provided evidence that Hb had a positive monotonic association with HRQoL even extending to >12 g/dl (10).

Patient Perspectives

In the kidney community, there is strong recognition of the central role of the patient voice in care and the need for ensuring that their priorities and goals are integrated in shared decision making. There have been significant advances in the understanding of patient priorities in CKD, with increasing efforts to involve patients in research and practice (14). Despite this, clinical trials frequently do not capture questions and outcomes that are important to patients (15), and patient-reported outcomes (PROs) are largely absent in trial reports (16).

Although health professionals tend to emphasize the importance of hospitalization and mortality as the most important outcomes to be improved or avoided, patients have indicated a higher priority for the ability to travel and dialysis-free time, which are rarely captured in clinical trials (15,16). Additionally, the outcomes measured are extremely variable, with >10,700 distinct metrics in an analysis of trials in hemodialysis (16). Establishing a set of common and standardized outcomes, therefore, is essential for improvements in patient-centered care for patients with CKD (16).

The Standardized Outcomes in Nephrology (SONG) Initiative aims to establish core outcomes, defined as an agreed set of outcomes that should be measured and reported in nephrology trials (15), across the spectrum of CKD (15). The SONG process involves systematic reviews; focus groups with nominal group technique with patients and caregivers; key informant interviews; international Delphi surveys; and consensus workshops with patients,

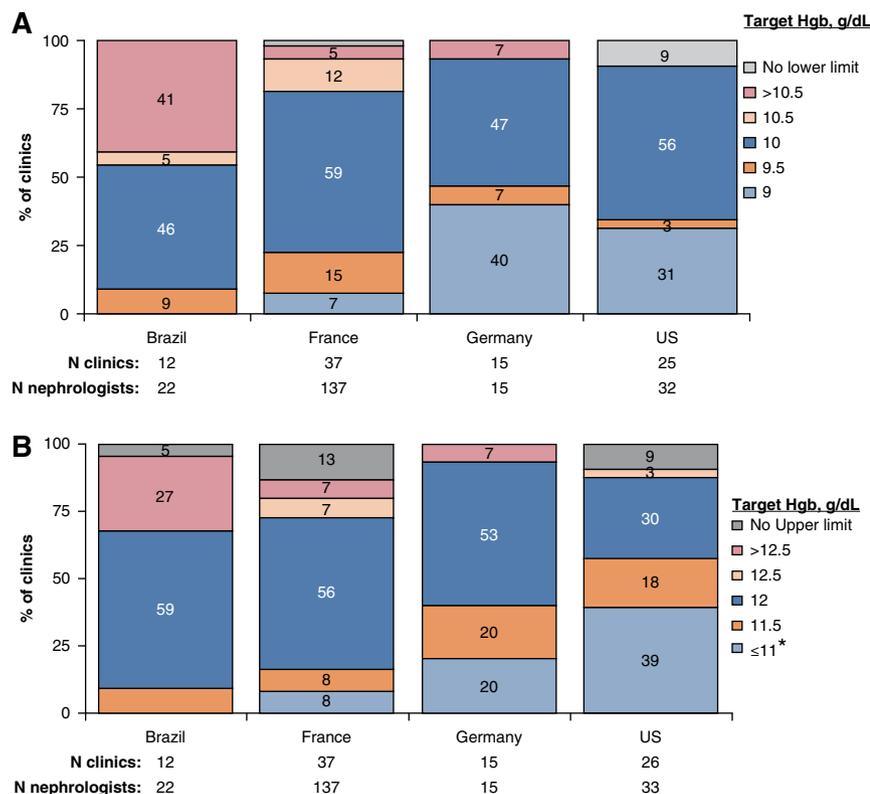


Figure 3. | Hemoglobin (Hgb) targets: the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) nephrologist practice survey (2015/2017). (A) Lower targets for Hgb. (B) Upper targets for Hgb. Clinic-level Hgb upper and lower targets were collected from nephrologist surveys from 44 clinics in the CKDopps from Brazil (12), Germany (15), the United States (25), and France (37).

caregivers, and health professionals (15). Of note, fatigue has been identified as a core outcome for trials in patients receiving hemodialysis (17). A systematic review and thematic analysis of qualitative studies identified four themes related to fatigue: burden of dialysis, restricted life participation, diminishing capacities to fulfill relationship roles, and perceived vulnerability to misunderstanding (18).

Anemia has been hypothesized to be one of the main drivers of the fatigue seen in patients with CKD (19,20). Patients with lower Hb levels often report having restricted energy levels, which may have an important effect on activities of daily living (4). In a systematic review of measures of fatigue in patients receiving hemodialysis, from 123 studies identified, 43 measures were used to assess fatigue (21). The SF-36 was the most commonly used instrument, and there were limited data on the psychometric properties of these measures for use in the hemodialysis population (21). There are few data on patient perspectives on anemia and anemia management in patients with ND-CKD. Standardized approaches for capturing validated patient-reported outcomes and a more active role of patient's voice in anemia care are long overdue steps to yield greater value for patients and caregivers in ND-CKD.

Management of Anemia in ND-CKD: Current Recommendations and Controversies

The management of CKD anemia includes ESAs (short and long acting), oral and intravenous (IV) iron formulations, and red blood cell transfusions when not possible to avoid (1). Optimal targets of Hb, TSAT, and ferritin remain unknown, and they may vary according to the various therapeutic approaches.

The cloning of the gene encoding EPO in 1985 led to the development of recombinant ESAs (22). Over the years, clinical trials with ESAs increased the Hb targets, with the hypothesis that Hb normalization would result in improvements in outcomes. The largest trial in ND-CKD (the TREAT) enrolled 4032 diabetic patients with CKD (23). The achieved Hb in the higher target group was 12.5 versus 10.6 g/dl in the placebo arm (23). Patients in the higher Hb arm presented a 92% higher relative risk of fatal or nonfatal stroke, with a 2.4% absolute risk difference (23), results that were confirmed in a subsequent meta-analysis (24).

Considering PROs, the effect of achieving Hb normalization with ESAs remains controversial (1). Distinct meta-analyses estimated modest effects on HRQoL, with potential differences only for particular subdomains, such as fatigue (25–27). The interpretation of these studies is limited mainly because the heterogeneity of the estimates is marginally high, and the differences between aimed versus achieved targets vary considerably across studies. Considering the current safety concerns associated with targeting higher Hb with ESAs, the potential benefits in HRQoL should be evaluated against the risks. This should be pursued in a trade-off model that may lead to individualization for targets in potential subpopulations and in the context of a shared decision process. Presumably, the benefits would be maximized against the risks in a selected group of low-risk patients, as the Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest (1). Regarding ESA initiation, the current recommendation is to initiate

therapy in selected patients with ND-CKD and Hb < 10 g/dl, considering factors such as Hb decline, risks associated with ESA use, risks of blood transfusion, and presence of symptoms (1).

Although iron replacement improves cardiovascular outcomes and PROs in patients with ID and heart failure, RCTs in ND-CKD have focused on the Hb response after iron administration as an outcome (28). The effect of iron treatment and the possible benefits of treating ID in the absence of anemia on outcomes beyond the Hb response in patients with ID and ND-CKD are unknown. Additionally, the ideal parameters for assessing iron status in clinical practice and for prediction of response in Hb remain largely controversial (29). In that sense, the recommendations of targets for TSAT and ferritin, the most commonly used iron parameters, are generally arbitrary and on the basis of boundaries determined by potential safety concerns, which have not been confirmed by robust evidence (29).

The safety and Hb response of IV iron therapy was evaluated in the FIND-CKD study, which randomized 626 patients with stages 3–5 CKD to ferric carboxymaltose with a target of ferritin between 400 and 600 $\mu\text{g/L}$ versus ferric carboxymaltose with a target between 100 and 200 $\mu\text{g/L}$ versus oral iron (30). The primary outcome was the time to initiation of other anemia management, defined by ESA use, blood transfusion, use of an alternative iron therapy, or occurrence of Hb < 10 g/dl (30). Compared with the oral iron group, the high-ferritin group had a 35% lower risk of reaching the primary outcome during the 52-week follow-up period (30). There was no difference across groups regarding the incidence of cardiovascular events or infections, although the study may have been underpowered to detect them (30). It remains to be determined if the strategy delineated in the FIND-CKD study (*i.e.*, proactive use of IV iron aiming high ferritin targets) yields benefits in terms of patient-reported or clinical outcomes for ND-CKD patients. The PIVOTAL trial, which included solely patients on hemodialysis, supports the concept that proactive strategies using high-dose IV iron are not only safe but could also result in lower incidence of cardiovascular events (31).

KDIGO guidelines recommend starting iron agents in anemic individuals with ND-CKD with the goal of either reducing ESA doses or obtaining an increase in Hb levels (1), with a trial of either oral or IV iron for patients with TSAT $\leq 30\%$ and ferritin $\leq 500 \mu\text{g/L}$ (1). Moreover, there is insufficient evidence to support the increased risk of infections associated with the use of IV iron (29,31).

Anemia Real-World Practice, with a Focus on the CKDopps

Observational studies are an invaluable tool to understand the adherence to guideline-based recommendations in real-world practice, and the CKDopps recently published work on anemia practice patterns in 10,000 patients with stages 3b–5 ND-CKD under nephrologist care in Brazil, France, Germany, and the United States. Despite the recommendation to monitor Hb every 3 months, the CKDopps data showed that < 50% of patients with Hb < 10 g/dl had a measurement in the following 3 months (6). This practice pattern may be associated with delays in anemia diagnosis and treatment, with the potential to adversely affect clinical outcomes and PROs.

Regarding ID, the recommended frequency of TSAT and ferritin measurements depends on Hb levels, CKD stage, and ESA use (1). The proportion of patients with Hb < 10 g/dl without measured ferritin and TSAT within ± 3 months from Hb measurement varied from 25% in Germany to 47% in the United States (6), indicating that many patients with CKD who may benefit from iron supplementation are not investigated and therefore, may be suboptimally managed.

Additionally, there were significant differences in Hb upper and lower limits reported by medical directors in the CKDopps and described in Figure 3, reflecting variation in the implementation of guidelines. Importantly, KDIGO recommends that Hb targets with ESA treatment be kept within the 10- to 11.5-g/dl range, with consideration to individualize by considering higher Hb targets for potentially better HRQoL, whereas the European Renal Best Practice guidelines state that keeping the target between 10 and 11 g/dl is reasonable. On the other hand, the Food and Drug Administration label for ESA in the United States emphasizes the risks of adverse cardiovascular events above 11 g/dl, suggesting to not start ESA treatment in patients with Hb > 10 g/dl and that the lowest possible dose should be used to avoid red blood cell transfusions. These findings suggest not only important heterogeneity in clinical practice by countries but also the influence of disparate clinical guidelines and regulations on practice variation by country. In turn, these differences in practice may have distinct effects on clinical outcomes and PROs.

An important question is whether patients with CKD anemia and an indication for treatment on the basis of guidelines are in fact being treated. In the CKDopps, among patients with Hb < 10 g/dl, only 48% of patients in the United States were treated with iron or an ESA within 3 months compared with 58% in Brazil, 66% in France, and 70% in Germany (6). Moreover, individuals with stages 4 and 5 CKD are also potentially undertreated, especially in the United States, where the proportions of any treatment for stages 4 and 5 ND-CKD were 24% and 32%, respectively (6). Longitudinal CKDopps data show that this scenario extends up to at least 12 months, when the cumulative incidence of anemia treatment for persons with Hb < 10 g/dl is < 40% for ESAs, 30% for oral iron, and 10% for IV iron. Notably, the 12-month rate of discontinuation of anemia agents is remarkably high: 51% of persons had discontinued all anemia treatment within 12 months of starting either iron or an ESA. Across different Hb ranges, the use of combined iron and ESA therapy was less common than strategies with ESA only. This may represent undertreatment and lack of optimization given the current guideline-defined goal of prescribing iron therapies to reduce ESA dose and obtain Hb response (6).

In summary, real-world studies evaluating the state of anemia management show that anemia is monitored less often than recommended; that clinical practice targets differ from recommendations that can be derived strictly from RCTs; and that not only are patients left untreated but also, the rate of discontinuation of therapy reaches high levels in 12 months. Potential reasons for these findings are safety concerns of anemia agents, particularly ESAs; different perceptions about individualization of therapy, which may lead to treatment heterogeneity; and potential restrictions in access to or impracticalities in administering parenteral

medications in the ND-CKD setting. For the nephrology community, it is fundamental to consider the challenges of real-world implementation of current clinical recommendations in the anemia field.

New Therapies and New Approaches to Outcomes

The treatment of anemia among patients with ND-CKD has evolved considerably in light of the evidence generated by RCTs in this field. New strategies and novel agents are expected to further change anemia management strategies, including new iron formulations and novel drugs targeting recently described mechanisms (Figure 1) (32). With the potential of addressing the interplay between iron metabolism, erythropoiesis, and inflammatory state, the hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) are promising options for improving CKD anemia outcomes. By stabilizing hypoxia-inducible factors within the cells, HIF-PHIs induce the production of EPO as well as stimulate the transport of iron from enterocytes and macrophages into the circulation (Figure 1). The first phase 3 RCT for an HIF-PHI agent was recently published, in which patients with low Hb were randomized to roxadustat versus placebo (33). Compared with placebo, roxadustat achieved higher Hb levels and a greater reduction in hepcidin levels, whereas transferrin levels were increased and serum iron levels remained clinically stable. Roxadustat has since been approved in China for both individuals with ND-CKD and individuals with ESKD and in Japan for individuals with ESKD. Whether HIF-PHIs are to play a major role in anemia management in ND-CKD is still an open debate and largely unknown until the data for cardiovascular safety are published (33). Recently, pooled cardiovascular safety results including 4270 patients with ND-CKD from phase 3 trials were presented at the 2019 American Society of Nephrology Annual Kidney Week Meeting (34), reporting that the incidence of major adverse cardiovascular events was not different between roxadustat and placebo groups in the intention-to-treat analysis (hazard ratio, 1.08; 95% confidence interval, 0.91 to 1.16) (34). The potential benefits compared with other anemia agents, particularly for the subset of inflamed and ESA-hyporesponsive patients among patients with ND-CKD, are promising and will be analyzed in several ongoing clinical trials with different molecules of the HIF-PHI class. Additionally, considering their oral formulation, these drugs may have fewer barriers for administration compared with current therapies, particularly in ND-CKD. The inclusion of several questions and metrics relevant to anemia in HIF-PHI clinical trials (Table 1) will be important to identify the effect of these new anemia therapies on PROs.

In light of the patient-valued care paradigm, the end users of the interventions, the patients should be in the center of the care process, be able to participate in medical decisions, and more importantly, be empowered to define their priorities and goals (15). In CKD care, this seems to be particularly important because patients are burdened with multiple comorbidities and severely impaired quality of life (35). A testimony of a person who has ND-CKD and anemia treated by a nephrologist is included in the link (Supplemental Material) to illustrate a patient perspective on this condition. For this person, anemia treatment had profound benefits on her energy level and life outlook,

Table 1. (Continued)

Drug and NCT Reference	Study Population	No.	Active Comparator(s) Drug	Primary Outcome	Duration	Start Date; Estimated Completion Date	PRO data	SF-36	FACT-An	EQ-5D-5L	EQ-VAS	WPAI-ANS	PGI-S	PGI-C	CKD-AQ
03350347 (MIYABI ND-M)	ND-CKD	162	Darbepoetin alfa	Mean Hb level	52 wk	12/2017–11/2019		36							

NCT, National Clinical Trial number; PRO, patient-reported outcomes; SF-36, Short-Form 36; functional assessment of cancer therapy-anemia; EQ-5D-5L, EuroQol 5-dimensions 5-levels; EQ-VAS, EuroQol Visual Scale; WPAI-ANS, work productivity and impairment questionnaire anemia symptoms; PGI-S, patient global impression of severity; PGI-C, patient global impression of change; CKD-AQ, CKD anemia questionnaire; ND-CKD, nondialysis CKD; Hb, hemoglobin; X, patient-reported outcomes captured in the studies; N/A, not applicable; MACE, major adverse cardiovascular events; DD-CKD, dialysis-dependent CKD; PD, peritoneal dialysis; ASCEND-NHQ, Anemia Studies in Chronic Kidney Disease (CKD); Erythropoiesis *Via* a Novel Prolyl Hydroxylase Inhibitor (PHI) Daprodustat in Non-Dialysis Subjects Evaluating Hemoglobin (Hgb) and Quality of Life; ASCEND-ND, Anemia Studies in Chronic Kidney Disease: Erythropoiesis *Via* a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Non-Dialysis; MIYABI ND-C, A Study of Molidustat for Correction of Renal Anemia in Non-Dialysis Subjects; MIYABI ND-M, A Study of Molidustat for Maintenance Treatment of Renal Anemia in Non-Dialysis Subjects.

transforming an overwhelming disease to a manageable condition.

Further development of new standardized and patient-focused instruments for capturing fatigue and other important metrics among patients with CKD, particularly those with CKD anemia, is therefore a necessary step in order to implement truly patient-centered care in anemia management. Incorporation of novel agents and innovative strategies for management will require not only a standardized approach to measure and report outcomes but also, efforts to innovative trial designs, patient engagement, and participation and coordination of stakeholders.

Disclosures

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Author Contributions

R. Pecoits-Filho and R.L. Pisoni conceptualized the study; M. Guedes reviewed the literature and wrote the manuscript; B.M. Robinson was responsible for methodology; G. Obrador and A. Tong were responsible for investigation; M. Guedes, R. Pecoits-Filho, and R.L. Pisoni wrote the original draft; and G. Obrador, R. Pecoits-Filho, R.L. Pisoni, B.M. Robinson, and A. Tong reviewed and edited the manuscript.

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