Management of Anemia in Non-Dialysis Chronic Kidney Disease: Current recommendations, real-world practice, and patient perspectives

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Abstract

In non-dialysis chronic kidney disease (ND-CKD), anemia is a multi-factorial 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 impact of treatment on clinical and patient-reported outcomes, remains controversial. In this review article, we explore the epidemiology of anemia in NDD-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 (CKDopp), we highlight the current challenges to translate current recommendations to clinical practice, providing patients’ perspectives of anemia and how it impacts 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.

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 chronic kidney disease (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 (ESA) 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 (HIF) 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 CKD patients and how they affect the management of patients is displayed in Figure 1.

Treatment with EPO was initially restricted to dialysis patients with very low Hb and with the aim of reducing red blood cell transfusion rates, but ESAs are currently used more broadly to include non-dialysis (ND)-CKD patients. Since serum EPO levels are not routinely measured, adequate erythropoiesis is indirectly evaluated in CKD by Hb measurements, which defines when treatment should be initiated and
serves 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 TSAT levels are below 20%-30% and ferritin is below 100 micrograms/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 impacted her life.

**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). Due to 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 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 (LVH) (12), a major risk factor for hospitalization and mortality in CKD patients.

Anemia has also been associated with worse HRQoL in CKD. In an analysis of ND-CKD patients in the Netherlands, individuals with Hb lower than 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 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 ensuring 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 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 more than 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 CKD patient-centered care (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, 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 impact 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 HD population (21). There are few data on patient perspectives on anemia and anemia management in ND-CKD patients. This urges to a standardized approach for not only capturing
validated and robust patient-reported metrics, but also to more data on patient’s voice in anemia care for 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 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 (TREAT), enrolled 4032 diabetic patients with CKD (23). The achieved Hb in the higher target group was 12.5 g/dL vs. 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 patient-reported outcomes (PROs), the impact 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 vs. achieved targets varies 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 KDIGO guidelines suggest (1). Regarding ESA initiation, the current recommendation is to initiate therapy in selected ND-CKD patients with 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 and PROs in ID patients with 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 absence of anemia, on outcomes beyond the Hb response in ID ND-CKD patients is 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 based on 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 stage 3-5 CKD patients to ferric carboxymaltose with a target of ferritin between 400-600 mcg/L vs. ferric carboxymaltose with a target between 100-200 mcg/L vs. 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<10g/dL (30). Compared to 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 FIND-CKD (i.e., proactive use of IV iron aiming high ferritin targets) translates into improved patient experience or fewer clinical complications in ND-CKD individuals. The PIVOTAL trial, which included solely patients on HD, supports the concept that proactive strategies using high dose IV iron is not only safe but could also result in lower incidence of cardiovascular events (31).

KDIGO guidelines recommend starting iron agents in anemic ND-CKD individuals 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 mcg/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 CKDopps**

Observational studies are an invaluable tool to understand the adherence to guideline-based recommendations in real-world practice, and CKDopps recently published on anemia practice patterns in 10,000 ND-CKD Stage 3b-5 patients under nephrologist care in Brazil, France, Germany, and the US. Despite the recommendation to monitor Hb every 3 months, CKDopps data showed that fewer than 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 impact clinical- and patient-reported outcomes.

Regarding ID, the recommended frequency of TSAT and ferritin measurement depends on Hb levels, CKD stage, and ESAs use (1). The proportion of patients with Hb <10 g/dL without measured ferritin and TSAT within $\pm$3 months from Hb measurement varied from 25% in Germany to 47% in the US (6), indicating that many CKD patients who may benefit from iron supplementation are not investigated and therefore may be sub-optimally managed.
Additionally, there were significant differences in Hb upper and lower limits reported by medical directors in CKDopps, and described in Figure 2 reflecting variation in the implementation of guidelines. Importantly, KDIGO recommends Hb targets with ESA treatment to be kept within the 10-11.5 g/dL range, with consideration to individualize by considering higher Hb targets for potential better HRQoL, while the European Renal Best Practice (ERBP) guidelines state that keeping the target between 10-11 g/dL is reasonable. On the other hand, the FDA label for ESA in the US 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 having an indication for treatment based on guidelines are in fact being treated. In CKDopps, among patients with hemoglobin lower than 10 g/dL, only 48% of patients in the US were treated with iron or an ESA within 3 months, compared to 58% in Brazil, 66% in France, and 70% in Germany (6). Moreover, CKD individuals with Stages 4 and 5 are also potentially under-treated, especially in the US, where the proportions of any treatment for ND-CKD Stages 4 and 5 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 lower than 10 g/dL is less than 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 after 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 patients are not only left untreated, but also that 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 ND-CKD patients 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 HIFs within the cells, HIF-PHIs induce the production of erythropoietin as well as stimulate the transport of iron from enterocytes and macrophages into the circulation (Figure 1). The first phase 3 RCT for a HIF-PHI agent was recently published, in which patients with low Hb were randomized to roxadustat vs placebo (33). Compared to placebo, roxadustat achieved higher Hb levels and a greater reduction in hepcidin levels, while transferrin levels were increased and serum iron levels remained clinically stable. Roxadustat has since been approved in China both for ND-CKD and end-stage renal disease (ESRD) individuals and in Japan for ESRD. 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 is 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 (HR 1.08 [95% CI 0.91, 1.16]) (34). The potential benefits compared to other anemia agents, particularly for the subset of inflamed and ESA-hypo-responsive patients among ND-CKD patients, 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 less barriers for administration compared to 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 impact 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, able to participate in medical decisions and, more importantly, to be empowered to define their priorities and goals (15). In CKD care, this seems to be particularly important, since patients are burdened with multiple comorbidities and severely impaired quality of life (35).
testimony of a person who has ND-CKD and anemia treated by a nephrologist is included in the link (see supplemental audio file) to illustrate a patient perspective on this condition. For this person, anemia treatment had profound benefits on her energy level and life outlook, 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 CKD patients, 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

M Guedes: Formal analysis; Writing - original draft; Writing - review and editing
B Robinson: Methodology; Writing - review and editing
G Obrador: Investigation; Writing - review and editing
A Tong: Investigation; Writing - review and editing
R Pisoni: Conceptualization; Writing - original draft; Writing - review and editing
R Pecoits-Filho: Conceptualization; Writing – original draft; Writing - review and editing

References

Table 1: Summary of recently published and ongoing trials with the new class of hypoxia-inducible factor prolyl hydroxylase (HIF-PHI) agents in CKD, including the patient reported outcomes captured in the studies (X).

<table>
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<th>Drug</th>
<th>NCT reference</th>
<th>Study population</th>
<th>No.</th>
<th>Active comparator(s) drug</th>
<th>Primary Outcome</th>
<th>Duration</th>
<th>Start date; estimated completion date</th>
<th>PRO data</th>
<th>SF-36</th>
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<th>EQ-5D 5L</th>
<th>EQ-VAS</th>
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<th>PGI-S</th>
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<td>Hb response</td>
<td>24 weeks- Up to 108 weeks</td>
<td>03/2014–04/2020</td>
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<td>X</td>
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<td>52 weeks- Up to 108 weeks</td>
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<td>12/2015 -06/2017</td>
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Figure 1: Treatment strategies targeting the pathophysiology of anemia in CKD and current limitations and challenges. As the oxygen tension reduces in kidneys and liver (1), the stabilization of HIF promotes the production of EPO (2) and induces the release of iron from enterocytes and macrophages into circulation (3). EPO stimulates the differentiation of proerythrocytes into mature red blood cells in the blood marrow (4), while iron is incorporated in the Hb synthesis (5). Finally, the increase in O2 delivery to the tissues destabilizes HIFs and inhibits EPO production (6). Current US approved treatment strategies target 4 (ESAs) and 5 (iron supplements). Novel therapies, as HIF-PHIs, target 2 and 3.
Figure 2: Hemoglobin and TSAT distributions according to CKD stage. Data from CKDopps. Panel A: Hemoglobin. Panel B: TSAT.
Figure 3: Hemoglobin targets CKDopps nephrologist practice survey (2015/2017). Panel A: Lower targets for Hb. Panel B: Upper targets for Hb. Clinic-level Hb upper and lower targets were collected from nephrologist surveys from 44 clinics in CKDopps, from Brazil (12), Germany (15), US (25) and France (37).