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KDIGO Controversies Conference on Optimal Anemia Management in CKD

**December 13-15, 2019
Barcelona, Spain**

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and ask what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline updating efforts and other times they highlight areas for which additional research is needed.

BACKGROUND

Anemia and disordered iron homeostasis are prevalent in patients with chronic kidney disease (CKD) and associated with significant adverse consequences.¹⁻¹⁵ In 2012, KDIGO issued an anemia guideline, providing recommendations on the diagnosis, evaluation, and treatment of anemia in CKD, including the use of iron agents, erythropoiesis stimulating agents (ESAs), and red-cell transfusions.¹⁶ As noted in the 2012 guideline, the recognition of adverse clinical outcomes associated with ESAs when dosed to normalize hemoglobin,¹⁷⁻²⁰ and several regulatory and reimbursement changes have shifted practice patterns in many countries toward increasing use of iron supplementation.²¹⁻²⁵ In 2014, KDIGO convened a Controversies Conference on iron therapies, focused primarily on potential safety issues, including iron overload; inflammation and oxidative stress; risk of infections; and hypersensitivity reactions.²⁶ At that time, the data were judged insufficient to consider new recommendations, but future research priorities were identified, including an urgent need for more randomized controlled trials.²⁶



Since the 2012 KDIGO anemia guideline and 2014 Controversies Conference, new basic research data, epidemiological studies and randomized trials have emerged that warrant a re-examination of a number of guideline recommendations. These include new molecular insights into the regulation of iron homeostasis by the hepcidin-ferroportin axis and hypoxia inducible factors (HIFs); the pathophysiology of dysregulated iron homeostasis and anemia in CKD; the relationship between iron status, anemia, iron therapy, ESAs and associated co-morbidities/outcomes in CKD patients (e.g., infection, cardiovascular outcomes, mortality); and new data regarding links between iron and anemia and other disorders, including CKD-mineral and bone disorder (CKD-MBD).²⁷⁻³⁹ Most notably, new randomized controlled trial data surrounding the use of existing therapies and new therapeutic agents, including iron-based phosphate binders, iron-containing dialysate, novel iron formulations, long-acting erythropoiesis-stimulating agents (ESAs), ESA biosimilars, and hypoxia-inducible factor (HIF)-stabilizers⁴⁰⁻⁴⁹ provide, in our opinion, sufficient justification to revisit specific guideline recommendations by the future Work Group panel.

Therefore, KDIGO will convene a pair of Controversies Conferences to review the latest evidence, explore new and ongoing controversies, propose a research agenda, and assess change implications for the current KDIGO anemia guideline. It is understood that studies of the effects of HIF-stabilizers on CKD patient outcomes are still in progress. Consequently, the first conference that will be held in December 2019 will focus largely on iron, including the contribution of iron pathophysiology to the anemia of CKD and adverse patient outcomes, diagnostic issues, treatment targets, iron therapeutic agents, and the impact of other current and emerging anemia therapies on hemoglobin targets, iron parameters, and iron supplementation needs. It is anticipated that the second conference will be convened in 2020 to discuss erythropoiesis-stimulating agents, including epoetins and HIF-stabilizers, once additional longer-term outcomes trial data have accrued.

CONFERENCE OVERVIEW

The objective of the December 2019 KDIGO conference is to gather a global panel of multidisciplinary clinical and scientific expertise (i.e., nephrology, cardiology, pediatrics,



pharmacology, hematology etc.) to identify key issues relevant to the optimal management of anemia in CKD, with particular focus on iron. The goal of this KDIGO conference is to determine best practice and areas of uncertainties in the treatment of anemia, review key relevant literature published since the 2012 KDIGO Anemia Guideline, address ongoing controversial issues, identify new topics or issues to be revisited for the next iteration of the KDIGO guideline, and outline research needed to improve anemia management in CKD.

Drs. Tilman B. Drüeke (INSERM U-1018, Hôpital Paul Brousse, Villejuif, France) and Jodie L. Babitt (Massachusetts General Hospital, Boston, MA, USA) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. Invited participants and speakers will include worldwide leading experts who will address key clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a summary report that will help guide KDIGO and others on therapeutic management and future research in anemia and CKD.

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APPENDIX: SCOPE OF COVERAGE

Group 1: Iron, anemia, and outcomes in CKD

1. What is the evidence that anemia and/or iron deficiency cause adverse outcomes in CKD patients?
2. What are the known or expected benefits from iron administration (e.g., reduction in mortality and/or morbidity, such as heart failure, cardiovascular disease, hospitalizations, exposure to ESAs, quality of life, fatigue, cognitive function)?
3. What are the known or expected harms from iron administration: (e.g., infection, cardiovascular disease, anaphylaxis, oxidant-mediated tissue injury, diabetes, neurodegenerative disorders, kidney disease progression, cancer)?
4. Are there data to support the known or expected benefits of iron administration, as defined in #2? Are there differential effects by the route of administration or dosing strategy?
5. Are there are data to support the known or expected harms of iron administration, as defined in #3? Are there differential effects by the route of administration or dosing strategy?
6. What is the differential risk of anaphylaxis for the currently available iron formulations? Can we develop a table of reported anaphylactic risk for all available iron formulations to help guide selection?
7. Are there special populations for which intravenous iron supplementation would be beneficial or should be avoided or minimized? What is the evidence to inform the withholding of IV iron supplementation in the context of active infections, hepatitis B or C, dialysis vintage greater than 4 years, use of a catheter rather than a fistula or graft, or other specialized populations?
8. How do iron status, anemia, and/or intravenous iron formulations impact CKD-mineral and bone disorder?
9. Do iron status, anemia, and/or iron supplementation affect the host immune response or host microbiome?



Group 2: Pathogenesis and diagnosis of iron deficiency and anemia in CKD

1. What new insights in systemic iron homeostasis have been obtained in the last decade? What is their relevance for new diagnostic and treatment strategies for iron deficiency in the CKD setting? Is this different for inflamed and non-inflamed patients?
2. What is the best definition of iron deficiency and anemia in the CKD setting? Is the definition/diagnosis of iron deficiency still relevant considering the large iron use?
3. What is the prevalence of iron deficiency and anemia in CKD? Is this different for various parts of the world?
4. How can iron deficiency and anemia be diagnosed? What laboratory parameters should be used and what are their limitations? Is there a role for functional tests? Is there a clinical relevance for distinguishing absolute iron deficiency from functional iron deficiency and how should they be defined? Is there a role for novel diagnostic tests?
5. What are the criteria to initiate therapy with ESA/iron? Should we use clinical or laboratory based criteria or both?
6. Are there differences in prevalence, pathophysiology, diagnosis, treatment initiation criteria for iron deficiency and anemia between patients with CKD (non-dialysis) vs on hemodialysis vs on peritoneal dialysis vs pediatric patients vs kidney transplant recipients?

Group 3: Use of iron agents in CKD anemia management

1. What are the properties, efficacy (e.g., hemoglobin, iron status, functional, and clinical endpoints), and safety profiles (occurrence of hypersensitivity reactions; occurrence of interaction with CKD-MBD parameters [FGF23]) of currently available oral iron agents to be used in anemia of CKD? How do oral iron agents compare with each other? with IV iron agents? How do we define effectiveness? How do we assess equal or unequal effectiveness?
2. What are the properties, efficacy (e.g., hemoglobin, iron status, functional, and clinical endpoints), and safety profiles (occurrence of hypersensitivity reactions; occurrence of interaction with CKD-MBD parameters [FGF23]) of currently available intravenous iron preparations to be used in anemia of CKD? What is the evidence-based data directly comparing efficacy and/or safety among different intravenous iron preparations (e.g., modern versus classic iron preparations and their stability and ligand properties)?
3. What should be the optimal treatment strategy with iron supplementation (e.g., how do we define different dosing regimens/strategies: high dose, low dose, maintenance, bolus, reactive versus proactive)? What are the optimal doses, frequency of administration, dosing strategies? Is there a maximal allowable dose?
4. What should be the optimal treatment targets? Which iron status parameters should be monitored: TSAT, ferritin, other parameters? How frequently should iron parameters be monitored? Does active therapy impact interpretation of iron status parameters? What guidance is there for the termination of iron therapy? Should there be an upper limit of TSAT and/or ferritin, and if so what is it? Is there a hemoglobin level at which iron supplementation should occur regardless of iron indices or at which iron supplementation should not occur? Is there a rationale for iron supplementation irrespective of iron indices?
5. How do we monitor for toxicity? Topics specifically to discuss: Which tests can be used to assess for iron overload/iron toxicity (e.g., MRI, labile iron, oxidative stress parameters)? What is the evidence demonstrating that these tests function as indicators of toxicity? What are their limitations (availability, cost, etc.)?



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6. How to use iron supplementation in various patient populations? Should the choice of iron preparation, dosing strategy, treatment targets, or other parameters be modified (and how so) in different patient populations (e.g., patients with CKD [non-dialysis] vs on hemodialysis vs on peritoneal dialysis vs pediatric patients vs kidney transplant recipients; patients with an active infection; patients with liver disease; patients with heart failure; patients with calciphylaxis; other special circumstances)?



Group 4: Impact of ESAs and novel therapeutic agents (e.g., HIFs) in relation to hemoglobin control, iron status, and iron supplementation needs

1. How do ESAs affect iron-related outcomes (i.e., iron parameters, iron supplementation needs)? Is there any impact of ESA dosing strategies (e.g., dose, frequency, rate of titration, use of protocols/artificial intelligence for decision support)?
2. Are there differences among ESA preparations relative to their impact on iron parameters/needs? Are there differences between short- or long-acting ESAs?
3. Is there evidence demonstrating an impact of biosimilars on iron-related outcomes (i.e., iron parameters, iron supplementation needs)? What is the evidence comparing biosimilars with originator ESAs?
4. What are the molecular mechanisms by which HIF stabilizers might impact iron homeostasis (e.g., via EPO production, hepcidin/ferroportin axis, iron transporters, inflammation, EPO-independent bone marrow effects)?
5. What is the evidence from Phase 2/3 clinical trials on the impact of HIF stabilizers compared with placebo or ESA on hemoglobin response, iron status, and iron supplementation needs in CKD patients? What is the therapeutic window of HIF stabilizers for impacting hemoglobin response, iron metabolism? Are there differences among HIF stabilizers, theoretical or demonstrated?
6. What new therapeutic strategies are being developed to treat iron deficiency and anemia in CKD patients (targeting hepcidin/ferroportin axis, activin receptor ligand traps, etc.)?
7. Is there a role for combination therapies/multi-target approach to treat anemia of CKD? Why only a single or two agent therapy? Should we target inflammation? Are there other adjunctive therapies that should be considered?
8. Are there additional biomarkers or diagnostic tests that are relevant to the evaluation and/or management of anemia with new therapeutic agents?
9. What is the evidence regarding cost-effectiveness of novel therapeutic agents for treating anemia of CKD?