



## **KDIGO Controversies Conference on Optimal Anemia Management in CKD**

### **- Breakout Group Questions -**

#### **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 serum iron parameters (TSAT, ferritin) independent from Hb levels? 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.)?
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?



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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?
10. How do / would new therapies impact pediatric patients with kidney disease?
11. What impact do new therapies have on mineral bone metabolism?