



## KDIGO Controversies Conference on Iron Management in Chronic Kidney Disease

### Breakout Questions

#### A. Iron overload

1. What are the benefits of iron supplementation in CKD patients?
  - a. What are the effects on hemoglobin (Hb)?
  - b. What are the non-anemia related effects (e.g., heart, respiration)?
  - c. Does the routing (oral/IV) or type of iron salt or iron complex make a difference?
  - d. What are the financial benefits in terms of cost-effectiveness?
2. What is the cause of iron overload in CKD patients treated with iron? Does iron overload depend on the type of iron salt/complex, on oral or IV administration?
3. What is the definition of iron overload in a CKD setting? Is there a threshold?
4. How best to diagnose iron overload in a CKD setting? What laboratory tests\*? Is there a threshold? Do we need to control lab tests for the inflammatory status? MRI scanning?
5. How best to guide decisions on initiation, maintenance and discontinuation of iron supplementation in CKD patients? What laboratory tests\*? MRI scanning (and what exact MRI-methodology)? SQUID? Do these decisions depend on the patient group (non-dialysis [ND], hemodialysis [HD] or peritoneal dialysis [PD]), gender, co-treatment with ESA, or co-morbidities (cardiovascular disease, chronic liver disease-hepatitis C, inflammation)?
6. What are short and long term effects of iron accumulation in various tissues and cells in CKD patients in terms of documented iron overload (biopsy, MRI; cellular distribution), morphological changes (e.g. fibrosis), or non-invasive measures of atherosclerosis (NIMA)?

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\*Lab tests:

- I. Conventional iron parameters: serum ferritin, TSAT
- II. More novel iron parameters: serum transferrin receptor (sTfR), erythrocyte zinc protoporphyrin (ZnPP), hepcidin, non-transferrin bound iron (NTBI), labile plasma iron (LPI), others(?);
- III. Red cell parameters: Hb, red cell indices (MCH, MCV, hypochromic cells); reticulocyte parameters (CHr, RetHe);
- IV. Inflammatory parameters, e.g. CRP



7. How does iron accumulation affect organs on a functional level? (e.g., liver, heart, pancreas, bone, kidney) Does iron supplementation contribute to CKD progression?
8. How does iron accumulation affect long term outcome measures (events, mortality)?
9. What is the optimal administration of iron in terms of doses, bolus versus maintenance, ESA-to-iron balance in CKD patients (dialysis vs. non-dialysis)? For consideration: routing, type of iron salt or iron complex, pediatric patients
10. What are the promises of novel therapeutic approaches? Heparin antagonists? Dialysate iron? Novel forms of oral and IV iron?

*Optional:*

11. What is the cause of iron deficiency in CKD patients?
12. What is the usual iron loss in ND, HD, and PD patients?

**B. Inflammation and oxidative stress**

1. Which methods best estimate oxidative stress in the clinical setting?
2. Do IV iron compounds aggravate oxidative stress and/or inflammation? If so, what mechanisms are involved?
3. Can antioxidants blunt the pro-oxidative effects of iron supplementation?
4. What is the role of free circulating iron: can iron compounds adequately be bound and metabolized when given intravenously?
5. Are there differences in the pro-oxidative and pro-inflammatory potential among different iron compounds?
6. Is there a difference in the oxidative stress potential between iron sucrose originators vs iron sucrose similars (i.e., iron generic follow-ons)?
7. Do IV iron dose and administration time matter among different iron compounds with respect to causing oxidative stress and inflammation?
8. Is there any evidence that IV iron compounds promote atherosclerosis and cardiovascular disease?
  - o Are there subgroups of patients that may be at risk?
  - o How does iron therapy link to vascular calcification? Effects of iron on FGF23?
9. What are the consequences of increased hepcidin and ferritin levels during inflammation?



### C. Iron and infections

1. What is the impact of iron supplementation on host immune function?
2. How could IV iron exacerbate the risk of infections? (e.g., neutrophil killing potential; bacterial proliferation)
3. Is it a real or just a theoretical risk? What are the laboratory, animal, observational and RCT data?
4. What is the evidence in favor or against an association between IV iron and infection in predialysis and dialysis patients?
5. Is there an increased risk of infection with different iron formulations including new ones?
6. Is there an increased risk of infection with different dosing strategies (e.g., bolus versus maintenance)?
7. What type of infections should we be concerned about? (e.g., bacterial, fungal, viral, or parasitic)
8. Is there an increased risk of infection associated with iron overload derived from blood transfusions?

### D. Hypersensitivity reactions

1. What are the characteristics of a drug hypersensitivity reaction? What are the risk factors for these reactions (e.g., asthma, atopy, previous drug hypersensitivity, previous iron hypersensitivity) and how should these reactions be diagnosed and classified?
2. What are the differences in propensity to hypersensitivity reactions between the different formulations of IV iron?
3. Does the incidence of hypersensitivity translate into a cost effective recommendation for the use of any IV iron formulation use over another?
4. What is the pathogenesis of immediate reactions to IV iron? Are they immune mediated?
5. Are some of the reactions to IV iron caused by 'free' iron in the circulation?
6. What is the difference between 'free' iron, 'labile' iron, and 'non-transferrin-bound' iron?
7. How commonly do reactions to IV iron occur?
8. How often are these reactions serious or life-threatening?



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9. Are there differences in the risk of reactions to IV iron between the various iron preparations?
10. How should reactions to IV iron be treated?
11. How should patients with previous reactions to IV iron be managed in the future? What is the utility of a test dose? Can another formulation be used and if so, what additional testing might be required?
12. How can such adverse drug reactions be better documented?