KDIGO Controversies Conference on
Novel Anemia Therapies in CKD
- Breakout Group Questions -

Group 1: Therapeutic use of HIF-PHIs vs. current therapies in anemia management:
CKD patients not on dialysis treatment

1. What is the efficacy of HIF-PHIs in the treatment of anemia in patients with CKD not on dialysis therapy and the mean hemoglobin change that we can expect under standard treatment?
2. What should the hemoglobin target be in relation to HIF-PHI use? Do higher hemoglobin levels remain an area for concern and should there still be an upper limit that is below normal?
3. What is the appropriate dose for HIF-PHIs and how should dosing be adjusted (based on what parameters)? How do we manage a patient converting from the use of ESAs to HIF-PHI? Is there a possible role for combining HIF-PHIs with ESAs?
4. Is there any evidence that the use of HIF-PHIs affect cardiovascular endpoints (MACE), progression of CKD, transfusion requirements, physical function, health-related quality of life compared with iron/ESAs?
5. What is the current data surrounding differences between HIF-PHI agents in patients with CKD not on dialysis?
6. What is the role of iron and EPO in the era of HIF-PHIs for patients with CKD not on dialysis treatment? What is the comparative advantage of HIF-PHIs relative to iron and EPO?
7. Are there particular advantages or disadvantages to the use of oral HIF-PHIs in the non-dialysis CKD population as compared to the dialysis population? Cost-savings, resource utilization, or COVID-19 pandemic-related considerations? Do HIF-PHIs reduce iron requirements among patients with CKD not receiving dialysis?
8. What are the patient values and preferences regarding oral vs SC or IV drugs for the management of anemia?
Group 2: Therapeutic use of HIF-PHIs vs. current therapies in anemia management:
CKD patients treated with dialysis (patients incident and prevalent to dialysis)

1. What is the efficacy of HIF-PHIs in the treatment of anemia in patients on dialysis therapy and the mean hemoglobin change that we can expect under standard treatment? Does this differ from patients with CKD not on dialysis treatment? Does this differ among patients treated with hemodialysis versus peritoneal dialysis?
2. What should the hemoglobin target be in relation to HIF-PHI use? Do higher hemoglobin levels remain an area for concern and should there still be an upper limit that is below normal?
3. What is the appropriate dose for HIF-PHIs and how should dosing be adjusted (based on what parameters)? How do we manage a patient converting from the use of ESAs to HIF-PHI? Is there a possible role for combining HIF-PHIs with ESAs? Are there subgroups who are hyporesponsive to HIF-PHIs?
4. Is there any evidence that the use of HIF-PHIs affect cardiovascular endpoints (MACE), transfusion requirements, physical function, health-related quality of life compared with iron/ESAs? Are there any differences between the incident vs prevalent dialysis populations?
5. What is the current data surrounding differences between HIF-PHI agents in patients treated with dialysis?
6. What is the role of iron and EPO in the era of HIF-PHIs for patients on dialysis therapy? Are there advantages or disadvantages to the use of oral HIF-PHIs as opposed to current therapeutic options in the dialysis population? What should be the optimal strategy to treat anemia in the hemodialysis population, including the incorporation or prioritization of currently available therapies and novel therapies?
7. Are there advantages or disadvantages to HIF-PHI use in patients who are hyporesponsive to ESAs or iron? Cost-savings, resource utilization, or COVID-19 pandemic-related considerations? Do HIF-PHIs reduce iron requirements among patients receiving dialysis?
8. Are there subgroups for which HIF-PHIs might be particularly beneficial, such as patients receiving home dialysis therapies?
Group 3: Safety profile of HIF-PHIs in CKD anemia management

1. What are the current available safety data surrounding use of HIF-PHIs in different populations: patients not on dialysis; patients who are incident or prevalent to dialysis? Is there any evidence that safety differs by level of GFR or inflammatory states or degree of anemia?
2. Does the use of HIF-PHIs apply to anemia of CKD in kidney transplant populations with low eGFR and anemia? Pediatric populations? Older adults? Patients with underlying liver disease, polycystic kidney disease, or diabetic retinopathy? Immunosuppressed patients (e.g., due to underlying GN)? Patients with AKI?
3. What parameters should be monitored during the treatment of anemia when using HIF-PHIs? Are there novel biomarkers or testing that should be made available to help with safety monitoring? What toxicities should providers monitor?
4. Are there theoretical or known safety differences between various HIF-PHI agents that are available or being developed in phase II/III trials?
5. What long-term post-marketing data may be needed given the potential unanticipated actions of HIF-PHIs? What theoretical risks may remain to be of concern (e.g., oncologic)?
6. Are there drug-drug interactions that should be considered with the use of HIF-PHIs?
7. Are there CKD subgroups for which HIF-PHIs use might be harmful? Are there concerns related to AKI or CKD progression?
Group 4: Pathophysiology of HIF-PHIs and pleiotropic effects beyond hemoglobin

1. What is the physiologic role of HIF-PHIs and their interaction with EPO and iron and effects on their metabolism? Are there any potential links between HIF-PHI-mediated effects on iron metabolism and increased rates of sepsis/infection or other effects of the HIF pathway that might explain this?

2. What are the pathophysiologic mechanisms by which use of HIF-PHIs may require special consideration as it relates to AKI, other kidney diseases including cystic disease, immune-mediated kidney diseases, etc.?

3. What are the theoretical off-target effects that warrant considerations as we assess the impact of HIF-PHIs on major adverse cardiovascular events as mediated by effects on BP, cholesterol, etc.? Do these benefits seem to be agent specific or common across the HIF-PHI class?

4. Do HIF-PHIs affect BP or dyslipidemia differentially among patients not on dialysis versus on dialysis? Electrolytes or acid-base disturbances? Coagulation cascade?

5. What are the benefits, risks, and differences of the current ESAs that are available (short-acting, long-acting [CERA], biosimilars/biogenerics)? How may or may not HIF-PHIs address the shortcomings of ESAs?

6. What data are available for HIF-PHIs surrounding symptoms and quality of life? Patient-centered outcomes? Patient preferences?

7. Are there other novel therapeutic agents (e.g., SGLT2i) or candidates on the horizon (non-HIFs such as ziltivekimab) for the treatment of anemia that need to be considered? How might they compare to HIFs or ESAs?

8. Is there evidentiary support to the suggestion that HIF-PHIs are associated with lower (or slower?) increases in EPO than ESAs, thus explaining the elevated CV risk/mortality in the latter? Has this purported benefit in HIF-PHIs been substantiated?

9. What are the pleiotropic effects of HIF-PHIs on CKD-MBD and is there a potential role for FGF23 in this process?