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Scope of Work

KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease Update 2022

Background

Anemia is a common complication of chronic kidney disease (CKD) associated with adverse outcomes. Relative erythropoietin deficiency and disordered iron homeostasis, including absolute and functional iron deficiency, are major contributors to the anemia of CKD. In 2012, KDIGO published a Clinical Practice Guideline for Anemia in CKD, 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. In the ensuing nine years, new evidence and novel anemia therapies, including hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), have emerged that prompted a re-examination of the 2012 anemia guideline. In 2019 and 2021, KDIGO convened a series of two Controversies Conferences to review the latest evidence and explore consensus points and controversies surrounding optimal anemia management in CKD. Conference members reached consensus regarding the need for an anemia guideline update. Together with the topics covered by the original guideline, the Controversies Conference conclusions serve as the basis for the KDIGO Anemia Guideline update Scope of Work.

The goal of the guideline is to generate a useful resource for clinicians and patients by providing actionable recommendations, based on a rigorous, formal systematic literature review, supplemented by practice points and useful infographics to aid in implementation. Another aim is to propose research recommendations for areas in which there are gaps in knowledge. This guideline is designed to apply to a broad population of patients with anemia and CKD. Special consideration will be given to patient-specific characteristics such as CKD severity (including hemodialysis [HD], peritoneal dialysis [PD], CKD without kidney replacement therapy [KRT]); pediatric CKD; kidney transplant recipients (KTRs); patients on ESA therapy; patients on HIF-PHI therapy; co-morbid conditions (e.g., heart failure, cirrhosis); and iron deficiency without anemia. In addition, particular attention will also be given to patient preference, accessibility, and cost.

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Chapter Outline and Rationale for Topic Selection

Chapter 1. Diagnosis and evaluation of iron deficiency and anemia in CKD

1.1. Testing for iron deficiency and anemia

1.1.1 Diagnosis of anemia

- What is the definition of anemia? Is a refinement in the definition of anemia from the prior guidelines needed?
- What is the probability of anemia in CKD based on stage and primary diagnosis?
- What are the adverse clinical events and/or adverse patient-reported outcomes associated with anemia?

1.1.2 Diagnosis of iron deficiency

- What is the clinical laboratory definition of iron deficiency?
    - Is it possible and/or clinically meaningful to distinguish between absolute and functional iron deficiency?
- What is the probability of iron deficiency in CKD based on stage, primary diagnosis, and presence or absence of anemia?
- Are there adverse clinical events and/or adverse patient-reported outcomes associated with iron deficiency that are independent of anemia?

1.1.3 Frequency of testing

- Is a refinement needed to the prior guideline in the testing frequency to screen for anemia?
- Should patients be screened for iron deficiency independent of anemia? If so, what is the testing frequency for iron deficiency that is recommended?

1.1.4 Investigation of iron deficiency

- If it is not recommended for patients to be screened for iron deficiency independent of anemia (see 1.1.2), what is the threshold Hb of untreated anemia that should trigger workup for iron deficiency?
- What parameters are recommended for the evaluation in the initial evaluation of iron deficiency?
- If iron deficiency is diagnosed, what additional evaluation (if any) should be conducted?

1.1.5 Investigation of anemia

- What is the threshold of untreated Hb that should trigger workup for the underlying cause of anemia? Is there a refinement to the threshold in the prior guideline?
- Is there a refinement needed to the recommended initial evaluation of anemia in the prior guideline? In patients with anemia and iron deficiency, is additional evaluation of anemia needed?

Chapter 2. Use of iron to treat iron deficiency and anemia in CKD

2.1 Treatment with iron agents

- What are the essential measures of treatment efficacy for iron therapy?
    - Distinguish hard outcomes, surrogate outcomes, and patient centered outcomes (e.g., survival, cardiac effects, hospitalizations, reduction of ESA use, reduction of transfusions, exercise tolerance, patient-reported outcomes)
- What are the safety concerns associated with treatment with iron agents?
- When should iron therapy be initiated in CKD patients?
- What are the treatment targets for iron therapy that define optimum treatment efficacy while minimizing safety concerns? Do treatment targets vary depending on the use of additional anemia therapies (ESAs, HIF-PHIs)?
- Are there upper limits of iron status tests beyond which iron therapy shows little or no benefit, evidence of risk, or both?
- What are the recommended doses, dose ranges, administration frequency, infusion rates of available IV iron agents?
- What are the recommended doses, dose ranges, and dosing frequency, of available oral iron agents?
- What are the recommended doses, dose ranges, and dosing frequency of dialysate iron?
- Are there preferred iron agents?
- Are there preferred dosing strategies?
    - routes of administration (e.g., oral vs. IV vs. dialysate)
    - administration frequency
    - dose ranges (e.g., bolus vs maintenance)?
- Is there a role for iron therapy in the absence of anemia? Is there a role for

iron therapy in the absence of iron deficiency to treat anemia and reduce ESA usage?

2.2 Monitoring response to therapy

- What is the recommended frequency of monitoring iron status tests during iron and anemia therapy (ESA, HIF-PHI) in each patient population?
- Are there any recommended tests to monitor for toxicity? Are there agent-specific adverse effects that should be monitored? Are there specific patient populations more vulnerable to toxicity that should be monitored differently?

2.3 Cautions and contraindications regarding iron therapy

2.3.1 Hypersensitivity reactions

- What is the incidence of hypersensitivity with currently available iron preparations?
- Are there any refinements needed in the monitoring for and management of hypersensitivity reactions from the prior guidelines?

2.3.2 Iron during infection and acute illness

- Should iron use be avoided/suspended during active infections? Does the type of infection or iron agent matter?
- Should iron use be avoided/suspended during acute illness requiring hospitalization beyond active infections?

Chapter 3. Use of ESAs, HIF-PHIs and other agents to treat anemia in CKD

3.1 Nomenclature

- Should we update the nomenclature for anemia therapies?
    - Should we replace the term ESA with more specific terminology (e.g., erythropoietin hormone replacement therapy [EHRT]) to distinguish from HIF-PHIs?

3.2 Treatment initiation

- What are the essential elements of treatment efficacy for ESA and HIF-PHI therapy?
    - Distinguish hard outcomes, surrogate outcomes, and patient-centered outcomes (e.g., survival, cardiac effects, hospitalizations, reduction of

transfusions, exercise tolerance, patient-reported outcomes (patient-reported quality of life, depressive symptoms, fatigue)

- What are the safety concerns of ESAs and HIF-PHIs for treating anemia in CKD?
- Is Hb a valid surrogate to assess important health outcomes of ESA or HIF-PHI therapy? Are there additional parameters to assess besides Hb to gauge important health responses to therapy?
- What is the threshold for treated Hb that affords optimum treatment efficacy while minimizing safety concerns?
    - Does this differ depending on the type of anemia therapy?

3.3 Maintenance therapy

- What are the Hb treatment targets for maintenance therapy in each population and how do patient-specific characteristics such as co-morbidities and functional status influence these?
    - Specifically address patients with known ASCVD; previous CVA; HF; active or prior cancer; hospitalized patients.
- What is the fraction of patients that should be expected to include or exceed the treated-Hb threshold?

3.4 Types of therapies

- What are the available ESAs and HIF-PHIs?
- Are there any efficacy differences between ESAs and HIF-PHIs? Are there any efficacy differences among ESAs? Among HIF-PHIs?
- Are there any differences in safety concerns between ESAs and HIF-PHIs? Are there any differences in safety concerns among ESAs? Among HIF-PHIs?
- Is there a preferred agent (or alternatively an absolute or relative contraindication) for initial ESA or HIF-PHI therapy in each patient population and how do patient-specific characteristics influence this choice?
- Should informed consent be obtained for ESA and/or HIF-PHI use?

3.5 Dosing

3.5.1 ESAs

- Provide new information on available ESA agents and their doses, dose ranges, dosing intervals and route of administration.

- Is there a preferred ESA, route of administration, dosing strategy in each population and how is this influenced by patient-specific characteristics (e.g., co-morbidities), patient preferences, accessibility, cost?
- What are potential indications for switch from HIF-PHI to ESA?
- What are conversion factors for shifting from existing HIF-PHIs to ESAs?

3.5.2 HIF-PHIs

- What are the available HIF-PHI agents, differences among them in terms of HIF selectivity (if important), optimal doses, dose ranges, dosing intervals?
- Is there a preferred HIF-PHI agent, dosing strategy?
- What are potential indications for switch from ESA to HIF-PHI?
- What are conversion factors for shifting from existing ESA to HIF-PHIs?

3.6 Frequency of monitoring

- How frequently should Hb be monitored during the initiation phase of anemia therapy? During the maintenance phase? Does this differ depending on the type of anemia therapy? Are there any changes in recommendation from the prior guideline?
- Are there any recommended tests to monitor for toxicity? Are there agent-specific adverse effects that should be monitored?

3.7 Evaluating and correcting persistent failure to reach or maintain intended hemoglobin concentration

3.7.1 Initial hyporesponsiveness

- How is initial hyporesponsiveness defined?
- How should hyporesponsive patients be evaluated and managed? What is the limit for dose escalation of ESAs or HIF-PHIs?
    - What constitutes the initial workup for hyporesponsiveness?
    - When should hyporesponsiveness trigger investigation of non-renal contributions?
    - What is the limit for dose escalation of ESAs or HIF-PHIs?
    - Should hyporesponsive patients be considered to switch from ESAs to HIF-PHIs or vice versa, and if so, when?
    - Is there a role of combination therapy with ESA/HIF-PHI?

3.7.2 Subsequent hyporesponsiveness

- How is subsequent hyporesponsiveness defined?
- How should hyporesponsive patients be evaluated and managed?
    - What is the limit for dose escalation of ESAs or HIF-PHIs?
    - Should hyporesponsive patients be considered to switch from ESAs to HIF-PHIs or vice versa, and if so, when?
    - Is there a role of combination therapy with ESA/HIF-PHI?

3.8 Additional or adjuvant anemia therapies

- Are there any new additional or adjuvant anemia therapies that should be considered for the management of anemia (e.g., SGLT2 inhibitors, anti-inflammatory therapies)? Are there any changes to these recommendations from the prior guideline?

3.9 Evaluation for pure red cell aplasia (PRCA)

- Is a refinement to the guidance on PRCA needed?

Chapter 4. Red cell transfusion to treat anemia in CKD

4.1 Use of red cell transfusion in chronic anemia

- Is a refinement to the guidance on use of red cell transfusion in chronic anemia needed?

4.2 Urgent treatment of anemia

- Is a refinement to the guidance on urgent treatment of anemia needed?