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Anemia in CKD: Understanding the KDIGO 2025 Clinical Practice Guideline

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is brought to you by Akebia Therapeutics. Here's your host, Dr. Gates Colbert.

Dr. Colbert:
Welcome to *Clinician's Roundtable* on ReachMD. I'm Dr. Gates Colbert, and joining me to discuss the KDIGO 2025 Clinical Practice Guidelines for treating anemia in chronic kidney disease, or CKD for short, is Dr. Glenn Chertow. He's a Professor of Medicine at Stanford University School of Medicine. Dr. Chertow, thanks for joining us today.

Dr. Chertow:
My pleasure.

Dr. Colbert:
So let's jump right in, Dr. Chertow. The guidelines recommend that in patients with anemia and CKD, the decision to use an erythropoiesis-stimulating agent, also known as an ESA, or hypoxia-inducible factor prolyl hydroxylase inhibitors, or HIF-PHIs for short, should be made together with patients and that we should consider symptoms, the potential for harm in red blood count transfusions, and the risk of adverse effects. So, with that in mind, could you give us some background on these two agents and the factors that influence treatment decisions?

Dr. Chertow:
We want to take into account not only the potential risks and benefits to patients, but also some individual patient decisions that might come into their decision making process. So the ESAs have been around for a number of decades. Epoetin alfa was initially approved in 1989 for the treatment of chronic kidney disease-related anemia and was transformational in the care of patients on dialysis who were extremely transfusion dependent.

The HIF-PHI class of drugs are newer. The mechanism by which they work was awarded the Nobel Prize in Medicine in 2019. And these drugs increased endogenous erythropoietin. The HIF-PHI drugs are oral, and so in many ways, more convenient for patients, particularly those not on dialysis or those on home dialysis. And the ESAs—the prototype of which was epoetin alfa, but there are several others—are administered perennially, either intravenously in the setting of hemodialysis or in subcutaneously for patients on peritoneal dialysis or those with non-dialysis requiring chronic kidney disease.

Dr. Colbert:
And diving deep into ESAs for a moment, the guidelines recommend this approach rather than HIF-PHIs as first-line therapy once all other causes of anemia have been addressed. Why is that the case? And when initiating ESA therapy, how can we best balance treatment goals and safety considerations?

Dr. Chertow:
The use of ESAs—primarily the fundamental reason for using drugs to correct anemia in chronic kidney disease, and particularly in advanced chronic kidney disease where the anemia is most severe—is to abrogate the need for blood transfusion. Now, blood transfusion in past years, carried a number of risks of infectious diseases. Those are much less prevalent now, but there are still risks of receiving blood transfusion for patients with advanced CKD or end-stage kidney disease. Packed red blood cell transfusions can cause acute pulmonary edema. They can be problematic. And for patients who are kidney transplant recipients, the exposure to even a

minimal amount of leukocyte antigens that remain in the packed red blood cell bag, even with filtering and preparation, can evoke a sensitization that can compromise access to kidney transplantation. So there are good reasons to avoid kidney transplantation. That's the fundamental reason to correct anemia.

Now, patients who are anemic can also experience symptoms of anemia—particularly a lack of stamina andverve. Difficulty exerting oneself. And for people who are otherwise relatively well and active in the stages of CKD with anemia—stages G3B and G4, G5, even for the patients who are not on dialysis—those patients often will experience improved levels of energy and stamina if their anemia is corrected.

To get to the first part of the question, why are ESAs considered for use after other means of correction of anemia? It's simply due to the fact that there are risks associated with the provision of ESAs. Over time, we've learned they are principally thromboembolic complications, an increased risk of deep venous thrombosis, and pulmonary embolism. There was an increased risk of stroke in the TREAT trial, which was a trial of moderate to advanced CKD in patients with diabetes. And in observational data, there have been some confirmed findings of increased risk of VTE, or venous thromboembolic disease, as well as stroke. So if we can correct anemia with the provision of oral or intravenous iron and do that safely, then we can avoid things like vitamin B12 deficiency or folate deficiency, which could also be causes of anemia. We should address those issues head-on before we introduce any therapy that carries some cardiovascular risk.

I should just point out, just because things have changed in the ecosystem of CKD management, we see many more patients now receiving the sodium glucose cotransporter-2, or SGLT-2 inhibitors, aiming to attenuate progression of chronic kidney disease and also prevent or treat treatments of heart failure. And the SGLT-2 inhibitors also have an anemia-correcting effect.

Dr. Colbert:
Now, in terms of ESA hypo-responsiveness, the guidelines state that a trial of HIF-PHIs may be considered after discussing the potential risks and benefits with patients if there's a desire to avoid transfusion or to improve symptoms. With that being said, what should we take into consideration when determining if a switch to a HIF-PHI is necessary?

Dr. Chertow:
Some patients respond better to one class of drugs, or even sometimes to one drug within a class. So if our objective is to abrogate the need for transfusion, and in the setting of symptomatic anemia, to correct some of the symptoms being experienced by the patients, we should use one class or another, and if the patient isn't responding to the patient's or our desire, we could certainly give the other class of drugs a try.

So hypo-responsiveness is hard to define, but generally, if a course of treatment has not resulted in a meaningful increase in the hemoglobin concentration to the range at which we're aiming—and that in CKD is generally above 9 gram per deciliter and somewhere between 9 and 11 or 9 and 12—I think it's reasonable to try the other class with the caveat that every region has different indications for different drugs.

Dr. Colbert:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. Glenn Chertow about the KDIGO guideline recommendations for treating anemia in chronic kidney disease, or CKD.

So let's focus solely on HIF-PHIs now, Dr. Chertow. The guidelines state that it's important to monitor a patient's hemoglobin levels for two to four weeks after initiation or dose changes, and subsequently, every four weeks. In your experience, how has careful monitoring of hemoglobin levels impacted outcomes for patients?

Dr. Chertow:
Well, we have some data from clinical trials that frequent monitoring of the HIF-PHI drugs can help to maintain hemoglobin concentrations within the desired ranges. In clinical trials comparing the use of vadadustat to darbepoetin, we found that there were fewer hemoglobin excursions and fewer dose requirements when hemoglobins were frequently monitored using vadadustat relative to darbepoetin.

But whether using HIF-PHIs or ESAs, it's prudent for us to monitor people on a relatively frequent basis to ensure that we're achieving the goals of our therapy, which is raising the hemoglobin to the point where the patient is unlikely to require transfusion, or where the symptoms are relieved, and certainly to avoid abrupt increases in the hemoglobin concentration.

Dr. Colbert:
And according to the guidelines, if a patient does experience adverse effects like cardiovascular or thromboembolic events, vascular access thrombosis, or newly diagnosed cancer, we should suspend HIF-PHI treatment. So, after suspension, how can we best support

patients through these adverse events?

Dr. Chertow:
So, because both HIF-PHIs and ESAs are growth factors, I think we all have some reservations about the use of these agents in patients with an active malignancy. When we consider vascular access thrombosis, I think we need to balance the risks of nontreatment of anemia with the likelihood that a vascular access thrombosis is attributable to a drug, be it a HIF-PHI or an ESA, because vascular access thrombosis events are so frequent.

So, for instance, if you've had a patient who's had a perfectly functional fistula with excellent blood flows for years with not a hint of problems, and then that patient suddenly has a vascular access thrombosis coming out of nowhere, that kind of patient would evoke a different reaction in my mind to someone who, for instance, has had an arterial venous graft and has had multiple vascular access thromboses and stenoses procedures for venoplasty over the course of the last year. It might be difficult to attribute the event to the drug. So, as in all instances, we really need to balance the risks and benefits of all treatments for anemia and engage the patient, the nursing staff, and any other physicians who are caring for our patients, including cardiologists or dietologists or internists, as we make these challenging decisions, because we are caring for a complicated, chronically ill population where adverse events are not infrequent.

Dr. Colbert:
Well, we're nearing the end of our program, Dr. Chertow, so I'd like to take a moment to reflect on these guidelines. Do you have any insights you'd like to share on what these updates mean for the management of CKD in anemia in clinical practice?

Dr. Chertow:
I think it shows us that as we advance as a field, we have sometimes more difficult decisions to make. But ultimately, when we have more choices, and the patients have more choices, we can afford patients opportunities for benefiting from treatments that they might not have had earlier. So you used the example of hypo-responsiveness, of a less-than-desired response to one class of drugs. If we have two classes of drugs, then patients have more options. Or if a patient lives far away from an infusion center and is needle-phobic and doesn't want to inject their own injectable ESA, if there's an option for that patient to take an oral drug that can help correct anemia, that provides more choices for patients.

Dr. Colbert:
With those final thoughts in mind, I want to thank my guest, Dr. Glenn Chertow, for joining me to explore the latest guideline recommendations for managing anemia in chronic kidney disease patients. Dr. Chertow, it was great having you on the program.

Dr. Chertow:
I appreciate being here. Thank you. It's a pleasure to talk with you.

Announcer:
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