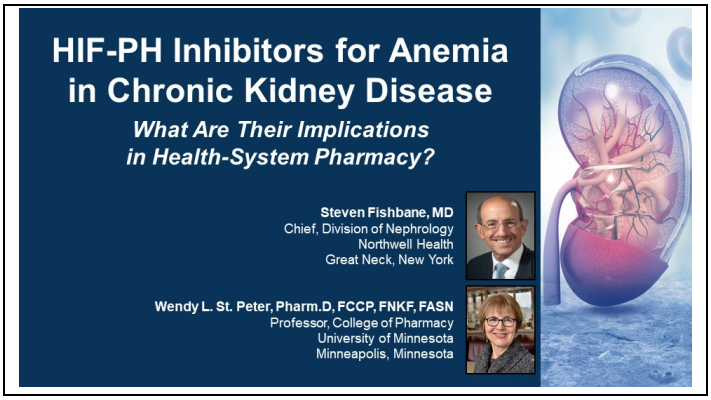
Slide 1

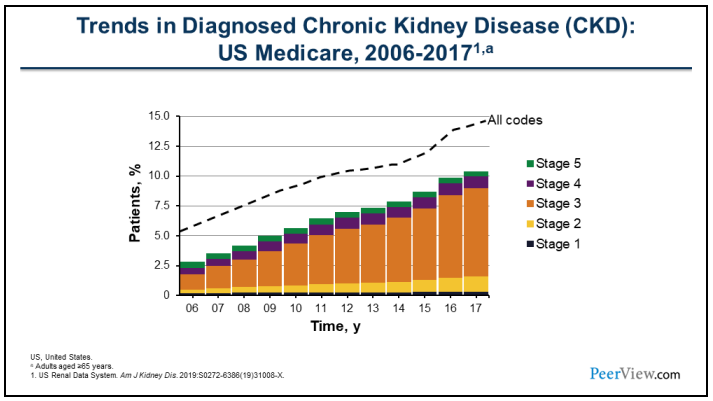


Dr. Fishbane: Welcome to "HIF-PH Inhibitors for Anemia in Chronic Kidney Disease: What Are Their Implications for Health-System Pharmacy?" I am Steven Fishbane, Chief of Nephrology at Northwell Health in New York, and very pleased to be joined by my co-moderator, Wendy L. St. Peter, PharmD. And the two of us will be taking you through today's presentation.

Welcome and Introduction

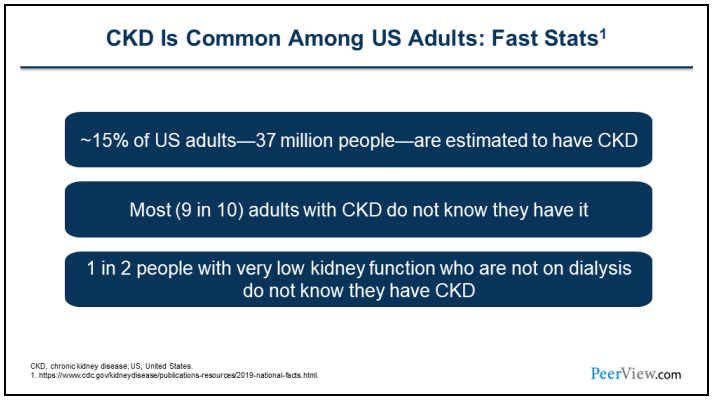
Steven Fishbane, MD

Slide 2



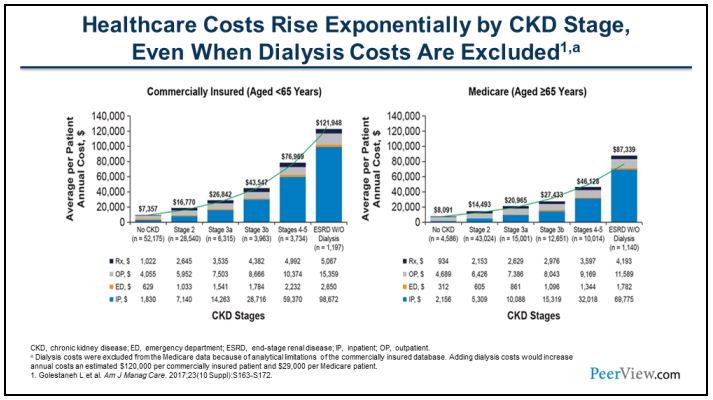
Dr. Fishbane: It's great to be with you today to speak about this subject. I'd like to start by reminding you about chronic kidney disease (CKD) in the United States. As you look on Slide 2, from the left to the right you will see that from 2006 to 2017, the amount of CKD has increased substantially over the course of that time. In addition, the percentage of patients with different stages of CKD has increased, with the majority of patients having stage 3 CKD by 2017.

Slide 3



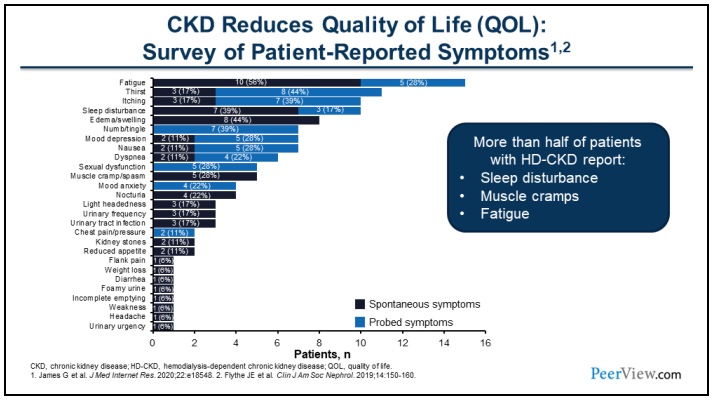
CKD is common among adults in the United States, affecting an estimated 15% of the US adult population, or 37 million people. Most patients with CKD don't even know that they have it, which is important, and one in two people with very low kidney function who are not on dialysis don't know that they have CKD, even at that advanced stage of the disease.

Slide 4



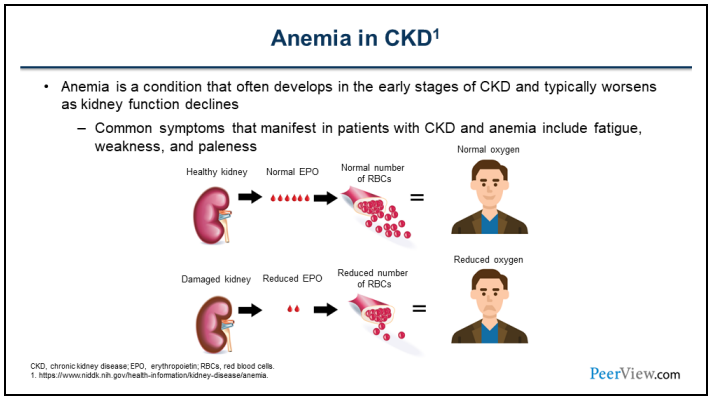
The healthcare costs rise exponentially, and this goes hand in hand with the CKD stage. On the left-hand side of Slide 4, you see patients with commercial insurance. On the right-hand side, you see patients with Medicare. For both though, it's very clear that as you go from no CKD on the left to stages 2, 3, 4, and 5, and right up to dialysis, the annual cost of care goes up and does so dramatically for both the commercially insured and Medicare populations.

Slide 5



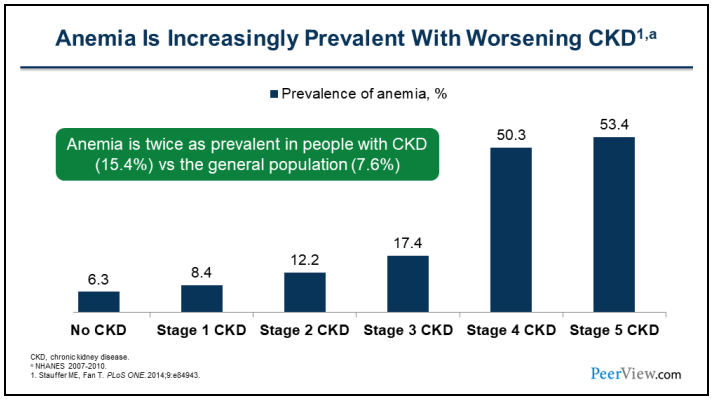
CKD affects the kidneys, and as it does so, it affects a patient's quality of life in a number of different ways. Slide 5 shows a number of different symptoms that are particularly affected. I'm not going to go through all of these symptoms, but I really would like you to take a note particularly at the top of the list: fatigue, thirst, itching, and sleep disturbances. These are such critical components of just who we are as human beings, and you can see how CKD affects these important facets. More than half of people on dialysis report sleep disturbances, muscle cramps, and fatigue.

Slide 6



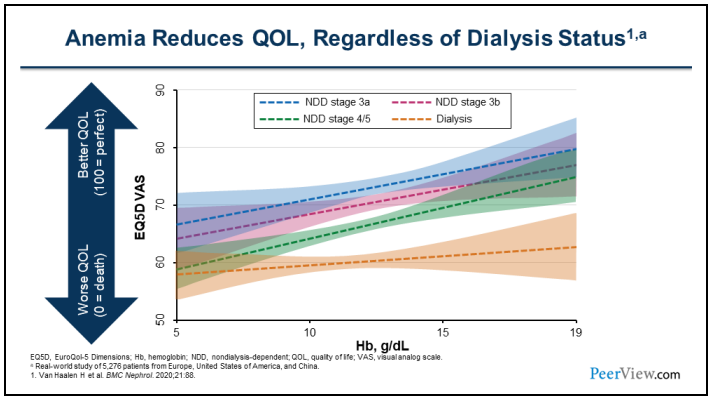
Now, although anemia in CKD can develop relatively early, it tends to develop later in the course of disease. The common symptoms that manifest in patients with CKD and anemia are the ones that you would expect to find upon physical exam: fatigue, weakness, and paleness. But it's a healthy kidney that produced normal erythropoietin and normal red blood cells, so patients have a normal amount of oxygen delivery to the organs and tissues of the body. At the bottom of Slide 6, you'll note that with damaged kidneys and reduced erythropoietin, anemia develops. That reduction in oxygen availability has such an important effect in terms of well-being, and the symptoms are so intuitive that patients feel fatigued and have shortness of breath.

Slide 7



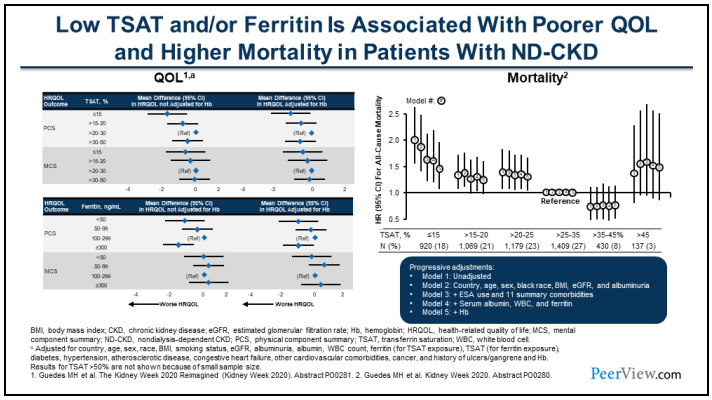
Anemia is increasingly prevalent, so that as we go from no CKD to stages 1 through 3, and then stages 4 and 5, you see a dramatic inflection, so half of patients at that point in stage 4 develop CKD-associated anemia. Additionally, anemia is twice as prevalent in people with CKD than it is in the general population, affecting 15% of patients with CKD.

Slide 8



Now, anemia has a further profound effect on quality of life. We've already seen how quality of life is affected by CKD, but in Slide 8, we can see how anemia in CKD reduces quality of life, regardless of dialysis status. On the x axis, at the bottom, we go from a hemoglobin level of 5 to 10 to 15 g/dL—you're looking at a visual analog scale for quality of life. You can see that, from right to left, quality of life clearly diminishes in relationship to lower hemoglobin levels.

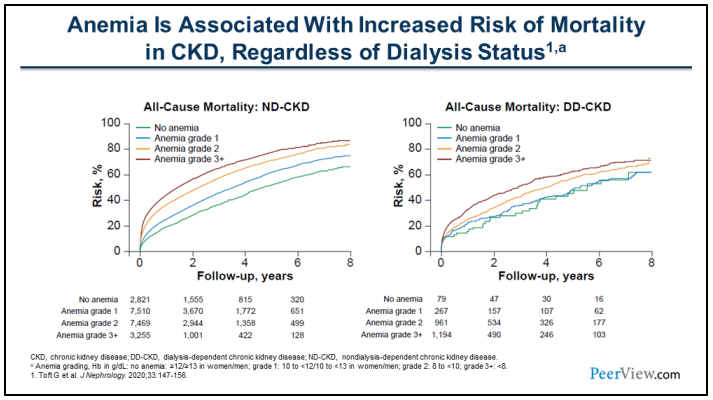
Slide 9



BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HRQOL, health-related quality of life; MCS, mental component summary; ND-CKD, nondialysis-dependent CKD; PCS, physical component summary; TSAT, transferrin saturation; WBC, white blood cell.
[a] Adjusted for country, age, sex, race, BMI, smoking status, eGFR, albuminuria, albumin, WBC count, ferritin (for TSAT exposure), TSAT (for ferritin exposure), diabetes, hypertension, atherosclerotic disease, congestive heart failure, other cardiovascular comorbidities, cancer, and history of ulcers/gangrene and Hb.
Results for TSAT >50% are not shown because of small sample size.
1. Guedes MH et al. The Kidney Week 2020 Reimagined (Kidney Week 2020). Abstract PO0281. 2. Guedes MH et al. Kidney Week 2020. Abstract PO0280.

Iron is an important part of this. Iron, of course as part of hemoglobin, is a critical aspect of the ability of red blood cells to carry oxygen. So we're not surprised when there's a low transferrin saturation (TSAT), carriage of iron in the circulation, low ferritin, or storage of iron in the body that this is associated with poorer quality of life. Iron is also associated with higher mortality in patients with nondialysis CKD (ND-CKD). In fact, if you look at the right-hand figure in Slide 9, you'll see that as you get to lower TSAT concentrations, there is an increase in the risk for all-cause mortality, and it's a large increase. It almost doubles by the time you get to a TSAT of less than 15%.

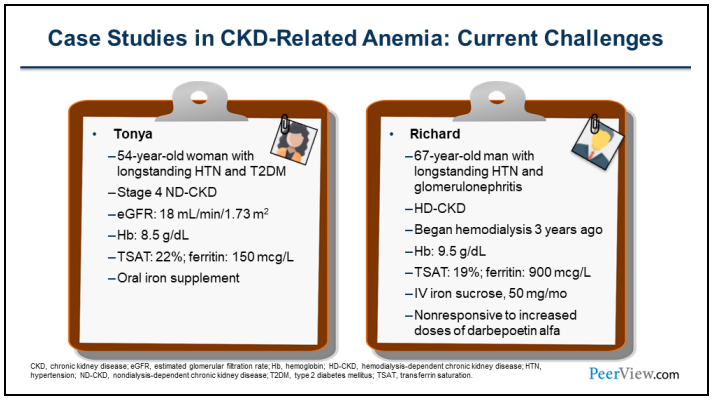
Slide 10



CKD, chronic kidney disease; DD-CKD, dialysis-dependent chronic kidney disease; ND-CKD, nondialysis-dependent chronic kidney disease.
[a] Anemia grading, Hb in g/dL: no anemia: ≥12/≥13 in women/men; grade 1: 10 to <12/10 to <13 in women/men; grade 2: 8 to <10; grade 3+: <8.
1. Tofi G et al. *J Nephrology*. 2020;33:147-156.

Anemia is associated with an increased risk of mortality in CKD, again, regardless of dialysis. So the figure on the left-hand side of Slide 10 shows patients with ND-CKD. The figure on the right-hand side shows patients with dialysis-dependent CKD (DD-CKD). Look at how similar these figures are. If you look from left to right, from 0 to 8 years, and at the relationship to the degree of anemia that's present, you will see that the green line is no anemia, and that anemia progressively worsens from the blue line to the reddish-brown line. You see that as time passes, anemia has a really important association with the increase in mortality risk in both ND-CKD patients and DD-CKD patients.

Slide 11



Let's look at a couple of cases, which is always the best way to illustrate some of the concerns. The first patient is Tonya. She is a 54-year-old woman with longstanding hypertension and type 2 diabetes mellitus (T2DM). She has stage 4 ND-CKD. Her estimated glomerular filtration rate is 18 mL/min/1.73 m^2. She's quite anemic; her hemoglobin is 8.5 g/dL, and that's going to be the important issue that we're going to have to try to help her with. But her iron parameters aren't dramatically reduced. Her TSAT is 22%. Her serum ferritin is 150 mcg/L, and she's currently receiving an oral iron supplement. So we're going to want to think as we progress through the conversation here in terms of how we're going to be able to help her with this significant anemia that she has.

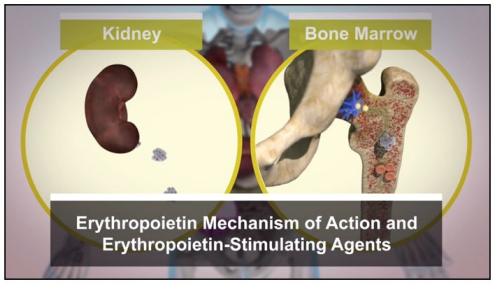
Now, Richard is a 67-year-old man with longstanding hypertension and glomerulonephritis. He's on hemodialysis, which he started 3 years ago. His hemoglobin is 9.5 g/dL, so it's slightly less than where we would like it to be. The iron parameters are interesting, so TSAT, or circulating iron, is 19%, and that would usually indicate to me that somebody is iron-deficient, whereas ferritin, which is storage iron—and these two should usually go together, but in patients on hemodialysis, they're often far, far apart, and here is exactly that situation. His TSAT is relatively low at 19%, and his serum ferritin is high at 900 mcg/L. So storage iron is elevated, circulating iron low. That's often a marker for hyporesponsiveness, and the patient is getting iron to try to deal with the issue. So intravenous iron sucrose at 50 mg/month.

But the patient has been nonresponsive to increased doses of darbepoetin alfa. The clinicians are trying to get that hemoglobin level up there, but despite increasing the doses of darbepoetin alfa, they are struggling to get the hemoglobin to 10 g/dL. So we're going to need to think about some of the interesting characteristics regarding Richard and his anemia. So those are two interesting patients. We will speak more about them. Now, it is my pleasure to hand it over to my co-moderator, Wendy St. Peter. Wendy?

Epidemiological and Pathological Factors Contributing to the Diagnosis and Management of CKD-Associated Anemia

Wendy L. St. Peter, Pharm.D, FCCP, FNKF, FASN

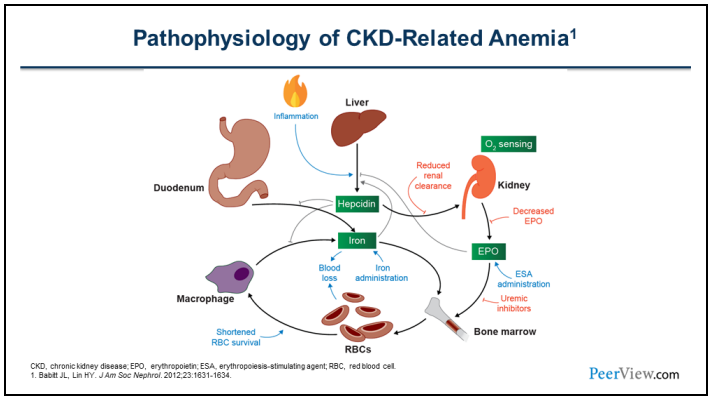
Slide 1



Dr. St. Peter: Thank you, Dr. Fishbane. In this section, I'm going to be talking about some of the epidemiological and pathological factors that contribute to the diagnosis and management of CKD-associated anemia. To start out with, you're going to see a little video clip of erythropoietin mechanism of action and erythropoietin-stimulating agents (ESAs).

Narrator: Erythropoietin (EPO) signals proerythrocytes to become erythrocytes. As kidney disease progresses, EPO production becomes insufficient to maintain normal numbers of erythrocytes. In the early stages of kidney disease, iron deficiency may restrict erythropoiesis, causing anemia. The administration of ESAs increases EPO levels in most patients, but using these agents to raise hemoglobin to normal levels may also increase cardiovascular risks.

Slide 2

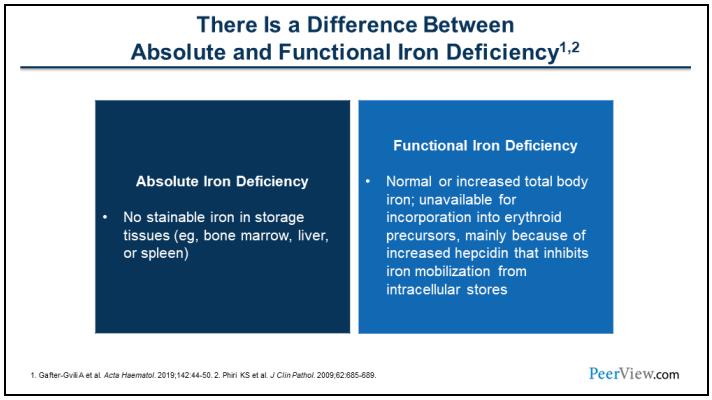


Dr. St. Peter: After watching that video clip, I think you understand that when we began this whole era of anemia and treatment of anemia and kidney disease, we recognized the fact that as kidney disease progressed, less EPO was produced, which produced less erythropoiesis, and thus anemia developed. We also recognized that these patients developed iron deficiency—basically, there's a need for iron to be incorporated to make normal red blood cells.

The last patient who Dr. Fishbane introduced showed that despite the treatment with an ESA and supplemental iron, lots of times we were still running into issues with low iron saturation levels, yet higher ferritin levels. So we discovered, over time, a hormone called *hepcidin*. Hepcidin helps regulate iron homeostasis and also erythropoiesis. But hepcidin is a bit of a bad actor in patients with CKD in that it is eliminated through the kidneys, so levels increase in patients with CKD.

Inflammation also induces hepcidin production, and that's a problem, particularly in our patients with comorbid conditions, sometimes with underlying kidney disease—that is an inflammatory type of kidney disease. We have patients on dialysis, and also, these patients are oftentimes infected, which causes an inflammatory state that raises the level of hepcidin. Well, what does hepcidin do? It puts the brakes on absorption of iron through the duodenum, and it puts the brakes on iron transport from the reticuloendothelial system—those are our storage iron, or ferritin supplies—and thus iron transport is reduced and patients don't get enough iron where they need it, in order to make red blood cells.

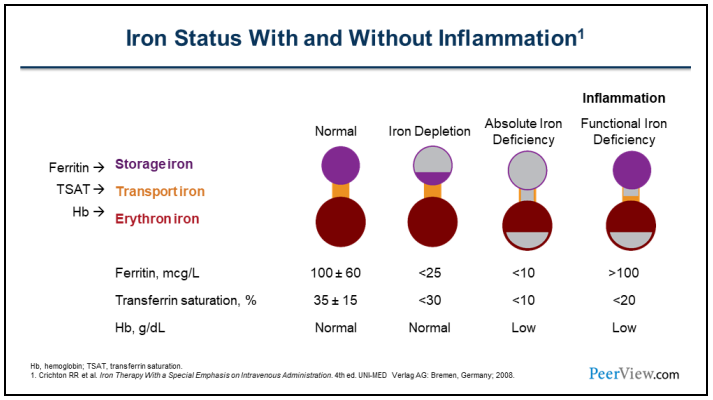
Slide 3



So we have two distinct types of iron deficiency that can occur in CKD. First is absolute iron deficiency, and that's where there's a reduction or actually no stainable iron in our storage issues. That's our reticuloendothelial system in bone marrow, liver, or spleen, so that can occur with iron deficiency. If there is a lot of erythropoiesis stimulated with ESAs, without giving adequate iron, we can see absolute iron deficiency.

What is more common in our patients is a functional iron deficiency. That is we have normal or increased total body iron. As Dr. Fishbane indicated in our last patient, a ferritin of 900 mcg/L is quite large. But the storage iron is unavailable for incorporation into new red blood cells, mainly because of these increased hepcidin levels that inhibit iron mobilization from those intracellular stores.

Slide 4

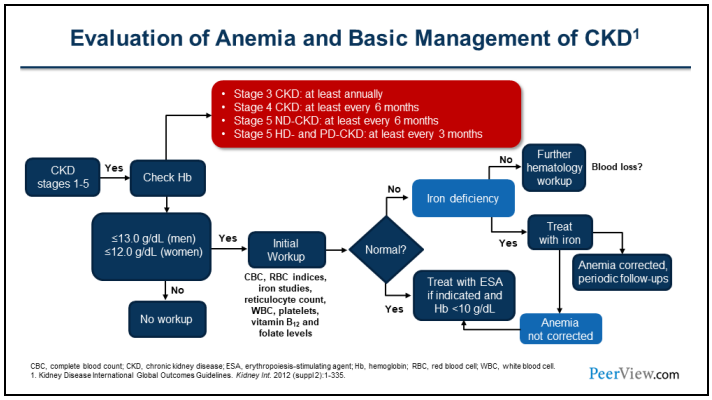


Slide 4 incorporates some of the laboratory values we've been talking about, so I just wanted to note on the left, storage iron, we represent it basically by our laboratory ferritin. Transport iron, which we evaluate a marker called TSAT that is the serum iron divided by the total iron binding capacity, which is mainly transferrin. And then our erythron iron, represented as hemoglobin.

You can see in the normal state where we have patients with normal iron levels and normal erythropoiesis. You see the ferritin levels may be up around 100 mcg/L. TSAT is normal, about 30%, and hemoglobin is normal. In patients who have iron depletion, which we see with ESAs, you see iron depletion, so the ferritin or storage iron is less. TSAT is also less. But there's still adequate circulating iron and transport iron that can go to the bone marrow for erythropoiesis, so you see a normal hemoglobin level.

In absolute iron deficiency, where there are no stainable iron supplies in the bone marrow or other parts of the reticuloendothelial system, you see a low serum ferritin, a low transport or TSAT and low hemoglobin. And then again, what's a particular problem in our patients, the functional iron deficiency, you see that they have adequate iron stores. You see the ferritin stores are filled up, yet you're seeing a low transport iron, so there's not enough iron being transported on the transferrin to where it needs to go to make red blood cells. So in this situation, you see a higher-than-normal ferritin, a TSAT that's below normal, and a low hemoglobin level.

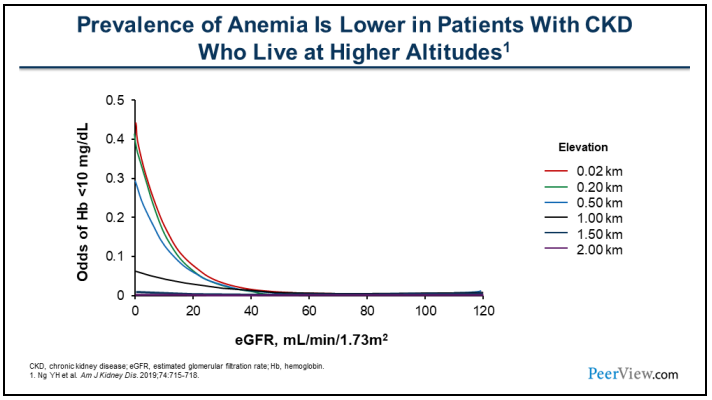
Slide 5



As pharmacists, you really need to think about evaluating anemia, because as Dr. Fishbane just noted, anemia is a common disorder and can lead to a reduced quality of life in affected patients, so knowing a little bit about the evaluation and basic management is very important. These guidelines come from the Kidney Disease International Global Outcome Guidelines, and these were last published in 2012. You can see at the very top, in the red box, that the rate of us measuring hemoglobin is dependent on the patient's stage of CKD. So as CKD progresses, we increase our frequency of monitoring. We check the hemoglobin, and if it's less than 13 g/dL for men or less than 12 g/dL for women, then we perform a workup for anemia. So what does that entail?

Get a CBC, red blood cell indices such as mean corpuscular volume, mean corpuscular hemoglobin, and red blood cell distribution width. If you see indications that there might be a macrocytic anemia present—that's a high-RDW or a high mean crepuscular volume—you will get vitamin B_{12} and folate levels. If all those levels are normal, and the patient has anemia and also CKD, then we make an assumption that it's an EPO deficiency. As you can see in the right-hand side of Slide 5, we treat with an ESA, and then if there's iron deficiency involved, we do further workup, checking to see if the patient is bleeding. We may now do a Hemoccult evaluation to see if they have GI bleeding and then treat with iron. Normally, you want to, of course, correct iron deficiency first before you treat with an ESA. So these are our normal pathways that we used for many years to treat patients with CKD.

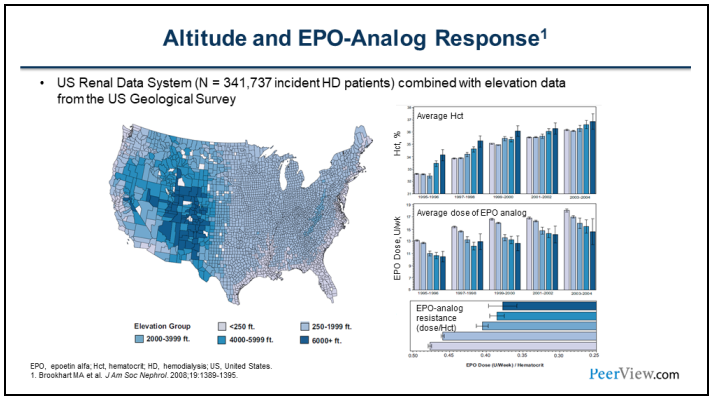
Slide 6



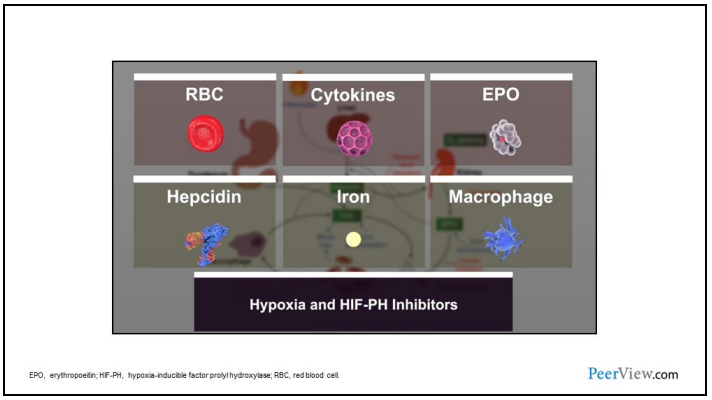
Now I wanted to evaluate and show you some really interesting data on what shows us that we have something else going on in this whole arena of anemia about which we need to think. This information comes from patients with CKD who were evaluated during kidney screening programs for CKD. Let me orient you to Slide 6: On the x-axis, you have estimated glomerular filtration rate, so from 0 to 120 mL/min/1.73 m^2, which is normal. The y-axis shows the odds of developing a hemoglobin level of less than 10 g/dL, or the odds of developing anemia.

You can see the different color curves; the red curve is an elevation of 0.02 km. It's sea level, essentially. So I'm going to ask you to look at that red line. You can see that that goes all the way up to the top. I'm also going to ask you to look at the very lowest line, the purple line at 2 km, which represents a city like Denver, or the Mile High City. You can see that patients with CKD who live in lower altitudes—basically at sea level—have much higher odds of having anemia than those patients who live at a higher elevation. Why is that?

Slide 7



Slide 8



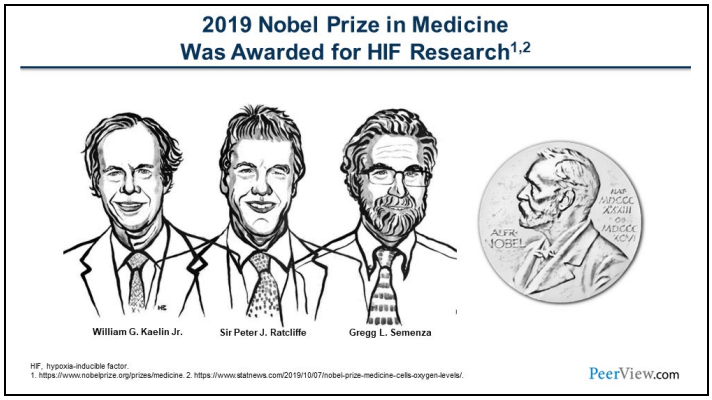
I want to show you another interesting study. This was done by Dr. Brookhart and colleagues using United States Renal Data Systems data and also along with data from the US Geological Survey. They looked at over 300,000 new patients with hemodialysis. You can see, let's look at the map on the left. The dark blue regions are areas of the Rocky Mountains, so you can see, going from New Mexico all the way up to Montana, those are the areas of highest elevation in the United States. And then you have the lighter gray areas, which show lower elevations.

If you look on the graphs on the right side on Slide 7, I just want you to look at the very last set of bars in each box. The first and top box is hematocrit. You can see that in the blue regions—the Rocky Mountain regions, where they're at high elevations—the patients experience relative hypoxia, in that their hematocrit is much higher than patients who are living at sea level. Also, when you look at the erythropoietin dose, you can see that the exact opposite is true. So the patients who are at sea level need the highest EPO doses, whereas those who live at the highest elevations, like in Denver, need the lowest ESA doses. So why is that?

Well, there has been a lot of research in this area, and this next 3D animation shows you a little bit about the mechanisms that can explain what I just showed you in the last couple of slides. So it's going to be talking about hypoxia and hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors.

Narrator: When hypoxia is detected, HIFs are activated, iron absorption and EPO production increase, indirectly suppressing hepcidin, increasing erythrocyte maturation, and redistributing iron stores. HIF-PH inhibitors prevent the degradation of HIFs, increasing EPO production, but not to supraphysiological levels, as the direct administration of ESAs can do.

Slide 9

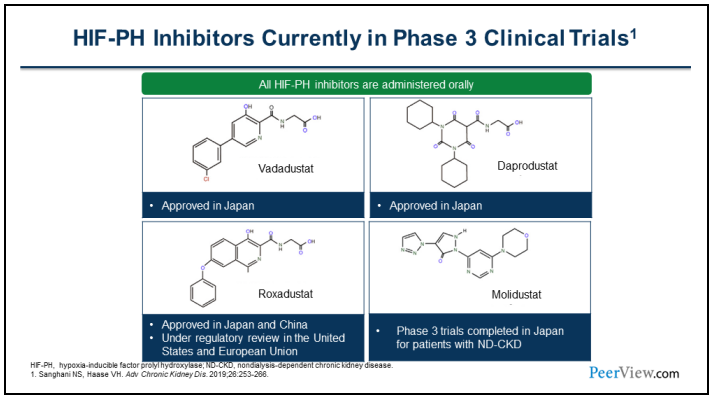


Dr. St. Peter: The research in the HIF area has been so revolutionary that three scientists—Dr. William Kaelin, Sir Peter J. Ratcliffe, and Dr. Gregg L. Semenza—received the 2019 Nobel Prize in medicine for their research focusing on cellular responses to hypoxia. It is their groundbreaking research that really laid the pathway for our new HIF-PH inhibitors, and Dr. Steve Fishbane will be talking about those in more detail in the next section.

Clinical Implications of HIF-PH Inhibitors in the Management of Anemia Associated With CKD

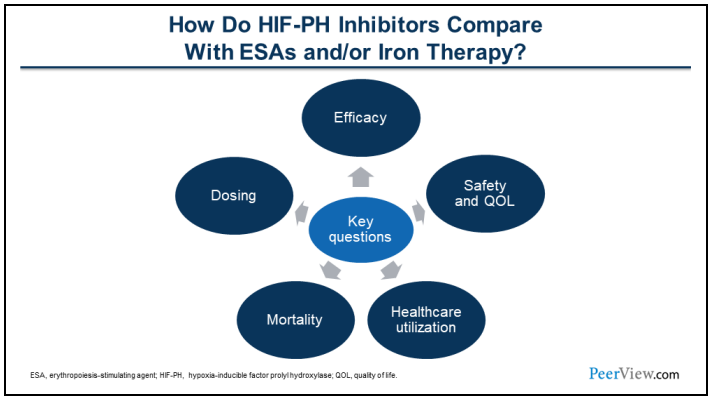
Steven Fishbane, MD

Slide 1



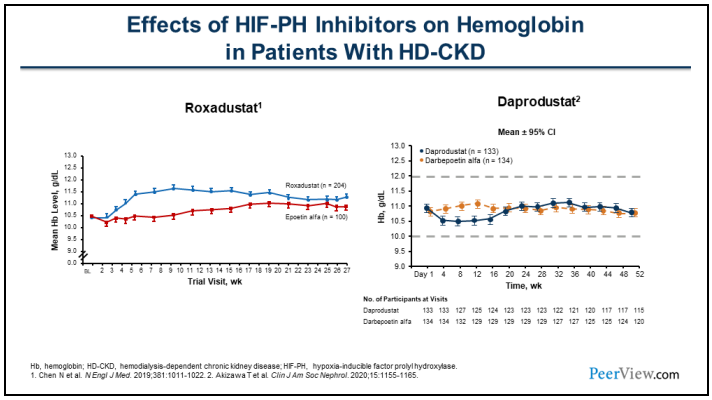
Dr. Fishbane: Great. Thank you, Dr. St. Peter. So now let's take what we've learned about the HIF system, the brilliant work of these individuals who won the Nobel Prize for their work, and think about where this has taken us therapeutically. I think it's just incredibly exciting that in a short period of time we have gone from learning about the basic biology to having four of these agents already in clinical testing. So these are the agents, are currently in phase 3 trials. Vadadustat, daprodustat, and roxadustat are already approved in Japan. Roxadustat is already approved in Japan and China. So, tremendous, tremendous progress.

Slide 2



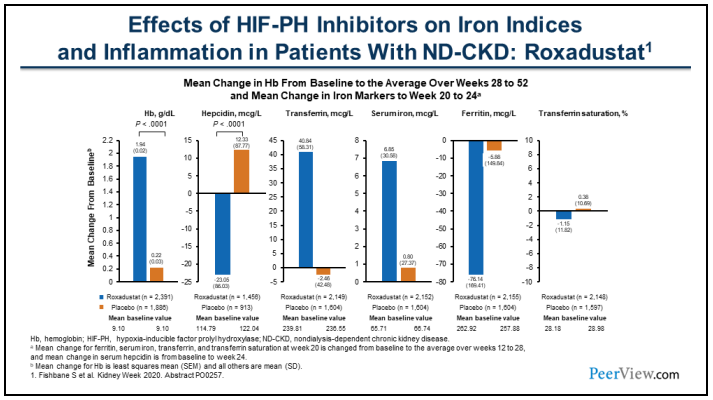
Now, how do these agents compare with the ESAs? How do they compare with iron therapy? This is all anemia treatment, and of course, to understand the overall utility, we need to understand dosing and efficacy, safety, issues related to high-level outcomes, cardiovascular mortality, and health care utilization. All of it is important.

Slide 3



First, let's just take a look at a couple of the agents and their effect on hemoglobin. So, can you use these orally administered treatments for anemia? And what kind of response do you get? On the left-hand side of Slide 3, you look at roxadustat. These were data from China published in *The New England Journal of Medicine* that showed that roxadustat in the blue curve compared with epoetin alfa in patients on dialysis with at least a similar—and in fact probably a superior—increase in terms of hemoglobin concentration. Another one of the HIF-PH drugs, daprodustat, is shown on the right. So you look at daprodustat here, and you see that compared with darbepoetin alfa, that's in the gold, and daprodustat is in the navy—you see similar effects in terms of the ability to maintain good, stable hemoglobin concentrations. Efficacy looks good.

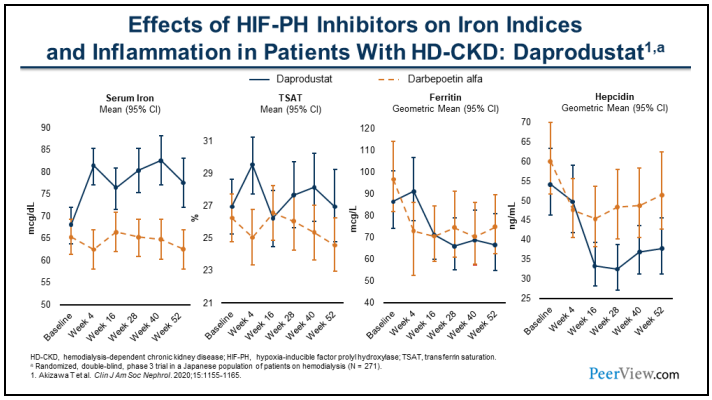
Slide 4



Slide 4 shows the effects of these drugs on a patient whose iron indices may not be normal or where inflammation may be an issue. As we go from left to right, we're looking at hemoglobin concentration first for roxadustat versus placebo in ND-CKD. You see a dramatically improved level of hemoglobin with roxadustat compared with placebo. We look next in the second figure at hepcidin levels. So Dr. St. Peter told us about hepcidin. Here, we see that for patients on placebo, in fact, there is not much of a change. Maybe there is a little bit of an increase in hepcidin concentration, but there is a dramatic decrease in hepcidin concentration in patients who were treated with roxadustat. And that could have really important effects in terms of the availability of iron in the body that could ultimately lead to less need for intravenous iron.

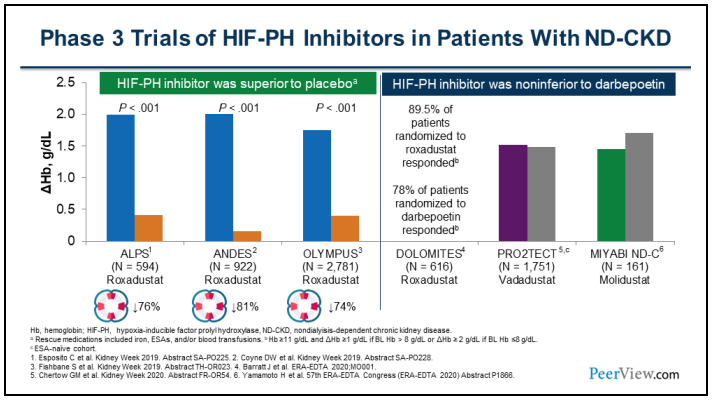
And just continuing along, transferrin, the carrier of iron, also improved with roxadustat. Serum iron, how much iron is available in the bloodstream, improved with roxadustat compared with placebo, and then storage iron, you see, actually decreases with roxadustat compared with placebo. And so where is that storage iron going? Well, the storage iron is going to make red blood cells. So essentially, the effect of using this agent and reducing hepcidin and freeing iron up from storage tissues is improving hemoglobin. It's giving you better iron availability and removing iron from storage tissues, so ferritin concentration decreases and TSAT, on the far right, remains stable.

Slide 5



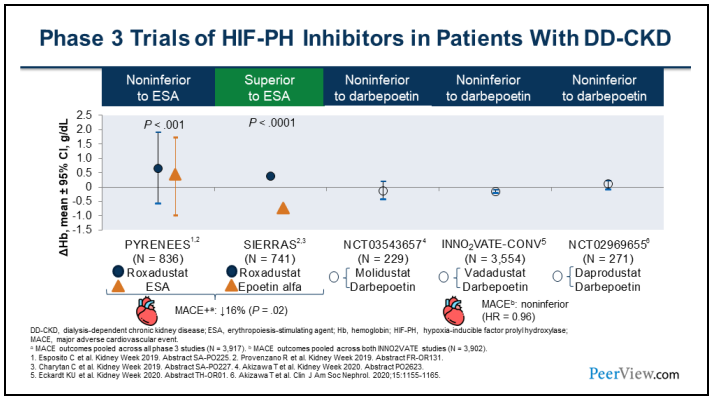
Now, when we look at the drugs, again, with respect to iron and inflammation, as seen in Slide 5 looking at daprodustat, we see the same thing, which is daprodustat compared with darbepoetin alfa increases serum iron and keeps TSAT stable. Here you see similar results in terms of serum ferritin and hepcidin, again, with daprodustat compared with darbepoetin alfa, you see that there is a nice decrease in the hepcidin concentration.

Slide 6



Slide 6 is shows phase 3 trials in patients with ND-CKD. So roxadustat, we're going to look on the left-hand side at three studies versus placebo. This is straightforward. In all three of these studies, the blue vertical bars show improved hemoglobin compared with placebo, efficacy clearly established. On the right-hand side, we're looking at one roxadustat study, one with vadadustat, and one with molidustat, which I have not yet mentioned. For all three, you see the same thing, that in comparison to active ESAs, you get essentially similar or noninferior effects. In the DOLOMITES study, 89% of patients randomized to roxadustat responded and 78% randomized to darbepoetin alfa responded.

Slide 7

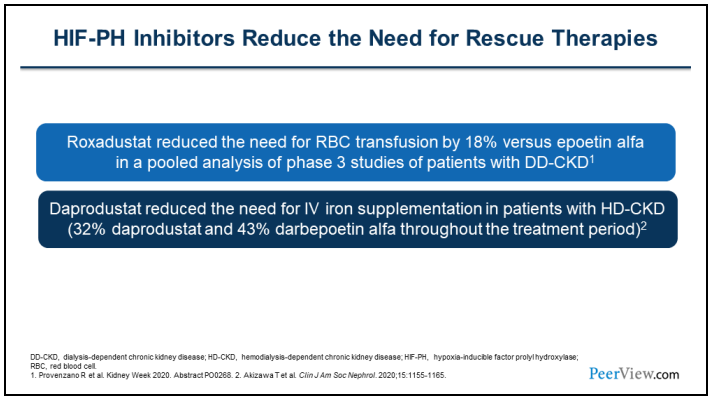


Now, looking at patients on dialysis, in terms of cardiovascular safety, so looking at MACE+ events, which are major cardiovascular outcomes, we see that in the PYRENEES study with roxadustat versus an ESA, there are similar hemoglobin concentrations, and yet we found that roxadustat was noninferior compared with ESAs. The SIERRAS, which I think was kind of exciting, was a large phase 3 study with 741 patients where the hemoglobin concentration was slightly different, but actually the oral drug roxadustat was superior compared with the ESA comparator in terms of MACE+ events.

With molidustat, in the third column, which was compared with darbepoetin alfa, you see results that are essentially noninferior, with hemoglobin results about the same.

The $INNO_2VATE$-CONV study that compared vadadustat with darbepoetin alfa also looked at cardiovascular events through MACE events. Hemoglobin was about the same, and there was a well-established safety profile with noninferiority for vadadustat compared with darbepoetin alfa. A study for which I can only give you the official name, you see the clinical trial number on the slide, compared daprodustat with darbepoetin alfa, and it showed noninferiority compared with darbepoetin alfa.

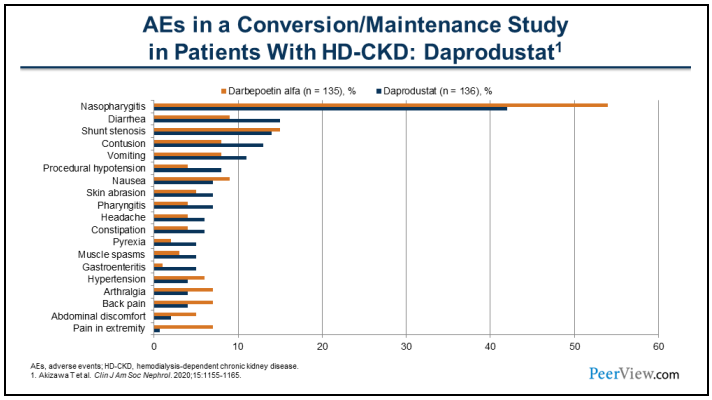
Slide 8



So HIF-PH inhibitors are interesting because of this really nice effect in terms of hemoglobin. But how does that affect the need for rescue treatment, like blood transfusion or intravenous iron or ESAs? With roxadustat, we've seen that even in patients on dialysis, there is a reduction in the need for blood transfusion by 18% compared with epoetin alfa. So blood transfusion is important not just for saving a very important resource, making life easier for the patient, but we're so concerned about allosensitization and the ability to transplant patients. So that's a really interesting finding.

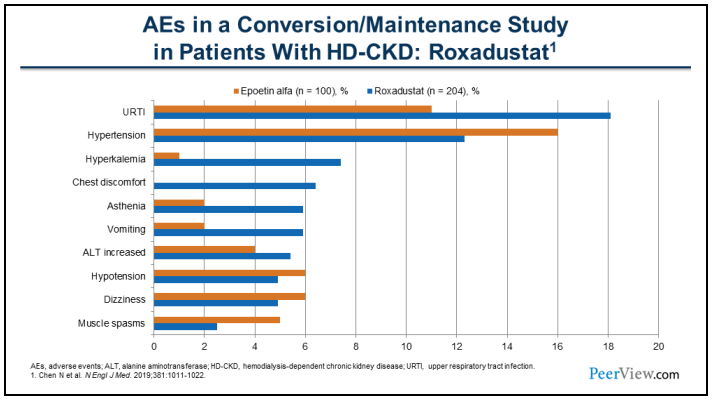
Daprodustat—a really interesting finding for that study—reduced the need for intravenous iron as a rescue therapy in patients on hemodialysis compared with darbepoetin alfa, only 32% of patients on daprodustat compared with 43% on darbepoetin alfa. So rescue therapy in terms of blood transfusion and intravenous iron for two of the HIF-PH inhibitors and the beneficial effects.

Slide 9



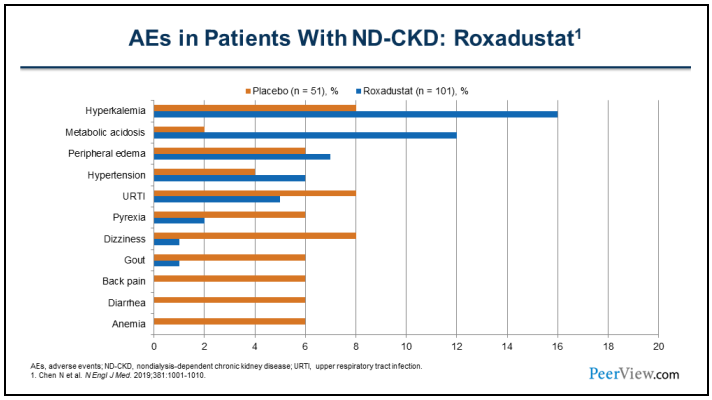
What about adverse events? Looking at daprodustat compared with darbepoetin alfa, I think it's fairly safe to say, without running all of these adverse events individually, that it's fairly similar to the profile that you see with darbepoetin alfa and so significant differences in one direction or the other, which is a reassuring finding.

Slide 10



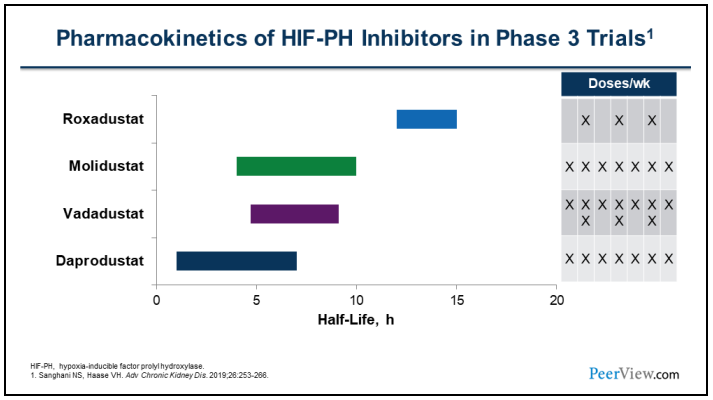
Slide 10 shows adverse events looking at roxadustat versus epoetin alfa, and again, fairly similar effects. This was from a study from China by Chen and colleagues, which published in the *The New England Journal of Medicine*. They found an increase in hyperkalemia, which was an interesting finding and one that wasn't seen in the phase 3 studies with roxadustat.

Slide 11



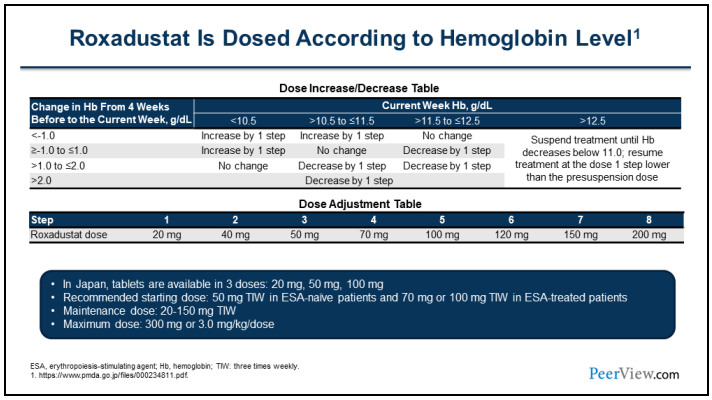
Looking further in patients with ND-CKD, again from the work of Chen and colleagues, similar between placebo and roxadustat, but again, in Slide 11, we see an increase in terms of hyperkalemia and metabolic acidosis, not seen in the larger US phase 3 program.

Slide 12



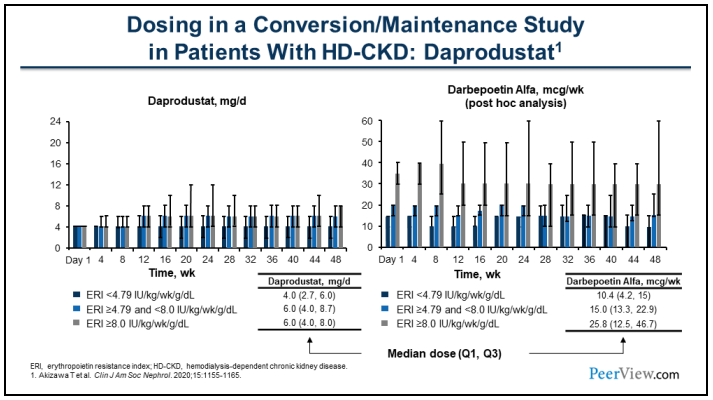
Regarding the pharmacokinetics of HIF-PH inhibitors: In this slide, we're looking at the half-life. How long are these agents in circulation? For roxadustat has the longest half-life, at about 13 hours, while molidustat, vadadustat, and daprodustat are a little bit shorter, about 5 hours. There may be an effect in terms of necessary dosing as well. Roxadustat currently is administered mostly orally, three times per week, which could fit with hemodialysis treatments. For the other agents, they're generally given as once daily, although there is research currently going on with vadadustat as three-times-weekly administration.

Slide 13



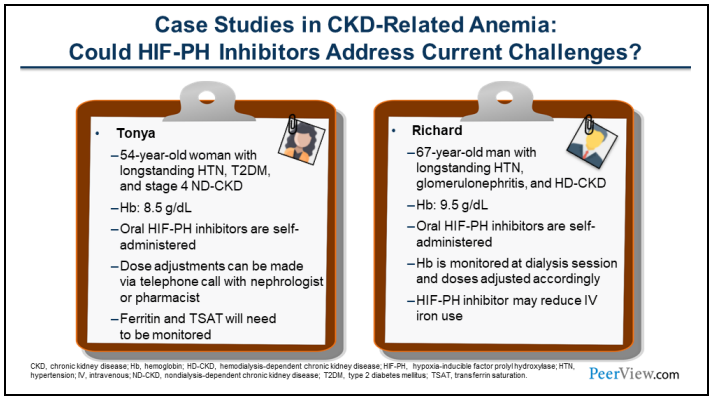
Now, roxadustat, of course, like any of these agents, is dosed according to hemoglobin levels, just like the ESAs that we use now. And I won't go through this in detail, but you see in a typical protocol that you're looking at things like, what is the hemoglobin concentration currently? What is the change in hemoglobin? And making adjustments in terms of dose, very simply orally, based on what the hemoglobin and the change is.

Slide 14



Slide 14 is looking at daprodustat dosing now, in a conversion maintenance study—so this is in patients on hemodialysis—and we're looking out with daprodustat from time 0 to week 48. And we're looking at EPO responsiveness. So you see the EPO response index with three different levels, and the number of milligrams of daprodustat that were required over the course of time is fairly similar. So for daprodustat, it looks to me like you don't necessarily need higher doses in patients who are EPO hyporesponsive. Compare that on the right with darbepoetin alfa. When you look at the dosing here, you see that over the course of time, the box on the bottom right shows that in patients with increasing EPO response indexes—so higher needs for EPO—the dose of darbepoetin alfa goes up substantially, so with a far greater need.

Slide 15



Now, let's come back to our patients. As we think about Tonya, remember that she is a 54-year-old woman. She's had hypertension and T2DM for a long time. She has stage 4 CKD, and we are worried about that hemoglobin of 8.5 g/dL. An oral HIF-PH inhibitor would be a thought in this patient, because it's self-administered. Dose adjustments can be made by telephone, because it's oral, rather than a patient coming in to the office on a regular basis. This could be done with a nephrologist or pharmacist, and it gives us a great opportunity to give the patient greater autonomy. Of course, iron status will need to be continually monitored for Tonya, as well as her ferritin and TSAT as we increase the hemoglobin. Remember, we're going to use a lot of iron to do that, and that could have effects in terms of iron stores.

Now, Richard had those interesting iron parameters. He was our patient with longstanding hypertension and glomerulonephritis. He was on dialysis, so this is a little bit different. His hemoglobin was 9.5 g/dL, which is a little bit lower than we wanted. And you remember the TSAT, circulating iron, was relatively low, while the storage iron, ferritin, was about 900 mcg/L, so quite high. These are very disparate findings. Again, there is the interesting question about the oral HIF-PH inhibitors. I'd argue this is a patient where there's been a lack of response to darbepoetin, and we've seen that these drugs seem to work well in these hyporesponsive patients, both from phase 2 and phase 3 data.

So it would be an interesting class of drugs to consider here, looking closely at the hemoglobin concentration. I'd love to see how the iron numbers would change if the patient were treated with one of these drugs. I think we're getting more and more evidence, as we're moving from phase 2 through phase 3 data, that the amount of intravenous iron required may be significantly less with the HIF-PHI inhibitors. So it would be interesting to know whether you could use the HIF-PH inhibitors with these two types of clinical challenges. Wendy, Dr. St. Peter, I'd like to see what your thoughts might be about these two.

Dr. St. Peter: I agree with all your thoughts, Dr. Fishbane. Basically, when I think back at the difference between Tonya and Richard, Richard has these really high ferritin concentrations, low TSATs, and low hemoglobin. Tonya has low hemoglobin, but normal iron—transport iron, TSAT, as well as ferritin. The difference between these two is that with Richard, I would probably be more intent on starting him on a new HIF-PH inhibitor because of his relative resistance to darbepoetin.

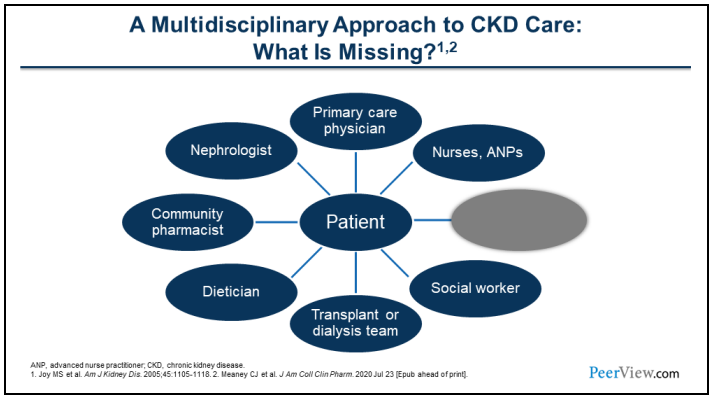
I think with Tonya, of course, you could use either an ESA or a HIF-PH inhibitor, but she is an ambulatory patient. She's working. It would make sense, perhaps, not to give an injectable. There are many patients who are resistant to injecting themselves, and if you have a busy life, you don't want to go into the doctor's office to have that injection given. So in both of these patients, certainly, a HIF-PH inhibitor could be considered.

Dr. Fishbane: Yeah, I think that's a really important point you make about patient autonomy. In the United States, ESAs are very often administered in doctors' offices, and patients already have so many doctor visits and other medical contacts. So if you can get away from that and have the patient take an oral agent, I think that would be really interesting, particularly with Tonya.

Clinical Implications of HIF-PH Inhibitors for Collaborative Care and the Evolving Role of Health-System Pharmacists

Wendy L. St. Peter, Pharm.D, FCCP, FNKF, FASN

Slide 1

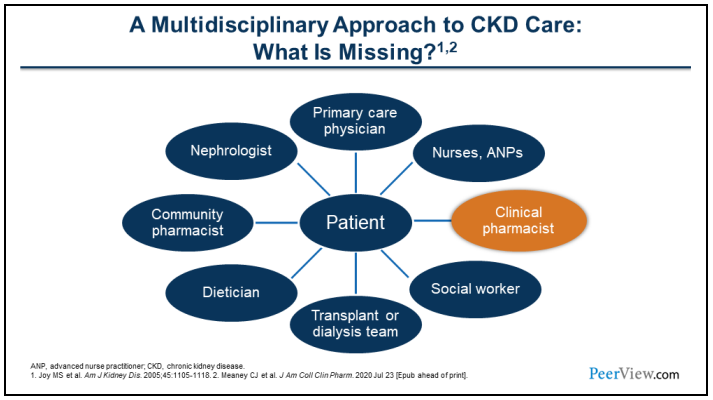


Dr. Fishbane: Now I would like to turn it back to Wendy, Dr. St. Peter, looking at the clinical implications for collaborative care and the evolving role of health-system pharmacists.

Dr. St. Peter: Thank you, Dr. Fishbane. Basically, I wanted to start by talking about the typical care team in patients with CKD and who is missing. Typically, with patients with CKD who are not on dialysis, they have a primary care physician and nurses who work with the primary care. They may be in stage 4 and 5 and have a nephrologist, but we've demonstrated that many of those patients, even in later stages of CKD, don't have one. But they'll be involved with a community pharmacist in terms of their medications.

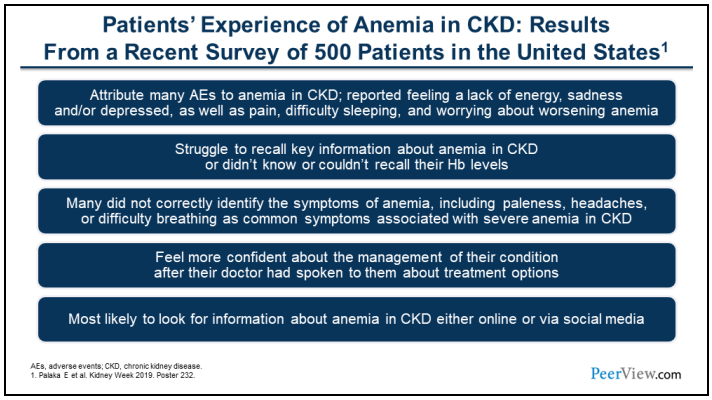
In patients who are on dialysis or have a transplant, they have other team members involved. With those on dialysis in particular, there's a very standard care team that includes a nephrologist, nurses, dialysis technicians, social workers, and dietitians. And of course, if the patient has a transplant, they'll have a transplant team. So they have a team, and it's actually outlined in policy at the level of Centers for Medicare and Medicaid Services (CMS).

Slide 2



But the one person who isn't officially part of the team is the clinical pharmacist. In this section, I want to advocate for the clinical pharmacist being important in the care, being a member of the care team for patients with CKD and, in this instance, anemia management.

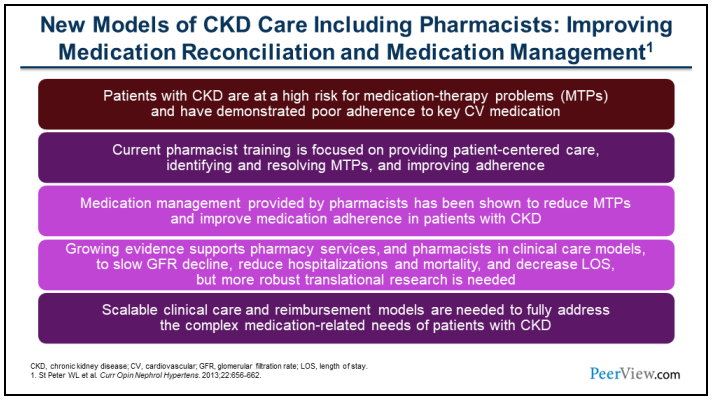
Slide 3



So, kind of segueing, again, into anemia, there was a recent survey of 500 patients with CKD in the United States that reported a lot of interesting factors. Basically, many of the patients attributed a lot of adverse effects to anemia. They reported feeling a lack of energy; a lot of patients understand that about anemia. They reported feelings of sadness and depression, as well as pain and difficulty sleeping. But they really struggled to recall key information about anemia and couldn't really recall their hemoglobin levels. And that's really unlike what we know now with lots of patients with hypertension and hyperlipidemia. They know their cholesterol levels. They know their blood pressure. But it's not very typical for patients with CKD to know their hemoglobin level, so it shows a lack of education in that area.

Many survey responders didn't correctly identify symptoms of anemia. They didn't realize what types of symptoms they should expect. We do know that the patients who got to talk to their doctor about their treatment options felt more confident about that, but the problem is a lot of patients weren't confident and didn't know that much about anemia. Of course, most of the patients, like a lot of our patients out there for a lot of their health conditions are likely to look for information about anemia and CKD either online or via social media. So there's a big role for healthcare providers—that includes pharmacists, physicians, and nurses—to get more involved with patients with anemia.

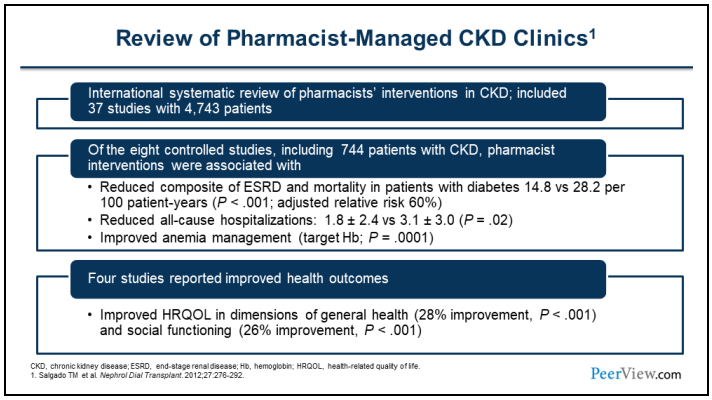
Slide 4



There is a lot that we know in terms of medication therapy problems. Anemia is only one of them. But patients with CKD have a high risk for medication-therapy problems, and that is because on average, when they get to severe anemia—so stage 5 and eventually needing dialysis or a transplant—they're on an average of 10 to 12 medications apiece, so lots of medication-related issues.

Currently, our pharmacy workforce is trained on providing that patient-centered care to identify and resolve those medication-therapy problems, including anemia. We know that medication management provided by pharmacists haves been shown to reduce medication-therapy problems, and there's growing evidence that supports pharmacy services and pharmacists in clinical care models. I'm going to be talking more specifically about CKD in a moment. But what we need, of course, are scalable clinical care and reimbursement models to fully address this issue, and I'm going to talk about that more near the end of the presentation.

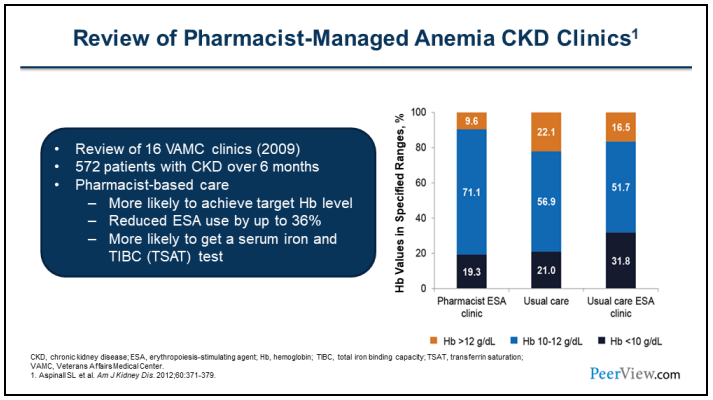
Slide 5



Dr. Selgado and her colleagues did a really nice systematic review of pharmacist-managed CKD clinics. But I think what was really kind of sad is that out of 37 studies, only eight were controlled. So it just shows you that we need to do a better job in the kidney disease space in doing nice and really well-designed studies. But what they did find out of those eight controlled studies is that one study showed that there was a reduced composite of end-stage renal disease and reduced mortality in patients with diabetes who were exposed to a pharmacist within the interdisciplinary care team.

We have one study that was reported within the systematic review, but another study that was published this year that was in patients on dialysis and showed that either comprehensive medication management or medication-therapy management reduced all-cause hospitalizations in patients on dialysis. Also, in terms of the anemia management issue, they showed improved anemia management in patients who had a pharmacist on the team, and four studies showed improved health-related quality of life.

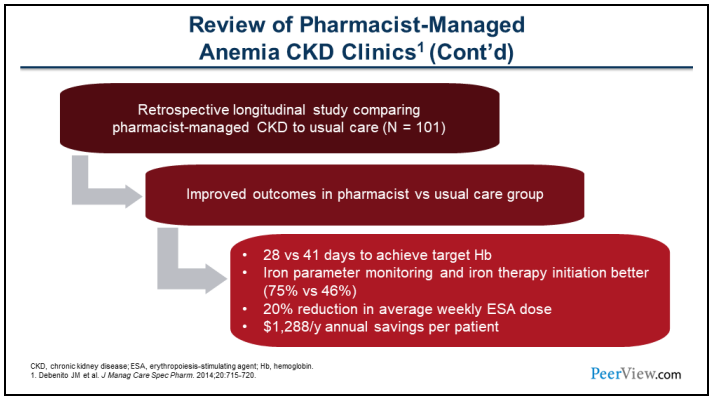
Slide 6



This was a specific study that was done on anemia, and it was in 16 VA medical clinics. They retrospectively evaluated almost 600 patients with CKD who had had care in that setting for at least 6 months. If you look on the right-hand side of Slide 6 at the graph, you will see they basically divided the patients into three different types of care settings for their anemia management. One was a pharmacist ESA clinic, or anemia management clinic. One was usual care that didn't have any ESA clinics within the setting, and the last was usual care with an ESA clinic but didn't include a pharmacist in the clinic.

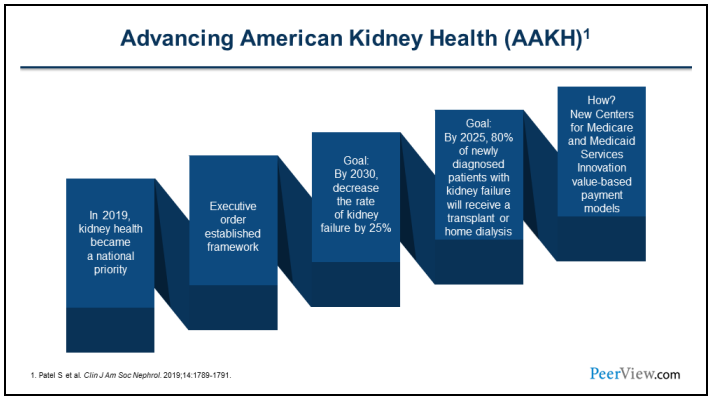
You can see that with the pharmacist-managed anemia clinic, more patients were likely to achieve the target hemoglobin level, so 71% compared with about 56.9% and 51.7%. They showed reduced ESA use, probably not surprisingly, because the other two settings without pharmacists basically had a number of patients who were at higher hemoglobin levels, which take more ESAs. Really importantly, they're more likely to get a serum iron and a total iron binding capacity or TSAT test more regularly, so you can manage anemia more regularly.

Slide 7



Another study, this was basically a pilot study, that retrospectively looked at 101 patients with CKD, about 30 of whom were managed by a pharmacist in a CKD clinic, specifically an anemia CKD clinic. They showed in this small pilot study that there were improved outcomes in the pharmacist versus the usual care group. They showed that there was a lesser time—so 28 days versus 41 days—to achieve the target hemoglobin level. They also showed, importantly, like the other study, that the iron parameter monitoring, and also iron therapy initiation in this case, was better in the pharmacist-managed group compared with the usual care group. There was a 20% reduction in the average weekly ESA dose, which resulted in over $1,000 per year annual savings per patient in their ESA dose. Now, having said that, they didn't look at the other therapies, which could have included iron or intravenous iron, and potentially even red blood cell transfusions in the cost. So it was just focused on the ESA cost.

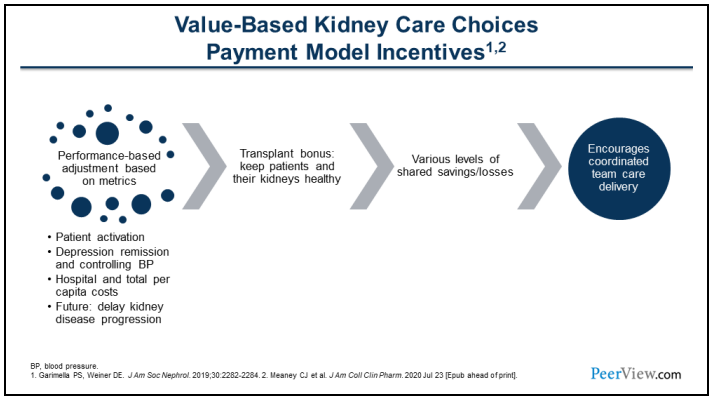
Slide 8



So there are a couple of really nice examples of anemia management clinics. There are a number of anemia management clinics in CKD that are run by pharmacists and integrated into the care loop of these patients across the country. But I wanted now to talk about the care and incorporating pharmacists into these models of care for patients with CKD. And so I wanted to talk to you about a new initiative.

In 2019, kidney health became a national priority in the United States, because a presidential executive order established a framework to advance American kidney health. As part of that framework, one of the goals was to decrease the rate of kidney failure by 25% by 2030 and to increase the number of newly diagnosed patients receiving transplants or home dialysis rather than in-center dialysis. How did they propose to make these kinds of changes and meet these goals? Well, they're doing it through new Centers for Medicare and Medicaid Services, so innovation value-based payment models.

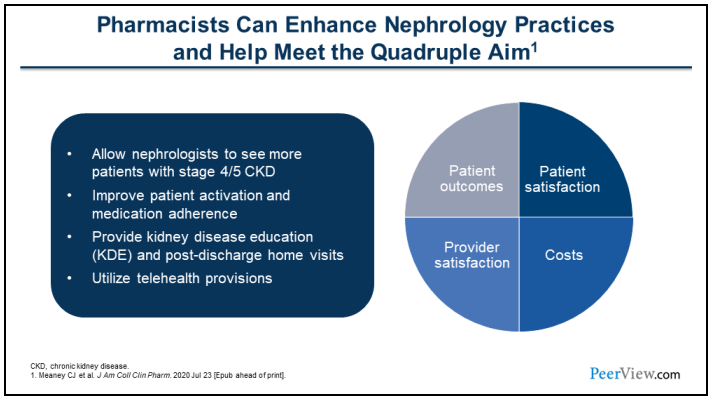
Slide 9



These value-based kidney care payment models provide incentives for nephrologists and nephrology practices to incorporate collaborative care within the models, and there are some performance-based adjustment metrics that they're using, such as patient activation, using the PAM score, which is one of the questions on the survey. It directly relates to medication behavior, how patients understand their medications and how to use their medications, depression remission, and controlling blood pressure.

CMS is looking very importantly at hospital and total per capita costs within these new value-based payment models. A future metric will evaluate the delay of kidney disease progression; all of these metrics are things that pharmacists can help nephrology practices achieve. In these models, in the third bullet on Slide 9, each one has various levels of shared savings and losses, and the bottom line is they encourage coordinated team care and delivery.

Slide 10

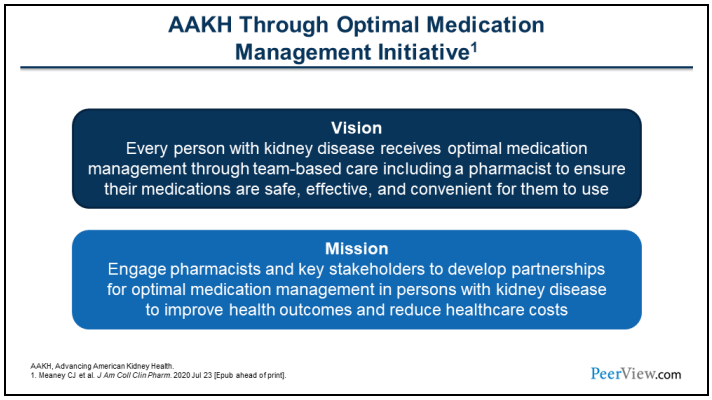


So pharmacists can enhance nephrology practices, and really help practices meet the quadruple aim of improving patient outcomes, improving patient satisfaction, activating them in their own self-care management. It can also help providers, and I'll show you in a moment why that's necessary in our nephrology space. Lastly, it can reduce healthcare cost. So we know that a lot of our patients with stage4/5 CKD are the ones who typically have anemia and are not being seen by nephrologists. Now, with these new value-based care models, they're hoping to get more patients with Medicare, so patient with stages 4 and 5 CKD, into nephrology care.

But the fact is that there are not enough nephrologists or advanced nursing practitioners to see all these patients. Pharmacists can add to those gaps in care that will occur and will actually allow nephrologists to see more of these patients. It will improve patient satisfaction and medication adherence. There's some piece of these models—they're called enhanced benefits—that pharmacists can get involved in and for which they can be reimbursed. That is kidney disease education, where we can teach patients about anemia, what anemia is, and how to manage it, and also post-discharge home visits, as those very important transitions of care.

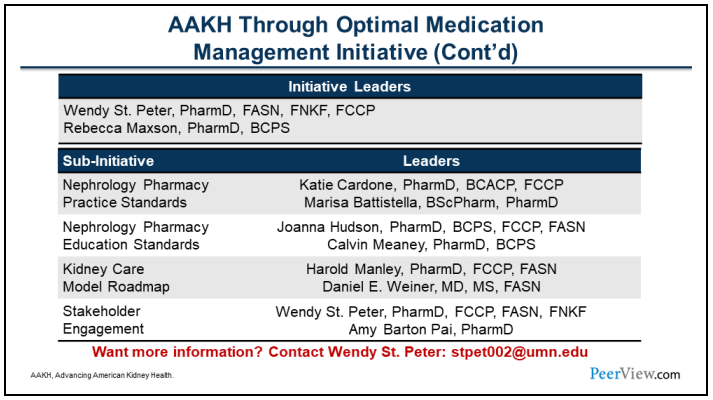
And then related to anemia, a very big issue is when patients are hospitalized. Oftentimes, they're in there for infections or perhaps surgeries. Their hemoglobin levels are low when they come home, and so anemia management becomes important in that transition. They also have telehealth provisions that will help us get into the patient's home.

Slide 11



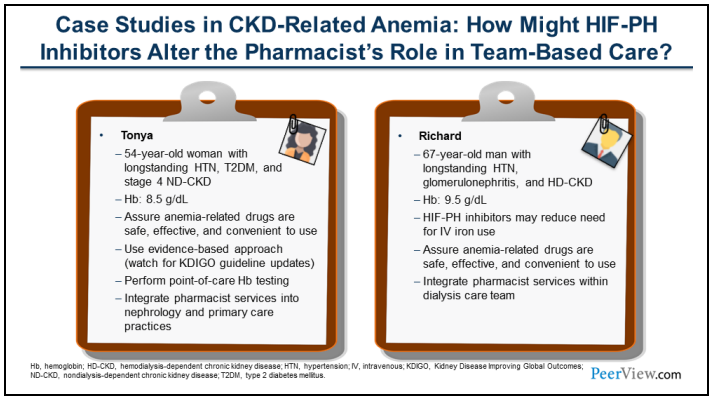
There was a core group of pharmacists who realized that these new value-based care models are really an opportunity to enhance optimal medication management, and so we created an initiative of Advancing American Kidney Health (AAKH) through optimal medication management. Our vision is that every person with kidney disease receives optimal medication management through team-based care, including a pharmacist, to ensure their medications are safe, effective, and convenient for them to use. Our mission is to engage pharmacists and key stakeholders, such as nephrologists, nephrology practices, and key stakeholders like the Renal Physicians Association, nurses and, most importantly, patients themselves, to develop those care partnerships for optimal medication management in persons with kidney disease.

Slide 12



I just wanted to show you that this initiative has several sub-initiatives, but we have several leaders. I'm one of the initiative overall leaders. Rebecca Maxson, one of my good colleagues from Auburn University, is one of the co-leaders. We have four different sub-initiatives that you can see in Slide 12 and different co-leaders. But I wanted to focus on the third one under the sub-initiatives, and that is the Kidney Care Model Roadmap. This is what I'm talking about, development of new care models, and this particular workgroup is headed by Dr. Harold Manley, who's a pharmacist and a good colleague, and Daniel Weiner, who is a nephrologist. The whole idea is now to work to develop a care map on how we can integrate pharmacists with nephrology practices and dialysis facilities to provide this type of medication management. I wish I could go on and say more about this, but if you want more information on this, please contact me at stpet002@umn.edu.

Slide 13



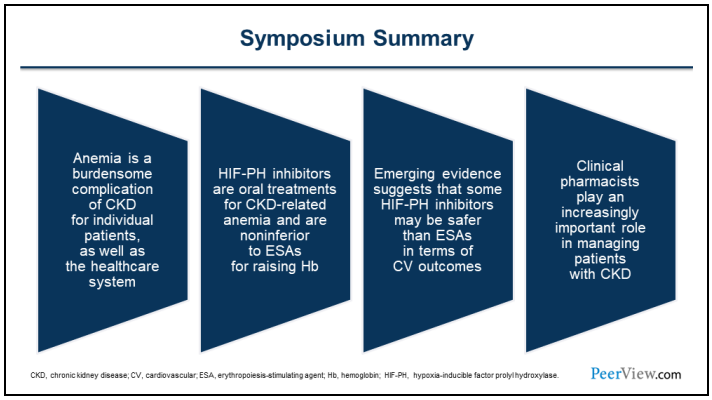
So, back to our cases. Dr. Fishbane did just a really good job of about Tonya and Richard, but now I want to place these two in the context of this integrated care management. One of the things that pharmacists are taught to do in the context of anemia is to assure that anemia-related drugs are safe, effective, and convenient to use. With Tonya, we would need to have a conversation about whether she wants to use an injectable ESA or whether it would be more convenient for her to use these new HIP PH inhibitors when they become available. Certainly, once you decide to start Tonya on one of these therapies, then you make sure that they are safe and effective for her to use, and that includes iron management and monitoring.

We need to use evidence-based approaches. The KDIGO guidelines that I presented to you earlier were from 2012, and now with all this new information on the HIF-PH inhibitors and the new studies, those will be updated. So please watch for those. It's important to also to realize that we have point-of-care hemoglobin testing, and I think this is a big opportunity for community pharmacists and clinic pharmacists to do hemoglobin testing for not only patients who have CKD with anemia but also other patients as well. And then, it's really important for us as pharmacists to realize we have an opportunity now to integrate pharmacy services into nephrology, as well as pairing and collaborating with primary care practices.

Now with Richard, it's the same issue. We, as pharmacists, need to think about Richard's needs. He is on dialysis; he's not responding to ESAs, and HIF-PH inhibitors may reduce the need for iron use and may be used to increase his hemoglobin. So, again, if we choose to start him on a HIF-PH inhibitor, we need to assure that it's safe and effective and that he remembers to take it. One of the things with some of these new HIF-PH inhibitors is that they're on a three-times-a-week schedule, so thinking about whether we should have it administered in the dialysis unit or if Richard can remember to take it three times a week at home will be important if it's something like roxadustat. Also then, there is the opportunity for pharmacists to integrate their services within the dialysis care team. That integration, both with patients who have CKD as well as dialysis, I think is open for us with these new value-based models of care. And Dr. Fishbane, would you like to make some comments?

Dr. Fishbane: No, thank you. I mean, I think you've laid it out so clearly in terms of how things may work. The real importance of collegiality in terms of anemia treatment, whether it's in the nephrology office or in the dialysis unit, that especially when we're introducing a new class of agents, and there are all those needs in terms of education and clinical protocols and understanding of efficacy and balancing with safety, that this is where we work so well together as physicians and pharmacists, and having integrated into care systems the ability to optimize care with these types of systems. So I have nothing to add other than that this is, I think, such a great opportunity for us.

Slide 14



Dr. St. Peter: I'm going to let you take it from there to summarize where we've gotten to.

Dr. Fishbane: Well, thank you. So thanks, everybody, for participating. What we've discussed today is that anemia is a burdensome complication of CKD. It's very troubling for patients, and it causes a number of difficulties for the healthcare system. The HIF-PH inhibitors are oral agents for the treatment of CKD-associated anemia, and that may be really important. We've seen so far that they're noninferior to ESAs with respect to raising hemoglobin. Emerging evidence is suggesting that some of these agents may be safer than ESAs in terms of cardiovascular outcomes, and that's certainly an area that's going to be of significant interest to dig deeper into.

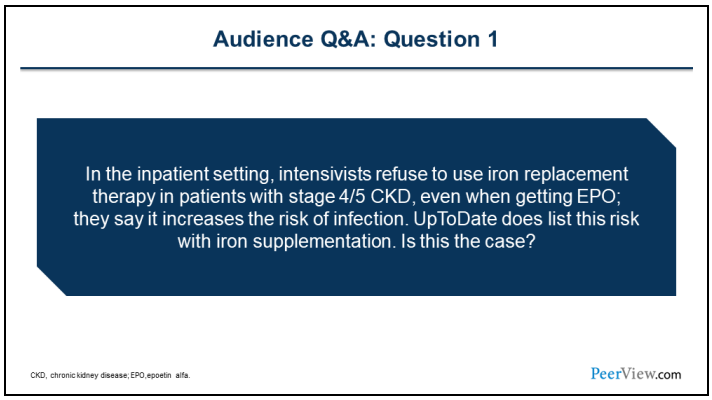
The clinical pharmacist, as we heard, will play an increasingly important role in managing patients not just with the anemia, but with the AAKH program, so things are going to be changing very, very dramatically over the next couple of years. This is a huge area of opportunity for pharmacists and physicians to be working closely together. So let's get to the questions. We are looking forward to speaking to you.

Audience Q&A

Steven Fishbane, MD

Wendy L. St. Peter, Pharm.D, FCCP, FNKF, FASN

Slide 1



Dr. Fishbane: We're going to jump right in. The first question has already got my attention and interest. The first question is—and I think we'll both speak to this a bit—"In the inpatient setting, intensivists refuse to use iron replacement in patients with stages 4 to 5 CKD, even when getting EPO, saying that it increases the risk of infection. UpToDate does list this risk with iron supplements. Is this the case?"

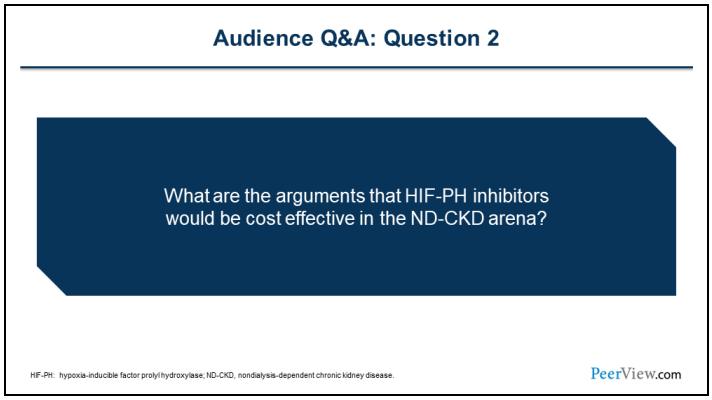
So, Wendy, I'm going to start it off by saying that generally, for people who are—I mean, this is about intensivists, so patients in the intensive care unit—replacing iron or treating iron deficiency is usually not urgently important. You can usually wait until the patient gets better, because infection might be present in many of these patients. So, you know, they may have a point, although I don't know that there are a lot of data to support that. But, Wendy, I'm kind of curious about your opinion. Do you see this practice?

Dr. St. Peter: So, yeah, I think it's a really common practice in the hospital. I can just say that I haven't seen any good clinical studies that have really evaluated that, but we do know—I'm talking about in the inpatient setting, not the outpatient setting—that various bacteria need iron for growth. And so, the theory has been that we can reduce the risk of infection in these patients. The other thing, too, is that these patients are highly inflamed. Whether they'll be mobilized correctly, with the high inflammation that occurs during the infection, whether iron will be utilized well, is also a question.

So as Dr. Fishbane pointed out, it's not an acute issue to replete during a hospitalization. Even though we don't have good studies on this, it makes sense from what we do know about bacterial growth in the outpatient setting that these infusions in hemodialysis patients who are prone to infections don't seem to be at increased infection risk. But again, I think it's a good practice not to do it in the inpatient setting.

Dr. Fishbane: Oh, good. Thank you.

Slide 2



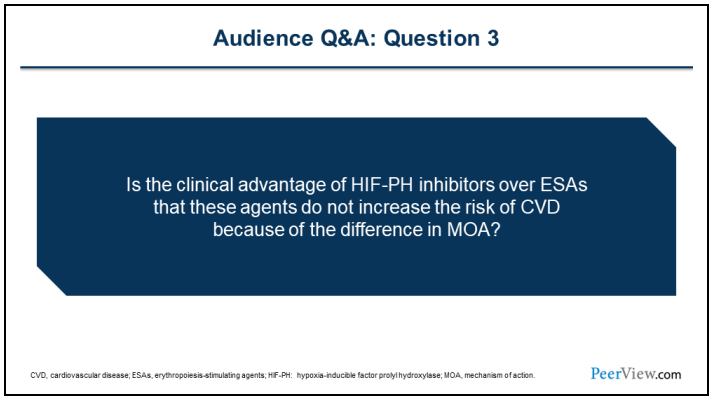
Dr. Fishbane: Let's get on to a question about the stabilizing drugs. So this question is, "What are the arguments that the HIF-PH inhibitors would be cost-effective in the ND-CKD arena?" And the writer notes that, "I would imagine this population has much less anemia-related healthcare costs related to those on dialysis." So I'm going to start it off by saying that I think there are a lot of moving pieces here, because, for one—and maybe most importantly—I don't think we have a sense for what the cost of these drugs would be. So we're missing, you know, one important piece of it. We have a large population, though, of patients, and when you're looking at a large population like this, maybe less anemia, how do you think the cost-effectiveness is likely to play out, Wendy, if the cost of the drug, say, is just similar to EPO? Do you have any feel for it yet?

Dr. St. Peter: Well, I don't. But that's a question that is probably going to be answered. I think our ICER group, which looks at the cost-effectiveness of medications, is pulling the trigger on a study of this very issue with roxadustat. I don't know if they're starting in February or ending in February, but they will be doing that study. I can say there have been a couple of observational studies that look at patients with CKD who are nonanemic versus those who are anemic. Patients with CKD who are anemic have much higher costs than patients who are not anemic.

So it ranges from these two studies from about $6,000 to $12,000 a year difference. Now, all that may not be attributable directly to anemia, because these are old observational studies. They couldn't correct or adjust for all the different things that may be implicated under the cost situation. But I think time will tell, and perhaps that ICER study will give us some of the information we need.

Dr. Fishbane: Okay, you're right. This is going to be really important in trying to understand the use of the drugs.

Slide 3

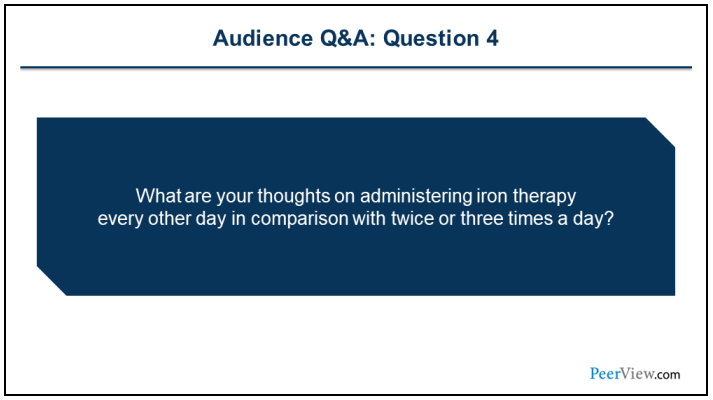


The next question is on the subject of the clinical advantages of the HIF-PH inhibitors over ESAs. Is It because of a difference in mechanism of action that it doesn't increase the risk of cardiovascular disease ? I would like to start by saying that what we know right now is that for the roxadustat program, we've seen that compared with placebo, roxadustat has cardiovascular outcomes that appear to be noninferior based on the phase 3 results that have been presented publicly. In terms of patients on dialysis, where roxadustat has been compared with ESAs, there is generally noninferiority compared with ESAs. However, in the incident dialysis population, there is actually something of a benefit that was seen, and that could be potentially really important.

I guess what I'm thinking about there is that every patient on dialysis obviously starts as a patients on incident dialysis, so that if nephrologists or dialysis organizations end up being interested by that improvement in cardiovascular events with roxadustat compared with epoetin alfa in the incident population, and patients get started because of that initially on roxadustat, I'm not thinking that people would likely get changed off the drug later. What are your thoughts, you know, in terms of those findings and how it might translate into use of the medication?

Dr. St. Peter: I don't think I have anything more to add than what you said there, Dr. Fishbane.

Slide 4

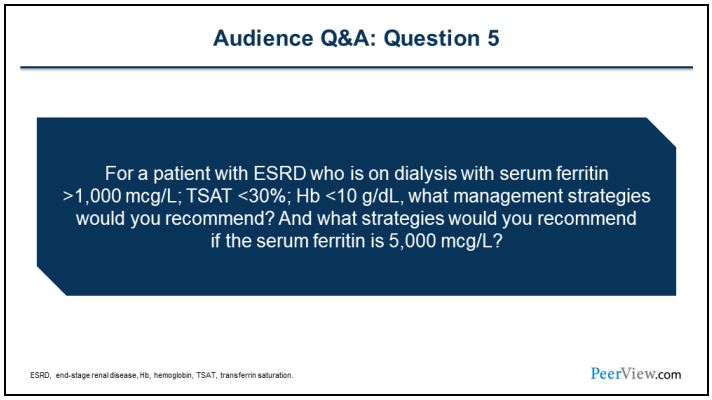


Dr. Fishbane: Okay. The next question is on iron, and this goes straight over to you, Dr. St. Peter. "What do you think about every-other-day administration of iron that has become more popular among nephrologists in comparison to twice-a-day or three-times-a-day administration?" I guess I've seen a little bit of data on this. Do you have a sense about this? Have you seen some results?

Dr. St. Peter: So this is a really good question, because this has come up when I'm teaching CKD to my students, because there are two or three fairly small studies that have shown that multiple administration of iron a day or larger doses of iron stimulate hepcidin. As you learned today, hepcidin is a problem in that the higher the hepcidin levels are, the less iron transport and iron absorption takes place. And so, those very small studies have suggested that you might get a better result in dosing iron every other day. I've proposed that as a mechanism to dose iron, but that was in the base of when we're working with ESAs. I really don't know what the answer would be to that in an era with these HIF-PHI inhibitors, because they are increasing iron absorption and increasing transport, and it may be that the tables are a bit turned, that we may have absorption that occurs even in multiple doses per day. So in the old paradigm, with ESAs and oral iron, I think that that approach seems reasonable. I don't know what the approach will need to be or whether that's reasonable in the era of HIF-PHI inhibitors.

Dr. Fishbane: Yeah, so that's really interesting that we may see differences in terms of iron availability, and perhaps that would change the way that we might look towards giving iron. So immediate applicability.

Slide 5



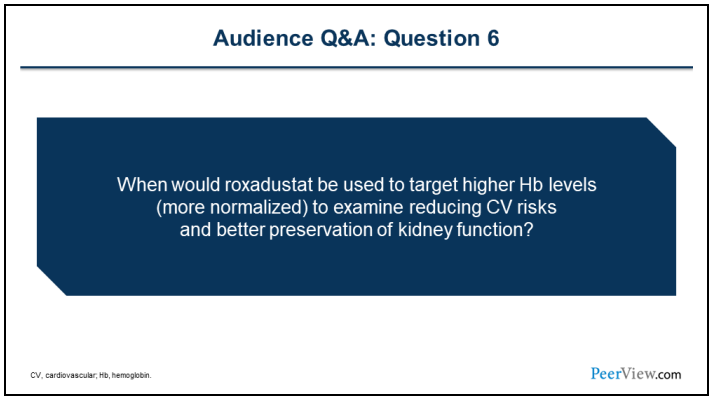
The next question is actually one that has been constant in the 25 years that I've been talking about iron or doing lectures, and it is about patients on dialysis who have high ferritin values, low TSAT, and hemoglobin less than 10 g/dL. What is the correct management in this case?

I think that the right answer here is going to be that there isn't necessarily a right answer. The KDOQI 2012 guidelines would tend to suggest that it depends on what you're trying to accomplish. Now, KDOQI would say for a ferritin above 500 mcg/L, just don't give intravenous iron. But I think we can look at this and think to ourselves that if the patient is having symptoms, and the anemia is causing problems, if the patient is on epoetin alfa and the dose is high, there may be a reason to treat. Now, I don't. I'm very conservative. I don't like to give intravenous iron when the ferritin's above 500 mcg/L.

Dr. St. Peter: I was just going to say that typically in the ESA era, the way that we deal with patients with higher ferritins who have a low TSATs is to administer intravenous iron in small doses, but at more regular intervals so that those doses could be more immediately available for transport for making red blood cells. So that's kind of what we've done in those situations. I think that, of course, with the new HIF-PHI inhibitors, it'll be interesting in those patients who have those high ferritin levels similar to what we saw with Richard and that those may be the patients where those drugs are of greatest benefit.

Dr. Fishbane: Yeah, that's interesting. And I do want to remind the questioner that that combination, though, of the high ferritin and relatively low TSAT, is kind of a fingerprint for hepcidin, a protein that is so active because of inflammation in our patients and causes iron to be locked away.

Slide 6



The last question is one related to roxadustat. So, Wendy, I guess I'll ask your opinion on this. "When would roxadustat be used to target higher hemoglobin levels, more normalized levels, to examine reducing cardiovascular risk and better preservation of kidney function?" I guess, do we think that in clinical use it would be used to target higher hemoglobin levels, maybe even normal hemoglobin levels again? And do we think further studies will be done? I guess I've got some opinions, but let me let you get a shot in here first.

Dr. St. Peter: Give me the shot? Boy. This is a really good question, because we don't know the answer to that. The studies that have been done to date with the HIF-PH inhibitors have been limited to hemoglobin levels between either 10-11.5 g/dL or 10-12 g/dL. That's been based on the information that we have with pushing hemoglobin levels to normal hematocrit trials that we tried with ESAs with both patients with dialysis-dependent and nondialysis-dependent CKD, which have shown in those studies that we have higher cardiovascular risk. I think the question that is really out there, is: With these new drugs, is it possible to push the hemoglobin up greater? Patients having potentially a better quality of life, perhaps, with a higher hemoglobin? But I think that we don't know, because the studies that we have to date have been limited to that kind of lower but not lower hemoglobin measurement of 10-12 g/dL.

Dr. Fishbane: Yeah, and that's interesting. I think you're right. This kind of gets to the subject of the unfulfilled potential of EPO that things like left ventricular hypertrophy and just a general idea of improving oxygen delivery through the body, it will be interesting to see. Now, remember, you know, at the time that we're speaking right now, it's just about 2 weeks away from the FDA's first announcement of approval or not of one of these drugs, roxadustat, which would be December 20th. We'll see when the announcements are made, what kind of label there is and what kind of hemoglobin targets are in there. I would guess that they're going to stress only going up to about 11 g/L or 11.5 g/L generally in terms of hemoglobin. But thank you to the questioner, because I think it is a good question. So, listen, great thanks to Dr. St. Peter for your excellent talks and responses to the questions, and for the audience in general, thank you so much for participating in this activity. Really glad that you took part.

Dr. St. Peter: Thank you. This has been a lot of fun.