

A Road Map for Managing *Anemia* in the Patient With Type 2 Diabetes and CKD



CME Satellite Symposium:

A Road Map for Managing Anemia in the Patient With Type 2 Diabetes and CKD

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Question and Answer Session

The following is a transcription of the audio recording from the Question and Answer Session of the live symposium. Bracketed texts indicate additions or modifications for clarity.

Audience Question: I have two questions about the safety of using antiplatelet drug therapy and statins in people with deteriorating renal function. With end-stage renal disease, my impression was that there is an increased tendency to bleed—is there an eGFR below which antiplatelet therapy is contraindicated or dose reduction required? And along the same lines with statins—is there one statin preferred over others, and what do you do with the dose?

George L. Bakris: Well, Richard can chime in on this as well. When you say antiplatelet therapy, that can mean aspirin, that can mean clopidogrel (Plavix®)—I'm not really sure what you're referring to. If you're referring to aspirin—low-dose aspirin, that is 81 mg of aspirin a day—does not have a GFR cut-point; in fact, it's recommended for people with low GFR. So that is not a contraindication. Clopidogrel is a different story. I don't know of any formal guidelines that say you shouldn't use it, but obviously that's going to be an issue, especially in dialysis patients. I'm not sure if you want to comment on that, Richard.

Richard A. Lafayette: Yes. Again I'd mainly just say that aspirin is safe. Whether it's effective or not in the chronic kidney disease or end-stage renal disease population has not been well studied—although in cardiovascular outcome studies that post hoc analyze for stage 3 and stage 4 patients, they do seem to benefit from both statins and aspirin therapy (although those are retrospective reviews of other prospective studies). Our patients do have increased bleeding rates compared to the general population. But certainly the cardiologists, once they're intervening with advanced coronary lesions, do routinely recommend therapies that are used for other patients, including clopidogrel and warfarin (Coumadin®). The patients have to be closely monitored. You have to accept their increased bleeding risk and assume that [the therapies are] going to have the same benefit as [in] other populations.

George L. Bakris: The only comment I'd make about statins is cerivastatin, which had by far the highest incidence of rhabdomyolysis in people with renal insufficiency and is no longer available. So is there a safer statin? There has been no prospective study to look at that. If you look at all the statins in the context of nondialysis patients with advanced kidney disease, they all seem to be pretty well tolerated. If you're really concerned about drug interactions, then, I guess, pravastatin would be the one to go for because it's water soluble and you don't have any issues. But then again, you'd have to use high doses to really get a meaningful effect—that is 80 mg. But low doses of rosuvastatin, like 5 mg, or atorvastatin 10 mg, seem to do pretty well in these patients as well.

Lawrence Blonde: Has ezetimibe been looked at in people with chronic kidney disease? Because it's an option, at least in terms of lowering LDL.

George L. Bakris: Right, ezetimibe is being looked at right now in a very large trial called the SHARP trial, which specifically looks at a spectrum of people with kidney disease from stage 3 all the way to dialysis. I'm one of the investigators in that trial in the US; it's a worldwide trial. The amount of reduction in LDL that you get with ezetimibe does not compare with something like atorvastatin or rosuvastatin, but nevertheless....

Lawrence Blonde: I meant in combination with a statin, because in people who don't have CKD, and who, for one reason or another, have had difficulty tolerating higher doses of statins, the combination of ezetimibe with a statin can get you a rather substantial LDL reduction—recognizing that there are, as yet, no long-term outcome trials, although we suspect the benefit is from lowering LDL.

George L. Bakris: Well, what I can tell you anecdotally is that I have a number of patients who cannot tolerate statins because of myalgia, not because of rhabdomyolysis or CPK evaluation. And what I have done is switch them to ezetimibe, along with high-dose pravastatin (Pravachol[®]) and they've done very well. In fact, there's no significant change between what they were on originally and their LDL cholesterol. So it does work.

Lawrence Blonde: So, actually, before we take other questions, because we asked people to fill out question cards, let me address a couple of those. "Does getting the hemoglobin above 12 raise the risk for thrombotic complications? Is concurrent aspirin recommended for patients who were on EPO?"

Richard A. Lafayette: So the answer would be, we're not really sure. In the very early days of erythropoietin, rapid, complete correction of anemia was associated with more dialysis access and complications of thrombosis in that setting. In CHOIR, there was no increased thrombotic stroke [with hemoglobin levels] going up, and there weren't increased thrombotic complications, in terms of large vessel thrombosis, in either the European or the American study—but it's still of significant concern. Aspirin is certainly not recommended for that purpose. I'm not saying that high-risk cardiovascular patients with chronic kidney disease should not receive aspirin, but aspirin is not a cotherapy for patients getting erythropoietin. And again, most important is [that] the target hemoglobin is 11 or 12. So I'm not recommending going above 12, and it appears that at this window of 11-12, you really don't have increased adverse events. In fact, you may have fewer. And so comparative studies need to be more carefully carried out in the future. And one final point is that when you have a target hemoglobin of 11-12, it doesn't mean that your patients are going to stay merrily between 11 and 12. So, I think everyone needs to be comfortable [with the realization]—if you are going to use these agents—patients will cycle above and below that target at times. And depending on how responsive they are, their hemoglobin will go above—but that's OK. I think you're looking at mean hemoglobin and a desired target of 11 or 12, which means most of [the hemoglobin levels] will be between 11 and 12, but sometimes they'll be in the tens and sometimes they'll be thirteen, which again seem to be very safe and effective.

Lawrence Blonde: And do you adjust the EPO dose?

Richard A. Lafayette: Yes. And again the monitoring recommended is at least every four weeks—making little, tiny adjustments, no greater than 25% of your dose, will often get you right back to goal.

Lawrence Blonde: So the ADA has recommended a blood pressure [goal] of less than 130/80 for people with diabetes. The question is, I presume, reflective of people who have chronic kidney disease with or without diabetes. "How far down do you drive the blood pressure before you back off from full doses of ACEs, ARBs, or any other hypertensive agents?" So I guess one of the questions is, "What is your goal in people who have chronic kidney disease with or without diabetes? Is it different from less than 130/80?"

George L. Bakris: No, in general, it is no different than diabetes, it's less than 130/80, with the exception of people with proteinuria. The data, albeit retrospective, are very consistent from every single trial—and that is—

if you have a gram of proteinuria or more, it behooves you to get the blood pressure down, actually to 120 if you can, because those people tend to have better outcomes than [those with] having higher pressures. With that exception, less than 130/80 is really where you want to be.

Richard A. Lafayette: And one additional comment is that the blood pressure goal itself may not be sufficient. If you do get the patient to goal at 130/80—I thought George would go in this direction—and the proteinuria is still not under control—actually maximizing your antiproteinuric therapy—even if it means lowering the blood pressure a little further, or even if it doesn't. Because often when you maximize ACEs or ARBs or combine them, you may not see further significant changes in blood pressure—you may see very significant reductions in proteinuria—and again retrospectively, that's been linked to reduced mortality rates and reduced progression rates.

George L. Bakris: I'm actually ashamed that I didn't tell you that, because we published some of the first data... So you do want to achieve at least a greater than 30% reduction in proteinuria. By the way, I didn't say this either, and it's important for you to know that you can give all the ACEs and ARBs you want, and you can get the blood pressure down, but you will not substantially reduce proteinuria unless you restrict salt. So salt is critical. You need to tell patients that it's a four-letter word and they need to be consuming a maximum of 3 g/day of sodium.

Lawrence Blonde: Where do the new renin inhibitors fit in your algorithm of antihypertensive therapy, and are there studies yet in patients with CKD?

George L. Bakris: It's too early to tell where they fit in. There is a trial just starting now, it's recruiting. It's an international trial that will look at this in people with diabetes—not necessarily advanced CKD, but in people with diabetes—to look at cardiovascular and renal outcomes. It remains to be seen. I think, right now, if you look at the profile of what is available, [a renin inhibitor] behaves like an angiotensin receptor blocker in terms of its overall side-effect profile. Its efficacy is similar to an ARB, however, its bioavailability is very low. If you're using furosemide (Lasix[®]) with it, you need to double or triple the dose of furosemide. Also if you're using irbesartan, that affects the drugs—so it's got a lot of drug interactions, and so I think one has to be cautious at this point where you go with it. It is being studied, it is approved for blood pressure lowering, but I'm certainly not going to put it first line right now.

Lawrence Blonde: There is a question, and I'm not sure what was intended, about the relationship between insulin and anemia. I'm not sure what this refers to. First of all, one thing that's clear is that severe or significant anemia affects A1c in terms of following the A1c and interpreting the values we sometimes forget about. But I'm not quite sure what was intended here.

Richard A. Lafayette: The question may reflect what is the reason that diabetics have more anemia than nondiabetics—and again this is seen both in type-1 insulin deficient and type-2 hyperinsulinemic patients. So I don't think it's an insulin issue, but again I'm going to defer to insulin experts, who are [certainly] present in the room.

Lawrence Blonde: I did make—and I'm not an expert in interpreting—a sort of laundry list of potential reasons. So let us take one of the questions from the floor.

Audience Question: My question relates to HbA1c and renal anemia and correction of anemia—you just touched on it. The first question is, "How does the use of erythropoietin affect HbA1c?" My understanding is that HbA1c is still very accurate—especially at levels <8%—in reflecting glycemic control in patients on dialysis. So I guess the question is, "How does EPO treatment in correction of anemia affect the HbA1c level? Has it been looked at in the studies that you went through, or any other studies?"

Richard A. Lafayette: I'm not aware of any studies that directly follow pre- and post therapy in terms of time average sugar control. There doesn't appear to be any direct effects with erythropoietin therapy on glycemic events. So, in nondiabetics, there's no hyper- or hypoglycemia; and in diabetics, they don't tend to change. Globally, the A1c in some small studies I've seen that looked at patients who were getting multiple interventions doesn't seem to change over a time period. So I think in the subtle change of hemoglobin levels of one, that's not enough reason to see a percentage change—but the data are extremely limited, and I'm not aware of any good study. I know that with severe anemia our own diabetologists often recommend other studies of diabetes control like fructosamine and other markers that are also not perfect. But yes, we do follow hemoglobin A1c in our diabetic ASRD patients.

Lawrence Blonde: At what level of anemia is the A1c impacted? If the anemia is constant, the A1c probably is a reasonable reflection of glycemic control; but at what level does a change in hemoglobin result in a change in A1c?

Richard A. Lafayette: Again, I am not an expert in that. My understanding is that at levels less than 10, people get uncomfortable using hemoglobin A1c as a good marker of absolute sugar control. The correlation between time average sugar and A1c becomes fuzzier at more severe levels of anemia.

Audience Question: Dr. Bakris, with the study you showed looking at the reduction in cardiovascular medication in patients with stage 5, did you look at any diabetic treatment in that study at all?

George L. Bakris: No, we did not, because this was just a focus on blood pressure treatment in typical cardiovascular risk reduction. So I didn't, I'm sorry.

Lawrence Blonde: I showed a proteomic study, that's a research study. To my knowledge, that test is not available commercially at the present time. This is a sort of investigation into other ways of predicting future development of chronic kidney disease.

There's a question here about looking at vitamin D levels and this is another crucial area among people with chronic kidney disease that we really don't have time to go into in detail. But, in general, vitamin D should be looked at because it's very common to have vitamin D deficiency in people who have chronic kidney disease. [Vitamin D] should be replaced when [a deficiency is] found. 1,25 vitamin D levels, generally, are not directly recommended, at least by K/DOQI, but rather people [should] look at PTH levels. When PTH levels are elevated, there are therapeutic goals, and those goals are addressed by giving activated vitamin D. There is a wealth of data in both the dialysis and the predialysis population about the benefits of this—but again we just did an entire symposium on this topic at the AACE meeting and there have been similar symposia at this meeting, so this is a topic in and of itself in terms of chronic kidney disease.

George L. Bakris: I was just going to say that this is probably going to be changing. There is a study that we just published, the SEEK trial, which is a cross-sectional study, with all its problems. But active vitamin D, the 1,25 vitamin D, actually starts dropping in GFR ranges in the low seventies—so there's a thought now [about] looking at intervening at higher GFRs—PTH is still not going up—to see if you can block that. And that is from a cardiovascular perspective, not a bone perspective.

Lawrence Blonde: That's the other piece of this, but at the moment, the recommendations are to focus on PTH and the efficacy and usefulness of the commercial assays of 1,25—I think in terms of wide availability of reliable assays, it is still maybe uncertain.

Richard A. Lafayette: This question asks “Are you concerned about reports of proteinuria with rosuvastatin? Would this sway one to avoid rosuvastatin in CKD?” My answer would be no, I think this is a rare phenomenon, not a proven phenomenon. Some studies actually suggest that statin use can reduce proteinuria, which is sort of interesting and due for further study. So presently, the benefits would outweigh these risks and we would monitor protein levels in our patients. But I wouldn’t avoid the drug altogether.

This has a 3 parter to it—so the newer IV iron formulations need to be given in a hospital, using precaution against anaphylaxis. And the answer is yes, there is still a rare episode of severe allergic reaction. They’re less than 1/1000, but since it is 1/1000, it needs to be given in a setting where medical attention can be given. It doesn’t have to be a hospital, but it needs to be an office setting where, again, someone can get emergency therapy if needed. An infusion center or doctor’s office that has a crash cart would be a very reasonable setting.

And finally, “This iron deficiency is common in CKD. When to investigate for a GI blood loss?” Again, if the setting is such that a patient is significantly iron deficient, particularly before using erythropoietic drugs, I think evaluation for GI blood loss is very reasonable at that point.

George L. Bakris: I just want to make a very quick comment about statins. All statins cause some degree of transient proteinuria or albuminuria, and that’s even in *The Medical Letter*. So there’s nothing unique about rosuvastatin. That’s a marketing thing, so don’t get sucked in by some of the propaganda. That’s true of all statins.

Lawrence Blonde: I think we’ll take the last question.

Audience Question: Actually two questions. One is “Why is aspirin regarded as free from the odium of NSAIDs in general and in CKD? Why is aspirin sort of an exception? Are there other NSAIDs we avoid?”

George L. Bakris: Well, aspirins and NSAIDs should not be in the same category because they work by different mechanisms. And, in fact, the dose of aspirin we’re taking, about 81 mg, doesn’t even work at the same level as higher-dose aspirin, certainly with regard to the kidney and its effects. So, I think that to say that a COX-1 or COX-2 inhibitor is in the same category as aspirin is a mistake, because they work totally differently and they certainly have different effects on cardiovascular outcome.

Lawrence Blonde: Last question...

Audience Question: The second question is, “Is anemia a bad thing in the diabetic patient only as an indicator of CKD, or is it an independent risk factor apart from CKD?”

Richard A. Lafayette: It’s independent, in fact, there’s been reviews of that. One of the studies that was shown here was a 5% Medicare study of patients with or without varying levels of chronic kidney disease, so these are patients older than 65. And again, as you know, diabetes itself is a very significant cardiovascular risk factor in the absence of chronic kidney disease, with the relative risk of death each year of about two. Anemia by itself—without diabetes—is also an independent risk factor, with a relative risk that approaches two. When you combine diabetes and anemia, that relative risk factor goes up to about 3 to 3.5. So, yes, anemia is an independent additional cardiovascular risk factor without chronic kidney disease. When you combine chronic kidney disease, anemia, and diabetes, you really have horrifically increased risk.