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Glycemic Control in T2DM: Opportunities and Challenges

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Here's your faculty Dr. John E. Anderson and Dr. Vivian Fonseca.

Dr. Anderson:
Unfortunately, almost half of all patients with type 2 diabetes, or T2DM, do not achieve optimal glycemic control. Not only that, but cardiovascular events and being overweight or obese is associated with a risk for type 2 diabetes and can correlate with poor outcome. So, how can we use the available treatment options to our advantage to overcome these common challenges facing our diabetic patients?

This is CME on ReachMD, and I'm Dr. John E. Anderson. Joining me today to discuss glycemic control in this discussion is Dr. Vivian Fonseca. Vivian, thanks for being here today.

Dr. Fonseca:
It's a pleasure, John. Good to be working with you.

Dr. Anderson:
Great. So to set the stage for our audience, Vivian, what are the macro and microvascular morbidities associated with poorly controlled hyperglycemia, especially related to poor cardiovascular outcomes? And when does treatment intensification come into play?

Dr. Fonseca:
So let me actually start with microvascular complications because those are the ones that are very closely and directly linked to hyperglycemia. You don't get microvascular disease if you don't have diabetes and don't have hyperglycemia, and the main ones are diabetic retinopathy, diabetic neuropathy and diabetic nephropathy. They are also interconnected in some ways. Maybe retinopathy is a little different. It is the leading cause of blindness, particularly peripheral retinopathy with bleeding, but you can also get macular edema. And in the eye there's also more cataracts. Diabetic neuropathy contributes to amputations, a lot of pain in many patients, numbness, and can cause autonomic neuropathy, which is associated with mortality.

And diabetic nephropathy initially manifests as proteinuria but then progressive renal disease, renal failure, and is the leading cause of end-stage renal failure leading to dialysis. Many patients have all 3 complications together, and all of these are in a way linked with the macrovascular complications. Now, the major macrovascular complications are heart disease, ischemic heart disease like myocardial infarction or angina, or congestive heart failure, as well as stroke and peripheral vascular disease, essentially atherosclerosis, but there is an increase in nonatherosclerotic congestive heart failure as well in people with uncontrolled diabetes.

Now, in terms of intensification of treatment, the best option is really prevention of these complications, and if you intensify treatment

very early in the natural history of the disease, people will never get complications. You could intensify later even after complications occur, and it will decrease the progression rate, but some people, particularly with type 2 diabetes in the late stages when they have multiple complications, don't do very well with intensification, as we saw in the ACCORD trial. But in many other trials, people have not done that badly, so there's always room for improvement in glycemic control.

So, Dr. Anderson, now it's your turn. Thinking about your own practice, what are the common patient barriers to achieving treatment intensification?

Dr. Anderson:
That's a great question, Vivian, and it's sort of complex, because I'm in a primary care setting, and as you know, we're taking care of all kinds of diseases, so I think the first thing I do and I have my nurses do when the patient's checking in is, "Are you taking your medicine?" I mean, this issue of nonadherence really rises up, especially when you have complex regimens for diabetes.

I mean, cost is always an issue. I just had a patient come in the other day. He's a nurse. He knows better. His A1c was near 10, but just because the third-party's mail order prescription service didn't send his GLP-1 receptor agonist in, he just stopped taking it, and then he got off of his SGLT2 inhibitors. So this is someone who really understands medicine but doesn't understand how complicated his disease is and how much worse it's going to get, like you said, for complications with this nonadherence.

Sometimes it's the complexity of the treatment regimen, right?—especially when patients are doing multiple daily injections, they are taking many medicines, or they have a lot of comorbidities so they are taking medicines for other conditions as well. I think you run into things like poor health literacy and that type of thing. And then there are patient barriers in terms of just overall support from family.

There are psychological barriers. I deal with a lot of depression in diabetes. And, you know, if you ever heard of Mark Peyrot, who's published a lot on diabetes distress, it really affects patients' ability to stay with their regimen.

And then sometimes we have, you know, this injection phobia. You and I have talked about this before. The injection phobia, if you can really show them the size of the needle you're talking about and demonstrate that to them, you can overcome a lot of that.

Dr. Fonseca:
Continuing on the topic of patient management, what physician factors form the basis of this so-called clinical inertia that leads to lack of intensification of therapy that we often see in management of type 2 diabetes?

Dr. Anderson:
That's a great question, because I think there's clinical inertia, Vivian, at the physician/provider level; I think there's clinical inertia at the patient level. I think it's what you said. We don't need to be taking forever to get our patients to goal. Set whatever A1c goal you have and achieve it, and that frequently may mean using combination therapy early. For a long time we did this treatment to failure. You know, you'd get a patient barely down to goal; they'd come back up; you'd treat barely to goal. I mean, if you're using combination medicines, much like we do in hypertension and depression, get the patient to goal and keep them there, and some of the newer agents, I think, help us do that.

A lot of times we have these patients, "Well, Dr. Anderson, I don't want to have another medicine. Give me 3 more months. Just give me 3 more months. I'll start that exercise regimen." And then, of course, they come back in 4 or 6 months, not 3 months, and so there's always this back and forth negotiation. One of the techniques I use if I really need to get a patient to goal, I say, "Look, I'm going to put you on this medication. We're going to get you down to goal. If you come back in 3 to 4 months and you've achieved those goals you've set out to do with lifestyle changes, then I'll be happy to be the first person to take you off the medicine." But I think there's been plenty of clinical trials that show we're waiting way too long to intensify both on oral agents as well as injectable agents.

Dr. Fonseca:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Vivian Fonseca, and with me today is Dr. John Anderson. Together we are discussing glycemic control in our patients with type 2 diabetes.

So, Dr. Anderson, with all the treatment options available, which therapeutic agents have been shown to have clinical efficacy in improving cardiovascular outcomes in patients with poorly controlled hyperglycemia. And what are their mechanisms of action?

Dr. Anderson:
You know, that's a great question, Vivian, because we have now 2 classes of medicines—the SGLT2 inhibitors, which work through the kidney, and GLP-1 receptor agonists, which work through the endocrine system of the gut—and not only have they shown good efficacy in A1c lowering, usually without hypoglycemia, most with some weight reduction, some systolic blood pressure reduction in terms of the SGLT2 inhibitors, but now we're learning there is a benefit in reduction of cardiovascular risk in our patients with type 2 diabetes.

In 2008, the FDA mandated that all new diabetes drugs go through cardiovascular outcomes safety trials, and so all of these newer agents are proven safe, but we have seen that some of these agents in particular have shown statistical superiority versus what we would call usual care in patients with type 2 diabetes, just looking at SGLT2 inhibitors, canagliflozin in the CANVAS and CANVAS-R program, empagliflozin in the EMPA-REG program. Dapagliflozin recently had a reduction in that co-primary endpoint of cardiovascular death and hospitalization for heart failure. The VERTIS-CV with ertugliflozin is pending for next year.

And then we look at the GLP-1 receptor agonists. Liraglutide in the LEADER trial had a reduction in that 3-point MACE—that's the major adverse cardiovascular events. HARMONY with albiglutide reported last year had a 20% reduction in cardiovascular events with 3-point MACE. And then more recently in June, REWIND, which was dulaglutide, had a reduction in 3-point MACE, and this was with an almost 70% primary cohort. In other words, these patients didn't even have cardiovascular disease. And then there's been SUSTAIN-6 and PIONEER with semaglutide, both injectable and oral, that while not powered as many patients and for as long, also showed reductions in cardiovascular outcomes.

So, Vivian, really we're dealing now with cardiovascular drugs that also are antihyperglycemic drugs, and I don't think many of us ever thought we would see that day.

Dr. Fonseca:
Sure. With regard to mechanisms, we don't fully understand the mechanisms. There are multiple mechanisms involved in these effects that are beyond glucose control, so for equal*9:00 glucose control, some drugs give you added benefit, but we need to be a little bit more precise in our choice of these, and the guidelines are moving in that direction.

Dr. Anderson:
You know, it is interesting, Vivian. We can talk about the way an SGLT2 inhibitor works in terms of lowering glucose. We can talk about GLP-1 receptor agonists and how there's a beta cell function, a depression of the glucagon and a slowing of gastric emptying, essential nervous system effect, but you're right; I think most of what we understand about the cardiovascular risk reduction is theoretical, and it may be more than 1 mechanism of action. It may be several mechanisms of action, and we may spend the next several years figuring that out.

Dr. Fonseca:
Sure. So let's think about how to summarize our take-home messages today. I think (inaudible)*9:42 complications are preventable. The microvascular complications are clearly linked with hyperglycemia, and if you intensify treatment early, you can reduce or even prevent the development of microvascular complications. And macrovascular complications are a little bit more complex. They are multifactorial. We need to address the lipids and blood pressure.

But now we have glucose-lowering drugs that also decrease macrovascular complications in different ways and with different effects on outcomes, which allows us to sort of tailor therapy to the patient. We're moving more and more to what we would call precision medicine and precision treatment in the management of diabetes.

Dr. Anderson:
I absolutely agree. And everyone who sits in our exam rooms that we talk to is an individual, and we need to be thinking about all their comorbidities, what they have going on in their lives, how we're going to tailor their treatment to their individual case of diabetes.

Vivian, that's a great way to round out the discussion. I want to thank you for helping us better understand glycemic control in type 2 diabetes.

Dr. Fonseca:
Thank you for your valuable input as well, John.

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