A QUICK DOSE OF CE
DEMYSTIFYING THE EVOLVING SCIENCE AND POTENTIAL ROLE OF INCRETINS IN T2D

This podcast activity will discuss the practical application of data and frequently asked questions from the independent satellite symposium, Demystifying the Evolving Science and Potential Role of Incretins in T2D, presented at IDF World Diabetes Congress on December 6, 2022.

Moderator
Given the growing twindemic of T2D and obesity, how can clinicians overcome clinical inertia to intensify treatment earlier? Is that something that's really a problem in other countries? I mean, in America, its doctors, you have a patient at eight, and they just keep them on metformin.

Dr. Bernhard Ludvik, MD:
Yeah, it's right. Yeah, it's cheap. And you don't want to do you tell the patients just come in, come again in three months, lose weight, do exercise, and then get out of my office. And then if it really increases, then okay, now I have to do something.

Moderator
But the cost of these other drugs are huge, like they got to get something worked out, well, in America. Is it not so much…

Dr. Thomas Forst, MD
In the course of complications, it's very hard.

Dr. Ludvik
That's the problem. These are not the same payers sometimes, right? The different payers – one pays for medication, outpatient… at least in Austria, for outpatient services, and the other one for inpatient, and they don't care about inpatient because they are only a very small amount. This is why they want to push the patients out of their practices and send into the hospitals.

Dr. Forst
A lot of colleagues, I think, still believe you can manage it with lifestyle modification, if the patient already wants to. But this isn't true.

Moderator
I'm a dietitian, and we've preached lifestyle modification for years. And it's not working.

Dr. Ludvik
Yeah, we have studies showing that it's very hard to achieve in a study. But when you stop the study, exactly. It's going up.

Dr. Forst
And if you if you look one year after, more than 90% are back to their original weight.

Moderator
I know I Yeah. So, given the growing twindemic of diabetes and obesity, how do you think, Dr. Ludvik, that we can overcome the clinical inertia and intensify treatment earlier?

Dr. Ludvik
Actually, the clinical inertia is a real problem. And this has been a problem for many, many years. Many doctors still regard obesity and diabetes is only lifestyle related diseases, but there's a genetic background for obesity, for diabetes, as well. And of course, we have to focus on lifestyle changes, nutrition and exercise. But we have to acknowledge this is a chronic disease, and we need to chronic treatment. And we haven't had perfect drugs so far, leading to weight loss and improving diabetes, but also not at the extent of hyperglycemia at the cost of hyperglycemia. So, I think now we have drugs, which promote weight loss, which have excellent data on diabetes control with no risk of hyperglycemia, but we have to use them. Most of the time, we try to persuade the patient still promote dietary counseling and exercise training. But I think we're now we need to use these drugs we have now. They're very potent drugs, but they expensive of course, and we need to find a way to give those drugs to as many patients is necessary. This will be quite a challenge in the future.

Moderator
And tirzepatide, obviously is now approved in several countries. Dr. Forst, can you explain to us, I think there's a lot of confusion, how do you explain the additive or complementary effects of dual agonism?

Dr. Forst
Yes, this is a new drug, it's one peptide, which is able to address two different receptors. One is the GLP-1 receptor, the other is a GIP receptor. And this indeed has a couple of complementary or additive effects. So, you see both improve the beta cell function, both have an effect on alpha cell function. But then with GIP, you also have more effects with regard to weight reduction. And you will have, and I think this is something which really makes a difference, you have additional effects in the lipid metabolism, which are not driven by GLP-1. So, this is something unique for the GIP component in this drug. And this, from my perspective, might be something which together with all the other effects, might be able to have an effect on arteriosclerosis and thereby reducing hopefully, the cardiovascular endpoints.

Moderator
You recently just gave a talk and one of the things that I learned from you, I was surprised that GLP-1 RA has kind of maybe nausea as a side effect, but you had explained that GIP actually is antiemetic. Can you explain that?

Dr. Forst
True. That's what we have learned with GLP-1 receptor agonists is that they have discussed two interesting side effects. They have nausea, they make vomiting. And what is known from let's say, at least from experimental data from animal studies, is that GIP has antiemetic effects, so maybe this antiemetic effects of GIP antagonize some of this gastrointestinal side effects. It's not able to totally avoid. So, if you look into the clinical study program, we see that tirzepatide, the dual agonist, is much more effective with regard to glucose control with regard to weight reduction, but does not increase the gastrointestinal side effects. And this might be due to the antiemetic effect of GIP.

Moderator
That's really great. Going back, Dr. Ludvik, to talking about initiating the practical aspects of tirzepatide, how do you initiate it? How do you dose escalate? How do you manage its adverse effects? How do people really use it?

Dr. Ludvik
You can use tirzepatide in addition to existing diabetes drugs, except of DPP-4 inhibitors, this doesn't make any sense. But you can use it as monotherapy, as well, you do have up titrate it starting with 2.5 milligrams. And we have at least in Europe, three therapeutic doses, which is 5, 10, and 15-milligrams. And sometimes you might have very good efficacy with 5-milligrams and you stay on 5-milligrams when you reach the goals. And you have to have an individual goal with the patient. And I think from the studies, we see that 50% of patients will become normal glycemic, that's to

remit remission, despite having a long diabetes duration, more than eight years, and having an HbA1C you have 8.2%. So long diabetes, duration, and bad control. Still, you get remission in 50% of the patients. So, I think this is very encouraging. And if you use this drug in obese patients T2D earlier on, you probably get most of them into what we can call remission. The side effects are mainly nausea, nausea, maybe vomiting, and then you have a slow titration. They usually occur during this titration period. And of course, you can first of all have some dietary counseling. And the other possibility is to step back, you know, with the dose, but this is what we do with a GLP-1 receptor agonists for a long time.

Moderator
And I think we're looking at just diabetes patients with obesity. And what about just obesity, all these patients that maybe haven't developed diabetes yet…

Dr. Ludvik
We do have a very good SURMOUNT study now being published, but it's not licensed for obesity without diabetes so far. We expect that to happen. It's the most potent drug we have for weight loss. It's the most potent drug we have for diabetes control. It's a much more potent than basal insulin as we've seen in the SURPASS-3 study. But for obesity, it's very potent, and I think you come close to the range you see with bariatric surgery, without the side effects of bariatric surgery.

Moderator
It's interesting, you use the word remission. I know that that's kind of a controversial word. Are you able to kind of explain a little bit more about what remission is or how you see it and why it might be controversial?

Dr. Ludvik
Yeah, there's a controversy about remission because some people say if you use the term remission, you must not treat the patient anymore with some medication. So bariatric surgeons, metabolic surgeons have this term remission for many, many years, but the bypass is still in place. They're still ongoing treatment. Oncologist, rheumatologists use the term remission when patients are on treatment and have no symptoms anymore, or no recurrence of disease. I think we have some, somehow sophisticated, I would say discussion. And I think if you don't want to term it remission, let's name it normoglycemia, or let's term it therapeutic remission, which implies that you have remission with a concurrent medication. But diabetes is a chronic disease. And if you stop treatment, you will come again. Of course, it's like obesity. It's a chronic disease, it needs chronic treatment. And as we see from two years data, tirzepatide is still very efficient. During the course at least of two years, I would expect long, even longer than normal glycemia is relieving the pressure on the islet cell. And I think this is very important for long term remission in patients with diabetes.

Moderator
Did you have anything to add?

Dr. Forst
Yeah, absolutely. On this argumentation, you'll see diabetes and as you mentioned, diabetes and obesity are both chronic diseases, and we need to treat them also, if we stopped diabetes treatment, glucose levels would start to increase again. And that's the same what happens with body weight and obesity.

Moderator
So, in the 2022, consensus report, the ADA and EASD guidelines for glucose control as well as weight management, we see semaglutide and tirzepatide in there. What are some of the key data that led to it being added to the guidelines? And what are those implications for clinicians?

Dr. Ludvik
I mean, the guidance for the first time, somehow individualizing therapy based on complications like cardiovascular disease, like heart failure, kidney disease, then you should use those drugs having shown data in CVOTs, or endpoint studies such as GLP-1 receptor agonists and SGLT2 inhibitors. But if you go look specifically at the patient, that the relation between obesity, overweight and diabetes, it's much more focused on weight loss because we know from bariatric surgery, from studies with diet, that weight loss can lead to significant improvement in diabetes control up to remission or normal glycemia. And then we have two strong actors which is semaglutide, which we know which is around for some time, and now tirzepatide. But tirzepatide is much more potent than semaglutide. And I think this is the drug we use for patients who really need to lose a lot of weight in order to achieve better diabetes control.

Moderator
Okay, so opposite of that are there are patients then that shouldn't be put on those drugs to manage their diabetes?

Dr. Ludvik
I mean, basically, you can expect that everybody will lose some weight, I mean, what we see and the heavier you are, the more weight you lose. So, if you're a little bit above normal weight, then probably you won't lose as much weight. But we don't have the data yet, we have to analyze the studies, look at different categories. Who loses how much? And what about the patient with BMI of 26, 25? How much will you lose weight? I think this we need to see. But I think there are, of course, patients who are very lean, who are older, where you expect if they lose weight, they might become frail? Probably there, you need to be cautious, but the majority of patients with T2D is obese.

Moderator
Okay, any last thoughts?

Dr. Forst
Yeah, I think that's exactly, it's a reduction of obesity, we do not have a drug which have shown stronger effects on body weight, compared to tirzepatide. And obesity is not only a driver of diabetes, it's a driver of hypertension. It's a driver of lipid disorders, of inflammation and also weight disorders, right, exactly, and altogether makes the increased risk of cardiovascular complications. And we expect that the sum of all these aspects, of all this efficacy we see in these different aspects, will improve the prognosis of these patients.

Moderator
I heard one time if you treat somebody's glucose, you treat their diabetes. If you treat their weight, you're treating the whole person.

Dr. Forst
Exactly. Yeah.

Moderator
Thank you very much.