CARDIOMETABOLIC HEALTH CONGRESS

Webinar #5: Emerging Treatment Options for Long-Term Obesity Management in Patients with Type 2 Diabetes

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DR. RYAN: Hello, everybody. I'm Donna Ryan, Professor Emerita at the Pennington Biomedical Research Center in Baton Rouge, Louisiana. Welcome to the fifth in our series on optimizing long-term weight loss in patients with type 2 diabetes.

We're very lucky today to have our expert, Juan Frias. He is the medical director at Velocity Clinical Research, and he's going to be talking to us about emerging treatment options for long-term obesity management in patients with type 2 diabetes. We're in for a treat. Juan is an expert clinician. He is an expert clinical researcher. And we're going to learn a lot. Juan?

DR. FRIAS: Alright. Well, thank you, Donna. I appreciate that introduction, and hello, everyone.

What I'll be doing over the next 15 minutes or so is discussing incretin-based therapies in the management of type 2 diabetes, with an emphasis on weight loss with these agents, and also an emphasis on the newest of these agents, which is a dual-agonist of both GIP and GLP-1 receptors. This medication is called tirzepatide.

Here are my disclosures.

I'd like to start with a case. This is a very typical patient that we may see either in the primary care office, sometimes in our office as well, an endocrinology office. This is the case of Susan, who's 42 years old. She works as an executive assistant, and she's had diabetes for about four years. You can see that her blood pressure is borderline or slightly elevated at 142/88, and she is obese, with a BMI of 34.

You can see the trajectory of her weight gain. About a year ago, she weighed 90kg, and today in the office, she's at 98.2, so has gained almost 20 pounds over the past year.

Her glycemic control is quite good. About four months ago, her A1c was 7.3%. Today, it's 6.8%. In someone like Susan, we probably would like a target of less than 6.5, or at least the best control we can get without side effects. Importantly, she has normal renal function, normal fundoscopic exam, and thyroid exam as well.

With respect to her medical history, she has a very long history of being overweight and obese since childhood. She suffers from mild depression. She has chronic knee and back pain, and she has two children, both of which were born by Cesarean section. She has no known atherosclerotic cardiovascular disease.

She really does no formal exercise; although, at work she's very busy and always up and about the office. She has a relatively poor diet, and does not smoke or drink alcohol. Over the years, she's been very frustrated by multiple attempts at different diets and lifestyle interventions to lose weight, and it's been, for the most part, unsuccessful.

So, lastly, we'll look at her current medications. She's on metformin at 1000mg twice daily, an SGLT-2 inhibitor at the maximal dose. She's also taking an antidepressant, so an SSRI, and, as needed, ibuprofen for knee and back pain.

At today's visit, really, her main concern continues to be not only her current body weight, but also this progressive increase in body weight that she's had, more so recently, over the past six months to a year.

A couple of questions here, and we'll touch on these a bit later after the presentation in greater detail. What therapeutic recommendations would you make to Susan at today's visit? We have several options here: to initiate dulaglutide, so a selective GLP-1 receptor agonist at 1.5mg once weekly, then escalate to the maximal dose of 4.5mg, based on her response; oral semaglutide at 3mg once a day, escalating to the maximal dose of 14mg once daily, based on her response; semaglutide once weekly, so 0.25mg as a starting dose, and escalate to the maximal dose of 2mg once weekly; initiate tirzepatide at 2.4mg once weekly and escalate as needed to 15mg once weekly; or semaglutide for obesity at 0.25mg once weekly and escalate to the maximal dose for that medication of 2.4mg once weekly; or refer for bariatric surgical evaluation.

I think the good news is we have a lot of options. Certainly, in my day, when I was starting as an endocrinologist, cutting edge was adding MPH insulin to glyburide, and clearly, that would not give us a good weight response. But, we have a lot of options for Susan today, and we'll discuss these further through the talk and after.

Now, if we were to initiate tirzepatide, and we initiated at 2.5mg once weekly, which of the following statements is true? The tirzepatide is administered once weekly by subcutaneous injection using a single-dose, prefilled autoinjector pen with a pre-attached needle? That there are six dose strengths, 0.25, 5mg, 7.5mg, 10mg, 12.5mg and 15mg, and each of these is in 0.5cc volume. But, after four weeks at the 2.5 initiation dose, it should be increased to 5mg once weekly, and if additional glycemic control is needed, the dose can be increased in 2.5mg increments after at least four weeks on the current dose? And, the maximal dose is 15mg once weekly? Or all of the above? And, again, we'll be discussing this further as the talk moves on.

Now, if we just take a step back and look at these selective GLP-1 receptor agonists, this is a very important study. This is the SUSTAIN-7 trial, which was a direct comparison, a head-to-head trial, looking at semaglutide versus dulaglutide in patients with type 2 diabetes, who were treated with metformin. What I'm showing here is the weight-loss data. The bottom line was that semaglutide, at the previous maximal dose of 1mg, was significantly more potent, not only in improving glucose, as measured by the A1c, but also with respect to weight loss, than dulaglutide at the previous highest dose of 1.5mg.

Here, we can see some of the clinically-relevant weight-loss targets. Approximately 63% of patients with the semaglutide 1mg dose achieved body weight reduction of greater-than-or-equal-to 5%. About a quarter, a little over a quarter, 27%, achieved a body weight reduction of greater-than-or-equal-to 10%. This was greater than what was achieved with dulaglutide. In general, these are the sorts of numbers we see with 1mg of semaglutide, anywhere from 60-70% of patients achieving greater-than-or-equal-to 5% weight reduction, and between 25% and 30% greater-than-or-equal-to 10% reduction.

So, then we move on to higher doses of the selective GLP-1 receptor agonists. This was a study, AWARD-11, which looked at higher doses of dulaglutide, so beyond 1.5mg once

weekly. It looked at 3mg and 4.5mg, and there was greater improvement in A1c with these higher doses. What's shown here is greater weight loss as well. Here, seeing up to, or slight greater than, 50% of patients at the 4.5mg dose achieving greater-than-or-equal-to 5% weight reduction, and at looked like it was potentially continuing past 52 weeks.

Likewise, semaglutide has been looked at doses higher than 1mg in type 2 diabetes. Here's the 2mg dose versus the previous highest dose of 1mg. As with dulaglutide, greater A1c reduction and greater weight reduction with the higher dose, the 2mg dose, compared to the 1mg dose. Again, you can see that there does not seem to be a plateau in this case after 40weeks of therapy. These were patients on metformin, with or without a sulfonylurea.

I'll mention that in both of these studies, SUSTAIN-FORTE and also AWARD-11, which I showed previously, the tolerability of the higher doses was similar to the tolerability of the previous highest dose, which is critically important.

There are no head-to-head trials looking at these higher doses of semaglutide versus dulaglutide, so 2mg of semaglutide versus 3mg and 4.5mg of dulaglutide. But there is a recent publication which described a network meta-analysis, again this is not head-to-head, but this is looking at completed trials: in this case SUSTAIN-FORTE, which I just showed; SUSTAIN-7, which compared semaglutide to dulaglutide; and AWARD-11, which looked at higher doses of dulaglutide. The bottom line in this analysis was what was found was that semaglutide at 2mg was superior, with respect to both A1c lowering and body-weight lowering, compared to dulaglutide at 3mg and 4.5mg. Again, not a head-to-head study, though.

Moving on now, what is sort of the next advancement in incretin-based therapy? These are the so-called unimolecular multi-agonists. In this case, the one that's recently been approved is tirzepatide. Tirzepatide is multifunctional peptide. Its structure is based on the structure of the second incretin hormone, glucose-dependent, insulinotropic polypeptide, so GIP, and it's modified, though, to bind to both GIP and GLP-1 receptors. Importantly, it's got a C20 fatty diacid moiety, which binds to albumin, increasing its half-life, so it has a half-life of about five days, and this enables once-weekly dosing.

One of its key pharmacodynamic effects is enhancing the incretin effect, so enhancing glucose-stimulated insulin secretion. It enhances first- and second-phase insulin secretion, and it's also been shown to reduce glucagon levels, both in a glucose-dependent manner. And studies in patients or subjects with various degrees of renal impairment have shown that even in patients end-stage renal disease, there's no difference in the difference in the pharmacokinetics compared to patients with normal renal function.

So, if you look at the label, there's no dose adjustment that's needed for EGFR, for example, and there's no lower limit for EGFR in which it cannot be used, although we clearly always need to be more careful with patients with chronic kidney disease.

So, it is a single molecule that possesses activity at two pharmacologic targets, the GIP and the GLP-1 receptors. And, if we look at the mechanism of action, GIP and GLP-1 receptors are found on some tissues sort of commonly, if you will. So, for example, in the central

nervous system, there are GIP and GLP-1 receptors, in areas of the brain that are very important in energy regulation, so in food intake and appetite and satiety, and also energy expenditure. At the level of the eyelet of the pancreas, in the pancreatic beta cells, GIP and GLP-1, as incretins, increase glucose-dependent insulin secretion.

Interestingly, GLP-1 reduces glucagon secretion, and GIP increases glucagon secretion in a glucose-dependent manner, but tirzepatide actually reduces glucagon concentrations.

But there are some tissues, such as adipocytes, that only have GIP receptors, and GLP-1, and not GIP, delay gastric emptying. So, some of the mechanisms are additive or synergistic, and others are complementary. But the two together, you'll see, have quite impressive pharmacodynamic effects.

So, if we look at the SURPASS program, this is the phase 3 clinical development program for tirzepatide, it's important to note that it spans across the spectrum of patients with type 2 diabetes for monotherapy. So, patients only receiving tirzepatide versus placebo, which you see on the left, all the way to combination with basal insulin in patients who were failing or suboptimally controlled with basal insulin. And, also, importantly, there's an ongoing cardiovascular outcomes trial versus dulaglutide, which is expected to report out in 2024.

So, let's take a look at some of the composite data from these trials, and what was shown across these studies in SURPASS-1 versus placebo, in SURPASS-2 versus semaglutide (so the selective GLP-1 receptor agonist), in SURPASS-3 versus the basal insulin (insulin degludec), in SURPASS-4 versus the basal insulin (insulin glargine), and in SURPASS-5, as I mentioned before, in patients already on basal insulin versus placebo.

If we look at the reduction in hemoglobin A1c, we see significantly greater hemoglobin A1c reduction with the three doses of tirzepatide that were studied, 5mg, 10mg, and 15mg, compared to placebo and compared to the active comparators in SURPASS-2, 3, and 4, again including semaglutide in SURPASS-2. With respect to proportion of patients achieving targets, very impressive, patients, in general, reached A1cs on average of 6% or less, with up to 90% of patients achieving A1cs of less than 7%; and, quite impressively in some studies, close to 50%, or slightly over 50%, of patients achieving normal glycemia less than 5.7%.

If we look at weight reduction, in each of these trials the mean BMI was greater than 30. So, on average, these were obese patients, and you see weight reduction either over the 40- or 52-week duration of these studies. Dose dependent, when we look at the tirzepatide arms, from 5mg to 15mg, so greater weight reduction with the greater doses, but you can see relative reductions in body weight, in some cases up to 14%. As with A1c, always greater loss versus either placebo or the active comparators in these studies.

And, if we look at clinically-relevant weight targets, so greater-than-or-equal-to 5% weight reduction, for example, we can see that up to 80% at the highest doses, so the 15mg tirzepatide dose, achieving greater-than-or-equal-to 5% weight loss. Again, greater than what was seen with the comparators. And, even a more stringent target, greater-than-or-equal-to 10%, reached by anywhere from 40% to almost 60% of the patients, depending on

the clinical trial.

Now, I want to focus in a little more detail on the once study, SURPASS-2, that compared tirzepatide at 5mg, 10mg, and 15mg once weekly to semaglutide, so the selective GLP-1 receptor agonist. These are patients with type 2 diabetes treated with metformin, not achieving glycemic target, and they were randomized either to 5mg, 10mg, or 15mg of tirzepatide, or to 1mg of semaglutide and treated for 40 weeks.

You'll note that all of the patients randomized to tirzepatide started with 2.5mg, and then they were escalated every four weeks in 2.5mg increments until they reached the randomized dose. This the way that the label actually states that it should be dosed in practice now. So, the 5mg dose was reached after four weeks, the 10mg dose was after 12 weeks, and the 15mg after 20 weeks of dose escalation. Semaglutide was escalated as per the label. Again, metformin was continued.

The primary endpoint was a change in A1c, which is shown here. Key secondary endpoint, change in body weight.

There was significantly greater A1c reduction down to mean of 5.8% with the 15mg dose. So, with each of the three doses, though, greater A1c reduction compared with semaglutide.

And, here, we see the dose dependent weight reduction. With semaglutide, about a 6.7% relative reduction in body weight. This is comparable to what's been seen in other diabetes trials with this dose of semaglutide. And, up to 13% relative reduction in body weight with the 15mg tirzepatide dose. Here, we see the weight target achievement, greater-than-or-equal-to 5%, 10%, and 15%. So, up to 40% of patients with the 15mg tirzepatide dose achieved greater-than-or-equal-to 15% weight reduction compared to about 9% with semaglutide 1mg.

Also, throughout the studies, all of the SURPASS trials have been very favorable changes in lipid profiles, primarily reductions in triglycerides and increase in HDL cholesterol.

Lastly, one final efficacy slide, which showed a prespecified composite endpoint in SURPASS 2 looking at the proportion of patients at week 40, so at the end of the study, that achieved all three of these, an A1c less-than-or-equal-to 6.5%, greater-than-or-equal-to 10% body weight reduction, without significant hypoglycemia, and this was achieved by 60% of patients treated with the 15mg dose of tirzepatide compared to about 1 in-5, or 22%, of the patients treated with 1mg of semaglutide.

With respect to safety and tolerability, the profile for tirzepatide is very comparable to that which is seen with selective GLP-1 receptor agonists, such as semaglutide and dulaglutide, with gastrointestinal side effects being the most common.

Here, I just show one of the, or the most common, GI side effect, which was nausea. It shows here by four-week increments, the incidence by four-week increments, during the trial. What you can see here is that most of it was mild-to-moderate in severity, generally occurred during the dose escalation period, and then tended to dissipate with time. This is what we see, if we see it clinically, and most patients won't experience this, but many will, and clearly, we need to tell patients, as we do with selective GLP-1 receptor agonists, about

the potential for GI side effects. But you can notice here that it's quite comparable with respect to the incidence, tirzepatide versus semaglutide 1mg on the right.

Lastly, hypoglycemia, given the mechanism of action, one would not expect much hypoglycemia as monotherapy or in combination with agents that do not cause hypoglycemia, such as metformin or SGLT-2 inhibitors. But, if combined with a sulfonylurea or with basal insulin, it may increase hypoglycemia induced by those agents. So, we should consider proactively reducing the dose of insulin secretagogues or insulin when tirzepatide is added to those agents.

Now, there's no direct comparison. SURPASS-2 looked at tirzepatide versus 1mg of semaglutide. There's no direct comparison versus semaglutide at the 2mg dose. But, as with the study I showed previously, this is a network meta-analysis, or comparing different clinical trials, not head-to-head. In this meta-analysis, which was recently published, what was shown is that the 10mg and the 15mg doses of tirzepatide were superior to semaglutide 2mg, with respect to both hemoglobin A1c and weight reduction.

Lastly, we have data which show cardiovascular safety for tirzepatide. These are data from a pooled analysis, which is a prespecified analysis of seven clinical trials looking at MACE, or cardiovascular safety, so major adverse cardiovascular events. This was cardiovascular death, nonfatal MI, nonfatal stroke, and hospitalization from unstable angina. What was shown was a reduction in the hazard ratio with tirzepatide versus the comparators. It was not statistically significant. The study wasn't powered for that. But, certainly shows cardiovascular safety.

As I mentioned previously, there is an ongoing cardiovascular outcomes trial which should complete in 2024.

So, let's go back to Susan now. Her options were discussed, and we decided to initiate tirzepatide at 2.5mg. Potential risks and side effects were discussed. She was instructed on how to use the pen. Important, we continued metformin and her SGLT-2 inhibitor. Had she been on a sulfonylurea, we may have discontinued it or lowered the dose. With insulin, we may proactively lower the dose in her case, particularly because she had very good glycemic control already. And, she was referred to a diabetes educator and registered dietician.

Two months later, she had escalated, after a month at 2.5, to the 5mg dose. So, she was taking 5mg weekly. Her A1c had actually come down from 6.8% to 6.5%, and she'd lost already about 4.2 kilos, so close to a little over 4% body weight in this time period, no hypoglycemia, no other side effects. And her tirzepatide, at that point, was increased to 7.5mg, and a phone follow-up was scheduled in four weeks, with a return to the clinic in three months. We'll discuss her a little bit further in a bit.

Now, if we look at other development programs for tirzepatide, we talked about the SURPASS program in type 2 diabetes, there's an ongoing program specifically for obesity, and this consists right now of four studies, one in patients with type 2 diabetes, the other in patients without type 2 diabetes; there's also a phase 2 NASH trial, so looking at fatty liver disease, a trial in patients with heart failure and obesity, a trial in obstructive sleep

apnea, so a number of other programs.

I'll briefly mention the SURMOUNT 1, which was the first of the obesity studies, so this is in people without diabetes, recently was reported and published in the New England Journal. The sort of high-level findings here were very significant reductions in body weight. You can see with the 15mg dose an average of 22.5% reduction in body weight. In fact, approximately 36%-37% of the patients had greater than 25% body weight reduction, with over 90% having greater-than-or-equal-to 5%. So, very robust data, and we certainly await the results of the other trials. If we look at emerging agents, there are many agents in development for management of obesity in patients with type 2 diabetes. Oral semaglutide is being looked at in doses higher than 14mg, 25mg and 50mg. There are nonpeptidic, so small molecule GLP-1 receptor agonists, that are being assessed in type 2 diabetes and in obesity. Not only the dual agonists and there are other GIP and GLP-1 receptor agonists, and GLP-1 and glucagon receptor agonists, but also triagonists, so GIP, GLP-1, and glucagon receptor in phase 2 moving in to phase 3 as well, for obesity and type 2 diabetes. Once-weekly semaglutide, the selective GLP-1 receptor agonist, in combination with cagrilintide, which is an amylin analog, the second beta cell hormone that has effects not only on glycemia, but also central effects to improve body weight. And, lastly, once-weekly semaglutide with once-weekly GIP-receptor agonist, so two separate molecules in this case together in one formulation, again to improve both glycemia and body weight management.

And, there are multiple other agents. I think this is where we're moving, though, with respect to the management of type 2 diabetes and obesity, is hitting multiple targets, if you will, with single agents, either in combination or these unimolecular multi agonists.

In, summary, GLP-1 receptor agonists have demonstrated important characteristics beyond glucose lowering, including reduction in body weight and cardiovascular risk reduction in patients with type 2 diabetes. Higher doses of GLP-1 receptor agonists have been shown to result in greater A1c and body weight reduction, without increasing issues with safety and tolerability.

Tirzepatide is the recently-approved dual GIP and GLP-1 receptor agonist, and it's been assessed across the spectrum of type 2 diabetes for monotherapy to combination with basal insulin, and has been shown to provide superior glucose and body weight control compared to selective GLP-1 receptor agonists and basal insulin. And there are several other agents that I just reviewed that are in clinical development, some starting late-phase clinical development, that I think may be available to us in several years, as we sort of progress in this journey, if you will, to manage a critically-important component of type 2 diabetes, which is overweight and obesity.

With that, I'll conclude, and thank you, and turn it back over to Donna.

DR. RYAN: Wow, that was fantastic. Thank you so much. Let's go back to your first question, where you showed all of the different options for treating this patient.

Recently, in the 2022 ADA Standards of Medical Care, for patients in whom weight loss is important, for the first time, these GLP-1 receptor agonists have been given a preferred status. So, you laid out all of the different options, and you even included bariatric surgery.

How do you go about identifying the best treatment for the patient? Does every patient get the medication that has the most robust weight-loss efficacy, tirzepatide?

DR. FRIAS: Yes, that's a great question. It depends. As you know well, oftentimes, it's not the patient or me necessarily deciding. It's the insurance companies. So, cost and access are critically important. There are some patients who, no matter how much explain that this is not insulin, that they may not even see the needle with the pen device, they absolutely refuse injectable, so they may be better off with an oral agent.

But, I would say, in general, if, as with Susan's case, weight was really her biggest concern, I would go with the agent which has been shown to produce the greatest amount of weight loss. So, I would say, no. It's not always based solely on efficacy, but all else being equal, and if there's not an issue with in injection, I think I might as well give her what has been proven to be most potent.

DR. RYAN: And she really is a great candidate. She's younger. She's not quite midlife yet. But, she has a lot of reasons to get her diabetes under better control now, and hopefully, to move back maybe even in to normal glycemia, if she can get enough weight loss.

But, not every candidate, not every patient is a candidate for intensive weight-loss efforts. What about older patients and patients who have more severe disease? Who is not a candidate for this weight loss approach?

DR. FRIAS: I would agree. She is the perfect candidate for sort of "more aggressive" therapy early. As you mentioned, she's got the knee pain, she's got the underlying depression. She's been very frustrated. To this point, she really hasn't had anything sort of at her disposal that can lead to the kind of weight loss that's needed.

But, yes, in an older patient, who might be frail as well, whose life expectancy may not be as long, for example, who may have some renal dysfunction, I think we need to clearly be more careful. These patients may not be looking for a lot of weight loss. But, at the very least, as we manage their glucose, we should avoid weight gain in a lot of these patients. And, some would definitely benefit from either modest or moderate weight reduction. So, I think what's important here is that we do have, with any of these agents, a variety of doses. So, it's not getting everyone to the maximal dose. There are patients who are going to do very well, for example with tirzepatide at 5mg, maybe with semaglutide at 0.5mg, and that may be good enough.

I think it speaks to the important of setting some targets, and then escalating as you go along. That's why that question said we'll escalate as needed. If we get to the goal with a lower dose, let's continue the lower dose, is my philosophy.

DR. RYAN: Historically, our targets have been A1c. Now, we're setting weight targets. So, what sort of weight target should we set, and at what time points?

DR. FRIAS: That's another great question. There's nothing set with that. I mean just sort of philosophically, what I personally sort of generally do is—I don't set or tell the patient the final target and get too aggressive, because we don't want to frustrate the patient, and sometimes it takes some time. But I would like to get to at least 5% in two-to-three months.

This would include with pharmacotherapy, but also with behavioral interventions, with a nutritious diet, with some physical activity also. It's important that that needs to be in the equation as well.

So, I'd like to see at least 5% in 12 weeks, I would say at a minimum. I think with these medications that's generally achievable, as we've seen in the clinical trials.

But, Susan, for example, is a patient that over the long term, I mean I think she weighed close to 100 kilos, 98 if I recall. She's sort of someone that a good 20 kilo reduction probably puts her slightly, at least in the overweight category, but puts her BMI certainly below 30, and would have tremendous health benefits for her, as well.

DR. RYAN: Absolutely. So, you sort of side-stepped a lifestyle intervention that you gave Susan. You said you sent her to a certified diabetes educator who was an RD. What sort of lifestyle recommendations should we be giving when we're using any diabetic medications to assist with weight loss?

DR. FRIAS: Yes. It depends. We have a dietician, and our dietician will generally give them a 500-calorie deficit diet. It really will depend on a lot—most of my patients are Latino. Certainly, I would give a different diet to someone who had sort of different maybe ethnicity or eats different foods. I think we just need to be very cognizant of that and make sure it is a diet that fits the patient's lifestyle. I don't think it's so much about how much carb, how much fat, how much protein, as it is just the total calories, quite frankly.

So, usually, it's approximately a 500-calorie deficit diet. They'll have the patients also keep diaries. They do weigh themselves as well. So, I think that's important to keep track of their weight. Then, very typical recommendations, and again, they need to be individualized with respect to physical activity, but getting out there at least 150 minutes a week, and sometimes more, and recommendations not to sort of go hog wild all at once and to step this up slowly but surely. Again, it's going to vary depending on the patient, but at the end of the day, it's a healthy diet, some physical activity, and oftentimes, seeing someone that can help them with some of their behavioral issues, with respect to sort of maladaptive eating.

DR. RYAN: My final question, this one's about safety. In LOOK AHEAD, we had an algorithm to reduce the insulin secretagogues and insulin when we put patients in to negative energy balance. What sort of strategy do you use in the office when patients are starting on this weight loss experience? What are your guidelines around insulin and sulfonylureas?

DR. FRIAS: Yeah, that's a great question, and again, it's going to depend somewhat. My general guideline, or the guiding light, if you will, is avoid significant hypoglycemia. In someone like Susan, who started off with an A1c of 6.8%. Had she been on a sulfonylurea, I would stop it with I started tirzepatide. If you look at the clinical trials with tirzepatide, in SURPASS-2, for example, during the initial four weeks, when all of the patients on tirzepatide were on the 2.5mg dose, there was an average reduction in A1c of about 0.8% from 8.3% to 7.5%. So, even that starter dose, which is not a maintenance dose, is quite potent, and you never know how a patient's going to react at the end of the day.

But, in general, if the patient has a higher A1c, let's say higher than 8%, I would cut the

sulfonylurea in half or potentially consider stopping it. And, with the insulin, generally a reduction of 10% to maybe 20%. We can always titrate it back up. But, as I'm dose escalating the tirzepatide or the semaglutide or whatever it may be, I will go sort of either reducing or, if needed, reducing the doses of the insulin. But, I think the sulfonylureas oftentimes, quite frankly, we can just stop them.

DR. RYAN: Great. Okay, this has been wonderful. I've so enjoyed listening to you. I'm going to give you an opportunity for a final word to our attendees.

DR. FRIAS: Yes. A final word would be we really need to be paying a lot of attention to overweight and obesity in our patients with type 2 diabetes. Losing weight can make a big difference, not only in their hemoglobin A1c, so their glucose control, but many of the other complications of obesity and cardiovascular risk factors, and even 5% weight loss, if it can be maintained, can have significant effects on blood pressure, on lipids, and it is progressive. The greater the weight reduction, generally, the greater the clinical benefit to the patients. So, I think we need to be more focused on that. And, today, we have the agents to do it, so we need to consider these agents in appropriate patients.

DR. RYAN: That's wonderful. I'll add to that. My final word is that I think what weight loss does, what better weight management does, is it gives us a chance to do better chronic disease management. So, it moves patients up stream in their diabetes journey. So, it improves not just glycemia, but all of those other cardiometabolic risk factors that are associated with diabetes, and it gives us a chance to improve patients and have really long-term results.

Thank you so much, Juan. I enjoyed this immensely.

DR. FRIAS: Likewise. Thanks, Donna.