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Global Perspectives on New Data in Type 2 Diabetes — Congress-to-Clinic Insights From ADA and EASD 2025

Announcer:
Welcome to CME on ReachMD. This activity, titled "Global Perspectives on New Data in Type 2 Diabetes — Congress-to-Clinic Insights From ADA and EASD 2025" is provided by Clinical Care Options, LLC. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Abrahamson:
Now let us look at the key conference highlights. Then that will be followed by an expert panel discussion with your questions and answers.

SOUL: CV Outcomes for Oral Semaglutide in Patients With High-risk T2D and ASCVD/CKD

The first study that I want to cover with you is the SOUL study. This is a cardiovascular outcome study with oral semaglutide in patients with very high-risk type 2 diabetes and atherosclerotic cardiovascular disease or chronic kidney disease. This was an international event-driven, double-blind, placebo-controlled, randomized, superiority phase III study enrolling adults with high-risk type 2 diabetes, A1C between 6.5 and 10% and with at least 1 atherosclerotic cardiovascular disease event or hospitalization within 60 days before screening for unstable angina or TIA.

They were randomized in addition to usual therapy, to taking oral semaglutide, starting with 3 mg and then escalating the dose as tolerated to 7 and 14 mg daily for 3.5-5 years or placebo.

The primary endpoint was time to first major adverse cardiovascular event, which is a composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

There were a number of key secondary endpoints which are listed in the slide in which you can look at, at your leisure.

SOUL: Significant Reduction of MACE (Primary Endpoint) Achieved

Now let us look at the primary outcome data. This showed, in this study, a significant reduction of major adverse cardiovascular events in the people enrolled in the active drug, semaglutide. The hazard ratio being 0.86 which was statistically significant.

SOUL: Investigators' Conclusions

What did we learn? What are the conclusions from the study?

Oral semaglutide reduced major adverse cardiovascular event risk by 14% compared to placebo in patients with high-risk type 2 diabetes and atherosclerotic cardiovascular disease and/or chronic kidney disease. In addition to that, there was a 26% reduction in nonfatal myocardial infarction, which drove much of this benefit.

No significant effect on renal events, cardiovascular death, or peripheral vascular disease events. There were fewer serious adverse events with oral semaglutide vs placebo.

This study then expands our option for GLP-1 receptor agonists in terms of offering an orally administered therapy that has cardiometabolic protection for people with type 2 diabetes and at high-risk or with established cardiovascular disease.

I am going to hand it over now to Dr Ji.

ACHIEVE-1: Orforglipron in Patients With Early T2D

Dr. Ji:
Now it is my great pleasure to report to you the ACHIEVE-1 study. This was reported at the ADA meeting and just published in *The New England Journal of Medicine*.

ACHIEVE-1 study is orforglipron in patients with early type 2 diabetes. Orforglipron is an oral GLP-1 small molecular receptor agonist. In this study, the investigators want to evaluate the effectiveness and the safety of this small molecule GLP-1 receptor agonist.

Type 2 diabetes with uncontrolled HbA1c and by lifestyle modification were randomized to orforglipron 3.0 mg, 12 mg, and 36 mg and also the placebo. The treatment period is 40 weeks.

The primary endpoint is the change of HbA1c from baseline at weeks 40. There is other secondary endpoints such as HbA1c less than 6.5 and its impact on lipid profiles.

ACHIEVE-1: Orforglipron Lowers A1C (Primary Endpoint) by Almost 1.5%

For the primary endpoint, you can perceive that as compared with placebo, all 3 doses lead to very robust HbA1c reduction. For example, those 36 mg treatments were associated with 1.48% of HbA1c reduction.

ACHIEVE-1: Investigators' Conclusions

ACHIEVE-1 study significantly reduced patients' HbA1c by 1.2 to 1.5 percentage against placebo at Week 40. There was a rapid onset glycemic control, with meaningful reduction noted as early as Week 4. Weight loss was dose-dependent, ranging from 7.6% with orforglipron 36 mg vs 1.7% with placebo.

Improvement in multiple metabolic parameters, including dose-dependence, reduction of fasting serum glucose, non-HDL cholesterol and triglycerides.

Safety profile was consistent with established injectable GLP-1 receptor agonist.

Now let us switch to Professor Del Prato's presentation.

Dr. Abrahamson:
No, we are not there yet. We are going to do the QWINT and then I am going to hand back to Dr Del Prato.

Dr. Ji:
I see. Okay.

QWINT-1: Insulin Efsitora Alfa in Patients With T2D Starting Basal Insulin Therapy

Dr. Abrahamson:
The QWINT study is a study evaluating a weekly insulin efsitora alfa in patients with type 2 diabetes who were previously insulin naive. It was a multicenter, treat-to-target, open-label, randomized, phase III study that enrolled adults with type 2 diabetes whose A1Cs ranged between 7% and 10%. BMI was under 45. No prior insulin therapy, except if they perhaps had gestational diabetes, or for an acute event. And prior treatment with stable 1-3 noninsulin antidiabetic agents for at least 3 before screening.

They were randomized to insulin efsitora weekly or insulin glargine daily for a 52-week period. They used a titration regimen with fixed doses of the insulin, and I am sure that you will be able to look up the titration regimen in the actual paper.

The primary endpoint was a change in A1C, looking at a noninferiority analysis at week 52. The secondary outcomes included A1C if there were superiority, basal insulin dose, changing fasting glucose, body weight and evaluation of satisfaction with insulin, hypoglycemic events and safety.

QWINT-1: Change in A1C

What did we find? Well, the study authors found that the mean change in A1C was no different. There was non-inferiority between the weekly insulin and the daily insulin, and that both study groups dropped their A1C to just over 7%, with no statistical difference between the 2 groups.

If you look at the right-hand side of the slide, you will see patients achieving A1C targets at the end of the study. You can see that there are slightly more people achieving A1C targets at all levels of A1C in the efsitora group than in the glargine group.

QWINT-1 Investigators' Conclusions

Once-weekly efsitora was clearly noninferior to once-daily insulin in reducing A1C. The A1C improvements, as you saw, were nearly identical between both treatment groups, roughly 1.2%. The weekly insulin required lower doses actually vs insulin glargine. They actually were severe or clinically significant hypoglycemic rates that were lower with the insulin efsitora compared to glargine.

Patients treated with this weekly insulin required fewer dose adjustments, which simplified its titration regimen.

Now I will hand over to Dr Ji.

CATALYST Part 2: Mifepristone in Patients With Uncontrolled T2D and Hypercortisolism

Dr. Ji:
I am happy to introduce the CATALYST Part 2 study. It is mifepristone in patients with uncontrolled type 2 diabetes and hypercortisolism. Probably, you are aware that in CATALYST Part 1 study has shown that there is an association between uncontrolled type 2 diabetes. Patients with multiple medications with poor glycemic control was associated with hypercortisolism.

In this study, the investigators test this hypothesis that hypercortisolism is behind the poor glycemic control. Adults with type 2 diabetes and uncontrolled hypoglycemic were randomized to receiving oral mifepristone, which is a steroidal antiprogesterone drug that also have a high dose exhibit partial antagonism of corticosteroid receptor.

The patients were randomized to mifepristone 300-900 mg per day for 24 weeks comparing with placebo treatment.

The primary endpoint is also the change in HbA1c from the baseline at Week 24. The secondary endpoints include change in body weight, waist circumferences, and antihyperglycemic therapy changes.

Of course there is safety observation.

CATALYST Part 2: Change in A1C at Wk 24 (Primary Endpoint)

The study found that mifepristone treatment, as compared with the placebo, lead to a 1.47% reduction in HbA1c at Week 24, where placebo groups leads to 0.15% HbA1c reduction. A significant reduction of HbA1c was observed.

CATALYST Part 2: Investigators' Conclusions

The CATALYST Part 2 study observed a significant reduction of HbA1c from the mifepristone treatment in patients with inadequately controlled type 2 diabetes and hypercortisolism, demonstrating improved glucose control compared with placebo.

This means the benefit occurred regardless of adrenal image result, highlighting a broad relevancy across this patient population.

Anti-diabetes medications, insulin and oral agents were reduced among study subjects treated with mifepristone.

Patients treated with mifepristone also reported great weight loss and reduction in waist circumstances. Mifepristone improved lipid parameters by increased lipid blood pressure in some study participants. Adverse events were consistent with known safety profile of mifepristone.

Now let us read through Professor Del Prato. He is going to present the REDEFINE 1.

REDEFINE 1: Coadministered CagriSema in Patients With Overweight or Obesity

Dr. Del Prato:
Now 2 studies have been presented at the 2025 Scientific Session of the ADA, reporting the efficacy and safety of a combination regimen of oral cagrilintide plus semaglutide.

Semaglutide, as you know, is a powerful GLP-1 receptor agonist, and cagrilintide is a long-acting human analog of amylin, a peptide co-secreted with insulin from the beta cells in the pancreas.

The first trial is REDEFINE-1, a phase III, randomized, double-blind, placebo-controlled trial carried out in a total of 3,500 adults with overweight and/or obesity without diabetes.

Participants were randomized to a 68-week treatment with CagriSema 2.5 mg each, semaglutide alone 2.5 mg, cagrilintide 2.4 mg, and placebo.

The coprimary endpoints included the change in total body weight from baseline, and the percentage of patients with 5 or more body weight loss at the end of the study. The trial also was complemented with several secondary endpoints, as listed here.

REDEFINE 1: Change in Body Weight and Those Achieving ≥5% Weight Loss (Coprimary Endpoints)

Here are the main results of the trial. CagriSema led to a prompt and progressive body weight loss that was greater as compared to either semaglutide or CagriSema alone. And of course, greater than placebo. At the end of the study, CagriSema elicited a 13.7 body weight reduction, whereas only a 3.4% loss was obtained in the placebo treated participants.

On the left-hand side is reported the average percentage body weight reduction in the 4 arms of the study. At the end of the study, the average body weight reduction was 20% with CagriSema, 15% with semaglutide, 12% with cagrilintide, and 3% with placebo.

Included in the coprimary endpoint was the percentage of people achieving at least 5% body weight reduction, and it was apparent that more than 90% of the participants treated with CagriSema achieved such a target, compared with no more than 31% on placebo.

REDEFINE 1: Investigators' Conclusions

The conclusions presented were:

- CagriSema produced a minus 20.4% mean weight loss over 60 weeks of treatment, which was significantly greater than placebo, which only accounted for 3% body weight loss;
- CagriSema enabled more patients to reach higher weight loss thresholds. 54% achieved more than 20%, 34.7% achieved 25% or more, and 19.3% achieved 30% or more. All statistically significant as compared to placebo;
- The weight loss reported in REDEFINE-1 with coadministration of CagriSema is comparable or, if not greater, than what has been obtained with the top anti-obesity medications;
- Further improvements in metabolic health, including waist circumference, systolic blood pressure, lipid profile, and physical function scores favoring CagriSema vs placebo were reported;
- Finally, CagriSema was generally well tolerated, with mild to moderate GI-related adverse events reported and the discontinuation from the study due to the adverse report, which accounted for no more than 6%.

REDEFINE 2: Coadministered CagriSema in Patients With T2D and Overweight or Obesity

REDEFINE-2 is the other trial that was reported at Scientific Session of the ADA last June. This too is a multicenter, double-blind, placebo-controlled, phase III 2:1 randomized trial assessing the efficacy and safety of 60-week CagriSema 2.4 mg each or placebo treatment in 1,200 adults with type 2 diabetes at this time with overweight or obesity.

Here too, the coprimary endpoints included the change in total body weight from baseline and the percentage of patients with a 5% or more body weight loss reduction at Week 68, along with several secondary endpoints as listed here.

REDEFINE 2: Change in Body Weight and Those Achieving ≥5% Weight Loss (Primary Endpoint)

Now let us take a look at the main results. CagriSema led to a prompt and progressive body weight loss, resulting in a 14% reduction at the end of the study, compared to 3.4% with placebo.

At Week 68, more than 80% of patients treated with CagriSema achieved a weight loss of 5% or more, with 66% and 44% achieving a weight loss of 10% or more and 15% or more, respectively. Of even greater interest, 23% as compared to 0.5% with placebo, achieved a staggering body weight reduction of more than 20%.

REDEFINE 2: Investigators' Conclusions

The investigators then concluded that CagriSema produced substantially greater weight loss than placebo in people with type 2 diabetes and overweight or obesity. A significant higher proportion of patients achieved 5% or more weight loss with CagriSema vs placebo, and a higher proportion of participants achieved more than 10%, 15%, and 20% or more as compared to placebo.

Glycemic control also improved in these type 2 diabetic individuals with obesity or overweight, with 74% of the participants with CagriSema treatment achieving an A1C less than 6.5% vs 16% in the placebo group.

The cardiometabolic parameters like waist circumference, systolic blood pressure, and lipid showed favorable changes with CagriSema treatment. The coadministration of CagriSema was generally well tolerated, with mostly mild to moderate GI-related adverse events reported.

The result of these 2 trials then suggests that CagriSema is a potential additional therapeutic option in people with obesity, with and

without type 2 diabetes.

Key Conference Highlights and Expert Panel Discussion EASD 2025

Now let us move to what has been reported at the most recent annual meeting of the EASD that has been held in Vienna just a couple of weeks ago.

SURPASS-CVOT: Tirzepatide vs Dulaglutide in Patients With T2D and Established ASCVD

In Vienna, at the Annual Meeting of EASD, the largest conference hall filled up at 7:15 in the morning for the presentation of the results of the SURPASS-CVOT trial. This is an international event-driven, double-blind, active-controlled, randomized phase III trial assessing the cardiorenal effect of tirzepatide vs dulaglutide, a GLP-1 receptor agonist with proven cardiovascular protection in more than 13,000 participants with type 2 diabetes and established cardiovascular disease.

Let me emphasize that this is the first head-to-head comparison in the now long history of cardiovascular outcome trial in people with type 2 diabetes.

The primary endpoint was non-inferiority of tirzepatide vs dulaglutide for time to first 3-point MACE: the typical cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Key secondary endpoints included time to all-cause death, cardiovascular death, first myocardial infarction, or first stroke, MACE-4 that is not the typical 3 plus revascularization, change in A1C, body weight, albumin excretion rate, lipids, GFR, and safety profile.

SURPASS-CVOT: Time to First MACE (Primary Endpoint)

Here is the main endpoint. Tirzepatide met the primary endpoint showing non-inferiority vs dulaglutide with a nominal risk reduction of 8% at 3 years and an upper 95% interval confidence boundary of 1.1.

SURPASS-CVOT: Investigators' Conclusions

Here is the summary of the many results of the study as reported by the investigators in their presentation. The investigators concluded that tirzepatide is:

- Not inferior to dulaglutide for MACE;
- Superior vs a putative placebo;
- Reduces all-cause mortality by 16%;
- Reduces MACE-4 by 12%;
- Superior as compared to dulaglutide, as far as A1C reduction and body weight reduction are concerned;
- Reduces the risk of a composite renal endpoint, including persistent microalbuminuria, persistent reduction greater than 50% in GFR, end stage kidney disease, death from kidney disease by 19% overall, and by only 22% in high-risk cardiovascular subgroup as defined by the KDIGO classification.

The authors concluded that tetrapeptide offers a new potential opportunity for really protecting and preserving cardiovascular risk and renal risk in people with type 2 diabetes.

SURPASS-PEDS: Tirzepatide in Patients With Inadequately Controlled Youth-Onset T2D

Dr. Ji:
Here I am reporting to you another important study reported during the EASD, which is SURPASS-PEDS. It is tirzepatide in patients with inadequately controlled youth-onset type 2 diabetes.

You all know that youth-onset type 2 diabetes, as compared with adult-onset diabetes, is more progressive, and also is very hard to control in the previous clinical trials.

This study evaluated the efficacy and safety of tirzepatide in this population. Patients 10 to 18 years of age with type 2 diabetes, inadequate control with metformin, with or without basal insulin were randomized to tirzepatide 5 mg group, 10 mg group, and placebo group. The study duration is 24 weeks.

The primary endpoint is change in HbA1C for pooled tirzepatide dose against placebo at Week 30. There is array of key secondary endpoints including the change in A1C, body weight, lipid, and fasting glucose levels.

SURPASS-PEDS: Change in A1C Over Time

As for the change in A1C, the primary endpoint shows tirzepatide 5 mg group, tirzepatide 10 mg groups, and also pooled tirzepatide treatment group as compared with placebo, all lead to significant HbA1C reduction. As you can see, the placebo group actually increased the HbA1c, whereas different dose of tirzepatide group lead to HbA1c reduction beyond the 2%.

SURPASS-PEDS: Investigators' Conclusions

The investigator concluded that tirzepatide achieved a superior reduction in A1C, BMI and fasting serum glucose against placebo in pediatrics with youth-onset type 2 diabetes, inadequately controlled with metformin with or without basal insulin treatment.

There was an observation of greatest reduction seen with tirzepatide 10 mg group. A high proportion from 71% to 86% of study participants achieved A1C of less than 6.5% against 28% in placebo arm at Week 30, highlighting tirzepatide's strong glycemic efficacy. There was also benefit sustained through 52 weeks supporting its long term use.

Safety profile was consistent with the previous studies, mostly GI-related adverse effect of mild to moderate severity.

Investigators concluded that tirzepatide could become a valuable treatment option for pediatrics and adolescents with inadequately controlled youth-onset type 2 diabetes. This is a population with limited treatment options.

TIRTLE1: Tirzepatide in Patients With Type 1 Diabetes

Dr. Abrahamson:
Okay. This is an interesting study presented at EASD called the TIRTLE1. This was the use of tirzepatide in people with type 1 diabetes. It was a single-center, double-blind, placebo-controlled, randomized phase II study, enrolling adults with type 1 diabetes A1C around 7.3% for at least 2 years, who had a BMI of above 30, ages 18 to 60, and who could be treated with either multiple injection regimen therapy or an insulin pump.

The primary endpoint was change in body weight, and the key secondary endpoints included change in insulin dose, change in A1C, change in diet and body composition.

TIRTLE1: Key Efficacy Outcomes

The key outcomes here showed a mean weight loss vs placebo of 8.8%, which was about just under 9 kg. 82% of the weight loss was found to be due to a decrease in fat mass rather than muscle mass. In these people, randomized to tirzepatide, daily insulin requirements dropped by 35% compared to placebo, and most of these reductions were seen early amongst those using insulin pumps.

In addition to that, the secondary endpoint of A1C showed a modest improvement of 0.35% reduction in people taking tirzepatide compared to the placebo.

TIRTLE1: Investigators' Conclusions

The conclusions were this. Tirzepatide showed significant weight loss in people with type 1 diabetes. Modest A1C improvement. There was a notable reduction in insulin requirements in people taking tirzepatide, 25% reduction in basal and an almost 50% reduction in their bolus insulin.

The A1C and time-in-range showed modest improvements. Most of the weight loss was due to fat loss, not lean muscle mass. There were no severe hypoglycemic or ketoacidotic events reported, suggesting that this drug in people with type 1 diabetes has an acceptable safety profile, at least in the short term.

Patients reported improvement in treatment satisfaction, less fatigue, decreased emotional stress when using the tirzepatide.

The conclusion of the investigators is that this medication represents a promising new territory in treating people with type 1 diabetes. But future studies are, in actual fact, still needed. Very small, single-center study.

Posttest 1

Now let us move on to post-test questions. These questions were given to you at the beginning. Now we are doing it at the end.

62-year-old patient with type 2 diabetes, A1C 8.6%, obesity BMI 38. History of atherosclerotic cardiovascular disease. Currently taking metformin and oral semaglutide. He is concerned about being able to keep up with daily injections. Based on recent data, which emerging therapeutic option would be most beneficial for this patient?

A. Add efsitora alfa to improve A1C without daily injections;
B. Add insulin glargine to improve A1C and reduce long-term beta-cell decline;

C. Change metformin to mifepristone to reduce A1C and weight; and
D. Change the oral semaglutide to an injectable semaglutide to improve adherence and reduce cardiovascular risk.

Please answer the question. I am going to ask our coordinators, who have done an amazing job with the technology in the back end or from Clinical Care Options, to show the results when they are available.

We have a balance between efsitora alfa and oral semaglutide. Actually, more of you have answered efsitora alfa than you did in the beginning. I am going to show the rationale for this.

Posttest 1: Rationale

The answer actually is A. Remember, oral semaglutide has got cardiovascular benefit. Changing to injectable would not necessarily improve cardiovascular outcomes. But in the QWINT study, once-weekly insulin, it was non-inferior to once-daily insulin in significantly reducing A1C.

We would not use mifepristone as this patient has not been diagnosed with hypercortisolism, so we do not want to just randomly put people on mifepristone. As I said, oral semaglutide now has shown major adverse cardiovascular event benefit in people with type 2 diabetes and atherosclerotic cardiovascular disease.

The answer here was A, and more of you got it right after the presentation than before the presentation. Let us go on to the next 1.

Posttest 2

In the recent REDEFINE trials, cagrilintide and semaglutide, which we will call CagriSema, demonstrated which of the following cardiometabolic outcomes?

A. Reduced weight in people with type 2 diabetes and obesity compared with semaglutide;
B. Reduced weight in patients with overweight or obesity compared with semaglutide;
C. Reduced the risk of MACE in people with type 2 diabetes and obesity compared with placebo; and
D. Reduced the risk of worsening CKD in people with type 2 diabetes and obesity compared with placebo.

Let us see how you answered this question. More of you are answering MACE here and less of you are answering the number 1 option. More of you in the previous pre-test answered the right number 2.

Posttest 2:Rationale

Number 2 is the right answer. Let me explain why. In REDEFINE-1, CagriSema reduced weight in people with overweight obesity compared to semaglutide alone, or cagrilintide alone or placebo. But in the REDEFINE-2 study, CagriSema was compared to placebo, so we cannot talk about it being as comparing it to semaglutide in people with type 2.

REDEFINE-2 was people with type 2 and/or obesity overweight. REDEFINE-1 was people with obesity or overweight alone. There is no cardiovascular outcome study yet with CagriSema. So C is wrong. There is no cardiorenal outcomes in people with type 2 diabetes and CagriSema at this point in time. The correct answer here is number 1.

Let us move on to the next question.

Posttest 3

This is a person with type 2 diabetes, A1C 7.9%, obesity BMI 42, atherosclerotic cardiovascular disease who is taking metformin and sitagliptin. The patient wants to focus on weight loss. Based on recent data, which emerging therapeutic option would likely be most beneficial for this patient?

A. Add empagliflozin to promote weight loss and cardiometabolic benefit;
B. Change sitagliptin to orforglipron to reduce A1C weight and cardiovascular risk;
C. Change sitagliptin to tirzepatide to reduce A1C weight and cardiovascular risk; or
D. Focus on tight A1C control first by adding efsitora alfa, the weekly insulin to the regimen.

What would you do here? When we have enough votes, let us see the result. Most of you got this right. Two thirds of you got it right the first time round. I think a little bit more than two thirds of you got it right the second time round.

Posttests 3: Rationale

The answer is C. Let me explain why it is C. In the SURPASS study cardiovascular outcome trial, which Dr Del Prato presented, tirzepatide was non-inferior to dulaglutide, which we know has cardiovascular benefit for reducing major adverse cardiovascular events and all-cause mortality. In terms of glycemic and weight outcomes, we know that in this study and in another study, tirzepatide is better than dulaglutide.

In the ACHIEVE-1 study, orforglipron did reduce weight and A1C, but we do not yet have cardiovascular outcomes data for this small molecule GLP-1 receptor agonist. Empagliflozin does improve cardiovascular outcomes, but is certainly not as beneficial for weight loss as the GLP-1 or incretin-based therapies.

Finally, if we add a basal insulin to this regimen, we might get A1C benefit. But there is certainly no benefit in terms of weight and cardiovascular risk. So the answer is C.

Posttest 4

Finally, after this program, I am familiar with data from the ADA and EASD of 2025, and I plan to translate these data into current or future strategies in my practice. Do you:

A. Strongly disagree;
B. Disagree;
C. Neither agree nor disagree;
D. Agree; or
E. Strongly agree with this statement.

What is the answer here? Well, we have an overwhelming majority of people who either agree or strongly agree with the statement. I certainly hope that presentation of these important clinical trials will translate to improving the outcomes of our patients with diabetes around the world.

Q&A

Now, let us move on to the question and answer session. You can ask questions in the Q&A block at the bottom of the page. I will read the first questions, Linong, if that is okay with you.

Dr. Ji:
Yes.

Dr. Abrahamson:
Let us see what we say. The question here was what new evidence was presented regarding cardiovascular outcomes with the latest GLP-1 receptor agonists or SGLT2 inhibitors? How does this data refine our patient selection criteria?

Dr. Ji:
Yes, this is actually, as Professor Del Prato reported, coming from the SURPASS-CVOT trial. Because the dulaglutide was shown to be heart protective in the previous studies. In this study, they used a positive control to measure the impact from tirzepatide to the cardiovascular outcomes.

Non-inferiority was achieved, but there was an observation that the mortality in the tirzepatide group was [inaudible] as compared with patient.

Dr. Abrahamson:
I think that is the answer. We have got a new drug, tirzepatide. We also have a new oral GLP-1, semaglutide.

Dr. Ji:
As you pointed from that SOUL study, it shows that the oral semaglutide also is heart protective from the SOUL study.

Dr. Abrahamson:
Yes. Right. I am trying to get more Q&A here. Tirzepatide was noninferior to dulaglutide on MACE, but lowered all-cause mortality. How do we interpret that?

Dr. Ji:
Yes. The detailed study results is going to publish soon. But from this report, at the Congress, the 1 observation in tirzepatide treatment group is that the infection was reduced. Probably also the mortality due to the infection were reduced more in the tirzepatide group. Probably 1 of reasons for reduced mortality observed in tirzepatide group.

Dr. Abrahamson:
Right. I am not sure if we know exactly why there is reduced mortality, but I think the conclusion that we can draw from this study is that this drug, in terms of some of the secondary endpoints, even more effective than dulaglutide, which we know has key cardiovascular benefit. What the mechanism is behind that? Could it be the dual incretin effect of this drug? One does not know. But it is certainly very powerful data.

What role could tirzepatide play in adolescents already on metformin and insulin?

Dr. Ji:
Yes. I had alluded in the previous study in this population, both natural history study and also the treatment study showed that the type 2 diabetes in adolescent and youth are more progressive than type 2 diabetes in adult. Metformin in combination with TZDs are not very effective in control of glucose levels, especially in the long term.

I think this new study with tirzepatide really showing a promising drug for treating type 2 diabetes in this population. We can observe a very robust HbA1c reduction. It is almost like 2%. Also it is sustained until the end of the study. That made a new tool for the physicians[?] to manage this more difficult group of type 2 diabetes.

Dr. Abrahamson:
Yes, I agree. I mean, I think that if we can get approval for these drugs in people with type 2, the youth type 2, we have potentially got a game changer here in terms of A1C reduction and weight loss.

Dr. Ji:
Yes. Also this is a weekly treatment. Previously like liraglutide also showed efficacy in body weight reduction, so is true for semaglutide. But that study from GLP-1 groups has shown to bring such a robust HbA1c reduction. This is something, as you said, practice changing.

Dr. Abrahamson:
Right. To the audience, please feel free to ask questions. There is still time. There is a question here about the tirzepatide in type 1 diabetes. Are we concerned from a safety point of view about the reduction in insulin dose?

I am not concerned. I mean, they looked at all safety parameters. There is no increased risk of ketoacidosis. This is not the same as using SGLT2 inhibitors in type 1 diabetes. That is a different story. SGLT2 inhibitor use is associated with an increased risk of ketoacidosis. These drugs work differently from SGLT2 inhibitors, and I think the weight loss and the fact that there may be having other effects like reduction of glucagon, may also be playing a role in reducing insulin requirements without increasing risk of hyperglycemia.

Linong, are you concerned?

Dr. Ji:
Yes. No. As you said, mechanistically it is very different because SGLT2 inhibitor actually increase glucagon concentration, which might increase risk of ketone body production and then ketoacidosis. Actually, GLP-1 based therapy can suppress glucagon production. That might very different from SGLT2 treatment.

Dr. Abrahamson:
How do we decide between an oral and an injectable GLP-1 in our patients? Do you want to take a stab at that first?

Dr. Ji:
Yes. I think that definitely depends on patients' preference. I have patients that really like the orals because they do not want to start with injections. They always want to test oral, and reverses this. Oral semaglutide was also shown very effective in glucose control and body weight reduction.

Also, as we had discussed in this webinar, in SOUL trials, oral semaglutide was shown to be heart protective in the SOUL study. But it is a small molecule GLP-1 receptor agonist. Often, how its impact on cardiovascular outcomes are still testing. The clinical trial is now ongoing, as you said.

Dr. Abrahamson:
The other interesting thing with orforglipron is that it does not have to be taken in a specific way, like, oral semaglutide.

Dr. Ji:
Yes.

Dr. Abrahamson:
With oral semaglutide, you have to take it first thing in the morning on an empty stomach with 4 ounces of water. You cannot have

anything else to eat or drink for at least 30 minutes. No other medications. If you are on levothyroxine, you have to figure out when else you are going to take levothyroxine because you cannot take the 2 together.

With orforglipron, it is going to be easier to take an oral medication because it can be taken with or without food any time of the day. Having said that, I think at the end of the day it is a patient preference situation, does somebody want to take an oral med or does somebody willing to take a weekly injection?

Then soon we are going to have an option of a monthly injection potentially. We are going to have lots of options for patients.

The CagriSema study. Are we concerned about the amount of weight loss with some of these drugs? Too much weight loss, side effect profile. Does that worry anyone about excessive weight loss?

Dr. Ji:
Yes, I think it is all about individualized treatment. Now we have a more efficacious drug for weight reduction as compared with GLP-1 based therapies. We provide more tools for our clinicians, as well as people with obesity to individualize treatment. In our clinical practice, people have different response to the different treatment.

For example, if patients who are treated with GLP-1 single receptor antagonist, they might lose like 30% of body weight. They do not need, like a dual agonist or triple agonist. It is all individualized choice.

Dr. Abrahamson:
That actually brings up an interesting question because do we have any data. There is a question here about the efficacy of tirzepatide. I think this applies to all of these drugs in different ethnic groups. For example, Asian Caucasian. Is there a difference in efficacy?

Dr. Ji:
Yes. Actually, semaglutide, tirzepatide and other GLP-1 based therapies were all tested in a Caucasian population and Asian population. They have very similar efficacy for the body weight reduction, but also for glucose control. I think there is no big inter-ethnical differences. The differences are much less than the difference among the same ethnic groups.

Dr. Abrahamson:
Then last question, which we did not cover today about CGM integration with closed loop systems that have implications for type 2 diabetes. That is beyond the purview of this presentation. But I think there is ongoing work looking at a more fully automated artificial pancreas using dual-insulin glucagon in type 1 diabetes.

I think that there is a study that has been recently published in *The New England Journal* showing the benefit of the hybrid closed loop pumps in people with type 2 diabetes. I would say stay tuned to see if there is anything more in that arena at future meetings.

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