

# DEMYSTIFYING THE EVOLVING SCIENCE AND POTENTIAL ROLE OF INCRETINS IN T2D

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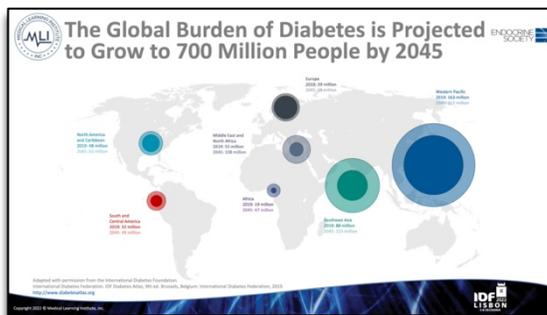


## ADDRESSING UNMET NEEDS IN T2D BERNHARD LUDVIK, MD



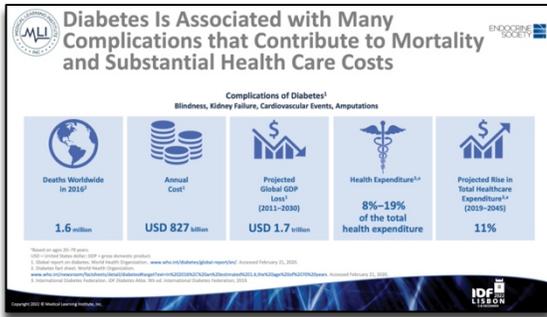
So now I will start with my talk about Demystifying the Evolving Science and Potential Role of Incretins in Type 2 Diabetes.

My name is Bernhard Ludvik. I'm an Associate Professor of Medicine and the Head of the 1st Medical Department at the Landstrasse Clinic in Vienna, Austria.



## The Global Burden of Diabetes is Projected to Grow to 700 Million People by 2045

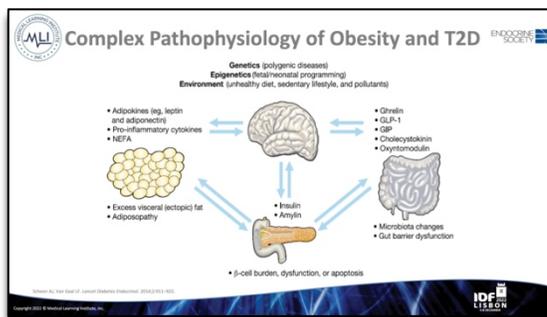
Here we can see the global burden of diabetes. And this is projected to grow to 700 million people by 2045, and you can see the geographical distribution. And you see at the southeastern region in Asia, Arab countries, you see a significant drop. This, of course, will cause burden to the individual being affected by diabetes and its complications and, of course, to the economy.



## Diabetes is Associated with many Complications that Contribute to Mortality and Substantial Health Care Costs

So diabetes is associated with many complications that contribute to mortality and, of course, to substantial healthcare costs. And if we take a close look at data being published, you can see it's responsible for really an increase in worldwide deaths. Of course, this corresponds to an increase in costs and this is a tremendous number. It's \$827 billion dollars. This is tremendous costs.

And, of course, it's a stress on the global economy of each country, and this is also something you have to take into account. And it makes up to 19% of the total healthcare expenditure, and this is a lot of money and, of course, this will affect the economy.

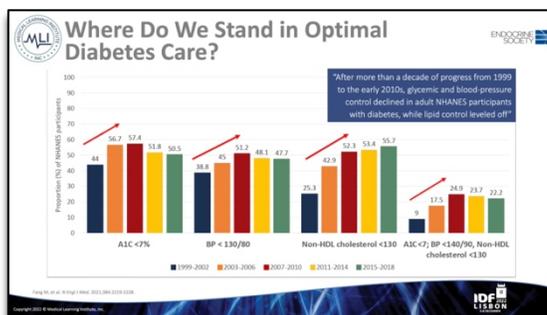


## Complex Pathophysiology of Obesity and T2D

So diabetes has a complex pathophysiology. And what you can see is, of course, we have genetics. It's a polygenetic disease type 2 diabetes. We do have epigenetics, which is neonatal programming, and, of course, we have the environment. We have the sedentary lifestyle, we have an unhealthy diet, and we have pollutants.

And then we have, of course, the adipose tissue which is expanding with obesity; and this expansion of adipose tissue leads to changes such as less secretion of adiponectin. It leads to secretion of proinflammatory adipokines or cytokines or free fatty acids. We find in those patients an excess of visceral fat. And this affects both the liver with ectopic fat accumulation and the pancreas, stressing the pancreas because of insulin resistance, the pancreas needs to secrete more insulin.

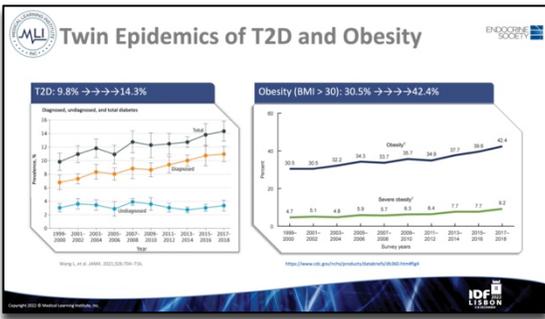
And there is an interplay between the pancreas, the gut, the brain, and the adipose tissue. What you can see here is that you have gut hormones which are affecting satiety as well as insulin and glucagon secretion. And we'll talk about two of them today. But you can see we have also microbiota changes and dysfunction of gut barrier.



## Where Do We Stand in Optimal Diabetes Care?

So where do we stand in optimal diabetes care? And you here can see the proportion of patients reaching goals such as an HbA1C below 7%, blood pressure below 130 over 80, non-HDL cholesterol less than 130, and then the composite endpoints. Between 2000 and 2020 you can see the first decade, actually, we find an improvement in achieving those goals, HbA1C, blood pressure, and lipid, and even the composite. But what you can see over the last ten years at least, you find a drop in these numbers. And this

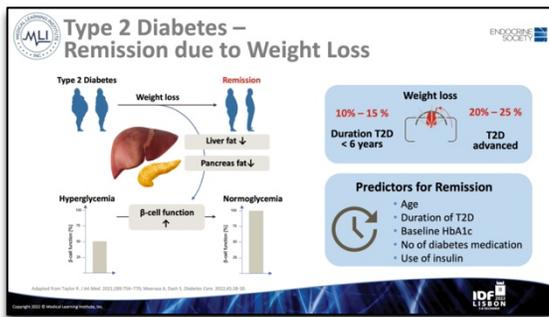
is quite astonishing because we have new drugs now, very efficient drugs despite that fact we see controls getting less good than it was before. And this is something we have really to be worried about because you see this, this decline in control.



## Twin Epidemics of T2D and Obesity

So what's the reason for that? Most probably there is a reason with a twin epidemics of type 2 diabetes and obesity. And you can see on the left type 2 diabetes and you can say, "Well those 20 years you see a significant increase of diagnosed type 2 diabetes from 9.8% of the general population to 14.3%" The number of undiagnosed diabetes is quite stable, so we probably are doing better with screening.

On the other hand, on the right side, you can see there was US data on obesity and a BMI above 30, and you can see that the prevalence increased from 30.5%, which is highly prevalent, up to 42.4%, and in the future probably the majority will be obese rather than overweight or lean.

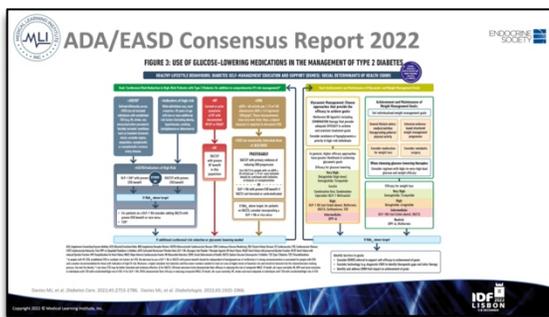


## Type 2 Diabetes – Remission due to Weight Loss

So what can we do about getting rid of diabetes? And we can call it diabetes remission. Some people don't like the term remission because we still use drugs, but if you have remission only weight loss, if it's due to weight loss, conservative without any medication, without bariatric surgery. And, of course, if you lose weight by any means, what you do is actually decrease not only your size and the adipose tissue in the abdomen but you also decrease the amount of fat in the liver and in the pancreas. By

improving insulin sensitivity, by decreasing liver fat and pancreatic fat, you're improving beta cell function and then people might turn from hyperglycemia to normoglycemia. And this is, of course, more likely in patients with a shorter duration of diabetes, less than six years, and where they need to go into remission by weight loss of between 10% and 15%. But if somebody has a more advanced stage of diabetes, they'll probably need to lose 20% to 25%.

And we do have predictors for diabetes remission. This is age, the younger the better; duration of type 2 diabetes, the shorter the better; the baseline HbA1C, of course, the lower the better; the number of diabetes medications; and, of course, the use of insulin. But I think following the next two talks you will see that diabetes remission is feasible even in patients who have longer diabetes duration and not good control.



## ADA/EASD Consensus Report 2022

So this is the new ADA/EASD Consensus Report of 2022, and it changed considerably from that of previous years. First of all, you won't see metformin as a first line anymore because it was concluded the data was not strong enough from the CVOT trial. But still is a drug which is effective, which is cheap, of course. But here the ADA/EASD stratifies patients based on the past history of complications, which is atherosclerotic cardiovascular disease, heart failure, renal failure. And I'll show you in a moment.

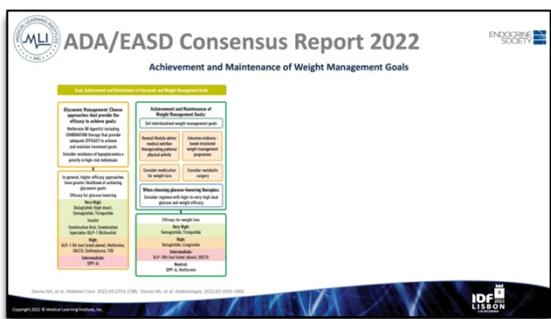
And then, of course, we have on the right side those patients who have no previous complication. They're so-called low-risk populations and they have slightly different strategy.



### ADA/EASD Consensus Report 2022

So let's go to this population which has some complications already or high risk being older than 55 years having two risk factors and then you stratify them when they have atherosclerotic cardiovascular disease. If yes, you can go for SGLT2 inhibitors, GLP-1 receptor agonists. If they have predominantly heart failure, you go for SGLT2 inhibitors. If you have renal disease, you go for SGLT2 inhibitors. If you do not reach the goal, you combine, but you combine most likely GLP-1 receptor agonists and SGLT2

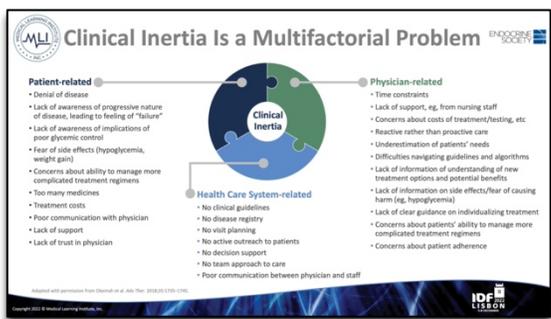
inhibitors. Of course, this is very often in most parts of the world now a matter of economy and restriction, so it's not so easy to combine these two substances at the beginning, but maybe over time this will get better.



### ADA/EASD Consensus Report 2022

If we turn to those without complications, then you can use medications which really focus on obesity because weight is a goal. And there they said what type of medication is effective in losing weight? And what you can see here, just want to draw a focus on the very strong medication for weight loss. This is semaglutide and tirzepatide and this is something we'll talk about. And I highlight this again here the high frequency of dulaglutide and liraglutide and the very high of semaglutide and tirzepatide

leading to weight loss. And as you will see today from the talks following weight loss, of course, to the improvement of diabetes control.



### Clinical Inertia is a Multifactorial Problem

So why aren't we there? We have so many drugs now, why aren't we there? Why don't we achieve the goals for HbA1C, for blood pressure, for lipids? I think this might be related to the patient, of course, to the physician, and to the healthcare system. And, of course, patients have sometimes denial of disease. They have a lack of awareness that diabetes has a progressive character unless you treat it, you hit hard and early. You will see that probably today.

Of course, they are not well educated about the consequences of bad diabetes control. They have fear of side effects – weight gain, hypoglycemia. Both we don't see with the newer drugs anymore.

They complain about too many medicines. Most of my patients complain about, "Oh, another medicine. Another one. Why do I need that?" I tell them, "Because you want you to live long and have a better quality of life." And then sometimes they say what we do is antiaging. We bring your cholesterol down to cholesterol of young people who do not have atherosclerosis. We bring your blood pressure back down to the normal values. I think you will see that during the course of the next talks, we can bring down diabetes control into normal range. And this, of course, will, translate into better, longer survival.

Of course, physicians also have time constraints. We don't have enough time to educate the patient. We sometimes do not have support from nursing staff. If you're alone in a practice, you probably don't have a dietician next to you. You don't have a diabetes educator with you.

Of course, you have some pressure of costs and you have to be very informed. If you look at those guidelines I showed you before, they're very complicated. So if you don't deal with patients with diabetes every day, as a GP for example, you have to do so many other things in addition to diabetes, treat other conditions, so you need to be informed.

And, of course, sometimes you have no real support from the healthcare system. Probably no guidelines, no disease registries. Apart from the Northern European countries, there are no registries. We don't know how many diabetic patients we have. What are their complications.

You probably have no decision support, and you have restrictions of costs for newer drugs which are more expensive.



### Social Determinants of Health

So at the end, what are the social determinants of health? There are so many we have to consider. There is, of course, access to healthcare and the quality of healthcare. Then we have neighborhood and built environment. That's very important. It's important where you grow up, your social community. And you have, of course, the economy. The economy and stability is an issue. And at the end, it's education, access, and quality. And all these determinants are important for the health of the patients.

We all have to consider these determinants when we treat our patients.

Thank you so much.

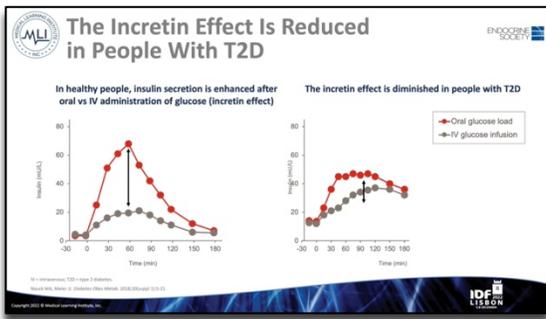
Okay, so now we move on to GIP/GLP Receptor Agonists Mode of Action. I'm very happy to welcome Professor Thomas Forst from the University of Mainz from Mannheim, Germany. Please, Thomas.

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### GIP/GLP-1 RECEPTOR AGONISTS MODE OF ACTION THOMAS FORST, MD



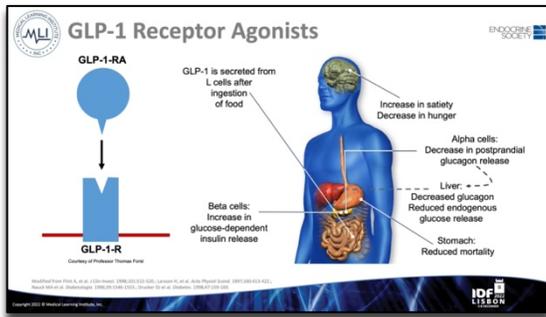
Thank you, Bernhard. Ladies and gentlemen, dear colleagues, it's a pleasure for me to be here and to speak about the incretin effects and especially about the effect of the combined GLP-1 and GIP receptor agonist.



## The Incretin Effect is Reduced in People with T2D

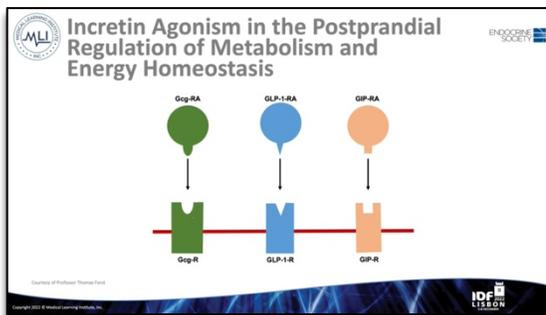
I'm sure you all have seen this picture. And this is early work on incretins, and what you can see on the left side is that after oral ingestion of a meal, you have a much greater response of the beta cell and the increase in the insulin release compared to intravenous glucose application.

And on the right side, you can see this is planted in patients with type 2 diabetes.



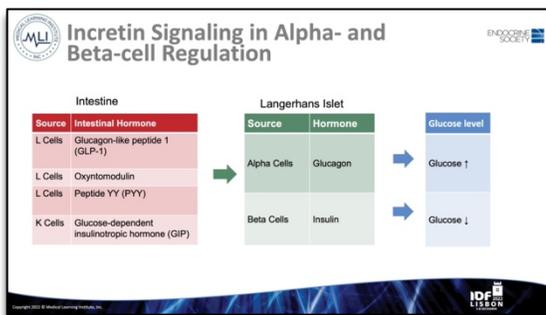
## GLP-1 Receptor Agonists

And in the recent years, we learned a lot about the GLP-1 receptor agonists, which is shown over here, and we have seen that the treatment with GLP-1 receptor agonists have very strong effects on glucose control. They are able to reduce bodyweight, and maybe the most important thing is that GLP-1 receptor agonist treatment improves the cardiovascular outcome in our patients with type 2 diabetes.



## Incretin Agonism in the Postprandial Regulation of Metabolism and Energy Homeostasis

And if we now look into these receptors, we know that the GLP-1 receptor agonist is very important in the regulation of insulin secretion keeping postprandial glucose homeostasis but also keeping the energy homeostasis. But there are other receptors when we think about metabolic control, when we think about body weight control, there are other receptors we should also address. And this is the glucagon receptor on one hand and the GIP receptor on the other end.



## Incretin Signaling in Alpha- and Beta-cell Regulation

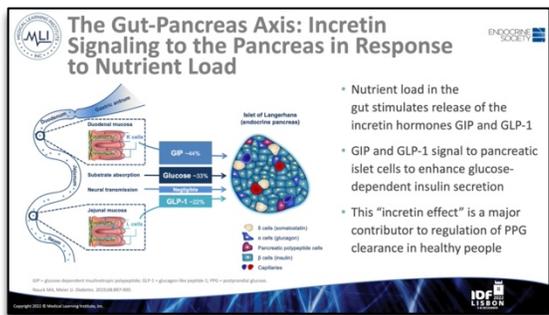
And let's look into the physiological incretin secretion from the intestine in the postprandial situation. And you see that over here. There're a couple of cells in the intestine which are able to secrete to release these incretins. And this is the L cells which are in the distal part of the small intestine and they release the well-known GLP-1. But they also release oxyntomodulin which is a peptide which is dual agonist if you like. It's an activator of the GLP-1 receptor agonist and of the glucagon receptor.

Then we have peptide YY released from the L cells. And this is another important peptide in the regulation of the energy homeostasis.

But we have also K cells which are more located in the proximal part of the small intestine and they release GIP. And GIP is another peptide which you will see is very, very important in our metabolic regulation and in our energy homeostasis.

All these so-called incretins have an effect on the Langerhans islet and have an effect on the beta cells as we have learned from GLP-1, but they have also an effect on the alpha cells which are responsible for the release of glucagon. And at the end of the day, this is then responsible for the glucose regulation as you can see over here.

But let's concentrate now a little bit more on GLP-1 and GIP because they are both secreted after a meal.



### The Gut-Pancreas Axis: Incretin Signaling to the Pancreas in Response to Nutrient Load

And you see here the effect of the GIP and GLP-1 on the beta cell activity. And what you see over here is that the GIP is responsible for more than 40% of the release of insulin from the beta cells. So GIP is a very strong stimulator of the beta cell compared to GLP-1, which is only responsible for a little bit more than 20% of the release of insulin from the beta cells.

And very interesting if you look to glucose alone, glucose without the activity of incretins only releases one-third of the insulin from the beta cell in the postprandial situation. This is a situation in a nondiabetic healthy subject what you see over here. We already have seen that this might be a little bit different in patients with type 2 diabetes where the GIP effect might be a little bit less than you see on this slide over here.

But you see if we have a meal, the nutrients stimulate the release of GLP-1 and GIP, which improves insulin release from the beta cell in a glucose-dependent manner. Both incretins improve the insulin release but, and this is really important, in a strictly glucose-dependent manner, and the incretin effect, what you have seen over here, is very, very important for postprandial glucose control. As you have seen, the incretin effect is around two-third of the insulin release after the meal.

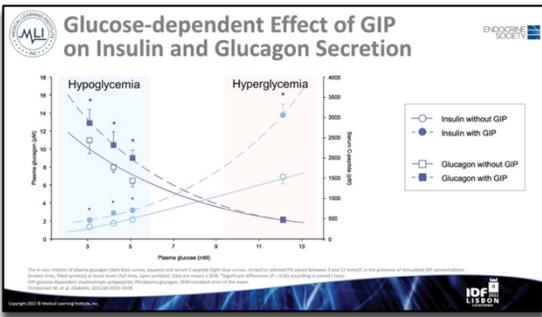
	GLP-1	GIP
<b>Islet of Langerhans</b>	<ul style="list-style-type: none"> <li>• Insulin ↑</li> <li>• Glucagon ↓ (postprandial)</li> </ul>	<ul style="list-style-type: none"> <li>• Insulin ↑</li> <li>• Glucagon ↑ (in case of low glucose)</li> </ul>

### Additive and Complementary Effects of GLP-1 and GIP

And now I want to compare what GIP is doing and what GLP-1 is doing. And we all have learned during the recent years that GLP-1 is responsible for the glucose-dependent insulin release and this lowers glucose levels. But the GLP-1 also reduces the glucagon release from the alpha cell in the postprandial situation, and there are a lot of studies which have shown that at least 50% of the improved postprandial glucose control during treatment with a GLP-1 receptor agonist is due to a reduction in the glucagon release and not an increase in the insulin release.

And on the other hand, GIP in addition to GLP-1 increases the insulin release from the beta cell, again, in a strictly glucose-dependent manner. But these are complementary effects on the beta cell.

But if you look on the glucagon release from the alpha cell, there GIP has different effect. It increases glucagon release from the alpha cell but only in the situation of low glucose levels. Again, this is an effect which is strongly glucose dependent.



### Glucose-dependent Effect of GIP on Insulin and Glucagon Secretion

And you can see that also in this study over here. And if you look on the right side, you see this is the insulin response in the case of hyperglycemia. And if you see the open circle, this is the insulin release without GIP and the dotted line is the insulin release with GIP. So there is a strong glucose-dependent effect of GIP on the insulin secretion.

But if you then go to the left side of this figure, then you see what happens with glucagon in the case of low glucose levels. And, again, you have the open circles over there. This is the glucagon release in hypoglycemia without GIP and the closed dotted line this is the effect with GIP. So you see in the case of hyperglycemia, you have an increase in insulin release due to the GIP effect, and in the case of hypoglycemia, you have an increased glucagon release from the alpha cell if you have GIP in place.

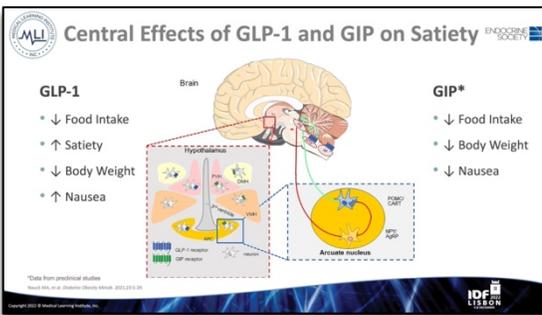
### Additive and Complementary Effects of GLP-1 and GIP

	GLP-1	GIP
Islet of Langerhans	<ul style="list-style-type: none"> <li>• Insulin ↑</li> <li>• Glucagon ↓ (postprandial)</li> </ul>	<ul style="list-style-type: none"> <li>• Insulin ↑</li> <li>• Glucagon ↑ (in case of low glucose)</li> </ul>
Central Nervous System	<ul style="list-style-type: none"> <li>• Satiety ↑</li> <li>• Nausea/Vomiting ↑</li> </ul>	<ul style="list-style-type: none"> <li>• Satiety ↑</li> <li>• Anti Emetic</li> </ul>

### Additive and Complementary Effects of GLP-1 and GIP

Looking into the effects of GLP and GIP in the central nervous system, and this is shown over here, you see both incretins, GLP-1 and GIP, increase satiety and thereby reduce food intake. But if you look on to the most common side effect of GLP-1, we know that it's gastrointestinal, it's nausea, it's vomiting.

And now if you go to the right side and look into the effect of GIP, it's antiemetic. It is exactly the opposite what is known from GLP-1 in the central nervous system.



### Central Effects of GLP-1 and GIP on Satiety

Then with GLP-1, we have the effects shown over here on certain areas in the brain where you have these satiety effects and where you have this increase in nausea. And you see GIP is working on different areas on different receptors in the brain and thereby, again, reducing food intake, increasing satiety, but, as I mentioned already, it decreases nausea. And this is known from animal experience. If this is also the case in humans and in humans with type 2 diabetes, we do not know very well. There is not much data addressing these antiemetic effects in human beings.

### Additive and Complementary Effects of GLP-1 and GIP

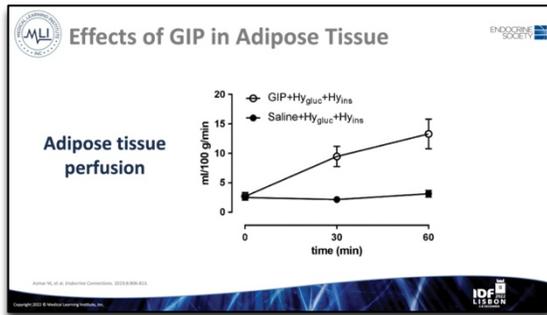
	GLP-1	GIP
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Central Nervous System	<ul style="list-style-type: none"> <li>• Satiety ↑</li> <li>• Nausea/Vomiting ↑</li> </ul>	<ul style="list-style-type: none"> <li>• Satiety ↑</li> <li>• Anti Emetic</li> </ul>
Stomach	<ul style="list-style-type: none"> <li>• Gastric Emptying ↓</li> </ul>	
Subcutaneous Fat Tissue		<ul style="list-style-type: none"> <li>• Blood Flow ↑</li> <li>• Insulin Sensitivity ↑</li> <li>• Lipid storage capacity ↑</li> <li>• Triglyceride storage capacity ↑</li> <li>• Adipo-Inflammation ↓</li> </ul>

### Additive and Complementary Effects of GLP-1 and GIP

Coming to the effect on the stomach. We know that GLP-1 receptor agonists inhibit gastric emptying. If this is also true for the long-acting ones is less clear, but we have no effect at all with GIP on gastric emptying.

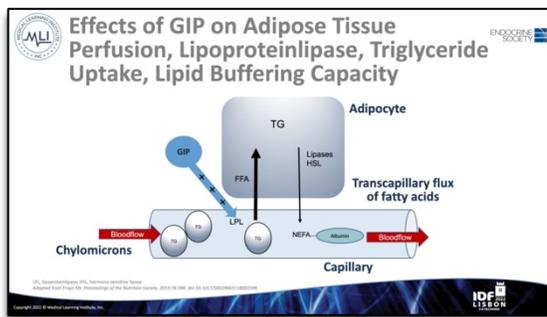
And then I come to a point which I think is very, very, very exciting. And this is shown over here. And you see that is an effect on the adipose tissue and especially on the subcutaneous white adipose tissue. And you see here that GIP has a couple of effects increasing the blood flow in the subcutaneous tissue,

increasing insulin sensitivity in the subcutaneous adipose tissue, the lipid storage capacity, and they decrease the release of these adipocytokines and of these proinflammatory mediators out of the adipose tissue. And this is specific for GIP. This effect is not found with a GLP-1 receptor agonist.



### Effects of GIP in Adipose Tissue

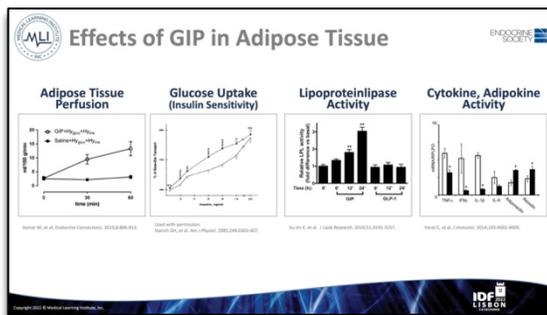
And what you see over here this is increase of tissue perfusion, adipose tissue perfusion. And at the lower end, you see this is hyperglycemia and the hyperinsulinic hyperglycemia and you see there is no effect on microvascular blood flow in the adipose tissue, but you see a clear effect if you add GIP to this experiment increasing the blood flow in the visceral adipose tissue.



### Effects of GIP on Adipose Tissue Perfusion, Lipoproteinlipase, Triglyceride Uptake, Lipid Buffering Capacity

And there's another effect in the adipose tissue which I think is very important if we talk about the GIP effects. And what you see over here, you have the bloodstream after a meal, and after a meal you have high fat content in the bloodstream. You have high chylomicrons, you have triglycerides in your bloodstream, and then you have on the endothelial surface in the adipose tissue, you have an enzyme which is a lipoprotein lipase. And this lipoprotein lipase is responsible for splitting free-fatty acids out of these triglycerides and then these these free-fatty acids flow into the adipose cells.

And this enzyme, this lipoprotein lipase is stimulated by insulin and by GIP. And thereby GIP increases the flow of free-fatty acids in the postprandial situation into the adipocytes which means it reduces the elevated triglyceride levels in the postprandial situation and it shortens the time of hyperlipidemia in the postprandial situation in patients with type 2 diabetes.



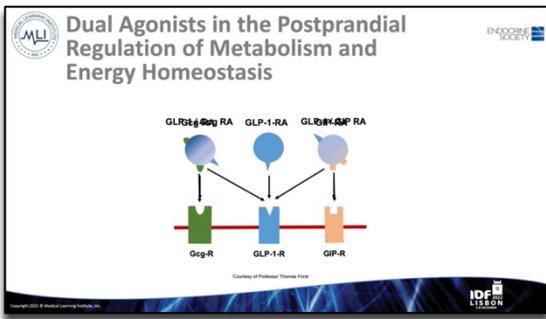
### Effects of GIP in Adipose Tissue

And you see these effects again over here. This is the effect on the adipose tissue perfusion, which I already showed you. This is insulin sensitivity in the adipocytes and, again, you see the effect of the GIP on this adipose tissue insulin sensitivity. And that's what I already showed you over here. This is this enzyme responsible for transporting the free-fatty acids from the bloodstream into the adipocytes and you see a dose-dependent effect of GIP, which is shown on the left side.

And on the right side what you see over there, this is the effect of GLP-1. And you see it's specific for GIP and there's no effect of GLP-1 at all on this enzyme which is responsible for regulating postprandial lipid excursions.

And in the last slide over here, you see the effect of GIP on the adipose cytokines released from the visceral adipose tissue or from adipose tissue at all. And you can clearly see that TNF-alpha, interferon gamma, interleukin-1 beta, and interleukin-6 all are reduced when you add GIP to this experiment.

But on the other hand, you see that these adipokines like adiponectin or resistin are increased by the activity of GIP.

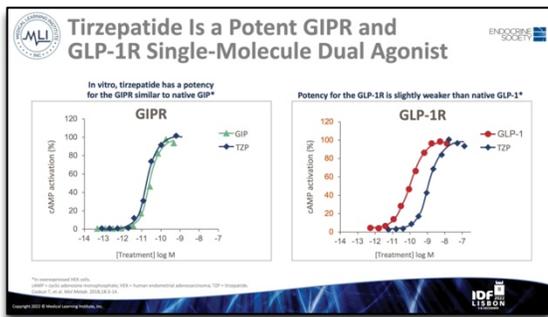


### Dual Agonists in the Postprandial Regulation of Metabolism and Energy Homeostasis

Let's now move over to the dual agonist and there are the dual agonist for glucagon and GLP-1 in place and in clinical studies, and we talk now about the GLP-1 and GIP receptor agonist tirzepatide.

### Tirzepatide is a Dual GIPR/GLP-1R Agonist

Tirzepatide is a molecule. It's a 39 amino acid peptide which is linked to a fatty acid, thereby increasing its half-life to around five days, and this makes it possible that it's injected once weekly. And very important is, the peptide sequence; tirzepatide is based on the backbone of GIP. And this GIP backbone is modified in a way that the tirzepatide is not only acting on the GIP receptor, but it's also acting on the GLP-1 receptor.



### Tirzepatide is a Potent GIPR and GLP-1R Single-Molecule Dual Agonist

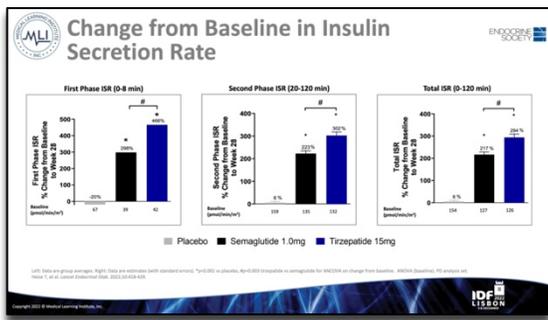
On the left side, you see tirzepatide activity on the GIP receptor compared to natural GIP. And you see it's absolutely identical. And it's not surprising because the backbone of this peptide is GIP.

But on the right side, you see the activity on the GLP-1 receptor, and you see it's much less effective on the GLP-1 receptor compared to native GLP-1. So you see it's five times more active on the GIP receptor compared to the GLP-1 receptor.

### Tirzepatide Mechanism of Action: Effects on Endocrine Function and Insulin Resistance in Patients with T2D: Study Design

And I now want to show you some data from the experimental study in patients with type 2 diabetes which were performed by Tim Heise.

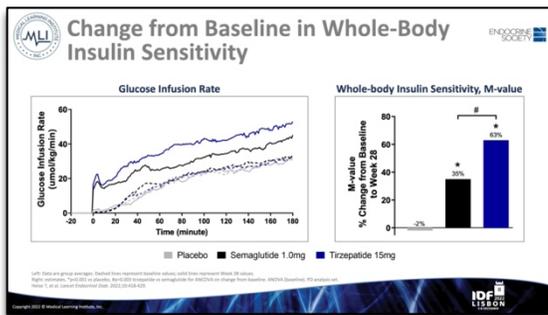




## Change from Baseline in Insulin Secretion Rate

And first you see the effect of tirzepatide compared to GLP-1 receptor agonist on beta cell function. And you see on the very left side, this is first phase insulin secretion; in the middle, you see the second phase insulin secretion; and on the right side, you see the overall secretion of insulin from the beta cells.

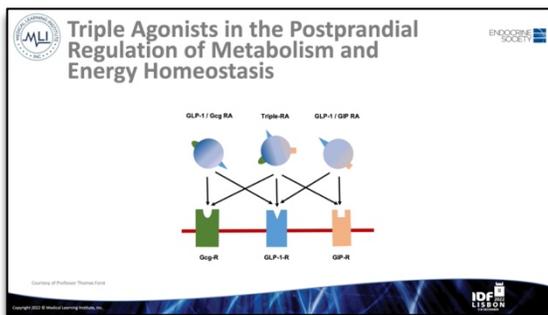
And what you can see over here is that the GLP-1 receptor agonist semaglutide has a very nice effect on insulin secretion in these type 2 diabetic patients after 28 days of treatment. But what you also can see is that the effect of tirzepatide is even much, much stronger compared to semaglutide on first phase insulin secretion, second phase insulin secretion, and overall insulin secretion.



## Change from Baseline in Whole-Body Insulin Sensitivity

And in this slide, you see the effect on insulin sensitivity. These are glucose infusion rates on the left side. And the dotted lines are before the application of the GLP-1 receptor agonist semaglutide or tirzepatide. And, again, you can see there is a nice effect of the GLP-1 receptor agonist semaglutide. You have an improvement in insulin sensitivity but, again, you see the effect is much, much stronger with the dual agonist, the GIP and GLP-1 receptor agonist tirzepatide.

And on the right side, this is the so-called M-value. It's a value which is calculated out of these glucose infusion rates and, of course, you see the same over there. Nice effect of semaglutide on insulin sensitivity, even much stronger effect of tirzepatide on this insulin sensitivity.



## Triple Agonists in the Postprandial Regulation of Metabolism and Energy Homeostasis

And this is very exciting, what we see over here, but maybe in the future it gets even more exciting when we also will see triple agonists coming up the road which are able in one molecule, in one peptide modified in a way that it's able to address all this three receptors, the glucagon receptor, the GLP-1 receptor, and the GIP receptor.

### Conclusions

- Dual GIP and GLP-1 agonism has shown several additive and complementary metabolic and pleiotropic effects
- Tirzepatide is a non-balanced GIP/GLP-1 receptor agonist with strong metabolic effects on glucose and lipid metabolism
- In patients with T2D tirzepatide has shown to improve
  - Insulin sensitivity
  - Alpha- and beta-cell response
  - Prandial glucose and lipid control

## Conclusions

So what we have with dual GIP and GLP agonism is several additive and complementary effects on metabolic systems but also on pleiotropic effects as shown over there.

With tirzepatide, we have a non-balanced peptide which addresses the GIP receptor five times more compared to the GLP-1 receptor. And we have shown that we have seen very strong effects, and Stefano will show us much more of the clinical effects of this molecule.

And in patients with type 2 diabetes, tirzepatide was shown to improve insulin sensitivity, improve alpha and beta cell function, and improve the prandial or postprandial glucose control but also, and I think this is something which makes really a difference, it also has a very strong effect in normalizing postprandial lipid control in patients with type 2 diabetes.

Thank you very much.

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## Q&A

**Dr. Ludvik:** Thank you very much Professor Forst, for this excellent presentation about the background. So we might take some questions maybe from the audience. There is one question which is very relevant when you treat patients. So "How can I explain to patients how tirzepatide works?"

**Dr. Forst:** Yeah, that's, that a good point. What we can say is that with tirzepatide, we have a peptide or a medication which is able to improve glucose control, lower bodyweight, and has strong effects in lipid metabolism. Again, this is something which I think makes a difference. Very, very strong effects on bodyweight, on energy homeostasis; and we will see the data later on from Professor Del Prato. But the next point is, and I think this makes a big difference in regards to cardiovascular risk, if we see this redistribution of lipids after a meal which I think would end up in a even stronger cardiovascular protection.

**Dr. Ludvik:** So it's, it's targeting all three effects, insulin secretion.

**Dr. Forst:** And what we didn't mention it has also effects on blood pressure.

**Dr. Ludvik:** Right.

**Dr. Forst:** So at the end, we have a treatment for all complements of the metabolic syndrome and thereby expecting that we have strong effects at the end of the day in cardiovascular risk reduction. But we have to wait until we see the CVOT trial.

**Dr. Ludvik:** Yes. It's obviously a drug which targets all three relevant mechanisms in the pathogenesis diabetes: insulin secretion, insulin sensitivity—

**Dr. Forst:** Yeah. We, we have—

**Dr. Ludvik:** -increased hepatic glucose output.

**Dr. Forst:** We have alpha/beta cell function, both are addressed; we have insulin sensitivity, which is addressed; we have a reduction in visceral adipose tissue; and we have an improvement in this diabetic dyslipidemia. So at the end, we reduce the overall atherosclerotic markers of risk predictors.

**Dr. Ludvik:** Not forget the liver. I mean—

**Dr. Forst:** Yeah.

**Dr. Ludvik:** -resolution of—



**Dr. Forst:** Right.

**Dr. Ludvik:** We probably will see that with the next talk. Is there any question in the audience?

**Professor Abdul Mannan:** Thank you. I'm Professor Abdul Mannan from Bangladesh. I have a question regarding the secretion of glucagon. You have shown there in your slide that is both a GIP effect and GLP-1 receptor effect of tirzepatide. Tirzepatide results in a glucagon effect that increases the blood sugar and GLP, GLP-1 inhibits the alpha cell to secrete that glucagon.

**Dr. Forst:** Right.

**Professor Mannan:** Then what is the effect? Is the neutralizing effect of the both?

**Dr. Forst:** That's an excellent question. To understand that you need to see that these effects are strongly glucose dependent. You see if you have high glucose levels, elevated glucose levels, then you have the effect of GLP-1 on the alpha cell decreasing the glucagon release and no effect of GIP at all. During hyperglycemia, GIP has no effect on the alpha cell.

The other way around, if you are in low glucose ranges, then you have no more effect of the GLP-1 receptor agonist but now GIP increases the glucagon release. So you see having the combination of GLP-1 and GIP, you have a reduced glucagon release in the postprandial in the hyperglycemic situation and you have an improved glucagon release in the hypoglycemic situation. That's pure benefit.

**Professor Mannan:** Thank you.

**Dr. Ludvik:** Can we say that GLP-1 sensitizes the beta cell for the action of GIP?

**Dr. Forst:** That's a good question. I don't know, but this is most probably the case.

**Professor Mustafa Yaman:** I'm from Bangladesh, and I'm Professor Mustafa Yaman. You have elaborately described the cardiovascular protections. I want to know about the pulse rate, about the bad blood pressure, lipid lowering mechanism, and ejection fraction and other things of cardiovascular protection. Have any head-to-head comparisons been done with semaglutide or other agents?

**Dr. Forst:** Yeah. That's very important.

There are some data in place, a meta-analysis and even the SURPASS-4 trial looking into high-risk cardiovascular patients. Stefano, I think you will show some of these results.

**Dr. Del Prato:** Yes.

**Professor Yaman:** Suppose in case of a heart failure patient, maybe ejection fraction 20% to 30%-

**Dr. Forst:** Yes.

**Professor Yaman:** -40%, 45%.

**Dr. Forst:** Y With regard to heart failure, I think this is, at this moment in time, clearly the area of the SGLT2 inhibitors. So the SGLT2 inhibitors have clearly shown very nice benefits in patients with heart failure. Up to

now, we have not seen this data in this range of efficacy with GLP-1 receptor agonists. And there are studies ongoing with tirzepatide in patients with heart failure, but to be very honest, I'm not sure if they will find a benefit there because we have not seen very strong effects with GLP-1 receptor agonists. And I wonder if we will see it with a GIP agonist. I think the heart failure is clearly SGLT2 inhibitors.

**Professor Yaman:** Thank you.

**Dr. Ludvik:** Okay. Thank you so much. Now we move on to the next presentation. We have some room for questions at the end of the session. And now we welcome Professor Stefano Del Prato from the University of Pisa and he's very well known to all of us not because of his excellent scientific work, but he's the current president of the EASD at least for some more weeks.

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### CLINICAL IMPLICATIONS OF A DUAL AGONIST'S EFFICACY AND SAFETY DATA STEFANO DEL PRATO, MD



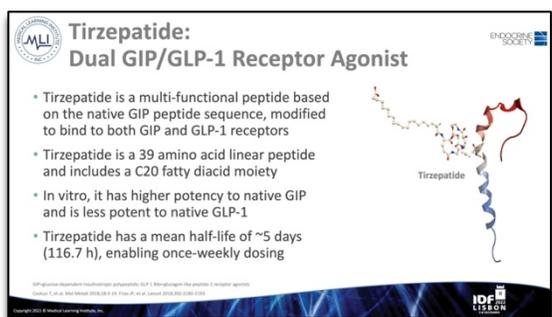
It's a great pleasure to meet you here. You know, I think everybody was expecting to have another opportunity to meet with friends and colleagues and, you know, to be able really to participate once again in this meeting.

And, I'd really like to thank the CME organizer here. Really thank you very much.

You heard a very interesting story so far from Professor Ludvik who introduced the unmet needs in diabetes and still we are facing a lot of requests to try to have more people with diabetes to achieve glycemic control that can reduce the burden of the complication.

Then we had heard Professor Forst telling us about the physiology and the pathophysiology of the incretin system and how this has brought up to this concept of dual agonism. And actually I think that we have really to recognize how smart it has been to come up with not just two hormones given together but rather too with a small molecule that can interact with two receptors.

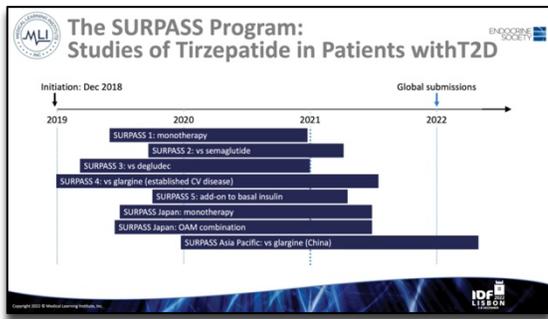
Now my duty is to try to give you a little bit more information about the clinical data relative to the use of tirzepatide in diabetes.



#### Tirzepatide: Dual GIP/GLP-1 Receptor Agonist

Now you already know this. It has been already shown to you. Tirzepatide is small molecule. It's only 39 amino acids and has this property to remain in the circulation for a long time because it has linked to a fatty acid. And because of that, it can bind to albumin and can stay around and it can be used once weekly, which is, obviously, a convenience for people who have diabetes. And tirzepatide can bind with a greater effect on the GIP receptor as compared to the GLP-1. This is information that comes mainly

from in vitro data. And, as I mentioned, tirzepatide has an average half-life of five days.



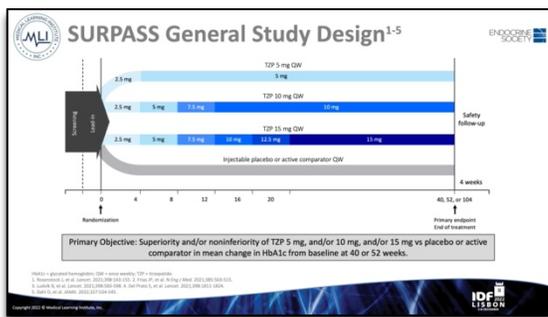
**The SURPASS Program: Studies of Tirzepatide in Patients with T2D**

These small molecules have been tested in a clinical development program which is known as the SURPASS Program. And these are all the SURPASS trials that have been so far performed, although not all of them have been completely reported. So you can go through the different trials, and you can see that, of course, tirzepatide has been tested against placebo, and that was the SURPASS-1.

Then tirzepatide has been tested against semaglutide. In other words, what is the effect of a dual agonist as compared to a GLP-1 receptor agonist versus insulin degludec in one case and in a second case versus glargine with the two different study populations because the one that has been evaluated in the comparison between tirzepatide and glargine was a population with a more severe condition with a greater risk in term of cardiovascular risk.

And then there has been the data from Japan and the Asian population. And just recently the SURPASS-5 results have been reported looking at the effect tirzepatide added on top of basal insulin. So many studies.

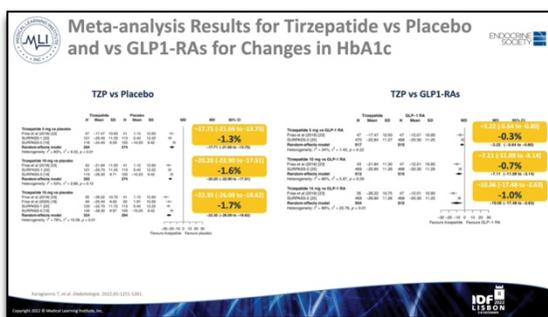
I'm going to show you one slide that Professor Forst already showed you before because all these trials are being performed with the same study design summarized here.



**SURPASS General Study Design**

So you can see the three final doses of tirzepatide that has been tested are 5 in the blue line, 10, and 15 milligrams. But all these trials have been started with a minimum dose of 2.5 milligrams tirzepatide and then there is a titration up to the final dose, and each step has been in four-week increments. So the tirzepatide has been increased by increasing the dose every four weeks. And then you have the comparator here, with varies depending on the trial. Could be a placebo, and so on, so forth.

So how can I try to summarize all this data here? I'll do that by using a meta-analysis that we have performed and just published a couple of months.



**Meta-analysis Results for Tirzepatide vs Placebo and vs GLP1-RAs for Changes in HbA1c**

A meta-analysis that we have recently published in Diabetologia in collaboration with Dr. Karagiannis, Dr. Apostolo Tsapas. So what you can see here is the comparison of tirzepatide versus placebo with the three different doses, 5, 10, and 15 milligrams, and here is the tirzepatide as compared to GLP-1 receptor agonist.

Now it's a small slide. It's not easy to read. I am going to make it more readable to you because I'm just taking out what is the main message. So if you compare tirzepatide

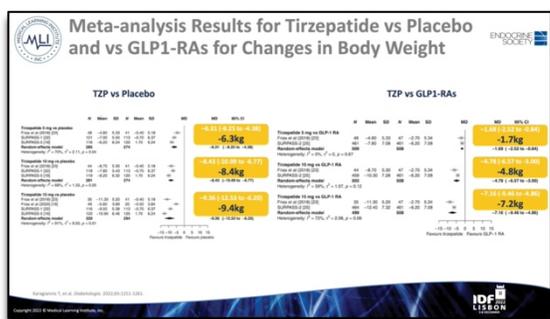


versus placebo, what you can appreciate here is this reduction in A1C that it's dose dependent. The greater the dose of the tirzepatide, the greater the reduction in A1C that has been reported.

And, of course, this is more than expected. This is versus placebo. Of course, if you start with with a glucose-lowering agent, you do expect that agent to lower glucose to a greater extent than placebo. But what is more important and more interesting is to compare tirzepatide versus the GLP-1 receptor agonist, and this mainly been reporting the data of SURPASS-2, which is versus semaglutide using the maximum dose of 1 milligram.

And here is the result that you can appreciate. And you can see, once again, the reduction is greater as compared to the one that's been obtained versus placebo, but still you have a sort of dose-dependent response with a greater effect with the highest dose of tirzepatide. And you can see that there is quite a substantial clinically meaningful difference here that is in the range of a 1%-point A1C reduction with tirzepatide versus semaglutide.

Now one point that is important to notice is that this is the effect in terms of the A1C. It has been already mentioned that tirzepatide and GIP and GLP-1 when used together may have a greater impact in term of the body weight. Here in the meta-analysis we have been looking at the effect on body weight using tirzepatide and versus placebo and versus GLP-1 receptor agonist.

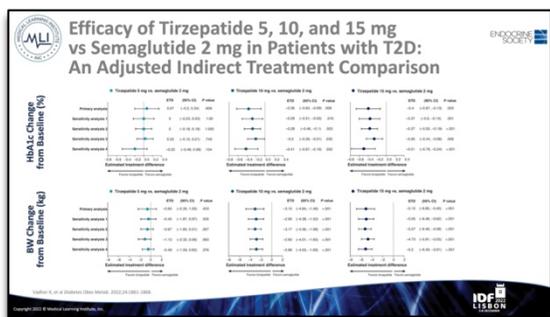


### Meta-analysis Results for Tirzepatide vs Placebo and vs GLP1-RAs for Changes in Body Weight

And, once again, I'm going to summarize these result for you showing here what is the average reduction in body weight in kilograms with 5, 10, and 15 milligram tirzepatide versus placebo. And what you can expect when you do the same kind of comparison versus semaglutide is a significant reduction in body weight that has been obtained with tirzepatide as compared to semaglutide.

Now you may know that more recently semaglutide has been also proposed to be used in a higher dose than that original 1 milligram. So someone can ask, "All right, what's the advantage of using tirzepatide versus using, for instance, 2 milligrams semaglutide?"

Now there is no direct comparison.

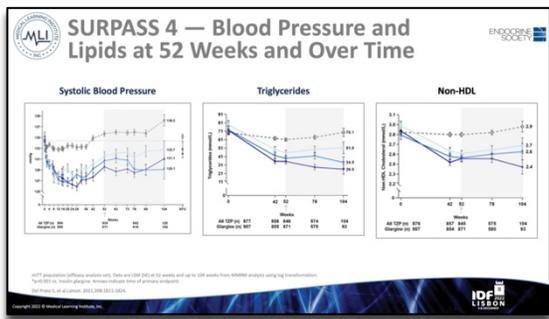


### Efficacy of Tirzepatide 5, 10, and 15 mg vs Semaglutide 2 mg in Patients with T2D: an Adjusted Indirect Treatment Comparison

However, this question has triggered some curiosity and some colleagues of ours have made an indirect comparison. And what is shown here is what you can obtain with a 5 milligrams, 10 milligrams, and 15 milligrams versus 2 milligrams semaglutide in term of A1C reduction or in term of body weight reduction. In all, you can appreciate that if you do focus on this part of the slide here, which is reporting the effect of a 5 milligram versus 2 milligram,

this cannot be taken as conclusive data because it is not a direct comparison, this is an indirect comparison, that the 5 milligram tirzepatide is as good as the 2 milligram semaglutide.

But when we look at the effect of a 10 milligram and 15 milligram, all the points and on the left-hand side of the plot suggest that tirzepatide exerts a greater effect in terms of reduction in glycemic control, A1C, and reduction in body weight. So, apparently, tirzepatide may provide a further step forward for what we have been achieving lately with the GLP-1 receptor agonist.



### SURPASS 4 – Blood Pressure and Lipids at 52 Weeks and Over Time

And this is important because it is combination of an important effect on glycemic control, reduction in A1C, and effect on the body weight reduction that comes together with other factors that are depicted in this slide here because tirzepatide use has been associated with a significant and sustained reduction in the systolic, and not shown here, diastolic blood pressure.

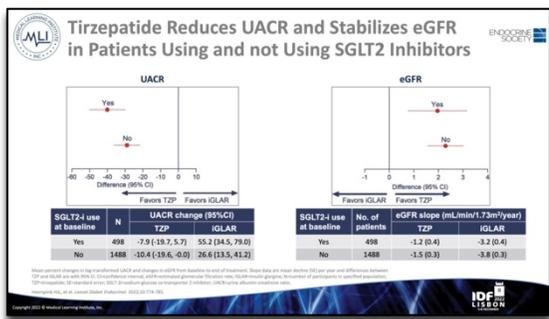
Now these are the data that have been obtained from SURPASS-4, an interesting study, I believe, not because I was coauthoring it but simply because it was extended up to two years. So here we can try to obtain initial information of what could be the persistence of the effect of tirzepatide in people with type 2 diabetes. And what has been not shown here is that, for instance, the reduction in A1C that you can achieve already after the first initial four weeks of treatment. It's further reduced and maintained throughout all the period of observation.

And the same is true for systolic blood pressure but also it is true for effects the tirzepatide exerts on the lipid profile. Here is, for instance, the triglyceride and the non-HDL cholesterol that you know may reflect to a greater extent the total amount of atherogenic lipoprotein in the circulation.

And you can see that the reduction achieved max at around one year, which is the same timepoint where you achieve the maximal effect in term of reduction in the body weight. And even more importantly, for blood pressure, for triglycerides, and for non-HDL cholesterol, the gray area is maintained throughout the second year of the treatment.

So with the tirzepatide what has been shown in the SURPASS Program, is a clinically meaningful reduction in A1C, a clinically meaningful reduction in body weight together with an improvement in cardiovascular risk factors like blood pressure, triglycerides, and non-HDL cholesterol.

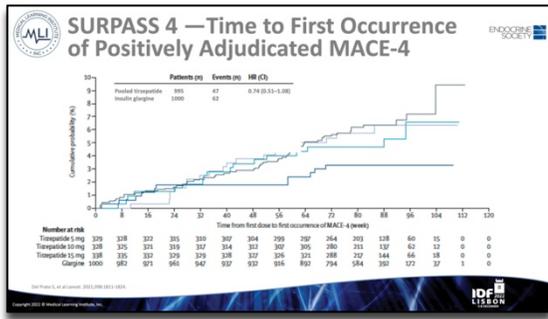
But there is even more. As a result of the predefined post hoc analysis of SURPASS-4, tirzepatide effect has been evaluated with respect to kidney outcomes.



### Tirzepatide Reduces UACR and Stabilizes eGFR in Patients Using and not Using SGLT2 Inhibitors

And what has been reported just recently in Lancet and Diabetes Endocrinology is that in terms of urine albumin excretion rate or in terms of a reduction or protection of the estimated glomerular filtration rate, tirzepatide has been associated with a positive outcome with these two important and independent cardiovascular risk factors, and this effect was independent of the presence of SGLT2 inhibitors, which we know are now considered the top treatment for protecting the kidney.

So it's easy now to make a simple calculation – better glycemic control, lower blood glucose, lower body weight, lower blood pressure, better lipid profile, protection of the kidney – so you are dealing with the five most important cardiovascular risk factors. And the question is what is the protection that we can expect in term of cardiovascular events with tirzepatide?

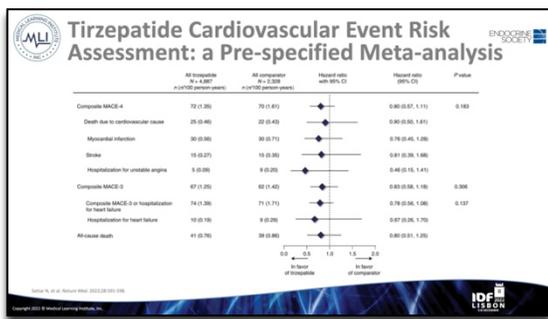


### SURPASS 4 – Time to First Occurrence of Positively Adjudicated MACE-4

In SURPASS-4, what we did was to adjudicate cardiovascular events. And here is the Kaplan-Meier curve for the first appearance of these cardiovascular events. And now what you can see is the different lines for the different doses of tirzepatide. And what you can see down here is the line for the highest dose of tirzepatide.

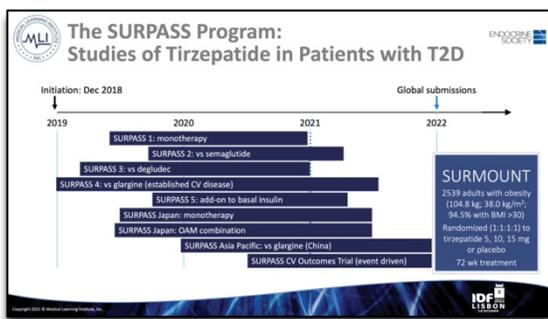
Just to make a long story short, let me put all the data together for tirzepatide versus glargine, the comparator in SURPASS-4. There was a trend for reduction of events, but you also perceive that the total number of events is more, so it cannot give any confidence in terms of statistical analysis. Moreover, the cardiovascular safety and protection was not a predefined outcome.

However, in order to gain more information in terms of the safety of tirzepatide with respect to cardiovascular risk, what has been done was to collect all the cardiovascular events that have been recorded throughout the SURPASS Program and to do a meta-analysis and that's what Naveed Sattar has done very recently.



### Tirzepatide Cardiovascular Event Risk Assessment: a Pre-specified Meta-analysis

And you can see here that overall the estimates go under on the right direction although none of them is statistically significant. So what we need to conclude is that tirzepatide, for the what we know so far, has to be considered safe, is not increasing the risk of cardiovascular events, and what needs to be proven or to be explored is to what extent improvement in the cardiovascular risk factors is being brought about by the use of tirzepatide, and if it can indeed translate into cardiovascular protection.



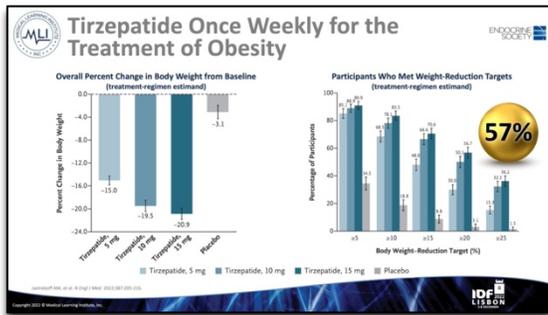
### The SURPASS Program: Studies of Tirzepatide in Patients with T2D

And this is something that we are waiting for because as Thomas was referring to, the SURPASS cardiovascular outcome trial is ongoing and that study will be answering an important question. It's going to evaluate to what extent tirzepatide used in the three doses, although there will be advice for investigators to try to increase as much as possible the dose of tirzepatide, can provide further benefit on top of a drug that's been already proven to be associated with cardiovascular protection. And that is dulaglutide.

So let's be patient for a while and maybe we can come back here and discuss what is the cardiovascular outcome results.

But there is more about tirzepatide that needs to be considered. It was just mentioned before during the discussion that tirzepatide may, by reducing body weight and by the beneficial manipulation of the lipid in the body, reduce fat accumulation in the liver. And there is a trial that is ongoing to look at that potential effect.

But even more, because of the significant reduction in body weight that I already pointed out, tirzepatide has been explored throughout the SURMOUNT program to evaluate the effects in an obvious population. And the first paper was published during the summer. It is the SURMOUNT study that included something like 2,500 adults with obesity. And you can see here they are really obese because the average BMI was 38 with an average body weight of 105 kilos. And even more importantly, which I think is important to notice here, is that 95% of the population in the study had a BMI greater than 30. So really this is a population of obese individuals.



### Tirzepatide Once Weekly for the Treatment of Obesity

Let me just very quickly summarize the results. And what is shown in the slide on the left-hand side is the percentage reduction in body weight with the 5 milligram, 10 milligram, and 15 milligram doses. And you can appreciate every fifth milligram, there is an average reduction of 15% of the initial body weight that reached a max of a 21% with 15 milligrams of tirzepatide.

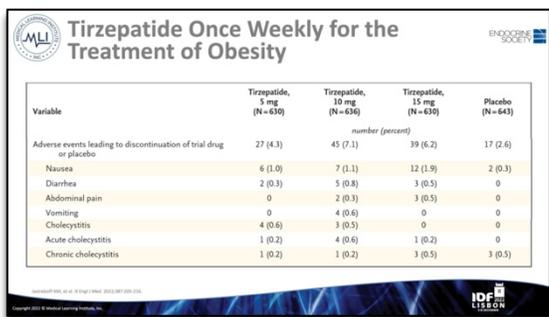
But what I think is even more intriguing is on the right-hand side of the slide. Here you can see predefined target people achieving a reduction in body weight greater than 5%, greater than 10%, 15%, 20%, and 25%. And now you can appreciate that almost 90% of the population treated with tirzepatide reduced their body weight by at least 5%. But even more, if you go here in the highest percentage reduction, you have close to 60% that will achieve a reduction in body weight greater than 20%, and 36% with the highest dose of tirzepatide achieving a weight reduction greater than 25%.

And I think this is important to consider because it has been already alluded to before. Now we know that weight reduction can be very important, of course, for obese individuals, but also most of our diabetic individuals, as has been pointed out by Professor Ludvik in the beginning, are indeed obese. And let me just remind you that it was one of the main results of SURPASS-4 where we analyzed the effect of tirzepatide versus glargine.

End Points	Pooled Tirzepatide Groups	Placebo (N=443)	Estimated Treatment Difference from Placebo (95% CI)
least-squares mean (95% CI)			
<b>Key secondary end points</b>			
Change from baseline to week 20 in body weight — kg	-12.8 (-13.1 to -12.5)	-2.7 (-3.2 to -2.2)	-10.1 (-10.7 to -9.6)
<b>Change in measure</b>			
SF-36 physical function score	3.6 (3.2 to 4.0)	1.7 (0.8 to 2.6)	1.9 (1.0 to 2.9)
Systolic blood pressure — mm Hg	-7.2 (-7.8 to -6.7)	-1.0 (-2.3 to -0.3)	-6.2 (-7.7 to -4.8)
<b>Percentage change in level</b>			
Triglycerides — mg/dl	-24.8 (-26.3 to -23.1)	-5.6 (-10.0 to -1.2)	-20.3 (-24.3 to -16.1)
Non-HDL cholesterol — mg/dl	-9.7 (-10.7 to -8.6)	-2.3 (-4.9 to -0.2)	-7.5 (-10.1 to -4.9)
HDL cholesterol — mg/dl	8.0 (6.9 to 9.1)	-0.7 (-2.9 to 1.5)	8.8 (6.1 to 11.5)
Fasting insulin — mIU/liter	-42.9 (-44.9 to -40.9)	-6.6 (-15.3 to 2.2)	-38.9 (-44.8 to -32.4)

### Tirzepatide Once Weekly for the Treatment of Obesity

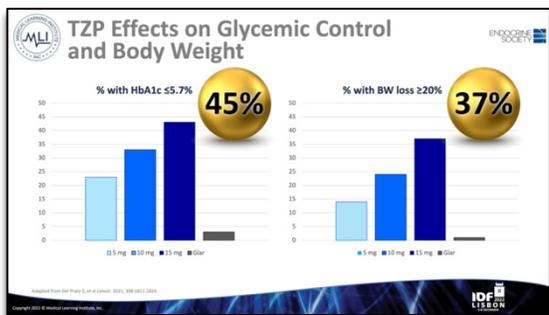
And this is the effect in terms of cardiovascular risk factors in this obese population. And you can appreciate that systolic blood pressure, triglycerides, lipids, fasting insulin all have a negative sign in front of them, which is highly significant and, also, are associated with an improvement in physical activity.



## Tirzepatide Once Weekly for the Treatment of Obesity

Maybe you will be wondering about safety and what has been reported for the use of tirzepatide in this obese population, which is very similar to what has been reported also in a diabetic population. Most of the side effects are gastrointestinal in nature, but are pretty limited. And overall they are not very much different from the ones that you can get for the typical GLP-1 receptor agonist.

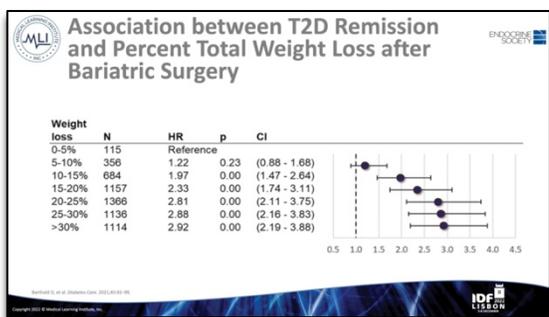
But I was telling you about the SURPASS-4.



## TZP Effects on Glycemic Control and Body Weight

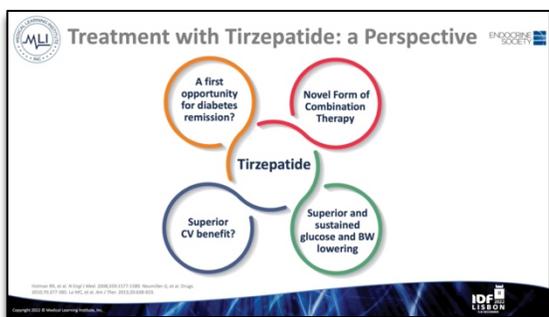
And what is reported here is the reduction in the number of people achieving an A1C lower than 5.7%. Now we have been trying for years to target an A1C of 7%. Here in SUPASS-4, you can see something like 43%, 45% of the population using the highest dose of tirzepatide achieved the A1C lower than 5.7%. And 5.7 is the upper limit of the normal range for A1C, which has been also coupled with something like 37% of the population achieving a body weight reduction greater than 20%.

Now if you go back to what Professor Ludvik was saying before, you can now consider how this may lead to the potential concept that we may be able to induce some sort of remission in these individuals.



## Association Between T2D Remission and Percent Total Weight Loss After Bariatric Surgery

And this idea is farther supported by the fact that 20% weight reduction is the cutoff point for diabetes remission that has been calculated out of the results of the bariatric surgery as is shown in this meta-analysis here. And you can appreciate that the top effect is here. And even though you go farther into the weight reduction, you do not gain very much in term of the expectation for diabetes remission.



## Treatment with Tirzepatide: A Perspective

So I think that we are looking to a very interesting scenario in front of us, a scenario where tirzepatide can be seen as a novel form of dual therapy because it is acting simultaneously on two different receptors. Tirzepatide has been shown to have a clinically meaningful effect in terms of glycemic and metabolic control and body weight. Whether this will translate into cardiovascular benefit will be determined by the results of the SURPASS CVOT, but I think that you are as eager to know the result as I am. And,

finally, I'm wondering to what extent tirzepatide may open up a new door which is the potential for remission in diabetes in the future. I know that this will generate a lot of discussion relating to the definition of remission and also to gain sufficient data to prove to which extent we can achieve this very ambitious target.

And I'll stop here. Thank you.

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## Q&A

**Dr. Yasmin:** Dr. Yasmin from Bangladesh, endocrinologist. I would like to know what percent of patients may rebound weight gain after discontinuation of tirzepatide?

**Dr. Del Prato:** This is not yet known. But you're right on the spot, it's an important question. But the point is why do you want to stop the treatment? I mean if you put someone on bariatric surgery, once you have reduced, you know, 20, 30, 40 kilos body weight reduction, you don't reoperate back then, correct?

**Dr. Yasmin:** Right. Yes. Actually, I know that GLP-1 receptor agonist is very costly, especially for a country like Bangladesh. And sometimes it's very difficult to continue for the long time in that case.

**Dr. Del Prato:** You thought right. You know, I'm just basing my answer on clinical and scientific point.

**Dr. Del Prato:** If the reduction in body weight can be maintained and for a substantial length of time must be properly investigated. Whether this will lead to intermittent use of this drug, we don't know yet.

**Dr. Yasmin:** Okay. And another question is does tirzepatide have an effect on NASH, that is the nonalcoholic fatty liver disease, and can it improve fatty liver disease?

**Dr. Del Prato:** There are initial data that have been generated in term of a proxy for NASH and NAFLD suggesting that the use of tirzepatide is associated with a significant improvement in this, and there are proper studies currently looking at the fat content and to what extent that fat content can be reduced by tirzepatide.

**Dr. Yasmin:** Thank you.

**Dr. Ludvik:** Thank you so much. You have been a great audience. We had three talks, three consequential talks starting with the problem of achieving glycemic goals and how to get their individual components. Then Professor Forst talked about the mechanism behind GIP and GLP-1 agonism. And at the end we saw the very impressive data presented by Professor Del Prato about the efficacy of tirzepatide on HbA1C glucose control and weight. Together we all hope that we will have the drug around pretty soon to share it with our patients.

I want to say thank you to you, the audience, to the speakers, to MLI organizing this symposium, and to Eli Lilly for supporting it. Have a nice evening and a good IDF. Thank you so much.