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SPEAKER: Let's get into a general overview of what we're talking about. A lot of people with diabetes in this country-- over 9% of the population. As you get into the elderly population, it's much higher. About 25% are undiagnosed. I think that number is dropping. It used to be 50%, has dropped to 25%, and is probably dropping quite fast because we have very simple ways of achieving diagnosis today.

And with that, we get almost 2 million new cases per year. The major problem is just the volume of people with diabetes. It's overwhelming the whole system. It's overwhelming your practice. And if you look at some of the other current developing countries, or should I say developed countries, now, India and China, they are completely overwhelmed with this because they don't have the infrastructure to deal with that.

And then 50% are not achieving glycemic targets, as you can see on this slide. It hasn't changed very much. And that's assuming a target of less than 7%. And as you know, in the last couple of weeks, we've had lots of controversy about that. I'd like to hear your views and the views of my colleagues here. Lots of debates. It's filled my email box. We'll talk about.

The causes for this are multiple. You have a complex disease, at least type 2 diabetes-- type 1 is very straightforward. Insulin deficiency, and you need to replace it, and a few other little things. Type 2 is a lot more complex. You have these eight abnormalities described by Dr. DeFranzo in the Ominous Octet, and he recently gave grand rounds in my institution where he talked about 12 or 13 abnormalities-- things that are not on this.

And when you think about it, we have several other diseases where we use more than one treatment right at the start to cover different aspects of the treatment target. Take tuberculosis or HIV, and we know combination therapy works better than giving just one drug where you get resistance.

And yet, we still only target the liver with metformin monotherapy. And it fails over a few years. We know from UKPDS, and you see here the UKPDS decline in beta cell function on metformin. They, in fact, published a paper-- that group. They call it *Coefficient of Failure.* Which means if you do nothing, A1C goes up by 0.3% per year on average. Some people it goes even faster.

And it goes up faster in people who are poorly controlled because you have glucose toxicity. So if you are at 7%, you'll go up by 0.3% per year. If you're at 8.5%, you'll probably go up by maybe 0.7%, 0.8%, 1% every year. So the disease is progressive because of this progressive loss of beta cell function.

The effectiveness of insulin has been proven. Often, it's the only agent that can replace this beta cell function adequately. You can keep titrating, limited, of course, by hypoglycemia. And apart from the hypoglycemia and mild to moderate weight gain, you have an excellent safety profile.

And it's generally well-accepted after initial reluctance. But we can overcome the reluctance with improved devices, recommendations from you, discussion with the patient, education of the patient. And all this is really critical for successful treatment.

Now, in relation to the controversy about goals we put in this slide, it's actually not a recent meta analysis. I'm an author on this paper-- it was in *Annals* several years ago-- looking at analysis of the glucose-lowering trials like ACCORD, ADVANCE, UKPDS, et cetera.

And it showed that there was no increase in mortality when you look at intensive therapy. And cardiovascular events, particularly non-fatal MI did decline. And we were looking in this meta analysis at microvascular disease. ACCORD study also showed in type 2 diabetes, that intensive therapy led to a reduction in kidney disease and retinopathy progression. So we should not forget the importance of microvascular complications.

There's another important factor when we treat patients with diabetes. In the UKPDS, we took newly-diagnosed diabetes, and we brought the A1C down to below 7% and attempted to keep it there. Now, they weren't always successful because that was a monotherapy study with very limited drugs in the 1980s. But they achieved prevention of microvascular complications in a lot of people.

In the ACCORD study, we took patients who had 10 to 15 years of diabetes with very poor control. They had established complications. And then we tried this very late stage to bring the A1C down. That's not what we should be doing because these patients have this bad glycemic legacy and established complications that are irreversible.

In fact, even if you do a pancreas transplant or bariatric surgery, the disease continues to progress. So retinopathy can progress after bariatric surgery and after retinopathy. So how are you going to reverse it with giving insulin or giving anything at this very late stage? We need to prevent microvascular complications.

But we don't do it in practice. So we have this so-called clinically inertia. People don't add new therapies, including sometimes adding new oral drugs. And certainly, adding insulin is a very low priority despite poor control. And some of that relates to patients not wanting to make that step. They say, give me a chance doc. I'm going to diet now-- hasn't dieted in 40 years. It's not realistic.

And there are studies showing that if at a late stage, somebody has an A1C of 9%, you're not going to get that patient to go with the routine lifestyle change advice that we give them. Yes, they did it in studies like Look AHEAD, but they didn't achieve much there in the late stage, either. They couldn't reduce mortality or cardiovascular events, but they did achieve an improvement in A1C and a reduction in weight.

But the average patient, where we don't have the resources like in the Look AHEAD study, it's very hard to do. If you add on insulin, you have a greater chance of achieving an A1C less than 7%. But let's look at an analysis from clinical trials that we did, along with Matt Riddle.

We showed that if you start off your A1C see less than 8%, you will need to reduce the A1C much less than if you start at 9.5%-- makes sense. And your chance of success is really much greater if your A1C is suddenly less than 8%, but maybe less than 8.5%, as compared to when it's 9.5%. Even insulin-- there are some challenges of getting the A1C 2.5 percentage points down. You may need insulin plus some of the newer agents.

There's another interesting concept, and that's on improving beta cell function. This is achievable in the early stages of the disease, but it hasn't been well studied. Yes, one large study done in China-- over 300 patients. They took newly-diagnosed diabetics and gave them pump therapy for two weeks, four injections a day for two weeks, or oral agents, and then stopped all therapy.

They got good control, discharged the patient, looked at them one year later, and they assessed beta cell function, et cetera. Patients who were treated with pumps-- 50% of them were able to manage with diet alone after one year. Now, that means 50% still needed other therapies. But people who started with oral agents, only 26% were able to manage and died alone.

And they looked at what was a predictor of this good outcome with good control for two weeks? And it invariably was that, yes, beta cell function before-- this is acute insulin response. No response to insulin when you give IV glucose. After two weeks of therapy, you get a very robust response. And in a lot of people that remains there after one year. So you're changing beta cell function by eliminating glucose toxicity for just two weeks.

This is not an easy thing to do. You can't take people with newly-diagnosed diabetes and give them pumps for two weeks in our health care system. It's not easy. But the concept of improving glycemic control early in the disease is doable. We can do it with whatever means you've got to get close to normal. You will keep that patient well-controlled for a long time.

We tried to do that with insulin, just a simple injection in the ORIGIN trial. And people were included if they had pre-diabetes or early diabetes with CBD-- this was a cardiovascular outcome trial. But they also assessed beta cell function. We took 12,000 patients, gave them glargine therapy or standard therapy, which was metformin first, then add on sulfonylurea, then add on something else.

And the follow-up was for seven years. And we learned a lot from this trial about the long-term safety of insulin, and what happens if you had good glycemic control starting early. And with standard therapy, you got some improvement in fasting glucose. With glargine titrate, you're titrating it, so you got fasting glucose down to near 90.

What is interesting is that they only used about 30 units a day. Relatively low dose, very little need to titrate up after the initial titration, maintained good glycemic control for seven years. Use the A1C-- metformin plus other oral agents-- came down, needed additional therapy. Insulin, hardly any additional therapy needed-- they remained very well-controlled.

Now, the primary outcome didn't change. Glargine did not prevent cardiovascular events. But what was its comparator? It was metformin. It was equally good as metformin, which we all believe prevents microvascular disease. So there did not appear to be a benefit. But the comparator was not placebos as an empirical leader. The comparator was metformin and sulfonylurea.

If you look at the safety side of it, there was no increase in a lot of adverse events that people were worried about. There was some modest increase in weight. There was a modest increase in hypoglycemia. But you slowed the progression of the disease. There was no increase in cancer, no increase in any other condition.

But again, I think that tells us a lot about the insulin, but it's not a practical thing. We're not going to take newly-diagnosed diabetes patients and give them insulin. It's not going to happen. The patient doesn't want it. The system doesn't want it. And I'm not recommending it. I just want to use that to talk about the safety, and long-term safety, and possible benefits of good glycemic control.

So what are the factors when using insulin strategies? You want A1C reduction. You want to achieve a target. Let's just say 7%, though some of you stand up and say you've paid your ACP membership, so it should be higher. You can titrate the insulin doses. How doable is that? How much hypoglycemia do you get, and how complex is it? So we will discuss some of these factors as we go along today.

When you think about insulin therapy, we have basal treatment, which provides glycemic control between meals and overnight-- near constant levels when we want instant insulin to be constant and not fluctuating a lot. And there's prandial treatment, which we use to limit hyperglycemia after meals. Immediate rise and sharp peak one hour after a meal bringing the glucose down.

This is critical in type 1 diabetes. It's less critical in type 2-- not unimportant, but less critical because you also want to avoid hypoglycemia. And prandial insulin is a big cause of hypoglycemia and weight gain.

And we now have tools to address postprandial excursions, such as GLP-1 and SGLT2 inhibitors that perhaps decrease the need for prandial treatment. But there is very little available that reduces the need for basal insulin treatment in some patients. If you're going to use only insulin, the replacement should be both components-- basal and prandial, and we'll talk about both.

Now, let's look at where we are with algorithms. This is the AACE algorithm, where their target is less than 6.5%. Always been a little bit more aggressive in the therapy than ADA. And we can discuss later the merits of that. They rate metformin monotherapy first, and GLP-1 quite high up there because of its effect on weight.

But they do recommend early combination therapy. Use combination therapy it's more than 7.5%. And they recommend using insulin at the start if your A1C is greater than 9%. And particularly, if the patient has symptoms. If the patient doesn't have symptoms, you could use dual therapy with any two agents, or even triple therapy. Once you start on insulin, you can add or intensify the insulin, mix it with other agents. But it's not forever.

So you could start with insulin therapy-- and we're often doing it. I have newly-diagnosed patients coming in symptomatic with blood glucose of 11%. We give them insulin for a few months along with oral agents, and then gradually withdraw the insulin.

We have a number of insulins, and we'll talk about all these today. We have intermediate-acting, the NPH family. We have the longer-acting, the glargine and detemir. And now, the newer, even longer-acting insulins, glargine 300, insulin degludec. And we also have some of the biosimilar insulins that have recently come-- one has come out, and one is waiting to come onto the market. And we'll discuss all that.