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Innovations in Insulin: New Opportunities to Individualize Therapy
A CE Activity

Overview

Vivian A. Fonseca, MD, and **Jonathan D. Leffert, MD,** combine their expertise and discuss emerging concepts, treatment advancements, and critical issues associated with the management of patients with type 2 diabetes mellitus. The discussion focuses on real-world patient management and includes case studies to facilitate integration of new knowledge into clinical practice.

Content Areas:

- Basal insulin
- Prandial insulin
- Cardiovascular safety
- Intensifying basal insulin
- Concentrated insulin

Faculty

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CE/CME Information

Target Audience
This activity was developed for primary care physicians, endocrinologists, physician assistants, nurse practitioners, nurses and other health care professionals who have an interest in type 2 diabetes mellitus.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Describe the contribution of fasting plasma glucose and postprandial glucose in cardiovascular risk
- Identify patients for whom insulin is appropriate based on current guidelines for the treatment of type 2 diabetes mellitus
- Initiate and titrate basal insulin to achieve glycemic control
- Identify patients who are appropriate candidates for prandial insulin
- Initiate and titrate prandial insulin to achieve glycemic control
- Initiate a concentrated insulin formulation in appropriate patients
- Individualize basal and prandial insulin therapy

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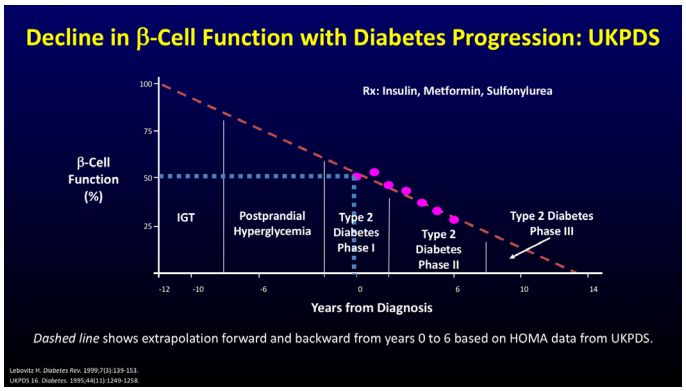
Acronyms

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AGI	alpha-glucosidase inhibitor
BID	twice daily
BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CV	cardiovascular
DM	diabetes mellitus
DPP-4i	dipeptidyl peptidase-4 inhibitor
FPG	fasting plasma glucose
GIR	glucose infusion rate
GLN	glinide
GLP-1RA	glucagon-like peptide-1 receptor agonist
HbA1c	glycated hemoglobin
HOMA	homeostasis model assessment
IDeg	insulin degludec
IDet	insulin detemir
IGlar	insulin glargine
IGT	impaired glucose tolerance
MET	metformin
MI	myocardial infarction
NPH	neutral protamine Hagedorn
NS	not significant
OAD	oral antihyperglycemic drug
OR	odds ratio
PIO	pioglitazone
PPG	postprandial plasma glucose
qAM	every morning
qHS	at bedtime
RHI	regular human insulin
RR	rate ratio
Rx	prescription medicine
SC	subcutaneous
SGLT-2i	sodium glucose cotransporter-2 inhibitor
SMBG	self-monitored blood glucose
SU	sulfonylurea
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
T-T-T	Treat-to-Target
TI	Technosphere insulin
TID	three times daily
TZD	thiazolidinedione
UA	unstable angina
UKPDS	United Kingdom Prospective Diabetes Study
wk	week
yo	year-old

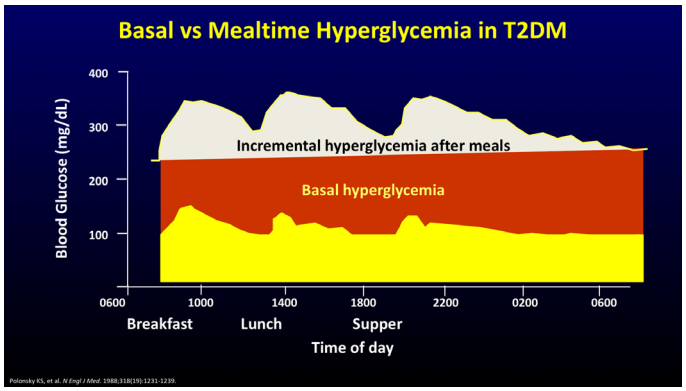
Module 1: Key Concepts of Type 2 Diabetes Mellitus

Vivian Fonseca, MD: Hello. Welcome to this program on Innovations in Insulin: New Opportunities to individualize therapy. My name is Vivian Fonseca. I'm Professor of Medicine at Tulane University in New Orleans, Louisiana. Joining me today is Dr. Jonathan Leffert, who's an endocrinologist in Dallas, Texas, and the current President of the American Association of Clinical Endocrinologists. Welcome Jonathan.



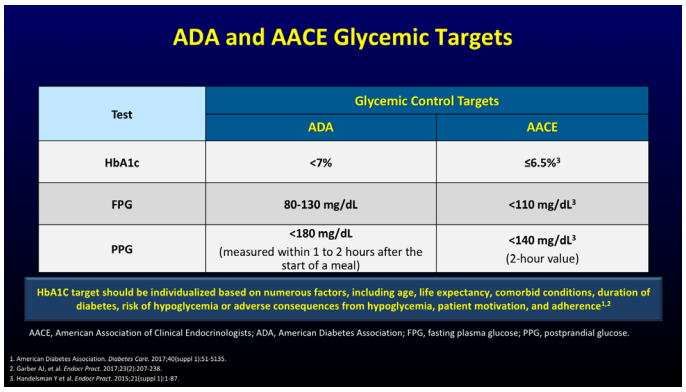
We're talking about type 2 diabetes, which is a complex disease, a major characteristic of which is decline in beta-cell function. This is present at the time of diagnosis and, with many of the therapies that we have, the disease continues to progress, in terms of beta-cell function, to the point where after many years of type 2 diabetes, you're almost like type 1, with very little function of the beta-cell, with quite a substantial insulin deficiency, requiring replacement in insulin. The other characteristic of diabetes is the long-term complications, which are related to damage caused by glucose being high. This is called glycemic exposure. It consists of some exposure in the fasting state, as well as very substantial exposure of the tissues to high blood glucose after meals. It's the net exposure of glucose, this hypoglycemia, that's damaging tissues.

When we look at it from a treatment perspective, we talk about controlling it in the basal state, which is essentially the premeal and fasting state, as well as the mealtime hypoglycemia. Both are important components, as we will discuss.



Now, Jonathan, we look at glucose and we look at A1C and there are a number of goals, and people get a little confused about what these goals should be. So could you update us on where we are with this?

Jonathan Leffert, MD: Certainly, Vivian. Thank you. We have the ADA goal for A1C, which is less than 7%, and the AACE goal, which is less than 6.5%. Fasting blood sugar should usually be in 80 to 130 range or thereabout. Postprandial blood sugar should be less than 180 according to the ADA and less than 140 according to AACE. This all results in excellent glycemic control, which decreases the overall complications of diabetes.



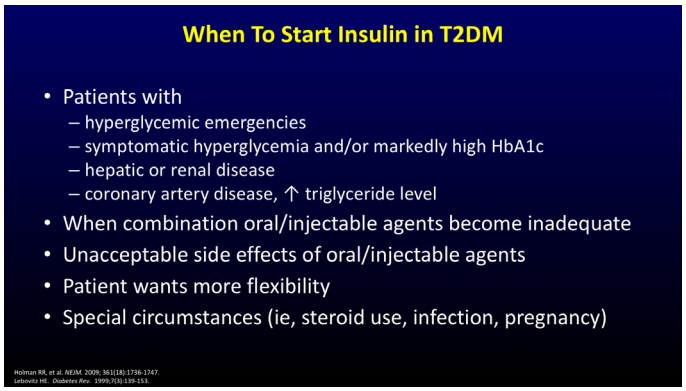
Vivian Fonseca, MD: Sorry to interrupt, but the goals are actual not that very far apart because both organizations emphasize individualization of goals.

Jonathan Leffert, MD: Yes, and that's really the most important thing. As a practicing clinical endocrinologist, we daily have to deal with individuals

and specific goals related to their problems. They all have different issues related to age and life expectancy, other comorbid conditions that are associated with their disease. We always are concerned about balancing the idea of good glycemic control against the concerns of hypoglycemia.

Vivian Fonseca, MD: And all the side effects as well.

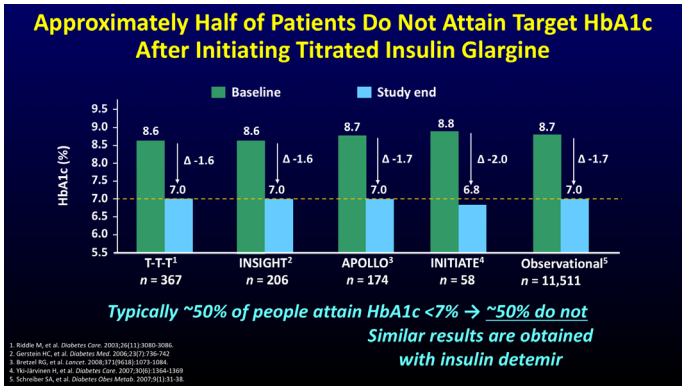
Jonathan Leffert, MD: Yes. This is interesting in the sense that we have to always have an idea of how we're going about taking care of our patients. There's an algorithm that is yearly put out by the American Association of Clinical Endocrinologists, which goes through how we decide what are going to be our next steps in treatment. As far as insulin is concerned, insulin can come anywhere along the pathway. It's important sometimes to give insulin early on, when patients are very ill and they have other problems which require it. And then there are also times when we start with oral agents and progress to insulin.



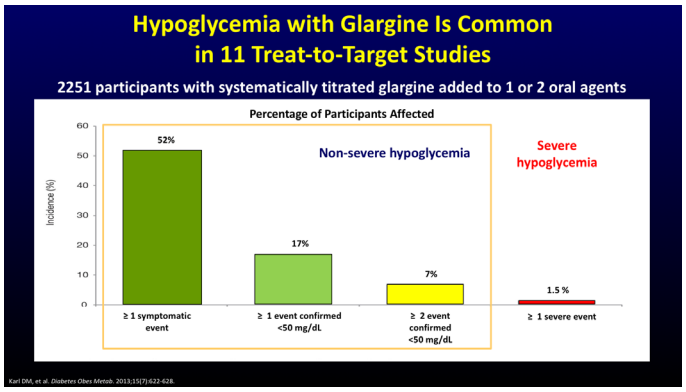
So patients who are started on insulin are of the usual type, which would be hyperglycemic emergencies. Those are patients who are usually in the hospital; hyperglycemia with very high A1Cs; if they have a hepatic or renal disease and can't take other medications; certainly patients who have coronary disease with high triglyceride levels. Then we always need to go to insulin when we can't get control with other combinations of oral or injectable agents, or we have side effects with those oral and injectable agents.

Sometimes patients want more flexibility, so we put them on insulin. Then there are a number of special circumstances. A common thing that happens in the office is that patients call and say, "I just got placed on steroids for some other cause" and we have to use insulin in those cases.

Vivian Fonseca, MD: Insulin works very well, as you discussed. You use it in emergencies, but there are a lot of people who still don't get to goal, despite taking insulin. We've got very used to titrating insulin. There are a number of studies that have looked at post-titration, based on some algorithms that are predetermined in protocols, that very often we translate into practice. We've actually also started teaching patients to do their own titration. If you look at the studies involved, they take people with very poorly controlled diabetes and get their mean A1C down very close to around 7%, which is not bad considering that they start well above 8%, but that means half the people are not really getting to goal on A1C.



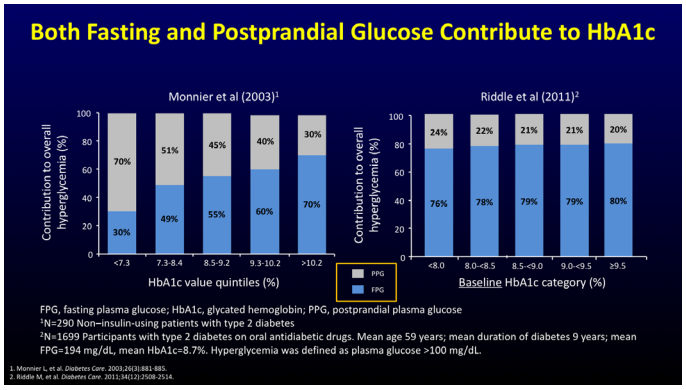
You also mentioned goals for individual glucose. Very often, when you're using basal insulin, that's the fasting glucose, and we're not fully addressing all the things that go with A1C. Having said that, I want to emphasize the importance of titrating appropriately to get to the goal that you've set for your patient for fasting glucose, while avoiding hypoglycemia. You many need to back titrate sometimes if your patient gets hypoglycemia. Hypoglycemia is actually quite common in these so-called treat-to-target studies. There's been an analysis done of pooled data from multiple treat-to-target studies. One particular study looked at over 2000 patients over a 6-week period of time and found that a lot of people had hypoglycemia.



Very often it's mild symptoms, but sometimes it can be fairly severe hypoglycemia, needing assistance of somebody else, or they've documented a blood glucose themselves. The ADA now defines it as below 54, but patients have recorded below 50. They get very frustrated and scared of this kind of situation. Very often, it leads to lack of compliance. It also has implications for cardiovascular events and other heart events.

While we focus on fasting glucose with the basal insulin, we also need to think about A1C as having multiple components. So could you tell us a little bit more, Jonathan, about what is A1C and when should we start thinking about postprandial glucose?

Jonathan Leffert, MD: Thanks, Vivian. I think that it's very important to make sure that we always recognize that A1C is a part of both a pre- and post-prandial blood sugar control. There've been multiple studies that have looked at that, and it's important to always think if you're not getting control of the diabetes with a basal insulin, that a prandial insulin may be required to get postprandial control of the blood sugar. That's a very crucial component of what we're doing in the overall aspect of taking care of patients with type 2 diabetes.



There are also other reasons why you would want to make sure that you are taking care of the postprandial blood sugars. That is that postprandial hyperglycemia independently predicts cardiovascular risk. There are a number of different studies that have looked at this issue and it turns out that many of these postprandial blood sugars have increased risk of coronary disease, and all-cause mortality increased with a number of these studies. It's a crucial component of our overall management—cardiovascular risk being the major component of mortality and morbidity for patients with type 2 diabetes.

Postprandial Hyperglycemia Independently Predicts CVD Risk

Clinical Trial	Association of PPG with CVD
Honolulu Heart Program (1987)	1-h glucose predicts coronary heart disease
DIS (1996)	Postmeal, not FPG, is associated with CHD
Chicago Heart Study (1997)	2-h postchallenge glucose predicts all-cause mortality
Whitehall Study, Paris Prospective Study, & Helsinki Policemen Study (1998)	2-h postchallenge glucose predicts all-cause and CHD mortality
Coutinho et al (1999)	2-h glucose associated with CHD
Hoom Study (1999)	2-h glucose better predicts all-cause and CV mortality than HbA1C
DECODE (1999; 2004)	High 2-h postload blood glucose associated with increased risk of death, independent of FPG; predicts cardiovascular death
Cavalot (2006)	Postprandial, not FPG, independently predicts CV events, particularly in women, in DM

CHD, coronary heart disease; CV, cardiovascular; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin

Adapted from Home P. *Curr Med Res Opin.* 2005;21(7):989-998.

So, Vivian, can you talk about how we target the hyperglycemia and how that reduces the cardiovascular risk?

Vivian Fonseca, MD: We have done a number of studies targeting postprandial hyperglycemia. The aims of these studies were different. There's a study with acarbose for example, that was a diabetes prevention study. Another one, called NAVIGATOR, that uses nateglinide. There we were looking mainly at prevention of progression to diabetes, the progression of the disease that we talked about earlier, but we also looked at cardiovascular events. They were a little disappointing. There was some suggestion of a benefit with acarbose. No benefit with nateglinide.

Do We Have Evidence that Targeting Postprandial Hyperglycemia Reduces CV Risk?

Clinical Trial	Description	Outcomes [HR (95% CI)]
STOP-NIDDM	Acarbose in IGT (N=1368)	MI: 0.09 (0.01-0.72) Any CV event: 0.51 (0.28-0.95)
Acarbose meta-analysis	N=2180	MI: 0.36 (0.16-0.80) Any CV event: 0.65 (0.48-0.88)
NAVIGATOR	Nateglinide in IGT (N=9306); 6 y	CV outcomes: 0.94 (0.82-1.09)
Heart2D	Lispro TID vs Glargine/NPH BID (N=1115); 2.6 y	CV event: 0.98 (0.8-1.21)

BID, two times daily; CV, cardiovascular; IGT, impaired glucose tolerance; MI, myocardial infarction; NPH, neutral protamine Hagedorn; TID, three times daily

1. Chiasson JL, et al. *JAMA.* 2003;290(4):486-494.
2. Hanefeld M. *Eur Heart J.* 2004;25(1):10-16.
3. Navigator Study Group. *N Engl J Med.* 2010;362(16):1463-1476.
4. Raz I, et al. *Diabetes Care.* 2009;32:381-386.

There was another study done with insulin, where they compared it with using lispro to target postprandial, or using glargine or NPH to target fasting glucose. This was done in patients with heart disease. The study was called HEART2D. It showed no difference. I think part of the problem in that study is they chose either postprandial or basal. I think you've got to target both.

You mentioned how you've got to identify patients who have a problem with basal. One little nuance there is that if you have people whose A1C is above goal, but yet their fasting glucose is not bad. Very often these are people have mild elevations in A1C. If your A1C is 10, it doesn't matter what insulin you use. But if you're using basal insulin and your A1C is around 7.5 or so, very often postprandial hyperglycemia is an important component in that. We need to address that.

We need to think about all these things when we are managing our patients who are not at the goals that we have set for them.

Module 2: Innovations in Basal Insulin Analogs

Jonathan Leffert, MD: Hello, I'm Dr. Jonathan Leffert. I'm a clinical endocrinologist in Dallas, Texas, and the current President of the American Association of Clinical Endocrinologists. With me today is Dr. Vivian Fonseca from Tulane Medical School. I'm going to talk about innovations in basal insulin analogs.

Basal Insulins Currently Available

	NPH Insulin	Insulin Glargine U-100	Insulin Detemir	Follow-on Insulin Glargine	Insulin Glargine U-300	Insulin Degludec
Insulin type	Human; intermediate-acting	Analog; long-acting	Analog; long-acting	Analog; long-acting	Analog; long-acting	Analog; long-acting
Onset	2-4 hours	1.3 hours	1.3 hours		6 hours	1 hour
Peak	4-10 hours	No pronounced peak	Relatively flat	No pronounced peak	Flat	Flat
Effective duration	10-16 hours	Up to 24 hours	Up to 24 hours	Up to 24 hours	≤36 hours	≤42 hours
Half-life	Unknown*	14 hours	5-7 hours		~23 hours	~25 hours
Time to steady-state	Unknown	2 days	2 days		4 days	2-3 days

Porcellati F, et al. *Diabetes Care.* 2007;30(10):2447-2452. Lucidi P, et al. *Diabetes Care.* 2011;34(6):1312-1314. Niswender K. *Clin Diabetes.* 2009;27:60-68. Novolin N [package insert]. Indianapolis, IN: Eli Lilly & Co.; January 2017. Lantus [package insert] Bridgewater, NJ: sanofi-aventis US LLC; August 2015. Basaglar [package insert]. Indianapolis, IN: Eli Lilly & Co.; April 2017. Levemir [package insert]. Princeton, NJ: Novo Nordisk US; February 2015. Toujeo [package insert]. Bridgewater, NJ: sanofi-aventis US LLC; October 2015. Becker RH, et al. *Diabetes Care.* 2015;38:637-643. Tresiba [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; December 2016. Heise T, et al. *Diabetes Obes Metab.* 2012;14(10):944-950.

First, I'd like to talk about the current basal insulins available. If we start with NPH insulin, which is a very old insulin, that insulin had a fairly short onset of action and a fairly short peak. It usually lasted about 10–16 hours.

The big advance was when we went to basal Insulin glargine U-100. It was a long-acting insulin, it did not have a peak, it lasted up to 24 hours, and had a half-life of around 14 hours.

Then we also have another insulin analog called insulin detemir, another basal long-acting insulin also with a relatively flat peak, and can last up to 24 hours, although sometimes one has to take more than one dose of insulin detemir a day in order to get control of diabetes.

Then, the newest insulin is the follow-on insulin glargine, which is… has no pronounced peak and also a 24-hour duration, similar to insulin glargine U-100.

Another insulin which has been recently introduced is insulin glargine U-300, which is another long-acting analog. It has a very flat peak and can last up to almost 36 hours with a half-life of around 23 hours.

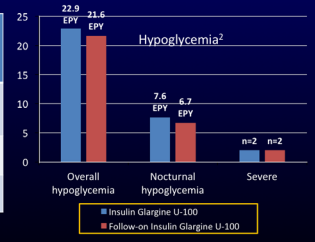
And the newest basal insulin on our… in our armamentarium, is insulin degludec. It has a short onset of action with about a 25-hour half-life. It takes a couple days to get to steady state with that insulin.

So, in summary, in the evolution of basal insulins, we've gone from a short-acting insulin requiring several shots a day, to long-acting insulin that requires one shot, possibly over at least 2–3 days.

In looking at another recent addition, we have Basaglar, which has recently come on the market, and in comparison to glargine U-100, in insulin-naïve patients, it was shown that hemaglobin A1C, insulin dose, weight gain, and hypoglycemia are essentially identical between glargine U-100 and Basaglar.

Efficacy and Safety of Follow-on Glargine U-100 (Basaglar®) vs Glargine U-100 (Lantus®) in Insulin-naïve Patients with T2DM[1]

Endpoint (N=455)	Insulin Glargine U-100	Follow-on Insulin Glargine U-100
HbA1c (%), change from baseline	-1.54	-1.48
Insulin dose (units/kg-day)	0.44	0.42
Weight gain (kg)	2.2	2.0



[1]Mean age = 58 years; duration of diabetes = 11 years; Baseline: HbA1c = 8.4% to 8.5%, weight = 89-91 kg, BMI = 32 kg/m²

[2]Overall (plasma glucose ≤70 mg/dL or sign or symptom of hypoglycemia) and nocturnal hypoglycemia (between bedtime and waking) are expressed as events/patient-year (EPY). Severe hypoglycemia (requiring assistance, baseline to month 6) is number of

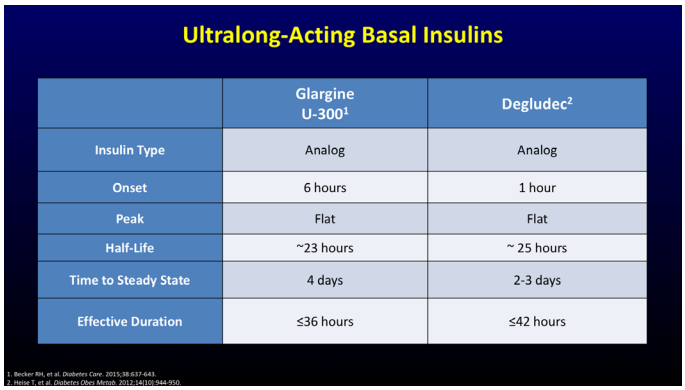
Rosenstock J, et al. *Diabetes Obes Metab.* 2015;17:714-741.

Dr. Fonsecca, would you talk about the ultra-long-acting basal insulins, please?

Vivian Fonseca, MD: So, we now have these ultra-long-acting basal insulins, U-300 glargine and degludec.

U-300 glargine is actually nothing but glargine itself. Same molecule as the U-100, it's just made more concentrated. And when you make it more concentrated, it lasts longer. It has something to do with changing the pharmacokinetics because it's a smaller droplet and it absorbs slower. Degludec, on

the other hand, is a different kind of molecule, it's an analog with some substitution. But, both are designed to work longer than glargine.

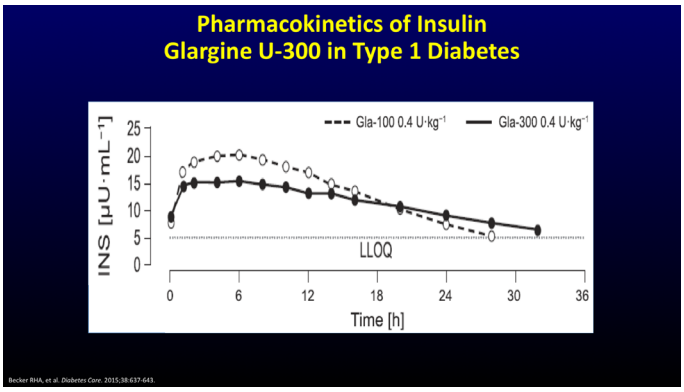


They also, as a result, are flatter in that they have less of a peak. The half-lives are like around 24 hours, they do take a little bit longer than glargine, and although the time to steady state, as you pointed out, is 2 to 3 days, which means we have to wait a little while before making any changes in dosage, and the effective duration on pharmacokinetic and dynamic studies is longer than 24 hours—up to 42 hours with degludec. They are really given once a day in clinical practice, because if you try to do it longer than that, it doesn't work that well for getting good glycemic control—so that's what we've learned from studies.

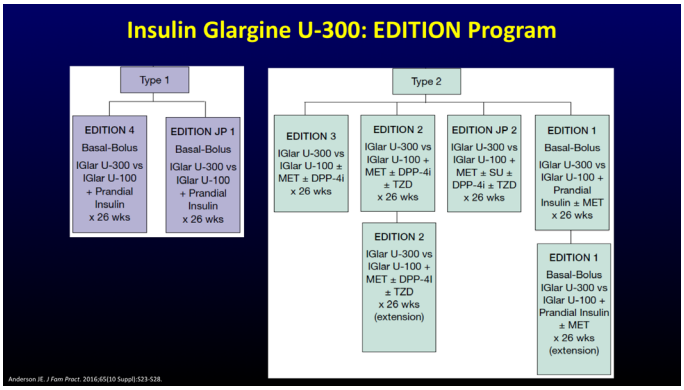
They're longer acting; there haven't been head-to-head studies between these; most of the comparisons have been with either detamir or U-100 glargine, with NPH.

So if you look at the pharmacokinetics, here's an example comparing U-100 with U-300. Exactly the same molecule. But the U-300 has less of a peak and a longer duration of action.

What that means in practice, with less of a peak, you're less likely to get hypoglycemia in those earlier time points, which might be important to patients who get hypoglycemia during the night. As we've seen from clinical trials, that has actually made a difference in trials.

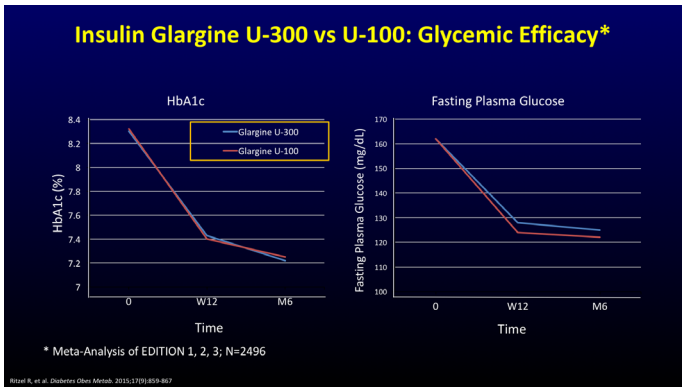


So, speaking of trials, let me first of all talk about the U-300 trials, where the comparison was made between U-300 glargine with U-100 glargine. And these studies were done in type 1 and type 2 diabetes separately. The program is called EDITION. In type 1 there were 2 studies, EDITION 4 and one in Japan called JP1. There were a number of studies done internationally, and also in Japan separately in type 2 diabetes, encompassing a wide range of people who were previously on basal-bolus therapy. There were studies in people who were just taking 1 basal insulin before. And also importantly, people who had never been on insulin before, failing on oral agents, starting their insulin answering the question, "Will it make a difference whether you started with U-100 or U-300?"



Jonathan, what would you expect with a difference between these? You know, it's the same molecule.

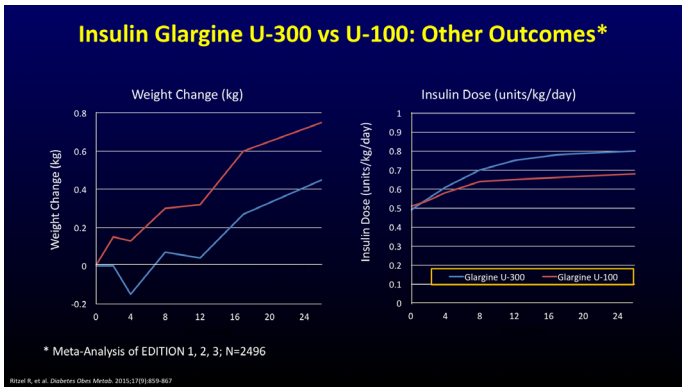
Jonathan Leffert, MD: So, in actuality, Vivian, there wasn't much of a difference at all. If you look at the data from the . . . in terms of hemoglobin A1C over the period of the study, the U-300 and U-100 essentially were the same over time.



Vivian Fonseca, MD: On glucose.

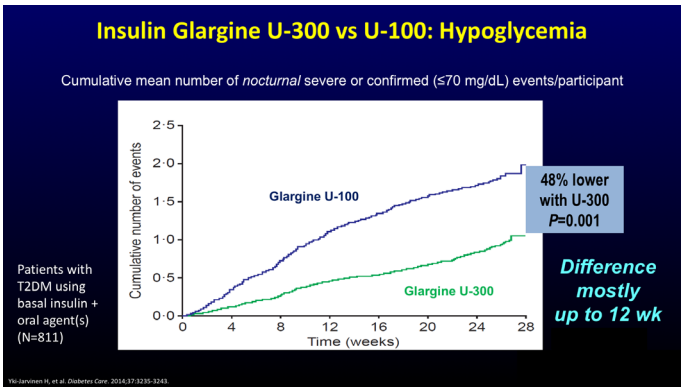
Jonathan Leffert, MD: As far as glucose is concerned. And also on fasting plasma, glucose is, you know, essentially the same between the U-300 and U-100.

But, if you look at a few other issues, for example weight change, it turns out that the U-100 insulin gained a little bit more weight with U-100. And in terms of the insulin dosage you required more insulin when you took… in the U-300 arm of the trials.



So that's something, again, to think about in clinical practice when you're taking care of patients with diabetes. To think about, maybe, up-titrating the dosage in patients who are on U-300 as compared to U-100.

Also, if you… the major issue though, is the issue of hypoglycemia. If you look at the studies, between glargine U-100 and glargine U-300, there was a significant 48% lower incidence of hypoglycemia as defined by a glucose less than 70 mg per dL in the patients who were on U-300 as compared to U-100.



This is a significant issue and is very important in relationship to taking care of patients on basal insulin. Because hypoglycemia is what prevents you, in large part, from improving glycemic control overall.

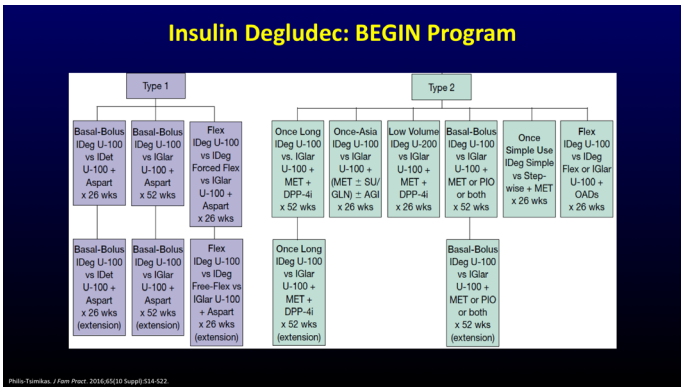
Vivian Fonseca, MD: And much of this difference is seen during the night, isn't it though?

Jonathan Leffert, MD: Yes.

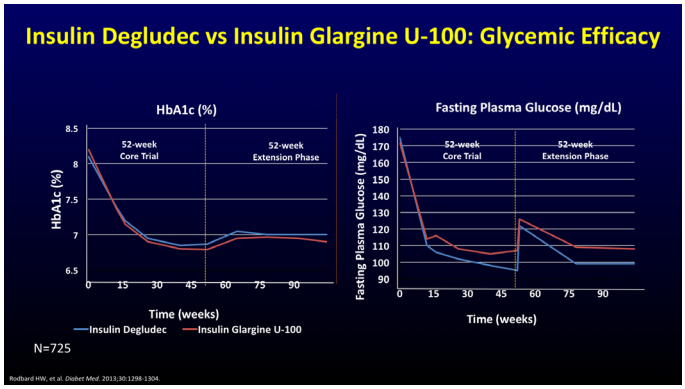
Vivian Fonseca, MD: Hypoglycemia, which is very distressing for patients.

Jonathan Leffert, MD: Yes. Vivian, will you talk about the other new insulin, degludec?

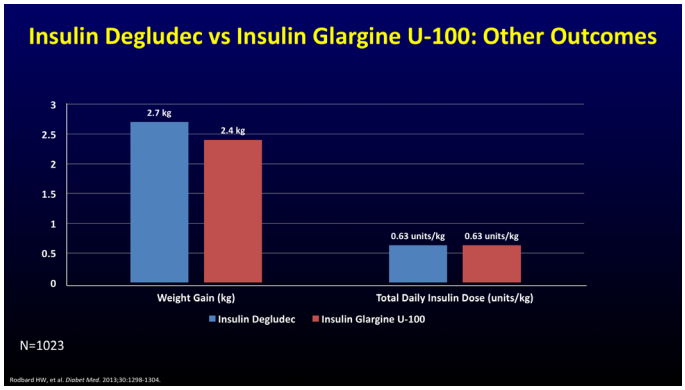
Vivian Fonseca, MD: So, insulin degludec has a wide range of studies, they call it the BEGIN program. And again, they did it with type 1 diabetes and in type 2 diabetes. The program is a little broader than what you just described with the U-300 insulin, because this is a relatively new insulin. In type 2, they just used it in people just starting insulin for the first time. They used it in people already on insulin. And they also have 2 strengths of the insulin degludec. There's a U-100 and a U-200.



So, in order to be a little comprehensive, they carried out a number of clinical trials. The bottom line is, insulin is insulin. And when you're comparing degludec and U-100, in terms of glycemic efficacy, as you just heard, when you compare Glargine U-100 and U-300, exactly the same thing happens when you compare degludec and glargine U-100. You have the ability to titrate, and you're titrating to a fasting glucose, you will end up with identical fasting glucose, and when you do that, the A1C is also identical.



So, all these insulins work. You're low on glucose, they work equally if you titrate enough. But there are other subtle differences that start appearing. At least in the degludec vs U-100 glargine studies, there was no difference in dose, there was no—very little if any—difference in body weight. The striking difference comes in hypoglycemia, just as you saw in the glargine U-300 trials.



I think this is very important for patients. There's one important thing to remember, though. That is, the definition of hypoglycemia.

So could you walk us through this? I think, they use different definitions in different studies and got different results.

Jonathan Leffert, MD: Right, so if we talk about the hypoglycemia in the different programs, there was the degludec and glargine U-300 vs the glargine U-100. In a meta-analysis of these phase 3 clinical trials, a number of different studies basically showed, in the definition of the degludec trials of less than 56 mg per dL and in the glargine U-300 trials of less than 70 mg per dL, there was a similar number of events shown, in terms of hypoglycemia.

Hypoglycemia with Degludec and Glargine U-300 vs Glargine U-100

Meta-analyses of phase 3 clinical studies in T2DM

	Degludec[1]	Glargine U-300[2]
# Studies	5	3
# Participants	3372	2496
Definition of confirmed hypoglycemia	<56 mg/dL and severe	≤70 mg/dL or severe
Anytime events [Rate ratio vs glargine U-100 (95% CI)]	0.83 (0.74-0.94)	0.86 (0.77-0.97)
Nocturnal events [Rate ratio vs glargine U-100 (95% CI)]	0.68 (0.57-0.82)	0.69 (0.57-0.84)

With both insulins, ~15% fewer overall and ~30% fewer nocturnal events vs glargine U-100

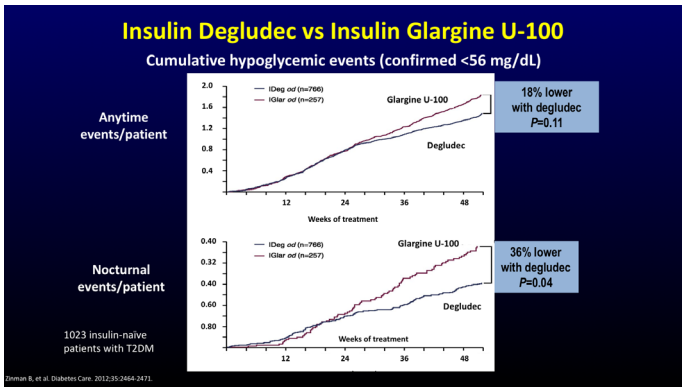
1. Ratner RE, et al. *Diabetes Obes Metab.* 2013;15(2):175-184.
2. Ritzel R, et al. *Diabetes Obes Metab.* 2015;17(9):859-867.

So thus, it seems again, to say, just as you said, insulin is insulin. Hypoglycemia is hypoglycemia. So if you have a low blood sugar, no matter whether its less than 56 to 70, you're going to get a certain number of events, but it's going to be similar or the same between the degludec and the glargine U-300.

Vivian Fonseca, MD: But they haven't really been compared directly with each other. This is compared to glargine U-100, the relative risk of hypoglycemia is reduced with both these insulins.

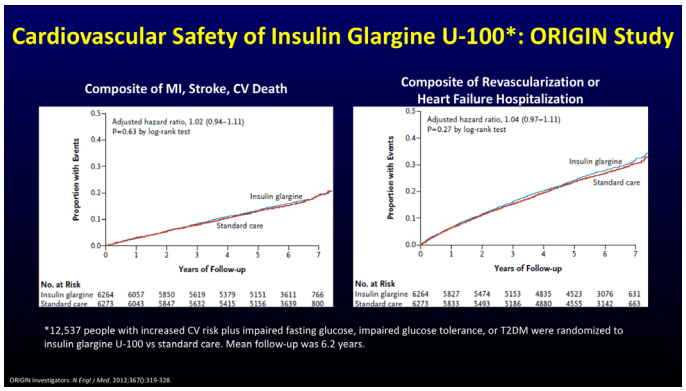
Actually people have done analysis of what it would be if you used the less than 56 with glargine U-300.

Jonathan Leffert, MD: Right. So, if you look at the insulin degludec vs the glargine U-100, you see that basically in the degludec arm, there were less hypoglycemic events when the blood sugar was, at a confirmed blood sugar of less than 56, and similarly, as you mentioned earlier, the issue of nocturnal events was significantly less as well.



Again, that always is a limiting factor in relationship to our ability to treat patients to their goal.

The other area of insulin management that is also very important is the issue of cardiovascular risk. If we look at the issues of noninferiority of insulin glargine vs standard of care, it appears in the ORIGIN study that there is no difference in insulin glargine and standard of care for the issues of myocardial infarctions, stroke, cardiovascular death, or heart failure requiring hospitalization, any aspect of the issues that we refer to as cardiovascular-related events.



I think that's another important component—and something that we're starting to see more and more as an issue in relationship to how we take care of diabetes—is the issue and the risk factors associated with cardiovascular risk. And this again was a nice way of proving that there wasn't any difference between insulin glargine and other standard care.

Vivian Fonseca, MD: There was some hope at that time that insulin might be better than standard care, but remember that standard care is metformin, so starting with metformin and merely diagnosing diabetes. So you've got good control, but it wasn't superior, but it was safe.

Jonathan Leffert, MD: Right. So that was the other thing. It gave us a lot of confidence in understanding glargine. Insulin glargine was a safe and effective medication.

Vivian Fonseca, MD: Can that be applied to U-300?

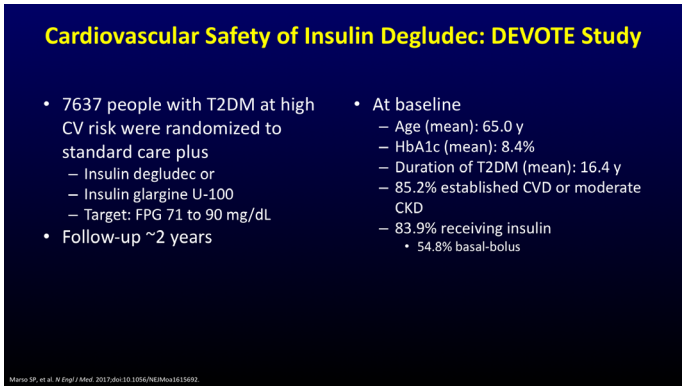
Jonathan Leffert, MD: Yes, it also is applied to U-300.

Vivian Fonseca, MD: It's the same molecule, after all.

Jonathan Leffert, MD: So the FDA concluded with that, glargine U-300 was essentially the same in relationship to glargine U-100.

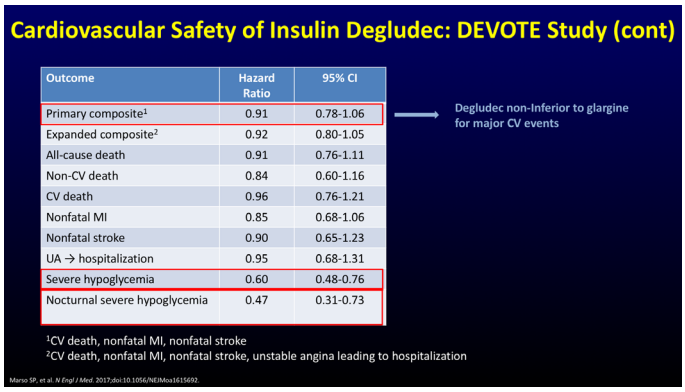
Vivian Fonseca, MD: To the long-term safety. So we can assume that it's safe—just as safe as insulin glargine.

Jonathan Leffert, MD: If we look at the cardiovascular safety of insulin degludec, which is the DEVOTE trial, this was a large trial looking at cardiovascular risk and they were randomized to a number of different arms of the trial. Insulin degludec vs insulin glargine U-100. The patients were typical patients with type 2 diabetes. The trial lasted for 2 years. This was a trial to actually look to see whether there was improvement in cardiovascular risk with this agent—insulin degludec.



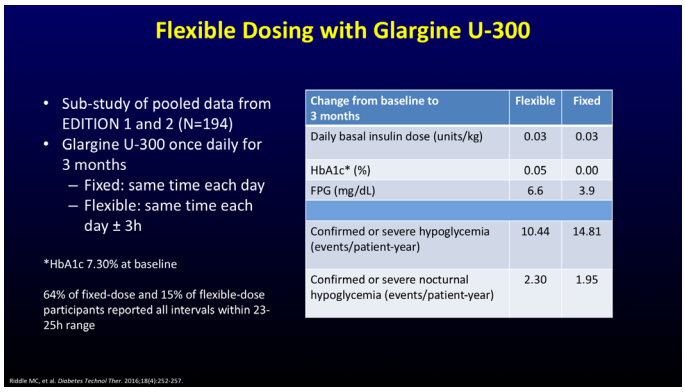
Why don't you tell us a little bit about that safety trial and what it showed.

Vivian Fonseca, MD: So, you know here you're comparing insulin glargine with degludec and in different combinations with different oral agents, and sometimes basal-bolus therapy—there was no difference in cardiovascular events. I think, cardiovascularly, they are equal.

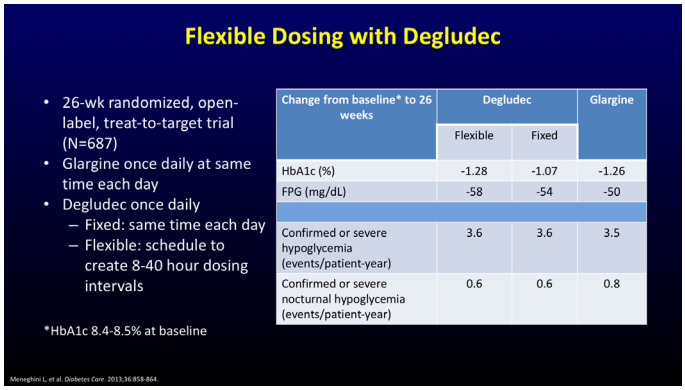


There was a difference, though, in hypoglycemia. Severe hypoglycemia was significantly less with insulin degludec, compared to glargine, and nocturnal hypoglycemia was particularly less. In the trial, insulin glargine was given at a fixed time of the day, mainly at night. There was some flexibility in degludec, which has been tested in a number of clinical trials, so that might have made a difference—in some of the earlier trials—to the timing of nocturnal hypoglycemia. If you took it in the daytime you might have less risk at night, but overall hypoglycemia was less. Severe hypoglycemia was less. This difference was statistically significant, perhaps because of the power of the study. This was a longer-term study in a large number of people.

Talking of flexibility of dosing, it's been one of the emphases of degludec, were these trials that they did about whether you took it in the morning or you took it at night, it didn't really matter. There's been no dedicated study with flexible dosing with glargine U-300, but there are some patients in the EDITION program, EDITION 1 and 2, where they did have some flexibility. Some patients took it at a fixed time, same time each day. Some people were a little flexible, giving themselves a window of about maybe 3 hours or so, and there was no difference in terms of A1C lowering, hypoglycemia rates, etc. I think there is some possibility of flexibility of glargine U-300, but it hasn't really been formally tested.



In contrast, with degludec there has actually been a randomized trial, treating to target and comparing it with glargine, given at the same time every day. Whereas degludec was given either at a fixed time, which is the same time every day, or a flexible schedule. Sometimes an 8-hour gap between insulins, and sometimes 40 hours. That can make a difference in terms of practical things for patients.



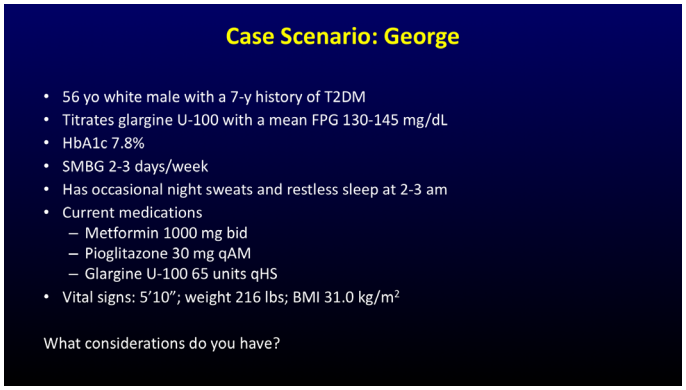
Say you're used to taking it every morning, but one morning you forget and you go off to work and you don't know when to take it. You could take it in the evening, and actually, it didn't make that much difference. The A1C reduction was very similar. The fasting glucose was very similar. The hypoglycemia was very similar. So in a formalized, structured manner in a clinical trial, flexible dosing with degludec was possible.

So, in summary, you have a wide range of insulins now, with a lot of different characteristics in terms of pharmacodynamics, pharmacokinetics. You can use it at different times, longer duration of action, less of a peak, differences in hypoglycemia. It gives us a lot of room to individualize even basal therapy with our patients.

Jonathan Leffert, MD: And Vivian, that's what I was going to say. As a practicing clinician, that's really valuable for our patients because we have a lot of opportunities to really identify and specifically try to target those particular insulins to the correct patient. That has been a revolution to how we take care of people with type 2 diabetes and type 1 diabetes. It's really been remarkable over the last several years to see that evolution go on forward.

Module 3: Escalation vs Intensification of Basal Insulin

Jonathan Leffert, MD: Hello, I'm Dr. Jonathan Leffert. I'm a clinical endocrinologist in Dallas, Texas, and the current President of the American Association of Clinical Endocrinologists. I'm here today with Dr. Vivian Fonseca, Professor of Medicine at Tulane Medical School and I'm going to talk about the escalation and intensification of basal insulin.

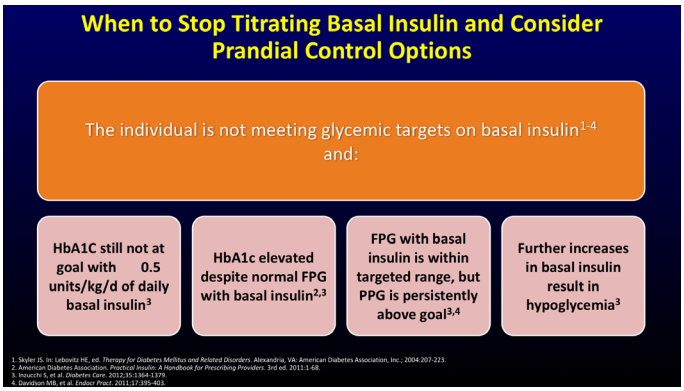


First, I'd like to talk about a case. Case number 1 is George, a 56-year-old white male with a 7-year history of type 2 diabetes. He titrates glargine U-100 with a mean fasting blood sugar of around 130-145. His A1C is 7.8. He checks his blood sugars 2-3 days a week. He has occasional nights sweats and restless sleep at 2 o'clock to 3 o'clock in the morning. His other medications include: metformin 1000 mg twice a day, pioglitazone 30 mg every morning, and glargine U-100, which he is taking 65 units at bedtime. He weighs about 216 lbs, he's 5'10" and has a BMI of 31.

So, Vivian, what would you do in this situation?

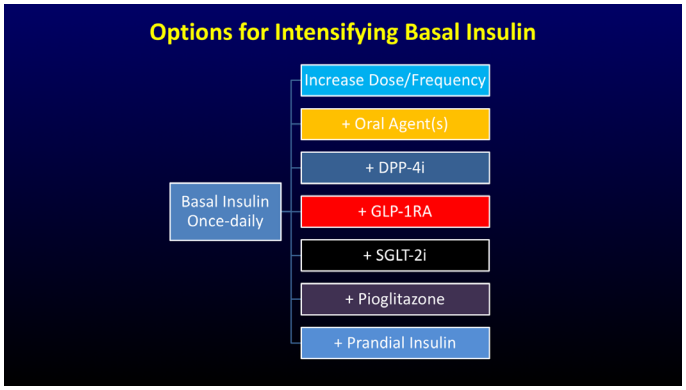
Vivian Fonseca, MD: So, this is a common scenario. The patient is not at goal; his A1C is 7.8; he's trying very hard. He's been titrating his insulin up, he's got up to 65 units, which is a fair amount of insulin. You know, we have a lot of insulin resistance among our obese patients, but he's taking a sensitizer, pioglitazone. He's also taking metformin. He could do with some weight loss, a BMI of 31, but he's really struggling with that. He's getting these night sweats and we've talked about hypoglycemia. He's now terrified about titrating his insulin. He's really worried about the fact that he might be dropping too low and that could be dangerous during the night. Yet, he's not at goal and this is really very challenging. So, you know, one of the considerations here is have we titrated this guy a little too much.

So, when people are not meeting targets and they're taking basal insulin there are a number of things that help us decide that somebody's getting a little too much basal insulin. One consideration, although I don't like to be too rigid about if someone is taking more than 0.5 units per kg of the basal insulin, then maybe they're taking too much, although I won't get too hung up on the 0.5. There are some people who have inherent insulin resistance and they might need a bit more. But I think the real problem here is that this guy's fasting glucose is not too bad, but his A1C is so high and that tells me he is probably high at other times of the day and all we're doing is checking his fasting glucose, which is convenient, and what we often do with basal therapy, but is not quite enough. If we do postprandial glucose testing—and today we can even do professional continuous glucose monitoring—you'll find that he is persistently above goal during the day. And of course, the last real critical problem is that he's getting hypoglycemia during the night, and if you increase his basal insulin, that might get even worse to the point where he might lose consciousness. He's getting some symptoms.



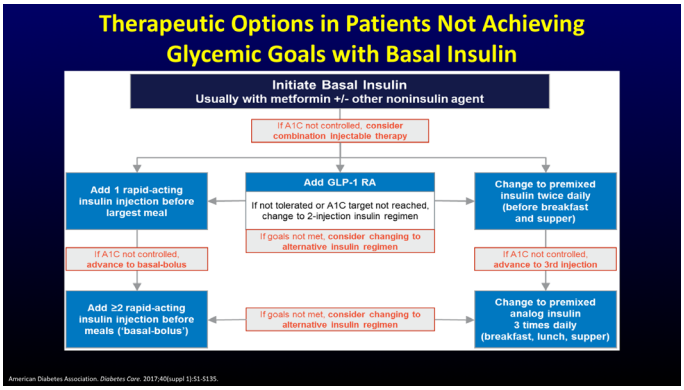
There are a number of reasons that point to this patient having too much basal insulin and fortunately we have other options now. We could do a number of things to stop him from getting the hypoglycemia and get better control. One option would be to change the dose frequency to allow more insulin. So, going from once a day to twice a day. However, then you're just not addressing all the pathophysiological abnormalities of diabetes.

So you could you choose oral agents, other oral agents or other injectables to go with that insulin. He's already on 2 oral agents and adding in more might add to complexity. You could argue that a DPP-4 inhibitor is used better early in the disease, but it has been tested with insulin, and you get a slight improvement in control. A GLP-1 receptor agonist could be an option, but that's another injection, although today we have fixed-ratio combinations. You could use a SGLT-2 inhibitor. You've already got pioglitazone, I wouldn't push the dose more because he's trying to lose weight, and you get weight gain when you have pioglitazone with insulin in high doses. And another option is prandial insulin, which is really the focus of our discussion today.



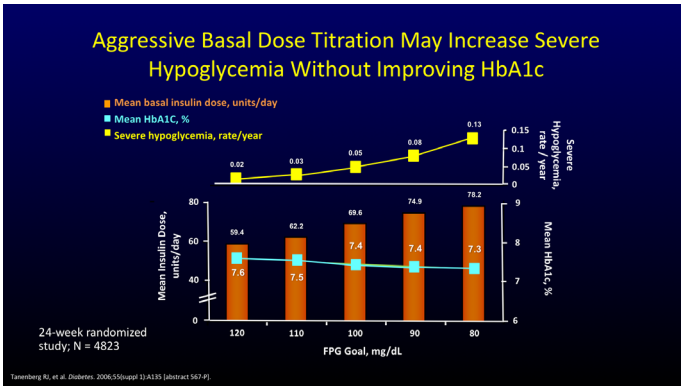
Jonathan, what do the guidelines tell us when someone is taking oral agents, goes on basal, still not controlled. What can we do?

Jonathan Leffert, MD: So we really have to think about how we're going to individualize the therapy for this gentlemen, and I think there are several different options. One of the options would be, as you mentioned, to add a GLP-1 receptor agonist and that would be helpful particularly in relationship to a man who is trying to lose weight. There are issues, of course, with added injections, but I think a lot of patients are very interested in losing weight, and if you can help them to lose weight and still get better glycemic control that might be an option.



Another is to add a rapid-acting insulin injection before the largest meal of the day. That's sometimes very convenient for a patient, so that they are not taking multiple bolus injections a day, but maybe one bolus injection prior to the biggest meal. And then the third option, which we use less frequently, is to use a premixed insulin twice daily. Again, to be able to achieve the compliance in getting a long-acting insulin and a short-acting insulin, and then if we go down the side of trying basal… excuse me, premeal insulin, and we don't get where we want to get with our one injection a day, then we may need to add more than one injection a day and go to wherever we need to go to be able to get postprandial control and improvement in his glycemic control.

So, if you look at basal dose titration what it does is that it may increase severe hypoglycemia but without improving A1C.



Vivian Fonseca, MD: Or you get very little improvement, but the hypoglycemia goes up quite a lot after a point.

Jonathan Leffert, MD: Right, so you start giving more and more basal insulin and you get more and more hypoglycemia, but less and less… but no

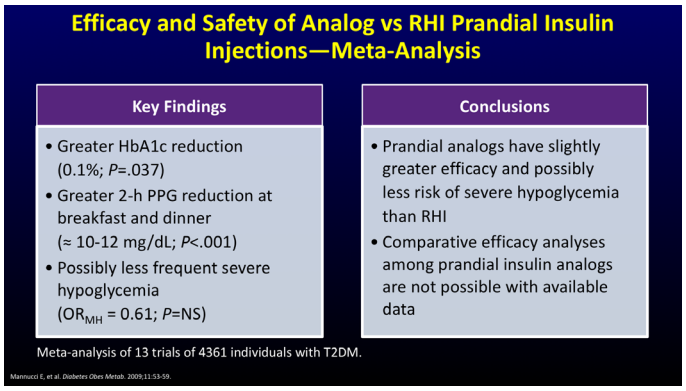
improvement in control, and this really tells you that you need to go to prandial insulin.

So, Vivian, tell us about prandial insulin therapy and how it works in type 2 diabetes.

Vivian Fonseca, MD: So, what would you do here? With basal insulin you're lowering the fasting, but the postprandial excursions remain. So, I think that you've got to address the prandial in some way. We're going to talk about using some form of prandial insulin. You talked about basal plus adding 1, but ultimately you would end up with a number of them.

But, Jonathan, just before I get there, could you tell us a little about the old-fashioned regular, human insulin as the prandial, or should we be using analogs?

Jonathan Leffert, MD: So, one of the problems, of course, with insulins, as they've evolved, is they become more and more efficacious, and with less hypoglycaemia. And the main issue with regular human insulin from years and years ago was you would get these very significant drops in blood sugar postprandially. Analogs have shown much better efficacy, less severe hypoglycemia, and this efficacy has been among all the prandial insulins in association with, and in meta-analysis in relationship to, regular insulin. So, I think in our current day, the analog insulins are really the way to go, and they provide so much more flexibility for the patient.



Vivian Fonseca, MD: It really relates to the pharmacokinetics. They are very quick-acting and short-acting, so that after the meal is metabolized… absorbed and metabolized regular insulin still keeps working.

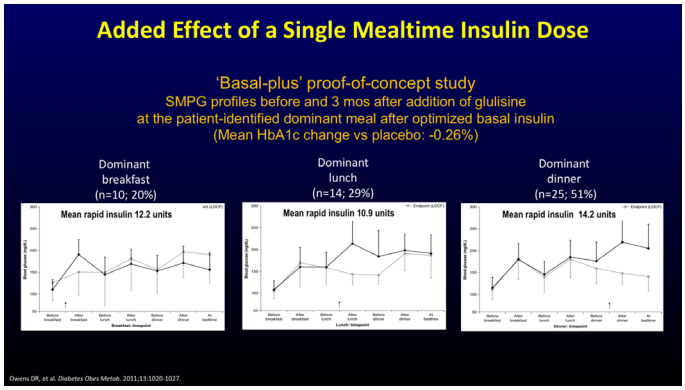
Jonathan Leffert, MD: Yeah, I have patients who tell me, "Vivian, give me that insulin that will get the fastest 'on' action so that I can bring that blood sugar down the fastest."

Vivian Fonseca, MD: And the fastest off.

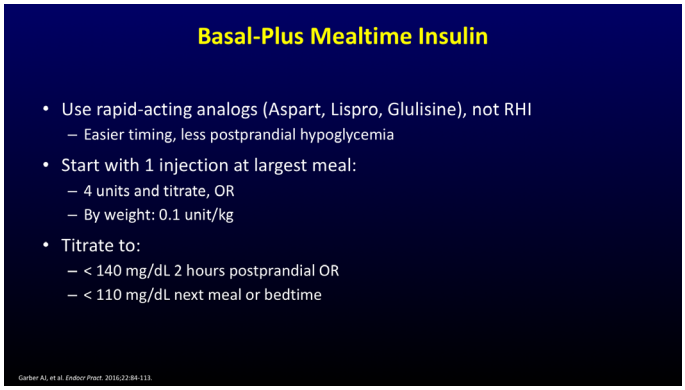
Jonathan Leffert, MD: And the fastest off too, as well.

Vivian Fonseca, MD: And you know, you can do that with regular insulin, but you've got to inject it 30 minutes before the meal, and people often forget that. They take it just before the meal. It's not absorbed fast enough, it doesn't quite work fast enough, where analogs have an advantage. So there are a number of studies done with lispro, aspart, glulisine, all the analogs, looking at the time of injection. So, you can give it 30 minutes before, though you get a little bit of a drop because it works very fast, but there's studies showing you can actually give it at the time of the meal, maybe 15 minutes before, which is generally recommended, and sometimes you can actually give it after you start the meal, maybe up to 15 minutes after. It's not quite as effective, but it's very useful in people who don't have good appetites, they're not eating very well and you don't know when they're going to eat the meal, so when they start eating… you're sure about that. Similarly, with children, it's been very useful to be able to give it just after they start eating so you're certain that they're going to be having the meal, rather than at fixed times. Useful in hospitals as well. So, that timing of the meal is important.

It's also important in relation to this basal-plus concept that you mentioned. Giving it before the main meal of the day. What is the main meal of the day? And sometimes the main meal might vary. For people taking lunchtime insulin, there is one study that showed that if you just gave that main meal rapid-acting at lunchtime you prevent that rise that particular patient had at lunchtime. If breakfast is the main meal, you give it at breakfast time. Similarly, if dinner is the main meal. You eliminate that one major peak of the day, and that leads to some improvement in overall glycemia by eliminating the highest exposure to glycemia.

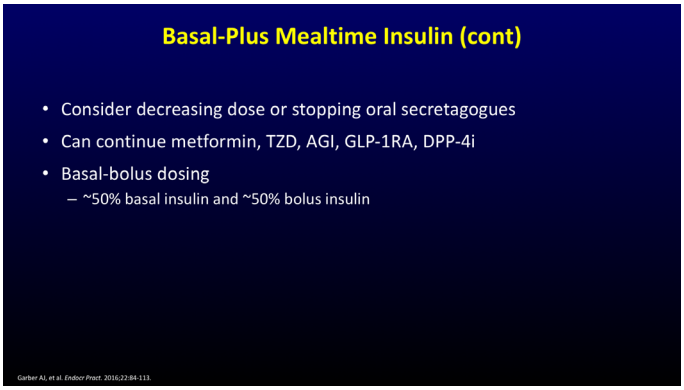


There's actually a study called OPAL, with glulisine, where they give it at different times. They give it at breakfast, they gave it at lunch, they gave it at dinner, and you saw that elimination of the big peaks that the patient had, depending on what was their main meal. And they got some improvement in control. You got an improvement in the spikes without using a very high dose of insulin. You're using it effectively at the correct time point that it needs to be done.



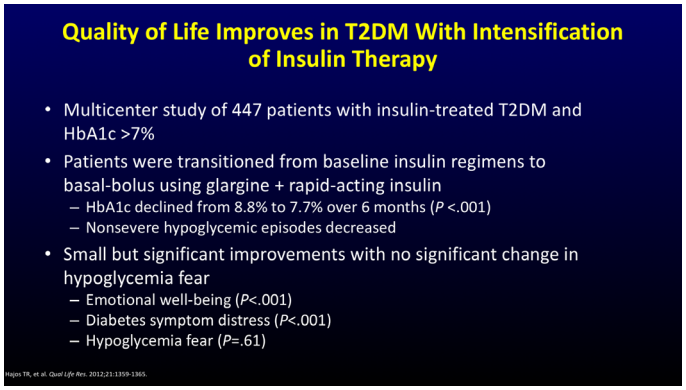
And, with that, has evolved this overall concept of basal, plus whatever analog you want to use, and it's probably best done with analogs because you want to do it at short… quick action… you start with one injection at the largest meal. I usually start with 4–5 units and then I titrate upwards. The titration is somewhat challenging. Some people like to test 2 hours after the meal, which is within AACE guidelines. Some people do it before the next meal, or if you're going to bed, take it at bedtime so that you're not too low. So you know where you are so you back-titrate if you're dropping too low, particularly at night. You up-titrate if your 2-hour postprandial is more than 140, you want to aim for around 140. At no time do you want the glucose to be over 180–200. You need to consider decreasing the dose at that time if a patient is on a secretagogue, like sulfonylurea, I often stop it. It's pointless; you're now giving insulin.

You can continue with other agents, continue with the metformin as is the case with your patient. Metformin, thiazolidinedione, you can continue; if your patient is taking an incretin, you can continue.



And then you have to think about the next phase. You know this is a step in this progressive disease. You're going from basal insulin to basal-plus 1 and, as you pointed out, maybe basal-plus 2 and basal-plus 3 like a type 1 basal-bolus, but it's a stepped approach to managing these patients. And surprisingly it may have a… what do you think, Jonathan, a quality of life affected by patients taking more insulin?

Jonathan Leffert, MD: Right, you know, Vivian, I also like the idea that it's very practical to use that mealtime insulin as a stepped approach, because I think that makes sense from the perspective of the patient, and also from the physician's perspective, in terms of looking down the road towards what the next steps might be, as you mentioned. And it's important also, from the patient's perspective in terms of the quality of their life. So, in patients who have had intensification of their insulin therapy, there's been a multicentered study that looked at this, and when they went from basal insulin to basal-bolus insulin, using glargine and a rapid-acting insulin, they got 2 good effects. One is their A1C declined from 8.8% to 7.7% over 6 months, and their hypoglycemic episodes decreased. But then there were significant, but small, improvements in their emotional well-being, their ability to deal with diabetes symptoms, and that all-important issue of hypoglycemic fear. That basically decreased because they weren't getting that big basal dose at the middle of the night, which lowered their blood sugars in the middle of the night, but then didn't control them during the day.



So, this is a very important part of the treatment of diabetes, which is really a lifetime treatment, and we have to be really cognizant, as we go forward in our treatment, of how these steps go forward with the patients. They really respond when they understand more about how we're doing this process.

Vivian Fonseca, MD: It's a very important thing. The ADA, in its last guideline, emphasized the psychosocial well-being of the patient and a concept that people have not really focused on enough is the one of diabetes distress. It's not depression, it's distress about the fact that you've got this terrible result: 8.8. You, yourself, as a patient, just feel like I'm not doing well although there is no specific symptom to it, and then, when you get down to 7.7, you sort of breathe a sigh of relief. Your distress is less. I think it's very important.

Jonathan Leffert, MD: I see it every day in the patients when they come into the office. It's really a very satisfying thing to see—as a physician—to see the patient so satisfied with getting a good result.

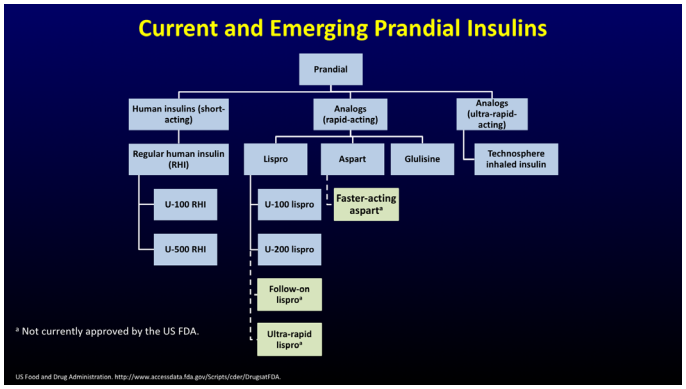
Vivian Fonseca, MD: Despite the complexity of having to take these multiple injections and advanced therapy.

Jonathan Leffert, MD: Exactly, they feel like they've overcome an obstacle and achieved a good result.

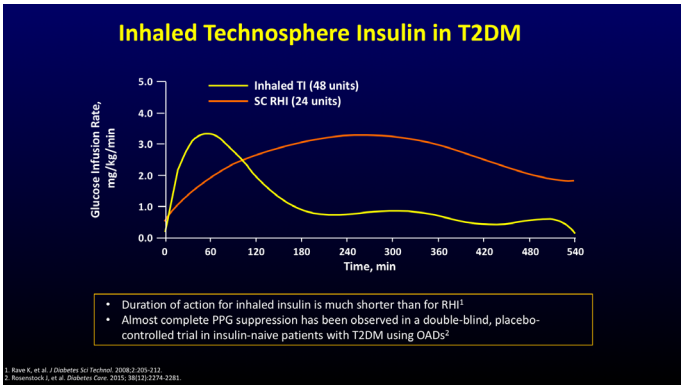
Module 4: Innovations in Prandial Insulin

Jonathan Leffert, MD: Hello, my name is Dr. Jonathan Leffert. I'm a clinical endocrinologist in Dallas, Texas, and the current President of the American Association of Clinical Endocrinologists. I'm here today with Dr. Vivian Fonseca, Professor of Medicine at Tulane Medical School. We're going to talk about innovations in prandial insulins.

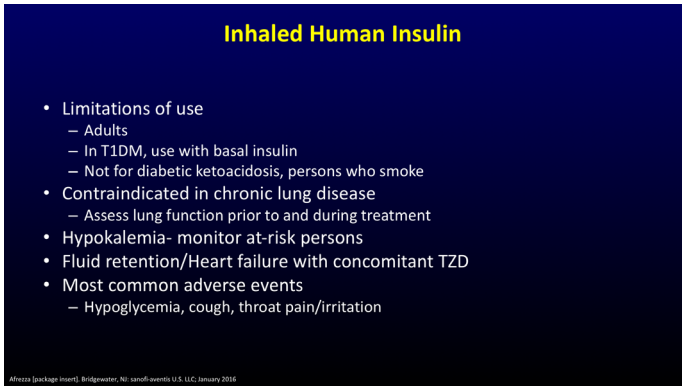
As you know, there are several prandial insulins. The beginning insulins were regular human insulin, which has the U-100 regular human insulin and U-500 regular human insulin. The regular human insulin, the U-100, has been replaced mostly by the analog insulins. And those include lispro, aspart, and glulisine. Lispro, as you know, has both a U-100 and a U-200 variety available. And there are some new lispros, a follow-on lispro and an ultra-rapid lispro, currently unavailable, but are in development. As far as the asparts are concerned, there is also a faster-acting aspart, which is also in development. And then, finally, there's the ultra-rapid-acting Technosphere inhaled insulin. Vivian, would you talk a little bit about those insulins for us?



Vivian Fonseca, MD: So, you know, inhaled insulin is not a new concept. One came on the market. It was a large device. It wasn't very successful. And now we have another. A much smaller device developed by Technosphere. It's a somewhat different formulation. Much easier to use than the previous one. It's very interesting. In the subcutaneous tissue, insulin is a little slow to be absorbed. The blood has to go and interact with that insulin and get absorbed; whereas, in the lung, it goes straight through. It's very, very fast, very short-acting. It has the advantage in that it can bring the blood glucose down very rapidly, if you're given enough, and it's gone in a short period of time, which means you don't get hypoglycemia. So, theoretically, a very appealing one, particularly for type 1 diabetes, but also for type 2. And it's been tried in people as the first insulin. Without basal insulin, you're taking oral agents, you add it on. It eliminates the postprandial peaks. Very effective, but there are some limitations to use.



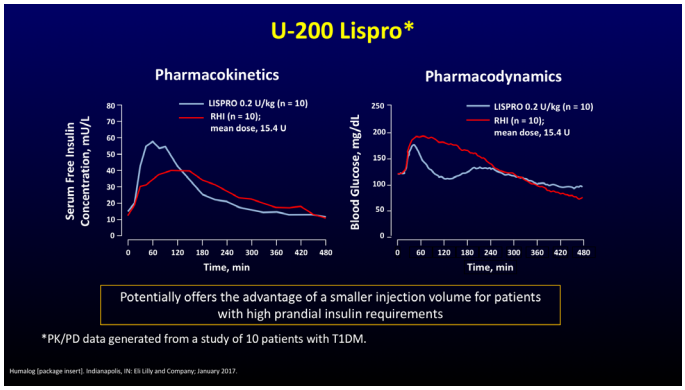
I think quite useful in type 1. In type 2, you've got to use higher doses. You know, you can't use it for ketoacidosis, you can't use it in people who are smoking because they weren't included in the clinical trials. It's contraindicated in chronic lung disease, so you've got to do lung function tests before starting treatment, and during treatment, which is a bit of a limitation. You've got to monitor a number of things related to insulin. What do you do when you have a cough and throat, and all that pain? You know, those kinds of things have to be worked out. But, in general, inhaled insulin is available for those who want it.



The other fairly recent development is U-200 insulin. You know, we'll get to U-500 later on, but U-200 is fairly new. Could you comment on that?

Jonathan Leffert, MD: Sure. U-200 insulin lispro is used in type 1 and in type 2 diabetes, and the pharmacokinetics and pharmacodynamics are similar to U-100, but different, of course, from regular human insulin. You get an earlier peak, and the time off of the insulin is less for the U-200 insulin lispro. And so, it does have the advantage of using smaller injection volumes for patients who require a lot of insulin. So it has its value in those patients who need a great deal of insulin preprandially, in order to make sure that their blood sugars are well controlled.
So, basically, it's half the volume. You do have to occasionally be concerned about hypokalemia.
There is also the potential concerns of always, with thiazoidinediones, the issues of fluid retention, and heart failure. And there's some adverse effects, of course, always hypoglycemia, some injection site reactions, and lipodystrophy.

Vivian Fonseca, MD: But not particularly more than other insulins.



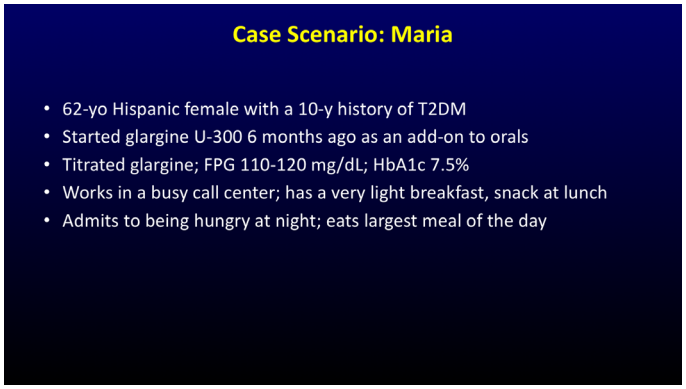
Jonathan Leffert, MD: Correct.

Vivian Fonseca, MD: U-500 insulin, on the other hand, is quite different. As you make insulin more and more concentrated, the pharmacokinetics and pharmacodynamics change very substantially. It's much longer acting. In fact, regular human insulin, or the analogs, don't really last overnight. You've got to add in a basal insulin. There's some people with type 2 diabetes who use U-500, who don't need a basal because that U-500 in the evening lasts overnight because of the change of the dynamics. Of course, some of them are taking oral agents, as well.

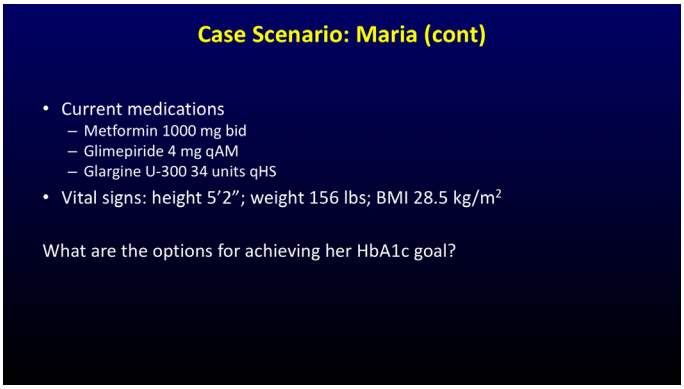
And why do we need U-500 insulin? It's because some people need a lot of insulin. And it's quite remarkable how much U-500 insulin we have been using in this country over the last few years. The sales have just gone up very dramatically. And that's related to insulin resistance in the population, obesity. On a per kilogram body weight .

Module 5: Putting it All Together, Case Scenario: Intensifying Basal Insulin

Jonathan Leffert, MD: Hello, my name is Dr. Jonathan Leffert. I'm a clinical endocrinologist in Dallas, Texas, and the current President of the American Association of Clinical Endocrinologists. I'm here today with Dr. Vivian Fonseca from Tulane Medical School. We're going to go over some cases to put the whole process together of how to treat people with diabetes in relationship to insulin and other medications.



The first one is Maria. She's a 62-year-old Hispanic female with a 10-year history of type 2 diabetes. She started glargine U-300 6 months ago as an add-on to her orals. Her glargine was titrated up, and her fasting sugars are in the 110 to 120 range. She currently has an A1C of 7.5%, which is not at goal. She works in a busy call center. She has a very light breakfast, and she snacks at lunch. She's very hungry at nighttime, and eats her largest meal of the day at that time. Her medications currently are: metformin, 1000 mg twice daily, glimepiride, 4 mg in the morning, and glargine U-300, 34 units at bedtime. She is 156 lb, is 5'2" tall, has a BMI of 28.5. Vivian, what do you think the options are for achieving her A1C goal?



Vivian Fonseca, MD: Again, common scenario here. She's trying a fairly new insulin. She's not on a huge dose of insulin, but she's not very obese. She's obviously titrated up to 34, and her fasting glucose is not bad. You'd have to titrate a fair bit more to get the A1C down to 7.5, and there's a risk of hypoglycemia there. You may want to discuss with her about her eating habits and spreading the meal through the day, avoiding weight gain as you get better. Clearly, she's getting postprandial hyperglycemia. It's probably that she's eating a very large meal when she comes home from work and the blood sugars are high for several hours after that. It's surprising how long postprandial hyperglycemia can last when you have a large fatty meal.

One option would be to use a GLP-1 receptor agonist, particularly one that addresses prandial glucose, like exenatide or lixisenatide, or even a once-a-day. You may consider once a week, but that addresses lowest fasting glucose more than postprandial glucose, so I'd probably go with one of the shorter-acting ones with that main meal or prandial insulin. So, you weigh the pros and cons of each, discuss with the patient what would be the more appropriate way, what her goals are for body weight, and changing her nutrition a little.

Jonathan Leffert, MD: Yeah, I think that's probably the way I would go, too. I'm always interested in trying to lower someone's weight, because I think they feel so much better with less weight—decrease their insulin resistance. But, I do think having a fasting glucose at 110–120 means that her postprandial sugars are high, and giving insulin preprandially would necessarily take care of that as well. Of course, I would be also concerned, depending upon how late she eats during the day, of that hypoglycemia that you sometimes can get postprandially with premeal insulin, and she would have to obviously change her diet appropriately to make sure that she was evening out her calories throughout the day, as you mentioned.

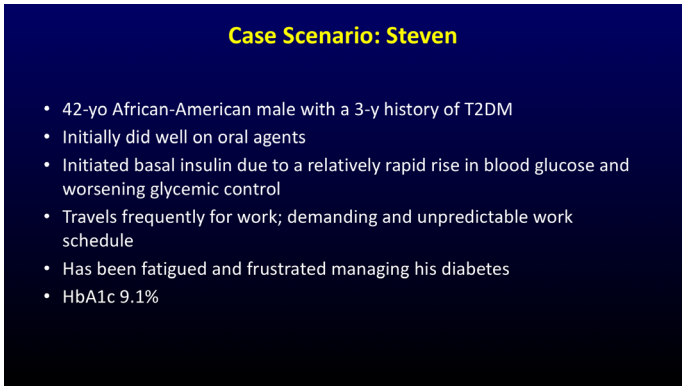
But, I think that I agree with the idea of a premeal insulin. Particularly, probably a predinner insulin might be the most appropriate way to go with this patient, and I think that she would probably get to her A1C goal relatively easily and have less likelihood for the nighttime hypoglycemia, which is very distressing to patients. They hate getting up in the middle of the night feeling like their bedclothes are soaked. They're feeling very uncomfortable. It often times makes them very nervous about taking insulin going forward, which, in this lady, is something that's probably going to be required forever.

Vivian Fonseca, MD: You might get some pushback from the patient, too, you know, who doesn't want to take another injection. This is a common thing. "I take this injection. I really don't want to do another one." You could discuss other options. Glimepiride could be done twice a day, although I'm not sure you're going to get her A1C down very much with just up-titrating the glimepiride. You'd probably get a very small incremental benefit. Or, maybe move it to the evening if that's the time of the main meal.

Another option would be an oral prandial agent like acarbose. We don't use it that much in this country. It's very popular in some other parts of the world where they have very high carbohydrate loads, and they seem to tolerate the side effects. I use it sometimes in very small doses, and it can be useful maybe just at that meal where she's having a lot of carbohydrate and maybe a lot of fat in the evening. I think some discussion about spreading the nutrition through the day might be appropriate.

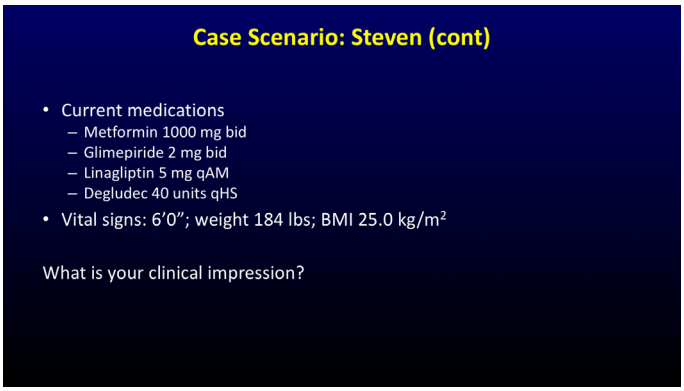
Module 6: Putting it All Together, Case Scenario: Insulin Resistance

Vivian Fonseca, MD: Hello. My name is Vivian Fonseca. I'm from Tulane University in New Orleans, Louisiana. Joining me today is Jonathan Leffert, who is an endocrinologist in Dallas, Texas, and the current President of the American Association of Clinical Endocrinologists. We're discussing insulin therapy in clinical practice in patients.



I want to discuss, with Jonathan, a patient. He's a 42-year-old African American male with a 3-year history of diabetes. He started oral agents, initially did reasonably well, then had to go on to basal insulin because he got very rapid worsening control. Started getting worse quite quickly. He related some of that to stress at work, a very demanding job, his unpredictable work schedule, he travels a bit, he gets a little tired with this, he's a little frustrated managing his diabetes, his sugars are high fairly frequently, and his A1C is 9.1.

You've been trying various medications. You advanced oral therapy fairly quickly. He started on metformin, went on, added glimepiride. He's taking metformin 1000 mg bid, glimepiride 2 bid. He then added linagliptin. He started initially with NPH insulin, changed that to degludec. He takes degludec U-200, 40 units at bedtime. Sometimes when he's traveling he takes it in the morning. He has some flexibility with that, but he's still not getting good control. He's a tall guy, 6 feet. He's 184 lb, but because of his height you work out his BMI—it's 25. What's your clinical impression?



Jonathan Leffert, MD: Vivian, this man looks like he has classic insulin deficiency. Whether he has true type 1 diabetes, or has latent diabetes, or autoimmune diabetes, or does he have type 2 diabetes with just the progression of the disease to insulin deficiency.

Vivian Fonseca, MD: Fairly quick, isn't it? Three years.

Jonathan Leffert, MD: Yes. He might need something like a GAD antibody to determine whether he truly has type 1 diabetes or not.

Vivian Fonseca, MD: Just to clarify, GAD is glutamic acid decarboxylase. It's an antibody that doesn't go away like islet cell antibodies go away. We use it in practice to identify type 1 diabetes. Well, all it tells you is you've got autoimmune disease, which makes it more likely that somebody has type 1. About 4% to 5% percent of people who we think have type 2 actually have these antibodies, and they tend to need insulin a little earlier. This guy, within 3 years, has gone on to insulin. He's not that obese. He hasn't got the classic features of type 2 diabetes.

Jonathan Leffert, MD: If you did find out that he had GAD antibodies and had type 1 diabetes, then the oral agents would be unnecessary in this patient. More than likely you would switch him just to a basal-bolus insulin. If he didn't, then you might continue on some of the medications. Most likely stopping the glimepiride, the sulfonylurea in this case.

Vivian Fonseca, MD: You raise a very good point. You talk about oral agents being unnecessary. I rarely hear that from people. Metformin is a great drug. It's being used because of the UKPDS data as the first-line therapy in diabetes. Remember in UKPDS, it was only the obese people who got metformin as monotherapy. This guy's not obese.

Jonathan Leffert, MD: Correct. If you're thinking about how you would go about managing him, I think first you really need to sit down with this gentleman and talk to him about what you're thinking about the type of pathophysiology that he has, and really get him to understand that his insulin deficiency is going to require insulin. Then it's most likely going to require a basal and bolus insulin. Have that conversation because he's very frustrated with the fact that he's been trying a number of different agents and really nothing has worked. Well, it's not going work if he doesn't get enough insulin. If you don't have insulin, you need insulin to be able to metabolize the glucose, and he just doesn't have that. That's going to be an important component of trying to deal with the frustration and onboarding this patient now to what you're going to try to do next, which is more than likely add bolus insulin on as most likely pre-meal, three meal a day if he's taking three meals, level.

That's a big component of what I do daily in practice, is I really spend the time to try to allow the patient to really understand where they're going. I think the compliance of taking insulin goes up tremendously if you get the patient to buy into the understanding of what they're doing.

Vivian Fonseca, MD: I think you're absolutely right. This guy needs to understand he's taking a good insulin in a fairly reasonable dose for his weight. He probably has type 1 diabetes, as you pointed out. If he understands that, he's going to take the insulin. Let me ask you, would you stop these oral agents in that case?

Jonathan Leffert, MD: Certainly, if I had the GAD antibodies, I would for sure. If I didn't, or if they were negative, then I would certainly stop the glimepiride and start peeling away the oral agents as we were adding the insulin and getting better glycemic control. Again, the whole idea is monitoring, making sure that he is following up with sugars and A1Cs and close care to be able to get this guy into a better range. Nine point one A1C! For one thing, he's not feeling well with that A1C. His energy level is probably decreased. He may be having some hyperglycemic symptoms. This is a situation where we really need to take some urgent steps and move forward quickly towards trying to achieve better control.

Vivian Fonseca, MD: Just to clarify, we do use oral agents in some people with type 1 diabetes, but it's mainly in those who are obese. This guy's not obese. I would follow what you just said, gradually taking him off, but putting in prandial. Which prandial would you use? Would you use a regular? Would you use an analog?

Jonathan Leffert, MD: I think that we've talked about the use of analog insulins as being much improved in terms of the time to peak and the ability to have less hypoglycemia. I would certainly use an analog insulin. I would start him out on an analog and I would use that on him. I would do it based upon insulin-to-carbohydrate ratios. You could start with a fixed dose, depending upon just the ability of the patient to understand all the nuances associated with dietary manipulations and carbohydrate-to-insulin ratios. You would want to prepare him, if you thought he was a type 1 diabetic, for those sorts of processes. Again, down the road you may be even intensifying his insulin regimen even more.

Vivian Fonseca, MD: He's going to need a lot more monitoring than just fasting glucose.

Jonathan Leffert, MD: Oh, yes.

Vivian Fonseca, MD: Probably continued glucose monitoring may be an option.

Jonathan Leffert, MD: Yes.

Vivian Fonseca, MD: I would reassure him that if he felt that the injections were too much, to consider a pump or something like that.

Jonathan Leffert, MD: Absolutely.

Vivian Fonseca, MD: There are a lot of options today for patients like this.

Jonathan Leffert, MD: I think, again, having the conversation initially with him about what his problem is, where he's going with it, what's that timeline, and what that looks like, I think is crucial towards buying into all these steps along the way. Patients are managing this disease for themselves. We're the guide, we're the map, but they do the work. We have to give them the opportunity to do it in a really appropriate way.

Vivian Fonseca, MD: I would also bring in the issue, or the fact, that he's not feeling well, and that if his glycemic control improved, he would feel better, it would improve the quality of his life, and despite having to take multiple injections or use a pump, it could very well fit in with his complex work schedule and lifestyle. There are ways to do it. It shouldn't detract from his ability to do whatever he wants with his life.

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