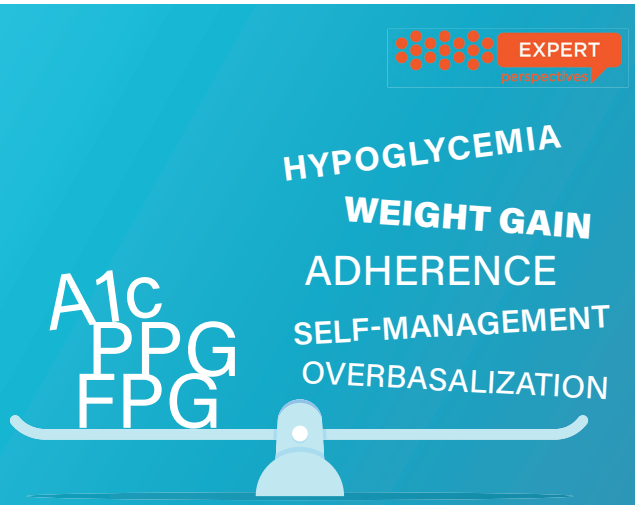
THE WHY AND HOW FOR COMBINATION BASAL INSULIN + GLP-1RA THERAPY IN TYPE 2 DIABETES



OVERVIEW

John Anderson, MD, and **Vivian Fonseca, MD**, provide their clinical insights into the rapidly evolving use of combined basal insulin and glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy for the treatment of patients with type 2 diabetes mellitus (T2DM). Based upon the pathophysiologic rationale for combining basal insulin and a GLP-1RA, Drs. Anderson and Fonseca discuss the benefits and limitations of adding a GLP-1RA vs prandial insulin in patients with inadequate glycemic control with basal insulin.

CONTENT AREAS

- Unmet needs
- Experience with basal insulin/GLP-1RA
- FRC basal insulin/GLP-1RAs
- Insulin degludec/liraglutide (DUAL)
- Insulin glargine/lixisenatide (LixiLan-L, -O)
- Using FRC basal insulin/GLP-1RAs
- Case studies

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CE STATEMENT

Target Audience

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

Learning Objectives

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

- Describe the unmet needs of patients with type 2 diabetes
- Outline the role of basal insulin and GLP-1RAs as described in current guidelines
- Compare the benefits and limitations of GLP-1RA vs prandial insulin as add-on to basal insulin
- Describe the glycemic and nonglycemic outcomes observed with fixed-ratio basal insulin/GLP-1RA combination products
- Initiate and titrate fixed-ratio basal insulin/GLP-1RA combination products

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Vivian A. Fonseca, MD

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John E. Anderson, MD

Consultant	Abbot, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi
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The estimated time to complete the activity is 1.5 hours.

This activity was originally released on October 5, 2018 and is eligible for credit through October 4, 2019.

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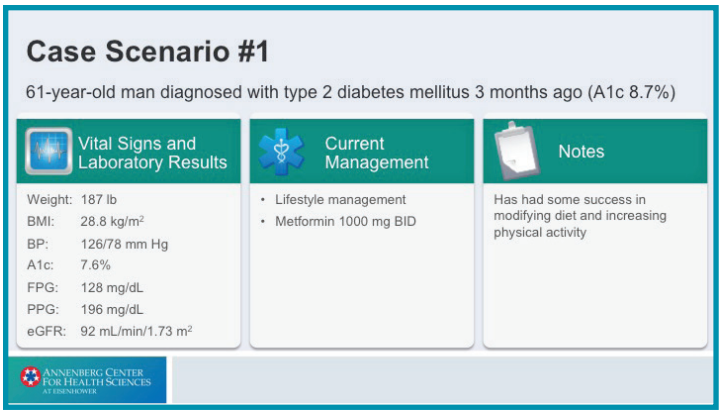
Editor's Note

This is a transcript of a discussion by John Anderson, MD, and Vivian Fonseca, MD, from "The Why and How for Combination Basal Insulin + GLP-1RA Therapy in Type 2 Diabetes" program.

UNMET NEEDS

John Anderson, MD: This module includes discussions of challenges encountered in the management of patients with type 2 diabetes mellitus such as medication adherence, as well as unmet needs such as increased risk of cardiovascular disease and diabetes distress.

This 61-year-old man is diagnosed with type 2 diabetes 3 months earlier with an initial A1c of 8.7%. He comes back in to see you today. His weight is 187 lbs, his BMI is 29 kg/m2, blood pressure is at target, his A1c has dropped from 8.7% to 7.6%. His fasting plasma glucose is 128 mg/dL, but his postprandial is still elevated at 196 mg/dL. He has a normal GFR. He has been put on lifestyle management as we do with all of our patients when we recently diagnose them with type 2 diabetes.

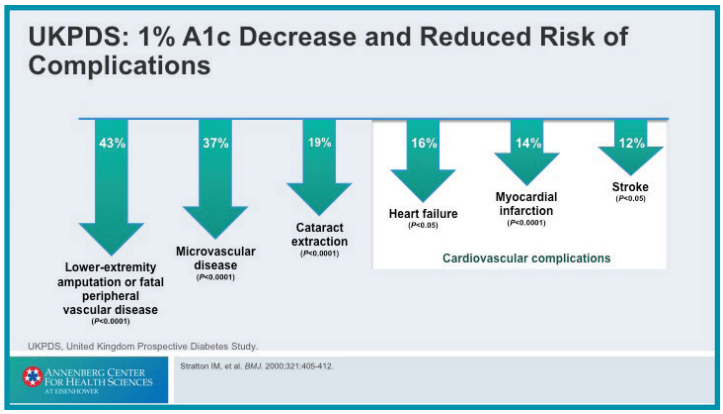


Hopefully, he may have seen a CDE or a diabetes educator because we know we need a team that will help take care of these patients. He's on metformin at a maximum dose of 1000 mg BID. He says to me that he's had some success in modifying his diet and increasing his physical activity. This is a typical patient of, "what do we think about after metformin?" Vivian, you know as well as I do, it's a different era now as we start to pick therapies. We're not just talking about glycemic lowering, we're also starting to talk about cardiovascular disease.

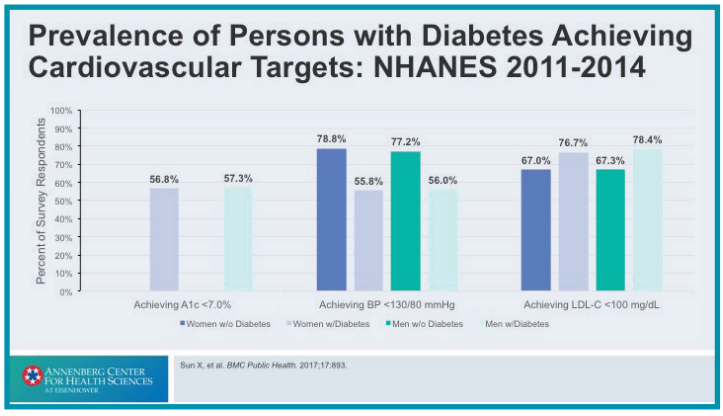
I think many of us would have talked about using combination therapy, but I think the key here is, what's the next step? We can talk about that a little bit later. We also need to talk about, maybe for our audience, about diabetes and cardiovascular disease. What do we know, Vivian, about diabetes as a cardiovascular risk factor?

Vivian Fonseca, MD: Diabetes is clearly a cardiovascular risk factor. We used to call it cardiovascular risk equivalent, that is, people with diabetes have the same risk of a heart attack as somebody who has had a previous heart attack. We know now that that's not entirely true because there's a whole spectrum of people with diabetes. For younger people who have had short duration of diabetes, maybe the risk is not as much as perhaps somebody who's had diabetes for 10 years.

John Anderson, MD: We know that diabetes has an increased risk for both cardiovascular disease–congestive heart failure is one we're talking a lot about now–cardiovascular death, peripheral vascular disease, and the old UKPDS data actually showed us that for every 1% A1c decrease, you decrease risk of complications by about 16% for heart failure, maybe 14% for MI and for stroke maybe 12%.



While glycemic control is not the main concern in terms of long-term lowering of cardiovascular risk, it still does play a role as we achieve better A1c results for our patients. It's surprising, though, that the National Health and Nutrition Examination Survey (NHANES) data shows us that about 55% of our patients are getting to the goal of less than 7% with their hemoglobin A1c. We're still struggling to get our patients with diabetes down to blood pressure goals and to lipid goals sometimes.

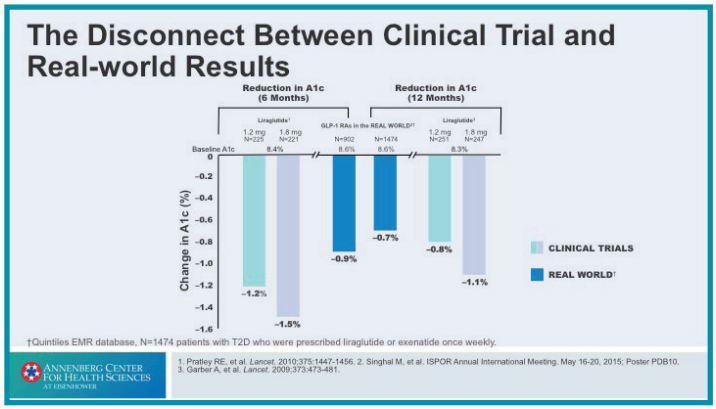


Again, as you said, this is a multifactorial complicated disease. You have to be looking at the ABCs of diabetes and looking at A1c, blood pressure, cholesterol and following standards of care. The other thing that we talk a lot about, Vivian, that's going to be true for this patient because he's just starting his journey with metformin is we have a lot of new medications but we're not always great about our patients taking medications.

What do you see in the difference between real world data vs what we see in clinical trials, because that's a real disconnect, I think, sometimes.

Vivian Fonseca, MD: A number of studies have shown that people don't take their medications for chronic disease, including people who've had major events like a heart attack. After a year or 2, they're not taking their statins and often not taking their ACE inhibitor and aspirin. I think, we need to keep emphasizing the importance of these therapies to patients when we see them.

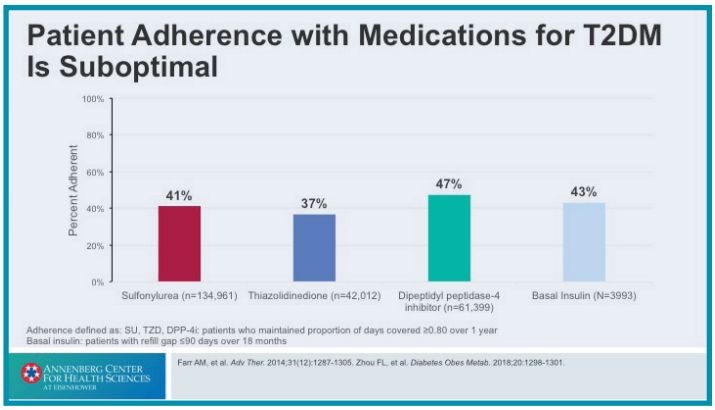
John Anderson, MD: There's been some real-world evidence by Pratley and others that looked at the disconnect between clinical trial and real-world results. They looked at reduction in A1cs with 2 doses of liraglutide with 1.2 mg and 1.8 mg both at 6 months and at 12 months follow-up. In the clinical trial, it's a –1.2% reduction and –1.5% reduction at 12 months and –0.8% and –1.1% reduction.



If you look at that same timeframe for a variety of GLP-1s in the real-world setting, the reduction at 6 months was –0.9% and –0.7% at 12 months. Again in a clinical trial, 44% and 56% of patients treated with liraglutide 1.2 mg and 1.8 mg per day, respectively, achieved their A1c goal at 6 months.4 In a real-world trial, 31% of patients treated with daily or weekly GLP-1 receptor agonist therapy achieved their A1c goal at 6 months.5 This rate declined to 26% at 12 months in the real-world trial. It's about persistence and adherence because it's not that the medication is working less well, it's that that patient is likely not getting the same sort of clinical trial support that they would be in a setting where they have regular interaction with that team member, they're coached, they're cajoled, they may be getting the medication for free.

In fact, there are a couple of studies looking at both sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 inhibitors (DPP4-is), and even basal insulins, which show that they're well below 50% refill persistence over 18 months.

I think that, for us, in the office is . . . the issue is really trying to ask those open-ended questions like, "Okay. You're on a difficult regimen. How many times do you miss an injection?" Or, "How many times do you miss a pill?" Or, "Do you have trouble affording your medications?" Because that's a conversation we're having now a lot with our patients.

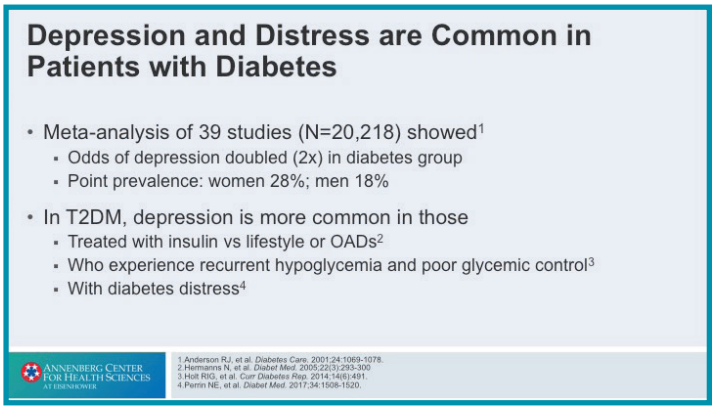


Vivian Fonseca, MD: There's one additional thing that we should be talking about that is related to strategies to make the treatment easier. Especially when it comes to injectables.

John Anderson, MD: We've got a lot of options and we'll talk about that. The other thing is that we know about the failure to adhere. The lack of adherence, the failure to persist on a medication is associated with increases in A1c, increased risk for complications, and those types of things.

I think it's important as we talk to our patients that we try to spend a little more time at the first part of that office visit understanding their medications, their medication list, their challenges. Asking those open-ended questions and do some real active listening.

One of the big 800 lb gorillas in the room is the coexistence of diabetes, stress and depression. There's this meta-analysis that the odds of depression are doubled in a diabetes cohort vs the nondiabetes age-matched things. Prevalence is up to 25%, 30%. It's more common in diabetes. It's more common in the patients treated with insulin vs oral agents and lifestyle, as well.



Obviously, the patients who have recurrent hypoglycemia and even severe hypoglycemia, this becomes a real barrier to good treatment, and then diabetes distress is a big problem too. You see that a lot in your practice, don't you?

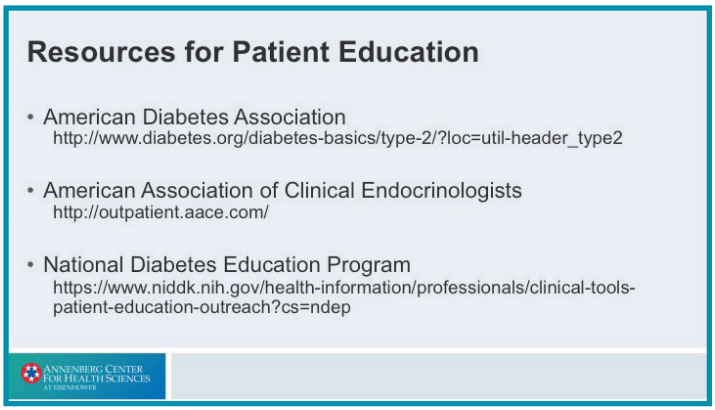
Vivian Fonseca, MD: If you look at it from a scientific perspective, there are very strong associations, but it's very hard to say that one causes the other. They often go together. People who are depressed are less inclined to help themselves in terms of lifestyle change. Some of the medications make people gain weight, some of them may make the blood glucose worse. Then, when the patients see their blood glucose number is not very good, they get more depressed. When they look at the cost of treatment they get depressed. One thing leads to another in very vicious cycles. It's not easy to break those.

John Anderson, MD: It's about active listening and motivational interviewing with your patient. It's about asking open-ended questions. Then, again, letting the patient participate in the decision-making. Let them feel like they're part of that team so that they can . . . so that if they feel like they're getting buy-in when you're making that decision about what's the next step, whether it's a lifestyle change or whether it's the next step with a medication therapy, getting that buy-in has been shown to markedly improve adherence. The patient takes ownership. I think that's important.

We also like to provide our patients [with] a lot of the resources. Vivian, you and I have both been intimately involved with the American Diabetes Association. They have a great website and materials. The American Association of Clinical Endocrinologists, AACE, the National Diabetes Educational Program all put out fantastic materials for patients.

I can't do it all in an office visit, you can't do it all in an office visit. It's about giving them resources so at the end of those 3 or 4 months between office visits, they have some place they can feel like they can go and get some questions answered and maybe dive a little deeper into their disease.

Vivian Fonseca, MD: I think we are fortunate to have drug therapies that help us get patients to goal while we work on these other things that you talked about. Just getting to goal does motivate some patients. They feel that they are achieving something.



John Anderson, MD: We celebrate every pound of success when they come back in. We're really big cheerleaders for our patients. For this particular patient, as we wrap up, this is a patient that's new to metformin and has some success. You and I both agree this might have been a patient who could have used combination therapy from the beginning. I think the real message for the clinician is now that this patient is back with an A1c of 7.6%, you are not done.

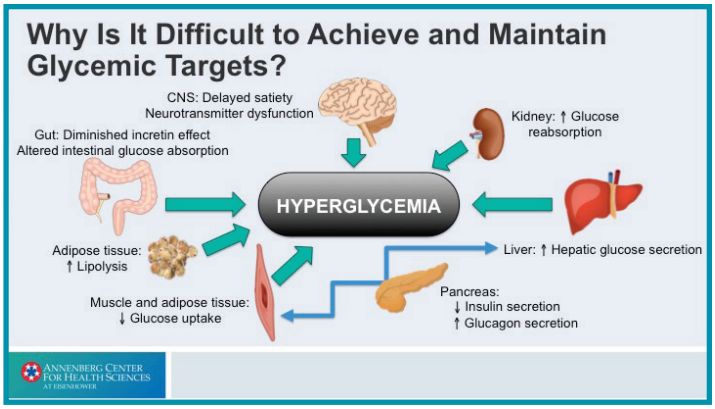
You need to be relentless in getting this patient down to goal because, as you know, all of the studies, longitudinal studies, with long-term follow-up, [show] there is something very special about getting these patients down to goal quickly and keeping them there safely for as long as you can. We don't want to look up 6 months from now and find out that this patient has still got an A1c of 6.5%, 7.5% to 7.8%. We want to see that A1c down at a target goal.

ROLE IN THERAPY

Vivian Fonseca, MD: This module includes an overview of the classes of medications currently available for treatment of patients with type 2 diabetes. However, the discussion will focus on the evolving roles of basal insulin and glucagon-like peptide receptor agonists as recommended in current guidelines, including their use in combination.

This is a 53-year-old woman with newly diagnosed type 2 diabetes. She weighs 198 lbs with a BMI of 32.9 kg/m2, blood pressure is 132/86 mmHg, fasting glucose 156 mg/dL, and A1c of 8.4% with a reasonable GFR of 84 mL/min/1.73 m2. She has not yet started medication because she was very upset with having yet another disease. She knew she had high blood pressure and she had hyperlipidemia. She wasn't sure about having heart disease, although she had some chest pain in the past and was prescribed nitroglycerin, so it's quite possible she has some, but it hasn't been fully worked up. She's just very reluctant to make changes in her lifestyle. Although she's been seeing a dietician, she's reluctant to accept another diagnosis. She does take her atorvastatin, ramipril, and aspirin though. She's trying to make some dietary changes but hasn't been very successful.

We are fortunate today to have many medications. In some ways, it's a good thing. We need many, because diabetes is such a complex disease. Hyperglycemia is driven by multiple abnormalities. Several years ago, the term "ominous octet" was coined to deal with 8 abnormalities in diabetes causing hyperglycemia.



We now know that that's not entirely true. There are more than 8 abnormalities, but there are still these 8 which we can target. For example, we know that the pancreas is one of the primary organs at fault in diabetes. You don't have enough insulin secretion to overcome your needs. The needs are greater in obese people because they have decreased glucose uptake in muscle and fat, due to insulin resistance.

The liver produces excessive glucose, what is called hepatic glucose production. The kidney tries to adapt to all this and reabsorbs more of the glucose that's being filtered. The gut doesn't send its signals well and that contributes to worsening obesity as well as increased glucose absorption. Finally, the CNS is involved with delayed satiety.

Multiple things causing hyperglycemia. One of the problems in our approach has been to only use 1 treatment to address 1 abnormality at a time, the so-called stepped approach, which is probably what we would do in such a patient. Unfortunately, the other abnormalities continue unchecked and may maladapt further and become worse.

Let me get back to our patient and how we can manage her, based on the guidelines. The American Diabetes Association recommendation, which is to use pharmacological therapy at the time of diagnosis, usually using metformin unless it's contraindicated or not tolerated. The ADA does recommend considering dual therapy for people with very high A1c at presentation or people who are symptomatic and have very high blood glucose, say, more than 300 mg/dL or A1c greater 10%, maybe using insulin for a short term.

You could, for most people, chose any therapy as the second-line therapy and when the 2 drugs fail, you can go on to the third-line therapy, which could be a third oral agent or adding in an injectable. Some of the injectables could be added on as second line, including insulin and GLP-1 receptor agonist, although patients often prefer oral therapy.

There are some new developments in these guidelines. The American Diabetes Association has emphasized this, as has AACE, to focus on other comorbidities a patient might have, such as heart disease. The recommendation is to consider drugs that have had positive cardiovascular outcome trials, such as some of the GLP-1 receptor agonist and the SGLT-2 inhibitors, as probably the drugs to add on to metformin for those particular patients.

Then, we have other guidelines from other organizations. Actually, they're not that much different. Since I mentioned the AACE guidelines, let me just talk very briefly about it since I'm involved with developing that as well. The goal is a little lower, the general goal less than 6.5%, but both organizations emphasize individualization of the goal.

The other difference, as I pointed out earlier, is that the AACE recommends combination therapy for lower levels of A1c, recognizing that all drugs are not strong enough to get people to goal. The ADA often has recommended cost as being part of making the choice, which I think is very realistic in real life, whereas AACE is focused on efficacy and suitability of the therapy.

John Anderson, MD: These guidelines are much more similar than they are dissimilar. I think there's a reason–and we can explore this a little later–why, after metformin, GLP-1 receptor agonists and SGLT2 inhibitors are at the very top of the list. It's not only for the A1c lowering, but it's also for those nonglycemic benefits. As you and I are going to discuss, now we have this whole world of potential cardiovascular benefits for certain members of this class. I think it's going to be one of these things that continues to support that hierarchal recommendation from AACE.

Vivian Fonseca, MD: Let me very briefly summarize the key characteristics of the medications for type 2 diabetes.

DPP-4 inhibitors are extremely well tolerated with very low risk of hypoglycemia. In fact, very rare adverse events, but their cost is fairly high and the A1c lowering is generally very modest.

Characteristics of Key Medications for Type 2 Diabetes Mellitus

	Magnitude of A1c Lowering†	Adverse Events	Risk of Hypoglycemia	Weight Effect	Cost
DPP-4i	0.4% to 0.5%	Rare	Low	↔	High
GLP-1RA	0.5% to 1.3%	GI	Low	↓	High
Insulin (basal analog)	Theoretically unlimited	Hypoglycemia	High	↑	High
SGLT-2i	0.5% to 1%	GU, dehydration, fracture	Low	↓	High
Sulfonylurea	~1%	Hypoglycemia	Moderate	↑	Low
TZD	0.4% to 0.9%	Edema, HF, fracture	Low	↑	Low

†When added to metformin
↑, decrease; ↔, no change; ↓, increase

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Bolen S, et al. https://www.effectivehealthcare.ahrq.gov/ehc/products/607/2215/diabetes-update-2016-report.pdf
American Diabetes Association. *Diabetes Care*. 2018;41(Suppl 1):S73-S85.
Garber AJ, et al. *Endocr Pract*. 2018;24:91-120.

Related to them in the incretin class, and because of the pharmacology, more effective–because you're getting higher levels of GLP-1 receptor stimulation–are the GLP-1 receptor agonists. These are injectable, and they cost a lot, but they have additional effects of greater A1c lowering, probably almost as good as insulin, if not better, in some studies. Weight loss and very low risk of hypoglycemia. Gastrointestinal (GI) side effects are very common. Some of them like semaglutide and liraglutide have been shown to have beneficial effects on atherosclerotic cardiovascular disease, which, if your patient has that, may be a reasonable choice.

SGLT2 inhibitors have also had positive cardiovascular outcome trials. Although the benefit appears more to be on reducing the risk for hospitalization for heart failure, as well as a risk in cardiovascular mortality, and less specific on reduction of myocardial infraction, stroke, etc. The A1c lowering is relatively more modest compared to GLP-1 receptor agonists, but they tend to work in most people provided they have reasonable renal function. They do cause some degree of weight loss.

Other options include sulfonylureas and thiazolidinediones. Sulfonylureas reduce blood glucose more rapidly than most other options and they are inexpensive. Limitations of sulfonylureas are that they often cause hypoglycemia and they cause some degree of weight gain in most patients.

Thiazolidinediones are not used as often as they once were, in part because they cause fluid retention and may increase the risk of bone fracture. The thiazolidinediones have good effects on pancreatic beta-cell function and insulin resistance and are effective in the long term.

GLP-1 receptor agonists have many benefits. They don't cause hypoglycemia. You get very good stimulation of insulin secretion in a glucose-dependent manner. You also improve cardiovascular risk. It's in the guidelines. It can be

Cardiovascular Safety and Benefit for GLP-1 RAs in Patients With T2DM

GLP-1 Receoptor Agonist	Primary endpoint	Heart failure hospitalization	All-cause death
Exenatide[1] (N=14,752; 3.2 y median F/U)	0.91[a] (0.83-1.00)	0.94 (0.78-1.13)	0.86 (0.77-0.97)
Liraglutide[2] (N=9340; 3.8 y median F/U)	**0.87[a] (0.78-0.97)**	0.87 (0.73-1.05)	0.85 (0.74-0.97)
Lixisenatide[3] (N=6068; 2.1 median F/U)	1.02[b] (0.89-1.17)	0.96 (0.75-1.23)	0.94 (0.78-1.13)
Semaglutide[4] (N=3297; 2.1 y median F/U)	**0.74[c] (0.58-0.95)**	1.11 (0.77-1.61)	1.05 (0.74-1.50)

CV, cardiovascular; F/U, follow-up; MI, myocardial infarction; UA, unstable angina.
[a] Composite of CV death, nonfatal MI, nonfatal stroke
[b] Composite of CV death, nonfatal MI, nonfatal stroke, hospitalization for UA
[c] Composite of CV death, nonfatal MI, nonfatal ischemic stroke

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1. Holman R, et al. *N Engl J Med.* 2017;377(13):1228-1239.
2. Marso SP, et al. *N Engl J Med.* 2016;375(4):311-322.
3. Pfeffer MA, et al. *N Engl J Med.* 2015;373(23):2247-2257.
4. Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-1844.

used for people who cannot tolerate metformin as the first-line therapy. The effects on weight loss in cardiovascular disease are actually very important and striking.

Here is a summary of the cardiovascular outcome trials showing a consistent reduction in events, with 2 of them, they were statistically significant. They were not with 1 of them, but that was done in the highest risk post-ACS patients, who many not have benefited from anything. The same with the SGLT2 inhibitors, canagliflozin and empagliflozin. They reduced, overall, the primary outcome, which is a composite, although most of that effect was in cardiovascular death. This was the first time that a reduction in death has been seen in a diabetes trial.

That brings me to insulin. Is there any place for it now in treating type 2 diabetes? People have been pushing back and suggesting we use these other drugs, but insulins are very effective and we have very good insulins now. There's data to suggest that if we don't wait too long, we start it early enough, you can get better A1c lowering and, in fact, less hypoglycemia. There are cardiovascular outcome trials done in people with diabetes showing that they are at least safe, if not effective. The ORIGIN trial showed that it was equivalent to standard care. Starting with glargine was equivalent to standard care, which is metformin. The DEVOTE trial showed both glargine and degludec were sort of equivalent in terms of cardiovascular events.

Cardiovascular Safety and Benefit for SGLT-2is in Patients With T2DM

SGLT-2 Inhibitor	Primary endpoint	Heart failure hospitalization	All-cause death
Canagliflozin[1] (N=10,142; 2.4 y median F/U)	**0.86[†] (0.75-0.97)**	**0.67 (0.52-0.87)**	0.87 (0.74-1.01)
Empagliflozin[2] (N=7020; 3.1 median F/U)	**0.86[†] (0.74-0.99)**	**0.65 (0.50-0.85)**	**0.68 (0.57-0.82)**

CV, cardiovascular; F/U, follow-up; MI, myocardial infarction.
[†]Composite of CV death, nonfatal MI, nonfatal stroke

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1. Neal B, et al. *N Engl J Med.* 2017;377(7):644-657.
2. Zinman B, et al. *N Engl J Med.* 2015;373(22):2117-2128.

We have multiple drugs, we have multiple abnormalities. They sort of fit with each other, some of them address multiple defects. Maybe I'll turn back to you, John, what do you think would be the best option for this case who may or may not have cardiovascular disease, she's reluctant to accept the diagnosis of diabetes. Would you push for her to have an injectable? She doesn't have heart failure right now, but would that help in your choice of therapy?

John Anderson, MD: I think it would. If she had definite heart failure, the SGLT2 class, at least 2 agents–canagliflozin and empagliflozin– have been shown to reduce admissions for heart failure. I think the other thing about this woman is just getting her to buy into the fact that she really does have a disease that needs to be treated and that diet and lifestyle are important. She's at the point at 8.4% where she definitely needs medical therapy.

The other thing is if this were a new patient, one of the main things that we do in terms of diagnosing cardiovascular disease is to have a talk with the patient. "Let's have a conversation about this chest pain and what got you a nitroglycerine PRN prescription." Because if there's any clinical indication this patient is having symptoms, we need to know that and we need to diagnose it, because it might influence our decision making.

This woman is at 8.4%, you and I would talk and have a conversation, what is she willing to do? Certainly, you might talk about metformin in this patient. Then, the question is, would you go with 1 agent and see her back in 3 months to see how she's done. Or would you say, she's at 8.4%, perhaps we think about dual therapy and there's a lot of different ways, as you outlined, to skin that cat, between oral agents and injectables. Again, a lot is going to be dependent upon what she's willing to do and how much of a buy-in she's willing to put to this.

Vivian Fonseca, MD: I agree with you. We need to share the decision-making process with the patient.

BASAL/GLP-1RA COMBINATION

Vivian Fonseca, MD: This module focuses on the clinical and pathophysiological rationales for intensifying basal insulin therapy with a glucagon-like receptor agonist, GLP-1 receptor agonist. We talk about the benefits and limitations of this intensification with added GLP-1 receptor agonist instead of a prandial insulin, which is the traditional way in which we manage these patients.

A 64-year-old woman with type 2 diabetes for at least 7 years. She's obese, with a BMI of 33.6 kg/m^2, A1c is 8.2%, LDL is at goal, GFR is reasonable at 60 mL/min/1.73 m^2, although that's slightly impaired, but not too bad. She's been taking metformin for a number of years. Was on other oral agents, started insulin, up-titrated up to 68 units at bedtime. Takes drugs for hypertension and dyslipidemia, which are her comorbidities.

Her A1c a few months ago was 7.2% but has now gone up to 8.2%. She's getting some episodes of symptomatic hypoglycemia, particularly at night, and it wakes her up and disturbs her a lot, and she's been into the emergency room with a glucose of 52 mg/dL.

Why are some people not able to get to goal? What do you do? When do you recognize that somebody needs more than insulin or needs a completely different approach?

John Anderson, MD: The first thing that comes to your mind about this is the first thing is safety, right? We have to figure out a better way of treating her and minimizing or at least markedly reducing her risk for hypoglycemia. She's already had 1 episode of what one would call severe hypoglycemia and a trip to an emergency room.

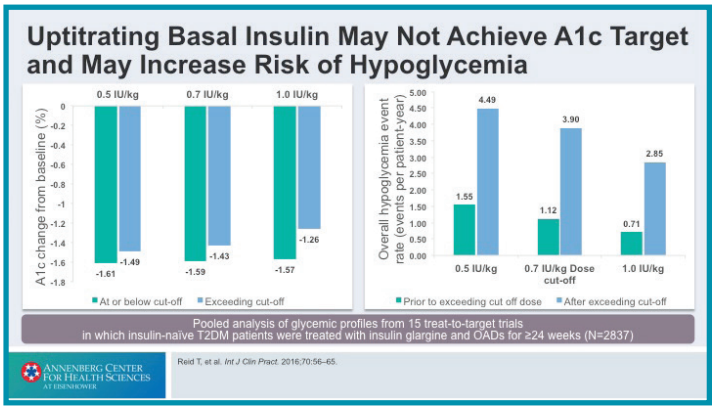
We have to look at that basal insulin dose, and in this case she's at 0.73 units per kg and I know you're going to cover how we look at that 0.5 units per kg number. The other thing is, this is what happens in primary care. Clinicians may push the dose of basal insulin because they say, "We finally got her fasting down to 118 mg/dL, but she's still not at goal. Let's just keep pushing," when they fail to realize that you really have to address that postprandial component.

I think this patient's A1c 13 months ago was 7.2% now it's 8.2%. Clearly, one of the things we need to do is let's measure something other than fastings and let's open our eyes after meals, particularly after that evening meal and see where we are heading to bed, because that will inform us on how we go forward.

Vivian Fonseca, MD: This is a common problem. People taking insulin, taking high doses of insulin, their fasting glucose is normal, but they are still not getting to goal. We need to recognize that this titration is not going to help, it increases the risk of hypoglycemia, which is a common scenario particularly as you get above 0.5 units per kg.

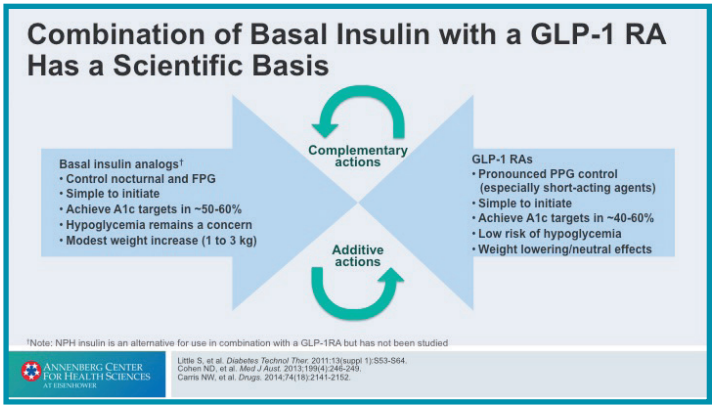
Patients with elevated A1c despite normal fasting plasma glucose generally have persistent postprandial hyperglycemia. To verify this, it is necessary to test the blood glucose several times throughout the day.

We now need to choose the right therapy. Do we add on prandial insulin during the day or should we add on something else to control the postprandial glucose? One of those that can be added is a GLP-1 receptor agonist. This concept of combining 2 injectables has been very attractive for a number of reasons because you're targeting different pathophysiological targets as well as different time points of the day.



For example, the nighttime basal insulin targets the fasting glucose, relatively simple to initiate and up-titrate, gets a lot of people to goal, but you still have a risk of hypoglycemia and weight gain. In contrast, the GLP-1 receptor agonists often titrate the postprandial glucose, particularly the short-acting agents. They can regulate some of the weight and maybe not allow the weight gain that occurs with insulin. They're both very powerful agents and complementary.

You could target both agents, but you could also use other drugs to target postprandial glucose like DPP-4 inhibitors and meglitinides, etc. They're not as powerful as GLP-1 receptor agonist and don't have the weight benefits.



The guidelines now talk about basal insulin, you initiate it and if you're not controlled, you have a choice. You can add 1 rapid-acting agent with the largest meal of the day or you can switch to premixed twice a day. I think that's actually less flexible. Or you can add a GLP-1 receptor agonist. How often do you make this choice and what do people find more acceptable?

John Anderson, MD: I love the fact these guidelines got updated about 3 years ago because, I think, one of the greatest points of clinical inertia is that period between. We got pretty good about giving basal insulin and titrating

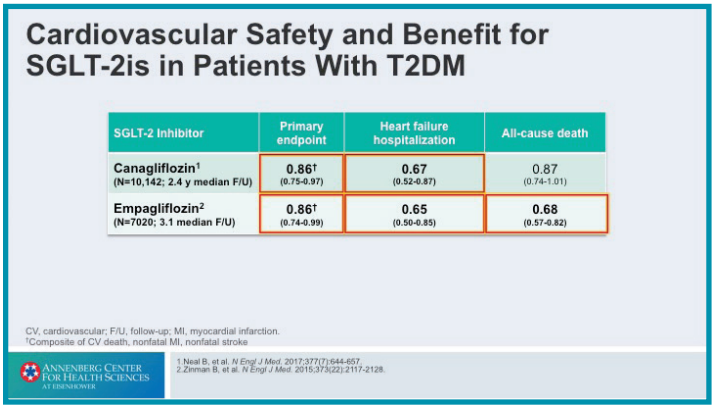
basal insulin, but we still are very poor about when to go to that postprandial component.

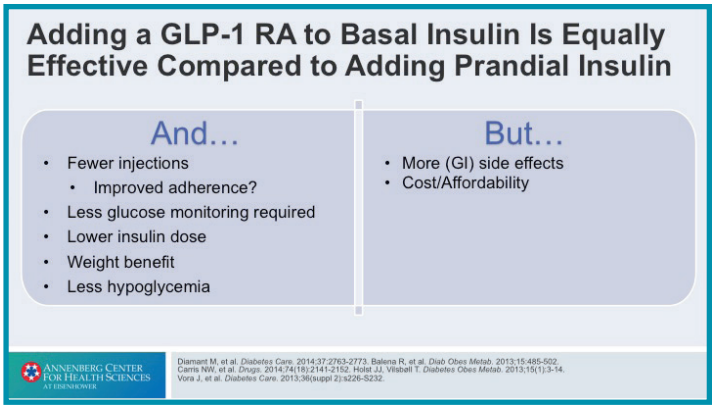
I know that in the primary care world, the idea of initiating a basal plus 1, 2, or full basal-bolus insulin therapy requires numeracy on [the] part of the patient. A tremendous [amount] more education, more injections, weight gain, the potential for hypoglycemia. It's just much more complex than the idea of adding a twice-a-day, once-a-day, or even a once-a-week GLP-1 receptor agonist that has been shown, and I'm sure we'll discuss the data here in just a second, as good or better in most cases, than full basal-bolus therapy, without all of those burdens that you just discussed.

Vivian Fonseca, MD: The guidelines also give you a lot of detail about how to titrate your insulin, both titrate up as well as titrating down if you get hypoglycemia. How to add prandial insulin and how to do it when you need to. Also consider the GLP-1 receptor agonist.

There are now multiple studies on the combination. Meta-analyses have been published showing not only reduction in A1c but actual weight loss. Over all, they may be weight neutral while you're getting better control, but a lot of patients do actually lose weight on this combination. This has been reviewed extensively. Another point that comes out is that the risk of hypoglycemia actually doesn't go up.

Adding a GLP- 1 receptor agonist to basal insulin is at least equally effective, maybe more effective than adding a prandial insulin. You'd get it with fewer injections and that gets around to the point Dr. Anderson made earlier about adherence to therapy.





Less glucose monitoring is required in the postprandial phase. Lower insulin dose, weight benefit. You also have to be aware of the increased GI side effects and talk to your patients about that. There's also the issue of cost and affordability and patient access based on formulary.

To get to our particular patient, John, what do you think? She's taking a lot of insulin. She's obviously not at goal and she's also had severe hypoglycemia, which should be a good candidate for GLP-1 receptor agonists and would you reduce the dose of insulin when you're doing that?

John Anderson, MD: I certainly would. I think, first of all, you would reduce her dose of basal insulin to a maximum 0.5 units/kg. Especially, if you're going to add a GLP-1 receptor agonist assuming she's willing to do that and you've discussed which type of agents you want to pick. I would reduce down maybe even further, I'd let her have a little hyperglycemia in fasting in the morning because you can always titrate back up.

The other thing we could talk about is do we consider one of the new novel basal insulin analogs that seem to have a little longer half-life, a little flatter curve, with maybe a little less peak that may also mitigate some of that nocturnal hypoglycemic risk.

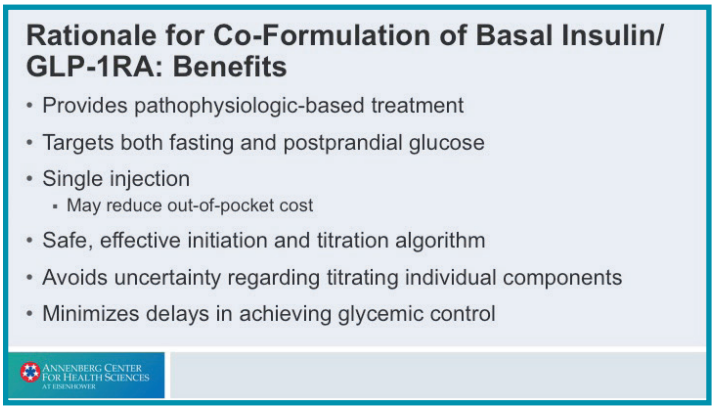
Vivian Fonseca, MD: She's got a long way to go in terms of A1c reduction. She clearly needs a fair bit more. Though, I might set a higher goal for her because of her hypoglycemia. Hopefully, we can get this patient near her goal with the appropriate choice of add-on injectable therapy.

FIXED-RATIO COMBINATION

John Anderson, MD: Currently, we have 2 fixed-ratio combination products available that combine a basal insulin with a glucagon-like peptide-1 receptor agonist or GLP-1 receptor agonist. This module provides an overview of these 2 products and what kind of advantages they have for patients.

This is a 69-year-old male with type 2 diabetes, pretty long duration, 12 years with type 2 diabetes and his weight is 187 lbs. His BMI is 29.5 kg/m^2, just under the obese range. Blood pressure is at target. His A1c is at target, as well, for most patients, 6.9%. With a fasting glucose of 106 mg/dL, postprandial is 176 mg/dL. LDL-cholesterol is 68 mg/dL, triglycerides at 126 mg/dL. The GFR, minimally compromised but at 56 mL/min/1.73 m^2. He's on lifestyle management, on maximum dose of metformin, insulin glargine at 46 units at bedtime, which is 0.54 units/kg. Exenatide, which is a short-acting GLP-1 that you have to take before meals twice a day, hydrochlorothiazide, valsartan, pravastatin, and aspirin. It has been modified through the years to keep that A1c less than 7%, and right now, he's at 6.9%. He also has hypertension, dyslipidemia, and he had a myocardial infarction 3 years ago. This is a patient with type 2 diabetes and defined cardiovascular disease. What he has expressed is that he's found it increasingly difficult to adhere to the treatment, and this is causing a tremendous amount of distress.

As we look at coformulations of basal insulin GLP-1 receptor agonists and the barriers to the use of individual products, what we know is that more injections equals clinical inertia. More injections also decreases adherence and persistence. You get reduced patient satisfaction, you get compromised self-management, and you get uncertainty in each of these individual products.



How do I choose a starting dose? What do I do and how do I add therapies? How do I titrate each of these? With a coformulation of basal insulin GLP-1, you get pathophysiologically-based treatment, you have a basal insulin that's truly treating that fasting component. You got a postprandial treatment with the GLP-1. This targets both fasting and postprandial glucose. It's in a single injection, which may reduce out-of-pocket cost. There's a safe and effective initiation and titration algorithm. It avoids some of the uncertainty regarding titrating 2 different components at the same time. It may help with that clinical inertia and in minimizing delays in achieving glycemic control.

I just want to go over a couple of the products that we have on the market. The first is insulin degludec and liraglutide, which we'll call IDegLira. We also have insulin glargine and lixisenatide which we'll call IGlarLixi. Both of these were approved for use in the United States by the FDA in 2016 in November.

IDegLira is approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (<50 units/day) or liraglutide (≤1.8 mg/day).[35] IGlarLixi is approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (<60 units/day).[36]

IDegLira is available as 100 units of degludec and 3.6 mg of liraglutide per mL.35 IGlarLixi is available as 100 units of glargine and 33 mcg of lixisenatide per mL.36 Both are available as 3 mL single-patient-use pens.

Then of course, these are both subcutaneous administrations, once daily at the same time each day without food for IDegLira. For the IGlarLixi, you really want to give it an hour before the first meal of the day so that you can really leverage that postprandial component after breakfast and after lunch.
The maximum dose, again, as I said before, is 50 units a day of degludec, 1.8 mg of liraglutide, and 60 units of glargine and 20 mcg of lixisenatide.

Fixed-Ratio Basal Insulin/GLP-1 RA Combinations

	Insulin Degludec/Liraglutide (Xultophy® 100/3.6)	Insulin Glargine/Lixisenatide (Soliqua® 100/33)
Administration	Subcutaneous	Subcutaneous
Dose timing	Once daily at same time each day with/ without food	Once daily within the hour prior to the first meal of the day
Maximum daily dose	50 units degludec, 1.8 mg liraglutide	60 units glargine, 20 mcg lixisenatide
Dosing	Based on degludec	Based on glargine

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XULTOPHY® 100/3.6 (insulin degludec and liraglutide injection). Prescribing Information. Novo Nordisk. November 2016.
SOLIQUA™ 100/33 (insulin glargine and lixisenatide injection) (package insert). Sanofi-Aventis U.S.; March 2016.

The interesting thing, I think, for the primary care world, which is probably not as savvy. How do I do these 2? You forget about the GLP-1 receptor component and you just let the titration occur with the basal insulin product like we would anyway.

Vivian, when you talk to your patients, because this is still relatively new in our practices, do you find that that explanation helps them understand how to use the medications?

Vivian Fonseca, MD: Yes, it does. The major problem that occurs, as in this particular patient, is the fact that they've got to down-titrate from where they are on what is failing. This particular patient, it is probably relatively easy since your patient is already on both components and is doing reasonably well. They may not need much up-titration. You could use either of the agents at a halfway dose of 30 or 25 and up-titrate back to that 45, 46, fairly quickly and the patient should be able to tolerate it.

But suppose your patient was taking only insulin and was not controlled taking 45 units going back down to 30 or 25 and then back up-titrating

would be limiting because you may need more than 50 or 60 units. In that case, you would not be able to use such a combination.

For the patient you described earlier, I think, you would go a long way to improving the patient's adherence by using this fixed-ratio combination going from 3 injections a day to 1 injection a day. I can tell you from my discussions with all my patients, or if I were in that position, I would certainly prefer 1 injection a day.

John Anderson, MD: I agree with you. The only thing that I do with some of my patients, as you would here, is if you'd pick IDegLira then, certainly, at bedtime is fine. If you wanted to pick IGlarLixi, you would have to get into the habit of using that in the morning instead of at bedtime. That would be one thing that most patients are willing to do. You would still titrate based on the fasting glucose.

This takes you down from 3 separate injections a day plus the timing of a short-acting GLP-1 30 minutes before [a] meal, which can be problematic, which is why a lot of patients, if they're going out, they'll miss that evening dose. You've gone from 3 injections a day down to 1.

The other thing that I see here that I would do is I'd combine the valsartan-hydrochlorothiazide into 1 pill and decrease at least by 1 pill, the pill burden that the patient has. We have some options for this patient, even though they're at goal, to try to address their number one concern, which is adherence to treatment. Again, when we get the patient and say, "What are you interested in?" "I'm interested in an easier regimen." It's our job to try to figure that out for them.

Vivian Fonseca, MD: I get back to the caveat of the dose limitation. If this patient was, for some reason, already on over 50 units of insulin, I would, in that case, take away the exenatide and use it once weekly, as going from 7 injections . . . Sorry, from 21 injections a week to 8 injections a week, as opposed to if you use this fixed-ratio, it would be 7, so it's not that different.

I think this combination is here to stay. It is not currently indicated as the first-line injectable in the United States by the FDA. In Europe, it is available. If you think about it, it's very attractive to be using 2 injectable drugs as 1 injection when oral agents fail. There are studies ongoing to address this. Hopefully, we will be using that sometime in the future.

John Anderson, MD: I think that is the number 1 use in Europe . . . after orals, this is the first injectable. I think the message is, stay tuned maybe we'll have a change in heart of the FDA sometime soon.

IDEGLIRA DUAL PROGRAM

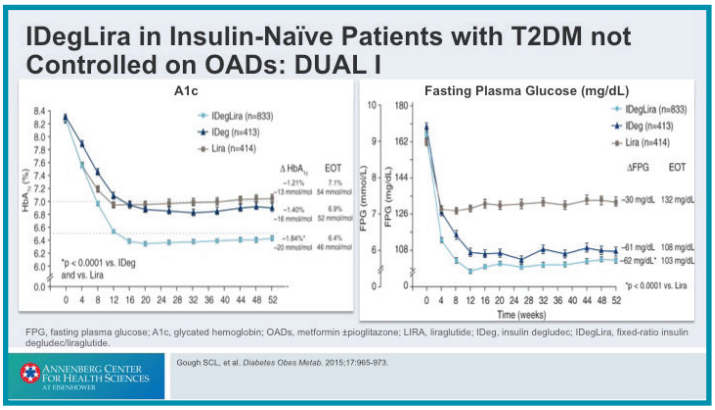
Vivian Fonseca, MD: We will review data from the key trials in the DUAL clinical trial program for the fixed-ratio combination of insulin degludec and liraglutide.

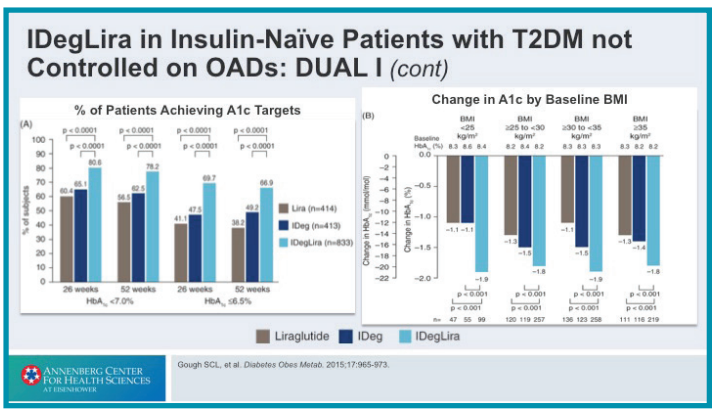
DUAL-I compared liraglutide alone with degludec insulin alone or the fixed-ratio combination in patients with type 2 diabetes who were poorly controlled on oral agents. They continued most of their oral agents, although I think if they were on sulfonylureas, they discontinued it. Most of them were taking metformin, some were taking pioglitazone.

The A1c at the start of the trial was about 8.3%. As you can see from the graph, both insulin and degludec and liraglutide were effective. They got the mean A1c below 7%. The combination had a really dramatic effect on A1c, very quickly dropping it not only down below 7%, but well below 6.5% and keeping it down there. This was probably the most effective treatment result that I have ever seen in the treatment of diabetes. Almost 2% drop and doing that very, very quickly and a reduction in A1c as well as fasting glucose.

If you look at the percentage of patients who were meeting goal at the end of 26 weeks and 52 weeks, clearly, it was far greater in those who were on the combination as opposed to either 1 drug alone. That's not surprising, you're using 2 drugs.

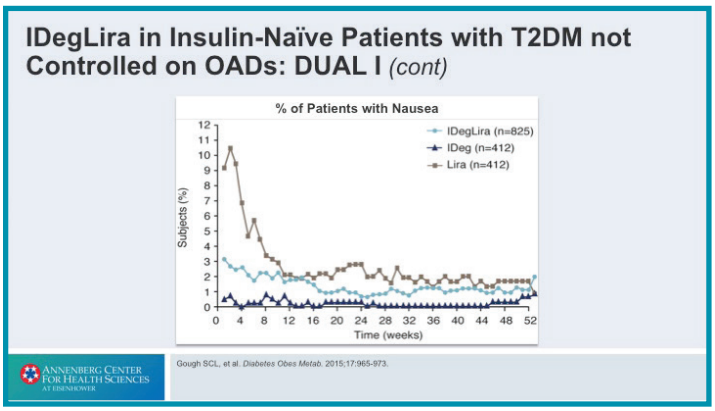
On the right-hand side of the slide, you see the reduction in A1c based on baseline A1c. It occurred in all groups of BMI, including very obese people, as well as people who are not so obese. They all got great reductions in A1c.

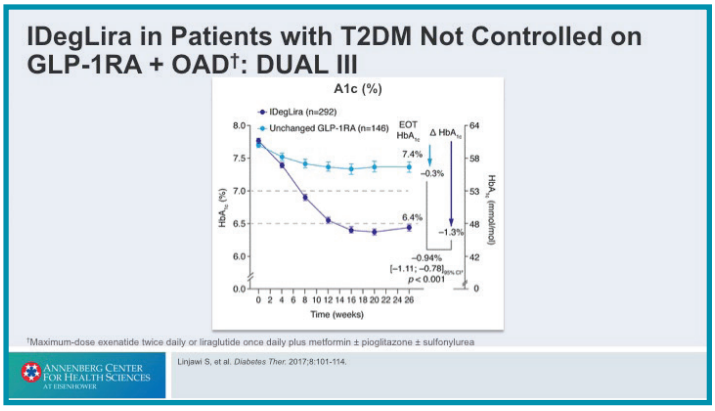




The insulin dose, the total dose of insulin that was used, was less with the combination, as well as the fact that you got a change in body weight. The body weight was slightly reduced with IDegLira. Obviously, reduced more with liraglutide alone because you used a higher dose of liraglutide and there was no insulin in those patients. But despite the beta glycemic control, you got no increase in body weight with IDegLira.

There was another very interesting finding in this trial, and it's been seen consistently in a lot of these fixed-ratio combination trials. That is on the side effect of nausea and other GI side effects. If you look on the slide, you see that there's [a] very tiny amount of background nausea in patients who were taking insulin degludec. That's maybe few people getting occasional GI upsets. With the liraglutide, about 10% of people reported nausea within a couple of weeks of starting the study drug. That's not surprising, it's





comparable with other studies with liraglutide. What is surprising is that the IDegLira group had only about a 3% report of nausea and it remained low throughout the duration of the trial.

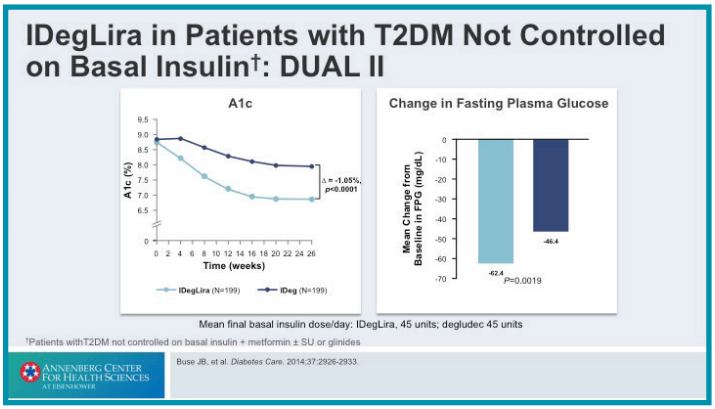
The likely reason for this is that the titration is based on the insulin, so there's a very, very slow titration. With liraglutide you go from 0.6 to 1.2 to 1.8. Here, you start with much less than 0.6 and you [are] very gradually increasing it as you increase your insulin dose by 1 or 2 units. This slow titration has been highly effective in reducing the GI side effects. That was the DUAL-I study.

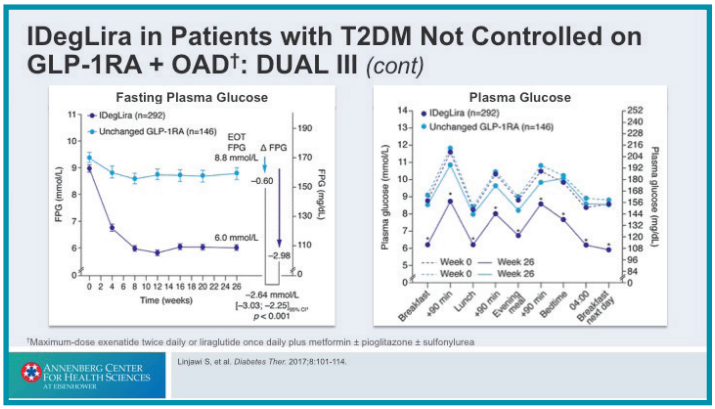
Another study was done around the same time called DUAL-II, where people were already taking insulin and they were not well controlled on insulin and they were randomized to either continue and optimize their basal insulin which improved their A1c a little bit, or take the combination of IDegLira. Both groups got some improvement in glucose control, but it was much, much greater on the IDegLira than degludec alone. The effect was seen with both fasting glucose as well as A1c. There was a reduction in body weight with the combination, with no change in body weight with the optimized basal insulin.

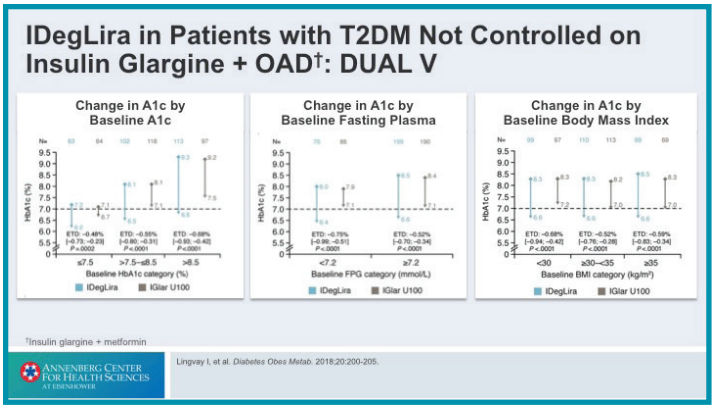
There's another study called DUAL-III which looked at the fixed-ratio in patients who had already started a GLP-1 receptor agonist. They were taking 1 injectable GLP-1, along with oral agents, and then they either optimized their GLP-1 receptor agonist, so had it unchanged and the A1c did not change. Adding in the insulin in a fixed-ratio with IDegLira, they got a 1.3% reduction in A1c. You wouldn't expect any weight loss with that because they've already had the benefit with the GLP-1 receptor agonist, but you got a greater lowering of fasting glucose. When you look at the 9-point glucose profile, there was reduction in fasting glucose, some reduction in postprandial glucose, but there was still a postprandial excursion which is what you would see with liraglutide. It didn't matter what your baseline A1c was or your fasting glucose or BMI. All patients seemed to respond very well.

DUAL -V looked at patients who were not controlled on glargine plus an oral agent, a very common scenario in clinical practice. Here, too, you see that there was a benefit across a wide range of patients.

In DUAL-V, a significantly greater proportion of patients treated with IDegLira achieved key composite endpoints of efficacy and safety compared with up-titration of insulin glargine.[40] For example, for patients with an A1c >7.5%



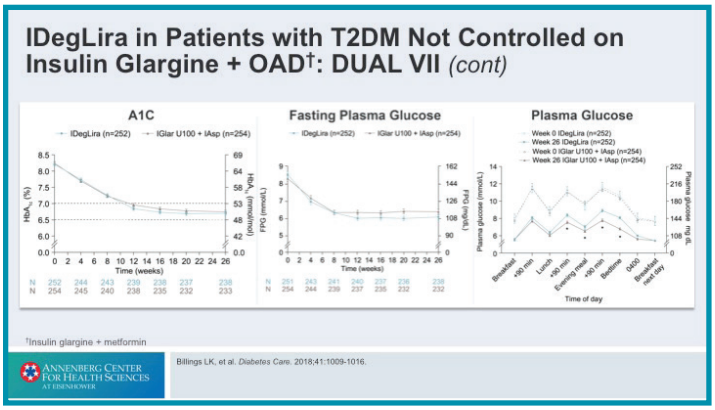




to ≤8.5% at baseline, 54.9% of patients treated with IDegLira achieved A1c <7% without hypoglycemia compared with 29.7% of patients treated with up-titrated insulin glargine.

Also, for patients with an A1c >7.5% to ≤8.5% at baseline, 39.2% of patients treated with IDegLira achieved A1c <7% without hypoglycemia and no weight gain, compared with 11.0% of patients treated with up-titrated insulin glargine.

The most recent study is DUAL-VII, which looks at patients who are not controlled on glargine plus oral agents. They were randomized to IDegLira or glargine and aspart. This gets around to something we discussed earlier, comparing a fixed-ratio combination of insulin and GLP-1 vs the combination of insulin with rapid-acting insulin.



Both were effective in lowering A1c and in fasting glucose and plasma glucose. In the combination with aspart, you're going to take a lot more insulin, more injections and get more hypoglycemia and weight gain. John, what do you think about this composite endpoint and the fact that counting hypoglycemia as part of your endpoint is very important?

John Anderson, MD: Some of the new recommendations that we just heard about from both EASD and ADA in Orlando at scientific sessions were picking agents that minimize weight gain and hypoglycemia. I think these do that.

I think the other thing that was interesting that I don't think anyone really expected from this particular set of trials was the way that the slow up-titration, as you mentioned, really minimizes the GI side effects. When I am talking to clinicians, I will sometimes say, "If you had a patient who failed a GLP-1, you're on basal insulin, you want to intensify with a GLP-1. You might not want to hesitate just because they had failed GLP-1 that has a nausea rate of 24%, 25% when you look at this particular product in the low nausea rate. This may be a way to tolerate GLP-1 that they had not been able to tolerate before perhaps."

I think it's an interesting phenomenon that came out of all these trials in addition to what, as you said, some really dramatic A1c reduction combination.

Vivian Fonseca, MD: Patients often bring up other side effects that they've heard about on the television or in the news media. This was looked at in this program, there was no increase in cardiovascular events, no increase in pancreatitis or pancreatic cancer or, for that matter, no reports of any case of medullary thyroid cancer, although there is a warning in the label.

IDegLira: Other Safety Events†

	DUAL I[1]	DUAL II[2]	DUAL III[3]	DUAL V[4]	DUAL VII[5]
Major adverse CV event	IDegLira 4/833 DEG 1/413 LIRA 1/414	IDegLira 1/199 DEG 2/199	IDegLira 2/292 GLP-1RA 0/146	IDegLira 1/278 GLAR 1/279	IDegLira 0/252 GLAR+ASP 0/254
Pancreatitis	IDegLira 0/833 DEG 0/413 LIRA 1/414	IDegLira 0/199 DEG 0/199	IDegLira 0/292 GLP-1RA 0/146	IDegLira 0/278 GLAR 0/279	IDegLira 0/252 GLAR+ASP 0/254
Pancreatic cancer	NR	IDegLira 0/199 DEG 1/199	NR	IDegLira 0/278 GLAR 0/279	IDegLira 0/252 GLAR+ASP 0/254
Medullary thyroid cancer	IDegLira 0/833 DEG 0/413 LIRA 0/414	IDegLira 0/199 DEG 0/199	IDegLira 0/292 GLP-1RA 0/146	IDegLira 0/278 GLAR 0/279	IDegLira 0/252 GLAR+ASP 0/254

†Positively adjudicated by a blinded monitoring committee and judged by the investigator as treatment-related
DEG, insulin degludec; GLAR, insulin glargine; IDegLira, fixed-ratio insulin degludec/liraglutide; LIRA, liraglutide; NR, not reported.

1. Gough SCL, et al. Diabetes Obes Metab. 2015;17:965-973. 2. Buse JB, et al. Diabetes Care. 2014;37:2926-2933. 3. Linjawi S, et al. Diabetes Ther. 2017;8:101-114. 4. Lingvay I, et al. JAMA. 2016;315:898-907. 5. Billings LK, et al. Diabetes Care. 2018;41:1009-1016.

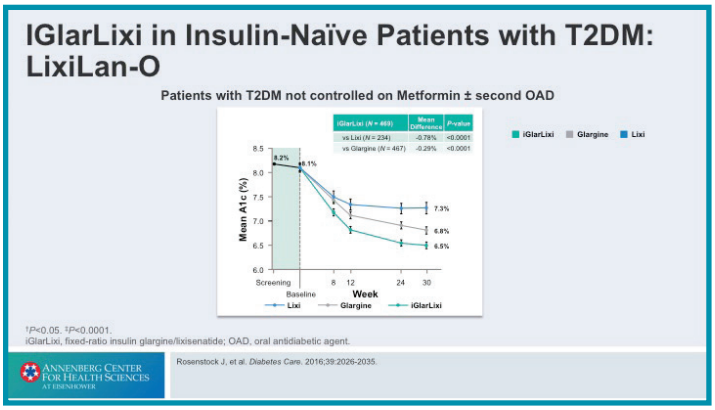
In summary, IDegLira provided significantly better glycemic control while reducing key adverse events associated with basal insulin and GLP-1 receptor agonist in both insulin naive and previously insulin treated patients. There's effective A1c lowering independent of baseline A1c duration of disease of previous insulin dose. Overall, it's insulin sparing, reduces glycemic excursions. There are weight benefits and that these glycemic and weight benefits are durable over a long period of time.

Lower rates of hypoglycemia and lower rates of nausea are very important benefits that patients can get with this type of treatment that will lead to an important improvement in patient-reported outcomes and treatment satisfaction.

IGLARLIXI LIXILAN PROGRAM

John Anderson, MD: This module reviews the data from key trials in the LixiLan clinical trial program for the fixed-ratio combination of insulin glargine and lixisenatide. There were 2 separate trials, LixiLan-O and LixiLan-L. I'll review both of those for us.

LixiLan-O was as an add-on to oral agents in patients with type 2 diabetes not controlled on metformin plus a second oral agent. They took these patients, they were on their orals. They had an initial run-in. I think all the other agents were stopped except metformin. Then, they were randomized to either lixisenatide, glargine, or IGlarLixi. As you can see here, clearly, the best hemoglobin A1c achieved was an average of about 6.5% with the IGlarLixi combination starting from a baseline A1c of about 8.1%.



You see that most of that benefit came from the postprandial glucose reduction of almost 42 mg/dL when you have a short-acting GLP-1 receptor agonist like lixisenatide included in it. Of course, the weight change is always going to be an intermediate between GLP-1 by itself and insulin by itself. You do minimize some of the weight gain you have if you were to continue to titrate the basal insulin.

In LixiLan-O, a significantly greater proportion of patients treated with IGlarLixi achieved a key composite endpoint of efficacy and safety compared with up-titration of insulin glargine.[43] Thirty-two percent of patients treated with IGlarLixi achieved A1c <7% without symptomatic hypoglycemia and no weight gain compared with 19% of patients treated with up-titrated insulin glargine.

As we look at adverse side effects, I always like to point out the GI side effects. The number one limitation for use of GLP-1 receptor agonists is nausea. In most clinical trials, you'll see that between 20%, 22%, 24%.

IGlarLixi in Insulin-Naïve Patients with T2DM: LixiLan-O *(cont)*

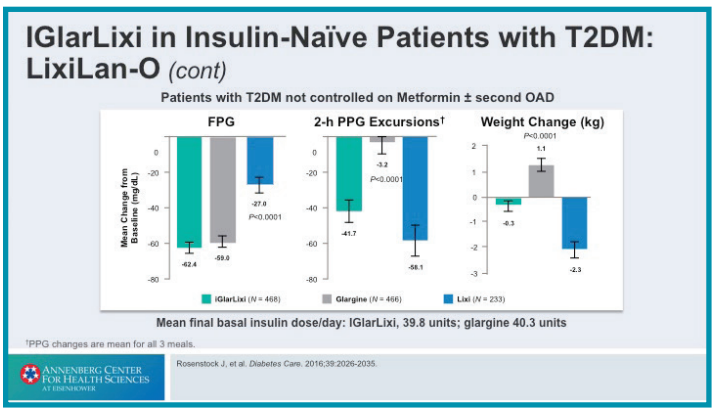
	iGlarLixi	Glargine	Lixisenatide
Adverse event leading to discontinuation	2.6%	1.9%	9%
GI adverse event Nausea	21.7% 9.6%	12.6% 3.6%	36.9% 24.0%
Symptomatic hypoglycemia, events/ patient-year	1.4	1.2	0.3
Cardiovascular event	0.4%	1.5%	0.9%
Allergic reaction	1.3%	0.6%	0.9%
Pancreatitis	0%	0%	0%
Pancreatic cancer	0%	0.2%	0%

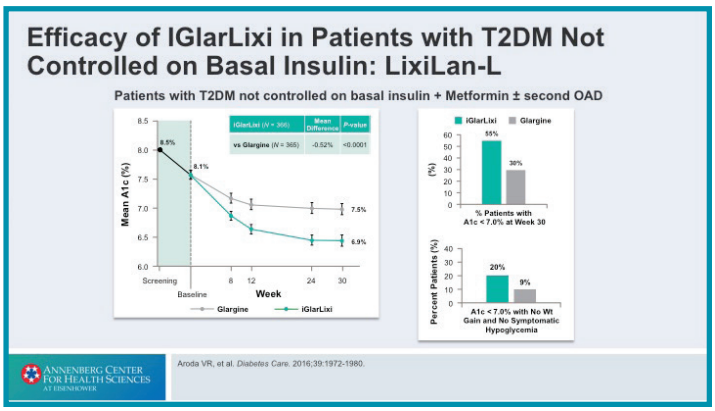
Annenberg Center For Health Sciences At Eisenhower
Rosenstock J, et al. Diabetes Care. 2016;39:2026-2035.

For lixisenatide, that's about 24%, yet for the IGlarLixi component, there's only 9.6%, right around 10%, which is markedly lower than what one would expect for a GLP-1 receptor agonist by itself. As we have said before, most of the thought about this is as you titrate the basal insulin component, the GLP-1 receptor agonist just rides along with the insulin, in which that smooth, slow, up-titration, without jumping between doses, that we think really minimizes the GI side effects. In this case, you can see that that held up.

Let's also look at the LixiLan-L trial. Again, this is patients with type 2 diabetes. These patients were already on basal insulin, they weren't controlled. This was an international study, as was LixiLan-O. There was a screening period and then a run-in period for what we call basal insulin optimization, because, remember, basal insulin doesn't mean everybody was on glargine. It means some of these people were on detemir, some even on NPH, internationally considered a basal insulin.

Everyone was put on glargine and, of course, you see the A1c went from about 8.5% vs 8.1%. That's when they started the trial. Again, as you can see

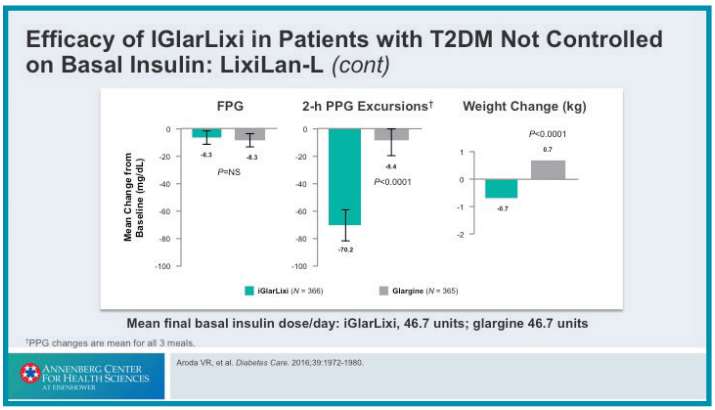




in this slide, continuing to titrate the glargine vs the IGlarLixi titration, you go from about 8.1% to 6.9%, clearly favoring the IGlarLixi combination.

Again, you see the percentage of patients getting to goal at week 30 was much greater with IGlarLixi. Again, that composite endpoint of less than 7% with no weight gain and no symptomatic hypoglycemia, clearly favors the IGlarLixi.

As we can see in this next graph, there was no change, really, in terms of fasting glucose, because these patients were already optimized on a basal insulin.



When you look at the postprandial component from that lixisenatide short-acting GLP-1 receptor agonist, you can see you have a 70 mg/dL in postprandial glucose. That is a very profound reduction. You can also see that you had a little weight gain if you continued to titrate the glargine vs the weight loss that you saw when you had IGlarLixi.

Again, as we've seen with IDegLira, it really doesn't matter where your BMI is, the duration of diabetes, those types of things. This worked in all of the cohorts.

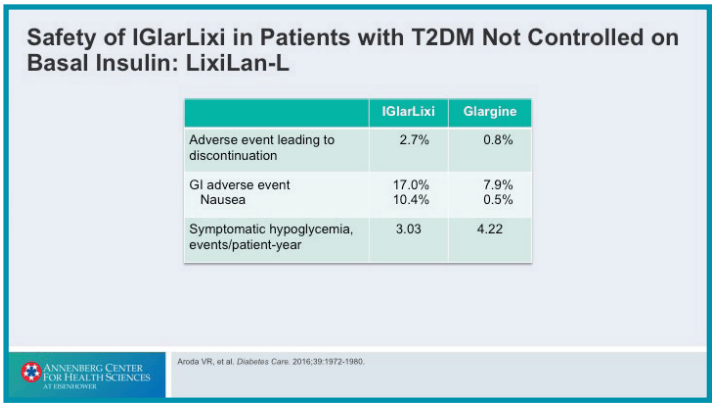
One of the things I also point out is for a long time we heard, "If my patient has had a duration of diabetes of 10 years, they have no beta cell function left, right? A GLP-1 receptor agonist is just not going to be that effective." This clearly, as we saw with IDegLira, discounts that. The GLP-1 receptor agonist clearly has benefit, even in patients with a long duration of diabetes.

Again , in this trial, similar to what we saw with LixiLan-O, the rate of nausea was right around 10%. Very, very similar between the 2 clinical trials. As I said, that is another recognizable benefit for using the coformulation.

These are viable options, minimizing weight gain, intensifying insulin. Many times, they're going to be using the same type of pen they may have already been experienced with in using a basal insulin. I think it's an attractive alternative.

Vivian Fonseca, MD: It's just the question when we change over. I think it's awareness at the comfort level of clinicians to start off combination injections. We are all used to combination pills. Combination injectables is a very new concept, it clearly works.

John Anderson, MD: Just to summarize, IGlarLixi provided significant and better glycemic control while reducing key adverse events associated with basal insulin and GLP-1 receptor agonist both in insulin-naive and in patients already on insulin.



It's not insulin sparing, but there were similar fasting glucose reductions and greater postprandial reduction vs glargine U-100. Of course, as we might expect, the weight effects were intermediate between what basal insulin and GLP-1 by itself would be.

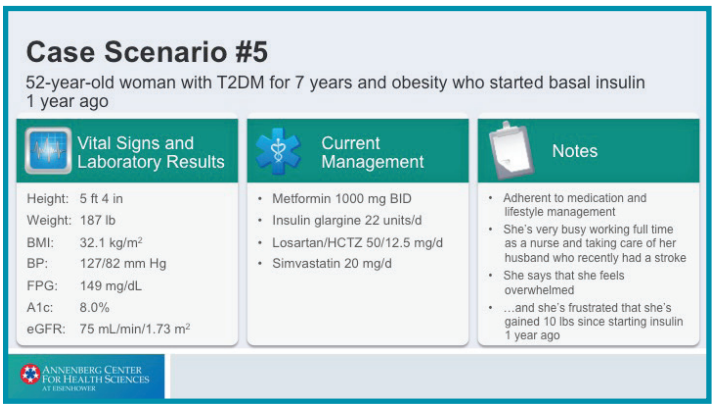
It had an adverse event profile similar to individual components except for that less nausea and common GI side effects with IGlarLixi that we saw vs lixisenatide. Incidence of symptomatic hypoglycemia is similar to glargine U-100 in insulin-naive and in insulin-treated patients. Adjudicated major adverse cardiovascular events (MACE) occurred in a very small percentage of patients. As we saw with IDegLira in the DUAL program, no pancreatitis, no pancreatic cancer and certainly no medullary thyroid cancer, which I think is very reassuring as we go forward.

We clinically, post marketing, just are not seeing those things that are listed in the label. It's reassuring for our patients, it's a way to have that discussion if it's ever brought up.

USE OF FIXED-RATIO COMBINATIONS

Vivian Fonseca, MD: In this module we will use case scenarios to discuss how to initiate therapy with fixed-ratio insulin degludec/liraglutide and insulin glargine/lixisenatide combination products, and how these products can be used to address key unmet needs in patients with type 2 diabetes.

The first patient is a 52-year-old woman with type 2 diabetes for 7 years, who's obese, and started basal insulin a year ago. She has a BMI of 32 kg/m^2, blood pressure 127/82 mmHg, A1c of 8.0%, with a GFR of 75 mL/min/1.73 m^2. She's been taking metformin for several years, was on other oral agents, which were stopped, and then glargine added. She's up-titrated a little bit to 22 units/day. She takes drugs for blood pressure and hyperlipidemia.



She's adherent to her medications, but she's very busy working full time as a nurse and taking care of her sick husband, and feels she is overwhelmed. She's most frustrated about the 10 lbs of weight gain since starting a year ago. When you hear that story about weight gain, John, what do you think about GLP- 1 receptor agonists?

John Anderson, MD: I think that that's a great combination. She's not at goal, her A1c is 8%. She's on maximum dose of metformin and glargine.

Vivian Fonseca, MD: She's not on a lot of glargine and that gut feeling of many docs looking at the A1c and her fasting glucose will say, "Well, we have to the Treat-to-Target Trial. You could titrate this." I tell all my patients to self-titrate and try to get the fasting glucose down to 150 mg/dL. I think she could get there. She could easily get to a fasting glucose down to 100 mg/dL, A1c around 7%, maybe with or without a little hypoglycemia. Her insulin dose is probably going to be about 45 or 50 units/day.

She'd probably gain some more weight although she says she's adherent with her lifestyle and family issues, etc, she's probably not adhering to her diet and not exercising enough. She will gain more weight. Since that's so important to her, I think we need to pay attention to it.

John Anderson, MD: I think that is a real barrier. She's not having hypoglycemia as a barrier, she's frustrated with the weight gain. When you come in and say, "You need to push the insulin further," my guess is she's going to give you tremendous pushback. The key for us is how we solve this problem for her.

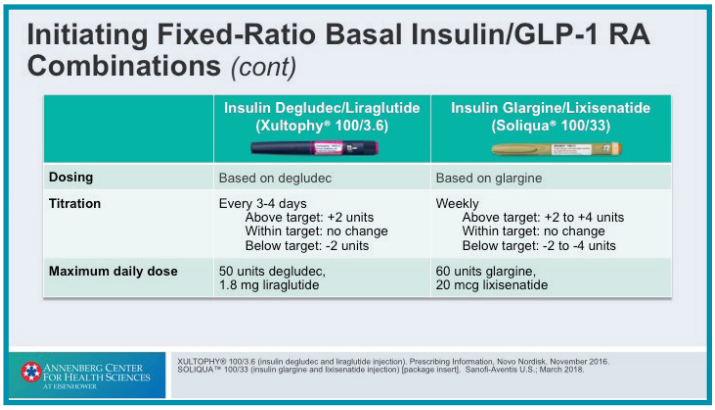
Vivian Fonseca, MD: Then, if you tell her, "How about another injection?" she's going to say, "You know I've got enough to do, I have such a busy job. I have so many things to do." I think a combination therapy may be very appropriate. Would you agree with that?

John Anderson, MD: I would absolutely agree with that.

Vivian Fonseca, MD: Some people would say, "What about an SGLT2 inhibitor?" I think that's not unreasonable as well. In general, the weight loss that you would get with that is a lot less than the weight loss you could potentially get with a GLP-1 receptor agonist. Now, not everybody would lose a huge amount of weight with SGLT2 inhibitor. With GLP-1 receptor agonist, it's very variable and she may be one of those lucky ones.

Let's discuss how we would start. You could choose either IDegLira or IGlarLixi remembering that the maximum dose . . . but that's not an issue here. You can go to 50 or 60 units. What I would do, if you're going to use this, is discontinue her basal insulin. If a patient was on GLP-1 receptor agonist, we would discontinue it. You would dose based on the one you chose.

For IDegLira, the initial dose is 16 units of insulin degludec (which includes 0.58 mg of liraglutide). IDegLira is given once daily at the same time each day with or without food.



For IGlarLixi, the initial dose depends on their current dose of basal insulin and if they are taking lixisenatide. For a patient inadequately controlled with <30 units of basal insulin or lixisenatide, the initial dose of IGlarLixi is 15 units (which includes 5 mcg of lixisenatide). For a patient inadequately controlled with 30 to 60 units of basal insulin, the initial dose of IGlarLixi is 30 units (which includes 10 mcg of lixisenatide). IGlarLixi is also given once daily at the same time each daily, but that should be within the hour prior to the first meal of the day.

The titration would be based on how you would titrate the insulin. With the degludec, you'd do that every 3 to 4 days. Patient is above target, go up by

Initiating Fixed-Ratio Basal Insulin/GLP-1 RA Combinations

	Insulin Degludec/Liraglutide (Xultophy® 100/3.6)	Insulin Glargine/Lixisenatide (Soliqua® 100/33)
Dose range delivered per injection	10 to 50 units	15 to 60 units
Prior to initiating	Discontinue basal insulin, GLP-1RA	
Initial dose	16 units	15 units: if inadequately controlled with <30 units basal insulin or lixisenatide 30 units: if inadequately controlled with 30-60 units basal insulin
Dose timing	Once daily at same time each day with/without food	Once daily within the hour prior to the first meal of the day

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XULTOPHY® 100/3.6 (insulin degludec and liraglutide injection). Prescribing Information, Novo Nordisk, November 2016.
SOLIQUA™ 100/33 (insulin glargine and lixisenatide injection) [package insert]. Sanofi-Aventis U.S.; March 2018.

2 units. If they're below, you'd go down a little bit. With glargine, it's variable. Some people do it weekly, some people do it every 3-4 days. I think, we have some flexibility there.

Bear in mind that there's a maximum dose, you could go up to 50 units and 1.8 mg for IDegLira or 60 units with glargine and 20 mcg of lixisenatide with IGlarLixi. My feeling is that that's going to be adequate for a patient like this. She did reasonably [well] on 22 units, but just needed a bit more and it will help control her weight as well. Would you agree with that, John?

John Anderson, MD: I would. I think that like you said, because she's on a relatively low dose of her basal insulin that her chances for success are really good. I think this would have a patient coming back in 3 months probably at target goal for her A1c. Hopefully, happy that you've spared her insulin dose maybe a little bit and she's lost a little weight.

John Anderson, MD: This patient is a 73-year-old male with previously well-controlled type 2 diabetes, whose adherence, we hear about this a lot, has declined over the past year. His weight is 164 lbs. His BMI is 27.5 kg/m^2. Blood pressure needs a little work at 136/92 mmHg. His A1c is at 7.7%. Fasting glucose of 132 mg/dL. Postprandial higher at 196 mg/dL. A GFR is 58 mL/min/1.73 m^2. Just a modest renal compromise.

The patient is on lifestyle management, a maximum dose of metformin. Insulin detemir at 34 units/day, which is really close at 0.46 units/kg/day, really close to that sort of magic point 0.5 units/kg/day that we talk about when you need to start thinking about prandial therapy.

Of course, he's got prandial therapy in terms of liraglutide of 1.2 mg/day, hydrochlorothiazide, aspirin, and then fluticasone (Flonase) nasal spray in the spring. He's had a history of grade 2 retinopathy, hypertension, seasonal allergies and mild cognitive impairment. Not only is he dealing with mild cognitive impairment, which may definitely be affecting his adherence, but his wife was diagnosed with stage lll breast cancer a year ago.

She may be partly the caretaker and now her health is compromised. You can see that maybe what we need to do is not think about dramatically lowering his A1c, but maybe finding a regimen that might work for him. Would you see a benefit in taking 2 injections a day and making them 1 and thinking about a coformulation in this patient?

Vivian Fonseca, MD: Yes, I would. I do feel here that there are some really important factors in this gentleman's life. He's developing cognitive impairment himself. He's probably very stressed with a spouse who's got fairly advanced disease, maybe life-threatening disease. I don't want to improve glycemic control greatly. His A1c is 7.7%, this fits in with the individualized goal of the American Diabetes Association being between 7% and 8% and I'm very comfortable with that.

I would not want his control to deteriorate too far because that's a slippery slope where if he stops taking his insulin, for example, he might get an infection and really deteriorate tremendously and get polyuria and polydipsia at his age. It would be tragic for him and his wife if he would get ill. I'm comfortable with his A1c. I'm also very comfortable with his weight being 27.6 kg/m^2. His blood pressure is not too bad. I think overall, the numbers are good, it's just the fact that he's got so many burdens in his life and he's probably going to forget taking 1 of these 2 injections a day.

This is a very good opportunity to consolidate his treatments. I would combine . . . he's on detemir and liraglutide. Now, that combination is not available, but you could use IDegLira and choose a dose that's halfway up 25-30 units or even go 34 units/day. He's likely to tolerate the liraglutide, so I'm not worried about the GI side effects.

This is an exception to the recommendation of starting right at the bottom and up-titrating. It's not in the guideline, it's not in the package insert, but I would make a pragmatic decision. You had to go with 30 or even 34 units of the fixed-ratio combination because that's what he's on anyway. It would really simplify his life and allow him to not have to deal with 2 injections a day.

John Anderson, MD: As you said, he's already on a middle dose of a fairly good GLP-1 receptor agonist. One would expect, if you switched to a coformulation, whether it's IDegLira or IGlarLixi, that you probably don't have to worry about that slow up-titration again, because he is experienced with his GLP-1 receptor agonist.

Vivian Fonseca, MD: The real reason for choosing that low dose is to start low with the GLP-1. That does not apply here. If I was switching between agents, sometimes you probably do need to go down because you can get side effects from a different GLP-1 receptor agonist.

Initiating Fixed-Ratio Basal Insulin/GLP-1 RA Combinations *(cont)*

	Insulin Degludec/Liraglutide (Xultophy® 100/3.6)	Insulin Glargine/Lixisenatide (Soliqua® 100/33)
Initial dose	16 units	15 units: if inadequately controlled with <30 units basal insulin or lixisenatide 30 units: if inadequately controlled with 30-60 units basal insulin

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XULTOPHY® 100/3.6 (insulin degludec and liraglutide injection). Prescribing Information, Novo Nordisk, November 2016.
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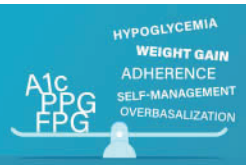

John Anderson, MD: I think the other point that you make is, and they don't tell us the duration of diabetes here, but it says this patient has been previously well-controlled with type 2 diabetes. Let's say he's had 15 to 20 years of well-controlled diabetes. What we know is that now as he gets cognitive impairment, is going to be just fine, as you said, to allow his A1c goal to be less than stringent.

If we were going to use this combination, as you said, with the last patient, Vivian, you would start with 16 units, if you're going to use IDegLira. You would start at 30 units if you're going to use IGlarLixi because he is above 30 units. Even if he were on as much as 50 units, you would want to still go back on IGlarLixi to 30 units and titrate back up.

One might have some flexibility to pick a reasonable dose and go ahead and switch the patient over. If you switch this patient from liraglutide to lixisenatide, which is a shorter acting GLP-1 and may be associated with little higher rate of nausea. I might caution not to do that unless you go back down to the 30 units and then titrate up from there. That would give you the starting dose of lixisenatide being 10 mcg.

Again, when you titrate, you're going to titrate just like you do with basal insulin. These studies were all done differently, but we all, as you said, Vivian, have self-titration algorithms that we like to give our patients. I like to have it written down for them. I like to have the patient repeat it back to me before they leave the office. I always like for them to check-in, either by phone or if you use email or something like that, sort of [every] 2 to 3 weeks in [order] to make sure that they are continuing to titrate and if they're not running into any problems.

The basal insulin and GLP-1 fixed-ratio combinations offer a more simplified regimen for this man who has cognitive impairment, we just decrease his injection burden daily by half and it may reduce the complexity vs something like a premix or certainly a basal-bolus regimen in someone who's got some cognitive compromise is not a great idea. It may increase patient adherence.

I think, we put out a lot of good points with this particular individual and the role that a coformulation may make in a decision plan for him.

SUMMARY

There are numerous unmet needs that we encounter in clinical practice, patient adherence, treatment complexity, psychosocial distress, the diagnosis of depression, assessing whether the patient has cardiovascular risk or not. We have medications, a variety of medications, I would say an explosion of medications over the last several years. Some with limited glycemic lowering, some with durability and safety and tolerability concerns. Cost is always a concern when we're trying to manage patients.

There are now agents with variable effects on cardiovascular risk and the question is, does that just apply to the patients who have noncardiovascular disease or is that going to also apply to the patients at high cardiovascular risk? Because we still have some clinical trials that have yet to report out, that may inform us on this.

Of course, we have dosing administration limitations of some of these agents. We know that there's a progressive loss of beta-cell function over the duration [of] type 2 diabetes. It's an important topic to discuss with patients so they don't feel like just because I need a new medication means that somehow I personally, as a patient, have failed. We talk a lot about the role of basal insulin and the intensification of basal insulin with GLP-1 receptor agonists.

I think that that is going to be something that becomes increasingly popular as more data comes in and as we get more experience using these in the marketplace. I think there's also some benefits with early insulin administration. Sometimes, there are patients who truly need insulin and it doesn't always need to be seen as "the last resort."

Vivian Fonseca, MD: Basal insulin and GLP-1 receptor agonists have different and complementary mechanisms of actions that result in improvement in both fasting and postprandial glucose control. Clinical trials have demonstrated the efficacy of a basal insulin GLP-1 receptor combination in the management of type 2 diabetes.

Now, we have fixed-ratio combinations of these 2 agents that allow greater ease of use of a basal insulin GLP-1 receptor combination in 1 injection. Addressing patient concerns about injections, and discussing the efficacy of combination insulin and GLP-1 receptor agonist therapy, can help mitigate barriers to injectable treatments for type 2 diabetes.

John Anderson, MD: When I started practice, I had glipizide, glyburide, NPH, and regular. That was the sum total of our armamentarium and it's almost an embarrassment of riches now that we have all of these new medications. Despite that, we still have adherence issues, we still have cost issues, and formulary and availability issues.

I'm looking forward to the day when we can make our clinical decisions and try to minimize, at least, some of those barriers to treatment to help us manage the right patient and the right medication.