Jay H. Shubrook, DO, FAAFP, FACOFP: Hello, and welcome. On behalf of MLI and the American College of Osteopathic Family Physicians, Less is More, The Promise of Weekly Insulin in Type 2 Diabetes. We'll be discussing the place of novel insulin therapies, including once-weekly insulin in treating type 2 diabetes. I'm Jay Shubrook, a professor and a diabetologist at Touro University, California. I'm delighted to be presenting with Dr. Wysham.

Carol H Wysham: Thank you, Jay. I'm Dr. Carol Wysham. I'm a Clinical Endocrinologist and a Clinical Professor of Medicine at the University of Washington in Spokane, Washington.

Dr. Shubrook Thank you for joining us today. I think you'll really enjoy this program. Let's get started.

Dr. Wysham: I'm going to start talking a little bit about some of the current state of treating patients with once-daily insulin. We know, Jay, that there's a lot of challenges associated with once-daily insulin, multiple doses, worry about hypoglycemia, patient's insecurity about the dosing adjustments that they need to make. Obviously, at least 365 doses of insulin per year. We know that insulin adherence is poor. There are concerns about weight gain, fluid retention, and really importantly, only between 5% and 45% of patients actually achieve the desired glycemic goals in the real world.

We know that around two-thirds or more people with type 2 diabetes report missing basal insulin doses. It takes only between three and four missed doses per month before it can affect the glucose control significantly, and somewhere between five and six miss-timed insulin doses is associated with impacts on glycemic control so obviously, daily insulin is not optimal for many patients.

Dr. Shubrook To see a timeline of how advances in insulin technology prolong duration of time of action, click "Next."

Dr. Wysham: Looking at other options for administering basal insulin, two companies are developing a once-weekly basal insulin, so pretty far down the process of approval. They have several goals. Obviously, they'd like to extend the time action profile to allow once-weekly administration, which they have done. They want to develop this once weekly basal insulin so it's a long flat exposure profile that mimics endogenous insulin secretion. They have done so with a couple of different mechanisms. One is to control the tissue distribution properties, but importantly, they've also attenuated the potency of the insulin at the insulin receptor, which also prolongs its circulation. This results in reduced variability and can control the fluctuations in glucose during the week.

We wanted to maintain an acceptable and manageable hypoglycemia profile. There may be limitations in that with this once-weekly dosing, there might be an inability to rapidly adapt to changes in insulin requirements, which of course, happens in normal physiology. However, talking with patients, their preference for fewer injections may actually improve the acceptance of insulin, their adherence, as well as their persistence, which is a big issue. There is some data, Jay, just to look at what is the difference in adherence if you go from a once daily to once weekly. This study was done with the first once-weekly GLP-1, extenatide, once weekly.

I know you remember when this was released, it wasn't exactly the most user-friendly device. Even so, they were able to demonstrate that the proportion of individuals that had good adherence to their once weekly compared to once daily was greater. We're hoping that by extending that information and looking at the difference between once daily and once-weekly basal insulin, that we'll be able to see similar benefits. I think there's other benefits. As you recall, most of our patients are going to be on once-weekly GLP-1s before we start insulin and that is going to make it easier for them to remember to take both of their injections at the same time.

Dr. Shubrook Yes, I think this is a really important point. We certainly learned from the GLP-1 receptor agonist that weekly [dosing] is certainly much more popular and convenient for most of our patients. Of course, this is new for a lot of people so they may have some questions. We actually have some quotes from social media that we'd like to use as discussion points.

Female Voice 1: I would worry about any weekly medication. If you have a bad reaction to it, you're stuck with it for a week.

Dr. Shubrook What are your thoughts, Carol?

Dr. Wysham: I have some information I'd like to share in just a little bit to address the concerns about hypoglycemia.

Dr. Shubrook I think it's also important that insulin is a molecule that very rarely has any other kind of reaction other than hypoglycemia so we're going to have to know about dosing. Outside of that, it's not a medicine that's highly allergic or other things that we're going to see a lot of reactions to.

Dr. Wysham: That's true. I've never seen an insulin allergy in my 40 years.

Dr. Shubrook We have another comment that's come in.

Male Voice 1: A weekly insulin, if they could make it, would be one heck of a huge shot too, though. Imagine someone who needs 100 units a day, that'd be a 700-unit shot. EGADS. You'd look like you'd have a golf ball under your skin.

Dr. Wysham: The insulins that are currently under development are being made in concentrated formulations. Insulin icodec is 700 units per ml, insulin efsitora is 500 units per ml, so obviously, the volume of insulin will be almost exactly the same as if they were doing the equivalent daily amount of insulin.

Dr. Shubrook Yes. I think this is so important. We already have concentrated insulins on the market. Certainly, when we're using pens for concentrated insulin, the patient experience is similar or even better. Because, again, you're not going to be injecting a higher volume. It's just a higher concentration.

Dr. Wysham: One of the problems that I foresee, Jay, is the adoption of what would be a major change in how we administer basal insulin. Physicians and providers are used to doing it the same way. Even though we have second-generation basal insulins, most patients are being started on glargine-based daily insulin doses, so we have to actually address some of the issues regarding trying to adopt a new paradigm. Obviously, people are used to the proven efficacy. There're good guidelines on how to use it. We, of course, have to deal with cost and insurance coverage.

We now have bio-similar options and different insulin formularies that we have to work with. We know insulin has a positive impact on comorbidities and we need to make sure that information is really processed with a patient. The current insulins are very familiar to the providers, and if patients are already on the daily insulin, obviously, to the patients as well. We'll have to deal with some of these issues as the availability of these once weeklies come out to help people make that paradigm shift.

Dr. Shubrook I might just add something here. I think that familiarity is so important, right? Habits are hard to change. I'm so glad that people are comfortable with insulin now, both patients and clinicians. You also highlighted that we're not doing a great job. We're not actually getting the goals that we're trying to achieve with insulin, and so, we're going to have to find novel ways to make it more effective and more attainable for patients to achieve their goal when they start insulin.

Dr. Wysham: Yes, I agree. I'm hoping they'll come up with a dosing app that will be helpful for the providers as well as the patients to appropriately titrate the insulins. We addressed earlier this concern that the patient posted on social media about hypoglycemia. They actually have looked at this in a very novel way. They did a study where they did a two-period crossover study in patients with type 2 diabetes, and they looked at all the different measures, clinical, physiologic, counter-regulatory, to what happened when you give two times the appropriate dose, or even three times the appropriate dose of the once-weekly insulin icodec compared to insulin glargine.

What they found is that neither were associated with an increased risk of hypoglycemia. The time for developing hypoglycemia and the time to recover were also comparable between the once weekly highest dose as well as insulin glargine. They also looked at CGM data and showed that the frequency and the amount of time spent in hypoglycemia with even these very high doses were not significantly different, was much less than 1% in both cases. As far as addressing it, you just address it the same way you currently address hypoglycemia, get 15 grams of glucose, and then monitor in 15 minutes for recovery and continue and repeat as appropriate. I think it's important to realize that this is not going to change the way we evaluate hypoglycemia and treat hypoglycemia.

I am incredibly excited about using CGM in all of my insulin-treated patients. Especially in the patients who I'm starting on basal insulin, because I'm going to be able to actually see when their highest blood sugar of the day is and when are their lowest blood sugar of the day and is it appropriate for us to continue to increase based upon the patterns. CGM is being used and has been studied at least in the European study comparing the outcomes with home glucose monitoring by finger sticks or CGM. They were able to demonstrate that the quality-adjusted life expectancy, the quality of life, and the length of time living that good quality of life was higher when CGM was used. The mean lifetime cost estimate was about €10,000 greater with the CGM and that was felt to be cost-effective.

The lower the patient age when you start the CGM, likely the better outcome and the more cost-effective it will be. Now, there are some considerations based upon the impact of CGM on food and behaviors that we may be able to use CGM as an alternative to advancing insulin or other therapies to improve glucose. That's really going to be interesting to see how that comes out. Then finally, also very excited about using CGM in telemedicine and the studies that show that telemedicine actually with CGM has a better outcome than usual care.

Dr. Shubrook I already think it's best practice that when you're making a change to an insulin regimen, CGM is a really valuable tool both for you and the patient to know that you're heading in the right direction. [There's] every reason to believe that this would also be a very valuable tool for those who are starting once-weekly insulin.

Dr. Wysham: Yes. In fact, we have studies that have been presented that show that you can use CGM instead of home glucose monitoring to titrate once weekly insulin. These are some examples that we have of the current CGMs. Some of them actually will broadcast to your Apple Watch. Importantly, whether it's the FreeStyle Libre system, the Guardian system, the Implantable Eversense, or the Dexcom G7 sensors, they all have the number of what the glucose is and some indication of how quickly the blood sugars are changing either up or down or stable, and you can see in each of those there are arrows available. It's highly important for patients, and they're making their decisions about how to manage their diabetes on an hour-to-hour basis.

Dr. Shubrook All right. We have another post to look at.

Female Voice 2: I was really happy that I only had to do an injectable once a week rather than at every meal or once a day. I was really just amazed how something could stay in your system for a week and work for the whole week.

Dr. Shubrook This was from a patient in one of the once-weekly trials. Any comments or reflections?

Dr. Wysham: I think, importantly, this was an insulin-naive patient, and they had a very positive response to the use of once-weekly insulin. I would think that the insulin-naive patient would possibly have had more difficulty getting started. I think this is very reassuring.

Dr. Shubrook Even someone that's brand new can do this.

Dr. Wysham: Yes. Exactly. Jay, we've talked about just some of the limitations of once-daily insulins and, hopefully, we're going to have available the once-weekly basal insulins because I think they do hold promise that can address some of the barriers associated with once daily. Of course, we'll prevent the need for twice daily, which a lot of our patients are already on.

Obviously, making the decision about using once weekly, we've got to involve the patient. We really have to have that shared decision-making and really address the individual needs and concerns. I love to ask patients what their barriers are, what their concerns are, what their schedule is, and help them really incorporate the insulin into their schedule. We can emphasize the importance of diabetes education for patients to get the best out of their diabetes management.

Dr. Shubrook Thank you so much for sharing that introduction to weekly insulins. I think there are some important things we can take from this. We're going to be introducing new insulin therapies to patients. I don't know if you have any best practices about how you introduce it to a patient or even a colleague to say how they might start with something that may be novel.

Dr. Wysham: The patients that are starting as insulin-naive patients I don't think we really need to address a whole lot differently than we currently do. Just making sure they understand why insulin, why it's important. As far as the colleagues, that's another issue altogether that if I was running into somebody at lunch hour and talking about insulin, I think understanding that the volume is small, the safety and the efficacy is equal to that of the once dailies. Just once we know more about what the recommendations are going to be for starting patients, I think it'll be-- It's going to take time. We're going to have to really emphasize the patient's voice as we've discussed already and how important it's going to be. What about you? What do you think?

Dr. Shubrook I think with any new technology or new treatment, there are going to be some early adopters among the patients. They'll be excited and having information will help us help them. I also think it's okay for us to have some positive experiences, know what's happening, and then start building our own repertoire of how we are going to introduce it. Because I do think everybody has a different threshold for which they want to try something new. I do think that in many ways, this is insulin, just like we've been using insulin all before. It's just a slightly different kinetic pattern. I do think there's an opportunity here for us to use the existing knowledge we have, use the tools that we already have so people can have a really pleasant and positive experience trying new technology and new insulin.

Dr. Wysham: I really think that, again, as I stated before, if we follow the ADA guidelines, most of our patients we're getting ready to start on basal insulin alone will have already been on a once-weekly GLP-1. That gets them over the injection barrier so that's not much of an issue anymore. We need to address their concerns about insulin, and patients have their own concerns about starting insulin. I think having a once-weekly insulin in a patient who's already on a once-weekly GLP-1 is just going to be, like I say, a match made in heaven.

Dr. Shubrook Yes. I think there's patients already excited about it.

Dr. Wysham: Yes, I agree.

Dr. Shubrook We're going to move now to practices that are initiating and dosing basal insulin because, remember, we talked earlier on that we really haven't optimized the dose of insulin and the titration of insulin today. I think we already heard about the number of people who aren't taking insulin regularly or not taking it on the right time. Ultimately, anytime we're not following a medication regimen, those delays in initiation and intensification really do affect us, our ability to achieve glycemic targets and ultimately, frustrate patients. If they're not getting the goal, they're probably not going to continue it.

We know that even 3 months in, 50% of patients might have already interrupted their basal insulin and 15% will discontinue it. I think that part of that is the burden of the work, maybe not seeing the results, and we really can make a big difference by doing proper initial dosing and regular titration. Now that not only affects glucose goals, but it also has been shown to affect quality of life as well as the risk of morbidity or mortality of patients with type 2 diabetes. That delay, as you can see here, is highlighting that there's higher rates of myocardial infarction, heart failure, and stroke in those patients who have a delay of insulin intensification more than a year, so time is not our friend. We need to get started and get moving.

We have a continuing widening of the variety of insulins that we could be using for our patients, and it's important to highlight that as we start to have more longer-acting insulins, they're going to have flatter curves. The relative curves of the insulins that preceded them are going to look a little bit more peaked. Ultimately, we're getting closer and closer to physiology by having more sustained release of these insulins. I think for the patient experience, that means less variability from day to day. That's going to be a positive thing and a more reliable thing for them.

Dr. Wysham: Yes, I agree. That's important.

Dr. Shubrook Do you want to add anything more there, Carol, to that?

Dr. Wysham: No. I think the point of variability, there's so much variability that happens in our day-to-day lives. Let's take the variability of the insulin out of the picture so that patients can have the best experience.

Dr. Shubrook When you're looking with your patients and you're initially going to dose insulin, I think you just have to start with a plan. There are multiple different choices you have. The ADA has come up with a generalized plan for starting insulin for those patients with type 2 diabetes, especially if you're newer to insulin or you feel less comfortable, this is a very safe way to go. The initial starting dose for an adult with type 2 diabetes would either be 10 units per day or, and, maybe, this is my preference, a weight-based dose, somewhere between 0.1 and 0.2 units per kilogram per day, daily dose of basal insulin. That gives you a big enough dose to start that your patient's going to see a difference right away, and that's so important. Then you could do titration one or two times a week, and you can determine what those days are.

Dr. Wysham: What is going to be in the label, at least for efsitora, we don't know yet. There were different strategies that were done with the different QWINT programs. I could say a 300 unit, which is what we did in QWINT-2, it was 2 times the starting dose. The QWINT-5, their loading dose was really highly variable in terms of the patients' A1C when they came into the study. I don't think that we can say for efsitora, what it's going to do.

Dr. Shubrook You're going to ask the patient to measure their fasting plasma glucose, and you can make a determination of the dose based upon where the glucose is at. Highlighted here, if there's been two or more hypoglycemic episodes, of course, we're going to need to subtract four units off of that dose. If they're meeting what we would think is a common target glucose in the morning, somewhere between 71 and 130, you can maintain the dose. If they're having no lows, but they're

having three or more high glucose readings in the morning, you might add two units. If they're having no lows and they're having even higher morning readings, you might need to add four units. You could use this decision tool each time you do titration, and you can even give it to the patient and the patient could do that self-titration with your assistance if needed.

Dr. Wysham: I like the idea of picking two days a week, maybe Wednesdays and Sundays, so that they know that those are the days they need to sit down and review their records and decide how to do it. I also want to point out, imagine if you just had your CGM in there instead of fasting plasma glucose, how much more information that a patient would have and more confidence you would have at adjusting their insulin?

Dr. Shubrook Absolutely, and work with your patients. How much technology do they want? How much regimen do they want in their schedule? I think those things all make it easier for the patient to be successful. We talked about some of the challenges, and we talked earlier on about not starting an effective dose, not necessarily doing titrations. To see information on patient preference for daily dose titration, click "Next." The other issue is to make sure that we are titrating insulin and we're not over-basalizing our patients. I think this is really important, particularly because if we don't pay attention to the trends, we might end up giving them too much insulin. Certainly, there's a few clues that you could use when you're looking to look with your patients, whether they are over basalized.

One of them I use is the weight-based dosing. For me personally, I like that 0.5 units per kilogram as a ceiling dose, at least to stop and look up and assess the glucose trends across the day. I also think it's very important to look at the variability from glucose at bedtime to the morning. We call that the BeAM. If that glucose level is too high in terms of the difference, and we'll say maybe 50 milligrams per deciliter, that means you're probably over basalized, and if the person has a change in their schedule, they'll likely drop low.

Then certainly anybody that is having frequent or severe hypoglycemia, nocturnal hypoglycemia, or high glucose variability in the morning, that might be an indicator that they are getting too much basal insulin. We know that not only is this a safety issue, but we know that when you're using more insulin than you really need, you increase the risk of weight gain and hypoglycemia. Carol, I don't know, I'd love to hear your thoughts about what you do with your patients when you're trying to assess over basalization.

Dr. Wysham: All of the above. I use actually a titer over the night. I don't like to see it drop more than 30 or 40 points. I also tell patients and residents that if a patient has a hypoglycemic reaction when they're not eating, that it's likely over-basalization, and that, frequently, I see this every day, patients say, "Oh, yes, I got to go to bed high or I'll drop, or I have to eat a large snack at bedtime, or I'll have hypoglycemia at night." Those are all warning signs that you probably have too much basal insulin on board.

Dr. Shubrook Yes. Excellent points. Then, of course, patients don't always love doing finger stick blood glucose readings or maybe they are overwhelmed with the data, but this data is so important when you're starting insulin and titrating insulin. Let your patients know what the data elements are the most important to determine their dose. Let them know why they're checking. Quite honestly, it reinforces the value of their titration because they can see the results. Whether they're using self-monitor blood glucose readings and making a chart, whether they're just looking at an average in the morning or they're utilizing CGM, that is a critical and a necessary component of starting insulin and titrating.

Dr. Wysham: I agree. You can't do it without it.

Dr. Shubrook Not safely. Then this one comment about whether the patient can titrate, or you really need the clinician to titrate. Many of us feel like we're responsible, we want to make sure it's safe, and that we want to oversee titration. I think there's really good evidence that shows that if you map out for your patient, they can not only safely do the titration, but in fact, you can sometimes get better outcomes. Shown here is really an example of a self-titration program given to patients. Basically, they're on a dose of insulin. They look at their glucose over the previous three days in the morning, and based upon that fasting glucose, they're either going to reduce by three units, keep the dose the same, or increase by three units.

You can see when you're looking at the graph to the right that the baseline A1C was very similar, but those patients that did self-titration actually had a better outcome than those who'd had clinician-driven titrations. It doesn't mean that we weren't trying to get them down. I just think that there's imperfections in that communication from communicating regularly with the clinician, making sure those doses have changed in a timely manner. I think we want people to know that this is something patients can do, especially if we give them the tools.

Dr. Wysham: Yes. I think that's really important in the real world. These are clinical trials, and they were talking to the patients weekly to make the adjustments, but in the real world, we can't do that. If patients feel empowered, they're going to do much better than waiting every three months to have an insulin adjustment.

Dr. Shubrook Carol, I think we talked a little about some of the challenges of titration. We talked about starting dose titration. As we talk about this with our patients, what do you think are the important things we communicate with our patients about the value of getting control of fasting glucose in a timely way with basal insulin?

Dr. Wysham: Just having them understand hyperglycemia is associated with organ damage, that the longer a person's hyperglycemic, the less chance that we can avoid the damage. We know from the UKPDS study that tight control from the beginning, you can see the difference in outcomes out to 40 years. It is a matter of kind of a horse race. We've got to get them down as quickly as possible so they can have the best possible outcomes.

Dr. Shubrook Yes, I agree with you 100%. I do think letting the patients know that this is an important step and they're a big part of this, that can really help. If you see patients stalling, what are some of your tricks to help patients get to goal?

Dr. Wysham: That is something that I think we're going to cover a little bit in more detail, but I really start from the beginning and tell them insulin deficiency defines hyperglycemia and diabetes. They are not making enough insulin for their demands, and we can change their demands, but over time, they're not going to be able to make enough insulin, even with multiple medications, and that we're going to need to replace the insulin, just like we replace thyroid hormone in somebody who can't make enough thyroid.

I really try to have them understand the physiology from the beginning, address insulin as an option for every step so that they're used to hearing it. Then if I get a lot of pushback, sometimes I say, "Please, let's just try for a month. I'll see you in a month. If you don't like it, we can stop it. You won't have lost anything." Virtually, everybody who is willing to do that has stayed on it. I think it's really important that you really listen to the patients, address their concerns, and push forward as much as you can.

Dr. Shubrook If we had someone on a once daily and they were potentially going to go on a once weekly, again, we're hypothetical here, but how would we make that transition?

Dr. Wysham: If we just made the transition, they took one shot of their once daily, and the next day they took once weekly, their glucose levels likely are going to go pretty high. Both insulins have been studied with a loading dose to get the blood levels up to a physiologic level so that you can maintain and not lose control, especially with that transition. We don't know what those numbers are going to look like, but I expect that there's going to be a 100%, just give a double dose or even a triple dose the first time you give it, and then the next week start with the equivalent amount of insulin once weekly.

Dr. Shubrook In terms of risk of hypoglycemia, that's one of the biggest questions we get. So far, it seems like the data is reasonably similar between daily insulin and weekly insulin. Is that correct?

Dr. Wysham: Yes. I think that probably has to do with the fact that the potency of the insulin on the insulin receptor is less. Even though you might have a lot more circulating, it's not actually impacting on the receptor as aggressively so the blood sugars, even with a lot of insulin around, aren't likely going to because as much low blood sugar. Let's talk a little bit more about the data that we have about once weekly. We have potential advantages of once weekly, which we've talked about. We would like to see improved or similar glycemic control compared to the once daily and because of the long half-life, we can hopefully see an effective insulin that's going to last a full week, the reduced treatment burden we've talked about related to the stabilization of the action of the insulin in the body.

Then, hopefully, we can overcome the therapeutic inertia, at least as it relates to the patient's willingness to accept insulin therapy. We hope that this is going to result in better treatment acceptance and adherence over time. Now, there are two studies or two different compounds that are in late-stage development. The first is efsitora. It has been studied with four clinical trials so far reported, at least in high levels. Those are the QWINT trial programs. Again, we have data with two of the studies and then just top-line results of the others. Then the icodec, there's eight clinical trials, all of whom have had full reports being shown. The icodec is studied under the ONWARDS trial programs.

If we start with looking at the efsitora, I think it is important just as a background, to understand that when new insulin is being studied, their first goal is to prove that it is at least as effective as something that's already being used in the market. They want to prove non-inferiority to the current insulin products. If they meet the non-inferiority, then they will look and evaluate the data, see if they meet a superiority outcome. In the case of the QWINT programs, we have, on the reports of the five studies that have been done, non-inferiority was confirmed. Whether it was compared to insulin glargine or insulin degludec, the A1C reduction was similar. It was not inferior but was not superior to the comparator insulin.

If we focus on the two studies, we have the most data on presented so far, the QWINT-2 trial was done in type 2 patients who were insulin naive, started with a baseline A1C of 8.22, and you can see that the A1C reduction was 1.26 with the efsitora compared to 1.17 with the degludec. The instance of hypoglycemia was rare, and the difference between the two insulins was not significantly different. If we go all the way over to the right, the QWINT-5 study was done in type 1 patients compared again to degludec, similar A1C reduction, but they did see a slight increase in the rate of hypoglycemia with efsitora compared to degludec.

Personal interpretation of this data had to do with a very aggressive loading dose that they gave the patients in this study and likely is something that will be addressed with the FDA, and hopefully, with a lowering dose, we won't see this as much with type 1 diabetes. Now moving on to the ONWARDS trials. Again, we have six studies that are presented here ranging from insulin naive patients. We have three studies, one comparing to glargine in gray, degludec in blue, and then just whatever basal insulin the patient came into the study in was continued in the beige color. What you can see is not

only did they meet the non-inferiority margin, but they also actually confirmed superiority of the insulin icodec compared to the other basal insulins.

We also have studies in patients who are already treated with type 2 diabetes. They did show non-inferiority in both studies, superiority in the ONWARDS 2, and the rate of hypoglycemia with the basal switch was again, very low with both groups. In the ONWARDS 4, whereas the basal-bolus treated patients with type 2 diabetes, you can see a similar reduction A1C, but a higher rate of hypoglycemia. Importantly, no difference between the insulin icodec as well as glargine. Then once again, in the ONWARDS 6, which is the type 1 basal bolus treated patients, A1C reductions were similar, but there was a significantly higher rate of hypoglycemia in the patients with the insulin icodec compared to degludec.

This is not completely understood but may have something to do with some minor differences in insulin activity from Days 1 to Days 7 in the week. Stay tuned. There's a lot of data that we need to understand in terms of why we saw this. Insulin efsitora as well as insulin icodec demonstrated non-inferior glycemic control compared to daily insulins, whereas insulin icodec had a superior glycemic control compared to daily insulins in four out of the six Phase 3 ONWARDS studies. They both had favorable safety profiles in type 2 diabetes with low rates of hypoglycemia that were no different between the once weekly compared to the once-daily basal insulin. They do appear to offer a safe and effective options with convenient dosing for patients with type 2 diabetes.

I think that issue with type 1 diabetes and hypoglycemia still needs to be teased out better. We know about the importance of adherence of medications in patients in type 2 diabetes so that they can attain good control. We discussed the fact that missing around four injections per month or having a missed time of injections of about five to six a month can significantly impact glycemic control so adherence and being able to get your medication on time and on a regular basis is, oh, so important.

We did talk about the fact that good control from the onset can help reduce risk of long-term complications. Just a reminder that people with type 2 diabetes are threefold more likely to develop cardiovascular disease, tenfold more likely to develop kidney disease. One out of three patients with diabetes will develop some form of vision loss during their lifetime and even today in the United States, more than 100,000 people with diabetes have limbs amputated each year. We have a long way to go to try to minimize the complications and the comorbidities associated with our patients with type 2 diabetes.

Dr. Shubrook As much improvement as we have, we still have more to do.

Dr. Wysham: We have a lot to do. Yes.

Dr. Shubrook I do think we need to bring the patient into this discussion. Again, we have another social media post.

Male Voice 2: Compliant? I don't really like that word. It's not like you're refusing the doctor's advice. You're just making the wrong decisions.

Dr. Shubrook What do you think?

Dr. Wysham: Well, we've all tried to get compliant out of our dictionary so that we don't act like we're punishing patients for not doing as well as we hope that they would do so I think it's important to realize how hard it is to have diabetes. I don't know about you, but I miss my thyroid medication from time to time, as hard as I try to make sure so I'm realistic. I understand and I like to just deal with their barriers and try to figure out how I can help them overcome their barriers to taking their medications.

Dr. Shubrook Yes. I think this is really important and this goes across all things in terms of managing chronic disease. We're meant to be resources for our patients. We might give information, we might give tools, we might give advice, but ultimately, they live with this condition the entire year and we might only see them one hour per year. I think often there may be reasons and sometimes it's maybe a lack of understanding or maybe it's a lack of appreciation, but maybe sometimes it's just a disagree or other plans.

I do think understanding where the patient is coming from, what are their priorities, and trying to make a plan that meets their priorities really can help. You're right. Even compliant and adherent, I've moved to the word engagement. I think, again, ultimately, we want to make sure the patient has the tools they need to be successful because we all win when the patient is healthier.

Dr. Wysham: Yes. I think that's a great word. I'll try to remember that. If you ask patients about their concerns about insulin and what they prefer, they're most concerned about weight gain and they would like to see their time and range be as good as possible when they're on CGM. Obviously, the timing of the insulin and the amount of insulin, and the issues related to weight gain, related to hypoglycemia, et cetera, all those are really important to patients. We need to be willing to address those concerns.

Dr. Shubrook Yes, I sometimes tell my patients it takes more insulin to catch up from a high blood glucose than to maintain a glucose. The sooner we use insulin to intervene, the less we'll have to use to maintain the glycemia.

Dr. Wysham: This is a study that basically asks, again, a survey of both patients and providers about what they would prefer in terms of once weekly versus once daily. What you can see from the top one, 91% of the patients and almost 90% of the providers would choose a once-weekly basal over any other type of basal insulin if it were available. It didn't matter if it was a patient who was currently on insulin or not on insulin, they all had a very similar answer in terms of what percentage of patients would prefer to be on a once-weekly basal insulin.

Dr. Shubrook We have some more patient comments. This is certainly something we have all heard.

Male Voice 3: Yesterday, I screwed up my basal injection and lost some of it, probably about half of it. I did not try to take any more because I didn't know how much I got.

Dr. Shubrook Boy, what do we say to the patient who has a good reason to believe they've got a partial dose?

Dr. Wysham: You just have to do the best you can. You can't tell them because there's no way for them to estimate accurately how much they've lost.

Dr. Shubrook I do think it's really important for one, I would just tell this patient, "That's so great that you're paying attention to your shot, and then you actually realize you didn't get all that medicine." That, again, will reinforce the fact that it is an imperfect system and sometimes you will not receive everything you think. Then we can't have a uniform set of advice, but more often than not, we're probably going to have that patient wait that out, rather than take more insulin, because we really don't know how much they got even if they could estimate it's imperfect at best.

Dr. Wysham: The impact of missing a little bit of insulin when you're on a once weekly is likely going to be less just because your blood levels aren't really going to change that much on that first day or two or three.

Dr. Shubrook Excellent point. Yes, I love that. This is another one we've heard before.

Female Voice 3: I've recently been put on insulin, and I put on 28 pounds. It's making me more miserable than diabetes does. Any advice on shifting insulin weight?

Dr. Shubrook You highlighted this, but I think this is a great way to say, how do we talk to our patients about the concern about weight gain?

Dr. Wysham: Obviously, again, just emphasizing, follow the guidelines, get them on the first injectable should be a GLP-1. Then when their A1C just goes above the target range, don't push back, don't let them push back. Just say, "Starting now is the safest thing to do. You won't gain weight; you won't have as much hypoglycemia. If we wait until your pancreas is completely burned out, you're going to have a lot more trouble with those complications."

Dr. Shubrook Yes. I want to really highlight some of the things you said that were so important. We now have the option of giving patients a multimodal pathway for treatment and so often, we're going to use non-insulin agents as well, and that allows us to use a lower dose of insulin and use it in a much more targeted way. If we're using those other agents that have extra glycemic benefits, including weight loss, the relative effect on weight will be quite a bit smaller, the amount of insulin we'll need to use will be quite a bit smaller and we still have to be very mindful to do that targeted intervention and not wait too long.

Dr. Wysham: We have to really communicate with them and collaborate with them. Really, whenever, as I said before, upon diagnosis or upon the first visit I have with the patient, I talk about progressive nature of diabetes and the need to review and adjust treatments, and that insulin eventually is going to be needed even if the patient has perfect diet and exercise. I really look at people's faces and try to understand if they are accepting what I'm saying or not. If I have any concerns that they have unanswered questions, I really address. "What are your concerns? Let's talk about them. Let's talk about the side effects." Injections, again, are less of an issue in my experience. Patients often find guilty. They don't feel like they're doing all they can to treat their diabetes.

One of the most important questions I ask patients is, "Tell me about your schedule. When's the first meal you have today? What time do you go to bed? What do you do in the evening?" I try to time the insulin dose to something that is already part of their daily schedule. Brushing their teeth, getting their first cup of coffee, dinner time, whatever they think would be the easiest to remember to take their insulin. I teach self-titration. I provide written instructions. I also have patients demonstrate back, if I write three blood sugars down now, if these are your next three blood sugars on this third day, what are you going to do with your insulin? Then I really make sure they understand that those glucose tests are really their roadmap for how they're going to adjust their insulin and get the best outcome that they can from their insulin.

Other very important tips that I've found over the years is I really like to ride this, people want things that are natural, so I tell them that insulin is the most natural therapy. It's replacing what's missing. Again, I use that thyroid hormone analogy. It has no drug interactions. It prevents complications. Again, if we use early, it can be used in most people with minimal weight gain and minimal hypoglycemia. Once again, just trying it for a month and saying they can stop if they don't want to continue it has really helped.

Then we have diabetes education staff in our office. When they teach them, when they go through their diabetes education, I have them actually demonstrate a dry shot at the same time they've learned glucose monitoring because the shot hurts less than pricking your finger, and that oftentimes takes care of one of the barriers to injectable therapies. How about you, Jay? Do you have any other points that you think would be helpful?

Dr. Shubrook I love all the points you've shared. I think you have hit really best practices in initiating injection therapy. I am a 100% dry injection in the office person because if someone has a concern, I want to know, is this a problem with injections, is this a problem with insulin, or both? Every treatment we do, let's try it. Let's see how you feel, let's see if you get a good effect, and if you're unhappy with it, we'll find another option. I think patients need to know that they have an out and they have a choice. When they do that, they're much more willing to try new things. I'm sure you've seen this too. Most patients feel quite a bit better once they start insulin because you've replaced and helped them with a problem that's been much harder for them, particularly basal insulin, to address by themselves.

Dr. Wysham: Oh, yes. There are patients who put themselves into a small little box to try to avoid insulin. They're not eating any carbs; they can't do their exercise or they're exercising all the time. They just really are in such a little tiny box that just the idea that they can relax, and they can enjoy their food better, that they can have more or less activity and still keep their glucose under control. I've seen that time and time again. People come back and they're just so relieved that their quality of life has improved since starting insulin.

Dr. Shubrook Yes, and why didn't they do this sooner?

Dr. Wysham: "Why didn't you make me do this sooner? [chuckles] Why didn't you force me to do this sooner?" I've had people say that.

Dr. Shubrook To see additional resources for communication and collaboration, click "Next."

Dr. Wysham: Hopefully, based upon what we've already talked about, Jay, you can agree that once-weekly basal insulin is an opportunity for our patients, and getting started on insulin and appropriately dosing it can help their glucose control their complications and the once weekly hopefully, can improve their adherence.

Dr. Shubrook This has been a really exciting program. Dr. Wysham, I really appreciate all the wisdom you shared, both in terms of the clinical data, the implication. One of the things is we look at all insulins. We talked about titration. We talked about initial dosing. What follow-up do you do with your patients once you start them on any insulin?

Dr. Wysham: That is a very important issue. We have a system because we have an RN who's a diabetes educator, but she's not scheduled to see patients. She works more as a coordinator for the office. I sent her a message through Epic and say, "I just started this patient on insulin. Could you give them a call in a couple of days just to see how they're doing," and so she does that, or I will reach out to the patient if they're on CGM and say, "I'm going to flag myself for a week and I'm going to look at your CGM and see how you're doing. If you have any have any questions, let me know." I just think they need some follow-up.

Some of the providers in our office see the patients within a couple of weeks or have the educators see the patient within a week or two. Just so that you can address any barriers to titration or the patient's forgetting to take their insulin, how can you help them anchor it again? I just think making sure that they have some frequent touchpoints that don't have to be the provider to make them ease their concerns related to insulin.

Dr. Shubrook Yes. Those are all really important points, and our team is a pharmacy team that will support once we start a treatment. I always tell my patients, "If you're having any trouble initiating this treatment, including maybe you don't have needles or whatever, call us immediately. We don't want you to have that delay." We always have that first injection be supervised and then we do plan a two-week follow-up, usually with our pharmacy team, and then I make sure they have an appointment

with the prescriber when they get to that 0.5 units per kilogram, or they have any problems if they have hypoglycemia, or they achieved their goal before so that we can optimize their treatment.

Patients actually, I think, like knowing that "Oh, in four weeks, we're going to have a follow-up, and I bet your glucose will be a lot better in the morning." I think that gives them hope and something to look forward to, and it also gives them the ceiling dose, knowing that we're not going to titrate this forever. I think those things help patients.

Dr. Wysham: I also think it really helps to give patients a target for what you might think would be too much, and you pointed out the 0.5 units per kilogram. I tell patients their weight divided by four since you're usually working on pounds because I want them also, from the other perspective, not to think that 20 units is too much. I've seen people stop at 20 because, oh my God, it was such a high dose. I like to say, "Well, you weigh 240 pounds. If you get up to 60 units, that's the point where I think we might need to talk about whether you need something else."

Dr. Shubrook Yes, very important. We've talked about this. I know that patients often are going to be concerned about hypoglycemia as we start looking at longer insulins. It really showed very good data, particularly, in type 2 diabetes, that the rates of hypoglycemia are not higher. What might be some talking points you might recommend to other clinicians as they talk to their patients?

Dr. Wysham: I just think understanding the data, that because of the way that these insulins work, that even if you have much higher blood levels of insulin, that their interaction with the insulin receptor is such that hypoglycemia does not occur more severely nor last any longer. For the patients, you just have to reassure them that the way that these insulins work is that it's hard to overdose yourself on insulin. We don't advise it, but the studies show it's very safe.

Dr. Shubrook Yes. I think also it's important to let our patients know that as we're starting new treatments, we're probably going to want to do this in a scenario where we feel like this introduction, that we have some idea of what's going on as well as the patient. Maybe when you're trying a new therapy, have a patient who's eager to try the new therapy, stack the cards in your favor. Make sure that they're checking their glucose regularly or they have a CGM so that you both can feel very comfortable about this experience and quite honestly, see improved control with really more steady insulin. I do think this is going to be an opportunity for us to have a win, not only for better control but also, more stability in patients control, which I think is so important.

Dr. Wysham: It's only taken me 40 years to figure out how to talk to patients about insulin in an optimal way. I'm sure we're going to need a little experience with once-weeklies.

Dr. Shubrook Imagine what they'll be saying in 40 more years.

Dr. Wysham: Oh, I can't even imagine.

Dr. Shubrook This brings us to the end of the activity, Less is More, The Promise of Weekly Insulin in Type 2 Diabetes. We've taken a look today at barriers and opportunities for once-weekly insulin, best practices for initiating dosing of insulin, and key clinical data, and the role of patient education in navigating advantages and hurdles as it relates to insulin. Dr. Wysham, what are some key take-homes you want to make sure patients have today?

Dr. Wysham: I just want to let you know I'm very excited about the availability of once-weekly insulin. Like we talked about, the patients are already on GLP-1, adding the basal insulin once a week is going to be really helpful to help improve their experiences at going on insulin. I'm excited. I'd like to see more data, obviously. I want to see what the recommendations are going to be in terms of starting the

dosing. There's a lot for us to learn, but I am very excited about this as one of our new opportunities for our patients with diabetes. What about you?

Dr. Shubrook I feel it's important for us to do better with our current insulin choices. We could certainly optimize both dosing and titration, and you already heard very clearly that most patients are looking forward to a once-weekly option as well as most clinicians. This is not something you need to be nervous about. I think the popularity vote is in, and this is something that would be welcomed as an additional option for our treatment algorithm. We will see you again soon. Thank you, again, for joining.