[MUSIC PLAYING]

JASON NG, MD: So the title of my talk is Managing Challenging Diabetes Patients. And I want to start off by saying that I've had the benefit of working with our UPMC clinical analytics people recently in the Department of Medicine. So I know all the hard work that the internists do in treating diabetes.

It's such a chronic disease, especially in Western Pennsylvania. And you guys really do an amazing job. So I think, you know, patting yourself on the back for sure today.

And since diabetes is such a chronic disease that has a lot of self-management principles, there's always this subset that we all see in our clinics and these patients that we just can't seem to help for whatever reason. Because a lot of the chronic nature of diabetes is based on decisions that they make every day, including diet, physical activity, stress, things that we always talk to them about. But it seems like in this subset of patients, they never seem to really be able to kind of get over the hump.

So today, I'd just like present for the next half an hour some recent studies, some evidence-based medicine, that kind of allows us to maybe help these patients in ways that we may have not been able to before. OK. So no conflicts of interest for me. I don't have any industry ties. And the goals of this talk are simply to talk about three main things.

So it's number one, to assess improvements in the way we can help patients monitor their sugars, especially as the disease gets advanced. It becomes more and more important that they know what their sugars are and in what context their sugars are trending in order to make good decisions in terms to avoid hypoglycemia, to treat hyperglycemia, and such.

Goal number two is to understand new insulin preparations that may make it easier for patients to be adherent to their treatment plan. And number three is to understand aspects of diabetes and psychosocial support that allow them to make better decisions. So a big part of this is-- you know, I talk about the two S's all the time to my Fellows. It's about when you see a challenging diabetes patient, it really is just simplifying things for them and supporting them. And hopefully, they learn the skills they need to make better decisions on a daily basis, and then their long term outcomes rapidly improve.

And to give you an example of this. In our own clinic, we see these patients all the time. I recently saw a 55-year-old man. He was diagnosed with type 2 diabetes back in 2002. And he has historically been depressed. So he's always had high blood sugars.

But he always mixes it, when he comes to the clinic complaining that if he's taking his insulin, he's always getting low blood sugars. And he eventually was put on U500 insulin, which is really powerful concentrated insulin, and ended up requiring almost 300 units, I think, a day.

So he couldn't regulate his meals. He kind of was a patient who would wake up at noon one day and then wake up at 9:00 the next day, go to bed at 1:00, go to bed at 3:00, eat when he was hungry. And so he never got an A1C below 13. The one that we checked when he first came to our clinic was 13.6.

So this is kind of like the typical challenging patient that you can meet sometimes in the clinic. And he's had everything done-- blood sugars, like three different types of insulin, and nothing's worked so far. So how can we help this guy?

And this is what you get commonly in the clinic. So you ask him to check his sugar four times a day, and you get maybe one, maybe two, if you're lucky. And you'll notice in the evening, they're always better, because he checks them when he's not feeling well. So this is the kind of challenge that it faces.

Because how do we even begin in the clinic setting? You have like a 20 minute visit, 30 minute visit. You have to talk about statins, you have to talk about blood pressure, you have to talk about foot exams, eye exams. And then in two minutes, you have to interpret this and say, OK, we're going to change your insulin. So that's a real challenge for everybody.

And so goal number one, so how do we get patients, especially patient's who are having challenging diabetes, how do we get them to recognize, and how do we get to simplify things for them so that they can improve their sugar monitoring? Now the importance of skeletal muscle blood glucose monitoring is depicted in this graph.

And basically what you see here, on the top part there, is that in patients who are on a basal-bolus insulin regimen. There are fixed times when they take their insulin-- with meals and their basal insulin once or twice a day. But you can see on the bottom graph that their sugars can fluctuate wildly. So depending on what they do, depending upon what they eat, they can have these wide variations in their sugars.

And so we tell them to test four times a day, and they do. A lot of patients do. And they do it well. But a lot of patients don't. And when they don't, they miss all these wide fluctuations, and this can give them a lot of unpredictability.

So we asked ourselves the question, how often are actually patients doing this? So this was a study done in the University of Texas back in the late 1990s, early 2000s. And so what they did, basically, is they invited 933 patients in their clinic, either with type 1 or type 2 diabetes. And they just simply asked the question of how often do you check your sugars, based on what the physicians telling you, the internist? Or the endocrinologist, or whoever.

And they made a cutoff point of 80% as adherent. So as you can see in the graph, there was about a third of patients that had 100% adherence, and then everybody else in declining fashion adhered to various percentages. So basically, a third of your patients are going to comply and are going to adhere to what you ask. And 2/3 are going to give you less information than what you request to make treatment decisions.

That's actually a pretty big-- it's a pretty big gulf there. So question is asked, why do these patients have trouble? And so they identify numerous things. So inconvenient. So when the environmental barriers is inconvenient, cost, doesn't fit with my lifestyle.

I go to work. I don't want to carry my glucometer. I go out to a restaurant, I forgot it at home. Things like that. So these are just very practical matters, but in challenging patients often are present.

So one way that at least endocrinology, we've tried to get around this is through the use of this new technology of continuous glucose monitors. I'm sure everyone's heard of this. It's a rapid technology that's been in the past few years rapidly coming to fore.

And so CGM is there's three main companies out now, the Dexcom, the Libre, and the guardian from Metronic. They're not as accurate as skeletal muscle blood glucose monitoring. But what they do is they give you a fairly easy way of measuring a patient's blood sugars, especially in the setting when they can't or won't do the necessary finger sticks on their own.

And so how does it work? So what the monitor is, basically, is it attaches to your skin, either in your abdomen or behind your arm. And there's a little sensor on the end. And the sensor measures the interstitial fluid. And within the interstitial fluid, there's sugar, which diffuses from the blood cell.

Then that glucose in the interstitial fluid gets measured by the sensor and then gets transmitted to the transmitter, which is sitting on top of the skin. And then that data gets wirelessly sent to some sort of receiver. And so the receiver is something that you can carry or is something that you can wear on your belt or in a pocket.

And this happens every couple minutes, every two to five minutes. Usually, it's like five minutes. And so what happens is that every five minutes, there's feedback in terms of where your sugar is, and is it going up or is it going down. And it allows patients who for whatever reason can't or won't check their sugars routinely. It gives them an avenue where they can easily access their sugars, so try to simplify things for them.

And there's data on how this works. So in Sweden, in 2017, there was the Gold Trial, published by the Lin Group, in which they looked at type 1 diabetics across 15 clinics, so a total of 161. And what they did was they randomized the groups into two, two separate groups, one that was continuing on skeletal muscle blood glucose monitoring and one that was given a CGM to complement their Accu-Cheks.

And so what you see in the black dots is that the group that had the continuous glucose monitor fared better than the group that was doing conventional therapy. And it was about a A1C of about a half a point. So what that told us is that if you had access to this CGM and you wore it continuously, you knew your sugar is better. And you knew your sugar is better because you were getting feedback all the time, instantaneously. And you could make decisions based on that.

So if you were going low, you would be able to intervene earlier before it became significant. If you were going high, you would be able to maybe give yourself a correctional insulin or something like that. If you were physically active, you could track your sugars to know when you could really be physically active and when you needed to take a break to get something to eat so that your sugar wouldn't drop.

And then to show that this was a function of the CGM, then they switched the groups. So right in the middle, they had a washout period, and then the two groups switched. And then you can see, the ones that had the conventional therapy first but then received a CGM second, in the white dots, then they got better. And then the group that had the CGM first and then went back to conventional therapy, they reverted back to where they used to be.

So it kind of gave us a little insight in that perhaps this is a way in the future that patients who could improve their sugars and improve their monitoring to have more knowledge of what to do. So it kind of amplifies that self-management. So if you know what your sugars are, then you can make better decisions. So in terms of monitoring, we now have ways to be able to help patients who for whatever reason, may not be able to follow skeletal muscle glucose monitoring as much as we would like.

So the next question is-- OK, getting back to our graph-- next question is, if we can get them to help improve their monitoring, how do we get them to also improve their compliance with the treatment? So on insulin, especially basal insulin, has had new formulations in the past recent years that have allowed us to kind of try and help our patients to improve when they inject and how often they inject so that they're more compliant with their insulin.

There really hasn't been any change in the literature lately about prandial insulin. So if you're on a basal bolus regimen and you need to take mealtime insulin, you just have to do it. But in the basal insulin realm, which is typically the first insulin that patients use especially if they're type 2 diabetics who are just having hyperglycemia continuously, the guidelines suggest that you do basal insulin before prandial, of course.

So there are some new therapies that allow us to better work around the lifestyle of our challenging patients to see if they'll be more compliant. So the two that I talk about today are degludec, the trade name's Tresiba U-200, and the Toujeo and Toujeo Max, which is U-300, the next generation of Lantus.

So the first question is, if they only had to take one insulin injection a day, why would they not do it? So there were surveys handed out. This group, Farsaei, in 2014 published some data in which they included a cross-sectional study of 507 patients with diabetes. And they listed all kinds of reasons why they would not be compliant with one shot a day. It could be anything from it takes too long or it hurts or I'm embarrassed. I don't want to do it out in public. I just forget. I can't afford it. And so on and so forth.

So the question becomes, how do we work around these barriers? And I'm going to start off with U-200 degludec. Because the first thing we needed to establish, if we were to use these new insulins, is are they as effective as our old ones?

So this is an efficacy study done by Gao back in 2013 in which she compared U-100 insulin Lantus, which we all know has been on the market for years, and the newer degludec U-200 in patients who have never been exposed to insulin before and who was previously being treated on just metformin and maybe a DPP-4 inhibitor.

So on the top in panel A over the course of 26 weeks the two groups-- one with U-200 degludec and one with U-100 glargine-- were shown to have no difference in their A1C levels. In panel B, in the middle, their fasting plasma glucose level, the bottom line is actually the degludec line, which showed mild improvement in their fasting plasma glucose.

And then the third panel, panel C, showed a nine point skeletal muscle blood glucose trend in which they had their patients in the trial check their sugars multiple times a day. And what they saw from week zero-- which is the beginning a trial on the top line-- and week 26-- which is the conclusion of the trial-- there was practically a lowering of the blood sugars with each insulin. So they were comparable.

And if you look at hypoglycemia, which we're always worried about when giving insulin, even though there was no significance, you could see in the degludec U-200, there was a trend towards less rates of both nocturnal hypoglycemia and overall hypoglycemia. So the rates were 1.22 overall and 0.18 a nocturnal. Versus in Lantus it was 1.42 overall and 0.28 nocturnal.

So there is evidence that suggests that degludec actually at least is not inferior to Lantus. And then a little bit later on we'll talk about advantages.

So the other insulin that's now available to us on the market is the next generation of Lantus, which they call now Toujeo or Toujeo Max. But it's basically just a more concentrated formulation of Lantus.

They too have run trials which have shown the efficacy of that compared to U-100 Lantus, or U-100 glargine. This was a six month, open label, multinational study done by Riddle, also published in *Diabetes Care* around 2013-2014. And in panel A you see they also show between the two groups that there was no significant change in the A1C. In panel B, you also see the fasting plasma glucose didn't materially change over the course of the six month trial.

And the insulin dose showed that the U-300 glargine may need a little higher dose to achieve equivalent fasting plasma glucose and A1C levels. But overall, again, in this efficacy study it showed that it was non-inferior, and it was just as efficacious.

And, again, these longer-acting insulins, in this case U-300 glargine, showed a trend towards less hypoglycemia. Both in terms of the cumulative number of events-- both nocturnally and at any time of the day. You can see the dashed lines are Lantus and the solid line there is U-300 glargine. And you can see a shift or a spread in which the U-300 seemed to trend towards having less nocturnal hypoglycemic events and less overall hypoglycemic events.

And so this suggested to us that actually this insulin may actually be better for patients because you could give them the insulin and worry less that it would cause hypoglycemia, both at night and overall, and it was non-inferior. And the less hypoglycemic events would then allow them to be more comfortable taking the insulin at the doses prescribed without worry that they're going to have an adverse event.

So that would make it easier for them, especially in the challenging populations, to trust the treatment plan without having any, or at least decreasing, the risk of that particular side effect, which people really don't like. Because when you get hypoglycemia, they feel it. So that's one of the main complaints.

And the challenging diabetic population is, well, I took the insulin and then I felt really bad. So I just cut it back on my own. So this actually is a way of allowing us to cut that off at the pass a little bit.

And the reason why hypoglycemia is less likely in these longer-acting insulins is because of their profile. So what I'm showing you here is a paper by Pettis, which compared what we used to have and what we have now.

So in panel A we used to only have NPH. A long time ago NPH was the go-to insulin for basal coverage. And you can see that insulin effect over time was much more erratic. So the NPH tended to peak and then drop over a 12 hour period. And so the risk of variable sugars with that basal insulin is much higher. But then you had to tell patients to take it at certain times of the day, the same time of the day, eating at certain times of the day, and compliance is just all over the place.

And then along came Lantus, or U-100 glargine, and that's depicted in the red in panel A. And you can see that it was much smoother, but still there are little peaks and valleys in that insulin. So although superior to NPH, there was still some variability in the delivery. So we could get by with one shot a day of Lantus, for the most part, unless the doses were very high. And it still wasn't perfect, though.

So if you look at panel B, which is detemir-- the trade name is Levemir-- versus glargine, you can also see that for a long time our two basal insulins were still not as flat as we would like the insulin to be. So you could still have some variability in their blood sugars.

And then recently, within the past few years, along came what we just talked about-- the glargine U-300 and the degludec. So in panel C you see glargine U-300 versus glargine U-100. And what you see is that the more concentrated Lantus is much more stable. So it is relatively flat. From the time the injection to the next 24 hours, there really is not a lot of change.

And the same can be said for degludec in panel D. Compared to U-100 glargine, it's flat. And that duration of action and that flat profile really allows us to be more confident that our patients, especially in the challenging population, will not get hypoglycemia.

And then the other thing that it does is that it allows us to counsel them that they don't have to actually take it at the same time of day. What this allows us is three things that would make it easier for the patients in part of our simplification and support that we are always trying to get our challenging patients to rely on.

So the first thing that the new basal insulins allow is that less hypoglycemia and less overall hypoglycemia because of longer duration of action. The second thing that the newer insulins allow is that you can dose the injections to higher doses-- about 80 units per injection-- and so in the majority of patients you can do it once per day. So once per day versus twice per day.

With Levemir you probably had to do it twice per day because of the duration of action if you go back and look at the profile. So if they're peaking and then they're trending down over the course of the 24 hours, they're not really lasting the whole time. So you would normally have to do it to at twice a day for detemir. And for some patients on glargine you would have to do it twice a day. Because again, it's not completely flat.

So the second benefit is that you can allow them to do one shot per day. Most patients will say one shot's easier than two shots. So they're more apt to do. They're more apt to remember.

And then the third thing is that you don't necessarily have to do it at the same time. So this study was done by Nishimura back in 2017 last year. And what they showed is that compared to U-100 glargine to U-200 degludec, panel B is just showing the insulin doses. But what's really interesting in the middle, in panel D, they showed that after 12 weeks switching from U-100 to U-200 they showed a reduction in the A1C even though the patient injected the degludec up to two hours after they were supposed to.

So what we tell patients in the clinic when they're on basal insulin is, if you decide you want to inject it like, let's say, 9:00 at night, for example, it has to be around 9:00 at night every single night. Because that is the profile of Lantus. We showed that the curve goes up and down a little bit. So if you don't inject around the same time of day, then it's not going to be as effective or you're going to run into issues.

And so this gets into this whole compliance. Because you know patients will say, I can't. I just couldn't do it today. I was out, and I forgot. So I came home, and it's was an hour and half later, so I just decided not to do anything. Or they'll say I was eating dinner, and then I was watching TV. If the Steelers are on, everyone forgets in the prime time. And then they say, I just forgot. It's like three hours later, and you told me I had to do it same time each day. So I just decided not to. I'll just wait for the next day.

So missing these doses then, of course, is going to throw their sugars off that night, the next day, and it actually take a couple of days to get back on track. Well, what this study showed is that even if they wait up to four hours-- So in the study they had about, I think was like a third to half, 40% of patients actually waited two hours after their initial injection the previous night or the previous day, and they didn't have any adverse events.

They had 10% in the study actually waited four hours. So 240 minutes. So they injected at 6:00 one day, and the next day they injected at 10:00 at night. There was no change. And if you look at panel F on the far right there, what they showed is that the frequency of hypoglycemia also decreased significantly, even though they injected up to four hours later.

So what that showed us is that there's less reason now for patients to say they can't inject. So they don't necessarily have to do it at the same time each day. Couple hours here and there-- up to four hours according to the Nishimura study-- the outcomes will still be better, the A1C will still be lower, and the rate of hypoglycemia will still be less.

So that was a big thing for us, because now that takes away another barrier when we counsel patients, especially the challenging patients, and they say, well, we can't do it because we can't remember or it doesn't work for our lifestyle. Well, we can say, well you don't have to do it immediately. You can do it up to two, three hours later, and it's not a big deal. The medicine's still going to work. So it takes away one of those barriers that patients are always talking about saying, I just can't do that. I just can't do it every day the same time of day. All right, now you don't have to necessarily.

So that was a big thing. So that also allows us to simplify their treatment regimen and say, OK. Within the construct of the time of day and what you're doing, you can actually do it around your lifestyle. So if you forget and it's a couple hours later, don't worry about it. Just go ahead and take it. And for the most part, things are going to be good.

And then finally, the third thing that we wanted to talk about. So in simplifying things so we can get patients-- the challenging diabetic population-- to monitor their sugars more, which you can do with their CGM and take their insulin more, especially their basal insulin. Because now we've provided them the means to do it at their own schedule and the medicine that we're giving them decreases their risk of low blood sugars and brings down their A1C, improves their sugars.

The third thing is support. So the other thing we can do in the office is we can actually engage their spouses and their family members and whatever support system they have. Because studies have shown that actually that has improved their overall diabetes glycemic management.

The study I'm showing you now was done by Zajdel, actually. And this group is actually here in Pittsburgh. So it's Vicki Helgeson at Carnegie Mellon and Leslie Hausmann and Mary Korytkowski at Pitt. And what they really are interested in is figuring out psychosocially how can we improve diabetes care?

And so what I'm showing you are beta coefficients. So the beta coefficients basically say that if the number is negative, that means that they're less likely to have something. If the number is positive, it means they're more likely to do something.

So there's this whole concept that Dr. Korytkowski, Hausmann, and Helgeson are working on called this "communal coping." So communal coping basically means that as a family if a patient has diabetes, they and their spouse tackle that as a joint problem, not an individual problem. So the solutions are joint. So basically spouses are there to-- or it could be any family member I guess or any friend or anything like that. Whatever the support system is.

But basically, when someone is treating their diabetes, the family is making decisions with that family member in order to encourage them and support them in making good decisions with their diet and their physical activity, taking their medications, et cetera, et cetera.

So what Leslie and Mary showed is that if you do have a supportive family structure, you are more likely to be happy, which makes sense, and less likely to be depressed and angry. But if that support structure is there, you are more than likely to also follow a good diet, and you are more likely to adhere to your medications.

So we saw the self-management behaviors improve in this challenging diabetes population if they had a good support system. And they did this just by taking diabetics who were recently diagnosed within five years, and they gave them like daily questionnaires for two weeks. They and their spouses. And so they reported on their mood, how they felt, and then what they did. And so it was interesting that for those two weeks their diet rapidly improved, and their ability to adhere to their medications rapidly improved.

And so what it told us is that if you engage the spouse-- and you can do that in the clinic setting in a simple 30 minute visit. You just encourage them to bring their family member. It's tough, because people work and things like that. But if you can get them there and you can actually talk to them a little bit-- just a few minutes even-- there is a chance that they can actually influence the patient much more than we can. Because they're with them every day.

So it doesn't work the other way, though. So they also did a similar study of this where they say they took 70 couples diabetes in the past three years, and they did daily questionnaires for two weeks. And they report on their mood and support and things like that. And so if the partner was what they call controlling-- they are trying to browbeat them to take care of their diabetes-- and that wasn't going to work. So then everything flew of the handle and things actually got worse. So it has to be positive. That's the only take-home message for that.

But the reason why I stress this so much is because more than what we can do, if we can get these challenging patients-- or for any patient, for that matter-- to do good self-management behavior, they can extend and improve their quality of life and extend their lifespan a great deal.

And so the last study I'll present is this KORA study that was done in southern Germany, and Laxy published this in 2014 in *Diabetes Care.* It was a retrospective analysis. They took 340 patients in the KORA study, which looked at different things, and his group said, well, let's take a look and see of patients who did routine self-managed behavior on a daily basis who have type 2 diabetes.

Which included just exercise-- which is not that much exercise. Just one hour a week-- foot care, which is checking your feet once a week, checking your sugar once a day if you're on insulin, just once a day, and twice a week otherwise. You weigh yourself once a week. You keep a little diary about what you do, and you adhere to some diet plan that you come up with on your own.

And they defined two groups-- the high-level group of self-managed behavior doing four of the six, and the low-level group did anything less. So either three variables or less. And what they showed was that uniformly in years all patients in the high-level group had a greater survival probability than a low-level group. All patients with cardiovascular disease had a significantly higher survival probability than the low-level group. Any patient on insulin had a higher level of survival probability than anyone in a low-level group.

And they even looked at education levels. So anyone that they deemed to have a-- well, they say in the paper a low level education, which I think is just up the high school-- they still had a better survival rate if they did four of the six variables over 12 years than the low-level group.

So it just clearly shows that self-management behavior is one of the most important things in diabetes. And anything more that we can do to promote that in a positive fashion will help patients.

All right. So how do we do that? So putting this to practice in our group. So again, the three things that I talked about today. Simplifying things for the patients and just supporting patients. So he wasn't checking a sugars as I showed you at the beginning. So we put him on a CGM. We put him on one of those Libre CGMs. And it showed fluctuations in his meals. And I'll show you that in a minute. And then we switched him to Tresiba from the U-500. And we just used his really concentrated insulin for when he ate.

So we said, just use your Tresiba once a day. You can take it up to four hours after you took the last dose. And then only when you eat, you can take your really concentrated insulin so you can control that.

And then we engaged his girlfriend. His girlfriend came to one of his visits, and we talked to her about the importance of self-managing behavior and just positive encouragement, things of that nature. So his A1C in three months went from 13.6 to 9.4. And we really didn't do all that much. Actually, his girlfriend did a lot more than we did. But those three easy things you can do in the clinic.

So what we actually found when he started wearing the CGM was that he was going low all the time. And he didn't check any of this. So you couldn't see it on the glucometer report. But he would eat, take his insulin, and sometimes it would go high. Sometimes it would go low. Then he'd take his insulin and not eat, because he just thought he had to take his insulin at the time. It was only U-500. So then he'd drop, and then he'd treat the low sugar with like whatever, candy bars. He told me a hoagie. All sorts of stuff. He was like, I had to get something in me. And then it would go way high. And then this pattern would just persist on and on and on.

And then he just got to the point where he was just eating, not checking, thinking he was quote unquote "going low" when his sugar was actually high. And then thinking he was high when he was low, and it was just all over the place. So with these three easy steps we were able to get him to a better place. And he was tough.

And so this is the daily presentation of the CGM recordings. And this is what I talked about. So he was going low and then he would get up and eat late. And then over time we were able to flatten that out a little bit with just that Tresiba and then the mild changes of his insulin regimen. And then having him have the CGM was big, too, because now he could see. He sees this every day now on his little machine. So he knows when he's going low, and he doesn't panic anymore. And so we're still working with him. 9.4 is still not quite a goal, but much better than 13.6.

So in summary, the challenging diabetes patient in any setting-- in the endocrinology setting, in the internist setting-- it can be really difficult. And it can be really frustrating because you don't have any of the data that you need to make good, sound treatment decisions. And really, when they leave the door, who knows what they're doing?

So the two S's I like to talk about with at least our trainees is about simplifying everything for this challenging population. If they can't or they won't monitor their sugars on their own with skeletal muscle blood glucose monitoring, you can do CGM. If they can't or won't take their basal insulin on time, the Basaglar or the Lantus or the Levemir, you can try one of the newer ones that allows you more flexibility and less hypoglycemia, both at night and overall.

And then engaging their family members. Psychosocial support goes a long way. It seems to really help these patients make good, sound decisions in terms of their diet, in terms of taking their medications every day. And then get them into this frame of mind where they feel confident about their self-management skills, and then the challenging diabetes patient actually becomes much, much easier overall. So that's it. Thank you very much. Thank you for your attention.

[APPLAUSE]

Thank you.

Thank you.