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Are You Seeing the Whole Picture? Test Your Skills for Intensifying Therapy in Patients with Type 2 Diabetes

Announcer:
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Dr. Green:
Hello, and welcome to this activity, Are You Seeing the Whole Picture: Test Your Skills for Intensifying Therapy in Patients with Type 2 Diabetes. I'm Jennifer Green, a Professor of Medicine in the Division of Endocrinology at the Duke University School of Medicine.

Dr. Thethi:
And I am Tina Thethi. I'm an Endocrinologist and an Associate Investigator at AdventHealth and Translational Research Institute and Diabetes Institute both in Orlando, Florida.

Dr. Green:
So Dr. Thethi and I will discuss three patient cases in this activity. This case is a 39-year-old man and his history with diabetes is in fact fairly typical. You can see that he was diagnosed with type 2 diabetes in late 2020, at which time his hemoglobin A1c was 7.9%. His BMI is 44. His family history is, though, remarkable for having had a myocardial infarction at 54 years of age. His blood pressure 136/80, LDL cholesterol 68 mg/dL at that time, and he was started on metformin, just 500 mg a day and was instructed to up-titrate. But he did require some coaching and counseling in order to manage the GI side effects associated with that medication. If we fast forward to early January of early 2021, you can see that he continued to experience some GI side effects and that they were troublesome enough that they interfered with work. And at that point, he was switched to an extended-release formulation of metformin and again encouraged to up-titrate the dose. At the end of that year, his hemoglobin A1c very slightly improved at 7.5%, and his BMI was a bit lower at 41. But as you can see at the bottom of the slide, he's still having GI side effects and it resulted in him periodically skipping doses of the medication due to those side effects. So at that time, he was switched to a sulfonylurea, to glipizide XL 10 mg a day. When he comes back about 6 months later, his hemoglobin A1c had in fact risen to 7.8. His BMI was stable. At that point, it appears that a change in regimen was discussed with him, but he wanted to continue using glipizide. He was referred to a dietitian and he had plans to increase his physical activity.

In the present day, however, his hemoglobin A1c is now higher at 8.3%. His BMI has risen to 43, blood pressure 128/78, and LDL cholesterol is 65. And this is all in his current medication regimen, which is glipizide monotherapy. At this point, he is frustrated with his lack of progress, and he is now interested in intensifying his therapy.

So at this point, it's reasonable for us to take some time to discuss therapeutic inertia, which is essentially a universal problem but a very significant problem in diabetes management. And Tina, we're to discuss whether or not we think this patient should have received therapy intensification sooner. And my guess is that both of us agree that this patient's therapy should have been intensified very shortly after his diagnosis or perhaps even at the time of diagnosis. He's now gone many years with the hemoglobin A1c that is really not at target for a young and otherwise healthy person.

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So, Tina, how often do you think a patient's diabetes regimen should be reevaluated and intensified if needed?

Dr. Thethi:
Oh, absolutely, Jennifer, I think you and I are on the same page. You know, ideally, you want patients' regimen to be evaluated and seeing if they need any further adjustment to the medications or whatever adjustments, be it even lifestyle changes that you need to talk to patients about at least every 3 to 6 months. And you know, I'll even say that also depends on the agent you put the patient on. It's really advisable to see them sooner if need be, as well.

So certainly, he's a young gentleman and you know, and I know you and I will discuss later as well, that when somebody first gets diagnosed with diabetes, it's really important to emphasize to them how important it is to really have good, adequate optimal control for that individual person right at the very beginning, rather than playing catch up, because once you do you have good optimal control at the very beginning, we know that there's a legacy effect that benefits them even later on. So you know, and that certainly brings up questions as to what we as clinicians can do, and what patient factors certainly influence therapeutic inertia.

What are some of your thoughts, Jennifer?

Dr. Green:
Oh, there are so many. I think that the top of the list always has to be the fact that it takes time on the part of clinician and the person with diabetes as well, to talk about changing the regimen and what the options are. So lack of time is tricky. Some practices have been very successful and engaging some other team members in those discussions such as their diabetes educators or clinical pharmacists, but this is something that we can't shortchange, and therapeutic inertia is such a problem, that what we're really seeing in many cases is that unfortunately, we're treating to failure. And as we saw with this particular young man, he's never had a hemoglobin A1c below 7%, despite having been diagnosed with the condition several years ago. So this is precisely what we want to avoid.

Clinical inertia is a shared problem, there is inertia on the part of the provider, that there is understandably resistance on the part of the individual with diabetes, that people are naturally reluctant to take more medications, they're concerned about the cost, they're concerned about potential side effects of these medications. And again, this is where a little bit of extra time and some counseling and reassurance, and also a review of the importance of good glycemic control and why we're doing this, why we're recommending good glycemic control, can really go a long way in helping that individual understand why these changes are important.

Dr. Thethi:
I absolutely agree. I think that investment in time and effort, as you mentioned, does go a long way in helping these patients. And you know, we use the term, it takes a village in so many concepts of our life, right? And I think the same concept applies here. It really truly is teamwork, taking many disciplines to focus on the patient. And I think also, when you talk to patients about this early on, they learn the importance of themselves taking responsibility for the health as well, which is important.

Dr. Green:
I agree. I agree. To a certain extent, individuals may fail to act because they're not aware of updated care guidelines. I think that's really less applicable to this particular patient, where it's very clear that he's not been treated adequately, consistently over several years. So I think that's less of an issue here. But certainly, in other circumstances, that may be possible.

Tina, you had already mentioned the legacy effect or benefits that we know are associated with early glucose control. And what that means is achieving better glucose control, essentially at the time that you're diagnosed with type 2 diabetes. And we know from the UKPDS trial, which was a large study conducted in the UK of people with newly or recently diagnosed type 2 diabetes, assigned to either more intensive or less intensive glycemic control, that the more intensive glycemic control strategy very clearly reduced the risk of microvascular complications during the actual study period. And when they followed those individuals after the active treatment period concluded, they found that after another 10 years, the individuals who had originally been treated more intensively, in fact, also had a reduced risk of myocardial infarction or death from any cause. So this is, I think, a very good justification for us to make investments in patients' futures. Even though these benefits may not be seen in the immediate future, over time, the benefits of good glycemic control from the outset of diabetes diagnosis are really quite clear.

Dr. Thethi:
Absolutely. And I think at our recent ADA meeting, the American Diabetes Association Scientific Session, the day data from 44 years of follow-up was presented that, you know, even 44 years later, intensive glycemic control early on showed a significant reduction in depth and fewer heart attacks as well. And, you know, this is a study that was done in a day and age when we did not have all the medications we have now. So we certainly have many more medications for use now to use for the benefits of preventing complications down the road.

Dr. Green:

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Yes, so a much broader array of options to choose from and help us to individualize that early care. You know, I'd also point out for those who weren't familiar with the UKPDS trial, that after that first 10-year interventional study period, people returned to their usual doctors. And in fact, the difference in glucose control between the two treatment groups really disappeared after that interventional study period. So what we're seeing over many years, really decades now, is that that early, better control continues to provide outcomes results and better health for people with type 2 diabetes.

Dr. Thethi:
Absolutely.

Dr. Green:
So, Tina, for this particular individual, 39-year-old man who has type 2 diabetes, who has a BMI that is clearly in the obesity range but may not have a lot of other comorbidities or other serious medical problems, what would you recommend, as his hemoglobin A1c goal?

Dr. Thethi:
You know, Jennifer, for this gentleman, as young as he is, and with the new onset, well, you know, relatively new, right, in the recent few years that he's had, I think we're certainly justified in saying we would like an A1c control less than 7%. But also, you know, if you can get his hemoglobin A1c down to 6.5% without any regular episodes of hypoglycemia, that would be ideal for him. And this is, I think, a point to be emphasized to all our colleagues, that whichever A1c that we aim for, to get there without necessarily incorporating hyperglycemia into your treatment. So I would definitely say he needs to be very well controlled. And if we can get him down to 6.5, I think that would be wonderful.

Dr. Green:
I agree. I agree. And that's where that broader array of medication options makes the job a little bit easier than it may have been in the past.

So of course, people with type 2 diabetes are at risk for a whole host of complications, including cardiovascular complications, so we need to think more broadly than glycemic targets. So, what should we think about with respect to management of his other cardiovascular risk factors like his lipids or blood pressure, weight or BMI?

I'll kick things off with the discussion about his LDL cholesterol. And he had an LDL cholesterol of, if I remember correctly, 68, not on a statin therapy that we know of. I would point out that he is 39 years old, so he's really right on the cusp of 40, at which point, the American Diabetes Association recommends that everyone with diabetes should start a statin because their risk of cardiovascular events is high enough that is warranted. His goal, according – his LDL cholesterol goal, according to current guidelines, would be less than 70. And he is in that range, so we don't need to dramatically reduce his LDL cholesterol from baseline. But he needs that statin on board to reduce his cardiovascular risk.

What do you think about blood pressure?

Dr. Thethi:
Well, first of all, very well said, Jennifer, about the LDL. And I will say what I've encountered is sometimes it's hard to explain to the patient that why they do need a medication for cholesterol when their blood pressure – cholesterol is not high. Now regarding his blood pressure, he definitely does need to be less than 130/80 for sure. And again, here too, he's right on the cusp. And you know, you can certainly have a discussion with them. And as he loses more weight, his blood pressure we expect, if it's a significant decline in weight, can also come down.

But the other information that I also want to look for is also if we know what his UACR is. Do we know his albuminuria? Then regardless of his blood pressure, if his UMACR is indeed greater than 30, we can certainly treat him with an ACE inhibitor or an ARB to keep – to treat the albuminuria as well and reduce further risk for this gentleman.

Dr. Green:
That's a great point. As far as his weight, I think it's important for us to understand that weight loss is considered a really a key strategy in the management of type 2 diabetes, and in reducing the risk of both diabetes-related complications and progression of diabetes itself, it's important to remember that a little bit can go a long way from a metabolic perspective. So if he were to lose 5% of his body weight, we would expect to see improvements in, for example, his glucose control, maybe some improvement in his lipids. However, we might want to consider a more substantial weight loss target for him, at least over time, in order to provide some additional outcomes benefits.

Okay, so what therapy would you select to optimize therapy for this gentleman at this point? So Tina, what treatment would you select for this man? Remember, he's on a bit of glipizide XL. How would you approach intensification of his therapy at this point?

Dr. Thethi:

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So you know, Jennifer, I was just looking at all the options he had up on the screen for him, and I think you and I would both agree it's between GLP-1 receptor agonist, and/or – or I should say, but GLP plus a GIP dual agonist. And the way I go about it is I look at what is the percentage of weight loss that a patient needs to get to his optimal weight, or you know, have at least a significant decline in weight. And I think we would agree that this gentleman with a BMI that he has, he certainly would benefit from GLP/GIP combination. As we've seen, the weight loss results from that, which is tirzepatide, certainly would benefit his BMI, getting to a much lower point.

And I do add that the caveat, though, that, as we'll probably discuss later on, but I think in any case, regardless of what we'd like to prescribe, at the end of the day, what does get – the patient does get depends on what the insurance covers, but my ideal choice would be a GIP/GLP agonist.

Dr. Green:
Right, right. And we need to think about whether or not if he were willing to use an injection or preferred oral medications, and the frequency with which he was able to take medication. So there are a number of choices that need to be made. Now, we've already brought up the concept of GLP-1 and GIP dual agonism. And we're very familiar, I think, for the most part with how the GLP-1 receptor agonists work. And GLP-1 in our bodies is released very soon from the small intestine after we start to eat, and this is a hormone that really helps to limit the rise in blood glucose after meals, both by increasing insulin secretion and decreasing glucagon secretion in response to food intake, by through central mechanisms, making us feel less hungry, by slowing stomach emptying, again, making us feel more satiated more full, so that we tend to eat less at meals. And some of these do provide some cardiovascular protection, which we'll discuss a bit later.

So why would we need to add GIP receptor agonism to all these good physiologic effects of a GLP-1 receptor agonist? Well, I will tell you that some of the effects of GIP might be a little - may seem a little bit counterproductive. So although GIP does increase the secretion of insulin when we start to eat, it actually increases levels of glucagon. But fortunately, when you give a GIP receptor agonist with the GLP-1 receptor agonist, that tendency for GIP receptor stimulation to cause hyperglycemia as a result, is really countered by what we know that GLP-1 receptor agonist can do.

There are also some other effects of GIP receptor agonism that are distinct from what GLP-1 can elicit, and this appears to also increase adipocyte metabolism, might increase energy expenditure a bit, but I will tell you the main rationale for agonizing both of these hormone receptors simultaneously is that the extra little kick from GIP appears to further suppress appetite and further promote weight loss beyond what we've been able to traditionally achieve with GLP-1 receptor agonism. So that's the physiologic rationale. And this has become increasingly important.

What you can see on the screen is part of a very comprehensive algorithm produced by the American Diabetes Association that guides the treatment of people with type 2 diabetes. And this is, if you're familiar with that algorithm, this is the right-hand side that applies to everybody with type 2 diabetes. And what's new about this algorithm is that now you can see that there are dual and equally important goals of both glucose management but also weight management and this is new this year. I think we always knew that weight management was fundamental to the management of type 2 diabetes, but this is really bringing it to the forefront because we know that excess weight is a driver in both the development of type 2 diabetes that and the progression of type 2 diabetes once it is in place.

So when you look at this guideline, what you can see is listed at the top as far as the agents that provide both potent glucose lowering and weight loss, you can see that the GLP-1 receptor agonists, a certain of them are highlighted here, as well as tirzepatide, which is a dual GLP-1 and GIP receptor agonists are really listed here as being most effective in achieving these dual goals.

This slide shows us a summary of some of the metabolic effects of treatment with the GLP-1 receptor agonists. You can see that their expected degree of hemoglobin A1c reduction shown on the left and weight reduction shown on the right appears to correspond with how long-acting the medications are, so you tend to see a bit more of an effect with the longer-acting medications. Of the groups shown on this slide, you can see that the most impressive reductions in glucose and weight are associated with use of the injected form of semaglutide. The currently available indicated doses for use of oral semaglutide appear to provide a bit more modest effects, but they're still quite effective compared to the effects of the other GLP-1 receptor agonist. So we have a wide array of medications that we can choose among. Obviously, we need to work with our patients to prescribe the one that they are able to access.

Some of these, not all of them, have shown that they reduce the risk of important cardiovascular outcomes. So for higher risk patients, we'll need to talk about use of certain of these agents with a demonstrated outcomes benefit, and we'll talk about that more, a bit later.

Well, what about the effects of the dual incretin agonist, tirzepatide? This slide shows us the demonstrated reductions in hemoglobin A1c and body weight, over 40 weeks of use of the medication, which was dose at either 5, 10, or 15 mg a week, compared to the effects of semaglutide 1 mg a week shown within the open circles. And what I'd like to draw your attention to here is, are the results achieved with the different doses of tirzepatide, where you can see at the end of 40 weeks, patients on average had a hemoglobin A1c ranging

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between 5.82 and 6.19%. And on the right-hand side, the changes in body weight out to 40 weeks being as impressive as 13.1% over time. And these effects did appear to be more dose-dependent than the effects on hemoglobin A1c.

Again, these are the available FDA approved, long-acting GLP-1 and dual receptor agonists. These are broken down into those that are administered once daily and those that are administered once weekly. On the right-hand side, we have injectable liraglutide and oral semaglutide as our daily options, the weekly options include exenatide once weekly, dulaglutide, semaglutide, and tirzepatide. And again, it's important to remember that only certain of these have a cardiovascular outcomes benefits, so we do need to choose carefully for our higher risk patients.

So for our patient, what percent of weight loss would we consider clinically significant given his BMI of 43? And to what extent do you factor weight loss potential into your therapy selection? So Tina, we've talked a lot about medications and the weight loss effect of newer medications, but what other interventions might you recommend to your patients to help with weight loss?

Dr. Thethi:
A very good question, Jennifer. I, you know, I know we, of course, use our medications as need be inappropriate cases for our sub – for our patients. But very important to keep in mind and really use these resources, and that is lifestyle changes. You know, we need to talk to our patients at the very beginning. But it's important for them to institute the needed lifestyle changes as well. And this is where not everyone does necessarily, as we know, know what changes to make. And this is where sending our patients with diabetes education in the very beginning could definitely be a very good option. And in fact, you know, it's a shame, but in spite of having these services, only about 5 to 7% of our patients who need them, actually have these resources available. And so definitely talking to patients about making lifestyle changes. And you know, these don't have to be right at the very beginning, big, huge steps; start with small changes that they can make, incorporate in their lifestyle, that's very important and refer them to diabetes education, or a dietitian to see even a small change will go in – go a long way in helping them. And so, what also happens is, it's very important to make this change where applicable as a family. So when you have seen one patient in your office, certainly ask them, you know, what their family unit and dynamic is like and see if the entire family does need to make a change and would benefit from that education.

Dr. Green:
That is a wonderful, wonderful idea, because often, that person can't do it alone. So that's a wonderful idea.

You know, I'd also like to make sure that even though we have medications available now that are really very potent at promoting weight loss, we still want our patients to eat a healthy diet. And often, they need a lot of coaching regarding optimal dietary or meal composition. And they still need to pay attention to things like simple sugars that might adversely affect their blood glucose. So we can't forget about what people are eating, even if they're eating less. It's really all important.

I have many patients who have successfully used other tools like wearables or apps, to help them achieve weight loss goals. So for select patients, that might be a really interesting and powerful, complementary approach.

But I think one of the most important things is, is though even our goal and target for that person's weight loss might be very, very substantial, we really need to think about this in steps and make sure that what we're recommending is their immediate target is something that seems achievable and not completely overwhelming or impossible for them to achieve. So one step at a time, I think is a good plan when counseling people regarding weight loss.

So please select another case in the series or proceed to the evaluation to receive credit.

Dr. Thethi:
Hello, everyone, and welcome to our second case in this series, where we'll talk about tailoring hemoglobin A1c targets, and really assessing the best treatment approach for this case that we're going to discuss. And you know, in that context, we'll talk about decision cycle, four person-centered glycemic management, and the guideline recommendations as well.

So with that background, let's jump into our next case, which is about a 50-year-old woman who was diagnosed with type 2 diabetes in June of 2020. Now, at that time, she started metformin 500 mg twice a day, and she had an A1c of 7.2% at initial diagnosis. She did want to wait a little longer before she increased the dose to 2,000 mg twice a day because of the side effects that she was having. And you sure did refer her for diabetes education classes.

So you know, unfortunately, almost 6 months have elapsed and you see her in January 21, and at that time, you're surprised that she has an A1c of 9.6. She tells you she's not taking metformin regularly. She has gained about 10 pounds since the last visit, and has unfortunately not been able to attend the diabetes education classes. So you talk to her about the different medications. You think that, you know, you'd like to start a GLP-1 receptor agonist for her, and you let her know ahead of time this process may take some time. And after your conversation, she says she is committed to losing 10 pounds till the next visit. And this is always good. You want the

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patient on board with decision and you want the personal commitment from the patient to take care of their health as well.

Now, fast forward to July of 2023, and you're surprised that you haven't seen her literally for a couple of years and longer. And that's where she tells you that she had lost health insurance, which is a very unfortunate situation to be in, but not uncommon that we see in our clinics, and she stopped the GLP-1 receptor agonist. She of course continues to metformin 1,000, twice a day, and has gained 20 pounds since you last saw her. Now she says she has a new job, new insurance, and does have medication coverage. So she of course is willing to restart some of the medications and also committed to losing weight and a regular follow-up.

So fast forward to your current visit with her. Once you get labs done, she does have an A1c of 9% with a BMI of 38. But blood pressure's 138/80 and her LDL cholesterol is 75 on the most recent labs. Now she does give you symptoms of peripheral sensory neuropathy, but no other known diabetes complications that you're aware of. And she certainly denies any polyuria and polydipsia. After your conversation with her, she is willing to start once weekly GLP/GIP receptor agonists. And you know, she has done a GLP receptor agonist before when you had started it, so she's very receptive to it. And you do start her on an ACE inhibitor as well. You ask her to monitor the blood sugars, and you'd refer her for diabetes education again.

So here's a question for our audience. And that is, what hemoglobin A1c target would you like for this woman? And you have the answers below. And so with that, Jennifer, now that we've talked about a wonderful 58-year-old woman, and as you've seen, she was under your care, then she lost insurance, and now she comes back, what are your thoughts about the hemoglobin A1c target for her?

Dr. Green:
Well, that's a good question. And I have to say that I haven't heard anything about this woman that makes me think that we should set a hemoglobin A1c target for her that is higher than 7%. So there are many factors that we need to take into consideration when we are making an individualized A1c target, but I think I'd like her to be under 7%, because although she does have diabetes, she doesn't have major other comorbidities. She has some peripheral neuropathy, which I would really like to keep from worsening. And she has no other known diabetes-related complications, and I'd like to keep it that way for as long as possible.

Dr. Thethi:
Absolutely. And, you know, thinking about her diabetes duration, it's just in the last few years, she now has the resources. Comorbidities, as you mentioned, not you know, nothing major that we know about except for peripheral neuropathy. It's certainly important to institute changes now so she does not develop those complications.

So with that, another question that I'll pose to our audience, and that is what therapy would you select for this woman? And you have the answers below? And you know, we've looked at our options for her. We know her BMI, her hemoglobin A1c, and so now it comes down to which therapy do we really select for her? You know, one that lowers glucose, consider a GLP-1 receptor agonist and other options? And what factors again, would we talk about when it comes to selecting therapy? Before we talk about whether she is open to an injectable or not? So what are some of your thoughts, Jennifer?

Dr. Green:
Well, when I look at this person's history and where they are now, I really want to, if possible, select an agent that will significantly lower her hemoglobin A1c over time. She's starting out at 9%; to get her down under 7%, there are some options that might get her there with individual therapy, but she is someone who may in fact need more than one medication. You'll have to follow her up very closely and assess her response to the initiation of whatever you do start to make sure that she didn't go on for years with uncontrolled diabetes in the future. So, but I think we already mentioned that she was willing to use an injectable therapy, and she'd done it before, so that makes our job a little bit easier. But that's not the case for everyone. I will say that, even though many of these GLP-1 receptor agonists and the dual incretin agonists, tirzepatide, are injectable, it's fairly rare for me to have a patient decline to take an injection once a week, so it's reasonably convenient. But we'd need to work around her preferences, we'd need to think about what else she were already taking. She's not taking any other medicines, so not many concerns there. We'd need to make sure that we discussed ways to make the medication side effects as minimal as possible, and to think about how the medication might interact with other medicines that she might be taking. Again, this is a woman who isn't on much already, but this is generally a consideration. So I think factoring in patient preferences, I like to when we're getting to a decision point like this, to offer several options moving forward, discuss in brief the pluses and minuses of each path forward, and allow the patient to weigh in as far as which option they feel is the best fit for them. And that way, we're really operating as a team.

Dr. Thethi:
I agree with you totally. You know, the very fact that, yes, she's taken an injectable and a GLP-1 before, so it does make things a whole lot easier. And I think in her, you know, as we target the A1c and I like, as we were talking earlier, as well, important to realize to really talk to her about her weight as a target as well, because she gives you a history of every single time when she's not had regular follow-up, she comes back, she's gained weight, and to make her realize that yes, along with her glycemic control, weight management is an

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equally important target. And in someone that you know that, yes, we're going to – she understands the importance of glycemic control, I also take the opportunity to talk about the other consequences of obesity, for example, liver disease, the mechanical effects of obesity. And I think that is an important conversation also to have with her when we talk about obesity management. And you know, here you can see so many different spokes of the wheel, so to say, when we talk about the goals of care that we provide for our patients, you know, when it comes to preventing complications and optimizing quality of life. And that's important. I think, an equally important point of discussion with our patients is not just about the numbers, but talk to them that as the numbers improve, their quality of life will improve as well. And that's something you know, sometimes patients have been at a place for so long, it's difficult for them to see past it. So I think that's an important conversation to have as well, with time. And here you can see the various different spokes of the wheel that I think we all talked about utilizing. And it really is about teamwork when it comes to taking care of our patients.

So this patient also then brings us the opportunity to discuss how do we handle stopping and starting therapy if the patient is indeed initiated on a GLP-1 receptor agonist and then loses access again, or gets access to a newer therapy? And you know, I think this is a very important thing to talk about. Because of late, we've had this, right? And I think every single year, insurances change formularies, and we're up against the same issue. So we, of course, want our patients to continue care. So what are some of your ideas, Jennifer, how we should tackle the situation?

Dr. Green:
So this is a very, very common clinical scenario. And I wish we had more firm evidence-based guidance about how to make these changes. But I think this is a situation where we need to exercise good clinical common sense. If you have a patient who was on a medication in the past and tolerated it at a given dose, but they've been off of it for several weeks or longer, when they restart, it is not unreasonable to go back to the starting dose and re up-titrate the medication just to ensure that starting them right back at a high dose is not an intervention that they find to be intolerable.

When switching medications within a class too, I'm always a bit conservative. I don't usually switch over from the max dose of one agent to the max dose of another agent, because I don't think that tolerability on a given medication guarantees tolerability of the either, and so often I'll cut back to a more moderate dose when I've made the change. But again, this is not particularly well studied, you cannot go wrong from a tolerability standpoint by making a switch to a very low dose and re up-titrating. The negative about doing that, though, is that the patient may have a deterioration in glycemic control if you start back at square one when switching the individual to a new medication. But I think keeping in mind how well the patient tolerated the previous medication, and how long they may have been off of the previous medication, those are really important factors and making these switches.

Dr. Thethi:
Absolutely. I think for me, the one thing that makes – that is for perhaps the first thing I consider is how long has the patient been off of the medication? Do I need to start from ground zero? Or if it's just been maybe about you know, 2 weeks, 3 weeks, can we restart the same dose of the same medication? And as you mentioned, when switching medications, of course, better to be more conservative, and then up-titrate.

And then for our audience, we have another question. So she did initiate the GLP-1 receptor agonist, semaglutide. And several weeks later, you get a call from her, and she says she has been experiencing some nausea since she has up-titrated the dose to 1 mg weekly. The nausea is mild, and there really is no associated vomiting or diarrhea. And so, the question for our audience is, what do you recommend?

So I think it's certainly very important to talk to our patients about managing side effects. And it's really a testimony to the communication she had with her physician, that she actually called back and told the office that she's having these side effects rather than just stopping the medication. Now, we know that nausea occurs in about 5 to 10% of these patients in the first few weeks. But then, of course, it does diminish, and everyone has their own timeline. There are some people that have absolutely no side effects. And the other side effects like, for example, constipation, diarrhea, also need to be known to patients, you know. But they can take fiber or increase their water intake to prevent constipation. And usually, these GI side effects are seen during initiation or up-titration. So as long as she knows these timelines, I think that's definitely helpful. And of course, you do let her know to eat small frequent meals. And I tell them, you know, since these medications act centrally, and they will not let you eat more food, so if you feel full or near full, I should say, and I tell them don't get to the feeling of full, stop before then. And if you get a signal from your body that says, please don't eat, then don't disregard that signal.

So with that being said, Jennifer, any additional tips for our audience that can help manage the side effects of these medications?

Dr. Green:
Yes, I'm going to give you two of my secrets. And one is that we do not have to up-titrate the drug as often as we're able to. So if I have a patient who was on a given dose of a GLP-1 receptor agonist, and they felt nauseated, and it's a little bit better but it's not gone, I'm

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not going to up-titrate the dose because it will make them feel worse. And as you had mentioned, they might stop the medication and not want to resume. So I wait until the GI side effects are either gone or very minor before I up-titrate to the next dose. It's perfectly fine to take your time doing that.

Now, you had mentioned nausea, which is the most common GI side effect. Another that my patients tend to have would be loose stools. And many of my patients are also on metformin. And I have found that in those individuals who experience loose stools when they add the incretin-based therapy, if I cut down on their metformin dose or even have them stop it, at least for a while, that can really minimize the frequency and severity of the loose stools.

So those are a couple of things that we can think about that might be very useful for a lot of our patients.

Dr. Thethi:
Absolutely. Thank you. I agree with you on all those points and, yes, a very important point to discuss that, you know, you don't necessarily have to increase or escalate the dose every 4 weeks; you can go a little bit longer and that's perfectly fine. In an effort to take two steps forward, you don't – or one step forward, you don't want to take two steps backward. That's a good analogy. And I think having small frequent meals, avoiding fatty food also goes a long way, because these drugs do slow down the GI tract. We know that.

And, you know, a question that does get posed to me quite often as well as is it okay to use an antiemetic with these agents if they're having side effects? And the question is, it depends on how long. If it's short term that will lead to the patient being on the drug to eventually tolerating the drug, then by all means. But yes, you know, there could be a subset of patients that really are not able to tolerate the drug. And if it comes down to using an antiemetic just to be able to take the drug long term, and then the question arises, you know, is the patient really able to tolerate the drug. So that being said, I think just we've discussed so many wonderful points about this patient, and very relevant discussion around these class of drugs, and including our GLP-1/GIP agonist combination.

And with that, I'll let the audience know that please do select another case in this series or proceed to the evaluation to receive credit.

Dr. Green:
Welcome to our third case. This is a 72-year-old man who was diagnosed with type 2 diabetes in early 2022. At the time, his A1c was 7.9% and he had a BMI of 31. He was hypertensive with a blood pressure of 152/86. And his LDL was also 120 mg/dL. He was started on metformin, as well as an ACE inhibitor. When he came back about 5 or 6 months later, his hemoglobin A1c was a little bit improved, 7.5% and his BMI was lower at 28. At that time, he was continued on his metformin, but sitagliptin 100 mg a day was added. Six months later, his hemoglobin A1c was improved to 7.3%. His BMI was 30. And his medications were not changed at that time. Now importantly, in early 2023, he was diagnosed with atherosclerotic cardiovascular disease after he experienced angina and had a cardiovascular workup. You can see that at present his hemoglobin A1c is 7.3%. His BMI has ranged most recently between 29 and 31. Blood pressure tends to range about 140/the upper 70s. And his LDL cholesterol is in the 80s. He remains on metformin and sitagliptin. He's taking his ACE inhibitor, and he was started on rosuvastatin 20 mg a day once he was diagnosed with cardiovascular disease. So what hemoglobin A1c target would you recommend for this man?

Well, let's talk about tailoring hemoglobin A1c targets for an older person with atherosclerotic cardiovascular disease and type 2 diabetes. I mean, I think that this is a situation where we need to take a moment to ensure that what we're recommending for patients is effective, but also safe. Tina, do you have any thoughts about the most appropriate A1c target for this gentleman?

Dr. Thethi:
So you know, he is a 72-year-old gentleman. And I think it really when we take age into consideration, lifespan into consideration, I think it's important to think about whether it's a 72-year-old, otherwise healthy gentleman, and you know, his A1c has ranged in the 7s, and he's undergoing cardiac workup. So I think it behooves us to try and aim for an A1c less than 7%, if we can get there without Hypoglycemia, additional excessive burden with medications, by all means – and even if that entails switching medications for him, and really seeing the overall other comorbidities that he has. But I would suggest it's important to realize that to really look at the patient as a whole and see if it's appropriate to target to less than 7, or also depending on the patient profile, their comorbidities, see if it's okay to keep between 7 and 8%. With this particular gentleman, I'm more inclined to see his A1c less than 7% if we can get there without hypoglycemia.

Dr. Green:
That's a good point. I think this is a little bit of a gray area. I think it's fair to say that given his A1c of 7.3% and his recent cardiovascular disease diagnosis, he certainly doesn't warrant aggressive, additional glucose lowering. So we need to keep that in mind as we think about his treatment plan.

So what therapy would you select for this older man with ASPVD? And how would you include it in his treatment regimen?

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So Tina, what treatment would you select for this older man with ASCVD? And how would you include it in his treatment regimen?

Dr. Thethi:
Oh, Jennifer, I think that's such an important topic to discuss. Because this is where you know, we leverage the data that we have from our cardiovascular outcome trials. And this is where you think, okay, he's got a BMI of 29, an A1c of 7.3%. And it's teetering right around 7, so what do I need to do additionally for this patient? And I think this is where I would think that, okay, can I use something to offer cardiovascular protection to this gentleman with the agent that he uses? And not just think about his targets as a number, but offering cardiovascular protection, offering protection for any further complications that he may have. So here, I'm actually inclined to using a GLP-1 receptor agonist for him, and preferably ones that we know offer cardiovascular protection.

With that being said, I think it's also important to keep in mind, as we've talked with our other cases, that, you know, just because we would like to prescribe something doesn't necessarily mean the patient would have access to it. So as much as we aim to have an optimal regimen and offer protection, I think if we use an agent in the same class that has shown no harm, and if the patient does have access to it, also would be a good option and becomes a practical option for the patient to have.

Dr. Green:
Right. Right. And I'd like to take a minute to review the part of the American Diabetes Association's algorithm for the care of people with type 2 diabetes that refers specifically to choosing glucose-lowering medication in people with high ASCVD risk and the recommendations and as part of the algorithm are irrespective of whether or not a person needs additional glucose lowering and also irrespective of whether or not they're already taking metformin. Because the medications recommended in this pathway provide an outcomes benefit, irrespective of whether or not someone's on that as background therapy or they need additional glucose lowering. And when we talk about high ASCVD risk patients, what this refers to would be a patient with type 2 diabetes and established ASCVD, or someone with multiple risk factors for ASCVD. So we can think about use of this pathway in a primary prevention perspective as well.

And here you have two choices. The regimen should include either a GLP-1 receptor agonist with proven cardiovascular outcomes benefit, or an SGLT-2 inhibitor with proven cardiovascular outcomes benefit; either is appropriate for this treatment – for this patient, or similar patients. You don't need to be on both. A benefit or an additive benefit to using both classes has not yet been clearly demonstrated. But we should, in all circumstances, include one of these beneficial medications. And we had already mentioned that some, but not all of the GLP-1 receptor agonists have demonstrated cardiovascular outcomes benefit.

And you can see summarized on this slide the results of the cardiovascular outcomes trials of the GLP-1 receptor agonist that have been studied thus far. And highlighted in red are the outcomes of the trials which tested the effects of liraglutide, injected semaglutide, and dulaglutide in high-risk patients with type 2 diabetes. And those are the three agents that we really need to try to select wherever possible when we're treating our patients with ASCVD or high ASCVD risk with the intention of improving cardiovascular outcomes.

Now there are other agents that are on the market of course for glucose lowering. Some of them have had trials performed that didn't show an outcomes benefit, such as the once-weekly formulation of exenatide. But others have not yet had their cardiovascular outcomes trial completed. One of those is the oral formulation of semaglutide, as well as the cardiovascular outcomes trial with tirzepatide, the dual GLP-1/GIP receptor agonist. Now, this medicine is available for the treatment of type 2 diabetes.

And this slide shows findings from a meta-analysis of several smaller premarketing trials, which was designed to assess the safety of the cardiovascular safety of tirzepatide in the treatment of type 2 diabetes. And the available data are reassuring in that tirzepatide does not appear to increase the risk of adverse cardiovascular events. But we cannot yet say that the drug conclusively reduces the risk of cardiovascular events in people with type 2 diabetes. So stay tuned, we'll have that information before too long. But tirzepatide is not a drug that you would choose to reduce cardiovascular outcomes.

This slide is a summary of the important outcomes of the SGLT-2 inhibitor trials, again in patients with type 2 diabetes and high ASCVD risk, like our patient. And you can see here that the outcomes trials testing the effects of canagliflozin, dapagliflozin, and empagliflozin were all positive in that they met their primary endpoint and were found to significantly reduce important cardiovascular outcomes in this high-risk patient population. So if you're going the SGLT-2 inhibitor route, and you're using that drug to reduce cardiovascular risk, I would recommend that you use one of those with a proven outcomes benefit.

But we need to think about how we're going to add these medications to the regimen of patients who often are taking one or more other diabetes medications. And this is an algorithm that was primarily designed to ensure safety. So anytime we add a new glucose-lowering medication to a regimen that already includes a sulfonylurea or insulin, the risk of hypoglycemia will be increased. So that's what we need to pay particular attention to. This algorithm recommends that if the person is on a sulfonylurea or insulin and their hemoglobin A1c is above 8.5%, for example, that you can probably go ahead and add the GLP-1 receptor agonist and not just those background therapies to reduce the risk of hypoglycemia. You may use a different threshold personally, such as 8%. But if the person has a

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hemoglobin A1c that is less than 8 or 8.5%, or certainly if they're already having hypoglycemia on their regimen, it is reasonable to reduce the dose of sulfonylurea or even stop it when you add a GLP-1 receptor agonist and/or to reduce their dose of insulin by about 20%. So you can't go wrong reducing the doses of these medications for safety. When you add back and up-titrate, the GLP-1 receptor agonist, you can assess whether or not they might need to have those doses reinitiated or up-titrated.

On the right-hand side, you can see that for a person who's already on medications for diabetes that don't have an inherent risk of hypoglycemia, like metformin, for example, or pioglitazone, you can add a GLP-1 receptor agonist without significantly increasing the risk of hypoglycemia. However, if the person doesn't need additional glucose lowering, look for opportunities to make medication substitutions, either for cost savings or to minimize the risk of side effects or to potentially stop a medication that the patient isn't tolerating well.

Reminder to you though, that we do not prescribe DPP-4 inhibitors, GLP-1 receptor agonist, or dual incretin agonists together, not because they're necessarily unsafe, but there's no additive benefit. And certainly, if you gave two incretin-based therapies, you might increase the risk of adverse side effects.

So question for the audience, how often do you use the American College of Cardiology and American Heart Association's ASCVD Risk Calculator, also referred to as the Risk Estimator Plus? So I'd like to talk for a minute about whose responsibility it is to reduce the risk of cardiovascular events in type 2 diabetes, and how we can address and calculate our patient's risk and take steps to mitigate the risk of adverse outcomes.

Tina, who you think is responsible for managing cardiovascular risk reduction in a patient such as the individual described in this case? Is that the cardiologist's responsibility? Or does the endocrinologist or primary care physician play a role?

Dr. Thethi:
So my simple answer to this, Jennifer, would be everyone. I think it's a shared responsibility. And, you know, we need to empower physicians and our primary care community, because here's what happens. Access, as we all know, is certainly a huge topic of discussion nationally for us. So be it at a primary care visit, an endocrinology visit, or a cardiology visit, I think everyone needs to look at what needs to be addressed for that patient and make those adjustments.

Now, here's the other thing to consider is that, for example, if the patient's physicians are not all in the same network, and you can't access that information, communication between physicians about their mutual patients, also goes a long way in making sure everyone's on the same page. So I certainly think any of the physicians that the patient is under the care of can look at the risk factors, make a change. Because the sooner the changes are made, the better it is, in fact, for the patient.

Dr. Green:
I agree. And risk reduction is not a hot potato that we can toss around from one of us to the next; we simply need to make sure that we are, at each visit, assessing our patient's cardiovascular risk and determining whether or not their care is consistent with current guidelines, or if there are gaps in care that need to be addressed. And in some situations, it's not appropriate for that physician to make the change. But it is always appropriate to communicate with the other physician so that the care is provided.

I actually think the trickiest patients to manage are those with type 2 diabetes who have not yet been diagnosed with a cardiovascular complication. We know that people with type 2 diabetes are inherently at very high risk for both atherosclerotic cardiovascular disease, but really in particular heart failure. So we need to have a very high level of suspicion, we need to be asking our patients if they have symptoms or changes in their activities or limitations to their activities that might be an early sign of a developing cardiovascular complication. And really be attuned to that and take the appropriate next steps so that we can best understand our patients risks.

I think that it's never wrong to refer a patient who is having a problem or who appears to be at very high risk or whose risk factors cannot be managed easily, to a cardiologist or other relevant specialist for help. That's why those doctors are there. They probably have a great deal of prior experience in managing patients whose care is very complicated or difficult, so we should not hesitate, I think, to reach out to our cardiology colleagues, if we're really stuck and just can't seem to move forward.

Well, we've come to the end of this case, so please select another case in the series, or proceed to the evaluation to receive credit.

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