In this episode of the Penn Primary Care Podcast, internist Kendal Williams, MD, MPH, has a meeting of the minds between primary care physicians and endocrinologists -- discussing common questions and management practices of Type 2 Diabetes with three Penn Medicine physicians: Internist Amber-Nicole Bird, MD; endocrinologist Carrie Burns, MD; and endocrinologist Christina Mitchell, MD.

Transcript

Kendal Williams, MD, MPH (host): Welcome everyone to the Penn Primary Care Podcast.

My name is Dr. Kendal Williams and I'm the host for this episode. I'm joined by my co-host, Dr. Amber Bird, a, Penn general internist, and two experts that we're going to pepper with questions about diabetes management for the next half hour, Dr. Carrie Burns and Dr. Christina Mitchell.

In this episode, we plan to have a very practical discussion about type 2 diabetes management with particular focus on the newer agents. This is one of the most common, if not the most common, eConsults the diabetes experts get from the primary care community. We thought we'd have a discussion about that.

Amber Bird, my co-host, is a Penn General internist and an Associate Program Director of the Penn Internal Medicine Residency Program and an Assistant Professor of Medicine. Amber, thanks for coming.

Amber-Nicole Bird, MD: Thank you for having me.

Dr. Williams: Dr. Carrie Burns is an endocrinologist and professor of medicine at Penn. She is the Director of the Diabetes and Pregnancy Program. She sees patients both at Perelman and also with the Radnor facility,

Carrie Burns, MD: I'm happy to be here. Thank you.

Dr. Williams: Thanks so much. Dr. Christina Mitchell is an endocrinologist and Associate Professor of Medicine at Penn. She also sees patients at Perelman as well as the Radnor facility, Christina, thanks for coming.

Christina Mitchell, MD: Thank you. Looking forward to this discussion.

Dr. Williams: You know, I started out as a primary care doc and then did hospitalist medicine for a bunch of years and then came back to primary care recently. So this was one of the most confusing areas for me. And I'm really appreciative having all of you on to talk about it.

The way I thought we would do this is that we would start with a case more or less typical of what we see in our offices, and then we'd work through the various branch points and scenarios that we encounter in different patients. And we don't need to go a lot through the pathophysiology or even the academic stuff, we can read that. We have experts here. We

really want to kind of ask you practical questions.

Let's start with a 56-year-old man who comes to our office for the first time. He's about 30 pounds overweight, has normal liver and kidney function and is found to have a hemoglobin A1c of 8.6. Let's first talk about non-pharmacological measures, diet and exercise.

And I'm going to ask all three of you, is there a particular approach you'd take to patients in educating them and hopefully inspiring them to lose weight? How do you go about that? Maybe Carrie, we'll start with you.

Dr. Burns: I think this is something we all universally talk about very frequently during our day of ambulatory medicine. You know, I would say there's not one successful program. And I think that's something to underline.

Patients will always ask, "What's the best diet?" And there's no one best diet and I think we all talk about the importance of caloric restriction and how to induce that core deficit in order to lose weight. And I try to advise just small kind of pieces to take to try to attack it in one way, maybe going for that 5% weight loss. Sometimes I talk about logging food as I find that's a really successful method for long-term weight loss. If you can encourage your patients to log food regularly, I think that works well. I think weekly weights is a very helpful measure as I think a lot of our patients don't weigh themselves, don't have a scale at home, so really have no idea where they stand.

And I think, you know, things like apps. We use a lot of apps that are free for doing that logging, but just getting a sense of how calorically dense foods are. So if someone even does that logging for a few days and they get a sense of how calorically dense certain foods are, how many carbs are in foods, that they may limit the amount of those.

So I think that's helpful. And I think we always encourage exercise. It maintains glycemia, especially if someone can exercise every other day. But I think also underlining that exercise is not a helpful mode of weight loss, it's a helpful mode for weight maintenance. I think some of those reminders seem to help, in my opinion.

Dr. Williams: Christina and Amber, are there any other approaches that you take?

Dr. Mitchell: You know, to echo kind of what Carrie said, I was going to say that like asking sometimes even more pointed questions, I mean, at least for our initial visits, I will ask about sugar sweetened beverages. "How many sugars might you add to coffee in the morning? Is there much soda and juice that's part of your diet on a regular basis?"

I find that if patients say yes to that, that counseling them about reducing or eliminating those sugar-sweetened beverages entirely is such a game changer with achieving normal glycemia. The way that the blood sugars spike after drinking a sugar sweetened beverages is so profound. So that's low-hanging fruit if they are drinking sugar sweetened beverages.

And then I ask about also are they achieving the goal intake of vegetables and fruit? Because

I think that's the other piece of it, is that when people are able to achieve kind of the recommended daily allowance of fruit and vegetable intake, that some of the foods that may be more calorically dense end up getting closed out a bit, because you've achieved some sense of satiety with foods that are actually going to give you more micronutrients.

Dr. Bird: Yeah. I would say I really liked that last point. And one thing that I oftentimes will see in the primary care clinic is patients come in and say that they're worried that they can't eat like fruits anymore. They have to give up fruits. And I think being able to focus on kind of more whole foods, natural foods that are not processed and saying, you know, "You can eat your fill of fruits and vegetables if that's going to take the place of more processed foods." I think that's a really good point.

Dr. Williams: Let's say that the either tries that and doesn't fully succeed, or there are some limitations in his ability to lose weight, then we start talking about meds. So let's start with Christina. Metformin remains first-line, I assume?

Dr. Mitchell: Yes. As long as someone's kidney function will allow it and they're not in an acute exacerbation of heart failure, we'll use metformin every time.

Dr. Williams: Yeah. You start with 500 a day or 500 twice a day, which do you use?

Dr. Mitchell: In an effort to improve adherence and not have people stop it because of the gastrointestinal side effects that so often, you know, accompany at least starting it, I start with the 500 milligrams once a day, but then try to increase weekly and we give them a little schedule where it's the 500 milligrams with dinner for a week and then 500 with breakfast and with dinner for a week. And if we want to go further, then 1000 milligrams with dinner, 500 with breakfast, and then graduating to 1000.

And prescribing the extended-release version does seem to help as far as the gastrointestinal side effects are concerned. There was an issue, has been a couple times in the past year and a half, where unfortunately extended-release metformin was recalled by some manufacturers. Certain lots were recalled because of contamination. And so that was an issue, a practice issue, because of patients calling and not being able to continue their current supply of medicine and us going then with the IR version, sometimes was tolerated, sometimes wasn't.

But that seems to be the biggest obstacle, is the GI tolerability.

Dr. Williams: Do you have them all take it with food? Do you always tell them to take it with food? That's what I was taught on what to tell patients. I'm curious if that holds water.

Dr. Mitchell: Yes. I think taking it with food is one of the best things that can happen to help improve that tolerability.

Dr. Williams: This gentleman's hemoglobin A1c was 8.6. But there's a point I think at which I

know as a hospital-based provider, we would think about this. If somebody came in with a hemoglobin A1c of 13, we'd often think about just getting them on insulin right away. I'm curious, what level of hemoglobin A1c would you actually think about just starting with insulin with the idea that you would eventually maybe wean to orals later?

Maybe I'll throw that to Carrie.

Dr. Burns: I would say an A1c of 9 or greater, or the presence of polyuria, polydipsia, blurry vision, you know, signs that there is catabolism going on in which you would really like the anabolic effects of insulin to help you out. So usually 9, you should start thinking about it. Ten definitely and above definitely. So I think that's where I definitely start thinking about at least the addition of a basal insulin at 9.

Dr. Williams: So maybe 8 units, 10 units of a long-acting?

Dr. Burns: Yes. That is right. That is correct. I will either use 0.2 times the weight in kilos, is a nice starting; 0.1 or 0.2 depending on how insulin-sensitive you think someone is. I think, yes, but that frequently is around 10, you know, and I think you wouldn't go wrong with 10 or 8, especially if they have normal renal function, maybe on the lower side if they already have CKD.

Dr. Williams: You would have them on insulin for how long? And then would you intend to get them off of it eventually and wean to orals once they get down toward normal range or would you just leave them on it?

Dr. Burns: Right. I think it depends on where they are in their diabetes disease, right?

If they are an early-onset person, we think that they likely have insulin. It's just that they're so hyperglycemic they're in this cycle where there's such toxicity to their beta cells that they can't secrete their own insulin. That's where cooling them off with insulin, like that person with that 13 A1c you described is a great idea. Because frequently, especially in west Philadelphia, we will see patients who arrive in the ED with hyperglycemia, polyuria, polydipsia, weight loss. And they're young and they've been eating all the things that Christina was talking about. And we cool them down with insulin late, they go home on usually multiple daily doses of insulin. We see them back in the office.

We'll frequently will start a little bit of metformin on their way out the door from the ER. And we are frequently quickly tapering that down in that young person who still has good pancreatic secretory ability of insulin, but we've kind of removed that toxicity, cooled things off, the diets better, the metformin is getting ramped up and I have patients who were in ketoacidosis with an A1c of 14 and a year later, they're on metformin with an A1c of 6.1. We see that a lot.

But if you have somebody who has had diabetes for 15 or 20 years, they have CKD and they don't have that secretory capacity, they may not be able to reach our goal A1c, whatever that is for that person without insulin somewhere in their regimen. It kind of depends on

where they are.

Dr. Williams: Yeah, that makes sense. I mean, this gentleman, I think sort of as a new presentation, but you're right, I mean, you have these people that are coming in and have really been diabetics for a long time.

Of course, we don't always know how long type 2 diabetics have actually been diabetics, but presumably, I guess you make that assessment in making these decisions.

Dr. Burns: Right. I think, you know, you can measure a C-peptide concentration while someone's blood sugar is elevated. So you could advise them to go after they've eaten to the lab and see what their C-peptide is.

And I think that is part of the conversation with your patient, that diabetes is a progressive disease and that frequently we expect that beta cells will atrophy or undergo apoptosis as the disease progresses so that they're not failing if they need insulin, that this is something that frequently happens and is somewhat expected.

Dr. Williams: Let's move away from insulin and get back to our case. I want to focus on the oral medications.

So let's assume he's on metformin at max dose and he's lost some weight, but a couple of years later, you know, first he gets down to 7, let's say, and then he starts to creep back up again over a couple of years. And now he's back at 8.6% where you started. Now, you're thinking about adding another agent.

And so what I'd like to do now is just review the options real quick of the oral hypoglycemic agents we have available by class. You know, when I was a resident, sulfonylureas were very commonly used and almost used before metformin.

Obviously, those potentiate insulin secretion, so they can cause hypoglycemia and, you know, they come in several different forms. Christina, is there any particular thing to say about the different sulfonylureas and how you use them?

Dr. Mitchell: I think the only thing that I would highlight about the sulfonylureas is that we really try to stay away from glyburide and our preference is to use either glipizide or glimepiride.

The issue with glyburide is that not only is the medication itself active, but it's subsequent metabolites are also active in terms of, you know, promoting lower blood sugar, depolarizing the beta cell to secrete insulin, so the idea that it really can cause pretty significant hypoglycemia, especially in the elderly.

And I think that we even have a pop-up in our electronic medical record with warnings, when you try to prescribe or even renew glyburide because of that issue. But as far as glipizide versus glimepiride are concerned, I think that they behave fairly similarly and, in practice, I don't tend to prefer one over the other.

Dr. Williams: That's great. I mean, I've seen a lot of that. As a hospital-based provider, I saw that was probably the most common side effect I saw from diabetic agents, was elderly patients coming in with sulfonylureas becoming hypoglycemic. And interestingly, I noticed a pattern oftentimes they were on a very low dose and you scroll back through and see that their last hemoglobin A1c was 5.6 or something. And for some reason, somebody decided to keep them on it. That was sort of a pattern I saw.

Dr. Bird: I was just going to ask one additional question about the sulfonylureas, which was, is there a preference between the immediate-release and extended-release? Because I think I see what Kendal has seen, certainly on the inpatient side, where we have patients, particularly who are elderly and on sulfonylureas still come in hypoglycemic and I tend to see a lot of extended-release formulations.

And I was just curious if there's any reason to choose IR versus ER in particular.

Dr. Burns: I try to use immediate-release.

I think you would use extended-release if you feel someone has a little bit of a basal need, but that's really not the right way to go about treating that. You know, metformin helps with basal need. I think the only time you would use extended-release sulfonylurea is in a younger patient who just doesn't want to take as many tablets a day. You could do an extended-release in the morning, and that would cover them the whole day in hopes that they don't skip meals and have hypoglycemia as a result.

And something I was thinking, Amber, before you asked that question, a drug that I do use more frequently than the sulfonylureas are the meglitinides. An example would be repaglinide or nateglinide which they work basically at the same spot on the beta cell, just right next to where the sulfonylureas dock at that sodium potassium ATPase channel and they are short-acting. So they kind of give you a little burst of insulin secretion power. But they're quick on and off, so they have that benefit that they won't stay around, like you were mentioning as an extended, and they're effective.

But at the flip side, they're also three times a day dosing, right? So you have that kind of quick burst of insulin, almost the oral equivalent of a fast-acting insulin in someone that has that secretory capacity. But you do have to take them three times a day, but sometimes they're helpful maybe if dinner is the largest meal and they can just take it with dinner and then it's out of their system. And it is effective in someone with CKD, it doesn't hang around as long. It's hepatically cleared.

Dr. Bird: That's really helpful. I will be honest, I don't think I generally grab for meglitinides. So that's helpful to know.

Dr. Williams: I want to talk about the GLP-1 process.

You know, when I was a medical student and resident, you know, we learned about insulin and glucagon and so forth, and nobody ever talked about this whole incretin process. And obviously, I think now, it seems like some of our most effective drugs are based on that hormonal process. Obviously, you have the GLP-1 agonist and then the DPP-4 inhibitor drugs, which are really inhibiting the breakdown of GLP-1.

I'm wondering if one of you wouldn't mind just giving us a brief physiological overview of that system.

Dr. Mitchell: Sure. I can talk a little bit about, you know, starting with the action of the GLP-1s and then how the DPP-4 inhibitors, you know, play into that. But I like to go into this actually with patients, because I think it helps to like contextualize the ads that are seen on TV. There are so many ads for the GLP-1 agonists now, but, you know, I explained to them that we make glucagon-like peptide 1, that cells in our small intestine are responsible for this, and that studies, you know, done in the 1990s demonstrated that unfortunately folks with insulin resistance had lower concentrations of circulating GLP-1 than "normal controls."

And that in fact in further studying the hormone, that it was really helpful to maintain normal blood sugars. That in fact it slows gastric emptying, so it leads to a more stable glucose profile in the blood as opposed to one of the defects that has been seen with insulin resistance and type 2 diabetes as a more rapid emptying of the stomach. And in turn, kind of a more of a spike and a fall with any nutrition from the gastrointestinal tract.

So the fact that these medications slow gastric emptying leads to a more stable glucose profile in the blood, they do also augment insulin release from the pancreas, but really in kind of a glucose-dependent way. So really only if your glucose exceeds a certain threshold, then do they kind of kick in, so that really limits the ability of these medications to cause hypoglycemia.

I like to emphasize that they suppress glucagon. So I described this as the anti-insulin made by the pancreas, by the alpha cells of the pancreas, where glucagon is a hormone that is so necessary to maintain our blood sugars if they start to go too low. But in fact in the setting of type 2 diabetes, there can be this excess production of glucagon that in turn causes the liver to overproduce glucose overnight and participate in gluconeogenesis and really make the blood sugars high overnight and into the morning the longer that you remain in that fasting state.

In any way, lastly, GLP-1 analogs and the hormone itself works centrally on the appetite centers of the brain to induce satiety. And that with the loss of that hormone or if that hormone isn't present in the same concentration, you can have this constant hunger in addition to your stomach emptying faster. So talking about all the different levels in which this hormone works is I think compelling when you're describing a treatment that might have more than one benefit for the patient.

Dr. Williams: That's actually very valuable. I didn't know all of that. That's very helpful. The DPP-4 inhibitors came out before the GLP agonists. But I thought it was helpful to talk about

GLP-1 agonists first in terms of physiology before talking about DPP-4, because DPP-4s are basically increasing the hormone through a different pathway, correct?

Dr. Mitchell: That's right. Our native GLP-1 lasts only a very short time in circulation. So it needs to be secreted with regularity. It's very quickly broken down and regulated by that enzyme dipeptidyl peptidase-4. And so by inhibiting the enzyme, you're prolonging the action of our native GLP-1. So you can increase the concentration of our native GLP-1 with the use of these DPP-4 inhibitors, but it turns out that you can't achieve really as high a concentration by just using a DPP-4.

For example, they tend to have more of a weight neutral effect, so they won't cause weight gain, but you're kind of not increasing the concentration of GLP-1 enough to have that weight loss effect that you can see with the analogs.

Dr. Williams: Because you're just potentiating what they already have, which may be reduced. So you have a ceiling of what you can achieve with a DPP-4 inhibitor.

Dr. Mitchell: That's a good way of describing it. Yeah.

Dr. Williams: When we talk about the DPP-4 inhibitors, by the way, we're talking about the gliptins, right? The sitagliptin is Januvia, the first one out as I recall and probably still the one most often used. My sense of these agents is that they have little side effects and can be helpful in certain patients, and I do use them. But they're just not that potent. Is that what you're finding as well?

Dr. Burns: I think they're helpful and they have an audience and kind of that patient you were discussing, you know, briefly a patient maybe who's on a low-dose sulfonylurea that was having hypoglycemia, maybe one of these agents would be appropriate for someone who just needs a little more to get to their A1c goal.

And I find frequently elderly patients probably would benefit from these medications because they're weight neutral. They do not cause hypoglycemia. They don't have gastrointestinal side effects. And sometimes, you know, that's all they need, is a little bit more than the metformin or maybe the metformin dose is limited by CKD. So I think someone who needs like a 0.5, maybe a 1% A1c reduction, you would think about this medication.

Sometimes what limits us is cost. And unfortunately, the patients who might benefit the most from these drugs are the ones who are on a limited budget or a fixed budget and can't use coupons and they don't have commercial plans. But that is a person I think about.

I, too, probably use sitagliptin or Januvia the most, because like you said, it was the first one out and it's the one I started using. I do find it has a very safe side effect profile. And I would underline just the use of saxagliptin, which I think is Onglyza, just to have caution with that in patients with heart failure as there was a trial called the TECOS trial that showed

increased hospitalizations for heart failure with that medication. Overall, very tolerated with the exception of very rare side effects, which is nasal congestion, sometimes arthralgias. It's a good option.

Dr. Williams: That's great. It seems to me they still have their place. I want to get to the GLP-1 inhibitors again in a minute, but actually let's go to the SGLT2 inhibitors.

So, these are the flozins, right? This is canagliflozin, which is Invokana, dapagliflozin (Farxiga); and empagliflozin (Jardiance), right? They've really generated a lot of excitement now. And I think that's partly because of their effects on cardiovascular health, right?

Dr. Mitchell: I agree with that as well. Yeah.

Dr. Bird: So I think our interest here is thinking about the patient profile, where you're choosing these agents early on.

So is there a typical profile of a patient where you're reaching for these? Is it just patients who have underlying heart failure or any patient populations where you're actually avoiding these early on?

Dr. Mitchell: So I feel like when a patient a cardiovascular patients, so these are folks who have already established care with cardiology for coronary artery disease. Certainly, if they are seeing a cardiologist for congestive heart failure or diastolic dysfunction, these are individuals that I am really thinking about adding one of the SGLT2 inhibitors. Or if in fact, a lot of times now, the request is even being initiated by cardiology where the cardiologist will reach out directly to say, "Have you considered an SGLT2 inhibitor for my patient?" because of the, you know, numerous studies that have demonstrated improvement.

I think, you know, the one that we will highlight that kind of is perhaps the first one was the EMPA-REG trial that involved empagliflozin and demonstrated that there was a significant reduction in negative cardiovascular outcomes and death from all causes compared to placebo. So it's a medication in its own right it seems for folks who have risk factors for cardiovascular disease, even if they haven't had a primary event yet.

So the issues though that can arise with using any of these agents, and then there's some more specific agent issues per agent, which we could discuss, but is that, you know, sometimes they can cause an increase in creatinine, even if it's only something that is apparent on labs, if you will, that may be that there's not actually an issue with the filtration of the kidney, but that you can see sometimes a bit of a creatinine jump in the initiation of these medications.

And then the mechanism of action, by enhancing the loss of glucose in the urine, and by that, I mean, like, you know, we're talking like 50 to 100 grams a day, you can create this glycosuria and that can really be a favorable environment for the growth of bacteria and yeast. So more admittedly more often in my female patients than my male patients, there can be the development of urinary tract infections and yeast infections.

So I do like to ask about that ahead of time. Because I feel like if someone is very prone to those types of infections already, especially in the setting of uncontrolled diabetes, it may not be the best choice. I kind of am willing to treat through one of those episodes, meaning, you know, treat a UTI, a single UTI. But I think that if one recurs in the next month or so, that we really have to reevaluate if the benefits are worth the risks of that kind of therapy.

Dr. Bird: That's helpful. And I just want to ask one follow up question to that, which is my understanding is that even if you improve glycemic control for your patients, if they are having these kinds of candidal infections, that won't improve with time necessarily, meaning if they're on the medication longer and they achieve better glycemic control, that doesn't necessarily mean that they're at lower risk for these candidal infections.

Dr. Mitchell: Right. I haven't seen that. And I haven't read about that in terms of there being an improvement, that may be that the body would reach a new homeostasis, so to speak. I haven't seen that or read that in particular that it might improve with time.

Dr. Williams: Is there one of them that you prefer to start first? And how do you make that choice?

Dr. Burns: I like to start with empagliflozin first. Although frequently, unfortunately we are all guided by coverage of insurance. But if given the choice, I do like Jardiance because I have found it to be a pretty acceptable profile as far as I found less candidal infections with that med.

And Invokana was for short while had a black box warning on it for increased risk of amputation. That is no longer on the labeling, but it was seen in two of the trials with Invokana and that there were two trials in which it was not seen, but that was not seen at all with Jardiance. I do like Jardiance a little more. Farxiga had some concerns, which is dapagliflozin, with some bladder cancer risk. And again, that hasn't been teased out. So I felt that with the EMPA-REG trial showing the improvement in survival I feel like that's my favorite one.

In the EMPA-REG trial, what's interesting is the A1c reduction that was seen in that was really low. Like it was 0.4 or 0.5% reduction in A1c. However, I have to say I see more of a reduction in real life practice than that. And I think perhaps patients who are not on trial may eat more realistically. I think of it in patients who maybe are eating carb-heavy diets, and I feel like drug uses that diuretic diuresis as a benefit and they really have an improvement in their glycemic control more than what's seen in the trials.

And just the other thing I like to underline about this drug class, which is newer, is more data has come out that has shown that they really are renally protective. The CANVAS trial being an example of that and that's Invokana, so that's canagliflozin, showed that in our patients that have GFRs in the, you know, 40 to 50 range, that these drugs seem to preserve renal function. So that's another population to think about.

Dr. Mitchell: Yeah, I'll second that, that also in fact I've now had a few nephrologists in addition to the cardiologists reach out and again, ask, "Have you considered or have you discussed, you know, canagliflozin for this patient?" and provide reassurance. It's amazing, again, if a patient's already seeing a nephrologist, how they are very willing to provide reassurance to the patients that that bump in creatinine that you might see, "Don't worry about that. You know, it's okay. It's not clinically relevant and you should stay on this medication."

Dr. Burns: And as a result, I've extended who I'm willing to try these drugs with, into GFRs in the high 30s where I didn't go anywhere near it before the trial came out. So I will do high 30 GFRs to try one of these drugs to help preserve their renal function.

Dr. Williams: That's terrific info. I've obviously been back at primary care for only a year now and I haven't used them very much. This is actually really helpful to me. Everything we've talked about thus far are oral agents, the flozins being Q day, I think they're all Q day. But when we start talking about the GLP-1 agonist, we're talking about an injectable. It's either once daily or twice a week or once a week. That would seem to be a downside, but there seems to be some real upside that both patients and physicians are appreciating.

And that seems to be the weight loss that's associated with them. And now we have some more recent work in which we're looking at them primarily for weight loss, irrespective of diabetes status. So let's talk about these.

The first one that came out is Byetta or exenatide, that was in 2005, a b.i.d. injectable; followed in 2010 by liraglutide, a Q day injectable, Victoza. And then there was a once weekly exenatide that came out in 2012. Trulicity once weekly came out after that, the dulaglutide. Semaglutide (Ozempic) is once a week. And then we have now a p.o. version of semaglutide, the drug called Rybelsus, which is actually a once daily PO.

Let's talk about these drugs. And, you know, I think practically for a lot of us, we're not sure exactly how to start this. So maybe let's first frame the question what's the patient you're thinking about this drug in? And then how do you have a conversation about starting it?

Dr. Burns: For the GLP-1 agonist, I think about it in anyone who is overweight or has obesity.

I think of it also when I'm taking my dietary history and I'm getting either a report or a sense of really increased appetite and difficulty with satiation, I guess. As Christina mentioned, the GLP-1 hormone works in the satiety center. I'll have a patient who will say, "You know, I'm really never full. I'm always hungry." The bells go off when I hear that. And also patients who might have a coronary artery disease history, so liraglutide was the first one to show benefit for cardiovascular disease in the LEADER trial. But as you're aware and most of the diabetes new drugs have come out in the last decade or so, they now have to show at least no harm in cardiovascular risk factors and ideally benefit to gain FDA approval.

So dulaglutide, liraglutide, semaglutide all have benefits in cardiovascular risk in reducing that risk. So that is, you know, a benefit when you're really thinking about, you know,

specifying care for each person, individualizing care. If they're either high risk for coronary disease or have coronary disease, you can think of it for these patients.

And I'll let Christina speak too as well. But I think, you know, it's become almost so easy for us, I mean, a weekly medication. In the beginning when it was Byetta or if it was Victoza, you say, "Is it okay if it's an injectable?" And you can almost see the body language of your patient change. And they would kind of sit back in their chair and look at you. And they say, "What? There's weight loss?" And then they would relax a little bit and soften and, "Okay, let me hear more."

Now, you say it's weekly and most people are really okay with that. And you see, you know, the needles combined, it comes in one package. It hurts less than what you're using to check your finger with the glucometer.

And as Christina alluded to, there's so much advertising, direct-to-consumer advertising, patients are frequently coming, asking us about these medications. And in fact, with semaglutide is now being marketed for weight loss under Wegovy. I have had patients calling me who are maybe my thyroid patients before it's even in pharmacies asking for it. I think the weight loss is really remarkable, especially with semaglutide and the efficacy is there.

The one thing I would just underline that I had thought about is, you know, just being careful of renal function. And dulaglutide seems to do pretty well with patients with CKD and is safer than some of the other ones in starting one of these meds with someone who already has a lower filtration rate because you can have a situation where if a patient can get dehydrated with nausea, vomiting, and can kind of have an acute renal episode and they kind of stay at that lower plateau and I've seen that happen. So dulaglutide seems to be safe for patients with GFRs in the 40s and 50s.

And the other thing that I'm not sure everyone might know is semaglutide, there is a risk of worsening retinopathy in those who have retinopathy at baseline. I always make sure that retinal exams are up-to-date in someone who wants to start Ozempic. And I do tell my patients that especially if they have a history, that there is a possibility it could worsen. And so if someone's undergoing treatment with a VEGF inhibitor, I won't start semaglutide.

Dr. Bird: I think that's really helpful. And maybe I'll pass this to Christina.

Practically when you're starting these, I think a lot of times we may not be getting the A1c results back in real time during an office visit. We may be reviewing between visits and we make a decision to start a GLP-1. How are you practically doing this? Are you bringing patients back into the office to teach them how to use these pens? Are you using some online resource or other resource that can give them some guidance on how to initiate these medications?

Dr. Mitchell: Yeah, that's a good point. And I will admit that I try to lay the groundwork. If I'm seriously considering this, even if it's a new patient visit, I think I try to lay the

groundwork to at least describe the class perhaps during an office visit. But ultimately, with the idea that, you know, say they've had their labs say one or two months before they've seen me.

And so now really the next set of labs may well be in between visits, so to speak. But then if the next set returns and it's obvious that something needs to be added and it makes sense to do a GLP-1, there are a couple options. I mean, we can have them come back to do a nurse visit. Our nurses will teach injection technique in the office, which is very helpful. I do understand that pharmacists can also do this. So sometimes if someone is going to a retail pharmacy, that is another option.

And then, you know, actually the tutorials online for these once-a-week injectables and the ease of use of the respective pens makes it such that if someone is technologically savvy or has a family member who can pull the video up on the computer or the phone is a great option because it can be reviewed even a few times at the moment that you're going to administer the injection.

So I think any of those options are good.

And actually one last one with the advent of telemedicine, we've had our nurses do some televisits where they've done a demonstration in real time on the screen with the patient, which I think is helpful and adds a personal touch. But really, the tutorials and the online videos for each of these products online are pretty helpful and they really are at baseline easy to use.

Dr. Williams: We could talk all day on this. This is a terrific discussion and very helpful to certainly me as a primary care physician. But I'm sensitive to our time. Maybe we just wrap up a little bit. Any closing thoughts about some of the practical aspects of using these drugs, any of the particular categories?

Dr. Mitchell: The only thing I think we didn't mention and it just bears mentioning here because I will kick myself if I don't say it, if I forgot to say it, about the SGLT2 inhibitors, so very rarely, but not rare to us who are on the diabetes inpatient service, will we see the side effects of euglycemic diabetic ketoacidosis.

And that is in the setting of using an SGLT2 inhibitor. What seems to exist in the background is, you know, a need for insulin. In other words, the patient is already on insulin or has a very high A1c, not yet on insulin therapy. And the idea of being NPO for a procedure, which then up being a prolonged NPO for any number of different reasons that might happen in the hospital and with the subsequent development of DKA. But the idea being that the glucose is actually normal, so you see the development of acidosis, but subsequently realize that it's not, you know, our traditional DKA, but rather this euglycemic DKA. And it is due to the SGLT2 inhibitors.

I bring it up to say that we really counsel our patients when we're starting this or at least try to do so, that it should be held before a procedure, ideally even up to a week before a

procedure for which you will need to be NPO. Although any number of days, I mean, you know, three days, five days is probably adequate, but the idea, you know, just to reduce the risk of the development of euglycemic DKA.

You know, so before colonoscopy, I think is a big one, the idea that this med should be held, you know, three to five days beforehand to avoid that is important. And something that I think if you're prescribing the med, the patient may forget, but that the idea that we've provided that counseling at the time of initiation, I think is something worth remembering.

Dr. Williams: Thank you, Christina. Carrie, you had wanted to say something as well.

Dr. Burns: Right. I always think of every one that comes in, I think of kind of their individual A1c goal, you know, with the recent lab tests they have, kind of how far away we are from that, sometimes we're too low, right? And thinking about risks, thinking about the ACCORD trial, if they're high cardiovascular risk, their A1c goal may not be 6.5 or lower. It might be 7.5, it might be 8. So i kind of have that goal in mind.

And then I think about my choices that we've all gone through today. And I think about what A1c reductions they might give me if they're more potent, like the GLP-1 receptor agonist, less potent like a DPP-4. And, you know, then I just think about their costs, the hypoglycemia risk. I'm looking for something for weight loss, I'm looking for something that's weight neutral.

I frequently, with a new patient, will kind of in a very smaller version and kind of just lay out all the categories and there may be more than one right answer for your next add-on therapy to metformin. And you just try one and if it doesn't work, then you go back to the drawing board and you try the next one.

So frequently, as long as you're, you know, making sure that you're looking at renal status and things like heart failure, there's more than one correct answer.

Dr. Williams: Amber, Carrie, Christina, thank you so much for joining the podcast. This is going to be I'm sure a very popular podcast because of the questions that are out there about these agents.

And so we went a little long today, but the discussion was great and it was really important for all of us to hear about it. I really appreciate you all coming on.

Dr. Mitchell: This was a great conversation. Thank you for the invitation.

Dr. Burns: Really enjoyed it. Thank you.

Dr. Bird: Thanks so much, Kendal. This was wonderful.

Dr. Williams: Check with us in a couple of weeks. We'll have another interesting podcast. We could honestly probably just continue this discussion. But I think we'll probably have the

three of you back on so that we can continue this or talk about another area of endocrinology.

Thank you all so much. See you next time.