#387: Diabetes Updates with Dr. Marie McDonnell:
New Tools for the New Rules

Matthew: Paul, I thought about skipping the joke for this diabetes episode, but Paul, I just can't help myself, you know why?

Paul: Tell me why.

Matthew: Well, Paul, it's a puncreatic disease.

[drumbeat]

Paul: You got more.

Matthew: Okay, not good.

Paul: Yeah, that was not. You can do better than that.

Matthew: Paul, most people don't know this about me, but I have a pristine collection of candy canes.

Paul: All right.

Matthew: Yeah, they're all in mint condition.

[drumbeat]

Matthew: Paul, in the summers, I used to do road work. You know what my favorite candy was back then, Paul?

Paul: Hmm-mm.

Matthew: It was a pavemint.

[drumbeat]

Matthew: And then, Paul--

Paul: These puns are mint puns.

Matthew: [laughs] Mints are sweet.

[laughter]

Matthew: Paul, at my grandmother's funeral-

Paul: Oh, my God.

Matthew: [laughs] -there was a bowl of her favorite candy on the table.

Paul: [chuckles]

Matthew: Yeah, they were bereavemints, Paul.

Paul: [laughs]

[drumbeat]

Paul: He searches candy jokes.

[laughter]

Matthew: All right, we'll go with the mint jokes.

Paul: Yeah. Great.

Matthew: Oh, gosh.

[Disclaimer]

[Curbsiders theme]

Matthew: Welcome back to the Curbsiders. I'm Dr. Matthew Watto, trying to recover from what was surely-

[laughter]

Matthew: -a legendary flurry of puns like no other. Paul, tonight on the show, we're going to be talking about diabetes with a fantastic educator, Dr. Marie McDonnell. Paul, how are you doing and [Paul laughs] will you tell people what is it that we do on the Curbsiders?

Paul: Yeah, I'm still recovering. I don't know if this goes out in video, you'll actually see tears in my eyes from the series of puns.

Matthew: [laughs]

Paul: But other than that, I'm okay, thanks. As a reminder, what do we do? We are *the* Internal Medicine Podcast. We use expert interviews to bring you clinical pearls and practice-changing knowledge. And tonight, what an expert we have. We have Dr. Marie McDonnell who talked us all the way through her approach to mostly, I think we focus on type 2 diabetes, but how do you even recognize that? But I'll let you tell us a little bit more about our fantastic guest.

Matthew: Sure. So, Marie McDonnell, MD. She is the Director of the Brigham Diabetes Program at Brigham and Women's Hospital. She is someone who I've known for a long time as I'll mention a little bit on the show, and came very highly regarded by the great Dr. Rahul Ganatra. She's a fantastic educator of diabetes and clinician. This episode certainly showcases that. So, without further ado, let's get to this conversation with Dr. Marie McDonnell.

Marie, welcome to the show. We've known each other for a long time. Haven't talked to each other for a very long time, not because of any bad blood, [Paul laughs] just it hadn't come up. So, welcome to the show. Thank you for joining us.

Marie: Thanks so much, Matt and Paul.

Matthew: Yeah. So, we will tell the audience. When I was a fourth-year medical student, I was very lucky to join Dr. McDonnell on the consult service at Boston U and I learned a ton about diabetes. I think that's probably led me on this path, Paul, to doing a podcast-

Paul: Oh, wow.

Matthew: -where we talk a lot about diabetes, all of that. So, thank you for that.

Matthew: Affirmative, great.

Marie: Oh, that's great. I love it. You're welcome. Happy to be here.

Paul: [laughs]

Matthew: So, we're happy to have you here. And Paul is going to give us a case from Kashlak and we'll get right into it.

Paul: We're going to hear about Ms. J. She is a 39-year-old female with a past medical history noteworthy for hypertension, dyslipidemia, new-onset diabetes, and class 3 obesity.

Her A1c was 6.4% over the past two years, but has now recently jumped to an A1c of 9.6%. She's symptomatic, she's having some polyuria and just generally doesn't feel great. She admits to enthusiastic participation in holiday food celebrations and she's not really been reaching her activity goals in the colder months of the year this wintertime. So, some of the guidelines would suggest starting at least one or more medications considering insulin therapy. I know even in my training, I think, like, once you hit 10 with no evidence behind this to my knowledge, that's when you start talking about insulin therapy.

I guess, for our patient to start, is this someone where we feel like we could maybe make a fair attempt with metformin and lifestyle changes initially before becoming more aggressive? How would you manage this patient out the gate who is presently not on anything?

Marie: Right. Yeah, Paul, it's a great case, because there're a couple of red flags that we want to just make sure that we hone in on before we make a decision. So, one is that she's young. She does have class 3 obesity. Of course, we're seeing an increase in even youth-onset type 2 related to obesity. So, that's not so shocking. But I would want to make sure there's a family history of diabetes just to make sure the story makes sense, because we're seeing even type 1 diabetes or autoimmune type of diabetes that progresses to insulin deficiency pretty rapidly. We're seeing that in adults more than we used to. So, in fact, 50% of what we used to call juvenile diabetes, which is type 1, happens in people over the age of 18. Actually, I think that's moving to more like 25. So, I would just make sure we're not missing that.

Then she also reports that she's polyuric and she doesn't feel well. So, instead of thinking about that magic number where we start insulin, it's better to just listen to the patient. She's telling you she doesn't feel good. That's not a good sign. A lot of patients, as you know, they have an A1c of 9 and they feel fine. Actually, [giggles] that's the biggest problem in diabetes. So, she's reaching out to you for help. I think we have to get to the bottom of her potential insulin deficiency. So, what I would probably do is thinking about treating her for sure. You could always start a therapy, get some blood tests, which I like to talk about, and then see her back quickly, because I don't think anything that you do today is going to make or break the situation. You do have a little time to figure out what the best course is. What do you think so far? Does that make sense?

Matthew: Yeah, because this happens a lot because nowadays almost every patient I'm seeing internal medicine, overweight or obesity is getting annual A1c. So, we have a lot of data on people and you can see where it's been 6 months or 12 months and all of a sudden, they just jump. Like, their A1c goes from prediabetes range 6 to 6.4 and now, it's like this one, 9.6 or sometimes even the low teens. The patients are really hesitant to start anything beyond like metformin in those cases. So, that's why I like this question. What sort of investigation are you doing here?

Marie: I wouldn't make it a big deal, but I would check for antibodies. It's only because we see the rise in this problem of autoimmune diabetes. So, I would check, it's called GAD65 or glutamic acid decarboxylase 65, which is the most prevalent islet cell antibody that we see in autoimmune diabetes. So, I would do that, get it out of the way, make sure we're not missing that. Then you could also check a C-peptide in a glucose level. I would say it's not necessary unless you see the patient's not responding to your next step, but I would get the antibody. Now, how would I treat her? I would want to treat her with something potent, because as you're saying she's falling off the cliff, as sometimes we say. This is actually something that is well described. It's similar to heart failure actually. We talk about the starling curve. I don't know if you guys remember that.

Matthew: Sure.

Paul: Very much.

Marie: You push that failing heart with more fluid and salt retention, and then at one point, you fall off the curve and the dynamics don't allow for compensation anymore. Same thing happens with diabetes in the beta cells. So, we see it in type 2 diabetes and in type 1. So, this sort of dramatic rise in the A1c, we see it. It's classic type 2. But sometimes in a young person, we don't want to miss type 1 diabetes hiding under the cloak of type 2. So, I'm going to say GLP-1 receptor agonist is in this patient's future. If she is who we think she is, which is somebody who has type 2 diabetes, probably familial, she had prediabetes for a few years, so it's probably quite classic. She's going to need something potent, because she's just quite hyperglycemic.

Paul: Before we move past, can I ask this? Seeing the later presentation of type 1 diabetes, is it an increase in prevalence or just an increase in recognition that's happening or some combination of those two things?

Marie: Oh, it's a great question. I think it is both because we saw in the 1990s, all of a sudden, the prevalence of diabetes ticked up rapidly definitely because our definition changed and detection changed. There were more process measures, all of a sudden, coming out from insurance companies to monitor for diabetes with blood glucose at least at the time. Nowadays, we can use A1c. So, I think it's both. But now, in the last 10 years, it's really true rise in prevalence rather than just increased detection. That's at least what we think. I think it's a combination of both.

[music]

Matthew: Let's recap the red flags from this case would be like, because she's young, if she didn't have a family history, that would be a little suspicious. The class 3 obesity makes it a reasonable story. But the fact that she's sick here is what's making you want to be more aggressive about the initial therapy, because you do see a lot of patients who if their A1c tips over a little bit or jumps from 6 to 8 or 6 to 9, and they're not feeling sick, you can start them on metformin. If their lifestyle is terrible and they really clean up the lifestyle, I've seen a lot of those patients just go right back down to the prediabetes range with metformin. But what you're saying in this case, what made you think, because she's feeling sick, you might be more aggressive and start more than one agent upfront?

Marie: yeah.

Matthew: Tell us how the conversation would go here or what you would think. What were you thinking for initial therapy here?

Marie: Yeah, that's great. So, I would basically explain to her that I'm concerned she doesn't feel well, but I do think this is likely progression of what she had before, which was prediabetes. I would go over quick things that she might be doing that are getting in her way. So, juice drinking, soda drinking, milk drinking are the big ones. If she's suddenly going crazy with that stuff, maybe it's a really big factor. But otherwise, if there's nothing really clearly identifiable, for example, let me just add a steroid injection into a joint. Just make sure we're not missing those things. But if we don't have something super identifiable, yes, I would move her to a GLP-1 and I would explain to her that because her A1c is so high, we want to get her under control.

She's young, she's going to benefit from that really rapid control and weight loss, because the guidelines now say, "Let's focus on weight loss and glucose control at the same time for

all patients with obesity and diabetes." Then it's such a potent agent. It's similar in potency to insulin and it'll give her so much more in terms of benefits. So, I think I would move there quickly. Now, I would get those lab tests. If she does have some concern for insulin deficiency, I would bring her back in and make sure that we do start insulin. But again, that's a small percentage, but don't want to miss it.

Matthew: The other question would be a lot of patients are just unwilling to go from no medications to giving themselves an injection. So, sometimes I'm starting metformin, lifestyle changes, and then maybe having them meet with a pharmacist or bringing them back within a month, and then we're talking about insulin, or like a GLP-1 agonist, or something like that. We can see how their finger sticks have done over that time, but it can be a little tricky to just get them right on a weekly injection if they're not used to taking any medications, in my experience.

Marie: I agree with you that it is hard. I'll tell you that it's easier lately because there's so much unfortunate in some ways of the GLP-1s, you know?

Matthew: Yes.

Marie: So, it's a little easier to move there early on with patients. I would say the current guidelines would say that it would be okay to start with a GLP-1 in this patient in the setting of her obesity, but the guidelines would also be supportive of metformin with behavioral lifestyle change.

Matthew: Yeah.

Marie: So, just to put that out there, I think you can offer either one. Probably the best thing to say for this patient is to bring her back soon.

Matthew: So, this was a question. One of our listeners, [unintelligible [00:16:29] on Twitter had asked about this like, "Is metformin still first line or why is metformin still first line for diabetes?" That seemed to be something now that the newer, the SGLT2 and the GLP-1s are around. We did get that question a lot. I think you answered it already. It's still a right answer to do metformin, especially if the patient's not sick. But in certain cases, if you wanted to be more aggressive as you said, GLP-1s are potency wise as strong as insulin, so it might be reasonable to start with them. But anything else to comment on that?

Marie: That's it. I think the other piece we didn't touch on was cardiovascular risk, which is with a big emphasis in the guidelines. For example, if you did the ASCVD risk or the AHA 2018 cardiovascular risk score, if you do that and somebody's really more than 13% or more than 15% risk of having an event in the next 10 years, you should be considering something that can impact that risk. So, that's another chip there that might help you move to a GLP-1 in the case of where you need potency to. I would say metformin is never wrong, unless, of course, it's completely contraindicated. It's never wrong.

Matthew: Right. Okay. So, eGFR under 30, those people were not starting it, but otherwise-

Marie: Yeah.

Matthew: -we're pretty liberal with the metformin, okay.

Marie: That's right.

Paul: Unless the patient is game for anything. "Whatever you say doc, you're the one who's in charge. I just want to get better." What would have to be different here where you would consider insulin as an initial therapy? Is there a percent threshold that you would go over

which you have to be really symptomatic, I guess? What would change that calculus for you, where you'd be offering--? You check the labs. It seems like this is type 2, where you'd be doing metformin, plus an insulin or an insulin plus another therapy, or ever at this point.

Marie: All right, Paul, that's a good one. I would say, really, there's one answer. It's weight loss and polyuria. The two of them together is insulin deficiency and we should just treat that. Otherwise, insulin is not the right medicine for type 2 diabetes unless it is really advanced. So, we often can use insulin early on. If somebody has those symptoms, you can use it to help relieve the insulin deficiency, which can actually be transient in type 2. We see that too. A lot of patients in the hospital, unfortunately, getting admitted, we try to keep them out of the hospital when this happens and give them insulin. Then my favorite thing to do is take insulin away.

Matthew: Oh, yeah, it's great.

Marie: [laughs]

Matthew: Yeah. On the prior episode with the great Dr. Jeff Colbert, we were talking about, because you mentioned the C-peptide and glucose, so you do a non-fasting glucose and C-peptide.

Marie: Got it.

Matthew: If their C-peptide is low despite a high glucose, that's suspicious for type 1. But we talked about those catabolic symptoms of weight loss and polyuria. That should make you scared. In this case, we just gave you the polyuria, so not necessarily the weight loss, but she's not feeling well.

Marie: Yeah, she's just making me a little, as a clinician, just want to be more thorough, like all of us.

Matthew: Yeah. Okay.

Marie: Yeah.

Matthew: All right. So, maybe we can go on a little bit and talk about, because I want to make sure we're going to move a little fast. We can come back to some of these topics, but A1c goal. She says, "Okay, my A1c was 6.4. It's now 9.6. What's my goal?" It's been a while since we've talked about these on the show. I know the ACP came out with these somewhat controversial, most people should between 7% and 8%, which I totally understand where it's coming from, but I think some people maybe misunderstand that kind of in tune with the way the 2016 opioid guidelines. Everyone took it so literal. I think that's how people took it. If anyone's below 7%, I should stop their medicine. So, how do you think about the A1c targets now or how do you stratify patients?

Marie: Yeah. So, the one thing that's really important with the ACP is that they really emphasize the ACCORD study. You guys might remember this one. This was a randomized trial similar to the UKPDS, which studied people in the early phases of type 2 diabetes, younger people, the beginning, randomized them to tight control versus less tight. The ACCORD, they were older people and they randomized them to super tight and not so tight. So, less than 8 versus less than 6.5 and they found an increased mortality rate. So, you might remember that. It was cardiovascular risk reduction, which is what they were looking for, which they found the opposite.

The ACP guideline really emphasized that study, even though everyone knows with the post hoc analyses, it was just a bizarre outcome. It didn't make a whole lot of sense. The mortality

risk wasn't related to hypoglycemia, which we thought it would be. In fact, these older people who achieved an A1c below 6.5 had the lowest mortality. It was the people who were in that tight control arm who couldn't do it, they were the ones that died. So, we don't totally know what the best approach is for the older adult, except that we shouldn't be hammering them down. We should not be-- or individuals who has heart disease especially, we shouldn't be trying to get below 7, even aggressively and somebody who's over 65 with a lot of comorbidities.

That's where that comes from, the 7 to 8, I fully respect that because that's where the money is. I always tell my patients the safe zone is actually, if you look at all the data, is below 7.5, like, a safe place. You're not going to have rapid progression of your disease, your kidney disease, for example. But the best place to be if you can do it is as low as you can. Some people would say normal. Isn't that the best? The challenge is achieving that is not necessarily reasonable from a treatment burden perspective, cost perspective. We literally don't have any data on people who achieve diabetes remission level glucose and what happens to them in their life. We don't have any study.

Matthew: That's so rare.

Marie: Yeah, in fact, it's 0.1% or something of people can achieve true remission off medicine. But a good number of people can achieve an A1c well below 6.5 on the GLP-1 receptor agonists or lifestyle plus metformin even, that's good number of people. We think that's good. I think that is very good. There's now a new concept. The diabetes prevention program showed us that, because they followed people for 15 years. They showed us that the more time you spend in the normal A1c range, and then they looked at below 6, actually, the less likely you are to have a complication. That sounds like a no brainer. But the concept is try to spend some more time down in the normal range. Even after you get diagnosed with diabetes, try to get there. If you can get there, spend some time there. That's good for you.

So, her target, our young 39-year-old, is definitely less than 7. We can tell her once she gets to below 7.5 that she's in the safe zone, but when we want to have her really in a guaranteed long-term disease control space, we want her below 7 and even below 6.5.

Paul: Yeah, because ACCORD, we didn't have so many good medications that we have right now too. It's like even the achieving the goals, yeah, insulin and sulfonylurea, we're throwing these things at patients that we now know probably don't have a lot of the effects that we like so much with the GLP-1s and the SGLT2s. I wonder how that would skew differently if we looked at things today having the tools that we have to get the A1c where we think it needs to be.

Marie: Totally agreed. That's another hypothesis related to that study that if we didn't have to use so much insulin that perhaps we-- Maybe not necessarily it was the insulin. It was just not being able to use drugs that were good for the heart, and at the same time as potent, then we wouldn't have seen that effect.

Matthew: Because it's how you get there, right?

Marie: I think so.

Matthew: If you put someone on metformin and lifestyle changes and their A1c normalizes, that's great. That's going to be a good outcome. But if you're hammering them with 150 units of insulin a day to get them down that's a much different situation. So, I think it's like the tools we're using. What was crazy about the newer agents and we've talked about this before is that the SGLT2 studies and I think the SGLT2 studies were the ones right where the A1c

wasn't that different between the treatment and the control groups. It was a much shorter time, like, under five years, and they were able to show benefit versus these other long studies in type 2 diabetes with the older agents. They really tried to push this A1c way down, give them like 10, 20 years and they're still having trouble seeing these outcomes when with these newer better tools in three years barely moving the A1c and you could show it. So, I think, we're in some sense focusing too much on the wrong thing.

Marie: Yeah, you got that right, Matt. It's not just about the glucose. That's we know for sure and that's why these agents, the cardiovascular outcome trials, they definitely were designed to not show a difference in glucose control. They did that on purpose as much as that could be controlled, just so that wouldn't be a factor. It clearly wasn't. But on the flipside, we know that if you can achieve good glucose control with these agents that have other benefits, you get a dual benefit, a dual effect that we're all trying to achieve now. So, yeah, you got it.

Matthew: So, right now, it seems like Paul and Marie, if you agree with blood pressure, with lipids, with diabetes, it's like lower is better, if you could get there safely and with the right tools, which every year we're learning more and more about which tools and which changes are the best. To summarize the A1c thing, so for your younger patients, if you can get them there with reasonable medications, less than 6.5, certainly less than 7, maybe even less than 6.5, what about the moderately sick, which is probably our majority of internal medicine patients? Is that 7 to 8 window okay there someone that already has some cardiovascular or microvascular complications?

Marie: Yeah, I would say, most of the time, and I'll tell you just a couple of anecdotes. The UKPDS really did show that below 7.5 was a much better place than above 8. So, that's where some nephrologists back in the day, they would harp on the less than 7.5 is really what we need, like, if we can just get there for most of our patients. I think that's fair. Once you're around 7.5 it's really about making sure you choose the right medicines for the other things that we're looking at. We're trying to make sure the statin is being adhered to. An SGLT2 would be great, especially if there's kidney disease and then of heart disease if you can get on a GLP-1, it's less about the A1c at that point. But there are some anecdotes.

So, we have some patients who are super sensitive for some reason to glucose exposure over time. They have neuropathy that appears to be progressing aggressively. Once we rule out B12 deficiency or excessive alcohol, it does seem like we really should be controlling their glucose better. It feels like there's data to support that if we control their glucose better, they're more likely to stabilize and not progress. That can be so disabling as you know. Then probably not so much with the kidney though I have to say. The SGLT2s are like magic. When you have somebody sitting in the 7.4 range and they're on an SGLT2, their microalbuminuria drops precipitously. So, maybe it's really just about the neuropathy.

Retinopathy tends to be pretty stable in the 7 to 7.5 range. So, I do like to get below 7.5, but it's based on the preponderance of data rather than what we know is really ideal for the individual.

Matthew: Certainly, our patient, Ms. J that we started with doesn't fit into this, but I have a handful of patients who are older, they have dementia. Maybe we have them on metformin, we're really trying to just keep them less than eight or just make it so they're not having complications of hyperglycemia. In those cases, sometimes, I'm almost forced to use a medicine that I normally wouldn't use, like, a baby dose of glipizide or something like that, which always feels wrong, but sometimes it just seems to stabilize people because you have these people that are 8%, 8.5%, or 9% and you don't want to give them an injection. So, I don't know if you have a trick for those kinds of cases.

Marie: [laughs] I know exactly what you're talking about. At that point, you do have to make sure adherence is well understood by everyone, the patient and whoever's helping the patient. I can't tell you how many incredibly diligent families tell me that, "Yes, the pill box is full and she's doing it right." Then they call me and they say, "You would not believe this, but she's been taking X." This actually just happened last week. She's been taking glimepiride this whole time. I had actually stopped it-

Matthew: Oh my God [crosstalk]

Marie: -because I did switch her to insulin. I did. I had to. She was polyuric and losing weight. This happens at the end of the natural history of type 2, but I didn't want her on both. Anyway, the point being is, it's hard when people have cognitive impairment. Nonadherence or screwing up the meds is so incredibly common that we just want to make sure we understand that they are taking what we're prescribing. Matt, I do try to use DPP-4 inhibitors in those patients. Try might not be the right word.

Paul: [laughs]

Marie: I use them because they can sometimes help to move an A1c from 9 to in the 8 range, and maybe protect somebody from more aggressive consistent hyperglycemia. They're safe, obviously, in advancing kidney disease. They're not potent as you know.

Matthew: Right.

Marie: What I often do when you have a patient like you're describing and you know the DPP-4 inhibitor is just not going to do anything. I do use low-dose glimepiride. The patient I just described, case in point, I did try that first because I knew insulin was going to change her life. It was going to change her family's life.

Matthew: Yeah. Someone has to go over and inject them sometimes-

Marie: Totally.

Matthew: - if you're not living with family, yeah.

Marie: It puts her at risk.

Matthew: I've been down that road.

Marie: Yeah.

Matthew: So, Paul, I think we have the A1c down, right? So, the younger, healthier people as low as we can safely get it with some of the newer agents, especially if we know they have other benefits, the middle-aged people with some comorbidities if we can do less than 7.5, and then for the older, sicker people, limited life expectancy, just try to prevent hyperglycemia side effects. I think that's about it. Anything else to add there, Marie, before we move on?

Marie: Ah, I think you got it. Nice encapsulation.

Matthew: Paul, do you want to get to the next part of our case with Ms. J?

Paul: So, for Ms. J, we decide to give it a go with metformin and lifestyle changes. She commits to these. We do some counseling, we give her some of our favorite handouts. She comes back for follow up several months later and she's not been able to make the changes, some of them because life is challenging and it's hard to make these changes. She's gained some weight and she's also not tolerating the metformin very well. She's having some GI

side effects that just are not making it worth her while right now. So, we repeat her A1c and unfortunately it has crept up to 11%. She still would like to avoid injections if at all possible and would like to try another oral medication. I would love to hear your approach to this situation specifically. We've alluded to the SGLT2s a couple of times now, but I would love to hear if this is someone where you might consider starting that as initial therapy or if there's a reason why you might not in this particular patient.

Marie: Right. Well, I'm going to assume, Paul, that we did evaluate her beta cell reserve and all of that stuff. So, she doesn't have type 1, this is type 2, and that's a really high A1c [unintelligible [00:35:47] don't have a threshold above which **we would start insulin**. I don't think insulin is the right medicine for her right now, but she's starting to make me nervous because we don't really know this, but we think even the first year A1c over 10% probably has some impact on your overall health. If you ask her, she very likely has a yeast infection and she's probably really miserable. So, I always make sure I do have my injectables in my pocket, so that I can take it out and make it very comfortable and casual. I often show videos to my patients. Sometimes, I accidentally put on a video of a child doing an injection.

[laughter]

Matthew: Are these from the manufacturer website or YouTube? Can we share this link?

Marie: Yeah.

Paul: TikTok video. [laughs]

Marie: Well, actually there are some pretty awesome TikTok videos, but I don't go there. I usually use the manufacturer ones.

Matthew: Okay.

Marie: But just so they understand that it's okay and that they're so fortunate that actually they're in a situation where they really could do once-a-week injection. That's actually not too bad. They're not really in a safe spot. So, serious things sometimes call for serious measures. I try to make sure they get that. But if really, she's not going to go there, I would make sure that we have her on extended-release metformin, because metformin is a potent drug. I doubt she's taking it. If she doesn't feel good on it, she's probably skipping it half the time, even if she doesn't know she's doing that or remember she's probably doing that. So, I would try that and make sure she's drinking enough water.

Now, the SGLT2 inhibitor is not ideal for somebody this hyperglycemic in my practice, especially for women but I'm going to say across the genders, because you do see more side effects related to the glucose, the glycosuria. Women will describe more yeast infections to the point where-- I've seen some pretty serious, like, perineal tinea. You just don't want to go there. You can have a patient requiring antifungal treatment for months if you make the wrong move here. For men and women, you can have that issue.

Then the polyuria is really miserable at this stage with that level of A1c. So, I do have a policy to get people below 9 before I start an SGLT2. That's my little-- Do I break that rule sometimes? Sure. But it's because I'm trying to protect my patient from that side effect that I can predict pretty nicely. Again, make sure you ask her about yeast infection. Women suffer in silence with yeast infections their whole life and they might not connect it to their diabetes. The worst thing to do would be to prescribe an SGLT2 if she already has [laughs] yeast infection.

Matthew: Yeah.

Marie: So, we would get to that. Sometimes, we're busy. So, if I consider the SGLT2, I'll describe that to her, and then that usually will make her say, "Oh, you know, I already have that right now. I have that going on." So, what would I do? Honestly, I would really just encourage her to do a GLP-1. There is an oral GLP-1 as we know. Semaglutide has an oral version and it's probably the best idea if she can afford it. Then I'm just going to put it out there. If cost is a real issue, her A1c is high enough that I would probably do a sulfonylurea temporarily in combination with metformin extended release to get some progress here. We got to get her A1c down. I like the temporary sulfonylurea even in a patient with obesity who cannot access the GLP-1 and is too high for the SGLP2. It works.

Paul: Tell us about the extended-release trick. I've heard this approach before. I'm not sure we've talked about this on the show. But for someone who has GI intolerance, how do you make that conversion? How do you switch them over to an extended release and what does that yield you, because I'm not sure that we've discussed this before?

Marie: Yeah, great. Most of our automatic titration programs that some of us have set up in different practices here with pharmacists. They actually always start with extended release. They don't even bother with the regular stuff because of the GI intolerance. The price is the same now, as long as you don't try to prescribe Glumetza, which is a brand name of metformin, which is completely unaffordable. So, it's the metformin ER or XR and it only comes in 500 milligram tablets. So, patients don't like that because they like their 1000 milligram. But it's a smaller tablet, so some people are fine with it. They can take two if they're on the maximum dose of 2,000. The dosing is the same. So, your max dose will be 2,000 a day, maximum effective dose. You can officially take 25, 50 of metformin. That's what the package insert says, but you don't get much more after 2,000 milligrams.

Matthew: So, they can take all four pills at the same time-

Marie: They could.

Matthew: -instead of having to take two in the morning, two at night?

Marie: They can do that. In my experience, the effect isn't truly 24 hours. So, I actually do split it up and do the two and two, even though that doesn't sound like it makes sense. But for adherence, you got to remember, guys, like 50% of the prescriptions we fill are not being taken in a year that the patients fill.

Matthew: Yeah.

Paul: I just want to be clear, because I feel like this comes up a lot in clinic. So, you're not changing the dose at all.

Marie: I'm not.

Paul: You're just thinking of the side effects, so it's still 1 gram twice a day. It's just a different formulation.

Marie: You got it. That's right.

Matthew: Can I just ask, because I've tried to look this up before like, does it work better? How good is the evidence that that formulation is tolerated better? Because I know that's the hope with it.

Marie: It's a good question. The only studies are with this Glumetza drug.

Matthew: Oh, okay.

Marie: Because remember, metformin is so old. Nobody's going to actually study it. Even the ER is generic.

Paul: Right.

Marie: But Glumetza, it's a different micro-- I forget, micronized formulation. So, it's unique. They did definitely prove in a randomized trial that it's better tolerated. It's not the same as the extended-release metformin. But in my practice, it makes a difference, I would say, 60% to 70% of the time.

Matthew: Oh, that's great.

Marie: Then there's a good chunk, who just-- If they don't feel well on extended release, you just have to say goodbye to metformin most of the time.

Matthew: This is the kind of expert opinion people come to the show for.

Paul: This is why [crosstalk]

Matthew: You're really delivering.

Marie: Okay. [laughs]

Paul: The other trick I've seen is actually having the patient when you're up titrating the dose for tolerability actually start at nighttime, is that something else that you recommend?

Marie: Yeah, I do.

Paul: Like starting at 500 at nighttime, then maybe increasing at nighttime, and then once they start develop tolerance and actually start doing during the daytime, is that a reasonable thing to try?

Marie: Yes, totally. I've seen my internal medicine colleagues do a much better job than I do at slow titration of metformin. I would just say that the extended release allows you to go a little faster. So, you don't have to do that 250 milligrams at night, which I see sometimes and I get it, believe me.

Paul: [laughs]

Marie: But that was when we couldn't get extended release, because it wasn't really cheaper, but it's the same. It wasn't as cheap, but it's actually safer.

Matthew: Yeah. Nowadays the generics, they're on the tier 1, whatever-

Marie: Yeah, they're all--

Matthew: -the lower tier.

Marie: Yeah.

Matthew: Okay, great. All right. This is awesome. Okay. So, our patient has an A1c 11%. If she's really not going to do an injection, our preference would be a GLP-1 agonist because of the potency here. But if she's really not willing to do that yet, we can temporarily maybe put her on a sulfonylurea with metformin to try to get that down, make sure she's tolerating metformin. We just talked extensively about the metformin ER or XR, maybe as a trick if she hasn't tolerated the plain metformin. Then with the SGLT2 would be a bad idea because of yeast infections and just because her sugar is so high, she's going to not feel well on it. So, we wouldn't want to add that just yet.

Anything else about this that we should talk about? Well, we had a question from a listener, **Mike Kelly on Twitter** asking about pancreatitis. What if he [unintelligible [00:45:15] said, "Oh, yeah, this one time I had a history of pancreatitis six years ago and we're not sure what it was from or does it matter if it was from gallstones or alcohol?" Would that make you just say no GLP-1?

Marie: So, the answer is no. Meaning, we wouldn't say no, that's a double negative.

[laughter]

Matthew: Okay. So, it's not an absolute contraindication.

Marie: It's not absolute. In my practice, gallstone disease is very common. People, as they get older, over 40s and 50s, it's comorbid almost with diabetes pretty frequently. So, most pancreatitis in the patient with diabetes is gallstone, or gallstone sludge, or whatever you want to call that, and triglyceride related, hypertriglyceridemia. That's actually probably about half. Then there's probably 20% alcohol unfortunately and the rest are really idiopathic. It's the idiopathic folks that I guess we worry the most about, but if we take a history and there's a family history of pancreatitis, that patient might have actually mutation in the CFTR gene, which is like if you're heterozygous this is the CF gene for cystic fibrosis. If you're heterozygous for that, which isn't that uncommon, you won't have CF, but you can have pancreatitis.

Matthew: Oh, interesting.

Marie: We want to make sure we get a family history. Family history is gold, if you have it. So, don't prescribe the GLP-1 in somebody who really has that clear underlying risk. I would say ongoing alcohol use is on the list, of course. So, you wouldn't prescribe. A couple of other examples, pancreatic divisum, if somebody has a known, that's rare. But I have a couple of patients, believe it or not, they referred to me [Matthew laughs] with the question, "Can I give them a GLP-1?" I wouldn't because I think that patient really is at risk of recurrent pancreatitis. The patient had the one-time episode and they have all the risk factors for gallstone disease. It's probably gallstone sludge.

We would prescribe the GLP-1 and probably go slow. The patient who had a cholecystectomy, because after the pancreatitis we would say, let's go full speed ahead. Then lastly, the patient with hypertriglyceridemia, those patients respond really well to GLP-1 therapy. Unfortunately, we see the 5,000 sometimes, these patients have familial hypertriglyceridemia, they respond to GLP-1. So, we should treat them with GLP-1s. Not avoid it for the pancreatitis risk, if that makes sense.

Matthew: I have never heard that before. That's good to know, that's good to know. I did not know that.

Marie: [laughs]

Paul: I didn't know it. I saw it. I actually had a case where what I was convinced was pancreatitis from hypertriglyceridemia, and then the A1c came back afterwards, and it turns out actually her triglycerides are up because she had uncontrolled diabetes.

Marie: Yes, they go together.

Paul: That's why she felt so crappy. So, it was a fascinating case.

Marie: Yeah. You have to be confident, but maybe you would go a little slower with the GLP-1, but I've never once seen recurrent pancreatitis in a patient with hypertriglyceridemia

who I've lowered the triglycerides with the GLP-1. It's basically you're treating the problem with the GLP-1. So, let's not forget, sorry to babble on, but the pancreatitis risk is very low. It's very small. It hasn't really borne out in the trials statistically speaking. So, it's real, but the risk is small and it's probably those unique people with the risk.

Matthew: So, along these lines, because on a recent episode, we talked about SGLT2s, the general fungal infections, which can be quite bothersome, but those are the main risk with those. So, on this one, I wanted to focus a little bit on the GLP-1 agonist, especially now that we're considering using these as long term for weight loss. I know they've been around for around 10 years. Is there any signal that you're worried about safety wise with patients taking these for decades going forward? I know patients with cancer, I think were not really enrolled in the trials, at least some of the trials that I looked at. So, I'm not sure what you think long term safety wise.

Marie: It's a good question. I'm going to say, to be fair, there are a couple of papers showing that actually there is a higher risk of finding thyroid cancer in people on GLP-1s. The problem with those studies, and the most recent one was published in diabetes care about a year ago now. I think it was actually not quite a year. The problem is that what you find is these are all retrospective. What you see is that somebody on a GLP-1 is more likely to have a thyroid ultrasound. So, it's a detection bias. The thyroid ultrasound will reveal a micropapillary cancer, something very small and nearly benign some percentage of time, maybe 10% to 15% of the time in patients that doesn't impact their survival.

So, actually, at our recent conference, we talked about-- This would be hard. I don't think I would ever counsel a patient this way, but you could literally say to the patient, "Do you want to take the risk of dying of a heart attack or do you want to take the risk of having a thyroidectomy someday? Because that's basically all that's going to happen to you when you have thyroid cancer." It's very unlikely for you to develop an advanced form of thyroid cancer in general. We have never seen that in GLP-1 trials. So, that sounds a little somber, but it's true. So, it looks like maybe we see more thyroid cancer, but it's probably detection because your patients are more likely to say, "Well, can I just get an ultrasound to make sure?" So, that's number one.

Number two, pancreatic cancer you're more worried about, I'm sure, Matt. We don't see an increased risk of pancreatic cancer even if there's a family history. So, there's no reason to withhold GLP-1 therapy in people with a family history or any concerns around pancreatic cancer. We don't prescribe it often if somebody has a history of a neuroendocrine tumor in their pancreas, which is rare, but we see that here at the Brigham. [giggles] We try to avoid getting in the mix there, certainly a personal history of pancreatic cancer. I think you're just asking for little trouble there, because I think that's why would you want to increase the concern around survival there.

Matthew: You've mentioned the benefits a couple of times. It seems like it's mostly a class effect. The first one out was exenatide. I don't know that we've seen the same benefits, but the newer, the dulaglutide, the liraglutide, and semaglutide, I'm not sure, those seem to have these cardiovascular benefits. Is that how you think of them?

Marie: Sure. Yeah.

Matthew: If people are thinking of going to these agents, do you have go-tos?

Marie: Yeah, for sure. You are so good, Matt. You got it right on there. The early ones-- [crosstalk]

Matthew: I told you, you set me on a good [crosstalk] a long time ago.

Marie: [laughs] I don't know. Yeah, the first ones that were very homologous to the Gila monster spit, you remember that story? For some reason, they haven't been shown to have a cardiovascular benefit and they're very different and distinct from the newer GLP-1 receptor agonists. So, liraglutide was the first to be shown to have the cardiovascular benefit, and then we saw semaglutide and-

Matthew: Dulaglutide.

Marie: -dulaglutide, like, where am I going?

Matthew: Yeah.

Marie: They should listen to you, Matt, not me. But you're right. So, I think that way. So, a couple of caveats, I think the stroke risk reduction in semaglutide studies is very impressive. So, I do think of that drug when I think of my patients who've had a TIA or for other reasons, I think, are at higher risk of stroke, that could be just because of the population that they studied, for sure, because there's not a good reason to think there would be a different effect, but I have to say it's really impressive.

Then for slow titration, because we talked about that a few times, you can only do that with liraglutide once daily or semaglutide because you can actually manipulate the pen in a much more nuanced way. Of course, tirzepatide is the new guy. So, probably worth discussing a little bit, I don't know if you want to [laughs].

Matthew: Yeah.

Paul: That was literally the next question I had is sort of what's your experience [unintelligible [00:55:22] There was a lot of wild enthusiasm. I think I had to prove for exactly one patient. But where are we headed with that and how are you using that in your arsenal?

Marie: So, I'm just going to tell you I like it a lot, and I'll tell you why I like it, and then I'll tell you we need to see the cardiovascular outcomes to be confident, because we haven't seen the pivotal trial results. But the reason I like it is because there are six doses and the company has realized that if you start low and go slow, you benefit the patient. It's very patient centered and I like that. The thing that we learned about the GIP, GLP-1 dual agonism is that for reasons that folks are still trying to figure out, it appears that GIP agonism allows the GLP-1 to do its thing with less GI side effects.

So, the two of them work together, but it's really the GIP allowing the GLP-1 to do its job without hurting the patient, [laughs] if you want to put it that way. So, that's based on actually animal data and its nice data. So, I like it and it works and the patients love it-

Matthew: And the weight loss, we talked to this--

Marie: Yeah.

Matthew: Yeah, it's 20% to 30% in a fair amount of the patients which is insane.

Marie: It's insane. Yeah, in diabetes it's less, which you'll always see. It's complicated, but it's really-- [crosstalk]

Matthew: I did not know that. Okay.

Marie: Yeah. There're two reasons, actually. My weight loss team tells me, it's because when you're in a weight loss study and that's the whole goal and nobody cares about your

A1c, they're giving you so much diet advice. And so, your patients in those trials are learning how to eat and taking the med, whereas in the diabetes studies, they're just given the med.

Matthew: Oh, interesting.

Marie: Maybe a little support around diet.

Matthew: Yeah.

Marie: So, probably you can get 20%, if you can really hammer home some reduced calorie diet advice.

Paul: Let's get back to the case and let's even for a change give the case a happy ending. So, let's say we start Ms. J on a weekly GLP-1 agonist. She tolerates it beautifully. We titrate the dose monthly like experts.

Matthew: [laughs]

Paul: She manages to find time in her life for therapeutic lifestyle changes and they work beautifully. There's a diabetes education program that she attends faithfully. She has wonderful peer support and we get her A1c to, let's say, 7.4. Let's put her right in the sweet spot. She's feeling well and thinks you're the greatest doctor on the planet. So, let's end the case there. So, thank you for saving our patient, Marie. I think this is probably the right time to see if you have any take-home points for our listeners.

Marie: Yeah, sure. That was great. Yeah, you know what I would say is insulin deficiency, we started talking about that ironically in the beginning. But it's pretty uncommon in type 2 diabetes. But when you see it and people are really miserable, losing weight and catabolic, recognize it and make sure that we don't miss that, but otherwise, very high blood glucose is common in type 2 diabetes, and it takes work, and happily we have potent agents to do that. So, that's number one.

Then I would say the second thing is just make sure you do consider what goals you have for the patient in terms of selecting the next therapeutic. Potency is important, but also the agent to help with weight loss, organ protection, and glucose control, we're trying to do all those three things at the same time. When we can do that at the same time choosing the right agent, it really pays off. I guess, the last point is trying to get a lower A1c in a young person, but trying to getting into that safer zone below 7.5 and the patient who's really up there is a good first step. But trying to get lower for the younger person is important for a long term.

Matthew: Yeah, we're going to do that.

Marie: Yeah, of course, we do that.

Matthew: Our audience very sophisticated at this point. With your training here, they're going to get everybody, yeah, to that goal. So, thank you.

Marie: Awesome.

[music]

Paul: This has been another episode of the Curbsiders bringing you a little knowledge food for your brain hole.

Matthew: Yummy.

Paul: Great. Get show notes at *thecurbsiders.com* and while you're there, sign up for our mailing list to get our weekly show notes in your inbox plus twice each month, you'll get our Curbsiders Digest recapping the latest practice changing articles, guidelines, and news in Internal Medicine.

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Paul: And as always, I'll remain Dr. Paul Nelson Williams. Thank you and goodbye.

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