Editor's Note: This is a transcript of an online course released in January 2024. It has been lightly edited for clarity.
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Cases

Today we're going to discuss mechanisms of action of GLP-1 receptor agonists, addressing how they intersect with pathophysiology in type 2 diabetes. We're going to compare and contrast the agents within the GLP-1 receptor agonists class. We're going to formulate strategies to ease patients' safety concerns and improve tolerability to GLP-1 receptor agonists which along the way helps us, as cardiologists and people who have not trained in endocrinology or have not encountered this as often, become more familiar with these drugs and make it easier for us to understand their use. We're going to review the justification for using GLP-1 receptor agonists for secondary prevention of cardiovascular disease in patients with type 2 diabetes and apply current evidence-based recommendations that come from professional societies, the ACC, the American Diabetes Association, American Heart Association and American Diabetes Association and EASD, about how to individualize integration of GLP-1 receptor agonist therapy in patients with type 2 diabetes.

The info provided here comes from consensus reports and guidelines that have now been developed that are all fairly recent. We're going to see more updates to these, given how much data we now have in this area about managing diabetes that's provided from the ADA and the EASD, Standards of Care in Diabetes from the American Diabetes Association and then the joint ACC/AHA Guideline for the Management of Patients With Chronic Coronary Disease.

Let's put this into clinical context of why is this relevant to us. Here's a case that I saw in clinic. I think it's one reason that when you go into their chart, you see so many of the key issues that are relevant for this field. This is a patient, CJ, who was returning at 60 years of age. He had a history of atherosclerotic cardiovascular disease, type 2 diabetes, and he's coming back for follow-up. When one digs into CJ's chart and looks at a chart review and the evolution of their history, I think it's quite striking. At 56, he had a visit with his primary care physician. He, at that point, was overweight, had hypertension, carried a label of having prediabetes, had evidence for dyslipidemia. This is very common. Our primary care physicians see these such patients perhaps more often than we do as cardiologists. Although, they do cross through our hands for a lot of different reasons: on consult services, for electrophysiology issues, hypertension management, and lipid cholesterol management. Here is this patient, CJ, at 56, seeing his primary care physician, already on lisinopril/hydrochlorothiazide 20 mg/25 mg split and atorvastatin 20 mg. Blood pressure 132/80. His BMI is elevated at 31. Here's an A1C that people will most easily identify as prediabetes: it's 6.2%. This does not qualify as having frank diabetes, but it's clearly not a normal A1C. We're looking for that to be less than 5.8%.

The LDL is 110, triglycerides are modestly elevated at 220—this population more often will show up as having [this issue]. The PCP note says, as we often hear from patients, that they want to focus on their lifestyle efforts: just joined a gym: he's about to turn a page. This is particularly timely as we turn into a new year. People make their resolutions that they're going to make a change and things are going to be different.

What's interesting about CJ is that prior to having another visit with his primary care physician, having missed a visit, that he presented to the emergency room at 58, having chest discomfort and evidence on EKG of an inferior NSTEMI. He was treated in the emergency room, became asymptomatic with sublingual nitroglycerin, had a small troponin leak. Went almost immediately to cardiac catheterization that showed a 90% lesion in the right coronary that was considered to be the culprit lesion, underwent stenting, percutaneous coronary intervention (PCI). He also had disease in his LAD, left anterior descending, that was not thought to be a culprit, was not intervened upon, but clearly has atherosclerosis. And, as we know and this case highlights, it's a systemic issue and so, even though we've intervened on what was thought to be the culprit for his NSTEMI, it's obvious he has coronary disease elsewhere.

Now, at 59, he does have a follow-up visit with the primary care physician. His A1C is 7.5%, and he receives the diagnosis of frank type 2 diabetes. His weight has further increased to a BMI of 32. This highlights another observation from the field that often patients are presenting first with their cardiovascular disease prior to their diagnosis of diabetes. We know that the runways for the development of cardiovascular disease, coronary

disease and diabetes are long runways and often, it's the cardiovascular events that manifest first before we see the presence of diabetes. I think it's relevant to this particular case.

Finally, here we are at his cardiology visit. He's asymptomatic. His regimen has evolved. He's on atorvastatin 80 mg; ezetimibe 10 mg has been added. He's on lisinopril/hydrochlorothiazide as before. He's now also on metoprolol 50 mg, aspirin, previously on a second antiplatelet agent, but that's no longer on board. He's on metformin that had been initiated for his diabetes back when he was first diagnosed. He's now had sitagliptin added at 100 mg. His blood pressure is 124/80. His BMI is still elevated at 32. His LDL is 70. We can talk about that. His triglycerides are 152. His A1C is 6.9% on the metformin and the sitagliptin.

Let's think a little bit more about this patient if we were seeing them in our practice on those meds, with that level of control. One of the ways to think about this is what if we, in terms of cardiologists and our cardiology practices, could offer this kind of patient a 25% reduction in major adverse cardiovascular events? What are the opportunities in this individual at 60 who's now undergone this intervention? He's on a statin, his blood pressure's okay. [What about] this excess weight and increased BMI and the presence of diabetes? What are the ways in which we could further improve cardiovascular outcomes, on top of what we already know as having worked, with the advances we've had in cardiology management?

This brings us to the very exciting evidence that has unfolded in terms of GLP-1 receptor agonists. Here's the data from SUSTAIN-6, a cardiovascular outcomes trial looking at semaglutide in patients with type 2 diabetes. It was a study that was oriented towards looking at major adverse cardiovascular events. It was driven by FDA requirements to prove safety. What we saw in SUSTAIN-6, which aligned with some prior data we had with liraglutide, was a study that not only showed that there was no harm from using semaglutide, but there was actual benefit. A significant 26% reduction in MACE, as one sees here across the top line. As you look at the individual components of the primary endpoint of major adverse cardiovascular events, they certainly align with that overall primary endpoint.

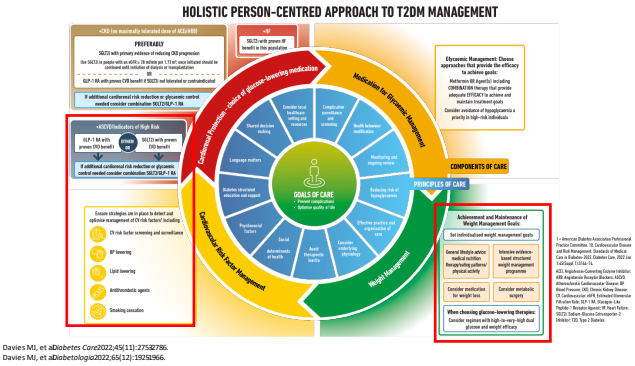
That's certainly been exciting. We're going to go through how that data is integrated into management practices. I do want to point a little bit to the future, go back a little bit into CJ's history: what about when he was presenting here even earlier? What about when he was presenting with an elevated BMI subsequent to his cardiovascular intervention? At that point, were there even earlier opportunities for reducing risk? Would there have been an opportunity back then—once he had shown stability and was not in his acute coronary syndrome immediate phase—for reducing cardiovascular risk on the order of 20% here, prior to his having the diagnosis of diabetes?

This case highlights how the field has advanced. What I'm referring to is the recently published data from the SELECT study using semaglutide as an intervention for improving cardiovascular outcomes in individuals who did not yet have diabetes.

The primary endpoint on the cardiovascular outcome efficacy response that showed a 20% reduction in events in people who did not have diabetes—very much like CJ after that intervention—of patients with obesity or just overweight and showing the 20 percent reduction superiority for the semaglutide.

Guideline Recommendations

Our focus is on diabetes, and we have seen the advent of GLP-1 receptor agonists and SGLT-2 inhibitors now integrated into our practice. There are a variety of excellent documents that help outline that. This is a schematic that comes from Diabetes Care and Diabetologia summarizing this kind of integration of these new agents into a more holistic approach for managing such patients. Once a patient has diabetes, we're thinking about their glycemic management and thinking about the use of these drugs. Metformin does improve diabetes. It is a cornerstone, has been used for a long time, safe, effective, generally weight-neutral to perhaps some modest benefit, and certainly a major component of treatment.

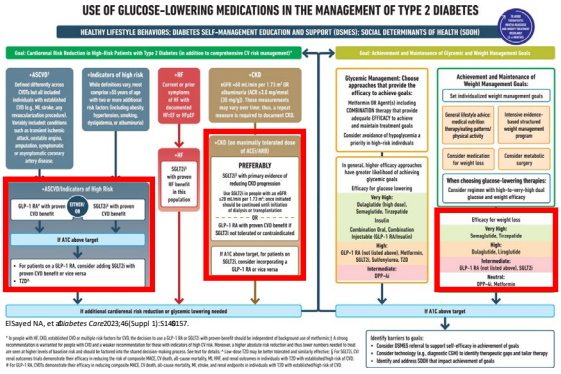


Davies MJ, et al. *Diabetes Care* 2022;45(11):2753–2786.
Davies MJ, et al. *Diabetologia* 2022;65(12):1925–1966.

As part of this holistic approach, it's not just about managing glucose. There's also a question about weight management. This is derived from the fact that we've known for a long time that obesity and overweight are contributing to the constellation of abnormalities that show up in these patients. This holistic approach begins to incorporate thinking about weight loss and weight management as part of one's integrated approach to diabetes in general. Providing lifestyle advice about managing weight, and also thinking about drug therapy for weight loss, and even surgical interventions for improving weight, as not being a component that should be ignored.

This holistic approach in the modern era continues with cardiovascular risk factor management. That, given the high-risk nature of diabetes that one can't ignore—cardiovascular risk—this circle is an integrated approach. It's not that one is ignored for the other. Cardiovascular risk factor management in such patients is critical. Screening, looking for appropriate blood pressure control, lipid and LDL lowering, use of antithrombotic agents, the importance of smoking cessation; and into this integrated approach are these drugs that now have cardiovascular benefit. GLP-1 receptor agonists and SGLT-2 inhibitors and specifically agents that have proven in cardiovascular outcome trials that they have benefit. This is highlighted in this approach in patients who may not have already manifested cardiorenal issues. The integration of the cardiorenal axis in terms of thinking about how to optimally manage such patients. The presence of CKD—we have considerable evidence—as we'll touch upon with SGLT-2 inhibitors and using those, given the evidence for reducing chronic kidney disease progression. We also have GLP-1 receptor agonists and additional data about how they may impact this cardiorenal axis. We've had more data to date with SGLT-2 inhibitors, but more coming as we'll touch upon. Importantly, lots of evidence about the benefit of SGLT-2 inhibitors in patients with heart failure, in terms of decreasing readmission for heart failure complications.

Coming out of *Diabetes Care*, the ADA consensus guidelines, of how to think about this kind of approach to agents that have cardiovascular benefit and cardiorenal benefit and how to integrate that into practice. It's a question I often get from my colleagues. As one goes around and interacts with other colleagues, the question about "Well, how do I sort out all of this new data?" In this particular approach in these guidelines from *Diabetes Care*, you see starting at the left that if there's ASCVD present or high-risk patients who may not have yet had an event, you want to take advantage of managing patients with diabetes with these agents that have benefit. We've seen that in CJ, he returns to clinic on sitagliptin and metformin, but he's not receiving management with agents that have established cardiovascular benefit. In a patient with ASCVD, using a GLP-1 receptor agonist with proven cardiovascular benefit or an SGLT-2 inhibitor with proven cardiovascular benefit, and that there may be times where those are combined. But certainly easy to do when the A1C is above target and not optimal, but I think we see the field evolving to saying, "Well, even if a patient has an appropriate A1C on an agent that doesn't have cardiovascular benefit, we may want to think about swapping out therapy rather than having someone have to stop a drug, have the A1C be higher to then add one back that has cardiovascular benefit."



ElSayed NA, et al. *Diabetes Care* 2023;46(Suppl 1):S140157.

As you see there, the top line, established ASCVD is easy. We often see those patients where we may be encountering other patients that are just at high risk or warrant some other kinds of considerations. Patients who have heart failure, whether it's heart failure with preserved ejection fraction, reduced ejection fraction, moderate ejection fraction, we have evidence for SGLT-2 inhibitors having benefit in this population. The presence of CKD also considering that as a factor and as a risk issue, then in the presence of appropriate ACE inhibitor and ARB, that including an SGLT-2 inhibitor that has evidence of reducing CKD progression and then also a GLP-1 receptor agonist if, for some reason, the SGLT-2 inhibitor is not tolerated or contraindicated. And looking for integration with some of the new data that I'll show you.

For a patient whose A1C is not on target and [who is] already on one of those agents, adding the second agent is also considered reasonable. I want to highlight, because these are the patients we often see in this red box, patients

with established cardiovascular disease. We're going to have much more attention being paid to chronic kidney disease as an important issue.

This guideline highlights that one is combining the use of those agents with also thinking about weight loss and lifestyle and how this couples to appropriate glucose management, but although these 2 classes of agents, the GLP-1s and the SGLT-2s, do lower glucose, they're having cardiovascular benefit. We wouldn't ignore the glucose aspect, but it's really moving on to other agents for additional glucose control once you have these on board. As part of this guideline, it's also [good] to think about agents that may have an impact on weight loss. And this right side is oriented to the additional steps one takes if the A1C is not yet at an appropriate targeted level.

We've had more evidence since then about cardiorenal risk reduction in patients with type 2 diabetes, especially when they're at high risk. If there's ASCVD and high risk, then a GLP-1 receptor agonist or SGLT-2 inhibitor, looking for agents in those classes that have cardiovascular benefit that's been proven. When there's heart failure, SGLT-2 inhibitor has been the primary agent moving on. In the presence of CKD, an SGLT-2 inhibitor or a GLP-1 if the SGLT-2 is not tolerated or contraindicated for any reason. Or if the A1C is not at goal and you're already on one of those agents, then moving on to a second agent, like the patient with CKD who's on a SGLT-2 inhibitor and still needs additional glucose control using a GLP-1 receptor agonist.

These guidelines really focus on these pillars of reducing diabetic complications, and I really can't reinforce this enough. I mean, diabetes is important, glucose is important, but it's really the complications of that. We want to control glucose because it has a strong relationship with microvascular disease, but we also want to make sure we're controlling blood pressure, seeing that as part of appropriate diabetes management. That we have the LDL controlled and are thinking about the lipids; that's part of appropriate diabetes management. And that we're, with a goal of reducing diabetic complications, also including agents that have known benefit. This is not independent of lifestyle modification, diabetes education; it's in addition to. There's the importance of the interventions we make for lifestyle that also matter, but this is really our focus.

ADA guidelines from 2023 are quite similar, looking at optimizing medical therapy for preventing events, as we talked about all of these various interventions that we have, and then really focusing on SGLT-2 inhibitors and GLP-1 receptor agonists. I think this recurring theme of the integration of this approach into managing diabetes highlights and reinforces for us how important it is for us, as cardiologists, to embrace this data. These are cardiovascular outcomes we're talking about, and we need to be comfortable with the use of these agents and comfortable not only with how to use them, but how to explain them and how to discuss them with patients, understand what the patient's preferences are and make sure that we're able to educate patients about why they would want to be on these drugs and the kinds of benefits they would offer them.

Those guidelines point to, as they often do, the levels of evidence we have. The highest level of evidence is class A, as you see here with a class of recommendation being class 1 strong, that the benefit greatly outweighs the risk. What you see here under recommendations is, in patients with chronic cardiovascular disease who have type 2 diabetes, using an SGLT-2 inhibitor or GLP-1 receptor agonist with cardiovascular benefit reduces MACE. Then there are steps through high value, intermediate value under this B-NR categorization that there's value even at cost. Cost is always something our patients present to us. We're hoping that we'll continue to see this improve over time with costs coming down and coverage increasing, based upon this evidence.

In terms of weight management in those guidelines, we do have this consensus expert opinion that, in chronic cardiovascular disease, BMI should be part of that. Thinking about that, probably most of you are not doing waist circumference. It can be a helpful tool in terms of identifying risk that's embedded in that, as we saw with CJ. That that should be part of what we're thinking about, given the evidence of a relationship between overweight and obesity and adverse outcomes, and that we need to include counseling on how to target that, that's part of our management strategy for these patients.

Pathophysiologic Targets

Let's go through some clinical questions related to what we've been talking about. In terms of GLP-1 receptor agonists, what are they invading on in terms of mechanism? We know there are many inputs into why people develop type 2 diabetes and why that type 2 diabetes is associated with adverse cardiovascular outcomes. States of insulin resistance: the beta cells of the pancreas are trying to compensate for that, trying to maintain appropriate glucose control, but there are shifts that are quite systemic involved with type 2 diabetes, including increased hepatic glucose production which is

not something that we would want as part of the pathophysiology of this. We have changes in lipolysis. There's impaired appetite regulation contributing to the obesity. The incretin axis is part of what the GLP-1 receptors and their endogenous actions are involved with and we know that this is dysregulated. There is, in type 2 diabetes, increasing glucose reabsorption that are all part of this and all of these are inputs that ultimately lead to this complex picture in type 2 diabetes that's associated with atherosclerotic disease and its complications.

The GLP-1 axis is part of this incretin axis, and I think what's supportive of what we've ultimately seen in terms of response to these drugs is multiple layers of the pathophysiology of type 2 diabetes being impacted through activation of GLP-1 receptors through these GLP-1 receptor agonist agents-. Systemically, one sees improvement in the metabolic picture, like in the liver shown here, increased insulin sensitivity, decrease in abnormal glucose production, changes to these agents that involve the brain, lipolysis, how the pancreas is responding, what's going on in the GI tract, changes in the kidney, changes in the muscles. A much bigger picture that relates to GLP-1s and GLP-1 receptor agonists that really can ultimately be thought of as what they are in terms of the endogenous natural system that's at work here. It's a satiety signal. There's intriguing research that maybe not all the benefits necessarily come through the GLP-1 receptor, but that's really something in terms of clinical issues may be relevant to outcomes but is more of a research topic. We know that the GLP-1 receptor agonists are having these effects, and it'll be exciting to see as we learn more and more about why are they having these benefits.

Glycemic/Nonglycemic Effects

One of the examples of why this is a complex area is when we look at the data between different GLP-1 receptor agonists and even on what's been studied more is just their effects on glucose. We know that there are short-acting GLP-1 receptor agonists, as outlined here, exenatide, lixisenatide, as you may have encountered in your practice, and then there are long-acting GLP-1 receptor agonists, dulaglutide, exenatide with a longer efficacy, liraglutide and semaglutide, which is available in both injectable and oral forms. There are differences in terms of these 2 different categories and that becomes important.

The fact that you see differences in the glucose responses really highlights what we now know in terms of their nonglycemic effects that we have seen differences in terms of nonspecific glucose responses; a separation between long-acting agents and short-acting agents.

Those changes seem to correlate perhaps with differences in cardiovascular outcomes. We've not had cardiovascular outcome benefits with the short-acting agents. The benefits have been with the long-acting agents and our use of agents that have established cardiovascular benefit is quite important to us.

The field is continuing to evolve. We now have tirzepatide which is a dual GLP-1 receptor agonist and combined with a glucose-dependent insulinotropic polypeptide, a GIP response. This has an augmented effect on glucose-dependent insulin secretion, changes glucagon's secretion, slows gastric emptying. It's been approved as an adjunct to diet and exercise improved glycemic control in adults with type 2 diabetes and also an obesity indication. Trials are underway in terms of their cardiovascular benefits, but [they are] an important additional component of our tools in terms of diabetes management and weight management.

Cardiovascular Benefits

What about GLP-1 receptor agonists in patients with type 2 diabetes and ASCVD or at high risk for ASCVD? Well, the ones with proven cardiovascular benefits out of clinical trials are liraglutide and semaglutide. That's always one indication of what's on the actual label. The FDA cardiovascular disease label is shown there in terms of reducing major cardiovascular events, CV death, non-fatal MI, non-fatal stroke, in patients with type 2 diabetes and established cardiovascular disease. Dulaglutide has shown benefit on major cardiovascular events or cardiovascular death, nonfatal MI, nonfatal stroke in patients with type 2 diabetes who have established cardiovascular disease or multiple cardiovascular risk factors. So, hereyour GLP-1 receptor agonists that have proven cardiovascular benefits and how the FDA lays out those indications.

Meta-analyses now have started to appear showing what one sees when you combine data. You can see here, from a variety of different GLP-1 receptor agonist studies, now combined in a meta-analysis. You can see at the bottom in the white diamond or the whole meta-analyses that is on the right side, the GLP-1 receptor agonists showing benefit in terms of 3-point major adverse cardiovascular events. You look a little bit more specifically in terms of the red, you

see that it's the liraglutide, semaglutide, dulaglutide that are falling to the left side of the line and helping contribute to that. They certainly line up with this idea that this is a way to improve outcomes.

What about GLP-1 receptor agonists in patients with type 2 diabetes and chronic kidney disease who can't be on an SGLT-2 inhibitor? Well, just as we saw in those guideline recommendations, if the patient can't be on an SGLT-2 inhibitor because it's not tolerated or contraindicated, that then you can consider that and you fall back on the fact that you have cardiovascular benefit with these agents. We do have meta-analysis data that supports improvement in composite kidney outcomes, including macroalbuminuria. Here again, in red, these long-acting GLP-1 receptor agonists, along the left side of this line. And we are going to have more data around this.

FLOW is a kidney outcome trial looking at semaglutide in patients with type 2 diabetes and chronic kidney disease. You see the participants there on the left, they had type 2 diabetes and had evidence for chronic kidney disease, and looking at renal outcomes along the way. We know that FLOW was stopped by their data and safety monitoring board for early benefit. So, we'll have a chance to look even further in this data, but it's certainly supportive of the fact that GLP-1 receptor agonists with cardiovascular benefit may also have specific indications in terms of chronic kidney disease. If the patient can't be on an SGLT-2 inhibitor, the guidelines that we have are certainly appropriate, and we'll see how those continue to evolve.

Individualizing Therapy

What about if you're in a cardiology practice and beginning to initiate a GLP-1 receptor agonist therapy, what about patient concerns, the kind of questions they might ask us? We're really educated around not doing harm, and so what are those contraindications and warnings so that we can be feeling more comfortable in using these drugs? They're actually very well-tolerated and certainly if they've ever had a prior hypersensitivity reaction to the drug, you wouldn't want to use them. A history of pancreatitis has shown up as a contraindication. That was not seen, for example, in the SELECT trial, but then in a cardiology practice, "I'm not going to treat patients who have a history of pancreatitis with a GLP-1 receptor agonist," and that's fine. I think the goal here is for us to all evolve in our use of these drugs and familiarity with these issues. There's nothing wrong with saying, "Well, I'm not certain here," engaging with a colleague and saying whether that's an appropriate use at that point, or interaction with a PCP or an endocrinologist. But the evidence seems to be pointing to that this is not a common or a frequent issue. Pregnancy or breastfeeding, medullary thyroid cancer, multiple endocrine neoplasia, type 2, you can see that these are relatively limited and not very common.

There have been reports about diabetic retinopathy complications with GLP-1 receptor agonists, maybe because the glucose control is improving quickly. I would tell you that doesn't need to be a reason to not use those drugs. They should just be having their appropriate follow-up regarding what's going on with their eyes as a common complication of diabetes. Patients are often concerned about cost. We are used to screening for that within our systems. There are prescription assistance programs from all the drugs we've been discussing.

In terms of initiating drug and monitoring, I continue to learn about this. If you have a patient who has had issues with hypoglycemia or who may be on another agent, instead of just adding it on, you can certainly stop, for example the DPP-4 inhibitor, before initiating. These agents, in and of themselves, do not cause hypoglycemia. It's really more when they're combined with other drugs. We can use these agents, the GLP-1 receptor agonists, for weight loss in people who don't have diabetes. The SELECT trial was in people who don't have diabetes. Hypoglycemia is not an issue. But if they're on other agents that are causing glucose lowering and they start losing weight and have glucose lowering with these drugs, then it is theoretically possible. An easy way around that is stopping other agents without cardiovascular benefit, like a DPP-4 inhibitor. There may be more hypoglycemia in a patient who is on insulin and sulfonylureas and, again, adjusting that can be quite appropriate for not looking for cardiovascular benefit. We know we haven't had cardiovascular benefit with insulin and sulfonylureas, so you certainly wouldn't want to preclude a patient from getting some of these drugs because you're worried about their glucose levels on some of these older agents. Of course, as appropriate, and depending on their A1C.

If you're having issues with hypoglycemia with a patient, you can stop the sulfonylurea, and an easy step is to reduce the insulin dose by 20%. If you don't feel comfortable with that, then involving whomever is prescribing the insulin and saying, "You know, this patient may be running into some hypoglycemia with the addition of a GLP-1 receptor agonist." It's really not a reason to keep someone from an agent with cardiovascular benefit and, in my practice, I don't find that it comes up very often. I am taking steps when I'm initiating these drugs about cutting back other

agents where I am concerned, but in general it's not been an issue.

What are the side effects anticipated? It's always helpful to mention this to patients when you're starting a drug. It does work through GI axis. There may be some initial nausea the patients might have. Sometimes it's with vomiting; sometimes it's not. Anticipating that for a patient it can be part of how they work, that it will get better. It's one of the reasons why we go through a titration approach with these drugs. Diarrhea can occur but it's not as common as the nausea and vomiting. Adjusting diet can help. and we often see the patients tend to move away from some of the high-simple carb, high-sugar diets on their own when they're on these drugs. Slow titration, adjusting the dose including reversing titration if a patient's having an issue and then often you can then go back to adjusting and titrating up. I'll also say that we've had very good experiences partnering with primary care physicians who we're initiating and they're titrating in terms of follow-up.

In terms of outside the GI axis, as mentioned, sometimes hypoglycemia, but if in combination with other drugs. Some patients might have an injection site reaction, also not a big issue. But you can see here, I want to make sure that I've conveyed the more global experience that these are well-tolerated agents for the vast majority of patients and any nausea they have initially often resolves as they make adjustments to their own diet, smaller meals, and then also adjusting the dose as needed, titrating slowly.

In terms of that, here are some of those points that I've learned along the way, and I think are very helpful is telling patients to eat more slowly, not to feel like they have to eat if they're not hungry, smaller portions can be helpful, avoiding lying down after meals is a good idea. Once you feel full, stopping. These are satiety signals, and patients will feel sooner than they would otherwise. To track how they respond to different kinds of foods can be helpful.

If a patient's having nausea, then waiting 30 minutes before you're eating can sometimes ease the nausea. Using some of these foods that are classically used when patients have nausea, like crackers and ginger ale can be helpful. Sometimes patients are triggered by strong smells. This is when the issue arises, and many patients don't have this. If a patient's actually having vomiting, of course you want to be attentive to their hydration and then adjusting their intake, as noted.

What about kidney function? Do you have to adjust dosing from that? Well, here's a nice little schematic summarizing that. I would focus mostly on the long-acting agents, the dulaglutide, liraglutide, semaglutide. There's no dosage adjustment required there. With the exenatide and lixisenatide, you can see that with more advanced chronic kidney disease, they are not recommended. Those are the shorter-acting agents when we really want to focus on cardiovascular benefit. Tirzepatide is that combination GLP-1/GIP and does not need a dose adjustment.

Cardiologist Collaboration

How do you bring this into practice as a cardiologist or within a cardiology practice, whether you're a PA or a nurse? How to bring this forward and do it with the other people also involved in this area? We've had input on that about decision pathways. The fact is, as noted, we're talking about cardiovascular benefit, cardiovascular outcomes. As I like to say, these are our endpoints within the cardiology community, so we can't expect other people to engage around these and to advance them based upon their cardiovascular benefit. We have to be part of that and so there's no doubt that a need for collaborative, interdisciplinary care exists, and I think that one way to think about this is that now that we have agents with cardiovascular benefit, we need to be screening for patients. Just like we saw with CJ, they may have diabetes subsequent to their already having cardiovascular disease. We need to find those patients and be able to offer them drugs that are appropriate. We want to manage their cardiovascular risk factors broadly and then we need to incorporate use of these drugs that have benefit. That can happen through prescribing them ourselves, which I think is important and is our focus here. Using these agents when their use is straightforward and obvious, in cases where you feel like "Well, I'm concerned about some other kind of issue or initiating the drug myself," that's where those discussions with our partners in managing patients, the primary care physician and endocrinologist, can be very valuable. Getting guidance or even just raising this to them such as saying, "I think that a GLP-1 receptor agonist or an SGLT-2 inhibitor would be very beneficial for this patient, I see that they're not on one yet, is there a reason why and how about initiating this?" It's all part of that ongoing dialog of collaborative, integrated, interdisciplinary care, but given the evidence we've had around cardiovascular benefits, I do think it is part of what we should be doing as a cardiology community.

The guidelines really underscore that this is an area that has a broad effect on our patients, has broad effects on their cardiometabolic health and it's not surprising that it requires a multidisciplinary team approach to improve outcomes. Make sure risk factors are under control, take advantage of these multiple visits someone might have with various providers to make sure that patients are getting treated appropriately and using those various visits. Engaging with the patient around so that they understand why you're using these drugs for cardiovascular benefit and the shared decision-making that is so important as we're talking to patients and has an impact on them staying on a drug rather than stopping it, as we know so often happens.

We really need to learn about this area, partner with our colleagues, get involved with the management of these patients. I would tell you that this has been an exceptionally exciting area of medicine in general and certainly within cardiology. Just tremendous advances that we've seen with these 2 classes of agents, SGLT-2 inhibitors and GLP-1 receptor agonists. Our focus today has been on GLP-1 receptor agonists and the opportunities they provide for reducing cardiovascular events in patients who have diabetes, with some of their effects being through an impact on overweight and obesity. New data that's now come out, even outside of diabetes, we'll see integrated into the guidelines, but now's the time to begin taking advantage of that data that we have about how the use of GLP-1 receptor agonists can improve outcomes in the patients you're managing and improvement in outcomes that we're responsible for, as we outlined here, these major adverse cardiovascular events.