CARDIOMETABOLIC HEALTH CONGRESS

Symposium from 2022 Annual: Assessing the Evolving Role of GLP1-RAs to Reduce Cardiovascular Risk: Emerging Evidence, Evolving Guidance, and Expert Perspectives

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How Did We Get Here? An Overview of GLP-1 RAs Therapy in T2D

FEMALE VOICE 1: Thanks, Earl. We next have our primetime CME symposium entitled, "Assessing the Evolving Role of GLP1-RAs to Reduce Cardiovascular Risk: Emerging Evidence, Evolving Guidance, and Expert Perspectives." The Chair for this that I'm going to turn over the stage for is my dear friend, Dr. Vanita Aroda. Good to see you.

VANITA R. ARODA, MD: So good to see you.

FEMALE VOICE 1: All right, now we're leaving and you're going to be up here in charge.

DR. ARODA: Welcome everyone. Good afternoon. Hello to the people in the balconies as well. What an honor to be here. The Congress has such phenomenal sessions every year. It's a great pleasure for me to introduce two dear colleagues that I get to work with day in and day out at the Brigham. Introducing Dr. Marie McDonnell. She is the director and chief of the Diabetes Section at Brigham and Women's Hospital. Dr. Jorge Plutzky, the director of Preventive Cardiology. We've had such wonderful conversations via Zoom, that it's so nice to see each other 3D in person.

I'm going to hand it over. You already know the basic announcements. This activity is provided by Partners for Advancing Clinical Education and CMHC through an educational grant. All your disclosures can be seen on your iPad. The presentations may contain off-label discussions. You already know how to use the iPad. Please keep the questions rolling. Now without further ado, Marie.

MARIE E. MCDONNELL, MD: Thank you, Vanita. I want to say thank you to the organizers for inviting us all to be here because I think we feel like a team up here and I hope you get that vibe, too. We really are talking about team care when we're talking about cardiometabolic health.

What I wanted to do is introduce the GLP-1 receptor agonists. This is a very celebrated drug, but there is a nice story. A lot of you have heard it, but I'll give you my brief synopsis of it and then hopefully segue into Dr. Plutzky's talk, really diving deep into why we're here today, which is talking about the heart health implications of this drug class.

What I'd like to do is first talk about why we're here, which is the cardiovascular disease impact in type 2 diabetes and why that is so relevant when we're talking about GLP-1 drug development and where we are today. We will spend some time on what we understood about the GLP-1 receptor or GLP-1 molecule early on, and how that evolved over time. We'll then go to

glycemic control, which is really the reason why this drug was developed and certainly highly relevant today, going beyond glycemic control, introducing the concept of cardiovascular benefits with this drug class.

Then where do the GLP-1 receptor agonists sit in the guidelines today, relatively hot off the presses with a combined guideline from the ADA and the European Association of Diabetes?

Okay, so first we all know that there is what some people call the cardiovascular gap or the glycemic paradox, which the first part of that story is that we know that people with diabetes--we've known this for a long time--have more cardiovascular disease. You can see this across the board. It varies, the cardiovascular conditions, including stroke and any heart condition without angina.

These data are from the U.S. and are dated back the early part of this century. If you look at recent data, interestingly, this is from a large population of VA patients in the U.S. also. You can see that difference is lowering. It's coming down. Before the year 2000, we used to say about three- to four-fold times the risk of cardiovascular disease, in people with diabetes versus non-diabetes. In the early part of this century, it's about two times. But just recently from recent data, it looks like that gap is narrowing a little bit.

The question is, at least my patients ask for sure: Is this related to glucose control? It's a reasonable question. We've been asking this for decades. The first question we have to ask I think is helpful is to understand the relationship between glycemic control and heart disease. This U-shaped curve that you see here relating the hazard ratio of mortality on the Y axis and the hemoglobin A1c on the X axis has been repeatedly seen in many different studies and environments. This is again from that VA population just recently published in the past few years.

You can see that it's disadvantageous to have an A1c above 7 and below 6. Now, this has been shown in the U.K. about a decade ago, maybe even longer. We've seen it in many datasets. We've actually seen it also in a large prospective study you all know probably or many of you, called the ACCORD study. We saw very similar pattern where it appears that there's probably some glycemic sweet spot for cardiovascular health. This is complex data understood. The question is: are more people arriving at the sweet spot? Maybe that's explaining the reduction in that relative risk.

Now this makes sense because we know actually from large prospective studies, including the UKPDS study in type 2 diabetes in relatively recent onset in adults that every 1% drop in the A1c in that particular study is associated with decreased risk of not just microvascular disease, but in the

25-year follow-up studies in actually macrovascular disease as well.

Now you can see the reduced risk in microvascular disease, for example, looking at general microvascular disease. We see reduced risk of 37% lower extremity amputation, 43% less potent potentially in the macrovascular space with reduction in MI by 14%. Again, this is the long-term follow-up of patients after the arms separated. But we did see that glycemic control probably makes a difference.

The problem is and really the end of my section here is that glycemic control hasn't improved. The reason we have seen an improvement in cardiovascular outcomes is probably not at all related to glycemic control and it still remains elusive for many. Imagine if we could achieve better control, I guess is what my point is.

You can see here from NHANES data that in fact, if you follow either line looking at the percent of individuals achieving an A1c below 7 or below 8, it's worse or the same if you look between the early part of the century to more recently. It's about 50%. About 50% of our patients are in the sweet spot. These are data from Europe looking similarly, even with aggressive treatment with three oral agents. You can see only 50% of individuals are achieving that A1c below 7% or around 7%.

Then I think what tells this story even in a stronger light - in a more glaring light - is the recent publication we saw, the GRADE study. This is a comparative effectiveness study that did include a GLP-1 receptor agonist. Over time in this study, unfortunately in this study, there were different ages, as many of you know, different people to randomized to different agents, but they were managed over time to achieve standard-of-care targets. Unfortunately, 70% of subjects at the end of the study had an A1c above 7. This is in the setting of a clinical trial. It's hard to do this.

Where does the GLP-1 sit in this story? Let's go back a little bit. Let's talk about the molecule before we get to the heart. First, as we have learned and I would say learning about the incretin molecules started in the early 1900s, probably in 1932. The observation was initially made that glycemic control measured in the way it was at the time, which was crude, was different when an oral load of carbohydrates was taken by animals and humans versus an IV load. There was something about the gut that made a difference on the glycemic impact of food.

The GIP molecule and the GLP-1 molecule were eventually identified and isolated. As we know, GIP and GLP-1 are both secreted mainly by the gut. There are other areas of the body that can produce these incretins, but the incretin effect is described as these hormones entering the bloodstream from the GI tract and traveling to the pancreas to specifically the islet cells in the

pancreas.

We're going to focus on GLP-1 for now. GLP-1, what we learned over time is that what it does is it enhances all fundamental beta cell functions. It's almost like a fuel injector for the beta cell. This is a picture, sort of a cartoon of the beta cell. I like to call it the four quadrants of the beta cell, where the beta cell needs to sense glucose. It needs to shut this potassium channel, which is what sulfonylureas do. It allows calcium to enter the cell and then eventually, insulin is secreted. These four quadrants require a lot of action, a lot of signaling. What the GLP-1 molecule does is when it gets to the beta cell and binds to its unique receptor, it basically supports the function of all of these.

This is what was so exciting in the development of the drug. Because we thought that perhaps in type 2 diabetes specifically, this mechanism could be dulled and potentially could be activated with therapy.

What we also learned interestingly as that was being studied is that GLP-1 secretion appears to be impaired before diabetes in any years potentially before the development of hypoglycemia. These are old data from Eva Rask. She was able to show that in individuals with different degrees of glucose intolerance, which is what you see here in the lower lines with the--we had the worst glucose tolerance and then the higher one. I guess I have a pointer here somewhere perhaps. Here you have the lowest insulin sensitivity or worse glucose tolerance, and this is the best glucose tolerance. You can see she was able to show the GLP-1 secretion appeared to be better in those with a little better glucose tolerance, not surprising to us now.

But the interesting thing about this in the prediabetic state is that we were accumulating evidence that prediabetes alone increased cardiovascular risk. Before glucose was elevated, we knew that there was cardiometabolic risk and risk of MI. The question came early on - actually more than two decades ago - about whether GLP-1 was related to the link between this metabolism and cardiovascular disease, even before we thought about hyperglycemia.

This was studied actually in animal models. I like this particular one because it's easy for me to understand, not being an animal scientist. In this particular study, GLP-1--there are a few represented here--was infused into animals that were predisposed to atherogenesis. For example, the apoE mouse, knockout mouse. They were able to demonstrate that over time, in the short time the animals were studied, that there was less atherogenesis in this particularly prone mouse in those who received continuous GLP-1 infusion. There were several other studies like this, but telling the story early on that probably there was a link between GLP-1 function and atherosclerosis and heart function.

We then also over time learned that GLP-1 doesn't just go to the beta cell.

That's a very simplistic understanding really of what the molecule does and probably glucocentric endocrinology focused perspective. But we know that GLP-1 has receptors all over the body. I think that's fair to say. We're potentially most interested in the brain for appetite and satiety and also the heart for not just potentially improving cardioprotection, which we'll talk about, but does have specific effects, including on heart rate and reducing blood pressure. Glycemic control as I mentioned was the real focus of drug development for the GLP-1, so let's talk about that and then we'll move on to understanding it in broader depth.

First, what are the agents available today? The only one missing here is lixisenatide, which is available, but it's mostly prescribed in a combination drug in the U.S. But as you can see, we have different drugs with different pharmacodynamics, which you can tell by how frequently you dose them. Exenatide is twice daily. Liraglutide came later. It's once daily. Exenatide is once a week. It was made long-acting. Then dulaglutide and semaglutide followed as once-a-week injections. Then lastly is the semaglutide oral tablet.

What we've seen in terms of drug development is not just the change in pharmacodynamics to make it easier for patients with the depo-type drugs, but also dosing. We've seen increased dosing opportunities in dulaglutide, as well as semaglutide. Liraglutide, as we know in its other form as Saxenda, which is the weight loss drug, does go up to 3 mg. That has been a big change in the drug development of the different agents.

Titration and then looking at the drugs across both A1c lowering and weight lowering. The A1c lowering of the drugs is similar, very excellent I would say, and as we'll talk about, highly potent. Weight loss does depend on dose. They're all dose-dependent, but we can see 2 to 4 kg of weight loss with most of the agents.

The other point I wanted to make was what is unique about this drug development is exenatide and lixisenatide are the only two that were actually developed from the originally discovered exendin-4, which is a GLP-like molecule secreted in Gila monster venom, which I'm sure you've heard that story. This is the native exendin-4-derived molecule. The rest of the molecules are human GLP-1 derived and therefore, may be telling us the story about how these drugs might differ in terms of their overall effect.

What we know is that the GLP-1s are highly effective in terms of glucose lowering. This is a network meta-analysis of about 450 trials relatively recently published. You can see here just looking at the A1c lowering on the right that the subcutaneous semaglutide as included amongst all these drugs was the most effective. What was surprising perhaps to some of us is that we can get as much efficacy, if not more, from semaglutide and other GLP-1s compared to insulin. Now we're understanding that GLP-1s, all things being

equal and understanding the patient with type 2 diabetes is as or if not more potent than insulin.

Beyond glycemic control--and I'm going to pass this baton to Dr. Plutzky in a moment so that we can dive deeper--of course, the big story with GLP-1s beyond the glucose-lowering effect and weight-lowering effect was its effect on the cardiovascular system and events, specifically. Over many, many years with cardiovascular outcomes trials that were launched after 2008, we see that the GLP-1 receptor agonists across the board have for the most part--excluding exenatide and lixisenatide essentially--we have reduced major adverse cardiovascular events.

Let's dive in a little bit to our concerns about the drug because I think in my practice I wish I could have more of my patients on these agents. But there are real issues and there are some not-so-real issues. First of all, GI intolerance as we know is very common with this drug class. Up to 30% to 40% of my patients will report nausea, but the nausea is really just the beginning for many patients. We see constipation. We see GERD. Many of those side effects are manageable and that's what we really try to educate our patients on, is how to prevent them and manage them. If we have time in our discussion, we can talk about how each of us does that. But very important to give anticipatory guidance to our patients on this.

Gallstone disease has been reported. I think we saw it in the liraglutide trials more so than the others, possibly due to patient selection. But most of the pancreatitis that we have seen in practice potentially due to GLP-1s has been related to the gallstone disease. The question of whether these drugs cause pancreatitis is really still a bit of a question because it's not entirely clear. We know people with diabetes have more pancreatitis than people without diabetes in general, regardless of their treatment. We also know that there is some biochemical elevation in lipase and amylase in people who are asymptomatic taking these drugs.

It's a little bit questionable I think. In the clinical trials, I think that we've seen that it's not a serious clinical problem, but we still do screen our patients very carefully and make sure that patients who are uniquely at risk for pancreatitis should not be on the drug.

What's not real is the thyroid cancer issue. My fellow today just asked me, "Dr. McDonnell, what about if somebody has a new nodule that could be cancer? Maybe we shouldn't prescribe the GLP-1." Actually, that's not borne out in any of the longitudinal studies, but also in our scientists that there is no GLP-1 receptor in our thyroid glands in humans. I think they're clearly established in rodent thyroid beds, producing the C-cell neoplasia that was reported in the preclinical studies before exenatide was released. So it's not an issue in humans.

Pancreatic cancer also happily has not borne out in clinical trials to be a concern.

Minimizing nausea I think is really important. Titration and time are the tools that we have. I will just point out that when you compare the IDegLira trials--this is a combination of insulin and liraglutide compared to semaglutide trials--not only do you see much less nausea, but what you look - and I thank Dr. Aroda for pointing this out to me years ago - you can see the titration schedule is much lighter. It's just 0.36 weekly in this trial versus a forced titration in the SUSTAIN trials where you go from 0.25 to 0.5 to 1. Starting relatively low and going slow is the strategy to producing better outcomes. I always remind my patients after about a month that they're going to feel much better, and this is borne out in most of the trials.

Now cost is the other side effect and I think I'll skip over this as we're going to come to that in our discussion, but we're still dealing with that in our patients. Let me just take a few minutes to let you know what the current guidelines say about using GLP-1s in practice.

First of all, putting the patient in the center is highly appreciated because if we don't do that, we will fail in achieving the goal we want for the patient, whether that be glycemic control, weight control, or reduced cardiovascular events.

Now this particular guideline does a good job of highlighting all of the areas we need to explore, including medications for glycemic management, weight management, cardiovascular risk factor management, and then cardiorenal protection. When we think about all the principles of care around the patient, what we're really saying to the patient is I want to help to protect your organs and help you with quality of life as you age. I do want to help you control your blood sugar and your weight. This is really what we do in type 2 diabetes. How do we do that? the guidelines suggest metformin as first step. As you read trough, the next step is an agent that will offer the patient both efficacy and organ protection.

Weight management is our consideration that we think of for most of our patients. We have to. Of course, GLP-1 receptor agonists are top of the list for weight management, a very important goal in the guidelines. Cardiovascular risk management includes non-glycemic-lowering agents, as we know. Then lastly, it's the cardiorenal protection that is really as we can see here at least a quarter of what we have to think about. In the clinic, the guidelines haven't really changed in the last few years, where we see for people with CKD we're preferring SGLT-2 inhibitors or GLP-1 receptor agonist is SGLT-2s are contraindicated or not as effective.

This is important. if additional cardiorenal reduction or glycemic control is

needed, you can consider combination of SGLT-2 and GLP-1 receptor agonist therapy. If ASCVD is your primary focus, the GLP-1 receptor agonist, that is where we should prioritize that drug class. Then the SGLT-2 again can be used either as an alternative or a therapy to enhance that effect.

Lastly, heart failure should push us to the SGLT-2 inhibitor because of the outcomes in that drug class, which I won't discuss in detail, but we've seen in other talks during the conference.

All right, I went over time, but let me just summarize here that the key points are that impaired incretin signaling is really an important contributor to type 2, but probably also to cardiovascular disease risk. GLP-1 therapy is both potent and safe for both glycemic control and weight loss, which are major priorities for the care for people with type 2 and prioritizing GLP-1 therapy for those with not just ASCVD, but those with high risk for ASCVD is now mainstream practice. Barriers, which we will discuss, include cost, access, and education to patients for side effect medication.

With that, I'm going to pass the baton over to my colleague, Jorge Plutzky.

GLP-1 RAs for CV Risk Reduction in T2D: A Closer Look

JORJE PLUTZKY, MD: That was great, Marie. It's a pleasure to be here and have a chance to welcome you all to Boston where really sort of Marie, Vanita, and I are part of a welcoming committee. We're glad you're here in person. We are not responsible for traffic, the cost of your lobster roll, Tom Brady, Tom Brady's divorce. None of things are really our fault, but we're glad you're here. We're especially glad to be here talking about really so dramatic for us and for cardiologists who have thought about these issues for a while and now really for the field of cardiology as a whole.

I think for context it's important with that evolution to make sure that we know where we're coming from. Here's just one example of one study that I pulled looking at a tremendous amount of effort by a lot of people and a lot of patients trying to look at whether treating diabetes could improve outcomes. This particular approach was one that had to do with the extent of control.

You see at the end here at the very bottom that there's just nothing. This is really where we're stuck and it led to a lot of thinking about this. This is from our own discussing these issues about the glucose paradox and so many different inputs into the arterial wall in the patient of diabetes that really just didn't have to do with glycemia. Maybe that was the issue, as we wrestled with this question about why we are not seeing some improvement with this unequivocal risk in cardiovascular disease among patients with diabetes. You had lots of answers for that and wringing of hands trying to understand that,

that the trials were wrong and off. They were too short. They were too small. They started too late in the disease process.

A1c was a problem as being our biomarker. We were looking at the wrong endpoints. We were looking at the wrong strategies, insulin-providing versus insulin-sensitizing, so a whole organizing theme for a large trial. Maybe we just had the wrong agents. The older agents were increasing risk and keeping us from benefit and the newer agents, at least at that time, also had hurdles maybe from side effects and maybe they weren't any better.

That changed. It is worth framing the discussion around that change because now we have to think about these things differently. LEADER was really the one that got us going with this with liraglutide. Let's go back and make sure we understand this because this is what we leverage in clinic, sitting across from an individual patient trying to decide how to improve their outcomes and how to begin having colleagues who may have even greater opportunities for improving those outcomes, like primary care physicians, understand that we're learning from the LEADER study.

This of course was a safety study, driven as you know by changes at the FDA about what would get an approval. But this study was under four years and here are the patients at baseline, very typical for the kinds of patients that we see in clinic. About 72% of them had established cardiovascular disease, 25% of them had some form of chronic kidney disease that appears combined very often in clinics, and they had diabetes for quite a while. Their median A1c was 8.7 at the start of the study.

Here's the outcome with LEADER. Primary endpoint going in the right direction really stunning to those of us who had been looking for those for so long and not finding it. When you broke it down, you see these trends for cardiovascular death, a decrease in MI. Not a lot signal in this particular trial over a short time period for stroke.

Then semaglutide also shows cardiovascular benefit. Primary outcome here is quite impressive. There were discussions at the time that maybe this was limited. Maybe there was just something about LEADER that let them realize that.

We can pull that back and see significant decrease in nonfatal MI. Nonfatal stroke is quite important and often overlooked. It's something that we'll return to around this.

Now the field has continued to evolve. We have more information. We can begin pulling this. Let's just what we look at, what we're seeing across the board. Here are the two trials we talked about. The green arrows are a positive outcome. Blue is a trend. Orange is going in the other direction. In terms of MACE with LEADER and SUSTAIN-6 with lira and sema, you see this

positive outcome and the breakdown of that. Of course, we look at this and say: “what’s driving the benefit?” Because the field is moving on now. We have to look for that.

As Marie alluded to, we didn’t see it with lixisenatide and exenatide. At least the trends were there for EXCEL. There are discussions about why that may be the case and why it wouldn’t be across the board. Then this notion of yes, GLP-1 is a mechanism. I’ve seen it with two different drugs with lira and sema, but then we also see it with dulaglutide. Oral sema of course is added to this and you see in PIONEER-6 a trend in the right direction. These did not have the same adjudication, the same study populations. Clinical trials of course are very challenging, but it’s nice to see this in the same direction for oral sema. Then we also have amplitude and another positive cardiovascular outcome.

The data from this can be pulled and we can start looking at this through that lens, recognizing the limitations of meta-analyses, but at least it’s a chance to now have more patients. These are a couple of these. Marie showed you one top line of this meta-analysis, but I just want to dig a little bit deeper into it.

Here are the MACE outcomes in these eight trials, some 60,000 patients. We see here on this identity curve that there is clearly in terms of the major adverse cardiovascular events benefit that’s showing up on MACE. Of course, that’s where most of them were oriented towards. A lot of discussions now in the cardiology community around the kidney, thinking more about the risk embedded with that and also how we’re going to begin thinking about these agents, as we’ll talk about some more in the case about SGLT-2 inhibitors and GLP-1 receptor agonists. What’s worth noting and worthy of further discussion is the composite kidney outcomes in these GLP-1 agents and that one can see things in the right direction for that, even in the context of the SGLT-2 inhibitors and all the evidence that they’ve provided.

Stroke I think is quite interesting. This top half here is fatal/nonfatal MI. But here’s fatal and nonfatal stroke. Again, we see the risk reduction. When you pool across these trials, encouraging. I think we’ll continue to drive this area. It’s interesting in talking to patients that they’re often much more concerned about having a stroke than they are about having a stent placed. Their neighbor went in, had a stent placed, and was back the same day. The idea of a stroke is much more motivating and has been an issue for us to think about. How do we continue to make progress around stroke and all the components related to stroke?

We have seen of course very important effects of SGLT-2 inhibitors on heart failure and heart failure hospitalization. This think about that in terms of the GLP-1 receptor agonists. The top half here is all-cause mortality, which is of course very challenging as an endpoint, especially with all of the therapies

and the treatments the patients in trials are getting. We want to be careful not to overstate that, but at least we do want to see it. Sometimes those don't all line up, where you're not seeing an improvement in cardiovascular events as strong, but seeing a change in mortality in the right direction here.

Here's hospital admission for heart failure that is on the right side of the identity curve and supportive of the idea that you can have an impact through many different ways of modulating the system.

Marie showed a different version of this, but I do think it helps us think about what's happening here and how we begin deconvoluting this and thinking about mechanism. The insights into mechanisms are going to drive application, better understanding of which patients are going to benefit, better predict who to give these agents to, and continue to pursue other alternatives in terms of reducing cardiovascular events in people.

We know the receptors are widely expressed and they are present in these locations. Obviously, the effects on eating, satiety, and weight loss are very important. Gastric emptying is I think quite relevant as you lose weight. Of course, that has an effect on insulin sensitivity and potential effects on the liver, but we know that the GLP-1 receptors are present in the heart, so now we have a basis for saying yes, there can be an impact through these other organs, but that directly in the vasculature one can see effects that we know are quite relevant for cardiovascular disease.

We've known cholesterol and LDL as being very important, but here are other aspects to how we're thinking in the modern era about atherosclerosis and its complications that involve inflammation, local effects of glucose, ventricular function, responses to ischemic injury, and also the level of vasculature and how you're going to change these various parameters. I didn't want to show you another study in mice, but there is some very intriguing work of when you delete the GLP-1 receptor in the endothelium, that you can have effects in preclinical models that are very supportive of this idea of a direct effect in the vasculature.

Of course, we know from a clinical perspective that these are going to relate to blood pressure and weight. I just want to again draw a circle around - put a frame around - these sorts of issues because to some extent, we can gloss over all the various components that are very relevant clinically and may not show up in a clinical trial when you ask how you look for the intersection of these various parameters about individual patients and their vascular system, not just the heart.

We're talking about the vasculature, but we have the myocardium and all components of that and its relationship with obesity is quite well recognized. Now that is macrovascular, as we've been talking about, but it's not just the

coronaries and the heart. It's also very relevant for stroke, as we've touched base upon, and peripheral arterial disease, so very challenging to change peripheral arterial disease outcomes. And yet, we know that those patients often have considerable cardiovascular risk.

One of the things we are trying to do is make sure that we're leveraging all the things that we know about reducing cardiovascular risk in patients who just have a history of peripheral arterial disease, making sure their LDL is under control, making sure their blood pressure is appropriate, and making sure that their diabetes is being managed either for a potential effect on the peripheral arterial system, which is very hard to modulate, but also the cardiovascular risk that those patients often have that isn't recognized.

Cardiomyopathy exists both for diabetes and for the patients who have had events and now of course we recognize heart failure with preserved ejection fraction. It's so common amongst patients with diabetes. Then one of the ones you don't hear enough about is arrhythmia. We're always concerned about ventricular tachycardia, but atrial arrhythmias. The data for the impact of weight loss in a patient who's had atrial fibrillation and has either gone back into normal sinus rhythm or who's undergone ablation, who's actually had an electrophysiologist buzz a circuit inside their heart to stop their atrial fibrillation, the impact of weight loss in those patients is very impressive and raises the possibility that this could yet be another component of what's at work here.

We really do think obesity is a pervasive driver through indirect effects, so modulation just when you're decreasing fat and often visceral fat on inflammation, hypertension, elevated triglycerides, hyperglycemia. These go hand in hand and are often together. You have effects on other cardiovascular disease states. I'm just pulling up two here, not just the diabetes, but also issues like sleep apnea and its risk for cardiovascular disease. Cardiovascular death and arrhythmia are quite important.

Of course, we think a lot about how obesity may be a direct mediator and a target in and of itself directly linked to cardiovascular risk and issues, the source of a whole host of mediators that are linked to atherosclerosis, potentially very relevant. Obesity is a functional stressor in terms of how much the heart is working. Hypoxemia and hypercapnia are linked to that. These may all be part of improved outcomes, but there's also the possibility that some of the benefit here could be because we're avoiding issues with hypoglycemia. It's just another embedded component at work.

I've loved this slide for a very long time because as you go around the circle here, the things that we think about in a preventive cardiology clinic like mine and in the world of cardiology, we can link the adipose tissue to mediators associated with each of these components. Certainly, this is a very plausible

hypothesis.

With a GLP-1 receptor agonist of course we know that they have a significant effect on body weight. Certainly tied into that is the possibility that some of these outcomes are influenced by that. We're going to learn more.

As the field moves forward, I am particularly excited about SELECT - 17,500 patients who don't have diabetes. They don't have diabetes and just as we've seen that evolve with SGLT-2 inhibitors, we're going to see that evolve with GLP-1 receptor agonists. Establish cardiovascular disease, prior MI, prior stroke, symptomatic peripheral arterial disease who are undergoing treatment with semaglutide versus placebo, but they had to have had a BMI greater than or equal to 27. This will certainly begin to push that forward. We would expect many of these patients that have components of prediabetes and metabolic syndrome, but let's see. Let's see how this pushes us along and further informs us in terms of the field.

Of course, that data is now robust enough that we've seen it integrated into guidelines. Here are the ADA standards of care in 2022. In the cardiovascular section, before we start talking about managing A1c, you see this discussion about patient and clinician preferences and integrated into that is SGLT-2 inhibitors and GLP-1 receptor agonists. Considering one class versus the other is going to be part of our staging and discussion, I think.

Here of course are the glucose guidelines and their management. Again, in this new world that fortunately the data is requiring us to breakdown silos, to stop thinking about, "That's not my disease; that's not my organ," these are shared endpoints we're after that we now have pulled out this idea of thinking about how we target the right patients for the right drugs and pursue not just their glucose control, but these cardiovascular benefits.

There's been a tendency to think about ASCVD and high risk or established cardiovascular disease as pointing towards GLP-1 receptor agonists, including obesity as a factor in that, and that in the setting of heart failure and CKD, that those patients point more towards SGLT-2 inhibitors. but there is the discussion here about them moving on and perhaps the combination, as my endocrine colleagues are teaching me, may also have some particular utility in those patients. Certainly, CKD in its progression is very relevant.

Here's part of that evolving notion that's exciting to see. Here are guidelines for stroke for neurologists and their discussion about a very active strategy around this. Here's type 2 diabetes or prior stroke or TIA are a high risk for stroke independent of baseline A1c. Patients on a DPP-4, there's an active step here. Yes, let's move towards agents that might have benefit at least on the stroke front, so stopping the DPP-4 or at least thinking about that, and adding a GLP-1 versus adding a GLP-1 in these other settings.

One of the things I love about this slide is that this call to action for neurologists, speaking to their own community, is the exact same language we were using in cardiology. We were using that language in the year 2000, where there's a major piece in the Journal of the American College of Cardiology, that was cardiologists and management of diabetes; a call to action. We know we didn't respond to that call. One of the notions of why we didn't was because we didn't have the data for benefit. So we've moved beyond that. We've turned that page, as we've talked about here. We have that evidence for benefit. Now it's interesting and exciting to see that we have to begin also tackling implementation science. How do we make this happen for patients and for their coverage in a way that's reasonable for them so you can get them access to this?

This is the glucose paradox. I may have to stop showing this slide because this is resolved. We've moved beyond. Yes, maybe many of those factors are at work, but it's hard to with the current database we have to not say that some of those agents weren't the right ones and that we've unlocked this with some of these other approaches that we have.

Positive outcomes and cardiovascular outcomes trials for the GLP-1s really points to atherosclerosis. There may be effects on kidney disease and heart failure. We'll keep looking at that, trying to understand that and these other factors like sleep apnea. There may be many mechanisms that are part of this that will be worthy of pursuing, the insight we get from SELECT and SOUL, which was oral semaglutide in patients with established cardiovascular disease. The guidelines now are providing us a roadmap for how to do this, especially outside of the field of endocrinology, but for primary care physicians and importantly cardiologists. Hopefully, this will help us continue to move forward and ensure better outcomes. Thank you.

DR. ARODA: Thank you so much, Jorge and Marie. We're going to move very quickly on to the case, but because we're short on time, we're going to go quickly through the case to save just a couple of minutes for the practical questions that are coming through.

DR. MCDONNELL: All right, great. What a great audience. Thank you for your participation here. Let's talk about this patient. This is a 54-year-old man, moderately well controlled type 2 diabetes for 12 years, maybe in the sweet spot. Significant obesity and coronary disease presenting for follow-up. His recent issue was new-onset angina, so he ended up having a cath, showing three-vessel multivessel CAD. This prompted a coronary artery bypass two months ago and he saw his cardiologist yesterday. His EF was found to be 45% with inferior wall hypokinesis. Now prior to bypass, his only diabetes complication was mild distal polyneuropathy.

On exam, his blood pressure as you can see is 138/78, pulse 68. BMI was 32.

Otherwise, looks okay. On laboratory testing, his A1c was 6.9. Serum creatinine was 1.4 with a GFR of 52. His UACR is 54, so mildly elevated. I think we went ahead a little too fast. No, that's okay.

All right, his current medications include metformin 1500 mg in divided doses and he left the hospital on glargine because he was managed with insulin in the hospital, but had not been on that prior to hospitalization. He's on atorvastatin, lisinopril, metoprolol, and aspirin.

He also states that because he's been on insulin, he really resents the injections, and he's telling you, "Whatever you want to do doc, I just don't want to inject myself."

Okay, so this is an audience response question. The question for you is: which of the following would you recommend as the best next step to optimize cardiometabolic health in this patient? Increase the lisinopril dose, add dapagliflozin and stop glargine, add finerenone, add oral semaglutide and stop glargine, or recommend no change? Please give me your answer.

[Music playing]

DR. MCDONNELL: Great. We have actually a preponderance of folks maybe because of the theme of our symposium today suggesting the oral semaglutide. In close second was adding dapagliflozin. So it sounds like folks have been listening, which is great. Can I move forward now? It's not letting me advanced. Good, okay.

I'm going to ask our panel here to talk about the answers here and this case in general. Do we agree with the audience around oral semaglutide? We know that certainly in the PIONEER trial there was a question of whether we saw some cardiovascular outcome or benefit. In network analyses we see that. Also, the patient has a reduced EF, so how do we prioritize the GLP-1 versus the SGLT-2 in this case?

DR. ARODA: I'll start. I think that was a trick question. The missing answer was a GLP-1 receptor agonist with proven CVD benefit. The SOUL trial is going on right now, so we'll find out the effects of oral semaglutide in a couple of years. But this is someone who's at high risk. His diabetes is well-controlled, but he does have cardiovascular risk, who's at risk of heart failure, of an atherosclerotic outcome, and renal outcome. He would benefit from probably both for the different outcomes and GLP-1 receptor agonist and an SGLT-2 inhibitor.

DR. MCDONNELL: What would you say, Jorge, knowing this patient's saying, "Doc, I don't want an injection"? What path might you put this patient down?

DR. PLUTZKY: Well, it is challenging. I think that decrease in his ejection fraction

when I was talking to him about whether he's short of breath, his volume status. Actually listening to his lungs is a radical concept, trying to understand how concerned one is, but you would be concerned. He just had bypass. We did that to avoid a decrease in his ejection fraction and when did that happen? Is that sort of stunning, some postoperative change? Going up on the ACE inhibitor has some component to it, but I think that he is set up for worsening volume status. His first step here may be the SGLT-2 inhibitor.

I wouldn't be as concerned about the injection part of it because as we all know, that depends on who you present that to the patient. When the patient says, "I don't want to inject myself anymore," a response is, "Would you like to have another coronary bypass surgery?"

They go, "No, I think I'd like to inject myself." That's part of the challenge for us, is teaching and educating patients around that. So I think that at this point I probably would be doing the SGLT-2 inhibitor, especially given his concerns, but I would be paying attention to the fact that he has a lot of significant obesity and that's often a motivator for patients who are very interested in losing weight. Typically, this is the window of time. This is a young person and he's got a long runway ahead of him. He's got to do better for him. Of course, as his cardiologist, I want to know his LDL. Just being on atorva 80 is very 2010 management. Pushing on.

DR. MCDONNELL: That's right. For time, we're not going to do an audience response system, but this sort of addresses Dr. Aroda's suspicion that this was a trick question. I do think that I'd like the two of you to answer that. This is forwarding automatically it looks like. Let's go back. Sorry, this is a trick here too.

Okay, so would these options change your choice? It sounds like from talking to you, that you would probably consider dual therapy if not now, in the near future. Do you ever actually start these two at the same time?

DR. ARODA: I usually talk to the patient and say, "We're going to start this one now and at your next visit we're going to fine-tune and tweak your regimen and optimize it. They both have such unique side effect profiles, that I think it's important to understand how the patient tolerates one.

DR. MCDONNELL: Right. It's good advice in my experience as well. The patients could assign nausea to the dapagliflozin, potentially usually incorrectly, and then they assign blame to one drug or the other. Vice versa, if they have issues with polyuria, they might assign that incorrectly to the semaglutide. I agree; I like to stagger them. But this is I think according to the guidelines really the patient who does benefit from dual therapy, the patient who's at highest risk. Again, attending to his lipid therapy with modern therapy is a good idea.

After discussing options, including organ protection, the patient decides to take combination semaglutide and dapagliflozin, semaglutide specifically in the injectable form, which is the one that we've found has cardiovascular benefit. Unfortunately, despite semaglutide being the preferred GLP-1, the combined copayment is $250 a month. He was recently laid off from work and he has a son in college. This is just going to be too much of a challenge for him.

So I do like to consider when I counsel my patients that cost is a side effect because it prevents them from continuing the drug, just like an actual side effect. After some counseling, he starts one and then the other one follows. Maybe I could pass this on to our panel members, but generally speaking, the way this is done is often through patient assistance programs, which can be accessible even to Medicare patients if you go right to the company. But there are ways to assist patients in affording these drugs. Do you have thoughts on that?

DR. ARODA: There are resources, and it takes advocacy from us as the care providers I think.

DR. MCDONNELL: Thank you.

DR. ARODA: Thanks so much. We have two minutes. This will be what I call a rapid-fire because you sent some really nice practical questions. I'm going to ask them quickly and I'm going to ask for quick answers. Marie, what is your practical approach on initiating GLP-1 receptor agonists in a patient with diabetes complicated by retinopathy?

DR. MCDONNELL: Yeah, you know that I had a slide on side effects. The retinopathy concern is probably between real and not real. It is real. We saw that in patients whose A1cs were high, over 9%, when we use a high-potency agent, whether it be insulin or a GLP-1 receptor agonist, there is a risk in those with retinopathy of worsening of the disease.

I think in any patient who you think you are about to embark on a high-potency course where you can have a significant 2% lowering of an A1c, for example, which we see in GLP-1 therapy, you need to have an ophthalmologic exam. You need to understand the status of the retinal disease. It makes sense to ask the ophthalmologists what they think. They have opinions about this because they can see the degree of macular edema and neovascularization, for example. Then go slower. It's as simple as that. Try to avoid a 2% lowering in somebody who really does have active, potentially unstable retinopathy. By that, we usually mean go slow with the titration, which the patient will probably do better with anyway.

But I don't tend to worry about it. I just make sure I understand what we're talking about, but we do that with all patients with high A1c.

DR. ARODA: Jorge, the blood pressure in the case was suboptimal. Would you have increased the ACE inhibitor?

DR. PLUTZKY: If I was going to be starting the SGLT-2, I probably wouldn't or a GLP-1 because I think they're going to have a benefit on that front. But I would follow it closely and that's a low dose of an ACE inhibitor. It wouldn't take very much to increase that, but I wouldn't do that as opposed to expanding their therapy and maybe not trying to do too many things at the same time. But it wouldn't take much.

DR. ARODA: Two more quick questions. Marie, would you discontinue the GLP-1 if you see a bump in amylase or lipase?

DR. MCDONNELL: Generally speaking, if it's two times the upper limit of normal, I would. But that's incredibly rare. We might do that and I do. I then explore the gallbladder and make sure we're not missing gallstone disease. Then I might rechallenge the patient if they were completely asymptomatic. But I do stop it and then potentially consider adding.

DR. ARODA: Jorge, any secrets of success in addressing cost?

DR. PLUTZKY: No, other than to say that I think that sometimes you just have to deal with the hurdles and appeal. I think that's one of the unfortunate things, that that initial denial is not the case. You just have to invest in the energy, sometimes assigning a person within a practice to deal with that because they get good at it.

DR. ARODA: There you have it. You've been a great audience with wonderful questions. A special round of applause to Dr. McDonnell and Dr. Plutzky.