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The Latest in Stroke Risk Reduction Strategies: Are Your Patients Protected?

Announcer:
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Dr. Rabinstein:
Okay, so my turn to talk to you about diabetes and stroke. Where are we now? What the guidelines are currently saying. What is the relationship between these two common diseases?

Epidemiologically, we know that the risk of stroke is approximately twofold higher, and the risk of stroke recurrence is approximately 50% higher in people with diabetes compared with people without diabetes.

Approximately 30% of all people with stroke have diabetes. Stroke occurs at younger age in people with diabetes, so it is not only more common but also more disabling in terms of productivity loss.

Diabetes can increase the risk of ischemic stroke by all the major stroke mechanisms large artery atherosclerosis, cardio embolism, and small vessel disease. And not only stroke is more common in patients with diabetes, but also stroke outcomes are worse in diabetic patients, does not matter whether you look at mortality, functional outcomes at 90 days, even cognitive performance. All of those are worse in people with diabetes than people without diabetes who have a stroke.

So it is a bad combination, and it is a bad combination that is very common and it is very well proven through multiple studies. The presence of diabetes is associated with an increased risk of stroke. And as we saw, it is associated with an increased risk of first stroke as it is in these studies reviewed here, but also with an increased risk of recurrent stroke.

Why does that happen? Well, I mean, there are multiple pathophysiological mechanisms, whereby the combination of diabetes, often with hypertension and obesity, form a triad that lead to vascular changes, both in terms of increased arterial stiffness and inflammatory changes that may lead to acceleration of atherosclerosis disease in the small vessels of the brain.

And also, diabetes is associated with an increased risk of atrial cardiopathy and in turn, atrial fibrillation, therefore increasing the risk of ischemic stroke from cardiac embolism.

By now, we have solid evidence that while controlling hyperglycemia in diabetes is not going to give you a lot of benefit in terms of stroke reduction, but certainly it can reduce the risk of stroke in patients with diabetes and potentially in patients who are obese and have glucose intolerance, is what medications you use to treat the diabetes.

And in particular, we are going to emphasize today the role of GLP-1 receptor agonist, because the bulk of the evidence favors these medications in terms of stroke reductions for cardiovascular risk reduction. In general, GLP-1 receptor agonist and SGLT2 inhibitors are both beneficial, but in terms of stroke as the precise endpoint, GLP-1 receptor agonists are the option to go.

Also, there is good evidence that pioglitazone can reduce the risk of stroke, particularly in patients with glucose intolerance and other risk factors for stroke. But the newer evidence clearly favors GLP-1 receptor agonists.

This has been noted in recent guidelines, the European Society of Cardiology management of cardiovascular disease in persons with diabetes guidelines clearly recommends as a class one recommendation, the use of GLP-1 receptor agonists or SGLT2 inhibitors for patients at very high 10-year risk of atherosclerotic cardiovascular events.

This includes stroke, but this recommendation is not limited to stroke. And as we said, if we limit the recommendation to stroke, there is a differential effect favoring GLP-1 receptor agonists.

Further, the guidelines differentiate the patient presentation as to whether patients present with cardiovascular disease and have diabetes vs present with diabetes and are at risk of cardiovascular disease or chronic kidney disease in delineating what would be the best possible medications.

And as we see that patients with confirmed diabetes mellitus type 2 and confirmed high risk of cardiovascular disease or established cardiovascular disease should receive either a GLP-1 receptor agonists or an SGLT2 inhibitor as class one recommendation.

And this recommendation is independent of the hemoglobin A1C level and what other medications the patients are taking for glucose lowering. So one thing is controlling the hyperglycemia when it comes to controlling complications from atherosclerosis. Then you do need these medications even if you have a good control of the patient's glucose.

The ADA guidelines from this year also provide a guidance in regards to the use of GLP-1 receptor agonist, and favor the use of these agents in patients with high risk or established atherosclerotic cardiovascular disease. Again, none of these guidelines specifically talk about stroke. They use a common endpoint of atherosclerotic cardiovascular disease. And that is why the recommendation is to go with GLP-1 receptor agonist or an SGLT2 inhibitor with proven cardiovascular disease benefit.

So, I am a stroke doc. And when I see patients with diabetes, again, 30% of patients presenting with the stroke have diabetes. The diabetes may be diagnosed at that time or it may have been known from before. Still, the majority of these patients are not taking either one of these agents.

It is part of my role, as a stroke specialist, to recommend the best possible strategy for secondary stroke prevention in these patients. Same thing when I see patients with atherosclerotic disease in the carotids who still haven't had a stroke, and they have diabetes, I feel that it is part of my responsibility to recommend what drugs they should be taking to control the diabetes and reduce the risk of atherosclerotic cardiovascular events.

In my recommendation at present, based on available evidence, is for GLP-1 receptor agonists. And I work with the primary internist or diabetes specialist of the patient to make sure that the patient does receive the appropriate medications. And later on, when I see the patients in follow-up, I make sure that they are taking these medications so they can derive the benefit that these medications can provide over time.

Now let us hear from people who actually know diabetes. I pass it on to Dr Richard Pratley, who is going to be talking to us specifically about the role of GLP-1 receptor agonists for stroke risk reduction.

Dr Pratley:
Well, thank you very much, Dr Rabinstein. It is indeed a pleasure to be with you tonight, specifically. I think this is an underappreciated area where we really have the opportunity to make some significant reductions in risk for our patients.

Unless you have been living under a rock, you have heard about GLP-1 receptor agonists and their benefits in terms of diabetes control, weight loss and other things like cardiovascular and now kidney indications.

So why all the excitement and how is this all working? Well, if we think about the mechanisms by which GLP-1 receptor agonists work in the body, I think initially we were focused on the pancreas. So enhancing insulin secretion, decreasing glucagon and other mechanisms, all tended to improve glycemic control. And that was great. That was a great start for these medications.

But as we have evolved, we now know that there are other mechanisms, extra pancreatic mechanisms that are very important. In the gut, there is decreased gastric emptying. There is effects in the brain to decrease food intake. And we will talk a little bit more about brain effects later on.

But in the vasculature, in the heart, we know that there are direct effects that are cardioprotective, and there are also indirect effects that may decrease risk in the kidney. There are effects to increase diuresis, natriuresis. And we also now know that there are kidney protective effects of the GLP-1 receptor agonists.

So it is not just about diabetes control anymore. It is about managing the total cardio-kidney-metabolic risk.

And as you will remember from your college days, it is not just the GLP-1 receptor that is an important incretin hormone. We also now have glucose-dependent insulinotropic polypeptide or GIP. The effects of GLP-1 and GIP are overlapping but not identical. They have similar effects on the pancreas, but they also have differing effects, for example, on the white adipose tissue to a certain extent in the central nervous system, and then peripherally as well.

So there is a lot of excitement nowadays about combining these two mechanisms of action for even better glycemic and cardiometabolic control.

I want to focus a little bit now on specifically the effects of GLP-1 on the brain. I will show you in a little bit data that suggest that GLP-1 receptor agonists decrease risk for stroke as well as other cardiovascular complications. But there is some really interesting data that has evolved that suggests that there are direct effects of GLP-1 on nerve cells. So the increased neuroprotection.

And they do so, we think through a variety of mechanisms. One is that they seem to decrease cell apoptosis. So the evolution of cells, death of cells that are controlled are decreased. The other mechanism that seems to happen is to increase neurogenesis. So GLP-1 receptor agonists actually enhance the vitality of nerve cells in much the same way that they are thought to do for beta cells in the pancreas. And that makes sense, because these 2 different cell lines are very closely related to one another.

But there are also other direct effects in the brain. So there may be decreases in cerebral inflammation that may be important. There may be important effects on the microcirculation that lead to decreased infarct volume. And there may even be effects on amyloid plaque.

When it comes to atherosclerosis, this is rather like what we see in other parts of the body, in the heart and periphery. And what we think are that there are both indirect effects that reduce risk for stroke, decreasing blood pressure, decreasing weight, decreasing A1C, as well as potentially direct effects of the drug, things like improved endothelial function, decreased smooth muscle cell activation, decreased vascular inflammation, probably a very important measure, and also decreased lipid accumulation.

So we have to think about both the neuroprotective effects as well as the anti-stroke type of effects. And they are distinct from one another.

So let us go to post-test question one. GLP-1 receptor agonists are thought to reduce the risk of stroke through which of the following mechanisms? Is it:

A. Decreased apoptosis and decreased neurogenesis;
B. Decreased apoptosis and increased neurogenesis;
C. Increased apoptosis and decreased neurogenesis; or
D. Increased apoptosis and decreased neurogenesis.

So lock in your answers, please.

All right. I wonder if we have enough votes here. We will take a look. It looks like the overwhelming majority of you chose decreased apoptosis and increased neurogenesis. And yes, those are the direct effects on neural cells that may promote brain health.

So let us move on now. And just to amplify that answer, the benefits of GLP-1 receptor agonists are thought to be in addition to the indirect effects of GLP-1 receptor agonists through such things as blood pressure control, weight loss, and improvements in glycemia.

We have now a lot of experience with GLP-1 receptor agonists. Going back now almost 20 years, we have been doing cardiovascular outcome trials with all new diabetes drugs, and they have taught us a whole lot.

But specifically, among the GLP-1 receptor agonists, what we have seen are some benefits on cardiovascular health and specific aspects of cardiovascular health. But this is not something that is shared by all members of the class, or at least we do not have the evidence to support that.

So, for example, with exenatide once-weekly, there is directionally an improvement in 3-point MACE, but it was not significant. With liraglutide, there was a reduction in 3-point MACE. Now MACE is major adverse cardiovascular events that includes nonfatal stroke, nonfatal MI, and cardiovascular death.

In terms of stroke risk for liraglutide, there is directionally a reduction in stroke risk, but that was not significant. There is also suggestions of improvements in chronic kidney disease and metabolic associated steatohepatitis with liraglutide.

Dulaglutide, in a large study called REWIND, showed a reduction in 3-point MACE, very similar to what liraglutide showed, as well as a

significant reduction in stroke risk. There are also some benefits on chronic kidney disease with dulaglutide.

Semaglutide once-weekly has shown significant reduction in MACE, probably the best effect that we have seen among these drugs. It has an indication for reducing cardiovascular disease. There was a reduction in stroke. And most recently we reported among patients with chronic kidney disease and type 2 diabetes, a 24% reduction in progression of chronic kidney disease, CV death or kidney death.

So it looks like there is very robust effects of semaglutide across the board for this constellation of vascular risk factors and CKD.

With oral semaglutide, the data are beginning to come in. There is a study that just completed called the SOUL Study, in which oral semaglutide was examined in another cardiovascular outcome trial. And they recently reported in a news release that 3-point MACE was significantly reduced. That was the primary outcome of the study.

They also said that all of the elements, so stroke, nonfatal MI, and cardiovascular death contributed to the benefit of this endpoint. So more to look at there.

Now in the last section, the last column there, there has been some really interesting effects on other brain diseases, including things like Parkinson's disease with exenatide, but also lixisenatide another GLP-1 receptor agonist and that was published recently in New England Journal in the last year.

With dulaglutide and semaglutide once weekly, although not studied in trials, there does seem to be a decreased risk of new onset dementia. A recent real world evidence report, a large segment of the US population suggested that this reduction in dementia risk may be as much as 50%.

Ther is an ongoing trial of semaglutide, only the oral version in patients with dementia, to see whether or not it can slow or reverse the progression of cognitive decline in this population. So there are a lot of very exciting things going on in the whole GLP-1 receptor agonist field.

I want to drill a little bit on some of the data from the CVOTs. These are the different endpoints in the CVOTs starting with 3-point MACE. You can see there that the relative risk reduction was 15% which was significant. Cardiovascular deaths, the relative risk reduction there across the trials was also 15%, and that was significant.

Fatal or nonfatal MI, a 12% significant reduction. And then finally, fatal or nonfatal stroke across all of the studies combined in this meta-analysis. A 19% reduction also highly significant.

And what you'll see with most of these comparisons is there is not a lot of heterogeneity. Most of the trials line up favoring the GLP-1 receptor agonist. And that gives us confidence in the effect of these medications.

Now, I wanted to talk a little bit about the SELECT trial. This was a trial that recently released results. It was a cardiovascular outcome trial with the obesity dose of semaglutide 2.4 milligrams in patients who are obese, who had preexisting cardiovascular disease. The main primary endpoint of this study was MACE, cardiovascular death, nonfatal MI, nonfatal stroke.

And that was a significant finding in this large trial that involved almost over 17,000 patients, a 20% reduction in the risk of MACE.

In this analysis, there was a trend towards a reduction in deaths from cardiovascular causes, a trend for a reduction in heart failure composite end point, and also a trend for a reduction in death from any cause.

Now, we could not call these as significant because of the hierarchical testing strategy. However, you can see that the benefit largely lines up for all of these endpoints.

In this SELECT trial, they looked at all of these different endpoints individually. And you can see that, for example, the expanded composite endpoint was significant. Nonfatal MI was significant and nonfatal stroke went in the right direction. It is about a 7% reduction, but the confidence intervals were from 0.74 to 1.15, including 1. So not statistically significant, but certainly directionally correct.

So let us move on to post-test 2. Based upon the SELECT trial, which we just reviewed, which of the following medications would it be best to initiate in an individual with obesity but without type 2 diabetes, when trying to reduce stroke risk? Would it be:

A. Empagliflozin;
B. Metformin;
C. Pioglitazone; or
D. Semaglutide.

All right. Let us take a look. Great job everyone. 96% voted for semaglutide. And that, of course, is what we just reviewed.

But let us dig in a little bit to the answer. Why would we select semaglutide? Well, we selected it because it demonstrated a statistically significant reduction in this primary composite outcome of CV death, nonfatal and MI nonfatal stroke. Even though the nonfatal stroke went in the right direction, it was not quite significant.

Now, you could also argue for pioglitazone. Alejandro has already pointed out that there is evidence that pioglitazone helps to reduce the risk of MACE in a stroke population. This was a study called the IRIS study, which I was a part of.

In that study, there was a reduction in MACE with pioglitazone treatment. But remember, here we are dealing with a population that is already obese, and pioglitazone is associated with weight loss. So that might not be our first choice.

Neither metformin nor empagliflozin have been shown to have a significant benefit on stroke.

This is an interesting meta-analysis, which compared the stroke risk with GLP-1 receptor agonist and SGLT2 inhibitors. And it is a compilation of different meta-analyses and different trials.

Now, in these trials, by and large, GLP-1 receptor agonists and SGLT2 inhibitors were not directly compared. And what we are looking at is oftentimes some data from real world sources. The main takeaway message there, though, is that when you compare an SGLT2 inhibitor and a GLP-1 receptor agonist, the hazard ratio actually favors the GLP-1 receptor agonist, that is the risk for stroke is lower compared to the risk with the SGLT2 inhibitor.

And that is consistent with the individual results of these cardiovascular outcome studies, where there is really no signal with the SGLT2 inhibitors of a stroke benefit.

This, again, is a meta-analysis of 11 randomized controlled trials of the GLP-1 receptor agonist, both weekly and daily administration. Like the other meta-analysis, not surprisingly, a 15% reduction that was significant.

A little bit more of a pointed analysis from seven selected CVOTs with GLP-1 receptor agonist demonstrated a significant reduction in 3-point MACE Cardiovascular mortality, all-cause mortality, a renal composite, with these patients who have this spectrum of cardio kidney disease.

And in terms of the safety, no increased risk of thyroid cancer, pancreatitis, pancreatic cancer, or even retinopathy. So the risk and benefit ratio clearly favors GLP-1 receptor agonist for these high-risk patient populations.

So as you know, the GLP-1 receptor agonists are approved for the treatment of diabetes. And these include, in the US at the moment, dulaglutide, exenatide, liraglutide, lixisenatide and oral or injectable semaglutide.

And their benefits are well known. They are among the best glucose lowering agents. Some of them have cardioprotective effects. We have seen benefits, especially with semaglutide on the kidney. But they have a low risk of hypoglycemia, and most of them are associated with some weight loss.

In terms of limitations, we know that the adverse events include primarily GI adverse events, things like nausea, vomiting, diarrhea.

Some of these are oral medications, oral semaglutide, but most are injectable. But they either come with auto injectors or they are delivered with very small needles. So really the pain is minimal. And this is something that is, in my experience, more psychological than it is real.

There is an FDA boxed warning about the risk of thyroid C-cell tumors, and we recommend that patients with either a personal or family history of medullary thyroid carcinoma or MEN2 not receive these medications. But other than that, there has not been demonstrated any risk of an increased risk of these types of tumors. It does occur in animals, but animals are not humans.

The pancreatitis risk, I think, has largely been put to bed now. I just wrote a review of this. And in all of the meta analyses and individual trials we looked at, they did not seem to be an increased risk of pancreatitis.

There is an increased risk of gallstone disease, so you have to be aware of that. There is a caution on renal impairment in patients treated with exenatide and lixisenatide because these are cleared by the kidneys. So should not be used in patients with an EGFR less than 30.

Finally, we do not know about the effects during pregnancy. If patients become pregnant they should stop the medications and report that.

So these drugs and the GIP/GLP-1 coagonist tirzepatide are either once-weekly injectable medications or once-daily administrations of either an injection or in the case of some oral semaglutide, a once-daily medication.

You can see the different requirements here. They are slightly different doses for all of the medications. But the thing I wanted to point out was with oral semaglutide, you do have to take it 30 minutes before food, beverage or other oral medications and take it with a small amount of water, because that does affect the oral absorption of the medication.

And again, liraglutide, dulaglutide and semaglutide all have an FDA indication for reducing risk for cardiovascular events in patients with diabetes. And semaglutide has an indication for reducing cardiovascular risk in obese patients who do not have diabetes.

Also, you will be aware that a couple of these medications have been developed for weight loss. This includes liraglutide and semaglutide and tirzepatide, the dual GLP/GIP coagonist.

You will notice that tirzepatide does not have a CV indication, and that is because they have not finished their CV outcome trial. But that is underway and we should know the results of that fairly soon.

So post-test question three. A patient with type 2 diabetes and high risk atherosclerotic cardiovascular disease is managed on metformin and dapagliflozin, an SGLT2 inhibitor. Their A1C remains above goal at 9.1%. Which of the following medications would best reduce their cardiovascular and stroke risk? Would it be:

A. Exenatide;
B. Dulaglutide;
C. Linagliptin; or
D. Rosiglitazone.

Please lock in your answers now. All right, let us take a quick look and see what people chose. Well, most of you chose dulaglutide, about 82%. And let us dive into that answer just a little bit more.

As I mentioned, dulaglutide is the correct answer, and the REWIND study, dulaglutide was shown to reduce the risk of MACE events in patients with either preexisting atherosclerotic cardiovascular disease, including stroke or high risk.

The exenatide GLP-1 receptor agonist had a trend in that direction but did not quite meet statistical significance. Linagliptin, which is a DPP4 inhibitor, also in their trial, did not show evidence of a cardiovascular benefit.

Rosiglitazone has had kind of a storied past, with some studies indicating an increased cardiovascular risk and others indicating a neutral cardiovascular risk. But it is not a prime choice for reducing cardiovascular risk in a patient such as this.

So how do we deal with the adverse events of GLP-1 receptor agonists? I think it is important to realize that they don't occur in all patients. I've had many patients start the medications and able to titrate to top doses with no problems at all.

Now, the GI adverse events occur in 20% to as many as 30% of patients. They are dose-dependent, and they typically happen when initiating the medications and titrating, so when you are getting increases in that dose. Most often they are mild and typically they resolve within a couple of weeks or so.

But you can do some things to help mitigate the risks. If patients are feeling GI adverse events, they should eat smaller meals and help and try to minimize the fat content. It is also acceptable to titrate the drug slower, and you do not have to go to the top dose for most of these medications to get the benefit. So think about how you can be flexible with these drugs to help reduce the risk.

Smaller meals, lower fat diet. If patients have early fullness, they may interpret that as nausea. But tell them that it is part of the expected effects of the medication and then make sure that they have the appropriate injection technique with these drugs. It is really pretty easy.

One of the things that we have learned over the years is that you can actually set expectations in a positive way around known side effects. We learned this from the vaccine trials when we told people that if they had a sore arm afterwards, that is actually a good sign. It means your body is mounting an immune response. Similarly, if we chose a similar pathway with a GLP-1 receptor agonist, we talk about early fullness, nausea, or some mild GI adverse events.

We do not interpret that as being a side effect of a medication. That is an effect of the medication. And what it means is people are likely to do quite well on the medication if they can get through that side effect, because they are very sensitive to the effects of the medication. And in my experience, it helps people get through these adverse events.

Dose titration is important. We educate our patients about that. You may have to adjust other diabetes medications, especially sulfonylureas and insulin, because you want to avoid hypoglycemia. The GLP-1 receptor agonists themselves do not cause hypoglycemia, but with insulin or sulfonylurea drugs on board, as you lower the glucose levels, you could induce hypoglycemia.

This is really, as Alejandro already intimated, a multidisciplinary collaboration between stroke neurologists in the case of treating patients with strokes, primary care physicians, diabetologists or endocrinologists, as well as other disciplines such as pharmacy, sometimes diabetes educators and nutritionists.

Finally, we have to be sensitive to the insurance costs. It is of note that liraglutide is now available as a generic medication. It is not widely available yet, but it will become so soon.

So I am going to turn it over now to my good colleague, Jay Shubrook, who is going to talk about a patient case. And we are going to discuss this collectively. Jay?

Dr. Shubrook:
Yes. Thank you so much. I have really enjoyed both your presentations, and I think give us a really great background. For the audience, I want to invite you to submit questions. I see one has come in already. Please keep them coming in and we will try to save time to answer your questions, in addition to the cases we are going to discuss today. So keep them coming.

So our first case is a 63-year-old male who presents for a diabetes recheck. And you can imagine it is rarely just diabetes. So he's got hypertension, dyslipidemia, type 2 diabetes, Class three, obesity, chronic kidney disease and metabolic associated steatotic liver disease and peripheral neuropathy.

He certainly has had multiple family members, had medical problems associated with diabetes, and he works as a pastor and really does not use any tobacco, alcohol products, does not follow any specific diet, but finds that it is quite hard for him to control what he eats because people are bringing him food and offering food all the time.

He does live with his spouse, his two adult children, and his three grandchildren, and his family is quite close. So he has a lot that he is living for. He enjoys playing with his grandkids, but unfortunately, walking long distances is hard on his knees.

And when we ask him, how are you holding up? He is okay. But he really does feel like there is a lot of life stress. And you can just imagine just from this medical history, there is a lot going on.

If you look at his medications, he has got a list commensurate with the problems that he has. You can see he is on losartan/HCT, max dose, amlodipine 10 mg, hydralazine 25. For his diabetes, he takes sitagliptin, metformin max effective dose, and insulin glargine 60 units per. Fay for his cholesterol, he takes atorvastatin and ezetimibe. And then you can see symptomatically he has gabapentin and acetaminophen.

He does check his glucose some mornings. He does not have any lows. And he forgot his meter today.

So when we talk with him a little bit about his goals, he is really worried about his hypertension and his type 2 diabetes. He knows that those things can affect his kidneys, and he has seen family members that have had adverse effects from the kidneys. He had a brother that had a stroke last month, and he was really surprised how hard this was on him and his family. And he really was not aware that stroke could be related to diabetes.

You can see he has got a BMI of 41. His blood pressure is 134 over 70. And he has got some evidence of peripheral vascular disease.

So you have got some labs. Highlighting the labs that he has got an EGFR of 52. He has got potassium within normal limits. He has got mildly elevated transaminases. We do not have a platelet count. So we cannot tell you his FIB-4 score, but he does have stage A2 proteinuria. And an A1C of 7.4%. So this is a lot to digest.

And I guess what I want to start with our faculty, is really how do you communicate cardiovascular and cerebrovascular risk in this person that has got so much going on. And, Alejandro, maybe I will ask you first. I realize that you might not see this person until after they had a stroke, but maybe he is there with his brother.

Dr Rabinstein:
Yes. Maybe he visited the brother. Maybe this is a common scenario in patients who present with asymptomatic carotid disease. But certainly the first thing that I would say regarding the surprise of the connection with diabetes and stroke, I would emphasize the truth of that association. But also the lucky fact that now we have medications that can modify that risk and emphasize that positive point.

And that atherosclerosis is a systemic disease that can affect the brain, can affect the brain in terms of stroke risk and also in terms of cognitive decline. But at the same way that hypertension can be controlled, diabetes can be controlled. The difference is that controlling the numbers of hypertension, maybe not controlling the numbers of diabetes, may not just be enough to reduce the stroke risk and therefore using certain medications we have been discussing at length why GLP-1 receptor agonists have a preferential role when it comes to stroke reduction, why the addition of such medication would be pertinent in his case.

Dr Shubrook:
I love that. Thank you. And Richard again, how do we communicate this? And if you are helping him set goals, let us see that you are seeing him now. How do you fit all this in and goal setting for him?

Dr Pratley:
Yes, it is a lot to fit in. He has got a lot going on. And I think that he is identifying the issues that he is worried about his kidneys and certainly this now family history of stroke. And if you look at his labs, he has pretty significant chronic kidney disease with a decreased EGFR and albuminuria. So he is at high risk for CKD progression, but also for cardiovascular events.

Also his BMI is 41. And this is affecting his risk for cardiovascular disease as well as ability to control his diabetes. So I think we need to think of this holistically, if we have an approach that will treat his excess weight, it will probably improve his blood pressure. It will also secondarily have beneficial effects on kidney function and risk for cardiovascular disease, not just stroke, but also heart attack and heart failure. So this is a person who might actually do well on a obesity dose of semaglutide as an example.

But what I wanted to emphasize is that we need to think of the patients holistically, not think of him as being siloed with one disease or another disease. These diseases are all linked together, and treating them with a GLP-1 receptor agonist will improve the outcomes across the board from what we know now based upon these long trials.

So I think that we have that discussion with him, but we try to stay positive because there are things that we can do.

Dr Shubrook:
Yes. As we think about this, this is really a great time to say, hey, I hear that you have got a lot going on and we can optimize your treatment to reduce multiple risks. And I do think this is a chance to tune up his meds and sometimes even simplify his meds, right? Something that is potent, like a GLP-1. He might end up on less medications in the long run and get additional benefit.

So I guess, Alejandro, I got one more for you here for this case, we have more to talk about. In the primary care setting, I feel like we have ample evidence that he has vascular disease already. Is there anything we should be doing proactively in the stroke space?

Dr Rabinstein:
Well, that is a matter of discussion. Certainly, I would make sure that there has been some screening for atrial fibrillation. I would make sure that there is no evidence of mild cognitive impairment. Does not seem to be. He is working as a pastor. But sometimes people who feel stressed, is because they are having more difficulty coping.

And the big question is, does it matter to diagnose asymptomatic carotid disease? I think for research, certification is important now. The recanalization treatment for asymptomatic artery diseases is coming and is under investigation. There is a large trial approaching conclusion that is going to give us an answer whether a contemporary treatment of cardiovascular risk factors, the invasive treatment of asymptomatic carotid diseases is beneficial.

And so the answer is not simple, but certainly, as a neurologist, and the same thing would go for primary internists and even endocrinologists just to keep this connection between diabetes and the brain, not just the blood vessels outside of the brain is important to keep in mind.

Dr Shubrook:
Excellent.

Dr Pratley:
So, Jay, if I could just make one more point, which is, his A1C is a little bit high. It is 7.4. And we do believe that he would have a benefit from a GLP-1 receptor agonist to bring him closer to goal. But the recommendations for managing cardiovascular disease in patients with diabetes are to start the GLP-1 receptor agonist, irrespective of the A1C.

So even if his A1C was already in the 6.5% range, he would be a candidate for a GLP-1 receptor agonist.

Dr Shubrook:
Yes, we would have to make room for an agent that has additional benefit and maybe remove meds that do not have [inaudible].

Dr Rabinstein:
Exactly.

Dr Shubrook:
Okay, I have a poll for you, a resource, and then we have another case. So which of the following barriers do you all considered the largest when it comes to prescribing GLP-1s in your practice? Is it:

A. Comfort level with the medications;
B. Comfort level identifying eligible patients;
C. Insurance coverage;
D. Patient preference; or
E. Other.

Please vote. And I see questions are coming in. I love it. Okay. And the results.

All right. And it is no surprise that insurance coverage is a big issue. I think it is an issue for us as well. I would love to hear if either of you have any tricks, we would love to hear it.

Dr Pratley:
No. I think you have to be persistent. I always refer to the guidelines. I am very objective with what the patient's pre-existing disease and risk factors are. I point out that these medications reduce risk for recurrent events and mortality. That is oftentimes enough to get you down the road, and having less problems with that lately.

Dr Rabinstein:
Yes, it seems to be getting better.

Dr Shubrook:
In California, we have to actually write on the SIG[?] what the indication is. So if you are doing for obesity, write obesity is code. Diabetes, diabetes code. And then add if it is additional indication.

Dr Rabinstein:
Yes. For me, it is still extremely annoying that you cannot start these medications in the hospital though.

Dr Shubrook:
Yes, for sure. This is a really wonderful resource that CCO has made for you. I think it is important to recognize that if this is something that is new to you or you really want to fine tune this, we give you a four-step panel that working through best practices and a PDF. You can scan it, but a PDF has also been put in chat for you all. We offer this as a follow up.

So we have one more case and then we will take your questions. This case is a 75-year-old gentleman who comes to clinic, followed up from an acute ischemic stroke three months ago. He did receive a thrombolytic. You can see he also has diabetes, obesity. He also has heart failure with reduced ejection fraction. And he has, as no surprise, a previous history of acute MI.

He does drink socially, but he did quit smoking ten years ago with his pretty significant past smoking history. And you can see his list of medications here.

This is a complicated patient. As we think about what to do next, is this a patient for GLP-1? And Richard, maybe I will start with you first and then Alejandro hear from you as well.

Dr Pratley:
Yes, I think he would be an excellent candidate. And I am not beyond using tirzepatide as an option either. More and more, I think that the overlapping benefits are pretty similar. And I think in the fullness of time, we are going to understand the cardiovascular benefits of tirzepatide, in the same way we now understand the GLP-1 receptor agonists.

Dr Shubrook:
Alejandro?

Dr Rabinstein:
Yes, I cannot agree more. But this is a patient that scares me. I mean, an MI 11 months before, now stroke. This guy has to get everything possible to reduce the risk of cardiovascular events in the future. So this is one that you really have to fight to get the right medications. And this one I would scare a little bit to make sure that compliance is not an issue.

Dr Shubrook:
Yes. And certainly we can optimize all of these therapies for statins, lipids all of them, full therapies.

All right, last question for everyone. And then we have a summary, and your questions. After this presentation, how likely are you to recommend a GLP-1 receptor agonist for stroke risk reduction in individuals with type 2 diabetes? Everything from very unlikely to very likely. Please vote.

All right. So we certainly see that the great majority are likely and very unlikely. And certainly some people may not be comfortable or may not have access. And we understand that.

So today we talked a lot about:

- GLP-1 receptor agonists and how they can reduce the risk of cardiovascular events in people with diabetes and in patients with obesity, with or without diabetes;
- GLP-1 receptor agonists have been shown to be beneficial in those with stroke, and should be prescribed for patients with type 2 diabetes and stroke, regardless of glycemic control and background therapy.

Dr Shubrook:
So I want to make sure we have a couple of minutes for your questions. And so I'll start throwing them out.

Dr Pratley:
And Jay, I think there are some great questions here. And I am going to start off with answering the first question, which is, is the molecular size of different GLP-1 receptor agonists, does that affect the neuroprotective effect? And I think this is a great, very insightful question. Do these larger molecules like dulaglutide get into the brain?

A dulaglutide is conjugated with Fc fragment of IgG. And the answer seems to be they are effective. So in the trials, dulaglutide was associated with reduced risk of stroke. So I do not worry too, too much about the molecular size.

Dr Shubrook:
Excellent. Thank you. There is a question here about using GLP-1 receptor agonists with Stage IV or V CKD? And is there a cutoff or what I would say monitoring or GLP-1 use. Maybe, Richard, you want to take that first?

Dr Pratley:
Yes. There is a cutoff for exenatide and lixisenatide because they are partially cleared by the kidney. They can build up in the setting of more severe chronic kidney disease, and that could lead to adverse events.

Other drugs like semaglutide and liraglutide are mainly metabolized. They do not accumulate in CKD. And I personally have had patients on dialysis doing just fine on a GLP-1 receptor agonist. They have to be treated gently because they are a little bit more prone to nausea. So you have to monitor them carefully. But they are very effective for glycemic control.

And in the FLOW study, we showed that even patients with pretty severe chronic kidney disease had benefits from being on Ozempic. These patients were not on dialysis, but they had pretty severe kidney disease. 93% of them were KDIGO high-risk patients.

Dr Shubrook:
There was a comment about injecting long-acting GLP-1 at night. I can tell you that I have also seen that. That is not the most convenient time for everyone, but sometimes you can bypass some of the side effects by taking it at bedtime. Because remember, once weekly GLP-1s can be taken independent of meals and eating.

So there is another question. Alejandro. A patient who does not have diabetes and who is not obese, would they benefit from a GLP-1 receptor agonists?

Dr Rabinstein:
I do not know. Maybe we do not know. I think that that begs to be studied.

Dr Shubrook:
And this question has a couple of pieces. But looking at the effects on diabetes sequelae like renal, I think that is rheumatoid arthritis and it is rheumatoid arthritis effect. And I guess, this is an inflammatory condition. But do you have any studies you want to call out about rheumatoid arthritis and diabetes outcomes?

Dr Pratley:
Actually, I think he corrected this to mean GLP-1 receptor agonists. He forgot the GLP-1 part of that. But I think we do have a large amount of accumulating data, particularly with cardiovascular disease, chronic kidney disease. And there are, as we mentioned, these studies underway, looking at dementia in patients with pre-existing cognitive dysfunction. So I think there is a lot of exciting stuff yet to be delivered on these drugs.

Dr Shubrook:
There was a comment about GLP-1s and DPP-4 inhibitors. If someone's on a DPP-4, yes, you stop that. If you are starting a GLP-1, there is no benefit for those two together.

And then I will close this with both of you. There were some questions about GLP-1s and hospitalization for heart failure or GLP-1s in liver transplant patients. Any experience or data regarding those?

Dr Pratley:
My anecdotal experience in liver transplant patients. Of course, they are at high risk for developing diabetes, in part because of the transplant medications. And there is no obvious reason why these drugs would not be as safe and effective in this patient population. There was another part of that question as well, Jay, like, another segment of the population.

Dr Shubrook:
Heart failure.

Dr Pratley:
Heart failure. Interesting. There is a lot of data released just in the last year. Patients with HFpEF specifically treated with semaglutide at the obesity doses, a marked improvements in function in patients who received semaglutide and actually lost a fair amount of weight. But their KCC/CSS scores improved markedly over the course of about a year or so.

And we also, in FLOW, saw about a 27% reduction in the incidence of heart failure in patients treated with semaglutide. So I think this is another area where there is pretty clear benefits.

Dr Rabinstein:
And from a from a pragmatic standpoint, I want to point out something that that I do not want to stop the conversation without emphasizing patients lose weight. Then in the case of a stroke, they can rehab the case of heart failure. They can do some physical activity, they can do cardiac rehabilitation, etc.. Losing weight is enormously useful to maintaining health.

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