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How GLP-1s Provide New Options to Manage Heart Disease

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Welcome to ReachMD. This Medical Industry Feature is titled, "How GLP-1s Provide New Options to Manage Heart Disease," featuring Dr. David Majure, a cardiologist and heart failure specialist at NewYork-Presbyterian and Weill Cornell Medicine. This audio is a production of NewYork-Presbyterian with world-class doctors from Columbia and Weill Cornell Medicine.

Dr. Majure: The population of people suffering from heart failure of any variety is tremendous. In the US we do about 3,500 heart transplants a year.

Erin Welsh: Dr. David Majure is a cardiologist and heart failure specialist at NewYork-Presbyterian and Weill Cornell Medicine.

Dr. Majure: I've been an attending physician for almost 20 years now, and over the years, obesity has been a real frustrating problem for us because, unfortunately, the outcomes with transplant are quite poor when people are obese.

Erin Welsh: Because of this, heart failure doctors would often try to get their patients bariatric surgery to help lower their BMI before performing a heart transplant so their patient's outlook would be much better after the procedure. This is not always the best option because it requires an additional surgery and the patients need to wait until they have recovered before undergoing the transplant. One way to eliminate the need for bariatric surgery is simply getting patients to a healthier weight with diet and exercise. But that can prove to be very challenging. And it's a clinician's goal to avoid unnecessary surgeries whenever possible.

Dr. Majure: One of our goals in heart failure is to prevent. So when we have people early on in the spectrum to delay the progression of it, prevent damage to their other organs, maximize their quality of life, and ideally prevent them from needing a transplant.

Erin Welsh: Preventing heart transplant by improving heart health has been changing in unexpected ways - beyond a patient losing weight, GLP-1s could offer a new solution, especially in cases of heart failure which are more challenging to treat such as heart failure with preserved ejection fraction, which is when the heart's pumping ability remains the same but it cannot pump enough blood to meet the body's needs.

Dr. Majure: It's only within the last five to ten years that we've had meaningful therapies for heart failure with preserved ejection fraction. And interestingly enough, most of those therapies coincided with diabetes management. So that's the SGLT2 inhibitors and then now the GLP-1 receptor agonist. And we are only starting to learn about the benefits associated with those.

Erin Welsh: I'm Erin Welsh and this is *Advances in Care*, a podcast about groundbreaking developments in modern medicine.

Today, Dr. David Majure, Medical Director of the Heart Transplant Service at NewYork-Presbyterian and Weill Cornell Medicine, explains the mechanisms of GLP-1s, his work applying the cutting-edge research behind new uses for GLP-1s and how these therapies are changing the landscape of heart disease treatment.

Dr. Majure, it's great to meet you. Thanks for joining me today.

Dr. Majure: Thanks for having me, Erin.

Erin Welsh: Well, let's get into GLP-1s in the first place.

Dr. Majure: Sure.

Erin Welsh: What is this class of drugs? We're just sort of almost scraping the surface of what they're found to be doing and the effects they're having.

Dr. Majure: Right. And they touch everything because we are really talking about energetics, we're talking about metabolism, and that affects all the cells in our body. The story behind these is really fascinating. You know, really what we're talking about are incretins and that term was coined in the 1930s.

Maybe there was a conception of these hormones earlier on that stimulated the pancreas at the beginning of the 20th century. But in the 1930s, a Belgian physiologist by the name of Jean Le Barre, he coined that term to signify the hormones that stimulate the pancreas to produce insulin. And those two hormones are GLP-1, which is glucagon-like polypeptide one and GIP, which is glucose dependent insulinotropic polypeptide. So both, I know it's a tough one to say. You really have…

Erin Welsh: It's a mouthful! I'm impressed. Yeah.

Dr. Majure: …have to practice that one. But they, both of those molecules stimulate the pancreas and they're released by the gut when you have food delivered to the gut.

But there are receptors for these–more GLP-1, but also GIP–receptors for these in the gut, obviously in the pancreas, in the nervous system like the vagus nerve in parts of the brain that are associated with hunger, in the heart, and importantly in adipocytes themselves. So there are receptors for these all over the place. And, basically you can think of these hormones as, I like this term the best, hormones of abundance. So when you eat, they are secreted. And they basically tell your body to do a number of things. Your gut slows down, which helps to delay the absorption of glucose and avoid the glucose spikes. Your brain is told, well you're eating, you're full, you're sated you don't need to eat quite so much. And obviously insulin is secreted in a glucose dependent fashion. Which is one of the reasons why these therapies are not associated with prominent hypoglycemia.

Erin Welsh: So these drugs were originally used to treat diabetes and it quickly became clear that they also caused weight loss. How did physicians discover that GLP-1s like semaglutide and tirzepatide have an effect beyond weight loss, like the reduction in cardiovascular events and stroke?

Dr. Majure: Well, diabetes patients, by the nature of them, have a very high incidence of cardiovascular disease that runs the gamut from coronary artery disease, heart attacks, strokes, peripheral arterial disease, and heart failure in all of its various forms. And so when you are studying patients with diabetes there will be events. And even if you create a trial that the primary endpoint is, say, improvement in hemoglobin A1c or some other marker of diabetic control, you might start to see signals if there is a salutatory effect of the medications for cardiovascular disease. And that's exactly what happened.

Why is that important? It's important because all of the diabetes medications up to this point, while they did a really good job at controlling hyperglycemia, we did not see improvements in cardiovascular outcomes until these drugs. And so it's really changed the way that we approach diabetes care.

But then the really cool question came about, well, do they need to have diabetes? And that's actually what happened, we started to branch out of diabetes and look at the event rates in people who let's say they just had heart failure or they had cardiovascular disease of some form, or they had obesity with or without comorbidities. What are the impacts? Are these things that could be helpful for improving patients' lives?

And as we study it in, let's say in heart failure with preserved ejection fraction, and now we have really a handful of trials looking both at semaglutide and tirzepatide showing, and this is one of the really fascinating things about it, decrease in inflammation, decrease in cardiac structure. So we're seeing left atrial remodeling. We're seeing decrease in left ventricular mass on MRI and seeing meaningful reductions in the case of tirzepatide with heart failure events. And we had a reduction in the combined endpoint of cardiovascular death and heart failure hospitalization.

Erin Welsh: And these effects, these results are not solely due to weight loss alone.

Dr. Majure: Right. The weight loss doesn't account for all of the benefits seen.

Erin Welsh: Wow. So this must be really exciting to you as a heart failure specialist. Especially since heart failure with preserved ejection fraction can be so challenging to treat effectively. And I understand there's a couple of recent studies that looked into the effects of semaglutide and tirzepatide on patients with heart failure with preserved ejection fraction. Can you walk me through those findings?

Dr. Majure: So in the setting of heart failure, with preserved ejection fraction, we studied semaglutide in the step HFpEF trials. And there's two, there's step HFpEF and there's step HFpEF with diabetes. And these are relatively small trials, 600 to 700 patients or so.

So in the trial with semaglutide, they looked really at quality of life and how far the patients were able to walk. And demonstrated just that: improved quality of life. Patient reported quality of life by scales that are well validated. And they did six minute walk tests to see how far they could walk. But they felt better and they were able to walk farther, about a little less than a city block in, on the Upper East

Side, for example. And they saw significant reductions in CRP levels. So once again, markers of inflammation.

So then the SUMMIT trial was released later, which looked at a very similar group of patients with heart failure with preserved ejection fraction, with tirzepatide instead of semaglutide. And they looked at more hard clinical outcomes. So they looked at heart failure admissions and cardiovascular death, and they showed significant reductions in that combined endpoint, which not surprisingly, was primarily driven by reductions in heart failure hospitalization.

And so it's not to say that you couldn't get that with semaglutide, but the nature of the trials might have shown it in one versus the other. I would say the best evidence that we have right now for that population, to my mind fits more with tirzepatide because we have hard clinical endpoints for that trial.

Erin Welsh: That is really interesting. So we may be looking at tirzepatide as an option for treating heart failure with preserved ejection fraction in the future, since the evidence really seems to be building there.

So I understand that there's been some research into the benefits of oral vs injectable GLP-1s. And I imagine that taking a pill over injecting could be a real game changer in terms of adherence. Like, if patients could take a pill every day, and really stay consistent with that, it might help them maintain weight loss and improve their heart health. And that's not to mention the other cardiovascular benefits that we're seeing with these therapies. Could you talk a little bit about what an oral therapy could offer and whether it could carry the same benefits as injectable semaglutides?

Dr. Majure: Right. So there's been an oral form of semaglutide now out for some time. It has an FDA approved indication for diabetes. And there was recently a paper released, which was the SOUL trial that looked at this. It was just released a few weeks ago.

And they looked at 8,000 patients, almost 9,000 patients who had a history of cardiovascular disease. So either they had had an MI in the past, they had had a stroke, or they had had a peripheral arterial disease. And they have diabetes. So basically looking at people with diabetes with cardiovascular risk and they randomized them to oral semaglutide versus placebo, and then followed them for about three, 3.3 years or so, and looked at outcomes.

And they looked at a combined endpoint of cardiovascular death, non-fatal MI, non-fatal stroke. And there were significant improvements with oral semaglutide. So there was a hazard ratio of 0.86. It was significant at a 0.06 level. The event rates were pretty low though, so we're talking about 3.1 events per 100 person-year in the semaglutide arm and 3.7 in the placebo arm.

So that ends up being a number needed to treat of about 50 patients over a 3.3 year period to reduce one endpoint. So it's not a huge effect, but when you amplify it over a population, especially when a lot of these therapies for diabetes don't seemingly impact hard cardiovascular outcomes, yeah, it becomes a meaningful therapy. But there still was a beneficial impact on the cardiovascular events.

Erin Welsh: So the oral medications, are they more concentrated in the gut? Do they also reach part of your nervous system, or is it a more localized approach?

Dr. Majure: Oral therapies would offer a lot of benefits over the injectables because people do not want to use injectables for understandable reasons. So, the actual details of what's going on from a molecular standpoint, I suspect that they are acting on the receptors throughout the body or else we wouldn't be seeing the cardiovascular benefits that we are potentially gonna be seeing here. But we still have a lot to learn.

Now, we should make a point, and I think it's important to make this point is that we have to, and we should be obligated to combine these therapies with appropriate guidance related to nutrition and guidance related to exercise in patients who are able to exercise.

But the nutrition is really, really important. When you take the therapies, it's not all loss of adipose tissue. Your caloric intake goes down and about 30% of the weight loss is said to be lean body mass. And so as a result, people can lose protein, they can lose muscle.

And that can be particularly bad in people who are sarcopenic and have a poor muscle mass at the baseline, and then if they stop the therapy and then regain the fat, but don't regain the muscle. Then you can get into a cyclical problem where you are regaining adipose tissue and losing muscle and potentially being worse off than you were before you even began. And we need to be really careful as a society that we are using these drugs appropriately. We need to make sure that people are using these therapies correctly and not causing harm.

Erin Welsh: I think that part of delivering treatments appropriately comes down to keeping an eye on the upcoming literature. Especially with heart failure, since it's such a common disease it makes sense that you'd need to stay on the cutting edge to treat it effectively. So I'm curious to get your take on how you see this class of drugs transforming medicine, or transforming the way that you treat your heart failure patients.

Dr. Majure: They're transformative. There's no doubt about it. The transformation in particular in the patients that I take care of, who invariably have high cardiovascular risk, who have heart failure syndromes, who often have diabetes, there's no question that they can benefit from these therapies. The greater societal questions are almost philosophical in nature. Certainly political and definitely cultural. And as we were saying before, it touches on how should we be viewing health in our society. We have to take care of the people that are in front of us with the problems as they are, but it behooves us to create a society that prevents these conditions to begin with. And we have a long way to go to get there, but we have to do it.

Erin Welsh: Definitely. And prevention is the best medicine, right? But also, finding new ways to treat these common diseases, like heart failure, is really exciting. Like, we're just now getting a glimpse into the potential of this class of medications. And that story is really just in its first chapter.

Dr. Majure: This is gonna be a story that's gonna be being told for the next couple of decades. And the nature of the medicines will probably change. The pharmacology will change, the pharmacokinetics will change, and we will learn more. Hopefully we will not learn of bad side effects that accumulate over time, but we need to be mindful of that potential. Sometimes as time goes by, that comes about and we need to keep an open mind about that. But I'm hopeful that that will not be the case. When I look at the totality of things that are published now, whether it be these retrospective studies or the randomized controlled trials, in the right patients, it is pretty clear to me that the benefits outweigh the risks. Does that mean it's the ultimate solution for diabetes and obesity? No. We would love, love, love to prevent these conditions prior to their onset. But right now this is a pretty good treatment.

Erin Welsh: Yeah it's really promising. And practicing at Cornell, I imagine you're really able to collaborate with other physicians who are also following this cutting edge research. And that means better care for the community overall, right?

Dr. Majure: Right. So the thing I love about being at Cornell is we take care of the whole community. Our patients are reflective of the world. They come from the Bronx, they come from Queens, they come from Brooklyn, they come from lower Manhattan. They come from every background you could possibly imagine.

The number of languages that I have to communicate with people over the course of the week is, it's just, it's fascinating. And so we get to take care of a huge range of people from every walk of life and realize the different type of treatments, the different type of approach that each and every person needs. And the program here really does emphasize that. We very much think of the person as a whole. In the nature of our work, we really have to think about everything. And that's not just the organs, it's the psychology, it's the personality. It's the whole thing. Or else you cannot be successful. Especially when we're talking about these sorts of therapies which touch on very sensitive cultural, psychological topics that influence the way that they think about therapy. You have to be keyed into and tuned to how people are perceiving them so that you deliver the treatments appropriately.

Erin Welsh: Well, this has been really just such a mind blowing and really fascinating conversation and I thank you so much for taking the time to chat with me today.

Dr. Majure: Well thank you, Erin. It's been a real pleasure.

Erin Welsh: Thank you to Dr. David Majure for taking the time to speak with me about the latest emerging science behind GLP-1s and how these therapies are affecting the course of care for people with heart disease.

I'm Erin Welsh. Advances in Care is a production of NewYork-Presbyterian Hospital. As a reminder, the views shared on this podcast solely reflect the expertise and experience of our guests. To listen to more episodes of Advances in Care, be sure to follow and subscribe on Apple Podcasts, Spotify, or wherever you get your podcasts. And to learn more about the latest medical innovations from the pioneering physicians at New York Presbyterian, go to nyp.org/advances.

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