

## **Pharmacologic Therapies for Obesity: The Future is Here**

Announcer: Welcome to the Mayo Clinic Cardiovascular Continuing Medical Education podcast. Join us each week to discuss the most pressing topics in cardiology and gain valuable insights that can be directly applied to your practice.

Dr. Hayes: Welcome back to the Mayo Clinic cardiovascular podcast series interviews with the experts. I'm our host, Sharonne Hayes. I'm a non-invasive cardiologist and vice chair of faculty development and academic advancement for the Department of Cardiovascular Medicine here in Rochester, Minnesota. Today I'm joined by Dr. Kyla Lara. She's a preventive cardiologist and echocardiographer and important for today's topic co-director of the Cardiometabolic Clinic. Today our topic is pharmacologic therapies for obesity. The future is here. Welcome Kyla.

Dr Lara: Thank you so much, Dr. Hayes. It's such a pleasure to be here talking about something I'm very passionate about and a lot of people out there want more information of. Yeah, so obesity's big, literally and figuratively. It's so prevalent and it particularly affects our patients our cardiovascular patients. And so we have some new therapies that are exciting but I think because they are new cardiologists wanna know a little bit more how they work. Who is the right patient they should that should receive them.

Dr. Hayes: So tell us about that.

Dr. Lara: Absolutely. Thank you for that question. And we know that obesity more and more research is coming out that it's a very complex disease. It's really more than calories and calories out. I'm sure you've had patients before that have tried everything in terms of lifestyle interventions and they really give it their greatest effort. But we know with every decade of life our resting energy expenditure and our caloric requirements really decrease. So all, a lot of things make it very challenging to lose weight. And we're in an era now with these new weight loss medications that were originally developed for diabetes where it's really gonna transform how we treat obesity as a chronic disease. And it's very exciting for us cardiology providers because we know that within our cardiovascular disease patients that many of them, many of them suffer from obesity. And a lot of the symptoms are intertwined right with cardiovascular symptoms shortness of breath, chest pain, reduced exercise tolerance and deconditioning that comes from obesity. And so it's really important that we understand these medications and also identify appropriate patients so to prevent the misuse of these medications and really target the correct patient population that would really benefit from from these. And so I'm really excited to talk with them talk with you about them. Excuse me.

Dr. Hayes: Yeah, so, so the, the indication for weight loss really came from treating diabetics and realizing they were losing weight and sometimes too much weight honestly. And so how do they work and what are we seeing as the short and long-term benefits and the side effects or consequences?

Dr. Lara: Absolutely. And so there are two main classes of these new GLP 1 receptor agonists and the dual GLP 1 GIP dual medication. So the GLP 1 receptor agonist, there's a daily dose if you have diabetes, it's called Victoza. And if you don't have diabetes, it's called Saxenda. And what it is is the generic word is or the name is liraglutide and that is our daily injectable. And what we, they found in the studies are that in diabetics and non-diabetics, there's about a 5% weight loss. From there, they develop more drugs, weekly injectables under the name semaglutide and semaglutide. When you reach the target doses that were seen in the trials of 2.4 milligrams you're seeing an upwards of about 15% weight loss in patients without diabetes and around 10% in patients with concomitant diabetes at 68 weeks or so. And then the newest kids on the block is TIR Peptide, also known as Mounjaro. And this is the dual medication. It has a GLP 1 receptor agonist and it also has GIP. And the synergistic mechanism of them working together in the trials actually showed weight loss of about 20 to 25% at 72 weeks which is pretty comparable to bariatric surgery. Now to go back to deter to talk about what do these medications even do? And so they're both in cretins which are naturally produce hormones by your gut. So GLP one or glucagon-like peptide one and GIP or glucose dependent insulintropic peptide they are released by your gut after you have a meal. And then this hormone will then go to multiple places as a pathway activator. So the most important ones are obviously the original indication was for diabetes, it goes to the pancreas and it improves insulin sensitivity and decreases glucagon secretion from the islet cells. It also goes to your brain. It's thought the theory right now as it goes to the hypothalamus to decrease appetite. And also importantly, it decreases thirst. So very important to talk to our patients when we're putting them on these drugs. If they're on concomitant diuretics and have underlying CKD, that it does decrease thirst. And lastly it goes to your gut and it decreases the motility. So all of the side effects are basically from this decrease in motility in the gut. And so you can imagine if you have a couple eggs or an omelet for breakfast or hopefully steel cut oats for breakfast instead of that food passing and digesting within 30 minutes to an hour that food will sit there over the course of the day. So by the time snack time, lunchtime afternoon snack, dinner time and maybe if you're a midnight eater, the portions in which you would otherwise consume normally are going to be cut by a significant amount. And so hence you're taking in less calories as well. And so that's the how they work to improve diabetes control and also for weight loss.

Dr. Hayes: And just talk briefly about side effects because I think we hear about that and that's why the doses are increased kind of gradually.

Dr. Lara: I understand. Absolutely. Yes. And similar to the trials is how our standard clinical practices we start at the very lowest dose and we increase every four weeks. So after four doses, once weekly injections. And the most common side effects from the decrease in gut motility are going to be nausea, vomiting, constipation, diarrhea pretty bad upset stomach and abdominal cramping. If you have a history of gallstones or pancreatitis you're at more risk for having these complications. A lot of patients who also have concomitant IBS or irritable bowel syndrome or any kind of irritable bowel disease, we'll have to be very careful about how we titrate these medications. And so all of these side effects are can be pretty uncomfortable to say the least but they're mild to moderate in terms of severity. The more severe reactions are going to be pancreatitis or gallstone pancreatitis. And then if you have a family history or a personal history of any thyroid cancers if you have a family history of men2 syndrome or men2 syndrome, then

there was a very small tick in the studies that showed there is an association with increased risk for those. So a lot of those need to be discussed with the patients. And then again, I can't emphasize enough in our cardiovascular patients with obesity a lot of them have underlying CKD. So it's really important to get a baseline creatinine on them, know their renal function, knowing that one of the side effects is to decrease the thirst. And so if you have a patient on lasix or furosemide, torsemide, bumex and you're giving these medications, understand that their diuretics may need to change as they lose weight we might need to change these diuretics and monitor that creatinine as well. And that goes the same for we know with significant weight loss or clinically meaningful weight loss, which is defined as at least 5% weight loss or more your requirements for blood pressure medications, beta blockers, et cetera all of those can change. So it's really important in our very special population of at least cardiovascular patients, to really work with a provider who understands that with this weight loss and it can be significant which is the goal that careful down titration and monitoring of these drugs is happening at the same time.

Dr. Hayes: So we've, we've talked about some of the, the secondary endpoints I guess related to cardiovascular ben, benefit. So with the weight loss we may have a drop in blood pressure less more easy to control or even back off on the meds. What are the other data about cardiovascular benefits in terms of actually hard end points? Are there any yet?

Dr. Lara: Right, and that is the most important question that all of us in cardiovascular medicine are itching to, to to know. And so currently, based on the scientific evidence all of the evidence is in secondary prevention and high risk type two diabetics. And what they found from these large trials is hard endpoints and decrease of MACE events or the major adverse cardiovascular events decrease atheromatous plaque improvement in renal function and improvement in all of those cardiometabolic factors. You know, there's, in addition to this to the pathways I mentioned these medications are, are associated, at least in the animal models right now, of anti-inflammatory improving endothelial function and it really having all these pleiotropic effects that we're still learning more. It's very exciting. I heard from a little birdie that I believe at AHA this year, they're going to come out with a select trial, which is basically looking at semaglutide and hard MACE outcomes. So we'll have an idea of how these drugs affect our cardiovascular patients without diabetes, which is going to really change the way that we treat obesity and cardiovascular disease. And it's really exciting. One thing that I've noticed since we launched our cardiometabolic clinic whenever you start these medications, one of the side effects is there's a trend in increased heart rate. Now there's no, hasn't been any association with increased arrhythmia, but patients will send me patient portal messages saying, Hey, I just want you to know my resting heart rate is around 85 or 90. I'm losing weight, I'm feeling good but I did notice my heart rate is increasing. What that means we have no idea at this point, but good to know.

Dr. Hayes: We have a lot of data for the benefits even in adolescents for bariatric surgery. What will this, will these drugs do you predict because you're an expert will they replace bariatric surgery be alongside them where, you know where are the roles for both of these treatments?

Dr. Lara: Yeah, and that's a question many people have surgeons non-surgeons alike. And the answer is, I think both have a role. Definitely. We know that in a lot of the select trials for semaglutide, they did extensions as to what happens when you discontinue these medications at one year and it's what you think happens, patients will gain weight. There's about, you know, they looked at it extra year after and what they found was patients still had a net negative about 5% weight loss. But they do lose all of those cardiometabolic benefits once they regain that weight once they stop these medications. Unlike bariatric surgery, for the most part this is an irreversible, depending on the type of weight loss surgery you undergo type of transformative transformative type of surgery to change that gut brain metabolism and how you malabsorbed a lot of nutrients and obviously calories to lose the weight. And so I think that it's important to have a medication like the GLP 1 receptor agonist as a first step especially in our cardiovascular patients who have a high operative risk for bariatric surgery. I think for the younger patients with longer lifespan thinking about the long-term effects of these drugs over decades, we don't have any data on that. But we do know from bariatric surgery all of those heart endpoints all cause mortality, et cetera are improved the bar with bariatric surgery. But for our adult congenital heart disease patients for our patients who've had reduced stern autotomies who are obese and they can't work out because of their cardiovascular symptoms. And I think medications would probably be the, the best least risky at least for those patients. But definitely a role for both.

Dr. Hayes: Yeah, and I think also consideration of cost. Obviously surgery has a big upfront cost and there's some ongoing follow up but we're committing patients to daily or weekly injections that currently are very expensive for a long time because just like when patients stop taking their statins their cholesterol goes back to baseline. My understanding is you stop taking these and your weight will drift up as well.

Dr. Lara: Absolutely. And so right now, because of the demand for the drug and the shortage, it's, it's, it's it's heartening and disheartening because for the patients who need it the most a lot of our patients who are 65 and older who are under state insurance or governmental aid right now, obesity related treatments by medications are unfortunately not approved. And so this is something that I think will hopefully change in the future to provide this opportunity for our most vulnerable patients. And I think something to put out there is, you know these medications, you see them in the news, Ozempic Wegovey, you know, Mounjaro, a lot of shaming and I have Ozempic face and this celebrity is taking it. And so it's really important to not make any judgments about whether or not an obese patient a relative yourself is taking it. We understand that all of the data shows that behavioral modification, modification lifestyle intervention over the long term is not sustainable in the current infrastructure of a convenient society as ours where we're, we're we're telling people to go out there, single parents parents who work nighttime shifts, parents who have no time they're single parents having to cook and clean and do everything, and then telling them to go work out for 45 minutes and to go grocery shopping every week for perishables that are healthy. You know, when you have calorie dense, ultra processed foods at whits end right next to them, cheap as can be and you're telling them to lose weight and have the willpower, I think we have to get with a program and understand that right now the way our society is, it's very, very difficult if you don't have the socioeconomic means to live that type of lifestyle that we need to embrace these medications. Just like you said we don't do any shaming on patients who take statins who still enjoy their red meat. We don't tell patients

who enjoy eating out with high sodium foods why are you taking blood pressure medications? And that's the same way we need to treat obesity. It's more than just calories and in calories out. And I really hope to contribute to everybody out there and de-stigmatizing that obesity is just shutting your mouth and exercising more.

Dr. Hayes: Yeah. My last question, I just wanna say what kinds of patients should be really perfect for your cardio-metabolic clinic? I mean, who are the ones who are gonna be benefited the most and who we cardiologist who, who who should we be sending to you?

Dr. Lara: Absolutely. So currently we are trying to help the most vulnerable patients who we know obesity has a high association with their cardiovascular disease. So those diseases are going to be atrial fibrillation. We know there's a strong association with obese patients who have atrial fibrillation. We know that heart failure with preserved ejection fraction has a very high and strong association with obesity. Patients who have heart failure with reduced ejection fraction. These patients are trying to get to LVAD or they're trying to get to transplant. And we know there are BMI cutoffs depending on what part of the country you're at to be a candidate for that. And if you're too big, then hey you're not gonna get listed. So those are patients that we would like to see too. Obviously they're gonna be more sensitive they're gonna be more challenging patients that we have to really hold their hand and make sure that we're watching the titration and the side effects like I said, with those diuretics and other medications. And then lastly, adult congenital heart disease patients. Here at Mayo, we have a very special group that takes care of these patients who've had fourth, fifth sternotomy. They're in their twenties, thirties, and their BMIs are above 40 and they, and they have high operative mortality with really high gradients across their conduits, across prosthetic valves. You name it. There's, you know the phenomena of patient prosthesis mismatch where patients are symptomatic, obese and they have high gradients across their prosthesis but maybe with weight loss those gradients can decrease along with their symptoms. And so these are the patients we're obviously focusing on right now. We understand that coronary disease pots I mean any disease that's associated with obesity probably will benefit but in terms of having that needing a special expert from a cardiology led program it's going to be those higher risk patients and obviously coronary disease as well because we know even with stable angina and stable coronary disease patients can be obese and deconditioned and they're constantly having repeat stress echoes. They're having other kind of non-invasive functional testing to really rule out what is causing their symptoms when maybe it's the obesity.

Dr. Hayes: I'm just excited about these drugs I'm excited about your clinic and I'm really grateful for you sharing your expertise today. So thank you for joining us.

Dr. Lara: Thank you so much, Dr. Hayes. It was such a pleasure.

Dr. Hayes: And thank you everyone for listening. This wraps up this week's episode of Interview with the Experts, and I'd like to thank Dr. Lara again for joining me today and discussing this important topic. We look forward to you joining us again next week for another interview with an expert. Be well.

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