Announcer: Welcome back to Mayo Clinic, cardiovascular podcast series, interviews with the experts. I'm your host, Sharonne Hayes. I'm a non-invasive cardiologist, vice chair of faculty development and academic advancement for the Department of Cardiovascular Medicine here in Rochester, Minnesota. Today I'm joined by my colleague Dr. Barry Borlaug. He's a professor of medicine chair of research for circulatory failure and invasive heart failure cardiologist, also here in Rochester, Minnesota. Today, our topic is managing heart failure with preserved ejection fraction. So, Barry, we know that half of patients with heart failure have HFpEF. Their EF is normal, but there haven't been many treatment options, and we've covered diagnosis in another podcast with you, which has been very helpful. But now that we can diagnose it better, we now are, can be, get excited perhaps, and perhaps educate ourselves about new treatments. This is exciting. So tell us how this traditional approach is evolving.

Dr. Barry Borlaug: Well, thanks Sharonne. So, you know, it is, it's, it's even more than half of all heart failure, and we've been saying this for years, but for years we've had nothing to offer. We started out very logically, I think, trying to treat HFpEF like heart failure with reduced EF or so-called systolic heart failure. But trials of drugs like angiotensin receptor blockers and ACE inhibitors, limited data and beta blockers, even digoxin, there really wasn't any significant, you know, evidence of significant efficacy. So for years, the, the mantra was, you know, give diuretics for congestion, level of evidence C and think about using things like ACE inhibitors to control blood pressure and treat comorbidities like that's gonna, you know, treat their heart failure. And of course, you're always gonna treat comorbidities, you're always gonna treat blood, you know, high blood pressure and things like that. But in the last couple of years, we've started to see more. It started with mineralocorticoid antagonists, spironolactone in the top CAT trial. Overall, that trial was neutral, was not significant. Spironolactone as compared to placebo, did not reduce the risk of heart failure, hospitalization, cardiovascular death. But about half of the patients were enrolled in the Americas, half were in Eastern Europe and Russia. And when they looked at the two sides of the world, they saw some important differences. The event rates were very low in Eastern Europe and Russia. And when they just looked at suggesting that they didn't really have HFpEF in the first place, and when they looked only in the Americas post hoc, they saw that pironolactone did work. So that was given a to-be recommendation in the guidelines, something we can consider, but not strongly evidence-based then came Sacubitril Valsartan, which was tested in the Paragon trial. And this was a very large trial as compared to placebo. Sacubitril Valsartan almost reduced the risk of total number of heart failure events or cardiovascular death. P value 0.06, it was a modest effect size and it was borderline significant. So the guidelines also gave that A to-be that we can, we can consider it, we can think about it. So we had some signal of evidence that we could think about these. But things really changed with the introduction of the SGLT two inhibitors. And as you know, the FDA required diabetes drugs to be tested on cardiovascular outcomes years ago. And we serendipitously noted that patients with diabetes treated with these drugs had lower rates of heart failure hospitalization. So that was first tested in heart failure with reduced ef. And then more recently in two large cardiovascular outcome trials in HFpEF, the emperor preserved trial. And then more recently in the DELIVER trial, they were both published in the New England Journal, and they both showed that as compared to placebo treatment with SGLT two inhibitors, empagliflozin and Dapagliflozin 10 milligrams once daily reduced the risk of heart failure hospitalization and cardiovascular death by about 20%. So now we have strong two trial level of evidence. A class one will be class one in the updated guidelines treatment for HFpEF. So this has been a

real, real game changer. In addition to all the other things that we've been thinking about with diuretics and maybe considering spironolactone and sacubitril Valsartan,

Dr. Sharonne Hayes: How do we think that these work?

Dr. Barry Borlaug: Yeah, that's a really good question. The SGLT two inhibitors have widespread protean effects, as you know. So they, they, they cause loss of glucose in the urine. This leads to a little bit of an energy deficit, a little bit of weight loss. It's usually not that remarkable. There can be a natriuretic effect. Of course, there's a little bit of a reduction in plasma volume, which can help. But after that, we don't know for sure at the cellular level, there's evidence that they enhance clearance of toxic accumulation byproducts in the cells. They reduce oxidative stress, they reduce signaling pathways that are indicative of a nutrient excess, which we think are bad for a number of reasons. We published a study earlier this year in the journal circulation where we looked at the invasive hemodynamic effects of dapagliflozin for six months, and we saw about a 20% reduction in both resting and exercise, left atrial pressure measured by wedge pressure. So there's definitely a hemodynamic benefit. And that sort of fits with what we've seen with improvement in quality of life, improvement in exercise capacity measured by six minute walk distance. This was both looked at in a trial called preserved hf, and then the reduction in heart failure events. But we still, th there's, you know, there's a lot of other possibilities. There may be direct myocardial effects, there may be antis sympathetic effects. A lot of research is still focusing on this because, you know, even though we've done better with treatment, the residual risk of people who are on guideline directed treatment is still high. So we've still got a long ways to go.

Dr. Sharonne Hayes: So can you share a little bit about safety and cautions related to the patient population we may be considering these medications for?

Dr. Barry Borlaug: Yeah, I think that's, that's always in addition to efficacy, safety is crucial. And the SGLT two inhibitors are quite safe. People, you know, worried about hypoglycemia, obviously their diabetes drugs. But unless you're being treated with insulin providing therapies, either insulin or sulfonylureas, for example, there wasn't an excess risk of hypoglycemia. So that's one important feature. There wasn't a, a significant excess risk of like ketoacidosis. What there is is an increase in the risk of uro, genital urogenital infections, which can happen. Obviously you're, you're increasing the content of glucose in the urine, you're making that a better environment for, for, for microbes. So that is one thing that we do run into a little bit more and something that we need to caution our patients about. But really the uptake has been very quick. You, you, as we were mentioning earlier, you know, primary care physicians are more comfortable prescribing these medicines. Now certainly cardiologists are more comfortable presiding prescribing these, and, and they, they work, they work a little bit better. The absolute risk reduction is even greater in people with obesity. And that takes us to an even more recent trial called STEP HFpEF. And you know, for years we thought about HFpEF as this disorder of, you know, older aged women, hypertensive hypertrophy, small hearts. But in the last 10 years we've really noted that a lot of people with HFpEF have obesity. And that's risen to become the dominant sort of phenotype. Is this people with

obesity related HFpEF. And they have many of the same features that we see in non-obese patients with HFpEF. But there are some important differences. They have more visceral fat, they have more epicardial fat, they have more volume overload, they have more systemic inflammation. Their CRP levels are higher. You know, obviously they have more diabetes and glucose intolerance. And the step trial step HFpEF trial followed on the heels of the other step trials of semaglutide GLP one receptor agonist that leads to pretty significant weight loss. And step HFpEF was a trial that randomized patients with obesity and HFpEF to treatment with semaglutide or placebo for one year and was just recently published. And the primary endpoint, dual primary endpoints were body weight reduction in quality of life. And both of those were highly significantly improved. Secondary endpoints included exercise capacity, six minute walk distance, a composite endpoint, and CRP levels as a major of inflammation. And all of those very consistently were very highly significantly improved. So now in addition to the SGLT two inhibitors for people that are living with obesity and HFpEF, we have semaglutide. Of course the issues are availability and cost. Yeah. But we have something else to offer as well. Exactly.

Dr. Sharonne Hayes: So getting to just a really practical, I'm a cardiologist, I'm not a heart failure doc, I'm a family medicine or general internist. I've got a patient who I either have made a diagnosis with the help of a cardiologist or pretty confident because of, of the, the likelihood when and how do I start these treatments? I mean right away do I, do I need to do much else before I initiate one of these, these drugs?

Dr. Barry Borlaug: I think so if they look like they're so SGLT two inhibitors clearly have the strongest data and they can treat volume overload and the with between patient variability and how much they reduce volume can be variable. So I would say the first thing once you've securely made the diagnosis would be to start them on an SGLT two inhibitor. Unless there's a contraindication for some reason, I would follow them up in not to, if they're volume overloaded, if they have jugular distension edema and things like that, I'd probably see them back within a couple weeks because if they're still volume overloaded after starting the SG SGLT two inhibitor, then you'd probably want to get them on a diuretic as well. But for some people who are congested, just starting the SGLT two inhibitor will take care of that. So that would be first and foremost. I think that if you see them back, if they weren't congested, you start the SGLT two inhibitor, you'll see them back in a couple months. If they still have significant symptoms, that's when you're gonna think about some of these other possibilities as I mentioned earlier, like spironolactone or sacubitril valsartan. And there are certain patient populations where you might lean on these earlier patients with the lower efs, like closer to 50 or you know, 49 or 52. They might respond better to both of those. People with more severe hypertension may do better with the sacubitril valsartan because of the blood pressure lowering effects. People with recent hospitalizations do a little bit better with those. And then in subgroup analysis there was a little more evidence of benefit in women than men for sacubitril valsartan. So that, those are all things that might push me if they're still significantly symptomatic on the SGLT two inhibitor plus or minus the diuretic to add those other drugs. And now with semaglutide, I think that if they're obese and they're on an SGLT two inhibitor, I would, I would have a variable threshold to treat with that. If, again, if you can get it, it's, it's currently not covered for this indication, but, but the trial evidence is very compelling.

Dr. Sharonne Hayes: This is just sort of more your experience, how, how many of the patients that you care for really have enough improvement with the single starter drug that you don't really have to resort to some of these others. I mean, is it, is it that good enough that we may even half of our patients that might be enough to, to render them substantially less symptomatic? Or is there still a fair amount of residual symptoms?

Dr. Barry Borlaug: I think there's still a fair amount of residual symptoms. And when you really push people, a lot of them will say, well I feel a lot better. But, and people like to minimize their symptoms, you know, heart failure symptoms come on gradually. And what people do, what do you do when you're short of breath with activity? Well, you reduce your activity level and then you're, you perceive less shortness of breath, but that's 'cause you're not being very active. And we know that that's very bad for, you know, many reasons. So I think that when you push push people on this, you see that most people are not cured by addition of these drugs and they, they do need more, you know, some other things I didn't go into, but you do want to think about the other comorbidities. And some of them are very common. AFib, you know, two thirds of people with HFpEF will have atrial fibrillation at some point in their life. We don't have a prospective RCT specifically looking at treat, you know, rate versus rhythm or catheter ablation versus drug therapy. But we do have a lot of a lot of smoke that suggests that there may be benefit there. The cabana trial randomized people with AFib in general to catheter ablation versus drug therapy. There were improvements, quality of life, there was a trend to improvement in the primary endpoint. When they looked at people with heart failure, the signal was even stronger. It's post hoc analysis. So we can't treat it as, you know, like sort of level of evidence. A but many of us I think really have a variable threshold to try to get people into sinus rhythm and keep them in sinus rhythm. If you suspect coronary disease, there is observational data that revascularization can help. If they have other things like high blood pressure, obviously you're gonna treat their high blood pressure. If they have sleep apnea, you're gonna treat their sleep apnea. So you, you want to be a good overall doctor and treat all these other problems as well, not just focusing on the heart failure.

Dr. Sharonne Hayes: I think you've made the case for really close follow up of these folks after initiation of whatever treatment you start with because there may be more than you can, that you can do for them that will continue to improve their, their outcomes and just their quality of life.

Dr. Barry Borlaug: Absolutely.

Dr. Sharonne Hayes: Anything else you wanna share about, you know, maybe what's next? What do we have to look, what are you looking forward to?

Dr. Barry Borlaug: Well, I'm looking forward to more, more evidence, you know, so there are a number of trials. There's a, a trial of a different mineralocorticoid antagonist, finerenone in HFpEF. There's a trial of another weight loss drug called Tirzepatide, which is a GLP one receptor agonist slash GIP agonist called

Summit. There's another trial. So the STEP HFpEF trial was only in patients with obesity and HFpEF, but no diabetes. There's a sister trial called Step HFpEF dm, which will report soon in the not too distance future to tell us more about how it does in diabetes patients. And also many of these patients will also be on SGLT two inhibitors. So how does the effect, you know, interact with that? And then there's a whole host of other therapies coming down the pipe as well. You know, we've made great strides, but these people, as I mentioned earlier, still have a lot of symptoms and a lot of risk of ho hospitalization and and death. So I think that there's plenty of room more in HFrEF. We've got seven or eight treatments and they still have risk. And it's the same thing in HFpEF. We've got a couple now in our toolbox, but there's a lot of room for more. So. We'll, we'll, it's a very exciting time and I think we're gonna have much more to offer in the years to come.

Dr. Sharonne Hayes: Well, thank you so much, Barry, because I know you've been involved in this space when it was unappreciated and people thought it was a dead end. And so I, I am thrilled that you and others are able to sort of reap this satisfaction of being able to help the people you've been studying so long. Thank you, Barry.

Dr. Barry Borlaug: You bet. Well that's what it's all about. Thank you Sharonne.

Dr. Sharonne Hayes: This wraps up this week's episode of Interview with the Experts and I'd like to thank Dr. Borlaug for joining me today and discussing this really important topic. We look forward to you joining us again next week for another interview with the Expert. Be well.