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Improving Symptoms, Function, and Weight Loss in HFpEF Patients with Obesity

Dr. Cheeley:
In recent findings presented at the 2023 ESC Congress, semaglutide, was seen to improve heart failure-related symptoms, physical function, and weight loss in patients with heart failure with preserved ejection fraction and obesity.

You're listening to *Heart Matters* on ReachMD. I'm your host, Dr. Mary Katherine Cheeley, and joining me today to discuss key findings from the STEP-HFpEF study is fellow ReachMD host Dr. Javed Butler. He's also the President of Baylor Scott and White Research Institute in Dallas, Texas.

Dr. Butler, thanks so much for joining me today.

Dr. Butler:
Absolutely a pleasure to be here. Thank you.

Dr. Cheeley:
You get to be on the other side of the microphone this time. This is going to be so fun.

Let's jump on in. So I, in particular, was so excited about this study. I want to talk about the patients that were included. So given that there's no approved therapies really for hardly anything specifically targeting obesity and HFpEF, how do we currently manage these patients that we're seeing in clinics now?

Dr. Butler:
Yeah, I think it gets a little bit even more complicated than just the fact that we don't have any approved specific therapy. There is this whole controversy about the obesity paradox that people who are overweight in patients who have heart failure tend to do better, but then there is a whole lot of confounding there and observational studies and whether this is selection bias, and cachectic patients have more advanced heart failure, therefore, they die, but it's not really about the weight loss, so the clinicians have really been confused to what recommendation to give.

Now we know that weight loss is incredibly important when it comes to prevention of cardiovascular diseases, but here we are talking about people who already have manifest heart failure, whether weight loss is a good idea or not. Now if you talk to most clinicians they would probably say that it is a good idea. There are data with surgery that substantial weight loss may be associated with good outcomes, but we had this discomfort. So on the basis of that, the only study that we have to rely on was a study on exercise and diet regimen in HFpEF patients showing that if you were to do that, you increase exercise capacity—this was an NIH-funded study—but we really needed more data, and in that sense right now the recommendation is to treat heart failure patients with obesity phenotype as any other HFpEF patients, and then just basically give some recommendation for diet and exercise but nothing really specific.

Dr. Cheeley:
So let's talk specifically about the STEP-HFpEF study. How is it designed? And what patients were included? You mentioned before cachectic patients, there might have been some selection bias there, so what particularly were you guys targeting in this study?

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Dr. Butler:
Yeah, so there are about almost 80 percent or so of the patients with HFpEF are obese or overweight, and there are enough pathophysiologic data, hemodynamic data, that these patients are not like any other patients with HFpEF. For instance, older patients with predominantly hypertension who are thin and may have fibrotic hearts, that the hemodynamics here are a little bit different, the pathophysiology is a little bit different, so we were targeting patients who were overweight with HFpEF. Now this was a program of two sister trials. Both of them enrolled patients with clinical diagnosis of HFpEF and some confirmatory evidence, either structural evidence, high NT-proBNP levels, hospitalizations, those kind of things, and BMI greater than 30, and one trial targeted primarily on those patients without type 2 diabetes and the other trial in patients with type 2 diabetes with the similar characteristics. So the study that we'll talk about today is in those patients without type 2 diabetes. The one with type 2 diabetes is ongoing. It's wrapping up, and hopefully, we'll get the results soon.

Dr. Cheeley:
What were some of the key findings? What was the primary endpoint you guys were looking for?

Dr. Butler:
So the primary endpoint was this dual endpoint of weight loss and improvement in quality of life or health status, which was measured with the use of Kansas City Cardiomyopathy Questionnaire, and then we looked at a bunch of secondary endpoints as well, which included clinically important endpoints like six-minute walk test and functional capacity for the patient, but also some pathophysiologic endpoints, like reduction in natriuretic peptide levels or inflammatory burden in terms of reduction in CRP. And then we had some exploratory analysis on clinical endpoints as well.

Dr. Cheeley:
This study sounds so interesting on so many different levels because I think so much we think about obesity as being just the number on the scale. If I can lower weight and handle these patients who have obesity, then of course everything will get better. I think that's what makes it such a robust study.

Dr. Butler:
I think that we will have a lot of academic discussion around this trial, whether it is treating HFpEF or whether it is treating obesity. So one can say, "Well, your quality of life will get better and you will walk more, and your inflammatory burden or C-reactive protein will go down if you have substantial weight loss by itself," so, one is that, okay, so even if it is weight loss, if you have proven that weight loss —forget about the obesity paradox. But it's actually substantially improved outcomes, then from our patient's perspective, it really doesn't matter whether you are treating HFpEF or whether you are treating obesity. But I would say that we have data that would really suggest that it is treating HFpEF, and the reason why I say this is that with weight loss, your NT-proBNP levels actually go up slightly because obese patients have low NT-proBNP. And if you look at some of the other trials with weight loss, NT-proBNP in here, the fact that the NT-proBNP levels are going down gives us some direct evidence that there are direct cardiovascular effects as well and not just the weight loss itself.

Dr. Cheeley:
For those of you just joining us, you're listening to *Heart Matters* on ReachMD. I'm Dr. Mary Katherine Cheeley, and I'm speaking with Dr. Javed Butler about the step HFpEF study.

So let's keep diving into this because I am loving this conversation. Tell me a little bit more about the findings. How significant is this in the world of HFpEF?

Dr. Butler:
So we met both components of the primary endpoint. There was a 10 percent body weight loss net in favor of semaglutide, but that would not come as a surprise. We know that these drugs are associated with weight loss. But there was substantial improvement in

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quality-of-life scores as well. So if you look at the KCCQ clinical summary score, on average that was improved by about 7.8 points, which was highly statistically significant as well, which allowed us to look at other endpoints as well. So there was about a 20-meter increase in six-minute walk test, and then there was significant reductions in both C-reactive protein and NT-proBNP levels. And then finally, we had a clinical composite score. Now remember that this is not a very large outcomes trial. There were about 500 odd patients, the relatively shorter follow-up, so the number of clinical events were less. But if you look at the composite clinical endpoints, they were substantially again in favor of the use with semaglutide.

Now how do you put this across other trials? Just to give you an idea, all trials in heart failure space that we have looked at, whether it is ARNI, SGLT2 inhibitors, other trials, we are looking at, 1.5 to 2.5 points improvement in KCCQ on average. The trial that has shown us the highest was the PRESERVED trial with dapagliflozin that showed about a five-point, but that also was an obese patient trial but was quite safe. And here we are exceeding all of those, and it is 7.8, so this is really substantial improvement in quality-of-life scores.

Dr. Cheeley:
Was there any safety signal that you guys saw? Any adverse effects that we should think about differently in this population of HFpEF?

Dr. Butler:
Yeah, certainly. There were adverse events that we have to be careful about, but if you look at the general adverse events, they were very well matched. Actually, the cardiovascular adverse events, if anything, were numerically lower in the semaglutide arm. The thing, which was significantly higher in the semaglutide arm, was the GI discomfort, but that is something that we have known for a very long time. So there was not only no surprises, the proportionality was also not different than what we already know from GLP-1 receptor agonists. So other than the GI discomfort in some patients, overall the safety signal was pretty comparable and nothing untoward that jumped out.

Dr. Cheeley:
What was the maximum dose that patients were able to tolerate in the study?

Dr. Butler:
So the target dose was 2.4 milligrams weekly.

Dr. Cheeley:
I've had multiple patients on these drugs, as I'm sure you have as well, and I will say that most of them can tolerate something, so it's not like an all or nothing. And I think that's really important when we are talking about these studies because we want to get you to the max dose, but just because you can't get there doesn't mean that we won't get some kind of benefit from that, so I think that's really important for everybody to understand. It's not an all or nothing.

Dr. Butler:
So I want to be super careful not to say that we have proven that in this particular trial,

but in general, what you're saying is incredibly important. We have seen that with ACE inhibitors and arbs and beta blockers in other trial that, yes target doses are great, but lower doses are far better than no doses. So whatever is tolerated, if you cover a particular pathophysiologic pathway, it is still better than stopping it all together.

Dr. Cheeley:
I totally agree. I think that's something that is hugely overlooked, especially in community practice or in patients who have polypharmacy.

So before we close, what does the future look like for semaglutide for clinicians, for these patients in the cardiovascular space? What do you think?

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Dr. Butler:
So I would say that first, obviously in the next few months, we will get the results of the sister trial in patients with type 2 diabetes, so we'll get the total picture of the entire population, so that's one thing. The second thing is that the world continues to move on in parallel directions at the same time. So for instance, the guidelines have now evolved for patients with HFpEF, and SGLT2 inhibitors are now a class 1 recommendation for patients with HFpEF, but when this trial was initiated, that was not the case, so a distinct minority in single digits who are on SGLT2 inhibitors. So I think one question, which will be raised, is that the combination therapy—we know from type 2 diabetes literature that combination therapy from a safety perspective is not an issue—but the issue here is, what is the incremental benefit. So some people will question that, although, as I said, the quality of life benefit with SGLT2 inhibitors at the population level that we have seen is relatively modest, and these are pretty substantial data, so we can, perhaps, extrapolate some.

The biggest question in my mind is that there was such a sharp difference in the heart outcomes, if you may, mortality and morbidity, hospitalization outcomes, but there were very few to make any conclusive decision on the basis of that that I think these data are now screaming to do a full large outcomes trial and beyond just the quality of life and functional capacity, so again, I'm going to be careful when I say just the quality of life and functional capacity. I'm not trying to lower the importance of that. At the end of the day, our patients really want to feel better and be more functional, so these are really important outcomes. But the signal is so intriguing that hopefully, we will move on and do larger trials as well.

Dr. Cheeley:
I think that's an excellent way to wrap this up. These are super exciting findings and a really, really important step in talking about our patients with obesity-related heart failure with preserved ejection fraction, a population that is extremely difficult to treat.

So thank you so much to my guest and fellow ReachMD host, Dr. Javed Butler, for joining me today to talk about these insights and findings from the STEP-HFpEF study.

Dr. Butler, this was a lovely discussion. Thanks for joining me.

Dr. Butler:
Absolutely a pleasure chatting with you today. Thank you so much.

Dr. Cheeley:
For ReachMD, I'm Dr. Mary Katherine Cheeley. To access this and other episodes in our series, visit ReachMD.com/HeartMatters where you can Be Part of the Knowledge. Thanks for listening.

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