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Direct from the Heart Failure Clinic: Novel Device Therapy for Patients with HFrEF

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Dr. Fudim:
As cardiologists, we know that many patients develop worsening heart failure despite the use of GDMT, or guideline-directed medical therapy. And some of our patients are not suitable candidates for treatments like CRT which is cardiac resynchronization therapy. Now there’s baroreflex activation therapy, also called BAT. It’s an implantable, FDA-approved cardiac autonomic modulation device. Let’s review its clinical trial evidence and see where your patients might benefit from its use.

This is CME on ReachMD, and I’m Marat Fudim, doctor at Duke University Hospital in North Carolina.

So let’s start with talking about the current gold standard management of heart failure patients, and specifically heart failure patients with reduced ejection fraction [HFrEF]. We call it a 4-pillar therapy. We have made great strides on improving morbidity and mortality – morbidities such as heart failure hospitalization. We were able to reduce heart failure hospitalization, and we are now able to prolong the life expectancy of patients with HFrEF by many years – up to 8 years of additional life gains if you use those 4 pillars of drug therapy. The problem becomes is that the game’s not over at this timepoint. We still have a lot of residual risk. Patients, despite GDMT, remain at a high risk for heart failure hospitalizations, so worsening heart failure and even cardiovascular death.

Notably, we now have additional therapies to fill the gap that is present in patients that get titrated on GDMT. Here is sort of a story of my clinic patients get titrated on GDMT over a matter of 3-6 months. We then consider ICD [implantable cardioverter defibrillator] or CRT therapy, if eligible, and what often happens is that about 70% of patients remain symptomatic with class 2 or class 3 symptomatic heart failure, despite GDMT, despite CRT in place. And in some patients, we now consider therapies such as remote monitoring at this timepoint, because patients’ general course is to continue to get worse with time in the presence of HFrEF. We continue watching those patients and continue getting worse with time, and then maybe consider advanced heart failure therapies, at my institution and many others. The problem with that is that at this timepoint, 95% of our patients are no longer candidates or are already deceased, and are not candidates for advanced heart failure therapy.

So I would argue that filling that gap from GDMT to advanced heart failure therapies, that this is a gap that we need to fill for additional therapies, such as the therapies that were recently highlighted that are available now in the United States, and are approved by the FDA. This includes mitral valve repair strategies, cardiac contractility modulation, but also baroreflex activation therapy, which was the first device approved under the breakthrough device designation law back in 2019, and that’s what I’ll be talking about today, because this device is approved for ejection fraction of 35 and less.

So where does the device get into action? It treats patients with HFrEF who have an autonomic dysfunction, and autonomic dysfunction as measured by a heightened sympathetic or a lowered parasympathetic tone, is highly prevalent in patients with heart failure with

reduced ejection fraction. As a matter of fact, the arterial baroreflexes – one of those autonomic reflexes which is very important to the maintenance of blood pressure and heart rate in every human being, every time we stand, every time we exercise – that reflex, the baroreflex, is downregulated in patients with heart failure with reduced ejection fraction. As a result, sympathetic tone gets out-of-control high, and the parasympathetic tone – that's the rest and digest tone – gets lowered, and there is no control over that reflex anymore in patients with heart failure with reduced ejection fraction. As a result, it is an imbalance of the autonomic tone that leads to an exacerbation of heart failure symptoms. So the baroreflex sensitivity is how we test the reflex in patients at our bedside, and this has been done again and again. It's a little bit cumbersome to do at a bedside right now, but in the past you could have done it very simply by applying either negative or positive pressure on the baroreflex, which is primarily having its afferent signal from the carotid, so on the right and left side in the carotid bulb. So if you apply suction, what happens is that you have a change in your blood pressure, as displayed here on the y-axis, and on the x-axis is the neck pressure, either positive or negative applied, and what you see is you can plot a curve. The more pressure you apply, the more changes occur as a result by the baroreflex in a healthy adult. As you see in patients in black, here with heart failure, the baroreflex sensitivity, measured by the slope, is down. So the reflex is just no longer as active in patients with heart failure with reduced ejection fraction. To make things more interesting and worse, the higher your symptom burden in patients with heart failure, the worse is the baroreflex downregulation. So the reflex is just numb in patients that have advanced systolic heart failure.

And then, you can also look whether the degree of baroreflex sensitivity is associated with outcomes, and it is. The lower the degree of BRS – baroreflex sensitivity – the lower it is, the worse the outcomes, and it's here measured as a propensity to survive. So it's associated with worse outcomes. It's associated with worse symptoms.

For those just tuning in, you're listening to CME on ReachMD, and I'm Dr. Marat Fudim. And I'm today discussing novel device therapies for heart failure patients, directly from the Heart Failure Clinic.

So the concept of stimulating the baroreflex is actually not new, believe it or not. Back in the '60s, Eugene Braunwald and colleagues actually stimulated that nerve with an implantable device, but what it found was that when you stimulate patients with angina and likely some degree of heart failure at that timepoint as well, that you were able to lower the blood pressure and the heart rate, and they were able to do that repeatedly, and when they exercised those patients, they found that the patients exercised with a lower peak blood pressure, lower peak heart rate, and were able to exercise further without symptoms of angina.

So now, that therapy didn't pan out back then, because now they had GDMT come on the market. They had diuretics that came around, and the device was just too clunky and too big. But the concept of baroreflex stimulation was then tested
With implantable devices that I'll show you the technology of shortly, where we can show that in humans, if you implant the device, you can increase the baroreflex sensitivity all the way out to 6 months. As measured with direct nerve activity, you can actually lower the sympathetic tone all the way out to 6 months. The follow-up was just aborted at that timepoint, but those implantable devices allow, of course now, the stimulation of the autonomic nervous system and the rebalancing of the autonomic nervous system for the years to come.

So there are also direct cardiac effects that were measured in patients with heart failure. Here, it's specifically in a patient with hypertension and heart failure with preserved ejection fraction, where you can see that there are also acute effects, not just chronic effects on the autonomic system, but the autonomic nervous system changes translate themselves directly to hemodynamic changes when these PD loop experiments, there's an improvement in stroke volume and a lowering in all over filling pressures – systemically, so the arterial pressure drops here and the patient was very hypertensive to begin with, on the 80s, on the 90s – but also there was a lowering of the left ventricular and diastolic pressure from 19 to 13. So direct hemodynamic effects seen as well as longitudinal autonomic rebalancing.

So can we now deduce that from these changes in the rebalancing with autonomic tone, direct hemodynamic changes, can we translate those acute changes, autonomic changes, to longitudinal changes that benefit, now, the clinical outcomes, such as heart failure symptoms, quality of life, and functional parameters?

So the device. Let's talk about what was approved by the FDA, and it was tested by the studies I will be showing in a second. It's a device that you usually implant on the right or on the left side of the chest. You want to be on the opposite side of the ICD ideally, or the pacemaker. You tunnel this extravascularly; it never enters your vascular space. This is not a, per se, like a regular pacemaker. A vascular surgeon would place the devices right on top of the carotid artery. He'd never cut into the carotid artery. It's stitched on top of it.

So the clinical evidence that led to the approval of the device in the United States is the so-called BeAT-HF study, was a phase 3 pivotal trial. This was a randomized, controlled study where patients either got Barostim or were having open-label medical management so they had just regular GDMT. And Barostim was added to GDMT, so this was not tested against GDMT, but as an additive strategy. Follow-up was for the 6 months, and then follow-up is going on thereafter, and I'll talk about that as well. So first of all, there were no

significant high-risk complications, so the MANCE rate – that's the adverse neurological cardiac events – was as predicted, 97%. It was actually relatively low; it's comparable to CRT devices, if not even lower. And if you look at the clinical outcomes – so the primary endpoint was a reduction in these components. So there was an improvement in exercise capacity. Everything more than 30 is clinically relevant, so there was an improvement of 60 meters compared to the control group. There's also an improvement of quality of life – a negative score is a good thing. So a drop by 14 points, highly clinically and statistically significant. Here, anything more than a 5-point drop would be clinically significant. Then you have also NYHA class. There was a 34% improvement in NYHA class. Also, there was a 25% reduction NT-proBNP. So that's the biomarker indicative of lower filling pressures, maybe an improved volume status as well. Notably, this compares very, very favorably to other studies such as the PARADIGM-HF study, Entresto in patients with HFrEF, where there was a 10% reduction of NT-proBNP only, which was then associated with hard clinical outcomes, such as heart failure hospitalization and death.

Let's talk about heart failure hospitalization and death, because what I have not presented to you yet is the hard clinical data. So I have hopefully convinced you now that there is pathological and pathophysiological rationale to suggest that stimulating the baroreflex, augmenting the baroreflex will reduce the sympathetic tone, lower filling pressures, reduce the amount of catecholamines swimming in the body, reduce the amount of hormones that are vasoconstrictive, will reduce NT-proBNP, will improve the quality of life and functional capacity. The data that is still pending, we will hopefully have in the beginning to mid of 2023, will be the outcomes data for the BeAT-HF study, which are currently still getting collected and looked at.

All right, let's summarize what we maybe have learned by now. So I hopefully was able to convince you that in heart failure, there's autonomic dysregulation with a lowered baroreflex sensitivity. I hopefully then convinced you that stimulating the baroreflex will improve baroreflex sensitivity, decrease autonomic tone, improve the amount of hormonal levels so they'll reduce the catecholamine levels. But as a result, there's an improvement in vascular compliance, leading to your reduced cardiac filling pressures, and those then translate, longitudinally in follow-up in trial patients, to an improvement in 6-minute walk distance, an improvement in quality of life, and a reduction in NT-proBNP, a surrogate of volume and pressure overloads. So whether those, then, translate into hard clinical outcomes, that jury is still out, but the good news is that the trial, the BeAT-HF trial that led to the FDA approval by the technology, that this trial is still collecting all the follow-up for the patients, and at some point, Q1, Q2 in 2023, we will have some additional data out that will show us hopefully a benefit also of heart failure hospitalizations and mortality. So that is still to come, so stay tuned.

I certainly thank you for your attention today, and hopefully you are as excited about this technology as I am. And again in summary, this is something that's FDA-approved now, since 2019, and approved for patients with ejection fraction of 35 and less.

Unfortunately, that's all the time we have today. I hope this information directly from the Heart Failure Clinic have been useful. Thank you for listening.

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