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Clinical Trials in HFpEF: What Have They Taught Us?

Announcer:
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Dr. Patel:
Okay, good afternoon, everyone. I'm happy to talk with you today about clinical trials in heart failure with preserved ejection fraction. And really what they've taught us about the overlap between HFpEF, PH, and the just the details that we've learned from doing clinical trials in HFpEF applied to the PH sphere. Okay, so the overall goal is to discuss these recent HFpEF clinical trials and their relevance to pulmonary hypertension.

As Dr. Raza mentioned, PH in HFpEF is actually quite common. And it's an extremely morbid condition. In this analysis, published in *JAMA Cardiology*, we see that the presence of pulmonary hypertension associated with left heart disease is associated with significant morbidity and worse survival. And so PH, the presence of PH, whether it is at rest or with exercise, identifies a very high-risk HFpEF group for subsequent hospitalization and for overall mortality. And so a very, very high-risk group.

What we know is that patients with PH and HFpEF benefit from standard guideline therapies for heart failure with preserved ejection fraction. So within the past 1 or 2 years, we've identified that across the LVEF spectrum, SGLT2 inhibitors are disease modifying, reducing heart failure hospitalizations across the spectrum of ejection fraction. And this has been shown through individual clinical trials along with meta-analyses of clinical trials.

So what is the effect of SGLT2 inhibitors in the presence of pulmonary hypertension? We do have some data through wireless PA pressure monitoring that SGLT2 inhibitors, when given even in a subacute period of 12 to 13 weeks, reduce pulmonary artery pressures. And so, we feel that there may be some effect on pulmonary hypertension. However, mechanisms is just simply decongestion due to natriuretic effect of SGLT2 inhibitors or there are other effects that could be occurring that reduce pulmonary pressures in this way, it's unclear, but there is a signal that those with group 2 PH would receive benefit.

Another recent group of clinical trials with regard to HFpEF that has been recently identified are those trials involving the compounds sacubitril-valsartan, sacubitril being a neprilysin inhibitor, and valsartan being an angiotensin receptor blocker. The first trial which was reported in 2015, actually, sorry, 2018-2019 with regard to this was the PARAGON-Heart Failure trial, which randomized patients to valsartan or sacubitril-valsartan alone. And this was a chronic HFpEF population and outpatient population of HFpEF with NYHA II to IV heart failure symptoms, and we see that sacubitril-valsartan just missed a significance in the combined endpoint of heart failure, hospitalizations, and death from cardiovascular causes. However, we did note in the trial that there was a significant interaction by left ventricular ejection fraction, such that those patients who had ejection fraction less than 65, seemed to benefit more than those patients on the higher end of ejection fraction.

In addition, there was a recently published trial of patients in a trial called PARAGLIDE, again, evaluating sacubitril-valsartan, but this in a much sicker population of worsening heart failure or acute heart failure recently hospitalized. And when pooling patients with both a kind of acute or subacute heart failure in recent hospitalization for heart failure and those in chronic heart failure with preserved ejection

fraction, we see that there's a signal for benefit of sacubitril-valsartan.

But what exactly is this doing and how is it relevant to pulmonary hypertension? Well, the effects of sacubitril-valsartan are probably underappreciated at the right ventricular level, there is some signal in both murine models of - in murine models of HFpEF along with in patients with HFpEF that sacubitril-valsartan relieves RV thickness. There's a significant benefit from a myofibril perspective at the level of the RV. And so yet – mechanisms yet to be understood completely, but we do feel that there might be some right ventricular myocardial benefits of this drug.

The kind of elephant in the room with regard to HFpEF, there are those patients who have obesity, and Dr. Raza mentioned that these patients tend to be underdiagnosed in terms of the diagnosis of HFpEF in general, and they're systematically excluded from clinical trials or the majority of clinical trials due to high – to BMI cutoffs in which they typically exceed. These patients typically have severe symptoms, frequent hospitalizations, and PH is very common in the setting of obesity. There are several shared mechanisms due to obesity that might drive the onset of pulmonary hypertension, in addition to heart failure with preserved ejection fraction.

And recently, as Dr. Raza also mentioned, the STEP-HFpEF trial recently reported, this was a novel trial of a little over 500 patients with obesity in HFpEF randomized to higher doses of semaglutide versus placebo treated for 1 year with a dual primary endpoint of change in KCCQ questionnaire, quality of life questionnaire, and body weight. And the trial met both of its primary endpoints in which patients randomized to semaglutide, had significant and market from an effect size perspective, improvements in KCCQ scores and changing body weight. So taking this into account, especially with regard to, for example, the case that Dr. Raza mentioned, an obese patient group 2 PH, marked quality of life improvements with GLP-1 receptor agonists. This is a new therapy that we now can offer our patients with group 2 PH secondary to HFpEF.

In addition, there has been kind of several device-related clinical trials that have taught us a lot about PH in the setting of HFpEF. And the first is interatrial shunting for the treatment of HFpEF. So the concept here is that in patients who have either resting left atrial hypertension with HFpEF or exercise-induced left atrial hypertension, would benefit from LA, essentially pressure decompression or interatrial shunt acting as a popoff valve to relieve pressure, increase the volume, essentially the effective volume of the left atrium, increasing the compliance essentially of the effective left atrium to reduce symptoms. And this trial was the REDUCE-LAP II trial published about a year ago, which randomized 626 patients who were required to have an elevated pulmonary capillary wedge pressure on right heart catheterization with exercise, so had the gold standard diagnosis of HFpEF. And were randomized to this interatrial shunt versus a sham procedure. The overall trial was neutral in terms of the overall effect of the shunt on a primary composite hierarchical endpoint. However, there was a subgroup that appears to benefit, and this is how we're learning a lot about PH is through some of these trials where we have invasive hemodynamics, both at rest and exercise, and we're learning a lot about HFpEF and a lot about PH as a result of this. And so, the REDUCE-LAP trial identified that there was a patient population who did not have the term latent PVD. So a PVR at peak exercise of less than 1.74. These patients as identified to the left of that vertical dotted line had benefits, as you can see on the upper left side of the graph, with regard to the primary composite endpoint, and specifically marked improvements in quality of life. And so, we think, and this trial has opened up a doorway to one understanding the physiology of HFpEF, two, understanding that this there may be patient population, again without latent pulmonary vascular disease that could benefit from this class of device therapies, interatrial shunts, and there are multiple other trials that are now under investigation, including the one that was studied in REDUCE-LAP II specifically to this responder population without latent PVD.

But it's brought us – REDUCE-LAP – this REDUCE-LAP trial has brought us to a kind of a really interesting understanding about pulmonary hypertension and HFpEF in which we see that with exercise, with perturbation, there are patients that have concomitant rise in their RA pressures and their pulmonary capillary wedge pressures, and marked rises in their PA pressures that have latent PVD that identify a group that has started probably to have abnormal remodeling of their pulmonary vasculature, a more high-risk group. More frequent hospitalizations may be more prone to non-response to traditional therapies or contemporary therapies, including SGLT2 inhibitors, sacubitril-valsartan, they may just not sustain the same amount of benefit. And there are therapies that those who don't have latent PVD, for example, may benefit from particular, like atrial shunt devices.

So what do we do for this more high-risk population of patients with combined pre and post-capillary PH? Well, there are some novel therapies under investigation for the combined pre/post-capillary PH group, one of which is pulmonary artery denervation, which has shown some benefit in group II PH, as compared to sildenafil; one could argue that's not the best comparator to pulmonary artery denervation. But marked improvements in 6-minute walk test with pulmonary artery denervation, so another potential therapy for this higher-risk group with intrinsic pulmonary vascular disease secondary to HFpEF. And again, sotatercept, a game changer in multiple ways, but in the combined pre/post-capillary pulmonary hypertension group, this is under investigation in a phase 2 trial of 150 individuals and the primary endpoint of change in PVR at 24 months.

So again, targeting this group of patients who may have resting PVD or latent PVD may benefit from these therapies in addition to

therapies that potentially target the right heart and the pulmonary circulation, like levosimendan. And levosimendan was studied in a phase 2 trial of group 2 PH in which benefits were seen in terms of a spectrum of exercise pulmonary capillary wedge pressure, and it's being studied in a follow-up trial as well.

So, sorry for going over. And thank you very much.

Announcer:
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