Radcliffe ACC 22: Mavacamten in Patients with Severely Symptomatic Obstructive Hypertrophic Cardiomyopathy

- Hello, everybody. My name is Milind Desai. I am a cardiologist at the Cleveland Clinic, and I'm the director of Hypertrophic Cardiomyopathy Centre at the Cleveland Clinic. I am also the principal investigator of the VALOR-HCM trial.

Background of the Study

So, hypertrophic cardiomyopathy has been known to exist for about a little over 60 years and we have now recognised that it has a prevalence of about 1:200 to 1:500 patients, which estimates about 15 to 20 million people. Two-thirds of them, typically, are thought to have obstructive HCM and symptoms often in obstructive HCM patients are due to what is called dynamic outflow tract obstruction. Current medical therapies, they were not designed specifically for this purpose. We just serendipitously got using them in this context. So, over the years, septal reduction therapy techniques have evolved, including surgical myectomy as well as, interventionally, alcohol septal ablation. These are highly effective techniques that help reduce gradient, that improve symptoms as well as improve quality of life. But, in order to achieve optimal results, you need to be at a highly experienced centre. Not enough of them exist. So, there is clearly an unmet need to expand the offering of available therapies to the patients with highly symptomatic obstructive HCM. So, that unmet need is potentially fulfilled by this drug, Mavacamten, which is a targeted cardiac myosin inhibitor. So, it is a drug specifically developed for HCM. It acts on the sarcomere. It reduces the hyper-contractility, helping, in previous studies, it has been shown to reduce LV outflow tract gradient as well as symptoms. So, that led us to the VALOR study, where the question we asked was, can this drug, which we know helps improve symptoms, can it reduce the patient's need for these invasive septal reduction therapeutic procedures? Can it reduce? Can it delay? Can it defer? Can it avoid? So, all things considered, that is the genesis of the VALOR-HCM study.

Study Design & Selection of Patient Cohort

So the study design, this was a double-blind placebo-controlled randomised controlled trial over 19 centres in the USA. 112 patients were recruited, 56 for Mavacamten and 56 for placebo. Starting dose was five milligrams for Mavacamten, and one month echo follow-up with up-titration or down-titration of dose at 8 and 12 weeks. All these patients, they're severely symptomatic, being referred for septal reduction therapy. They have obstructive HCM. They were highly symptomatic. They were maxed-out on available treatment. So their next road was, it's time for a procedure. So those were the kind of sick patients that we recruited for this study.

Key Findings

So as part of the follow-up strategy, dose titration strategy, we chose clinically-meaningful endpoint of echo-driven EF and gradient assessment, because we wanted to make sure that this is practically applicable in the real world. So, the main findings here, as I told you at the beginning, 100% of patients met criteria for septal reduction therapy. So the goal was at week 16, we wanted to test how many patients still continue to meet the SRT criteria by guideline or how many people no longer meet the criteria and fall out of needing a septal reduction procedure. So that was the primary endpoint and the secondary endpoints were: what happens to the gradients, what happens to the NYHA class, what happens to the biomarkers, what

happens to their cardiomyopathy questionnaire score. So what we found was, after 16 weeks in the Mavacamten group, only 18% remain guideline eligible or chose to undergo SRT. So from 100%, it dropped down to 18%. 82% no longer remain eligible, versus placebo, where 77% still remain eligible. So that was an absolute difference of 58 and a very high p-value of 0.0001. In addition to that, all the secondary endpoints we talked about trended in favour of Mavacamten and the difference was statistically and highly significant.

Effect on Clinical Practice

As I alluded to earlier in my presentation, we are increasingly recognising these patients. So, there's an increasing number of patients out there. We do not have targeted therapies for these patients. These are broad therapies with a broad set of side effects. So what we needed to do was a precision-type therapy that works on the specific heart muscle. Now, the reason why there is this need is, if they do not get better with the standard therapy then their only option is heart surgery or an interventional cardiology procedure. It's great when it works. It's great at a fantastic centre of excellence. But there's not enough of those. There's a lot more patients and not enough centres. So there's that gap we need to fill. So how do I think it will translate in clinical practice? You can think about a patient, a group of patients, in whom they no longer meet criteria for any invasive procedure. There will be a group of patients where, they choose to defer surgery or procedure for an extended period of time for whatever reason, this can get them through that. There could be a group of people that are high risk for a procedure or do not have the anatomy suitable for a procedure. They need some alternative therapy. So, I see it playing out in multiple different arenas. More than likely, the way I envision it, people will start off with is you try standard therapy, it doesn't work, add this. If it works, then great. If it doesn't work, or it works for a little bit, then continue. So, it could be an alternative or a stopgap to SRT.

Next Steps

So the next step specifically for this 16-week study, which was placebo-controlled. So now all patients were offered a chance to go for surgery. 95% of patients chose not to go for surgery or alcohol ablation. 95% of patients are continuing on medications. So the obvious next step is: is there a right dose? Or is it different dose for different people? What is the optimal way of monitoring this medication? How many people really say, 'I don't want to deal with this, send me for surgery'? What is the turnover rate? What is the transition from medical therapy to surgical therapy rate? All these questions and plus importantly, safety, long-term safety. So these are the things we will be testing in the long-run. And plus, there are some mechanistic questions. Which patients may drop EF? Or which patients improve better? Are there some biomarkers? Are there some imaging markers that we can look into? So there's plenty of questions that could be asked.

Take-home Messages

In severely symptomatic, obstructive HCM patients who are referred for septal reduction therapy, Mavacamten, titrated using simple echocardiographic measurements, significantly reduced the eligibility for SRT, compared to placebo. In addition to that, it significantly improved NYHA class by at least one. It improved LVOT gradient, biomarkers, as well as Kansas City Cardiomyopathy Score. Additionally, it was safe with no new additional signals

in spite of being used as combination therapy or on top of combination therapy, as well as with Dysopyramide.