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Emerging Therapies in Hypertrophic Cardiomyopathy: The Potential Role of Cardiac Myosin Inhibition

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Dr. Masri:
Hello. My name is Ahmad Masri. I am a cardiologist and the Director of the Hypertrophic Cardiomyopathy at Oregon Health and Science University. I’m here at ACC 2022 in Washington D.C. and bringing to you some breaking news from couple of late-breaking trials and presentations of novel cardiac myosin inhibitors in hypertrophic cardiomyopathy.

VALOR-HCM is another randomized clinical trial of mavacamten in symptomatic obstructive hypertrophic cardiomyopathy. It was done in patients who are considered or eligible for septal reduction therapy such as septal myectomy and alcohol septal ablation. The trial adds to our knowledge about mavacamten. It enrolled 112 patients, they were randomized to mavacamten versus placebo, and this is the primary outcome, which at 16 weeks, the dose ranges from 5 mg as a starting dose, but eventually from 2.5 to 15 mg. And it’s titrated based on echo read by a Core Lab. And primary endpoint at week 16 was eligibility for septal reduction therapy based on a combination of symptoms and LVOT obstruction as directed by the ACC/AHA guidelines. The primary outcome occurred in about 18% of patients on mavacamten and 77% of patients in placebo. What does that mean? So about 18% of these patients on mavacamten said that they want to proceed with surgery or alcohol septal ablation, while 77% on the placebo said they want to proceed with surgery or alcohol septal ablation. And so, this trial showed that mavacamten was effective over 16 weeks in this population in relieving their symptoms as well as LVOT obstruction, obviating the need to proceed with septal reduction therapies. There were two events of reduced LV ejection fraction and no other serious adverse events that we were aware of.

So, mavacamten is a new agent. It’s a first in class cardiac myosin inhibitor. Whenever we’re talking about the new myocardial, a new medication that works in the myocardium, you really are in need of safety data as well as long-term efficacy data. And this is the rationale for MAVA-LTE study. MAVA-LTE study is a long-term extension study up to 5 years that has both EXPLORER-HCM patients who are obstructive as well as MAVERICK-HCM patients who were non-obstructive. This is a late-breaking clinical trial focused on the obstructive cohorts from EXPLORER. There were 231 patients, 40% women, all obstructive at baseline when they were enrolled in the EXPLORER trial and symptomatic at the time. They were then offered the enrollment into the long-term extension arm with the goal of improving their symptoms, reducing their LVOT gradient and improving their biomarkers as well as quality of life.

And what’s important from the study to see that over a long period of follow-up, the effect of mavacamten on LVOT gradient was sustained and so there wasn’t for example, return of LVOT obstruction over a longer duration of follow-up compared to what EXPLORER-HCM trial showed. Also, the safety data showed that a number of patients with decreased LVEF was as expected and as was shown in EXPLORER-HCM about 5% of the patients had reduced LVEF; 8 out of the 12 were restarted on mavacamten. So, the reduced LVEF resulted in 4 of these patients having permanent discontinuation.

So, REDWOOD-HCM trial is a phase 2 sequential cohort trial which was presented at ACC 2022 was the results of the Cohort 3 of REDWOOD-HCM which included patients with obstructive hypertrophic cardiomyopathy who had resting obstruction above 30 mmHg and provoked obstruction above 50 mmHg despite being on an AV nodal blocking agent such as a beta blocker or a calcium channel blocker and disopyramide. And so, this represents a unique cohort of patients that is not extremely common, because if you are tolerating disopyramide but yet you have resting and provoked obstruction, but this is essentially a study that shows us the efficacy of aficamten despite being on disopyramide as well as the safety of aficamten when combined with two other negative inotropes. The study enrolled 13 patients, it was an open-label study where everyone was put on 5 mg of aficamten to start with and the titration was capped at 15 mg, which is considered on the lower dose range; not the full range of aficamten because again this is the first time this is begin done for safety reasons. And what's reassuring is that patients were actually very symptomatic. Patients had higher NT-proBNPs than even seen in any other HCM clinical trial despite begin on 20 g- of inotropes at baseline including disopyramide. And what we found is that these patients did derive benefit from aficamten in terms of improvement in symptoms, yet this is an open-label trial, not a blinded one. But also, their LVOT gradients nicely responded to incremental doses of aficamten. You can see how their resting gradient drops as well as the provoked gradient drops. Now, there were still gradients between 30 and 50 for the provoked gradient in some patients. But this is likely because we didn't have access to the full range of aficamten dose to use in these patients. Also, what's reassuring is that there were no interactions that would have resulted in prolonged QTc interval on electrocardiogram. And again, this supports the hypothesis that the practice now that you can actually use a cardiac myosin inhibitor in patients who are using disopyramide.

Finally, the last take-away is there has been a traditional thinking about failure of disopyramide that it represents more of a fixed obstruction with some dynamic component or some anomalous papillary muscle causing some of these issues.

What this study shows is that while these patients are harder to treat and while they might require actually higher doses of aficamten, there was still response and there was still reduction in LVOT gradient, despite failing disopyramide. And so, for us this is reassuring.

Thank you for listening, now, onto the rest of the program.

Dr. Masri:
Why is there a need for better medical therapies in the management of hypertrophic cardiomyopathy [HCM], and what can we expect in the near future from cardiac myosin inhibitors?

This is CME on ReachMD, and I'm Dr. Ahmad Masri. I'm here with Dr. Deepak Bhatt, and together we'll explore answers to those questions and more.

Welcome, Deepak.

Dr. Bhatt:
Great to be with you.

Dr. Masri:
So let's get started. Tell us, Dr. Bhatt, why do so many patients with hypertrophic cardiomyopathy progress on the current medical management?

Dr. Bhatt:
It's a great question. I think one problem is that it's not diagnosed, so people are progressing, and nobody knows about it. As it turns out, HCM is the most inheritable type of cardiomyopathy; men and women are equally affected. It's also the case that there haven't really been large, randomized, controlled trials in the past to evaluate therapies. But again, there is now a lot of activity in research in HOCM [hypertrophic obstructive cardiomyopathy], lots of new compounds being studied. So that, I think, has the collateral benefit of raising disease awareness, in addition to advancing things on a research front.

So now perhaps I can turn to you now and ask you to tell us about a new class of agents that work through cardiac myosin inhibition. I was referring to how there's sort of underdiagnosis and then for that reason undertreatment, but there is something new now on the horizon. Do you want to tell us about it?

Dr. Masri:
Absolutely. So first, let's talk a little bit about the pathophysiology of hypertrophic cardiomyopathy. While the pathophysiology is complex, really, there is a central role for hypercontractility where there is increased myosin actin interactions because of the increase of the available myosin heads, which leads to increase in energy expenditure in both systole and diastole. This eventually would lead to besides the hypercontractility symptoms as well as the diastolic dysfunction and progressive adverse remodeling. So cardiac myosin inhibitors, they would target the cardiac myosin ATPase. They decrease the number of myosin heads available for engagement with

actin, and that would improve hypercontractility and diastolic function.

In terms of the cardiac myosin inhibitors that have been tested so far, there have been various clinical trials for both mavacamten and aficamten; many of them are still ongoing to date. I will highlight EXPLORER-HCM clinical trial. This was a pivotal, phase 3 clinical trial of mavacamten versus placebo in about 250 patients or so that showed that mavacamten improved the endpoint of peak VO2 [pVO2] and NYHA class. So, what they did is that they had the co-primary endpoint. Either you improved the peak VO2 by an absolute value of 3.0 mL/kg/minute or you improve it by 1.5 but with improvement in the NYHA class. And so that endpoint occurred in 37% of patients on mavacamten compared to 20% of those on placebo.

There was a decrease in LVF [left ventricular function] as you'd expect. This is a drug that works on relaxing the heart, so there was a decrease in LVF in 7 patients on mavacamten and 2 patients on placebo. But really, the majority were self-limited and reversible with either dose reduction or stopping the medication.

There was a subsequent analysis using the Kansas City Cardiomyopathy Questionnaire, which showed significant gains in quality of life. Really few interventions in cardiology have a similar magnitude of effects, especially medical interventions.

There is another ongoing trial for mavacamten called VALOR-HCM. This trial will investigate if mavacamten can obviate the need to proceed to septal reduction therapy at 16 weeks for patients with high symptomatic burden. In EXPLORER, patients were enrolled with NYHA class with 2 or 3, two-thirds of them having NYHA class 2. This trial, VALOR-HCM, is trying to target the more severe symptomatic patients who would qualify for septal reduction therapy such as myectomy and alcohol septal ablation.

There is a second-generation cardiac myosin inhibitor I alluded to called aficamten. This was investigated in the phase 2 REDWOOD-HCM trial, and that showed also a significant reduction in LVOT [left ventricular outflow tract] gradients, NT-proBNP, other endpoints. And currently, the phase 3 SEQUOIA-HCM is underway.

In terms of the non-obstructive space – so all of these trials I mentioned were in the obstructive space. In terms of the non-obstructive hypertrophic cardiomyopathy space, MAVERICK-HCM trial showed that mavacamten can really decrease NT-proBNP and troponin with overall encouraging results in this small phase 2 study, and we expect it to progress to a phase 3 trial to evaluate more functional as well as patient-centered endpoints. Aficamten is currently undergoing evaluation for non-obstructive HCM in the REDWOOD Cohort 4 study.

And so, as these cardiac myosin inhibitors become available in clinical practice, how will we identify the right patient who will benefit from these therapies, Dr. Bhatt?

Dr. Bhatt:
So, you know, it's a terrific question, and it's a combination of clinical suspicion but then imaging as well. And, you know, historically, people have thought about echo as the way to do it. Some cases are classic in terms of how they look on the echo in terms of the septum and septal hypertrophy and so forth. But in other cases, it's sometimes a little tricky to tell whether it's just left ventricular hypertrophy or HCM, and in those cases, sometimes just having an expert set of echo eyes can help. But sometimes MR, magnetic resonance imaging, can also be useful, and I think will be increasingly used. There can be a left ventricular outflow tract obstruction or not with HCM. Historically, we've been focused on treating people that have significant obstructive disease, but there's, as you have mentioned, good work going on even in those with HCM without obstructive disease to see if we can modify their clinical trajectories. But certainly, in those that are symptomatic and that have large outflow tract gradients, there, medical therapy is often indicated, and we've certainly got things that have been used historically. I, you know, alluded to beta-blockers and even the fact that just recently there was a clinical trial supporting them. You focused on some of the newer therapies as well. And I think what we're going to see increasingly with HCM is tiered therapy that is, you know, first, identification of the disease, second, establishing impact on symptoms and quality of life – an important aspect that you alluded to. You know, then starting with commonly available generic sorts of therapies and then potentially escalating to some of these novel therapies in patients who remain symptomatic, which is not a trivial proportion of those sorts of patients.

Dr. Masri:
That's an excellent point you mentioned, that non-obstructive HCM. It's interesting that people always, almost always, associate HCM with having obstruction of LVOT gradient, but about one-third of the patients don't actually have obstruction. And whenever we do septal reduction therapies, in a large proportion of patients we actually transform their disease from obstructive hypertrophic cardiomyopathy to simply non-obstructive hypertrophic cardiomyopathy. So, this class of agents is promising for this specific type, also.

Dr. Bhatt:
Yeah, absolutely agree with you. I think it's one of those things that everyone learned about HCM, or in many cases back then it was called HOCM, and that association with left ventricular outflow tract obstruction, but we've learned so much more about the disease

since then. And I think it's, you know, important to keep up with the sort of – not just the newer nomenclature HCM versus HOCM, but also just a better understanding of the physiology and pathophysiology.

Well, let's say you've gone ahead and decided to use a cardiac myosin inhibitor in a patient. You've already sort of maxed them out on other available therapies to the extent they can tolerate. Do you want to just go through some of the specifics about things like dosing and, you know, what you might consider as you're putting together a treatment plan?

Dr. Masri:
That's a great question. We can focus on obstructive hypertrophic cardiomyopathy since those really are the phenotype that's been the focus of that phase 3 trial so far. Non-obstructive HCM would take further out, couple of years to get to the clinic. And so, for both mavacamten and aficamten, the starting dose is typically 5 mg. That's a low dose in comparison to the range because for mavacamten you can get all the way up to 15, and for aficamten to 20 mg. Those are the doses that have been investigated in trials and continue to be investigated to date. The majority of the patients require doses in the middle of that range. And then the strategy really should be to start at the 5-mg dose and then use LVF, LVOT gradients, NT-proBNP, and symptoms – most important thing is symptoms – to guide further up-titrations. These could occur at the minimum interval if a patient and physician are interested in getting rid of the symptoms quickly, but you need to allow for the drugs to achieve their steady state, typically 2 weeks for aficamten, 4 weeks or so for mavacamten. And so, in general, patients start feeling much better even with the low dose because relaxation improves also with the low dose, and diastolic function improves. And then with experience, really, one starts to predict how much of the drug the patient will eventually require, and, you know, there are scenarios where some patients become asymptomatic despite having residual gradient and, in general, until we have more data about this, we probably should just follow symptoms and not continue to up-titrate just to get rid of the gradient per se, because we want to treat, really, the patient not a number necessarily.

And in terms of titrations, every titration has to be done with an echocardiogram, but once you have a stable dose and the patient is doing well, really, that is spaced out. Right now, in clinical trials, it goes anywhere between 3 months to 6 months. Most of the trials are doing 3 months' routine follow-up. And a lot of data is going to be generated from these long-term extension trials to tell us once somebody is in a maximum tolerated dose that they need, how is monitoring happening, and are there any surprises during, you know, let's say 2, 3 years after being on the drug? But for now, you know, start slow, up-titrate slowly, and make sure that you have a good quality echocardiogram every time you consider up-titration.

Dr. Bhatt:
That sounds like really good advice. Really very practical information.

Dr. Masri:
Excellent. And let me ask you, Dr. Bhatt, as these agents become available, what advice would you offer your colleagues? In particular, what does the broader collaborative care team need to be aware of?

Dr. Bhatt:
You know, that's a key question, I think, especially for disease states where, you know, various members of the cardiovascular team may not have a lot of personal experience and may not be aware of the full range of therapeutic options. So, I do think approaching this, like many things in cardiovascular medicine – or maybe just I could even say medicine as a whole – you know, there is value in just having a broader team involved.

But then, now we've got this novel class of agents to consider, and I think this is going to require a lot of education because it's sort of like what happened with pulmonary hypertension or amyloid, you know? You never really saw any of it until there were specific new drugs for it and then it's really popping up all over the place. And I think, therefore, it'll be important to keep general cardiologists in this loop. I think even PCPs, at least on an awareness level, will need to know. I don't think they'll be involved with actually prescribing these treatments. I think initially it'll be for, especially the more novel therapies, more specialized clinics, maybe heart failure clinics that are doing it. But then it's going to rapidly disseminate to general cardiology, sort of what happened to PCSK9 inhibitors, where they start off in preventive cardiology but then it just makes its way into general cardiology or with some of the heart failure drugs that start in heart failure clinics but then general cardiologists become more familiar with it. So I think it'll be important for all those different physician types to stay in communication, especially early on in the learning curve with any new therapy, and in particular in this case, any new drug, and just making sure all the different options that I mentioned and that you and I've been discussing, are considered so that the right patients get the right therapies.

So there are a lot of different things that do need to be factored in, and a collaborative team-based approach probably is the best way to make sure all the appropriate boxes are checked and nothing's overlooked.

Dr. Masri:

Well, fantastic. This has really been a fascinating conversation. But before we wrap up, Dr. Bhatt, can you please share your one take-home message with our audience?

Dr. Bhatt:
Sure, well, I guess the first thing I'd say is, you know, you can't ever even see a disease if you're not thinking about it. So, you know, keep in mind that HCM is out there, there's a higher prevalence than has historically been appreciated, and identifying these patients can make a big difference, because for the ones that are symptomatic, as you nicely alluded to in terms of quality of life data, we can actually improve their quality of life. And it's a pretty substantial impact that's possible. So the first step, though, is to make sure you look for these patients and are thinking of the diagnosis, otherwise none of the therapies we discussed can possibly be applicable or help them.

And perhaps you can just give the audience your final bottom line as well, Dr. Masri.

Dr. Masri:
Yeah, I fully agree with your take-home message. And, you know, for me to add on that, I think, really, cardiac myosin inhibitors are promising therapies; they will improve our care for patients with HCM. And then we will really have to keep an eye on these long-term, open-label trials because they're going to help us understand further the safety and continued efficacy of this class of medication. But it is really an exciting time to be taking care of patients with HCM and a time where we're hopeful that we're going to have more options for patients with HCM.

Dr. Bhatt:
Yeah, really wonderful point, totally agree.

Dr. Masri:
Unfortunately, that's all the time we have today. So, I want to really thank our audience for listening in and thank you, Dr. Bhatt, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Bhatt:
Likewise, really wonderful speaking with you. I learned a lot, as I always do, hearing you speak. Thank you so much.

Dr. Masri:
Thank you.

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