Beneath the Surface: Moving Beyond Symptomatic Control in Obstructive Hypertrophic Cardiomyopathy

CMEO Podcast Transcript

Theodore Abraham, MD, FACC:

This is indeed a historic meeting in the sense that it might be the first meeting CME on treating obstructive HCM after the FDA announced its very momentous decision to approve mavacamten. And we'll be touching on that and I'm sure there'll be questions on that, but I am Ted Abraham and on behalf of CME Outfitters, I'd like to thank you for joining us today for this educational activity on obstructive hypertrophic cardiomyopathy.

This activity is supported by an educational grant from Bristol Myers Squibb. Today's activity is brought to you by CME Outfitters, an award winning accredited provider of continuing education for clinicians worldwide. CME Outfitters is a joint accreditation provider to provide continuing education for the team and by the team.

I'm Ted Abraham. I'm here at University of California, San Francisco, and part of the HCM center of excellence here. And I'm delighted and honored to be here with two very luminary individuals in HCM, starting with Dr. Ho and I'll have her introduce herself.

Carolyn Ho, MD:

Hi everybody. I'm Carolyn Ho. I'm the medical director of the cardiovascular genetic center at Brigham and Women's Hospital.

Theodore Abraham:

And over to Dr. Ommen.

Steve Ommen, MD, FACC, FAHA:

Hi, I'm Steve Ommen. I'm the medical director of the hypertrophic cardiomyopathy clinic at Mayo Clinic in Rochester, Minnesota.

Theodore Abraham:

Thank you both. We do have a hot topic today, obviously. And our first learning objective is to apply the current evidence-based diagnostic and treatment strategies for the care of patients with HCM. And I think there's no one to better start us off than Steve Ommen who chaired the guidelines committee for the most recent 2020 HCM guidelines for representing both ACCH and multiple other organizations. So I'll hand this over to you. Steve.

Steve Ommen:

Thanks, Ted. Yeah, we thought it would be good to start off with a case to frame this around. So this is a 36 year old man who's short of breath with effort. It's been going on for about six months. It is worse for him when he's

warm or after meals. On physical examination, his lungs are clear. He has a brisk carotid upstroke and he has a two over six systolic ejection murmur that increases when you have him do a squat to stand maneuver.

Echocardiography was obtained, which shows a maximum wall thickness of 24 millimeters, but there was no evidence of systolic anterior motion or outflow tract obstruction on the images. And you can see the still frame echo images there. So there's a question for you to ponder next, based on this case history and findings, which is the next best step for this patient, is it to get CMR? Is it to do an echo with provocation? Is it to send him to the cath lab to do a TEE or you don't know?

All right, so there's a split here between CMR and echo with provocation and just to talk about this case a bit, the features that were important were the patient has shortness of breath and on physical examination, there was actually evidence of outflow tract obstruction because they had a dynamic murmur. And the teaching point here is that the resting echocardiogram doesn't always give you the answer about whether the patient has dynamic outflow tract obstruction. It's a very load dependent thing and when a patient's laying down, you're maximizing their preload. And so that may be the lowest their gradient is all day long.

So a standard part of an echocardiogram for a patient with HCM should be to include some provocative maneuvers to see if there's outflow tract obstruction there. So echo with provocation is the next step. At Mayo, we have that built into our stenographer standard program when they have a patient referred with HCM. And if we still don't get that with their provocation, then that's when you might consider doing things like stress echocardiography or a hemodynamic catheterization, depending on the circumstances of the patient.

Many of you voted for CMR. That's going to be useful in many patients, but it's not as helpful for outflow tract obstruction as a provoked echocardiogram is. So moving forward, these are kind of the six things that I say that all of the patients that come to our HCM clinic need to understand once they're referred. First of all, HCM is not that rare. The estimates worldwide range from one in 500 to one in 200. The overall prognosis can be very good, but there are important consequences that each patient needs to learn about.

It can be familial as Carolyn will talk about. It can be inherited in an autosomal dominant fashion, so we need to talk about screening programs, either using genetic testing or using an imaging-based protocol on a periodic basis. Cardiac arrest can occur in patients with HCM to the rate of about 0.8% per year. And so we do a complex analysis of their sudden cardiac death risk and a shared decision making approach to deciding whether a patient wants to get an ICD or not.

All the rest of our therapies have been directed at relief of symptoms, which means if a patient is asymptomatic, they don't require you to start medications, but if they are symptomatic, then we have both pharmacologic options and invasive options to relieve those symptoms. And we do want our patients to lead an active, healthy lifestyle to mitigate all their other cardiovascular and lifestyle risks. But so we're going to really focus on this treating symptoms today.

It feeds into that headline that Ted told you about in terms of the new drug being approved. But let's talk about how we treat patients with HCM. And really when you think in medicine about why we treat people, these are the four things you're typically trying to do. In HCM, we don't have any way to cure disease and we really don't have solid data on how to prevent disease progression for most people.

The only thing we have that saves lives is the ICD, so everything else we're going to talk about is relief of symptoms. It's important to understand why patients get symptoms with HCM. First of all, on the right hand side of this diagram, most patients with HCM have some form of diastolic dysfunction. The thick heart muscle is stiffer than a normal thickness heart muscle. Also the abnormalities of actin and myosin mean that the ventricle relaxes more slowly and more stiffly. So most patients can develop increased, left atrial pressure or increased wedge pressure either at rest or with activities.

Obviously, the thing that's attracted the most attention for decades now, though, is the dynamic left ventricular outflow tract obstruction, which has a myriad of things that can cause patients to get symptoms. First of all, it results in a supply demand mismatch with respect to oxygen. The capillary network isn't as dense and thick heart muscle. The heart is working harder, so it has more myocardial oxygen demand. And so patients can get ischemic. That can certainly cause symptoms such as angina and dyspnea.

The fact that the mitral valve gets pushed into the outflow tract can cause various degrees of mitral regurgitation. And all of these things can lead to this classic triad of symptoms of effort related dyspnea, chest pain, or presyncope. What is unique about HCM patients is that their symptoms can vary from day to day.

It's very common for patients to come in and say, "There are some days where I can do about anything I want and other days where I can't go get the mail." And that's because of the fact that the loading conditions, preload, afterload, contractility have such a dramatic effect on the severity of the outflow tract obstruction. But that also means those things are manipulable, that we can use that to our advantage, to help patients feel better.

Now, one thing we do like to point out and this is relevant to that opening question we had, we define patients as having obstructive physiology if they're peak gradient's at least 30 millimeters of mercury, but to really cause significant symptoms at the class three level, the gradient probably has to be at more than 40 to 50. The important point there is if you haven't seen a gradient of that high, you need to look harder for it in the provocation. And even with provocation, you don't get that, then maybe you need to look for other causes for shortness of breath in that patient. So don't forget that patients can be short of breath for things unrelated to their HCM.

Now, I mentioned that the obstruction gets worse with increased contractility, decreased after load, and decreased preload. All of these things happen as soon as you stand up and walk across the room. So again, those things can be manipulated and that's been the basis of our functional approach to treating patients outflow tract obstruction.

Our patient, Lawrence, was diagnosed with obstructive HCM after his stress echocardiogram showed he had a very high gradient and he was put on a beta blocker. Beta blockers form what is usually the first line therapy for our patients. Beta blockers in the two non-dihydropyridine class calcium channel blockers, Verapamil and Diltiazem are negative inotropes. They decrease contractility and they also slow the heart rate down. And remember when the heart rate changes, it's diastole that soaks up most of that change. So when you slow the heart rate down, you give the ventricle more time to fill which maximizes preload for that patient.

So those three agents hit two of the three major things that impact the severity of the outflow tract obstruction. Norpace or disopyramide is something that can be added on to those agents for some patients who

remain drug refractory. But it's also important to remember that we also want to make sure we get rid of things on patients' medication lists that might make things worse. Pure vasodilators can make our patients very symptomatic, so patients who might have concomitant hypertension might be on something like amlodipine while switching them from amlodipine to verapamil might still control their hypertension and get rid of that pure vasodilator effect. And that patient can go from class three to class one with a simple medication change.

The other thing is to make sure patients are staying hydrated, avoiding dehydration to maintain their pre-load. And I put this slide in many of my discussion points. Remember that a patient is who determines whether therapy is successful or not. It's not an echo lab measurement. Because that gradient changes from day to day, you may hit them on a good day one time and a bad day another time. But if the patient says they feel better since you changed their last medication dose, that's success.

And this graphic is very biased because this is 1500 patients that referred to us as drug refractory that were sent to us for invasive procedures. And yet two-thirds of them, we were able to successfully manage by changing their medications. So don't forget that these standard therapies can be very effective in patients in helping relieve their symptoms. So unfortunately, Lawrence continued to be symptomatic after his beta blocker. So let's see what the audience thinks we should do next. Should we consider putting him on disopyramide? Should we send him for surgery, for alcohol septal ablation, enroll him in a clinical trial, or you don't know?

Theodore Abraham:

Steve, looking at these results and knowing that you're going to talk about the algorithm, you want to start off with maybe a comment on diso versus clinical trial, because that's the big split here?

Steve Ommen:

Yeah. Yep.

Theodore Abraham:

And then maybe launch into something that you and your committee felt or spent a lot of time thinking about, which is a stepwise algorithm of going through the various available drugs.

Steve Ommen:

Yeah, absolutely. So obviously, if you have a clinical trial that's ongoing at your center, it's always important to talk to patients about that so that we can build our science base to make decisions. So that's always going to be a reasonable choice. Disopyramide is also reasonable at this point, as it's been shown in a case series that about two thirds of patients that can take disopyramide don't need to escalate their therapy for another three years.

Now, disopyramide is a negative inotropic, negative chronotropic agent. It probably should be added to one of the other AV nodal blocking agents just in case the patient develops AFib, because it can accelerate through the AV node a bit. There are some challenges with it. Often there's a supply problem with the long-acting form of disopyramide. So patients are usually taking it three times a day, which is not great for their lifestyles.

And many patients have anticholinergic side effects, so dry eyes, dry mouth, urinary retention in men. So you talk to patients about this, but it can be very effective for some patients. And I kind of lump disopyramide, myectomy, ablation under the advanced therapies on the right hand side of this slide. So remember, in the management of a patient with obstructive HCM, first of all, we haven't mentioned it yet, but make sure you treat the rest of them as well. Their obesity, their sleep apnea, their diabetes, their hyperlipidemia, all those things need to be managed as well.

And just reemphasizing here that if a patient is asymptomatic, they do not require you to start a medication for their obstructive HCM. If the patient is asymptomatic, they don't require new drugs. If they are symptomatic, you try to get them off of the offending agents onto the right agents. Switch between them if you're trying to play with side effects. Beta blockers cause a lot of people to have side effects and maybe they might tolerate the calcium channel blockers better or vice versa.

So you can play around with those, but if they remain symptomatic, then you move to these options that we just discussed. And they're both valid options in the guideline. Both of these are listed as class 2A indications for someone who has drug refractory symptoms. And it's that shared decision making discussion.

Is a patient ready to consider an invasive therapy or they want to try more medication? That's part of the discussion that you're trying to learn about the patient's goals and where they're at emotionally and physically with their condition. If a patient is considering a mechanical relief of their obstruction, because remember we've been dealing with functional changes to try to deal with their loading conditions, to treat their symptoms. But sometimes the anatomy is so severe, you need an anatomic solution to provide them with relief.

If they're not a surgical candidate at all, then septal ablation becomes really the best option for that patient up till now. If they are a surgical candidate, then you talk about both options unless there's other surgical indications, in which case surgery becomes the option there. So it's a long discussion with each patient.

Remember, the baseline indications for both of these are the same. It's drug refractory symptoms attributable to outflow tract obstruction. And these are kind of the pros and cons of each of the procedures. It's kind of a checklist. You can go through. Advantages from myectomy in some cases, advantages for ablation in others, and there's some anatomic things that you have to consider as well.

One of the things we did put in the guidelines was target outcome metrics, because we know for both of these procedures that volume and expertise matters. You really don't want to be having your patients have these procedures and aren't doing a high volume of them and who can't be aiming for these procedural outcome variables. So patients should expect to get this when they're having an invasive therapy.

So in our case, Lawrence's anatomy was not favorable for ablation. Septal myectomy was then discussed with him, but he really didn't want to have surgery. And that's where as of today we might have a new option. And that is what is the role of potential new agents in Lawrence's pathway as a patient? So Ted, what do you think about that?

Theodore Abraham:

Absolutely. But maybe before that, I had a couple of questions for both of you and I'll start with Carolyn. Carolyn, the guidelines talk about beta blockers. Given some of the data in both mice and other early clinical trials, what is your thought on maybe calcium blockers maybe being the first line of therapy?

Carolyn Ho:

Yeah. I mean I think that it's a little bit dealer's choice and if there are other compelling reasons to go forward with beta blockade, then oftentimes we'll defer to that, particularly in middle age or older patients who might have some amount of concomitant coronary artery disease. In younger patients, I feel like they probably tolerate calcium channel blockers a little bit better, especially younger males. So, oftentimes I'll start with a calcium channel blocker. So I think it's a little bit dealer's choice, a little bit trial and error to see what patients tolerate the best.

Theodore Abraham:

Awesome.

Steve Ommen:

Yeah. I would agree with that. We probably pay too much attention to this, but there's this very old data that calcium channel blockers in patients who have very high rest ingredients might paradoxically make them worse. But other than that, I agree complete with what Carolyn said.

Theodore Abraham:

And Steve maybe, comment on is there a role to combine a calcium and a beta blocker before you go to disopyramide?

Steve Ommen:

There aren't solid data on that, but I think if you're balancing side effect profiles, it makes sense to give it a try. So if a patient got all the side beta blocker side effects when you went up to 50 milligrams, but they didn't have them at 25, maybe back them off to 25 and see if you can add a little bit of a calcium channel blocker. And the duality there may provide them with the best recipe for that individual patient.

Theodore Abraham:

And last question for the both of you before we move on to the next learning objective is on beta blockers, what are the ranges you're going after? When do you say this is enough of beta blocker and we need to call this a beta blocker failure?

Steve Ommen:

Yeah, this is a really important point. So again, if the patient feels better, you don't need to go higher than that. If a patient doesn't feel better and it's not due to side effects from the beta blocker, it's still their original symptoms, if their heart rate isn't suppressed, then they aren't getting full beta blocker effect. So if they still have shortness of breath like they had before you started the drug and they're resting heart rate's 70, you have room to titrate the beta blocker further. But if their heart rate's already in the 50s, then you're probably not going to get more bang for your buck by increasing the beta blocker.

Carolyn Ho:

Yeah, absolutely. I think that we start at a low to moderate dose just to try to not immediately precipitate side effects. And then we'll keep going up until about 200 in metoprolol, as the dose that we typically say we're not going to get any more benefit from this if the patients still have room in terms of heart rate and blood pressure and aren't having adequate symptom relief.

And I think one of the really key points that Steve brought up was trying to figure out if it's really the obstruction that's the cause of symptom because trying to decipher symptom burden in HCM can be really challenging, especially in our patients that have multiple comorbidities be it lung disease, obesity, deconditioning, older age. So really trying to figure out how much of their symptoms is related purely to the obstruction, how is it related to diastolic abnormalities or other comorbidities can be really challenging.

Theodore Abraham:

So that leads me to one more question, which is someone comes in, has really high gradients and says they're asymptomatic. Are you taking them at their word? Are you pushing them with some testing to actually validate that they are truly asymptomatic?

Carolyn Ho:

Depends on what they're doing. If somebody's really active, they're running around playing sports or exercising regularly, and they have a gradient of a hundred millimeters of mercury but aren't limited, then I take them at the word. But we do tend to get baseline CPED echoes on everybody, just so we have a line in the sand to like compare against if functional capacity doesn't seem as great in the future. But if there are people that are not as active and they say that they're asymptomatic and they're not wishing to become more active than you might want to just declare victory on that.

Theodore Abraham:

Steve.

Steve Ommen:

Yeah. I agree. We tend to do objective exercise test measures on those patients. I haven't ever had a patient who was very active and asymptomatic who horribly underperformed on an exercise test and therefore changed their

treatment strategy. But you had some people who maybe had decreased their expectations of themselves over the years kind of subconsciously. And when you show them their exercise capacity is only 60% of expected for a person their age, it just planted the seed to say, "Let's think about this. Let's try to get in better shape. And if you can't do it, then maybe we should being more aggressive with your care." So we try to document and correlate the two.

Carolyn Ho:

Yeah. Because remember, the treatments that we have are really just geared at symptoms. So trying to find another excuse to put somebody on a beta block or a calcium channel blocker, it's probably not going to do that much more for them overall. So it's really a matter of their symptoms and their quality of life, but making sure that everybody's being honest is always helpful.

Theodore Abraham:

Awesome. Well, that was a great setup for our second learning objective, which is going to be led by Dr. Ho to talk about the chemo mechanical cycle, cardiac myosin, impact of mycin and ambition again, very timely and develops nicely on symptoms in the setting of obstructive HCM. All yours.

Carolyn Ho:

Right. So I just want to take you back a little bit to bring in some of the key points that Steve had brought up and also to have us think a little bit more holistically about what hypertrophic cardiomyopathy is. So oftentimes, hypertrophic cardiomyopathy is a genetic disease caused by pathogenic or disease causing variants in the gene set and code the sarcomere apparatus.

So you can think of having inherited that sarcomeric variant as starting the clock. We know that there are some primary effects of these sarcomeric variants. So early phenotypic manifestations that are present, even when left ventricular wall thickness is normal and you can't diagnose somebody with having HCM. And that includes having a smaller than normal LV cavity size, having hyper contractile systolic function, having diastolic abnormalities, profibrotic milieu, and impaired myocardial energetics. So all of these features have been documented even when LV wall thickness is normal.

And then with the continued modifiers that are brought in by aging, common and genetic modifiers, and lifestyle choices, and comorbidities, then clinically overt HCM can emerge. That's associated with the adverse remodeling that we're all familiar with in terms of increased left ventricular wall thickness that leads us to the diagnosis of HCM. And also with the adverse outcomes and symptoms that are associated with clinically overt disease.

And as Steve beautifully outlined, if there's outflow tract obstruction, we try medical and then invasive therapies to try to reduce it if it causes symptoms. We are on the lookout for ventricular arrhythmias to try to figure out who would most appropriately benefit from primary prevention ICDs. We're constantly looking for atrial fibrillation, because patients with HCM are at higher risk for developing atrial fibrillation and also at higher

risk for thromo mallah complications. So we routinely look for it and we started anticoagulation as well as rate and rhythm control strategies as appropriate.

And then there are some patients that unfortunately develop advanced remodeling, either restrictive physiology or left ventricular systolic dysfunction. And here, we have to think about our guideline directed medical therapy for heart failure and also potentially transplantation for those who are truly refractory.

So you can see that our current treatment targets symptoms and it's effective for many, but not all patients. It starts relatively late in disease evolution and really in the path, there hasn't been any disease specific or disease modifying therapies available. And there's very sparse evidence regarding efficacy because clinical trials at a meaningful level have not previously been done in HCM.

And so we had to recognize that HCM is a very complex disease and that multiple different approaches would be helpful for management. Medical therapy may not provide adequate symptom relief. Septal reduction therapy can be effective, but it may not be for everyone due to lack of access to the appropriate expertise, anatomical factors, comorbidities which may limit the amount of improvement that people may enjoy after septal reduction therapy, and also patient preference and the associated morbidity and mortality associated with these invasive procedures.

And so the more tools and options that we have for our patients, the better we are. And so there is a clear, unmet clinical need about being able to provide more effective medical therapy that can improve symptom burden, but also avoid the risk of invasive therapy. And furthermore, even invasive therapy, oftentimes and almost always effective is not effective in a hundred percent of our patients, so we really need to have more therapeutic options.

And so to think about this, we really need to go back to basics a little bit and think about how the sarcomere works and how this might be impacted by hypertrophic cardiomyopathy. So if you remember the chemo mechanical cycle of how actin and myosin interact with each other, there's initial hydrolysis of ATP and binding of calcium to allow the conformational changes that allow the myosin head to interact with the actin thin filament. And then with additional ATP hydrolysis, we have the power stroke, which allows the myosin head to ratchet against the actin thin filament and lead to contraction.

And then relaxation is also an energy dependent activity. And so ATP has to again be hydrolyzed for the actin and myosin to detach from each other, for the myosin head to detach from, from actin and then reset itself to get ready for the next time through the cycle. And looking in that a little bit more in a detailed fashion, there's actually a functional equilibrium between three different states of the myosin head that have important implications for energy usage.

So we have the actin bound myosin which is actively participating in force generation. And then there are two states of relaxation. One is the DRX state or the disordered relaxation state where myosin is not attached to actin, but it could reattach and initiate another power stroke. And then there's this super relaxed state or the SRX state of myosin in which the myosin heads are not attached to actin and they cannot be attached to actin for some period of time.

And so the ATPase activity of the actin bound myosin is the highest and it's a thousand fold higher than the super relaxed state and a hundred fold higher than the disordered relaxed state. So if we think about how we might be able to address this, it's important to have that framework in your mind. So with normal contractility and effective relaxation and the normal state that's really provided by this highly orchestrated, highly coordinated interaction of actin and myosin.

But with hypertrophic cardiomyopathy, one model of HCM pathophysiology is that there are too many actin myosin cross bridges that are formed. So too many myosin heads that are engaged in with the actin thin filament. And so this leads to hyper contractility, impaired relaxation, and altered myocardial energetics. And so myosin inhibitors have been developed and they are first in class medications and they're targeted allosteric inhibitors of cardiac myosins.

So they help to increase the proportion of the myosin heads in that lowest energy utilizing super relaxed or SRX state. And they reduce ATP hydrolysis in the number of actin myosin cross bridges that can form. They allosterically inhibit the initial rate limiting step of myosin binding to actin by inhibiting that ATP hydrolysis. And so with a myosin inhibitor, the HCM sarcomere has decreased hyper contractility and improved myocardial energetics. So any thoughts from the Ted or Steve?

Steve Ommen:

Yeah, I think this is an important step, obviously, for patients with HCM because this is the first time that pharmacology has been directed specifically at HCM. We've taken advantage of drugs, other side effect properties rather than a principle mechanism of action. And if you think about that scheme of treatment, we started off with functionally trying to manipulate the loading conditions, to mechanically altering the anatomy of the heart, but this is a cellular level functional approach to the primary abnormality that is occurring at the cellular level. And it's a very interesting approach. And the agent that we're talking about today is first in class. There are a couple of others that are in the pipeline and we'll maybe get some time for that later on. But I think this is a fabulous step for patients and for research investigation for our patients with HCM.

Carolyn Ho:

Yeah. And I think one thing that's interesting that comes up periodically in thinking about this is that the understanding and the characterization of the genetic form of HCM, the sarcomeric HCM really helped to spark these discoveries of what happens when your sarcomere is not normal. How these mutations and actin and myosin, and myosin binding protein C, and troponin I, and troponin T, how do they actually lead to HCM?

So there's been intense, basic science research on that for a couple of decades now and really has helped us understand this model of pathophysiology in terms of the alterations between myosin and actin and the hyper contractility and the decrease in the SRX state of myosin. But the benefit of myosin inhibitors are not just confined to those with genetic sarcomeric hypertrophic cardiomyopathy, but they create hemodynamic and pathophysiologic changes that are helpful to all forms of HCM. So however you arrive at your hyper contractility and your dynamic obstruction, taking the edge off with a myosin inhibitor can be helpful.

Steve Ommen:

Yep.

Carolyn Ho:

All right. So next we were going to talk about some of the... Sorry, I'm reading your side.

Theodore Abraham:

Go right ahead.

Carolyn Ho:

We're going to value some of the study results from these specific treatments targeting the cardiac myosin and HCM. And so there have been a number of different trials in myosin inhibitors and to first set the stage, we have an audience response question, which of the following was compared with Mavacamten in the explorer HCM trial? So was it alcohol ablation, disopyramide, placebo, septal myectomy, or not sure?

Theodore Abraham:

So Carolyn, these results looks like they're really a good basis for the rest of your presentation. About a half thought this was placebo and then I guess a fair majority of the remainder thought they were not sure. So maybe the rest of your talk will enlighten the 45% of the folks who are not on the placebo side.

Carolyn Ho:

Yeah. And I feel that it's like a slightly trick question because there are nuances where all responses could be correct. So, Explorer HCM was a phase three pivotal trial that enrolled 251 patients with symptomatic obstructive hypertrophic cardiomyopathy to receive either mavacamten or placebo for a 30-week treatment period. And so, there were 123 individuals randomized to receive ma mavacamten and 128 randomized to receive placebo.

And the primary endpoint was an interesting one because luckily, hypertrophic cardiomyopathy is not a highly mortal disease. So trying to construct a clinical trial that was based on mortality or the usual MACE outcomes was not going to be very successful. So EXPLORER was what is referred to as a feel and function type of study. So did the patients feel better and did they have functional improvement with treatment?

And so the way that was assessed was by this primary endpoint which was comprised of achieving either at least a 1.5 milliliter per kilogram per minute increase in peak VO2 with at least a one class improvement in NYHA class, or having at least a three milliliter per kilogram per minute increase in peak VO2 and no worsening of NYHA class.

And so, EXPLORER was positive with 37% of the participants randomized to mavacamten achieving the primary endpoint versus 70% of those on placebo for a between group difference of 19.4 in a highly significant P value. And then there was an additional assessment to see if people could achieve an even more challenging

endpoint, which was both at least a three milliliter per kilogram per minute increase in peak VO2 and at least a one class improvement in NYHA class. And 20% of those on mavacamten and only 8% on placebo achieved this more challenging endpoint. Also clinically and statistically significant.

And then there have been a number of different secondary studies and ancillary studies, which have shown that mavacamten use was associated with a decrease in NT-proBNP and troponin levels and improvement, an KCCQ score, an improvement in E prime velocity, and even some remodeling with a decrease in LV mass, and a decrease in left atrial volume, as well as a decrease in E over E prime values.

And then we know that mavacamten through its mechanism of action is a myosin inhibitor and it's going to reduce left ventricular ejection fraction. And so indeed, those individuals that were randomized to mavacamten had about a four EF percent reduction in their left ventricular ejection fraction from baseline to the 30 week end of study assessment.

So, a baseline EF of 74% decreased to 70% as an average in the group, but this relatively modest change in left ventricular ejection fraction was associated with a very substantial decrease in left ventricular outflow tract radiant, where you can see that the participants that were randomized to mavacamten had about a 50 millimeter mercury drop in their LVOT gradient. This gradient is the post exercise gradient, whereas those randomized to placebo had about a 10 millimeter of mercury drop.

And then more recently and just presented at the ACC meeting a couple weeks ago was the VALOR-HCM study. So, VALOR sought to determine if the addition of mavacamten to existing medical therapy would allow more severely symptomatic patients with obstructive HCM improve sufficiently so that they no longer met guideline criteria for sepal reduction therapy or chose not to undergo septal reduction therapy.

So, 56 patients were randomized to mavacamten and 56 to placebo. So patients initially presented being considered candidates for SRT and considering SRT. And at that time, they were randomized to mavacamten or placebo. And then at 16 weeks, there was going to be a reassessment of echo parameters, functional stress tests, and their eligibility for sepal reduction therapy. And at that point, they could elect to either move forward with septal reduction therapy or to enter into a long-term extension in active use of mavacamten in all.

So here are the baseline data for the VALOR-HCM study. So, similar to the EXPLORER study, the patients were predominantly in the middle age with an average age of about 60 years. Almost 50% were female. And the eligibility criteria required that patients be either NYHA class three or four. The vast majority being class three and most were on background, either beta blocker or calcium channel blocker therapy. And they had robust resting and post exercise gradients.

And the primary endpoint again was a composite of either the decision to proceed with SRT at week 16 or remaining guideline eligible at week 16. And 18% of those on mavacamten met the primary endpoint, whereas 77% of those on placebo met the primary endpoint with, again, a highly significant P value. And 95% of patients actually chose to continue in the long term extension after week 16.

So, a couple things to recognize about VALOR. The dose titration was based on echo, not a combination of echo parameters and drug level as was used in EXPLORER-HCM, but these echo parameters concentrating on

LVEF and obstruction were core lab assessed rather than site assessed. And we saw the expected improvement in LV outflow tract gradient. The gradient reduction was very similar to what was seen in Explorer. And the also seen was a consistent benefit in decrease in NT-proBNP and troponin levels, as well as an improvement in quality of life as assessed by NYHA and KCCQ score.

Again, about 18% on of those on mavacamten versus 77% of those on placebo remained guideline eligible for SRT, but only two patients in each group chose SRT. So that really suggested that patients were holding out to see if this new medical therapy might help them. Remember that all patients elected to move forward with mavacamten were entered into an active phase from week 16 to 32, and then a long-term extension phase after week 32.

And then in late breaking news, as many of you may have already heard, mavacamten was approved by the FDA just yesterday for treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy, so NYHA class two to three with the intent to improve functional capacity and symptoms.

So, this was the Explorer HCM based cohort, but to prescribe mavacamten, healthcare providers, patients, and pharmacists must all become certified in the mavacamten risk evaluation mitigation strategy or REMS program. And this is a URL if you're interested in learning more about the REMS program and that's because myosin inhibitors are drugs that need to be treated with a great deal of respect.

They will decrease systolic dysfunction. You can in a dose dependent manner decrease your left ventricular eject infraction all the way down to zero, if you give enough of it. So these are powerful drugs that require respect and monitoring, but luckily there's quite a comfortable safety margin for us to be comfortable with clinical use and to hopefully replicate the benefit that patients enjoyed in the clinical trials. But something that does require respect and monitoring, particularly as this is new to everybody. And there is also a black box warning for the risk of heart failure due to systolic dysfunction.

Steve Ommen:

I think it's worth focusing on that just a little bit before we go into the REMS program. So when you look at the data from Explorer and from Valor, there's about 15% of patients who were kind of super responders. There's another about 20 to 25% of patients who were definite responders with objective criteria. And then there's a large group which were also responders, because all those substudy analyses were pointed in the right direction, but there was the troubling issue that in EXPLORER, there was almost 10% of patients whose EF dropped to below 50%, which is why this REMS program was required by the FDA.

So it can be very important that we do that, but so not every patient's going to be that person who gets the three to 10 ML per kilogram per minute improvement in their VO2, but it might be enough to help the patients be symptomatic. But this is why we are going into this REMS program which actually makes it easier on the providers in some way because your steps in dose titration are specified for you based on how the patient is doing, what we're going to see on their echocardiogram in terms of their EF and their gradient.

But I just wanted to kind of make sure people understood that that systolic heart failure thing, as you mentioned, is real. You can't start it in a person who has clinical low EF heart failure, or even borderline EF. You

probably need to be careful about that. And there are dose adjustments and temporary cessation measures in the REMS program if the EF does drop.

Carolyn Ho:

Right. And the guidance is to not consider mavacamten if the baseline EF is 55% or lower and there's a specified way to react in terms of interrupting drug and monitoring closely if the EF drops below 50% at any point during therapy. So again, as with all of our treatments, it's not going to be the be all and end all for every patient. Some patients may react very well, but there are some patients that may be at risk. And so that's why we need to move forward cautiously, but optimistically.

And I'll just go through some of the outlines of how the guidance is to start and maintain individuals on mavacamten. So again, you're going to have a baseline evaluation to assess symptoms and echo. So in the echo, we're always going to be looking at left ventricular ejection fraction, trying to make sure that it remains robust and also outflow tract obstruction. And both of those metrics are going to be used to titrate dose.

So the first dose that is suggested is five milligrams. And then as people are initiated on mavacamten, there are going to be assessments clinical and echo assessments at week four, week eight, and week 12. And then again, based on the gradient and the EF, there will be pre-specified per the REMS dose adjustments at those different intervals. And then after week 12, there will be continued echo and clinical surveillance every 12 weeks thereafter. And that's expected to continue indefinitely for now or until new information comes to light, but these are the basics of the REMS program.

Steve Ommen:

Yeah. I think it'll be interesting to see where these fit into therapy going forward and you kind of alluded to something earlier. So there will definitely be patients for whom myosin inhibitors will be their destination therapy, to borrow a term from the advanced heart failure people. That is going to be the therapy that they want to be on for their symptoms.

I think there'll be another group of patients who may decide that they want septal reduction therapy for one reason or another. They don't want to take a medication lifelong, but they know they're going to have to delay that for various reasons. And they might be on one of these agents as a bridge to septal reduction therapy.

And I also think that we're going to have some patients for whom we use it, this is your point before, as a diagnostic therapeutic trial. You have the person who has multiple reasons to be short of breath. One of which may be their outflow tract obstruction. And you might start one of these agents and if their symptoms get tremendously better, that might be your clue that outflow tract obstruction was in fact the cause of their symptoms. And whether you choose to stay on the agent at that point or not, or switch to something else, it might be a way to sort out for a person who's got multifactorial dyspnea.

Carolyn Ho:

Yeah. I think that's a great point, Steve. And just having an easier way to sort that out without committing somebody to cardiac surgery to see if that was the right step or not. Yeah. Could be incredibly helpful with that because it's really the first drug that we have that can provide nearly surgical levels of gradient reduction. Although people can feel better on beta blockers or calcium channel blocker or disopyramide, oftentimes the gradient doesn't really change that much even if they feel a little bit better.

Steve Ommen:

Other than the EF drop, are there other common side effects that mavacamten results in or were reported in the trials?

Carolyn Ho:

Not that I'm aware of. I think that it was generally really quite well tolerated otherwise.

Steve Ommen:

Yeah.

Theodore Abraham:

So 77% of them had side effects, but most of them were related to placebo or non mavacamten. And also to your point, Steve, while I agree that there's a dose response relationship and the EF could drop, it's interesting to note that in the actual EXPLORER trial, almost everybody completed the study. Very few people had a drop that resulted in termination of the drug.

Carolyn Ho:

Right.

Theodore Abraham:

Some had temporary drops. Everybody completed the trial.

Steve Ommen:

Right. Yeah and that's an important point. It said temporary drop. The EF rebounds when the drug is discontinued.

Carolyn Ho:

Exactly.

Theodore Abraham:

And I like the way you put people in three buckets. I agree with that. But on the second bucket, which is this a stop gap to another therapy, like a sepal reduction therapy, we put a fair number of patients, a significant number of patients on mavacamten and on the next trial that Carolyn's going to refer to on REDWOOD and almost all of them were septal reduction candidates. And in our center, we essentially recapitulated what Valor said as nobody decided after close to three years now being on the drug, I've had off of this drug. I'd rather just go get an ablation or a surgery.

So I think there are signals in EXPLORER and in MAVA LTE, which is a long term extension, that tells you where the patients are going to choose to go. That'll be instructive. But I agree with the three buckets. I think that really perfectly elucidates where people should be thinking about where these therapies fall.

Carolyn Ho:

Yeah. Yeah. So these are reversible inhibitors. So if you stop the treatment, the EF will rebound and one thing that's tough and that's why it's important to have a REMS in place is that we can't predict from the outset who might have that overly exuberant response to mavacamten, who will actually decrease the left ventricular eject fraction below 50%. So it's good we just have to monitor until we learn more.

Theodore Abraham:

And it's pretty steady. The dose response is pretty steady. As you keep increasing the dose, the folks with the higher dose are the ones with a higher chance of getting a problem. The only other comment I'll make before I let you continue is that in our experience with mavacamten and frankly, with aficamten, people on steady doses who had nothing else going on in their life did pretty well.

Dose reductions were really related to some intercurrent problem, either getting into AFib or having some other problem got them into trouble. And it was reassuring to note that most folks on steady doses or even incremental doses did not get into trouble or had predictable drops in EF that had protocol driven temporary transient decrements in dose or temporary termination. I shouldn't say terminate. Stoppage of the drug and restarts.

Carolyn Ho:

Right. All right. And so of course mavacamten is not the only myosin inhibitor. The new kid on the block is aficamten and it's being explored in the REDWOOD-HCM phase two clinical trial, where it started off. There are a number of different cohorts that have been evolving over time and this was the initial experience with aficamten as reported at the HFSA meeting last September.

And so there are two different dosing cohorts, cohort one and two. Total of 41 individuals on aficamten. And we see what we now have come to expect to see from myosin inhibitors, that LV outflow tract radiant decreased by 80% after 10 weeks of therapy. And this was similar in both of the cohorts, but as Ted alluded to,

there's a dose response. And so there's a greater degree of gradient reduction in those with a higher dosing cohort. And we also similarly see that there's a substantial reduction in NT-proBNP associated with aficamten use.

The baseline or the stable decrease in LV ejection fraction was similar to what has been seen with mavacamten about five to 10 EF percent with the initiation of therapy. And the phase three SEQUOIA trial is now enrolling in many sites in the United States and internationally. And there's also a phase two trial for non-obstructive hypertrophic cardiomyopathy in planning.

And so kind of with that in mind, so the focus on myosin inhibitors initially has been to target individuals with symptomatic obstructive hypertrophic cardiomyopathy, but that's kind of the low lying fruit with this. The symptoms related to obstruction can be fixed by addressing and fixing the obstruction. So that's something that the myosin inhibitor seem to be doing very well. There's a predictable decrease in left ventricular outflow tract gradient which is really substantial and far greater than we've seen with any other medical therapy.

But one intriguing thing is are there other pleiotropic benefits from these myosin inhibitors that extend beyond just decrease in contractility and decrease in obstruction and might there be improvement in diastolic function? We know that theoretically there should be a saltatory benefit in both diastolic function and myocardial energetics based on how we think myosin inhibitors affect the sarcomere. And there's been some fundamental research trying to see if that actually plays out in a couple different models.

So here is looking at a tissue model using human myectomy specimens and measuring the proportion of myosin heads in the super relaxed or SRX state. You can see that normally with HCM, there is a reduction in the proportion of myosin heads in this super relaxed state. And you can see the dot line of it shows what is expected in a healthy heart. And that in HCN, there's a substantial reduction in that.

But applying mavacamten to these myectomy specimens actually increased the proportion of heads in that SRX state. And then looking at a mini pig model. So these are genetically engineered pigs that carry the myosin heavy chain mutations that cause human HCM. And there's evidence looking at invasive hemodynamics that mavacamten actually improves diastolic filling with an increase in end diastolic volume and a decrease in end diastolic pressure.

And so with these in mind, the MAVERICK-HCM trial was completed a couple of years ago and this was a phase two trial that looked at the potential use of mavacamten in individuals with symptomatic non-obstructive hypertrophic cardiomyopathy. So this is a patient population that we really struggle for because there's not a clear target for therapy and we don't have really highly effective drugs to treat what might be underlying this.

What might be underlying it is really unclear, so we kind of shrug our shoulder and say, "Oh, it's got to be diastolic dysfunction." But we all know that diastolic dysfunction is a very heterogeneous group of potential disorders. So there are people that have primary abnormality of myocardia genetics, primary abnormalities of relaxation. There are those that have restrictive physiology and so it can be a really difficult cohort to try to treat.

And those that have really refractory symptoms, we have nothing to offer except for heart transplantation. So having any kind of medical therapy would be a real benefit for these individuals. Trying to throw beta blockers and diuretics at patients only gets you so far. So with MAVERICK-HCM, one of the exciting

findings was that there was a reduction in NT-proBNP level. So MAVERICK had two different dosing schema, group one and group two with a higher dose compared to placebo. And the dotted gray line, you can see that there was a relatively rapid and consistent decrease in NT-proBNP levels, which was notable by week four of therapy and continued to the week 16 mark at the end of treatment. And then once treatment was stopped, you can see that there was an increase in the NT-proBNP level, back up to the baseline values.

And so this suggests that there is some physiologic benefit that might be imparted by mavacamten in this group. MAVERICK was not adequately powered to look at the feel and function type endpoints that were used in Explore, but a phase three trial is in planning to try to sort that out a little bit more. And again, there's the aficamten phase two trial looking at the use of aficamten in non-obstructive HCM.

So just to think about some take home points, more choices is really welcome by all of us and certainly our patients. Myosin inhibitors offer HCM patients an effective medical option for improving symptoms, particularly in those with obstructive HCM. A direct comparison of SRT versus medical therapy, including mavacamten has not been performed.

So remember VALOR-HCM was not comparing SRT versus mavacamten. It was designed to see if the addition of mavacamten would be enough to cause patients to not proceed with septal reduction therapy, or if they still wished to proceed. So it's unclear if the benefit from mavacamten and SRT are truly equivalent or not.

And then there's also limited cumulative experience with these myosin inhibitors. Only about 400 human beings have taken mavacamten since 2018. It adds up to about 360 patient years of experience, so there's a lot to be learned. I think that's why there's this REMS program to put some guard rails around the use and help us all get some more experience with how to do this, because certainly the impact that these agents can have on contractile function requires respect. All right. So I think that we can go back to our case study.

Theodore Abraham:

Sure. So, Lawrence has read about mavacamten and asked if it would be an inappropriate option, especially reading the news last night or this morning. He's calling your office. He asks about how is it administered, safety issues, asks about the phase three Sequoia study. And this might be a good launch to multiple questions and there's a whole slow of them.

And maybe this is a good launching point for that. Let's see. Let's start with maybe have Steve take these first two, which are more on the beta blocker side. Do you have a beta blocker of choice? And would you start a beta blocker if the patient is not symptomatic, but they have obstruction.

Steve Ommen:

I generally use metoprolol as my first agent, just because it's the most ubiquitous used one, so people understand the dosing sequences. There are some concerns with metoprolol that some of the generic manufacturers, the bioavailability isn't as high. So sometimes switching pharmacies can make a difference for patients, but I typically use metoprolol as my first agent. But if someone's on bisoprolol, I don't change them from that if that's what they come with.

I tend not to use carvedilol. Some people are putting them on it because they said the patient is having heart failure symptoms, but the alpha effects in carvedilol is counter to the mission in terms of their outflow tract obstructions. So I usually try to switch them from carvedilol to metoprolol.

I do not automatically start a beta blocker if someone has obstruction, even a very high level of obstruction, if they are active and asymptomatic. That might be the patient if they say they're asymptomatic, they've got a grading to over a hundred and their treadmill test shows they're only performing at half of age expected exercise capacity. You might consider a beta blocker in that person just to see if they get a little bit better ability to exercise. But if they are active and asymptomatic, gradient does not equal drug.

Carolyn Ho:

Yeah. I totally agree with that. And in fact, I've taken away drug from some people that come to me on beta blockers, because sometimes there's this reflex of diagnosis of HCM start a beta blocker. Especially if you identify a high gradient and sometimes patients struggle more with side effects from beta blockers than any benefit. So a lot of times, if I have somebody that's active and doesn't have any symptoms that seem to be directly related to their HCM, but are feeling kind of fatigued and lethargic, we'll wean off the beta blocker and a lot of times they'll feel better.

Steve Ommen:

Agreed. And it's not as hard to get people to admit to this now, but remember to ask about a erectile dysfunction in men, because that is a big side effect of beta blockers. And sometimes they weren't even aware that was why they were having this issue and you get some great thank you letters when you switch them from beta blockers to calcium channel blockers from the family.

Theodore Abraham:

Carolyn, what do you recommend or what do you do with starting dose of disopyramide? How high do you take it?

Carolyn Ho:

Yeah, so we usually start at if we can get our hands on the sustained release, which as Steve said, sometimes is not a trivial matter, we'll usually start with 300 milligrams total daily dose. So 150 milligrams BID. And so we used to back in the day actually admit patients so we could watch their QT interval and make sure that nothing terrible was going to happen to them, but there's been good experience now in the rest of the world and in this country in a retrospective manner that it's really quite safe to start in the outpatient setting.

So we'll usually have them start it and they'll come in and just get in the ambulatory setting get EKGs for the first handful of doses. You will see QT prolongation, that's part of its mechanism, but you just want to make sure that the QT's not getting too long, not more than a half the RR interval. Most people do pretty well on 300 milligrams a day. Usually we'll max out around 600 milligrams a day. And if there is a shortage of the longer acting

version, the Norpace CR, then you can use the shorter acting version of disopyramide. And we usually dose that as 100 milligrams TID rather than 150 milligrams BID of the CR version.

Theodore Abraham:

So Steve, is it important for HCM patients to get care at a specialized center or can anybody take care of it?

Steve Ommen:

Oh, that's a great question. So we actually wrote about that in the guidelines because it is a specific concern. Much of care about HCM patients doesn't have to be at centers, but there are key moments in a patient's journey that they really do benefit from going to one of the big centers. Initial diagnosis, class one, first therapies, those kind of things can be started about anywhere. But for education about the outcomes of the long term things, sometimes allowing patients to visit with a center early in their course to get that comprehensive education about expectations, et cetera, is important.

Any HCM specific therapy should be done by someone who does a lot of them. There is great data to show that mortality from our invasive septal reduction therapies is magnitudes of order better at experienced centers than at less experienced centers. So any of those are important.

The other thing that we noticed when we were writing the guidelines is that anything that ended up as a class 2B indication, whether it was a diagnostic test or a therapy took weeks of debate. And this is amongst people who are supposed to be informed about the disease and they couldn't agree. So if you're not someone who sees a lot of HCM, if you're contemplating a class 2B something, that's probably a great time to get one of the centers involved to see if they recognize the nuances in this patient that might influence whether that's the right thing or not.

But things like once a decision is made to implant a defibrillator, there's lots of great people who can implant an ICD. That doesn't have to be done at an HCM center once the decision is made. Sometimes helping the patient make that decision is done at the center and the implantation occurs with their local team. So it's important to have a referral kind of pathway that's greased and that, remember, we're all trying to work on behalf of the patient. It's not the center that's at the center. It's the patient that's at the center and we're there to help manage that patient holistically with their local team and step in when it's needed for that patient's healthcare journey.

Carolyn Ho:

Yeah. We're thrilled to co-manage patients in this manner. And I would totally agree with all the points that Steve raised. In addition with the invasive therapy, it's not just the mortality, but just the anticipated benefit can be very different with an experienced operator versus a less experienced operator.

Less experienced surgeons tend to be a little bit more timid about how much tissue is removed in myectomy and that can lead to suboptimal results and residual striction. So just having that extra bit of experience and confidence can make a big difference in the outcome.

And I would also say that genetic testing is something that can be very well handled in a more experienced center. Really teasing out the family history, constructing a detailed pedigree, and going over with the patients the nuances of the potential limitations and benefits of genetic testing is can be really crucial. So that patients are really adequately counseled before deciding whether genetic testing is for them and having appropriate expectations. And I think that we've all become very facile with telemedicine and virtual visits and genetic counseling is something that is really well handled by those types of technologies.

Theodore Abraham:

Great, great discussion. I love the comment about the patient being the center, not the center being the center. That's really good. So this is to Carolyn. What do you think of Valsartan as a disease modifier?

Carolyn Ho:

Yeah, so we were super excited about the VANISH trial, which looked at valsartan as potentially being able to attenuate disease progression in early sarcomeric hypertrophic cardiomyopathy. And this was based on a lot of really beautiful basic science work, which indicated that the profibrotic pathways were up regulated very early in the life of these mice that had myosin heavy chain mutations introduced into them.

So mice are like humans. They develop HCM in an age dependent fashion. So it's usually not until the mouse is fully mature in about 30 weeks of age that you actually see phenotypic HCM with left ventricular hypertrophy. But before that, they have all those early phenotype manifestations that we discussed. And in fact, that's how we knew to look for them in humans. It was all guided by the mouse models.

And so prefibrotic pathways were unregulated, and that all seemed to center around TGF beta activation. And inhibiting TGF beta either with neutralizing antibody or with Losartan seemed to attenuate disease progression if it was started early before the mice actually had a phenotype of HCM. So we wondered whether that might be translated to human HCM, but there's of course huge differences and huge challenges in trying to go from mouse to human.

And we felt that if we started with a truly preclinical human population, we'd have a hard time showing anything and a relatively short feasible duration of a clinical trial. So instead of taking the truly preclinical humans, we thought we would try to target early disease. So early being defined as being relatively young, not having severe remodeling, and being asymptomatic. And that might be a more plastic time in disease evolution where we might still have the ability to modify what goes on in disease course, rather than waiting until somebody has really advanced, established disease and trying to get the horse back into the barn at that point. Biologically seems more feasible to act earlier.

So that type of patient was randomized to receive either Valsartan or a placebo. And we looked not again at MACE or even feel and function because all those people felt fine when they started. So we looked at a composite endpoint that would report out different spheres of cardiac structure, function, and biology.

So we looked at troponin and NT-proBNP. We looked at LV cavity size. And we looked at E prime and S prime velocity. So all these metrics that were found to differentiate preclinical HCM sarcomere variant carriers

from normal and also the preclinical HCM from clinical HCM, we thought might be metrics of disease evolution. And after two years of treatment with Valsartan, there did seem to be a significant benefit from those receiving off valsartan versus placebo, where there was stabilization or even improvement in those metrics on the valsartan treated group and worsening in the placebo treated group.

So we would love to do a large phase three trial to really try to prove the point, but that trial at a practical level would be almost impossible to do because we'd need to have thousands of patients or at least many hundreds of patients followed over decades to see what actually happens. Again, luckily HGMS not highly mortal and a natural history plays out over years and years so trying to do that, I think would be really hard.

So now we are adopting a shared decision-making strategy with our patients to see if using valsartan with the intent of disease modification might be for them. So there's some people that say, "That sounds great." There's not much risk or there's really minimal risk of taking valsartan. There might be some benefits, "Sure. I'm game to try." And other people say, "Well, if you can't prove to me that's going to make me better, than I'd rather not take anything." So I think that those are both completely appropriate responses to that and I think it's up to the patient.

Theodore Abraham:

Awesome. Steve, do you put everybody on prophylactic antibiotics? I mean anticoagulants.

Steve Ommen:

No. Patients who have AFib, yes. So we don't use the CHADS 2 VASc scoring system at HCM. Having HCM and AF has this annual stroke risk of at least 3%, so it's like having an automatic CHADS VASc score of three. So they qualify for DOAC therapy based on that. But the patient with HCM who doesn't have a burden of A Fib does not necessarily require anticoagulation.

Carolyn Ho:

So what is enough AFib?

Steve Ommen:

Yeah. Good question and I think that we appropriately tap danced around that. So if you look at the general AFib data, there's some data that stroke risk can occur with even minutes of AFib. I think you do that on a case by case basis. If it's someone who has had a single episode of AFib and there might be a provocation for it, they had an intrathoracic operation and they developed post-op AFib. They had COVID and got AFib or something there was an inflammatory response and that's not going to happen again, maybe that person doesn't have lifelong risk for recurrent AFib. But someone who does have a big left atrium and you look at them and you just feel as a clinician this is a person who's going to have more and more AFib, I think it makes sense to do that. The other option is to consider some sort of recording device to see if they're having asymptomatic A Fib, whether you do a month long ambulatory ECG, or you do an implantable loop recorder to monitor or something like that if you've got someone who kind of falls in between those two categories.

Theodore Abraham:

So moving on. Carolyn, if you combine a beta blocker with a calcium blocker and you end up with low heart rate, should we just use Amlodipine as the calcium blocker?

Carolyn Ho:

Oh, so amlodipine would not meet with Dr. Ommen's seal of approval in HCM, right? So there are two different classes of calcium channel blockers. So there's a dihydropyridine like, am amlodipine and nifedipine. And then there's the L type calcium channel blockers like verapamil and diltiazem. And so it's the L type calcium channel blockers that have a role in HCM because they're more similar to beta blockers where you have some decrease in inotropy and decrease in chronotropy. So a little bit of less contractility, some slowing of the heart rate to try to help enhance diastolic filling time and to decrease obstruction. Whereas the dihydropyridine calcium channel blockers are vasodilators, so they can actually make obstruction worse. So would be something to try to avoid.

Theodore Abraham:

Steve, where does TEE fit into your screening for HCM? Do you use TEE ever?

Steve Ommen:

Yeah, TEE is really only in special circumstances. So particularly in the era of CMR, if the transthoracic echo images aren't satisfactory, then CMR is usually the first reflex. Sometimes though, if you need to look for primary mitral valve disease, that you might have a strange looking mitral valve motion, or it's a central anterior jet of mitral regurgitation on your transthoracic echocardiogram, then doing TEE to understand the mitral valve anatomy and dynamics can be important.

We also obviously use TEE during the invasive procedures, particularly myectomy as part of inoperative TEE, but sometimes is also part of septal ablation to make sure that the impact of that septal reduction therapy is appropriate. And then other standard indications for TEE is someone who's had a neurologic event or someone for whom endocarditis is suspected. But in terms of routine testing for HCM, TEE really is not a part of the standard algorithm.

Theodore Abraham:

Thank you. Carolyn, you sort of answered this question, but I'm paraphrasing it. Who do you send for genetic testing in HCM?

Carolyn Ho:

We tend to be pretty broad with our genetic testing. We'll have a conversation with the patient initially to try to get people to understand what we can and can't learn from genetic testing. Certainly if there's a family history of HCM or something that seems suggestive of a family history, we would be encouraging of it because our likelihood of having positive actionable results would be higher. But I think that a lot of times we don't know much

about the family history and a lot of times as much as we would love to have echoes on all first degree relatives, that's not practically available. So we will have a discussion about it with all of our patients.

Steve Ommen:

Yeah. Likewise.

Theodore Abraham:

Steve, when will mavacamten be available?

Steve Ommen:

So in unofficial conversations we've had with people in the manufacturer, they feel that the drug supply will be steady by mid-May. So, the issues are for Medicare covered patients, there isn't coverage yet. And that might take another two to three months. So for Medicare age patients, it's probably not going to be mid-May that you want to start it because it might be not affordable for them, but for commercial pay or low income patients, there should be steady supply of tablets in the second week of May.

Theodore Abraham:

Carolyn, during initiation of mavacamten, do you need to see the patient every time they get an echo? We're testing you on the REMS.

Carolyn Ho:

It's left deliberately a little bit flexible. I would say until you get a patient on their study dose, it would be appropriate to physically lay eyes and hands on the patient at the time that they're getting the baseline, four week, and eight week, and 12 week echo, just to make sure that all is going well. After they're more in the maintenance phase, then I think that it's up to the provider discretion as to how those visits would be best accomplished

Steve Ommen:

Somehow you need to ascertain whether the patient is having heart failure symptoms or clinical deterioration, so that's part of it. It's not just an echo assessment.

Carolyn Ho:

Right.

Theodore Abraham:

So Steve, if I complete the REMS, how soon can my patient get mavacamten? There are lots of rapid fire questions. I want to get to most of them before we end though.

Steve Ommen:

It's probably about the same. So if you have this patient Lawrence here and he wants to start mavacamten and you are registered in REMS, he's registered in REMS, and you write the prescription, then he will work with a specialty pharmacy of his choice to get that agent. And it could be within a few weeks.

Theodore Abraham:

Thank you. Carolyn, does everybody need to do REMS, including nurses and PAs and NPs?

Carolyn Ho:

Yeah. So everybody that's going to be potentially prescribing or interacting with the patients and the required follow-up needs to go through the certification process.

Steve Ommen:

Yeah. I think it's important to note that if the patient or you are not compliant with the REMS, the patient will not receive their next shipment of medication. So they will go off of drug.

Carolyn Ho:

Yeah.

Theodore Abraham:

So Steve-

Carolyn Ho:

And the patients will receive 35 pills at a time. So there's a little bit of wiggle room for monthly dosing, but not a lot.

Theodore Abraham:

Steve, would myosin inhibitors be recommended earlier in the disease so they can prevent people from becoming obstructive?

Steve Ommen:

Well, those will obviously be some of the next sets of studies that we need to be done. It is a question that begs to be answered. We can't say that based on the data we have now because these are all patients who are class two or class three in EXPLOERE and VALOR respectively. But obviously, we're all going to ask that question coming soon, if you have someone family history, gene positivity, does starting a myosin inhibitor in some change disease progression? So I would say stay tuned.

Carolyn Ho:

Yeah. And there have been studies in the mouse model of HCM in exactly that. So providing mavacamten to the preclinical mice, again before they developed left ventricular hypertrophy. And it really seemed pretty optimistic about the ability to attenuate the development of left ventricular hypertrophy and also to attenuate the development of fibrosis. So that's been shown for multiple agents and it was pretty striking with mavacamten, but I think that there's going to be a lot between getting this initial experience with symptomatic patients with obstruction and then what safety information and comfort are we going to need to then set back the clock to providing it to a healthy young person. I think that there's still a lot to be learned.

Steve Ommen:

Exactly.

Theodore Abraham:

Carolyn, do sarcomere and I think they mean gene negative patients have more LVOT obstruction?

Carolyn Ho:

Typically, sarcomeric HCM and if we look at some of the registry, studies have had slightly more obstruction.

Theodore Abraham:

Got it.

Carolyn Ho:

Sorry, sorry. Slightly less obstruction than the non sarcomeric. So non sarcomeric patients tend to have a little bit more obstruction. Not a huge amount difference, but they tend to be a slightly more obstructed.

Theodore Abraham:

Steve, do you use the Valsalva maneuver when assessing LVOT? Do you do any other maneuvers?

Steve Ommen:

Yes. So when we're talking about physical examination, we do Valsalva maneuvers. We will have the patients do squat to stand maneuvers.

Theodore Abraham:

I think they meant echo gradient.

Steve Ommen:

I'm going to get to that as well.

Theodore Abraham:

Oh, sorry.

Steve Ommen:

Yeah. And then I also have them walk up a flight of stairs with me if I haven't got it at that point. In the echo lab, our standard protocol is if the rest ingredient is 40 or more, they don't have to do any provocation. If it's not, then they do Valsalva. If the Valsalva gradient's 40 or more, they can stop. If it's not, then we actually do squat to stand maneuvers in the echo lab and image those patients standing.

And then we used to use amyl nitrate. That is all that's not as available either. Drug supply for that isn't as good. So it's usually just those physical exam maneuvers in the standard resting echocardiogram. If they don't have it at that point, then we decide whether to go on with stress echo. Yep.

Theodore Abraham:

Thank you. Carolyn, I'll send this one to you. The question was what is the demographic of the patients? What they really mean, I think, is how symptomatic were the patients? So they said, were this mostly mild disease or severe disease, so maybe you can answer it. And I think they mean EXPLORER.

Carolyn Ho:

In EXPLORER, so-

Theodore Abraham:

I'm just going to say EXPLORER.

Carolyn Ho:

So in EXPLORER, patients had to be NYHA class two to three to qualify. In Valor, they had to be NYHA class three to four. And in Vanish, they had to be NYHA class one or two.

Theodore Abraham:

Awesome. Steve, I'll direct this to you. How available is myectomy in other parts of the world compared to the US?

Steve Ommen:

It's a lot lower in other parts of the world as compared to the US. And it's a challenging procedure to teach because only one person who can see what's going on, because remember the operation is done through an incision in the aorta and looking down through the aortic valve. So it's difficult to teach. So there are a handful of centers in North America that do a really good job. There are a handful of centers around the world, but in many countries around the world, septal ablation is the primary septal reduction therapy.

Theodore Abraham:

Carolyn, how soon do you expect symptom relief once you get on mavacamten?

Carolyn Ho:

Yeah, pretty quickly. I would say probably within a couple of weeks based on the informal feedback that we've heard from our patients in the trials.

Steve Ommen:

And that's usually what I say about any drug dose change, because remember patients have those good days and bad days and you want to even those out anyway. And so I would probably say the same thing with a new agent.

Theodore Abraham:

Steve, is there still a role for RV pacing?

Steve Ommen:

So the answer is sure, if they already have an RV lead in place. I haven't put in a pacemaker for the sole purpose of reducing outflow tract obstruction. But if they have a dual chamber pacemaker or a dual chamber ICD in place and they aren't responding to the standard medical therapies and the other ones aren't looking good for some reason, having a trial of AV optimization with RV apical pacing is worth trying if they already have hardware in.

Theodore Abraham:

Carolyn, how would we measure if mavacamten is able to modify disease?

Carolyn Ho:

That's a great question.

Theodore Abraham:

Yes.

Carolyn Ho:

The question that we all... Like what does improvement look like when you're starting with somebody that feels fine? It's easy to show you've made a stick or symptomatic patient better, but it's really hard to show that you've made a healthy, well person better. So I think that the approach that we took in Vantage is to see if there are improvements in the hemodynamics structure, function of the heart. So I think it's going to have to be some kind of holistic approach like that, but we are still trying to figure out what are markers of disease progression in early preclinical disease and what are they once disease is established. And I don't think that they're going to be the same necessarily.

Theodore Abraham:

Steve, should mavacamten be offered prior to any septal reduction on a surface systematic basis?

Steve Ommen:

I think that's a good question. I think that we're going to learn that over the next few years, to be honest. The way I classify it right now, if you go back to that slide I had after the first line therapies, there was this right hand side that said advanced therapies. I would consider mavacamten as one of the advanced therapies.

So I think you discuss all of them together with the patient and make a decision on pathways and sequences at that point with each patient. Because again, there'll be some reasons why patients will choose each of those over the other ones. So I think at that point, you have a broader description of disopyramide, mavacamten, myectomy, and ablation at that point.

Theodore Abraham:

So I think we're at the two minute mark, I'm going to direct the last question. There's maybe 20 or 30 more questions, so we can't actually get through them, but Carolyn, will drugs like mavacamten work for patients with severe left ventricular hypertrophy, but without LVOT gradient? You alluded to that in MAVERICK a little bit. What are your thoughts?

Carolyn Ho:

I think that we're going to have to like figure out those people have symptoms. I think that for the foreseeable future, mavacamten and myosin inhibitors are going to be for symptomatic disease.

Theodore Abraham:

Steve, any comment there?

Steve Ommen:

I agree.

Theodore Abraham:

All right, thanks. So great discussion. so want to remind our audience, both here in the room and virtually wherever you are in your pajamas, consider SMART goals. And SMART really stands for specific measurable, attainable, relevant, and timely. Consider HCM in the differential diagnosis for patients presenting with relevant symptoms and you've heard beautiful talks on all this use. Complimentary imaging echo MRI for reliable diagnosis and management. Apply current practice guidelines to the care of patients with HCM and you've people here who've done the guidelines. And keep pace with developments in HCM management that might improve the quality of care and outcomes.

And I think today's session with two outstanding speakers covered not only all these topics, but hit each of those SMART goals. And thank you for joining us. Do not forget to collect your credit. This is how you visit the cardiology hub, which also gives you more information on HCM.

This is how you would request your credit. You have to complete the post test and evaluation online and click the request credit tab to complete the process and then you could get your certificate. So thank you all. Thank you, Dr. Ho for your excellent series of talks, both right from basic, which nicely led up to these very novel and historic therapies and Steve for laying the groundwork for such a great session. Thank you, both. It was really a pleasure and honor to be on the podium with the two of you.

Steve Ommen:

Thank you.

Carolyn Ho:

Thank you.