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https://reachmd.com/programs/cme/translating-evidence-into-practice-myosin-inhibition-across-the-hcm-spectrum/54343/

Released: 10/14/2026
Valid until: 10/14/2027
Time needed to complete: 45 minutes

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Translating Evidence Into Practice: Myosin Inhibition Across the HCM Spectrum

Opening:
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Chapter 1

Dr. Michels:
Welcome. My name is Michelle Michels. I'm a cardiologist based in Rotterdam, the Netherlands, and today I'm going to talk about translating mechanistic insight into clinical decision-making in obstructive hypertrophic cardiomyopathy.

These are my disclosures.

So if we're talking about hypertrophic cardiomyopathy, this is not a new disease. This disease has been around for decades. First been described 70 years ago, but the big innovation in the treatment of hypertrophic cardiomyopathy actually happened the last decade, where we see more and more randomized controlled trials, especially with cardiac myosin inhibitors, that already changed the guidelines and the way we treat our patients today.

If we dive into hypertrophic cardiomyopathy, the definition over the years stays the same. So it's a maximal wall thickness equal or exceeding 50 mm in the absence of loading conditions. The threshold lowers in first degree relatives or genotype-positive subjects.

The definition of obstructive hypertrophic cardiomyopathy is a bit more complex, where obstructive hypertrophic cardiomyopathy is defined by left ventricular outflow tract gradient equal or exceeding 30 mmHg, but we think it's a threshold for treatment and hemodynamically important if it exceeds or is equal to 50 mmHg.

The prevalence of hypertrophic cardiomyopathy across the world is 1 in 500 for the phenotype, increasing to 1 in 200 if we also include genotype-positive, phenotype-negative subjects.

If we talk about hypertrophic obstructive cardiomyopathy, it's very important to realize that left ventricular outflow tract obstruction can be absent at rest, and the amount of patients with an obstructive phenotype increase significantly if you do provocation measurements. And what we're supposed to do, according to the guidelines, is that we at least perform measurements at rest, at Valsalva, and if we're still not sure, you can also exercise your patient. And this is an example of one of our own patients with hypertrophic obstructive cardiomyopathy, without a significant left ventricular outflow tract gradient at rest, but you see it increasing at Valsalva and after

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squatting.

The impact of left ventricular outflow tract obstruction on outcomes has first been described more than 20 years ago by Martin Maron in a *New England* paper, where he clearly showed that the freedom from HCM-related death is higher in non-obstructive patients compared to obstructive patients. He also already showed that this is also true for patients in NYHA Class I, so those actually without symptoms. And a more recent paper from the SHaRe Consortium published last year actually repeated this data. So also in NYHA Class I patients, we do see more outcomes, especially in patients of older age with increased left atrial size and female sex.

So do we still have a therapeutic unmet need in obstructive hypertrophic cardiomyopathy? Well, over decades we've been treating this disease with standard of care treatment, especially beta-blockers and calcium channel blockers, and this is only true for patients with symptoms. Both works are non-HCM specific, and there's a limited level of evidence, so very small or absent randomized controlled trials. In NYHA Class III patients, we already for decades have the possibility to perform septal reduction therapy, but clearly there was an unmet need before CMIs were introduced in this field.

If we talk a little bit more about septal reduction therapy, it's a great therapy in experienced centers, and actually guidelines recommend also that SRT should be performed in experienced centers. If we look into the results of septal reduction therapy of experienced centers, as centers that are part of the SHaRe HCM Consortium, and these are data of over 1,000 patients who underwent very effective septal reduction therapy with low complication rate, if you follow the patients, that you see that 1 in 10 actually develops heart failure and has an ongoing cardiomyopathy process that it's not being addressed by the SRT.

And I think this is where the cardiac myosin inhibitors are of interest because what we learned over the years of researching this disease is that in hypertrophic cardiomyopathy, the number of actin-myosin cross bridges in the sarcomere is increased. This leads to hypercontractility and also reduced diastolic function. CMIs are able to reduce the number of active actin-myosin cross bridges, and we already have four pivotal phase 3 randomized placebo-controlled trials with CMIs in patients with symptomatic obstructive hypertrophic cardiomyopathy.

So the first trial, which impressed us all, was the EXPLORER-HCM trial published in 2020 by Iacopo Olivotto in *The Lancet* including 251 patients with symptomatic obstructive hypertrophic cardiomyopathy, comparing mavacamten to standard of care. And the trial reached its composite functional endpoint, which was a composite of both feel and function. It improved NYHA Class, improved peak VO2, improved KCCQ, reduced peak LVOT gradient, and we saw a decrease in NT-proBNP.

VALOR came a little bit later, and VALOR was a trial in more symptomatic patients with a primary endpoint of the reduction of SRT eligibility, and also this trial was heavily positive.

And these 2 trials actually led to the introduction of mavacamten on the market.

Of course, if we are trying to work on hypercontractility, we're also afraid of left ventricular ejection fraction drops. They were observed in both trials, but I think what's very reassuring is that it's reversible upon interruption.

Then aficamten was tested in symptomatic obstructive hypertrophic cardiomyopathy first in the SEQUOIA trial. Again, a little bit more than 250 patients NYHA Class II and III, and this trial was also really positive for feel and function for the patient, what is extremely important, and saw a large decrease in NT-proBNP, and we did see less ejection fraction below 50. And because of the pharmacodynamic aspects of aficamten, they were all reversible upon down-titration.

MAPLE was the first trial who compared head-to-head beta blockade to aficamten, and aficamten exceeded the effects of beta blockade and was a very positive trial.

So these trials, they really changed the treatment paradigm for obstructive hypertrophic cardiomyopathy, and both works are in the guidelines. Mavacamten has been approved 4 years ago now in the United States, and 3 years ago in the European countries, and it's been available commercially. Aficamten was first approved December last year, beginning of this year in Europe, and Germany is actually the first European country where aficamten is commercially launched on June 1st.

Thank you very much for your attention.

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Chapter 2

Dr. Schulze:
Welcome to our session today, From Bench to Bedside: Patient-Centered Care and Shared Decision-Making in Patients with Hypertrophic Obstructive Cardiomyopathy. My name is Christian Schulze. I'm the chair of cardiology at the University Hospital in Jena, Germany.

These are my conflicts of interest.

Cardiac myosin inhibitors are a new field. These are new medications that have changed the way we treat patients with hypertrophic obstructive cardiomyopathy. And they have a very distinct molecular mechanism; they interfere with the interaction of actin and myosin in the heart. And by changing that interaction, they change the hypercontractility that is typical for patients with obstructive hypertrophy cardiomyopathy.

Right now, we have 2 medications that both are cardiac myosin inhibitors, and both medications, mavacamten and aficamten, interact with the cardiac myosin interaction. They both have comparable effects, but there is not just a class effect. Mavacamten stabilizes myosin into a super-relaxed off state, and by doing that, it decreases the ATPase activity and slows the interaction with myosin. Aficamten, on the other hand, binds to a distinct allosteric site at the S1 domain of myosin, and by doing that, it reduces the ATPase activity by slowing the phosphate release. Doing that, it stabilizes a weak actin binding state. So both have the same effects, but they are very distinct molecular interactions.

Mavacamten versus aficamten are 2 different drugs, and they have central differences in their titration schemes. These are based on their molecular capacities and are linked to the interaction of actin and myosin.

We have 2 different starting doses. Aficamten is being started at a 5-mg dose. You can start it at 10 mg if the left ventricular outflow tract obstruction is more than 100 mmHg. Mavacamten, on the other hand, is being started at 2.5 mg, and because the half-life of aficamten is shorter than mavacamten, you have a more rapid dose titration scheme. Half-life of aficamten is only 3.4 to 3.5 days, and the half-life of mavacamten is 5 to 9 days. There's a different time, of course, until you reach the steady state. This is around 2 weeks in aficamten and 6 weeks in mavacamten. And of course, you have a faster washout period if you stop the aficamten compared to mavacamten.

Based on the study design, when both drugs were tested, we have also introduced different dose titration schemes, and this is relevant for the safety of the drugs. In the studies, aficamten in this case, was used on an upscaling titration scheme, and if the patient in a review echocardiography showed in stable left ventricular ejection fraction, the dose of aficamten was increased. If the patient showed a decrease in ejection fraction to less than 50%, the dose was reduced, and the patient could later then again expose to a higher dose of aficamten.

An individualized dose titration scheme was used until the Valsalva LVOT gradient was less than 30 mmHg, and the left ventricular ejection fraction was preserved at more than 50%.

Based on the European Union label considerations, these 2 cardiac myosin inhibitors have some differences. We have to do a genotyping for the introduction of mavacamten. This is not required before you introduce aficamten to the patients. The patients with aficamten have less of a risk of different drug-drug interactions, and this is based on the metabolism of aficamten with multiple CYP enzyme systems. On the other hand, mavacamten is primarily used with one single CYP system. Based on that there's a higher risk of interactions. Mavacamten is also contraindicated in pregnancy.

Well, how might aficamten differ from what we know so far? Well, there's actually an advantage that the once-daily dosing with a half-life of 3.4 days is typical for aficamten. We have a very rapid onset of the adjustments every 2 weeks, hence there's a rapid reversibility. We have a wide therapeutic window, small changes in left ventricular ejection fraction as aficamten dose is being increased. And it allows for very individualized dose adjustment, and we have a minimal risk of drug-drug interactions.

There are some long-term safety concerns that I still want to mention. We know that atrial fibrillation occurs in around 2% to 6% of our patients. We don't know whether this is related to de novo episodes or prior conditions, and we also know that this is not associated

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with deterioration in left ventricular ejection fraction. But left ventricular ejection fraction on the long run is one of our concerns because we don't know at this point whether left ventricular ejection fraction is further decreasing this and longer use of aficamten.

Thank you very much.

Chapter 3

Dr. Masri:
Hello, my name is Ahmad Masri. I'm a cardiologist at Oregon Health and Science University in Portland, Oregon, and I'm a cardiomyopathy specialist. And today I will be presenting a hypertrophic cardiomyopathy case of a patient with obstructive HCM.

Here are my disclosures.

So this is a very typical scenario that you see every day in your clinic: a 35-year-old woman with progressive dyspnea on exertion. She presents with NYHA Class III symptoms, systolic ejection murmur on exam that is exaggerated with Valsalva, and not on any medications, and family history is unknown; patient is adopted. EKG was unremarkable, but an echocardiogram was obtained, given that she has dyspnea and murmur on exam, that showed, as you can see, hyperdynamic left ventricular function, systolic anterior motion of the mitral valve, and likely severe LVOT obstruction. However, you have to perform Doppler in order to quantify that LVOT gradient.

So as you can see here, this is the resting gradient, and patient had a 27 mmHg at rest, and with Valsalva, that went up all the way to about 64 mmHg. So significant LVOT obstruction. Maybe at rest is not getting to the usual caliber of 30 mm, but it's pretty close there, and more than 50 mmHg with Valsalva. So this defines this as having obstructive hypertrophic cardiomyopathy. Patient also obviously had left ventricular hypertrophy above 15 mm.

And so when you encounter such a patient who is not on any medical therapy at this point, what would be the next best step in management? Is it beta-blockers? Is it mavacamten, aficamten, septal myectomy, or alcohol septal ablation? Think about it. But let's go through these options one by one.

First, beta-blockers. Guidelines recommend that we use beta-blockers as first-line therapy in symptomatic patients with obstructive hypertrophic cardiomyopathy. However, that is actually not based on any multicenter, randomized, blinded clinical trials or any strong evidence. And as such, this specific strategy, even though it's still the most commonly used first-line therapy, has been trialed in the MAPLE-HCM study.

In MAPLE-HCM, patients were randomized to aficamten versus metoprolol as a representative of beta-blockers, and showed that metoprolol led to a reduction in patients' exercise capacity and also led to worsening in how these patients performed on their exercise test. Also, beta-blockers led to worsening in the left atrial volume index as well as NT-proBNP. Patients had improvement in their symptoms, but it wasn't different from a placebo trial done previously called SEQUOIA-HCM.

As such, I think it is very reasonable at this stage not to necessarily go through a beta-blocker strategy, especially in a younger patient who is active and wants to maintain their heart rate and chronotropic competence and be able to do different activities. I think it is very reasonable to skip that class of medications unless you have no other options or you are enforced to do it through different coverage mechanisms.

The second drug that can be considered is mavacamten. Mavacamten has been studied in the EXPLORER-HCM study, which led to its approval for such a patient. However, in the EXPLORER-HCM trial, mavacamten was studied against placebo in patients who are already on standard of care therapy. So more or less thought of it as a second-line therapy and was not trialed head-to-head against beta-blockers or as a first-line therapy at this stage.

There's another point here which I think is worth mentioning. I told you that the patient is not on any medications, so with mavacamten you have to worry about drug-drug interactions. And I also told you that the patient is 35 years old, so you have to be careful about discussing plans for starting a family, getting pregnant because mavacamten is teratogenic at the clinically used doses. However, all that being said, it's still a very reasonable strategy to talk to your patient and consider the start of mavacamten.

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The third option could be aficamten. Aficamten has some favorable pharmacological properties that allow for more rapid titration, easier to use drug overall, has much less drug-drug interactions, and is not teratogenic at the clinically used doses. That doesn't necessarily mean that it's safe to get pregnant on aficamten, but if something is to happen, you are probably safer in general compared to some other medications that can be used in this scenario.

And so aficamten also was trialed in the MAPLE-HCM study as a head-to-head comparison, and so aficamten in general can be used based on this randomized clinical trial as a first-line therapy instead of using beta-blockers there.

Finally, when we look at septal myectomy and alcohol septal ablation, the patient does have an NYHA Class III, and they do have also a peak LVOT gradient that is above 50 mmHg. However, they have not been trialed on other medical therapy before, and as such, in such scenario, we actually would reserve these septal reduction therapies to patients who have failed medical therapy, or they are intolerant of medical therapy, or they continue to be symptomatic and obstructive with medical therapy.

As such, in here, I think the most appropriate answer would be aficamten based on the data available to us. However, based on the guidelines, your answer would be beta-blockers as a first-line therapy, since the guidelines have not yet changed to reflect that. So those 2 options are reasonable to start this patient on. The third option is mavacamten. Again, was not trialed as a first-line therapy, but is reasonable if it's available to you to consider it in such patient. I don't think you should be considering septal myectomy or alcohol septal ablation for such patient up front.

Thank you for joining us for this case.

Chapter 4

Dr. Masri:
Hello, my name is Ahmad Masri. I'm a cardiologist at Oregon Health and Science University in Portland, Oregon, United States, and I'm a cardiomyopathy specialist. It's my pleasure today to talk to you about non-obstructive hypertrophic cardiomyopathy. What's on the horizon?

These are my disclosures.

And so there is a large unmet need in hypertrophic cardiomyopathy, and especially in non-obstructive hypertrophic cardiomyopathy. These data are from an international registry called the SHaRe Registry, showing you really significant burden of the disease over the lifetime for patients. The earlier the patients develop hypertrophic cardiomyopathy, the worse their outcome can be. And these outcomes are not soft at all; we're talking about ventricular arrhythmias, heart failure composite, and atrial fibrillation as well.

And so up until this point, we have not had a positive trial for patients with non-obstructive hypertrophic cardiomyopathy who are symptomatic and who have also exercise intolerance or limited exercise capacity. The ACACIA-HCM trial that I'm going to talk about is the first trial to report positive results in this disease space. So this is a trial of aficamten as compared to placebo in patients with non-obstructive hypertrophic cardiomyopathy. As many of you are aware, diastolic dysfunction is a primary factor that is seen in the pathophysiology of non-obstructive HCM, and aficamten can address that.

As such, what we did is that we enrolled 517 patients, 1:1 randomization to aficamten versus placebo in patients with symptomatic non-obstructive hypertrophic cardiomyopathy. The trial ran up to 72 weeks of treatment plus 4 weeks of washout. The trial continued until the last patient crossed week 36, and patients remained blinded throughout the study. There was no part of unblinding here.

We tested 2 dual primary endpoints. One is KCCQ Clinical Summary Score, and the other one is peak VO2. I'll start with KCCQ Clinical Summary Score, which the primary point was assigned at week 36 to align with the peak VO2, but KCCQ was tested throughout the trial. So at week 36 there was a 3-point difference in favor of aficamten compared to placebo, with a p-value of 0.021.

Now, at all other time points beyond the titration phase and week 12, KCCQ change was 4.8 to 7 points as compared to placebo in favor of aficamten with a p-value less than 0.005. After washout, aficamten group had reduction in their KCCQ Clinical Summary Score to become similar to placebo. This is really an important point. If you look at the curves here, patients on aficamten continued to have

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improvement in their KCCQ throughout, while patients on placebo had a lot of fluctuation up and down, and that's the result of what you see in this variation in the delta KCCQ between the 2 groups.

The second dual primary endpoint was change in peak VO2. As you can see, aficamten positively influenced that by 0.67 mL/kg/min, with a p-value of 0.003. Aficamten then also improved the whole host of secondary endpoints, including NYHA Class, Z-score, which is a comprehensive exercise capacity score, and wall stress, which is NT-proBNP. As you can see, 14% difference at week 36 in NYHA Class.

The VE/VCO2, which is an important component of the submaximal exercise capacity, aficamten improved it by 0.91 with a p-value of 0.016, and NT-proBNP improved very early in the trial and continued to improve throughout the titration phase and remained stable there with a geometrically mean square ratio of 0.43.

Importantly, upon washout, look at the quick rebound of NT-proBNP from the end of the treatment to the end of the study in the aficamten group, while there was no change in the placebo group.

In terms of safety outcome, a serious heart failure event occurred in 4.7% of patients on aficamten versus 1.2% of patients on placebo. However, all these heart failure events were simple events, and they were treated with short course of diuretic therapy. These events happened during the initiation and titration phase of aficamten. Just think about it this way: these patients are living with this disease for a very long time, and we're introducing a new contractility modulating agent. These patients did not necessarily have systolic dysfunction; it's just they have a reported event of heart failure.

Aficamten did reduce ejection fraction by 4.4% at week 36. This is similar to what we have seen in previous trials of aficamten in obstructive hypertrophic cardiomyopathy. However, here the incidence of LVEF less than 50% was higher than previously observed, 10.5% versus 1% in placebo. It's important to note that this trial is different. Here we used aficamten to push the dose to the maximum level through monitoring of LVEF. So it's really a trial of maximizing drug level and drug dose as monitored by LVEF. That's compared to obstructive HCM trials, where what you do is that you use the least needed dose to target relief of LVOT obstruction.

But more importantly, even though 10% had reduction in their LVEF, the majority of them remained on the same or lower doses of aficamten. So 21 out of 27, to be specific. Only 3% of the patients in the trial had to withhold their aficamten because of an ejection fraction read that was lower than guidance. And out of these 27 patients, only 2 patients—1%—had concurrent serious cardiac adverse event.

There is significant clinical development activity in non-obstructive hypertrophic cardiomyopathy. I'm including those here with clinical or near-term clinical data that are expected. Sotagliflozin is being trialed in SONATA-HCM phase 3 trial. It's a combined SGLT1 and 2 inhibitor and being compared to placebo. The ninerafaxstat is being trialed in FORTITUDE-HCM study, which is an energy modulator, and we already had the phase 2a for it before, called IMPROVE-HCM. EDG-7500 is a myosin modulator that is being trialed in both obstructive and non-obstructive HCM. And BHB/HRS-1893 is a third-generation CMI that is being trialed in non-obstructive and obstructive hypertrophic cardiomyopathy. And finally, HTX-001 is a drug that is targeting a new modality of WISPER modulation. This is a long non-coding RNA that is associated with fibrosis in the heart. And the thought process here is that if you turn down WISPER, you can improve fibrosis in the heart muscle.

So in conclusion, patients with symptomatic non-obstructive HCM have no options for therapy. Transplant is not a treatment; it's a bailout strategy for those patients who progress and who are candidates for such a treatment. Aficamten improved symptoms and exercise capacity in patients with non-obstructive HCM. And through the ACACIA-HCM trial, SEQUOIA-HCM trial, and MAPLE-HCM trial, aficamten now has been trialed across the whole spectrum of HCM with preserved systolic function. And as I've shown you, there is a lot of activity happening in the non-obstructive HCM space.

Closing:
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