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Released: 10/14/2026

Valid until: 10/14/2027

Time needed to complete: 30 minutes

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Moving the Needle in oHCM: The Era of Cardiac Myosin Inhibitors

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Chapter 1

Dr. Martens:

Hi. I was asked to talk about provocation and HCM. In provoking our patients with HCM to assess symptoms is an intrinsic component of the holistic care of our patients with HCM. And here in this consensus document, we propose a framework for holistic evaluation of our patients with HCM, indicating first we want to establish the right diagnosis. We want to assess whether the patient has symptoms attributed to HCM, and assessing LVOT gradient is an intrinsic component in this. We want to assess the risk for sudden cardiac death, do genetic testing, manage families, manage comorbidities, and give some education and lifestyle advice.

It's important to recognize that the LVOT gradient is dependent on the loading conditions of our patients. So it depends on the preload, the afterload, and the contractile state of our patient. And ever since the first description of HCM by Eugene Braunwald, we have recognized that there is a lot of variability within the patient of their LVOT gradient. And so this also implies that just labeling a patient as nonobstructive based on a single resting value is inappropriate, and we really need to stress our patients appropriately, performing provocative maneuvers with Valsalva or exercise to really label whether somebody is nonobstructive.

And here you can actually see simply what happens with the LVOT signal when performing Valsalva in the outpatient department, and you can see the signal change from this normal appearance to this dagger-shaped pattern with late-peaking obstruction. And here we quantify our patient as being obstructive.

And so it's very important to recognize obstruction because obstruction in HCM is a disease-specific marker that is correlated with symptoms and is also associated with the risk of disease progression. Furthermore, it's also associated that we have specific therapies that we can use to target our therapies. And here we see that patients who are obstructive at rest, so without provocation and already obstructive, they're at the highest risk to have progression to NYHA Class III or IV heart failure. But patients who have provokable obstruction (this means after Valsalva or in exercise), their risk is also much higher in comparison to patients who are truly nonobstructive. And I very often use these numbers with my patients. If you're obstructive at rest, you have about 7.4% risk per year to have progression of your disease to symptomatic Class III/IV heart failure. On the other hand, if you're provokable obstruction, that risk is still elevated at 3.2% per year. So we really want to detect obstruction in our patients and really do our due diligence to detect obstruction.

This is data from our own institution in which we performed exercise echocardiography, and in our institution we combine this with ventilatory gas exchange. The benefit of using ventilatory gas exchange is we really can understand why our patients are symptomatic. And a few things that you can see, on the left-hand side, you see that with increasing exercise load during peak exercise, we see a lot of patients who become obstructive. But very often, what we notice is, immediately after exercise, so the first minute after, in that recovery phase, we find the highest levels of obstruction. And this is because after exercise, what happens, your contractility is still very high, your preload all of a sudden drops, and this really creates the perfect mixtures to find that maximal obstruction.

And looking at their level of functional limitation measured by peak VO_2 , we see that the LVOT gradient is one of the biggest determinant of their symptoms. So it's important to really recognize this.

So I brought with you a case, a patient of mine. This is a 50-year-old patient. He has a genetic form of HCM. He's symptomatic in NYHA Class II. His resting LVOT gradient is 17, and we performed Valsalva. And after Valsalva, we see that his gradient goes up to 31 mm Hg. And so this patient has obstruction. Remember, the definition of LVOT obstruction is more than 30 mm Hg. So we already established that this is obstructive HCM. This patient is receiving beta-blocker bisoprolol 10 mg, and his HCM risk score is at 4.9%.

And I'm going to ask you this: In this patient, would you perform exercise echocardiography? We already established that he is obstructive, but would you perform exercise echocardiography: no, yes, or only in case when his symptoms get worse?

So what we did in this patient was we performed an exercise test. Like I mentioned, in our institution we perform an exercise test combined with ventilatory gas exchange. When we're doing this exercise test, we want to get our patient in the most upright position because then the preload is going to be the lowest, provoking the most gradient. Here we use ventilatory gas exchange to understand why patients are also symptomatic. We get our setup, we take our images at rest, mid, peak, and following exercise, and here again you can see really the HCM of the patient. You see the reverse curvature of the septum. You see the apical displacement of the papillary muscle. So this is bona fide HCM.

And then next we want to really map that level of maximal obstruction here at the LVOT, and we're trying to get a nice gradient with the maximal obstruction. This is at rest, and as you can see, this patient is not obstructive at rest. His LVOT gradient here measured is around 17 mm Hg. So we start our exercise protocol. We have an increase in wattage, and during the protocol we will measure certain things. Not only going to measure the LVOT gradient; we're looking at diastolic pressures, filling pressure, pulmonary pressures. On the left-hand side, very often we have our image at baseline as a comparator, and then during the exercise protocol, we'll start to measure things. Here, our nurse sometimes gets agitated saline to also measure what the pulmonary pressures are. It's useful in our protocol.

Okay, so now we're very close to getting to peak exercise, and again, we try to get a nice pattern. You see, again, this dagger-shaped late peaking appearance, and if you look very closely here during peak exercise, that LVOT gradient becomes 71 mm Hg.

Okay, so why did we perform an exercise test in this patient? It was already obstructive after Valsalva with 30 mm Hg; still, we did an exercise test. This is because our patient is symptomatic despite treatment with a first-line therapy of beta blockers, and we want to establish whether the patient is eligible for other therapies such as myosin inhibitors. Used to be very often myectomy, and this is very often only when your LVOT gradient becomes above 50.

And so this is a nice evaluation that we did of consecutive patients that we initiated with a myosin inhibitor, and, in Belgium, it's only reimbursed if that LVOT gradient goes above 50. And so if we were to use only resting data, only 14% of patients would be eligible in our cohort for a myosin inhibitor. On the other hand, if we start to provoke them and we do Valsalva, then another 43% of patients become eligible for a myosin inhibitor. But another 43%, and this is our patient, remember, only becomes eligible for a myosin inhibitor if we also perform exercise echocardiography. Patient had a Valsalva gradient of 31. Only once we did exercise that the gradient was higher than 50, and he became eligible for therapies.

This is data from a US registry, the MARVEL-HCM registry, which is a registry of real-world use of myosin inhibitors. And in this subanalysis, they looked at that cohort of patients who only have this latent obstruction, that provokable obstruction. These were 177 patients, and they looked how they respond to a myosin inhibitor. Obviously, the resting gradients, they were always normal, but what you nicely see with incremental doses of mavacamten, we see that that gradient nicely comes down. And very interestingly, we see a same response rate, even though the patients have provokable obstruction, their symptomatic response to a myosin inhibitor is just as

great.

So to conclude, we really must trust our patients. Only label them nonobstructive if we really did our due diligence. LVOT gradient is a disease-specific marker for obstruction and associated with symptoms, and it responds equally well if you have latent obstruction. Thank you.

Chapter 2

Dr. Owens:

Good day. I'm Anjali Owens from the University of Pennsylvania. Welcome to our segment about the evidence behind cardiac myosin inhibition for patients with obstructive HCM. I'll walk you through the pivotal phase 3 data for the 2 approved cardiac myosin inhibitors: mavacamten, the first-in-class agent, and aficamten, the next-in-class agent.

Let's start with mavacamten. We've had two phase 3 trials in patients with symptomatic obstructive HCM. The first is the EXPLORER trial. It was done in patients who were mainly NYHA Class II, all of whom had provokable or resting LVOT obstruction and an ejection fraction >55%. All of the patients were on background therapy with either a beta blocker or a calcium channel blocker, and what we saw in this randomized controlled trial with mavacamten versus placebo is the 3 things that you really want to see for patients with obstructive HCM. We saw patients on mavacamten improve their exercise tolerance, improve their symptoms, and improve their gradients, and those were all statistically significant results for this trial.

The VALOR trial, the second phase 3 for mavacamten, extended the population to a sicker group of patients, those who had predominantly NYHA Class III symptoms, and they were all on maximally tolerated medications, including a subset of patients who were on disopyramide. This trial had an interesting primary endpoint. It was whether patients remained eligible for septal reduction therapy or actually underwent septal reduction therapy. So at baseline, all of these patients, 100%, were eligible and actively considering septal reduction therapy, which we know by the guidelines is really reserved for those with refractory LVOT obstruction despite first-line medical therapy.

And what we found with the 16-week primary endpoint is that the vast majority of patients who had mavacamten up-front no longer needed septal reduction therapy either because their symptoms improved, their gradients improved, or both. And this was quite a remarkable result for a drug to achieve similar to what we saw with septal reduction therapy.

Importantly, by mechanism of action, we know that a cardiac myosin inhibitor like mavacamten can reduce ejection fraction. And what we saw in these 2 trials is about 5% of patients in the EXPLORER trial versus 1% on placebo and 3.5% in VALOR versus none in placebo had a reversible change in LVEF to <50, and importantly, when you stop the drug temporarily, the ejection fraction goes back up.

Next, let's look at evidence from the phase 3 trials of aficamten. The first trial, the pivotal, was SEQUOIA-HCM. This trial looked at patients again with symptomatic obstructive HCM Class II and III, all of whom were on background medical therapy, including disopyramide. And this trial had a different primary endpoint than EXPLORER. This trial looked at a single primary endpoint of peak VO_2 . And what we saw after the 24-week treatment period was a least-squares mean difference of 1.7 mL/kg/min, favoring aficamten. Again, in this trial, we saw improvement in NYHA functional class, improvement in patient-reported outcomes, and improvement in biomarkers and gradients.

The next trial, MAPLE-HCM, was the latest phase 3 trial to be done with cardiac myosin inhibitors in obstructive HCM, and this was the first trial that pushed the envelope looking at beta blocker, our current first-line therapy, versus a CMI. In this case, aficamten. This was a double-blind, double-dummy trial, metoprolol versus aficamten for a period of 24 weeks, again with a primary endpoint of peak VO_2 . And you can see here a least-squares mean change of 2.3 mL/kg/min, favoring aficamten. And again we saw improvements in NYHA functional class, gradients, health status, and biomarkers. So that served as the first comparison pushing the envelope against guideline therapy.

Again, with the CMI aficamten, we know that by mechanism of action, you can get a transient drop in LVEF. In this case, 3.5% of patients in SEQUOIA versus 0.7% on placebo, and about 1% in MAPLE versus 0% on placebo. All of these are reversible changes in ejection fraction.

So what do we have now available in 2026 in this class of medications? We know that mavacamten was approved in 2022 in the US and is now approved in 60 countries worldwide. In April of 2025, we had an update in the US to the label of mavacamten that spaced out the safety monitoring echoes from every 3 months to every 6 months in eligible patients, which makes it easier for patients to access this therapy. We also had some changes with regard to medication contraindications and drug-drug interactions, and we now have over 20,000 patients in the US who are commercially treated with mavacamten.

Aficamten came along a little bit later. It was FDA approved in December of 2025. And the European Commission approval came in February of 2026. The starting dose for aficamten is 5 mg, similar to mavacamten, but there is a difference in the REMS, at least in the United States, where you can titrate aficamten every 2 to 8 weeks, so a wider window for titration. And this drug is metabolized mainly by the CYP2C9, reducing the number of drug-drug interactions.

Both of these drugs, because they inhibit myosin, carry the risk of dropping the ejection fraction to <50%, and that's why we have mandated safety echoes to make sure that the ejection fraction isn't dropping, and I'll remind you there is no head-to-head comparison of these 2 drugs.

Next, let's look at long-term durability, and the way we'll look at this is with the long-term extension data. On the left, I have the MAVA-LTE study. That's mavacamten. Patients from the parent EXPLORER pivotal trial who went on for open-label, long-term extension out through 180 weeks. And what you can see is that decrease in LVOT obstruction and gradients and improvement in NYHA is durable out through 180 weeks of treatment, where over 90% of patients maintained a Valsalva gradient <30, which is our threshold for defining obstructive HCM. So we've essentially taken patients who were obstructive, now they're nonobstructive, and about 66% achieved Class I asymptomatic status.

On the right is the FOREST-HCM data. These are patients from the parent aficamten trials who have rolled over into open-label, long-term extension. And you can see a similar improvement and durability in terms of LVOT obstruction, with gradient reduction sustained out to 168 weeks, and 84% were <30 mm Hg at that time; 73% were asymptomatic at Class I.

What do we know from the real world? Let's take ourselves out of the trial realm. Does this drug or do these drugs perform the same in our real-world population? This is data from the US REMS program, which is the Risk Evaluation and Mitigation Strategy, where we had 12,000 patients in this report, over 34 months of REMS data. And what you can see as over 100,000 drug interaction checklists, the number of drug-drug interactions that led to a dose reduction or stopping of a concurrent medication or stopping of mavacamten was exceedingly low. The safety profile was similar to what we've seen in trials in terms of exposure-adjusted incidence rates of AEs of clinical significance, like drop in ejection fraction, heart failure, or heart failure hospitalization.

In addition to the REMS data, we also have real-world registry data that's coming out, including the COMPASS study, the DISCOVER study, and MARVEL-HCM, all of which have confirmed the efficacy and safety of this drug in a real-world population.

Let's look at COLLIGO-HCM. This is real-world outcomes in a global population. And I'll call your attention to the demographics of this population, which included about 23% Black patients, so a much more diverse population than we found in the trials. And I've highlighted here patients that were able to go onto monotherapy either from the beginning with mavacamten or because their background therapy was reduced over time. And you see similar outcomes in terms of gradient reduction, improvement in symptoms, and those who had to interrupt for a transiently low ejection fraction.

Finally, the newest data in this field is a study in adolescence, so we've now moved beyond the adult population into symptomatic obstructive adolescence. This is with mavacamten, the SCOUT-HCM trial, which was recently presented and published. This is the Valsalva gradient pictured here, placebo in gray and mavacamten in blue over 28 weeks of therapy. And you can see quite a rapid and remarkable reduction in LVOT obstruction in these young patients, ages 12 to 17. And notably, on the right, very few adverse events, with no patients dropping their ejection fraction to <50%. So this really extends into a new population with a high unmet need. We also saw in this trial improvement in LV septal wall thickness. This brings up the question of whether or not, if you start this class of medication early, can you prevent long-term adverse remodeling?

So what does this mean for your practice? These agents are proven with four phase 3 clinical trials encompassing a worldwide population, real-world data that is growing to support their use. And we now know that treatment can start earlier and in a broad range of

patients. The barriers are shrinking over time as we gather safety data to extend the period of monitoring for safety echoes.

Thank you again for listening on this data for cardiac myosin inhibitors in symptomatic obstructive HCM.

Chapter 3

Dr. Reza:

Let's apply what you've learned in this case-based application. My name is Nosheen Reza. I'm an assistant professor of medicine at the Penn Center for Inherited Cardiovascular Disease in Philadelphia, Pennsylvania.

This is a 59-year-old woman with shortness of breath with exertion. Her past medical history includes hypertension, obesity, hyperlipidemia, hypothyroidism, irritable bowel syndrome, prior carpal tunnel release surgery, and symptomatic premature atrial contractions. Her medications include lisinopril, rosuvastatin, metoprolol, levothyroxine, and over-the-counter laxatives.

This is at the time of your evaluation. You see a representative electrocardiogram here. Her blood pressure is 143/88, and a 2-dimensional echocardiogram demonstrates an ejection fraction of 67%. Her maximal left ventricular wall thickness is 17 mm at the intraventricular septum. Her resting gradient is 11 mm Hg, with a Valsalva gradient of 28. She has mild mitral regurgitation and aortic valve sclerosis.

What is the appropriate next step in management? Things you may consider including asking her to check her home blood pressure and TSH. As you can see here, her home blood pressures were elevated. You may also consider a cardiac MRI. We did so, and we found asymmetric left ventricular hypertrophy with a maximal wall thickness of 17 mm at the anteroseptal, with LGE <5% of the left ventricular mass. Her genetic testing was negative, and evaluation for cardiac amyloidosis was also negative.

At her 4-week check-in, she tells you she still has NYHA functional Class II to III limitation. She's breathless, particularly with walking upstairs in the home and walking on inclines. What is the appropriate next step here? Would you consider another transthoracic echocardiogram, coronary CT angiography, initiating incretin-based therapy, a treadmill exercise echo, or referral for pulmonary evaluation and evaluation for sleep apnea?

To look for latent obstruction, she was referred for a treadmill exercise echocardiogram. She achieved a peak heart rate of 152 beats a minute and a peak blood pressure of 178/84. She exercised for 7 minutes and 30 seconds, achieving 9 METs, and she stopped because of dyspnea and fatigue. She had no significant ST segment changes during the tests, and her blood pressure response was normal without hypotension. Her left ventricular outflow tract gradient increased to 76 mm Hg with exercise, and her mitral valve had sustained systolic anterior motion of the anterior leaflet with moderate mitral regurgitation.

What would be your next best step? Would you like to increase the beta-blocker dose? Refer for septal myectomy? Refer for alcohol septal ablation? Initiate a cardiac myosin inhibitor? Or refer for a SESAME procedure?

Ultimately, she was started on a cardiac myosin inhibitor with mavacamten, and here we're showing you her week 12 echo. She was on metoprolol at 25 mg and mavacamten at 5 mg daily, with an ejection fraction of 58% and significantly reduced LVOT gradients at rest and with exercise and Valsalva. She had no systolic anterior motion of the mitral valve, and her mitral regurgitation remained mild. Her symptoms, most importantly, significantly improved.

Thank you for your participation in this case.

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