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## New Insights in the Management of HCM: Exploring the Clinical Spectrum

### Announcer:

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### Chapter 1

#### Dr. Olivotto:

Hello, my name is Iacopo Olivotto. I'm a cardiologist working in Florence, Italy. And these are my disclosures.

So my case deals with a young male patient who has a family history of hypertrophic cardiomyopathy. The father was affected in a severe way and they both share a beta-myosin heavy-chain mutation, arginine 453 histidine, which is obviously pathogenetic in this case. So his phenotype was classic with maximal LV wall thickness of 21 mm, which is really a bit of the average we find in patient with such genotype. And he had a mild to moderate resting gradient, increasing to 56 mmHg with Valsalva. But was doing quite okay, actually, with no symptoms on effort until about 19 years of age, he developed a syncopal episode at the very end of a short, brisk exercise. At that time, because no arrhythmias were detected on the ECG, the Holter was negative, exercise test was not remarkable, it was actually quite good, the syncope was interpreted as being vasovagal at the end of exercise.

There were no other symptoms reported, and he continued to do quite well with a slightly elevated anti-proBNP level. He was started on nadolol, and at that point because of higher heart rates during exercise, he did report some improvement, subjectively, particularly after meals, but otherwise remained quite asymptomatic with good quality of life, exercising moderately. As you can see, this is his echo, which is classic HCM pattern of asymmetric septal hypertrophy, hypercontractile LV, but no clear SAM and the left atrium is small suggesting largely nonobstructive sort of pattern.

A couple of years later, had a new episode of presyncope which was during mild exercise. So at that point, again, workup was inconclusive, including a tilt test, which we did at that time. We do send these patients to syncope unit for evaluation, but nothing came out of it. And so because there was no clear vasovagal trait in this patient, a loop recorder was implanted. He remained doing quite well, but he concentrated his effort mostly during weekends, which tend to be not particularly sporty. And he also admitted gradually, over the years, to developing symptoms that which limited the effort.

So you could now talk about NYHA Class II as compared to a Class I, which he had been previously. And again, at age 21, he has a syncopal episode during exercising on a bike, going sort of moderate effort as described by himself.

Luckily, the loop recorder was completely negative for sustained VT or VF. So again, this is his echo at that point. You can see that something has changed. His LVH is probably a little more impressive. Left atrium remains sort of normal size, but SAM is quite evident both on 2D and on M-mode echo. And of course, we now do have an obstruction that is quite consistent. It's about 40 mmHg at rest, up

to 60, 65 with Valsalva. There's also a midventricular obstruction evident at the end of systole here.

So at this point, we have a patient that has repeated episodes of syncope, has symptoms, although not severe symptoms, and has obstruction that's quite demonstrable, both at rest and with Valsalva. What do we do at this point? Because we do have several options, including a defibrillator or even surgery, potentially.

So if you look at the indications from the ESC guidelines regarding implantation of an ICD, you see here that only patients that have syncope associated with spontaneous sustained ventricular arrhythmia, so clearly arrhythmic syncope, have an indication for that. And if you look at the indications below, you can see that only exertional or unexplained recurrent syncope are also an indication for septal reduction therapies. So here, we again talk about exertional unexplained.

Unexplained recurs very often when we talk about risk in hypertrophic cardiomyopathy and syncope. Again, this is not trivial because if you use the ESC risk calculator—and you can see that history of unexplained syncope is the last item but may be the most important that you add when you do the risk score. This individual patient has a risk of 7.23% at 5 years, which would mean high risk if the syncope is considered to be unexplained/arrhythmic. But if you remove that, so if you consider the syncope to be something else, vasovagal or not arrhythmic in any case, then risk goes down to 3.6. So the pattern changes completely and the indication changes completely. This is not a patient for an ICD anymore.

So unexplained means a lot here. And how good are we at explaining syncope? Are we good at finding the explanation of syncope? Are we trying hard enough? The response is we're not. We don't. In this recent meta-analysis, looking at over 21,000 patients from 57 studies with HCM, you can see that about 16% of patients had syncope in their clinical history. But of these, only less than 10%, only 9% had some kind of explanation. The remaining 91% had unexplained syncope. Does that mean that this was thoroughly searched for a cause? No, it means just that there was no effort, or at least no reported effort, to look for a cause of syncope in these patients. And of course, that is important.

We do have guidelines for hypertrophic cardiomyopathy, but we do have also guidelines for syncope. And as HCM physicians, we tend to be good at following guidelines, but the syncope guidelines, a bit less. This is the syncope guidelines 2018. You should have an ILR, so a loop recorder should be considered in patients with recurrent episodes of unexplained syncope who are otherwise at low risk of sudden cardiac death. Which is exactly the case of this patient. Why? Because you don't want to put an ICD in somebody who may have other reasons for fainting. And you don't want to not put an ICD in somebody who would need one.

So at this point, it's clear that this patient does not have arrhythmic syncope. We know because we followed the guidelines. We did the tilt testing, we put in a loop recorder, and it's a good thing we did that because when he had recurrent symptoms, we were able to rule out arrhythmias. And at this point, what we need to target on is not the ICD, is treating the gradient, treating the obstruction as a cause of their exercise-related syncope.

How do you do that? Of course there is presence of mild limiting symptoms otherwise. So young person, risk of pacemaker associated with alcohol ablation, risks associated with myectomy, having a pharmacological option is really nice. Can we use myosin inhibitors? Would they have been around? Mavacamten has been approved; aficamten will likely be approved in the future. Can we use that as an option in patients who faint without any arrhythmias, faint because of obstruction but otherwise have low indications, no indications for surgery, or don't meet the surgical threshold in this case.

Well, it would be really nice. The thing is we don't have data. It's very likely that these drugs may have an impact. Mavacamten particularly has widespread use. We don't really know, however, how effective this might be because patients with syncope were routinely excluded from the registration trial, the phase 3 trials.

So this is our patient. Because of the symptoms associated with obstruction, he was enrolled in a compassionate use, early-access program, with mavacamten, in this case to treat obstruction. And at 2 years, you can see now the echo. You can see the hypertrophy remains important, but the cavity size looks better. You can see that the ventricle is less hypercontractile, has a normal systolic function. The left atrium remaining small. The SAM has been abolished. The gradient has been abolished at rest with exercise. He has not had syncope. He's being monitored for arrhythmias. No arrhythmic episodes, and no further symptoms, whether it's limiting symptoms or syncope, at 2 years.

So interesting. Very promising. This is, again, the 4-chamber and 5-chamber view before and after treatment. You can see the SAM has gone away and the cavity looks a bit nicer now.

What can we conclude from this case? Well, as I mentioned before, I think syncope remains a major unmet need in patients with hypertrophic cardiomyopathy, particularly when you have to decide whether it's arrhythmic or hemodynamic. We often follow the HCM guidelines. We should follow also the syncope guidelines. Don't go for just an easy explanation of unexplained. A label of unexplained

syncope is not acceptable until we have done all we could to explain the syncope, so we should really work hard to follow the syncope guidelines in these patients.

If there is an underlying cause such as obstruction, this should be treated radically and hopefully, pharmacologically. What we don't have right now is data regarding the efficacy of myosin inhibitors in this particular context, but we know that they are very effective to treat symptoms and obstruction, so likely to be effective here. But real-world data are needed to specify this very specific point.

Thank you very much.

### Chapter 2

#### Dr. Desai

Hello, everybody. My name is Milind Desai from the Cleveland Clinic in United States, and it is my honor to present to you some of the complex cases in hypertrophic obstructive cardiomyopathy, where we had to make complex decision-making and navigate these patients towards an optimal cure.

So the first case. We'll get straight to it. The first case here is "Cut me once or keep doing it until you get it right." This is one of my patients, a 23-year-old male patient who flew in from the Middle East. Patient had a history of known obstructive HCM for more than 10 years. So 23 years old with a 10-year history. Primary prevention ICD placed 8 years prior. This patient, unfortunately, had a myectomy at a European site 8 years prior to presentation, with residual symptoms.

Four years prior to coming to see us, underwent a redo myectomy, including an apical myectomy at a high-volume center in the United States by highly experienced surgeons. So patient was not lacking in terms of expertise in surgery. But unfortunately, now presents with severe dyspnea on exertion and class III NYHA symptoms. The echo images, you can see on the right, still continue to have, after 2 myectomies, extremely thick LV with SAM. At rest, the LVOT gradient was 51. With Valsalva, it jumped up to 86. Maximum wall thickness was still 3.2 cm, and you can see the contrast-enhanced images in the middle which shows an apical scar.

Patient's scared about having a third myectomy before the age of 25. Comes in wanting mavacamten. Unfortunately, at that time, mavacamten was not available in his country. We explored options about going to Germany, but because of out-of-pocket costs and logistics, he decided to ultimately have a third redo myectomy at the Cleveland Clinic.

The images on the right show a post-op image, which shows extremely well-done myectomy where I remember we removed about 18 g of muscle. No LVOT gradient, and now in NYHA Class I. Unfortunately, it took about 3 tries for the patient to get an optimal result. But the expectation is that these are long-term results.

Moving on to the second case, "Not all alcohol in your body gives you joy," apparently. This is a 71-year-old patient with known obstructive HCM. The guy is 71 but has known of HCM for only 3 years. Symptomatic for more than a decade. Unfortunately, prior to presentation, he had a failed alcohol septal ablation at a lesser-experienced center. You can see the echo images. You can see on the top left there is an area where the myocardium is thin because of alcohol septal ablation, yet you can see severe outflow tract obstruction with SAM. Gradients reaching up to 84 mm at rest, and 118 with Valsalva. And you can see a nice scar on the bottom right of the MRI where the alcohol was injected.

This patient was referred for surgical myectomy. Unfortunately, he was not too keen on having surgery because there were concerns about needing a pacemaker in the setting of a prior alcohol ablation and followed by myectomy. He very quickly agreed to be part of the VALOR-HCM trial. Initially, he was put on mavacamten versus placebo, but subsequently, he rolled over to long-term mavacamten. These are the data from long-term extension of his mavacamten. As you can see, the gradient is gone, LV function is normal, and the patient is asymptomatic. I have his permission to show his picture. This person was in NYHA Class III symptoms, now planting his whole backyard.

Importantly, what happened was his ECG on the top left, which shows severe LVH, after 32 weeks ECG was normalized. Patient remains on mavacamten 5 mg a day. No LVOT obstruction. No residual and asymptomatic.

Case 3, "Is it always hypertrophic obstructive cardiomyopathy? Do you always need the H?" This is a 27-year-old patient—again, my patient—positive for HCM genotype, comes in for a second opinion. He was told that he was phenotype negative for HCM and because of his symptoms of dizziness, he was asked to consult with a psychiatrist as he was also anxious and concomitantly dizzy. Patient's mother had undergone myectomy at the Cleveland Clinic.

Essentially, if you look at the images, at rest there was no outflow tract obstruction. When we provoked him with amyl nitrite as well as stress, he developed severe SAM with the velocity across the LVOT reaching 5.2 m/s. But as you can see, the patient has no significant LVH but severe SAM.

This is one of the earlier patients where we ended up doing a papillary muscle reconstruction reorientation. And I like to often joke, we cured his psychiatric problem with cardiac surgery. But in 2025, should this person have undergone open-heart surgery, or could we have tried mavacamten first? That's an important question that we can discuss.

Changing gears a little bit, this case is a patient presented with subaortic obstruction. Not all of it is HCM. This was a 72-year-old female, referred from outside experienced center, for further management of what they described as hypertrophic obstructive cardiomyopathy. Again, patient underwent alcohol ablation 2 years prior and was complicated by permanent pacemaker implantation. But unfortunately, the symptoms persisted, and she was then started on mavacamten.

The doctor locally decided they did not do well on mavacamten, was deemed a failed mavacamten patient, and referred to us. As we did the echocardiogram, you can see on the top images that there is evidence of subaortic obstruction. In the bottom 2 Doppler panels, you see mixed aortic regurgitation as well as a fixed profile of LVOT obstruction, not a late-peaking dynamic obstruction. The MRI confirms that the aortic valve is okay, and there was no SAM. This was indeed a subaortic membrane. Not really an ideal cardiac myosin inhibitor patient. So this is a patient where we ended up doing open-heart surgery to do a little myectomy as well as remove the subaortic membrane. The aortic valve should always be inspected during these operations to see if it needs replacement.

Another one always have to think about, nowadays, 58-year-old man, 9-year diagnosis of obstructive HCM, referred to Cleveland Clinic again for septal myectomy. When we repeated the workup, what we were able to show that, yes, patient has SAM, posteriorly directed jet of MR, and also resting gradient that was high, Valsalva gradient that was more than 100. But additionally, when we did tissue Doppler analysis we were able to show that patient had reduced lateral and annular velocities, and strain assessment showed apical sparing pattern. So this raised the possibility that could this person have amyloidosis in addition to obstructive physiology?

So we obviously did additional testing including cardiac MRI, which confirmed that patients LGE scar pattern was very suspicious for amyloidosis. A technetium pyrophosphate scan was also performed, which confirmed that patient indeed had amyloidosis.

So we have to be careful. We cannot mavacamten-ize an amyloid patient and give tafamidis to a patient with HCM. We have to be very diligent in our ability to diagnose these things and offer the right test. But in this patient's case, would you give them a surgical myectomy before you try tafamidis or one of these newer anti-amyloid agents? That remains a question for discussion.

Indeed, patient underwent myectomy followed by tafamidis, and the biopsy did confirm transthyretin-type amyloidosis.

Last case, one of the recent cases, "Old dog, new tricks." Again, I'll walk you through our thought process. This patient was a 61-year-old executive coming to the Cleveland Clinic for an executive physical. Has positional dizziness, effort intolerance, and all the other risk factors of being a successful executive; coronary artery disease, hypertension, hyperlipidemia, sleep apnea. But he also had hyperaldosteronism, and he was treated appropriately with antihypertensive.

We had recently started an AI screening tool for all ECGs and patient underwent this screening evaluation, which was subsequently flagged for possible hypertrophic cardiomyopathy and was referred to me for workup. If you look at the ECG on the bottom, there is no suggestion of LVH. This person, we would have missed this person as anything suspicious for HCM. But looking at the echos on the right, there is upper septal hypertrophy, posteriorly directed jet of MR, and SAM with a Valsalva gradient reaching about 68 mmHg.

What we did was, subsequently, this patient was identified on AI and then we put the patient on mavacamten. He did not clearly want surgery at this time and he's done well with resolution of LVOT gradient. We have recently reported our analysis. Out of the first 45,000 patients that underwent the ECG screening, we found about 2.7% had potential HCM, and essentially, we diagnosed 63 new patients in a 6-month span at Cleveland Clinic. This paper, we have recently published our experience on an AI ECG.

So to conclude, ladies and gentlemen, I must say the future is bright in HCM. With the availability of these precision medicine drugs, it does provide an additional option in the fight towards a normal life in HCM. Remember, it is not about my pill is better than your procedure; it is not this versus that; it is this plus/minus that, and it is about how and what we can do to provide the best quality of life in that given patient. Because remember, ultimately it is about the patients first.

Thank you so much.

### Chapter 3

#### Dr. Arbelo:

Hello. I'm Elena Arbelo. I'm the head of the Familial Cardiomyopathy and Sudden Cardiac Death Unit at Hospital Clinic Barcelona, and I'm very happy to be here today to talk about cardiac myosin inhibitors and their use in the real world.

These are my disclosures.

So since its description, hypertrophic cardiomyopathy has experienced many therapeutic advances. But it wasn't until 2019-2020 where we actually had the first mechanistic targeting the pathophysiology obstructive cardiomyopathy treatment, which were the cardiac myosin inhibitors. As you all know by now, the cardiac myosin inhibitors act by reducing the binding between actin and myosin and therefore reducing contractility and outflow tract obstruction. Their usefulness has been shown in two landmark phase 3 trials, the EXPLORER-HCM trial evaluating mavacamten and the SEQUOIA-HCM trial evaluating aficamten. And that's why cardiac myosin inhibitors are now one of the key treatments in hypertrophic cardiomyopathy.

So when we're evaluating, in the 2023 ESC guidelines, the management of outflow tract obstruction, what you see is that cardiac myosin inhibitors is indicated as a second-line treatment after beta-blocker therapy or calcium channel blockers. It can be given either in association or in monotherapy.

In the US guidelines, what you see is the same. Cardiac myosin inhibitors are indicated as a second-line treatment together at the same level as disopyramide. And here's where the main difference with the ESC guidance is. It's that septal reduction therapies are at the same level for the US, while for the Europeans, we leave it only for patients that are refractory to medical treatment.

So what's new from the real world in the implementation of cardiac myosin inhibitors? So the first data that we have is the extension evaluation of the EXPLORER-HCM trial, which is the mava long-term extension trial. And what we see is that improvements in outflow tract obstruction, both at resting and with Valsalva, remain over 3.5 years of treatment. This improvement, importantly, is in over 80% of the patients and it's stable over time. That means that a gradient below 30 mmHg, meaning no obstruction, is seen in most of the patients.

Improvements in proBNP are also sustained over time. And very importantly, although during the titration phase we see small reductions in the left ventricular ejection fraction, after adjustment of the dosing, in most cases, what you see is that this doesn't get worse, so it's stable over 3.5 years of follow-up.

So to summarize with the mava long-term extension trial is that the mavacamten positive effects are durable over time and the mean left ventricular ejection fraction remains within normal limits at all visits.

We have some data, 48-week data from the extension trial for aficamten. And what we see is very similar. The relief of left ventricular outflow tract obstruction is stable. We see improvements that remain over time in quality of life and biomarkers also in cardiac remodeling, and there's no significant deterioration of left ventricular ejection fraction. But the largest data set that we have in real world is actually the pharmacovigilance program in the US, the REMS program. And what we see here is that in over 6,000 patients, with a follow-up of at least 22 months, we see that 4.6 of patients had a small or some deterioration of the left ventricular ejection fraction. We see that 1.3 had an episode of heart failure and only 0.3 had both, concomitantly.

If we look at those patients that have at least 1-year follow-up, and that's about 2,000 patients, the numbers are similar. So 4% for deterioration of ejection fraction, 1.5 for heart failure, and 0.2 for both. But importantly, the timing was seen throughout the year, not just the clustering of the titration phase.

Another important fact that we can see is that about 70% of patients had an outflow tract gradient during the follow-up that was below 30 mmHg. That means no significant obstruction. Conversely, you have 1 in 3 that still has some obstruction.

And the safety measures initiated by the REMS program were very well met. All of the patients underwent the checklist to evaluate for contraindications and drug-to-drug interactions, and all the drug was prescribed by only authorized centers or pharmacists.

This data from the COLLIGO-HCM prospective registry are the most recent ones and they were just presented. And basically what I want to highlight here is that they have a more diverse population included, especially when you look at the racial representation. And you see that what we saw in the landmark trials, and the REMS and the extension trials is that there is sustained improvement in outflow tract obstruction, and this improvement in clinical status evaluated with NYHA.

In Europe, this drug was approved in June 2023. And there's also a mandatory prospective registry that EMA made Bristol Myers develop, so we'll probably have some data in the near future.

So now we've talked about real-world results. Let's talk about practical aspects. For instance, do we step down or stop background medication? If we look at the landmark trials, especially the EXPLORER trial, what we see is that the response in patients taking beta-blockers was planted in the peak VO<sub>2</sub>, not in the outflow tract obstruction, probably suggesting that rate-limiting drugs are limiting exercise capacity and probably we may want to consider stopping them once the outflow tract obstruction has been relieved. To be fair, we did not see this in the aficamten trial.

When you analyze the effect of beta-blocker in the subgroup of patients of the EXPLORER and mava long-term extension trial, what you

see is that there are similar improvements, whether you're taking beta-blockers or not, in gradients, NYHA class, and quality of life. But when you look at the parameters that are associated with exercise capacity, this is worse in the group taking beta-blockers.

We now have some data from the aficamten extension trial, where they downscaled or even stopped drugs in some of the patients. This was attempted in 64 of them, and in 92% of these patients, they achieved either reducing the background therapy or even stopping it. And by doing that, they did not change the improvements that was produced by the drug, either in gradients, in functional class, or quality of life or in biomarkers.

For mavacamten, we don't have published data. These are the only data that were presented at the European Society of Cardiology Congress in 2023. Results seem very similar, but we should wait for the actual publication.

So from a practical perspective, how should we attempt to taper down the cardiac myosin inhibitor? First, we stabilize the treatment, targeting for an outflow tract obstruction below 30 to 50 mmHg, always with a left ventricular ejection fraction above 55%. First, we start tapering down or reducing the drugs with anticholinergic effects, so disopyramide. And once we've done that over 2 to 4 weeks, then we go for beta-blockers. We do it gradually, and we always monitor left ventricular outflow tract, clinical symptoms, and as a safety measure, also that the resting heart rate is above 55 to 60 beats per minute. Every time you do a change, you have to monitor with echo the effects of it.

And how do we implement cardiac myosin inhibitors in my clinical practice? So basically, we look at the indications according to the guidelines and then we're filling a specific pre-start checklist. This pre-start checklist, of course, evaluates the inclusion criteria but also evaluates things like the background therapy. We do a pregnancy test to make sure and advise on appropriate contraception medication. We evaluate drug-to-drug interactions and we look at baseline labs. In Spain, it's mandatory also to evaluate the metabolism because that's going to guide how we start, whether with 2.5 mg or 5 mg. Then we start and then we monitor every 4 weeks with echo and clinical evaluation. Basically targeting, first, of course, we want to achieve gradually a reduction of the outflow tract obstruction, but it's very important to remember that we have to maintain left ventricular ejection fraction about 55%. If it's below 50%, you have to stop mavacamten and then reevaluate. We do this every 4 weeks until we find a stable dosing, and then we can follow up the patient every 3 to 6 months.

We consider septal reduction therapies after 12 to 24 weeks to see the effect of treatment in that period or in those patients where we see structural abnormalities and that we foresee that the improvement with the medication is not going to happen or be sufficient.

So the key messages for my presentation is that CMIs deliver durable clinical benefit. The safety is good with echo-guided dosing and program safeguards. Thoughtful de-escalation of legacy therapy is reasonable in responders, but it needs to be echo-anchored and patient-specific. Septal reduction therapy remains important because cardiac myosin inhibitors reduce their need, but some patients do still need it. And the next frontier is going to assess whether cardiac myosin inhibitors is actually useful in nonobstructive HCM, structural remodeling of cardiac myosin inhibitors happening, and especially what the long-term outcomes of cardiac myosin inhibitors in patients with hypertrophic cardiomyopathy is.

Thank you.

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