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From Pixels to Practice: Advancing HCM Care With Multimodality Imaging

Chapter 1

Dr. Dweck:
So hello, everybody, and welcome to this set of talks about hypertrophic cardiomyopathy. My name is Professor Mark Dweck. I'm a cardiologist in Edinburgh in the United Kingdom. It's a great pleasure to be here. We're going to have some excellent talks on how imaging can be used in patients with hypertrophic cardiomyopathy. But my job is really to give an introduction to this disease, to hypertrophic cardiomyopathy, to tell you a little bit about what causes it, and to give you some insights into where imaging could play a role.

These are my disclosures for the talk.

And so, yeah, so hypertrophic cardiomyopathy is a very common condition. It's the most commonly inherited cardiovascular disease. The estimated prevalence is 1 in 500, with an equal prevalence in men and women, although we think that a very large majority of these people are not diagnosed. So there's a lot of people out there who don't know that they have the condition.

It's really defined clinically by unexplained left ventricular wall thickness, a wall thickness of greater than 15 mm without a clear explanation. In patients who have a positive gene or a first-degree relative with hypertrophic cardiomyopathy, then we use a 13-mm cutoff. And in 1/2 of those cases, there's a clear familial genetic cause with a thick filament gene.

It is a disease of the cardiac sarcomere. The sarcomere is the unit of contraction in the heart muscle. It's what drives contraction. It's what drives the function of the heart. And when we look at the genetic causes of this condition, then these genes relate to the cardiac sarcomere. So 70% are in the 2 most common genes. There's a series of other less common genes that account for around 5%.

And it's useful if we have a gene because that allows us to screen family members. It also potentially is associated with a more severe phenotype. So genetic assessment in this condition is an important component.

So what happens? How do you get from the sarcomeric gene mutation all the way to the end stage of the disease? So these genetic mutations in the sarcomere increase the actin–myosin cross-linking that we see in the heart muscle, and that results in myocardial hypercontractility. So frequently, when we measure ejection fractions in these patients, we get supernormal values.

That is something that the heart responds to. We get myocardial fibroblast activation, and these cells then can help drive hypertrophy as a consequence, but also the development of ischemia, because the blood supply doesn't match the increase in hypertrophy, and then ultimately myocardial disarray and cardiac fibrosis.

And in combination, these can then lead to the clinical phenotype, where we have problems due to the adverse remodeling. We can get

arrhythmias and heart failure, and of course, the most dreaded complication is the risk of sudden cardiac death in these patients.

So how does imaging help? Well, we are lucky. We have all these different imaging modalities that we can use to help in the assessment of patients with hypertrophic cardiomyopathy, and we're going to hear a lot about that in this session today. But we have echocardiography. That is the first-line test. That's what we go to first of all when we're assessing people with heart muscle disease, and of course, that's the same with hypertrophic cardiomyopathy. Frequently we're using MRI to aid, to help in the diagnosis, but also to risk-stratify patients. And then finally, we have emerging novel imaging techniques. We can use molecular imaging with PET to study processes of fibrosis, inflammation, the role of the activated fibroblasts in the myocardium of patients.

And when we're using these techniques, we're trying to do 3 things. We're trying to make a diagnosis. That's obviously critically important. We're trying to risk-stratify patients to understand which patients are most at risk of the life-threatening complications that can be involved with this disease. And with the advent of novel therapies for hypertrophic cardiomyopathy, of which there are many potential therapies, we're interested in trying to track disease progression and also monitor response to therapy. And each of these things are active in clinical practice at the moment.

So we have a range of diagnostic tools that we can use, not just imaging. Of course, at the most fundamental level, we can do myocardial biopsy, and that tells us about the classical pathological phenotype, myocardial and myocyte hypertrophy, fibrosis disarray. We can use the ECG. Let's not forget the ECG, which is often a very sensitive marker as to the presence of hypertrophic cardiomyopathy. And then we go on to using echocardiography, usually as the first line. We can assess for left ventricular wall thickness, outflow tract obstruction, diastolic dysfunction, etc. We're going to hear a lot more about that in the upcoming talks.

And then finally, MRI is often used, again, to give a bit more detail. And really the key added benefit of MRI is that it tells us about myocardial tissue composition. We can look at fibrosis. We can rule out other phenocopies, etc.

So wall thickness is central to hypertrophic cardiomyopathy. That's how we define it. We need to take accurate measurements of wall thickness, frequently with echo, but sometimes with cardiac MRI.

And we have these thresholds. And so 15 mm is the classical threshold. That can be anywhere in the left ventricle. Don't forget apical variants. Now, the apex is a thinner thing, so we might need to think about different cutoffs at that area. But generally, 15 mm is our cutoff. And we can reduce that cutoff to 13 mm when people have a positive gene or a family history.

So we need to be aware that wall thickening can occur anywhere. It can occur classically in the septum, but also in the anterior wall, inferior wall, lateral wall, and also at the apex. So these are the thresholds that we have.

So once we've made that diagnosis based on the combination of genes, ECG, wall thickness measurements, then we can subdivide hypertrophic cardiomyopathy into 2 groups, really. So we have patients who have non-obstructive hypertrophic cardiomyopathy. In these patients, there's no impedance of outflow of blood from the heart. And then we have patients with obstructive hypertrophic cardiomyopathy. And here, often the thickened heart muscle kind of gets in the way. We can't eject blood efficiently from the heart because of the thickened heart muscle, and because that sucks in the mitral valve and further narrows the outflow tract, this so-called systolic anterior motion of the mitral valve. So this is a kind of key part of the pathophysiology of hypertrophic cardiomyopathy. It can be present. It doesn't have to be present for the diagnosis, but it's common. If you look at provocation testing, then we can identify in up to 70% of patients with hypertrophic cardiomyopathy.

This is a classical appearance. This is an MRI image showing it. You can see the mitral valve flicking towards the thickened interventricular septum. And as a consequence, you see this acceleration of blood flow in the LVOT as a marker of outflow tract obstruction. And MRI gives you nice pictures, clear visualization of this process, but it's really echocardiography that allows us to measure how severe that outflow tract obstruction is. We can use Doppler echocardiography to measure the velocity of this jet in the outflow tract to give us an assessment. And we get this classical shape of the outflow tract obstruction with this dagger-shape color Doppler profile, which crucially is different from the shape that we classically would get with other conditions of outflow tract obstruction, such as aortic stenosis.

So the classical features of obstructive hypertrophic cardiomyopathy are here. It can be present at rest, but sometimes it is only present when we do provocation testing.

Up to 70% of people can have transient outflow tract obstruction. We define that as a gradient of greater than 30 mmHg, and then 50 mmHg is a sign that we have really quite severe outflow tract obstruction.

And of course, this can be associated with symptoms. This is associated with morbidity for our patients. And so we should be looking for it, because it may well explain their symptomatic status. It's not necessarily there at rest. We need to look for it at the time of echocardiography using provocation maneuvers, classically the Valsalva maneuver, an easy thing to do at the time of your echocardiogram, but also potentially with exercise and standing. And we should be looking for it. You have to be proactive in your echo department, looking for outflow tract obstruction.

An important feature in hypertrophic cardiomyopathy is the idea that there's a broad spectrum of symptoms that can be associated with the disease. So actually, most commonly this is an asymptomatic condition that patients live with and are okay with for long, long periods of their life.

But at the other end of the spectrum, we have life-threatening problems, sudden cardiac death; ventricular arrhythmias are real problems. And in between, we have the spectrum of symptoms due to dysrhythmia, atrial dysrhythmia, breathlessness, angina, blackouts, etc.

And this is not necessarily an easy thing to do. This is where images have to be really attuned. We have to understand that there are different mechanisms that might be driving these different symptoms, and we just try and identify what those different mechanisms might be. They might have outflow tract obstruction, as we've discussed. They may have diastolic dysfunction due to hypertrophy and stiffness of the thickened heart muscle. They may have chronotropic dysfunction, where they can't increase their heart rate. You can identify that potentially with exercise testing. And finally, they might have microvascular ischemia, because the heart blood supply has not increased in a way that meets the demands of the hypertrophic myocardium.

So the cardiopulmonary exercise test is an assessment that we can use to help understand what's causing symptoms. It provides us with objective quantification of a patient's exercise status, their symptomatic status. You can see the patient exercising in front of you. You can understand more clearly whether they do have symptoms as they exercise.

We can look at ECG changes. But of course, this is a difficult thing to look at in hypertrophic cardiomyopathy, because frequently—commonly—they have a very abnormal ECG. And so trying to look at changes in that can be challenging. But if we combine it with other things, like echocardiography assessments of the peak VO_2, then we can get more objective information in our patients with hypertrophic cardiomyopathy. So it can provide diagnostic information, information about symptoms, but also prognostic information.

And we need to be thinking in hypertrophic cardiomyopathy that it is a challenging thing to diagnose. We want to think about the different ways that we can diagnose it with the different imaging modalities, principally echocardiography and MRI.

But there is a long asymptomatic phase, so frequently patients don't have symptoms, but we want to find them early, because we can potentially track them. We can potentially prevent later complications.

We need to think about outflow tract obstruction, but we need to be proactive in assessing it. We need to do the provocation maneuvers at the time of their echocardiography. And we need to be proactive also about genetic testing, which is frequently not performed in clinical practice. We need to rule out phenocopies. We're going to hear much more about how we can do that with imaging, in particular cardiac MRI. And we need to be attuned to apical hypertrophic cardiomyopathy. This is an area of the heart that can be poorly visualized on echocardiography. And so if we have a patient who has a very abnormal ECG and a normal-looking echocardiogram, we need to think about other imaging modalities, like MRI, to pick up the apical variants.

So we do have some quick case studies. We're going to just highlight some important things with this. This is a patient who presented with breathlessness and a murmur. There was some left ventricular hypertrophy on the ECG with some subtle ST changes. But actually, when the patient came in for presentation, this ECG was picked up, and people said, "Well, hang on a minute, what's going on here?" There was no family history. The patient had a normal treadmill test and a normal Holter monitor.

And then this is their echocardiogram. And we see some features of hypertrophic cardiomyopathy. We have the increased wall

thickness. We have a dilated left atrium. And of course, when we do the provocation test, we see that there's clear evidence of outflow tract obstruction with high velocities, high gradients through the valve. So a diagnosis of obstructive hypertrophic cardiomyopathy was made, and the clue was in the ECG, that abnormal ECG.

This is another patient. This is a patient who had palpitations and syncope. There's a family history of sudden death, so an immediate red flag, a warning sign. We have quite an abnormal ECG, as you can see, with hypertrophy and repolarization abnormalities. And the patient had an echocardiogram, but the views weren't good, and we didn't get great images of the heart, but it was reported as normal. So what do we do there?

Well, the answer is we don't stop there because we have this very abnormal ECG and the family history. The patient had a cardiac MRI, and we can see here clear features of apical hypertrophic cardiomyopathy. And so we shouldn't give up. When we have these very abnormal ECGs and difficult echo images, we need to really work hard to make the diagnosis.

So in conclusion, hypertrophic cardiomyopathy is a common inherited condition. It is a disease of the sarcomere. It all starts with problems in the sarcomere. It's associated with hypercontractility that leads to wall thickening, to fibrosis, fibroblast activation. It is often asymptomatic, but it can present with a wide range of symptoms that are due to different mechanisms. We need to work hard to make accurate diagnosis, to understand the mechanisms of symptoms in patients. And multimodality imaging, as we're going to hear much more about, has a key role in the diagnosis of this condition, risk stratification, and the monitoring of therapy.

I would like to thank you for your attention, and I hope you enjoy the rest of the talks that we'll hear. Thank you.

Chapter 2

Dr. Schulz:
Ladies and gentlemen, friends, dear participants, I'm really thankful that you are here, and I am convinced your aim is to follow me on the following talk, *Echocardiography and Beyond*—please care for the beyond—*Comprehensive Imaging Strategies for HCM Evaluation.*

My disclosures, nothing relevant to the topic, but I love CMR. When you think about HCM and, to my opinion, it's extremely important that in the last cardiomyopathy guidelines, the phenotyping, and especially based on CMR phenotyping, really got a new level. On the other hand, we got a new experience. And what we are talking about—that is the following—that not only based on echocardiography, but also using CMR, a certain phenotype, here indicated by late gadolinium enhancement, got a new role.

And on the other hand, it's important for me to mention that it is not always the case is that you have that pattern of late gadolinium enhancement that may be there, but not necessarily. At that moment, I want to say for sure, and also in our ESC guidelines, of course, we have it there. Echocardiography is the method we are doing in the beginning. No doubt at all. But as all of you know, it's not too easy then to differentiate, for instance, the different causes for the diseases now, what caused many of the cases with LVH, then to say, is it HCM? Is there an overlap, or whatever we are talking about?

And usually the diagnosis is based on a diameter. But diameters are diameters. They depend on how you measure, where you measure, and if you have a good image quality in the case. And of course, there's a difference if a female or men, a large one, a small one, just as he has a 15 mm, it was a reason to take that. It was really a reason to take that in the beginning, also in the more apical part, the famous 13 mm. But it's not always true. So please be aware, and that is a nice work about it, that just in small persons, or depending on the sexes, it may be different.

On the other hand, be also aware, please, there is a model in that paper, and not all the patients were characterized by genetics, so we also have a mixture here.

But important, keep in mind, using echo, using CMR, it's not always about the famous 15 mm.

And one may also have different phenotypes of HCM, as you see here. And as well as you can go into the details that is based on the HCM registry, the hypertrophy can be localized in different places. It may be eccentric, maybe concentric, but also care for the other features. Care for the insertion of the papillary muscles. Care for thinning of the wall.

And you know that also using late gadolinium enhancement, especially in the apical region, one may have a transmural scar. And that is not due to a stenosis or obliteration of subepicardial stenosis. That is a characteristic finding also in hypertrophic obstructive cardiomyopathy of the more apical type, with the aneurysm there.

And when one is talking about HCM, then usually we have standard parameters in echocardiography where to measure, whereas in CMR, you are able really to go to the different locations, mainly based on the short-axis view. You can look into that, but of course, you could also assess the long-axis view, as you see here.

And to my experience, it's really important not only to go to a classical septal thickening, but also look for the thinnings and also look for the RV wall.

And furthermore, you can assess the CMR images before contrast media and after contrast media, having, for instance, also a suspicion of fibrosis in areas like in the septal wall.

And interestingly, also in the cited guidelines, we have CMR in a very high place. You see that it's important to run it there for differentiation. But when I'm talking about HCM, then here we are mainly talking about the obstructive form. You know that those patients, of course, are at danger, by the way, regarding sudden cardiac death and heart failure; it's not more worse than in non-obstructive forms. But never mind, there are really hemodynamic problems in the LVOT. And there it is extremely important to assess the obstruction. That is a class IB—the gradient itself using echocardiography. There are clear definitions how to get it done, when it can be dangerous.

But here again, I would say if it's 50 or 55—and it heavily depends on the loading conditions of the disease—but you really have to get it done.

Also, if you are not able, for instance, to run a high-quality echocardiography, there is a class IIb indication that one can also run a cath, like in former times.

And one has to point out, finally, a really pressure gradient that can be only assessed using caths. Our measures using echocardiography—that is just velocity—and we put it in the famous Bernoulli formula, and then we get a result. Whereas in CMR, one could also use the quantification of a pressure gradient and flow velocity, but that's difficult. Due to the high velocity, you can also run into technical issues.

So I'm totally convinced that all of you know those images—that is echocardiography with and without Doppler. So color Doppler indicating just a higher flow, whereas it is important really to use a CW—continuous-wave—Doppler really to assess the gradient.

And sometimes it's really difficult to get it done. And go also for the same phenomenon, but then also measure the gradient, addressed, but probably also after Valsalva or after some exercise. To my opinion, extremely important.

And you should assess the LVOT. And here, I am sure you are recognizing the interesting pattern of that. That was after a test, but there is still a gradient in there. But go for the details all the time using echocardiography. But as you see here, it was a very experienced investigator. But it's not always the case that you really get really good images.

Another way to see the LVOT obstruction is the CMR. And here you also see the signal void starting on the left side here, but you may also see it here, also the calcification of the mitral ring. And if a patient is not able to hold the breath, like you see it here, you can also at least assess the anatomy and see the aneurysm here. And at least in the European guidelines, that is also accepted as a risk marker.

When we assess the LVOT obstruction in CMR, in our group, we usually don't use the estimation of the flow velocity, because in case of high-accelerated flow, our measures are based on technical assumptions, not really accurate. That is a reason why we are quantifying just the area.

Here you see the same phenomenon, and you see the LVOT obstruction. And here you see nicely the LVOT area. Here also the mitral insufficiency. I don't want to lie; it's not always easy really to quantify that LVOT area, but extremely helpful.

And when you go over again through all the flow charts, and I can only advise you check just the ESC document, and you will get a really nice help when to do what. And that really depends highly on that if a patient has symptoms or not. So when you run a usual echocardiography, then you have to assess if the LVOT obstruction, just a gradient, is larger than 50 mmHg, and then you really see how to go on, if you have just to control of patient or if you go towards therapy.

On the other hand, to my opinion, it's also important to be aware of the fact when I really have to give a medication here. I don't want to go into the details. That will be the next talk. But when talking about a therapeutic guidance, it's not only about the pressure gradients. That is then also about cause of a disease, right, and about all the other aspects one can assess. And that is a possibility of multimodality imaging, again, nicely shown in our guidelines and with a focus on HCM. It's important because it will highly influence our therapy. If there is another underlying cause, like amyloid, like Fabry disease, you are aware of it, and CMR can help to guide you. But by the way, if you don't get a reliable result, don't forget about the possibility of the biopsy, and of course, at first, multimodality imaging.

So just know the recommendation is that contrast-enhanced CMR is recommended in patients with cardiomyopathy at initial evaluation, and that is also, of course, true for HCM, because that will help you with the guidance.

I want to share with you a very common pitfall, because usually when we think about HCM, we just think about hypertrophy. But here you see a patient, yes, with a hypertrophy. But what do you see as well, that down here in the T2-weighted images, the signal is high. And here you see there is a very bad suppression. That is not an amyloid. That is really acute myocarditis. So it's not always about hypertrophy, similar to arterial hypertension or HCM or other underlying causes, that can be also the acute stage of inflammatory disease. Just keep it in mind.

And I want to add one aspect. Are we sure that we understand fully the LVOT obstruction? I don't know, and I don't believe it, because we, one, put a work forward saying there are at least 3 different just pattern forms of LVOT obstruction, and if that makes a difference, that had to be clarified. It was built in a phantom. And let's see, I can only convince you if you have large groups. Do it. Go into that. It's not only about that gradient; it's also just about the anatomy behind.

And I would assume, and there is a first paper, currently only the proof. They did not go primarily in obstructive cardiomyopathy. It's a group of Reza Nezafat from Boston, that they tried to use CMR to assess also the blood flow in HCM using CMR exercise. We will see what it remains in future, but that is both what you see here about the understanding of pathophysiology, and that probably will guide the further understanding of the disease.

And if you just want to read it in a comprehensive manner, go for the Table 17 in the already-cited ESC guidelines, and I'm somehow convinced that will help you.

Thanks for following me. And as always, I want to thank my working group, because they are amazing. Thanks a lot.

Chapter 3

Dr. Podlesnikar:
Hello. My name is Tomaž Podlesnikar. I'm coming from Slovenia, and my topic today is imaging in the assessment of left ventricular outflow obstruction in hypertrophic cardiomyopathy.

I have nothing to disclose.

And as you have heard from our previous speakers, echocardiography is really instrumental to the detection and to the assessment of LVOT obstruction. As you can see here nicely on the right bottom image, LVOT obstruction can be visualized with any functional technique like CMR. You can see very nicely the chordal SAM. You see the signal void that corresponds to the flow acceleration in the LVOT, but it's really difficult to assess the grade of LVOT obstruction, and Doppler echo has to step in, in this case.

You also see in the slide for the protocol of the assessment of LVOT, both European and American guidelines here have very common, very similar recommendations. I just want to stress that in every patient with hypertrophic cardiomyopathy, it needs to be assessed, and it needs to be looked for, the LVOT obstruction. So it needs to be done. And with echocardiography at rest, you have to start with the patient, the Valsalva, and other provocative maneuvers like standing. And you see this on the pictures on the right.

So if the patient is asymptomatic, and we don't confirm a significant LVOT obstruction with 50 mmHg, then this patient can be just reassessed on a yearly basis. However, if he or she is still symptomatic, then we need to proceed with exercise echo. And this can be done on a treadmill, or it can be done on a cycle ergometer, as you see on the pictures on the right side, and can be even supplemented with a gas exchange measurement, the so-called CPET echo.

Regarding the treatment of LVOT obstructions, here are some small differences, but important differences, between the 2023 European guidelines and 2025 American guidelines. In a symptomatic patient with significant LVOT obstructions, both guidelines give a class Ib recommendations to use beta-blockers. And if beta-blockers are contraindicated or people are intolerant, then it can be substituted by non-dihydropyridine calcium channel blockers.

However, if the patient is still symptomatic, then the European guidelines give recommendations to use disopyramide or mavacamten. But disopyramide has a class I and mavacamten has a class IIa recommendations in European guidelines, while the American guidelines have the same recommendations for both drugs. Only if the patient is still symptomatic with the maximum medical therapy, then the European guidelines suggest to proceed to septal reduction therapies, while the American guidelines actually consider evaluating the patient in a heart team to maybe start septal reduction therapies even instead of medical therapy.

Where else? Multimodality imaging can help in the assessment of LVOT obstruction, especially in patients who are actually candidates for septal reduction therapy. Then, really, anatomical imaging with a high precision to define the septal hypertrophy to the segments to help the surgeon to excise the septum in a proper way are really instrumental. So MRI, CT, both imaging techniques are perfectly suited for that.

Also, if the patient has an indication for mitral valve surgery, meaning he has SAM, he has mitral regurgitation, needs to be done something, then really the surgeon needs this information. How to repair, how to proceed, to be the mitral valve repair, replacement, what shall be done. So MRI and CT are really important in this setting.

In alcohol septal ablation, then the myocardial contrast echocardiography is mandatory. Why? Because the septal blood supply is really variable between patients and needs to be tested before. So it needs to be intracoronary injection of the contrast followed with echo—transthoracic, transesophageal—to see which part of the septum or even other walls enhance, in order to see if the candidate is really suitable for this kind of therapy or not.

And then the new kids on the block are the cardiac myosin inhibitors. These are the new drugs that act by reducing actin–myosin cross-bridge formation, and in such a way they, of course, affect the LV contractility. So close monitoring of LV function is really mandatory in these patients, in both drug administration, titration, and also in the maintenance treatment.

And as you can see, ejection fractions of 55% for mavacamten and 60% for aficamten are actually the prerequisite to start the therapy. And then according, for different drugs, but these patients need to be monitored either on 2-weeks or 4-weeks basis to see if there is no impairment of LV function.

This is the drug prescription guidance, the SmPC in Europe. It's quite comprehensive. So every time we prescribe these drugs, we have to look at it. But I'm just going to give you a few hints that seem important. So as already mentioned, the initial left ventricular ejection fraction is important to start the therapy. Before the starting, actually, we need to check the patient liver enzymes, the cytochrome 2C19 metabolizing activity. And if the patient is a poor metabolizer, we need to start with a lower dosage of 2.5 mg. Otherwise, the starting dose for mavacamten is 5 mg.

Then, as I said, these patients are followed up clinically and echocardiographically on a 4-week basis for 3 months. And after 3 months, reassessment is done in a way that, if the patient is at any point symptomatic and has a decrease of left ventricular ejection fraction, then the treatment needs to be paused. And if that happens several times, then also discontinued.

If the patient is stable, but left ventricular ejection fraction is just a little bit above 50%, or if the drug is so effective that the Valsalva gradient is below 30 mmHg, then just maintain the dose. In other words, you have to up-titrate up to 15 mg. So if the left ventricular ejection fraction is still above 55% and the gradients are still above 30 mmHg, we go with the dose higher.

The treatment interruption is always when the left ventricular ejection fraction is below 50%. However, if the patient recovers and the left ventricular ejection fraction recovers, we start again with a lower dosage than the dosage when the side effects occurred.

With aficamten, the drug is still not available in Europe, but based on the phase 3 initial trial, we know roughly how the treatment and monitoring will be. So, as I said, a ventricular ejection fraction of 60% is probably the prerequisite to start the treatment, and then every 2 weeks the reassessment.

Also, other modalities can help in following the response to cardiac myosin inhibitors therapy. This is a small subset of patients from the EXPLORER-HCM trial that was followed with CMR. And a CMR could show that these patients had also left ventricular mass index reduction, left ventricular wall thickness reduction, and left atrial volume index reduction in the response to cardiac myosin inhibitor therapy.

We know from the phase 3 trials, and the EXPLORER-HCM and SEQUOIA, that actually very few patients needed to be put off the treatment. But it is really important also to know what happens in a real-world scenario.

So for this, we have just published the evidence from the COLLIGO-HCM trial. That was an international retrospective study involving more than 270 patients that received mavacamten. And they received mavacamten in two-thirds, roughly, as background therapy to beta-blockers and calcium channel blockers, and in one-third as monotherapy, because patients were either intolerant or have other contraindications for beta-blockers or calcium channel blockers.

And as you can see, either the mavacamten as a standalone therapy or in combination therapy, it was really, really effective. So the NYHA class status improved in those patients. The LVOT gradient, both at rest and in Valsalva, they both improved very much. And also the drug needs to be discontinued in very few patients. And also left ventricular ejection fraction was reduced a little bit in the whole cohort, but still above the normal values, so enough to continue the effective drug treatment.

I would like to conclude with a case study from our hospital. This is a 50-year-old man that was diagnosed with obstructive hypertrophic cardiomyopathy in 2024. He was a NYHA class II, and he had elevated NT-proBNP levels. He had already titrated the maximum dose of bisoprolol, of the beta-blocker. And based on his echocardiography in April 2025 we started mavacamten treatment with 5 mg.

As you can see on the echo images, he had asymmetric septal hypertrophy with a maximum hypertrophy in the basal and mid septum. It was measured 19 mmHg. You can see on the right upper image that he had SAM. He has mild to moderate mitral regurgitation, and his resting gradients were very high, were 63 mmHg. Valsalva even higher. And a short exercise test with squats next to the echo machine revealed even higher gradients.

You may spot in the continuous-wave Doppler image the mixture of both signals, LVOT obstruction and mitral regurgitation. So it was a little bit difficult to assess the LVOT obstruction. But still, in experienced echocardiographic hands, this is possible.

So 12 weeks—so 3 months after initiation of mavacamten therapy, he reported mild improvement of symptoms. His BNP levels dropped significantly. He was still with a systolic function in the normal range. So ejection fraction was 55, the maximum Valsalva gradient that we tested, that we managed to find out, was 30 mmHg.

So with this, I would like to ask you: How would you proceed with this patient? Would you maintain his treatment with a 5-mg dose of mavacamten? Would you up-titrate the dose to 10 mg? Maybe decrease the dose to 2.5? Or would you interrupt the treatment?

So the patient was quite borderline, as you see, because the gradients dropped significantly. Also, the left ventricular ejection fraction was 55%. But still, according to the prescription guidelines, he was in that group that needs to be up-titrated to 10 mg.

Yeah, we did so. But 2 months later, the patient came to the scheduled visit complaining of severe dyspnea. He was, we say, NYHA class III status at that point. He had signs of hypervolemia, as you can see on the right side, dilated vena cava, B-lines on the lung ultrasound. And his ejection fraction dropped significantly. We measured it at 29%. His resting gradient was fine, but still the patient was not doing well.

So how would you proceed now? Would you still maintain the 10-mg dose and reassess him in 4 weeks? Would you decrease the dose

to 5, 2.5 mg? Or would you interrupt the treatment, or even permanently stop the treatment?

So here, the guidelines are pretty straightforward. We need to interrupt the treatment, and we did so. We also gave him diuretics. We gave him the combination of sacubitril and valsartan and spironolactone.

And he came back only 4 weeks after that, again with a normal left ventricular ejection fraction. He had improvement of symptoms. He had no signs of hypervolemia. His NT-proBNP was somewhere in between his initial values and the lowest value at the end of 5-mg dose. His resting gradient and Valsalva gradients were still normal.

Again, I would like to ask you: How would you proceed now? Would you still pause the treatment, reassess him in 4 weeks? Would you restart with 10 mg, 5 mg, 2.5 mg, or permanently stop the treatment?

So again, based on the recommendations, we can start again if left ventricular ejection fraction improves above 50% with half of the dosage that the side symptoms developed. So we gave him again the 5 mg, and we reassessed him in 4 weeks, just a week ago, and he's doing fine with this dose.

In order to conclude, I would like to stress again, echocardiography with provocative maneuvers is recommended in all patients with HCM to detect LVOT obstruction, even if they are asymptomatic.

Exercise echocardiography and stress echocardiography is recommended in every symptomatic patient. And if we need details, LVOT assessment and anatomy of the septum, prior to septal reduction therapies, then TOEs, CMR, and CT come into play in the precise assessment of both the septal hypertrophy and mitral valve apparatus. Myocardial contrast echocardiography is mandatory prior to alcohol septal ablation, and echocardiography is really important in the monitoring of patients with cardiac myosin inhibitors, both during administration, dose titration, and maintenance of treatments.

And with this, I would like to thank you for your attention and also draw your attention to the recently published imaging consensus paper of the ESCVI for multimodality imaging in hypertrophic cardiomyopathy, where you may find answers to many questions which were not addressed in my talk.

Thank you very much.