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Optimizing Outcomes in Patients With oHCM: The Emerging Role of Cardiac Myosin Inhibitors

Announcer:
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Chapter 1

Dr. Coats:
Welcome to everybody. I'm Dr. Caroline Coats. I'm a cardiologist in Glasgow in the United Kingdom, and I'm pleased to be joined by Professor Iacopo Olivotto, a cardiologist from Florence in Italy

So there's been a lot of interest in hypertrophic cardiomyopathy over the last few years because we've finally got some treatments, but how good are we at diagnosing patients?

Dr. Olivotto:
After so many years, this is still a topical question. And the more data we acquire, the more we realize we can do better. For example, the fixed cutoff of 15 mm, unexplained hypertrophy, is clearly not good. We are underdiagnosing women and people of small sizes, so it's clear that from emerging evidence that if you normalize – and there are tools to do this online now – thickness per body size and age and gender, that will help you increase your sensitivity and specificity for the diagnosis. Also, we are probably not that good at diagnosing phenocopies, rare phenocopies like Fabry disease, Danon disease, even initial amyloidosis. So that we can do just by increasing our clinical skills, looking at the ECG, extracardiac science, and then addressing diagnosis based on the clinical suspicion

Dr. Coats:
What are the patients presenting with? What are the symptoms to be alert to?

Dr. Olivotto:
So classically, hypertrophic cardiomyopathy patients have subtle symptoms to begin with, and many of our patients, for reasons we don't really know, seem to start having symptoms around their 40s. This is the average age of diagnosis. Sometimes they can be children; sometimes they can be older. But the common thing is usually shortness of breath, particularly in situations like hot weather or after meals, which is really quite specific, particularly obstructive HCM.

And then of course, exercise limitation. There can be chest pain, which is not clear-cut angina. Sometimes it can be more atypical, but it is recurrent. And then of course, you can have hemodynamic instability, syncope, or palpitations in case of arrhythmias. These are the

presentations. They can be aspecific, and some of the patients may have lived with symptoms without really vocalizing them for many, many years.

Dr. Coats:
Yeah, exactly. Particularly if they're diagnosed young, they often don't realize they have symptoms until we make them feel better.

Dr. Olivotto:
They think it's sort of normal to be somewhat limited. They're labeled as lazy or they say, "I'm not good at sports," and that's quite often the case.

Dr. Coats:
Yeah. It's normal to them.

Dr. Olivotto:
Even in other cardiac diseases, right, in the end.

Dr. Coats:
Exactly. Yeah, yeah. So the approach to treatment, we've obviously seen a new class of medication with cardiac myosin inhibitors, which has made us question, really, have we been treating these patients well in the past. So can you talk us through our current approach to treatment and some of the sort of questions that have been raised?

Dr. Olivotto:
Well, first of all, we have changed our ambitions very much. When I started, we were happy with having patients survive and preventing the complications that we could. And quality of life was not high on our list, and therefore the treatments we used were used to control arrhythmias or gradients without much success. But this is really what we have been aiming at.

Now, it's clear that this is usually a low event rate, chronic condition, sometimes disabling condition, so that quality of life is becoming as important. And it's definitely important to patients, at least as much as controlling clinical manifestations. And it's clear that we have been running on experience rather than on data for so much.

And now, the data are beginning to appear – and we'll discuss this later – it's clear that some of the things we thought were not as clear. I don't know what your view is on this

Dr. Coats:
Beta-blocker has been around for 60 years. They're first line in the guidelines. Why have we been using beta-blockers? Because it might have been right at the time.

Dr. Olivotto:
It's partly because early data showed that there is some effect on gradients. In my experience, it's mostly provokable gradients, not so much on resting gradients. And we also had published a limited series. It's all like retrospective or poorly systematized data, but it's still showing that there may be, in selective patients, some advantage. But of course, it's anecdotal, and it's not placebo-controlled.

I do think in my personal experience that beta-blockers can still be important in selected patients with additional indications. But for the pure control of obstruction and HCM-related specific symptoms, we really don't know what the case is. Or at least we didn't know until recently.

Dr. Coats:
Yeah. And the other drugs we use, calcium blockers, disopyramide, where do they fit into treating patients?

Dr. Olivotto:
So calcium antagonists come in when beta-blockers are poorly tolerated. And in some of these patients, controlling the AV node and controlling heart rate may be important to improve filling time or sometimes because of angina, sometimes because of arrhythmias, that may be helpful. But usually, it's not enough to really resolve symptoms and the obstruction. Disopyramide can be extremely effective in a

selection of patients. It's usually not long-lasting and it has some nasty side effects, anticholinergic side effects, so that usually we use it more as a bridge to surgery rather than in the long term. But it can be used, for example, for initial Afib associated with LVOT obstruction.

Dr. Coats:
Yeah, exactly. So the cardiac myosin inhibitor class is a new drug class. We have two phase 3 studies in obstructive HCM that were previously reported, and some new data coming out. How do they work? What are they doing?

Dr. Olivotto:
Well, in patients that have proven sarcomere mutations, we know that HCM is caused by a hyperactivation of the sarcomere. I will not go into the details because of time, but of course it is a disease of sort of natural doping of the heart, where hypercontractility is an important part of both in determining the symptoms and also creating the basis for disease progression. So by normalizing this quota of excess contraction, you are obtaining a double effect. One is to control the gradient, to reduce the gradient, and also to trigger a ventricular remodeling, which we know to occur in sort of longer times compared to its study design trials. And then, at this point, to really sort of change the geometry of the heart, which seems to be beneficial and may sort of hint at the long-term modifying effect. So that symptom reduction is really quite effective and rate reduction is quite striking. Which raises the question, do we still need other treatments on top of that?

Dr. Coats
Yeah, exactly. So, I mean, really what we're doing is tackling the fundamental root cause of the biology of hypertrophic cardiomyopathy.

Dr. Olivotto:
Exactly. We still don't know whether this is the case for every single HCM patient, but definitely there's very good animal data and also now clinical data to suggest that at least in sarcomeric patients, we definitely are assessing that and we're seeing that.

Dr. Coats:
Yeah, excellent. Well, thank you so much for that discussion.

Dr. Olivotto:
Thank you.

Dr. Coats:
That was a really nice introduction to some of the challenges that we face in clinical practice with patients with hypertrophic cardiomyopathy, and we look forward to sharing some trial data later.

Thank you

Chapter 2

Dr. Coats:
Welcome, everybody. I'm Caroline Coats, a cardiologist from Glasgow in the United Kingdom, and I'm delighted to be joined today by Ahmed Masri, a cardiologist in Portland from the United States. I'm going to be talking about cardiac myosin inhibitors in hypertrophic cardiomyopathy

So, Ahmed, these drugs have really been a massive move in hypertrophic cardiomyopathy. Can you tell me a little bit – you've been involved in the trials – about what's the evidence that we've now accumulated for mavacamten and aficamten?

Dr. Masri:
Indeed. So myosin inhibition really highlighted the move from using medications that don't directly target the underlying pathophysiology of hypertrophic cardiomyopathy to drugs that go after the myosin-actin interactions and target the hypercontractility that is seen in hypertrophic cardiomyopathy. And so these drugs, each of them individually, have undergone multiple series of trials.

The first was mavacamten. We started with PIONEER trial, which was a phase 2 trial, moved to EXPLORER-HCM; that was a phase 3

trial. In EXPLORER-HCM, we saw that mavacamten is effective in treating LVOT gradients, LVOT obstruction, and improving symptoms. And then subsequently, VALOR-HCM trial was conducted, and VALOR-HCM objective was to show the same plus the fact that it can actually avert the need for septal reduction therapy.

Now, these trials have established the efficacy of mavacamten in treating symptomatic obstructive hypertrophic cardiomyopathy. Now, in terms

the efficacy of aficamten, which is a second-generation cardiac myosin inhibitor, the safety and efficacy were established in REDWOOD-HCM phase 2 followed by the pivotal trial which was SEQUOIA-HCM that showed that aficamten can influence symptoms, LVOT gradients, quality of life, peak VO2, exercise capacity, and all the endpoints that usually we do in hypertrophic cardiomyopathy trials.

This was followed by a second phase 3 clinical trial called MAPLE-HCM, which is a head-to-head trial of metoprolol versus aficamten that was just recently reported and showed that aficamten reproduced its effect while metoprolol was detrimental on exercise capacity and anti-proBNP, left atrial volume index, along with some other endpoints as well.

Dr. Coats:
Excellent. So a real wealth of randomized trial data now. For the benefit of our audience, could you just explain the differences between mavacamten and aficamten

Dr. Masri:
Definitely. So it's interesting that we try to say that there is a family of drugs, correct? But they truly are distinct from each other. They work differently. They bind to different sites in the sarcomere at the myosin level. If you give patients, which you shouldn't, but if you give a model 2 drugs at the same time, aficamten, mavacamten, they don't essentially compete against each other. And so they're distinct from that nature. They're distinct in their pharmacology and their tissue metabolism and their pharmacokinetics and pharmacodynamics profile, their drug-drug interactions, and also their safety.

For example, the half-life of aficamten is shorter than mavacamten, which has enabled, with its consistent metabolism, for all of our programs that we use aficamten in to have down-titration as a strategy to dealing with any reduction in LVEF. While with mavacamten, you actually have to stop, reevaluate the patient with an echocardiogram, and then decide on when to restart that. So that's, for example, a major difference there.

Now in terms of safety itself, which we focus on a lot, and I encourage everyone to go back and review that as well when they need to. With mavacamten, there is a wealth of data from the randomized clinical trials and also from the long-term extension arm that generally have shown anywhere between 5%, 6%, to up almost to 14% reduction in LVEF. There have been events related to heart failure. There have been events also related to other things there.

On the other side, you have aficamten, which is recently reported in integrated safety analysis, about 460 patients over almost 700 patient-years' worth of follow-up, that showed that the rate of reduction in LVEF was about 4% over the combined analysis there.

So there is a difference in the degree of systolic effect that these drugs have. And in general, we feel that you need some of it to be beneficial, but too excessive reduction in LVEF might be detrimental and we'd like to avoid that.

And then I will end with one important point. When we do cross-trial comparison, it's always hard. But one important point to remember about this safety issue is that with mavacamten, you usually are on the lower doses of the drug. It's a very powerful drug, so those lower doses typically are sufficient to reduce your LVOT gradient and maintain ejection fraction.

While, if you look at aficamten, the majority of the patients are actually on the higher doses, and so when you evaluate safety, for example, you have to put that into perspective

Dr. Coats:
Absolutely. So the trials have been really powerful. There's long-term data as well, isn't there, with open-label extension studies. What have we learned from those in both mavacamten and aficamten

Dr. Masri:
Great question. I think with myosin inhibition, the long-term data are as important as the pivotal trials. It's not the same as other drugs in heart failure where you usually just take the trial and move on. I think these are very important. And so we already covered some of the safety aspects related to left ventricular ejection fraction. The good news is that the efficacy continues, and the efficacy continues over the long term, and we don't see necessarily, an attrition in terms of that. What we sometimes see in certain trials, if you look, for example, at the combined experience with mavacamten versus aficamten, there are more patients who have discontinued mavacamten during longer-term follow-up compared to aficamten. Again, cross-trial comparison doesn't necessarily mean head-to-head.

The other piece of evidence that we also have seen to be emerging slowly is that there seem to be a signal for atrial fibrillation in some of these longer-term mavacamten trials that is not necessarily being replicated with aficamten trials. And there have been several recent presentations on that; more presentations are to come. But I think the bottom line is we need to continue in a vigilant way to study the longer-term effect of these drugs because these are hemodynamic modulators. We need to understand what happens on the longer term.

Dr. Coats:
Yeah, absolutely. And we've talked about mavacamten and aficamten. Is there anything else coming down the line?

Dr. Masri:
Definitely. So the story doesn't stop here. First, with even these drugs themselves, recently mavacamten reported the neutral results of the ODYSSEY trial. So mavacamten for nonobstructive HCM, we don't know if it's going to have a path forward or not. For aficamten, the ACACIA-HCM trial is ongoing. It's a trial in nonobstructive HCM. We expect to see the results next year. So that's from the ongoing programs that we have.

Now, there is also myosin inhibition being trialed in HFpEF, so that's also something to keep an eye on. Now, in terms of newer drugs, there is a more recent drug that is in phase 2 clinical trial, called EDG7500. It's a myosin modulator. We still don't know the exact mechanism of action, but it's meant to be working more on the diastolic phase or diastole. And there are non-myosin approaches right now being employed in HCM, including combined SGLT1 and 2 inhibitors in the SONATA-HCM trial with sotagliflozin. And there is also an energy modulator in a trial called FORTITUDE-HCM, also another phase 2 trial.

Dr. Coats:
Yes, exciting time. And also perhaps also to mention these have been adult studies, but there is studies now ongoing in adolescents.

Dr. Masri:
That's a great point. So this is one of the few programs early on that is being pushed toward the pediatric population because, as we know, HCM manifests at any age, really. We have a trial for mavacamten that is ongoing for adolescents, and there's a trial for aficamten, as well. The trial for aficamten is called CEDAR-HCM. It is ongoing, too. And the difference a little bit there is that with pediatrics, you need a smaller sample size. You need to show the same consistent directionality of effect on LVOT gradients and whatnot. And that's typically how these trials are designed

And the next step is going to be to go to even younger patient population. Even though these populations are small in size, they are extremely important. If you can avert the need for septal reduction therapy in younger patients, that's a big win for all of us.

Dr. Coats:
Yeah, completely. Yeah, so really exciting program for hypertrophic cardiomyopathy. Thank you so much for sharing all your knowledge about the trials and I hope our audience found that a helpful discussion

Chapter 3

Dr. Coats:
Welcome, everybody. I'm Caroline Coats, a cardiologist in Glasgow in the United Kingdom, and I'm delighted to be joined today by Pablo Garcia-Pavia from Madrid in Spain.

Welcome, Pablo. I'm delighted to be talking to you about the MAPLE-HCM study. I wonder if you could start by just explaining the

rationale for undertaking this study.

Dr. Garcia-Pavia:
Sure. The MAPLE-HCM study has evaluated aficamten monotherapy compared to metoprolol monotherapy in patients with symptomatic obstructive HCM. We already knew that aficamten, a new cardiac myosin inhibitor, can correct the underlying pathophysiology of hypertrophic cardiomyopathy by decreasing hypercontractility. We already knew from the previous SEQUOIA study that it was effective when added to standard of care therapies in patients with symptomatic obstructive HCM.

In this study, we wanted to assess if it was effective in monotherapy as compared to the standard of care therapy that is mostly used worldwide, which is metoprolol

Dr. Coats:
We would typically start at beta-blocker in a patient with symptomatic obstructive cardiomyopathy, but this is asking the question of starting aficamten in place of a beta-blocker.

Dr. Garcia-Pavia:
Exactly. Moreover, this is the largest study that has assessed the effect of a beta-blocker in obstructive HCM patients. Because we have been using beta-blockers for more than 60 years, but there was very limited evidence about what is the efficacy and safety of these drugs in this particular setting.

So I think it's a very important study for 2 reasons because it gives us an answer to what should be the first-line therapy in this disease but also it provides very important information on a medication that we have been using for more than 50 years

Dr. Coats:
Yeah, a great study indeed. Can you tell me the headline results?

Dr. Garcia-Pavia:
The main takeaway message of the study is that aficamten is superior to metoprolol in several parameters in patients with symptomatic obstructive HCM. The primary endpoint of the study was the change in exercise capacity assessed through peak VO2, and we observed that in this study, while the patients on metoprolol had a mean reduction in peak VO2 of 1.2 mL/kg/min, we observed an increase in mean peak VO2 in those on aficamten of 1.1 mL/kg/min. The absolute difference of the 2 groups is 2.3, which is important difference in this disease.

Dr. Coats:
And there was all this marked gradient reduction in the aficamten group but surprisingly not gradient reduction in the metoprolol group.

Dr. Garcia-Pavia:
That’s one of the secondary endpoints that we have assessed, which is very important. And surprisingly, we did not observe a reduction in gradients with metoprolol, despite we pushed with very high doses in the study, either at rest or with Valsalva.

Regarding symptoms, the findings were also very important because we observed that at the end of the trial, 40% of participants on aficamten were in NYHA Class I, while these occur onlya 9% of patients on metoprolol.

Dr. Coats:
Yeah, impressive. And did you see any structural changes, any changes in the biomarkers

Dr. Garcia-Pavia:
We assessed both anti-proBNP and other diastolic markers like left atrial volume index, and it was interesting to see that while these 2 parameters worsened in those receiving metoprolol, they improved dramatically in those receiving aficamten. In fact, by the end of the trial, the mean level of anti-proBNP was at the upper limit of normality in those patients receiving aficamten.

Dr. Coats:
Truly impressive. It really is. Some people might be reluctant about taking beta-blockers away for other reasons. How was the safety

outcomes in the study?

Dr. Garcia-Pavia:
Aficamten was well tolerated. In the study, there were 3 patients on metoprolol that had to stop the medication due to adverse event, as compared to only 1 patient on aficamten. Consistent with the mode of action of aficamten, we observed a mean reduction in left ventricular ejection fraction of around 5% at the end of the trial as compared to 0.5% reduction in those on metoprolol. But only 1 individual in the aficamten group developed a left ventricular ejection fraction below 50%. And in this case, the patient was asymptomatic, had no signs and symptoms of heart failure, and in fact, did not stop the medication and it resolved. Afterwards, the left ventricular ejection fraction decreased.

Dr. Coats:
So it's reversible.

Dr. Garcia-Pavia:
Reversible, exactly.

Dr. Coats:
So how do you think this study is going to change your clinical practice

Dr. Garcia-Pavia:
I think it's going to have a profound change in how we treat patients with symptomatic obstructive HCM. Nowadays, we were using a drug that is not effective according to the data of the MAPLE-HCM, or is not as effective as we thought, and now we have an alternative that seems to be very effective and also safe. Therefore, I think when it gets approved, I think aficamten has the potential to become the first-line therapy of choice for these patients.

At least with aficamten, we now have the data to support that monotherapy is safe and effective. Obviously, this allows us to change completely the way we position the drugs to treat obstructive HCM, and I guess this will need to be covered in future guidelines in order to expand the recommendation.

Dr. Coats:
Yeah, absolutely. Well, thank you so much for your discussion and congratulations and thank you for your leadership in the trial.

Dr. Garcia-Pavia:
Thank you very much, Caroline.

Dr. Coats:
Thanks to the audience for watching. I hope you found the discussion helpful.

Chapter 4

Dr. Coats:
Welcome, everybody. I'm Dr. Caroline Coats, a cardiologist in Glasgow in the United Kingdom, and I'm delighted to be joined today by Professor Knebel from Berlin in Germany

We're going to be talking today about the implementation of cardiac myosin inhibitor therapy in clinical practice

So thanks for joining. You're a cardiologist in a busy clinic. How have you managed to implement these new and exciting treatments into day-to-day clinical practice

Dr. Knebel:
So I had the chance of being one of the first centers in Berlin to have access to myosin inhibitors. We started treating patients with mavacamten from the early stage on, and it was a very fascinating thing for me to learn how these patients react to this therapy and which therapeutic benefits you can see in these patients

Dr. Coats:
And how have you selected patients for starting treatment

Dr. Knebel:
So basically, the selection went by patients that were referred to me because I had an experience in cardiac amyloidosis. So referring centers sent patients with increased wall thickness and cardiomyopathies since the longer time already to me, and then, since the myosin inhibitors were available, mavacamten, I got many patients that were sent with the specific question, “Is there an indication for mavacamten?”

Dr. Coats
And just remind us of the indications within the European guidelines.

Dr. Knebel:
So we were looking for patients who have symptoms of hypertrophic cardiomyopathy and that have an outflow tract obstruction of more than 50 mmHg at rest or under provocation with the Valsalva maneuver

Dr. Coats:
And do you undertake an echo, an exercise echo with the patients before initiating?

Dr. Knebel:
Yes, definitely. So we check if the patient has got an outflow tract obstruction of more than 50 mmHg at rest and if not, in every patient we perform a stress test consisting, first of all, in a Valsalva maneuver. If the Valsalva is positive and the gradient goes above 50, or the patient has an indication already, but in case we see there's an increase but we do not reach the threshold of 50, we then exaggerate the stress by, for example, doing hand grip exercises or the patient does some squats, or we ask the patient, for example, to come after lunch to the echo examination, so a postprandial gradient is also something that can unmask an underlying outflow tract obstruction.

And in some cases, we had to do exercise stress echo, meaning treadmill and not dobutamine

Dr. Coats:
Ejection fraction. So this is an important prerequisite before starting, isn’t it?

Dr. Knebel:
Yeah. So we do ejection fraction in echocardiography. I'm personally a little bit skeptical if this is really the best parameter. But we know in all studies, ejection fraction was the core parameter that was measured because the fear is that under myosin inhibition, you get a reduction of ejection fraction; then you have to pause or reduce the dose of the myosin inhibitor

Dr. Coats:
And in Europe, pharmacogenomic testing, is that something you've adopted in your center before initiating

Dr. Knebel:
We started with cardiogenetic testing, and in our setting, we have a cardiogenetician who takes care of these patients, and we get the possibility to really understand what the story behind this hypertrophy is. And I think it’s very important because we have to educate our patients, that they look into their family history, because sometimes if you really ask specifically for the family history, you find out that there are many, many patients who suffer from this disease that was previously unknown

Dr. Coats:
So you're really phenotyping the patient well before initiating a cardiac myosin inhibitor. Yeah. Are you undertaking CYP testing, CYP2C19?

Dr. Knebel:
In Germany, we have to do the CYP2C19 testing prior to initiating the therapy. We could start on a very low dose without the testing, but we have decided in our center that we do the genetic testing, the CYP2C19 testing, in every patient because then we can start with an

adequate dose from the beginning, and it is also very important in younger patients, in childbearing-age females to really make sure that they are under contraception because this should not be prescribed to a patient who is in childbearing.

Dr. Coats:
And do you involve pharmacy or anything with those discussions with the drug interactions, or is that all handled by a cardiologist?

Dr. Knebel:
It's handled by us in the cardiology team. Up until now, we did not have to consult pharmacologists.

Dr. Coats:
Yeah, because I think different centers have slightly different setups of how they're implementing the medicines.

And then, can you talk us through, once you've initiated a patient, their sort of follow-up procedure. Do they come back to the same clinic, and how is that handled?

Dr. Knebel:
So we offer our patients to come back 4 weeks after starting the therapy with mavacamten, and then we do an echo check. We check for ECG and we check the biomarker anti-proBNP, and in the vast majority of patients, we see a dramatic reduction of the outflow tract gradient and we see a decline of anti-proBNP. Usually after 4 weeks, we don't see any change in the ECG; that takes usually a little bit longer time. And clinically, some patients start improving after 4 weeks, but the more dramatic improvement clinically is after 8 or 12 weeks. When the outflow tract obstruction goes down, the patient improves clinically a lot.

Dr. Coats:
And logistically, how has it been for the patients to come back for those 4-weekly echos?

Dr. Knebel:
The patients usually do not love to come back to a dentist because he hurts the patient, but coming back after myosin inhibition, the patients are very happy to come back because usually they feel better, and they want to have the kind of imaging proof that the medication is also working

Dr. Coats:
Yeah. I think that's our experience as well. People feel better and want the next dose. So that's great. And what's the longest duration you've had people on myosin inhibitors now in clinical practice

Dr. Knebel:
The longest patient that we have is 30 months, and this patient, interestingly, has such an increase in his physical activity that he has lost lots of body weight due to more activity. He's counting his steps that he's taking every day. He’s now above 10,000 a day. That’s really fine.

His anti-proBNP is in normal levels and his ECG has normalized

Dr. Coats:
Brilliant. Yeah. No, it's very dramatic, isn't it? That's a very positive story. Challenging and important to really phenotype the patients, but hopefully that gives a flavor to the audience about the practicalities of implementing these medicines within our clinical practice.

Thanks very much for talking through. And thanks very much to our audience. I hope you've found that session helpful

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