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Unblocking Clinical Inertia: The CMI Era in oHCM Care

Opening:
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Dr. Olivotto:
Ladies and gentlemen, in the next 10 minutes I hope to give you a sufficient rationale to convince you that cardiac myosin inhibitors are indeed a revolution for patients with hypertrophic obstructive cardiomyopathy.

These are my disclosures.

So in this interesting book by David Wootton about the invention of science, talking about the Royal Society, the birth of the Royal Society, there is a quote from Vincenzo Antinori who's from my hometown in Florence. He says that the real difference between revolutions in history and those in science is that revolutions in science successfully achieve what they set out to do. And this indeed is a story of a level of revolution in the way we perceive hypertrophic cardiomyopathy.

For decades, we have been obsessed with the concept of hypertrophy, the distribution, the extent. Now we realize that equally important to the phenotype and the pathophysiology is the fact that this is a hypercontractile disease, as you can see on the right. If you forget about the hypertrophy and you just look at the ventricle inside—what happens in this ventricle—you see how much hypercontraction sometimes you can really see in this ventricle due to genetic reason, a genetic doping of the heart muscle.

And the reason behind this is that, irrespective of the genotype, the net effect that you see in these patients at the molecular level is a hyper-representation of the active state of myosin. There are 3 stages of myosin: an active, a super-relaxed, and a disordered state. And of course, the representation of the active state is only about 10%. Why? Because the heart has to be sustainable over decades, and it would be unthinkable to have all the actin-myosin heads involved in contraction at any given time. And so the percentage of high-energy-consumption molecules needs to be a small minority compared to the lower-energy-consumption states.

This is what happens in HCM. The shift, because of allosteric deformation of the molecules, increases calcium sensitivity, leading to overrepresentation of the high-energy-consumption state, which leads to hyperfunction, but in the end also to a number of adverse remodeling effects at the molecular, cellular, and organ level, including hypertrophy, but also ischemia and myocardial fibrosis.

So myosin inhibitors reverse this. They can return states to a normal or quasi-normal status of things, and by doing this, stop this vicious circle leading to progression of disease.

So these are incredible molecules. When it came to showing their efficacy in clinical practice, we had a problem. How do you show in a disease that's slowly evolving, has low event rates, how do you show that something is so exciting and effective and so much so that it can be justified for introduction in clinical practice? Well, of course, the initial target was obstruction, and it was ideal because obstruction is very reproducible, is an obvious cause of symptoms, and it is a very reproducible sort of relief of the symptoms that you can obtain when you treat obstruction, for example, with surgery.

This is a patient, for example, with classic systolic anterior motion of the mitral valve, high gradients on exercise and with Valsalva and at rest, of course, very symptomatic. And this is the same patient after a 30-week course with a myosin inhibitor. In this case, it's mavacamten during the EXPLORER study. And you can see how the relief of the gradient, the remodeling of the cavity, the relief of this systolic anterior motion is quite impressive. And of course, the gradients disappear, and the patient is now completely asymptomatic.

As you know by now, this is recent, but not so recent, phase 3 studies that establish the efficacy and safety of the two available molecules, mavacamten, which is already registered and is already in use worldwide, and aficamten, which is still not registered but soon will be available to patients as well.

The study endpoints of these trials, again, were largely functional. And based on the improvement in functional capacity, you can see here improvement in peak VO_2 consumption of 1.4 mL and 1.7 for the 2 molecules are similar advantage in terms of functional capacity, very marked drop in gradients, about 50-mm drop in provocable gradients, and about 65% to 60% of patients improving at least 1 NYHA class with a marked improvement in quality of life assessed by Kansas City questionnaire. Quite reproducible, quite similar. Slight differences, of course, the molecules have some pharmacological differences. But overall, the effects were similar.

And also very sustained over time. This is a long-term extension from EXPLORER with mavacamten, showing very sustained benefit in terms of gradient reduction with biomarkers, quality of life, and the same recently published FOREST with aficamten. Over 48 weeks, you can see how nicely the effect is sustained over time when treatment is discontinued.

The other thing we're learning now is that we have for many, many decades given patients drugs such as beta-blockers, calcium antagonists in hopes of improving these gradients. Some of the initial early records have shown benefits in terms of gradient reduction, symptoms improvement, but the data were really quite limited and mostly not of high quality compared to modern standards.

What happens in about 50% of the patients is that if you remove background therapy once the myosin inhibitor—in this case aficamten—have become ineffective, you really don't lose any efficacy. It doesn't really make a lot of difference if you remove background therapy. Of course, not in all patients, but in about 50% you can do that, and you're limiting the side effects. You're removing the side effects without losing efficacy and the hemodynamic effect and symptomatic effect.

The other things we learned from the MAPLE study released only a year ago was that if you compare head-to-head a myosin inhibitor—in this case aficamten—with metoprolol, which has been the standard of care for many years, of course you're not surprised to see a good performance of aficamten, which lowers the gradient very convincingly, lowers proBNP very convincingly. This replicates the phase 3 study SEQUOIA. But at the same time, you see how poorly beta-blockers perform with no virtual effect on gradients, and if anything, a little raise in NT-proBNP.

So there's a lot of rethinking about the way we use the beta-blockers, the way we are maybe sometimes inducing chronotropic incompetence and side effects, and how we should really reconsider not avoiding beta-blockers—beta-blockers remain important from symptomatic standpoint—but trying to avoid the side effects of chronotropic incompetence remains a novel objective—becomes a novel objective, and it's really quite important.

A couple of words about the safety profile. These drugs are negative inotropic agents. They are used in a tailored manner, so usually quite safe. But of course, you can expect to have a proportion of patients who will develop systolic dysfunction. You can see here, for example, in this meta-analysis that especially in the context of paroxysmal atrial fibrillation, patients may drop the ejection fraction and may require washout and resumption of a lower dose with mavacamten or a reduction in dose with aficamten. This is why virtually every country has implemented risk-mitigation programs with mavacamten at present. We still have to see what is going to happen with aficamten, requiring regular checks in patients to exclude the possibility of or to mitigate the risk associated with systolic dysfunction. However, very rarely these events turn into heart failure events or lead to hospitalization. Most of these can really be quite nicely dealt with in the clinic.

This is the last published trial to date on mavacamten. It's the SCOUT-HCM trial reporting data in adolescents, 12- to 18-year-olds, with symptomatic obstructive HCM. The data again recapitulated very well those seen in adult patients. So very effective in children and adolescents with the disease. The doses required to lower gradients are quite high in view of the very active metabolism of these patients. So hopefully moving even to younger cohorts in the future because, of course, children are also a major unmet need when they are symptomatic.

What about the real world? So trials are very exciting. We've never seen such wealth of data in this particular disease. There are now thousands of patients treated worldwide, many national registries, many have been published and are ongoing work, and they basically recapitulate very well what we know from trials. So about 9 patients out of 10 have some kind of improvement, often quite remarkable improvement in terms of gradient reduction, improved quality of life, initial evidence that there is a favorable remodeling in the ventricle, some reduction in LV mass, increase in cavity size. The safety profile is actually quite good, even better sometimes than in trials because the titration in real world is quite cautious. This is part of what we sometimes see with the new drugs, but it's probably not a good thing in this particular case when we still have to sort of get our own feeling for this new class of drugs. So in general, it's really quite an enticing sort of introduction of these drugs—of mava in particular in this case because it's the only registered drug today in the real world.

So in conclusion, what cardiac myosin inhibitors do in obstructive hypertrophic cardiomyopathy is that they turn a highly energetic, expensive sports car, but polluting sports car in terms of, for example, an accumulation of free radicals, fibrosis because of the hypercontractile state, into a clean diesel engine, which is really what the heart is supposed to be. And by doing this, they have incredible benefits in most patients in terms of quality of life, which is really what matter most to the patients. And they, of course, have all this sort of range of persistent advantages for the patient.

We have a number of open questions that remain, including the costs and the need for repeated sort of echocardiograms because of the risk-mitigation programs, which are a burden to the healthcare sort of system and to the patients themselves. We still have limited data regarding the long-term safety and efficacy, the need for potentially lifelong treatment, the contraindication or relative contraindication in pregnancy—still no data about this and so better to avoid—and the fact that not all patients respond. So what do we do in these patients? But overall, I think this can be really redefined as a potential revolution for the management of our patients with symptomatic obstructive hypertrophic cardiomyopathy.

Thank you very much.

Dr. Arbelo:
Hello. I'm very happy to be here to talk about where do cardiac myosin inhibitors fit in the present and future guidelines. I'm Elena Arbelo, a cardiologist working in Barcelona.

And these are my disclosures. But probably the most important disclosure that I have to make is that I'm the chair of the 2023 ESC Guidelines for the Management of Cardiomyopathies, together with Juan Pablo Kaski and a fantastic group of experts on cardiomyopathies.

And I will discuss briefly what we have so far so that we think about what's happening in the next coming years. So we have 2 major guidelines covering hypertrophic cardiomyopathy, the 2023 ESC guidelines and the American ones that came out a year later.

In the ESC guidelines, when we discuss LV outflow tract obstruction, basically what we gave cardiac myosin inhibitors was a second-line indication with a IIa indication; that means should be considered, in addition to beta-blocker or even as monotherapy. When we look at the US guidelines—I remind you it was 1 year later, some extra evidence had come out—they do prescribe or suggest a second-line indication for cardiac myosin inhibitors, but at the same level with a class 1 indication and septal reduction therapy being a decision that needs to be made together with the alternative of cardiac myosin inhibitors or disopyramide.

Since then, we had many, many important evidence, RCTs from phase 2 and phase 3 that have shown the efficacy and safety of cardiac myosin inhibitors. So by now, we now know that cardiac myosin inhibitors reduce outflow tract gradients, they improve symptoms and health status, they improve exercise capacity, they've reduced the necessity for septal reduction therapies, but they do require structured safety monitoring.

So for the topic of my talk, for the guidelines, it's not a question any longer of efficacy, which is what we were discussing in 2023; it is more about where should cardiac myosin inhibitors sit in the treatment pathway of patients with obstructive hypertrophic cardiomyopathy.

So I will try to cover 5 different questions over my talk regarding the next update of the guideline. First, should cardiac myosin inhibitors be upgraded as second-line therapy? So still IIa? Should they become class Ia, stronger wording? One? Both drugs? How strong is the evidence for the classical drugs? What should we do with background therapy? Can CMIs become first-line therapy? And finally, if they become a first-line therapy, is it a class effect?

So starting with the first question, we have major trials, as you can see in the summary tables, that have shown the efficacy and safety of cardiac myosin inhibitors. So as I said, this is not a question of knowing whether it works or not. We already even know that the indication of patients for a need of septal reduction therapy practically disappears with cardiac myosin inhibitors. And we have data for efficacy, but we have very long data, 2 and a half years of follow-up data showing that this is sustained over time.

So as I say, CMI therapy should be considered a core second-line option in adults with symptomatic obstructive hypertrophic cardiomyopathy who remain limited despite initial therapy. And the only question that we need to consider is that we stay in class IIa or we go for stronger.

And for that, we need to cover my second question, which is what evidence do we have for the classical drugs? So beta-blockers, we are the first-line option in hypertrophic cardiomyopathy with obstruction, we have some data and we have a very recent systematic review and meta-analysis. Unfortunately, the data that we have for beta-blockers is mostly observational. Only 5 RCTs, and most of them have very small sample sizes. But still, we do have some data, and the data show that when you pool the studies that evaluated LVOT gradients before and after beta-blockers, beta-blockers do reduce or improve outflow tract obstruction.

When you look at class function—NYHA class function—9 studies evaluated this. And of 189 patients, 83 improved. So there was some improvement from the NYHA class.

And when you look at symptom burden, it was 4 studies that evaluated this, overall, patients noted improvement in symptoms, although 1 study reported that dyspnea and other complaints persisted.

If we go in depth with the 2 more recent randomized trials—it's actually 1 trial with 2 separate analyses—it's a very nice study. It's a crossover design, unfortunately very small and with short follow-up. What they did is that they had 2 groups. A group started with metoprolol, the other group with placebo. They stayed 2 weeks, then 1 week washout, and they crossed over to the other therapy. Their primary effectiveness parameter was peak exercise LVO tract gradient. They had some secondary endpoints, which was quality of life and peak VO_2, and then they had some other exploratory parameters.

And what they showed is that beta-blockers, or metoprolol in this case, did reduce gradients at different stages, rest and with exercise. And this also turned into an improvement in NYHA class function and also quality of life. And these are the main conclusions. So reduced LVO tract obstruction, symptom improvement, improved quality of life. But unfortunately, maximum exercise capacity remained unchanged.

So now we go on to the separate analysis of the same study where they evaluated the exercise hemodynamics in this group of patients that had crossover with metoprolol versus placebo. And what they saw is that the capillary wedge pressure did increase with exercise to pathological levels, and this difference was exactly the same. So there was no difference between taking the beta-blocker or not taking it.

They did see an improvement in stroke volume in patients with beta-blockers. When we look at mitral regurgitation, a baseline beta-blocker intake had the impact and improved some of these hemodynamics. And this was seen also with exercise.

The other parameters I would highlight, I would say that heart rate obviously was lower in patients taking beta-blockers. The stroke volume, as we said, was higher. But overall, the peak VO_2 did not change, probably because of the overall hemodynamic problem of diastolic filling. Interestingly, also vascular function was also not different between those patients that were taking beta-blockers or not.

So in summary, patients taking beta-blockers in this year, we have that most evidence derives from old and small studies with limited survival data, but they do seem to improve gradients, particularly on peak exercise, but have variable impact on symptoms and hemodynamics. But they do remain an important part of managing patients with obstructive hypertrophic cardiomyopathy, especially in those patients with arrhythmias. And this is the evidence that I remind you we have for CMIs.

So to reply to this second question, I think that beta-blockers remain important because we have long clinical experience, we have low-cost access, they are useful for the rate control and management of arrhythmias and prevention of arrhythmias in this group of patients, and clinicians and patients are familiarized with it. But we do have to take into account, as I said, that much of the evidence is small and old. They have heterogeneous endpoints, they have limited survival and outcome data, variable effect on exercise capacity. There's a chronotropic limitation that may matter in these patients, and we have no direct sarcomeric mechanism that will treat the actual disease.

So for the guidelines, I would say that historical use is not the same as contemporary evidence, and what we need to do is—of course, beta-blockers are not obsolete, but we need to justify their positioning in the treatment algorithm based on evidence.

Let me go to the third question. Do we go for monotherapy? Will we try step-down or not? We do include that, as I mentioned before, as an indication in the 2023 guidelines. We had limited evidence at the time. It was the EXPLORER trial, and there we had 3% of patients that were not taking any background therapy.

But we do have subsequent data showing, like in SEQUOIA, they had 13 without background therapy. What we see, interestingly, is that with mavacamten—the main trial—what they saw was that patients taking beta-blocker did worse than patients that were not taking them. This was not seen for the aficamten trial.

There's a further subsequent subanalysis for the mavacamten group. And what they saw is that patients taking beta-blockers compared those that were not taking them had similar improvements regardless of the use of beta-blocker in those that were not heart rate–dependent, so NT-proBNP and NYHA class, quality of life, and gradients. But when you look at those outcomes that are heavily dependent, patients on beta-blockers did worse, like peak VO_2, peak exercise capacity, peak heart rate, and exercise time.

And we do have data on withdrawing from aficamten, the main trial and the extension trial. So there they included 145 patients. Withdrawal was attempted in about half of the population, 64 patients. From those 64 patients where they attempted withdrawal, they actually managed to reduce the medication and even stop it in 92% of them. 64 discontinued at least 1 medication, and even from those, 71% achieved aficamten monotherapy. And what's more important is actually that the outcomes—gradients, functional class, and quality of life biomarkers—they all remained improved under a monotherapy with aficamten.

So my take-home message for this section is that we have several options in clinical practice. We can go for the withdrawal model. So this is the experience that we have now. We have people with background therapy, and we put the cardiac myosin inhibitor on top of it, and then we may or may not consider de-escalation. We have to take into account that these medications, as we were discussing before about beta-blockers, may have some secondary effects, and they may produce fatigue, negative inotropy, hypotension, bradycardia. So it is something that we need to consider, that maybe we need to withdraw.

On the other model that we could consider is like, okay, so we start with the cardiac myosin inhibitors, and then we decide on the concomitant medication. That may be an approach, but at this point, the data that we have do not allow to suggest this as a universal rule. So my recommendation would be we do individualized re-prescribing of the medication. We have to reassess every drug, every indication, and we decide whether we keep it, we reduce it, we try to withdraw it, or even substitute it, depending on the patient characteristics.

Let's move on now to the first-line considerations. We all know that the MAPLE study was presented in August 2025 and that they showed a positive result for the primary outcome, which was peak oxygen uptake, and it improved clearly for patients with aficamten. And in fact, it was even surprising to see—not surprising after reviewing the evidence—but people were quite astonished to see that metoprolol did worse. But we've seen that this is an effect on exercise because of the negative chronotropy.

So on top of that being positive, we also see that subgroup analysis was consistent across all groups, meaning that this was a trustworthy outcome measure and improvement. Not only that, they improved also secondary outcomes that included quality of life,

NYHA functional class, and biomarkers and atrial remodeling markers.

So the only problem or issue that we can consider when we're considering first-line therapy for cardiac myosin inhibitors is the patient characteristics. This study, designed to be the answer for first-line, actually allowed inclusion of patients that were taking background therapies or beta-blockers to be washed out of them. And then if they tolerated it, they would be included. And the thing is that about 75 of the population of this study were not naive to any drug. Basically, they were on the drug, and they were washed out. This may introduce a bias of those that were not able to be washed out of the medication because they did not tolerate it.

So when we discuss the guidelines again, we can consider the first-line therapy. First, we need to make a case regarding beta-blockers. This, as I said, may come from historical evidence, safety, some symptom relief, improvement of LVOT gradients, but we're not sure about the exercise performance.

With the other hand, if we're going to go say, hey, you go for cardiac myosin inhibitor first, first you need to consider that some patients may have implications for beta-blockers for other reasons, for rate control, preventing ventricular arrhythmias, etc. Then you have those patients that may not be the perfect patient for cardiac myosin inhibitors. Women that want to get pregnant, patients with borderline left ventricular ejection fraction are other groups that you may possibly not consider cardiac myosin inhibitors as a first line and could still benefit from beta-blockers.

And of course, depending on the socioeconomic context of your country, your regulatory framework, you may need to take into account the cost and availability in your particular geographical region.

So regarding the guidelines, I cannot say whether they will make it as first line or not make it, but we need to justify their position based on the evidence that we have now.

And if we go for first line, we need to discuss the final question that I have. Should we consider this a class effect or not? And we have some small but accumulated data, but this systematic review analyzed whether the effect of mavacamten and aficamten were comparable. And as you can see, they do have similar improvements across groups. So this finding suggests that both mavacamten and aficamten significantly improve symptoms, enhance exercise performance, improve cardiac biomarkers, reduce LV outflow tract obstruction, and promote favorable cardiac remodeling. So this suggests more of a class effect.

So with that, what can I say regarding the next update of the 2027 guidelines? We know that second-line use is evidence-based. Background therapy needs clearer guidance. First-line use is a legitimate question, and the class-effect language probably needs some new answering and that we need to discuss. What I cannot say at this point, what the final recommendation class is going to be, whether there's going to be a first-line placement or not, whether we should treat those CMIs equally or not, on how much the algorithm will move. We don't get into cost-access consideration because we decide our recommendations on evidence, but this is something that needs also to be taken into account. For the rest, you need to wait until the 2027 guidelines are presented.

So my take-home message would be, first, CMIs have moved from experimental promise to guideline-recognized therapy. Second-line now deserves clearer and potentially stronger recommendation language. Classic drugs remain useful, but their evidence base should be appraised honestly. Background therapy should be individualized and actively re-prescribed when CMI are started. MAPLE-HCM makes first-line CMI a real but possibly selected guideline question. And finally, future recommendations need to consider class strategy from molecule-specific evidence.

So thank you.

Dr. Aguiar:
This presentation, I will address the real-world implementation of myosin inhibitors.

These are my disclosures.

Despite the robust evidence of efficacy in guidelines, there is some inertia in using myosin inhibitors in clinical practice. And why does it occur? Let's see the main reasons. First of all, it can be underdiagnosis. Estimating the true prevalence of HCM remains challenging to the intrinsic individuality of the disease. Different studies with different methodologies reported diverse prevalences. Echocardiography-

based studies demonstrated the prevalence of left ventricle hypertrophy of 0.2%. On the other hand, CMR-based studies, with its high sensitivity to detect hypertrophy, demonstrated a prevalence of 1.3%. Data from the health record database in US demonstrated the prevalence of clinical diagnosed HCM of 0.07%, whereas UK Biobank documented a prevalence of sarcomeric variants of 0.25%. Nevertheless, this entity is likely underdiagnosed because patients may be paucisymptomatic, echocardiographic changes may be subtle, and as the screening programs are lacking.

From the regulatory and system levels, some countries have restricted tests with compassionate use limited for more symptomatic patients in class III. These therapies may be perceived as complex since dose titration depends on a structured algorithm based on ejection fraction and dynamic gradient, with frequent echocardiographic monitoring necessary. And this monitoring infrastructure may represent the significant clinical and administrative burden that may deter prescribing.

Also, logistic constraints may limit since drug dispensing is done just for a short period of time.

From the provider levels, clinicians must navigate multiple therapeutic options as beta-blockers, disopyramide, septal reduction therapy, and adding one more treatment option may add one more level of complexity to an already nuanced treatment approach. Incomplete response rates may temper enthusiasm, and limited awareness in the expertise outside comprehensive HCM centers may also delay adoption. The optimal use of myosin inhibitors may require HCM programs and expertise teams, which are not yet widely available.

The main safety concern is ejection fraction reduction. It is generally reversible and asymptomatic. However, it underscores the need of a careful patient selection and monitoring. Drug-drug interaction should also be taken into consideration in clinical practice. Overall, these therapies are safe when appropriately used, but they demand a well-structured monitoring program. Availability and affordability remain concerns, and cost consideration may affect patient and system adoption. Real-world data will show us the long-term value and cost-effectiveness.

And how can we overcome this inertia? First of all, it's important to improve detection and early diagnosis by increasing awareness, expanding access to CMR, and by implementation of screening programs. Clear patient-selection criteria and shared decision-making frameworks are essential. The optimal candidates are symptomatic patients with obstructive HCM in class II or III with a negative response to first-line therapy, ejection fraction higher than 55%, and patients who prefer medical therapy over invasive septal reduction. Referral to a comprehensive HCM center should be considered mainly in complex cases and particularly during initial program developments.

The integration with echocardiographic service to support monitoring is essential, and cytochrome genotyping to guide initial and maximum dose may also contribute for a safer use. The process should be streamed to reduce administrative burden while maintaining safety.

I can share our experience at Hospital Santa Marta in Lisbon. We do the surveillance of these patients with echocardiography, ECG, blood biomarkers, CMRs in order to assess reverse early remodeling as well as assess the impact on microvascular dysfunction, and CPET to objectively assess the functional capacity.

Before starting mavacamten it is important to recheck the candidacy criteria that I mentioned before and also review background therapies. Disopyramide should be stopped and drug-drug interaction reviewed. Pregnancy tests should be done when appropriate, and women should avoid pregnancy for 6 months after mavacamten interruption.

In the first surveillance at week 4, if the gradient is lower than 20, the dose should be reduced. If the gradient is higher than 20, the dose is kept the same. This approach is applicable for week 8 and week 11. If the gradient is solved, the patient keeps the same dose and repeat echo every 6 months. If not, the dose is titrated. If at any point in time ejection fraction is below 50%, the drug should be stopped and echo repeats in 4 weeks. If the ejection fraction is recovered, the mavacamten can be reintroduced at a lower dose. Discontinuation should be done if the ejection fraction drops twice on 2.5 mg of mavacamten.

Despite the enthusiasm for myosin inhibitors, there is still a place for septal reduction therapies, namely for patients who want to avoid lifelong therapy, in cases of limitation, intolerance, or adverse events to myosin inhibitors, and in situations of contraindications, such as pregnancy. A surgical intervention may also approach anatomical changes, mainly in mitral valve apparatus and concomitant cardiac or surgical indications such as valve disease or coronary artery disease also points in favor of myectomy.

So shared decision-making between medical treatment for intermittent treatment should be based on patient profile and preference and center expertise. Myosin inhibitors and septal reduction therapies are not competing, but complementary therapies best applied to careful phenotyping, patient-centered decision, and appropriate system organization. Myectomy and septal ablation outcomes are strongly dependent on operator and center experience, but in the real world, there is a limitation of availability of these centers.

Myosin inhibitors may provide a real option for patients who remain symptomatic despite medical treatment and who do not have access to high-volume septal reduction treatment centers. However, myosin inhibitors may reduce the referrals for invasive therapies with the risk of loss of expertise and training opportunities. To address this problem, care should be centralized in high-volume centers based on multidisciplinary HCM programs with clear referral pathways.

Another point that I would like to highlight is the need for early intervention. LVOT obstruction is not just a hemodynamic issue; it drives progressive remodeling, such as left-atrial enlargement, atrial fibrillation, diastolic dysfunction, myocardial fibrosis, or large venous symptoms. And myosin inhibitors have the potential to change this trajectory. These therapies showed to lead to a reverse remodeling effect with decreasing left atrial enlargements, improving diastolic dysfunction, and generating diastolic function beyond the decrease in gradient. CMR studies further demonstrated a favorable impact in microstructure with decreasing T2/1, decrease in extracellular volume beyond the decrease in left ventricular mass.

In conclusion, myosin inhibitors are transforming HCM management. Therapeutic inertia persists at multiple levels. Early diagnosis and structured pathways are essential. Future relies on earlier and broader intervention in order to relieve symptoms but also with the potential to change the disease progression.

Thank you very much.

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