Best Practices for Treating HCM: Global Views

CMEO Podcast Transcript

Martin S. Maron, MD:

Hello, I am Dr. Martin Maron, and on behalf of CME Outfitters, thank you for joining us for a new CMEO snack series titled, A Global Response to Hypertrophic Cardiomyopathy, Sharing Experience and Sharing Resources. This activity is sponsored or supported, I should say, by an educational brand from Bristol-Myers Squibb. This is the second of three CMEO snacks and we'll cover best practices for treating ACM from a global perspective. Again, I'm Marty Maron. I'm the director for the HCM center at Tufts Medical Center in Boston. And again, it's very much a pleasure to be with you. I'm incredibly pleased to be joined today by my friend and colleague over many, many years, Dr. Iacopo Olivotto, who is head of the cardiomyopathy unit at Careggi University Hospital at the University of Florence in Florence, Italy. Iacopo, welcome.

Iacopo Olivotto, MD:

Thank you, Marty. Thank you for having me.

Martin Maron:

Great. It was pleasure for you to join us. We've got incredible opportunity to have a discussion with you today is really without a doubt one of the world experts in this disease, an incredible perspective that you're going to be able to give the listening community here about HCM, particularly from your view in Europe, will maybe have an opportunity to compare and contrast European and US perspectives and where they overlap and where they may differ.

Martin Maron:

So, here is our learning objective on that note for today's activity. After participating in this activity, learners should be better able to implement practice guideline recommendations, to improve care for patients with HCM. Okay. With that said, let's get started. Iacopo, maybe the best place in that sense to start the conversation is just getting you to tell us a little bit about first the definition. How do you diagnose? What's the definition for the clinical diagnosis of HCM? So, let me ask you. You've made a diagnosis of HCM. What's the next step in evaluating that patient from a management standpoint? What's the first thing you really want to know after you've made the diagnosis of HCM that would drive how you're going to start to think about treatment?

Iacopo Olivotto:

Okay. Well, first of all, I need to find out about symptoms. So, the burden of disease in terms of quality of life and symptoms, and whether I can do anything to improve this quality of life. That is course the main task we all have as physicians. And sometimes the disease can impact quality of life in subtle ways. The symptoms may be hard to elicit from patients because they've grown accustomed to these diseases. They have in some way learned to live with some of the symptoms and may not even realize these are cardiac symptoms, including, for example, shortness of breath after meals, or being unable to do certain exercises, certain sports.

Iacopo Olivotto:

On the other hand, some of these more severe symptoms are quite evident and patients will complain about angina on effort or after meals, syncope, shortness of breath, palpitations. So some of the patients are really well. They have low impact. They should really must be reassured. There's a lot of discussion nowadays about how much of our time in the office is spent with a patient reassuring the patient because he or she may have read something terrible on the internet, and maybe they only have a very mild form of disease that will not require treatment.

Iacopo Olivotto:

On the other hand, of course, we need to get rid of the symptoms, and that goes into the evaluation of whether the patient is obstructive or nonobstructive, and how to approach these two different presentations. And the final thing that you want to do right from the start, and then continuously update during follow up is of course assess arrhythmic risk, risk of potentially lethal ventricular arrhythmias, which is something that is not necessarily related to symptoms, but is of course equally important to ascertain.

Martin Maron:

Right. And so if we come back to, we'll get to maybe arrhythmias in a minute. So for terms of the first part, symptoms, I think what you're saying is that the clinical history taking here is so important because the decision to move forward with treatment and how aggressive may be in a way to be with treatment really is driven by the burden of symptoms as they are perceived by the patient to impact their quality of life. Am I saying that right?

Iacopo Olivotto:

Yes. As far as we know, we don't have any treatment that has disease modifying properties. Unfortunately we still don't have diseases that have shown to modify the substrate or the national history of the disease. So what we are doing right now with the drugs we have available right now is largely to impact symptoms and control of arrhythmias.

Martin Maron:

Right. And it's true then that the treatment discussion in a symptomatic patient would be different potentially, or there are different options, I should say, available depending on if the patient is in the obstructive group versus nonobstructive group. Right?

Iacopo Olivotto:

It's totally different. Yes. So this is why it's so important to actually investigate obstruction properly, not only at rest, but also with provocation maneuvers and on physiological exercise. If a patient has obstruction, meaning systolic interior movements of the mitral valve causing gradients within the heart and therefore impedance to flow, which will obviously be a cause of symptoms, this is usually a reversible state whereby the left ventricle is quite healthy, has little fibrosis, has super normal function, and therefore the relief of the gradient will almost always restore a very good or even normal quality of life and exercise performance and potentially longevity.

Iacopo Olivotto:

There are no randomized studies looking at this, but we have a very long follow up on very nice cohorts including yours and ours that show that. On the other hand, if you have symptoms in the context of a failing left ventricle, either because of diastolic and/or systolic dysfunction, these hearts don't have obstruction, but they do have extensive fibrosis occupying sometimes huge portions of the left ventricle. And of course the heart becomes very stiff, sometimes also develops systolic dysfunction.

Iacopo Olivotto:

There are various several stages to this process, but of course at the end, at the bottom of the descent, we find so-called end stage disease, which is not amenable to pharmacological treatment, and may even require heart transplant, luckily in a minority of these patients, but a very challenging minority.

Martin Maron:

Great. So in that sense, it'd be great to get your perspective on how to approach the most common scenario that we see, symptomatic obstructive HCM. So you've imaged the patient and they've got mitral valve septal contact, you've got gradients that are greater than 30 millimeters of mercury either at rest or with some form of provocation, which is about two thirds of the patient, patients reporting that they've got some symptoms, most commonly that's usually exertional dyspnea, occasionally chest pain or decreased exertional capacity, but they're limited in some way by symptoms with gradients that are present. What do you do?

Iacopo Olivotto:

Well, we do give it a shot with drugs. Of course, if it's a naive patient, some of the patients may respond, and may do so well, but usually it's the mild exercise related obstructions that respond, or again, so the milder forms in general. We definitely try beta blockers that act as negative inotropes, and will, again, be particularly effective on exercise-related obstruction, but they do cause side effects and they may cause chronotopic incompetence.

Iacopo Olivotto:

So they need to be used judiciously as always. Non-dehydrodiagenic calcium antagonists such as verapamil may be used as an alternative in patients who don't tolerate beta blockers. But again, it's quite hard to achieve complete remission of symptoms and complete control of gradients with these drugs so that very often, particularly if resting gradients are in a range of 50 or above, you will need to quickly move to a second line agent, which is disopyramide, which is a class one antirrhythmic agent, which is used again, because it's a strong negative inotrope.

Iacopo Olivotto:

It has shown good efficacy in controlling symptoms, although even in very expert hands, such as in the cohort published by Mark Sherrod, many of the patients who are on disopyramide eventually move to invasive options, either because the drug is not tolerated due to side effects, or because the effect wanes over time, vanishes over time. So again, if this is the case, if symptoms are refractory to maximum tolerated pharmacological therapy, we would then obviously move according to guidelines, both US and European guidelines to either septal myectomy or alcohol septal ablation.

Martin Maron:

Right. So let's talk about those two options. Tell me about those in the following kind of sense. How do you first determine, are there things that you look at in an individual patient that may help you determine whether that patient would be a better candidate for one of those two procedures over the other, or do you consider them to be equivalent? Are there aspects of the treatments that differ or that would impact your enthusiasm for the procedure to an individual patient? How does your general conversation go with a patient who is now a candidate for septal reduction therapy in terms of the two options?

Martin Maron:

And also on that note, is access to the procedures, which is so important here, I'm sure you'll touch on the fact that both of those procedures need to be done in what we call higher volume expert centers to get the results that we want. Is that a limitation for you as well?

Iacopo Olivotto:

Yes. I think this is also one of the main differences. I mean, maybe the only real difference in terms of guidelines that I see as really relevant between, of course, we will talk about risk stratification as well, but in terms of treatment of obstruction, the European guidelines seem to put almost on the same level, alcohol ablation, a surgical myectomy, don't really give us gold standard versus second best indication. Whereas the American guidelines are much more leaning towards surgery.

Iacopo Olivotto:

And I tend to agree more with this approach. I tend to see surgery as a real gold standard in view of the, well, first of all, reliability of the results. In best hands, you really know you can target the physiopathology of the obstruction. The result is almost always guaranteed, again in best hands. The intervention is really safe. Mortality should be very, very low in centers that perform the procedure well. Although, of course, mortality can vary hugely depending on the experience, not only of the surgeon, but of the whole team.

Iacopo Olivotto:

On the other hand, alcohol ablation to me should really be reserved to those patients that either have a very high surgical risk or that for other reasons are not amenable to surgery. And in my personal experience, the percentage has shifted in favor of myectomy hugely because we now operate more and more frail patients because of the experience on older patients with aortic stenosis and other stuff. So patients that really have prohibitive operative risks are now quite rare, in my opinion.

Iacopo Olivotto:

And again, I strongly favor surgery in the vast majority of my patients. Of course, there may be other issues. We do have patients that are high risk or patients that have minimal hypertrophy and may not be a amenable to classic myectomy, in which you may want to consider alcohol ablation. You may have other conditions that may, for example, if a patient presents with right bundle branch block, you know that with surgical myectomy almost always you will develop complete AV block and make the patient pacemaker-dependent, whereas alcohol ablation likely would not.

Iacopo Olivotto:

But again, I consider this a small minority. Again, talking about my practice, if you talk about Europe in general, we do have that problem, problem of patients accessing care. There are entire countries in Europe even, quite wealthy countries that have not developed skills for surgery for alcohol ablation, and that don't have centers where the procedures are performed in a sufficient flow, sufficient numbers to make the procedure really available to patients in best possible hands and safely. We have lost a lot of our surgical tradition with the advent of alcohol ablation in the nineties that really took the stage in a very rapid, and maybe too rapid way, sweeping away a very sound surgical tradition over development over decades.

Iacopo Olivotto:

I think we don't feel the urge now to rebuild surgical expertise. Countries should have at least one or two centers where this is developed, but unfortunately this is not the case. In Florence, we are fortunate because we do have a surgical center that performs, and we are very happy with the results, but it took time. It takes time.

Martin Maron:

Sure. But in the right hands like you have and others, for surgery you'd consider it to be a high benefit, low risk intervention that really can dramatically improve the quality of life for the vast majority of patients who undergo successful myectomy.

Iacopo Olivotto:

Yes, absolutely. It's a very clean surgery, doesn't leave in prosthesis, doesn't require anticoagulation long term. So, it's one of those procedures like metroplasty where you're really happy to see the good results and know you've changed the course of the patient.

Martin Maron:

Yep. Good. So we're getting close to the end here and I'd be remiss not to at least ask you, I know we're going to have probably another whole session on this topic, but since we've got you here and we're talking about treatment of obstructive HCM, and you were, of course, the lead investigator on the recent EXPLORER clinical trial that looked at a new class of drug called myosin inhibitor, mavocamten, being advanced for the treatment of symptomatic obstructive HCM.

Martin Maron:

Maybe you could tell us a little bit about how you view. I know we're at the beginning of what will ultimately be a journey with these drug class and this disease in terms of better understanding of its efficacy and safety, but where we are right now in 2022, tell us just in your view how you look at this drug in terms of where it would maybe be, ultimately lie in the treatment algorithm. What do you expect to see coming up in the future? Will it become available? Will there be limitations? That kind of thing. Just give us your view and we'll end on that.

Iacopo Olivotto:

Thank you, Marty. Well, myosin inhibitors are really a very interesting set of molecules. They're actually two out there now. And mavacamten is the only one that has completed phase three experimentation in obstructive disease, although it was not primarily designed to treat obstruction, but rather to treat the molecular underpinnings of HCM. So to normalize the hypercontractile state and the energetic consequences of genetic mutations in HCM.

Iacopo Olivotto:

So what we know right now is that the drug is effective and quite effective in reducing symptoms and gradients in patients with severe obstruction who are not immediate surgical candidates. Explorer excluded from the study patients that were immediate surgical candidates. It was a milder population compared to surgical series. And in those patients, the great relief in symptomatic improvement were quite striking. And I must say my personal experience in patients studied in Florence, some whom have been now on the drug for almost two years, results seem to be sustained and the drug is overall safe.

Iacopo Olivotto:

Of course, there are safety concerns in the sense that we still don't know about individual variability in response, as well as long term use of the drug. But on average, the drug proved to be sufficiently safe, that we are hoping to have the drug approved for clinical use soon. What we still don't know is whether we can use the drug to modify the long-term course of the disease, whether the drug may be effective in preventing or reducing the need for surgery or alcohol ablation.

Iacopo Olivotto:

There is a study that has been completed on that and will be presented soon called VALOR-HCM. We also don't know whether we can use it in nonobstructive HCM. So, whether that's going to be an asset for non-obstructive symptomatic HCM to, again, prevent disease progression, for example. I think it's an exciting development, particularly as it is part of a new strategy that is emerging in cardiovascular medicine as well, because don't forget, we also have myosin-promoter enhancers, such as omecamtiv mecarbil that are also promising in certain subset of patients with systolic dysfunction. So, if we learn to modulate myosin, whether we want to promote it or to inhibit it, this may actually be a further weapon that we have in cardiovascular diseases. We just began the exploration of these strategy, and I hope that our patient will benefit very soon from it.

Martin Maron:

Iacopo, as always, it's great to talk to you to get your perspectives, get your insights on HCM. Always incredibly helpful. I'm sure the audience also appreciated your insights as well. I want to just thank you for taking the time to join us today to lend those insights to everybody. So appreciate it very much. Thank you and be safe.

Iacopo Olivotto:

Thank you, Marty. Thank you for having me.

Martin Maron:

Absolutely.

Martin Maron:

Okay. So just a couple points about what we call smart goals. Number one, I think it's really important to think about hypertrophic cardiomyopathy on the top of your differential diagnosis list in patients presenting with short of breath, chest pain, exertional fatigue, for which there's no other obvious cause. And that best is approached diagnostically with echocardiography and also in select patients as well, consideration to using MRI to make the diagnosis.

Martin Maron:

But again, really important to consider HCM at the top of that differential list in patients that present with symptoms like shortness of breath, chest pain, or exertional fatigue, lightheadedness as well, and dizziness. The practice guidelines in both the US and Europe for this disease really complement each other very well and can provide a very important framework to guide practitioners and patients in terms of management for all aspects of the disease.

Martin Maron:

We touched today on symptomatic obstructive HCM, the use of negative inotropic agents, including beta blocker, calcium channel blocker and Norpase. And in those that remain refractory to that, the incredibly important impact of septal reduction therapies like surgical myectomy and alcohol ablation, as well as the potential soon for additional medical therapy in the form of myosin inhibitors. We also touched on the importance of expert HCM centers and what they can provide patients in terms of additional insights in terms of management, particularly in complex situations for symptom and risk stratification.

Martin Maron:

And again, it's an evolving disease. We've got continued advancements along the way here over the last 50 to 60 years. And those advancements are continuing, and to be on the lookout for new drug therapies, which we hope that will be available soon. As I mentioned, this is the second of three new CMEO snacks on HCM. Please visit the cardiology education hub at www.CMEOutfitters.com to participate in part one and part three. And don't forget to complete the evaluation to claim credit for today's activity. And thank you again for your attention. We hope you'll find the information today particularly helpful in caring for your patients. Thank you.

